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., multistesting 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. © 2014 Elsevier Inc. All rights reserved.

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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
the first multicenter, randomized prospective study (ClinicalTrials.gov/NCT-00126958) on urine markers in NMIBC surveillance became available. This study, the first to investigate the possibility of reducing UCS frequency, was performed in 10 centers including 2 academic teaching hospitals in a cohort of 448 patients with low- and intermediate-risk NMIBC [10]. Over 2 years of surveillance, subjects were randomized to receive standard UCS every 3 months or a decreased regimen, excluding the 5 UCS scheduled at 6, 9, 15, 18, and 21 months after initial resection (Fig.). All patients had urinary microsatellite analysis (MA) performed quarterly. In the intervention group, endoscopy was performed only in the setting of a positive MA result, whereas in the control arm, results were not communicated to the physician to avoid influencing clinical decision making.

The overall sensitivity of MA (58%) was disappointing. However, an earlier review [11] and an earlier phase II study assessing urinary MA [12] highlighted that a lower sensitivity of urine markers must be anticipated for patients with NMIBC. Importantly, this study did find a sensitivity of 70% in the intervention arm where the urologist was aware of the MA result, as compared with a much lower sensitivity (29%) in the control arm of the study where the urologist was not aware of the MA outcome [9,10]. In 131 UCSs performed with knowledge of a positive MA result, 42 recurrences were detected. Only 6 recurrences were detected in 120 UCSs without prior knowledge ($P < 0.001$). Notably, there was no difference in the detection of recurrence when urine test results were negative [intervention arm, 18/260 (7%) and control arm, 18/326 (6%); $P = 0.45$] [10]. Moreover, the BC detection rate in a recent prospective study by Kamat et al. [13] was 6.5% or 13/200 UCS, similar to the detection rate in the control arm of this trial 24/446 (5.4%) [10]. These findings suggest that urologists perform a more thorough examination of the bladder when equipped with knowledge of a positive urine marker test.

The results from this study demonstrate the general feasibility of this approach and suggest that information from urine marker tests can improve detection rates. Thus, incorporating urine marker analyses into patient follow-up may be a particularly attractive strategy for surveillance of tumors at high risk for progression, when immediate diagnosis is of utmost relevance. In low-/intermediate-risk NMIBC with a very low risk of progression, it must be determined if the frequency and invasiveness of follow-up procedures can be decreased.

Based on these findings, a prospective phase III study comparing best supportive care defined by the urologist vs. noninvasive follow-up using commercially available diagnostic markers and ultrasound in patients with low-/intermediate-risk NMIBC is currently under consideration. This approach will evaluate whether markers may be used to substitute for UCS in part or permit extension of the time intervals between UCS. The focus of the study will primarily be after the second year following diagnosis when recurrence rates level off to less than 10%.

Although high sensitivity appears to be relevant in this patient cohort, the low risk of progression and high tumor-specific survival rates suggest that marker sensitivity between 80% and 90% may be sufficient in this situation. Supporting this hypothesis, office UCS is known to overlook smaller lesions without apparent disadvantage to the patient. Delayed tumor detection and removal, therefore, may be acceptable as long as the progression rate does not increase. On the contrary, patient quality of life is likely to improve with decreased frequency of invasive and painful endoscopic procedures with associated morbidity. Investigation of the effect of noninvasive follow-up on patient compliance is another relevant question as withdrawal from follow-up due to the discomfort of examination is conceivable.

Specificity may not be of utmost relevance in this group of patients at risk for tumor recurrence because an unnecessary UCS represents the only consequence. Therefore, a certain amount of false-positive tests would be acceptable. It should be emphasized at this point that a false-positive test may also indicate early cellular changes associated with carcinogenesis, in an anticipatory way [14]. Positive tests may thus alert the clinician to initiate subsequent screens over shorter time intervals. A similar procedure was employed for suspicious findings in screening for lung cancer with imaging methods [16].

**Role of urine cytology in follow-up of patients with low-/intermediate-risk NMIBC**

The surveillance of patients with BC usually includes collection of a urine sample (fresh voided, catheterized, or bladder washing) for cytologic examination. Features of urothelial cells stained with the Papanicolaou technique are interpreted to assess the risk of malignancy (Table). Methods used to prepare specimens, including smears from centrifuged specimens, cytocentrifugation, membrane filter techniques, and filter imprints, may affect the degree of cellular clarity, cellular distortion, and architectural pattern [17,18].

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**Fig.** Flowchart of the multicenter, randomized prospective study (ClinicalTrials.gov/NCT-00126958) on urine markers in NMIBC surveillance [10]. (Color version of the figure is available online.)
There is no standard definition for reporting urine cytology results, although the terms “benign, atypia, suspicious for malignancy, and positive for malignancy” are most commonly applied [19]. Pathologists differ in opinion on the meaning of “atypia,” and thus, reporting rates of atypia vary among institutions. Mokhtar and Al-Ghamedi [20] have put forth that atypia should be regarded as a means of communicating concern for malignancy to clinicians as 55% of atypical urine cytologies correlated with histopathologic presence of BC. Cytopathologists at Johns Hopkins Hospital have advocated subdividing atypia into high- and uncertain-risk categories [21]. Others have described atypia as a waste-basket term, and studies have grouped normal and atypical together as benign and suspicious and positive together as malignant for analyses [22].

An individual learning curve for pathologists in reading urine cytologies has been reported [23]. Poor interobserver and intraobserver agreements amongst pathologists with and without fellowship training in cytopathology have been reported for the grading of urothelial carcinoma on urine samples [24]. Altogether, each of these factors influences the sensitivity and specificity of urine cytology for detection of BC.

Although the strength of urine cytology is thought to lie in its high specificity, Kassouf et al. [25] have recently reported that the specificity of urine cytology ranged from 83% to 88% depending on urine collection technique and clinical presentation, and is therefore lower than historically reported. Urine cytology for the surveillance of low-risk BC is negatively affected by factors including inflammation, instrumentation, and the effect of treatment. Sensitivity ranged from 10% for low-grade tumors to 51% for high-grade tumors. Furthermore, urine cytology cannot be used to discriminate between papillary urothelial neoplasms of low malignant potential and low-grade papillary urothelial carcinoma (1998 World Health Organization/International Society of Urologic Pathology classification) [22].

The likelihood of a positive urine cytology finding during surveillance for low-risk NMIBC may be related to the interest and experience of the cytopathologist in detecting low-grade tumors. Raab et al. [26] identified increased nuclear/cytoplasmic ratios, irregular nuclear membranes, and cytoplasmic homogeneity as indicative of low-grade bladder tumors. Murphy et al. [27] found that studying the morphology of cells from previously resected low-grade bladder tumors from an individual patient increased the likelihood of detecting similar cancer cells in a follow-up urine cytology specimen from the same patient. However, this labor-intensive study of prior tumors is impractical in a routine follow-up setting.

In summary, the greatest value of urine cytology for patients with low-risk NMIBC is in the detection of those lesions that may progress to high-grade urothelial neoplasia (papillary, CIS, or invasive). Jackson et al. [28] reported that a suspicious or positive urine cytology result in patients with low-grade BC was associated with high-grade recurrence (58% vs 19%, \( P = 0.009 \)). Although only a small proportion of patients with low-risk NMIBC will progress and the use of urine cytology to detect recurrent low-grade tumors is limited, its relatively low cost and ready availability could be arguments for the use of cytology in this indication. Others, however, do not feel that the routine use of urine cytology in all patients with bladder tumor is justified [29].

### Marker requirements for follow-up of patients with low-/intermediate-risk NMIBC

#### General requirements

In general, a very high sensitivity is of key importance for diagnostic markers used for follow-up of patients with low-/intermediate-risk NMIBC, as disease prevalence is high in this group and missing events should be avoided. For patients with low-grade BC, the challenge for diagnostic markers is particularly high owing to the fact that morphologic and molecular alterations may be small.

Although specificity of a given marker may be of high relevance, e.g., in a screening setting, in follow-up of patients with a history of BC, a specificity of 70% to 80% appears acceptable. Working with a 20% to 30% false-positive rate, it must be kept in mind that at least some of these cases are not really false positive but rather represent an anticipatory positive test with a visible tumor developing subsequently.

#### Potential confounders

Little attention has been directed toward the importance of urine collection. Urine characteristics must be technically

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Table

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<thead>
<tr>
<th>Low-grade urothelial neoplasia</th>
<th>High-grade urothelial neoplasia</th>
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<tbody>
<tr>
<td>● High cellularity of urothelial cells in a voided urine sample</td>
<td>● Cellularity may be variable</td>
</tr>
<tr>
<td>● Small and large cohesive groups including papillary clusters</td>
<td>● Papillary clusters and loosely cohesive, dispersed urothelial cells (CIS)</td>
</tr>
<tr>
<td>● Normal cytology or minimal nuclear atypia (mild nuclear enlargement and overlapping)</td>
<td>● Marked nuclear atypia (hyperchromasia, high nucleocyttoplasm ratio, irregular nuclear membrane)</td>
</tr>
<tr>
<td>● Necrotic background</td>
<td>● Necrotic background</td>
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NB. The aforementioned features may be seen in instrumented samples so collection method must be specified on request form.
satisfactory as they influence test positivity [2]. There is currently no guideline for the consideration of leukocytes or urine density. In diluted urines, protein-based markers, e.g., NMP22, may have false-normal values, and low cell content may impair cell-based assays. On the contrary, urinary leukocytes are associated with a high fraction of false-positive NMP22 tests [30] whereas erythrocytes have been shown to compromise the results of other molecular tests, such as the bladder tumor antigen (BTA) Stat [31].

**Single-marker testing vs. multiple-marker testing**

The role of combined application of several urine markers for the detection of urothelial carcinoma, especially in a follow-up setting of patients with low-/intermediate-risk NMIBC, is controversial. Horstmann and colleagues investigated the combined use of cytology, FISH (UroVysion), immunocytology (Immunocy/UrCyT), and NMP22 enzyme-linked immunosorbent assay in a cohort of 106 patients undergoing surveillance for NMIBC [32]. Positivity was defined as one or more tests with a positive result. The test combination yielded a considerable increase of sensitivity (>90%) and high negative predictive value. However, specificity decreased considerably as compared with single tests to <30% depending on the combination. The 2-test combinations with best sensitivities were cytology and NMP22 (sensitivity 94% and specificity 34%), cytology and immunocytology (sensitivity 93% and specificity 56%), and NMP22 and FISH (sensitivity 93% and specificity 53%).

The results of this study show that every gain in sensitivity is associated with a considerable loss in specificity when combining urine markers and using each single positive test as a criterion for a positive test combination. In contrast, a combination, which requires multiple tests to be positive for overall positivity, is expected to be associated with an increase in specificity and a decrease in sensitivity [33]. One approach to find the optimal combination of tests/markers and set optimal criteria for a combination to be considered positive is receiver operating characteristic analysis of models with multiple test/marker combinations [5,34,35]. A study including 808 patients investigated whether the combined use of cytology, FISH, immunocytology, and NMP22 may improve test performance compared with a single test [34]. The area under the curve (AUC) of a single analysis or combination was used to compare test performances, and the cutoff for an optimal correlation of specificity and sensitivity was determined by receiver operating characteristic analysis. By using this method, a single positive test was not sufficient in many combinations to fulfill the criteria of a positive combination. It was observed that depending on the type of combination, AUC increased with the number of tests used in the combination. Promising 2-test combinations included FISH and cytology (AUC: 0.83) and FISH and immunocytology (AUC: 0.85). The AUC of the combination of all 4 markers was 0.86. As the dichotomized consideration of combination of urine markers (positive combination/negative combination) might lead to a considerable loss of information, future studies should focus on the use of nomograms incorporating combinations of urine markers and clinical parameters (such as grade of hematuria) to calculate the risk of BC recurrence.

**Sequential testing or reflex testing**

Use of molecular markers for “reflex testing” has recently gained interest. Although multiple-marker testing considers the results from several tests performed simultaneously, use of the reflex testing strategy dictates that a second test is only performed if the primary test yields a predefined result. In most studies, urine cytology is used as a primary marker and patients with negative cytology results are subsequently subjected to a second test. The idea behind this strategy is to improve the accuracy of the first test while minimizing the expense associated with molecular assays. Thus, sequential or reflex testing represents a modification of multitesting. Previous studies using reflex testing of patients with BC have frequently made use of the high specificity of urine cytology and have followed negative cytology with a more sensitive assay, aiming to improve the sensitivity of noninvasive analyses. Two studies on reflex testing have been published using FISH assays (UroVysion) [14,15]; however, the feasibility of this concept is unclear and warrants further consideration.

The stepwise use of 2 markers showing good performance in the detection of recurrent BC (immunocytology and FISH) has been investigated in a cohort of 505 patients undergoing surveillance for NMIBC [35]. At the time of immunocytology and FISH analysis, all patients received UCS. The sequential performance of immunocytology and FISH in patients with immunocytology-negative results was simulated. At the time of investigation, 130 patients showed BC recurrence. Immunocytology alone had a sensitivity of 66.1% [72.2% for high-grade (G3/CIS) or invasive (>pT1) BC], a specificity of 70.7%, and a negative predictive value of 85.9% (95.9% for high-grade or invasive BC). Performing FISH in patients with immunocytology-negative results increased the sensitivity and negative predictive value to 86.2% and 92.1% (96% and 99.3% for high-grade or invasive BC).

**Discussion**

NMIBC is a Janus-faced disease. Although a larger group of patients with low-/intermediate-risk disease harbor a significant risk for tumor recurrence, there is only a minor risk of tumor progression. Conversely, a smaller group of patients with high-grade disease is characterized by a high risk of progression to life-threatening muscle-invasive cancer.

Until a few years ago, follow-up for both groups was more or less identical. More recent guidelines discriminate between the different risk groups [7]; however, this innovation has not
yet been translated into clinical practice. An analysis of Surveillance, Epidemiology, and End Results Medicare-linked data revealed a marked underuse of current guidelines [36]. It remains unclear if this observation is based on physician ignorance, guideline impracticality, or a lack of patient compliance.

### How can molecular markers be included into clinical decision making in low-/intermediate-risk NMIBC?

Key clinical requirements in the follow-up of patients with low-/intermediate-risk disease include timely diagnosis and the necessity not to overlook high-risk tumors. As such, current practice includes the regular use of UCS and urine cytology in low-/intermediate-risk tumors. Although UCS is considered a “gold standard,” it is neither 100% sensitive nor 100% specific. Furthermore, in this predominantly male patient cohort, routine cystoscopy is not appreciated. As discussed earlier, the contribution of urine cytology is predominantly limited to the diagnosis of a portion of the few high-grade tumors expected to occur.

The main goal of an introduction of molecular markers in the follow-up of patients with low-/intermediate-risk NMIBC would be to decrease the use of UCS. This effect may not be relevant in low-risk NMIBC because the current EAU guidelines already recommend a decreased frequency of UCS [7]. However, this recommendation is restricted to a small group of patients at very low risk. Most NMIBCs in current clinical practice would be so-called intermediate-risk tumors and are suggested to undergo a different, poorly defined follow-up.

Follow-up of low-grade BC requires particularly sensitive markers. In addition, tumor volume would likely be small, thus making the task even more challenging. As cell-based assays—which also consider cytologic alterations of urothelial cells—apparently perform better in low-grade tumors as compared with urine-based markers, immunocytoLOGY, or the UroVysion assay would be superior options [1,11]. However, it may be questioned if a single test—although desirable for several reasons—may have sufficient sensitivity.

Combining several tests is another option; however, as discussed, multiple-marker testing harbors the risk of compromising the specificity if performed in a simple combinatorial approach [32]. To maintain high specificity when combining marker results as suggested by Todenhöfer et al. [35] strategies such as sequential procedures/reflex testing or application of more sophisticated multimarker classifiers following characterization of their confounders are conceivable. This approach would also likely minimize costs. Integration of additional risk factors in this algorithm, e.g., ultrasound findings or microhematuria or both, is another option.

There is an explicit need to evaluate the follow-up of patients with low-/intermediate-risk NMIBC in prospective trials as no information from phase III studies is currently available. Given the complexity of the issue, it is unlikely that a single study would provide a definitive answer to the questions we have raised here. Nevertheless, an intelligent study design would be helpful in guiding future research in the right direction.

### Considerations on cost-effectiveness

Without a doubt, cost-effectiveness of urine markers and UCS is an important aspect in defining treatment guidelines, however, this aspect is highly complex and difficult to assess. The complexity comes in part from the fact that a cost comparison of procedures would yield different results in different health care systems. In addition, the costs for complications of UCS are not included in current analyses. Furthermore, in low-/intermediate-risk NMIBC, it may be speculated that a potential delay in therapy may postpone interventions and may even reduce costs and complication rates. Thus, current analyses represent incomplete “snapshots” instead of definite answers to the consideration of cost.

As part of a multicenter, randomized prospective study on urine markers in NMIBC surveillance, de Bekker-Grob et al. [37] investigated whether replacing UCS in part by MA would reduce costs for low- and intermediate-risk NMIBC surveillance. Kamat et al. [38] analyzed if urinary markers were cost-effective in all NMIBC risk groups. In this study, all patients routinely had UCS. Unfortunately, both prospective studies found that the urine markers used were not cost-effective.

If doing cost-effectiveness analysis, it should be considered that laboratory tests tend to become less expensive with time if used routinely. The prostate-specific antigen assay may serve as an example that has come down in cost. It is currently less than €2/test, reduced from approximately €8 to €10 when it was first introduced in the clinic. Finally, today there is virtually no information on the potential effect of replacement of an invasive examination by urine testing on quality of life, an aspect that also could be relevant in considering cost-effectiveness and deserves prospective examination.

### Conclusions

In spite of the development of multiple molecular assays for BC diagnosis and surveillance, these markers are not implemented in clinical decision making and, as such, have shown little added value. Within this analysis, we discuss the current options and limitations of the use of markers for surveillance of low-/intermediate-risk NMIBC. We conclude that a sequential use of markers with high sensitivity for low-grade disease may have the potential to support patient follow-up and decrease the frequency of UCS without compromising patient prognosis. There is consensus that...
further randomized controlled studies are urgently needed to address the clinical usefulness of modern urine markers.

References


