Research Article

Diagnostic Efficacy of Urine Cytology for Screening of Bladder Cancer: A Retrospective Study

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Abstract

Background: Exfoliative urine cytology is considered to be an essential non-invasive procedure for the diagnosis of bladder cancers and also for monitoring the patients with bladder cancers. **Objective:** The present study was carried out to determine the efficacy of urinary cytology in detecting the bladder cancer by analyzing the cytological findings in histopathologically proven bladder cancer patients. **Methods:** Urine cytology findings in 56 patients, who were histopathologically diagnosed to have bladder cancer were analyzed retrospectively. Urine specimen was centrifuged and sediment was examined for tumor cells. **Results:** Out of 56 patients studied, 28 patients showed malignant cells in urine (50%), 6 patients (10.71%) showed suspicious cells, 3 patients (5.36%) showed dysplastic cells and 19 patients (33.93%) urine cytology was negative for malignant cells. Urine cytology for malignant cells was positive in most cases having high grade bladder tumors and in tumors in advanced stage showing muscle infiltration. **Conclusion:** Urinary cytology is a less expensive, non-invasive procedure used for screening bladder tumors and can detect the high grade tumors and tumors with higher staging effectively.

Keywords: Urine cytology, Bladder Tumors, Tumor Grade

Introduction

World wide Urinary bladder carcinomas are 7th most common caners in men and 17th most common cancers in women. Most common risk factor is smoking. Other risk factors include occupational exposure to aromatic amines, and polycyclic aromatic hydrocarbons. Genetic predisposition has also been suggested [1].

Urinary cytology is considered to be the most established non-invasive method for detecting bladder cancers and also in the follow up of patients with history of bladder cancer. Though the tumors with high cytological grade can be readily detected by urine cytology, the results in detecting the low grade tumors are not satisfactory [2].

The efficacy of the urinary cytology in bladder tumors can be improved by multiple examinations of the patients. The problems in this areas are mainly because of paucity of exfoliated cellular elements and less experienced cytopathologists in recognizing and evaluating cellular changes. The exfoliated cells in urine samples are evaluated using the criteria developed for other organs like uterine cervix. This approach is satisfactory for determining the high grade tumors but is not applicable for evaluating low grade tumors [3]. In our study we conducted the retrospective analysis of urine cytology in histopathologically proven bladder cancer cases.

Recent development of molecular technologies helps in detecting the molecular markers on exfoliated cells in urine. Tumor specific markers can be detected by immunoflourescence. Flourescence insitu hybridization (FISH) is used to detect the chromosomal abnormalities in exfoliated urothelial cells. Automated image cytometry detects abnormality in DNA ploidy and nuclear shape.

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Materials and methods

Urinary cytology of 56 patients who had been histologically proven to have bladder carcinoma were studied retrospectively. Urine samples received were centrifuged in the cytospin and the sample was fixed and stained with Haematoxylin and Eosin. The cytological findings in the specimens were classified as negative for malignancy, dysplastic cells, suspicious for malignancy and positive for malignancy. These findings were compared with histological grade and stage of tumors.

Results

In this study, we correlated retrospectively the urine cytology findings in the 56 patients who had been histologically diagnosed to have bladder cancer. Urine cytology findings were classified as positive for malignant cells, suspicious cells, dysplastic cells and negative for malignant cells.

Table 1- Urine cytology results in bladder tumors

Urinary cytology results	Number of cases	Percentage
Positive for malignancy	28	50
Suspicious cells	6	10.71
Dysplastic cells	3	5.36
Negative for malignant cells	19	33.93

Out of 56 patients, 28 patients (50%) showed malignant cells in urine, 6 patients (10.71%) showed suspicious cells, 3 patients (5.36%) showed dysplastic cells and 19 patients (33.93%) were negative for malignant cells (Table -1) (Figure 1)

Table 2- Urine cytology results in relation to grades of bladder tumors

Urine cytology results	Low grade tumors	High grade tumors
Positive for malignant cells	3 (15.7%)	25 (67.6%)
Suspicious cells	1 (5.3%)	5 (13.5%)
Dysplastic cells	1 (5.3%)	2 (5.4%)
Negative for malignant cells	14 (73.7%)	5 (13.5%)
Total	**19**	**37**

Bladder tumors were histologically graded as low grade and high grade. The urinary cytology findings were correlated with grade of bladder tumors. Maximum number of high grade tumors showed malignant cells in urine (67.6%) and most of the low grade tumors were cytologically negative for malignant cells (73.7%). Only 3 cases (15.7%) showed malignant cells in urine (Table -2) (Figure 2).

Table 3- Urine cytology results in relation to stage of bladder tumors.

Urine cytology results	pTa	pT1	pT2
Positive for malignant cells	4 (21.05%)	6 (54.55%)	18 (69.23%)
Suspicious cells	2 (10.53%)	1 (9.09%)	3 (11.54%)
Dysplastic cells	0	1 (9.09%)	2 (7.69%)
Negative for malignant cells	13 (68.42%)	3 (27.27%)	3 (11.54%)
Total	**19**	**11**	**26**

56 bladder tumors were staged pathologically and compared with urinary cytology. 19 tumors were non-invasive (pTa), 11 tumors invaded subepithelial connective tissue (pT1), 26 tumors invaded the muscle (pT2). Maximum number of cases in the stage of pT1 (54.55%) and pT2 (69.23%) showed tumor cells in urine. Urine cytology in maximum number of cases in the stage of pTa (68.42%) were negative for malignant cells (Table - 3) (Figure 3).

Discussion

Urine cytology involves microscopic examination of voided urine and bladder washes and identification of exfoliated tumor cells. The mid stream voided urine sample is centrifuged and sediment is fixed and stained, which is examined microscopically for detecting the exfoliated cells in urine. The potential value of urine cytology is reduced due to lack of specific cellular criteria for diagnosing the low grade papillary and flat lesions of bladder. The recognition of morphological features of cellular elements specific for urothelial neoplasia and dysplasia can enhance the role of urine cytology in detecting bladder cancers and also in follow - up of these patients [4,5]

The specific cytologic criteria for diagnosing high grade, low grade neoplasia as well as dysplasias in the cytological samples had been discussed in few studies [5]. In high grade transitional carcinomas, the cells are large, pleomorphic with amphophilic cytoplasm and increased nuclear cytoplasmic ratio. The nuclei have irregular borders, coarse chromatin and prominent nucleoli. In the low grade transitional tumors, the cells are larger, having eccentric nuclei with increased nuclear cytoplasmic ratio and have slightly basophilic cytoplasm. The nuclei show indentation with granular chromatin and presence of small or inconspicuous nucleoli.

The cytological features of cells in flat dysplastic lesions and non-invasive urothelial tumors are similar to low grade. They differ in that the cells are less abundant in samples and occur as loose and small clusters. The cells have slight increase in nuclear cytoplasmic ratio and more fine granular chromatin then the cells of low grade tumors [3]. Reactive or reparative urothelial cells are enlarged but the cytoplasm is vacuolated and has centrally placed nuclei with smooth borders and prominent nucleoli.

Though the cytological criteria have been given for defining the lesions, yet there are several factors which contribute to the poor ability of urine cytology in detecting the bladder cancer cells. Some of them arer sample of urine examined is only a fraction of the sample which decreases the chance of capturing all cells, and the erythrocytes and leukocytes which are present as background cells may confound the cytologic technique [6].

Urine cytology has relatively low sensitivity and high specificity, particularly for well differentiated bladder tumors [7]. Novel molecular markers present on the exfoliated cells in voided urine can be detected by the application of new molecular tools. This will increase the specificity of urine cytology. Certain substances like mucin glycoproteins [8], protein dimmers [9], and lewis X antigen are expressed on the bladder tumor cells which can be detected bymolecular technologies. This increases the advantage of urine cytology as non-invasive procedure. Cytologists depend upon the identification of alterations in the nuclear shape and characteristics of tumor cells in urine specimens which can be analyzed by 'Automated image cytometry' on a more objective scale. The Quanticyt system employs image analysis to identify DNA ploidy abnormalities and nuclear morphometry [10].

Most commonly associated genetic aberration is homozygous loss of band 9p21which is the site for the tumor suppressor gene p16 and is known to be the earliest genetic event in the development of papillary carcinoma and urothelial carcinoma in situ[11]. Increased chromosomal instability and aneuploidy have been implicated in tumor progression. Polysomy of chromosomes 3, 7 and 17 and deletions of 9p21 were the most sensitive and specific markers for the detection of 95% of recurrent Urothelial carcinoma [12].

A commercial FISH assay (Urovysion Bladder Cancer Kit) which includes probes for the centromeres for chromosomes 3,7, nd 17 and has a locus specific probe for 9p21 was developed to screen for recurrent urothelial carcinoma. The intended use is as an aid for initial diagnosis of bladder cancer patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer [13]

Conclusion

Exfoliative urine cytology, a non-invasive procedure is a useful and less expensive method for detecting high grade tumors but has limitations in detecting the low grade tumors. Though the efficacy of the urine cytology can be increased by the use of molecular diagnostic tests along with the automated technologies, yet it is still useful in many hospitals as more expensive tests are still not available.

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References

1. Maximilian Burger, James W.F Catto, Guido Dalbag N, H.Barton Grossman, Harry Herr, Pierre Karkiewicz, Wassim Kassouf, Lambertus A.Kiemeney,Carlo La Vecchia, Shahrokh Shariat and Yair Lotan. Epidemiology and risk factors of Urothelial Bladder cancer.European Urology 2013;vol 63 issue1:234-241.

2. Freidell GH, Hawkins AR, Ahmed SW, Schmidt JE. The role of urinary tract cytology in the detection and clinical management of bladder cancer.In: Bonney WW,ed.AUA Monograph, Bladder Cancer vol 1. Baltimore: The Williams and Wilkins Co.,1982;49-62.

3. William M. Murphy, Mark S. Soloway, Alina F. Jukkola, William N. Crabtree and Kimball S Ford. Urinary cytology and bladder cancer. The cellular features of transitional cell neoplasms. Cancer 1984;53:1555-65.

4. Murphy WM, Irving CC. The cellular features of developing carcinoma in murine urinary bladder. Cancer 1981;47:514-522.

5. Murphy WM, Soloway MS. Developing carcinoma (dysplasia) of urinary bladder. Pathol Annu 1982;17:197-217.

6. Weiner HG, Voojis GP, Van't Hof-Grootenboer B. Accuracy of urinary cytology in the diagnosis of primary and recurrent bladder cancer. Acta Cytol 1993;37(2):163-9.

7. Carmack AJ, Soloway MS. The diagnosis and staging of bladder cancer: From RBCs to TURS. Urology 2006;67(3 suppl 1):3-8;discussion-10.

8. Mitra AP, Birkhahn M, Penson DF,Cote RJ. Molecular screening for bladder cancer. Waltham,MA: Upto date;2009[cited October 2009]; Available from:http://www.uptodate.com.

9. Gilbert SM, Veltri RW, Sawczuk A, Shabsigh A, Knowels DR, Bright S, et al. Evaluation of DD23 as a marker for detection of recurrent transitional cell carcinoma of the bladder in patients with a history of bladder cancer. Urology 2003;61(3):539-43.

10. Van der Poel HG, Witjes JA, van Stratum P, Boon ME, Debruyne FM, Schalken JA. Quanticyt: karyometric analysis of bladder washing for patients with superficial bladder cancer. Urology,1996;48(3):357-64.

11. Halling KC, King W, Sokolova IA, Meyer RG, Burkhardt HM, Halling AC, et al. A comparision of cytology and flourescence in situ hybridization for the dwetection of urothelial carcinoma. J Urol 2000;164(5):1768-75.

12. Sokolova IA, Halling KC, Jenkins PB, Burkhardt HM, Meyer RG, Seelig SA, et al. The development of multi target, multicolor flourescence insitu hybridization for the detection of Urothelial carcinoma in urine. J Mol Diagn 2000;2(3):116-23.

13. Veeramachaneni R, Nordberg ML, Shi R, Herrera GA, Turbat-Herrara EA. Evaluation of flourescence in-situ hybridization as an ancillary tool to urine cytology in diagnosing urothelial carcinoma. Diagn Cytopathol 2003;28(6):301-7.

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