International Journal of Medicine and Biomedical Research
Volume 2 Issue 3 September – December 2013
www.ijmbr.com

Review Article

A review of molecular biomarkers for bladder cancer

Miakhil I[1], Parker S.G[2]*, Kommu S.S[3], Nethercliffe J[1]

[1]Urology Department, Peterborough City Hospital, Edith Cavell Campus, Bretton Gate, Peterborough, PE3 9GZ, United Kingdom. [2]Urology Department, Princess Royal University Hospital, Bromley, London, United Kingdom. 59a Knatchbull road, Camberwell, London SE5 9QR, UK.[3]Urology Department,Guy's Hospital, London, United Kingdom.

*Corresponding author: samparker@nhs.net

Received: 09.06.13; Accepted: 26.10.13

ABSTRACT

Background: Numerous molecular markers for bladder cancer have been identified and investigated with various laboratory techniques. Molecular markers are isolated from tissue, serum and urine. They fall into proteomic, genetic and epigenetic categories. Some of molecular markers show promising results in terms of facilitating early diagnosis and guiding treatment. Molecular markers or the so- called biomarkers can provide additional information alongside staging, grading and lymphovascular invasion, for better prognostication.**Aim:**This studyprovides an up-to-date review of the frequently studied and most important biomarkers that have shown consistent relevance in relation to bladder cancer. **Methods:** The key words were searched on the PubMed, Google scholar and NHS library search engines. **Results:** More than twenty biomarkers as per our methodology were identified but only half of them have shown consistence relevance in bladder cancer. **Conclusion:** It is envisaged that a combination of a few biomarkers, which are investigated frequently and have shown clinical relevance, could possibly provide useful information in predicting recurrence and provide useful prognostic information. So far none of the biomarkers for bladder cancer are adopted in the UK standard practice. Despite that the Food and Drug Administration (FDA) had approved some of these biomarkers, none of the urology associations incorporated them in to their guidelines as yet. However, it won't be long before a final consensus is reached to integrate molecular staging in to the current TNM staging system.

Key words: Molecular markers, biomarkers, proteomics, tumour markers, bladder cancer, oncology

INTRODUCTION

Bladder cancer is one of the most prevalent and lethal malignant tunours. It wasreported that in the year 2008 almost 10,335 people were diagnosed with bladder cancer in the United Kingdom and it is the seventh most common cancer in the aforementioned.[1] Despite all the achievements in the field of bladder cancer such as early detection and better treatment in the form of refined surgical techniques, improved radiotherapy techniques along with newer chemotherapeutic agents, the tumour remains a lethal disease.[2] It is known that

early detection of cancers improve survival, outcome and reduce recurrence.[3] Hence several investigators have routed to identify and investigate molecular markers, which could further contribute to early diagnosis, guide treatment and provide accurate prognostication.[2-5]

A biomarker is a molecular compound that can indicate a biological state. Several biomarkers are identified and investigated in various studies in relation to bladder cancer. These molecular markers are broadly classified into proteomic, genomic and epigenetic markers.[2]

Proteomic means the study of protein structure and its function with techniques such as electrophoresis and mass spectrometry.[2] Nuclear matrix proteins (NMP 22) are bladder cancer markers that can be identified in the urine utilizing electrophoresis.[2] This marker is being investigated in some UK centres as an alternative to urine cytology.[6] Proteomics have become very popular due to the availability of latest techniques to help identify markers for bladder cancer.[2]

Genomic means study of DNA or RNA sequence and the gene expression differences between tissue samples.[7] This requires technologies such as gene microarray, which can analyse thousands of DNA sequences in a very short time. Gene microarray can identify gene duplication and aberration that are thought to be contributing to tumour pathogenesis.[2] Examples of genomic markers include p53, fibroblast growth factor receptor -3 (FGFR-3) and retinoblastoma (pRB) genes. These markers have helped identify aberrant pathways in the pathogenesis of bladder cancer.[2] Single nucleotide polymorphism in certain genes is also investigated in relation to bladder cancer.[2]

Epigenetic means changes in the genes function without any alteration in its structure. The common epigenetic processes, which are investigated in the balder cancer, are methylation of DNA and histone acetylation.[8] In normal circumstances DNA methylation is an important part of homeostasis as it results in stability and transcription of genes. However, hypermethylation results in “silencing” especially those of tumour suppressors genes can result in tumour formation.[9] Similar observations had been made by others as well that hypermethylation of the DNA causes inactivation of certain genes, which is an important step in the early phases of tumour pathogenesis.[10]

At least more than twenty different biomarkers for bladder cancer have been investigated; some of them have been discarded and labelled as irrelevant.[2] Whilst others that are investigated frequently and show consistence relevance have been incorporated into certain prognosis programmes.[2] One such programme is Bladder Cancer Prognosis Programme (BCPP) at University of Birmingham, UK.

The aim of this article is to provide an up-to-date and in depth review of the most frequently studied biomarkers. We aimed to illustrate the most important biomarkers that have shown consistent relevance in relation to bladder cancer, in a logical and easily understandable approach to all those interested in bladder cancer biology.

METHODOLOGY

Biomarkers that were mentioned in crucial urological textbooks or those accepted by authoritative institutions were searched individually for new evidence. The key words used for the literature review were ‘biomarkers’, ‘bladder cancer’ and ‘molecular markers’. The search was conducted on the PubMed, Google scholar and NHS library search engines. The biomarkers mentioned and referenced in Campbell- Walsh Urology (10th edition). The Scientific Basis of Urology (3rd edition) and the BCPP were searched individually for further new evidence to support their significance in the bladder cancer. We additionally paid specific attention to bladder cancer biomarkers that are FDA approved. Biomarkers that were not supported by level-3 or above evidence and unidentified genes located on the long arm of chromosomes 9 were excluded form this review. Unidentified genes, which are believed to be located on the long arm of chromosome 9 that have shown relevance to the low-grade bladder urothelial cancer were also excluded form this review.

RESULTS

Most frequently studied biomarkers

NMP22 is a nuclear matrix protein that is extensively studied in relation to bladder cancer diagnosis and surveillance.[6] This nuclear protein is responsible for cell separation during cellular division and for keeping nuclear chromatid in order. Small quantities of the this protein is daily excreted in urine in normal circumstances, however exceeded amount of this protein beyond certain threshold is considered diagnostic of bladder cancer.[11] It is identified and measured in the urine through quantitative ELISA laboratory technique.[11] Attempts had been made with conflicting results to replace this with urine cytology in both initial diagnosis and subsequent follow-up of the bladder cancer. The sensitivity and specificity of the original NMP22 immunoassay has ranged from 47%- 100% and 60% -90%, respectively.[12] However, a prospective trial, which analysed the significance of NMP22 in a screening scenario of high-risk patients, based on 1,609 chemical workers from Germany reported the sensitivity and specificity at 28%and 89%, respectively.[13] Furthermore, the specificity of NMP22 is substantially reduced in the presence of inflammation, infectious diseases, urinary calculi, foreign body, instrumentation and bowel interposition used for bladder augmentation or repair.[14]

Bladder tumour antigen (BTA) is a protein that is released from normal human cells in order to protect them from autoimmunity.[15] This protein is akin to human complement factor H (FH) both structurally and functionally. It is believed that BTA is released from cancerous cells to evade destruction by the host immunity.[15] The test is based on the reagent that identifies higher levels of FH in the urine.[16] There are two variants of the test, the BTA Stat and BTA Trak. Reported sensitivity and specificity for BTA Stat and BTA Trak are 52%–780%, 51%–100% and 69%–871%, 73%–92%, respectively.[16] These variants of the BTA test are comparatively more sensitive but less specific to urine cytology as those conditions that affects NMP22 performance also disturbs BTA performance.[14] A recent case control study found that BTA assays might be measuring serum FH present in the haematuria rather than detecting BTA, which can result in false-positive BTA tests for conditions other than bladder cancers.[17]

Fibroblast growth factors are a clan consisted of 18 growth factors (FGFs) and 4 FGF-homologous factors (FHFs).[18] They have a vital role during both homeostasis (embryogenesis, development, and wound healing) and in pathological process.[18] FGFR-3 mutation of these genes can occur due to various factors.[19] Mutated genes results in over-expression that has a strong association with low-grade non-muscle invasive (PTa) transitional cell carcinomas (TCCs) of the uroepithelium. However, there is a negative correlation between the grade and stage of transitional cell carcinomas and the degree of FGFR-3 over-expression. High grades and higher stage TCCs are associated with decreasing expression of FGFR-3, whilst lower grades non-muscle invasive bladder cancers are associated with increased expression. Hence this particular marker can provide valuable prognostic information in the bladder carcinoma.[19] FGFR-3 mutations detectable in the urine assays are potential future non -invasive screening tests for non- muscle invasive bladder cancers.[20] It is reported that in most benign bladder lesions (low malignant potential neoplasms and urothelialpapillomas) and low-grade and -stage tumours (papillary urothelialneoplasia of low malignant potential; TaG1), FGRF-3 mutations are reaching in over 80%.[20] Furthermore, it is shown that FGFR inhibition has a cytotoxic role on urothelial cancer cells; hence targeting these pathways are currently being studied in trails as potential treatment options for urothelial cancers.[21]

p53 is a tumour suppressor gene that is found at the short arm of chromosome 17.[22] This gene has an important role in the cell cycle regulation and apoptosis.[23] Mutation of p53 has strong association with high grade and high stage bladder cancers.[22] Up to 50% of muscle invasive bladder cancers show mutation in p53.[23] Although some studies have shown that p53 has association with progression but a recently well-designed study has found no utility for p53 in predicting survival.[22-24] It is suggested by a meta-analysis of 117 studies that there is insufficient evidence to conclude that p53 is a good prognostic marker.[25] Similarly, a recent trail has shown that there was no significant

difference in the recurrence rate in patients with urothelial cancer that had positive or negative p53 mutations.[26] However, others grade and stage as follows.[10]

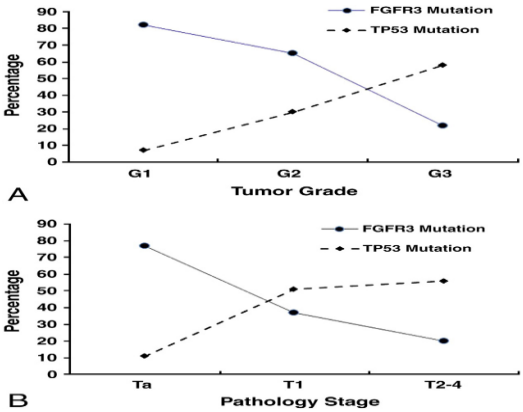

Figure 1: Prevalence of the TP53 mutation increasing with tumour grade and pathology stage. Prevalence of the FGFR3 mutation decreasing with tumour grade and pathology stage.[10]

pRB or the retinoblastoma gene is also a tumour suppressor gene, which has a central role in apoptosis and cell growth regulation.[8]Mutation or deletion of this gene has strong association in many cancers including early phases of bladder carcinogenesis.[8] pRB genes deletion or mutation can represent higher grades, stages and even poor prognosis.[8] It can also predict failure of BCG and hence it could prove to be a good prognostic tool.[8]

EGFRs and its related proteins (HER1-4) are other tumour promoters, which are part of tyrosine kinase growth factor receptors.[27] These receptors send signals to cells, controlling growth and differentiation.[27] Over-expression of these markers has strong association with high grade and high stage bladder cancers.[8] Clinical trials are underway evaluating the therapeutic effect of EGFR inhibitors in bladder cancer.[8] These markers can provide both prognostic and therapeutic information in bladder cancer.[2]

VEGF is a tumour promoter gene that promotes angiogenesis, an essential step in carcinogenesis.[7] The expression of this particular marker is present in almost all types of bladder TCCs and its increased expression is associated with increased stage and grade.[7] VEGF can be isolated both from urine and serum; the presence of high level of VEGF in the latter could represent tumour metastasis.[27,28] Some have reported p53 significance. One such study has shown the frequency of FGFR-3 and p53 mutation according to the tumour

trails are currently underway investigating the therapeutic role of VFGF inhibitors in cancers.[29] Suramin is a strong inhibitor of the VEGF and other angiogenic factors, which has shown efficacy in preventing angiogenesis during in vitro studies.[29] Thus VEGF is a marker of huge interest and might help oncologists to provide us with drugs that could help fight the disease.

Ki-67 is a proteomic marker and is present in the nucleus of the cells that are rapidly dividing such as those of cancer cells.[30] It is used as a measurement of cell growth fraction, which can help identify tumours with aggressive properties.[31] Ki-67 can be identified both in the tissue sample with immunohistochemistry (IHC) and in the urine. Urinary Ki-67 can help differentiate low-grade urothelial cancers from high-grade cancers.[30] Increased expression of the marker has strong correlation with increased grade, stage, increased risk of recurrence and poor prognosis.[31,32]

Survivin is another biomarker of huge current interest, which is investigated in various human cancers including bladder cancer.[33] It was first investigated in 2001 as urinary marker for bladder cancer diagnosis.[33] Survivin is located at the short arm of chromosome 17 and is normally expressed only by embryonic and foetal tissues.[34] However, it is reported that survivin is minimally expressed in normal human tissues as well. It has important role in normal cell division and inhibition of apoptosis.[34] The expression of survivin has been reported in various malignancies and is a marker of grave prognosis.[34] Als and colleagues have identified survivin and another protein called emmprin as independent prognostic factors of poor outcome following chemotherapy for bladder cancer.[35] It is believed that survivin is almost solely extracted from malignant tissues, which can be gauged in urine at the mRNA and protein level.[35] A study based on 278 Egyptian patients with bladder cancer showed that urinary survivin was positive 75.5% and 10.7% in malignant and benign cases respectively.[36] Chinese publishers recently published a paper on the role of survivin in the bladder cancer.[37] They found that none of the adjacent normal

urothelial tissues to the cancerous bladder tissue had expressed survivin whilst 60% of bladder cancerous had expressed surviving.[37] They also found the expression of survivin was correlated with grade and stage of bladder cancer.[37] The following table shows the frequency of survivin expression in their sample of bladder cancers in terms of grades, recurrence and metastasis.

Item	n	Positivity
Grade		
I	**8**	**2**
II	**15**	**10**
III	**7**	**6**
Recurrence		
Yes	**20**	**15**
No	**10**	**3**
Metastasis		
Yes	**18**	**15**
No	**12**	**2**

Figure 2: 30 patients screened for the expression of surviving. Patients categorised according to their histologcal grade, recurrence and metastasis. [37]

A recent systematic review looking at the role of urinary survivin in the bladder cancer diagnosis found that the pooled sensitivity and specificity of the urinary survivin tests were 0.772 (95% confidence interval [CI] 0.745 - 0.797) and 0.918 (95% CI 0.899 - 0.934), respectively.[38] It also reported that urinary survivin had better sensitivity than urinary cytology for diagnosing bladder cancer.[38]

Cytokeratin-20 is normally present in the umbrella cells of the urothelium.[39] The expression of the CK-20 in the deeper cells layers represents bladder carcinoma. CK-20 expression in the deeper cells layer has association with disease recurrence and progression.[39] Normal staining behaviour, that is, the expression of CK-20 only in the umbrella cells has almost no association with carcinoma in-situ.[40] Thus expression of CK-20 in the deeper layers of urothelium could mean aggressive behaviour.[8] The level of CK-20 expression in the urine can also predict the level of invasiveness. It has been shown that the expression of CK-20 in the urine was comparatively lower in pTa tumours than ≥pT2 tumours.[41]

The “epigenetic” word refers to changes that are not resulted from or caused by shifts in the primary nucleotide sequence of the DNA.[9] In other words, the epigenetic alterations are transferable changes to offspring’s that does not involve any structural changes of the DNA.[42] Due to the accumulation of quality data supporting genetic alterations in cancer pathogenesis back in 1980s and 1990s, the interest in epigenetics declined.[9] However, convincing evidence has re-emerged involving silencing of genes due to DNA methylation in cancer pathogenesis.[43] It is believed that DNA methylation leads to the inactivation of the tumour suppressor genes that consequently ensues in neoplasia formation.[43] DNA hypermethylation is frequent epigenetic alterations that are seen in most cancers and is widely linked to the bladder cancer pathogenesis and aggressiveness.[44] These altered (hyper-methylated) genes could be identified noninvasively in the urine samples.[45] A recent well-designed publication studied 10 of the most frequently hypermethylated genes identified in the urine sediments of patients and control group.[44] Based on their multigene predictive model, they found 4 out of the 10 mentioned genes had 81% and 97% sensitivity and specificity, respectively for bladder cancer diagnosis.[44]

Hedgehog signalling is a pathway of new interest in bladder cancer that is studied by Michelin and colleagues.[46] They reported that hedgehog signalling is essential in embryonic stage for tissue morphogenesis.[46] Increased activity of this

pathway is considered to be highly carcinogenic and donates increased invasive behaviour to some tumours.[47] They concluded although hedgehog singling is not likely to be involved in bladder cancer, but a downstream hedgehog signalling mediator (Gli2) is been reported to be associated with invasive behaviour of the bladder cancer cells.[46]

DISCUSSION

As previously mentioned that more than twenty different biomarkers for bladder cancer have been investigated; some of them have been discarded and labelled as irrelevant. Whilst others that are investigated frequently and have shown consistence relevance have been incorporated into prognosis programmes. One such programme is BCPP at University of Birmingham, England. They argued that they have incorporated the seven most common and most relevant markers in their study. These markers include FGFR-3, epidermal growth factor receptor (EGFR), pRB, p53, Ki-67, vascular endothelial growth factor (VEGF) and cytokeratin (CK) -20.[3] Some other investigators have incorporated four markers (p53, pRB, p21 and p27) in their study.[20] It is interesting observation that these two well-known studies have only two markers (p53 and pRB) in common. While various other researchers had been investigating the role of one or two markers in the bladder cancer such as the predictive role of CD44v6 absence have been investigated in relation to bladder cancer.[47] CD44v6 is a protein located on the surface of the uroepithelial cells and is believed to be an important protein for cell adhesion and migration.[47] Its absence is shown to help tumour progression and distant metastasis.[47] Hideaki Miyake and colleagues studied the prognostic value of Insulin-like growth factor (IGF) binding protein -2 to IGF binding protein-3 ratio in 97 patients, which had undergone radical cystectomy for muscle invasive bladder cancer.[48] The study group was divided in to those with recurrence (group A) and without recurrence (group B). They found that IGFBP-2 mRNA expression was statistically higher in group A than in B, while the expression of IGFBP-3 mRNA was significantly lower in group A than in B.[48] They have also shown a significant difference in the relative expression ratio of IGFBP-2 to IGFBP-3 (BP-2/BP-3 ratio) between the groups studied.[48]

Clinical and laboratory science had shown that there are two distinct pathways in bladder cancer pathogenesis the Ta (non muscle invasive) and carcinoma in-situ (CIS) pathways.[44] Non-invasive tumours are believed to be arising from hyperplasia of the urothelium, have a greater (80%) tendency of recurrence following resection, but they rarely (5–10%) progress to invasive tumours and unpredictably to high-grade T1 tumours and then to invasive tumours.[50] However, one in two CIS (arising from dysplasia of urothelium) progress to T1 and then to muscle-invasive tumours.[50] Muscle-invasive bladder cancers are reported to arise through the CIS pathway in 80% of cases.[45] A recent review article on molecular genetics of the bladder cancer have reported that muscle invasive bladder cancers are associated with molecular markers that are characteristic to the process of EMT (epithelial–to-mesenchymal transformation).[51] FGFR-3 mutation is commonly associated with non-muscle invasive bladder cancers whilst a p53 mutation is seen in half of the muscle invasive bladder cancers.[49]

There is no doubt that understanding of the pathogenesis of bladder carcinogenesis at its molecular level will help identify and explain the heterogeneous clinical behaviour observed in various urothelial cancers. Molecular level knowledge can help provide individualized prognostication and would be invaluable for better risk stratification, which can guide clinical decisions with precision. The standard prognostic information in the form of tumour grade, stage and lymph node status is regarded as insufficient to explain the varied biological potential and varied clinical behaviour observed in the bladder cancers.[15] Hence, various investigators have routed to understand bladder cancer at the molecular level and find biomarkers that can be used alongside the standard prognostic information to stratify risk and guide adjuvant therapy. It is believed that non-muscle invasive and muscle invasive bladder urothelial carcinomas have different molecular entities and identifying these markers can help differentiate them.[51] FGRF-3, H-RAS, P13K and deletion of the chromosome9 (long arm) are markers of the non-muscle invasive

cancer while mutation or deletion in the pRB, p53 and PTEN are associated with carcinoma in-situ.[51] It is increasingly appreciated that vast majority of patients that undergoes cystectomy and were thought to have had organ-confined tumours, had been under-staged.[52] The current standard staging system will under-stage up 70% patients that are undergoing cystectomy, which poses an important problem in the management of bladder cancer.[53] Despite the fact that no specific marker can accurately predict extravesical extension of the tumour, some of markers, which are associated with high stage and grade, can predict to a degree the possibility of extravesical extension.[52] Bladder cancer is notorious for the nuisance that it causes due to the high risk of recurrence.[10] The recurrence rate can be as much as 90%, and 25% of the tumours that recur become muscle invasive.[10] Clinical and pathological parameters such as tumour stage and grade are used in standard practice to predict outcome, but have been disputed as an insufficient with limited value.[10] Molecular markers can provide additional information to predict outcome and the risk of recurrence. FGRF-3 mutation is associated with a low risk of recurrence while p53 mutation is associated with a high risk of recurrence.[10]

It is worth mentioning that so far no single marker that could reliably detect, predict the stage and outcome of surgery for bladder cancers had been identified. Nonetheless, some markers have unique value in various aspects of the disease. Such as they can provide diagnostic and prognostic information while others can help in targeting the therapy. Some of these biomarkers such as fluorescence in-situ hybridisation (FISH), Immuno-Cyt, NMP22, BTA Stat, and BTA Trak have been granted approval by the American FDA in bladder cancer screening of high-risk populations and for bladder cancers follow up. However, their supplemental role in predicting disease aggressiveness is yet to be validated.[50]

CONCLUSION

The number of biomarkers investigated in relation to bladder cancer exceeds more than twenty but a handful of them have shown consistence relevance and only a few of them had been incorporated in to certain prognosis programmes. So far no single marker has been identified, which can predict the overall status of the disease but a combination of a few markers can provide additional information to help diagnosis, provide prognostics and guide therapy. Multi centre validation studies are required to identify and validate these novel markers. As knowledge about molecular markers expands and data accumulates, it is possible that molecular grading and staging would be finally incorporated in to the standard practice.

REFERENCES

1. Office for National Statistics 2011, Cancer statistics registration: registration of cancers diagnosed in 2008.
2. Shirodkar S.P and Lokeshwar V.B. Potential new urinary markers in the early detection of bladder cancer. CurrOpinUro 2009;19:488-93.
3. Messing EM, Madeb R, Young T, GilchristKW,BramL. Long-term outcome of haematuria home screening for bladder cancer in men. Cancer 2006;107:2173-2179.
4. Shirodkar SP, Lokeshwar VB. Bladder tumor markers: from haematuria to molecular diagnostics - where do we stand? Expert Rev Anticancer Ther 2008;8:1111-1123.
5. Adekola S.A, Popoola O.A, Ogundiran S.M, Oparinde D.P, Onuegbu A.J. Is gamma glutamyl transferase a diagnostic marker of prostate disease? Int J Med Biomed Res 2013;2:147-151
6. Bott S, Chanawani M and Mostafid H. The use of the NMP22 BladderChek test for bladder cancer to optimise investigations in a one-stop haematuria clinic. Br J Med SurgUrol 2008;1:126-30.
7. Vrooman O.P and Witjes J.A. Molecular markers for detection, surveillance and prognostication of bladder cancer. Int J Urol 2009;16:234-43.
8. Bryan R.T, Zeegers M.P, James N.D, Wallace D.M.A and Cheng K.K. Biomarkers in bladder cancer. BJU Int 2010;105:608-13.
9. Herman J.G and Baylin S.B. Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 2003;349:2042-54.
10. Cheng L, Zhang S, MacLennan G.T, Williamson, S.R, Lopez-Beltran A and Montironi R. Bladder cancer: translating molecular genetic insights into clinical practice. Hum pathol 2011;42:455-81.
11. vanRhijn B.W.G, Van der Poel H.G and van Der Kwast T.H. Urine markers for bladder cancer surveillance: a systematic review. EurUrol 2005;47:736-48.
12. Tilki D, Burger M, Dalbagni G, Grossman H.B, Hakenberg O.W, Palou J, Reich O, Rouprêt M, Shariat S.F and Zlotta A.R. Urine markers for detection and surveillance

of non-muscle-invasive bladder cancer. EurUrol 2011;60:484-92.
13. Banek S, Schwentner C, Tager D, Nasterlack M, Leng G, Pesch B, Sievert K.D, Eberle F, Wiens C and Bierfreund K.G. 444 Predictive value of urine-based tumor markers in a bladder cancer screening population. EurUrolSuppl 2012;11:444-444a.
14. Sharma S, Zippe C.D, Pandrangi L., Nelson D and Agarwal A. Exclusion criteria enhance the specificity and positive predictive value of NMP22 and BTA stat. J Urol 1999;162:53-7.
15. Kinders R, Jones T, Root R, Bruce C, Murchison H, Corey M, Williams L, Enfield Dand Hass G.M. Complement factor H or a related protein is a marker for transitional cell cancer of the bladder. Clin Cancer Res 1998;4:2511-20.
16. Budman L.I, Kassouf W and Steinberg J.R. Biomarkers for detection and surveillance of bladder cancer. Can UrolAssoc 2008;2:212-221.
17. Miyake M, Goodison S, Rizwani W, Ross S, Bart Grossman H and Rosser C.J. Urinary BTA: indicator of bladder cancer or of hematuria. World J Urol 2012;30:869-73.
18. Di Martino E, Tomlinson D.C. and Knowles M.A. A Decade of FGF Receptor Research in Bladder Cancer: Past, Present, and Future Challenges. Adv Urol 2012:Article ID 429213.
19. Shariat S.F, Chade D.C, Karakiewicz P.I, Ashfaq R, Isbarn H, Fradet Y, Bastian P.J, Nielsen M.E, Capitanio U, Jeldres C, Montorsi F, Lerner S.P, Sagalowsky A.I, Cote R.J and Lotan Y. Combination of Multiple Molecular Markers Can Improve Prognostication in Patients With Locally Advanced and Lymph Node Positive Bladder Cancer. J Urol 2010;183:68-75.
20. Van Rhijn B.W, Montironi R, Zwarthoff E.C, Jöbsis A.C and van derKwast T.H. Frequent FGFR3 mutations in urothelial papilloma. J. Pathol 2002;198:245-51.
21. Lamont F.R, Tomlinson D.C, Cooper P.A, Shnyder S.D, Chester J.D and Knowles M.A. Small molecule FGF receptor inhibitors block FGFR-dependent urothelial carcinoma growth in vitro and in vivo. Br J Cancer 2011;104:75-82.
22. Ecke T.H, Sachs M.D, Lenk S.V, Loening S.A and Schlechte H.H. TP53 gene mutations as an independent marker for urinary bladder cancer progression. Int J Mol Med 2008;21:655-61.
23. Salinas-Sánchez A.S, Atienzar-Tobarra M, Lorenzo-Romero J.G, Sánchez-Sánchez F, Giménez-Bachs J.M, Donate-Moreno M.J, Pastor-Navarro H, Hernández-Millán I, Segura-Martín M and Escribano-Martínez J. Sensitivity and specificity of p53 protein detection by immunohistochemistry in patients with urothelial bladder carcinoma. UrolInt 2007;79:321-7.
24. Youssef R.F, Mitra A.P, Bartsch G, Jones P.A, Skinner D.G and Cote R.J. Molecular targets and targeted therapies in bladder cancer management. World J Urol 2009;27:9-20.
25. Malats N, Bustos A, NascimentoC.M, Fernandez F, Rivas M, Puente D, Kogevinas M. and Real F.X. P53 as a prognostic marker for bladder cancer: a meta-analysis and review. Lancet Oncol 2005;6:678-86.
26. Stadler W.M, Lerner S.P, Groshen S, Stein J.P, Shi S.R, Raghavan D, Esrig D, Steinberg G, Wood D, Klotz L, Hall C, Skinner D.G and Cote R.J. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. J ClinOncol 2011;29:3443-9.
27. Villares G.J, Zigler M, Blehm K, Bogdan C, McConkey D, Colin D and Bar-Eli M. Targeting EGFR in bladder cancer. World J Urol 2007;25:573-9.
28. Bian W and Xu Z. Combined assay of CYFRA21-1, telomerase and vascular endothelial growth factor in the detection of bladder transitional cell carcinoma. Int J Urol 2007;14:108-11.
29. Tomaszewski J.J and Smaldone M.C. Emerging intravesical therapies for management of nonmuscle invasive bladder cancer. J Res Reports Urol 2010;2:67-84.
30. Menke T.B, Boettcher K, Krüger S, Kausch I, Boehle A, Sczakiel G and Warnecke J.M. Ki-67 protein concentrations in urothelial bladder carcinomas are related to Ki-67-specific RNA concentrations in urine.ClinChem 2004;50:1461-3.
31. GönülI,Akyürek N, Dursun A and Küpeli B. Relationship of Ki67, TP53, MDM-2 and BCL-2 expressions with WHO 1973 and WHO/ISUP grades, tumor category and overall patient survival in urothelialtumors of the bladder. Pathol-Res Pract 2008;204:707-17.
32. Yurakh A.O, Ramos D, Calabuig-Fariñas S, López-Guerrero J.A, Rubio J, Solsona E, Romanenko A.M, Vozianov A.F, Pellin A and Llombart-Bosch A. Molecular and immunohistochemical analysis of the prognostic value of cell-cycle regulators in urothelial neoplasms of the bladder. EurUrol 2006;50:506-15.
33. Smith S.D, Wheeler M.A, Plescia J, Colberg J.W, Weiss R.M and Altier D.C. Urine detection of survivin and diagnosis of bladder cancer. JAMA Int Med 2001;285:324-8.
34. Adida C, Crotty P.L, McGrath J, Berrebi D, Diebold J and Altieri D.C. Developmentally regulated expression of the novel cancer anti-apoptosis gene survivin in human and mouse differentiation. Am J Pathol1998;152(1):43-49
35. Margulis V, Lotan Y and Shariat S.F. Survivin: a promising biomarker for

detection and prognosis of bladder cancer, World J Urol 2008;26:59-65.
36. Eissa S, Swellam M, Shehata H, El-Khouly I.M, El-Zayat T and El-Ahmady O. Expression of HYAL1 and Survivin RNA as Diagnostic Molecular Markers for Bladder Cancer. J Urol 2010;183:493-498.
37. Wang Y, Zhu Z, Zeng F, Wang L, Wu Y, Xia W and Xing S. Expression and prognostic significance of survivin in the progression of bladder transitional cell cancer.JHuazhongUnivSci Tech 2007;27:444-7.
38. Ku J.H, Godoy G, Amiel G.E and Lerner S.P. Urine survivin as a diagnostic biomarker for bladder cancer: a systematic review. BJU Int 2012;110:630-6.
39. Barbisan F, Santinelli A, Mazzucchelli R, Lopez-Beltran A, Cheng L, Scarpelli M, van der Kwast T and Montironi R. Strong immunohistochemical expression of fibroblast growth factor receptor 3, superficial staining pattern of cytokeratin 20, and low proliferative activity define those papillary urothelial neoplasms of low malignant potential that do not recur. Cancer 2008;112:636-44.
40. vanOers J.M, Wild P.J, Burger M, Denzinger S, Stoehr R, Rosskopf E, Hofstaedter F, Steyerberg E.W, Klinkhammer-Schalke M, Zwarthoff E.C, van der Kwast T.H and Hartmann A. FGFR3 mutations and a normal CK20 staining pattern define low-grade noninvasiveurothelial bladder tumours. Eur Urol 2007;52:760-8.
41. Christoph F, Weikert S, Wolff I, Schostak M, Tabiti K, Müller M, Miller K and Schrader M. Urinary cytokeratin 20 mRNA expression has the potential to predict recurrence in superficial transitional cell carcinoma of the bladder. Cancer Lett 2007;245:121-126.
42. Bird A. DNA methylation patterns and epigenetic memory. Genes Dev 2010;16:6-21.
43. Jones P.A and Baylin S.B. The fundamental role of epigenetic events in cancer. Nature Rev Genet 2002;3:415-28.
44. Chung W, Bondaruk J, Jelinek J, Lotan Y, Liang S, Czerniak B and Issa J.P.J. Detection of Bladder Cancer Using Novel DNA Methylation Biomarkers in Urine Sediments. Cancer Epidemiol Biomarkers Prevent 2011;20:1483-91.
45. Frantzi M, Makridakis M and Vlahou A. Biomarkers for bladder cancer aggressiveness. Curr Opin Urol 2012;22:390-6.
46. Mechlin C.W, Tanner M.J, Chen M, Buttyan R, Levin R.M and Mian B.M. Gli2 Expression and Human Bladder Transitional Carcinoma Cell Invasiveness. J Urol 2010;184:344-51.
47. Klatte T, Seligson D.B, Rao J.Y, Yu H, de Martino M, Garraway I, Wong S.G, Belldegrun A.S and Pantuck A.J. Absent CD44v6 Expression is an Independent Predictor of Poor Urothelial Bladder Cancer Outcome. J Urol 2010;183:2403-2408.
48. Miyake H, Hara I, Yamanaka K, Muramaki M and Eto H. Prognostic significance of insulin-like growth factor (IGF) binding protein-2 to IGF-binding protein-3 ratio in patients undergoing radical cystectomy for invasive transitional cell carcinoma of the bladder. BJU Int 2005;95:987-91.
49. Neuzillet Y, Paoletti X, Ouerhani S, Mongiat-Artus P, Soliman H, Sibony M, Denoux Y, Molinie V, Herault A and Lepage M.L. A Meta-analysis of the relationship between FGFR3 and TP53 Mutations in bladder cancer. PloS one 2012;7:e48993.
50. Wu X.R. Urothelialtumorigenesis: a tale of divergent pathways. Nat Rev Cancer 2005;5:713-25.
51. Castillo-Martin M, Domingo-Domenech J, Karni-Schmidt O, Matos T and Cordon-CardoC. Molecular pathways of urothelial development and bladder tumorigenesis. Uro Oncol 2010;28:401-408.
52. Stec A.A, Cookson M.S and Chang S.S. Detection of Extravesical Disease: A lack of bladder cancer markers. Bladder Cancer 2010;7;55-65.
53. Lotan Y, Shariat S.F, Schmitz-Dräger B.J, Sanchez-Carbayo M, Jankevicius F, Racioppi M, Minner S.J, Stöhr B, Bassi P.F and Grossman H.B. Considerations on implementing diagnostic markers into clinical decision making in bladder cancer. Urol Oncol 2010;28:441-8.

doi: http://dx.doi.org/10.14194/ijmbr.235

How to cite this article: Miakhil I, Parker S.G, Kommu S.S, Nethercliffe J. A review of molecular biomarkers for bladder cancer. Int J Med Biomed Res 2013;2(3):186-194

Conflict of Interest: None declared