

The Role of BTA stat in Clinical Practice

P Quek, *_{FRCS}, C M Chin, **_{FAMS, FRCS}, P H C Lim, ***_{FAMS, M Med (Surg)}

Abstract

Objective: BTA stat is a rapid, urine-based test for bladder cancer that detects human complement factor H related protein (HCFHrp) by monoclonal assay. This aim of this study was to assess the efficacy of BTA stat as a diagnostic tool for bladder cancer in symptomatic patients suspected of bladder cancer and in the surveillance of patients with a history of treated bladder cancer. **Patients and Methods:** One hundred and six patients presenting with haematuria (gross or microscopic) or irritative bladder symptoms presenting to the urology outpatient clinic of Changi General Hospital and 13 patients under bladder cancer surveillance were recruited for this prospective study. All underwent voided urine cytology (VUC), urine culture, urine BTA stat, intravenous urogram and cystoscopy. Sensitivity, specificity, positive and negative predictive values were calculated for both tests. The stage and grade of bladder tumours detected were also correlated with both test results. Causes of false positives and specificity in different patient groups were analysed. **Results:** BTA stat is more sensitive than VUC in detecting primary and recurrent bladder tumours (85% versus 55%) but is less specific (62.6% versus 100%). Urinary tract infections and urinary calculi accounted for 62% of false positives with BTA stat. When patients with positive urine cultures and benign IVU abnormalities were excluded, specificity of BTA stat improved (93.9% cf. 62.6%). BTA stat was highly specific (100%) and more sensitive than VUC (75% versus 25%) in detecting recurrent tumours in asymptomatic patients on cancer surveillance. **Conclusion:** A high false positive rate and low predictive value limits the use of BTA stat in screening symptomatic patients. However, it has a role in cancer surveillance and in the screening of high-risk asymptomatic individuals. Further prospective trials should be performed to better assess its role in this respect.

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Introduction

Cystoscopy, supplemented by urine cytology, remains the gold standard in detecting primary and recurrent bladder cancer. Urine cytology, although highly specific, detects only 29% to 45% of bladder tumours and is subject to considerable inter- and intra-observer differences.¹⁻⁴

Several urinary bladder tumour marker assays such as human complement factor H related protein (BTA stat), fibrin/fibrinogen degradation products (AccuDx, USA),^{5,6} Nmp22 (Matritech, USA),^{1,7-11} hyaluronic acid/hyaluronidase,¹¹ telomerase and cytokeratins 8 and 18 (UBC rapid test)¹² are thought to be more sensitive and less subjective than urine cytology and have thus been recommended for the screening and surveillance of bladder cancer in the hope that they may supplant urine cytology and to decrease the frequency of surveillance cystoscopies.^{5-7,9-12}

BTA stat, which detects human complement factor H related protein (HCFHrp), is an immunochromatographic urinary assay that is rapid, objective and can be read at the

point of care. It has been shown to be 67% sensitive in archived bladder cancer positive urine samples and is 72% and 95% specific in patients with benign genitourinary disease and healthy asymptomatic volunteers, respectively.¹³ However, the main modes of presentation for bladder cancer include gross or microscopic haematuria and vesical irritability, and the presence of haematuria and inflammation may cause false positives that can limit the clinical usefulness of BTA stat as a screening tool in symptomatic patients.

In this study, we aimed to determine the accuracy of BTA stat in patients with symptoms suggestive of bladder cancer and in patients on bladder cancer surveillance to determine its applicability in clinical practice by comparing the sensitivity, specificity and diagnostic efficacy of BTA stat and voided urine cytology (VUC) in these patients.

Material and Methods

From July to November 1998, 106 patients presenting to the urology outpatients clinic in Changi General Hospital

* Registrar

** Consultant

*** Chief

Department of Urology

Changi General Hospital

Address for Reprints: Dr Pearlyn Quek, Department of Urology, Changi General Hospital, 2 Simei Street 3, Singapore 529889.

E-mail: pharoahpug@yahoo.co.uk

with symptoms suggestive of bladder cancer and 13 patients on bladder cancer surveillance follow-up were recruited for this prospective analysis. A single urine specimen was taken at the time of presentation, divided into 3 aliquots and sent for culture, cytology and BTA stat testing. All patients underwent an intravenous urogram and cystoscopy (rigid or flexible). Diagnosis of bladder cancer was made on biopsy at cystoscopy. The TMN system was used for staging and grade was assessed using the World Health Organisation grading system.

The final diagnosis of patients not detected to have bladder cancer was made after collating clinical findings, investigations and cystoscopy.

The final diagnosis and mode of presentation were correlated with BTA stat test and VUC results. Sensitivity, specificity, positive and negative predictive values were calculated for both tests. The stage and grade of bladder tumours detected were correlated with both test results.

Sensitivity was defined as the ratio of true positives to the number of bladder cancers detected. Specificity was defined as the ratio of true negatives to the number of patients without bladder cancer.

Results

There were 81 males and 38 females. Their ages ranged from 17 to 95 years, with a mean of 54.2 years. Table I shows the distribution of presenting complaints.

Sixteen primary and 4 recurrent bladder cancers were detected following cystoscopy and biopsy, giving an overall prevalence of 16.8%.

Sensitivity and Predictive Values of BTA stat and VUC

Sensitivity for BTA stat was 85% versus 55% for VUC (Table I). BTA stat detected 33.3%, 100%, 100% of Ta, T1 and T2-T4, respectively, compared to 0%, 90% and 33% for VUC (Table II). There were no cases of Tis in this series. Sensitivity by tumour grade was 57%, 100%, 100% for G1, G2, and G3, respectively, for BTA stat and 18%, 83% and 57%, respectively, for VUC (Table III). Sixty-five patients tested BTA stat negative, of whom 3 had

TABLE II: SENSITIVITY (%) OF BTA stat AND VOIDED URINE CYTOLOGY (VUC) ACCORDING TO TUMOUR STAGE

	No. of cases	No. detected by BTA n (% sensitivity)	No. detected by VUC n (% sensitivity)
Ta	4	1 (25)	0
T1	10	10 (100)	9 (90)
T2-T4	6	6 (100)	2 (33)

TABLE III: SENSITIVITY (%) OF BTA stat AND VOIDED URINE CYTOLOGY (VUC) ACCORDING TO TUMOUR GRADE

	No. of cases	No. detected by BTA n (% sensitivity)	No. detected by VUC n (% sensitivity)
G1	7	4 (57)	1 (18)
G2	6	6 (100)	5 (83)
G3	7	7 (100)	4 (57)

TABLE IV: FINAL DIAGNOSES OF PATIENTS WITH FALSE POSITIVE BTA stat RESULTS

Diagnosis	n
Urinary tract infection	13
Genitourinary tumour	4
Benign genitourinary disease	6
Calculi	10
No abnormalities detected	4
Total	37

bladder cancer (Table V), thus giving a negative predictive value of 95.3%. These were 2 TaG1s and a T1G1 tumour. All 3 also had negative VUCs; hence, combining BTA stat and VUC did not improve sensitivity. Fifty-four patients tested positive for BTA stat, of whom 17 had bladder cancer, giving a positive predictive value of 35.2% (17/54) (Table V).

Specificity of BTA stat and VUC

There were 37 false positives for BTA stat, of which urinary tract infections and urinary calculi accounted for

TABLE I: SENSITIVITY AND SPECIFICITY FOR BTA stat AND VUC ACCORDING TO PRESENTING SYMPTOMS

Presenting symptom	n	BTA stat		Urine cytology	
		Sensitivity	Specificity	Sensitivity	Specificity
All	119	85%	62.6%	55%	100%
Gross haematuria	60	93.3%	48.8%	60%	100%
Microhaematuria	29	NA	69.9%	NA	100%
Cancer surveillance	13	75%	100%	25%	100%
Vesical irritability	13	NA	75%	NA	100%
Others	4	NA	25%	NA	100%

NA: not applicable

TABLE V: OVERALL RESULTS FOR BTA stat

	BTA positive	BTA negative	n
Bladder cancer	17	3	20
No bladder cancer	37	62	99
Total	54	65	119

TABLE VI: SPECIFICITY OF BTA stat IN THE PRESENCE OF OTHER GENITOURINARY PATHOLOGY

Diagnosis	n	True negative	BTA stat positive	% specificity
Urinary tract infection	28	15	13	53
Urinary calculi	16	6	10	38
Benign genitourinary disease	18	12	6	67
Other genitourinary tumours	5	1	4	20
No abnormalities detected	32	28	4	89

62% (Table IV). Overall specificity of BTA stat was 62.6% versus 100% for VUC. In patients with gross haematuria, BTA stat was only 48.8% specific but it was highly specific (100%) in asymptomatic patients on cancer surveillance (Table VIIb). Specificity ranged from 20% to 56% among the various genitourinary pathologies (Table VI) and increased to 93.9% when patients with positive urine culture and benign IVU abnormalities were excluded (Table VIIc). In those in whom no definite genitourinary abnormality was detected, BTA stat was 89% specific (Table VI).

Discussion

Urine cytology remains the standard *in vitro* urine test to detect primary and recurrent bladder cancer. It is highly specific (90% to 100%) and has been shown to enhance the sensitivity of cystoscopies.¹⁴⁻¹⁷

The limitations of VUC are well documented. It requires specimen preparation, a trained cytopathologist, has a 10% to 15% non-interpretable rate,^{2,3} and has significant inter-observer differences in sensitivity and specificity.^{3,4} The sensitivity of VUC in detecting bladder tumours is only 29% to 45%¹⁻³ and is particularly low for well-differentiated tumours. In our series, overall sensitivity of VUC was 55% and VUC was significantly less sensitive than BTA stat in all patient categories.

Apart from the use of bladder wash cytology (BWC), other methods that may increase the sensitivity of VUC such as Lewis X Ag immunostaining^{15,16} and DNA image cytometry^{15,18} are not widely practiced. BWC may improve the yield of cytology from 41% (VUC) to 61%.¹⁸ It is, however, invasive and may introduce instrumentation artifacts that produce more equivocal “atypical cells”. The Lewis X antibodies are available commercially and it has been shown to have a sensitivity and specificity of 80% and

TABLE VIIa: % SPECIFICITY OF BTA stat IN PATIENTS AGED < OR ≥ 40 YEARS

Patient group	n	True negative	False positive	% specificity
Overall	119	62	37	63
Less than 40 years old	28	14	4	77
More than 40 years old	91	47	33	59

TABLE VIIb: % SPECIFICITY OF BTA stat ACCORDING TO MODE OF PRESENTATION

Patient group	n	True negative	False positive	% specificity
Gross haematuria	60	22	22	48.8
Microhaematuria	29	20	9	70
Lower urinary tract symptoms	13	10	3	75
Cancer surveillance	13	9	0	100
Others	4	1	3	25

TABLE VIIc: % SPECIFICITY OF BTA stat IN PATIENTS WITH NEGATIVE URINE CULTURES AND/OR BENIGN IVU

Patient group	n	True negative	False positive	% specificity
Culture negative urine	91/119	62	30	68
Benign intravenous urogram (IVU)	90/119	62	8	88
Culture negative and benign IVU	90/119	62	4	93.9

86%, respectively.¹⁶ It does have a problem with false positives in well-differentiated tumours and lowers the highly specific nature of urine cytology. DNA image cytometry is a sensitive and objective method to identify malignant cells. Its use is, however, limited as it requires hardware that can only be available in large institutions and it requires a high cellular yield for reading.

Bladder tumour associated by-products that have been utilised as urinary bladder tumour markers include human complement factor H related protein (BTA stat), fibrin/fibrinogen degradation products (Accu Dx, USA),^{5,6} Nmp22 (Matritech, USA),^{1,7-11} hyaluronic acid/hyaluronidase,¹¹ telomerase and cytokeratins 8 and 18 (UBC rapid test).¹² Of these, only BTA stat, fibrinogen degradation products and UBC are rapid point of care tests.

BTA stat detects human complement factor H related protein (HCFHrp), an inhibitor of the alternative complement pathway that has been isolated in bladder cancer but not in normal epithelial cell lines. HCFHrp interacts with complement C3B to inhibit the formation of membrane attack complex, thereby preventing cell lysis. It has thus been postulated that HCFHrp may confer a survival

advantage to cancer cells *in vivo*.¹³ Sarosdy et al¹³ demonstrated that in archived bladder cancer positive urine, BTA stat detected 67% of cancers and was significantly more sensitive than VUC or the Bard BTA test. They also showed that BTA was 95% specific in healthy asymptomatic volunteers.

In our series, BTA stat detected 84.4% of bladder cancers compared to 55% for VUC. This concurs with other studies in which BTA stat demonstrated superior sensitivity over VUC in detecting bladder tumours.^{1,19-21} Adding cytology positive cases did not improve its sensitivity. As expected, the yield of VUC increased with tumours of higher grade and stage. In our small series, VUC sensitivity for Ta and G1 tumours however, were 0% and 18%, while BTA stat detected 25% and 57% of Ta and G1 tumours, respectively. Leyh et al²¹ and Gutierrez Banos et al²² have similarly shown, with larger numbers, that BTA stat is at least twice as sensitive as VUC in detecting well-differentiated tumours.

Many of the urinary bladder tumour markers lack specificity. Similarly, in the presence of calculi, haematuria, infection, other tumours and benign pathology of the genitourinary tract like benign prostatic hypertrophy, BTA stat will often test positive and be only 20% to 56% specific. Bladder cancer may account for up to 24.2% of patients presenting with gross haematuria, but significant non-malignant disease accounts for 34.5% of patients in this group.²³ Hence the use of BTA stat in gross haematuria is particularly non-specific. Taking an age cut-off of 40 years and above did not significantly increase specificity (Table VIIa). Sharma et al¹ have shown that excluding these 6 clinical categories—benign inflammatory or infectious conditions, renal or bladder calculi, recent history of foreign body in the urinary tract, bowel interposition segment, another genitourinary cancer or an instrumented urinary sample—improved the specificity and positive predictive value of BTA stat.

Excluding patients with positive urine cultures and benign IVU abnormalities in our series increased specificity to 93.9%. In clinical practice, however, patients presenting with haematuria are subject to basic investigations which include cystoscopy and radiological screening of the genitourinary tract. Given the high rate of false positives in this group, including BTA stat as a screening tool is not cost-effective and attempting to increase its specificity as suggested above is not practical in standard clinical practice. The high rate of false positives would also lead to needless anxiety in these patients.

BTA stat has, however, been shown to be highly specific (95% to 98%) in asymptomatic, healthy individuals.^{13,24} In our small series of 13 asymptomatic follow-up patients, BTA stat detected 3 out of 4 recurrent cancers and there were no false positives. Gutierrez Banos et al² compared

the use of BTA stat and VUC in 122 patients on bladder cancer surveillance. In their series, sensitivity of BTA stat and VUC was 60.78% and 45%, respectively, and BTA stat was 87.32% specific in diagnosing recurrent cancer. If similar results are found in further large series, it may have a role in decreasing the frequency of surveillance cystoscopies.

Thus, given its accuracy and high negative predictive value in asymptomatic individuals, it would appear to be useful in cancer surveillance and as a screening tool in asymptomatic high-risk individuals. The small number of follow-up patients in our series precludes making a definitive conclusion of the role of BTA stat in such patients. Further clinical trials on BTA stat should be directed at its use in surveillance rather than as a diagnostic tool.

Conclusion

BTA stat has been shown to be more sensitive in detecting bladder cancers compared to urine cytology. However, its low specificity in symptomatic patients precludes its usefulness as a diagnostic tool. It is, however, more sensitive and as specific as VUC in asymptomatic individuals and has a likely role in cancer surveillance as well as in screening asymptomatic high-risk populations. Further studies should be performed to better assess its role in this respect.

REFERENCES

1. Sharma S, Zippe C D, Pandranji L, Nelson D, Agarwal A. Exclusion criteria enhance the specificity and positive predictive value of NMP22 and BTA stat. *J Urol* 1999; 162:53-7.
2. Gutierrez Banos J L, Martin Garcia B, de Diego Rodriguez E, Hernandez Rodriguez R, Portillo Martin JA, Correias Gomez M A, et al. The BTA stat test in the follow up for bladder cancer. *Arch Esp Urol* 1999; 52: 56-61.
3. Paez A, Coba J M, Murillo N, Fernandez P, de la Cal M A, Lujan M, et al. Reliability of the routine cytological diagnosis in bladder cancer. *Eur Urol* 1999; 35:228-32.
4. Sharkey F E, Sarosdy M F. The significance of central pathology review in clinical studies of transitional cell carcinoma *in situ*. *J Urol* 1997; 157:68-72.
5. Johnston B, Morales A, Emerson L, Lundie M. Rapid detection of bladder cancer: a comparative study of point of care tests. *J Urol* 1997; 158:2098-101.
6. Schmetter B S, Habicht K K, Lamm D L, Morales A, Bander N H, Grossman H B, et al. A multicenter trial evaluation of the fibrin/fibrinogen degradation products test for detection and monitoring of bladder cancer. *J Urol* 1997; 158:801-5.
7. Stampfer D S, Carpinito G A, Rodriguez-Villanueva J, Willsey L W, Dinney C P, Grossman H B, et al. Evaluation of NMP22 in the detection of transitional cell carcinoma of the bladder. *J Urol* 1998; 159:394-8.
8. Ramakumar S, Bhuiyan J, Besse J A, Roberts S G, Wollan P C, Blute M, et al. Comparison of screening methods in the detection of bladder cancer. *J Urol* 1999; 61:388-94.

9. Gutierrez Banos J L, Rebollo Rodrigo M H, Antolin Juarez F, Martin Garcia B, Hernandez Rodriguez R, Portillo Martin J A, et al. Comparative study of BTA stat test, NMP 22 and cytology in the diagnosis of bladder cancer. *Arch Esp Urol* 2000; 53:21-7.
10. Giannopoulos A, Manousakas T, Mitropoulos D, Botsoli-Stergiou E, Constantinides C, Giannopoulos M, et al. Comparative evaluation of the BTA stat test, NMP22 and voided urine cytology in the detection of primary and recurrent bladder tumors. *Urology* 2000; 55:871-5.
11. Lokeshwar V B, Obek C, Pham H T, Wei D, Young M J, Duncan R C, et al. Urinary hyaluronic acid and hyaluronidase: markers for bladder cancer detection and evaluation of grade. *J Urol* 2000; 163:348-56.
12. 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; 56:228-31.
13. Sarosdy M F, Hudson M A, Ellis W J, Soloway M S, deVere White R, Sheinfeld J, et al. Improved detection of recurrent bladder cancer using the Bard BTA stat test. *Urology* 1997; 50:349-53.
14. Halachmi S, Linn J F, Amiel G E, Moskovitz B, Nativ O. Urine cytology, tumour markers and bladder cancer. *Br J Urol* 1998; 82:647-54.
15. Planz B, Striepecke E, Jakse G, Bocking A. Use of Lewis X antigen and deoxyribonucleic acid image cytometry to increase sensitivity of urinary cytology in transitional cell carcinoma. *J Urol* 1998; 159: 384-8.
16. Pode D, Golijanin D, Sherman Y, Lebensart P, Shapiro A. Immunostaining of Lewis X in cells from voided urine cytopathology and ultrasound for noninvasive detection of bladder tumors. *J Urol* 1998; 159:389-93.
17. Wiener H G, et al. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? *J Urol* 1998; 59:1876-80.
18. Badalament R A, Hermansen D K, Kimmel M, Gay H, Herr H W, Fair W R, et al. The sensitivity of bladder wash flow cytometry, bladder wash cytology and voided cytology in the detection of bladder carcinoma. *Cancer* 1987; 60:1423-7.
19. Raitanen M P, Martilla T, Kaasinen E, Rintal E, Aine R, Tammela T L. Sensitivity of human complement factor H related protein (BTA stat) test and voided urine cytology in the diagnosis of bladder cancer. *J Urol* 2000; 163:1689-92.
20. Pode D, Shapiro A, Wald M, Nativ O, Laufer M, Kaver I. Non-invasive detection of bladder cancer with the BTA stat test. *J Urol* 1999; 161:443-6.
21. Leyh H, Marberger M, Conort P, Sternberg C, Pansadoro V, Pagano F, et al. Comparison of BTA stat test with voided urine cytology and bladder wash cytology in the diagnosis and monitoring of bladder cancer. *Eur Urol* 1999; 35:52-6.
22. Gutierrez Banos J L, Martin Garcia B, Hernandez Rodriguez R, Portillo Martin J A, Correias Gomez M A, del Valle Schaan J L, et al. Usefulness of BTA stat test (Bard) in the diagnosis of bladder cancer. Preliminary results and comparison with cytology and cystoscopy. *Arch Esp Urol* 1998; 51:778-82.
23. Khadra M H, Pickard R S, Charlton M, Powell P H, Neal D E, Messing E M. A prospective analysis of 1,930 patients with haematuria to evaluate current diagnostic practice. *J Urol* 2000; 163:524-31.
24. Raitanen M P, Tammela T L. Specificity of human complement factor H related protein test (Bard BTA stat Test). *Scand J Urol Nephrol* 1999; 33:234-6.