RESEARCH ARTICLE

Identification of Patients with Microscopic Hematuria who are at Greater Risk for the Presence of Bladder Tumors Using a Dedicated Questionnaire and Point of Care Urine Test - A Study by the Members of Association of Urooncology, Turkey

Levent Turkeri[1]*, Naşide Mangir[1], Bulent Gunlusoy[2], Asif Yildirim[3], Sumer Baltaci[4], Mustafa Kaplan[5], Murat Bozlu[6], Aydin Mungan[7]

Abstract

In patients with microscopic hematuria there is a need for better identification of those who are at greater risk of harbouring bladder tumors. The RisikoCheck© questionnaire has a strong correlation with the presence of urothelial carcinoma (UC) of the bladder and in combination with other available tests may help identify patients who require detailed clinical investigations due to increased risk of presence of bladder tumors. This study aimed to evaluate the efficacy of RisikoCheck© questionnaire together with NMP-22® (BladderChek®) as a point-of-care urine test in predicting the presence of bladder tumors in patients presenting with microscopic hematuria as the sole finding. In this multi-institutional prospective evaluation of 303 consecutive patients without a history of urothelial carcinoma (UC) , RisikoCheck© risk group assessment, urinary tract imaging and cystourethroscopy as well as urine cytology and Nuclear Matrix Protein- 22 (NMP- 22 BladderChek) testing were performed where available. The sensitivity, specificity, negative predictive value (NPV), and positive predictive values (PPV) for the risk adapted approach were calculated. All patients underwent cystoscopy, and tumors were detected in 18 (5.9%). Urine cytology and NMP-22 was positive for malignancy in 9 (3.2%) and 12 (7.5%) of patients, respectively. A total of 43 (14%) patients were in the high risk group according to the RisikoCheck© questionnaire. The sensitivity and specificity of the questionnaire in detecting a bladder tumor was 61.5 % and 84.0 % in the high risk group. In patients with either a positive NMP-22 test or high risk category RisikoCheck©, 23.6% had bladder tumors with a corresponding sensitivity of 54.2% and specificity of 88.6%. If both tests were negative only 3.3% of the patients had bladder tumors. The results of our study suggest that the efficacy of diagnostic evaluation of patients with microscopic hematuria may be further enhanced by combining RisikoCheck© questionnaire with NMP- 22.

Keywords: Microscopic hematuria - bladder neoplasms - RisikoCheck© - NMP-22 - bladder check

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Introduction

Microscpic hematuria is a common incidental finding and its prevalence is between 9 to 20% in apparently normal population and defined by the American Urologic Association (AUA) best practice guidelines as 3 or more red blood cells per high power field on microscopic examination of a properly collected urine specimen in the absence of any obvious benign cause (Grossfeld et al., 2001; Davis et al., 2012). It may be due to a multitude of urological problems however urothelial carcinoma of the bladder (UC) is probably the most significant one which is a major health problem across the world. Although not all patients are at the same risk for UC, approximately 3 % of male patients above the age of 40 with microscopic hematuria may have bladder cancer (Jung et al., 2011). Thus, microscopic hematuria, as a screening test for bladder cancer, has a limited effectiveness (Khadra et al., 2000). Therefore, better identification of patients at greater risk of bladder cancer who needs to undergo further imaging of the urinary tract and cystoscopic evaluation is needed.

The open-access questionnaire RisikoCheck© has been devised from the available information in the literature based on socioeconomic factors and lifestyle information and proved to have a strong correlation with the presence of UC (Ludecke and Weidner, 2006; Turkeri et al., 2008). Combination with other available tests, as suggested by the International Consensus Panel on Bladder Tumour Markers (Lokeshwar et al., 2005), may

*Department of Urology, Faculty of Medicine, [1]Marmara University, [4]Ankara University, Ankara, [5]Trakya University, Edirne, [6]Mersin University, Mersin, [7]Karaelmas University Zonguldak, [3]Urology Clinic, Göztepe Teaching and Research Hospital, Istanbul, [2]Izmir Teaching and Research Hospital, Izmir, Turkey *For correspondence: turkeri@marmara.edu.tr*

further improve the performance of this questionnaire. The NMP22 "BladderChek" test is approved by the Food and Drug Administration for the diagnosis of UC in high risk individuals (Lotan et al., 2009) and may be an efficient adjunct in further stratification of cases requiring detailed urological work-up while sparing the rest. Medical and financial consequences of such an improvement in proper case selection would be substantial.

In this prospective, multi-institutional study we evaluated the efficacy of RisikoCheck© and NMP-22 urine test in predicting the presence of UC in patients presenting with microscopic hematuria as the sole finding.

Materials and Methods

A total of 303 patients presenting with microscopic hematuria from 7 medical centers in Turkey were enrolled in this prospective study. Patient characteristics, along with urine analysis and culture results as well as urine cytology, NMP-22 BladderChek and radiologic imaging findings, were recorded in a prospective database. For the purposes of this study the choice of radiological examination is left to the discretion of referring physician. All patients eventually underwent cystoscopy with biopsy of the any suspicious lesion(s). Tumor staging and grading were performed according to TNM (UICC) and WHO (1973) systems. The latter was the most commonly used grading system among the pathologists of the participating institutions when the study was initiated and it was used throughout the patient enrolment period. All patients completed the RisikoCheck© questionnaire and were stratified into three possible risk groups (low-, intermediate- and high-risk). Cystoscopic findings were compared with the results of the urine cytology, NMP-22 test and RisikoCheck© questionnaire. The sensitivity and specificity of each diagnostic tool and various combinations were also determined.

Results

The mean age of the study population was 56.6 (±11.4) years with 146 male and 157 female patients. Four patients in the entire study population were found to be ineligible due to incomplete data and excluded from analysis. No tumors were found on cystoscopy in these patients.

Twenty two patients had radiologic findings suspicious of a bladder tumor and the most common radiologic diagnostic modality was ultrasound examination of the urinary system (84.2%) followed by CT/MRI (11.2%). Urine cytology was positive for malignancy in 9 (3.2%) and indeterminate in 20 (7%) patients. NMP-22 BladderChek was available only in some of the participating centers which limited its utilization. A total of 159 patients underwent NMP-22 BladderChek testing and it was reported as positive in 12 (7.5%) cases. An abnormal urine cytology suggesting malignancy was reported in 9 patients (3.2%).

At cystoscopy tumors were detected in 18 patients (6%), Among these 14 (77.8%) were males and 4 (22.2%) were females. The majority (66.6 %) of the tumors were low grade, non-invasive lesions (TaG1) on pathological examination. Only one patient had muscle invasive bladder cancer (T2G3) and 5 had tumors with invasion of the lamina propria (T1G1-3).

A total of 42 patients were in high and 76 patients were in intermediate risk groups according to the RisikoCheck© questionnaire, respectively (Table 1). The sensitivity and specificity of the questionnaire in detecting a bladder tumor was 44 % and 87% in high risk group and 27% and 74 % in intermediate risk group, respectively. Combined high and intermediate risk category had a respective sensitivity and specificity of 72% and 62% (Table 2).

The sensitivity and specificity of urine cytology was 23 % and 97 %, where the sensitivity and specificity of NMP-22 BladderChek was 45% and 95 % according to the cystoscopic findings (Table 3).

In patients with either a positive NMP-22 test or high risk category RisikoCheck©, positive predictive value (PPV) was 22% with a corresponding sensitivity of 73% and specificity of 75% (Table 2), whereas only 2.8% of the patients with Low risk category RisikoCheck© and 4.1% of NMP-22 negative patients were found to have a bladder tumor (Tables 1,3). If both tests were negative the possibility of presence of a bladder tumor was 3.2%.

Table 1. Number of Patients in Each RisikoCheck© Risk Group and their Cystosopy Findings

Risiko Check© risk group	Cystoscopy finding		Total
	Tumor detected	Tumor not detected	
Low (%)	5 (2.8)	176 (97.2)	181
Intermediate (%)	5 (6.6)	71 (93.4)	76
High (%)	8 (19.0)	34 (81.0)	42

Table 2. The Sensitivity, Specificity, PPV and NPV Values

	Sensitivity (%)	Spesificity (%)	PPV (%)	NPV (%)
RisikoCheck©				
High risk	44	87	19	96
High or intermediate risk	72	62	11	97
NMP				
22 positive	45	95	41	95
22 positive or RisikoCheck© high risk	73	75	22	96
22 positive and RisikoCheck© high risk	14	99	50	95
22 positive and RisikoCheck© highor intermediate risk	16	98	33	96
22 positive or RisikoCheck© high or intermediate risk	94	40	12	98

*PPV: Positive Predictive Value; NPV: Negative Predictive Value

Table 3. Urine Cytology and NMP 22 Results and Cystoscopy Findings

	Cystoscopy finding		Total
	Tumor detected	Tumor not-detected	
Urine cytology			
Negative for malignancy (%)	8 (3.1)	248 (96.9)	256
Indeterminate for malignancy (%)	2 (10.0)	18 (90.0)	20
Positive for malignancy (%)	3 (33.3)	6 (66.7)	9
NMP 22			
Positive (%)	5 (41.7)	7 (58.3)	12
Negative (%)	6 (4.1)	141 (95.9)	147

Discussion

Hematuria is the most common finding in the presence of a bladder tumor. Up to 5% of patients with microscopic hematuria may harbour tumors in their urinary tract (Khadra et al., 2000). Hematuria, as a screening test for bladder cancer, has a wide range of sensitivity and specificity in different studies. The prevalence of microscopic hematuria in the general population varies markedly (2% to 38%) depending on whether single or multiple tests are done and on the population studied (Grossfeld et al., 2001; Jung et al., 2011). The incidence of bladder tumors in patients with microscopic hematuria is reported to be 1% to 5% (Lokeshwar and Soloway 2001). In a study by Ng et al the rate of asymptomatic microscopic haematuria was 31% among all patients presenting with microscopic haematuria and only 3 of 245 (1.2%) patients with microscopic haematuria had newly diagnosed bladder tumors compared with 8 of 145 (5.5%) patients with frank haematuria (Ng et al., 2012).

In our study group, the incidence of bladder tumor in patients with microscopic hematuria was 5.9 % which clearly indicates an excessive rate of false positivity. Gender was associated with risk and men had almost four-fold increased risk of harbouring a bladder tumor in comparison to females. This finding was also observed in a previous study by Hee et al where gender, a history of cigarette smoking and the presence of gross hematuria were all significant risk factors (Hee et al., 2013). Based on these findings a scoring system using four clinical parameters was created. The scores ranged between 6 to 14, and a score of 10 and above indicated high risk for having bladder cancer with an area under the ROC curve of 80.4%. However, this was a mixed cohort of gross and microscopic hematuria patients and the latter was not analyzed as a separate group.

Although, the risk of bladder cancer is not high, it is recommended that in the presence of microscopic hematuria, full evaluation is required in all high risk patients (ie. age over 40 years, smoking or chemical exposure history, or irritative voiding symptoms) without symptoms of a benign disorder that could account for the hematuria (Grossfeld et al., 2001). Also, low risk patients with persistent hematuria and no symptoms of primary renal disease require imaging and either cytology or cystoscopy. However, medicolegal implications may result in a lower threshold for imaging and cystoscopy (Arianayagam et al., 2011), thus leading to a high rate of unnecessary testing and increased expenditure. In a screening study of high risk patients based on age, smoking and environmental risk factors, the incidence of microscopic hematuria was 73.2%. Of these 12.8% underwent cystoscopy and 2% were found to have bladder cancer (Elias et al., 2010). Although suffered from verification bias, this study similar to our findings indicates that microscopic hematuria as a trigger for further evaluation has a very high false positivity rate.

Urine biomarkers for bladder cancer, such as NMP22 can be reasonable adjuncts for improved selection of cases for further investigations. The NMP22 test uses nuclear matrix protein, a specific nuclear protein that is responsible for the chromatid regulation and cell separation during replication in voided urine (Moonen et al., 2005). Two NMP22 tests are available for daily practice. The original NMP22 bladder cancer test (BCT) is a quantitative immunoassay and the NMP22 BladderChek is a qualitative point-of-care test cartridge containing the NMP22 detecting and reporter antibodies. In a review of these tests, sensitivity for the NMP22 BCT and BladderChek assays were reported as 34.6-100% and 49.5-65% while specificity was 60-95% and 40-89.8%, respectively (Budman et al., 2008). Performance of NMP-22 BladderChek test used in the current study reflects previous reports with a sensitivity of 45% and specificity of 95%. However, many studies have evaluated urine biomarkers with their focus mainly as a diagnostic tool for recurrent bladder cancer or in patients with gross hematuria or lower urinary tract symptoms (Chou and Dana, 2010). Therefore, true role of NMP-22 in asymptomatic microscopic hematuria still needs to be defined.

Evidence from epidemiological studies may also allow us to identify cases at risk of urothelial cancer development and/or recurrence. The questionnaire RisikoCheck© has been devised from the available information in the literature and successfully proved to effectively assess the risk of patients developing bladder cancer based on socioeconomic factors and lifestyle (Ludecke and Weidner, 2006). An internet-based tool using this questionnaire was developed, which calculates the risk automatically and presents the user his actual personal risk to develop bladder cancer. Consequently, the available epidemiological data concerning the risk exposure to oncogenic toxins for bladder cancer is transferred into a calculation model within the questionnaire, with a resulting accuracy of 62.5% and a sensitivity of 71.5% (Turkeri and Tinay, 2008; Turkeri et al., 2008).

In this study we further studied this tool in patients who presented with microscopic hematuria. The sensitivity and specificity of the questionnaire for a bladder tumor was 44 % and 87 % in high risk and 27 % and 74 % in intermediate risk RisikoCheck© group.

Analysis of data from our study identified NMP-22 test as the most specific diagnostic tool in patients with microscopic hematuria (95% specificity) and RisikoCheck© (high or intermediate risk category) as the most sensitive (72% sensitivity). In addition, every other patient with a bladder tumor was accurately identified if they were in high risk RisikoCheck© category plus had a positive NMP- 22 test, which raises the possibility of identifying very high risk patients with the combination of the two methods, albeit the number of such patients were quite low.

Accurate bladder tumor detection rate was 22% if the results of NMP 22 BladerChek was positive or the patient was categorized as high RisikoCheck© risk, with a corresponding sensitivity and specificity of 73% and 75%, respectively. If both of these tests were negative, the risk of a bladder tumor was only 3.2% in this study population. Based on these findings, the use of NMP-22 BladderChek and RisikoCheck© questionnaire in patients with microscopic hematuria appears to be a step forward to

distinguish those with a higher risk of bladder tumors that require further diagnostic evaluation and spare the others from unnecessary, costly work-up with an acceptable margin of safety.

In conclusion, the results of our study indicates a possibility of a further improvement in diagnostic evaluation of patients with microscopic hematuria by combined utilization of RisikoCheck© questionnaire and NMP- 22, which may identify the population with a higher risk of bladder cancer and allow for a risk-adapted approach for further detailed clinical investigation.

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