MED ARH. 2012; 66(1): 41-44

doi: 10.5455/medarh.2012.66.41-44
Received: November 15th 2011
Accepted: January 24th 2012

ORIGINAL PAPER

Influence of the Prostate Volume, Prostate Specific Antigen Density and Number of Biopsy Samples on Prostate Cancer Detection

Damir Aganovic, Alden Prcic, Benjamin Kulovac, Osman Hadziosmanovic
Department of Urology, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Aim: Establish the main differences in the prostate volume, prostate specific antigen density (PSAD), number of biopsy samples in patients with primarily or rebiopsy detected prostate cancer. **Materials and methods:** In the 2007-2009 period, at the KCUS Urology Clinic, there were 379 TRUS guided prostate biopsies in 323 patients with known prostate volume. The total of 56 patients (17.3%) underwent the first rebiopsy, primarily due to precancerous lesions. The mean prostate volume, ranges of prostate size, PSAT, PSAD and the number of biopsy samples were analysed retrospectively, and the main characteristics in patients with primarily and rebiopsy diagnosed Pca were evaluated as well. **Results:** The first biopsy cancer detection rate was 29.6% (112/379). The rebiopsy detection rate was 30.3%. There was no statistically significant difference in the prostate volume and the number of biopsy samples among the total number of patients with prostate cancer against the group with benign (suspected) findings. There was a higher Pca detection rate in patients with the prostate volume <40 cm3 and 40-60 cm3, against the group with the prostate volume >60 cm3. PSAD was significantly higher in patients with PCa (0.24 vs. 0.18; p=0.013). The total of 27.2% of the patients with negative biopsy findings and 48% of the patients with diagnosed Pca had PSAD >0.15. PSAD showed sensitivity and specificity in prostate cancer detection of 50% and 75%, with PPV of 48%. Furthermore, the patients with PSAD >0.15 had a higher Gleason score versus the patients with PSAD <0.15 (6.7 ± 2.4 vs. 5.9 ± 1.7; p <0.003). A comparison of the main characteristics in patients with primarily and rebiopsy detected prostate cancer gave a statistically significant difference only in the number of biopsy samples (10.9 vs. 14.1, p <.0000). **Conclusion:** Patients with a smaller prostate volume, lower PSAD and a higher number of biopsy samples in rebiopsy have a higher chance of prostate cancer detection. PSAD carries a higher specificity in rebiopsy decision, and a higher PSAD is related to a higher Gleason score. **Key words: PCa, prostate biopsy, prostate volume, PSAD.**

Corresponding author: Prof. Damir Aganovic, MD, PhD. Department of Urology, KCUS, Bolnicka 24, Sarajevo, Bosnia and Herzegovina, tel. ++38733 297754, Email: dagano@lsinter.net

1. INTRODUCTION

A routine use of the value of serum total prostate specific antigen (PSAT), modification of the prostate biopsy technique and the use of transrectal ultrasound (TRUS) guided prostate biopsy, as well as correct prostate biopsy indications have significantly improved the prostate cancer detection in the past two decades. Among the main prostate biopsy indications are PSA values above 4ng/ml (1) as well as suspicious digital rectal examination (DRE) of the prostate. Schroeder et al proved that the prostate DRE has a low predictive value in detection, at which point a substitution with a more sensitive test was proposed (2). On the other hand, Carvalhal et al suggest the use of the prostate DRE in patients with low PSA values, as prostate cancer was established in 14-30% of the cases with PSAT values between 1 and 4 ng/ml, with abnormal DRE findings (3).

It is recognised that a larger prostate decreases the prostate cancer detection rate. Namely, the major component of the total enlarged prostate volume is, in fact, benign prostatic hyperplasia, which makes it logical to suppose that the serum PSA level and the prostate volume must be related. For this purpose, the PSA density (PSAD) was shown to increase the PSA specificity, and that there was a higher probability of prostate cancer detection in patients with increased PSAT and PSAD values, particularly in the group with the PSAT value of 4-10 ng/ml, and PSAD >0,15 (4). The PSAD value is arrived at by dividing the value of serum total PSA with the prostate volume expressed in cm^3 (5). The given result expresses the relation between the quantity of total PSA and the quantity of prostatic tissue.

Transrectal ultrasound guided prostate biopsy is a recommended diagnostic method with the minimum of 6-10 systematically taken, peripherally directed biopsy samples (6). A higher

number of biopsy samples increases the degree of prostate cancer detection.

2. MATERIALS AND METHODS

In the period from 2007 to 2009, at the KCUS Department of Urology outpatient TRUS prostate biopsies were performed in 323 patients with evaluated prostate volume, serum PSA values and pathological DRE. The total of 379 biopsies was performed in the above number of patients. 56 (17.3%) patients underwent the first rebiopsy due to precancerous lesions. An analysis of the patients' records shows an increase in the number of biopsy samples on the timeline; from 6 towards extended biopsy (10-12 samples) and saturation biopsy (up to 20 samples), depending on rebiopsy or enlarged prostate volume. All the patients underwent biopsy according to the standard protocol (preoperative antibiotic protection, NSAID suppository and local 2% lidocain gel anaesthesia). Rebiopsy indications were basically findings of premalignant lesions, suspect digital rectal examination (DRE) or increased PSA kinetics over a short period (6-12 months). All the samples were examined by the same clinical pathologist.

3. RESULTS

The overall cancer detection rate amounted to 34% (129/379). The first biopsy showed a detection rate of 34.7% (112/323), while the first rebiopsy confirmed cancer in 30.3% of the cases (17/56); p> 0.05.

The total number of premalignant lesions for the considered number of biopsies was 12.1% (47/379). Out of this number, ASAP was found in u 3.7% of the cases (14/379), while HGPIN and the ASAP + HGPIN combination in 7.4% (28/379) and 1.3% (5/379), respectively.

The main characteristics of the entire group were taken into consideration, i.e. the main age differences, PSAT, PSAr, prostate volume, PSAD, the number of biopsy cores taken; it was shown that the patients with diagnosed prostate cancer were older and had a higher total PSA, as well as that there was a considerable group difference in PSA density, although there was no significant difference in the prostate volume or the mean number of biopsy samples taken (Table 1). With respect to the total number of analysed biopsies, PSAt <4 ng/ml appears in 61 cases (16.1%), PSAt 4-10ng/ml appears in 195 cases (51.5%), and PSAt ≥10 ng/ml in 123 cases (32.4%).

	Biopsy group No 379 (Mean, SD)	Pca group No 129 (Mean, SD)	Non Pca group No 250 (Mean, SD)	T test P
Age	66.6 (7.02)	68.5 (7.3)	65.7 (6.7)	<.000
PSA t	10.5 (10.7)	12.7 (14.2)	9.4 (8.1)	0.015
PSA t <4 ng/ml	61 (16,1%)	14 (23%)	47 (77%)	*
PSA t 4-10 ng/ml	195 (51.9%)	67 (34.4%)	135 (65.6%)	*
PSA t ≥10 ng/ml	123 (32.4%)	48 (37.5%)	68 (62.5%)	*
PSA r	0.15 (0.1)	0.15 (0.13)	0.154 (0.07)	0.23
Prost. Volume (ccm)	54.4 (13.3)	53.3 (12.2)	55 (13.8)	0.2
No biopsy cores	11.02 (0.09)	10.9 (0.12)	11.2 (0.12)	0.26
PSAD	0.20 (0.2)	0.24 (0.16)	0.18 (0.15)	0.013

Table 1. Main characteristics of the analysed group * chi 2 test for trend=6.12; p=0.013; there is significant difference among cancer detection rate according to the PSAT values

Prostate vol.	≤ 39 cc N0 43 (11.1%)	40-59 cc No 224 (58.6%)	≥ 60 cc No 113 (29.3%)
Adeno ca	14 (32.5%) – 10.9%	78 (34.8%) – 60.5%	37 (33%) – 28.6%
Benign, suspect	29 (67.5%)	147 (65.2%)	75 (67%)
Chi ^{2}(p)	<0.03	<0.01	0.07

Table 2. PCA detection rate, depending on the prostate volume

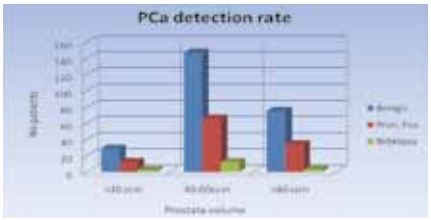

Figure 1. Rebiopsy PCA detection rate, depending on the prostate volume

In the group of patients with PSAT <4 ng/ml prostate cancer was confirmed in 14 cases (23%), or in 10.9% of all the confirmed Pca cases. In the group with PSAt 4-10 ng/ml, prostate cancer was confirmed in 67 cases (34.4%), or in 51.9% of all the confirmed Pca cases. In the group with Pca ≥10 ng/ml prostate cancer was confirmed in 48 cases (37.5%), or in 37.2% of all the confirmed prostate cancer cases. Chi ^{2} test for trend showed a statistically significant difference in cancer detection among the groups with PSAt <4 ng/ml and PSAt 4-10 ng/ml and PSAt >10 ng/ml (p=0.013), Table 1, in relation to the entire Pca group.

The prostate volume of up to 39 cc was present in 43 cases (11.1%). In this group, the presence of Pca was confirmed in 14 patients (32.5%), or 10.9% for the entire group. The prostate volume between 40 and 59 cc was present in 224 cases (58.6%), while Pca was confirmed in 78 cases (34.8%), or 60.5% of the entire group. The prostate volume of >60 cc was present in 113 cases (29.3%), while Pca was confirmed in 37 cases (33%), or 28.6% of the entire Pca number (Table 2). A proportion test comparison (chi2 test with Yates' correction) shows a statistically significant difference in prostate cancer detection between the first two subgroups in relation to the overall number of patients. Such a difference is not demonstrated in the third subgroup.

First rebiopsy for the three groups of patients, according to the above prostate volume, showed the rebiopsy rate for the first group of two new cases or 14.3% (2/14), while the rebiopsy for the second and third groups showed a detection of 12 new cases or 52.1% (12/23) and 3 new cases or 15.8% (3/19%) (Figure 1).

Out of 250 patients with negative biopsy findings, 68 (27.2%) had PSAD higher than 0.15. Out of 129 patients with confirmed prostate cancer, 62 (48%) of them had PSAD higher than 0.15. PSAD showed sensitivity and specificity in prostate cancer detection of 50% and 75%, respectively, with the post-test

	Primary PCA No 112	Rebiopsy Pca No 17	T test (p)
Age (Mean, SD, range)	68.4 (7.4) 52-79	69.2 (6.3) 57-76	0.66
Prostate Vol. (cc) (Mean, SD, range)	53.4 (12.6) 32-80	51.2 (9.13) 34-68	0.5
PSAD (Mean, SD, range)	0.26 (0.28) 0.03-1.36	0.16 (0.08) 0.06-0.32	0.14
PSAT (Mean, SD, range)	13.5 (15.1) 1.5-100	7.4 (3.6) 2.9-14.2	0.09
Gleason score (Mean, SD, range)	6.4 (1.5) 3-9	5.7 (1.2) 3-7	0.06
No biopsy samples (Mean, SD, range)	10.9 (2) 6-12	14.1 (3.4) 10-20	.0000

Table 3. Main characteristics between primary and rebiopsy prostate cancer

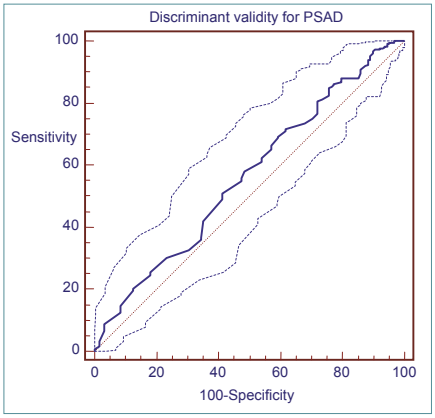

Figure 1. Receiver operating characteristic curve for PSAD in detection of PCa (AUC = 0.562, p=0.048)

probability of only 52% (Figure 2.).

The mean Gleason score for confirmed cancer amounted to 6.34 (1.5), with 3-9 range. The difference between the patients with PSAD lower or higher than 0.15, according to Gleason score, was significant; the T-test showed that patients with higher PSAD >0.15 had the mean Gleason score of 6.7 (±2.4) against 5.9 (±1.7); $p < 0.003$.

A comparison of the characteristics of patients with primarily and rebiopsy diagnosed prostate cancer did not show a statistically significant difference in age (p=0.66) or in the mean prostate volume (p=0.5). PSAD in patients with primarily diagnosed prostate cancer was higher (0.26) in comparison to rebiopsy diagnosed Pca (0.16); however, there was no statistically significant difference (p=0.14), which also applied to PSAT, even though the patients with primarily diagnosed Pca had the mean PSAT value higher than that of the rebiopsy group (13.5 vs. 7.4; p=0.09). The mean Gleason score for the first group was higher 6.4 (1.5) with respect to the rebiopsy group 5.7 (1.2), but there was no statistical significance established. The only statistically significant difference appeared in the number of biopsy samples between the primary and rebiopsy prostate cancer (10.9 vs. 14.1, p<.0000).

4. DISCUSSION

Serum PSA ≥4ng/ml is the accepted standard for prostate biopsy indication. However, several studies have shown that the value of serum PSA is just a rough basis in deciding on biopsy and is even less useful in reliable prostate cancer diagnosis. Furthermore, it is shown that, with the borderline value of PSAT≤4ng/ml, a significant number of cancers remain undetected (7). Some research shows that 22% of patients with normal DRE and PSAT values from 2.6 to 4.0 ng/mL have prostate cancer, while 81% of them have organ-limited disease (8).

Early studies indicate that PPV in cancer detection grows from 12% to 32% for PSAT values PSAT of 4-10 ng/mL, as well as 60-80% for PSA values of over 10 and 20 ng/mL (9, 10). Therefore, patients with PSAT values higher than 10 ng/mL and benign DRE findings face the probability of 60% that prostate cancer will be diagnosed, which is why they will poorly benefit from possible additional examinations of other PSA forms (PSAD, PSA velocity, PSAr). These percentages are even more prominent for PSAT values of over 20ng/mL, or for DRE suspected cancer (11).

This study showed statistically significant difference in terms of PSAT values of <4 ng/mL, 4-10 ng/mL and over 10 ng/mL with respect to the entire group with diagnosed prostate cancer. Further, no statistically significant difference was established for PSAr values, where the mean value was 0.15 for both the PCA group and the non-PCA group, although the research done by Kuriyama et al (12) suggests that the PSA ratio is very efficient in CAP differential diagnosis with regard to benign hyperplasia in the group with PSAT values in the grey area (4-10 ng/mL) and with specificity increasing to 60.7% in comparison with the PSAT group of up to 4 ng/mL with 18.8% specificity, where sensitivity is identical for both groups, amounting to 90%.

The research by Ficcare et al suggests that the prostate volume influenced the number of biopsy samples taken. It is their conclusion that 8 biopsy samples are sufficient for prostates smaller than 30 cc, while 10-12 biopsy samples were taken for the prostate volume of 30-50 cc. The results of lower cancer detection with regard to the prostate volume of over 50 cc indicated a larger number of samples. Therefore, the prostate volume is a relevant variable in planning a biopsy protocol. The probability of prostate cancer diagnosis decreases with the growth of prostate volume, provided that the same number of biopsy samples is used (13). Earlier, Uzzo et al stated that, through sextant biopsy, the cancer detection rate was 23% for prostates with volume exceeding 50 cc, in comparison with 38% for prostates with volume under 50 cc (14). Within our material, prostate biopsy was first performed through sextant biopsy, but later on through 12-sample biopsy and prostate biopsy according to the Vienna Nomogram, and afterward with saturation biopsy. In the first group (prostate volume up to 39 cc), the detection rate was 32.5%; in the second group (prostate volume 40-59 cc), the detection rate was 34.8%; in the third group (prostate volume >60 cc), the detection rate was 28.6%. Similarly, the rebiopsy results for the first group showed a detection rate of 14.3%, while the detection rate for the second group was 52.1% and 15.8% for the third group. These results show an inverted correlation between the prostate size and detection rate. More precisely, the detection rate was considerably lower with regard to the prostate volume of >60 cc in comparison with the prostate volume of up to 60 cc. The first group showed a high detection rate with the first biopsy and a low detection rate in rebiopsy; this is an indirect sign that the first biopsy is sufficient for prostate can-

cer detection with regard to smaller prostate volume. The biopsy and rebiopsy results for larger prostates suggest the need for taking a larger number of biopsy samples, typically from the prostate periphery that is thinner than the transition zone, and a higher number of samples from the transition zone that accounts for the most part of large prostates. In line with this statement is also the number of biopsies performed on our material. The average number of first biopsies was 10.9, and that of rebiopsies 14.1 (p 0.000).

A frequent clinical problem today is a lack of correspondence between PSA findings and biopsy findings. Urologists usually suggest rebiopsy in patients with the first negative biopsy, provided that the PSA level is elevated. The PSA value of PSA 4-10ng/mL poses a particular problem. As already mentioned, the detection rate is lower in larger prostates, while the PSAT value of PSAT 4-10ng/mL can vary, *inter alia*, due to the prostate size, as PSA is an organ-specific antigen. In order to facilitate clinical decisions and reduce the number of unnecessary rebiopsies, PSAD (PSA density) findings were introduced in practice, arrived at through the relation between PSAT and prostate volume. The concept of PSAD is based on the fact that BPH elevates the level of serum PSA due to gland tissue hyperplasia. With prostate cancer, the serum PSA elevation results from disruption of vascular architecture without a significant increase in the prostate volume. The cut-off value used for PSAD is 0.15. Levels above 0.15 are indicative of a malignant process, while levels below it of a benign process. BPH and prostate cancer frequently coexist, due to which calculating PSAD can theoretically minimise the influence of BPH on serum PSA (15). It should also be noted that the prostate size measured by TRUS and transabdominal ultrasound is different, as the true value of cephalocaudal diameter is obtained using TRUS alone. Transabdominal ultrasound can only represent an alternative method for measuring the prostate volume (5). In our research, PSAD showed specificity and specificity in prostate cancer detection of 50% and 70%, PPV 48%. There is a statistically significant difference (<0.013) in the group with diagnosed cancer and the group where cancer is not confirmed, though there is none within the groups with cancer diagnosed at primary rebiopsy, which is probably a consequence of a small number of patients and a wide variance. It is interesting to see a statistically significant difference in PSAD and Gleason score values. It is confirmed that patients with a higher PSAD level have a higher Gleason score, while patients with lower PSAD have a lower Gleason score. It was also observed that the Gleason score was lower in the rebiopsy group. This can be explained by the fact that, by taking a larger number of biopsy samples, the risk of a significant grade increase drops due to the increased density of the sampling area and a more precise pathohistological evaluation of biopsy samples (16). Some studies show that the probability of developing a prostate cancer increases with age, while other studies do not suggest this, as the range of the age group is limited and it does not represent a reliable variable (17). Our research also failed to produce a statistically significance in age of the patients with first rebiopsy diagnosed cancer, although it was shown in the total primary biopsy group.

5. CONCLUSION

A negative primary prostate biopsy should not convince the patients that they do not have a prostate cancer. It is necessary to perform the second, third and fourth biopsies, particularly with regard to prostates larger in volume, where PSATvalues are in the range of 4-10 ng/mL. In such cases, it is necessary to take a larger number of samples, with particular focus on the prostate transition zone.

With smaller volume prostates, the primary biopsy is usually sufficient in diagnosing prostate cancer and, if there are no premalignant lesions on the first examination, it is necessary to consider and, in strictly indicated cases, indicate rebiopsy. The frequently used PSAT borderline value of 4ng/mL is nowadays not sufficient. In order to minimise the PSAT values due to benign hyperplasia, PSAD values should also be used. PSAD carries a greater specificity in deciding on rebiopsy. Higher PSAD values can also be used in Gleason grade prediction, as well as in indicating rebiopsy.

Conflict of interest: none declared.

REFERENCES

1. Catalona WJ, Smith DS, Ratliff TL. Measurement of prostate specific antigen in serum as a screening test for prostate cancer. N Engl J Med. 1991; 24 (17): 1156-1161.
2. Schröder FH, van der Maas P, Beemsterboer P, Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 1998; 90(23): 1817-1823.
3. Carvalhal GF, Smith DS, Mager DE. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng/ml or less. J Urol. 1999; 161(3): 835-839.
4. Urdiales-Ortiz A, Camarena-Reynoso H, Cantellano-Orozco M, Morales-Montor J, Pacheco-Gahbler C, Calderón-Ferro F. Nine and twelve specimens from prostate biopsy and their impact on cancer detection: a comparative study, Rev Mex Urol. 2010; 70(4): 206-210.
5. Presti JC, Kane JC, Shinohara K, Carroll PR: Neoplasms of the Prostate Gland, in Tanagho, EA, McAninch JW, Smith's General Urology, 17th edition, The McGraw-Hill Co, USA, 2008.
6. Aus G, Abbou CC, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol. 2005; 48: 546-551
7. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level <or=4.0 ng per millilitre. N Engl J Med. 2004; 350: 2239-2246.
8. Berger AP, Volgger H, Rogatsch H, et al. Screening with low PSA cutoff values results in low rates of positive surgical margins in radical prostatectomy specimens. Prostate. 2002; 53: 241-245.
9. Catalona WJ, Hudson MA, Scardino PT, et al: Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: Receiver operating characteristic curves. J Urol. 1994; 152: 2037-2042.
10. Brawer MK: Prostate-specific antigen: Current status. CA Cancer J Clin. 1999; 49: 264-281.
11. Polascik TJ, Oesterling JE, Partin AW: Prostate specific antigen: A decade of discovery. What we have learned and where we are going. J Urol. 1999; 162: 293-306.
12. Kuriyama M, Kawada Y, Arai Y, Maeda H, Egava S, Koshiba K, et al. Significance of free to total PSA ratio in men slightly elevated serum PSA levels: a cooperative study. Jpn J Clin Oncol. 1998; 28: 661-665.
13. Ficarra V, Novella G, Novara G, Galfano A, Pea M, Martignoni G, Artibani W, The Potential Impact of Prostate Volume in the Planning of Optimal Number of Cores in the Systematic Transperineal Prostate Biopsy, Eur Urol, 2005; 48: 932-37.
14. Uzzo RG, Wei JT, Waldbaum RS, Perlmutter AP, Byrne JC, Vaughan Jr ED. The influence of prostate size on cancer detection. Urology. 1995; 46(6): 831.836.
15. Aref I, Eapen L, Agboola O, Cross P. Is prostate specific antigen density an important prognostic indicator for patients with prostate cancer treated with external beam therapy. The British Journal of Radiology. 1998; 71: 868-871.
16. Campos-Fernandes JL, Bastien L, Nicolaiev N, Robert G, Terry S, Vacherot F, Salmon L, Allory Y, Vordos D, Hoznek A, Yiou R, Patard JJ, Abbou CC, de la Taille A. Prostate Cancer Detection Rate in Patients with Repeated Extended 21.Sample Needle Biopsy. Eur Urol. 2009; 55: 600-609.
17. Finne P, Auvinen A, Aro J, Juusela H, Määtänen L, Rannikko S, Hakama M, Tammela TLJ, Stenman UK. Estimation of Prostate Cancer Risk on the Basis of Total and Free Prostate-Specific Antigen, Prostate Volume and Digital Rectal Examination. Eur Urol. 2002; 41: 619-27.