Routine Urine Cytology has No Role in Hematuria Investigations

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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

Abbreviations and Acronyms

CTU = computerized tomography urogram
FISH = fluorescence in situ hybridization
IVP = excretory urogram
NVH = nonvisible hematuria
TCC = transitional cell carcinoma
VH = visible hematuria

Accepted for publication October 10, 2012.

Presented at annual meeting of American Urological Association, Atlanta, Georgia, May 20–25, 2006.

Nothing to disclose.

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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-

0022-5347/13/1894-1255/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2012.10.022
Vol. 189, 1255-1259, April 2013
Printed in U.S.A.

tigation.[5] 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.[6] Urine cytology has a high specificity of 90% to 100%[6–8] 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.[8–10] The variability in the sensitivity rates may be due to interobserver discrepancy in analysis and sampling.[11]

Urine cytology has a low false-positive rate of 1% to 12% but this may lead to further invasive investigations such as ureteroscopy.[12] 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.[13]

The estimated cost of a single urinary cytology test reportedly ranges from £22 to £163.[3,8,14,15] In the United Kingdom the most expensive estimate in the context of the NHS (National Health Service) is £92.[8] 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. Followup 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 followup 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 followup 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 1. *Cancers found in hematuria clinic*

	NVH	VH + Age 40 Yrs or Younger	VH + Age Older than 40 Yrs
No. pts	974	190	1,614
No. bladder Ca (%)	42 (4.3)	5 (2.6)	329 (20.3)
No. renal Ca (%)	3 (0.3)	1 (0.5)	39 (2.4)
No. renal TCC (%)	0	0	8 (0.5)
No. urothelial melanoma (%)	0	0	1