

However, the results of other authors differed from these data: they stated that only 24% biopsies would be avoided with a loss of 1% of patients (Zlotta et al., 1997). Djavan et al (1998) reported that the cut-off value for transition zone PSA was 0.35, which provided the highest positive predictive value (74%) for prostate cancer detection in 939 men with PSA less than 10 ng/ml.

In a prospective multicentric study, Djavan et al. (1999) found that the values f/t PSA (ratio of free/total PSA) and PSA-TZ were the most decisive parameters when differentiating between BPH and PC. They have also demonstrated significantly lower values of PSAD and PSA-TZ in patients with a higher volume of prostate and transition zone. They have calculated the threshold values of PSA-TZ depending on the total prostate volume (0.44 at the volume  $\leq 30 \text{ cm}^3$  and 0.26 at the volume  $> 30 \text{ cm}^3$ ) and depending on the volume of the prostatic transition zone (0.38 at the volume  $\leq 20 \text{ cm}^3$  and 0.23 at the volume  $> 20 \text{ cm}^3$ ).

### *PSA velocity (PSAV)*

PSA velocity represents another parameter enabling better specificity of PSA itself. In 1992, Carter et al. published the possibility to use PSA velocity to improve the ability of PSA to detect PC. They have described increasing PSAV in men with PC as compared to the men without PC already 5 years before it was possible to diagnose it. PSA velocity is calculated by the equation,  $1/2 ([\text{PSA}_2 - \text{PSA}_1 / \text{time}_1, \text{ in years}] + [\text{PSA}_3 - \text{PSA}_2 / \text{time}_2, \text{ in years}])$ , where PSA<sub>1</sub> equals the first, PSA<sub>2</sub> the second and PSA<sub>3</sub> the third serum PSA measurement. At least 3 PSA measurements should be obtained during a 2-year period or at least 12 to 18 months apart to obtain maximal benefit using velocity measurements (Carter et al., 1992).

PSA velocity (PSAV) depends on the aggressiveness of the tumor; it is not changed in healthy subjects (0.04 ng/ml/year), in patients with BPH it is increased by 0.07–0.27 ng/ml/year, in patients with PC the increase is usually higher (0.75 ng/ml/year and more [72% sensitivity, 95% specificity]) (Carter et al., 1992).

In the cases where, based on the first detected level of PSA 4–10 ng/ml, prostate biopsy was performed with a negative result, repeated PSA determination can accelerate the decision about repeated biopsy if the increase in the PSA level, i.e. PSAV, is higher than 0.75 ng/ml per year. According to Carter, only 5% of men with such or higher annual increase has not detectable PC. On the contrary, for 70% of men with PC detectable by biopsy, the PSAV value is  $> 0.75 \text{ ng/ml/year}$  (Carter and Pearson, 1997).

The limitations of PSA velocity are that it is difficult to calculate, PSA is not cancer specific, and PSA varies significantly with time and different assays. However, a PSA velocity greater than 0.75 ng/ml/year is useful to determine prostate cancer risk if an individual is followed with a minimum of 3 serial PSA measurements

spanning at least a 2-year PSA history. PSA velocity can be used to assess the need for prostate biopsy in men with a total PSA in the normal range or the need for repeated biopsy in those with an increasing PSA at any range (Polascik et al., 1999).

### *PSA doubling time (PSADT)*

PSADT is the time during which the original PSA concentration doubles, under the conditions of non-influenced tumor growth. Compared to PSAV, this parameter is independent of the original PSA value.

Patel et al. (1997) described an exponential growth pattern in the tumor recurrence after radical prostatectomy. In this manner, a correlation between the log of PSA level and time is linear. PSADT is calculated by natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement for each patient (Pound et al., 1999). In the presence of more than two PSA measurements after the PSA recurrence, a slope of the curve obtained by linear regression of logarithmically transformed PSA data can be used (Koch et al., 2000). In the case of two PSA measurements after the PSA recurrence, PSADT can be calculated from the formula,  $T \times (\ln 2) / \ln(\text{PSA}_2 / \text{PSA}_1)$ , where PSA<sub>1</sub> represents PSA date from former measurement, PSA<sub>2</sub> represents PSA date from the later measurements and T represents time between these two subsequent PSA measurements.

The rate of PSA progression after radical prostatectomy has been carefully assessed with respect to its significance for predicting disease progression and death from disease. PSA recurrence is best characterized as PSA doubling time. Trapasso et al. (1994) demonstrated that metastatic disease was associated with doubling time of only 4.3 months versus 11.7 for local recurrence. Similar data were established by Koch et al. (2000). Mean PSA doubling time in the group with metastatic disease and local recurrence was  $4.4 \pm 3.5$  and  $11.2 \pm 21.5$  months, respectively.

PSADT cut-off value of 10 months was assessed by Pound et al. (1999) and is the most statistically significant predictor of time to distant disease progression after PSA elevation. In the study an algorithm for predicting a man's likelihood of developing metastatic disease within various periods following initial biochemical recurrence was constructed. Using a cut-off value of 10 months, PSADT provided further substratification for men with a Gleason score of less than 8. Men with rapid PSA level elevation ( $< 2$  years), a Gleason score of 5 to 7 and a PSADT  $> 10$  months demonstrated a 76% probability of remaining free of metastatic disease for 5 years following initial PSA level elevation compared with men with shorter PSADT ( $< 10$  months), who had only 35% chance of remaining free of metastatic disease for 5 years after biochemical recurrence.

### PSA and age

The standard reference range of PSA is 0–4 ng/ml. However, already in 1993, Oesterling et al. (1993b) pointed out that the upper threshold of PSA should be set according to the age of examined patients. The total PSA increase in general man population was determined to be 3.2% per year, i.e. 0.04 ng/ml/year. For patients aged 40–49, the upper threshold was proposed to be 2.5 ng/ml, for those aged 50–59 it was 3.5 ng/ml, between 60–69 it was 4.5 ng/ml, and for  $\geq 70$  years it was set to 6.5 ng/ml (at 95% specificity). In this study the authors also demonstrated that the PSA level positively correlates with the prostate volume. Anderson et al. (1995) determined, at the 95% significance level, the normal serum level of total PSA for men aged 40–49 up to 1.5 ng/ml, between 50–59 up to 2.5 ng/ml, 60–69 up to 4.5 ng/ml and for 70–79 up to 7.5 ng/ml. If we accept such age criterion, we can avoid unnecessary prostate biopsy in men in their 8<sup>th</sup> age decade.

Morgan et al. (1996) have recently pointed out the fact that the serum PSA concentrations positively correlate with the age of patients. They have suggested to always relate the upper PSA threshold with the age of the examined patient. They have also proposed different thresholds for inhabitants of countries populated by different human races. While setting the upper PSA threshold, Oesterling included the aspect of age and race in the diagnostic algorithm. He thus significantly increased the sensitivity of this test, particularly in the age category of men between 40–50 years. He also pointed out that with each cm<sup>3</sup> of tissue above the prostate volume of 20 cm<sup>3</sup>, the level of serum PSA increases by 4% (Oesterling, 1996).

The use of age-specific PSA reference ranges in clinical practice may increase the sensitivity for prostate cancer detection in men younger than 60 years at the expense of a greater negative biopsy rate. In older men use of these ranges improves the specificity of prostate cancer detection, possibly obviating treatment of some clinically insignificant tumors.

### Free PSA

Benign prostatic hyperplasia or various forms of prostatitis or prostatic trauma as well as urinary retention are often connected with an elevated serum PSA level. The values of PSA display a high number of false positive results, based on which a series of unnecessary biopsies in patients with BPH are performed. The finding that PSA exists in the serum in several different molecular forms and that the concentration and ratio of these forms differ in malign and benign diseases represents another important step in the diagnostics of early, potentially curable PC, and in its differentiation from BPH. In the case of benign disease, the serum PSA is prevalently in the free form. This may be caused by the existence of different enzyme isoforms. The isoelectric point of PSA molecules in patients with BPH lies in the pH range signifi-

cantly lower than in patients with PC, which might be caused by a different PSA glycosylation process in dysplastic and malignant cells and by consequent different binding of PSA to  $\alpha_1$ -antichymotrypsin, or  $\alpha_2$ -macroglobulin (Huber et al., 1995).

The ratio of free/total prostate-specific antigen (f/t PSA) is significantly lower in patients with PC than in patients with BPH. Determination of the threshold of free PSA for clinical practice is complicated by partial dependence of the free PSA on the age of the patient, on the prostate volume and on the total PSA concentration. It should also be pointed out that the threshold values of free PSA and the clinical results differ when different examination methods for detection of free and total PSA from different producers are combined.

The majority of European authors opt for a lower reference value of free PSA, with the usual approach to its calculation respecting the rule of required 90 to 95% specificity (the sensitivity is, however, low). On the other hand, the American authors state that the main interest of the physician or patient in these cases should be to perform prostate biopsy in all potentially malignant cases, which means that their prerequisite is a high, 90 to 95% sensitivity.

Lukeš et al. (1997) state that prostate biopsy in men with the ratio f/t PSA  $\leq 0.18$  and PSA 3.5–20.0 ng/ml would allow detection of 88% PC and avoid 36% unnecessary biopsies. Catalona and Smith (Catalona et al., 1995; Smith et al., 1996b) demonstrated that determination of the free fraction (f-PSA) at PSA values in the range 2.5–10.0 ng/ml would decrease the percentage of prostate biopsies by 38%, while up to 90% of PC cases would still be detected. They considered 20% of free PSA as a decisive threshold.

In the following prospective multicentric study Catalona et al. (1998) have proposed the threshold value for PSA to be 25% for patients with PSA concentrations in the range 4–10 ng/ml having a benign palpable prostate tumor, irrespective of the age of the patient and the prostate volume. The threshold value of 25% free PSA enabled detection of 95% PC cases and avoided 20% unnecessary biopsies. PC with free PSA exceeding 25% was more often found in older men and was generally less dangerous as concerns the tumor volume and grading. Determination of f/t PSA is also important for patients with serum PSA concentrations 2.5–4.0 ng/ml having negative rectal examination. However, the threshold values of f/t PSA are set lower in these cases (0.1 at 30% sensitivity and 94% specificity – 0.15 at 54% sensitivity and 67% specificity) (Catalona et al., 1999).

The age, prostate volume and serum PSA level are important factors, which have to be taken into account when determining the threshold value of the f/t PSA ratio. Oesterling et al. (1995) state that the serum levels of all three molecular forms of PSA (free, bound and total PSA) depend on the age of the patient. They have