Prostate cancer (PCa) is the most commonly diagnosed male malignancy after 60 years old. Today, the problem is to distinguish between low-risk and aggressive cancers, especially in patients with Prostatic Specific Antigen (PSA) less than 10 ng/ml. The use of PSA as a biomarker for diagnosis and prognosis of prostate cancer has the potential to improve the clinical management of the patients. PSA levels, together with clinical examination, prostate ultrasound and histopathological examination are essential for the diagnostic of PCa, risk assessment and therapeutic decisions. The aim of our study is to evaluate the patients with PSA values less than 10 ng/mL and to determine the correct indications for treatment depending on the risk scale of the disease. The inclusion criteria for the patients are described in the paper. For improving the early diagnosis of PCa in patients with PSA below 10 ng/mL we developed an algorithm based on current opportunities.

Keywords: Prostatic Specific Antigen, prostate cancer, radical prostatectomy, active surveillance

Experimental part

We performed a retrospective study during 5 years, between 2012-2016, in the Urology Department of the Academic Emergency Hospital Sibiu. We analyzed the data between 2012-2016, in the Urology Department of the Academic Emergency Hospital Sibiu. We analyzed the data of 260 patients taking into consideration all patients with PSA values less than 10 ng/mL. The inclusion criteria of the patients were as follow: (1) the age: 50 years or older with or without family history of prostate cancer; (2) PSA level between 2 and 10 ng/mL; (3) patients with or without an abnormal digital rectal examination (DRE); (4) patients who submitted a prostate biopsy for diagnostic of PCa; (5) patients with or without an abnormal digital rectal examination; (6) patients with or without an abnormal digital rectal examination; (7) patients who submitted a prostate biopsy for diagnostic of PCa; (8) patients who submitted a prostate biopsy for diagnostic of PCa; (9) patients who submitted a prostate biopsy for diagnostic of PCa; (10) patients who submitted a prostate biopsy for diagnostic of PCa.

The PSA and PSA derivatives (%fPSA, PSA velocity (PSAV), PSA doubling time (PSADT), PSA density (PSAD), age PSA) hold an important role in the monitoring of prostate cancer at various stages of its oversight, establish therapeutic option, predicting prognosis and evaluation of the effectiveness of the treatment (surgery, hormonal). PSA after radical prostatectomy should drop to undetectable levels; persistently elevated PSA values indicate the presence of residual disease. Increasing PSA after radical surgery represents an indicator of relapse of the disease which may precede other clinical signs.

The aim of our study is: 1) evaluate the patients with PSA values lower than 10 ng/mL; 2) using PSA derivatives to determine the correct indications and avoid unnecessary prostate biopsys for diagnostic of PCa; 3) detect PCa in early stages and differentiate between indolent and aggressive cancer; 4) indicate the correct treatment (radical prostatectomy, Rx therapy or active surveillance) depending on the risk scale of the disease; 5) follow-up these patients to identify local or systemic recurrences.

For improving the early diagnosis of PCa in patients with PSA below 10 ng/mL we developed an algorithm based on current opportunities.
Biopsies were performed using an end-fire ultrasound transducer and an automatic 18-gauge needle. We performed a 12-core systematic, laterally directed, TRUS-guided biopsy in all the patients.

Prostate cancer diagnosis was established after consulting the histopathological examination.

Patients were assigned in groups of diagnosis and treatment. A separate group consisted of active surveillance (AS) patients undergoing during the last year which were monitored by clinical and PSA control in three months to capture the evolution to increase PSA's. Prostate biopsy was repeated at three months for the patients under observation.

Results and discussions

Out of 260 patients aged between 50-75 years, 5 patients (1.9%) and 51 patients (19.6%) were without urinary symptoms. All of them has serum PSA values less than 10 ng/mL as follows: 2-4 ng/mL - 32 patients (12.3%), age < 60 years and 228 patients (87.7%) with PSA 4-10 ng/mL.

DRE was modified at 12 patients (4.6%). We performed in all the patients TRUS and we found prostate volume between 35-70 mL.

In order to establish the indication for prostate biopsy we divided the patients in 8 groups (fig. 1).

Group A (5 p) with PSA 2-4 ng/mL and reflex PSA < 22. (risk for Pca).

Group B (27 p) with PSA 2-4 ng/mL and reflex PSA > 22.

Group C (110 p) with PSA 4-10 ng/mL and reflex PSA < 25.

Group D (118 p) with PSA 4-10 ng/mL and reflex PSA > 25.

Group B (27 p) was excluded from prostate biopsy because it is known from literature that the risk of cancer in these patients is low. From groups A,C,D (233 p), 61 p (group E) received AB and AINS and the rest of them were included in group F (184 p) which received prostate biopsy. From group E patients were clinical monitored 3 months, repeated PSA and 12 were also been included in group F. Candidates for prostate biopsy were group F (184 p). The histopathological result was Pca in 103 p (group G) and 81 patients with negative biopsy (group H) (fig. 1).

In group G, 2 p, were from group A and the others from group C, D. There was no patient from group B.

All the positive cases were low risk cancers in D'Amico classification (PSA<10, Gleeson score 6, T2b).

The treatment for the group G (103 p) was as follows: 73 patients had radical prostatectomy, 20 patients had external beam radiation and 10 active surveillance.

Favorable evolution for patients with radical prostatectomy: 12 p with partial urinary incontinence, 25 p with erectile disfunction, no biochemical PSA relaps during one year follow up.

Active surveillance, 10 patients has PSA evaluation every 3 months which reveal slight increase in patients group C, D. In the same group prostate biopsy repeated at one year to all patients shows cancer progression at 4 patients which where put on active treatment.

For group H they were rebiopsiated at 3-6 months and 7 patients were cancer positive and surgical treated.

PSA is an essential component of seminal liquid, having a molecular weight of 33kDa. It is synthesized in the acinar cells and the ductal epithelium of the prostate, after that it is secreted in the ductal system where it achieves high concentrations. It was observed that PSA has a role in sperm, being involved male fertility. The PSA is present in low concentrations in the serum. In cases where the alteration occur at microscopic prostate (benign prostatic hypertrophy, acute prostatitis, prostate biopsy) PSA will spread in stroma, where it will end up in the general circulation, lymphatic and capillary system [16, 17].

In serum PSA forms stable complexes with α1-antichimotripsin (ACT) and α2-macroglobulin. 86% of circulating PSA is the PSA-ACT complex; a small portion of PSA is related to α2-macroglobulin and the rest constitutes unbound PSA (free-PSA).

However, due to the instability of fPSA compared to complexed PSA, the percentage of fPSA exhibits a wide analytical variability and is, therefore, not used as primary screening parameter [18, 19].

International recommendations concerning early detection of prostate cancer include annual PSA testing combined with prostate exam (DRE) in men aged over 50 years, with moderate risk. Screening at a younger age (40-45 years) is indicated only in those cases with family history of prostate cancer (first-degree relatives). Although the PSA represents a good laboratory test for detecting prostate cancer, the result obtained must always be interpreted in conjunction with the clinical data provided by rectal examination [20, 21].

The diagnosis of prostate cancer (Pca) has mostly relied on prostate-specific antigen (PSA) levels and digital rectal examinations (DRE) [1]. Nevertheless, the main drawback of PSA is its lack of specificity, resulting in a high negative biopsy rate. In patients with PSA levels between 4 and 10 ng/mL, the negative biopsy rate is as high as 60-70% [22], causing a huge burden for patients and society. Thus, the critical question for improving the diagnosis of Pca should...
focus on the diagnosis of PCa in patients with PSA levels between 4 and 10 ng/mL. Prostate cancer cases with elevated PSA levels typically undergo biopsy for assessment of prostate cancer. However, more recent studies have shown that ~20% of men with PSA levels <4 ng/mL have prostate cancer and that many men with higher levels do not have prostate cancer [23-25].

Prostate biopsy (PBx) is the standard method for diagnosing prostate cancer (PCa) but the diagnostic yield of this procedure remains low. In current clinical practice the cancer detection rate of a first extended PBx is less than 30% and less than 10% for a second extended PBx. 

Recently, prostate MRI and biopsy Gleason score are contained in a classification (D'Amico classification) that stratifies patients with PCa into low-, intermediate-, and high-risk groups. Optimal treatment is indicated according to these risk classes. Radical surgery, brachytherapy, external beam radiotherapy, hormone suppression, and combinations of these modalities are all feasible treatment options [26].

Conclusions

PSA values between 4-10 ng/mL raise suspicion of PCa. In these cases clinical examination including digital rectal examination, prostate ultrasound and histopathological examination (prostate biopsy) are essential for the diagnostic of PCa, risk assessment and therapeutic decisions.

PSA can detect PCa in early stages but can not differentiate between indolent and aggressive cancer.

The main drawback of PSA is its lack of specificity, resulting in a high negative biopsy rate. Using PSA as the sole biomarker can determine the correct indications and avoid unnecessary prostate biopsies for diagnostic of PCa.

PCa with PSA under 4 ng/mL is rare; there are low risk cancers and the patient can be treated on active surveillance.

% f PSA can increase the sensibility and specificity for PCa. Free-PSA alone does not provide clinical information relevant for the diagnostic of PCa and for the monitoring of the disease, so it is recommended to use the test to this end.

Active surveillance was defined a priori as monitoring by means of PSA, digital rectal examination and repeat biopsies, with the potential for curative-intent treatment in the event of disease progression.

PSA is an important biomarker to follow-up patients with PCa and to identify local or systemic recurrences.

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