

PERFORMANCE OF PSA AND OF PSA DENSITY IN THE DIAGNOSIS OF PROSTATE CARCINOMA¹

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ABSTRACT

Objective - The aim of the study was to investigate the influence of the prostate volume and PSA density on the performance of total PSA to diagnosis of prostate carcinoma. **Methods** - We analyzed 217 patients (PSA 0-10ng/ml) submitted to transrectal sextant prostate biopsy. Criteria for biopsy indication was PSA >2ng/ml and/or digital rectal exam suspicious of prostate cancer. **Results** - Fifty five patients had prostate neoplasia (25.3%) and in 8/55 (25.3%) the serum PSA was under 4ng/ml. The sensitivity and specificity of the test were respectively 98.2% / 16.6% at a cut-off point of 2.5ng/ml and 85.4% / 38.8% at cut-off of 4ng/ml. The corresponding values for prostates >40ml or <40ml were: 96.2% / 8.1% and 100% / 27.2% at the cut-off point of 2.5ng/ml, and 92.5% / 20% and 78.5% / 62.3% at a cut-off level of 4ng/ml. For prostates <40ml a PSA cut-off point of 4ng/ml leads to a misdiagnosis in 21.4% of the malignant tumors. The median PSAD of benign prostates are different according to prostate volume (>40ml or <40ml). PSAD at cut-off of 0.08 increases the PSA specificity at both PSA cut-off points. **Conclusions** - Prostate volume affects the sensitivity and specificity of PSA and the median values of PSAD. PSAD of 0.08 increases the PSA specificity specially at a cut-off point of 2.5ng/ml in prostates smaller than 40ml. Available from URL: <http://www.scielo.br/acb>

Key Words - Prostate specific antigen, PSA, PSA density, prostate carcinoma

INTRODUCTION

The initial enthusiasm on the utility of prostate specific antigen (PSA) for the diagnosis of prostate adenocarcinoma was counterbalanced by reports

PSAD cut-off of 0.08 seems to have a better performance than PSA at a cut-off point of 4ng/ml alone or in combination with PSAD specially for prostates < 40ml, showing that benign prostate hyperplasia (BPH) could also rise serum levels of this tumor marker^{1,2}. Soon afterwards, Stamey et al.³ reported that the elevation of serum concentration of PSA promoted by prostate carcinoma was 10 times higher than that of BPH³. Because of the increasing frequency of BPH and consequent prostate growth from 40 years on, some additional parameters were proposed in association with PSA. One of these parameters is the PSA density (PSAD) that at the cut-off level of 0,15, for patients with PSA between 4-10ng/ml, would discriminate most of the cases of carcinoma from BPH⁴. But, other studies show that PSAD has no value for such discrimination⁵. Others recommend the PSAD at the cut-off level of 0,15 to make a decision on the indication of a 2nd set prostate biopsy when the 1st set gave a negative result⁶.

The aim of our study was to investigate the influence of PSAD and prostate volume on the performance of PSA to the diagnosis of prostate carcinoma in a subset of patients (with serum PSA \leq 10ng/ml) submitted to prostate biopsy.

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METHODS

From January of 1999 to December of 2001, 217 volunteers with total PSA \leq 10ng/ml had undergone transrectal ultrasound guided sextant prostate biopsy at HCFMRP-USP. The age range of patients varied from 42 to 90 years (Mean value \pm SD: 65.4 \pm 8.9 years). Prostate volume was recorded by transrectal ultrasound at the time of biopsy. Criteria of biopsy indication was PSA higher than 2.5ng/ml and/ or digital rectal exami-

nation (DRE) suspicious of cancer. The cores were fixed in 10% formalin and thereafter processed for histology under coloration of hematoxylin-eosin. PSA determination was carried out by the DPC-Immulatea assay.

We investigate the performance of PSA for the total sample and for subgroups of patients with prostates >40ml and <40ml. PSAD was also analyzed to test its ability to enhance PSA performance.

Series characteristics are displayed on Table 1.

Table 1 - Groups of patients according to the diagnosis and PSA range.

PSA Range	N	Carcinoma N (%)	BPH N (%)
0 – 2,4ng/ml	28	1 (3.6%)	27 (95.4%)
2,5 – 3.9ng/ml	43	7 (16.3%)	36 (83.7%)
4 – 10ng/ml	146	47 (32.2%)	99 (67.8%)
Total	217	55 (25.3%)	162 (74.7%)

Statistical analysis was performed with assistance of a software program. Continuous variables that did not get through the normality test were compared by the Mann-Whitney test. The level of significance was established by double-tailed p value <0.05. The influence of PSAD on PSA sensitivity and specificity was studied

through the receiver operating characteristic curves (ROC)

RESULTS

The performance of PSA to the diagnosis of prostate carcinoma at cut-off levels of 2.5ng/ml and 4.0ng/ml is presented on Table 2.

Table 2 - Overall PSA performance at two cut-off levels.

PSA cut-off	Sensitivity	Specificity	PPV	NPV	Overall Accuracy	Biopsy #/ Tumor	Tumor # missed
2.5ng/ml	98.2%	16.6%	28.5%	96.4%	37.3%	4.2	1(1.8%)
4.0ng/ml	85.4%	38.8%	32.2%	88.7%	50.7%	3.1	8(14.5%)

PPV – Positive Predictive Value; NPV – Negative Predictive Value

The influence of prostate volume on the performance of PSA is showed on Table 3.

Table 3 - Influence of prostate volume on PSA performance.

PSA cut-off	N	Sensitivity %	Specificity %	PPV %	NPV %	Overall % Accuracy	Biopsy #/ Tumor	%Tumor missed
2.5ng/ml								
>40ml	112	96.2	8.1	24.7	83.3	20.4	3.6	3.7
<40ml	105	100	27.2	33.3	100	46.6	3.0	0.0
4.0ng/ml								
>40ml	112	92.5	20.0	26.3	88.2	37.5	3.8	7.4
<40ml	105	78.5	62.3	43.1	88.8	66.6	2.3	21.4

PPV – Positive Predictive Value; NPV – Negative Predictive Value; N – Number of patients

The analysis of PSAD according to diagnosis and prostate volume is summarized on Table 4.

Table 4 - Comparison of PSAD in subsets of patients according to diagnosis and prostate volume.

Match A X B	PSA cut-off ng/ml	Prostate volume	PSAD Values		P* Value
			Median	Lower/Upper 95% CI	
A - Cancer (N=54)	2.5	all	0.14	0.14 / 0.20	0.01
B - BPH (N=135)			0.11	0.13 / 0.17	
A - Cancer (N=47)	4.0	all	0.16	0.14 / 0.19	0.22
B - BPH (N=99)			0.13	0.12 / 0.15	
A - Cancer (N=26)	2.5	>40ml	0.10	0.09 / 0.12	0.75
B - BPH (N=79)	2.5	>40ml	0.10	0.10 / 0.12	
A - Cancer (N=28)	2.5	<40ml	0.21	0.18 / 0.25	0.01
B - BPH (N=56)	2.5	<40ml	0.14	0.14 / 0.20	
A - Cancer (N=22)	4.0	<40ml	0.23	0.20 / 0.28	0.73
B - BPH (N=29)	4.0	<40ml	0.22	0.20 / 0.28	
A - Cancer (N=25)	4.0	>40ml	0.10	0.09 / 0.13	0.70
B - BPH (N=70)	4.0	>40ml	0.10	0.10 / 0.13	
A - Cancer (N=28)	2.5	>40ml	0.21	0.18 / 0.25	<0.0001
B - Cancer (N=26)	2.5	<40ml	0.10	0.09 / 0.12	
A - BPH (N=56)	2.5	>40ml	0.14	0.14 / 0.20	0.0004
B - BPH (N=79)	2.5	<40ml	0.10	0.10 / 0.12	
A - Cancer (N=22)	4.0	>40ml	0.23	0.20 / 0.28	<0.0001
B - Cancer (N=25)	4.0	<40ml	0.10	0.09 / 0.13	
A - BPH (N=29)	4.0	>40ml	0.20	0.20 / 0.28	<0.0001
B - BPH (N=70)	4.0	<40ml	0.10	0.10 / 0.13	

N – Number of patients; * - two-tailed p (Mann-Whitney test)

Table 5 shows those PSAD cut-off levels required to keep PSA sensitivity in the same range and its specificity according to some sample characteristics

as determined through the receiver characteristics operating curve (Figure 1).

Table 5 - Influence of PSAD on PSA specificity.

PSA Cut-off level	Prostate Volume (ml)	PSAD Required	Sensitivity %	Specificity %	Number biopsies/ Tumor	Tumors Missed %
4ng/ml	All	0.08	85.4	46.9	3.1	14.5
2.5ng/ml	All	0.06	98.2	21.6	3.3	1.8
2.5ng/ml	All	0.08	94.5	30.8	3.1	5.4
4ng/ml	>40ml	0.08	92.5	46.9	3.6	7.4
4ng/ml	<40ml	0.11	78.5	62.3	2.3	21.4
2.5ng/ml	>40ml	0.08	96.2	19.7	3.6	3.7
2.5ng/ml	<40ml	0.08	100	32.4	2.8	0.0

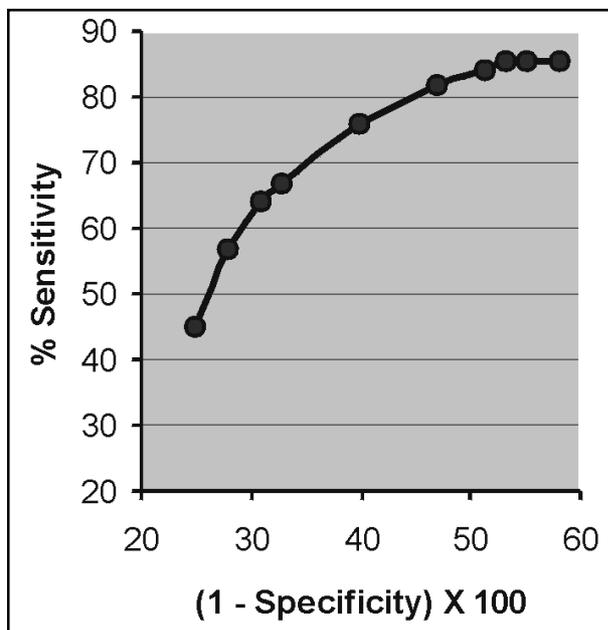


Figure 1 – Receiver characteristics operating curve (ROC) at different cut-off levels of PSAD using PSA at cut-off level of 4ng/ml as a reference for all patients.

DISCUSSION

Our results show in the whole sample that PSA specificity is higher at a cut-off level of 4ng/ml than at 2.5ng/ml. However, this cut-off point is associated with a lower sensitivity leading to misdiagnosis of 14.5% of neoplasias. On the other hand, PSA specificity is lower at cut-off level of 2.5% and associated with a higher proportion of unnecessary prostate biopsies.

On Table 3 one can see that the performance of PSA in detection of cancer is influenced by prostate volume. It is worth to mention that 21.4% of tumors are missed in the subset of patients with prostate volume lower than 40ml by using PSA cut-off level of 4ng/ml. The figure for prostates over 40ml is 7.4%. Catalona et al.⁷ were the first to notice that discrimination between cancer and BPH would require a free-to-total PSA cut-off point of 14% in prostates < 40ml and of 23% in those >40ml. But, others reported that this ratio is utile in distinction of cancer only in prostates <60ml⁸ or <40ml^{9,10}.

The PSA value depends on the cancer volume (and differentiation) as well as the prostate volume³. The PSAD parameter was developed to undermine the influence of the prostate volume on the serum level of PSA. However, BPH is heterogeneous and the stroma/epithelium ratio may vary with the prostate size. Table 4 shows that prostates <40ml exhibit higher PSAD values than those >40ml, which seems in disagreement with the general believe that prostates >40ml are of the “glandular” type according to the histology. It is

interesting to stress that this phenomenon occurs in prostates with benign or malignant disease. On the other side, median values of PSAD are similar in patients with prostates larger than 40 ml bearing cancer or BPH independently of the cut-off level of PSA. The median values of PSAD differentiates BPH from prostate carcinoma only for the entire series of patients, or for the subset with prostates smaller than 40ml, at a PSA cut-off level of 2.5ng/ml but not at 4ng/ml^{5,6}.

The analysis of our data through the receiver characteristics operating curve showed that the PSAD at a cut-off level of 0.15 does not enhance PSA sensitivity or specificity. This is in agreement with reports published elsewhere^{5,6}. But, a PSA cut-off level of 2.5ng/ml associated with a PSAD cut-off point of 0.08 for prostates of all sizes (patients with PSA ≤ 10ng/ml) seems a better option for taking the decision on biopsy indication than a PSA cut-off point of 4ng/ml alone or in combination with PSAD.

CONCLUSIONS

Prostate volume affects the sensitivity and specificity of PSA and the median values of PSAD. PSAD of 0.08 increases the PSA specificity specially at a cut-off point of 2.5ng/ml in prostates smaller than 40ml.

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