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The value of the NMP22 test for superficial bladder cancer diagnosis and follow-up

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ABSTRACT

Objective: In this study, we investigated the efficacy of nuclear matrix protein 22 (NMP22) in the diagnosis and surveillance of bladder cancer.

Material and methods: Patients with hematuria or who applied for cystoscopic control of proven bladder cancer were prospectively enrolled in this study. Routine cytologic examination and NMP22 test were performed on the voided urine sample obtained before the cystoscopy. The patients who had been diagnosed with bladder cancer were categorized according to stage, grade, number, size of the tumor and risk of the disease. Then the diagnostic performance of the NMP22 and the cytology test, alone or in combination, were evaluated separately using ROC curves in the diagnosis and surveillance groups.

Results: A total of 87 patients (87/136) were investigated because of hematuria. The sensitivity, specificity, positive and, negative predictive values, and positive likelihood ratio (LR+) of the NMP22 test were 70, 80, 68, 81, and 3.42%, respectively. While, the sensitivity, specificity, positive and, negative predictive values, and positive likelihood ratio (LR+) of the cytology examination were 27, 96, 82, 68, and 7.36%, respectively. There were 49 patients in the bladder cancer group. The sensitivity, specificity, positive, and negative predictive values and positive likelihood ratio (LR+) of the NMP22 test in these patients were 33, 76, 31, 78 and 1.37%, respectively. The sensitivity, specificity, positive and, negative predictive values, and positive likelihood ratio (LR+) of the cytology examination were 25%, 97%, 75%, 80% and 9.25, respectively.

Conclusion: NMP22 test can be used as an adjunctive tool for the detection of bladder cancer, but its diagnostic performance is limited in surveillance when used alone or in combination with a cytology examination.

Key words: Bladder cancer; cytology; detection; NMP22; surveillance; tumor marker.

Introduction

Bladder cancer ranks fifth among the most frequently detected cancers. The first population based data demonstrate that bladder cancer is not the only most frequently seen urological cancer among men in Turkey, but also it is the most prevalent cancer type among all cancer types.^[1] Dependent on the histological grade and/or stage of the tumor, recurrences, and disease progression are observed in 50-90, and 10-50% of the cases, respectively.^[2]

Nowadays, in the diagnosis, and follow-up of the patients with bladder tumor, cytology, and cystoscopy (rigid or flexible) are main diagnostic tools.^[3] Sensitivity of cytology is dependent on degree of differentiation of the tumor from the normal tissue, and the interpreter of the results. Sensitivity of cytology is weaker in early stage, and lower grade tumors.^[4]

In the diagnosis, and follow-up of the superficial transitional epithelial cell carcinomas, additional tests are required. Among them nuclear matrix protein 22 (NMP22) is the most frequently studied biomarker. Our aim in this study is to determine the value of NMP22 test in the diagnosis of bladder tumor, and follow-up of the patients diagnosed as superficial bladder tumor.

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Material and methods

The study was initiated after the Ethics Committee approval (date: 01.02.2008; decree #: 42/K) of the Istanbul Medeniyet University Faculty of Medicine was obtained. Among patients who consulted to our Clinics of Urology between January 2008, and December 2008 a total of 204 cases with hematuria or those with established diagnosis of bladder cancer who presented for a control visit were included in this prospective study after their approval was obtained. Patients with indwelling urethral catheter, urinary infection, and other genitourinary malignancies, those receiving active chemotherapy, immunotherapy or radiotherapy or cases who had undergone endoscopic urinary intervention or urinary system surgery were excluded from the study. The remaining 136 patients were included in the study. The patients in the first group consisted of patients with microscopic hematuria whose urinalysis revealed ≥ 3 erythrocytes per field of vision (Group 1, n=87). The second group comprised of patients previously diagnosed as bladder cancer who consulted for a control visit (Group 2, n=49). Detailed medical histories including age, gender, smoking status, profession, laboratory, andd imaging information were obtained from all patients.

Following upper urinary system imagings (ultrasound/intravenous urography/contrast -enhanced computed-tomography) of all patients were obtained, urine samples were collected for NMP22 test, and cytologic analysis. Then cystoscopic examinations were performed. Cytologic analysis was done by the hospital pathologist. The results were reported as benign, suspicious, and malign. Results indicated as benign, and suspicious were accepted as negative outcomes. In cases where apparent malignant cells were seen, cytology was reported as positive.^[4,5]

Dimensions (<3 cm or \geq 3 cm) or number of (single or multiple) tumors or tumor suspect areas detected during cystoscopy were recorded. Patients with tumors or tumor suspect area(s) were resected through transurethral route under general or spinal anesthesia. Staging of the tissues with malignant characteristics was based on the criteria recommended by 2002 American Joint Committee on Cancer (AJCC)/Tumor size-Lymph Nodes affected-Metastases (TNM), and their grading was performed according to 1973 WHO criteria.^[6,7] Cases with benign cystoscopy or biopsy results, despite positive NMP22 or cytology results were considered to be false-positive if their upper system images were within physiologic limits.

Statistical analysis

Number Cruncher Statistical System (NCSS) 2007 package

program (NCSS, Utah, USA) was used for statistical analysis. In the evaluation of data, descriptive statistical methods (mean, standard deviation, and frequency distributions), and for the comparison of qualitative data chi-square test were used. Sensitivity, specificity, positive, and negative cut-off values, likelihood ratio (LR-) of precision, and positive test results were calculated individually, and in combination.

Results

Group 1 consisted of 60 (69%) male, and 27 (31%) female patients with a mean age of 60 (21-98 yrs) years. Histopathological evaluation detected 33 (37.9%) cases with bladder cancer.

In Group 1, sensitivity rate (70%) of NMP22 test was higher than that (27%) of the cytological analysis. On the contrary, cytology was more specific than NMP22 test (96 vs. 80%, respectively). When NMP22 test, and cytology results were evaluated in combination as for sensitivity, and specificity, combined specificity of these two tests was lower (78%), but their combined sensitivity was higher (73%) than NMP22 test, and cytology results per se (Table 1).

Group 2 consisted of 42 (86%) male, and 7 (14%) female patients with a mean age of 64.75 (22-82 yrs) years. Histopathological evaluation detected bladder cancer in 12 (24.5%) cases.

In Group 2, sensitivity rate (33%) of NMP22 test was found to be higher than that (25%) of the cytological analysis. Specificity rate of cytology (97%) was higher than that (76%) of NMP22 (76%). When NMP22 test, and cytology results were evaluated in combination as for sensitivity, and specificity, combined specificity of these two tests (76%) was equal to that of NMP22 test, but lower than that of cytology. However combined sensitivity rate (42%) was higher than that of NMP22 test, and cytology per se (Table 1).

When two groups were evaluated in combination, sensitivity (60%), and specificity (78%) rates of NMP22 test in Group 2 were lower than those of Group 1, but higher than those of the patients in Group 2. Sensitivity (35%), and specificity (97%) rates of cytology were found to be higher than those of Group 1 patients. While combined sensitivity rate was higher than , but equal to that of Group 2 patients (Table 2).

When patients with detected bladder cancer were categorized based on the size, number, grade, and stage of the tumor, then sensitivity rate of NMP22 test was found to be increased with tumor size, and stage, while higher sensitivity of cytology was observed in all categories (Table 3).

Discussion

Grossman et al.^[8] found sensitivity, and specificity of cytology as 15.8, and 99.2%, and NMP22 test performed using a bedside NMP22 kit, as 55.7, and 85.7% in 1331 patients without a history of bladder cancer. They indicated that specificity of NMP22 test was lower than that of cytology, but its sensitivity was higher than that of cytology which makes NMP22 test as an adjunct to cystoscopy. In their study, 79 of a total of 1331 patients (5.9%) bladder cancer was detected, however in our study, detection rate was higher (37.9%) in Group 1. This rate is relatively higher when compared with the study results published by Grossman et al.^[8] Our higher rates were attributed to inclusion of patients in our study with only benign pathology. In our study, our cytology results were comparable to the study results published by Grossman et al.^[8], while sensitivity of our NMP22 test results was relatively higher. However, in our study, likelihood ratio of a positive test result was 7.36 for cytology, and 3.42 for NMP22 test which indicates that positive NMP22 test has a lower diagnostic accuracy when compared with the cytology. If we consider that positive cut-off value of NMP22 test is lower

than that of cytology (68, and 82%, respectively), we think that NMP22 test is not superior to cytology in the diagnosis of bladder cancer, but it can be an adjunctive diagnostic tool. In a recent study which enrolled 1609 risky factory employees who were working with a chemical substance containing aromatic amine, diagnostic sensitivity, specificity, negative, and positive predictive values of NMP22 test were 97.2, 28.5, 99, and 12.2%, respectively.^[9]

In a study performed by Tritschler et al.^[5] on 100 patients without previous diagnosis of bladder cancer, sensitivity, and specificity of the NMP22 test, and cytology were found to be 65 vs 44%, and 40 vs. 78%, respectively. The authors concluded that with lower sensitivity, and specificity rates NMP22 could not be recommended in daily practice as a bedside test in the diagnosis, and monitorization of the bladder cancer. However in our study, specificity, and sensitivity of patients in Group 1 were found to be relatively higher

In a study performed by Sarilar et al.^[10] on 64 patients, sensitivity, and specificity of NMP22 test, and cytology were found to be 69, and 45.2%, and 81.8%, and 86.4% respectively. In our study, in a group investigated for hematuria, we obtained values comparable to those found by Sarilar et al.

Table 1. NMP22 test, and cytology results of the patients in Groups 1, and 2								
		Sensitivity	Specificity	PCV	NPV	Accuracy	LR (+)	LR (-)
Group 1								
	NMP22	0.70	0.80	0.68	0.81	0.76	3.42	0.38
	Cytology	0.27	0.96	0.82	0.68	0.70	7.36	0.76
	NMP22+cytology	0.73	0.78	0.67	0.82	0.76	3.27	0.35
Group 2								
	NMP22	0.33	0.76	0.31	0.78	0.65	1.37	0.88
	Cytology	0.25	0.97	0.75	0.80	0.80	9.25	0.77
	NMP22+cytology	0.42	0.76	0.36	0.80	0.67	1.71	0.77
PCV: positive cut-off value; NPV: negative cut-off value; PPV: positive predictive value; LR: likelihood ratio								

Table 2. NMP22 test, and cytology results of the patients in Groups 1, and 2, combined							
	Sensitivity	Specificity	PCV	NPV	Accuracy	LR (+)	LR (-)
NMP22	0.60	0.78	0.57	0.80	0.72	2.73	0.51
Cytology	0.35	0.97	0.80	0.80	0.80	10.71	0.67
NMP22+cytology	0.64	0.77	0.57	0.81	0.73	2.76	0.47
PCV: positive cut-off value; NPV: negative cut-off value; PPV: positive predictive value; LR: likelihood ratio							

Table 3. Sensitivities of NMP22, and cytology based on stage, grade, size, and number of tumors								
	NMP2	2 test	Cytology					
	Test + bladder cancer (n)	Sensitivity (95% CI)	Test + bladder cancer (n)	Sensitivity (95% CI)*				
Stage								
Та	4/12	33.3% (9.9-65.1)	1/12	8.3% (0.2-38.4)				
T1	19/29	65.5% (45.6-82)	8/29	27.5% (12.7-47.2)				
T2	4/4	100% (39.7-100)	3/4	75% (19.4-99.3)				
Grade								
Gr1	1/2	50% (1.2-98.7)	0/2	8.3% (0-84.2)				
Gr2	16/30	53.3% (34.3-71.6)	5/30	16.7% (34.7-56.4)				
Gr3	10/13	76.9% (46.2-94.9)	7/13	53.8% (25.1-80.7)				
Tumor size								
<3 cm	12/27	44.4% (25.5-64.6)	5/27	18.5% (6.3-38)				
≥3 cm	15/18	83.3% (58.5-96.4)	7/18	38.9% (17.3-64.2)				
Number of tumors								
Single	18/29	62% (42.2-79.3)	7/29	24.1% (10.2-43.5)				
Multiple	9/16	56.2% (29.9-80.2)	5/16	31.2% (11-58.7)				
* CI: confidence interval								

In the second study published by Grossman et al.^[11] which included 631 patients with a previous diagnosis of bladder cancer, sensitivity, and specificity of NMP22 test, and cytology were 49.5 vs. 12.2%, and 87.3 vs. 99.6%, respectively. The authors indicated that combined use of NMP22 test, and cystoscopy was important in the detection of tumor recurrences. Compared with the second study published by Grossman et al.^[11] performed on patients with a previous diagnosis of bladder cancer, our sensitivity results were higher for cytology, but lower for NMP22 test.

Kumar et al.^[12] found sensitivity, and specificity of NMP22 test, and cytology in 131 patients with previous diagnosis of bladder cancer as 85 vs. 41%, and 77 vs. 96%, respectively. They indicated that when they combined results of NMP22 test, and cytology, then sensitivity climbed to 91%, but in cancer patients they couldn't attain 9% sensitivity. They also concluded that NMP22 test might not be an alternative to cystoscopy, but it might increase diagnostic accuracy of cystoscopy. Schalke et al.^[13] used NMP22 test, and cytology in the monitorization of 391 patients with previous diagnosis of bladder cancer, and reported sensitivity, and specificity of NMP22 test, and cytology as 51 vs. 35%, and 96 vs. 97%, respectively. In our study, sensitivity rates of NMP22 test, and cytology in Group 2 were lower, but comparable to those found in the study by Kumar et al.^[12].

When we compared our study results with other similar studies performed in our country, in our study (Group 2) rates of sensitivity, and specificity for NMP22 test were relatively lower, in another study sensitivity of both NMP22 test, and cytology was found to be lower than that observed in our study.[14-16]

Ayyıldız et al.^[16], evaluated 93 patients with or without previous diagnosis of bladder cancer in combination, and sensitivity, specificity, positive, and negative cut-off values of NMP22 test were noted to be 65, 56, 65, and 56%, respectively. However in our study specificity, and negative cut-off values of NMP22 were comparatively higher, while sensitivity, and positive cutoff values were relatively lower.

Miyanaga et al.^[17], Boman et al.^[18], Sanchez-Carbavo et al.^[19], and Del Nero et al.^[20] indicated that sensitivity of NMP22 test increases with the size, grade, and stage of the tumor. In our study, when patients with detected bladder cancer were categorized according to the size, number, grade, and stage of the tumor, apart from number of tumors, sensitivity of NMP22 test was found to increase with size, grade, and stage of the tumor which all substantiates the results of Boman et al.^[18], Sanchez-Carbayo et al.^[19], Miyanaga et al.^[17] and Del Nero et al.^[20].

Generally speaking in our study which included a total of 136 patients, sensitivity, and specificity of NMP22 test, and cytology were comparable to those reported in the literature (60 vs. 35%, and 78 vs. 97%, respectively). Likelihood ratios of positive test results (LR+) of NMP22 test, and cytology were found to be 2.73, and 10.71 which indicate that diagnostic accuracy of a positive NMP22 test result is nearly one fourth of cytology. When NMP22 test was combined with cytology, sensitivity, specificity, positive, and negative cut-off values, and likelihood ratio of a positive test result (LR +) were 64, 77, 57, 81%, and 2.76, respectively. Based on these results, it can be said that combination of NMP22 test, and cytology does not confer an additional advantage.

In conclusion, NMP22 test is not an alternative to cystoscopy in the diagnosis of bladder cancer, but it can be used as an adjunctive tool. If we think that the physicians expect 100 % sensitivity, and specificity from the tumor marker they use in the patients' follow-up, diagnostic value of NMP22 test both per se or in combination with urine cytology for the determination of tumor recurrence is very limited. NMP22 test has a limited role in the diagnosis and follow-up of bladder cancer, and further studies are needed on this subject.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medeniyet University, School of Medicine (02.01.2008 42/K).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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