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ORIGINAL ARTICLE

Prognostic Value of Progranulin in Patients with Colorectal Cancer Treated with Curative Resection

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Abstract

Progranulin (PGRN) has been characterized as an autocrine growth and survival factor and is known to stimulate tumorigenesis and proliferation of several types of cancer cell. However, little is known about the prognostic role of PGRN in colorectal cancer (CRC). A retrospective analysis was performed for patients with colorectal cancer who underwent curative resection between May 2013 and June 2015. PGRN expression in tumor cells was semi-quantitatively categorized (no expression, 0; weak/focal, 1+ ; moderate/focal or diffuse, 2+; strong/diffuse, 3+), and high expression was considered for tumors graded ≥2+ staining intensity. A total of 109 patients (28 stage I, 32 stage II, and 49 stage III) were analyzed. Thirty-eight patients (35%) had tumors with high PGRN expression, and there was a trend of elevated pre-operative CEA and CA19–9 levels in patients with high PGRN-expressing tumors compared to those with low PGRN-expressing tumors (CEA, 49% vs. 21%; CA19–9, 21% vs. 7%). The 3–year recurrence-free survival (3Y–RFS) and overall survival rates were 83.7% (95% CI, 76.8–90.6) and 96.0% (95% CI, 92.3–99.7), respectively. Patients with high PGRN-expressing tumors had a worse rate of 3Y–RFS (66.8%) compared to those with low PGRN-expressing tumors (92.4%; $p = 0.010$). Multivariate analysis showed that high PGRN expression, age (>66 years), stage (III), and perineural invasion (+) were independent prognostic factors associated with poor RFS after adjusting for confounding factors including sex, MSI, tumor location, *KRAS*, and lympho-vascular invasion. PGRN overexpression was significantly associated with poor RFS in patients with CRC who have undergone curative resection.

Keywords Progranulin · Colorectal neoplasms · Recurrence · Prognosis

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Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide. CRC is the second and third most commonly diagnosed cancer in women and men, respectively, with an estimated 1.4 million cases and 693,900 deaths in 2012 [1]. Although the overall survival rate of CRC patients has increased, the prognosis of patients with advanced or metastatic disease remains poor [2].

Progranulin (PGRN) is a secreted glycoprotein that is involved at multiple steps in the tumor progression cascade, including proliferation, survival, migration, and angiogenesis [3]. Recently, Yang et al. demonstrated that upregulation of PGRN in CRC is positively correlated with increased Ki-67 and vascular endothelial growth factor A (VEGF-A) expression, as well as increased microvessel density [4]. In addition, they showed that the increased Ki-67 and VEGF-A expression were mediated by both tumor necrosis factor receptor-2 (TNFR2)/Akt and ERK signaling pathways, suggesting that PGRN might represent a new type of growth factor in CRC.

Nevertheless, little is currently known about the pattern of PGRN expression in CRC according to clinicopathological features or the prognostic role of PGRN overexpression in patients with CRCs who have undergone curative resection. Therefore, the aim of this study was to evaluate PGRN expression in patients with CRC who underwent curative resection and determine its prognostic role.

Materials and Methods

Patients

We retrospectively reviewed the medical records of patients with colorectal cancer underwent surgery at Kangbuk Samsung Hospital (Seoul, Korea) between May 2013 and June 2015, and evaluated the tumor tissues. Patients who met the following criteria were included in our analysis: ≥18 years old; histologically confirmed adenocarcinoma with a colorectal origin; curative R0 surgery without evidence of metastatic lesions; no history of other malignancies; and tumor tissue available for immunohistochemical (IHC) examination of PGRN expression and polymerase chain reaction (PCR) for microsatellite instability (MSI) assay. Multiplex PCR to test for MSI was performed with a 3130 × Il genetic analyzer (Applied Biosystems™, USA) using five quasi-monomorphic mononucleotide markers (NR27, NR21, BAT26, BAT25, and NR24). Tumors that showed instability in two or more markers were classified as MSI tumors, while those that showed instability in no more than one marker were classified as microsatellite stable (MSS) tumors [5]. *KRAS* mutation detection was carried out by well-established methods of direct DNA sequencing of KRAS exons 2 and 3 [6]. The study protocol was approved by the Institutional Review Board of Kangbuk Samsung Hospital.

Immunohistochemical Analysis

Specimens from formalin-fixed and paraffin-embedded samples at the time of surgery were collected for histological review and immunohistochemical analysis. IHC was performed using a Bond-max autoimmunostainer (Leica Biosystems, Melbourne, Australia) as described previously [7]. Briefly, slides were incubated with mouse monoclonal anti-progranulin antibody (PG359–7) (AG-20A-0052, Adipogen Life Sciences, Liestal, Switzerland) at a dilution of 1:500 for 15 min at room temperature. Negative controls (substitution of the primary antibody with TBS) were run simultaneously. Overall, PGRN was expressed in the cytoplasm of tumor cells with a granular pattern. PGRN expression in tumor cells was semi-quantitatively categorized as previously described (no expression, 0; weak/focal, 1+; moderate/focal or diffuse, 2+; strong/diffuse, 3+) [8]. Tumor cells with ≥2+ PGRN staining were considered high PGRN-expressing tumors, while tumors with ≤1+ staining were considered low PGRN-expressing tumors (Fig. 1).

Statistical Analysis

Associations between PGRN expression and clinical characteristics were assessed by univariate chi-square analysis using a dichotomized cut-off value for IHC positivity. Recurrence-free survival (RFS) was calculated as the duration from the date of surgery to the date of documented recurrence, death, or last follow-up (whichever occurs first). Overall survival (OS) time was calculated as the duration from the date of surgery to the date of death or last follow-up. Survival curves were constructed using the Kaplan-Meier method and were compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard regression model with enter method. A two-sided p value <0.05 was considered significant, and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using IBM SPSS ver. 18.0 (IBM Co., NY, USA).

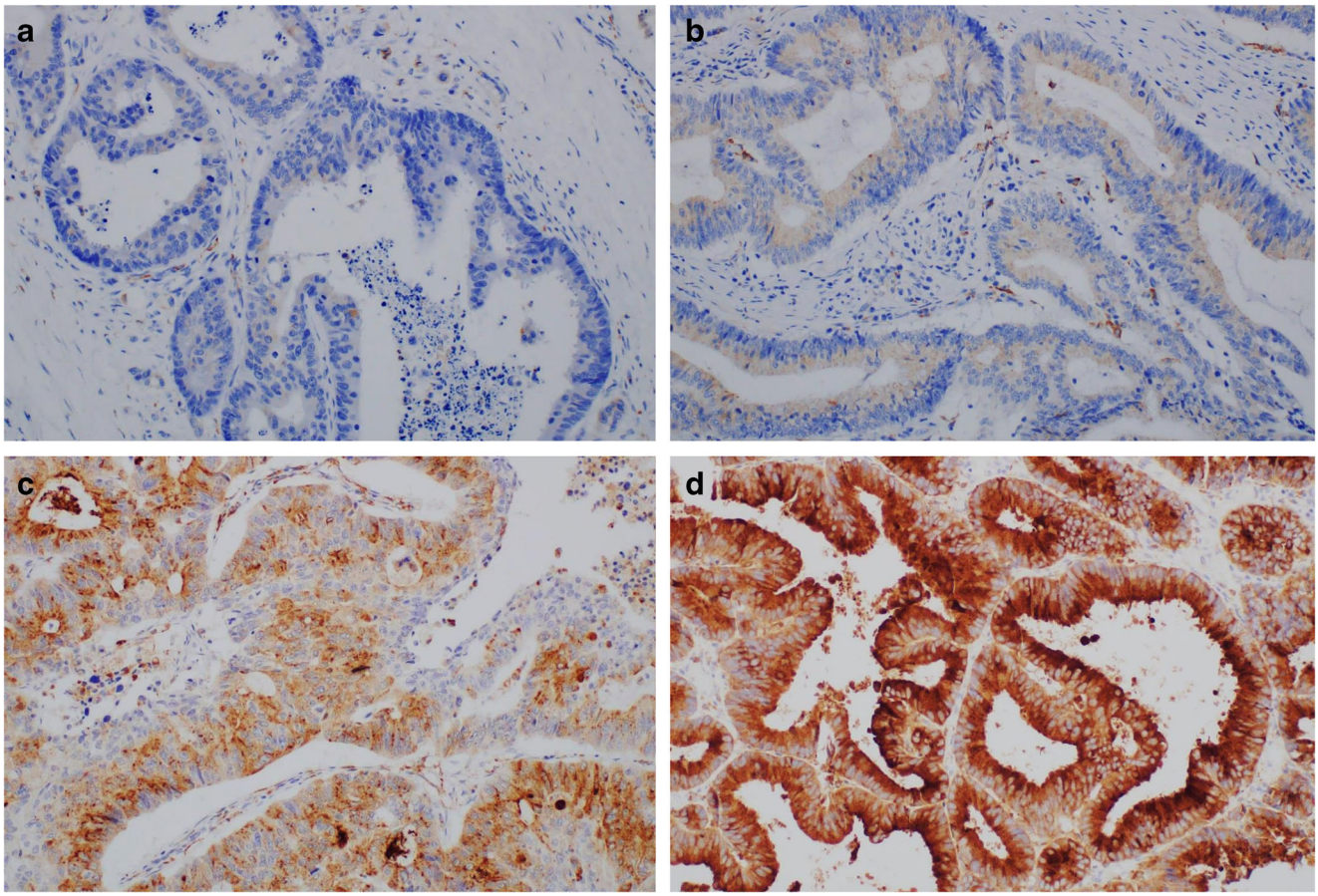

Fig. 1 Progranulin expression (×200). (**a**) intensity 0; (**b**) intensity 1+; (**c**) intensity 2+; (**d**) intensity 3 +

Results

Baseline Characteristics

A total of 109 patients were evaluated in the present study. Sixty-six patients (61%) were male, and the median age at the time of surgery was 67 years (range 30–86). CRC stages were as follows: I, 28 patients (26%); II, 32 patients (29%); and III, 49 patients (45%). All patients with stage II or III disease received fluoropyrimidine-based adjuvant thermotherapy for six months. A total of 27 patients (25%) had tumors localized to the right side (ascending and transverse colon). MSI-H and *KRAS*-wild type status was identified in 19 (17%) and 64 patients (59%), respectively. The clinicopathologic characteristics of the study patients are summarized in Table 1.

Clinicopathological Features According to PGRN Expression

Thirty-eight patients (35%) had high PGRN-expressing tumors with ≥2+ staining intensity. There was no significant difference in clinicopathologic factors including sex, age, T stage, N stage, tumor size, tumor location, histopathology, MSI, and *KRAS* mutation status between patients with tumors expressing high and low levels of PGRN (Table 2). However, there was a trend toward elevated pre-operative CEA and CA19–9 levels in patients with high PGRN-expressing tumors compared to those with low PGRN-expressing tumors (CEA, 49% vs. 21%, $p = 0.003$; CA19–9, 21% vs. 7%; $p = 0.077$).

Survival Outcomes According to PGRN Expression

The median follow-up duration of living patients was 28.9 months (interquartile range [IQR], 22.5–33.9), and the median RFS and OS were not reached. The 3–year RFS and OS rates were 83.7% (95% CI, 76.8–90.6) and 96.0% (95% CI, 92.3–99.7), respectively. The 3–year RFS rates at stages I, II, and III were 100.0%, 82.9% (95% CI, 69.9–95.9), and 74.9% (95% CI, 94.8–87.0), respectively (Fig. 2a). Patients with high PGRN-expressing tumors had worse RFS rates (66.8% at 3–years, 95% CI, 51.8–81.8) compared to patients with low PGRN-expressing tumors (92.4% at 3–year, 95% CI, 86.2–98.6; $p = 0.01$; Fig. 2b). Multivariate analysis for RFS showed that high PGRN-expression (hazard ratio [HR] 4.61, 95% CI, 1.26–16.93; $p = 0.021$), age

Table 1 Baseline clinicopathological characteristics

Characteristic	Value
Sex	
Male	66 (60.6)
Female	43 (39.4)
Age at surgery	67 (30–86)
Stage	
I	28 (25.7)
II	32 (29.4)
III	49 (44.9)
Tumor location	
Ascending	21 (19.3)
Transverse	6 (5.5)
Descending	59 (54.1)
Rectal	23 (21.1)
Histology	
WD/MD	103 (94.5)
PD	6 (5.5)
T stage	
T1/2	38 (34.9)
T3/4	71 (65.1)
Tumor size (cm)	
< 3	35 (32.1)
3–6	54 (49.5)
> 6	20 (18.3)
Dissected lymph nodes	24 (6–78)
N stage	
N0	61 (56.0)
N1	36 (33.0)
N2	12 (11.0)
Lympho-vascular invasion (Yes)	41 (37.6)
Peri-neural invasion (Yes)	19 (17.4)
Pre-operative CEA ($n = 108$)	33 (30.6)
Pre-operative CA19–9 ($n = 87$)	10 (11.5)
Microsatellite status	
MSI	19 (17.4)
MSS	90 (82.6)
KRAS	
Wild	64 (58.7)
Mutant	45 (41.3)
Progranulin expression	
High	38 (34.9)
Low	71 (65.1)

Values are presented as number (%) or median (range)

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; MSI, microsatellite instable; MSS, microsatellite stable

Table 2 Patient characteristics according to progranulin (PGRN) expression

Characteristic	High progranulin ($n = 38$)	Low progranulin ($n = 71$)	*p* value
Sex			0.678
Male	22 (57.9)	44 (62.0)	
Female	16 (42.1)	27 (38.0)	
Age at surgery (67 or more)	19 (50.0)	39 (55.0)	0.623
Stage			0.909
I	9 (23.7)	19 (26.8)	
II	12 (31.6)	20 (28.2)	
III	17 (44.7)	32 (45.1)	
Tumor location			0.261
Rt. side	7 (18.4)	20 (28.2)	
Lt. side	31 (81.6)	51 (71.8)	
Histology			0.936
WD/MD	36 (94.7)	67 (94.4)	
PD	2 (5.3)	4 (5.6)	
T stage			0.599
T1/2	12 (31.6)	26 (36.6)	
T3/4	26 (68.4)	45 (63.4)	
Tumor size (cm)			0.679
< 3	11 (28.9)	24 (33.8)	
3–6	21 (55.3)	33 (46.5)	
> 6	6 (15.8)	14 (19.7)	
N stage			0.678
N0	21 (55.3)	40 (56.3)	
N1	14 (36.8)	22 (31.0)	
N2	3 (7.9)	9 (12.7)	
Lympho-vascular invasion (Yes)	17 (44.7)	24 (33.8)	0.261
Peri-neural invasion (Yes)	9 (23.7)	10 (14.1)	0.208
Pre-operative CEA ($n = 108$)	18 (48.6)	15 (21.1)	0.003
Pre-operative CA19–9 ($n = 87$)	6 (20.7)	4 (6.9)	0.077
Microsatellite status			0.164
MSI	4 (10.5)	15 (21.1)	
MSS	34 (89.5)	56 (78.9)	
KRAS			0.132
Wild	26 (68.4)	38 (53.5)	
Mutant	12 (31.6)	33 (46.5)	

Values are presented as number (%)

Rt. side, ascending and transverse colon; Lt. side, descending colon and rectum; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; MSI, microsatellite instable; MSS, microsatellite stable

(>66 years, HR 8.87, 95% CI, 1.94–40.53; $p = 0.005$), stage (III, HR 8.56, 95% CI, 2.02–36.27; $p = 0.004$), and perineural invasion (HR 4.64, 95% CI, 1.05–20.62; $p = 0.043$) were independent prognostic factors associated with poor RFS after adjusting for possible confounding factors including sex, MSI status, tumor location, *KRAS* status, and lympho-vascular invasion

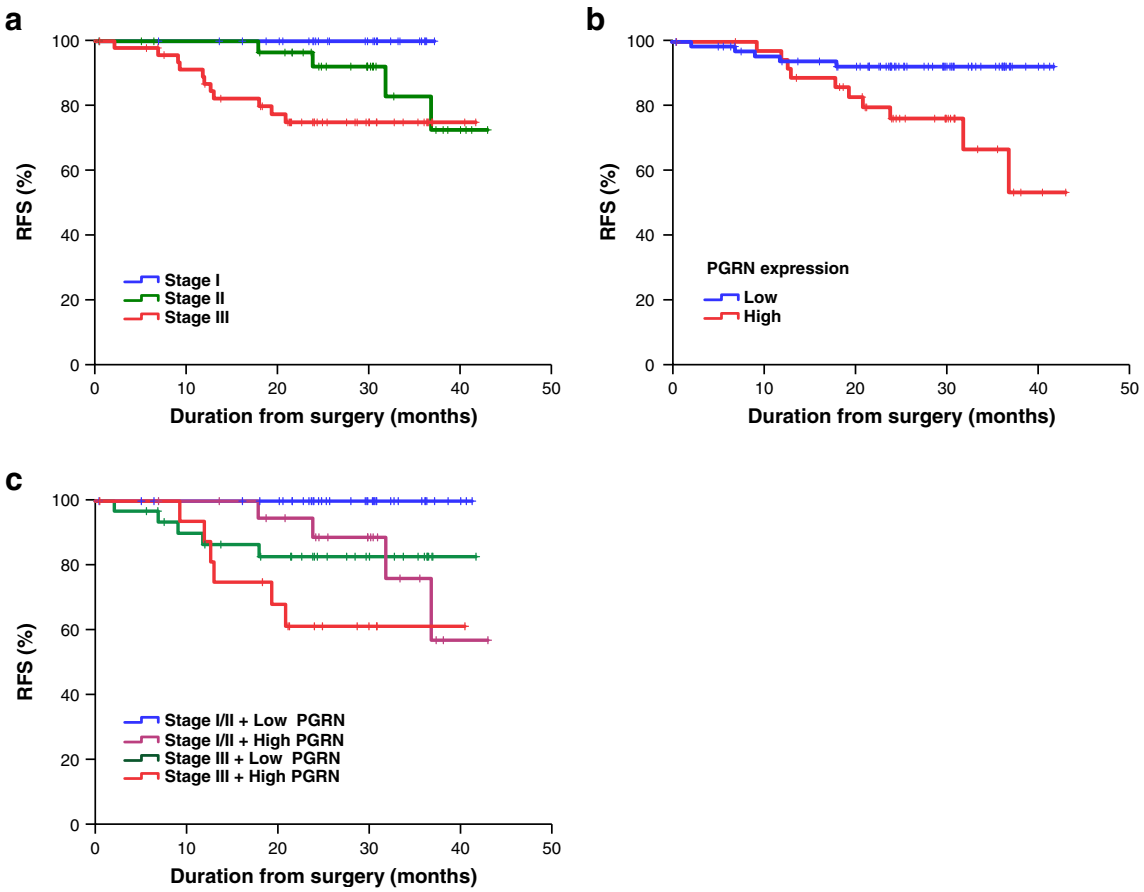

Fig. 2 Recurrence-free survival (RFS) according to stage (**a**), progranulin expression (**b**), and stage/progranulin expression (**c**)

(Table 3). Multivariate analysis for OS could not be performed due to the rarity of the event (3 of 109 patients; <3%).

Discussion

In this study, we evaluated the expression of the putative tumor marker PGRN using IHC analysis in cases of completely resected CRC. High expression of PGRN (2+ or 3+) was observed in 35% patients, and these patients had significantly worse RFS. Multivariate analysis confirmed that high PGRN expression was an independent factor associated with poor RFS.

PGRN has been investigated for its significant biological effects in many types of cancer cells [9]. PGRN overexpression has previously been demonstrated to be associated with tumorigenesis [10–14]. PGRN was first reported to be overexpressed in breast cancer tissues compared to normal tissues, a finding that was later extended to several other types of human cancer [3]. As one of regulators of tumorigenesis, PGRN stimulates cell proliferation, migration, invasion, angiogenesis, malignant transformation, inhibition of apoptosis, survival, and resistance to anticancer drugs. With respect to a prognostic role, overexpression of PGRN in tumors has been reported to be associated with poor prognosis in breast cancer [8, 15, 16], ovarian cancer [11, 17], hepatocellular carcinoma [18], and biliary tract cancer [7].

There is limited understanding of the role of PGRN in CRC at present. PGRN is known to promote proliferation and angiogenesis through TNFR2/Akt and ERK signaling pathways in CRC, and further research will focus on the role of PGRN as a biomarker and therapeutic target in tumor proliferation and angiogenesis [4]. In terms of the role of PGRN as a prognostic biomarker, a recent study showed that survival outcomes of CRC patients with high levels of PGRN expression are worse compared to patients whose tumors have low PGRN expression [4], which was consistent with our results.

We did not identify any clinicopathologic differences between high and low expressing PGRN tumors including stage, age, and perineural invasion, which were poor independent prognostic factors. However, it was noted that patients with stage I/II CRC with high PGRN expression had worse 3–year RFS rates (76.1%; 95% CI, 57.9–94.3) compared patients with stage III CRC with low PGRN expression (82.8%; 95% CI, 69.7–95.9; Fig. 2c. These findings suggest that, even

Table 3 Univariate and multivariate analyses for recurrence-free survival

Characteristics	Univariate analyses		Multivariate analysis	
	3Y–RFS (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Sex		0.550		0.576
Female	84.7 (73.9–95.5)		1.00 (Reference)	
Male	82.6 (73.5–91.7)		1.44 (0.40–5.22)	
Age at surgery (years)		0.010		0.005
≤ 66	94.0 (87.5–99.9)		1.00 (Reference)	
> 66	73.1 (61.7–84.5)		8.87 (1.94–40.53)	
Stage		0.008		0.004
I/II	90.8 (83.5–98.1)		1.00 (Reference)	
III	74.9 (62.8–87.0)		8.56 (2.02–36.27)	
Microsatellite status		0.299		0.158
MSI	94.7 (84.6–99.9)		1.00 (Reference)	
MSS	81.7 (73.7–89.7)		4.94 (0.54–45.46)	
Tumor location		0.774		0.280
Lt. side	83.7 (75.7–91.7)		1.00 (Reference)	
Rt. side	83.5 (69.5–97.5)		2.24 (0.52–9.70)	
KRAS		0.849		0.803
Mutant	84.8 (74.3–95.3)		1.00 (Reference)	
Wild	83.5 (74.4–92.6)		1.17 (0.35–3.96)	
Lympho-vascular invasion		0.823		0.092
(−)	83.9 (75.2–92.6)		1.00 (Reference)	
(+)	84.0 (72.8–95.2)		3.51 (0.81–15.13)	
Peri-neural invasion		0.003		0.043
(−)	88.1 (81.4–94.8)		1.00 (Reference)	
(+)	64.2 (42.6–85.8)		4.64 (1.05–20.62)	
PGRN expression		0.010		0.021
Low	92.4 (86.2–98.6)		1.00 (Reference)	
High	66.8 (51.8–81.8)		4.61 (1.26–16.93)	

Rt. side, ascending and transverse colon; Lt. side, descending colon and rectum; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; MSI, microsatellite instable; MSS, microsatellite stable

for patients with very early stage CRC, a tumor with a high level of PGRN expression may be associated with increased risk of an unfavorable outcome.

Association between diabetes mellitus, inflammation, and cancer incidence and prognosis has been proposed [19]. Recently, PGRN was evaluated as an adipose tissue hormone (adipokine) implicated in obesity and insulin resistance [20], as well as an inflammatory modulator in rheumatic disease and sepsis [21, 22]. Interestingly, PGRN has also been actively investigated as a biomarker in other tumor types that are well-known to be associated with diabetes, including breast cancer, colorectal cancer, biliary cancer, ovarian cancer, and bladder cancer [23–27]. In addition, suppression of PGRN may inhibit the growth of bladder cancer and sensitize cancer cells to cisplatin [28]. Further studies to investigate the potential role of PGRN are warranted not only in the field of oncology, but for metabolic disease and inflammation as well [29].

Although the PGRN expression status was a statistically significant factor in terms of prediction of poor RFS, the results should be interpreted with caution. This study might be biased by small size of patients and retrospective design; therefore, further studies are needed to confirm our results.

In conclusion, patients with CRC expressing high levels of PGRN who undergo curative resection have significantly poorer outcomes compared to patients whose tumors express low levels of PGRN. Therefore, PGRN expression status may be a prognostic factor for patients with CRC who have undergone curative resection.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare, except of GS who is an employee of A&G Pharmaceutical.

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