



Clinical Significance of PRR13 Expression in Colorectal Cancer and Its Correlation with Patients' Prognosis

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KEYWORDS Clinicopathological Features. Colorectal Cancer. PRR13. Survival and Prognosis. TXR1

ABSTRACT This paper aimed to investigate the differential expression patterns of PRR13 gene in colorectal cancer, and to analyze the correlation between the staining degree of PRR13, clinicopathological features, survival and prognosis of patients with colorectal cancer. Clinical data and tumor tissues were collected from 161 patients with pathologically confirmed colorectal cancer who received radical surgery and standard treatment. Tissue sections were prepared and the PRR13 expression in colorectal cancer tissues was detected by immunohistochemistry. PRR13 expression was correlated with differentiation type, pTNM staging, lymph node metastasis, distant metastasis and of colorectal cancer ($P < 0.05$) while no significant difference exist in age, gender, affected sites, mucus secretion, infiltration depth and cancerous nodes ($P > 0.05$). The five-year overall survival (OS) decreased significantly in patients with high PRR13 expression than in those with low PRR13 expression ($P < 0.01$). Intensity of PRR13 expression can reflect the clinicopathological features of colorectal cancer and serve as a prognostic indicator.

INTRODUCTION

Colorectal cancer is a common malignancy of the digestive tract, and its global incidence has been increasing at a rate above four percent yearly (Siegel et al. 2013). Stage III colorectal cancer with lymph node metastasis is associated with a poor prognosis, and the five-year survival is only about fifty percent (Lan et al. 2012). Although preoperative neoadjuvant radiochemotherapy, radical tumor resection and adjuvant radiochemotherapy can control the progression of colorectal cancer in some patients, local relapse, distant metastasis, and chemotherapy resistance are still the major causes of poor prognosis of patients with colorectal cancer (Stintzing et al. 2016).

PRR13 (taxol-resistant gene, TXR1) gene was first discovered as a transcriptional regulator of thrombospondin-1 (TSP1) that modulates cellular sensitivity to taxanes in human prostate cancer cells (Lih et al. 2006). The TXR1/TSP1 pathway was widely reported to be associated with chemotherapeutic drug resistance. Upregulating the expression of TSP1 reversed taxol resistance in nasopharyngeal carcinoma (Peng et al. 2010) and expression of TXR1 and TSP1 was able to predict overall survival of patients with lung adenocarcinoma (Papadaki et al. 2009). TXR1 gene was found to mediate oxaliplatin re-

sistance by inducing autophagy in human nasopharyngeal carcinoma cells. Extensive studies have focused on the role of TXR1 in chemotherapy for gastric cancer, which showed that TXR1 was an important factor in oxaliplatin and cisplatin resistance in gastric cancer (Bai et al. 2010; Bi J et al. 2014; Liu et al. 2016; Duan et al. 2018). Additionally, TXR1 and TSP1 expression varied by the molecular subtypes of breast cancer patients and inhibition of TXR1 sensitized breast cancer cells to taxol (Bai et al. 2012; Zhang et al. 2016). While playing an important role in chemotherapy resistance, TXR1 gene has been researched as a prognostic biomarker by several studies recently. The expression of TXR1 mRNA, in conjunction with other genes, was confirmed to be a valuable biomarker for the prediction of resistance to treatment of non-small cell lung cancer and epithelial ovarian cancer patients (Boiarskikh et al. 2011; Papadaki et al. 2011; Pontikakis et al. 2017; Tryfonidis et al. 2019).

Although massive researches have been done on the PRR13 gene in various cancers, little information have been revealed on the correlation between PRR13 gene and colorectal cancer. Hence there is a pressing need to better understand the correlation between PRR13 expression in tumor samples and clinicopathological features of colorectal cancer, before performing

cell and animal experiments on this basis. This paper found that the differential expression can reflect the clinicopathological features of colorectal cancer and may serve as a prognostic indicator.

Objective

This paper was designed to investigate the differential expression of PRR13 in cancer and non-cancerous tissues and analyzed the correlation between the intensity of staining for PRR13 and clinicopathological features of colorectal cancer.

MATERIAL AND METHODS

Baseline Data

From January 2012 to December 2013 patients with pathologically confirmed colorectal cancer who received radical resection with postoperative standard adjuvant chemotherapy according to NCCN guidelines at Beijing Friendship Hospital, Capital Medical University were recruited. Intact clinical data and tumor specimens were collected from each patient. All of them received long-term outpatient and telephone follow-up. The primary endpoint was 5-year overall survival (OS). Inclusion criteria were as follows: 1. colorectal cancer confirmed by postoperative pathology; 2. receiving radical resection (laparotomy or laparoscopic total mesorectal excision (TME); 8. or laparoscopic complete mesocolic excision (CME); 9. surgical approaches including left hemicolectomy, right hemicolectomy, transverse colectomy, sigmoid colectomy, Dixon surgery, Miles' resection, Hartmann's operation) or palliative excision for colorectal cancer; 3. intact paraffin block specimens of cancer and normal tissues; 4. complete clinical data; 5. regular follow-up; 6. satisfactory pathological staining results. Subjects satisfying any of the following conditions were excluded: 1. colorectal cancer denied by postoperative pathology; 2. having received neoadjuvant radiochemotherapy; 3. dying shortly after surgery due to severe surgical complications; 4. no pathological sections of cancer tissues available; 5. incomplete clinical data; 6. unsatisfactory immunohistochemical staining results. The present study was ap-

proved by the ethics committee of Beijing Friendship Hospital, Capital Medical University.

Histological Section Preparation and Immunohistochemical Staining

The paraffin block specimens of colorectal cancer were collected and made into histological sections. PRR13 expression in the normal colorectal mucosa and colorectal cancer tissues was detected by streptavidin/peroxidase (S-P) immunohistochemistry. The cell nuclei were stained blue by hematoxylin. DAB substrate was added, and yellowish brown color indicated positive PRR13 expression. The staining results were interpreted by two experienced pathologists in a double-blind method. Relevant literatures on pathological immunohistochemistry were reviewed (10), and the criteria for immunohistochemical staining described were used: the scores of 0, 1, 2 and 3 were assigned to the percentage of positive cells of zero percent, one - twenty nine percent, thirty - fifty nine percent and e" sixty percent, respectively. As to the intensity of staining, the scores of 0, 1, 2 and 3 were assigned to colorless, light yellow, brownish yellow and brown, respectively. The total score was calculated by multiplying the two subscores. The total score of 0, 1-2, 3-4, and 6-9 indicated negative (-), weakly negative (+), moderately positive (++), and strongly positive (+++), respectively. The first three score levels were collectively defined as "negative or low expression", and the strongly positive as "high expression". As to nuclear staining, four intensities, namely, (-), (+), (++) and (+++) were set up.

Data Arrangement

The clinical data and statistics of all patients were tabulated. Statistical analysis was performed for immunohistochemistry results and the 5-year OS was calculated.

Statistical Process

The experimental data were analyzed by using SPSS 21.0 software. Count data were represented in the R×C contingency table and analyzed by Z-test. Count data not satisfying the requirements for Pearson's test were analyzed by the adjusted χ^2 test. Survival analysis was conducted by means

of Kaplan-Meier curve and log-rank test. Prognostic factors were identified by univariate Cox regression. Factors with $P < 0.05$ were preliminarily chosen for multivariate Cox regression.

RESULTS

A total of 200 specimens of colorectal cancer (100 pretreated sample sections and 100 large paraffin blocks) were borrowed from experimental sample library at the Department of General Surgery, Beijing Friendship Hospital. All sections were subjected to immunohistochemical staining using anti-PRR13 antibody. No tumor tissues were found in 23 pathological sections, probably because the tumor tissues were not contained in the sections. Another 16 pathological sections had poor staining quality and could not be scored. Excluding the above 39 cases, 161 cases were finally included. All of the pathological sections included contained tumor tissues; 145 sections contained both tumor and normal tissues, and 21 sections contained only tumor tissues. As the comparison was to be made between cancer tissues and the paired normal tissues, only 145 cases were finally recruited.

Baseline Features of Patients

Of 161 patients, there were 93 males and 68 females with an age of 34-89 years old (average 67.32 ± 17.04 years). All of them received radical resection for colorectal cancer at Department of General Surgery of Beijing Friendship Hospital, Capital Medical University. The surgical pathway was divided into laparotomy or laparoscopy; and surgical methods were total mesorectal excision (TME) and complete mesocolic excision (CME); surgical approaches included left hemicolectomy, right hemicolectomy, transverse colectomy, sigmoid colectomy, Dixon surgery, Miles' resection, and Hartmann's operation. Palliative excision for colorectal cancer was performed depending on the patients' conditions. All of the included patients had complete data on name, gender, age, registration No. or inpatient No., serial No. in the sample library, affected site of tumor, pathological type, differentiation degree, pTNM AJCC categories, number of positive lymph nodes, lymph node yield, with or without vascular and neural invasion, and with or without cancerous nodes. Statistical comput-

ing was performed for the baseline and follow-up information of 161 patients. There were 102 patients aged 65 or above, and 59 patients below 65; 94 patients had tumors located in the colon (including cecum), and 67 patients had tumors in non-colon positions (rectum and interface between rectum and sigmoid colon). The pathological type was mucoid carcinoma or adenocarcinoma containing mucinous components in 35 patients; it was adenocarcinoma not containing mucinous components in 126 patients. The differentiation was of a low degree in 114 patients and of a high degree in 47 patients. According to the eighth version of AJCC staging system for colorectal cancer (11), the 161 patients were classified as follows: stage I in 13 patients, stage II in 65 patients (stage IIa in 33 patients, stage IIb in 21 patients, stage IIc in 1 patient), stage III in 60 patients (stage IIIa in 1 patient, stage IIIb in 42 patients, stage IIIC in 17 patients), and stage IV in 23 patients (stage IVa in 16 patients, stage IVb in 3 patients, and stage IVc in 4 patients) (Table 1).

PRR13 Expression in Normal Colorectal Mucosa and Colorectal Cancer Tissues

By reviewing the staining results, it was found that PRR13 was expressed in the cell nuclei of normal colorectal cancer tissues, but very lowly expressed or not expressed in the cytoplasm. In contrast, in the colorectal cancer tissues, PRR13 expression increased significantly in the cytoplasm, and it decreased significantly in the nuclei (Fig. 1).

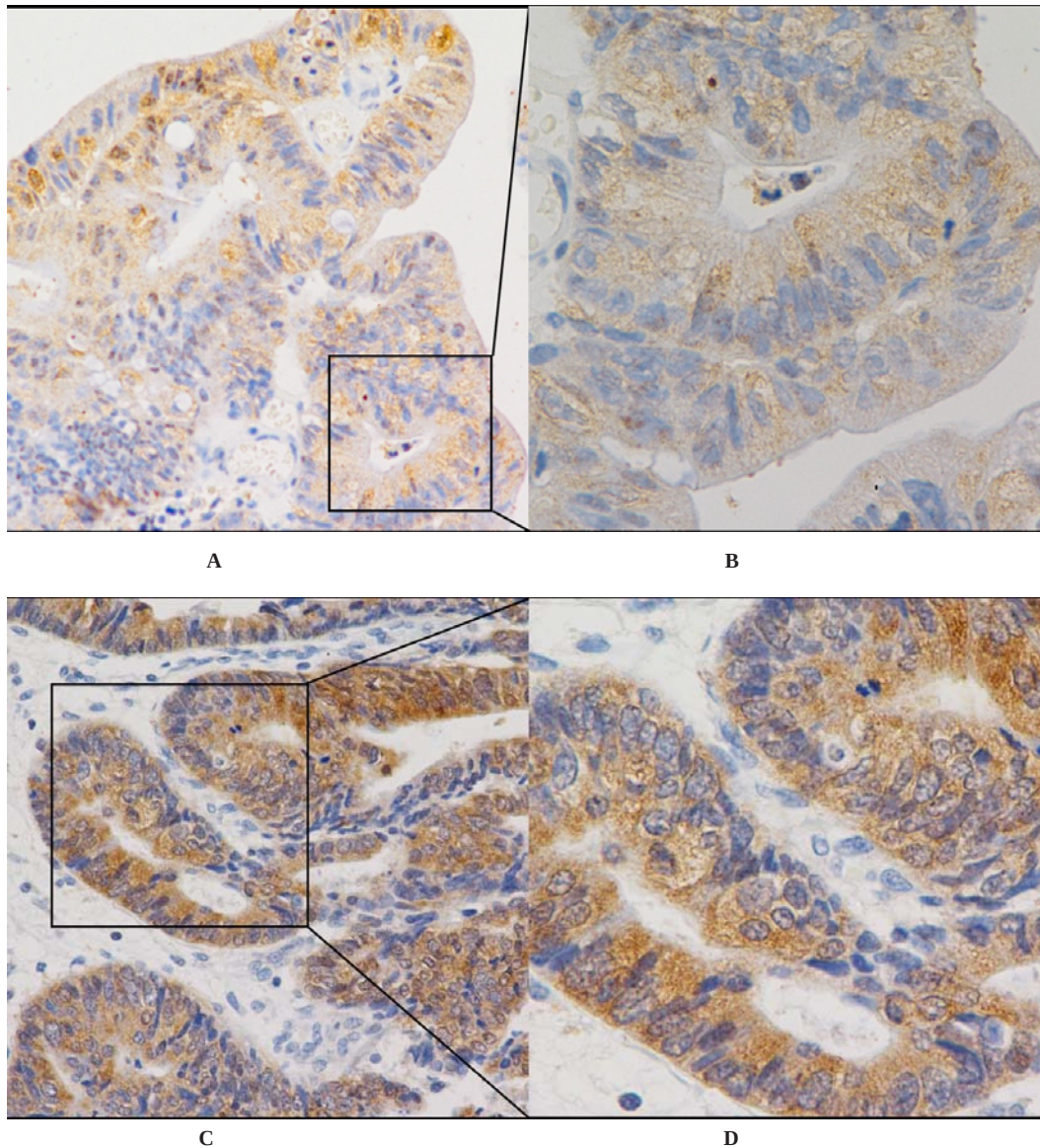
PRR13 was expressed in both colorectal cancer tissues and normal tissues. It was largely expressed in the cell nuclei of the normal colorectal tissues (142/145, 97.9%). Only a small amount of PRR13 was found in the cytoplasm of the normal tissues (27/145, 18.6%), which was typical of PRR13 as a nuclear protein. PRR13 expression decreased significantly in the cell nuclei of cancer tissues (30/145, 20.7%), and it was not expressed in most of the cancer tissue specimens (131/145, 79.3%). However, PRR13 expression increased considerably in the cytoplasm than in the normal tissues (61/145, 42.1%). PRR13 expression differed significantly in the cell nuclei and cytoplasm of both colorectal cancer tissues and normal colorectal tissues ($P < 0.01$) (Table 2).

Correlation between PRR13 Expression in Colorectal Cancer Tissues and Prognosis

All 161 patients received regular follow-up by telephone calls or outpatient visits. The follow-up ranged from 6 months to 60 months, with a median of 55 months. K-M curve was plotted based on the survival. Cox regression was per-

formed to identify the risk factors. K-M curve indicated that the mean survival of patients with high PRR13 expression was significantly shorter compared to those with low PRR13 expression or no PRR13 expression (Fig. 2).

Subgroup analysis was then performed by classifying the patients into Duke Stage AB, Duke Stage C, and pTNM stage IV. K-M curves were



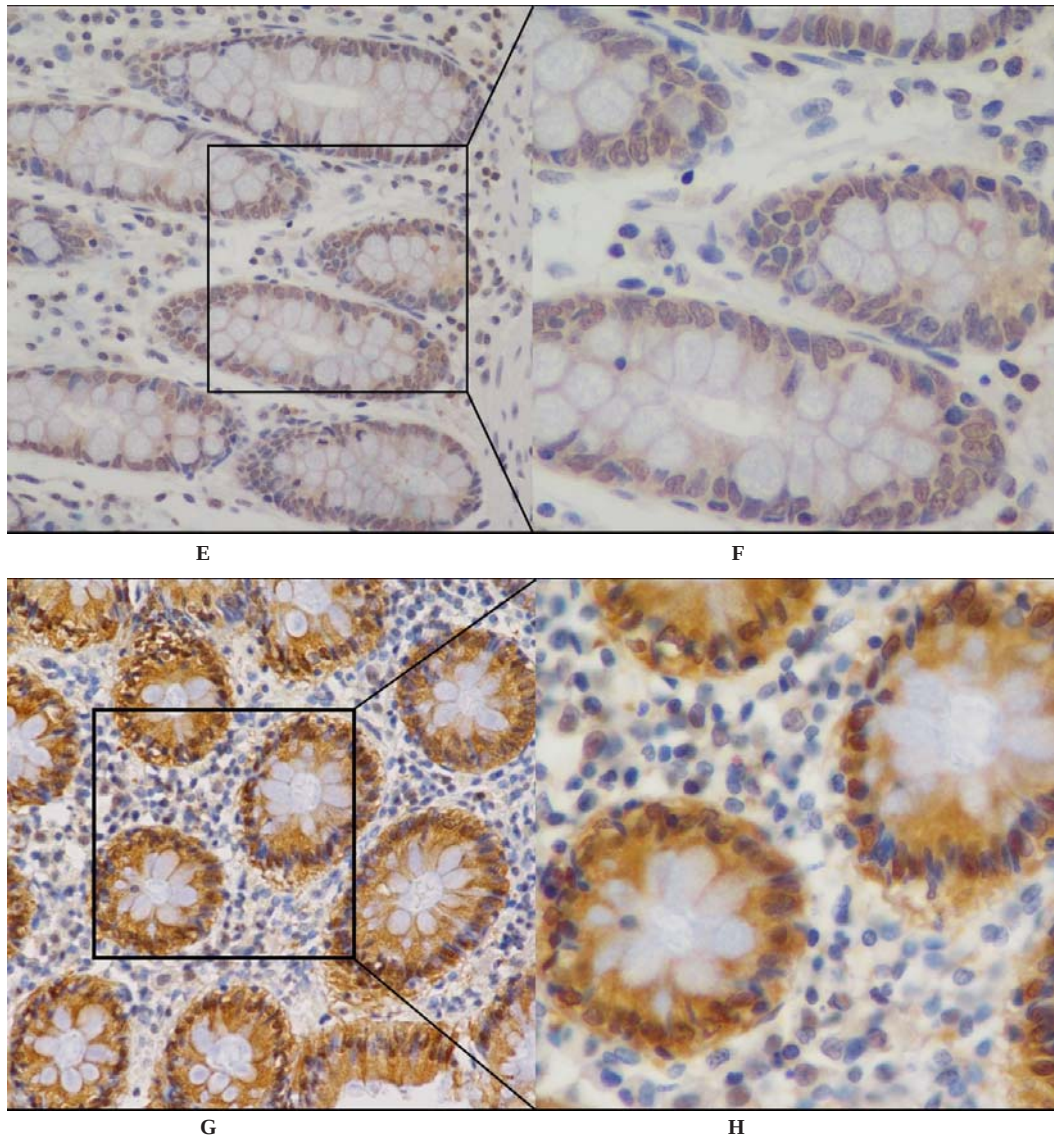


Fig. 1. Expression of PRR13 in colorectal carcinoma tissues immunohistochemical staining of tissues was performed. (A)(B) In the colorectal cancer tissues, the percentage of positively stained cells was scored 1, and intensity of staining 1; the nuclear staining of the cancer tissue was negative (-); thus the total score of immunohistochemical staining was 1, indicating weak PRR13 expression; (C)(D) In the colorectal cancer tissues, the percentage of positively stained cells was scored 3, and intensity of staining 3; the nuclear staining of the cancer tissues was negative (-); thus the total score of immunohistochemical staining was 9, indicating strong PRR13 expression; (E) (F) In the normal colorectal tissues, the percentage of positively stained cells was scored 0, and intensity of staining 0; the nuclear staining of the normal colorectal tissues was positive (++); thus the total score of immunohistochemical staining was 0 indicating no PRR13 expression; (G) (H) In the normal colorectal tissues, the percentage of positively stained cells was scored 3, the intensity of staining was scored 3, and the nuclear staining of the normal colorectal tissues was positive (+++); thus the total score of immunohistochemical staining was 9, indicating strong PRR13 expression in the nuclei. PRR13 was expressed in the cell nuclei of normal colorectal tissues, but very lowly expressed or not expressed in the cytoplasm; in contrast, in the colorectal cancer tissues, PRR13 expression increased significantly in the cytoplasm, and the percentage of positively stained nuclei decreased considerably

Table 1: Clinical prognosis and immunohistochemical features of PRR13

	Cases	Prognosis			Expression of PRR13		
		Survival	Death	p value	High	Negative or low	p value
<i>Gender</i>							
Male	93	48	45	0.592	41	52	0.713
Female	68	38	30		28	40	
<i>Age (years)</i>							
>65	102	45	57	0.002	45	57	0.671
≤65	59	41	18		24	35	
<i>Location</i>							
Colon	94	52	42	0.566	37	57	0.288
Non-colon	67	34	33		32	35	
<i>Mucus Structure</i>							
Containing	35	12	23	0.01	20	15	0.054
Not containing	126	74	52		49	77	
<i>Differentiation</i>							
Poor	114	70	44	0.002	29	18	0.002
Moderate or good	47	16	31		40	74	
<i>pTNM</i>							
I	13	11	2	0.001	2	11	0.025
II	65	40	25		25	40	
III	60	30	30		27	33	
IV	23	5	18		15	8	
<i>Invasion Depth</i>							
T2	14	10	4	0.1011	3	11	0.0964
T3	78	38	40		31	47	
T4	69	28	41		35	34	
<i>CA Lymph Node</i>							
Yes	78	34	44	0.015	40	38	0.036
No	83	52	31		29	54	
<i>Metastasis</i>							
Yes	19	5	14	0.03	13	6	0.0165
No	142	75	67		56	86	
<i>Vascular Invasion</i>							
Yes	35	12	23	0.01	22	13	0.007
No	126	74	24		47	79	
<i>Cancer Nodules</i>							
With	29	6	23	0.001	12	17	0.859
Without	132	80	52		57	75	

Table 2: Frequencies of cytoplasmic and nuclear staining sections in normal tissue and carcinoma tissue

	Frequency of PRR13 staining in cytoplasm (n=145)				Frequency of PRR13 staining in nucleus (n=145)			
	Normal tissue				Normal tissue			
	Positive	Negative	Total	P value	Positive	Negative	Total	P value
<i>Carcinoma tissue</i>								
Positive	12 (8.27)	49 (33.79)	61 (42.06%)	<0.01	30 (20.69)	0 (0)	30 (20.69%)	<0.01
Negative	15 (10.34)	69 (47.6)	84 (57.94%)		112 (77.24)	3 (2.07)	115 (79.31%)	
Total	27 (18.61%)	118 (81.39%)	145 (100%)		142 (97.93%)	3 (2.07%)	145 (100%)	

plotted for each subgroup. The results showed that in these three subgroups, the survival of Duke

Stage AB was correlated with the intensity of PRR13 expression. But in the patients of Duke

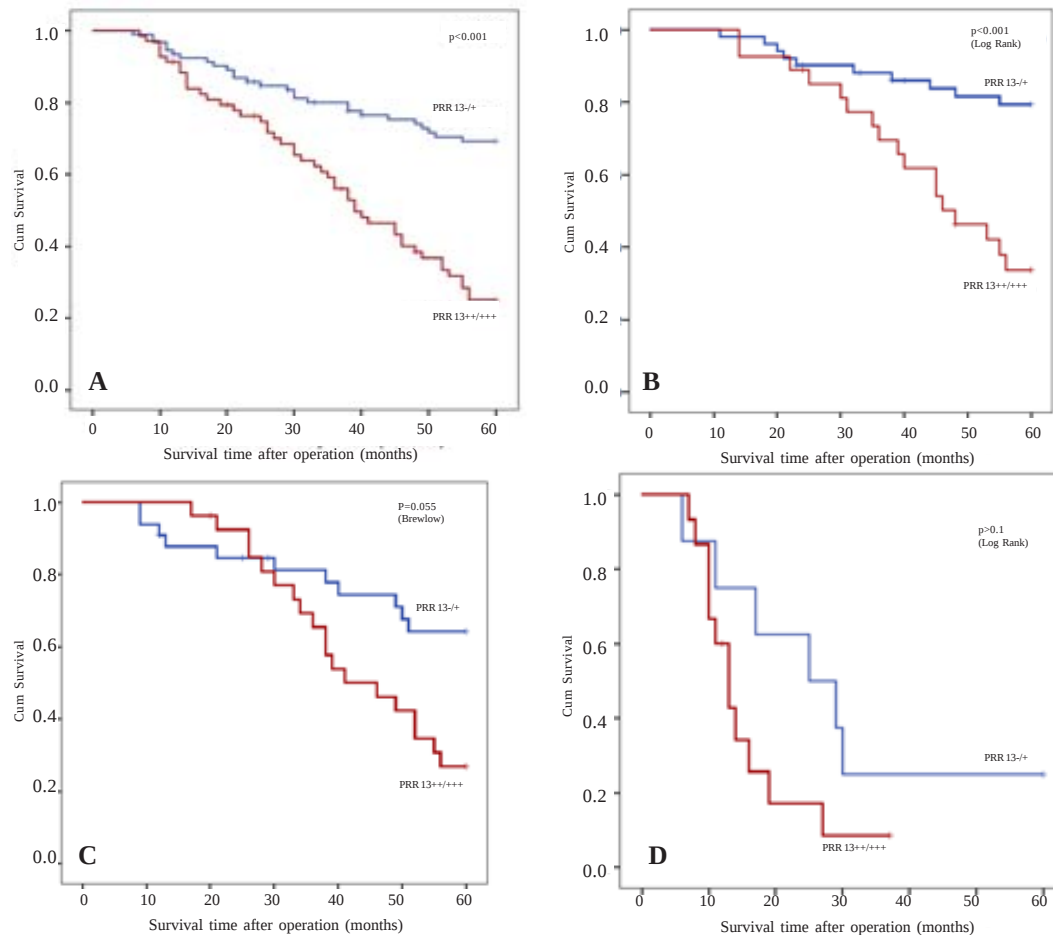


Fig. 2. Kaplan-Meier survival curves for the colorectal cancer patients receiving radical resection of carcinoma and categorized by PRR13 expression. (A) All patients, n=161, $p<0.001$; (B) Patients in Duke A and Duke B, n=78, $p<0.01$; (C) Patients in Duke C, n=60, $p>0.05$; (D) Patients in stage IV, n=23, $p>0.05$

Stage C and stage IV, the survival was not correlated with the intensity of PRR13 expression.

Univariate Cox Regression to Identify the Prognostic Indicators in Colorectal Cancer Patients

The potential prognostic indicators tested were age, gender, anatomical position of cancer, pTNM stage found by postoperative pathology, intensity of PRR13 expression in immunohistochemical staining, distant metastasis, lymph node metastasis, and differentiation degree of tumor, presence or absence of mucinous

components, vascular invasion, and cancerous nodes. They were included into the univariate Cox regression (Table 3). The results showed that the following 9 variables were correlated with the prognosis: age ($p=0.002$, HR: 2.37, 95% CI: (1.39, 4.03)), pTNM stage IV ($p<0.001$, HR: 19.91, 95% CI: (4.57, 86.75)), intensity of PRR13 expression ($p<0.001$, HR: 3.23, 95% CI: (2.01, 5.20)), postoperative distant metastasis ($p=0.021$, HR: 5.30, 95% CI: (1.11, 3.49)), lymph node metastasis ($p=0.005$, HR: 1.94, 95% CI: (1.23, 3.08)), differentiation degree of tumor ($p<0.001$, HR: 2.36, 95% CI: (1.49, 3.74)), absence or presence of mucinous components ($p=0.002$, HR: 2.22, 95% CI:

Table 3: Univariate Cox regression analysis on prognosis of patients with colorectal cancer

Variable	β	SE	χ^2	P	HR	95% CI
<i>Age (years)</i>						
<65	Reference					
>65	0.86	0.27	10.06	0.002	2.37	(1.39, 4.03)
<i>Gender</i>						
Male	Reference					
Female	-0.14	0.24	0.37	0.543	0.87	(0.55, 1.38)
<i>Location</i>						
Colon	Reference					
Non-colon	0.09	0.23	0.15	0.696	1.1	(0.69, 1.73)
<i>pTNM</i>						
I	Reference					
II	1.05	0.73	2.05	0.152	2.86	(0.68, 12.09)
III	1.4	0.73	3.67	0.055	4.05	(0.97, 16.96)
IV	2.99	0.75	15.87	<0.001	19.91	(4.57, 86.75)
<i>Expression of PRR13</i>						
Negative or low	Reference					
High	1.17	0.24	23.4	<0.001	3.23	(2.01, 5.20)
<i>Metastasis</i>						
No	Reference					
Yes	0.68	0.29	5.3	0.021	1.96	(1.11, 3.49)
<i>CA Lymph Node</i>						
No	Reference					
Yes	0.66	0.23	7.98	0.005	1.94	(1.23, 3.08)
<i>Differentiation</i>						
Moderate or well	Reference					
Poor	0.86	0.24	13.27	<0.001	2.36	(1.49, 3.74)
<i>Mucus Structure</i>						
Not containing	Reference					
Containing	0.8	0.25	10.05	0.002	2.22	(1.36, 3.63)
<i>Vascular Invasion</i>						
No	Reference					
Yes	0.65	0.25	6.82	0.009	1.92	(1.18, 3.14)
<i>Cancer Nodules</i>						
Without	Reference					
With	1.18	0.25	22.13	<0.001	3.26	(1.99, 5.34)

(1.36, 3.63)), vascular invasion ($p=0.009$, HR: 1.92, 95% CI: (1.18, 3.14)), and cancerous nodes ($p<0.001$, HR: 3.26, 95% CI: (1.99, 5.34)). Therefore, these 9 variables were further subjected to multivariate Cox regression.

Multivariate Cox Regression to Identify the Prognostic Factors in Colorectal Cancer Patients

The above-mentioned 9 variables were further analyzed by multivariate Cox regression (Table 4). Among them, 4 variables, age ($p<0.001$, HR: 2.71, 95% CI: (1.62, 4.54)), pTNM stage IV ($p=0.002$, HR: 10.23, 95% CI: (2.38, 43.95)), intensity of PRR13 expression ($p<0.001$, HR: 2.72, 95% CI: (1.71, 4.32)) and cancerous nodes ($p=0.001$, HR: 2.72, 95% CI: (1.47, 5.01)) were still correlated with the prognosis of colorectal cancer patients.

DISCUSSION

This paper mainly investigated the expression patterns of PRR13 gene in colorectal cancer and its correlation with survival and prognosis of patients with colorectal cancer. The pathological results confirmed that the expression of PRR13 in cytoplasm increased significantly in the colorectal cancer tissues, whereas in normal colorectal tissues it was mainly located in nucleus. In addition, statistical analysis showed that high PRR13 expression was correlated with low differentiation, advanced pTNM stage, lymph node metastasis, distant metastasis and vascular tumor thrombosis in colorectal cancer.

In recent years, taxol/paclitaxel and taxotere/docetaxel, a semisynthetic taxane identified in the 1980s, are widely used in a wide spectrum of human cancers (Rowinsky 1997). PRR13 was

firstly found in to be a transcriptional regulator of thrombospondin-1 that modulates cellular sensitivity to taxanes (van Amerongen and Berns 2006). Lately a great lot of researches have proved that PRR13/TSP-1 pathway played an important role in the chemotherapeutic modulation of taxanes in breast cancer (Bai et al. 2012; Zhang et al. 2016), nasopharyngeal carcinoma (Peng et al. 2010; Chi et al. 2019), lung adenocarcinoma (Papadaki et al. 2009), non-small-cell lung cancer (Papadaki et al. 2011), cervical carcinoma (Bi W et al. 2014). Additionally, aberrant expression of PRR13 gene also contributed to the resistance of gastric cancer cells to cisplatin and oxaliplatin (Bi J et al. 2014; Liu et al. 2016; Duan et al. 2018).

Since resistance to chemotherapeutic drugs may lead to poor prognosis in cancer patients, PRR13 gene may be one of the biomarkers for predicting the survival condition of patients. Researchers have found that PRR13 gene, together with other differentially expressed genes, may potentially be an effective biomarker in non-small cell lung cancer and epithelial ovarian cancer (Boiarskikh et al. 2011; Zhao et al. 2012; Pontikakis et al. 2017; Hamanaka et al. 2018; Tryfonidis et al. 2019). In the present study, the researchers firstly confirmed the high expression and aberrant distribution of PRR13 gene in colorectal cancer tissues. Meanwhile, the survival data of 161 cases were analyzed statistically and the Kaplan-Meier curve indicated that high PRR13 expression predicted poor prognosis and advanced clinical phenotypes, which was consistent with the previous studies.

The cox regression model was used to evaluate the predictive value of PRR13 gene. Due to limited sample size, the significant factors were first identified by univariate Cox regression ($P < 0.05$) and then they were included into the multivariate Cox regression with the elimination of confounding factors. It was found that PRR13 expression was an independent risk factor for postoperative death of colorectal cancer patients. Thus researchers found that PRR13 expression may be used as a prognostic predictor in colorectal cancer.

The researchers have to point out that some variables were found significant in univariate Cox regression, but not in the subsequent multivariate Cox regression. Moreover, there was no significant difference in the prognosis of pTNM stage II, III and I patients according to Cox regression. The following two reasons are pro-

posed: first, in univariate Cox regression, there may be some false or indirect connections between independent and dependent variables. One of them has no impact on outcomes, but the other one has. Due to the strong correlation between the two, colinearity phenomenon occur. In that case, in univariate Cox regression, these two factors may be both identified as significant. However, in multivariate Cox regression, by adjusting one factor, the false collection between the other factor and the dependent variable disappears. Secondly, since the total sample size is definite, the sample size for each subgroup may be in an imbalance. For example, only 13 cases with stage I colorectal cancer were included in the present study, accounting for eight percent. In contrast, the overall prognosis of patients of stage I and II was good. The longest follow-up duration was only 60 months in the present study, and there were no follow-up visits after that. For these reasons, the bias in Cox regression seems inevitable. However, these were not the dominant factors in the present study, and the researchers were most concerned with the effect of PRR13 expression on prognosis. The sample size of each subgroup stratified by PRR13 expression was sufficiently large, and both univariate and multivariate Cox regression showed that PRR13 expression was a significant variable.

CONCLUSION

Collectively, the aberrant PRR13 expression in colorectal cancer is closely related to the occurrence and malignant progression of colorectal cancer. It can be potentially a biomarker of the clinicopathological features of colorectal cancer, which may facilitate the research and development of specific anti-metastasis and anti-resistance drugs.

RECOMMENDATIONS

Larger sample size are expected and follow-up visits deserve to be strengthened to investigate more precisely. More specific functions of PRR13 in colorectal cancer warrant further study.

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Paper received for publication in March, 2019
Paper accepted for publication in May, 2019