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The Effect of Bladder Outlet Obstruction on Bladder Cancer Recurrence and Progression

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What's known on the subject? and What does the study add?

It is known that the risk of bladder tumour detection is higher in patients with benign prostatic obstruction (BPO). In this study, the effect of BPO on the recurrence and progression of existing bladder cancer was investigated.

Abstract

Objective: To investigate the effect of bladder outlet obstruction (BOO) on cancer recurrence and progression in patients with non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: A retrospective analysis was conducted on 256 male patients diagnosed with primary NMIBC at Kartal Dr. Lütfi Kırdar City Hospital between 2010 and 2018. Patients were divided into two groups according to the presence of BOO (BOO group, n=123; control group, n=133). Demographic and pathological data, as well as intravesical treatments, recurrence and progression status of both groups were recorded and compared according to cystoscopy findings in five years of follow-up.

Results: Patients with BOO were older and had higher rates of comorbidities, larger prostate volumes, higher prostate-specific antigen levels, and more frequent cystoscopic findings of trabeculation and diverticula (p<0.001). Initial pathology showed higher rates of T1 stage and high-grade tumors in the BOO group (50% *vs.* 24%, p=0.003 and 42.6% *vs.* 21%, p=0.008, respectively). A multivariate logistic regression model indicated that BOO was not an independent variable to predict any initial bladder cancer pathology, recurrence, or progression rate (p>0.05). The presence of trabeculation in cystoscopy was found to be an independent predictor of the initial diagnosis of high-grade/carcinoma *in situ* urothelial carcinoma, with an odds ratio of 4.62 (95% confidence interval, 1.3-17; p=0.021), following adjustment for potential confounding variables.

Conclusion: Findings of this study indicate that BOO does not affect disease recurrence or progression, nor does it affect the pathological features of the tumour at the time of diagnosis. Conversely, increased bladder trabeculation resulting from BOO may be associated with a higher-grade tumor at the time of initial diagnosis.

Keywords: Bladder cancer, bladder outlet obstruction, benign prostatic hyperplasia

Introduction

Bladder cancer (BLCA) is one of the most prevalent cancers worldwide, with an estimated increase in incidence of approximately 30-40% over the past few decades, particularly among men aged 64-75 years (1). Bladder outlet obstruction (BOO) is a prevalent pathology among men of similar age categories, typically resulting from conditions such as benign prostatic hyperplasia (BPH). The prevalence of BPH is known to be 70-80% in men aged 70 and over (2). Although BPH and BLCA are distinct diseases with disparate pathophysiological alterations, epidemiological profiles, and risk factors (3,4), it has

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been demonstrated that the incidence of BLCA in patients with BOO is 20-30% higher than in those without BOO (5).

It is postulated that BOO plays a pivotal role in the pathogenesis of BLCA, resulting in significant alterations to bladder histology and physiology. BOO is associated with a number of histological changes, including hypertrophy and hyperplasia of the detrusor muscle, fibrosis, increased collagen deposition, and chronic inflammation (6). These conditions may trigger cancer development by causing cellular stress and DNA damage (7). Additionally, increased intravesical pressure and high poliovirus receptor (PVR) can trigger malignant transformation by causing mechanical stress in bladder epithelial cells and prolonged contact with carcinogenic substances (8). It has been demonstrated that conditions that cause BOO, particularly BPH, may increase the risk of BLCA by triggering increased intravesical pressure (5). Nevertheless, there is evidence that establishes a causal relationship between the two diseases. In a mendelian randomization study by Du et al. (9), genetically predicted BPH was associated with a higher risk of BLCA in all histological subtypes. Similarly, many population-based cohort studies have shown that lower urinary tract symptoms (LUTS) or BOO is associated with a high incidence of BLCA (2,5,7,10-12). However, few studies have investigated the effect of LUTS or BOO on cancer recurrence or progression after local treatment of BLCA (13). Important risk factors for recurrence and progression of BLCA include tumor characteristics as well as patient factors such as age, comorbidities, initial response, and non-response to intravesical therapies (14). The objective of this study was to examine the impact of BOO and associated cystoscopic findings on the recurrence and progression of BLCA over a five-year period.

Materials and Methods

Data Collection

A total of 256 male patients diagnosed with primary non-muscle invasive bladder cancer (NMIBC) between 2010 and 2018, who were followed for five years at the Urology Department of Kartal Dr. Lütfi Kırdar City Hospital, were included in this study. Data on the patients were reviewed retrospectively. Patients were divided into two groups based on the presence of BOO (Group 1: BOO, Group 2: Control). The inclusion criteria for the BOO group were defined as the presence of an obstructive uroflowmetry test with a voided volume over 150 cc and a maximum flow rate (MFR) below 15 mL/s, or a MFR between 15-20 mL/s accompanied by at least 6 months of α-blocker medication use, for the purposes of this study. The control group consisted of patients with a MFR of 20 mL/s or above. Patients who did not comply with the BLCA clinical follow-up protocol, underwent surgery for BOO, in the past or during the follow-up period, or had a uroflowmetric voiding volume below 150 mL were excluded from the study. Accordingly, 123 patients were included in the BOO group and 133 in the control group, making a total of 256 patients included in the study. The findings of the digital rectal examination (DRE) were recorded in accordance with the grading system proposed by Barnes et al. (15). Accordingly, prostate penetration of 1-2 cm into the rectum was classified as grade I, greater than 2 but less than 3 cm as grade II, greater than 3 but less than 4 cm as grade III, and greater than 4 cm as grade IV. The demographic data, medical histories, prostate-specific antigen levels, uroflowmetry values, cystoscopy findings, pathology results, and intravesical treatments were documented. The recurrence rate, time to recurrence, and progression during follow-up were recorded and compared between the two groups. Patients who underwent radical cystectomy/chemoradiotherapy due to MIBC development or Bacillus Calmette-Guérin (BCG) non-response or incomplete transurethral resection (TUR) were enrolled. The follow-up data of these patients after this stage, were not included in the study. Those who had at least one diverticulum larger than 3 cm and/or extensive trabeculation according to cystoscopy findings in the first or subsequent months were enrolled.

Clinical Management and Follow-Up

Patients were treated according to the European Association of Urology (EAU) guidelines for NMIBC (16). All patients underwent initial imaging of the upper urinary tract with CT urography or renal USG. After the initial transurethral resection of bladder tumor (TURBT), resection was performed within 6 weeks in patients with the relevant indication (Re-TURBT). Early intravesical chemotherapy (mitomycin-C) was administered to eligible patients within the first 6 hours. Patients were stratified according to EAU-NMIBC prognostic factor risk groups. The low-risk group was typically followed without adjuvant intravesical chemo/immunotherapy, while patients in the high-risk group received at least one-year adjuvant intravesical BCG induction cycle 2-4 weeks after re-TURBT. The intermediate-risk group received either routine clinical follow-up or at least one six-week course of adjuvant intravesical mitomycin-C.

Clinical follow-up after TURBT was performed with cystoscopy and urine cytology every 6 months for the first 2 years and annually thereafter in the low-risk group; in the intermediate- and high-risk groups, follow-up was every 3 months for the first 2 years, then every 6 months, and annually after the 5th year. Upper system imaging was performed every 1-2 years. Recurrence and progression status were determined according to the final histopathologic diagnosis obtained from repeat TURBT or urinary tract biopsy during follow-up.

This study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (approval number: 2024/010.99/6/20,

date: 26.07.2024). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Statistical Analysis

Continuous variables were presented as median (interquartile range), and categorical variables were presented as patient numbers and percentages (%). The Mann-Whitney U test was used for the comparison of continuous variables, while the chi-square test or Fisher's exact test was used for the comparison of categorical variables. Logistic regression analysis was performed to evaluate the relationship between tumor aggressiveness and BOO/cystoscopic parameters, adjusting for potential confounding variables such as age and comorbidities. The results were reported as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was considered at $p<0.05$, and all analyses were conducted using Statistical Package for the Social Sciences.

Results

Various clinical (Table 1) and pathological parameters (Table 2) were compared in patients with BLCA, categorized by the presence or absence of BOO. Patients with BOO were older than controls (69 *vs.* 61 years, p=0.001). Additionally, the rate of comorbidities was higher in patients with BOO (1 or 2 comorbidities: 73% *vs.* 38%, p=0.001). DRE grading of BPH showed higher grades in patients with BOO (grade 3: 52% *vs.* 8%, p=0.001). Prostate volume was also larger in patients with BOO (45 cc *vs.* 25 cc, p=0.001). Total prostate-specific antigen levels were higher in patients with BOO (2.1 ng/dL vs. 1 ng/dL, p=0.001). According to uroflowmetry results, the MFR value was lower in patients with BOO (11.7 mL/s *vs.* 24.5 mL/s, p=0.001). Cystoscopy findings showed more frequent trabeculation (63% *vs.* 5%, p=0.001) and diverticula (32% *vs.* 3%, p=0.001) in patients with BOO. The use of α-blockers was also more common in patients with BOO (50% *vs.* 2%, p=0.001) (Table 1).

Regarding cancer parameters, patients with BOO had higher stage (T1: 50% *vs.* 24%, p=0.003) and more advanced grade [high grade/carcinoma *in situ* (CIS): 42.6% *vs.* 21%, p=0.008] tumors at initial diagnosis. Despite the median follow-up period being 61 months for both groups, there were no statistically significant differences between the groups in terms of follow-up duration, number of recurrences, time to first recurrence, recurrence rate, and initiation rate of intravesical therapy. Although the progression rate was higher in patients with BOO, the difference was not statistically significant (16.4% *vs.* 6%, p=0.059) (Table 2).

Table 3 shows the relationship between tumor aggressiveness and presence of BOO, trabeculations, and diverticula, which were investigated in a multivariate logistic regression model, following

Table 1. Characteristics, findings related with voiding functions of the patients with bladder cancer and its subgroups according to having bladder outlet obstruction or not

	Total (n=256)	Control (n=133)	BOO (n=123)	p
Age (years)	65 (14)	61 (12)	69 (12)	**0.001**
BMI (kg/m²)	25 (5)	25 (5)	24 (5.5)	**0.76**
Comorbidities, n (%)				
None	93 (36%)	72 (54%)	21 (17%)	**0.001**
1 or 2	141 (55%)	51 (38%)	90 (73%)	
3 or more	22 (9%)	10 (8%)	12 (10%)	
Smoking status	178 (70%)	95 (72%)	83 (68%)	**0.87**
Digital rectal grading of BPH, n (%)				
Grade 1	29 (11%)	26 (20%)	3 (2%)	**0.001**
Grade 2	132 (52%)	94 (71%)	38 (31%)	
Grade 3	75 (29%)	11 (8%)	64 (52%)	
Grade 4	20 (8%)	2 (2%)	18 (15%)	
Prostate volume (cc)	32 (22)	25 (10)	45 (26)	**0.001**
Total PSA (ng/dL)	1.4 (1.8)	1 (0.8)	2.1 (3)	**0.001**
MFR (mL/sn) in uroflowmetry	18.6 (9.9)	24.5 (7.1)	11.7 (4.9)	**0.001**
Cystoscopy findings n (%)				
Trabeculation	84 (33%)	6 (5%)	78 (63%)	**0.001**
Diverticule	43 (17%)	4 (3%)	39 (32%)	
Usage of alfa blockers, n (%)	64 (25%)	3 (%2)	61 (50%)	**0.001**

Data are presented as median (interquartile range for continuous variables and number of patients (%) for categorical variables. P<0.05 is a significant diffences between the groups, PSA: Prostate-specific antigen, BOO: Bladder outlet obstruction, BPH: Benign prostatic hyperplasia, BMI: Body mass index, MFR: Maximum flow rate

adjustment for potential confounding variables, including age, comorbidities, smoking status and tumor size and number of tumors at first cystoscopy. The presence of trabeculation was an independent predictor of tumor recurrence and the initial diagnosis of high-grade/CIS urothelial carcinoma (OR 4.62; 95% CI, 1.3-17; p=0.021). The parameters related to bladder functions could not be associated with the categories determining tumor aggressiveness (p>0.05).

Table 2. A comparison of the findings in primary pathology and the recurrence and progression status in follow-up between the groups

	Control (n=133)	BOO (n=123)	p
Cancer parameters at first diagnosis			
Size (mm)	30 (20)	30 (20)	0.96
Number	2 (3)	2 (1)	0.11
Stage			
Ta	101 (75%)	62 (50%)	**0.003**
T1	32 (24%)	61 (50%)	
Grade			
Low grade	106 (79%)	70 (57.4%)	**0.008**
High grade/CIS	28 (21%)	52 (42.6%)	
Cancer parameters at follow-up			
Follow-up period (months)	61 (12)	61 (12)	0.79
No. recurrens	2.5 (3)	2 (2)	0.09
Time to first recurrence (months)	12 (12)	12 (18)	0.29
Annual recurrens rate	0.33 (0.58)	0.40 (0.47)	0.11
Progression in stage, n (%)	8 (6%)	20 (16.4%)	0.059
Intravesical treatment			
No	71 (53%)	64 (52%)	0.441
Mitomycin	22 (17%)	13 (10%)	
BCG	40 (30%)	46 (38%)	

Data are presented as median (interquartile range for continuous variables and number of patients (%) for categorical variables. P<0.05 is a significant diffences between the groups, BOO: Bladder outlet obstruction, BCG: Bacillus Calmette-Guérin, CIS: Carcinoma *in situ*

Table 3. Relationship between tumor aggresiveness and bladder outlet obstruction and cystoscopic parameters via multivariate logistic regression analysis

	Bladder outlet obstruction		Presence of trabeculation		Presence of diverticule	
	No (n=133)	Yes (n=123)	No (n=172)	Yes (n=84)	No (n=212)	Yes (n=44)
T1 stage at first diagnosis **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	32 (24%) Reference	60 (49%) 2.21 0.131	50 (29%) Reference	42 (50%) 2.36 0.170	73 (34%) Reference	19 (45%) 0.56 0.366
High grade/CIS at first diagnosis **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	28 (21%) Reference	52 (43%) 1.41 0.538	39 (23%) Reference	41 (48%) **4.62** **0.021**	63 (29%) Reference	17 (41%) 0.49 0.280
Recurrence rate more than 0.5/year **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	41 (30%) Reference	42 (34%) 1.25 0.67	56 (33%) Reference	27 (31%) 1.44 0.56	74 (35%) Reference	9 (18%) 0.25 0.054
Progression in stage **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	8 (6%) Reference	20 (16%) 4.2 0.054	18 (11%) Reference	10 (12%) 0.83 0.83	26 (12%) Reference	2 (5%) 0.11 0.09

[a]: Adjustment for potential confounding variables, including age, comorbidities, smoking status and tumor size and count in first cystoscopy, OR: Odds ratio, CI: Confidence interval, CIS: Carcinoma *in situ*

Discussion

The association between BOO/BPH and urologic cancers has received increasing attention in recent years. The frequent co-occurrence of these pathologies, especially in elderly males, has stimulated studies to investigate the potential link between them. Recently, a meta-analysis of observational studies was published (12) that clarified the conflicting results regarding the association between BPH and BLCA. Accordingly, BPH was shown to increase the risk of BLCA. Upon examination of the included studies, the most frequently cited mechanism is that the elevated intravesical pressure observed in patients with BPH, may result in lower urinary tract damage, prolonged exposure to urinary carcinogens due to high residual urine, and potential carcinogenesis (12,17). The only mendelian randomization study investigating causality in this regard was published by Du et al. (9). The results of this study indicated that BPH exhibited a weak positive effect on the occurrence of BLCA (OR: 1.095, 95% CI: p=0.003); however, no causal effect was identified for BLCA on BPH. In contrast to the aforementioned studies, our investigation focused on the presence of BOO and its effect on response to treatment in patients with NMIBC. We sought to determine whether BOO was associated with differences in pathologic variables at diagnosis and/or influenced the recurrence and progression of the disease over time.

In our study, we employed uroflowmetric evaluation (18), which is regarded as one of the most efficacious non-invasive tests for the diagnosis of BOO (8). The observation that the prostate size of the patients included in the BOO group was significantly higher indicates that BPH is a significant condition affecting these patients. In a study by Ham et al. (19), men with concurrent bladder urothelial carcinoma and BPH underwent simultaneous TURBT and transurethral resection of the prostate (TURP). It has been demonstrated that the recurrence of BLCA can be reduced by the treatment of BPH, with a 60-month recurrence-free probability of 52%, compared to 43%. However, there was no significant difference in the progression rates. A similar study corroborated this finding, demonstrating that in men with BLCA and BPH/BOO, the 5-year recurrence rate was lower in patients who had TURBT and TURP performed in the same setting compared to TURBT alone (56% *vs.* 80%, p<0.01) (20). Given that the methodology of these studies was based on dependent groups, a comparison with our data would be erroneous. If a urothelial tumor develops in the context of elevated intravesical pressure and augmented carcinogen exposure as a consequence of BOO, a reduction in the incidence of recurrence or progression following BOO treatment may be anticipated. Nevertheless, this issue continues to be a source of debate since there are studies indicating that individuals who have undergone surgical or medical treatment for BPH may be at an elevated risk of developing cancer compared to those who have not. Kang et al. (10) published a cohort study investigating the risk of BLCA in 79,280 patients hospitalized with a diagnosis of BPH. The findings indicate that BPH is not associated with an increased risk of BLCA. However, among men who underwent TURP, particularly those with other genitourinary tract conditions (such as bladder stones or infections), the risk of BLCA was elevated. The authors proposed that this is due to chronic bladder inflammation caused by recurrent urinary infection, high residual urine, or retention in treated patients (21,22). To eliminate the confounding effect of prostate surgery on BLCA and thereby more clearly demonstrate the effect of BOO on recurrence and progression, we excluded these patients from our study.

In their 2019 study, Lin et al. (2) observed that patients with BOO exhibited higher stage and grade of primary BLCA. This finding suggests that BOO may not only increase the risk of BLCA but also affect tumor aggressiveness. Similarly, in our study, the first pathology data following TURBT revealed that both the T1 tumor and high-grade tumor rates were higher in the BOO group. However, this patient group was older, had more comorbidities, and had larger tumor sizes and higher multifocality rates. It was unavoidable that these covariates would have resulted in the development of more advanced-stage disease. Consequently, we conducted a multivariate regression analysis to ascertain whether BOO was a predictor of grade and stage at the time of initial diagnosis of BLCA, which failed to prove it as an independent variable.

The relationship between LUTS occurring after TURB and BLCA recurrence was investigated in a study by Lunney et al. (13). It was shown that moderate or severe LUTS (defined as International Prostate Symptom Score ≥8) occurring within 30 days after TUR was an independent predictor for NMIBC recurrence (OR: 19.1). However, from a different perspective, there are no clear data in the literature on the effect of chronic LUTS or BOO on BLCA recurrence. The data we obtained in this study suggest that there is no association between BOO and BLCA recurrence and progression. The limited number of studies showing the effect of BOO on cancer recurrence and progression increases the importance of this study in terms of its contribution to the literature.

Bladder trabeculation is a phenomenon that develops in patients with chronic increased intra-bladder pressure. It causes bladder smooth muscle cell proliferation and hypertrophy, which are followed by fibroproliferative changes in the bladder wall (23). A similar mechanism, whereby the bladder mucosa herniates through weak gaps in the muscular layer, is observed in acquired diverticula (24). It is hypothesized that diverticula and trabeculations, which are bladder structural disorders diagnosed cystoscopically in the developmental stages of the three-stage model of BOO-induced bladder remodeling

(hypertrophy, compensation, and decompensation) (25), may also play a role in the development of BLCA. According to our hypothesis, these may have a detrimental effect on recurrence and progression, or affect TURBT success by reducing wall thickness and contributing to heterogeneity. Given the low prevalence of diverticula in our study population, the statistical reliability of our findings may be limited. However, multivariate regression analysis of 84 patients revealed that the probability of high-grade/CIS pathology being present at the time of diagnosis was 4.6 times higher compared to patients without any trabeculation. Nevertheless, our findings indicated that it had no effect on recurrence and progression. In a multicentre observational study investigating the association of detrusor wall thickness (DWT) with BLCA (26); patients with DWT >2.5 mm were significantly older, had larger and more tumors and experienced more prior NMIBC than patients with a DWT ≤2.5 mm. At univariate analysis, DWT >2.5 was a predictive risk factor for cancer recurrence and progression: OR: 4.9 (95% CI: 2.5-9.5), p=0.001, and OR: 2.21 (95% CI: 1.71-4.73), p=0.001. One of the reasons for the discrepancy between the results of this study and our own is that an increase in DWT does not necessarily coincide with an increase in trabeculation. Trabeculations are most prevalent in the decompensated stage, when bladder contractility is reduced due to the presence of fibrosis (27). This decline may negate the impact on progression and recurrence. However, it is essential to recognise that further investigation through histopathological or clinical urodynamic studies is necessary to elucidate the intricate mechanisms at play. To the best of our knowledge, this is the first study to investigate the effect of the presence of trabeculation and diverticula on initial pathology, as well as recurrence and progression.

Study Limitations

This study has several limitations. First, given the retrospective design of the study, the lack of homogenization between groups due to higher tumor grade and stage may have caused bias through reverse causality, although multivariate analysis was performed in men with NMIBC and concurrent BOO. Furthermore, since we used MFR as the main inclusion criterion for BOO, patients with underactive bladders were also likely to be evaluated in the BOO group. In addition, we could not investigate the effect of residual urine on BLCA recurrence and progression because PVR data was incomplete. Finally, we could not investigate the relationship between BOO subgroups and urothelial carcinoma due to the limited number of patients in our study population.

Conclusion

The existing literature has suggested the relationship between BOO and BLCA through observational studies. However, the underlying pathophysiology remains unclear due to the limited number of studies on causality. This study adds to the existing literature by demonstrating the prevalence of BOO in BLCA patients. It shows that BOO is not associated with the primary stage of BLCA, nor is it linked to recurrence or progression. However, bladder trabeculation may be associated with a higher primary grade of BLCA. Further research is needed to evaluate the long-term effects of BOO on BLCA development and progression, with larger studies and longer follow-up periods. Future studies should also focus on elucidating the molecular mechanisms underlying this association.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (approval number: 2024/010.99/6/20, date: 26.07.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.C., E.D., A.C., C.Ç., F.N., Concept: U.C., F.N., Design: U.C., F.N., Data Collection or Processing: U.C., E.D., A.C., C.Ç., Analysis or Interpretation: U.C., A.C., Literature Search: U.C., Writing: U.C., E.D., C.Ç., F.N.

Conflict of Interest: Fehmi Narter MD is editor-in-chief in Journal of Urological Surgery. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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