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Cholangiocarcinoma

A Spectrum of Intrahepatic, Perihilar, and Distal Tumors

Attila Nakeeb, M.D.,* Henry A. Pitt, M.D.,* Taylor A. Sohn, M.D.,* JoAnn Coleman, R.N.,* Ross A. Abrams, M.D.,† Steven Piantadosi, M.D., Ph.D.,† Ralph H. Hruban, M.D.,‡ Keith D. Lillemoe, M.D.,* Charles J. Yeo, M.D.,* and John L. Cameron, M.D.*

From the Departments of Surgery, Oncology,† and Pathology,‡ The Johns Hopkins Medical Institutions, Baltimore, Maryland*

Objective
The objective of this article is to introduce a simple method for classifying cholangiocarcinomas and to apply this system to analyze a large number of patients from a single institution.

Summary Background Data
For the past 2 decades, most western reports on cholangiocarcinoma have separated intrahepatic from extrahepatic tumors and have subclassified this latter group into proximal, middle, and distal subgroups. However, "middle" lesions are uncommon and are managed most often either with hilar resection or with pancreatoduodenectomy. The spectrum of cholangiocarcinoma, therefore, is best classified into three broad groups: 1) intrahepatic, 2) perihilar, and 3) distal tumors. These categories correlate with anatomic distribution and imply preferred treatment.

Methods
The records of all patients with histologically confrmed cholangiocarcinoma who underwent surgical exploration at The Johns Hopkins Hospital over a 23-year period were reviewed.

Results
Of 294 patients with cholangiocarcinoma, 18 (6%) had intrahepatic, 196 (67%) had perihilar, and 80 (27%) had distal tumors. Age, gender, race, and associated diseases were similar among the three groups. Patients with intrahepatic tumors, by definition, were less likely ($p < 0.01$) to be jaundiced and more likely ($p < 0.05$) to present with abdominal pain. The resectability rate increased with a more distal location (50% *vs.* 56% *vs.* 91%), and resection improved survival at each site. Five-year survival rates for resected intrahepatic, perihilar, and distal tumors were 44%, 11%, and 28%, and median survival rates were 26, 19, and 22 months, respectively. Postoperative radiation therapy did not improve survival. In a multivariate analysis resection ($p < 0.001$, hazard ratio 2.80), negative microscopic margins ($p < 0.01$, hazard ratio 1.79), preoperative serum albumin ($p < 0.04$, hazard ratio 0.82), and postoperative sepsis ($p < 0.001$, hazard ratio 0.27) were the best predictors of outcome.

Conclusions
Cholangiocarcinoma is best classified into three broad categories. Resection remains the primary treatment, whereas postoperative adjuvant radiation has no influence on survival. Therefore, new agents or strategies to deliver adjuvant therapy are needed to improve survival.

Cholangiocarcinoma is a rare malignancy that can occur anywhere along the intrahepatic or extrahepatic biliary tree. The hepatic duct bifurcation is the most frequently involved site, and approximately 60% to 80% of cholangiocarcinomas encountered at tertiary referral centers are found in the perihilar region.[1-4] Most classification systems have separated intrahepatic from extrahepatic tumors and have further subdivided this latter group into proximal, middle, and distal subgroups. However, in this system, middle third lesions are relatively rare and usually are managed either as a proximal lesion with hilar resection or as a distal lesion with pancreatoduodenectomy. Moreover, intrahepatic cholangiocarcinomas usually are treated like liver lesions with hepatectomy. Therefore, the spectrum of cholangiocarcinoma is best classified into three broad groups: 1) intrahepatic, 2) perihilar, and 3) distal. This classification correlates with anatomic distribution and implies preferred treatment. This classification system was applied to 294 patients with cholangiocarcinoma who underwent surgical management over a 23-year period.

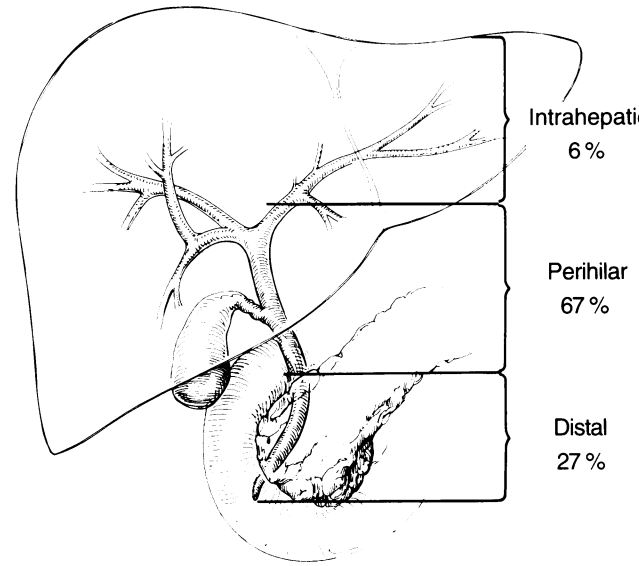

Figure 1. Distribution of 294 cholangiocarcinomas into intrahepatic, perihilar, and distal subgroups.

METHODS

Study Design

The records of all patients with histologically confirmed cholangiocarcinoma who underwent operative exploration at The Johns Hopkins Hospital between January 1, 1973, and December 31, 1995, were retrospectively reviewed. Cholangiocarcinomas were classified into three groups: 1) intrahepatic, 2) perihilar, and 3) distal. Intrahepatic tumors were defined as those confined to the liver that did not involve the extrahepatic biliary tree, did not present with obstructive jaundice, and had no evidence of a primary tumor elsewhere. Perihilar tumors were defined as those involving or requiring resection of the hepatic duct bifurcation. Distal cholangiocarcinomas were defined as tumors that involved the distal extrahepatic, or intrapancreatic, portion of the bile duct and potentially were amenable to pancreatoduodenectomy. Thus, patients with a significant intrahepatic component with involvement of the hepatic duct bifurcation were included with the perihilar rather than the intrahepatic tumors. Patients with cholangiocarcinomas that were treated nonoperatively and those undergoing liver transplantation as primary therapy were excluded from this analysis. Patients with pancreatic, ampullary, or duodenal adenocarcinomas also were excluded. Diffuse tumors involving extensive portions of the intrahepatic and extrahepatic ducts were not managed surgically and, therefore, were not included in this report.

Incidence

During the 23-year period of this study, 294 patients underwent surgical exploration. Eighteen (6%) of the tumors were intrahepatic, 196 (67%) were perihilar, and 80 (27%) were distal (Fig. 1). The number of cases of cholangiocarcinoma per year is shown in Figure 2. From 1973 to 1979, only 18 (6%) patients underwent operative therapy (0 intrahepatic, 17 perihilar, and 1 distal). Dur-

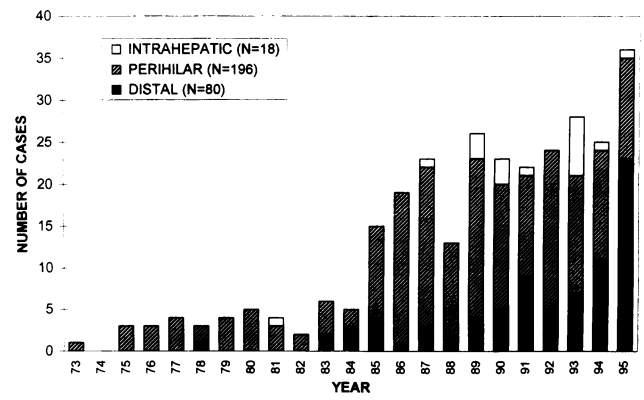

Figure 2. Yearly number of patients with intrahepatic, perihilar, and distal tumors.

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Address reprint requests to Henry A. Pitt, M.D., Blalock 679, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287-4679.

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Table 1. PATIENT CHARACTERISTICS

	Intrahepatic (n = 18)	Perihilar (n = 196)	Distal (n = 80)	Total (n = 294)
Patient characteristics				
Age (years)	59.0 ± 2.6	61.6 ± 0.9	64.8 ± 1.3	62.2 ± 0.7
Male (%)	50	54	59	55
White (%)	94	89	91	90
Associated diseases				
Diabetes (%)	11	15	6	13
IBD (%)	24	4	3	5
PSC (%)	18	4	0	4

IBD = inflamatory bowel disease; PSC = primary sclerosing cholangitis.

ing the 1980s, 118 patients (40%) were treated (5 intrahepatic, 94 perihilar, and 19 distal). Since 1990, 158 patients (54%) have been treated (13 intrahepatic, 85 perihilar, and 60 distal). Over the past decade, the number of perihilar cholangiocarcinomas has remained relatively constant, whereas the number of distal tumors has increased. This phenomenon is due, in part, to increased referrals of periampullary tumors to this institution.

Patient Characteristics

Characteristics of the patients with intrahepatic, perihilar, and distal tumors are presented in Table 1. Ages ranged from 23 to 84 years with a mean age of 62.2 years. Patients with intrahepatic tumors tended to be slightly younger than patients with more distal lesions (59 *vs.* 62 *vs.* 65 years), but these differences were not significantly different. Of the 294 patients, 161 were men and 133 were women. Fifty percent of the patients with intrahepatic tumors were men, whereas 54% of the perihilar and 59% of the distal patients were men. Thirty-eight patients (13%) had diabetes mellitus, whereas 14 patients (5%) had a history of inflammatory bowel disease, and 11 patients (4%) had primary sclerosing cholangitis. None of the differences among the three groups were statistically significant.

The most common presenting symptoms for patients with cholangiocarcinoma were jaundice followed by abdominal pain, weight loss, and fever (Table 2). Approximately 90% of the patients with extrahepatic bile duct tumors were jaundiced (91% perihilar and 87% distal) in contrast to none of the intrahepatic patients ($p < 0.01$). The absence of jaundice, however, was part of the definition if an intrahepatic tumor. Abdominal pain occurred more frequently ($p < 0.05$) in the patients with intrahepatic tumors. Weight loss was slightly more common in the patients with extrahepatic tumors. Fever was an uncommon presenting symptom but was slightly more prevalent in the patients with perihilar tumors.

Laboratory data 1 day before surgery are summarized in Table 3. Serum total bilirubin was significantly lower ($p < 0.05$), and serum creatinine was significantly higher ($p < 0.05$) in the patients with intrahepatic tumors. Serum aspartate aminotransferase was similar among the groups, but the distal tumors had significantly elevated ($p < 0.05$) serum alanine aminotransferase levels. Albumin and hematocrit levels also were significantly lower ($p < 0.05$) in the perihilar group as compared to those in the intrahepatic group.

Preoperative Workup

Computed tomography was used in the evaluation of all 18 patients with intrahepatic cholangiocarcinoma as well as in the majority of patients with perihilar and distal cholangiocarcinomas. Cholangiography *via* either the percutaneous transhepatic or endoscopic retrograde approach was performed in all 196 patients with a perihilar cholangiocarcinoma (191 percutaneous transhepatic and 40 endoscopic retrograde). One hundred-seventy patients with perihilar tumors (87%) had percutaneous transhepatic biliary stents placed preoperatively to decompress the biliary system and to aid the surgeon at the time of laparotomy. The mean length of preoperative biliary drainage was 19 days in the perihilar group. In the distal group, 65 patients (81%) had preoperative cholangiography (45 percutaneous transhepatic and 27 endoscopic retrograde). Fifty-five patients (69%) underwent preoperative biliary drainage (40 transhepatic and 15 endoscopic).

Visceral angiography was performed in five patients with intrahepatic cholangiocarcinoma (28%) and showed no encasement or occlusion of either the hepatic artery or the portal vein in any case. One hundred forty-two angiograms were performed in the perihilar group (72%) and results were normal in 102 patients (72%), showed vascular encasement in 27 patients (19%; 14 he-

Table 2. PRESENTING SYMPTOMS

Symptom (%)	Intrahepatic (n = 18)	Perihilar (n = 196)	Distal (n = 80)	Total (n = 294)
Jaundice	0*	91	87	84
Abdominal pain	61†	36	27	35
Weight loss	11	36	30	33
Fever	6	14	2	10

* $p < 0.01$ *vs.* others.
† $p < 0.05$ *vs.* others.

Table 3. PREOPERATIVE LABORATORY DATA

	Intrahepatic (n = 18)	Perihilar (n = 196)	Distal (n = 80)	Total (n = 294)
Liver function				
Bilirubin total (mg/dL)	1.6 ± 0.6*	6.0 ± 0.5	5.9 ± 1.0	5.8 ± 0.4
Alkaline phosphatase (IU/L)	268 ± 74	353 ± 20	324 ± 29	345 ± 17
AST (IU/L)	44 ± 7	74 ± 5	89 ± 16	77 ± 5
ALT (IU/L)	47 ± 10	86 ± 6	138 ± 27*	97 ± 8
Albumin (gm/dL)	4.0 ± 0.3	3.5 ± 0.1†	3.6 ± 0.1	3.5 ± 0.1
Renal function				
Creatinine (mg/dL)	1.5 ± 0.1*	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1
Hematology				
Hematocrit (%)	40.0 ± 1.1	34.4 ± 0.4†	36.8 ± 1.6	34.6 ± 0.4
Leukocyte count (K/mm^3)	8.7 ± 1.2	9.7 ± 0.3	9.3 ± 0.4	9.5 ± 0.3

AST = aspartate aminotransferase; ALT = alanine aminotransferase.
* $p < 0.05$ *vs.* others.
† $p < 0.05$ *vs.* intrahepatic.

patic artery and 13 portal vein), and showed occlusion of the portal vein in 13 patients (9%). Angiograms also were performed in 42 of the patients with distal tumors (53%) and findings were normal in 31 patients (76%) and showed vascular encasement in 10 patients (24%).

Operative Procedures

In the intrahepatic cholangiocarcinoma group, nine patients (50%) had disease amenable to resection (three right hepatic lobectomy, five left hepatic lobectomy, and one extended right hepatic lobectomy). The other nine patients (50%) had unresectable disease (four extrahepatic disease, three bilateral hepatic involvement, one vena cava invasion, and one diaphragm invasion) and had a noncurative procedure that included open liver biopsy in five patients, laparoscopic liver biopsy in three patients, and laparotomy with a wedge resection and cryotherapy in one patient.

In the patients with perihilar tumors, 109 patients (56%) underwent operative resection. Resection consisted of excision of the hepatic duct bifurcation, placement of bilateral transhepatic stents, and reconstruction with Roux-en-Y hepaticojejunostomies. Fifteen patients (14%) also had hepatic lobectomy (4 right and 11 left) in addition to the bile duct resection in an attempt to remove all of the tumor. In 73 of the resected patients (67%), all gross tumor was removed; however, in 36 patients (33%) gross tumor was left behind after resection. Eighty-seven patients (44%) had unresectable tumors. In 31 patients (23 intraperitoneal metastasis and 8 hepatic metastases), inability to resect was because of disseminated disease, and in the remaining 56 patients, local invasion into the liver, portal vessels, or periportal soft tissue prevented resection. The palliative procedures performed in the perihilar cholangiocarcinoma patients included tumor dilatation, transhepatic silastic stenting, and hepaticojejunostomy in 54 patients (28%) and simple biopsy usually with cholecystectomy in 33 patients (17%).

Seventy-three patients (91%) with distal cholangiocarcinoma underwent resection. Sixty-two patients (85%) had a pylorus preserving pancreatoduodenectomy, and 11 patients (15%) had a more standard pancreatoduodenectomy, including an antrectomy. The remaining seven patients (*i.e.*, total distal group = 80 patients) were palliated with a choledochojejunostomy, and four patients also received a gastrojejunostomy to prevent late gastric outlet obstruction.

Tumor Characteristics

Histologic evaluation of the tumors was reviewed by one pathologist (RHH). All of the intrahepatic tumors were typical sclerotic adenocarcinomas. The average size of the intrahepatic lesions was 7.0 cm and ranged from 1.0 to 15.0 cm in diameter. Negative microscopic margins were achieved in seven (78%) of the nine patients undergoing resection. None of the patients undergoing hepatic resection had positive lymph nodes, whereas four of the patients being palliated had periportal lymph nodes that were positive.

Of the 196 perihilar tumors, 184 (94%) were sclerotic adenocarcinomas, and 12 (6%) were papillary tumors. Ten (84%) of the 12 papillary tumors were resected compared to 99 (54%) of the 184 adenocarcinomas. The distribution of the perihilar tumors by Bismuth type[5] was as follows: type I, 15%; type II, 42%; type IIIA, 14%; type IIIB, 19%; and type IV, 10%. The mean tumor length for the 109 resected perihilar tumor was 2.6 ± 0.1 cm

compared to an estimated 4.1 ± 0.3 cm for the palliated tumors. Twenty-eight (26%) of the resected patients had negative microscopic margins. Information on lymph node status was available in only 45 of the patients undergoing resection. Six patients (13%) had lymph node metastases.

Results of histologic evaluation of the 80 distal cholangiocarcinomas showed 79 sclerotic adenocarcinomas and 1 papillary carcinoma. Information on tumor differentiation was available in 59 (74%) of the 80 specimens and showed the tumor to be well differentiated in 5 patients (8%), moderately differentiated in 37 patients (63%), and poorly differentiated in 17 patients (29%). As expected, the diameter of the tumor tended to be smaller in the resected patients compared to that of the palliated patients (2.2 ± 0.1 cm *vs.* 2.6 ± 0.5 cm). Negative microscopic margins were obtained in 66 (90%) of the 73 resected patients. In addition, 35 (52%) of 67 resected specimens including lymph nodes showed metastatic disease.

Adjuvant Therapy

In addition to surgical resection for cholangiocarcinoma, both radiation therapy and chemotherapy have been used as adjuvant therapy. One hundred twenty-nine patients (44%) received external beam radiation therapy with a mean dose of 48 Gy (range, 11 to 68 Gy). Fifty-six percent of the intrahepatic group, (33% resected, 78% palliated) 47% of the perihilar group, (53% resected, 39% palliated), and 35% of the distal group (33% resected, 43% palliated) received adjuvant external beam radiation therapy. Forty-one patients (45%) with perihilar cholangiocarcinoma (62% resected, 15% palliated) also had iridium (^{192}Ir) implants placed *via* transhepatic biliary stents to provide additional radiation to the tumor bed. Adjuvant chemotherapy, usually without concomitant radiation therapy, was used in 39 patients (13%) with cholangiocarcinoma and was more likely to be used with intrahepatic tumors as compared to the perihilar and distal groups (33% *vs.* 7% *vs.* 25%). Most patients receiving chemotherapy were treated with 5-fluorouracil-based protocols. Combined adjuvant chemotherapy and radiation therapy was used in 33 patients (5 intrahepatic, 9 perihilar, and 19 distal).

Statistical Analysis

All data are presented as percentage of patients or mean ± standard error of the mean. Percentages were compared by chi square analysis, and means were analyzed by analysis of variance. Survival curves were constructed by the Kaplan–Meier technique and were compared by the log-rank test. Cox's proportional hazard survival analysis was used to determine which parameters affected survival. A p value < 0.05 was considered significant.

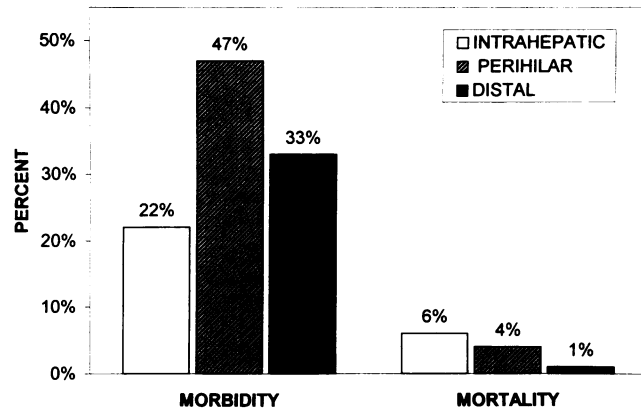

Figure 3. Morbidity and hospital mortality stratified by tumor location.

RESULTS

Mortality and Morbidity

Operative morbidity and mortality rates for intrahepatic, perihilar, and distal cholangiocarcinomas are shown in Figure 3. Ten (3.4%) of the 294 patients died after surgery without being discharged from the hospital. In the intrahepatic group, postoperative sepsis developed in one patient undergoing resection, and he died of multisystem organ failure (operative mortality rate of 5.6%). Among the 196 patients with perihilar tumors, 8 (4.1%) died after surgery. Of the 109 resected patients, 4 patients (3.6%) died secondary to sepsis. Only 1 (6.6%) of the 15 patients undergoing hepatic resection for a perihilar tumor died after operation. Of the 87 patients with perihilar tumors undergoing palliative procedures, 4 (4.6%) died, 3 as a result of sepsis and 1 from cardiac arrest. No operative mortalities occurred in the 73 patients undergoing pancreaticoduodenectomy for distal cholangiocarcinoma. However, multi-system organ failure developed in one patient with an unresectable distal tumor, and he died after surgery. Thus, the overall mortality rate for patients with distal tumors was 1.3%.

The overall perioperative morbidity rate was 39%. One hundred fifty-nine patients did not have any complications. The complication rate in the intrahepatic group was 22% (three of nine patients in the resected group and one of nine in the palliated group). The highest morbidity rate was observed in patients with perihilar cholangiocarcinoma (47%). This rate was higher in resected patients than in those undergoing a palliative procedure (54% *vs.* 39%). The morbidity rate for patients with distal cholangiocarcinoma was 33%. Twenty-eight (35%) of the 73 patients who had a pancreatoduodenec-

Table 4. POSTOPERATIVE COMPLICATIONS

Complication (%)	Intrahepatic (n = 18)	Perihilar (n = 196)	Distal (n = 80)	Total (n = 294)
Wound infection	6	16	13	14
Cholangitis/sepsis	6	13	4	10
Biliary/pancreatic fistula	0	6	13	8
Hepatic/intra-abdominal abscess	6	7	3	6
Respiratory complications	6	4	3	4
Gastrointestinal bleeding	0	5	1	4
Delayed gastric emptying	0	1	12	4
Renal failure	6	2	1	2

tomy had a postoperative complication. The complications stratified by location of tumor are presented in Table 4. Wound infections were the most common complication (14%) followed by cholangitis (10%) and pancreatic or biliary fistula (8%). Postoperative fistulas and delayed gastric emptying occurred more frequently in patients with distal tumors as compared to patients with more proximal cholangiocarcinoma.

The mean postoperative length of stay was 20 ± 0.9 days for all patients with cholangiocarcinoma. The patients with perihilar cholangiocarcinoma had a significantly longer length of stay than either the distal or intrahepatic cholangiocarcinoma patients (23.0 ± 1.3 *vs.* 17.0 ± 1.3 *vs.* 10.0 ± 0.9 days, $p < 0.05$).

Survival

The 5-year actuarial survival for all 294 patients with cholangiocarcinoma was 10%, and the median survival was 14 months. In the 191 patients who were resected, the 5-year actuarial survival was 17%, and the median survival was 20 months. To date, 16 (8%) of these 191 patients have lived longer than 5 years (9 patients in the perihilar group and 7 patients in the distal group). No patient whose tumor was not resected has survived 5 years after surgery, and the median survival was 8 months. The overall 5-year actuarial survival rates for the intrahepatic, perihilar, and distal tumors were 23%, 6%, and 24%, respectively. Actuarial survival for intrahepatic, perihilar, and distal tumors stratified by resection *versus* palliation is presented in Figures 4A, B, and C. The 5-year survival rates for the resected intrahepatic, perihilar, and distal tumors were 44%, 11%, and 28%, respectively (Fig. 4D). Operative resection prolonged survival for intrahepatic ($p < 0.08$), perihilar ($p < 0.01$), and distal ($p < 0.01$) cholangiocarcinomas.

In the 18 patients with intrahepatic cholangiocarcinoma the overall 1-, 3-, and 5-year actuarial survival rates were 57%, 23%, and 23%, respectively. The median survival was 22 months. No patient with an unresectable tumor survived for more than 25 months, and the median survival was 7 months. However, resection of the intrahepatic tumor resulted in a 5-year survival of 44%, and the median survival was 26 months (Fig. 4A). In the seven patients who were resected with negative microscopic margins, the 5-year actuarial survival was 57%.

In the 109 patients with resected perihilar tumors, the 1-, 3-, and 5-year actuarial survival was 68%, 30%, and 11%, respectively (Fig. 4B). The median survival was 19 months. The addition of hepatic lobectomy to resection of the extrahepatic bile duct did not alter the survival rate (Fig. 5A). The 1-, 3-, and 5-year survival rates for the 15 patients who underwent hepatic lobectomy as well as extrahepatic bile duct resection were 64%, 50%, and 10%, respectively. The median survivals was 18 months. In the 94 patients treated with bile duct resection alone, the 1-, 3-, and 5-year survival rates were 68%, 26%, and 11%, respectively (Fig. 5A). The median survival rate was 19 months. However, if a negative microscopic margin was obtained after resection, survival was significantly prolonged ($p < 0.05$). In the 28 patients with negative microscopic margins, the 5-year actuarial survival rate was 19% as compared to a 9% 5-year survival rate for the 81 patients with positive margins (Fig. 5B). In addition, median survival increased to 41 from 18 months. None of the six patients with perihilar lymph node metastases who underwent resection of the extrahepatic bile duct survived past 18 months. In the remaining 39 patients without evidence of lymph node involvement, the 5-year survival rate was 15%. Negative lymph node results increased median survival rate from 5 to 12 months. The histologic type of tumor, adenocarcinoma *versus* papillary, did not alter survival in patients with perihilar cholangiocarcinoma (Fig. 5C). Postoperative adjuvant radiation therapy also did not provide a benefit to patients with perihilar cholangiocarcinoma (Fig. 5D).

The 1-, 3-, and 5-year survival rates for the 73 patients with distal cholangiocarcinoma who underwent pancreatoduodenectomy was 70%, 31%, and 28%, respectively (Fig. 4C). The median survival was 22 months.

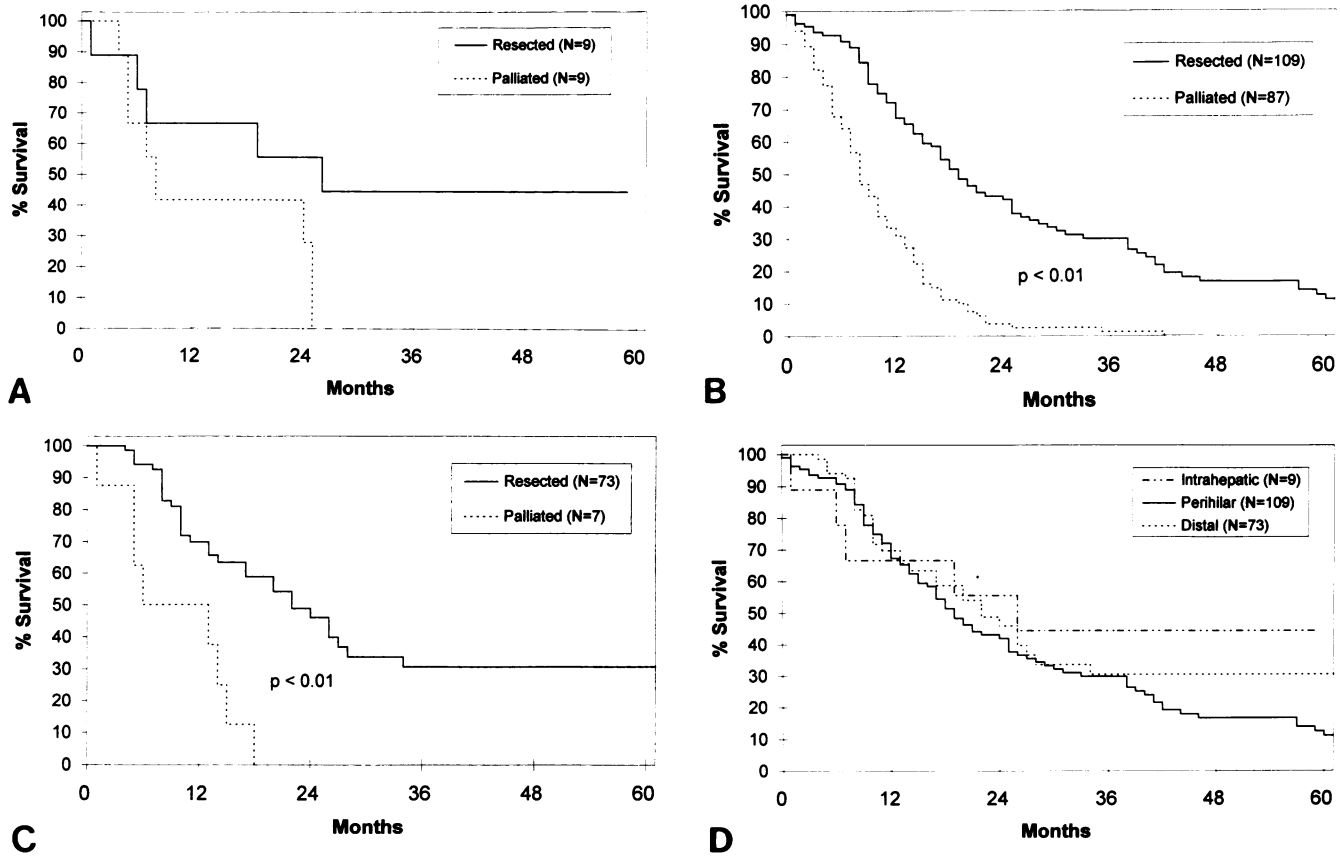

Figure 4. (A) Survival of resected and palliated intrahepatic cholangiocarcinomas. (B) Survival of resected and palliated perihilar cholangiocarcinomas. (C) Survival of resected and palliated distal cholangiocarcinomas. (D) Survival of resected intrahepatic, perihilar, and distal cholangiocarcinomas.

Five-year survival in the 66 patients with negative microscopic margins was 29%, and the median survival was 24 months. Factors associated with prolonged survival in patients with resectable distal cholangiocarcinoma were lymph node status and tumor differentiation. The 1-, 3-, and 5-year survival was 89%, 38%, and 30%, respectively, in the 32 patients with negative lymph nodes. Survival was significantly less ($p < 0.01$) in the 35 patients with at least 1 lymph node metastasis (Fig. 6A). Negative nodes increased median survival from 17 to 27 months. Patients with poorly differentiated adenocarcinomas of the distal bile duct had a significantly ($p < 0.01$) worse prognosis than patients with better differentiated tumors despite resection (Fig. 6B). The 1-, 3-, and 5-year survival was 44%, 9%, and 0%, respectively, for patients with poorly differentiated tumors. In contrast, better differentiated tumors resulted in survival rates of 76%, 30%, and 30%, respectively. Better differentiation increased median survival from 10 to 22 months. The diameter of the distal tumor (Fig. 6C) was not a significant factor in determining prognosis in resected patients. As with the perihilar tumors, postoperative adjuvant radiation therapy did not significantly alter patient survival (Fig. 6D).

Multivariate Analysis

To determine which factors were important in predicting survival in patients with cholangiocarcinoma, a multivariate analysis was performed. Factors analyzed included patient demographics, presenting symptoms, preoperative laboratory values, tumor characteristics, postoperative complications, and adjuvant therapy. Factors that were statistically significant for all patients with cholangiocarcinoma in predicting survival were resection ($p < 0.001$, hazard ratio 2.80), negative microscopic margins ($p < 0.01$, hazard ratio 1.79), preoperative serum albumin ($p < 0.04$., hazard ratio 0.82), and postoperative sepsis ($p < 0.001$, hazard ratio 0.27). Multivariate analysis also was performed on the subgroup of patients with perihilar and distal cholangiocarcinoma who were successfully resected. In the patients with perihilar cholangiocarcinoma, factors that were important included negative microscopic margins ($p < 0.04$, hazard ratio 1.75), preoperative serum albumin level ($p < 0.002$, hazard ratio 0.55), and postoperative sepsis ($p < 0.01$, hazard ratio 0.37). In the patients with distal cholangiocarcinoma undergoing pancreatoduodenectomy, factors

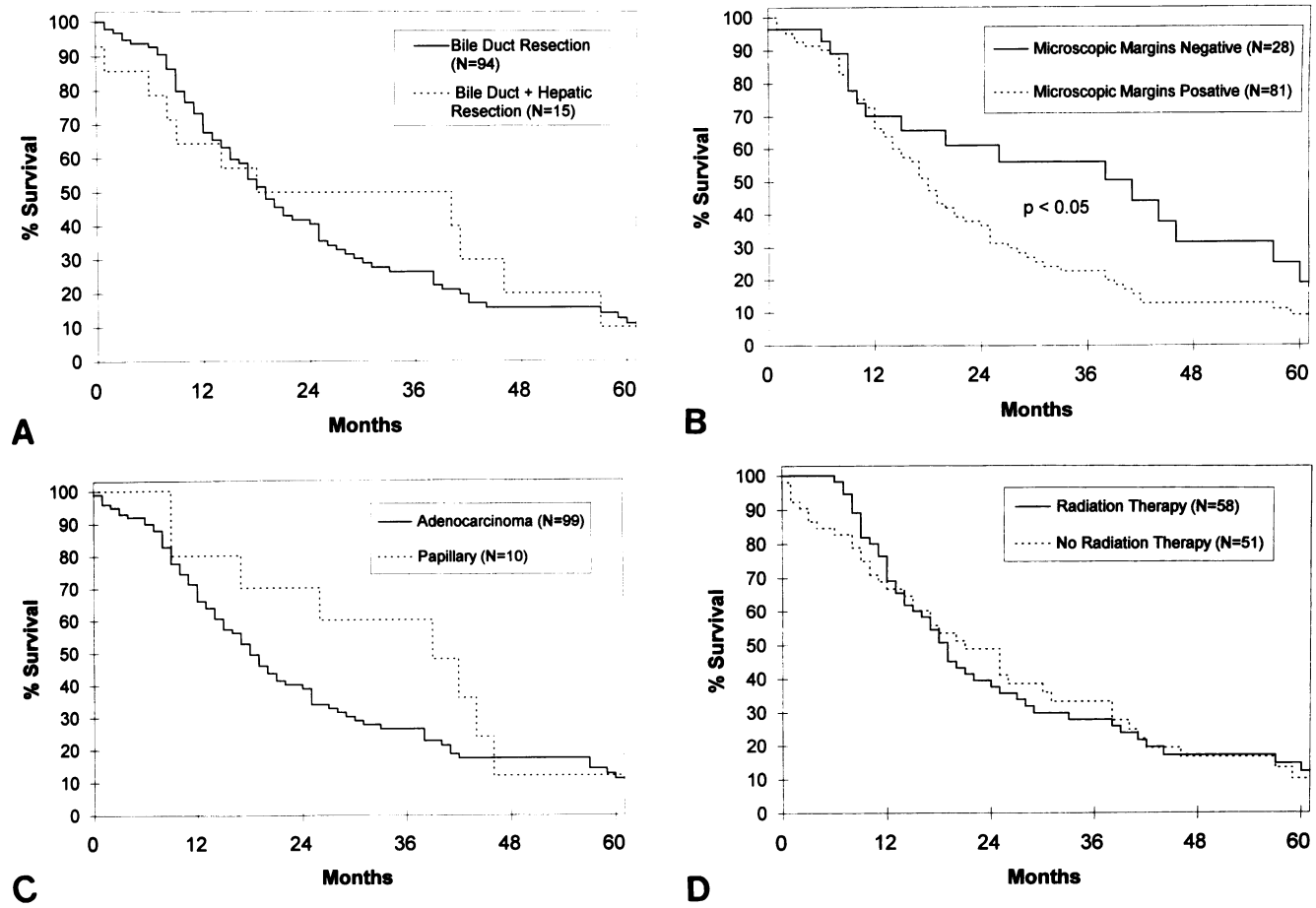

Figure 5. (A) Influence of hepatic resection on survival of patients with resected perihilar cholangiocarcinomas. (B) Influence of microscopically negative margins on survival of patients with resected perihilar cholangiocarcinomas. (C) Influence of tumor type on survival of patients with resected perihilar cholangiocarcinoma. (D) Influence of radiation therapy on survival of patients with resected perihilar cholangiocarcinoma.

that were important were negative lymph node status ($p < 0.02$, hazard ratio 3.08) and poor tumor differentiation ($p < 0.04$, hazard ratio 0.44).

DISCUSSION

The majority of surgically treated cholangiocarcinomas occur in the perihilar region.[3–8] In reviewing a 23-year experience at The Johns Hopkins Hospital, 196 (67%) of 294 patients with cholangiocarcinoma who underwent surgery had perihilar tumors. In comparison, intrahepatic and distal cholangiocarcinomas occurred in 18 patients (6%) and 80 patients (27%), respectively. Patient demographics were similar among the three tumor locations; however, by definition, patients with purely intrahepatic tumors did not present with jaundice ($p < 0.01$) but were more likely ($p < 0.05$) to have abdominal pain. Resection was more likely with more distal tumors, and resection significantly improved survival at each tumor site.

Five-year survival rates for resected intrahepatic, perihilar, and distal tumors were 44%, 11%, and 28%, respectively. In a multivariate analysis, the factors that were most likely to improve survival were resection ($p < 0.001$, hazard ratio 2.80) and negative microscopic margins ($p < 0.01$, hazard ratio 1.79). Conversely, factors that were most likely to predict a poor outcome were a low serum albumin at the time of surgery ($p < 0.04$, hazard ratio 0.82) and sepsis in the postoperative period ($p < 0.001$, hazard ratio 0.27). Postoperative external beam radiation therapy with a mean dose of 48 Gy was administered to 44% of the patients, and 45% of the patients with perihilar tumors also received iridium implants. However, radiation therapy did not improve median or 5-year survival rates. This retrospective analysis is consistent with a recent prospective evaluation of the effect of adjuvant radiation from this institution.[9]

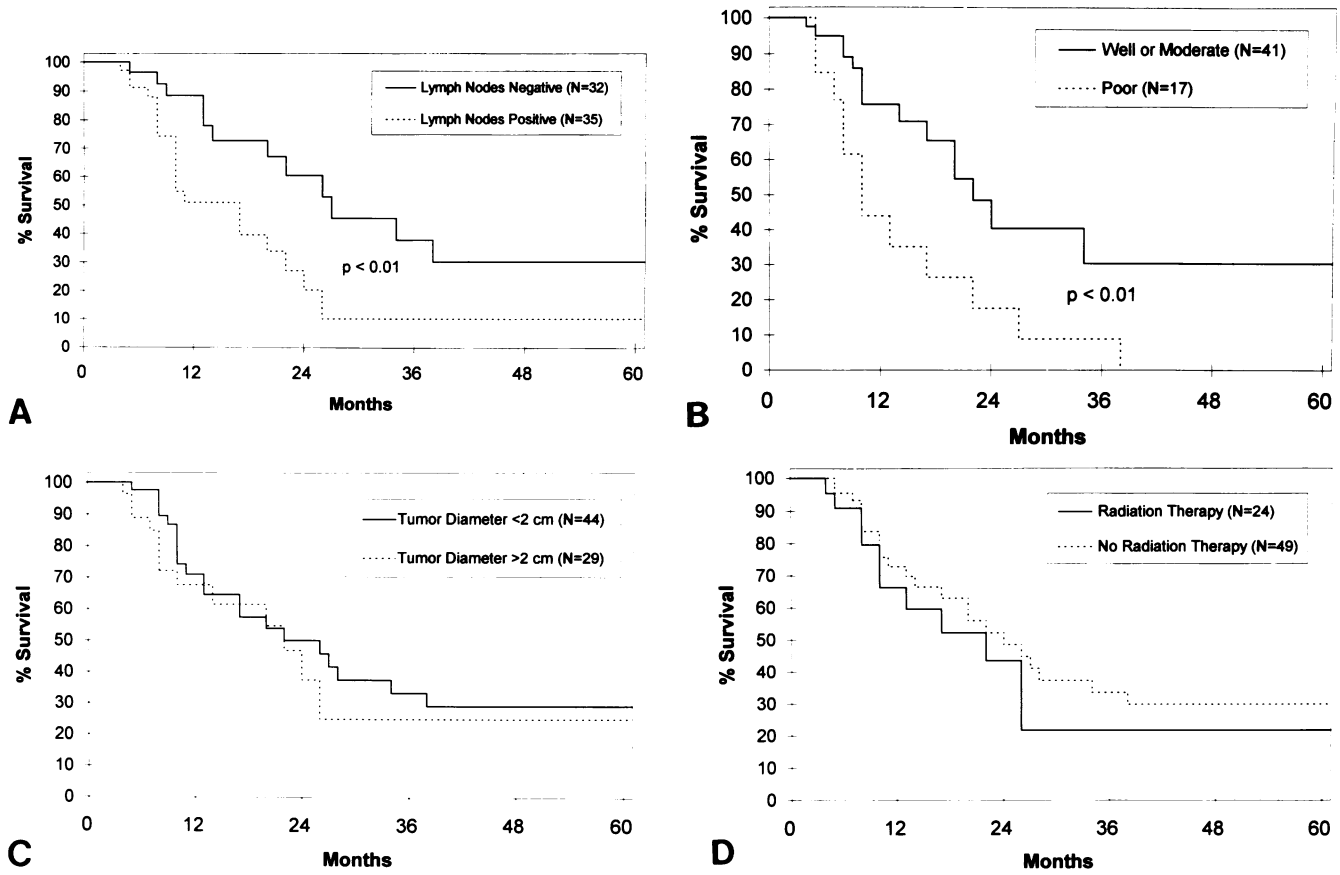

Figure 6. (A) Influence of lymph node status on survival of patients with resected distal cholangiocarcinoma. (B) Influence of tumor differentiation on survival of patients with resected distal cholangiocarcinoma. (C) Influence of tumor size on survival of patients with resected distal cholangiocarcinoma. (D) Influence of radiation therapy on survival of patients with resected distal cholangiocarcinoma.

This report differs from previous analyses of cholangiocarcinomas in that the tumors were divided into three groups: 1) intrahepatic, 2) perihilar, and 3) distal. Over the past 2 decades, most reports have focused on either intrahepatic[10–13] or extrahepatic tumors[3,4,6–8] but have not included both in the same series. In addition, extrahepatic tumors usually have been subdivided into proximal, middle, and distal subgroups.[3,6,7] With this method for classification, the proximal tumors are most common followed by the distal and middle lesions. In addition to being uncommon, the middle lesions almost always require either hilar resection or pancreatoduodenectomy when they are resectable. In this article, the subclass of middle lesions has been eliminated, and these tumors have been grouped with either the perihilar or distal tumors depending on how they were treated.

Bismuth[5] has subclassified the perihilar tumors into four types. This system has been useful for analyzing this subgroup of tumors. However, the Bismuth classification does not account for intrahepatic or distal nor gallbladder malignancies. Pitt et al.[1] at Johns Hopkins University have proposed a new system with nine subgroups that includes intrahepatic, perihilar, distal, and gallbladder tumors. By describing individual areas in the perihilar region, this system incorporates the advantages of the Bismuth classification but also is able to characterize biliary tract malignancies outside of the perihilar region. In this report, the Hopkins system was used to group cholangiocarcinomas into three broad categories: 1) intrahepatic, 2) perihilar, and 3) distal. More complex descriptions of the individual intrahepatic bile ducts also have been described in Japan.[14] These systems are useful for cholangiocarcinomas with significant intrahepatic extension but do not adequately classify extrahepatic tumors.

Intrahepatic cholangiocarcinoma is associated with a different clinical, laboratory, and radiologic presentation than either perihilar or distal cholangiocarcinomas. Intrahepatic cholangiocarcinoma is managed optimally with hepatic resection. However, intrahepatic cholangiocarcinomas often present at an advanced stage, and in some series, only 15% to 20% of these patients have re-

sectable tumors.[12,13] However, patients with resectable intrahepatic disease tend to have a better prognosis than do patients with extrahepatic cholangiocarcinoma. The median survival rate for resected intrahepatic cholangiocarcinoma has been reported to range from 9 to 30 months.[10,12,13,15] In the current series, patients with resectable intrahepatic cholangiocarcinoma had a median survival rate of 22 months and a 5-year survival rate of 44%. Liver transplantation has been proposed as an alternative therapy for intrahepatic cholangiocarcinoma. Pichlmayr et al.[10] report a median survival rate of 5.0 months in 18 patients treated with liver transplantation and a 12.8-month median survival rate for 32 patients treated with hepatic resection. Their data suggest that liver transplantation is not an effective therapy for intrahepatic cholangiocarcinoma, leaving hepatic resection as the best treatment option.

The prognosis for patients with perihilar cholangiocarcinoma is highly dependent on whether the patient is treated with surgical resection or palliation. In the current series, mean survival rate was 10 months for patients undergoing a palliative procedure, and no patient survived 5 years. In an attempt to increase the length of survival, the recent trend has been toward more aggressive surgery for perihilar cholangiocarcinoma. The 5-year survival rate reported for resected perihilar cholangiocarcinomas ranges from 0% to 30%, and median survival rate ranges from 9 to 38 months.[2,6,7,16–20] Results of the current series of 109 patients with resectable perihilar cholangiocarcinoma are similar. The median survival rate was 19 months, and the 5-year survival rate was 11%. In patients with negative microscopic margins, the 5-year survival rate was 29%, and the median survival rate was 41 months.

Several groups have advocated combined hepatic lobectomy with local resection of the extrahepatic bile ducts for perihilar tumors.[14,19–24] The addition of hepatic resection increases the length of survival but is associated with an increased operative mortality. In a collective review of 389 patients with perihilar cholangiocarcinoma,[25] the mean 1-year, 3-year, and 5-year survival rate for 201 patients undergoing a hilar resection was 21 months, 76%, 21%, and 7%, respectively. By comparison, for 188 patients treated with hepatic plus hilar resection, the survival rate was 24 months, 61%, 28%, and 17%, respectively. The operative mortality rate was 8% in the hilar resection group and 15% in the hepatic plus hilar resection group. In the current series, the operative mortality rate was 6.7% for patients undergoing hepatic and hilar resection compared to 3.2% for hilar resection alone. However, both median survival and 5-year survival rates were similar.

The survival data for patients with distal cholangiocarcinoma are more favorable than for perihilar cholangiocarcinoma. In the current series of 73 patients undergoing pancreatoduodenectomy for distal bile duct tumors, the 5-year survival rate was 28%, and the median survival rate was 22 months. These results are comparable to those reported for distal bile duct tumors by others.[4,6,7,21,26] In a collective review of 221 patients with resected distal bile duct tumors,[16] the 5-year survival rate ranged from 17% to 39%, and the mean survival rate was 39 months. No operative mortality rate occurred in this series of resected distal cholangiocarcinomas, which compares favorably with the 3% to 8% operative mortality rates reported for pancreatoduodenectomy.[4,6,21,26] As in other series, none of the patients in this series with unresectable disease were long-term survivors.

In the current series of cholangiocarcinomas, several factors were shown to be predictors of survival by multivariate analysis. In the entire group resection, microscopic margin status, preoperative albumin level, and postoperative sepsis all were important factors in predicting survival. In a univariate analysis of 88 patients, Washburn et al.[21] identified several factors that were predictive of survival, including serum bilirubin concentration, alkaline phosphatase level, preoperative jaundice, abdominal pain, tumor stage, lymph node status, resection, and negative margins. Nagorney et al.[4] have identified curative resection, Eastern Cooperative Oncology performance status, total bilirubin concentration, and tumor grade as variables predictive of outcome by multivariate analysis. Thus, in each of these analyses, resection with negative margins is key to long-term survival. Nutritional status and underlying sepsis also may play an important role in the eventual outcome.

Cholangiocarcinoma is best classified into three broad categories based on its anatomy and preferred treatment. Intrahepatic tumors do not involve the hilar bile ducts and are managed by hepatic resection. Perihilar tumors require resection of the hepatic duct bifurcation and also may need resection of liver parenchyma, including the caudate lobe. Distal tumors are best managed with pancreatoduodenectomy. Resection remains the primary treatment for cholangiocarcinomas regardless of site. A primary goal of resection should be negative microscopic margins, which is an independent predictor of outcome. In comparison, postoperative adjuvant radiation therapy without concomitant chemotherapy does not improve long-term survival. Preliminary data suggest that adjuvant chemoradiation therapy may be of some benefit for these patients,[27–30] but no randomized studies have been performed. Therefore, the combination of aggressive, but safe, surgery and new agents or strategies to deliver adjuvant therapy will be needed to improve survival.

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Discussion

DR. HENRI BISMUTH (Villejuif, France): This paper has the important merit to report one large series from a single institution. Because the main objective was to introduce a new classification, I will discuss this point first.

The classification that Dr. Pitt proposes does not seem to me to bring any advantages over the usual one. The only difference is that the authors create the new type of perihilar cholangiocarcinoma comprising the hilar type and the pedicular type of the usual classification. I believe there are important differences between these two. Pedicular cholangiocarcinoma usually requires only biliary surgery, whereas hilar cholangiocarcinoma most often requires a hepatic and a biliary procedure. In addition, any kind of surgical treatment for the hilar type, resection, or bypass is more complex and more difficult than for the pedicular variety. This is true not only for the surgical treatment, but also for stenting. These are the reasons why I think that the hilar type deserves a place on its own in the classification.

The original classification of hilar carcinomas in four types did not include tumors below the hilum. Later on, an extension of this classification was introduced, with the denomination of "Bismuth O" for pedicular cancer. I disagree with that not only because I do not like that "O" is added to my name, but I think it is just simpler to say "pedicular cancer."

The authors analyze the factors associated with outcome and survival, and it appears that one of the most important is resection. This is not surprising. Resection is associated with better results than palliation in any type of gastrointestinal cancer, because not only may resection bring a chance of cure but, maybe more importantly, the patients who are resected are different from the patients for whom only palliative surgery is possible, both in their general condition and as far as spread of the tumor is concerned; the best patients are selected for resection.

Many crucial problems remain unresolved and I would like to ask Dr. Pitt, because he had the chance to study a really unique series, if he has any answers for the following questions. In hilar