F1000Prime REPORTS

Published: 01 July 2013

Urinary markers for bladder cancer

Zachary L. Smith and Thomas J. Guzzo*

Address: Division of Urology, Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine, 3rd Floor, West Pavilion, 3400 Civic Center Blvd, Philadelphia, PA 19104

* Corresponding author: Thomas J. Guzzo (thomas.guzzo@uphs.upenn.edu)

F1000Prime Reports 2013, **5**:21 (doi:10.12703/P5-21)

Abstract

Bladder cancer has the fifth highest incidence of all malignancies in the United States, with a propensity to recur, requiring lifelong surveillance after diagnosis. Urinary markers of disease have been of extreme interest in this field in an effort to simplify surveillance schedules and improve early detection of tumors. Many markers have been described, but most remain investigational. However, some markers have undergone clinical trials and are approved for clinical use. In this review, urinary markers and their application for screening and surveillance of bladder cancer are discussed.

Introduction

Bladder cancer (urothelial carcinoma) has the fifth highest incidence of all malignancies in the United States, with an estimated 72,570 new cases and 15,210 deaths in 2013 [1]. At presentation, approximately 70% are non-muscle-invasive (stage Tis, Ta, T1) and 30% muscle-invasive (stage T2, T3, T4) [2]. Of the non-muscle-invasive tumors, 50-70% will recur despite conservative measures such as transurethral and intravesical therapy [3,4]. It is because of this natural history that, once diagnosed, bladder cancer requires lifelong surveillance. Unfortunately, this management paradigm contributes to bladder cancer carrying the highest cost from diagnosis to death of all cancers, ranging from $96,000 to $187,000 (2001 values) in the United States [5]. Consequently, there is a need for an accurate marker of disease in order to decrease the cost associated with surveillance. An accurate marker would also have the added benefit of improving quality of life by potentially minimizing the number of invasive endoscopic evaluations.

An accurate bladder cancer marker should ideally be capable of both screening high risk populations as well as surveillance of patients with a known history of bladder cancer. Given the relatively low overall prevalence of bladder cancer in the general population, widespread screening is not cost effective and, therefore, not recommended at this time [6,7]. However, screening individuals who are at high risk for bladder cancer, such as those with a history of tobacco abuse, high risk occupational exposure, cyclophosphamide exposure, or pelvic radiation, may be beneficial for early detection of bladder cancer.

Recent advances

For decades, cystoscopy with the addition of urine cytology has been the gold standard in the detection and surveillance of bladder cancer. Current surveillance protocols after initial diagnosis typically include cystoscopy and urine cytology every 3 months for the first 1 to 3 years, every 6 months for an additional 1 to 3 years, and then annually thereafter. Cystoscopy is a minimally traumatic office procedure and is successful in identifying most bladder tumors. However, it may be inconclusive if a patient has a grossly abnormal appearance to their bladder mucosa, such as patients with an indwelling catheter or an active inflammatory condition. While still the gold standard for diagnosis, cystoscopy has a false-negative rate either from operator error, or from small areas of sessile tumor (carcinoma *in situ*), which may be difficult to detect [8,9]. Additionally, although cystoscopy is a minor procedure, it can still cause significant patient discomfort, stress, and anxiety [10,11].

An abundance of data supports the idea that urine cytology with cystoscopy is superior to cystoscopy alone in detecting high-grade urothelial carcinoma, as well as upper tract tumors [12,13]. Accordingly, any new marker must have its performance considered against this current gold standard. A meta-analysis of 36 studies found a sensitivity and specificity of 44% and 96%, respectively, for urine cytology [14]. Additionally, the positive predictive value of cytology is approximately 90% [15,16]. However, one major limitation of urine cytology is its low sensitivity for the detection of low-grade tumors, at approximately 4% to 31% [17]. Unfortunately, thus far, a similar correlation is being identified in the current investigational urinary markers as well.

Therefore, the addition of a commercially available bladder tumor marker would add to the armamentarium of bladder cancer detection. The ideal screening and surveillance test should be non-invasive, rapid, easily accessible to providers and patients, and have high sensitivity and specificity. Because urine comes into direct contact with bladder tumors, urinary markers have been of extreme interest in this field. Many markers have been described, but most of them remain investigational and are still undergoing preclinical evaluation (see Table 1). Few have undergone clinical trials and are approved for clinical use.

When investigating the utility of a new marker, it is important to delineate the difference between screening and surveillance applications. One function of an accurate urinary marker for bladder cancer would be in surveillance of patients with a history of bladder cancer, with the goal of detecting early recurrence of disease and potentially minimizing the need for invasive testing. The other use would be in screening the general population, or patients at high risk, for bladder cancer. When examining the current literature on the various urinary markers, it must be understood that the overwhelming majority of studies have used mixed population cohorts (i.e. patients with history of bladder cancer, patients at risk of getting bladder cancer, and asymptomatic low risk patients). Few studies have evaluated markers in purely surveillance or purely screening populations and this limits the analysis of the sensitivity and specificity of these assays. When evaluating the performance of a marker, one must be careful to consider the study population in which it is being applied as disease prevalence will impact the performance of the marker. Although low in number, some of these markers have undergone focused studies, and we have attempted to segregate these data in Table 2, accepting that uniform data are not available for each marker.

A recent analysis of 21 screening cohort studies examined the use of these markers for screening [18]. Using various methods and markers in addition to cystoscopy, bladder cancer was diagnosed in 0.0% to 51.2% of high-risk screening populations (removing the single highest outlier, the range was 0.0% to 1.64%), with a median

Table 1. Summary of urinary markers for bladder cancer

Test (Manufacturer)	Marker detected	Assay type	FDA approval
Cytology	Tumor cells	Microscopy	N/A
BLCA-4 (Eichrom Technologies)	Nuclear matrix protein	Sandwich ELISA (rabbit polyclonal antibody)	–
BTA stat® (Polymedco)	Complement factor H-related protein and complement factor H	Immunoassay or point-of-care	For diagnosis & follow-up
BTA TRAK® (Polymedco)	Complement factor H-related protein and complement factor H	Sandwich ELISA	For diagnosis & follow-up
CYFRA 21-1 (Bio International; Roche Diagnostics)	Cytoskeletal protein (cytokeratin 19)	Immunoradiometric assay or ELISA	–
DD23 (UroCor Labs)	185-kDa tumor associated antigen	Immunocytochemistry	–
NMP22/BladderChek® (Alere)	Nuclear mitotic apparatus protein	Sandwich ELISA or point-of-care	For diagnosis & follow-up
Survivin (Fujirebio Diagnostics)	Inhibitor of apoptosis gene	Bio-dot test (rabbit polyclonal antibody)	–
UBC™ (IDL Biotech)	Cytoskeletal proteins (cytokeratin 8 and 18)	Sandwich ELISA or point-of-care	–
ImmunoCyt™/uCyt+™ (Scimedx)	Carcinoembryonic antigen, two bladder tumor cell-associated mucins	Immunocytochemistry	For follow-up
UroVysion™ (Abbott, Vysis)	Alterations in chromosomes 3, 7, 17, and 9p21	FISH	For diagnosis & follow-up

ELISA, enzyme-linked immunosorbent assay; FISH, fluorescence in-situ hybridization

Table 2. Sensitivity and specificity of urinary markers for bladder cancer

Test	Surveillance*			Screening		
	Sensitivity (%)	Specificity (%)	References	Sensitivity (%)	Specificity (%)	References
Cytology	22-52	96-98	[14,28,29]	15-55	81-99	[30,31,29]
BLCA-4	89-96	100	[32,33]	–	–	–
BTA stat®	53-83	67-72	[34,35,29,36]	90	76	[29]
BTA TRAK®	66-72	51-75	[37-39]	–	–	–
CYFRA 21-1	67-97	67-89	[40-42]	79	89	[41]
DD23	70-81	60	[43,44]	–	61-86	[43]
NMP22/BladderChek®	47-100	60-90	[24,25,35,40,45-51]	55-97	29-85	[30,52]
Survivin	64-100	87-93	[53-55]	–	–	–
UBC™	66-82	83-90	[34,56]	–	–	–
ImmunoCyt™/uCyt+™	50-100	69-79	[28,57-60]	–	–	–
UroVysion™	36-100	89-98	[61,62]	–	–	–

*Also includes mixed cohorts

incidence of 0.64%. Given this low prevalence, screening of both the general population and high-risk populations has been called into question.

In similar fashion, final results of a screening program using home hematuria testing and molecular markers were recently published [19]. 1747 asymptomatic men completed home hematuria testing and, if positive, were screened with a variety of molecular markers and underwent subsequent cystoscopy if warranted. Of this cohort, four patients were diagnosed with bladder cancer and one with a kidney tumor. Screening missed one patient with bladder cancer and one with a kidney tumor. The authors concluded that a sequential screening approach may help minimize unnecessary invasive testing with very few missed cancers. However, this mass screening program had a very low diagnostic yield.

Innumerable assays have been developed over the last few decades, with many of them claiming good performance initially, only to have this fade with long-term follow-up. We have focused on some of the more common, and more promising, urinary markers to date. This includes urine-based assays (BLCA-4, BTA stat®, BTA TRAK®, CYFRA 21-1, NMP22, Survivin, UBC™) and cell-based assays (DD23, ImmunoCyt™/uCyt+™, UroVysion™). To date, the only urinary markers that have Food and Drug administration (FDA) approval for diagnosis and follow-up of bladder cancer are BTA stat®, BTA TRAK®, NMP22, and UroVysion™, with ImmunoCyt™/uCyt+™ only being approved for follow-up of bladder cancer. The molecular targets of each assay differ widely and are summarized in Table 1.

One of the few markers to gain widespread clinical use is the UroVysion™ test, which utilizes fluorescence in-situ hybridization (FISH) to identify chromosomal abnormalities. This test seems to be more sensitive, but less specific, than urinary cytology across all tumor grades. A recent meta-analysis showed that the overall performance of UroVysion™ was better than that of cytology (area under the curve: 87% vs 63%) [20]. However, the difference was almost entirely attributable to the ability of FISH to diagnose stage Ta patients better than cytology, as the value decreased when these patients were excluded from the analysis (area under the curve: 94% vs 91%). Another reason for the popularity of FISH is in its usefulness for monitoring patients with superficial bladder cancer after treatment with intravesical bacillus Calmette-Guérin (BCG). In this group, FISH has shown superiority to cytology and is beneficial when cytology results are equivocal [21-23].

Another marker with promise is nuclear mitotic apparatus protein (NMP22), a member of the nuclear matrix protein family. NMP22 is quite prevalent in malignant urothelial cells, but not in their normal counterpart. A recent study compared NMP22, cytology, and cystoscopy by performing both urine tests during 351 consecutive cystoscopies [24]. NMP22, cytology, and cystoscopy demonstrated sensitivity/specificity of 51%/96%, 35%/97%, and 92%/88%, respectively. Importantly, the cost of NMP22 and cytology were $8,750 and $52,500, respectively, showing that not all new markers will be more expensive than the current gold standard. However, because this protein is released from apoptotic urothelial cells, many benign conditions of the urinary tract contribute to a significant false-positive rate. One study found that greater than 80% of the false-positive results were categorized as benign inflammatory or infectious conditions, stone disease, recent foreign body in the urinary tract, bowel interposition segment, another genitourinary cancer, or an instrumented urine sample [25]. In fact, the presence of ureteral stents or any bowel interposition segment had a 100% false-positive rate.

Table 3. Summary of International Consultation on Urological Diseases recommendations regarding urinary markers for bladder cancer [27]

Bladder cancer screening and early detection using urinary markers is promising but cannot be recommended at present.
Marker-guided follow-up of patients with low-grade NMIBC appears attractive; however, based on current levels of evidence, this procedure cannot be recommended at present.
A use of molecular markers in surveillance of patients with high-grade NMIBC cannot be recommended.
Reflex testing is considered experimental at present and should be evaluated in clinical studies
NMIBC, non-muscle-invasive bladder cancer

Head to head comparison of markers is limited by a variety of factors. Firstly, while some markers have a similar sensitivity for both low- and high-grade tumors, most have a higher sensitivity for high-grade (this must be remembered when interpreting the data in Table 2). Additionally, specificity is highly dependent upon the level of these markers in the urine of the tumor-negative cohort. Another limitation lies in the threshold definitions used by each investigator. We see a similar phenomenon as we do with prostate-specific antigen (PSA) screening, in that an increased cut-off value will both decrease sensitivity and increase specificity, while the inverse is true for a decreased cut-off value. Lastly, as mentioned above in regard to NMP22, the technical limitations of the accuracy of these markers in patients with non-cancerous urological conditions are not insignificant.

To date, there has only been one prospective trial on a marker-guided surveillance protocol, which has only preliminary results [26]. More prospective trials for marker-guided follow-up of bladder cancer patients are currently underway and their results will be anxiously awaited. Because of this paucity of data, the International Consultation on Urological Diseases has released recommendations regarding urinary markers for bladder cancer [27]. These recommendations are summarized in Table 3.

Conclusions

Urinary markers represent a promising frontier for diagnosis and follow-up of bladder cancer. Some of these markers are currently being used in practice, with many more still under investigation. However, at this time the routine use of these markers cannot be recommended for either screening or early detection. Prospective studies as well as close evaluation of focused screening and surveillance cohorts are needed to further our understanding of the role of these markers.

Abbreviations

ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug administration; FISH, fluorescence in situ hybridization; NMP22, nuclear mitotic apparatus protein; PSA, prostate-specific antigen.

Disclosures

The authors declare that they have no disclosures.

References

1. Siegel R, Naishadham D, Jemal A: **Cancer statistics, 2013.** *CA Cancer J Clin* 2013, **63:**11-30.

2. Ro JY, Staerkel GA, Ayala AG: **Cytologic and histologic features of superficial bladder cancer.** *Urol Clin North Am* 1992, **19:** 435-53.

3. Saad A, Hanbury DC, McNicholas TA, Boustead GB, Morgan S, Woodman AC: **A study comparing various noninvasive methods of detecting bladder cancer in urine.** *BJU Int* 2002, **89:**369-73.

4. Soloway MS, Sofer M, Vaidya A: **Contemporary management of stage T1 transitional cell carcinoma of the bladder.** *J Urol* 2002, **167:**1573-83.

5. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R: **The health economics of bladder cancer: a comprehensive review of the published literature.** *Pharmacoeconomics* 2003, **21:**1315-30.

6. Lokeshwar VB, Soloway MS: **Current bladder tumor tests: does their projected utility fulfill clinical necessity?** *J Urol* 2001, **165:**1067-77.

7. Svatek RS, Sagalowsky AI, Lotan Y: **Economic impact of screening for bladder cancer using bladder tumor markers: a decision analysis.** *Urol Oncol* 2006, **24:**338-43.

8. van der Poel HG, Debruyne FM: **Can biological markers replace cystoscopy? An update.** *Curr Opin Urol* 2001, **11:**503-9.

9. Herr HW: **The natural history of a T1 bladder cancer: life-long tumour diathesis.** *BJU Int* 1999, **84:**1102-3.

10. Botteman MF, Pashos CL, Hauser RS, Laskin BL, Redaelli A: **Quality of life aspects of bladder cancer: a review of the literature.** *Qual Life Res* 2003, **12:**675-88.

11. Herr HW, Schneider M: **Outpatient flexible cystoscopy in men: a randomized study of patient tolerance.** *J Urol* 2001, **165:**1971-2.

12. Babjuk M, Soukup V, Pesl M, Kostírová M, Drncová E, Smolová H, Szakacsová M, Getzenberg R, Pavlík I, Dvorácek J: **Urinary cytology and quantitative BTA and UBC tests in surveillance of patients with pTapT1 bladder urothelial carcinoma.** *Urology* 2008, **71:**718-22.

13. Lokeshwar VB, Habuchi T, Grossman HB, Murphy WM, Hautmann SH, Hemstreet GP, Bono AV, Getzenberg RH, Goebell P, Schmitz-Dräger BJ, Schalken JA, Fradet Y, Marberger M,

Messing E, Droller MJ: **Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers.** *Urology* 2005, **66:**35-63.

F1000Prime RECOMMENDED

14. Mowatt G, Zhu S, Kilonzo M, Boachie C, Fraser C, Griffiths TRL, N'Dow J, Nabi G, Cook J, Vale L: **Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer.** *Health Technol Assess* 2010, **14:**1-331 iii-iv.

F1000Prime RECOMMENDED

15. Bastacky S, Ibrahim S, Wilczynski SP, Murphy WM: **The accuracy of urinary cytology in daily practice.** *Cancer* 1999, **87:**118-28.

16. Planz B, Jochims E, Deix T, Caspers HP, Jakse G, Boecking A: **The role of urinary cytology for detection of bladder cancer.** *Eur J Surg Oncol* 2005, **31:**304-8.

17. Lotan Y, Roehrborn CG: **Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses.** *Urology* 2003, **61:**109-18 discussion 118.

F1000Prime RECOMMENDED

18. Larré S, Catto JWF, Cookson MS, Messing EM, Shariat SF, Soloway MS, Svatek RS, Lotan Y, Zlotta AR, Grossman HB: **Screening for bladder cancer: rationale, limitations, whom to target, and perspectives.** *Eur Urol* 2013, **63:**1049-58.

F1000Prime RECOMMENDED

19. Bangma CH, Loeb S, Busstra M, Zhu X, Bouazzaoui SE, Refos J, van der Keur KA, Tjin S, Franken CGAM, van Leenders GJLH, Zwarthoff EC, Roobol MJ: **Outcomes of a Bladder Cancer Screening Program Using Home Hematuria Testing and Molecular Markers.** *Eur Urol* 2013.

F1000Prime RECOMMENDED

20. Hajdinjak T: **UroVysion FISH test for detecting urothelial cancers: meta-analysis of diagnostic accuracy and comparison with urinary cytology testing.** *Urol Oncol* 2008, **26:**646-51.

F1000Prime RECOMMENDED

21. Savic S, Zlobec I, Thalmann GN, Engeler D, Schmauss M, Lehmann K, Mattarelli G, Eichenberger T, Dalquen P, Spieler P, Schoenegg R, Gasser TC, Sulser T, Forster T, Zellweger T, Casella R, Bubendorf L: **The prognostic value of cytology and fluorescence in situ hybridization in the follow-up of nonmuscle-invasive bladder cancer after intravesical Bacillus Calmette-Guérin therapy.** *Int J Cancer* 2009, **124:**2899-904.

F1000Prime RECOMMENDED

22. Mengual L, Marín-Aguilera M, Ribal MJ, Burset M, Villavicencio H, Oliver A, Alcaraz A: **Clinical utility of fluorescent in situ hybridization for the surveillance of bladder cancer patients treated with bacillus Calmette-Guérin therapy.** *Eur Urol* 2007, **52:**752-9.

F1000Prime RECOMMENDED

23. Kipp BR, Karnes RJ, Brankley SM, Harwood AR, Pankratz VS, Sebo TJ, Blute MM, Lieber MM, Zincke H, Halling KC: **Monitoring intravesical therapy for superficial bladder cancer using fluorescence in situ hybridization.** *J Urol* 2005, **173:**401-4.

F1000Prime RECOMMENDED

24. Schlake A, Crispen PL, Cap AP, Atkinson T, Davenport D, Preston DM: **NMP-22, urinary cytology, and cystoscopy: a 1 year comparison study.** *Can J Urol* 2012, **19:**6345-50.

F1000Prime RECOMMENDED

25. Sharma S, Zippe CD, Pandrangi 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.

26. Mian C, Maier K, Comploj E, Lodde M, Berner L, Lusuardi L, Palermo S, Vittadello F, Pycha A: **uCyt+/ImmunoCyt in the detection of recurrent urothelial carcinoma: an update on 1991 analyses.** *Cancer* 2006, **108:**60-5.

27. Kamat AM, Hegarty PK, Gee JR, Clark PE, Svatek RS, Hegarty N, Shariat SF, Xylinas E, Schmitz-Dräger BJ, Lotan Y, Jenkins LC, Droller M, van Rhijn BW, Karakiewicz PI: **ICUD-EAU International Consultation on Bladder Cancer 2012: screening, diagnosis, and molecular markers.** *Eur Urol* 2013, **63:**4-15.

F1000Prime RECOMMENDED

28. Comploj E, Mian C, Ambrosini-Spaltro A, Dechet C, Palermo S, Trenti E, Lodde M, Horninger W, Pycha A: **uCyt+/ImmunoCyt and cytology in the detection of urothelial carcinoma: An update on 7422 analyses.** *Cancer Cytopathol* 2013.

F1000Prime RECOMMENDED

29. Pode D, Shapiro A, Wald M, Nativ O, Laufer M, Kaver I: **Noninvasive detection of bladder cancer with the BTA stat test.** *J Urol* 1999, **161:**443-6.

F1000Prime RECOMMENDED

30. Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, Shen Y: **Detection of bladder cancer using a point-of-care proteomic assay.** *JAMA* 2005, **293:**810-6.

31. Miyanaga N, Akaza H, Tsukamoto T, Ishikawa S, Noguchi R, Ohtani M, Kawabe K, Kubota Y, Fujita K, Obata K, Hirao Y, Kotake T, Ohmori H, Kumazawa J, Koiso K: **Urinary nuclear matrix protein 22 as a new marker for the screening of urothelial cancer in patients with microscopic hematuria.** *Int J Urol* 1999, **6:**173-7.

32. van Le T, Myers J, Konety BR, Barder T, Getzenberg RH: **Functional characterization of the bladder cancer marker, BLCA-4.** *Clin Cancer Res* 2004, **10:**1384-91.

33. van Le T, Miller R, Barder T, Babjuk M, Potter DM, Getzenberg RH: **Highly specific urine-based marker of bladder cancer.** *Urology* 2005, **66:**1256-60.

34. 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.

F1000Prime RECOMMENDED

35. Wiener HG, Mian C, Haitel A, Pycha A, Schatzl G, Marberger M: **Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer?** *J Urol* 1998, **159:**1876-80.

F1000Prime RECOMMENDED

36. Sarosdy MF, Hudson MA, Ellis WJ, Soloway MS, deVere White R, Sheinfeld J, Jarowenko MV, Schellhammer PF, Schervish EW, Patel JV, Chodak GW, Lamm DL, Johnson RD, Henderson M, Adams G, Blumenstein BA, Thoelke KR, Pfalzgraf RD, Murchison HA, Brunelle SL: **Improved detection of recurrent bladder cancer using the Bard BTA stat Test.** *Urology* 1997, **50:**349-53.

37. Thomas L, Leyh H, Marberger M, Bombardieri E, Bassi P, Pagano F, Pansadoro V, Sternberg CN, Boccon-Gibod L, Ravery V, Le Guludec D, Meulemans A, Conort P, Ishak L: **Multicenter trial of**

the quantitative BTA TRAK assay in the detection of bladder cancer. *Clin Chem* 1999, **45:**472-7.

38. Heicappell R, Wettig IC, Schostak M, Müller M, Steiner U, Sauter T, Miller K: **Quantitative detection of human complement factor H-related protein in transitional cell carcinoma of the urinary bladder.** *Eur Urol* 1999, **35:**81-7.

F1000Prime RECOMMENDED

39. Ellis WJ, Blumenstein BA, Ishak LM, Enfield DL: **Clinical evaluation of the BTA TRAK assay and comparison to voided urine cytology and the Bard BTA test in patients with recurrent bladder tumors. The Multi Center Study Group.** *Urology* 1997, **50:**882-7.

F1000Prime RECOMMENDED

40. Sánchez-Carbayo M, Urrutia M, Silva JM, Romaní R, de Buitrago JM, Navajo JA: **Comparative predictive values of urinary cytology, urinary bladder cancer antigen, CYFRA 21-1 and NMP22 for evaluating symptomatic patients at risk for bladder cancer.** *J Urol* 2001, **165:**1462-7.

41. Nisman B, Barak V, Shapiro A, Golijanin D, Peretz T, Pode D: **Evaluation of urine CYFRA 21-1 for the detection of primary and recurrent bladder carcinoma.** *Cancer* 2002, **94:**2914-22.

42. Pariente JL, Bordenave L, Jacob F, Gobinet A, Leger F, Ferriere JM, Le Guillou M: **Analytical and prospective evaluation of urinary cytokeratin 19 fragment in bladder cancer.** *J Urol* 2000, **163:**1116-9.

43. Sawczuk IS, Pickens CL, Vasa UR, Ralph DA, Norris KA, Miller MC, Ng AY, Grossman HB, Veltri RW: **DD23 Biomarker: a prospective clinical assessment in routine urinary cytology specimens from patients being monitored for TCC.** *Urol Oncol* 2002, **7:**185-90.

44. Gilbert SM, Veltri RW, Sawczuk A, Shabsigh A, Knowles DR, Bright S, O'Dowd GJ, Olsson CA, Benson MC, Sawczuk IS: **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:**539-43.

45. Hughes JH, Katz RL, Rodriguez-Villanueva J, Kidd L, Dinney C, Grossman HB, Fritsche HA: **Urinary nuclear matrix protein 22 (NMP22): a diagnostic adjunct to urine cytologic examination for the detection of recurrent transitional-cell carcinoma of the bladder.** *Diagn Cytopathol* 1999, **20:**285-90.

46. Takashi M, Schenck U, Kissel K, Leyh H, Treiber U: **Use of diagnostic categories in urinary cytology in comparison with the bladder tumour antigen (BTA) test in bladder cancer patients.** *Int Urol Nephrol* 1999, **31:**189-96.

47. Gutiérrez Baños JL, Martín García B, Hernández Rodríguez R, Portillo Martín JA, Correas Gómez MA, del Valle Schaan JI, Roca Edreira A, Villanueva Peña A, Gutíerrez García R, de Diego Rodríguez E, Rado Velázquez MA: **Utilidad del BTA Stat TEST (Bard) en el diagnóstico del cáncer vesical. Resultados preliminares y comparación con citología y cistoscopia.** *Arch Esp Urol* 1998, **51:**778-82.

48. Del Nero A, Esposito N, Currò A, Biasoni D, Montanari E, Mangiarotti B, Trinchieri A, Zanetti G, Serrago MP, Pisani E: **Evaluation of urinary level of NMP22 as a diagnostic marker for stage pTa-pT1 bladder cancer: comparison with urinary cytology and BTA test.** *Eur Urol* 1999, **35:**93-7.

49. Serretta V, Lo Presti D, Vasile P, Gange E, Esposito E, Menozzi I: **Urinary NMP22 for the detection of recurrence after transurethral resection of transitional cell carcinoma of the bladder: experience on 137 patients.** *Urology* 1998, **52:**793-6.

50. Witjes JA, van der Poel HG, van Balken MR, Debruyne FM, Schalken JA: **Urinary NMP22 and karyometry in the diagnosis and follow-up of patients with superficial bladder cancer.** *Eur Urol* 1998, **33:**387-91.

51. Grossman HB, Soloway M, Messing E, Katz G, Stein B, Kassabian V, Shen Y: **Surveillance for recurrent bladder cancer using a point-of-care proteomic assay.** *JAMA* 2006, **295:**299-305.

52. Huber S, Schwentner C, Taeger D, Pesch B, Nasterlack M, Leng G, Mayer T, Gawrych K, Bonberg N, Pelster M, Johnen G, Bontrup H, Wellhäusser H, Bierfreund H, Wiens C, Bayer C, Eberle F, Scheuermann B, Kluckert M, Feil G, Brüning T, Stenzl A: **Nuclear matrix protein-22: a prospective evaluation in a population at risk for bladder cancer. Results from the UroScreen study.** *BJU Int* 2012, **110:**699-708.

F1000Prime RECOMMENDED

53. Altieri DC: **Survivin, versatile modulation of cell division and apoptosis in cancer.** *Oncogene* 2003, **22:**8581-9.

54. Smith SD, Wheeler MA, Plescia J, Colberg JW, Weiss RM, Altieri DC: **Urine detection of survivin and diagnosis of bladder cancer.** *JAMA* 2001, **285:**324-8.

55. Shariat SF, Casella R, Khoddami SM, Hernandez G, Sulser T, Gasser TC, Lerner SP: **Urine detection of survivin is a sensitive marker for the noninvasive diagnosis of bladder cancer.** *J Urol* 2004, **171:**626-30.

56. 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.

F1000Prime RECOMMENDED

57. Olsson H, Zackrisson B: **ImmunoCyt a useful method in the follow-up protocol for patients with urinary bladder carcinoma.** *Scand J Urol Nephrol* 2001, **35:**280-2.

58. Mian C, Pycha A, Wiener H, Haitel A, Lodde M, Marberger M: **Immunocyt: a new tool for detecting transitional cell cancer of the urinary tract.** *J Urol* 1999, **161:**1486-9.

F1000Prime RECOMMENDED

59. Vriesema JL, Atsma F, Kiemeney LA, Peelen WP, Witjes JA, Schalken JA: **Diagnostic efficacy of the ImmunoCyt test to detect superficial bladder cancer recurrence.** *Urology* 2001, **58:**367-71.

60. Pfister C, Chautard D, Devonec M, Perrin P, Chopin D, Rischmann P, Bouchot O, Beurton D, Coulange C, Rambeaud J: **Immunocyt test improves the diagnostic accuracy of urinary cytology: results of a French multicenter study.** *J Urol* 2003, **169:**921-4.

61. Sarosdy MF, Schellhammer P, Bokinsky G, Kahn P, Chao R, Yore L, Zadra J, Burzon D, Osher G, Bridge JA, Anderson S, Johansson SL, Lieber M, Soloway M, Flom K: **Clinical evaluation of a multi-target fluorescent in situ hybridization assay for detection of bladder cancer.** *J Urol* 2002, **168:**1950-4.

F1000Prime RECOMMENDED

62. Halling KC, King W, Sokolova IA, Meyer RG, Burkhardt HM, Halling AC, Cheville JC, Sebo TJ, Ramakumar S, Stewart CS, Pankratz S, O'Kane DJ, Seelig SA, Lieber MM, Jenkins RB: **A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma.** *J Urol* 2000, **164:**1768-75.

F1000Prime RECOMMENDED