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The Role of Urinary Cytology for Detection of Urothelial Cancer in Asymptomatic Hematuria Investigations

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Authors' contributions

This study was carried out in collaboration among all the authors. Author DH analyzed data and wrote up the manuscript. Authors MY, YI, SH collected data. Author YK reviewed the histopathological data. Author s FS, SO did statistical analysis. Authors HY and KK corrected the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To determine the diagnostic accuracy of urinary cytology to diagnose urothelial cancer for patients with asymptomatic hematuria.
Patients and Methods: A retrospective cohort study was undertaken of asymptomatic hematuria patients referred from primary care to the Department of Urology in our institution. All patients with asymptomatic hematuria received urinary cytology examination. Urinary cytology was classified according to the Paris System. Patients with visible hematuria (VH) underwent to examine the kidney and bladder with filling using ultrasonography (KBFU), computed tomography urography

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(CTU) and flexible cystoscopy, while patients with non-visible hematuria (NVH) underwent initially KBFU, and in cases of having risk factors such as smoking history and exposed to chemical substances CTU and flexible cystoscopy were additionally performed.

Results: The study included 790 patients with a median age of 69 years. Of these patients 235 (29.7%) had VH and 555 (70.3%) were referred for NVH. In the VH patients 61 (30.0%) and 5 (2.1%) were histologically diagnosed as bladder cancer and upper tract urothelial cancer (UTUC), while in the NVH patients 30 (5.1%) and 2 (0.4%) were histologically identified as bladder cancer and UTUC, respectively. In the VH group the accuracy of urothelial cancer in the urinary cytology was: sensitivity 24.2% and specificity 100%, while in the NVH group sensitivity 31.2% and specificity 100%. In histologically confirmed 98 patients with bladder cancer / UTUC the rate of sensitivity in the urinary cytology for even high-grade cancers had only 46.0%. The rates of sensitivity in any type of hematuria and grade increased by approximately two times with adding atypical cytology results as positive.

Conclusion: Although urinary cytology is a convenient and noninvasive test with histologically high specificity for urothelial cancer, the rates of sensitivity of urinary cytology are inferior. However, adding atypical cytology results as positive improves accuracy of detection of urothelial cancer and prevent from the missing diagnosis. Nevertheless, urinary cytology has its place as an additive diagnostic tool to cystoscopy and imaging diagnosis for the investigations of asymptomatic hematuria.

Keywords: Asymptomatic hematuria; urinary cytology; Urothelial cancer; bladder cancer; upper tract urothelial cancer.

ABBREVIATIONS

VH : Visible hematuria
NVH : Non-visible hematuria (NVH)
CTU : Computed tomography urography
UTUC : Upper tract urothelial cancer
KBFU :Kidney and bladder with filling using ultrasonography
PPV : Positive predictive value
NPV : Negative predictive value
ROC : Receiver-operating characteristic
WHO : World health organization
EAU : European Association of Urology
AUA : American Urological Association
BTA : Bladder tumor antigen;
NMP : Nuclear matrix protein
FISH : Fluorescence in situ hybridization

1. INTRODUCTION

Hematuria including visible hematuria (VH) and non-visible hematuria (NVH) is a common cause for urological referrals as it can be a sign of urothelial malignancies [1], and in such hematuria patients it is general to examine using cystoscopy for bladder cancer and computed tomography urography (CTU) for upper tract urothelial cancer (UTUC). However, these tests are invasive and cause significant discomfort as to especially cystoscopy for patients.

Urinary cytology is a non-invasive method for detection of urothelial cancer of the urinary bladder and upper tract, and a frequency used examination, and has been available in most institutions since it was demonstrated by Papanicolaou and Marshall [2]. Urinary cytology has a high specificity but a low sensitivity, in extremely lower sensitivity for low grade cancer [3]. Therefore, positive urinary cytology is helpful in diagnosing urothelial malignancies, while a negative result does not exclude the possibility of a tumor, especially of low-grade urothelial tumors. Many guidelines [4-8] recommend the use of urinary cytology in selected patients presenting with hematuria: for high grade tumor and carcinoma in situ (CIS) in the EAU guideline [4], and VH in the Japanese guideline of hematuria [7] and Canadian Consensus Statement [8]. However, there have been no consensus among guideline bodies with respect to the inclusion of urinary cytology for assessment of hematuria. We evaluated the diagnostic ability of urinary cytology to diagnose bladder cancer and UTUC in patients with asymptomatic hematuria based on a retrospective cohort study.

2. PATIENTS AND METHODS

Between January 2016 and December 2018, a retrospective observational study was undertaken of all patients referred from primary care to the Department of Urology, in our institution, for the evaluation of asymptomatic hematuria. Urine tests including dipstick, urinalysis and cytology were performed using fresh urine. VH was defined as hematuria

reported by the patient, while NVH was defined as a value of ≥1+ of blood on urine dipstick, and greater than 4 red blood cells per high power field on collected urinalysis. All patients with asymptomatic hematuria underwent urinary cytology examination. Urinary cytology was obtained from either the bladder voided or catheterized, and classified according to the Paris System [9]. A positive urinary cytology was defined as the presence of malignant cells and suspicious of malignant cells. All patients with VH underwent to examine the kidney and bladder with filling using ultrasonography (KBFU), CTU and flexible cystoscopy, while patients with NVH were initially conducted to examine with KBFU, and if they had risk factors such as smoking history and exposed to chemical substances, additional investigations with CTU and flexible cystoscopy were performed. In cases of negative urinary cytology and normal KBFU in the NVH investigations flexible cystoscopy was omitted in the patients without risk factors. Urothelial cancers were confirmed by histological evaluation of the specimens obtained by surgeries or biopsies. Tumor grading was assigned according to the 2004 WHO / International Society of Urologic Pathology consensus classification [10].

Univariate and multivariate analysis by logistic regression models was used to determine the variables of significance with respect to the bladder cancer/ UTUC. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for correct identification of bladder cancer/ UTUC. JMP® 10 (SAS Institute Inc., Cary, NC, USA) and EZR (Easy R) software [11] were used to performed all statistical analyses. A p-value less than 0.05 was considered as significant.

3. RESULTS

The study included 790 patients with a median age of 69 years (range:17-97 years). There were 461 (58%) men and 329 (42%) women, with a man to women ratio of 1.4 to 1. Of these patients 235 (29.7%) had VH and 555 (70.3%) were referred for NVH. Positive urinary cytology was found in 16 patients (3.2%), while 32 patients (4.1%) had atypical urinary cytology. In total, 91 bladder cancers (11.5%) and 7 UTUCs (0.9%) were histologically identified. In the VH patients 61 (30.0%) and 5 (2.1%) were diagnosed as bladder cancer and UTUC, while in the NVH patients 30 (5.1%) and 2 (0.4%) were identified as bladder cancer and UTUC, respectively (Table 1).

As to the relationship between bladder cancer / UTUC and variables, univariate analysis identified the following factors as associated with bladder cancer / UTUC: age ($p=0.0007$), gender ($p<0.0001$), type of hematuria ($p<0.0001$), smoking histology ($p<0.0001$) and urinary cytology ($p<0.0001$). By multivariate analysis age ($p=0.0194$), type of hematuria ($p<0.0001$), smoking history ($p=0.0028$) and urinary cytology ($p<0.0001$) were independent predictors related to bladder cancer / UTUC (Table 2).

The outcomes of the diagnostic ability of urinary cytology are shown in Table 3. The overall accuracy of positive urinary cytology for the diagnosis of bladder cancer / UTUC was: sensitivity 26.5%, specificity 100%, PPV 100%, NPV 90.6% with a receiver-operating characteristic (ROC) of 0.633 in all the hematuria patients. In the patients with VH the accuracy of positive urinary cytology for the diagnosis of bladder cancer / UTUC was: sensitivity 24.2%, specificity 100%, PPV 100% and NPV 77.2% with a ROC of 0.621, while in the patients with NVH sensitivity 31.2%, specificity 100%, PPV 100% and NPV 96.0% with a ROC of 0.656. The diagnostic ability of positive / atypical urinary cytology (adding atypical cytology as positive) to identify bladder cancer / UTUC was better in the sensitivity and NPV but the specificity and PPV were worse in the overall and each subgroup. The rates of sensitivity in the overall and both type of the hematuria increased by approximately two times.

Table 4 shows the urinary cytology outcomes in the 98 patients with bladder cancer / UTUC histologically confirmed with surgical interventions stratified by tumor grade and stage. Overall, 27% of the patients had positive cytology, 28% had atypical cytology and 45% had negative cytology. Of the 26 patients with positive cytology, 88% had high grade and 31% had pT2 or more stages. Of the 45 patients with negative cytology 80% had low grade, and all of them had pTa or pT1.

As to the sensitivity of urinary cytology for grade and pT stage in histologically confirmed 98 patients with bladder cancer / UTUC, positive urinary cytology had the sensitivity of only 46.0% for even high-grade urothelial cancers, and 72.7% for pT2 or more, respectively. If cytologic

interpretation was broadened to include positive and atypical cytology, the rates of sensitivity increased in any grades and stages (Table 5). However, 5 of 32 (16%) patients with atypical cytology revealed no evidence of urothelial cancer on the initial inspection, and then received a periodic repeat urinary cytology examination with cystoscopy and imaging diagnosis during the follow-up. Of these patients two had several atypical urinary cytology results despite the normal cystoscopy and upper tract imaging. We subsequently performed further investigations of urinary cytology obtained by selective ureteral catheterization, ureteroscopy and randomly bladder biopsies, and resulted in no evidence of urothelial cancer in both of the patients. However, a ureteral cancer was identified in one of both with re-examination of selective ureteral catheterization and ureteroscopy one year after the investigations.

4. DISCUSSION

Hematuria is one of the most hallmarks of urological malignant diseases. The most common cause of hematuria of these malignant diseases is urothelial cancer, and especially asymptomatic VH is the commonest presentation of a malignant disease of the bladder and upper urinary tract. The prevalence of urological malignancy among patients with VH has been reported to be ranged from 18.9 to 31.5% [12,13], while for NVH in a US cohort study of urological evaluation of secondary care patients with NVH urinary tract cancers were found 2.1% [14], and a recent meta-analysis study reported the detection rate of bladder cancer of 3.2% with ranged from 0 to 16% in 37 studies [15]. In our study the prevalence of urothelial cancer in the VH and NVH patients was 32.1% and 5.5%, respectively, which were slightly higher prevalence in both types of hematuria.

As to the risk factors for the development of bladder cancer in hematuria patients, advanced age, male gender, smoking history and occupational exposures have been demonstrated [16,17]. Recently, Cha et al. [13] developed a highly accurate, well-calibrated nomogram to predict the risk of bladder cancer based on variables of increasing age, smoking history, gross hematuria and positive cytology in patients with asymptomatic hematuria. Their multivariable model achieved 83.1% accuracy for predicting the presence of bladder cancer in the patients with asymptomatic hematuria. In our study the accuracy in urinary cytology for predicting urothelial cancer in the patients with hematuria was 90.9%, and the predicting risk factors for urothelial cancer were mostly consistent with previously reported studies [16,17] except for gender.

Table 1. Patient demographics

・Median age, ys,	**(range): 69 (17-97)**	**・Bladder cancer, n (%)**	
・Gender, n (%)		Grade	
Men	: 461 (58.4)	Low	: 46 (50.5)
Women	: 329 (41.6)	High	: 45 (49.5)
・Smoking history, n (%)		pT stage	
Non-smoker	: 238 (30.1)	pTa	: 60 (50.5)
Current smoker	: 68 (8.6)	pT1	: 22 (24.2)
Previous smoker	: 108 (13.7)	pT2 or more	: 6 (6.6)
Unknown	: 376 (47.6)	pTis	: 3 (3.3)
・Type of hematuria		・UTUC, n (%)	
Non-visible	: 555 (70.3)	Grade	
Visible	: 235 (29.7)	Low	: 2 (28.6)
・Urinary cytology, n (%)		High	: 5 (71.4)
Negative	: 732 (92.7)	pT stage	
Atypical	: 32 (4.1)	pTa,1	: 2 (28.6)
Positive	: 16 (3.2)	pT2	: 1 (14.3)
・Urothelial cancer, n (%)		pT3,4	: 4 (57.1)
Bladder cancer	: 91 (11.5)		
UTUC	: 7 (0.9)		

N: number of patients, ys: years, UTUC: upper tract urothelial cancer, pT: pathological

Table 2. Univariate and multivariate logistic regression models associated with bladder cancer/UTUC in the hematuria patients

Variables	Odd (95%CI)	p value
• Univariate analysisAge		
Age	1.028 (1.012-1.044)	0.0007
Gender (M vs. F)	2.754 (1.703 -4.628)	<0.0001
Type of hematuria (V vs. Non-V)	6.383 (4.075 - 10.181)	<0.0001
Smoking history (+ vs. -)	3.236 (1.982 - 5.372)	<0.0001
Urinary cytology (posi vs. atypi/neg)	2.84e+8 (123.612 -)	<0.0001
• Multivariate analysis		
Age	1.025 (1.004 – 1.047)	0.0194
Gender (M vs. F)	1.597 (0.733 - 3.620)	0.2410
Type of hematuria (V vs. Non-V)	4.284 (2.353 - 8.045)	<0.0001
Smoking history (+ vs. -)	2.719 (1.404 - 5.430)	0.0028
Urinary cytology (posi vs. atypi/neg)	7.61e+9 (55.789 -)	<0.0001

M: male, F: female, V: visual, Non-V: non-visual, posi: positive, atypi: atypical, neg: negative, vs: versus

The reported sensitivity of voided urinary cytology for detecting bladder cancer ranges from 40% to 76%, and is dependent on a number of factors such as high stage and high grade, disease prevalence, and the expertise of the cytopathologist [18]. In a study of 3556 patients presenting with hematuria who were recruited as part of the prospective DETECT I trial, of the 3556 patients, urinary cytology was performed in 567 patients (15.9%). Bladder cancer was diagnosed 39 patients (6.8%) and UTUC was diagnosed 8 (1.4%). For diagnosing bladder cancer / UTUC, urinary cytology had a sensitivity of 43.5%, specificity of 95.7%, PPV of 47.6%, and NPV of 94.9%. Urinary cytology missed 21 bladder cancers and 5 UTUCs, and of the 21 bladder cancers missed 4 (19%) were pT2 or higher, 2 (9.5%) were G3 pT1, 10 (47.6%) were G3/2 pTa, and 5 (23.8%) were G1 pTa [19]. They concluded urinary cytology will miss a significant number of muscle invasive bladder cancer and high-risk non-muscle invasive disease. In our study the rates of sensitivity of urinary cytology for the detection of urothelial cancer were only 26.5% in the overall asymptomatic hematuria patients, and also only 24.2% in even the VH patients. Additionally, the diagnostic ability of urinary cytology for even high-grade cancers was also poor because of the rate of sensitivity of only 46.0% in the high-grade diseases. The routine use of urinary cytology for even VH and high-grade tumor is of limited value in diagnosis.

The interpretations of atypical urinary cytology for diagnosis seem to be conundrum. The prognostic value of atypical urinary cytology is also debatable, and the accuracy of urinary cytology depends on which threshold is used to consider a cytologic result positive. Raab et al. [20] reported that by considering any atypical diagnosis as positive the sensitivity values of cytology for high-grade urothelial cancer lesions as well as low-grade ones improved. In our study, when the atypical urinary cytologic outcomes were considered as positive diagnosis, the rates of sensitivity of urinary cytology also increased in any type of hematuria, grade and stage as well. Atypical cytology as positive diagnosis reduces to miss the detection of urothelial cancer. However, even if the initial inspections with CTU and cystoscopy are normal in the atypical cytology results, further investigations such as selective ureteral catheterization, ureteroscopy and random bladder biopsies in such cases should be considered because we experienced to identify an UTUC with the additional investigations during follow-up.

There have been a number of guidelines for the diagnosis and evaluation of hematuria from national organizations and specialty societies [4-8]. Urological referral for evaluation is recommended for all patients who have a single episode of VH, and urinary cytology is routinely recommended for the diagnosis of urothelial cancer in patients with VH according to the Japanese guidelines of management of hematuria [7] and Canadian Consensus Statement [8], while the investigation of patients with asymptomatic NVH is inconsistent among the available guidelines [4-8]. Recently, Linder et al [21] reviewed major organizational guidelines on the evaluation and management of asymptomatic microscopic hematuria, and identified the variations in the existing guidelines

Table 3. Diagnostic accuracy of urinary cytology to diagnose bladder cancer/UTUC in the hematuria patients

	Diagnostic accuracy				
Urinary cytology	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**PPV (95%CI)**	**NPV (95%CI)**	**ROC**
All patients (VH+NVH)					
・Positive	26.5 (18.1-36.4)	100 (99.2-100)	100 (81.0-100)	90.6 (88.3-92.6)	0.633
・Positive/atypical	54.1 (43.7-64.2)	99.4 (98.5-99.8)	93.0 (83.0-96.1)	93.9 (91.9-95.5)	0.768
Patients with VH					
・ Positive	24.2 (14.5-36.4)	100 (96.8-100)	100 (71.3-100)	77.2 (71.0-82.6)	0.621
・ Positive/atypical	56.1 (43.3-68.3)	98.8 (95.8-99.9)	94.9 (82.7-99.4)	85.2 (79.4-89.9)	0.774
Patients with NVH					
・ Positive	31.2 (16.1-50.0)	100 (98.9-100)	100 (58.7-100)	96.0 (94.0-97.5)	0.656
・ Positive/atypical	50.0 (31.9-68.1)	99.6 (98.6-100)	88.9 (65.3-98.3)	96.8 (94.9-98.1)	0.748

VH: visible hematuria, NVH: non-visible hematuria, UTUC: upper tract urothelial cancer, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval, ROC: receiver operating characteristic

Table 4. Urinary cytology outcomes in 98 patients with bladder cancer/UTUC treated with surgical interventions stratified by tumor grade and stage

	Positive	**Atypical**	**Negative**
• Total, n (%)	26 (27)	27 (28)	45 (45)
• Grade, n (%)			
Low	3 (12)	9 (33)	36 (80)
High	23 (88)	18 (67)	9 (20)
• pT stage, n (%)			
pTa	8 (31)	15 (56)	38 (84)
pT1	8 (31)	8 (30)	7 (16)
pT2 or more	8 (31)	3 (11)	0
pTis	2 (7)	1 (3)	0

N: number of patients, pT: pathological, UTUC: upper tract urothelial cancer

Table 5. Sensitivity of urinary cytology for grade and pT stage in 98 patients with bladder cancer/UTUC managed by surgical interventions

Urinary cytology	Sensitivity (95%CI)
•Positive	
•Grade, %	
Low	6.2 (1.3-17.2)
High	46.0 (31.8-60.7)
•pT stage, %	
pTa	13.1 (5.8-24.2)
pT1	34.8 (16.4-57.3)
pT2 or more	72.7 (39.0-94.0)
pTis	66.7 (9.4-99.2)
•Positive/atypical	
•Grade, %	
Low	25.0 (13.6-39.6)
High	82.0 (68.6-91.4)
•pT stage, %	
pTa	37.7 (25.6-51.0)
pT1	69.6 (47.1-86.8)
pT2 or more	100 (61.5-100)
pTis	100 (19.4-100)

pT: pathological, CI: confidence interval, UTUC: upper tract urothelial cancer

reflected the absence of level 1 evidence on the subject, as well as differences in relative prioritization across healthcare systems of diagnostic certainty vs fiscal control. The use of urinary cytology or urinary markers such as BTA-stat, NMP22 and UroVysion FISH in the initial evaluation for patients with NVH is not recommended by a number of guidelines. The AUA guidelines shows that urinary cytology may be useful in cases of persistent NVH after negative evaluation or those with risk factors for carcinoma in suite [5], while the EAU guidelines acknowledge the urinary cytology for the investigation of high-grade urothelial cancer and carcinoma in site as an adjunct to cystoscopy [4]. Nabi et al. [22] described that urinary cytology should be only performed in the proper clinical situation such as in patients with negative investigations using cystoscopy and imaging modalities for hematuria and in patients with previous urothelial cancers and high risks of recurrences in the upper tract. Although some guidelines [7,8], as described above, recommend routine use of urinary cytology for VH patients, urinary cytology should be ordered in negative investigations with cystoscopy and imaging modalities because of the low rates of sensitivity of urinary cytology in even VH patients.

5. CONCLUSION

Although urinary cytology is a convenient and noninvasive test with histologically high specificity for urothelial cancer, the rates of sensitivity of urinary cytology are inferior for even VH patients and high-grade cancers. However, adding atypical cytology results as positive improves accuracy of detection of urothelial cancer and prevent from the missing diagnosis. Nevertheless, urinary cytology has its place as an additive diagnostic tool to cystoscopy and imaging diagnosis for the investigations of asymptomatic hematuria.

CONSENT

The consensus of patients to review the medical record was not required by the committee due to the retrospective nature of the study. All the data was anonymized and maintained with confidentiality.

ETHICAL APPROVAL

Ethical approval was provided by the Higashimatsuyama Municipal hospital Ethics Committee as instituted by the Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Svatek RS, Lotan Y, Karakiewizc PI, et al. Screening for bladder cancer using urine - based tumor markers. Minerva Urol Nefrol. 2008;60:247-253.
2. Papanicolaou GN, Marshall VF. Urine sediment smears at a diagnostic procedure in cancers of the urinary tract. Science 1945;101:519-520.
3. N P Caraway NC, Katz RL. A review on the current state of urine cytology emphasizing the role of fluorescence in situ hybridization as an adjunct to diagnosis. Cancer Cytopathol. 2010;118; 175-183.
4. Babjuk M, Burger M, Compe´rat EM, et al. European Association of Urology Guidelines on Nonmuscle-invasive Bladder Cancer (TaT1 and Carcinoma in Situ) - 2019 Update. Eur Urol 2019;76:639-657.
5. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of

asymptomatic microhematuria (AMH) in adults. AUA guideline. J Urol. 2012;188: 2473-2481.
6. Spiess PE, Agarwal N, Bangs R, et al. Bladder cancer, version 5. 2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15:1240-1267.
7. Horie S, Ito S, Okada H, et al. Japanese guidelines of the management of hematuria 2013. Clin Exp Nephrol. 2014;18:679-689.
8. Wollin T, Laroche B, Psooy K. Canadian guidelines for the management of asymptomatic microscopic hematuria in adults. Can Urol Assoc J. 2009;3:77-80.
9. Bhatia A, Dey P, Kakkar N, et al. Malignant atypical cell in urine cytology: a diagnostic dilemma. CytoJournal. 2006;3:28. doi: 10.1186/1742-6413-3-28
10. Sauter G, Algaba F, Amin MB, et al. Non-invasive urothelial tumours. In: Eble JN, Sauter G, Epstein JI et al. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organ. Lyon, France: IARC Press. 2004;110-123.
11. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452-458.
12. Edwards TJ, Dickinson AJ, Natale S, et al. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU Int. 2006;97: 301-305.
13. Cha EK, Tirsar LA, Schwenter C, et al. Accurate risk assessment of patients with asymptomatic hematuria for the presence of bladder cancer. World J Urol. 2012;30:847-852.
14. Loo RK, Lieberman SF, Slezak JM, et al. Stratifying risk of urinary tract malignant tumors in patients with asymptomatic microscopic hematuria. Mayo Clin Proc. 2013;88:129-138.
15. Jubber I, Shariat SF, Conroy S, et al. Non-visible haematuria for the Detection of Bladder, Upper Tract, and Kidney Cancer: An Updated Systematic Review and Meta-analysis. Eur Urol. 2020; 77:583-598.
16. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology. 2005;66(6 Suppl 1):4-34.
17. Silverman DT, Levin LI, Hoover RN, et al. Occupational risks of bladder cancer in the United States: I. White men. J natl Cancer inst. 1989;81:1472-1480.
18. Karakiewicz PI, Benayoun S, Zippe C, et al. Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. BJU Int. 2006;97: 997-1001.
19. Tan WS, Sarpong R, Khetrapal P, et al. Does urinary cytology have a role in haematuria investigations? BJU Int. 2019;123:74-81.
20. Raab S, Grzybicki DM, Vrbin CM, et al. Urine cytology discrepancies: frequency, causes, and outcomes. Am J Clin Pathol 2007;127:946-53.
21. Linder BJ, Bass EJ, Mostafid H, et al. Guideline of guidelines: asymptomatic microscopic haematuria. BJU Int. 2018;121:176-183.
22. Nabi G, Greene DR, O'Donnell M. How important is urinary cytology in the diagnosis of urological malignancies? Eur Urol. 2003;43:632-636.

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