The role of light urine cytology in the diagnosis of transitional cell carcinoma (TCC) of the bladder; a retrospective clinical audit

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Abstract

Objective

To assess the role of light urine cytology in diagnosing TCC bladder.

Methods

704 patients who presented with visible and non-visible haematuria between January 2013 and December 2013 at the haematuria clinic were audited retrospectively.

All of these patients' urine samples were sent off to pathology department for light urine cytology analysis before cystoscopy and imaging being done. Urine cytology analysis was offered as per local cancer guidelines. During this audit urine cytology, radiological and cystoscopy results were reviewed and compared to tissue histology results were applicable.

Results

704 patients' urine cytology was evaluated, 14 cases had cytology suspicious for malignancy. Overall 34 patients out of the 704 had TCC bladder confirmed on tissue histology. Out of 34 patients, 6 had a positive cytology, 28 cases were diagnosed on flexible cystoscopy and imaging.

Conclusion

No transitional cell carcinoma cases identified with light urine cytology were missed with cystoscopy and imaging in this cohort.

Key words: TURBT: Trans-urethral resection of the bladder, urine cytology, Haematuria. TCC: Transitional cell carcinoma, USS-KUB: Kidney, Ureter and bladder.

Introduction

The use of urinary cytology in diagnosis or surveillance of urological cancers has been part of haematuria investigations in addition to cystoscopy and imaging. Urinary cytology has been proven to be more sensitive in high grade urological tumours reported in a review by Gaston[1] where urinary cytology sensitivity was 17% in grade 1 tumour, 72 grade 2 tumour, 94 % in grade 3 tumour and 100% sensitive in carcinoma insitu.

A recent clinical audit by Ram[2] evaluating the diagnostic value of urine cytology in detecting bladder urothelial tumours in 215 cases by comparing urine cytology results to bladder biopsy histology revealed an overall sensitivity of 69.30% and specificity of 58.66%, this was increased to 88.6% and 91.67% sensitivity and specificity respectively. From the existing evidence like the works of Ramkumar[3], Talwa[4], Khadra[5], Karakiewicz[6] and Brown[7] suggest that the sensitivities and specificities rates reported increases with the severity of the urological tumours. However there is also evidence that highlights the main concern of using urine cytology as part of the primary investigations of haematuria, this is mainly because it gives rise to high false positives and in fact urine cytology sensitivities and specificities varies from institution to institution. The work of Edwards[8] where a review of 4020 patients were evaluated in the haematuria clinic, urine microscopy was not used as part of the primary investigations because of similar concerns.

Aim

The aim of this clinical audit was to assess the relevance of light urine cytology in detecting transitional cell carcinomas (TCC) of the bladder. The primary outcome was to assess whether light urine cytology identified any TCC that was missed on imaging (CT and USS–KUB) and cystoscopy combined.

Criteria

This clinical audit's criterion is that Hull and East Yorkshire Hospitals NHS Trust urine cytology sensitivity and specificity rates should be in range with the known detection rates of other institutions nationally.

Standard

After an extensive search of Medline between 20/10/14 and 4/11/14, we could not identify any standardised urine cytology detection rates of urological cancers by either the National Institute of Clinical Excellence (NICE) or other international organisation recommendations to act as our standard to compare our results. Therefore our results were compared to those in the latest published audits or studies.

Methods

Patient Identification:

Two clinical auditors obtained the database containing patients' identifiers of 704 patients whose urine samples had been sent to pathology department for urine cytology as part of haematuria investigation.

Data collection:

All 704 patients (415 males, 289 females) referred with visible or persistent non-visible haematuria were investigated with light urine cytology, USS-KUB and or CT urogram and flexi-cystoscopy. All patients who had a lesion on flexible cystoscopy or imaging of upper tract were offered TURBT procedure or nephoureteroctomy depending on site of the lesion. Tissue histology was used as the gold standard for diagnosis.

Using patients' identifiers recorded by the pathology department, two clinical auditors independently retrieved urine cytology results, subsequent imaging reports of CT and USS-KUB, Cystoscopy reports and where applicable tissue histology diagnosis. The data was tabulated data into an Excel-2010 Microsoft data sheet.

Light urine cytology results were reported in four categories as normal, acute inflammation, negative for malignancy and atypia cells suspected for malignancy. CT and USS-KUB were reported by the radiology consultant, and the flexible cystoscopies were performed by a urology middle grade or consultant.

Results

As illustrated in table 1, seven hundred and four patients (704) patients urine which was sent off for light urine cytology; 14/704 (2.0%) were reported as suspicious of malignancy, 519/704 (73.7%) were negative for malignancy and 171/704 (24.3%) were reported as acute inflammation. 34 of 704 patients were found to have urothelial lesions which were confirmed on tissue histology for urological malignancy. Secondary analysis of these 34 cases with a tissue diagnosis of cancer with regards as to what urine cytology results had predicted revealed that 6/34 (17.7%) were reported as suspicious of Malignancy, 20/34 (58.8%) negative for malignancy and 8/34(23.5%) acute inflammation (see table 1). Analysis of the 6 cases which were positively predicted by light urine cytology to be malignant in origin showed that 5/6 (83.3%) cases were high grade tumours in origin and the remaining case was of low grade tumour (see table 2). 28/34 (82.4%) cases of cancers diagnosed in this cohort had been reported as negative for malignancy or acute inflammation in the urine cytology pathology reports. 17/28 (60.7%) of these cases turned out to be high grade tumours and 11/28 (39.3%) were low grade tumours on histology diagnosis (see table 3).

Discussion

From this data we illustrate that the use of light urine cytology at this institution has similar results in comparison to existing published urine cytology specificities and sensitivities results. Most importantly the use of urine cytology did not add any diagnostic value to the haematuria investigations as the same malignancy cases were identified by other

Table 1: Urine cytology, imaging, Cystoscopy and histology findings for the 704 patients.

Urine cytology results category	Participants (%) Total= 704	Imaging: CT &USS-KUB (%)	Cystoscopy (%)	Tissue histology diagnosis (%)
Suspicious of Malignancy	14 (2.0)	AD = 10 (71.4) NAD = 4 (28.6)	AD =6(42.9) NAD = 8(57.1)	AD = 6(42.9) NAD =8(57.1)
Negative of malignancy	519 (73.7)	AD = 104(20.0) NAD =412(79.4) Not done = 3(0.6)	AD = 62(12) NAD = 303 (58.4) Not done =154(29.6)	AD= 20(3.9) NAD = 499(96.1)
Acute Inflammation	171 (24.3)	AD = 71 (41.5) NAD = 100 (58.5)	AD = 18(10.5) NAD = 115(67.3) Not done=38(22.2)	AD =8(4.7) NAD = 7(73.1) Not done =156(91.2)

AD: Abnormality detected, NAD: No abnormality detected.

Table 2: Histology results for patients who were positively identified by urine cytology.

Number	Age (years)	Sex	Histology diagnosis	High grade
1	72	F	G2 pT1	Yes
2	69	M	Carcinoma Insitu	Yes
3	67	F	TCC grade 2 (ureteric)	Yes
4	72	F	TCC bladder (G3 pT1)	Yes
5	78	M	Carcinoma insitu	Yes
6	60	M	TCC grade 2 (pta ureteric)	No
Total	Average age=70	M=3, F=3		High grade: 5/6 (83.3%) Low grade: 1/5 (16.7%)

modes of investigations like CT urogram, USS of the renal tract and or with cystoscopy.

Only 6 out of the 34 cases with a urological malignancy had a positive urine cytology report. These cases were identified where cystoscopy was the imaging modality used. Therefore these patients who had a lesion identified by other tests did not need urine cytology as it had no added diagnostic value. Also our data revealed that out of the cancers detected by urine cytology, 5/6 (83.3%) of these were high grade tumours in origin (table 2). This is in keeping with existing literature where that urine cytology has a high sensitivity in the high grade tumours[2].

Close inspection of the cancers in this cohort that were missed by urine cytology showed that 17/28(60.7%) were in high grade tumours category. Despite all existing evidence suggesting that urine cytology sensitivity is highest in the high grade tumours, this evidence suggests otherwise. This is the first clinical audit to reveal that urine cytology still misses high grade tumours. This could explain why different institutions or pathology departments report different sensitivities and specificities of urine cytology because cytology reports will vary from pathologist to pathologist.

In this cohort the cause for false positives were largely accounted for by renal calculi, renal cyst disease, hydronephrosis, and benign enlarged prostate and urine tract infections. Similar causes of false positive urine cytology have been reported in the work of Mansoor[9] and Siddappa[10].

Table 3: Tissue histology results of patients with negative urine cytology.

Number	Age	Sex	Tissue histology diagnosis	High / low Grade	Imaging results	Cystoscopy results
1	83	M	TCC/G2 pta	low	✓	✓
2	89	F	TCC (low grade bladder) G1 Pta	low		✓
3	78	M	CIS (carcinoma insitu)	high	X	✓
4	71	M	TCC grade 3 (ureteric)	high	✓	✓
5	61	M	High grade TCC Bladder	high	✓	✓
6	85	M	carcinoma insitu	high	✓	✓
7	75	M	carcinoma insitu	high	✓	✓
8	46	M	carcinoma insitu	high	✓	✓
9	84	F	G3 pT1	high	✓	✓
10	62	F	TCC renal / grade 3	high	✓	X
11	79	M	carcinoma insitu / Bladder	high	X	✓
12	70	M	TCC grade 3 (ureteric)	low	✓	X
13	73	M	TCC grade 2 (ureteric)	low	✓	X
14	50	M	TCC (grade 1) bladder	low	✓	✓
15	69	M	TCC / G1 PTa	low	✓	✓
16	63	M	G3 pTa, TCC bladder	high	X	✓
17	68	F	G1 pTa / TCC	low	✓	✓
18	64	M	G2 pTa / TCC bladder	low	✓	✓
19	86	F	TCC grade 3 / ureteric	high	X	X
20	63	M	carcinoma insitu	high	X	✓
21	76	F	carcinoma insitu	high	X	✓
22	84	F	Squamous cell carcinoma (G2 pT1)	high	✓	✓
23	55	F	TCC bladder (G1 pTa)	low	✓	✓
24	69	M	TCC bladder (grade 3)	high	✓	✓
25	65	M	TCC bladder (G1 pta)	low	X	✓
26	79	M	G3 Pt1 bladder	high	X	✓
27	83	M	TCC bladder (G2 pTa)	low	✓	✓
28	86	M	TCC bladder (G2 pTa)	high	X	✓
	Mean: 72	M=23 F=9		High: 17/28 (60.7%) Low:11/28 (39.3%)	✓=19/28 (67.9%) X=9/28 (32.1%)	✓=24/28 (85.7%) X=4/28 (14.3%)

✓: Positive finding, X: negative finding

Conclusion

Urine cytology does not have additional benefit in detecting urological malignancy when used in conjunctions with imaging modalities (CT-KUB, USS-KUB) and cystoscopy. Urine cytology still misses a high proportion (60.7%) of the high grade tumours if used alone. Therefore one needs to question the role of light urine cytology as part of primary haematuria investigations.

With this evidence suggesting that the use of urine cytology in every patient presenting with haematuria adds no benefit in detecting urological malignancy and also with increasing financial pressures of direct and indirect costs of processing the urine cytology to both urology and pathology departments, it would be reasonable to exclude urine cytology or reserve this test for a few cases; for example when a patient still has haematuria and all the other tests are negative or follow up in a patient with previous high grade tumour or carcinoma in-situ.

This evidence, together with the existing literature questions the role of light urine cytology as part of primary haematuria investigations.

Practice points

a) **Urine cytology is an additional cost for zero benefit in this cohort**

a) **Light urine cytology should be restricted to follow up of previous high grade tumours or carcinoma in-situ.**

References

1. Gaston Kris E. Value of urinary cytology in the diagnosis and management of urinary tract malignancies. *Journal of Urology*. 2004;63 (6), 1009-16.
2. Manisha Ram, Nazar Alsanjari. Audit of urine cytology in bladder urothelial tumours, the professional standards. *The bulletin of the royal college of pathologists*. 2010; 149 (1), 52-55.
3. Ramakumar S, Bhuiyan J, Besse JA, Roberts SG, Wollan PC, Blute ML. Comparison of screening methods in the detection of bladder cancer. *Journal of urology*.1999; 161 (2), 388-94.
4. Talwar R, Sinha T, Karan SC, Doddamani D, Sandhu A, Sethi GS. Voided urinary cytology in bladder cancer: is it time to review the indications? Journal of *Urology*. 2007; 70 (2), 267-71.
5. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1930 patients with haematuria to evaluate current diagnostic practice. *Journal of urology*, 2000; 163 (2), 524-7.
6. Karakiewicz PI, Benayoun S, Zippe C, Lüdecke G, Boman H, Sanchez-Carbayo M, Casella R, Mian C, Friedrich MG, Eissa S, Akaza H, Huland H, Hedelin H, Rupesh R, Miyanaga N, Sagalowsky AI, Marberger MJ, Shariat SF. Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. *BJU International*. 2006; 97 (5), 997-1001.
7. Brown FM. Urine cytology: Is it still the gold standard for screening? *Urologic Clinics of North America,2000;* 27, 25-37
8. Edwards Tom J, Andrew j. Dickinson, Salatore Natale, Jane Gosling and John S. McGrath. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. *BJU international,* 2006; 97, 301 – 305.
9. Mansoor I. Analysis of urine cytology at a community hospital. *Journal of Ayub Medical College* 2003; 15 (2), 20-3.
10. Siddappa S, Mythri K, Kowsalya R. Cytological findings in routine voided urine samples with hematuria from a tertiary care center in south India. *Journal of Cytology/ Indian Academy of Cytologists*. 2012; 29 (1), 16-9.