ANNALS OF SURGERY
Vol. 227, No. 1, 70–79

Liver Resection for Hilar and Peripheral Cholangiocarcinomas: A Study of 62 Cases

Juan R. Madariaga, M.D.,* Shunzaburo Iwatsuki, M.D., Ph.D.,* Satoru Todo, M.D.,* Randall G. Lee, M.D.,† William Irish, M.Sc.,* Thomas E. Starzl, M.D., Ph.D.*

From the Departments of Surgery and Pathology,† University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania*

Objective

To analyze a single center's 14-year experience with 62 consecutive patients with hilar (HCCA) and peripheral (PCCA) cholangiocarcinomas.

Summary Background Data

Long-term survival after surgical treatment of HCCA and PCCA has been poor.

Methods

From March 1981 until December 1994, 62 consecutive patients with HCCA (n = 28) and PCCA (n = 34) underwent surgical treatment. The operations were individualized and included local excision of the tumor and suprapancreatic bile duct, lymph node dissection, vascular reconstruction, and subtotal hepatectomy. Clinical and pathologic risk factors were examined for prognostic influence.

Results

Patients were followed for a median of 25 months (12–102 months). Postoperative morbidity and mortality (at 30 days) were 32% and 14%, respectively, for HCCA and 24% and 6% for PCCA. The survival rates for HCCA and PCCA were 79% (±8%) and 67% (±8%) at 1 year; 39% (±10%) and 40% (±9%) at 3 years; and 8% (±7%) and 35% (±10%) at 5 years, respectively. The median survival was 24 (±4) months for HCCA and 19 (±8) months for PCCA. The disease-free survival rates for HCCA and PCCA were 85% (±10%) and 77% (±9%) at 1 year; 18% (±11%) and 41% (±12%) at 3 years; and 18% (±11%) and 41% (±12%) at 5 years, respectively. Nearly 80% of these patients had TNM stage IV tumors. With HCCA, no risk factors were associated with patient survival. For PCCA, multiple tumors (relative risk [RR] = 3.5; 95% confidence interval [CI] = 1.2–10.5) and incomplete resection (RR = 8.3; 95% CI = 2.3–29.6) were independently associated with a worse prognosis. For HCCA, there was a trend for lower disease-free survival in females ($p = 0.056$; log rank test). For PCCA, tumor size >5 cm was the only factor associated with disease recurrence ($p = 0.024$; log rank test).

Conclusions

Even though rare, 5-year survival by resection can be achieved in both HCCA and PCCA, but new adjuvant treatments are clearly needed.

Cholangiocarcinomas arise from the bile duct epithelium. When the disease originates in the common hepatic duct as well as in the first and second bifurcations, it can be classified as hilar-type cholangiocarcinoma (HCCA); the peripheral intrahepatic type (PCCA) takes origin in a segmental duct or more peripheral duct.[1-5] Duct cell carcinomas of the common and proper bile duct[6] and gallbladder were excluded from this study. Although there have been numerous reports of surgical treatment of HCCA and PCCA, long-term survival has been poor, with few exceptions.[7-12] In this report, we analyze our 14-year experience.

MATERIALS AND METHODS

Patients

Between March 1981 and December 1994, 62 consecutive patients with HCCA and PCCA underwent surgical treatment at the University of Pittsburgh Medical Center. There were 28 cases of HCCA and 34 cases of PCCA. Patient follow-up (for survivors) as of December 1995 ranged from 15 to 102 months (median 22 months) for HCCA and from 12 to 91 months (median 28 months) for PCCA. A retrospective review of all inpatient and outpatient records, including operative and surgical pathology reports, was performed.

Preoperative Investigations

Percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography, or both, were used to study the precise anatomic extension in HCCA. If indicated with HCCA, angiographic (hepatic artery, portal vein) studies were also performed. When total bilirubin exceeded 10 mg/dL, percutaneous transhepatic biliary drainage was used.[10,13,14] Before resection, the diagnosis of HCCA and PCCA was confirmed by either surgery or percutaneous or endoscopic biopsy in 46% and 76% of cases, respectively.

Classification

The tumors were divided into HCCA and PCCA categories primarily by their macroscopic location and extent, as detailed in surgical pathology reports, and reviewed with available histologic material. If the classification was uncertain or ambiguous, the presence of epithelial dysplasia or carcinoma *in situ* was taken as an indication of origin from a major bile duct, and the tumor was designated as HCCA.[15,16]

Cases of HCCA were stratified by a modification of the Bismuth-Corlette categories.[17] Because the anatomic extension in nine cases precluded the use of this classification, we incorporated five new types: 1) type IIIa$^+$, in which the tumor extended to the right anterior and posterior ducts; 2) type IIIb$^+$, in which the tumor extended up to the bile ducts of segments 4, 3, and 2; 3) type IVa, in which the tumor extended to the second bifurcation in the right side; 4) type IVb, in which there was extension to the bile ducts of segments 4, 3, and 2; and 5) type V, a combination of IVa and IVb. Seven patients were classified as type IIIa, three as IIIa$^+$, seven as IIIb, one as IV, two as IVa, two as IVb, and two as V. Four cases could not be classified: one patient had anatomic variations, and in the other three, the extension of the tumor was unclear by cholangiography and pathology (Fig. 1).

Histopathology

All tumors were mucin-secreting adenocarcinomas composed predominantly of small glands or single malignant cells embedded in a dense desmoplastic stroma.[1-5,18,19] Two cases of HCCA and one case of PCCA showed focal papillary features. In six cases of PCCA, the cholangiocarcinoma was accompanied by foci of hepatocellular differentiation. Five patients with HCCA and two with PCCA had cirrhosis.

Tumor Staging

All patients were staged according to the pTNM classification for HCCA and PCCA (Tables 1 and 2).[20,21] In the HCCA group, 11% of the patients were stage II, 11% stage III, 71% stage IVA, and 7% stage IVB. In the PCCA group, 2% were stage I, 19% stage II, 31% stage III, 42% stage IVA, and 6% stage IVB. The surgical resection was considered complete when all pathologic margins were free of tumor or incomplete when margins were positive or when there was residual tumor.

Surgical Procedures

HCCA

Operations were individualized according to tumor extension and included local excision of the tumor and suprapancreatic bile duct, with lymph node dissection in most cases. Vascular reconstruction and excision of the hepatic parenchyma were used when indicated. The liver resections comprised nine right trisegmentectomies (RT-T), one left trisegmentectomy (LT-T), two right lobectomies (RT-L), one extended right lobectomy (Ext-RT), seven left lobectomies (LT-L), seven extended left lobec-

Address reprint requests to Juan R. Madariaga, M.D., Pittsburgh Transplant Institute, 3601 Fifth Avenue, 4th Floor, Falk Clinic, Pittsburgh, PA 15213; phone: (412) 648-3200; fax: (412) 648-3184.
Accepted for publication November 13, 1996.

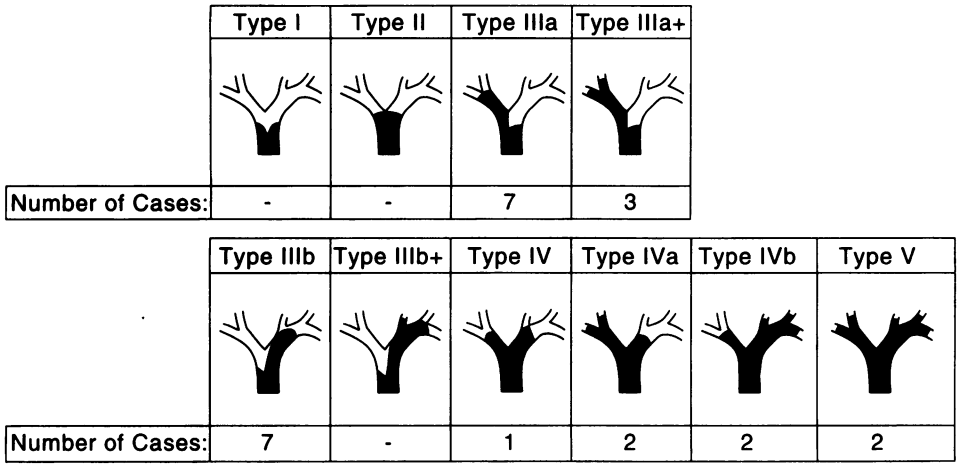

Figure 1. Anatomic classifications in patients with hilar cholangiocarcinomas.

tomies (Ext-LT), and one central excision (CE) (Table 3).[22-25] Excision of the caudate lobe was done in 20 of the 28 patients (71%).[10,22-24] Systematic lymph node dissection was done in 24 patients (86%).[10,12,26,27] There were nine vascular reconstructions, including four segmental excisions of the main portal vein, one primary reconstruction of the right portal vein, two segmental excisions of the right hepatic artery, one primary reconstruction of the artery of the left lateral segment, and one replacement of both the main portal vein and proper hepatic artery graft with cadaver iliac vein and artery grafts, respectively.[28-33] Biliary reconstruction was accomplished in all patients by Roux-en-Y hepaticojejunostomy to one duct (n = 17), two ducts (n = 6), or three ducts or more (n = 5).[10,30-32,34]

PCCA

The standard approach was liver resection with lymph node dissection or vascular reconstruction, or both, when indicated. Liver resections comprised six RT-T, one RT-T with wedge resection (WR) of the left lateral segment, four LT-T, five RT-L, three Ext-RT, one Ext-RT with right adrenalectomy, seven LT-L, five Ext-LT and two WR. Caudate lobe excision was done in 12 cases (35%).[22-24] Systematic lymph node dissection was performed in 18 (53%) of the 34 patients. Excision of the retrohepatic vena cava and replacement was performed in one case with a synthetic graft. A segment of main portal vein was excised in three patients, with primary repair in two and replacement with a cadaveric vein allograft in the other. In one case, an iliac vein graft was used to reconstruct a transected left hepatic vein to the inferior vena cava during RT-T. In five cases, biliary reconstruction with Roux-en-Y hepaticojejunostomy was required.

Adjuvant Therapy

HCCA

Twenty-four (85.7%) of the 28 patients survived the postoperative period. Of these 24, 22 (92%) received radi-

Table 1. pTMN CLASSIFICATION (HILAR CHOLANGIOCARCINOMA)

Stage 0	TIS	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1, N2	M0
	T2	N1, N2	M0
Stage IV-A	T3	Any N	M0
Stage IV-B	Any T	Any N	M1

TIS = carcinoma *in situ;* T1 = tumor invades mucosa or muscle layer; T2 = tumor invades the perimuscular connective tissue; T3 = tumor invades adjacent structures: liver, pancreas, duodenum, gallbladder, colon, stomach; N1 = cystic duct, pericholedochal and/or hilar nodes; N2 = peripancreatic, periduodenal, periportal, celiac, superior mesenteric, and/or posterior pancreaticoduodenal nodes; M1 = distant metastasis.

Table 2. pTNM CLASSIFICATION (PERIPHERAL CHOLANGIOCARCINOMA)

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1, N0	M0
Stage IV-A	T4	Any N	M0
Stage IV-B	Any T	Any N	M1

T1 = solitary ≤ 2 cm, without vascular invasion; T2 = solitary ≤ 2 cm, with vascular invasion; multiple, one lobe, ≤2 cm, without vascular invasion; T3 = solitary, >2 cm, with vascular invasion; multiple, one lobe, >2 cm, with or without vascular invasion; T4 = multiple, > one lobe; invasion of major branch of portal or hepatic veins; N1 = regional node metastasis; M1 = distant metastasis.

Table 3. THE TYPE OF LIVER RESECTION PERFORMED IN 28 PATIENTS WITH HILAR CHOLANGIOCARCINOMA ACCORDING TO ANATOMIC CLASSIFICATION

	RT-L	EXT-R	RT-T	LT-L	EXT-L	LT-T	CE
Anatomic classification							
IIIa (n = 7)	1	—	6	—	—	—	—
IIIa+ (n = 3)	1	—	2	—	—	—	—
IIIb (n = 7)	—	—	—	4	3	—	—
IV (n = 1)	—	—	—	—	1	—	—
IVa (n = 2)	—	1	1	—	—	—	—
IVb (n = 2)	—	—	—	1	1	—	—
V (n = 2)	—	—	—	1	1	—	—
Unknown (n = 4)	—	—	—	1	1	1	1
Number of patients	2	1	9	7	7	1	1
Number of deaths within 30 days of the operation	1		1		2		

RT-L = right lobectomy; LT-L = left lobectomy; LT-T = left trisegmentectomy; EXT-R = extended right lobectomy; EXT-L = extended left lobectomy; CE = central excision; RT-T = right trisegmentectomy.

ation therapy (n = 6), chemotherapy (n = 1), or both (n = 15).[35,36]

PCCA

Thirty-two (95%) of these 34 patients survived the postoperative period. Of the 32, 24 (75%) received radiation therapy (n = 6), chemotherapy (n = 15), or both (n = 3). One patient underwent preoperative radiation therapy.[36]

Prognostic Factors

HCCA

Sex, age, tumor differentiation, vascular invasion, lymph node involvement, type of operation, presence of underlying cirrhosis, and tumor stage were analyzed (See Table 4). Because this tumor often involves the bifurcation of the common hepatic bile duct and usually does not form a discrete liver mass, it was impossible to determine tumor size, tumor distribution (unilobar *vs.* bilobar), and tumor number (single *vs.* multiple tumor). Adjuvant chemotherapy was not analyzable as a risk factor because >90% of the patients received some form of treatment.

PCCA

The risk influence was analyzed of sex, age, tumor size, tumor distribution, number of tumors, vascular invasion, type of treatment, tumor stage, lymph node involvement, and adjuvant treatment (See Table 4). Information on tumor differentiation was incomplete, and the effect of cirrhosis as a risk factor could not be analyzed because it was present in only 6% of the patients.

Statistical Analysis

The standard two-sample Student's t test was used to compare group means; Pearson's chi square test or Fisher's Exact test was used to compare proportions. The Wilcoxon rank sum test, a nonparametric equivalent to the standard two-sample Student's t test, was used for highly skewed data.

Patient survival was calculated from the date of liver resection until death, disease-free survival from the date of liver resection until the time of disease recurrence. Disease-free survival was calculated only for patients who had complete resection. Patients who were alive or disease-free as of December 1995 were censored. Disease recurrence was defined as measurable tumor by radiologic studies or by laparotomy. Survival curves were generated using the Kaplan-Meier (product-limit) method[37] and were compared by the log rank (Mantel-Cox) test.[38] For each survival rate, Greenwood's formula was used to calculate the standard error.[39] Deaths within 30 days of surgery were defined as postoperative deaths. Analyses of risk factors were performed according to hilar and peripheral type of tumor.

Cox's proportional hazards model was used to compute the relative risk (RR) of mortality and disease recurrence and 95% confidence intervals (CI).[40,41] A stepwise multivariate analysis (backward elimination method) was performed using Cox's regression to identify factors independently associated with mortality and disease recurrence. Based on univariate analyses, the criterion for inclusion in the multivariate analysis was a p value <0.05.

One patient with PCCA had recurrent disease in the liver within 7 months of surgery and underwent cluster transplantation.[42] This patient died 4 years later with re-

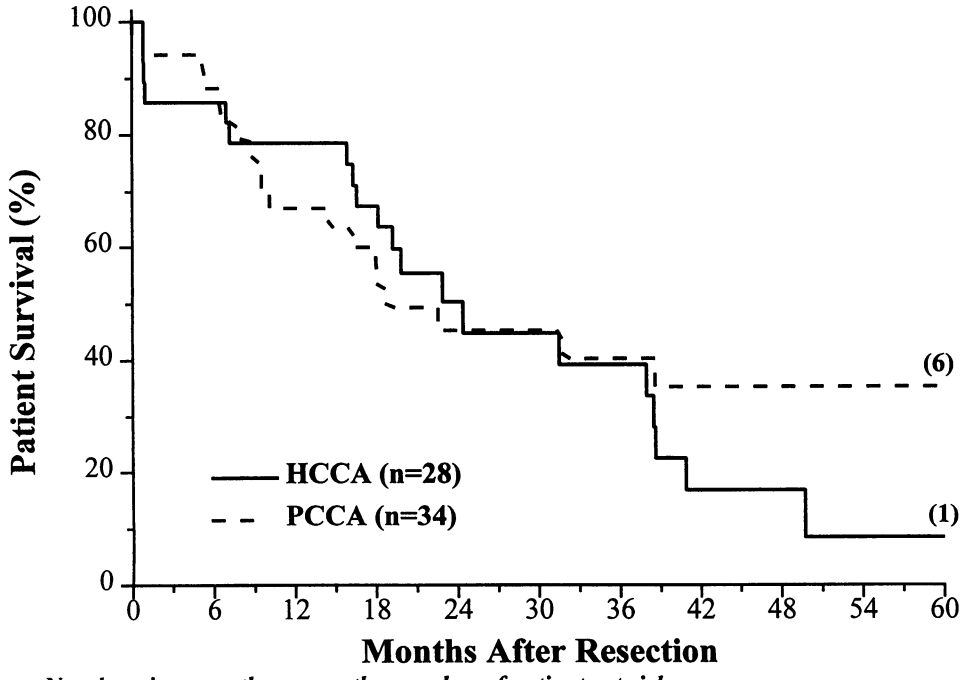

Figure 2. Overall patient survival in hilar and peripheral cholangiocarcinomas.

Numbers in parentheses are the number of patients at risk

current disease. For the analysis of patient survival, this patient was censored at the time of transplantation. Another patient with PCCA required orthotopic liver transplantation for liver failure 1 month after surgery. For the analysis of patient and disease-free survival, this patient was censored at the time of transplantation.

All tests were two-tailed. A p value <0.05 was considered statistically significant.

RESULTS

Clinical Manifestations

HCCA

The most frequent complaint was jaundice (96%), followed by weight loss (29%), abdominal pain (20%), fever (16%), and hepatomegaly (a palpable mass) (4%).

PCCA

The most frequent complaints were abdominal pain (71%), hepatomegaly (34%), weight loss (15%), jaundice (12%), and fever (9%). One patient with PCCA had been exposed to *Clonorchis sinensis*.[43]

Postoperative Morbidity and Mortality

HCCA

The postoperative (30-day) mortality rate was 14% (4 of 28). Complications occurred in 9 patients (32%); the most common complication was bile leak and abscess (n = 4; 19%), followed by subphrenic abscess (n = 2; 7%), liver necrosis (n = 2; 7%), and seroma (n = 1; 4%). Of the nine complications, four required open drainage and one excision of the right anterior segment. Four patients died as a result of complications. These complications were concentrated in the 14 patients with positive margins and the 9 patients who also required vascular reconstruction. However, the increased morbidity observed with incomplete resection was not significantly different from complete resection (5 of 14 [36%] *vs.* 4 of 14 [29%]; p = 1.0). Likewise, the increased morbidity in patients who required vascular reconstruction was not statistically different from those who did not require vascular reconstruction (5 of 9 [56%] *vs.* 4 of 19 [21%]; p = 0.10).

PCCA

The postoperative mortality rate was 6% (2 of 34). Eight major complications occurred in eight patients (24%): bile leak and abscess (n = 5; 15%), portal vein thrombosis (n = 1; 3%), peritonitis (n = 1; 3%), and cardiac arrest (n = 1; 3%). Four of the 8 complications were in the 10 patients with positive resection margins, and the other 4 were in the 5 who required vascular reconstruction. The increased morbidity with incomplete resection was not statistically different from complete resection (40% *vs.* 17%; p = 0.195). However, a higher rate of morbidity was observed in patients who required vascular reconstruction compared to patients who did not require

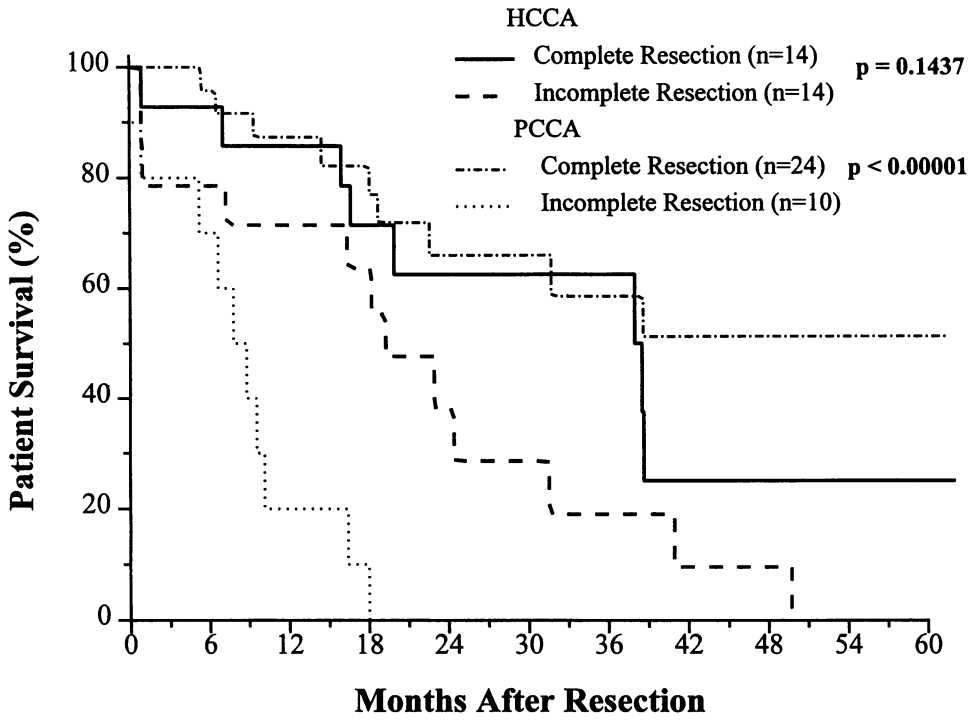

Figure 3. Patient survival according to type of treatment in hilar and peripheral cholangiocarcinomas.

vascular reconstruction (80% *vs.* 14%; p = 0.0007). One of the patients who developed bile leak, abscess, and biliary necrosis had received preoperative radiation therapy, eventually was treated with orthotopic liver transplantation, and recovered. The patient with peritonitis required laparotomy and recovered. One patient died intraoperatively from cardiac arrest.

Actuarial Patient Survival

Kaplan-Meier patient survival according to hilar and peripheral type is shown in Figure 2. Survival rates for HCCA and PCCA were 79% (±8%) and 67% (±8%) at 1 year; 39% (±10%) and 40% (±9%) at 3 years; and 8% (±7%) and 35% (±10%) at 5 years, respectively. The median survival was 24 (±4) months for HCCA and 19 (±8) months for PCCA. Patient survival according to type of treatment is shown in Figure 3.

Seven patients survived ≥5 years (Table 5); only 1 of these had HCCA. Of the 6 patients with PCCA who reached this milestone (median follow-up = 89.5; range, 75.3–167.7 months), all had complete resections, single tumors, and negative lymph nodes (see Table 5). Five of the six patients had unilobar disease.

Prognostic Factors: Univariate Analysis

HCCA

With univariate analysis, none of the clinical and pathologic risk factors were associated with patient survival.

PCCA

Worse survival (log rank) was associated with bilobar disease (p = 0.029), multiple tumors (p = 0.0005), vascular invasion (p = 0.009), lymph node involvement (p = 0.003), and incomplete resection (p < 0.00001) (see Fig. 3). There was a trend for lower survival among patients whose tumor size was >5 cm and who had an advanced stage (p = 0.052). Survival was not influenced by adjuvant therapy (p = 0.423).

Disease-Free Survival

Disease-free survival was calculated for patients who underwent complete resection (see statistical analysis section). The disease-free survival rates for HCCA and PCCA were 85% (±10%) and 77% (±9%) at 1 year; 18% (±11%) and 41% (±12%) at 3 years; and 18% (±11%) and 41% (±12%) at 5 years, respectively (Fig. 4).

HCCA

None of the analyzed factors were statistically associated with disease-free survival. However, there was a trend for lower disease-free survival in females (p = 0.056; log rank test).

PCCA

The only factor associated with poor disease-free survival was tumor size >5 cm (p = 0.024; log rank test).

Table 4. THE DISTRIBUTION OF POTENTIAL PROGNOSTIC FACTORS ACCORDING TO TYPE OF TUMOR

Factor	HCCA	PCCA
Sex (M/F)	15/13	11/23
Age (yr)* (mean ± SD)	56 ± 12	59 ± 8
Tumor size ≥ 5 cm	3 (19%)	26 (76%)
Tumor distribution†		
Unilobar	NA	21 (62%)
Bilobar		13 (38%)
Number of tumors‡	NA	
Single		18 (53%)
Multiple		16 (47%)
Tumor differentiation§		
Well	8/25 (32%)	4/21 (19%)
Moderate to poor	17/25 (68%)	17/21 (81%)
Vascular invasion		
Yes	15 (54%)	24 (71%)
Lymph node involvement		
Yes	13 (46%)	6 (18%)
Type of treatment		
Complete resected	14 (50%)	24 (71%)
Incomplete resected	14 (50%)	10 (29%)
Underlying cirrhosis		
Yes	5 (18%)	2 (6%)
Tumor stage		
I, II, or III	6 (11%)	19 (56%)
IV-a or IV-b	22 (79%)	15 (44%)
Adjuvant therapy‖		
Yes	22/24 (92%)	24/32 (75%)
Anatomic classification¶		NA
IIIa	7 (25%)	
III-a+	3 (11%)	
III-b	7 (25%)	
IV	1 (4%)	
IVa	2 (7%)	
IVb	2 (7%)	
V	2 (7%)	
Unknown	4 (14%)	

NA = not applicable.
* At time of hepatic resection.
† For HCCA patients, the tumor usually involves bifurcation of the common hepatic bile duct.
‡ For HCCA patients, there is no discrete liver mass.
§ Three patients with HCCA and 11 patients with PCCA tumor differentiation unknown.
‖ Postoperative radiotherapy and/or chemotherapy for these patients who survived at least 30 days following surgery.
¶ Anatomic classification only for HCCA patients.

Of the patients with tumors <5 cm, 100% were rendered disease-free.

Multivariate Analysis

Clinical and pathologic risk factors with a p value <0.05 based on univariate analyses were incorporated into a multivariate analysis using Cox's proportional hazards model.

HCCA

None of the clinical and pathologic risk factors for mortality or disease recurrence met the criterion for inclusion in the multivariate analysis.

PCCA

Multiple tumors (adjusted RR = 3.50; 95% CI, 1.2–10.5) and incomplete resection (adjusted RR = 8.3; 95% CI, 2.3–29.6) were independently associated with poor prognosis. Only tumor size >5 cm was associated with disease recurrence.

DISCUSSION

Although the radiologic appearance of HCCA is characteristic, the preoperative pathologic diagnosis can be difficult.[44,45] In our study, preoperative investigations, intraoperative findings, and pathologic studies were used to distinguish HCCA from PCCA and to differentiate both varieties from tumors rising in "large" bile ducts.[4,6,16,20] There have been no previously reported series with this precise delineation of duct cell lesions, exclusive of those in the common and proper bile ducts.

Assessment of the extent of HCCA with preoperative studies and intraoperative findings, including the presence or absence of vascular invasion, was crucial in deciding on the optimal operation.[10,36] Treatment consisted of liver resection (including the caudate lobe) in continuity with excision of the extrahepatic bile duct all the way to the level of the pancreas and lymph node dissection.[10,26,28–32,34]

During excision of HCCA, the proximal and distal bile duct, parenchyma, and vascular margins were checked with frozen sections to establish clear margins and to determine prognosis in cases where there was no possibility of further dissection. The most common postoperative complication was bile leak and abscess, followed by subphrenic abscess and liver necrosis. Bile leak and abscess was not associated with early mortality, but subphrenic abscess and liver necrosis (complications often preceded by vascular reconstruction) were responsible for three deaths.

In contrast, PCCA treatment was based primarily on liver resection, the extent of which was dictated by the location and dimensions of the tumor. Excision of the extrahepatic bile duct and lymph node dissection also were done if the malignancies were near the hilum or diffusely infiltrating. Vascular reconstruction was performed when necessary. As in the HCCA cases, the most common complication was bile leak and abscess, but only one patient died as a result of this complication.

In both HCCA and PCCA, careful attention to technical

Table 5. CHARACTERISTICS OF PATIENTS WITH AT LEAST 5 YEARS OF FOLLOW-UP

Type of Tumor	Patient Numbers	Follow-Up (mo)	TNM Stage	Type of Treatment	Outcome	Vascular Invasion	Multiple Tumors	Lymph Node Involvement	Lobe Distribution	Tumor Size ≥5 cm
HCCA	1	101.69	IV-A	CR	AWD	Yes	NA	No	NA	NA
PCCA	1	75.31	III	CR	AWOD	Yes	Single	No	Unilobar	Yes
	2	77.69	II	CR	DWD	No	Single	No	Unilobar	Yes
	3	87.77	II	CR	AWOD	No	Single	No	Unilobar	No
	4	91.24	IV-A	CR	AWOD	No	Single	No	Bilobar	Yes
	5	92.69	II	CR	DWD	No	Single	No	Unilobar	Yes
	6	167.67	III	CR	DFD	Yes	Single	No	Unilobar	No

HCCA = hilar cholangiocarcinoma; PCCA = peripheral cholangiocarcinoma; CR = complete resection; AWD = alive with disease; AWOD = alive without disease; DWD = death with disease; DFD = dead free of disease; NA = not applicable.

details is necessary to avoid postoperative complications, especially those related to vascular reconstruction.[10,46]

Although long-term patient survival for HCCA and PCCA remains low, it can be achieved by aggressive surgical treatment, as previously emphasized by Blumgart,[28,29,36] Lygidakis,[30–32,34] and other authors.[10–12] It was clear, however, that part of the gain achieved by extended operations was lost because of the increased morbidity and postoperative mortality. The actuarial 5-year survival for HCCA and PCCA was 8% ± 7% and 35% ± 10%, respectively; these figures are comparable to most other studies[11,12,47] but inferior to some.[10] Such comparisons are difficult to make because determinants other than the surgical treatment are so inherently influential on outcome, particularly the extent of the disease.

In view of the higher morbidity and postoperative mortality in the HCCA group, one may question the justification for resection in these patients. Although resection is performed with a curative intent, most of the resections are incomplete and are only palliative.[36,47] We, as well as other authors,[36,47] advocate palliative resection because the results are better (longer duration of survival, quality of life, and long-term palliation) than those obtained by interventional radiology techniques or surgical bypass.[16,29,36,47] However, this recommendation is justified only if early morbidity and mortality are minimized. To improve early outcome, we need better patient selection (*i.e.*, earlier staging of disease) and improved surgical techniques to avoid technical complications. If this can be achieved, then the incomplete resection approach is certainly justifiable.

For HCCA, however, none of the analyzed clinical and

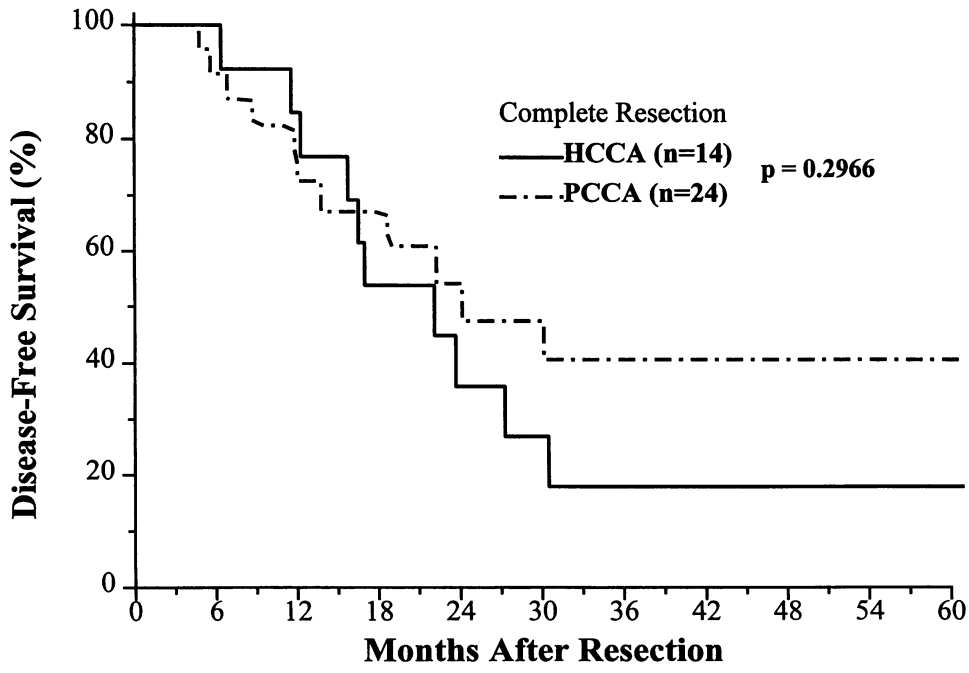

Figure 4. Disease-free survival in the complete resection group for hilar and peripheral cholangiocarcinomas.

pathologic risk factors were associated with patient survival. Although patients who had incomplete resection had a lower survival curve than those who underwent complete resection, the difference was not significant ($p = 0.1437$), presumably because 75% of the patients (22 of 28) had stage IV disease. However, this observation should be interpreted with caution. The inability to identify statistically significant prognostic factors, including a clear distinction between outcome of incomplete (palliative) *versus* complete (curative) resection, could be an artifact of the small sample of patients with favorable pathology. In other series, long-term survival has been associated with complete resection.[10,12]

Five-year survival was more than fourfold higher in patients with PCCA than in those with HCCA. The only prognostic factors independently associated with poor prognosis were multiple tumors and incomplete resection. Eighty percent of PCCA patients whose treatment was palliative (incomplete resection) had stage IV disease, compared to 29% of those considered to have had potentially curative operations ($p = 0.010$; Fisher's Exact test). Moreover, 100% of the patients in the palliation group had vascular invasion. The much better outcome with PCCA <5 cm has not been reported before.

In conclusion, 5-year survival can be obtained by resection in an occasional patient with HCCA and in as many as a third of those with PCCA. New adjuvant therapies, presumably based on different principles than current ones, are clearly needed to improve these results. This is particularly true for the historically frustrating HCCA, whose strategic location so limits radical extirpation.

References

1. Okuda K, Kubo Y, Okazaki N, et al. Clinical aspects of intrahepatic bile duct carcinoma including hilar carcinoma: a study of 57 autopsy-proven cases. Cancer 1977;39:232–246.
2. Edmondson HA, Steiner PE. Primary carcinoma of the liver. A study of 100 cases among 48,900 necropsies. Cancer 1954;51:462–503.
3. Altemeier WA, Gall EA, Zinniger MM, Hoxworth LH. Sclerosing carcinoma of the major intrahepatic ducts. Arch Surg 1957;75:450–461.
4. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis: an unusual tumor with distinctive clinical and pathological features. Am J Med 1965;38:241–256.
5. Nakajima T, Kondo Y, Miyazaki M, Okui K. A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: histologic classification and modes of spreading. Hum Pathol 1988;19:1228–1234.
6. Tompkins RK, Thomas D, Wile A, Longmire WP. Prognostic factors in the bile duct carcinoma: analysis of 96 cases. Ann Surg 1981;194:447–457.
7. Chen MF, Jan YY, Wang CS, et al. Clinical experience in 20 hepatic resections for peripheral cholangiocarcinoma. Cancer 1989;64:2226–2232.
8. Schlinkert RT, Nagorney DM, Heerden JAV, Adson MA. Intrahepatic cholangiocarcinoma: clinical aspects, pathology and treatment. HPB Surgery 1992;5:95–102.
9. Hadjis NS, Blenkharn JI, Alexander N, et al. Outcome of radical surgery in hilar cholangiocarcinoma. Surgery 1990;107:597–604.
10. Nimura Y, Hayakawa N, Kamiya J, et al. Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. World J Surg 1990;14:535–544.
11. Yamamoto J, Kosuge T, Takayama T, et al. Surgical treatment of intrahepatic cholangiocarcinoma: four patients surviving more than five years. Surgery 1992;111:617–622.
12. Sugiura Y, Nakamura S, Iida S, et al. Extensive resection of the bile ducts combined with liver resection for cancer of the main hepatic duct: a cooperative study of the Keio bile duct cancer study group. Surgery 1994;115:445–451.
13. Stambuk EC, Pitt HA, Pais O, et al. Percutaneous transhepatic drainage. Arch Surg 1983;118:1388–1394.
14. Su CH, Tsay SH, Wu CC, et al. Factors influencing postoperative morbidity, mortality and survival after resection for hilar cholangiocarcinoma. Ann Surg 1996;223(4):384–394.
15. Kurashina M, Kozuka S, Nakasima N, et al. Relationship of intrahepatic bile duct hyperplasia to cholangiocellular carcinoma. Cancer 1988;61:2469–2674.
16. Suzuki M, Takahashi T, Ouchi K, Matsuno S. The development and extension of hepatohilar bile duct carcinoma. A three-dimensional tumor mapping in the intrahepatic biliary tree visualized with the aid of a graphics computer system. Cancer 1989;64:658–666.
17. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet 1975;140:170–178.
18. Weinbren K, Mutum SS. Pathological aspects of cholangiocarcinoma. J Pathol 1983;139:217–238.
19. Qualman SJ, Haupt HM, Bauer TW, Taxy JB. Adenocarcinoma of the hepatic duct junction. A reappraisal of the histologic criteria of malignancy. Cancer 1984;53:1545–1551.
20. Intrahepatic bile ducts. In Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ, eds. American Joint Committee on Cancer: Manual for Staging of Cancer, 4th ed. Philadelphia: JB Lippincott, 1992:89–91.
21. Extrahepatic bile ducts. In Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ, eds. American Joint Committee on Cancer: Manual for Staging of Cancer, 4th ed. Philadelphia: JB Lippincott, 1992:99–103.
22. Starzl TE, Bell RH, Beart RW, Putnam CW. Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 1975;141:429–437.
23. Starzl TE, Koep LJ, Weil R, et al. Right trisegmentectomy for hepatic neoplasms. Surg Gynecol Obstet 1980;150:208–213.
24. Starzl TE, Iwatsuki S, Shaw BW, et al. Left hepatic trisegmentectomy. Surg Gynecol Obstet 1982;155:21–27.
25. White TT. Skeletonization resection and central hepatic resection in the treatment of bile duct cancer. World J Surgery 1988;12:48–51.
26. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg 1992;215:31–38.
27. Bengmark S, Ekberg H, Evander A, et al. Major liver resection for hilar cholangiocarcinoma. Ann Surg 1988;207:120–125.
28. Blumgart LH. Liver resection: liver and biliary tumors. In Blumgart LH, ed. Surgery of the Liver and Biliary Tract, vol. 2. Edinburgh: Churchill Livingstone, 1988:1251–1280.
29. Blumgart LH, Benjamin IS, Hadjis NS. Surgical approaches to cholangiocarcinoma at the confluence of the hepatic ducts. Lancet 1984;1:66–70.
30. Lygidakis NJ, van der Heyde MN, van Dongen RJAM, et al. Surgical approaches for unresectable primary carcinoma of the hepatic hilus. Surgery Gynecol Obstet 1988;166:107–114.
31. Lygidakis NJ, van der Heyde MN, Houthoff HJ. Surgical ap-

proaches to the management of primary biliary cholangiocarcinoma of the porta hepatitis: the decision-making dilemma. Hepato-Gastroenterology 1988;35(6):261–267.
32. Lygidakis JN, van der Heyde MN, Verrbeek PC, van Leeuwen DJ. Technical considerations for the management of primary cholangiocarcinoma of the porta hepatis. Sem Liver Dis 1990;10(2):126–130.
33. Sukaguchi S, Nakamura S. Surgery of the portal vein in resection of cancer of the hepatic hilus. Surgery 1986;99:344–349.
34. Lygidakis NJ, Brummelkamp WH, Lubbers ME, et al. A new surgical approach for the management of carcinoma of the junction of the main hepatic ducts. Ann Surg 1986;18:297–310.
35. Gonzalez D, Gerard JP, Maners AW, et al. Results of radiation therapy in carcinoma of the proximal bile duct (Klatskin tumor). Seminars in Liver Disease 1990;10:131–141.
36. Vauthey JN, Blumgart LH. Recent advances in the management of cholangiocarcinomas. Semin Liv Dis 1994;14:109–114.
37. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
38. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163–170.
39. Greenwood M. The natural duration of cancer. Reports on Public Health and Medical Subjects, 1926. London: Her Majesty's Stationary Office, pp. 1–26.
40. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
41. Cox DR. Partial likelihood. Biometrika 1975;62:269–276.
42. Starzl TE, Todo S, Tzakis A, et al. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 1989;210:374–386.
43. Choi BI, Park JH, Kim YI, et al. Peripheral cholangiocarcinoma and clonorchiasis: CT findings. Radiology 1988;169:149–53.
44. Evander A, Fredlund P, Hoevels J, Bengmark S. Evaluation of aggressive surgery for carcinoma of the extrahepatic bile ducts. Ann Surg 1980;191:23–29.
45. Rossi RL, Heiss FW, Beckmann CF, Braasch JW. Management of cancer of the bile ducts. Surg Clin North Am 1985;65:59–78.
46. Pitt HA, Dooley WC, Yeo CJ, Cameron JL. Malignancies of the biliary tree. Curr Probl Surg 1995;32:36–70.
47. Boerma EJ. Research into the results of resection of hilar bile duct. Surgery 1990;108:572–80.