ORIGINAL ARTICLE

Inflammation-based prognostic score is a useful predictor of postoperative outcome in patients with extrahepatic cholangiocarcinoma

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Abstract

Background/purpose: Recent studies have revealed that the Glasgow prognostic score (GPS), an inflammation-based prognostic score, is useful for predicting outcome in a variety of cancers. This study sought to investigate the significance of GPS for prognostication of patients who underwent surgery with extrahepatic cholangiocarcinoma.

Methods: We retrospectively analyzed a total of 62 patients who underwent resection for extrahepatic cholangiocarcinoma. In 62 patients we calculated the GPS as follows: Patients with both an elevated C-reactive protein (CRP) (>10 mg/L) and hypoalbuminemia (<35 g/L) were allocated a score of 2. Patients with either one or none of these abnormalities were allocated a score of 1 or 0, respectively. Prognostic significance was analyzed by the log-rank test and a Cox proportional hazards model.

Results: Overall survival rate was 25.5% at five years for all 62 patients. Venous invasion (p=0.01), pathological primary tumor (pT) category (p=0.013), lymph node metastasis (pN) category (p<0.001), TNM-stage (p<0.001), and GPS (p=0.008) were significantly associated with survival by univariate analysis. A Cox model demonstrated that increased GPS was an independent predictive factor with poor prognosis.

Conclusions: The preoperative GPS is a useful predictor of postoperative outcome in patients with extrahepatic cholangiocarcinoma.

Introduction

Of all gastrointestinal malignancies, pancreatobiliary carcinomas continue to have poor survival rates.[1-12] Multiple studies have examined potential prognostic factors in patients undergoing resection for extrahepatic cholangiocarcinoma, including the presence of lymph node metastases,[2,3,5,6,8-12] the number of lymph node metastases,[11,12] resection margin,[1,3,5-9] tumor differentiation,[1,9] and depth of invasion.[7,12] There is increasing evidence that the GPS, a score based on the systemic inflammatory response (SIR) that evaluates CRP and albumin serum levels, is a useful scoring system to determine the prognosis of patients with advanced cancers.[13-15] The SIR encompasses the infiltration of proinflammatory lymphocytes, which produce cytokines and chemokines within the tumor microenvironment, predisposing the tumor to further progression, invasion, and metastases.[16] A state of chronic inflammation is thought to play a key role in the initiation, promotion, and progression of malignant diseases.[17]

To our knowledge, the GPS has not been investigated in patients with extrahepatic cholangiocarcinoma. This study sought to examine the relationship between an inflammation-based prognostic score, Glasgow prognostic score (GPS), and survival in patients undergoing resection for extrahepatic cholangiocarcinoma. In addition, we evaluated the relative prognostic power of the GPS in comparison to other clinicopathologic factors after surgical resection.

Patients and Methods

This study retrospectively analyzed 62 consecutive patients (41 men and 21 women) with extrahepatic cholangiocarcinoma who underwent surgical resection at Tsukuba University Hospital between January 2001 and December 2009. Mean patient age was 69.0 years (range; 34 to 88 years). The mean value of preoperative serum total bilirubin level was 7.1 ± 6.9 mg/dl and 36 patients (58%) had preoperative biliary drainage due to obstructive jaundice (Table 1). The appropriate biliary drainage procedures were performed in the 36 patients. Twenty-four patients underwent percutaneous transhepatic biliary drainage (PTBD), 10 patients underwent endoscopic nasogastric biliary drainage (ENBD), and 2 patients underwent endoscopic retrograde biliary drainage (ERBD).

The predominant sites of the primary tumor were the hilar bile duct in 17 patients (27%), proximal bile duct in 15 patients (24%), middle bile duct in 12 patients (19%), and distal bile duct in 18 patients (30%). The appropriate surgical procedures depended on the location of the primary tumor. Twenty-five patients underwent hepatectomy with extrahepatic bile duct resection (Hx), 24 patients underwent a pancreaticoduodenectomy (PD) or subtotal stomach-preserving pancreaticoduodenectomy (SSPPD), 11 patients underwent extrahepatic bile duct resection (EBDR), and 2 patients underwent a combined hepatectomy and pancreaticoduodenectomy (HPD) (Table 1). Systemic regional lymphadenectomy, which involved resection of the lymph nodes in the hepatoduodenal ligament, posterior pancreatoduodenal nodes, and along the common hepatic artery, was performed in all patients.

After surgical resection, we opened the extrahepatic bile duct longitudinally. Specimens were fixed in 10% formalin for several days, and then serially sectioned at 5-mm intervals. Specimens were prepared in the standard manner for microscopic examination by

hematoxylin and eosin staining. Histopathological findings were described in accordance with the tumor-node-metastasis (TNM) staging of the American Joint Committee on Cancer (AJCC) as well as the General rules for Surgical and Pathological Studies on Cancer of the Biliary Tract of the Japanese Society of Biliary Surgery (JSBS). [18, 19] Primary tumor status, lymph node category, and histopathological tumor grade were classified according to the AJCC-TNM classification system. We examined the histopathological factors of lymphatic invasion, venous, and perineural invasion and recorded our findings in accordance with JSBS guidelines.

In the patients who underwent the biliary drainage procedures, we diagnosed whether they had cholangitis or not according to systemic inflammatory response syndrome (SIRS) criteria; including fever, abnormal white blood cell count, tachypnea, and tachycardia, as well as filthy colored bile juice which is suspect of bile contamination. Blood samples were always taken from the patients within one week before surgery in order to confirm there were no other problems or abnormality in the patients prior to receiving anesthesia and surgery. We used the blood sample data at that time; i.e., serum CRP and albumin for the GPS system. In the present study, we used the blood sample data for the GPS system in accordance with the above mentioned way by which we had diagnosed no cholangitis. We routinely investigated bacterial culture of the drained sample bile juice in the patients who underwent the biliary drainage procedures. In the culture of the bile juice in 36 patients who underwent the biliary drainage procedures, we confirmed negative pathogenic bacteria in 15 patients and normal bacterial flora in 15 patients. Data was not found in the other 6 patients. It is said that after the biliary drainage procedures, secondary exogenous contamination of bile juice occurs in most patients [20], so we always use antibiotics for 2-3 days just after the drainage procedures. In fact, only 4 of 36 patients had fever after the

biliary drainage procedures and their fever went down soon, and the serum bilirubin level decreased gradually in all patients. After we confirmed that the patients had no cholangitis, they underwent surgical resection 31.1 (mean, range; 6-88) days after the biliary drainage procedures. The coefficient of variation for these methods, over the range of measurement, was less than 5%, as established by routine quality control procedures.

Briefly, patients with both an elevated CRP level (>10 mg/L) and hypoalbuminemia (<35 g/L) were allocated a score of 2, while patients with only one of these biochemical abnormalities were allocated a score of 1. Patients with neither of these abnormalities were allocated a score of 0, as described previously. [13-15]

Patients were followed regularly in outpatient clinics every 1-6 months. Follow-up information for all 62 patients was obtained from records of routine clinic appointments and telephone calls to the patients and their referring physicians. Sites of disease recurrence were determined from imaging studies including computed tomography (CT) and magnetic resonance imaging (MRI).

Survival curves were calculated using the Kaplan-Meier method.[21] Differences between curves were evaluated using the log-rank test. P values < 0.05 were considered statistically significant. We used a multivariate Cox proportional hazard model to determine if factors independently affected postoperative survival.[22] Correlations between GPS classification and age, predominant location, histological grade, venous invasion, pathological primary tumor (pT) category, lymph node metastasis, and TNM-stage were analyzed by the χ^2 test or Fisher exact test as appropriate. Statistical analyses were performed using a statistical analysis software package (StatView version 5.0 Abacus Concepts, Inc., Berkeley, CA).

Results

A GPS of 0, 1, and 2 were assigned to 32, 20, and 10 patients, respectively. There were no significant differences in tumor characteristics of extrahepatic cholangiocarcinoma such as age, predominant location, histologic grade, venous invasion, pathological primary tumor (pT) category, lymph node metastasis, TNM-stage, carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) across the different GPS groups (Table 2).

At last follow-up, 36 patients had died of tumor recurrence, while five patients had died of other causes without evidence of tumor recurrence. Two patients were alive with metastases and the other remaining 19 patients were alive without evidence of disease. One patient died within 30 days of surgical resection, and two patients died in the hospital, yielding a surgical mortality rate of 4.8%. Overall survival rates were 37.3% at three years and 25.5% at five years for all 62 patients. Venous invasion, pathological primary tumor (pT) category, lymph node metastasis (pN) category, TNM-stage, and GPS were found to be significant prognostic factors by univariate analysis (Table 3). In contrast, age, gender, predominant location, operative time, intraoperative bleeding, histological grade, lymphatic invasion, perineural invasion, surgical margin, CA19-9, and CEA were not found to be significant predictors of survival.

Kaplan-Meier analysis demonstrated significant differences in survival among the GPS groups of 2 (mean survival, 12.7 months; 95%CI, 7.8-17.6 months), 1 (mean survival, 37.2 months; 95%CI, 20.0-54.4 months), and 0 (mean survival, 34.1 months; 95%CI, 24.9-43.3 months) (p=0.008) (Figure 1). Although there was significant difference between the GPS of 1 and the GPS of 2 (p=0.031), no significant difference was seen between the GPS of 0 and the GPS of 1 (p=0.866). Considering the results of Figure 1, we aggregated the categories “GPS of 0” and “GPS of 1” into one category (“GPS of 0-1”) (Figure 2).

Kaplan-Meier analysis also demonstrated a significant difference between the GPS of 2 (mean survival, 12.7 months; 95%CI, 7.8-17.6 months) and the GPS of 0-1 (mean survival, 34.9months; 95%CI, 26.5-43.3 months) (p=0.002) (Figure 2). Thirty-six patients without lymph node metastases had a five-year survival of 44.2% in comparison to a five-year survival of 0% for 26 patients with lymph node metastases (P<0.001) (Figure 3). A multivariate analysis with a Cox proportional hazards model, utilizing venous invasion, pathological primary tumor (pT) category, lymph node metastasis (pN) category, and GPS, revealed that a GPS of 2 was an independent predictive factor of survival (HR=2.787, p=0.022) (Table 4). TNM-stage, pT, and pN factors are considered to have a strong correlation because pT and pN are components of TNM-stage. In fact, in our multivariate analysis, analysis including these three factors was not able to show estimators because of multicollinearity (data not shown). Therefore, we excluded TNM-stage from the multivariate analysis and adopted pT and pN, which are medically essential and impressive, to obtain medically meaningful results.

Discussion

McMillan and coworkers[13-15, 23-26] demonstrated that GPS is a useful predictor of postoperative death for multiple cancers including non small-cell lung[13], breast[14], gastro-esophageal[15, 23], pancreatic[24], renal[25], and colorectal[26] cancers. The cases in these studies, however, were typically inoperable or metastatic. Recently, several reports have investigated GPS in patients with operable primary colorectal cancers. [16, 27-30] As yet, no reports have addressed the association between GPS and survival in extrahepatic cholangiocarcinoma. To our knowledge, this is the first report evaluating the use of GPS in patients undergoing resection for extrahepatic cholangiocarcinoma.

In this study, a Cox proportional hazards model revealed that a GPS of 2 was an independent predictive factor of survival (Table 4). This data suggests that GPS is a prognostic factor of outcome; higher GPS portends poor tumor biology and worse survival. On the other hand, a Cox proportional hazards model revealed that lymph node metastasis had a marginal significance for survival (HR=2.066, p=0.071) (Table 4). Numerous studies have demonstrated that lymph node metastasis is the most accurate prognostic factor used for pancreatobiliary carcinoma; patients with lymph node metastases have a significantly worse survival than patients with node-negative disease. Jang et al. and Sasaki et al. reported that lymph node metastasis is a significant factor affecting patient outcome after surgery [3, 11].

A wide range of systemic inflammatory responses results from infection, tissue injury, immunological disorders, and cancer. C-reactive protein (CRP) is an acute-phase protein produced by liver. The liver is central to the elaboration of the systemic inflammatory response. Cytokines such as interleukin-8 (IL-8), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) stimulate hepatocytes to synthesize and release into the systemic

circulation a variety of acute-phase proteins, such as CRP, which initiate and sustain the systemic inflammatory response. [16, 31] McMillan et al. demonstrated that CRP concentrations were independently associated with overall survival in patients who underwent potentially curative resection for colorectal cancer.[32]

In the past, hypoalbuminemia in cancer patients was thought to result from nutritional depletion secondary to the tumor. However, it has been postulated that reduction in albumin concentrations is secondary to the presence of the systemic inflammatory response.[29] The acute phase protein response (APPR) is characterized by lower serum concentrations of several serum proteins, such as albumin and transferrin, which results from both decreased synthesis and altered distribution. Serum concentration of CRP and immunoglobulins increase due to increased synthesis.[33,34] In patients with cancer, there is evidence that the stereotypical APPR, with an increase in CRP and decreased albumin, occurs across a wide range of different tumor types.[31] Therefore, albumin levels may not only reflect underlying nutritional status, but also the presence of comorbidities.[29]

The relationship between the systemic inflammatory response (GPS) and decreased survival in patients with extrahepatic cholangiocarcinoma is not clear and is likely to be complex. Ishizuka et al. [16] commented that cancer promotes the release of proinflammatory cytokines, leading in extreme cases to cachexia and malnutrition. Crozier et al. [29] suggested that an elevated GPS may reflect compromised cell-mediated immunity as an elevated CRP and hypoalbuminemia are associated with lymphcytopenia and an impaired T-lymphocytic response within tumors. Elevated CRP concentrations and hypoalbuminemia have also been shown to be associated with an up-regulation of the components of an innate immune system, including complement and macrophage activity. These results suggest that immune function is compromised prior to surgery, resulting in faster disease progression and

decreased long-term survival. There has been no clear basis of the relationship between a high GPS prior to surgery and poor survival in various cancers. However, based on the previous reports[16, 29], we could speculate that there might be a kind of extrahepatic cholangiocarcinoma that produces or promotes cytokines such as IL-6 and TNF-α. Therefore, SIR induced by the cytokine causes the impaired immunity in patients, resulting in fast progression of the carcinoma and decreased survival. Furthermore, because there was a marginal significant difference in lymph node metastasis across the different GPS groups (P=0.059), a high GPS might have the characteristic of having a high tendency for lymphatic spread of the extrahepatic cholangiocarcinoma.

Many previously reported prognostic factors have been evaluated only after surgery, because these were pathological factors. In contrast, GPS can easily be calculated from the serum CRP and albumin levels prior to surgery. Due to lower costs and improved convenience, preoperative GPS is a useful system to assess postoperative survival in patients with extrahepatic cholangiocarcinoma.

Several limitations of this study, however, need to be addressed. This study had a retrospective design and was limited by a small number of patients. In addition, there is a possibility that the heterogeneity of the primary tumor location or the surgical procedures affected the results of this study. These results will need to be confirmed by a multi-institutional cohort of patients.

GPS should be routinely used for patients with extrahepatic cholangiocarcinoma, as it can help stratify those patients who need additional treatment. Use of this classification system in the analysis of future clinical trials investigating extrahepatic cholangiocarcinoma will also help determine appropriate treatments according to disease severity.

Conclusions

In conclusion, preoperative GPS is a promising predictor of postoperative outcomes in patients with extrahepatic cholangiocarcinoma.

Conflict of interest statement: No conflict of interest

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FIGURE LEGENDS

Fig. 1

Survival curves stratified by Glasgow prognostic score (GPS) 0, 1, and 2.

There was a statistically significant difference among the three groups (five-year survival rates: GPS of 0, 26.8%; GPS of 1, 42.6%; GPS of 2, 0%) (p=0.008). While there was a significant difference between the GPS of 1 and the GPS of 2 (p=0.031), there was no significant difference between the GPS of 0 and the GPS of 1 (p=0.866).

Fig. 2

Survival curves stratified by Glasgow prognostic score (GPS) 0-1 and 2.

There was a statistically significant difference between the GPS of 0-1 and the GPS of 2 (p=0.002).

Fig. 3

Survival curves stratified by lymph node status.

There was a statistically significant difference in survival between patients with positive lymph nodes and those with negative nodes (p<0.001).

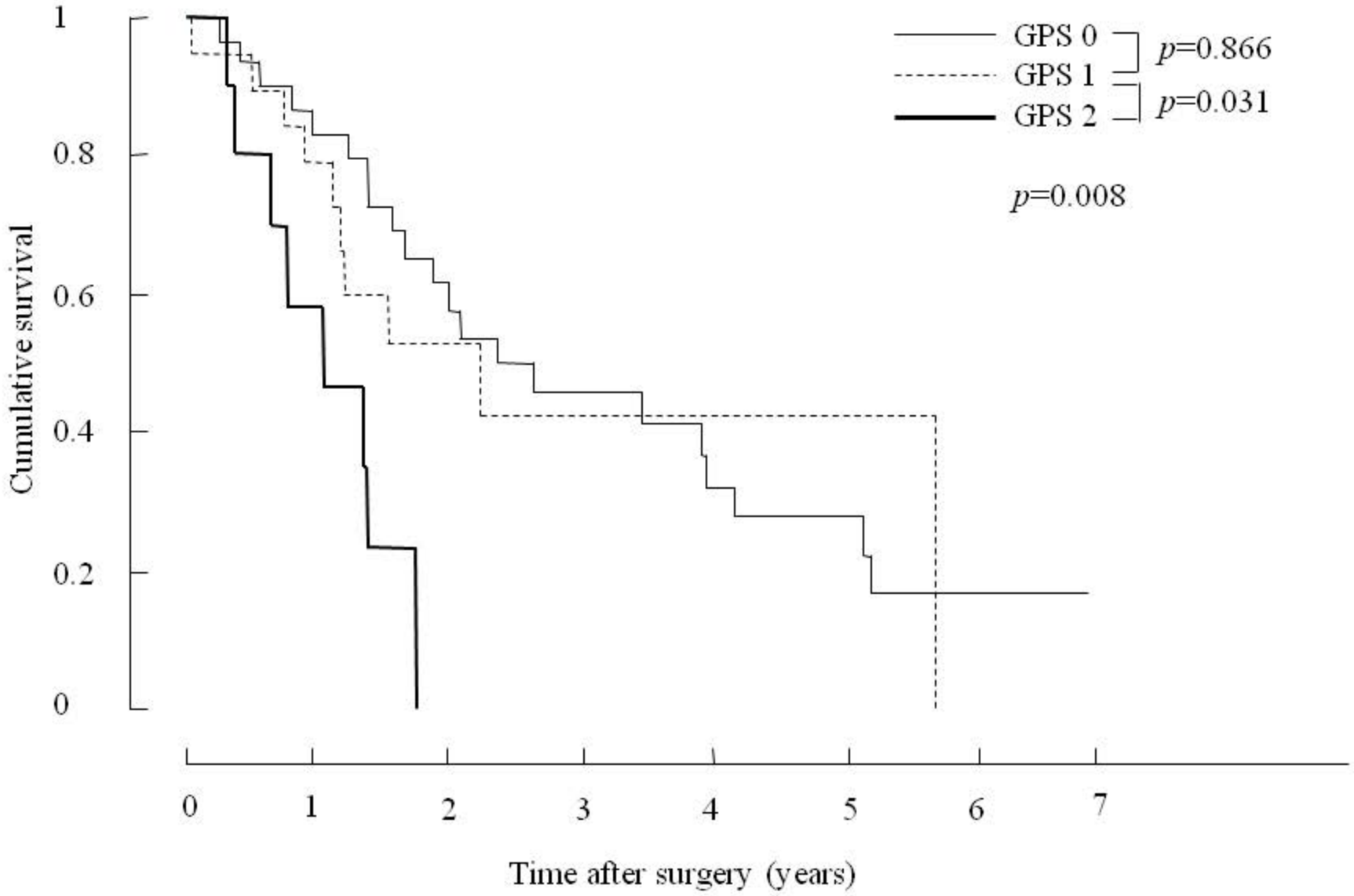
1
0.8
0.6
0.4
0.2
0
Cumulative survival
GPS 0
GPS 1
GPS 2
p=0.866
p=0.031
p=0.008
0
1
2
3
4
5
6
7
Time after surgery (years)

Fig. 1

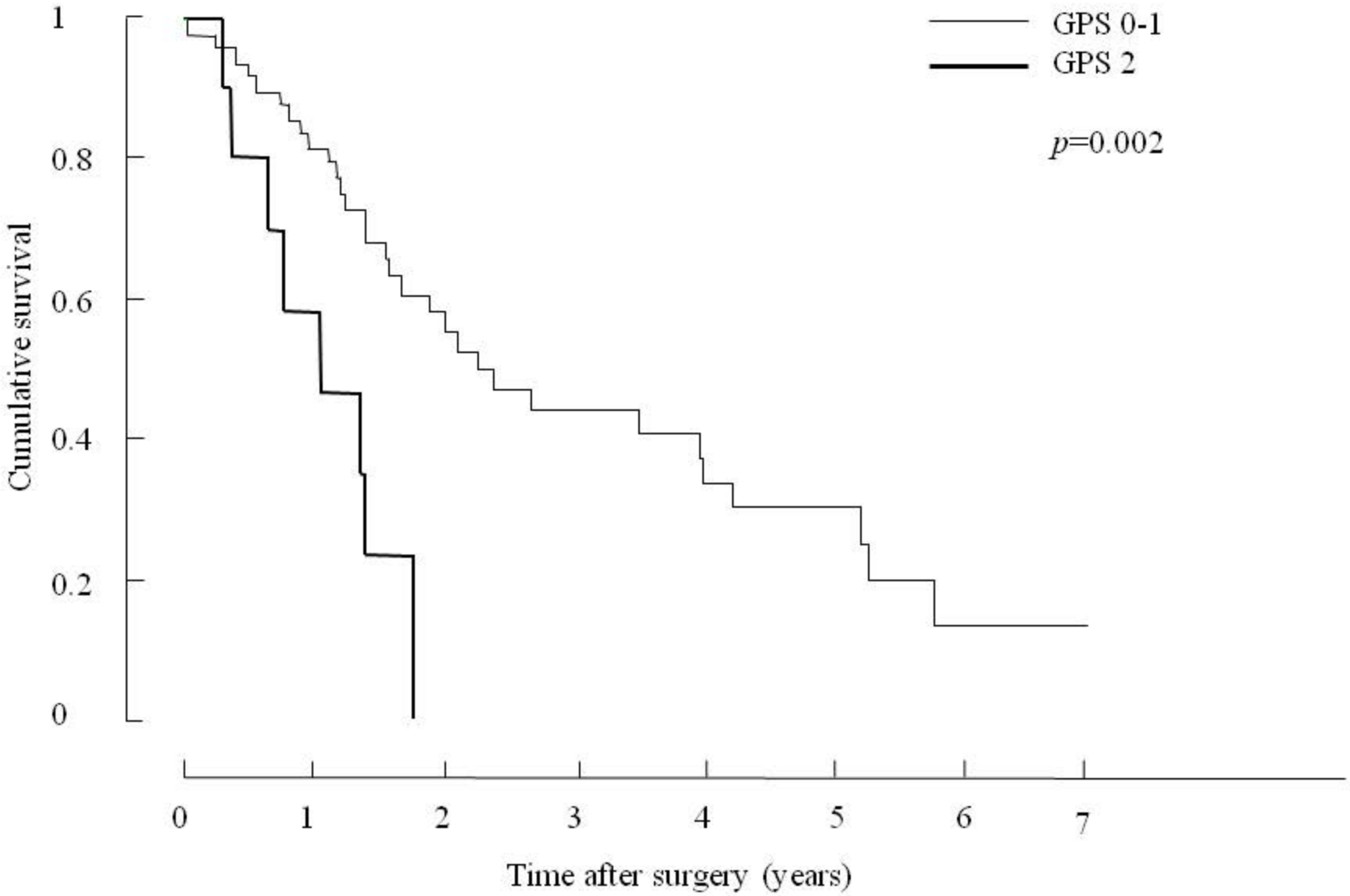
GPS 0-1
GPS 2
p=0.002
Cumulative survival
1
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
6
7
Time after surgery (years)

Fig. 2

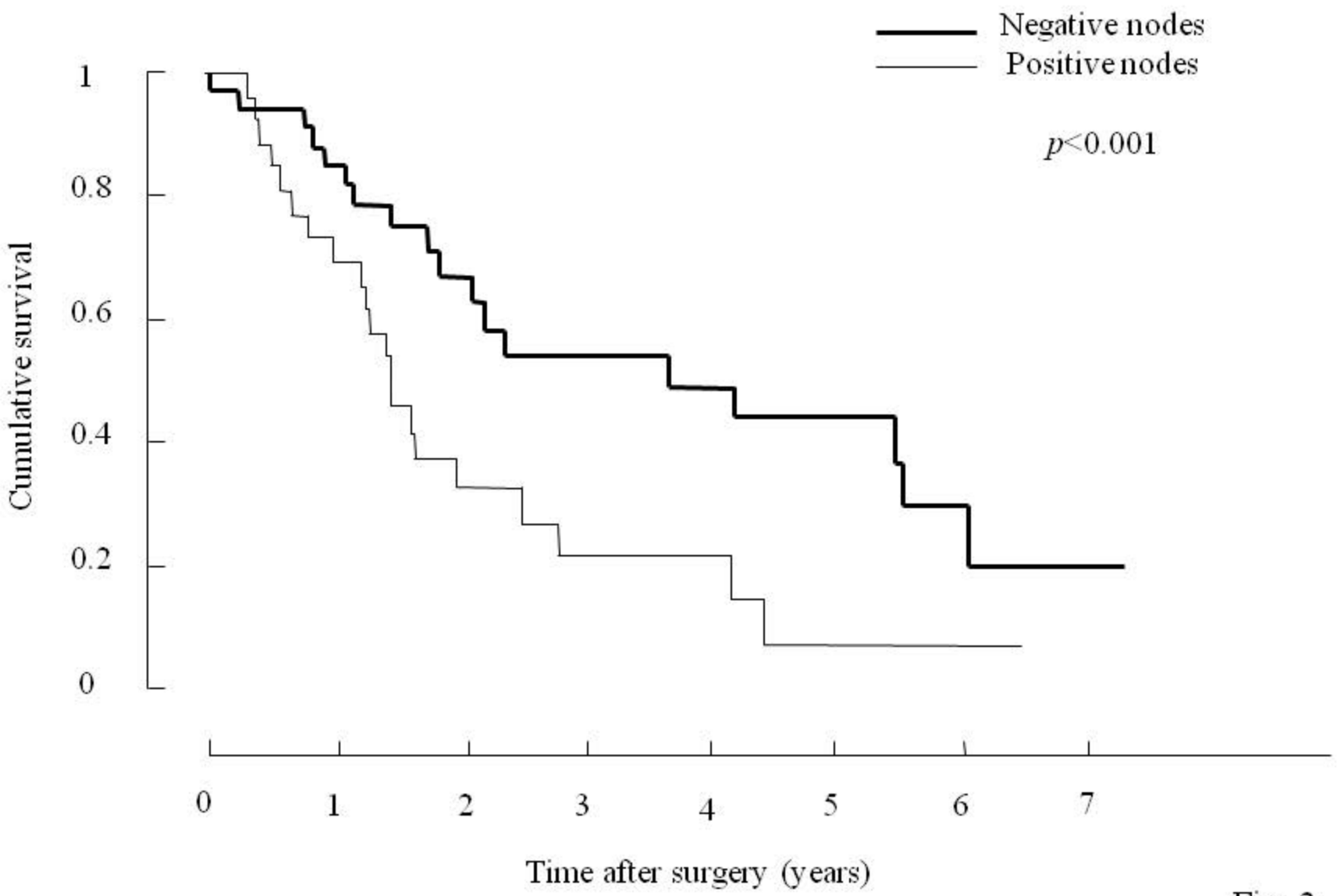
Negative nodes
Positive nodes
$p<0.001$
Cumulative survival
1
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
6
7
Time after surgery (years)

Fig. 3

Table 1. Clinical and morphological features of patients

Variable	Number of patients (%)
Age (year)	
(mean, range)	69.0 (34-88)
Gender	
Male (n, %)	41 (66)
Female (n, %)	21 (34)
Preoperative serum total bilirubin level (mg/dL)	
(mean, range)	7.1 (0.4-22)
Preoperative biliary drainage (yes/no)	36/26
PTBD	24(39)
ENBD	10(16)
ERBD	2(3)
Site (n, %)	
Hilar	17 (27)
proximal	15 (24)
middle	12 (19)
distal	18 (30)
Surgery (n, %)	
Hx	25 (40)
PD, SSPPD	24 (39)
EBDR	11 (18)
HPD	2 (3)
TNM stage (n, %)	
0	5 (8)
IA	9 (15)
IB	7 (11)
IIA	13 (21)
IIB	15 (24)
III	11 (18)
IV	2 (3)
GPS (n, %)	
0	32 (50)
1	20 (34)
2	10 (16)

PTBD, Percutaneous transhepatic biliary drainage; ENBD, endoscopic nasogastric biliary drainage; ERBD, endoscopic retrograde biliary drainage; Hx, Hepatectomy combined with extrahepatic bile duct resection; PD, Pancreaticoduodenectomy SSPPD, Subtotal stomach-preserving pancreaticoduodenectomy; EBDR, Extrahepatic bile duct resection; HPD, Hepatectomy combined with pancreaticoduodenectomy; GPS, Glasgow prognostic score

Table 2. Relationships between tumor characteristics of extrahepatic cholangiocarcinoma and GPS

Variables	GPS 0	GPS 1	GPS 2	*P-value*
Age (year)				0.874
<70	17	10	6	
≥70	15	10	4	
Predominant location				0.291
Hilar/proximal	17	8	7	
Middle/distal	15	12	3	
Histological grade				0.538
Well/moderately	27	15	7	
Poor	5	5	3	
Venous permeation				0.668
Negative	21	12	5	
Positive	11	8	5	
T stage				0.781
Tis	4	1	0	
T1	6	2	2	
T2	8	3	2	
T3	10	10	4	
T4	4	4	2	
Lymph node metastasis				0.059
Negative	18	15	3	
Positive	14	5	7	
TNM stage				0.14
0	4	1	0	
IA	5	2	2	
IB	5	2	0	
IIA	4	8	1	
IIB	9	2	4	
III	5	4	2	
IV	0	1	1	
CA19-9 (U/ml)				0.419
Normal	9	6	5	
High	23	14	5	
CEA (ng/ml)				0.405
Normal	22	15	9	
High	10	5	1	

Table 3. Prognostic factors by a univariate analysis

Factor	Number of Patients	3-year rate (%)	5-year rate (%)	*P-value*
All	62	37.3	25.5	
Age (year)				0.211
<70	31	43.4	29.7	
≥70	31	32.4	21.6	
Gender				0.408
Male	41	39.2	27.5	
Female	21	33.6	22.4	
Predominant location				0.053
Hilar/proximal	32	23.9	19.1	
Middle/distal	30	51.4	32.1	
Operation Time (minutes)				0.584
<600	32	37.5	25.0	
≥600	30	29.1	29.1	
Intraoperative bleeding				0.084
<1300	37	47.0	29.9	
≥1300	25	17.0	17.0	
Histological grade				0.838
Well/moderately	49	37.5	21.9	
Poor	13	40.2	40.2	
Tumor invasion				
Lymphatic invasion				0.197
Negative	21	54.4	43.5	
Positive	41	30.2	18.9	
Venous invasion				0.01
Negative	38	48.9	36.2	
Positive	24	16.6	0	
Perineural invasion				0.29
Negative	10	56.3	28.1	
Positive	52	33.9	24.3	
T stage				0.013
Tis	5	80.0	60.0	
T1	10	40.0	40.0	
T2	13	48.5	32.3	
T3	24	35.2	21.1	
T4	10	0	0	
Lymph node metastasis				<0.001
Negative	36	54.0	44.2	
Positive	26	16.9	0	
TNM stage				<0.001
0	5	80.0	80.0	
IA	9	38.1	38.1	
IB	7	47.6	47.6	
IIA	13	67.9	40.7	
IIB	15	22.2	0	
III	11	0	0	
IV	2	0	0	
Surgical margin				0.081
Negative	36	43.1	31.5	
Positive	26	29.9	17.9	
CA19-9				0.595
Normal	20	49.0	32.6	
High	42	33.9	23.3	
CEA				0.461
Normal	46	32.9	20.6	
High	16	46.8	37.4	
GPS				0.008
0	32	44.6	26.8	
1	20	42.6	42.6	
2	10	0	0	

Table 4. Multivariate analysis for survival

Parameter	HR	95% CI	*P-Value*
Venous invasion : positive	1.237	0.561 – 2.727	0.598
T stage : T3,4	1.817	0.884 – 3.736	0.104
Lymph node metastasis : positive	2.066	0.938 – 4.549	0.071
GPS : 2	2.787	1.153 – 6.735	0.022

GPS, Glasgow prognostic score; HR, hazard ratio; CI, confidence interval