

## Prostate specific antigen: blessing or curse?

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The PSA has been the most useful tumour marker in the medical diagnosis so far. No other markers or screening methods reach the specificity and sensitivity of PSA. On the other hand the PSA has also false positive and negative results as well.

The advantages and disadvantages of the PSA determination are discussed in our paper. The proper counselling with the papers and right evaluation of results should be diminished the disappointments in PSA.

Diagnosing prostate cancer seemed to be “simple” 30 or 40 years ago, since we diagnosed it by rectal digital examination (RDE). 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 RDE, 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 EAU conference in London in 1988; following this conference I presented the same poster at the Hungarian Urological Congress – however, few were interested.

Also in the same year we were given reagents for carrying out 100 examinations, therefore we started to use them at our department.

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 Budapest in 1991. Thanks to our efforts, the use of PSA examinations started to spread. Hence, in 2010 there were about 7000 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 RDE.
- In the case of negative RDE, but the patient has frequency.
- If the patient has already been treated with  $\alpha$ -receptor inhibitors due to the complaints of benign prostatic 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 isotope scan.
- In case of a patient with prostate cancer to follow up the effectiveness of the treatment.
- After radical prostatectomy, PSA levels could provide information on biochemical failure, recurrence of disease.

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

Vrijednosti PSA u odnosu na starosnu dob, temeljene na istraživanjima pojedinih autora

Authors/ Autori	Age 40-49/ Dob 40-49	Age 50-59/ Dob 50-59	Age 60-69/ Dob 60-69	Age 70-79/ Dob 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

- The list of indications seems to be long, but whether patients always benefit from this examination?
- During general medical check-ups the rate of diagnosing prostate tumours 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 tumour 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 the local tumours can be detected in 30%. Therefore, RDE is not capable of detecting all the tumours 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) we measured at our patients, tumours 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 tumour could occur at those patients who have normal PSA levels (> 2.5 ng/ml) (4). In 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 case of proved malignant disease the follow-up of PSA level is inevitable. However, we can face surprising events in case of hormone resistance: tumorous progression may as well occur besides normal PSA levels, 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 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 the 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 level divided by prostate volume) might help us to avoid mistakes. The problem is that calculating proper prostate volume seems to be difficult. In addition, PSA level increases in case of prostate inflammation. This higher level of PSA could be detected three months later as well in 30% of the cases. The pathological level can be normalized only after 6 months if treated properly. Therefore, in case of a patient with chronic prostatitis, several biopsies might be performed because of increased PSA level if the prostatitis is symptom-free and the urologist does not think of 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%. I wonder whether I have managed 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) a perifocal inflammation occurs. The method of performing biopsy might provide us reasons. It is no use mentioning those cases where the biopsy samples cannot be analyzed and assessed. In these cases 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 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 do have to think of tumours. 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 does not have a proper effect and therefore the patient's status gets no 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, though the data are very variable (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, and then we remove it from the bladder neck 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 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 sur-

gery or when the tumour infiltrated the capsule (stage higher 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... Nor does anybody...

### 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 tumour was not significant ( $< 0.2 \text{ cm}^3$ ); the patient might have lived without any symptoms for long – 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 enlarged (for example 80 g) which might explain higher PSA level; however since the doctor as well as the patient are in doubts, biopsy will surely be performed.

*PSA is a blessing* for the patient who had been checked for 6-8 years, many biopsies were performed and finally he was cured with brachytherapy at the age of 72.

*PSA is a curse* for the patient who underwent a surgery even though his tumour 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 tumour-free, moreover taking sildenafil, he became potent as well. (His PSA is 0.0 ng/ml).

*PSA is a curse* for all those patients where biopsy was performed just because of an increased PSA level. He is waiting for admission to the hospital, waiting for the histology results – meanwhile he is being nervous, having “PSA-it is”. If the PSA is positive, he becomes more nervous, if negative he still remains anxious about the future (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, transrectal US or by MR examination). Control the PSA levels in order to get closer to the real PSA level. If we have doubts about the results, we do 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 residual urine 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 (it costs 100 or 200 Euros).

I wish everybody more blessing than curse!

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### SPECIFIČNI ANTIGEN PROSTATE: SPAS ILI PROKLETSTVO?

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Stručni članak

SAŽETAK

PSA je poznat kao najkorisniji tumorski biljeg do sada u medicinskoj dijagnozi. Niti jedan drugi marker ili metoda probira ne postižu takvu specifičnost i osjetljivost. S druge strane, PSA također daje kako lažno pozitivne tako i lažno negativne rezultate.

U članku se raspravlja o prednostima i nedostacima u određivanju PSA. Pravilno praćenje nalaza te korektna evaluacija rezultata trebale bi umanjiti moguća razočarenja koja donosi PSA.