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# Prostate Specific Antigen versus Prostate Specific Antigen Density as a Prognosticator of Pathological Characteristics and Biochemical Recurrence following Radical Prostatectomy

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## Abstract

**Purpose—**The utility of PSAD for predicting pathological stage and biochemical recurrence after radical prostatectomy (RP) has not been well defined. The goal of this study was to investigate whether PSAD yielded an advantage over total PSA in predicting adverse pathologic characteristics and disease recurrence following RP.

**Materials and methods—**A total of 13,434 men who underwent radical prostatectomy for clinically localized prostate cancer between 1984 and 2006 were included in this study. The study population was stratified by Gleason score (≤ 6, 7, and ≥ 8) and clinical and pathological characteristics of each group were compared. We constructed receiver operating characteristic (ROC) curves and determined the areas under the receiver operating curves (AUC) and c-index to specifically investigate the accuracy of PSA and PSAD for the prediction of pathological stage and biochemical recurrence.

**Results—**PSAD was better than PSA in predicting EPE ($p<0.001$) and BCR ($p<0.001$) in patients with a biopsy Gleason score ≤ 6. In patients with biopsy Gleason scores of 7, PSA was more predictive than PSAD for SV involvement ($p<0.001$), LN involvement ($p=0.017$), and BCR ($p<0.001$). For men with biopsy Gleason scores ≥ 8, there was no statistical difference between PSA and PSAD in prognostic value for pathological or clinical outcomes.

**Conclusions—**PSAD is highly associated with pathological stage and biochemical free survival following RP. In lower grade prostate cancers, PSAD is significantly more accurate in predicting EPE and BCR compared to total PSA and should be considered when counseling patients on outcomes following RP.

### Keywords

Prostate cancer; PSA; PSA density; biochemical recurrence; radical prostatectomy

## Introduction

Since its introduction in the late 1980s, total serum prostate specific antigen (PSA) has become the most widely used biomarker for prostate cancer screening and follow up after surgical

treatment. PSA is produced by both benign prostatic epithelial cells and malignant prostate cancer cells, and serum PSA has been shown to increase with aging parallel to the increase in volume of benign prostatic tissue.[1,2] Recent data support the hypothesis that benign prostatic hyperplasia (BPH) is the main source of PSA when total serum PSA is between 2 – 10 ng/mL. Pathological stage and biochemical recurrence following radical prostatectomy may be less accurately predicted if pretreatment total PSA is below 10 ng/mL.[3] Concomitantly, there has been a migration toward earlier stage disease at the time of radical prostatectomy (RP) with the majority of patients being now being diagnosed with low (only moderately elevated) PSA levels. Therefore, improved tools to predict pathological stage and biochemical recurrence for these patients are required.[4,5]

Various calculations based upon total serum PSA measurements have been investigated including PSA density (PSAD), PSA doubling time, and PSA velocity with the goals of improving prostate cancer detection, determination of disease severity, and prognostication of recurrence after treatment. PSAD was initially introduced by Benson et al to determine its utility in improving the sensitivity and specificity compared to total serum PSA for prostate cancer detection.[6] PSAD is defined as total serum PSA concentration divided by prostate volume, and is intended to account for the contribution of PSA from benign prostatic tissue.

PSAD has also been shown to potentially be a predictor of advanced pathological findings and biochemical recurrence following radical prostatectomy [7-10] However, the utility of PSAD for predicting pathological stage and biochemical recurrence after RP has not been well defined. Some studies suggest an advantage of PSAD compared to PSA alone whereas others do not. A major limitation of most prior studies is that comparison of the predictive accuracy of PSA and PSAD for outcome measurements was rarely performed. The goal of this study was to investigate whether PSAD yielded an advantage over total PSA in predicting adverse pathologic characteristics and disease recurrence following RP.

## Material and Methods

Between 1984 and 2006, more than 14,800 men underwent radical prostatectomy with bilateral pelvic lymphadenectomy for clinically localized adenocarcinoma of the prostate at our institution. Patients treated with neoadjuvant hormonal therapy (n = 193) were excluded from the study, as were those with incomplete pathological data (n = 55) or lacking data necessary to calculate PSAD (n = 1,116). Thus, the study population was comprised of 13,434 men. Prostate volume was obtained by pathological analysis after radical prostatectomy. PSA values were available for the majority of patients prior to radical prostatectomy. PSA was measured retrospectively from stored serum samples for patients in the pre PSA era. PSAD (ng/ml/$cm^3$) was calculated by dividing preoperative PSA (ng/ml) by volume of the prostatectomy specimen ($cm^3$). Patients were stratified based on biopsy Gleason score groupings as follows: Gleason score $\leq 6$ (n = 10,326), Gleason score 7 (n = 2,650), and Gleason score $\geq 8$ (n = 458). All data were collected under an internal review board-approved protocol with Health Insurance Portability and Accountability Act compliance. All patients provided informed consent when indicated by the institutional review board.

We compared clinical and pathological characteristics of each Gleason score group using the chi-square test and one-way ANOVA analysis for categorical and continuous variables, respectively. Patient age, preoperative PSA and PSAD values, prostate weight, and year of surgery were evaluated as continuous variables. Biopsy and prostatectomy Gleason score grouping ($\leq 6, 7, \geq 8$) as well as race were considered categorical variables. Logistic regression was used to predict pathological stage. Biochemical progression was defined as a single postoperative increase in PSA $\geq 0.2$ ng/mL. Time to PSA recurrence was compared between groups using a Cox proportional hazards model with forward stepwise selection. The actuarial

risk of PSA recurrence was calculated using the Kaplan-Meier method and compared across groups using log-rank survivor analysis. Odds ratios and hazard ratios for the effects of PSA and PSAD were based on increases of 1.0 ng/ml and 0.1 ng/ml/cm$^3$, respectively. AUC for prediction of pathological stage and Harrell's c-index for prediction of BCR were calculated using the predicted probabilities of the multivariable logistic and Cox proportional hazards regression models. All statistical analyses were performed using SPSS, version 13.0 (SPSS, Chicago, IL) and MedCalc for Windows (Version 9.210, Mariakerke, Belgium).

## Results

The clinical and pathological characteristics of the entire study population divided into biopsy Gleason score groupings are shown in Table 1. There were statistically significant differences across the three Gleason score groupings with respect to preoperative variables including: the median year of surgery ($p < 0.001$), age ($p < 0.001$), race ($p < 0.001$), preoperative PSA ($<p < 0.001$), preoperative PSA density ($p <0.001$), and clinical stage ($p < 0.001$). Examination of postoperative variables demonstrated significant differences across the Gleason score groupings for prostate weight ($p < 0.001$), prostatectomy Gleason score ($p < 0.001$), extraprostatic extension (EPE) ($p < 0.001$), seminal vesicle (SV) involvement ($p < 0.001$), lymph node (LN) involvement ($p < 0.001$), and positive surgical margin (SM) rate ($p < 0.001$).

Table 2 shows the association of preoperative PSA and preoperative PSAD with postoperative pathological outcome measures and biochemical recurrence for all patients as well as stratified across Gleason score groupings. Multivariable logistic and Cox proportional hazards regression models revealed that both preoperative PSA and preoperative PSAD were statistically significant independent predictors of EPE ($p < 0.001$), SV involvement ($p < 0.001$), LN involvement ($p < 0.001$), and biochemical recurrence ($p < 0.001$) for the overall study population. Across every Gleason score grouping, both PSA and PSAD remained statistically significant independent predictors of the pathological outcomes noted and biochemical recurrence.

AUC and c-index calculations for multivariable logistic and cox regression analyses are displayed in Table 3 comparing the accuracy of PSA versus PSAD in predicting EPE, SV, LN, and biochemical recurrence (BCR). For all patients in the study, PSAD exhibited a slightly higher AUC than PSA for prediction of EPE. However, because of the extremely large sample size, this difference was statistically significant. There was no statistical difference between the two measures in predicting SV involvement ($p = 0.205$) or LN involvement ($p = 0.095$). Conversely, among all patients in our study, PSA exhibited a slightly higher c-index for prediction of BCR than did PSAD; this difference, although small, was again statistically significant ($p < 0.001$).

AUC and c-index analysis of patients stratified by biopsy Gleason score showed that PSAD was better than PSA in predicting EPE ($p < 0.001$) and BCR ($p < 0.001$) in patients with a biopsy Gleason score $\leq 6$. However, in patients with biopsy Gleason scores of 7, PSA was more predictive than PSAD for SV involvement ($p < 0.001$), LN involvement ($p = 0.017$), and BCR ($p < 0.001$), while the two measures are equally predictive of EPE ($p = 0.603$). Again, these were very small differences with the exception of EPE prediction in men with biopsy Gleason score $\leq 6$. For men with biopsy Gleason scores $\geq 8$, there was no statistically significant difference between PSA and PSAD in prognostic value for determining EPE ($p = 0.569$), SV involvement ($p = 0.059$), LN involvement ($p = 0.414$), or BCR ($p = 0.287$). In a separate analysis, the effect of prostate gland size on accuracy of PSAD in predicting pathology and BCR was investigated. We did not find a statistically significant impact of prostate size on accuracy of PSAD in predicting of either outcome variable (data not shown).

## Discussion

It has been previously shown that PSAD is an independent predictor of pathological stage and disease recurrence following radical prostatectomy.[11,12] In contrast to PSA, PSAD may be more commonly used in the context of prostate cancer detection to decide whether or not a prostate biopsy should be performed. There remains debate whether PSAD might be better compared to total PSA in predicting pathological characteristics and biochemical recurrence following radical prostatectomy. A subgroup of patients may benefit from additional information provided by PSAD.

In the current study, we demonstrated that although overall PSA was more accurate in predicting biochemical recurrence following radical prostatectomy, PSAD yielded a statistically significant increase in accuracy compared to PSA for predicting biochemical recurrence in patients with lower grade disease (Gleason score ≤ 6) on prostate biopsy. To our knowledge, this is the first study to report this association. The proportion of PSA derived from cancerous tissue versus BPH is known to be less in low grade disease compared to higher grade prostate cancer. The fact that our results demonstrate a very small increase in the predictive accuracy of PSAD among patients with biopsy Gleason score ≤ 6 is consistent with knowledge that patients with lower grade prostate cancer generally exhibit lower PSA levels, thus reducing the predictive value of PSA in this subgroup.[13]

Kundu et al recently demonstrated that measurement of PSAD was useful for determining the aggressiveness of prostate cancer. Specifically, PSAD was associated with positive SM rates, prostatectomy Gleason score, cancer volume, PSA velocity in the year prior to diagnosis, and biochemical recurrence.[13] These findings are in agreement with our results showing that PSAD is highly associated with biopsy and prostatectomy Gleason grade, biochemical recurrence, and positive SM rate. However, Kundu et al did not compare the relative accuracy of PSAD and PSA in predicting these pathological and clinical findings.[13]

Jones et al recently reported that PSAD was significantly associated with patient age, prostate weight, cancer volume, Gleason score, and positive SM rates. Furthermore, PSAD was also found to be an independent predictor of biochemical recurrence. However, a comparison of ROC curves yielded no significant difference between PSA and PSAD in predicting biochemical recurrence following RP.[8] This differs from our current findings with respect to biochemical recurrence and may be explained by the limited cohort size in their study (n = 348).

Freedland et al demonstrated that PSAD was an independent predictor of positive SM, non-organ confined disease, SV invasion, and biochemical recurrence following RP. However, they did not find that PSAD was superior to PSA alone for predicting adverse pathological findings and biochemical recurrence. Stratification of PSAD combined with Gleason score cutoffs yielded better risk stratification for biochemical failure compared to cutoffs based on PSA combined with Gleason score.[7,12] However, stratification of tumor grade and calculation of predictive accuracy of PSA and PSAD for each Gleason subgroup was not performed. Brassell et al reported that PSA and PSAD were equivalent predictors of SM status and EPE. However, in ROC analysis PSA was significantly better than PSAD in predicting tumor volume and biochemical recurrence following RP. A comparison to our current study is limited by the fact that AUC calculations in their study were performed only for a univariate model including either PSA or PSAD.[14]

A limitation of our study is that we calculated PSAD based on the volume of the radical prostatectomy specimen instead of based on pre-operative transrectal ultrasound volume measurement (TRUS-PSAD). However, it has been shown that pathological PSAD and TRUS-PSAD are highly correlated.[14] Kimura et al. have reported that the error of ellipse volumetric

measurements compared to multislice planimetric volume calculations is approximately 5 - 10%.[15] A disadvantage of PSAD as a screening marker is the requirement for prostate volume measurements in all patients. Inter-operator variability in accurately measuring prostate volume may also affect the accuracy of PSAD. The retrospective design of our study also limits the feasibility of analyzing other variables of interest associated with PSAD including tumor volume and PSA-velocity.

Another limitation of our study is that we did not take into account the Will Rogers phenomenon. This phenomenon in prostate cancer describes the impact on grade migration on outcomes following radical prostatectomy. Albertson et al recently reported that the decline in low grade prostate cancer over time appears to be a result of Gleason score reclassification over the past decade resulting in apparent improvement in clinical outcomes – the so called Will Rogers phenomenon.[16] By stratifying patients into different Gleason cohorts, this could potentially influence outcomes analysis, since patients in the low GS cohort diagnosed prior to the 1990s are more likely to be assigned a higher Gleason score in the present. Furthermore, the clinical impact of small differences in AUCs for PSA and PSAD (although statistically significant) remains to be determined. Additional prospective studies are needed to investigate the practical and clinical relevance of statistically significant differences that were observed between PSA and PSAD AUCs.

## Conclusion

PSA density is a well-established tool for prostate cancer detection and decision making for performing prostate biopsies. Its application for the prediction of clinical outcomes compared to PSA alone is not as well established. Our data suggest that PSAD is highly associated with pathological stage and biochemical free survival following RP. In low grade prostate cancer, PSAD exhibits small, statistically significant increments in accuracy for predicting biochemical recurrence compared to total PSA and should be considered when counseling this subgroup of patients on outcomes following RP.

## Acknowledgements

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## Abbreviations

**TRUS**
: Transrectal Ultrasound

**PSA**
: Prostate Specific Antigen

**PSAD**
: Prostate Specific Antigen Density

**RP**
: Radical Prostatectomy

**AUC**
: Area Under the Curve

**LN**
: Lymph Node Metastasis

**SV**

Seminal Vesicle Invasion

**EPE**

Extraprostatic Extension

**SM**

Surgical Margin Positive

**ROC**

Receiver Operating Characteristics

**BCR**

Biochemical Recurrence

**BPH**

Benign Prostatic Hyperplasia

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**TABLE 1**

**Clinicopathologic characteristics of prostate cancer patients undergoing radical prostatectomy**

| | Biopsy Gleason Grouping | | | | |
|---|---|---|---|---|---|
| **Characteristic** | **GS ≤ 6** | **GS 7** | **GS 8-10** | **Total** | **p-value*** |
| Patients (n) | 10,326 | 2,650 | 458 | 13,434 | |
| Follow up (yr) | | | | | |
| Median (Range) | 4.0 (0-22) | 4.0 (0-20) | 5.0 (0-19) | 4.0 (0-22) | |
| Mean ± SD | 5.4 ± 4.5 | 5.5 ± 4.5 | 6.4 ± 4.6 | 5.5 ± 4.5 | |
| Median year of surgery | 2000 | 2000 | 1999 | 2000 | <0.001 |
| Age | | | | | <0.001 |
| Median (Range) | 58 (33-77) | 59 (35-75) | 60 (36-75) | 58 (33-77) | |
| Mean ± SD | 57.7 ± 6.5 | 59.0 ± 6.3 | 59.9 ± 6.6 | 58.1 ± 6.5 | |
| Race (%) | | | | | < 0.001 |
| Caucasian | 9,370 (91.0) | 2,326 (88.3) | 406 (89.2) | 12,102 (90.1) | |
| African-American | 592 (5.8) | 204 (7.7) | 36 (7.9) | 832 (6.2) | |
| Other | 332 (3.2) | 103 (3.9) | 13 (2.9) | 448 (3.3) | |
| PSA (ng/ml) | | | | | <0.001 |
| Median | 5.6 (0.2-151.0) | 6.6 (0.3-129.0) | 7.6 (0.2-68.1) | 5.8 (0.2-151.0) | |
| Mean ± SD | 6.7 ± 5.5 | 8.7 ± 8.2 | 10.1 ± 8.6 | 7.3 ± 6.3 | |
| PSA density | | | | | |
| Median (Range) | 0.10 (0.01-2.30) | 0.13 (0.01-7.28) | 0.15 (0.01-1.14) | 0.11 (0.01-7.28) | <0.001 |
| Mean ± SD | 0.13 ± 0.10 | 0.17 ± 0.20 | 0.19 ± 0.15 | 0.14 ± 0.13 | |
| Clinical Stage (%) | | | | | < 0.001 |
| cT1 | 7,128 (69.2) | 1,360 (51.6) | 182 (40.0) | 8,670 (64.8) | |
| cT2 | 3,113 (30.2) | 1,238 (46.9) | 255 (56.2) | 4,606 (34.4) | |
| cT3 | 55 (0.5) | 39 (1.5) | 17 (3.7) | 111 (0.8) | |
| Prostate weight (g) | | | | | <0.001 |
| Mean ± SD | 56.4 ± 21.6 | 53.6 ± 18.3 | 56.6 ± 19.8 | 55.9 ± 20.9 | |
| Prostatectomy Gleason score (%) | | | | | < 0.001 |
| ≤ 6 | 7,756 (75.3) | 551 (20.8) | 28 (6.1) | 8,335 (62.1) | |
| 7 | 2,358 (22.9) | 1,783 (67.4) | 143 (31.2) | 4,284 (32.0) | |
| 8-10 | 189 (1.8) | 312 (11.8) | 287 (62.7) | 788 (5.9) | |
| Extraprostatic extension | 2,863 (27.7) | 1,470 (55.5) | 302 (65.9) | 4,635 (34.5) | < 0.001 |

| | Biopsy Gleason Grouping | | | | |
|---|---|---|---|---|---|
| **Characteristic** | **GS ≤ 6** | **GS 7** | **GS 8-10** | **Total** | **p-value*** |
| Seminal vesicle invasion | 74 (2.7) | 325 (12.3) | 93 (20.3) | 692 (5.2) | < 0.001 |
| Lymph node invasion | 126 (1.2) | 155 (5.9) | 57 (12.4) | 338 (2.5) | < 0.001 |
| Positive surgical margin | 1,306 (12.7) | 494 (18.7) | 116 (25.4) | 1,916 (14.3) | < 0.001 |

* Indicates test for comparison among the three Biopsy Gleason sum cohorts. All tests for categorical data are chi-squared, ANOVA was used for continuous data

**TABLE 2**

**Multivariable logistic and Cox proportional hazards regression models adjusted for clinical stage, age, and race predicting EPE, SV, LN, and BCR for different biopsy GS categories**

| | | PSA | | | PSA Density | | |
|---|---|---|---|---|---|---|---|
| **Group** | **Variable** | **OR/HR*** | **95% CI** | **p-value** | **OR/HR*** | **95% CI** | **p-value** |
| All Patients | EPE | 1.10 | 1.09-1.11 | <0.001 | 1.83 | 1.75-1.92 | <0.001 |
| | SV | 1.07 | 1.06-1.08 | <0.001 | 1.35 | 1.29-1.41 | <0.001 |
| | LN | 1.07 | 1.06-1.08 | <0.001 | 1.36* | 1.29-1.44 | <0.001 |
| | BCR | 1.03 | 1.03-1.04 | <0.001 | 1.07* | 1.06-1.08 | <0.001 |
| GS ≤ 6 | EPE | 1.10 | 1.09-1.11 | <0.001 | 1.96 | 1.86-2.07 | <0.001 |
| | SV | 1.08 | 1.07-1.10 | <0.001 | 1.51 | 1.41-1.61 | <0.001 |
| | LN | 1.08 | 1.06-1.09 | <0.001 | 1.43 | 1.31-1.55 | <0.001 |
| | BCR | 1.04 | 1.03-1.04 | <0.001 | 1.38 | 1.33-1.42 | <0.001 |
| GS 7 | EPE | 1.10 | 1.08-1.12 | <0.001 | 1.55 | 1.42-1.69 | <0.001 |
| | SV | 1.06 | 1.04-1.07 | <0.001 | 1.18 | 1.11-1.26 | <0.001 |
| | LN | 1.06 | 1.05-1.08 | <0.001 | 1.30 | 1.20-1.40 | <0.001 |
| | BCR | 1.03 | 1.02-1.04 | <0.001 | 1.05 | 1.04-1.07 | <0.001 |
| GS 8-10 | EPE | 1.06 | 1.02-1.10 | 0.002 | 1.38 | 1.14-1.67 | 0.001 |
| | SV | 1.06 | 1.04-1.09 | <0.001 | 1.36 | 1.17-1.58 | <0.001 |
| | LN | 1.04 | 1.01-1.07 | 0.004 | 1.35 | 1.15-1.60 | <0.001 |
| | BCR | 1.02 | 1.00-1.03 | 0.019 | 1.11 | 1.02-1.22 | 0.017 |

Abbreviations: OR, odds ratio (from logistic regression); HR, hazard ratio (from proportional hazards model)

* Indicates an increase of PSA of 1 ng/mL and PSA density of 0.1 ng/mL/$cm^3$

**TABLE 3**

**AUC for multivariable logistic and cox regression analyses including PSA and PSA Density**

| | | PSA | | PSA Density | | | |
|---|---|---|---|---|---|---|---|
| **Group** | **Variable** | **AUC/C-Index** | **95% CI** | **AUC/C-Index** | **95% CI** | **Difference** | **p-value** |
| All Patients | EPE | 0.743 | 0.735-0.750 | 0.759 | 0.751-0.766 | 0.016 | <0.001 |
| | SV | 0.807 | 0.800-0.813 | 0.803 | 0.796-0.810 | 0.003 | 0.205 |
| | LN | 0.846 | 0.839-0.852 | 0.839 | 0.833-0.846 | 0.006 | 0.095 |
| | BCR | 0.801 | 0.792-0.810 | 0.786 | 0.777-0.796 | 0.015 | <0.001 |
| GS ≤ 6 | EPE | 0.705 | 0.696-0.714 | 0.732 | 0.723-0.740 | 0.027 | <0.001 |
| | SV | 0.757 | 0.749-0.765 | 0.760 | 0.752-0.768 | 0.003 | 0.568 |
| | LN | 0.817 | 0.809-0.825 | 0.810 | 0.802-0.818 | 0.007 | 0.368 |
| | BCR | 0.751 | 0.739-0.762 | 0.774 | 0.763-0.785 | 0.024 | <0.001 |
| GS 7 | EPE | 0.688 | 0.670-0.706 | 0.686 | 0.668-0.704 | 0.002 | 0.603 |
| | SV | 0.689 | 0.671-0.707 | 0.665 | 0.647-0.683 | 0.024 | <0.001 |
| | LN | 0.760 | 0.743-0.776 | 0.742 | 0.752-0.759 | 0.018 | 0.017 |
| | BCR | 0.708 | 0.684-0.732 | 0.683 | 0.658-0.707 | 0.026 | <0.001 |
| GS 8-10 | EPE | 0.692 | 0.647-0.735 | 0.688 | 0.643-0.731 | 0.004 | 0.569 |
| | SV | 0.705 | 0.661-0.747 | 0.685 | 0.640-0.728 | 0.020 | 0.059 |
| | LN | 0.701 | 0.657-0.743 | 0.714 | 0.669-0.755 | 0.012 | 0.414 |
| | BCR | 0.676 | 0.616-0.732 | 0.687 | 0.627-0.742 | 0.011 | 0.287 |