

Orthotopic Liver Transplantation in Patients with Mixed Hepatocellular Carcinoma-Cholangiocarcinoma

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Abstract

Introduction: Primary liver cancer arises from hepatocytes or biliary epithelium resulting in hepatocellular carcinoma or cholangiocarcinoma, respectively. Mixed hepatocellular carcinoma-cholangiocarcinomas are rare; therefore, medical literature addressing these tumors is limited. As treatment modalities for mixed hepatocellular carcinoma-cholangiocarcinomas are few, the role of orthotopic liver transplantation remains controversial.

Aim: To determine the survival outcomes of patients with incidentally discovered mixed hepatocellular carcinoma-cholangiocarcinomas after orthotopic liver transplantation.

Methods and Materials: We present five patients with mixed hepatocellular carcinoma-cholangiocarcinomas who received orthotopic liver transplantation at our institution between September 1998 and July 2011. Characterization of the combined lesion was based on the Allen and Lisa classification scheme: type A: separate neoplasms of liver cell or bile duct cell; type B: different masses that mingle as they grow; and type C: masses that display both features of liver and bile duct cells.

Results: Preoperatively, all patients met Milan criteria based on presumed hepatocellular carcinoma prior to orthotopic liver transplantation. Multifocal disease was present in all patients on pathological diagnosis, which was not appreciated during preoperative screening, and histologic characterization of the lesions revealed both Allen and Lisa types A (60%) and C (40%). All of our patients had underlying cirrhosis. The post-operative course was uneventful in all of the cases. Vascular invasion was observed in one patient who developed bone metastases and subsequently died 600 days post-transplant despite post-transplant chemoradiation therapy. The other four patients have remained disease-free; the mean overall survival is 800 days. Our population is unique in prevalence of cirrhosis and multiple hepatic lesions as compared to other case series.

Conclusions: Although orthotopic liver transplantation is not recommended for patients with known mixed hepatocellular carcinoma-cholangiocarcinomas, in the event that a patient is transplanted, this case series shows that orthotopic liver transplantation is an acceptable treatment modality with appropriate survival outcomes.

Keywords: Hepatocellular; Cholangiocarcinoma; Combined; Mixed; Liver transplant

Abbreviations: HCC-CC: Mixed Hepatocellular Carcinoma – Cholangiocarcinoma; HCC: Hepatocellular Carcinoma; CC: Cholangiocarcinoma; OLT: Orthotopic Liver Transplantation; BCM: Baylor College of Medicine; HR: Hepatic Resection

Introduction

Primary liver cancer is the fifth most common cancer worldwide and the third most common cause of cancer mortality [1]. Of primary liver tumors, tumors arising from hepatocytes, namely hepatocellular carcinoma (HCC), are the most common. HCC has an estimated 1,000,000 new cases diagnosed annually worldwide and accounts for approximately 660,000 deaths per year [2]. Although the greatest prevalence of HCC remains in Asia and Africa, there are 18,000 new cases in the United States per year, and incidence is reported to be increasing [1-3]. Moreover, HCC is the fastest growing cause of cancer-related death in males in the United States [1].

Cholangiocarcinoma (CC) is the second most common primary liver cancer, arises from biliary epithelium, and can be intrahepatic or extrahepatic in location [2]. Intrahepatic CC accounts for approximately 1/3 of CC's, and the mainstay of treatment is resection due to poor outcomes post-transplantation and organ shortage [2]. Primary sclerosing cholangitis along with infestation of liver flukes are predisposing factors towards the development of CC [3].

Even more uncommon is the presence of tumor cells of both

cholangiocellular and hepatocellular origins [3]. Unfortunately, due to the rarity of disease, and the limited treatment options offered to patients with known mixed disease, few reports in the medical literature offer guidelines to treat these patients. Our center has performed over 1,000 orthotopic liver transplantation (OLT) since September 1998. Over this timeframe we have incidentally discovered that five patients transplanted for presumed HCC actually had HCC-CC based on pathological diagnosis. We describe our experience with this patient population to help define the role of transplantation in treatment of patients with HCC-CC.

Methods and Materials

Five patients with HCC-CC were identified who received OLT

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Received October 31, 2011; **Accepted** November 07, 2011; **Published** November 12, 2011

Citation: Harring TR, Kuten DA, Nguyen NT, Goss JA, O'Mahony CA (2011) Orthotopic Liver Transplantation in Patients with Mixed Hepatocellular Carcinoma-Cholangiocarcinoma. J Transplant Technol Res 1:104. doi:10.4172/2161-0991.1000104

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at this institution between September 1998 and July 2011. During this same time period, our transplantation team has performed over 1,000 OLT. Our database was queried to look for patients with post-transplant pathology consistent with HCC-CC.

Characterization of the combined lesions was based on the Allen and Lisa classification scheme: type A: separate neoplasms of liver cell or bile duct cell; type B: different masses that mingle as they grow; and type C: masses that display both features of liver and bile duct cells [4]. Survival time was based on retrospective review of the patients' medical charts and calculated through September 15, 2011. This study was approved by Baylor College of Medicine Institutional Review Board under protocol H-22045.

Results

The patients underwent pre-operative evaluation for liver transplantation, including metastatic imaging surveys. End-stage-liver-disease was secondary to alcoholism in two patients, hepatitis B virus in one patient, non-alcoholic steatohepatitis in one patient, and primary biliary cirrhosis in one patient. As is custom in some institutions, biopsy of the liver lesions was not performed in any of the patients pre-operatively; the liver masses were presumed to be HCC based on imaging characteristics. All five patients met Milan criteria [5] pre-operatively based on presumed HCC.

Each patient received OLT as a suitable allograft was made available. The operative and post-operative course was uneventful for all the patients, and they were discharged between post-operative day four to seven. Patient demographics and pathology characteristics are listed in Table 1. Multifocal disease demonstrated by tumor burden of two or three lesions per patient was present on pathological diagnosis, but not appreciated during pre-operative imaging. Of note, all tumors ranged between 0.8 and 3.5 centimeters, thereby still falling under Milan criteria [5]. In total, three patients received transarterial chemoembolization and two patients received radiofrequency ablation pre-operatively to treat accessible tumors: one patient underwent both therapies, one patient received no therapies.

Histologic characterization of the lesions revealed both Allen and Lisa types A (60%) and C (40%). All of our patients had underlying cirrhosis. Vascular invasion was observed in two patients; one post-operatively developed bone and brain metastases and subsequently died 600 days post-transplant, the other remains disease-free. Both of these patients received post-operative chemotherapy due to vascular invasion noted in the explanted liver, and the patient with bone metastases also received radiation therapy. The other three patients have not required chemotherapy or radiation therapy. The overall

median survival of our patients in days after transplantation is 800 days, range 471 to 1891 days, and the median disease-free survival is 759 days, range 394 to 1891 days (calculated through September 15, 2011). Patient survival at 1-month, 18-months, and 36-months is 100%, 67%, and 50%, respectively (Table 2).

Discussion

Overall, our patients demonstrate encouraging results for incidentally discovered HCC-CC on pathological review of the explanted liver. Only one of five patients experienced post-operative recurrence and subsequent death. However, this patient succumbed to metastatic disease 600 days post-transplantation. The other four patients have survived a range of 471 to 1891 days, proving that long-term survival is possible in this population. Additionally, only two out of the five patients had post-operative chemotherapy due to vascular invasion noted on pathology. Again, one of these patients succumbed to disease, but the other patient is alive without evidence of recurrent or metastatic HCC-CC at 548 days post-transplant.

Our population is unique in prevalence of cirrhosis and multiple hepatic lesions as compared to other reports [6]. All of our patients had cirrhosis: due to alcoholism, hepatitis B virus, non-alcoholic steatohepatitis, or primary biliary cirrhosis. Moreover, all our patients had multiple lesions, yet they still qualified for OLT under Milan criteria [5]. Interestingly, the patient that died from metastases to her bone and brain, had end-stage-liver-disease due to primary biliary cirrhosis; primary biliary cirrhosis has a well-documented association with cholangiocarcinoma.

HCC-CC occurs in approximately 0.4% to 14.2% of primary liver tumors [4,6-12]. Our center classified the HCC-CC by Allen and Lisa classification [4]; alternatively, some authors use the Goodman classification [13] (Table 3). Per these classification guidelines, the most interesting subtypes are Allen and Lisa type C and Goodman type II, because these subtypes represent truly mixed tumors with elements of hepatocellular carcinoma and cholangiocarcinoma [6]. Therefore, these subtypes are expected to have different clinical characteristics that underscore their different histopathological characteristics.

Unfortunately, HCC-CC is such a rare entity that it is difficult to deduct meaningful conclusions from small cohorts. Oftentimes HCC-CC is confused with HCC during the workup for OLT, and it isn't until after transplantation that the transplant team realizes that the patient is at higher risk for recurrence or metastasis. Several authors have tried to expound on the clinical outcomes of patients diagnosed with HCC-CC. There is a widespread understanding that similarly to HCC and CC, patients with HCC-CC have a poor prognosis with expectantly

Patient	Age	Sex	Race	Survival (Days)	Allen and Lisa Type	Cirrhosis Present on Histology	Number of Tumors
1	69	F	Caucasian	600*	A	Yes	3
2	63	M	Caucasian	492	C	Yes	2
3	56	M	Caucasian	548	C	Yes	2
4	57	M	Hispanic	1891	A	Yes	2
5	67	M	African-American	471	A	Yes	2

*= this patient is deceased; the other patients are still living and their survivals were calculated through September 15, 2011

Table 1: Demographics and Survival of Patients with HCC-CC.

	1-Month	6-Month	12-Month	18-Month	24-Month	36-Month
Survivals (%)	100	100	100	100	50	50
Disease-Free Survival (%)	100	100	100	67	50	50
Number of Patients	5	5	5	3	2	2

Table 2: Survival of Patients with HCC-CC.

Allen-Lisa [4]		Goodman [13]	
Type	Description	Type	Description
A	Separate neoplasms of liver cell or bile duct cell	I	Collision tumor: occurrence of HCC and CC within same liver
B	Different masses that mingle as they grow	II	Transitional tumor: transition of elements of HCC to elements of CC
C	Masses that display both features of liver and bile duct cells	III	Fibrolamellar tumor: resembles fibrolamellar subtype of HCC but with mucin-producing pseudoglands

Table 3: Histological Classification of HCC-CC: Allen and Lisa versus Goodman Classification Schemes.

	Panjala et al. [8]	Chan et al. [17]	Sapisochin et al. [18]	Kim et al. [19]	BCM
Number of Patients	9*	3	10	29***	5
Median Survival (months)	43.2	25.5	19.5 **	28.8	26.7
Surgical Treatment	OLT	OLT	OLT	25 HR/4 OLT	OLT

Legend:

HR = Hepatic Resection

OLT= Orthotopic Liver Transplantation

* = study examined only Allen-Lisa type C or Goodman type II

** = this survival includes patients who received OLT for either HCC-CC or intrahepatic CC; the authors did not delineate between these disease when calculating survival

*** = 3 patients with Allen-Lisa type A were removed from this study

Table 4: OLT for Patients with HCC-CC: Reports in the Medical Literature.

low survival rates with non-surgical treatment. Jarnagin et al. suggests that HCC-CC more closely resembles CC in survival outcomes [6]; however, other authors suggest that HCC-CC may have a completely unique survival pattern than HCC or CC. Liu et al. demonstrated that patients with HCC-CC have different survivals compared to patients with HCC after hepatic resection, concluding that survivability of these patients is not due to the tumor origin of HCC [14]. Finally, Lee et al. determined that patients with HCC-CC have higher recurrence rates and higher mortality after resection compared to patients with HCC or CC [15]. Several authors agree that patients with HCC-CC have poor survival prognosis after hepatic resection [14-16]. Our center agrees with Lee et al. in the notion that based on these findings HCC-CC may actually represent a distinct disease process [16].

There remains a paucity of data as to the effectiveness or role of OLT in the management of HCC-CC (Table 4). Hepatic resection outcomes remain questionable as to effectiveness of controlling disease [6,14-16], and non-surgical therapies are plainly inadequate. The medical literature contains arguments pertaining to the use of OLT in the treatment of patients with HCC-CC: Chan et al. suggests that OLT may have a role in the management and treatment of these patients [17]; but Sapisochin et al. suggests additional testing, including biopsy of suspicious lesions, to prevent patients with HCC-CC from consideration of OLT [18]. Others suggest additional radiographic and/or laboratory testing to increase identification of HCC-CC prior to operation [8,18], or additional aggressive surgical techniques including lymph node dissections [19].

HCC-CC is difficult to diagnose on imaging alone, and thus the majority are misdiagnosed at presentation and only correctly diagnosed postoperatively. OLT is not a recommended treatment modality for patients with known HCC-CC due to poor survival outcomes as demonstrated by few reports available in the medical literature. Hepatic resection remains the standard operative treatment for these patients to ease the burden of organ shortage and to increase survivability of the patients as much as possible. If the patient has disease not amenable to surgical resection, then chemotherapy, transarterial chemoembolization, and radiofrequency ablation should be attempted first to shrink disease and potentially allow for future resection. However, in the event that a patient is transplanted with an incidentally diagnosed HCC-CC during pathologic examination of the

explanted liver, our case series shows that acceptable survival outcomes can be achieved.

Acknowledgement

This work was not funded by grants. Approval to conduct this study is through the Baylor College of Medicine Institutional Review Board, H-22045.

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