

Estimation of usefulness of monitoring tissue polypeptide antigen – TPA-M concentrations in the effectiveness of surgical treatment of urinary bladder cancer

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Abstract

BACKGROUND: Of all cancer tumours, urinary bladder cancer is the fourth most common in men and the seventh in women. The aim of this work was to answer the question whether tissue polypeptide antigen (TPA-M) determination in patients after electroresection of urinary bladder cancer can be used to establish the probability of tumour recurrence.

MATERIAL AND METHODS: The research included 98 patients, all of whom had undertaken electroresection of urinary bladder tumour (TURBT), which enabled its removal, and then estimation of malignancy and progression stage according to the international TNM scale. The mean age was 62.7 years. All patients had blood samples taken to determine TPA-M and then underwent routine cystoscopy examination.

RESULTS: The patients with tumour recurrence (60, mean age 64 ± 10) had TPA 30.2 ± 4.3 U/l, the patients without recurrence (38, mean age 61.3 ± 11) had TPA-M 26.2 ± 3.18 U/l ($p > 0.1$). Taking the TPA-M threshold point 85 U/l as normal, true-positive results were 16.3%, true-negative were 31.6%, false-positive results were 7.1% and false-negative were 44.9%. The ROC curves with the calculated area under them are the measurement of the diagnostic estimation of TPA-M concentrations in specificity and sensitivity categories.

CONCLUSIONS: For the examined group the calculated P was 0.45. If P value is under 0.5 it is considered that the test should not be used in diagnosing recurrence of urinary bladder cancer.

Key words: TPA-M, monitoring, urinary bladder cancer

Introduction

Urinary bladder cancer is one of the most often occurring malicious tumours. Initially urinary bladder cancer develops intraepithelium, however most first detected cancers take the form of superficial papilloma, which if not treated infiltrates into the submucosa and muscular layer as well as into neighbouring organs.

Transurethral resection of tumour (TURBT) is a basic method of treatment of superficial urinary bladder cancer. For patients with tumour resection, the cystoscopic check-ups were performed three months after operation in order to establish a probability of tumour recurrence. Staging and grading of the tumour were estimated after TURBT by histopathological examination. To diagnose the possibility of recurrence, for patients with tumour resection cystoscopic check-up was performed after three months. After resection continual cystoscopic check-ups are necessary. The aim

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is to exclude any recurrence or progression appearing as an increase of tumour local progression. No reliable tumour markers are available for urinary bladder cancer [1].

Bjorklund discovered tissue polypeptide antigen (TPA) in cancer tissue. This is a complex of polypeptide fragments of cytokeratin 8, 18 and 19 circulating in blood, appearing commonly in healthy epithelium as well as in epithelium-derived tumours. TPA is a single protein of 43 kDt molecular mass. This is protein of cellular and cytoplasmic membrane synthetised mainly in stage S of cellular divisions. It has two specific epitopes of cytokeratin 18 which are also found in tissue polypeptide special antigen (TPS), that is why TPA was considered to be a proliferation marker (its second name is prolifigen), but now it is known as an apoptosis marker.

It possesses also 33 nonspecified epitopes, some with epitopes of cytokeratin 8, 18 and 19. In urinary bladder tumour cells TPA exists mostly on the tumour surface in proliferation places — group of cells attacking surrounding tissue [2, 3]. Serum TPA is a clinically appreciated marker of monitoring patients with tumours originating from epithelial cells, e.g. neoplasma of lungs [4], breast [5], large intestine and urinary bladder. Its physiological concentration in serum should not exceed 85 U/l.

The aim of this research was to find out whether monitoring TPA-M in patients after electroresection of urinary bladder cancer is useful in the detection of the probability of tumour recurrence.

Material and methods

98 patients were taken under research, all of whom underwent electroresection of urinary bladder cancer (mean age 62.7 years). During the three-month period no cytostatic drugs were administered. In the case of tumour recurrence the second check-up allowed the next histopathological examination to be performed. TPA was estimated during routine check-ups three months after the operation (TUR). Blood samples were taken before cystoscopy. The progression stage and malignancy of the tumour TUR was estimated in the case of recurrence after the next TUR. Serum TPA was determined using the Prolifigen TPA-M IRMA kit supplied by Byk-Sangtec. In this kit monoclonal antibodies against TPA are used for immunological reaction. Radioactivity of obtained complexes was measured in two-detector gamma Wallac-Wizard-1470 radiation meter.

Statistical analysis

The values obtained are expressed as a geometric mean and a geometric standard deviation. Differences between distribution

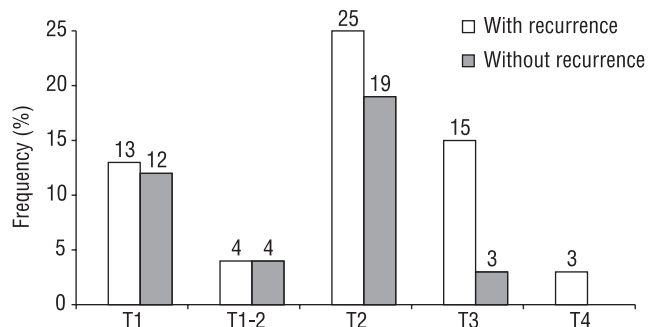


Figure 1. The percentage of patients according to the progression stage of urinary bladder cancer.

groups were assessed using the Kolmogorov-Smirnov two-sample test. P values of < 0.05 were considered statistically significant. ROC curve is presented of the TPA depicting the true-positive rate (sensitivity) v. the false-positive rate. The area under the curve was calculated with the Wilcoxon statistic [6–8].

Results and discussion

All patients were divided into two subgroups depending on the result of check-up cystoscopy: the patients with recurrence (60 people, mean age 64 ± 10) and patients without recurrence (38 people, mean age 61.3 ± 11). The percentage of patients according to the progression stage of urinary bladder cancer in both subgroups is presented in Figure 1. Mean geometrical concentration of TPA-M in the group of patients with recurrence of cancer was 30.2 ± 4.3 U/l and in the group of patients without recurrence of cancer it was 26.2 ± 3.18 U/l, the difference not being statistically significant. Mean geometrical concentration of TPA-M together with geometrical standard deviation according to the progression stage of urinary bladder cancer in both subgroups are presented in Table 1.

Taking the physiological norm for TPA-M as 85 U/l, true-positive results make up 16.3%, true-negative 31.6%, false-positive 7.1% and false-negative 44.9%. The measurement of the complete assessment of the diagnostic precision of TPA-M concentration in monitoring the effectiveness of treatment using the TUR method in categories of specificity and sensitivity is the evaluation of ROC curve and calculation of the area under the curve (Fig. 2). For the studied group of patients this value was $P = 0.45$.

Analysing the percentage of patients in subgroups differing in the progression stage of urinary bladder cancer, it can be said

Table 1. Concentration of TPA according to the progression stage of urinary bladder cancer

Stage infiltration	Geometric means with geometric standard deviation TPA [U/l]				
	T1	T1-2	T2	T3	T4
With recurrence (n = 60)	30.4 ± 3.12	10.2 ± 6.65	23.2 ± 4.44	44.36 ± 4.15	161.6 ± 1.71
Without recurrence (n = 38)	25.5 ± 3.25	32.5 ± 2.03	24.7 ± 3.77	32.32 ± 1.76	

Stage of infiltration of the urinary bladder: T1 — epithelium, T2 — stroma interstitium, T3 — muscular layer, T4 — perivesical fatty tissue, infiltration stages T1–T4 with recurrence has been obtained after the second electroresection, whereas T1–T4 without recurrence are after the first electroresection

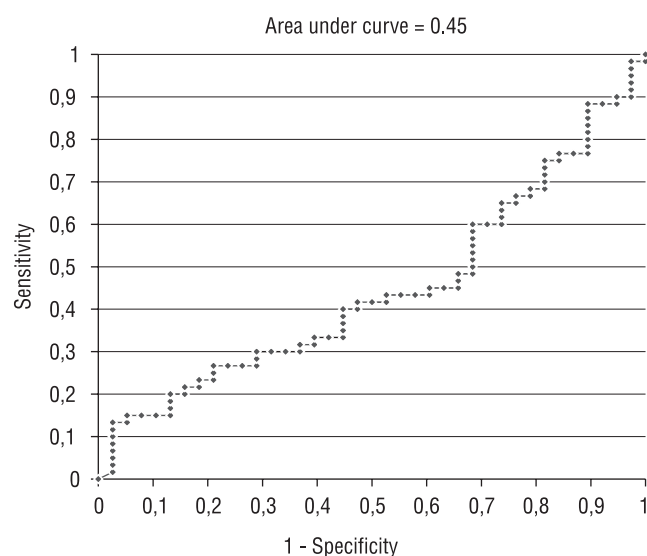


Figure 2. The receiver-operating characteristic (ROC) curve for retrospective urinary bladder cancer detection based on serum TPA-M.

that most patients, both cured and with recurrence, were with the cancer infiltrating the stroma (T2). They are also the largest number of patients of the urology department treated with electroresection because of urinary bladder cancer.

Analysing mean geometrical values of TPA-M concentrations in subgroups of patients both with and without recurrence no functional dependence was found between obtained concentrations of TPA-M and progression stages of urinary bladder cancer. In patients both with and without recurrence in whom cancer in T1, T1/2, T2 stage was diagnosed, mean geometrical TPA-M concentrations oscillated between 10 and 30 U/l. The lack of a clear difference in TPA-M concentrations between patients both with and without recurrence confirms the lack of a statistically significant difference between patients with and without recurrence. The highest mean geometrical TPA-M concentrations twice exceeding the physiological norm were found in patients with recurrence in whom urinary bladder cancer of T3/4 stage was diagnosed. Similar results can be found in literature [1, 9–11]. Estimating diagnostic usefulness of TPA-M estimation in monitoring the effectiveness of treatment of urinary bladder cancer using the TURP method in the category of the number of true-positive or false-negative results, taking threshold point as 85 U/l, it was shown that the percentage of true-positive results was low (16.3%) and of false-negative results was high (44.9%). The question is whether for patients monitored for the effectiveness of treatment of urinary bladder cancer a different threshold point for TPA-M test than for TPA test should be taken. The results published by Bennink show that TPA-M test is more precise and has clinical use in the follow-up of bladder cancer patients with poorly differentiated superficial, locally advanced tumour or systemic disease after cura-

tive or palliative therapy [12]. The study of the ROC curve and calculation of the value of the area under the curve below 0.5 shows unambiguously that the value of serum TPA-M concentration estimated three months after TURP cannot be the basis of the prognosis of the progression stage in cases of low progression stage tumours [13].

Conclusions

Estimation of TPA-M at check-ups in patients after urinary bladder cancer electroresection is useless for establishing the probability of tumour recurrence.

High TPA concentration was however found in patients with advanced stage of the disease (T3–4).

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