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ORIGINAL ARTICLE

Improved Post-Transplant Survival in the United States for Patients with Cholangiocarcinoma After 2000

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Abstract
Background The incidence of cholangiocarcinoma (CCA) continues to rise. Orthotopic liver transplantation (OLT) can be used for selected patients with localized but unresectable hilar CCA. Although initial post-OLT survival rates were poor, outcomes after introduction of the Mayo Clinic protocol have been more promising and there has been increased interest in OLT for CCA nationally.
Aims The aim of this study is to determine post-transplant survival and prognostic factors for patients undergoing OLT for CCA.
Methods A retrospective analysis of all patients with CCA listed nationwide for OLT between October 1987 and May 2008 was performed using the Scientific Registry of Transplant Recipients database. Survival curves were generated using the Kaplan–Meier method and compared using log-rank test.
Results Of 595 patients with CCA listed for OLT, 359 (60.3 %) underwent OLT. Median age at OLT was 49 years, 66 % were male and 91 % were Caucasian. The median follow-up time was 2 years. There has been an increasing number of liver transplants performed for CCA since 2000. The 1- and 5-year probability of survival was 85.8 and 51.4 %, respectively. On multivariate analysis, significant prognostic factors for decreased post-OLT survival included transplant before 2000 (HR 11.25, 95 % CI 1.28–98.7) and acute cellular rejection (HR 5.64, 95 % CI 1.14–27.8).
Conclusions Survival after transplant for CCA has improved over time, and OLT is being used more frequently in the treatment of CCA. Significant predictors of post-OLT survival include a history of acute rejection and date of transplant in relation to the publication of Mayo protocol results.

Keywords Cholangiocarcinoma · Liver transplant · Outcomes · Survival

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Introduction

Cholangiocarcinoma (CCA), the second most common primary hepatic malignancy, accounts for 3 % of all gastrointestinal cancers and has an increasing incidence worldwide [1–3]. Several prognostic factors have been reported, including stage of disease, CA 19-9 levels, and type of treatment [4, 5]. Surgical resection has long been the mainstay of curative treatment for CCA, with 5-year survival rates of 27–48 %, but only 10–20 % of patients are candidates for resection [6–11]. Orthotopic liver transplantation (OLT) has been proposed as an alternative treatment for those patients that are deemed unresectable. OLT is able to achieve a wider excision and a more complete removal of the tumor, thereby reducing the risk of intra-operative tumor spillage. OLT is a particularly attractive option in patients with PSC or underlying liver disease as it offers a cure for both the tumor and the underlying liver disease.

The initial experience of OLT for CCA in the 1980s and early 1990s yielded dismal results, with 5-year survival rates of 5–17 % [12–14], leading many surgical centers to abandon OLT as a possible therapy for CCA [15]. In January 1993, the Mayo Clinic developed a protocol of external beam irradiation, endoluminal irradiation, chemosensitization with 5-fluorouracil, and exploratory laparotomy prior to OLT for selected patients with unresectable hilar CCA located above the cystic duct (Fig. 1) [16]. Their initial experience, published in May 2000, demonstrated a 1-year disease-free survival rate of 92 % [16]. Five-year survival rates among the 125 patients who underwent OLT for hilar CCA from 1993 to 2009 were recently reported to be 73 % [17]. These encouraging results over the past decade have revived the enthusiasm for OLT as an option for patients with hilar CCA. Although additional centers have started to perform OLT for CCA, it is unclear if these published results are generalizable or limited to the experience at the Mayo Clinic. The aims of our study were to determine 1-, 3-, and 5-year post-transplant survival rates for patients undergoing liver transplantation for hilar CCA and to identify prognostic factors affecting post-transplant survival.

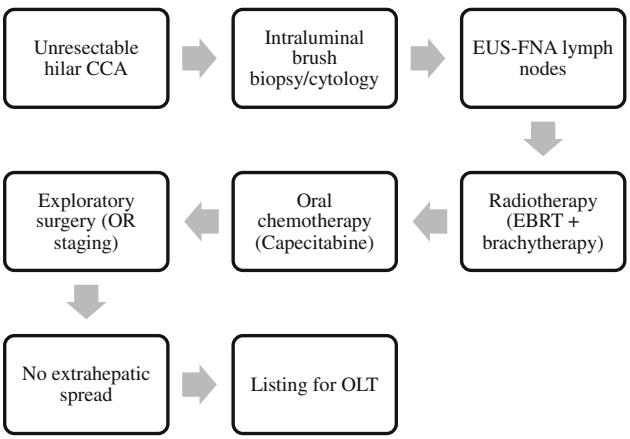

Fig. 1 Pre-transplant Mayo protocol. *EUS* endoscopic ultrasound, *FNA* fine needle aspirate, *EBRT* external beam radiation therapy (adapted from J Natl Compr Canc Netw 2009;7[4])

Methods

Patients and Study Variables

This study was performed with approval of the University of Michigan Institutional Review Board. Donor and recipient data was collected from the Scientific Registry of Transplant Recipients (SRTR) database for all adult patients, 18 years or older, with a diagnosis of hilar CCA who were listed for liver transplantation between October 1987 and May 2008. The diagnosis of hilar CCA was established by the transplant center indicating the corresponding diagnostic codes in the SRTR database at the time of listing. This nationwide registry obtains transplant-related and patient-related data from the Organ Procurement and Transplantation Network (OPTN), the United Network for Organ Sharing (UNOS), and Social Security. Individual centers report the information to the OPTN/UNOS. Social Security records are utilized to verify date of death.

Demographic information including age, race, gender, ABO blood group, and history of chronic liver disease as well as laboratory data from the time of transplant including creatinine, albumin, bilirubin, INR, MELD, and MELD exception points were recorded. The transplant variables of interest included type of transplant (cadaveric vs. living-donor), cold ischemia time, incidental versus known diagnosis of CCA, history of acute rejection, immunosuppression regimen (standard vs. nonstandard), and date of transplantation. Data regarding tumor stage at diagnosis, receipt of neo-adjuvant therapy, identification of center where the transplant was performed, and post-transplant recurrence rates were not included in the database. The patients were categorized by time period, as a pre-protocol group and post-protocol group, as patients transplanted prior to May 1, 2000 were considered to be in the pre-Mayo protocol era, and those transplanted after May 1, 2000 were considered in the post-Mayo protocol era. Although the Mayo protocol was initiated in 1993, results were first published in 2000. We chose this latter time point as we were trying to determine the impact of this publication on results nationwide.

Statistical Analysis

The demographic and laboratory data, as well as transplant characteristics were compared between patients transplanted

prior to 2000 and those transplanted after 2000. Chi-squared tests were used for categorical variables and *t* tests were used for continuous variables. Survival curves were generated using the Kaplan–Meier method and compared using log-rank test. Patients were censored at the time of death, or at the time of last data entry if they were lost to follow-up. Prognostic factors predictive of survival were identified by Cox regression analysis. A p value < 0.05 was considered statistically significant for both univariate and multivariate analyses. All analyses were performed using Stata 10.0 (College Station, TX, USA).

Results

Patient Characteristics

There were a total of 595 patients listed for a primary diagnosis of hilar CCA between October 1987 and May 2008, with 330 patients (55.5 %) undergoing transplantation. An additional 29 patients had an incidental diagnosis of CCA at the time of transplantation, and thus a total of 359 patients received a liver transplant. Eighteen patients (5 %) underwent re-transplantation—nine due to vascular thrombosis, three for primary non-function, and six for unknown causes of graft failure.

Baseline patient characteristics are shown in Table 1. The median recipient age at the time of OLT was 49 years (range 18–71). More than 90 % of patients were Caucasian and 66 % were male. One hundred twenty-one patients (34 %) had underlying chronic liver disease, with 84 (23 %) having a history of PSC. The median bilirubin at the time of transplant was 2.1 mg/dL (range 0.3–40.3 mg/dL), and the median creatinine was 0.9 mg/dL (range 0.3–4.2 mg/dL). One hundred sixty-four patients (46 %) were transplanted before the model for end-stage liver disease (MELD) score was implemented in February 2002. The remaining 195 patients had a median lab MELD score of 12 (range 6–40), with 79 (41 %) reporting MELD exception points after listing for OLT.

There were 150 patients transplanted for CCA prior to May 2000 (pre-protocol group), and 209 patients underwent OLT between May 2000 and May 2008 (post-protocol group). Patients in the post-protocol group were older (median 52 vs. 46 years, $p < 0.01$) and more likely to be male (71 vs. 59 %, $p = 0.02$). There were similar rates of underlying liver disease ($p = 0.72$) and PSC ($p = 0.14$) between the two groups. The post-protocol group had a higher rate of nonstandard immunosuppression (42 vs. 4 %, $p = 0.01$) and higher rates of acute rejection (4.3 vs. 0 %, $p = 0.16$). Three hundred nineteen recipients (88 %) received whole cadaveric allografts, 40 (11 %) received allografts from living donors, and five patients (1 %) received split cadaveric allografts. All of the living donor transplantations occurred in the post-protocol group. Recipient laboratory values at the time of transplantation

Table 1 Characteristics of patients undergoing OLT for CCA

Variable	All patients (1987–2008) $N = 359$	Pre-Mayo (1987–2000) $N = 150$	Post-Mayo (2000–2008) $N = 209$	p value
Age	49 (18–71)	46	52	<0.01
Gender (% male)	66 %	59 %	71 %	0.02
Race (% Caucasian)	91 %	93 %	90 %	0.33
Underlying chronic liver disease	121 (34 %)	49 (33 %)	72 (34 %)	0.72
PSC	84 (23 %)	41 (27 %)	43 (21 %)	0.14
Cold ischemia time (h)	7.24	8.8	6.7	<0.01
Acute graft rejection	9 (2.5 %)	0	9 (4.3 %)	0.16
Non-standard immunosuppression	94 (26 %)	6 (4 %)	88 (42 %)	0.01
Laboratory MELD[a,b]	12	a	12	b
MELD exception	79 (22 %)	0	79 (38 %)	<0.01
Living donor transplants	40 (11 %)	0	40 (19 %)	<0.01
Creatinine (mg/dL)	0.9 (0.1–4.4)	0.9 (0.1–4.4)	0.9 (0.3–4.2)	0.69
INR	1.2 (0.8–13.7)	b	1.2	b
Albumin (g/dL)	3.3 (1.1–5.1)	3.4 (1.9–5.0)	3.3 (1.1–5.1)	0.15
Total bilirubin (mg/dL)	2.2 (0.2–50)	2.8 (0.2–46.3)	2.1 (0.3–50)	0.12

All values are medians unless otherwise specified

[a] Not applicable; MELD score implementation started in 2002

[b] Insufficient data

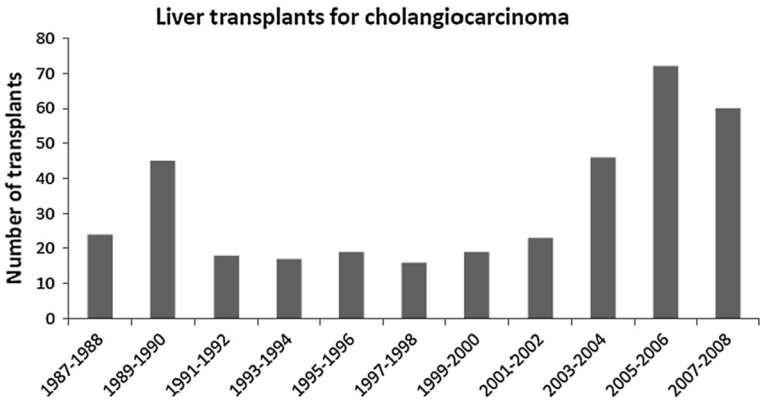

Fig. 2 Liver transplants performed for cholangiocarcinoma (CCA) (October 1987 to May 2008)

including creatinine, albumin, and total bilirubin were similar between the two groups (Table 1).

Transplants for Cholangiocarcinoma by Year

Over this 21-year time period, there were a varying number of transplants performed annually for a diagnosis of hilar CCA. Figure 2 reflects the initial interest in performing OLT for CCA, with approximately 10–20 transplantations per year between 1987 and 1990. Over the following decade in the 1990s, there was a significant decrease in the number of transplants, likely related to poor initial outcomes. During this time period there were less than ten transplants per year. Beginning in 2001, shortly after the initial results of the Mayo protocol were published in May 2000, there was a resurgence in the number of annual transplants being performed for CCA.

Survival and Prognostic Factors

The median post-transplant follow-up time for all 359 patients who underwent OLT for hilar CCA was 2.0 years (range 0.2–20.9 years). Overall survival of patients is depicted in Fig. 3. For all 359 patients who underwent OLT for a diagnosis of hilar CCA, the median post-transplant survival was 5.4 years (range 0.2–20.9 years), with 1-, 3-, and 5-year survival rates of 85.8, 63.5, and 51.4 %, respectively. A total of 14 (3.9 %) patients were lost to follow-up.

On univariate analysis, significant predictors of post-transplant survival were pre-transplant bilirubin levels ($p = 0.01$), incidental tumor found at the time of transplant ($p < 0.01$), transplant before the year 2000 ($p < 0.01$), graft rejection ($p < 0.01$), and use of standard immunosuppression ($p < 0.01$). Other variables that were included in the analysis but were not statistically significant included age, race, gender, candidate body mass index, MELD exception, Child-Turcotte-Pugh score, donor death mechanism, cold ischemia time, history of chronic liver disease, type of transplant (cadaveric vs. living-donor), and pre-transplant candidate albumin, INR, and creatinine ($p > 0.05$ for all these variables). There was no difference in survival between transplant regions ($p = 0.40$). On multivariate analysis, significant prognostic factors for worse post-OLT survival included undergoing liver transplantation before May 2000 (HR 11.25, 95 % CI 1.28–98.7) and having acute cellular rejection (HR 5.64, 95 % CI 1.14–27.8; Table 2).

The use of neoadjuvant chemoradiation has been shown to be associated with improved post-transplant outcomes for patients with CCA; however, these data are unfortunately not available in the SRTR database [18]. We performed a subset analysis on patients who received MELD exception points, as these were potentially the patients who received neoadjuvant therapy. Patients who received MELD exception points had 1- and 3-year survival rates of 89 and 74 %, respectively, compared to 82 and 56 % for those without MELD exception points ($p = 0.01$).

Prior to publication of the Mayo results in May 2000, the median survival was 3.3 years (range 0.2–20.9 years), compared to 7.8 years (range 0.03–8.2 years) after May 2000 ($p < 0.01$). Prior to May 2000, the 1-, 3-, and 5-year probabilities of survival were 82.0, 52.0, and 43.6 % respectively. After May 2000, the 1-, 3-, and 5-year probabilities of survival were 88.6, 74.2, and 58.7 % respectively (Fig. 4).

Discussion

The introduction of the Mayo protocol in 2000 demonstrated that good long-term survival was possible with liver transplantation for CCA. As the interest in liver transplantation for CCA is growing in other centers, it is increasingly important to know if these outcomes are generalizable. Our study intended to determine if the results by the Mayo clinic are being replicated in other centers. Although we found that patients who underwent

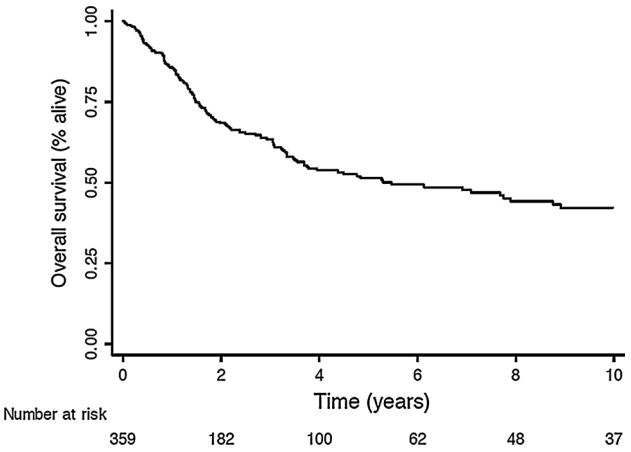

Fig. 3 Overall survival post-OLT for 359 patients undergoing transplantation for cholangiocarcinoma (CCA) between 1987 and 2008. Overall 5-year survival was 51.4 % and median survival 5.4 years

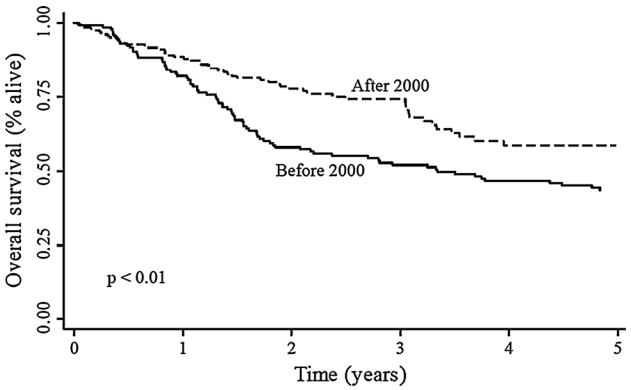

Fig. 4 Comparison of post-transplant survival pre- and post-2000. There were 150 transplants before publication of the Mayo protocol results, and 209 transplants performed after publication in 2000. One-year survival was 82.0 and 88.6 %, respectively. Three-year survival was 52 and 74.2 %, and 5-year survival was 43.6 and 58.7 %, respectively ($p < 0.01$)

liver transplantation after publication of the Mayo protocol results had significantly better survival than those transplanted earlier, with 5-year survival rates improving from 44 to 59 % ($p < 0.01$), this is lower than the 5-year survival rate reported by the Mayo clinic of 73 %. This difference in survival is potentially due to our study accounting for multi-center data and variability in the pre-transplant protocol utilized at each center.

While this improved survival is likely due largely to the implementation of the Mayo Clinic protocol, patient selection likely also has an impact on improving survival. Our results show that the group of patients transplanted after 2000 were slightly older in age, more likely to be male, and beginning in 2003 they qualified for MELD exception points, thus decreasing the waitlist times for these patients prior to receiving a donor organ. Other factors that may have improved outcomes over time include improved tumor staging accuracy based on advances in radiographic and endoscopic tools, advances in surgical technique and other peri-operative factors. Our analysis also shows that worse outcomes were associated with a history of graft rejection. It is unclear, however, if this is due to the malignancy itself or if this is secondary to other transplant-related factors. Improvements in immunosuppressive regimens and standardization over time of post-transplant regimens may be in part responsible for improved outcomes.

There have been two prior registry-based studies that have reported post-OLT outcomes for patients with CCA. In a study using the Cincinnati Transplant Registry, the 5-year post-transplant survival was 23 % among 207 CCA patients transplanted worldwide between 1968 and 1997. Notably, this study showed that 51 % of patients had disease recurrence after transplantation, with a median time to recurrence of 9.7 months. The primary factors associated with tumor recurrence and mortality included positive surgical margins and advanced tumor stage [19]. Another study by Becker and colleagues using the UNOS/OPTN patient database reported on outcomes of 280 recipients of liver transplants for CCA between 1987 and 2005. Their results included an overall 1- and 5-year patient survival of 74 and 38 %, respectively. In this study, significant

Table 2 Prognostic factors for post-OLT survival for cholangiocarcinoma (CCA)

Variable	Univariate analysis[a]		Multivariate analysis	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Pre-transplant bilirubin (continuous)	HR 1.02 (1.01–1.05)	0.01	0.97 (0.90–1.05)	0.49
Incidental tumor at time of transplantation	HR 3.24 (1.89–5.55)	<0.01	2.21 (0.71–6.87)	0.17
Standard immunosuppression	HR 0.26 (0.15–0.44)	<0.01	0.40 (0.15–1.08)	0.07
Date of transplant (pre-2000)	HR 0.59 (0.42–0.83)	<0.01	11.25 (1.28–98.7)	0.03
History of graft rejection	HR 8.92 (3.38–23.5)	<0.01	5.64 (1.14–27.8)	0.03

[a] Additional variables included in univariate analysis: age, race, gender, ABO blood group, BMI, candidate's medical condition and functional status, MELD exception, CTP score, donor death mechanism, cold ischemia time, chronic liver disease, type of transplant, pre-transplant sodium, albumin, INR, and creatinine

predictors of decreased survival included incidental diagnosis of CCA at the time of transplant as well as transplantation prior to 1994 [20]. On multivariate analysis our study did not find the incidental diagnosis of CCA to be an independent predictor of survival. One explanation is that these patients likely had underlying chronic liver disease and thus likely were diagnosed with early-stage CCA. In our study, the number of patients with an incidental diagnosis of CCA was lower than that in the Becker study. In our study the date of transplantation relative to the initial publication of the Mayo protocol results and a history of graft rejection were significant predictors.

There is no center-specific data available in this database, and therefore we could not determine which transplants were performed at the Mayo Clinic versus other centers. However, our analysis by region shows that there was no significant difference in survival by region.

Although our data suggest that post-transplant survival for CCA is improving after publication of the Mayo protocol, resection still plays a central role in the management of CCA. Surgical resection has comparable 5-year survival rates to OLT and should be regarded as the treatment of choice in patients who are deemed good resection candidates [6–8].

Our study has a number of limitations based on the information recorded by the SRTR. First, our study only establishes an association between publication of the Mayo protocol and improved post-transplant outcomes. Given the retrospective nature, we are unable to comment on causality. Furthermore, the SRTR database does not include tumor data such as specific modalities used to diagnose CCA, staging information including lymph node status, or specific details regarding pre-transplant therapy to confirm which neoadjuvant chemoradiotherapy protocol was implemented. Our analysis was also limited by the presence of missing data and unmeasured confounders. For example, we were also unable to determine impact of other possible prognostic variables such as history of cholecystectomy, CA 19-9 levels, waiting time, and histologic features from the explant. Several of these factors were previously shown in a study by the Mayo clinic to be significant predictors of tumor recurrence [21]. Similarly, the incidence of acute rejection in our study is lower than those previously reported, which may be related to underreporting and subsequent missing data. Furthermore, details regarding some data from SRTR are unfortunately not available, such as the differences between standard and non-standard immunosuppression. Finally, we were unable to quantify rates of tumor recurrence and its role in post-transplant survival. Our study's strengths include the nationwide data with a large sample size and many variables to evaluate for predictors of long-term survival.

In conclusion, our nationwide database study shows that for selected patients with hilar CCA, liver transplantation can have a favorable outcome. Over time, graft survival rates have improved, with an overall 5-year survival rate of 51.4 % for all patients transplanted between 1987 and 2008. Moreover, survival has significantly improved since the Mayo protocol was published, with a 5-year survival rate of 58.7 % since 2000. This data suggests that highly selected patients with unresectable early stage hilar CCA may benefit from OLT, with notably improved outcomes and renewed interest in OLT over the past decade.

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Conflict of interest None.

References

1. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis*. 2004;24:115–125.
2. Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol*. 2004;40:472–477.
3. Taylor-Robinson SD, Toledano MB, Arora S, et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998. *Gut*. 2001;48:816–820.
4. Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut*. 1996;38:610–615.
5. Singal AG, Rakoski MO, Salgia RJ, et al. The clinical presentation and prognostic factors for intrahepatic and extrahepatic cholangiocarcinoma in a tertiary care centre. *Aliment Pharmacol Ther*. 2010;31:625–633.
6. Ahrendt SA, Cameron JL, Pitt HA. Current management of patients with perihilar cholangiocarcinoma. *Adv Surg*. 1996;30:427–452.
7. Madariaga JR, Iwatsuki S, Todo S, Lee RG, Irish W, Starzl TE. Liver resection for hilar and peripheral cholangiocarcinomas: a study of 62 cases. *Ann Surg*. 1998;227:70–79.
8. Malhi H, Gores GJ. Review article: the modern diagnosis and therapy of cholangiocarcinoma. *Aliment Pharmacol Ther*. 2006;23:1287–1296.
9. Guthrie CM, Haddock G, De Beaux AC, Garden OJ, Carter DC. Changing trends in the management of extrahepatic cholangiocarcinoma. *Br J Surg*. 1993;80:1434–1439.
10. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg*. 1992;215:31–38.
11. Tan JC, Coburn NG, Baxter NN, Kiss A, Law CH. Surgical management of intrahepatic cholangiocarcinoma—a population-based study. *Ann Surg Oncol*. 2008;15:600–608.
12. Grossman EJ, Millis JM. Liver transplantation for non-hepatocellular carcinoma malignancy: indications, limitations, and analysis of the current literature. *Liver Transpl*. 2010;16:930–942.
13. Castaldo ET, Pinson CW. Liver transplantation for non-hepatocellular carcinoma malignancy. *HPB (Oxf)*. 2007;9:98–103.

14. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery*. 1991;110:726–735.
15. Singal A, Welling TH, Marrero JA. Role of liver transplantation in the treatment of cholangiocarcinoma. *Expert Rev Anticancer Ther*. 2009;9:491–502.
16. De Vreede I, Steers JL, Burch PA, et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. *Liver Transpl*. 2000;6:309–316.
17. Gores GJ, Heimbach JK, Rosen CB. Liver transplantation for non-hepatocellular carcinoma malignancies. *Liver Transpl*. 2010; 16:S22–S25.
18. Murad D, Kim WR, Harnois DM, et al. Effects of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology*. 2012;143:88–98.
19. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation*. 2000;69:1633–1637.
20. Becker NS, Rodriguez JA, Barshes NR, O'Mahony CA, Goss JA, Aloia TA. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. *J Gastrointest Surg*. 2008;12:117–122.
21. Heimbach JK, Gores GJ, Haddock MG, et al. Predictors of disease recurrence following neoadjuvant chemotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. *Transplantation*. 2006;82:1703–1707.