Bladder Cancer Screening in a High Risk Asymptomatic Population Using a Point of Care Urine Based Protein Tumor Marker

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Abbreviations and Acronyms

BC = bladder cancer
CT = computerized tomography
IVP = excretory urogram
PPV = positive predictive value
RBC = red blood cell
UA = urinalysis
UTSW = University of Texas Southwestern Medical Center
VA = Veterans Affairs Health Care System

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Purpose: We evaluated whether screening high risk asymptomatic individuals with a bladder tumor marker can lead to earlier detection and resultant down staging of bladder cancer.
Materials and Methods: Subjects at high risk for bladder cancer based on age and smoking or occupational status were solicited from 2 well patient clinics from March 2006 to November 2007. NMP22® BladderChek® testing was performed on voided urine samples. Those with positive test results underwent office cystoscopy and cytology testing. Participants were contacted for followup at 12 months after study enrollment to evaluate for unrecognized bladder cancer.
Results: A total of 1,175 men and 327 women underwent BladderChek testing. Mean participant age was 62.5 years (range 46 to 92). Based on 10-year or greater smoking history 1,298 participants were enrolled while 513 were enrolled based on a greater than 15-year high risk occupation for bladder cancer. Positive BladderChek testing was observed in 85 (5.7%) participants and 69 agreed to undergo cystoscopy. Three types of lesions were diagnosed including multifocal, high grade Ta (1); Ta, low grade tumor (1) and marked atypia (1). Followup was available in 1,309 subjects. Mean followup was 12 months (range 0.9 to 25.5) and 2 of 1,309 participants had low grade noninvasive bladder cancer. Evaluation of patient records revealed that 73.4% of participants had urinalysis within 3 years before screening.
Conclusions: NMP22 BladderChek for screening an asymptomatic, high risk population can detect noninvasive cancers but the low prevalence of bladder cancer in this population did not permit assessment of intervention efficacy. Frequent use of urinalyses in high risk persons may attenuate future efforts to study the effects of bladder cancer screening tests.

Key Words: urinary bladder neoplasms, mass screening, nuclear matrix protein 22

BLADDER cancer is the 4th most common cancer in men and 5th most common cancer overall.[1] Although progress has been made in understanding BC biology, to date these efforts have translated into a minimal survival benefit. Approximately 70% to 80% of patients diagnosed with bladder cancer currently present with hematuria (gross and microscopic) and muscle invasion is present in 25% of patients at diagnosis. Overall survival rates for BC are stage dependent and 5-year survival for tumors confined to the mucosa

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(70%) are significantly higher than for cancers that are muscle invasive (40%) or metastatic (less than 30%).[2]

At this time BC screening is not standard of care. BC has known risk factors including increasing age, male gender, smoking and occupational exposures such as workers in the dye, petroleum and chemical industries.[3,4] Down staging of BC with screening has been demonstrated using hematuria screening by Messing et al.[5] Only 4.8% of tumors in an asymptomatic screening group older than 50 years were muscle invasive compared with 23.9% in an unscreened population. In addition, at 14 years of followup no men with screen detected BC had died of their disease compared with 20.4% of men with unscreened BC.[6] This study, while limited by use of a contemporary control rather than randomization of patients, suggests that BC screening can identify cancers early and improve survival. However, the use of hemoglobin dipstick was never adopted for BC screening because of low positive predictive value of only 5% to 8%.[7,8] Urine based bladder markers such as NMP22 have been shown to have superior sensitivity and specificity compared with hemoglobin dipstick.[9]

The NMP22 BladderChek test is approved by the Food and Drug Administration for the diagnosis of BC in high risk participants. The BladderChek test is a point of care test that provides immediate results and does not require a clinical laboratory for evaluation. A multi-institutional study by Grossman et al used the BladderChek test to evaluate urine specimens from a large cohort of participants at increased risk for BC due to factors such as age, history of smoking or hematuria.[10] They found cancer in 6% of their cohort, and NMP22 rendered a sensitivity, specificity and PPV of 55.7%, 85.7% and 19.7%, respectively.

In this prospective study we evaluated the use of a point of care urine based tumor marker (BladderChek) for screening subjects older than 50 years who are at high risk for bladder cancer based on smoking history or occupational exposure without other symptoms.

METHODS

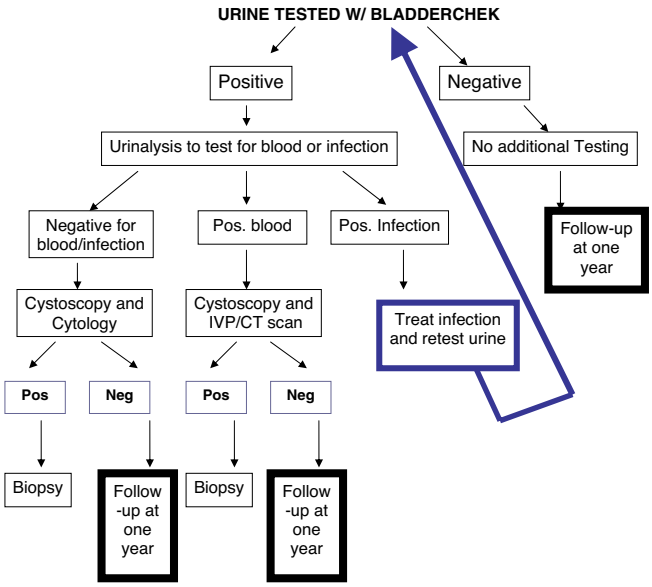
All studies were performed with the approval and oversight of the Institutional Review Board for the Protection of Human Subjects. Subjects were solicited from well patient clinics from the University of Texas Southwestern Medical Center at Dallas and the Dallas Veterans Affairs Health Care System from March 2006 to November 2007.

Subjects were recruited who were older than 50 years and had a 10-year or greater smoking history (any number of cigarettes) or a significant (15 or more years) high risk occupation such as working in the dye industry, petroleum industry or chemical industry. Subjects with a history of urological malignancy or gross hematuria were excluded from analysis. Participants with active urinary tract infection, urinary retention, active nephrolithiasis, kidney failure, ureteral stents, nephrostomy tubes, bowel interposition or recent genitourinary instrumentation were excluded to avoid a high rate of false-positive results.

The protocol flow diagram is shown in the figure. The BladderChek test was performed on voided urine samples. The test is performed by adding 4 drops of voided urine to the sample well of the point of care device. Positive or negative results were read 30 to 50 minutes later in the test window. A built-in control indicated that the assay was complete. The BladderChek point of care device is a lateral flow immunochromatographic qualitative assay that detects increased amounts of the nuclear mitotic apparatus protein.[10]

Those with a positive test underwent dipstick urinalysis to test for the presence of blood or infection. In the presence of increased nitrites or leukocytes, urine culture was obtained and the test was repeated following antibiotic treatment and documented clearance of infection. Only participants with positive BladderChek test results underwent office cystoscopy and bladder wash cytology testing. In the presence of trace or more blood on the dipstick analysis, urine microscopy was performed to evaluate for microscopic hematuria which was defined as 3 or more RBCs per high power field. Those participants with microscopic hematuria also underwent upper urinary tract evaluation including 3-phase contrasted CT or IVP with or without renal ultrasound to evaluate the kidney parenchyma, renal pelvis and ureters. If the BladderChek test was negative no further testing was required. However, all participants were contacted for followup to determine if BC was diagnosed or if the patient had experienced gross hematuria.

Following study design and trial enrollment it became apparent that several subjects had received urine evaluation during routine evaluation before study participation. Because this practice could dilute the expected prev-



Screening protocol