Original Article

Associations between antibody to hepatitis B core antigen positivity and outcomes in hepatocellular carcinoma patients undergoing hepatic resection

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Aim: We aimed to evaluate the effect of antibody to hepatitis B core antigen (HBcAb) positivity on clinical outcomes after hepatic resection in hepatocellular carcinoma (HCC) patients with negative hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb), termed non-B, non-C HCC (NBNC-HCC), or with HCV-related HCC.

Methods: Two hundred and sixty-three patients who underwent hepatic resection for HCC and measurements of HBsAg, HCVAb, and HBcAb were enrolled in this study.

Results: The percentages of HBcAb positivity were 52.3% (n = 57) and 56.9% (n = 66) in patients with NBNC- and HCV-related HCC, respectively. The proportion of multiple NBNC-HCCs was significantly greater in patients with HBcAb positivity compared to HBcAb negativity (P = 0.028). There were no significant differences in the recurrence-free and overall survival rates between NBNC-HCC patients with HBcAb positivity versus negativity (P = 0.461 and P = 0.190, respectively). Furthermore, for HCV-related HCC patients, there were no significant differences in the baseline factors between patients with positive versus negative HBcAb. The proportion of patients with HBcAb-positive HCV-related HCC who underwent anatomical resection of the liver was significantly greater than that of HBcAb-negative patients, whereas the recurrence-free and overall survival rates were not significantly different (P = 0.158 and P = 0.191, respectively).

Conclusion: In our study, the presence of HBcAb had no impact on surgical outcomes after hepatic resection in patients with NBNC- and HCV-related HCC. Occult HBV infection might be associated with hepatocarcinogenesis in patients with NBNC-related HCC.

Key words: hepatitis B core antigen, hepatocellular carcinoma, prognosis

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the most prevalent epithelial cancer of the liver, and one of the most common causes of cancer-related death in many countries, especially in Japan.1,2 Hepatic resection has been established as a safe and effective treatment for HCC.3,4 There is a high prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in the general population of Japan; however, the proportion of HCC cases negative for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb), termed non-B, non-C HCC (NBNC-HCC), is currently increasing.5,6 Patients with antibody to hepatitis B core antigen (HBcAb) positivity and HBsAg negativity are considered to have occult HBV infection.7 Antibody to hepatitis B core antigen is present in approximately 20% of healthy individuals.5,9 Moreover, the HBcAb-positive rate has been reported as 53.6% in HCV-related chronic liver disease,10 and a recent study reported that the positive rate of HBcAb in patients with NBNC-HCC reached 40%.6 However, because measurement of HBcAb is not included in the regular screening protocol for HBV infection at many institutions, the actual prognostic influence of HBcAb positivity in HCC patients remains unclear. Thus, given the apparently high proportion of patients with a history of HBV, the clinical features of the HBcAb-positive subgroup of NBNC-HCC or HCV-related HCC patients

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need to be explored to allow for better clinical management of HCC. The aim of the present study was, therefore, to investigate the relationship between HBcAb positivity and clinical outcome in patients with NBNC-HCC or HCV-related HCC undergoing hepatic resection.

METHODS

Patients

Between July 2000 and December 2015, 510 patients underwent hepatic resection for HCC at the Department of Surgery and Science, Kyushu University Hospital (Fukuoka, Japan). We excluded 241 patients because HBcAb was not measured, and 6 patients who were both HBsAg- and HCVAb-positive were further excluded from this analysis. The data of the remaining 263 patients were studied in detail. This study was approved by the Ethics Committee of Kyushu University (approval code: 28–212).

Surgical procedures

The details of our surgical techniques and patient selection criteria for hepatic resection for HCC have been previously reported. The resection volume was decided based on the patients’ indocyanine green dye retention rate at 15 min (ICGR15). Patients with an ICGR15 ≥ 35% were generally selected for limited resection. Parenchymal transection was carried out using the Cavitron Ultrasonic Surgical Aspirator (Valleylab, Boulder, CO, USA). Inflow vascular control was carried out with intermittent hemi- or total Glisson’s sheath occlusion (Pringle maneuver) and, if required, with a selective hepatic vein-clamping method. Inflow occlusion was applied intermittently with 15 min of occlusion alternating with 5 min of reperfusion.

Histological examinations

The histologic grade of tumor differentiation, degree of fibrosis in the background liver, and presence or absence of vascular invasion were assessed microscopically based on the classification system proposed by the Liver Cancer Study Group of Japan. Fibrosis staging was scored using the Scheuer classification on a scale of 0–4 as follows: F0, no fibrosis; F1, enlarged fibrotic portal tracts; F2, periportal or portal–portal septa but intact architecture; F3, fibrosis with architectural distortion but no obvious cirrhosis; and F4, probable or definite cirrhosis.

Follow-up assessment

The patients were strictly followed after the hepatic resection, with monthly measurements of the levels of α-fetoprotein and des-γ-carboxy prothrombin, as well as monthly ultrasonography. Dynamic computed tomography was carried out every 3 months by radiologists, and angiographic examination was undertaken on admission if there was a strong suspicion of disease recurrence. We treated recurrent HCC by repeat hepatic resection, local ablation therapy, or transcatheter arterial chemoembolization.

Statistical analysis

The data are expressed as the median and range. Continuous variables without normal distribution were compared by the Mann–Whitney U-test. Categorical variables were compared by the χ2-test or Fisher’s exact test. The overall survival (OS) and recurrence-free survival (RFS) rates were calculated by the Kaplan–Meier (product limit) method and compared by the log–rank test. All statistical analyses were carried out using JMP software (SAS Institute, Cary, NC, USA), with P < 0.05 considered statistically significant.
patients with NBNC-HCC were 82.5% versus 75.4% and 54.6% versus 52.8%, respectively.

Table 2 summarizes the baseline characteristics of the 116 patients with HCV-related HCC. There were no significant differences in the baseline factors between positive and negative HBCab patients, except for in the percentage of anatomical resection. The RFS and OS curves of HCV-related HCC patients after hepatic resection are

![Figure 1 Recurrence-free survival (RFS) and overall survival (OS) curves after hepatic resection in antibody to hepatitis B core antigen (HBCab)-positive versus HBCab-negative patients with non-B, non-C or hepatitis C virus-related hepatocellular carcinoma.](image)

| Variables                        | HBCab-negative (n = 52) | HBCab-positive (n = 57) | P-value |
|----------------------------------|-------------------------|-------------------------|---------|
| Age, years                       | 72 (28–87)              | 71 (17–85)              | 0.958   |
| Sex, male, %                     | 44 (84.6)               | 45 (78.9)               | 0.470   |
| BMI, kg/m²                       | 22.7 (17.6–32.6)        | 23.5 (17.2–30.8)        | 0.343   |
| Diabetes mellitus                | 21 (40.3)               | 25 (43.8)               | 0.713   |
| Hypertension                     | 21 (40.3)               | 28 (49.1)               | 0.359   |
| Heavy alcohol intake             | 13 (25.0)               | 13 (23.2)               | 0.823   |
| Child–Pugh class, A / B          | 51/1                    | 57/0                    | 0.477   |
| Albumin, g/dL                    | 4.0 (2.8–4.8)           | 4.0 (2.9–5.0)           | 0.867   |
| Total bilirubin, mg/dL           | 0.65 (0.3–1.5)          | 0.70 (0.3–1.5)          | 0.684   |
| Prothrombin time, %              | 91.5 (62–117)           | 93 (68–114)             | 0.915   |
| ICGR15, %                        | 11.7 (2.0–36.0)         | 13.0 (2.7–26.6)         | 0.820   |
| Platelets, ×10^4/mm³             | 18.7 (9.3–35.6)         | 19.0 (1.4–43.5)         | 0.809   |
| AST, IU/L                        | 29.5 (15–149)           | 30.0 (13–220)           | 0.690   |
| ALT, IU/L                        | 25.5 (8–110)            | 26.0 (8–168)            | 0.815   |
| Total cholesterol, mg/dL         | 182 (109–274)           | 174 (103–305)           | 0.327   |
| F0–1 / F2 / F3 / F4              | 20/27/4/1               | 17/35/4/1               | 0.870   |
| Tumor size, cm                   | 4.9 (2.0–20)            | 4.5 (1.0–20)            | 0.504   |
| Solitary / multiple              | 44/8                    | 38/19                   | 0.028   |
| AFP, ng/mL                       | 4.3 (0.5–161 884)       | 7.0 (0.9–170 668)       | 0.162   |
| DCP, mAU/ml                      | 96.5 (14–63 849)        | 176 (9–175 610)         | 0.707   |
| Poor differentiation             | 19 (36.5)               | 19 (33.3)               | 0.725   |
| Microvascular invasion           | 17 (32.6)               | 22 (38.6)               | 0.520   |
| Anatomical resection             | 43 (82.6)               | 39 (68.4)               | 0.084   |
| Surgical margin, mm              | 6 (0–65)                | 3 (0–40)                | 0.185   |

Values are presented as n (%) or median (range).

AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DCP, des-γ-carboxy prothrombin; F, fibrosis stage; ICGR15, indocyanine green dye retention at 15 min.
provided in Figure 3. There were no significant differences in RFS or OS between positive and negative HBcAb patients ($P = 0.158$ and $P = 0.191$, respectively). The 5-year RFS rates in the positive and negative patients with HCV-related HCC were 15.8% and 37.2%, respectively. The 5- and 10-year OS rates in the positive versus negative patients were 72.0% versus 71.3% and 36.2% versus 65.9%, respectively.
DISCUSSION

OUR STUDY ANALYZED the oncologic outcomes of the subgroup with occult HBV infection among patients with NBNC- or HCV-related HCC. The HBcAb-positive patients showed similar RFS and OS to HBcAb-negative NBNC- or HCV-related HCC patients. Non-alcoholic steatohepatitis, alcoholic liver disease, autoimmune liver disease, diabetes mellitus, and occult HBV infection (i.e. HBcAb-positive status), in addition to active HBV or HCV infection, have been reported as potential risk factors for HCC. The surgical outcomes of hepatic resection for NBNC-HCC were reported in previous single center studies and in a nationwide study in Japan. However, these reports did not describe the proportion of HBcAb positivity in patients with HCC. Therefore, we undertook the current investigation into the role of occult HBV infection in patients with NBNC- or HCV-related HCC.

Omichi et al. reported that patients with a history of HBV infection among patients with NBNC-HCC had better survival outcomes after hepatic resection than patients with HBcAb-negative NBNC-HCC, HBV-related HCC, or HCV-related HCC, because the patients with HBcAb-negative NBNC-HCC showed a larger tumor size, a higher incidence of vascular invasion, and a higher serum level of des-γ-carboxy prothrombin than patients with HBcAb-positive NBNC-HCC. Nishikawa et al. reported that HBcAb positivity was a useful predictor for recurrence in patients with NBNC-HCC after treatment with transcatheter arterial chemoembolization or local ablation therapy in addition to hepatic resection. Furthermore, Ikeda et al. reported that, in patients with NBNC liver cirrhosis, occult HBV infection increased the initial carcinogenesis rate. In our study, the proportion of multiple tumors in patients with HBcAb-positive NBNC-HCC was the only significantly higher factor compared to HBcAb-negative NBNC-HCC patients, and there was no significant difference in DFS or OS following hepatic resection between HBcAb-positive and -negative NBNC-HCC patients. These data suggest that a history of obscure HBV infection is not associated with long-term outcome following hepatic resection, but might be associated with the initial, rather than second, hepatocarcinogenesis in patients with NBNC-HCC.

In HCV-related HCC patients, we found that there were no significant differences in baseline factors, RFS, or OS between those with positive and negative HBcAb. To the best of our knowledge, this is the first comparative study to investigate the relationship between surgical outcomes and HBcAb positivity in patients with HCV-related HCC. In regard to HCC development in patients with HCV-related chronic liver disease, some studies have investigated whether there is a relationship with occult HBV infection or not. A prospective study in 275 patients with HCC-related liver cirrhosis indicated that HBcAb was the only factor associated with progression to HCC, whereas Lok et al. reported that occult HBV infection was not a risk factor in HCC development among patients with chronic hepatitis C liver disease in the USA. Another study showed that the presence of HBcAb had no effect on the prognosis, development of HCC, and progression of hepatic fibrosis in patients with HCV infection. In the present study, there was no significant difference in terms of RFS or OS between HBcAb-positive and -negative patients with HCC with or without liver fibrosis (data not shown). Taken together, occult HBV infection in HCV carriers might promote development of HCC in patients with liver cirrhosis; however, our results suggest that occult HBV infection might not have an effect on tumor progression in patients with HCV-related HCC.
In this study, the proportion of anatomical resection of the liver for HBcAb-positive patients with HCV-related HCC was significantly greater than that in HBcAb-negative patients. There were no significant differences in RFS or OS between patients undergoing anatomical resection and partial hepatic resection for HCV-related HCC (data not shown). Anatomical resection is one of the curative treatments for HCC, and yields a better RFS than partial hepatic resection, especially for tumors between 2 and 5 cm in diameter.25 Hence, further investigations of a greater number of patients are needed to confirm the advantage of anatomical resection.

There are several limitations to the present study. This was a single-center retrospective study. In addition, the number of patients was relatively small, and data on the HBV DNA findings were missing. Further multi-institutional studies with a greater number of patients and additional data are required to confirm these results.

In conclusion, the presence of occult HBV infection had no effect on the oncological outcomes for patients with NBNC- or HCV-related HCC following hepatic resection.

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