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Glasgow Prognostic Score Predicts Outcome After Surgical Resection of Gallbladder Cancer

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Abstract

Background Systemic inflammation as evidenced by the Glasgow prognostic score (GPS) predicts cancer-specific survival in various types of cancer. The aim of this study was to evaluate the significance of GPS in therapeutic outcome after surgical resection of gallbladder cancer.

Methods The subjects were 51 patients who underwent surgical resection for gallbladder cancer. For the assessment of systemic inflammatory response using the GPS, patients were classified into three groups: patients with normal albumin (≥3.5 g/dl) and normal C-reactive protein (CRP) (≤1.0 mg/dl) as GPS 0 ($n = 38$), those with low albumin (<3.5 g/dl) or elevated CRP (>1.0 mg/dl) as GPS 1 ($n = 8$), and those with low albumin (<3.5 g/dl) and elevated CRP (>1.0 mg/dl) as GPS 2 ($n = 5$). We retrospectively investigated the relation between patient characteristics including GPS, and disease-free as well as overall survival.

Results In disease-free survival, advanced tumor stage based on pathology ($p = 0.006$), positive lymph node metastasis ($p = 0.001$), and GPS 1 or 2 ($p = 0.006$) were independent predictors of cancer recurrence in multivariate analysis. In overall survival, positive lymph node metastasis ($p = 0.002$) and GPS 1 or 2 ($p = 0.032$) were independent predictors of poor patient outcome in multivariate analyses.

Conclusion The GPS in patients with gallbladder cancer is an independent prognostic predictor after surgical resection.

Introduction

Gallbladder cancer is a relatively rare neoplasm [1], and often diagnosed at advanced stages [2, 3]. The therapeutic outcome was favorable for pT1 cancer with the 5-year survival rate of 85.9 %, whereas quite poor for pT3 and pT4 cancer with the 5-year survival rate of 19.2–14.1 % in Japan [4]. In addition, optimal extent of liver resection including extended lobectomy, resection of segment 4b and segment 5, and liver bed resection is still controversial [5]. Although pre-operative prognostic indicators of gallbladder cancer are limited, elucidation of such parameters is important for the post-operative management after surgical resection.

The presence of systemic inflammatory response, as evidenced by an elevated C-reactive protein (CRP) concentration, may be associated with poor therapeutic outcome for malignant tumors. Several recent investigators reported that the systemic inflammatory response by the combination of serum CRP and albumin concentrations, i.e., Glasgow prognostic score (GPS) predicts cancer-specific survival, including colorectal [6], gastro-esophageal [7], urinary bladder [8], pancreatic [9], renal [10], and non-small-cell lung cancers [11]. In this study, we

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retrospectively investigated the relation between GPS and disease-free as well as overall survival after surgical resection of gallbladder cancer.

Patients and methods

Between January 2004 and December 2011, 57 patients with gallbladder cancer underwent surgical resection at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Of these, 6 patients were excluded, 3 patient for insufficient data, 2 patients for palliative resection, and 1 patient who were lost to follow up, leaving the remaining 51 patients for the study. Basically, patients with incidental diagnosis of gallbladder cancer after noncurative cholecystectomy underwent additional hepatic resection with or without bile duct and lymph node resection.

For the assessment of systemic inflammatory response using the GPS, the patients were classified into three groups: patients with normal albumin ($\geq$3.5 g/dl) and normal CRP ($\leq$1.0 mg/dl) as GPS 0 ($n = 38$), those with low albumin (<3.5 g/dl) or elevated CRP (>1.0 mg/dl) as GPS 1 ($n = 8$), and both low albumin (<3.5 g/dl) and elevated CRP (>1.0 mg/dl) as GPS 2 ($n = 5$).

We investigated the relation between clinicopathologic variables and disease-free as well as overall survival after surgical resection by univariate and multivariate analyses. The factors consisted of the following 8 factors: age, gender, pre-operative hemoglobin, post-operative complications, tumor stage based on tumor pathology (T stage), status of lymph node metastasis on pathology, the presence or absence of gallstones, and status of GPS.

Next, we investigated the relation between clinicopathologic variables and GPS by univariate and multivariate analyses. The factors consisted of the following 11 variables: age, gender, pre-operative hemoglobin, surgical procedure, additional radical resection after cholecystectomy, duration of operation, intra-operative blood loss, post-operative complications, T stage based on tumor pathology, status of lymph node metastasis on pathology, and the presence or absence of gallstones.

Clinicopathologic continuous variables were classified into two groups for the Log-rank test and the Cox proportional hazard regression model as follows: age <70 or $\geq$70 years, and pre-operative hemoglobin <12 or $\geq$12.

Recurrence of gallbladder cancer was defined as newly detected local, or distant metastatic tumors by ultrasonography, computed tomography or magnetic resonance image with or without increase in serum carcinoembryonic antigen or carbohydrate antigen 19-9.

This retrospective study was approved by the Ethics Committee of Jikei University School of Medicine (#21-121).

Statistical analysis

Data are expressed as a mean ± standard deviation (SD). Univariate analysis was performed using the non-paired Student's t and χ^2 tests. Analysis of disease-free and overall survival was performed using the Log-rank test for univariate analysis, and the Cox proportional regression model and the logistic regression model with backward elimination stepwise approach for multivariate analysis. All p values were considered statistically significant when the associated probability was less than 0.05.

Results

Patient characteristics

Patient characteristics are outlined in Table 1. Among the study population, the mean age was 67.8 years with a range from 38 to 88 years, and 27 of them were male. Operative procedures consisted of cholecystectomy in 19, liver bed resection with in 22, hepatic resection of segment 4b and segment 5 in 8, and extended right lobectomy in 2 patients, respectively. GPS consisted of GPS 0 in 38, GPS 1 in 8, and GPS 2 in 5 patients, respectively. In GPS 1, 3 patients were classified due to low albumin, and 5 patients were classified due to elevated CRP. Post-operative

Table 1 Patients' characteristics

Factor	Mean ± SD or Rate	Range
Age (years)	67.8 ± 9.7[a]	38–88
Gender (male:female)	27:24	
Pre-operative hemoglobin (g/dl)	12.8 ± 1.6	7.6–16.3
Surgical procedure (C:LBR:S4b + S5:ERL)	19:22:8:2	
Additional radical resection after C (yes:no)	6:35	
Duration of operation (min)	326.7 ± 219.9	45–1,005
Blood loss (g)	925.6 ± 1,357.5	0–7,230
Post-operative complications (present:absent)	12:39	
T stage (pT1: pT2: pT3: pT4)	17:21:5:8	
Lymph node metastasis (pN0:pN1:pN2)	38:6:7	
Gallstones (present:absent)	28:23	
Glasgow prognostic score (GPS 0:GPS 1:GPS2)	38:8:5	

T stage tumor stage based on tumor pathology, *C* cholecystectomy, *LBR* liver bed resection, *S4b + S5* hepatic resection of segment 4b and segment 5, *ERL* extended right lobectomy

[a] mean ± SD

Table 2 Univariate and multivariate analyses of clinicopathologic variables in relation to disease-free and overall survival after elective resection of gallbladder carcinoma

Factor	*N*	DFS univariate analysis		DFS multivariate analysis		OS univariate analysis		OS multivariate analysis	
		Hazard ratio (95 % CI)	*p* Value	Hazard ratio (95 % CI)	*p* Value	Hazard ratio (95 % CI)	*p* Value	Hazard ratio (95 % CI)	*P* value
Age (years)									
≥70	26	1.459	0.402		NS	1.168	0.784		NS
<70	25	(0.6028–3.530)				(0.3867–3.525)			
Gender									
Male	27	0.6590	0.355		NS	0.7008	0.526		NS
Female	24	(0.2722–1.595)				(0.2334–2.104)			
Pre-operative hemoglobin (g/dl)									
≥12	37	0.2928	0.021		NS	0.4005	0.169		NS
<12	14	(0.1032–0.8306)				(0.1087–1.476)			
Post-operative complications									
Present	12	4.757	0.008		NS	7.738	0.006		NS
Absent	39	(1.494–15.15)				(1.818–32.94)			
T stage									
pT3 or pT4	13	18.21	<0.001	3.842	0.006	18.25	<0.001	3.225	0.072
pT1 or pT2	38	(5.172–64.11)		(1.459–10.118)		(3.588–92.85)		(0.901–11.539)	
Lymph node metastasis									
Positive	13	14.13	<0.001	5.817	0.001	26.92	<0.001	7.676	0.002
Negative	38	(4.409–45.26)		(2.077–16.289)		(6.156–117.7)		(2.068–28.487)	
Gall stones									
Present	23	0.6140	0.279		NS	0.9701	0.957		NS
Absent	28	(0.2537 - 1.486)				(0.3250 - 2.895)			
Glasgow prognostic score									
GPS 1 or 2	13	3.321	0.031	4.282	0.006	3.488	0.078	3.782	0.032
GPS 0	38	(1.117–9.876)		(1.527–12.014)		(0.8709–13.97)		(1.119–12.786)	

DFS disease-free survival, *OS* overall survival, *T stage* tumor stage based on tumor pathology, *CI* confidence interval, *NS* not significant

complications developed in 12 of 51 patients (23.5 %), consisting of SSI in 6 (11.8 %), pulmonary complications in 7 (13.7 %), and bile leakage in 2 patients (3.9 %), respectively. In this study, the five-year disease-free and overall survival rates after surgical resection for gallbladder cancer were 49.7 and 67.9 %, respectively.

Univariate and multivariate analyses of clinicopathologic variables in relation to disease-free and overall survival after surgical resection of gallbladder cancer

Table 2 lists the relationship between the clinicopathologic variables and disease-free and overall survival after surgical resection of gallbladder cancer. In univariate analysis of disease-free survival, pre-operative hemoglobin less than 12 g/dl ($p = 0.021$), the presence of post-operative complications ($p = 0.008$), advanced T stage ($p < 0.001$), positive lymph node metastasis ($p < 0.001$), and GPS 1 or 2 (Fig. 1a; $p = 0.031$) were significantly associated with cancer recurrence. In multivariate analysis, advanced T stage ($p = 0.006$), positive lymph node metastasis ($p = 0.001$), and GPS 1 or 2 ($p = 0.006$) were independent risk factors associated with poor disease-free survival.

In univariate analysis of overall survival, the presence of post-operative complications ($p = 0.006$), advanced T stage ($p < 0.001$), and positive lymph node metastasis ($p < 0.001$) were significantly associated with poor overall survival. GPS 1 or 2 tended to be associated with poor overall survival, but not significantly (Fig. 1b; $p = 0.078$). In multivariate analysis, positive lymph node metastasis ($p = 0.002$) and GPS 1 or 2 ($p = 0.032$) were independent

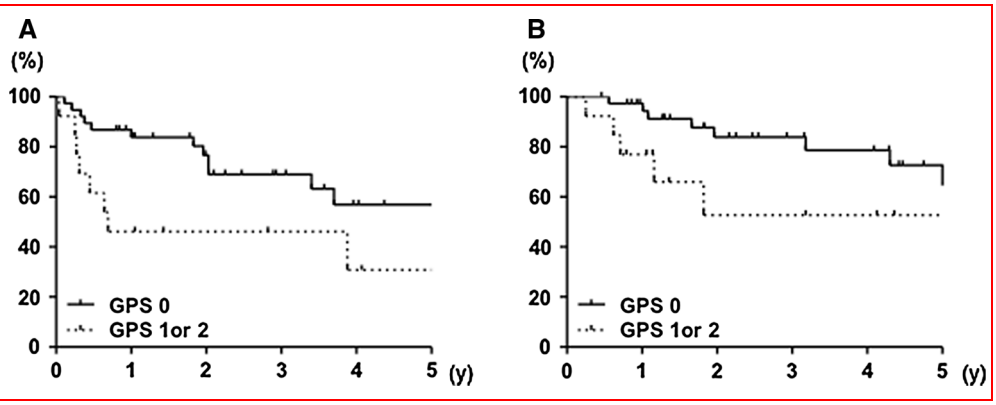

Fig. 1 In statistical analysis, GPS 1 or 2 was an independent risk factor of poor disease-free survival (**a**), and overall survival (**b**)

Table 3 Univariate and multivariate analyses of clinicopathologic variables in relation to Glasgow prognostic score

Factor	Glasgow prognostic score		*p* Value	*p* Value
	GPS 0 ($n = 38$)	GPS 1 or GPS 2 ($n = 13$)	(Univariate)	(Multivariate)
Age (years)	68.0 ± 10.6	67.4 ± 7.0[a]	0.859	NS
Gender (male:female)	21:17	6:7	0.749	NS
Pre-operative hemoglobin (g/dl)	12.9 ± 1.6	12.2 ± 1.6	0.129	NS
Surgical procedure (C:LBR:S4b + S5:ERL)	15:17:6:0	4:5:2:2	0.105	NS
Additional radical resection after C (yes:no)	3:35	3:10	0.165	NS
Duration of operation (min)	269.6 ± 172.7	493.5 ± 262.9	0.001	0.049
Blood loss (g)	711.6 ± 955.6	1,551.2 ± 2,072.1	0.053	0.012
Post-operative complications (present:absent)	8:30	4:9	0.474	NS
T stage (pT1 or pT2:pT3 or pT4)	30:8	8:5	0.274	NS
Lymph node metastasis (positive:negative)	9:29	4:9	0.716	NS
Gallstones (present:absent)	16:22	7:6	0.529	NS

T stage tumor stage based on tumor pathology, *C* cholecystectomy, *LBR* liver bed resection, *S4b + S5* hepatic resection of segment 4b and segment 5, *ERL* extended right lobectomy, *NS* not significant

[a] mean ± SD

risk factors associated with poor overall survival. Advanced T stage tend to be associated with poor overall survival, which however was not significant ($p = 0.072$).

Association between clinicopathologic variables and Glasgow prognostic score

Table 3 lists the relationship between patient characteristics and GPS. Duration of operation in patients with GPS 1 or 2 was longer than those in GPS 0 patients ($p = 0.001$) on univariate analysis. Patients with GPS 1 or 2 tended to have advanced T stage ($p = 0.274$), needed more invasive procedures, such as hepatic resection of segment 4b and segment 5 or extended right lobectomy ($p = 0.105$) and had greater intra-operative blood loss ($p = 0.053$) as compared to those with GPS 0, which however was not significant. In multivariate analysis, duration of operation ($p = 0.049$) and intra-operative blood loss ($p = 0.012$) were independent factors associated with GPS.

Discussion

In patients with gallbladder cancer, the resection rate and the curative resection rate were 69.8 and 37.7 %, respectively in Japan [4]. The depth of tumor invasion through the gallbladder wall and status of lymph node metastasis were strongly associated with therapeutic outcome after resection [4, 12]. In this study, advanced T stage, positive lymph node metastasis, and GPS 1 or 2 were independent risk factors of cancer recurrence in multivariate analysis. Positive lymph node metastasis and GPS 1 or 2 were also independent risk factors of poor overall survival, and advanced T stage tended to be associated with poor overall

survival, but not independently by multivariate analysis. To the best of our knowledge, this is the first report of correlating therapeutic outcome after surgical resection of gallbladder cancer with GPS.

GPS had been reported as a predictor of prognosis in patients with various unresectable cancers of the lung [13, 14], breast [15], esophageal or gastric [16], pancreatic [17], renal [18], and colorectal cancer [19]. For primary resectable cancer patients, GPS is associated with therapeutic outcome in colorectal [6], gastro-esophageal [7], urinary bladder [8], pancreatic [9], renal [10], and non-small-cell lung cancers [11]. We previously reported GPS as a predictor of therapeutic outcome in patients with carcinoma of the ampulla of Vater after pancreaticoduodenectomy [20], unresectable colorectal cancer liver metastasis [21], and of post-operative complication in patients with hepatocellular carcinoma after hepatic resection [22]. However, the reasons for the association between GPS, pre-treatment elevated serum CRP or low serum albumin concentrations, and therapeutic outcome in patients with various malignancies remain unclear [23]. In this study, pre-operative patients status including age, primary resection or additional radical resection after noncurative cholecystectomy, positive or negative lymph node metastasis, and presence or absence of gallstone were comparable in patients with GPS 0, and in those with GPS 1 or 2. On the other hand, patients with GPS 1 or 2 tended to have advanced T stage, and needed more invasive procedure, such as hepatic resection of segment 4b and segment 5 or extended right lobectomy as compared to those with GPS 0, but not significantly. These results suggest that GPS may reflect malignant potential of primary tumor rather than lymph node or distant organ metastasis.

Because survival benefit of adjuvant chemotherapy has not been established on gallbladder cancer after surgery [24], further assessments of mechanism(s) between pre-operative systemic inflammatory response and poor outcome may improve therapeutic outcome of gallbladder cancer after curative resection. Patients' risk stratification using GPS is easy and less invasive, because GPS is composed only of pre-operative serum CRP and albumin concentration, which are routine examinations for peri-operative patients management. GPS therefore is useful for identification of patients at risk of cancer recurrence and poor prognosis after resection for gallbladder cancer.

Conclusion

In conclusion, the GPS upon diagnosis in patients with gallbladder cancer was an independent predictor in disease-free and overall survival after surgical resection. Measurement of the GPS may help decision making in the post-operative management of patients with gallbladder cancer.

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