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Seminar article

Considerations on the use of urine markers in the management of patients with high-grade non–muscle-invasive bladder cancer

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Abstract

Objective: Diagnosis and surveillance of high risk non muscle-invasive bladder cancer (NMIBC) represent specific challenges to urologists. In contrast to low/intermediate risk tumors, these tumors recur more frequently. A significant number will eventually progress to muscle-invasive bladder cancer, a life threatening disease requiring extensive therapeutic efforts. Although clinical risk factors have been identified that may predict tumor recurrence and progression, additional biomarkers are desperately needed to improve tumor diagnosis and guide clinical management of these patients. In this article, the role of molecular urine markers in the management of high risk NMIBC is analyzed.

Methods: In this context, several potential indications (diagnostic, prognostic, predictive) were identified and the requirements for molecular markers were defined. In addition, current knowledge within the different indications was summarized.

Results: Significant progress has been made in the last decade studying the impact of molecular urine markers in patients with high risk NMIBC.

Conclusions: Although we may not be ready for the inclusion of molecular markers in clinical decision-making, and many questions remain unanswered, recent studies have identified situations in which the use of molecular markers in particular in high grade tumors may prove beneficial for patient diagnosis and surveillance.

Keywords: Urine markers; Non–muscle-invasive bladder cancer; High grade; Diagnosis; Disease management

Introduction

High-risk non–muscle-invasive bladder cancer (NMIBC) is characterized by tumors that recur frequently and often progress to muscle-invasive bladder cancer, a deadly disease.

This article reflects and summarizes discussions held at the 10th Meeting of the International Bladder Cancer Network (IBCN e.V.), Nijmegen, The Netherlands, 20—22.9.2012.

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Table 1
FDA-approved urine tests for diagnosis or surveillance of patients with bladder cancer or both

Assay	Source	Target	Assay type
Urine cytology	Cells	Morphology	Microscopy
BTA stat (Polymedco)	Urine	Complement factor H and complement factor H-related protein	Immunoassay or point-of-care device
BTA TRAK (Polymedco)	Urine	Complement factor H and complement factor H-related protein	Sandwich ELISA
NMP22 (Alere)	Urine	Nuclear matrix protein 22	Sandwich ELISA
NMP22 BladderChek (Alere)	Urine	Nuclear matrix protein 22	point-of-care device
ImmunoCyt/uCyt+ (Scimedx)	Cells	Two mucin glycoproteins, high molecular carcinoembryonic antigen, and morphology	Immunofluorescence microscopy
UroVysion (Abbott, Vysis)		Morphology, alterations in chromosomes 3, 7, 17, and 9p21	FISH

ELISA = enzyme-linked immunosorbent assay.

Thus, urologists are faced with the specific challenges of early diagnosis and lifelong patient surveillance. To reduce tumor recurrence rates and potentially halt tumor progression, reresection of the tumor bed and maintenance intravesical BCG instillation are recommended to patients with high-risk NMIBC. Several clinical risk factors have been identified that may predict tumor recurrence and progression in NMIBC [reviewed in Refs. 1 and 2]; however, additional biomarkers would likely improve tumor diagnosis and guide clinical management of these patients.

Through the last decades, numerous molecular urine markers for diagnosis of bladder cancer (BC) have been developed. Although some of them have been approved for diagnostic use and surveillance by the Food and Drug Administration (FDA) (Table 1), no molecular marker has been incorporated into guideline recommendations or clinical decision making for patients with high-risk NMIBC. It may be argued that the performance of current markers may be not sufficient, but multiple studies and reviews demonstrate that most diagnostic urine markers are more sensitive than conventional urine cytology, including in high-grade disease [3–6] (Tables 2 and 3). We therefore conclude that marker evaluation has been insufficient in the past, which is exemplified by the fact that in contrast to low/intermediate-risk BC [2], randomized controlled trials comparing the use of urine markers vs. standard care, including cystoscopy and urine cytology, are still lacking in high-risk NMIBC.

There is a growing body of evidence that molecular markers may predict tumor progression and risk-stratify patients who are being treated with intravesical therapies. In particular, cell cycle–regulating genes, epigenetic events (e.g., altered methylation), and apoptotic genes have been suggested to contribute to defining the prognosis of patients with BC [1,7,8,9]. Using markers such as fluorescence in situ hybridization (FISH) to identify patients who are likely to fail intravesical therapy would allow urologists the

Table 2
Marker sensitivity and specificity of cytology and commercially available markers (data from reviews/meta-analyses)

Marker	Median sensitivity (range)	Median specificity (range)	Total number of patients
Cytology			
Lotan and Roehrborn [3]	34 (20–53)	99 (83–99)	2,767
van Rhijn et al. [4]	35 (13–75)	94 (85–100)	5,545
Mowatt et al. [5]	44 (38–51)[a]	96 (94–98)[a]	14,260
BTA stat			
Lotan and Roehrborn [3]	71 (57–82)	73 (61–82)	2,534
van Rhijn et al. [4]	58 (29–74)	73 (56–86)	3,461
NMP22 (assay/BladderChek)			
Lotan and Roehrborn [3]	73 (47–87)	80 (58–91)	2,413
van Rhijn et al. [4]	71 (47–100)	73 (55–98)	2,041
Mowatt et al. [5] (pooled)	68 (62–74)[a]	79 (74–84)[a]	10,119
Mowatt et al. [5] (BladderChek)	65 (50–85)	81 (40–87)	2,426
uCyt+/Immunocyt			
van Rhijn et al. [4]	67 (52–100)	75 (62–82)	959
Mowatt et al. [5]	84 (77–91)[a]	75 (68–83)[a]	3,041
Schmitz-Dräger et al. [6]	81 (42–100)	75 (62–95)	4,899
FISH (Urovysion)			
Mowatt et al. [5]	76 (65–84)[a]	85 (78–92)[a]	3,101
Schmitz-Dräger et al. [6]	72 (23–100)	80 (40–100)	2,852

[a]95% CI.