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Original Research Article

Evaluation of bladder washings cytology in diagnosis of neoplasms of urinary bladder

Sonia Chhabra[1], Gourav Tehri[1], Niti Dalal[1,*], Hemant Kamal[2], Monika Gupta[1], Rajeev Sen[1]

[1]*Dept. of Pathology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India*
[2]*Dept. of Urology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India*

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ABSTRACT

Context: Urinary cytology functions as the primary screening and surveillance modality for the detection of urothelial neoplasia.
Aims: To determine the significance of urinary bladder wash cytology in predicting various grades of urothelial carcinoma of urinary bladder along with their histological confirmation.
Materials and Methods: The prospective study was conducted in Department of Pathology, PGIMS, Rohtak. A total of thirty-one urinary bladder washing samples (processed by Conventional method, Cytospin and Liquid based cytology) were taken prior to biopsy from clinically suspected patients of urinary bladder neoplasm. The cytological examination of bladder washings was reported according to The Paris System for Reporting Urinary Cytology and Bladder biopsies were reported according to WHO/ISUP grading of Urothelial Tumors 2004.
Statistical analysis used: All the data were statistically analysed using SPSS version 20.0 software.
Results: There was no significant difference in diagnostic accuracy among three techniques of processing bladder washings. Correlations of cytological diagnosis on bladder wash specimens with histopathological diagnosis were statistically significant and shared good agreement.
Conclusions: A negative bladder wash cytology coupled with a negative cystoscopy is quite specific. A diagnosis of positive or suspicious bladder wash should be thoroughly investigated and followed closely. The Paris System is easy, reproducible, consistent ad has good histopathological correlation.

1. Introduction

Bladder cancer is most common malignancy of the urinary tract. The worldwide age standardized incidence rate is 8.9 per 1 lakh males and 2.2 per 1 lakh for females.[1]

Approximately 75% of bladder cancers are diagnosed as non-muscle invasive bladder cancer (NMIBC) and 30% are muscle invasive at the time of diagnosis. Correct histological grading and tumor staging is crucial for optimal patient management and to keep patients at high risk on surveillance for early detection of recurrence. The field of urology has undergone tremendous improvement over the years in the management protocol for patient care with cystoscopy being the gold standard for the detection of primary and recurrent bladder cancer.[2] Neoplastic urothelial cells were first recognized in urine in 1864; it was until 1945 that Papanicolaou and Marshall described the utility of urinary cytology in the diagnosis of urothelial malignancy.[3] An important principle of urinary cytology is that higher the grade of the tumour, more accurate the diagnosis.[4] Urinary cytology functions as the primary screening and surveillance modality for the detection

* *Corresponding author*.
E-mail address: drnitidalal@gmail.com (N. Dalal).

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of urothelial neoplasia. The bladder washing sample is obtained during or prior to cystoscopy which is an invasive diagnostic procedure for the macroscopic evaluation of the bladder mucosa. Bladder washing exfoliates large sheets of urothelium and even three-dimensional urothelial fragments. Therefore, bladder washing samples are highly cellular and contain well preserved cells.

Hence, we undertook this study to determine the significance of bladder wash cytology along with cystoscopic examination in predicting various grades of urothelial carcinoma of bladder along with histological confirmation.

2. Materials and Methods

The present prospective study was conducted in Department of Pathology in collaboration with Department of Urology, Pt. B. D. Sharma, PGIMS, Rohtak over a period of one year i.e. 2017- 2018. A total of thirty-one urinary bladder washing samples taken prior to biopsy from clinically suspected patients of bladder neoplasm constituted the material for our study.

All the bladder washing samples were processed by following techniques viz, Conventional method, Cytospin and Liquid based cytology (LBC). Bladder biopsy specimens from transurethral resection of bladder tumour (TURBT), were taken after bladder washings and tissue obtained was fixed and processed as per routine histopathological technique for paraffin embedded sections and haematoxylin and eosin staining were carried out as per standard procedure. Special stains were also used wherever necessary.

The bladder washing sample processed by various techniques were reported according to The Paris System for Reporting Urinary Cytology (TPS). Bladder biopsy was reported according to WHO/ISUP grading of Urothelial Tumors 2004. The cytological findings and histopathological diagnosis were correlated in cases of bladder carcinoma. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of various cytological techniques were calculated and correlated with histopathological diagnosis. Descriptive statistics was analyzed with SPSS version 20.0 software. For all statistical tests, a p value less than 0.05 was taken to indicate a significant value.

3. Results

In present case study, age of the patient ranged from 35-80 years.

The highest incidence was seen in the age groups of 41-50 and 61-70 years constituting

76.4% of total cases with a mean age of 57.03 years. Out of total 31 cases, 24 were males (77.4%) suggesting significant male preponderance. (Table 1)

Our study showed that out of total 31 cases, 13 cases (42%) were diagnosed as HGUC by conventional & cytospin method and 10 cases (33%) as HGUC by LBC as per The Paris System for Reporting Urinary Cytology. (Table 2) (Figure 1A,B,C).

Out of total cases maximum number of cases 16(59.3%) were diagnosed of high-grade urothelial carcinoma (Table 3) on histopathology. (Figure 1D) On comparing cytological diagnosis on conventional preparation with the histopathological diagnosis, it has a sensitivity of 85.2 % and specificity of 75% with a significant p value. The cytological diagnosis and histopathological diagnosis agree on 26 out of 31 cases having a diagnostic accuracy of 83.87%.(Table 4) On comparing cytological diagnosis on cytospin preparation with the histopathological diagnosis, it has a sensitivity of 81.5 % and specificity of 100% with a significant p value. The cytological diagnosis and histopathological diagnosis agree on 26 out of 31 cases having a diagnostic accuracy of 83.87%.(Table 5) On comparing cytological diagnosis on LBC preparation with the histopathological diagnosis, it has a sensitivity of 77.8 % and specificity of 100%. The cytological diagnosis and the histopathological diagnosis agree on 25 out of 31 cases having a diagnostic accuracy of 80.64% with a significant p value. (Table 6)

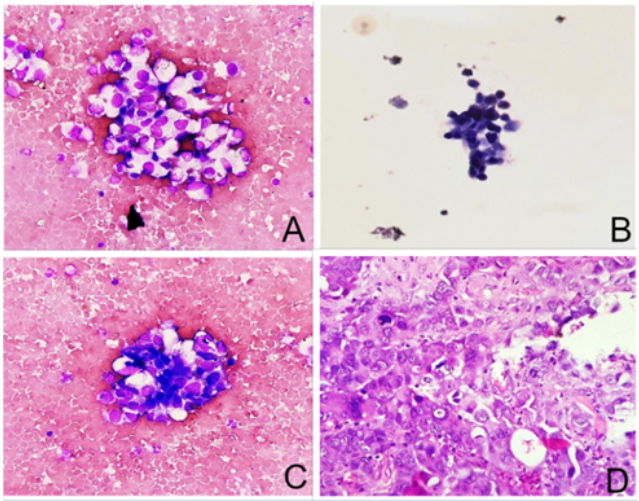

Fig. 1: A: HGUCshowing clear cell change (Conventional, Leishman, 400X); **B:** HGUC showing cluster of malignant cells (LBC, PAP, 400X); **C:** HGUC showing nuclear pleomorphism along with clear cell change(Cytospin, H&E, 400X); **D:** HGUC showing high N:C ratio, nuclearpleomorphism and atypical mitotic activity on bladder biopsy (H&E, 400X)

4. Discussion

As per the WHO reports, with increase in use of tobacco products and smoking there is increasing incidence of urinary bladder cancer in both males and females in the

Table 1: Distribution of cases according to age and sex (N=31)

Age (In Years)	Male	Female
31-40	3 (9.6%)	0 (0%)
41-50	6 (19.3%	4 (12.9%)
51-60	3 (9.6%)	1 (3.2%)
61-70	11 (35.4%)	1 (3.2%)
71-80	1 (3.2%)	1 (3.2%)
Total	24 (77.4%)	7 (22.5%)

Table 2: Distribution of casesas per the paris system of reporting urinary cytology on smears prepared byconventional, cytospin & LBC method (n=31)

Diagnostic categories	Number of cases by conventional method	Number of cases by cytospin method	Number of cases by LBC method
Non Diagnostic	4 (13%)	5 (16%)	8 (25%)
NHGUC	3 (10%)	4 (13%)	2 (6%)
AUC	5 (15%)	4 (13%)	6 (20%)
SHGUC	3 (10%)	4 (13%)	4 (13%)
HGUC	13 (42%)	13 (42%)	10 (33%)
LGUN	3 (10%)	1 (3%)	1 (3%)
Other	0	0	0

Table 3: Distribution ofhistopathological diagnosis of CASES (n=31)

Diagnostic categories	Number of cases	Percentage
Low grade urothelial carcinoma	11	40.70%
High grade urothelial carcinoma	16	59.30%

Table 4: Correlation ofcytological findings on conventional methods with histopathological diagnosis.

		HP Findings		Total
		Benign	Malignant	
Conventional	Benign Count	3	4	7
	Benign % within conventional	42.90%	57.10%	100%
	Benign % within HP findings	75%	14.80%	22.60%
	Malignant Count	1	23	24
	Malignant % within conventional	4.20%	95.80%	100%
	Malignant % within HP findings	25%	85.20%	77.40%
Total	Count	4	27	31
	% within conventional	12.90%	87.10%	100%
	% within HP findings	100%	100%	100%

Symmetric Measures

	Value	Asymp. Std. Errora	Approx. Tb	P value (significant if <0.05)	P value (significant if <0.05)
Measure of Agreement Kappa	0.456	0.199	2.687	0.007	0.028
N of Valid Cases	31				

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy	Kappa Statistics	P value
85.20%	75%	95.80%	42.90%	83.87%	0.456	0.028

Table 5: Correlation ofcytological findings on cytospin method with histopathological diagnosis.

			HP findings		Total
			Benign	Malignant	
Cytospin	Benign	Count	4	5	9
		% within Cytospin	44.40%	55.60%	100%
		% within HP Findings	100%	18.50%	29%
	Malignant	Count	0	22	22
		% within Cytospin	0%	100%	100%
		% within HP Findings	0%	81.50%	71%
Total		Count	4	27	31
		% within Cytospin	12.90%	87.10%	100%
		% within HP Findings	100%	100%	100%

Symmetric Measures

	Value	Asymp. Std. Errora	Approx. Tb	P value (significant if <0.05)	P value (significant if <0.05)
Measure of Agreement Kappa	0.532	0.169	3.351	0.001	0.004
N of Valid Cases	31				

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	Kappa statistics	P Value
81.50%	100%	######	44.40%	83.87%	0.532	0.004

Table 6: Correlation ofcytological diagnosis on liquid based cytology with histopathological diagnosis.

			HP Findings		Total
			Benign	Malignant	
LBC	Benign	Count	4	6	10
		% within LBC	40%	60%	100%
		% within HP findings	100%	22.20%	32.30%
	Malignant	Count	0	21	21
		% within LBC	0%	100%	100%
		% within HP findings	0%	77.80%	67.70%
Total		Count	4	27	31
		% within LBC	12.90%	87.10%	100%
		% within HP findings	100%	100%	100%

Symmetric Measures

	Value	Asymp. Std. Errora	Approx. Tb	P value (significant if <0.05)	P value (significant if <0.05)
Measure of Agreement Kappa	0.475	0.164	3.106	0.002	0.007
N of Valid Cases	31				

a. Not assuming the null hypothesis.

Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy	Kappa statistics	P value
77.80%	100%	100.00%	40.00%	80.65%	0.475	0.007

developing countries.[5] Although diagnosis of a bladder carcinoma may sometimes be suspected on ultrasound or computed tomography scan, it is to be confirmed by cystoscopic biopsy. The confirmatory diagnostic test for bladder cancer is cystoscopy followed by biopsy.

In our study, the highest incidence of bladder carcinoma was seen in 61-70 years (38.7%) with a mean age of 57.03 years. These findings are comparable to Pierconti et al[6] with maximum cases seen in 55-87 years, Abdullah et al[7] and Blick et al.[8] Mean age was higher in study by Blick et al (71 years)[8] and Pierconti et al (75 years).[6] Difference in mean age of our and other's study group may be due to variation in selection of the study group. Male patients constituted 77% of the study group with male: female ratio of 3:1. Our findings are concordant with Mikou et al, Siddappa et al, Freedman et al.[9–11] Over the years, there has been a widespread development in technological advancements in concentration techniques for better cellular preservation and to increase the yield of diagnostic urothelial cells in urinary specimens. Our study showed that maximum cases were diagnosed as HGUC by conventional method (42%), cytospin (42%) and LBC (33%) respectively as per various diagnostic categories of The Paris System for Reporting Urinary Cytology. The overall sensitivity of diagnosing HGUC on bladder washings samples by various techniques was 82%, 75%, 82%. These findings are comparable with Raab et al with 49.2% to 65%, Brimo et al with 46.3%, Yafi et al with 51% sensitivity for HGUC.[12–14]

In cytology, specimens of low grade papillary urothelial carcinoma do not display marked cytological atypia. Hence, cytology is more likely to pick up high grade urothelial carcinoma with cells showing marked atypia, mitosis and necrosis.

Several studies were conducted comparing the role of Liquid based cytology, cytospin and conventional methods and no significant differences in the sensitivity and specificity were observed. Though some studies have described LBC as superior technique with increased cellular morphology and cleaner background. In present study sensitivity of conventional, cytospin and Liquid based cytology is 85.2%, 81.5% and 77.80% and specificity is 75%, 100% and 100% respectively which is in agreement with the study done by Abdullah et al and Kim et al. Abdullah et al reported sensitivity of 66 - 77% and specificity of 97%.[8] Kim et al compared LBC and cytospin methods and found sensitivity of LBC and cytospin methods to be 60.9% and 59.9% respectively whereas specificity was 94.7% and 95.2%.[15] The better results in our study can be attributed to the usage of The Paris System of reporting urinary cytology.

Our study demonstrates that implementing The Paris System on bladder washings improved overall utility of bladder washings in diagnosing urothelial carcinoma with increased sensitivity and specificity of 77 - 85% and 75 - 100%, respectively. The diagnostic accuracy of urinary cytology is dependent on various factors resulting in wide contrast in results reported in literature. Thus, the use of The Paris System provided a common framework and ensured better diagnostic criteria for better clinical management by both urologists and pathologists by removing subject bias in reporting urinary cytology.

Our study exhibited good correlation between cytological diagnosis by all three methods and histopathological diagnosis which is evident by significant kappa and P value. The diagnostic accuracy of all three methods showed that there was no significant difference among three techniques. Thus, our study demonstrated statistically significant and positive correlation between conventional, cytospin, LBC and histopathological diagnosis in bladder carcinoma patients. The results in our study are in concordance with studies by Kim et al, Gregoire et al, Zein et al and Raab et al who signified sensitivity and specificity of bladder washings in diagnosing bladder carcinoma.[12,15–17] Kim et al compared sensitivity and specificity of bladder washings on LBC and cytospin.[16] Gregoire et al investigated diagnostic accuracy of urine cytology and bladder washings on conventional preparations during follow up of bladder tumors. During follow up for bladder tumor sensitivity and specificity of urine cytology was 59% and 85% respectively. Sensitivity was increased to 66% using bladder wash cytology whereas, specificity was slightly decreased to 83%.[16]

Zein et al suggested superiority of bladder washing over urinary cytology and this might be attributed to better preservation of cells, less contamination in the background, better preservation of bladder epithelium, more detail of the nucleus and the cytoplasm and immediate fixation.[17] Raab et al reported sensitivity for voided and instrumented lower tract urine specimens ranging from 8.9% to 33% for low grade lesions and from 49.2% to 65% for high grade lesions as well as specificity ranging from 85.7% to 89% when the atypical category was collapsed with the negative category.[12] As per the TPS in both equivocal categories, AUC and SHGUC, the atypia refers to the probability of HGUC. Of course, the prediction of HGUC is much lower in AUC compared with SHGUC.[18]

In bladder washings cytology, specimens of low grade papillary urothelial carcinoma do not display marked cytological atypia hence it can be a diagnostic modality to detect high grade urothelial carcinoma with moderate sensitivity and high specificity as cells show marked cytological atypia and necrosis. The Paris System of reporting urinary cytology provided a better diagnostic criterion for better clinical management by both urologists and pathologists and improved overall utility of bladder washings in diagnosing urothelial carcinoma with increased sensitivity and specificity.

5. Conclusion

A negative bladder wash cytology coupled with a negative cystoscopy is quite specific and reassuring that a potentially lethal high-grade malignancy is most likely absent. However, a diagnosis of positive or suspicious bladder wash should be thoroughly investigated and followed closely, regardless of the cystoscopic findings. The Paris System is easy, reproducible, consistent and has good histopathological correlation. However larger prospective studies may be required using The Paris System to study sensitivity and specificity of bladder wash cytology in a better way to establish significant correlation of urinary cytology and histopathology.

6. Acknowledgment

All the authors have contributed to concept, literature search, data acquisition, data analysis, manuscript editing and review.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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None.

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Author biography

Sonia Chhabra, Professor

Gourav Tehri, Resident

Niti Dalal, Senior Resident https://orcid.org/0000-0003-0862-0426

Hemant Kamal, Assistant Professor

Monika Gupta, Associate Professor

Rajeev Sen, Senior Professor & Head

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