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Value of Free Prostate-Specific Antigen (Hybritech Tandem-R) in Symptomatic Patients Consulting the Urologist

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Abstract
Introduction: Prostate-specific antigen (PSA) is a widely used tumor marker in the detection and follow-up of adenocarcinoma of the prostate. Selection of candidates for prostate biopsies is hampered by the lack of specificity resulting in a large number of unnecessary biopsies. The intention of our study was to compare the percent free PSA (f-PSA; Hybritech Tandem-R) with total PSA and age-specific PSA reference values to evaluate the clinical benefit in detecting patients with prostate cancer (PC) in a selected group of patients consulting the urologist. The question was whether cutoff points are influenced by this selection of patients. ***Methods:*** A total of 188 patients, 114 with benign prostate hyperplasia (BPH) and 74 with PC were selected. It is a selected group of patients consulting the urologist. Diagnosis was confirmed in the BPH and PC groups by either ultrasound-guided biopsy or transurethral resection of the prostate or suprapubic adenomectomy or cystoprostatectomy. Total PSA (t-PSA) and f-PSA of all patients were measured before any manipulation by Tandem-R assay for f-PSA and Tandem-E assay for t-PSA (Hybritech). Mean values of age, prostate volume, t-PSA, f-PSA, percent f-PSA were compared in patients with BPH and PC by Mann-Whitney U test. The sensitivity and specificity of t-PSA and age-specific PSA were compared to the sensitivities and specificities of different cutoff points of percent f-PSA. ***Results:*** The mean value of t-PSA, f-PSA and percent f-PSA in patients with BPH (n = 114) and PC (n = 74) were statistically significantly different. At PSA levels between 4 and 10 ng/ml 19% of negative biopsies could be avoided by the use of percent f-PSA (cutoff point 25%). There was no additional benefit of age-specific PSA. At a PSA of <4 ng/ml 6 of 7 PCs could be diagnosed by percent f-PSA (cutoff point 25%), whereas only 1 patient would be diagnosed by age-specific PSA. ***Conclusion:*** Percent f-PSA seems to decrease the biopsy rate at PSA levels from 4 to 10 ng/ml without missing a relevant number of cancers and to increase the detection rate at PSA <4 ng/ml. Our data

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indicate that it might be necessary to choose high cutoff points (25%; Tandem-E and R assay, Hybritech) in a selected study population consulting the urologist with large glands and a high prevalence of disease. However, this situation is not comparable to testing of screening populations. No benefit of age-specific PSA could be observed in this study.

Introduction

Prostate cancer (PC) is a major cause of morbidity and mortality among men in Europe and North America. It is the most common tumor and second leading cause of cancer death. It was estimated that 22,000 new cases of PC are diagnosed in Germany every year, and that 9,000 patients would die of the disease. Most cancers are detected in elder men; 20%, however, are younger than 65 years [1, 2].

Screening for PC is usually performed by prostate-specific antigen (PSA) and digital rectal examination (DRE). Transrectal ultrasonography can be added for visualization of lesions and prostate volumetry. Selection of candidates for prostate biopsy is hampered by the lack of specificity of PSA. This results in a large number of unnecessary biopsies [3–5].

Efforts to improve the performance of PSA have included PSA density (the quotient of serum PSA divided by the prostate volume) [6], PSA velocity (change in PSA over time) [7], PSA doubling time [8], age-specific PSA [9, 10] and percent free PSA (f-PSA).

Percent f-PSA seems to be a new useful parameter in the differentiation of benign prostate hyperplasia (BPH) and PC. In 1991 Stenman et al. [11] and Lilja et al. [12] reported independently that different molecular forms of PSA exist in the serum. In serum, PSA forms complexes with α_1-antichymotrypsin (ACT) and several other protease inhibitors. The total PSA (t-PSA) measured by commercially available PSA assays includes the reactivity with f-PSA and PSA complexed with ACT (ACT-PSA). PSA complexed to α_2-macroglobulin has not been measured by commercially available PSA assays. The proportion of t-PSA that forms a complex with ACT appears to be higher in patients suffering from PC. As a result, the percent f-PSA of patients with PC is lower than of patients with BPH [13].

In most studies percent f-PSA demonstrated clinical utility only in men whose total serum PSA concentration was 2.5–10 ng/ml. These studies from several countries, using a variety of assays, have documented the ability of percent f-PSA to improve the specificity of PC screening [14–17].

The availability of numerous assays for the determination of PSA and its molecular forms has led to substantial problems in the interpretation of PSA concentrations. The antibodies of these assays have different affinities and specificities for various epitopes of PSA forms. They have different characteristics such as monoclonal or polyclonal antibodies, equimolar or nonequimolar measurement of the PSA forms. Thus, different assays report different PSA concentrations in a given serum sample. These differences are of a magnitude that is clinically significant. Consequently, deviations between assays depend on the nature of the underlying prostatic disease. Therefore, each assay has its own specific reference range [18].

The intention of our study was to compare percent f-PSA (Hybritech Tandem-E) with t-PSA and age-specific PSA to evaluate the clinical benefit in detecting patients with PC in a selected group of patients coming to the urologist. The question was whether the cutoff points must be changed in this selected group of patients.

Materials and Methods

Patients

A total of 188 patients, 114 with BPH and 74 with PC, were selected. Diagnosis was confirmed by ultrasound-guided biopsy as described by Niesel et al. [19] in 42 BPH and 54 PC patients because of a suspicious DRE and/or a PSA level of >4 ng/ml; by transurethral resection of the prostate (TURP) in 40 BPH and 13 PC patients, and by TURP and biopsy in 27 BBH and 7 PC patients. Three BPH patients were diagnosed by suprapubic adenomectomy and 2 by cystoprostatectomy. The mean age was 68 years.

Immunoassays

t-PSA and f-PSA of all patients were measured before any manipulation by Tandem-R assay for f-PSA and Tandem-E assay for t-PSA (Hybritech). This is a monoclonal but not equimolar test system. The age-specific PSA ranges described by Oesterling et al. [10] (40–49 years, <2.5 ng/ml; 50–59 years, <3.5 ng/ml; 60–69 years, <4.5 ng/ml; 70–79 years, <6.5 ng/ml) were used in all patients.

Measurement of Prostate Volume

The prostate volume of patients was measured by transrectal ultrasonography using the ellipsoid formula.

Statistical Analysis

The distribution of age, prostate volume, t-PSA, f-PSA, percent f-PSA were compared in patients with BPH and PC by the Mann-Whitney U test. A p value of <0.05 was considered statistically significant.

Table 1. Mean values of age, prostate volume, t-PSA, f-PSA and percent f-PSA in patients with BPH (n = 114) and PC (n = 74)

	BPH	PC	p value
Age, years	68.1	70.3	0.09
Prostate volume, ml	83.2	63.0	0.0006
Percent f-PSA	20.2	13.0	<0.0001
t-PSA, ng/ml	8.4	21.5	<0.0001
f-PSA, ng/ml	1.7	2.8	0.02

Table 2. Areas under the receiver operating characteristic curves (AUC) for percent f-PSA, t-PSA (Tandem-E, Hybritech) and f-PSA (Tandem-R, Hybritech) in different t-PSA ranges

	AUC		
	all patients (BPH n = 114, PC n = 74)	4–10 ng/ml t-PSA (BPH n = 52, PC n = 32)	<4 ng/ml t-PSA (BPH n = 33, PC n = 7)
Percent f-PSA	0.75	0.67	0.63
t-PSA, ng/ml	0.74	0.61	0.47
f-PSA, ng/ml	0.60	0.41	0.38

Table 3. Sensitivities and specificities for t-PSA (cutoff point 4 ng/ml), age-specific PSA and different cutoff points of percent f-PSA in 114 patients with BPH and 74 patients with PC

	Cutoff point	Sensitivity %	Specificity %
t-PSA	4 ng/ml	92	29
Age-specific PSA		88	44
Percent f-PSA	14%	71	69
	18%	83	52
	21%	88	41
	25%	92	28

The sensitivity and specificity of t-PSA and age-specific PSA [10] were compared to the sensitivities and specifities of different cutoff points of percent f-PSA.

The receiver-operating characteristic (ROC) for percent f-PSA was estimated within various ranges of total PSA to determine the range that maximized the accuracy of percent f-PSA. Within the optimal range, the ROC curves were utilized to evaluate different cutoff points of percent f-PSA.

Results

The mean values of age, prostate volume, t-PSA, f-PSA and percent f-PSA in patients with BPH (n = 114) and PC (n = 74) are shown in table 1. The mean prostate volume of patients with BPH and PC (83.2 vs. 63.0 ml, $p = 0.0006$) and mean t-PSA (8.4 vs. 21.5 ng/ml, $p < 0.0001$) were statistically significantly different. The mean f-PSA was 1.7 vs. 2.8 ($p = 0.02$), and the mean percent f-PSA was 20.2 vs. 13.0% ($p < 0.0001$) in the BPH and PC groups, respectively.

When sensitivity was plotted against 1–specificity, the area under the resulting ROC curve for percent f-PSA was 0.75, compared to 0.74 for t-PSA and 0.60 for f-PSA (table 2).

Corresponding sensitivities and specificities at certain cutoff points are shown in table 3. The sensitivity and specificity for t-PSA (cutoff point 4 ng/ml) was 92 and 29%, respectively. At a corresponding sensitivity of 92% (cutoff point 0.25%) percent f-PSA showed a specificity of 28%. At a corresponding sensitivity of 88% the specificity of age-specific PSA was 44% compared to 41% for percent f-PSA (cutoff point 0.21).

t-PSA: 4–10 ng/ml (n = 75)

The area under the ROC curve for percent f-PSA was 0.67 compared to 0.61 for t-PSA and 0.41 for f-PSA (table 2).

The sensitivities and specificities are shown in table 4. At corresponding sensitivities the specificity of age-spe-

Table 4. Sensitivities and specificities for age-specific PSA and different cutoff points of percent f-PSA in 52 patients with BPH and 23 patients with PC (t-PSA 4–10 ng/ml)

	Cutoff point	Sensitivity, %	Specificity, %	PC, ignored %
Age-specific PSA		88	31	12 (n = 3)
Percent f-PSA	14%	74	58	26 (n = 6)
	18%	87	44	13 (n = 3)
	21%	91	35	9 (n = 2)
	25%	96	19	4 (n = 1)

cific PSA was 31 versus 44% for percent f-PSA (cutoff point 0.18).

A loss of sensitivity of percent f-PSA represents a loss of detection rate of patients with PC compared to a cutoff point of 4 ng/ml of t-PSA. At high sensitivity of percent-free PSA (cutoff point 25%) 19% of negative biopsies could be avoided.

t-PSA: <4 ng/ml (n = 40)

The area under the ROC curve for percent f-PSA was 0.63 compared to 0.47 for t-PSA and 0.38 for f-PSA (table 2).

Most of the patients with PC would be missed by age-specific PSA (sensitivity 14%). The higher the cutoff point of percent f-PSA, the higher the detection rate and the rate of biopsies. The corresponding sensitivities and specificities are shown in table 5.

Six of 40 patients with a PSA of <4 ng/ml had a positive DRE. Five of these 6 patients had no PC, whereas 1 had PC. Two of 14 patients with a PSA of <2 ng/ml and a positive DRE had no PC.

Discussion

PSA is a valuable tool for the early detection of PC. One third of patients with a normal DRE are biopsied because of a elevated PSA level [20]. However, there is a high false-positive rate of PSA-indicated biopsies resulting in unnecessary invasive diagnostic procedures leading to unnecessary morbidity and psychological problems of patients.

Efforts to improve the specificity include PSA density (the quotient of serum PSA divided by the prostate volume) [6], PSA velocity (change in PSA over time) [7], PSA doubling time [8], age-specific PSA [9, 10] and percent f-PSA.

The different modalities must be able to identify PC with high sensitivity and high probability that eliminated biopsies would not be false-negative. Age-specific PSA and percent f-PSA investigated in this study are objective examinations not influenced by the investigator like the volume measurement of the prostate needed in the calculation of PSA density.

Many studies show that by using percent f-PSA up to 40% of biopsies could be eliminated while still detecting most cancers [21–23].

In this investigation 19% of negative biopsies (PSA 4–10 ng/ml, cutoff point 25%) could be avoided while missing only one carcinoma. There was no additional benefit of age-specific PSA. At comparable sensitivity the specificity was 31% compared to percent f-PSA with a specificity of 44%.

On the other hand it seems desirable to detect patients with PC with a normal PSA of <4 ng/ml. Catalona et al. [24] examined a screening population of patients with serum PSA levels from 2.6 to 4 ng/ml and negative DRE by biopsy. A cutoff of 25% f-PSA would have detected 91% of the cancers and avoided 26% of negative biopsies. The great majority of cancers detected had the features of clinically important tumors [24]. In our series of radical retropubic prostatectomies 13% of 420 previously untreated patients with PC, who underwent radical prostatectomy had a PSA of ≤4 ng/ml, 7% a PSA of ≤2 ng/ml (fig. 1). Although there was a small number of patients with a PSA of <4 ng/ml in our series, it seems that percent f-PSA could increase the cancer detection rate. With a cutoff point of 25% 6 of 7 of PCs could be diagnosed, whereas only 1 patient would have been diagnosed by age-specific PSA or DRE.

Both outcomes – higher specificity at intermediate PSA and increase of cancer detection at PSA <4 ng/ml – are clinically desirable in attempting to diagnose early, curable PCs. Our results are not representative for a screening population because these are selected patients consulting the urologist. This may influence the interpretation of cutoff points.

Table 5. Sensitivities and specficities for age-specific PSA and different cutoff points of percent f-PSA in 33 patients with BPH and 7 patients with PC (t-PSA <4 ng/ml)

	Cutoff point	Sensitivity, %	Specificity, %	PC, ignored %
Age-specific PSA		14	94	86 (n = 6)
Percent f-PSA	14%	29	79	71 (n = 5)
	18%	43	67	57 (n = 4)
	21%	57	58	43 (n = 2)
	25%	86	52	14 (n = 1)

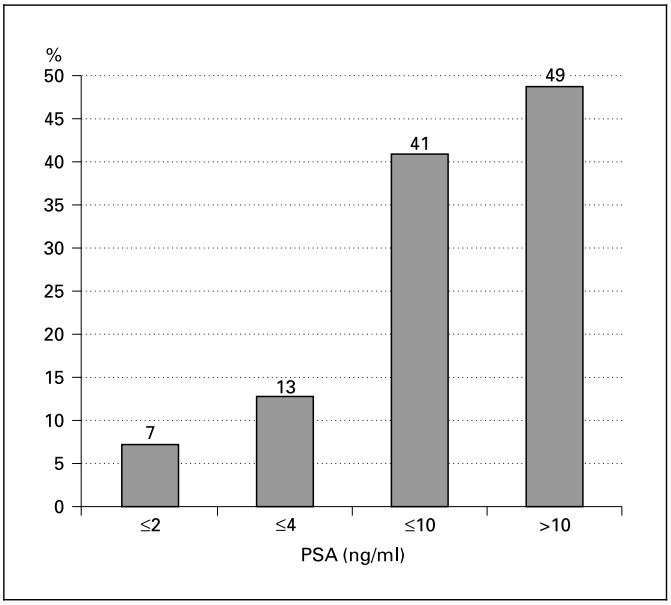

Fig. 1. PSA values of 420 untreated patients with PC who underwent radical prostatectomy.

The patients often consulting our hospital because of obstructive voiding symptoms had predominantly large glands. Partin et al. [22], Catalona et al. [26] and Van Cangh et al. [27] found that in their cancer groups as the prostate volume increased the mean percent free PSA also increased, suggesting that coexistent BPH and prostate cancer may be difficult to differentiate from cancer or BPH alone. In the publication of Van Cangh et al. [27] the mean percent f-PSA was 0.1 for cancers in low-weight glands (<40 g), 0.14 in middle-weight (40–55 g) and 0.16 in higher-weight glands (>55 g). Woodrum et al. [28] concluded that if patients of a cancer group study have predominantly small glands, the corresponding percent f-PSA cutoff points can be lower than if they have large glands. This might be the reason why our cutoff point of 25%, chosen to receive a high sensitivity, is high compared to other f-PSA studies and leads to a comparable low specificity.

On the other hand the high cancer prevalence in our study population may influence the interpretation. Van Cangh et al. [27] presented an analysis showing how the prevalence of disease in the study cohort can affect cancer probability calculations. They presented PC probability as function of cancer prevalence in a study population and the free-to-total PSA ratio. A higher prevalence and resulting cancer probability leads to higher cutoff points of percent f-PSA to detect most of prostate cancers. They concluded that useful results on predictive values are only obtained when the prevalence of PC is high, such as in a urology clinic population.

Our data indicate that it might be necessary to choose high cutoff points (25%; Tandem-R assay for f-PSA and Tandem-E assay for t-PSA, Hybritech) in a selected study population with large glands and a high prevalence of disease, which is not comparable to screening populations.

Nevertheless it seems that percent f-PSA for these selected people in our present study may improve the clinical utility of the PSA test for detecting early, curable PC.

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