

# Detection of the recurrence of superficial urothelial carcinoma of urinary bladder by combined urine cytology and cystoscopy

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## Article Info

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## Abstract

The study was aimed to evaluate the accuracy of combined urine cytology and cystoscopy for the detection of the recurrence of superficial urothelial carcinoma of urinary bladder without bladder biopsy. A total 60 patients [males 48, females 12; age range 41-80 years (mean age- 63.15 years)] were included. Urine cytology as well as cystoscopy were done with a targeted biopsy taken from any apparently visible growth in the bladder. The systematic biopsy was taken where there was no growth. Reports of the cytology and cystoscopy were compared with the histopathology reports. It was found that 18 patients were cytology positive (false positive 2) and 42 patients were cytology negative (false negative 10) with sensitivity 61.5% and specificity 94%. During cystoscopy 24 patients were found recurrent growth in the bladder (false positive 3) and 36 patients were negative (false negative 5) with sensitivity 80.7% and specificity 91%. But when combined urine cytology and cystoscopic findings evaluated, the sensitivity and specificity were found 100% and 91% respectively. In conclusion, combined urine cytology and cystoscopy can be used for the detection of recurrence of superficial urothelial carcinoma of urinary bladder.

## Introduction

Urothelial carcinoma of the bladder is the most common malignancy of the genitourinary tract. Superficial type accounts for 70% of the urothelial carcinoma that has a high probability of recurrence (48–71%) within 5 years of initial diagnosis and treatment. Seventy percent of patients who present with the superficial bladder carcinoma have a low-grade superficial tumor and the initial treatment should be the complete clearance by transurethral resection.<sup>1</sup>

With the long-term follow-up, 50-60% of these tumors will recur and the progression to muscle-invasive disease is observed in 10-20%.<sup>2</sup> Cystoscopic biopsy is the most accurate technique in diagnosing the recurrence of such tumors.<sup>3</sup> Once superficial urothelial carcinoma with a poor prognosis or high-risk (high-grade tumor T1, multiple location, recurrence) has been diagnosed, the adjuvant treatment is given either by intravesical chemotherapy or intravesical immunotherapy (Bacillus Calmette-Guérin, BCG).<sup>4</sup> After BCG treatment, high-risk tumor is cured in the long-term in one-third of the cases, with recurrence in the same form in another one-third of the cases, and as infiltrating tumor in the remaining one-third.<sup>5</sup>

The efficacy of treatment is usually monitored

by cystoscopy with biopsy from the suspicious lesion or random biopsy under general anesthesia if there is no visually suspicious lesion.<sup>6</sup> This practice has been criticized owing to its morbidity, invasiveness, being time-consuming and costly that is burdensome to the patient and the hospital.<sup>7,8</sup>

The study emphasizes that in patients with high-grade tumor or carcinoma *in situ*, urine cytology is more sensitive.<sup>9</sup> The definitive histopathologic report is the gold standard diagnosis with which the cytological report is compared.<sup>10</sup> Cystoscopy and urine cytology are used for the follow-up superficial urothelial carcinoma of urinary bladder in different parts of the world with variable findings, but not in Bangladesh.

Because of long-term survival and the need for lifelong routine monitoring a cheaper, minimally invasive, patient-friendly tool needs to be implemented in following-up the patient with superficial bladder cancer. This study was designed to set a guideline tool for detection of recurrence of bladder tumor.

## Materials and Methods

This prospective study was conducted from April 2015 to May 2016 among the patients with



superficial bladder cancer treated by transurethral resection of bladder tumor. With a purposive sampling technique, 60 patients were selected following standard sampling formula. The age of the patients (range 45-80 years; mean 63.2 years), gender (48 males, 12 females), stage of the disease were the independent variables and cytological findings, cystoscopic findings, cystoscopic biopsy findings were the dependent variable. The patient with a) superficial bladder cancer, b) adult patients (both gender) aged more than 40 years, c) history of transurethral resection of bladder tumor, d) history of intravesical chemotherapy/immunotherapy, e) come for follow-up and f) those patients who were voluntarily agreed to participate in this study were selected. Patient having a) muscle-invasive bladder cancer, b) urinary tract infection, c) uncontrolled bleeding disorder, d) bladder outlet obstruction, e) pregnant woman, f) upper tract superficial urothelial carcinoma of the urinary bladder, and g) non-availability of the informed consent were excluded.

A detailed history was taken and clinical examination was done for each patient. Some investigations were done for proper selection of the patient. Urine for routine examination and culture/sensitivity to exclude the urinary tract infection. Then pre-operative routine investigations were done for fitness for anesthesia.

A freshly voided urine specimen was obtained for cytology prior to cystoscopy for all patients and subsequent cystoscopic biopsy was done for each patient. Each cytologic sample (about 50 mL of urine) was centrifuged for 10 min, the supernatant decanted, and the cell pellet again was cytocentrifuged. Two glass slides were prepared. The slides were fixed in 95% isopropyl alcohol for 30 min.

Then, the slides were stained by the Papanicolaou technique. For the purpose of clarity and potential practical application, cytologic preparations were reviewed by a cytopathologist who reported the diagnosis as positive for malignancy and negative for malignancy. Atypical cells that had been comfortably (i.e. did not raise any unnecessary suspicion) categorized as due to inflammation/degeneration were included in the negative group of cytology, whereas atypical cells which suggested/favored malignancy or dysplasia, and hence were found to be suspicious, were included in the positive for malignancy group of cytology according to the Bladder Consensus Conference Committee of 1998.

Cystoscopic findings were categorized as negative, suspicious or positive for the recurrence and reported during the follow-up of patients every three months. Suspicious findings by cystoscopy corresponds to small papilloma or to any lesion with petechial appearance. For the purpose of clarity and safe estimation, suspicious cases were included within the positive cases.

Resection bladder biopsy was performed from any gross lesion or cold cup biopsy was systematically taken from the right and left lateral wall, the trigone, anterior wall and the dome if the reported cystoscopic findings were normal. The cystoscopic biopsy was examined histologically and categorizes into grade (high grade or low grade) and stages (T) according to TNM classification of malignant tumors.<sup>11</sup> The histologic report was considered as the gold standard with which the cytologic and cystoscopic reports were compared.

All patients were nothing by mouth in the morning of the operative day and given intravenous fluid up to 2 hours after the procedure. All patients were under antibiotic prophylaxis during the cystoscopic procedure. The cystoscopic biopsy was done under spinal anesthesia and discharged within 24 hours of the procedure.

The demographic information, relevant history, examination findings and investigation reports of all the study subjects were recorded in the data collection sheet. Any complication during the procedure and hospital admission was also recorded. However, there was no remarkable complication during this study period.

After compilation, the data were presented in the form of tables, figures and graphs, as necessary.

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## Results

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According to cytology, 18 cases were positive (2 of them false positive) and 42 were negative for recurrence (10 of them were false negative) (Figure 1). Cystoscopic findings were positive in 24 cases including 5 suspicious cases and negative in 36 cases (Figure 2). In the histopathological results, 26 cases were found positive for recurrent superficial urothelial carcinoma, while 34 cases were reported as negative.

It was found that 3 out of the reported 24 cystoscopically positive cases show false positive results (all of them were documented originally as suspicious cases). While 5 out of the 36 cases documented cystoscopically negative were reported histologically as positive and considered as false negative with estimated specificity of 91% and sensitivity of 80.7% (Table I).

Most of the false negative cases were detected in low grade superficial urothelial carcinoma. None of the carcinoma *in situ* cases was falsely reported cytologically as negative. The estimated sensitivity was 61.5% and specificity was 94.0%.

The correlation between cytology reports, cystoscopy findings and histopathology reports is illustrated in Table I. Two out of 13 cases, which were documented as positive by cystoscopy and cytology

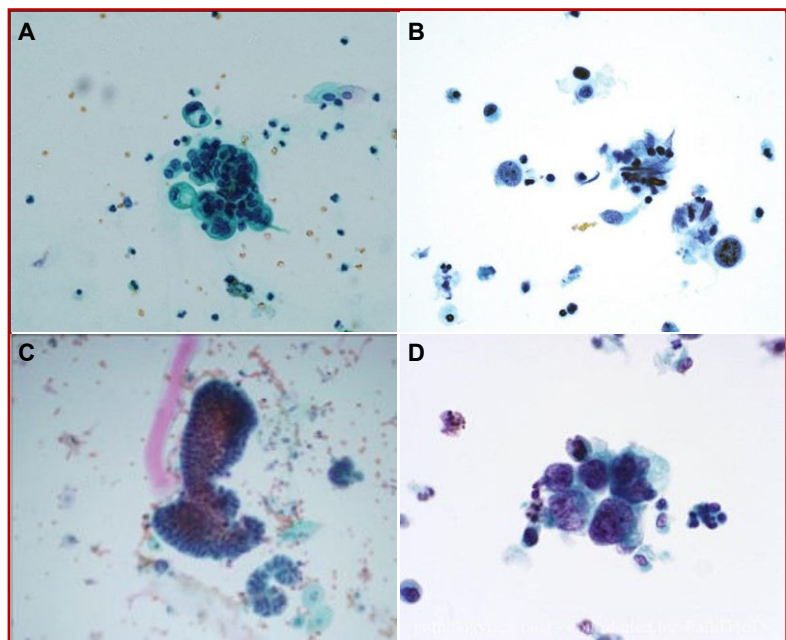


Figure 1: Cytology of the urine. A: A case of atypical urothelial cells favoring reactive showing crowded, hyperchromatic groups of urothelial cells with focal cytoplasmic vacuolization (Papanicolaou stain, ×600); B: Atypical urothelial cells, cannot exclude high-grade urothelial carcinoma. Rare atypical urothelial cells with cytomorphologic features suggestive of high-grade urothelial carcinoma (ThinPrep®, Pap stain ×40) (suspicious case); C: Papillary clusters of crowded, hyperchromatic urothelial cells favoring neoplasm (Papanicolaou stain, ×400), low grade superficial urothelial carcinoma of urinary bladder; D: Malignant cells in high grade urothelial carcinoma

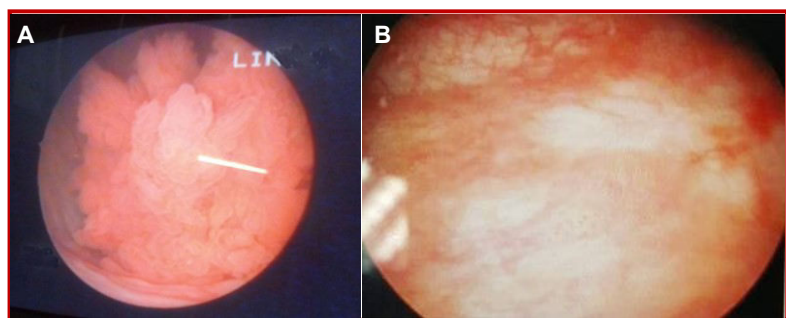


Figure 2: Cystoscopy of a typical superficial urothelial carcinoma of urinary bladder (A) and carcinoma *in situ* (B)

Table I

Comparison of combined urine cytology and cystoscopic findings with bladder biopsy and histopathology report				
Cytology	Cystoscopy	n	Biopsy	
			Positive (26)	Negative (34)
Positive	Positive	13	11	2
Positive	Negative	5	5	0
Negative	Positive	11	10	1
Negative	Negative	31	0	31

were diagnosed histopathologically as negative for recurrence and none of the 31 patients who were reported negative by cytology and cystoscopy presented tumor recurrence on biopsy and histopathology. Estimated sensitivity and specificity of combined urine cytology and cystoscopy were 100 and 91%; respectively. Accuracy, positive predictive value and negative predictive value were 95.0, 89.7 and 100.0% respectively.

## Discussion

Bladder tumor usually recurs and progresses to muscle-invasive tumor. So, detection of early recurrence is necessary with urinary bladder.<sup>12-14</sup>

Cystoscopy, urine cytology and bladder biopsy are the tools to detect recurrence. But none of the patient negative by cytology and cystoscopy presented in recurrence on biopsy and histology. Highshaw et al. (2003) recommended limiting biopsies to patients with positive cystoscopic findings.<sup>8</sup> In the present series, this tactic would have resulted in 5 false negatives in the 36 patients (13.9%) with a negative cystoscopy. This would appear to be minor, but 2 out of these 5 false-negative cases presented high-grade tumor on histology (1 case with carcinoma *in situ*). In contrast to Highshaw et al. (2003)<sup>8</sup>, we consider such strategy (limiting biopsies to patients with positive cystoscopic findings) as inappropriate.

This is consistent with Oosterlink et al. (2001) who discussed the frequency of positive biopsies after visual disappearance of considerable superficial bladder cancer lesions which was estimated to be 10-17% and this met with our results.<sup>6</sup>

With the advent of modern logistics like cytopspin technique, is cytology alone sufficient for the follow-up? In our study, there were 2 false positive cases. One of them was due to cystitis and one was due to BCG therapy. There is group of atypical cells that are more or less uniform with hyperchromasia, high nuclear cytoplasm ratio set in a necro/inflammatory background. These features are consistent with BCG effect as well as marked cystitis which may induce considerable atypia and increase the cellular denudation that may raise suspicion of malignancy. This emphasizes the importance of complete and detailed history to be provided to the reporting cytologist/ histopathologist.

In low-grade lesion, false negative diagnoses especially, is a problem probably due to lesser degrees of exfoliation and subtle cytological features of malignancy in low-grade lesions.

In our study, false negativity was documented in 10 out of 42 (23.8%) negative cases reported cytologically. As in our study, many authors were unable to identify malignant cells in low-grade lesion and

reported that the efficacy of urinary cytologic examination improved with the higher grades.<sup>15,16</sup>

In the present study, the sensitivity of cytology was 61.5% and its specificity was 94%. These results are comparable with other published data of Bardales (2002).<sup>17</sup> In the literature, the sensitivity of urine cytology for the recurrence of high-risk tumor is a parameter that varies from 44 to 97%. However, it is important to note that the sensitivity of this technique is reduced by its inability to detect low-grade tumor, as in our study. In our study, combined cystoscopy and urine cytology had a specificity of 91% and a sensitivity of 100%, accuracy = 95%, positive predictive value = 89.65%, and negative predictive value = 100%. If cytology or cystoscopy or both reported positive, the cystoscopic biopsy and histopathology results are also positive for the detection of bladder recurrence.<sup>18</sup> This is similar to the study done by Bardales (2002).<sup>17</sup>

Urine cytology is increasingly accepted as a diagnostic tool in the detection and follow-up of the patient with bladder cancer.<sup>19-26</sup> So, combined urine cytology and cystoscopy can be safely used to rule out the recurrence of superficial bladder cancer and the negativity of these two investigations, therefore, makes it possible to avoid cystoscopic biopsy.

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## Conclusion

As combined cystoscopy and urine cytology had high specificity and sensitivity, these two investigation tools can be used reliably for the detection of recurrence of superficial urothelial carcinoma of urinary bladder.

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## Ethical Issue

Ethical clearance for the study was taken from the Institutional Review Board (IRB) of BSMMU prior to the commencement of this study. The aims and objectives of the study along with its procedure, risks and benefits of this study were explained to the study subjects in an easily understandable local language. Written informed consent was taken from all the study subjects without exploiting any of their weakness. All the study subjects were assured of adequate treatment of any complications developed in relation to the purpose of the study and their confidentiality and freedom to withdraw themselves from the study at any time.

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