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PROSTATE-SPECIFIC ANTIGEN VERSUS PROSTATE-SPECIFIC ANTIGEN DENSITY AS PREDICTOR OF TUMOR VOLUME, MARGIN STATUS, PATHOLOGIC STAGE, AND BIOCHEMICAL RECURRENCE OF PROSTATE CANCER

STEPHEN A. BRASSELL, TZU-CHEG KAO, LEON SUN, AND JUDD W. MOUL

ABSTRACT

Objectives. To compare prostate-specific antigen (PSA) and PSA density (PSAD) calculated by transrectal ultrasound (TRUS) volume (TRUS PSAD), pathologic volume (Path PSAD), and weight (Weight PSAD) for their ability to predict pathologic characteristics and biochemical recurrence of prostate cancer. We also compared all PSAD derivatives to determine consistency.

Methods. Between 1993 and 2002, 306 patients were retrospectively identified who had had PSAD determined preoperatively by TRUS and subsequently underwent radical prostatectomy with whole mounting and close step sectioning. The determination of stage, margin status, tumor number, individual tumor volume, and total tumor volume was obtained from the pathologic evaluation. Clinical follow-up was available for 265 patients.

Results. The mean patient age was 62 years, the median Gleason score was 7, the median PSA level was 5.80 ng/mL, and the median TRUS PSAD was 0.16. The percentages of concordance for PSA, TRUS PSAD, Path PSAD, and Weight PSAD were similar in predicting margin status and extracapsular extension. Using linear regression analysis, PSA was more efficacious than TRUS PSAD, Path PSAD, or Weight PSAD in predicting the total tumor volume (R^2 0.11, 0.08, 0.04, and 0.06, respectively). A significant positive correlation was found among TRUS PSAD, Path PSAD, and Weight PSAD. PSA was significantly better in predicting biochemical recurrence than TRUS, Path, or Weight PSAD (concordance 75.5%, 66.6%, 66.5%, and 70.4%, respectively).

Conclusions. PSA and TRUS PSAD are significant and equivalent predictors of margin status and extracapsular extension. A marked difference may exist between PSA and TRUS PSAD in predicting the total tumor volume and biochemical recurrence. UROLOGY **66:** 1229–1233, 2005. © 2005 Elsevier Inc.

Controversy exists concerning the utility of serum prostate-specific antigen (PSA) as a screening tool for prostate cancer, as well as its prognostic value in determining tumor burden and posttreatment biochemical recurrence and survival. Recent data support the idea that benign prostatic hyperplasia is the major contributor to serum PSA values between 2 and 10 ng/mL. Moreover, tumor volume and biochemical recurrence might not be predicted by a pretreatment PSA level within this range.[1] With the advent of more rigorous screening efforts and ensuing stage migration, most cancers detected presently fall within these relatively low PSA values. We are now challenged to search for a more reliable prognostic marker to assess these tumors accurately and assist in preoperative planning and subsequent follow-up.

The original research concerning PSA density (PSAD) by Benson[2] focused on its utility in improving the sensitivity and specificity of PSA in prostate cancer screening. Less investigation has been done into evaluating its role as a predictor of tumor characteristics. It has been predicted that, on average, 1 g of benign prostatic hyperplasia tis-

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From the Center for Prostate Disease Research, Department of Surgery and Division of Epidemiology and Biostatistics, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland; and Urology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, DC

Reprint requests: Stephen A. Brassell, M.D., 1 Hermann Museum Circle, Apt. 2084, Houston, TX 77004. E-mail: stephen.brassell@us.army.mil

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sue increases the serum PSA concentration by about 0.3 ng/mL. Furthermore, 1 g of prostate cancer tissue increases the serum PSA level by about 3.5 ng/mL.[3] Thus, the hypothesis could be made that the PSAD would be a more accurate marker of tumor volume, extracapsular extension, and eventual PSA recurrence. Several groups have conducted preliminary investigations into this topic with small data sets. One such study directly compared PSA versus PSAD in predicting regional lymph node involvement and found that PSAD had a 30% greater sensitivity than PSA alone using a value of 0.15 ng/mL/cm^3 and 10 ng/mL, respectively.[4] It has also been demonstrated that for a PSAD of less than 0.15 ng/mL/cm^2, favorable pathologic features (organ-confined, Gleason score less than 7, and tumor volume less than 10%) can be predicted with a sensitivity of 74%.[5] More recently, it has been shown that PSAD is a strong predictor of biochemical failure after prostatectomy.[6] Our goal was to determine whether PSAD was a more accurate predictor of tumor volume, margin status, pathologic stage, and biochemical recurrence than PSA using a cohort of men enrolled in a large outcomes study and who had had unique close-step sectioned pathologic assessment.

MATERIAL AND METHODS

A retrospective analysis between 1993 and 2002 revealed 306 patients treated at 1 of 10 military medical centers included in the Center for Prostate Disease Research database who had had preoperative PSAD measured by transrectal ultrasonography (TRUS) and subsequently proceeded to radical prostatectomy with whole mounting at the Armed Forces Institute of Pathology, as previously described.[7,8] Clinical data were obtained, including clinical stage, biopsy Gleason score, race, age, TRUS volume, PSA, and PSAD as determined by TRUS volume (TRUS PSAD). Pathologic data were reviewed to document prostate size, tumor number, individual and total tumor volume, pathologic stage, Gleason score, and margin status. The pathologic PSAD (Path PSAD) was then calculated using the preoperative PSA level and the prostate volume as determined on gross pathologic examination using the solid ellipse formula: 0.52 × (length × width × height). PSAD was also calculated using the pathologic weight of the prostate (Weight PSAD). Clinical follow-up was available for 265 patients. In the 41 patients for whom a postoperative PSA level was not available, 26 were less than 1 year from surgery and 15 were lost to follow-up. Evidence of biochemical recurrence, defined as a solitary PSA value greater than 0.2 ng/mL, and clinical disease-free survival were noted. All PSA values were obtained using the Elecsys E170/2010 (Roche/Boehringer Mannheim, Indianapolis, Ind) "ultrasensitive" PSA assay.

Statistical Analysis

The association among TRUS PSAD, Path PSAD, and Weight PSAD was evaluated using Spearman's correlation. Risk factors such as pathologic Gleason score, age, and the PSA-related variables (PSA, TRUS PSAD, Path PSAD, and Weight PSAD) were treated as continuous variables. For a binary outcome, a forward selection procedure was used to build the adjusted logistic regression models by including race, pathologic Gleason score, age, and one PSA-related variable with an entry significance level of 0.15. The area under the corresponding receiver operating characteristic curve (AUC) was used to compare the logistic regression models for a given outcome. Also, to determine which predictor was better among the logistic regression models for a given outcome, the percentage of concordance (C) was used. To predict the time to biochemical recurrence after radical prostatectomy, Cox proportional hazards models were used. Risks were assessed in hazard ratios. A forward selection procedure with similar criteria was applied. To predict the total tumor volume, R^2 of linear regression analysis was used. The 95% confidence interval was used with the corresponding estimate.

All the models were done in two ways: univariate (or unadjusted) analysis using only one independent variable in the model, and multivariate (or adjusted) analysis using more than one independent variable in the model. C, AUC, and R^2 were used in comparing the 1993 to 1997 and 1998 to 2002 data sets. A statistical software program, Statistical Analysis Systems, version 8.2, was used for computations. The significance level for a statistical test was set at 5%.

RESULTS

The demographics of our study group consisted of a mean age of 62 years, with a racial distribution of 69% white and 26% black. The clinical parameters consisted of a mean PSA level of 7.34 ng/mL, mean TRUS volume of 40 cm^3, pathologic volume of 32 cm^3, and median TRUS PSAD, Path PSAD, and Weight PSAD of 0.16, 0.21, and 0.14, respectively.

First, we examined the association among TRUS PSAD, Path PSAD, and Weight PSAD. A strong correlation was seen among all the measurements. This was indicated by a Spearman correlation coefficient of 0.792 between TRUS PSAD and Path PSAD, 0.837 between TRUS PSAD and Weight PSAD, and 0.928 between Path PSAD and Weight PSAD.

PSA, TRUS PSAD, Path PSAD, and Weight PSAD were then analyzed individually and found to have a significant association in predicting margin status (C = 60.3%, 58.3%, 60.8%, and 60.2%, respectively). Similar results were obtained in relation to extracapsular extension (C = 65.1% for PSA, 62.9% for TRUS PSAD, 62.6% for Path PSAD, and 65.5% for Weight PSAD). Next, we determined which factor would be more predictive of the total tumor volume. Using linear regression analysis, PSA was somewhat superior to TRUS PSAD, Path PSAD, and Weight PSAD (R^2 = 0.11, 0.08, 0.05, and 0.06, respectively).

Finally, each risk factor was evaluated for its ability to predict the time to biochemical recurrence. With a mean follow-up of 43 months, 49 patients (16%) had biochemical recurrence. When proceeding with multivariate analysis using forward selection, Gleason score, PSA level, TRUS PSAD, Path PSAD, and Weight PSAD were all significant predictors of the time to biochemical recurrence. To negate the impact of scale, a direct comparison using the percentage of concordance revealed PSA

TABLE I. *Percentage of concordance and areas under operating characteristic curve for logistic regression models during 1993 to 2002*

	1993–1997		1998–2002		1993–2002	
Variable	C (%)	AUC	C (%)	AUC	C (%)	AUC
Surgical margin						
PSA	62.5	0.632	58.6	0.591	60.3	0.610
TRUS PSAD	60.9	0.617	56.3	0.573	58.3	0.592
Path PSAD	63.6	0.641	58.5	0.590	60.8	0.613
Weight PSAD	63.7	0.642	57.4	0.580	60.2	0.607
Extracapsular extension						
PSA	66.3	0.666	64.0	0.644	65.1	0.655
TRUS PSAD	64.5	0.653	61.7	0.626	62.9	0.638
Path PSAD	63.2	0.637	61.8	0.624	62.6	0.631
Weight PSAD	65.8	0.661	65.3	0.656	65.5	0.658
Biochemical recurrence						
PSA	75.0	0.753	75.7	0.763	75.5	0.760
TRUS PSAD	59.6	0.605	71.1	0.724	66.6	0.678
Path PSAD	65.6	0.658	67.1	0.679	66.5	0.673
Weight PSAD	67.3	0.673	73.1	0.736	70.4	0.709

Key: C = concordance; AUC = area under receiver operating characteristic curve; PSA = prostate-specific antigen; TRUS PSAD = PSA density determined from transrectal ultrasound volume; Path PSAD = PSAD determined from pathologic volume; Weight PSAD = PSAD determined from prostate weight.

as a better predictor than TRUS, Path, or Weight PSAD (C = 75.5%, 66.6%, 66.5%, and 70.4%, respectively; Table I).

Next, consideration was given to the impact of lower tumor volumes on the predictive ability of PSAD. Specifically, we wondered whether the recent stage migration and downsizing of tumor burden made PSAD more or less relevant currently than in the past. To address this issue, we divided our analysis into two year-groups: 1993 to 1997 and 1998 to 2002. Both PSA and the PSAD derivatives had a 4% to 6% greater percentage of concordance and AUC in the 1993 to 1997 subgroup than in the 1998 to 2002 subgroup in determining margin status ($P = 0.0022$ for C and $P = 0.0018$ for AUC; Table I). Additionally, the earlier subgroup exhibited greater predictive capacity for extracapsular extension (1% to 3%; $P = 0.0410$ for C and $P = 0.0413$ for AUC). No difference between PSA and the PSAD derivatives was discernible in predicting these outcomes.

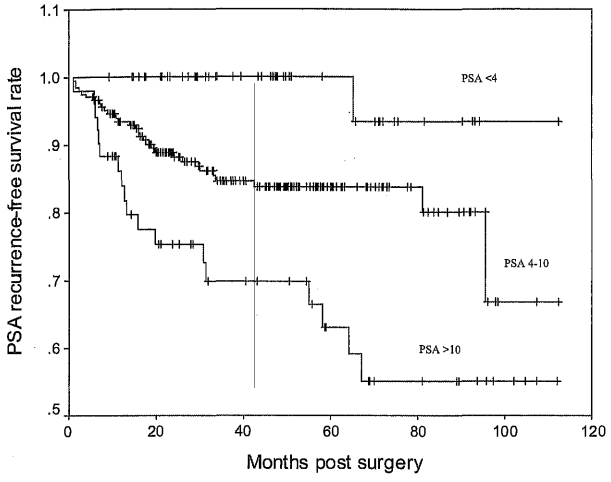
No significant difference was noted between the two year-groups in predicting biochemical recurrence ($P = 0.1202$ for C and $P = 0.1436$ for AUC). However, the PSA level was consistently greater than the PSAD derivatives in both year groups for determining biochemical recurrence.

To investigate this difference further, the preoperative PSA level was categorized into the following subgroups: group 1, PSA less than 4; group 2, PSA of 4.0 to 10; and group 3, PSA greater than 10 ng/mL. The same was done with TRUS PSAD: group 1, TRUS PSAD less than 0.15; group 2, TRUS PSAD 0.15 to 0.26; and group 3, TRUS PSAD greater than 0.26. Stratified PSA values were increasingly predictive of the time to biochemical recurrence, with a hazard ratio of 8.56 and 19.91 comparing groups 2 and 1 and groups 3 and 1, respectively. This was not the case with TRUS PSAD (hazard ratio 1.77 and 2.45 comparing groups 2 and 1 and groups 3 and 1, respectively). Furthermore, these individual groups were evaluated for their ability to predict the time to biochemical recurrence expressed in Kaplan-Meier curves (Fig. 1). The separation was not as apparent in the TRUS PSAD subgroups as it was in the PSA subgroups, with crossover occurring at the 8-year interval for groups 2 and 3.

COMMENT

Few studies have focused on PSAD's prognostic value as a determinant of tumor burden and biochemical recurrence. Zentner *et al.*[9] found that the biochemical disease-free survival rate of those patients treated with external beam radiotherapy was 100% for those with a PSAD less than 0.3 and 62% for those with a PSAD greater than 0.3 at a mean follow-up of 13 months. A surgical series published in 1994 found that patients with a PSAD less than 0.3 had an 80% chance of operative success compared with 46% for patients with a PSAD greater than 0.3.[10]

Additional analysis by Zlotta *et al.*[11] determined that PSAD of the transition zone was the most significant predictor of extracapsular disease by multivariate and receiver operating characteristic anal-



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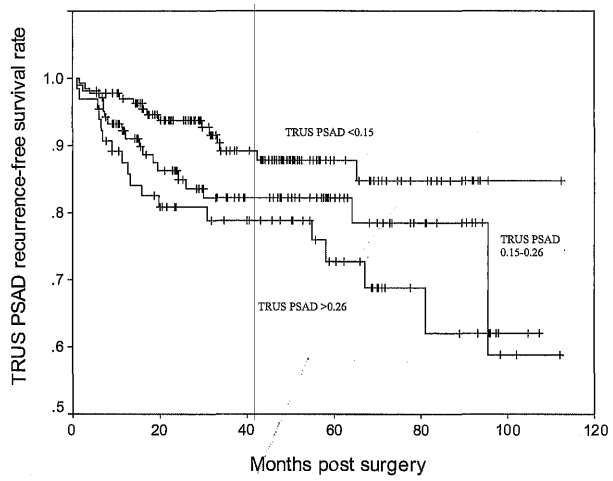

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FIGURE 1. *(A) Kaplan-Meier curve for PSA subgroup analysis.* P = *0.0001 (log-rank test). (B) Kaplan-Meier curve for TRUS PSAD subgroup analysis.* P = *0.0390 (log-rank test).*

ysis, superseding PSA and Gleason score. A more recent study by Freedland *et al.*[6] indicated that PSAD, when using the weight of the prostate as measured on pathologic examination as a surrogate for volume, was the strongest predictor of extracapsular extension. They also showed that only PSAD and Gleason score were predictors of biochemical recurrence. Furthermore, PSAD was the only clinical variable that was a significant independent predictor of margin status, extracapsular extension, and seminal vesicle involvement, and PSA alone was not an independent predictor of these pathologic parameters in multivariate analysis.[6] The same group then went on to compare PSAD determined by TRUS against PSA in predicting biochemical recurrence, finding a slight benefit for PSAD in determining biochemical recurrence.[12]

Our data reflect different results, indicating that PSA has a greater likelihood of predicting recurrence and tumor volume than the PSAD derivatives. Additional advantages to using PSA are the ease of acquisition, universal use, and the ability to obtain it preoperatively. This is not always the case with PSAD.

Some may argue that the use of TRUS PSAD has inherent inaccuracy owing to the reliance on volumetric measurements in its determination, which may bias its comparison with PSA. Kimura *et al.*[13] evaluated ellipse volumetric measurements, the mechanism by which TRUS determines the volume, and multislice planimetric volume calculations. The error was only 5% to 10% in comparative measurements. We set out to confirm the reliability of TRUS PSAD by comparing all known modalities of calculating PSAD, thereby substantiating its consistency. Our data confirm their work, with significant correlation between the TRUS measurements and the pathologic volume and weight measurements. It is our belief that it is the inherent value of the PSA test, not human error in determining PSAD, that led to this difference. In addition, controversy exists concerning making the determination of biochemical recurrence on the basis of a PSA value of greater than 0.2 ng/mL. Using this definition is more acceptable when using the "ultrasensitive" PSA assay, as was done in this study.

It has been postulated that prostate size alone can affect outcomes, because the apical dissection of smaller prostates is more difficult, leading to an increased rate of positive margins. In our analysis, we had 62 prostates of less than 20 g. Of these, 23 had positive margins (37%). For the 244 prostates greater than 20 g, 74 had positive margins (30%). Although interesting, statistical significance was not achieved ($P = 0.594$), arguing against technical issues being a contributory factor.

When evaluating whether stage migration played a role in limiting PSAD's utility, we found that both PSA and the PSAD derivatives had increased predictive value in earlier series for margin status and extracapsular extension; no significant difference was noted for biochemical recurrence over time. The percentage of concordance and AUC of PSA remained greater than the PSAD derivatives in predicting biochemical recurrence for each subgroup.

Because it is known that the total tumor volume in the radical prostatectomy specimen is an independent predictor of tumor stage and disease progression, we sought to determine whether PSAD could be used as a surrogate for the tumor volume preoperatively.[14,15] Our data indicated that TRUS PSAD provides no additional benefit in predicting tumor volume than PSA alone (R^2 0.085 versus 0.11). Neither value is highly predictive of tumor volume; however, the purpose of this analysis was not to emphasize the predictive ability but to pro-

vide a comparison of these two values. Furthermore, PSA and TRUS PSAD are similar in predicting margin status and extracapsular extension by the percentage of concordance analysis. It appears that PSA is more efficacious as a predictor of biochemical recurrence (C = 75.5% compared with C = 66.6% for TRUS PSAD). Also, when evaluating the predictive capacity of TRUS PSAD subgroups (PSAD less than 0.15, 0.15 to 0.26, and greater than 0.26), as distinctive a relationship was not found between the time to biochemical recurrence and the PSAD. This was in contrast to the PSA subgroup analysis (PSA less than 4, 4.0 to 10.0, and greater than 10 ng/mL) in which a definitive separation was apparent.

Our study had a number of limitations. First, the PSA and PSAD subdivisions might have been somewhat broad for present day comparisons. Second, even though we had the strength of whole mounting and close step sectioning at the Armed Forces Institute of Pathology, a larger cohort with longer follow-up might have provided more definitive results. In particular, our mean follow-up of 43 months was short, and only 16% of these patients had developed recurrence. Longer follow-up with increased outcome events may alter the conclusions about the value of PSA.

CONCLUSIONS

The results of our study have indicated that TRUS PSAD is a reliable preoperative measurement and has a consistent association with both Path PSAD and Weight PSAD. Despite similar results for PSA and PSAD derivatives in predicting pathologic characteristics, a marked difference may exist between these two variables in their association with total tumor volume and biochemical recurrence. PSA was the strongest predictor of biochemical recurrence of all the variables tested. Although not without limitations, PSA still remains a valid preoperative parameter from which clinical predictions can be made. This holds true despite the recent stage migration.

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