Efficacy of Voided Urine Cytology Compared to Cystoscopic Findings in the Detection of Bladder Cancer- A Pakistani Perspective

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ABSTRACT

Objective: To compare the efficacy of voided urine cytology with findings of cystoscopy and histopathology of biopsy specimens in the diagnosis of bladder cancer.

Study Design: Comparative cross-sectional study

Place and Duration of Study: Armed forces Institute of Urology (AFIU), Rawalpindi Pakistan from Jan 2019 to Jan 2020.

Methodology: All patients presenting to the urology clinic with complaints of haematuria, visible and non-visible, and any radiologic evidence of bladder growth were included in the study after informed consent. Urine cytology was performed for all patients, followed by cystoscopy under anaesthesia, transurethral resection was conducted, and biopsy was taken where needed.

Results: 170 patients were included in the study134 (78.8%) were males, while 36 (21.2%) were females. The mean age was 54 ± 9.47 years (range 36 to 73 years). The overall sensitivity of voided urine cytology was 46.7%, while specificity was 79.2%. The positive predictive value was 85.1%, and the negative predictive value was 36.9%.

Conclusion: Bladder cancer is a disease which demands an early diagnosis, prompt treatment, and long-term follow-up. Cystoscopy remains the gold standard for this purpose; urine cytology can be used as a supplement as it is non-invasive, more specific and cost-effective.

Keywords: Bladder carcinoma, Diagnosis, Transitional cell, Urine cytology.

INTRODUCTION

Carcinoma of the bladder has been documented to be the 9th most common cancer worldwide and the 13th most common factor leading to deaths worldwide. According to the American Cancer Society data, bladder cancer accounted for 7% of cancer cases in 2013.[1] Unfortunately, the incidence rate is growing faster in underdeveloped countries, most likely due to the increased exposure to occupational carcinogens secondary to industrialization. In addition, the incidence is higher in men, nearly 3 to 4 times as compared to women; however, it has been found that when diagnosed in female patients, bladder cancer is usually a more aggressive disease due to unknown reasons.[2]

The most common histopathology encountered is transitional cell cancer (TCC); almost up to 90%, about 5% of cases have squamous cell carcinoma, and adenocarcinoma is found in less than 2%. The most common form of TCC is non-muscle invasive bladder cancer (NMIBC), formerly known as superficial cancer, about 70% to 85%.[3] These are the patients who are going to have prolonged treatment, require repeated follow-up, and would need multiple cystoscopies and biopsies. Therefore because of the need for lifelong monitoring and follow-up, a test is needed which would be reproducible, minimally invasive and cost-effective. Cystoscopy and biopsy have been the gold standard to detect bladder cancer and monitor its recurrence but are invasive and expansive.[4] In order to make this follow-up hassle-free and cost-effective, there has been a constant struggle over the years, leading to a better understanding and reporting of urine cytology, development of various tumour markers and improvement in endourologic surgery.[5,6]

Urine cytology is inexpensive and easy to perform, but there has been documented variability in the specificity and sensitivity. The median specificity has been reported by Van Rhjin *et al.*[7] in their review of the literature to be 94%, which was the highest as compared to other tumour markers. However, the sensitivity is lower, 48%, as seen in the review. Cytology is beneficial in the case of high-grade tumours, and positive predictive value increases in the case of high-grade tumours.

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The problem with cytology reporting occurs mostly due to the inadequacy of cellular components in the specimen, which may be due to cellular degeneration prior to fixation. The Paris system (TPS) of classification was introduced to minimize the chances of error and better understand histopathological diagnosis.[8] TPS has standardized the reporting system for urine cytology to make it universally acceptable; categories have been based on various cytopathologic criteria. One of the main aims of TPS was to clarify the poorly defined categories like atypia (atypical urothelial cells-AUC) and reduce reporting of this category as it led to inconclusive results. However, cystoscopy clarifies the category of AUC and suspicious of high-grade urothelial cancers-HGUC remains further clarified. In a comparative study, Vlajnic et al.[9] reported that multiprobe FISH could improve differentiation between those cases where atypia is doubtful.

Urine cytology can be performed on voided urine or a sample from bladder washings. A comparative study conducted by Sarfaraz et al.[10] found no significant difference between bladder washing cytology and voided urine cytology; however, the sensitivity was stated to be 94% which is quite high compared to international data.

The intent of conducting this study was to present findings of the local population compared to international statistics in diagnosing cases of bladder cancer using urine cytology with cystoscopy as the gold standard.

METHODOLOGY

This comparative cross-sectional study was conducted over one year, from January 2019 to January 2020, at the Armed Forces Institute of Urology (AFIU) Rawalpindi Pakistan. After the approval from the Ethical Review Board (ERB ref. number Uro-Adm-Trg-1/IRB/2020/102), patients were recruited through the non-probability convenience sampling, and informed consent was taken. The sample size was calculated in the light of literature by using the WHO sample size calculator calculated the sample size with a 95% confidence level, utilizing parameters from Sarfaraz et al. study.[10]

Inclusion Criteria: Patients of either gender presenting to the urology clinic with complaints of haematuria, visible, non-visible, and any radiologic evidence of bladder growth were included in the study.

Exclusion Criteria: Patients with known cases of urothelial cancer, history of the previously treated disease, treatment at present, or not giving consent were excluded from the study. In addition, the patients with urolithiasis, active urinary tract infection and indwelling catheters were also excluded.

For urine cytology, the mid-stream urine specimen was either obtained in the urology ward, transported to the laboratory within 15 to 30 minutes to prevent degeneration of cells and growth of bacteria; or was collected in the laboratory itself. The PARIS classification system was used to interpret cytology specimens and generate the report in collaboration with the Armed Forces Institute of Pathology (AFIP). All urine smears were classified as: 1) inadequate specimen, 2) Negative for high-grade urothelial carcinoma (HUGC), 3) Atypical urothelial cells, 4) Suspicious of High-Grade Urothelial Carcinoma; 5) High-grade urothelial carcinoma, 6) Low-grade urothelial carcinoma, 7) for others.[11]

All patients underwent rigid cystoscopy under general anaesthesia, and resection of bladder growth or biopsy of any suspicious area (if detected) was taken. Demographic details like age, gender, presence of hematuria, ultrasound and computerized tomography findings were documented. Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Specificity, sensitivity, and positive and negative predictive values were calculated.

RESULTS

170 patients were enrolled in the study. Out of 170 patients, 134 (78.8%) were males, while 36 (21.2%) were females (M:F ratio 3.7:1). The mean age was 54± 9.47 years (range 36-73 years). Table-I demonstrated the demographic and radiologic details. Most of the patients presented with painless visible haematuria.

Table-I: Demographic data and Radiological Findings (n=170)

Parameters		Age n (%)
Gender	Male	134 (78.8)
	Female	36 (21.2)
Hematuria	Visible	105 (61.8)
	Non-visible	65 (38.2)
Ultrasound Bladder Findings	Growth detected	132 (77.6)
	Growth not detected	38 (22.4)
Contrast Enhanced Computerized Tomography Findings	Upper tract growth detected	12 (7.0)
	Bladder growth detected	155 (91.2)
	Both detected	3 (1.8)

Out of 170 patients, urine cytology was found to be positive in 67 patients (39.4%). True positives were 57, while true negatives were 38 (Table-II). The overall sensitivity of voided urine cytology was 46.7%, while specificity was 79.2%. The positive predictive value was 85.1%, and the negative predictive value was 36.9%.

Table-II: Comparison of Urine Cytology with Cystoscopic Findings (n=170)

Urine Cytology	Cystoscopic Findings	
	Positive	**Negative**
Positive	57 (True positive)	10 (False positive)
Negative	65 (False negative)	38 (True negative)

Urine cytology was able to identify positive cases with HG TCC (high-grade transitional cell carcinoma), CIS (carcinoma in situ), and UTUC (upper tract urothelial carcinoma) with greater sensitivity of up to 72%. In comparison, for LG TCC (low-grade transitional cell carcinoma), sensitivity fell to 18% (Table-III).

Table-III: Comparison of Cytological findings with Cystoscopic Biopsy Report (n=170)

Cytology	Cystoscopic Biopsy Report				
	High grade Transitional Cell Carcinoma pTa/pT1	**Low grade Transitional Cell Carcinoma pTa**	**Negative for Malignancy**	**Carcinoma in Situ**	**Upper tract Urothelial Arcinoma**
Positive	42	11	0	6	8
Negative	11	49	38	2	3

The the likelihood ratio was calculated to be 94.79, with a p-value of less than 0.05. It was statistically significant in detecting true positives with urine cytology for high-grade cancers comparable to cystoscopic biopsy.

DISCUSSION

Carcinoma of the bladder is a commonly seen disease in our setup, the majority of patients present with complaints of painless, visible haematuria, which is the first alarming symptom. As observed in our study, the mean age at the time of diagnosis was 54 ± 9.47 years for both genders, and a similar mean age was also reported by Hussain et al.[11] However, internationally the documented mean age is 70 years. It has been noted that the incidence and disease-related mortality also increase with increasing age. Bladder cancer requires early detection and long-term follow-up and monitoring; urine cytology, cystoscopy, and other tumour markers have been employed for this purpose. The ideal test or tumour marker should be easier to interpret, readily available and cost-effective.[12,13] Unfortunately, tumour markers are not routinely employed for detecting bladder cancer, and

only clinical trials are present. Therefore, tests with 100% sensitivity and specificity do not currently exist.

Urologists have recognized urine cytology worldwide to be important in detecting and monitoring bladder cancer patients.[14] It is cost-effective, reproducible, and easily available at most centres. This study evaluated the efficacy of voided urine cytology in detecting a tumour in patients who presented with haematuria. We found that simple cytology was able to detect high-grade TCC with good sensitivity, it missed 11 cases of high grade, and it was able to detect CIS and upper tract TCC as well. However, poor sensitivity was observed for low-grade lesions. This observation was similar to other studies from around the world, like Zuiverloon et al.[4]

It has been observed that carcinoma of the bladder can progress from low-grade lesion to high grade, which is why close follow-up is crucial. Various tumour markers have been employed lately for managing carcinoma bladder: NMP22 and BTA stat are a few examples. When compared to cytology, these markers have higher sensitivity but lower specificity.[15] In 2017 Pichler et al.[16] carried out a study in which they compared NMP22 and urinary bladder cancer antigen with urine cytology; they reported a much lower sensitivity for both the tumour markers, but specificity was comparable to urine cytology (12.9% and 100% vs 25% and 100%). In 2017 a study published by Lotan et al.[17] also showed lower sensitivity for NMP22 compared to cytology.

Various authors have compared the tumour markers in combination with urine cytology; Todenhofer et al.[18] reported better sensitivity of cytology with FISH. However, the addition of NMP22-ELISA did not have any added effect. In our study, we found the specificity of cytology to be 79.1%. Although the tumour makers are more sensitive to the detection of tumours, the problem is their availability and cost, which makes their feasibility questionable in our setup. Therefore, the importance of adequate urine cytology must be highlighted, with the advantage of being easily available and reproducible with good specificity.[19] However, it should be noted that cytology has

to be supplemented with cystoscopy, flexible or rigid, for low-grade lesions. Low-grade TCC requires monitoring for fear of progression to high grade. As urine cytology has been reported in various studies to have poor sensitivity for low-grade cancer, cystoscopy is an important component of follow-up Etuk *et al.*[20] In our particular group of patients, we found the sensitivity to be less than 20%, less malignant cells observed on the smears.

Over time, repeated rigid cystoscopy can be replaced with flexible cystoscopy under local anaesthesia. Blue light cystoscopy is associated with a significantly higher detection rate of carcinoma in situ compared to white light Daneshmand *et al.*[14] Therefore, many authors have recommended the use of office-based blue light flexible cystoscopy on follow up which reduces the burden of operating rooms.

In 2018, in a systematic review and meta-analysis, Dong *et al.*[21] found the effectiveness of urine fibronectin as a promising non-invasive biomarker for carcinoma bladder detection. The continued search for a reliable and cost-effective marker has been the main aim of many researchers.

In 2017, Buekers *et al.*[22] considered the role of FGFR3, TERT and OTX1 as a urinary biomarker combination for surveillance of patients with bladder cancer in a large prospective multicenter study. Indeed tumour markers and urine cytology are minimally invasive; cystoscopy and biopsy remain the gold standard for detection and follow-up of bladder cancer.[23]

Because carcinoma bladder needs lifetime surveillance and follow-up, managing recurrent tumours, and the cost associated with complications, it has a significant economic burden.[24] Newer tumour markers are more sensitive but are not recommended for routine use in clinical practice; these markers to date are costly compared to urine cytology, which makes urine cytology when performed adequately, a suitable test for diagnosis and follow-up along with cystoscopy.

CONCLUSION

Our study demonstrates good specificity and adequate sensitivity for urine cytology in detecting bladder cancer. Although cystoscopy remains the gold standard for this purpose, a non-invasive, more specific and cost-effective urine cytology can be used as an adjunct to cystoscopy.

Conflict of Intrerest: None.

Author's Contribution

SK: Data collection, article writing, ZIM: Proof reading, HA: Data analysis,

BM: Proof reading, statistical analysis, MY:, KS: Final manuscript.

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