Bladder Cancer 2000: Molecular Markers for the Diagnosis of Transitional Cell Carcinoma

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The search continues for better tumor markers to improve the rate of detection of transitional cell carcinoma (TCC) more quickly in larger populations and to predict the possibility of disease recurrence. Among several new tests currently being screened, telomerase and hyaluronic acid/hyaluronidase (HA/HAase) have shown sensitivity and specificity equal to or better than cytology, and other promising tumor markers are being investigated. Although no marker has yet replaced the need to perform cystoscopy and cytology, the new tests can minimize the cost and difficulty of screening and long-term surveillance of patients who have or are at risk for bladder cancer. [Rev Urol. *2001;3(2): 85-93*]

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Bladder cancer is the second most common genitourinary malignancy in the United States. In 2000, a projected 53,200 new cases will be diagnosed and over 12,200 are expected to die from the disease.[1] Fortunately, the majority of bladder cancer patients will present with superficial papillary disease, which is usually amendable to transurethral resection and intravesical immuno- or chemotherapy and has a high 5-year survival rate.[2] However, 70% of patients will have recurrent disease.[3] And while most are also superficial in nature, 10% to 15% will progress to muscle invasive disease. Once muscle invasion occurs, two thirds of patients die within 5 years.[4]

A strong correlation exists between tumor grade and risk of progression and recurrence. In grade 1 lesions, progression and muscle invasion occurs in ≤10% of patients. This contrasts with grade 3 lesions, where 33-45% progress, 71% recur, and 82% have muscle invasion.[3,5] These statistics emphasize the need for

close long-term follow up for all bladder cancer patients, regardless of grade and apparent completeness of initial tumor resection. The typical surveillance schedule for superficial transitional cell carcinoma (TCC) entails cystoscopy with bladder washing cytology every 3 months for the first 18 to 24 months, then every 6 months for 2 years, and annually thereafter. Thompson and associates[6] routinely followed 124 patients with superficial bladder cancer and found 20 patients who had no evidence of recurrence in the first 5 years but subsequently developed muscle invasive disease. This underscores the importance of long-term surveillance.

New Tumor Markers Needed

Despite the effectiveness of cystoscopy and urinary cytology for the surveillance of TCC, this approach is invasive and causes inconvenience and discomfort to patients. Moreover, the cost of long-term surveillance is high. The utility of a urine- or serum-based marker would be invaluable. Ideally, this marker would be noninvasive, inexpensive, simple to use, unaffected by interpreter variability, have near-perfect sensitivity and specificity for all stages and grades of tumor, and have the ability to reflect the severity and aggressiveness of the disease. Such a marker could potentially become the preferred method for surveillance or assist a physician in deciding what the most appropriate interval for cystoscopic examinations should be for each individual patient. A good marker could also help patients with hematuria or irritative voiding symptoms avoid invasive tests. Finally, high-risk populations (eg, smokers, patients with exposure to pelvic radiation and carcinogens such as aromatic amine compounds, and spinal cord injury patients) could easily be screened for bladder cancer.

In our aging population, where the incidence of bladder cancer has increased by 36% over a decade,[7] the role of bladder cancer screening could be significantly expanded, similar to colon and prostate cancer screening. This review will examine state-of-the-art, molecular-based urinary screening techniques. These new methods are noninvasive and utilize voided urine specimens for the detection of various tumor-associated antigens for diagnosis and follow-up of TCC. Comparison of accuracy and potential uses will be made among these innovative tests as well as the present gold standard of urine cytology.

Cytology

Before the search for urine-based tumor markers, the standard for noninvasive testing was the voided urine cytology. This remains the most commonly used urine marker in clinical practice. The overall sensitivity of voided urine cytology range from 25%-95%.[8-14] Cytology has proven to be very useful for the detection of high-grade and high-stage disease. High-grade lesions and carcinoma in situ (CIS) can be detected by voided cytology with a sensitivity of 80-90% and a specificity of 98%-100%.[9,15] Morphologic changes associated with these highly malignant cells include increased size, increased nuclear-to-cytoplasmic ratio, nuclear pleomorphism, coarse and irregular chromatin, and frequent mitotic figures. These characteristics indicate a high risk for the development of bladder cancer, even in the presence of a negative cystoscopic exam.[16]

The utility of a urine- or serum-based marker would be invaluable.

Despite its effectiveness in detecting high-grade lesions, cytology has the propensity to miss low-grade disease. Based on a comprehensive review by Renshaw and colleagues,[17] sensitivity for detecting low-grade lesions varies from 0% to 100% and specificity from 6% to 100%. Low-grade malignant cells are sometimes only subtly different from dysplastic or normal cells and cytologists can find it difficult to make definite distinctions. Conditions that can cause inflammatory changes in the bladder, such as recent intravesical therapy, radiation treatment, and infections, can cause false-positive readings up to 1%-12%.[18] Moreover, the definition of a positive cytology reading can be variable.[12,13] Cytology is also relatively expensive and time consuming, costing approximately $100 per test and taking 24 hours for results to become available.[18]

Bladder Tumor Antigen

There are three types of bladder tumor antigen (BTA) tests, BTA, BTA stat, and BTA TRAK. The original BTA test was a latex-agglutination assay that measured a basement membrane protein that is released into the urine as the tumor invades the underlying bladder wall.[19] The BTA test has higher sensitivity than voided cytology especially in the detection low-grade disease. However, the test has high false-positive readings in patients with urinary infections, stones, benign prostatic hypertrophy (BPH), and recent manipulation of the bladder or prostate.[20-25]

The shortcomings of the original BTA test led to the development of the BTA stat and BTA TRAK tests, both of which detect the complement factor H-related protein. This protein is thought to assist tumor cells in the evasion of cellular lysis by the alternative complement pathway.[26] The

Table 1
Advantages, Disadvantages, and Potential Uses of Currently Tested Bladder Cancer Markers

Marker	Advantages	Disadvantages	Potential Uses
Cytology	High specificity, high sensitivity for high-grade TCC	Low sensitivity for low-grade TCC; subject to interpreter variability; 24 hours for results	Screening for recurrence in patients with history of bladder cancer
BTA stat	Fast, inexpensive; can be done in office setting; high sensitivity for all tumors grades/stages; high specificity in the healthy	Low specificity with benign genitourinary conditions; non-urothelial malignancies; recent intravesicle therapy or bladder/ prostate manipulation	May be useful in combination with another marker
BTA TRAK	High sensitivity for all tumor grades/stages; good specificity in the healthy; quantitative	Same as BTA stat	Predict likelihood of recurrence using serially measured levels
NMP22	High sensitivity for all tumor grades/ stages; quantitative	Specificity lower than cytology	Predict tumor stage and likelihood of recurrence; can utilize high negative predictive value to individualize surveillance schedule
Telomerase	High sensitivity for all tumor grades/stages; equal/ better specificity than cytology	Instability in urine has yielded dramatically different results in different studies; not widely available	Potentially replaces cytology as first-line surveillance for recurrence; can be used for screening the high-risk or general population; can possibly predict likelihood of recurrence
HA/HAase	High sensitivity and specificity for all tumor grades and stages and in the presence of other genitourinary conditions; can distinguish between high-low-grade tumors	Not widely available	Potentially replaces cytology as first-line surveillance for recurrence; can be used for screening the high-risk or general population
FDP	Fast, inexpensive; can be done in office setting; higher sensitivity than cytology for low-grade tumors	Lower specificity than cytology, especially in the presence of benign genitourinary conditions	May be useful in combination with another marker
CK20	High sensitivity for all tumor grades and stages; high specificity in the healthy	Very few studies have been done; results not yet confirmed	Can potentially detect pre-malignant disease; predict likelihood of recurrence

BTA stat is a qualitative test, while the BTA TRAK test is quantitative.

The BTA stat is a simple test that can be performed in the clinic setting and requires just 5 drops of urine. The results are available in 5 minutes and the test costs approximately $5.00.[13] Sensitivity of the BTA stat test is higher than that of cytology and ranges from 57% to 83%.[13,25,27-31] Sensitivity improves with increasing tumor grade, stage, and size.[12,28,29,31] The BTA stat also has improved sensitivity over the original BTA test.[25]

The BTA stat has false-positive rates of 2% to 5% in healthy individuals.[24,29] However, problems encountered with the original BTA test continue to plague this second-generation test. When hematuria and/or irritative voiding symptoms are present, specificity falls to 80%.[12,32] The presence of infection, stones, BPH, or prostate cancer lowers the specificity even more. Instillation of BCG, especially within 2 years of performing the BTA stat test, can lower specificity to just 28%,[12] seriously altering the utility of this test for the surveillance of patients following immunotherapy. BTA stat also has high false-positive rates in a mixed diseased and healthy patient population. Nasuti and colleagues[32] reported false-positive rates of up to 84% in the presence of dysuria, incontinence, and gross- or microhematuria. In a recent study comparing cytology, BTA stat, and other urine tumor markers, BTA stat had the highest sensitivity but fell short in specificity.[13]

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It remains unclear if false-positive readings from the BTA stat assay actually reflect early detection of pre-malignant lesions or recurrences not yet seen on cystoscopy. Until such issues are resolved, the role of BTA stat remains unclear.

BTA TRAK is a quantitative assay with a sensitivity of 54%-77% using a cutoff for normal between 14 to 23 U/mL.[27,33-38] In comparisons with cytology and the BTA stat test, the BTA TRAK assay has shown to be more sensitive.[27,34,35,38] The assay is also better than cytology for the detection of low-grade and low-stage tumors.[34,38] However, like the other BTA assays, this test suffers from low specificity. In the general patient population, specificity is 50%-97%.[27,34-37] The conditions that adversely affect specificity in other BTA tests also cause high rates of false-positive results in the BTA TRAK test. Although all BTA assays appear to be more sensitive than voided urine cytology, their lack of specificity make them unlikely candidates for replacement of urine cytology.

A potential novel use for the BTA TRAK assay was recently reported by Blumenstein et al[39] where 187 patients with superficial TCC had serial collections of urine samples for BTA TRAK assays. The study found that patients with serially rising assay levels were significantly more likely to have disease recurrences following transurethral resection. This suggests that the BTA TRAK assay may be useful in determining the most optimal interval between cystoscopic exams for individual patients. Patients with increasing levels would be candidates for closer cystoscopic follow-up while those with stable or decreasing levels could have longer intervals between exams. More studies are needed to confirm these exciting findings.

NMP22 and BLCA-4

Nuclear matrix proteins (NMPs) have a structural role in cellular nuclei and participate in DNA replication, transcription, RNA processing, and gene expression. NMP22, a mitotic spindle-associated protein, functions to distribute the proper number of chromatids to daughter cells. NMP22 has been shown to be present in higher amounts in the urine bladder cancer patients versus healthy controls.[40] The NMP22 test (Matritech, Newton, Mass) is a quantitative enzyme-linked immunoassay that utilizes a monoclonal antibody directed against NMP22. The test costs $20 and results are available in 8 hours.[13,41] It is one of the tests, along with BTA stat and fibrinogen degradation product (FDP), currently FDA-approved for use to detect occult or rapidly recurring disease after transurethral resection.

The overall sensitivity and specificity of the NMP22 is 68%-100% and 61%-85%, respectively.[41-49] Most studies indicate that NMP22 has a higher sensitivity but a lower specificity than voided urine cytology.[8,42] However, Menendez and associates[40] recently reported no significant difference of NMP22 levels in patients currently with TCC, with a history of TCC but no current evidence of disease, with benign urologic conditions, and in healthy controls. They found the sensitivity of NMP22 to be just 37.8%. False-positive results can also be seen in the presence of urolithiasis (50%), urinary tract infections (50%), BPH (15.6%), and other benign urologic conditions (25.6%).[23,40]

Some studies have found positive correlations between NMP22 levels and tumor size, grade, and stage.[40,43] The presence of such relationships suggests that NMP22 levels could be used to assess the severity of disease

and to predict prognosis. Soloway and colleagues[48] examined patients with TCC after transurethral resection and measured NMP22 levels on postoperative day 5. The patients were followed by cystoscopy at 3 to 6 months. Patients who had post-transurethral resection NMP22 levels of less than 10 U/mL had lower rates of recurrence than patients whose levels were higher than 10 U/mL. Patients with levels higher than 20 U/mL were particularly prone to disease recurrence. The negative predictive value of NMP22 is 81%-100%,[14,48,50] which may allow physicians to distinguish high risk patients from those who are low risk. Overall, NMP22 lacks the specificity to be useful in routine screening, but it may have a role in the assessment of disease recurrence and prognosis.

Konety and coworkers[51] have identified 6 NMPs that are unique to bladder cancer cells. Comparing tissue samples from patients with TCC to healthy controls using immunoblot analysis, one particular NMP, BLCA-4, was identified. All neoplastic and morphologically normal tissue samples from TCC patients were positive for BLCA-4, while all samples from healthy subjects were negative. A quantitative immunoassay technique resulted in a sensitivity of 96.4% and specificity of 100%. BLCA-4 could be detected in the urine sample of TCC patients with falsely negative cytologies. In addition, there is early evidence that BLCA-4 is not positive in patients with urinary tract infections, smoking history, catherizations, or cystitis.[52] Furthermore, BLCA-4 may have the potential to predict recurrent disease. The overall high sensitivity and specificity of BLCA-4 relative to urine cytology makes BLCA-4 a promising urine-based tumor marker for patient screening. However, correlation with disease grade, the presence of concurrent benign or malignant genitourinary disease, and the effect of intravesical therapy still require further study.

Telomerase

Telomeres exist at the ends of vertebrate chromosomes as repetitive TTAGGG hexameter sequences. With each somatic cell replication cycle, 50 to 200 nucleotides of telomeric sequence are lost. When a critical length is reached, chromosomal instability and subsequent cell death ensues.[53] Telomerase has the ability to reconstitute these end-sequences to circumvent the damage that occurs during the life of a cell. Abnormal telomerase activity gives tumor cells the potential for immortality. Its presence in the urine is indicative of abnormal cellular activity within the urinary tract. Telomerase is detected in the urine using the telomeric repeat amplification protocol (TRAP) assay. The test takes 10 hours to complete and costs around $17.[13]

Telomerase may also have a role in predicting the risk of recurrence.

The original studies on telomerase were based on activity levels measured in tumor biopsy specimens. These early studies reported a sensitivity of 80%-98%, regardless of tumor stage or grade.[54-57] Unfortunately, the sensitivity of telomerase in voided urine samples has been inconsistent and ranges from 0% to 85%.[55,58-63] Linn and associates[64] tested paired frozen tissue and urine samples of 12 patients with TCC for telomerase activity and found positive results in 11 of 12 tissue samples but negative results in all the urine samples. Several factors can play into this discrepancy. Arai et al[65] examined the effects of cold storage and urinary stasis on telomerase activity and found that exposure to such conditions for a few hours resulted in loss of activity. It has also been suggested that the acidic environment of the urine and the presence of salts, enzymes, and urea can cause destabilization of the telomerase.[66] However, when the TRAP assay is performed successfully, it is significantly more sensitive than voided urine cytology for the detection of low-grade and low-stage tumors. However, this assay does not correlate with tumor grade or stage.[59,60,68]

Table 2
Sensitivity and Specificity of Urine-based Markers for TCC

Marker	Overall Sensitivity (%)	Overall Specificity (%)
Cytology	25-95	6-100
BTA stat	57-83	28-98
BTA TRAK	54-77	50-97
NMP22	68-100	61-85
Telomerase	80-98	66-100
HA / HAase	92	85
CK20	91	67-74

The specificity of telomerase is 95%-100% in healthy controls[59,63,67] and drops to 66%-80%.[59,68] in the presence of hematuria.

Ramakumar and colleagues[13] compared various urine-based tumor markers, including NMP22, BTA stat, FDP, and cytology, and found telomerase to have the highest sensitivity and specificity. Telomerase also had the highest sensitivity in the detection of grade 1 and pTa tumors. Another study looked at various tumor markers for their ability to differentiate patients with TCC from those with benign hematuria. The results indicated that telomerase and NMP had the highest sensitivity for Ta and grade 1 tumors while telomerase and voided urine cytology had the highest specificity.[68]

Telomerase may also have a role in predicting the risk of recurrence. Kitsukawa and associates[61] examined 26 patients with known TCC and found 22 with positive telomerase activity. Of the 11 patients available for follow-up, 10 had positive preoperative assays. Six of the 10 patients tested positive for postoperative telomerase activity. Three of the 6 patients subsequently developed recurrent disease at 3-month surveillance suggesting that the presence of telomerase activity in patients following transurethral resection may be a predictor for tumor recurrence.

Overall, telomerase is a sensitive and specific bladder tumor marker that has performed well against other urine based markers. It is a possible candidate for surveillance, screening, and predicting the risk of recurrence of bladder cancer.

Hyaluronic Acid/Hyaluronidase

Hyaluronic acid (HA) is a glycosaminoglycan that has osmotic, homeostatic, and structural properties in normal tissues.[69] Through interactions with specific cell surface receptors, HA also has a role in cellular adhesion, migration, and proliferation. HA is broken down by hyaluronidase (HAase), a group of related endoglycosidases. The resulting small fragments express angiogenic properties necessary for tumor growth and propagation. HA and HAase both can be measured in the urine of patients with TCC using quantitative ELISA-like assays.

Urine HA is detectable in higher levels in all grades and stages of TCC compared to non-TCC patients.[70] The sensitivity and specificity is 92% and 93%.[70] No correlation exists between the level of expression and tumor grade or stage. However, the molecular size of HA fragments may differ in high- and low-grade tumors. In higher-grade tumors, high molecular weight fragments and small angiogenic fragments can be detected in higher level. In grade 1 tumors and healthy controls, only intermediate molecular weight fragments are detected.[70] Additional studies are needed to confirm the relationship between HA molecular mass and tumor grade.

HAase is detected in higher levels in patients with high-grade tumors.[71,72] The enzymatic activity of HAase is necessary for the production of the small HA fragments involved in tumor growth and invasion. HAase can be detected at levels 5 to 8 times higher in patients with grade 2-3 disease in comparison to healthy patients and patients with grade 1 tumors and is 4.5 times higher in TCC patients versus patients with benign urologic disorders.[71,72]

HYAL1 is 1 of 3 genes known to encode for human HAase. HYAL1-type HAase is detectable in the urine of patients with grade 2-3 TCC but undetectable in healthy patients, those with grade 1 tumors, or in patients with a history of TCC but no active evidence of disease.[73] High levels of HYAL1 are present in human serum so patients with hematuria are likely to get false-positive results. This problem can be circumvented by normalizing urinary HYAL1 levels to total urine protein content.[73]

Recently, Lokeshwar and associates[69] compared HA levels in TCC patients to patients with benign urologic conditions, those with a past history of TCC, and healthy individuals. The HA levels were significantly higher in the TCC patients with a sensitivity of 83%

Main Points

- Bladder cancer is the second most common genitourinary malignancy in the United States.
- Most patients present with superficial papillary disease, which has a high 5-year survival rate.
- In up to 70% of patients, however, bladder cancer can recur. Most are superficial, but 10% to 15% have muscle invasive disease, from which two thirds will die within 5 years.
- Close, long-term follow-up is essential for all bladder cancer patients, regardless of grade and apparent completeness of initial tumor resection.
- Cytology, although useful for detecting high-grade and high-stage disease, does not consistently detect low-grade lesions and other inflammatory bladder changes, such as recent intravesical therapy, radiation, and infections, and can result in false-positive readings.

and specificity of 90%. The HAase activity was then compared in patients with grade 2-3 tumors versus patients with grade 1 tumors and healthy controls. HAase levels were higher among patients with high-grade tumors. The sensitivity and specificity for detecting grade 2 and grade 3 tumors were 81% and 84%.

Although this marker holds great promise, it is not yet widely available, and further testing with larger patient samples is required.

If the results of the HA and HAase tests were combined, positive results on both indicated a high-grade disease. A positive result on the HA test combined with negative results on HAase indicated the presence of low-grade disease. Any positive result on either or both tests was indicative of some tumor presence. The overall sensitivity and specificity of the combined HA-HAase test were 92% and 85%, regardless of tumor grade or stage.[74]

The combined HA-HAase test has demonstrated both high sensitivity and specificity. This test has the potential to accurately detect all grades and stages of tumors and to distinguish high-grade from low-grade tumors with a low incidence of false-positive results. Although this marker holds great promise, it is not yet widely available, and further testing with larger patient samples is required.

Fibrin/Fibrinogen Degradation Products

Bladder tumor cells have increased vessel wall permeability relative to nonmalignant cells. This allows the leakage of various cellular proteins, including plasminogen and fibrinogen, into the urine. Urokinase, also present in the urine, converts plasminogen to the active form, plasmin. Plasmin catalyzes the breakdown of fibrin and fibrinogen into fibrinogen degradation products (FDPs).[75]

FDP can be detected in the urine by a monoclonal anti-FDP antibody latex-agglutination assay. The results are available in 7 minutes and the cost is approximately $15.[13] The overall sensitivity of FDP is 52% to 81%.[13,76,77] Several studies have shown that FDP is more sensitive than voided urine cytology.[13,76,77] However, Ramakumar and colleagues[13] showed that the sensitivity of telomerase, BTA stat, and NMP22 were all higher than FDP. The use of FDP as a tumor marker may be limited in that several studies have found FDP to be less specific than urine cytology.[13,76,77]

Cytokeratins

Cytokeratins (CK) are a major component of the intermediate filaments found in all epithelial cells. A number of cytokeratins are being studied as potential tumor markers for TCC.

CK20 is a very promising tumor marker because it has high sensitivity for all grades of tumor and low rates of false-positives in healthy patients.

Some of the tests available for the detection of the cytokeratin include CYFRA 21-1, tissue polypeptide antigen (TPA), tissue polypeptide-specific antigen (TPS) and urinary bladder cancer (UBC) tests. These urine-based tests measure the overexpression of cytokeratins 8, 18, and 19 in varying combinations.[36,78-85]

Unlike other cytokeratins which are ubiquitous, cytokeratin 20 (CK20) has been shown to be expressed only in malignant bladder cells.[86,87] Klein and colleagues[87] examined urine samples in patients with hematuria and in healthy patients for the presence of CK20. Among the healthy patients, there were no detectable levels of CK20. Among patient with hematuria, 48 of 73 patients were diagnosed with TCC by biopsy. All patients with confirmed TCC had detectable CK20 levels. In the patients without TCC, 7 had detectable levels of CK20. Six of these patients had cytology results showing cellular atypia, hyperplasia, or metaplasia suggestive of a premalignant state. The overall sensitivity and specificity of CK20 were 91% and 67%. There was no correlation between the level of CK20 expression and tumor grade. Buchumensky et al.[86] also studied CK20 expression as a predictor of bladder cancer and found a sensitivity and specificity of 91% and 74% with no false negatives. CK20 had a higher sensitivity in detecting stage Ta to stage T2 disease compared to cytology. Again, specimens with false-positive results had cytologic evidence of premalignant potential. Finally, CK20 expression in patients with a history of TCC may be a predictor of disease recurrence.[88]

CK20 is a very promising tumor marker because it has high sensitivity for all grades of tumor and low rates of false-positives in healthy patients. It may also have the potential to detect premalignant disease and predict the likelihood of recurrence. However, it remains unclear whether the presence of benign urologic disorders or other genitourinary malignancies will affect the expression of CK20 in the urine. The effect of intravesical therapy and/or bladder

manipulation is also unknown. Finally, the role, if any, of CK20 in the differentiation of high-grade from low-grade disease is still unclear.

Conclusions

The search for a suitable bladder cancer marker has been challenging. PSA was readily accepted into routine use as a prostate cancer marker because it was compared with the digital rectal exam, which has relatively low sensitivity and specificity in cancer detection.[89] In the case of bladder cancer, tumor markers are compared with urine cytology, which has very high specificity and acceptable sensitivity for detecting high-grade and high-stage disease.

The problem with tumor markers in general is that sensitivity is achieved at the cost of specificity, and vice versa. A marker that perfectly displays both characteristics remains elusive. Combining multiple tests so that the strength of one makes up for the weakness of the other seems like a logical solution. However, this has so far not proven to be true. Pode and associates[12] combined the BTA stat (which has good sensitivity) with urine cytology (which has good specificity) and found that overall sensitivity and specificity were not improved. Combining tumor markers can be potentially useful, but the optimal combination has yet to be determined.

Are any of the markers currently being tested potential candidates for the replacement of cystoscopy or cytology? The answer is a qualified yes. Table 1 summarizes the advantages, disadvantages, and potential uses for cytology and the tumor marker tests discussed in this article. Table 2 summarizes the overall sensitivity and specificity of these various markers. The markers that emerge as potential replacements for current methods are telomerase and hyaluronic acid/hyaluronidase. Both markers show better sensitivity in all grades and stages of tumor, and both have specificities that are equal to or better than cytology. These markers could potentially improve the detection rate of TCC and expand the role of tumor markers to include screening of larger populations and to predict the likelihood of disease recurrence. Although currently available tumor markers cannot replace the need to perform cystoscopy, they have demonstrated that these new tests may eventually minimize the cost and difficulty associated with screening and long-term surveillance of patients with or at risk for bladder cancer. ■

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