Prognostic analysis of surgical treatment of peripheral cholangiocarcinoma: Two decades of experience at Chang Gung Memorial Hospital

Yi-Yin Jan, Chun-Nan Yeh, Ta-Sen Yeh, Tse-Ching Chen

INTRODUCTION
Peripheral cholangiocarcinoma (PCC) is a malignant tumor occurring in the liver or arising from the second or more distal branches of the intrahepatic bile ducts\(^1\). The incidence of PCC exhibits wide geographical variation, and generally accounts for between 5% and 30% of primary liver cancers\(^1\). According to the Japan Liver Cancer Society, histologically proven PCC represented 3.58% of all primary liver cancers\(^2\).

Although no specific etiological factor has been identified for PCC, various well-recognized predisposing conditions involving chronic inflammation of the bile ducts exist. These conditions include infestation with the liver flukes *Opisthorchis viverrini* in Thailand\(^3\) and *Clonorchis sinensis* in other Asian countries\(^4,5\); hepatolithiasis, prevalent in countries such as Taiwan and Japan\(^6-8\); primary sclerosing cholangitis\(^9,10\); choledochal cysts\(^11,12\); and Caroli’s disease\(^13,14\).

Clinically, PCC remains challenging because it is difficult to diagnose in its early stages, and patients typically do not present because of vague symptoms until the disease is quite advanced. Curative resection with clear margins and without vascular or lymphatic invasion is infrequent and recurrence is common. Three- to five-year survival rates even with resection remains dismal\(^15-18\). Moreover, radiation therapy or current chemotherapy does not significantly improve long-term survival rates\(^16,19\). Tumor biological behavior and early intrahepatic and extrhepatic spread limit the efficacy of surgery, and yet complete surgical removal currently is the curative option for PCC. Although liver transplantation has provided an alternative in the surgical management of PCC, high rates of PCC recurrence following transplantation limit liver transplantation for PCC patients\(^20\). Despite considerable progress in diagnostic procedures, surgical techniques, and adjuvant therapies, the prognosis of PCC remains extremely poor, because most tumors are advanced by the time of diagnosis. The literature contains few reports of successful surgical treatment of PCC and evaluation of its prognostic factors, and most
such reports deal with small numbers of cases. This study examines the influence of clinicopathologic characteristics of PCC undergoing surgical treatment on PCC patient’s overall survival to improve the prognosis of PCC patients.

MATERIALS AND METHODS

From January 1977 to December 2001, 608 consecutive patients with histologically proven bile duct adenocarcinoma underwent surgical treatment at the Department of Surgery, Chang-Gung Memorial Hospital, Taipei, Taiwan. Based on tumor location, the 608 patients were classified into common bile duct cancer \( n = 102; 16.8\% \), bile duct adenocarcinoma with hilar invasion \( n = 133; 21.9\% \), and PCC \( n = 373; 61.3\% \). PCC was defined as carcinoma arising from second order or more distal branches of the intrahepatic ducts. IP-PCC is histologically defined as intraductal papillary neoplasia of the liver (IPN-L) type 3 and 4, as described previously. Type 3 showed an IPN-L lined by in situ and microinvasive adenocarcinoma, and type 4 showed with types 2 and 3 biliary lesions with variable invasion of adenocarcinoma. Meanwhile, curative resection was defined as negative resection margin observed during histopathological examination. The 373 PCC patients comprised 159 men and 214 women with a mean age of 57.8 years (range 28-93 years). Table 1 lists the clinical manifestations and histological classifications. Right upper abdominal pain with tenderness was the most common symptom and sign on admission. Table 2 lists the distribution of the operative procedures, and indicates that 187 patients had hepatectomy, with a 36.2% curative resectability rate (curative resection cases: 135/373). Meanwhile, Table 3 lists the causes of surgical mortality, and reveals a surgical mortality rate of 6.7% (25/373). Surgical mortality is defined as the death occurring within one month after surgery. PCC patients undergoing non-hepatectomy procedure had a significantly higher surgical mortality (2.7 vs 10.8%; \( P = 0.002 \)). Sepsis due to biliary tract infection is the main cause of surgical mortality. Laboratory tests were conducted on the day before surgery. Serum carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were measured by radioimmunoassay. The tumors were preoperatively evaluated by abdominal ultrasonography (US), endoscopic retrograde cholangiopancreatography, percutaneous transcatheter cholangiography, computed tomography (CT), magnetic resonance image with cholangiopancreatography (MRCP), and hepatic arteriography, as appropriate. Tumor stage was defined according to the pathological tumor node metastasis (pTNM system) classification proposed by the UICC. Stages I and II were conditioned as early-stage, and stages III and IV as advanced-stage PCC. Adjuvant chemotherapy was systemically performed with a 5-flourouracil-based regimen due to either a positive section margin or local recurrence. Meanwhile, adjuvant radiotherapy was performed with intra-operative radiotherapy, external beam radiotherapy and/or brachytherapy due to either a positive section margin or local recurrence.

### Table 1 Clinical manifestations and histological classification of 373 PCC patients who underwent surgical treatment

| Symptoms                                      | Case no. | %  |
|-----------------------------------------------|----------|----|
| Right hypochondria                            | 266      | 71.7|
| Fever and chills                              | 135      | 36.4|
| Body weight loss                              | 99       | 26.7|
| Jaundice                                      | 76       | 20.5|
| Negative                                      | 14       | 3.8 |
| Physical findings                             |          |    |
| Abdominal tenderness or rebounding pain       | 160      | 43.1|
| Icteric sclera and yellow discoloration       | 72       | 19.4|
| Abdominal mass                                | 17       | 4.6 |
| Negative                                      | 109      | 29.4|
| Histological classifications                  |          |    |
| Papillary adenocarcinoma                      | 50       | 14.9|
| W-D adenocarcinoma                            | 32       | 15.8|
| M-D adenocarcinoma                            | 66       | 20.5|
| P-D adenocarcinoma                            | 56       | 15.8|
| Mucinous adenocarcinoma                       | 32       | 8.6 |
| Adenosquamous carcinoma                       | 14       | 3.8 |
| Hepatocellular carcinoma                      | 9        | 2.4 |
| Adenocarcinoma; unclassified                  | 56       | 15.1|

W: well; M: moderately; P: poorly; D: differentiated.

### Table 2 Surgical procedures of 373 PCC patients

| Surgical procedures                        | Patient number | %  |
|--------------------------------------------|----------------|----|
| Hepatectomy                                | 187            | 50.1|
| Left hepatectomy                           | 125            |     |
| Segment 1, 2, 3, and 4                      | 6              |     |
| Segment 2, 3, and 4                        | 67             |     |
| Segment 2 and 3                            | 49             |     |
| Segment 2, 3, and bile duct resection       | 2              |     |
| Segment 1                                  | 1              |     |
| Right hepatectomy                          | 36             |     |
| Segment 5, 6, 7, and 8                      | 15             |     |
| Segment 5, 6, 7, 8, and bile duct resection | 5              |     |
| Segment 5, 6, 7                            | 1              |     |
| Segment 5 and 6                            | 9              |     |
| Segment 6 and 7                            | 4              |     |
| Segment 7 and 8                            | 2              |     |
| Bilateral hepatectomy                      | 14             |     |
| Segment 4, 5, 6, 7, and 8                  | 9              |     |
| Segment 4, 5, 6, 8                         | 3              |     |
| Segment 2, 3, 4, 5, and 6                  | 1              |     |
| Partial hepatectomy                        | 12             |     |
| Choledochotomy with T-tube                 | 104            | 27.9|
| Laparotomy with biopsy                     | 82             | 22.0|
| Total                                      | 373            | 100 |

### Table 3 Operative mortality of 373 PCC patients undergoing surgical treatment

| Cause of death                     | Hepatectomy (\( n = 187 \)) | Non-hepatectomy (\( n = 186 \)) |
|------------------------------------|-------------------------------|----------------------------------|
| Sepsis (biliary)                   | 2                             | 8                                |
| GI bleeding                        | 0                             | 1                                |
| Intra-abdominal bleeding with shock| 0                             | 2                                |
| Terminal status of cancer          | 0                             | 6                                |
| Necrotizing fascitis with sepsis   | 0                             | 1                                |
| CVA                                | 0                             | 1                                |
| Hepatic failure                    | 1                             | 0                                |
| Respiratory failure                | 0                             | 1                                |
| Gastrocutaneous fistula            | 2                             | 0                                |
| Total                             | 5                             | 20                               |
| Mortality rate                     | 2.7%                          | 10.8%                            |

GI: gastrointestinal; CVA: cerebrovascular accident; mortality rate of hepatectomy vs non-hepatectomy: 2.7% vs 10.8% (\( P = 0.002 \)); whole series mortality rate: 25/373 = 6.7%.
Follow-up study

Follow-up evaluation included clinical physical examinations and blood chemistry tests at each visit. Additionally, serum CA 19-9 and CEA were measured, and the remnant liver was examined with US every three months. When US detected a new lesion or elevated CA 19-9 or when CEA were noted, abdominal CT or MRCP was performed for confirmation. Moreover, when patients complained of bone pain, bone scans were performed to detect metastasis. If any of the above procedures indicated recurrence, the patient was readmitted for more compressive assessment, including angiographic evaluation or MRI. Methods for treating recurrence include surgery, systemic chemotherapy, external beam radiotherapy, intraluminal radiotherapy, interventional radiological therapy, and conservative treatment.

Statistical analysis

The cumulative survival rates were calculated with the Kaplan-Meier method. Seventeen clinicopathological variables were selected for difference analysis by the log-rank test. The Cox proportional hazards model was employed for multivariate regression analysis. SPSS for Windows statistics software (SPSS version 10.0, Chicago, IL) was used for the statistical analysis. $P \leq 0.05$ was considered statistically significant.

RESULTS

Survival

Three hundred and seventy-three PCC patients undergoing surgical treatment received regular follow-up until death. This study showed that 187 PCC patients underwent hepatectomy and 135 had curative resection (curative resectability rate: 36.2%). Sixty-two patients were excluded from the survival analysis, including 25 patients who died within one month after surgery and a further 37 patients who were lost to follow-up. Totally 312 PCC patients undergoing surgical treatment were enrolled into survival analysis. The follow-up duration ranged from 1.05 to 167.6 mo (mean/median = 14.1/7.2 mo). Overall cumulative survival rates at 1, 3, and 5 years were 32.5%, 9.2%, and 4.1%, respectively.

Prognostic factors for survival

Univariable log-rank analysis identified the following as adverse influences on overall survival of 312 PCC patients, namely: presence of symptoms, absence of mucobilia, elevated CEA and CA 19-9 levels, non-papillary tumor type, lack of hepatectomy, advanced tumor staging, lack of post-operative chemotherapy, and radiotherapy (Table 4 and 5). Meanwhile, multivariable Cox’s proportional hazard analysis demonstrated that absence of mucobilia, non-papillary tumor type, non-hepatectomy, and lack of post-operative chemotherapy were the five independent prognostic factors that adversely affected overall survival (Table 6, Figures 1A-F).

| Table 4 | Univariate analysis of factors influencing the overall survival of the 312 PCC patients |
| Factors | Survival time (mo) | $P$ | Median | mean | 3-yr (%) | 5-yr (%) |
|---------|-------------------|-----|--------|------|----------|----------|
| Gender  |                    |     |        |      |          |          |
| Male ($n = 128$) | 7.79 | 14.66 | 11.78 | 2.27 |
| Female ($n = 184$) | 6.84 | 18.41 | 10.88 | 8.61 | 0.941 |
| Age (yr) |                    |     |        |      |          |          |
| $\leq 58$ ($n = 163$) | 6.21 | 17.07 | 11.69 | 6.86 |
| $>58$ ($n = 149$) | 8.35 | 17.15 | 10.70 | 6.05 | 0.471 |
| Symptoms |                    |     |        |      |          |          |
| Positive ($n = 303$) | 6.90 | 16.58 | 10.75 | 6.00 |
| Negative ($n = 9$) | 20.45 | 41.67 | 30.48 | 30.48 | 0.024 |
| Physical examination |                    |     |        |      |          |          |
| Positive ($n = 222$) | 6.64 | 15.70 | 8.08  | 4.54 |
| Negative ($n = 90$) | 9.67 | 20.33 | 20.46 | 13.56 | 0.053 |
| ALT (IU/L) |                    |     |        |      |          |          |
| $\leq 36$ ($n = 139$) | 7.33 | 14.94 | 9.26  | 5.15 |
| $>36$ ($n = 107$) | 8.35 | 21.38 | 15.12 | 9.30 | 0.326 |
| AST (IU/L) |                    |     |        |      |          |          |
| $\leq 54$ ($n = 63$) | 10.39 | 26.31 | 12.12 | 3.64 |
| $>54$ ($n = 214$) | 6.64 | 17.22 | 10.75 | 6.46 | 0.2143 |
| Serum CEA (ng/dL) |                    |     |        |      |          |          |
| $\leq 3$ ($n = 103$) | 10.39 | 23.17 | 17.96 | 9.95 | 0.0001 |
| $>3$ ($n = 70$) | 4.57 | 9.58  | 1.99  | 1.99 |
| Serum CA 19-9 (ng/dL) |                    |     |        |      |          |          |
| $\leq 37$ ($n = 78$) | 7.40 | 11.93 | 10.27 | N.A. |
| $>37$ ($n = 29$) | 13.28 | 25.49 | 23.76 | 15.84 | 0.008 |
| Associated with biliary stones |                |     |        |      |          |          |
| With biliary stones ($n = 186$) | 6.94 | 17.86 | 11.96 | 7.18 |
| Without biliary stones ($n = 126$) | 7.40 | 16.50 | 9.77  | 5.86 | 0.693 |
| Type of operation |                    |     |        |      |          |          |
| Hepatectomy ($n = 157$) | 12.99 | 25.31 | 17.88 | 10.15 |
| Non-hepatectomy ($n = 155$) | 3.65 | 9.03  | 4.42  | 2.76 | <0.0001 |

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; CEA: carcinoembryonal antigen; CA 19-9: carbohydrate antigen; IU: international unit.
This study used univariate and multivariate analysis to calculate overall survival rates of 312 PCC patients after surgical treatment in terms of 17 clinicopathologic factors. In univariate analysis, patients’ symptoms, preoperative tumor marker (CEA and CA19-9), presence of mucobilia, tumor spreading pattern, treatment option, tumor staging, and post-operative adjuvant therapy (chemotherapy and radiotherapy) significantly influenced overall survival of PCC patients after surgical treatment. Applying the multivariate Cox’s proportional hazards model to data from this investigation revealed that long-term overall survival depends on the presence of mucobilia, hepatectomy, early tumor stage, type of operation, tumor staging, and post-operative adjuvant chemotherapy, and radiotherapy.

Patients with PCC diagnosed asymptptomatically and incidentally had a favorable survival, demonstrated by univariate log-rank survival analysis. This study revealed the fact that PCC remains clinically challenging because it is difficult to diagnose in its early stages, and patients typically do not present because of vague symptoms until the disease is quite advanced. So we should seek a certain novel tumor marker for the early detection of PCC in high-risk patient groups.

Diagnostic adjuncts for PCC, such as a serum marker, are useful for the clinical management of this disease. Several investigators have reported that CA 19-9 and CEA determinations are useful for diagnosing PCC in primary sclerosing cholangitis[26]. These investigators also demonstrated that serum CA 19-9 values are related to tumor burden, and suggested that values were elevated in patients with PCC related to unresectable disease[26]. A previous Japanese study has also demonstrated that elevated serum tumor marker, including CEA and CA19-9, was a predictor of a dismal prognosis[27]. Although the reason is unclear, this study also demonstrated that elevated serum CA and CA19-9 were predictors of dismal prognosis in univariate log-rank analysis. The association between intrahepatic stone and PCC is well recognized.

Mucobilia occurs in various conditions, including biliary papillomatosis, cholangiocarcinoma, and biliary cystadenoma and cystadenocarcinoma of the liver[28]. The presence of mucobilia is important for the early diagnosis of PCC, even preoperatively[29]. Our previous study demonstrated that mucobilia was a prognostic variable predicting better survival in PCC patients undergoing surgical treatment[29]. This study confirmed the same observation and reemphasizes the importance of recognition in this specific clinical presentation as a hope of favorable overall survival of PCC patients.

Papillary type PCC, namely intraductal papillary neoplasia of the liver, is a specific type of biliary epithelial neoplasia with frequent gastrointestinal metaplasia associated with
overproduction of mucin and mucobilia\(^{[8]}\). The special nature of this condition explains why more papillary adenocarcinoma and mucobilia were noted in this study. Tumor spreading type was also a favorable prognostic variable for PCC survival\(^{[35-37]}\). Patients with intraductal papillary type PCC had displayed significantly better survival rates than periductal infiltrating or mass forming type PCC. Meanwhile, this study confirmed that the absence of papillary growing in PCC patients undergoing surgical treatment increased the chances of reducing long-term survival by 1.946 times according to multivariate Cox’s proportional hazard analysis.

Although a previous Japanese report has proposed a new staging system mainly based on mass forming type PCC to challenge the TNM staging system\(^{[33]}\), this study revealed that TNM staging system remains the most reliable prognostic factor for predicting the outcome of PCC patients undergoing surgical treatment for various types of PCC. Patients with more advanced tumors displayed a significantly worse prognosis, revealed not only by univariate log-rank analysis but also multivariate Cox’s proportional hazard analysis.

Hepatic resection is the preferred treatment for PCC\(^{[9]}\). This study demonstrated that PCC patients undergoing hepatic resection had significantly better survival than those without hepatic resection\(^{[20,34]}\). However, prognosis of PCC in our series is poor when compared with the other series\(^{[35]}\). The fact that only about 50.1\% of 373 PCC patients receive hepatic resection and more advanced tumor staging patients exist may explain the poor prognosis in this study. This poor prognosis may be caused by the large number of PCC patients presenting with advanced tumors and unresected status (76.9\% and 49.9\%, respectively). Hepatic resection significantly prolongs the survival of PCC patients, as demonstrated by multivariate Cox’s proportional hazard analysis.

The utilization of adjuvant chemotherapy and radiation in PCC remains controversial\(^{[10]}\). However, this study showed that postoperative adjuvant chemotherapy was independent significant predictors for PCC patients with good long-term survival undergoing surgical treatment. Several authors have reported varying degrees of success with chemotherapy, either by systemic route or by intra-arterial hepatic route in PCC treatment\(^{[11,35]}\). The efficacy of chemotherapy has not been evaluated prospectively in patients with PCC\(^{[35]}\). No good chemotherapy regimen is currently available, but 5-fluorocil (5-FU) is the standard base regimen. Several combinations with 5-FU have been reported to produce transient partial remission in a small portion of patients\(^{[35-37]}\).

In conclusion, long-term survival of PCC patients undergoing surgical treatment depends on early tumor stage, presence of mucobilia and papillary tumor type, hepatic resection, and post-operative chemotherapy.

REFERENCES

1. Chen MF. Peripheral cholangiocarcinoma (cholangiocellular carcinoma): clinical features, diagnosis and treatment. J Gastroenterol Hepatol 1999; 14: 1144-1149
2. Liver Cancer Study Group of Japan. Classification of primary liver cancer. Kanehara, Tokyo (1997) 1st English ed.
3. Suzuki H, Isaji S, Pairojkul C, Uttaravichion T. Comparative clinicopathological study of resected intrahepatic cholangiocarcinoma in northeast Thailand and Japan. J Hepatobiliary Pancreat Surg 2000; 7: 206-211
4. Sirica AE, Gainey TW, Harrell MB, Caran N. Cholangiocarcinogenesi and biliary adaptation responses in hepatic injury. In: Sirica AE, Longnecker DS, eds. Biliary and Pancreatic Ductal Epithelia-Pathobiology and Pathophysiology New York: Marcel Dekker 1997: 229-290
5. Chapman RW. Risk factors for biliary tract carcinogenesis. Ann Oncol 1999; 10 Suppl 4: 308-311
6. Chu KM, Lo CM, Liu CL, Fan ST. Malignancy associated with hepatolithiasis. Hepatogastroenterology 1999; 44: 352-357
7. Su WC, Shiesh SC, Liu HS, Chen CY, Chow NH, Lin XZ. Expression of oncogene products HER2/Neu and Ras and fibrosis-related growth factors bFGF, TGF-beta, and PDGF in bile from biliary malignancies and inflammatory disorders. Dig Dis Sci 2001; 46: 1387-1392
8. Chen TC, Nakanuma Y, Zen Y, Chen MF, Jan YY, Yeh TS, Chiu CT, Kuo TT, Kami J, Oda K, Hamaguchi M, Ohno Y, Hsieh LL, Nimura Y. Intraductal papillary neoplasia of the liver associated with hepatolithiasis. Hepatology 2001; 34: 651-658
9. Ponsioen CI, Tytsgt GN. Primary sclerosing cholangitis: a clinical review. Am J Gastroenterol 1998; 93: 515-523
10. Harrison PM. Prevention of bile duct cancer in primary sclerosing cholangitis. Ann Oncol 1999; 10 Suppl 4: 208-211
11. Jan YY, Chen HM, Chen MF. Malignancy in choledochal cysts. Hepatogastroenterology 2000; 47: 337-340
12. Imazu M, Iwai N, Tokiwa K, Shimotake T, Kimura O, Ono S. Factors of biliary carcinogenesis in choledochal cysts. Eur J Pediatr Surg 2001; 11: 24-27
13. Weber SM, Jarnagin WR, Klimstra D, DeMatteo RP, Fong Y, Blumgart LH. Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. J Ann Coll Surg 2001; 193: 384-391
14. Uenishi T, Hirohashi K, Kubo S, Yamamoto T, Hamba H, Tanaka H, Kinoshita H. Histologic factors affecting prognosis following hepatectomy for intrahepatic cholangiocarcinoma. World J Surg 2001; 25: 865-869
15. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, Youssef BA M, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001; 234: 507-517; discussion 517-519
16. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. N Engl J Med 1999; 341: 1368-1378
17. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001; 33: 1353-1357
18. Shirabe K, Shimada M, Harimoto N, Sugimachi K, Yamashita Y, Tsujita E, Aishima S. Intrahepatic cholangiocarcinoma: its mode of spreading and therapeutic modalities. Surgery 2002; 131: S159-S164
19. Bathe OF, Pacheco JT, Oss P, Hamilton KL, Franceschi D, Vleumand D, Levi JU, Livingston AS. Management of hilar bile duct carcinoma. Hepatogastroenterology 2001; 48: 1289-1294
20. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000; 69: 1633-1637
21. Ohitsuuka M, Ito H, Kinuma F, Shimizu H, Togawa A, Yoshidome H, Miyazaki M. Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. Br J Surg 2002; 89: 1525-1531
22. Kawarada Y, Yamagita K, Das BC. Analysis of the relationships between clinicopathological factors and survival time in intrahepatic cholangiocarcinoma. Am J Surg Pathol 2002; 183: 629-685
23. Suzuki S, Sakaguchi T, Yokoi Y, Okamoto K, Kurachi K, Tsuchiya Y, Okumura T, Konno H, Baba S, Nakamura S. Clinicopathological prognostic factors and impact of surgical
treatment of mass-forming intrahepatic cholangiocarcinoma. *World J Surg* 2002; 26: 687-693

24 Hanazaki K, Kajikawa S, Shimozawa N, Shimada K, Hiraguri M, Koide N, Adachi W, Amano J. Prognostic factors of intrahepatic cholangiocarcinoma after hepatic resection: univariate and multivariate analysis. *Hepatogastroenterology* 2002; 49: 311-316

25 Okabayashi T, Yamamoto J, Kosuge T, Shimada K, Yamasaki S, Takayama T, Makuuchi M. A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. *Cancer* 2001; 92: 2374-2383

26 Patel AH, Harnois DM, Klee GG, LaRusso NF, Cores GJ. The utility of CA 19-9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. *Am J Gastroenterol* 2000; 95: 204-207

27 Chen MF. Mucobilia: the clinical spectrum, diagnosis and treatment. *J Gastroenterol Hepatol* 1998; 13: 1084-1090

28 Chen MF, Jan YY, Chen TC. Clinical studies of mucin-producing cholangiocellular carcinoma: a study of 22 histopathology-proven cases. *Ann Surg* 1998; 227: 63-69

29 Jan YY, Jeng LB, Hwang TL, Wang CS, Chen MF, Chen TJ. Factors influencing survival after hepatectomy for peripheral cholangiocarcinoma. *Hepatogastroenterology* 1996; 43: 614-619

30 Cattel RB, Brausch JW, Kahn F. Polypoid epithelial tumors of the bile ducts. *N Engl J Med* 1962; 226: 57-61

31 Suh KS, Roh HR, Koh YT, Lee KU, Park YH, Kim SW. Clinicopathological features of the intraductal growth type of peripheral cholangiocarcinoma. *Hepatology* 2000; 31: 12-17

32 Buskirk SJ, Gunderson LR, Adson MA, Martinez A, May GR, Mcllrath DC, Nagorney DM, Edmundson GK, Bender CE, Martin JK. Analysis of failure following curative irradiation of gallbladder and extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1984; 10: 2013-2023

33 Yeh CN, Jan YY, Yeh TS, Hwang TL, Chen MF. Hepatic resection of the intraductal papillary type of peripheral cholangiocarcinoma. *Ann Surg Oncol* 2004; 11: 606-611

34 Kokudo N, Makuuchi M. Extent of resection and outcome after curative resection for intrahepatic cholangiocarcinoma. *Surg Oncol Clin N Am* 2002; 11: 969-983

35 Cantore M, Rabbi C, Guadagni S, Zamagni D, Aitini E. Intra-arterial hepatic chemotherapy combined with continuous infusion of 5-fluorouracil in patients with metastatic cholangiocarcinoma. *Ann Oncol* 2002; 13: 1687-1688

36 Hejna M, Pruckmayer M, Raderer M. The role of chemotherapy and radiation in the management of biliary cancer: a review of the literature. *Eur J Cancer* 1998; 34: 977-986

37 Ellis PA, Norman A, Hill A, O’Brien ME, Nicolson M, Hickish T, Cunningham D. Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. *Eur J Cancer* 1995; 31A: 1594-1598

*Science Editor* Li WZ  *Language Editor* Elsevier HK