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Combined hepatocellular and cholangiocarcinoma: clinical features and prognostic study in a Thai population

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Abstract
Background/Purpose. Combined hepatocellular and cholangiocarcinoma (HCC-CC) is an uncommon subtype of primary liver cancer, the clinicopathological features of which have rarely been reported in detail. Some authors believe that HCC-CC behaves like HCC, but biliary differentiation may be associated with poorer prognosis. Moreover, CC has more frequent lymph node metastases. In this study, we aimed to determine the clinical course and survival outcome of HCC-CC patients in a Thai population by comparing them with patients with ordinary HCC.
Methods. The clinicopathological features of patients who were diagnosed with HCC-CC at Ramathibodi Hospital during 2000–2004 were retrospectively studied by comparing them with the features of patients suffering from ordinary HCC. Twenty-five patients who were diagnosed with HCC-CC were included in this study, and subsequently 50 patients with HCC who had tissues taken during the same period were selected randomly from among 148 HCC patients. Statistical analysis was done by using SPSS version 10.0. The Kaplan-Meier method was used to assess the survival rate. Multiple logistic regression analysis was performed to assess correlations. A value of $P < 0.05$ was considered statistically significant.
Results. There were no significant differences in etiologic risk factors between HCC-CC and HCC patients: cirrhosis (50% vs 44%), chronic alcohol abuse (36% vs 43%), presence of hepatitis B surface antigen (HBsAg; 66% vs 78%) and presence of hepatitis C virus (HCV) antibody (13% vs 3%). The serum alpha-fetoprotein (AFP) value in the HCC-CC group was lower than that in the HCC group (5.87 vs 41.46 ng/ml). No differences in tumor characteristics or liver status (tumor size, presence of multinodular lesions, portal vein thrombosis, intrahepatic bile duct dilatation, intraabdominal lymphadenopathy, extrahepatic metastasis, liver cirrhosis, portal hypertension, and ascites) between these two groups were found. The overall median survival of HCC-CC patients was 38 weeks while that of HCC patients was 54 weeks. Multivariate analysis showed that elevated carbohydrate antigen (CA)19-9 (≥80 U/ml) and the presence of intrahepatic bile duct dilatation were independent risk factors for worse survival.
Conclusions. The demographic and clinical features of patients with combined HCC-CC were similar to those of patients with HCC. The presence of cholangiocellular differentiation appeared to worsen the prognosis when compared with pure HCC, although this difference did not reach statistical significance. An increased CA19-9 level and intrahepatic bile duct dilatation in patients with HCC-CC were considered to be independent factors that suggested poor prognosis.

Key words Cirrhosis · Liver tumor · Hepatectomy

Introduction

Primary liver cancer is a major health problem worldwide. It is classified into two major types: hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). Combined hepatocellular and cholangiocarcinoma (HCC-CC) is a rare tumor in which dual differentiation toward hepatocytes and bile duct epithelia coexists in the same tumor or in the same liver. According to the World Health Organization classification, such tumors are designated as "combined hepatocellular and cholangiocarcinoma (HCC-CC)". The clinicopathological characteristics of HCC-CC are still obscure because it is relatively infrequent.[1] In addition, comparing the outcome of patients with a combined tumor with that of patients with HCC or CC yielded conflicting results in a few studies. Many reports have suggested that the clinical features of HCC-CC resemble those of HCC rather than those of CC,[2–5] and some investigators have shown distinct differences in the clinicopathological features of HCC and CC.[5] Jarnagin et al.[6] demonstrated that the clinical features of combined HCC-CC were most similar to those of CC. Many studies showed that the prog-

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nosis of HCC-CC was worse than that of pure HCC.[1–7] Prognostic risk factors that suggested poor prognosis were considered in just a few studies.[1,5]

In Thailand, the incidence of HCC and HCC-CC has been studied from nationwide surveys of liver cancer since 1978;[8] however, the details of clinical course, survival, and prognostic factors of HCC-CC have not been reported. Thus, the aim of this study was to clarity the characteristics, survival, and prognostic factors in HCC-CC patients and to compare their survival with that of HCC patients.

Patients and methods

All clinical histories of patients at Ramathibodi hospital who were diagnosed with combined HCC-CC, confirmed by tissue findings, between 2000 through 2004 were reviewed. The pathological specimens were obtained from needle biopsy or hepatectomy. The data records of HCC patients who had tissues taken during the same period were selected randomly and reviewed for comparison. All patients included in the trial had had at least one imaging procedure such as ultrasonography and/or computed tomography. Patients with serious cardiac, pulmonary, or renal insufficiency, and those with preexisting tumors, were excluded.

The reviewed parameters included: age; sex; alcohol ingestion; clinical presentation; viral hepatitis B and C status; biochemical data (serum aspartate aminotransferase [AST], serum alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGT], bilirubin, albumin, prothrombin time [PT], serum alpha-fetoprotein [AFP], carbohydrate antigen [CA] 19-9, and carcinoembryogenic antigen [CEA]); tumor subtype (uninodular, multinodular); size of tumor; the presence of ascites; portal vein thrombosis; intrahepatic bile duct dilatation; lymphadenopathy; and extrahepatic metastasis at initial presentation.

The degree of hepatic disease, Child–Pugh status, and Cancer of the Liver Italian Program (CLIP) score were defined in each patient. Patient treatment data were classified into three groups: surgery, palliative procedures, and no definitive treatment. The surgery group included patients who received a curative-attempt operation (hepatic resection and liver transplantation). The palliative treatment group incorporated the patients who underwent transcatheter arterial chemoembolization (TACE), percutaneous alcohol injection (PEI), or radiofrequency ablation (RFA).

Data values are reported as means ± SD. Student's *t*-test and χ^2 test were used for statistical analysis. Univariate analysis to identify predictors of survival was performed using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Results of the univariate analysis were considered significant if the probability of occurrence by chance was 5% or less ($P < 0.05$). For continuous variables, the cutoff was set at the median value. Multivariate analysis was performed using Cox regression analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 11.5.0; SPSS, Chicago, IL, USA).

Results

Patient characteristics, tumor characteristics, staging, and treatment (Table 1)

Twenty-five patients with a diagnosis of HCC-CC were included in this study, and subsequently 50 patients with HCC who had tissues taken during the same period were selected randomly from among 148 patients. There was no significant difference in age between the groups. The median ages in the HCC-CC group and HCC group were 53.4 years (range, 28 to 77 years) and 53.3 years (range, 30 to 75 years), respectively. The male-to-female ratio was not different in the two groups. Eighteen HCC-CC patients (72%) were male and 37 patients (74%) in the HCC group were male. There were no significant differences etiologic risk factors among the patients with combined HCC-CC and the HCC patients: cirrhosis (50% vs 44%), chronic alcohol abuse (36% vs 43%), presence of hepatitis B surface antigen (HBsAg; 66% vs 78%), and presence of hepatitis C virus (HCV) antibody (13% vs 3%). The first presenting symptom in the HCC-CC patients was abdominal pain, which was found more frequently than in the HCC group (80% vs 56%; $P = 0.025$). Differences in laboratory data between the HCC-CC and HCC patients were found in the serum AST and AFP values. The median AFP value in the HCC-CC group was lower than that in the HCC group (5.87 vs 41.46 ng/ml; $P = 0.012$). There were no differences in tumor characteristics or liver status (tumor size, presence of multinodular lesions, portal vein thrombosis, intrahepatic bile duct dilatation, intraabdominal lymphadenopathy, extrahepatic metastasis, liver cirrhosis, portal hypertension, and ascites).

There were no significant differences in either the percentages of HCC-CC and HCC patients classified as Child-Pugh A and B or the percentages classified according to the CLIP score. There were also no significant differences between the HCC-CC and HCC patients in regard to treatment groups ($P = 0.683$). In the study, 10 patients (40%) in the HCC-CC group and 18 patients (36%) in the HCC group had been treated with supportive care without any definite procedure. Nine HCC-CC patients (36%) and 23 HCC patients

Table 1. Characteristics of the HCC-CC and HCC patients

	HCC-CC ($n = 25$)	HCC ($n = 50$)	P value
Sex			
Male	18 (72.0)	37 (74.0)	0.854
Female	7 (28.0)	13 (26.0)	
Age (years)			
Mean ± SD	53.4 ± 12.1	53.3 ± 10.4	0.970
Range	(28–77)	(30–75)	
Chronic alcohol abuse			
Positive	9 (36.0)	19 (43.2)**	0.559
Hepatitis profile			
HBsAg-positive	12 (66.7)**	32 (78.0)**	0.517
Anti-HCV-positive	2 (13.3)**	1 (3.1)**	0.235
Clinical presentation			
Abdominal pain	14 (56.0)	39 (79.6)**	0.033*
Laboratory tests			
AST (IU/l)	52 (18–336)	68 (22–661)	0.046*
ALT (IU/l)	55 (16–151)	74 (18–353)	0.143
ALP (IU/ml)	106 (21–661)	152 (44–730)	0.076
GGT (mg/dl)	135 (11–1028)	205 (22–1232)	0.235
Total bilirubin (mg/dl)	0.8 (0.3–4.7)	0.9 (0.3–28.5)	0.331
Direct bilirubin (mg/dl)	0.3 (0.1–1.7)	0.3 (0.1–13.5)	0.223
Total protein (g/dl)	77.5 ± 6.8	76.8 ± 13.8	0.838
Albumin (g/dl)	39.6 ± 5.7	38.5 ± 6.4	0.459
Coagulogram			
PT (s)	14.3 ± 2.2	14.0 ± 3.2	0.681
INR	1.19 ± 0.17	1.19 ± 0.16	0.992
Tumor markers			
AFP (ng/ml)	5.87 (0.60–10 950.00)	41.46 (1.40–18 325.00)	0.012*
CA 19-9 (U/ml)	76.47 (1.00–16 116.10)	22.09 (0–737.0)	0.049*
CEA (ng/ml)	1.97 (0.20–170.60)	2.51 (0.41–32.53)	0.851
Tumor characteristics			
Tumor nodule (s)			
Uninodular	13 (56.5)	24 (50.0)	0.607
Multinodular	10 (43.5)	24 (50.0)	
Tumor size (cm)	6.38 ± 4.84	7.64 ± 3.88	0.248
Portal vein thrombosis	3 (13.6)**	16 (33.3)**	0.085
Intrahepatic bile duct dilatation	1 (4.5)**	4 (8.3)**	0.999
Lymphadenopathy	5 (22.7)**	10 (20.8)**	0.999
Distant metastasis	4 (17.4)**	4 (8.3)**	0.423
Underlying liver decompensation			
Cirrhosis	11 (50.0)**	20 (44.4)**	0.432
Portal HT (GEV)	3 (13.6)**	8 (16.7)**	0.999
Splenomegaly	5 (22.7)**	12 (25.0)**	0.837
Ascites	1 (4.5)**	4 (8.3)**	0.999
Child-Pugh			
A	21 (91.3)	43 (86.0)	0.710
B	2 (8.7)	7 (14.0)	
CLIP score			
0	10 (45.5)	10 (20.8)**	0.256
1	6 (27.3)	17 (34.7)**	
2	3 (13.6)	10 (20.4)**	
3	1 (4.5)	7 (14.3)**	
4	2 (9.1)	4 (10.2)**	
Treatment			
No treatment	10 (40.0)	18 (36.0)	0.683
Palliative treatment	9 (36.0)	23 (46.0)	
Surgery	6 (24.0)	9 (18.0)	

* $P < 0.05$; significant difference between groups
** Total number of patients is not 25 or 50 due to some missing data

(46%) had undergone palliative procedures, mainly transcatheter arterial chemoembolization (TACE; in 6 and 23 patients in the HCC-CC and HCC groups, respectively) while 1 patient in each group had undergone radiofrequency ablation (RFA), and 1 patient in each group had undergone both TACE and RFA. Only 6 patients (24%) in the HCC-CC group and 9 patients (18%) in the HCC group had undergone tumor resection. In the HCC-CC group, 3 patients underwent left hepatic lobectomy, 1 underwent right hepatic lobectomy, and 1 patient underwent liver transplantation, whereas in the HCC group, 4 patients underwent nonanatomical wedge resection, 2 patients underwent left hepatic lobectomy, and 3 patients underwent right hepatic lobectomy.

Survival analysis

The overall median survival of the HCC-CC patients was 38 weeks as compared with 54 weeks for the HCC patients; however, no significant difference was found ($P = 0.1122$; Fig. 1).

There was no significant difference in median survival between the HCC-CC patients and HCC patients who were in Child-Pugh classification A (46 vs 64 weeks). However, in Child-Pugh B, the median survival of the HCC-CC patients was worse than that of the HCC patients (4 vs 34 weeks; $P = 0.0315$). Comparison of HCC-CC and HCC patients stratified by CLIP score yielded no significant differences in median survival between the two groups (Table 2).

In subgroup survival analysis according to treatment modality, there was no significant difference in median survival time between the HCC-CC and HCC patients who had surgery (128 vs 223 weeks; $P = 0.6633$; Table 3 and Fig. 2). In patients who received a palliative procedure (mostly TACE), the median survival of the HCC-CC patients was worse than that of the HCC patients (31 vs 98 weeks).

Prognostic study of HCC-CC patients

Variables in the univariate analysis that correlated with worse survival were submitted to multivariate analysis.

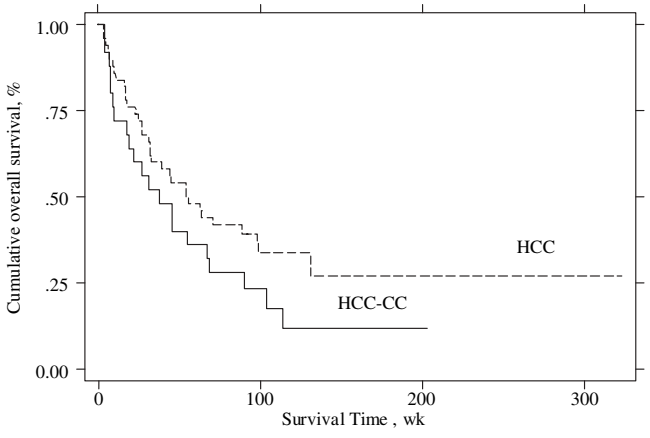

Fig. 1. Survival of combined hepatocellular and cholangiocarcinoma (*HCC-CC*) and HCC patients. *wk*, weeks

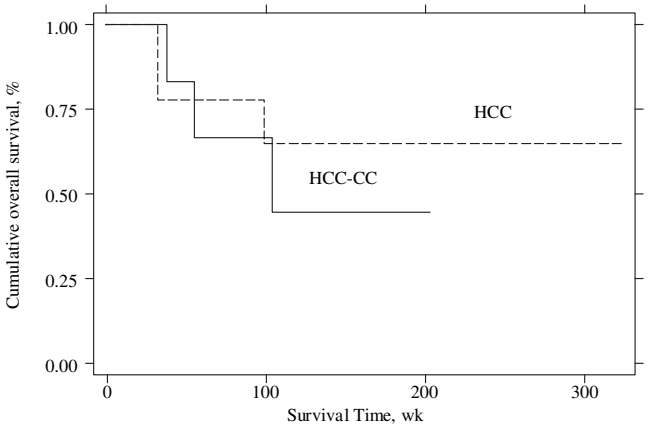

Fig. 2. Survival of HCC-CC and HCC patients undergoing surgery

Table 2. Staging comparison (Child-Pugh classification and CLIP scores)

	HCC-CC				HCC				
Staging	*n*	Median survival (weeks)	SE	95% CI	*n*	Median survival (weeks)	SE	95% CI	*P* value
Child A	21	46	12.87	20.58–71.42	42	64	24.81	15.38–112.62	0.1507
Child B	2	4	2.00	2.08–9.92	6	34	9.15	16.06–51.94	0.0315*
CLIP 0	10	55	18.18	19.36–90.64	10	99	12.59	74.32–123.68	0.2470
CLIP 1	6	38	29.39	23.14–126.53	17	64	34.94	102.22–239.20	0.3099
CLIP 2	3	46	12.25	22.00–70.00	10	45	17.39	10.91–79.09	0.9047
CLIP 3	1	4	—	—	7	25	9.17	7.04–42.96	0.1284
CLIP 4	2	8	0.50	7.52–9.48	4	6	2.50	1.10–10.90	0.6540

Table 3. Survival of HCC-CC and HCC patients according to treatment modality

	HCC-CC				HCC				
	n	Median survival (weeks)	SE	95% CI	*n*	Median survival (weeks)	SE	95% CI	*P* value
No treatment	10	10	7.91	0–25.50	18	17	2.12	12.84–21.16	0.6274
Palliative treatment	9	31	5.96	19.31–42.69	23	98	28.13	42.86–153.14	0.0025*
Surgery	6	128	28.86	70.31–187.36	9	223	46.21	132.92–314.06	0.6633

These variables were: age, sex, alcohol consumption, abdominal pain, serum levels of liver enzymes, albumin, bilirubin, prothrombin time, AFP, CEA, CA 19-9, serology of viral hepatitis B and C, tumor size, number of tumors, presence of liver cirrhosis, intrahepatic duct dilatation, portal hypertension, ascites, lymphadenopathy, portal vein thrombosis, extrahepatic metastasis, and treatment modality. Significant factors that predicted worse prognosis were the presence of abdominal pain, prothrombin time (INR ≥ 1.3), CA19-9 more than 80 U/ml, tumor size more than 5 cm, presence of intrahepatic bile duct dilatation, presence of ascites, presence of portal vein thrombosis, and no treatment or palliative therapy.

The multivariate analysis showed that elevated CA19-9 (≥80 U/ml) and the presence of intrahepatic bile duct dilatation were independent risk factors for worse survival, with Hazard ratios of 7.757 and 7.004, respectively. The presence of abdominal pain, tumor size, presence of ascites, portal vein thrombosis, coagulopathy (INR more than 1.3), and modality of treatment were not significant factors affecting survival.

Discussion

Primary liver cancer is a major health problem worldwide. It is classified into two major types: hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). Hepatocellular carcinoma (HCC) is common in areas where hepatitis B (HBV) or hepatitis C (HCV) viral infections are endemic.[4] The highest incidence of HCC is encountered in the countries of southeast Asia, including Taiwan, Korea, Thailand, Hong Kong, Singapore, Malaysia, and southern China, and those of tropical Africa.[4] Combined HCC and CC (HCC-CC) is a rare tumor in which dual differentiation toward hepatocytes and bile duct epithelia coexists in the same tumor or in the same liver. In 1949, Allen and Lisa[9] designated such carcinomas as "combined liver and bile duct carcinoma" and categorized them into three types: (i) carcinoma originating from different liver sites, but consisting of a uniform cell type (double carcinoma); (ii) contiguous HCC and CC, which originates from different cells and intermingles as they grow (combined type); and (iii) completely integrated HCC and CC, where both neoplastic masses are explained as originating from the same site (mixed type). Since the initial description of combined HCC-CC in 1949, several studies have examined the clinical and pathologic features of the entity. In previous studies of the biological behavior and clinicopathological features of HCC-CC, it was shown that HCC-CC was not simply a combination of ordinary HCC plus ordinary CC.[10–12] However, because the combined tumor is encountered infrequently, useful clinical data about it have been limited. In particular, information about the clinical outcome of HCC-CC is very rare.[9,10,13,14]

The incidence of HCC-CC as reported by several studies is considerably diverse; this type of tumor has been reported to account for 1.0% to 14.2% of primary liver cancers.[1,6,7] Goodman et al.[10] reported the incidence to be 2.4%, Allen and Lisa[9] reported the value as 1.4%, and the study by Liu et al.[3] reported an incidence of 2.0%. The Liver Cancer Study Group of Japan[14] reported that the HCC-CC group accounted for 1.2% of surgical cases and 1.6% of autopsy cases. Koh et al.[5] reported that the proportion of the HCC-CC group was 6.5%. In Thailand, Bunyaratvej et al.,[8] at Ramathibodi hospital, reported the incidence to be 3%.

From the study by Jarnagin et al.,[6] the prevalence of positive serology for hepatitis B or hepatitis C and the presence of underlying cirrhotic liver in the HCC-CC group was very low, resembling that in the CC group. In contrast, in Hong Kong, the prevalence of positive serology for hepatitis and the presence of cirrhotic liver in the HCC-CC group were lower than the values in the HCC group and higher than those in the CC group.[3] A report from Korea showed that the prevalence of cirrhotic change and positive serology for hepatitis B in the HCC-CC group were lower than in the HCC group.[5] In Japan, Taguchi et al.[1] stated that about 40% of HCC-CC patients presented with cirrhosis and positive hepatitis serology. Yano et al.[2] showed great similarity in the status of hepatitis B and C viral infection and the presence of an underlying cirrhotic liver in patients with HCC-CC and those with HCC. In our study, in the HCC-CC group, the prevalence of cirrhotic change was

50% and the prevalence of positive serology for hepatitis B and C were about 67% and 13%, findings which were similar to those in the HCC group. These studies show that the prevalence of associated chronic liver disease or cirrhotic change is quite different in Eastern and Western HCC-CC populations.

In our study, the AFP level in the patients with HCC-CC was lower than that in the patients with HCC, in contrast with other reports showing no significant difference in AFP levels between HCC-CC and HCC groups. Yano et al.[2] and Jarnagin et al.[6] reported that the CEA levels were not different in patients with HCC-CC and those with HCC, a finding which is similar to our study. In addition, our study showed that the level of serum CA 19-9 was significantly higher in the patients with HCC-CC than in the HCC group. There has been no previous report comparing CA 19-9 levels between these two groups.

In comparisons of the tumor characteristics between the patients with HCC-CC and those with HCC, our study showed no differences in tumor size, number of tumors, presence of major vascular invasion (portal vein and hepatic vein), or presence of lymph node metastasis, similar to the data in the reports of Liu et al.[3] and Jarnagin et al.[6] In contrast, the data of Koh et al.[5] and Yano et al.[2] showed that the patients with HCC-CC had higher frequencies of the presence of multifocal tumors, vascular invasion, and lymph node metastasis than the HCC group.

Many reports have shown that the survival of patients with HCC-CC was poorer than that in HCC patients.[1–7] Similar to other reports, our study demonstrated the patients with HCC-CC tended to have a worse survival outcome compared with those with HCC, although this difference did not reach statistical significance. In subgroup analysis for staging by the Child-Pugh and CLIP scoring systems, the patients with HCC-CC seemed to have a worse prognosis than the pure HCC patients. However, only in the palliative treatment group did HCC-CC patients have a significantly worse survival than HCC patients.

In our study, increased CA19-9 level and intrahepatic bile duct dilatation in the patients with HCC-CC were considered to be independent prognostic factors that suggested a poor prognosis ("intrahepatic bile duct dilatation" included both localized and diffuse intrahepatic bile duct dilatation). Koh et al.[5] reported that increased tumor multiplicity in the HCC-CC group was considered a factor that suggested poor prognosis. Taguchi et al.[1] reported that vascular invasion, the presence of satellite lesions, and large tumor size were factors for a poor prognosis in inoperable patients. In our univariate study, in the patients with HCC-CC, the presence of abdominal pain, coagulopathy (PT; INR ≥1.3), tumor size 5 cm or larger, the presence of ascites, and the presence of vascular invasion were likely to be prognostic factors for worse survival, but they were not found to be significant factors in the multivariate analysis.

In conclusion, the demographic and clinical features of patients with HCC-CC were similar to those of patients with HCC. The presence of cholangiocellular differentiation appeared to worsen the prognosis when compared with pure HCC, although this difference did not reach statistical significance. Increased CA19-9 level and intrahepatic bile duct dilatation in the patients with HCC-CC were considered to be independent factors that suggested a poor prognosis.

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