World J. Surg. 19, 637–641, 1995

WORLD
Journal of
SURGERY

Hepatolithiasis Associated with Cholangiocarcinoma

Shoji Kubo, M.D., Hiroaki Kinoshita, M.D., Kazuhiro Hirohashi, M.D., Hiroyuki Hamba, M.D.

Second Department of Surgery, Osaka City University Medical School, 1-5-7 Asahimachi, Abeno-ku, Osaka 545, Japan

Abstract. Hepatolithiasis is a risk factor for cholangiocarcinoma. It is difficult to make an accurate diagnosis before treatment. In a retrospective study, we identified characteristic clinical features of 103 patients with hepatolithiasis (group H) and 10 patients with hepatolithiasis associated with cholangiocarcinoma (group HC), and examined the methods for diagnosis and treatment. The main symptoms were abdominal pain, fever, and jaundice, although few patients in group HC had jaundice. The incidence of abnormal serum levels of carcinoembryonic antigen (CEA) in group HC was higher than in group H. The incidence of cholangiocarcinoma in cases in which most of the stones were present in the intrahepatic ducts of the left lobe (type I-L) was higher than the incidence in the other patients. Of the patients who underwent portography in group HC, portal veins in the portion of the liver containing the cholangiocarcinoma were not seen, and this region was atrophic in the operative specimens. The incidence of portal obstruction in portograms in group HC was higher than that in group H. The possibility of carcinoma should be kept in mind if there are high levels of CEA, if the location of the stones is classified as type I-L, or if portal veins cannot be seen on portograms. In such patients, liver resection should be considered because there may be undiagnosed cholangiocarcinoma.

Sanes and MacCallum [1] first reported two cases of cholangiocarcinoma occurring together with hepatolithiasis in 1952. It is still difficult to make an accurate diagnosis before treatment [2, 3]. The aim of this study is to describe the characteristic clinical features of patients with hepatolithiasis and of patients with hepatolithiasis associated with cholangiocarcinoma.

Subjects and Methods

Over the past 21 years we have treated 113 patients with hepatolithiasis at our hospital. Group H contained 103 (91%) patients with hepatolithiasis only, and group HC contained 10 (9%) patients with cholangiocarcinoma as well. We compared the clinical features of the groups, including sex, age, signs and symptoms, results of laboratory tests including assays of tumor markers, radiologic and operative findings, and outcome. We retrospectively examined the diagnosis (methods and accuracy) and treatments chosen for all patients.

Chi-square and Fisher's exact tests were used for unadjusted comparison of study groups. All p values reported were two-tailed.

Correspondence to: S. Kubo, M.D.

Results

Patients

Characteristics of the two groups are summarized in Table 1. In group H, there were 40 men and 63 women (1.0:1.6). Group HC contained 6 men and 4 women. Overall, 6 (13%) of the 46 male patients and 4 (6%) of the 67 female patients had cholangiocarcinoma. In group H, the main symptoms were abdominal pain (87%), fever (65%), and jaundice (51%) (Table 2). In group HC, the main symptoms were abdominal pain (90%) and fever (80%); jaundice occurred in only two patients (20%). The time since onset of symptoms in group H ranged from 3 days to 40 years, with a mean of 12 years. In group HC, the period was from 3 months to 27 years, with a mean of 13 years. There was no significant difference in the mean periods. Forty-seven (46%) patients in group H and five (50%) patients in group HC had had biliary surgery. Cholecystectomy with or without choledochotomy was done in 37 (36%) of the patients in group H and in 4 (40%) patients of group HC. Biliary drainage procedures including hepaticojejunostomy and choledochojejunostomy were done in 10 (10%) patients of group H and in one (10%) patient of group HC. There was no significant difference in the incidence of such procedures.

Laboratory Test Results

There were no significant differences between the groups in terms of blood cell counts or results of liver function tests. Serum levels of carcinoembryonic antigen (CEA) were measured in 40 patients in group H and in 9 patients in group HC. In group H, the levels in seven patients (18%) were above normal. In three of these seven patients (8% of the 40 patients), the levels were more than twice normal. In six of the nine patients (67%) in group HC, the levels were more than twice normal. The incidences of CEA levels above normal in the two groups were significantly different ($p < 0.01$). The incidence of CEA levels above twice normal in the groups also was significantly different ($p < 0.005$). The sensitivity of the CEA level to diagnose cholangiocarcinoma was 67% and the specificity 83%. If a CEA value of more than twice normal is taken to be abnormal, the specificity was 93%. In group H, 19 patients were tested for serum levels of carbohydrate antigen (CA) 19-9, and three patients had results above normal. In group

Table 1. Characteristics of patients with hepatolithiasis only and with both hepatolithiasis and cholangioma.

Characteristic	Group H (n = 103)	Group HC (n = 10)
Age (years), range, mean	10–83 (54)	43–79 (59)
Sex (male/female)	1.0:1.6	1.0:0.7
Time since onset of symptoms (years)	12	13
Treated surgically earlier	47 (46%)	5 (50%)

H: hepatolithiasis only; HC: hepatolithiasis and cholangioma.

Table 2. Symptoms of the patients.

Symptom	Group H (n = 103)	Group HC (n = 10)
Abdominal pain	90 (87%)	9 (90%)
Fever	67 (65%)	8 (80%)
Jaundice	53 (51%)	2 (20%)

HC, the level was measured in one patient, and the value was above normal.

Classification of Hepatolithiasis

The location of stones in the two groups was classified as previously reported [4]. Results are shown in Table 3, with definition of the various types in the footnote. In group HC, nine cases (90%) were classified as type I and one case (10%) was type IE; most stones were in the intrahepatic bile ducts. In group H, types L, R, and LR accounted for 56 cases (54%), 24 cases (23%), and 23 (22%) cases, respectively. The incidence of cases classified as type I in group HC was higher than that in group H ($p < 0.05$). In group HC, nine cases (90%) were of type L and one case (10%) was of type R. The incidence of cases classified as type L was higher in group HC than in group H ($p < 0.05$). The incidence of cholangiocarcinoma in cases classified as type I-L (8 of the 45 patients, or 18%) was higher than the incidence in the remaining patients (2 of the 58 patients, or 3%; $p < 0.05$). Ten of the thirty-seven type I-L cases in group H and all of the eight type I-L cases in group HC had stones in the intrahepatic ducts only. Therefore the incidence of cholangiocarcinoma in patients classified as type L and in whom stones were present in the intrahepatic ducts only (8 of the 18 patients, or 44%) was significantly higher than the incidence in the remaining patients (2 of the 95 patients, or 2%; $p < 0.0001$).

Table 4 shows the site of stenosis in the bile duct when present. Stenosis was not detected in 33 patients in group H. In the other 70 patients, there was stenosis at two sites in the bile ducts in eight patients and in three sites in two patients. In group HC, one patient did not have stenosis. Stenosis was detected in the left hepatic duct in six patients, in bile ducts in the left lobe in two patients, and in a bile duct in the posterior segment in one patient. Therefore in most patients (80%) in group HC, stenosis was found in the bile ducts in the left lobe. The locations of the stenotic lesion and the cholangiocarcinoma corresponded.

Table 3. Classification of hepatolithiasis by location of stones.

Type	No. of cases classified by type I	IE	E	Total
L	37 (8)	10 (1)	9	56 (9)
R	18 (1)	4	2	24 (1)
LR	11	9	3	23
Total	66 (9)	23 (1)	14	103 (10)

I: most stones in the intrahepatic bile ducts; E: most stones in the extrahepatic bile duct; IE: stones in both intrahepatic and extrahepatic bile ducts; L: most stones in the left lobe; R: most stones in the right lobe; LR: stones in both lobes.

Numbers not in parentheses are for patients with hepatolithiasis only; numbers in parentheses are of patients with both hepatolithiasis and cholangioma.

Table 4. Site of stenosis of the bile ducts.

Site of stenosis	Group H	Group HC
Bile duct		
Anterior segment	6	
Posterior segment	9	1
Lateral segment	22	2
Medial segment	2	
Left hepatic duct	21	6
Right hepatic duct	7	
Common hepatic duct	10	
Common bile duct	5	

Diagnosis of Cholangiocarcinoma

In group HC, hepatolithiasis was not difficult to diagnose; and for its detection, ultrasonography, computed tomography (CT), and direct cholangiography by percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography were all useful. Of the 10 patients in group HC, 5 patients were initially diagnosed as having hepatolithiasis with liver abscess or cholangitis (Table 5). CT scans of these five patients showed a space-occupying lesion in the liver, but it was difficult to differentiate between liver abscess and malignancy. Two patients seen during the first 10 years of the study period were diagnosed preoperatively as having hepatolithiasis with cholangiocarcinoma, but both tumors were too advanced for surgery. In one patient, a correct diagnosis was made by percutaneous transhepatic cholangioscopy (done only in this patient), and extension of the carcinoma was confirmed by intraoperative examination of frozen sections.

To determine if there were differences in the results of medical imaging in the two groups, we next investigated the findings by portography done during the portal phase by angiography or percutaneous transhepatic portography. In group H, 14 patients underwent portography. In two (14%) of the 14 patients, portal veins in the lobe with stones could not be seen. Portography was done in five patients in group HC. In all five, portal veins in the lobe with the cholangiocarcinoma could not be seen in their entirety. The incidence of portal obstruction in group HC was higher than that in group H ($p < 0.005$). The sensitivity of the findings from portograms for the diagnosis of cholangiocarcinoma was 100% and the specificity 86%. In three of the five patients who underwent both portography and cholangiography, parts of the bile ducts more peripheral than the portal vein were visualized (Fig. 1). These results indicate that portography may be useful for diagnosing hepatolithiasis associated with cholangiocarcinoma.

Table 5. Preoperative diagnosis, treatment, and outcome of patients with hepatolithiasis and cholangiocarcinoma.

Case no.	Preoperative diagnosis (in addition to hepatolithiasis)	Treatment	Outcome after treatment or admission[a]
1[b]	Cholangitis	—	Died at 2 months[a]
2	Cholangioma	Biliary drainage	Died at 1 month
3	Liver abscess	Left lobectomy	Died at 11 months
4	Cholangioma	—	Died at 1 month[a]
5	Liver abscess	Left lobectomy	Died at 1 year 6 months
6	Liver abscess	Left lobectomy	Died at 2 months
7	Liver abscess	Lateral segmentectomy	Died at 8 months
8	—	Lateral segmentectomy	Died at 1 year 5 months
9	Cholangioma	Left lobectomy, lymph node resection	Alive at 2 years 4 months
10	—	Left lobectomy	Alive at 11 months

[a]Outcome for the two patients left untreated was evaluated after admission not treatment.

[b]Cholangioma was diagnosed 2 years 3 months after the first operation for hepatolithiasis.

Treatment, Operative Findings, and Outcome of Hepatolithiasis with Cholangiocarcinoma

Table 5 lists treatments used and the outcomes. Surgery could not be done in two patients with advanced cholangiocarcinoma. Left lobectomy was done in five patients and lateral segmentectomy in two patients. The cancerous lesions, all adenocarcinomas, were in the same area as most of the stones and spread as a rule toward the hepatic hilum. The patients whose cancer could not be resected died within 2 months. Five patients who underwent liver resection without a correct preoperative diagnosis and whose operative specimens suggested that there was residual carcinoma in the liver remaining died because of recurrences of cholangiocarcinoma and recurrent cholangitis within 1 year 5 months. The one patient in whom the preoperative diagnosis was correct and in whom the carcinoma was resected completely is alive 2 years 4 months after surgery, without recurrence. The operation involved left lobectomy and lymph node resection in the hepatic hilum and along the proper and common hepatic arteries. The histologic examination showed that some of the resected lymph nodes along the proper and hepatic arteries were involved.

Discussion

Hepatolithiasis is a risk factor for cholangiocarcinoma [5]. From 2.3% to 10.0% of cases of hepatolithiasis are associated with cholangiocarcinoma (9% in our patients) [2, 3, 6–8]. Some investigators have reported that mechanical stimuli from intrahepatic calculi and chemical irritation to the bile duct wall by the infected bile are causes of the cancer [9]. Other studies [8, 10] suggest that recurrent cholangitis results in atypical epithelium, which may give rise to cancerous lesions. In both groups most patients had Charcot's triad. The lower incidence of jaundice in group HC than in group H may be explained by most of the stones in all patients in group HC being in the intrahepatic bile ducts; the common bile duct was rarely obstructed by stones.

The incidence of associated carcinoma in type I-L (especially when all stones were in the intrahepatic bile ducts) was significantly higher than in the other types. When patients whose hepatolithiasis is classified as type I-L are treated, the possibility of carcinoma should be kept in mind. The finding of abnormal serum levels of CEA suggests that cholangiocarcinoma may be present. Measurement of CA 19-9 may also give information useful for the diagnosis of cholangiocarcinoma associated with hepatolithiasis.

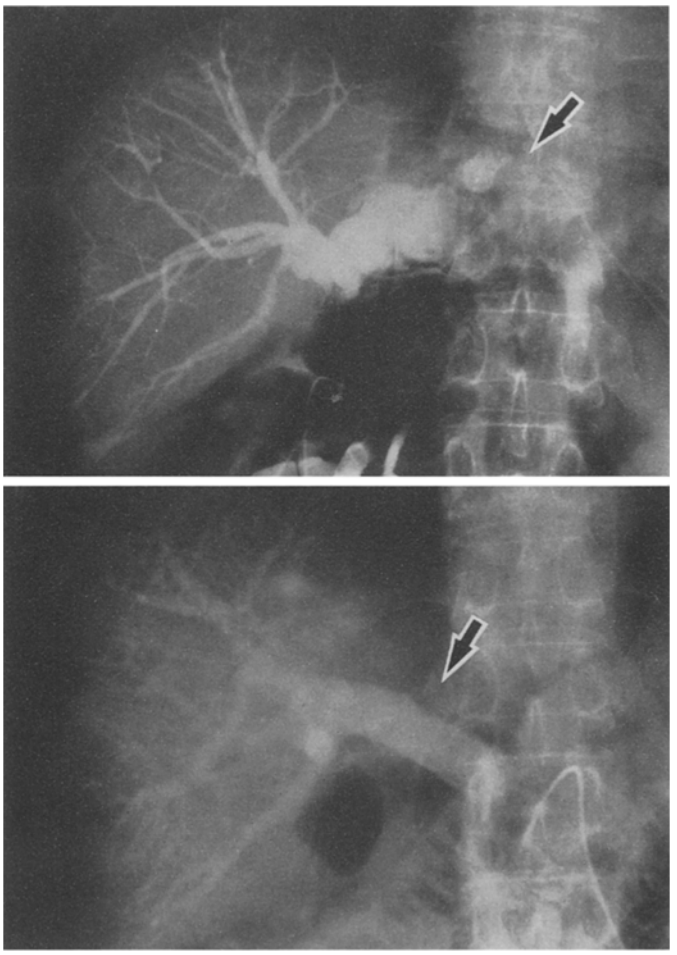

Fig. 1. Cholangiogram and portogram of a patient with hepatolithiasis associated with cholangioma (case 10). **Top.** Cholangiogram shows peripheral intrahepatic bile ducts in the left lobe (arrow). **Bottom.** Portogram shows that the left portal vein is obstructed at the branching point (arrow).

Chen et al. [3] reported that early diagnosis can be aided by any of the following findings: detection of a hyperechoic mass in the liver parenchyma during abdominal ultrasonography; detection of a scintigraphic defect near the hilum; filling defects or obliteration of intrahepatic ducts seen during percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography; a nodular hepatic tumor mass or atrophic fibrotic liver seen during surgery; and intraoperative choledochoscopic findings of an intraluminal tumor or infiltrating lesion. Sonography and computed tomography are useful for detecting stones and dilated bile ducts in the liver. These methods of imaging sometimes show a space-occupying lesion that suggests the presence of a liver abscess, as was the case here for four of our patients. Cholangiography is insufficient to demonstrate the intraluminal changes in cholangio-

carcinoma because when stones are present, obstruction or stenosis caused by cholangiocarcinoma is not easy to differentiate from that caused by stones. In our patients, intrahepatic bile ducts were sometimes visualized from the central part to the peripheral part despite the existence of cholangiocarcinoma. Percutaneous transhepatic cholangioscopy may be useful for identifying the changes in the bile ducts. However, the existence of carcinoma should be confirmed by intraoperative examination of frozen sections because percutaneous transhepatic cholangiography is invasive, may cause seeding of cancer cells, and it takes time to expand the fistula enough for passage of the cholangioscope.

We usually use portography during angiography (portal phase) or percutaneous transhepatic portography to detect changes in the portal veins, to decide on indications for liver resection, and to plan operative methods for liver surgery [11]. In this study, we showed portography to be useful for diagnosing hepatic atrophy and cholangiocarcinoma. Portography should be tried in cases classified as type I, and especially type I-L, because the incidence of cholangiocarcinoma in such cases was higher than that in the other patients. Portography should be done in patients without cholangitis or after biliary drainage for cholangitis. In group HC, there was atrophy of the hepatic tissue in the operative specimens corresponding to the location where portal veins were not seen by portography. In group H, portal veins could be seen by portography in 12 of the 14 patients, although the portal veins were thin in five of these patients. Terada et al. [12] reported that portal stenosis may be caused by an inflammatory extension of cholangitis and may worsen, causing parenchymal atrophy. Therefore obstruction of portal veins means deterioration of the hepatic tissue and strongly suggests the existence of cholangiocarcinoma. The prognosis of this disease is poor. The main objectives of the treatment of hepatolithiasis are to remove all stones and to eliminate bile stasis in the biliary tract to help prevent recurrence. However, for hepatolithiasis with most of the stones in the intrahepatic bile ducts, if the liver parenchyma has deteriorated and associated cholangiocarcinoma is suspected, resection of that portion of the liver should be considered. At that time, frozen sections should be examined intraoperatively to help decide the operative method, including lymph node resection. The one patient who underwent liver and lymph node resection after an accurate diagnosis had a good outcome.

In conclusion, high levels of CEA, type I-L, or portal obstruction strongly suggests the existence of cholangiocarcinoma. In such patients, liver resection should be considered because of the possibility of undiagnosed cholangiocarcinoma. It is important to make a correct pre- or intraoperative diagnosis and to undertake the appropriate operative methods including lymph node resection.

Résumé

La lithiase intrahépatique est un facteur de risque de cholangiocarcinome. Il est difficile d'en faire le diagnostic pécis avant le traitement, Dans une étude rétrospective, nous avons identifié les caractères cliniques chez 103 patients ayant une lithiase intrahépatique (groupe H) et chez 10 patients ayant une lithiase intrahépatique associée à un cholangiocarcinome (groupe HC) en examinant les moyens diagnostiques et thérapeutiques. Les symptômes principaux étaient la douleur abdominale, la fièvre et l'ictère, mais très peu de patients du groupe HC avait un ictère. Il y aviat plus de patients ayant un taux élevé d'antigène carcinoembryonnaire (ACE) dans le groupe HC que dans le groupe H. L'incidence de cholangiocarcinome associé à une lithiase intrahépatique du lobe gauche (type IL) était plus élevé que chez les autres patients. Des patients ayant une portographie dans le groupe HC, on n'a pas visualisé les veines portes dans la région du cholangiocarcinome et eette partie du foie était souvent atrophique sur la pièce de résection. L'incidence de l'obstruction porte dans le groupe HC était plus élevéc que dans le groupe H. La possibilité de cancer doit rester présent à l'esprit si on a des niveaux élevés d'ACE surtout si la lithiase est du type IL ou si l'on ne peut visualiser les veines portes sur la portographie. Chez de tels patients, il faut envisager une résection hépatique car il peut s'agir d'un cholangiocarcinome autrement difficilement diagnostiqué.

Resumen

La hepatolitiasis es un factor reconocido de riesgo de colangiocarcinoma. Su diagnóstico es dificil de establecer. En un estudio retrospectivo hemos identificado las características clínicas en 103 pacientes con hepatolitiasis (grupo H) y en 10 pacientes con hepatolitiasis asociada con colangiocarcinoma (grupo HC); y también hemos examinado los métodos de diagnóstico y tratamiento. Los síntomas principales fueron dolor abdominal, fiebre e ictericia, pero pocos pacientes en el grupo HC tenían ictericia. La incidencia de niveles séricos anormales de antígeno carcinoembrionario (CEA) en el grupo HC fue mayor que en el grupo H. La incidencia de colangiocarcinoma en aquellos casos en que los cálculos se hallaban en los canales intrahepáticos del lóbulo izquierdo (tipo I-L) fue más alta que la incidencia en el resto de los pacientes. De los pacientes sometidos a portografia en el grupo HC, las venas portales en la porción del hígado que contenía el colangiocarcinoma no fueron visualizadas y esta región apareció atrófica en los especímenes operatorios. La incidencia de obstrucción portal en los portogramas en el grupo HC fue más alta que la del grupo H. La posibilidad de carcinoma debe ser tenida en cuenta si se hallan niveles elevados de Ca, si la ubicación de los cálculos es clasificada como tipo I-L o si las venas portas no son visualizadas en los portogramas. En tales pacientes la resección del hígado debe ser considerada, puesto que puede existir un colangiocarcinoma no diagnosticado.

References

1. Sanes, S., MacCallum, J.D.: Primary carcinoma of the liver: cholangioma in hepatolithiasis. Am. J. Pathol. *18*:675, 1952
2. Sheen-Chen, S-M., Choum, F-F., Eng, H-L.: Intrahepatic cholangiocarcinoma in hepatolithiasis: a frequently overlooked disease. J. Surg. Oncol. *47*:131, 1991
3. Chen, M-F., Jan, Y-Y., Wang, C-S., Jeng, L-BB., Hwang, T-L., Chen, S-C.: Intrahepatic stones associated with cholangiocarcinoma. Am. J. Gastroenterol. *84*:391, 1989
4. Hamba, H., Kinoshita, H., Hirohashi, K., et al.: One hundred cases of hepatolithiasis treated surgically. In New Frontiers in Hepato-Biliary-Pancreatic Surgery, T. Takada, T. Vaniyapongs, N. Nimsakul, T. Shaipanich, editors. Bangkok, Bangkok Medical Publisher, 1992, pp. 386–389
5. Yamaguchi, K., Nakayama, F.: Hepatolithiasis associated with cholangiocarcinoma. Asian J. Surg. *14*:120, 1991
6. Chen, P-H., Wang, C-S., Tsai, K-R., et al.: Cholangiocarcinoma in hepatolithiasis. J. Clin. Gastroenterol. *6*:539, 1984
7. Koga, A., Ichimiya, H., Yamaguchi, K., Miyazaki, K., Nakayama, F.:

Hepatolithiasis associated with cholangiocarcinoma: possible etiologic significance. Cancer *55*:2826, 1985
8. Ohta, T., Nagakawa, T., Konishi, I., et al.: Clinical experience of intrahepatic cholangiocarcinoma associated with hepatolithiasis. Jpn. J. Surg. *18*:47, 1988
9. Falchuk, K.R., Lesser, P.B., Galdabini, J.J., Isselbacher, K.J.: Cholangiocarcinoma as related to chronic intrahepatic cholangitis and hepatolithiasis: case report and review of the literature. Am. J. Gastroenterol. *66*:57, 1976
10. Nakanuma, Y., Terada, T., Tanaka, Y., Ohta, G.: Are hepatolithiasis and cholangiocarcinoma aetiologically related? A morphological study of 12 cases of hepatolithiasis associated with cholangiocarcinoma. Virchows Arch. [Pathol. Anat.] *406*:45, 1985
11. Inoue, T., Kinoshita, H., Hirohashi, K., Sakai, K., Uozumi, A.: Ramifications of the intrahepatic portal vein identified by percutaneous transhepatic portography. World J. Surg. *10*:287, 1986
12. Terada, T., Nakanuma, Y., Ueda, K.: The role of intrahepatic portal venous stenosis in the formation and progression of hepatolithiasis: morphological evaluation of autopsy and surgical series. J. Clin. Gastroenterol. *13*:701, 1991

Invited Commentary

Miin-Fu Chen, M.D.

Department of General Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan, Republic of China

Hepatolithiasis associated with cholangiocarcinoma is not often encountered. The overall incidence of cholangiocarcinoma in association with hepatolithiasis was 5.0% (55 of 1105). During the past 5 years, an increased incidence to 13.7% (35 in 255) was noted [1, 2].

Preoperative accurate diagnosis of cholangiocarcinoma associated with hepatolithiasis is difficult. In one of our studies cholangiography was required for all patients who underwent surgery for hepatolithiasis. It was performed in conjunction with and guided by ultrasonography. Those with filling defects or obliteration or faint visualization of the intrahepatic ducts by cholangiography had a thorough preoperative workup, including a computed tomography (CT) scan, percutaneous needle biopsy, or percutaneous transhepatic cholangioscopic biopsy [3]. Those without a definite diagnosis underwent meticulous common bile duct exploration. Operative observations, such as the gross appearance of the liver or mucobilia found by common bile duct exploration, were significant in suggesting the possible diagnosis of the bile duct carcinoma. Intraoperative choledochoscopy or a frozen section microscopic diagnosis were useful for diagnosing biliary tree neoplasms [4].

There have been conflicting data regarding the elevation of carcinoembryonic antigen (CEA) in serum and bile related to biliary malignancies associated with hepatolithiasis. In our study [5], one-third of patients had an elevated serum CEA level when they had cholangiocarcinoma. We also found that the concentration of CEA in bile is unusually high not only in patients with cholangiocarcinoma but also in those with hepatolithiasis. The results were in agreement with the other series from Taiwan reported by Ker et al. [6]. Therefore the diagnosis of hepatobiliary malignancies, especially in an early stage, may be further improved by another tumor marker.

We have no experience regarding portography in the diagnosis of cholangiocarcinoma associated with hepatolithiasis. According to many authors [7, 8], it is suspected that a decrease in portal venous flow is important in the formation and progression of hepatolithiasis in animal models. The vascular changes may be caused by an inflammatory extension of cholangitis and may deteriorate, causing parenchymal atrophy during the progression of hepatolithiasis. Therefore the absence or faint visualization of the portal vein by portography may exist in patients with hepatolithiasis only.

Hepatic resection is the only treatment for this disease [9]. Palliative intrahepatic tubing or percutaneous transhepatic biliary drainage and intraluminal radiation therapy [10] can alleviate jaundice and cholangitis, thereby prolonging survival. In the current series [2, 5, 9], the overall median survival time of patients with cholangiocarcinoma in association with hepatolithiasis was 10.4 months; the 1-, 2-, and 4-year cumulative survival rates were 30.0%, 12.7%, and 3.6%, respectively. Patients with hepatectomy or the presence of mucobilia had better survival rates.

References

1. Chen, M.F., Jan, Y.Y., Wang, C.S., Jeng, L.B., Hwang, T.L., Chen, S.C.: Intrahepatic stones associated with cholangiocarcinoma. Am. J. Gastroenterol. *84*:391, 1989
2. Chen, M.F., Jan, Y.Y., Wang, C.S., et al.: A reappraisal of cholangiocarcinoma in patients with hepatolithiasis. Cancer *71*:2461, 1993
3. Chen, M.F., Jan, Y.Y., Lee, T.Y.: Percutaneous transhepatic cholangioscopy. Br. J. Surg. *74*:728, 1978
4. Chen, M.F., Jan, Y.Y., Wang, C.S., Jeng, L.B., Hwang, T.L.: Intraoperative fiberoptic choledochoscopy for malignant biliary tract obstruction. Gastrointest. Endosc. *35*:545, 1989
5. Chen, M.F., Jan, Y.Y.: Late occurrence of cholangiocarcinoma after the treatment of hepatolithiasis. Submitted
6. Ker, C.G., Sheen, P.C., Chien, C.H.: Elevation of carcinoembryonic antigen related to biliary malignancy in hepatolithiasis. Jpn. J. Surg. *23*:496, 1993
7. Terada, T., Nakanuma, Y., Ueda, K.: The role of intrahepatic portal venous stenosis in the formation and progression of hepatolithiasis: morphological evaluation of autopsy and surgical series. J. Clin. Gastroenterol. *13*:701, 1991
8. Saji, Y.: The effect of decreased portal blood flow on the biliary system. Jpn. J. Surg. *18*:558, 1988
9. Chen, M.F., Jan, Y.Y., Wang, C.S., Jeng, L.B., Hwang, T.L.: Clinical experience in 20 hepatic resections for peripheral cholangiocarcinoma. Cancer *64*:2226, 1989
10. Venu, R.P., Geenen, J.E., Hogwan, W.J., Johnson, G.K., Klein, K., Stone, J.: Intraluminal radiation therapy for biliary tract malignancy: an endoscopic approach. Gastrointest. Endosc. *33*:236, 1987