RESEARCH COMMUNICATION

Implications of PSA Kinetics for an Adverse Pathology after Radical Prostatectomy

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Abstract

Objective: To determine and compare the prognostic value of PSA density, PSA velocity and free/total PSA ratio in predicting adverse pathological findings after radical prostatectomy. Materials: We analyzed the medical records of 142 patients who underwent a radical prostatectomy from May 2009 until February of 2011. After exclusion of of them for defined criteria, preoperative PSA and its derivatives were analysed for their ability to predict unfavorable pathology after radical prostatectomy. Results: From the 105 patients included in the analysis, 23.8% had extraprostatic cancer extension, 8.6% had seminal vesicle involvement and positive surgical margins found in 38.1% of them. PSA density value >0.2ng/ml2 was the solitary and most significant predictor for surgical margin status (p=0.015) and for extracapsular disease (p=0.050) as well, in multivariate analysis. Preoperative PSA was the only significant parameter for seminal vesicle invasion prediction (p=0.033). Both PSA velocity and ratio failed to reach predictive significance in all analyses. Conclusion: The present results demonstrate a significance of PSA density in preoperative estimation of adverse pathological findings in patients who undergo radical prostatectomy for clinically localized prostate cancer. A value of 0.2ng/ml^2 seems to be a reliable cutoff. PSA density is a bettgerer predictor than PSA velocity and the PSA ratio.

Keywords: PSA density - PSA ratio - PSA velocity - prostatectomy - adverse pathology

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Introduction

Prostate specific antigen (PSA) is the main tool for prostate cancer (PCa) screening programs and currently the majority of patients who are diagnosed with PCa come to medical attention because of elevated or rising levels of PSA (Miller et al., 2003). In addition to its utility as a screening tool, PSA is a well known predictor of adverse pathological findings and outcome after primary treatment (Kattan et al., 1998; 1999; Partin et al., 2001).

Early in the PSA era, it became apparent that its value is determined by malignant, as well as benign, prostatic tissue. This observation is limiting its specificity in cancer diagnosis, especially in moderately elevated concentrations (4-10ng/ml). Due to these limitations, several PSA related parameters have been investigated and introduced in the clinical practice to increase its diagnostic specificity. Known as PSA kinetics, PSA density (PSAD), free/total PSA ratio (PSAR) and PSA velocity (PSAV) are widely used nowadays and accompanying primary PSA value estimation for cancer and benign hypertrophy differentiation.

Apart of PSA kinetics significance in cancer diagnosis, their role in prognosis of PCa is controversial. Several studies have evaluated their predictive role in outcome after radical prostatectomy, however the results are mainly conflicting.

The aim of the present study was to evaluate the potential role of these parameters in prediction of adverse pathological findings, in terms of positive surgical margins (PSM), presence of extracapsular disease (ECD) and seminal vesicle invasion (SVI) in patients who undergo a radical prostatectomy for clinically localized PCa.

Patients and Methods

After we obtained an approval by the Human Investigation and Ethics committee of our institution, we retrospectively reviewed the medical records of 142 patients who undergone a radical prostatectomy for organ-confined prostate cancer from May 2009 until February of 2011. Any preoperative therapies like active surveillance, hormone therapy and radiation therapy were supported as exclusion criteria from the study. The analysis comprised preoperative value of PSA, PSAD, PSAR and PSAV.

Preoperative PSA was measured before digital rectal examination, transrectal ultrasound or biopsy. In all patients, cancer suspicion, because of PSA elevation and/or abnormal digital rectal examination was confirmed by transrectal ultrasound biopsy and positive for malignancy histological examination of the obtained cores.

PSAD was calculated by dividing the preoperative PSA and the pathological volume of prostate. The latter was estimated by using the prostate ellipse dimension

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theory formula (D1xD2xD3xπ/6), whereas D1 was the maximum transverse diameter, D2 was the maximum anteroposterior diameter and D3 was the maximum longitudinal diameter. The above diameters were obtained by the report of pathologoanatomical examination of the surgical specimen. Even though the original value of PSAD should be supported by the preoperative calculation of prostate volume, using the transrectal ultrasound, it has been proved by earlier studies that there is a great positive correlation between preoperative and postoperative calculation of prostate volume (Wolff et al., 1995).

PSAV was calculated by linear regression using at least 2 PSA values more than 180 days apart prior to histological confirmation of PCa.

An open retropubic or laparoscopic extraperitoneal radical prostatectomy was performed in all patients. The 2009 TNM (Tumour Node Metastasis) classification was used to classify the pathological stage and the Gleason system was used for grading.

All statistical analyses were performed by using SPSS version 17 (SPSS Inc, Chicago, IL, USA). All tests were 2-tailed. A p value <0.05 was considered as statistically significant. The descriptive statistics are presented as the mean ± standard deviation (std) for continuous variables and as the absolute and percent frequency for categorical variables. The normality condition of the numerical variables was studied by means of the Kolmogorov-Smirnov test. With one exception (PSAR), none of them had normal distribution. For this reason, the Mann-Whitney test was used to compare means between numerical groups and Students't-test for comparing PSAR between groups. The Chi-square $\chi 2$ test was used for categorical variables. Preoperative PSA, PSAD, PRAR and PSAV were tested for their ability to predict adverse pathological findings after radical prostatectomy.

Results

A total of 105 patients who met the inclusion criteria entered the study. The median age at the time of the operation was 66 years (65.7 ± 6.1, 8). Median preoperative PSA at the time of diagnosis was 8.96ng/ml (11.3 ± 9.1, 6.5) and prostate volume was 35ml (39.6 ± 23.1, 26). PSA kinetics were estimated and their median values were 2.20ng/ml/year (2.64 ± 1.73, 1.50), 14% (13.4 ± 4.7, 7) and 0.26ng/ml^2 (0.40 ± 0.42, 0.26) for PSAV, PSAR and PSAD respectively.

After a radical prostatectomy was performed, 80 patients (76.2%) were found with organ confined disease (pT≤T2c) and in 25 of them (23.8%) had an advanced cancer (pT≥T3a). Actually, 25 patients (23.8%) had ECD and 8 patients (8.6%) had seminal vesicle involvement. PSM were noticed in 40 patients (38.1%). The characteristics regarding the pathological results of the surgical specimen examination are seen in table 1.An aggressive pathological tumor grade (Gleason score≥7) was found in 57 cases (54.3%). In this cohort, an upgrade of the primary Gleason score was noticed in 43 patients (41.0%).

The preoperative values of PSA, PSAD, PSAV and PSAR were then examined for the ability to predict adverse pathologic findings after radical prostatectomy. Preoperative PSA≥10ng/ml (as a categorical variable) was statistical significant variable on univariate analysis

Table 1. Patients' Characteristics According to the Presence of Positive Surgical Margins, Extracapsular Disease and Seminal Vesicle Invasion

Characteristics	PSM -	PSM +	p value	ECD -	ECD +	p value	SVI -	SVI +	p value
No of patients	65 (61.9)	40 (38.1)		80 (76.2)	25 (23.8)		96 (91.4)	9 (8.6)	
Age (years) mean ± std (IQR)									
	65.1±6.1 (9)	66.8±5.9 (8)	0.160†	65.4±6.1 (8)	66.9±5.9 (8)	0.205†	65.6±6.2 (8)	66.8±4.8 (8)	0.684†
Prostate volume (ml) mean ± std (IQR)									
	39.7±22.9 (28)	39.5±23.6 (21)	0.898†	41.1±24.4 (27)	35.1±18.2 (21)	0.393†	40.0±23.7 (29)	35.8±16.0 (17)	0.814†
PSA (ng/ml) mean ± std (IQR)									
	10.2±8.2 (5.8)	13.1±10.2 (7.0)	0.012†*	10.3±7.6 (5.3)	14.5±12.3 (8.3)	0.031†*	11.1±9.3 (6.1)	13.2±5.8 (8.8)	0.083†
<10, n (%)	44 (71.0)	18 (29.0)	0.022‡*	52 (83.9)	10 (16.1)	0.026‡*	60 (96.8)	2 (3.2)	0.019‡*
≥10, n (%)	21 (48.8)	22 (51.2)		28 (65.1)	15 (34.9)		36 (83.7)	7 (16.3)	
PSA velocity (ng/ml/year) mean ± std (IQR)									
	2.7±1.9 (1.5)	2.5±1.5 (1.7)	0.976†	2.6±1.8 (1.7)	2.9±1.6 (1.8)	0.097†	2.60±1.66 (1.0)	3.17±2.38 (2.1)	0.478†
<2, n (%)	28 (59.6)	19 (40.4)	0.658‡	40 (85.1)	7 (14.9)	0.053‡	44 (93.6)	3 (6.4)	0.471‡
≥2, n (%)	37 (63.8)	21 (36.2)		40 (69.0)	18 (31.0)		52 (10.3)	6 (89.7)	
<3, n (%)	48 (65.8)	25 (34.2)	0.220‡	58 (79.5)	15 (20.5)	0.236‡	67 (91.8)	6 (8.2)	0.846‡
≥3, n (%)	17 (53.1)	15 (46.9)		22 (68.8)	10 (31.3)		29 (90.6)	3 (9.4)	
Free PSA ratio (%) mean ± std (IQR)									
	14 ± 5 (7)	12 ± 4 (5)	0.137§	13.3 ± 4.9 (8)	13.4 ± 4.3 (6)	0.950§	13.4 ± 4.8 (7)	13.1 ± 3.9 (5)	0.870§
<10, n (%)	15 (62.5)	9 (37.5)	0.945‡	20 (83.3)	4 (16.7)	0.350‡	23 (95.8)	1 (4.2)	0.380‡
≥10, n (%)	50 (61.7)	31 (38.3)		60 (74.1)	21 (25.9)		73 (90.1)	8 (9.1)	
<15, n (%)	34 (55.7)	27 (44.3)	0.125‡	48 (78.7)	13 (21.3)	0.479‡	56 (91.8)	5 (8.2)	0.872‡
≥15, n (%)	31 (70.5)	13 (29.5)		32 (72.7)	12 (27.3)		40 (90.1)	4 (9.1)	
PSA density (ng/ml^2) mean ± std (IQR)									
	0.35±0.34 (0.3)	0.47±0.53 (0.2)	0.112†	0.34±0.31 (0.2)	0.59±0.64(0.4)	0.035†*	0.39±0.42 (0.26)	0.49±0.45 (0.4)	0.303†
<0.2, n (%)	28 (82.4)	6 (17.6)	0.003‡*	31 (91.2)	3 (8.8)	0.013‡*	33 (97.1)	1 (2.9)	0.154‡
≥0.2, n (%)	37 (52.1)	34 (47.9)		49 (69.0)	22 (31.0)		63 (88.7)	8 (11.3)	
pGleason score, n (%)									
≤6	32 (66.7)	16 (33.3)	0.356‡	40 (83.3)	8 (16.7)	0.115‡	46 (95.8)	2 (4.2)	0.139‡
≥7	33 (57.9)	24 (42.1)		40 (70.2)	17 (29.8)		50 (87.7)	7 (12.3)	

†Mann Whitney U test; ‡Chi-square test; §Student's t test; *statistical significant; PSM=positive surgical margins; ECD,extracapsular disease; SVI, seminal vesicles invasion; std=standard deviation; IQR, interquartile range

Table 1. Univariate and Multivariate Analysis of PSA and its Derivatives for Positive Surgical Margins, Extracapsular Disease and Seminal Vesicle Invasion

Univariate analysis	PSM	ECD	SVI	PSM	ECD	SVI
PSA (continuous)	0.138	0.080	0.516	1.039	1.045	1.020
PSA (≥10ng/ml)	0.023*	0.030*	0.033*	0.390	0.359	0.171
PSA velocity (continuous)	0.489	0.384	0.348	0.919	1.115	1.174
PSA velocity (≥2ng/ml/year)	0.658	0.058	0.475	1.196	0.389	0.591
PSA velocity (≥3ng/ml/year)	0.222	0.239	0.846	0.590	0.569	0.866
Free PSA ratio (continuous)	0.138	0.949	0.869	0.001	1.363	0.292
Free PSA ratio (<10%)	0.945	0.354	0.395	0.968	0.571	0.397
Free PSA ratio (<15%)	0.128	0.480	0.872	1.894	0.722	0.893
PSA density (continuous)	0.179	0.051	0.494	1.916	3.329	1.584
PSA density (≥0.2ng/ml^2)	0.004*	0.019*	0.186	0.233	0.216	0.239
Multivariate analysis	PSM	ECD	SVI	PSM	ECD	SVI
PSA (≥10ng/ml)	0.125	0.120	-	0.513	0.468	-
PSA density (≥0.2ng/ml^2)	0.015*	0.050*	-	0.279	0.267	-

*statistical significant; PSA, prostate specific antigen; PSM, positive surgical margins; ECD, extracapsular disease; SVI, seminal vesicle invasion

for PSM, ECD and SVI prediction with p values of 0.023, 0.030 and 0.033 respectively (Table 1). In addition, PSAD≥0.2ng/ml^2 was a significant predictor on univariate a nalysis for PSM (p=0.004) and ECD (p=0.019) but not for SVI. None of the other PSA kinetics, either as continuous or categorical variables, found to be able to predict adverse pathology and, therefore, they were not included in the multivariate analysis. It was only the case of PSAV≥2ng/ml/year that reached significance (p=0.058) for extraprostatic disease prediction, however, it did not enter the multivariate analysis.

On multivariate analysis, PSAD was the only parameter found to be significant for prediction of ECD (p=0.050) and PSM (p=0.015) (Table 2). No multivariate analysis for seminal vesicle metastasis prediction was performed, since PSA was the solitary significant variable in univariate analysis.

Discussion

PSA-based screening programs, introduced in the early 1990s, have contributed to a dramatic increase in PCa incidence and simultaneously in a subtle decrease in disease specific mortality (Tarone et al., 2000). A rise in insignificant PCa diagnosis is the result of PSA-based over diagnosis which led to overtreatment for patients whom a significant number of them will die from other causes even if the primary malignancy is left untreated (Albertsen et al., 2005). Because of this phenomenon, improved risk stratification is of paramount importance in improving treatment strategies, especially as we explore adjuvant and neoadjuvant therapies after surgery (Kibel 2005).

In a review of 925 men with PCa treated by radical prostatectomy from 2000 until 2006, it was debated whether PSA remains an important prognostic variable in more recent patients and if it can predict pathological stage and biochemical progression after surgery (Freedland et al., 2008). PSA found to be a very important and statistically significant predictor of adverse outcomes, such as advanced, high grade disease and biochemical progression after surgery, even in patients with low risk cancer.

However, the ability of PSA to adequately prognosticate outcomes among men with PCa has recently been challenged (Stamey et al., 2004). In a large cohort of a total of 1317 consecutive radical prostatectomies, it was assessed how well PSA reflects large and aggressive cancer during the last 20 years. Authors concluded that PSA was well related to PCa 20 years ago. In the last 5 years serum PSA has only been related to benign prostatic hyperplasia and subsequently, there is an urgent need for serum markers that reflect the size and grade of PCa.

Controversies regarding the modern impact of PSA in PCa prognosis and outcome after radical prostatectomy have stimulated several investigations and comparative analyses of PSA-based parameters as potential predictors of adverse pathology after surgery. In an effort to better confine PCa aggressiveness, PSA kinetics have been evaluated for its ability to predict unfavorable cancer characteristics.

PSAD seems to be the most studied parameter among the other PSA kinetics and the results reported by several studies are mainly promising. There is a significant trend for worsening pathological features as PSAD increased, as it has been reported by a large cohort of 1662 patients' study (Kundu et al., 2007). In another large study of 325 patients, PSAD (using pathological weight of the surgical specimen) was a better predictor of ECD, PSM, SVI and biochemical recurrence than PSA (Freedland et al., 2002). The authors of the above study suggested a novel nomogram, defined by the pathological PSAD and Gleason score, that improved risk stratification compared with a combination of PSA and Gleason score.

However, only a slight predictive benefit, but not substantial enough, was shown when PSA was compared to PSAD obtained by the preoperative volume estimation of transrectal ultrasound (Freedland et al., 2003). This was not the case of a recent study of 1327 patients. The authors reported that PSAD obtained either by prostatic weight or transrectal ultrasound is a strong predictor of advanced pathological features and biochemical recurrence after radical prostatectomy (Radwan et al., 2007). In another study, which compared the predictive ability of transrectal ultrasound PSAD and PSA, the authors reported that both parameters are equivalent and significant for prediction of margin status and extracapsular cancer extension

(Brassel et al., 2005). However, in the same report, there was a marked difference in favor of PSA for prediction of biochemical recurrence and tumor volume.

PSAR and its correlation with PCa pathology has been reported in several studies with conflicting results and its predictive role remains controversial. It has been reported that higher PSAR values (values >15% to have the greatest discrimination) were associated with favorable histopathological findings in prostatectomies specimens (Southwick et al., 1999). The same authors reevaluate PSAR significance and they compare it with PSAD predictive ability for adverse pathology (Catalona et al., 2000). They reported that PSAR and PSAD provide comparable results and, therefore, PSAR can be used in place of PSAD in algorithms for prediction of less aggressive tumors since its determination does not require ultrasound. In addition to these results, in a series of 108 men with clinically localized PCa who were treated with radical prostatectomy, it was shown that lower PSAR has predicted capsular penetration (Arcangeli et al., 1998). Moreover, PSAR has been correlated with surgical margin status when it was evaluated in 76 consecutive patients with clinical stage T1c PCa and a preoperative serum PSA level of 4-20ng/ml (Morote et al., 1999). On the other hand, other studies have demonstrated no association of PSAR value and PCa adverse pathology. In a study of 170 patients who underwent a radical prostatectomy, the authors concluded that PSAR provides no help in the preoperative prediction of final tumor stage (Noldus et al., 1998). Similarly, in another patients' series, when investigators tried to determine whether PSAR could predict extraprostatic spread of PSAR, no correlation was revealed (Henricks et al., 1998).

Recently, it has been reported that among men who underwent radical prostatectomy for clinically localized PCa, patients with PSAV >2ng/ml/year had significantly greater possibilities for advanced disease and increased risk for dying of the disease (D'Amico et al., 2004). Similarly, in a group of 202 patients, those with PSAV>2ng/ml/year were more likely to have pathological stage T3 and PSM (Patel et al., 2005). In contrast, PSA velocity did not contribute independent prognostic information when it was evaluated for the ability to predict the risk of high-grade PCa (Thompson et al., 2006) or advanced pathological stage after radical prostatectomy (Pinsky et al., 2007).

In the present study, we tried to evaluate 3 of the most commonly used PSA kinetics and their implication in PCa pathology. Our primary goal was to make a comparative analysis between PSAD, PSAV, PSAR, and PSA to identify their predictive capacity in adverse pathology after radical prostatectomy. For this reason, we analysed them as continuous variables and as categorical variables as well, using the most common cutoff points published in the literature. Based on our results, we demonstrate that PSAD values >0.2ng/ml^2 are significantly correlated with adverse pathological features, in terms of ECD and PSM, and its prognostic ability is higher than the other kinetics and than PSA. However, this was not the case of SVI prediction, where PSA values >10ng/ml found to be the solitary significant predictor. The results of the present study confirm the high value of PSA in PCa prognosis, since it was found to be statistically significant in univariate analyses for both ECD and PSM, when it was entered as a categorical variable. However, it did not reach significance in multivariate analyses. In contrast, PSAR and PSAV failed to prove their place in predictive armamentarium for PCa aggressiveness, even though PSAV reached significance (p=0.058) in univariate analysis for ECD prediction.

Based on our knowledge, this is the first study to examine and compare PSA and 3 of its derivatives for their predictive role in PCa advance pathology. Our data supports the potential utility of PSAD to predict adverse pathological features after radical prostatectomy. With the exception of seminal vesicle involvement, extraprostatic disease extension and surgical margin status are highly correlated with PSAD and can be predicted more strongly than PSA. Values of more than 0.2 ng/ml2 seems to be a reliable cutoff. The incorporation of PSAD into risk assessment might provide additional prognostic information and its inclusion into nomograms assessing preoperative risk should be considered.

We can identify several limitations of this study. PSAD values were estimated based on the prostate dimensions reported by the pathologists who evaluated the surgical specimen. Thus, we used pathological prostate volume as a surrogate of preoperative prostate volume. However, several reports have confirmed that preoperative, based on transrectal ultrasound, and postoperative prostate volume are significantly correlated (Wolff et al., 1995). In addition, we did not evaluate other PSA kinetics, such as complexed PSA, PSA doubling time and age-specific PSA that might be more predictive measures. Another caveat of our study is that we analyze patients as a single population group without prior categorization in PSA-based risk groups. The present results may altered if the analyses are made separately for patients with low (<10ng/ml), medium (10-20ng/ml) or high (>20ng/ml) risk PCa.

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