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Effects of delayed diagnosis on tumor size, stage and grade in bladder cancer

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Abstract

Objective This study is planned based on the hypothesis that if bladder cancer is detected early, the disease would be less advanced and the possibility of treatment will increase, at least the recurrence-free survival will be longer. Regarding this hypothesis, it is aimed to investigate the effect of delayed diagnosis primarily on the disease factors.

Materials and methods The study included 169 patients, who underwent TUR-BT with the suspicion of bladder cancer in the urology clinic of Afyonkarahisar Faculty of Medicine between April 2018 and April 2023. Demographic and clinical data of the patients were recorded and compared.

Results It was observed that the delay in diagnosis was significantly longer in patients with tumors larger than 3 cm compared to patients with tumors smaller than 3 cm ($p < 0.001$). In the correlation analysis between tumor size, duration of diagnosis delay, age, T stage, and tumor grade, a low level of positive correlation was observed between tumor size and duration of diagnosis delay, and it was statistically significant ($r = 0.215$, $p = 0.005$).

Conclusion In our study, it was shown that the tumor size increases as the duration of diagnosis delay increases and this increase causes an increase of 0.088 mm in the pathological size of the tumor in the 1-day delay period. Considering that tumor size changes the risk group of the disease in bladder tumors, and relatedly the follow-up and treatment process changes, we believe that these data will be valuable in the management of bladder cancer.

Keywords Bladder cancer · Diagnosis · Malignancy · TNM staging

Introduction

Bladder cancer is the 10th most common cancer in the world, with a gradually increasing prevalence in developed countries [1]. Early diagnosis and treatment is very important in bladder cancer, like all other cancer types. At the time of diagnosis, approximately 75% of bladder cancers are not invasive to the muscle. With a good treatment and follow-up program, the disease can be managed without muscle invasion [2].

Many factors have been shown to be effective in the etiology. Tobacco use is the most important of these factors and accounts for approximately 50% of cases [3]. It has also been defined that the risk of bladder cancer is related to the duration and intensity of tobacco use [4]. Aromatic amines, genetic factors, dietary habits, exposure to chemicals such as arsenic, and schistosomiasis are important causes identified in the etiology of bladder cancer [3]. In a study examining patients with localized prostate cancer, pelvic radiotherapy was also shown to be associated with primary bladder cancer [5].

The most common symptom in bladder tumor is hematuria. Besides the presence of hematuria, its features are also important. It has been observed that macroscopic hematuria at the time of diagnosis is associated with a higher stage of disease than microscopic hematuria [6]. CT-Urography (computed tomography urography), which is one of the

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imaging methods used in bladder tumors, especially shows papillary tumors in the urinary system as filling defects [7]. Ultrasonography (USG) is a valuable noninvasive method used in the urinary system for detection of hydronephrosis, the diagnosis of renal masses, and the imaging of intraluminal masses in the bladder. However, it cannot rule out all possible causes of hematuria [8]. The role of Multiparametric Magnetic Resonance Imaging (MpMRI) in the diagnosis and follow-up of bladder cancer has not been determined. However, recently, VI-RADS (Vesical Imaging-Reporting and Data System), a standardized scoring system, has been defined that can accurately distinguish muscle-invasive bladder cancer from non-muscle-invasive bladder cancer with high consistency rates among the observers [9]. Positive urine cytology indicates malignancy in any part of the urinary system, while negative cytology does not exclude malignancy [10].

Definitive diagnosis of bladder tumor is made by transurethral resection (TUR-BT) and histological examination of the material obtained with this procedure. Risk group classification should be performed after diagnosis, for the correct management of the disease. Non-muscle-invasive bladder cancers are classified as low, moderate, high, and very high risk. The treatment and follow-up of the disease are carried out according to this classification. This treatment and follow-up plan includes regular cystoscopic controls, intravesical BCG or chemotherapy instillations if necessary, and radical cystectomy in the very-high-risk group [11].

We planned our study based on the hypothesis that if bladder cancer is detected earlier, the disease would be less advanced, the possibility of treatment will increase, and at least the recurrence-free survival of the disease will be prolonged. In accordance with this plan, we primarily aimed to investigate the effect of delay in diagnosis on the stage and grade of the disease and factors such as tumor size.

Materials and methods

This study was conducted in the Urology Clinic of Afyonkarahisar Health Sciences University Hospital. The sample size was not calculated in the study because we tried to reach the entire universe. The data were recorded retrospectively, after obtaining ethical approval (Afyonkarahisar Health Sciences University Clinical Research Ethics Committee. 2011-KAEK-2, 2023/306). Our study was carried out in accordance with the principles of the Declaration of Helsinki.

Our study included 184 patients who underwent TUR-BT with the suspicion of bladder cancer in the Urology Clinic of Afyonkarahisar Health Sciences University Faculty of Medicine between April 2018 and April 2023 and whose pathology results were compatible with bladder cancer. TUR-BT was performed on 9 patients who were admitted to the hospital for other reasons and whose imaging showed suspicion of bladder tumor and bladder cancer was detected. These patients were excluded from the study as they did not have symptoms related to bladder cancer. Pathology results of 6 patients was found to be compatible with variant histologies. Because of the different clinical course of variant histologies in bladder cancer, 6 patients were excluded from the study and the study was continued with 169 patients. The patient's age, gender, smoking status, complaints for admission, time from symptom onset to operation (diagnosis delay), tumor localization, tumor size observed in cystoscopy, tumor stage, and tumor grade detected in the pathology were retrospectively scanned and recorded. The relationship between the duration of delayed diagnosis and other parameters was evaluated and their correlation was analyzed. The relationship between the duration of delayed diagnosis and increase in tumor size was also analyzed. Dysuria and hematuria were considered symptoms of bladder cancer. In TUR-BT, the longest diameter of the tumor was calculated as the tumor size and was measured according to the width of the loop. The tumor size of patients with multiple tumors detected on cystoscopy was calculated by adding the longest diameter of all present tumors. Tumor localization was classified as trigonal, non-trigonal, and multiple localized.

Statistical analysis

Statistical analysis of the study data was performed in a computer with IBM SPSS (Statistical Package for the Social Sciences) version 20.0 program. The conformity of the variables to the normal distribution was evaluated using the Kolmogorov–Smirnov (K–S) test. For the comparison of binary groups, the Student's *T* test was used for normally distributed parameters and the Mann–Whitney *U* test was used for non-normally distributed parameters. Evaluation of multi-well crosstabs was performed with the Chi-square test or Fisher Exact test. The correlations between the duration of diagnosis delay and other parameters were analyzed using the Spearman correlation test, Pearson correlation test, Student's *t*-test, Mann–Whitney *U*, and ANOVA tests. Using a univariate linear regression model, the independent effects of diagnosis delay on tumor size were examined. The model of fit was examined using the required residual and fit statistics. Results were considered as statistically significant when $p < 0.05$.

Results

The mean age of 169 patients included in the study was 65.90 ± 11.78 years, 149 (88.2%) of the patients were male, and 138 (81.7%) patients used to smoke before or were still smokers. It was observed that during admission

the first complaint of 156 (92.3%) patients was hematuria. Tumor localization of the patients was evaluated as trigonal, non-trigonal, and multiple localized. There was no significant correlation between the patients' gender, smoking status, complaint for admission and tumor localization, and the delay in diagnosis ($p=0.977$, $p=0.290$, $p=0.759$, $p=0.820$, respectively). The mean tumor size of all patients was 42.21 ± 24.74 mm. Tumor size was smaller than 3 cm in 48 (28.4%) patients and larger than 3 cm in 121 (71.6%) patients. The tumor grade of 85 (50.3%) patients were found to be low grade. When the T stages were examined, the invasion stage of the tumor was detected as Ta in 61 (36.1%) patients, T1 in 59 (34.9%) patients, and T2 in 49 (29%) patients. A statistically significant difference was not found between tumor grade and T stage and duration of diagnosis delay ($p=0.090$, $p=0.283$, respectively). When the relationship between the tumor size detected in cystoscopy and duration of diagnosis delay was examined, it was observed that the diagnosis delay was significantly longer in patients with tumors larger than 3 cm compared to patients with tumors smaller than 3 cm ($p<0.001$) (Table 1). In the correlation analysis between tumor size, duration of diagnosis delay, age, T stage,, and tumor grade, a low level of positive correlation was observed between tumor size and duration of diagnosis delay, and it was statistically significant ($r=0.215$, $p=0.005$) (Table 2).

Based on the hypothesis that the increase in the duration of diagnosis delay had a significant and positive effect on the pathological size of the tumor, the two data were analyzed by linear regression analysis (Enter method). The model was statistically significant ($F=8.130$ $p=0.005$) and without significant auto-correlation issues (Durbin–Watson = 1.844), it could explain 4.6% of the variance in pathological tumor size. In linear regression analysis, diagnosis delay was found to be a significant predictor of pathological tumor size. According to the standardized regression coefficients (β), a 1-day increase in the duration of diagnosis delay caused an increase of 0.088 mm in the pathological size of the tumor (Table 3).

Table 1 Comparison of the tumor features of the patients and the duration for admission

	$N=169$ n (%)	Duration of diagnosis delay * (days)	p
Age	65.90 ± 11.78	14	0.277
Gender			
Male	149 (88.2)	14	0.977
Female	20 (11.8)	15	
Smoking			
Yes	138 (81.7)	14	0.290
No	31 (18.3)	18	
Complaint of admission			
Hematuria	156 (92.3)	14	0.759
Dysuria	13 (7.7)	16	
Tumor localization			
Trigonal	40 (23.7)	12	
Non-trigonal	55 (32.5)	14	0.820
Multiple	74 (43.8)	15	
Tumor size			
< 3 cm	48 (28.4)	7	**< 0.001**
> 3 cm	121 (71.6)	18	
Tumor grade			
Low grade	85 (50.3)	12	0.090
High grade	84 (49.7)	18	
Tumor stage			
Ta	61 (36.1)	11	
T1	59 (34.9)	18	0.283
T2	49 (29)	15	

Bold value indicate statistically significant

(*median)

Discussion

In many kinds of cancers, the effects of delayed treatment on disease progression and survival have been investigated. In 2020, a meta-analysis including bladder, breast, colon, lung, rectum, cervix, and head and neck cancers was published by Hanna et al. In this report, treatment delay was defined as the time from diagnosis to curative treatment. This meta-analysis included 1,274,681 patients and 34 studies. As a result of the study, it was shown that a 4-week delay in curative treatment caused an increase in mortality [12].

It has been observed that, in the literature, the studies in bladder cancer seem to focus on treatment delay, especially in muscle-invasive bladder cancers. In the study by Gore et al. in 2009 study, that involved 441 patients with stage 2 bladder cancer, it was shown that surgical treatment performed after the 12th week increased mortality compared to early surgery (4–8 weeks) [13].

Also, in 2009, Kulkarnive et al. have reported in their retrospective evaluation of 2535 patients who underwent radical cystectomy for bladder cancer between 1992 and 2004 that the mean time between TUR-BT and cystectomy was found to be 50 days and mortality started to increase after 40 days [14].

The fact that some health services had to be postponed during the COVID-19 pandemic period, caused a delay in the diagnosis and treatment of cancer, prompted researchers to investigate the effect of delay in diagnosis and treatment on oncological outcomes. In one of the studies conducted on this respect by Doğan et al. in 2022, patients who underwent TUR-BT for bladder cancer in the last 5 years before the

Table 2 Correlation analysis of demographical and the clinical data

		Diagnosis delay (days)	Age	Tumor size (mm)	T stage	Tumor grade
Diagnosis delay (days)	*r*					
	p					
Age	*r*	− 0.84				
	p	0.277				
Tumor size (mm)	*r*	0.215	0.198			
	p	**0.005**	**0.010**			
T stage	*r*	0.087	0.214	0.276		
	p	0.260	**0.005**	**< 0.001**		
Tumor grade	*r*	0.131	0.123	0.385	0.537	
	p	0.090	0.112	**< 0.001**	**< 0.001**	

Bold values indicate statistically significant

Table 3 Linear regression analysis regarding the duration of diagnosis delay and increase in tumor size

Variables	*B*	Standard error	*β*	*t*	*p*	95% Confidence interval
(Constant)	38.796	2.215	–	17.514	**< 0.001**	34.423 to 43.170
Tumor size	**0.088**	0.031	0.215	2.851	**0.005**	0.027 to 0.150
Dependent variable Pathological tumor size						
***R*:0.215 R^2: 0.046 F: 8.130 *p* = 0.005 Durbin–Watson: 1.844**						

Bold values indicate statistically significant

pandemic and during the pandemic period were evaluated retrospectively. In the study, the time between the onset of macroscopic hematuria and the diagnosis, the time between diagnosis and treatment, and the time between the operation date and the pathology report were evaluated. As a result, they showed that the time elapsed between the onset of hematuria and diagnosis was significantly higher during the pandemic period than before the pandemic. Also in the same study, the pathological features of the patients in the pandemic and pre-pandemic period were compared, and it was revealed that the features such as tumor size, stage, grade, presence of CIS, presence of lymphovascular invasion, and presence of variant histology were similar. It has shown that patients were admitted to the hospital significantly later during the pandemic period [15].

Unlike many studies in the literature, in our study, we focused on the possible consequences of the delay in the time from symptom to treatment, instead of the time from diagnosis to treatment. The study by Öztürk et al. in 2015, which was on delay in diagnosis of testicular cancer, was conducted on 60 patients, and the factors related to the delay in diagnosis of these patients were examined, and the sociodemographic characteristics and educational status of these patients were examined. In the study, it was determined that as the education level decreased, the patient-related delay in diagnosis increased [16]. In addition to the fact that our study evaluated the possible consequences of the delay in diagnosis on the course of the disease, we think that it may be related to health literacy about how patients take their symptoms seriously, and how long it takes to admit the hospital, which can be supported by future studies.

We think that the relationship of the duration of admission to the hospital, especially in similar periods, and the accessibility of health services in the country and health literacy should be evaluated. We also believe that it would be more accurate to make this evaluation apart from the time periods when the accessibility to health services is seriously affected, as in the COVID-19 pandemic. Because in this period, the measures taken by the states against the pandemic were different from each other, and the measures taken at different times of the pandemic period were also different. This fact can seriously affect the time to hospital admission and, thus, the delay in diagnosis.

In the model developed by Andersen et al., which is one of the most accepted theoretical models about the delay in cancer diagnosis, they defined and addressed the delay in diagnosis separately as the time passed until a person recognized a symptom as a disease, the time passed until deciding to seek medical help after noticing his illness, and the time passed to admit to a health professional after deciding to seek medical help [17]. To provide high-quality health care to patients in a short time, necessary arrangements should be made in terms of patients, doctors, and health policies to reduce the delay in diagnosis. Increasing health

literacy, ensuring the patient's accessibility to the physician, and establishing sustainable quality health policies may be beneficial for reducing the duration of delay in diagnosis.

The limitation of our study is that in the study that measures the delay in diagnosis in a patient centered manner, there may be difficulty in remembering the times. However, the mean duration of diagnosis delay in our study was 7 days for tumors < 3 cm and 18 days for tumors > 3 cm. Since these periods are not long, we do not think that this seriously affects our study. The strengths of our study are that due to the good patient information form, the diagnosis delay can be calculated with high accuracy, and the effect of the daily delay on the tumor is measured with the linear regression model.

Conclusion

As a result of our study, we conclude that the reason for the absence of a statistically significant difference between the duration of diagnosis delay and T stage and grade is that these parameters are more related to the genetic features of the disease. However, it should be kept in mind that the long-term follow-up of these patients should not be interrupted, and that these data may change in long-term follow-ups. In our study, we have shown that the tumor size increases as the duration of diagnosis delay increases, and this increase causes an increase of 0.088 mm in tumor size for the period of 1-day delay. Considering that tumor size changes the risk group of the disease in bladder tumors, and accordingly the follow-up and treatment process changes, we believe that these data will be valuable in the management of bladder cancer. In addition, we think that the increase in tumor size may affect parameters such as the need for recurrent resection, more hospital admissions and longer hospital stays, and increased treatment costs. We think that more research should be performed on this subject.

Author contributions OG and KU designed the study; OG, KU, and KT recruited the participants and collected the data; OG, VMY, and KT performed the statistical analysis; OG, KU, VMY, and KT interpreted the data; OG, VMY drafted the first manuscript; and all authors critically reviewed the paper.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and consent to participate The data were retrospectively recorded after obtaining ethical approval (Afyonkarahisar Health Sciences University Clinical Research Ethics Committee. 2011-KAEK-2, 2023/). The study was carried out in accordance with the principles of the Declaration of Helsinki. This study was approved by the local ethics committee (AFSU 2011-KAEK-2/2023/306) and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Informed consent As this study involved an retrospective review, consent was not required. The authors have obtained approval from the Ethics Committee for the analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Research involving human and animal rights The authors declare that no experiments were performed on humans or animals for this study.

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