

## Prostate Specific Antigen: Blessing or Curse?

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Stručni članak

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Early detection and diagnosis improve both the management and the survival of patients with prostate cancer.

The PSA is an excellent tool in urologist's hand, can help in early detection of prostate cancer, in the follow up of the medical treatment or after radical prostatectomy with the purpose of checking the effectiveness of the treatment. On the other hand, the PSA can result in unnecessary biopsies, causing patient's anxiousness, therefore bearing both advantages and disadvantages. One has to learn and be familiar with the evaluation of the PSA concentration, as well as different PSA derivatives such as PSA velocity, PSA density and free PSA level.

PSA should not only be performed in patients with prostate cancer, but also for screening purposes, in combination with rectal digital and transrectal ultrasound examination.

**Key words:** Prostate specific antigen, Prostatic neoplasms-therapy, Screening.

Diagnosing prostate cancer seemed to be "simple" 30 or 40 years ago, since we diagnosed it by digital rectal exam. After this, we carried out castration and the patient was administered a terrible amount of estrogen hormone (cca 20-25 mg). As a consequence, he died either due to the tumorous disease or the side effects of our treatment. In the case of false positive rectal exam, the treatment turned out to be false as well...

### The beginning

The discovery of PSA was an extremely important event in our clinical practice, however we were not aware of its importance at that time. I was working in West Germany in the middle of 1980s when the measurement of PSA was clinically introduced - still surrounded by many doubts. We carried out prostate biopsy (not too often) and had to rely on its results. We also recorded the PSA levels; however only afterwards, since it was first measured every other week - later weekly.

After collecting the cases where we measured PSA, I presented a poster on the topic at the European Urology Conference in London in 1988; following this conference I presented the same poster at a Hungarian Congress - however, few were interested. Also in the same year I was given reagents for carrying out 100 examinations, therefore we started to use them at our hospital.

We did not really know which groups of patients we had to involve and we had troubles with assessing the results as well. Moreover, we lacked patients, so we needed to get serums from other hospitals. My boss was not really certain about PSA either...

For all this, we managed to publish the first Hungarian study on PSA examinations at our department in Orvosi Hetilap (1) (Medical Weekly). Following this event we succeeded in organizing an international conference in the Hotel Gellért Budapest in 1991. Thanks to our efforts, the use of PSA examinations

started to spread. Hence, in 2007 there were 5000 PSA examinations at Semmelweis University, most of which were indicated by urologists. Since then assessing PSA has become a daily clinical practice.

### Indications

In what cases should PSA be determined?

- For medical check-ups, at male patients without symptoms (not financed by the Hungarian insurance).
- In the case of positive rectal palpation.
- In the case of negative rectal exam, but the patient has frequency.
- If the patient has already been treated with alpha receptor inhibitors due to the complaints of benign prostate hyperplasia, but there are still symptoms.
- If PSA level - checked after a three month interval - is increasing.
- Bone pains, in the case of tumor suspected X-ray or isotop scan.
- In the case of a patient with prostate cancer (without p. history) to follow up the effectiveness of the treatment.
- After radical prostatectomy, PSA levels could provide us information of the biochemical failure of disease.
- The list of indications seems to be long, but do patients always benefit from this examination?
- During general medical check-ups the rate of diagnosing prostate tumors is very low, therefore it is not economical. However, those recognized at an early stage will definitely recover.

Moreover, the effectiveness of PSA is better than colonoscopy and its sensibility is high above other tumor markers. There was, however, an editorial article published in the European Urology where it was noted that "The PSA era and its challenges are not over." (2)

Throughout rectal examination local tumors can be detected in 30% of cases. Therefore, rectal digital examination is not capable of detecting all the tumors at an early stage without PSA examination. We cannot, however, apart from the practice!

### **PSA level, what should we do with it?**

What level is positive in fact?

Higher levels (> 3 or > 4 ng/ml) than the level authorized by the laboratory?

This is not true in this way. Regardless of the higher PSA levels (4-10 ng/ml) which were measured at our patients, tumors were detected only in 20-40 % by biopsy. Biopsy is said to be unnecessary in 60-80%. Unnecessary? The number of tumorous patients with normal PSA levels could reach up to 15% (3). This means that prostate tumor could occur at those patients who have normal PSA levels (> 2.5 ng/ml) (4). In the case of bone metastasis of prostate cancer, which causes pain to the patients, we can definitely be sure of finding an increased level of PSA. However, if we detect a suspicious shadow on the X-ray image besides normal PSA levels, prostate cancer or at least metastasis could likely be excluded. Furthermore, in the case of proved malignant disease the follow-up of PSA level is inevitable. However, we can face surprising events is the case of hormone resistance: tumorous progression may occur besides normal PSA levels, as well, furthermore, increasing PSA levels during hormone treatment should indicate change in drug treatment. It is also important to know that cycling, horse riding, ejaculation or even rectal examination before blood test will increase PSA levels. Finasterid (drug) administered due to prostate hypertrophy will decrease PSA levels by 50%.

### **Annoying factors**

PSA level arises in accordance with patient's age. At the age of 45, the normal figure is 2.5 ng/ml, whereas at the age of 80 it might be 6,5 ng/ml. This is, however, not always true. 30% of patients between the age of 70-80 have the PSA level under 3 ng/ml (Table 1) Moreover, PSA level arises in accordance with the prostate volume. It could be true since an enlarged prostate might indicate an increased PSA level. The calculation of PSA density (PSA divided by prostate volume) might help us to avoid mistakes. The problem is, however, that calculating proper prostate volume seems to be difficult. In addition PSA level increases in the case of prostate inflammation. This higher level of PSA could be detected three months later, as well, in the 30% of the cases. The pathological level can be normalized only after 6 months, if treated properly. Therefore, in the case of a patient with chronic prostatitis, several biopsies might be performed because of an increased PSA level if the prostatitis is symptom-free and the urologist does suspect a chronic inflammation. Nevertheless, the biopsy results do not always describe inflammation since the pathologist usually searches for tumorous disease as indicated by the examining urologist. Therefore, in the case of suspected prostatitis causing higher PSA levels, biopsy should be preceded by an antibiotic treatment. As a consequence, the number of unnecessary biopsies could be reduced. We could suspect chronic prostate inflammation in the case of pyuria after a massage, however, the lack of pyuria would not definitely exclude prostatitis. The diurnal change of PSA might reach 10-20%. Did I manage to confuse my readers?

### **Other matters**

#### **Biopsy**

What should we do with the patient whose PSA levels are steadily increasing but the biopsies are all negative? The reason could either be traced in the patient or in the method of biopsy. One reason can be the inflammation explained before, for instance in the case of prostate stones (which normally should not be treated) occurs a perifocal inflammation. The method of performing biopsy might provide us reasons. It is no use mentioning those cases where the biopsy sample cannot be analyzed and assessed. In this case, the urologist is informed of the insufficient sample, and the pathologist does not give any opinion. There are few biopsies performed without ultrasound guidance, however, biopsies taken in this way are rather leading to inadequate results. On the contrary, ultrasound guided biopsy might provide us insufficient samples. For example, the pathologist is not aware of which part of the prostate the samples are taken from, therefore, in the case of two samples taken very close from each other the pathology result might be misleading since cancer could be hidden in the untouched part of the prostate. In addition, the sample can be too short, too crumpled, or the pathologist can also make mistakes, even when he is a beginner, or he works at an institution where there are few urological samples. If voiding symptoms are not better regardless of alpha inhibitors, we have to think of tumors. Also we can think of the fact that the patient does not take the drug regularly or of a progressed stage where the administered drug is not having a proper effect and therefore the patient's status is not getting better. The annual increase in PSA level is 0.17 ng/ml, thus in the case of a higher annual level, biopsy is definitely indicated (5).

#### **Radical surgery**

The radical prostatectomy is a curative treatment. We remove the prostate, the seminal vesicle and often the regional lymph nodes as well. This latter treatment is not necessary under 10 ng/ml, but we usually perform this surgery. We try to cut through the urethra under the apex, then we remove it from the bladder cervix in order not to leave any prostate tissue there. The proof of our success is the PSA level of 0.0 ng/ml 8 weeks after the surgery. However, in the 30% of the cases, PSA level can be detected 10 years after the surgery (biochemical failure). If there is a prostate tissue remained, PSA level can be detected 8 weeks after the surgery, however, this is rather rare. Biochemical failure occurs more often in those patients who had higher PSA levels before the surgery (let's call it 25 ng/ml) or when the tumor infiltrated the capsule (stage more than pT2) and the Gleason score is high (more than 8). But why will some patients have detectable PSA levels 3-5 years after the surgery? I truly do not know... Nobody knows...

#### **Blessing or curse?**

PSA is a blessing for those whose cancer was detected in an early stage.

PSA is a curse for those whose prostate cancer is recognized in an early stage, but during the histology examination the tumor was not significant (< 0.2 cm<sup>3</sup>); the patient might have lived without any symptoms for a long time - but he had to undergo a surgery with all its side effects and complications.

PSA is a curse for those whose PSA level is higher (more than 4 ng/ml) and his prostate is bigger (for example 80 g) which might explain higher PSA level; however since the doctor as well as the patient has in doubts, biopsy will surely be performed.

PSA is a blessing for that patient, who had been checked for 6-8 years, many biopsies were performed and finally he was cured with brachytherapy at the age of 74.

PSA is a curse for the patient who underwent a surgery even though his tumor was local and became incontinent. The correction surgery, however, was successful.

PSA is a blessing for that 52-year-old father with three children, who after undergoing the surgery became tumor-free, moreover taking VIAGRA®, he became potent as well. (His PSA is 0.0 ng/ml now).

PSA is a curse for all those patients where biopsy was performed just because of an increased PSA level. They are waiting for the adoption to the hospital, waiting for the histology results - meanwhile they are being nervous. If the PSA is positive, they become more nervous, if it is negative, they still remain anxious about he results (6).

PSA is a blessing for the man who has a zero level PSA, symptom-free and even more he remains potent. This is the so-called "trifecta", which we are struggling to achieve. How could we apart from these paradoxes? We cannot put PSA aside, since there is no better solution regardless of all the critical remarks. In the USA, 80-100 of the male patients want to know the level of PSA, whereas this number is only 30-50% in Europe (3).

#### What can we do?

We have to consider PSA level very important. Examine the patient carefully (rectally, transvesical US or by MR examina-

tion). Control the examination (is it not after a massage, etc?) in order to get closer to the real PSA level. If we have doubts about the results, we have to repeat the test. In the case of suspected prostatitis, administrate antibiotics and antiphlogistics promptly, and check PSA afterwards. The treatment is the same if the inflammation is proved. We should measure the residuum after voiding, if the volume is higher, we can allow for an increased PSA level. The blood should be taken before rectal examination. We can dream of a new marker - which exists already PC3, by which we can make diagnosis after massage. We are also taking part in a study (7) with experts from London and Bruxelles, throughout which we try to set up diagnosis via three dimensional transrectal ultrasound examination. We should patiently wait for the new results -

I hope to inform you about them afterwards...

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TABLE I  
PSA in accordance with age (based on the studies of certain authors)  
TABLICA 1.

PSA u odnosu na starosnu dob (temeljeno na istraživanjima određenih autora)

Authors Autori	Age 40-49 40-49	Age 50-59 50-59	Age 60-69 60-69	Age 70-79 70-79
Oesterling	2.5	3.5	4.5	6.5
Anderson	1.5	2.5	4.5	7.5
Reed	2.5	3.5	3.5	3.5

## PROSTATE SPECIFIČNI ANTIGEN: BLAGOSLOV ILI PROKLETSTVO?

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### SAŽETAK

Rano otkrivanje i dijagnoza poboljšavaju liječenje i preživljavanje kod pacijenata koji boluju od raka.

PSA je izvrsna urološka metoda koja može pomoći prilikom ranoga otkrivanja raka prostate povećavajući učinkovitost medicinskoga liječenja ili nakon radikalne prostatektomije kako bi se provjerila uspješnost liječenja. S druge strane, PSA može dovesti do obavljanja nepotrebnih biopsija, kao i prouzročiti zabrinutost pacijenta, što također uključuje mnogo prednosti i mana. Moramo učiti i moramo biti upoznati s procjenom koncentracije PSA i različitih derivata PSA, kao što su brzina, gustoća i slobodna razina PSA.

PSA se ne treba koristiti samo kod svih pacijenata koji boluju od raka prostate, nego i za screening, u kombinaciji s rektalnim digitalnim i transrektalnim ultrazvučnim pregledom.

**Ključne riječi:** Prostata specifični antigen; Rak prostate - liječenje; Screening (probir)