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Prostate-specific Antigen Density: The Role in Benign Prostate Hyperplasia, Prostate Intraepithelial Neoplasm, Organ-confined Prostate Carcinoma and Advanced Prostate Carcinoma

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To determine the relative role of prostate-specific antigen density (PSAD) in the early detection of prostate cancer and to assess the hypothesis that PSAD offers significant advantages over prostate-specific antigen (PSA) alone in the evaluation of patients with benign (BPH), pre-malignant (PIN) and malignant prostatic diseases, we studied retrospectively 149 patients who were evaluated with either prostatic biopsies or by surgical means. Mean PSAD was calculated to be 0.1 for BPH patients; 0.09 for PIN-1 patients; 0.1 for PIN-2 patients; 0.51 for organ-confined prostatic carcinoma (CaP) patients and 1.7 for advanced CaP patients. Although we could not be able to differentiate BPH from PIN-1 and PIN-2 by using PSAD alone ($p>0.05$), there were statistically significant differences between BPH versus localized CaP, PIN-2 versus localized CaP and localized CaP versus advanced CaP ($p<0.05$). In conclusion we suggest that the information provided by PSAD is superior to absolute PSA values in the differentiation between BPH and CaP but PSAD was not able to add more information on differentiating BPH from pre-malignant conditions.

Introduction

Since the discovery by Wang et al. [1] prostate-specific antigen (PSA) has become an important marker in both the diagnosis and management of patients with cancer of the prostate. PSA is a 34,000 Dalton serine protease that is produced only in the epithelial cells of prostatic origin. Although both normal and malignant cells produce PSA, there is a gradual increase in the levels of this protein, approximately tenfold higher, as one progresses from the benign to the malignant state. It is also recognized that PSA increases as prostate volume increases [2]. Recently the incidence of prostatic intraepithelial neoplasm (PIN) detected in the pathologic specimens has increased, and a new question arises whether the elevated serum PSA values can be accounted for by PIN [3].

In order to clarify reasonably these problems and enhance the usefulness of PSA as a diagnostic test, Benson et al. introduced a new concept called PSA density (PSAD). PSAD was defined as serum PSA divided by the total volume of the prostate [4].

To determine the relative role of PSAD in the early detection of prostate cancer and to assess the hypothesis that PSAD offers significant advantages over PSA alone in the evaluation of patients with benign, pre-malignant (PIN)

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and malignant prostatic diseases, we studied retrospectively 149 patients who were evaluated with either prostatic biopsies or by surgical means: transurethral prostatectomy (TUR-P), transvesical prostatectomy (TV-P) or retropubic radical prostatectomy and bilateral pelvic lymphadenectomy. The results are presented in this paper.

Patients and methods

Between November 1991 and July 1994, 205 consecutive male patients aged 53–83 years underwent evaluation at our department. Fifty-six were excluded from the study because of incomplete data. Thus, the final population analyzed was 149 men. Each subject underwent evaluation including PSA determination, digital rectal examination (DRE), transrectal ultrasonography (TRUS) and if one or both tests were suspicious prostatic biopsies were performed. Serum samples for PSA were obtained before DRE and TRUS and monoclonal PSA assays were used. After the initial diagnosis the patients were either operated (TUR-P, TV-P, radical retropubic prostatectomy + bilateral pelvic lymphadenectomy) or were given medical anti-androgen treatment for advanced prostatic carcinoma.

Prostate volume was calculated by using the ellipse method and PSAD was determined by dividing PSA (ng/ml) by the volume of the entire prostate. No unit was assigned to PSAD determination.

The 149 patients were divided into five pathologically different groups: benign prostatic hyperplasia (BPH), PIN-1, PIN-2, organ-confined prostatic carcinoma and advanced prostatic carcinoma. The BPH group included 50 patients, the PIN-1 group 18 patients, the PIN-2 group 6 patients, the organ-confined prostatic carcinoma group 14 patients and the advanced prostatic carcinoma group 61 patients.

Student's *t*-test was used to determine statistical significance.

Results

Figure 1 illustrates the mean PSA levels in patients with BPH, PIN-1, PIN-2, organ-confined CaP and advanced CaP. The mean serum PSA level was 5.7 ng/ml (SD: 5.8) in the BPH group and 13.0 ng/ml (SD: 10.1) in the organ-confined CaP group; this difference is statistically significant ($p<0.05$). Also the difference between both organ-confined CaP and advanced CaP is statistically significant ($p<0.05$). However, PSA cannot be used to differentiate BPH either from PIN-1 or PIN-2. On the other hand, the mean PSA difference was statistically significant in both PIN-2 versus organ-confined CaP, and organ-confined CaP versus advanced CaP ($p<0.05$) groups.

As shown in Fig. 2, PSAD did not supply more information than PSA alone. The mean PSAD in the BPH group was 0.10 (SD: 0.08), whereas in organ-confined CaP PSAD was calculated to be 0.51 (SD: 0.48). This difference

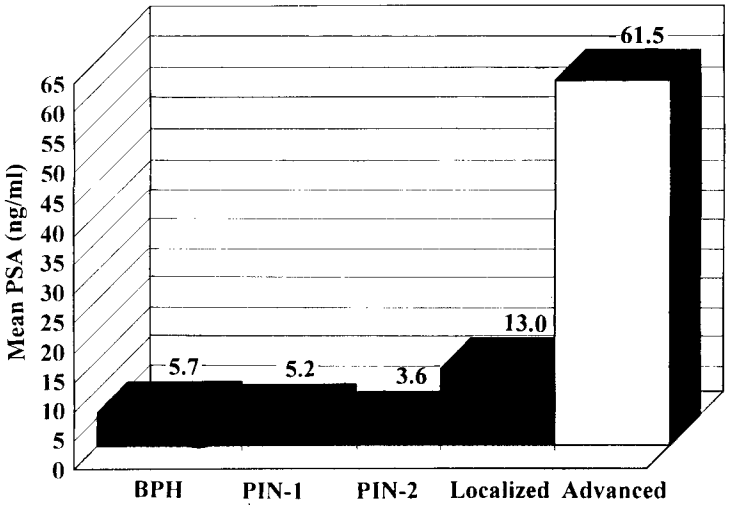

Fig. 1. Mean PSA levels of patients

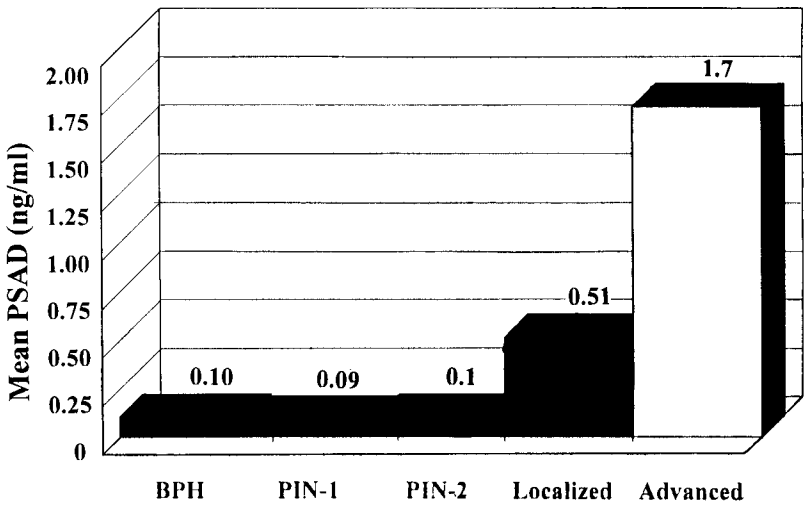

Fig. 2. Mean PSAD levels of patients

was statistically significant ($p<0.05$). However, PSAD did not differentiate BPH either from PIN-1 or PIN-2. Also the values of PSAD differences were statistically significant in both PIN-2 versus organ-confined CaP, and organ-confined CaP versus advanced CaP ($p<0.05$) groups.

Discussion

To date serum prostate-specific antigen (PSA) is the most useful marker in the evaluation of prostatic carcinoma (CaP). On the other hand, serum PSA value is merely a reflection of the number of prostatic epithelial cells present, it lacks specificity in distinguishing BPH from pre-malignant lesions (PIN-1, PIN-2) and CaP. Although earlier studies [4, 5, 6, 7] claimed PSAD to be a parameter to distinguish BPH from CaP, there is no consensus on the cut-off level of PSAD and we could not find any study reported in the literature relating to the value of PSAD in prostatic intraepithelial neoplasms.

In our study, in the pathologically pure BPH group (50 patients) the mean serum PSA level was 5.7 ng/ml. We suggest that this slightly elevated value is due to the prostate volumes in our BPH patients (mean prostate volume was 38.4 ml with a SD of 14.2). By using serum PSA as a parameter we could not differentiate BPH from either PIN-1 or PIN-2. Also, PSAD was not useful in this respect. The PSAD value of our BPH patients was 0.10. This was lower than the already accepted 0.15 value [8, 9, 10].

At the beginning of the study we expected to find a difference between the PSAD values of BPH and PIN-2, but we could not observe elevated PSAD in PIN-2 patients as Ronnett et al. [3] suggested the elevation of PSA in high grade PIN.

Patients with organ-confined CaP had a mean PSA value of 13.0 ng/ml (SD: 10.1). This result is compatible with the generally accepted opinion that CaP is probably organ-confined when the PSA value is below 20 ng/ml [11]. At the same time the mean serum PSA in our advanced CaP patients was 61.5 ng/ml (SD: 37.0).

Mean PSAD of the organ-confined CaP patients was calculated to be 0.51 (SD: 0.48). This value is significantly higher than that in BPH patients (0.10). On the other hand, PSAD in advanced CaP patients was 1.70 (SD: 1.18).

In conclusion, we suggest that PSAD does not distinguish BPH from either PIN-1 or PIN-2, but accepting the level of 0.10 as the cutoff value it can easily differentiate the patients of BPH from CaP. Finally, although we had not enough organ-confined CaP patients by taking the cutoff level of 0.51 the patients can be distinguished to undergo any kind of radical treatment to cure prostatic carcinoma.

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