PSA density is superior than PSA and Gleason score for adverse pathologic features prediction in patients with clinically localized prostate cancer

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Abstract

Introduction: Prostate-specific antigen (PSA) and its kinetics have changed prostate cancer screening and diagnosis. The aim of the present study was to evaluate their value in prostate cancer prognosis by determining the predictive potential of PSA density for adverse pathologic features after radical prostatectomy, in terms of positive surgical margins (PSM), extracapsular disease (ECD), seminal vesicle invasion (SVI) and/or lymph node invasion (LNI), and to compare their predictive ability with preoperative PSA and biopsy Gleason score.

Methods: We retrospectively analysed 285 patients diagnosed with prostate cancer and underwent a retropubic radical prostatectomy for clinically localized disease. Data concerning preoperative PSA, biopsy Gleason score and PSA density were collected and analyzed. PSA density was calculated by dividing preoperative PSA and the pathological volume of the prostate.

Results: There was a significant difference in PSA density values between patients with PSM, ECD, SVI and LNI. Areas under the curve for PSA density were higher than those of PSA and Gleason score for all parameters of adverse pathology. In multivariate analyses, it was shown that PSA density and Gleason score were the only statistically significant predictors for PSM and ECD, PSA density and PSA for SVI and only PSA density for LNI.

Conclusion: PSA density is an accurate predictor for adverse pathology prediction in patients undergoing radical prostatectomy. These results demonstrate that this parameter is useful to determine the aggressiveness of prostate cancer and can be used as an adjunct in predicting outcomes after surgery.

Introduction

Radical prostatectomy can be applied in patients with localized prostate cancer and a life expectancy of more than 10 years.[1] However, preoperative staging tools, such as digital rectal examination, transrectal ultrasound and imaging techniques (computer tomography, magnetic resonance imaging), can understage prostate cancer.[2,3] For many patients who undergo a radical prostatectomy for organ-confined disease, a greater stage, in terms of extracapsular disease (ECD), seminal vesicle invasion (SVI) and/or lymph node invasion (LNI), can be determined after surgical specimen analysis;[4] these results can affect prognosis and survival.

Several preoperative parameters have been studied as potential predictors for prostate cancer aggressiveness and postoperative pathological stage. Prostate-specific antigen (PSA), biopsy Gleason score and clinical stage are commonly used to estimate the risk of adverse pathology after radical prostatectomy.[5] Furthermore, modifications of the standard surgical technique, like nerve-sparing, are now used and the criteria for candidates' selection are based on the above preoperative factors.

Although PSA density has a significant and established role in prostate cancer screening by increasing the diagnostic value of PSA,[6] its role as a predictor of tumour characteristics has not been identified.

The aim of the present study was to determine the potential role of PSA density as a predictor of radical prostatectomy outcome, in terms of positive surgical margins (PSM), ECD, SVI and LNI. Furthermore, we compared widely used preoperative parameters (PSA and Gleason score) in the prediction of postoperative staging.

Methods

We retrospectively reviewed patients who had a radical prostatectomy for organ-confined prostate cancer between

January 2000 and November of 2010. Patients who underwent preoperative therapies, such as active surveillance, hormone therapy and radiation therapy, were excluded. Patients with incomplete medical records were also excluded. The analysis included preoperative Gleason score, preoperative value of PSA and PSA density.

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

An open retropubic or laparoscopic extraperitoneal radical prostatectomy was performed in all patients by 4 experienced surgeons. The surgical specimen was sent for pathological examination and a histological report concerning the prostate dimensions and pathological stage was obtained. Information regarding PSM, ECD, SVI and LNI was recorded. According to the information obtained by the pathologoanatomic report of the maximum transverse diameter (D1), the maximum anteroposterior diameter (D2) and the maximum longitudinal diameter (D3), the pathological prostate volume was calculated using the prostate ellipse dimension theory formula ($D1 \times D2 \times D3 \times \pi/6$). PSA density was calculated by dividing the preoperative PSA value by prostate volume. Even thought prostate volume was calculated postoperatively, according to the prostate dimensions outlined in the pathology report, there is a high positive correlation between preoperative (during transrectal ultrasound) and postoperative calculation of prostate volume.[7]

Table 1. Preoperative characteristics based on the pathological results of the radical prostatectomy's specimen

	PSM+	PSM–	*p*
n (%)	122 (42.8%)	163 (57.2%)	
PSA, mean ± SD	13.25 ± 12.69	11.55 ± 10.72	<0.001*
PSAD, mean ± SD	0.38 ± 0.33	0.33 ± 0.42	<0.001*
GS, mean ± SD	6.68 ± 0.91	6.12 ± 1.47	0.006*
	ECD+	ECD–	
n (%)	98 (34.4%)	187 (65.6%)	
PSA, mean ± SD	15.29 ± 16.37	10.38 ± 6.46	<0.001*
PSAD, mean ± SD	0.49 ± 0.49	0.26 ± 0.26	<0.001*
GS, mean ± SD	6.71 ± 0.89	6.15 ± 1.43	0.002*
	SVI+	SVI–	
n (%)	43 (15.1%)	242 (84.9%)	
PSA, mean ± SD	19.15 ± 22.82	10.85 ± 6.63	<0.001*
PSAD, mean ± SD	0.53 ± 0.61	0.31 ± 0.31	<0.001*
GS, mean ± SD	6.85 ± 0.99	6.27 ± 1.31	0.002*
	LNI+	LNI–	
n (%)	24 (8.4%)	169 (59.3%)	
PSA, mean ± SD	18.52 ± 17.64	11.43 ± 10.31	0.007*
PSAD, mean ± SD	0.56 ± 0.68	0.32 ± 0.31	<0.001*
GS, mean ± SD	6.92 ± 0.97	6.30 ± 1.29	0.55

* Statistically significant; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; n: number of patients; GS: Gleason score; PSM: positive surgical margins; ECD: extracapsular disease; SVI: seminal vesicle invasion; LNI: lymph node invasion; SD: standard deviation, Mann-Whitney U test was used for all statistics.

Statistical analysis

The descriptive statistics are presented as the mean ± standard deviation (SD) 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. As none of them had normal distribution, the Mann-Whitney test was used to compare means between groups. PSA, PSA density and preoperative Gleason score were tested for their ability to predict PSM, ECD, SVI and LNI by using receiver operating characteristic (ROC) curves. The overall performance of the ROC analysis was quantified by computing the area under the curve (AUC). An area of 1 indicated perfect performance, while 0.5 indicated a performance that was no different than chance. The use of ROC analysis is to determine the optimal sensitivity and specificity by using various cut-off values. Positive [true positive/(true positive+false positive)] and negative predictive value [true negative/(true negative+false negative)] were also estimated. To find independent factors associated with the prediction of the aggressiveness of prostate cancer, we performed a multivariate analysis of PSA, PSA density (as a binary variable) and Gleason score.

All tests were 2-tailed. A p value <0.05 was considered statistically significant. All analyses were performed using SPSS version 17 (SPSS Inc, Chicago, IL).

Results

A total of 285 patients were included in the study. Patients' ages ranged from 46 to 79 years (66.54 ± 6.23). The median preoperative PSA was 8.50 ng/mL (11.13 ± 9.93) and the median PSA density was 0.23 ng/mL2 (0.31 ± 0.34). Two patients had preoperative Gleason scores equal to 2 (0.7%), 9 patients had 3 (3.2%), 16 had 4 (5.6%), 28 had 5 (9.8%), 101 had 6 (35.4%), 101 had 7 (35.4%), 22 had 8 (7.7%) and 6 patients had 9 (2.1%). Positive surgical margins were found in 122 patients (42.8%), 98 patients had non-organ confined disease (34.4%) and 43 patients (15.1%) had invasion of the seminal vesicles. No lymph node dissection was performed in 92 patients. From the 193 patients who had a radical prostatectomy and lymph node dissection, we noted invasion in 24 (8.4%). We tallied the correlation of preoperative clinical and pathological characteristics and pathological findings after radical prostatectomy (Table 1).

PSA, PSA density and Gleason score were significant predictors for PSM, ECD and SVI, as shown in ROC analyses (Table 2). However, Gleason score was not significant in

Table 2. Areas under the curve for PSA, PSA density and Gleason score for prediction of tumour status after radical prostatectomy

	Area	SE	p	95% CI Lower bound	95% CI Upper bound
AUC for positive surgical margins					
PSA	0.629	0.033	0.000	0.564	0.693
PSAD	0.637	0.033	0.000	0.572	0.701
GS	0.591	0.034	0.009	0.525	0.656
AUC for extracapsular disease					
PSA	0.660	0.034	0.000	0.593	0.727
PSAD	0.772	0.028	0.000	0.717	0.828
GS	0.609	0.034	0.003	0.542	0.676
AUC for seminal vesicle invasion					
PSA	0.709	0.043	0.000	0.625	0.792
PSAD	0.732	0.038	0.000	0.659	0.806
GS	0.639	0.048	0.004	0.545	0.733
AUC for lymph node invasion					
PSA	0.670	0.061	0.007	0.552	0.789
PSAD	0.722	0.043	0.000	0.638	0.806
GS	0.615	0.058	0.069	0.501	0.728

AUC: area under the curve; SE: standard error; CI: confidence interval; PSA: prostate-specific antigen; GS: Gleason score; PSAD: prostate-specific antigen density.

Table 3. Predictive accuracy of PSA density*

	Sensitivity	Specificity	PPV	NPV
PSM	67.2%	55.8%	53.3%	69.5%
ECD	84.7%	62.0%	53.9%	88.5%
LNI	95.8%	47.9%	20.7%	98.8%
SVI	83.7%	51.2%	23.4%	94.7%

* Cut-off: 0.2 ng/mL2; PSM: positive surgical margins; ECD: extracapsular disease; LNI: lymph node invasion; SVI: seminal vesicle invasion; PPV: positive predictive value; NPV: negative predictive value.

predicting LNI. The optimal cutoff value of PSA density for the prediction of the aggressiveness of prostate cancer (PSM, ECD, SVI, LNI) was 0.2 ng/mL2. We recorded the sensitivity, specificity, positive and negative predictive values (Table 3).

The multivariate analysis demonstrated PSA density as the most important predictor for PSM (p = 0.001), ECD (p < 0.001), SVI (p = 0.004) and LNI (p = 0.005) (Table 4). Interestingly, PSA was statistically significant only to predict SVI, while the Gleason score was found to be a significant predictor for PSM and ECD.

Discussion

Preoperative parameters predictive of tumour status in patients with prostate cancer are of great concern. Since the incidence of the disease has increased in the PSA era, more patients are undergoing surgery for radical excision of the disease. However, there are times when adverse pathology is revealed by the histopathological examination of the specimen, like ECD, SVI, LNI. All of them are poor predictors of biochemical failure, recurrence and prognosis. Most patients who meet these conditions will enter an adjuvant treatment protocol, either with radiotherapy or hormonal manipulations. Furthermore, conservative surgical differentiations of the standard radical prostatectomy, including sparing of the neurovascular bundle, have intrinsic dangers of PSM or incomplete removal of the disease. Therefore, preoperative factors, either clinical or pathological, to predict advanced prostate cancer can benefit patients and urologists.

The most used nomograms to predict pathological stage are Partin tables, which estimate the potential of a certain prostate cancer to meet ECD, SVI and LNI.[5] These nomograms use clinical stage, PSA and biopsy Gleason score as preoperative factors to predict adverse pathology. Many surgeons also use them to guide treatment decisions.

Few studies have focused on the correlation of PSA density and PSM, ECD, SVI and LNI and the results are controversial, mainly when the PSA density value is compared with preoperative PSA.

A study of a large cohort of patients (1662 patients) found a significant trend of worsening pathological features as PSA density increases.[8] In another large study of 325 patients, Freedland and colleagues found that PSA density (using pathological weight of the surgical specimen) was a better predictor of ECD, PSM, SVI and biochemical recurrence than PSA.[9] The authors suggested a novel nomogram, defined by the pathological PSA density and Gleason score, that improved risk stratification compared with a combination of PSA and Gleason score.

However, only a slight, but unsubstantial, predictive benefit was shown when PSA was compared to PSA density obtained by the preoperative volume estimation of transrectal ultrasound.[10] This was not the case of a recent study of 1327 patients. The authors reported that PSA density obtained either by prostatic weight or transrectal ultrasound is a strong predictor of advanced pathological features and biochemical recurrence after radical prostatectomy.[11] In another study, which compared the predictive ability of transrectal ultrasound PSA density and PSA, the authors reported that both parameters are equivalent and significant in predicting margin status and extracapsular cancer extension.[12] However, in the same report, there was a marked difference in favour of PSA to predict biochemical recurrence and tumour volume.

Positive results for PSA density use in ECD prediction have also been reported in 2 other studies.[13,14] PSA density was shown to be the strongest predictor of ECD in patients with clinical T1c disease followed by preoperative Gleason score, while PSA was the most inferior.[15] Similarly, in a study of 114 patients, the multivariate analysis showed that PSA density and biopsy Gleason score were significant predictors of ECD (PSA density was more significant than Gleason score), while PSA was not.[16] This was the case in our

Table 4. Multivariate analyses of PSA, PSA density and Gleason score in predicting positive surgical margins, extracapsular disease, seminal vesicle invasion and lymph node invasion

	B	SE	Wald	df	*p**	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Multivariate analysis for prediction of PSM								
PSA	0.001	0.013	0.004	1	0.947	1.001	0.975	1.028
PSAD	-0.884	0.264	11.191	1	0.001*	0.413	0.246	0.693
GS	0.265	0.110	5.797	1	0.016*	1.303	1.050	1.616
Multivariate analysis for prediction of ECD								
PSA	0.021	0.018	1.294	1	0.255	1.021	0.985	1.058
PSAD	-2.042	0.334	37.302	1	0.000*	0.130	0.067	0.250
GS	0.271	0.127	4.506	1	0.034*	1.311	1.021	1.683
Multivariate analysis for prediction of SVI								
PSA	0.045	0.021	4.744	1	0.029*	1.046	1.005	1.089
PSAD	-1.324	0.456	8.441	1	0.004*	0.266	0.109	0.650
GS	0.238	0.163	2.125	1	0.145	1.269	0.921	1.747
Multivariate analysis for prediction of LNI								
PSA	0.009	0.015	0.389	1	0.533	1.009	0.981	1.038
PSAD	-2.949	1.044	7.972	1	0.005*	0.052	0.007	0.406
GS	0.432	0.235	3.382	1	0.066	1.540	0.972	2.439

*: statistically significant; PSA: prostate-specific antigen; GS: Gleason score; PSAD: prostate-specific antigen density; PSM: positive surgical margins; ECD: extracapsular disease; LNI: lymph node invasion; SVI: seminal vesicle invasion; SE: standard error; CI: confidence interval; Exp(B): odds ratio; Wald: Wald distribution; df: degree of freedom; PSM: positive surgical margins; ECD: extracapsular disease; LNI: lymph node invasion; SVI: seminal vesicle invasion; B: regression coefficient.

study, in which the multivariate analysis for extracapsular tumour extension prediction showed that only PSA density ($p < 0.001$) and preoperative Gleason score ($p = 0.034$) were significant in contrast with PSA ($p = 0.255$) that was not.

PSA superiority, when compared to PSA density, to predict ECD in patients with insignificant cancer and in patients with a Gleason score ≥7, was noted in a study of 102 patients.[17] Similar results have been reported for patients with PSA <20 ng/mL and Gleason score ≤7.[18]

Our study evaluated the predictive potential of PSA and Gleason score and compared them with PSA density. The results of our data suggested that PSA density can be used to further refine the risk of non-organ-confined cancer or the presence of local metastatic disease in patients planning to undergo a radical prostatectomy. All 3 parameters were significantly correlated with adverse pathology. However, PSA density was the one that predicted cancer aggressiveness with major accuracy. Furthermore, a PSA density of 0.2 ng/mL2 was an optimal cutoff and found to be the most significant predictor in multivariate analyses. PSA density is a tool with high sensitivity, but relatively low specificity, to predict adverse pathology after radical prostatectomy. Conservative surgical modifications of radical prostatectomy, like nerve-sparing, are mainly provided to patients with low risk for ECD or local and/or distant metastases. Therefore, we need tests with high sensitivity that can rule out the possibility of adverse pathology. Tests with high sensitivity and high specificity would optimize patients' selection or exclusion. Consequently, we believe that the predictive value of PSA density would be maximized if we used it in combination with other valuable predictors, such as PSA and Gleason score.

The present study is the first, to our knowledge, to address the superiority of PSA density compared to PSA and Gleason score for the prediction of PSM, ECD, SVI and LNI after a radical prostatectomy. We have shown that PSA density can be an accurate parameter to estimate the risk of adverse pathology after radical prostatectomy. This would also be a valuable tool to guide treatment modality and to counsel patients on cure and the risk of recurrence after surgery.

A limitation of our study is that PSA density was calculated based on the pathological volume of the surgical specimen.

Conclusion

Although PSA density is a preoperative tool derived by the calculation of prostate dimensions during transrectal ultrasound, the present study had a retrospective design and thus an estimate of preoperative prostate volume was impossible. For this reason, postoperative information was used. Studies have compared preoperative and postoperative prostate volume calculation. There is a strong correlation between the two methods, reaching or even overcoming 90%, which shows that the estimation of prostate volume postoperatively by using prostate ellipse formula is reliable with minimal deviation from transrectal ultrasound results.[7]

Competing interests: None declared.

This paper has been peer-reviewed.

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