



## Original Article

# Efficacy of Urine Cytology, Ultrasonography and Cystoscopy as a First Line Screening Test in Detection of Urinary Bladder Carcinoma

Authors

**Dr Nitin Negi<sup>1</sup>, Dr Namrata Aggarwal<sup>2</sup>, Dr Vijeta Tomar<sup>3\*</sup>**

<sup>1</sup>M.S.,MCh Urology, Sr. Consultant & Head, Metro Mas Hospital, Jaipur.

<sup>2</sup>MD Pathology, SMS medical college, Jaipur.

<sup>3</sup>MD, DNB Pathology, SMS medical college, Jaipur.

Department of Urology, Metro Mas Hospital, Jaipur

\*Corresponding Author

**Dr Vijeta Tomar**

## Abstract

**Introduction:** Urothelial carcinoma of the bladder is the 7<sup>th</sup> most common cancer presenting in majority of the patients as painless hematuria.

**Objectives:** To compare urine cytology, ultrasonography and cystoscopy as screening tests for bladder cancer. To recommend a diagnostic protocol that improves the overall sensitivity and specificity of detection of carcinoma bladder in patients.

**Subjects and Methods:** A prospective analysis of 165 patients with painless hematuria was done in at a urology centre in North India from June 2016 to April 2020. Patients were subjected to voided urine cytology, ultrasonography and cystoscopy. The results were compared with histopathological examination of the biopsy or resected tumor, whichever applicable considering it to be gold standard.

**Results:** The sensitivity of urine cytology, ultrasonography and cystoscopy was (30.8%), (63.1%) and (78.5%) respectively, whereas the specificity of urine cytology, ultrasonography and cystoscopy was (100%), (96%) and (97%), respectively. Urine cytology was found to have least sensitivity in low grade cases with only 10% cases being positive whereas ultrasonography and cystoscopy had a sensitivity of 60% and 77% respectively. Sensitivity for high grade carcinoma for urine cytology, ultrasonography and cystoscopy were 49%, 66% and 80% respectively.

**Conclusions:** Best technique amongst the three is cystoscopy. However, ultrasonography can be used as the initial investigation for patients presenting with hematuria. Voided urine cytology can be used along with these two owing to its high specificity. Therefore, to further increase the sensitivity and specificity, a combination of these diagnostic modalities may be considered.

**Keywords:** Urine cytology, ultrasonography (USG), cystoscopy, bladder carcinoma.

## Introduction

Urothelial carcinoma (UC) of the bladder is the 7<sup>th</sup> most common cancer.<sup>1</sup> Seventy-five percent of patients present with either noninvasive disease or invasion limited to the lamina propria, whereas 20% and 5% present with invasive and metastatic

disease, respectively. Carcinoma of the bladder affects men more than women at a ratio of 3 to 4:1. This difference is probably accounted by differences in smoking habits and occupational exposure in the two sexes.<sup>2</sup> Approximately 90% of malignant bladder tumors are transitional cell

carcinomas (TCC). The remaining 10% comprise all other types of carcinoma, a small number of sarcomas, and miscellaneous tumors.<sup>2,3,4</sup> Typically, bladder carcinoma patients present with hematuria.<sup>5</sup> The combination of urinary cytology and cystoscopy are currently accepted procedures for the diagnosis and follow up of bladder tumors and urinary tract malignancies.<sup>6-9</sup> Urine cytology has been used for a long time because of its merits such as easy availability and noninvasive testing, high sensitivity, and specificity for high-grade urothelial carcinoma (HGUC), and great effectiveness to evaluate the entire urothelial tract. With urine cytology, the high-grade malignant cells can be identified even in occult carcinoma that is not visible cystoscopically. However its sensitivity is very low for low grade urinary neoplasm.<sup>10</sup> The sensitivity of urine cytology ranges from 10 to 43.6 % for low grade to 50–85 % for HGUC; and specificity ranges from 26.3 to 88 %, depending on the type of urine sample collection and type of clinical presentation.<sup>11,12</sup>

The aim of our study was to evaluate the efficacy of voided urine cytology, USG and cystoscopy in the diagnosis of bladder cancer and to devise a protocol for improving the overall sensitivity and specificity of detection of patients with bladder cancer.

### Material and Methods

In our study, a retrospective and prospective analysis of patients of bladder cancer was done at a urology centre in north India from June 2016 to April 2020. A total of 165 patients suspected of bladder cancer were evaluated after obtaining their informed written consent. Of all the suspected cases of bladder carcinoma, 165 cases were selected where urine cytology, ultrasonography, and cystoscopy as well as bladder biopsy were available. If any of the three procedures was not done, the case was not included. Bladder biopsy was considered as the gold standard for final confirmation of diagnosis.

Detailed history of the patients was taken in a structured proforma to note the indication for

which patient was being evaluated for Carcinoma Bladder. Any past or concomitant co morbidity was noted. Detailed clinical examination including vitals were recorded. Abdomen was examined thoroughly for abnormalities like lump, tenderness, oedema etc. with special reference to suprapubic region.

All the suspected patients for bladder carcinoma were subjected to freshly voided urinary cytology with 100 ml of random urine samples on three consecutive days. A well mixed sample of urine (10-12 ml) was centrifuged in a centrifuge tube for 5 min at 1500 rpm and supernatant was discarded. 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 H&E stain. Atleast 3-4 slides per sample were prepared. The slides were then examined under the microscope by an expert pathologist for presence of malignant cells. Malignant transitional cells were seen as having high N:C ratio, hyperchromatism, prominent nucleoli, irregular nuclear outline, pleomorphism and moderate amount of cytoplasm.

USG was done in all cases prior to cystoscopy. Both pre and post micturition scans were taken. This was followed by cystoscopy with transurethral resection of lesions and their histopathological examination. The bladder was evacuated before cystoscopy. The results were compared with the histopathological examination of the resected tumor. The findings were analyzed in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy of voided urine cytology, USG and cystoscopy in the diagnosis of Carcinoma Bladder with respect to histopathological diagnosis as the gold standard.

### Results

A total of 165 patients suspected of Carcinoma urinary bladder were included in the study. The mean age of the patients was 58.5 years with a range of 35–82 years. Out of 165 suspected cases

of bladder carcinoma who presented with hematuria only 65 cases were having bladder carcinoma. Rest 100 cases were diagnosed as either inflammatory pathology, hyperplasia or reactive atypia. Only 5 cases were seen in females out of 65 cases, thereby giving a male:female ratio of 8:1.

In the 65 cases, urine cytology was positive in 20 cases, USG in 41 cases and cystoscopy in 51 cases (Table 1). Out of these 65 positive cases, 30 patients had low grade urothelial carcinoma and 35 patients had high grade tumor. Urine cytology was positive in 3 low grade urothelial carcinoma and 17 high grade urothelial carcinoma. USG was positive in 18 low grade and 23 high grade tumors. Whereas, cystoscopy was positive in 23 low grade and 28 high grade tumors. (Tables 2,3).

**Table 1** Diagnostic yield of cystoscopy, urine cytology and ultrasonography (USG).

	CYTOSCOPY	UC	USG
TP*	51	20	41
TN‡	97	100	96
FP†	3	0	4
FN‡‡	14	45	24

\* = True positive; ‡ = True negative; † = False positive; ‡‡ = False negative; UC = urine cytology, USG = Ultrasonography

**Table 2.** Comparison of cystoscopy, urine cytology and ultrasonography (USG).

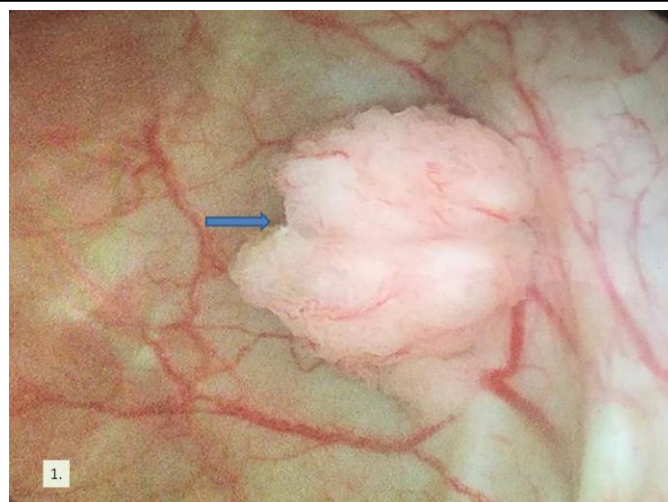
STATISTICS	CYTOSCOPY	UC	USG
SENSITIVITY	78.50%	30.80%	63.10%
SPECIFICITY	97%	100%	96%
PPV <sup>v</sup>	94.40%	100%	91%
NPV <sup>†</sup>	87.40%	69%	80%
ACCURACY	89.70%	72.70%	83%

<sup>v</sup> = Positive predictive value, <sup>†</sup> = Negative predictive value, UC = urine cytology, USG = Ultrasonography

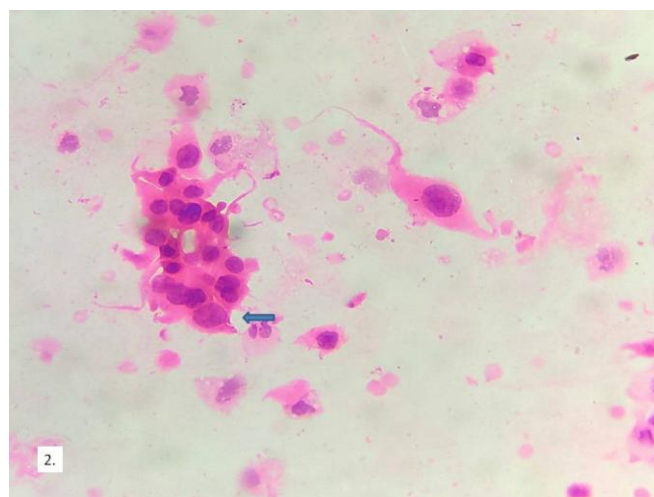
**Table 3** Diagnostic yield and comparison of cystoscopy, USG and urine cytology in diagnosing bladder tumor as per histological grade.

Test Modality	Low Grade Tumor (30)	Sensitivity	High Grade Tumor (35)	Sensitivity
Cytoscopy	23	77%	28	80%
USG	18	60%	23	66%
UC	3	10%	17	49%
USG+UC	18	60%	27	77%
USG+Cystoscopy	28	93%	33	94%
UC+Cystoscopy	23	77%	31	89%
USG+UC+Cystoscopy	28	93%	34	97%

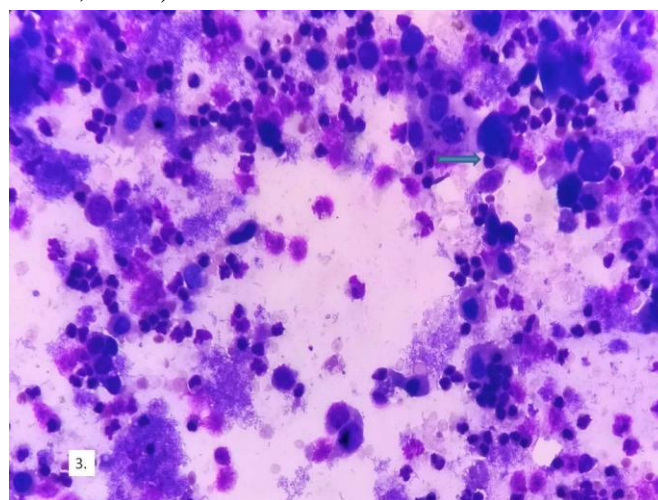
UC = urine cytology, USG = Ultrasonography



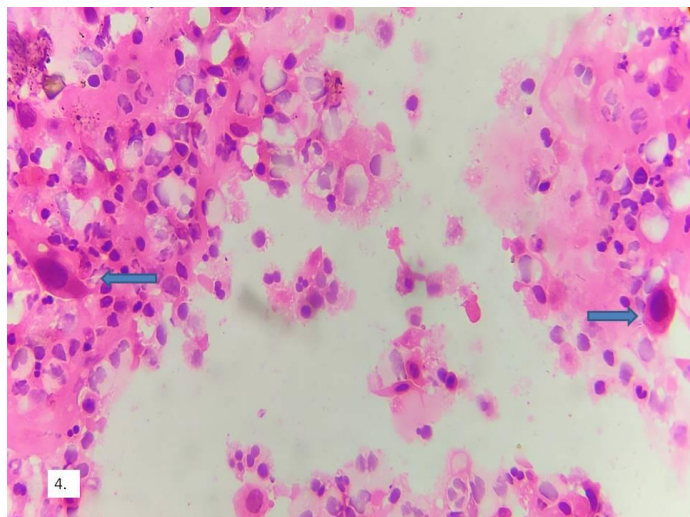
**Figure 1.** Cystoscopy revealing a vascular exophytic polypoid growth on urinary bladder wall



**Figure 2.** Voided urine cytology of urinary bladder tumor showing pleomorphic and hyperchromatic cells in sheets (Hematoxylin and Eosin, 400x).



**Figure 3.** Urine cyto-centrifuge smear showing malignant cells with high N:C ratio, irregular nuclear outline (Giemsa, 400x).



**Figure 4.** Urine cytocentrifuge smear showing few malignant cells in an inflammatory background. (Hematoxylin and Eosin, 400 $\times$ ).

### Discussion

A total of 165 cases were included in this study. Mean age of patients was 58.5 years. The male-to-female ratio of bladder cancer prevalence was 8:1 and the disparities may be due to lack of awareness about the disease and difference in smoking habits.

The overall sensitivity of voided urine cytology was found to be 31%. The factors affecting the sensitivity of urinary cytology include specimen quality, number of exfoliated cells, and pathologist's expertise. On the other hand, USG had a sensitivity of 63% which was significantly higher than that of cytology. Factors affecting the diagnosis of bladder tumor on USG include the operator's skill, amount of abdominal fat and bladder distension during procedure. Cystoscopy was found to have highest sensitivity of 79%.

The overall specificity of urine cytology USG and cystoscopy was 100%, 96% and 97%. Most studies have similarly reported very high specificity of urinary cytology.<sup>12-16</sup>

The positive predictive value of urine cytology, USG and cystoscopy was found to be 100%, 91% and 94.40% respectively. The negative predictive value of urine cytology, USG and cystoscopy 69%, 80% and 87.40% respectively. The accuracy for urine cytology, USG and cystoscopy was

found to be 72.70%, 83% and 89.70% respectively.

On grade wise evaluation, the sensitivity of urine cytology, USG and cystoscopy was lower for low grade tumors as compared to high grade tumors. Urine cytology was found to have lowest sensitivity of just 10%, USG 60% and cystoscopy 77%. For high grade tumour, sensitivity of urine cytology, USG and cystoscopy was 49%, 66% and 80% respectively.

The sensitivity of voided urine cytology is too low to use it as solo investigation technique in screening 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 and high specificity.

### Conclusions

Voided urine cytology is not suggested as a solo screening test owing to its low sensitivity (31%). However it can be used in combination with USG or cystoscopy due to its high specificity especially in high grade tumors. USG can be recommended as initial investigation for detection of bladder carcinoma in patients presenting with hematuria as it is non invasive and cheaper than cystoscopy. However, cystoscopy remains best technique amongst three with highest sensitivity in both low and high grade tumors.

### Acknowledgement

We would like to thank the management and staff of department of Urology, Metro MAS Hospital, Jaipur for helping and guiding us through this work.

**Financial Support and Sponsorship:** Nil

**Conflicts of Interest:** There are no conflicts of interest

### References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9-29.
2. Sternberg, page 1837, 5<sup>th</sup> ed

3. Cohen SM, Johansson SL. Epidemiology and etiology of bladder cancer. *Urol Clin North Am* 1992;19:421.
4. Johansson SL, Cohen SM. Epidemiology and etiology of bladder cancer. *Semin Surg Oncol* 1997;13:291.
5. Raghavan D, Shipley WU, Garnick MB, Russell PJ, Richie JP. Biology and management of bladder cancer. *N Engl J Med.* 1990;322:1129–38.
6. Tostain J, Laurent JL, Pasteur X, Crochet J, Hugonnier G, Gilloz A. Cytology in the detection and followup of urothelial tumors. Critical review of 500 cytologic investigations (authors transl). *J Urol (Paris)* 1982;88:91-6.
7. Lewis RW, Jackson AC Jr, Murphy WM, Leblanc GA, Meehan WL. Cytology in the diagnosis and followup of transitional cell carcinoma of the urothelium: A review with a case series. *J Urol* 1976;116:43-6.
8. Brown FM. Urine cytology. It is still the gold standard for screening? *Urol Clin North Am* 2000;27:25-37.
9. Rathert P. Urinary cytology in cases of bladder cancer: A critical evaluation. *Urologe A* 2003;42:908-11.
10. Dorothy L. Rosenthal. High-Grade Urothelial Carcinoma (HGUC). In: Dorothy L. Rosenthal, Eva M. Wojcik and Daniel F. I. Kurtycz, editors. *The Paris system for reporting urinary cytology*. 1<sup>st</sup> ed. Switzerland: springer;2016. p. 61.
11. Sauter G, Algaba F, Amin MB, Busch C, Cheville J, Gasser T, et al. Noninvasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, editors. *World Health Organization classification of tumours. Pathology and genetics of tumors of the urinary system and male genital organs*. Lyon: IARCC; 2004. p. 110–23.
12. Renshaw AA, Nappi D, Weinberg DS. Cytology of grade 1 papillary transitional cell carcinoma. A comparison of cytologic, architectural and morphometric criteria in cystoscopically obtained urine. *Acta Cytol.* 1996;40:676–82.
13. Helenius M and Brekkan et al. Bladder cancer detection in patients with gross haematuria: Computed tomography urography with enhancement-triggered scan versus flexible cystoscopy. *Scandinavian journal of urology.* 2015; 49: 377-381.
14. Kelen L. Gandrup and Vibeke B. Logager et al. Diagnosis of bladder tumours in patients with macroscopic haematuria: A prospective comparison of split-bolus computed tomography urography, magnetic resonance urography and flexible cystoscopy. *Scandinavian journal of urology.* 2015; 49: 224-249.
15. G Nabi, D Greene, M O Donnel. Suspicious urinary cytology with negative evaluation for malignancy in the diagnostic investigation of haematuria: how to follow up? *J Clin Pathol.* 2004;57:365–368.
16. Nisman B and Yutkin et al. The follow-up of patients with non-muscle-invasive bladder cancer by urine cytology, abdominal ultrasound and urine CYFRA 21-1: a pilot study. *Anticancer Res.* 2009;29 :4281–5.