

ASSESSMENT OF SERUM LEVEL OF PROSTATE-SPECIFIC ANTIGEN ADJUSTED FOR THE TRANSITION ZONE VOLUME IN EARLY DETECTION OF PROSTATE CANCER

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ABSTRACT

Objective: To determine the clinical usefulness of prostate-specific antigen (PSA) density in the transition zone (PSADTZ) for increasing the specificity in early detection of prostate cancer (PCa) and reducing unnecessary biopsies in males with PSA between 4.0 and 10 ng/mL.

Materials and Methods: This cross-sectional study obtained PSADTZ measurements in 68 patients with PSA between 4.0 and 10 ng/mL. All patients underwent transrectal ultrasonography (TRUS) with biopsies. PSADTZ was estimated by dividing the PSA value by the volume of the transition zone (TZ) obtained. We compared performance measurements for these parameters with those from the PSA itself, PSA density (PSAD) and free PSA/total PSA ratio (F/T PSA). The ability of the method in increasing PSA specificity was demonstrated and compared in univariate and multivariate analyses, and by Receiver Operating Characteristic Curves (ROC).

Results: Of the 68 patients under study, 17 (25%) were diagnosed with PCa. The TZ volume ($p = 0.001$) and PSADTZ ($p = 0.001$) variables presented means that exhibited statistically significant differences. When compared with the area under the curve (AUC), ROC curves obtained by this method revealed that PSADTZ was the strongest predictor for PCa when considering the cut-off point provided by the curve; that is, 0.35 ng/mL/cc. When PSADTZ was employed, the detection failure would be close to 20%, and less than 45% of cases would undergo unnecessary biopsies. On the other hand, when F/T PSA was used, the loss would reach almost 40%; however less than 30% would undergo unnecessary biopsies. Nevertheless, PSADTZ had the only AUC presenting $p < 0.05$ in significance when compared with 50%, and was consequently discriminative.

Conclusions: PSADTZ increased PSA specificity in early detection of PCa in males with PSA between 4.0 and 10 ng/mL. However, it was shown to have lower predictive value and lower accuracy than the percentage of free PSA since it presents a higher negative predictive value than all other parameters assessed, and it can be considered clinically useful for reducing unnecessary indications for biopsy.

Key words: prostatic neoplasms; diagnosis; prostate-specific antigen; neoplasm staging
Int Braz J Urol. 2005; 31: 137-46

INTRODUCTION

Prostate cancer (PCa) is considered the most frequent neoplasia in men and the second cause of death by cancer in males. Over the past 12 years, the

incidence of PCa has increased over 50% and deaths from the disease risen 40% (1).

The isolation of the prostate-specific antigen (PSA) in 1979 led to a dramatic change in the diagnosis and management of PCa (2). PSA is the most

sensitive serum marker in males with prostate disease. Though periurethral glands are known to release PSA into the urine, it is usually accepted that, at least for practical purposes, PSA is produced exclusively by prostate epithelial cells (3).

Therefore, PSA has proven its usefulness as a serum marker for PCa. However, PSA sensitivity and specificity are not yet enough to turn it into the ideal screening test for PCa, since increased levels can also be seen in prostatitis and benign prostate hyperplasia (BPH) (4). The majority of PSA that is released by the prostate into the serum comes from the transition zone and BPH results almost exclusively from the transition zone hyperplasia. Kalish et al. (5) introduced the concept of serum PSA adjusted for the transition zone volume (called PSADTZ) and some studies, like his own, have suggested higher accuracy of this method for early detection of PCa. From all the referenced studies, we can extract a clear impression that their conclusions are not definitive. The introduction of this new concept opens a wide range of new diagnostic possibilities; however, though its usefulness has been statistically demonstrated, it must still be confirmed and validated through other studies that are equally well controlled and methodologically well conducted (reproducible).

In this study, we intend to assess the potential role of PSADTZ in the early diagnosis of PCa in our setting through measurement of early detection from a screening study.

MATERIALS AND METHODS

This research has been performed with a cross-sectional design in a screening study. The study factor was PSADTZ and other tests for early diagnosis of PCa, and the end-point was the pathological identification of BPH or PCa.

The sample consisted of 68 patients undergoing screening for early diagnosis of PCa and with indication of transrectal ultrasound (TRUS) with biopsy (altered PSA and/or digital rectal examination). In this research, population, in relation to PSA, only individuals with total PSA values between 4.0 and 10 ng/mL were included.

The exclusion criteria were a total PSA lower than 4.0 ng/mL or higher than 10 ng/mL, patient refusal to participate in any assessment procedure, a history of PCa, prostatitis, prostate intraepithelial neoplasia (PIN), urinary tract infection, bladder catheterization or urinary retention and previous prostate surgery.

Variables under study were total prostate volume, transition zone volume, total PSA, free PSA, free-to-total PSA ratio, age, PSADTZ, result of biopsy and digital rectal examination.

All patients from the screening study were assessed for lower urinary tract symptoms by completing the international prostate symptom score, then had their blood collected for determining PSA levels and underwent digital rectal examination.

TRUS with prostate biopsy was indicated for patients who presented changes in their digital rectal examination, which suggested the presence of PCa, and for those with total PSA higher than 4.0 ng/mL. Also, regardless of any adjustments for age, their free PSA was dosed in serum before the TRUS. The serum PSA level was determined by radioimmunoassay method performed on serum collected before digital rectal examination and analyzed with the Immulite-PSA kit (CA, USA).

A digital rectal examination was classified as suspected or non-suspected for neoplasia.

The TRUS measured the total prostate volume and the specific volume of the transition zone (TZ) through a bi-planar 2-probe transducer with 7.5 MHz in the sagittal probe and 6.5 MHz in the transversal probe, coupled to a model AI 5200 S Envision Acoustic Imaging device (Dornier Co.). Prostate was measured in its transversal and sagittal planes using the formula for estimating the ellipsoid volume (width x length x height x 0.52). Once the measures were obtained, sextant puncture biopsies were systematically performed using a 16-gauge needle mounted on a Pro-Mag 2.2 automatic pistol.

Biopsy results were generically classified as PCa or BPH and/or prostatitis.

The value of PSADTZ was estimated by dividing the serum PSA level value (between 4.0 and 10 ng/mL) by the value obtained in an echographic measurement of the TZ volume and expressed as ng/mL/cc.

As a post-diagnosis approach, individuals who were identified as having PCa were referred to the staging protocol and their therapeutic follow-up was based on the protocol's findings.

Statistical Analysis

Receiver Operating Characteristic (ROC) curves were used to graphically demonstrate the sensitivity and specificity of the assessed tests (PSA parameters), over a variety of "cut-off" points. The area under the curve (AUC) was calculated using PEPI version 3.0 (Computer Programs for Epidemiologists by J.H. Abramson and P.M. Gahlinger).

Different AUCs were compared as described by Hanley & McNeil, using the correlation coefficient corrected for AUC as a test for comparing proportions, while the McNemar test uses data that have been previously categorized by their cut-off points.

Wilcoxon-Mann-Whitney U test (WMW) was used for non-parametric analysis of intergroup comparison of data from patients with and without PCa, considering the analysis of means and medians. The relationship between variables was analyzed using Spearman's correlation coefficient.

On the other hand, the linear correlation coefficient (Pearson Product-Moment) was calculated in order to assess the association intensity between total gland volume, TZ volume and PSA.

Finally, we used the multivariate logistic regression analysis model in the "stepwise" system for assessing PSA parameters in relation to its ability to predict PCa by applying systematic selection procedures based on data from the general and negative digital rectal examination groups. The statistical sig-

nificance level established for all described tests was $p < 0.05$.

RESULTS

Of the 68 assessed patients, 17 were diagnosed as having PCa, and BPH was detected in 51. The digital rectal examination revealed changes suggestive of malignant neoplasia in 15 patients (22.1%) where the presence of PCa was confirmed in only 4 (26.7%). Additionally, among patients with normal (unsuspected) digital rectal examination, histology compatible with malignancy was subsequently found in 13 (24.5%) cases. These findings indicate that, in this study group, due to its low sensitivity (23%), the digital rectal examination was not good as a method for early diagnosis of PCa, despite its good specificity (78%) and low positive (29%) and negative (24%) predictive value.

When considering their asymmetrical distribution, mean values for parameters in both groups, cancer and benign disease, did not show statistically significant differences for the variables age, PSA, total gland volume and PSAD. On the other hand, the variables TZ volume ($p = 0.001$) and PSADTZ ($p = 0.001$) presented means that revealed statistically significant differences in both groups. For estimating the means, the p value considered the Levene's test for equality of variances when applying the t test for independent samples (Table-1).

In relation to the median analysis, the only variables presenting statistical differences were TZ volume ($p = 0.0002$) and PSADTZ ($p = 0.0012$) (Table-2).

Table 1 – Association between pathology examination and PSA parameters (mean) in the general group.

	Total	Benign	Cancer	P value
PSA	6.1	6.2	5.7	0.207
Total Volume	38.3	39.9	33.8	0.153
PSAD	0.18	0.16	0.17	0.534
TZ Volume	18.6	21.2	10.9	0.001*
PSADTZ	00.48	0.36	0.62	0.001*
F/T PSA	00.12	0.11	0.14	0.190

$p < 0.05$ Student's "t" test; * significant

PSAD = PSA density; TZ = transition zone; PSADTZ = PSA density in the transition zone; F/T = free/total

Table 2 – Association between pathology examination and PSA parameters (medians) in the general group.

	Total	Benign	Cancer	P value
PSA	5.6	5.6	5.6	0.565
Total Volume	35.7	36.5	35.2	0.218
PSAD	0.16	0.16	0.18	0.470
TZ Volume	16.8	18.5	9.5	0.001*
PSADTZ	0.36	0.31	0.7	0.001*
F/T PSA	0.11	0.11	0.13	0.145

$p < 0.05$ Mann-Whitney “U” test. * significant

PSAD = PSA density; TZ = transition zone; PSADTZ = PSA density in the transition zone; F/T = free/total

Bivariate analysis of correlations between total prostate volume and TZ volume using the scatter plot presented a regression straight line (Figure-1) as demonstrated by the plot’s points, suggesting a strong correlation between them ($r = 0.825$, $p = 0.0001$). On the other hand, when analyzing PSA and other volumes, the correlation coefficient was very low both at the crossing of PSA and total volume ($r = 0.05$, $p = 0.664$) and at the crossing of PSA and TZ volume ($r = 0.01$, $p = 0.928$).

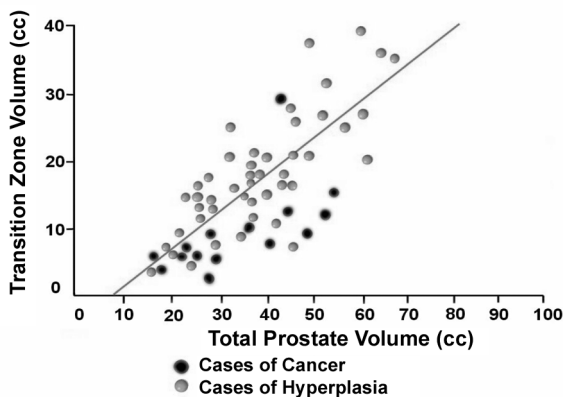


Figure 1 – Scatter graph with regression straight line showing the correlation between total prostate volume (X axis) and transition zone volume (Y axis).

Data on each parameter shown in the Tables demonstrating performance measurements were obtained from the best cut-off value for each parameter (which, in turn, was determined by the ROC curve), considering both the general and the negative digital rectal examination groups (Table-3). In relation to absolute values in the negative digital rectal examination group, the AUC of PSADTZ presented higher absolute values than did F/T PSA, in addition to being more significant (considering the significance compared with 50%). Its specificity, positive predictive value (PPV) and accuracy are surpassed by the performance of F/T PSA; however, its sensitivity and its negative predictive value (NPV) are clearly superior.

When compared, ROC curves obtained for each parameter from their specific cut-off values revealed that PSADTZ was the strongest predictor of PCa when considering the cut-off point in the upper left area of the curve – that is 0.35 ng/mL/cc (Figure-2). It means that when considering the best cut-off point for PSAD (0.15 ng/mL/cc), in the group with negative digital rectal examination approximately 40% of PCa cases would be missed (since sensitivity was approximately 60%) and about 60% would undergo unnecessary biopsies (since specificity was approximately 40%). Using the PSADTZ parameter, the missing rate would be close to 20% and less than 45% of patients would undergo unnecessary biopsies.

The “box plot” percentile graphs demonstrated central trend values for PSADTZ, whose me-

ASSESSMENT OF PSA DENSITY IN THE TRANSITION ZONE

Table 3 – Performance measurements for PSA parameters in the general (G) and negative digital rectal examination (DRE) groups.

Parameters	Cut-off Point	Specificity	Sensitivity	Positive Predictive Value	Negative Predictive Value	Accuracy
PSA (G)	5	35.3	70.6	26.6	78.2	44.1
PSA (DRE)	5	37.5	69.2	26.4	78.9	45.2
PSA (G)	0.15	45.1	94.1	27.5	90.0	36.7
PSA (DRE)	0.15	42.5	61.5	25.8	77.2	47.1
Free PSA (G)	0.15	78.2	50.0	46.1	80.6	70.4
Free PSA (DRE)	0.15	72.0	62.5	41.7	85.7	69.7
PSADTZ (G)	0.35	56.9	82.4	38.8	90.6	63.2
PSADTZ (DRE)	0.35	55.0	76.9	35.7	88.0	60.3

PSADTZ = PSA density in the transition zone; F/T = free/total

dian was 0.62 ng/mL/cc for PCa and 0.28 ng/mL/cc for BPH. The cut-off value for PSADTZ was 0.36 ng/mL/cc, which corresponded to values between the 75th percentile for cancer (75% of cases of PCa were above this value) and the 25th percentile for benign disease (75% of cases of BPH were below this value). When considering the values obtained by the same analysis, we verified a statistically significant difference between PSADTZ values for both groups ($p = 0.0012$), Figure-3.

Considering the ROC curves for each parameter in the parameter analysis, PSA presented a smaller area (AUC = 45.7%) and low specificity (35%), while PSADTZ showed a larger area (AUC = 74.6%) and higher specificity (56.9%) and was the only parameter to present significance compared with 50% at significant levels; that is, it was discriminative. At its best cut-off point (0.35 ng/mL/cc) whose sensitivity reached 82.4%, there would be a more accentuated reduction in the number of unnecessary biopsies (over

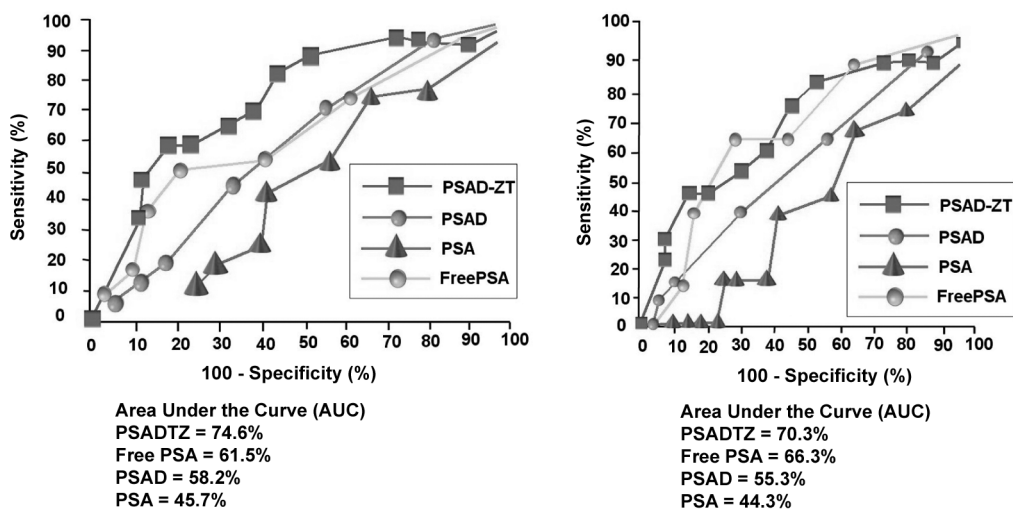


Figure 2 – Comparison of ROC curves with specification of AUCs in the general (left) and negative digital rectal examination (right) groups. PSAD-ZT = PSA density in the transition zone.

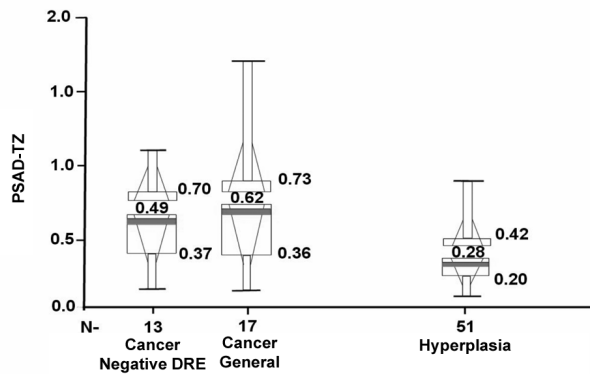


Figure 3 – “Box Plot” graphs showing the distribution of mean and median PSADTZ values for cancer (n = 17) and hyperplasia (n = 51) in the general and negative digital rectal examination (n = 13) groups. PSAD-ZT = PSA density in the transition zone.

55%) in comparison with other diagnostic tests (PSA parameters), Table-4.

In the comparative analysis of the respective AUCs, using the Hanley-McNeil method, statistically significant differences were observed between the AUC of the PSADTZ parameter and those of the PSA and PSAD parameters (Table-5). The area under the curve of the parameter F/T PSA, however, was not statistically different from the PSADTZ, thus suggesting a similar overall performance for both tests in increasing PSA specificity.

Results obtained with the multiple logistic regression analysis model for prediction of PCa, which applied the “stepwise” selection procedure based on the 4 variables, excluded non-significant variables – that is PSA and PSAD – demonstrating that PSADTZ and free-to-total PSA ratio were the strongest and most significant predictors of PCa. When considering values obtained at the best cut-off points in the original ROC curves, the odds ratio was 9.07 (with p = 0.032) for PSADTZ and 7.45 (with p = 0.027) for free-to-total ratio. When the assessment was performed using cut-off points with highest specificity of the ROC curve, odds ratio was 13.71 (p = 0.005) and 6.33 (p = 0.069) respectively, showing statistical superiority of PSADTZ in predicting PCa (Table-6).

COMMENTS

Studies have indicated that 2/3 of patients undergoing biopsy based exclusively on the finding of an intermediary PSA value show no histological evidence of PCa (6). In this respect, several new concepts have been introduced regarding PSA, all of them intended to optimize the clinical usefulness of PSA by increasing its sensitivity and specificity and, thus, trying to reduce the numbers of unnecessary biop-

Table 4 – Analytical and descriptive results from performance measures of parameters in the general (G) and negative digital rectal examination (DRE) groups.

Parameters	PSA (G)	PSA (DRE)	PSAD (G)	PSAD (DRE)	F/T PSA (G)	F/T PSA (DRE)	PSADTZ (G)	PSADTZ (DRE)
Comparison Significance in AUC ***	0.71	0.75	0.13	0.28	0.12	0.06	0.001*	0.008*
AUC	45.7	44.3	58.2	55.3	61.5	66.3	74.6	70.3
Best Cut-off Point	5	5	0.15	0.15	0.15	0.15	0.35	0.35
Sensitivity	70.6	69.2	94.1	61.5	50.0	62.5	82.4	76.9
Specificity	35.3	37.5	45.1	42.5	78.2	72.0	56.9	55.0
Positive Predictive Value	26.6	26.5	27.5	25.8	46.1	41.7	38.8	35.7
Negative Predictive Value	78.2	78.9	90.0	77.2	80.6	85.7	90.6	88.0
Accuracy	44.1	45.2	36.7	47.1	70.4	69.7	63.2	60.3

* significant value, ** significance compared with 50% in AUC considering p < 0.05, AUC = area under the curve PSAD = PSA density; TZ = transition zone; PSADTZ = PSA density in the transition zone; F/T = free/total

ASSESSMENT OF PSA DENSITY IN THE TRANSITION ZONE

Table 5 – Comparative analysis of areas under the curves (AUCs) of PSA density in the transition zone with areas AUCs of the other parameters in the general and negative digital rectal examination groups.

PSA Parameters	AUCs of PSADTZ	AUCs of other parameters	r value	Means of Compared AUCs	Z value	P value
PSA (G)	74.6	45.7	0.3673	60.15	3.459	0.001*
PSA (DRE)	70.3	44.3	0.3028	57.3	2.559	0.01*
PSAD (G)	74.6	58.2	0.7950	66.4	3.321	0.001*
PSAD (DRE)	70.3	55.3	0.6940	62.8	2.102	0.036*
F/T PSA (G)	74.6	61.5	-0.107	68.05	1.124	0.261
F/T PSA (DRE)	70.3	66.3	-0.249	68.30	0.328	0.743

* $p < 0.05$, r = Pearson's correlation coefficient, Z = Coefficient of Hanley-McNeil table
 PSAD = PSA density; TZ = transition zone; PSADTZ = PSA density in the transition zone; F/T = free/total

sies in men with benign disease. These new concepts include PSA density, PSA velocity, PSA adjusted for age, and determination of molecular forms of PSA (free versus conjugated to proteins) (7,8).

For this purpose, the concept of PSADTZ has been recently suggested as a valuable approach. When comparing the results from the assessment of mean and median values for the parameters obtained in our study with those demonstrated by the majority of reviewed authors, we found an important similarity in the significant differences obtained in the 2 subgroups (PCa and BPH) for the variables TZ volume and PSADTZ (6-8).

On bivariate analysis of correlations, results observed in the literature have presented correlation coefficients between the variables total volume and TZ volume that, when compared, confirm those obtained in our study (7,9-11). Comparative analyses of the areas under ROC curves of several parameters

demonstrate that higher indexes are observed by the PSADTZ parameter, both in the total group and in the segment's negative digital rectal examination, volume < 30cc and volume \geq 30 cc. These results are comparable in the total group to those found by other authors (6,7,9-13). However, in a deviation from the study by Maeda et al. (7) who detected a higher index in the group with negative digital rectal examination, the present project did not attain such an outcome. On the other hand, Lin et al. (15), Akduman et al. (16), Gohji et al. (17) and Rietbergen et al. (18) did not find significant statistical differences between the AUCs of PSAD and PSADTZ, even if they used different sampling criteria and statistical methods in relation to our study.

When using the method described by Hanley and McNeil for comparison between the AUC parameters estimated both for the total group and for the group with negative digital rectal examination, we

Table 6 – Multivariate analysis by logistic regression considering the best cut-off point (CP) and sensitivity (S) of 90-95%.

Variable	Estimate *	Standard Error	Wald **	Significance ***	Odds Ratio
PSADTZ (CP)	2.2055	1.0283	4.60	0.032	9.074
PSADTZ (S)	2.6188	0.9491	7.61	0.005	13.718
F/T PSA (CP)	2.0084	0.9118	4.85	0.027	1.248
F/T PSA (S)	1.8457	1.0169	3.29	0.069	0.863

* test's coefficient, ** test's p, *** p value
 PSAD = PSA density; TZ = transition zone; PSADTZ = PSA density in the transition zone; F/T = free/total

observed that they showed significant differences, especially when comparing PSADTZ with the PSA and PSAD parameters. These differences have been demonstrated by other studies as well, thus revealing the high predictive power of this diagnostic test (6,7,10,12).

On the other hand, when PSADTZ was compared with the F/T PSA parameter, no statistically significant difference was found in either group ($p = 0.261$ and $p = 0.743$, respectively). The same result has been obtained by the majority of previous studies observing the absolute value of AUC for PSADTZ (6,7,9,11,13,14). Searching for a cut-off limit for all parameters that maintained the sensitivity for cancer detection around minimal limits of 90 to 95%, values were defined that, in addition to being close to those evidenced in the literature (except for F/T PSA), presented very similar corresponding specificity as well with no exceptions. At 0.3 ng/mL/cc, PSADTZ reached 47% of specificity, the same one obtained by the cut-off value of 0.25 in the study by Djavan et al. (6).

Finally, by applying the “stepwise” selection procedure which has been performed by a few authors, our results were in agreement with those demonstrated by Djavan et al. (6,12) in 2 of their studies ($n = 559$ and $n = 1051$ respectively) where the same exclusions for the PSA and PSAD parameters were performed due to their low predictive value in both studies, thus revealing the F/T PSA and PSADTZ parameters as the strongest and highly predictive for PCa. This result was also similar to the one presented by Moon et al. (9).

Among limitations observed in our analysis is the sample “n” itself, which, despite being regarded as reduced and consequently presenting a wide confidence interval, was surprisingly able to provide statistical results that were comparable to larger series. Analyses related to the predictive ability for extraprostatic disease were not performed as well, despite being the object of study in some of the reviewed references (19).

The need for cost-effectiveness studies is evident as the main components of this diagnostic test involve the performance of 2 procedures, which, in turn, have their specific costs – even if we can infer a decreased cost when considering savings due to

fewer indications of TRUS with biopsies, its own associated costs, and risks that are certainly more relevant. Another fact to be considered, which is still unedited, is the proposal for using the method presented here in the routine for performance of transrectal biopsies in patients with indication who, in case of a benign diagnosis even in the presence of suggestive changes (PSA and/or digital rectal examination) could benefit from another parameter for increasing the specificity of PSA when altered values are maintained. When considering the possibility in the near future that these patients undergo a new invasive procedure that is not exempt from risks, we must remember the recent studies published by Okegawa et al. (20) and Singh et al. (21), showing that PSADTZ, as well as advanced age and presence of high grade PIN, is one of the strongest predictors for PCa in subsequent biopsies following the initial biopsy.

CONCLUSION

The PSA parameter known as PSADTZ has shown itself to possess a statistical power for increasing the specificity, positive predictive value, negative predictive value and accuracy, which, in addition to being similar to performance measures verified in the comparative analysis with F/T PSA, were superior to the latter in some analyses. The best cut-off point established by our study was 0.35 ng/mL/cc.

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Received: September 20, 2004

Accepted after revision: March 17, 2005

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EDITORIAL COMMENT

In this study, the authors used ultrasound to determine the volume of the transition zone where BPH would be expected to occur and where cancer is less likely to occur. When the PSA is factored by the volume of the transition zone, they found that the PSA density in transition zone was more predictive of prostate cancer than either serum total PSA or PSA density as routinely determined in patients with a PSA of 4 to 10 ng %. The percentage of free PSA and transition zone PSA density enhance the specificity of PSA when determining which patients should undergo repeat biopsy. Overall, 25% of the patients were diagnosed with prostate cancer. The high cancer rate can be explained by the fact that patients included in this study were referred for early diagnosis and not for screening purposes. Accuracy of transition zone volume measurement is ultrasonographer-dependent, which may influence the reproducibility of the pro-

cedure. Of some concern may be the fact that the predictive power of the PSA transition zone is significantly affected by prostate size in prostates weighing less than 30g in which the transition zone is not markedly enlarged and is therefore more difficult to measure. The usefulness of the PSA transition zone density is significantly diminished and less accurate than free-to-total PSA (1). Finally, unlike PSA parameters, PSA density in the transition zone requires the use of transrectal ultrasound, escalating the costs of the test.

REFERENCE

1. Djavan B, Zlotta A, Kratzik C, Remzi M, Seitz C, Schulman CC, et al.: PSA, PSA density, PSA density of transition zone, free/total PSA ratio, and PSA velocity for early detection of prostate cancer in men with serum PSA 2.5 to 4.0 ng/mL. *Urology*. 1999; 54: 517-22.

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