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ORIGINAL ARTICLE

Long-term outcome of patients undergoing liver transplantation for mixed hepatocellular carcinoma and cholangiocarcinoma: an analysis of the UNOS database

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Abstract

Background: Mixed hepatocellular and cholangiocarcinoma (HCC-CC) have been associated with a poor prognosis after liver transplantation (LT). We aimed to evaluate long-term outcomes in patients undergoing LT for HCC-CC versus patients with hepatocellular carcinoma (HCC) or cholangiocarcinoma (CC).

Methods: Retrospective analysis of the United Network for Organ Sharing (UNOS) database from 1994–2013. Overall survival (OS) in patients with HCC-CC, HCC, and CC, were compared.

Results: We identified 4049 patients transplanted for primary malignancy (94 HCC-CC; 3515 HCC; 440 CC). Mean age of patients with HCC-CC was 57 ± 10 years, and 77% were male. MELD score did not differ among the groups (p = 0.637). Hepatitis C virus was the most common secondary diagnosis within the HCC-CC (44%) and HCC (36%) cohorts, with primary sclerosing cholangitis in the CC (16%) cohort. OS rates at 1, 3 and 5 years for HCC-CC (82%, 47%, 40%) were similar to CC (79%, 58%, 47%), but significantly worse than HCC (86%, 72%, and 62% p = 0.002).

Discussion: Patients undergoing LT for HCC had significantly better survival compared to those transplanted for HCC-CC and CC. LT for mixed HCC-CC confers a survival rate similar to selected patients with CC. Efforts should be made to identify HCC-CC patients preoperatively.

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Introduction

Mixed hepatocellular and cholangiocarcinoma (HCC-CC) comprise a minority of primary liver malignancies with histological features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC).[1] The first histological classification of mixed HCC-CC was made by Allen *et al.* and included 3 types: type A for separate nodules of HCC and intrahepatic cholangiocarcinoma (ICC), type B for contiguous masses that may mingle with continued growth, and type C for those HCC and CC that are combined within the same tumor.[2] A second classification was formulated later on by Goodman *et al.*, including type I for HCC and ICC coincidental occurrence as separate nodules, type II for Transitional Tumors, and type III for the Fibromellar HCC variant.[3]

While mixed HCC-CCs have been reported to be more common in male patients and those with cirrhosis and/or chronic hepatitis,[4–6] their clinical behavior remains poorly understood. Although some authors have described that imaging showing contrast enhancement in the arterial and portal venous phases without washout could suggest the presence of HCC-CC,[7] others have reported that these tumors may share

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characteristics of both CC and HCC but with enhancement pattern and ancillary features similar to CC.[6] These tumors may be associated with higher carbohydrate antigen (CA) 19-9 and alpha-fetoprotein levels.[8] Therefore, distinguishing between HCC-CC, HCC, and CC continues to be a challenge without biopsy, and malignancies other than HCC are still encountered typically unexpectedly in explanted liver specimens. The mainstay of treatment for HCC-CC has been liver resection with most series reporting a 3-year survival rate of 25–50%.[1,9]

HCC is now a primary indication for liver transplantation (LT) in properly selected patients, where a 70% overall survival can be obtained. Recently, there has been increasing interest in determining the usefulness of liver transplantation (LT) for the treatment of select CC. The reported 5-year overall survival (OS) rate using LT to treat early-stage unresectable hilar CC ranges from 79% for patients with underlying primary sclerosing cholangitis (PSC) to 63% for those with *de novo* CC.[10] Unfortunately, only a small number of studies have been published to date regarding the use of LT for mixed HCC-CC. These studies have been limited by small sample sizes precluding meaningful conclusions. Chan *et al.* were the first known to report on LT for mixed HCC-CC on 3 patients, 2 of them alive with no evidence of disease 25 and 35 months after the procedure, respectively.[11] Panjala *et al.* reported the largest single-institution series including 12 patients undergoing LT for HCC-CC. Among this cohort, 1 patient died 48 days after the procedure from LT-related complications and the median overall survival of the remaining patients was 3.6 years.[12]

The prognosis of HCC-CC compared with HCC and CC has not been established, with most reports showing slightly worse prognosis with intermediate survival. The United Network for Organ Sharing (UNOS) has no formal statement regarding the use of LT for mixed HCC-CC, and to our knowledge only one previous publication has used this database to describe outcomes for patients with HCC-CC who underwent liver transplantation.[13] Hence, the aim of our study was to determine long-term outcomes of patients undergoing LT for mixed HCC-CC in the United States and to compare them to transplanted patients diagnosed with HCC and CC alone.

Methods

The UNOS database was queried for all patients undergoing transplantation in the United States from October 1, 1994 through October 31, 2013. Data from all patients undergoing LT for HCC-CC, HCC and CC were captured for analysis. Of 123,167 LT procedures, 94 were performed for HCC-CC. For patients identified as having HCC-CC, data collected included recipient age, gender, serum creatinine level, total bilirubin level, international normalized ratio, serum sodium level, coexisting liver disease, height and weight at the time of transplantation, length of hospital stay, type of donor (living vs. deceased), incidence of multiorgan transplantation, incidence of acute cellular rejection at 6 months, tumor recurrence, and overall patient and graft survival. Body mass index was calculated as weight in kilograms divided by height in meters squared. Donor characteristics, including age, cold ischemia time, warm ischemic time, and fatty infiltration, were also identified. Information from all patients with a diagnosis of HCC and CC was recorded to compare outcomes within the three groups. Recurrence was defined by observation of tumor recurrence by imaging (eg, computed tomography or ultrasonography) or by histologic confirmation. Recurrence data was only available for 16% of the study population, starting from October 1999, when records began. Rejection data was available in 71% of the HCC-CC cohort.

Statistical analysis

Data was expressed as mean and standard deviation or as median and range when a nonparametric distribution was identified. We compared categorical variables by the χ^2 test and continuous variables by Kruskal–Wallis. Survival was estimated by the Kaplan–Meier method, and the log-rank test was used to compare differences in OS. Multivariable analysis was performed to define predictors of outcome ($p \leq 0.05$ was considered significant). P values were not calculated in those variables when the majority of the data was unavailable. Statistical analysis was performed using SPSS software, version 21 (SPSS Inc, Chicago, Illinois).

Results

From October 1, 1994 through October 31, 2013, 123,167 LTs were recorded in the UNOS database. Among these, 4049 patients had a primary malignancy (94 HCC-CC; 3515 HCC; 440 CC). Out of the 94 patients diagnosed with HCC-CC, only 5 underwent LT before the MELD score was implemented in 2002. Fig. 1 illustrates the number of transplant for HCC-CC performed in the United States by year to October 2013.

The mean (SD) age of the patients undergoing transplantation for HCC-CC was 57 ± 10 years and 79 patients (74.7%) were male. Seventy-nine patients (74.5%) were white, 11 (10.6%) were black, 11 (10.6%) were hispanic and 3 (3.2%) were asian. The mean (SD) total bilirubin level was 2.96 (3.98) mg/dl, the mean (SD) international normalized ratio was 1.32 (0.31), the mean (SD) creatinine level was 0.97 (0.35) mg/dl, and the mean (SD) sodium level was 138 (4) mEq/L. The mean (SD) BMI was 28.1 (3.98) kg/m^2. The median days on waiting list were 61. None of the patients undergoing LT for HCC-CC had multi-organ transplantation. Six patients (6.3%) underwent living donor LT. Six (6.3%) of the tumors were reported as incidentally found. The mean (SD) post transplantation length of stay was 9.8 (4.7) days. Table 1 summarizes patient characteristics for those who underwent LT for HCC-CC, HCC, and CC.

The mean (SD) donor age was 40 ± 19 years and did not significantly differ between patients undergoing LT for HCC-CC

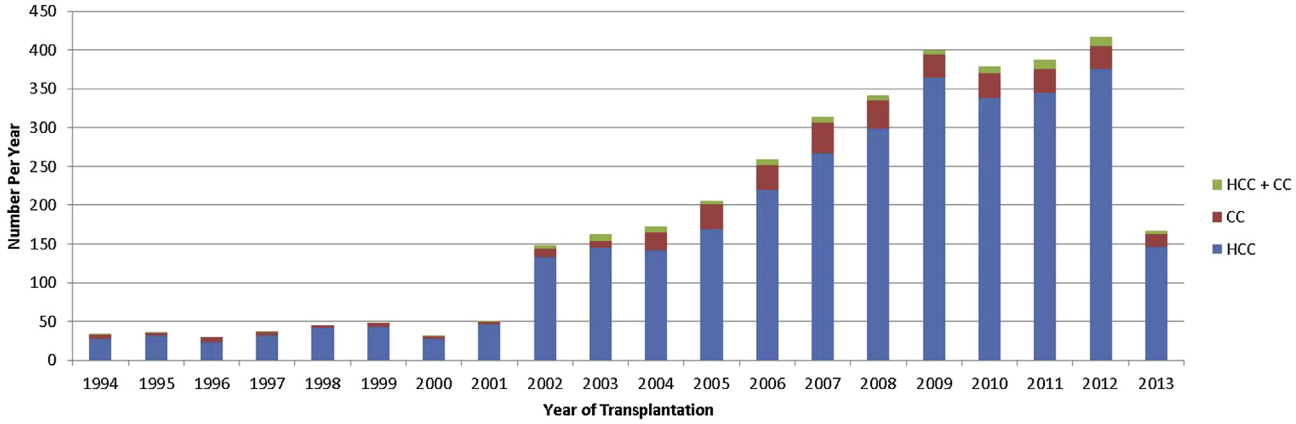

Figure 1 Patients transplanted for primary liver malignancy in UNOS database since 1994 to 2013. Out of 4049 patients, 94, 3515 and 440 have been transplanted for HCC-CC, HCC and CC, respectively. Liver primary malignancy as an indication of liver transplantation has increased since 2002, when the MELD score was implemented. Only 5 patients with HCC-CC where transplanted before 2002

and those undergoing LT for HCC and CC. The mean (SD) cold ischemic time was 7.2 ± 3.1 h, and the mean (SD) warm ischemic time was 10.2 ± 6.8 min Table 2 summarizes donors characteristics.

Two patients who underwent LT for HCC-CC have previous history of other malignancies: one with meningioma and one with prostate cancer. Hepatitis C virus was the most common secondary diagnosis within the HCC-CC (44%) and HCC (36%) cohorts, compared to primary sclerosing cholangitis (PSC) in the CC (16%) cohort. Alcoholic cirrhosis was the second most common secondary diagnosis within the three groups (HCC-CC 9%, HCC 9%, and CC 2%). Other secondary diagnoses are presented in Table 3.

The incidence of acute cellular rejection within 6 months after transplantation was 19%, 12.7%, and 22.4%, for those patients undergoing LT for HCC-CC, HCC, and CC, respectively.

Table 1 Characteristics of patients undergoing LT for HCC-CC, HCC, and CC

Variable	HCC-CC (n = 94)	HCC (n = 3515)	CC (n = 440)	p-value
Mean age at transplant (SD)	56.7 (10.0)	55.9 (10.9)	49.9 (11.9)	<0.001
Percentage of male	74.7	75.7	66.2	<0.001
Ethnicity/race				
White, %	74.5	67.2	88.7	<0.001
Black, %	10.6	9.3	4.8	
Hispanic, %	10.6	11.9	4.8	
Asian, %	3.2	10.5	0.9	
Other/unknown, %	1.1	1.1	0.8	
MELD score	12.9 (6.3)	14.3	15.1	0.637
Creatinine (mg/dl)	0.97 (0.35)	1.15	1.06	<0.001
Bilirubin (mg/dl)	2.96 (3.98)	3.86	7.26	<0.001
INR	1.32 (0.31)	1.52	1.36	<0.001
Initial sodium level (mEq/L)	137 (5)	137 (4)	137 (4)	0.447
BMI (kg/m^2)	28.1 (5.0)	27.8	25.0	<0.001
Living donors (%)	6.4	2.6	16.1	<0.001
LOS post transplantation (days)	9.8 (4.7)	15.7	17.8	<0.001
Incidental tumor	6.3%	3.9%	5.4%	0.174
Median waiting list time (days)	61	103	86	=0.002

Patient and graft survival

Overall, 1-, 3-, and 5-year OS rates were 82%, 47%, 40% respectively, in patients undergoing isolated LT for HCC-CC; with a median OS duration of 29 months (Fig. 2A). Overall survival at 1-, 3- and 5-year for HCC-CC was similar to CC (79%, 58%, 47%) but significantly worse compared to HCC (86%, 72%, and 62% p = 0.002) (Fig. 2B). Recurrence rate at 3 years for 27 patients with HCC-CC were information was available was 93%.

Graft survival at 1-, 3-, and 5-year, for HCC-CC (78%, 45%, 38%) was similar to CC (75%, 55%, 44%) but significantly worse than HCC (82%, 68%, 54%, p = 0.006) (Fig. 2C).

Table 2 Donor clinicopathological characteristics

Variable	HCC-CC (n = 94)	HCC (n = 3515)	CC (n = 440)	p-value
Mean age (SD) years	40 (19)	42 (18)	40 (18)	0.236
Male (%)	67	60	60	<0.001
Cold ischemic time (h)	7.2 (3.1)	7.3 (4.0)	6.9 (4.4)	0.009
Warm ischemic time (N = 208) (min)	10.2 (6.8)	12.8 (8.5)	17.0 (13.0)	0.259
Median fatty infiltration (N = 1020)	5 (0, 29)	5 (0, 10)	0 (0, 10)	0.144

Table 3 Secondary diagnosis of patients undergoing LT for HCC-CC, HCC, and CC

Secondary diagnosis	HCC-CC	HCC	CC
Hepatitis C	41 (44%)*	1260 (36%)*	9 (2%)*
Alcoholic cirrhosis	8 (9%)*	328 (9%)*	7 (2%)*
Alcoholic cirrhosis and hepatitis C	3 (3%)	153 (4%)	2 (0.5%)
Autoimmune hepatitis	4 (4%)	33 (0.9%)	1 (0.2%)
Cryptogenic cirrhosis	1 (1%)	91 (3%)	7 (0.2%)
NASH	3 (3%)	159 (5%)	1 (0.2%)
PSC	2 (2%)	11 (0.3%)	71 (16%)*
PBC	1 (1%)	40 (1%)	2 (0.5%)
No secondary diagnosis listed	24 (26%)	568 (16%)	4 (0.9%)

*p-value < 0.001.
NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis.

On Cox Regression analysis, no other factors (e.g. age, gender, any secondary diagnosis or waiting-time) were predictors of OS in patients undergoing LT for HCC-CC.

Discussion

In the United States, there are approximately 6000 LTs performed each year, and more than 70% of recipients now survive for at least 5 years at most centers.[14] Malignancy as a primary indication for LT increased from 7.7% in 2002 to 22.4% in 2012.[15,16] Liver transplantation for HCC has evolved over the last several decades. Patients within Milan criteria have an overall survival rate of 86% and 62% at 1- and 5-year, respectively; equivalent to those patients undergo LT without primary liver malignancy. Due to the increasing incidence of mixed HCC-CC and the scarcity of reports in the setting of LT, our group was interested in determining the long-term outcome of patients undergoing LT for mixed HCC-CC and compared them with those patients undergoing transplantation for HCC and CC.

Cholangiocarcinoma represents approximately 10% of primary hepatobiliary malignancies.[17] Based on their location within the biliary tree, three different types have been described: intrahepatic cholangiocarcinoma (ICC), perihilar cholangiocarcinoma (PHC), and distal cholangiocarcinoma (DCC).[18] Resection for potential cure can be offered to less than 20% of patients with a reported 5-year survival of 20–30%.[10] Lymph node invasion, bilateral liver involvement, and vascular encasement frequently preclude potentially curative resection. While LT was once thought to be an ideal operation for ICC, several multicenter series demonstrate low 3 and 5-year patient survival (20–30%) and high recurrence rates (50–60%) with liver transplant alone.[19–21] During the last decade, LT (in combination with neoadjuvant therapy and operative staging) has achieved remarkable success for appropriate selected patients with early-stage unresectable PHC, with an overall 5-year survival up to 73% and recurrence rate of 18%.[10] Factors associated with recurrence included age above 45 years old, high CA 19-9 levels and tumor size.[22] We found 1-, 3- and 5-year overall survival rates of 79%, 58%, and 47%, respectively; in patients undergoing LT for CC. We should consider that UNOS database does not distinguish between ICC and PHC within the CC diagnosis.

According to limited reports, HCC-CC represents less than 5% of all liver cancers,[23,24] and although CC and HCC may develop distantly in the liver, the majority of the HCC-CC specimens appear to be transitional tumor subtypes. It has been described that HCC-CC clinicopathologic characteristics include more frequent multifocal lesions, as well as more microvascular emboli, portal vein and lymph node invasion[25]; which perhaps could explain the relative poor prognosis associated with this type of tumor.[1–9]

To best of our knowledge, this study analyzed the largest series of patients undergoing LT for HCC-CC in the United States. From 1994 to 2013, we identified 4049 patients transplanted for primary liver malignancy, including 94 with HCC-CC, 3515 with HCC and 440 with CC; with a sustained increased incidence of this indication for LT after 2002. Patients within HCC-CC group

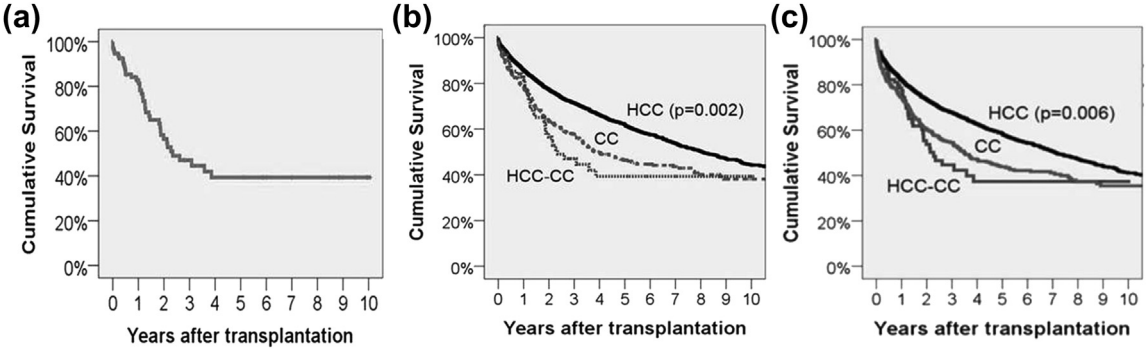

Figure 2 (a) Patient survival after liver transplantation for mixed hepatocellular and cholangiocarcinoma. (b) Patient survival after liver transplantation for mixed hepatocellular and cholangiocarcinoma vs. hepatocellular carcinoma and cholangiocarcinoma. (c) Graft survival after liver transplantation for mixed hepatocellular and cholangiocarcinoma vs. hepatocellular carcinoma and cholangiocarcinoma

had a mean age at transplant of 57 years and 74.7% were male, in congruence with previous reports.[4–6] Patients in the CC group were found to have higher serum bilirubin levels (mean 7.26 mg/dl), when compared to those within the HCC-CC (mean 2.96 mg/dl) and HCC (mean 3.86 mg/dl) groups ($p < 0.001$). However, laboratory MELD score did not significantly differ between the three groups and the majority had a MELD score lower than 15. This finding supports that most of these patients were transplanted with MELD exception. The percentage of HCC-CC reported as being incidentally found was low (6.3%), even though the lab MELD score at time of transplant was low. We believe this is because the majority of these patients were thought to have HCC prior to transplant but were found to have HCC-CC on explant so the true percentage of incidental finding of HCC-CC is probably not reflective in this percentage.

We identified hepatitis C and alcoholic cirrhosis as the most common secondary diagnosis in patients undergoing LT for HCC-CC, 44% and 9% respectively; similar to those patients with HCC. This suggests that the presence of HCC-CC is frequently complicated by chronic parenchymal liver disease, as previous reports have described.[9] It is not surprising therefore, that resection for HCC-CC can be considered difficult in a majority of cases. Only 2% of patients within the HCC-CC group were reported to have primary sclerosing cholangitis (PSC), differing from those patients transplanted for CC in which it is the most common secondary diagnosis (16%). This finding supports the relevance of PSC as a known risk factor for the development of CC.[18,21]

Patients with HCC-CC who are unresectable rarely survive more than 2 years. While poor survival after resection has been reported previously, data on outcomes after LT for this type of tumor is very limited.[7,12,13] Jarnagin *et al.* assessed outcomes in 27 patients with HCC-CC. Seventy-eight percent of them underwent resection with a 5-year survival of 24%, not significantly different compared to that in the CC and HCC cohort, 33% and 37% respectively. Notably, all patients with HCC-CC that were not amenable to resection died within 18 months.[10] Liu *et al.* retrospectively analyzed 10 patients with HCC-CC who underwent resection in their center with similar clinicopathological characteristics when compared with patients with HCC and ICC. The overall survival was 17 months for the HCC-CC group, similar to the CC group (26 months), but significantly worse than that of the HCC group (52 months).[9] Zhan *et al.* evaluated prognostic features of 27 patients with combined HCC-CC that underwent either liver resection or LT. In all cases, diagnosis was performed by postoperative biopsies. Twenty-five patients underwent hepatic resection and three received LT. Mean follow-up was 25.8 months with overall survival rates at 1- and 2-year of 72.5 and 49.4%, and disease-free survival rates at 1- and 2-year of 54.2 and 41.3%, respectively.[24] Park *et al.* performed a retrospective study of 15 patients who underwent LT for pathologically confirmed HCC-CC with a pretransplant diagnosis of HCC over a period of 10 years. Seven patients experienced tumor recurrence. The overall survival rates were 66.7%, 60%, and 60% at 1-, 3-, and 5-year, respectively; while disease-free survival rates were 60% at 1 year and 53.3% at 3- and 5-year, respectively.[26]

Recently, Groeschl *et al.* performed a retrospective analysis of the Surveillance, epidemiology and end results (SEER) database comparing the survival of mixed HCC-CC and HCC patients undergoing both LT and hepatic resection. Their results showed that patients undergoing LT for HCC have a significantly longer survival compared to patients with HCC-CC (68 months vs. 36 months), with a 3 year survival rate of 78% in the HCC group compared to 48% in the HCC-CC counterpart. The authors inquired clinical characteristics and survival data of patients with a pathologic diagnosis of HCC-CC from UNOS Database up to October, 2011. Their analysis included 65 patients transplanted for HCC-CC since 1994, with a median age of 55 years and overall 1-, 3-, and 5-year patient survival of 75%, 45%, and 28%, respectively. In this report, the authors did not compared outcomes in between patients undergoing LT for HCC-CC, HCC, and CC.[13]

Over our study period patients undergoing LT for HCC-CC had an overall 1-, 3-, and 5-year survival rate of 82%, 47%, and 40%, respectively; with a median survival time of 29 months. In accordance to previous reports,[13] patients undergoing LT for HCC had significantly better survival at the same time points (86%, 72%, and 62%) compared to those transplanted for HCC-CC and CC. LT for mixed HCC-CC confers a survival rate similar to carefully selected patients that underwent LT for CC in UNOS database. Similarly, graft survival rate was significantly better within the HCC group (82%, 68%, 54% at 1-, 3-, and 5-year) when compared to those in the HCC-CC and CC cohort. Interestingly, acute rejection rate at 6 months was higher in patients with CC (22.4%) when compared with those with HCC-CC (19%) and HCC (12.7%).

Our study has some limitations that we should address. This was a retrospective analysis of the UNOS database, which was not developed to study cancer population. The absence of a specific HCC-CC diagnosis in the UNOS database could lead to selection bias. Key variables were not captured including tumor characteristics (eg, tumor size, location, number, percentage of liver parenchyma involved with tumor, vascular invasion and cell differentiation), pre- and post-transplantation treatments, and pre-transplantation imaging used to determine the diagnosis and extent of the disease. We were unable to find differences in the frequency, features and outcomes of HCC-CC subtypes. Additionally, recurrence data was not available for the vast majority of the study population. Despite these limitations, the strength of our study comes not only from the large number of patients with HCC-CC included in the database, but also from its clinically robust definitions of patient characteristics.

In conclusion, our results demonstrate that patients undergoing LT for HCC have better overall survival from those with HCC-CC and CC. Outcomes of HCC-CC may more closely follow the CC phenotype. We believe that early diagnosis of mixed HCC-CC is essential for a potential cure. As the

experience in LT for HCC-CC is very limited, controversial issues which arise in our study include the following questions. How can mixed HCC-CC be best diagnosed definitively prior to liver transplantation? If unresectable, what is the role of LT in HCC-CC treatment? Would transplantation with neoadjuvant therapy be better treatment than resection, even for patients with potentially resectable disease? Attempts should be made to identify HCC-CC patients prior to transplantation and to better understand predictors of outcomes, which could help to standardize selection criteria. Future studies should also address special consideration for immunosuppression modification and/or adjuvant therapy in those patients found to have HCC-CC on explanted specimens.

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Author contributions

Study conception and design: Vilchez, Gedaly and Maynard.

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Analysis and interpretation of data: Vilchez, Pena, Shah, Daily, Tzeng, Davenport, Hosein, Gedaly and Maynard.

Drafting of manuscript: Vilchez, Gedaly, and Maynard.

Critical revision of the manuscript: Vilchez, Pena, Shah, Daily, Tzeng, Davenport, Hosein, Gedaly and Maynard.

Conflicts of interests/financial disclosures

None to declared.

References

1. Jarnagin WR, Weber S, Tickoo SF *et al*. (2002) Combined hepatocellular and cholangiocarcinoma: demographic, clinical and prognostic factors. *Cancer* 94:2040–2046.
2. Allen RA, Lisa JR. (1949) Combined liver and bile duct carcinoma. *Am J Pathol* 25:647–655.
3. Goodman ZD, Ishak KG, Langloss JM, Sesterhenn IA, Rabin L. (1985) Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. *Cancer* 55:124–135.
4. Ng IO, Shek TW, Nicholls J, Ma LT. (1998) Combined hepatocellular-cholangiocarcinoma: a clinicopathological study. *J Gastroenterol Hepatol* 13:34–40.
5. Taguchi J, Nakashima O, Tanaka M, Hisaka T *et al*. (1996) Clinicopathological study on combined hepatocellular and Cholangiocarcinoma. *J Gastroenterol Hepatol* 11:758–764.
6. Fowler KJ, Sheybani A, Parker RA *et al*. (2013) Combined hepatocellular and cholangiocarcinoma (Biphenotypic) tumors: imaging features and diagnostic accuracy of contrast-enhanced CT and MRI. *AJR* 201: 332–339.
7. Sapisochin G, Fidelman N, Roberts JP *et al*. (2011) Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. *Liver Transpl* 17:934–942.
8. Kim KH, Lee SG, Park EH *et al*. (2009) Surgical treatments and prognoses of patients with combined hepatocellular carcinoma and cholangiocarcinoma. *Ann Surg Oncol* 16:623–629.
9. Liu CL, Fan ST, Lo CM *et al*. (2003) Hepatic resection for combined hepatocellular and cholangiocarcinoma. *Arch Surg* 138:86–90.
10. Rosen CB, Heimback JK, Gores GJ. (2010) Liver transplantation for cholangiocarcinoma. *Transpl Int* 23:692–697.
11. Chan AC, Lo CM, Ng IO *et al*. (2007) Liver transplantation for combined hepatocellular cholangiocarcinoma. *Asian J Surg* 30:143–146.
12. Panjala C, Senecal DL, Bridges MD *et al*. (2010) The diagnostic conundrum and liver transplantation outcome for combined hepatocellular-cholangiocarcinoma. *Am J Transpl* 10:1263–1267.
13. Groeschl RT, Turaga KK, Gamblin C. (2013) Transplantation versus resection for patients with combined hepatocellular carcinoma-cholangiocarcinoma. *J Surg Oncol* 107:608–612.
14. Agopian VG, Petrowskly H, Kaldas FM *et al*. (2013) The evolution of liver transplantation during 3 decades: analysis of 5347 consecutive liver transplants at a single center. *Ann Surg* 258:409–421.
15. Kim WR, Smith JM, Skeans MA *et al*. (2014) OPTN/SRTR 2012 annual data report: liver. *Am J Transpl* 14:69–96.
16. Dutkowski P, Linecker M, DeOliveira ML *et al*. (2015) Challenges to liver transplantation and strategies to improve outcomes. *Gastroenterology* 148(2):108–120.
17. Grossman EJ, Millis JM. (2010) Liver transplantation for non-hepatocellular carcinoma malignancy: indications, limitations, and analysis of the current literature. *Liver Transplant* 16:930–942.
18. Blechacz B, Komuta M, Roskams T *et al*. (2011) Clinical diagnosis and staging of cholangiocarcinoma. *Nat Rev Gastroenterol Hepatol* 8: 512–522.
19. Sudan D, DeRoover A, Chinnakotla S, Fox I *et al*. (2002) Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transpl* 2:774–779.
20. Heimback JK, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, Rosen CB *et al*. (2004) Transplantation for hilar cholangiocarcinoma. *Liver Transpl* 10:S65–S68.
21. DeOliveira ML, Cunningham SC, Cameron JL *et al*. (2007) Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 245:755–762.
22. Heimbach JK, Gores GJ, Haddock MG, Alberts SR *et al*. (2006) Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. *Transplantation* 82:1703–1707.
23. Razumilava N, Gores GJ. (2014) Cholangiocarcinoma. *Lancet* 383: 2168–2179.
24. Zhan Q, Shen BY, Deng XX *et al*. (2012) Clinical and pathological analysis of 27 patients with combined hepatocellular-cholangiocarcinoma in an Asian center. *J Hepatobiliary Pancreat Sci* 19:361–369.
25. Yano Y, Yamamoto J, Kosuge T *et al*. (2003) Combined hepatocellular and cholangiocarcinoma: a clinicopathologic study of 26 resected cases. *Jpn J Clin Oncol* 33:283.
26. Park YH, Hwang S, Ahn CS, Kim KH, Moon DB, Ha T *et al*. (2013) Long-term outcome of liver transplantation for combined hepatocellular carcinoma and cholangiocarcinoma. *Transplant Proc* 45:3038–3040.

