ORIGINAL ARTICLE

Does prostate specific antigen density correlates with aggressiveness of the prostate cancer?

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Abstract

Background: As already documented, a high prostate specific antigen in men with normal size of prostate gland is more likely to be associated with an aggressive cancer as compared to others with the same prostate specific antigen and a large gland size. In this retrospective study we tested the association between Prostate Specific Antigen Density (PSAD) and tumor aggressiveness in patients with clinically localized Prostate Cancer (PCa) surgically treated by radical prostatectomy.

Methods: We evaluated data from patient's records in a cohort of 72 patients who underwent radical prostatectomy between January 2000 and June 2007. PSAD was calculated as ratio between the preoperative total prostatic specific antigen (PSA) in nanograms per milliliter with the prostate weight (PW) of prostatectomized specimen in grams or prostate volume measured with ultrasound (US). The patients were stratified into four PSAD categories: 0.1-0.15, 0.16-0.20, 0.21-0.5 and greater than 0.51 ng/ml/gr. Parameters that were included into analysis were: PSA, measurement of the prostate volume by ultrasound (preoperatively) and prostate weight, pathological tumor stage, Gleason sum, Gleason grade, metastatic lymph nodes, seminal vesicle involvement and organ confine disease (postoperatively). Worsening of the clinicopathological properties was defined as aggressiveness.

Results: There was a significant correlation between US-PSAD and PW-PSAD ($p<0.001$). In US-PSAD categories the statistic tests found significant correlation with the primary tumor ($R=0.303$, $p<0.01$), metastatic lymph nodes ($R=0.331$, $p<0.01$), and the organ confine disease ($R=0.296$, $p<0.05$). The PW-PSAD categories correlated significantly with the pathologic findings from other parameters. Hence, a statistically significant correlation was found with Gleason sum ($R=0.246$, $p<0.05$), Gleason grade ($R=0.234$, $p<0.05$), primary tumor ($R=0.285$, $p<0.05$), metastatic lymph node ($R=0.287$, $p<0.05$) and organ confine disease ($R=0.303$, $p<0.01$).

Conclusions: Prostate specific antigen density measurement is useful tool for the assessment of the degree of aggressiveness in clinically localized prostate cancer, and further investigation regarding its possible use as a prediction marker is justified. Hippokratia 2009; 13 (4): 232-236

Key Words: prostate-specific antigen, prostatic cancer, aggressiveness of prostate cancer

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Prostate cancer (PCa) is the most common form of cancer and the second leading cause of cancer death among US men, with an incidence of slightly less than 190,000 new cases and mortality of around 29,000 in 2008[1]. Since 1995 the incidence has been increased by 1% annually, whereas mortality decreased by 4%[2]. International incidence rates vary more than 65-fold time, from a low-risk (China) to a high-risk range population in US[1,3].

PSA is a glycoprotein which belongs to the kallikrein family of neutral serine proteases, weighing approximately 34 kDa[4]. It is a product of secretion of the prostate epithelium produced by normal, benign and cancerous cells[5]. Moreover, PSA is present in the seminal fluid, serum and urine[6].

Flocks was the first who experimented with the antigens in the prostate[7]. Thereafter, the presence of the precipitative antigens in prostate was reported by Ablin et al[8]. The first description of PSA referred to a prominent protein in human seminal plasma as seminoprotein[9]. Furthermore, Wang et al purified a tissue-specific antigen "Prostate antigen"[10], which was at the beginning measured quantitatively in the blood[11].

As a screening tool PSA is known predictive factor of adverse pathologic findings[12] and outcome after primary treatment[13,14]. Normal PSA levels are defined as between 0-4.0 ng/ml[15]. Increased levels of PSA may suggest the presence of prostate cancer. However, prostate cancer can also be present in the complete absence of an elevated PSA level, in which case the test result would be a false negative[16]. PSA levels can be also elevated due to the prostate infection, irritation, benign prostatic hypertrophy

Table 1: Clinical data related to the prostate measurements in all patients (n=72).

Parameter	Mean ± SD	Range
Age (years)	66.5 ± 6.39	51-84
US prostate volumen (cm^3)	55.77 ± 26.96	19-151
Pathologic prostate weight (gr)	48.61 ± 21.07	20.0-140.0
PSA (ng/ml)	25.8 ± 22.40	0.95-100.0
US-PSAD ($ng/ml/cm^3$)	0.60 ± 0.74	0.01-4.3
PW-PSAD (ng/ml/gr)	0.7 ± 1.02	0.2-7.23

(BPH), i.e. enlargement or recent ejaculation[17], in which cases it may again give false positive results[18].

To distinguish the condition between BPH and prostate cancer (in order to minimize unnecessary biopsies in men without cancer) and slow the fast growing cancers, various PSA markers have been used: PSA velocity, age-adjusted PSA, PSA density (PSAD) and free versus attached PSA.

The PSA density can be calculated when the PSA value in ng/ml is divided by the prostate volume measured by transrectal ultrasonography (US-PSAD), or by its weight measured from the prostatectomised specimens in grams (PW-PSAD). However, the goal should be to improve the specificity of PSA testing for prostate cancer screening, at the same time preserving its sensitivity[19].

Material and Methods

Between January 2000 and June 2007, seventy nine (79) patients underwent radical retro-pubic prostatectomy for treatment of clinically localized prostate cancer, at the Department of Urology, University Hospital, Skopje. Seven cases were excluded because of insufficient data. All patients were in clinical stage of T2N0M0, in a good health condition and life expectancy of about 10 years. They had not received neoadjuvant hormonal or radiotherapy before the surgery. Parameters that were analyzed included preoperative PSA (measured before or 28 days after biopsy in Clinical laboratory with immunodiagnostic system "Vitros ECI") and measurement of prostate volume by transrectal ultrasound, and after prostatectomy measurement of the prostate weight, pathological tumor stage, Gleason sum (is a sum of the primary grade and a secondary grade of the tumor and is a number ranging from 2 to 10), Gleason grade (information determined by the pathologist who examines the biopsy specimen taken from the prostate), metastatic lymph nodes, seminal vesicle involvement and organ confine disease. Patients were stratified into four PSAD categories: 0.1-0.15; 0.16-0.20; 0.21-0.5 and greater than 0.51 ng/ml/gr.

Descriptive statistics such as frequency and cross tabulation were used for data analysis. Data from parametric variables were expressed as mean ± SD (range) and as proportion (percentage) when appropriate. Comparisons between groups were made by using x-square test, and Fisher's exact test when appropriate, while correlation between investigated parameters was assessed with the help of Spearman's rank correlation coefficient. The acceptable levels of probability for rejecting the null hypotesis in compatibility with the international biostatistical standards for "p" were <0.05. The statistical program used was SPSS for windows, version 10 (SPSS, Chicago, IL, USA).

Results

The data from 72 patients who underwent radical prostatectomy for treatment of localized prostate cancer were analysed. The patients' data and data related to prostete measurements are shown in Table 1. Pathologic data from cancer tissue of prostatectomized specimens are summarized in Table 2.

Table 2: Pathologic and data related to the cancer tissue of prostatectomized specimen.

	Gleason sum (5-10)						Gleason grade (2-5)				Primary tumor					
	5	6	7	8	9	10	2	3	4	5	T2a	T2b	T2c	T3a	T3b	T4
n	5	11	42	7	6	1	4	49	18	1	6	8	26	1	26	5
%	6.9	15.3	58.3	9.7	8.3	1.4	5.6	68.1	25	1.4	8.3	11.1	36.1	1.3	36.1	6.9

In addition, histopathologic data from the prostatectomized and lymphadenectomized specimen related to the local progression of the disease are summarized in Table 3.

Table 3: Pathologic and data related to the prostatectomized and lymphadenectomized specimen.

	Seminal vesicle involvement		Metastatic lymph nodes		Organ confine	
	No	Yes	No	Yes	No	Yes
n	41	31	55	17	32	40
%	56.9	43.1	76.4	23.6	44.4	55.6

The distribution of patients in various groups according to the PSAD levels measured by ultrasound and weight of the prostate specimens after radical prostatectomy are presented in Table 4.

Table 4: The distribution of patients in categories according to PSAD levels.

PSAD categories	US-PSAD		PW-PSAD	
ng/ml/gr; ng/ml/cm³	Frequency	Percent	Frequency	Percent
I (0.01-0.15)	10	13.89	13	18.06
II (0.16-0.2)	7	9.72	8	11.11
III (0.21-0.5)	27	37.50	27	37.50
IV (>0.5)	28	38.89	24	33.33

A cross tabulation between PSAD categories and Gleason sum, Gleason grade, primary tumor, vesiculo-seminal involvement and metastatic lymph nodes are presented in Table 5.

In addition, with the non-parametric Spearman's correlation we found highly significant association between US-PSAD and PW-PSAD (R=0.837, p<0.01); and a statistically significant correlation with primary tumor (R=0.303, p<0.01); metastatic lymph nodes (R=0.331, p<0.01); and with organ confine disease (R=0.296, p<0.05). On the other hand, there was a statistically significant association between PW-PSAD and organ confined disease (R=0.303, p<0.01); Gleason sum (R=0.246, p<0.05); Gleason grade (R=0.234, p<0.05); metastatic lymph nodes (R=0.287, p<0.05); and primary tumor (R=0.285, p<0.05). In addition, there was a significant trend of worsening the clinicopathological prognostic features associated with an increase in the prostate specific antigen density as presented in the Table 6.

In US-PSAD groups there were 10 (76.9%), 6 (75%), 16 (55.6%) and 8 (33.3%) patients with organ confined disease according to the particular PSAD strata adopted standards (I – IV), respectively.

Table 5: Cross tabulation between PSAD categories and pathologic results.

Pathologic findings		PSAD categories (ng/ml/cm³ /or /gr)								
		0.1-0.15		0.16-0.2		0.21-0.5		>0.5		Sum
		US PSAD	PW PSAD	US PSAD	PW PSAD	US PSAD	PW PSAD	US PSAD	PW PSAD	
Gleason sum (5-10)	5	1	1	3	2	1	2	0	0	5
	6	2	2	1	1	4	2	4	6	11
	7	9	7	3	3	17	19	13	13	42
	8	0	0	1	0	2	4	4	3	7
	9	0	0	0	0	3	0	3	6	6
	10	1	0	0	1	0	0	0	0	1
Gleason grade (2-5)	2	1	1	2	2	1	1	0	0	4
	3	9	9	5	3	18	18	17	19	49
	4	2	0	1	1	8	8	7	9	18
	5	1	0	0	1	0	0	0	0	1
Primary tumor	T2a	2	2	2	1	2	1	0	2	6
	T2b	2	0	0	2	2	3	4	3	8
	T2c	6	6	4	3	12	11	4	6	26
	T3a	0	0	0	0	1	1	0	0	1
	T3b	3	2	2	1	7	10	14	13	26
	T4	0	0	0	0	3	1	2	4	5
Seminal vesicle involvement	No	8	8	6	6	16	16	11	11	41
	Yes	5	5	2	2	11	11	13	13	31
Metastatic lymph nodes	No	13	8	7	6	21	16	14	9	55
	Yes	0	5	1	2	6	11	9	15	16

Table 6: The distribution of patients in categories according to PSAD levels and organ confine disease.

PSAD categories	US-PSAD					PW-PSAD				
	Organ confine		Extraprostatic extension		Sum	Organ confine		Extraprostatic extension		Sum
	n	%	n	%		n	%	n	%	
0.1-0.15	10	76.9	3	23.1	13	8	80.0	2	20.0	10
0.16-0.20	6	75.0	2	25.0	8	6	85.7	1	14.3	7
0.21-0.50	16	55.6	11	44.4	27	15	55.5	12	44.5	27
>0.5	8	33.3	16	66.7	24	11	39.3	17	60.7	28

In PW-PSAD groups there were 8 (80%), 6 (85.7%), 15 (55.5%) and 11 (39.3%) patients with organ confined disease if PSAD was found less than < 0.15, 0.16 to 0.2, 0.21 to 0.50 and greater than 0.51 ng/ml/gr, respectively ($p < 0.001$).

Discussion

According to previous reports in the literature prostate cancer tissue releases approximately 10-fold higher PSA into serum per gram of tissue than benign prostate tissue[20]. With the introduction of PSA-based screening in the early 1990s the number of new cases of prostate cancer dramatically raised although the mortality from the disease was significantly reduced[21].

Benson et al introduced the concept of PSAD in order to correlate PSA levels in serum with the prostate volume[22]. Several studies suggested that PSA density higher than 0.15 ng/ml/cm^3 increases the cancer detection rate[23-25]. In addition, Radwan et al suggested that value of PSAD higher than 0.2 ng/ml/gr strongly correlated with the extracapsular extension of the cancer[26].

The present study is among the very few others addressing the association of PSA density with the pathological features in prostatectomy specimens. Our study results suggest that an increase in PSAD, may be associated with worsening of the Gleason sum, Gleason stage, primary tumor, seminal vesicle and the lymph node involvement. We also confirmed that the value of PSAD higher than 0.2 ng/ml/gr correlated well with the extracapsular extension of the cancer.

We also conformed with the results from the study of Brassell et al. who examined patients with radical prostatectomy and reported that PSA level and PSAD predicted the adverse pathologic features[27]. Freedland et al examined PSAD in the preoperative and postoperative settings, as well, finding PW-PSAD as a strong predictor of adverse pathologic features and biochemical failures in patients undergoing radical prostatectomy[28].

However, a serious shortcoming of our study was the lack of data about the time to progression or median time of survival of our patients. Hence, here the term "aggressiveness" was solely related to the pathological findings and not to the clinical course of the disease itself.

Conclusion

Concluding the incorporation of the PSAD into the work-up for the risk assessment might provide useful prognostic information in addition to the grade, stage and PSA level in patients with prostate cancer. Prostate specific antigen density measurements can be useful in determining the aggressiveness of the clinically localized prostate cancer, and might be used as an adjunct in predicting insignificant cancers, their outcome after local therapy and further prognosis of the patients.

The PW-PSAD is not clinically useful to predict the adverse pathologic features, since in this case the prostate has already been removed. The strong correlation between US-PSAD and PW-PSAD strongly suggests the usefulness of the US-PSAD as a prognostic tool in the treatment and follow up of the prostate cancer.

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