

Indexing Atypical Cytology in Bladder Cancer to NMP22 Decreases False-positive Results—Can It Replace Surveillance Cystoscopy?

a report by

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The early detection of bladder cancer allows for effective local treatment and optimizes the success of surgical therapy. Survival rates reflect the importance of early diagnosis. When detected at the superficial clinical stage Ta and T1, the five-year survival rate of bladder cancer ranges between 82% and 95%, whereas corresponding survival rates for invasive muscle disease and metastatic disease are 50% and 6%, respectively.^{1,2}

Currently, no standard method exists for non-invasive early identification of bladder cancer. Patients who present with symptoms of microscopic or gross hematuria or other irritative voiding symptoms are often screened with an upper-tract study, urine analysis, urinary cytology, and office cystoscopy. However, urine cytology lacks sensitivity and office cystoscopy lacks specificity. The sensitivity of voided urine cytology ranges from 40% to 50% in high-grade disease but is reported to be as low as 20–30% in low-grade, low-stage disease. Conversely, the specificity of office cystoscopy for cancer detection is less than 10% in the evaluation of patients with microscopic hematuria. While cystoscopy remains the reference standard for invasive testing, the primary indication for cystoscopy, which is hematuria, has a low specificity (large number of false positives).

The development of a highly sensitive urinary test for the detection of transitional cell carcinoma of the

bladder could greatly impact the ability to effectively screen symptomatic patients at risk for bladder cancer. Many researchers have tried to evaluate non-invasive methods to accurately and easily identify the presence of bladder cancer.^{3–6} A number of diagnostic urinary tumor markers evolving from new molecular technologies—NMP22, BTA stat, telomerase—are being tested for screening and monitoring in high-risk populations.^{5,6}

The recent introduction of urinary tumor markers potentially challenges the efficacy of the current diagnostic evaluation. In a series of recent studies, researchers have evaluated the efficacy of urinary tumor markers for detection of recurrent bladder cancers. These studies show that the new urinary markers have excellent sensitivity, particularly in the ability to detect low-grade, low-stage tumors. Sensitivity of these tumor markers was reported to be two to three times greater than that of cytology, which translates into improved cancer detection. Despite excellent sensitivities, low specificities, and, more importantly, low positive predictive values limit these tumor markers. Specificity is frequently cited as an efficacy measure for screening tests.^{7,8}

Despite low sensitivity, voided cytology is a widely accepted adjunctive test for diagnosis and monitoring of patients with bladder cancer due to its non-invasive nature. Several investigators have suggested increasing its

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sensitivity by considering all atypical cytology as positive, a valuable aid in the identification of bladder cancer.^{9,10}

Compared with the NMP22, atypical cytology is less sensitive for the identification of bladder cancers, and has lower positive predictive value (PPV) in both the screening and monitoring populations.¹¹⁻¹⁴ Thus, treating an atypical cytology as positive significantly improves the cancer detection rate; however, this is at the cost of an increased false positive rate.

The authors conducted a study to determine whether indexing atypical cytology to NMP22 could enhance the clinical utility of atypical cytology by increasing the PPV, in both the screening and monitoring patient populations.

One hundred and ninety-seven patients with atypical urine cytologies at risk for bladder cancer (January 1997 to October 2000) presenting to the Urological Center at The Cleveland Clinic Foundation were identified. Of the 197 urine cytologies, 126 were incident (screening) and 71 were prevalent (known/monitoring) cases of bladder cancer. Outpatient cystoscopy was performed in all incident cases presenting with microhematuria, gross hematuria, and/or irritative voiding symptoms, and as part of monitoring in the prevalent cases. If a tumor was identified, biopsies were taken and subsequent transurethral resection of bladder tumor was performed. All cancers were histologically confirmed; an experienced urologist performed all surgical procedures. The urinary tests were performed at the authors' institution, and all patients had a negative upper-tract study within a 12-month interval. Atypical cytology was retrospectively indexed to NMP22 values, taken at the same time as the initial cytology.¹¹⁻¹²

An NMP22 value of greater than 10U/ml was considered positive for potential urothelial malignancy in screened high-risk patients who presented with hematuria or chronic irritative voiding symptoms. The cut-off value of 10U/ml was determined to be optimal by receiver operator characteristic analysis performed in

Table 1: Cancer Detection Rate of Atypical Cytology Indexed with NMP22 in Screening Group

Screening	
Atypical Cytologies (%CA): (n=171/126, 13%)	
Positive NMP 22	Negative NMP 22
16.7%	83.3%
(21/126)	(105/126)
CA 71%	CA 11.7%
(15/21)	(2/17)

Table 2: Cancer Detection Rate of Atypical Cytology Indexed with NMP22 in Monitoring Group

Monitoring	
Atypical Cytologies (%CA): (n=43/71, 61%)	
Positive NMP 22	Negative NMP 22
53.5%	46.5%
(38/71)	(33/71)
CA 92.1%	CA 18.6%
(35/38)	(8/43)

previous studies by the group. Monitoring patients with a history of bladder cancer, a cut-off value greater than 6U/ml was considered positive.^{7,8}

A total of 197 patients with atypical cytology were evaluated, of whom 60 (30%) had histologically confirmed bladder cancer. When stratified with NMP22, cancer was detected in 50 of the 60 (83%) cases. Gross hematuria was the presenting symptom in 24% (47/197) of the patients, and microscopic hematuria in 25% (49/197). When all atypical cytologies were considered as positive and indexed with NMP22, the overall specificity improved to 93.4% and the cancer detection rate—PPV—improved to 84.7% (from 30.5%).

In the screening (incident) group, the 126 atypical cytologies detected all 17 cancers (100% sensitivity by design), with a PPV of 13.5%—or a false positive rate of 87%—(17/17+109). When stratified by NMP22, cut-off value of >10U/ml, PPV increased to 71% (15/(12+6)), but the sensitivity decreased to 88.2% (15/17).

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Table 3: Sensitivity of Atypical Cytology Indexed to NMP22 To Detect Specific Stages and Grades

Bladder cancer stage	Atypical +NMP22	NMP22>10U/MI	NMP22 >6 U/MI
	Overall	Incident	Prevalent
CIS	60.0%	33.3%	100.0%
Ta	64.7%	100.0%	62.5%
T1	75.0%	0%	75.0%
T2	100.0%	100.0%	100.0%
T3	100.0%	100.0%	100.0%
Grade	Overall	Incident	Prevalent
I Low	36.4%	0%	36.4%
II Moderate	90.5%	80.0%	93.8%
III High	95.5%	83.3%	100.0%

In the remaining 105 cases with a NMP22 of less than 10U/ml, two cancers were detected (11.7%), yielding a negative predictive value (NPV) of 98% (see Table 1).

In the monitoring (prevalent) group, 71 atypical cytologies detected 43 cancers (100% sensitivity by design), with a PPV of 61%—or a false positive rate of 39%—(43/43+28). When stratified by NMP22 cut-off >6U/ml, PPV increased to 92.1% (35/35+3—see Table 2), but the sensitivity decreased to 81.4% (35/43). In the

as monitored, for bladder cancer. The results show that considering all atypical cytologies as positive and indexing them with NMP22 means the specificity and PPV could be increased to 93.4% and 84.7%, respectively. In the screening group, atypical cytology alone has a low PPV, limiting its usefulness.

When indexing atypical cytology to a positive NMP22, the PPV in the screening population increased from 13% to 71% and diagnosed 100% of both early and invasive bladder carcinomas. In the monitoring group, the atypical cytology alone had a cancer detection rate of 61%. Indexing atypical cytology to a positive NMP22 increased the cancer detection rate from 61% to 92%, enhancing its clinical utility in monitoring patients with a history of bladder cancer. The sensitivity of NMP22 when indexed to atypical cytology to diagnosed early bladder cancer was only 33% compared with 100% in the incident group, but its utility in the detection of invasive bladder cancers was 100%.

This refinement in the clinical application of atypical cytology indexed with NMP22 can have a significant impact on the early detection of patients with predisposing factors for bladder cancer. Although

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remaining 33 cases with an NMP22 value of less than 6U/ml, only eight cancers were detected (18.6%), yielding a NPV of 75.8% (see Table 2).

When NMP22 was combined with atypical cytology, 60% of carcinoma *in situ* and 100% of invasive cancers were identified. In the incident group, the sensitivity of NMP22 to detect carcinoma *in situ* when indexed to atypical cytology was 33%; however, it was 100% in the prevalent group. In both the incident and prevalent groups, the NMP22 test alone was able to detect 100% of invasive cancers. When stratified by the grade of the tumor, NMP22 combined with atypical cytology detected 36% of grade 1 tumors, 90.5% of grade 2 tumors, and 95.5% of grade 3 tumors (see Table 3).

In this study, the authors retrospectively evaluated the cancer detection rate and false positive rate generated by indexing atypical cytology results to the NMP22 tumor marker assay for patients being screened, as well

cystoscopy is gold standard for diagnosis, its sensitivity is variable, especially in lesions difficult to visualize, such as carcinoma *in situ* and low-grade papillary lesions. When an atypical cytology is indexed to NMP22, the pre-cystoscopy work-up alerts the physician to the likelihood of a neoplasm and can therefore enhance the disease detection rate of cystoscopy to 92% in the prevalent group and 71% in the incident group.

It is impractical to screen all people at elevated risk for bladder cancer by cystoscopy. Therefore, a cost-effective, non-invasive method is necessary. The predicted advantage of indexing atypical cytology with NMP22 test is that it is equally effective in diagnosing superficial tumors, as well as muscle invasive cancers. Evaluating those patients with hematuria utilizing NMP22 and urinary cytology could enhance this paradigm by reducing the number of cystoscopies. This also allows for the identification of all invasive disease, and the ability to detect more cancers than with cytology alone, with minimal added expense. ■