Original Research Article

Detection of malignant lesions of the urinary bladder using urine cytology and correlating with the histopathology findings - A prospective study

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Abstract

Background: Bladder cancer is the fourth most common cancer in men and the tenth most common cancer in women. It is common in industrialized countries than in developing countries, and in urban than in rural dwellers. Transitional cell carcinoma of urinary bladder may be papillary or non papillary and invasive or in situ. Non papillary tumors or at least the poorly differentiated papillary tumors arise from areas of atypical urothelial proliferation.

Materials and methods: A total of 54 cases were included in the study. 67 urine samples from all the 54 cases were categorized on the basis of the guidelines of the "Five-category cytological classification". The cases were identified on the basis of clinical features of hematuria, frequency, urgency, dysuria or past history of bladder tumor. The criteria for inclusion in our study was either a positive urine cytology with a subsequent positive/ negative biopsy or positive/ negative urine cytology followed by a subsequent biopsy, positive for malignancy.

Results: In our study, 54 patients were included and 67 samples were taken. 67 Urine samples from all the 54 cases were categorized on the basis of the guidelines of the "Five-category cytological classification". Out of 67 urine specimens from 54 patients, 16 were categorized as negative and 51 were categorized as positive for atypical or suspicious cells. Out of the 51 positive suspicious of malignancy or atypical cells, there were 20 cases of high grade lesions and 29 cases of low grade lesions. 3 out of 54 patients were less than 40 years of age and all had low grade lesions on biopsy.
Conclusion: Urine cytology is simple, cost effective, non-invasive diagnostic test used for screening and detection of the early cases of bladder cancers. The sensitivity of cytology for detection of low grade and high grade lesions of bladder was 44% and 74% respectively. The specificity for both was 78%.

Key words

Urine cytology, Bladder cancer, Transitional cell carcinoma, Histopathological examination (HPE), Five category classification.

Introduction

Bladder cancer is the fourth most common cancer in men (6%) and the tenth most common cancer in women (2%), accounting in men for 3% of cancer deaths in 2004 in United States. The carcinoma of the bladder is more common in men than in women, in the industrialized countries than in developing countries, and in urban than in rural dwellers [1]. There are approximately 50,000 new cases and 10,000 deaths from urothelial carcinoma in each year in United States [2, 3] the male to female ratio for transitional cell tumour is approximately 3-3.5: 1 [4]. About 80% of patients are usually between the ages of 50 and 80 years. A number of factors (multi-factorial) have been implicated in the causation of transitional cell carcinoma. The ideal diagnostic test should be rapid, inexpensive and non-invasive with high sensitivity and specificity. Urinary Cytology is an accepted procedure for screening and follow-up of patients with bladder tumors. Despite the advent of several newer techniques for screening and diagnosis of urothelial malignancies, cytomorphology still remains an important tool. "Atypical Cells" in urine have been recognized and studied time and again. The accurate interpretation of the character of "Atypical Cell" in urine is a major challenge for cytopathologist and may be the harbinger of an underlying malignant process. Aim of this study was to compare urinary cytology with bladder biopsy findings in carcinoma of the urinary bladder using five-category cytological classification and also to evaluate the efficacy of the classification.

Material and methods

The present study was conducted in the Department of Pathology in collaboration with the Department of Urology, St Stephen's Hospital, Delhi, India. A total of 54 cases were included in the study. 67 urine samples from all the 54 cases were categorized on the basis of the guidelines of the "Five-category cytological classification" as mentioned below. The cases were identified on the basis of clinical features i.e. hematuria, frequency, urgency, dysuria or past history of bladder tumor. The criteria for inclusion in our study was either a positive urine cytology with a subsequent positive/ negative biopsy or positive/ negative urine cytology followed by a subsequent biopsy, positive for malignancy. Types of specimens for urine cytology used were voided urine, catheterized urine, bladder wash, ureteral wash, renal pelvis wash. These pathological specimens were processed by various methods like direct smear method, filter preparation, cytocentrifuge, saccomanno blending technique and cell block preparations. For histopathological examination (HPE), biopsy bits from the lesions and representative areas of the cystectomy specimens were used.

Five-category classification of cytological diagnoses [5]

- Negative or absence of suspicious cells (Neg)
- Suspicious of low grade cellular atypia (S-Lg)
- Consistent with low grade cellular atypia (Lg)
- Suspicious of high grade cellular atypia (S-Hg)
- Consistent with high grade cellular atypia (Hg)

In our study, the histopathological diagnosis on cystoscopic biopsies grouped into four broad categories WHO/ISUP guidelines i.e.

- Negative for malignancy
- Low grade lesions
    - Papilloma
    - Papillary urothelial neoplasm of low malignant potential (LMP)
    - Low grade Transitional cell carcinoma (TCC)
- High grade lesions
    - High grade Transitional cell carcinoma
    - Sarcomatoid variant of Transitional cell carcinoma
    - Carcinoma in situ
- Others

Results

In our study, 54 patients were included and 67 samples were taken. Out of total 54 patients, 6 were females (12.5%) and 48 were males (87.5%). Male to female ratio was 8:1 in our study **(Table - 1)**. The ages of the patients in our study were in the range of 28-86 years, with maximum patients in the age group of 61-70 years. The mean age of presentation was 64.1 years **(Table - 2)**.

67 Urine samples from all the 54 cases were categorized on the basis of the guidelines of the "Five-category cytological classification". Out of 67 urine specimens from 54 patients, 16 were categorized as Negative (Neg) and 51 were categorized as positive for atypical or suspicious cells **(Table - 3)**. All the negative cytology specimens had a subsequent positive biopsy, because the criteria for inclusion in our study was either a positive urine cytology with a subsequent positive or negative biopsy or positive or negative urine cytology followed by positive subsequent biopsy.

Table - 1: Sex distribution of cases.

Sex	No. of patients	%
Male	48	89
Female	6	11
Total	54	100

Table - 2: Age-wise incidence of the cases.

Age group (Years)	No. of patients	%
21-30	1	1.9
31-40	3	5.6
41-50	1	1.9
51-60	14	25.9
61-70	19	35.2
71-80	9	16.7
81-90	7	13.0
Total	**54**	**100**

Table - 3: Categorization of urine cytology.

Categorization of urine cytology	No. of specimen	%
Negative (Neg)	16	23.9
Suspicious of low grade atypia (S-Lg)	11	16.4
Consistent with low grade atypia (Lg)	11	16.4
Suspicious of high grade atypia (S-Hg)	13	19.4
Consistent with high grade atypia (Hg)	16	23.9
Total cases	**67**	**100**

Out of the total 16 urine specimens reported as negative, 5 had only few squamous epithelial cells and no recognizable urothelial cells. Out of these 5 specimens 1 had sarcomatoid TCC, 1 had high grade TCC, 1 had low grade TCC, 1 had

inverted papilloma and 1 had LMP on subsequent biopsy. So, due to low cellularity, no urothelial cells and the fact that only one sample was received, these cases were reported false negative. In rest of the 11 specimens, 8 had low cellularity and 3 had moderate cellularity. None of the negative urine specimens had high cellularity. The cause for the negative cytological diagnoses in 1 case with urothelial cells may be either the cells in the sample were few or the sample was small. Only one patient had three urine specimens reported as negative followed by a biopsy showing low grade TCC. One patient had two samples out of which one was reported negative and the other as consistent with low grade atypia (Lg) emphasizing the fact that even in presence of a tumour atypical urothelial cells may not be shed in the urine at all occasions. This was supported by the presence of low grade TCC in the subsequent biopsy.

The subsequent histopathological diagnoses or the histological variants corresponding to the 16 specimens of negative urine cytology were 1 inverted papilloma, 1 papillary urothelial neoplasm of low malignant potential (LMP), 10 Low grade Transitional cell carcinoma, 3 High grade Transitional Cell Carcinoma and 1 sarcomatoid variant of Transitional Cell Carcinoma **(Table - 4)**.

Table - 4: Histopathological diagnosis of the urine cytology negative cases.

Histopathological diagnosis	**No. of cases**
Inverted papilloma	1
Papillary urothelial neoplasm of low malignant potential	1
Low Grade TCC (LG)	10
High Grade TCC (HG)	3
Sarcomatoid TCC (Sarc TCC)	1
Total	**16**

In our study, the overall sensitivity of cytology for detection of bladder tumour was 75%, while sensitivity of cytology for detecting low grade and high grade lesions of bladder was 44% and 74% respectively. The frequencies of cytological diagnosis was compared against the reference standard, overall sensitivity ranged from 37% to 81% and specificity from 95% to 99%. For all thresholds of cytological diagnosis, sensitivity increased with the grade of non-invasive papillary urothelial tumors and was the highest for CIS and invasive carcinoma.

In our study, out of the 51 positive suspicious of malignancy or atypical cells, there were 20 cases of high grade lesions with ages ranging 52-86 years with maximum patients in the age group of 51-60 years. Mean age of presentation was 64.8 years.

The ages of 29 cases of low grade lesions ranged from 28-85 years with maximum patients in the age group of 61-70 years. Mean age of presentation was 64.8 years. Youngest patient in our study was 28 years of age with Low grade papillary urothelial neoplasm. 3 out of 54 patients were less than 40 years of age and all had low grade lesions on biopsy.

Out of 20 patients with high grade lesions, 2 were females and 18 were males. Male to female ratio for high grade lesions was 10: 1, in our study. Out of the 29 cases of low grade lesions in our study, 2 were females. So, in our study, Male to Female ratio for low grade lesions was 13.5:1.

Out of the 51 positive cytology specimens, 11 were categorized as Suspicious of low grade cellular atypia (S-Lg), 11 were categorized as Consistent with low grade cellular atypia (Lg), 13 as Suspicious of high grade cellular atypia (S-Hg) and 16 as Consistent with high grade cellular atypia (Hg) **(Table – 5 and 6, Figure - 1, 2, 3, 4)**

Cystoscopy and biopsy was done in all the cases. The bladder biopsies of all the case were studied and were categorized on the basis of WHO/ISUP classification.

Out of the 29 specimens which were categorized as S-Hg or Hg, the subsequent histopathological diagnoses corresponding to each sample were Papillary urothelial neoplasm of low malignant

potential - LMP (1) **(Figure - 5)**, low grade Transitional cell carcinoma (8), High grade Transitional Cell Carcinoma (12) **(Figure - 6)**, Carcinoma In-Situ (4), Sarcomatoid Transitional carcinoma (1) and adenocarcinoma of prostate involving bladder mucosa (3). 9 of these specimens from 5 patients were graded higher when compared with the reference standard i.e. cystoscopic biopsies.

Table - 5: Histopathological diagnosis of urine cytology low grade positive cases.

Histopathological diagnosis	No. of cases
Negative	4
Papillary urothelial neoplasm of low malignant potential (LMP)	6
Low Grade TCC (LG)	10
High Grade TCC (HG)	1
Carcinoma in situ (CIS)	1
Total	**22**

Table - 6: Histopathological diagnosis of urine cytology high grade positive cases.

Histopathological diagnosis	No. of cases
Papillary urothelial neoplasm of low malignant potential (LMP)	1
Low Grade TCC (LG)	8
High Grade TCC (HG)	12
Carcinoma in situ (CIS)	4
Adenocarcinoma prostate (Adeno Pr)	3
Sarcomatoid TCC (Sarc TCC)	1
Total	**29**

Out of the 22 specimens categorized as S-Lg or Lg, the subsequent histopathological diagnoses were negative (4), papillary urothelial neoplasm of low malignant potential - LMP (6), low grade Transitional Cell Carcinoma (10), high grade Transitional Cell Carcinoma (1) and Carcinoma In-Situ (1). Two specimens which were graded lower had only one urine specimen and cellularity was low in both cases.

Figure - 1: Pie chart showing number of high grade tumors on HPE.

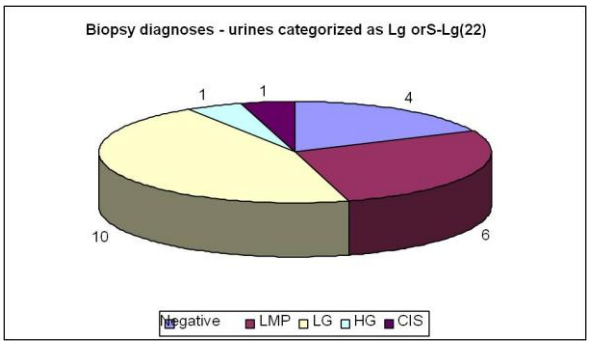


Figure - 2: Pie chart showing number of high grade tumors on HPE.

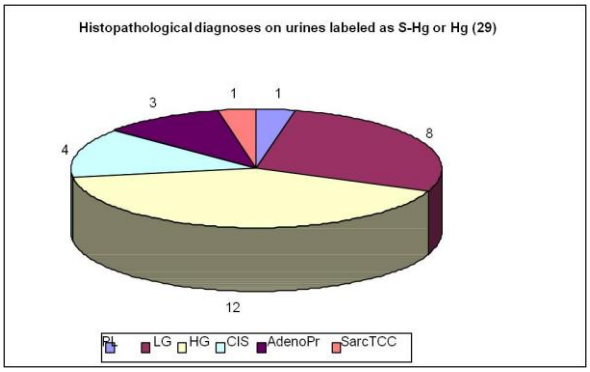
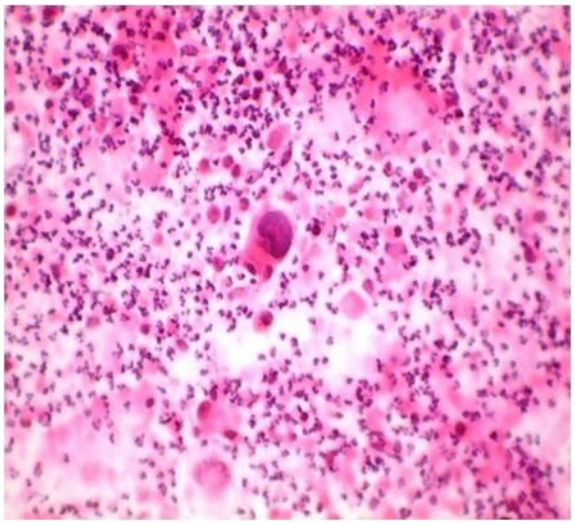


Figure – 3: Atypical cells in urine in the background of Neutrophils.



Discussion

Bladder is a hollow viscous with the shape of a four sided inverted pyramid when empty and of a

rounded structure when distended. It is divided into the following portions:

- Superior surface (also known as dome and covered by pelvic parietal peritoneum)
- Posterior surface (also known as the base)
- Two inferio-lateral surfaces.

Figure – 4: Clusters of atypical cells in urine with ragged borders.

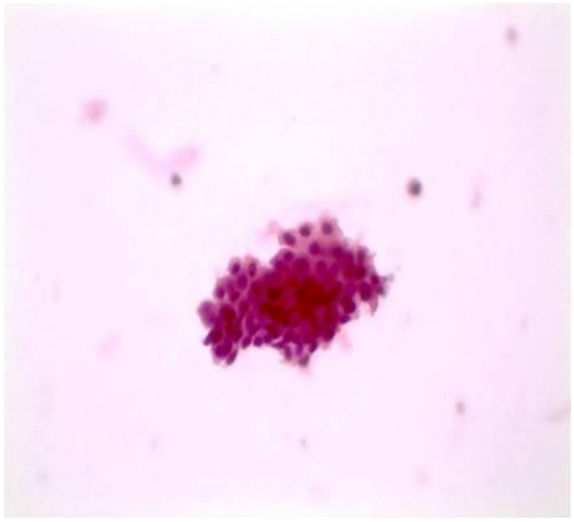
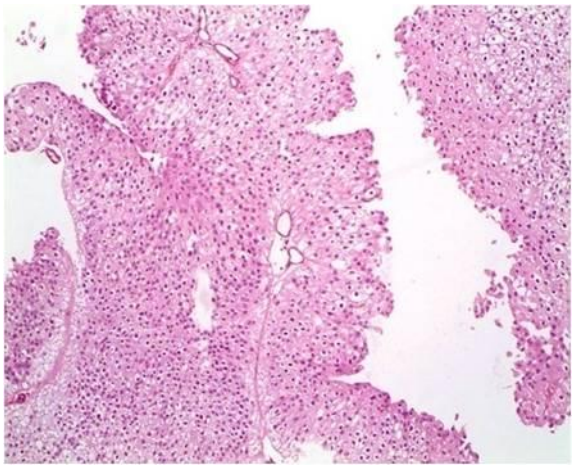


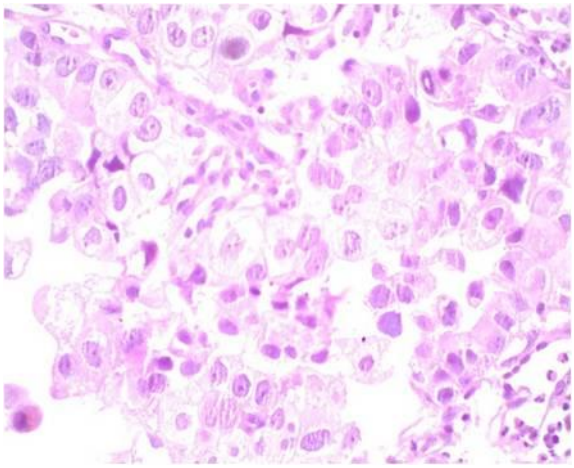
Figure – 5: Papillary urothelial neoplasm Low malignant potential (LMP).



Trigone is located at the base of bladder and is continuous with the bladder neck. Structure on which bladder neck rests is known as bladder bed [6]. Mucosa is formed by epithelium, lamina propria and (rarely) continuous or discontinuous muscularis mucosae. The epithelium of the bladder has been traditionally referred to as transitional also known as urothelium and is thrown into many folds in the relaxed state. The transitional epithelium is stratified, comprising 3-6 layers of cells, the number of layers being greatest when the epithelium is least distended. It has three layers-superficial, intermediate and basal. The cells of the basal layer are compact and cuboidal in form, while those of the intermediate layer are more columnar with their nuclei oriented at right angles to the basement membrane. The surface cells are umbrella or dome cells. The umbrella cells are large and ovoid with round nuclei and plentiful eosinophilic cytoplasm. Transitional cell carcinoma of urinary bladder may be papillary or non papillary and invasive or in situ. Non papillary tumors or at least the poorly differentiated papillary tumors arise from areas of atypical urothelial proliferation. Papillary and non papillary tumors often coexist in the same patient, but the development of well-differentiated papillary tumors from area of epithelial atypia is not as clearly demonstrable and these tumors are often surrounded by normal appearing urothelium. All the tumors of urothelial tract exfoliate readily into the urinary stream. The great majority occur in urinary bladder [7]. Cigarette smoking is clearly the most important influence, increasing the risk 3 fold to 7 fold, depending on pack-years and smoking habits [1]. Cigarette smoking is believed to contribute to up to 50% of the diagnosed urothelial cancers in men and up to 40% in women. The risk of developing urothelial malignancy in male smokers is increased two- to fourfold relative to nonsmokers and continues for 10 years or longer after cessation. Industrial exposure to arylamines particularly 2-Naphthylamine as well as related compounds. Schistosoma hematobium infections in areas where these are endemic (Egypt, Sudan) are an established risk. Long term usage of analgesics. Heavy long term exposure to cyclophosphamide, an immuno suppressive agent. Prior exposure of bladder to radiation, often performed for other

pelvic malignancies, increases the risk of urothelial carcinoma [1].

Figure – 6: High grade transitional cell carcinoma.



Bladder tumors classically produce painless hematuria. This is their dominant and sometimes only classical manifestation [1]. Hematuria may be intermittent, so a urine analysis without RBCs does not exclude the diagnosis of urothelial cancer. In those with macroscopic hematuria the reported rates of bladder cancer range from 13-34.5% [8]. The rates of bladder cancer in patients with microscopic hematuria has been reported to range from 0.5- 10.5% in several studies in different populations [8]. Other irritative symptoms like frequency, urgency and dysuria occasionally accompany Hematuria .They may be the initial presentation of bladder cancer. The Mayo clinic experience with CIS reveals that 80% of the patients presented with irritative symptoms. Two thirds of these patients did not have hematuria. In patients with irritative bladder symptoms not related to an active infection or other defined urologic disease, the clinician must consider a diagnosis of bladder cancer [8].

The earliest mention of urine cytology for the diagnosis of bladder cancer is Sander's report of finding neoplastic tissue in urine in 1864. The results of cytological examination of urinary sediment for the diagnosis of urinary tract carcinomas were later published by Papinacolaou in 1945 and are now established as a part of routine investigation of the patients with hematuria, prostatism and suspected urinary tract neoplasias [9]. Urinary cytopathology is used as a screening test to detect a urologic malignancy – to monitor patients after treatment for a urologic malignancy and to establish a diagnosis in patients who present with signs and symptoms of urologic disease [10].

The importance of urinary cytology in the detection and follow up of patients with urothelial carcinoma has become well established in recent years [11-14]. Individuals with a positive cytology but a negative evaluation have a higher risk of developing macroscopic lesions within the following 3-12 month period especially if the cytology remains positive. Patients with transitional cell carcinoma of bladder are at risk of concurrent or subsequent cancer of upper tract. Following the diagnosis of TCC bladder the frequency of an upper tract urothelial neoplasm ranges between 1.5 to 5% However, if one selects only patients with high risk superficial bladder TCC rate of subsequent upper tract urothelial neoplasm has been reported to be as high as 20-29% in 15 years [15]. Prostate cancer may also result in positive cytology in <5% of the patients. Superficial urothelial carcinoma of the bladder is characterized by a high risk of recurrence (60-65%), consequently long term follow up is required. Cystoscopy as a monitoring tool is expensive and often associated with patient discomfort. In addition, its sensitivity is limited to tumors that can be visualized, and therefore recurrences in the upper tract and often quite normal appearing carcinoma in situ can be missed .Cytology, however exhibits variable sensitivity depending on the tumour grade with lowest sensitivity for low grade tumors. In addition the interpretation of a urine specimen is highly dependent on the skill of the examiner and high inter and intra observer variation in the sensitivity has been observed [16].

In our study, out of total 54 patients, 6 were females (12.5%) and 48 were males (87.5%). In National Cancer Data base report by Neel E

Fleishner, et al. [17], of all the patients diagnosed with bladder cancer, 73.5% were males. A retrospective study of the Netherlands Cancer registry [18] spanning the period 1989-1994 identified 20 541 patients diagnosed with UCB of whom 80% were males and 20% females. We have also observed similar incidence in our study.

The ages of the patients in our study were in the range of 28-86 years, with maximum patients in the age group of 61-70 years. The mean age of presentation was 64.1 years. In similar study by Ramkumar S, et al. [19], where he studied 196 patients undergoing cystoscopy and bladder cancer surgery, mean age of patients was 66 years (range 29-102 years). In another similar study by Desai F, et al. [20], age range of patients was 25-80 years with mean age of 54.5 years. In our study, the overall sensitivity of cytology for detection of bladder tumour was 75%, while sensitivity of cytology for detecting low grade and high grade lesions of bladder was 44% and 74% respectively. The specificity for both was 78%. A similar study that supports our study was conducted by C Garbar, et al. [21]. Between 2002 and 2004, 592 bladder washings were obtained using a flexible cystoscope from 139 patients. For each sample reference standard was histology when a lesion was present at the time of cystoscopy. The frequencies of cytological diagnosis was compared against the reference standard, overall sensitivity ranged from 37% to 81% and specificity from 95% to 99%. For all thresholds of cytological diagnosis, sensitivity increased with the grade of non-invasive papillary urothelial tumors and was the highest for CIS and invasive carcinoma. Ramkumar S, et al. [19] studied voided urine specimens from 196 patients undergoing cystoscopy and found the overall sensitivity of urine cytology to be 44%.

Out of the 29 specimens which were categorized as S-Hg or Hg, the subsequent histopathological diagnoses corresponding to each sample were Papillary urothelial neoplasm of low malignant potential - LMP (1), low grade Transitional cell carcinoma (8), High grade Transitional Cell Carcinoma (12), Carcinoma In-Situ (4), Sarcomatoid Transitional carcinoma (1) and adenocarcinoma of prostate involving bladder mucosa (3). 9 of these specimens from 5 patients were graded higher when compared with the reference standard i.e. cystoscopic biopsies. Out of the 22 specimens categorized as S-Lg or Lg, the subsequent histopathological diagnoses were negative (4), papillary urothelial neoplasm of low malignant potential - LMP (6), low grade Transitional Cell Carcinoma (10), high grade Transitional Cell Carcinoma (1) and Carcinoma In-Situ (1). Two specimens which were graded lower had only one urine specimen and cellularity was low in both cases.

Conclusion

Urine cytology is simple, cost effective, non-invasive diagnostic test used for screening and detection of the early cases of bladder cancers. The cases with clinical features of hematuria, frequency, urgency, and dysuria, history of exposure to various types of dye material or past history of bladder tumor are to be seen more stringently. The sensitivity of cytology for detection of low grade and high grade lesions of bladder was 44% and 74% respectively. The specificity for both was 78%.

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