Prostatic Specific Antigen Less then 10 ng/mL in the Diagnostic and Surveillance of Prostate Cancer

NICOLAE GRIGORE, VALENTIN PIRVUT, IONELA MIHAI, ADRIAN HASEGAN*, SEBASTIAN IOAN CERNUSCA MITARIU
Lucian Blaga University of Sibiu, Faculty of Medicine, 2A Lucian Blaga Str., 550169, Sibiu, Romania

Prostate cancer (PCa) is the most commonly diagnosed male malignancy after 60 years old. Today, the problem is to distinguish between low-risk and agrressive cancers, especially in patients with Prostatic Specific Antigen (PSA) less than 10 ng/ml The use of PSA as a biomarkers 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 histopatological examination are esential for the diagnostic of PCa, risk assessment and therapeutic decisions. The aim of our study is to evaluate the patients with PSA values less then 10 ng/mL and to determine the correct indications for tratment 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 algoritm based on current opportunities.

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

Prostate cancer (PCa) is the most commonly diagnosed male malignancy after 60 years old. It has a heterogeneous clinical evolution ranging from indolent and organ-confined to aggressive metastatic lethal disease. The results of screening programmes were the overdiagnosis of low-risk cancers, which lead to unnecessary treatment and decreased the quality of life in many cases. Treatments varied from medical to natural remedies. During the past decades a spectacular number of remedies from nature turned in classical therapy, well accepted by an increasing number of patients. Recent studies show that soy total extract induce apoptosis in prostate cancer cells and it is used by those who suport the natural remedies in prostate cancer treatment.Among the flavonoids, 5-hydroxyflavone is a bioderivative with anti-inflammatory antiatherogenic, vasorelaxing effects, and is a well-known androgen receptor antagonist used to treat prostate cancer [1,2].

The last decades we faced the overtreatment of men with relatively indolent PCa and the undertreatment of those with aggressive tumors [3].

The use of biomarkers for prostate cancer screening, diagnosis and prognosis has the potential to improve the clinical management of the patients. PSA Clinical examination (digital rectal examination), prostate ultrasound and histopatological examination (prostate biopsy) are essential for the diagnostic of PCa, risk assessment and therapeutic decisions [4, 5].

PSA is the most important marker in the evaluation of prostate cancer and is useful in detecting and monitoring the disease. PSA is almost exclusively associated with diseases of the prostate but is not specific for PCa, elevated levels being encountered in other conditions (prostatitis, acute or chronic, prostate adenoma) [6, 7].

PSA exists in blood either in its free form (fPSA) or in a complex with serum protease inhibitors. fPSA accounts for 5–35% of total PSA (tPSA) and can occur in three molecular forms: pro-PSA, benign PSA and intact PSA [8]. The ratio of fPSA to tPSA (free PSA ratio or % fPSA) has been found to be lower in PCa and has been shown to improve the specificity of cancer detection in men with tPSA values of 4–10 ng/mL and a normal DRE [9,10].

The PSA and PSA derivates (%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 [11-15].

The aim of our study is: 1) evaluate the patients with PSA values lower then 10 ng/mL; 2) using PSA derivates to determine the correct indications and avoid unnecessary prostate biopsys for diagnostic of PCa; 3). detect PCa in early stages and diferentiate beetween indolent and agresive cancer; 4) indicate the correct treatment (radical prostatectomy, Rx therapy or active survaillance) depending on the risk scale of the disease; 5) follow-up this 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 algoritm based on current oportunities.

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 of 260 patients taking into consideration all patients with the 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 transrectal ultrasound (TRUS) and guided systematic prostate biopsy. The indications for biopsy were: elevated PSA and/or suspicious findings on DRE. These patients had no urinary tract infections or catheterization of the urethra within the previous 2 weeks. The patients with elevated PSA levels and alpha 5 reductase inhibitors treatment were monitored after interupting the medication.

* email:office@urologiesibiu.ro; Phone: 0745381064

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. Al 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 escluded from prostare 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 recieved prostate biopsy. From grup E patients were clinical monitorised 3 mounts, repet PSA and 12 were also been included in group F. Candidates for prostate biopsy where grup F (184 p). The histopatological 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, Glesson score 6, T2b)

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

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

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

For group H patients 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 á1-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

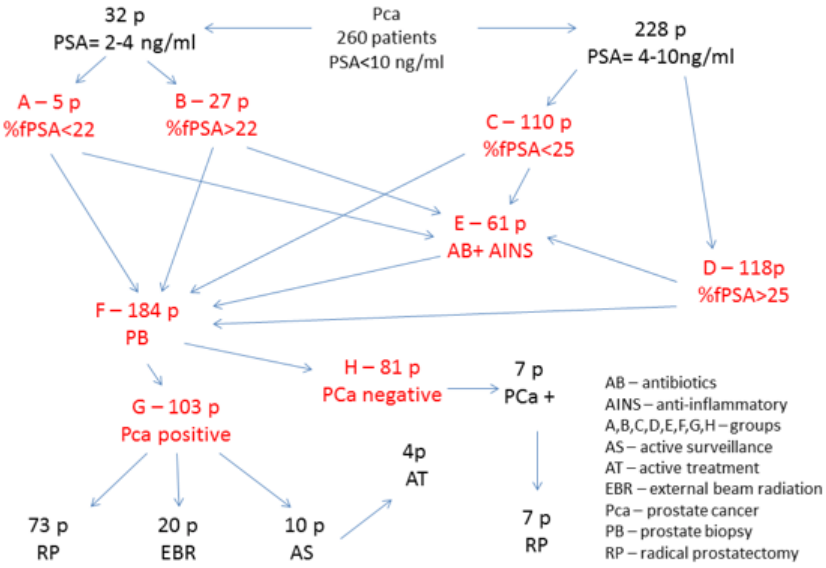

Fig. 1.

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 prompted by an elevated serum prostate-specific antigen (PSA) level and/or an abnormal digital rectal examination (DRE) is in the range of 40%.

Currently, preoperative PSA levels beside clinical stage and and biopsy Gleason score are contained in a classification (D'Amico classification) that stratify 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].

Recently, several investigators have reported the appropriateness of active surveillance (AS) in select men with PCa, demonstrating favorable outcomes [27, 28]. Active surveillance is different from watchful waiting, which is usually reserved for elderly men with reduced life expectancy. In watchful waiting, the physician will not perform serial tests such as biopsies because there is no curative intent, so treatment is only given for symptomatic progression. In contrast, active surveillance infers that the patient is followed with a schedule of serial PSA tests and biopsies, with the latter meant to detect patients who convert from a low-grade to an intermediate- or high-grade tumor over time. PSA has also an inportant rol in monitoring patients in active surveillance [29, 30].

Conclusions

PSA values between 4-10 ng/mL raise suspicion of PCa. In these cases clinical examination including digital rectal examination, prostate ultrasound and histopatological 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 diferentiate beetween indolent and agresive cancer.

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

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

% f PSA can increse 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 not 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 inporatat biomarker to follow-up this patients with PCa and to identify local or systemic recurrences.

Acknowledgements: This study, being a retrospective one, did not require a written consent from the patients involved. The authors declare no conflict of interests and no sponsorship was provided by the manufacturer of the mesh involved in this study. All authors have read and approved this publication and had equal scientific contribution in publishing this material.

References

1.DANCIU, C., BIRIS, M., BALAZS, B., CSANYI E., PAVEL ,I.Z., POP, G., SOICA, C., CEUTA, L., NITA, L., MORGOVAN, C., STOIAN,D., Pro-apoptotic Effect of Soy Total Extract Incorporated in Lyotropic Liquid Crystals Formulation, REV. CHIM. (Bucharest), **66**, no. 7, 2015, p. 1038
2.UIVAROSI, V., PAHONTU, E.M., MUNTEANU, Al., Synthesis, Characterization and Fluorescent Properties of New Complexes of 5-hydroxyflavone with Some Divalent Metal Ions. Rev. Chim. (Bucharest), **65**, no.1 2014, p. 33
3.ILIC D, NEUBERGER MM, DJULBEGOVIC M. Screening for prostate cancer. Cochrane Database Syst Rev 2013;1:CD004720. [PubMed]
4.BELL N, CONNOR-GORBER S, SHANE A, ET AL. Recommendations on screening for prostate cancer with the prostate-specific antigen test. CMAJ 2014;186:1225–34. [PMC free article] [PubMed]
5.HERNANDEZ J, THOMPSON IM. Prostate-specific antigen: a review of the validation of the most commonly used cancer biomarker. Cancer. 2004;101:894–904. [PubMed]
6.MIKOLAJCZYK SD, MARKER KM, MILLAR LS, KUMAR A, SAEDI MS, PAYNE JK, ET AL. A truncated precursor form of prostate-specific antigen is a more specific serum marker of prostate cancer. Cancer Res. 2001;61:6958–6963. [PubMed]
7.CATALONA WJ, PARTIN AW, SLAWIN KM, BRAWER MK, FLANIGAN RC, PATEL A, ET AL. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA. 1998;279:1542–1547.
8.SHARANJOT SAINI, PH.D. PSA and beyond: alternative prostate cancer biomarkers, Cell Oncol (Dordr). 2016 Apr; 39(2): 97–106.
9.D'AMICO AV, CHEN MH, ROEHL KA, CATALONA WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med. 2004;351:125–135.[PubMed]
10.RODRIGUES DN, BUTLER LM, ESTELLES DL, DE BONO JS. Molecular pathology and prostate cancer therapeutics: from biology to bedside. J Pathol. 2013;232:178–184. [PubMed]
11.GUAZZONI G, NAVA L, LAZZERI M, SCATTONI V, LUGHEZZANI G, MACCAGNANO C, ET AL. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting. Eur Urol. 2011;60:214–222. [PubMed]
12.HEIDEGGER I, KLOCKER H, STEINER E, SKRADSKI V, LADURNER M, PICHLER R, ET AL. [-2]proPSA is an early marker for prostate cancer aggressiveness. Prostate Cancer Prostatic Dis. 2014;17:70–74. [PubMed]
13.BUSCH J, HAMBORG K, MEYER HA, BUCKENDAHL J, MAGHELI A, ET AL. Value of prostate specific antigen density and percent free prostate specific antigen for prostate cancer prognosis. J Urol. 2012;188:2165–70. [PubMed]
14.HORI S, BLANCHET JS, MCLOUGHLIN J. From prostate-specific antigen (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer. BJU Int. 2013;112:717–728. [PubMed]
15.LAZZERI M, HAESE A, ABRATE A, DE LA TAILLE A, REDORTA JP, MCNICHOLAS T, ET AL. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. BJU Int. 2013;112:313–321. [PubMed]
16.LOEB S, CURNYN C, SEDLANDER E. Perspective of prostate cancer patients on Gleason scores and the new grade groups: initial qualitative study. Eur Urol. 2016 Jun 6.
17.SIEGEL RL, MILLER KD, JEMAL A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.[PubMed]
18.HO WON KANG, HAE DO JUNG, JOO YONG LEE, JONG KYOU KWON, SEONG UK JEH, KANG SU CHO, WON SIK HAM, YOUNG

DEUK CHOI.Prostate-specific antigen density predicts favorable pathology and biochemical recurrence in patients with intermediate-risk prostate cancer .Asian J Androl. 2016 May-Jun; 18(3): 480–484.Published online 2015 Jul 7. doi: 10.4103/1008-682X.154313
19.LUIGI CORMIO, MD, PHD, GIUSEPPE LUCARELLI, MD, PHD, OSCAR SELVAGGIO, MD, GIUSEPPE DI FINO, MD, VITO MANCINI, MD, PAOLO MASSENIO, MD, FRANCESCO TROIANO, MD, FRANCESCA SANGUEDOLCE, MD, PANTALEO BUFO, MD, AND GIUSEPPE CARRIERI, MD MONITORING EDITOR: GIANDOMENICO ROVIELLO. Absence of Bladder Outlet Obstruction Is an Independent Risk Factor for Prostate Cancer in Men Undergoing Prostate Biopsy,Medicine (Baltimore). 2016 Feb; 95(7): e2551
20.LOBERG RD, LOGOTHETIS CJ, KELLER ET, PIENTA KJ. Pathogenesis and treatment of prostate cancer bone metastases: targeting the lethal phenotype. J Clin Oncol. 2005;23:8232–8241.[PubMed]
21.WILT TJ, BRAWER MK, JONES KM, BARRY MJ, ARONSON WJ, ET AL. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367:203–13. [PMC free article][PubMed]
22.D'AMICO AV, WHITTINGTON R, MALKOWICZ SB, SCHULTZ D, BLANK K, ET AL. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280:969–74. [PubMed]
23.LAURENCE KLOTZ, Active surveillance and focal therapy for low-intermediate risk prostate cancerransl Androl Urol. 2015 Jun; 4(3): 342–354.doi: 10.3978/j.issn.2223-4683.2015.06.03
24.CRISTEA O, LAVALLEE LT, MONTROY J, STOKL A, CNOSSEN S, MALLICK R, FERGUSSON D, MOMOLI F, CAGIANNOS I, MORASH C, MD, BREAU RH, Active surveillance in Canadian men with low-grade prostate cancer CMAJ. 2016 May 17; 188(8): E141–E147. Published online 2016 Feb 29. doi: 10.1503/cmaj.150832
25.PETER L. CHOYKE, MD AND STACY LOEB, MD, MSC, Active Surveillance of Prostate Cancer, Oncology Journal, Prostate Cancer January 15, 31(1):67–70, 2017 |
26.TOSOIAN JJ, CARTER HB, LEPOR A, LOEB S. Active surveillance for prostate cancer: current evidence and contemporary state of practice. Nat Rev Urol. 2016;13:205
27.KLOTZ L, EMBERTON M. Management of low risk prostate cancer: active surveillance and focal therapy. Curr Opin Urol 2014;24:270–9. [PubMed]
28.THOMSEN FB, RODER MA, HVARNESS H, ET AL. Active surveillance can reduce overtreatment in patients with low-risk prostate cancer. Dan Med J 2013;60:A4575. [PubMed]
29.KLOTZ L. Active surveillance: the Canadian experience. Curr Opin Urol 2012;22:222–30.[PubMed]
30.DE COBELLI O, TERRACCIANO D, TAGLIABUE E, ET AL. Predicting pathological features at radical prostatectomy in patients with prostate cancer eligible for active surveillance by multiparametric magnetic resonance imaging. PLoS One 2015; 10:e0139696. [PMC free article] [PubMed]

Manuscript received: 23.12.2016