DIAGNOSIS OF BLADDER CANCER USING A POINT-OF-CARE PROTEOMIC ASSAY (NMP22 BLADDERCHEK): A MULTICENTER STUDY

A review of the presentation at the 2005 American Urological Association (AUA) podium session: Bladder Cancer Detection and Screening, including a discussion with Giora Katz, MD
Twenty-three academic, private practice and veterans' facilities in 10 states prospectively staffed Urologists, Department of Surgery-Urology Service, Lake City Veterans Administration Hospital, Lake City, Fla; and is in private practice at Lakeshore Urology, Manitowoc, Wis.

Methods: Twenty-three academic, private practice and veterans' facilities in 10 states prospectively enrolled consecutive patients from September 2001 to May 2002. Participants included 1,331 patients at elevated risk for bladder cancer due to factors such as history of smoking, or symptoms including hematuria and dysuria. All patients at risk for malignancy of the urinary tract provided a voided urine sample for analysis of NMP22 and cytology prior to diagnostic cystoscopy. The reference standard was cystoscopy with biopsy. The performance of the NMP22 test as an aid to cancer diagnosis was compared to voided urine cytology. NMP22 testing was conducted in a blinded manner.

Results: Bladder cancer was diagnosed in 79 patients. Ten of the malignancies were muscle invasive. NMP22 was positive for 9/10 (90%). By comparison, voided cytology was positive in only 2/9 (22%). Overall, the NMP22 assay detected more than three times as many tumors as voided urine cytology, identifying the presence of 32 malignancies that were missed by cytology. The proteomic marker detected 4 cancers that were not visualized during initial cystoscopy; 3 were muscle invasive and one was carcinoma in situ. The specificity of NMP22 BladderChek Test was 90% for patients with no urinary tract disease. The accuracy of NMP22 was 83.7%. The combination of NMP22 with cystoscopy detected malignancies in 74 of 79 patients versus 70 of 79 detected by initial cystoscopy alone. Cytology detected only one cancer that was neither seen during cystoscopy nor detected by NMP22 test.

Conclusions: Combining cystoscopy with the noninvasive point-of-care assay for urinary NMP22 can increase the accuracy of cystoscopy, with results available during the patient visit. The NMP22 BladderChek Test was less than half the expense for voided cytology.

Author disclosures

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Early diagnosis of bladder cancer can save lives. Bladder cancer occurs primarily in men age 60 and older and roughly twice as frequently in white men as in black men. Men are 4 times more likely to be diagnosed with bladder cancer than women; age-adjusted mortality rates from bladder cancer are similarly higher for men than for women. Women, however, tend to be diagnosed at a more advanced stage in the disease. Among US males, the incidence of new bladder cancer cases is almost as high as the incidence of colon cancer.1

Bladder cancer is the fifth most common form of cancer in the United States and the ninth most common form of cancer in the world. The American Cancer Society estimates that more than 63,000 new cases of bladder cancer will be diagnosed in the United States this year.2

Yearly, more than 13,000 people die of the disease (nearly 9,000 men and 4,000 women). Worldwide bladder cancer accounts for 330,000 new cases and 100,000 deaths each year. It is also one of the most chronic cancers, recurring in almost 70% of patients.2

The most common risk factor for bladder cancer is smoking. Smokers are twice as likely to develop bladder cancer as nonsmokers. In the United States, smoking is estimated to be associated with approximately 50% of bladder cancer deaths among men and 30% among women.2

Occupational exposure to chemicals (aromatic amines) used in dry-cleaning facilities and the production of dyes, paper, rope, apparel, rubber, and petroleum products have been associated with increased risk for bladder cancer. Soot and carcinogens from exposure to slow burns have put firefighters and arson investigators at increased risk for bladder cancer. Other industrial exposures implicated as risk factors for developing bladder cancer include combustion gases and soot from coal, chlorinated aliphatic hydrocarbons, and chlorination by-products in heated water.

If diagnosed in its early stages, bladder cancer has a 5-year survival rate of 95%. If diagnosed at an advanced stage, however, the 5-year survival rate can be less than 10%. It has been estimated that this year in the United States about 25% of bladder cancer patients will be diagnosed after their disease has become invasive or metastatic, significantly lowering the 5-year survival rate.2

HEMATURERIA WORK-UP

Hematuria is an early sign of bladder cancer. It is also the most common symptom of bladder cancer. AUA guidelines for workup of hematuria currently include cystoscopy and urine cytology.4 To expedite early diagnosis, we developed a patient management protocol using the NMP22® BladderChek® Test (Matritech, Inc.) as an adjunct to cystoscopy. This protocol is based on data from the bladder cancer multicenter study (see the list of collaborators on page 2).2,3

Earlier this year, The Journal of the American Medical Association published NMP22 BladderChek Test results from a multicenter study.3 Data demonstrated the NMP22 BladderChek Test identified 4 life-threatening cancers missed during cystoscopic examination. The study further showed that when the BladderChek Test is combined with cystoscopic examination, it increases overall bladder cancer detection to 94%.4

As a principal investigator for the multicenter study at a Veterans Administration hospital in Florida, I found this test had significant clinical utility as an adjunct to cystoscopy.

Urologists are challenged to improve detection of bladder cancer at the first sign of hematuria. While men tend to react quickly to signs of hematuria, women or their physicians tend to dismiss initial hematuria indicators. Patient education is essential to communicate the significance of hematuria and the need to follow up on this symptom.

At Lakeshore Urology in Manitowoc, Wisc, and across the United States, the current ratio of adults investigated with hematuria to those diagnosed with bladder cancer is 20:1. This type of work-up typically involves multiple noninvasive tests and invasive procedures. The NMP22 BladderChek Test is being used to help focus our search on those with cancer, expediting early diagnosis and helping urologists to be more confident in determining the cause of hematuria (Figure 1).

Initial evaluation shows that the NMP22 BladderChek Test plays a role in directing attention to benign and malignant causes of hematuria, better directing additional testing and procedures.

Case in point: The Veterans Health Administration (VA) is the largest provider of health care in the country. As part of the multicenter study, we observed a large percentage of VA patients (older males with a history of smoking) at high risk for bladder cancer. At the urology clinic, significant VA resources are used to investigate and find patients with hematuria caused by cancer. The NMP22 BladderChek Test gives the VA a cost-effective, point-of-care test to help direct resources to patients with the highest suspicion of cancer.
The NMP22 BladderChek Test is enhancing the early diagnosis of bladder cancer for these high-risk patients.

**NUCLEAR MATRIX PROTEIN AND TRANSITIONAL CELLS OF THE URINARY TRACT**

Nuclear matrix proteins (NMP) make up the structural framework of the nucleus and organize its function. NMP22 is specific for transitional cells in the urinary tract. Malignant transitional cells contain up to 80 times higher concentration of NMP22 than normal transitional cells and release it into the urine upon cell death. Unlike urine cytology and fluorescence in situ hybridization (FISH) testing, detection of NMP22 in the urine is not dependent on recovery of intact cells. Based on previous studies, an NMP22 level above 10 U/mL in the urine is associated with a high probability of TCCB. The NMP22 BladderChek Test is a point-of-care device that was designed to identify urine with NMP22 levels above 10 U/mL. This test can be performed by non-physician staff members (CLIA waived). The test cassette requires 4 drops of freshly voided urine, and results are available in 30 minutes. This device has a built-in quality control.
REVIEW OF THE METHODS, STUDY DESIGN, AND EXECUTION OF THE MULTICENTER STUDY

From September 2001 to May 2002, 1,331 patients scheduled for cystoscopy due to suspicion of bladder cancer were included in the study.1,5 The mix included private, academic, and Veterans Administration urology practices in 23 locales and 10 states. Of this patient population, 92% presented with hematuria. Other risk factors included a history of smoking and irritative voiding symptoms. All patients provided a voided urine sample for analysis of NMP22 and cytology prior to diagnostic cystoscopy. Urologists were blinded to NMP22 results while performing and reporting the results of cystoscopy. Further work-ups were based on clinical findings and results of cystoscopy and cytology. TCCB was diagnosed based on the pathology report of excised tissue.

Of the 1,331 patients enrolled in the study, 79 were diagnosed with TCCB (Figure 2),9 10 of whom were found to have muscle-invasive disease.1,5 While initial cystoscopy visualized 6 of 10 (60%) invasive tumors, the NMP22 BladderChek Test was positive for 9 of 10 (90%).1,5

Voided urine cytology, by comparison, was positive in 2 of 9 (22%) patients with muscle-invasive cancer. The NMP22 BladderChek Test identified 4 life-threatening malignancies, including 3 muscle-invasive tumors and a carcinoma in situ (CIS) that were missed on initial cystoscopy.

The NMP22 Test was significantly more sensitive than voided urine cytology (Figure 3).1,5,9 Study results reported the specificity of cytology to be greater than the NMP22 Test (Table 1).1,5,9

MULTICENTER STUDY CONCLUSIONS

Cystoscopy combined with the NMP22 BladderChek Test detects more bladder cancers than cystoscopy alone or combined with cytology (Figure 4).1 The NMP22 BladderChek Test is significantly more sensitive than cytology in detecting bladder cancer (3x more cancers, P<0.001). This test can be performed by clinic staff in any doctor’s office with results in 30 minutes, at half the cost of voided cytology. The NMP22 BladderChek Test is consistent with AUA guidelines recommending use of a urine test as an adjunct to cystoscopy.
Q&A WITH GIORA KATZ, MD
Based on questions and answers following the presentation by Dr. Katz at the May 23, 2005, AUA podium session: Bladder Cancer Detection and Screening, Abstract 846.¹

Q: How many cancers were detected by cytology versus the NMP22 Test?

Katz: The NMP22 BladderChek Test detected 32 cancers missed by cytology and 4 cancers not visualized during initial cystoscopy. There was only 1 case where the cytology was positive and the NMP22 and cystoscopy were negative.

Q: Can you explain why the cytology numbers for invasive cancers in this study are much lower than those typically reported around the country?

Katz: This study included 23 facilities in 10 states. Cytology specimens were sent to their usual laboratories according to standard practice at each office. These results reflect the subjectivity and variability of cytology results.

Q: What accounts for invasive tumors missed by cystoscopy?

Katz: Cystoscopy is an excellent tool, but as other studies have shown, conventional cystoscopy can miss up to 50% of cancers.¹⁰ Blood in the urine can hamper visibility, and some cancers are mistaken for benign conditions. When NMP22 is positive, a flag of warning is raised. Even when you do not see something on the initial cystoscopy, you sometimes have a sense that you should look again. Adding a test that gives you new information helps determine the next course of action.

Q: Who was involved in the study?

Katz: The study involved 23 clinical sites in 10 states, and included qualified urologists, pathologists, and laboratories. Each site followed its own internal protocols and procedures. Laboratories analyzing cytology are directed by qualified pathologists. I believe this data to be representative.

Q: You seem to suggest that cytology can be replaced by the NMP22 BladderChek Test. Is that the case?

Katz: The AUA guidelines, written in 2001, support the use of ancillary tests. At the time the AUA guidelines were written, the NMP22 BladderChek Test had not yet been developed. This study was conducted to identify the clinical utility of the NMP22 Test as an ancillary test to be used with cystoscopy in the clinic.¹ Our multicenter study data demonstrate that the NMP22 Test performed in the clinic delivered much more meaningful results than cytology.¹,⁵

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REFERENCES


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