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Routine Urine Cytology Has no Role in Hematuria Investigations

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This paper has been presented:

1. **Poster:** Is urine cytology obsolete in investigating haematuria? A large prospective study. Janjua K, Martindale A, Ong E, Royle J, Mishriki SF. British Association of Urological Surgeons in Glasgow, June 2005
2. **Oral presentation:** Urine cytology may be redundant in investigating haematuria: Large prospective study. Mishriki SF, Janjua K, Shaikh S, Lam T, Ong EK. American Urological Association, annual meeting, Atlanta, U.S.A, May 2006
3. **Poster:** Is urine cytology a relevant investigation for urological malignancies? Mishriki SF, Molokwu CN, Sweeney C, Lam T, Janjua K. European Association of Urology, Barcelona, 2010
4. **Poster:** Urine Cytology has no role in Urological Malignancies. Mishriki SF, Vint R, Grimsley SJS, Somani BK, Lam T

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Abstract

Purpose: Urine Cytology has been a longstanding first line investigation for haematuria and is recommended in current major guidelines. Objectives are to determine the contribution of urine cytology in haematuria investigations and its cost implications

Materials and Methods: Data prospectively collected for 2778 consecutive patients investigated for haematuria at a UK teaching hospital January 1999 to September 2007 with final analysis in October 2010. All patients underwent standard haematuria investigations; urine cytology, flexible cystoscopy and renal tract US with IVU or CTU performed for visible haematuria patients without diagnosis following first line tests. Patients with positive urine cytology as the only finding underwent further cystoscopy, retrograde studies or ureteroscopy with biopsy under general anaesthetic. Outcome in terms of eventual diagnosis were cross-referenced with initial urine cytology results (classified as malignant, suspicious, atypical, benign or unsatisfactory). Cost of urine cytology was calculated.

Results: 124 (4.5%) patients had malignant cells and 260 (9.4%) atypical/ suspicious. 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, cost for cytology was £111,120.

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

Introduction:

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

Standard haematuria investigations include upper tract imaging and cystoscopy.

Depending on available resources, upper tract imaging may include ultrasound (U/S) and subsequent intravenous urography (IVU) or CT urogram (CTU) if necessary. It has been recognised for many years that urine cytology is an operator dependent investigation.⁵

Interpretation of the characteristics of voided transitional cells does not just depend on the operator but also on the method and timing by which urine cytology has been collected.⁶ Urine cytology has high specificity of 90-100%⁶⁻⁸ but a sensitivity that is significantly dependent on the grade of the tumour. Sensitivity rates can be 20%, 45% and 75% for G1, G2 and G3 tumours respectively.⁸⁻¹⁰ The variability in the sensitivity rates may be due to inter-observer discrepancy in analysis and sampling.¹¹

Urine cytology has a low false positive rate of 1-12% but this may lead to further invasive investigations such as ureteroscopy.¹² The false positive rate is dependent 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 tumours invalidates its use as a cost-effective screening test in general unless its use is restricted to individuals at high risk of having the disease.¹³

The estimated cost of a single urinary cytology test is reportedly variable ranging from £22-163.^{3,8,14,15} In the UK, the most expensive estimate within the context of the National Health Service (NHS) is £92.⁸ Urine cytology has to be sent before cystoscopy to avoid distortion of the cells by instrumentation. **Urine cytology was sent** from the haematuria clinic even if an obvious pathology is found. In an era when resources are limited, the additional costs of cytology in the initial assessment of haematuria should be evaluated.

Materials and Methods

2778 consecutive patients were prospectively studied from January 1999 to September 2007. The data set included age, sex, smoking, visible haematuria (VH) or non-visible haematuria (NVH). NVH patients underwent U/S scan of the renal tract and flexible cystoscopy. VH patients underwent ultrasound scan of the renal tract and flexible cystoscopy and IVU or CTU to complete the investigations. Voided urine cytology was routinely submitted for all patients and was collected prior to 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. Main outcomes analysed were the results of the investigations which included cystoscopy, U/S, cytology and, when done, IVU/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 “no malignant cells” identified result. Pathology reporting was performed by one 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 undertaken on all patients to identify any significant recurrences. The utility 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 carried out using the SPSS (*Statistical Package for the Social Sciences*) version 17.0 software.

Results

The patient cohort included 1867 men and 911 women (M:F=2:1) with 1804 presenting with VH and 974 with NVH. Of the VH group 382 (21.2%) harboured a urological malignancy, the majority of these (87%) had a bladder tumour. Of the NVH group 45 (4.6%) harboured a urological malignancy, the majority of these (93%) had a bladder tumour (Table 1). **Mean follow-up (+/- standard deviation) was 7.3 (+/- 2.4) years. Median follow-up was 7.3 (range 2.9 – 11.6) years. Data analysis was completed in October 2012.**

Regarding cytology results, 124 (4.5%) patient samples returned with malignant cells. A further 260 (9.4%) showed atypia or were classified as suspicious for malignancy.

Cytology was negative in 2123 (76.4%) of patients. 207 (7.5%) had no urine sample sent from haematuria clinic. In 64 (2.3%) patients the specimen was unsatisfactory for analysis (Table 2). **Four patients with malignant cytology had no diagnosis found. One hundred and twenty five patients with atypical/suspicious cytology had no diagnosis found.**

For the analysis of utility of urinary cytology as a test for detecting urothelial carcinoma, suspicious and atypical cytology are included along with malignant samples. Patients in whom urine samples were not sent or in whom the specimen was unsatisfactory were excluded from the analysis. The sensitivity for diagnosing urothelial carcinoma was 45.4% and the specificity was 89.5% (Table 3). The false positive rate was 10.5%, false negative rate was 54.6%, positive predictive value was 40.9%, and negative predictive value was 89.5%.

Of all 2778 patients only two had a negative cystoscopy, ultrasound and IVU with a positive cytology that was eventually diagnosed as urothelial carcinoma. The first case had cystoscopy that reported inflammation of unknown cause which should have warranted biopsies. This was not done but positive cytology returned and the subsequent biopsies showed TCC with carcinoma in-situ. The second case had intermittent positive cytology and VH over the course of a year which prompted progressive investigations. Initial cystoscopy/ultrasound and IVU and CTU were negative. The patient then had bilateral retrogrades studies were unremarkable. However, subsequent bilateral diagnostic ureteroscopy revealed a right ureteric TCC (T1G3).

Discussion:

Urine cytology lacks sensitivity for low and intermediate grade superficial tumours which represent the majority of transitional cell carcinoma. In this study more than 85% of tumours were either 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 haematuria investigation and cancer surveillance. A systematic review showed that

involving cytology was considered to be the least worthwhile.⁸ Cytology followed by white light cystoscopy in initial diagnosis and follow-up is likely to be the least costly (£1043 per patient) but it was also the least effective in terms of life-years (**11.6**) per patient.⁸ The review suggested the use of other urinary biomarkers along with photodynamic diagnosis (PDD) was the most effective albeit having higher cost associated with it (£2370 per patient and **11.7** life-years). With its increasing use in clinical practice, the use of urine cytology is perhaps going to be even less useful.⁸ Other promising tests are Nuclear Matrix protein-22 (NMP22), ImmunoCyt and Fluorescence in-situ hybridisation (FISH). Elevated levels in urine can be detected with excessive cell division seen in transitional cell carcinoma.¹⁶ NMP22 has been developed into a point-of-care bedside test without requiring laboratory evaluation. As with other biomarkers it is more sensitive than cytology but less specific since it is elevated in other benign bladder disorders. ImmunoCyt is an immunocytological fluorescence assay designed to improve the sensitivity of lower grade tumours by combination with cytology.¹⁷ It therefore carries the same problems of subjectiveness due to operator dependence and is even more expensive than cytology alone. In addition its use lowers 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, expensive test requiring trained personnel has specificity second only to cytology.^{8,18} Due to its technique of examining the cell nucleus, it has been suggested that FISH may detect tumours that are undetectable macroscopically on cystoscopy.¹⁹ The cost of NMP22, Immunocyst and FISH are £39.30, £54.80 and £54.8 respectively.⁸ This

does not include labour which may double these figures. The ideal urinary biomarker has not been found to date.

Other studies with smaller patient cohorts presenting with haematuria have published similar findings in regard to the extremely small number of patients in whom urine cytology diagnosed urothelial cancers which would otherwise have been missed by other investigations such as flexible cystoscopy and upper tract imaging.^{3,4,11,14} Consequently it is highly unlikely that the benefits of cytology will outweigh its costs in the context of its use on patients presenting with haematuria. We no longer use routine cytology for haematuria investigation. Urine is sent for cytology only if no pathology is found at cystoscopy.

The cost of cytology is difficult to estimate being an operator-dependent investigation, merely using the cost of the cytology equipment would underestimate this. The official United Kingdom NHS estimate is £92⁸ but this is significantly more than other European estimates in other literature. This is in the region of £30-40.^{3,14,15}

Continuing use of cytology in the current manner i.e. for all patients at initial presentation, there are significant costs. The estimated costs associated with performing urinary cytology on 2778 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 have been estimated at approximately £12,000 per patient on average.³ Costs must be balanced against the benefits of diagnosing urothelial carcinoma which were missed through other routine tests. A systematic review on economic evaluation suggests that urine cytology has no application in ruling out malignancy or

excluding patients from further investigation. Furthermore it mentions that neither tumour markers nor urine cytology can currently be used alone to rule out malignancy or to rule out patients from further investigation.²⁰ In this study, only 2 out of 2778 patients benefited from urine cytology. **Limitations of the study include the non-inclusion of those cytology specimens which were unsatisfactory for analysis or where the urine cytology results have not been 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 haematuria, urine cytology adds very little to the diagnostic value of standard haematuria 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.

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Table 1

Cancers found in Haematuria Clinic (NVH= Non-visible Haematuria, VH = Visible haematuria, >40: age more than 40 years, <=40: age less than or equal to 40 years)

Diagnosis	NVH n = 974	VH <= 40 n = 190	VH > 40 n = 1614
Bladder cancer	42 (4.3%)	5 (2.6%)	329 (20.3%)
Renal cancer	3 (0.3%)	1 (0.5%)	39 (2.4%)
Renal TCC	0	0	8 (0.5%)
Urothelial melanoma	0	0	1

Table 2

Cytology findings in Haematuria Patients

Cytology	No Path	Bladder Ca	UT TCC	RCC	Benign	All (%)
Clinical findings						
Malignant Cells	4	93	3	2	22	124 (4.5%)
Atypical/suspicious	125	60	1	6	68	260 (9.6%)
No Malignancy	1362	185	4	33	539	2123 (76.4%)
Unsatisfactory	57	6	0	1	0	64 (2.3%)
Not Recorded	153	32	0	1	21	207 (7.5%)

Table 3

Utility analysis of urine cytology (TCC: Transitional cell carcinoma)

Cytology/Diagnosis	No TCC	TCC	Total
No malignancy	1934	189	2123
Malignant or atypical/suspicious	227	157	384
Total	2161	346	2507

Sensitivity = $157/346 = 45.4\%$

Specificity = $1934/2161 = 89.5\%$

False positive rate = $227/2161 = 10.5\%$

False negative rate = $189/346 = 54.6\%$

Positive predictive value = $157/384 = 40.9\%$

Negative predictive value = $1934/2161 = 89.5\%$