Serum vascular cell adhesion molecule-1 (VCAM1) level is elevated in colorectal cancer regardless of the tumor stage

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Original Article

Abstract

Purpose: Vascular cell adhesion molecule-1 (VCAM1) is a transmembrane glycoprotein, which is expressed on endothelium and plays role in inflammation. It is over-expressed on colorectal cancer (CRC) cells and plays role in metastasis development and angiogenesis. We aimed to compare serum VCAM1 levels of CRC patients with heathy controls and evaluate its relationship with clinicopathological parameters, treatment response and overall survival (OS). **Methods:** The study enrolled 111 patients with histopathologically confirmed CRC followed-up in our clinic and 30 sex- and age-matched healthy controls. Pre-treatment serum VCAM1 levels were determined by the solid-phase sandwich ELISA method. **Results:** Metastatic disease was present in 57 patients. Forty percent of 40 metastatic patients receiving systemic therapy had partial or complete response. The median serum VCAM1 level was significantly higher in CRC patients than controls ($p<0.001$). In addition, serum VCAM1 level was significantly higher in diabetic CRC patients than those without diabetes ($p = 0.03$). There was no significant relationship between VCAM1 and other clinicopathological parameters including stage and response to systemic therapy. The median follow-up period was 12 (±8.2) months. Twenty patients were dead at the time of analysis. The presence of metastasis ($p < 0.001$) and elevated CEA level ($p < 0.001$) were factors affecting OS significantly. However, serum VCAM1 did not have a significant impact on OS ($p = 0.55$). **Conclusion:** Serum VCAM1 level is significantly elevated in CRC patients regardless of the tumor stage. However, it has no prognostic or predictive role for response to systemic therapy.

Keywords: Colorectal Cancer; Serum VCAM1; Survival

1. Introduction

Carcinogenesis and metastasis development are multi-step processes which require the interaction of endothelium and tumor cells. Adhesion molecules play an important role in this interaction. Vascular cell adhesion molecule-1 (VCAM1) is a transmembrane glycoprotein from the immunoglobulin superfamily, which is expressed on activated endothelium and contributes in leukocyte adhesion and extravasation during inflammation.[1,2] VCAM1, which acts as a ligand of VLA-4 (α4β1 integrin), is also expressed on proximal renal tubuli and dentritic cells.[1]

VCAM1 is thought to be involved in inflammatory response against the tumor but also in metastasis

development and angiogenesis.[3,4] Inflammatory cytokines and reactive oxygen species are the main inducers of endothelial VCAM1 expression and blockage of VCAM1 inhibits leukocyte extravasation and inflammation.[1,5] It has been demonstrated that VCAM1 expression is decreased on endothelium infiltrated by tumor cells, inside the lung metastasis site of melanoma and carcinoma cells in vivo.[6] Tumor may decrease VCAM1 expression on vessels of metastatic sites, prevent extravasation of cytotoxic T lymphocytes into the tumor and consequently escape from the immun system.[6]

Fifty seven percent of colorectal cancer (CRC) patients have elevated VCAM1 mRNA level in CRC tissue compared to normal tissue around the tumor.[7] The intensity of VCAM1 staining on tumor vessels is also associated with increased T lymphocyte infiltration, suggesting that VCAM1 over-expression may play role in anti-tumor immunity of the host via T lymphocytes.[7]

Vessels surrounding CRC tissue over-express VCAM1. Vascular endothelial growth factor (VEGF) and cytokines secreted by tumor cell, such as tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ) and interleukin-1(IL-1) induce VCAM1 expression[5,7,8], which facilitates metastasis development in vitro.[2,3] Besides, presence of soluble VCAM1 has been shown in both CRC and activated endothelial cells.[2,7] Secretion of VCAM1 from endothelium activated by leukocyte adhesion may induce chemotaxis of endothelial cells suggesting the role of VCAM1 in neovascularization.[9]

Levels of circulating adhesion molecules are elevated in many inflammatory and malignant diseases associated with endothelial activation. However, few studies revealed the relationship between the level of these molecules and tumor behavior.[1,2,10-14] It has been shown that blood VCAM1 level is elevated in some solid tumors, such as breast, ovary, bladder, pancreas, gastric and head and neck carcinoma.[10,12,14-17] In addition, blood VCAM1 level is associated with disease stage and poor prognosis and may decrease with anti-cancer treatment in different solid tumor types.[10,12,14,15,17-19]

Revealing serum VCAM1 level of CRC patients and its relationship with other clinicopathological parameters, treatment response and survival may improve individual treatment strategies and provide a better understanding of the pathogenesis of the disease. Few studies have addressed the clinical significance of circulating VCAM1 level in CRC and these studies included very heterogeneous patient groups, unfortunately.[2,3,11,20-23] In addition, conflicting results have been obtained about serum VCAM1 level and its relationship with tumor burden and prognosis.[2,3,11,20-23] In the current study, we aimed to compare serum VCAM1 levels of CRC patients with healthy controls and evaluate its relationship with clinicopathological

parameters, treatment response and overall survival (OS).

2. Methods and Materials

2.1 Patients
This study included 111 patients with histopathologically confirmed colon or rectal carcinoma who were treated and followed-up between February 2010 and September 2013, in Istanbul University, Institute of Oncology. In addition, 30 sex- and age-matched healthy controls were included in the serum VCAM1 analysis for comparison. Tumor staging (TNM classification) was performed according to the American Joint Committee on Cancer (AJCC) staging system (7th edition). Informed consent was obtained from all patients and the study was reviewed and approved by our local ethical committee.

Clinical (age, gender, date of diagnosis, stage, smoking status, comorbidities, body mass index (BMI), ECOG (Eastern Cooperative Oncology Group) performance score (PS), treatment modalities and responses, last status (progression/exitus)), laboratory (pretreatment serum CEA and CA19.9 levels) and histopathological (angiolymphatic invasion (ALI), venous invasion (VI), perineural invasion (PNI), grade, KRAS status (for metastatic patients), regression score (for rectum cancer patients who received neoadjuvant radiotherapy)) data were obtained from medical charts of patients. Patients were treated and followed-up according to accepted international treatment guidelines, taking their tumor stages, PS, comorbidities and preferences into account. RECIST (Response Evaluation Criteria In Solid Tumors) criteria were used to evaluate response to systemic therapy in metastatic patients. Those with complete or partial responses were considered as responsive to systemic therapy.

2.2 Measurement of serum VCAM1 levels
Blood samples were obtained from the CRC patients and healthy controls (n = 30) by venipuncture and clotted at room temperature. The blood samples of early stage patients were taken within 30 days after surgery and within 14 days before adjuvant therapy. For metastatic patients, blood samples were obtained within 14 days before systemic therapy.

The sera were collected following centrifugation and frozen immediately at -20°C until analysis. Serum VCAM1 (eBioscience, Austria) levels were determined by the solid-phase sandwich ELISA method.

The VCAM1 ELISA (eBioscience, Austria) uses a double-antibody sandwich enzyme-linked immunosorbent assay to determine the level of Human Vascular Cell Adhesion Molecule-1 (VCAM1) in samples. Serum samples and standards are added to the wells which are pre-coated with Human VCAM1 monoclonal antibody.

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Biotin-conjugated anti-human VCAM1 antibody and Streptavidin-HRP is added. Biotin-conjugated anti-human VCAM1 antibody binds to human VCAM1 captured by the first antibody. Streptavidin-HRP binds to the biotin-conjugated anti-human VCAM1 antibody. Following incubation unbound Streptavidin-HRP is removed during a wash step, and substrate solution reactive with HRP is added to the wells. A colored product is formed in proportion to the amount of human VCAM1 present in the sample or standard. The reaction is terminated by an addition of acid (stop solution) and absorbance is measured using an automated ELISA reader (Rayto, RT-1904C Chemistry Analyzer, Atlanta GA, USA) at wavelenght of 450±10 nm. The results were expressed as ng/mL.

2.3 Statistical analysis

Comparisons of numerical variables including serum VCAM1 levels in CRC patients and controls, in addition to patient subgroups according to various clinical/ pathological/laboratory parameters were carried out using the independent samples t test for normally distributing groups and the Mann–Whitney U test for non-normally distributing groups. Comparisons of numerical variables between multiple groups were performed by using One –Way Anova test for normally distributing groups and Kruskal-Wallis test for non-normally distributing groups. While investigating the associations between serum VCAM1, CEA, CA19.9 and BMI, Spearman or Pearson tests were used for calculation of correlation coefficients and their significance. Overall survival (OS) was calculated from the date of venous blood sampling to death resulting from any cause or to last contact with the patient or any family member. Kaplan–Meier method was used for the estimation of the OS and differences in survivals were assessed using the log-rank test. A p value less than 0.05 was accepted as statistically significant. Statistical analysis was carried out using SPSS 16.0 software (SPSS Inc., Chicago, Illinois, USA).

3. Results

Between February 2010 and September 2013, 111 CRC patients (female/male = 40/71) were included in the study. The baseline histopathological and the demographic characteristics of the patients are listed in Table 1. Median (±SD) age and BMI of patiens were 60±13 years and 24.7±4.8 kg/m^2, respectively. Most of the patients (n = 103) had good ECOG performance score (0-1). BMI was ≥30 kg/m^2 in 21 patients. Metastatic disease was present in 57 (51.4%) patients. Among 54 early stage patients, 25 patients (46.3%) had node-positive disease. Treatment modalities and outcomes of patients are summarized in Table 2. Forty percent of 40 metastatic patients who received palliative systemic therapy was responsive (partial or complete response).

Table 1: Patient and disease characteristics.

Variables		n (%)
Number of patients		111(100)
Gender	Male	71 (64)
	Female	40 (36)
Smoking status	(+)	48 (43.2)
	(-)	53 (47.8)
	Unknown	10 (9)
Type 2 DM	(+)	17 (15.3)
	(-)	94 (84.7)
HT	(+)	31 (27.9)
	(-)	80 (72.1)
IHD	(+)	7 (6.3)
	(-)	104 (93.6)
Stage of tumor	I	1 (0.9)
	II	22 (19.8)
	III	31 (27.9)
	IV	57 (51.9)
Location of tumor	Right colon+hepatic flexura	24(21.6)
	Transvers colon	4 (3.6)
	Splenic flexura+left colon+sigmoid colon	28 (25.2)
	Rectosigmoid junction	6 (5.4)
	Multiple synchronous colon tumors	4 (3.6)
	Rectum	45 (40.5)
Site of metastasis ¥	Liver	33 (57.8)
	Peritoneum	22 (38.5)
	Lung	11 (19.2)
	Bone	8 (14)
Grade	1	10 (9)
	2	54 (48.6)
	3	8 (7.2)
	Unknown	39 (35.2)
ALI	(+)	38 (34.2)
	(-)	17 (15.3)
	Unknown	56 (50.5)
VI	(+)	16 (14.4)
	(-)	38 (34.3)
	Unknown	57 (51.3)
PNI	(+)	23 (20.7)
	(-)	34 (30.6)
	Unknown	54 (48.7)
Regression score*	0-2	16(47)
	3-4	18(53)
KRAS status¥	Mutant	15 (26.3)
	Wild	30 (52.7)
	Unknown	12 (21)
CEA	Normal (<5 ng/ml)	53 (47.7)
	High (>5 ng/ml)	22 (19.9)
	Unknown	36 (32.4)
CA19.9	Normal (<38 U/ml)	62 (55.8)
	High (>38 U/ml)	13 (11.8)
	Unknown	36 (32.4)

PS: Performance score; DM: Diabetes mellitus; HT: Hypertension; IHD: Ischemic heart disease; ALI: Angiolymphatic invasion; VI: Venous invasion; PNI: Perineural invasion
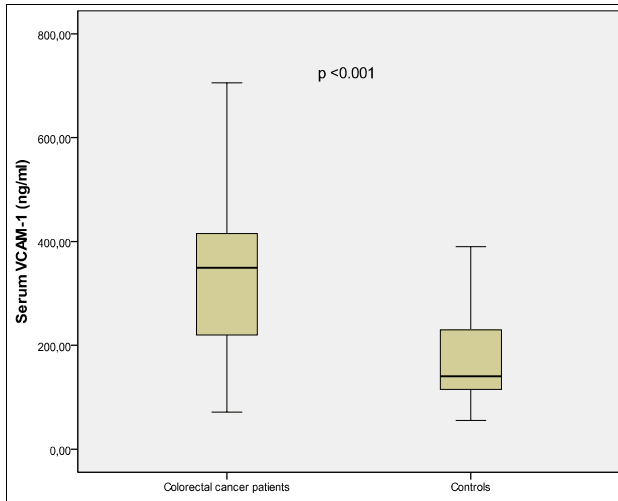
Figure 1: Comparison of serum VCAM-1 levels in CRC patients and controls.
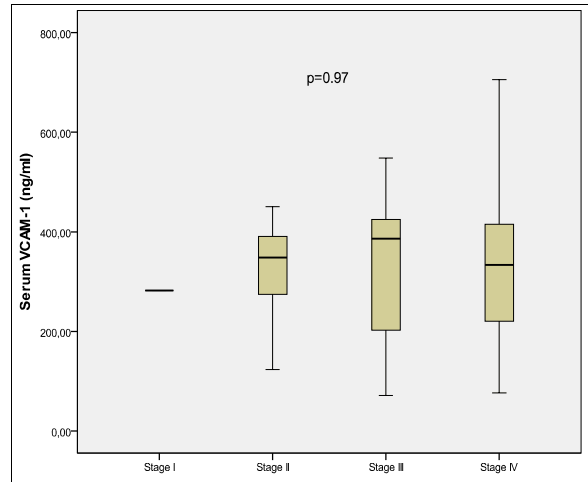
Figure 2: Comparison of serum VCAM-1 levels according to stage in CRC patients.

Table 2: Summary of treatment of patients and outcomes.

Variables		n (%)
Treatment of early stage disease		
Neoadjuvant CRT+adjuvant CT*		26 (23.4)
Neoadjuvant short-term RT+adjuvant CT*		8 (7.2)
Adjuvant CRT+CT*		7 (6.3)
Adjuvant CT only		12(10.8)
Observation after surgery		1(0.9)
Treatment of metastatic disease		
Palliative treatments	Palliative CT±targeted gents+BSC	40 (36)
	BSC alone	10 (9)
	Unknown	7 (6.3)
CT regimens**	FUFA/Capecitabine	3 (7.5)
	Irinotecan- based CT	15 (37.5)
	Oxaliplatin-based CT	21 (52.5)
Targeted agents**	Bevacizumab	22 (55)
	Cetuximab	13 (32.5)
Response to systemic therapy**	CR+PR	16 (40)
	SD+PD	18 (45)
	Unknown	6 (15)
Outcomes		
Progression	(+)	18 (16.2)
	(-)	93 (83.2)
Last status	Exitus	20 (18)
	Alive with disease	37 (33.3)
	No evidence of disease	54 (48.6)

*For rectum cancer only; **For 40 metastatic patient receiving systemic treatment; CT: Chemotherapy; CRT: Concurrent chemoradiotherapy; RT: Radioterapy; BSC: Best supportive care; CR: Complete response; PR: Partial response; SD: Stabil disease; PD: Progressive disease

Table 3: Comparison of serum VCAM1 levels of CRC patients and controls (median±SD).

	CRC group	Control group	*p*
Serum VCAM1 level (ng/ml)	349.2±131.5	140.6±110.2	<0.001*

*Student's T test; CRC: Colorectal cancer

Table 4: Results of comparisons between the median (±SD) values of serum VCAM1 and various clinical/pathological parameters.

Variables		VCAM1 level (ng/ml) (median±SD)	p
Age (years)	<50	347.3±145.3	0.56
	≥50	349.5±128.1	
BMI (kg/m2)	<30	354±140	0.34
	≥30	347.1±111.2	
Gender	Male	359.4±124.5	0.42
	Female	346.3±143.8	
Smoking status	(+)	372.8±136.1	0.7
	(-)	342.5±130.6	
Type 2 DM	(+)	372.5±118	0.03
	(-)	346.3±131.3	
HT	(+)	347.1±111.5	0.94
	(-)	349.3±139.1	
IHD	(+)	318.1±98.2	0.6
	(-)	349.3±133.6	
Stage	I	282.2	0.98*
	II	348.1±101.5	
	III	386.5±134.1	
	IV	333.5±142.9	
Tumor location	Colon	354±136.2	0.61
	Rectum	338.2±125.9	
Liver metastasis	(+)	342.5±145.5	0.8
	(-)	314.3±118.5	
Lung metastasis	(+)	361.5±98.9	0.56
	(-)	323.1±144	
Bone metastasis	(+)	339.8±105.1	0.8
	(-)	328.1±141.3	
Peritoneal metastasis	(+)	310±146.3	0.86
	(-)	366.1±129.2	
Grade	1	409.8±108.2	0.12*
	2	358.9±130.9	
	3	286±105.4	
ALI	(+)	348.1±131.2	0.16
	(-)	358.5±105.4	
VI	(+)	357.6±115.4	0.52
	(-)	348.3±126.1	
PNI	(+)	342.5±140.8	0.22
	(-)	352.8±112.7	
Regression score#	0-2	340.3±126.7	0.68
	3-4	295±108.1	
KRAS status╪	Mutant	409.1±131.6	0.13
	Wild	313±140.3	
Response to systemic therapy╪	Responsive (CR+PR)	362.5±149.3	0.57
	Unresponsive (SD+PD)	389.6±151.8	
Progression	(+)	369.3±136.5	0.25
	(-)	347.1±130.3	
Last status	Exitus	355.5±120.9	0.82*
	Alive with disease	328.1±150.8	
	No evidence of disease	363.8±122.8	

Student's T test; *One Way Anova test; ≠For 34 rectum cancer patients who received neoadjuvant therapy; ╪ For metastatic patients; BMI: Body mass index; PS: Performance score; DM: Diabetes mellitus; HT: Hypertension; IHD: Ischemic heart disease; ALI: Angiolymphatic invasion; VI: Venous invasion; PNI: Perineural invasion; CR: Complete response; PR: Partial response; SD: Stabil disease; PD: Progressive disease

Table 5: Univariate analysis of overall survival.

| Variables		No of events (death)	Median OS (months±SE)	95% CI	*p*
Age (years)	<50	2	22.2±1.1	19.8-24.5	0.11
	≥50	18	35.8±2	31.7-39.9	
BMI (kg/m2)	<30	10	38.9±2	34.9-43	0.23
	≥30	5	35.4±4	26.6-42.4	
Gender	Male	10	38.7±2.1	34.5-42.8	0.17
	Female	10	33.7±3	27.8-39.7	
Smoking status	(+)	6	32.9±1.9	29.2-36.7	0.27
	(-)	12	35.4±2.6	30.2-40.6	
Type 2 DM	(+)	4	18.9±1.7	15.5-22.3	0.59
	(-)	16	37.6±1.8	34-41.3	
HT	(+)	7	19.7±1.6	16.4-23	0.26
	(-)	13	38.1±1.9	34.2-42	
IHD	(+)	2	16.4±3.1	10.2-22.6	0.36
	(-)	18	37.5±1.8	33.9-41	
Metastasis	(+)	19	31.7±2.6	26.5-36.9	<0.001
	(-)	1	43.6±1.3	40.9-46.2	
Tumor location	Colon	14	34.9±2.3	30.9-39.5	0.29
	Rectum	6	39.3±2.5	34.3-44.2	
Response to systemic treatment*	Responsive (CR+PR)	4	30.3±3.3	23.8-36.8	0.76
	Unresponsive (SD+PD)	5	34±4.5	25.1-42.9	
Grade	1	2	17.9±2.5	12.9-22.9	0.55
	2	5	40.6±1.8	37-44.2	
	3	1	16±1.8	12.3-19.6	
ALI	(+)	3	41.2±2	37.2-45.3	0.67
	(-)	2	17.8±0.2	16.4-19.2	
VI	(+)	2	24.8±2	20.8-28.9	0.6
	(-)	3	40.6±2.3	35.9-45.3	
PNI	(+)	3	33±2.6	27.7-38.2	0.33
	(-)	2	28.1±1.2	25.6-30.5	
KRAS status*	Mutant	6	12.8±1.4	10.1-15.6	0.26
	Wild	7	36.2±3.2	29.9-42.5	
CEA	Normal (<5ng/ml)	2	43±1.3	40.3-45.7	<0.001
	High (>5ng/ml)	9	16±1.7	12.5-19.4	
CA19.9	Normal (< 38U/ml)	7	39.9±1.8	36.4-43.5	0.08
	High (>38U/ml)	4	15.1±1.1	12.8-17.4	
Serum VCAM1 level	< median	9	38.3±2.3	33.8-42.8	0.55
	≥ median	11	35.1±2.6	29.8-40.3	

Kaplan-Meier and log rank test; * For metastatic patients; OS: Overall survival; CI: Confidence interval; BMI: Body mass index; PS: Performance score; DM: Diabetes mellitus; HT: Hypertension; IHD: Ischemic heart disease; ALI: Angiolymphatic invasion; VI: Venous invasion; PNI: Perineural invasion; CR: Complete response; PR: Partial response; SD: Stabil disease; PD: Progressive disease; SE: Standart error

The median serum VCAM1 level was significantly higher in CRC patients than controls (349.2 vs 140.6 ng/ml, *p*<0.001) (Table 3; Figure 1). In addition, serum VCAM1 level was significantly higher in diabetic CRC patients than those without diabetes (372.5 vs 346.3, *p* = 0.03). However, there was no significant relationship between VCAM1 and other clinicopathological parameters including stage and response to systemic therapy (Table 4, Figure 2). Further analysis revealed that when diabetic patients are excluded, serum VCAM1 is similarly higher in CRC patients (346.3±131.9 vs 140.6±110.2 ng/ml, *p*<0.001) than controls regardless of the stage.

The median follow-up period was 12 (±8.2) months. Twenty (18%) of patients were dead at the time of analysis. In univariate analysis, the presence of metastasis (31.7 vs 43.6 months, *p*<0.001) and elevated CEA level (16 vs 43 months, *p*<0.001) were factors

affecting OS significantly (Table 5). Neither serum VCAM1 level, nor the other clinicopathological parameters had a significant impact on OS in our study (Table 5; Figure 3). There were no significant correlations between serum VCAM1 level and CEA (Rho: -0.05, *p* = 0.64), CA19.9 (Rho: 0.11, *p* = 0.34) and BMI (Rho: -0.007, *p* = 0.95).
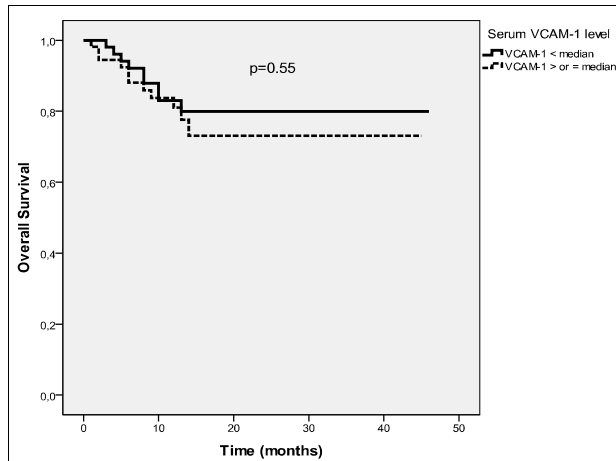
Figure 3: Kaplan-Meier curves according to VCAM-1 level.

4. Discussion

The current study demonstrated that serum VCAM1 level is elevated in CRC patients regardless of the disease stage. Most of the previous studies have determined the circulating VCAM1 level of CRC patients to be higher than controls[2,3, 11,13,23], which means that our results are consistent with the literature. However, there is only one study suggesting that serum VCAM1 level is not elevated in CRC.[20] This study excluded metastatic patients and serum VCAM1 level was measured preoperatively, while we included both early stage and metastatic patients and we analyzed serum VCAM1 level postoperatively for early stage patients.

Endothelial VCAM1 expression is known to be induced by VEGF, TNF-α, IL-1 and IFN-γ [5], although it is not well known whether these cytokines originate from the tumor cells or from the host cells surrounding the tumor.[1,5] While the mechanism of passage of adhesion molecules into the circulation is not known exactly, it is believed to occur after the adhesion of leukocytes or tumor cells to the endothelium.[24] In cancer, circulating VCAM1 may elevate due to increased production of VCAM1 in cancerous tissue or cytokines secreted during host immun response against tumor.[2,3,7,15] In fact, the source of circulating adhesion molecules, their molecular characteristics and biological significance is not known in detail.[3] The most likely source is enzymatic degradation of the adhesion molecules on the cell surface. VCAM1 can be released into the circulation from the endothelial surface via ADAM (a disintegrin and metalloprotease) 17, 8 and 9 enzymes.[1] In addition, half-life of circulating VCAM1 is not known exactly.

TNF-α-induced VCAM1 expression on the cell surface has been shown that continued up to 4 hours[25], suggesting that elevated VCAM1 level of patients after surgery is not related to long half-time of VCAM1 in our study.

Serum VCAM1 level may be influenced by a number of factors associated with endothelial activation, such as type 2 diabetes, atherosclerosis, asthma, rheumatoid arthritis and allergic events.[1] We have shown that CRC patients with diabetes have higher VCAM1 levels compared to non-diabetics. However, our re-analysis excluding the diabetic patients revealed that VCAM1 elevation in CRC is regardless of diabetes. Shear-stress, reactive oxygen radicals, microbial agents, cytokines, oxide low-density lipoprotein, homosysteine, hyperglysemia, adipokines and nitric oxide are well-known factors affecting VCAM1 expression during endothelium activation.[1] In our study, we could not measure all these factors which might have affected our results.

Conflicting results were obtained from the studies on the relationship between blood VCAM1 levels and the stage of CRC.[2,3,11,22,23] Moreover the studies suggesting that VCAM1 level is associated with disease stage are very heterogeneous. For example, one study (n = 46) included early stage and metastatic patients to only liver.[23] Another study measured VCAM1 level after surgery for early stage (n = 91) but during CT for metastatic disease (n = 63) and concluded that VCAM1 level is positively correlated with CRC stage, comparing rates of patients with elevated VCAM1 level between early stage (33%) and metastatic disease (49%).[11] Another study measured VCAM1 before surgery and concluded that VCAM1 is higher in metastatic disease, however VCAM1 level was not different according to stage in non-metastatic patients.[2] Two other studies suggested that preoperative VCAM1 level is not associated with stage in early stage disease.[3,22] In our study, we measured VCAM1 level of early stage patients after surgery and prior to CT for both early stage and metastatic patients. Interestingly, VCAM1 level was similar in all stages, including even metastatic patients. Given that we could not find any association between VCAM1 and disease stage, our study seems consistent with other studies revealing that VCAM1 is not different between stages in non-metastatic CRC patients.[2,3,22] However, we do not agree with the studies suggesting that VCAM1 level is much more higher in metastatic CRC patients than those without metastasis.[2,11,23]

Similar VCAM1 levels in patients with tumor burden and those with no evidence of disease suggest that VCAM1 may have different roles in early and late stages of CRC. Circulating VCAM1 produced by tumor may protect tumor cells from leukocytes, facilitate adhesion of tumor cells to endothelium of targeted metastasis site and then induce angiogenesis and tumor progression. In contrast,

VCAM1 of vessels surrounding the tumor may have anti-tumor effects providing leukocyte adhesion to cancerous tissue.[2,3,5] Unfortunately, current techniques can not discriminate biological function of circulating VCAM1 and whether its source is tumor cell or endothelium. Circulating VCAM1 is thought to have dual effects on leukocytes by both inhibiting binding of leukocytes to endothelium and inducing leukocyte chemotaxis.[1,5] Hypothetically, it can be suggested that endothelial VCAM1 expression is initiated in order to increase the immune response to the tumor, but then it contributes to tumor growth and metastasis by stimulating angiogenesis.

Correlation between VCAM1 and CEA has been examined in a few studies. One of these studies suggested that preoperative VCAM1 level is positively correlated with CEA and significantly decreases after surgery.[2] However, we have found no correlation between BMI, CEA, CA19.9 and VCAM1, in accordance with the two previous studies.[3,20] Based on our results it can be hypothesized that VCAM1 may reflect the vascular and inflammatory component of the tumor better, in contrast to CEA which reflects epithelial tumor load generally.[5]

Few studies examined the role of VCAM1 level on survival of CRC patients and the results are contradictory.[2,11,20,21] Two of these studies suggested that VCAM1 level has no impact on survival, while the other two concluded that high VCAM1 level is associated with decreased OS.[2,11,20,21] In addition, a prospective study showed that preoperative high VCAM1 level is associated with significantly increased recurrence rates.[22] In our study, we could not find any relationship between VCAM1 level and OS. Besides, we could not analyze whether VCAM1 level is associated with relapse rates or disease-free survival, because only one patient with early stage disease had recurrence and only 20 patients were dead at the time of analysis. Our follow-up time was probably not long enough for survival analysis, therefore we were unable to indicate prognostic effect of VCAM1 in CRC.

Dynamic changes in VCAM1 level during systemic treatment of CRC were evaluated in two studies.[13,21] The first study revealed that an increase in the level of serum VCAM1 is associated with early relapse and poor prognosis.[13] The second study included 38 metastatic CRC patients and indicated that VCAM1 levels increase during CT.[21] One of the major limitations of our study is that we could not evaluate neither serum VCAM1 level changes during systemic therapy, nor its significance for CT response and survival. However, none of the studies in the literature have examined whether pretreatment VCAM1 level is predictive for CT response. Our study is the first study providing insight in this regard and we indicated that pretreatment serum VCAM1 level has no predictive role for CT response.

5. Conclusion

Our study has demonstrated that VCAM1 level is elevated in CRC patients compared to controls and interestingly similar in patients with tumor burden and those with no evidence of disease, suggesting that VCAM1 may have different roles in early and late stages of CRC. We could not find any association with VCAM1 level and CT response or survival, probably due to short follow-up period. The real source or biological activity of serum VCAM1 in CRC patients is not known exactly. Unfortunately, we could not measure the all known endothelium activating factors which may affect our results and dynamic changes of VCAM1 level during CT in our study. Larger scale prospective studies which include more homogeneous patient and treatment groups with longer follow-up are required to find out the exact significance of serum VCAM1 level in CRC.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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