Editorial Commentary

Significant lack of urine-based biomarkers to replace cystoscopy for the surveillance of non-muscle invasive bladder cancer

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One of the clinical issues in non-muscle invasive bladder cancer (NMIBC) is the high rate of intravesical recurrence, which requires follow-up cystoscopy at regular intervals. However, cystoscopy is an invasive examination associated with pain, discomfort, and urinary tract infection. The European Association of Urology guideline states, "Patients with high-risk tumors should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for two years, and every six months after that until five years, and then yearly" (recommendation level: weak) (1). In our previous study, we reported the recurrence detection rate by follow-up cystoscopy using the standard protocol and observed 41 (5.2%) recurrences in 784 cystoscopic examinations after the initial transurethral resection of bladder tumor (TURBT) during the follow-up period (2). Thus, 19.1 cystoscopies are required to detect a recurrence.

Regarding the medical cost, cystoscopy coupled with urine cytological analysis is expensive to perform at outpatient clinics, as it costs approximately $160 in Japan concerning the exchange rate against the US dollar as of Apr 2019. Urine cytological analysis is a noninvasive examination but has many limitations, including interobserver variability and low sensitivity, especially for low-grade tumors. Both the poor cost performance of cystoscopy and poor diagnostic accuracy of urine cytological analysis evoke the urgent need for advancement of useful urine biomarkers for surveillance of NMIBC.

Numerous efforts have been made to identify useful urine-based markers to reduce the number of cystoscopies. In a recent issue of Translational Research, Montalbo *et al.* (3) reported a novel urine gene expression classifier with a high diagnostic accuracy that is clinically feasible to detect primary NMIBCs and recurrent tumors during surveillance after treatment. The authors previously developed several gene expression classifiers in exfoliated urinary cells with a diagnostic accuracy equal or superior to the gold standard tests (4-6). These classifiers had a significant limitation in that they lacked sensitivity in the recurrence of low-grade NMIBC and were only evaluated in case-control cohorts. Montalbo *et al.* attempted to develop a urine gene expression signature associated explicitly with non-high-risk NMIBC tumors in a bid to identify a specific set of urine biomarkers in this subpopulation (3). Hundreds of urine samples were collected from patients with bladder cancer, patients who underwent follow-up cystoscopy for bladder cancer, and non-cancer controls. The present study consisted of three different phases. The first was the urinary biomarker discovery phase with a rigorous analysis by RNA sequencing (84 urine samples from bladder cancer and control groups). The second was the classifier development phase, a panel of 132 selected genes was analyzed using nCounter in 214 prospectively collected urine samples from patients who underwent follow-up cystoscopy for bladder cancer, including 98 patients with bladder tumor recurrence. In the final step, the classifier validation phase,

a multicentric and international cohort of urine samples from 134 patients with bladder cancer and 114 patients without recurrence of treated bladder cancer) was used to validate classifier performance. Among 521 genes that showed different expression patterns between the urine samples from patients with non-high-risk NMIBC and all other groups, an 8-gene diagnostic classifier with an area under the curve of 0.893 was selected for further validation. The validation result was striking, with an overall sensitivity of 96% and a negative predictive value of 97%. Also, this diagnostic accuracy was achieved even in the non-high-risk NMIBC group (sensitivity, 94%; negative predictive value, 98%). The authors concluded that the use of the panel of the 8-gene expression classifier could be clinically feasible for decreasing the number of follow-up cystoscopies for patients with treated non-high-risk NMIBC. To prove a definitive conclusion, the classifier must be validated by conducting prospective large-scale randomized clinical trials for assessing its clinical usefulness.

In several decades, various types of conventional urine-based tests, including immunoCyt/uCyt+, NMP-22, BTA, and UBC, have been evaluated for their usefulness in the diagnosis of recurrent bladder tumors after TURBT (7). However, none of these markers succeeded in replacing the routine cystoscopy during follow-up. Owing to the recent advancements in molecular technologies, new-generation urine tests, including UroVysion (8,9), CxBladder Monitor (10), Xpert Bladder Cancer Monitor (11), and FGFR3 gene mutation, have been developed (12). A large-scale meta-analysis of the UroVysion test revealed a diagnostic accuracy of 72% sensitivity and 83% specificity (13). Moreover, UroVysion was superior to urine cytological analysis as a detection marker of intravesical recurrent disease (8,9). The Cxbladder test quantifies five mRNA targets (IGFBP5, MDK, HOXA13, CDK1, and CXCR2) by real-time polymerase chain reaction (PCR). The Cxbladder Monitor could improve the sensitivity as compared with that of cytological analysis (82% *vs.* 56%). In an external validation study that included 803 patients who underwent post-TURBT surveillance, the sensitivity was 91%, and the negative predictive value was 96% (10). The Xpert BC Monitor quantifies five mRNA targets (ABL1, CRH, IGF2, UPK1B, and ANXA10) by real-time PCR. The first prospective study that included 155 urine samples from 140 patients with a history of NMIBC showed high sensitivity (84%) and specificity (91%) of the Xpert BC Monitor (11). FGFR3 mutation is one of the highest observed genomic DNA alterations in low-grade NMIBC (66% of Ta and 38% of T1 tumors). In our previous study, we found that this mutation, which was detected in voided urine, was a useful diagnostic marker of recurrence in NMIBC, with 78% sensitivity and 100% specificity (12).

According to previous reports, DNA alteration- or mRNA-based urinary tests have achieved high diagnostic performance in terms of accuracy in detecting recurrence in patients with NMIBC, even low-grade tumors. Patients and physicians have preferred a decreased number of cystoscopies for post-TURBT surveillance for several decades. However, subsequent external validation using different cohorts is significantly lacking. Further prospective validation studies and greater cost-effectiveness are required for the widespread use of these promising tests.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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