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Living Donor Liver Transplantation for Combined Hepatocellular Carcinoma and Cholangiocarcinoma: Experience of a Single Center

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Background: Because the outcome of liver transplantation for cholangiocarcinoma is often poor, cholangiocarcinoma is a contraindication for liver transplantation in most centers. Combined hepatocellular carcinoma and cholangiocarcinoma is a rare type of primary hepatic malignancy containing features of hepatocellular carcinoma and cholangiocarcinoma. Diagnosing combined hepatocellular carcinoma and cholangiocarcinoma pre-operatively is difficult. Because of sparse research presentations worldwide, we report our experience with living donor liver transplantation for combined hepatocellular carcinoma and cholangiocarcinoma.

Material/Methods: A total of 710 patients underwent living donor liver transplantation at our institution from April 2006 to June 2014; 377 of them received transplantation because of hepatocellular carcinoma with University of California San Francisco (UCSF) staging criteria fulfilled pre-operatively. Eleven patients (2.92%) were diagnosed with combined hepatocellular carcinoma and cholangiocarcinoma confirmed pathologically from explant livers; we reviewed these cases retrospectively. Long-term survival was compared between patients diagnosed with combined hepatocellular carcinoma and cholangiocarcinoma and patients diagnosed with hepatocellular carcinoma.

Results: The mean age of the patients in our series was 60.2 years, and the median follow-up period was 23.9 months. Four patients were diagnosed with a recurrence during the follow-up period, including one intra-hepatic and three extra-hepatic recurrences. Four patients died due to tumor recurrence. Except for patients with advanced-stage cancer, disease-free survival of patients with combined hepatocellular carcinoma and cholangiocarcinoma compared with that of patients with hepatocellular carcinoma was 80% versus 97.2% in 1 year, and 46.7% versus 92.5% in 3 years ($p<0.001$), and overall survival was 90% versus 97.2% in 1 year, and 61.7% versus 95.1% in 3 years ($p<0.001$).

Conclusions: Outcomes of liver transplantation for patients with combined hepatocellular carcinoma and cholangiocarcinoma were worse than those for patients with hepatocellular carcinoma in this study. Combined hepatocellular carcinoma and cholangiocarcinoma are presumed to be a relative contraindication for liver transplantation.

MeSH Keywords: Carcinoma, Hepatocellular • Cholangiocarcinoma • Liver Transplantation

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Background

Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) is a rare type of primary liver malignancy that is comprised of hepatocellular carcinoma (HCC) and cholangiocarcinoma in one liver at the same time [1]. cHCC–CC was first described by Wells in 1903, and classified into three categories by Allen and Lisa in 1949 [2]. It was further classified by Goodman et al. in 1985 [3].

Cholangiocarcinoma was generally thought to be one of the contraindications for liver transplantation due to poor outcomes. However, that liver transplantation with neoadjuvant chemoradiation achieved better survival rates with less recurrence than did conventional resection in patients with localized, node-negative hilar cholangiocarcinoma had been proved at the Mayo Clinic in Rochester [4]. Surgical resection remains the mainstay of definitive treatment for patients with cHCC-CC, which comprises hepatectomy, occasionally combined with lymphadenectomy, and resection of the extrahepatic bile duct and/or the portal vein in order to achieve an R0 resection [5]. The outcome of tumor resection for cHCC-CC has been reported to be worse than resection for HCC, and was more similar to surgical resection for cholangiocarcinoma [6]. On the other hand, one Spanish matched multicenter cohort, which included 24 cHCC-CC patients, reported comparable outcomes of liver transplant for cHCC-CC and HCC [7]. Groeschl et al. analyzed the Surveillance, Epidemiology, and End Results (SEER) Database (1973-2007) and evaluated 3432 patients (3378 with HCC and 54 with cHCC-CC) who underwent liver resection or liver transplantation for hepatic tumors [8]. The study could not define a difference in 3-year survival rates between cHCC-CC patients who underwent liver transplantation and those who underwent resection. Because of sparse research presentations worldwide, we report our experience with living donor liver transplantation (LDLT) for cHCC-CC.

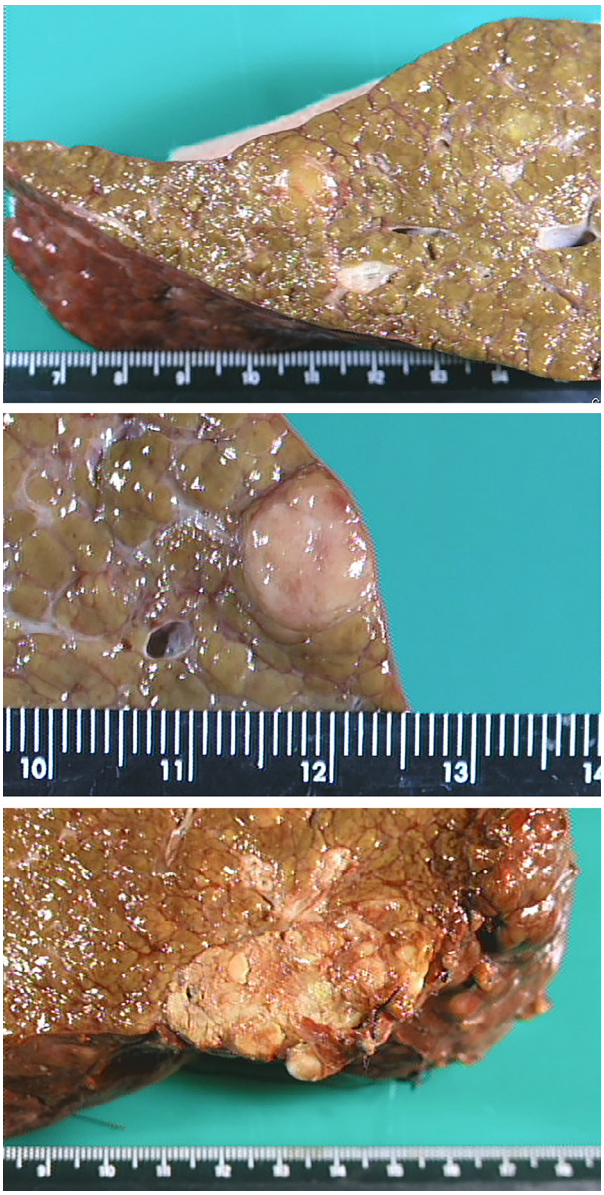

Figure 1. Grossly undistinguished pathological features of cHCC-CC.

Material and Methods

A total 710 patients received LDLT in Kaohsiung Chang Gung Memorial Hospital (KCGMH) between April 2006 and June 2014. Three hundred seventy-seven patients received transplantation because of HCC, with University of California San Francisco (UCSF) staging criteria fulfilled pre-operatively. Eleven patients (2.92%) were diagnosed with cHCC-CC confirmed pathologically from explant livers. The demographic data, pathological results, and surgical outcomes of these 11 patients were reviewed retrospectively.

Pre-operative imaging studies included liver echography, dynamic liver computed tomography (CT) including CT angiography, and magnetic resonance cholangiopancreatography. Brain magnetic resonance imaging, chest CT, bone scintigraphy, and positron emission tomography were regularly performed for inpatients with HCCs to exclude extra-hepatic malignancy. Blood tumor markers included serum α-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9). Living donors were between 18 and 55 years of age, up to fifth-degree relatives according to the laws in Taiwan. The explant livers were reviewed grossly (Figure 1) and microscopically (Figure 2) to define the exact histological types of tumors. If the histological pattern demonstrated an intermediate presentation between HCC and cholangiocarcinoma, immunohistochemical staining was performed.

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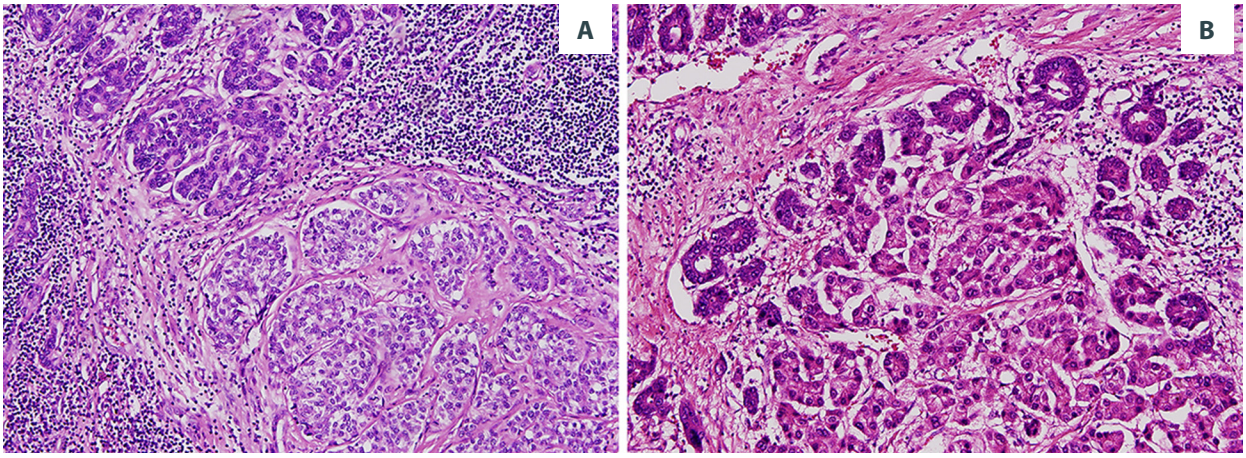

Figure 2. Microscopic pathological features of cHCC-CC (**A, B**).

Post-operative immunosuppressants included prednisolone and tacrolimus as baseline therapy, which was combined with sirolimus in patients with proved or suspected HCC before transplantation [9]. The proportion of sirolimus increased progressively to replace tacrolimus if patients were diagnosed with cHCC-CC from explant livers or had confirmed intra- or extragraft recurrences of HCC, cHCC-CC, or other variants of HCC. Liver sonography was performed every 3 months.

The comparison group included the patients receiving LDLT for pure HCCs confirmed by pathological examination of the explants. After excluding patients with advanced cancer (T3, T4, and N1) and those lost to follow-up, 290 patients receiving LDLT for pure HCCs were available for survival analysis.

Results

Seven male and four female patients were diagnosed with cHCC-CC. The mean age at transplant was 60.2 (±5.5) years old, and all patients had predisposing hepatitis B and/or were hepatitis C virus-positive. The most common (45%) comorbidity was type II diabetes mellitus. Preoperative MELD score was 10.3 (±3.5). In two patients, one who received a pre-transplantation tumor biopsy and the other who underwent a pre-transplantation hepatectomy, HCC was diagnosed histologically. A preoperative survey defined a solitary tumor in six patients and multiple tumors in five patients with a median tumor size of 2.7 (±0.9) cm. AFP and CA19-9 levels were 29.2 (±33.3) ng/mL and 25.9 (±14.5) U/mL, in respectively. Five patients received pre-transplant treatment for HCCs, including one hepatectomy, three trans-arterial embolizations, three radiofrequency ablations, and one percutaneous ethanol injection (Table 1).

The histological tumor characteristics are provided in Table 2. Only three patients retained the diagnosis of solitary tumor. One patient was diagnosed as stage T4 due to invasion of the periductal soft tissue, and four patients had microvascular tumor invasion. With regard to tumor differentiation, two tumors were well differentiated and nine tumors were moderately differentiated. No poorly differentiated tumors were identified in this series. A resection margin free of tumor was achieved in all patients. No lymph node metastases were found. Five

Table 1. Demographics of patients with cHCC-CC (n=11).

Age (years)	60.2±5.5
Gender	
Male	7 (63.6%)
Female	4 (36.4%)
Predisposing viral hepatitis	
HBV only	7 (63.6%)
HCV only	2 (18.2%)
HBV+HCV	2 (18.2%)
Diabetes mellitus	5 (45.5%)
Pre-operative mean MELD score	10.3±3.5
Pre-operative tumor biopsy	1 (9.1%; result: HCC)
Pre-operative tumor number	1.6±0.7
Single tumor	6 (54.6%)
Multiple tumor	5 (45.4%)
Tumor size (cm)	2.7±0.9
AFP (ng/mL)	29.2±33.3
CA19-9 (U/mL)	25.9±14.5
Pre-operative treatment	5 (45.5%)
Hepatectomy	1 (9.1%)
TAE	3 (27.3%)
RFA	3 (27.3%)
PEI	1 (9.1%)

cHCC-CC – combined hepatocellular carcinoma and cholangiocarcinoma; TAE – transarterial embolization; RFA – radiofrequency ablation; PEI – percutaneous ethanol injection.

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Table 2. Histological characteristics of explants.

Mean tumor number	2.5±1.6
Single tumor	3 (27.3%)
Multiple tumors	8 (72.7%)
Mean tumor size (cm)	2.5±1.0
TNM staging	
Stage I	3 (27.3%)
Stage II	7 (63.6%)
Stage III	0 (0%)
Stage IV	1 (9.1%)
Microvascular invasion	4 (36.4%)
Tumor differentiation	
Well diffe rentiated (G1)	2 (18.2%)
Moderately differentiated (G2)	9 (81.8%)
Poorly differentiated (G3)	0 (0%)
Free resection margin	11 (100%)
Goodman classification	
Type I	5 (45.4%)
Type II	6 (54.6%)
Beyond UCSF criteria	3 (27.3%)

UCSF – University of California San Francisco.

tumors presented as Goodman type I and six as Goodman type II. Histopathologic features of cHCC-CC were intermediate between those of HCC and cholangiocarcinoma throughout, or showed a gradual transition from tubular cholangiocarcinoma areas toward HCC elements exhibiting trabecular patterns. Immunohistochemical staining of tubular parts of cHCC-CC presented moderate-to-strong expression of CK7, CK20, and/or CK-LMW, which were absent in HCC. Post-operatively, three patients were no longer within UCSF criteria.

The median follow-up time was 23.9 (10.1–68.0) months. Two patients experienced acute rejection during follow-up (18.2%). Four tumor recurrences were diagnosed during follow-up (36.4%), including one intra-hepatic recurrence and three extra-hepatic recurrences. Locations of extra-hepatic recurrence included the lung, peritoneum, and para-aortic lymph nodes. The interval to recurrence was 12.7 (4.3–31.5) months. The 1-year and 3-year disease-free survival rates were 80.8% and 47.1% (p<0.001), respectively. All four patients with recurrence had died by the end of the study. The 1-year and 3-year overall survival rates were 90.9% and 62.3% (p<0.001), respectively. After excluding the one patient with diagnosed stage IV cancer from the cHCC-CC group (n=10), we compared tumor characteristics with those of the HCC group (n=290), who were diagnosed with stage I and II cancer (Table 3). There was no

Table 3. Tumor-related characteristics of cHCC-CC and HCC.

	cHCC-CC (n=10)	HCC (n=290)	p value
Age (years)	60.1±5.8	55.3±7.4	0.447
Gender			
Male	7 (70%)	236 (81.4%)	0.408
Female	3 (30%)	54 (18.6%)	
T1	3 (30%)	94 (32.4%)	1.000
T2	7 (70%)	196 (67.6%)	
HBV+	8 (80%)	177 (61.0%)	0.327
HBV–	2 (20%)	113 (39.0%)	
HCV+	4 (40%)	107 (36.9)	1.000
HCV–	6 (60%)	183 (63.1)	
Child A	3 (30%)	135 (46.6%)	
Child B	5 (50%)	104 (35.9%)	0.566
Child C	2 (20%)	51 (176%)	
MELD score >15	1 (10%)	46 (15.9%)	1.000
MELD score <15	9 (90%)	244 (84.1%)	
1-year disease-free survival rate	80.0%	97.2%	
3-year disease-free survival rate	46.7%	92.5%	<0.001
5-year disease-free survival rate	46.7%	91.8%	
1-year overall survival rate	90.0%	97.2%	
3-year overall survival rate	61.7%	95.1%	<0.001
5-year overall survival rate	41.1%	89.8%	

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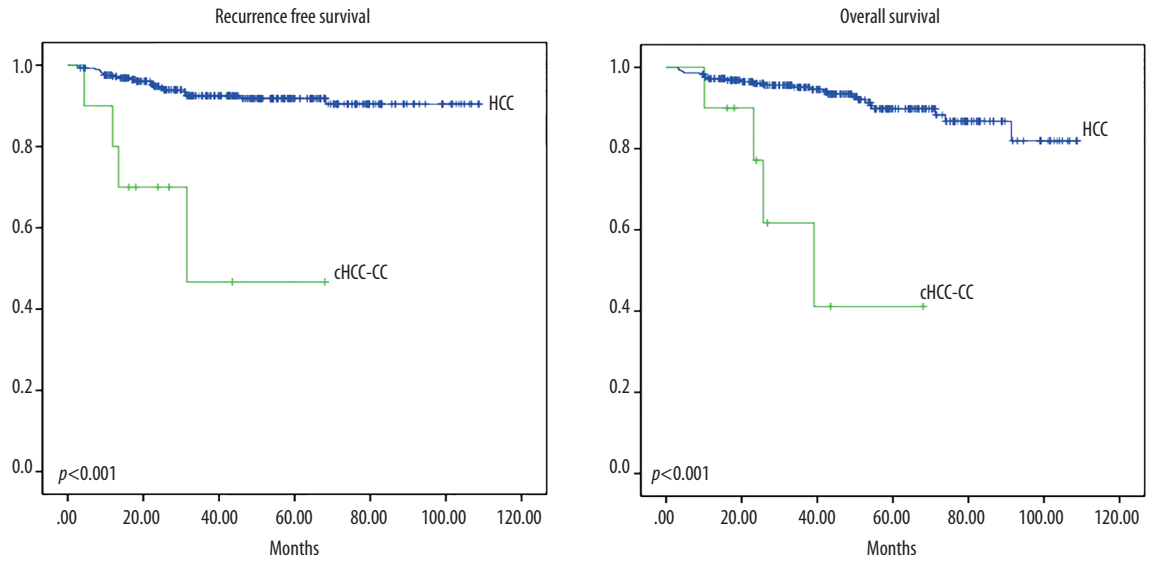

Figure 3. Comparison of survival after living donor liver transplantation between patients diagnosed with cHCC-CC and patients diagnosed with pure HCC. Survival analysis demonstrated that patients diagnosed with HCC only have better post-transplantation disease-free survival and overall survival than those diagnosed with cHCC-CC.

significant difference between the cHCC-CC and HCC groups when comparing characteristics of tumors. Recurrence-free survival of patients with cHCC-CCs and HCC was 80% versus 97.2% at 1 year and 46.7% versus 92.5% at 3 years (p<0.001), and the overall survival was 90% versus 97.2% at 1 year, and 61.7% versus 95.1% at 3 years (p<0.001) (Figure 3).

Discussion

The incidence of cHCC-CC was reported to be 0.4% to 14.2% [10]. Because of the complex imaging features of the two entities and the rarity of this tumor, pre-operative diagnosis could be made in only a minority of cases [11]. The representative imaging features were comprised of not only typical characteristics of HCC, such as arterial enhancement and venous washout, but also included the irregular tumor surface, peripheral arterial enhancement, and late central enhancement found in cholangiocarcinoma. Inconsistency between tumor markers, such as AFP, CEA, CA19-9, and vitamin K absence or antagonists-II (PIVKA-II), might point to a hint for possible diagnosis of cHCC-CC [12]. One patient in our series with cHCC-CC received a pre-operative tumor biopsy, but the diagnosis was not correctly made. In addition, distinguishing cHCC-CC from other tumors with gross appearance is also difficult during surgery. Histological examination of the explant or specimen after hepatectomy seems to be the only way to confirm the diagnosis.

Song and colleagues reported a series comparing survival rates between patients with resection and transplantation for cHCC-CCs, which demonstrated no difference between these two groups [13]. The study compared surgical outcomes of 68 patients who were diagnosed with cHCC-CC after hepatic resection and 8 patients diagnosed after liver transplantation. There was no statistical difference in disease-free survival and overall survival between hepatectomy and liver transplantation patients (5-year disease-free survival: 26.2% *vs.* 37.5%, p=0.333; 5-year overall survival: 42.1% *vs.* 50%, p=0.591). Anthony et al. presented similar survival outcomes in a series with 11 patients who received hepatic resection for cHCC-CC in our institution (4-year disease-free survival: 45.45%; overall 1- and 3-year survival rates were 80% and 69.3%) [14]. Building on the experience of published study series, it attested to a consensus that it is more appropriate to adopt hepatic resection as the treatment for patients who are diagnosed with cHCC-CC with small tumor size and with preserved liver function.

However, controversy still exists about whether liver transplantation is a therapeutic choice for cHCC-CCs. Sapisochin et al. reported that no difference in survival rates for cHCC-CC could be observed between cHCC-CC and their control group (1- and 3-year overall survival rates for cHCC-CC of 93% and 78% *vs.* control group rates of 97% and 86%; p=0.9), which suggested that patients with cHCC-CC should not be excluded from liver transplantation, even if they were diagnosed pre-operatively [7]. Lee et al. published a series comparing the clinicopathological features and long-term prognosis of patients with cHCC-CC after surgery with those of the patients with stage-matched HCC and CC [16]. Patients with cHCC-CC shared factors that indicated poorer surgical outcomes than those of

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patients with HCC or CC: frequent microscopic vessel invasion (MVI), high level of serum AFP from HCC, increased bile duct invasion, and decreased capsule from CC. MVI and high level of serum AFP had been defined as negative prognostic factors for both overall survival and recurrence of HCC after liver transplantation in the series of Sotiropoulos et al. [17]. Meyer and colleagues failed to indicate any positive prognostic variables from the experience of treating 207 patients with liver transplantation, and their patients presented with frequent recurrence (84% in 2 years) and low 1-year and 5-year survival rates (72% and 23%, respectively) [18]. These results offer a rational explanation for worse survival after liver transplantation of patients diagnosed with cHCC-CC compared with patients diagnosed purely with HCC pathologically in our series. Regrettably, we did not analyze possible influences from pathological factors, donor source, variation of peritransplantation treatments, or related surgical complications in this study. Further studies are required for elucidating possible prognostic factors after liver transplantation in patients diagnosed with cHCC-CC.

Conclusions

Outcomes of liver transplantation for patients with cHCC-CC were worse than those with HCC in this study. Combined HCC-CC is presumed to be a relative contraindication for liver transplantation. However, liver transplantation may be an optional, alternative treatment for patients who are diagnosed with cHCC-CC with an early tumor stage but who are poor candidates for hepatic resection because of poor liver function.

Abbreviations

cHCC-CC – combined hepatocellular carcinoma and cholangiocarcinoma; **HCC** – hepatocellular carcinoma; **LDLT** – living donor liver transplantation; **CT** – computed tomography; **AFP** – a-fetoprotein; **CEA** – carcinoembryonic antigen; **CA19-9** – Carbohydrate antigen 19-9; **CK** – cytokeratin; **CK-LMW** – cytokeratin-low molecular weight.

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