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UROONCOLOGY

Review

What are the currently available and in development molecular markers for bladder cancer? Will they prove to be useful in the future?

Mesane kanseri için mevcut ve geliştirilmekte olan moleküler belirteçler nelerdir? Gelecekte de faydalı olacaklarını nasıl kanıtlayabilirler?

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ABSTRACT

Urothelial carcinoma is the 9th most common cancer worldwide. Most urothelial tumors are non-muscle invasive on presentation. However, two-thirds of non-invasive bladder cancers will eventually recur with a 25% risk of progression to muscle-invasive bladder cancer. Tumor stage, histological grade and pathological invasion of blood vessels and lymphatic tissue are the main indicators for urothelial cancer prognosis. The gold standard for diagnosing bladder cancer is conventional white-light cystoscopy and biopsy. Urine cytology is a highly specific, sensitive test for high-grade tumors or carcinoma in situ (CIS). Urinary NMP22 has an overall sensitivity and specificity for detecting bladder cancer of 49% and 87%, respectively. However, there are false-positive results in the presence of urinary tract infection or hematuria. The detection of specific gene mutations related to urothelial cancers has been studied and employed to reproduce markers helpful for diagnosis. According to current studies, molecular markers can be used to predict tumor recurrence. From a prognostic point of view, new molecular markers have yet to be established as reliable indicators of tumor aggressiveness. We aimed to review the molecular markers with possible prognostic significance that have been discussed in the literature. This review examined the literature for various molecular markers under development for bladder cancer in an attempt to optimize patient care and reduce the costs of treating these patients.

Key words: Bladder cancer; molecular markers; predictor of tumor recurrence.

ÖZET

Mesane kanseri; dünyada en yaygın 9. kanserdir. Ürotelyal tümörlerin çoğu başvuru esnasında kasa invaze olmamıştır. Bununla birlikte, non-invaziv mesane kanserlerinin üçte ikisinde rekürrens gelişecek ve %25 kasa invaze mesane kanserine progresyon göstereceklerdir. Ürotelyal kanser prognozu için temel göstergeler; tümör evresi, histolojik grade, kan damarlarına ve lenfatik dokuya patolojik invazyondur. Mesane kanserinin teşhisinde altın standart yöntem, geleneksel sistoskopi ve biyopsidir. İdrar sitolojisi, yüksek grade'li tümörler veya karsinoma in situ (CIS) için oldukça sensitif ve spesifik bir testtir. Üriner Nükleer Matriks Protein-22'nin (NMP-22) mesane kanserini saptamada sensitivitesi %49, spesifitesi ise %87'dir. Ancak, üriner enfeksiyon ya da hematüri durumunda, yanlış-pozitif sonuçlar olabilmektedir. Son yıllarda, ürotelyal kanserle ilişkili spesifik gen mutasyonlarının saptanmasına çalışılmakta ve bu gen mutasyonları, teşhis için yardımcı olabilecek belirteçlerin üretiminde kullanılmaktadır. Son zamanlarda yapılan araştırmalara göre, moleküler belirteçler tümör rekürrensinin önceden tahmininde kullanılabilmektedir. Yine de, prognostik açıdan, yeni moleküller tümör agresifliğinin güvenilir göstergesi olarak henüz tam kabul görmemişlerdir. Biz bu çalışmamızda, literatürde tartışılan muhtemel prognostik önemi olan moleküler belirteçleri gözden geçirmeyi amaçladık. Bu derleme, mesane kanserli hastaların tedavilerini daha uygun hale getirip bu hastaların tedavi masraflarını azaltan, mesane kanserine yönelik çeşitli moleküler belirteçleri inceleyen literatürü içermektedir.

Anahtar kelimeler: Mesane kanseri; moleküler belirteçler; tümör nüks prediktörü.

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Introduction

The urinary bladder is lined by urothelium, previously known as transitional epithelium, and urothelial carcinoma is the 9th most common cancer worldwide, with more than 300,000 cases registered in 2002.[1]

A noticeable increase in the incidence of bladder tumors in Asia has been observed secondary to an increase in smoking. However, almost two-thirds of all bladder cancer patients are in the developed world; half of which are located in North America and Europe.[2]

Urothelial cancer is the most common type of bladder cancer, comprising up to 80% of all bladder cancer cases.[3] Urothelial cancer can have different appearances on first presentation, including flat carcinoma in situ (CIS) and sessile, papillary or solid tumors.[4]

Three out of 4 urothelial tumors are non-muscle invasive on presentation.[5] However, two-thirds of non-invasive bladder cancers will eventually have a recurrence within 3 years of the initial diagnosis with a 25% risk of progression to muscle-invasive tumors requiring aggressive treatment.[6,7]

The tumor stage and histological grade are accepted as the main indicators of urothelial cancer prognosis.[4] Pathological invasion of blood vessels and lymphatic tissue are also considered to be independent prognostic factors.[8-10] More recently, a number of molecular markers with possible prognostic significance have been discussed in the literature.[11]

Currently, the gold standard for diagnosing of bladder cancer is conventional white-light cystoscopy and biopsy.[4] Cystoscopic examination could be improved using Narrow Band Imaging (NBI) or fluorescence-guided cystoscopy (blue light cystoscopy).[12,13] In contrast, urine cytology is a highly specific (>90%) and reasonably sensitive test for high-grade bladder cancer and hence it is a useful tool for identifying high-grade tumors or CIS. However, the accuracy of urine cytology, can be impaired by a paucity of cells retrieved, urinary tract infection or stones and intravesical treatments.[14]

Urothelial carcinoma, especially the non-muscle invasive type, is known to be very-expensive to treat and follow.[15] This expense is largely because of the need for frequent and long-term surveillance due to the high recurrence rate and risk of progression to muscle-invasive cancer.

An accepted surveillance regimen following primary tumor resection generally includes regular cystoscopy and urine cytology testing. Conventional white-light cystoscopy can reliably identify up to 80% of non-muscle invasive tumors and 68% of CIS. In contrast, the more expensive fluorescence-guided cystoscopy is more sensitive in diagnosing non-muscle invasive tumors (96%) and CIS (93%).[10]

Approximately one-third of the deaths related to bladder cancer are potentially avoidable. Thus, the recommendation is to provide more timely care and aggressive management for such patients.[16] Accordingly, enormous efforts currently are in place to identify molecular markers with robust diagnostic and prognostic value in patients with urothelial bladder cancer.

Here, we review the literature examining and developing various molecular markers for bladder cancer to optimize patient care and cut costs.

Main body

Molecular markers as a diagnostic tool

In 1996, a urinary protein called NMP-22 was isolated with 20-fold higher levels in bladder cancer patients compared to non-cancer individuals.[17] In a large multi-centric study, a urinary NMP22 level of 10 units/mL was considered to be positive for bladder cancer with an overall sensitivity and specificity for detecting bladder cancer of 49% (up to 88% in T2 tumors) and 87%, respectively. In the same study, NMP-22 was able to identify 8 out of 9 cancer patients with normal cystoscopy.[18] However, the downside of NMP-22 testing is false-positive results in the presence of a urinary tract infection or hematuria.[19]

Another relatively sensitive (75%) and specific (85%) test for detecting bladder cancer is the Lewis blood group antigen X, which is generally, but not always, missing from adult urothelial cells.[20,21] To date, no kit for this test is readily available.

A retrospective study in Spain suggested incorporation of urinary cytoskeletal proteins, namely CK 20 and CYFRA 21.1, into regular follow-up testing for bladder cancer patients. The study showed that CK 20 has a sensitivity and specificity of 85% and 76%, respectively.[22] However, a more recent multi-institutional analysis revealed a 33% sensitivity and 43% specificity for CYFRA 21.1 in detecting Ta tumors, precluding its use in clinical practice.[23]

The detection of specific gene mutations related to urothelial cancers have been studied and employed to reproduce markers helpful for diagnosis. FGFR-3 is a good example, involving 11 possible mutation loci detected in 3 out of 4 non-invasive urothelial cancers.[24] However, the dilemma lies in precisely locating all potential mutations in a solitary urine specimen. In addition, errors related to cancer grade and patient age cause the sensitivity and specificity of the tests to range from 50% to 90% and 60% to 90%, respectively.[25]

More DNA-based markers for bladder cancer have been investigated. Telomerase, a protein on the ends of chromosomes and preventer of cell death, has been linked to bladder cancer with 90% sensitivity and 88% specificity.[26]

Survivin, a protein with anti-apoptotic function, has been linked to urothelial cancer, and its role in diagnosing bladder cancer has been extensively studied over the years.[27] However, in a recent review article, the clinical application of such a marker in reliably diagnosing bladder cancer has been questioned due to low specificity.[28]

In 2002, an American prospective study examined the role of hyaluronic acid, an extracellular matrix produced by fibroblasts, in predicting bladder cancer using the urinary hyaluronic acid-

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hyaluronidase (HA-HAase) test. The results showed relatively high sensitivity (91-100%) and specificity (84-90%) rates, and the authors recommended its use as a screening tool in high-risk individuals.[29]

One year later, a French multi-center study evaluated the role of the ImmunoCyt test (Diagnocure, Canada) in detecting bladder cancer (sensitivity of 61-92% and specificity of 71-90%). ImmunoCyt is a three monoclonal antibody fluorescent test. The study claimed that such a test will help reduce the need for cystoscopy and urine cytology in post-tumor resection follow-up of bladder cancer patients.[30]

In Australia, the role of a multi-mRNA assay (*Cxbladder*, Pacific Edge Ltd) for detecting bladder cancer in 485 patients who presented with macroscopic hematuria was compared to conventional urine cytology and NMP22 testing. This study also developed a newer version of *Cxbladder* (*Cxbladder-D*). With a specificity fixed at 85%, the multi-mRNA assay was shown to have a superior overall sensitivity compared to urine cytology and NMP22 testing. Therefore, the authors recommended replacement of urine cytology and NMP22 assays by *Cxbladder-D* in conjunction with cystoscopy for bladder cancer follow-up. However, pitfalls related to *Cxbladder-D* use have also been described. Of note, the false positive rate of the multi-mRNA test in the presence of urinary stone disease is an issue. In addition, Cxbladder-D specificity was affected, but to a lesser extent, by patient age, sex and creatinine levels.[31]

Similarly, in a recent UK study, fifteen microRNAs were tested using polymerase chain reaction on 121 urine samples taken from 68 bladder cancer patients and 53 non-cancer individuals. The results revealed a possible diagnostic role for urinary microRNAs, being able to identify 94% of urothelial cancers. However, this study admitted missing 3% of invasive cancers using microRNAs (n=2).[32]

Molecular markers as a predictor of tumor recurrence

Using fluorescent-labeled DNA segments to detect chromosomal abnormalities associated with urothelial cancer is known as fluorescence in-situ hybridization (FISH). FISH has been shown to be 79% sensitive and 70% specific for diagnosing urothelial cancer.[20] A review article published in 2008 concluded that FISH is able to detect most concomitant bladder recurrences and predict recurrent disease.[33]

More similar studies have assessed the value of FISH for bladder tumor surveillance. These studies revealed a possible place for FISH as a predictor of bladder recurrence, but not as a replacement for the currently accepted gold standard, cystoscopy.[34,35]

Notably, the US Food and Drug Administration has actually approved the use of FISH (UroVysion-Abbott Molecular Inc) for urothelial cancer screening for hematuria and surveillance in known bladder cancer patients.[36] Nevertheless, compared to urine cytology, the routine use of UroVysion is still debatable; this test is a costly method to diagnose clinically insignificant low-grade bladder tumors.[37,38] In addition, the false positive rate related to the presence of benign urothelial umbrella cells with abnormal DNA ploidy makes the routine use of UroVysion relatively unfavorable.[39]

Microsatellite analysis has been described in the literature since 1997, and its role in detecting low-grade non-invasive bladder cancer has been evaluated.[40,41] Microsatellite analysis involves a polymerase chain reaction (PCR) recognizing tumor DNA. The findings from the latter study suggested a possible anticipatory value for this test in bladder recurrence with a recurrence rate of 83% in patients with a positive microsatellite analysis compared to only 22% in those with a negative test.

Recently, a group of urologists in Denmark studied the efficiency of methylation biomarkers in predicting urothelial malignancy recurrence in 390 urinary specimens retrieved from 184 known non-invasive bladder cancer patients. The authors are optimistic that the ZNF 154 methylation marker can potentially be incorporated into a bladder cancer surveillance regimen with an observed sensitivity and specificity of 94% and 67%, respectively.[42]

Molecular markers as a prognostic tool

In a Spanish study published in 2004, the expression of certain markers, including cyclins and p27kip1, was linked to tumor aggressiveness and hence claimed to be 'predictors of survival'.[43]

In addition, emmprin and survivin gene profiling has been shown to possibly determine the chemo-sensitivity of invasive bladder tumors. More recently, 57 mRNA levels were used to classify urothelial cancer patients at each stage into high or low risk for progression categories.[44,45]

In a recent publication, two independent cohorts were studied to analyze the prognostic significance of protein expression in invasive bladder cancer and concluded that measuring TIP60 and MRE11 expression is potentially useful in directing treatment of invasive bladder tumors.[46]

Furthermore, the 2nd International Consultation on Bladder Cancer (ICUD) listed the common genetic alterations linked to urothelial bladder cancer, four of which are thought to have prognostic significance in bladder cancer patients.[47] Those genes are the tumor suppressor genes TP53, RB1 and FHIT and the oncogene FGFR3.

What does the future hold?

Currently, more effort is being put into new trials to consolidate current findings and identify 'ideal' molecular markers that are

cost-effective, non-invasive, and able to confidently and precisely provide prognostic value and help determine therapeutic options.[4]

In conclusion, a significantly large percentage of the population suffers from bladder cancer and a considerable proportion of these cancers are in the non-muscle invasive category, requiring repeat, costly investigations on a regular basis, making bladder cancer very expensive to treat worldwide.

Over the last twenty years, there has been a remarkable increase in the number of scientific studies exploring the possible diagnostic and prognostic value of molecular markers in bladder cancer, revealing an enormous number of the currently available potential molecular markers.

Unfortunately, most of these molecular markers have failed to reproduce enough sensitivity and specificity to reliably replace current mainstay for investigating bladder cancer, cystoscopy; therefore, the authors recommend the clinical use of molecular markers alongside cystoscopy and urine cytology in an attempt to reduce the need for and delay invasive and expensive cystoscopy, provide early diagnosis and lower costs related to patient follow-up.[48]

Lastly, from a prognostic point of view, new molecular markers have yet to be established as reliable indicators of tumor aggressiveness. Until then, tumor stage and grade are the current cornerstone factors in establishing prognosis and planning treatment strategies.

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