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Multi-Center Analysis of Liver Transplantation for Combined Hepatocellular Carcinoma-Cholangiocarcinoma Liver Tumors

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Abstract

Background: Combined hepatocellular-cholangiocarcinoma liver tumors (cHCC-CCA) with pathologic differentiation of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma within the same tumor are not traditionally considered for liver transplantation due to perceived poor outcomes. Published results are from small cohorts and single centers. Through a multi-center collaboration, we performed the largest analysis to date of the utility of liver transplantation for cHCC-CCA.

Study Design: Liver transplant and resection outcomes for HCC (n=2998) and cHCC-CCA (n=208) were compared in a 12-center retrospective review (2009–2017). Pathology defined tumor type. Tumor burden was based on radiologic Milan criteria at time of diagnosis and applied to cHCC-CCA for uniform analysis. Kaplan-Meier survival curves and log-rank test were used to determine overall survival and disease-free survival. Cox regression was used for multivariate survival analysis.

Results: Liver transplant for cHCC-CCA (n=67) and HCC (n=1814) within Milan had no significant difference in overall survival (5-yr cHCC-CCA 70.1%, HCC 73.4%, p=0.806) despite higher cHCC-CCA recurrence rates (23.1% vs 11.5% 5-years, p<0.001). Irrespective of tumor burden, cHCC-CCA tumors undergoing liver transplant had significantly superior overall survival (p=0.047) and disease-free survival (p<0.001) compared to resection. For cHCC-CCA within Milan, liver transplant was associated with improved disease-free survival over resection (70.3% vs 33.6% 5-years, p<0.001).

Conclusions: Regardless of tumor burden, outcomes following liver transplant are superior to resection for patients with cHCC-CCA. Within Milan criteria, liver transplant for cHCC-CCA and HCC results in similar overall survival justifying consideration of transplantation due to the higher chance of cure with liver transplantation in this traditionally excluded population.

Précis

Within Milan criteria, liver transplant for combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) results in similar overall survival to transplant for hepatocellular carcinoma justifying consideration of transplantation for cHCC-CCA due to the higher chance of cure with liver transplantation in this traditionally excluded population.

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) liver tumors have features of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). Other terminologies for cHCC-CCA tumors are *biphenotypic*, *mixed hepatocellular-cholangiocarcinoma*, *cholangiolocellular carcinoma*, and *cholangiohepatoma*. cHCC-CCA comprises of approximately only 2% of all primary liver tumors. The pathologic diagnosis of cHCC-CCA is made when the tumors have cells that have dual phenotypic expression on one cell type. Although this tumor type was first recognized in the literature over 100 years

ago (1), the diagnosis and terminology have recently been standardized in an international consensus document (2).

For patients with cHCC-CCA tumors identified pre-operatively, the majority are directed towards resection. However, the 5-year survival for resection of cHCC-CCA tumors is poor, ranging from 20–40% (3). Liver transplant may have improved outcomes compared to resection as is seen in patients with HCC eligible for transplant (4). With varied degrees of long-term outcomes in resection and transplant, there has been an attempt to better classify tumors and identify outcomes (2).

When meeting specific criteria, HCC has been widely acceptable for liver transplantation due to good outcomes following liver transplantation (5, 6). There are also positive outcomes following liver transplantation for hilar cholangiocarcinoma on a protocol with strict criteria (7, 8). Historically, liver transplantation for intrahepatic cholangiocarcinoma has been associated with poor long term outcomes (9–14). Similar to intrahepatic cholangiocarcinoma, cHCC-CCA tumors are not traditionally considered for liver transplantation due to perceived poor outcomes in prior published results from small cohorts and single centers (9, 15–17). Some studies grouped cHCC-CCA together with intrahepatic cholangiocarcinoma, which may skew the results negatively (9, 18). Retrospective large database reviews have indicated worse outcomes of liver transplant for cHCC-CCA compared to liver transplant for HCC but lack important granular data such as tumor burden and pre-operative therapy (17). In some single-center small cohorts, liver transplantation for cHCC-CCA has satisfactory outcomes equivalent to HCC (10, 18–21). Currently, patients with cHCC-CCA are not eligible for deceased donor organ allocation prioritization based on the Model for End Stage Liver Disease (MELD) system in the United States.

Several factors have made standardizing treatment for cHCC-CCA difficult. First, due to similarity in radiographic features of the two tumor types, it is difficult to differentiate cHCC-CCA from HCC on imaging (15, 22, 23). Unlike HCC, where radiographic features are diagnostic without biopsy, imaging criteria for the diagnosis of cHCC-CCA tumors have not been standardized, which may lead to pre-operative mis-classification when biopsy is not used (16, 24). Secondly, the pathologic diagnosis has been varied from including cases with two separate tumors (one HCC and one intrahepatic cholangiocarcinoma), a single “collision” tumor with two different cell types of both HCC and intrahepatic cholangiocarcinoma mixed in one tumor, or tumors that have expression of both HCC and cholangiocarcinoma (2, 25, 26). Thirdly, cHCC-CCA is rare compared to HCC making it difficult for single institutions to acquire a significant number of cases for study (3, 27).

Due to mixed reports in the literature of small mostly single-center cohorts, we sought to overcome the limitations of prior studies through a multi-center collaboration. We performed the largest retrospective cohort analysis to date of the utility of liver transplantation for cHCC-CCA. The aim of this study is to assess outcomes of liver transplantation for cHCC-CCA. We hypothesize that if size and number of cHCC-CCA tumors are comparable to HCC cases that are currently considered transplant-eligible, liver transplantation provides better outcomes than resection. Due to the limited supply of livers for transplantation, outcomes following liver transplantation for cHCC-CCA must be comparable to other

indications for liver transplantation. Recognizing this, our second hypothesis is that for small cHCC-CCA, liver transplantation will be acceptable with outcomes that are not statistically worse than liver transplantation for HCC.

Methods

Data Collection

Liver transplantation and resection outcomes were compared in a 12-center retrospective review for cases of HCC and cHCC-CCA (2009–2017). Data were collected at each center through retrospective chart review. The Washington University in St. Louis institutional review board (IRB) approved this study as did each individual IRB for each center. Data use agreements were signed between centers. Limited datasets were transferred securely to Washington University in St. Louis.

Case Definition

Tumors were defined as either HCC or cHCC-CCA based on final surgical pathology report from the participating center. The actual pathology slides were not re-reviewed; however, the pathology reports for all centers were centrally reviewed to ensure consistency in classification. Tumor burden was determined based on initial imaging report. The Milan criteria and University of California San Francisco (UCSF) criteria were applied to cHCC-CCA as well as HCC for uniform analysis. Within Milan criteria was defined as: a solitary lesion with diameter less than or equal to 5 cm *or* up to three lesions, each with a diameter less than or equal to 3 cm and no evidence of gross vascular invasion (5). UCSF criteria was defined as: a solitary lesion smaller than or equal to 6.5 cm *or* up to three lesions with the largest lesion smaller than or equal to 4.5 cm and a total tumor burden 8 cm or less (28).

Analysis Plan

The aim of the study was to study the outcomes of liver transplantation for cHCC-CCA, which we approached using three different analyses: 1) outcomes of resection of cHCC-CCA and liver transplantation for cHCC-CCA, 2) outcomes of resection of cHCC-CCA and HCC, and 3) outcomes of liver transplantation for cHCC-CCA and HCC. Within each analysis category, we also completed sub-analyses for cases based on tumor burden: beyond UCSF criteria, beyond Milan criteria but within UCSF criteria, and within Milan criteria.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism v 5.0 (GraphPad Software, Inc. La Jolla, CA) and SPSS version 26 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Categorical variables were compared using Fisher's exact test or Chi Square test as applicable. Student's T test was used to compare continuous variables. Survival graphs were plotted using Kaplan Meier curves and survival rates were compared using Log Rank test. Cox regression method was used to run multivariate survival analysis. For every comparison, difference with a p value <0.05 was considered statistically significant.

Results

The cohort consisted of 3206 surgically managed patients with primary liver tumor (HCC (n=2998) and cHCC-CCA (n=208)). Gender and age were available for the entire cohort. Race data was missing in 423 (13.2%) cases and distribution of missing data was almost similar in all groups. Among the patients receiving resection, HCC cohort had significantly higher proportion of males and cHCC-CCA cohort had higher proportion of Caucasian patients (Table 1).

Locoregional Therapy

Though pre-operative Trans-arterial Chemoembolization (TACE) and Ablation were significantly more common in HCC cases than in cHCC-CCA cases in the entire cohort of 3206 cases, this difference between the groups was not seen when the cohort was divided by the type of surgery. In patients undergoing transplant, Yttrium-90 (Y-90) was the only locoregional therapy (LRT) used more frequently in cHCC-CCA patients (7.5%) than in HCC patients (2.8%) with 7.5% of cHCC-CCA patients and 2.8% of HCC patients having Y-90 prior to transplant ($p=0.014$) (Table 1).

Pre-Transplant Diagnosis and Tumor Burden of cHCC-CCA Cases

There were 208 patients with cHCC-CCA based on final surgical pathology. In the pre-operative setting only 11 (5.3%) had a pre-operative diagnosis of cHCC-CCA. Nine received resection and two underwent liver transplantation (Table 2). Of the 11 pre-operatively diagnosed cHCC-CCA tumors, five were beyond Milan criteria at the time of diagnosis (of which only two were beyond UCSF) and none had major vascular invasion. One of those five received transplant (beyond Milan, but within UCSF at diagnosis with no measurable disease after Y90) whereas four received a resection. Remaining six patients with pre-operative diagnosis of cHCC-CCA were within Milan. One of those six received a transplant whereas other five were resected. Total 125 patients with cHCC-CCA on final surgical pathology received a surgery with a pre-operative imaging diagnosis of HCC. Forty-four patients were beyond Milan (26 beyond UCSF) at the time of diagnosis. Twenty-seven (14 beyond UCSF) received transplant (Table 3).

Entire Cohort Outcomes

In the entire cohort, total 2273 patients underwent liver transplantation (99 cHCC-CCA; 2174 HCC) and 933 patients underwent resection (109 cHCC-CCA; 824 HCC). When comparing all cases regardless of surgical treatment strategy, there was significantly better overall survival and disease-free survival in the HCC group compared to the cHCC-CCA group. Additionally, the recurrence rate was significantly lower in the HCC group (all $p<0.001$).

In the multivariable analysis of the full cohort, only cHCC-CCA as the type of tumor (HR = 1.63 [95% CI = 1.28 – 2.09], $p<0.001$) and transplant versus resection (HR = 0.71 [95% CI = 0.57 – 0.90], $p=0.005$) were the independent variables affecting the overall survival. Overall survival was worse in cHCC-CCA cases and better in transplant cases. Similarly, recurrence rate was higher in cHCC-CCA cases (HR = 1.36 [95% CI = 1.03 – 1.79], $p=0.03$)

than in HCC cases, and lower in transplantation (HR = 0.16 [95% CI = 0.12 – 0.21], $p < 0.001$) versus resection.

cHCC-CCA Cohort: Resection of cHCC-CCA and liver transplantation for cHCC-CCA

Within the cHCC-CCA cohort, 99 transplant recipients and 109 patients that underwent resection were compared. Irrespective of tumor burden, cHCC-CCA tumors undergoing liver transplantation had significantly superior overall survival ($p = 0.047$) (Figure 1a) and disease free-survival ($p < 0.001$) (Figure 1b) compared to resection.

On multivariable analysis, though tumor burden within Milan Criteria was the only variable that independently affected the overall survival (HR = 0.53 [95% CI = 0.34 – 0.84], $p = 0.007$). Transplantation (HR = 0.50 [95% CI = 0.25 – 1.02], $p = 0.047$) as well as tumor burden within Milan Criteria (HR = 0.51 [95% CI = 0.31 – 0.83], $p = 0.007$) were associated with decreased disease recurrence. To investigate further the impact of disease burden and transplant versus resection, we performed sub-analyses by disease burden: beyond UCSF criteria, within UCSF criteria but beyond Milan Criteria, and within Milan criteria.

Resection versus liver transplantation for cHCC-CCA with tumor burden beyond UCSF criteria—Among the 52 patients with cHCC-CCA beyond UCSF criteria, there was no significant difference in overall survival ($p = 0.780$), disease-free survival ($p = 0.105$) or recurrence rate ($p = 0.152$) between transplant ($n = 18$) and resection ($n = 34$) cases.

Resection versus liver transplantation for cHCC-CCA with tumor burden beyond Milan, but within UCSF criteria—Similar to cHCC-CCA tumors beyond UCSF criteria, there was no statistically significant difference in outcomes for patients with cHCC-CCA tumor burden beyond Milan criteria but within UCSF criteria (all $p > 0.2$); however, numbers in this cohort were small (transplant $n = 14$, resection $n = 17$).

Resection versus liver transplantation for cHCC-CCA with tumor burden within Milan criteria—At one year, liver transplantation and resection for cHCC-CCA had similar overall survival (89.1% transplant vs. 89.3% resection). While it did not reach statistical significance, there was disparate overall survival at 5 years (liver transplantation 70.1%; resection 49.7%; $p = 0.078$). However, for cHCC-CCA within Milan criteria, liver transplantation ($n = 67$) was associated with lower recurrence rate (5-year 23.1% vs 45.7%, $p = 0.009$) and improved disease-free survival over resection ($n = 58$) (5-year 70.3% vs 33.6%, $p < 0.001$).

Resection Cohort: Resection of cHCC-CCA and Resection of HCC

In the cohort undergoing resection (109 cHCC-CCA; 824 HCC), irrespective of tumor burden there was better overall survival for HCC than cHCC-CCA ($p = 0.020$) but no difference in disease-free survival or recurrence rates.

Resection for tumor burden beyond UCSF criteria—For cases beyond UCSF criteria, there was no statistically significant difference in the overall survival ($p = 0.136$),

recurrence rate ($p=0.231$) and disease-free survival ($p=0.079$) between HCC ($n=339$) and cHCC-CCA ($n=34$) groups. However, there was disparity between the two groups with overall survival of 40.1% at 5 years in the HCC group compared to 26.9% at 5 years in the cHCC-CCA cohort.

Resection of tumor burden beyond Milan, but within UCSF criteria—Similarly, there was no statistically significant difference in outcome for patients with cHCC-CCA ($n=17$) or HCC ($n=116$) beyond Milan criteria but within UCSF criteria undergoing resection. Overall survival, disease-free survival and recurrence rate were similar in this cohort (all $p>0.088$).

Resection of tumor burden within Milan criteria—In the cohort of cases that underwent resection and were within Milan criteria (58 cHCC-CCA; 369 HCC), overall survival was significantly better for HCC cases (93.2%, 77.4% and 66.6% vs 89.3%, 67.7% and 49.7% at 1-, 3- and 5-years, $p=0.015$). However, there was no statistically significant difference between the two tumor types regarding disease free-survival and recurrence rate (all $p>0.493$).

Transplant Cohort: Liver transplantation for cHCC-CCA and liver transplantation for HCC

Liver transplantation for HCC ($n=2174$) was associated with better overall outcomes than liver transplantation for cHCC-CCA ($n=99$). Patients transplanted for HCC had better overall survival, disease-free survival, and lower recurrence rates after liver transplantation (all $p < 0.007$) than patients transplanted for cHCC-CCA.

In multivariable analysis of the transplant cohort, only tumor type (HCC vs cHCC-CCA) and tumor burden were independently associated with overall survival. For the entire transplant cohort, overall survival was worse for patients with cHCC-CCA (HR = 1.65 [95% CI = 1.16 – 2.36], $p=0.005$) and better in patients with within Milan criteria (HR = 0.40 [95% CI = 0.24 – 0.69], $p=0.001$). Also, on multivariable analysis of the transplant cohort, cHCC-CCA was the only independent variable with significantly higher disease recurrence (HR = 3.14 [95% CI = 2.03 – 4.85], $p<0.001$).

Due to these findings of the association of tumor type and tumor burden with outcomes after transplantation, we analyzed the transplant cohort based on tumor burden.

Liver transplantation for tumor burden beyond UCSF criteria—One hundred eighty four patients (18 cHCC-CCA; 166 HCC) with tumor burden beyond UCSF criteria underwent liver transplantation with statistically significantly better overall survival, disease free-survival and lower recurrence rate (all $p<0.001$) for patients with HCC beyond UCSF criteria compared to patients with cHCC-CCA beyond UCSF criteria. Five-year overall survival for HCC was 67.3% versus 15.8% for cHCC-CCA.

Liver transplantation for tumor burden beyond Milan, but within UCSF criteria—Fourteen patients with cHCC-CCA and 162 patients with HCC with tumor burden beyond Milan criteria but within UCSF criteria underwent liver transplantation. There was no statistically significant difference in overall survival. 5-year overall survival for cHCC-CCA

was 64.3% and HCC was 67.3%, ($p=0.094$). There was a statistically significant difference with longer disease-free survival for HCC, as well as a lower recurrence rate ($p=0.013$ and <0.001 respectively).

Liver transplantation for tumor burden within Milan criteria—The majority of patients that underwent liver transplantation had tumor burden within Milan criteria (67 cHCC-CCA, 1814 HCC) (Table 4). In this cohort, there was no statistically significant difference in overall survival (5-yr cHCC-CCA 70.1%; HCC 73.4%) (Figure 2a) or disease-free survival (Figure 2b) (both $p>0.7$). There was a statistically significant difference in recurrence rates with HCC having a lower recurrence rate (11.5% at 5 years) compared to cHCC-CCA (23.1% at 5 years) ($p<0.001$) (Figure 2c).

Discussion

Liver transplantation for cHCC-CCA was associated with better overall survival and disease-free survival as well as lower recurrence rates than resection for cHCC-CCA, irrespective of the tumor burden (all $p<0.05$). Specifically, for cHCC-CCA within Milan criteria, liver transplantation was associated with improved disease-free survival when compared to resection for cHCC-CCA. This is consistent with findings for transplant versus resection for HCC (4). Ideally, all medically and socially eligible cHCC-CCA patients should undergo liver transplantation given the superior outcomes and better long-term survival compared to resection. However, given the shortage of available livers for transplantation, it is imperative that outcomes for liver transplant for cHCC-CCA are equivalent to patients undergoing transplant for other currently accepted indications for liver transplantation. We compared the outcomes of liver transplantation for cHCC-CCA to transplantation for HCC. When comparing liver transplantation for cHCC-CCA and HCC within Milan, despite higher cHCC-CCA recurrence rates, there was no significant difference in overall survival. For greater tumor burden, survival outcomes were worse for patients with cHCC-CCA than HCC.

A study of the SEER and UNOS databases concluded worse outcomes for transplant for patients with cHCC-CCA compared to HCC, and similar outcomes for resection and transplant for cHCC-CCA; however, that study did not differentiate outcomes based on size and lacked granular data due to the retrospective use of large databases. There was no data on pre-operative locoregional therapy (17). In our analysis, we found that there was a difference in liver transplant outcomes for cHCC-CCA based on pre-operative tumor burden, and patients with cHCC-CCA beyond Milan criteria had worse outcomes following transplantation than those with similarly sized HCC. Unlike this study, overall survival for transplantation of tumors within Milan criteria in our study was comparable between HCC and cHCC-CCA. Differences in our results and the results from this previously published study could be because of their inability to differentiate outcomes based on tumor burden.

Another small cohort compared survival for liver transplantation for cHCC-CCA with HCC within Milan criteria in only 12 patients and found worse outcomes than patients with HCC but better outcomes than those with intrahepatic cholangiocarcinoma. Interestingly, this group could not identify pre-operative tumor markers or imaging criteria to differentiate

these tumors from HCC (15). Similar to this small study, we found a difference in transplant outcomes for the entire cohort regardless of tumor burden, but when analyzing the data in subsets based on tumor burden, we found that liver transplantation for cHCC-CCA was comparable to transplant for HCC within Milan criteria. Additionally, very small number of cases was a limitation of that study.

Some studies have similarly reported positive outcomes for patients with cHCC-CCA undergoing liver transplantation. Facciuto et al. from Mount Sinai, in a retrospective review, analyzed 32 patients with intrahepatic cholangiocarcinoma and mixed cHCC-CCA on pathology (only half were cHCC-CCA), and found 78% 5-year survival following liver transplant in patients with early-stage tumors within Milan criteria (18). Sapisochin et al. published a multicenter study from Spain of 27 patients with cHCC-CCA (15 patients) or intrahepatic cholangiocarcinoma (total 27 patients) matched 1:2 with controls of HCC patients. While discordant outcomes were seen in the intrahepatic cholangiocarcinoma group compared to those with HCC, the cHCC-CCA patients had outcomes similar to the HCC controls with 5-year survival of 78% for the cHCC-CCA group (9). Furthermore, patients with single small tumors (2 cm or less) had better outcomes than patients with multinodular tumors or tumors > 2 cm (10).

Lunsford et al. matched 12 patients with cHCC-CCA 3:1 with patients with HCC based on pre-transplant characteristics and found that low-grade, well to moderately differentiated cHCC-CCA have good outcomes with low risk of recurrence (20). One limitation of this study is that pathologic findings are not universally available pre-transplant for cHCC-CCA given the difficulty in differentiation from HCC based on imaging findings. Similarly, Antwi et al. with 19 cHCC-CCA patients found that overall survival post liver transplant was good for patients with either cHCC-CCA or HCC (21). Each of these small single-center reports corroborates our findings in this larger multicenter cohort of positive outcomes for transplantation for cHCC-CCA, especially for cHCC-CCA with favorable features and tumor burden within Milan criteria.

Limitations

While this study has many merits of being a multicenter study with a large cohort, it was a retrospective review and has some associated limitations. As discussed in methods, the actual pathology slides were not centrally re-reviewed. Limitations to a central re-review included the transfer of actual slides, the burden to review over 3000 cases, and concern that limitations in slide availability might reduce the potential number of available cHCC-CCA cases. Additionally, we felt the study results should realistically be applicable with the pathology available at each transplant program. While the definition of cHCC-CCA cases is quite nuanced and the classification recently published (2), it would be unrealistic to make clinical management recommendations based on every primary liver tumor being centrally reviewed long-term. Additionally, some of these tumors undergo locoregional therapy, resection and transplantation without prior biopsy for pathologic diagnosis.

For similar reasons, we chose to use the tumor burden available on pre-operative imaging. We discussed using actual tumor burden from final pathology, but post-operative pathology is not a criterion that can be used in determining candidacy for liver transplantation.

Transplant candidacy is determined based on pre-operative imaging, and this should be consistent for an indication for transplantation even for cHCC-CCA.

Future Study

Future research is needed to develop the ability to better diagnose cHCC-CCA via imaging criteria pre-operatively. Ideally, this would be similar to the currently used LIRADS or OPTN criteria for HCC. Based on our data, liver transplantation for patients with cHCC-CCA within Milan criteria, even those with a known pre-transplant diagnosis could be considered for liver transplantation. Further discussion is required regarding possible MELD exception points for patients with cHCC-CCA. Criteria for liver transplantation for patients with cHCC-CCA should be defined and prospective data should be collected on the outcomes of transplantation for cHCC-CCA.

Conclusions

Regardless of tumor burden, outcomes following liver transplantation are superior to resection for patients with cHCC-CCA. Within Milan criteria, liver transplantation for cHCC-CCA results in overall survival similar to liver transplantation for HCC justifying consideration of transplantation due to the higher chance of cure in this traditionally excluded population.

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Abbreviations:

HCC	hepatocellular carcinoma
cHCC-CCA	combined hepatocellular-cholangiocarcinoma
iCCA	intrahepatic cholangiocarcinoma
MELD	Model for End Stage Liver Disease
UCSF	University of California San Francisco

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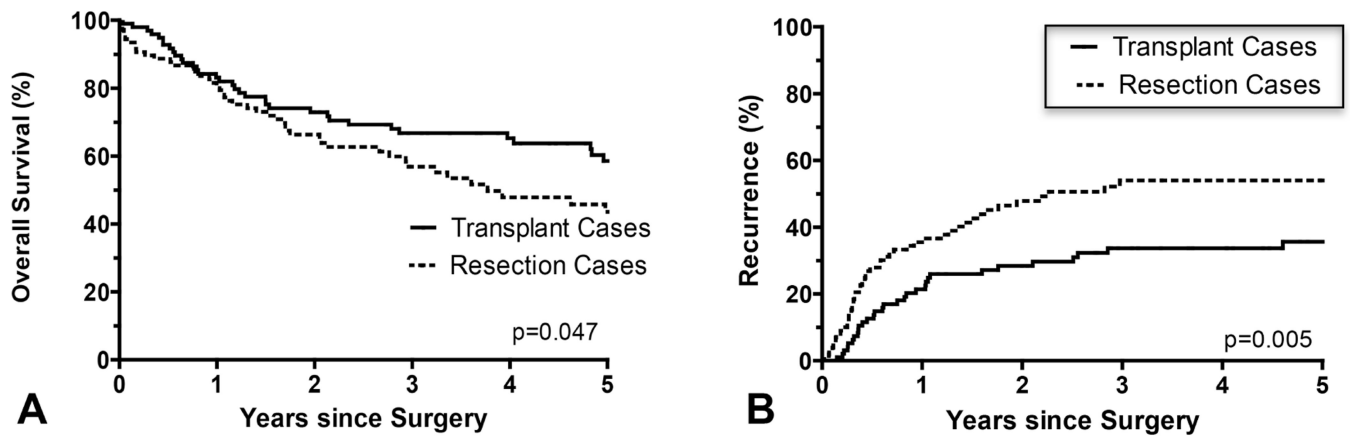


Figure 1.

(A) The overall survival rate was statistically significantly higher ($p=0.047$) and the (B) disease recurrence rate significantly lower ($p=0.005$) in patients with combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) with liver transplantation compared to resection.

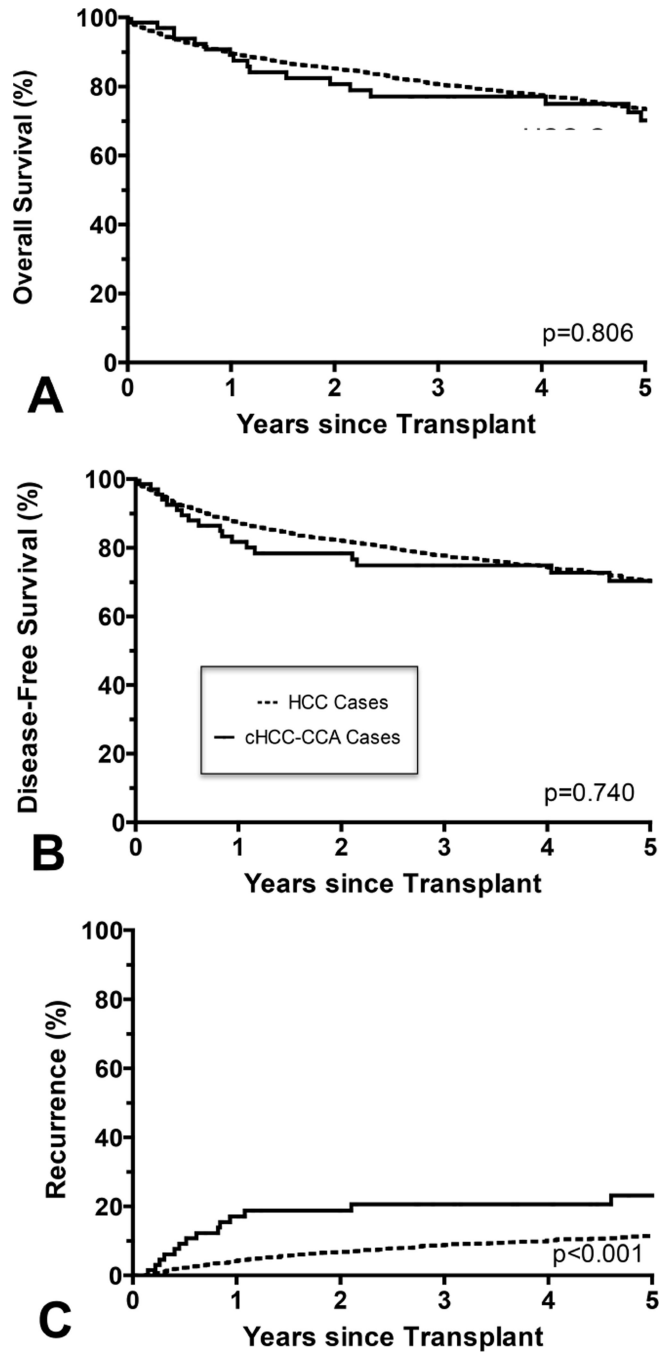


Figure 2. (A) In patients with tumor burden within Milan criteria, the overall survival rate for combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) was comparable to the overall survival rate for HCC ($p=0.806$). (B) Similarly, there was no significant difference in disease-free survival ($p=0.740$). (C) The recurrence rate was significantly higher for cHCC-CCA within Milan criteria compared to HCC within Milan Criteria lower ($p<.001$).

Table 1.

Demographic Characteristics

Variable	cHCC-CCA	HCC	p Value
Full cohort			
Total, n	208	2998	
Sex, m, n (%)	146 (70.2)	2296 (76.6)	0.036
Race, Caucasian, n (%)	132 (72.1)	1551 (59.7)	<0.001
Age, y, mean±SD	60.2 ± 11.4	60.5 ± 9.2	0.598
BMI, kg/m ² , mean±SD	29.3 ± 6.6	28.6 ± 5.8	0.150
TACE, n (%)	66 (33.0)	1486 (60.9)	<0.001
Y90, n (%)	8 (4.3)	65 (2.6)	0.193
Ablation, n (%)	13 (7.0)	465 (19.0)	<0.001
Within Milan cases, n (%)	125 (60.1)	2183 (73.6)	<0.001
Beyond Milan, within-UCSF cases, n (%)	31 (14.9)	278 (9.4)	0.009
Beyond UCSF cases, n (%)	52 (25.0)	505 (17.0)	0.004
Resection			
Total, n	109	824	
Sex, m, n (%)	71 (65.1)	622 (75.5)	<0.001
Race, Caucasian, n (%)	74 (68.5)	256 (46.8)	<0.001
Age, y, mean±SD	61.6 ± 12.8	62.0 ± 12.5	0.792
BMI, kg/m ² , mean±SD	29.0 ± 6.9	28.1 ± 6.1	0.219
Cirrhosis, n (%)	32 (29.4)	424 (51.5)	<0.001
TACE, n (%)	4 (3.7)	24 (7.8)	0.146
Y90, n (%)	2 (1.9)	5 (1.7)	0.889
Ablation, n (%)	2 (1.9)	8 (2.7)	0.639
Within Milan cases, n (%)	58 (53.2)	369 (44.8)	0.097
Beyond Milan, within-UCSF cases, n (%)	17 (15.6)	116 (14.1)	0.670
Beyond UCSF cases, n (%)	34 (31.2)	339 (41.1)	0.046
Transplant			
Total, n	99	2174	
Sex, m, n (%)	75 (75.8)	1674 (77.0)	0.774
Race, Caucasian, n (%)	58 (77.3)	1295 (63.1)	0.012
Age, y, mean±SD	58.5 ± 9.5	60.0 ± 7.6	0.070
BMI, kg/m ² , mean±SD	29.8 ± 6.3	29.9 ± 5.7	0.180
Liver disease, n (%)			
HCV	56 (56.6)	1192 (54.8)	0.813
NASH	18 (18.2)	203 (9.3)	0.006
Alcoholic	11 (11.1)	216 (9.9)	0.834
None	2 (2.0)	7 (0.3)	0.070

Variable	cHCC-CCA	HCC	p Value
TACE, n (%)	62 (67.4)	1462 (68.6)	0.801
Y90, n (%)	6 (7.5)	60 (2.8)	0.014
Ablation, n (%)	11 (13.9)	457 (21.3)	0.113
Within Milan cases, n (%)	67 (67.7)	1814 (84.7)	<0.001
Beyond Milan, within-UCSF cases, n (%)	14 (14.1)	162 (7.6)	0.017
Beyond UCSF cases, n (%)	18 (18.2)	166 (7.7)	<0.001
cHCC-CCA	Resection	Transplant	
Total, n	109	99	
Sex, m, n (%)	71 (65.1)	75 (75.8)	0.095
Race, Caucasian, n (%)	74 (68.5)	58 (77.3)	0.191
Age, y, mean±SD	61.6 ± 12.8	58.5 ± 9.5	0.049
BMI, kg/m ² , mean±SD	29.0 ± 6.9	29.8 ± 6.3	0.421
TACE, n (%)	4 (3.7)	62 (67.4)	<0.001
Y90, n (%)	2 (1.9)	6 (7.5)	0.058
Ablation, n (%)	2 (1.9)	11 (13.9)	0.001
Within Milan cases, n (%)	58 (53.2)	67 (67.7)	0.033
Beyond Milan, within-UCSF cases, n (%)	17 (15.6)	14 (14.1)	0.769
Beyond UCSF cases, n (%)	34 (31.2)	18 (18.2)	0.030

cHCC-CCA, combined hepatocellular carcinoma-cholangiocarcinoma; NASH, non-alcoholic steatohepatitis; TACE, transarterial chemoembolization; UCSF, University of California-San Francisco

Table 2.

Preoperative Diagnoses of Combined Hepatocellular Carcinoma-Cholangiocarcinoma Tumors

Preop tumor diagnosis	Data	Liver transplantation, n	Resection, n
Biphenotypic tumor, n (%)	11 (5.3)	2	9
Cholangiocarcinoma, n (%)	24 (11.5)	1	23
Hepatocellular carcinoma, n (%)	125 (60.1)	84	41
Indeterminate lesion, n (%)	33 (15.9)	6	27
Other tumors, n (%)	10 (4.9)	2	8
Incidental tumor, n (%)	2 (1.0)	2	0
Unknown diagnosis, n (%)	3 (1.4)	2	1
Total, n	208	99	109

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Table 3:

Tumor Burden of Combined Hepatocellular Carcinoma-Cholangiocarcinoma Tumors Based on Preoperative Imaging

Tumor burden at diagnosis	N	Received transplant, N (pre-diagnosed as)	Received resection, N (Pre-diagnosed as)
Beyond UCSF	48	16 (14 HCC; 1 Indeterminate, 1 Other)	32 (9 iCCA; 12 HCC; 2 cHCC-CCA; 5 Indeterminate; 4 Other)
Beyond Milan, within-UCSF	30	14 (13 HCC; 1 cHCC-CCA)	16 (4 iCCA; 5 HCC; 2 cHCC-CCA; 5 Indeterminate)
Within Milan	122	64 (1 iCCA; 56 HCC; 1 cHCC-CCA; 5 Indeterminate; 1 Other)	58 (9 iCCA; 24 HCC; 5 cHCC-CCA; 16 Indeterminate; 4 Other)
Tumor size/ number details unknown	6	3 (1 HCC; 2 Unknown)	3 (1 iCCA; 1 Indeterminate; 1 Unknown)
Incidental tumor	2	2	0

HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; cHCC-CCA, combined hepatocellular-intrahepatic cholangiocarcinoma

Table 4:

Outcomes for Liver Transplantation for Cases within Milan Criteria

Years since operation	Overall survival, %		Disease-specific survival, %		Disease-free survival, %		Recurrence rate, %	
	cHCC-CCA	HCC	cHCC-CCA	HCC	cHCC-CCA	HCC	cHCC-CCA	HCC
1	89.1	89.8	90.5	98.3	81.7	87.3	17.1	4.2
3	77.1	80.7	81.6	94.5	74.8	77.7	20.6	8.8
5	70.1	73.4	76.4	91.9	70.1	70.3	23.1	11.5
Median	N/A	13.0	N/A	N/A	N/A	12.7	N/A	N/A
p Value	0.806		<0.001		0.740		<0.001	

cHCC-CCA cases, n=67; HCC cases, n=1814

HCC, hepatocellular carcinoma; cHCC-CCA, combined hepatocellular-intrahepatic cholangiocarcinoma

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