

• CLINICAL RESEARCH •

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

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Received 2001-08-09 **Accepted** 2001-09-12

Abstract

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^[7-13]. 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 cholangiojejunostomy, 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	0.007 ^b	1.254	(1.064-1.479)
Perineural invasion	0.691	0.236	0.012 ^a	2.408	(1.221-4.753)
Lymph node metastasis	0.894	0.489	0.023 ^a	2.762	(1.164-6.557)

^a $P<0.05$, ^b $P<0.01$, 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.

Pancreatic 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 %^[24-28], leading to a worse prognosis. Since bile duct cancer possess biological characteristic 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 %^[29].

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.

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Edited by Ma JY