담도암의 수술 후 재발에 대한 예후 인자로서의 수술 전 C-반응성 단백질의 역할

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Preoperative C-reactive protein as a prognostic factor for recurrence after surgical resection of biliary tract cancer

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Purpose: C-reactive protein (CRP) has been identified to be associated with cancer development and progression. However, the role of CRP in tumor recurrence is less well defined in biliary tract cancer. Therefore, the aim of this study was to determine the clinical importance of CRP in terms of recurrence of biliary tract cancer after surgical resection.

Methods: Seventy-six patients who underwent curative resection for biliary tract cancer from April 2006 to July 2014 were reviewed. Demographics and tumor characteristics were evaluated retrospectively by review of a clinical database and review of pathologic reports.

Results: The study group was comprised of 48 men and 28 women, with a mean age of 62.2 ± 10.8 years. Clinical diagnoses of these patients included intrahepatic cholangiocarcinoma (n=6), hilar cholangiocarcinoma (n=13), extrahepatic cholangiocarcinoma (n=21), gall bladder cancer (n=11), and ampullary cancer (n=25). Median follow-up was 35 months. Recurrence-free survival at 1-, 2-, and 5-year was 89%, 76%, and 53%, respectively. On univariate analysis, high CRP level (>3.0 mg/dL) was a significant risk factors for recurrence. Multivariate analysis showed high CRP, poor tumor differentiation, vascular invasion were independent risk factor for tumor recurrence.

Conclusion: Preoperative CRP level is significantly associated with recurrence in patients with biliary tract cancer, suggesting the possibility of using CRP as an independent prognostic indicator for biliary cancer.

Keywords: Biliary tract neoplasms, C-reactive protein, Recurrence

INTRODUCTION

Biliary tract cancers, which can be divided anatomically into intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder carcinoma, and ampulla of Vater

cancer [1], are relatively low-incidence malignancies which carry a poor prognosis compared to other types of cancer. Complete resection of these tumors is the only potentially curative treatment. In spite of improved surgical technique, numerous studies have demonstrated that the benefit of surgical resection for biliary tract cancer is limited with 5-year survival rates as high as 50% [2,3]. Despite significant improvements in survival rates among patients who have undergone resection, however, recurrence remains a major cause of mortality for such patients. Statistics show that approximately 60% of patients who undergo surgical resection of biliary tract cancer develop postoperative recurrence of the disease [4]. It is therefore desirable to identify factors predictive of recurrence after surgery.

Elevation of serum C-reactive protein (CRP), an acute phase reactant, is most often noticed in infection and inflammation, injury,

Received: Sep 25, 2015 Accepted: Nov 4, 2015

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and in some forms of neoplasia [5]. Several studies have reported that the elevations in CRP are associated with reduced survival rate for various malignancies [6-9]. To date, however, the association between preoperative CRP level and tumor recurrence has not been fully elucidated for biliary tract cancer. As such, the purpose of the current study is to examine the prognostic value of preoperative CRP levels in biliary tract cancer patients after surgical resection.

METHODS

Patients

A total of 76 patients who underwent curative resection of biliary tract cancer between April of 2006 and July of 2014 at Kyung Hee University Hospital were examined retrospectively through their electronic medical records and pathology reports.

Patients were diagnosed with cancer of ampulla of Vater, extrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, and gallbladder cancer, and they underwent pylorus-preserving pancreaticoduodenectomy (PPPD), bile duct resection, hepatectomy, and extended cholecystectomy. We only included R0 resection in our study. Cases where R0 resection was not possible during surgery, postoperative pathology results showing R1 resection and palliative operation cases were excluded.

Laboratory evaluations

The laboratory data, CRP levels, bilirubin levels, carcinoembryonic antigen (CEA) levels, and carbohydrate antigen (CA) 19-9 levels were obtained by routine blood tests prior to surgery. The cut-off value for CRP was 0.3 mg/dL because levels below 0.3 mg/dL could not be accurately measured in routine assays at our institute. As CRP elevation is also observed in cholangitis and biliary obstruction or after invasive intervention, in order to preclude such instances, the CRP values used in the study were obtained prior to surgery. Patients exhibiting signs of infection or other ongoing inflammatory processes were also excluded. In order to rule out CRP elevation due to cholangitis or biliary obstruction (needing intervention procedures such as percutaneous transhepatic biliary drainage, percutaneous transhepatic gallbladder drainage) that was associated with cancer at diagnosis, we used the CRP values obtained after amelioration of inflammation before operation. Patients with continued leukocytosis (white blood cells > 10,000/ μ L) or those with no preoperative CRP values were excluded. Staging was made according to the American Joint Commission on Cancer, 7th edition staging system.

Patient follow-up

Patients were examined for tumor recurrence by contrast enhanced computed tomography every 3 months and blood tests including

the tumor markers CEA and CA 19-9 every 2-3 months thereafter. Disease recurrence was determined radiologically. The median follow-up time was 31 months (range, 1 to 118 months).

Statistical analysis

Data are presented as mean $\pm$ standard deviation. Chi-square or Fisher's exact test was used for comparative analysis of categorical data. Kaplan-Meier method was used to estimate recurrence-free survival, which was compared using log-rank tests. Multivariate Cox modeling was performed using all clinical and pathologic potential risk factors. Forward stepwise selection using likelihood ratios for entry and exit criteria were employed to develop the final multivariate Cox proportional hazards model. The significance level was set at $P < 0.05$.

Table 1. Characteristics of patients

Variable	No. (%)
Age (yr)	
≤ 65	37 (48.7)
> 65	39 (51.3)
Sex	
Male	48 (63.2)
Female	28 (36.8)
Final diagnosis	
Intrahepatic cholangiocarcinoma	6 (7.9)
Hilar cholangiocarcinoma	13 (17.1)
Extrahepatic cholangiocarcinoma	21 (27.6)
Gall bladder cancer	11 (14.5)
Ampulla of Vater cancer	25 (32.9)
T Stage	
T1	8 (10.5)
T2	40 (52.6)
T3	28 (35.5)
N stage	
N0	57 (75.0)
N1	19 (25.0)
Histology (differentiation)	
Well	14 (18.4)
Moderate	48 (63.2)
Poor	14 (18.4)
Invasion (present)	
Lymphatic	15 (19.7)
Vascular	5 (6.6)
Mean CRP (mg/dL)	1.38 $\pm$ 2.26
Treatment	
Hepatectomy	16 (21.1)
Bile duct resection	6 (7.9)
PPPD	43 (56.6)
Extended cholecystectomy	11 (14.5)

Values are presented as number (%) or mean $\pm$ standard deviation.

CRP, C-reactive protein; PPPD, pylorus-preserving pancreaticoduodenectomy.

RESULTS

Patient characteristics

The study group was comprised of 48 males and 28 females, with preponderance towards males. Thirty-seven patients were of age 65 or younger, while thirty-nine patients were older than 65 years, with a mean age of 62.2 ± 10.8 years. The mean body mass index was 23.8 kg/m^2 (range, 17.7 to 33.2 kg/m^2). Patients were diagnosed with intrahepatic cholangiocarcinoma ($n=6$), hilar cholangiocarcinoma ($n=13$), extrahepatic cholangiocarcinoma ($n=21$), gall bladder cancer ($n=11$), and ampullary cancer ($n=25$). The mean preoperative CRP value was $1.3858 \pm 2.26433 \text{ mg/dL}$. All patients underwent curative surgical resection, including hepatectomy in 16 patients, PPPD in 43 patients, bile duct resection in 6 patients, and extended cholecystectomy in 11 patients. Patients with T stages of 2 and 3 were more numerous, at 52.6% and 35.5%, respectively. Most patients had an N stage of 0. Among the 76 cases in our study, 19 patients underwent adjuvant chemotherapy. The mean follow-up duration was 35 months, and the minimum follow-up period was 12 months (Table 1).

CRP and pathological parameters of the primary tumor

Table 2 shows the CRP level in relation to pathological parameters. Elevations in CRP correlates significantly with poorer tumor differ-

entiation but no significant elevation in CRP levels was found in patients with increased age, T stage, nodal positivity, lymphatic, and vascular invasion in this study.

CRP and prediction of recurrence

Recurrence-free survival at 1-, 2-, and 5-years was 89%, 76%, and 53%, respectively (Fig. 1). Univariate analysis showed that factors significantly associated with tumor recurrence was high CRP (Table 3, Fig. 2). Multivariate analysis showed high CRP level ($P=0.004$, hazard ratio 3.786, 95% confidence interval 1.517–9.445), poor tumor differentiation ($P=0.047$, hazard ratio 4.921, 95% confidence

Table 3. Univariate analysis of risk factors for recurrence free survival

Variable	No recurrence	Recurrence	P-value
Age (yr)			0.489
≤ 65	24 (31.6)	13 (17.1)	
> 65	22 (28.9)	17 (22.4)	
Sex			0.636
Male	28 (36.8)	20 (26.3)	
Female	18 (23.7)	10 (13.2)	
T stage			0.605
1	6 (7.9)	2 (2.6)	
2	24 (31.6)	16 (21.1)	
3	16 (21.1)	11 (14.5)	
N stage			0.189
0	37 (48.7)	20 (26.3)	
1	9 (11.8)	10 (13.2)	
Tumor differentiation			0.057
Well	12 (15.8)	2 (2.6)	
Moderate	28 (36.8)	20 (26.3)	
Poor	6 (7.9)	8 (10.5)	
Lymphatic invasion			0.084
Absent	40 (52.6)	21 (27.6)	
Present	6 (7.9)	9 (11.8)	
Vascular invasion			0.076
Absent	45 (59.2)	26 (34.2)	
Present	1 (1.3)	4 (5.3)	
CEA (ng/mL)			0.527
≤ 5	37 (51.4)	23 (31.9)	
> 5	6 (8.3)	6 (8.3)	
CA19-9 (U/mL)			1.000
≤ 37	19 (25.7)	13 (17.6)	
> 37	26 (35.1)	16 (21.6)	
CRP (mg/dL)			0.044
≤ 3	43 (56.6)	23 (30.3)	
> 3	3 (3.9)	7 (9.2)	

Table 2. CRP differences according to prognostic parameters

Variable	Mean CRP	P-value
Age (yr)		0.616
≤ 65	1.51 ± 2.96	
> 65	1.26 ± 1.33	
T stage		0.275
1	0.62 ± 0.62	
2	1.45 ± 2.72	
3	1.38 ± 1.70	
N stage		0.580
0	1.08 ± 1.27	
1	2.28 ± 3.89	
Histology (differentiation)		0.002
Well	0.40 ± 0.10	
Moderate	1.31 ± 1.47	
Poor	2.61 ± 4.35	
Lymphatic invasion		0.497
Absent	1.11 ± 1.27	
Present	2.48 ± 4.34	
Vascular invasion		0.627
Absent	1.42 ± 2.33	
Present	0.85 ± 0.78	

Values are presented as number or mean $\pm$ standard deviation.
CRP, C-reactive protein.

Values are presented as number (%) of patients.

CEA, Carcinoembryonic antigen; CA, carbohydrate antigen; CRP, C-reactive protein.

Fig. 1. Recurrence-free survival curves of patients with biliary tract cancer.

Table 4. Multivariate analysis of risk factors for recurrence free survival

Variable	Hazard ratio (95% confidence interval)	P-value
C-reactive protein (mg/dL)		
≤ 3	Reference	
> 3	3.786 (1.517–9.445)	0.004
Differentiation		
Well	Reference	
Poor	4.921 (1.019–23.779)	0.047
Vascular invasion		
No	Reference	
Yes	5.100 (1.421–18.300)	0.012

interval 1.019–23.779), vascular invasion ($P=0.012$, hazard ratio 5.100, 95% confidence interval 1.421–18.300) were independent risk factor for tumor recurrence (Table 4).

DISCUSSION

Previous epidemiologic studies have reported that elevated CRP levels may be associated with poor prognosis in several types of solid cancers [6–9]. CRP below 12 mg/L was shown to be a significant prognostic factor for cholangiocarcinoma [5], and CRP less than 5 mg/L was associated with better prognosis in pancreatic cancer [10] in previous studies. However, its role as a prognostic factor for postoperative recurrence for biliary tract cancer has not been investigated.

Fig. 2. Recurrence-free survival curves of patients according to the CRP cutoff value. CRP, C-reactive protein.

CRP is an acute phase reactant most often encountered in elevated amounts in a cancer specific systemic response or a degree of sub-clinical biliary sepsis [10]. Many tumors arise at sites of chronic inflammation, or they trigger inflammatory responses that result in the formation of an inflammatory microenvironment around the tumors, and, since inflammation in the tumor microenvironment stimulates tumor growth, invasion, and metastasis, inflammation seems to facilitate invasion and metastasis rather than pose as an effective host anti-tumor response [11–13]. CRP elevation is observed in cholangitis and biliary obstruction or after invasive intervention in biliary tract cancer. In order to preclude such instances, the CRP values used in the study were obtained immediately before surgery. Patients exhibiting signs of infection or other ongoing inflammatory processes were excluded.

There is no standard CRP cut-off value defining the prognosis in patients with bile duct cancer. In our study, we compared multiple cut-off intervals and found that using 3 mg/dL as our cut off value resulted in statistically significant results. In the same manner, cut-off value of CEA (5 ng/mL) and CA19-9 (37 U/mL) were significant determinant. The cases examined in this study exclusively involved R0 resections, as this study was aimed at assessing the relevance of CRP after complete resection; palliative operations were excluded. In this study, retrospective analysis of patients undergoing radical surgery for biliary tract cancer was carried out to determine the significance of CRP as a predictive factor for postoperative recurrence. The study was performed at a single, tertiary-care teaching hospital. Data were extracted from a clinical database. Laboratory values and of the clinical outcomes were determined retrospective-

ly from hospital charts. The limitations of the study include its retrospective nature and the small sample population.

In conclusion, in the present study, preoperative CRP level was shown to bear a significant correlation to postoperative recurrence in patients with biliary tract cancer, and the results suggest that CRP may be of utility as an independent prognostic factor for biliary cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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