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Can Use the NMP22 BladderChek Decrease the Frequency of Cystoscopy in the Follow up of Patients with Bladder Carcinoma?

Adel Allam[1*], Badawi Hathout[1], Salah Alnusif[1]

[1]Urology Unit, Department of Surgery, Farwania Hospital, Kuwait

Abstract

Background and Aim: Bladder cancer is one of the most common cancers. Its diagnosis, management and follow up represent a burden in urology practice. "NMP22 BladderChek" is a urine test that measures levels of NMP22 (nuclear matrix protein 22), which is a protein found in both normal and cancerous cells of the bladder. However, levels of NMP22 are usually elevated in the presence of bladder cancer. To assess the accuracy of urinary NMP22 qualitative assay for the detection of recurrence of transitional cell carcinoma (TCC) during follow up period compared to the radiological investigations, urine cytology and check cystoscopy; and if it can be relied upon for the follow up to decrease the frequency of check cystoscopy.

Methods: 38 patients known to have bladder cancer, undergoing surveillance, were subjected to abdominal-pelvic ultrasonography, NMP22 BladderChek test; urine cytology followed by check cystoscopy and biopsy if indicated. The accuracy of these tools was compared by their sensitivity and specificity as well as diagnostic likelihood ratio in detecting recurrence of bladder cancer.

Results: The sensitivity and positive likelihood ratio of NMP22 BladderChek were superior to urine cytology (95% and 8.5 vs 50% and 4.5, respectively), while both diagnostic modalities were equal in terms of specificity (88.9%).

Conclusions: NMP22 BladderChek is a simple in-office test which proved in the current study to be highly sensitive in detecting recurrence, it can change the classical regimen for follow up of bladder cancer cases; reducing the number of check cystoscopies for these patients.

Keywords: Bladder Cancer, Tumor Markers, Nuclear Matrix Protein 22

Introduction

Bladder cancer is a common disease. Its diagnosis and management have always been a burden to the urologist and lifelong screening of patient; at least once a year is recommended in the high risk group. Cystoscopy and urine cytology are the standard methods for surveillance (1, 2). However, examination by cystoscopy is invasive, subjective, with poor sensitivity in case of flat urothelial tumors, costly and above all has impact on patient's quality of life. Voided urine cytology has also its own drawbacks such as the training required for the screener to make evaluation and the insufficient sensitivity of the test (3-5).

*Correspondence:
Adel Allam, Prof. of Urology
Dept. of Surgery (Division of Urology), Farwania Hospital, Kuwait
P.O. Box: 355, Jahra, 01005, Kuwait
Tel.:00965 7180066
Fax:00965 4882617
E-Mai: adelallam@hotmail.com
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In 1985 nuclear matrix protein 22 was discovered. NMP22 is a protein that is essential for cell division. It is normally present in urine at low concentrations. The shedding of NMP22 into the urine by tumors is the result of cellular apoptosis and other mechanisms of cell death. NMP22 is elevated up to 80-fold in tumor cells within the urinary tract. However, in theory, nonmalignant, inflammatory urothelial conditions could elevate urinary NMP22 values and give rise to false positives (6-8).

NMP22 BladderCheck test (Matritech, Inc, Newton, USA) is an immunoassay for the qualitative detection of nuclear matrix protein 22 in urine. The protein was originally titrated by micro plate testing, but now BladderCheck NMP22 has exactly the same accuracy. It has been approved by FDA as a marker for the diagnosis and monitoring the patients with bladder cancer. The test is not affected by hematuria (9).

The aim of this work is to study the reliability of this test in detecting tumor recurrence in patients known to have bladder carcinoma and if it can be relied upon for follow up of cases to decrease the frequency of check cystoscopy.

Material and methods

The current study was performed in the Urology Unit, Farwania hospital, MOH, Kuwait over one year (September 2006 - October 2007). It included 38 patients known to have bladder carcinoma and due for check cystoscopy. The mean age of the patients was 54 (range: 36-75) years and all patients were males.

Each patient had undergone abdominal and pelvic ultrasonography, NMP22 BladderCheck test, urine cytology and check cystoscopy and biopsy if indicated.

Urine sample was collected in a plastic specimen cup (glass cups and catheter urine avoided). Four drops of fresh voided urine was used. Test result is red at 30 minits (Fig 1).

The results of NMP22 BladderChek test as

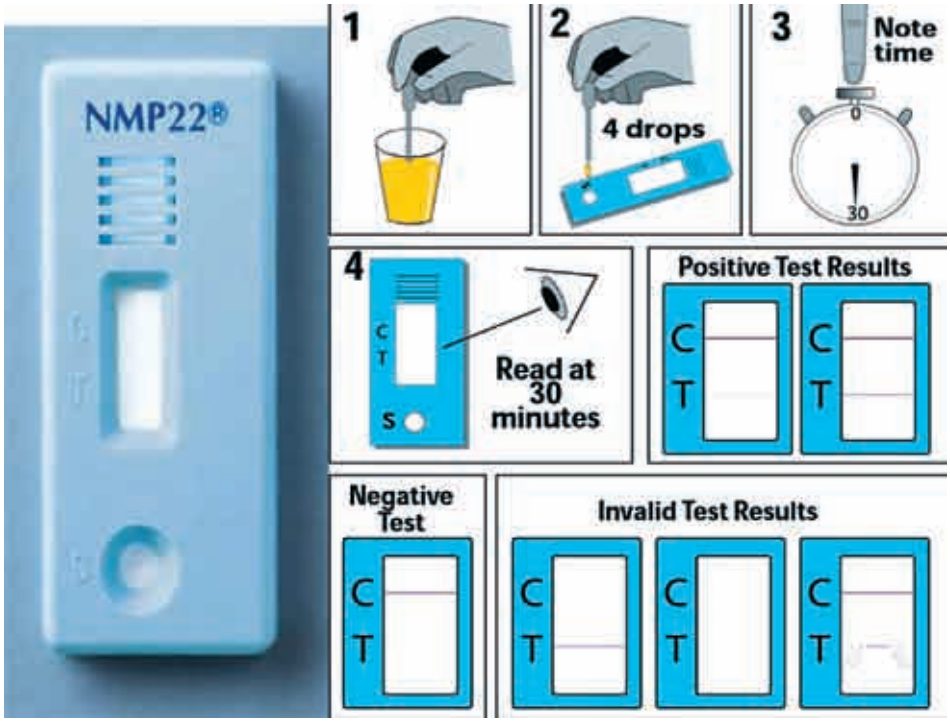

Figure.1: Procedure of NMP22 BladderChek Test, Urine sample was collected in a plastic specimen cup (glass cups and catheter urine avoided). Four drops of fresh voided urine was used. Test result is red at 30 min.

Table 1: Results of the four diagnostic modalities employed in this work

Test		Recurrence of Tumor Yes (n=20)	No (n=18)	Sensitivity (%)	Specificity (%)	LR+	LR-
Cystoscopy	Positive	20	1	100	94.4	17.8	0
	Negative	0	17				
NMP22	Positive	19	2	95	88.9	8.5	0.06
	Negative	1	16				
U/S	Positive	16	3	80	83.3	4.8	0.24
	Negative	4	15				
Cytology	Positive	10	2	50	88.9	4.5	0.56
	Negative	10	16				

LR+, Positive Likelihood Ratio; **LR-,** Negative Likelihood Ratio; **U/S,** Ultrasonography; **n,**Number.

well as ultrasonography, urine cytology and check cystoscopies were compared for sensitivity and specificity as well as positive and negative diagnostic likelihood ratios (LR+ and LR-). In the light of these results, the accuracy of the NMP22 BladderChek was evaluated.

Results

Thirty-seven out of 38 patients with bladder cancer undergoing surveillance for recurrence of tumor had TCC and one case with colonic adenocarcinoma infiltrating of urinary bladder, who was subjected to left hemi-colectomy and partial cystectomy 3 years ago.

The ***grades*** of the tumors at initial diagnosis were: GI: 13 (35.14%), GII: 15 (40.54%) and GIII: 9 cases (24.32%). While ***stages*** were: Ta: 25 (67.57%) and T1: 12 cases (32.43%).

Twenty out of 38 patients were found to have recurrence during check cystoscopy (52.63%). NMP22 BladderChek could detect 19 out of 20 cases of bladder cancer recurrence (95% sensitive). The only missed case was concurrently receiving BCG installation therapy. However, Sensitivity of NMP22 BladderChek for diagnosis of bladder cancer recurrence was higher than urine cytology and ultrasound. On the other hand, its specificity was equal to cytology and was higher than ultrasonography (Table 1). NMP22 BladderChek and cystoscopy had larger LR+, i.e. more useful tests; while urine cytology and ultrasonography had smaller LR+, i.e. less useful tests (Table 1).

Discussion

The management of superficial TCC accounts for a considerable proportion of the urological workload. Many reports during the last 30 years show the importance of this disease in the daily practice of the urologist. Therefore it is mandatory to continue scientific trials and basic research to improve its management (1).

Currently, there are no tests alternatives to check cystoscopy usually done with cytology for the follow up of urothelial cancer (2). It is always claimed that check cystoscopy is 100% sensitive, a claim, which is not substantiated by consistent clinical evidence.

Because of the long-term survival and the need for lifelong routine monitoring and treatment, the cost per patient of bladder cancer from diagnosis to death is the highest of all cancers (10). Thus, we should consider new approaches in diagnosis and management. Nuclear DNA measurements by flow-cytometry and determination of urine CEA and BTA have been investigated as new diagnostic methods.

However, these methods have insufficient sensitivity when used alone. Besides, nuclear DNA measurements by flow cytometry require expensive equipment and are relatively time-consuming (2, 11-13).

Many patients with low grade papillary tumors would undergo cystoscopy less frequently if a reliable, noninvasive procedure were available to screen for recurrence. This particularly became more justified after the new classification of the superficial TCC that also considered a new category known as papillary urothelial neoplasm with low malignant potential (PUNLMP). For the category, PUNLMP, the prognosis is excellent. The recurrence rate is much less than other superficial bladder tumors. If patients are tumor free at 3 months check cystoscopy 68% remain tumor free for 5 years. An accurate non-invasive test would release these patients from the uncomfortable procedure of repeated cystoscopic examination (14).

Recently, the NMP22 test kit, an enzyme immunoassay for nuclear protein in voided urine, has been approved by the United States Food and Drug Administration (FDA) for the detection of occult or rapidly recurring disease after transurethral resection of bladder tumor (9). The FDA expert opinion indicates that NMP22 test is far superior to cytology alone.

Therefore, we focused on NMP22 as a urinary marker and investigated its clinical usefulness as a substitute for voided-urine cytology and check cystoscopy for urothelial cancer detection.

In the current study, NMP22 BladderCheck test was positive in 19 out of the twenty positive cases, taking the sensitivity up to 95%. However, it should be noted that the only case missed was receiving BCG treatment at the time of the test, which could have affected its accuracy.

It is obvious that MMP22 test is more sensitive than urine cytology, which was sensitive in almost only 50% of cases.

There is a growing body of evidence now in the literature supporting our results that NMP22 offers advantages over cytology in terms of reduced cost and increased sensitivity. The use of NMP22 may supplant urinary cytology in the near future (15).

MMP22 is highly sensitive test. Oehr in the 2004 AUA meeting has shown that if both cytology and NMP22 are positive, it is 100% accurate (16). There are exclusion criteria to avoid false positive results. Benign inflammatory condition such as: UTI, the presence of foreign bodies like stents (2) and probably concurrent BCG instillation.

The high sensitivity of NMP22 test in the present study (95%) and in many other series support the argument that, in selected cases, we can reduce the frequency of check cystoscopies and rely upon NMP22 test in detecting recurrence of superficial bladder tumor.

The suggested criteria of the cases in which NMP22 BladderCheck can replace check cystoscopy for follow up includes: asymptomatic patients with history of low grade TCC (PUNLMP) who have no Hematuria or recent BCG instillation.

In conclusion**,** urinary NMP22 is a simple, non-invasive, cost-effective tumor marker, which proved in the current study to be highly sensitive in detecting recurrence of bladder cancer. It can reduce the frequency of diagnostic cystoscopy in selective cases in the future, thus reducing morbidity and improving the quality of life beside its economic impact. The FDA has approved the test for initial diagnosis and for surveillance of bladder cancer. However, this conclusion should be proved in a wider scale of patients through randomized controlled trials.

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