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Original Article

High PCA3 scores in urine correlate with poor-prognosis factors in prostate cancer patients

Wei Wei, Jiangyong Leng, Hongxiang Shao, Weidong Wang

Department of Urinary Surgery, Ningbo No. 2 Hospital, No. 41 Xibei Street, Ningbo 315000, Zhejiang Province, China

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Abstract: Background: To improve the prediction of prostate cancer (PCA) risk and pathological type of PCA by non-invasive approaches before performing prostatic biopsy are the current challenges for the management of PCA. The aim of this present study was evaluate the clinical validity of prostate cancer associated 3 (PCA3) gene in the prediction of PCA and the correlations between the PCA3 level and prognostic factors. Methods: A total of 207 patients with suspected prostate cancer in Ningbo No. 2 hospital between June 2012 and July 2014 were enrolled in this study. All patients included underwent prostate biopsy under the direction of digital rectal examination (DRE) and were divided into PCA group and no evidence of malignancy (NEM) group according to the pathological diagnosis. We analyzed the association between PCA3 score and indicators of prognosis (Gleason score, percentage of positive cores and clinical stage) by multivariate analysis. Results: The levels of total prostate-specific antigen (t-PSA), prostate health index (PHI) and PCA3 score in patients with PCA were significantly higher than those in NEM group ($P<0.05$). In PCA group, PHI value and t-PSA were both factors significantly correlated with high Gleason score and clinical stage ($P<0.05$). A high PCA3 score in urine was significantly correlated with a high Gleason score, % positive cores and an advanced clinical stage ($P<0.05$). Conclusion: PCA3 score might be one of useful diagnostic tools for determining suitable therapeutic programs for PCa and predicting the prognosis.

Keywords: Prostate cancer, PCA3 score, prognosis

Introduction

Prostate cancer (PCA) is one of the most frequent internal cancers and most frequent cause of cancer-related deaths among men worldwide [1]. It is illustrated that PCA has been an important public health problem worldwide. The etiology of PCA still remains unclear and it is multi factorial including genetic, environmental and dietary causes [2]. Intensive treatment is necessary for the prevention of castration-resistant prostate cancer development, so to predict the PCA behavior is very important. The clinical stage and pathological grade can strongly predict the aggressiveness of PCA, however, sensitive and effective molecular markers remain unidentified. The prostate-specific antigen (PSA) has been widely used as screening marker for PCA with debates [3]. Published data indicate that serum PSA level remains significant predictive factor for men with increased risk for PCA in clinical [4]. However, serum PSA can't be the standard first-line test because it lacks a lowermost cut-point and has a continuum of PCA risk with increasing values [5]. PSA is identified to be not an exclusive PCA-specific but an organ-specific marker [6] with a low predictive value of 24% and 37% reported by two extensive multicenter studies [7, 8]. The abnormality of serum PSA level and/or digital rectal examination (DRE) usually requires prostatic biopsy to detect PCA. As a consequence of no effective and sensitive predictive markers, a lot of expensive and unnecessary prostate biopsies were suggested for patients with possible interventional complications [9]. Therefore, to improve the prediction of PCA risk and pathological type of PCA by non-invasive approaches before performing prostatic biopsy are the current challenges for the management of PCA. In recent years, numerous approaches including sophisticated imaging techniques, different PSA derivatives (e.g. prostate health index, Phi) and novel biomarkers have been suggested for the challenges [10]. Recently micro RNAs (miRNAs) in serum and

urine of patients with PCA have attracted numerous attentions as potential markers [11, 12]. The long non-coding RNA prostate cancer associated 3 (PCA3) gene test in urine is widely used as a promising predictive tool for PCA [13]. However, due to the limitations of different study designs including the sample size, reference standard test and statistical analysis, the study about the role of PCA3 in PCA area are with conflicting results [14, 15]. The aim of this present study was evaluate the clinical validity of PCA3 in the prediction of PCA and the correlations between the PCA3 level and prognostic factors.

Material and methods

Patients

This study was approved by the Medical Institutional Ethics Committee of Zhejiang province. A total of 207 patients with suspected prostate cancer underwent prostate biopsy for pathological diagnosis in Ningbo No. 2 hospital between June 2012 and July 2014 were enrolled in this study. Blood samples were collected and handled before digital-rectal examination (DRE) and biopsy as described previously [16]. Urine samples were collected before prostate biopsy and following a standardized DRE with three strokes per lobe from patients included who were suspected for PCA and received 8-12 core biopsies as described by Groskopf *et al.* previously [17]. Afterwards, the urine samples were immediately stored in a Progensa urine specimen transport kit for the measurement of PCA3 mRNA. Patients included were divided into two groups according to the biopsy results, PCA group (patients diagnosed with PCA, n=94) and NEM group (patients with no evidence of malignancy, n=113).

Histopathology

A central pathologist was invited to review all the prostate biopsy samples included. The Gleason classification system was used for the performance of pathological grading. The central pathologist was always blinded to the patients' serum or prostate androgen measurements while making histological diagnoses.

PCA3 score measurement

All PCA3 mRNA measurements were carried out by Progensa PCA3 assay (Gen-Probe Inc., San Diego, CA, USA) in accordance with the manufacturer's protocols. In brief, the exfoliated prostate cells in urine samples collected before prostate biopsy were used to extract the PCA3 mRNAs. Afterwards, DNA probes tagged with a chemiluminescent substance were used for the amplification and hybridization of extracted PCA3. The hybridized number of PCA3 and PSA mRNA copies counting were performed by using a luminometer and PCA3 score was calculated as PCA3/PSA mRNA ×1000.

Other analytical methods

As described previously [16], the measurements of serum total PSA (t-PSA), free PSA (f-PSA), and [-2] pro-PSA (Beckman-Coulter, Brea, CA, USA) were performed. PHI value was calculated according to the formula [-2] pro-PSA/f-PSA×$\sqrt{}$t-PSA [18]. PHI value and PCA3 score are both FDA-approved approaches in the diagnosis of PCA.

Statistical analysis

SPSS 19.0 (SPSS, Inc.) statistical software was used in this study for statistical analysis. Data are presented as number (n) and percentage (%), or mean ± standard error (SD). Chi-square test and Mann-Whitney U-test are used for the statistical analysis. Multivariate analyses using a logistic regression model was used for the analysis of relationships between PCA3 score and prognostic factors including Gleason score, clinical stage, and % positive cores. Each statistical test was two-sided and $P<0.05$ was accepted as statistically significant.

Results

Patient and sample characteristics

The 207 patients who underwent prostate biopsy for pathological diagnosis were included, with 94 in PCA group and 113 in NEM group. The clinical and pathologic characteristics of the patients included are detailed summarized in **Table 1**. % fPSA and tPSA, as the conventional serum markers were detected and analyzed as usual. In addition, some other most promising non-invasive markers for PCA reported recently (such as serum parameter PHI, PCA3 score in urine and prostate volume) were also included in our present study with purposes of meaningful comparison. The results showed that the levels of t-PSA, PHI value and PCA3

Table 1. Clinic characteristics of the patients included

	PCa group (n=94)	NEM group (n=113)	*P*-value
Age (years)	63 (54-77)	65 (49-78)	0.395
History of chronic prostatitis	14 (14.89%)	12 (10.62%)	0.248
Family history of cancer	4 (4.26%)	3 (2.65%)	0.526
t-PSA (ng/mL)	12.6 (6.4-42.5)	7.6 (5.60-35.5)	0.009*
% fPSA	16.4 (3.3-29.7)	17.7 (6.3-37.9)	0.068
PHI value	57.8 (22.8-256)	33.8 (17.6-124)	0.018*
Prostate volume (cm^3)	47.2 (19.1-118.2)	56.4 (20.4-122.1)	0.023*
DRE, n (%)			
Positive	30 (31.91%)	23 (20.35%)	
Negative	64 (68.09%)	90 (79.65%)	0.258
PCA3 score	35.6 (14.2-212)	19.4 (6.5-145)	0.014*

PCa, prostate cancer; NEM, no evidence of malignancy; t-PSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; PHI, prostate health index; DRE, digital-rectal examination; PCA3, prostate cancer associated 3. *P<0.05 by Mann-Whitney U-test or Fisher exact test.

Table 2. Pathologic characteristics of patients with PCA

No. of patients	PCa group (n=94)
Age (years)	63 (54-77)
t-PSA (ng/mL)	12.6 (6.4-42.5)
Prostate volume (cm^3)	47.2 (19.1-118.2)
PHI value	57.8 (22.8-256)
PCA3 score	35.6 (14.2-212)
PCA3 score	
<15	9 (9.6%)
15-35	15 (16.0%)
35-70	30 (31.9%)
>70	40 (42.5%)
Gleason score	
≤7	62 (66.0%)
≥8	32 (34.0%)
% Positive core	
<30%	70 (74.5%)
≥30%	24 (25.5%)
Clinical stage	
≤III	78 (83.0%)
≥IV	16 (17.0%)

PCa, prostate cancer; t-PSA, total prostate-specific antigen; PHI, prostate health index; PCA3, prostate cancer associated 3.

score in patients with PCA were significantly higher than those in NEM group (P<0.05). Furthermore, patients in PCA group were with significant lower prostate volume in comparison with NEM group (P<0.05). Other indexes including age, history of chronic prostatitis, family history of cancer and positive rate of DRE did not statistically differ between the patients in two groups (P>0.05). As shown in **Table 2**, the pathologic characteristics of 94 patients IN PCA group were with a median PCA3 score of 35.6, t-PSA of 12.6 ng/mL and prostate volume of 47.2 cm^3.

Correlation of clinical factors to Gleason score in patients with PCA

The relationships between Gleason score and clinical factors including age, t-PSA, prostate volume, PHI value and PCA3 score are shown in **Table 3**. The results of multivariate analysis by logistic regression identified that high levels of serum t-PSA (hazard ratio [HR]: 1.020, *P*=0.012), PHI value (HR: 1.008, P=0.023) and PCA3 score (HR: 0.715, P=0.016) were factors significantly correlated with high Gleason score.

Correlation of clinical factors to % cancer-positive cores

The high level of PCA3 score in urine (HR: 0.881, *P*=0.009) was statistically correlated with the high % cancer-positive cores (**Table 4**). While no significant correlations between t-PSA, age, prostate volume and PHI value with % cancer-positive cores were observed (P>0.05).

Correlation of clinical factors to clinical stage

As shown in **Table 5**, high levels of serum t-PSA (HR: 1.014, *P*=0.023), PHI value (HR: 1.033, P=0.034) and PCA3 score (HR: 1.709, P=0.011) in urine were significantly related to advanced clinical stage.

Discussion

The therapeutic strategies to localized PCA including active surveillance or focal therapy were affected by preoperative anticipation of histological prognostic features. The best therapeutic goal of PCA should be the maximization of oncologic and functional outcomes [19]. By using inaccurate tools currently, some patients with low-risk PCA might undergo inappropriate

Table 3. Correlation between Gleason score and clinical factors

	Gleason score				
Parameter	≥8	≤7	HR	95% CI	*P* value
NO. of patients	62	32	-	-	-
Age (years)	60 (57-74)	65 (54-77)	1.048	0.992-1.104	0.084
t-PSA (ng/mL)	25.9 (18.4-42.5)	8.3 (6.4-19.7)	1.020	1.008-1.035	0.012*
Prostate volume (cm^3)	44.8 (19.1-101.3)	48.5 (23.4-118.2)	0.989	0.958-1.016	0.358
PHI value	65.2 (33.1-201.4)	45.1 (22.8-256)	1.008	0.989-1.023	0.023*
PCA3 score	54.4 (33.1-212)	27.8 (14.2-186.3)	0.715	0.533-0.928	0.016*

t-PSA, total prostate-specific antigen; PHI, prostate health index; PCA3, prostate cancer associated 3; HR, Hazard ratio; CI, confidence interval. *Multivariate analysis by logistic regression, $P<0.05$.

Table 4. Correlation between % positive core and clinical factors

	% Positive core				
Parameter	≥30%	<30%	HR	95% CI	*P* value
NO. of patients	24	70	-	-	-
Age (years)	66 (56-77)	60 (54-70)	1.057	0.984-1.114	0.154
t-PSA (ng/mL)	24.5 (10.8-42.5)	18.9 (6.4-36.5)	1.023	1.010-1.127	0.143
Prostate volume (cm^3)	43.6 (19.1-99.8)	49.4 (25.1-118.2)	0.978	0.949-1.002	0.176
PHI value	53.9 (22.8-225.1)	60.3 (30.6-256)	0.772	0.571-1.068	0.134
PCA3 score	48.8 (28.3-212)	28.1 (14.2-195.6)	0.881	0.811-0.959	0.009*

t-PSA, total prostate-specific antigen; PHI, prostate health index; PCA3, prostate cancer associated 3; HR, Hazard ratio; CI, confidence interval. *Multivariate analysis by logistic regression, $P<0.05$.

Table 5. Correlation between clinical stage and clinical factors

	Clinical stage				
Parameter	≥IV	≤III	HR	95% CI	*P* value
NO. of patients	16	78	-	-	-
Age (years)	59 (54-70)	67 (57-77)	1.041	0.969-1.142	0.285
t-PSA (ng/mL)	30.1 (11.4-42.5)	7.7 (6.4-23.5)	1.014	1.006-1.014	0.023*
Prostate volume (cm^3)	43.0 (19.1-113.7)	49.8 (20.2-118.2)	1.027	0.993-1.055	0.063
PHI value	64.5 (35.3-256)	46.0 (22.8-189.2)	1.033	1.013-1.028	0.034*
PCA3 score	45.8 (25.3-212)	26.9 (14.2-176.7)	1.709	1.218-2.298	0.011*

t-PSA, total prostate-specific antigen; PHI, prostate health index; PCA3, prostate cancer associated 3; HR, Hazard ratio; CI, confidence interval. *Multivariate analysis by logistic regression, $P<0.05$.

treatment. Therefore, efforts should be made to help clinicians determine PCA pathological characteristics by finding new preoperative biomarkers. PSA is one of the most used biomarkers for the diagnosis and treatment of PCA, however, PSA has also been demonstrated significantly increased in patients with the presence of inflammation in >20% of prostate glands [20]. Serum PSA levels could be suddenly and markedly increased by the stimulation of acute and chronic prostatitis along with the trauma of biopsy or cystoscopy [21, 22]. The cellular integrity might be altered by mild or moderate inflammation, and then the leakage of PSA into the serum is followed. Histological inflammation and an elevated level of serum PSA were commonly found among asymptomatic men, and prostate biopsy is always suggested. As a result, overdiagnosis and overtreatment are probably unavoidable. Recently, several studies have suggested that PHI might be one of the valid tools for discriminating PCA from other prostate diseases [23]. PHI was suggested as one of the strongest predictors of PCA with a better accuracy than the usual tests (such as tPSA, %PSA and PSA density) at initial

and repeat biopsy [24]. PHI value could also be used to discriminate PCA from chronic histological prostatic inflammation, but no significance was found between patients with chronic prostatitis and benign prostatic hyperplasia (BPH) [23].

Recent studies have introduced the PCA3 assay test as the potential candidates for prostate biopsy [25]. As a result of gross over expression of the gene by cancer cells, PCA3 has a good specificity for PCA at the cellular level. The over expression of PCA3 is observed in up to 95% of PCA patients and PCA3 canbe expressed 60-100 times higher in cancerous tissues than noncancerous tissues [26, 27]. Researchers suggest the PCA3 score as a valid biomarker for the discrimination of patients with PCa or chronic prostatitis/BPH with raised PSA [28]. Vlaeminck-Guillen *et al.* reported that the increased PCA3 score was not correlated with chronic prostatitis/BPH but with the increased incidence of PCa, which offered a suggestion for performing a biopsy [29]. The correlation between PCA3 and pathologic PCA characteristics has attracted numerous attentions, however the evidence reported by different groups are with conflicting results [24, 30].

In this present study, we aimed at investigating the roles of different biomarkers including t-PSA, % fPSA and PHI in the anticipation of histological prognostic features. We also evaluated PCA3 score by using a reference standard test, the FDA-approved PCA3 Progensa test as suggested by the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines [31]. Furthermore, it is a typical example to translate a tissue-based over expressed biomarker to a promising urinary marker supporting the diagnosis in clinical practice [17]. As shown by the results, the median levels of t-PSA, PHI value, prostate volume and PCA3 score differed significantly in patients with PCa versus those with no evidence of malignancy by prostate biopsy. Then we analyzed the relationship between these indexes and indicators of prognosis (Gleason score, % positive cores and clinical stage) using multivariate analysis by logistic regression. PHI value and t-PSA were both factors significantly correlated with high Gleason score and clinical stage. However, no statistical significance was observed between levels of PHI or t-PSA with % cancer-positive cores. As for PCA3 score, it was significantly related to all the three indicators of prognosis. Recently, studies have shown that PHI varied significantly in patients with prostatitis versus BPH, while PCA3 score could be a main determinant for prostatitis *versus* high-grade prostatic intraepithelial neoplasia (HG-PIN). PCA3 score was also significantly lower in patients with HG-PIN *versus* PCA [24].

In conclusion, our results confirmed that a high PCA3 score in urine has a close correlation with indicators of poor prognosis, including a high Gleason score, a high % positive cores and an advanced clinical stage. We concluded that PCA3 score measured by PCA3 Progensa test might be suggested as a useful prognostic factor. Taking the significant association between PCA3 score and Gleason score, % positive biopsy cores and clinical stage into consideration, PCA3 might be one of useful diagnostic tools for determining suitable therapeutic programs for PCA and predicting the prognosis. However, to confirm the validity of PCA3 score as a prognostic marker, further studies with more patients and longer follow-ups in the future are warranted.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wei Wei, Department of Urinary Surgery, Ningbo No. 2 Hospital, No. 41 Xibei Street, Ningbo 315000, Zhejiang Province, China. E-mail: zhangbingtg12@163.com

References

[1] Miyoshi Y, Uemura H, Umemoto S, Sakamaki K, Morita S, Suzuki K, Shibata Y, Masumori N, Ichikawa T, Mizokami A, Sugimura Y, Nonomura N, Sakai H, Honma S, Harada M, Kubota Y. High testosterone levels in prostate tissue obtained by needle biopsy correlate with poor-prognosis factors in prostate cancer patients. BMC Cancer 2014; 14: 717.

[2] Mohler JL, Gregory CW, Ford OH 3rd, Kim D, Weaver CM, Petrusz P, Wilson EM, French FS. The androgen axis in recurrent prostate cancer. Clin Cancer Res 2004; 10: 440-8.

[3] Wilt TJ, Scardino PT, Carlsson SV, Basch E. Prostate-specific antigen screening in prostate cancer: perspectives on the evidence. J Nat Cancer Inst 2014; 106: dju010.

[4] Roobol MJ, Schroder FH, Crawford ED, Freedland SJ, Sartor AO, Fleshner N, Andriole GL. A framework for the identification of men

at increased risk for prostate cancer. J Urol 2009; 182: 2112-20.
[5] Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ, Parnes HL, Coltman CA Jr. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. JAMA 2005; 294: 66-70.
[6] Bunting PS. Screening for prostate cancer with prostate-specific antigen: beware the biases. Clin Chim 2002; 315: 71-97.
[7] Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Berenguer A, Määttänen L, Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg BG, Moss SM, de Koning HJ, Auvinen A; ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360: 1320-8.
[8] Grubb RL 3rd, Pinsky PF, Greenlee RT, Izmirlian G, Miller AB, Hickey TP, Riley TL, Mabie JE, Levin DL, Chia D, Kramer BS, Reding DJ, Church TR, Yokochi LA, Kvale PA, Weissfeld JL, Urban DA, Buys SS, Gelmann EP, Ragard LR, Crawford ED, Prorok PC, Gohagan JK, Berg CD, Andriole GL. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int 2008; 102: 1524-30.
[9] Stephan C, Jung M, Rabenhorst S, Kilic E, Jung K. Urinary miR-183 and miR-205 do not surpass PCA3 in urine as predictive markers for prostate biopsy outcome despite their highly dysregulated expression in prostate cancer tissue. Clin Chem Lab Med 2015; 53: 1109-18.
[10] Stephan C, Ralla B, Jung K. Prostate-specific antigen and other serum and urine markers in prostate cancer. Biochim Biophys Acta 2014; 1846: 99-112.
[11] Kelly BD, Miller N, Healy NA, Walsh K, Kerin MJ. A review of expression profiling of circulating microRNAs in men with prostate cancer. BJU Int 2013; 111: 17-21.
[12] Mlcochova H, Hezova R, Stanik M, Slaby O. Urine microRNAs as potential noninvasive biomarkers in urologic cancers. Urol Oncol 2014; 32: 41, e1-9.
[13] Pal RP, Elmussareh M, Chanawani M, Khan MA. The role of a standardized 36 core template-assisted transperineal prostate biopsy technique in patients with previously negative transrectal ultrasonography-guided prostate biopsies. BJU Int 2012; 109: 367-71.
[14] Haj-Ahmad TA, Abdalla MA, Haj-Ahmad Y. Potential Urinary miRNA Biomarker Candidates for the Accurate Detection of Prostate Cancer among Benign Prostatic Hyperplasia Patients. J Cancer 2014; 5: 182-91.
[15] Srivastava A, Goldberger H, Dimtchev A, Ramalinga M, Chijioke J, Marian C, Oermann EK, Uhm S, Kim JS, Chen LN, Li X, Berry DL, Kallakury BV, Chauhan SC, Collins SP, Suy S, Kumar D. MicroRNA profiling in prostate cancer--the diagnostic potential of urinary miR-205 and miR-214. PLoS One 2013; 8: e76994.
[16] Stephan C, Jung K, Semjonow A, Schulze-Forster K, Cammann H, Hu X, Meyer HA, Bögemann M, Miller K, Friedersdorff F. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2] proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clin Chem 2013; 59: 280-8.
[17] Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, Brentano S, Mathis J, Pham J, Meyer T, Cass M, Hodge P, Macairan ML, Marks LS, Rittenhouse H. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clin Chem 2006; 52: 1089-95.
[18] Jansen FH, van Schaik RH, Kurstjens J, Horninger W, Klocker H, Bektic J, Wildhagen MF, Roobol MJ, Bangma CH, Bartsch G. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. Eur Urol 2010; 57: 921-7.
[19] Lazzeri M, Guazzoni G. Focal therapy meets prostate cancer. Lancet 2010; 376: 1036-7.
[20] Simardi LH, Tobias-MacHado M, Kappaz GT, Taschner Goldenstein P, Potts JM, Wroclawski ER. Influence of asymptomatic histologic prostatitis on serum prostate-specific antigen: a prospective study. Urology 2004; 64: 1098-101.
[21] Lin YK, Gettle L, Raman JD. Variable prostate-specific antigen management patterns by non-urologist providers at a tertiary care medical center. Urology 2011; 78: 244-8.
[22] Habermacher GM, Chason JT, Schaeffer AJ. Prostatitis/chronic pelvic pain syndrome. Ann Rev Med 2006; 57: 195-206.
[23] Lazzeri M, Abrate A, Lughezzani G, Gadda GM, Freschi M, Mistretta F, Lista G, Fossati N, Larcher A, Kinzikeeva E, Buffi N, Dell'Acqua V, Bini V, Montorsi F, Guazzoni G. Relationship of chronic histologic prostatic inflammation in biopsy specimens with serum isoform [-2]proPSA (p2PSA), %p2PSA, and prostate health index in men with a total prostate-specific antigen of 4-10 ng/ml and normal digital rectal examination. Urology 2014; 83: 606-12.
[24] De Luca S, Passera R, Bollito E, Manfredi M, Scarpa RM, Sottile A, Randone DF, Porpiglia F. Comparison of prostate cancer gene 3 score, prostate health index and percentage free prostate-specific antigen for differentiating histological inflammation from prostate cancer and other non-neoplastic alterations of the

prostate at initial biopsy. Anticancer Res 2014; 34: 7159-65.
[25] Okada K, Kojima M, Naya Y, Kamoi K, Yokoyama K, Takamatsu T, Miki T. Correlation of histological inflammation in needle biopsy specimens with serum prostate- specific antigen levels in men with negative biopsy for prostate cancer. Urology 2000; 55: 892-8.
[26] Auprich M, Haese A, Walz J, Pummer K, de la Taille A, Graefen M, de Reijke T, Fisch M, Kil P, Gontero P, Irani J, Chun FK. External validation of urinary PCA3-based nomograms to individually predict prostate biopsy outcome. Eur Urol 2010; 58: 727-32.
[27] Schalken JA, Hessels D, Verhaegh G. New targets for therapy in prostate cancer: differential display code 3 (DD3(PCA3)), a highly prostate cancer-specific gene. Urology 2003; 625 Suppl 1: 34-43.
[28] Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ, van Balken B, de Reijke T, Fisch M, Kil P, Gontero P, Irani J, Chun FK. DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. Eur Urol 2003; 44: 8-15; discussion 15-6.
[29] Vlaeminck-Guillem V, Bandel M, Cottancin M, Rodriguez-Lafrasse C, Bohbot JM, Sednaoui P. Chronic prostatitis does not influence urinary PCA3 score. Prostate 2012; 72: 549-54.
[30] Tallon L, Luangphakdy D, Ruffion A, Colombel M, Devonec M, Champetier D, Paparel P, Decaussin-Petrucci M, Perrin P, Vlaeminck-Guillem V. Comparative evaluation of urinary PCA3 and TMPRSS2: ERG scores and serum PHI in predicting prostate cancer aggressiveness. Int J Mol Sci 2014; 15: 13299-316.
[31] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC; STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for Reporting of Diagnostic Accuracy. Clin Chem 2003; 49: 1-6.