High grade intraepithelial neoplasia of prostate is associated with values of prostate specific antigen related parameters intermediate between prostate cancer and normal levels

Nermina Obralic[1]*, Benjamin Kulovac[2]

[1] Oncology Clinic, Clinical Center University of Sarajevo, Bolnicka 25, 71 000 Sarajevo, Bosnia and Herzegovina. [2] Urology Clinic, Clinical Center University of Sarajevo, Bolnicka 25, 71 000 Sarajevo, Bosnia and Herzegovina

Abstract

High grade prostatic intraepithelial neoplasia (HGPIN) is widely regarded as the precancerous. The aim of this study was to determine PSA related parameters in patients with initial PSA values 2-10 ng/mL and diagnosis of HGPIN without finding carcinoma at the time of their first needle biopsy. Study groups consisted of 100 men who were diagnosed HGPIN, 84 with cancer and 183 with benign hyperplasia on first biopsy of prostate. Total PSA and free PSA were measured and ratio free/total PSA and PSA density calculated. Mean values of these parameters were compared, and receiver operating characteristic curves were used for comparison of PSA related parameters to discriminate groups of patients. Total PSA, free PSA level and PSA density in patients with HGPIN (6.388 ng/mL) did not differ significantly compared to prostate carcinoma (6.976 ng/mL) or benign prostatic hyperplasia (6.07 ng/mL) patients. Patients with HGPIN had significantly higher ratio free/total PSA than those with prostate carcinoma (0.168 vs 0.133), but significantly lower than patients with benign prostatic hyperplasia (0.168 vs 0.185). Ratio of free/total PSA significantly discriminate HGPIN from prostate carcinoma with sensitivity 84.52 and specify 45.00 at cut-off point of ≤ 0.18. Values of PSA, free PSA and ratio free/total PSA in cases of HGPIN appear to be intermediate between prostate cancer and normal levels. Ratio of free/total PSA may help in decision to repeat biopsies in the presence of HGPIN on biopsy, without concomitant prostate cancer, in patients suitable for curative treatment, with normal digito-rectal examination and trans-rectal sonography.

KEY WORDS: prostate intraepithelial neoplasia, prostate specific antigen

INTRODUCTION

High-grade prostatic intraepithelial neoplasia (HGPIN) is proliferation of highly atypical cells within the pre-existing prostatic acini and ducts [1]. HGPIN shows no specificity on digital rectal examination (DRE) and transrectal ultrasonography (TRUS) [2, 3].

The natural biological behavior of HGPIN is yet poorly understood, but it is considered as a precursor of prostate cancer and is frequently associated with it. HGPIN is found in 85% of radical prostatectomies performed for prostate carcinoma. HGPIN in prostate biopsy is a risk factor for detection of prostate carcinoma in subsequent biopsies with the incidence ranges from 21% to 73% [4, 5, 6, 7]. Atypical small acinar proliferation (ASAP) adjacent to HGPIN seems to confer an even higher risk for subsequent cancer detection of 53% [8, 9, 10]. HGPIN seems to be more often associated with the characteristics of the poor prognosis for relapse of prostate cancer [11]. HGPIN and prostate carcinoma share many similarities in epidemiology, genetics, morphology, as well as in location and clinical features [12]. HGPIN often shows moderately increased serum level of PSA. Levels of PSA in prostatic intraepithelial neoplasia have been correlated with its grades [4]. Coexistence of HGPIN with prostate carcinoma has been considered the most likely cause of PSA elevation. A low percentage of free PSA (fPSA) has also been observed in HGPIN. The question is whether an elevation of serum PSA and decrease of fPSA in HGPIN can be explained by concomitant prostate cancer or by a premalignant lesion itself [13]. It is widely thought that simple HGPIN detected by extended needle biopsy has no therapeutic implications, but should be followed up at regular intervals [14]. HGPIN has a substantial risk for prostate cancer in subsequent biopsies and should necessitate further investigation in patients who are candidates for radical treatment of localized prostate cancer [2, 15, 16]. The aim of this study was to determine level of total prostate

* Corresponding author: Nermina Obralic,
Oncology Clinic, Clinical Center University of Sarajevo,
Bolnicka 25, 71 000 Sarajevo, Bosnia and Herzegovina
Tel: +387 33 666 479; Fax: +387 33 666 479
E-mail: nerminaobralic@gmx.net

Submitted: 12. March 2011 / Accepted: 12. October 2011

specific antigen (tPSA), free prostate specific antigen (fPSA), ratio free to total PSA (R fPSA/tPSA) and prostate specific antigen density (PSAD) in patients with initial PSA values 2-10 ng/mL and negative or indeterminate digital rectal examination (DRE) findings, who had diagnosis of HGPIN without concurrent carcinoma at the time of their first needle biopsy. We also wanted to compare obtained values with results in patients with the same characteristics but diagnosis of prostate carcinoma (PCa) and benign prostate hyperplasia (BPH). The aim also was to explore if PSA related parameters can be useful for optimal biopsy strategy in this setting.

MATERIALS AND METHODS

Patients

Our study included 367 patients with HGPIN, PCa and BPH at the time of their first needle biopsy performed at Urology Clinic of Clinical Centre University of Sarajevo during the years 2007 and 2008. Indications for biopsy were elevated PSA and/or suspicious DRE. All patients gave informed consent for biopsy. Exclusion criteria were initial PSA above 10 ng/mL, determinate DRE and/or TRUS finding of PCa. According to their diagnosis after first needle biopsy patients were divided into 3 groups for analysis: patients with PCa (Group 1), patients with HGPIN without concomitant prostate cancer (Group 2) and patients with BPH (Group 3).

Procedures

All patients underwent echography–guided biopsy. Number of samples depended on prostate volume and age of patients according to Vienna nomogram [17]. Three days after biopsy serum fPSA and tPSA levels were measured, and their ratio (R fPSA/tPSA) and PSAD were calculated. Total PSA (free and PSA complexed to alpha-1-antichymotrypsin) and free PSA measuring were performed by Chemiluminescent Microparticle Immunoassay (CMIA) in human serum with ARCHITECT Total PSA assay and ARCHITECT Free PSA assay (ABBOTT Diagnostic Division, Sligo, Ireland) by manufacturer's instructions.

Statistical analysis

Mean values of prostate volume, tPSA, fPSA, R fPSA/tPSA and PSAD were calculated for each group and values were compared. Continuous variables were transformed into logarithmic scale. Equality of Variances was tested by LOG ANOVA Test on log-transformed data. Student-Newman-Keuls test was used for pair wise comparisons and Kruskal Wallis tests for intercomparison of three groups. Receiver operating characteristics (ROC) curve analysis was used to compare the tests evaluated in the study. Statistical analyses were performed using software MedCalc for Windows, version 9.5.1.0 (MedCalc Software, Mairiakerke, Belgium).

TABLE 1. Mean age, prostate volume and total PSA (PSA), free PSA (fPSA), ratio free to total PSA (R fPSA/PSA) and PSA density (PSAD) in patients with PCa, HGPIN and BPH.

	N	Mean	95% CI	Variance	SD	SEM	Median	Minimum	Maximum	10 - 90 P	Normal Distr.
Age											
PCa	85	65.12	64.09 - 66.16	23.01	4.79	0.52	66.00	52.00	70.0	59.0 - 70.0	0.0172
HGPIN	100	65.16	64.08 - 66.23	29.42	5.42	0.54	67.00	52.00	70.0	56.0 - 70.0	0.00108
BPH	183	64.36	63.61 - 65.12	26.81	5.17	0.38	66.00	50.00	70.0	56.0 - 70.0	0.000407
Prostate volume											
PCa	85	44.41	41.50 - 47.32	182.00	13.49	1.463	40.00	25.00	100.0	30.0 - 60.0	0.000000048
HGPIN	100	48.37	44.95 - 51.79	291.20	17.06	1.723	45.00	25.00	110.0	30.0 - 75.0	0.00000469
BPH	183	48.69	46.01 - 51.38	338.22	18.39	1.359	45.00	25.00	120.0	30.0 - 76.4	0.000
PSA											
PCa	85	6.97	6.54 - 7.41	4.06	2.017	0.218	7.07	2.33	10.0	4.30 - 9.50	0.138
HGPIN	100	6.38	5.92 - 6.85	5.48	2.342	0.234	6.50	0.57	10.0	3.09 - 9.65	0.219
BPH	183	6.07	5.71 - 6.42	5.88	2.426	0.179	6.26	1.45	10.0	2.61 - 9.23	0.0518
fPSA											
PCa	85	0.91	0.81 - 1.01	0.21	0.458	0.050	0.86	0.03	2.67	0.419 - 1.403	0.000085
HGPIN	100	1.12	0.99 - 1.25	0.43	0.661	0.066	1.12	0.04	3.05	0.220 - 1.970	0.323
BPH	183	1.13	1.02 - 1.24	0.59	0.770	0.056	0.98	0.10	4.80	0.320 - 2.034	0.000
PSAD											
PCa	85	0.16	0.14 - 0.17	0.005	0.076	0.008	0.14	0.02	0.600	0.089 - 0.240	0.000
HGPIN	98	0.15	0.13 - 0.17	0.010	0.100	0.010	0.13	0.01	0.800	0.070 - 0.277	0.000
BPH	183	0.15	0.13 - 0.18	0.031	0.176	0.013	0.14	0.02	2.000	0.050 - 0.250	0.000
R fPSA/tPSA											
PCa	85	0.13	0.12 - 0.14	0.0027	0.0525	0.005	0.13	0.007	0.300	0.070 - 0.190	0.299
HGPIN	100	0.16	0.15 - 0.18	0.0059	0.0768	0.007	0.17	0.008	0.380	0.060 - 0.270	0.889
BPH	183	0.18	0.17 - 0.19	0.0099	0.0995	0.007	0.16	0.040	0.900	0.100 - 0.272	0.000

TABLE 2. Geometric mean of PSA, free PSA (fPSA), ratio free to total PSA (RfPSA/PSA) and PSA density (PSAD) among patients with prostate carcinoma (PCa), high grade prostatic intraepithelial neoplasia (HGPIN) and benign prostatic hyperplasia (BPH)

	PCa	HGPIN	BPH	Significance level	Different (p<0.05) from factor nr
PSA	6.62	5.83	5.50	*p*=0.007	G1 from G3
Free PSA	0.75	0.84	0.89	*p*=0.256	
R fPSA/PSA	0.11	0.14	0.16	*p*<0.001	G1 from G2 and G3 G2 from G1 and G3 G3 from G1 and G2
PSAD	0.14	0.13	0.12	*p*=0.082	
Age	64.94	64.92	64.15	*p*=0.372	
Prostate volume	42.70	45.82	45.85	*p*=0.201	
Age	64.94	64.92	64.15	*p*=0.372	
Prostate volume	42.70	45.82	45.85	*p*=0.201	

(Student-Newman-Keuls test for all pair wise comparisons)

TABLE 3. . Performance of PSA, free PSA, ratio free PSA/PSA and PSA density to discriminate HGPIN from prostate carcinoma by Receiver operating characteristics curve analysis

Test	Compared groups	Area Under the Curve	Standard error	95% confidence interval	Significance level	Cut-off with highest accuracy		
							sensitivity	specificity
PSA	PCa/HGPIN	0.572	0.0423	0.497 to 0.644	*p* =0.0892	**>6.8**	56.47	59.00
Free PSA	PCa/HGPIN	0.603	0.0415	0.528 to 0.674	*p* =0.0130	**≤1.24***	80.95	44.00
Ratio Free/total PSA	PCa/HGPIN	0.658	0.039	0.585 to 0.726	*p* =0.0001	**≤0.18**	84.52	45.00
PSA density	PCa/HGPIN	0.558	0.0428	0.483 to 0.632	*p* =0.1718	**>0.11***	76.19	42.86

RESULTS

Study included 367 men, ages 50 to 70 years and initial PSA values 2-10 ng/mL. Among them, PCa was diagnosed in 84, HGPIN without concurrent PCa in 100, and BPH in 183 patients. Mean age, prostate volume and PSA related parameters are presented in Table 1. We compared mean values of presented parameters in patients with HGPIN, PCA and BPH by two statistical methods. There was no significant difference in patient age and prostate volume (p = 0.372 and p = 0.201 respectively). Comparisons of PSA, fPSA, R fPSA/PSA and PSAD are presented on Table 2, and Figure 1. Receiver operating characteristic curves were used for comparison of PSA related parameters to discriminate patients with PCa, HGPIN and BPH. The greatest area under the curve was observed for R fPSA/PSA both between PCa and HGPIN and PCa and BPH (0.658 and 0.682 respectively). According this analysis PSA significantly discriminate PCa from BPH, fPSA PCa from HGPIN and PSAD PCa from BPH (Table 3).

DISCUSSION

HGPIN is considered to be a premalignant lesion, with a close association of prostate cancer in biopsy and prostatectomy specimens. A biopsy finding of HGPIN necessitates further investigation in patients who are candidates for radical treatment for localized prostate cancer. Serum PSA, DRE and TRUS are predictors of later cancer found on repeated biopsy [15, 16]. A palpable nodule or tumour-suspicious TRUS finding, in conjunction with a finding of HGPIN on prostate biopsy, should prompt repeated biopsy [5]. The incidence of later cancer is extremely high when PSA > 10 ng/mL, and this is indication for repeated biopsies even in the absence of HGPIN [5]. A substantial overlap was found between patients with and without cancer in intermediate PSA level from 4 to 10 ng/mL [17]. There is no consensus on clinical management of patients with HGPIN, indeterminate DRE finding and PSA level between 4 and10 ng/mL. Our study group consisted of 100 men who were diagnosed HGPIN without concomitant prostate cancer on first biopsy. These patients were age between 50 and 70 years, mean 65.1 years. They were without definitive signs of prostate carcinoma on DRE and TRUS. All had PSA level in grey zone. Such patients, if they had prostate carcinoma, would be candidates for radical treatment [18]. Serum free and total PSA levels were measured. Ratio of free and total PSA, and PSAD were calculated. These parameters were compared to that in 85 men with prostate cancer (mean age 65.1 years), and 183 with biopsy proved BPH (mean age 64.3 years). Mean level of PSA in patients with HGPIN was 6.388 ng/mL. Patients with prostate carcinoma had higher, and with BPH lower level of PSA (6.976 ng/mL and 6.02 ng/mL respectively). And other authors have found PSA level in cases of HGPIN intermediate between prostate cancer and normal levels [19]. This elevation may be explained by concomitant prostate cancer, less probably by HGPIN itself [3, 5]. Level of free PSA in patients with HGPIN (1.126 ng/mL)

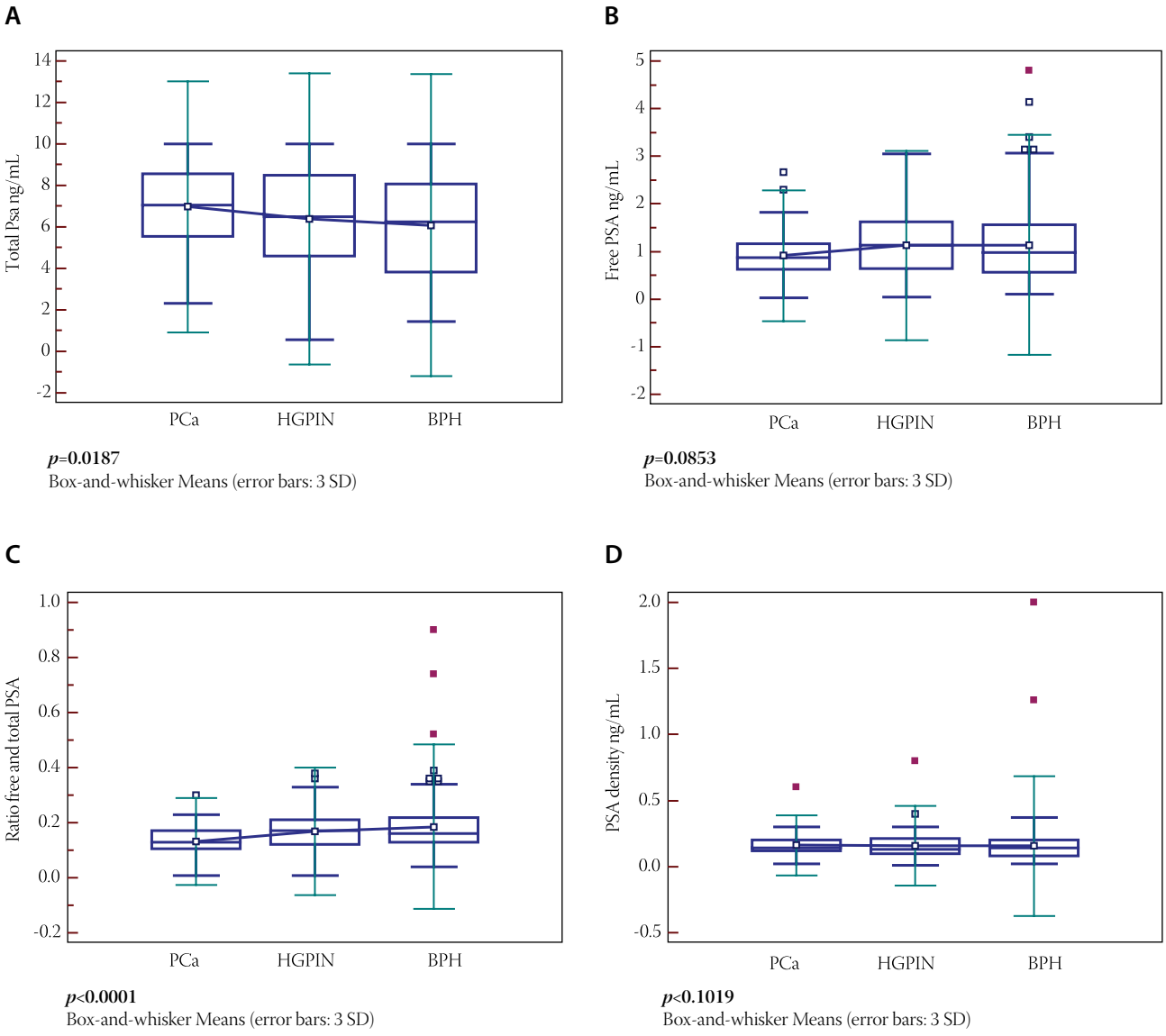

FIGURE 1. Comparisons of total PSA (A), free PSA (B), ratio free and total PSA (C), and PSA density (D) among patients with prostate carcinoma, high grade PIN and benign prostatic hyperplasia (Kruskal Wallis test)

was also intermediate between PCa (0.912 ng/mL) and BPH (1.137). Differences are not statistically significant. The concentration of non-complexed (free) PSA contributes little disease specific information in comparison with total PSA. R fPSA/tPSA on the other hand significantly enhances the efficiency of test, in particular in the "diagnostic grey zone" of PSA. For reasons yet poorly understood, higher ratio occurs in patients without carcinoma than in these with prostate cancer [16]. In our study, patients with HGPIN had significantly higher R fPSA/tPSA than these with PCa (0.168 vs 0.133), but significantly lower than patients with BPH (0.185). These parameters and results of comparisons have been numerically similar to the respective value in other studies [9, 10, 20, 21]. The volumes of prostate in patients with BPH and HGPIN were similar (48.699 mL and 48.378 mL respectively). Patients with PCa had mean value of prostate volume of 44.412 mL. The differences from previous groups were not statistically significant. PSAD were similar in patients with HGPIN, PCa and BPH (0.1564, 0.1616 and 0.1564 respectively). In other studies, PSAD also differed in none of the subgroups, and did not provide additional information [3]. According to our results, and results from other studies, HGPIN has levels of PSA related parameters intermediate between PCa and BPH. More probably that may be explained by concomitant prostate cancer, as they are two closely related entities [15]. But intermediate level of PSA and R fPSA/tPSA might be result of higher production of PSA in HGPIN like carcinoma, as they share many similarities. HIPN occurs most frequently in the peripheral zone of the prostate and is usually located in close proximity to prostate cancer. Deoxyribonucleic acid ploidy in HGPIN follows the

aneuploid proportion as in the concomitant prostate cancer. Prostate cancer and PIN show evidence of loss of putative tumour suppressor genes on chromosome 8p [5, 22]. Indication for repeated biopsy in patients with HGPIN may depend on PSA level, but on the value of R fPSa/tPSA as well [23]. There are different cut-of points for these parameters. According to our study value of PSA cannot discriminate PCa from HGPIN. Level of fPSA ≤ 1.24 has sensitivity 80.95 and specificity 44.00 in discriminating PCa from HGPIN (AUC 0.603, p=0.013). Better performance characteristic has R fPSA/tPSA. Cut-off level between PCa and HGPIN of ≤0.18 has sensitivity 84.52 and specifity 45.00 (AUC 0.658 ; p=0.0001). According to the literature proposed cut-off points for R fPSA/PSA between PCa and non-malignant findings are between 0.18-0.20 [9, 20]. Ratio fPSA/tPSA of ≤ 0.18 differentiates malignant from benign prostate pathology or latent from manifest cancer with a specificity of 91% and selectivity of 69% [22].

CONCLUSIONS

Values of total prostate specific antigen, free PSA and ratio free/total PSA in cases of HGPIN appears to be intermediate between prostate cancer and benign prostate. Ratio of free/total PSA significantly discriminates HGPIN from prostate carcinoma with sensitivity 84.52 and specificity 45.00 at cut-off point of ≤ 0.18. Combination of PSA and percent of free PSA may help in decision making for repeat biopsies in the presence of HGPIN on biopsy without concomitant prostate cancer in patients suitable for curative treatment, with intermediate level of PSA, and without definitive signs of carcinoma on DRE and TRUS.

DECLARATION OF INTEREST

Authors have no conflict of interest to declare.

REFERENCES

1. Montironi R, Vela Navarrete R, Lopez-Beltran A, Mazzucchelli R, Mikuz G, Bono AV. Histopathology reporting of prostate needle biopsies. 2005 update. Virchows Arch. 2006;449(1):1-13
2. Zhou M, Magi-Galluzzi C. Genitourinary pathology: Churchill Livingstone/Elsevier; 2007.
3. Bostwick DG, Meiers I. Atypical small acinar proliferation in the prostate: clinical significance in 2006. Arch Pathol Lab Med. 2006;130(7):952-7
4. Raviv G, Zlotta AR, Janssen T, Descamps F, Vanegas JP, Verhest A, et al. Do prostate specific antigen and prostate specific antigen density enhance the detection of prostate carcinoma after initial diagnosis of prostatic intraepithelial neoplasia without concurrent carcinoma? Cancer. 1996;77(10):2103-8.
5. Zlotta AR, Raviv G, Schulman CC. Clinical prognostic criteria for later diagnosis of prostate carcinoma in patients with initial isolated prostatic intraepithelial neoplasia. Eur Urol. 1996;30(2):249-55.
6. Antonelli A, Tardanico R, Giovanessi L, Pesenti N, Gatti L, Zambolin T, et al. Predicting prostate cancer at rebiopsies in patients with high-grade prostatic intraepithelial neoplasia: a study on 546 patients. Prostate Cancer Prostatic Dis. 2011;14(2):173-6.
7. Gallo F, Chiono L, Gastaldi E, Venturino E, Giberti C. Prognostic significance of high-grade prostatic intraepithelial neoplasia (HGPIN): risk of prostatic cancer on repeat biopsies. Urology. 2008;72(3):628-32.
8. Schlesinger C, Bostwick DG, Iczkowski KA. High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. Am J Surg Pathol. 2005;29(9):1201-7.
9. Kronz JD, Shaikh AA, Epstein JI. High-grade prostatic intraepithelial neoplasia with adjacent small atypical glands on prostate biopsy. Hum Pathol. 2001;32(4):389-95.
10. Aganovic D, Prcic A, Kulovac B, Hadziosmanovic O. Prostate cancer detection rate and the importance of premalignant lesion in rebiopsy. Med Arh. 2011;65(2):109-12.
11. Auskalnis S, Milonas D, Jievaltas M, Vaiciunas K, Mickevicius A, Gudinaviciene I. The role of high-grade prostatic intraepithelial neoplasia for biochemical relapse of prostate carcinoma after radical prostatectomy. Medicina (Kaunas). 2010;46(9):604-10.
12. Morote J, Rigau M, Garcia M, Mir C, Ballesteros C, Planas J, et al. Behavior of the PCA3 gene in the urine of men with high grade prostatic intraepithelial neoplasia. World J Urol. 2010;28(6):677-80.
13. Ramos CG, Carvahal GF, Mager DE, Haberer B, Catalona WJ. The effect of high grade prostatic intraepithelial neoplasia on serum total and percentage of free prostate specific antigen levels. J Urol. 1999;162(5):1587-90.
14. Haggman MJ, Adolfsson J, Khoury S, Montie JE, Norlen J. Clinical management of premalignant lesions of the prostate. WHO Collaborative Project and Consensus Conference on Public Health and Clinical Significance of Premalignant Alterations in the Genitourinary Tract. Scand J Urol Nephrol Suppl. 2000(205):44-9.
15. Haggman MJ, Macoska JA, Wojno KJ, Oesterling JE. The relationship between prostatic intraepithelial neoplasia and prostate cancer: critical issues. J Urol. 1997;158(1):12-22.
16. Park S, Shinohara K, Grossfeld GD, Carroll PR. Prostate cancer detection in men with prior high grade prostatic intraepithelial neoplasia or atypical prostate biopsy. J Urol. 2001;165(5):1409-14.
17. Remzi M, Fong YK, Dobrovits M, Anagnostou T, Seitz C, Waldert M, et al. The Vienna nomogram: validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. J Urol. 2005;174(4 Pt 1):1256-60; discussion 60-1; author reply 61.
18. Aus G, Abbou CC, Pacik D, Schmid HP, van Poppel H, Wolff JM, et al. EAU guidelines on prostate cancer. Eur Urol. 2001;40(2):97-101.
19. Lakhey M, Ghimire R, Shrestha R, Bhatta AD. Correlation of serum free prostate-specific antigen level with histological findings in patients with prostatic disease. Kathmandu Univ Med J (KUMJ). 2010;8(30):158-63.
20. Christensson A, Bjork T, Nilsson O, Dahlen U, Matikainen MT, Cockett AT, et al. Serum prostate specific antigen complexed to alpha 1-antichymotrypsin as an indicator of prostate cancer. J Urol. 1993;150(1):100-5.
21. Tarle M, Kraljic I. Free and total serum PSA values in patients with prostatic intraepithelial neoplasia (PIN), prostate cancer and BPH. Is F/T PSA a potential probe for dormant and manifest cancer? Anticancer Res. 1997;17(3A):1531-4.
22. Filella X, Truan D, Alcover J, Quinto L, Molina R, Luque P, et al. Comparison of several combinations of free, complexed, and total PSA in the diagnosis of prostate cancer in patients with urologic symptoms. Urology. 2004;63(6):1100-3; discussion 3-4.
23. Borboroglu PG, Sur RL, Roberts JL, Amling CL. Repeat biopsy strategy in patients with atypical small acinar proliferation or high grade prostatic intraepithelial neoplasia on initial prostate needle biopsy. J Urol. 2001;166(3):866-70.