



## Original Article

# Cytohistic Correlation of Urothelial Cancers– A study of 57 Cases

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### Abstract

Transitional cell carcinoma (TCC) comprises about 90% of all primary tumors of urinary bladder. The accuracy of multiple voided urine cytology justifies its continued use as a first line diagnostic and detection technique, particularly for high grade invasive cancers and clinically unsuspected case of carcinoma particularly carcinoma in-situ. In this study 57 cases were taken to see correlation of cytology, histology, stage, morphological pattern and sensitivity and specificity of urothelial cancers. Out of 57, 53 (92.99%) were positive for malignancy and 4(7.01%) were negative. There were 14 (24.56%) non-invasive papillary tumors, 1(1.76%) carcinoma in-situ and 42 (76.68%) invasive carcinoma of all grades and types. Of 14 grade-II non-invasive papillary tumors, 12 (85.72%) were cytologically positive. With only two exceptions, out of 39 all of the invasive carcinomas of all grades and types were identified by cytology as cancerous. A 100% positive cytology was noted in the detection of flat carcinoma in-situ, papillary adenocarcinoma and squamous cell carcinoma of the urinary bladder. Of the total 57 cases of malignant lesions of urinary tract, 53 (92.99%) were positive on cytological examination. The two TCC of the renal pelvis also gave a 100% positive cytologic results. Among invasive carcinoma, stage B1 and B2 urothelial cancers yield highest positive cytologic diagnosis rather than stage 0 and stage A urothelial cancers. For all tumors the sensitivity was 92.99%. The specificity was 100% since there were no false positive cases. The diagnostic accuracy was 93% (approximately). Comparison with previously published data this study showed highest diagnostic accuracy, sensitivity, specificity of voided urine cytology, good correlation with cytology histology and stage of tumor. So voided urine cytology, a very cheap and purely non invasive technique, can be done as an effective method to diagnose urothelial cancers in a developing country like Bangladesh where facilities for other investigations are practically limited.

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### Introduction

Carcinoma of the urinary bladder affects men more often than women at a ratio of 3:1 to 4:1.<sup>1</sup> Most cases present in-patients over the age of 50 years, but they can also occur in younger adults and children. Transitional cell carcinoma (TCC) comprises about 90% of all primary tumour of urinary bladder, about 75% of these tumors arises

in the region of trigone, though they can also be located elsewhere in the bladder mucosa.<sup>2</sup>

The urothelial tumors may be papillary or non-papillary (flat) and invasive or in-situ (noninvasive).<sup>3,4</sup> Transitional cell carcinoma of the urinary bladder is generally divided into three groups: superficial papillary, carcinoma in-situ and invasive. Superficial bladder tumors are largely

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grade-I or II papillary transitional cell carcinomas that may or may not invade the lamina propria.<sup>5</sup> Usually, non-invasive lesions are often referred to as “superficial” to differentiate them from carcinoma in-situ (C.I.S).<sup>4</sup>

The prognosis of papillary tumors depends not only on the grade of tumour abnormality but also on the level of histologic abnormality of the urothelium peripheral to the visible lesion.<sup>6,7</sup> The low-grade tumors such as papilloma or grade-I tumors are less likely to be followed by new tumors than are tumors of grade II or III. The non-papillary tumors of the urothelium have a natural history different from the papillary tumour.<sup>6</sup> It has now been documented that in about 80% of the cases, primary invasive carcinoma of the bladder are not preceded by papillary tumors, hence the conclusion that most of these tumors are derived from invisible and asymptomatic flat lesions namely carcinoma in-situ. In approximately 20% of cases of invasive carcinoma preceded by papillary tumors, it has been documented by mapping the urinary bladder that invasive cancer is usually derived not from the papillary tumors but from adjacent epithelial segments showing abnormalities consistent with carcinoma in-situ or related lesions.<sup>6,7,8</sup>

One of the major achievement of urine cytology is the detection of urothelial carcinoma in its preclinical phase, long before its cystoscopic and radiographic recognition.<sup>1,4</sup> Cytological examination of voided urine is the technique of choice for detection, diagnosis and follow up of tumors of the lower urinary tract. The most important value of cytology of voided urine is the diagnosis of clinically unsuspected case of carcinoma particularly carcinoma in-situ.<sup>9</sup>

Moreover cytological examination of voided urine is the only totally harmless non-invasive method,<sup>9,10</sup> easy to obtain<sup>10</sup> and can be done on an outpatient basis.<sup>11</sup> Cytology has the distinct advantage of sampling of entire urothelial mucosa.<sup>3</sup> The simplicity, convenience and accuracy of multiple voided urine cytology justifies its continued use as a first line diagnostic and detection technique.<sup>10</sup>

### **Aims and Objectives:**

This study is designed to see correlation with voided urine cytology with histology, stage, morphological pattern, diagnostic sensitivity & specificity of urothelial cancers and to compare the results with cytologic diagnosis of other studies done elsewhere.

### **Materials and Methods**

The study was carried out in the Department of Pathology, B.S.M.M.U. Dhaka, during one year period.

A. Selection of the Patients: A total of fifty seven patients clinically suspicious of having urinary bladder malignancy or histologically confirmed patients, admitted in the Urology Department of B.S.M.M.U., D.M.C.H. and private clinics were included in this study. Out of 57 patients, two cases of transitional cell carcinoma of the renal pelvis were also included in this study to see the accuracy of cytological diagnosis in T.C.C., other than urinary bladder origin.

B. Cytological Examinations: Tissue diagnosis was compared with the cytological diagnosis in this study. Cytologic diagnosis was constantly earlier than pathologic diagnosis in this series.

1. Selection of Specimens: From all patients at each admission, the diagnostic work up included cytological examinations of three samples of morning's second voided urine.
2. Sample Preparations: Fifty (50) ml of urine specimen is centrifuged at 10g for 5-10 minutes, the supernatant decanted and the pellet is directly smeared on glass slides.<sup>10</sup> Albuminized slides are recommended for better attachment of cells to the slides.<sup>3,6,14,15,29</sup> The slides are then stained with Papanicolaou method.<sup>3,5,6,9,14,15</sup>
3. Pattern of Smears (Smear Criteria): The smears undergoing cytological examination were diagnosed as: negative, atypia or atypical, suspicious, positive or malignant cells present, non diagnostic or unsatisfactory. Finally the negative and atypical diagnoses were combined in to one group (cytologic negatives) and the suspicious and positive diagnoses were

combined in to a second group (cytologic positives).<sup>9,12,16-19</sup>

D. Histopathological Examination: Biopsy / biopsies were taken usually from the lesion proper and represent cystoscopic biopsy, cystectomy or

nephrectomy specimens. All biopsy specimens were collected on 10% formalin. The Haematoxylin and Eosin stained slides were critically examined to evaluate histological features.

### Results:

The purpose of the present study is to see the correlation of cytologic and histologic diagnosis of urothelial cancers. A total of 57 cases were collected from the Urology Departments of the B.S.M.M.U., D.M.C.H. and private clinics during one year period. Out of total 57 cases, 55 were from the urinary bladder and the rest two was from renal pelvis.

Table I shows that the tumour cells were arranged in sheets and clusters in 1.76% of the patients and isolated in 38.60%. All two aspects were observed in 59.64% of the patients. The smear background was clean in 8.77% of the patients; 91.23% showed a "tumour background" composed of more or less altered polymorphonuclear leukocytes, erythrocytes, histiocytic cells and necrotic cells.

Smear pattern	No. of Patients	Percentage
Single cell	22	38.60%
Clusters/Sheets	01	1.76%
Clusters, Sheets and Single cell	34	59.64%
Background		
Clean	05	8.77%
Necrotic / inflammatory	52	91.23%

Table I: Smear pattern in 57 patients of having urothelial cancers.

### Gross appearance of the specimens received:

The volume of the biopsy samples received was variable. About 52 specimens were transurethral resection of bladder tumour (TURBT specimens) having a combined percentage of 91.23%. There were 03 (5.27%) cystectomy specimens and 02 (3.50%) nephrectomy specimens. The TURBT chips were of various size and shape, very friable and most of them had papillary configuration.

Biopsy size / volume	No.	Percentage
0 - 0.5 c.c.	27	47.36%
0.6 – 1 c.c.	03	5.27%
1.1 - 2.5 c.c.	09	15.79%
2.6 – 5 c.c.	09	15.79%
5.1 – 7.5 c.c.	02	3.50%
7.6 – 10 c.c.	01	1.76%
More than 10 c.c.	01	1.76%
Cystectomy specimen	03	5.27%
Nephrectomy specimen	02	3.50%
<b>Total</b>	<b>57</b>	<b>100%</b>

Table II: Gross appearance of the specimens.

**Cytologic diagnoses in 57 cases:**

There were no atypical, suspicious or unsatisfactory cases. Out of 57, 53 (92.99%) were given positive for malignancy and 4 (7.01%) were negative.

No.	Cytologic diagnosis	No. of cases	Percentage
1.	Negative	04	7.01%
2.	Atypical	00	00%
3.	Suspicious	00	00%
4.	Positive	53	92.99%
5.	Unsatisfactory	00	00%
<b>Total</b>		57	100%

Table III: Cytologic diagnosis of 57 cases.

**Histologic diagnosis of 57 cases:**

Table IV shows the histologic diagnoses of 57 cases. There were 14 (24.56%) non-invasive papillary tumors, 1 (1.76%) carcinoma in-situ and 42 (73.68%) invasive carcinomas of all grades and types.

No.	Histologic Diagnosis	No. of cases	Percentage
1.	Non-invasive Papillary tumour	14	24.56%
2.	Non-papillary carcinoma in situ	01	1.76%
3.	Invasive carcinoma (all grades/types)	42	73.68%
<b>Total</b>		57	100%

Table IV: Histologic diagnosis of 57 cases.

**Correlation of cytologic and histologic diagnoses in 57 patients:**

Table V listed the highest histologic and cytologic diagnoses for each of the 57 cases. There were no grade-I and grade-III non-invasive papillary tumors in this series. Of 14 grade-II non-invasive papillary tumors, 12 (85.72%) were cytologically positive. With only two exceptions, out of 39 all of the invasive carcinomas of all grades and types were identified by cytology as cancerous. A 100% positive cytology was noted in the detection of flat carcinoma in-situ, papillary adenocarcinoma and squamous cell carcinoma of the urinary bladder.

Of the 43 high-grade lesions (comprising grade-III papillary lesions, invasive carcinomas and flat carcinomas in-situ), 41 (95.34%) gave positive cytologic results. Of the total 57 cases of malignant lesions of urinary tract, 53 (92.99%) were positive on cytological examination. The two TCC of the renal pelvis also gave a 100% positive cytologic results.

Diagnoses	Histologic diagnoses		Cytologic diagnoses			
	No	%	Positive	%	Negative	%
Non-invasive papillary tumour:						
Grade I	00	00	00	00	00	00
Grade II	14	24.56	12	85.72	02	14.28
Grade III	00	00	00	00	00	00
Non-papillary CIS	01	1.76	01	100	00	00
Invasive carcinomas all grade	39	68.42	37	94.88	02	5.12
Other						
Papillary Adenocarcinoma	01	1.76	01	100	00	00
S.C.C.	02	3.50	02	100	00	00
<b>Total</b>	<b>57</b>	<b>100</b>	<b>53</b>	<b>92.99</b>	<b>04</b>	<b>7.01</b>

Table V: Correlation of cytologic and histologic diagnoses in 57 patients

**Correlation of invasive carcinoma and cytologic diagnoses:**

In the present series, there were 42 invasive carcinomas out of total 57 patients. Among 42 patients, invasive papillary lesions were 25 (59.53%), invasive flat 14 (33.33%), invasive papillary adenocarcinoma 01 (2.38%) and invasive squamous cell carcinoma 2 (4.76%). Invasive flat lesions, invasive papillary adenocarcinoma and invasive squamous cell carcinoma gave 100% positive cytologic results. Out of 25 invasive papillary lesions, 21 belonged to grade-II and rest 04 to grade-III. Among 21 grade-II tumors, 19 (90.48%) lesions were identified correctly in voided urine and the grade-III lesions gave 100% positive results.

Histologic diagnoses	No.	%	Positive	Cytologic diagnoses.		
				%	Negative	%
Invasive papillary	25	59.53				
Grade I	00		00	00	00	00
Grade II	21	50	19	90.48	02	9.52
Grade III	04	9.53	04	100	00	00
Invasive Flat	14	33.33				
Grade I	00	00	00	00	00	00
Grade II	00	00	00	00	00	00
Grade III	14	33.33	14	100	00	00
Invasive papillary adenocarcinoma	01	2.38	01	100	00	00
Invasive S.C.C.	02	4.76	02	100	00	00
<b>Total</b>	<b>42</b>	<b>100</b>	<b>40</b>	<b>95.24</b>	<b>04</b>	<b>4.76</b>

Table VI: Invasive carcinomas and cytologic diagnoses. \*S.C.C. Squamous cell carcinoma.

**Stage (Jewett-Marshall) and cytologic diagnoses:**

In the present series as shown in table VII, out of 57 patients, 14 were non-invasive papillary tumour in which, in 10 cases, stage couldn't be determined because of very superficial nature of the biopsy and the remaining four was in stage 0. Positive cytology was observed in 9 (90%) and 03 (75%) cases respectively. One carcinoma in-situ gave 100% positive cytologic result. Among 39 invasive carcinomas,

27 were in stage A which gave 92.60% positive cytology, 07 were in stage B1 which gave 100% positive cytology and 05 were in stage B2 which also gave 100% positive results. Both invasive papillary adenocarcinoma (01) and squamous cell carcinoma (02) were in stage A and gave 100% positive cytology results.

Histologic diagnoses	Stage	No	%	Cytologic diagnoses.			
				Pos. +	%	Neg. -	%
Non-invasive papillary	No Stage*	10	17.55	09	90	01	10
	Stage 0	04	7.01	03	75	01	25
Carcinoma in situ (CIS)	Stage 0	01	1.76	01	100	00	00
Invasive carcinoma (All grade)	Stage A	27	47.36	25	92.60	02	7.40
	Stage B1	07	12.29	07	100	00	00
	Stage B2	05	8.77	05	100	00	00
Papillary Adenocarcinoma	Stage A	01	1.76	01	100	00	00
Invasive S.C.C.	Stage A	02	3.50	02	100	00	00
<b>Total</b>		57	100	53	92.99	04	7.01

Table VII: Stage (Jewett-Marshall) and cytologic diagnoses. \* Staging not possible  
S.C.C.: Squamous cell carcinoma.

#### Diagnostic sensitivity and specificity of cytologic diagnosis:

Table VIII shows sensitivity, specificity and accuracy of voided urine cytology. For all low-grade tumors the sensitivity was about 85.72% and for all high-grade tumors, it was about 95.34% with a sensitivity of 100% and 95.24% for flat CIS and invasive carcinomas respectively. For all tumors the sensitivity was 92.99%. The specificity was 100% since there were no false positive cases. The diagnostic accuracy was 93% (approximately).

Type of Lesion	No	True +	True -	False +	False -	Sensitivity	Specificity
Low grade cancer	14					85.72%	
Grade I	00	00	00	00	00	00%	00%
Grade II	14	12	00	00	02	85.72%	100%
High grade cancer	43					95.34%	
Grade III	00	00	00	00	00	00%	00%
Flat CIS	01	01	00	00	00	100%	100%
Invasive cancer	42	40	00	00	02	95.24%	100%
<b>Total</b>	57	53	00	00	04	92.99%	100%

Table VIII: Diagnostic sensitivity and specificity of cytologic diagnosis.

#### Comparison of cytohistologic correlation of the present study with previous studies:

The data showed a good cytohistologic correlation in the present series and is comparable in a more or less similar way with the results of other previous studies.

Lesion	Kern WH. (18)			Murphy WM et. al. (10)			Kern WH (4)			Present study		
	Total	Pos. +	Neg. -	Total	Pos. +	Neg. -	Total	Pos. +	Neg. -	Total	Pos. +	Neg. -
TCC	860			66			898			57		
Grade I	152	96(63%)	56(37%)	21	16(76%)	5(24%)	159	103(65%)	56(35%)	00		
Grade II	248	196(79%)	52(21%)	22	22(100%)	-	268	214(80%)	54(20%)	35	31(89%)	4(11%)
Grade II	237	223(94%)	14(6%)	16	16(100%)	-	242	228(94%)	14(6%)	18	18(100%)	-
CIS	62	61(98%)	1(2%)	5	5(100%)	-	63	61(98%)	1(2%)	01	1(100%)	-
Inv. Pap.	15	13(87%)	2(13%)	-	-	-	16	14(88%)	2(12%)	01	1(100%)	-
ADCA												
SCC	15	14(93%)	1(7%)	2	2(100%)	-	16	15(94%)	1(6%)	02	2(100%)	-
Others	131						134					

Table IX: Comparison of cytohistologic correlation of the present study with previous studies.

TCC: Transitional cell carcinoma.

CIS: Carcinoma in-situ.

ADCA: Adenocarcinoma

SCC: Squamous cell carcinoma.

## Discussion

Cytologic study of the urine as a diagnostic procedure was first introduced by Papanicolaou and Marshall in 1945.<sup>20</sup> Urinary tract cytology is requested by Urologists as a diagnostic aid rather than as a detection technique for urinary tract cancer. The Urologists seek the assistance of diagnostic cytology only in those cases where a suggestion of a malignant neoplasm of the urinary tract exists. The exception is the high-risk group such as the workers in petrochemical industry.<sup>21</sup> In 1961, Crabbe initiated urine cytology as a successful method for screening high-risk population or industrial population.<sup>3,22</sup>

The practical value of cytological examination of urine is, first in reducing the chance of biopsy sampling error and second, in the detection of cancer in patients who refuse frequent cystoscopy.<sup>23</sup> Urine cytology before review cystoscopy may help in avoiding unnecessary general anaesthesia and reduce both cost and patient morbidity.<sup>15</sup> As a follow up procedure, cytology may enhance the value as well as reduce the number of cystoscopies performed by

accurately indicating when a search for cancer needs to be undertaken.<sup>12</sup>

Since 50-70% of the patients with transitional cell carcinoma particularly the superficial transitional cell carcinoma will experience a recurrent tumour, it is important to have a non-invasive assay that can predict the likelihood of bladder transitional cell carcinoma recurrence.<sup>24</sup> In the majority of these patients, clinical evidence of carcinoma followed, often many years.<sup>7</sup> The most important advantage of the method is its ability to indicate the presence of a tumour at a very early stage of its development, often before any presenting symptom or other urinary abnormalities have given an indication of its presence.<sup>2,4,16</sup> Early precancerous lesion in the bladder may not be visible cystoscopically and cytology may therefore allow for an earlier diagnosis of malignancy, months to years before the cancer would be found cystoscopically.<sup>12,25,26</sup>

Regarding smear pattern the cells are disposed often singly and with a tumor background posing some limitations in diagnosis. The smears were satisfactory in most of the cases in this study, though some claims cytospin or membrane filter

preparations to be more satisfactory as far as cell harvest is concerned.<sup>20</sup> The histologic specimen received is often TURBT chips and was adequate for histologic evaluation. This study demonstrated the accuracy of cytology by evaluating comparison of cytologic and histopathologic diagnoses. In the present study, results of urine cytology of 57 patients were correlated with tissue diagnosis. Histopathological diagnoses were non-invasive papillary tumors 14 (25%), carcinoma in-situ 1 (2%) and invasive carcinoma 42 (74%). Out of 57 cases, cytological diagnosis was positive in 53 cases (93%) and negative in 4 cases (7%). There were no atypical or suspicious cases. Of the total cases, cytology was negative only in 7% cases. Among 42 invasive carcinomas 14 (33%) grade III invasive flat carcinoma, one (2%) invasive papillary adenocarcinoma and two (5%) invasive squamous cell carcinoma, each of them gave 100% positive cytology. Of the remaining 25 (60%) invasive papillary TCC, 21 were in grade II and 4 were in grade III. They gave 90% and 100% positive cytologic results respectively.

Correlating stage of primary tumour with cytologic diagnosis, it was observed from the study that higher stage tumors gave more consistent positive cytologic results. Marshall stages A or above gave positive results ranging from 92 – 100%. Diagnostic accuracy and sensitivity was 93% for all tumors and specificity was 100%. The positive and negative predictive value was also 100%. In a study of 114 patients having known bladder cancer, cytology was positive for malignant cells in 80 cases (70.2%), negative in 23 patients (20.2%) and doubtful in 11 cases (9.6%).<sup>20</sup> In a study by Farrow based on 10338 patients cytology was positive in 84% of 78 invasive cancers and 83.5% of 152 carcinoma in-situ. In 650 papillary tumors, cytology was abnormal in 47.4%.<sup>20</sup>

L.G. Koss made cytohistologic correlation in 203 cases and noted that only one of the six grade I papillary tumors had cancer cells in the urinary sediment. Of 64 grade II papillary tumors, 48 (70.5%) were cytologically positive. With only four exceptions, all of the 62 grade III tumors were identified by cytology. Cytology was also positive

in 100% and 92% cases of carcinoma in-situ and invasive carcinomas respectively. Of the 103 high grade lesions (comprising grade III papillary lesions, invasive carcinomas and flat carcinoma in-situ), 97 (94%) gave positive cytologic results.<sup>9</sup> Comparison of cytohistologic correlation with previous studies also gave similar results which is in concordance with the present study. In this series there were no papilloma or grade I papillary carcinoma that is why the diagnostic accuracy was so high. The results also point to the higher accuracy of cytologic positive cases when the lesions become high grade and particularly invasive.

The well-differentiated tumors are not readily detected cytologically but results improve with more undifferentiated higher-grade lesions.<sup>13</sup> Consistent with previously published data, this study showed the highest diagnostic accuracy with high-grade tumors and lowest with low-grade tumors with maximum invasion limited to the lamina propria. The percentage of false negative reports in this series can be partly due to poor sampling or low-grade tumor. Urine is a very inhospitable fluid for cells but the basis for deleterious effects is not known. Quick removal of the fluid portion of urine and prompt fixation of the freshly desquamated cells is the main reasons for improved presentation.<sup>27</sup> One comment about false negative, which applies to any fluid in which cells are suspended, is that collectors must be trained to pour a sample immediately or shake the container if the fluid has stood for a while (say 15 minutes) and the cells have settled, thus the specimen collected gets its share of the cells.<sup>28</sup>

False negative cytology in low-grade lesions is therefore not unexpected. False positive diagnoses are probably not important. A positive cytological diagnosis of bladder cancer does not lead directly to cystectomy or other radical therapy.<sup>27</sup>

In a study of 91 patients, urine cytology was 75% sensitive and 94% specific.<sup>27</sup> Sensitivity of urine cytology in 860 patients with urinary tract cancer was 77% and the specificity is 97%.<sup>18</sup> L.G. Koss in a study of 183 cases having bladder cancer, described the sensitivity of 82.5% for all tumors.

If one excludes grade-I and II tumors, the sensitivity for all high-grade lesions and flat CIS was 100%.<sup>6,9</sup> In low-grade cancers, the sensitivity is 66.2%, for grade-I 16.7 % and for grade-II 71.6%. The specificity was 100% since there were no false positive cases.<sup>9</sup>

In this study the non- invasive technique was adopted and voided urine specimen was chosen over bladder washings or barbotage as an ideal method of collection of urine. The purpose of this is to see how a simple test can be helpful in diagnosing malignant tumors of urinary bladder. Urine cytology is not a popular method for screening or detection of malignancy in our country. Urine cytology has immense value as a non- invasive technique, not only as a diagnostic tool but also as a prognostic factor. Positive cytology correlates well with grade, stage and prognosis of bladder tumors, so it can be used in the detection, diagnosis and follow-up of the primary tumour and for recurrent tumors receiving therapy.

### Conclusion:

A definitive pre-operative diagnosis of malignant tumors of urinary bladder can help the urologists to make decision about the plan of surgery or radiotherapy or chemotherapy. The outcome of the therapy instituted can also be monitored through cytology. There are several methods of making a pre-operative diagnosis. Among all of the invasive and non- invasive techniques, voided urine cytology is one of the important non-invasive method which can give results very closer to the histologic diagnosis or at least can say about the nature of the tumour.

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