Glasgow Prognostic Score as a Prognostic Factor in Patients Undergoing Curative Surgery for Colorectal Cancer

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Key Words

Glasgow Prognostic Score · Prognostic factor · Colorectal cancer · Hypoalbuminemia · C-reactive protein · Inflammation

Abstract

Background/Aims: Systemic inflammatory responses have been reported to be independent predictors of cancer-specific survival in colorectal cancer. The Glasgow Prognostic Score (GPS), which is an inflammation-based prognostic factor, is defined by the presence of elevated C-reactive protein and hypoalbuminemia. The purpose of this study was to estimate whether GPS can be a prognostic factor in patients undergoing curative surgery for colorectal cancers. **Methods:** We studied 166 patients with stage II (TNM classification) and 200 patients with stage III who had undergone curative surgery for colorectal cancer between 1999 and 2004. Univariate and multivariate analyses were performed to evaluate the relationship between clinicopathological factors and prognosis. **Results:** Among patients with stage II, location and GPS were independent factors on multivariate analysis. In particular, GPS was revealed to be the strongest factor in cancer-specific survival (HR: 7.43, 95% confidence interval, CI: 2.86–19.30, $p < 0.0001$). On the other hand, among patients with stage III, the number of metastatic

lymph nodes was the only independent factor on multivariate analysis (HR: 1.14, 95% CI: 1.07–1.20, $p < 0.0001$). GPS was not a prognostic factor in cancer-specific survival in stage III. **Conclusion:** Among patients with stage II, GPS was predictive of cancer-specific survival.

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Introduction

Colorectal cancer remains one of the most common causes of cancer death in Japan, where it accounts for the greatest number of deaths from malignant neoplasms in women and the third greatest number in men [1]. Whereas TNM stage has been widely used in colorectal cancer, it fails to clearly distinguish patients who will survive long-term from those with poor outcome after potentially curative surgery [2]. In particular, there is considerable interest in identifying those patients with TNM stage II disease who are at high risk of developing recurrence and subsequently dying of their disease, as they may be suitable for adjuvant chemotherapy [3]. Therefore, there remains a continuing need to identify clinically relevant factors that would improve the prediction of survival in patients undergoing potentially curative surgery for colorectal cancer [2]. It has long been recognized that low

circulating albumin concentrations before surgery are associated with poor outcome in patients with colorectal cancer [4–6]. It has also been shown that elevated circulating C-reactive protein (CRP) concentrations before surgery are associated with poor outcome after resection for colorectal cancer [7–9]. It is therefore of interest that the combination of hypoalbuminemia and an elevated CRP, as in the Glasgow Prognostic Score (GPS), has been reported to be useful for providing additional prognostic information in patients with advanced cancer [2, 10, 11]. However, there are few reports about the prognostic value of this combination in primary operable colorectal cancer. In this study, we investigated the significance of GPS as a prognostic factor in patients with colorectal cancer.

Methods

Patient Selection

We retrospectively reviewed the database of 166 patients with stage II (TNM classification, ed 7 [12]) and 200 patients with stage III who had undergone curative surgery for colorectal cancer at our Department between 1999 and 2004. None of these patients had received preoperative chemotherapy or radiation therapy. Cases of emergency operation due to perforation and ileus, bowel obstruction requiring transnasal or transanal drainage, other inflammatory morbidities such as collagen-vascular disease, and patients that died because of noncancer-related causes were excluded from this study. The median follow-up period for survivors was 70.8 months.

About GPS

We used laboratory data on admission to calculate GPS. GPS was estimated as described previously [2]. Briefly, GPS consists of the combination of an elevated CRP (>10 mg/l) and hypoalbuminemia (35 g/l). Patients with both abnormalities were given a score of 2, and they were placed in the high GPS group. Patients that demonstrated only one or none of these abnormalities were given a score of 1 or 0, respectively, and were placed in the low GPS group.

Clinicopathological Analysis

Clinicopathological factors such as gender (male/female), age ($\leq 70/71 \leq$), location (colon/rectum), invasion depth (TNM classification, ed 7: T1–T3/T4), differentiation (well-differentiated adenocarcinoma/other), presence of lymphatic invasion (–/+), degree of lymphatic invasion (none-mild/moderate-severe), presence of venous invasion (–/+), degree of venous invasion (none-mild/moderate-severe), preoperative serum carcinoembryonic antigen, number of dissected lymph nodes ($<12/12 \leq$), number of metastatic lymph nodes, residual tumor (R0: no residual tumor/R1: no residual tumor; however, tumor is suspected at the resection margin), postoperative adjuvant chemotherapy (–/+), GPS (low/high) and survival data were analyzed to determine prognostic factors related to cancer-specific survival.

Pathological Examination

All specimens were examined in the following manner. After resection of the primary tumor, the excised specimen was opened on the antimesenteric side by the surgeon. The surgeon identified the lymph nodes, isolated them, and recorded both their number and distribution. After formalin fixation, the specimens and lymph nodes were examined by the pathologist.

Postoperative Adjuvant Chemotherapy

The eligibility criteria in this study included high-risk stage II or stage III colorectal cancer. Stage II colorectal cancers with serosa invasion or lymphatic/venous invasion were defined as the high-risk stage II patients. Patient criteria included an Eastern Cooperative Oncology Group performance status of 0–2. Additionally, patients had to have no serious or uncontrolled comorbidities. Patients received 5-FU drugs orally for more than 6 months.

Statistical Analysis

Discrete variables were compared using Fisher's exact probability test, and continuous variables were compared using the Mann-Whitney U test. Clinicopathological factors, for which there was a significant difference in the univariate analysis, were used as covariables for the multivariate analysis. For the multivariate analysis, the Cox proportional-hazard model was used, with the hazard ratio as a measure of association by applying a stepwise procedure. The survival rate was calculated using the Kaplan-Meier method, and univariate analyses were performed using the log-rank test. Data were analyzed statistically using JMP 9.0.2 software (SAS Institute Inc., Cary, N.C., USA). Differences were considered statistically significant at $p < 0.05$. Values are expressed as median (range).

Results

Comparisons of clinicopathological factors between the high GPS group and the low GPS group are shown in table 1. We discovered there were two factors that affected GPS levels. In terms of age, the high GPS group was significantly higher than the low GPS group ($p = 0.02$). And, there was a tendency toward a higher proportion of invasion depth T4 in the high GPS group compared with the low GPS group ($p = 0.08$). However, there was no significant difference in other clinicopathological factors. Table 2 shows the relationship between the clinicopathological factors and cancer-specific survival. On univariate analyses, there were significant differences in tumor invasion depth ($p < 0.0001$), the degree of lymphatic invasion ($p < 0.0001$), the degree of venous invasion ($p = 0.0003$), the number of metastatic lymph nodes ($p < 0.0001$), residual tumor ($p = 0.0001$) and GPS ($p = 0.0002$). On multivariate analyses using these clinicopathological factors that had significant differences in univariate analyses, tumor invasion depth (HR: 4.06, 95% confidence interval, CI: 1.54–10.72, $p = 0.005$), de-

Table 1. Comparisons of clinicopathological factors between the high GPS group and the low GPS group

Clinicopathological factor	Category	High GPS (n = 31)	Low GPS (n = 335)	p value
Gender	M/F	14/17	195/140	0.19
Age	≤70/71≤	14/17	226/109	0.02
Location	colon/rectum	26/5	267/68	0.81
Invasion depth	T1–T3/T4	16/15	227/108	0.08
Differentiation	well/other	13/18	149/186	0.85
Presence of lymphatic invasion	–/+	1/30	3/332	0.30
Degree of lymphatic invasion	NM/MS ^a	17/14	155/180	0.45
Presence of venous invasion	–/+	1/30	22/313	0.71
Degree of venous invasion	NM/MS ^a	17/14	207/128	0.45
Preoperative serum CEA	≤3.0/>3.0 µg/dl	14/17	140/195	0.71
Dissected lymph nodes	<12/12≤	5/26	67/268	0.81
Metastatic lymph nodes		0 (0–5)	1 (0–26)	0.17
Residual tumor	R0 ^b /R1 ^c	21/10	232/103	0.84
TNM stage ^d	II/III	18/13	148/187	0.19

CEA = Carcinoembryonic antigen.

^a None-mild invasion/moderate-severe invasion. ^b No residual tumor. ^c No residual tumor; however, tumor is suspected at the resection margin. ^d TNM ed 7.

Table 2. Relationship between clinicopathological factors and cancer-specific survival in all cases

Clinicopathological factor	Category	Univariate analysis p value	Multivariate analysis	
			HR (95% CI)	p value
Gender		0.81		
Age	≤71	0.17		
Location	rectum	0.15		
Invasion depth	T4	<0.0001	4.06 (1.54–10.72)	0.005
Differentiation	Mod, Por, Muc	0.06		
Presence of lymphatic invasion	+	0.33		
Degree of lymphatic invasion	moderate-severe invasion	<0.0001	2.03 (1.14–3.60)	0.02
Presence of venous invasion	+	0.05		
Degree of venous invasion	moderate-severe invasion	0.0003	1.35 (0.81–2.24)	0.24
Preoperative serum CEA	>3.0 µg/dl	0.06		
Dissected lymph nodes	<12	0.38		
Metastatic lymph nodes		<0.0001	1.15 (1.09–1.21)	<0.0001
Residual tumor	R1 ^a	0.0001	0.51 (0.19–1.35)	0.17
Postoperative adjuvant chemotherapy ^b	+	0.13		
GPS	high	0.0002	3.09 (1.65–5.79)	0.0004

Mod = Moderately differentiated adenocarcinoma; Por = poorly differentiated adenocarcinoma; Muc = mucinous adenocarcinoma.

^a No residual tumor; however, tumor is suspected at the resection margin.

^b 5-FU drugs administrated orally for more than 6 months after the operation.

gree of lymphatic invasion (HR: 2.03, 95% CI: 1.14–3.60, $p = 0.02$), number of metastatic lymph nodes (HR: 1.15, 95% CI: 1.09–1.21, $p < 0.0001$) and GPS (HR: 3.09, 95% CI: 1.65–5.79, $p = 0.0004$) were associated significantly with cancer-specific survival. Kaplan-Meier analysis

demonstrated a significant difference between the low GPS group (5-year cancer-specific survival: 84.0%) and the high GPS group (5-year cancer-specific survival: 57.6%; $p = 0.0002$; fig. 1). Moreover, comparing cancer-specific survival between the high GPS group and the low

Fig. 1. Relationship between GPS and cancer-specific survival (CSS).

Table 3. Relationship of clinicopathological factors and cancer-specific survival in patients with stage II

Clinicopathological factor	Category	Univariate analysis p value	Multivariate analysis	
			HR (95% CI)	p value
Gender		0.06		
Age	≤71	0.20		
Location	rectum	0.005	2.68 (1.14–6.29)	0.02
Invasion depth	T4	0.0002	1.74 (0.38–8.07)	0.48
Differentiation	Mod, Por, Muc	0.21		
Presence of lymphatic invasion	+	0.50		
Degree of lymphatic invasion	moderate-severe invasion	0.05		
Presence of venous invasion	+	0.06		
Degree of venous invasion	moderate-severe invasion	0.13		
Preoperative serum CEA	>3.0 µg/dl	0.11		
Dissected lymph nodes	<12	0.28		
Residual tumor	R1 ^a	0.007	1.93 (0.43–8.65)	0.39
Postoperative adjuvant chemotherapy ^b	+	0.54		
GPS	high	<0.0001	7.43 (2.86–19.30)	<0.0001

^a No residual tumor; however, tumor is suspected at the resection margin.

^b 5-FU drugs administrated orally for more than 6 months after the operation

GPS group in each stage, among patients with stage II there was a significant difference between the two groups ($p < 0.0001$; fig. 2). However, among patients with stage III, there was no significant difference ($p = 0.53$). Prognostic factors for each stage are shown in tables 3 and 4. Among patients with stage II, location and GPS were independent factors on multivariate analysis (table 3). In

particular, GPS was revealed to be the strongest factor in cancer-specific survival (HR: 7.43, 95% CI: 2.86–19.30, $p < 0.0001$). On the other hand, among stage III patients, number of metastatic lymph nodes was the only independent factor on multivariate analysis (HR: 1.14, 95% CI: 1.07–1.20, $p < 0.0001$; table 4). GPS was not a prognostic factor in cancer-specific survival in stage III. Com-

Fig. 2. Comparisons of CSS between the high GPS group and the low GPS group in each stage.

Fig. 3. Comparisons of CSS between the subgroups in each stage.

parisons of cancer-specific survival between the subgroups in each stage are shown in figure 3. Cancer-specific survival among patients with high GPS in stage II was worse than that among patients in stage IIC. On the other hand, cancer-specific survival among patients with

low GPS in stage III was equivalent to that among patients in stage IIIB. Cancer-specific survival among patients with high GPS in stage III was equivalent to the middle between that among patients in stage IIIB and IIIC.

Table 4. Relationship of clinicopathological factors and cancer-specific survival in patients with stage III

Clinicopathological factor	Category	Univariate analysis p value	Multivariate analysis	
			HR (95% CI)	p value
Gender		0.29		
Age	≤71	0.21		
Location	rectum	0.81		
Invasion depth	T4	0.001	3.06 (0.72–12.97)	0.13
Differentiation	Mod, Por, Muc	0.22		
Presence of lymphatic invasion	+	0.54		
Degree of lymphatic invasion	moderate-severe invasion	0.003	2.04 (0.83–5.03)	0.12
Presence of venous invasion	+	0.24		
Degree of venous invasion	moderate-severe invasion	0.001	1.54 (0.81–2.95)	0.19
Preoperative serum CEA	>3.0 µg/dl	0.23		
Dissected lymph nodes	<12	0.83		
Metastatic lymph nodes		0.003	1.14 (1.07–1.20)	<0.0001
Residual tumor	R1 ^a	0.003	0.55 (0.13–2.43)	0.43
Postoperative adjuvant chemotherapy ^b	+	0.05		
GPS	high	0.53		

^a No residual tumor; however, tumor is suspected at the resection margin.

^b 5-FU drugs administrated orally for more than 6 months after the operation.

Discussion

The GPS, a combination of sensitive (CRP) and insensitive (albumin) acute-phase proteins, has a number of advantages compared with other biological markers that are considered to have prognostic value [2]. Primarily, GPS can be estimated by both CRP and albumin, which are simple and standard reliable laboratory measurements. Therefore, it is likely that the GPS would be useful in the routine assessment of patients with primary operable colorectal cancer [2]. The results of this study also showed that the combination of an elevated CRP concentration and hypoalbuminemia (GPS) was associated with cancer-specific survival after potentially curative resection in patients with colorectal cancer. The results of the present study in patients with primary operable colorectal cancer are consistent with the prognostic value of the GPS previously reported in patients with advanced colorectal cancer [2, 10, 11]. Moreover, in this study, GPS was predictive of cancer-specific survival in patients with stage II colorectal cancer. However, in patients with stage III, GPS was not a predictive factor for cancer-specific survival. McMillan et al. [2] also reported a similar result that GPS was predictive of cancer-specific survival in patients with stage II. It was of interest that, in this study, elevated GPS before surgery was

not associated with TNM stage. McMillan et al. [2] also described that the prognostic value of preoperative GPS was independent of TNM stage. On the other hand, it was reported that TNM stage showed a close relationship with GPS in patients with all stages including stage IV [10]. The reason GPS was not a predictive factor for cancer-specific survival in patients with stage III should be considered. Because stage III appears at the advanced stage of colorectal cancer, cancer-specific survival will be low regardless of GPS.

The mechanism by which GPS might reflect cancer-specific survival is not clear. However, it is believed that systemic inflammatory response-related factors reflect the tumor microenvironment, including tumor versus host interaction, and are regarded as host-related factors induced by the tumor [13]. Several studies have also revealed that cancer promotes the release of proinflammatory cytokines from tumor cells [14] or the immunovascular system [15], and that a close relationship exists between inflammation and cancer. In addition, increased CRP levels in patients with cancer could also be caused by an inflammatory response to tumor infiltration or the microenvironment of a tumor infiltrated by lymphocytes [16], reflecting immunoreactive processes. Indeed, there is increasing evidence that high serum CRP level also correlated with shorter survival in pa-

tients with colorectal cancer [17–19]. Similarly, it is estimated that low albumin levels are associated with a significantly decreased survival time because low albumin level likely reflects some type of systemic compromise [20].

The results of this study indicate that GPS, which reflects both the contribution of the tumor and the host response, differentiates between low- and high-risk stage II in patients undergoing curative resection for colorectal cancer. In this study, there were few patients with high GPS in stage II. Cancer-specific survival among patients with high GPS in stage II was worse than that among pa-

tients with low or high GPS in stage III. Therefore, GPS may be useful in identifying high-risk stage II patients that are suitable for adjuvant therapy.

Conclusions

The results of this study indicate that GPS is predictive of cancer-specific survival among patients with stage II undergoing curative resection for colorectal cancer. Therefore, GPS may be useful in identifying high-risk stage II patients that are suitable for adjuvant therapy.

References

- 1 Kayama T, Wakao F, Sobue T, Katanoda K, Tsukuma H, Mikami H, Kitai A: Cancer statistics in Japan-2011. Tokyo, Foundation for Promotion of Cancer Research, 2011.
- 2 McMillan DC, Crozier JE, Canna K, Angerson WJ, McArdle CS: Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. *Int J Colorectal Dis* 2007;22: 881–886.
- 3 Graziano F, Cascinu S: Prognostic molecular markers for planning adjuvant chemotherapy trials in Dukes' B colorectal cancer patients: how much evidence is enough? *Ann Oncol* 2003;14:1026–1038.
- 4 Longo WE, Virgo KS, Johnson FE, Wade TP, Vernava AM, Phelan MA, Henderson WG, Daley J, Khuri SF: Outcome after proctectomy for rectal cancer in Department of Veterans Affairs Hospitals: a report from the National Surgical Quality Improvement Program. *Ann Surg* 1998;228:64–70.
- 5 Heys SD, Walker LG, Deehan DJ, Eremin OE: Serum albumin: a prognostic indicator in patients with colorectal cancer. *J R Coll Surg Edinb* 1998;43:163–168.
- 6 Longo WE, Virgo KS, Johnson FE, Oprian CA, Vernava AM, Wade TP, Phelan MA, Henderson WG, Daley J, Khuri SF: Risk factors for morbidity and mortality after colectomy for colon cancer. *Dis Colon Rectum* 2000;43:83–91.
- 7 Nozoe T, Matsumata T, Kitamura M, Sugimachi K: Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. *Am J Surg* 1998;176:335–338.
- 8 Nielsen HJ, Christensen IJ, Sorensen S, Moesgaard F, Brunner N: Preoperative plasma plasminogen activator inhibitor type-1 and serum C-reactive protein levels in patients with colorectal cancer. The RANX05 Colorectal Cancer Study Group. *Ann Surg Oncol* 2000;7:617–623.
- 9 McMillan DC, Canna K, McArdle CS: Systemic inflammatory response predicts survival following curative resection of colorectal cancer. *Br J Surg* 2003;90:215–219.
- 10 Ishizuka M, Nagata H, Takagi K, Horie T, Kubota K: Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. *Ann Surg* 2007;246:1047–1051.
- 11 Ishizuka M, Kita J, Shimoda M, Rokkaku K, Kato M, Sawada T, Kubota K: Systemic inflammatory response predicts postoperative outcome in patients with liver metastases from colorectal cancer. *J Surg Oncol* 2009; 100:38–42.
- 12 Sobin LH, Gospodarowicz MK, Wittekind Ch: TNM Classification of Malignant Tumours, ed 7. New York, Wiley-Blackwell, 2009, pp 100–105.
- 13 Ishizuka M, Nagata H, Takagi K, Kubota K: Systemic inflammatory response Associated with distant metastasis of T1 or T2 colorectal cancer. *Dig Dis Sci* 2010;55:3181–3187.
- 14 Balkwill F, Mantovani A: Inflammation and cancer: back to Virchow? *Lancet* 2001;357: 539–545.
- 15 ten Kate M, Holfland LJ, van Koetsveld PM, Johannes J, van Eijck CHJ: Pro-inflammatory cytokines affect pancreatic carcinoma cell. Endothelial cell interactions. *JOP* 2006;7: 454–464.
- 16 Canna K, McArdle PA, McMillan DC, McNicol AM, Smith GW, Mckee RF, McArdle CS: The relationship between tumour T-lymphocyte infiltration, the systemic inflammatory response and survival in patients undergoing curative resection for colorectal cancer. *Br J Cancer* 2005;92:651–654.
- 17 Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ: C-reactive protein and the risk of incident colorectal cancer. *JAMA* 2004;291:585–590.
- 18 Gunter MJ, Stolzenberg-Solomon R, Cross AJ, Leitzmann MF, Weinstein S, Wood RJ, Virtamo J, Taylor PR, Albanes D, Sinha R: A prospective study of serum C-reactive protein and colorectal cancer risk in men. *Cancer Res* 2006;66:2483–2487.
- 19 Wong VK, Malik HZ, Hamady ZZ, Mukhtar AAI, Gomez D, Prasad KR, Toogood GJ, Lodge JPA: C-reactive protein as a predictor of prognosis following curative resection for colorectal liver metastasis. *Br J Cancer* 2007; 96:222–225.
- 20 Dixon MR, Haukoos JS, Udani SM, Naghi JJ, Arnell TD, Kumar RR, Stamos MJ: Carcinoembryonic antigen and albumin predict survival in patients with advanced colon and rectal cancer. *Arch Surg* 2003;138:962–966.