

Outcomes Analysis for 280 Patients with Cholangiocarcinoma Treated with Liver Transplantation Over an 18-year Period

Natasha S. Becker · Joel A. Rodriguez ·
Neal R. Barshes · Christine A. O'Mahony ·
John A. Goss · Thomas A. Aloia

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Abstract Cholangiocarcinoma is an aggressive malignancy with 5-year survival rates <15%. Selected patients present with localized but unresectable disease and are candidates for orthotopic liver transplantation (OLT). The purpose of this study was to evaluate a multi-institutional experience with liver transplantation for this malignancy. Two hundred eighty patients with cholangiocarcinoma treated with OLT from 1987 to 2005 were identified in The United Network for Organ Sharing database. Patient and allograft survivals were calculated and the potential prognostic value of multiple clinicopathologic variables was assessed. At a median follow-up interval of 452 days (range: 0–6,166 days), 1- and 5-year patient survivals were 74 and 38%, respectively, with 49 actual 5-year survivors and 21 actual 10-year survivors. Posttransplant 1- and 5-year allograft survivals were 69 and 36%, respectively. Study variables associated with improved survivals included diagnosis of cholangiocarcinoma pre-OLT [5-year overall survival (OS): 68 vs. 20% for patients with incidental diagnoses at the time of OLT, $p<0.001$] and OLT after 1993 (5-year OS: 45 vs. 30% pre-1994, $p<0.01$). In contrast, the diagnosis of concomitant primary sclerosing cholangitis did not impact survivals (5-year OS: 41 vs. 50% without primary sclerosing cholangitis, $p=0.402$). Selected cholangiocarcinoma patients treated with OLT experience a survival benefit. Diagnosis of cancer prior to OLT allows for better staging and pre-OLT therapy that may translate into improved outcomes. These data support the continued development of multimodality cholangiocarcinoma treatment protocols that include OLT.

Keywords Bile duct cancer ·
Orthotopic liver transplantation · Survival analysis

Introduction

Cholangiocarcinoma is an uncommon, but aggressive, malignancy of the biliary tract. Unlike many other cancers, its incidence in the USA and worldwide is increasing.

Between 1973 and 1997, the incidence increased by almost 10%, as did the mortality rate from the disease.^{1,2} Although no specific etiologic factor can be found in most patients, there is an association between long-standing biliary inflammation [as in the case of primary sclerosing cholangitis (PSC)] and development of cholangiocarcinoma.³ In the population of patients with PSC, the prevalence of cholangiocarcinoma ranges from 5 to 15%.⁴

Results of nonsurgical therapies for cholangiocarcinoma have been disappointing, with the majority of patients surviving less than 1 year after diagnosis.⁵ In cases where complete resection is possible, 5-year patient survivals between 27 and 48% have been reported.² However, due to patient age, tumor location, distant disease, and/or underlying liver disease, candidacy for complete resection is more often the exception than the rule.² In selected cases of cholangiocarcinoma that are early-stage, but anatomically not resectable, orthotopic liver transplantation (OLT) has been investigated as a treatment modality.^{6–8}

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N. S. Becker · J. A. Rodriguez · N. R. Barshes ·
C. A. O'Mahony · J. A. Goss · T. A. Aloia (✉)
Michael E. DeBakey Department of Surgery,
Division of Hepatobiliary Surgery and Abdominal
Transplantation, Baylor College of Medicine,
1709 Dryden, Suite 15.37,
Houston, TX 77030, USA
e-mail: taaloia@tmhs.org

Early experience with OLT in cholangiocarcinoma was disappointing, with reported 5-year survivals ranging from 18 to 25%.^{9–11} However, more recent single-center reports indicate that 5-year patient survivals of over 80% can be achieved when liver transplantation is combined with neoadjuvant radiation and chemotherapy in patients with early-stage disease (stage I/II).^{12,13} Given these recent favorable results, the aim of this study was to examine overall trends in outcomes following OLT for cholangiocarcinoma using the multi-institutional United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) patient database.

Materials and Methods

The UNOS/OPTN database encompassing 71,224 liver transplants from 1987 to 2005 was used for data collection. Analysis of this data set identified 280 patients who had a diagnosis of cholangiocarcinoma at listing ($n=102$) or at discharge ($n=245$) (67 patients were included in both groups). To determine allograft survival rates, data were collected on first OLTs ($n=280$) and subsequent retransplants ($n=22$) received by these patients, yielding a total of 302 analyzed transplants in 280 study patients.

Of the 280 patients analyzed, 101 patients (36%) were transplanted prior to 1994, before a standard system for listing pretransplant and posttransplant oncologic diagnoses was routinely utilized in the database. For these 101 patients, there was an overall treatment diagnosis listed as “cholangiocarcinoma,” but knowledge of the presence of cholangiocarcinoma prior to transplant vs. incidentally found cholangiocarcinoma could not be confirmed. The remaining 179 patients (64%), transplanted after 1993, had clearly defined listing diagnoses in the UNOS database and, therefore, the analyses concerning indication for transplant were limited to these patients.

Examined study variables included recipient age, race, gender, indication for transplant, pretransplant clinical status, ABO blood group, allograft type, date of transplant, patient and allograft survivals, and cause of allograft failure or death (cancer-related vs. other cause). Kaplan–Meier curves were used to calculate survivals and log-rank tests were used to determine the influence of study variables on outcomes. A p value <0.05 was considered statistically significant.

Results

Demographics

Of the 280 patients who underwent liver transplantation for cholangiocarcinoma between April 1987 and December

2005, 64.3% were male. The most common race was Caucasian (86.8%), followed by African-American (4.6%) and Asian (2.2%). The median age of recipients was 48 years (range: 18–73 years). The recipient ABO blood group distribution was as follows: O, 128 patients; A, 107 patients; B, 37 patients; and AB, 8 patients.

Preoperative Status/Allograft Type

The median waitlist time for first-transplant recipients was 58 days (range: 0–3,147 days). One hundred and seventy-seven patients were transplanted before the model for end-stage liver disease (MELD) score was utilized for waitlist ranking. For the remaining 103 patients, the median lab MELD score was 14 (range: 6–47). At transplant, 35 patients (12.5%) were listed as status 1. One-hundred and four patients (37%) were hospitalized immediately prior to transplant. Of these patients, 37 were in the intensive care unit and 14 patients were requiring ventilator support. At time of transplant, the median serum creatinine was 0.9 mg/dL (range: 0.1–13 mg/dL), the median serum total bilirubin was 2.6 mg/dL (range: 0.2–53.7 mg/dL), and the median serum alanine aminotransferase was 70.5 U/L (range: 2–7,891 U/L). Two-hundred fifty-four recipients (91%) received whole cadaveric allografts, 21 patients (7%) received allografts from living donors, and 5 patients (2%) received reduced or split cadaveric allografts.

Indication for OLT

One hundred and two of the 179 patients (57%) with complete pretransplant oncologic diagnosis data had a pre-OLT listing diagnosis of cholangiocarcinoma. For 38 of these 102 patients with known cholangiocarcinoma, PSC was listed as a concomitant pre-OLT diagnosis. The remaining 64 patients with known pre-OLT cholangiocarcinoma were not reported to have PSC. Seventy-seven patients (43%) transplanted after 1993 had an incidental diagnosis of cholangiocarcinoma at the time of transplantation. The indications for OLT in these patients included PSC with liver failure in 31 (40%), other malignancy in 8 (11%), and nonmalignant, non-PSC-related liver failure in 38 (49%).

Patient Survivals

Twelve patients died within 30 days of primary transplant, yielding a 30-day mortality rate of 4.0%. At a median patient follow-up interval of 452 days (range: 0–6,166 days), 1- and 5-year patient survivals for all 280 study patients were 74% and 38%, respectively. There were 49 actual 5-year survivors and 21 actual 10-year survivors.

Patient Survivals: Impact of Demographic and Clinical Variables

Age, race, gender, and blood group had no impact on patient survivals. Allograft type and status 1 listing also had no impact on survivals. Clinical variables that were significant predictors of worse survival included inpatient hospitalization prior to transplant ($p=0.006$), ICU admission prior to transplant ($p<0.001$), serum creatinine ≥ 1.5 mg/dL ($p<0.001$), and serum bilirubin ≥ 2.0 mg/dL ($p=0.015$) (Table 1).

Patient Survivals Stratified by Indication

When stratified by indication for transplant, there were differences in patient survival. Those patients transplanted prior to 1994, without specific oncologic listing diagnoses in the database, had 1- and 5-year survivals of 67 and 30%, respectively. Patients transplanted from 1994 to 2005 with a listing diagnosis of cholangiocarcinoma in the setting of PSC had 1- and 5-year survivals of 90 and 79%, respectively. Patients with known cholangiocarcinoma in the absence of PSC had 1- and 5-year survivals of 90 and

64%, respectively. Those with known PSC but an incidental finding of cholangiocarcinoma had 1- and 5-year survivals of 79 and 18%, respectively, and those with no known PSC or cholangiocarcinoma at listing had 1- and 5-year survivals of 82 and 30%, respectively.

Patients could therefore be stratified into a historical group, transplanted prior to 1994 with cholangiocarcinoma listed as the overall diagnosis ($n=101$), those transplanted from 1994 to 2005 with known cholangiocarcinoma ($n=102$), and those transplanted from 1994 to 2005 with an incidental diagnosis of cholangiocarcinoma ($n=77$). When comparing survivals between these groups, the historic group and the incidental cholangiocarcinoma group had similar 5-year survivals (30 vs. 20%, respectively, $p=0.646$). However, patients with known cholangiocarcinoma prior to OLT experienced an improved 5-year survival rate of 68% (compared with historic survivals, $p<0.001$; compared with incidental diagnosis, $p<0.001$) (Fig. 1).

Patient Survivals Stratified by PSC Status

Of the 179 patients with a defined listing diagnosis, 69 (39%) patients were listed with a diagnosis of PSC. The 5-

Table 1 Posttransplant Survival Analysis Stratified by Study Variables

Variable	Strata	N	5-year OS	<i>p</i> Value	
Age	<50 years	145 (52%)	42%	0.280	
	≥ 50 years	135 (48%)	34%		
Sex	Male	178 (64%)	36%	0.213	
	Female	102 (36%)	44%		
Race	Caucasian	243 (87%)	37%	0.365	
	Other	37 (13%)	56%		
	Black	13 (5%)	69%		0.339
	Other	267 (95%)	37%		
Blood group	O	128 (46%)	46%	0.189	
	A	107 (38%)	31%		
	B	37 (13%)	40%		
	AB	8 (3%)	30%		
Status 1	Yes	35 (13%)	37%	0.929	
	No	245 (87%)	39%		
Pre-OLT location	Home	176 (63%)	45%	0.006	
	Hospital	104 (37%)	29%		
	ICU	37 (13%)	13%		<0.001
	Other	243 (87%)	43%		
Allograft type	Cadaveric whole	254 (91%)	49% (3 year)	0.866	
	Living donor	21 (8%)	58% (3 year)		
	Cadaveric split	5 (2%)	36% (3 year)		
Serum ALT	<200 U/L	166 (59%)	37%	0.281	
	≥ 200 U/L	54 (19%)	36%		
Serum creatinine	<1.5 mg/dL	239 (85%)	42%	<0.001	
	≥ 1.5 mg/dL	38 (14%)	20%		
Serum bilirubin	<2.0 mg/dL	119 (43%)	44%	0.015	
	≥ 2.0 mg/dL	149 (53%)	35%		
MELD score	<15	55 (20%)	85% (2 year)	0.081	
	≥ 15	48 (17%)	65% (2 year)		

Bold *p* values indicate statistical significance.
 N = number of patients, OS = overall survival, ICU = intensive care unit, ALT = alanine aminotransferase

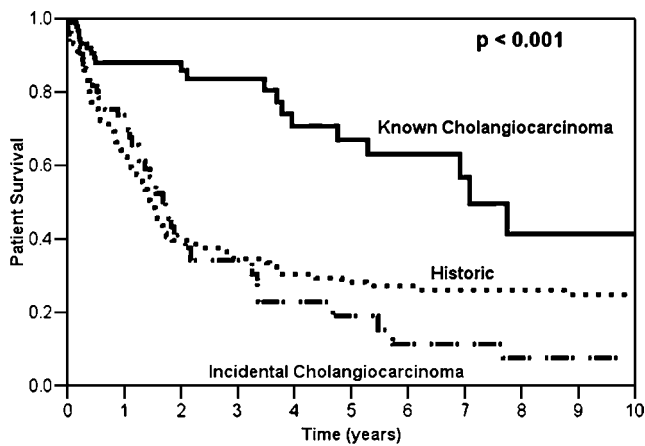


Figure 1 Patient survivals stratified by indication for liver transplantation. One hundred one patients transplanted prior to 1994 with no oncologic listing data in the UNOS database (“historic”) are represented by the *dotted line*. The 102 patients with a known diagnosis of cholangiocarcinoma are represented by the *solid line*, and the 77 patients with incidental cholangiocarcinoma transplanted from 1994 to 2005 are represented by the *dotted-dashed line*.

year survival rate in patients with PSC was 41%, compared to 50% in patients without PSC ($p=0.402$).

Patient Survivals Stratified by Cause of Death

Of the 128 patients who died more than 30 days post-OLT, the cause of death was known in 114 of these 128 cases (89%). Of these, 55 patients died from locally recurrent (19 patients) or metastatic disease (36 patients), 24 patients died from infection, 13 patients died from allograft failure, and 22 patients died from other causes. Patients who died from recurrent disease had 1- and 5-year survival rates of 76 and 17%, respectively, with a median survival of 601 days compared with 1-year, 5-year, and median survivals of 44%, 3%, and 322 days for those who died from non-cancer causes ($p<0.005$) (Fig. 2).

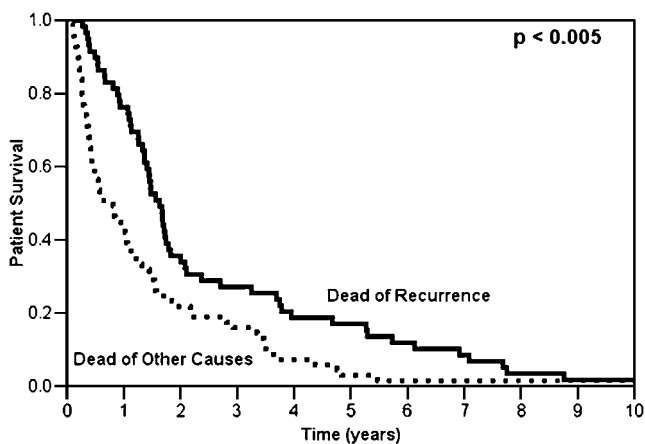


Figure 2 Patient survivals stratified by cause of death. Patients who died from cholangiocarcinoma local and/or distant recurrence are represented by the *solid line*, those who died from other causes are represented by the *dotted line*.

Patient Survival after Retransplant

Twenty patients underwent one retransplant after their initial transplant for cholangiocarcinoma, and two patients were transplanted a third time. Two patients died within 30 days of retransplant. Median survival after retransplant was 479 days. One- and 3-year patient survivals after retransplant were 50 and 37%, respectively. Comparing patient outcomes for those requiring retransplant (median survival: 595 days) to those not requiring retransplant (median survival: 1,069), overall survivals were statistically similar ($p=0.407$).

Era of Transplantation

For the 101 UNOS-listed patients transplanted prior to 1994, the 5-year survival rate was 30% and the median survival time was 587 days. For the 179 patients with complete diagnostic data for cholangiocarcinoma transplanted between 1995 and 2005, the 5-year survival rate was 45% and the median survival time was 1,413 days ($p<0.01$) (Fig. 3). Dividing this group by era (1994–2000 vs. 2001–2005), no survival improvement was observed. The 66 patients transplanted from 1994–2000 experienced a 3-year survival rate of 58% and the median survival time was 1,367 days. The 3-year and median survivals for the 113 patients transplanted from 2001–2005 were 60% and 1,242 days, respectively ($p=0.569$).

Allograft Survivals

At a median graft follow-up interval of 390 days (range: 0–6,166 days), 1- and 5-year allograft survivals were 69 and 36%, respectively. Twenty patients required retransplant, including two patients who received a third allograft. Time to first retransplant ranged from 4 to 2,673 days, with a

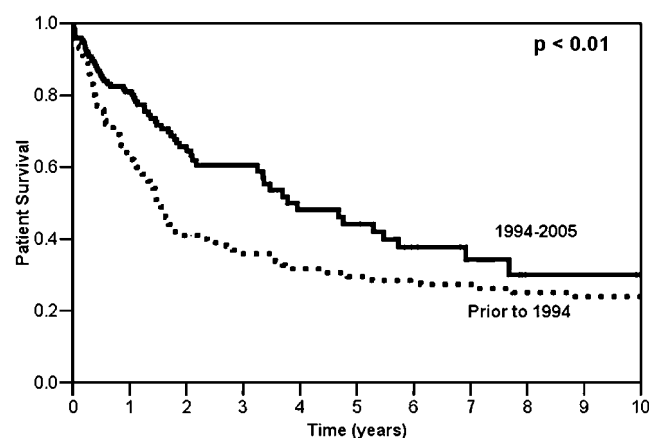


Figure 3 Patient survivals stratified by those transplanted from 1994 to 2005 ($n=179$, *solid line*), compared to those transplanted prior to 1994 ($n=101$, *dotted line*).

median of 44 days. The indication for retransplant was available in 9 of these 22 cases. Vascular thrombosis was the cause of allograft failure in six cases, whereas primary nonfunction was the cause in three cases, one of which was a second retransplant.

Discussion

Cholangiocarcinoma presents significant challenges to the hepatobiliary surgeon, the medical oncologist, and the radiation oncologist. The disease is often diagnosed at a stage or in a location that precludes complete resection. In addition, concomitant PSC is often considered a contraindication to resection due to the high likelihood of multifocal disease, clinically significant underlying liver dysfunction, and the high risk of recurrence following resection.² Based on these factors, liver transplantation has been used to treat patients with local disease.

Recent single-center studies have reported favorable outcomes in selected patients with hilar cholangiocarcinoma. The largest such series is from the Mayo Clinic.⁸ Eligibility for their protocol is limited to patients with unresectable hilar cholangiocarcinoma or hilar cholangiocarcinoma in the setting of PSC. Operative exploration was used to rigorously confirm that patients were stage I or II, without nodal or other metastases, prior to OLT. The treatment included neoadjuvant chemoradiotherapy followed by a staging laparotomy in all patients. Of the 106 patients initially enrolled to this protocol, 11 patients died or had evidence of disease spread before neoadjuvant treatment was completed, and one was transplanted elsewhere. An additional 18 patients experienced disease progression diagnosed at laparotomy and were, therefore, excluded from the study. Of the remaining 87 patients, 65 transplants have been reported to date. In these 65 patients, 1- and 5-year survivals were 91 and 76%, respectively, with a median follow up interval of 18 months.⁸

In addition to the Mayo Clinic experience, there are two registry-based reports that have examined outcomes in patients transplanted for cholangiocarcinoma. In 2000, Pascher et al. reported on patients treated with OLT for cholangiocarcinoma recorded in the European Liver Transplant Registry and found a 5-year patient survival of 29%.¹⁴ Likewise, a report from the Cincinnati Transplant Registry of 207 patients with cholangiocarcinoma who received liver transplants between 1968 and 1997 found a 5-year patient survival of 23%.¹⁵ Since this report, there have been no US-based multicenter studies that have assessed more recent outcomes data.

Our analysis of 280 patients identified an overall 5-year patient survival of 38%, and a 60% 3-year survival rate in patients transplanted after 2000. In addition, 21 patients had

actual survivals of greater than 10 years. The apparent improvement in overall outcomes over time may be related to several factors. These factors include improved staging, improved patient selection, and possibly more effective adjuvant therapies. With regard to staging, several groups have reported that nodal or other extrahepatic involvement and/or advanced disease stage (stage III or IV) are independent predictors of adverse outcomes following OLT.^{8,16,17} Likewise, the favorable outcomes reported by the Mayo Clinic reflect the strict inclusion of patients with early-stage disease.^{12,13,18} Combined, these findings support the use of a multimodality oncologic approach to patients with early-stage (stage I or II), but unresectable, cholangiocarcinoma that includes liver transplantation as part of a protocol-based treatment plan.

For the more recent cohort, who had complete data regarding the setting and timing of the cholangiocarcinoma diagnosis, several important clinical observations were made. Patients who were incidentally found to have cholangiocarcinoma had a significantly worse prognosis following transplant. The 5-year survival rate for patients with known cholangiocarcinoma was 68%, and the median survival time was not reached. In contrast, patients with incidental cholangiocarcinoma found in the explanted liver experienced 5-year survivals of only 20%, with a median survival time of only 640 days.

The prognostic value of the timing of cholangiocarcinoma diagnosis (pre-OLT vs. incidental at the time of OLT) was stronger than the presence or absence of PSC. Patients with PSC and known cholangiocarcinoma experienced higher survival rates compared to PSC patients with incidentally found cholangiocarcinoma. Likewise, patients without PSC were more likely to survive if their cholangiocarcinoma was identified prior to OLT.

The prognostic impact of cholangiocarcinoma developing in the setting of PSC is controversial. In this clinical situation, cholangiocarcinoma may be difficult to diagnose and is often an incidental finding during transplantation.¹⁹ A review of the Canadian experience with incidental cholangiocarcinoma reported good short-term survivals, but this benefit was lost after the second year post-transplant.²⁰ Other single-center studies have found no difference in prognosis.^{8,15,18}

These observations can be explained in several ways. First, independent of PSC status, patients with known cholangiocarcinoma may undergo additional staging studies to confirm the absence of metastases prior to OLT listing (i.e., selection bias). Patients with incidental cholangiocarcinoma may harbor undetected distant disease, have a higher stage at the time of transplant, and have a concomitant poorer prognosis. Second, only the patients with known cholangiocarcinoma can benefit from pre-OLT cancer therapies. The UNOS/OPTN database does not record the

presence or absence of pre-OLT chemoradiotherapy for cholangiocarcinoma, so direct evidence of its efficacy cannot be determined from this analysis.

Conclusions

This multi-institutional analysis of the US experience with liver transplantation for cholangiocarcinoma determined that outcomes following OLT for cholangiocarcinoma have improved over time with a 5-year survival rate of 45% during the most recent era of transplantation. Compared to outcomes in similar patients treated with medical therapy alone, patients with known cholangiocarcinoma that presents at an early, but unresectable, stage appear to benefit from OLT. However, patients incidentally found to have cholangiocarcinoma at the time of transplant, independent of the presence or absence of PSC, have a poorer prognosis.

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