

# Comparison of Nuclear Matrix Protein-22 and Urine Cytology in Diagnosing Bladder Cancer

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## ABSTRACT

**Background:** Urine cytology (UC) is a classic marker used to detect bladder malignancy through urine examination microscopically at the presence of malignant transitional cells that are released. UC is also used to evaluate recurrence after past treatment. A new method that is simpler, faster and easier is by measuring protein in urine produced by malignant cells, namely nuclear matrix protein-22 (NMP-22). The aim of this study was to compare the diagnostic value of NMP-22 and UC to histopathological biopsy in diagnosing bladder carcinoma and to evaluate whether the NMP-22 test could be used for bladder carcinoma screening and recurrence monitoring.

**Methods:** Diagnostic tests on 24 suspected bladder malignancies were performed by taking urine samples for NMP22 examination and UC. Sensitivity, specificity, positive predictive value and negative NMP-22 and UC on histopathological biopsy were analyzed.

**Results:** Positive results were obtained in 21 (87.5%) and negative in 3 (12.5%) NMP22 examinations. The sensitivity, specificity, positive and negative predictive values of NMP-22 on histopathological biopsy were 95%; 67%, 95%, 67%. Sensitivity, specificity, positive predictive value and negative UC on histopathological biopsy were 38.1%; 100%, 100%, 18.8%.

**Conclusions:** NMP-22 sensitivity is higher than UC in diagnosing bladder carcinoma. NMP-22 can be used for bladder carcinoma screening and for recurrence monitoring.

## INTRODUCTION

Bladder cancer is the fifth most common malignancy in the world, the second most common tumor of the urinary tract and the second leading cause of death of patients with malignant urinary tract (1-3). The prevalence of bladder malignancy in Indonesia in 2008 was 49,531 cases, and the prevalence of Indonesian women suffering from bladder malignancy in 2002 was 5.8% (6). Based on its superficial transitional cells, bladder carcinoma can be treated only with transurethral resection of bladder tumor (TURBT), with and without chemotherapy (4,5). So, early diagnosis of bladder cancer determines the success of therapy.

Cystoscopy and UC are effective diagnostic methods for diagnosing superficial bladder carcinoma.

Cystoscopy is a gold standard examination to identify bladder carcinoma, as well as a modality to diagnose and monitor bladder carcinoma. UC is a classic marker used to detect malignancy. Microscopic UC is used to identify the presence of malignant and abnormal cells found in the urine of patients with bladder cancer. UC examination is very specific and non-invasive as a complement to cystoscopy. This examination has a fairly good sensitivity to detect bladder cancer with a high degree of malignancy but has very low sensitivity for cancers with low malignancy. In addition, the accuracy of cytology diagnosis is very dependent on the level of expert pathology that examined it (4,7,8,9).

Non-invasive, objective and accurate biomarkers are needed not only for primary detection but also for monitoring. NMP-22 is a test that uses a specific nuclear

matrix protein (NMP) to detect bladder tumors in the urine. Nuclear matrix protein is part of the internal skeletal structure of the cell nucleus which was first proposed by Berezney and Coffey (1974). This protein plays an important role in regulating DNA replication and cell division. One component of the matrix protein is nuclear mitotic apparatus (NuMA) or NMP-22. This protein is involved in the distribution of cell chromatin to derived cells during mitosis and is found in the nucleus matrix of all cells. NMP-22 is released from the nucleus of cancer cells after cell apoptosis and is detected in urine (2,5,7,10). In normal conditions, NMP-22 is found at low levels (mean 2.9 ng/ml) while patients with bladder carcinoma are found to have 25 times higher level of NMP-22 (5,7,9).

The purpose of this study was to determine the diagnostic ability of NMP-22 compared with UC by using histopathological biopsy as the standard for diagnosing carcinoma of the bladder and evaluating whether the NMP-22 test can be used for screening and monitoring of bladder carcinoma.

## METHODS

The study was conducted at Academic Medical Center Dr.Kariadi Hospital Semarang. The study design was a diagnostic test using a cross sectional method between August 2010 - April 2011. Samples were patients with suspected bladder malignancy who were treated at Dr. Kariadi Hospital Semarang.

Urine cytology was performed examination using Shandon Cytospin, a tool used to deposit cells in glass objects using centrifugal force so that it is expected to get a representative smear preparation.

### Urine Sampling Method

Morning urine specimens, central emission were collected and divided into 2 aliquots for urine cytology examination and NMP-22. The NMP-22 test is carried out according to the procedure contained in the NMP-22 BladderCheck test kit (Matriech, inc). Examination uses the principle of immunochromatography, with monoclonal antibodies. Four drops of urine were inserted into the well and the results were read after 30 minutes. Urine cytology examination was carried out in the Anatomical Pathology Department, evaluated by qualified pathologist. The results were classified as malignancy, suspected malignancy, no malignant cells, non-specific and normal inflammatory processes. No malignant cells, non-specific and normal inflammatory processes were considered negative.

Patients underwent cystoscopy by qualified urologist, and if a suspicious tumor or lesion is seen, patients will be biopsied. The results of biopsy with cystoscopy were considered as the gold standard to determine the true positive.

## Statistics

Data was processed using SPSS 17.0 for Windows. Data was processed using descriptive inferential (distribution, frequency, mean, standard deviation). Diagnostic test was done using 2x2 table then sensitivity, specificity, positive predictive value and negative predictive value were calculated.

## RESULTS

The total count of the samples was 24. It consisted of 5 (20.8%) women and 19 (79.2%) men. The average age of the study subjects was  $60.92 \pm 12.90$  and the mostly were at the age of 64 years old (65.2%). Of the 24 urine samples examined by NMP-22, 21 (87.5%) were positive and the remaining 3 (12.5%) were negative.

UC examination results were 8 (33.3%) positive and 16 (66.7%) negative. Histopathological biopsy results showed that 14 (58.3%) were transitional cell carcinomas with various levels, 3 (12.5%) were urothelial carcinoma, 3 (12.5%) were adeno-carcinoma, squamous cell carcinoma, urothelial carcinoma papillary, non-specific inflammation and prostate hyperplasia amounting to 1 (4.17%), respectively. The total number of bladder carcinomas was 22 (91.7%) and non bladder carcinoma was 2 (8.3%). (Table 1)

**Table 1.** Subjects characteristics

Parameter	(n=24)	
Subject	Men	19 (79.2%)
	Women	5 (20.8%)
Age (average $\pm$ SD)	60.92 $\pm$ 12.90	
NMP-22	Positive (+)	21 (87.5%)
	Negative (-)	3 (12.5%)
Urine cytology	Positive (+)	8 (33.3%)
	Negative (-)	16 (66.7%)
Biopsy results (histopathology)	Carcinoma	22 (91.7%)
	Non Carcinoma	2 (8.3%)

**Table 2.** Comparison between NMP-22 examination results and histopathological biopsy

	Biopsy result (histopathology)		Total	
	+	-		
NMP-22				
Test	+	20	1	21
	-	1	2	3
Total		21	3	24

This study showed that NMP-22 gave more positive results (87.5%) compared to UC (33.3%). This is in accordance with research conducted by Craig Zippe, et al who obtained 100% results for NMP-22 in detecting bladder cancer while UC was only 55.5% (11). (Table 2 and Table 3)

**Table 3.** Comparison between the results of urinary cytology examination with histopathological biopsy

		Biopsy result (histopathology)		Total
		+	-	
Urine Cytology	+	8	0	8
	-	13	3	16
Total		21	3	24

The sensitivity and specificity of NMP-22 were 95% and 67%. The same results were obtained for positive predictive values and negative predictive values of 95% and 67%. UC sensitivity was 38.1% and specificity was 100%. The positive and negative estimates were 100% and 18.8%, respectively (Table 4).

**Table 4.** Diagnostic value of NMP-22 and urine cytology

Variable	Sensitivity (%)	Spesificity (%)	PPV (%)	NPV (%)
NMP22	95	67	95	67
Urine Cytology	38,1	100	100	18,7

\*PPV: positive predictive value; NPV: negative predictive value

## DISCUSSION

Several studies have shown varying sensitivity and specificity of NMP-22. The average sensitivity of NMP-22 was 66% (range 47% - 89%) and specificity 75% (range 60% -84%). Sensitivity increases according to increasing tumor stage and grade. Reported UC sensitivity on average was 10% - 40%. Other literature mentions that the sensitivity ranges between 20% - 53% with an average of 34%, and specificity of 83% - 99.7% with an average of 99% (2,12).

This study only differentiated bladder carcinoma and non bladder carcinoma, so that NMP-22 sensitivity was higher than its specificity. Another factor is due to inadequate number of samples. The low sensitivity of UC can be caused by several things such as making poor preparations, poor staining, difficulty in detecting tumors with low gradations due to their similarity to inflammation, as well as the factors of expertise of the pathologist.

In this study one sample gave false positive result. False positives on NMP-22 results can occur in situations of acute inflammation of the urinary tract including cystitis, prostatitis (43.8%), kidney stones or blisters (83.3%), other genitourinary cancers such as prostate and kidney (20.7%), even with false-positive ileus reaching 100% (10,13). This is due to the fact that there is a process that requires rapid epithelial cell turnover. In this study false positive results were probably caused by inflammation. Ponsky, et al. stated that exclusion of the above can increase the specificity and positive predictive value of the NMP-22 test while the sensitivity remains high.

It seems that NMP-22 test was easier to be accepted by patients. The examination time is relatively short (30 minutes) and can be interpreted easily so that the patient management becomes faster. The test was also suitable for low-grade tumors which are difficult to be detected by UC.

## CONCLUSIONS

NMP22 sensitivity was better than UC (95% vs 38.1%) in diagnosing bladder malignancy. NMP-22 can be used to screen bladder malignancy, especially in patients with high risk factors and also to monitor recurrence of diseases.

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