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Review

Urine Markers for Bladder Cancer Surveillance: A Systematic Review

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Abstract

Introduction: The follow-up of patients with urothelial cell carcinoma (UCC) of the bladder is done by cystoscopy and, in most cases, cytology. The last decade, many urine-based tests for UCC have been developed and tested in different populations. For the urological practice, considering the amount of follow-up cystoscopies, especially urine markers for recurrent disease would be useful. Therefore, we reviewed the literature on these markers for recurrent UCC and compared our findings with recent review-articles.

Methods: We performed a PubMed search. In case of primary and recurrent disease, the study was included if the patients under surveillance were reported separately. Patients with no evidence of disease at surveillance cystoscopy were considered to determine specificity. A marker was included if at least 2 studies from 2 different institutions/authors were available.

Results: The literature review yielded 64 articles. We found 18 markers (BTAstat, BTAtrak, NMP22, FDP, ImmunoCyt, Cytometry, Quanticyt, Hb-dipstick, LewisX, FISH, Telomerase, Microsatellite, CYFRA21-1, UBC, Cytokeratin20, BTA, TPS, Cytology) that met our criteria. BTAstat, NMP22, ImmunoCyt and cytology were evaluated in more than 750 patients. Telomerase, Cytokeratin20 and Hb-dipstick were tested in less than 250 patients. The highest median sensitivities were reported for CYFRA21-1 (85%), Cytokeratin20 (85%) and Microsatellite analysis (82%). The highest specificities were reported for Cytology (94%), BTA (92%) and Microsatellite analysis (89%). In comparison with recent reviews, median sensitivity was $\geq$5% lower for the surveillance group in 13/18 urine-based tests while specificity remained relatively constant between different patient groups.

Conclusions: To our knowledge, this is the first review that assesses sensitivity and specificity of urine markers solely for UCC surveillance. In our view, Microsatellite analysis, ImmunoCyt, NMP22, CYFRA21-1, LewisX and FISH are the most promising markers for surveillance at this time. Nevertheless, clinical evidence is insufficient to warrant the substitution of the cystoscopic follow-up scheme by any of the currently available urine marker tests. Future studies may test some of the most sensitive and specific assays to reduce the cystoscopy frequency. However, our results show that initiators of these studies should anticipate a lower sensitivity than reported in the current literature.

Keywords: Bladder cancer; Cystoscopy; Urine; Marker; Recurrence

1. Introduction

Around 70% of the patients with urothelial cell carcinoma (UCC) of the bladder initially present with superficial (pTa, pT1 or pTis) disease. These UCC have a high chance of recurrence (60–85%) but more than 80%

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remains confined to the (sub)mucosa and, therefore, these patients do not influence UCC-related survival [1]. Nevertheless, extensive and long-term follow-up is needed to prevent progression to invasive, potentially lethal UCC. The current standard of care consists of urethro-cystoscopy (UCS), the gold standard, and urine cytology every 3–4 months for the first two years and at a longer interval in subsequent years. This approach is costly, invasive and uncomfortable. Even for flexible UCS, the risk to develop a urinary tract infection is around 10% [2]. The current follow-up schemes with more than 500.000 UCS per year in the USA for follow-up alone, largely contribute to the fact that total Medicare payments per patient are the highest for UCC compared to other malignancies [3,4]. In addition, especially for the low-grade lesions, urine cytology is of limited value because of operator dependency and a low sensitivity [5]. For these reasons, many new urine-based tests for UCC have been developed. Among them, BTAstat, BTAtrak, NMP22, FDP, ImmunoCyt and FISH (UroVysion) have been approved by the FDA [6,7].

Initial studies with new markers are mostly promising, but successive reports often fail to show comparable results. Patient selection seems the most likely explanation for the discrepancies between the studies on urine markers. For the urological practice, in terms of cost-reduction and convenience of our patients, particularly markers to detect recurrent disease would be useful. In order to reduce the number of UCS needed for follow-up, the specificity of a urine-based test is important. However, high specificity may be at the cost of sensitivity, conventional cytology being a good example of this [6]. As outlined earlier, positive (percentage in whom the test is positive and the disease is present) and negative (percentage in whom the test is negative and the disease is absent) predictive values are less useful for comparison of two populations with different UCC incidences because they vary by their definition [6,7]. Conversely, sensitivity and specificity stay constant between populations with different numbers of tumor and non-tumor cases and additionally, they are more commonly used in studies [6,7].

Our systematic review of the literature on the performance (sensitivity and specificity) of urine markers was confined to publications on recurrent UCC and we compared our findings with data on the same tests that were reported in reviews without this selection criterion.

2. Methods

We performed an online PubMed search up to 2004 to obtain references for the various urine tests. The terms used for the PubMed search included urine, the name of the individual urine-based test, bladder, cancer, urothelial/transitional (cell) carcinoma, tumor marker and recurrence. The material and methods section of each article was screened in order to be sure that the patients were under surveillance with UCS. In case of a mixed study population composed of both primary and recurrent UCC, we only included the particular study if the results of the patients under surveillance were reported separately. Only patients with no evidence of disease at surveillance cystoscopy or pathological evaluation were considered as controls to determine specificity. We did not select on FDA-approval, single or multi-center trials, number of patients involved in the study, tumor grade, urine or bladder wash cytology and/or comparison of more tests in the same study population. A urine marker was included in our review if a minimum of 2 studies from 2 different institutions/authors were available. A comparison was made with recent review-articles to investigate whether our selection criterion (recurrent disease) influenced the performance of the various urine markers.

The usefulness of the urine-based tests for UCC was assessed with sensitivity and specificity. Sensitivity of a test was defined as the percentage of patients with UCC (as defined by the authors) for whom the test is positive (tested positive/patients with recurrent UCC). Specificity was defined as the percentage of patients with a negative cystoscopy in whom the test is also negative (tested negative/no evidence of disease at follow-up).

3. Results

The literature review on recurrent UCC yielded 64 publications in which we found 18 markers (conventional cytology included) that met our strict criteria. We have listed the studies per marker in the appendix section. Other promising markers (examples: BCLA-4, Survivin, HA-HAase, DD23 and BTF) that were not included in our analysis may also prove to be of value for patients under surveillance and require further study by other groups. Table 1 shows the median sensitivity and specificity as well as the number of studies, institutions and patients. The number of institutions/authors varied from 2 to 14. BTAstat ($n = 3461$), NMP22 ($n = 2041$), ImmunoCyt ($n = 959$) and conventional cytology ($n = 5535$) were evaluated in more than 750 patients in all studies combined. Telomerase ($n = 146$), Cytokeratin20 ($n = 178$) and Hb-dipstick ($n = 230$) were tested in less than 250 patients.

All the 17 urine markers had a higher sensitivity for recurrent UCC than conventional cytology. The highest sensitivities were reported for CYFRA21-1 (85%), Cytokeratin20 (85%) and Microsatellite analysis (82%). Of the FDA approved tests, FISH (79%), BTAtrak (71%) and NMP22 (71%) had the highest sensitivity. The highest specificities were reported for conventional cytology (94%), BTA (92%) and Microsatellite analysis (89%). ImmunoCyt (75%) had the highest specificity of the FDA approved tests. The specificity (patients in follow-up with no evidence of