Glasgow Prognostic Score Predicts Clinical Outcomes in Patients with Pancreatic Cancer Undergoing Adjuvant Gemcitabine Monotherapy After Curative Surgery

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Abstract. *Background/Aim: The Glasgow Prognostic Score (GPS), an inflammation-based prognostic score, has been shown to predict the clinical outcomes of a variety of cancer types. The aim of this study was to determine whether the GPS predicts clinical outcomes of patients with pancreatic cancer treated with adjuvant chemotherapy after surgery. Patients and Methods: Forty patients resected for pancreatic cancer who underwent adjuvant gemcitabine monotherapy after curative surgery were included. The GPS was measured prior to adjuvant therapy and correlated with clinical outcomes. Results: The disease-free survival (DFS) and overall survival (OS) in patients with an elevated GPS (GPS1 or GPS2) were significantly poorer (p=0.001 and p=0.035, respectively, by log-rank test) than patients with a GPS of 0. An elevated GPS was found to be independently associated with poor DFS (p=0.002, by Cox regression model). Conclusion: The pre-adjuvant GPS may predict clinical outcome in patients with pancreatic cancer undergoing adjuvant chemotherapy after surgery.*

Pancreatic cancer remains a malignancy with one of the worst prognoses despite recent advances in cancer treatment. At present, surgery is the only curative approach, and combined treatment with adjuvant gemcitabine, which represents the current gold-standard therapy for resected pancreatic cancer, improves outcomes, although with limited benefits (1). Therefore, predicting the outcomes of such patients is a major challenge in providing more appropriate management for this patient population.

The presence of an ongoing systemic inflammatory response (SIR) has been recognized to be associated with a poor prognosis among oncological patients, and markers of SIR may serve as valuable prognostic or predictive biomarkers in these patients (2). To date, a variety of inflammation-based prognostic scores have been proposed and investigated for their prognostic and predictive value in determining the clinical outcomes of patients with a wide range of cancer types (3, 4).

The Glasgow Prognostic Score (GPS) is an inflammation-based prognostic score derived from the plasma acute-phase C reactive protein (CRP) and serum albumin concentrations (2). A number of studies have identified the prognostic or predictive value of the GPS in patients with various cancer types in either advanced inoperable or operable stages. The GPS is prognostic in patients with inoperable pancreatic cancer (5) as well as inoperable non-small-cell lung cancer (6), and gastroesophageal cancer (7). It is also predictive for survival in patients with pancreatic cancer undergoing surgery (8) similar to that observed for cases of colorectal (9) and gastroesophageal cancers (10). However, its role in patients with pancreatic cancer undergoing adjuvant chemotherapy after curative surgery remains to be clarified. The aim of present study was to determine the relationship between the GPS, which was measured prior to adjuvant therapy, and clinical outcomes of patients undergoing adjuvant gemcitabine monotherapy after curative surgery for pancreatic cancer.

Patients and Materials

Patients. A total of 40 patients with resected pancreatic cancer (23 males and 17 females, 44-76 years of age), who received adjuvant gemcitabine monotherapy after curative surgery at Kanagawa Cancer Center between April 2006 and December 2009, and also

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underwent measurements of both the CRP and albumin levels prior to starting adjuvant chemotherapy were included in this study.

Tumor staging was performed according to the International Union Against Cancer (UICC) classification guidelines 2009 (11). Informed consent was obtained from all patients to use their clinical data for this study, according to the institutional rules of the Kanagawa Cancer Center. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in *a priori* approval by the institution's Human Research Committee (no. 22-38).

Calculation of the GPS. The GPS values of the patients enrolled in this study ware calculated from the CRP and serum albumin levels measured prior to adjuvant gemcitabine chemotherapy. The GPS was calculated with a modification, as follows: patients with both an elevated CRP level (>0.3 mg/dl) and hypoalbuminemia (<3.5 g/dl) were allocated a score of 2; 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.

Adjuvant treatment. Each patient received adjuvant gemcitabine monochemotherapy using one of the following protocols: a biweekly gemcitabine protocol (gemcitabine 1,000 mg/m^2, biweekly for six months) or the standard gemcitabine protocol (gemcitabine 1,000 mg/m^2, days 1, 8 and 15; every four weeks for six months). The treatment was planned to start within 10 weeks after the surgery.

Statistical analysis. The cumulative disease-free survival (DFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method and compared according to the log-rank test. Predictors of outcome were assessed with univariate and multivariate analyses applying the Cox proportional hazard regression model. The stepwise variable selection process was used in the multivariate analysis to identify the most concise model for predicting cumulative survival. For all of the statistical analyses, the level of significance was set at 0.05. The SPSS statistical software program (SPSS for Windows 11.0J; SPSS Inc.; Chicago, IL, USA) was used for all analyses.

Results

Patients. The patient demographics and clinical characteristics are listed in Table I. A total of 29 patients had a primary tumor located in the head of the pancreas, and 11 patients had a primary tumor in the body to tail region. Out of the 40 patients, 39 patients had pT3 stage lesions and 29 had pN1 disease.

Survival analysis. There were 24 patients assigned a score of 0, 12 patients assigned a score of 1 and four patients assigned a score of 2. The median DFS in the patients with a score of 0, 1 and 2 was 11.0, 5.9, and 3.6 months, respectively. The median OS in the patients with a score of 0, 1 and 2 was 23.9, 10.3, and 9.9 months, respectively.

When the DFS and OS were compared between patients with a GPS of 0 and those with a GPS of 1or 2, the DFS and OS rates for patients allocated a GPS of 1 or 2 were significantly poorer (p=0.001 and p=0.035, respectively, by log-rank test) than for patients with a GPS of 0 (Figure 1).

Table I. *Baseline patient characteristics*.

Characteristic	Value
Age, median (range), years	62.5 (44-76)
Gender, male/female	23/17
Primary location, head/body to tail	29/11
Tumor size	
≤4.0 cm	23
>4.0 cm	17
pT Stage	
T1,T2	1
T3	39
pN Stage	
N0	11
N1	29
Resection status	
R0	24
R1	16
Histology	
Well to moderately differentiated	33
Poorly differentiated	5
Mucinous	2

The GPS (p=0.002) and microscopic lymphatic invasion (p=0.036) were significant factors affecting DFS according to the univariate analysis, and a multivariate analysis using these variables indicated that both the GPS (p=0.002) and microscopic lymphatic invasion (p=0.032) were independently associated with the DFS in patients receiving adjuvant chemotherapy (Table II).

According to the univariate analysis, the GPS (p=0.039) and microscopic lymphatic invasion (p=0.024) were significant factors affecting OS. The results of a multivariate analysis using the GPS, microscopic lymphatic invasion and microscopic vascular invasion indicated that microscopic lymphatic invasion (p=0.035) was an independent factor associated with OS (Table III).

Discussion

In the present study, we found that the presence of SIR, as evaluated according to the GPS, is significantly associated with a poor clinical outcome of patients with pancreatic cancer undergoing adjuvant gemcitabine monotherapy after curative surgery. An elevated GPS, measured prior to the administration of adjuvant gemcitabine therapy, significantly correlated with a poor DFS and remained an independent risk factor for early recurrence as did microscopic lymphatic invasion.

It has been recognized that the outcomes of oncological patients are determined by both tumor-related and patient-related factors, such as the presence of an ongoing SIR (2).

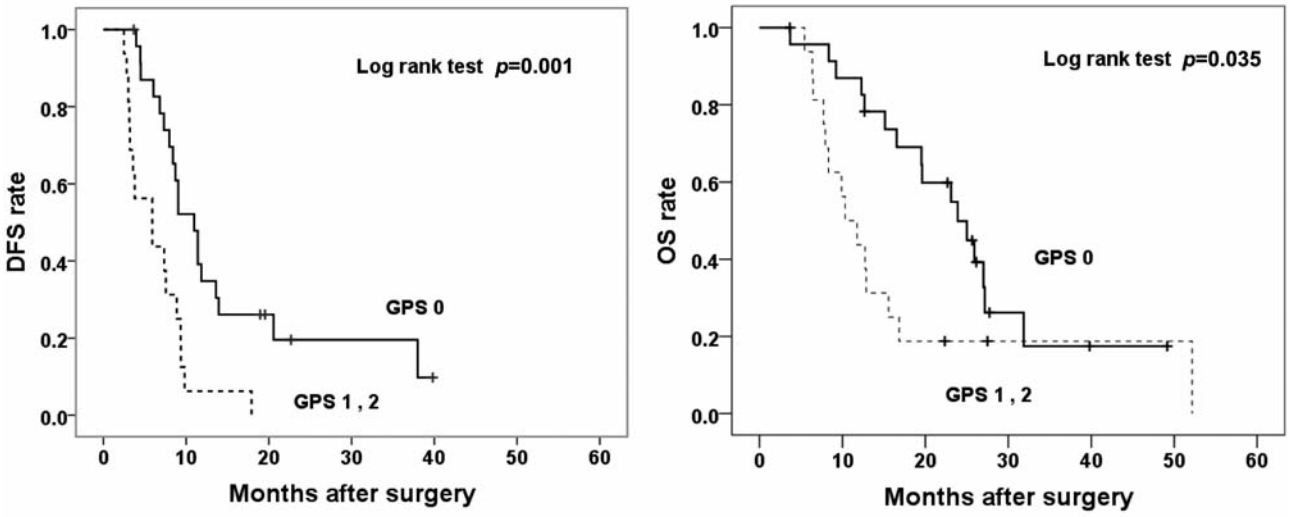

Figure 1. *DFS and OS according to the GPS. The DFS and OS of the patients with elevated GPS values (GPS 1 or 2) were significantly shorter (p=0.001 and p=0.035, respectively by log-rank test) than those recorded for the patients with normal CRP and albumin levels.*

Table II. *Univariate and multivariate analyses for disease free survival.*

		Univariate		Multivariate	
Variable	No.	HR(95%CI)	*p*-Value	HR(95%CI)	*p*-Value
Primary location					
Head	29	1			
Body-tail	11	0.902 (0.420-1.935)	0.790		
Tumor size					
≤4.0 cm	23	1			
>4.0 cm	17	1.707 (0.851-3.426)	0.132		
pN Stage					
N0	11	1			
N1	29	1.475 (0.686-3.168)	0.319		
Resection status					
R0	24	1			
R1	16	1.421 (0.720-2.806)	0.311		
Histology					
Well to moderately differentiated	33	1			
Poorly differentiated	5				
Mucinous	2	1.270 (0.605-2.503)	0.567		
GPS status					
0	24	1		1	
1,2	16	3.118 (1.536-6.333)	0.002	3.263 (1.564-6.805)	0.002
Microscopic vascular invasion					
None	13	1			
Minimal to moderate	25				
Marked	2	1.653 (0.891-3.056)	0.111		
Microscopic lymphatic invasion					
None	8	1		1	
Minimal to moderate	30				
Marked	2	2.304 (1.055-5.035)	0.036	2.424 (1.079-5.447)	0.032
Microscopic perineural invasion					
None	9	1			
Minimal to moderate	17				
Marked	14	1.281 (0.832-1.974)	0.261		

Table III. *Univariate and multivariate analyses for overall survival.*

Variables	No.	Univariate		Multivariate	
		HR(95%CI)	*p*-Value	HR(95%CI)	*p*-Value
Primary location					
Head	29	1			
Body-tail	11	1.213 (0.551-2.673)	0.631		
Tumor size					
≤4.0 cm	23	1			
>4.0 cm	17	1.426 (0.686-2.963)	0.341		
pN Stage					
N0	11	1			
N1	29	1.918 (0.776-4.738)	0.158		
Resection status					
R0	24	1			
R1	16	1.268 (0.597-2.691)	0.537		
Histology					
Well to moderately differentiated	33	1			
Poorly differentiated	5				
Mucinous	2	1.078 (0.492-2.359)	0.851		
GPS status					
0	24	1		1	
1,2	16	2.196 (1.040-4.633)	0.039	2.049 (0.969-4.293)	0.061
Microscopic vascular invasion					
None	13	1		1	
Minimal to moderate	25				
Marked	2	1.922 (0.922-4.005)	0.081	1.714 (0.791-3.715)	0.172
Microscopic lymphatic invasion					
None	8	1		1	
Minimal to moderate	30				
Marked	2	3.179 (1.165-8.670)	0.024	3.195 (1.086-9.397)	0.035
Microscopic perineural invasion					
None	9	1			
Minimal to moderate	17				
Marked	14	1.178 (0.736-1.884)	0.494		

To date, a variety of inflammation-based prognostic markers, including the CRP level (12, 13), GPS (5-10), neutrophil to lymphocyte ratio (NLR)(14, 15) or platelet lymphocyte ratio (PLR)(15, 16), have been proposed and investigated for their prognostic and predictive value for determining the clinical outcomes of patients with a variety of cancer types and stages. These markers have been shown to be prognostic in patients with inoperable advanced cancer, and predictive of the clinical outcomes of patients undergoing surgery or palliative chemotherapy (17).

However, only few reports are available that have investigated the prognostic/predictive value of inflammation-based prognostic markers in the adjuvant setting. The presence of an SIR, as measured based on the CRP level, was significantly associated with a poor outcome in patients receiving adjuvant 5-FU-based chemotherapy after potentially curative resection for colorectal cancer (13), as was the modified GPS (18).

As in other cancer types, the association of SIR with the clinical course of pancreatic cancer has been fully-investigated in patients with advanced inoperable disease and those undergoing surgery. Higher levels of CRP (19) or an elevated GPS at diagnosis (5) have been shown to be significantly associated with a poor survival in patients with metastatic or locally advanced pancreatic cancer. Elevated CRP (12), PLR (16), or modified GPS (8) values have also been shown to be predictive of poor survival in patients undergoing surgery for pancreatic cancer.

However, the relationships between inflammation-based prognostic markers and the clinical outcomes of pancreatic cancer patients undergoing adjuvant chemotherapy after surgery have not been thoroughly investigated. A sub-group analysis of the above study (8), which investigated the prognostic value of the GPS in patients undergoing potentially curative surgery for pancreatic cancer, showed that an elevated preoperative GPS was associated with

reduced survival in the subgroup of patients who received adjuvant chemotherapy.

However, the results of this previous study may have some limitations, as the GPS was measured prior to surgery, not before adjuvant chemotherapy. In that study, the preoperative GPS was found to be associated with OS in both the whole patient analysis, which included patients treated with and without adjuvant therapy, and the sub-group analysis, which included patients treated with adjuvant therapy. In order to clearly estimate the predictive value of the GPS in patient undergoing adjuvant chemotherapy, the GPS values should be measured prior to adjuvant therapy with the goal of excluding the treatment effect of surgery. To our knowledge, the present study is the first to calculate the GPS values before starting adjuvant therapy and to correlate the values with the clinical outcomes of patients undergoing adjuvant gemcitabine therapy.

Our results indicate that the GPS measured prior to adjuvant therapy is predictive of early recurrence in patients with pancreatic cancer undergoing adjuvant gemcitabine monotherapy after curative surgery and may lead to more appropriate management of such patients. However, a further prospective validation study in a larger sample size is required to confirm these findings, as the present study was retrospective and small in scale.

Conclusion

An elevated pre-adjuvant GPS is significantly associated with a poor DFS in patients with pancreatic cancer undergoing adjuvant gemcitabine monotherapy after curative resection and may serve as a significant predictive or prognostic biomarker for appropriately managing these patients.

Conflicts of Interest

The Authors declare no conflicts of interest with regard to this study.

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