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Glasgow prognostic score and combined positive score for locally advanced rectal cancer

Yanru Feng[1,2], Jialin Luo[1,2], Peng Liu[1,2], Luying Liu[1,2], Yuan Zhu[1,2], Guoping Cheng[3], Linfeng Zheng[3]

[1]Department of Radiation Oncology, The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer, Chinese Academy of Sciences, Hangzhou, China
[2]Zhejiang Key Laboratory of Radiation Oncology, Hangzhou, China
[3]Department of Pathology, The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer, Chinese Academy of Sciences, Hangzhou, China

Purpose: This study was performed to investigate the association of Glasgow prognostic score (GPS), combined positive score (CPS), and clinicopathological characteristics of locally advanced rectal cancer.
Methods: Between February 2012 and February 2018, 103 patients with locally advanced rectal cancer treated by neoadjuvant chemoradiotherapy and total mesorectal excision (TME) were retrospectively evaluated.
Results: According to the classification of the GPS, 85 (82.5%), 13 (12.6%), and 5 patients (4.9%) were classified as a score of 0, 1, and 2, respectively. Patients were classified into the GPS-low group (GPS of 0, n = 85) and GPS-high group (GPS of 1 or 2, n = 18) with an area under the curve of 0.582 for overall survival (OS). The mean programmed death-ligand 1 (PD-L1) CPS of the whole group was 2.24 (range, 0–70). The PD-L1 CPS of the GPS-high group was higher than the GPS-low group ($P < 0.001$). Multivariate analysis by Cox proportional hazards model indicated that GPS was associated with OS and disease-free survival (DFS). Furthermore, PD-L1 CPS was associated with DFS (hazard ratio, 1.050; 95% confidence interval, 1.017–1.083; $P = 0.003$).
Conclusion: Elevated GPS was related to the PD-L1 CPS. GPS and PD-L1 CPS were associated with the prognosis of locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy followed by TME.
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Key Words: Inflammation, Programmed cell death 1 ligand 2 protein, Rectal neoplasms, Survival

INTRODUCTION

Currently, the standard treatment of locally advanced rectal cancer consists of neoadjuvant chemoradiotherapy and total mesorectal excision (TME) [1]. About 30% of patients develop treatment failure after this multidisciplinary approach [1,2]. Immune checkpoint inhibitors, such as programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies, have recently been incorporated in treatment regimens for some gastrointestinal malignancies including locally advanced rectal cancer [3,4]. A meta-analysis of PD-L1 indicated that PD-L1 did not appear useful as a prognostic marker for rectal cancer [5]. As the combined positive score (CPS) is adopted for gastric and gastroesophageal junction cancer, the role of CPS for rectal cancer should be evaluated.

Systemic inflammation including elevated serum proinflam-

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Corresponding Author: Linfeng Zheng
Department of Pathology, The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer, Chinese Academy of Sciences, No. 1, East Banshan Road, Gongshu District, Hangzhou 310022, China
Tel: +86-571-88128148, **Fax:** +86-571-88122062
E-mail: linfengzheng2016@126.com
ORCID: https://orcid.org/0000-0001-9889-4919

matory cytokines and acute-phase proteins levels is an indicator of poor prognosis for rectal cancer. Many markers of systemic inflammation include ratios, or scores of acute-phase proteins or circulating white cells, such as Glasgow prognostic score (GPS) determined by serum CRP and albumin [6,7]. In tumor microenvironments, immune cells could produce cytokines and chemokines. However, the relationship between local immune response and systemic inflammation is controversial [6]. During the course of azoxymethane (AOM)/dextran sulfate sodium (DSS)-induced colitis and colitis-associated colorectal cancer, upregulation of PD-L1 throughout the AOM/DSS regime was observed and upregulation of PD-1 expression on mucosal T-cell subsets of the colon and the ileum correlated with disease progression [8]. The aim of the present study was to investigate the association of GPS, CPS, and clinicopathological characteristics of locally advanced rectal cancer.

METHODS

This study was approved by the independent ethics committee of Zhejiang Cancer Hospital (No. IRB-2020-15). It was performed in accordance with the Declaration of Helsinki and written informed consent was waived due to its retrospective nature.

Patients

Between February 2012 and February 2018, 108 patients with locally advanced rectal cancer treated by neoadjuvant chemoradiotherapy and TME were retrospectively evaluated. Of these 108 patients, 5 were excluded from the present analysis for limited rectal biopsy specimens. Pelvic intensity-modulated radiotherapy (IMRT) consisted of 45–50.4 gray (Gy) in 25–28 fractions at 1.8–2.0 Gy per daily fraction. Capecitabine or capecitabine plus oxaliplatin was given concurrently with pelvic IMRT excluding 2 old-age patients. TME was performed 6 to 8 weeks after completion of neoadjuvant chemoradiotherapy. Adjuvant capecitabine-based chemotherapy was used at the discretion of the attending physicians of the individual patients. All patients were staged by the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. The system is used to grade tumor response after neoadjuvant chemoradiotherapy as recommended by the AJCC Cancer Staging Manual, 8th edition.

Definition of Glasgow prognostic score

Blood samples were drawn and assayed within 2 weeks before neoadjuvant chemoradiotherapy. Based on a previous study, the GPS was determined as follows: patients with neither elevated CRP level (>10 mg/dL) nor hypoalbuminemia (<3.5 g/dL) were classified as a score of 0, and patients developing 1 or both of these blood chemistry abnormalities were classified as a score of 1 or 2, respectively.

Immunohistochemistry

Immunohistochemistry (IHC) of 5-μm sections from formalin-fixed paraffin-embedded tissue of rectal biopsy specimens was performed with PD-L1 (Clone MIH1, dilution of 1:50; eBioscience, San Diego, CA, USA). H&E sections were also reviewed for the presence of tumors. Each section was evaluated by 2 experienced pathologists according to the CPS (PD-L1-stained tumor cells and immune cells/total number of viable tumor cells × 100) in rectal biopsy specimens prior to neoadjuvant chemoradiotherapy [9].

Table 1. Clinicopathologic characteristics

Characteristic	GPS-low group	GPS-high group	P-value
No. of patients	85	18	
Age (yr)[a]	58.0 (28–72)	57.5 (29–73)	0.825
Sex			
Male	60 (70.6)	15 (83.3)	0.385
Female	25 (29.4)	3 (16.7)	
Distance from anal verge (cm)			
≤5	53 (62.4)	10 (55.6)	0.591
>5	32 (37.6)	8 (44.4)	
cT stage			
T3	55 (64.7)	6 (33.3)	0.046
T4a	14 (16.5)	5 (27.8)	
T4b	16 (18.8)	7 (38.9)	
cN stage			
N0	12 (14.1)	3 (16.7)	0.114
N1	45 (52.9)	5 (27.8)	
N2	28 (32.9)	10 (55.6)	
Concurrent chemotherapy			
Yes	85 (100)	16 (88.9)	0.029
No	0 (0)	2 (11.1)	
Adjuvant chemotherapy			
Yes	67 (78.8)	14 (77.8)	>0.999
No	18 (21.2)	4 (22.2)	
pCR			
Yes	12 (14.1)	2 (11.1)	>0.999
No	73 (85.9)	16 (88.9)	
TRG distribution			
0	12 (14.1)	2 (11.1)	0.332
1	10 (11.8)	2 (11.1)	
2	63 (74.1)	13 (72.2)	
3	0 (0)	1 (5.6)	
PD-L1 CPS[b]	1.34 (0–50)	6.50 (0–70)	<0.001
Microsatellite instability status			
Proficient	25 (29.4)	6 (33.3)	0.641
Deficient	4 (4.7)	2 (11.1)	
NA	56 (65.9)	10 (55.6)	

Values are presented as number only, [a]median (range), number (%), or [b]mean (range).
GPS, Glasgow prognostic score; pCR, pathologic complete remission; TRG, tumor regression grade, PD-L1, programmed death-ligand 1; CPS, combined positive score; NA, not available.

Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics ver. 22.0 (IBM Corp., Armonk, NY, USA). The disease-free survival (DFS) and overall survival (OS) were measured from the 1st day of neoadjuvant chemoradiotherapy to the date of the event and were estimated by use of the Kaplan-Meier method. The chi-square test, t-test, and Fisher exact tests were used to compare the differences between the GPS-low and the GPS-high group. Multivariate analyses with the Cox proportional hazards model were used to test independent significance by using backward elimination of insignificant explanatory variables. Host factors (age and sex) were included as covariates in all tests. Statistical tests were based on a two-sided significance level. A P-value of <0.05 indicated statistical significance.

RESULTS

General information

A total of 103 locally advanced rectal cancer patients were included. According to the classification of the GPS, 85 (82.5%), 13 (12.6%), and 5 patients (4.9%) were classified as having a score of 0, 1, and 2, respectively. Patients were classified into the GPS-low group (GPS of 0, n = 85) and GPS-high group (GPS of 1 or 2, n = 18) with an area under the curve of 0.582 for OS. The details of the microsatellite instabilities for 66 patients (64.1%) were not available. For the 37 patients with data of microsatellite instabilities status, no significant difference was observed in terms of microsatellite instability status between the GPS-high and GPS-low groups (P = 0.591). The clinical characteristics of the patients in the GPS-low and GPS-high groups are listed in Table 1.

Association between Glasgow prognostic score and combined positive score

The mean PD-L1 CPS of the whole group was 2.24 (range, 0–70). The representative IHC staining of PD-L1 in locally advanced rectal cancer biopsies was shown in Fig. 1. The PD-L1 CPS of the GPS-high group was higher than the GPS-low group (P < 0.001). Pathological complete response (pCR) rate was observed in 14 patients (13.6%) after neoadjuvant chemoradiotherapy. The pCR rates of the GPS-low and GPS-high groups were 14.1% and 11.1%, respectively (P > 0.999). The pCR rates of patients with PD-L1 CPS of 0 and >0 were 17.5% (10 of 57) and 12.5% (4 of 32), respectively (P = 0.766).

Prognostic significance of Glasgow prognostic score and combined positive score

The median follow-up time was 64.5 months (range, 3.5–109.8 months). The value of various potential prognostic factors including age, sex, distance from anal verge, clinical (c) T stage, cN stage, concurrent chemotherapy, adjuvant chemotherapy, pCR, PD-L1 CPS, microsatellite instability status, and GPS (low group *vs.* high group) on predicting DFS and OS were evaluated. The 5-year OS rate in the GPS-low group was higher than the patients in the GPS-high group (78.4% *vs.* 49.8%, P = 0.017). The 5-year DFS rate in the GPS-low group was higher than the patients in the GPS-high group (67.2% *vs.* 38.6%, P = 0.010) (Fig. 1). In this study, the CPS of 0, 1–10, and ≥10 were observed in 56 (54.4%), 53 (51.5%), and 4 patients (3.9%), respectively (Fig. 2). No statistically significant difference was observed in terms of DFS or OS between the patients with PD-L1 CPS of 0 and >0 (P > 0.050). Multivariate analysis by Cox proportional hazards model indicated that T classification and GPS were associated with OS and DFS. Furthermore, PD-L1 CPS was associated with DFS (hazard ratio [HR], 1.050; 95% confidence interval [CI], 1.017–1.083; P = 0.003). The outcomes of univariate analysis

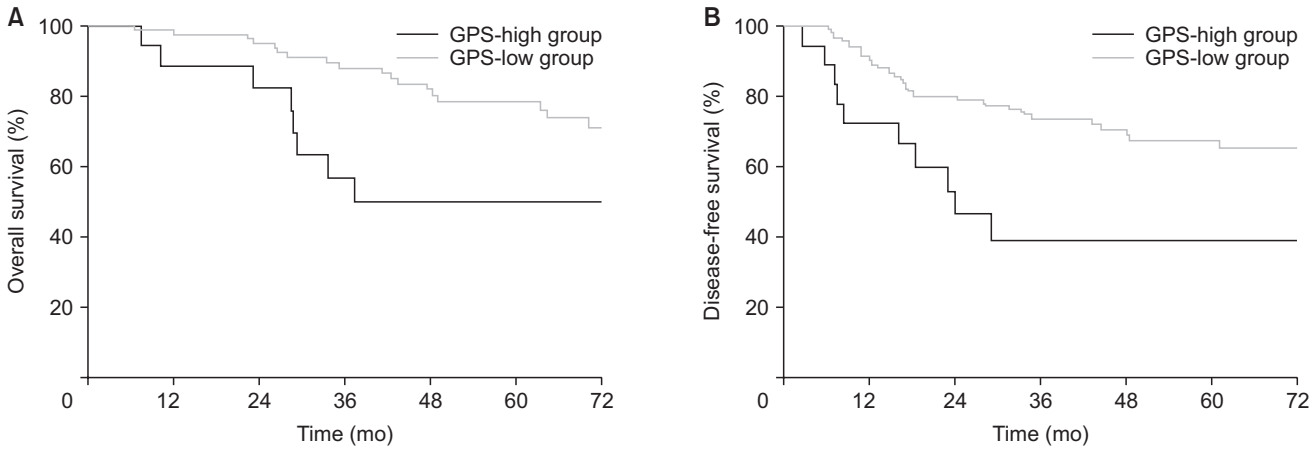

Fig. 1. Kaplan-Meier curves of overall survival and disease-free survival in the Glasgow prognostic score (GPS)-low group and the GPS-high group.

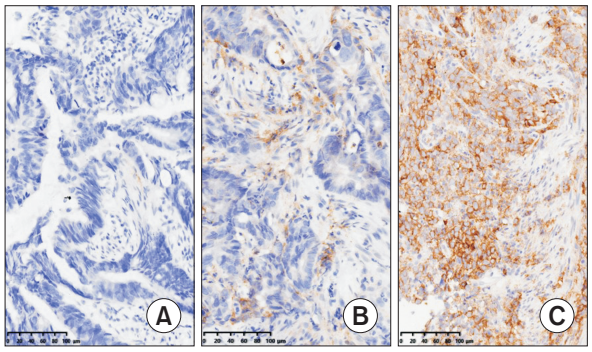

Fig. 2. Representative immunohistochemistry staining of programmed death-ligand 1 combined positive score with 0 (A), 1–10 (B), and ≥10 (C) in locally advanced rectal cancer biopsies (original magnification, ×200).

and multivariate analysis are reported in Tables 2 and 3.

DISCUSSION

In the present study, the relationship between GPS and PD-L1 CPS and survival of locally advanced rectal cancer patients treated by neoadjuvant chemoradiotherapy and TME was evaluated. We found that the PD-L1 CPS of the GPS-high group was higher than the GPS-low group and GPS and PD-L1 CPS were associated with the prognosis of locally advanced rectal cancer.

GPS determined by serum CRP and albumin is considered a hallmark of inflammatory response in the tumor environment. In 2007, McMillan et al. [10] firstly reported that the baseline GPS could predict overall and cancer-specific survival of patients with colon and rectal cancer receiving surgery. In their study, 123 patients (38.9%) with rectal cancer were included, and the elevated GPS was related to older age but not tumor stage. In another prospectively collected data set of 1,590 patients with colorectal cancer (510 patients with rectal cancer) receiving curative surgery, GPS was a prognostic factor for OS (HR, 2.344; 95% CI, 1.621–3.390; P = 0.001) and DFS (HR, 1.532; 95% CI, 1.030–2.278; P = 0.035) [11]. In the present study, GPS was associated with DFS and OS of locally advanced rectal cancer; the elevated GPS was related to T classification but not age (Table 1).

Based on KEYNOTE-059, KEYNOTE-012, and KEYNOTE-028 studies, a CPS of >1 has been standardized for predicting response to pembrolizumab in gastric and gastroesophageal junction cancer [12]. However, CPS of ≥10 was considered as a biomarker for predicting response to pembrolizumab in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 studies [13]. In the present study, the median PD-L1 CPS of the whole group was 0 (range, 0–70), and no statistically significant difference was observed in terms of DFS or OS between the patients with PD-L1 CPS of 0 and >0 (P > 0.050) by univariate analysis. In multivariate analysis, PD-L1 CPS was adopted as a continuous variable and PD-L1 CPS was observed as a biomarker for DFS. One study of colorectal cancer comparing the PD-L1 expression patterns using 3 primary PD-L1 antibodies (assay 1, MIH1; assay 2, E1L3; and assay 3, 22C3) by IHC indicated that the percentage scorings and positivity rates of the 3 assays differed [14]. In Huemer et al.'s study [9], 72 patients with rectal cancer treated by neoadjuvant chemoradiotherapy were included and the anti-PD-L1 antibody (22C3, SK006; Agilent, Santa Clara, CA, USA) was adopted for PD-L1 staining. PD-L1 CPS prior to neoadjuvant chemoradiotherapy was not associated with pCR or survival,

Table 2. Univariate analysis of variables correlated with various clinical endpoints

Variable	5-Year OS	P-value	5-Year DFS	P-value
Age (yr)				
≥58	72.3	0.339	59.6	0.467
<58	75.0		66.0	
Sex				
Male	70.9	0.264	59.0	0.344
Female	80.8		71.1	
Distance from anal verge (cm)				
≤5	65.8	0.028	61.0	0.385
>5	85.4		64.4	
cT stage				
T3	86.9	0.001	67.9	0.079
T4a	66.8		73.0	
T4b	48.3		40.3	
cN stage				
N0	64.6	0.025	57.4	0.112
N1	84.5		70.0	
N2	62.6		54.1	
Concurrent chemotherapy				
Yes	73.9	0.490	62.7	0.868
No	50.0		50.0	
Adjuvant chemotherapy				
Yes	76.6	0.350	62.4	0.587
No	63.5		63.9	
pCR				
Yes	91.7	0.104	83.9	0.201
No	70.5		59.0	
PD-L1 CPS				
0	74.9	0.907	65.4	0.374
>0	70.8		56.5	
Microsatellite instability status				
Proficient	67.0	0.242	64.9	0.618
Deficient	100.0		80.0	
NA	74.0		59.9	
GPS				
Low group	78.4	0.017	67.2	0.010
High group	49.8		38.6	

OS, overall survival; DFS, disease-free survival; pCR, pathologic complete remission; PD-L1, programmed death-ligand 1; CPS, combined positive score; NA, not available; GPS, Glasgow prognostic score.

Table 3. Multivariate analysis of variables correlated with various clinical endpoints

Endpoint	Item	HR (95% CI)	P-value
Overall survival	Sex		
	Male *vs*. female	2.224 (0.873–5.667)	0.094
	T classification		0.002
	T3	1	
	T4a	2.032 (0.635–6.505)	0.232
	T4b	6.009 (2.232–16.178)	<0.001
	GPS		
	Low group *vs*. high group	0.356 (0.141–0.902)	0.030
	pCR		
	Yes *vs*. no	6.679 (0.890–50.112)	0.065
Disease-free survival	T classification		0.045
	T3	1	
	T4a	0.784 (0.289–2.125)	0.632
	T4b	2.575 (1.125–5.891)	0.025
	PD-L1 CPS	1.050 (1.017–1.083)	0.003
	GPS		
	Low group *vs*. high group	0.417 (0.183–0.946)	0.036

HR, hazard ratio; CI, confidence interval; GPS, Glasgow prognostic score; pCR, pathologic complete remission; PD-L1, programmed death-ligand 1; CPS, combined positive score.

likely due to the limited number of patients included and the different PD-L1 antibodies used [9].

In the study of investigating the relationships between the serum levels of 13 cytokines (interleukin [IL]-1ra, IL-4, IL-6, IL-7, IL-8, IL-9, IL-12, interferon-γ, CXL10, CCL2, CCL4, CCL11, and PDGF-BB) and the densities of 8 types of tumor-infiltrating inflammatory cells (CD1a, CD3, CD8, CD68, CD83, FoxP3, mast cell tryptase and neutrophil elastase) in 147 colorectal cancer patients, elevated serum IL-12 levels were related to the densities of intratumoral neutrophils, peritumoral $CD8^+$ T cells, and intraepithelial $CD3^+$ T cells [15]. However, in another study including 396 stage II colon cancer patients, local (intratumoral chronic inflammatory cell density) and systemic (neutrophil-to-lymphocyte ratio) inflammation was assessed and no significant inverse relationship between local and systemic inflammation was observed [16]. The PD-L1 CPS of the GPS-high group was higher than the GPS-low group in this study. The relationship between immunity and inflammation would deserve further investigation in the era of cancer immunotherapy [17].

There were several limitations in this study including the retrospective nature of the study design; 66 patients (64.1%) with unavailable microsatellite instability status and all the included patients treated at a single center. In addition, no locally advanced rectal cancer patients treated by PD-1/PD-L1 antibodies were included, leaving the prediction value of GPS and PD-L1 CPS uncertain at this moment.

In conclusion, elevated GPS was related to the PD-L1 CPS. GPS and PD-L1 CPS were associated with prognosis of locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy followed by TME.

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Conflict of Interest

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

ORCID iD

Yanru Feng: https://orcid.org/0000-0001-6364-8400
Jialin Luo: https://orcid.org/0000-0003-4935-972X
Peng Liu: https://orcid.org/0000-0002-3659-0052
Luying Liu: https://orcid.org/0000-0001-6325-1518
Yuan Zhu: https://orcid.org/0000-0001-5871-4418
Guoping Cheng: https://orcid.org/0000-0001-8505-4777
Linfeng Zheng: https://orcid.org/0000-0001-9889-4919

Author Contribution

Conceptualization, Project Administration: YF, YZ, LZ
Formal Analysis, Methodology: YF, LZ
Investigation: JL, PL, LL, YZ, GC, LZ
Writing – Original Draft: All authors
Writing – Review & Editing: YF, YZ, LZ

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