

MINI-REVIEW

Research Progress in Potential Urinary Markers for the Early Detection, Diagnosis and Follow-up of Human Bladder Cancer

Hai-Feng Wang, Jian-Song Wang*

Abstract

Objective: To summarize and evaluate various urinary markers for early detection, diagnosis and follow-up of human bladder cancer. **Methods:** A MEDLINE and PUBMED search of the latest literature on urinary markers for bladder cancer was performed. We reviewed these published reports and made a critical analysis. **Results:** Most urinary markers tend to be less specific than cytology, yielding more false-positive results, but demonstrating an advantage in terms of sensitivity, especially for detecting low grade, superficial tumors. Some tumor markers appear to be good candidates for early detection, diagnosis, and follow-up of human bladder cancer. **Conclusion:** A number of urinary markers are currently available that appear to be applicable for clinical detection, diagnosis, and follow-up of bladder cancer. However, further studies are required to determine their accuracy and widespread applicability.

Keywords: Bladder cancer - tumor marker - detection - diagnosis - follow-up

Asian Pacific J Cancer Prev, **13**, 1723-1726

Introduction

Bladder cancer, which is often detected late and has a high rate of recurrence and progression, is the most common genitourinary cancer, and it is among the top eight most frequent cancers. The main symptom of bladder cancer is hematuria, but in some patients, there are no symptoms in an early stage. Early detection of cancers is essential for improved prognosis and long-term survival, and can only be beneficial regarding mortality if the high risk cancers are recognized and treated at a localized stage. Nowadays, bladder cancers can be diagnosed and followed-up using a combination of cystoscopic examination, cytology and histology (Proctor et al., 2010). However, these methods are not only expensive, but also highly subjective investigations and reveal little about the underlying molecular characteristics of the cancers (eg. bladder cancer in situ and upper tract disease). In recent years, in order to cut costs and reduce the frequency of cystoscopies or replace them by non-invasive tests, a number of urinary markers are under study. This paper describes both new and well-studied urinary markers in the early detection, diagnosis, and follow-up of human bladder cancer and predicts its clinical outcome.

The MEDLINE® and Pubmed® databases up to 2011 were used to search related literatures. We put subject headings (Mesh) and a free text strategy with the name of known individual urinary tests to use. The key words are 'bladder cancer', 'bladder carcinoma', 'urothelial/transitional carcinoma', 'urine', 'tumor marker', 'diagnosis', 'progression', 'follow-up' and 'recurrence'.

The search was limited to humans and the English language.

The most relevant 78 articles were selected for this review, and part of these were listed in the following reference. Abstracts of all retrieved articles were reviewed by all authors, using the software EndNote.

Individual Markers

Some tumor markers seem to be good candidates for early detection, diagnosis, and follow-up of human bladder cancer. However, some markers are required to study deeply for validating potential clinical applications.

Urinary markers of bladder cancer **NMP22**

Several studies have demonstrated that abnormal levels of nuclear matrix protein 22 (NMP22) are associated with bladder cancer and urinary levels of NMP22 are 25 times higher than healthy individuals. However, the clinical significance of NMP22 remains unclear (Shariat et al., 2011). Kehinde et al compared the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of urine cytology, Bladder Chek NMP22 and fluorescence in situ hybridization (FISH) tests in patients with newly diagnosed bladder cancer. They found that NMP22 was most cost-effective and rapid, with relatively high sensitivity and specificity in all categories of patients (Kehinde et al., 2011). Lau et al assessed the use of NMP22 to predict which high-risk superficial UCB (urothelial carcinoma of the bladder)

Department of Urology, Yunnan Institute of Urology, The Second Affiliated Hospital of Kunming Medical University, Kunming, China *For correspondence: jiansongwang@126.com

patients would have a recurrence, progression or disease-related death. According to their finding, they deem that the NMP22 assay appears to have predictive value for future tumour recurrences (Lau et al., 2009). Kundal et al assess the clinical utility of NMP22 Bladder Check Test and compare it with voided urine cytology and cystoscopy in early detection of bladder cancer. The results showed that the sensitivity and specificities of NMP22 Test in recurrent bladder cases were 81.3% and 92%, which was significantly greater than that of cytology 44% and 96.1% respectively. In non-invasive lesions of TCC, NMP22 Test and cytology were positive in 71.8% and 42.8% of cases respectively. In muscle-invasive lesions, NMP22 Test was positive in 82.2% and 44.4% cases were positive for cytology. The sensitivity of the NMP22 test was 81.3%, which was significantly greater than that of cytology at 44% (Kundal et al., 2010). There are a number of research papers in terms of early detection, diagnosis, and follow-up of bladder cancer by NMP22 assay (Arora et al., 2010; Choi et al, 2010; Iwabuchi et al., 2010; Hwang et al., 2011). The conclusion of these research literatures all demonstrate that NMP22 is a useful adjunct to urine cytology in atypical and low-grade cancer and can be used for mass screening of bladder cancer.

BLCA-4

The BLCA-4 (bladder cancer specific nuclear matrix protein 4) nuclear matrix protein belongs to a member of the ETS transcription factor family. Early study reveals that BLCA-4 is a bladder cancer marker that is highly specific and occurs early in the development of the disease (Van Le et al., 2004). Recently, Guo et al screened and identified differentially expressed genes in invasive bladder transitional cell carcinoma (BTCC), and they found that the detection rates of BLCA-4 at the Ta, T1 and >T1 stages of bladder cancer were 90%. The combination of BLCA-4 and HOXA13 could distinguish between low- and high-grade tumors, with specificity and sensitivity of 80% (Guo et al., 2011).

Survivin

Survivin is one of the three well-known inhibitors of apoptosis and is considered a potent target for cancer treatment. Survivin is an endogenous protein, which is a promising marker for the detection, diagnosis and follow-up of bladder cancer. Studies have also indicated that survivin splice variants appeared to have unique subcellular localizations and functions as well (He et al., 2009). Gradilone et al studied 54 patients with T1G3 non-muscle-invasive bladder cancer. The results showed that the survivin was found in half of the tumors, and 92% of CTC (circulating tumour cell) expressed survivin (Gradilone et al., 2010). Shariat et al studied the role of survivin in predicting the recurrence of bladder cancer (Shariat et al., 2009). The study comprised 726 patients treated with radical cystectomy and bilateral pelvic lymphadenectomy. They found that patients with pT (1-3) N(0)M(0) disease (n = 398), addition of survivin improved the accuracy of standard clinicopathologic features for prediction of the recurrence and cancer-specific survival. Other recent researches also manifested that survivin was

a potent urinary marker of bladder cancer (Akhidova et al., 2010; Yang et al., 2010).

UPK3A

In our country, UPK3A was found to be a promising novel urinary marker for the detection of bladder cancer by Lai et al. (2010). They quantified the urine UPK3A levels of 32 healthy volunteers, 44 patients with benign urological disorders and 122 patients with bladder cancer. The results showed that the UPK3A levels of the patients with bladder cancer and those of normal individuals or benign urological disorders are statistically significant ($P < 0.01$). The sensitivity of urine UPK3A was 83%, and the specificity was also 83%. They deemed that UPK3A is a sensitive marker for the detection of bladder cancer.

BTA

The BTA-test is an agglutination assay that qualitatively detects the presence of complexes of basement membrane within the urine of patients (Jovanovic et al., 2007). It has been extensively studied, and is used in detecting human bladder cancer. However, Raitanen et al studied the voided urine samples of 501 patients in terms of the follow-up of bladder cancer by BTA-Test and cytology. The results showed that the overall sensitivities and specificities for the BTA-Test and cytology were 56.0, 19.2 and 85.7%, and 98.3%, respectively. Hence, they believed that BTA-Test cannot replace cystoscopy in the follow-up of patients with bladder cancer, but could replace routine cytology, especially in patients with low-grade disease (Raitanen et al., 2008).

HYAL-1

Hyaluronoglucosaminidase 1 (HYAL-1)-type hyaluronidase (HAase) promotes tumor growth, invasion, and angiogenesis (Kramer et al., 2010). Recently, a number of studies demonstrated that HYAL-1 was a potential urinary marker for predicting progression to muscle invasion and recurrence of human bladder cancer. Eissa et al studied 166 patients diagnosed with bladder carcinoma, 112 with benign bladder lesions and 100 healthy volunteers who served as controls, using HYAL1 as a diagnostic molecular marker for bladder cancer (Eissa et al, 2010). They found that the positivity rates of HYAL1 RNA on qualitative reverse transcriptase-polymerase chain reaction were significantly different among the 3 groups. Using these cutoffs HYAL1 RNA sensitivity was 91%. Kramer et al also regarded HYAL1 was a potential prognostic indicator for progression to muscle invasion and recurrence in bladder cancer (Kramer et al., 2010).

Telomerase

Most human cancer cells maintain telomere to immortalization through telomerase activity (Xue et al., 2010). Telomerase activity assessment in voided urine is an important noninvasive tool for detection, diagnosis and follow-up of human bladder cancer. Casadio et al verified that Telomerase activity assessment can detect tumor cells in urine with high sensitivity and specificity (Casadio et al., 2009). They evaluated the urinary telomerase activity of 515 patients, and found that the overall accuracy, in

terms of true positives and true negatives, was 80%. Iwabuchi et al used a modification of the TeloTAGGG telomerase polymerase chain reaction (PCR) enzyme-linked immunosorbent assay kit to develop a simple urine telomerase activity assay. According to this method, the sensitivity and specificity of bladder cancer diagnosis on 100 patients and 25 healthy volunteers were 81% and 92%. Many studies indicate that urine telomerase activity is a good marker for the early detection, diagnosis and follow-up of human bladder cancer.

bFGF

Basic fibroblast growth factor (bFGF) is a heparin-binding cationic protein, and involves in the angiogenesis and growth of many solid cancers (Marzioni et al., 2009). Gravas et al evaluated the levels of bFGF in bladder cancer patients (Gravas et al., 2004). They found that there was a statistically significant difference between median bFGF levels of patients with active bladder cancer and those of the other groups. However, the research of bFGF is not studied deeply, and further studies are required to validate the potential clinical applications of bFGF.

There are other urinary markers for detection, diagnosis and follow-up of bladder cancer, such as NMP52, DD23, et al.. However, these studies are carried out in a very long time before, and there was no new progress in the last 5 years. Consequently, those are not necessary for us to dwell on them..

Conclusion

Due to life-long surveillance involving upper tract imaging, urinary cytology, and cystoscopy, bladder cancer is also an expensive cancer. Cytology combines with cystoscopy has been historically used to help doctors to detect or diagnose bladder cancers. However, bladder cancer in situ and upper tract disease are often missed diagnosis with this method. Hence, it is necessary to look for an economical and efficient method to replace the traditional methods. Many of the urinary markers which are currently available appear to have the advantages of lower price and higher sensitivity, especially in detecting low-grade, non-muscle invasive cancers. The role of urinary markers as an alternative to cytology deserve consideration. In the future, more sensitive and specific markers may replace routine cystoscopy. However, the urinary marker of bladder cancer for a clinic tool must be accurate with high sensitivity and specificity, cost effective for life-long surveillance, and minimally invasive to minimize the burden to the patient. At present, there are no prognostic markers for bladder cancer that are superior to conventional grading and staging, despite its imperfections. Consequently, further and in-depth studies are required to determine the accuracy and widespread applicability of urinary markers in guiding early detection, diagnosis and follow-up of bladder cancer.

References

Akhidova EV, Volkova TD, Koroev DO, et al (2010). Antibodies to synthetic peptides for the detection of survivin in tumor

tissues. *Bioorg Khim*, **36**,178-86.

- Arora VK, Sarungbam J, Bhatia A, et al (2010). Usefulness of NMP22 as an adjunct to a typical urine cytology and low-grade urothelial carcinoma. *Diagn Cytopathol*, **38**, 788-90.
- Casadio V, Bravaccini S, Gunelli R, et al (2009). Accuracy of urine telomerase activity to detect bladder cancer in symptomatic patients. *Int J Biol Markers*, **24**, 253-7.
- Choi HS, Lee SI, Kim DJ, et al (2010). Usefulness of the NMP22BladderChek Test for Screening and Follow-up of Bladder Cancer. *Korean J Urol*, **51**, 88-93.
- Eissa S, Swellam M, Shehata H, et al (2010). Expression of HYAL1 and survivin RNA as diagnostic molecular markers for bladder cancer. *J Urol*, **183**, 493-8.
- Gradilone A, Petracca A, Nicolazzo C, et al (2010). Prognostic significance of survivin-expressing circulating tumour cells in T1G3 bladder cancer. *BJU Int*, **106**, 710-5.
- Gravas S, Bosinakou I, Kehayas P et al (2004). Urinary basic fibroblast growth factor in bladder cancer patients. Histopathological correlation and clinical potential. *Urol Int*, **73**, 173-7.
- Guo B, Che T, Shi B, et al (2011). Screening and identification of specific markers for bladder transitional cell carcinoma from urine urothelial cells with suppressive subtractive hybridization and cDNA microarray. *Can Urol Assoc J*, **5**, E129-37.
- He XF, Wen DG, Hou JQ, et al (2009). Expressions of survivin and the splice variants survivin-2B and survivin-DeltaEx3 in bladder cancer and their clinical significance. *AI ZHENG*, **28**, 1209-13.
- Hwang EC, Choi HS, Jung SI, et al (2011). Use of the NMP22 BladderChek test in the diagnosis and follow-up of urothelial cancer: a cross-sectional study. *Urology*, **77**, 154-9.
- Iwabuchi I, Mori K, Yamamoto H, et al (2010). Significance of a simple assay of urine telomerase activity for the detection of bladder cancer. *Hinyokika Kiyo*, **56**, 551-7.
- Jovanovic M, Hadzi-Djokic J, Dzamic Z, et al (2007). Evaluation of the Bard BTA-test in the diagnosis of upper urinary tract tumours. *Acta Chir Jugosl*, **54**, 19-24.
- Kehinde EO, Al-Mulla F, Kapila K, et al (2011). Comparison of the sensitivity and specificity of urine cytology, urinary nuclear matrix protein-22 and multitarget fluorescence in situ hybridization assay in the detection of bladder cancer. *Scand J Urol Nephrol*, **45**, 113-21.
- Kramer MW, Golshani R, Merseburger AS, et al (2010). HYAL-1 hyaluronidase: a potential prognostic indicator for progression to muscle invasion and recurrence in bladder cancer. *Eur Urol*, **57**, 86-93.
- Kundal VK, Pandith AA, Hamid A, et al (2010). Role of NMP22 bladder check test in early detection of bladder cancer with recurrence. *Asian Pac J Cancer Prev*, **11**, 1279-82.
- Lai Y, Ye J, Chen J, et al (2010). UPK3A: a promising novel urinary marker for the detection of bladder cancer. *Urology*, **76**, 514. e6-11.
- Lau P, Chin JL, Pautler S, et al (2009). NMP22 is predictive of recurrence in high-risk superficial bladder cancer patients. *Can Urol Assoc J*, **3**, 454-8.
- Marzioni D, Lorenzi T, Mazzucchelli R, et al (2009). Expression of basic fibroblast growth factor, its receptors and syndecans in bladder cancer. *Int J Immunopathol Pharmacol*, **22**, 627-38.
- Proctor I, Stoeber K, Williams GH (2010). Biomarkers in bladder cancer. *Histopathology*, **57**, 1-13.
- Raitanen MP (2008). The role of BTA stat Test in follow-up of patients with bladder cancer: results from FinnBladder studies. *World J Urol*, **26**, 45-50.
- Shariat SF, Karakiewicz PI, Godoy G, et al (2009). Survivin as a prognostic marker for urothelial carcinoma of the bladder:

- a multicenter external validation study. *Clin Cancer Res*, **15**, 7012-9.
- Shariat SF, Savage C, Chromecki TF, et al (2011). Assessing the clinical benefit of nuclear matrix protein 22 in the surveillance of patients with nonmuscle-invasive bladder cancer and negative cytology: a decision-curve analysis. *Cance*, **13**, 2892-7.
- Van Le TS, Myers J, Konety BR, et al (2004). Functional characterization of the bladder cancer marker, BLCA-4. *Clin Cancer Res*, **10**, 1384-91.
- Xue Y, Li L, Zhang D, et al (2010). Telomerase suppression initiates PML-dependent p53 activation to inhibit bladder cancer cell growth. *Oncol Rep*, **24**, 1551-9.
- Yang D, Song X, Zhang J, et al (2010). Therapeutic potential of siRNA-mediated combined knockdown of the IAP genes (Livin, XIAP, and Survivin) on human bladder cancer T24 cells. *Acta Biochim Biophys Sin*, **42**, 137-44.