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# Hepatectomy for hepatitis B-, hepatitis C-, and dual hepatitis B- and C-related hepatocellular carcinoma in Taiwan

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**Abstract:** To evaluate the surgical results of patients with hepatitis B-, hepatitis C- and dual hepatitis B- and C-related hepatocellular carcinoma (HCC), we reviewed the clinical records 252 patients (196 men and 56 women) with complete profiles of hepatitis B and hepatitis C infection who had hepatectomies to treat HCC from March, 1992, to August, 1998. The patients were divided into four groups, 30 patients (11.9%) without either hepatitis B surface antigen or anti-hepatitis C antibody (N-HCC group), 133 patients (52.8%) with hepatitis B infection only (B-HCC group), 66 patients (26.2%) with hepatitis C infection only (C-HCC group), and 23 patients (9.1%) with dual hepatitis B and C infection (BC-HCC group). Compared with the patients in the other groups, the patients in the C-HCC group were older and had more severe cirrhotic change of the liver. The surgical complication rates and hospital mortalities in the C-HCC and BC-HCC groups were 30.3% and 12.1% and 30.4% and 17.4%, respectively, which were higher than those in the N-HCC (13.3%, 3.3%) and B-HCC (15.8%, 3.8%) groups. The mean disease-free survivals for the N-HCC, B-HCC, C-HCC, and BC-HCC groups were 31.4, 25.4, 38.9 and 13.8 months, respectively, with the difference between the four groups being significant ($P < 0.05$). However, the mean overall survival times, 38.3 months for the N-HCC group, 37.2 months for the B-HCC group, 52.1 months for the C-HCC group, and 32.7 months for the BC-HCC group, were not significantly different ($P = 0.146$). In conclusion, surgical treatments for HCC related to hepatitis C or dual hepatitis B and C infection were associated with a higher surgical complication rate and hospital mortality. Hepatocellular carcinoma related to dual hepatitis B and C infection recurred earlier after hepatectomy, but the overall survival of the four groups was not significantly different.

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**Key words:** hepatocellular carcinoma, hepatitis B, hepatitis C, hepatectomy

## Introduction

Hepatocellular carcinoma (HCC) is a highly prevalent malignancy in Taiwan, and it is now the first ranking cause of death of malignancy in men. Because the carrier rate of hepatitis B virus (HBV) in the general population was about 15%, the high prevalence of HCC in Taiwan was mostly considered to be related to HBV.[1–3] However, since the development of an assay to detect hepatitis C virus (HCV) infection,[4] more and more HCCs were found to be related to HCV.[5] Moreover, some patients with HCC had dual HBV and HCV infections. Consequently, the influence of dual HBV and HCV infection on the surgical results of HCC, and whether the surgical results are different for HCCs related to HBV and HCV, need to be clarified.

We previously described 13 patients with dual HBV and HCV-related HCC who underwent hepatic resection, emphasizing the short-term results.[6] In this study, more patients were enrolled, and we reappraised the surgical results of patients with hepatitis virus-related HCC. Surgical morbidity, mortality, disease-free survival, and overall survival were analyzed statistically. We found that HCV-related HCC had a higher complication rate than HBV-related HCC, and dual HBV and HCV viral infection led to earlier tumor recurrence.

## Subjects and methods

The clinical records of patients who had hepatectomies to treat HCC at Chang-Gung Memorial Hospital Taipei, Taiwan, from March 1992 to August 1998 were

reviewed. We chose this period because the assay to detect anti-HCV antibody was introduced in late 1991. Excluding 11 patients in whom the tumors were incompletely resected, 252 patients with complete records of hepatitis B infection, hepatitis C infection, or dual hepatitis B and C infection and complete removal of HCC were enrolled in this study. Hepatitis B infection was defined as positivity for hepatitis B surface antigen, and hepatitis C infection was evidenced by the existence of anti-hepatitis C antibody. Of the 252 patients, 196 were men and 56, women. The patients' ages ranged between 9 and 87 years, with a mean of 54.3 years.

To compare the influence of hepatitis B, hepatitis C, or dual hepatitis B and C infection on the surgical results of hepatectomy for HCC, the patients were divided into four groups: N-HCC, B-HCC, C-HCC, and BC-HCC. Group N-HCC, 30 patients (11.9%), was negative for hepatitis B surface antigen and anti-HCV antibody; group B-HCC, 133 patients (52.8%), was positive for hepatitis B infection and negative for hepatitis C infection; group C-HCC, 66 patients (26.2%), was positive for hepatitis C infection and negative for hepatitis B infection; and group BC-HCC, 23 patients (9.1%), was positive for both hepatitis B and C infections. The general preoperative clinical data for the four groups, including age, sex, liver function, liver cirrhotic status, and quantitative liver function tests were collected, and are listed in Table 1. Table 2 shows the operative procedures, perioperative blood loss, and amount of blood transfusion. Because the tumor condition may affect prognosis, we examined the histopathologic features of the tumors; these are listed in Table 3.

**Table 1.** Clinical features of 252 patients with hepatitis B-, hepatitis C-, and dual hepatitis B and C-related HCC

| | N-HCC | B-HCC | C-HCC | BC-HCC | *P* Value |
|---|---|---|---|---|---|
| Number of patients (%) | 30 (11.9%) | 133 (52.8%) | 66 (26.2%) | 23 (9.1%) | |
| Age (years) | 54.3 ± 13.3 | 49.4 ± 12.7 | 61.7 ± 9.2 | 57.4 ± 12.0 | 0.001 |
| Sex | | | | | |
| Male (%) | 20 (66.7%) | 112 (84.2%) | 48 (72.7%) | 16 (69.6%) | NS |
| Female (%) | 10 (33.3%) | 21 (15.8%) | 18 (27.3%) | 7 (30.4%) | |
| Diabetes mellitus (%) | 4 (13.3%) | 20 (15.0%) | 23 (34.8%) | 6 (26.1%) | 0.004 |
| Renal insufficiency (%) (Cr > 1.2 mg/dl) | 5 (16.7%) | 23 (17.3%) | 18 (27.3%) | 4 (17.4%) | NS |
| Liver cirrhosis (%) | 13 (43.3%) | 70 (52.6%) | 42 (63.6%) | 15 (65.2%) | NS |
| Child's A (%) | 11 (36.7%) | 51 (38.3%) | 27 (40.9%) | 12 (52.2%) | NS |
| B (%) | 2 (6.7%) | 17 (12.8%) | 15 (22.7%) | 3 (13.0%) | |
| C (%) | 0 | 2 (1.5%) | 0 | 0 | |
| Serum AST (IU/l) | 51.9 ± 50.9 | 76.0 ± 93.5 | 87.3 ± 64.8 | 77.9 ± 69.8 | NS |
| Serum ALT (IU/l) | 39.5 ± 68.7 | 58.5 ± 66.2 | 75.2 ± 57.2 | 76.9 ± 91.7 | NS |
| Total bilirubin (mg/dl) | 0.9 ± 1.0 | 1.1 ± 1.2 | 1.2 ± 1.2 | 0.8 ± 0.3 | NS |
| INR of prothrombin time | 1.03 ± 0.01 | 1.11 ± 0.16 | 1.12 ± 0.15 | 1.03 ± 0.01 | 0.049 |
| $ICG_{15}$ | 15.9 ± 17.8% | 11.2 ± 13.7% | 26.0 ± 18.5% | 10.5 ± 9.4% | 0.021 |
| α-Fetoprotein level (%) | | | | | |
| <100 (ng/ml) | 18 (60%) | 47 (35.3%) | 26 (39.4%) | 5 (21.7%) | 0.039 |
| >100 (ng/ml) | 12 (40%) | 86 (64.7%) | 40 (60.6%) | 18 (78.3%) | |

NS, Not significant; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalization ratio; $ICG_{15}$, 15-min retention rate of indocyanine green; HCC, hepatocellular carcinoma; Cr, creatinine; N-HCC, hepatitis B surface antigen (HBsAg) (−), anti-hepatitis C virus antibody (anti-HCV) (−); B-HCC, HBsAg (+), anti-HCV (−); C-HCC, HBsAg (−), anti-HCV (+); BC-HCC, HBsAg (+), anti-HCV (+)

**Table 2.** Operative data of 252 patients with hepatitis virus-related HCC

| | N-HCC ($n$ = 30) | B-HCC ($n$ = 133) | C-HCC ($n$ = 66) | BC-HCC ($n$ = 23) | *P* Value |
|---|---|---|---|---|---|
| Right lobectomy | 10 (33.3%) | 37 (27.8%) | 17 (25.8%) | 6 (26.1%) | NS |
| Left lobectomy | 3 (10%) | 26 (19.5%) | 11 (16.7%) | 4 (17.4%) | NS |
| Extended right lobectomy | 2 (6.7%) | 6 (4.5%) | 1 (1.5%) | 2 (8.7%) | NS |
| Extended left lobectomy | 0 | 1 (0.8%) | 1 (1.5%) | 1 (4.3%) | NS |
| Segmentectomy | 15 (50%) | 63 (47.4%) | 36 (54.5%) | 10 (43.4%) | NS |
| Blood loss (ml) | 1598.2 ± 1991.1 | 1130.6 ± 1387.2 | 1092.2 ± 923.7 | 1887.0 ± 2382.7 | NS |
| Blood transfusion (ml) | 1136.7 ± 1992.8 | 842.3 ± 1656.0 | 805.5 ± 1150.2 | 1482.6 ± 2248.0 | 0.032 |

NS, Not significant

**Table 3.** Histopathological features of the tumors of 252 patients with hepatitis virus-related HCC

| | N-HCC ($n$ = 30) | B-HCC ($n$ = 133) | C-HCC ($n$ = 66) | BC-HCC ($n$ = 23) | $P$ Value |
|---|---|---|---|---|---|
| Tumor size (%) | | | | | 0.006 |
| <2 cm | 2 (6.7%) | 8 (6.0%) | 4 (6.1%) | 4 (17.4%) | |
| 2–5 cm | 13 (43.3%) | 62 (46.6%) | 48 (72.7%) | 11 (47.8%) | |
| >5 cm | 15 (50%) | 63 (47.4%) | 14 (21.2%) | 8 (34.8%) | |
| Encapsulated tumor (%) | 20 (66.7%) | 81 (60.9%) | 52 (78.8%) | 14 (60.9%) | NS |
| Capsule invasion (%) | 8 (26.7%) | 45 (33.8%) | 12 (18.2%) | 8 (34.7%) | NS |
| Daughter nodules (%) | 8 (26.7%) | 39 (29.3%) | 17 (25.8%) | 6 (26.1%) | NS |
| Vascular invasion (%) | 4 (13.3%) | 42 (31.6%) | 9 (13.6%) | 3 (13.0%) | 0.022 |
| Resection margin <1 cm (%) | 14 (46.7%) | 43 (32.3%) | 32 (48.5%) | 8 (34.8%) | NS |

NS, Not significant

**Table 4.** Postoperative complications and surgical mortality of 252 patients with hepatitis virus-related HCC

| | N-HCC ($n$ = 30) | B-HCC ($n$ = 133) | C-HCC ($n$ = 66) | BC-HCC ($n$ = 23) | ($n$ = 252) | $P$ Value |
|---|---|---|---|---|---|---|
| Postoperative complication | 4 (13.3%) | 21 (15.8%) | 20 (30.3%) | 7 (30.4%) | 52 (20.6%) | 0.046 |
| Intraabdominal bacterial infection | 0 | 2 (1.5%) | 2 (3.0%) | 0 | 4 (1.6%) | |
| Liver failure | 0 | 6 (4.5%) | 9 (13.6%) | 3 (13.0%) | 18 (7.1%) | |
| Ascites | 2 (6.7%) | 5 (3.8%) | 4 (6.1%) | 0 | 11 (4.4%) | |
| Bile leak | 1 (3.3%) | 1 (0.7%) | 1 (1.5%) | 0 | 3 (1.2%) | |
| Pleural effusion | 1 (3.3%) | 7 (5.3%) | 4 (6.1%) | 4 (17.4%) | 16 (6.3%) | |
| Hospital mortality | 1 (3.3%) | 5 (3.8%) | 8 (12.1%) | 4 (17.4%) | 18 (7.1%) | 0.021 |

The details of surgical complications and hospital mortality are listed in Table 4.

All patients were followed up regularly at outpatient clinics. Serum α-fetoprotein level was checked and liver sonography was performed when needed, or at intervals of at least 3 months. When a nodule or nodules were detected by sonography, this was recorded as tumor recurrence.

Statistical analysis of differences among the four groups was carried out using Pearson's $\chi^2$ test or independent samples $t$-test. Survival was analyzed by the Kaplan-Meier method, and survival curves were compared by the generalized Wilcoxon test. A $P$ value less than 0.05 was considered to be statistically significant.

## Results

The patients in group C-HCC were older than those in the other groups ($P$ = 0.001), and also had a higher incidence of diabetes mellitus than the others ($P$ = 0.004). The incidence of liver cirrhosis and differences in Child's classification in the four groups were similar, and results of qualitative liver function tests in the four groups were also not significantly different. However, the 15-min retention rate of indocyanine green was higher in the C-HCC group than in the other groups. ($P$ = 0.021) (Table 1).

Operative procedures and blood loss during operations in the four groups were not significantly different (Table 2). When the resected specimens were examined for histological features, influential factors, such as the existence of a tumor capsule, capsule invaded by tumors, presence of daughter nodules, and resection margin, were not significantly different among the group. However, most of the tumors in the C-HCC group were less than 5 cm in diameter, which was significantly different from findings in the other groups. ($P$ = 0.006) (Table 3).

Liver function insufficiency (11.5%), pleural effusion (6.3%), and bacterial infection (1.6%) were the major complications after hepatectomy in this series (Table 4). Compared with the complication rates in the N-HCC (13.3%) and B-HCC (15.8%) groups, the complication rates in the C-HCC (30.3%) and BC-HCC (30.4%) groups were significantly higher ($P$ = 0.046). In this series, 18 patients died during hospitalization. Ten patients died of hepatic failure within 1 month of the operation, 4 patients died because of massive bleeding during operation followed by coagulopathy and adult respiratory distress syndrome, 2 patients with intraabdominal abscess died of sepsis and multiple organ failure, 1 patient died of pulmonary artery thrombosis, and 1 patient died of ventricular tachycardia. The overall hospital mortality was 7.1%. The hospital mortality for the C-HCC (12.1%) and BC-HCC (17.4%) groups

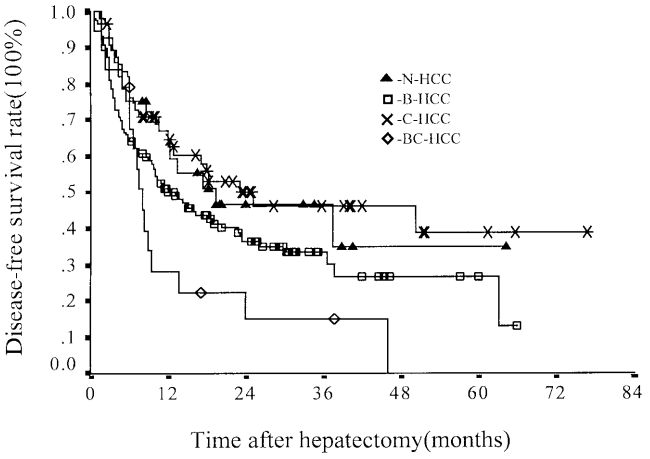


**Fig. 1.** Disease-free survival rates after hepatectomy in 252 patients with hepatitis virus-related hepatocellular carcinoma (*HCC*). *N-HCC*, Negative for hepatitis B surface antigen (HBsAg) and anti-hepatis C virus antibody (anti-HCV); *B-HCC*, HBsAg (+), anti-HCV (−); *C-HCC*, HBsAg (−), anti-HCV (+); *BC-HCC*, HBsAg (+), anti-HCV (+). *$P = 0.0203$. Difference between the four groups

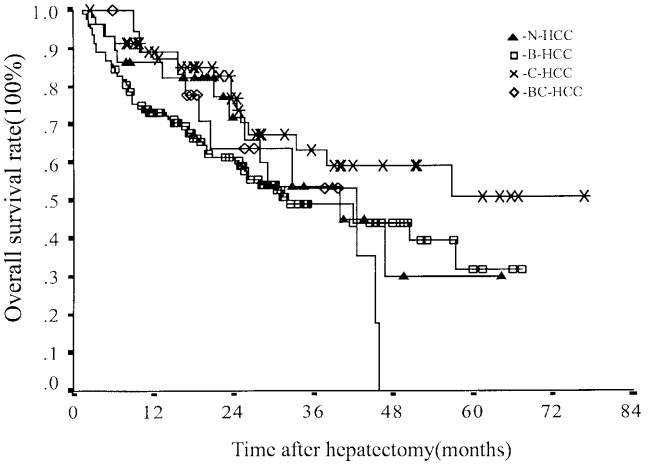


**Fig. 2.** Overall survival rates of patients after hepatectomy for HCC. *$P = 0.1460$. Difference between the four groups

was higher than that in the N-HCC and B-HCC groups ($P = 0.021$) (Table 4).

All the patients were followed up after hepatectomy for a mean period of 23.5 ± 16.3 months (range, 2 to 76 months). In the whole series, the tumor recurrence rate and cumulative survival rates in the first to fifth years were 46.5%, 60.9%, 64.9%, 70.2%, and 72.9%, and 80%, 66.7%, 53.4%, 42.1%, and 34.2%, respectively. For the four groups, the mean disease-free survival in the N-HCC, B-HCC, C-HCC, and BC-HCC groups was 31.4, 25.4, 38.9, and 13.8 months, respectively. The difference between these four groups was significant ($P = 0.0203$; Fig. 1). However, the overall survival in these four groups was not significantly different ($P = 0.146$), as the mean survival times for the N-HCC, B-HCC, C-HCC, and BC-HCC groups were 38.3, 37.2, 52.1, and 32.7 months, respectively (Fig. 2).

## Discussion

Hepatocellular carcinoma is a highly prevalent malignancy in Taiwan, and may be closely related to the high prevalence of HBV infection in the general population.[1–3] However, since a serological test for antibody to HCV was developed,[4] more and more HCCs are known to be related to HCV, and HCV has been recognized as a major risk factor for HCC.[5] In our hospital, a serological assay to detect antibodies to HCV was set up in 1991, and the surgical results of patients with HCC related to HBV and HCV who were treated from 1991 to 1995 have been evaluated.[6] As more and more HCC patients in Taiwan were found to have antibodies to HCV, in this latest series, we divided patients with HCC who had had hepatectomies into four groups, and reappraised the surgical results for patients with of HBV-, HCV-, or dual HBV and HCV-related HCC. In the whole series, the hospital mortality was 7.1% and the mortality directly related to the operation was 6.3%, findings which were similar to those in other reports.[7–9] Among the four groups, the surgical complication and hospital mortality rates were higher in patients with HCV infection (30.3% and 12.1%, respectively, in the C-HCC group, and 30.4% and 17.4%, respectively, in the BC-HCC group). The disease-free survival in the four groups also differed. Dual viral infection-related HCC was associated with the worst disease-free survival (13.8 months), followed by HBV-related HCC (25.4 months). However, the overall survival in the four groups was not significantly different.

The surgical complication rate and the hospital mortality were higher in the C-HCC and BC-HCC groups, findings which were compatible with previous reports in the literature.[10–12] Similar to other reports,[10–13] patients in the C-HCC and BC-HCC groups were older than those in the other groups, and this may have contributed to the higher morbidity and mortality rates. In this series, HCV infection was also associated with a higher incidence of diabetes mellitus (DM). Although the association between HCV and DM is still in debate,[14] several studies[15–17] have reported that DM is associated with chronic HCV infection, but not with HBV infection, and that patients with DM have a higher risk of postoperative morbidities.[18] Consequently, the high incidence of DM in our C-HCC patients may be a factor that led to the high morbidity and mortality. In our series, although the results of qualitative liver function tests, and Child's

classifications, were not significantly different between the groups, the results of the quantitative liver function test (15-min retention rate of indocyanide green) in C-HCC patients was worse than those in the other groups. This meant that the severity of cirrhosis was worse in the HCV-related HCC patients than in the non-viral infected or HBV-related HCC patients. The poorer liver function in the HCV-related HCC patients may be the major factor involved in their higher rate of surgical complications and hospital mortality.

In our present series, the patients in the C-HCC group had the best disease-free survival. This may be because of the smaller size of the tumors in the C-HCC group, compared with those in the other groups ($P = 0.006$). Most of the tumors in the C-HCC patients were less than 5 cm in diameter; this may have reflected their regular more frequent follow-up, carried out because the liver function in HCV-related patients was always abnormal. The BC-HCC group had the worst disease-free survival, especially compared with those in the N-HCC group ($P = 0.028$) and the C-HCC group ($P = 0.025$). The survival in the B-HCC group was also worse than that in the C-HCC group ($P = 0.0445$). Whether HBV contributes to tumor recurrence is not clear at present. Whether dual infections of HBV and HCV change the behavior of HCC is also not clear. The interactions of HBV and HCV are still controversial; Liaw et al.[19] reported that HCV may exert a suppressive effect on HBV, and Zarski et al.[20] pointed out that HBV DNA replication inhibited HCV RNA replication and increased the severity of histological lesions. Therefore, the mechanism of the earlier HCC recurrence in dual HBV and HCV infection is still a mystery, and further studies are needed to clarify this. Our patients in the C-HCC group had a longer mean overall survival time (52.1 months) than those in the other groups, but the difference was not significant.

In conclusion, hepatic resections for HCV or dual HBV- and HCV-related HCC were associated with higher surgical complication rates and hospital mortality. Dual HBV and HCV infection was also associated with earlier tumor recurrence. However, the survival times for the four groups we studied were not significantly different.

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