LIVER RESECTION FOR HILAR AND PERIPHERAL CHOLANGIOCARCINOMAS:

A STUDY OF 62 CASES

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MINI ABSTRACT

We present our 14-year experience of liver resection for hilar and peripheral cholangiocarcinomas with an analysis of the clinical and pathologic prognostic factors, overall survival and disease-free survival.

STRUCTURED ABSTRACT

Objective

The objective of this study was 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 achieved 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. Clinical and pathological risk factors were examined for prognostic influence.

Results

The survival rates for HCCA and PCCA at one-year were 79% (± 8%) and 67% (± 8%); at three years, 39% (± 10%) and 40% (± 9%); and at five years, 8% (± 7%) and 35% (± 10%), respectively. 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. With HCCA, no risk factors were associated with patient survival. For PCCA, multiple tumors (RR=3.5; 95% confidence interval=1.2 to 10.5) and incomplete resection (RR=8.3; 95% confidence interval=2.3 to 29.6) were independently associated with a worse prognosis. For HCCA, there was a trend for lower disease-free survival in female patients (p=0.056; logrank test). For PCCA, tumor size greater than 5 cm was the only factor associated with disease-recurrence (p=0.024; logrank) . Postoperative morbidity and mortality (30 day) were 32% and 14%, respectively for HCCA, and 24% and

6% for PCCA.

Conclusions

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

ABSTRACT

Background. Long term survival achieved after surgical treatment of hilar cholangiocarcinoma (HCCA) and peripheral cholangiocarcinoma (PCCA) has been poor.

Methods. During a 14-year period, 62 consecutive patients (HCCA=28, PCCA=34) underwent surgical treatment. The operations were individualized and included local excision of the tumor and supra pancreatic bile duct, lymph node dissection, vascular reconstruction and subtotal hepatectomy. Clinical and pathological risk factors were examined for prognostic influence.

Results. Patients were followed for a median of 25 months (12 to 102 months). Postoperative morbidity and mortality (30 day) were 32% and 14%, respectively for HCCA, and 24% and 6% for PCCA. The survival rates for HCCA and PCCA at one-year were 79% (± 8%) and 67% (± 8%); at three years, 39% (± 10%) and 40% (± 9%); and at five years, 8% (± 7%) and 35% (± 10%), 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 (RR=3.5; 95% confidence interval=1.2 to 10.5) and incomplete resection (RR=8.3; 95% confidence interval=2.3 to 29.6) were independently associated with a worse prognosis. For HCCA, there was a trend for lower disease-free

survival in female patients (p=0.056; logrank test). For PCCA, tumor size greater than 5 cm was the only factor associated with disease-recurrence (p=0.024; logrank) .

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

INTRODUCTION

Cholangiocarcinomas (CCA) 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 (HCCA); whereas 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.

CASE MATERIAL AND METHODS

Patients

Between March 1981 and December 1994, 62 consecutive patients with hilar and peripheral cholangiocarcinomas 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 and/or endoscopic retrograde

cholangiography were used to study the precise anatomical 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).

Prior to resection, the diagnosis of HCCA and PCCA was confirmed by either surgery, or percutaneous/endoscopic biopsy in 46% and 76%, respectively, of cases.

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. In cases in which 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).

The HCCA's were stratified by a modification of the Bismuth-Corlette categories (17). Since the anatomic extension in nine cases precluded the use of this classification, we incorporated five new types: type IIIa+ when the tumor extended to the right anterior and posterior ducts; type IIIb+ when the tumor extended up to the bile ducts of segments 4,3, and 2; type IVa when the tumor extended to the second bifurcation in the right side; type IVb when there was extension to the bile ducts of segments 4, 3 and 2; and type V when there was 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) (Figure 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 cases of HCCA and two cases of PCCA had cirrhosis.

Tumor Staging

All patients were staged according to the pTNM classification for hilar and peripheral cholangiocarcinomas (20,21). [see Table I and II]. 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 pathological margins were free of tumor or incomplete when margins were positive or when there was residual tumor.

Surgical Procedures

HCCA group --- Operations were individualized according to tumor extension and included local excision of the tumor and supra pancreatic 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 lobectomies (Ext-LT) and one central excision (CE) (22-25). [See Table III] . Excision of the caudate lobe was done in 20 of the 28 (71%) patients (10,22-24). Systematic lymph node dissection was done in 24 (86%) patients (10,12,26,27). There were nine vascular reconstructions, including: four segmental excision of main portal vein; one primary reconstruction of right portal vein; two segmental excisions of 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 hepatico-jejunostomy either to: one duct (n=17); two ducts (n=6); three ducts or more (n=5) (10,30-32,34).

PCCA Group --- The standard approach was liver resection with lymph node dissection and/or vascular reconstruction 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 3 patients with primary repair in 2 and replacement with a cadaveric vein allograft in the other. In one case, an iliac vein graft was used to empty a transected left hepatic vein to the inferior vena cava during RT-T. In five cases, biliary reconstruction with

Roux-en-Y hepatico-jejunostomy was required.

Adjuvant Therapy

HCCA--- Twenty four (85.7%) of the 28 patients survived the postoperative period. Of these 24, 22 (92%) received either radiotherapy (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 either radiotherapy (n=6), chemotherapy (n=15), or both (n=3). One patient underwent preoperative radiotherapy (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. Because this tumor often involves the bifurcation of the common hepatic bile duct and usually does not form a discrete liver mass, it was not possible to accurately 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 over 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. 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 t-test was used to compare group means while Pearson's chi-square test or Fisher's Exact test was used to compare proportions. The Wilcoxon rank sum test, a non-parametric equivalent to the standard two-sample t-test was used for highly skewed data.

Patient survival was calculated from the date of liver resection until death, and 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 radiological 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 (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 less than 0.05.

One patient with PCCA had recurrent disease in the liver within seven months of surgery and underwent cluster transplantation (42). This patient died four years later with recurrent 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 one month after surgery. For the analysis of patient and disease-free survival, this patient was censored at time of transplantation.

All tests were two-tailed. A p-value less than 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% (4/28). Complications occurred in nine patients (32%). The most common 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 patients required open drainage and one excision of the right anterior segment. Four patients died as a result of the 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 than with complete resection (5/14 (36%) versus 4/14 (29%); p=1.0). Likewise, the increased morbidity in patients who required vascular reconstruction was not statistically different than those who did not require vascular reconstruction (5/9 (56%) versus 4/19 (21%); p=0.10).

PCCA --- The postoperative mortality rate was 6% (2/34). 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 eight complications were in the 10 patients with positive resection margins and the other 4 were in the five who required vascular reconstruction. The increased morbidity with incomplete resection was not statistically different than with 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 vascular reconstruction (80% vs 14%; p=0.0007). One of the patients who developed bile leak, abscess and biliary necrosis

had received preoperative radiotherapy and eventually was treated with orthotopic liver transplantation and recovered. The one 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 at one-year were 79% (+ 8%) and 67% (+ 8%); at three years, 39% (+ 10%) and 40% (+ 9%); and at five years, 8% (+7%) and 35% (+ 10%), respectively. The median survival was 24 (+ 4 months) for HCCA and 19 (+ 8 months) for PCCA. Patient survival according to type of treatment in HCCA and PCCA is shown in Figure 3.

Seven patients have actual survival of 5 years or longer (table V), of which only one had HCCA. Six patients with PCCA have reached this milestone (median follow-up=89.5; range=75.3 to 167.7 months) of whom all had complete resections, had single tumors, and negative lymph nodes (table V). 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 (logrank) 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 ($p<0.00001$) (Figure 3). There was a trend for lower survival among patients whose tumor size was greater than 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 (Figure 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 ($p=0.056$ logrank test).

PCCA --- The only factor associated with poor disease-free survival was tumor size over 5 cm ($p=0.024$ logrank test). Of the patients whose tumor size was less that 5 cm, 100% were rendered disease-free.

Multivariate Analysis

Clinical and pathological risk factors with a p-value less than 0.05, based on univariate analyses were incorporated into a multivariate analysis using Cox's proportional hazards

model.

HCCA--- None of the clinical and pathological 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 to 10.5) and incomplete resection (adjusted RR=8.3; 95% ci=2.3 to 29.6) were independently associated with poor prognosis . Only tumor size greater than 5 cm was associated with disease-recurrence.

DISCUSSION

Although the radiological appearance of HCCA is characteristic, the preoperative pathologic diagnosis can be difficult (44,45). In our study, preoperative investigations, intraoperative findings, and pathological studies were used to delineate HCCA from PCCA and to further 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 upon 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 in which there was no possibility for further dissection. The most prevalent postoperative complication was bile leak and abscess followed by subphrenic abscess and liver necrosis. Bile leak and abscess were not associated with early mortality, but subphrenic abscess and liver necrosis (complications often preceded by vascular reconstruction) were responsible for 3 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 prevalent 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 details is necessary in order 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 five year survival for HCCA and PCCA was 8% + 7% and 35 + 10%, respectively, 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, like many other authors, most of the resections are incomplete and are only palliative (36,47). We as well as other authors (36,47) advocate palliative resection because results are better (i.e., 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 only justifiable if the early morbidity and mortality is kept to a minimum.

In order to improve early outcome we need better patient selection (i.e., earlier staging of disease) and improved surgical techniques in order 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 pathological 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 ($p = .1437$), presumably because three quarters of the patients had stage IV disease (22 of 28). 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 4-fold higher in patients with PCCA than when the

diagnosis was 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 Exact test). Moreover, 100% of patients in the palliation group had vascular invasion. The much better outcome with PCCA less than 5 cm has not been reported before.

In conclusion, it is possible to occasionally obtain five year survival by resection in patients with HCCA and in as high as a third of those with PCCA. New adjuvant therapies which presumably will be based on different principles than current ones are clearly needed to substantially improve these results. This is particularly true for the historically frustrating hilar cholangiocarcinomas whose strategic location so limits radical extirpation.

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LEGENDS

Table I: pTNM classification for hilar cholangiocarcinomas.

Table II: pTNM classification for peripheral cholangiocarcinomas.

Table III: The type of liver resection performed in 28 patients with hilar cholangiocarcinoma according to anatomical classification.

Table IV: The distribution of potential prognostic factors according to type of tumor.

Table V: Characteristics of patients with at least five years follow-up.

FIGURES

Table I: pTNM 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 peri-muscular 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 II: 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 ≤ 2cm, with vascular invasion

Multiple, one lobe, ≤ 2 cm, without vascular invasion

Solitary, > 2 cm, with 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 III: The type of liver resection performed in 28 patients with hilar cholangiocarcinoma according to anatomical classification.

	RT-L	EXT-R	RT-T	LT-L	EXT-L	LT-T	CE
Anatomical 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		

KEYS:

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

Table IV: The distribution of potential prognostic factors according to type of tumor.

Factor	HCCA	PCCA
Sex M/F	15/13	11/23
Age (years)[a] mean ± ds	56 ± 12	59± 8
Tumor Size ≥ 5 cm	3 (19%)	26 (76%)
Tumor Distribution[b] Unilobar Bilobar	N/A	21 (62%) 13 (38%)
Number of Tumors[c] Single Multiple	N/A	18 (53%) 16 (47%)
Tumor Differentiation[d] Well Moderate to poor	8/25 (32%) 17/25 (68%)	4/21 (19%) 17/21 (81%)
Vascular Invasion Yes	15 (54%)	24 (71%)
Lymph Node Involvement Yes	13 (46%)	6 (18%)
Type of Treatment Complete resected Incomplete resected	14 (50%) 14 (50%)	24 (71%) 10 (29%)
Underlying Cirrhosis Yes	5 (18%)	2 (6%)
Tumor Stage I, II, or III IV-a or IV-b	6(11%) 22 (79%)	19 (56%) 15 (44%)
Adjuvant Therapy[e] Yes	22/24 (92%)	24/32 (75%)
Anatomic Classification[f] III-a III-a + III-b IV IVa IVb V Unknown	 7 (25%) 3 (11%) 7 (25%) 1 (4%) 2 (7%) 2 (7%) 2 (7%) 4(14%)	n/a

a = age (in years) at time of hepatic resection
b = for HCCA patients, the tumor usually involves bifurcation of the common hepatic bile duct
c = for HCCA patients, there is no discrete liver mass
d = three patients with HCCA and eleven patients with PCCA tumor differentiation unknown
e = post-operative radio-and/or chemotherapy for these patients who survived at least 30 days following surgery
f = anatomic classification only for HCCA patients

Table V: Characteristics of patients with at least five years follow-up.

Type of Tumor	Patient #	Follow-Up Months	TNM Stage	Type of Treatment	Outcome	Vascular Invasion	Multiple Tumors	Lymph Node Involvement	Lobe Distribution	Tumor size $\geq$ 5 cm
HCCA	1	101.69	IV-A	CR	AWD	YES	N/A	NO	N/A	N/A
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: Death free of disease

XXXXX: Postoperative morbidity and mortality in hilar cholangiocarcinomas (HCCA).

Complication	Margins Positive	Vascular Reconstruction	Reoperations	Outcome (30 Days)
Seroma (n=1)	N	N	N	Recovered
Bile leak (n=1)	N	Y	N	Recovered
Bile leak, abscess (n=1)	Y	N	N	Recovered
Bile leak, abscess (n=2)	N(1), Y(1)	Y(1), N(1)	Open drainage (2)	Recovered (2)
Subphrenic abscess (n=2)	Y(2)	Y(1), N(1)	Open drainage (2)	Died (2)
Liver necrosis (n=1)	Y	Y	N	Died
Bile leak, Partial liver necrosis (n=1)	N	Y	Excision RAS	Died

Y = Yes
N = No
RAS = Right anterior segment
Numbers in parentheses are the number of patients

XXXX: Postoperative morbidity and mortality in peripheral cholangiocarcinomas (PCCA).

Complication	Margins Positive	Vascular Reconstruction	Reoperations	Outcome (30 Days)
Bile leak (n=1)	N	N	None	Recovered
Bile leak, abscess (n=1)	Y	Y	None	Recovered
Biliary fistula, sepsis (n=1)	N	Y	None	Recovered
Portal vein thrombosis (n=1)	N	Y	None	Recovered
Peritonitis (n=1)	Y	N	Laparotomy	Recovered
Bile leak, abscess, biliary necrosis (n=1)	N	N	OLTX	Recovered
Bile leak, abscess, sepsis (n=1)	Y	Y	None	Died
Cardiac arrest (n=1)	Y	N	None	Died **

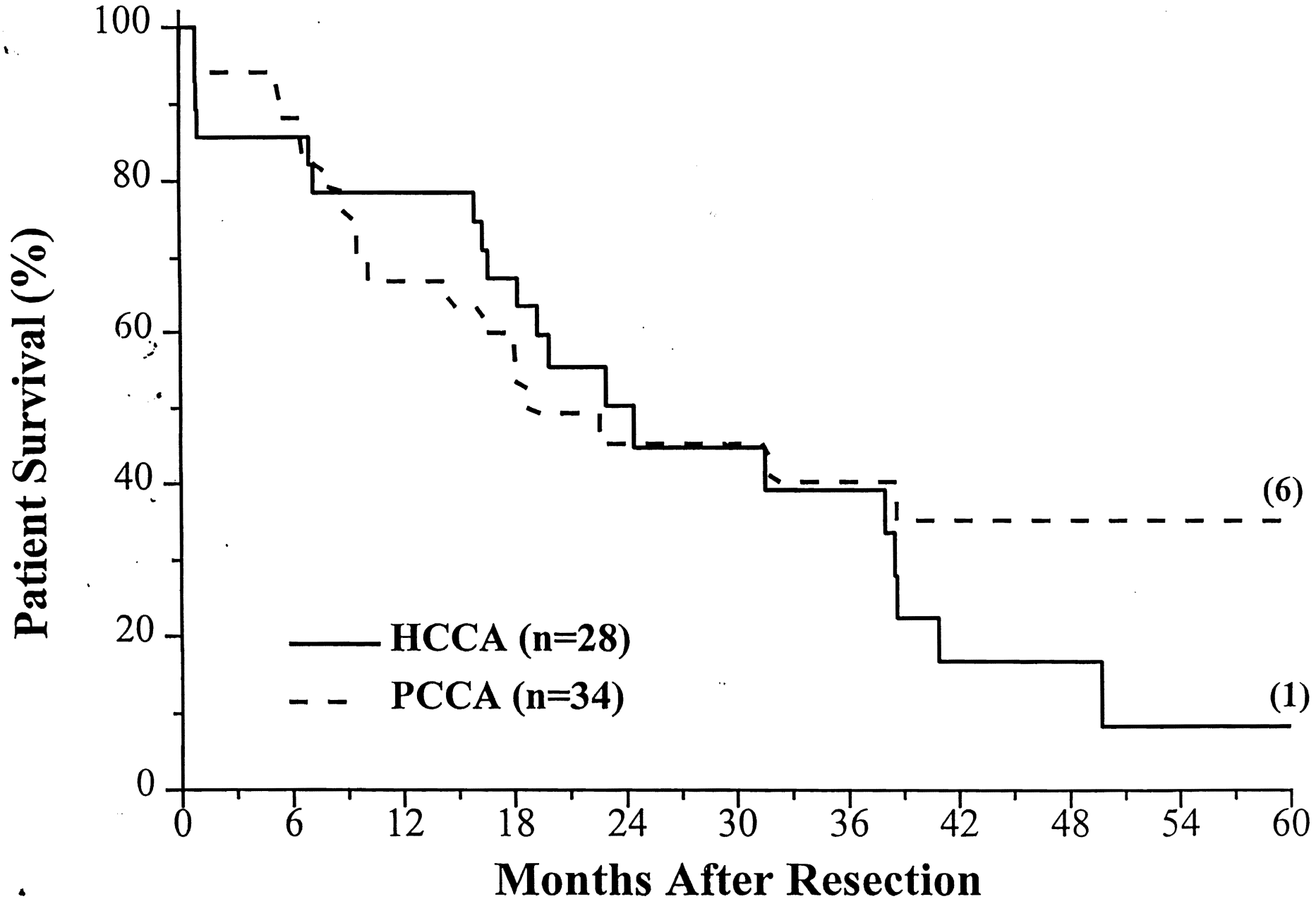
** Intraoperative death
Y = Yes
N = No
OLTX = Orthotopic liver transplantation

Anatomical Classifications in Patients with Hilar Cholangiocarcinomas

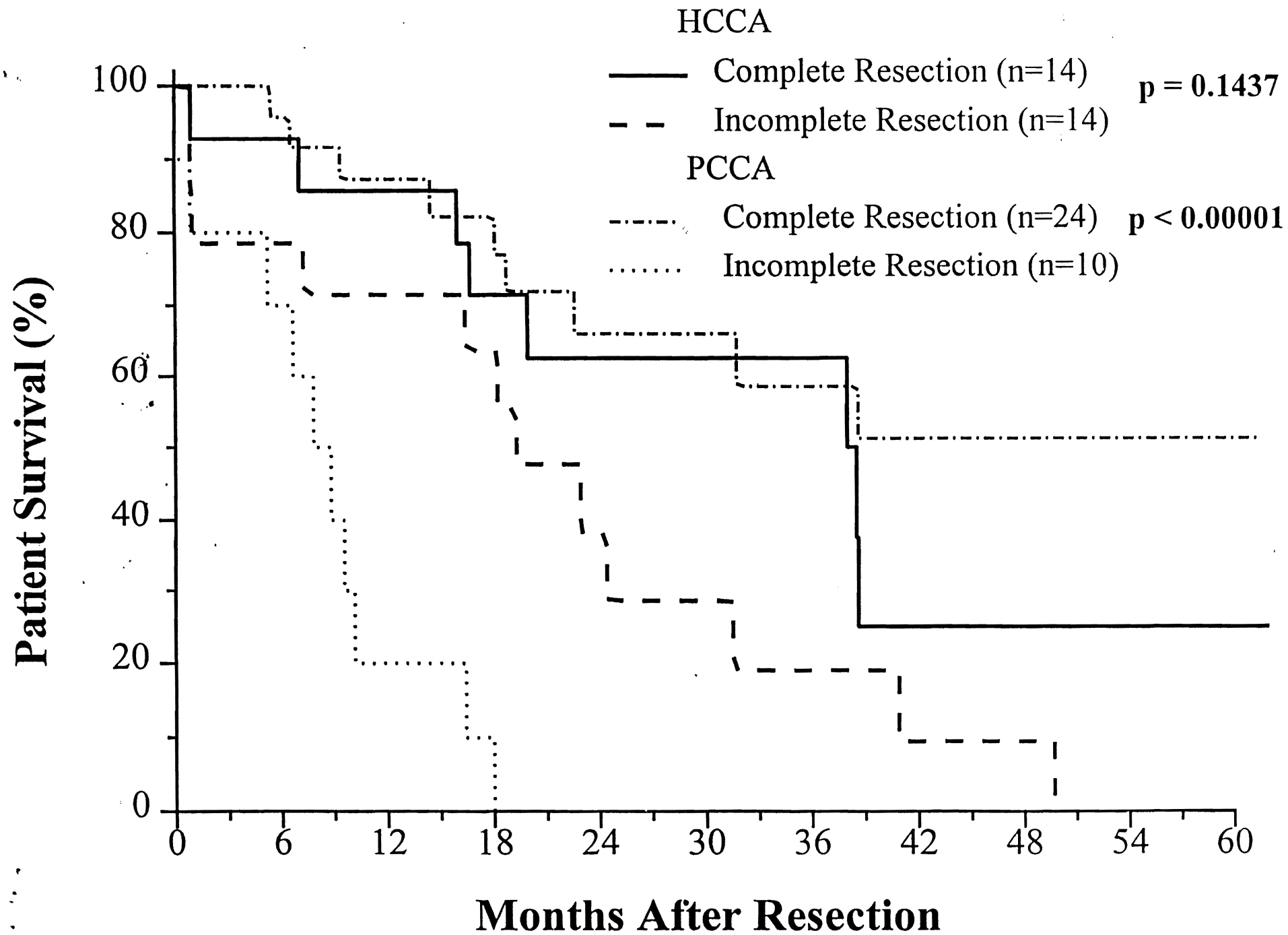
	Type I	Type II	Type IIIa	Type IIIa+
				
Number of Cases:	-	-	7	3

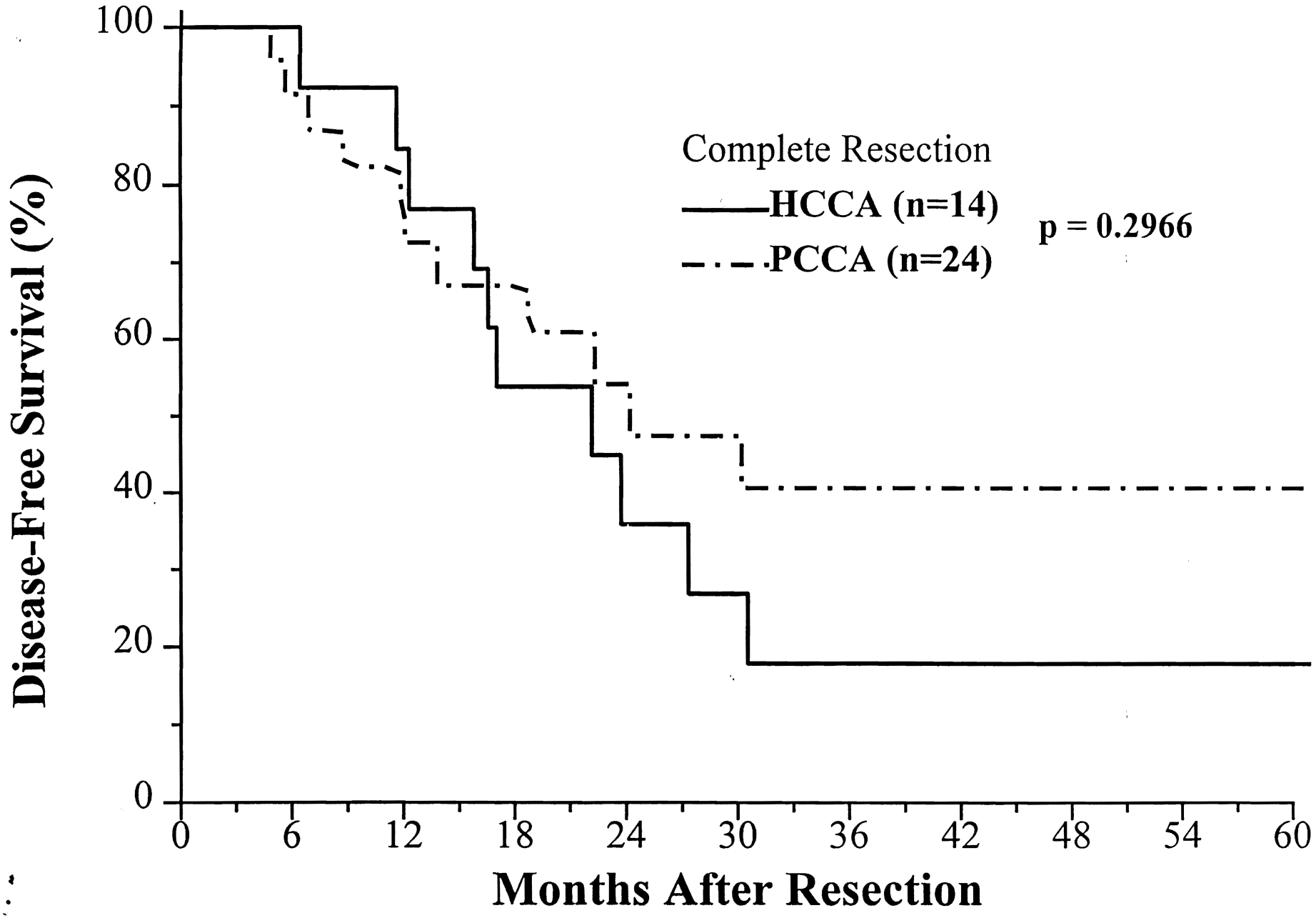
	Type IIIb	Type IIIb+	Type IV	Type IVa	Type IVb	Type V
						
Number of Cases:	7	-	1	2	2	2

FIGURE 1



Numbers in parentheses are the number of patients at risk


HCCA
Complete Resection (n=14)
Incomplete Resection (n=14)
p = 0.1437
PCCA
Complete Resection (n=24)
Incomplete Resection (n=10)
p < 0.00001
Patient Survival (%)
100
80
60
40
20
0
0
6
12
18
24
30
36
42
48
54
60
Months After Resection


Disease-Free Survival (%)
100
80
60
40
20
0
0
6
12
18
24
30
36
42
48
54
60
Months After Resection
Complete Resection
HCCA (n=14)
PCCA (n=24)
p = 0.2966