Multivariate statistical analysis of clinicopathologic factors influencing survival of patients with bile duct carcinoma

Ping He, Jin-Sen Shi, Wu-Ke Chen, Zuo-Ren Wang, Hong Ren, Hua Li

AIM: To evaluate the influence of various clinicopathologic factors on survival of patients with bile duct carcinoma after curative resection.

METHODS: A retrospective analysis was made for 86 cases of bile duct carcinoma treated from January 1981 to September 1995. Fifteen clinicopathologic factors possibly influencing survival were selected. Independent variables were first analyzed by univariate methods. Survival for variable was estimated by the method of Kaplan and Meier. The variables that were statistically significant by univariate analysis were included in a multivariate analysis, which were confirmed using the Cox stepwise proportion hazard model with the help of SPSS 10.0 for Windows software.

RESULTS: The overall cumulative survival rate was 72.6 % at 1 year, 32.4 % at 3 years, and 18.7 % at 5 years. The results of univariate analysis showed that the major significant prognostic factors influencing survival of these patients were histological type of lesion, lymph node metastasis, pancreatic invasion, duodenal invasion, perineural invasion, macroscopic vessel involvement, resected surgical margin and depth of cancer invasion (P=0.02, 0.02, 0.004, 0.005, 0.01, 0.43, 0.03 and 0.04). Age, sex, location of tumor, size of tumor, macroscopic type of lesions, hepatic metastasis, and hepatic invasion were not significantly associated with prognosis (P>0.05). Pancreatic invasion, perineural invasion and lymph node metastases were the three most important prognostic factors by multivariate analysis using the Cox proportional hazards model.

CONCLUSION: Pancreatic invasion, perineural invasion and lymph node metastases are the most important prognostic factors for bile duct carcinoma after curative resection.

He P, Shi JS, Chen WK, Wang ZR, Ren H, Li H. Multivariate statistical analysis of clinicopathologic factors influencing survival of patients with bile duct carcinoma. World J Gastroenterol 2002; 8(5):943-946

INTRODUCTION

With the recent improvement of surgical techniques in hepatobiliary surgery, a curative surgical resection of bile duct carcinoma can be accomplished with acceptable morbidity and mortality[1-8]. However, the prognosis for such patients is frustrating, although this tumor is small, grows slowly and metastasizes late[9-12]. In the present article, an effort is made to evaluate the influence of various clinicopathologic factors on survival of patients with bile duct carcinoma using the Cox proportional hazards model. The results of these analyses were used when surgical treatment was performed for patients with bile duct carcinoma.

MATERIALS AND METHODS

General data

Eighty-six cases of bile duct carcinomas were resected in the Department of Hepatobiliary Surgery, First Hospital of Xi’an Jiaotong University from January 1981 through September 1995. The resected specimens were examined pathologically, and the relation between clinicopathologic findings and patient survival was studied.

Variables

The following clinicopathologic variables were considered for prognosis: age, sex, location of primary tumor, size of the tumor, macroscopic type of lesion (papillary, nodular, infiltrating), histological type of lesion (papillary adenocarcinoma, well-differentiated, moderately differentiated, and poorly differentiated adenocarcinoma, and adenosquamous cell carcinoma), hepatic metastasis, lymph node metastasis, hepatic invasion, pancreatic invasion, duodenal invasion, perineural invasion, vascular invasion, resected margin of the bile duct, depth of cancer invasion (invasion limited to fibromuscular layer, to adventitia and subserosal layer, to and beyond the serosal exposure).

Analysis

Independent variables were first analyzed by univariate methods. Statistical significance of the variables was determined by t-test and Chi-square test. Survival for variable was estimated by the method of Kaplan and Meier. The variables with statistical significance in univariate analysis were included in a multivariate analysis, which were further confirmed using the Cox stepwise proportion hazard model with the help of SPSS 10.0 for Windows software.

RESULTS

Clinical findings

Of the 86 surgically treated patients, 51 were male and 35 female aged from 33 to 78 years, averaging 58.6 years. The patients aged from 50 to 78 years made up 66.5 %. Of the lesions, 40 (47 %) were upper bile duct cancer, 13 (15.2 %) were middle bile duct cancer, and 33 (38.8 %) lower bile duct cancer. All the lesions were resected at operation. The type of operation depends on the site and extent of tumor. Bile duct resection was done with cholangiojejunostomy in 17 patients,
bile duct resection in 26 with irregular hepatectomy and cholangiojejunosomy, pancreatoduodenectomy in 42 patients, and hepatopancreatoduodenectomy in one.

**Overall survival**
The overall cumulative survival rates were 72.6 % at 1 year, 32.4 % at 3 years, and 18.7 % at 5 years. Fifteen clinicopathologic factors were analyzed, and the prognoses were significantly related to 8 of the 15 variables analyzed by univariate method (Table 1).

**Table 1** Univariate analysis of the clinicopathologic factors for the survival of 86 patients with bile duct carcinoma

| Factors                              | No. of patients | P value |
|--------------------------------------|-----------------|---------|
| Sex                                  |                 | 0.90    |
| Male                                 | 51              |         |
| Female                               | 35              |         |
| Age (yrs)                            |                 | 0.33    |
| <50                                  | 29              |         |
| ≥50                                  | 57              |         |
| Location of tumor                    |                 | 0.15    |
| Upper                                | 40              |         |
| Middle                               | 13              |         |
| Lower                                | 33              |         |
| Size of tumor                        |                 | 0.21    |
| <2cm                                 | 11              |         |
| 2 - 4cm                              | 62              |         |
| >4cm                                 | 13              |         |
| Macroscopic type of lesions          |                 | 0.43    |
| Papillary                            | 17              |         |
| Nodular                              | 32              |         |
| Infiltrating                         | 37              |         |
| Histological type of lesion          |                 | 0.02    |
| Papillary adenocarcinoma             | 7               |         |
| Well differentiated adenocarcinoma   | 27              |         |
| Moderately differentiated adenocarcinoma | 36          |         |
| Poorly differentiated adenocarcinoma | 14              |         |
| Adenosquamous cell carcinoma         | 2               |         |
| Hepatic metastasis                   |                 | 0.88    |
| Present                              | 2               |         |
| Absent                               | 84              |         |
| Lymph node metastasis                |                 | 0.02    |
| Present                              | 37              |         |
| Absent                               | 49              |         |
| Hepatic invasion                     |                 | 0.36    |
| Present                              | 29              |         |
| Absent                               | 57              |         |
| Pancreatic invasion                  |                 | 0.004   |
| Present                              | 21              |         |
| Absent                               | 65              |         |
| Duodenal invasion                    |                 | 0.005   |
| Present                              | 14              |         |
| Absent                               | 72              |         |
| Resected margin of the bile duct     |                 | 0.03    |
| Present                              | 19              |         |
| Absent                               | 67              |         |
| Perineural invasion                  |                 | 0.01    |
| Present                              | 65              |         |
| Absent                               | 21              |         |
| Vascular invasion                    |                 | 0.04    |
| Present                              | 17              |         |
| Absent                               | 69              |         |
| Depth of cancer invasion             |                 | 0.04    |
| Invasion limited to fibromuscular layer | 9            |         |
| Invasion limited to adventitia and subserosal layer | 59 |         |
| Invasion to and beyond the serosal exposure | 18 |         |

The significant variables were lymph node metastasis, duodenal invasion, pancreatic invasion, perineural invasion, vascular invasion, resected margin of the bile duct, histological type of lesion, and depth of cancer invasion. The following factors were not significantly associated with prognosis: age, sex, location of tumor, size of tumor, macroscopic type of lesions, hepatic metastasis, and hepatic invasion.

Multivariate analysis using the Cox proportional hazards model involving the 8 significant factors determined by univariate analysis identified the three prognostic variables (Table 2). They were the pancreatic invasion, the perineural invasion and the lymph node metastasis. Pancreatic invasion was observed in 21(24.4 %) of the 86 patients with bile duct carcinoma. The 5-year survival rates for patients with negative and positive pancreatic invasion were 36 % and 2 %, respectively. A statistically significant difference in survival could be observed between the patient with positive and negative pancreatic invasion (P=0.005). Perineural invasion was seen in 75.6 % of the patients with bile duct cancer. Univariate analysis showed a statistically significant difference of survival between the perineural invasion and perineural noninvasion groups (P= 0.01) (Table 1). The 5-year survival rate was 47 % for patients without perineural invasion, whereas 13 % for the perineural invasion-positive patients. Lymph node metastasis was observed in 37(43 %) of the 86 patients with bile duct carcinoma. The 5-year survival rate was 44 % for patients without lymph node metastasis, and 11 % for patients with lymph node metastasis.

**Table 2** Relative values of three prognostic variables derived from Cox stepwise proportional hazards model

| Variables                         | β     | SE   | Sig(P) | Exp(B) | 95%CI for Exp(B) |
|-----------------------------------|-------|------|--------|--------|------------------|
| Pancreatic invasion               | 0.226 | 0.084| 0.007a | 1.254  | (1.064-1.479)    |
| Perineural invasion               | 0.691 | 0.236| 0.012a | 2.408  | (1.221-4.753)    |
| Lymph node metastasis             | 0.894 | 0.489| 0.023a | 2.762  | (1.164-6.557)    |

aP <0.05, bP <0.01, vs control

**DISCUSSION**

With the continuing progress of diagnostic and surgical techniques in biliary surgery, a great deal of biliary cancers can be resected with acceptable morbidity and mortality. However, the 5-year survival was only 10-20 %, and only one-third of the patients could be treated surgically at the time of diagnosis[14-18]. The local recurrence of bile duct cancer is relatively high even after curative resection of this lesion. Therefore, a proper surgical procedure should be considered for preventing this undesirable outcome. It is important to know what prognostic factors relate to the survival of the patients with bile duct cancer.

In our study, the overall cumulative survival rates for 86 patients with bile duct carcinoma were 72.6 % at 1 year, 32.4 % at 3 years, and 18.7 % at 5 years. This study showed that the prognoses for patients with bile duct cancer were significantly associated with pancreatic invasion, perineural invasion, duodenal invasion, histological type of lesion, lymph node metastasis, vascular invasion, resected margin of the bile duct, and depth of cancer invasion (P<0.05). Age, sex, location and size of tumor, macroscopic type of lesions, hepatic metastasis, and hepatic invasion were not significantly associated with survival (P>0.05).
Our study also showed that pancreatic invasion, perineural invasion and lymph node metastases were the three most important prognostic factors by multivariate analysis using the Cox proportional hazards model (Table 2). Todoroki et al revealed that the primary tumor and tumor node metastasis (TNM) stage were independent predictors of survival using multivariate analysis of 67 patients with bile duct cancer\[^{[19]}\]. Havlik et al found that lymph nodes, vascular invasion, advanced tumor stage, positive tumor margins, and p53 mutation were associated with poor survival by multivariate analyses\[^{[20]}\]. Inoue et al identified that surgical margin, lymph node metastasis, lymph node dissection, vascular invasion, and left-side location of the main tumor were significant risk factors for overall survival using univariate analysis and confirmed that surgical margin, lymph node metastasis, and vascular invasion were independently significant variables for overall survival using multivariate analysis\[^{[21]}\]. All of them did not mention pancreatic and perineural invasion were prognostic factors for the survival of patients with bile duct carcinoma. Other scholars\[^{[22,23]}\] and we, however, have all observed a significant correlation between perineural invasion and postoperative survival.

Perineural invasion is the first prognostic variable (Table 2). Patients with negative pancreatic invasion survived significantly longer than those with positive pancreatic invasion after resection of the lesion. Our findings show that the 5-year survival rate for patients with negative pancreatic invasion was 36 %, whereas it was 2 % for patients with positive pancreatic invasion. This poor prognosis might be due to the fact that when the bile duct cancer invades pancreatic tissue it behaves like a primary pancreatic cancer, and the 5-year survival rate was only around 6 %\[^{[14-20]}\], leading to a worse prognosis. Since bile duct cancer possesses biological characteristics of the invasive growth and anatomical location, lower bile duct carcinoma mostly invade pancreas, making that the 5-year survival rate for postoperative patients with lower bile duct carcinoma less than 10 %\[^{[20]}\].

Perineural invasion and lymph node metastasis were also determined to be the independent prognostic factors for survival by the multivariate analysis (Table 2). Some scholars had studied extensively the clinicopathologic significance of perineural invasion, and the results of this study substantiated these findings\[^{[22,23]}\]. In our study, the 5-year survival rate for patients with negative perineural invasion was 47 %, whereas it was 13 % for patients with positive perineural invasion. It is well accepted that lymph node metastasis is an independent prognostic factor for bile duct cancer patients\[^{[19-21,30]}\]. According to our study, the 5-year survival rate was 44 % for patients without lymph node metastasis, and 11 % for patients with lymph node metastasis. As a result of abundant lymphatic, blood vessel, nerve fibers and loose connective tissue around the bile duct, the cancer cells provided with the way of “jump model” growth. The excessive metastasis fashion results in the inevitable local recrudescence postoperatively. Consequently, we emphasize the need for dissection of autonomic nerve fibers and plexuses around the hepatic and celiac arteries and the portal vein during operation. In addition the lymph nodes, lymphatic vessels, and connective tissues must be dissected for radical operation on bile duct carcinoma.

REFERENCES

1. **Huang QZ**, Zhuo LX, Wang DD, Lu JG, Chen YM. Clinical and laboratory research of hilar cholangiocarcinoma surgical treatment. Shijie Huaren Xizhoubu Zazhi 2000; 8: 961-964

2. **Gerhards MF**, van Gulik TM, de Witt LT, Obertop H, Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma—a single center experience. Surgery 2000; 127: 395-404

3. **Nimura Y**, Kamiyaj, Kondo S, Nagino M, Uesaka K, Oda K, Sano T, Yamamoto H, Hayakawa N. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 2000; 7: 150-162

4. **Nagino M**, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Kanai M, Nimura Y. Complications of hepatectomy for hilar cholangiocarcinoma. World J Surg 2001; 25: 1277-1283

5. **Tang D**, Liang LJ, Huang JF. The preparative assessment and surgical treatment of hilar cholangiocarcinoma: a study of 86 cases. Zhonghua Pu Tong Wai Ke Zazhi 2001; 16: 517-519

6. **Doglietto GB**, Alfieri S, Pacelli F, Mutigiani M, Costamagna G, Carrieri C, Di Giorgi A, Papa V. Extrahepatic bile duct carcinoma: A western experience with 118 consecutive patients. Hepatogastroenterology 2000; 47: 349-354

7. **Yoshimi F**, Asato Y, Amemiya Y, Shioyama Y, Itabashi M. Comparison between pancreaticoduodenectomy and hepatopancreato-duodenectomy for bile duct cancer. Hepatogastroenterology 2001; 48: 994-998

8. **Launois B**, Reding R, Lebeau G, Buard JL. Surgery for hilar cholangiocarcinoma: French experience in a collective survey of 552 extrahepatic bile duct cancer. J Hepatobiliary Pancreat Surg 2000; 7: 128-134

9. **Blom D**, Schwartz SI. Surgical treatment and outcomes in carcinoma of the extrahepatic bile ducts: the University of Rochester experience. Arch Surg 2001; 136: 209-215

10. **Mena FJ**, Veligia R, Valbuena MC, Gonzalez JM, Caro-Paton A, Perez-Miranda M, Bellido J. Carcinoma of the extrahepatic biliary tree: analysis of 15 cases. Rev Esp Enferm Dig 1999; 91: 297-304

11. **Ahrendt SA**, Nakeeb A, Pitt HA. Cholangiocarcinoma. Clin Liver Dis 2001; 5: 191-218

12. **Blanchet MC**, Ducerf C, Benoit L, Gerard JP, Baulieux J. Proximal bile duct cholangiocarcinomas. Ann Chir 2000; 125: 825-831

13. **Gerhards MF**, van Gulik TM, de Witt LT, Obertop H, Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma—a single center experience. Surgery 2000; 127: 395-404

14. **Launois B**, Terblanche J, Lakehal M, Catheline JM, Bardaxoglou E, Landen S, Campion JP, Sutherland F, Meunier B. Proximal bile duct cancer: high resectability rate and 5-year survival. Ann Surg 1999; 230: 266-275

15. **Blom D**, Schwartz SI. Surgical treatment and outcomes in carcinoma of the extrahepatic bile ducts: the University of Rochester experience. Arch Surg 2001; 136: 209-215

16. **Reed DN Jr**, Vitale GC, Martin R, Bas H, Wiemien T, Larson GM, Edwards M, MCMasters K. Bile duct carcinoma: trends in treatment in the nineties. Ann Surg 2000; 266: 711-715

17. **Hilemoe KD**, Cameron JL. Surgery for hilar cholangiocarcinoma: the Johns Hopkins approach. J Hepatobiliary Pancreat Surg 2000; 7: 115-121

18. **Burke EC**, Jarnagin WR, Hochwald SN, Pisters PW, Feng 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

19. **Todoroki T**, Kawamoto T, Koike N, Fukao K, Shoda J, Takahashi H. Treatment strategy for patients with middle and lower third bile duct cancer. Br J Surg 2001; 88: 364-370

20. **Havlík R**, Sbisa E, Tullo A, Kelly MD, Mitry RR, Jiao LR, M ansour MR, Honda K, Habib N. Results of resection for hilar cholangiocarcinoma with analysis of prognostic factors. Hepatogastroenterology 2000; 47: 927-931
21 Inoue K, Makuuchi M, Takayama T, Torzilli G, Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Konishi M, Kinoshita T, Miyagawa S, Kawasaki S. Long-term survival and prognostic factors in the surgical treatment of mass-forming type cholangiocarcinoma. Surgery 2000; 127: 498-505

22 Bortolasi L, Burgart LJ, Tsiosos GG, Luque-De Leon E, Sarr MG. Adenocarcinoma of the distal bile duct. A clinicopathologic outcome analysis after curative resection. Dig Surg 2000; 17: 36-41

23 Wang DD, Huang ZQ, Wang JX, Wang YS, Chen LZ. Relationship between perineural invasion and the coupling expression of DPC4 with NCAM in cholangiocarcinoma. Zhonghua Shiyan Wake Zazhi 2000; 17: 12-13

24 Lu XH. Development of diagnosis and treatment in pancreatic and bile duct carcinoma. Zhonghua Xiaohua Zazhi 1999; 19: 8-10

25 Cooperman AM, Kini S, Snady H, Bruckner H, Chamberlain RS. Current surgical therapy for carcinoma of the pancreas. J Clin Gastroenterol 2000; 31: 107-113

26 Ginsberg GG. New developments in pancreatic cancer. Semin Gastrointest Dis 2000; 11: 162-167

27 Meyer W, Jurowich C, Reich M, Steinhauser B, Wunsch PH, Gebhardt C. Pathomorphological and histological prognostic factors in curatively resected ductal adenocarcinoma of the pancreas. Surg Today 2000; 30: 582-587

28 Shankar A, Russell RCG. Recent advances in the surgical treatment of pancreatic cancer. World J Gastroenterol 2001; 7: 622-626

29 Ouyang YZ, Sun WB. The diagnosis and treatment of lower bile duct carcinoma: result of 85 cases. Zhonghua Putong Waike Zazhi 2000; 15: 555-557

30 Kitagawa Y, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Nimura Y. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. Ann Surg 2001; 233: 385-392

Edited by Ma JY