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The impact of antithrombotic therapy on the time of detection of bladder cancer

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Introduction The aim of this article was to investigate the impact of chronic antithrombotic therapy (AT) use on the time of detection of bladder cancer, assuming that patients taking AT experience episodes of macroscopic hematuria earlier, and therefore have a more favorable histopathological grade and stage, as well as a smaller number and size of tumors compared to patients not taking AT.

Material and methods A retrospective, cross-sectional study was conducted, including 247 patients who underwent bladder cancer surgery for the first time at our institution during the three-year period (2019–2021) and who experienced macroscopic hematuria.

Results A lower frequency of high-grade bladder cancer (40.6% vs 60.1%, P = 0.006), T2 stage (7.2% vs 20.2%, P = 0.014), and a lower frequency of tumors larger than 3.5 cm (29% vs 57.9%, P <0.001) were found in patients using AT compared to patients not using them. The patients using AT had a smaller mean tumor size (2.98 vs 4.51 cm, P <0.001). A multivariable regression analysis, adjusted for age, sex, and number of comorbidities, showed a lower probability of having a high-grade cancer (OR 0.393, 95% CI 0.195–0.792, P = 0.009), T2 stage (OR 0.276, 95% CI 0.090–0.849, P = 0.025), and tumors larger than 3.5 cm (OR 0.261, 95% CI 0.125–0.542, P <0.001) in patients using AT.

Conclusions More favorable histopathological grades, stages, and smaller tumor sizes were found in patients with bladder cancer who experienced macroscopic hematuria and were using AT compared to patients not taking AT.

Key Words: antithrombotic therapy ‹› bladder cancer ‹› hematuria

INTRODUCTION

Bladder cancer is one of the most common urologic malignancies [1]. Macroscopic hematuria is the first symptom most patients experience [2]. Rapid evaluation after the initial episode of macroscopic hematuria can lead to an earlier diagnosis of bladder cancer, as well as a better treatment and clinical outcomes [3]. The incidence of bladder cancer increases with age [2]. Elderly patients often have associated cardiovascular comorbidities, which is why they commonly take antithrombotic therapy (anticoagulants and antiplatelet agents) – drugs that may enhance and precipitate bleeding from the tumors more frequently [4, 5].

The aim of the present study was to investigate the impact of antithrombotic therapy on the time of detection and characteristics of bladder cancer. We hypothesized that the patients chronically using antithrombotic therapy for various cardiovascular indications will experience episodes of macroscopic hematuria earlier in the bladder cancer development. For these reasons, these patients may have a more favorable histopathological grade and stage, as well as a smaller number and average size of tumors compared to patients not using antithrombotic therapy.

MATERIAL AND METHODS

A retrospective, cross-sectional study was carried out. The present study protocol was reviewed and approved by the Ethics Committee of our institution. The study included 247 adult patients who underwent urothelial cancer surgery for the first time at our institution in the three-year period considered (2019–2021) and who experienced macroscopic hematuria. Patients with recurrent bladder tumors and non-urothelial bladder tumors, as well as those with other initial symptoms (other than macroscopic hematuria), were excluded from the study. The data were extracted from the hospital's electronic medical records. The patients were identified with an identification number, and their identities remained anonymous. Variables that were of interest included age, sex, smoking history, the use of antithrombotic drugs during episodes of macroscopic hematuria (anticoagulants and antiplatelet agents), associated comorbidities, histopathological bladder cancer grade according to the World Health Organization (WHO) classification systems from 2004 [6], the presence of concomitant carcinoma in situ (CIS), the histopathological stage of bladder cancer after the initial transurethral resection, as well as the number and total cumulative size of tumors described by the surgeon during urologic surgery.

Statistical analysis

All data analyses were performed using SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Continuous data were shown as mean ± standard deviation (SD), while categorical variables were shown as whole numbers (N) and percentages (%). The normality of data distribution was examined with the Kolmogorov-Smirnov test. The independent samples t-test was used to measure differences in continuous variables between two groups of interest (for instance, the patients using vs. those not using antithrombotic therapy). Similarly, a Chi-squared (χ^2) test was used to examine the differences between groups of interest with respect to categorical variables. Tumor variables potentially associated with antithrombotic therapy use were first evaluated using the univariate logistic regression model. Variables that were significantly associated with the antithrombotic therapy use in the univariate model were then entered in the multivariable logistic regression model for each variable separately. Each variable was then adjusted for the co-variates of age, sex, and mean number of comorbidities. A two-tailed significance value (P) was reported in all instances, and the results that reached P values <0.05 were considered statistically significant.

RESULTS

Table 1 shows the general baseline and demographic characteristics of patients included in the study, as well as their bladder cancer characteristics (number of tumor(s), size, histopathological grade, and stage). Out of 247 patients, 69 (27.94%) were identified as actively using antithrombotic therapy (oral anticoagulant or antiplatelet agents).

A comparison of bladder cancer characteristics was performed between patients using versus not using antithrombotic therapy (Table 2). A significantly lower frequency of high-grade cancer (P = 0.006), a lower frequency of stage T2 cancer (P = 0.014), and a lower frequency of cumulative tumor size larger than the median of 3.5 cm (P <0.001) were found in patients using antithrombotic therapy. Furthermore, patients using antithrombotic therapy had a significantly smaller mean cumulative tumor size compared to patients not using antithrombotic therapy (2.98 ±2.03 vs 4.51 ±3.14 cm, P <0.001, respectively). There were no significant differences

Table 1. *Overview of demographic characteristics of patients included in the study and their bladder cancer characteristics*

Variable	N (%) or mean ±SD
Baseline patient characteristics	247 (100)
Male	165 (66.8)
Female	82 (33.2)
Age (years)	70.26 ±10.03
Smoking history	147 (59.51)
Mean number of comorbidities	1.59 ±1.42
Antithrombotic therapy use	69 (27.94)
Oral antiplatelet use	47 (19.03)
Oral anticoagulant use	22 (8.91)
Bladder cancer characteristics	
Tumor focality	132 (53.44)
Single	115 (46.56)
Multiple	4.08 ±2.95
Bladder cancer grade (WHO 2004)	
PUNLMP	30 (12.1)
Low-grade	82 (33.2)
High-grade	135 (54.7)
Concomitant CIS	20 (8.1)
Pathologic bladder cancer stage	
Ta	134 (54.25)
T1	72 (29.15)
T2	41 (16.6)

N – number of patients; SD – standard deviation; WHO – World Health Organization; PUNPLMP – papillary urothelial neoplasm of low malignant potential; CIS – carcinoma in situ

between the two groups concerning the frequency of associated CIS, the mean number of detected tumors, and the occurrence of multiple tumors.

The results of univariate and multivariable regression analyses examining the impact of antithrombotic therapy use on bladder cancer characteristics are shown in Table 3. The univariate regression analysis showed a significantly lower probability of having a high-grade bladder cancer, stage T2 cancer, and a cumulative tumor size greater than 3.5 cm in patients using antithrombotics, which was also confirmed by the multivariable regression analysis adjusted for covariates including age, sex, and the number of the comorbidities. No correlation was found between the use of antithrombotic therapy and the concomitant occurrence of CIS or multiple tumors.

DISCUSSION

Antithrombotic therapy is associated with an increased risk of various forms of bleeding, such as gastrointestinal, respiratory, intracranial, or genitourinary bleeding [7]. Any relevant bleeding in patients taking antithrombotic therapy is a symptom that should not be ignored by the clinicians. Such bleedings can unmask previously asymptomatic malignant diseases and therefore require detailed clinical evaluation [8–11]. The results of a recent systematic review showed that 3% of patients with atrial fibrillation experience a bleeding episode while taking anticoagulant therapy, and such episodes are associated with a 9-fold higher odds for cancer diagnosis on any site [10]. The incidence of hematuria in patients taking antithrombotics varies between 2 and 24% [12, 13]. The research conducted on patients with atrial fibrillation reports a higher and increased incidence of urinary tract cancers, especially bladder cancer, in anticoagulated patients with hematuria [11, 14].

Previous research has also shown a connection between the use of antithrombotic therapy and more favorable characteristics of tumors detected after the evaluation of bleeding, which is probably a consequence of earlier bleeding from existing pathological sites. Warfarin use was found to be associated with a lower incidence of Dukes' stage D cancers following gastrointestinal bleeding episodes in the Korean population [15]. As for bladder cancer, an increased frequency of low-grade papillary urothelial cancers has been described in patients taking oral anticoagulants compared to those not taking oral anticoagulants [11]. Moschini et al. found that the patients first diagnosed with bladder cancer after presenting with an episode of macroscopic hematuria are more likely to have experienced a lower grade and lower stage bladder cancer if they were receiving antithrombotic therapy during a hematuria episode [16]. Complementary to previous results, we report on a significantly lower probability of having a high-grade and stage T2 cancer in patients using antithrombotic therapy compared to non-users,

Table 2. *Comparison of bladder cancer characteristics between patients using antithrombotic therapy and those not using them*

Variable	Antithrombotic therapy use		P-value
	YES	NO	
High-grade bladder cancer, %	40.6	60.1	0.006[a]
Concomitant CIS, %	5.8	9.0	0.415[a]
T2 bladder cancer stage, %	7.2	20.2	0.014[a]
Number of tumors, mean ±SD	1.87 ±1.36	2.13 ±1.5	0.205[b]
Multiple tumors (≥2), %	40.6	48.9	0.242[a]
Total tumor size, cm, mean ±SD	2.98 ±2.03	4.51 ±3.14	<0.001[b]
Total tumor size >3.5 cm, %	29.0%	57.9%	<0.001[a]

CIS – carcinoma in situ; SD – standard deviation
[a]Chi-square test, [b]independent samples t-test

Table 3. *Results of the univariate and multivariable regression analysis of the impact of antithrombotic therapy on histopathological stage, grade, size, and number of bladder cancers*

Variable	Antithrombotic therapy use			
	Univariate logistic regression		Multivariable logistic regression	
	OR (95% CI)	P-value	OR (95% CI)	P-value
High-grade bladder cancer	0.453 (0.257–0.798)	0.006	0.393 (0.195–0.792)	0.009[a]
Concomitant CIS	0.623 (0.201–1.934)	0.413	–	–
T2 tumor stage	0.308 (0.116–0.822)	0.019	0.276 (0.090–0.849)	0.025[a]
Multiple tumors (≥2)	0.714 (0.407–1.255)	0.242	–	–
Total tumor size ≥3.5 cm	0.297 (0.163–0.541)	<0.001	0.261 (0.125–0.542)	<0.001[a]

OR – odds ratio; CI – confidence interval; CIS – carcinoma in situ
[a]the multivariable logistic regression model adjusted for covariates of age, sex, and number of comorbidities

as previously described by other authors [11, 16]. To our knowledge, our research was first to explore additional characteristics of bladder cancer in such patients (apart from the grade and stage), namely the average size and number of tumors. Therefore, we report that the patients using antithrombotic therapy had a significantly smaller mean cumulative tumor size, as well as a lower probability of detecting a tumor with a total size larger than the median in our study (>3.5 cm). On the other hand, we found no correlation between antithrombotic therapy use and associated CIS or the occurrence of multiple tumors. The use of antithrombotic therapy is a relevant phenomenon since it is increasingly becoming more common in the aging population [17]. In case of bleeding during oral antithrombotic therapy, a diagnostic evaluation is warranted in order to detect or exclude occult cancer [18]. Our results are clinically relevant in the context of previously known data from the literature stating that bladder cancers of lower histopathological grade, stage, and smaller size are associated with better outcomes, survival, and a lower recurrence rate [3, 19, 20]. The detection of bladder cancer with more favorable characteristics in patients chronically using antithrombotic therapy may be explained by the earlier onset of drug-induced tumor bleeding, which may allow for an earlier diagnosis and treatment, and consequently better clinical outcomes [3, 11, 16, 19].

There are some limitations to this study. Of note, this is designed as an observational retrospective study, and this limited the quality of some of the collected data. The operators subjectively estimated the largest tumor dimension based on intraoperative results. Information on the exact dose and duration of antithrombotic therapy was missing for some patients, which made it impossible to perform sub-analyses based on the duration of therapy.

CONCLUSIONS

More favorable histopathological grades, stages, and smaller tumor sizes were found in patients with bladder cancer who experience macroscopic hematuria and are using antithrombotic therapy compared to those not taking antithrombotic therapy. These results are likely due to an earlier onset of bleeding from bladder cancer in patients using antithrombotics, when the aforementioned tumors have more favorable histopathological and morphological characteristics.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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