Pathol. Oncol. Res. (2017) 23:409–416
DOI 10.1007/s12253-016-0128-8

ORIGINAL ARTICLE

Prognostic Significance of CD24 in Clear Cell Renal Cell Carcinoma

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Received: 30 April 2016 / Accepted: 5 October 2016 / Published online: 13 October 2016

Abstract The role of cancer stem cells in the initiation and progression of cancer has become a well-studied area of emerging research, and stem cells with different surface markers have been identified in various types of cancer. CD24 is a membrane protein that acts as the ligand for P-selectin and has been defined as a stem cell marker of colonic cancer. The immunohistochemical expression of CD24 is associated with worse patient outcomes in small cell lung cancer, hepatocellular carcinoma, breast cancer, and colon cancer. In this study, we used immunohistochemistry to determine CD24 expression in clear cell, papillary and chromophobe renal cell carcinoma and investigated its relationship with other clinicopathological parameters and prognosis. A total of 108 cases of clear cell, 12 papillary and 13 choromophobe renal cell carcinoma were examined. Clinicopathological features including age, gender, vascular invasion, tumor necrosis, and T stage were recorded. Clinical stage and overall survival and disease-free survival times were recorded. The immunohistochemical expression of CD24 was classified as low or high based on the percentage and intensity of positive staining. CD24 expression was associated with both tumor grade and recurrence rates. The survival analysis revealed that patients with high CD24 expression exhibited significantly lower overall and disease-free survival. Increased expression of CD24 is related to the prognosis of clear cell renal cell carcinoma. This is the first study identifying a strong association between CD24 expression levels and survival. Thus, CD24 expression may aid in predicting prognosis in clear cell renal cell carcinoma.

Keywords Clear cell renal cell carcinoma · Cancer stem cell marker · CD24 · Prognosis

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Introduction

Renal cell carcinoma is currently the 9th most common cancer in men and the 14th most common cancer in women worldwide. This cancer is the 16th most common cause of death from cancer [1]. Approximately 70 % of tumors are clear cell carcinomas derived from the proximal tubule epithelium. The papillary subtype occurs in 10–15 % of patients, and the chromophobe subtype is observed in up to 5 % of patients [1]. Renal cell carcinomas are resistant to radiotherapy, hormonal treatments, and chemotherapy [2].

Cancer stem cells possess a high tumor-forming capacity in animal models [3]. These cells are able to self-renew and undergo asymmetric cell division, which can generate phenotypically different cells with uncontrolled proliferation properties [4]. Several previous studies have demonstrated the association between the cancer stem cells and unfavorable prognosis in carcinomas [5, 6]. The cell surface proteins CD24, CD44, CD29, CD90, CD133 and epithelial specific antigen (ESA) and the enzyme aldehyde dehydrogenase (ALDH1) have all previously been used as markers of cancer stem cells [7–9].

CD24 is a glycosylphosphatidylinositol (GPI)-anchored membrane protein that acts as the ligand of P-selectin, which is an adhesive molecule present on activated endothelial cells and platelets [10]. CD24 is also expressed by B and T lymphocytes, neutrophils, neuronal tissue,

keratinocytes, and renal tubular epithelial cells [11]. CD24 plays important roles in the regulation of B-cell apoptosis, leukocyte signal transduction, leukocyte adhesion and cell selection or maturation during hematopoiesis [12]. This ligand may facilitate tumor cell invasion by increasing the interaction between endothelial cells and cancer cells [13]. Immunohistochemical expression of CD24 has been identified in various cancers, including small cell lung cancer, hepatocellular carcinoma, breast cancer, and colon cancer [13]. CD24 expression is associated with a poor prognosis in many studies. However, there are a limited number of studies investigating the prognostic role of the CD24 in renal cell carcinoma.

The objective of this study was to determine the immunohistochemical expression of CD24 in renal cell carcinoma. We then examined the relationship between CD24 expression and clinicopathological parameters and patient prognosis.

Materials and Methods

Tissues and Clinical Parameters

This study included 133 renal cell carcinoma cases with 108 clear cell, 12 papillary and 13 choromophobe subtypes with known prognostic features diagnosed from 1995 to 2010 at the Pathology Department of Eskişehir Osmangazi University. Hematoxylin & eosin-stained slides obtained from radical nephrectomy specimens were re-evaluated, and the paraffin blocks best representing the morphology were selected for immunohistochemical analyses. Clinicopathological features such as age, gender, vascular invasion, tumor necrosis and T stage were noted. The tumors were graded according to the Fuhrman system. The clinical stage and patient survival rate data were provided by the Urology department.

Immunohistochemistry

The paraffin blocks that best reflected tumor morphology were studied via immunohistochemical staining for CD24 (Ab-2, clone SN3b, Neomarkers, Fremont, CA, USA). The paraffin blocks were cut into 5 μm-thick sections, and the slides were deparaffinized. Then, immunoperoxidase staining was completed using an automatic staining machine (Ventana BenchMark XT Automated IHC/ISH slide staining system) in accordance with the manufacturer's instructions. Chromogeneous DAB (diaminobenzidine) was used for signal detection, and the cells were counterstained with Harris hematoxylin. The negative controls were incubated with the same concentration of immunoglobulin (IgG1; Dako, Ely, UK) instead of the primary antibody. The positive controls were gastric mucosa specimens.

Evaluation of Slides

All tissue slides were examined by four pathologists. The CD24 expression level was evaluated using the following scale: 0 (no stain), 1+ (<10 % of tumor cells), 2+ (10–50 % of tumor cells), and 3+ (>50 % of tumor cells). The staining intensity was also evaluated as 1+ (mild), 2+ (moderate) or 3+ (intense). The total expression score was obtained by multiplying the scores for the staining percentage and intensity. The critical expression score was determined by using an ROC curve.

Table 1 Clinicopathological features of the patients

Features		Clear cell		Papillary		Chromophobe	
		n	%	n	%	n	%
Age	<60	70	64.8	7	58.3	8	61.5
	≥60	38	35.2	5	41.7	5	38.5
Gender	Male	60	55.6	10	83.3	4	30.8
	Female	48	44.4	2	16.7	9	69.2
Grade	1	17	15.7				
	2	44	40.8				
	3	34	31.5				
	4	13	12.0				
T stage	I	52	48.1	4	33.3	5	38.5
	II	27	25.0	3	25.0	5	38.5
	III	26	24.1	5	41.7	3	23.1
	IV	3	2.8	0	0	0	0
Dimension	≤7 cm	63	58.3	5	41.7	7	53.8
	>7 cm	45	41.7	7	58.3	6	46.2
Lymph node metastasis	(−)	101	93.5	9	75.0	13	100
	(+)	7	6.5	3	25.0	0	0
TNM stage	I	54	50.0	3	25.0	5	38.5
	II	21	19.4	3	25.0	5	38.5
	III	27	25.0	6	50.0	3	23.1
	IV	6	5.6	0	0	0	0
Distant metastasis	(−)	103	95.4	12	100.0	13	100
	(+)	5	4.6	0	0	0	0
Vascular invasion	(−)	84	77.8	10	83.3	11	84.6
	(+)	24	22.2	2	16.7	2	15.4
Necrosis	(−)	68	63.0	2	16.7	8	61.5
	(+)	40	37.0	10	83.3	5	41.7
Recurrence	(−)	85	78.3	11	91.7	13	100
	(+)	23	21.3	1	8.3	0	0
CD24 expression	Low	63	58.3	6	50	9	69.2
	High	45	41.7	6	50	4	30.8
total		108		12		13	

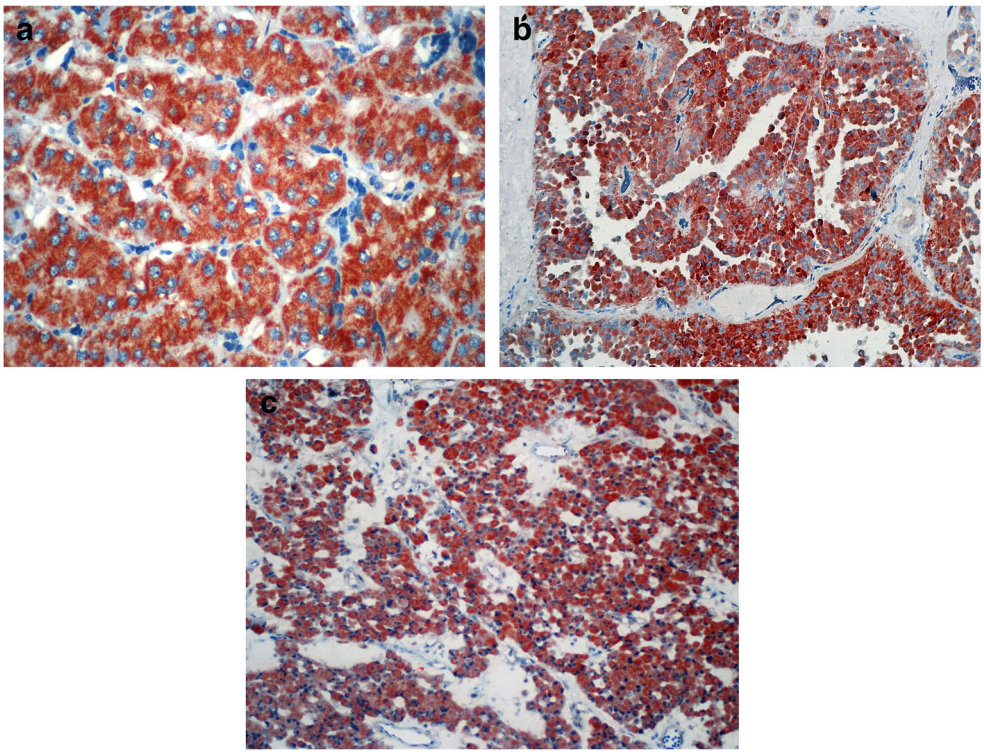

Fig. 1 Diffuse and intense CD24 cytoplasmic positivity in clear cell **a** papillary **b** and choromophobe **c** subtypes (Sn3b x 400)

Statistical Analysis

Fisher's exact test, continuity corrections and Pearson chi-square tests were used in the 2 × 2 crosstabs. In other crosstabs, the Pearson chi-square test was employed to evaluate the statistical association between the clinicopathologic variables and CD24 expression. A post hoc test (Bonferroni correction) was applied in crosstabs with more than three groups. The survival analysis was based on the Kaplan-Meier method, and statistical significance was assessed via the log-rank test. A *p*-value of less than 0.05 was considered significant in all statistical analyses.

Results

Our study includes 133 renal cell carcinoma. There are 108 clear cell, 12 papillary and 13 chromophobe subtypes. The mean patient age was 56.4 years (range, 26–79 years) in clear cell, 59.3 years (range, 28–82 years) in papillary and 51.2 years (range, 23–72 years) in choromophobe RCC. The mean tumor size was 7.3 cm (2–18 cm). The majority of tumors (63/133 cases) were stage I. Stage IV tumors were found in 6 patients and all were clear cell RCC. In clear cell RCC, vascular invasion and tumor necrosis were observed in 24 and 40 cases, respectively. The average follow-up period was 70.1 months (4–192 months). The clinicopathological features of the cases are shown in Table 1.

Cytoplasmic CD24 staining was observed in the tumor cells (Fig. 1a-c and 2). The staining scores were calculated by considering the percentage and intensity of staining. The critical expression score was determined by using an ROC curve. The surface under the curve was 0.609 (95 % CI: 0.470–0.748) and "2.5" was determined to be an acceptable cut off point (61.1 % sensitivity, 61.7 % specificity). Values above this point were grouped as high expression, while those below were grouped as low expression. Acoording to this system, in clear cell RCC; 63 cases (58.3 %) have low expression while 45 cases (41.7 %) have high. The statistical analysis revealed that high-grade tumors showed higher CD24 expression than low-grade tumors ($P = .023$). Tumors with high CD24 expression tend to recur too ($P < .001$). There were no statistically significant relationship between expression

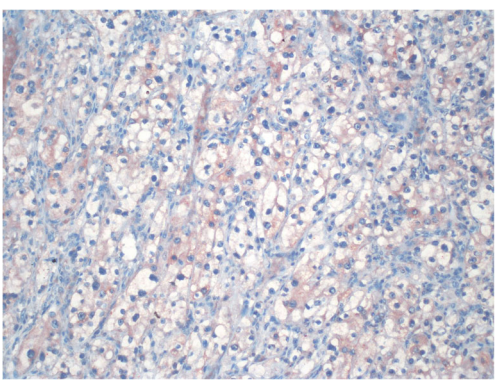

Fig. 2 Low expression of CD24 in clear cell renal cell carcinoma (Sn3b x 200)

levels and clinicopathological parameters such as tumor size, tumor necrosis, vascular invasion, distant metastases, lymph node metastasis, T stage, TNM stage, age and gender . In papillary and choromophobe subtypes there were no statistically significant difference between these clinicopathological parameters and CD24 expression level (Table 2).

In clear cell RCC, the survival analysis indicated that overall survival was significantly lower in patients with higher CD24 expression (P = .032) (Fig. 3). Tumor grade, lymph node metastasis, T stage and TNM stage were valso associated with overall survival. A multivariate analysis (Cox regression test) showed that CD24 expression levels and lymph node metastases were independent prognostic factors (Table 3). CD24 expression was associated with disease-free survival as well (P < .001) (Fig. 4). Vascular invasion, tumor grade, TNM stage, and lymph node metastases were all related to disease-free survival. The multivariate analysis indicated CD24 expression levels, tumor grade, and lymph node metastases as independent prognostic factors for disease-free survival (Table 3). In papillary and choromophobe subtypes the survival times and CD24 expression level were found not to be associated.

CD24 expression level was not statistically different in subtypes of RCC. In survival analysis survival times were not different too. However some of the clinicopathological parameters were different in subtypes of renal cell carcinoma such as, patients with chromophobe renal cell carcinoma have less lymph node metastasis (P = .047) and this subtype is significantly more common in women (P = .003), and papillary renal cell carcinoma has more tumor necrosis than the clear cell and chromophobe subtypes (P = .008).

Table 2 CD24 expression levels and clinicopathological parameters of RCC subtypes

		Clear cell			Papillary			Chromophobe		
		Low n	High n	*P* value	Low n	High n	*P* value	Low n	High n	*P* value
Age	<60	39	31	.586	3	4	.557	6	2	.571
	≥60	24	14		3	2		3	2	
Gender	Male	34	26	.844	5	5	1.000	2	2	.530
	Female	29	19		1	1		7	2	
Grade	1	12	5	***.023***						
	2	31	13							
	3	13	21							
	4	7	6							
T stage	I	35	17	.198	3	1	.603	3	2	.566
	II	15	12		1	2		3	2	
	III	11	15		2	3		3	0	
	IV	2	1		0	0		0	0	
Dimension	≤7 cm	42	21	.060	4	1	.242	5	2	1.000
	>7 cm	21	24		2	5		4	2	
Lymph node metastasis	(−)	58	43	.697	6	3	.182	9	4	-
	(+)	5	2		0	3		0	0	
TNM stage	I	36	18	.074	3	0	.323	3	2	.579
	II	11	10		1	2		**3**	**2**	
	III	11	16		2	4		3	0	
	IV	5	1		0	0		0	0	
Distant metastasis	(−)	59	44	.399	6	6	-	9	4	-
	(+)	4	1		0	0		0	0	
Vascular invasion	(−)	51	33	.481	6	4	.455	9	2	.077
	(+)	12	12		0	2		0	2	
Necrosis	(−)	40	28	.893	1	1	1.000	7	1	.217
	(+)	23	17		5	5		2	3	
Recurrence	(−)	57	28	***.001***	6	5	1.000	9	4	-
	(+)	6	17		0	1		0	0	

Bold entries are statistically significant p values

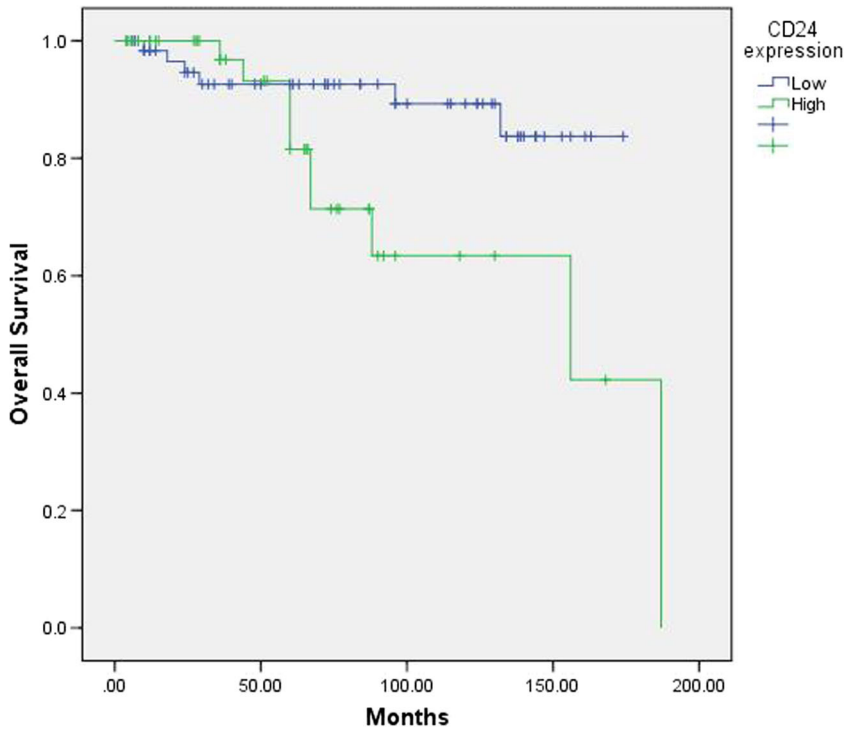

Fig. 3 Kaplan-Meier analysis of overall survival for tumors showing low versus high CD24 expression in clear cell renal cell carcinoma

Discussion

The role of cancer stem cells in the development of cancer was determined for the first time in 1994 by Lapidot et al. [14] in a study of acute myeloid leukemia (AML) patients. The authors showed that AML development was possible in severe combined immune-deficient (SCID) mice following the transplantation of cells (CD34+/CD38−) from AML patients. Subsequent studies by Al Hajj et al. [7] and Singh et al. [8] identified tumor-inducing cell populations in breast cancer and brain tumors, respectively. The studies were initiated to investigate cancer stem cells in various types of tumors. It has been suggested that in different cancers, there are specific cancer stem cells with different stem cell surface markers [15]. For example, CD44+ CD24- and ALDH+ stem cells are present in breast cancer, while CD133+ stem cells are

Table 3 Univariate and multivariate analysis results for overall and disease-free survival in clear cell RCC

	Overall survival		Disease-free survival	
	P value		*P* value	
Univariate analysis				
CD24 expression level (low vs. high)	= **.032**		< **.001**	
Tumor grade (1,2 vs. 3,4)	= **.003**		< **.001**	
T stage (I, II vs. III, IV)	= **.028**		= **.008**	
TNM stage (I, II vs. III, IV)	= **.012**		= **.001**	
Lymph node metastasis (− vs. +)	< **.001**		= **.002**	
Vascular invasion (− vs. +)	= .098		= **.032**	
Multivariate analysis		95 % confidence intervals		95 % confidence intervals
CD24 expression level (low vs. high)	= **.008**	1.589–22.811	= **.009**	1.433–11.715
Tumor grade (1,2 vs. 3,4)	= .373	.173–1.944	= **.007**	1.543–14.849
T stage (I, II vs. III, IV)	= .998	.028–3.247	= .563	.303–1.916
TNM stage (I, II vs. III, IV)	= .698	.416–5.298	= .946	.676–21.909
Lymph node metastasis (− vs. +)	< **.001**	7.211–197.450	= **.017**	1.361–23.905
Vascular invasion (− vs. +)	= .861	.220–4.662	= .718	.376–2.600

Bold entries are statistically significant *p* values

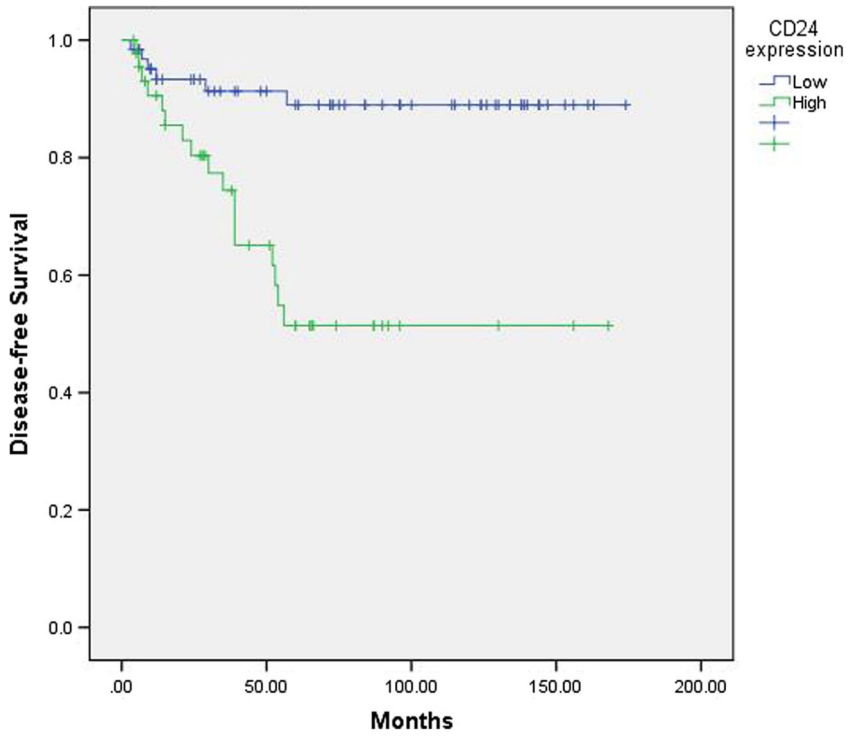

Fig. 4 Survival analysis showing the association between CD24 expression levels and disease-free survival in clear cell renal cell carcinoma

found colon, brain, and lung cancers. Furthermore, CD34+/CD38- cells are found in leukemia, and CD44+ cells are present in head and neck cancers. Finally, CD90+ cells drive liver cancer, and CD44 + / CD24 + / ESA + cells are found in pancreatic cancer [15]. A recent study reported an association between cancer stem cells and renal cell carcinoma [3].

CD24 is a heavily glycosylated and mucin-like surface protein that acts as the ligand of P-selectin [16]. It has also been defined as a stem cell marker in the colonic epithelium [17] and as cancer stem cell marker in several neoplasms [18]. In breast cancer, it has been reported that CD24-negative cancer stem cells are responsible for tumor initiation and progression [7]. Conversely, there are studies showing a relationship between a poor prognosis and high CD24 expression in breast cancer [19]. CD24 facilitates the integrin-dependent adhesion of tumor cells [11]. CD24 also increases the transcriptional activity and oncogenic role of STAT3 [20]. Additionally, CD24 can confer resistance to HER2-targeting treatments in HER2-positive cancer cells by increasing the expression of EGFR [18].

Our data indicated that CD24 expression was low in 58.3 % of the examined patients and high in 41.7 % of the patients. Droz et al. [21] reported that all tumor cells showed diffuse CD24 staining in renal cell carcinoma. However, our staining results showed a lower percentage; the results of the present study indicated that 26 of 108 cases (24.1 %) were CD24 negative in clear cell RCC. This discrepancy could be explained by the primary antibody clones used in the immunohistochemistry analyses. In the present study, the "SN3b" clone of the CD24 antibody was used. In the study by Droz et al. [21], the "OKB2" clone was used. Different antibody clones may show diverse staining results. Another difference was in the tissues evaluated. Droz et al. [21] conducted immunohistochemistry staining in fresh frozen tissue, and it is known that diffuse and intense staining results may be obtained by this method. Thus, all tumor cells were positive for CD24 in their study. In our study, we tested formalin-fixed and paraffin-embedded tissue.

It has been shown that CD24 expression affects the outcome of cancers of the breast, stomach, colon and pancreas [5, 13, 22, 23]. Senner et al. [24] reported that CD24-positive glioblastoma cells are more aggressive in mouse models. Other studies have found the CD24 / P-selectin pathway promotes the lung colonization of human A125 adenocarcinoma cells in mouse models [25]. CD24 overexpression also enhances the invasive potential of uterine cervical cancer cells through activation of both the Akt and ERK1/2 signaling cascades [26]. In renal cell carcinoma, the role of CD24 has not been clearly elucidated. Lee et al. [22] concluded that high immunohistochemical expression of CD24 was associated with a higher nuclear grade, larger tumor size, and shorter progression-free survival in renal cell carcinoma. The authors reported that CD24 expression was an independent prognostic factor and that higher CD24 expression may be a novel prognostic marker for tumor recurrence or metastasis in clear cell renal cell carcinoma patients. In our study, only a higher nuclear grade and recurrence rate were related to CD24 expression (P = .023 and .001). The other clinicopathological parameters evaluated were not associated with CD24 expression levels. In clear cell RCC, overall survival was significantly

reduced in patients with higher CD24 expression ($P = .032$). The multivariate analysis showed that CD24 expression levels and lymph node metastasis status were independent prognostic predictors of overall survival. CD24 expression levels were also associated with disease-free survival ($P < .001$). Furthermore, the multivariate analysis indicated that CD24 expression levels, lymph node metastasis, and tumor grade were independent prognostic factors for disease-free survival. The relationship between the expression level of CD24 and the biological behavior of clear cell renal cell carcinoma has been linked to the role of CD24 as a ligand for P-selectin [13]. Thus, tumor cells with high CD24 expression may exhibit a higher capacity to form thrombi with platelets. These cells may also show a better adhesion ability to endothelial cells, which could improve spreading [19]. The data obtained the present study demonstrated that CD24 expression was associated with a poor prognosis in patients with clear cell renal cell carcinoma.

In conclusion, CD24 expression is an important prognostic factor for clear cell RCC and is associated with both overall and disease-free survival. Additionally, CD24 expression can provide information regarding tumor behavior. Further studies may reveal whether CD24 is a potential target molecule for the treatment of clear cell renal cell carcinoma.

Compliance with Ethical Standards

Ethical Approval Our study was approved by the Non-Drug Clinical Research Ethics Board of Medicine Faculty of Eskişehir Osmangazi University (14 March 2013, Order No: 07).

Funding This study was supported by the Eskişehir Osmangazi University Scientific Research Projects Commission (Project No: 2014–132).

Conflict of Interest The authors declare no conflict of interest.

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