

# Detection of Urological malignancies using urine cytology as a basic diagnostic tool – A study on 54 patients

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## ABSTRACT

**Background:** Bladder cancer is the fourth most common cancer in men and the tenth most common cancer in women. There are approximately 50,000 new cases and 10,000 deaths from urothelial carcinoma each year. Cigarette smoking is believed to contribute to upto 50% of the diagnosed urothelial cancers in men and 40% in women. Bladder tumors classically produce painless hematuria. The importance of urinary cytology in the detection and follow up of patients with urothelial carcinoma has become well established in recent years. Individuals with a positive cytology but a negative evaluation have a higher risk of developing macroscopic lesions.

**Aim of the Study:** The present study aims to detect atypical cells/urological malignancies using urinary cytology as a basic diagnostic tool and also classifying lesions using five-category cytological classification

**Materials and Methods:** A total of 54 cases were included in this study. 67 Urine samples from all the 54 cases were categorized on the basis of the guidelines of the "Five-category cytological classification". The cases were identified on the basis of clinical features i.e hematuria, frequency, urgency, dysuria or past history of bladder tumor. The criteria for inclusion in our study was either a positive urine cytology with a subsequent positive / negative biopsy or positive / negative urine cytology followed by a subsequent biopsy, positive for malignancy.

**Results:** A total of 67 urine samples were received from 54 patients. Majority i.e 94% of the specimens were voided urine samples. 67 Urine samples from all the 54 cases were categorized on the basis of the guidelines of the "Five-category cytological classification". Out of 67 urine specimens from 54 patients, 16 were categorized as Negative (Neg) and 51 were categorized as positive for atypical or suspicious cells.

## Conclusion:

Urinary cytology is the first simple, easy and non-invasive method with good overall median specificity of 99% and acceptable overall median sensitivity of 34% (20-53%) to detect bladder cancer.

## Keywords:

Urine Cytology, Atypical Cells, Urological Malignancy, Smoking, Hematuria Low Grade Lesions , High Grade Lesions.

## INTRODUCTION

There are approximately 50,000 new cases and 10,000 deaths from urothelial carcinoma in each year in United States<sup>1,2</sup>. The risk of developing a urothelial malignancy in male smokers is increased two- to fourfold relative to nonsmokers and continues for 10 years or longer after cessation. Other causes include industrial exposure to arylamines particularly 2-Naphthylamine as well as related compounds, schistosoma hematobium infections in areas where these are endemic (Egypt, Sudan) are an established risk, long term use of analgesics, heavy long term exposure to cyclophosphamide, an immunosuppressive agent, prior exposure of bladder to radiation, often performed for other pelvic malignancies, increases the risk of urothelial carcinoma<sup>3</sup>. Bladder tumors classically produce painless hematuria. This is their dominant and sometimes only classical manifestation<sup>3</sup>. Hematuria may be intermittent, so a urine analysis without RBCs does not exclude the diagnosis of urothelial cancer. In those with macroscopic hematuria the reported rates of bladder cancer range from 13- 34.5%<sup>4</sup>. The importance of urinary cytology in the detection and follow up of patients with urothelial carcinoma has become well established in recent years<sup>5,6,7, 8</sup>. Individuals with a positive cytology but a negative evaluation have a higher risk of developing macroscopic lesions within the following 3-12 month period.

## AIM OF THE STUDY

The present study aims to detect atypical cells/urological malignancies using urinary cytology as a basic diagnostic tool and also classifying lesions using five-category cytological classification

## MATERIALS AND METHODS

A total of 54 cases were included in this study. 67 Urine samples from all the 54 cases were categorized on the basis of the guidelines of the "Five-category cytological classification". Types of specimens for urine cytology used were voided urine, catheterized urine, bladder wash, ureteral wash, renal pelvis wash. These pathological specimens were processed by various methods like direct smear method, filter preparation, cytocentrifuge, and cell block preparations.

## RESULTS

In our study, the age of the patients was in the range of 28-86 years with maximum patients in the age group of 61-70years. The mean age of presentation was 64.1years and median age was 66.5years. Out of total 54 cases, there were 6 females and 48 males with Male to Female ratio of 8:1. Male predominance was seen. Hematuria was the most common symptom present in 80 % of the cases, followed by frequency, dysuria, urgency and urinary retention. Majority i.e 94%of the specimens were voided urine samples. Out of 67 urine specimens from 54 patients, 16 (23.89) were categorized as Negative (Neg) and 51(76.11) were categorized as positive for atypical or suspicious cells. All the negative cytology specimens had a subsequent positive biopsy (Figure 1).

Among all the 67 urine cytology specimens, the number of specimens in each category was as follows:

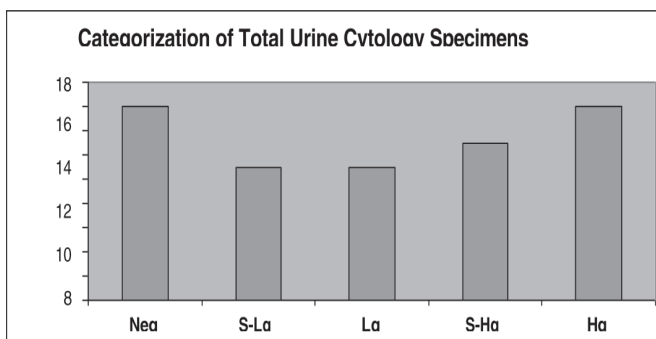


Figure 1: Categorisation of total urine cytology specimens

The following cytological features were noted in every urine specimen and were thus categorized according to the guidelines of the Five –category classification of cytological diagnosis (Table 1).

**Table 1: Comparison of the cytological features of urines with high grade and low grade atypia**

CYTOLOGICAL FEATURE	LOW GRADE ATYPIA(S-Lg & Lg)	HIGH GRADE ATYPIA(S-Hg & Hg)
Cellularity		
Low	7	9
Moderate	11	8
High	4	12
Nuclear atypia		
Present	15	29
Absent	7	0
Cellular discohesion		
Present	9	22
Absent	13	7
Borders of cell clusters		
Regular	13	0
Papillaroid	2	3
Ragged	7	26(24+2acinar)
Nuclear overlapping		
Absent	20	15
Present	2	14
Nuclear overlapping		
Absent	20	15
Present	2	14
N:C Ratio		
High	14	28
Not increased	8	1
Nuclear hyperchromasia		
Present	12	26
Absent	10	3
Nuclear membrane		
Regular	12	1
Irregular	10	28
Thickened	0	0
Nucleolus		
Inconspicuous	20	16
Prominent	2	13

In our study, the overall sensitivity of cytology for detection of bladder tumour was 75%, while sensitivity of cytology for detecting low grade and high grade lesions of bladder was 44% and 74% respectively. The frequencies of cytological diagnosis was compared against the reference standard, overall sensitivity ranged from 37% to 81% and specificity from 95% to 99%. For all thresholds of cytological diagnosis, sensitivity increased with the grade of non-invasive papillary urothelial tumors and was the highest for carcinoma in-situ (CIS) and invasive carcinoma.

In our study, out of the 51 positive suspicious of malignancy or atypical cells, there were 20 cases of high grade lesions with ages ranging 52-86 years with maximum patients in the age group of 51-60 years. Mean age of presentation was 64.8yrs. Out of 20 patients with high grade lesions, 2 were females and 18 were males (**Table 2**). Male to female ratio for high grade lesions was 10:1, in our study. Out of the 29 cases of low grade lesions in our study, 2 were females. So, in our study, Male to Female ratio for low grade lesions was 13.5:1.

The ages of 29 cases of low grade lesions ranged from 28-85 years with maximum patients in the age group of 61-70 years. Mean age of presentation was 64.8 yrs. Youngest patient in our study was 28 years of age with Low grade papillary urothelial neoplasm. 3 out of 54 patients were less than 40 yrs of age and all had low grade lesions on biopsy. Out of 29 cases, 27 cases were males , 2 cases were females (**Table 3**).

Out of the 51 positive cytology specimens, 11 were categorized as Suspicious of low grade cellular atypia (S-Lg), 11 were categorized as Consistent with low grade cellular atypia (Lg), 13 as Suspicious of high grade cellular atypia (S-Hg) and 16 as Consistent with high grade cellular atypia (Hg).

**Table 2:-Sex distribution for high grade lesions**

SEX	No.of Patients	Percentage
Males	18	90%
Females	2	10%
Total	20	100%

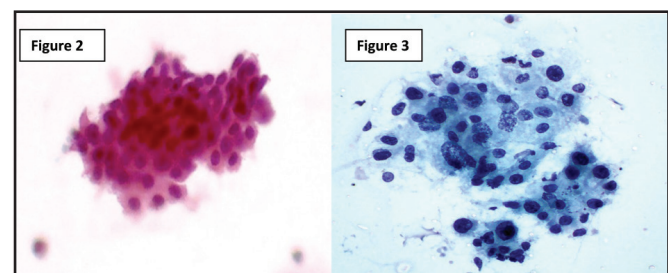
**Table 3:-Sex distribution for high grade lesions**

SEX	No.of Patients	Percentage
Males	27	93.1%
Females	2	6.9%
Total	29	100%

Radiology was done in 51 of all the 54 cases, and the findings on radiology were broadly categorized as follows, radiology showing echogenic content or hypo echoic lesion in 6 cases, growth in 34 and mural thickening in 4cases. In 7 cases no obvious abnormality was detected on radiology (Table 4). The sensitivity of radiology was found to be 86% and specificity 33%.

**Table 4:- Categorization of Radiology findings**

Categorization Of Radiology Findings	No.of Cases	%
No Abnormality Detected (NAD)	7	13.7%
Echogenic content or Hypoechoic Lesion	6	11.8%
Growth	34	66.7%
Mural thickening	4	7.8%
TOTAL CASES	51	100%



**Figure 2:-** H & E Stain showing low grade cytological atypia of the urothelial cells with ragged borders [x40]

**Figure 3:-** Giemsa Stain showing High grade cytological atypia of the urothelial cells [x40]

## DISCUSSION

Urine is a liquid by-product of the body secreted by the kidneys through a process called urination. Average urine production in adult humans is around 1.8 liters of urine per person per day with a normal range of 0.6 to 2.6 liter per person per day, produced in around 6 to 8 urinations per day depending on the state of hydration, activity level, environmental factors, weight, and the individual's health. Producing too much or too little urine needs medical attention. About 90 to 95 % of urine consists of water. Urine also contains an assortment of inorganic salts and organic compounds, including proteins, hormones, and a wide range of metabolites, varying by what is introduced into the body. Normal urine contains little cellular material with cells usually single in voided urine. The three cell types of urothelium seen in normal urine are a) Superficial umbrella cells b) Intermediate pyramidal cells

c) Cuboidal cells which are present adjacent to the basement membrane may be present. In women urine samples may contain large number of squamous cell contaminants from the vagina. Urine in males may contain spermatozoa and seminal vesicle cells. In addition, there may be some atypical cells which should raise suspicion of malignancy of the urinary tract.

The earliest mention of urine cytology for the diagnosis of bladder cancer is Sander's report of finding neoplastic tissue in urine in 1864. The results of cytological examination of urinary sediment for the diagnosis of urinary tract carcinomas were later published by Papinacolaou in 1945 and is now established as a part of routine investigation of the patients with Hematuria, prostatism and suspected urinary tract neoplasia<sup>9</sup>.

Urinary cytology is the first non-invasive method with good overall median specificity of 99% (83 – 100%) and acceptable overall median sensitivity of 34% (20-53%) to detect bladder cancer reported in a comprehensive literature review and meta-analysis. The importance of urinary cytology in the detection and followup of patients with urothelial carcinoma has become well established in recent years. Individuals with a positive cytology but a negative evaluation have a higher risk of developing macroscopic lesions within the following 3-12 month period. Patients with transitional cell carcinoma of bladder are at risk of concurrent or subsequent cancer of upper tract.

In our study, hematuria was the most common symptom and was present in 43(80%) patients. Other symptoms that were present were frequency in 16(30%) patients, dysuria in 13(24%) patients, urgency in 9(17%) patients, and urinary retention in 3(6%) patients. Our findings are consistent with the findings of Zingbo zhang et al, where he found that hematuria is the most common symptom leading to the detection of bladder cancer in over 80% of the patients. Similar findings were found in the study by Shahrokh E. Shariat et al where it was found that most of the patients with urinary bladder carcinoma are diagnosed based on gross or microscopic hematuria. In another study by Khadra et al<sup>10</sup>, where 1194 patients with hematuria were evaluated and 12% were found to have bladder cancer.

In our study, the overall sensitivity of cytology for detection of bladder tumour was 75%, while sensitivity of cytology for detecting low grade and high grade lesions of bladder was 44% and 74% respectively. The specificity for both was 78%. A similar study that supports our study was conducted by C Garbar et al<sup>11</sup> between 2002 and 2004, 592 bladder washings were obtained using a flexible cystoscope

from 139 patients. For each sample reference standard was histology when a lesion was present at the time of cystoscopy. The frequencies of cytological diagnosis was compared against the reference standard, overall sensitivity ranged from 37% to 81% and specificity from 95% to 99%. For all thresholds of cytological diagnosis, sensitivity increased with the grade of non-invasive papillary urothelial tumors and was the highest for Carcinoma In-Situ (CIS) and invasive carcinoma. Ramkumar et al studied voided urine specimens from 196 patients undergoing cystoscopy and found the overall sensitivity of urine cytology to be 44%<sup>12</sup>.

In our study, out of 67 urine specimens from 54 patients, 16 were categorized as negative (Neg) and 51 were categorized as positive for atypical or suspicious cells. All the negative cytology specimens had a subsequent positive biopsy, because the criteria for inclusion in our study was either a positive urine cytology with a subsequent positive or negative biopsy or positive or negative urine cytology followed by positive subsequent biopsy.

Radiology assessment was done on 51 out of 54 patients, in our study. Radiology showed echogenic content or hypoechoic lesion in 6 cases, growth in 34 and mural thickening in 4. In 7 cases no obvious abnormality was detected on radiology. The sensitivity of radiology was found to be 86% and specificity 33%. In the study by Cheryl A. Sadow et al<sup>13</sup>, the overall sensitivity and specificity for bladder cancer detection were 79% and 94% for CT urography. Sensitivity and positive predictive value of MR Imaging for detecting bladder tumors is >90%. Sonographic detection of bladder tumors depends on the size and location of the neoplasm. Bladder tumors < 0.5 cm in size and tumors located in bladder neck or dome areas are difficult to detect. On the other hand, diagnostic accuracy may approach 95% for tumors >0.5cm in size, situated on posterior or lateral walls of the bladder.

## CONCLUSION

Urinary cytology is the first simple, easy and non-invasive method with good overall median specificity of 99% and acceptable overall median sensitivity of 34% (20-53%) to detect bladder cancer. The cases with clinical features of hematuria, frequency, urgency, and dysuria, history of exposure to various types of dye material or past history of bladder tumor are to be seen more stringently. All the urine cytology negative cases with suspicion of malignant lesions on radiology are to be kept under follow up as there is a chance of detection of the atypical cells in the urine cytology after a considerable gap.

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