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Original Article

Clinical Importance of Serum and Urinary Fractalkine Level in Primary Non-Muscle Invasive Bladder Cancer

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ABSTRACT

Objective: Fractalkine is a chemotactic agent that shows both tumorogenic and anti-tumorogenic activity in some cancer types. In this study, we investigated the role of fractalkine in the diagnosis, progression and recurrence of primer non-muscle-invasive bladder cancer (NMIBC) and compared it with the healthy population.

Methods: Overall, 84 people that consisted of 44 cases with primary NMIBC and 40 healthy controls enrolled for this study. Blood and urine samples were collected and fractalkine levels were measured by the ELISA method. Urinary creatinine levels were calculated and urinary fractalkine levels were optimized. Demographic data, tumor stage (Ta, T1), grade (low and high), number of tumors, tumor size, recurrence and progression status of patients were recorded. NMP22 test was performed on the patient group and urine cytology was sent from the patients. Fractalkine levels and subgroup analyses were compared between two groups.

Results: The mean age of patients was 63.9±11.1 and 62.3±9.6 in the control group. The mean urinary fractalkine level was7.8±0.9 ng/ml in the study group and 7.7±0.6 ng/ml in the control group; there was no statistically significant difference between the two groups (p=0.426). Mean urinary fractalkine/creatinine level was similar between the study group and control group (16.0±32.2 ng/mgCr and 11.1±7.0 ng/mgCr, respectively, p=0.781). Mean serum fractalkine level was 2.9±1.2 ng/ml in the study group and 2.9±0.7 ng/ml in the control group; there was not a statistically significant difference (p=0.183). Also, we could not find any relation of fractalkine levels with tumor size, number, recurrence and progression. NMP 22 test was positive in half of the study group and Fractalkine levels were higher in the patients that NMP22 tests were negative that was statistically significantly. Cytology was positive for 45.5% of patients, but there was not any statistical correlation between fractalkine levels and cytology.

Conclusion: In this study, we did not find a significant difference concerning serum and urinary fractalkine level between the two groups. These findings do not support the use of fractalkine as a biomarker for bladder cancer diagnosis and follow-up.

INTRODUCTION

Bladder cancer (BC) is the second most frequentlycarcinoma of the genitourinary tract. The average age at the time of diagnosis is 65 years. Transitional cell carcinoma accounts for 90% of all BCs.[1] While the NMIBC are responsible for 80% of the newly diagnosed BCs, the muscle-invasive tumors are responsible for 20% of all BCs.[2]

Cystoscopy, which is an invasive procedure, is used for the diagnosis and monitoring of patients with non-muscle-invasive bladder cancer (NMIBC). The use of urine cytology is limited in diagnosis and follow-up because it has acceptable sensitivity and specificity for high-grade tumors; its specificity and sensitivity remain 60%–20% for low-grade tumors.[3] To date, many urinary biomarkers have been specified for diagnosis and follow-up of BC. The purpose of the development of these urine markers is to decrease

the employment of invasive cystoscopy for the detection and monitoring of BCs. An ideal diagnostic marker for BC should reliably detect the tumor and reduce the use of cystoscopy in the follow-up of the NMIBC.[4] In addition to the urinary markers put into service, such as Nuclear matrix protein 22 (NMP22), fluorescent in situ hybridization (FISH), bladder tumor antigen (BTA), and immunocytes, there are many other urinary markers reported by experimental studies.

Fractalkine is a unique fourth-class member of the chemokine family and has a high selective receptor (CX3CR1) that is chemotactic for Natural killer (NK) cells, monocytes, and T lymphocytes. Many studies have shown that fractalkine has a role in the pathogenesis of inflammatory diseases, such as atherosclerosis, chronic pancreatitis, rheumatoid arthritis, human immunodeficiency virus (HIV), transplant rejection, and glomerulonephritis, and also induce an antitumor effect in some cancer types, such as colorectal cancer, ovarian and prostate cancer.[5] The clinical role of CX3CL1 in tumors is contradictory. Fractalkine has a dual function as a chemoattractant for leukocytes and an adhesion molecule for tumor cells, which meanly exerts both protumor (breast cancer) and anti-tumor (hepatocellular cancer) activity.[6,7] Thus, we hypothesize that fractalkine located in the urinary bladder may take part in the carcinogenesis of BC.

In our study, we investigated the function of fractalkine in diagnosis, progression and recurrence of primary non-muscle-invasive BC, making comparisons with a healthy population.

MATERIALS AND METHODS

This study was conducted prospectively after the obtainment of approval no. 25/R dated 28.08.2012 of the Research Assessment Commission. Patients, who were diagnosed with primary NMIBC between August 2012 and September 2013, were included in this study. Also, 40 healthy individuals with similar demographical characteristics with the patients were enrolled in this study as the control subjects.

The exclusion criteria included benign transurethral resection (TUR) pathology, muscle-invasive carcinoma in TUR pathology, upper urinary tract cancer, and other cancer types out of the urinary tract and non-sterile urine cultures. Also, the presence of any disease was accepted as the exclusion criteria for the control group.

The stage (Ta, T1), grade (low-grade, high-grade), number and size of the tumors, carcinoma in-situ (CIS) existence, recurrence and progression status, smoking status, and body mass index (BMI) were recorded for each patient. The patients with BC underwent the NMP 22 Bladder Check test (Matritech Inc., Newton, A.B.D.) before the operation. The results of the NMP22 test were obtained according to the manual's guidelines, i.e., four drops of urine were dropped on the kit, and after 30 minutes, the changes on the kit were checked and recorded.

Fresh urine samples were collected into sterile containers for cytologic examination and all samples were blindly (independent from the diagnosis of bladder tumor) analyzed by a pathologist. While the presence of atypical and malignant cells in the cytology examination was considered as malignant cytology, the absence of atypical and malignant cells was defined as benign cytology. After the surgery, the patients received intracavitary treatment as recommended in the guidelines. The patients were followed-up with cystoscopy according to the risk classifications. Detection of tumors during cystoscopy follow-up was defined as recurrence and such patients underwent TUR. The progression of the TUR pathology to muscle-invasive cancer was defined as progression.

The blood samples were taken from the patients after one-night fasting. Blood samples were allowed to clot for a maximum of one hour before centrifugation and then centrifuged at 2500 rpm for 10 minutes. After centrifugation, the samples were stored at -80°C until analysis. Midstream urine samples were collected into sterile collection tubes. After centrifugationat 3000 rpm for 10 minutes, the supernatants were transferred to 1.5 mL microcentrifuge tubes and stored at -80°C until analysis. The urine fractalkine levels were measured using commercial ELISA type kits (Aviscera Bioscience, Inc., CA, USA). The urine creatinine concentration of each sample was determined by the kinetic Jaffe method on the COBAS 8000 analyzer (Roche Diagnostics GmbH., Germany). The urinary concentrations of fractalkine were normalized to the concentration of urinary creatinine, and the results were expressed in nanograms per milligram of creatinine (ng/mg). The serum fractalkine, urinary fractalkine and urinary fractalkine/creatinine levels of the patients were compared with those of the control subjects. Additionally, the association of these levels with smoking, size, grade and number of tumors, age, BMI, tumor recurrence, and progression status was investigated.

Statistical analysis

The median, minimum and maximum rate, the mean, standard deviation, and frequency values were used for demographics. The distribution of the variables was checked using the Kolmogorov-Smirnov test. The qualitative data were analyzed using the Independent Sample T-test, ANOVA (Tukey test), Kruskal-Wallis and Mann-Whitney U-test. When the conditions of the Chi-squared test were not fulfilled, Fisher's exact test was used to evaluate the quantitative data. The Spearman correlation analysis was employed to assess associations. The analyses were conducted with SPSS 21.0 (August 2012, IBM corp., NY, USA).

RESULTS

A total of 84 patients (44 patients with a bladder tumor and 40 healthy control subjects) were included in this study. The mean age of the study group was 63.9±11.1 years and the mean age of the control subjects was 62.3±9.6 years.

There was no statistically significant difference among the groups regarding age (p=0.488). When the gender distribution was analyzed, there were 14 women and 30 men in the study group and there were 15 women and 25 men in the control group. No statistically significant difference was observed among the groups regarding gender distribution (p=0.256) (Table 1).

The mean BMI of the study group was 27.2±4.3 kg/m^2, and the average BMI of the control group was 26.5±2.63 kg/m^2. Thus, no statistically significant difference was seen among the groups (p=0.345). We found a statistically significant difference between the groups regarding smoking status because 88.6% reported smoking in the study group, whereas this rate was 62.5% in the control group (p=0.005) (Table 1).

In the study group, the number of patients with stage Ta tumors was 13 (29.5%), and the number of patients with stage T1 tumors was 31 (70.5%). While 25 (56.8%) of the patients had low-grade tumors, 19 patients (42.3%) had high-grade tumors. There were six (13.6%) patients with positive CIS. The NMP22 was positive in 22 (50%) patients, but cytology was positive in 20 (45.2%) patients. The average tumor number was 2.4±2.0, and the average tumor size was 35.0±17.7 mm. The average length of follow-up was 11.6±2.5 (9–17) months. When recurrence and progression were considered, recurrence was observed in 16 patients (36.3%) and progression was observed in three patients (6.8%) (Table 2).

As the mean urinary fractalkine level was 7.8±0.9 ng/ml in the study group and 7.7±0.6 ng/ml in the control group, there was no significant difference between the groups regarding the fractalkine levels (p=0.426). The mean urinary fractalkine/creatinine level was 16.0±32.2 ng/mgCr in the patient group, while it was 11.1±7.0 ng/mgCr. No statistically significant difference was found between the two groups (p=0.781). When it came to the serum fractalkine levels, the mean level was 2.9±1.2 ng/ml in the study group and 2.9±0.7 ng/ml in the control group. There was no statistically significant difference between the groups (p=0.183) (Figs. 1–3).

Table 1. The demographic data of the patients and the control group

	Control Group	Case Group	p
	Mean±SD/n (%)	Mean±SD/n (%)	
Age	62.3±9.6	63.9±11.1	0.488
Sex			
Female	15 (37.5)	7 (17.5)	0.256
Male	25 (62.5)	37 (92.5)	
Smoking			
No	15 (37.5)	5 (12.5)	0.005
Yes	25 (62.5)	39 (97.5)	
BMI	26.5±2.6	27.2±4.3	0.345

BMI: Body mass index; SD: Standard deviation.

Table 2. Histopathological and clinical data of the patients

	Med (Min-Max)	Mean±SD/n (%)
Follow-up time (month)	11 (9–17)	11.6±2.5
Tumor size (mm)	30 (7–80)	35.0±17.7
Tumor number	2 (1–10)	2.4±2.0
Tumor grade		
Ta		13 (29.5)
T1		31 (70.5)
Grade		
Low grade		25 (56.8)
High grade		19 (43.2)
Carcinoma in-situ		
Negative		38 (86.4)
Positive		6 (13.6)
NMP 22		
Negative		22 (50)
Positive		22 (50)
Cytology		
Benign		24 (54.5)
Malign		20 (45.5)
Recurrence		
No		28 (63.7)
Yes		16 (36.3)
Progression		
No		41 (93.2)
Yes		3 (6.8)

NMP 22: Nuclear matrix protein 22; SD: Standard deviation; Med: Median; Min: Mnimum; Max: Maximum.

According to the sub-group analysis, no statistically significant difference was seen between the smokers and non-smokers regarding the urinary fractalkine (p=0.217), urinary fractalkine/creatinine (p=0.515) and serum fractalkine (p=0.737) levels (Table 3). Also, there was no statistically significant difference between the patients with stage Ta tumor and those with stage T1 tumors concerning

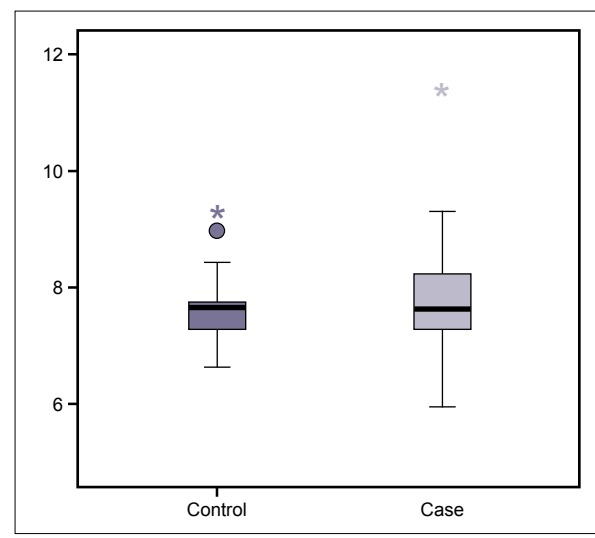

Figure 1. Urinary fractalkine level (p=0.426).

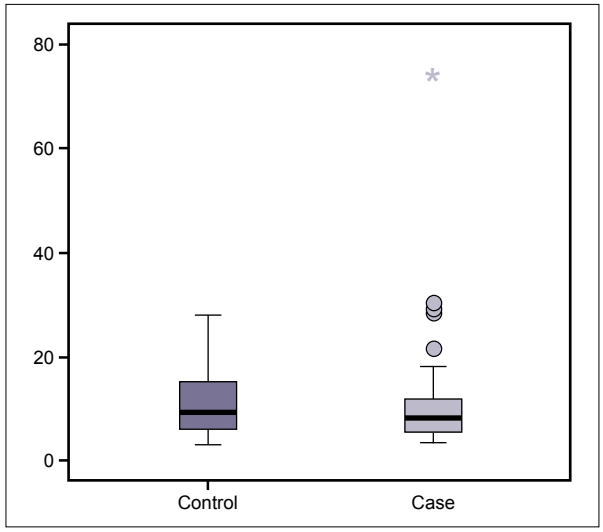

Figure 2. Urinary fractalkine/urinary creatinine level (p=0.781).

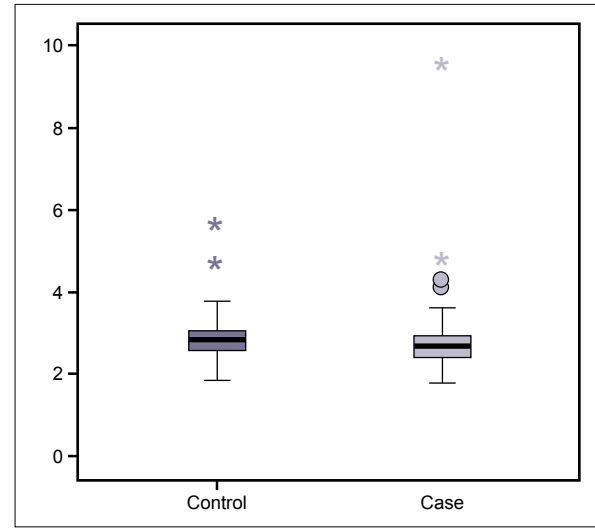

Figure 3. Serum fractalkine level (p=0.183).

the urinary fractalkine (p=0.051), urinary fractalkine/creatinine (p=0.847) and serum fractalkine (p=0.280) levels (Table 3). Furthermore, when the sub-group analysis was performed considering tumor grade, we could not find any statistically significant difference between the urinary fractalkine (p=0.229), urinary fractalkine/creatinine (p=0.420) and serum fractalkine (p=0.107) levels of the patients with low-grade and high-grade tumors (Table 3). On the other hand, there was a significant negative correlation between the urinary fractalkine levels of the NMP22 positive and negative patients (p=0.032). However, no statistically significant difference was seen between those patients concerning the urinary fractalkine/creatinine (p=0.542) and serum fractalkine levels (p=1.00) (Table 3). Moreover, the urinary fractalkine (p=0.114), urinary fractalkine/creatinine (p=0.924) and serum fractalkine levels (p=0.383) were not statistically significantly different between the patients with benign cytology and malignant cytology (Table 3).

Table 3. Subgroup analysis according to the histopathology and test results

	Urinary Fractalkine (ng/ml)	p	Urinary F./Kr. (ng/mgCr)	p	Serum Fractalkine	p
	Mean±SD		Mean±SD		Mean±SD	
Smoking						
No	7.5±0.5	0.217	21.7±45.1	0.515	2.8±0.4	0.737
Yes	7.8±0.8		11.2±10.2		2.9±1.1	
Tumor grade						
Ta	8.2±1.2	0.051	11.7±8.6	0.847	3.1±0.8	0.280
T1	7.6±0.7		17.8±38.0		2.8±1.3	
Grade						
Low	7.9±1.0	0.229	9.1±4.6	0.420	3.2±1.5	0.107
High	7.6±0.8		25.1±47.9		2.6±0.4	
NMP 22						
Negative	8.1±1.0	0.032	11.7±14.8	0.542	3.0±1.6	1.00
Positive	7.5±0.6		20.4±43.2		2.8±0.6	
Cytology						
Benign	8.3±1.3	0.114	17.1±21.3	0.924	3.3±2.4	0.383
Malign	7.9±1.1		20.8±43.5		2.8±0.3	
Recurrence						
No	7.7±0.8	0.652	11.9±13.8	0.393	2.9±1.4	0.634
Yes	7.9±1.1		23.2±50.4		2.8±0.6	
Progression						
No	7.8±0.9	0.421	16.4±33.3	0.826	2.9±1.2	0.505
Yes	8.0±0.5		10.7±6.0		3.3±1.3	

NMP 22: Nuclear matrix protein 22; SD: Standard deviation.

Table 4. Relationship between fractalkine level, age, body mass index, tumor size and tumor number

		Age	Body mass index	Tumor size (mm)	Tumor number
Urinary Fractalkine (ng/ml)	r	-0.029	0.014	-0.133	-0.153
	p	0.796	0.903	0.389	0.322
Urinary Fractalkine/Creatinine (ng/mgCr)	r	0.334	0.245	-0.082	-0.033
	p	0.002	0.026	0.601	0.831
Serum Fractalkine	r	0.010	0.143	0.049	0.016
	p	0.927	0.195	0.750	0.920

No statistically significant difference was seen between the patients with recurrent and non-recurrent tumors concerning the urinary fractalkine (p=0.652), urinary fractalkine/creatinine (p=0.393) and serum fractalkine (p=0.634) levels (Table 3). Additionally, the urinary fractalkine (p=0.421), urinary fractalkine/creatinine (p=0.826) and serum fractalkine levels (p=0.505) did not show a significant difference between the patients with progressive and non-progressive cancer (Table 3).

Urine fractalkine level was not significantly correlated with age, BMI, tumor size, the number of tumors and the length of follow-up (p>0.05) (Table 4).

We did not observe any statistically significant correlation between the urine fractalkine/creatinine level and the size and number of tumors, and the duration of follow-up (p>0.05). However, we observed a positive correlation between the urine fractalkine/creatinine level, age and BMI (p=0.002, p=0.026, respectively) (Table 4).

Serum fractalkine did not show a significant correlation with age, BMI, tumor size, the number of tumors and the length of follow-up (p>0.05) (Table 4).

DISCUSSION

The risk of recurrence and progression is relatively high in patients with high-grade NMIBC. However, it is not possible to predict the recurrence and progression potential of a tumor. Routine follow-up cystoscopy is applied for the detection of recurrence and progression in patients being monitored for NMIBC. There are nomograms used for predicting the recurrence and progression of NMIBC, but there were also on-going studies on various biomarkers to facilitate the prediction of disease recurrence and progression.

Fractalkine seems to be a promising therapeutic candidate for cancer treatment. Guo et al.[8] indicated in their animal study that a strong anti-tumor response was generated in mice immunized with fractal-transfected Lewis Lung Carcinoma cells through strong chemoattraction of natural killer cells in the tumor area. In another animal study, bone marrow-derived dendritic cells with higher fractalkine release were injected into the tumor in different tumor models (namely, B16-F10 melanoma, H-2b, Colon-26 colon adenocarcinoma, H-2d). In the examined tumor models, the fractalkine-expressing dendritic cells significantly suppressed tumor growth, and thus, improved survival.[9] Furthermore, another study reported fractalkine to enhance the T cell and NK cell-dependent antitumor mechanism.[10]

Robinson et al.[11] made use of blocking antibodies against fractalkine and its receptor CX3CR1 in their study and indicated that fractalkine played a significant role in the elimination of YAC-1 tumor cells, which were intravenously administered into the lung. The fact that fractalkine is present in locally high concentrations in some tumors provides a protective effect on tumor growth which depends on the antitumor effect of NK cells, dendritic cells, and T-cells.[7] On the other hand, fractalkine has been indicated to be correlated with a higher local recurrence risk and metastatic potential. Although this mechanism of fractalkine has not been completely elucidated, it is thought that the antitumor mechanism is of immunological origin, and the protumoral mechanism is induced by the fractalkine-mediated adhesion and migration of tumor cells.[12]

Blum et al.[13] examined the prostate tissue samples of 82 patients, who developed biochemical recurrence within five years of prostatectomy, and of an age-matched control group of 98 subjects, who were free of recurrence within the same time frame, and they found that the fractalkine/CX3CL1 expressed by the prostate tissue was associated with recurrence-free survival. For this reason, they included fractalkine in their nomogram. In this study, we examined the serum and urinary fractalkine levels but did not investigate fractalkine expression in tumor tissue. Fractalkine was not found as a predictor of the recurrence and progression of BC. However, different results may be obtained if tumor tissue is also examined.

The sensitivity of the NMP22 Bladder Check Test, which is a diagnostic adjunct to urine cytologic examination for diagnosis and follow-up of BC, has been reported to range from 47% to 100%.[14] Grossman et al.[15] found the sensitivity and specificity of NMP22 as 55.7% and 85.7%, respectively, whereas Doğan et al.[16] reported the sensitivity and specificity of NMP22 as 70% and 80%, the sensitivity and specificity of NMP22 for follow-up of the patients diagnosed with BC were 33% and 76%, respectively. In our study, the test was positive in 50% of the patients with BC. There was no link between NMP22 positivity and serum fractalkine and urinary fractalkine/creatinine level, but the urinary fractalkine levels of the patients with NMP22 (-) were statistically higher.

The urine cytology has high specificity, and positive cytology has been reported to be associated with the severity of the disease. Nevertheless, the cytologic examination of urine is dependent on the experience of the histopathologist.[17–21] Kumar et al.[22] reported the sensitivity and specificity of cytology to be 41% and 96% respective in 131 patients who had been diagnosed with BC previously. Schlake et al.[23] used cytology for the follow-up of 391 patients who had bladder carcinoma, with 35% sensitivity and 97% specificity. In this study, cytology was positive in 45% of the patients. We did not observe a significant link between fractalkine levels and positive cytology.

Smoking is the most prominent etiological factor in patients with bladder carcinoma. The risk of developing BC is four times higher among smokers as compared to non-smokers.[24] In our study, 88.6 of the patients with BC were smokers and the proportion of smokers in the patient group was significantly higher as compared to the control group. Studies have evidenced the association between tobacco use and recurrence;[25,26] however, the link between smoking and fractalkine level is not known yet. We did not identify a relationship between smoking and serum and urinary fractalkine levels. In the studies examining the correlation between BMI and BC, the risk of development of BC and recurrence was higher among obese patients.[27,28] Kluth et al. suggested that increased BMI is correlated with the risk of recurrent disease, progression, cancer-related deaths, and death from any cause.[29] The serum fractalkine and urinary fractalkine levels of the patients and control subjects were not associated. Nevertheless, there was a significant correlation between BMI and urinary fractalkine/creatinine levels (p=0.026). BMI was higher in 56.25% of the patients that developed recurrence.

Due to the small study population, the cases of recurrence and progression were limited in this study. Also, if our results are considered, fractalkine has no association with the disease stage and. However, this relationship can be further examined in a study that will also include patients with muscle-invasive BC. In the present study, the fractalkine level in the urine samples was measured, and no significant result was obtained to clarify the role of fractalkine in the BC. However, the investigation of the fractalkine expression in the bladder carcinoma tissue may contribute to the literature with new information. The results of the studies to date indicated the anti-tumor effect of fractalkine and the increase of fractalkine expression in some cancers; this information has opened up new horizons for the development of new diagnostic and therapeutic methods for carcinomas. However, further research should go on for clarification of the cancer types for which fractalkine may be beneficial.

CONCLUSION

Neither the intergroup comparisons nor the sub-group analysis did indicate a statistically significant difference regarding fractalkine levels. However, fractalkine/CX3CL1 is a new and remarkable member of the family of chemotactic cytokines, and studies on other cancer types have yielded promising results regarding this particular chemokine. Further studies should be conducted to identify the role of fractalkine in cancer pathogenesis and develop a biomarker to be used in the diagnosis and follow-up of non-muscle-invasive BC.

Ethics Committee Approval

Approved by the local ethics committee (approval no. 25/R dated 28.08.2012).

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: C.Ç., Ö.A., A.Y.; Design: C.Ç., Ö.A., B.İ.B., F.K.İ.; Supervision: T.Ç., A.Y., F.K.İ.; Materials: T.Ç., G.A., C.G.; Data: C.Ç., Ş.Ö., C.G.; Analysis: C.G., B.İ.B., G.A.; Literature search: Ş.Ö., Ö.A., B.İ.B.; Writing:. C.Ç., Ş.Ö., G.A.; Critical revision: T.Ç., F.K.İ., A.Y.

Conflict of Interest

None declared.

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Serum ve İdrar Fraktalkine Düzeyinin Primer Kas İnvaziv Olmayan Mesane Kanserinde Klinik Önemi

Amaç: Fraktalkine, bazı kanser tiplerinde hem tümörojenik hem de anti-tümoörojenik aktivite gösteren bir kemotaktik ajandır. Bu çalışmada, fraktalkinenin primer kas invaziv olmayan mesane kanserinde tanı, nüks ve progresyondaki rolünü araştırdık.

Gereç ve Yöntem: Çalışmaya primer kas invaziv olmayan mesane kanseri tanısı konulan 44 hasta ve sağlıklı kontrol grubu olan 40 kişi olmak üzere toplam 84 kişi alındı. Kan ve idrar örnekleri toplandı ve fraktalkine düzeyi ELISA yöntemi ile değerlendirildi. İdrar kreatinin düzeyleri hesaplanıp idrar fractalkine düzeyi optimize edildi. Demografik veriler, tümör evresi (Ta, T1), derecesi (düşük, yüksek), sayısı, boyutu ve rekürrens, progresyon durumu kaydedildi. Fraktalkine düzeyleri ve alt grup analizleri her iki grup arasında karşılaştırıldı. Hasta grubuna NMP22 test yapıldı ve hastalardan idrar sitolojisi gönderildi.

Bulgular: Hasta grubun ortalama yaşı, 63.9±11.1, kontrol grubunda ise 62.3±9.6 idi. Ortalama idrar fraktalkine düzeyi hastalarda 7.8±0.9 ng/ml ve kontrol grubunda 7.7±0.6 ng/ml olup iki grup arasında istatistiksel anlamlı fark izlenmedi (p=0.426). Ortalama idrar fraktalkine/kreatinin değeri iki grup arasında benzerdi (sırasıyla, 16.0±32.2 ng/mgCr ve 11.1±7.0 ng/mgCr, p=0.781). Ortalama serum fraktalkine düzeyi hasta grubunda 2.9±1.2 ng/ml ve sağlıklı kontrol grubunda 2.9±0.7 ng/ml olup, iki grup arasında istatistiksel anlamlı fark izlenmedi (p=0.183). Aynı zamanda, fraktalkine düzeyi ile tümör boyutu, sayısı, nüks ve progresyon durumu arasında ilişki tespit edilmedi. Fraktalkine düzeyi NMP22 test pozitif hastalarda negatif olanlara göre istatiksel anlamlı olarak daha yüksekti. Sitoloji hastaların %45.5'inde pozitifti fakat fraktalkine değerleriyle istatiksel anlamlı bir ilişki görülmedi.

Sonuç: Bu çalışmada, her iki grup arasında serum ve idrar fraktalkine düzeyi benzer bulunmuş olup, fraktalkinenin primer mesane kanserli hastalarda biomarker olarak kullanılamayacağı gösterilmiştir.

Anahtar Sözcükler: Biomarker; fraktalkine; mesane kanseri.