Routine Urine Cytology has No Role in Hematuria Investigations

Said F. Mishriki,* Omar Aboumarzouk, Ross Vint, Samuel J. S. Grimsley, Thomas Lam and Bhaskar Somani

From the Urology Department, Aberdeen Royal Infirmary, Aberdeen, Scotland (SFM, RV, TL), Urology Department, University Hospital North Staffordshire, Stoke-on-Trent (SJSG), and Southampton General Hospital, Southampton, Hampshire (BS), England, United Kingdom

Purpose: Urine cytology has been a long-standing first line investigation for hematuria and is recommended in current major guidelines. We determined the contribution of urine cytology in hematuria investigations and its cost implications.

Materials and Methods: Data were prospectively collected for 2,778 consecutive patients investigated for hematuria at a United Kingdom teaching hospital from January 1999 to September 2007 with final analysis in October 2010. All patients underwent standard hematuria investigations including urine cytology, flexible cystoscopy and renal tract ultrasound with excretory urogram or computerized tomography urogram performed in those with visible hematuria without a diagnosis after first line tests. Patients with positive urine cytology as the only finding underwent further cystoscopy, retrograde studies or ureteroscopy with biopsy under general anesthesia. Outcomes in terms of eventual diagnosis were cross-referenced with initial urine cytology results (classified as malignant, suspicious, atypical, benign or unsatisfactory). Costs of urine cytology were calculated.

Results: Of the patients 124 (4.5%) had malignant cells and 260 (9.4%) had atypical/suspicious results. For urothelial cancer cytology demonstrated 45.5% sensitivity and 89.5% specificity. Two patients with urine cytology as the only positive finding had urothelial malignancy on further investigation. For the entire cohort the cost of cytology was £111,120.

Conclusions: Routine urine cytology is costly and of limited clinical value as a first line investigation for all patients with hematuria, and should be omitted from guidelines.

Key Words: urine; cytological techniques; hematuria; carcinoma, transitional cell

Urine cytology has been a standard hematuria investigation for many years, recommended by major guidelines including those of the American Urological Association and the European Association of Urology.1,2 The validity of routine urine cytology in the routine investigation of hematuria has been questioned due to several shortcomings and it is doubtful if it adds any benefit beyond other standard investigations.3,4

Standard hematuria investigations include upper tract imaging and cystoscopy. Depending on available resources, upper tract imaging may include ultrasound and subsequent IVP or CTU if necessary. For many years it has been recognized that urine cytology is an operator dependent inves-
Urine cytology has to be sent before cystoscopy in the context of the NHS (National Health Service) is the most expensive estimate in the United Kingdom. The initial assessment of hematuria should be evaluated. Limited resources, the additional costs of cytology in even if obvious pathology is found. In an era of urinary tract investigation. Interpretation of the characteristics of voided transitional cells depends not only on the operator, but also on the method and timing by which urine cytology was collected. Urine cytology has a high specificity of 90% to 100% but has a sensitivity that is significantly dependent on the grade of the tumor. Sensitivity rates can be 20%, 45% and 75% for G1, G2 and G3 tumors, respectively. The variability in the sensitivity rates may be due to interobserver discrepancy in analysis and sampling.

Urine cytology has a low false-positive rate of 1% to 12% but this may lead to further invasive investigations such as ureteroscopy. The false-positive rate depends on whether atypia and suspicious samples are included. These changes are common in a variety of benign disorders and after instrumentation of the urinary tract. Low sensitivity in low grade tumors invalidates its use as a cost-effective screening test in general unless its use is restricted to individuals at high risk for the disease.

The estimated cost of a single urinary cytology test reportedly ranges from £22 to £163. In the United Kingdom the most expensive estimate in the context of the NHS (National Health Service) is £92. Urine cytology has to be sent before cystoscopy to avoid distortion of the cells by instrumentation. Urine cytology is sent from the hematuria clinic even if obvious pathology is found. In an era of limited resources, the additional costs of cytology in the initial assessment of hematuria should be evaluated.

MATERIALS AND METHODS
A total of 2,778 consecutive patients were prospectively studied from January 1999 to September 2007. The data set included age, gender, smoking, visible hematuria or nonvisible hematuria. Patients with NVH underwent ultrasound of the renal tract and flexible cystoscopy. Patients with VH underwent ultrasound of the renal tract and flexible cystoscopy and IVP or CTU to complete the investigations. Voided urine cytology was routinely submitted for all patients and was collected before flexible cystoscopy. Flexible cystoscopy was performed by a urology consultant, senior trainee or nurse specialist. Follow-up of all patients was done through the pathology database in 2010 by identifying patients who had tumor identified after initial evaluation of hematuria.

Data analysis was completed in October 2010. The main outcomes analyzed were the results of the investigations which included cystoscopy, ultrasound, cytology and, when performed, IVP/CTU in terms of establishing a diagnosis of urothelial malignancy. Cytology findings were recorded as malignant cells identified, atypical/suspicious cells identified, unsatisfactory specimen or cytology not recorded. Atypical/suspicious results had repeat urine cytology until yielding a result of no malignant cells. Pathology reporting was performed by a single pathologist with an interest in uro-oncology in accordance with universally adopted protocols (WHO grading of urothelial neoplasms). Pathological reports from any initial procedure were collected and follow-up was performed on all patients to identify any significant recurrence. The usefulness of urine cytology as a test was assessed by calculating its sensitivity, specificity, negative predictive value, positive predictive value, false-negative rate and false-positive rate. Statistical analyses were performed using SPSS® version 17.0.

RESULTS
The patient cohort included 1,867 men and 911 women (male-to-female ratio 2:1), with 1,804 presenting with VH and 974 with NVH. Of the VH group 382 (21.2%) harbored a urological malignancy and the majority of these patients (87%) had a bladder tumor. Of the NVH group 45 (4.6%) harbored a urological malignancy and the majority of these patients (93%) had a bladder tumor (table 1). Mean SD follow-up was 7.3 ±2.4 years (median 7.3, range 2.9 to 11.6). Data analysis was completed in October 2010.

In terms of cytology results 124 (4.5%) patient samples returned with malignant cells. A further 260 (9.4%) samples showed atypia or were classified as suspicious for malignancy. Cytology was negative in 2,123 (76.4%) patients. There were 207 (7.5%) patients who had no urine sample sent from the hematuria clinic. In 64 (2.3%) patients the specimen was unsatisfactory for analysis (table 2). Of the patients with malignant cytology 4 had no diagnosis and of those with atypical/suspicious cytology 125 had no diagnosis.

For the analysis of the utility of urinary cytology as a test to detect urothelial carcinoma, suspicious and atypical cytology were included along with malignant samples (table 3). Patients for whom urine samples were not sent or whose specimen was unsatisfactory were excluded from analysis. The sensitivity for diagnosing urothelial carcinoma was 45.4% (157/346) and the specificity was 89.5% (1,934/2,161). The false-positive rate was 10.5% (227/2,161), the false-negative rate was 54.6% (189/346), the positive predictive value was 40.9% (157/384) and the negative predictive value was 89.5% (1,934/2,161).

<table>
<thead>
<tr>
<th>Cancers found in hematuria clinic</th>
<th>NH</th>
<th>VH + Age 40 Yrs or Younger</th>
<th>VH + Age Older than 40 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>974</td>
<td>190</td>
<td>1,614</td>
</tr>
<tr>
<td>No. bladder Ca (%)</td>
<td>42 (4.3)</td>
<td>5 (2.6)</td>
<td>329 (20.3)</td>
</tr>
<tr>
<td>No. renal Ca (%)</td>
<td>3 (0.3)</td>
<td>1 (0.5)</td>
<td>39 (2.4)</td>
</tr>
<tr>
<td>No. renal TCC (%)</td>
<td>0</td>
<td>8 (0.5)</td>
<td>1</td>
</tr>
<tr>
<td>No. urothelial melanoma (%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
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Of the 2,778 patients only 2 had a negative cystoscopy, ultrasound and IVP with a positive cytology that was eventually diagnosed as urothelial carcinoma. Cystoscopy in the first patient showed inflammation of unknown cause which should have warranted biopsy. This was not done but positive cytology returned and the subsequent biopsies showed TCC with carcinoma in situ. The second patient had intermittent positive cytology and VH during the course of a year which prompted progressive investigations. Initial cystoscopy/ultrasound, IVP and CTU were negative. The patient then had bilateral retrograde studies which were unremarkable. However, subsequent bilateral diagnostic ureteroscopy revealed a right ureteral TCC (T1G3).

**DISCUSSION**

Urine cytology lacks sensitivity for low and intermediate grade superficial tumors which represent the majority of TCC. In this study more than 85% of tumors were G1 or G2. There have been attempts to create new useful urinary tests with higher sensitivity than cytology that would be an improvement on cytology for hematuria investigation and cancer surveillance. A systematic review by Mowatt et al showed that involving cytology was considered to be the least worthwhile option.\(^8\) Cytology followed by white light cystoscopy in initial diagnosis and followup was likely the least costly (£1,043 per patient) but it was also the least effective in terms of life-years (11.6) per patient.\(^8\) Mowatt et al suggested the use of other urinary biomarkers along with photodynamic diagnosis was the most effective strategy, albeit with higher associated costs (£2,370 per patient and 11.7 life-years). With its increasing use in clinical practice, urine cytology is perhaps going to become even less useful.\(^8\)

Other promising tests are NMP22®, ImmunoCyt® and FISH. Increased levels in urine can be detected with excessive cell division seen in TCC.\(^16\) NMP22 has been developed into a point of care bedside test that does not require laboratory evaluation. As with other biomarkers it is more sensitive than cytology, but less specific since it is increased in other benign bladder disorders. ImmunoCyt is an immunocytochemical fluorescence assay designed to improve the sensitivity of lower grade tumors in combination with cytology.\(^17\) Therefore, it carries the same problems of subjectiveness due to operator dependence and is even more expensive than cytology alone. In addition, its use decreases the specificity of cytology. FISH (known commercially as UroVysion®) is based on the inspection of transitional cell chromosomes for genetic alterations commonly present in bladder cancer. This time-consuming and expensive test requires trained personnel and has a specificity second only to cytology.\(^8,18\) Due to its technique of examining the cell nucleus, it has been suggested that FISH may detect tumors that are undetectable macroscopically on cystoscopy.\(^19\) The costs of NMP22, ImmunoCyt and FISH are £39.30, £54.80 and £54.80, respectively.\(^8\) These figures do not include labor, which may double these amounts. To date, the ideal urinary biomarker has not been found.

Other studies with smaller patient cohorts presenting with hematuria have similar findings in terms of the small number of patients in whom urine cytology diagnosed urothelial cancers which would have otherwise been missed by investigations such as flexible cystoscopy and upper tract imaging.\(^3,11,14\) Thus, it is highly unlikely that the benefits of cytology will outweigh the costs in the context of use in patients presenting with hematuria. We no longer use routine cytology for the investigation of hematuria and urine is sent for cytology only if no pathology is found at cystoscopy.

The cost of cytology is difficult to estimate as it is an operator dependent investigation and merely using the cost of the cytology equipment would underestimate this figure. The official United Kingdom NHS estimate is £92,\(^8\) but this is significantly more than other European estimates in the literature which range from £30 to £40.\(^3,14,15\)

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**Table 2. Cytology findings in patients with hematuria**

<table>
<thead>
<tr>
<th>Baseline Characteristics of Cytology</th>
<th>No. of pathology</th>
<th>Atypical/Suspicious</th>
<th>No Malignancy</th>
<th>Unsatisfactory</th>
<th>Not Recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. no pathology</td>
<td>4</td>
<td>125</td>
<td>1,362</td>
<td>57</td>
<td>153</td>
</tr>
<tr>
<td>No. bladder Ca</td>
<td>93</td>
<td>60</td>
<td>185</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>No. upper tract TCC</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. renal cell Ca</td>
<td>2</td>
<td>6</td>
<td>33</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. benign</td>
<td>22</td>
<td>60</td>
<td>539</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Total No. (%)</td>
<td>124 (4.5)</td>
<td>260 (9.6)</td>
<td>2,123 (76.4)</td>
<td>64 (2.3)</td>
<td>207 (7.5)</td>
</tr>
</tbody>
</table>

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**Table 3. Utility analysis of urine cytology**

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>No TCC</th>
<th>No TCC</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>No malignancy</td>
<td>1,934</td>
<td>189</td>
<td>2,123</td>
<td></td>
</tr>
<tr>
<td>Malignant or atypical/suspicious</td>
<td>227</td>
<td>157</td>
<td>384</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>2,161</td>
<td>346</td>
<td>2,507</td>
<td></td>
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</tbody>
</table>
Continuing to use cytology in the current manner, i.e., for all patients at initial presentation, will result in significant costs. The estimated cost associated with performing urinary cytology in 2,778 patients at £40 each was approximately £111,120. In addition, there are costs associated with false-positives at the rate of 10.5%. These are incurred by way of further invasive endoscopic assessment, repeat cytology, and radiological upper tract imaging. These costs have been estimated at approximately £12,000 per patient on average. These costs must be balanced against the benefits of diagnosing urothelial carcinoma which was missed through other routine tests. In a systematic review and economic evaluation Rodgers et al suggest that urine cytology has no application in ruling out malignancy or excluding patients from further investigation. Furthermore, the authors mention that neither tumor markers nor urine cytology can currently be used alone to rule out malignancy or exclude patients from further investigation. In this study only 2 of 2,778 patients benefited from urine cytology. Limitations of the study involve the noninclusion of cytology specimens which were unsatisfactory for analysis or for which the results were not recorded.

CONCLUSIONS

Guidelines for the routine use of urine cytology should be revised. When used in conjunction with cystoscopy and upper tract imaging in the investigation of patients presenting for the first time with hematuria, urine cytology adds little to the diagnostic value of standard hematuria investigations. On the contrary, urine cytology is associated with relatively high costs, and can potentially result in additional expensive and morbid investigations because of false-positives. The routine use of urine cytology is of limited value and should not be included in guidelines.

REFERENCES


EDITORIAL COMMENT

The use of urine cytology to detect urothelial malignancy has been considered a standard part of the diagnostic evaluation of patients with hematuria. While specificity of urine cytology is reasonably high enough to confirm the presence of malignancy, its overall sensitivity remains too poor to rule out malignancy or omit other investigations (reference 20 in article). The diagnostic performance of cytology is
hampered by a number of pitfalls including inappropriate collection and processing of specimens, poor interobserver and intra-observer reliability, and heterogeneous tumor biology (reference 8 in article). Two of the most important, and all too often overlooked, determinants of the clinical value of urine cytology are significant interobserver variability and lack of standardized reporting.

An online quiz on the reporting standards and diagnostic accuracy of urine cytology revealed at least 7 different classifications (each with a 3 to 9-point diagnosis spectrum between benign and malignant) were used/preferred by the participating cytotechnologists and cytopathologists.1 Also the percentage of correct answers about the 52 test cases ranged from 8.5% to 93%. Even in the hands of “expert” participants, the best concordance for high grade cancers was only 56% to 78%, and an alarmingly high rate of misclassification of benign cells as suspicious or positive for cancer was given in 18% to 31% cases. Does urine cytology provide a unique contribution to the detection of urothelial malignancy which otherwise would not have been detected through imaging and cystoscopy? In a previous report of 1,000 cases urine cytology alone was responsible for the diagnosis of urothelial cancers in 4, including 2 cases of visible abnormalities on the excretory urogram or cystoscopy, thus potentially benefiting 0.2% to 0.4% of the cases.2

Mishriki et al report that urine cytology alone resulted in the diagnosis of a malignancy in 2 patients, including one with a bladder erythematous lesion that should have been biopsied, providing unique benefit to only 0.07% of the subjects. Furthermore, the false-positive rates of 10% in the current study and 5% to 20% in the literature are significant. Such results often lead to expensive interventions and their associated morbidity including psychological distress, general anesthesia and hospital admission, as well as the potential complications of endoscopic procedures.

A commonly cited reason for the ongoing use of cytology is that it may allow for the adjustment of one’s index of suspicion for the equivocal findings on cystoscopy or imaging. However, in the era of cost conscious medicine these rare and anecdotal cases cannot justify the routine use of a test with such a limited net contribution. The scarcity of data demonstrating unique benefit combined with the potential for actual harm is the main reason why urine cytology has not been a part of our routine investigation of patients with hematuria for nearly 10 years. It is refreshing to note that the recently amended American Urological Association guidelines3 and this article by Mishriki et al do not support the routine use of cytology in cases of asymptomatic microhematuria. Hopefully, these publications will lead to the judicious use of urine cytology in only those few select cases that are at high risk for harboring urothelial cancers.

Badar M. Mian
Albany Medical Center and Stratton VA Medical Center
Albany, New York

REFERENCES

REPLY BY AUTHORS

We completely agree with the editorial comment. Our study stresses that routine urine cytology has no role in cases of microscopic hematuria. For frank hematuria, careful judgment should be made as to whether cytology adds to the clinical diagnosis, especially in high risk cases, but it is not recommended routinely in all such cases.