Objectives: To estimate the ratio between urinary prostate specific antigen (uPSA) and tumor volume after prostate biopsy.

Methods: From 2000 to July 2008, uPSA concentration was determined in 60 patients with clinically organ-confined prostate cancer (PCa). All patients underwent six-area transrectal ultrasound (TRUS) - guided biopsy, with at least 12 biopsy cores. Single pathologist determined tumor grade (G), Gleason score (GS), the percentage of tumor infiltration (%TI) and the percentage of positive cores (%PC) in all biopsy cores. Additionally, relative tumor-biopsy volume (RTV) was calculated by multiplying %PC, %TI and prostate ultrasound-derived volume (Vol). Forty-one patients underwent retropubic radical prostatectomy (RRP), while 19 patients underwent radiation therapy.

Results: Average uPSA was $308.6 \pm 311.9$ ng/ml (range 0.06-988 ng/ml), average PSA was $9.7 \pm 5.5$ ng/ml (range 1.2-24.3 ng/ml), tumor grade $1.7 \pm 0.8$, Gleason score $5.2 \pm 1.3$, the percentage of tumor infiltration $27.6 \pm 21.8\%$, and the percentage of positive cores $52.2 \pm 30.7\%$. Average RTV was $6.3 \pm 8.4$ ml (0.29-56 ml). All patients were divided into two groups: I, with RTV $\leq 4$ ml and II, with RTV $= 4$ ml. The patients with RTV $4$ ml had lower G ($1.4 \pm 0.6$ vs. $2.1 \pm 0.8$, $p=0.0002$), lower GS ($4.5 \pm 1$ vs. $5.8 \pm 1.3$, $p=0.003$) and higher uPSA ($389.4 \pm 340.8$ vs. $193.1 \pm 229.7$, $p=0.014$). There were no differences in serum PSA levels between the groups.

Conclusion: Relative tumor-biopsy volume (RTV) is useful parameter in the preoperative assessment of tumor volume. Patients with higher RTV had significantly higher G and GS. However, these patients had significantly lower uPSA. This phenomenon could be the consequence of compromised PSA drainage from the peripheral zone of the prostate, caused by the tumor.

Key words: Prostate cancer, prostate specific antigen, tumor volume, urinary PSA.

INTRODUCTION

Prostate specific antigen (PSA) is the main secretory product of the prostate gland.

The physiological function of PSA is liquefaction of seminal coagulum; this process is crucial for the deliberation of spermatozoa from the seminal gel and their progressive movement. The natural reason for the transfer of PSA molecules from prostatic glands to the blood is not clearly understood.

However, this proteolytic enzyme is successfully inactivated in the blood by serine protease inhibitors, alpha-2 macroglobulin (A2M) and antichymotripsine (ACT).

The concentration of PSA in the prostatic tissue is $0.01 - 0.08$ mg/ml and it is similar in the normal prostatic tissue, benign prostatic hyperplasia (BPH) and prostate cancer (PCa).

The synthesis of PSA is dihydrotestosterone (DHT) – dependent. After entering the epithelial cell, androgens react with 5-alpha reductase, which converts them into more potent hormone, DHT.

The molecules of DHT bind to androgen receptor and enter the nucleus. In the nucleus, DHT-androgen receptor complex stimulates the transcription of various genes, for the synthesis of PSA, growth factors and other proteins. After the synthesis, PSA molecules are contained in prostatic secretory granules (PSG), which discharge their content out from the cell.
Following that, PSA molecules leak through prostatic ducts to the prostatic urethra, where they collect, until the next micturition or ejaculation happens.

Central and transition zone ducts enter the prostatic urethra at the sharp angle, lateral to the verumontanum. Peripheral zone ducts enter the urethra perpendicularly, along the distance between verumontanum and distal urethral sphincter.

Ductal drainage of the prostatic secretions can be compromised in the presence of infection, prostatic calculi and the cancer. Additional PSA molecules are secreted diffusely, along entire urethra, from so-called minor prostatic glands (MPG).

All MPG are made of prostatic glands, or of prostatic and mucinous epithelium. Some authors believe that these glands could be responsible for persistent PSA levels after radical prostatectomy. It seems that MPG represent evolutionary remnant.

Namely, early mammals, that appeared 65 million years ago, probably had primitive prostate consisted of disseminated prostatic glands in the urethra, so-called disseminated prostate. In the present time, small, microscopic disseminated prostates can be seen in whales and dolphins, and larger one in other mammals, like boar, ram and bull; the mammals on the higher evolutionary position, including primates, developed compact organ.

In primates and humans, these glands probably provide diffuse presence of PSA in the urethra and, maybe, take place in the cleansing of the urethra after the ejaculation.

All PSA molecules detected in the urine, are washed-out from the urethra during the micturition. Namely, 32.9 kDa heavy PSA molecule, cannot pass the glomerular membrane; it is proved that no PSA can be detected in the urine from ileal conduits, or nephrostomy catheters.

In 1992, DeVere White reported that average uPSA concentration in the group of BPH patients was 216 ng/ml. Later on, it was found that the average uPSA in the PCa group was 915 ng/ml in the first stream and 246 ng/ml in the middle stream . In the recent works, it is found that patients with BPH have higher uPSA than the patients with PCa (123.2 vs. 52.6 ng/ml. Cut-off value of 150 ng/ml differentiate BPH and PCa with the sensitivity of 92.5%)14.

In addition, in some recent works uPSA is used as a marker which reflects total androgen activity. Rising concentration of uPSA is the simple method for the detection of early puberty in boys, as well as the test for the detection of androgen insensitivity and inadequate virilization.
It is worthy to note that in some primates uPSA rise in the breeding season: in Japanese makaka monkeys, the rise of uPSA appears just after the termination of the menstrual bleeding in 16.

**METHODS**

From 2000 to July 2008, in Urological Clinic, Clinical Center of Serbia, the concentration of urinary PSA was determined in 60 patients with clinically organ-confined prostate cancer (PCa). Prior to curative therapy, all patients underwent six-area TRUS-guided biopsy, with at least 12 biopsy cores. Transrectal ultrasound and TRUS-biopsies were performed on Toshiba-Tosbee machine, with transrectal probe IVE-506S. Prostate volume was calculated on usual manner: a x b x c x pi/6.

Biopsy was performed with 160mm/16G needles, using Gallini or Bard biopsy gun. All patients gave first 70 ml of fresh urine just prior to biopsy. The urine was titrated with NaOH until the pH of 7.5 was reached. Urine samples were spun in the centrifuge at 2000 rpm for 10 minutes.

Aliquots of 500 l samples were frozen at -20C and stored. Urinary PSA was determined using IRMA-PSA test, produced in Institute for Nuclear Energy Application (INEP), Zemun, Belgrade. Single pathologist (R.R.) determined tumor grade (G), Gleason score (GS), the percentage of tumor infiltration (% TI) and the percentage of positive cores (% PC) in all biopsy cores.

Relative tumor-biopsy volume (RTV) was calculated by multiplying % PC, % TI and prostate volume derived by ultrasound (RTV = % PC x % TI x Vol)

Forty-one patients underwent retropubic radical prostatectomy (RRP), while 19 patients underwent radiation therapy.

**RESULTS**

Average uPSA was 308.6 ± 311.9 ng/ml (range 0.06 - 988 ng/ml), average PSA was 9.7 ± 5.5 ng/ml (range 1.2 - 24.3 ng/ml), tumor grade 1.7 ± 0.8, Gleason score 5.2 ± 1.3, the percentage of tumor infiltration 27.6 ± 21.8 %, and the percentage of positive cores, 52.2 ± 30.7 %.

Average RTV was 6.3 ± 8.4 ml (0.29 - 56 ml). All patients were divided in two groups: I, with RTV < 4 ml and II, with RTV = 4 ml. The patients with RTV > 4 ml had lower G (1.4 ± 0.6 vs. 2.1 ± 0.8, p=0.0002), lower GS (4.5 ± 1 vs. 5.8 ± 1.3, p=0.003) and higher uPSA (389.4 ± 340.8 vs. 193.1 ± 229.7, p=0.014). There were no differences in serum PSA levels between the groups. (Table 1, Figure 1, 2)

**DISCUSSION**

It has been said that PSA is the best and most widely used tumor marker in medicine. Its influence on urology is so great, that some authors differentiate pre-PSA and PSA era in the prostate cancer management. Indeed, PSA enabled male population screening and early cancer detection, as well as preoperative staging and postoperative follow-up.

It is not completely clear why PSA molecules leak from prostatic ductal system and enter the circulation. However, it is clear that high PSA concentration in seminal plasma is necessary for the liquefaction of the seminal coagulum after the ejaculation. Namely, PSA concentration in seminal plasma is million-time higher than in the blood.

In the absence of ejaculations, the synthesis and the secretion of PSA are maintained; these processes depend on testosterone and DHT level. From the other side, the most important source of PSA is the peripheral zone, rich in prostatic glands. Prostatic ducts from the peripheral zone possess wide lumina and wide openings in the prostatic urethra. However, some processes can compromise prostatic drainage. At the first
place, prostatic tumors, which are the most common in the peripheral zone, can obstruct prostatic ducts. Small tumors can block prostatic drainage in few ducts, but large tumors can completely stop prostatic drainage. In such cases, the majority of PSA molecules that reach the prostatic urethra and urine are of urethral origin. (Figure 3)

The term “urinary PSA” is not completely correct: there are no PSA molecules in the urine from the kidneys to the urinary bladder. In fact, PSA is present only in the urine out of the body, after voiding. Therefore, the word that is more correct would be “washed-out PSA”, or “secreted PSA”. Nevertheless, today urinary PSA has no place in the urology that it deserves. The most common reasons for that are the fluctuations in results due to hormonal influences, various biochemical conditions in the urine, the absence of agreement of the best way of collecting the urine, etc. The specificity of this test will surely rise when all these factors would be routinely considered.

Using the new parameter- relative tumor-biopsy volume (RTV), it was possible to approximate tumor volume in the cases when pathologist cannot determine it in the radical prostatectomy specimen, or in the cases that were treated by radiation therapy.

Patients with RTV greater than 4 ml had significantly higher tumor grade and Gleason score. This observation agrees with known facts that greater tumors are more aggressive. From the other side, the fact that the patients with RTV = 4 ml had significantly lower uPSA than the patients with RTV > 4 ml, could be the consequence of compromised PSA drainage from the peripheral zone of the prostate caused by the tumor.

CONCLUSION:

Urinary PSA, or washed-out PSA, is valuable marker which characteristics are not completely explored. The fact that uPSA is significantly lower in the patients with greater prostate tumors gives hope that the researches in the field of urinary PSA have the future.

SUMMARY

NIVO PSA U URINU I RELATIVNOG VOLUMENA TUMORA POSLE BIOPSIJE PROSTATE

Cilj rada: ustanoviti da li postoji odnos izmedju nivoa prostata specifičnog antigena (PSA) u urinu i zapremine tumora prostate, odredjene na osnovu rezultata biopsije prostate.

Materijal i metode: od 2000. godine do jula 2008, kod 60 bolesnika Urološke klinike Kliničkog centra Srbije je određivana koncentracija urinarnog PSA (uPSA). Kod svih bolesnika je postojao karcinom prostate u kliničkom stadiju T2, odnosno tumor ograničen na prostatu. Kod svih bolesnika je uradjena biopsija prostate vodjena transrektalnim ultrazvukom (TRUS-biopsija), iz šest standardnih polja, sa najmanje 12 isečaka. Kod svih bolesnika je patolog u biopriranom materijalu određivao gradus tumora (G), Gleasonov skor (Gleason score, GS), procenat tumorske infiltracije (% TI) i procenat pozitivnih isečaka (% PC) u materijalu.

Osim toga, kod svih bolesnika je posle toga odredjivan relativni volumen tumora posle biopsije (RTV), koji se izračunava kao proizvod % TI, % PC i zapremine prostate odredjene na TRUS (Volp). Kod 41 bolesnika je uradjena radikalna prostatektomija, a kod 19 zračna terapija na Institutu za onkologiju i radiologiju u Beogradu.

Rezultati: Prosečna koncentracija uPSA je iznosila 308.6+311.9 ng/ml, (0.06 - 988 ng/ml) a prosečna koncentracija PSA je bila 9.7+5.5 ng/ml (1.2 - 24.3 ng/ml). Prosečan gradus tumora je bio 1.7+0.8,a prosečni Gleasonov skor 5.2+1.3. Prosečna tumorska infiltracija je iznosila 27.6+21.8 %, a procenat pozitivnih isečaka 52.2+30.7 %. Prosečna vrednost RTV je bila 6.3+8.4 ml (0.29-56 ml).

Svi bolesnici su podeljeni u dve grupe: I (RTV > 4 ml) i II (RTV ? 4 ml). Bolesnici sa RTV > 4 ml su imali niži G (1.4+0.6 prema 2.1+0.8, p=0.0002), niži Gleasonov skor (4.5+1 prema 5.8+1.3, p=0.003) i viši uPSA (389.4+340.8 vs. 193.1+229.7, p=0.014). Nisu nadjene značajne razlike u koncentraciji serumskog PSA izmedju dve grupe.

Zaključak: Relativni volumen tumora posle biopsije (RTV) je koristan parametar za preoperativnu procenu zapremine tumora. U ovoj studiji, bolesnici koji su imali veći RTV, imali su i viši gradus i Gleasonov skor tumora. Sa druge strane, bolesnici sa većim RTV su imali značajno niži uPSA. Ovaj fenomen je verovatno posledica prisustva tumora prostate, koji vrši opstrukciju prostaticnih duktusa i otežava drenažu PSA, uglavnom iz periferne zone prostate.

Ključne reči: karcinom prostate, prostata specifični antigen, urinarni PSA, volumen tumora.

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