Evaluation of a new quantitative point-of-care test platform for urine-based detection of bladder cancer

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Abstract

Objective: Several commercial point-of-care (POC) tests are available for urine-based detection of bladder cancer (BC). However, these tests are restricted to dichotomized results (positive or negative), which limits their diagnostic value. Quantitative protein-based tests offer improved risk stratification but require complex methods restricted to specialized centers. Recently, the first quantitative POC system based on the detection of cytoskeleton fragments became available. The aim of the study was to evaluate the diagnostic accuracy of this quantitative POC test.

Patients and methods: A total of 198 patients having symptoms suspicious for BC were included. All patients received urethrocytoscopv and upper-tract imaging. Urine samples were analyzed by the urine BC antigen (UBC) rapid POC system and evaluated both visually and quantitatively using the concile Omega 100 POC reader. For visual evaluation, different thresholds of band intensity for considering a test positive were applied. Moreover, the UBC enzyme-linked immunosorbent assay (ELISA), urine cytology, and the nuclear matrix protein 22 BladderChek were performed. Sensitivities and specificities were calculated by contingency analyses. Optimal cutoffs of quantitative tests were determined by receiver operating characteristic curves.

Results: A total of 61 patients (30.8%) were diagnosed with BC. Visual evaluation of the UBC revealed sensitivities of 38.1% to 71.4% with corresponding specificities of 54.1% to 89.1%, dependent on the threshold of band intensity applied. The quantitative UBC rapid showed a sensitivity of 60.7% and a specificity of 70.1% at optimal cutoff (area under the curve = 0.68). A constant increase of both the probability of BC and high-risk BC with increasing UBC rapid values was observed. UBC concentrations determined by the reader significantly correlated with the UBC ELISA (P < 0.001). The UBC ELISA, the nuclear matrix protein 22 BladderChek and cytology showed sensitivities of 48.3%, 16.4%, and 51.7% with specificities of 71.3%, 95.3%, and 78.1%, respectively.

Conclusion: The UBC rapid in combination with a quantitative POC-reader system for the first time enables quantitative determination of a BC marker under POC conditions. Diagnostic accuracy is at least equivalent to elaborate ELISA-based measurement. The quantitative use of the UBC rapid test facilitates risk prediction compared with conventional nonquantitative dichotomized POC testing.

Keywords: bladder cancer; urine markers; UBC rapid; point of care; NMP22; cytology; surveillance

1. Introduction

Cystoscopy is still considered as the gold standard in the diagnosis of bladder cancer (BC). In current guidelines, cytology is recommended as an adjunct to cystoscopy. Cytology is the most widely adopted noninvasive urine test [1] although it has low sensitivity especially for low-grade tumors [2,3]. Several urinary marker tests have been investigated in the last few years regarding their diagnostic accuracy and possibility of complementing cystoscopy in the diagnosis of BC. Although several tests and combinations of markers [4] have shown promising performance, their diagnostic accuracy cannot be considered sufficient to replace cystoscopy. One limitation of some of the broadly
available urine tests, such as fluorescence in situ hybridization (FISH), is that they are relatively complex to perform and they are expensive [5,6]. At the present time, various point-of-care (POC) test systems are available on the market allowing fast and simple urine marker determination. The nuclear matrix protein 22 (NMP22) BladderChek detects the NMP regulating critical aspects of mitosis [7]. Urinary BC antigen (UBC) rapid is a test that detects fragments of cytokeratins 8 and 18 in urine samples. These cytokeratins are frequently overexpressed in tumor cells [8]. The disadvantage of all these tests is their limitation to a simple positive or negative result. Owing to a lack of studies assessing this issue, no recommendations regarding the semiquantitative use of POC tests for BC exist. Moreover, semiquantitative test bands anticipate reproducibility of test results.

Test systems, such as enzyme-linked immunosorbent assays (ELISA), can provide quantitative results for BC tumor markers. However, they are relatively expensive, complex, and time consuming compared with POC tests.

The concile Omega 100 reader is a photometric POC system for the use with several rapid tests, such as troponin and C-reactive protein. Recently, the system was adopted to the UBC rapid lateral flow test cassette. This platform has been developed to provide quantitative results of the UBC test with the advantage of an easy and fast application.

The aim of this study was to investigate the feasibility and diagnostic accuracy of this new system. Moreover, the performance of the system was compared with conventional visual evaluation of the POC test, the established ELISA method for UBC, the NMP22 BladderChek, and urine cytology.

2. Materials and methods

2.1. Patients

For this prospective study, 198 patients having symptoms suspicious for primary BC (such as hematuria or irritative voiding syndromes) or undergoing surveillance for BC were included between April and December 2012 in the Department of Urology, University of Tübingen, Germany. The study was approved by the local institutional review board (No. 032/2013BO2). All patients underwent cystoscopy, bladder ultrasound, upper-tract imaging (ultrasound, intravenous urography, retrograde pyelography, or computed tomography), and transurethral resection of bladder tumor in case of abnormal findings. Exclusion criteria were any kind of mechanical manipulation (cystoscopy, transrectal ultrasound, and catheterization) within 10 days before urine sampling, as well as existing gross hematuria.

2.2. Procedure

Midstream urine was collected in a sterile plastic container and processed subsequently. Urine samples were analyzed by the UBC rapid test (IDL, Bromma, Sweden), the NMP22 BladderChek test (Alere, Waltham, USA), the UBC ELISA (IDL, Bromma, Sweden), and urine cytology. All tests were done as advised by the manufacturer’s instructions. First, results of the UBC rapid test were evaluated visually. The occurrence of a test band after 10 minutes of incubation was subdivided into 4 categories (no band, weak band intensity, intermediate, and strong band intensity). After visual evaluation, the test cartridges were analyzed by the photometric POC system concile Omega 100 reader (concile GmbH, Freiburg, Germany) for quantitative analysis. The Omega 100 reader illuminates the test field with a complementary color light to reduce interference in the analysis. The built-in charge-coupled device–matrix sensor takes a photograph of the light reflection, which is analyzed by the device.

For performing the NMP22 BladderChek, 4 drops of fresh urine sample were given on the test field of the cassette, as advised by the manufacturer, and results were obtained after 30 minutes. For cytology, urine was processed according to Papanicolaou [9] and microscopically reviewed by a urologist experienced in cytopathology. Accepted characteristic features of malignancy were considered [10].

2.3. Statistical analysis

Test performances were evaluated by contingency analysis. Statistical calculations were done with JMP (SAS Institute Inc, Cary, USA). P < 0.05 was considered significant. Receiver operating characteristic curves were performed to determine the area under the curve (AUC) and the optimal cutoff for the UBC ELISA and quantitative values of the reader.

3. Results

Overall, 198 patients were included in the study, 51 of these patients were under surveillance of non–muscle invasive BC (NMIBC) and 147 patients had no history of BC. Reasons for performing workup for BC in patients without history of BC included gross hematuria (32.7% of patients), microscopic hematuria (26.5%), irritative voiding syndromes (20.4%), suspicious bladder ultrasound (8.8%), and other reasons (11.9%; e.g., hydronephrosis, recurrent urinary tract infection). During workup in our hospital, 32 patients (16%) had suspicious findings in ultrasound (of whom 26 were diagnosed with BC). Median age of the study population was 70 years (range 20–90). Of these patients, 151 (76.3%) were men and 47 (23.7%) were women. Of the 198 patients, 61 (30.8%) had BC. Among the 61 patients, 39 had primary and 22 had recurrent BC; 48 (78.7%) had NMIBC (pTa and pT1 tumors), 4 (6.6%) had stage pT2, 6 had pT3 tumors (9.8%), and 3 had pure carcinoma in situ. A total of 17 (29.3%) patients had G1 tumors, 26 (44.8%) G2, and 15 (25.9%) had G3 tumors.
3.1. Test performance

Visual detection of the cartridge revealed a weak, intermediate, and strong test band intensity in 39, 21, and 39 patients, respectively. In 99 patients, no band was visible. Sensitivities, specificities, positive predictive values (PPVs), and negative predictive values (NPVs) as well as AUCs for visual detection are shown in Table 1. Sensitivity, specificity, PPV, and NPV of the quantitative UBC rapid using the optimal threshold obtained by receiver operating characteristic analysis (12.3 μg/l) were 60.7%, 70.1%, 46.8%, and 79.3%, respectively (Table 2). The AUC was 0.68. For UBC ELISA (optimal cutoff value 12.0 μg/l) sensitivity, specificity, PPV, and NPV were 48.3%, 71.3%, 42.7%, and 75.8%, respectively, with an AUC of 0.64. Concentrations of UBC ELISA and UBC rapid determined quantitatively correlated significantly ($r^2 = 0.55$, $P < 0.001$).

NMP22 BladderChek had a sensitivity of 16.4% and specificity of 95.3%. PPV and NPV were 62.5% and 70.5%, respectively. For cytology, sensitivity, specificity, PPV, and NPV were 51.7%, 78.1%, 51.7%, and 78.1%, respectively. Results are summarized in Table 2 including influence of tumor stage and grade on sensitivity.

3.2. Test results in patients undergoing primary evaluation and patients undergoing surveillance of NMIBC

Sensitivities, specificities, NPVs, PPVs, and AUCs for UBC rapid evaluated visually, quantitative UBC rapid, UBC ELISA, NMP22 BladderChek, and cytology in patients without and with history of BC are shown in Tables 3 and 4.

Table 1

<p>| Test performance of the UBC rapid evaluated visually. Sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), and areas under the curve (AUCs) for visual detection using different cutoffs of band intensity are shown |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
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<tr>
<th></th>
<th>Sensitivity</th>
<th>Specifcity</th>
<th>PPV</th>
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semiquantitative evaluation process. In general, bands on lateral flow test cassettes are evaluated visually and compared with a control band. As it is not possible to determine an exact threshold for test positivity, this process leads to considerable intraobserver and interobserver variability, which might contribute to the broad range of test results in prior studies [16,17]. The aim of this study was to evaluate the performance of a POC test for BC, which can be determined quantitatively by the use of a special POC test reader.

The results of the present study show that cytokeratin concentrations determined by the POC reader significantly correlated with those of the UBC ELISA test, implicating that the simplicity of the POC test is not associated with a loss of test accuracy. Second, the AUC—as a parameter of diagnostic quality—of the quantitative UBC rapid was even improved compared with complex ELISA testing. This does not inevitably mean that detection of cytokeratin fragments by the POC reader is more accurate compared with ELISA. However, it implicates that the POC test might separate patients with BC from healthy patients more adequately.

The test accuracy of a manual (visual) analysis of the UBC rapid strongly depended on the intensity of test bands required for a positive test. When considering test bands with strong and intermediate intensity as positive tests, the manual analysis of the UBC rapid showed similar results compared with the quantitative determination. This might raise concerns whether quantitative analysis of the UBC rapid is really necessary to achieve good test accuracy. We and other authors have shown that UBC is a continuous parameter: the higher the value, the more likely the existence of BC [18]. The dichotomization of every continuous parameter leads to a significant loss of information. For example, a PSA level of 100 ng/ml has other implications for the treating urologist than a PSA level “higher than 4.” The semiquantitative categorization of test band intensity of POC test cassettes with different thresholds for test positivity is rarely performed. Therefore, POC tests are mostly performed as tests with dichotomized results. The stratification of test band intensity performed in our study has a strong interobserver variability and is complex to reproduce (reference images of test bands, strict criteria regarding incubation time, and volume of urine). Neither for UBC nor for other BC POC tests (such as BTA and NMP22) do manufacturers provide protocols or images enabling adequate semiquantitative assessment.

In case of UBC rapid determined quantitatively, not only the risk for BC in general but also the risk of having a high grade tumor (G3, Cis) increased with higher test values. This feature underlines the significance of a quantitative consideration of the UBC rapid test and can be observed also for other quantitative urine markers [19,20]. A dichotomized use of this marker is not able to fully exploit its predictive potential. When using the POC reader,
interpretation of the UBC rapid results needs to include the absolute value of the test and not only a stratification into positive or negative. Otherwise, there might be no additional benefit of performing the POC test quantitatively.

In general, both for UBC rapid and UBC ELISA, the results of the present study are in accordance with prior studies evaluating these tests. For the UBC rapid test (evaluated visually) prior studies revealed a high variability of sensitivities (35.6%–78.4%) and specificities (63.6%–97.4%). A study conducted by Hakenberg et al. [21] showed a sensitivity and specificity of 64.4% and 63.6%, respectively, for UBC rapid in a collective of 181 patients of which 90 had BC. Similar to our results, they also observed a better sensitivity for UBC rapid compared with UBC ELISA (64.4% compared with 46.6%). Mian et al. [3] showed a sensitivity for UBC rapid of 66.0% with a specificity of 90.0%. However, their collective consisted of 68% patients in follow-up after transurethral resection, which might account for the difference compared with our study. Schröder et al. [22] reported a sensitivity and specificity for UBC rapid of 35.6% and 75.0%.

For UBC ELISA, May et al. [18] reported a sensitivity and specificity of 40.3% and 75.0%, respectively. Although in their collective only 19.8% were free of BC or without history of BC, results are quite similar to our study. A relatively low sensitivity for UBC ELISA (12.1% with a specificity of 97.2%) was observed by Babjuk et al. [23] in 88 patients undergoing surveillance for NMIBC. The cohort included in our study is best comparable to a study published by Hakenberg et al. [21] observing a sensitivity and specificity of 70.5% and 63.6% for UBC ELISA, respectively.

In our cohort, the UBC rapid determined quantitatively showed superior performance compared with urine cytology because of improved sensitivity. It is noteworthy that the combination of UBC rapid and cytology led to the detection of 12 additional tumors (including 3 high-risk tumors) compared with cytology alone. This is in accordance with the study conducted by Hakenberg et al. [21] showing an increase of sensitivity by combining cytology and UBC rapid. Combining urine markers has been shown to be a promising approach for improvement of urine test

| Test performance of UBC rapid determined visually, quantitatively, UBC ELISA, nuclear matrix protein (NMP)22 BladderChek, and urine cytology in patients without history of bladder cancer (n = 147). Sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), and areas under the curve (AUCs) of UBC rapid determined visually and quantitatively, UBC ELISA, nuclear matrix protein (NMP)22 BladderChek, and urine cytology are shown |
|-----------------|-----------------|----------------|----------------|----------------|
|                  | Sensitivity    | Specificity   | PPV            | NPV            | AUC            |
| UBC rapid visual evaluation (strong and intermediate band intensity = positive) | Overall       | 53.9          | 82.4           | 52.5           | 83.2           | 0.68 |
|                  | pTa            | 40.7          |                |                |                |        |
|                  | pT1            | 100           |                |                |                |        |
|                  | ≥ pT2          | 66.7          |                |                |                |        |
|                  | G1/G2          | 40.0          |                |                |                |        |
|                  | G3/Cis         | 78.6          |                |                |                |        |
| Quantitative UBC rapid (optimal cutoff 12.3 µg/l) | Overall       | 61.5          | 69.4           | 42.1           | 83.3           | 0.66 |
|                  | pTa            | 55.6          |                |                |                |        |
|                  | pT1            | 83.3          |                |                |                |        |
|                  | ≥ pT2          | 66.7          |                |                |                |        |
|                  | G1/G2          | 52.0          |                |                |                |        |
|                  | G3/Cis         | 78.6          |                |                |                |        |
| UBC ELISA (cutoff 12.0 µg/l) | Overall       | 50            | 69.2           | 36.5           | 79.6           | 0.62 |
|                  | pTa            | 38.5          |                |                |                |        |
|                  | pT1            | 83.3          |                |                |                |        |
|                  | ≥ pT2          | 66.7          |                |                |                |        |
|                  | G1/G2          | 37.5          |                |                |                |        |
|                  | G3/Cis         | 71.4          |                |                |                |        |
| NMP22 BladderChek | Overall       | 20.5          | 93.9           | 57.1           | 75.0           | 0.57 |
|                  | pTa            | 3.7           |                |                |                |        |
|                  | pT1            | 50.0          |                |                |                |        |
|                  | ≥ pT2          | 66.7          |                |                |                |        |
|                  | G1/G2          | 4.0           |                |                |                |        |
|                  | G3/Cis         | 50.0          |                |                |                |        |
| Cytology      | Overall       | 56.8          | 81.4           | 52.5           | 83.8           | 0.69 |
|                  | pTa            | 44.0          |                |                |                |        |
|                  | pT1            | 83.3          |                |                |                |        |
|                  | ≥ pT2          | 100           |                |                |                |        |
|                  | G1/G2          | 39.1          |                |                |                |        |
|                  | G3/Cis         | 85.7          |                |                |                |        |
performance. Whether the quantitative UBC rapid might be a promising marker for inclusion into a multimarker-panel remains to be elucidated [24].

The performance of NMP22 BladderChek was worse compared to prior studies owing to a sensitivity of only 16%. Although most studies reported NMP22 to be a marker with improved sensitivity compared with cytology, the results in the present cohort are in accordance with some other studies reporting sensitivities far below 50% for NMP22 [16,17,25]. The performance of NMP22 BladderChek in our study could also be the result of a high proportion of low-grade papillary tumors [26]. Furthermore evidence exists that gross hematuria not only affects specificity but also sensitivity of protein-based urine markers [27]. As existing gross hematuria (at time of sampling) was defined as exclusion criterion, this might have led to reduced test sensitivity compared with other studies. The relatively high specificity might be explained by the selection process of the study (exclusion of patients with existing gross hematuria or prior mechanical manipulation of the urinary tract), leading to a low rate of false-positive tests [1,25].

Compared with study results of elaborate cell-based urine tests such as FISH and immunocytology, the performance of the UBC rapid is inferior with regard to sensitivity and specificity [14,24]. However, the quantitative UBC rapid does not require complex testing and can be also performed in a setting independent of complex laboratory facilities. Although no studies have been conducted so far addressing this issue, this might lead to improved cost efficacy. One clear advantage is that in contrast to ELISA-based protein detection, the POC test can be performed immediately without concerns of raising costs when performing only one single analysis. In case of ELISA, the obligatory performance of dilution series to determine exact protein concentrations makes single analysis cost inefficient.

The optimal use of the UBC rapid in daily practice or (if implemented) in one stop hematuria clinics remains to be defined. The test might be of particular interest for

### Table 4

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<thead>
<tr>
<th>Test Performance</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
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<tr>
<td><strong>UBC rapid visual evaluation</strong> (strong and intermediate band intensity = positive)</td>
<td>Overall</td>
<td>59.1</td>
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<td><strong>Quantitative UBC rapid (optimal cutoff 12.3 µg/l)</strong></td>
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<td>58.6</td>
</tr>
<tr>
<td></td>
<td>pTa</td>
<td>38.5</td>
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<td></td>
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<tr>
<td></td>
<td>pT1</td>
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</tr>
<tr>
<td></td>
<td>≥pT2</td>
<td>33.3</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td>30.8</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>G3/cis</td>
<td>62.5</td>
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institutions not having access to elaborate tests, such as FISH or immunocytoLOGY. In contrast to dichotomized urine tests, its quantitative character enables to perform risk stratification for BC based on the absolute UBC rapid value. A positive UBC rapid result should not inevitably lead to cystoscopy. The test results rather have to be combined with clinical information (such as hematuria, age, smoking status, and possible exogenous factors, such as infection) and the result of urine cytology for optimal interpretation and clinical decision making. Thereby, the test might not only contribute to improved detection of BC but also to improved prediction of high-risk tumors, which has been also shown for other quantitative protein-based urine tests [4,28]. One approach to objectify risk stratification including various parameters would be to develop a nomogram (including quantitative UBC rapid, grade of hematuria, smoking status, age, and gender), which was beyond the scope of this study but could be a promising goal for further studies [29]. This could be of particular interest in patients with microscopic hematuria, as the recommendations for workup of these patients including invasive cystoscopy are discussed controversially. As the use of cell- and protein-based tests in the screening setting has shown inconclusive results [25], we do not recommend using the UBC rapid in a screening population without risk factors for BC.

5. Conclusions

The present study represents the first clinical evaluation of a POC test platform for BC providing quantitative results. The accuracy of the system is at least equivalent to a complex ELISA test. Quantitative results provide higher reproducibility and enable improved risk stratification compared with simple dichotomized POC test results. The simple-to-use test platform might therefore be used as an adjunct tool to cystoscopy and cytology in a laboratory-independent fashion. Before routine application of the test platform, further clinical evaluation is needed.

Acknowledgments

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References


Fig. 1. Positive predictive values (PPVs) of the quantitative UBC rapid depending on different values. Bright grey and dark grey show the probability of bladder cancer and high-risk bladder cancer (defined as ≥pT1 or G3 or Cis).


Soloway MKS. Bladder Cancer. ICUD Guidelines. 2nd ed. ICUD; 2012. p. 27.


