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Efficacy of voided urinary cytology and ultrasonography compared to cystoscopy in the detection of urinary bladder cancer

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Abstract
Introduction: Painless hematuria is the presenting symptom in 85–90% of patients with bladder cancer.
Objectives: To evaluate the efficacy of voided urinary cytology and ultrasonography in the diagnosis and follow up of bladder cancer compared to cystoscopy as a gold standard with reference to its grade. To recommend a protocol that improves the overall sensitivity and specificity of detection of new cases and recurrence in the follow up of patients with bladder cancer.
Subjects and methods: A prospective analysis of patients with painless hematuria and follow up patients of bladder cancer was done. They were subjected to voided urinary cytology and ultrasonography. The results were compared with the inferences drawn from cystoscopy and histopathological examination of the resected tumor, wherever applicable.
Results: The sensitivity of urinary cytology and ultrasonography was 13.33% and 66.67%, respectively, compared to cystoscopy as a gold standard, whereas the specificity of urinary cytology and ultrasonography was 100% and 93.33%, respectively. Cytology was positive only in high grade cases.
Conclusions: Voided urinary cytology can be omitted as a screening test. Ultrasonography can be recommended as the initial imaging investigation for detection of bladder carcinoma in patients presenting with hematuria and for follow up of bladder carcinoma patients.

Introduction

Bladder cancer is the fourth most common cancer in men and the ninth most common cancer in women [1]. The commonest histological variant is transitional cell carcinoma (TCC) and accounts for more than 95% of all the cases of bladder cancer [2,3].

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Painless hematuria is the presenting symptom in 85–90% of patients with bladder cancer [4]. The workup of suspected bladder cancer should include cytology, a cystoscopy, and an upper tract study. The most important modality for detection of bladder tumor in a new patient with hematuria or a known patient of bladder cancer is cystoscopic evaluation followed by histopathological examination of resected tumor, if present.

Although cystoscopy is the gold standard for the detection of bladder cancer, the false negative results associated with cystoscopy can range from 10 to 40%. Lesions of Carcinoma in situ (CIS) may escape detection even by cystoscopy [5,6]. Also tumors of the upper tract and very small bladder tumors at relatively less optimally visualized areas on cystoscopy may be missed.

To overcome this, voided urine cytology is used as an adjunctive test in identifying occult cancers that may be missed on cystoscopy. It can identify exfoliated cells from both normal and neoplastic urothelium and may be useful in detecting cancer in symptomatic patients and assessing response to treatment. Detection rates are high for tumors with high grade and stage as well as CIS [7,8]. Cytology is illustrative of the problems of non-invasive screening. Poorly differentiated tumors have a 20% false-negative detection rate, whereas well-differentiated tumors have up to an 80% false-negative detection rate. Cytology, however, remains the preferred bladder tumor marker for specificity [9].

Bladder cancer may also be detected by various imaging techniques. CT urogram is the imaging modality of choice to detect bladder masses. Large tumors can also be detected on ultrasonographic study of the KUB region, in which case cystoscopy may be planned with transurethral resection of bladder tumor.

The aim of our study was to evaluate the efficacy of voided urinary cytology and ultrasonography in the diagnosis and follow up of bladder cancer compared to cystoscopy as a gold standard with reference to its grade and to devise a protocol that improves the overall sensitivity and specificity of detection of new cases and recurrence in the follow up of patients with bladder cancer.

Subjects and methods

In this study, a prospective analysis of new and follow up patients under evaluation for bladder cancer was done at urology center of Command Hospital (EC), Kolkata from Feb 2013 to July 2014. Sixty (60) patients being evaluated for Carcinoma Bladder both freshly detected and those on follow-up were included as per convenience sampling after obtaining their informed written consent.

Inclusion criteria were (1) patients of painless hematuria on evaluation for bladder cancer, and (2) known patients of bladder cancer under follow up. Following categories of patients were excluded from the study: (1) patients with major co-morbidities requiring acute intensive medical care, (2) patients with major psychiatric illnesses, (3) benign inflammatory or infectious conditions of bladder, (4) renal or bladder calculi, (5) foreign body (stent or nephrostomy tube), (6) other genitourinary cancer, (7) recent instrumentation, (8) bleeding disorders, (9) bowel interposition.

The study was approved by the ethical committee of the institute. Demographic profile of patient's such as name, age, sex, etc. was recorded. Under structured pro forma in depth history of the patients was taken to note the indication for which patient was being evaluated for Carcinoma Bladder and the duration of illness in known cases of Carcinoma Bladder. Any past or concomitant co morbidity was noted. Detailed clinical examination including vital parameters recording was done. Abdomen was examined thoroughly to look for any abnormality like swelling, tenderness, lump, etc. with special reference to suprapubic region.

All patients fulfilling the inclusion criteria were subjected to freshly voided urinary cytology with 100 ml of random urine samples on three consecutive days. A well mixed sample of urine (12 ml) was centrifuged in a centrifuge tube for 5 min at 1500 rpm and supernatant was poured off. The tube was tapped at the bottom to resuspend the sediment in 0.5 ml of urine. One drop of this sediment was placed on a glass slide and smear was made, which was fixed and stained with Pap stain. Another drop was placed on a separate slide and stained with Leishmann-Geimsa stain. The slides were examined immediately under the microscope using first the low power and then the high power objective. Malignant transitional cells were seen having pleomorphic hyperchromatic nuclei, high nucleus: cytoplasmic ratio and moderate amount of cytoplasm. Imaging of the KUB region in the form of ultrasonographic study was done in all cases prior to cystoscopy. CECT/IVU was done as and when indicated. Ultrasonography was performed with Logiq P5 with an electronic curved array transducer available in the radiology department. Patients were asked to present with a full bladder. Ultrasound examination of the KUB region was performed on all patients. The bladder was imaged with transverse and longitudinal scans with the patient in the supine position. Scanning was performed both pre and post micturition.

This was followed by cystoscopy with transurethral resection of lesions, if found and their histopathological examination. The bladder was evacuated before cystoscopy. Under local anaesthesia with the patient in lithotomy position, after proper cleaning and draping, a Karl Storz 19 Fr rigid cystoscope with 30° lens was introduced with prophylactic antibiotic cover and the entire urinary bladder was inspected systematically. The tumor(s) if found was mapped diagrammatically over the data collection sheet. If tumor was found on cystoscopy or in patients with tumor visible during ultrasonography, transurethral resection of bladder tumor was done under spinal anaesthesia (under general anaesthesia, if growth was on lateral bladder wall to avoid obturator jerk during surgery). A 26 Fr continuous flow rotating sheath resectoscope was used and the tumor was completely resected, proper haemostasis was done and resected tissue was sent for histopathological examination. Finally examination under anaesthesia was done again for clinical staging. A 3-way Foley's catheter (22Fr) was placed per urethrally and irrigation with normal saline was started if hematuria was present.

The results were compared with the inferences drawn from cystoscopy and histopathological examination of the resected tumor, wherever applicable. Histologically confirmed urothelial carcinoma was graded according to WHO/ISUP consensus classification [10]. The findings were analyzed in terms of sensitivity, specificity, positive predictive value and negative predictive value of voided urine cytology and imaging in the diagnosis of Carcinoma Bladder with respect to grade keeping cystoscopy as the gold standard. The results were collected, evaluated, calculated, tabulated and statistically ana-

Table 1 Demographic data and clinical characteristics of patients.

Mean age (min–max)	48.1 (21–82)
Gender	
Male	56 (93.33%)
Female	04 (6. 66%)
Indication for evaluation	
Painless hematuria	48 (80%)
Check cystoscopy	12 (20%)
Karnofsky performance score	
90–100	53 (88.33%)
80–90	07 (11.67%)
Mean BMI (min–max)	19.77 (18.22–25.46)
Abdominal lump	
Present	01 (1.67%)
Absent	59 (98.33%)

Table 2 Comparison of imaging with cystoscopy.

n = 60	Cystoscopy positive	Cystoscopy negative	Total
Imaging positive	20	02	22
Imaging negative	10	28	38
Total	30	30	60

Table 3 Comparison of voided urine cytology with cystoscopy.

	Cystoscopy positive	Cystoscopy negative	Total
Voided urine cytology positive	04	00	04
Voided urine cytology negative	26	30	56
Total	30	30	60

Table 4 Comparison of imaging versus voided urine cytology.

	Imaging	Voided urine cytology
Sensitivity (%)	66.67 (CI 54.74%–78.6%)	13.33 (CI 4.73%–21.93%)
Specificity (%)	93.33 (CI 87.02%–99.64%)	100 (CI 100%)
PPV (%)	90.91 (CI 83.64%–98.18%)	100 (CI 100%)
NPV (%)	73.68 (CI 62.54%–84.82%)	53.57 (CI 40.95%–66.19%)

Table 5 Imaging and urinary cytology in diagnosis of bladder tumor as per histological grade.

Total no. of patients in whom biopsy done (30)	Low grade (19)	High grade (11)
Imaging positive	10	10
Imaging negative	9	01
Voided urinary cytology positive	00	04
Voided urinary cytology negative	19	07

Table 6 Grade wise comparison of sensitivity of imaging and voided urine cytology.

Grade	Sensitivity	
	Low grade	High grade
Imaging	52.63%	90.91%
Voided urinary cytology	0%	36.36%

lyzed using a Chi-square test. P value less than 0.05 was considered significant.

Results

Sixty (60) patients of Carcinoma urinary bladder, both freshly detected and those on follow-up were included in the study. The mean age of the patients was 48.1 years ± 16.05 years with a range of 21–82 years. Table 1 shows demographic and clinical characteristics of the patients.

Out of the 60 cases enrolled in the study, 30 were found to have no growth on cystoscopy. The remaining 30 patients were found to have bladder growth on cystoscopy for which they underwent transurethral resection followed by histopathological examination of the resected tissue. Out of these 30 cases, 19 patients had low grade urothelial carcinoma and 11 patients had high grade tumor.

All 60 patients included in the study underwent imaging of the KUB region in the form of ultrasonographic study. It was positive in 22 cases and negative in 38 cases. Few patients also underwent CECT KUB region or IVU as per the indications (Tables 2–6).

Voided urine cytology was done in all 60 cases. It was negative in 56 cases. It was positive in 4 cases. Out of the 56 cases which were negative on cytology, 26 were subsequently found to have bladder cancer on histopathological examination. All 4 cases found positive on cytology were confirmed to have bladder cancer on histopathological examination.

Using McNemar Chi-square test, McNemar Chi-squared statistic with Yates correction of 1.0 was 24.038462 with corresponding p-value being 0.000001, which implies that the difference between the sensitivity and specificity of imaging and urinary cytology is statistically significant ($p < 0.05$).

The differences between sensitivity, specificity and positive predictive value of imaging and voided urinary cytology were statistically significant, as reflected by the non overlap of the 95% confidence intervals, whereas the difference between negative predictive values was not statistically significant.

Out of 60 patients, biopsy was done in 30 cases as the rest of the cases had no visible growth on cystoscopy. 19 patients had low grade papillary urothelial neoplasm and 11 patients had high grade neoplasm. Among 19 patients with low grade cancers, imaging was positive in 10 cases as compared to voided urine cytology which was not positive in any case. In 11 high grade cancer patients, imaging was positive in 10 cases where as voided urine cytology was positive in 4 cases only.

Discussion

A total of 60 cases were included in this study. Mean age of patients was 50 years, commensurate with it being common in middle aged and elderly people.

The distribution of patients according to gender revealed that only 23.33% patients under study were female, thus reflecting the male-to-female ratio of bladder cancer prevalence being nearly 3:1 and the disparities in case reporting and loss of patients to attrition due to lack of awareness about the disease.

The overall sensitivity of voided urinary cytology was found to be 13.33%. The factors affecting the sensitivity of urinary cytology include specimen quality, number of exfoliated cells, and pathologist's expertise. Also inflammatory conditions of the bladder can confound the results, so patients with inflammatory conditions of bladder were excluded from the study.

On the other hand, imaging had a sensitivity of 66.67% which was significantly higher than that of cytology. This is in accordance with previous observations that ultrasonography has not proven itself as an accurate tool for detecting small flat tumors and CIS [11,12]. However, transabdominal ultrasonography is a simple and inexpensive imaging modality. It is not associated with contrast administration and its risks viz allergic reaction or nephropathy. Factors affecting the diagnosis of bladder tumor on ultrasound include the operator's skill, amount of abdominal fat and bladder distension during procedure. So, ultrasonography may prove a useful adjunct to cystoscopy as a screening test for bladder tumor. We recommend transabdominal ultrasound as the initial investigation for detecting bladder carcinoma in patients presenting with painless hematuria and for followup of bladder carcinoma patients.

The overall specificity of urine cytology was 100% and was found to be higher than that of imaging (93.33%). Most studies have similarly reported very high specificity of urinary cytology [12–18]. However, the specificity of ultrasonography as the basic imaging modality in this study was also found to be comparable to that of cytology.

The positive predictive value of urine cytology was found to be 100%, significantly higher compared to PPV of imaging (90.91%). All patients who had positive urinary cytology for malignant cells were positive for bladder tumor on imaging. The negative predictive value of urinary cytology in the present study was 53.57% and was lower than that of imaging (73.68%). However, the difference between the NPV of both tests was not statistically significant, as evident by overlapping of 95% confidence intervals of NPV of both tests.

The positive likelihood ratio of imaging was calculated to be 10 whereas the positive likelihood ratio of urinary cytology was found to be infinity. So, if either imaging or urinary cytology would be reported as positive, there would be very high likelihood of bladder tumor evident on cystoscopy (LR+ > 10). So if malignant cells are seen in a patient's urine, there is almost 100% possibility of bladder tumor being present and the patient may directly be taken for cystoscopy and transurethral resection of bladder tumor. Patients diagnosed to have bladder carcinoma on ultrasound should be further evaluated promptly with cystoscopy and histopathological examination of the resected tumor.

The negative likelihood ratio of imaging was calculated to be 0.357 whereas the negative likelihood ratio of urinary cytology was found to be 0.867. So if imaging would be negative, there would be small decrease in likelihood of bladder tumor being found on cystoscopy (LR− 0.2–0.5), while if voided urinary cytology was negative in a patient, there would be minimal decrease in likelihood of bladder tumor being found on cystoscopy (LR− 0.5–1.0).

On grade wise evaluation, the sensitivity of imaging was lower for low grade tumors (52.63%) as compared to high grade tumors (90.91%).

Voided urine cytology had a sensitivity of 0% in case of low grade tumors and sensitivity of 36.36% for high grade tumors. There are two main reasons for such low sensitivity [19]. First, tumor cells of the low grade tumors are not routinely shed into the urine because of their cohesive nature. Second, and probably more important, is the fact that low grade tumor cells by definition have similar cytomorphology to normal urothelial cells microscopically [19]. The sensitivity of voided urine cytology is too low to justify its continuing use in evaluation of bladder carcinoma, especially low grade. Cytology may still be used because of its higher sensitivity in detecting high grade tumors and carcinoma in-situ.

Various studies have shown that the sensitivity of voided urine cytology is particularly low for low grade and is around 80% for high grade tumors. Overall sensitivities reported for urinary cytology are in the order of 7–65% [12–17,20].

Conclusions

1. Voided urinary cytology can be omitted as a screening test owing to its very low sensitivity (13.33%), high cost and requirement of pathological facilities.
2. Ultrasonography as an imaging modality can be recommended as the initial investigation for detection of bladder carcinoma in patients presenting with hematuria and for followup of bladder carcinoma patients.
3. Patients suspected to be suffering from bladder carcinoma by urinary cytology (in cases where it is performed) and by imaging should be scheduled directly and promptly for cystoscopy and bladder tumor resection, based on their high specificity (93.33% and 100%, respectively).
4. Imaging is significantly more sensitive compared with cytology in both low and high grade tumors, although imaging cannot be relied upon in low grade tumors.
5. Cystoscopy cannot be replaced even by dynamic transabdominal ultrasonography in the diagnosis or followup of patients with bladder tumors.

Authors' contributions

The contributions of the authors are as follows:

1. Conception and design of the study: Naveen Kumar, Raghav Talwar.
2. Collection of data: Naveen Kumar, Raghav Talwar, PR Nandy.
3. Drafting: Naveen Kumar, PR Nandy.
4. Revision of the manuscript: Naveen Kumar, Raghav Talwar, PR Nandy.

Conflict of interest

The authors declare that this study was conducted as part of mandatory thesis for award of degree of Master of Surgery by WBUHS Kolkata to Naveen Kumar.

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