The Prevalence of Bladder Cancer During Cystoscopy for Asymptomatic Microscopic Hematuria

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OBJECTIVE To investigate the rate of bladder cancer in patients undergoing cystoscopic evaluation for asymptomatic microscopic hematuria (AMH) in order to identify groups at sufficiently low-risk for bladder cancer in whom invasive testing may be avoided.

METHODS We performed a retrospective review of patients who underwent cystoscopic evaluation for AMH between 2010 and 2018. Age, gender, smoking status, history of pelvic radiation, and number of red blood cells per high-power field on urine microscopy were recorded. We used logistic regression to explore the association between specific risk factors and a diagnosis of bladder cancer on cystoscopy.

RESULTS Among the 2118 patients who underwent cystoscopy for AMH, 25 patients (1.2%) were diagnosed with a bladder cancer, all of which were nonmuscle invasive urothelial carcinoma. There were no bladder cancers detected in patients under the age of 50. Older age and positive smoking history were significantly associated with bladder cancer.

CONCLUSION Bladder cancer was an uncommon finding on cystoscopy among patients being evaluated for AMH, especially in younger patients. We confirmed several known risk factors for bladder cancer, including older age and smoking history. Further studies are required to evaluate the utility of cystoscopy for identifying latent bladder cancers in low-risk patients. UROLOGY 126: 34–38, 2019. © 2019 Elsevier Inc.

The significance of asymptomatic microscopic hematuria (AMH) has been under investigation for over 60 years, when Greene et al first described a cohort of 500 patients with AMH.[1] Since then, subsequent studies have investigated this common laboratory finding and described the potential etiologies of AMH including medical renal disease, nephrolithiasis, benign prostatic enlargement, urethral strictures, cystitis, and urologic malignancies including kidney and bladder cancer.[2,3] It is generally accepted that no amount of hematuria is normal in the absence of pathology, but defining clinically significant hematuria and the appropriate diagnostic work-up for patients with AMH remains a challenge.[4]

Following a single episode of microscopic hematuria, defined as ≥3 red blood cells per high-power field (RBCs/HPF) on urine microscopy, the American Urologic Association (AUA) guidelines recommend upper tract imaging and cystoscopy in all patients over age 35 and in those patients younger than 35 with risk factors for urinary tract malignancies (including irritative voiding symptoms, chemical exposures, positive smoking history, and pelvic radiation).[5] While these guidelines are designed to maximize diagnostic sensitivity to detect urologic pathology, they subject many low-risk patients to invasive testing.

Asymptomatic bladder cancer is one of the many lower urinary tract causes of AMH that requires cystoscopy for diagnosis. Rates of bladder cancer detected during cystoscopic evaluation for microscopic hematuria vary widely based on the populations under investigation and criteria used for significant hematuria. There are numerous, well-established risk factors for bladder cancer including tobacco smoking, age, male gender, and occupational exposure to carcinogens.[6] Cigarette smoking is associated with a 3-fold higher risk of bladder cancer.[7] Bladder cancer is 3-4 times more common in males than females, but this association remains poorly understood and may be related to differential exposure to carcinogens, physiologic responses, and urologic referral patterns.[8,9] In general, bladder cancer is a disease of the elderly, with a median

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age of diagnosis of 70 years and peak incidence over 85 years of age in both males and females.[8,10] In higher risk populations of men over 50 and 60, rates of bladder cancer detected during screening are around 5% and decrease to 0.57%-2.6% in recent studies investigating all patients undergoing AMH work-ups.[3,4,11-15]

While flexible cystoscopy is the gold standard for diagnosing occult bladder cancer during AMH work-up, there must be a balance between cost, predictive value, and risks when recommending testing to a group of patients. It is possible that more restricted use of cystoscopy among low-risk AMH patients can minimize invasive procedures without compromising the detection of life-threatening lesions. We sought to describe the prevalence of newly diagnosed bladder cancers at the time of cystoscopic evaluation in patients undergoing work-up for AMH, and identify risk factors that can better inform which AMH patients should be undergoing cystoscopy to diagnose bladder cancer.

MATERIALS AND METHODS

Patients

We retrospectively queried the institutional database of our tertiary referral urology clinic for patients who underwent cystoscopy using current procedural treminology (CPT) code 52000 between May 2010 and April 2018. The present study was conducted under institutional review board (IRB) protocol AAAQ9509. The patient cohort was restricted to those with microscopic hematuria as an indication using international classification of diseases (ICD)-9 (599.70, 599.72) and ICD-10 (31.9, 31.2, 31.21, and 31.29) diagnosis codes. Individual patient charts were reviewed to validate the diagnosis of AMH and cystoscopic findings. AMH was defined in accordance with current AUA guidelines as ≥3 RBCs/HPF on a properly collected specimen in the absence of an obvious benign cause. For patients with multiple cystoscopies in our records, the results from the initial AMH work-up are included. Patients with recent kidney stone passage ($n = 5$), urinary tract infection (UTI) ($n = 33$), known renal disease with proteinuria or casts on urinalysis ($n = 4$), and patients with a history of bladder cancer ($n = 50$) were excluded. Patients with a self-reported history of gross hematuria noted in their records were excluded during chart review ($n = 192$) yielding the final study population of 2118 patients. Demographic information, age at time of evaluation, smoking history, number of RBCs/HPF, history of pelvic radiation, and new diagnosis of genitourinary malignancy were recorded for all patients.

Statistical Analysis

The primary outcome of interest was a diagnosis of bladder cancer during initial work-up for AMH. We used Chi-squared tests or Fisher's exact test to compare differences in percentages and Student's *t* test to compare differences in means. We use logistic regression to estimate the risk of a bladder cancer diagnosis according to patient age and smoking status. We then used the model output to generate a clinically useful lookup table. Our initial model included gender, history of pelvic radiation, and RBCs/HPF, but these covariates were not statistically significant and were therefore excluded from the table. Smoking status was treated as a continuous variable and so the designation of former smoker was maintained as a clinically important reference point between current and never smokers. *P* values of <.05 were considered statistically significant. Statistical analysis was performed using R (version 3.4.2).

RESULTS

We identified 2118 patients who were evaluated for AMH (Table 1). The majority of patients (65%) were female with a median age of 61 years (Interquartile range (IQR) 52-70). Thirty-five percent had a history of smoking and 1.3% had a history of pelvic radiation.

A total of 25 patients (1.2%) were found to have bladder cancer during cystoscopy (Table 1). Of the patients diagnosed with bladder cancer, 15 (60%) had low-grade Ta tumors, while 9 (36%) had high-grade features. No muscle-invasive tumors were diagnosed.

The rate of bladder cancer among men was 1.9% compared to 0.8% in women. The youngest man and woman diagnosed with bladder cancer in our cohort was 52 and 56 years old, respectively. None of the 444 patients under the age of 50 (comprising 21% of our study group) were found to have bladder cancer.

In bivariate analyses, current smoking status, age, and a history of prior pelvic radiation were significantly associated with bladder cancer, while gender and RBCs/HPF did not reach significance (Table 2). On multiple regression analysis (Table 3), age and smoking history maintained significance and were used as predictive variables to construct a look-up table to estimate bladder cancer risk for patients undergoing AMH work-up (Table 4).

Table 1. Cohort characteristics

Variable	*N* (%)
Total	2118
Age, median (IQR)	61 (52-70)
Gender	
Male	750 (35.4)
Female	1368 (64.6)
Ethnicity	
Caucasian	559 (26.4)
Hispanic or Latino	630 (29.7)
African American	109 (5.1)
Asian	49 (2.3)
Unknown/Other	771 (36.4)
Smoking history	
Current	176 (8.3)
Former	574 (27.1)
Never	1368 (64.6)
Pelvic radiation history	27 (1.3)
RBCs/HPF, mean ± SD	15.8 ± 28.0
Patients newly diagnosed with bladder cancer	25 (1.2)
Male	14 (1.9)
Female	11 (0.8)
Age of patients newly diagnosed with bladder cancer (IQR)	69 (65-82)
Pathology at time of diagnosis	
Low-grade Ta	15 (60)
High-grade Ta/T1	7 (28)
High-grade Ta + CIS	1 (4)
CIS	1 (4)
Unknown	1 (4)

CIS, carcinoma in situ; IQR, interquartile range; SD, standard deviation.

Table 2. Bivariate associations for bladder cancer

	Bladder Cancer ($n = 25$) No. Patients (%)	No Bladder Cancer ($n = 2093$) No. Patients (%)	*P* Value
Gender			
Male	14 (1.9)	736 (35.2)	.081
Female	11 (0.8)	1357 (64.8)	
Age, median (IQR)	69 (65-82)	61 (52-70)	<.001
Smoking history			
Current	5 (20.0)	171 (8.2)	.0047
Former	11 (44.0)	563 (26.9)	
Never	9 (36.0)	1359 (64.9)	
Pelvic radiation history	2 (8.0)	25 (1.2)	.039
RBCs/HPF, mean ± SD	7.5 ± 3.2	15.8 ± 28.2	.521

IQR, interquartile range; RBCs/HPF, red blood cells per high-power field; SD, standard deviation.

Table 3. Logistic regression model predicting presence of bladder cancer on cystoscopy

	OR	95% CI	*P* Value
Age	1.07	1.03-1.11	<.001
Male gender	1.86	0.81-4.28	.14
Current smoker	5.10	1.66-15.73	.005
Pelvic radiation history	2.69	0.55-13.20	.22

DISCUSSION

Cystoscopy is the current gold standard method for detecting bladder cancer, as there are no noninvasive tests or urinary biomarkers that can take its place for this purpose; it is therefore recommended in nearly all patients with AMH under current AUA guidelines.[5] In our cohort of over 2000 patients undergoing work-up for AMH, cystoscopy identified bladder cancer in 25 patients (1.2%), all of which were nonmuscle invasive and detected in patients over the age of 50. Our bladder cancer rate is consistent with recent publications, which have found bladder cancer rates between 0.57% and 2.6% in patients undergoing cystoscopy for AMH.[3,13-15]

In their retrospective cohort study of 1049 patients in a suburban population undergoing work-up for AMH, Samson et al identified bladder cancer in only 6 patients (0.57%), with a median age of 77 and the youngest diagnosed at 59 years of age.[13] Another large retrospective study identified over 150,000 patients with hematuria, of whom only 0.68% were diagnosed with a urologic malignancy over a 3-year follow-up period.[3] While this study included a large cohort of patients within a managed care organization and was not limited by the referral biases of many studies, it did not address bladder cancer specifically or adherence to urologic follow-up with cystoscopy.[3] The same group has since published a prospective analysis of 4414 patients who had a standardized work-up consistent with AUA guidelines and observed a bladder cancer rate of 2.3%.[14] This rate is higher than the 1.2% reported in our population but may be accounted for by their inclusion of 875 patients with gross hematuria.[14] The most recent publication on the topic to date described a population of 3556 patients across 40 hospitals, including 1245 patients with microscopic hematuria, in whom bladder cancer was detected in 32 patients (2.6%).[15] Of those 32 patients, all were over the age of 50 aside from 1 male aged 40-44 and 1 female aged 45-49.[15]

AMH is a relatively common finding on routine urinalysis, with population-based studies reporting rates as high as 13% depending on the group under investigation and the method of detection (dipstick vs microscopic).[2,16] Although nearly all patients with AMH are recommended to have upper tract imaging and cystoscopy to determine an underlying cause, urology referral occurs inconsistently in 36%-80% of patients.[5,9,17] One study of 2455 patients across 19 primary care clinics found that only 13.7% of patients underwent cystoscopy within 180 days of hematuria diagnosis.[18] Possible explanations for inconsistent referral patterns include lack of guideline dissemination to primary care providers, disagreement with the recommended AMH evaluation, and attempts to only send patients perceived to have the highest risk of serious underlying pathology. In fact, older age, male gender, and repeated hematuria episodes are all positively associated with urology referral for AMH.[9,18] It is possible that a guideline with more restrictive recommendations on which patients require an AMH evaluation would increase referrals.

Table 4. Probability (%) of bladder cancer in patients with AMH based on age and smoking history

Age Range	Never Smoker	Former Smoker	Current Smoker
51-60	0.34	0.79	1.73
61-70	0.68	1.57	3.42
71-80	1.35	3.11	6.63
81-90	2.67	6.05	12.47

AMH, asymptomatic microscopic haematuria.

The application of age thresholds is a common first step in the decision to perform an AMH evaluation. The AUA and Canadian Consensus Statement have the lowest age threshold, recommending cystoscopy for all patients with a single episode of AMH over age 35.[5,19] This contrasts with the National Institute for Health and Care Excellence (NICE) referral guidelines for suspected cancers (with an appointment within 2 weeks) which are underpinned by a threshold positive predictive value (PPV) of 3% for symptoms being predictive of cancer.[20,21] NICE recommendations are based on systematic reviews with a committee of experts including specialists, generalists, and lay members, taking into account the views of registered stakeholders.[21] Owing to the low PPV of microscopic hematuria for bladder cancer, NICE recommends referral as part of its suspected cancer pathway only in patients aged 60 and over with AMH in combination with either dysuria or an elevated white blood cell count.[20,21] These specific recommendations are based on PPVs of AMH for bladder cancer from a single paper which described PPVs of 1.6% and 0.8% in patients ≥ 60 and 40-59, respectively.[22] It was only as a symptom pair with dysuria (PPV = 4.5%) and elevated white blood cell count (PPV = 3.9%) that microscopic hematuria reached the threshold 3% PPV to warrant referral.[22,23] While the more restrictive NICE guidelines have been critiqued by others who show that they would fail to diagnose some urologic malignancies, they highlight the challenges in reaching a consensus on managing AMH.[15]

The number of red blood cells on urine microscopy has also been proposed as a threshold for initiating the AMH work-up, although the association between bladder cancer and degree of microscopic hematuria is highly variable.[3,13,14] Jung et al have previously proposed a cutoff of ≥25 RBCs/HPF for initiating the AMH work-up based on their findings that bladder cancer was positively associated with this more restrictive threshold.[3] Citing these findings, The American College of Obstetricians and Gynecologists recommend a threshold of 25 RBCs/HPF in women aged 35-50 for AMH evaluation based on expert opinion and an emphasis on reducing the number of women requiring referral and work-up in light of the low rates of urologic malignancies diagnosed.[3,24] In our cohort, the number of RBCs/HPF was not associated with bladder cancer, and we found that in both the bladder cancer and no bladder cancer groups, hematuria ranged as low as 3 RBCs/HPF, cautioning against degree of hematuria as a criterion for evaluation.

Although commonplace in urology clinics, cystoscopy is a costly and invasive diagnostic test with some risk. The AUA Best Practice Statement recommends prophylaxis for simple cystoscopy only in patients with risk factors for UTI including advanced age, anatomic anomalies of the urinary tract, smoking, chronic steroid use, or immunodeficiency.[25] Therefore, among patients not receiving antibiotic prophylaxis, a low rate of symptomatic UTI is observed in 2%-7.5% of patients.[26,27] Cystoscopy is also associated with patient discomfort and bothersome postprocedure voiding symptoms such as dysuria, hematuria, and difficulty voiding.[28,29] Recent work by Halpern et al describing their decision-analytic model to determine the most cost-effective strategy for initial AMH work-up address some important financial considerations with regard to cystoscopy.[30] Based on the Medicare Physician Fee Schedule, which prices cystoscopy from the payer perspective between $166-$258, Halpern et al calculate an incremental cost per cancer detected of $10,287 with cystoscopy alone for the detection of genitourinary malignancies. As expected, this cost decreases in subgroup analyses of higher risk populations of men, smokers, and those ≥50 years, with incremental costs per cancer detected of $6047, $6918, and $7594, respectively.[30]

While there remains controversy about which patients should be undergoing cystoscopy for AMH, our findings suggest that cystoscopy for the diagnosis of occult bladder cancer is not necessary in many younger patients, and should be most strongly considered in elderly patients who are current smokers. We found that no patients under the age of 50 were diagnosed with an occult bladder cancer and the risk of finding bladder cancer increased with each subsequent decade (Table 4). A smoking history was strongly associated with risk of bladder cancer, such that even the oldest nonsmokers in our cohort had only a 2.67% risk of bladder cancer. There may, however, be some benefit to cystoscopy in patients with AMH who do not have a high risk of bladder cancer through the diagnosis of nonmalignant lower urinary tract pathology, such as urethral strictures and prostatic enlargement. Ultimately, the decision to perform cystoscopy for AMH should be individualized by incorporating patient preferences and risk factors, procedural risks, and current guideline recommendations.[5,15] The emerging use of urinary biomarkers may offer an alternative or adjunct in the evaluation of low-risk patients with AMH as their sensitivity and specificity improve, however to date they are not considered first-line options.[31]

There are several limitations of this study that should be noted. Our study population had a disproportionate number of women, which may decrease the prevalence of underlying bladder cancers. Since our cohort was based on patients who underwent cystoscopy, it is subject to referral bias, although it is reasonable to posit that this would have resulted in an increased rate of bladder cancer. We did not include patients who had cystoscopy for urinary symptoms, such as dysuria or pelvic pain, which would have likely increased the risk of finding a bladder cancer. We also are not considering findings from upper tract imaging with regards to newly diagnosed upper tract malignancies, although this is an important component of the broader AMH work-up. Finally, cystoscopy is useful for identifying pathologic causes of hematuria other than bladder cancer, such as urethral stricture, bladder stones, and benign prostatic enlargement, none of which were included as potentially relevant outcomes in our cohort.

CONCLUSION

During cystoscopy for AMH, we observed a 1.2% prevalence of bladder cancer among over 2000 patients.

Smoking history, age, and prior pelvic radiation all increased the risk of occult bladder cancer on cystoscopy. There were no bladder cancers diagnosed among 444 patients younger than age 50. Our findings suggest that cystoscopic evaluation for the diagnosis of occult bladder cancer may be minimized in select low-risk patients presenting with AMH, although it may be beneficial for identifying nonmalignant causes of hematuria.

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