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Seminar article

Considerations on the use of urine markers in the management of patients with low-/intermediate-risk non–muscle invasive bladder cancer

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Abstract

Objectives: Many molecular assays for bladder cancer diagnosis and surveillance have been developed over the past several decades. However, none of these markers have been routinely implemented into clinical decision making. Beyond their potential for screening high-risk populations, urine markers likely have the greatest potential in the follow-up of patients with non–muscle invasive bladder cancer (NMIBC).

Methods: Here, we discuss the current options and limitations of the use of urine markers for patient surveillance, focusing on patients with low-/intermediate-risk NMIBC.

Results: As these patients have a very low risk of tumor progression, the primary goal of surveillance is detection of recurrent disease. Although urine cytology seems to be limited to detection of few patients who would develop high-grade tumors, we conclude that the use of markers with high sensitivity for low-grade disease for patient follow-up has the potential to decrease the frequency of urethrocystoscopy without compromising patient prognosis. Because a single marker may not have sufficient sensitivity for detection of low-grade tumors, different scenarios, e.g., multitesting and reflex or sequential approaches, are discussed.

Conclusions: There is consensus that currently available markers have the potential to support clinical decision making in follow-up of patients with low-/intermediate-risk NMIBC. In light of our analysis, further additional randomized controlled studies to effectively assess the clinical usefulness of modern urine markers are required.

Keywords: Urine markers; Non–muscle invasive bladder cancer; Low risk; Disease management; Costs

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Introduction

Bladder cancer (BC) is a heterogeneous disease comprising low-grade and high-grade tumors. Non–muscle invasive bladder cancer (NMIBC) represents most cases. Decades after development and introduction of urine markers, several have been approved for BC diagnosis and surveillance by the Food and Drug Administration. Additionally, molecular urine markers have been assessed as an adjunct to urethrocystoscopy (UCS) in patients under surveillance for NMIBC. Surprisingly though, none have yet been routinely incorporated into clinical decision making. This is reflected by the fact that the use of diagnostic molecular markers is not recommended by any of the existing clinical guidelines thus far. A key reason that urine markers have not been incorporated into current clinical guidelines is the apparent lack of randomized controlled trials as the most rigid study design to assess their performance and benefit against current care guidelines. Following from randomized controlled trials, the necessity would exist to develop guidelines for the integration of markers into clinical decision making [1].

Prospective studies among at-risk asymptomatic subjects have been performed by our group members and presented at previous meetings. Although findings from these studies demonstrated the feasibility of using urine markers in screening for BC, they identified the underlying problem that the relatively low incidence of BC, even in high-risk cohorts, impairs efficient screening [2–4]. This has led to the question of whether molecular markers may be helpful in the assessment of patients with hematuria. Results from a recent multi-institutional trial suggest that the use of risk tables, including immunocytology (immunocyt/uCyt^{+}) results in conjunction with other risk factors, may have the potential to spare patients from invasive testing without compromising diagnostic efficacy [5].

A long-term goal of this group is the introduction of relevant molecular diagnostic markers into routine clinical practice. Potential applications of urine markers include screening asymptomatic patients, assessment of patients with hematuria, and monitoring patients with BC for tumor recurrence. In this article, we focus on the use of diagnostic markers in the surveillance of patients with low-/intermediate-risk NMIBC. The definition for low-/intermediate-risk NMIBC is based on the European Organization for Research and Therapy of Cancer risk score [6] and includes patients with a progression score of 0 to 6. In contrast to the European Organization for Research and Therapy of Cancer score, patients with T1 BC are excluded, translating into a 5-year progression rate of less than 5% to 8% for the defined cohort. The latter definition is also used in the current European Association of Urology (EAU) guidelines [7].

Within this article, the following questions are discussed:

1. What is the role of urine cytology in follow-up of patients with low-risk NMIBC?
2. Which marker or combination of markers is most suitable in follow-up of patients with low-risk NMIBC?
3. Is marker-based surveillance for follow-up of patients with low-risk NMIBC cost-effective?
4. How can molecular markers be included into clinical decision making in low-/intermediate-risk NMIBC?

Based on the risk of recurrence and progression, the EAU guidelines recommend either UCS or an ill-defined combination of UCS and urine cytology for follow-up of patients with low-/intermediate-risk NMIBC [7]. The sensitivity of cytology in low-risk BC is insufficient, with an estimate of 27% in a pooled analysis of studies [8]. By contrast, the sensitivity of UCS is much higher, although white-light office-based cystoscopy may fail to detect certain tumor types, most notably, carcinoma in situ (CIS) [9]. Although UCS is more sensitive, it is also a costly and invasive procedure with the potential for associated morbidity. These caveats likely reduce patient compliance with screen schedules in the absence of overt symptoms.

A key problem of low-/intermediate-risk NMIBC is tumor recurrence, which occurs in more than 30% of patients. Early detection and timely removal of the tumor is recommended. Diagnostic markers may support the management of these patients in several ways:

- Similar to the EAU guidelines for urine cytology [7], a positive marker result may suggest the presence of high-risk tumors, subsequently leading to random biopsy or investigation of the upper urinary tract.
- Positive marker results may prompt urologists to initiate a more thorough inspection of the bladder during UCS, thereby increasing the sensitivity of this diagnostic test [9,10].
- Given that delayed diagnosis of low-/intermediate-risk NMIBC may not pose significant risk to the patient, substitution with diagnostic marker tests to reduce the frequency of UCS is conceivable.

Current status

A pooled analysis of predominantly cross-sectional studies yielded a sensitivity of 44% for cytology for all types of BC but higher sensitivity for immunocytology (84%, 95-CI 77%–91%), fluorescence in situ hybridization (FISH) (UroVysion) (76%, 95-CI 65%–84%), and nuclear matrix protein 22 (NMP22) (68%, 95-CI 62%–74%) [8]. Similar results were obtained in the EAU-International Classification on Urological Diseases consensus statement on diagnostic markers [1]. In the latter review, marker performance was stratified along tumor grade, confirming a high sensitivity of ImmunoCyt/uCyt^{+} and UroVysion in low-grade disease.

The paucity of prospective validation studies presents a challenge for the introduction of molecular urine marker results into clinical decision making. Recently, results from