Eur J Cancer, Vol. 29A, No. 4, pp. 570–571, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Tissue Polypeptide-specific Antigen: A Discriminative Parameter Between Prostate Cancer and Benign Prostatic Hypertrophy

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The serum concentration of the cell proliferation marker TPS (tissue polypeptide-specific antigen) was compared with the tumour marker PSA (prostate specific antigen). PSA was found elevated in 50% of the benign prostatic hypertrophy (BPH) patients, in 88% of the patients with active prostate cancer and in 40% of the patients who were in an inactive phase. For TPS these values were 6, 34 and 0%, respectively. The metastatic progression was biochemically mirrored by pronounced elevations of PSA and TPS. These data suggest that TPS might be a valuable adjunct in the diagnosis and follow-up of patients with prostate cancer, especially in differentiating benign from malignant deterioration of the disease.
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INTRODUCTION

PROSTATE-SPECIFIC ANTIGEN (PSA) has been documented as a valuable parameter in the diagnosis and follow-up of patients with prostate cancer. Though a useful marker during follow-up with respect to monitoring the effect of surgery and other therapy in the course of the disease, its value for the early detection and staging of prostate cancer is not known. The specificity of the marker is limited since in a marked percentage (21–68%) of patients with benign prostatic hypertrophy (BPH), PSA is also elevated, though to a lesser extent than in the case of the malignant counterpart [1–3].

Tissue polypeptide-specific antigen (TPS) is measured by an *in vitro* monoclonal immunoradiometric assay for the measurement of M3, a specific epitope of tissue polypeptide antigen (TPA). TPA is synthesised during late S- and G_2-phase of the cell cycle and is released immediately after mitosis. Since the release of TPA is a function of cell division, TPA differs from the variety of other substances collectively referred to as tumour markers [4]. Monoclonal mapping of TPA revealed two essential and 33 non-essential epitopes [5]. Monoclonal antibody M3, with kappa chains and an affinity constant above 10^{11} mol/l was selected for the commercial TPS assay. TPS is proposed as an indicator of tumour proliferation rather than tumour burden. We investigated the use of TPS in conjunction to PSA to assess its ability to discriminate BPH from prostatic cancer.

PATIENTS AND METHODS

Sera were collected from patients seen at three institutes: University Hospital Groningen, University Hospital Dijkzigt, Rotterdam and the Dutch Cancer Institute, Amsterdam. In total 48 patients with BPH, 64 patients with prostate cancer (PC) with active disease, and 20 PC patients with inactive disease were studied. The subgroup with active PC included patients with a primary process and those undergoing relapse, progression and/or metastases. The subgroup with inactive PC was defined on the basis of clinical complete remission, having no demonstrable tumour activity and no recorded metastases. The primary diagnosis in all cases was made by prostatic histology.

TPS was measured using the TPS-IRMA kit (Beki Diagnostics, Sweden), which has a reported cut-off upper limit of 70 U/l.

PSA was assayed using an in-house ELISA. In short, rabbit-anti-PSA antibody (Dakopatts, Denmark) was bound to the wells of microtitre plates. Standards and serum samples were incubated at 37°C for 45 min. Non-bound material was expelled and after washing, biotin-labelled rabbit-anti-PSA was allowed to react at 37°C for 45 min. Streptavidinhorseradish peroxidase (Amersham) was then added and incubated at 37°C for 30 min. Reaction products were visualised with *o*-phenylenediamine as substrate and absorbance was then measured at 492 nm.

Our assay results correlated with the PSA-Abbott-IMx [regression coefficient (r.c.): 0.968], to the PSA-Hybritech-Tandem-EIA (r.c.: 0.988) and the PSA-DPC Milenia-IRMA (r.c.: 0.994). 4 μg/l was considered the upper limit for normal levels.

RESULTS

The overall results are given in Table 1. 50% of the BPH patients had PSA levels greater than 4 μg/l, whereas TPS was greater than 70 U/l in only 6%. In the group of patients with active prostatic carcinoma PSA was > 4 μg/l in 88% and TPS was > 70 U/l in 34%. All PC patients with an elevated TPS level also had a PSA value above 4 μg/l. Thus, the sensitivity of PSA+TPS for detecting PC is 34% and the specificity (in excluding BPH) is 98%. These figures change to 42 and 92%, respectively, when the cut-off level for TPS is set at 30 U/l. From these data the following predictive values can be calculated for these markers in active PC. At a level of 4 μg/l PSA has a positive predictive value of 70% (PPV) and a negative predictive

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Revised 20 Aug. 1992; accepted 21 Sep. 1992.

Table 1. Elevations of PSA and TPS in BPH and PC

	BPH (n=48)	Active PC (n=64)	Inactive PC (n=20)
PSA>4 μg/l	24 (50%)	56 (88%)	8 (40%)
Median	53 μg/l	470 μg/l	63 μg/l
Range	5–487 μg/l	5–8010 μg/l	9–166 μg/l
TPS>70 U/l	3 (6%)	22 (34%)	0 (0%)
Median	169 U/l	404 U/l	—
Range	84–303 U/l	85–1808 U/l	—
PSA>4 μg/l and TPS>70 U/l	1 (2%)	22 (34%)	0 (0%)

PSA, Prostate specific antigen; TPS, tissue polypeptide specific antigen; BPH, benign prostatic hypertrophy; PC, prostate cancer.

value of 75% (NPV). At a level of 70 U/l for TPS, these values are 88 and 52%, respectively.

In Table 2 the patients with active PC are subdivided with respect to localised or metastatic expression. PSA is elevated in 76% and TPS in 16% of the cases with localised PC, in the patients with metastatic disease values are 95 and 46%, respectively.

When the TPS results are interpreted at an arbitrary cut-off value of 30 U/l, 59% of the patients with metastatic disease had elevated TPS levels, whereas still only 16% of the patients with localised disease had a TPS value greater than 30 U/l.

DISCUSSION

PSA is a reliable parameter for the follow-up of patients with PC [6]. However, since this marker is also found elevated in the serum of patients with non-cancerous prostatic disease like BPH, the predictive value of PSA is limited. In our study PSA was found elevated in 88% of the patients with active cancer of the prostate, whereas in BPH patients this marker was elevated in 50%, which is in line with other reports [6, 7].

Therefore, a marker which could discriminate between both presentations of the disease would be most helpful in addition to the clinical findings.

Table 2. PSA and TPS elevations in active PC

	Prostatic carcinoma	
	Localised (n=25)	Metastatic (n=39)
PSA>4 μg/l	19 (76%)	37 (95%)
Median	102 μg/l	659 μg/l
Range	6–710 μg/l	5–8010 μg/l
TPS>70 U/l	4 (16%)	18 (46%)
Median	242 U/l	440 U/l
Range	85–580 U/l	86–1808 U/l

PSA, Prostate specific antigen; TPS, tissue polypeptide specific antigen.

TPA is made by dividing cells [4, 5]. The monoclonal TPS assay is advocated to monitor cell multiplication in cancer patients. The concept of the use of this marker is to measure the degree of cell proliferation in cancer patients. As a consequence, TPS should not be related to tumour burden, not be present in necrotic cells nor be released by stable tumours. Based on this concept it might be possible that TPS could help in distinguishing benign from malignant disease.

Our study supports this hypothesis since in patients with BPH TPS was only elevated in 6% of the cases, in contrast to the 34% elevations in the group with active PC. The metastatic progression of the disease is reflected in more pronounced elevations of TPS (46 vs. 16% for localised PC), as well as for PSA (95 and 76%, respectively). No TPS elevations were encountered in those patients whose tumours were stable, being in line with the assumption that stable tumours have normal TPS values but still can show supranormal values for the tumour markers (like PSA).

In general practice most clinicians would exclude BPH in favour of carcinoma at PSA levels greater than 20 μg/l. In our patient population 88% of the BPH patients had levels below this arbitrary limit, whereas still 22 of 64 patients with known (active) PC had levels below 20 μg/l. On the contrary, TPS was normal in all BPH patients and elevated in 4 of these 22 carcinoma patients, giving additional support for an active process in these patients with a marginally elevated PSA level.

Therefore, we think that the simultaneous determination of PSA and TPS gives complementary information in differentiation and follow-up of patients with benign/malignant prostate disease. When both markers are elevated this is strong evidence for active metastatic PC. However, it should be stressed that PSA is more sensitive for indicating a relapse in a patient with known PC. On the other hand, when PSA is elevated and TPS is normal, we are most likely dealing with the localised form of PC or BPH and these patients may be candidates for a treatment with curative intention.

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Acknowledgements—We thank Laboratorium-service Benelux for the supply of reagent (TPS-) kits.