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Evaluation of the urinary nuclear matrix protein (NMP22) as a tumour marker in bladder cancer patients

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Introduction. The aim of this study was to evaluate the clinical use of the urinary nuclear matrix protein 22 (NMP22) assessment in bladder cancer patients.
Patients and methods. 98 patients with bladder cancer were examined. All tumours were verified histopathologically. Urine samples were collected before cystoscopy and assayed for NMP22 levels with Diagnostic Products Corporation tests. Urine samples of 15 healthy volunteers served as controls. For the statistical analysis the Mann-Whitney test was employed.
Results. Urine NMP22 concentrations were significantly higher ($p<0.0003$) in patients with bladder cancer than in controls. No significant differences between the NMP22 concentrations in patients with complete remission and patients with recurrent disease were found.
Conclusions. Urinary NMP22 is a potential marker for the diagnosis of bladder cancer, but not for the differentiation between disease-free patients and those with recurrent disease.

Ocena przydatności oznaczania NMP22 w moczu jako markera nowotworowego u chorych na raka pęcherza

Wstęp. Celem pracy było zbadanie, czy oznaczanie markera nowotworowego NMP22 może być pomocne w monitorowaniu chorych na raka pęcherza.
Pacjenci i metody. Do badania zakwalifikowano 98 chorych z potwierdzonym histologicznie rakiem pęcherza. Próbki moczu pobierano przed cystoskopią. Stężenie NMP22 w moczu oznaczano zestawami firmy DPC. Własne normy ustalono w oparciu o oznaczenia stężeń NMP22 w grupie 15 zdrowych osób. Do analiz statystycznych zastosowano test Mann-Whitney'a.
Wyniki. Porównując rozkład stężeń NMP22 w grupie chorych na raka pęcherza z grupą referencyjną osób zdrowych, stwierdzono znamiennie wyższe stężenia u osób chorych ($p<0,0003$). Nie stwierdzono znamiennych różnic pomiędzy stężeniami NMP22 u chorych z całkowitą remisją, a stężeniami tego markera u chorych ze wznową.
Wnioski. Oznaczanie markera NMP22 może być pomocne tylko w diagnostyce różnicującej osoby z rakiem pęcherza od osób zdrowych, natomiast nie różnicuje chorych w remisji od chorych z nawrotem choroby.

Key words: bladder cancer, cystoscopy, nuclear matrix protein 22 (NMP22), tumour markers
Słowa kluczowe: rak pęcherza, cystoskopia, NMP22, markery nowotworowe

Introduction

Tumour markers have been employed for the diagnosis and monitoring of cancer patients for many years. In urology, PSA is assessed in patients with prostate cancer and AFP and hCG in patients with testicular germ cell tumours. These markers are characterised by relatively high sensitivity and specificity, although they do fail to meet the criteria of "an ideal marker", and until now, the urinary bladder cancer marker has not been identified.

Cancer of the urinary bladder shows a distinctive prevalence in men. The standardised mortality index classified the bladder cancer as the second most common malignancy of the genito-urinary tract [1].

The diagnosis and monitoring of patients with bladder cancer are based upon an invasive technique, the cystoscopy. A urinary marker is extensively searched for as a potential, easily-accessible, low-cost screening tool. The identification of a specific and sensitive marker could limit the number of cystoscopies performed for monitoring and follow-up purposes. In the recent studies telomerase, the bladder tumour antigen (BTA) and nuclear matrix protein-22 (NMP22) [2-9] were examined in the urine of bladder cancer patients. The authors assessed not only the relationships between the markers

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and the clinico-pathological features of the tumours but also the possibility of applying the markers for monitoring of patients [2, 6, 7, 10]. The results of numerous studies on NMP22 were contradictory and difficult to compare due to the different cut-off levels applied.

In the study presented here, we set our own normal urine NMP22 range and aimed to assess whether there is a significant relationship between urine NMP22 concentrations and the results of urinary bladder cystoscopic examinations.

Materials and methods

Ninety eight patients with pathologically confirmed urinary bladder cancer were studied after they had undergone TURT (TransUrethral Resection of Tumor, one procedure in 36 and numerous procedures in 62 patients). Patients with a second primary malignancy, with any signs of infection and/or with lithiasis were excluded from the study. In 94 cases the stage of the disease was determined, and the grade of malignancy in 95 cases. Patient characteristics is summarised in Table I.

Table I. Patient characteristic

Number of patients:	98
Men	84
Women	14
Median of age and range:	
Men	67 (36-96)
Women	63.5 (38-89)
T:	
Ta	39/94
Tis	2/94
T1	42/94
T2	9/94
T3	2/94
Histology:	
G1	28/95
G2	59/95
G3	8/95
Clinical stage:	
CR (clinical remission)	79
PD (progressive disease)	19

Urine samples were obtained just before control cystoscopy and stored in stabilizing solution at – 20°C until analysed. NMP22 concentration was assessed with the DPC kits following the instructions of the manufacturer. Normal NMP22 range was set in 15 healthy volunteers.

The non-parametric Mann-Whitney test was employed to examine the distribution of NMP22 concentrations in patients and controls and to compare the results obtained in patients in remission and with progressive disease.

Results

Urine NMP22 concentrations were found significantly higher in patients with bladder cancer than in healthy subjects ($p<0.0003$, Figure 1). Also patients in remission as well as those with recurrent disease presented significantly higher urine NMP 22 concentrations than healthy controls ($p<0.0003$ and $p<0.001$, respectively, Figure 2, 3).

No statistically significant differences of NMP22 concentrations were found between patients in remission and those with recurrent disease (Figure 4).

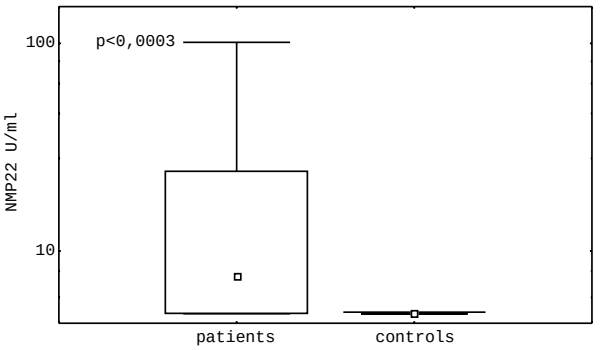

Figure 1. Comparison of NMP22 concentrations in healthy subjects (controls) and bladder cancer patients

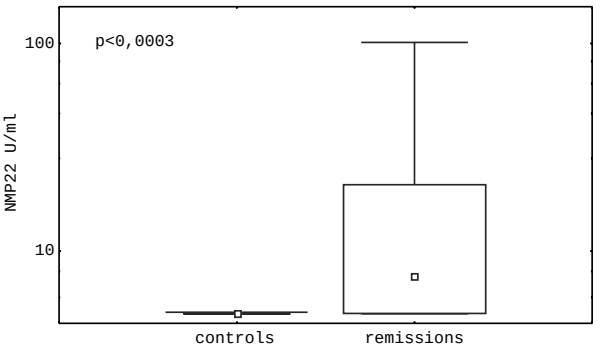

Figure 2. Comparison of NMP22 concentrations in healthy subjects (controls) and disease-free bladder cancer patients

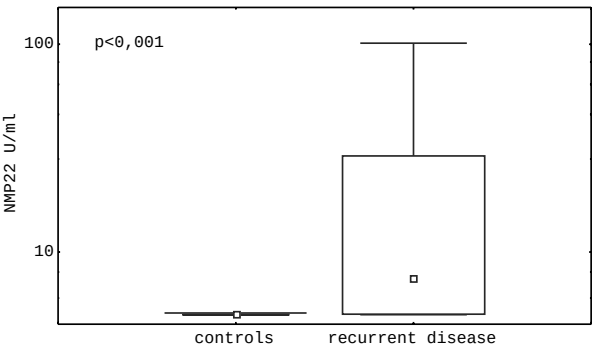

Figure 3. Comparison of NMP22 concentrations in healthy subjects (controls) and bladder cancer patients with recurrent disease

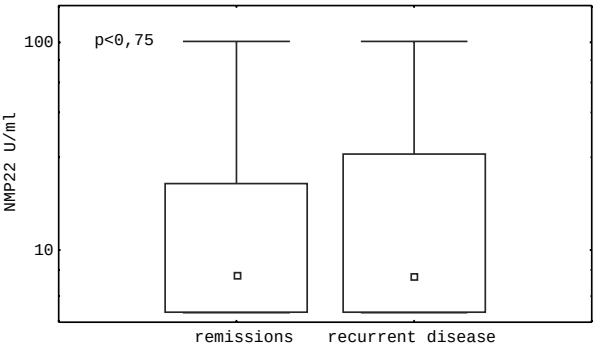

Figure 4. Comparison of NMP22 concentrations in bladder cancer patients in remission and with recurrent disease

Out of 79 patients with cystoscopically confirmed remission, urine NMP22 concentrations fell within the normal range in 36, thus correlated with their clinical status. In the remaining 43 patients, despite cystoscopic remission, the NMP22 concentrations were increased. Of these 43 patients, 5 presented recurrent disease within the following 4-12 months.

In 19 patients with cystoscopically confirmed recurrent disease urine NMP 22 level was increased in 10 cases, while in 9 patients NMP22 concentrations fell within the normal range, thus did not relate to their clinical status.

Discussion

Bladder cancer morbidity increases with age. It is a frequently recurrent disease, and the risk of repeated recurrences is increased in patients who had experienced recurrence within the first year following diagnosis [11, 12]. Due to the growing incidence and frequent recurrence of this malignancy, as well as because of the relatively high costs of cystoscopy applied as a routine diagnostic and monitoring method, there is a need for less costly and non-invasive diagnostic tools. Tumour markers are likely candidates to serve this purpose.

In our study, in order to assess the relationship between cystoscopy results and NMP22 urine concentrations, we have paid a special attention to the followed-up patients. In both groups of patients, in remission and with recurrent disease, concentrations of NMP22 did in fact confirm the cystoscopic findings in only half of the cases. Similar results have been reported by other authors [13, 14].

Some authors suggest that increased NMP22 concentrations may have a prognostic value [2]. In our study, the observation period was too short to conclude on the prognostic value of urine NMP22 levels in bladder cancer patients. However, in 5 patients who had developed recurrent disease in 4-12 months after complete remission assessed by cystoscopy, the elevated NMP22 concentrations preceded the relapse.

A number of authors have attempted to set the optimal cut-off level in order to increase specificity. Thus the sensitivity of the applied markers was decreased. This would enable their better relevance in monitoring of treatment [7, 15]. Glas et al. [8] in an extensive paper summarise the results of a multi-centered long-term study on the sensitivity and specificity of BTA, NMP22 and telomerase and they do not recommend the use of any of these markers in clinical practice due to their limited specificity. Some other authors recommend the use of a combination of NMP22 assessment and cytology examination in bladder cancer patients [7].

Conclusions

In conclusion, both the literature data and our own results show that the analysis of urine NMP22 concentrations cannot reduce the number of cystoscopies performed in bladder cancer patients. This parameter may only provide an additional information for differentiating between healthy individuals and patients with bladder cancer.

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