

Role of bladder washing cytology with fresh voided urine cytology in the diagnosis of urothelial malignancy

Rahat Sarfaraz¹, Muhammad Imran², Shahzada Khalid Sohail³, Tazeen Anis⁴, Fatima Rizvi⁵

¹Associate Professor, Department of Pathology Fatima Jinnah Medical University, Lahore, ²Assistant Professor, Department of Pathology Allama Iqbal Medical College, Lahore, ³Assistant Professor, Department of Pathology Bisha Medical University, Saudi Arabia, ⁴Senior Demonstrator, Department of Pathology Allama Iqbal Medical College, Lahore, ⁵Assistant Professor, Department of Pathology Bisha Medical University, Saudi Arabia

Correspondence to: Dr Rahat Sarfaraz, Email: sahmad555@gmail.com

ABSTRACT

Background: Bladder cancer is one the most common lesion treated by urologists. Since decades cystoscopy has been the gold standard for the diagnosis of primary and recurrent urothelial cancers. Exfoliative urinary cytology of fresh voided urine and bladder washings is usually performed to preceding or to complement cystoscopy. This study aims to determine the role of exfoliative cytology of fresh voided urine and bladder washings in the diagnosis of primary and recurrent urothelial malignancy and to compare the diagnostic efficacy (sensitivity, specificity) of bladder washings cytology with voided urine cytology in the diagnosis of urothelial carcinoma.

Patients and methods: The study was performed in the department of Pathology, Allama Iqbal Medical College, Lahore in collaboration with the department of Urology, Jinnah Hospital, Lahore. Sixty patients of both genders above 45 years of age presenting with painless hematuria, imaging evidence of urinary bladder lesion or recurrent tumor were included. Fresh voided urine and bladder washings were obtained in all the cases and cytology was performed.

Results: The sensitivity of voided urine cytology was 94.7% and specificity 33.3% with positive predictive value of 96.4% and negative predictive value of 25%. The accuracy was calculated as 91.6%. The sensitivity, specificity, positive predictive value and negative predictive value for bladder washing cytology were 94.7%, 33.3%, 96.4% and 25% respectively. The accuracy for bladder washing cytology was the same as that of the fresh voided urine cytology (91.6%).

Conclusion: Fresh voided urine cytology in patients with painless hematuria is a noninvasive, cost effective and readily available tests to detect the presence of any malignancy before further invasive work up. The fresh voided urine cytology and bladder washing cytology revealed same sensitivity, specificity and predictive values so noninvasive cytology of fresh voided urine may be recommended over bladder washing cytology which is an invasive procedure. Urine cytology is useful in differentiating high grade urothelial carcinoma but it's difficult to diagnose low grade urothelial tumor if superadded infection or any reactive atypia is present. It can be reported as suggestive or suspicious for low grade malignancy if the clinical history and radiologic investigations support a vesicle growth.

Keywords:

Bladder washing, fresh voided urine, urothelial malignancy, cytology

INTRODUCTION

Bladder cancer (BC) is among the top nine most frequent cancers.^{1,2} Despite improvements in detection and management of these neoplasms, the death toll remains high. Morbidity and mortality may be prevented with early detection of new tumors and vigilant surveillance for recurrence.¹ About 95% of bladder tumors are of epithelial origin, the remainder being mesenchymal in origin. Majority of epithelial tumors are composed of urothelial (transitional) type cells and are thus interchangeably called urothelial or transitional cell tumors. However squamous and

glandular carcinomas may also occur.² BC is diagnosed on the basis of clinical features, cystoscopy examination and laboratory investigations, which includes exfoliative cytology of urine and bladder washings followed usually by the cystoscopic biopsy. Exfoliative cytology has a role especially in follow up cases and recurrent urothelial tumors.³ Cystoscopy has been accepted as the 'gold standard' for the diagnosis of primary and recurrent urothelial cancers. Even with the flexible instruments, the process remains invasive and bothersome to the patient. The diagnostic modality of exfoliative urinary cytology of fresh voided urine or bladder washings are routinely performed to complement cystoscopy. This modality can detect even the precancerous lesions in the urinary bladder months to years before the cancer would ordinarily be visible

Competing interest: The authors have declared no competing interests exist.

Citation: Sarfaraz R, Imran M, Sohail SK, Anis T, Rizvi F. Role of bladder washing cytology with fresh voided urine cytology in the diagnosis of urothelial malignancy. J Fatima Jinnah Med Univ 2018; 12(4):137-141.

cystoscopically.⁴ Exfoliative cytology is highly effective in picking up carcinoma-in-situ even when cystoscopic examination fails to reveal a lesion. In certain cases, the prostate gland, prostatic urethra, and endoscopically apparently normal areas of bladder epithelium may be found to harbor neoplastic foci. Therefore, urinary cytology is usually performed to complement cystoscopy.⁵ The diagnostic output of urinary cytology depends on the appropriate specimen collection and handling, adequacy of the specimen, grade and volume of the tumor. It also varies with the training and expertise of the cytopathologist and as in all morphological evaluations, it has high inter- and intra-observer variation.⁶ This study aims to determine the sensitivity, specificity, positive predictive value and negative predictive value of exfoliative cytology of fresh voided urine and bladder washings in diagnosis of primary and recurrent urothelial malignancy and to compare the diagnostic accuracy (sensitivity, specificity) of bladder washings cytology with voided urine cytology in diagnosis of urothelial carcinoma.

PATIENTS AND METHODS

It was prospective study over the period of six months. Pathology and urology department collaborated with each other. Sixty clinically and radiologically suspected cases of urothelial malignancy were included. Patients above 45 years of age from both genders, patients having macroscopic hematuria, patients having imaging evidence of urinary bladder lesion and patients with recurrent tumor were included. Patients with long term indwelling urinary catheter, patients with history of urolithiasis and patients with clinical and/or laboratory confirmed urinary tract infection were excluded. Respect of humanity was observed. Written consent was procured from the patients before the invasive procedure on the consent form. The urine and bladder washing samples were collected observing sterile

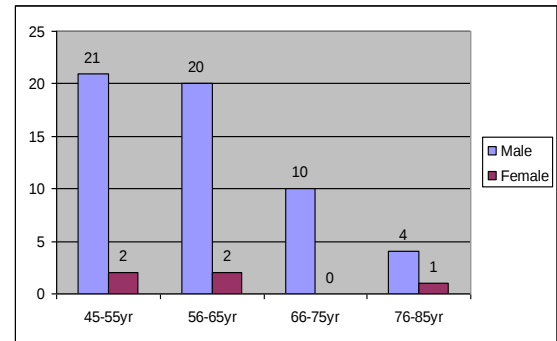


Figure 1. Bar graph showing age groups and gender distribution.

standards and sent for cytology. The samples of voided urine and bladder washings were received fresh in the pathology laboratory. Both the samples were obtained in the urology ward and immediately transported to the pathology laboratory within 15 minutes. The volume of urine obtained was 2-3ml and the volume of bladder washings was 4-5 ml. Both samples were grossly examined, and findings were noted. Both samples were then centrifuged at 2000 revolutions per minutes for 5 minutes. The supernatant was discarded. Smears were prepared on glass slides from the deposit obtained after centrifugation. Minimum of four slides were prepared from each sample. Two of these slides were air dried for Giemsa stain and two fixed in ethanol for Haematoxylin and Eosin staining. The x10 objective lens was used to note the cellularity and cytological features of the smears. Cells were then examined under high power objective to confirm the findings. The smears were reported as: 1. Negative for malignant cells, 2. Suspicious for low grade urothelial carcinoma, 3. Positive for high grade urothelial carcinoma. The criteria used to differentiate between low and high grade urothelial and reactive atypia of exfoliated urothelial cells is depicted in Table 1.

Table 1. Differential diagnosis between reactive, low-grade and high- grade transitional cell carcinoma

Features	Reactive	Low grade TCC	High grade TCC
Groups	Pseudopapillae	Papillae; loose or crowded clusters	Loose clusters / syncytia / single
Cells	Enlarged, pleomorphic, variable in number	Enlarged, relatively uniform, often numerous, but fewer than in high-grade TCC	Enlarged, pleomorphic, usually numerous
N/C Ratio	Normal / Increased	Increased (slight to moderate)	Increased (moderate to marked)
Nucleus	Central, uniform	Eccentric, enlarged, variable	Eccentric, pleomorphic
Nuclear membrane	Smooth, "thick"	Slightly irregular, thin	Moderately to markedly irregular, thin
Chromatin	Fine, even	Granular, even	Coarse, dark, irregular
Nucleoli	Often large	Small to none	Macronucleoli, many cells
Cytoplasm	Vacuolated	Homogeneous	Often vacuolated; also squamous, glandular
Background	Inflamed or clean	Clean	Diasthesis

(Ref: The Art & Science of Cytopathology / Richard DeMay, 1996, Vol I: Exfoliative Cytology, pg:403).

Table 2. Histological evaluation of biopsy (total number. of cases positive for malignancy=57)

Grade of tumor		Architectural pattern		
High grade	Low grade	Exophytic	Flat	Nested
31 (54.3%)	26 (45.6%)	53 (92.9%)	3 (5.2%)	1 (1.7%)

Table 3. Cross tabulation between voided urine cytology and tissue biopsy

Urine cytology	Positive Biopsy	Negative Biopsy	Total
Positive urine cytology	54	2	56
Negative urine cytology	3	1	4
Total	57	3	60

RESULTS

The results of exfoliative cytology of fresh voided urine and the bladder washings were compared. Age of the patients in the present study ranged from 50 to 81 years. The mean age was 61 years. There were 55 males (91.7%) and 5 females (8.3%) amongst the total of 60 patients included in the present study (Figure 1). The male to female ratio was 4:1 for the study population.

Out of the 57 cases with positive cytology, 31(51.7%) were reported as “high grade urothelial tumor”. The remaining 26 (43.3%) were categorized into “suspicious for low grade urothelial carcinoma” (Table 3 and 4). In thirty cases which were reported as high grade urothelial carcinoma, the cytological smears revealed high cellularity with groups of neoplastic cells and individually scattered tumor cells (Figure 2)

The biopsy samples were processed and examined using ISUP system of tumor classification was used which categorizes the tumors into high and low grade urothelial carcinomas. Fifty seven (95%) cases were positive for urothelial tumor, with 31(51.7%) being graded as high grade, 26(43.3%) as low grade urothelial carcinoma. No tumor was detected in 3 (5.0%) cases (Table 2). Out of these, one case was negative for malignancy on cytology smears also. Two cases were cytologically categorized as suspicious for low grade malignancy. These two cases were negative on tissue biopsy for any tumor; however they were diagnosed as chronic cystitis which could account for atypia in the cytology smears (Figure 3).

DISCUSSION

Cytological examination of urinary specimens is increasingly recognized as an essential component of detection and monitoring for patients with bladder neoplasms. Among the available techniques, urinary cytology is reported as the most useful diagnostic modality. The present study evaluated the diagnostic efficacy of urinary exfoliative cytology for the diagnosis of urothelial cancer comparing the sensitivity and specificity of voided urine and bladder washings

cytology, taking cystoscopic biopsy findings as the gold standard.⁷

Urinary cytology is the basic adjunct to cystoscopy and transurethral resection in the diagnosis of urothelial carcinomas of the bladder. Both voided urine cytology and bladder washings cytology are practiced as useful diagnostic modalities. Several workers have evaluated the sensitivity and specificity values of these procedures for diagnosis of bladder cancer. Many of the studies were based on the urinary cytology obtained from bladder washings.⁸

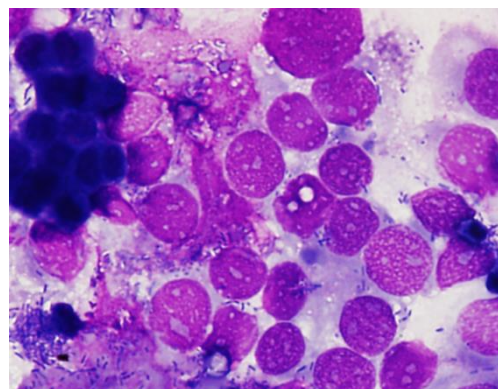


Figure 2: Cytology smear of fresh voided urine showing neoplastic urothelial cells. The cells are mostly discohesive and reveal highly pleomorphic nuclei (Magnification at 40x)

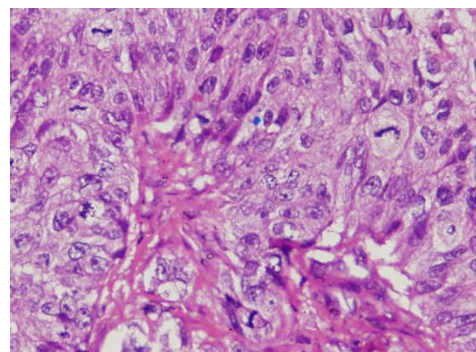


Figure 3. Histology slide from a biopsy specimen from bladder growth showing high grade urothelial carcinoma. The cells are reveal highly pleomorphic nuclei and are arranged in closed papillary pattern with

delicate central fibrovascular core. Atypical mitotic figures are also visible. (Magnification at 40x)

Table 4. Cross tabulation between bladder washing cytology and tissue biopsy

Bladder washing cytology	Positive biopsy	Negative biopsy	Total
Positive bladder washing cytology	54	2	56
Negative bladder washing cytology	3	1	4
Total	57	3	60

Planz and coworkers studied the role of voided urine and bladder washing cytology in the diagnosis of bladder cancer. The sensitivity and specificity of fresh voided urine cytology was reported as 38.0% and 98.3% with a positive and negative predictive value of 90.6 and 78.6 respectively. Authors reported no significant difference between sensitivity and specificity of voided urine and bladder washing samples which is concurrent with the results in the present study as well.⁹ On the contrary, one of the earlier studies reported the superiority of bladder washings over voided urine cytology and recommended its routine use despite its additional cost and associated patient discomfort. Supporting this report, Misra and colleagues reported a higher sensitivity, specificity and overall diagnostic accuracy of bladder washings compared to voided urine cytology (71.05%, 65.0%, and 78.85% vs. 47.37%, 41.18% and 61.54%).¹⁰ Nevertheless in most of the studies the sensitivity for urinary cytology is reported to be much lower compared to its specificity. Bhujan and coauthors reported the sensitivity of urine cytology to be 62%.¹¹ In another study comparing the screening methods in the detection of bladder cancer the sensitivity of urine cytology was reported as 44%.¹² Schroeder and colleagues reported in their study the sensitivity and specificity of urine cytology as 70.6% and 81% respectively; the accuracy, and negative and positive predictive values were 77.2%, 82.5% and 68.6% respectively.¹³ On the other hand, some of the workers produced results on the contrary, reporting a higher sensitivity values compared to the specificity. In

another screening study the statistical diagnostic values of the bladder washing cytology at the time of cystoscopic workup were: sensitivity 77%, specificity 31%, positive predictive value 13% and negative predictive value 91%.¹⁴ The specificity in this study is close to specificity of voided urine and bladder washing cytology calculated in the present study population (33%). Significant variation in the reported values for accuracy of urinary cytology have been observed in reports from different parts of the world. Spanish study revealed sensitivity and specificity of urine cytology to be 97%, and 96-100% respectively.¹⁵ Tables 5 and 6 present comparison of fresh voided urine cytology and bladder washing cytology results of previous studies with present study. Such high variations could reflect expertise of the interpreting cytopathologist.

The results of sensitivity and specificity of voided urine and bladder washing cytology present study are comparable to one of the previous reports.⁹ Although bladder washing cytology alone has a greater diagnostic yield than voided urine cytology alone, voided urine remains a valuable source of diagnostic information and should be evaluated, even when simultaneously collected bladder washings are available.¹⁶ Voided urine can be easily obtained on outpatient basis and thus is ideal for screening or follow up of bladder carcinoma.¹⁷ In bladder washing cytology, nuclear changes and cytoplasmic homogeneity are evaluated for diagnosis of carcinoma.¹⁸ Urinary cytology is extremely valuable for the diagnosis of high grade transitional cell cancers (TCC) and for carcinomas in situ and is

Table 5. Comparison of efficacy of voided urine cytology with previous studies

Study reference (year)	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Misra (2000)	80	47.37	41.18			61.54
Bhuiyan (2003)		62				
Schroeder (2004)	92	70.6	81	68.6	82.5	77.2
Planz (2005)	495	38.0	98.3	90.6	78.6	
Garcia Castro (2008)	109	97	96-100			
Present study (2010)	60	94.7	33.3	96.4	25	91.6

Table 6. Comparison of efficacy of bladder washing cytology with previous studies

Study reference (year)	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Misra (2000)	80	71.05	56.0			78.85
Planz (2005)	495	38.0	98.3	90.6	78.6	

Present study (2010)	60	94.7	33.3	96.4	25	91.6
----------------------	----	------	------	------	----	------

considered indispensable in the management of patients with BC.¹⁹ Pathologic examination of urinary specimens is increasingly recognized as an essential component of detection and monitoring for patients with bladder neoplasms. Among the available techniques, urinary cytology is the most useful.²⁰ Urinary cytology is currently an essential procedure for monitoring all patients with urothelial neoplasms and, if consistently used, can actually decrease the frequency with which patients need to be subjected to cystoscopy.²¹ The most useful type of urinary specimen for routine diagnostic interpretation is freshly voided, randomly collected sample. Bladder washings may yield more and betterpreserved cells. However, considering the invasiveness and similar sensitivities, these maneuvers can not be recommended for routine screening over the voided urine sample, excepts perhaps in follow up of patients with known BC for early detection of recurrence. Urine cytology is useful in differentiating high grade urothelial carcinoma but it's difficult to diagnose low grade urothelial tumor if superadded infection or any reactive atypia is present. It can be reported as suggestive or suspicious for low grade malignancy if the clinical history and radiologic investigations supports a vesicle growth.

CONCLUSION

Fresh voided urine cytology in patients with painless hematuria is one of the noninvasive, cost effective and readily available tests to detect the presence of any malignancy before further invasive work up. The fresh voided urine cytology and bladder washing cytology revealed nearly same sensitivity, specificity and predictive values so we recommend non-invasive urine cytology over bladder washing cytology which is an invasive procedure.

REFERENCES

- Rafieemaneh H, Lotfi Z, Bakhtazad S, Ghoncheh M, Salehiniya H. The epidemiological and histological trend of bladder cancer in Iran. *J Can Res Ther* 2018;14(3):532.
- Mendiratta P, Grivas P. Emerging biomarkers and targeted therapies in urothelial carcinoma. *Ann Transl Med* 2018;6(12):250.
- Tan WS, Tan WP, Tan M-Y, Khetrpal P, Dong L, Feber A, et al. Novel urinary biomarkers for the detection of bladder cancer: A systematic review. *Cancer Treat Rev* 2018;69:39-52.
- Zhang ML, Zhou AG, Rosenthal DL, VandenBussche CJ. Urinary tract washing specimens containing atypical urothelial tissue fragments are significantly associated with urothelial neoplasia. *Diagn Cytopathol* 2017;45(9):795-9.
- Zhang ML, Rosenthal DL, VandenBussche CJ. The cytomorphological features of low-grade urothelial neoplasms vary by specimen type. *Cancer Cytopathol* 2016;124(8):552-64.
- Onur I, Rosenthal DL, VandenBussche CJ. Atypical urothelial tissue fragments in noninstrumented voided urine specimens are associated with low but significantly higher rates of urothelial neoplasia than benign-appearing urothelial tissue fragments. *Cancer Cytopathol* 2015;123(3):186-92.
- Thiriyai S, Rana D. Urine cytopathology: challenges, pitfalls, and mimics. *Diagn Cytopathol* 2012;40(11):1019-34.
- Keller AK, Jensen JB. Voided urine versus bladder washing cytology for detection of urothelial carcinoma: which is better? *Scand J Urol Nephrol* 2017;51(4):290-2.
- Planz B, Jochims e, deix T, caspers HP, Jakse G, Boecking A. The role of urinary cytology for detection of bladder cancer. *Eur J Surg Oncol* 2005;31(3):304-8.
- Misra V, Gupta SC, Tandon SP, Gupta AK, Sircar S. Cytohistological study of urinary bladder neoplasms. *Indian J Pathol Microbiol* 2000;43(3):303-9.
- Bhuiyan J, Akhtar J, O'kane DJ. Performance characteristics of multiple urinary tumor markers and sample collection techniques in the detection of transitional cell carcinoma of the bladder. *Clin Chim Acta* 2003; 331(1-2):69-77.
- Ramakumar S, Bhuiyan J, Besse JA, Roberts SG, Wollen PC, Blute ML, et al. Comparison of screening methods in the detection of bladder cancer. *J Urol* 199;161(2):388-94.
- Schroeder GL, Lorenzo-Gomez MF, Hautmann SH, Fredrich MG, Ekici S, Huland H, et al. A side by side comparison of cytology and biomarkers for bladder cancer detection. *J Urol* 2004; 172(3):1123-6.
- Konety BR, Metro MJ, Melham MF, Salup RR. Diagnostic value of voided urine and bladder barbotage cytology in detecting transitional cell carcinoma of the urinary tract. *Urol Int* 1999; 62(1):26-30.
- Garcia castro M, Fernandez Fernandez E, Martin Corriente MC, Garcia Hernandez S, Alvarez – Arguelles CH. [Usefulness of urine cytology for bladder carcinoma diagnosis: comparative study with biopsy]. *Actas Urol Esp* 2008;32(9):904-7.
- Murphy WM, Crabtree WN, Jukkola AF, Soloway MS. The diagnostic value of urine versus bladder washing in patients with bladder cancer. *J Urol* 1981;126(3):320-2.
- Brown FM. Urine cytology. Is it still gold standard for screening? *Urol Clin North Am* 2000;27(1):25-37.
- Chu YC, Han JY, Han HS, Kim JM, Suh JK. Cytologic evaluation of low grade transitional cell carcinoma and instrument artifact in bladder washings. *Acta Cytol* 2002;46(2):341-8.
- Rathert P. [Urinary cytology in cases of bladder cancer: a critical evaluation]. *Urologe A* 2003 Jul;42(7):908-11.
- Zwarthoff EC. Detection of tumors of the urinary tract in voided urine. *Scand J Urol Nephrol Suppl* 2008;(218):147-53.
- Macleod LC, Pham KN, Agoff SN, Dahl KL, Pritchett TR, Corman JM. Cytologic persistence of malignant cells after transurethral resection of bladder tumors: Implications for concomitant manipulation of the urinary tract at the time of endoscopic resection. *Cancer Cytopathol* 2017;125(2):114-9.
- DeMay RM. The Art & Science of Cytopathology. Volume I, Exfoliative Cytology: American Society for Clinical Pathology 1996. p. 403.