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FROM THE DEPARTMENT OF UROLOGY, KAROLINSKA HOSPITAL, STOCKHOLM, AND THE DEPARTMENT OF SURGERY, MORA HOSPITAL, MORA, SWEDEN.

SERUM TUMOUR MARKERS IN HUMAN PROSTATIC CARCINOMA

The value of a marker panel for prognostic information

P. EKMAN and A. LEWENHAUPT

Abstract

Serum from 102 patients was analysed with regard to its content of prostatic acid phosphatase (PAP), prostate specific antigen (PSA), neopterin, osteocalcin, thymidine kinase, C-reactive protein, and of tissue polypeptide antigen (TPA). The levels were related to the short-term survival (death from cancer within 3 years) and compared by statistical means. A comparison was also made with tumour grade and stage and the presence or not of metastatic lesions. In this study neopterin was found to be most closely related to the clinical course followed by tumour grade, thymidine kinase and PSA. When all these four variables were in the equation no other parameter added any information of statistical signficance. The importance of selecting appropriate cut off values ('normal' vs 'elevated') when using the serum marker as a prognostic indicator is also discussed.

Key words: Prostate cancer, serum markers, prognosis.

Tumour markers in serum can be used for several purposes: to detect disease, to follow pro- or regression of disease and to reflect the biological activity of the tumour and, hence, act as a prognostic marker. As far as prostatic carcinoma is concerned the second of these points is fairly uncontroversial and will not be discussed further. The value of using prostate tumour markers in health screening surveys will be addressed in detail in other parts of this publication. In this report we, therefore, concentrate on the prognostic information which may be obtained from measuring serum markers in prostate cancer.

The natural course of prostatic cancer is highly unpredictable and the treatment alternatives vary; from multimodality regimens including radical surgery, radiotherapy and adjuvant chemo- and endocrine treatment to no therapy at all. Any marker reflecting the biological activity of the tumour should be of value to select the optimal treatment in the individual case. In recent years several such markers have been introduced and tested, some of which have been discussed by us before (1–3).

When considering the marker level from a prognostic point of view, also the degree of elevation is of importance (4, 5). It should be observed that marker kits are primarily designed for detection purposes. The recommended cut-off levels between normal and elevated values are based on a healthy control group not suffering from the disease to be tested for. If the test is to be used as a prognostic indicator the basis should be a comparison within a diseased population, i.e. comparing the levels in prostatic cancer patients with good prognosis to prostate cancer patients with poor prognosis. Up to a certain limit it is found that a higher cut-off value has to be selected to efficiently predict a rapid deterioration of the disease. Such adjustments of the cut-off levels can be made with only minor increase in the number of false negative subjects (5).

Probably one single marker will not suffice to act as a reliable indicator of the biological activity of the individual cancer. Possibly, though, the accumulated information from a limited number of markers might provide the necessary information (2, 6). We herein report on a statistical comparison of the value of seven different serum tumour markers, as compared with tumour grade and stage plus presence of metastases in predicting the short-time survival in human prostate cancer.

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Material and Methods

From a series of 102 patients, serum was collected at the time of diagnosis, before onset of any treatment, and analysed with regard to its content of 7 different tumour markers. All patients were followed for at least 3 years. Tumour grade as estimated by cytological examination of fine-needle aspiration biopsies and tumour stage as estimated by digital rectal examination was also registered. The presence or not of skeletal metastates as demonstrated by means of bone scan was also studied with regard to the relation to short-term prognosis (death from prostate cancer within 3 years).

Prostatic acid phosphatase (PAP, Hoechst, AG, Frankfurt am Main, West Germany), and C-reactive protein (CRP, Sophar, Brussels, Belgium), which reflects the proliferative activity of the tumour, were analysed by ELISA techniques. Prostate specific antigen (PSA, Diagnostic Prod. Inc., Los Angeles, USA), neopterin (Henning AG, Berlin, Germany), a substance which is increased in serum as a sign of an evoked immune response, osteocalcin (INC, Stillwater, Minnesota, USA) a gla-protein which seems to indicate an increased osteoblastic activity, thymidine kinase (Sangtec, Bromma, Sweden) which signals an enhanced proliferative activity, were all analysed by radioimmuno assays (RIA). Also the non-specific tumour marker, tissue polypeptide antigen (TPA, Sangtec, Bromma, Sweden), was tested by means of a RIA-technique, since this marker in a previous study performed superior to PAP (1).

The extent, to which the cut-off levels had to be adjusted to provide optimal information in predicting death in prostatic cancer within 3 years, is shown in Table 1. As can be seen the cut-off level for PSA had to be changed from 10 to 50 μg/l (4) and PAP from 1.6 to 10.0 μg/l (5).

Table 1

Comparison between recommended cut-off levels for the various markers and the optimal cut-off value to predict short-term survival which was used in this study (5)

Marker	Cut-off	Optimal cut-off
PAP	1.6	10
PSA	10	50
Neopterin	10	12
Osteocalcin	5	5
TPA	100	120
TK	5	5
CRP	20	20

Results and Discussion

In this series all markers studied were able to provide statistically significant information in separating high- from low-risk patients ($p < 0.05$). Also tumour grade and presence of metastases provided information of statistical significance in this respect. In contrast, tumour stage, as evaluated by digital rectal examination, was poorly related to short-term survival. This is somewhat surprising in view of some reports on a close relation between the size of the primary tumour and the risk of metastatic disease (7).

Table 2

Statistical comparison between 7 different serum tumour markers and between tumour grade and stage and the presence or not of metastatic lesions. Calculations have been made with regard to the ability of the parameter to predict death from prostatic carcinoma within 3 years (9)

Variable	χ^2-value	p-values
Neopterin	24.06	0.0000
Metastases*	20.12	0.0000
Thymidine kinase	18.85	0.0000
Osteocalcin	18.06	0.0000
PSA	15.20	0.0001
Tumour grade*	14.79	0.001
C-reactive protein	13.70	0.0002
PAP	8.95	0.0028
Tissue polypeptide antigen	4.38	0.0363
Tumour stage*	0.13	0.7211

*coding: Metastases: no = 0, yes = 1; Tumour grade (WHO) 1 + 2 = 0, 3 = 1; Tumour stage 1 + 2 = 0, 3 + 4 = 1.

Table 2 presents the data obtained in χ^2 analysis. Neopterin appeared to be the most effective marker with a χ^2 value of 24.30. Thereafter, in order of efficiency, came thymidine kinase, osteocalcin, PSA, and CRP.

When carrying out a Cox's stepwise regression analysis (8) and excluding the information embraced by neopterin, tumour grade turned out to be the second most important parameter (9). By eliminating both tumour grade and neopterin in the calculations thymidine kinase became the most informative marker. The fourth most important variable was PSA. When including the information from neopterin, tumour grade, thymidine kinase and PSA in the equation, no other variable added any information of statistical significance (9).

Table 3 compares the four variables selected by means of multivariate analysis. No statistically significant difference was seen favouring one before the other.

When comparing the performance of the markers by

Table 3

Multivariate analysis of the 4 statistically significantly most important parameters in predicting short-term survival in prostatic carcinoma (9)

Variable	χ^2-value	p-value
Thymidine kinase	6.23	0.0126
Neopterin	5.82	0.0159
Tumour grade	4.98	0.0256
PSA	4.60	0.0319

means of life-table analysis and log-rank test a common observation has been that the markers seem to efficiently differ 'benign' from 'malignant' cancers when looked upon after 2 to 4 years. Later the curves have a tendency to approach each other again. This indicates that tumour markers could be of value primarily to predict short-term prognosis. This phenomenon does not necessarily mean any drawback, since the cancers we want to identify are those with an expected rapid progress. We know from experience that all patients will eventually die from their prostatic cancer—provided they are allowed to live long enough. Perhaps, by identifying those with biologically more active tumours, aggressive, multi-modality regimens could be worthwhile starting at an early stage of the disease. We believe that serum tumour markers will become increasingly important in designing the therapeutic strategy in the individual case of human prostatic carcinoma.

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Corresponding author: Dr Peter Ekman, Department of Urology, Karolinska Hospital, P.O. Box 60500, S-104 01 Stockholm, Sweden.

REFERENCES

1. Lewenhaupt A, Ekman P, Eneroth P, Nilsson B, Nordström L. Tissue polypeptide antigen (TPA) as a prognostic aid in human prostatic carcinoma. Prostate 1985; 6: 285–91.
2. Lewenhaupt A, Ekman P, Eneroth P, Eriksson A, Nordström L. Serum levels of prostatic acid phosphatase (PAP), CA-50, neopterin, and of osteocalcin in patients with prostatic carcinoma. Scand J Clin Lab Invest 1985; 45 (Suppl 179): 75–80.
3. Lewenhaupt A, Ekman P, Eneroth P, Eriksson A, Nilsson B, Nordström L. Serum levels of neopterin as related to the prognosis of human prostatic carcinoma. Eur Urol 1986; 12: 422–5.
4. Killian CS, Yang N, Emrich LJ, et al. Prognostic importance of prostate-specific antigen for monitoring patients with stages B2 to D1 prostate cancer. Cancer Res 1985; 45: 886–91.
5. Lewenhaupt A, Ekman P, Eneroth P, Kallner A, Nordström L. Tumor markers in human prostatic carcinoma. On optimation of reference values. Eur Urol 1990; 17: 7–11.
6. Killian CS, Emrich LJ, Vargas FP, et al. Relative reliability of five serially measured markers for prognosis of progression in prostate cancer. J Natl Cancer Inst 1986; 76: 179–85.
7. McNeal JE, Bostwick DG, Kindrachuk RA, Redwine EA, Freiha FS, Stamey TA. Patterns of progression in prostatic carcinoma. Lancet 1986; 1: 60.
8. Cox DR. Regression model and life-tables. J R Statist Soc B 1972; 34: 187–220.
9. Lewenhaupt A, Ekman P, Eneroth P, Nilsson B. Tumour markers as prognostic aids in human prostatic carcinoma. Br J Urol 1990; 66: 182–7.