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World J Gastroenterol 2006 September 14; 12(34): 5495-5500
World Journal of Gastroenterology ISSN 1007-9327

CLINICAL RESEARCH

C-reactive protein is a prognostic indicator in patients with perihilar cholangiocarcinoma

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Received: 2006-04-14 Accepted: 2006-05-25

Abstract

AIM: To evaluate prognostic indicators for the outcome of patients with perihilar extrahepatic cholangiocarcinoma in an unselected cohort.

METHODS: We retrospectively analyzed 98 patients with perihilar cholangiocarcinoma. Twenty-three patients (23.5%) underwent tumor resection. Patients with non-resectable tumors underwent either transpapillary or percutaneous transhepatic biliary drainage. Additionally, 32 patients (32.7%) received photodynamic therapy (PDT) and 18 patients (18.4%) systemic chemotherapy. Predefined variables at the time of diagnosis and characteristics considering the mode of treatment were entered into a Cox's proportional hazards model. Included in the analysis were age, tumor stage following the modified Bismuth-Corlette classification, bilirubin, prothrombin time (PT), C-reactive protein (CRP), carbohydrate antigen 19-9 (CA19-9), history of weight loss, surgical resection, chemotherapy and PDT.

RESULTS: The Kaplan-Meier estimate of overall median survival was 10.5 (95%CI: 8.4-12.6) mo. In the univariate analysis, low Bismuth stage, low CRP and surgical resection correlated significantly with better survival. In the multivariate analysis, only CRP (P = 0.005) and surgical resection (P = 0.029) were found to be independently predictive of survival in the cohort. Receiver operating characteristic (ROC) analysis identified a CRP level of 11.75 mg/L as the value associated with the highest sensitivity and specificity predicting a survival > 5 mo. Applying Kaplan-Meier analysis, patients with a CRP < 12 mg/L at the time of diagnosis had a significantly longer median survival than patients with higher values (16.2 *vs* 7.6 mo; P = 0.009).

CONCLUSION: This retrospective analysis identified CRP level at the time of diagnosis as a novel indicator for the prognosis of patients with perihilar cholangiocarcinoma. It should be evaluated in future prospective trials on this entity.

Key words: Perihilar cholangiocarcinoma; Prognostic factors; C-reactive protein; Resection; Outcome

Gerhardt T, Milz S, Schepke M, Feldmann G, Wolff M, Sauerbruch T, Dumoulin FL. C-reactive protein is a prognostic indicator in patients with perihilar cholangiocarcinoma. *World J Gastroenterol* 2006; 12(34): 5495-5500

http://www.wjgnet.com/1007-9327/12/5495.asp

INTRODUCTION

Cholangiocarcinoma is a rare tumor[1]. The global incidence varies between 0.5 and 1.1 per 100 000[2]. High-risk groups have been defined. Thus, the life-time risk of intrahepatic and extrahepatic cholangiocarcinoma among patients with primary sclerosing cholangitis (PSC) ranges between 8%-20%[3]. Further risk factors for the occurrence of cholangiocarcinoma are infections with liver flukes[4], hepatolithiasis[5], choledochal cysts[6] or application of thorotrast[7]. While recent data show that incidence and mortality rates of intrahepatic cholangiocarcinoma are increasing in several areas in the world, the incidence and mortality rates of extrahepatic carcinoma are declining[8]. The 5-year survival of patients with extrahepatic cholangiocarcinoma is poor and was found to be less than 20% in a large population-based epidemiological study from the United States[1].

Perihilar cholangiocarcinoma is mostly diagnosed at an advanced stage. Therefore, more than two-thirds of patients are not suitable for surgery due to either expansion of the tumor or age and comorbidity[9]. Nevertheless, the prognosis of patients undergoing tumor resection has improved in recent years owing to advancements in surgical techniques resulting in a more aggressive resectional approach[10,11]. Furthermore, liver transplantation may be an option in highly selected patients after neo-adjuvant

radiochemotherapy and invasive staging[12,13].

Prognostic factors predicting the outcome of patients undergoing tumor resection have recently been extensively evaluated[10,14]. In contrast, less attention has been paid to overall outcome and possible prognostic indicators in unselected patients suffering from cholangiocarcinoma. Therefore, we performed a retrospective analysis of 98 consecutive patients with perihilar cholangiocarcinoma treated at a tertiary medical center within a period of 5 years in order to identify the most relevant predictors of outcome.

MATERIALS AND METHODS

Data acquisition

Using our hospital database, we identified the records of 98 consecutive unselected patients with extrahepatic perihilar cholangiocarcinoma type Bismuth I to IV admitted to our hospital between October 1997 and March 2003. Charts were reviewed retrospectively. Data for further analysis were available from all patients.

Diagnostic criteria

Cholangiography showed a perihilar stricture in all patients. Positive histology and/or cytology were present in 68 (69.4%) patients. In the remaining patients, diagnosis was made by the coexistence of a CA19-9 serum level greater than 250 IU/L and typical findings at cholangiography, ultrasound and CT scan.

We recorded patients' age, gender, clinical presentation, tumor stage following the modified Bismuth-Corlette classification[9], laboratory parameters at presentation (blood count, CRP, bilirubin, alkaline phosphatase, GPT, CA19-9), histology, cytology, type of medical treatment and outcome including date of death.

Statistical analysis

Numeric data were recorded as median and range or 95% confidence intervals (95% CI). To identify prognostic factors, we used the Cox's proportional hazards regression analysis. Survival analysis was performed using the Kaplan-Meier method and comparisons were made employing the log rank test. The Mann-Whitney rank sum test was used for inter-group comparisons. Statistical analysis was performed using the SPSS®- (SPSS Inc., Chicago, IL, USA) and the StatView 5.0®-Software (Version for Windows; SAS Institute Inc., Cary, NC, USA). A P value less than 0.05 was considered statistically significant.

RESULTS

Demographics and results of initial evaluation

We conducted this retrospective analysis on 98 consecutive patients (female/male: 48/50) with a median age of 69.5 (range: 35.8-89.9) years. Two patients of the cohort were known to suffer from PSC. Major clinical symptoms at admission were jaundice (73.5%), weight loss (43.9%) and pruritus (33.7%), whereas pain (22.5%), ascites (11.2%) and fever (9.2%) were present in less than one third of patients. The tumors were described as Bismuth types I (n = 12), II (n = 7), III (n = 30) and IV (n = 49), respectively. The laboratory findings at time of diagnosis are given in Table 1. CA19-9 levels did not correlate significantly to either serum bilirubin level (r = 0.068; P = 0.54) or Bismuth stage (r = 0.085; P = 0.44). Higher CRP-levels correlated significantly to leukocyte count (r = 0.569; P < 0.0001), but did not depend on bilirubin levels (r = 0.153; P = 0.16) and tumor extent according to the Bismuth-Corlette classification (r = 0.160; P = 0.15).

Table 1 Laboratory findings at time of diagnosis

Value (normal range)	Median	Range	
Total bilirubin (0.1-1.2 mg/L)	9.1	0.3	38.3
Alkaline phosphatase (50-175 U/L)	375	26	2572
ALT (GPT) (- 19 U/L)	61.5	8	464
Leucocytes (4.3-10.5 G/L)	11	3.6	95
CRP (- 3 mg/L)	8.4	0.06	207
CA19-9 (0.25-20 U/L)	232.9	0.25	24385
PT (70%-130%)	98.5	36	190

ALT: Alanin-Amino-Transferase; GPT: Glutamat-Pyruvat-Transaminase; CRP: C-reactive protein; CA 19-9: Carbohydrate-Antigen 19-9; PT: Prothrombin time.

Modality of treatment

Explorative laparotomy was performed in 43 patients (43.9%), and tumor resection could be performed in 23 (23.5%) patients of the cohort. Surgical therapy consisted of resection of the extrahepatic bile-ducts in 9 (39.1%) patients, partial duodenopancreatectomy with hilar resection in 2 (8.7%) patients, hilar resection with right hemihepatectomy in 5 (21.7%) patients, hilar resection with left hemihepatectomy in 4 (17.4%) patients, hilar resection with atypical liver resection in 2 (8.7%) patients and hepatectomy with consecutive liver transplantation in 1 (4.3%) patient. The resected patients were younger, had a lower Bismuth stage and had lower levels of serum bilirubin at diagnosis than the patients who did not undergo surgery, whereas CRP at diagnosis did not differ significantly between both groups (Table 2).

Patients with non-resectable tumors underwent either transpapillary or percutaneous transhepatic biliary drainage. Sixty-two (82.6%) of these patients received unilateral or bilateral plastic stents as biliary endoprosthesis, whereas in 34 (45.3%) patients, metal stents were placed during the course of the disease. In 30 (40%) patients, a percutaneous drainage had to be placed on at least one occasion during their clinical course.

Fifty-one patients received additional therapy. This therapy consisted of intraluminal photodynamic therapy using porfimer sodium (Photofrin™, Axcan, Canada) in 32 patients and systemic chemotherapy in 18 patients.

Survival analysis

At the end of observation, 85 of 98 (86.7%) patients had deceased with a median survival of 8.8 (0.8-55.1) mo. Sixteen patients were alive with a median follow-up of 12.3 (1.4-71.7) mo. The Kaplan-Meier estimated overall median survival was 10.5 (95% CI: 8.4-12.6) mo (Figure 1).

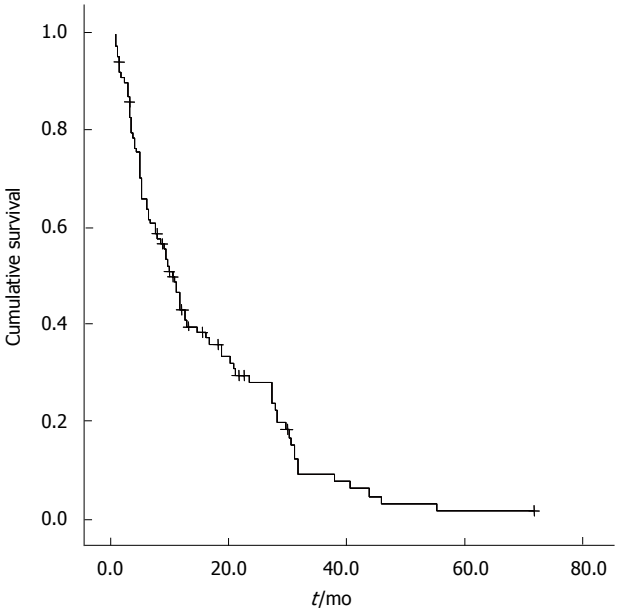

Figure 1 Kaplan-Meier estimate for survival of the whole cohort.

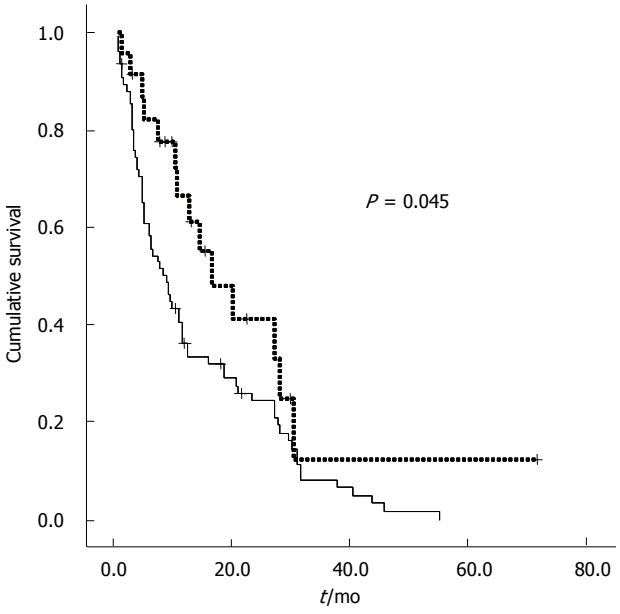

Figure 3 Kaplan-Meier estimate for survival of patients, who underwent resection (dotted line) *versus* non-resected patients (solid line).

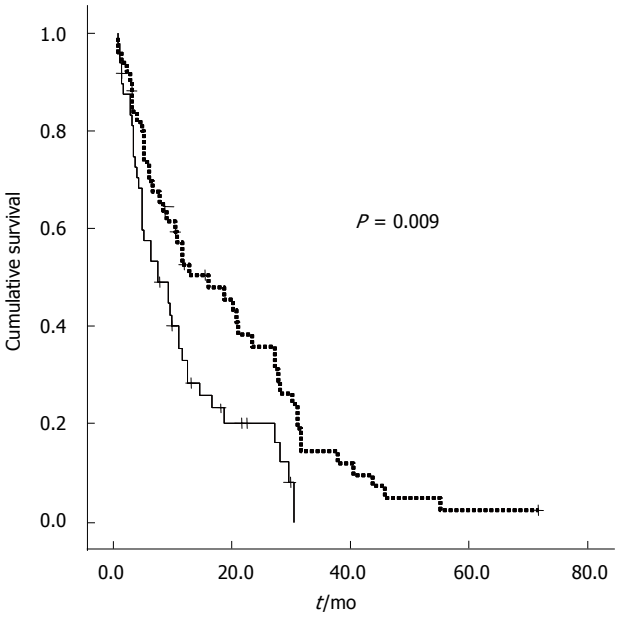

Figure 2 Kaplan-Meier estimate for patients with a serum CRP level < 12 mg/L (dotted line) *versus* ⩾ 12 mg/L (solid line).

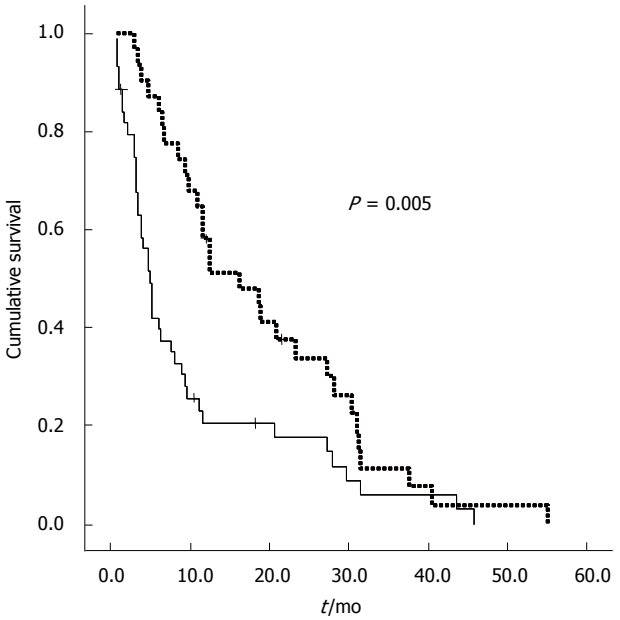

Figure 4 Subgroup analysis of patients without surgical resection: Kaplan-Meier estimate for survival of patients treated with PDT (dotted line) *versus* non-treated patients (solid line).

Prognostic factors and impact of treatment modality

The parameters examined and the results of the uni- and multivariate analyses are shown in Table 3. In the univariate analysis, low Bismuth stage, low CRP and surgical resection correlated significantly with better survival. In the multivariate analysis, only surgical resection ($P = 0.029$) and CRP ($P = 0.005$) were found to be independently predictive of survival in the cohort. ROC analysis identified a CRP level of 11.75 mg/L as the value associated with the highest sensitivity and specificity to identify patients surviving more than 5 mo.

Patients with a CRP level < 12 mg/L at the time of diagnosis had a significantly longer median estimated survival than patients with higher CRP values (16.2 *vs* 7.6 mo; $P = 0.009$) (Figure 2). The median survival in the subgroup of patients who underwent resection was significantly longer compared to patients receiving palliative treatment [16.6 (95% CI: 7.7-25.5) *vs* 9.0 (95% CI: 5.6-12.5); $P = 0.045$] (Figure 3). In contrast to the analysis of the whole cohort, in the subgroup of patients with irresectable tumors, PDT was associated with a significant improvement of survival [16.2 (95% CI: 7.0-25.5) *vs* 5.0 (95% CI: 3.8-6.3) mo ($P = 0.005$)] (Figure 4). Systemic chemotherapy was not correlated to a better outcome

Table 2 Inter-group comparison between patients undergoing surgical resection and patients with irresectable tumors

	Resection (n = 23)	No resection (n = 75)	P
Age	65.8 (36.4-74.1)	71.8 (35.8-90)	0.0003
Bismuth	Ⅱ (Ⅰ-Ⅳ)	Ⅳ (Ⅰ-Ⅳ)	0.001
Bilirubin	3.3 (0.3-17.5)	9.6 (0.4-38.3)	0.0026
CRP	15.6 (0.5-101)	9.9 (0.1-207)	0.445
CA19-9	71 (0.3-2910)	322 (0.3-24 385)	0.0098

Data are expressed as median (range).

Table 3 Results of univariate analysis for prognostic factors of survival

Variables	Hazard ratio	90% CI		P
Age	1.028	1.004	1.052	0.053
Bismuth type	0.784	0.656	0.927	0.023
Bilirubin	1.024	1.002	1.046	0.067
PT	0.996	0.989	1.004	0.402
CRP[a]	1.007	1.003	1.011	0.002
CA19-9	1.000	1.000	1.000	0.079
History of weight loss (yes/no)	1.125	0.783	1.615	0.592
Resection (yes/no)[a]	0.559	0.345	0.908	0.049
Chemotherapy (yes/no)	0.700	0.437	1.123	0.215
PDT (yes/no)	0.670	0.458	0.980	0.084

PT: Prothrombin time, CRP: C-reactive protein, CA 19-9: Carbohydrate-Antigen 19-9. Significant in the multivariate analysis ([a]P < 0.05).

neither in the multivariate analysis of the whole group nor in the subgroup of non-resected patients [11.6 (95% CI: 0.6-25) with chemotherapy *vs* 8.6 (95% CI: 5.0-12.2) mo without chemotherapy; P = 0.33].

DISCUSSION

Our study evaluated outcome and prognostic factors in a large series of unselected patients with perihilar cholangiocarcinoma treated at a tertiary medical center. The prognosis of these patients was poor. The median overall survival in our series was only 10.5 mo. Serum CRP level at diagnosis was identified as a new prognostic indicator for patients with perihilar cholangiocarcinoma. Surgical resection was also associated with prolonged survival. Moreover, in the subgroup of patients with irresectable tumors, additional therapy with PDT apart from biliary drainage, but not chemotherapy, was correlated with a better outcome. Certainly, particularly our data on the impact of treatment modalities on survival are influenced by all the restrictions of a retrospective analysis. There may be biases, such as selection for surgery and less complete follow-up in comparison to a prospective study. Unfortunately, prospective data on the clinical course of non-selected patients with perihilar cholangiocarcinoma are rare. Nevertheless, we were able to analyze a relatively large unselected cohort.

Prognostic factors in patients with cholangiocarcinoma undergoing resection have been extensively evaluated in retrospective series[11]. In a large series presented by Jarnagin *et al*[15], negative histologic margins, concomitant partial hepatectomy and a well-differentiated tumor were associated with an improved outcome. Accordingly, residual tumor as well as lymph node involvement were significant prognostic factors in a cohort of long-term-survivors[14]. Much less is known about the overall outcome of a more heterogeneous non-selected cohort with respect to its possible prognostic factors. Weight loss has previously been reported to be significantly associated with the outcome of patients with malignant strictures of the distal bile duct[16]. However, this factor could not be confirmed in our cohort of patients with perihilar tumors. Although a retrospective study of 49 cases of resected hilar cholangiocarcinoma identified total bilirubin greater than 10 mg/L to be associated with poorer survival[17], the bilirubin level was not significantly correlated to the outcome in our study. CRP, on the other hand, was a statistically significant prognostic factor, even in the multivariate analysis. Patients with a CRP < 12 mg/L at the time of diagnosis had a significantly longer median survival than patients with higher CRP values (16.2 *vs* 7.6 mo; P = 0.009). CRP belongs to the family of acute-phase proteins. Its concentration changes in response to injury, infection and neoplasia. It is up-regulated by cytokines, such as interleukin-8 (IL-8), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α)[18]. *In vitro* studies have identified IL-6 to be an autocrine growth factor of cholangiocarcinoma (CC) cell lines[19,20], in which it induces the expression of the anti-apoptotic protein Mcl-1[21]. Moreover, IL-6 was found to be markedly elevated in the serum of patients with CC and dropped sharply after resection[22]. Thus, high CRP levels might reflect an increased IL-6 level in patients with advanced cholangiocarcinoma. In this respect, the lack of IL-6 serum level determination displays a limitation of our study. In general, increased CRP levels in malignant disease could also be caused by an inflammatory response to tumor invasion[23]. Others showed in immunohistochemical studies that neoplastic tissue itself can express CRP[24]. In cholangiocarcinoma, one might also speculate that elevated CRP serum levels were caused by complicated tumor-induced strictures and subsequent cholangitis. Whereas in our study initial CRP levels correlated to leukocyte count, they were not significantly correlated to tumor size as assessed by the Bismuth-Corlette classification. Interestingly, increased serum CRP levels also correlated with shorter survival in patients with other gastrointestinal malignancies, including pancreatic, esophageal and colorectal cancer[25-27]. Recently, a CRP level ≤ 1.0 mg/dL was identified as favorable prognostic factor in a group of 65 patients with biliary tract cancers receiving chemotherapy[28]. However, this cohort consisted of 82% patients with gallbladder carcinoma, an entity with potentially different biological behavior and less frequent occurrence of cholestasis as compared to ours.

CA19-9 has been shown to be useful in the diagnostic evaluation of cholangiocarcinoma[29,30] and the resectability of intrahepatic and periampullary carcinomas[31,32]. Those of our patients who underwent resection had significantly lower CA19-9 levels at diagnosis, which might reflect a smaller tumor mass, but yet the marker was not correlated to overall outcome. This is in contrast to patients with

inoperable pancreatic cancer undergoing chemotherapy with gemcitabine, in whom CA 19-9 was prognostic[33].

The definitive role of chemotherapy and radiotherapy in the treatment of CC has not been fully established, although both options are commonly used[34]. In our cohort, a small number of patients receiving chemotherapy did not show favorable outcome compared to those without. Also PDT, which had been shown to be a promising palliative approach in several non-randomized and randomized studies on patients with irresectable cholangiocarcinoma, failed to be associated with favorable outcome in the overall analysis. However, it demonstrated a significant influence on survival in the subgroup of non-resected patients. Survival in these patients is comparable to previously published results from prospective trials[35-37].

In accordance with the literature, somewhat one fourth of our patients (24.8%) underwent surgical resection. In the univariate and the multivariate analyses, resection was significantly associated with a better outcome. Patients undergoing resection of their tumor were significantly younger, although age itself was not an independent prognostic parameter. Conclusions of the influence of tumor resection on the outcome of patients with perihilar CC in comparison to conservative treatment are clearly limited by the retrospective character of this analysis, which implements possible bias by patient selection.

In summary, our study evaluated the outcome of a heterogeneous non-selected cohort of patients with cholangiocarcinoma. In agreement with previous studies, surgical resection was identified as a prognostic factor for prolonged survival. In addition, the serum level of CRP at diagnosis was identified as a novel and independent prognostic indicator in patients suffering from perihilar cholangiocarcinoma and should, therefore, be considered as a prognostic parameter in the design of future prospective studies on this kind of patients.

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