Applied Medical Informatics
Original Research Vol. 32, No. 1/2013, pp: 61-68

Validation of the Diagnostic Value of Nuclear Matrix Protein 22 Depending on Tumoral Stage and Grade

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Received: 1 February 2013 /Accepted: 18 February 2013 / Published online: 25 February 2013

Abstract
Objectives: The aim of the present study was to validate the sensitivity and specificity of the NMP22® BladderChek® test in our group of patients according to the tumoral stage and grade and to identify the patient categories that might benefit from the non-invasive nature of NMP22® BladderChek® test. *Methods:* Voided urine samples from 266 consecutive patients with imagistic suspicion of bladder cancer were collected to perform the NMP22® BladderChek® test. The nuclear matrix protein 22 (NMP22) levels were measured by a lateral flow immunochromatographic qualitative assay, using 10 U/ml as the cut-off value. After this patients underwent transurethral resection of bladder tumors (TUR-BT) followed by histological grading and tumor staging for a proper and optimal patient management. Sensitivity, specificity and positive predictive value of the NMP22® BladderChek® test were defined for different tumoral stage and grade. *Results:* Two hundred thirty-eight of the 265 patients had urothelial malignancies (76 pTa, 81 pT1, 37 pT2, 32 pT3, 12 pT4, 27 pT0; 118 G1, 54 G2, 64 G3). The sensitivity was 0.629 [0.612; 0.629] for the NMP22® BladderChek® test while the specificity was equal to 1 [0.851; 1]. Positive predictive values was 1 [0.973; 1], and the negative predictive value was 0.235 [0.200; 0.235]. *Conclusions*: The results demonstrate that the even if the NMP22® BladderChek® is an easily applied test, giving diagnostic findings within 30 min, cannot be recommended for screening or surveillance in clinical routine use in non muscle invasive bladder cancer because of its poor sensitivity.

Keywords: Bladder cancer; Cystoscopy; Urine marker; NMP 22.

Introduction

The urothelial bladder cancer is a major public health issue, represented by a heterogeneus goup of tumors, with oncological outcomes that depend on early diagnosis followed by prompt intervention [1].

Cystoscopy is the standard investigation for diagnosis and monitoring of bladder tumors allowing the physician to visualize the bladder wall directly. The sensitivity of cystoscopy is very good, but the invasive nature of the procedure prompted physicians to search for adjacent or alternative methods for monitoring the disease [1,2]. For the urological practice, considering the amount of follow-up cystoscopies, especially urine markers for recurrent disease would be useful [3]. Several tumor markers have been tested for the detection and monitoring of bladder cancer [4].

NMP-22 marker shows the urinary level of NUMA protein which is a nuclear matrix protein involved in cell proliferation by interfering with the transmission of genetic information and stimulating cell adhesion [3]. NMP22 is a nuclear matrix protein and is an important regulator of mitosis. In tumour cells, the nuclear mitotic apparatus is elevated and NMP22 is released from cells in detectable levels. Papers published so far recommends further studies with careful patient selection to identify the patient population that might benefit from the NMP22® BladderChek® test.

The aim of the present study was to assess the sensitivity and specificity of the NMP22® BladderChek® test in our group of patients with urothelial bladder cancer, according to the tumoral stage and grade and to identify the patient categories that might benefit from the NMP22® BladderChek® test.

Material and Method

Voided urine samples from 266 patients with imagistic suspicion of bladder cancer were collected to perform the NMP22® BladderChek® test. Patients with urinary tract infection, urolithiasis and intravesical treatment were excluded. Urine was collected before any urological instrumentation complying recommendations of the product. The nuclear matrix protein 22 (NMP22) levels were measured by a lateral flow immunochromatographic qualitative assay, using 10 U/ml as the cut-off value. This is a relatively simple test that is carried out by pipetting four drops of urine harvested 2 hours before. The electrophoretic migration of proteins to the right of the line C (control) emphasizes validity of the test (Figure 1). Migration to the line T supports the existence of tumoral material and raises suspicions of urothelial cancer.

Figure 1. The NMP22 Bladder Check OncoScan test (blank test – left hand picture and positive test – right hand picture)

All these patients with bladder cancer suspicion underwent transurethral resection of bladder tumors (TUR-BT) followed by histological grading according to 1973 WHO grading (G1: well differentiated, G2: moderately differentiated, G3: poorly differentiated) [5], and tumor staging in accordance with 2009 TNM classification of urinary bladder cancer (Non-invasive papillary carcinoma pTa, Tumour invades subepithelial connective tissue pT1, Tumour invades muscle pT2, Tumour invades perivesical tissue pT3, Tumour invades any of the following: prostate, uterus,

vagina, pelvic wall, abdominal wall pT4) [6,7] for a proper and optimal patient management.

Statistical Analysis

Quantitative variables were summarized as mean and standard deviation for normal distributed data; otherwise the median and 25th (Q1) and 75th (Q3) percentiles were reported. Qualitative variables were summarized using percentages and associated 95% confidence intervals computed using formula similar with the methods presented by Jäntschi and Bolboacă [8,9]. Mann-Whitney test was applied to compare different groups whenever variables were not normal distributed. Z-test for two proportions was applied for comparing two groups.

Taking the NMP22 as a diagnosis test a series of statistical parameters were computed on 2×2 contingency table along with associated 95% confidence interval: overall fraction correct (accuracy, AC), miss-classification rate (probability of a wrong classification as positive of negative cases, MCR), sensibility (Se), specificity (Sp), positive and negative predictive values (PPV, NPV), Youden's index (YJ, difference between the true positive rate and the false positive rate; take values in the range [-1; +1]; a perfect test will have a value of +1), and number needed to diagnose (NND, number of patients that need to be examined in order to correctly detect one person with the disease).

The summaries of data were conducted with Microsoft Excel. Estimators calculated on 2×2 contingency table along with associated 95% confidence intervals were computed using dedicated software [10] at a significance level of 5%.

Results

A sample of 265 patients were included in the study; 35 women (13%, 95%CI [9; 18]) and 230 men (87%, 95%CI [82; 91]). The percentage of women included in the sample was significantly lower compared to the percentage of men (Z-test: Statistics = 35.82, $p < 0.0001$). The median of age for the whole sample was 66 years (interquartile range [56; 72]), with a value of 65.5 years for female (interquartile range [55.3; 72.5]) and of 66 years for male (interquartile range [56; 72]).

Classification of tumors according to the deep of invasion is presented in Table 1 while tumor grading according to gender is presented in Table 2.

Table 1. Tumor's classification according to the deep of invasion

Class	Female: n (% [95%CI])	Male: n (%[95%CI])	Z-test (p)
pTa	12 (43 [25; 64])	64 (30 [24; 37])	1.3163 (0.1881)
pT1	9 (32 [14; 53])	72 (34 [28; 41])	-0.2127 (0.8315)
pT2	4 (14 [4; 32])	33 (16 [11; 21])	-0.2846 (0.7760)
pT3	3 (11 [4; 28])	29 (14 [10; 19])	-0.4703 (0.6382)
pT4	0 (0 [0; 11])	12 (6 [3; 10])	-3.6310 (0.0003)

95%CI = 95% confidence interval;
pTa: Non-invasive papillary carcinoma; pT1: Tumor invades subepithelial connective tissue;
pT2: Tumor invades muscularis; pT3: Tumor invades perivesical tissue; pT4: Tumor invades adjacent organs

Table 2. Tumor grading according with gender

Tumor gradding	Female: n (% [95%CI])	Male: n (% [95%CI])	Z-test (p-value)
Well differentiated	19 (68 [47; 87])	99 (48 [41; 55])	2.1115 (0.0347)
Moderately differentiated	6 (21 [7; 39])	48 (23 [17; 29])	-0.2430 (0.8080)
Poorly differentiated	3 (11 [4; 28])	56 (27 [21; 34])	-2.4001 (0.0164)
Undifferentiated	0 (0 [0; 11])	5 (2 [1; 5])	-2.0122 (0.0442)

95%CI = 95% confidence interval

One hundred and forty-nine patients had positive NMP22 test. The positivity of NMP22 test according to tumor deep of invasion is presented in Table 3.

Table 3. NMP22 vs tumor invasion

Class	NMP22=+: n (%)	NMP22=-: n (%)	Z-test (p-value)
pTa	43 (29)	32 (28)	0.1786 (0.8583)
pT1	41 (28)	40 (35)	-1.2128 (0.2252)
pT2	28 (19)	9 (8)	2.6894 (0.0072)
pT3	30 (20)	2 (5)	3.8900 (0.0001)
pT4	7 (5)	5 (4)	0.3914 (0.6955)
pT0	0 (0)	27 (23)	-5.8571 (< 0.0001)
Total	149	115	

pTa: Non-invasive papillary carcinoma; pT1: Tumor invades subepithelial connective tissue;
pT2: Tumor invades muscularis; pT3: Tumor invades perivesical tissue; pT4: Tumor invades adjacent organs;
pT0 No malignancy

The risk of false negative NMP22 test, calculated as the ratio of patients with negative NMP22 results reported to total number of patients for each class of tumor invasion is presented in Figure 2.

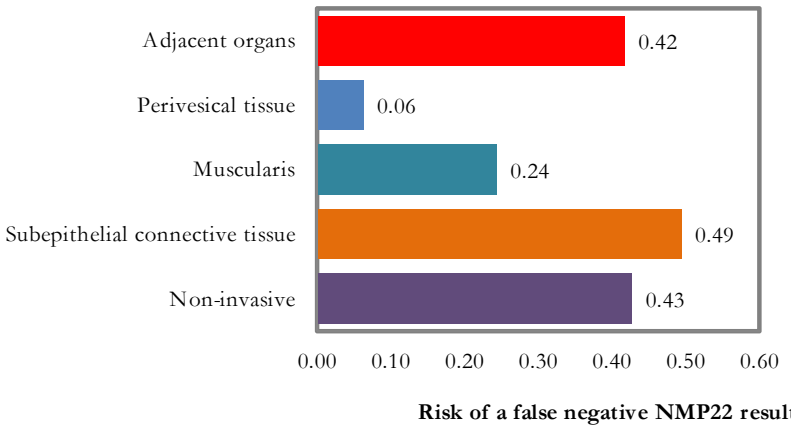

Figure 2. Risk of false negative NMP22 result according to tumor invasion

The positivity of NMP22 test according to tumor grading is presented in Table 4.

Table 4. NMP22 vs tumor grading

Tumor grading	NMP22+: n (%)	NMP22-: n (%)	Z-test (p-value)
Well differentiated	66 (45)	51 (44)	0.1619 (0.8714)
Moderately differentiated	33 (22)	21 (18)	0.8093 (0.4183)
Poorly differentiated	45 (30)	14 (12)	2.3084 (0.0210)
Undifferentiated	3 (2)	2 (2)	0 (0.9999)
No tumoral evidence	1 (1)	27 (23)	-5.4882 (< 0.0001)
Total	148	115	

The risk of false negative NMP22 test, calculated as the ratio of patients with negative NMP22 results reported to total number of patients for each class of tumor grading is presented in Figure 3.

The NMP22 diagnostic test was analyzed for the whole sample and the results are presented in Table 5. Furthermore, the analysis was conducted according to tumor invasion and the results are presented in Table 6, as well as according to tumor grading and the results are presented in Table 7.

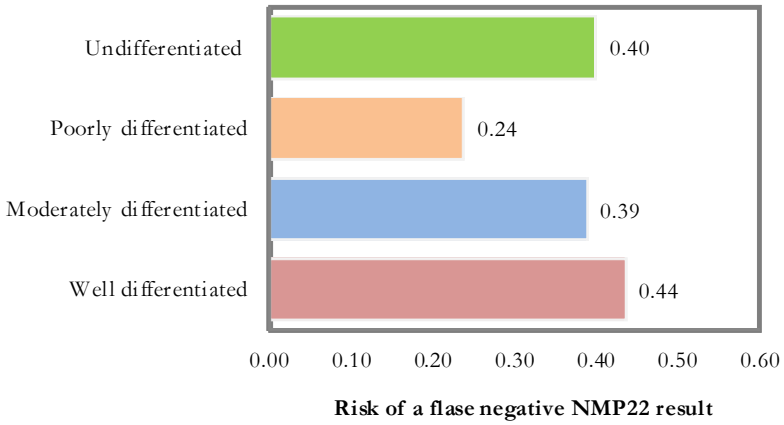

Figure 3. Risk of false negative NMP22 result according to tumor grading

Table 5. NMP22 diagnostic test assessment: whole sample

	Tumor +	Tumor -	Total
NMP22+	149	0	149
NMP22-	88	27	115
Total	238	27	265

Overall Fraction Correct = 0.667 [0.636; 0.667]; Miss-classification rate = 0.333 [0.333; 0.364]
Sensibility = 0.629 [0.612; 0.629]; Specificity = 1 [0.851; 1];
Positive predictive value = 1 [0.973; 1]; Negative predictive value = 0.235 [0.200; 0.235]
Youden's J = 0.629 [0.463; 0.629]; Number needed to diagnose = 1.591 [1.591; 2.161]

Table 6. NMP22 diagnostic test assessment: tumor invasion

pT1	Tumor+	Tumor-	Total
NMP22+	41	0	41
NMP22-	40	27	67
Total	81	27	108

AC = 0.630 [0.560; 0.630]; MCR = 0.370 [0.370; 0.440];
Se = 0.506 [0.460; 0.506]; Sp = 1 [0.860; 1];
PPV = 1 [0.908; 1]; NPV = 0.403 [0.347; 0.403];
YJ = 0.506 [0.320; 0.506]; NND= 1.976 [1.976; 3.129]

pT2	Tumor+	Tumor-	Total
NMP22+	28	0	28
NMP22-	9	27	36
Total	37	27	64

AC = 0.878 [0.785; 0.878]; MCR = 0.122 [0.122; 0.215];
Se = 0.757 [0.663; 0.757]; Sp = 1 [0.907; 1];
PPV = 1 [0.877; 1]; NPV = 0.804 [0.729; 0.804];
YJ = 0.757 [0.570; 0.757]; NND = 1.321 [1.321; 1.754]

pT3	Tumor+	Tumor-	Total
NMP22+	30	0	30
NMP22-	9	27	29
Total	32	27	59

AC = 0.864 [0.760; 0.864]; MCR = 0.136 [0.136; 0.240];
Se = 0.769 [0.682; 0.769]; Sp = 1 [0.874; 1];
PPV = 1 [0.874; 1]; NPV = 0.750 [0.655; 0.750];
YJ = 0.769 [0.556; 0.769]; NND = 1.300 [1.300; 1.800]

pT4	Tumor+	Tumor-	Total
NMP22+	7	0	7
NMP22-	5	27	32
Total	12	27	39

AC = 0.872 [0.732; 0.872]; MCR = 0.128 [0.128; 0.268];
Se = 0.583 [0.356; 0.583]; Sp = 1 [0.899; 1];
PPV = 1 [0.610; 1]; NPV = 0.844 [0.758; 0.844];
YJ = 0.583 [0.254; 0.583]; NND = 1.714 [1.714; 3.930]

pTa	Tumor+	Tumor-	Total
NMP22+	43	0	43
NMP22-	32	27	59
Total	75	27	102

AC= 0.686 [0.613; 0.686]; MCR = 0.314 [0.314; 0.387];
Se = 0.573 [0.523; 0.573]; Sp = 1 [0.861; 1];
PPV = 1 [0.973; 1]; NPV = 0.458 [0.394; 0.458];
YJ= 0.573 [0.384; 0.573];
NND = 1.744 [1.744; 2.602]

Overall Fraction Correct = AC; Miss-classification rate = MCR; Sensibility = Se; Specificity = Sp; Positive predictive value = PPV; Negative predictive value = PNV; Youden's J = YJ; Number needed to diagnose = NND; pTa: Non-invasive papillary carcinoma; pT1: Tumor invades subepithelial connective tissue; pT2: Tumor invades muscularis; pT3: Tumor invades perivesical tissue; pT4: Tumor invades adjacent organs

Table 7. NMP22 diagnostic test assessment: tumor grading

Grade1	Tumor+	Tumor-	Total
NMP22=poz	67	0	67
NMP22=neg	51	27	78
Total	118	27	145
AC = 0.648 [0.595; 0.648]; MCR = 0.352 [0.352; 0.405]; Se = 0.568 [0.535; 0.568]; Sp = 1 [0.856; 1]; PPV = 1 [0.942; 1]; NPV = 0.346 [0.296; 0.345]; YJ = 0.568 [0.391; 0.568]; NND = 1.761 [1.761; 2.559			

Grade2	Tumor+	Tumor-	Total
NMP22=poz	34	0	34
NMP22=neg	21	27	48
Total	55	27	82
AC = 0.744 [0.655; 0.744]; MCR = 0.256 [0.256; 0.345]; Se = 0.618 [0.552; 0.345]; Sp = 1 [0.865; 1]; PPV = 1 [0.893; 1]; NPV = 0.563 [0.487; 0.563]; YJ = 0.618 [0.418; 0.618]; NND = 1.618 [1.618; 2.394];			

Grade3	Tumor+	Tumor-	Total
NMP22=poz	46	0	46
NMP22=neg	14	27	41
Total	60	27	87
AC = 0.839 [0.756; 0.839]; MCR = 0.161 [0.161; 0.244]; Se = 0.767 [0.707; 0.767]; Sp = 1 [0.867; 1]; PPV = 1 [0.922; 1]; NPV = 0.659 [0.571; 0.659]; YJ = 0.767 [0.574; 0.767]; NND = 1.304 [1.304; 1.743];			

Undifferentiated	Tumor+	Tumor-	Total
NMP22=poz	4	0	4
NMP22=neg	2	27	29
Total	6	27	33
AC = 0.939 [0.805; 0.939]; MCR = 0.061 [0.061; 0.195]; Se = 0.667 [0.296; 0.667]; Sp = 1 [0.918; 1]; PPV = 1 [0.444 1]; NPV = 0.931 [0.854; 0.931]; YJ = 0.667 [0.213; 0.667]; NND = 1.500 [1.500; 4.689]			

Overall Fraction Correct = AC; Miss-classification rate = MCR; Sensibility = Se; Specificity = Sp;
Positive predictive value = PPV; Negative predictive value = PNV; Youden's J = YJ;
Number needed to diagnose = NND;
Grade1: well differentiated; Grade2: moderately differentiated; Grade3: poorly differentiated; Grade4: Undifferentiated

Discussion

In Eastern Europe the age standardized incidence rate of bladder cancer is 14.7 per 100,000 for males and 2.2 per 100,000 for females. This represents an incidence among men 5-6 times higher than among women [1,2]. The percentage of women included in the sample was significantly lower compared to the percentage of men, 35 women to 230 men, numbers that corresponds with this data.

Most studies evaluated the NMP 22 bladder tumor marker for screening of symptomatic patients or categories at risk. Although NMP22 revealed some tumors omitted by cystoscopy, have not proved effective, providing poor overall specificity (40-87.3%) and sensitivity (49.5-65%) [11].

Grossman et al. [12] investigated the capability of this test in detecting malignancy in 1331 patients with risk factors of bladder cancer. They found sensitivity of 55.7% and specificity of 85% for NMP22 compared with 15.8% and 99.2% for cytology.

In a recent study [13], NMP22 was compared with photodynamic diagnosis (PDD) as the gold standard. The authors found sensitivity of 65% and specificity of 40% for NMP22, and 44% and 78%, respectively, for voided cytology.

In our study we performed the NMP22 test only in patients with imagistic or endoscopic suspicion of bladder tumor achieving a specificity of 100% and a sensitivity of 62.9%. Although the literature describes a significant percentage of false positive tests [4], which can lead to unnecessary investigations in our lot of patient no false positive responses was found.

In our study, we evaluated this urinary marker according to tumoral stage and grade, to identify the group of patients who could benefit from this marker in the diagnostic or postoperative monitoring, in order to decrease the amount of follow-up cystoscopies.

A tumor marker is effective when detects a lesion at an early stage when the treatment significantly improves the prognosis. If a marker can diagnose urotelial bladder cancer whilst confined to the urotelium (pTa, pT1), could fulfilled this criterion [14].

Around 70% of patients with bladder tumors initially presents with non muscle invasive disease (pTa, pT1) [15].

Unfortunately the poor sensitivity of NMP 22 in our patients with superficial tumors, 58% pTa, 50% pT1, is not sufficient for using it as a diagnostic or follow-up method for non muscle invasive bladder tumors. For these tumors early diagnosis could reduce recurrence rates and morbidity by

treating smaller tumors [14].

Detection of the disease at an early stage improves the prognosis for a minority of tumours, around a quarter, with the invasive phenotype (G3, pT2, pT3) [16].

High grade tumors should be detected early and the percentage of tumors missed should be as low as possible. The diagnostic tool for these patients is cystoscopy, and cytology for invisible lesions.

In our group of patients the NMP 22 test shows the highest sensibility in those patients with invasive phenotype: 75.7% in pT2, 76.9% in pT3 and 76.7% in G3 patients. For these reasons the optimal approach for these patients could include besides uretrocystoscopy and cytology the NMP 22 test as an adjunct to detect invasive disease. The tumors of the invasive pathway (a quarter of all bladder tumors) would benefit from early diagnosis and treatment [17,18].

The positive predictive value of a diagnostic test is directly related to the prevalence of disease in the population for which the test is being employed. Lotan and Shariat and the NMP22 Study Group aimed to provide the estimates for the PPV of NMP22 among populations at different risks for development of bladder cancer. The PPV was 51.2% in case of gross haematuria and 70.6% in patients with a combination of smoking and gross haemauria. The PPV of any diagnostic test is not fixed but is dependent on the disease prevalence in the population to which the test is applied [19]. The patients from our study had a high suspicion of bladder cancer (imaging or cystoscopy) so our PPV exceeds 80% in every group of patients.

The risk of false negative NMP22 test calculated as a ratio is highest in superficial well differentiated tumors 0.49 for pT1, 0.43 for pTa, 0.39 for G2, 0.44 for G1. Negative test results could dissuade physicians from referring patients for proper evaluation and may provide false reassurances for the patient while the tumor progress in dimension, depth and grade.

The current generation of markers is promising but can not be used as a single diagnostic tool in diagnostic or surveillance and lower the frequency of urethrocystoscopy [11].

Conclusions

The results demonstrate that the NMP22® BladderChek® is an easily applied test, giving diagnostic findings within 30 min. However in non muscle invasive bladder tumors the test demonstrates poor sensitivity and, therefore, cannot be recommended for screening or surveillance in daily clinical routine use.

The patients who initially presents with invasive disease or progress in muscle invasive during surveillance might benefit from the NMP22® BladderChek® test.

Currently, no single marker can guide us in surveillance and lower the frequency of urethrocystoscopy.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

The research activity of Zoltán Attila MIHÁLY, M.D. was supported by the European Commission and by the Romanian Government through the project POSDRU/88/1.5/S/58965 "Doctoral Scholarships for increasing competitiveness in the medical and pharmaceutical field". "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca is a Partner institution in this Financial Contract.

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