Comparison of the Clinical Value of Complexed PSA and Total PSA in the Discrimination between Benign Prostatic Hyperplasia and Prostate Cancer

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Key Words

Prostate-specific antigen · Benign prostate hyperplasia ·
Prostate cancer · ROC analysis

Abstract

Background: To compare the clinical value of the measurement of complex and total PSA in the discrimination between benign prostatic hyperplasia (BPH) and prostate cancer. **Methods:** In serum samples collected from 166 men with histopathologically proven clinically localized prostate cancer and of 97 men with BPH, total prostate-specific antigen (PSA), complexed PSA and the free to total PSA ratio were determined. The statistical analysis was done by the comparison of the receiver operator characteristic (ROC) curves. **Results:** The areas under the ROC curves were 0.776 for total PSA, 0.799 for complexed PSA (total PSA vs. cPSA: $p < 0.0001$) and 0.812 for the free to total PSA ratio. With a cut-off of 3.0 ng/ml for complexed PSA, the sensitivity was 90%, the specific-

ity 58%, the positive and the negative predictive values 79 and 78%, respectively. With a cut-off of 4.0 ng/ml for total PSA, the sensitivity was 87%, the specificity 59%, the positive and the negative predictive values were 78 and 72%, respectively. **Conclusions:** There was a statistically significant advantage for complexed PSA compared to total PSA in the discrimination between BPH and prostate cancer. The difference was, however, small and its clinical relevance is questionable.

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Introduction

Prostate-specific antigen (PSA) determination is of paramount importance in the diagnosis and management of prostate cancer [1]. Several studies suggested that the measurement of PSA bound to serum proteins (complexed PSA) might improve the performance of PSA testing in the discrimination between benign and malignant prostatic conditions [2–5]. The aim of this study was to investigate whether the substitution of total PSA testing by measurement of complexed PSA may represent an advantage in clinical practice.

Possible conflict of interest/source of funding: The Bayer Company provided the complexed PSA assay for testing purposes.

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Table 1. Sensitivity, specificity, positive and negative predictive value for different complexed (cPSA) and total PSA (tPSA) and free to total PSA ratio (%fPSA) thresholds in the whole study population

Threshold	Sensitivity, %	Specificity, %	Predictive value, % ¹	
			positive	negative
cPSA 2.0 ng/ml	95	44	75	84
tPSA 2.5 ng/ml	95	44	75	84
%fPSA 28%	95	29	70	78
cPSA 3.0 ng/ml	90	58	79	78
tPSA 4.0 ng/ml	87	59	78	72

¹ Valid for a prevalence of 63%.

Table 2. Sensitivity, specificity, positive and negative predictive value for different complexed (cPSA) and total PSA (tPSA) and free to total PSA ratio (%fPSA) thresholds in the total PSA range of 2–10 ng/ml

Threshold	Sensitivity, %	Specificity, %	Predictive value, % ¹	
			positive	negative
cPSA 2.0 ng/ml	95	16	70	62
tPSA 2.5 ng/ml	95	16	70	62
%fPSA 28%	95	31	74	75
cPSA 3.0 ng/ml	87	43	76	62
tPSA 4.0 ng/ml	81	45	75	54

¹ Valid for a prevalence of 68%.

Materials and Methods

Serum samples were obtained from 166 men with histopathologically proven clinically localized prostate cancer prior to radical prostatectomy and of 97 men with benign prostatic hyperplasia (BPH) prior to transurethral or transvesical surgery of the prostate. The latter patients had no evidence of malignancy in their resection specimens. Patients with a history of neoadjuvant androgen deprivation were not included into this study. The mean age was 65 years (range 48–78 years) among the cancer patients and 69 years (range 45–84 years) in the BPH patients ($p < 0.0001$). The serum samples were processed immediately after collection and stored no longer than 8 h at 4°C before being frozen at –80°C. In all samples, total PSA (Abbott AxSym Total PSA, Abbott, Wiesbaden, Germany), the free to total PSA ratio (Abbott AxSym Free PSA) and the complexed PSA (Bayer Diagnostics, Fernwald, Germany) were determined. The statistical analysis was done by the comparison of the receiver operator characteristic (ROC) curves [6]. p values are raw values.

Results

The mean value of total PSA was 10.6 ng/ml (range 0.2–61 ng/ml) in the prostate cancer and 5.1 ng/ml (range 0.3–35 ng/ml) in the BPH group ($p < 0.0001$). The mean value of complexed PSA was 9.3 ng/ml (range 0.2–59 ng/ml) in the cancer patients and 4.0 ng/ml (range 0.2–27 ng/ml) in BPH patients ($p < 0.0001$). The mean free to total PSA ratio was 14% (range 2.5–38%) in cancer patients and 23% (range 6.3–47%) in the BPH patients ($p < 0.0001$). The ROC curves for total and complexed PSA and for the free to total PSA ratio are shown in figure 1. The areas under the ROC curves (AUC) were 0.776 for total PSA, 0.799 for complexed PSA and 0.812 for the free to total PSA ratio. The ROC curves for total PSA and complexed PSA differed significantly (fig. 1; $p < 0.0001$). There were no significant differences between the ROC curves for total PSA and the free to total PSA ratio ($p = 0.07$) and for complexed PSA and the free to total PSA ratio ($p = 0.25$). At a sensitivity level of 95%, threshold values of 2.0 ng/ml for complexed PSA, 2.5 ng/ml for total PSA and 10% for the free to total PSA ratio were obtained. The figures for sensitivity, specificity, positive and negative predictive values for the 95% thresholds and for cut-off-values of 3 and 4 ng/ml are given in table 1, corresponding figures for the total PSA grey zone of 2–10 ng/ml are shown in table 2. In the total PSA grey zone between 2 and 10 ng/ml, the following AUC values were obtained: 0.723 for complexed PSA, 0.673 for total PSA ($p < 0.0001$ for the comparison of the ROC curves of total and complexed PSA) and 0.795 for the free to total PSA ratio ($p < 0.01$ for the comparison of the ROC curves of total and of the free to total PSA ratio). The comparison between the ROC curves of complexed PSA and the free to total PSA ratio narrowly failed the significance level ($p = 0.05$). The ROC curves in the total PSA grey zone between 2 and 10 ng/ml are shown in figure 2.

Discussion

Complexed PSA has been suggested to be a superior initial test in the detection of prostate cancer [2–5]. The measurement of complexed PSA instead of total PSA has been found to be able to reduce the number of unnecessary biopsies [5, 7]. Other authors, however, questioned the clinical relevance of the statistically detectable advantage of complexed PSA [8]. Patients with an elevated PSA referred for surgical treatment of BPH represent a com-

Fig. 1. Receiver operator characteristic curves for complexed PSA, total PSA and the free to total PSA ratio in the discrimination between benign prostate hyperplasia and prostate cancer in the whole study population.

Fig. 2. Receiver operator characteristic curves for complexed PSA, total PSA and the free to total PSA ratio in the discrimination between benign prostate hyperplasia and prostate cancer in the total PSA range of 2–10 ng/ml.

mon problem in the setting of a hospital. In this population, it can be difficult to decide whether a prostate biopsy should precede surgical treatment of BPH. Therefore, we choose such patients for comparison with candidates for radical prostatectomy to evaluate the usefulness of the complexed PSA assay. Compared with multiple studies involving patients with positive and negative prostate biopsies [2, 4, 5, 8–15], in our study, the AUCs were higher for all PSA derivatives (indicating a better discrimination between benign and malignant prostatic conditions by the determination of PSA-related laboratory values). A selection effect might be a possible explanation for this phenomenon. It has been suggested that several ratios of PSA-related laboratory values may improve the discrimination between benign and malignant prostatic conditions [2, 11, 13]. The results were, however, inconsistent [11], and it is questionable whether one of the suggested ratios will gain general acceptance [16, 17]. Therefore, we dispensed with the analysis of ratios other than the free to total PSA ratio in this study. Compared to ROC curves, definite cut-off values are likely to be preferred in the clinical setting. Some authors report rather arbitrary cut-off values for complexed and total PSA (for instance 2.9 ng/ml for complexed PSA and 3.9 ng/ml for total PSA representing the 93rd sensitivity percentile [3] or 2.9 for complexed PSA and 4.0 ng/ml for total PSA representing the 90th sensitivity percentile in their studies [12]) or a broad range of possible cut-off val-

ues for complexed PSA [2]. Other authors used the 95th sensitivity percentile to define cut-off values and obtained differing results [8, 9]. We considered two pairs of cut-off values suitable for clinical application, the 95% sensitivity threshold (in this study 2.0 ng/ml for complexed and 2.5 ng/ml for total PSA) and 3.0 ng/ml for complexed PSA and 4.0 for total PSA in agreement with values suggested by others [3, 12] and with the most commonly used total PSA threshold of 4.0 ng/ml. At these cut-offs, there was no appreciable difference in the performance of the complexed and total PSA tests in our study reflected by the associated specificity and positive and negative predictive values.

This study has several limitations. Since patients with symptomatic BPH, partially at advanced age, were included as a cohort with a benign prostatic condition, the results may not necessarily apply to a screening population. Patients with BPH were in average four years older than those with prostate cancer. There was, however, only a weak and non-significant trend towards higher complexed and total PSA values with increasing age (data not shown). Furthermore, transrectal prostate biopsy is not entirely equivalent to transurethral (or transvesical) resection of the prostate in the verification or ruling out of prostate cancer. The described limitations are, however, not likely to interfere meaningfully with the interpretation of the study results.

In summary, in the discrimination of BPH and prostate cancer, complexed PSA added little information to the conventional approach with determination of total PSA and the consideration of the free to total PSA ratio in cases of uncertainty. Even if complexed and total PSA were considered alone (and the free to total PSA ratio is ignored) and even if only the total PSA grey zone of 2–

10 ng/ml was considered, the statistically significant advantage for complexed PSA was too small to be of clinical relevance in the setting of this study (tables 1, 2).

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