

Urological Oncology

Comparative Evaluation of Urinary Bladder Cancer Antigen and Urine Cytology in the Diagnosis of Bladder Cancer

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ABSTRACT

Introduction: The diagnostic value of the urinary bladder cancer (UBC) antigen as a tumor marker is not clear yet. We designed this study to compare the accuracy of the UBC antigen and voided urine cytology in patients with bladder cancer.

Materials and Methods: Fifty-four consecutive patients admitted for a diagnostic workup for bladder cancer were enrolled. Two voided urine samples were taken for urinalysis, both before performing cystoscopy. The samples were examined for urinary urine cytology and UBC antigen. Cystoscopy was done. Resection of pathologic lesion, if any, or random biopsies of multiple foci of the bladder was performed. The results of the diagnostic tests were compared with the pathology examination results.

Results: Of 54 patients, 31 had histologically confirmed transitional cell carcinoma. Results were positive for UBC antigen in 28 and for urine cytology in 16 patients. Sensitivities and specificities were 74.2% and 78.3% for UBC antigen, 48.4% and 95.7% for urine cytology, and 87.1% and 73.9% for combined UBC antigen and cytology, respectively. Positive and negative likelihood ratios were 3.42 and 3.03 for UBC antigen, 11.3 and 1.85 for urine cytology, and 3.34 and 5.73 for combined UBC antigen and cytology, respectively.

Conclusion: The UBC antigen test had acceptable sensitivity and specificity in our study. However, results of voided urine cytology are significantly more reliable. A combination of tumor markers may help diagnose new tumors and lower the requirements for cystoscopy during follow-up. Further studies are warranted to find a more accurate noninvasive test or a complex of tests comparable with cystoscopy for diagnosis of bladder cancer.

KEY WORDS: bladder cancer, diagnosis, tumor marker, urine cytology, urinary bladder cancer antigens

Introduction

Bladder cancer is more prevalent in men, being the second most common malignancy in older men, following prostate cancer.⁽¹⁾ Painless gross hematuria is a hallmark, but nonspecific symptoms such as frequency, urgency, and

dysuria may be seen, especially in association with carcinoma in situ or invasive bladder cancer. However, microscopic or macroscopic hematuria is almost always present. We speculate that tumors with microscopic hematuria are smaller than those with gross hematuria, and consequently, the diagnostic tests are a less sensitive. Given the difficulty of diagnosis in such cases and also the short preclinical latency of bladder tumors, special attention must be paid to

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introduction of an accurate noninvasive test for early diagnosis. Recent studies have shown the diagnostic values of some urinary tumor markers.⁽²⁻⁸⁾ However, their clinical role has not yet been confirmed.

Although cytokeratins are seen in all normal epithelial cells, an association between their concentrations and malignancy has been shown. As most malignant tumors originate from epithelial cells, cytokines could be a valuable marker. Degenerative changes of bladder cells can lead to release of cytokeratins or their fragments in urine, mostly cytokeratins 8 and 18. Using urinary bladder cancer (UBC) antigen, we can measure these urinary cytokines.^(4,6) Using an enzyme-linked immunosorbent assay (ELISA), the cytokines are traced with an anti-UBC monoclonal antibody and a labeled antibody.⁽²⁾

Diagnostic value of the UBC antigen is a matter of controversy. We designed this study to compare the accuracy of UBC antigen and voided urine cytology in patients with bladder cancer.

Materials and Methods

This study was done at the Shaheed Hasheminejad Hospital, Iran University of Medical Sciences, in Tehran, Iran, between 2001 and 2002. Fifty-four consecutive patients (44 men, 10 women; mean age, 59.5 ± 8.4 years; range, 29 to 87 years) admitted for a diagnostic workup for bladder cancer were enrolled. Informed consent was obtained from all patients. Physical examination was performed and history was taken in all patients. Two separate morning midstream voided urine samples were taken for urinalysis, both before performing cystoscopy. The samples were examined for urinary creatinine level, urine cytology, and UBC antigen. All of the patients underwent cystoscopy by a single experienced urologist. Resection was performed in the presence of an apparent pathologic lesion, and if there were no lesions, random biopsies of multiple foci of the bladder were taken. The specimens were examined histologically, based on the Ash grading system.⁽⁹⁾

Voided urine specimens were centrifuged for 10 minutes, and the supernatant was frozen at -20°C and used for monoclonal ELISA and creatinine level measurements. The ideal UBC rapid ELISA is a 2.5-hour test specifically designed to determine antigens in urine. Specimens were incubated with a monoclonal anti-UBC catcher antibody. During incubation, the immobilized

antibody and horseradish-peroxidase-labeled antibody bind to the UBC antigen, forming a sandwich. The wells were washed and a substrate solution was added. The resultant color was an indicator of cytokeratin-8 and cytokeratin-18 concentrations.^(2,4)

Creatinine was measured in urine samples, and the UBC results were corrected for creatinine concentration in urine by dividing their values by milligrams of urinary creatinine.

Sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios were calculated for the diagnostic tests, according to standard statistical methods, using SPSS software (Statistical Package for the Social Sciences, version 11.5, SSPS Inc, Chicago, Ill, USA).

Results

Forty patients (74.1%) had tumoral lesions in cystoscopy, and random biopsies were performed in 14 (25.9%). On pathologic examination, transitional cell carcinoma (TCC) was confirmed in 31 patients (57.4%), of whom 27 had TCC grade 2/4 and 4 had TCC grade 3/4. Results of the biopsy specimens of the 23 remaining patients were normal or otherwise contained benign tumoral cells.

Details of the results of UBC antigen and urine cytology in association with histologic results are shown in Table 1. UBC antigen tests were positive in 28 patients (51.9%), while urine cytology was positive for TCC in 16 (29.6%). The sensitivity of UBC antigen was significantly higher than that of urine cytology (74.2% versus 48.4%), while urine cytology had a higher specificity (95.7% versus 78.3%). Considering the positive results of both tests, the combined sensitivity and specificity of the UBC antigen test and of cytology were 87.1% and 73.9%. Of 28 patients with a positive UBC antigen, 11 had positive urine cytology, and 21 out of 26 with a negative UBC antigen test had negative urine cytology too.

Likelihood ratios and other characteristics for urine cytology, UBC antigen, and both are listed in Table 2.

Discussion

A noninvasive method for diagnosing bladder cancer has yet to be established. Several immunohistochemical assessments of urine have been proposed as tumor markers for bladder

TABLE 1. The results of biopsy and diagnostic tests

		Biopsy Results		Total number of patients
		Patients with positive for TCC	Patients with negative for malignancy	
UBC	Positive	23	5	28
	Negative	8	18	26
Urine cytology	Positive	15	1	16
	Negative	16	22	38
Combined UBC and Cytology	Positive	27	6	33
	Negative	4	17	21
Cystoscopy	Positive	31	9	40
	Negative	0	14	14
Total		31	23	54

cancer, such as urinary concentrations of cytokines, fibronectin, matrix protein-22, and cytokeratin fragments 21-1. The UBC ELISA is a recently advocated method; however, the results remain a matter of controversy. In this study, we compared UBC ELISA with urine cytology, a current diagnostic tool, and considered histologic examination as the standard reference. Our results indicate that the UBC test was superior to urine cytology when the sensitivity of the test was of importance, but the specificity of cytology is significantly higher. However, a combination of the two tests (a positive result of either UBC antigen or cytology) may bring about an acceptable sensitivity of 87.1%. When considering positive likelihood ratios, a UBC antigen positive result is less reliable than a positive urine cytology (3.41 versus 11.2); however, to achieve a better negative likelihood ratio, a combination of the two tests is superior to either cytology or UBC alone (4.7 versus 1.8 and 3.04, respectively).

Eissa and colleagues⁽²⁾ have evaluated the UBC antigen test, urine cytology, fibronectin, and nuclear matrix protein-22 in 168 patients of whom 100 had been histologically diagnosed with bladder cancer. They found that the sensitivity of the UBC antigen test was higher than that of cytology (67% versus 55%), while the specificity of

cytology was significantly higher (100% versus 80.8%). They showed that fibronectin and nuclear matrix protein-22 are more accurate markers, and that a combination of cytology with other markers can increase the sensitivity to as much as 95%. UBC antigen and urine cytology had an 82.8% sensitivity. Our results agree with the Eissa and coworkers study.

The sensitivity of the UBC antigen test has been reported to be as low as 20.7% in one study by Mungan and colleagues⁽⁸⁾ and as high as 82.0% in another study by Sumi and coworkers.⁽¹⁰⁾ However, in most studies, it has been over 60% and superior to urine cytology.^(2,3,5,7,10-12) Concerning the specificity, urine cytology has proven to be a better test with a rate of 86.9% to 100%^(2,3,10); while specificity ranges for the UBC antigen test range from 79.3% to 92%,^(3,8,11,12) which are higher than our results. It appears, then, that although the UBC antigen test can provide relatively valuable information, cystoscopy cannot be replaced by this test.

Boman and colleagues⁽⁵⁾ have shown that tumor size, grade, and stage have a strong impact on the diagnostic power of tumor markers. They concluded that these tests may be more appropriate for the follow-up of the patients with bladder cancer, as recurrent tumors are usually

TABLE 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios of UBC, urine cytology, and cystoscopy

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Positive likelihood ratio	Negative likelihood ratio
UBC	74.2	78.3	82.1	69.2	3.42	3.03
Urine cytology	48.4	95.7	93.8	57.9	11.3	1.85
UBC + Cytology	87.1	73.9	81.8	81.0	3.34	5.73
Cystoscopy	100	60.9	77.5	100	2.55	-

smaller. In their study, the sensitivity of the UBC antigen test was 72% for recurrent and 60% for new tumors.

Mian and colleagues evaluated tumor markers during follow-up of patients with transurethral resected urothelial cell carcinoma and reported the sensitivity and specificity of the UBC test to be 66% and 90%.⁽¹¹⁾ Sanchez-Carbayo and colleagues followed 232 patients with a previous bladder carcinoma and found that monitoring the disease with the UBC test was able to detect recurrence sooner than scheduled cystoscopies in 87% of the patients.⁽⁴⁾ In another study, they also showed that monitoring patients with urinary tumor markers, including the UBC antigen, could detect early recurrence in Bacillus Calmette-Gurein nonresponders.⁽⁶⁾ However, none of the researchers advocate substitution of the UBC test or other tumor markers over cystoscopy. They simply suggest that these tests could lower the number of cystoscopies needed or individualize the intervals between cystoscopies during follow-up of patients with bladder carcinoma.^(4,11) Even Mungan and coworkers found no diagnostic value for the UBC antigen test during follow-up of patients with superficial bladder cancer.⁽⁸⁾

Cystoscopy remains the preferred standard, provided that random biopsies are considered in cases of no apparent lesion. Our study showed its sensitivity to be 100%. Still, further investigation of urinary tumor markers is warranted. Some tumor markers other than UBC antigen have been shown to be more accurate in some studies. For instance, it has been shown that the nuclear matrix protein (NMP22) assay surpasses the UBC antigen test.^(2,5) The results yielded by BTA stat and cytokeratin fragments are also comparable.^(3-5,11) It seems that an appropriate combination of these tests may offer a favorable noninvasive diagnostic tool.

Conclusion

The diagnostic value of urinary tumor markers is not yet clear. The UBC antigen test demonstrated acceptable sensitivity and specificity in our study. However, positive results of voided urine cytology are significantly more reliable. Further studies are warranted to find a more accurate noninvasive test or a combination of tests comparable with cystoscopy.

References

1. Messing EM. Urothelial tumors of the renal pelvis and ureter. In: Walsh PC, Retik AB, Vaughan ED Jr, et al,

editors. *Campbell's urology*. 8th ed. Philadelphia: WB Saunders; 2002. p.2737-41.

2. Eissa S, Swellam M, Sadek M, Mourad MS, Ahmady OE, Khalifa A. Comparative evaluation of the nuclear matrix protein, fibronectin, urinary bladder cancer antigen and voided urine cytology in the detection of bladder tumors. *J Urol*. 2002;168:465-9.
3. Babjuk M, Kostirova M, Mudra K, et al. Qualitative and quantitative detection of urinary human complement factor H-related protein (BTA stat and BTA TRAK) and fragments of cytokeratins 8, 18 (UBC rapid and UBC IRMA) as markers for transitional cell carcinoma of the bladder. *Eur Urol*. 2002;41:34-9.
4. Sanchez-Carbayo M, Urrutia M, Gonzalez de Buitrago JM, Navajo JA. Utility of serial urinary tumor markers to individualize intervals between cystoscopies in the monitoring of patients with bladder carcinoma. *Cancer*. 2001;92:2820-8.
5. Boman H, Hedelin H, Holmang S. Four bladder tumor markers have a disappointingly low sensitivity for small size and low grade recurrence. *J Urol*. 2002;167:80-3.
6. Sanchez-Carbayo M, Urrutia M, Romani R, Herrero M, Gonzalez de Buitrago JM, Navajo JA. Serial urinary IL-2, IL-6, IL-8, TNFalpha, UBC, CYFRA 21-1 and NMP22 during follow-up of patients with bladder cancer receiving intravesical BCG. *Anticancer Res*. 2001;21(4B):3041-7.
7. Giannopoulos A, Manousakas T, Gounari A, Constantinides C, Choremi-Papadopoulou H, Dimopoulos C. Comparative evaluation of the diagnostic performance of the BTA stat test, NMP22 and urinary bladder cancer antigen for primary and recurrent bladder tumors. *J Urol*. 2001;166:470-5.
8. Mungan NA, Vriesema JL, Thomas CM, Kiemeny LA, Witjes JA. Urinary bladder cancer test: a new urinary tumor marker in the follow-up of superficial bladder cancer. *Urology*. 2000;56:787-92.
9. Ash JE. Epithelial tumors of the bladder. *J Urol*. 1940;44:135-45.
10. Sumi S, Arai K, Kitahara S, Yoshida KI. Preliminary report of the clinical performance of a new urinary bladder cancer antigen test: comparison to voided urine cytology in the detection of transitional cell carcinoma of the bladder. *Clin Chim Acta*. 2000;296:111-20.
11. Mian C, Lodde M, Haitel A, Egarter Vigl E, Marberger M, Pycha A. Comparison of two qualitative assays, the UBC rapid test and the BTA stat test, in the diagnosis of urothelial cell carcinoma of the bladder. *Urology*. 2000 Aug 1;56(2):228-31.
12. Mian C, Lodde M, Haitel A, Vigl EE, Marberger M, Pycha A. Comparison of the monoclonal UBC-ELISA test and the NMP22 ELISA test for the detection of urothelial cell carcinoma of the bladder. *Urology*. 2000;55:223-6.