

# Surgical procedure and prognosis of hilar cholangiocarcinoma

Bin Yi, Bai-He Zhang, Yong-Jie Zhang, Xiao-Qing Jiang, Bao-Hua Zhang, Wen-Long Yu, Qing-Bao Chen and Meng-Chao Wu

Shanghai, China

**BACKGROUND:** Hilar cholangiocarcinoma has a low radical resection rate and a poor long-term survival rate. In recent years, its prognosis has been improved with advancement of preoperative diagnostic techniques and surgical techniques. The aim of this study was to evaluate the prognostic factors of hilar cholangiocarcinoma and the relations of surgical procedure to the prognosis of the carcinoma.

**METHODS:** A retrospective cohort study was done in 198 patients with hilar cholangiocarcinoma (117 men and 81 women, aged from 27 to 81 years), who had been admitted to this hospital from December 1997 to December 2002. Their symptoms were jaundice (94.5%), pruritus (56.6%) and abdominal pain (33.8%). Bismuth-Corlette classification showed type I in 14 patients, type II in 19, type IIIa in 12, type IIIb in 15, type IV in 112, and unclassifiable type in 26. 144 patients underwent laparotomy and others received bile drainage endoscopically (including endoscopic retrograde biliary drainage (ERBD) or endoscopic metal biliary endoprosthesis (EMBE) in 21 patients, endoscopic nose-biliary drainage (ENBD) in 31 or percutaneous transhepatic cholangiodrainage in 2. 120 patients (83.3%) received tumor resection including radical resection in 59 patients (41.0%). Twenty-three patients underwent paunched biliary exploration and drainage.

**RESULTS:** Cox's regression model analysis showed that occupation, preoperative total serum bilirubin level, operative procedure and postoperative adjuvant radiation were significantly related to postoperative survival rate in contrast to gender, age, choledocholithiasis, hepatitis, preoperative serum CA19-9 level, Bismuth-Corlette type, histopathologic grading and postoperative chemotherapy. The survival of patients in groups of biliary drainage, palliative resection and radical resection differed statistically and prolonged in a descending order. No statistical difference was found between ERBD or EMBE group and palliative resection group. So was between ERBD or EMBE group and

biliary drainage group, or between ENBD group and biliary drainage group. The survival differed statistically between ERBD or EMBE group and ENBD group.

**CONCLUSIONS:** Operative procedure is the most important prognostic factor affecting the operative results of hilar cholangiocarcinoma. Radical resection is still the primary measure for a cure and long-term survival of the patients. For patients with irresectable hilar cholangiocarcinoma, no evidence has shown that the prognosis after treatment of ERBD or EMBE is poorer than that after laparotomy.

(*Hepatobiliary Pancreat Dis Int* 2004; 3: 453-457)

**KEY WORDS:** cholangiocarcinoma/surgery; prognosis; cholangiopancreatography; endoscopic retrograde

## Introduction

Hilar cholangiocarcinoma or proximal bile duct carcinoma arising from the upper one-third of the main bile duct to transverse hilar fissure has low rates of radical resection and poor long-term survival. In recent years, prognosis of hilar cholangiocarcinoma has been improved with the advancement of preoperative diagnostic techniques<sup>[1]</sup> and surgical techniques. The reported radical resection rates ranged from 28.9% to 84.6%, even beyond 40%.<sup>[2-6]</sup> The postoperative 3-, 5-, and 10-year survival rates ranged from 30% to 43%, 11% to 43%, and below 18% respectively. The median survival ranged from 19 to 35 months.<sup>[2-4,7-13]</sup> To find the prognostic factors of this disease and its relations of operative procedure to prognosis, we retrospectively studied 198 patients with hilar cholangiocarcinoma who had been admitted to our hospital from December 1997 to December 2002.

## Methods

### Patients

The inclusion criteria for patients with hilar cholangiocarcinoma included signs of jaundice, pruritus or abdominal pain, and images of hilar biliary obstruction confirmed by endoscopic retrograde cholangiopancreatogra-

**Author Affiliations:** Department of Biliary Surgery, Eastern Hepatobiliary Surgery Hospital, Shanghai 200438, China (Yi B, Zhang BH, Zhang YJ, Jiang XQ, Zhang BH, Yu WL, Chen QB and Wu MC)

**Corresponding Author:** Bai-He Zhang, MD, PhD, Department of Biliary Surgery, Eastern Hepatobiliary Surgery Hospital, Shanghai 200438, China (Tel: 86-21-25070788; Fax: 86-21-25070788; Email: billyyi@citiz.net)

© 2004, Hepatobiliary Pancreat Dis Int. All rights reserved.

phy (ERCP) without celiotomy/operative diagnosis. The exclusion criterion for non-epithelial malignancy determined by postoperative pathological diagnosis. From December 1997 to December 2002, 198 inpatients were admitted to our hospital. They were 117 men and 81 women, aged from 27 to 81 years (mean 55.9 years). No severe diseases were encountered in their circulatory, respiratory and urinary systems except for such symptoms as jaundice (94.5%), pruritus (56.6%) and abdominal pain (33.8%). Their highest level of serum bilirubin before operation ranged from 7 to 633.4  $\mu\text{mol/L}$ , in which above 342  $\mu\text{mol/L}$  was noted in 34 patients. Sixty-eight patients received computerized tomography (CT), 24 magnetic resonance cholangiopancreatography (MRCP) and 100 endoscopic retrograde cholangiography (ERC). Ninety-eight patients were diagnosed as having hilar cholangiocarcinoma and 48 patients received preoperative biliary drainage via endoscopic approach. According to the Bismuth-Corlette classification, 14 patients belonged to type I, 19 type II, 12 type IIIa, 15 type IIIb, 112 type IV, and 26 unclassifiable type. Accompanying diseases in this group of patients included hepatitis B virus infection (21 patients), hepatitis C virus infection (1), biliary stones (35), and biliary operative infection (16).

### Surgical treatment and pathological diagnosis

144 patients underwent laparotomy including tumor resection in 120 patients (83.3%), radical resection in 59 (41.0%), and palliative resection in 61 (42.3%). The resection included removal of the suprapancreatic extrahepatic biliary tract together with tumor, skeletonization of the hepatoduodenal ligament combined with partial hepatectomy (quadrate lobectomy, left/right lobectomy, caudate lobectomy), removal of the hepatic artery, and shortening of the partial portal vein (Table 1). Twenty-three patients were subjected to paunched biliary exploration and one patient had tumor biopsy but endoscopic retrograde biliary drainage before operation. Fifty-two patients were treated with endoscopic retrograde biliary drainage (ERBD) or endoscopic metal biliary endoprosthesis (EMBE) (21 patients) and, endoscopic nose-biliary drainage (ENBD) (31). The other 2 patients received percutaneous transhepatic cholangiodrainage. Tumor specimens from 126 patients showed adenocarcinoma (well-differentiated in 9 patients, moderately-differentiated in 73 and poorly-differentiated in 40) (122), mucinous adenocarcinoma (3), and papillary adenocarcinoma (1).

### Follow-up

Follow-up started on the date of paunched operation or ERCP. Complications included pleural effusion in 10 patients, liver failure in 4 and gastric paralysis in 1, but no postoperative in-hospital death was found. Sixteen patients were subjected to postoperative adjuvant radia-

tion, and 19 patients to postoperative chemotherapy. 117 patients (59.1%) were followed up for 6 to 36 months.

### Results

Single factor analysis by Log-rank test showed that the overall postoperative survival rates of 5 different groups (ENBD, ERBD or EMBE, biliary exploration & drainage, palliative resection and radical resection) were statistically significant ( $\chi^2 = 87.049$ ,  $P < 0.0001$ ). In the groups of biliary exploration & drainage, palliative resection, and radical resection, the survival rates differed each other statistically, or prolonged in a descending order. No statistical difference was found between the ERBD or EMBE group and palliative resection group. So was between the ERBD or EMBE group and biliary drainage group, or between the ENBD group and biliary drainage group. The survival rate differed statistically between the ERBD or EMBE group and ENBD group (Table 2).

Multiple factors analysis of postoperative survival by Cox showed some covariates. Four factors affecting the survival significantly included occupation, the highest total serum bilirubin level before operation, operative procedures, and postoperative adjuvant radiation (Table 3).

**Table 1.** Procedures for resection of hilar cholangiocarcinoma (%)

Operative procedures	Potential curative resection	Negative margin
Removal of cholangiocarcinoma & the suprapancreatic extrahepatic bile duct	100	100
Combined with		
Skeletonization of the hepatoduodenal ligament	95.0	98.3
Partial hepatectomy (caudate lobectomy)	54.2 (18.3)	57.6 (22.0)
Removal of the proper hepatic artery	5.0	1.7
Partial resection and restoration of the portal vein	8.3	8.5

**Table 2.** Estimated postoperative survivals in patients receiving different operative procedures (months)

Operative procedures (group)	Estimated median of survival	Standard error
Radical resection (A)	21.4664	1.3384
Palliative resection (B)	10.2258	1.0729
Biliary drainage (C)	6.0714	1.2944
ERBD or EMBE (D)	6.2500	1.1050
ENBD (E)	3.8947	0.9045

The value of  $\chi^2$  between the groups C and D was 0.3586 ( $P = 0.5493$ ), between groups B and D 1.3054 ( $P = 0.2532$ ), between groups C and E 1.9954 ( $P = 0.1578$ ), between groups D and E 4.0130 ( $P = 0.0452$ ), between groups B and C 5.2719 ( $P = 0.0217$ ), and between other groups,  $P < 0.001$ .

**Table 3.** The hazards screened by Cox proportional hazards model and parametric estimation

Hazards	Quantified value	Coefficient of regression (B)	Wald statistics ( $\chi^2$ )	P value	Relative risk
Operative procedure	Biliary drainage: 3 Palliative resection: 2 Radical resection: 1	1.41929	46.3971	<0.0001	4.134
Highest total level of serum bilirubin ( $\mu\text{mol/L}$ )	$\geq 342$ : 1 < 342: 0	1.11456	8.4951	0.0036	3.048
Occupation	Farmer: 1 Others: 0	-0.71699	4.1752	0.0410	0.488
Postoperative radiation	Yes: 1 No: 0	-1.13526	6.6489	0.0099	0.321

Other factors such as gender, age, choledocholithiasis, hepatitis, preoperative serum CA19-9 level, Bismuth-Corlette type, histopathologic grade, and postoperative chemotherapy were not significant.

## Discussion

### Impact of different operative procedures on prognosis

In this study, the results of single factor analysis or multiple factors analysis showed that operative procedure is a significant prognostic factor of hilar cholangiocarcinoma. It has a relative risk of 4.134, the highest in all significant prognostic factors. In statistical analysis, operative procedure was regarded as an orderly classified variable and biliary exploration and drainage as the worst effect as the maximally quantified value. So the regression coefficient of this factor was positive, and radical resection could be considered as a protective factor of prognosis. The postoperative survival time prolonged in a descending order in groups of biliary exploration and drainage, palliative resection and radical resection. Radical resection was found to be the most important measure for a cure and long-term survival. In the biliary exploration and drainage group, the procedures included single external drainage with an intrahepatic supporting tube, bridge internal drainage, and Roux-en-Y choledochojejunostomy with or without external drainage. The effect of these procedures were not verified in this group, but another study<sup>[14]</sup> concluded that Roux-en-Y choledochojejunostomy is the best choice for palliative operation for hilar cholangiocarcinoma. The survival differed statistically between ERBD or EMBE group and ENBD group, but the outcome of the former group was better, presumably because endoscopists preferred ERBD or EMBE to ENBD when endoscopic drainage was successful; ERBD or EMBE was more acceptable than ENBD by patients, and the nose-biliary tube of ENBD was apt to be drawn; internal biliary drainage tallied with physiological condition and restored circulation between the intestine and the liver.

### Techniques for radical resection

To excise tumor with negative margins (R0 resection), we<sup>[15]</sup> removed entire cholangiocarcinoma including the suprapancreatic extrahepatic biliary tract, gallbladder, and cystic duct, together with clearance of the suprapancreatic tissues and related lymph nodes. We proposed that the bile duct be transected 5 mm above the tumor, or 10 mm above if possible. Skeletonization of the hepatoduodenal ligament (95% of patients with tumor resection) should be done. Partial hepatectomy is dependent on Bismuth-Corlette type of the tumor. Because the tumor extending well above the bifurcation of the hepatic duct may involve the caudate duct frequently, semihepatectomy for the affected side and ipsilateral caudate semilobectomy are feasible for type III patients, and severely atrophied half of the liver, en bloc caudate lobe, and quadrate lobe are resected for type IV patients. Reports<sup>[2-4, 8, 9]</sup> also suggested that combined caudate lobectomy could increase radical resection rate or improve postoperative survival. Semihepatectomy should be a regular right/left lobectomy. In this series 54.2% patients underwent combined partial hepatectomy and 18.3% underwent caudate lobectomy, so 49.2% patients obtained negative margins. We consider that to achieve negative margins combined partial hepatectomy should be individually designed in some patients according to the precise assessment of cancer involvement and accurate evaluation of hepatic functional reserve. With similar opinion,<sup>[12]</sup> Lillemoe stated that negative margins and lymph nodes were associated with improved survival. The residual duct orifices should be examined immediately after resection. If possible, frozen sections of margins together with surrounding tissues should be made to confirm clearance of tumor. Consequently, extended resection could be determined according to the status of residual margins and conditions of patients.

If the hepatic artery is involved, the ipsilateral hepatic artery branches or the main trunk of the proper hepatic artery could be removed without severe complications. When the bifurcation or the trunk of the portal vein is involved, partial wall or bifurcation of the portal vein could be resected to achieve a radical cure, and men-

ding or reconstruction of the vein may be necessary.<sup>[15]</sup> However, reported prognoses in patients with combined portal vein resection are different. Ebata<sup>[16]</sup> reported that the prognosis was worse in patients with portal vein resection than in those without resection (5-year survival, 9.9% vs 36.8%;  $P < 0.0001$ ), and the primary tumor was more advanced in patients undergoing portal vein resection. No significant difference of median survival was noted between patients with portal vein resection and those without resection.<sup>[17]</sup> Neuhaus et al<sup>[13]</sup> reported that after R0 resection, additional portal vein resection was the only significant factor. The 5-year survival rate of patients after formal curative liver resection combined with portal vein resection was 65% versus 28%. In this series, combined pancreaticoduodenectomy or liver transplantation was not performed for an extended radical resection. Neuhaus stated that,<sup>[18]</sup> although the rate of curative resection increased significantly after liver transplantation and partial pancreatoduodenectomy, favorable effect with respect to survival was not evident. We consider that pancreaticoduodenectomy should be adopted if general conditions of patients are good and extended resection could reach negative margin. Orthotopic liver transplantation for patients with irresectable hilar cholangiocarcinoma requires necessary skills and techniques, clearance of lymph nodes, perioperative management. The high risks of postoperative lymph node metastasis<sup>[19]</sup> and tumor recurrence<sup>[20]</sup> must be taken into consideration.

### Prognosis of open and endoscopic surgical treatments

In this series, statistical results showed that the survival of the radical resection group was better than that of other groups. No significant difference was found between the ERBD or EMBE group and the palliative resection group, so was between the ERBD or EMBE group and the biliary drainage group, or between the ENBD group and the biliary drainage group. Because inpatients underwent surgery, we could not exclude the possibility that patients who only had undergone surgery via ERCP might receive radical resection. Some patients treated via ERCP might be at an early stage of the disease, and this condition brought about bias to the results of investigation. For irresectable hilar cholangiocarcinoma, no evidence has shown that the prognosis of patients treated by ERBD or EMBE is poorer than that by open operation. Researchers also considered that intubation through ERCP is safe and effective in treating patients with nonresectable hilar cholangiocarcinoma.<sup>[21]</sup>

### Operative procedures and other prognostic factors

A multivariate Cox analysis showed that radical resection, preoperative maximum serum total bilirubin level below 342  $\mu\text{mol/L}$ , factors, and postoperative ra-

diation are protective factors of prognosis in this series. Klempnauer and coworkers<sup>[11]</sup> reported that only lymph node metastasis and residual tumor stage proved to be of independent prognostic significance, and a favorable outcome after resection is mainly determined by curative resection and the absence of lymph node metastasis. Jarnagin et al<sup>[22]</sup> reported that negative histologic margins, concomitant partial hepatectomy, and well-differentiated tumor histology were associated with improved outcome after all resections. After R0 resection, concomitant partial hepatectomy was the only independent predictor of long-term survival. In our 144 patients after open surgery, the radical resection rate was 11.8% (2/17) in patients with a bilirubin level of above or at 342  $\mu\text{mol/L}$ , and 44.9% (57/127) in patients with a bilirubin level of below 342  $\mu\text{mol/L}$ . Obviously, between the two groups the proportion of radical resection affecting prognosis differed most significantly; the radical resection rate in the lower bilirubin level group was higher. It is known that preoperative serum bilirubin level may be related to the type, obstruction, and stage of hilar cholangiocarcinoma. In this study, the serum bilirubin level was also a significant prognostic factor with a relative risk of 3.048. Whether it is linear with operative procedures needs further investigation.

Follow-up of patients in our study ranged from 6 to 36 months, it was not long enough in some patients. Unfortunately the low rate of follow-up patients from all part of China travelling population and others produced bias to the results although the Cox model allows the existence of censored values.

In summary, operative procedures is the most important prognostic factor of hilar cholangiocarcinoma, and radical resection is still the primary measure for a cure and long-term survival. How to select or create proper personalized operative procedures for hilar cholangiocarcinoma? How to take interventional procedures in combination with etiological, biological and pathological methods, and perioperative adjuvant treatment? How to promote the prognosis maximally? These issues remain to be further studied.

### Competing interest

No benefits in any form have received or will be received from a commercial party related directly or indirectly to the subject of this article.

### References

- 1 Xu AM, Cheng HY, Jiang WB, Chen D, Jia YC, Wu MC. Multi-slice three-dimensional spiral CT cholangiography: a new technique for diagnosis of biliary diseases. *Hepatobiliary Pancreat Dis Int* 2002;1:595-603.
- 2 Nimura Y, Kamiya J, Kondo S, Nagino M, Uesaka K, Oda

- K, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. *J Hepatobiliary Pancreat Surg* 2000;7:155-162.
- 3 Tabata M, Kawarada Y, Yokoi H, Higashiguchi T, Isaji S. Surgical treatment for hilar cholangiocarcinoma. *J Hepatobiliary Pancreat Surg* 2000;7:148-154.
  - 4 Santoro E, Sacchi M, Carboni F, Santoro R, Scardamaglia F. Diagnostic and surgical features of Klatskin tumors. *Chir Ital* 1999;51:1-7.
  - 5 Bathe OF, Pacheco JT, Ossi PB, Hamilton KL, Franceschi D, Sleeman D, et al. Management of hilar bile duct carcinoma. *Hepatogastroenterology* 2001;48:1289-1294.
  - 6 Lee SG, Lee YJ, Park KM, Hwang S, Min PC. One hundred and eleven liver resections for hilar bile duct cancer. *J Hepatobiliary Pancreat Surg* 2000;7:135-141.
  - 7 Burke EC, Jamagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998;228:385-394.
  - 8 Tsao JI, Nimura Y, Kamiya J, Hayakawa N, Kondo S, Nagino M, et al. Management of hilar cholangiocarcinoma: comparison of an American and Japanese experience. *Ann Surg* 2000;232:166-174.
  - 9 Gazzaniga GM, Filauro M, Bagarolo C, Mori L. Surgery for hilar cholangiocarcinoma: an Italian experience. *J Hepatobiliary Pancreat Surg* 2000;7:122-127.
  - 10 Figueras J, Llado L, Valls C, Serrano T, Ramos E, Fabregat J, et al. Changing strategies in diagnosis and management of hilar cholangiocarcinoma. *Liver Transpl* 2000;6:786-794.
  - 11 Klempnauer J, Ridder GJ, von Wasielewski R, Werner M, Weimann A, Pichlmayr R. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. *J Clin Oncol* 1997;15:947-954.
  - 12 Lillemoe KD, Cameron JL. Surgery for hilar cholangiocarcinoma: the Johns Hopkins approach. *J Hepatobiliary Pancreat Surg* 2000;7:115-121.
  - 13 Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, et al. Extended resections for hilar cholangiocarcinoma. *Ann Surg* 1999;230:808-819.
  - 14 Li HM, Dou KF, Sun K, Gao ZQ, Li KZ, Fu YC. Palliative surgery for hilar cholangiocarcinoma. *Hepatobiliary Pancreat Dis Int* 2003;2:110-113.
  - 15 Jiang XQ, Zhang BH, Yi B, Zhang BH, Chen H, Wu MC. Partial hepatectomy with skeletonization of the hepatoduodenal ligament for hilar cholangiocarcinoma. *Chinese-German J Clin Oncol* 2002;1:204-207.
  - 16 Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T, Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. *Ann Surg* 2003;238:720-727.
  - 17 Munoz L, Roayaie S, Maman D, Fishbein T, Sheiner P, Emre S, et al. Hilar cholangiocarcinoma involving the portal vein bifurcation: long-term results after resection. *J Hepatobiliary Pancreat Surg* 2002;9:237-241.
  - 18 Neuhaus P, Jonas S. Surgery for hilar cholangiocarcinoma—the German experience. *J Hepatobiliary Pancreat Surg* 2000;7:142-147.
  - 19 Pichlmayr R, Weimann A, Oldhafer KJ, Schlitt HJ, Klempnauer J, Bornscheuer A, et al. Role of liver transplantation in the treatment of unresectable liver cancer. *World J Surg* 1995;19:807-813.
  - 20 Partensky C. Treatment of hilar cancers. *J Chir (Paris)* 1998;135:162-167.
  - 21 Cheng JL, Bruno MJ, Bergman JJ, Rauws EA, Tytgat GN, Huibregtse K. Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: efficacy of self-expandable metallic Wallstents. *Gastrointest Endosc* 2002;56:33-39.
  - 22 Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001;234:507-517.

*Received October 17, 2003*

*Accepted after revision May 20, 2004*