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The Efficient and Effective Use of Exfoliative Urinary Markers

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Abstract

Introduction: Multiple exfoliative urinary markers are available and commonly used in various clinical settings. However despite an abundance of primary data and reviews an evidence-based application in the detection and monitoring of bladder cancer is lacking. We provide a framework in which the clinician caring for patients at risk for and diagnosed with bladder cancer can easily understand and incorporate these tools into routine practice.

Methods: We reviewed the English language literature regarding voided urinary markers for bladder cancer, focusing on prior systematic reviews published since 2003. Available data on sensitivity and specificity were analyzed in the context of 3 scenarios of application, including screening for bladder cancer, evaluating patients with hematuria and monitoring disease after a bladder cancer diagnosis. We defined and applied the relevant statistical tools, and provide rational recommendations for clinical application. We also summarized issues of cost-effective utilization of these tests.

Results: Consistent with existing opinions there is no current role for any urinary marker in screening for bladder cancer. This is the result of low disease prevalence even in purportedly high risk groups. In patients with microscopic hematuria a negative urinary biomarker may spare further evaluation with cystoscopy while regardless of the urinary marker result those with gross hematuria are at sufficient risk to justify cystoscopy. Patients with lower risk bladder urothelial carcinoma may require less frequent cystoscopy if urinary markers are negative. Patients at high risk are at low risk for undetected cancer if cystoscopy and voided marker are negative.

Conclusions: Available information on exfoliative urinary markers suggests a clear role in bladder cancer diagnosis and monitoring. We provide an evidence-based practical approach to application in routine clinical practice. Our approach must be considered in the context of current practice guidelines. Additional studies are required to determine the most cost-effective algorithms and novel markers that may further enhance the role of these biomarkers.

Key Words: urinary bladder neoplasms; tumor markers, biological; algorithms; urine; diagnosis

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin

EAU = European Association of Urology

LR = likelihood ratio

PPV = positive predictive value

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The diagnosis and management of urothelial carcinoma remain clinical challenges. While gross hematuria is the most common presenting sign and voided urine provides a readily available specimen for analysis, a standardized evidence-based recommendation for incorporating the numerous available urinary markers does not exist. However these are critical issues given the facts that 1) noninvasive disease is most common, 2) patients undergo frequent and invasive surveillance procedures, and 3) cost-effective management is a priority in the current health care environment. Thus we sought to provide a context in which to evaluate the role of exfoliative markers based on what is known about disease prevalence and the operating characteristics of the current tests.

Many urine based markers for bladder cancer have been developed, tested and used in the course of routine care of patients. Table 1 lists the urinary markers included in our discussion. Each marker will perform differently in various disease states and individuals as well as for specific biology based on molecular or genetic changes. In addition the characteristics of an ideal test (favoring high sensitivity or specificity) will vary depending on the current standard of care. The traditional characterization of medical tests, describing overall accuracy or a ROC AUC, is inadequate and lacks clinical usefulness.

An important aspect of any diagnostic test is the specific clinical scenario in question. The 3 primary indications are screening for disease, diagnosis of disease in those with signs or symptoms (ie hematuria) and monitoring disease after cancer diagnosis. The role and performance of the various tests differ depending on the population evaluated. Therefore it is critical to assess the value of a test when considering the various prevalences in each setting.

Statistical Definitions

The purpose of a diagnostic test is to obtain a result that informs the clinician as to the probability that the patient has a particular condition and then to determine whether that probability is sufficient to warrant additional tests or treatment. Before a test the patient has some pretest probability of disease (ie prevalence) and afterward there is a posttest probability of disease.

The LR of a test is the means by which one incorporates information from a test result into this calculation. A negative and a positive LR exist based on the result of the test and each is readily determined from sensitivity and specificity (table 2). Unfortunately most studies and analyses of urinary markers and diagnostic tests in general merely report performance in terms of sensitivity and specificity rather than of LR. This makes using the information less facile to the clinician. We compiled data from published contemporary (since 2003) systematic reviews of the commercially available and FDA (Food and Drug Administration) approved voided urinary markers, and used the information to provide the basis for our analyses. The focus is on identifying actual performance in specific clinical situation.

There are a few interesting things to remember about sensitivity and specificity, such as they apply only to the same disease spectrum as that of the population originally studied. For instance a referral population with bulky muscle invasive tumors may show exfoliative marker results with high sensitivity. However if in practice most tumors are relatively small at presentation, the markers may not perform as well. In addition PPV and negative predictive value are only applicable when there is the same disease prevalence. A similar analogy would be that a test studied at

Table 1.
Urinary markers

Test	Setting	Assay	Cost ($)	Limitation/Clinical Use
Hemoglobin dipstick	Point of care	Hematuria, hemoglobinuria, myoglobinuria	0.25	False-pos findings
Urinary cytology	Cytopathology	Microscopy of cellular feature	60−100	Equivocal, atypical + artifact from treatment
BTA stat®/BTA TRAK®	Point of care/enzyme-linked immunosorbent assay	Qualitative/quantitative measure of complement factor H related protein	10−15/175	Pts with known Ca + in conjunction with cystoscopy*
NMP22	Point of care/enzyme-linked immunosorbent assay	Nuclear matrix apparatus protein	10−30/125−150	Initial diagnosis + monitoring,* not for screening
ImmunoCyt	Send out	Carcinoembryonic antigen + 2 bladder Ca specific mucins	130−385	Monitoring†
UroVysion	Send out	Fluorescence in situ hybridization detecting aneuploidy of chromosomes 3, 7 + 17, loss of 9p21 locus	475−700	Diagnosis with hematuria* + monitoring

*FDA approved for initial diagnosis and surveillance as adjunct to standard tests (ie cystoscopy).
†FDA approved for surveillance only to evaluate for bladder cancer recurrence.