**Bladder tumor antigen sensitivity in bladder cancer patients**

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**Abstract**

With its incidence continuing to increase, bladder cancer is now the fifth most common cancer in the world. Approximately half of these patients will have muscle-invasive disease at diagnosis and have distant metastasis within 2 years and 60% die within 5 years despite treatment. Therefore, rapid and sensitive urine based markers are still under investigation. In this study, we aim to find the BTA stat results for 259 Turkish patients (200 patients with and 59 without bladder cancer) whose voided urine samples were samples were available before cystoscopy or other surgical intervention. Histopathological results compared with BTA results. The mean age of 200 patients included in the study was 67 years and range was 25 to 81. 164 of 200 patient was follow up patients and the rest of them was first diagnosed group. In our study groups BTA stat test’s sensitivity and specificity was 75% and 80% respectively. However it is not enough specific and more variability of obtained data is not reliable. Besides of these, healthy donors’ urine tests were 40% positive. This means BTA stat have specificity problems. Therefore BTA stat test is not a sufficient diagnostic test.

**Key words:** BTA stat, bladder cancer, urine based tests

**Mesane kanseri hastalarında mesane tümör antijen hassasiyeti**

**Özet**


**Anahtar sözcükler:** BTA stat, mesane kanseri, idrar testleri

**Introduction**

With its incidence continuing to increase, bladder cancer is now the fifth most common cancer in US, with an estimated 56,500 new cases predicted for 2002, of which 12,600 patients are expected to die of the disease (Buhijian et al., 2003). The three main types of cancers that affect the bladder are urothelial carcinoma (transitional cell carcinoma or TCC), squamous cell carcinoma, and adenocarcinoma. TCC, by far the most common form of bladder cancer accounting for more than 90% of these cancers in US,
is the second most common malignancy of the genitourinary tract and third most common cause of death among genitourinary tumors (Arisan, 2003). Bladder cancer is currently diagnosed using cystoscopy and cytology in patients with suspicious signs and symptoms. Most patients with bladder cancer are diagnosed upon a gross or microscopic hematuria (Bhuiyan et al., 2003; Arisan, 2003; Konety and Getzenberg, 2001). Approximately 75-80% of newly diagnosed bladder neoplasms are confined to the urothelium or invade the lamina propria (Ta and T1) and can be managed with transurethral resection (TUR) and intravesical therapy. The recurrence rate of these neoplasms is high with progression (Simon et al., 2003). Patients having high-grade disease have a worse prognosis. Approximately half of these patients will have muscle-invasive disease at diagnosis and have distant metastasis within 2 years and 60% die within 5 years despite treatment. Systemic treatment options for bladder cancer include surgery, chemotherapy, radiation, and immunotherapy (Konety and Getzenberg, 2003).

This situation indicates the importance of exact and sensitive diagnosis at initial level of illness. Current follow-up procedure after initial presentation typically includes cystoscopy and urine cytology every 3 months for 1-2 years, every 6 months for an additional 2-3 years and then annually, assuming no recurrence (Simon et al., 2003).

Cystoscopy is a relatively short, minimally traumatic office procedure performed with topical anesthesia that identifies nearly all papillary and sessile lesions. However, despite the introduction of the flexible cystoscope, it is still an invasive procedure, and causes some discomfort. Cystoscopy aided by cytology is the mainstay for diagnosing bladder cancer (Konety et al., 1999). Voided urine cytology has been used since 1945 as a screening test for this condition (Papanicolaou and Marshall, 1945). Cytology has a high sensitivity and specificity for the detection of high-grade tumors. However its sensitivity for low-grade tumor is poor and also expensive. It also requires a highly trained cytopathologist, who may not be available in all areas. On the other hand, cystoscopy is invasive and relatively expensive too, and it may also be inconclusive at times. Especially in many patients with an indwelling catheter or active inflammation, cystoscopy may not be definitive due to the grossly abnormal appearance of the bladder mucosa. The deficiencies of cytology and the invasiveness of cystoscopy again render each test suboptimal for tumor surveillance. Therefore, a noninvasive method for detecting and monitoring bladder cancer would be objective, noninvasive, and easy to administer and interpret, and have high sensitivity and specificity (Wiener et al., 1998; Malik and Murphy, 1999).

Other urological malignancies such as prostate cancer have an existing serum based marker that has been well studied or they are not likely to release potential marker substances into the urine, making urine based testing less useful (Saad et al., 2001; Bhuiyan et al., 2003). There are many investigations to find the most sensitive, useful for clinics and cheap marker for bladder cancer. However some Food and Drug Administration (USA) proved tests or still under research ones are not sufficient and enough for urine based diagnosis.

These tests detect human complement factor H related protein. This protein can be isolated from urine samples of bladder cancer patients. BTA stat is a spectrophotometric assay and it is really rapid and single step test (Malkowicz, 2000; D’Hallewin and Baert, 1995). Its sensitivity rate is 75% for carcinoma in situ patients and its specificity is over 85%. This test takes only 5-7 min for each specimen. Easy applicable test can advice office usage without trained laboratory technician and equipment (Arisan, 2003; Konety and Getzenberg, 2001). However BTA stat test, under benign genitourinary conditions, particularly hematuria, may yield false positive results (Messing et al., 1995). Therefore it is not a golden standard for diagnosis.

This study designed for showing BTA stat test sensitivity rates in Turkish bladder cancer patients in expanded patient population with other diagnostic features. These results may be useful for clinic diagnosis of bladder cancer in Turkish population.

**Materials and methods**

**Patients**

Total 259 patients (200 patients with and 59 without bladder cancer) whose voided urine samples were available before cystoscopy or other surgical intervention at the Sisli Etfal Research and Training Hospital, 1st urology clinics between March 1998-October 2002, histopathological results
compared with BTA results. Table 1 showed the details for the study group patients. All the tumor specimens were histological diagnosed as transitional cell carcinomas. A half of the patients with bladder cancer had a past history of the disease. The patients without bladder cancer included 59 with benign urological diseases such as urolithiasis and benign prostate hyperplasia and 19 who had a past treatment history of bladder cancer and were followed up with no evidence of recurrence.

**Study procedure**

Before any manipulation, an urine specimen from spontaneous miction was collected from the patient. The specimen was divided into two different samples; one for the BTA stat test and the other analysis, with the pathologist unaware of the test results. Next, cystoscopy was performed. Endoscopic resection and histopathological analysis were performed on those patients diagnosed with vesical cancer by at least one of the three tests, with cancer staging per the TNM classification and cancer grading as per the World Health Organization criteria.

**Histopathological analysis**

Tumors were classified by the criteria of the World Health Organization and staged according to TNM system by one pathologist who was unaware the study. Also sensitivity and specificity of the test were compared with these data and applied SPSS statistical software version 11.0. *p* value less than 0.05 were considered significant.

**BTA test**

The BARD BTA test (Bard Diagnostic Sci. C.R. Bard, Redmond, WA, USA) is a latex aggregation assay that qualitatively detects basement membrane complexes

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**Table 1**: Characteristics of 259 patients whose voided urine was evaluated by urinary cytology and the Bard bladder tumor antigen (BTA) test.

<table>
<thead>
<tr>
<th>Patients</th>
<th>With bladder cancer</th>
<th>Without bladder cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>Male/Female</td>
<td>129/71</td>
<td>28/22</td>
</tr>
<tr>
<td>Past medical history of bladder cancer</td>
<td>164</td>
<td>19</td>
</tr>
</tbody>
</table>

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**Table 2**: Relationship between BTA test results and histopathological findings for 200 patients with bladder cancer.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients number</th>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>41</td>
<td>BTA stat test</td>
<td>40</td>
<td>32-62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>120</td>
<td>BTA stat test</td>
<td>85</td>
<td>72-96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>T2-4</td>
<td>39</td>
<td>BTA stat test</td>
<td>91</td>
<td>89-95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>54</td>
<td>BTA stat test</td>
<td>43</td>
<td>40-51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>86</td>
<td>BTA stat test</td>
<td>70</td>
<td>67-76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>60</td>
<td>BTA stat test</td>
<td>95</td>
<td>85-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>
of the bladder wall in the urine samples. This test was performed in a blinded fashion by an impartial observer on all patient specimens in accordance with the manufacturer instructions. It is a one-step qualitative assay that recognizes a tumor antigen of the complement factor H family associated with transitional cell carcinoma. Five drops of fresh or previously frozen urine are placed on the entrance pool of a small immunochromatographic environment. The urine reacts with a colloidal gold-conjugate antibladder tumor associated antigen antibody. Antigen complexes are captured by another antibladder tumor-associated antigen antibody. A positive result is indicated by a red line after 5 minutes. A second line indicates an internal control zone. Excluded from the study were patients who had undergone surgical treatment or instrumentation within 14 days of testing, as well as patients active urinary tract infections.

**Statistical analysis**

Statistical values within the data were analyzed by SPSS statistical software (version 11.0).

**Results**

The mean age of 200 patients included in the study was 67 years and range was 25 to 81. 164 of 200 patient was follow up patients and the rest of them was first diagnosed group. In our study groups BTA stat test's sensitivity and specificity was 75% and 80% respectively. The BTA stat test results were decreased in low staged and graded patients. Table 2 explains the relationship between histological findings for bladder cancer and cytology and BTA test results for 200 patients with and 40 without bladder cancers. The histopathological diagnoses of the patients with bladder cancer were available and related with BTA test results. Positive BTA test results were found showed in Table 3 with cytological results. With BTA stat test, we had 24 false positive (40%) results.

These data is not statistically significant. Table 2 demonstrates the relationship between histopathological results and BTA test results for 200 patients with bladder cancer.

Diagnostic categories enabled us to calculate the sensitivities and specificities of clinical outcomes based on different decision thresholds or decision levels such as pathological investigations. In every clinical finding for diagnosis has different sensitivity and specificity rate.

**Discussion**

Various predominantly monoclonal antibodies directed against tumor associated antigens are receiving increased attention for the primary diagnosis and follow up of bladder cancer. Immunocytochemical methods using voided urine specimens have the advantage of being noninvasive. Several soluble markers have been previously described. The bladder tumor antigen (BTA Trak), nuclear matrix protein (NMP22), and urinary bladder antigen (UBC) have been investigated as diagnostic methods to substitute for voided urine cytology examination (Rife et al., 1979; Simon et al., 2003; Lokeshwar and Soloway, 2001). Unfortunately these techniques need upper degree laboratory supply and they are not providing office use strip test. Also Food and Drug Administration proved and under preclinical researches type tests have extremely variable sensitivity.

The first generation of the BTA test consisted of a latex agglutination test conducted in several steps that detected basement membrane complexes in the urine. The test provided better results than those provided by cytologic analysis. Its range is between 40.4% and 78% against a cytologic sensitivity of 16% and 39.3%. However Lee et al. (2000) demonstrated a greater sensitivity in cytologic analysis (54%). There are no superior results for BTA in published studies (Ian et al., 2001; Konety and Getzenberg, 2001).

The characteristics of the patients who underwent diagnostic test in our hospital did not differ from the series of other investigators, with a similar mean age and range. Ravery et al. (1998) and Sarosdy et al. (1995) reported sensitivity higher than that of cytological analysis in the different stages. (45% Ta, 85% T1, 75% T2-4) for BTA stat test. When they compared the grades for BTA stat test, 38% G1, 64% G2 and 71% G3 were obtained.

In our study group, the sensitivity of test 40% in Ta, 85% in T1 and 91% in T2-4. When grades investigated for BTA stat test results, 43% sensitivity for G1, 70% for G2 and 95% for G3 was determined (Table 2). The sensitivity of the BTA test is better than cytological experiments. However it is not enough
specific and more variability of obtained data is not reliable. Besides of these, healthy donors’ urine tests were 40% positive. This means BTA stat have specificity problems.

In conclusion, urine tests for bladder cancer should have the highest sensitivity and also must be easy applicable and cheap. Therefore more valuable urine tests or such biological response tests should be investigated for exact diagnosis. BTA stat test is not a gold standard for diagnosis.

References


