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Predicting bladder cancer risk in patients with hematuria. A single-centre retrospective study

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Summary ***Introduction: The presence of blood in the urine should be promptly investigated to rule out urological malignancies, bladder cancer being the most frequent. Given its frequency among general population and the lack of unlimited health resources in an era of cost-effectiveness, it is important to prioritize patients with higher risk of malignancy.***
Objectives: To identify predictive factors of bladder cancer among patients presenting with hematuria.
Patients and Methods: We retrospectively reviewed 296 cases referred to our department for hematuria. We evaluated different demographic, clinical and ultrasound features to uncover possible associations with diagnosis of bladder cancer in those patients, to estimate the individual risk of being diagnosed with bladder cancer during the investigation of hematuria.
Results: A total of 296 patients were studied for hematuria between January 1, 2017 and December 31, 2019, 23.6% of those having ultimately bladder cancer confirmed after transurethral resection. Older age, male gender (OR 2.727, p = 0.069), a history of smoking (OR 3.84, p < 0.05), recurrent hematuria (OR 3.396, p < 0.05) and positive ultrasound exam for bladder cancer (OR 30.423, p < 0.05) were identified as predictors of bladder cancer in patients with hematuria.
Conclusions: This study suggests that it is possible to reliably estimate the risk of bladder cancer in patients with hematuria, using clinical and imaging data to help defining who should be investigated first and in whom the investigation could be postponed.

KEY WORDS: Bladder cancer; Hematuria; Smoking; Ultrasound; Male gender.

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INTRODUCTION

Hematuria is defined as presence of blood in urine. It can either be microscopic (only detected in urinalysis and with variable definition among regions) or macroscopic.
Hematuria is one of the most frequent causes of referral to emergency department or urology appointment. There are many etiologies, most being benign, like *urinary tract infection* (UTI), *benign prostatic enlargement* (BPe) or *urolithiasis* (UL) but the existence of a subjacent urological cancer, most often bladder cancer, must be dismissed.
The need to investigate almost all patients who present with macroscopic and microscopic hematuria is well established, yet the majority will not be diagnosed with urological cancer and the cause will be attributed to transient benign physiological conditions, including UTI, UL or BPE. The extent of investigation and timing of this investigation in not well defined.
Taking in consideration the finitude of available resources, it would be important to prioritize the patients with more risk of suffering from urological cancer, to quickly diagnose, evaluate and treat. There are known risks factors to urological cancer, such as smoking history, exposure to occupational chemical and dyes or pelvic radiation, but there is no algorithm available that allow the physicians to estimate an approximate risk of bladder malignancy.
With our study we intend to help physicians assessing the likelihood of urologic malignancy based in general clinic, laboratory, and image data.
The aim of the study was to identify predictive factors of bladder cancer among patients presenting with hematuria.

PATIENTS AND METHODS

Patients eligible for this study were referred to urology appointment by the *General Practitioner* (GP) or from de emergency department because of hematuria, between January 1, 2017 and December 31, 2019.
Patients otherwise asymptomatic who were referred due to incidental imaging findings suspicious of bladder cancer or upper tract urothelial carcinoma were excluded.
All patients had cystoscopy and upper tract imaging.
Main outcome of interest was bladder cancer diagnosis, defined as presence of urothelial carcinoma in pathological study after *transurethral bladder resection* (TURB) according to TNM WHOW tumor classification and *European Association of Urology* risk classification.
Variables such as demographics, imaging and clinical factors were evaluated (including age, gender, smoker status, anticoagulation or antiaggregating drug use, previous pelvic irradiation, number of hematuria episodes, presence of *lower urinary tract symptoms* (LUTS), urine culture positivity, back pain, history of urolithiasis, fever, ultrasound and cystoscopy results). The demographic and clinical features are shown in Table 1.

Statistical analysis

Descriptive statistics were calculated for all patients

included in the present study. The crude association between each individual categorical covariate and bladder cancer diagnosis was accessed by Chi-square and binary logistic regression.
All analysis were conducted using IBM SPSS statistics version 26. All comparisons were made using 2-sided tests, with $p < 0.05$ considered statistically significant.

Results

A total of 296 patients were studied for hematuria between January 1, 2017 and December 31, 2019. Overall, 23.6% of those patients were diagnosed with bladder cancer after TURB results.
Clinical and imaging predictors were found to be statistically significative. Some are well known risk factors for bladder cancer: patients diagnosed with bladder cancer were older (73.74 vs 66.8 years, $p < 0.05$); men had roughly 2.5 times (OR: 2.519, $p < 0.05$) more risk of being diagnosed with bladder cancer; patients ever exposed to tobacco had 3.8 times (OR 3.852, $p < 0.05$) more risk of bladder cancer.
The number of hematuria episodes and urine microbiology seem to have a predictive value for the diagnosis of bladder cancer, in univariate analysis. Patients with multiple episodes of hematuria have a higher risk of being diagnosed with bladder cancer (OR: 2.093, $p < 0.05$) *vs* patients with a single episode. An identification of bacteria in the urine microbiology was inversely correlated with bladder cancer diagnosis (OR: 0.737, $p < 0.05$); a total of 29 patients had a positive urine culture, none of those were found to have bladder cancer.
Ultrasound evaluation had a sensitivity and specificity for bladder cancer of 71% and 87%, respectively. While there was a bladder cancer suspicion at ultrasound examination in 70% of the patients with subsequent diagnosis of bladder cancer, only 16% of patients diagnosed with bladder cancer had a normal ultrasound evaluation. Those patients were older (OR: 1.084, $p = 0.011$) and had more frequently a smoking history (OR: 4.503, $p = 0.048$). The second most common finding in the ultrasound exam among patients diagnosed with bladder cancer was unilateral hydronephrosis, found in 6.6% of those patients.
In the multivariate analysis, using a binary logistic regression, age, tobacco exposure, multiple episodes of hematuria and a positive ultrasound were found to be correlated with risk of bladder cancer. The calculated model showed an accuracy of 86.5%, with a sensitivity of 64.9% and a specificity of 93.1%.
Twelve (15.4%) out of 78 patients with suspected bladder cancer at cystoscopy had negative histology for bladder cancer after TURB.
Among patients studied for microscopic hematuria (10.6% of the total), only 6% were diagnosed with bladder cancer. All patients with microscopic hematuria diagnosed with bladder cancer were male older than 40 years of age and had ultrasound positive for bladder. Only 1.4% and 0.3% of the patients were diagnosed with upper tract urothelial carcinoma and renal cell carcinoma, respectively.
Among patients with a diagnosis other than bladder cancer, 25% had prostatic bleeding, 15.9% UTI-related hematuria and 8.1% were diagnosed with urolithiasis. Results are shown in Table 2.

Table 1.
Demographic and clinical features of patients referred because of hematuria.

	Total (n = 296)	Non-BC (n = 226)	BC (n = 70)
Age (years)	68.45 ± 15.94	66.81 ± 15.92	73.74 ± 14.92
Gender			
Female	95 (32.1%)	84 (37.2%)	11 (15.7%)
Male	201 (67.9%)	142 (62.8%)	59 (84.3%)
Tobacco			
Never user	225 (76%)	184 (81.8%)	41 (58.6%)
Ever user	48 (16.2%)	28 (12.4%)	20 (28.6%)
Not known	23 (7.8%)	14 (6.2%)	9 (12.9%)
Hematuria episodes			
> 1x	147 (49.7%)	103 (45.6%)	44 (62.9%)
1x	118 (39.9%)	98 (43.4%)	20 (28.6%)
Microscopic hematuria	31 (10.5%)	25 (11.1%)	6 (8.6%)
Urine culture			
Negative	216 (73.2%)	161 (71.6%)	55 (78.6%)
Positive	29 (9.8%)	29 (12.9%)	0 (0%)
Not known	50 (16.9%)	35 (15.6%)	15 (21.4%)
Ultrasound			
Normal	126 (42.9%)	115 (42.9%)	11 (15.9%)
Suspicious	76 (25.9%)	27 (12%)	49 (71%)
Urolithiasis	31 (10.5%)	28 (12.4%)	2 (4.3%)
Renal mass	12 (4.1%)	12 (5.3%)	0
Bladder wall thickness	8 (2.7%)	8 (3.6%)	0
Hydronephrosis	13 (4.4%)	9 (4%)	4 (5.8%)
Prostate enlargement	18 (61%)	18 (8%)	0
Vesical blood clot	1 (1.7%)	1 (0.4%)	0
Bladder stone	3 (1%)	3 (1.3%)	0
Suspicion of UTUC	1 (0.3%)	1 (0.4%)	0
Anticoagulation/anti aggregation			
No	180 (60.8%)	135 (59.7%)	45 (64.3%)
Yes	116 (39.2%)	91 (40.3%)	25 (35.7%)
Pelvic radiation			
No	281 (95.3%)	215 (95.6%)	66 (94.3%)
Yes	14 (4.7%)	10 (4.4%)	4 (5.7%)
UTI suspicion			
No	224 (75.7%)	167 (73.9%)	57 (81.4%)
Yes	72 (24.3%)	59 (26.1%)	13 (18.6%)
Back pain			
No	249 (84.7%)	187 (83.1%)	62 (89.9%)
Yes	45 (15.3%)	38 (16.9%)	7 (10.1%)
Fever			
No	286 (96.6%)	216 (95.6%)	70 (100%)
Yes	10 (3.4%)	10 (4.4%)	0
Previous LUTS			
No	183 (61.8%)	139 (61.5%)	44 (62.9%)
Yes	104 (35.1%)	79 (35%)	25 (35.7%)
Not known	9 (3%)	8 (3.5%)	1 (1.4%)
Urolithiasis history			
No	268 (90.5%)	201 (88.9%)	67 (95.7%)
Yes	28 (9.5%)	25 (11.1%)	3 (4.3%)
Cystoscopy			
Normal	130 (43.9%)	130 (57.5%)	0
Dubious	25 (8.4%)	21 (9.3%)	4 (5.7%)
Suspicious	78 (26.4%)	12 (5.3%)	78 (94.3%)
Prostate enlargement	50 (16.9%)	50 (22.1%)	0
Bladder Trabeculation	6 (2%)	6 (2.7%)	0
Urethral stenosis	3 (1%)	3 (1.3%)	0
Bladder stone	3 (1%)	3 (1.3%)	0

UTI: Urinary tract infection; LUTS: Lower urinary tract symptoms.

Table 2.
Univariate and multivariate analysis for predictors of bladder cancer in patients with hematuria.

Predictors of bladder cancer for 265 visible hematuria referrals					
	Univariate		Multivariate		
	OR	CI	OR	CI	
Age (years)	-	-	1.047 *	1.012-1.080	
Gender (0 = f, 1 = m)	2.519 *	1.236-5.131	2.843	0.952-8.489	
Ever smoker	2.876 *	1.435-5.764	3.852 *	1.301-11.405	
Hematuria episodes (0 = 1, 1 = > 1x)	2.093 *	1.153-3.801	3.471 *	1.435-8.395	
Urine culture (0 = neg, 1 = pos)	0.737 *	0.677-0.802	0.496	0.698-2.100	
Ultrasound suspicion	24.425 *	11.483-51.955	31.633 *	12.867-77.772	
		Test	□²	d□	P
Overall model evaluation					
R square Nagelkerke			0.545		
Goodness-of-fit test					
Hosmer & Lemeshow			8.531	8	0.383

Uf: female; m: male; neg: negative; pos: positive. * *p < 0.05.*

Discussion

Our study, as others (1), highlights the need for investigating almost every patient presenting with hematuria. In our cohort, the overall probability of being diagnosed with bladder cancer throughout the investigation of hematuria was 23.6%. *NICE* states that a signal or a symptom associated with ≥ 3% risk of cancer should prompt referral for diagnostic test (2) and many patients want that investigation be made for a symptom associated ≥ 1% risk of cancer (3). *American Urology Association* (AUA) recommends that all patients with visible hematuria and patients with microscopic hematuria (≥ 3 red blood cells/high-power field), aged ≥ 35 years, should be investigated (4).

In an era of relative lack of health resources when compared with demands, it is of the most importance to prioritize patients regarding diagnostic procedures (i.e. cystoscopy, CT scan). This way, patients with higher probability of bladder cancer can be prioritized to receive said tests, and patients with lower probability being safely postponed (but studied nonetheless).

We were not able to define thresholds for strictly risk-based categories, but the data allow us to roughly estimate the risk of bladder cancer in a single patient. Some predictors for bladder cancer were uncovered, as age, gender, tobacco exposure history, number of episodes of visible hematuria and ultrasound evaluation. Older patients, male (OR 2.843, p = 0.061), a history of smoking (OR 3.852, p < 0.05), with recurrent hematuria (OR 3.471, p < 0.05) and positive ultrasound exam for bladder cancer (OR 31.663, p < 0.05) are at highest risk and should be investigated promptly. Univariate analysis showed that negative urine culture was a risk factor for bladder cancer, but not in multivariate analysis. None of patients with a positive urine culture at the moment of hematuria had a subsequent diagnosis of bladder cancer.

In our study, ultrasound had sensibility of 71% and specificity of 87% for bladder cancer. It can be a good screening test but cannot be an alternative to cystoscopy, because 16% of patients diagnosed with bladder cancer had a normal ultrasound evaluation.

In patients investigated for non-visible hematuria the diagnostic rate of bladder cancer was 8.6% and all of them had a positive ultrasound. According to our results and in agreement with *National Board of Health and Welfare of Sweden* (5), it seems plausible that patients with nonvisible hematuria with a negative ultrasound evaluation are at low risk of bladder cancer and the investigation can be postponed.

We uncovered some new clinical predictors for bladder cancer in patients with hematuria, like recurrent hematuria and a negative urine culture.

Our study has some limitations. It is a retrospective study with a relatively small number of patients that limits the statistically power of the analysis. Urinary cytology was not included in co-variates, because, in our department most patients collect a bladder washing during cystoscopy procedure. The incidence of bladder cancer in our cohort is probably higher than its real incidence in overall patients with hematuria because it represents the detection rate in a secondary care setting.

This study suggests that it is possible to reliably estimate the risk of bladder cancer in patients with hematuria, using clinical and imaging data to manage available healthcare resources without compromising the standard of care.

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