

Comparative Analysis of Resection and Liver Transplantation for Intrahepatic and Hilar Cholangiocarcinoma

A 24-Year Experience in a Single Center

Johnny C. Hong, MD; Christopher M. Jones, MD; John P. Duffy, MD; Henrik Petrowsky, MD; Douglas G. Farmer, MD; Samuel French, MD, PhD; Richard Finn, MD; Francisco A. Durazo, MD; Sammy Saab, MD, MPH; Myron J. Tong, MD, PhD; Jonathan R. Hiatt, MD; Ronald W. Busuttil, MD, PhD

Objectives: To compare the survival difference between 2 surgical modalities in the treatment of locally advanced intrahepatic and hilar cholangiocarcinoma (CCA) and to identify factors that predict mortality.

Design: Retrospective study.

Setting: University transplant center.

Patients: Of the 132 patients with a diagnosis of CCA treated from February 1, 1985, through June 30, 2009, 75 had metastatic disease at presentation and were excluded from the study, whereas 57 patients were candidates for surgical therapy. Tumor type was intrahepatic in 37 patients and hilar in 20 patients. Surgical therapy included orthotopic liver transplant (OLT) in 38 patients and combined radical bile duct resection with partial hepatectomy (RR) in 19 patients.

Results: Tumors were locally advanced in 35 of 37 patients (95%) with intrahepatic tumors and 16 of 20 pa-

tients (80%) with hilar tumors. Adjunctive therapy was used in 35 patients (61%). The 5-year tumor recurrence-free patient survival was significantly higher in the OLT group compared with the RR group (33% vs 0%; $P = .05$). In the OLT group, neoadjuvant and adjuvant therapies resulted in better patient survival compared with no therapy or adjuvant therapy only (47% vs 20% vs 33%, respectively; $P = .03$). Multivariate factors predictive of worse survival outcomes included hilar CCA, multifocal tumors, perineural invasion, and RR as the treatment modality compared with OLT. Tumor sizes—5 cm or larger for intrahepatic and 3 cm or larger for hilar CCA—were not predictors of poor outcome.

Conclusion: Orthotopic liver transplant in combination with neoadjuvant and adjuvant therapies is superior to RR with adjuvant therapy in locally advanced intrahepatic and hilar CCA.

Arch Surg. 2011;146(6):683-689

Author Affiliations:

Dumont-UCLA Transplant and Liver Cancer Centers, Pflieger Liver Institute, Division of Liver and Pancreas Transplantation, Department of Surgery (Drs Hong, Jones, Duffy, Petrowsky, Farmer, Hiatt, and Busuttil), and Departments of Pathology (Dr French) and Medicine (Drs Finn, Durazo, Saab, and Tong), David Geffen School of Medicine at University of California, Los Angeles.

CHOLANGIOCARCINOMA (CCA) is a malignant neoplasm arising from epithelial cells of the extrahepatic and intrahepatic bile ducts, excluding the papilla of Vater and the gallbladder. Anatomically, CCA is classified into extrahepatic and intrahepatic types (**Figure 1**). The extrahepatic type is divided into proximal and distal subtypes. The proximal subtype, also known as *hilar*, *perihilar*, or *Klatskin tumor*, accounts for 60% to 70% of CCA, and the distal subtype, for 20% to 30%. Intrahepatic or peripheral CCA makes up the remaining 5% to 10% of the cases.

The incidence of CCA is increasing, and its prognosis remains grim.^{1,2} Early diagnosis has been a constant challenge because there is no effective screening test,

and most patients with unresectable disease die within 6 to 12 months of diagnosis. Treatment of CCA is similarly challenging because of the lack of effective adjuvant therapy, aggressive nature of the disease, and critical location of the tumor in close proximity to vital structures.

Complete extirpation of tumor including all microscopically detectable disease by R0 (complete) resection offers the only possibility of long-term survival in patients with CCA. The 5-year survival rates with negative margins approach 10% to 33%; there are no survivors with residual disease.³⁻⁹ Unfortunately, up to 50% of patients who undergo exploration with curative intent are found to have locally aggressive, unresectable tumors, and usual management is palliative despite the absence of distant metastasis at the initial presentation.

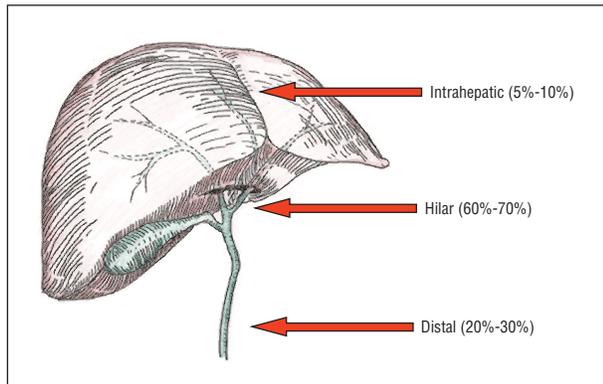


Figure 1. Distribution of intrahepatic and extrahepatic cholangiocarcinoma.

The development and evolution of liver surgery including orthotopic liver transplant (OLT) during the past 4 decades has significantly improved the surgical management of CCA. Although excellent long-term recurrence-free survival has been achieved by using a combination of neoadjuvant chemoradiotherapy and OLT in patients with small (<2 cm) hilar tumors,¹⁰⁻¹² the role of OLT for intrahepatic and locally advanced CCA remains controversial. The present study was undertaken to compare outcomes for 2 surgical modalities in the treatment of locally advanced intrahepatic and hilar CCA and to identify factors that predict mortality and recurrence.

METHODS

PATIENT SELECTION AND SURGICAL THERAPY

Using a prospectively collected database, we performed a retrospective analysis of all patients undergoing evaluation for intrahepatic and hilar CCA at the Pflieger Liver Institute, University of California, Los Angeles, from February 1, 1985, through June 30, 2009. Patients with metastatic disease at presentation were excluded from the study. For patients without tumor spread beyond the liver and bile duct, the type of surgical therapy (OLT vs combined radical bile duct resection and partial hepatectomy [RR]) was determined by the feasibility of excising the tumor with a negative margin and the adequacy of the hepatic functional reserve based on preoperative imaging studies. In the absence of gross tumor invasion of major vessels (ie, the main portal vein and hepatic artery), bilobar involvement, and chronic liver disease, partial hepatectomy was performed for intrahepatic CCA, whereas the RR procedure was the primary therapy for hilar tumors. In patients with evidence of bilobar tumor involvement or insufficient hepatic functional reserve due to underlying liver parenchymal disease or inadequate future liver remnant volume, total hepatectomy and OLT were performed for intrahepatic and hilar tumors. Patients underwent exploratory staging laparotomy when the liver allograft became available before transplantation. Tumor spread beyond the confines of the operative field for total hepatectomy and regional lymphadenectomy precluded OLT. The institutional review board of the University of California, Los Angeles, approved the study. The median follow-up time was 2.5 years. Outcomes were analyzed by the location of the tumor (intrahepatic and hilar) and type of surgical therapy (OLT vs RR).

TUMOR CHARACTERISTICS

We used the American Joint Committee on Cancer staging system¹³ to define locally advanced disease as follows: for intrahepatic CCA, a tumor size of at least 5 cm, involvement of a major branch of the portal vein or the hepatic artery or adjacent organs other than gallbladder, or metastasis to the regional lymph nodes; for hilar CCA, tumor size of at least 3 cm¹¹; invasion beyond the wall of the bile duct to the liver, gallbladder, and ipsilateral branches of the portal vein or the hepatic artery; or metastasis to the regional lymph nodes.

ADJUNCTIVE THERAPY

The administration of adjunctive therapy was based on clinical practice during the study period. Chemotherapy alone or a combination of chemotherapy and radiotherapy was given before (neoadjuvant) and/or after surgical treatment (adjuvant). A fluorouracil- or capecitabine-based regimen in combination with oxaliplatin, leucovorin calcium, and gemcitabine hydrochloride was used for adjuvant and neoadjuvant protocols.

STATISTICAL ANALYSES

Disease recurrence-free patient survival curves were computed using Kaplan-Meier methods and compared using log-rank tests. Means and medians were compared using the Wilcoxon test, and proportions were compared using the χ^2 test. Univariate and multivariate analyses were conducted using the Cox proportional hazards model. The backward stepwise procedure was used for variables selection with retention criteria at a level of significance of $P \leq .25$. In the multivariate analysis, a $P < .05$ was considered significant. Statistical analysis was performed using commercially available software (SAS, version 9.1; SAS Institute, Inc, Cary, North Carolina).

RESULTS

During the study period, 132 patients with CCA underwent evaluation. Of these, 75 were excluded from the analysis owing to the presence of metastatic disease at initial presentation, whereas 57 patients were candidates for surgical therapy and constituted the study group. The tumor type was intrahepatic in 37 patients and hilar in 20. Surgical therapy included OLT in 38 patients and RR in 19. No patient in the OLT group demonstrated clinical tumor progression beyond the liver and bile duct during staging laparotomy; thus, all 38 patients underwent OLT.

Patient characteristics are compared in **Table 1**. Age and sex were similar in all groups. For intrahepatic CCA, the OLT group included more white patients (24 [96%] vs 7 [58%]; $P = .003$) and fewer Asian American patients (1 [4%] vs 5 [42%]; $P = .003$). In the OLT group, 21 of 38 patients (55%) had cirrhosis, whereas none in the RR group had chronic liver disease. The common causes of chronic liver disease were primary sclerosing cholangitis in 14 of 21 patients (67%) and hepatitis C virus infection in 4 of 21 (19%).

Adjunctive therapy was used in 35 patients (61%) overall (Table 1). Among these patients, 11 (19%) were given neoadjuvant and adjuvant therapies, whereas 24 (42%) received adjuvant treatment only. Table 1 shows the distribution of patients who received adjunctive therapy for each tumor type and each surgical therapy. Only pa-

Table 1. Patient Characteristics^a

Characteristic	Intrahepatic Tumors (n=37)			Hilar Tumors (n=20)		
	OLT Group (n=25)	RR Group (n=12)	P Value	OLT Group (n=13)	RR Group (n=7)	P Value
Patients						
Mean age, y	50	55	.17	50	57	.13
Age ≥60 y	5 (20)	5 (42)	.17	2 (15)	3 (43)	.18
Male sex	16 (64)	7 (58)	.92	8 (62)	4 (57)	.85
Ethnicity						
White	24 (96)	7 (58)	.003	11 (85)	5 (71)	.48
Asian American	1 (4)	5 (42)	.003	1 (8)	2 (29)	.21
African American	0	0	NA	1 (8)	0	.45
Adjunctive therapy						
None	9 (36)	7 (58)	.19	6 (46)	0	.03
Neoadjuvant and adjuvant	9 (36)	0	.02	2 (15)	0	.27
Adjuvant only	7 (28)	5 (42)	.40	5 (38)	7 (100)	.02

Abbreviations: NA, not applicable; OLT, orthotopic liver transplant; RR, combined radical bile duct resection with partial hepatectomy.

^aUnless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

Table 2. Tumor Characteristics^a

Characteristic	Intrahepatic Tumors (n=37)			Hilar Tumors (n=20)		
	OLT Group (n=25)	RR Group (n=12)	P Value	OLT Group (n=13)	RR Group (n=7)	P Value
Locally advanced tumor	24 (96)	11 (92)	.58	10 (77)	6 (86)	.64
Tumor size						
Mean size, cm	6.5	5.3	.70	3.0	2.5	.77
≥3 cm (hilar) or ≥5 cm (intrahepatic)	16 (61)	9 (73)	.50	7 (50)	3 (40)	.72
Adverse tumor characteristics						
Multifocal	16 (60)	4 (36)	.19	4 (31)	1 (17)	.52
Poorly differentiated	7 (29)	1 (8)	.17	3 (20)	3 (43)	.31
Lymphovascular invasion	7 (29)	7 (55)	.15	4 (33)	4 (51)	.34
Perineural invasion	4 (15)	1 (9)	.64	4 (33)	5 (71)	.13
Periductal extension	4 (15)	0	.18	7 (56)	4 (57)	.95
Parenchymal invasion	21 (81)	4 (36)	.01	7 (56)	2 (29)	.28
Positive margin	9 (35)	2 (18)	.32	4 (33)	3 (43)	.70
Metastasis to regional lymph node	6 (22)	0	.12	6 (43)	3 (43)	>.99

Abbreviations: OLT, orthotopic liver transplant; RR, combined radical bile duct resection with partial hepatectomy.

^aUnless otherwise indicated, data are expressed as number (percentage) of patients.

tients in the OLT groups received neoadjuvant and adjuvant treatments.

Cholangiocarcinoma was histologically proved in 97% of explanted liver in the OLT group and in 100% of excised tumor in the RR group. Tumor characteristics are compared in **Table 2**. Tumors were locally advanced in 35 of 37 patients (95%) with intrahepatic tumors and 16 of 20 patients (80%) with hilar tumors. The proportion of patients with locally advanced tumors did not differ by treatment group for either tumor location: intrahepatic tumors were locally advanced in 24 of 25 patients (96%) who underwent OLT and 11 of 12 (92%) who underwent RR ($P=.58$); hilar tumors were locally advanced in 10 of 13 patients (77%) who underwent OLT and 6 of 7 (86%) who underwent RR ($P=.64$). Most adverse tumor characteristics were similar in all groups. For intrahepatic CCA, the OLT group included more-frequent tumor invasion of the liver parenchyma compared with the RR group.

The overall 5-year survivals for intrahepatic and hilar CCA after surgical therapies were 34% and 29%, respectively ($P=.43$). Overall survival curves by surgical treatment are shown in **Figure 2**. Disease recurrence-free patient survival after OLT was superior at 3 and 5 years, compared with RR (39% vs 6% and 33% vs 0%, respectively; $P=.05$). When the data were analyzed separately for locally advanced CCA by tumor location and type of surgical therapy, there was a trend toward better patient survival after OLT compared with RR for intrahepatic and hilar tumors (**Figure 3**).

Univariate analysis (**Table 3**) showed that, for RR compared with OLT, perineural invasion and multifocal tumors were significantly associated with diminished tumor recurrence-free survival. Multivariate analysis (**Table 4**) showed that statistically significant independent predictors of diminished survival included RR compared with OLT, hilar compared with intrahepatic tu-

mors, perineural invasion, and multifocal tumors. A large tumor size (≥ 5 cm for intrahepatic and ≥ 3 cm for hilar tumors) was not a predictor of patient survival.

When the data were analyzed separately to evaluate the effect of adjunctive therapy on patient survival (Figure 4), there were distinct differences in outcomes for both treatment groups. For the OLT and RR groups, patient and tumor characteristics were similar for patients who did or did not receive adjunctive therapy. In the OLT group, long-term disease recurrence-free survival was significantly higher in patients who received neoadjuvant and adjuvant therapy compared with patients who received no therapy or adjuvant therapy only (Figure 4A). Overall tumor recurrence rate for patients receiving combination neoadjuvant and adjuvant therapy was significantly lower compared with patients who received no additional therapy or adjuvant therapy only (28% vs 40% vs 50%, respectively; $P=.03$). In the RR group, for whom neoadjuvant therapy was not used, adjuvant therapy did not improve survival (Figure 4B).

COMMENT

Complete tumor resection is the only treatment that offers the possibility of long-term survival for CCA. For intrahepatic and hilar tumors with extension to the liver, innovative strategies with preoperative portal vein occlusion

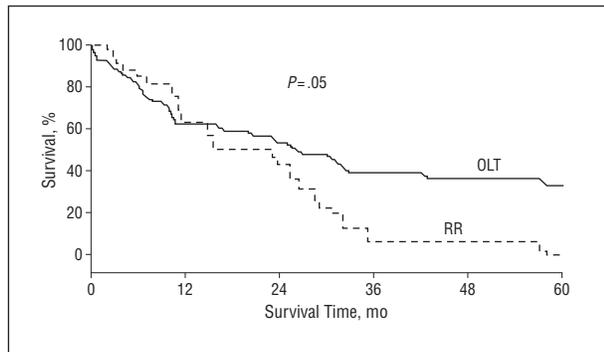


Figure 2. Kaplan-Meier overall tumor recurrence-free survival comparing orthotopic liver transplant (OLT) with combined radical bile duct resection and partial hepatectomy (RR).

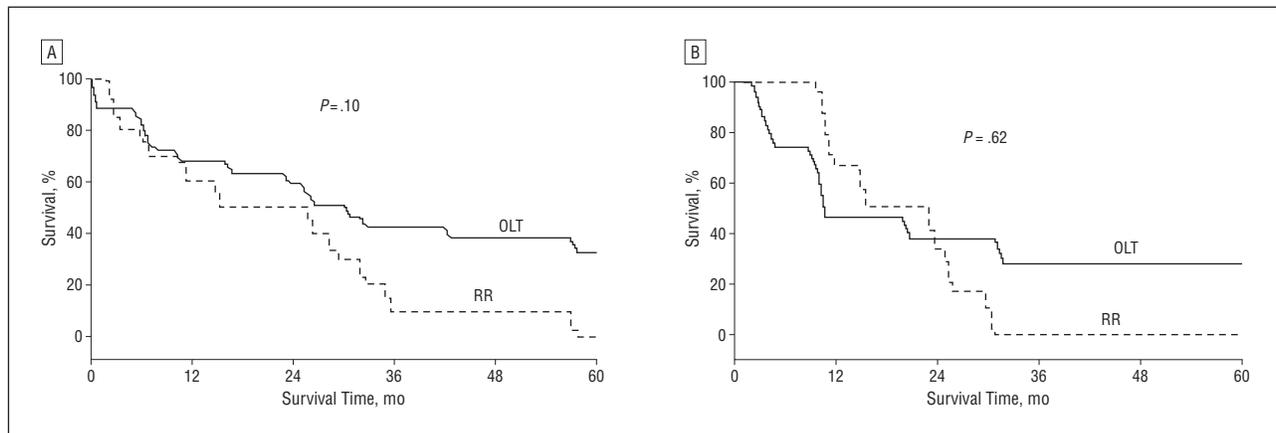


Figure 3. Kaplan-Meier disease recurrence-free survival in locally advanced cholangiocarcinoma by tumor location and operative treatment. Treatments included orthotopic liver transplant (OLT) and combined radical bile duct resection and partial hepatectomy (RR) for intrahepatic tumors (A) and hilar tumors (B).

to facilitate regeneration of the future liver remnant has allowed safer major liver resection with negative margins, improving tumor recurrence-free survival.^{14,15} For

Table 3. Univariate Analysis of Predictors of Tumor Recurrence-Free Survival

Variable	HR	P Value
Patient		
Age ≥ 60 y	1.6	.24
Surgical therapy		
RR (vs OLT)	1.9	.055
Tumor location		
Hilar (vs intrahepatic)	1.4	.32
Tumor size		
≥ 3 cm (hilar)	1.6	.45
≥ 5 cm (intrahepatic)	1.6	.28
Tumor histological features and extension		
Perineural invasion	2.6	.03
Multifocal	2.4	.008
Metastasis to regional lymph node	1.8	.20
Positive margin	1.6	.16
Lymphovascular invasion	1.2	.64
Periductal extension	1.1	.77
Poorly differentiated	1.0	.98
Hepatic invasion	0.9	.78

Abbreviations: HR, hazard ratio; OLT, orthotopic liver transplant; RR, combined radical bile duct resection with partial hepatectomy.

Table 4. Multivariate Analysis of Predictors of Tumor Recurrence-Free Survival

Variable	HR	P Value
Surgical therapy		
RR (vs OLT)	4.3	.003
Tumor location		
Hilar (vs intrahepatic)	3.2	.03
Tumor histology and extension		
Perineural invasion	5.1	.003
Multifocal	4.7	.001
Tumor size		
≥ 3 (hilar) and ≥ 5 cm (intrahepatic)	2.0	.09

Abbreviations: HR, hazard ratio; OLT, orthotopic liver transplant; RR, combined radical bile duct resection with partial hepatectomy.

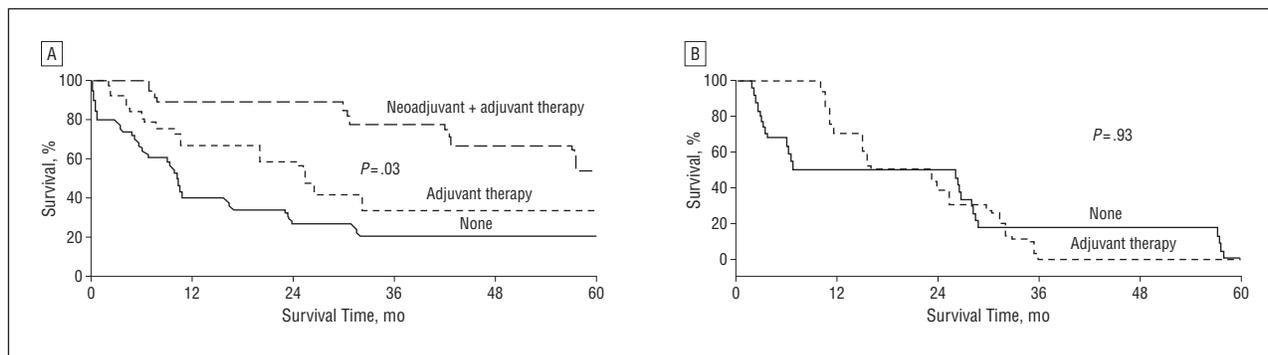


Figure 4. Effects of adjunctive therapy on recurrence-free survival in the orthotopic liver transplant group (A) and the combined radical bile duct resection and partial hepatectomy group (B).

Table 5. Outcomes After Orthotopic Liver Transplantation

Source	Study Period	No. of Patients	Adjunctive Therapy	Recurrence Rate, %	Patient Survival, %		
					2 y	3 y	5 y
Stieber et al, ¹⁹ 1989	1980-1988	10	Adjuvant	60	30
Goldstein et al, ²⁰ 1993	1984-1992	17	Adjuvant	78	21
Meyer et al, ²¹ 2000	1968-1997	207	Adjuvant	51	48	...	23
Shimoda et al, ²² 2001	1984-2000	25	Adjuvant	41	...	35	...
Sudan et al, ¹¹ 2002	1987-2000	11	Neoadjuvant	18	30
Robles et al, ²³ 2004	1988-2001	59	Adjuvant	46	42 (Intrahepatic) and 30 (hilar)
Ghali et al, ¹⁸ 2005	1996-2003	10	None	80	...	30	...
Heimbach et al, ¹² 2006	1993-2004	65	Neoadjuvant	17	76
Becker et al, ¹⁷ 2008	1987-2005	280	38
Morris-Stiff et al, ²⁴ 2008	1981-2004	13	46
Present study	1985-2009	38		41	52	38	32
			None	40	27	20	20
			Neoadjuvant + adjuvant	28	88	75	47
			Adjuvant	50	58	33	33

Abbreviation: ellipses, not reported.

hilar tumors, aggressive operative approaches, including routine partial hepatectomy, segment 1 (caudate lobe) resection, selective same-setting pancreatectomy, and portal vein resection, have been used to achieve curative resections.¹⁶ Although earlier studies on long-term survival outcomes with radical resection of early stage tumors report a 5-year survival rate of up to 34%,⁸ outcomes for tumors with aggressive features including multifocality and large tumor size (>5 cm for intrahepatic and >2 cm for hilar tumors) remain poor owing to the limitations of resection as a treatment modality in achieving clear margins.^{3,4,6,7} For tumors that are locally unresectable due to the invasion of major vessels, bilobar tumor involvement, or insufficient hepatic reserve, total hepatectomy with regional lymphadenectomy and OLT addresses all relevant resection margins and treats the underlying liver disease. However, data on outcomes after OLT are limited (**Table 5**). The present study compared the long-term survival outcomes for locally advanced intrahepatic and hilar CCA treated with OLT and RR.

Our study showed that OLT resulted in a better patient survival compared with RR for locally advanced intrahepatic CCA. When patients were stratified by tumor

location, multivariate analysis showed that hilar CCA was associated with significantly poorer survival outcomes compared with intrahepatic CCA. Although Becker et al¹⁷ used pooled data from the United Network for Organ Sharing transplant registry and reported poor outcomes after OLT for intrahepatic CCA, the analysis did not include tumor characteristics, adjuvant therapy, or pathological staging. Ghali et al¹⁸ reported a high rate of disease recurrence even in stage I and II intrahepatic tumors. Approximately 80% of the patients developed recurrence, with a 3-year survival rate of only 30% despite presumably favorable tumor characteristics such as tumor size of less than 1 cm, absence of perihepatic lymph node involvement, and well- or moderately differentiated histologic features. We found that perineural invasion and multifocal tumor were associated with disease recurrence. However, we did not find intrahepatic tumor size of at least 5 cm to be an independent predictor for diminished patient survival.

With regard to hilar tumors, excellent long-term, recurrence-free survival has been achieved using a combination of neoadjuvant chemoradiotherapy and OLT in patients with small hilar CCA.^{11,12} With the apparent benefits of chemotherapy and radiotherapy before OLT, the Mayo

Clinic group¹² developed a protocol to treat a highly select group of patients with hilar CCA by using a strict regimen of preoperative staging and neoadjuvant treatment followed by OLT; the investigators reported 1- and 5-year survival rates of 91% and 76%, respectively. In a subgroup analysis, Rea et al²⁵ also reported a higher survival outcome after OLT compared with RR. However, the excellent results from the Mayo Clinic have not been replicated by other centers, most probably because of their highly rigorous selection bias in favor of patients with biologically favorable disease. For example, only 58% of the patients had histologically proved cancer in explanted livers. Their study showed that residual tumor larger than 2 cm in the explant specimen and advanced tumor grade were associated with tumor recurrence. They also proposed that hilar CCA of at least 3 cm seen on preoperative imaging should be considered a contraindication to OLT.¹² These stringent inclusion criteria for OLT exclude patients with locally advanced tumors from a potentially curative procedure despite the absence of metastatic disease.

Currently, the role of OLT for locally advanced intrahepatic and hilar tumors remains controversial because of organ shortage, frequent disease recurrence, and the risk that immunosuppression will accelerate the progression of unidentified tumor. Our study also showed that OLT, in combination with neoadjuvant and adjuvant therapy, is superior to RR and adjuvant treatment in patients with locally advanced intrahepatic and hilar CCA. When patients in the OLT group were stratified to evaluate the effect of adjunctive therapy, long-term recurrence-free survival was significantly longer in patients who received neoadjuvant and adjuvant therapy compared with patients who received adjuvant therapy only or no adjunctive therapy. Furthermore, the 5-year disease-free patient survival of 47% in this subgroup of patients almost approaches the suggested threshold of a 50% survival rate at 5 years to justify the use of a deceased-donor organ for the treatment of a hepatic malignant neoplasm.

At our institution, we have developed a neoadjuvant treatment protocol using stereotactic body radiotherapy followed by chemotherapy for locally advanced intrahepatic and hilar CCA based on findings from the present study. Stereotactic body radiotherapy integrates tumor imaging with precision-oriented radiotherapy that allows delivery of high doses of radiation (a total of 40 Gy) in 5 treatment sessions across 7 to 12 days compared with 25 to 30 sessions using conventional methods.^{26,27} The short treatment course allows the administration of full, uncompromised doses of chemotherapy as early as 10 to 14 days from the last radiotherapy session. In addition, stereotactic body radiotherapy appears to result in less inflammatory reaction in the surrounding tissue and thus potentially allows an easier dissection of the porta hepatis compared with patients who received conventional radiotherapy. For intrahepatic CCA of larger than 6 cm, transarterial chemoembolization is given instead of stereotactic body radiotherapy.²⁸ Neoadjuvant chemotherapy includes a fluorouracil- or capecitabine-based regimen until the time of transplant.^{29,30} Other agents include oxaliplatin, leucovorin, and gemcitabine.³¹ All patients undergo surgical staging before OLT. Adjuvant chemotherapy is based on liver explant tumor biology. A pro-

spective clinical study with this treatment protocol is currently under way.

At present, the major challenge is the long interval from neoadjuvant chemoradiotherapy to OLT for these patients because of a lack of donor organs. Under the current Model for End-stage Liver Disease (MELD) organ allocation system, patients with locally aggressive unresectable intrahepatic or hilar tumors and uncompromised hepatic function rarely have a MELD score that is competitive to receive a deceased-donor organ. In addition, the United Network for Organ Sharing review board grants MELD exception points to patients with CCA only under the strict criteria proposed by the Mayo Clinic, and there is no guideline for MELD exception for intrahepatic CCA.³² With our current organ allocation system, patients with locally advanced large intrahepatic and hilar tumors may be denied a potentially lifesaving procedure. We propose expansion of the tumor size criteria to 8 cm for intrahepatic and 3.5 cm for hilar CCA in patients with demonstrated good response to neoadjuvant therapy. Progression of disease beyond the bile duct and liver during neoadjuvant treatment should preclude OLT.

In conclusion, a prospective randomized study comparing OLT and radical resection after neoadjuvant therapy for CCA is timely and clearly warranted. Our study shows that OLT, in combination with neoadjuvant and adjuvant therapy, provides superior overall long-term outcomes for large, locally aggressive intrahepatic and hilar CCA compared with RR plus adjuvant therapy. Expansion of the current tumor size criteria for OLT in CCA has the potential to improve recurrence-free survival in patients with locally advanced disease.

Accepted for Publication: April 23, 2010.

Correspondence: Johnny C. Hong, MD, Dumont-UCLA Transplant and Liver Cancer Centers, Pflieger Liver Institute, Division of Liver and Pancreas Transplantation, Department of Surgery, David Geffen School of Medicine at University of California, Los Angeles, 10833 Le Conte Ave, Room 77-120 CHS, PO Box 957054, Los Angeles, CA 90095 (johnnyhong@mednet.ucla.edu).

Author Contributions: *Study concept and design:* Hong, Farmer, Durazo, Tong, and Busuttil. *Acquisition of data:* Hong, Jones, Duffy, Petrowsky, Farmer, Finn, and Tong. *Analysis and interpretation of data:* Hong, Duffy, French, Finn, Saab, Hiatt, and Busuttil. *Drafting of the manuscript:* Hong, Petrowsky, French, Saab, Tong, Hiatt, and Busuttil. *Critical revision of the manuscript for important intellectual content:* Hong, Jones, Duffy, Farmer, Finn, Durazo, Hiatt, and Busuttil. *Statistical analysis:* Hong and Duffy. *Administrative, technical, and material support:* Hong and Jones. *Study supervision:* Hong, Farmer, and Busuttil.

Financial Disclosure: None reported.

Previous Presentation: This paper was presented at the 81st Annual Meeting of the Pacific Coast Surgical Association; February 16, 2010; Maui, Hawaii; and is published after peer review and revision.

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