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ORIGINAL ARTICLE

Prognostic Significance of High Phosphatase of Regenerating Liver-3 Expression in Patients with Gastric Cancer Who Underwent Curative Gastrectomy

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Abstract
Background Although a close correlation between PRL-3 overexpression and lymph node metastasis has been reported in gastric cancer, its clinical utility as a useful prognostic molecular marker remains unclear.
Methods Prognostic significance of PRL-3 expression was analyzed immunohistochemically in 110 patients with gastric cancer who had undergone curative gastrectomy.
Results There was a significant correlation between gender, histology, lymph node metastasis, the presence of recurrence, and the level of PRL-3 expression. Recurrence in patients with high PRL-3 expression was significantly higher than that for patients with low PRL-3 expression ($p < 0.001$). The median overall survival (OS) time and 2-year OS rate for patients with high or moderate PRL-3 expressed tumors were worse than those of patients with low PRL-3 expressed tumor ($p = 0.001$). In addition, patients with low PRL-3 expression had a higher DFS rate and the median DFS interval than those of moderate or high PRL-3 expressed patients ($p < 0.001$). Multivariate analysis indicated that the rate of PRL-3 expression was an independent prognostic factor, in addition to the already-known important clinicopathological prognostic indicator for both DFS and OS.
Conclusions The potential value of PRL-3 expression as a useful molecular marker in gastric cancer progression should be evaluated comprehensively; it may predict recurrence and poor prognosis in patients with gastric cancer after curative resection.

Keywords Gastric cancer · PRL-3 expression · Lymph node metastasis · Recurrence · Prognosis

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Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide. Although early diagnosis and the development of new treatment approaches improve the outcome of gastric cancer, advanced stage disease still has a poor prognosis [1, 2]. The identification of poor prognostic factors that may predict the tumor recurrence and prognosis of patients is important for the selection of appropriate treatment protocols [3]. Recently, new prognostic indicators have been documented by advances in molecular and histochemical studies [4, 5].

Protein tyrosine phosphatases (PTPs) are key regulatory enzymes in some signal transduction pathways and protein phosphorylation is one of the most important posttranslational modifications affecting apoptosis, cell cycle progression, protein degradation, and oncogenesis [6]. Phosphatase of regenerating liver (PRL) family represents a PTPs superfamily, have a unique COOH-terminal prenylation motif and a PTP-active site signature sequence CX5R [7, 8]. PRL-3, also known as PTP4A3, is a member

of a small class of tyrosine phosphatases and plays an important role in cancer cell migration, invasion, and metastasis. The other two members of the PRL family are PRL-1 and -2 [9–11]. Saha et al. [10] found that PRL-3 was overexpressed in liver metastases of patients with colorectal cancer by gene expression technology. Afterwards, some studies indicated that elevated PRL expression (especially PRL-3) was associated with metastatic potential and poor prognosis of multiple cancer types [12–18]. In patients with node-negative breast cancer, PRL-3 was found to be an unfavorable prognostic marker [15]. In addition, it was associated with liver metastasis and a shorter survival in colorectal cancer [12]. The rate of PRL-3 overexpression has been reported as 36.2–70.4% by immunohistochemistry (IHC) or in situ hybridization in gastric cancer. High PRL-3 expression was found to be closely correlated with lymph node metastasis or peritoneal metastasis in gastric cancer [19–22]. However, the prognostic value of PRL-3 expression in gastric cancer tissues has not been completely understood and a consensus has not been reached on its clinical significance.

In the present study, PRL-3 expression was detected by IHC in tumor tissues. The aim of our study was to investigate the value of PRL-3 as a prognostic factor in 110 gastric cancer patients who had undergone curative gastrectomy. In addition, the association of PRL-3 expression with other clinicopathological factors and its impact on survival were also evaluated.

Patients and Methods

A total of 110 paraffin-embedded surgical tumor specimens of patients with gastric cancer who had undergone radical gastrectomy at the Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul, Turkey, between December 2006 and October 2009, were retrospectively evaluated. All patients underwent either distal partial gastrectomy, proximal partial gastrectomy, or total gastrectomy with lymph node dissection for curative intent. The eligibility criteria consisted of histologically confirmed R_0 gastric resection with sufficient regional lymphadenectomy, which was defined as no macroscopic or microscopic residual tumor and the patients with postoperative survival expectancy of >3 months. The patients with inadequate histological specimens, distant metastases, peritoneal metastases, and positive surgical margin at diagnosis were excluded from the study.

Tumor Characteristics

Details concerning age, gender, resection type, tumor location, histopathology, pT stage, tumor size, histologic grade, lymph node involvement, lymphatic vessel invasion, blood vessel invasion and perineural invasion, resection margins, adjuvant chemotherapy and radiation therapy, responses to treatment, and survival were obtained from patients' charts.

The primary tumor was staged according to the American Joint Committee on Cancer (AJCC) TNM staging classification for gastric cancer (6th edn.) [23]. Moreover, the clinicopathologic findings were determined according to the Japanese Classification of Gastric Carcinoma (JCGC) [24]. Histologic tumor specimens were reevaluated by a pathologist who was an expert in matters of gastric cancer after all patients or their relatives gave written consent.

Immunohistochemical Staining of PRL-3

Four-μm sections were cut from each block, deparaffinized with xylene, and rehydrated through a graded alcohol. IHC was performed by using the 'streptavidin-biotin-peroxidase' method. The sections were subjected to a 15-min microwave pretreatment in 10 mmol/l citrate buffer (pH 6.0) at 125°C to retrieve antigenicity. They were allowed to cool in the box at room temperature for 60 min before being immersed in 3% H_2O_2 for 30 min to block endogenous peroxidase. After incubating with Protein Block solution for 10 min, the primary polyclonal rabbit antibody, anti-PRL-3 (1/450 dilution; Sigma, St. Louis, MO, USA) was applied to sections and incubated for 1 h at room temperature. Subsequently, the sections were incubated with biotinylated secondary antibody for 30 min and streptavidin-HRP for 30 min. Chromogenic fixation was carried out with diaminobenzidine at room temperature and the sections were then counterstained with Mayer's hematoxylin.

Evaluation of PRL-3 staining was performed by an experienced pathologist without any knowledge of the clinical information. Normal gastric tissue was used as a negative control in the slides. Staining was then scored semiquantitatively. Stained tumor cells were proportioned to all tumor cells. The score for PRL-3 staining was ranked as follows: low, no staining, or staining observed in <10% of tumor cells (score 0), or faint/barely perceptible staining detected in ≥10% of tumor cells (score 1+) (Fig. 1a); moderate, moderate complete staining found in ≥10% of tumor cells (score 2+) (Fig. 1b); and high, strong ≥10% of tumor cells (score 3+) (Fig. 1c).

Adjuvant Treatment

In total, 70 patients (63.6%) had received adjuvant chemoradiotherapy with 5-fluorouracil 425 mg/m^2 per day, plus leucovorin 20 mg/m^2 per day, for 5 days, followed by 4,500 cGy of radiation at 180 cGy per day, given 5 days per week for 5 weeks, with modified doses of fluorouracil

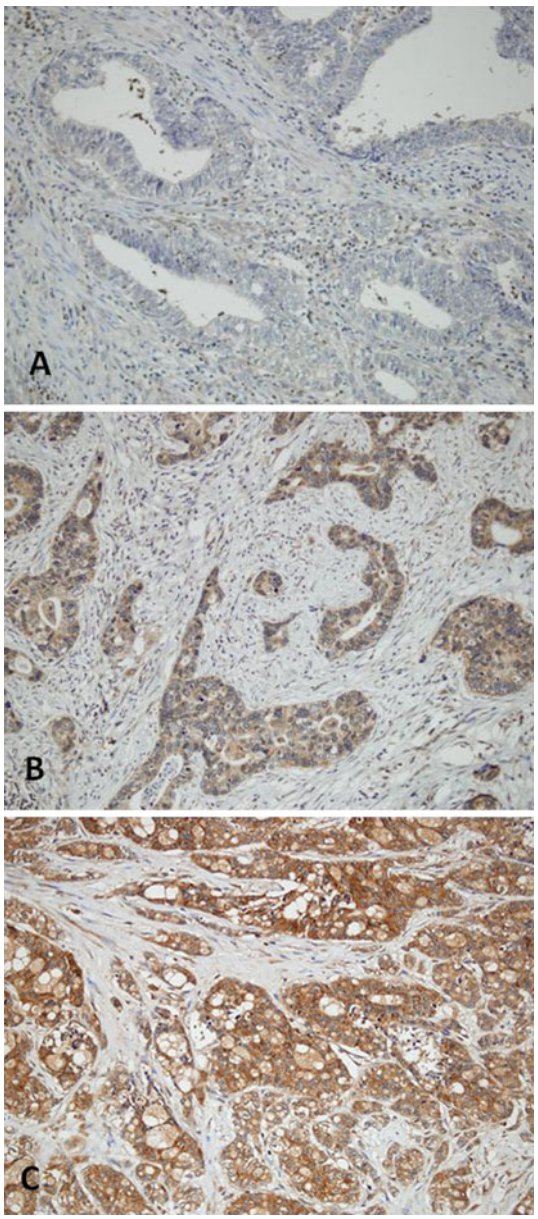

Fig. 1 Expression of PRL-3 in tumor tissues of primary gastric cancer. Representative negative expression (**a**), moderate expression (**b**) and high expression (**c**) of PRL-3 were detected using the IHC method, respectively (×200)

and leucovorin on the first four and the last 3 days of radiotherapy, within 4 weeks after surgery. Nevertheless, 40 patients (36.4%) had not received adjuvant chemoradiotherapy.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. The χ^2 test and Fisher's exact test were used to analyze the relationships between PRL-3 expression and other clinicopathological factors. Survival analysis and curves were established according to the Kaplan–Meier method and compared by the logrank test. Disease-free survival (DFS) was defined as the time from curative surgery to disease progression or recurrence, or to the date of death or the loss in follow-up. Overall survival (OS) was described as the time from diagnosis to the date of the patient's death or the loss in follow-up. Univariate analyses were carried out to evaluate the significance of PRL-3 expression and other clinicopathological features as prognostic factors and then multivariate analysis with the Cox proportional hazards model was performed in order to further analyze the PRL-3 expression and all of the significant prognostic factors that were found in the univariate analysis. Multivariate p values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in the tests and p values <0.05 were considered to be statistically significant.

Results

Forty-four patients (40%) were women and 66 (60%) were men, with a median age of 62 years (range: 30–87 years). Sixty patients were older than 60 years (54.5%). Eight patients (7.3%) were classified as stage I, 20 (18.2%) as stage II, and 82 (74.5%) as stage III. In 58 patients (52.7%), the histology of the tumor was poorly differentiated, in 48 patients tumors was moderately differentiated, and in the remaining four patients tumors were well differentiated. The majority of patients had pure adenocarcinoma histology ($n = 76$, 69.1%), while 31 cases (28.2%) had adenocarcinoma with signet-ring cell component. The mean tumor size was 6 ± 3.03 cm (range: 1–17 cm). Moreover, the median number of dissected and metastatic lymph nodes was 21 (range: 15–61) and five (range: 0–40), respectively. Based on the presence of lymph node metastasis, 73 (66.3%) patients were classified as node-positive, and the remaining 37 patients (33.7%) were node-negative. The primary tumor was located in the upper third of the stomach in 25 patients (22.7%), in the middle third in 25 patients (22.7%), and in the lower third in 54 patients (49.1%); in the six patients (5.5%), the tumor involved the stomach diffusely.

After IHC analysis was carried out to evaluate the frequency of PRL-3 overexpression in 110 gastric tumor samples, high PRL-3 expression was detected in 34 (31%) and moderate expression was found in 45 (41%) tumor samples. In addition, 31 tumor samples (28%) were stained as negative ($n = 14$, 12.7%) or low ($n = 17$, 15.5%) with respect to PRL-3 expression. Significant differences were detected in gender, histology, lymph node metastasis, and

the presence of recurrence between different PRL-3 expression groups. The rate of high PRL-3 expression was significantly higher in male patients than female patients ($p = 0.02$). High PRL-3 expression was closely correlated with lymph node metastasis ($p = 0.04$) compared to low PRL-3 expression. However, tumor with pure adenocarcinoma histology highly expressed PRL-3 more than other types ($p = 0.006$). The prevalence of recurrence for patients with high PRL-3 expression was significantly higher than that for patients with low PRL-3 expression ($p < 0.001$). The correlations between the rate of PRL-3 expression and clinicopathological findings are shown in Table 1.

At the median follow-up of 20.5 months (range: 3.5–58 months), 2-year OS rate and the median OS interval of the entire cohort of patients were 50.7% and 21.3 months, respectively. Moreover, the median DFS time and 2-year DFS rate were 16.5 months and 40.4%, respectively. Eighty patients (72.7%) completed the 2-year follow-up, while 30 patients (27.3%) (two in group 1, nine in group 2, and 19 in group 3) died due to their disease. When the survival analysis was performed according to PRL-3 expression, the median OS time and 2-year OS rate for patients with high or moderate PRL-3 expressed tumors were worse than those with low PRL-3 expression (23.3%, 16.3 months vs. 51.8%, 25.6 months vs. 86.7%, not reached, respectively, $p = 0.001$, Fig. 2). In addition, patients with low PRL-3 expression had a higher DFS rate and the median DFS interval than those with moderate or high PRL-3 expression (85.1%, not reached vs. 23.1%, 16.1 months vs. 24%, 12.2 months, respectively, $p < 0.001$, Fig. 3). In the univariate analysis for OS in the entire cohort of patients, lymph node metastasis, TNM stage, blood vessel invasion, lymphatic vessel invasion, perineural invasion, and the presence of recurrence were found to be significant prognostic factors. In addition, the univariate analysis for DFS indicated that lymph node metastasis, blood vessel invasion, and perineural invasion were important prognostic indicators. For patients with low PRL-3 expression, the univariate analysis showed that only the presence of recurrence ($p < 0.001$) was an important prognostic indicator for OS. However, histology ($p = 0.04$), pT stage ($p = 0.004$), TNM stage ($p < 0.001$), blood vessel invasion ($p = 0.01$), and recurrence in patients with moderate PRL-3 expression and lymphatic vessel invasion and recurrence for patients with high PRL-3 expression were found to be important prognostic factors for OS.

A multivariate analysis with the Cox proportional hazards model was carried out in order to further evaluate all of the significant prognostic factors that were found in the univariate analysis for survival. It was found that the rate of PRL-3 expression was an independent prognostic factor ($p = 0.003$, HR: 2.25), as were lymph node metastasis and the presence of recurrence. Furthermore, the multivariate analysis showed that the rate of PRL-3 expression and lymph node metastasis were independent prognostic indicators for DFS ($p = 0.001$, HR: 1.98 and $p = 0.03$, HR: 1.60, respectively). Table 2 shows the results of multivariate analysis for both OS and DFS.

The majority of patients were treated with postoperative chemoradiotherapy (63.6%). The median DFS time for patients having received chemoradiotherapy was similar to that of patients who were not treated with chemoradiotherapy (16.5 vs. 16.4 months, $p = 0.31$). In addition, median OS interval in the treatment group was longer compared to patients who were not receiving chemoradiotherapy, but this difference was not statistically significant (28.6 vs. 18.2 months, $p = 0.23$). Recurrent disease was detected in 51 (46.4%) of the patients. The rate of recurrence for patients with low PRL-3 expression was significantly low compared to patients with high PRL-3 expression (12.9 vs. 73.5%, $p < 0.001$). The most frequently relapsing sites were the liver and peritoneum (40.5 and 24.5%, respectively). After recurrent disease was detected, patients were treated with second-line chemotherapy or best supportive care alone.

Discussion

In the present study, high PRL-3 expression was significantly correlated with gender, histology, lymph node metastasis, and the presence of recurrence. Using multivariate analysis, we found that the PRL-3 expression level was an independent prognostic factor for both OS and DFS, in addition to the already-known important clinicopathological prognostic indicators such as lymph node metastasis and the presence of recurrence in patients with gastric cancer who had undergone radical surgery.

PTPs play a fundamental role in regulating different proteins and PRL family (PRL-1, -2, and -3) represent a new class of PTP superfamily members. PRL phosphatases regulate key pathways involved in tumorigenesis and metastasis, and are overexpressed in varieties of cancer tissues [7, 8, 25, 26]. In recent years, the role of PRL-3 expression has been evaluated in tumor metastasis and some studies indicated that high PRL-3 expression is associated with invasion, metastasis, and poor prognosis in several human cancers [12–18, 27]. PRL-3 overexpression was found to be closely correlated with lymph node metastasis or peritoneal metastasis in gastric cancer patients [19–22]. However, the prognostic value of PRL-3 expression in gastric cancer tissues is not completely understood and a consensus has not been reached on its clinical significance.

Table 1 Relationship between clinicopathological factors and PRL-3 expression in primary lesions of patients who had curative gastrectomy

Factor	Low, *n* (%)	Moderate, *n* (%)	High, *n* (%)	*p* value
All patients	31 (28)	45 (41)	34 (31)	
Gender				0.02
Male	19 (61.3)	21 (46.7)	26 (76.5)	
Female	12 (38.7)	24 (53.3)	8 (23.5)	
Age (years)				0.33
≤60	13 (41.9)	18 (40)	19 (55.9)	
>60	18 (58.1)	27 (60)	15 (44.1)	
Tumor site				0.11
Upper	4 (12.9)	15 (33.3)	6 (17.6)	
Middle	11 (35.5)	9 (20)	5 (14.7)	
Lower	14 (45.2)	18 (40)	22 (64.7)	
Diffuse	2 (6.5)	3 (6.7)	1 (2.9)	
Surgery type				0.42
Proximal	4 (12.9)	8 (17.8)	5 (14.7)	
Distal	16 (51.6)	16 (35.6)	19 (55.9)	
Total	11 (35.5)	21 (46.7)	10 (29.4)	
Tumor size (cm)				0.46
≤5	10 (32.3)	17 (37.8)	16 (47.1)	
>5	21 (67.7)	28 (62.2)	18 (52.9)	
Histology				0.006
Adenocarcinoma	18 (58.1)	39 (86.7)	19 (55.9)	
Signet-ring cell carcinoma	11 (35.5)	5 (11.1)	15 (44.1)	
Mixed	2 (6.5)	1 (2.2)	–	
Tumor differentiation				0.26
Well differentiated	3 (9.8)	1 (2.3)	–	
Moderately differentiated	10 (32.2)	24 (53.3)	14 (41.2)	
Poorly differentiated	18 (58)	20 (44.4)	20 (58.8)	
Lymph node metastasis				0.04
Absence	21 (67.7)	10 (22.2)	6 (17.6)	
Presence	10 (32.3)	35 (77.8)	28 (82.4)	
pT stage				0.54
T1	2 (6.5)	1 (2.2)	3 (8.8)	
T2	8 (25.8)	16 (35.6)	6 (17.6)	
T3	18 (58.1)	22 (48.9)	19 (55.9)	
T4	3 (9.7)	6 (13.3)	6 (17.6)	
TNM stage				0.60
I	2 (6.5)	2 (4.4)	4 (11.8)	
II	7 (22.5)	9 (20.0)	4 (11.8)	
III	22 (71.0)	34 (75.6)	26 (76.4)	
Blood vessel invasion				0.29
Absence	6 (19.4)	13 (28.9)	5 (14.7)	
Presence	25 (80.6)	32 (71.1)	29 (85.3)	
Perineural invasion				0.12
Absence	9 (29)	6 (13.3)	4 (11.8)	
Presence	22 (71)	39 (86.7)	30 (88.2)	
Recurrence				<0.001
Absence	27 (87.1)	23 (51.1)	9 (26.5)	
Presence	4 (12.9)	22 (48.9)	25 (73.5)	

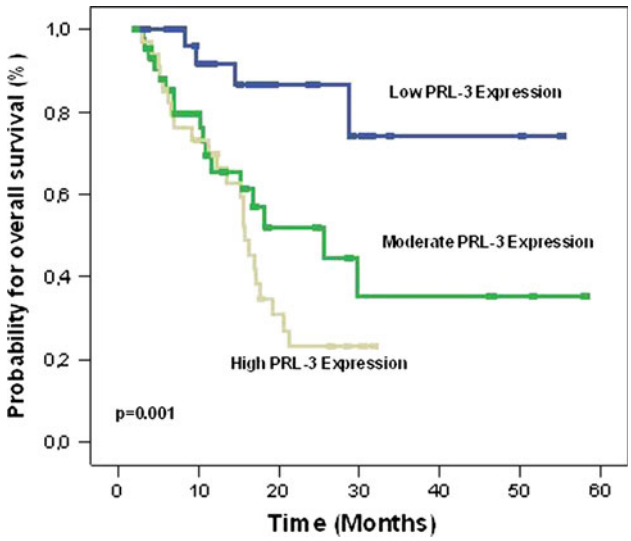

Fig. 2 OS curves according to the PRL-3 status

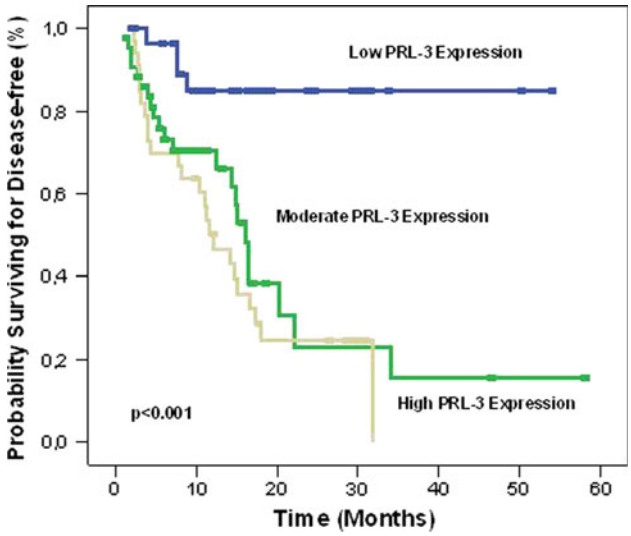

Fig. 3 DFS curves from resection to recurrence according to the level of PRL-3 expression

Miskad et al. [19] showed that PRL-3 is positively correlated with lymph node metastasis and tumor stage in gastric cancer. In the study carried out by Wang et al. [22], high PRL-3 expression was more frequently detected in the lymph node metastasis than in the matched primary lesion and it had a negative impact on the prognosis of patients with gastric cancer. Moreover, Li et al. [21] reported that PRL-3 expression was associated with peritoneal metastasis and poor prognosis in gastric cancer patients. Dai et al. [28] showed that high PRL-3 expression was correlated with tumor size, depth of invasion, high TNM stage, and tumor recurrence, and patients with positive PRL-3 expression had a significant shorter OS and DFS. In light of all these findings, the authors concluded that PRL-3 expression was a novel prognostic factor for predicting the potential of recurrence and survival in patients with gastric cancer.

In the present study, we analyzed the expression of PRL-3 by IHC in tumor tissues of gastric cancer patients. We excluded patients with peritoneal or hepatic metastasis, and only patients with R_0 gastric resection and without distant metastasis were included. Therefore, our study may be noteworthy in determining the prognostic significance of PRL-3 expression in patients with curative gastrectomy who have no metastasis. Significant differences were detected in gender, histology, lymph node metastasis, and the presence of recurrence between PRL-3 expression groups. Thus, our results are compatible with the literature with respect to lymph node metastasis [19, 20, 22, 28–30] and gender [20] but differ from previous reports according to histological subtype [19, 20, 28–30].

Several studies have demonstrated that PRL-3 expression is a valuable prognostic marker for breast cancer, colorectal cancer, as well as gastric cancer [12, 15, 17, 20, 22]. In this study, we found that there is a statistically significant difference with respect to DFS or OS between PRL-3 expression groups. The median OS time and 2-year OS rate of patients with low PRL-3 expressed tumors were better than those of patients with high or moderate PRL-3 expressed tumors. In addition, patients with low PRL-3 expression had a higher DFS rate and the median DFS interval compared to moderate or high PRL-3 expression. For patients with low PRL-3 expression, univariate analysis showed that only the presence of recurrence was an important prognostic indicator for OS. When univariate analysis was carried out for patients with moderate and high PRL-3 expression, histological type, pT stage, TNM stage, blood vessel invasion, and recurrence in patients with moderate PRL-3 expression, however, lymphatic vessel invasion and recurrence for patients with high PRL-3 expression were detected to be important prognostic factors. Our results are compatible with previous reports [19, 20, 28–30].

When multivariate analysis was performed according to the level of PRL-3 expression for OS, it was found that the rate of PRL-3 expression was an independent prognostic factor, as were the presence of lymph node metastasis and recurrence. For DFS, multivariate analysis also indicated that PRL-3 expression level and lymph node metastasis are independent prognostic indicators. Prognostic significance of TNM staging could not be shown by multivariate analysis. This may be related to the retrospective nature of our study and short follow-up period. In light of all these findings, PRL-3 expression was found to provide additional prognostic information for patients with gastric cancer who had undergone radical gastrectomy. Previous studies have been confirmed to be an important role of PRL-3

Table 2 Multivariate analysis for OS and DFS in patients with gastric cancer

Factor	Wald value	*p* value	HR	95% CI
OS				
Lymph node metastasis	4.57	0.03	2.10	1.06–4.17
TNM stage	0.77	0.38	0.74	0.38–1.43
Blood vessel invasion	1.31	0.25	2.31	0.55–9.64
Lymphatic vessel invasion	0.03	0.85	0.89	0.27–2.96
Perineural invasion	0.05	0.81	0.83	0.18–3.81
Recurrence	11.41	<0.001	3.21	1.21–4.67
PRL-3 expression level	9.00	0.003	2.25	1.32–3.84
DFS				
Lymph node metastasis	4.72	0.03	1.60	1.04–2.45
TNM stage	0.20	0.65	1.26	0.46–3.44
Blood vessel invasion	0.48	0.48	1.40	0.53–3.67
Perineural invasion	0.02	0.87	1.13	0.25–5.08
PRL-3 expression level	10.67	0.001	1.98	1.31–2.98

HR hazard ratio, *CI* confidence interval, *OS* overall survival, *DFS* disease-free survival

expression in cancer metastasis [27]. They showed that elevated PRL-3 expression was associated with the progression of several types of human carcinoma. PRL-3 expression was elevated during the development or advancement of colorectal, breast, gastric, ovarian, and liver carcinomas [31]. Furthermore, previous studies also suggested that PRL-3 plays a causative role in promoting cell motility, invasion, and metastasis, but little is known about the molecular mechanisms by which PRL-3 promotes motility, invasion, and metastasis [13, 14, 18, 31]. It was reported that PRL-3 exerted its functions by regulating Rho family GTPase, activating Src, and modulating the PI3K–Akt pathway [32–34] in a context-dependent manner. On the other hand, a transcriptional regulation of PRL-3 by p53 has been reported [35]. In addition to these evidences, high PRL-3 expression was more frequently found in primary colorectal and liver tumors compared to normal tissue [10, 12], in advanced versus early stage primary ovarian tumors [36], and in colorectal, breast, and gastric cancer metastases compared to primary tumors [10, 12–14, 19–21, 27]. In light of all these findings, the PRL-3 expression level in primary tumors had a significant predictive value for the development of liver and lung metastases of colorectal, breast, and gastric cancer [27], but not ovarian cancer, according to the study recently performed by Ren et al. [16]. Our study also confirmed that high PRL-3 expression was associated with short DFS and OS in patients with gastric cancer who underwent radical gastrectomy. Moreover, high PRL-3 expression was an independent prognostic factor for both OS and DFS, and thus our results are compatible with the literature.

Very recently, Ooki et al. [37] analyzed PRL-3 genomic amplification using polymerase chain reaction and/or fluorescence in situ hybridization in 77 primary gastric tumors. In addition, they evaluated the anticancer activity of PRL-3 inhibitor (1,4-bromo-benzylidene rhodanine). The authors found that PRL-3 genomic amplification was closely concordant with a high PRL-3 expression level in cell lines. In addition, PRL-3 genomic amplification was related to metastatic lymph node status. They found that PRL-3 inhibitor had dose-dependent anticancer efficacy and remarkably resulted in apoptosis on all of the tested cell lines with PRL-3 expression. In the present study, we analyzed PRL-3 expression using only the IHC method. However, we planned to evaluate PRL-3 expression using both IHC and microRNA interference, and PRL-3 genomic amplification in both early and advanced-staged gastric cancer tissues, which is similar to Ooki et al.'s study [37].

The major limitation of our study is the retrospective nature. The other limitations of this study are the relatively small sample size and short follow-up interval. These factors might have influenced our results. Although our results should be confirmed by prospective studies, we believe that our results contribute to the literature because our trial included only gastric cancer patients without distant metastasis who had undergone curative gastrectomy, and univariate and multivariate analysis were performed for both OS and DFS, and also for PRL-3 subgroups.

In conclusion, our study indicates that a high PRL-3 expression level is an important prognostic indicator in patients with gastric cancer who had undergone R_0 radical surgery. Although more studies are required to fully determine the potential value of PRL-3 expression as a useful molecular marker in gastric cancer progression, it may help as a guide to detect patients with gastric cancer who have a poor prognosis and also to identify patients more accurately in terms of their mortality after curative resection.

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