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Factors Influencing Postoperative Morbidity, Mortality, and Survival After Resection for Hilar Cholangiocarcinoma

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Objective
Morbidity and mortality involved in the resection of hilar cholangiocarcinoma were reviewed retrospectively. The clinicopathologic and laboratory parameters that might influence the patient's survival also were re-evaluated.

Summary Background Data
Although much progress has been made in the diagnosis and management of hilar cholangiocarcinoma, long-term outlook for most patients remains poor. Surgical resection is usually prohibited because of its local invasiveness, and most patients can only be managed by palliative drainage. Recently, many surgeons have adopted a more aggressive resection with varying degrees of success. Several prognostic factors in bile duct carcinoma have been proposed; however, no reports have specifically focused on resected hilar cholangiocarcinoma and its prognostic survival factors using multivariate analysis.

Methods
The clinical records and pathologic slides of 49 cases with resected hilar cholangiocarcinoma were reviewed retrospectively. Twenty clinical and laboratory parameters were evaluated for their correlation with postoperative morbidity and mortality, whereas 31 variables were evaluated for their significance with postoperative survival. Variables showing statistical significance in the first univariate analysis were included in the following multivariate analysis using stepwise logistic regression test for factors affecting morbidity and mortality and Cox stepwise proportional hazard model for factors influencing survival.

Results
There were 5 in-hospital deaths, and the cumulative 5-year survival rate in 44 patients who survived was 14.9%, with a median survival of 14.0 months. Multivariate analysis disclosed that co-existent hepatolithiasis and lower serum asparate aminotransferase levels (≤90 U/L) had a significant low incidence of postoperative morbidity, whereas a serum albumin of less than 3 g/dL was the only significant factor affecting mortality. Regarding survival, univariate analysis identified eight significant factors: 1) total bilirubin ≥10 mg/dL, 2) curative resection, 3) histologic type, 4)

perineural invasion, 5) liver invasion, 6) depth of cancer invasion, 7) positive proximal resected margin, and 8) positive surgical margin. However, multivariate analysis disclosed total bilirubin ≥10 mg/dL, curative resection, and histologic type as the three most significant independent variables.

Conclusions

Surgical resection provides the best survival for hilar cholangiocarcinoma. An adequate nutritional support to increase serum albumin over 3 g/dL is the most important factor to decrease postoperative mortality. Moreover, preoperative biliary drainage to decrease jaundice and a curative resection with adequate surgical margin are recommended if longer survival is anticipated. Patients with well-differentiated adenocarcinoma seem to survive longer compared to those with moderately or poorly differentiated tumors.

Adenocarcinoma arising at the hepatic hilar region is a rare cause of obstructive jaundice. It usually grows slowly and patients frequently die of cholangitis and hepatic failure before distant metastasis is evident.[1,2] Because of the slow rate of growth and the difficulties encountered during tumor resection, surgical treatment usually has consisted of either exploration alone or palliative decompression of the biliary tract by either internal or external drainage.[3-6] However, with the recent improvement of diagnostic and surgical techniques, many surgeons have adopted a more aggressive surgical approach to these malignancies with varying degrees of success.[7-18]

The prognosis of such patients is usually frustrated. Not only are these lesions frequently unresectable, but also their invasiveness hinders a curative resection. Moreover, adjunctive chemotherapy and/or radiation therapy usually do not help prolong survival.[19-21] Recently, several reports have analyzed the prognostic factors in bile duct carcinoma[22-24]; aside from surgical resection, perineural invasion and pancreatic invasion had been found to be two most significant factors of survival.[25]

The purposes of the present study were to evaluate the morbidity and mortality involved in resection of the hilar tumor and to re-examine the clinical and pathologic factors that might influence patient survival in our own series.

MATERIALS AND METHODS

From June 1983 through April 1995, 49 cases of hilar cholangiocarcinoma involving hepatic duct confluence were resected; of them, 40 cases were treated at Veterans General Hospital-Taipei and the additional 9 patients were resected at Veterans General Hospital-Taichung. The term *hilar cholangiocarcinoma* included lesions arising from the common hepatic duct, right, left, or both hepatic duct and intrahepatic bile duct cancer invading the hepatic hilus.[13] The middle and lower as well as the lesions arising from the papilla of Vater and gallbladder were excluded from this study. Of the 49 cases, 34 were men and 15 were women. Their ages ranged from 32 to 74 years (mean, 62 years).

Clinical assessment of the potential prognostic factors was made for each patient. Particular interest was paid to the presence of hepatolithiasis, the anatomic location of tumor according to modified Bismuth–Corlette classification,[26] preoperative biliary drainage, operative procedures as well as its curability, and postoperative radiation therapy. The most recent laboratory data before operation also were recorded to assess the laboratory parameters. All the pathologic slides were re-evaluated by a pathologist, and special attention was paid to the histologic type of the lesion and tumor invasiveness, that is, nerve, lymphatic, blood vessel, lymph node, liver, depth of tumor invasion, and TNM staging (Table 1).

Thirteen patients (26.5%) had co-existent hepatolithiasis. Thirty-three patients (67.3%) underwent preoperative percutaneous transhepatic biliary drainage (PTBD). A wide variety of surgical procedures was performed as listed in Table 2. The tumor locations according to modified Bismuth–Corlette classification (types I, II, IIIa, IIIb, and IV)[26] were 8 (16.3%), 11 (22.4%), 10 (20.4%), 17 (34.7%), and 3 (6.1%), respectively (Fig. 1). A curative resection was defined as macroscopic and microscopic free of tumor cell at the resected bile duct or liver margin; there were 24 curative and 25 palliative resections. Thirty-eight patients had documented lymph node dissection, whereas 11 patients did not have this information in their operation or pathologic records. The operative procedures performed in various locations of the

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Table 1. PRINCIPAL VARIABLES

Clinical	Age, sex, duration of symptoms and jaundice, presence of hepatolithiasis, modified Bismuth type, preoperative biliary drainage
	Operative procedure
	with or without liver resection
	with or without caudate lobe resection
	curative or palliative resection
	Postoperative radiotherapy
Laboratory	Hemoglobin, albumin, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), asparate aminotransferase (AST)
	Total bilirubin
	≥3 mg% *vs.* <3 mg%
	≥5 mg% *vs.* <5 mg%
	≥10 mg% *vs.* <10 mg%
Pathologic	Macroscopic: serosal invasion, vascular invasion
	Microscopic: histologic type: papillary, well differentiated, moderately differentiated, poorly differentiated, adenosquamous carcinoma
	Vascular invasion, lymphatic invasion, perineural invasion, liver invasion, lymph node metastasis, resected proximal and distal margin of bile duct, exposed surgical margin.
	Depth of cancer invasion
	limited to fibromuscular layer
	limited to adventitia and subserosal layer
	invasion to and beyond serosa
	TNM stage

tumor according to modified Bismuth–Corlette classification also were tabulated in Figure 1. Postoperative radiation therapy was performed in 11 patients, consisting of external irradiation in all of them and additional intracavitary irradiation with Iridium-192 in 4 patients.

Forty-four hospital survivors were followed up periodically or until their death. The mean follow-up period was 26.2 months, ranging from 1 to 116 months.

Statistical Analysis

Each clinical and laboratory parameter was tested for its ability to predict postoperative morbidity and mortality by chi square analysis. For those significant parameters ($p < 0.05$), the stepwise logistic regression test was applied to identify the independent factors. As far as the survival factors were concerned, the independent variables were first analyzed by univariate analysis. The survival for each variable was estimated by Kaplan–Meier method, and the significance of survival was determined by the generalized Wilcoxon method. Only the variables of statistical significance ($p < 0.05$) were included in a following multivariate analysis, BMDP 2L, for evaluation using the Cox multiple stepwise regression model.

RESULTS

Operative Mortality and Morbidity

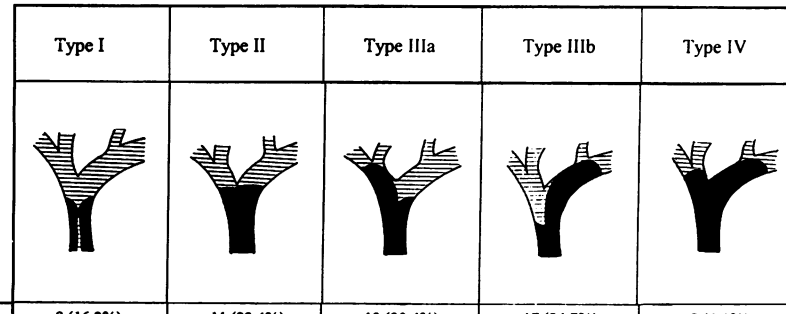
Five patients died after operation without leaving the hospital and 23 patients had various postoperative complications (Table 3), resulting in a mortality rate of 10.2% and a complication rate of 46.9%. Hepatic failure was the most serious postoperative complication. Six patients died of hepatic failure, including all five in-hospital mortalities and one patient who died 3 months after operation.

The patients with each of the 20 clinical and laboratory parameters were evaluated, and the correlation between each risk factor and postoperative morbidity and mortality is listed in Table 4. Two of the 20 parameters were found to be indicators of an increased morbidity and mortality in univariate analysis. Regarding the postoperative morbidity, the presence of co-existent hepatolithiasis was found to have a lower complication rate, and patients with more than twofold the normal asparate aminotransferase levels (*i.e.*, ≥91 U/L) had a higher complication rate. These two factors all were independent variables in a multivariate analysis (Tables 4 and 5). Regarding the postoperative mortality, it was well demonstrated that a lower serum albumin (≤3 g/dL) and hemoglobin (<10 g/dL) level had a significantly higher mortality rate (Table 4). However, only the albumin factor was identified to be significant in a stepwise logistic

Table 2. OPERATIONS PERFORMED IN 49 PATIENTS WITH HILAR CHOLANGIOCARCINOMA

	No. of Patients
Local resection of extrahepatic bile duct with hilar bile duct	21 (1)*
Bile duct resection with liver resection	28 (4)*
without caudate lobe resection	17
Wedge liver resection	2
Segmentectomy	1
Right lobectomy	4 (1)*
Left lobectomy	9
Central lobectomy (segment 4, 5, 8)	1 (1)*
with caudate lobectomy	11
Right lobectomy	2
Left lobectomy	6 (1)*
Right trisegmentectomy	2 (1)*
Right trisegmentectomy with portal vein resection	1
Curative resection	24 (4)*
Palliative resection	25 (1)*

* Postoperative inhospital mortality.



	Type I	Type II	Type IIIa	Type IIIb	Type IV
Cases (%)	8 (16.3%)	11 (22.4%)	10 (20.4%)	17 (34.7%)	3 (6.1%)
Operative procedurs					
CBD & Liver resection	0 (0)	2 (18.2%)	10 (100%)	15 (88.2%)	1 (33.3%)
CBD resection only	8 (100%)	9 (81.8%)	0 (0)	2 (11.8%)	2 (66.6%)
L.N dissection	7 (87.5%)	8 (72.7%)	10 (100%)	12 (70.6%)	1 (33.3%)
Curative surgery	2 (25.0%)	4 (36.4%)	6 (60%)	12 (70.6%)	0 (0)

Figure 1. Operative procedures performed according to the tumor location (modified Bismuth-Corelette Classification).

regression analysis (Table 5). There was no correlation of the morbidity and mortality with the rest of the parameters evaluated, which included age, bilirubin level, use of preoperative biliary drainage, as well as the extent of operation as it was anticipated.

Overall Survival

The cumulative 5-year survival rate for the 44 surviving patients was 14.9% with a median survival of 14.0 months. These results were statistically significant when compared with those of 113 nonresected patients treated during the same period in Veterans General Hospital-Taipei. None of the latter group survived 5 years, and the median survival was only 3 months (Fig. 2).

Univariate Analysis

Thirty-one clinicopathologic and laboratory factors were analyzed with univariate method to find 8 of them to be significant: 1) total bilirubin ≥10 mg/dL, 2) curative resection, 3) histologic type, 4) perineural invasion, 5) liver invasion, 6) depth of cancer invasion, 7) positive proximal resected margin, and 8) positive surgical margin (Table 6).

Table 3. POSTOPERATIVE COMPLICATIONS

	No. of Patients
Hepatic failure	8 (5)*
Renal failure	3 (2)*
Anastomotic leakage	6 (1)*
Intraabdominal abscess	10 (1)*
Upper gastrointestinal bleeding	3 (2)*
Sepsis	5 (1)*
Congestive heart failure	1 —

* Inhospital mortality.

Multivariate Analysis

Multivariate analysis using Cox proportional hazard model involving the eight significant factors determined by univariate analysis identified three significant independent variables: 1) total bilirubin ≥10 mg/dL, 2) curative resection, and 3) histologic type (Table 7).

Preoperative Total Bilirubin Level and Survival

Three cutoff points of the bilirubin level were examined in the univariate analysis (*i.e.*, 3 mg/dL, 5 mg/dL, and 10 mg/dL). It was interesting to find that the preoperative total bilirubin of 10 mg/dL was so easily detected as the first prognostic variable by Cox stepwise proportional hazard model. There were no 5-year survivors in patients with serum bilirubin greater than 10 mg/dL, and the median survival was only 6.0 months. On the contrary, the 5-year survival rate was 24.1% for patients with serum bilirubin less than 10 mg/dL, and its median survival was 18.0 months ($p = 0.0006$) (Table 7, Fig. 3).

Curative Resection and Survival

A curative resection was usually defined as a tumor-free resection margin plus an adequate lymph node dissection. Because lymph node dissection was only recognized in 38 cases and the extent of dissection was not standardized among them, a curative resection was arbi-

Table 4. CLINICAL AND LABORATORY RISK FACTORS CORRELATED WITH MORBIDITY AND MORTALITY

	No. (%) of Patients	Morbidity %	Morbidity p Value	Mortality %	Mortality p Value
Clinical parameters					
Age (yrs)					
≥65	26 (53.1)	53.8		15.4	
<65	23 (46.9)	39.1	NS	4.3	NS
Sex					
Male	34 (69.3)	47.1		8.8	
Female	15 (30.6)	46.7	NS	13.3	NS
Duration of symptom (mos)					
≥1	28 (42.9)	47.6		14.3	
<1	21 (57.1)	46.4	NS	7.1	NS
Duration of jaundice (mos)					
≥1	10 (20.4)	40.0		10.0	
<1	39 (79.6)	48.7	NS	10.3	NS
Presence of cholangitis					
Yes	23 (46.9)	34.8		8.7	
No	26 (53.1)	57.7	NS	11.5	NS
Presence of hepatolithiasis					
Yes	13 (26.5)	23.1		7.7	
No	36 (73.5)	55.6	p < 0.05	11.1	NS
Modified Bismuth-Corlette Classification					
Type I	8 (16.3)	25.0		0	
Type II	11 (22.4)	36.4		9.1	
Type IIIa	10 (20.4)	70.0		30.0	
Type IIIb	17 (34.7)	52.9		5.9	
Type IV	3 (6.1)	33.3	NS	0	NS
PTBD					
Yes	33 (67.3)	51.5		15.2	
No	16 (32.7)	37.5	NS	0	NS
Laboratory parameters					
Total bilirubin (mg%)					
≥3	29 (59.2)	44.8		6.9	
<3	20 (40.8)	50.0	NS	15.0	NS
≥5	24 (49.0)	45.8		4.2	
<5	25 (51.0)	48.0	NS	16.0	NS
≥10	17 (34.7)	41.2		5.9	
<10	32 (65.3)	50.0	NS	12.5	NS
Albumin (gm%)					
≥3	45 (91.8)	44.4		6.7	
<3	4 (8.2)	75.0	NS	50.0	p < 0.05
Hemoglobin (gm%)					
≥10	44 (89.8)	45.5		6.8	
<10	5 (10.2)	60.0	NS	40.0	p < 0.05
BUN (mg%)					
≥20	8 (16.3)	37.5		12.5	
<20	41 (83.7)	48.8	NS	9.8	NS
Creatinine (mg%)					
≥1.3	9 (18.4)	33.3		0	
<1.3	40 (81.6)	50.0	NS	12.5	NS
ALT (U/L)					
>120	13 (26.5)	53.8		0	
81–≤120	7 (14.3)	57.1		0	
41–≤80	13 (26.5)	46.2		30.8	
<40	16 (32.7)	37.2	NS	6.3	NS
AST (U/L)					
>135	6 (12.2)	83.3		0	
91–≤135	5 (10.2)	80.0		0	
46–≤90	23 (46.9)	30.4		17.4	
<45	15 (30.6)	46.7	p < 0.05	6.7	NS
Operative procedures					
Curative	24 (49.0)	54.2		16.7	
Palliative	25 (51.0)	40.0	NS	4.0	NS
Liver resection					
Yes	28 (57.1)	57.1		14.3	
No	21 (42.9)	33.3	NS	4.8	NS
Lymph node dissection					
Yes	38 (77.6)	47.4		13.2	
No	11 (22.4)	45.5	NS	0	NS

PTBD = percutaneous transhepatic biliary drainage; BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: asparate aminotransferase; NS: not significant.

trarily defined as macroscopic and microscopic tumor free at the resected specimen margin in this study.

There were 20 curative and 24 palliative resections in the patients who survived the operation. The 5-year survival rate for the curative resection was 34.5%, and its median survival was 19.0 months, whereas the palliative resection gave no 5-year survivors and a median survival of 9.0 months ($p = 0.001$) (Table 7, Fig. 4).

Histologic Type and Survival

Well-differentiated adenocarcinoma was recognized in nine patients and its 5-year survival rate was 50.8% with a median survival of 58 months. These results were statistically significant compared with those from 18 patients with moderately differentiated tumor (16.7%, 11.0 months) and 15 patients with poorly differentiated tu-

Table 5. FACTORS SIGNIFICANTLY AFFECTING POSTOPERATIVE MORBIDITY AND MORTALITY USING LOGISTIC REGRESSION ANALYSIS

Variable	β	SE	χ^2	P	HR	95% CI
Morbidity						
Hepatolithiasis	0.77	0.41	4.24	0.04	2.17	0.97–4.82
AST	−0.56	0.59	8.21	0.04	0.57	0.18–1.82
	1.08	0.92	8.21	0.04	2.94	0.48–17.88
	0.90	0.94	8.21	0.04	2.47	0.39–15.65
Mortality						
Albumin	2.59	1.27	4.71	0.03	13.3	1.03–172

β = Coefficient; SE = standard error; χ^2 = chi square; HR = hazard ratio; CI = confidence interval; AST = asparate aminotransferase.

mor (0%, 9.3 months). Two patients with adenosquamous carcinoma had the worst outcome. They survived 3 and 4 months after operation (p = 0.007), respectively (Table 7, Fig. 5).

DISCUSSION

The surgical treatment of bile duct cancer is difficult, particularly in cases of lesions involving hepatic hilum.[1,2] Despite the small and slow-growing tumor, surgical resection is usually prohibited by its local invasiveness and can be managed only by palliative procedures to decompress the biliary tract.[3–6] With the improvement of diagnostic and surgical techniques, a good number of cases can be resected with acceptable morbidity and mortality;[7–18] in fact, a better prognosis in association with resection than with palliative procedure has been reported previously[7,9,10,16,22,23] and also was found in our experiences (Fig. 2).

The correlation between the extent of operation and the tumor location was clearly shown in this study (Fig. 1). Major liver resection was performed frequently in type IIIa and IIIb patients, whereas simple common duct resection was performed mainly in type I and II lesions. Types IIIa and IIIb had a higher chance to achieve a potential curative surgery after liver resection, whereas palliative operation should only be expected in patients with type IV lesions.

Despite the extensive resectional surgery with a high percentage of liver resection (28/49), the morbidity and mortality rates in this series (46.9% and 10.2%) are in agreement with other authors' experiences, whether hepatectomy was performed.[10,11,13,23,27,28] It is to be expected that the mortality associated with extensive surgery in

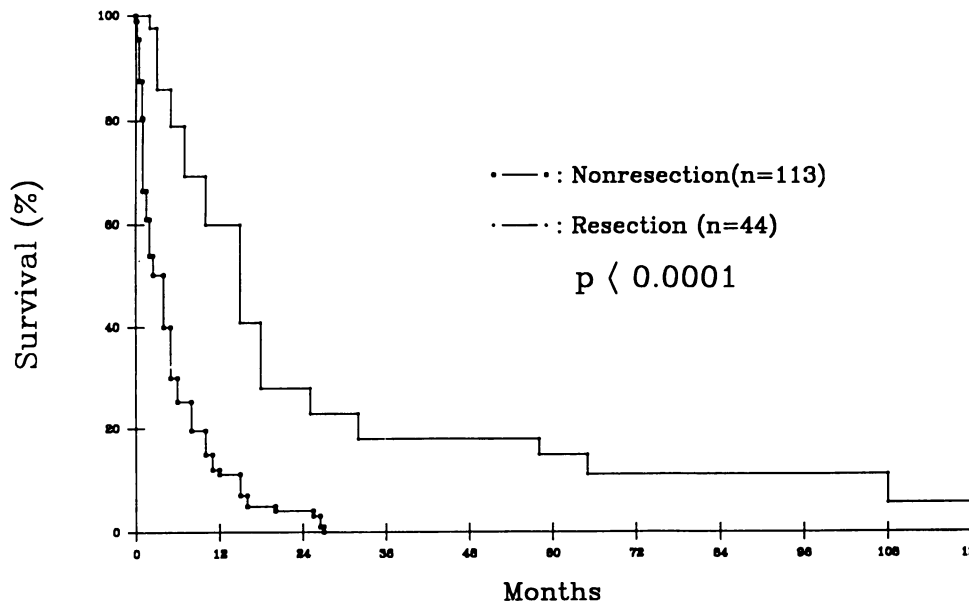


Figure 2. Postoperative survival curves in resected and nonresected hilar cholangiocarcinoma. Differences between the groups are statistically significant (p < 0.0001).

Table 6. UNIVARIATE ANALYSIS OF THE CLINICOPATHOLOGIC AND LABORATORY PARAMETERS

Factor	No. of Patients	Mean/Median Survival (mos)	p Value
Total bilirubin			
≥10 mg%	16	8.6/6.0	0.0006
<10 mg%	28	37.0/18.0	
Curative resection	20	44.3/19.0	0.001
Palliative resection	24	11.8/9.0	
Histologic type of lesion			0.007
Well-differentiated adenocarcinoma	9	51.8/58.0	
Moderately differentiated adenocarcinoma	18	28.6/11.0	
Poorly differentiated adenocarcinoma	15	11.8/9.3	
Adenosquamous cell carcinoma	2	3.5/3.0	
Perineural invasion			0.03
Present	36	19.9/13.0	
Absent	7	56.1/65.0	
Liver invasion			0.01
Present	28	24.0/10.0	
Absent	11	40.3/26.0	
Depth of cancer invasion			0.04
Invasion limited to fibromuscular layer	3	96.3/108.0	
Invasion limited to adventitia and subserosal layer	8	18.0/16.0	
Invasion to and beyond serosa	33	16.9/10.0	
Resected proximal margin of bile duct			0.004
Cancer positive	19	10.4/9.0	
Cancer negative	25	35.8/17.0	
Exposed surgical margin			0.002
Cancer positive	23	11.1/9.0	
Cancer negative	21	40.4/18.0	

patients with cancer and complicating jaundice will be high. Indeed, a 13% to 28% mortality rate associated with major surgery in patients with serum bilirubin greater than 10 mg/dL has been reported.[29-31]

Regarding the postoperative complications, Nimura reported that hyperbilirubinemia (>5 mg/dL) occurred in 51.4% of patients with curative hepatic resection and 14% developed hepatic failure with increased total bilirubin above 10 mg/dL. Five patients ultimately died of this complication.[32] Among the eight patients who developed hepatic failure in this series, the mean preoperative bilirubin was 5.4 mg/dL (range, 0.7–15.3 mg/dL) and seven patients had preoperative PTBD. No patients had portal vein embolization. One patient underwent bile duct resection and seven patients had concomitant liver resection. Six of the eight patients died after operation, including five patients who died in hospital and one who was re-admitted and died from liver failure 3 months after operation. To minimize this complication, routine preoperative biliary drainage has been suggested, and a bilirubin level of less than 3 mg/dL was recommended by Nimura and Makuuchi[13,32,33] before a major operation was undertaken. Furthermore, preoperative portal vein embolization also was recommended to increase the safety of major liver resection in hilar bile duct carcinoma.[33]

Several studies have identified preoperative factors in biliary tract surgery and tried to define groups of patients at high risk.[30,34-36] The prognostic factors regarding postoperative morbidity and mortality in resected hilar cholangiocarcinoma also was evaluated here. It was interesting to find that, for unexplained reasons, patients with co-existent hepatolithiasis and low asparate aminotransferase levels possessed a lower complication rate. Moreover, patients with a lower serum albumin (<3 g/dL) had a significantly higher mortality rate, which was consistent with previous reports.[30,34,36] It is clearly shown that an adequate nutritional support is the most important factor to decrease postoperative mortality.

Regarding the survival of bile duct cancer, surgical resection has been reported to have a better prognosis,[22,23] whereas radiation therapy seemed to have some benefit in patients undergoing palliative stent.[19] Depth of invasion was suggested by Mizumoto et al. to be an important pathologic factor,[24] whereas perineural invasion and pan-

Table 7. FACTORS SIGNIFICANTLY ASSOCIATED WITH SURVIVAL AFTER MULTIVARIATE ANALYSIS USING COX STEPWISE PROPORTIONAL HAZARD MODEL

Variable	β	SE	χ^2	P	HR	95% CI
Total bilirubin ≥10 mg%	−0.90	0.45	10.47	0.001	0.41	(0.17–0.99)
Curative resection	1.10	0.43	5.98	0.015	2.99	(1.30–6.89)
Histologic type	0.68	0.27	6.54	0.011	1.97	(1.17–3.34)

β = coefficient; SE = standard error; χ^2 = chi square; HR = hazard ratio; CI = confidence interval.
Chi square = 24.47.
$p < 0.0001$.

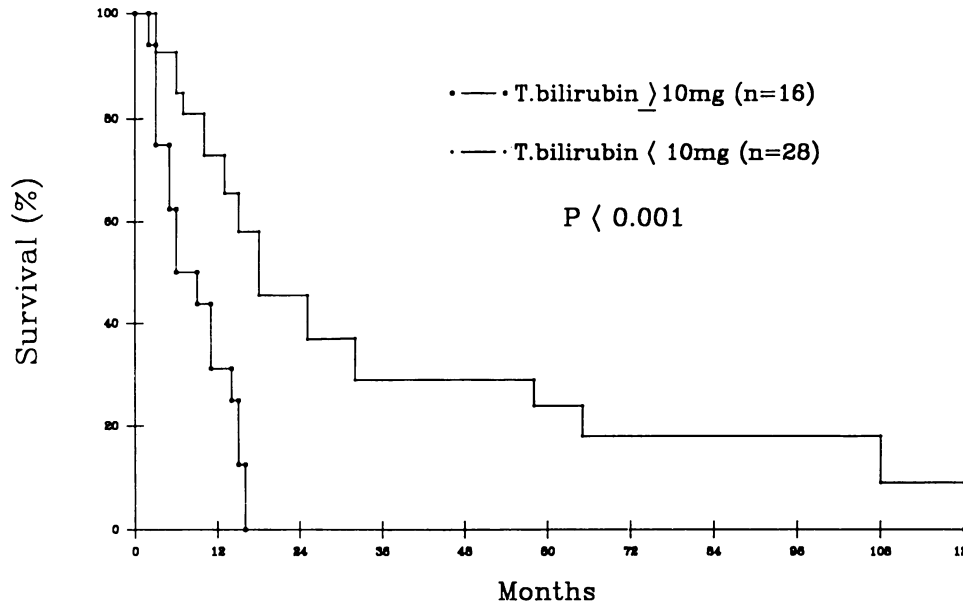


Figure 3. Survival curves of hilar cholangiocarcinoma according to the preoperative total bilirubin level. A statistically significant difference of survival is observed between the patients with total bilirubin ≥ 10 mg% and < 10 mg% ($p < 0.001$).

creatic invasion were proposed by Bhuiya et al. as two independent prognostic factors in a multivariate analysis using the Cox stepwise proportional hazard model.[25] Until now, no reports in the world literature have specifically focused on the resected hilar cholangiocarcinoma and its prognostic factor using multivariate analysis, and this study identified three independent prognostic variables that were significantly correlated with survival.

It has been shown that elevated bilirubin affects the morbidity and mortality significantly in biliary tract surgery[30,34,36]; however, no data have shown that severe jaundice was correlated with patient survival. Interestingly, total bilirubin of 10 mg/dL or more was the first prognostic factor detected in the present study. Patients with lower bilirubin levels (<10 mg/dL) had 5-year survival of 24.1%, whereas it was 0% for patients with higher value (≥10 mg/dL). When operative morbidity and mortality regarding the serum bilirubin levels were examined, there were no differences in terms of 3 mg/dL, 5 mg/dL, or 10 mg/dL. However, when the operative procedures were analyzed at the cutoff value of 10 mg/dL, it was clearly shown that more patients had major liver resection (60.7% *vs.* 31.3%)

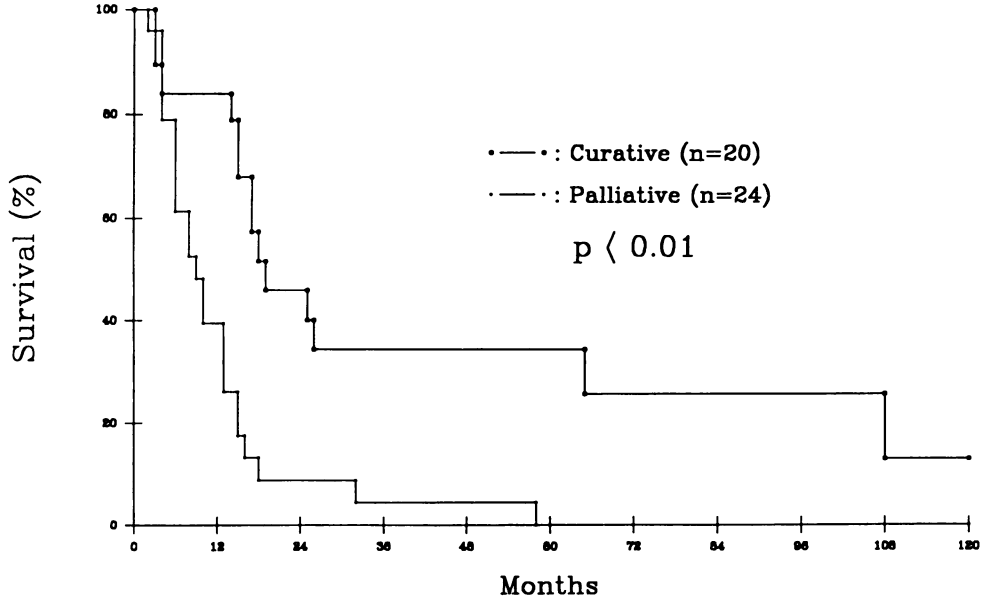


Figure 4. Survival curves of hilar cholangiocarcinoma in patients with curative resection and palliative resection. A statistical significance is observed ($p < 0.01$).

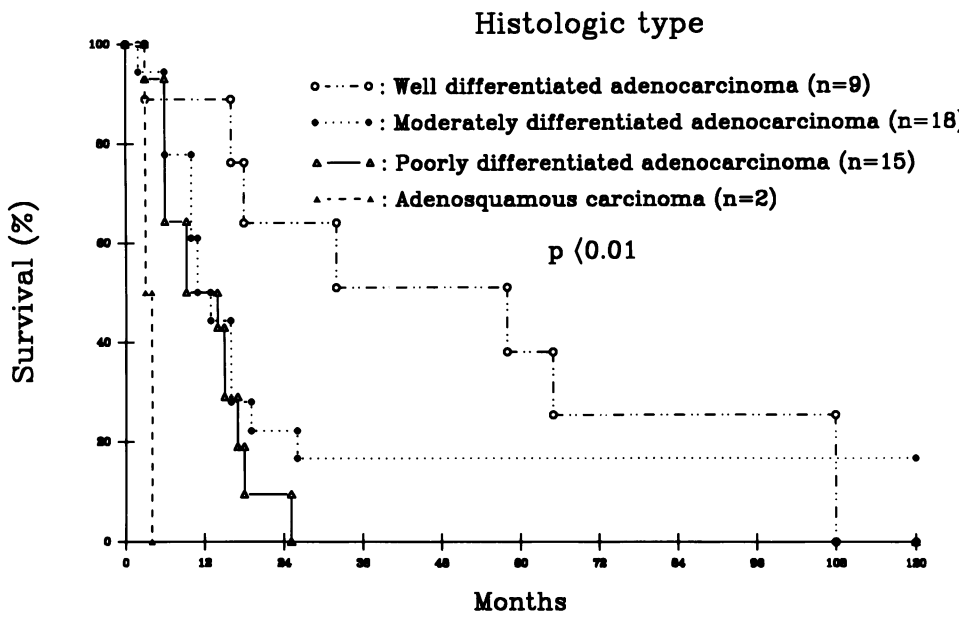


Figure 5. Survival curves of hilar cholangiocarcinoma according to the histologic type of the lesion. A statistically significantly longer survival ($p < 0.01$) is observed in well-differentiated tumor.

and curative resection (57.2% *vs.* 25.0%, $p < 0.05$) with mild jaundice (<10 mg/dL) than with severe jaundice (≥10 mg/dL) (Table 8). It seems that a higher bilirubin level will jeopardize the surgeon's decision making to perform a less-extensive surgery, which will result in a poor survival outcome. Thus, the issue of preoperative PTBD in hilar cholangiocarcinoma remains debatable. Although prospective randomized studies have not evidenced PTBD as being beneficial to patients with jaundice concerning postoperative morbidity and mortality,[37-39] as far as the patient's condition and surgical extent are concerned, a preoperative PTBD seems advisable for hilar bile duct cancer with severe jaundice (≥10 mg/dL).

Table 8. OPERATIVE PROCEDURES PERFORMED IN PATIENTS WITH DIFFERENT BILIRUBIN LEVELS

	T.Bil ≥ 10 mg	T.Bil < 10 mg	p Value
CBD resection	9	11	
	11 (68.8%)	11 (39.3%)	
Wedge hilar resection	2	0	
			0.05 < p < 0.1
	5	17	
Major liver resection	(31.3%)	(60.7%)	
Curative resection	4	16	
	(25.0%)	(57.2%)	
			<0.05
Palliative resection	12	12	
	(75.0%)	(42.9%)	

T.Bil = total bilirubin level.

The second prognostic factor identified in this study was curative resection. It has been shown that a curative operation with cancer-free margin had a better survival in various cancer surgeries.[40-42] Although extensive retroperitoneal dissection was not performed routinely in our series and the lymph node status could not be assessed accordingly, a good correlation of patient's survival with curative surgery also was well demonstrated when a macroscopic- and microscopic-free margin of the resected specimen were taken into consideration. Regarding the liver resection, a high percentage of caudate lobe tumor involvement has been reported by Japanese surgeons,[8,13] and a rational hepatic segmentectomies with total caudate lobectomy has been recommended by Nimura et al.[13] However, our data did not show any correlation of liver resection or caudate lobectomy with the survival (Table 9), despite liver invasion being identified as a significant factor in univariate analysis. Perhaps the liver invasion is not a dominant factor of tumor invasiveness; other factors such as depth of invasion, resected margin, and exposed surgical margin of the bile duct also should be considered in a curative resection (Table 6).

Histologic type of the lesion has been reported to be an important factor in bile duct cancer[24,25] and was the third independent variable identified in this study. Patients with well-differentiated tumor were found to survive longer than those with moderately or poorly differentiated tumor, and adenosquamous carcinoma was the

Table 9. POSTOPERATIVE SURVIVAL VS. LIVER RESECTION IN PATIENTS WITH HILAR CHOLANGIOCARCINOMA

	n	Median (mos)	Mean (mos)	p Value
Without liver resection	20	15.0	24.1	NS
With liver resection	24	9.3	29.3	
With caudate lobectomy	9	8.0	20.7	NS
Without caudate lobectomy	15	9.3	29.1	

NS = not significant.

worst (Fig. 5). As far as the papillary tumor was concerned, our data did not show any correlation with a good survival as it was pointed out by others.[24,25] The tumor invasiveness still played a major role in its outcome. Eight patients in this series had microscopic papillary tumor: two were at TNM stage I and survived 65 and 108 months, respectively; one was at stage II and survived 26 months; and five were at stage IVa and survived with a mean survival of 8.9 months (range, 2.5–15.0 months).

Theoretically, lymph node metastasis and TNM staging should have prognostic significance to the postoperative survival. Unfortunately, it was not the case in the present study. Perineural invasion, repeatedly emphasized by Bhuiya et al. as a strong prognostic factor,[25,43] was significant in univariate analysis but excluded in this multivariate analysis. None of the other factors, including age, sex, modified Bismuth type, presence of hepatolithiasis, postoperative radiation therapy, macroscopic or microscopic vascular invasion, and lymphatic invasion, were statistically associated with prognosis here. Although much progress has been made in the diagnosis and management of the hilar cholangiocarcinoma, the long-term outlook for most patients is still dismal. There is some evidence from our patients that surgical resection provided the best survival. An adequate preoperative biliary drainage to decrease jaundice and a curative resection with adequate surgical margin are recommended if a longer survival is anticipated. Further improvement certainly depends on effective adjuvant therapy; however, the role of radiation therapy and chemotherapy in the management of this disease is unclear.[19–21] Further prospective randomized studies are warranted.

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