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Clinical Studies of Mucin-Producing Cholangiocellular Carcinoma

A Study of 22 Histopathology-Proven Cases

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Objective
We present the clinical features and outcomes of 22 surgically treated and histopathology-proven cases of mucin-producing cholangiocellular carcinoma (MPCCC).

Background
Cholangiocellular carcinoma (CCC) is an uncommon malignancy. Unlike hepatocellular carcinoma, it is difficult to set up a high-risk group, and a specific tumor marker has yet to be found. Chronic liver disease is usually not found to be associated with CCC. Information about patients with MPCCC is limited, and the frequency of MPCCC in all patients with CCC has not been reported.

Methods
The clinical features of 22 surgically treated and histopathology-proven cases of MPCCC were reviewed, including morbidity, mortality, and follow-up results. Factors that may influence the outcomes were also analyzed. Clinical features and outcomes of 148 patients with non–mucin-producing cholangiocellular carcinoma (non-MPCCC) were also summarized for comparison.

Results
Of 170 cases of CCC, 22 (12.9%) were MPCCC. Imaging studies were important in the differential diagnosis of CCC. Operative findings (*e.g.*, gross appearance of the liver, mucobilia found by common bile duct exploration, choledochoscopic findings, and frozen section) were useful in the diagnosis of MPCCC. Surgical procedures included common bile duct exploration, or hepaticostomy, and intraoperative choledochoscopy in all 22 patients. Hepatic resection was done in 14 of the 22 cases (63.6%). No early surgical mortality was noted. Wound infections (two patients), bile leak (one patient), and intraabdominal abscess (one patient) were the postoperative complications. The 1-, 2-, 3-, 4-, and 5-year survival rates were 86.5%, 68.5%, 59.0%, 38.5%, and 31.0%, respectively. A significant difference in survival pattern was found between the MPCCC and non-MPCCC patient groups. Patients with hepatic resection had a significantly better prognosis than those without resection. Although patients with hepatolithiasis had a better survival pattern than those without hepatolithiasis, the difference was not statistically significant.

Conclusions

We present the clinical features and outcomes of 22 surgically treated and histopathology-proven cases of MPCCC. Patients with hepatic resection were found to have better survival rates.

Bile duct carcinoma, the tumor derived from bile duct epithelium, reportedly occurs less frequently in most parts of the world than hepatocellular carcinoma. Intrahepatic bile duct carcinoma is also called cholangiocarcinoma or cholangiocellular carcinoma (CCC).[1] Okuda et al.[2] separated intrahepatic bile duct carcinoma into peripheral and hilar types with quite different clinical presentations and features. Hilar carcinoma is also called Klatskin tumor. In this paper, CCC is considered to be synonymous with peripheral cholangiocarcinoma.[3,4] Unlike hepatocellular carcinoma, a high-risk group is difficult to identify, and a specific tumor marker of CCC has yet to be found. Chronic liver disease is usually not found to be associated with CCC.[3,4]

Some biliary neoplasms that arise from the liver produce mucin; CCCs, biliary cystadenomas, and cystadenocarcinomas belong to this category.[5-7] The mucin varies in amount but in most cases is retained in the tumor cells or in the cysts. Mucobilia, a rare condition, is characterized by copious mucin secretion within the extrahepatic bile ducts, resulting in obstructive jaundice and cholangitis.[8] However, there have been few reports in the literature providing details on patients with mucin-producing cholangiocellular carcinoma (MPCCC).[9] We analyzed the clinical records of 22 patients with MPCCC who underwent surgical treatment, and we report our findings here. We also compared the results with those of patients with non–mucin-producing cholangiocellular carcinoma (non-MPCCC).

MATERIALS AND METHODS

From 1979 to 1995, 170 patients with CCC underwent surgery at the Chang Gung Memorial Hospital, Taipei, Taiwan. Among them, 22 (8 men, 14 women) were found to have MPCCC. The patients were 46 to 82 years old (mean age, 56.7 years). The associated disease was found to be intrahepatic stones in 15 patients (68.2%). Eighteen of the 22 patients (81.8%) had mucobilia. Seven patients had a previous history of biliary tract operation. In the same period, 1362 patients with hepatolithiasis underwent surgery at our institution, and 110 of them were found to have CCC.[10-12]

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Most of the patients (90.9%) experienced repeated episodes of right upper abdominal pain. Tenderness could be demonstrated in six and jaundice in ten of the patients. Weight loss, anemia, and liver enlargement were the most common signs on admission (Table 1). The results of the major laboratory tests on admission are shown in Table 2. There was moderate anemia and leukocytosis. Serum protein was within normal limits for most of the patients. Serum asparate transaminase and alanine transaminase levels were mildly elevated. Cholestatic features (*e.g.*, elevated serum bilirubin, alkaline phosphatase (Alk-P), and gamma glutamyl transpeptidase (GGT) levels) were not found in most of the patients. Alpha-fetoprotein was measured by radioimmunoassay in 15 patients; none of them had levels >20 μg/L. Radioimmunoassay was used to assess hepatitis B surface antigen in the 22 patients, with only 7 positive results. Serum carcinoembryonic antigen and CA19-9 were also measured by radioimmunoassay. The serum carcinoembryonic antigen level was 5 ng/mL or more in 8 of the 20 patients (40%), and the CA19-9 level was 120 u/mL or more in 4 of the 11 patients (36.3%). The major diagnostic procedures, such as endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, liver scans, and ab-

Table 1. SIGNS AND SYMPTOMS OF MUCIN-PRODUCING AND NON-MUCIN-PRODUCING CHOLANGIOCELLULAR CARCINOMA

	Mucin-Producing (n = 22) (%)	Non-Mucin-Producing (n = 148) (%)	p
Abdominal pain (RUQ and/or epigastric)	90.9	72.3	NS
Fever, chills	81.8	48.6	0.017
Abdominal tenderness	27.3	52.0	NS
Body weight loss	54.5	54.7	NS
Poor appetite	54.5	33.1	NS
Nausea, vomiting	45.5	34.5	NS
Jaundice	45.5	26.4	NS
Weakness, fatigue	18.2	47.3	0.045
Hepatomegaly	18.2	36.5	NS
Anemia (hemoglobin < 12 g/dL)	54.5	50.0	NS
Leukocytosis (WBCs > 10^4/mm)	45.5	39.2	NS

RUQ = right upper quadrant; WBCs = white blood cells; NS = not significant (chi square test).

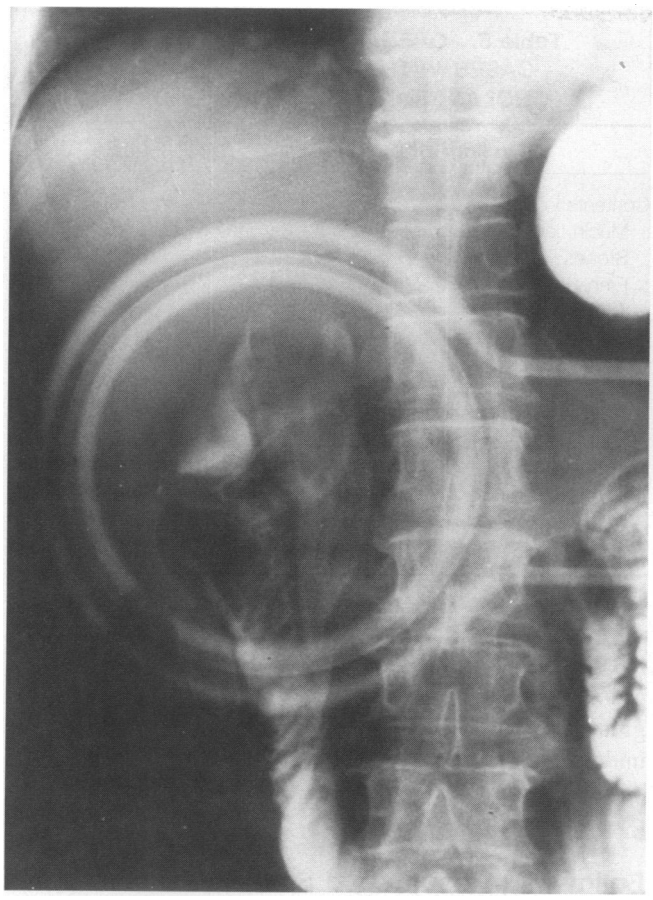

Figure 1. Multiple filling defects and faint visualization in extra- and intrahepatic ducts shown on endoscopic retrograde cholangiopancreatography.

dominal ultrasonography were used in the workups for liver tumor and intrahepatic stones (Figs. 1–3). The findings were summarized in Table 3.

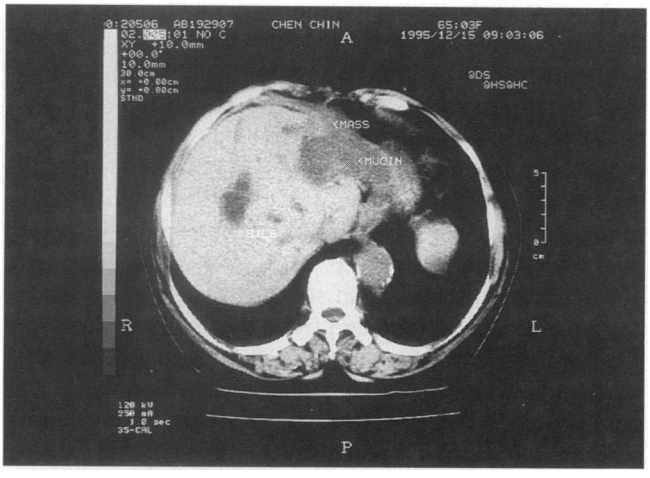

Figure 2. Computed tomography scan revealed a mass and mucinlike substance in the liver parenchyma with dilated intrahepatic ducts.

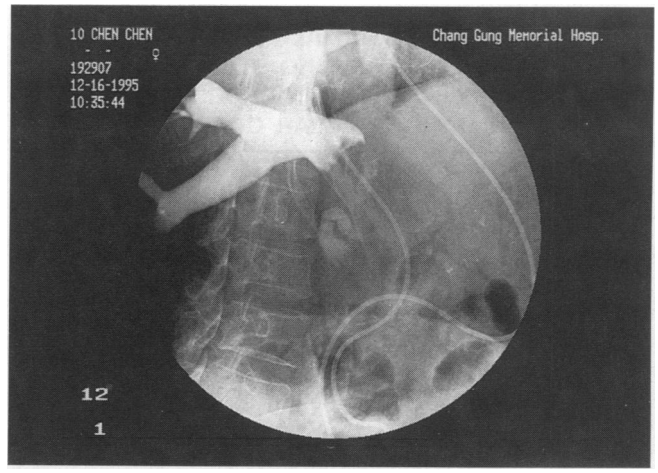

Figure 3. An intraductal tumor in the left hepatic duct shown on endoscopic nasal biliary drainage cholangiography.

During surgery, the exact location of stones and gross pathology of the tumor were recorded (Tables 4 and 5). We found that the left lobe of the liver was much more commonly affected than the right (17 *vs.* 8). The stones found in each of the 15 patients were composed of calcium and bilirubinate. No evidence of parasitic infection was found. Mucobilia was found in 18 patients (Fig. 4). Common bile duct exploration and intraoperative choledochoscopy were performed in 21 of the 22 patients; hepaticostomy and liver biopsy were performed in the other patient. Hepatic resection was done in 14 patients (63.6%); 4 had left hemihepatectomy, 9 left lateral segmentectomy, and 1 right anterior segmentectomy. In 3 of the 14, hepatic resection was done as a second operation after malignancy was confirmed histopathologically. *Escherichia coli*, *Klebsiella*, and *Enterobacter* species were the organisms cultured most

Table 2. LIVER FUNCTION TESTS OF MUCIN-PRODUCING AND NON-MUCIN-PRODUCING CHOLANGIOCELLULAR CARCINOMA

	Mucin-Producing (n = 22)		Non-Mucin-Producing (n = 148)	
	Range	Mean	Range	Mean
Bilirubin (mg/dL)	0.5–8.8	2.35	0.2–19.2	3.38
Alk-P (mU)	72–980	320	20–1200	375
ALT (mU)	15–420	85.5	10–349	69.3
AST (mU)	20–460	80.8	10–370	68.6
Albumin (g/dL)	2.8–4.2	3.2	2.0–6.3	3.4

Alk-P = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Table 3. ABNORMAL FINDINGS OF PREOPERATIVE IMAGING STUDIES OF 22 CASES WITH MUCIN-PRODUCING CHOLANGIOCELLULAR CARCINOMA

Finding	%
Abdominal US + CT	
Hyperechoic mass in the liver parenchyma	20.0
Presence of liver tumor	20.0
Severe dilatation of the intrahepatic and extrahepatic ducts distal to the tumor	30.0
Presence of intrahepatic stones	75.0
Left lobe liver atrophy	30.0
Cholangiogram (PTC or/and ERCP)	
Amorphous filling defects (caused by retention of mucin) in the dilated ducts	45.5
Defect or obliteration of intrahepatic ducts	72.7

US = ultrasonography; CT = computed tomography; PTC = percutaneous transhepatic cholangiography; ERCP = endoscopic retrograde cholangiopancreatography.

Table 5. OPERATIVE FINDINGS OF 22 CASES WITH MUCIN-PRODUCING CHOLANGIOCELLULAR CARCINOMA

Finding	%
Contents in the bile ducts	
Mucin, jelly-like substance	81.8
Stones	68.2
Frank pus	31.8
Tumor debris	18.2
Gross appearance of liver	
Whitish nodular mass	27.3
Atrophic, fibrotic liver	45.5
Cholangitic appearance	27.3
Choledochoscopic findings	
Intraductal tumors	40.9
Infiltrative lesion, ductal stricture	45.5
Obliterance of intrahepatic ducts	9.0
Normal duct	4.5

frequently from patients with hepatolithiasis. Microscopically, the liver revealed papillary adenocarcinoma of the bile ducts. The tumor spread into the lumen of the intrahepatic bile ducts and mildly invaded the portal area or liver parenchyma (Fig. 5).

Postoperative complications were carefully monitored. Clinical features and outcomes of the 148 patients with non-MPCCC are summarized in the tables and figures for comparison. Survival was analyzed by the Kaplan–Meier method, and survival curves were compared by the generalized Wilcoxon test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Mortality and Morbidity

No early surgical mortality was noted. The major postoperative complications were wound infections in two patients, bile leak in one patient, and intraabdominal abscess in one patient. Most of the complications were related to surgery for hepatolithiasis with recurrent cholangitis. Intermittent obstruction of the bile ducts and cholangitis was found in patients with mucobilia who did not undergo hepatic resection.

Table 4. LOCATION OF CHOLANGIOCARCINOMA AND INTRAHEPATIC STONES: NUMBER OF CASES

	Cholangiocarcinoma	Stones
Left lobe	14	9
Right Lobe	5	4
Bilateral	3	2

Follow-Up Results and Survival

All the 22 patients were available for long-term assessment. The duration of follow-up was 8 months to 12 years and 6 months. Overall median survival was 30.8 months (range, 4 to 144 months). The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates for the 22 MPCCC patients were 86.5%, 68.5%, 59.0%, 38.5%, and 31.0%, respectively. When the survival rates of MPCCC and non-MPCCC patients (22.3%, 10.8%, 8.1%, 5.4%, and 4.0% at 1, 2, 3, 4, and 5 years, respectively) were compared, MPCCC patients had significantly better survival rates ($p < 0.05$) (Fig. 6). One patient had repeated hepatectomy because of recurrence. Four of the 8 patients who underwent choledochotomy had received intraluminal radiation therapy, external beam radiation therapy, and systemic chemotherapy. Two of them survived for more than 3 years with the disappearance of mucobilia. Four patients lived more than 5 years (5.5 years, 6 years, 8 years, and 12 years).

Significant differences in survival patterns were noted when the surgical procedures and associated diseases were analyzed. Patients with hepatic resection had a significantly better prognosis than those without resection ($p < 0.05$) (Fig. 7). Although patients with hepatolithiasis had a better survival pattern than those without hepatolithiasis, the difference was not statistically significant ($p > 0.05$) (Fig. 8).

Table 6. PROGNOSIS OF MUCIN-PRODUCING AND NON-MUCIN-PRODUCING CHOLANGIOCELLULAR CARCINOMA

		Survival time (mo)		Cumulative Survival Rate (%)	
	Number of Patients	Range	Median	1-yr	2-yr
Mucin-producing	22	4–144	30.8	86.5	68.5
Non-mucin-producing	148	1–118	5.3	22.3	10.8

$p < 0.05$ (Kaplan–Meier).

DISCUSSION

In this study, 22 (12.9%) of 170 patients with CCC had mucin-producing tumors. To our knowledge, this is the first reported series on the frequency of MPCCC in patients with CCC. Although mucin secretion is a characteristic microscopic feature of MPCCC, profuse mucorrhea within the extrahepatic bile ducts is not often encountered.[6,7,9] However, in this series 81.8% (18 of 22) of the patients were found to have mucobilia. This appears to impede the passage of bile, creating obstructive jaundice and cholangitis.

CCC has been reported to occur coincidentally with other diseases, such as cystic disease of the liver, congenital dilatation of the bile duct, *clonorchis sinensis,* chronic ulcerative colitis, chemical agents, and hepatolithiasis.[13–17] The incidence of CCC in association with hepatolithiasis has been reported to range from 2.43% to 10%,[7,10,11] consistent with the 5.0% rate at our institution.[11] Conversely, few published studies have discussed the incidence of hepatolithiasis in patients with CCC. We previously reported that the incidence of hepatolithiasis in patients with CCC was 66.6% (50 of 75)[12]; it was 68.2% (15 of 22) in the present series.

Hepatolithiasis is a common disease in Asia and is especially prevalent in Taiwan.[18–21] The pathogenetic relation between hepatolithiasis and cholangiocarcinoma is not well established. Most authors suggest that bile stasis and repeated cholangitis may be the main etiologic factors.[22] They report that repeated cholangitis and bile stasis induced by hepatolithiasis can lead to the development of periductal inflammation, mucosal epithelial hyperplasia, papillary adenomatous hyperplasia, and bile duct carcinoma.

Various imaging studies, such as liver scans, abdominal

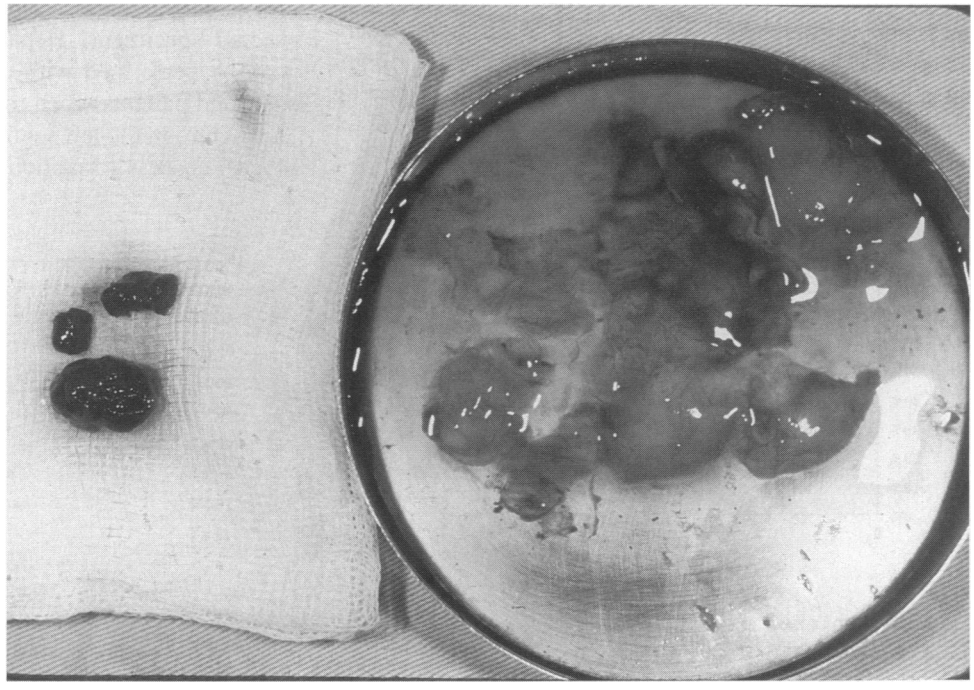

Figure 4. Inspissated mucin substance obtained from the common bile duct.

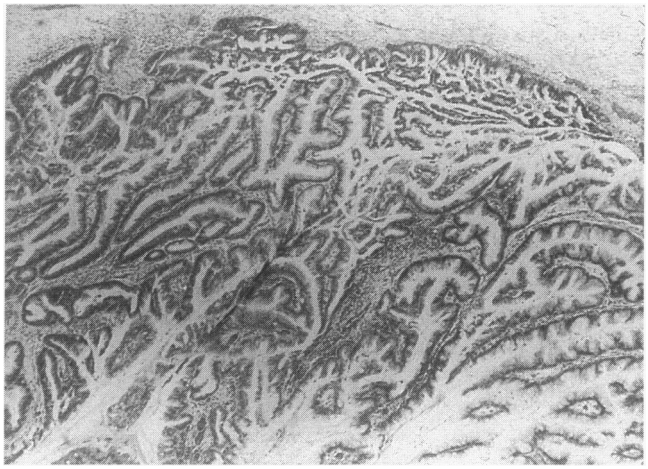

Figure 5. Photomicrograph of a papillary neoplasm of the bile duct. Villous and tubular glands show some bulging at the base of crypts, but stromal invasion is not definite (H&E, ×20).

ultrasonography, and computed tomography scans, were found to be useful in the diagnosis of space-occupying liver lesions. On computed tomography, intrahepatic biliary carcinoma usually appears as a solid mass with or without dilatation of the proximal bile ducts, or as localized intrahepatic biliary dilatation without a definite mass. However, the most characteristic appearance of MPCCC on computed tomography or ultrasonography scans is marked dilatation of the intra- and extrahepatic bile ducts distal to the hepatic mass.[6] In patients with jaundice, the intrahepatic bile ducts are diffusely dilated. On cholangiograms, a filling defect or large, amorphous defects in the dilated ducts are characteristic. In most cases, computed tomography and ultrasonography cannot differentiate mucin from bile. However, echogenic spots in the dilated ducts on ultrasonography or high-attenuation computed tomography are helpful in suggesting the retention of mucin.[6]

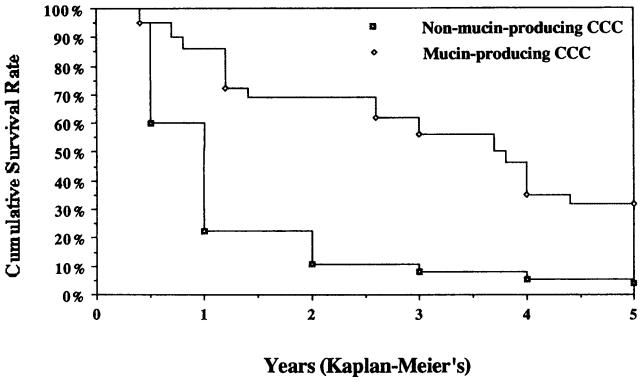

Figure 6. Cumulative survival rate of 22 patients with mucin-producing cholangiocellular carcinoma *versus* 148 patients with non–mucin-producing cholangiocellular carcinoma ($p < 0.05$).

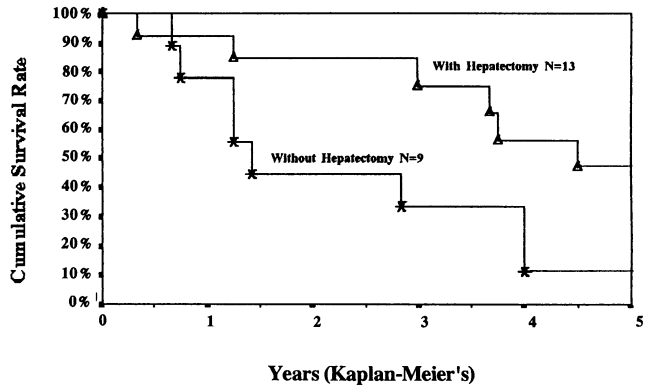

Figure 7. Cumulative survival rates of patients with mucin-producing cholangiocellular carcinoma with or without hepatic resection ($p < 0.05$).

The presence of mucobilia found on common bile duct exploration was significant for the early diagnosis of intrahepatic bile duct carcinoma.[5,8] All 18 patients with mucobilia in this series had papillary adenocarcinoma in the intrahepatic bile ducts. The first five patients with bile duct carcinoma were diagnosed postoperatively by histopathologic examination of the resected specimens. Since 1986, for the remaining 13 patients with mucobilia, the diagnosis of bile duct carcinoma was established at laparotomy by using choledochofiberoscopy or frozen section. Recently, mucobilia was suggested in two patients preoperatively by abdominal ultrasonography and endoscopic retrograde cholangiography.[11,21,23]

In this series, four patients underwent hepatic resection for recurrent cholangitis, but histopathologic diagnosis revealed cholangiocarcinoma after examination of the resected specimens. Hepatic resection for hepatolithiasis can be performed with a low mortality rate in properly selected patients when the stones are located proximal to a stricture in the left segmental duct. Atrophic and fibrotic lobes, abscess formation, or a cholangitic appearance of

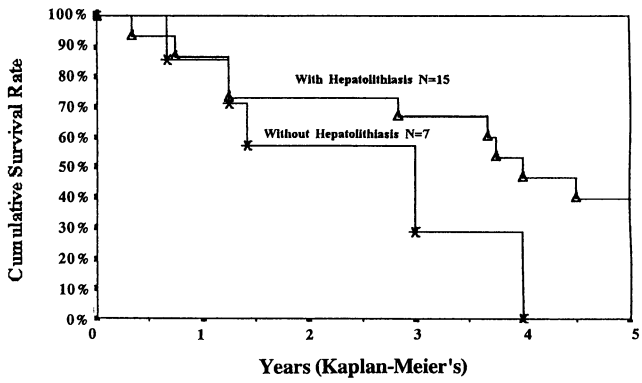

Figure 8. Cumulative survival rates of patients with mucin-producing cholangiocellular carcinoma with or without hepatolithiasis ($p > 0.05$).

the surrounding liver parenchyma, and recurrent or retained stones that cannot be removed by other methods are conditions suitable for hepatic resection. No early operative mortality was reported, and the immediate postoperative morbidity rate was acceptable.[24,25] However, because the resections were not intended to be radical in this group of patients, the overall survival rate was poor.[26]

Intrahepatic bile duct carcinoma is a relatively slow-growing tumor.[2] Radical surgery is the only treatment. Hepatic resection is advocated if the lesion is limited to one lobe or one segment and liver function is not severely impaired.[26,27] Palliative intrahepatic tubing or percutaneous transhepatic biliary drainage can alleviate jaundice and cholangitis to prolong survival.[2] In 1987, Venu et al.[28] introduced intraluminal radiation therapy as another palliative treatment for biliary tree neoplasms. It can be performed using an endoscopic approach or by the percutaneous transhepatic route. Its effectiveness has been evaluated postoperatively by: 1) tumor disappearance under direct vision by choledochofiberoscopy; 2) tumor disappearance shown by cholangiography; 3) subjective improvement in symptoms; and 4) decreasing jaundice and subsiding cholangitis.

In the current series, histopathologic pattern was recognized to be an important factor in prognosis. Most of the patients with MPCCC had papillary adenocarcinoma, and they were found to have a better survival than patients with other types of bile duct adenocarcinoma. The significant influence of the histopathologic patterns of bile duct carcinoma on prognosis has also been noted in other reports.[29,30]

In conclusion, patients with hepatic resection had a better prognosis than those without resection. Although patients with hepatolithiasis demonstrated a better survival pattern than those without hepatolithiasis, the differences was not statistically significant.

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