Published online: 27/07/2016 Published print: 08/2016

ORIGINAL PAPER

doi: 10.5455/medarh.2016.70.288-292
Med Arch. 2016 Aug; 70(4): 288-292
Received: FEB 15, 2016 | Accepted: MAY 28, 2016

Actual Contribution of Free to Total PSA Ratio in Prostate Diseases Differentiation

Alden Prcic[1], Edin Begic[2], and Mustafa Hiros[3]

[1]Bahrain Specialist Hospital, Bahrain
[2]Health Centre Maglaj, Maglaj, Bosnia and Herzegovina
[3]Clinic of Urology, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina

Corresponding author: prof Alden Prcic, MD, PhD. Bahrain Specialist Hospital, Bahrain.

ABSTRACT

Objectives: To determine significance and sensitivity of the Free to Total prostate specific antigen (PSA) ratio (%fPSA) in diagnosis of prostate cancer and to correlate its sensitivity and specificity with diagnosis. **Methods:** Research included 220 patients, who had indication for biopsy (Clinic for Urology, University Clinical Center Sarajevo). **Results:** Average age of patients was 64.6 ± 8.1 years. Kruskal Wallis test indicates that there is a significant difference in age in relation to the diagnosis (KW $\chi 2=12.508$; $p=0.006$). The correlation between the %fPSA level and diagnosis is positive and statistically significant ($r=0.211$; $p=0.002$) in the sense that cancer patients have the lowest %fPSA. Analysis of the sensitivity at 95% specificity of %fPSA compared to particular diagnosis shows the highest sensitivity for prostate cancer - 20.61% (8.35-31.02) with statistically significant AUC $p<0.05$. Analysis of %fPSA test in detecting prostate cancer, at cut-off values ≤ 0.16, shows a sensitivity of 72.3% and specificity of 50.4 (at cut-off values <0.07, sensitivity is 8.4%, and specificity is 97.8%). **Conclusion:** PSA is organ specific but not cancer specific marker, whose total value, as well as the %fPSA serve as a basis, with a digitorectal exam, in the detection of prostate cancer. By increasing the cut-off values sensitivity of %fPSA increases and specificity decreases. %fPSA has a relative importance in the detection of prostate cancer, and should not be used as a guideline, without prior clinical examination.

Key words: prostate specific antigen, Free to Total PSA ratio, prostate cancer.

1. INTRODUCTION

Digitorectal examination (DRE), level of prostate specific antigen (PSA) and transrectal ultrasound (TRUS) guided biopsy of the prostate, represent the basis of detection of prostate cancer, and the main tool of a urologist in the differential diagnosis of prostate diseases. The introduction of PSA testing and TRUS in clinical practice had a significant effect on the detection of prostate cancer during the past 20 years (1). DRE due to simple execution, is routine method, and the basis of clinical examination. It is used to estimate the size, limitations of the environment, symmetry, sensitivity and firmness of the prostate, and to assess the existence of suspected changes in the structure of the prostate. It has low sensitivity and low specificity. Digitorectally only peripheral zone can be palpated and the suspect induration must be larger than 0.2 cm. DRE is an essential part of the assessment that can independently predict prostate cancer in the setting of a normal PSA level (2). Analysis of PSA levels in combination with DRE, increases the chance of early detection of prostate cancer (3). Positive DRE, and the increased value of PSA indicate a greater chance of the existence of cancer. PSA is an organ specific antigen and is secreted by the epithelial cells of the prostate. Prostate-specific antigen (PSA) testing has changed early detection and management of prostate cancer dramatically since its introduction into clinical practice in the early 1980s (4). Its introduction in daily urological practice has led to a significant rise in registered prostate cancer, for better and easier diagnosis of cancer. In the serum of healthy men in physiological conditions there is a very

low concentration of PSA which has prostatic origin. In the normal male, PSA is detected in low concentrations of 0-1 ng/mL (5). PSA in serum appears only in cases of disrupted microarchitecture of prostate tissue, and that is the reason that PSA crosses into the surrounding extracellular space, than by lymph it is flushed in the systemic circulation and is always an indication of trauma or prostate disease. Elevated concentrations of PSA are found not only in patients with prostate cancer, but also in those with a diagnosis of benign prostatic hyperplasia (BPH) and prostatitis. Prostatic intraepithelial neoplasia (PIN) does not appear to raise serum PSA levels (6, 7).

Today, PSA is considered to be the leading tumor marker in conducting evaluation of effectiveness of therapy of patients with prostate cancer, prognostic parameters, assessment of tumor mass, early detection of recurrence, and it is very useful in the screening and early diagnosis of prostate cancer. As member of human kallikrein family, PSA shares considerable structural and functional homology with all other 14 human kallikrein, together with gene location on the long arm of chromosome 19 (19q13.2-q13.4) (5).

PSA exists in three forms. The main form of immunoreactive PSA in serum is PSA bound by alpha-1 antichymotrypsin, approximately 75% of the total PSA in the circulation (5). PSA bound to alpha-2 macroglobulin exists in less than 0.1% (undetectable by a commercial test), while the free PSA (enzymatically inactive form), exists 5-50% in serum (5). The main disadvantage of the PSA is its low specificity, particularly in patients with total PSA concentration in the "diagnostic gray zone" (total PSA concentration range of 4-10 ng/mL). In order to achieve greater specificity in determining the PSA, different indexes were developed: age-specific PSA, PSA density, acceleration of PSA, PSA density of the transition zone, the proportion of free and total PSA, and their ratio (%fPSA). In addition to total PSA, the most useful diagnostic index for distinguishing benign hypertrophy from prostate cancer is the Free to Total PSA ratio (PSA free/PSA total).

Searching for this ratio is extremely important in patients who have negative digitorectal examination. Free to Total PSA Ratio (%fPSA) is a method that increases sensitivity and specificity of PSA in diagnosing prostate cancer, and its determination allows easy diagnosis of the disease, or malignant processes. The likelihood of finding prostate cancer, based on %fPSA, increases with age of the patient. Prostate cancer is a continuous progressive disease of the prostate, which constantly increases the release of PSA and the majority of patients with low %fPSA (less than 10% free PSA, more than 90% bound PSA) will have prostate cancer.

After the development of immunoassay, it has been proven that the %fPSA is lower in men with prostate cancer. Men with consistently elevated levels of PSA should have assessed %fPSA. If the ratio is below 8%, the risk of prostate cancer is nearly 80%. The serum %fPSA is found to be an effective indicator in order to differentiate the diagnosis of BPH from prostate cancer, and therefore it was utilized for discriminating benign and malignant diseases of the prostate gland in order to improve the poor specificity of serum total PSA examination alone (8).

The aim of the work was to determine the significance and sensitivity of the Free to Total PSA ratio in diagnosis of prostate cancer, to correlate diagnosis with sensitivity and specificity of %fPSA, to determine the specificity and sensitivity of the %fPSA at different cut-off values in the detection of prostate cancer, and to stress the importance of the results %fPSA, without digitorectal exam of the prostate.

2. METHODS

The study included 220 patients (n= 220), who had indication for biopsy, because of suspicion on prostate cancer. This research was conducted at Clinic of Urology, University Clinical Center Sarajevo, and laboratory findings of patients were subsequently monitored, and total PSA, free PSA and Free to Total PSA ratio were recorded. Results are shown through number of cases, percentage, arithmetic mean, standard deviation, median and interquartile range, area under the curve (AUC), sensitivity and specificity, and confidence interval (CI). Analysis of the distribution by the Shapiro-Wilk test showed that none of the observed variables did not meet the criteria of normal distribution and non-parametric tests (Mann-Whitney, Kruskal-Wallis and Spearman's rank correlation coefficient) were used in the analysis. Analysis of the ROC (receiver operating curve) was used to determine the sensitivity and specificity. All results of the analysis with $p < 0.05$ or at the level of confidence of 95% were considered statistically significant.

3. RESULTS

Average age of patients was 64.6 ± 8.1 years (36-82 years). The histogram with normal distribution curve showed that the majority of patients were aged from 50 to 80. In total sample the most common pathological change in the prostate was prostate cancer in 37.7% of cases, followed by BPH in 31.8% of cases, precancerous conditions (atypical small acinar proliferation–ASAP and high-grade prostatic intraepithelial neoplasia–HGPIN) in 16.4% of cases, and atrophic and inflammatory changes in the prostate in 14.1 % of cases.

Based on the diagnosis patients were divided into four groups. All patients with prostate cancer had total PSA level from 4 to 10 ng/mL, while patients in the other group had total PSA level ranging from 1.4 to 14.8 ng/mL. The age distribution of pathological changes on prostate demonstrates that patients with prostate cancer were the oldest, with an average age of 66 years. After patients with cancer, patients with precancerous conditions (HGPIN and ASAP) with 64 years were next, while the youngest were patients with BPH with an average age of 62 years. The analysis by Kruskal Wallis test indicates that there is a significant difference in age in relation to the diagnosis (KW $\chi 2 = 12.508$; $p = 0.006$), and the subsequent analysis of diagnosis by the Mann-Whitney test shows that there is a significant difference between prostate cancer and benign prostatic hyperplasia ($p = 0.006$).

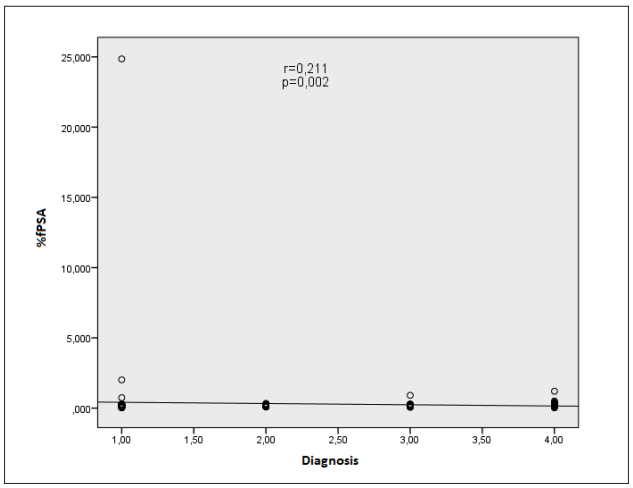

Figure 1. Correlation between diagnosis and %fPSA level

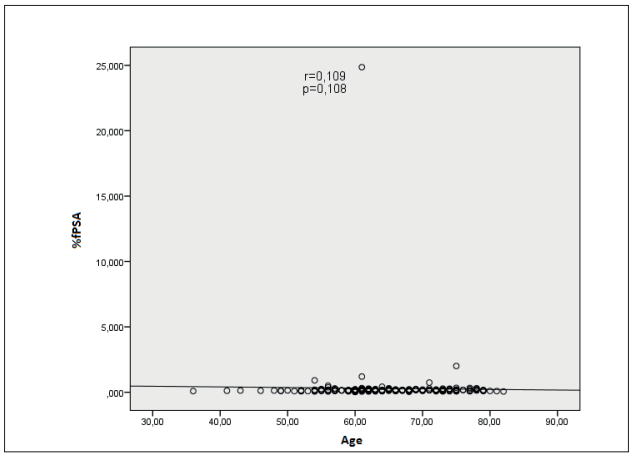

Figure 2. Correlation between age and %fPSA level

The correlation between the %fPSA level and diagnosis is positive and statistically significant (r = 0.211; p = 0.002) in the sense that cancer patients have the lowest %fPSA levels and the patients with benign prostatic hyperplasia the highest %fPSA levels (Figure 1).

Correlation between %fPSA levels and age is also positive but not statistically significant (r = 0.109; p = 0.0108) indicating a slight increase in %fPSA levels with age (Figure 2).

Analysis of the sensitivity at 95% specificity of %fPSA compared to particular diagnosis shows the highest sensitivity for prostate cancer- 20.61% (8.35-31.02) with statistically significant AUC p <0.05, followed by a sensitivity for benign prostatic hyperplasia–12.86% (4.29 to 20.38) and statistical significant AUC, with low sensitivity to atrophic and inflammatory changes in the prostate- 3.23% (0-6.45) and precancerous conditions- 2.78% (0-13.74) (Table 1).

Analysis of the ROC curve estimates the best possible sensitivity and specificity at a specific cut-off values (Table 2). Analysis of %fPSA test in detecting prostate cancer, at cut-off values ≤ 0.16, shows a sensitivity of 72.3% and specificity of 50.4%.

With the increase at cut-off values sensitivity increases and specificity decreases in the detection of prostate cancer, so at cut-off values <0.07, sensitivity of %fPSA is 8.4%, and specificity is 97.8%, while at cut-off <0,3 sensitivity is 96.4% and specificity is 58.4% (Table 3.).

Diagnosis	%fPSA		
	Sensitivity (%) (95% spec)	Specificity (%) (95% sens)	AUC
Precancerous conditions	2.78 (0-13.74)	13.91 (4.24-23.71)	0.521 p=0.683
Prostate cancer	20.61 (8.35-31.02)	9.49 (0-15.33)	0.626 p=0.0015
Atrophic and inflammatory changes of the prostate	3.23 (0-6.45)	7.38 (1.07-26.5)	0.556; p=0.2704
Benign prostatic hyperplasia	12.86 (4.29-20.38)	13.67 (1.67-20.67)	0.593 p=0.0225

Table 1. Analysis of the sensitivity and specificity of %fPSA in com

Diagnosis	%fPSA		
	Sensitivity (%)	Specificity (%)	Cut off
Prostate cancer	72.3	50.4	≤0.16
Precancerous conditions	94.4	14.7	>0.09
Atrophic and inflammatory changes of the prostate	80.6	38.6	>0.137
Benign prostatic hyperplasia	67.1	51.3	>0.14

Table 2. Evaluation of the best possible sensitivity and specificity at specific cut-off values

Range	Sensitivity	Specificity	PPV	NPV
< 0.07	8.4%	97.8%	70.0%	63.8%
< 0.1	27.7%	88.3%	58.9%	66.9%
< 0.12	38.6%	86.6%	65.3%	68.3%
< 0.15	62.7%	53.3%	44.8%	44.8%
< 0.2	84.3%	23.4%	40.0%	71.1%
< 0.25	91.6%	10.2%	38.2%	66.7%
< 0.3	96.4%	58.4%	38.3%	72.7%

Table 3. The sensitivity and specificity of the %fPSA at the different ranges

4. DISCUSSION

Due to many inconsistencies when selecting biopsy techniques, as well as the invasiveness of the procedure, the importance of proper interpretation of PSA gained significance. This study wanted to show that complementarity of invasive and non-invasive methods, with gradualism, analyticity, rationalization, and maximum utilization, either individually or in general, can reduce the number of "unnecessary" biopsies, and put the emphasis on the determination of the PSA, with aforementioned digitorectal exam. Before routine PSA determination (until 1987) in 35% of patients who were thought to have clinically confined prostate cancer, it was determined that they have positive lymph nodes, while two-thirds had pathologically advanced disease (9). At the moment lymph node involvement is present in less than 5% of patients, and there is evidence that serial PSA testing (annual screening tests) have reduced the number of patients with pathologically advanced disease (10).

PSA testing detects more cancers than digitorectal exam, and reveals them much earlier, which is extreme-

ly important. Although many of these cancers have aggressive characteristics, there are cancers that can grow slowly enough to not present a risk to the patient. Still, there is no way to identify with certainty cancers that do not have the risk of spreading and potentially causing premature death or morbidity (11). PSA is the most sensitive test for the detection of early prostate cancer, but the combination of PSA and digitorectal exam is much better. The reason is that digitorectal exam will reveal some of the cancer patients who have prostate cancer despite normal PSA levels (less than 4.0 ng/mL). PSA is not a cancer specific marker and its positive predictive value (PPV) to detect prostate cancer for the range of 4-10 ng/mL and normal rectal examination is around 30% (12). With such a low PPV, 70% of men undergo unnecessary trans rectal ultrasonography (TRUS) guided biopsy to diagnose prostate cancer (13). To reduce this percentage of unnecessary biopsy, %fPSA has been described to improve specificity of total PSA in the PSA range of 4-10 ng/mL, without affecting its sensitivity (14). Approximately 70% of men with an increased serum PSA levels, defined as >4.0 ng/mL, do not have prostate cancer and this percentage undergoes unnecessary prostate biopsy (15).

This research has shown that the correlation between the %fPSA level and diagnosis is statistically significant and positive in the sense that patients with prostate cancer have the lowest values and patients with BPH maximum %fPSA levels. %fPSA level depends on the age of the patient. The results indicate a slight increase in the %fPSA level with. Analysis of the sensitivity at 95% specificity %fPSA in relation to individual diagnosis showed the highest sensitivity for prostate cancer. Tanguay et al. had at cut off 0.27 30% specificity with sensitivity 95%, and at cut-off of 0.21 50% specificity (16). Miller et al. had at cut off 0.2 31% specificity (17). This research showed that at cut-off values <0.07 %fPSA sensitivity is 8.4%, and specificity 97.8%, and at %fPSA levels <0.25, sensitivity was 91.6%, and specificity 10.2%.

Best combination of sensitivity (72.3%) and specificity (50.4%) is at cut-off value of ≤0.16 for %fPSA levels in diagnosing prostate cancer. This research showed that at cut-off <0.2 %fPSA had 84.3% sensitivity and 23.4% specificity. Another study has shown that the optimal cut-off value for the %fPSA (≤14.7854) showed sensitivity of 89.29% and 54.29% specificity (18).

It should be noted that the likelihood of finding prostate cancer, based on %fPSA, increases with the age of the patient, and that ratio is useless in patients in whom the serum PSA is greater than 10 ng/mL (19). Chakraborty et al. analyzed patients with cancer and their %fPSA and obtained values in cancer patients 0.144 ± 0.152 compared to ± 0.328 ± 0.076 in patients with benign disease (20). Sensitivity and specificity of the test was calculated at different cut-off values of ratio of free and bound PSA, and at 0.1 cut-off value, sensitivity of %fPSA test was 64% and specificity was 84%, and PPV was 58%, and negative predictive value (NPV) was 87% (20). In this research at aforementioned cut-off sensitivity was slightly lower, specificity was 88.3%, PPV 58.9% and NPV 68.3%.

When the cut-off value was from 0.12 to 0.16, the sensitivity increased from 64% to 91%, but the specificity decreased from 84% to 59%. PPV did not show much change and NPV increased from 89% to 95%. A similar shift of parameters is shown in this research. Results of the study by Chen et al. showed the same thing as in this research, that the %fPSA level is significantly lower than in benign prostate disease (21). %fPSA is a sensitive test for ASAP and HGPIN, and atrophic and inflammatory changes, but its specificity is not at an adequate level, and its role in the detection of these diseases is questionable. %fPSA greater than 25%, reduces the risk of prostate cancer in comparison when the ratio is less than 10% (22). The general opinion is that the analysis of the PSA is not perfect test, and that it should still improve. %fPSA is one of the ratio, which greatly helps urologist in daily clinical practice, but not so good predictor of malignancy diseases. Currently, perhaps the most useful applications of the %fPSA ratios in the management of prostatic diseases may be for identifying older patients with a less than 10-year age-adjusted life expectancy in whom the biopsy might be deferred (23). Additionally, the %fPSA ratios may be beneficial in patients with a negative first biopsy to identify those who would benefit from a repeated biopsy (24).

Researchers are turning to development of new tests, which should show better results. The first test is "Progensa", which seeks PCA3 antigen in the urine after a digitorectal exam (assuming that digitorectal exam "pushes" cancer cells during examination in the urine). Another test is the analysis of presence of the gene "TMPRSS2: ERG", in prostate cells from collected urine after digitorectal exam, which is not present in men who have prostate cancer (25). The identification of novel molecular and immunohistochemical methods enabled the identification of potential biomarkers in relation to prognosis (26). Detection of prostate cancer, one of the leading health problems of the male population, is still an open field, where there can be numerous innovations, and correction of the above mentioned findings.

5. CONCLUSION

Prostate specific antigen is organ specific but not cancer specific marker, whose total value, as well as the Free to Total PSA ratio (%fPSA) serve as a basis, with a digitorectal examination, in the detection of prostate cancer. Based on the significance and sensitivity of the %fPSA, it can be concluded with certainty, complemented with digitorectal examination, diagnosis of prostate cancer (by increasing the cut-off values sensitivity of %fPSA increases and specificity decreases). Prostate biopsy remains the gold standard for final diagnosis of prostatic diseases. %fPSA finding is a good predictor of the existence of prostate cancer, at certain cut-off values, compared to other diseases of the prostate.

• Conflict of interest: none declared.

REFERENCES

1. Pinthus JH, Pacik D, Ramon J. Diagnosis of prostate cancer. Recent Results Cancer Res. 2007; 175: 83-99.
2. Walsh AL, Considine SW, Thomas AZ, Lynch TH, Manecksha RP. Digital rectal examination in primary care is important for early detection of prostate cancer: a retrospective cohort analysis study. Br J Gen Pract. 2014; 64(629): e783-7.
3. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6,630 men. J Urol. 1994;151: 1283-90.
4. Partin AW, Hanks GE, Klein EA, Moul JW, Nelson WG, Scher HI. Prostate-specific antigen as a marker of disease activity in prostate cancer. Oncology (Williston Park). 2002; 16(8): 1024-38.
5. Li B. Prostate Cancer Targeted Therapy. In: Schwab M. Encyclopedia of Cancer, 3rd edition. Berlin: Springer-Verlag Berlin Heidelberg, 2012: 3065.
6. Alexander EE, Qian J, Wollan PC. et al. Prostatic intraepithelial neoplasia does not appear to raise serum prostate-specific antigen concentration. Urology. 1996; 47: 693.
7. Ramos CG, Carvahal GF, Mager DE. et al. The effect of high grade prostatic intraepithelial neoplasia on serum total and percentage of free prostate specific antigen levels. J Urol, 1999; 162: 1587.
8. Catalona WJ, Smith DS, Wolfert RL, et al. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA. 1995; 274, 1214-20.
9. Partin AW, Kattan MW, Subong ENP. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. JAMA. 1997; 277: 1445-45.
10. Smith DS, Catalona WJ, Herschman JD. Longitudinal screening for prostate cancer with prostate specific anti gen. JAMA. 1996; 276: 1309-15.
11. Coley CM, Barry MJ, Fleming C, Fahs MC, Mulley AG. Early detection of prostate cancer. Part I: prior probability and effectiveness of tests. Ann Intern Med. 1997; 126: 394-406.
12. Cooner WH, Mosley BR, Rutherford CL, Jr, Beard JH, Pond HS, Terry WJ, et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. J Urol. 1990; 143: 1146-52.
13. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6,630 men. J Urol. 1994; 151: 1283-90.
14. 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: 1542-7.
15. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006,. CA Cancer J Clin. 2006; 56(2): 106-30.
16. Tanguay S, Bégin LR, Elhilali MM, Behlouli H, Karakiewicz PI, Aprikian AG. Comparative evaluation of total PSA, free/total PSA, and complexed PSA in prostate cancer detection. Urology. 2002; 59(2): 261-5.
17. Miller GJ, Brawer MK, Sakr WA, Thrasher JB, Townsend R. Prostate Cancer: Serum and Tissue Markers. Reviews in Urology. 2001; 3(2): S11-S19.
18. Brawer MK, Meyer GE, Letran JL, Bankson DD, Morris DL, Yeung KK, et al. Measurement of complexed PSA improves specificity for early detection of prostate cancer. Urology. 1998; 52(3): 372-8.
19. Finne P, Auviena A, Aro J, Juusela H, Määttänen L, Rannikko S, et al. Estimation of prostate cancer risk on the basis of total and free prostate specific antigen, prostate volume and digital rectal examination. Eur Urol. 2002; 41: 619-27.
20. Chakraborty L, Ahmed AN, Paul BK, Haque A, Ara A, Nabi S, et al. Comparative study of total prostate specific antigen and free to total prostate specific antigen ratio in the diagnosis of prostate cancer. Med J. 2012; 21(1): 98-102.
21. Chen ZD, Wei SM, Cai SL. Significance and limitations of f/tPSA in differential diagnosis of prostate cancer with tPSA levels between 4 and 10 ng/. Zhonghua Wai Ke Za Zhi. 2004; 42(10): 593-5.
22. Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol. 1992; 147(3): 815-6.
23. Veltri RW, Miller MC. Free/total PSA ratios improve differentiation of benign and malignant disease of the prostate: critical analysis of two different test populations. Urology. 1999; 53: 736-45.
24. O'Dowd GJ, Miller MC, Orozco R, Veltri RW. Analysis of repeat biopsy results within one year following a non-cancer diagnosis. Urology. 2000; 55: 553-9.
25. Mosquera JM, Perner S, Demichelis F, Kim R, Hofer MD, Mertz KD, et al. Morphological features of TMPRSS2-ERG gene fusion prostate cancer. J Pathol. 2007; 212: 91-101.
26. Ziaran S, Varchulova Novakova Z, Bohmer D, Danisovic L. Biomarkers for determination prostate cancer: implication for diagnosis and prognosis. Neoplasma. 2015 Aug 17. doi: 10.4149/neo_2015_082.