The Ability of Prostate Health Index (PHI) to Predict Gleason Score in Patients With Prostate Cancer and Discriminate Patients Between Gleason Score 6 and Gleason Score Higher Than 6—A Study on 320 Patients After Radical Prostatectomy

Olga Dolejsova, MD[1], Radek Kucera, PhD[2] , Radka Fuchsova, MD[2],
Ondrej Topolcan, prof., MD, PhD[2], Hana Svobodova, MD[1],
Ondrej Hes, prof., MD, PhD[3], Viktor Eret, MD, PhD[1],
Ladislav Pecen, PhD[2], and Milan Hora, prof., MD, PhD[1]

Abstract

Aim: The purpose of this study was to investigate the Prostate Health Index as a marker for tumor aggressiveness in prostate biopsy and the optimization of indication for treatment options. **Methods:** Our cohort consisted of 320 patients indicated for radical prostatectomy with preoperative measurements of total prostate-specific antigen, free prostate-specific antigen, [-2]proPSA, calculated %freePSA, and Prostate Health Index. The Gleason score was determined during biopsy and after radical prostatectomy. Using the Gleason score, we divided the group of patients into the 2 subgroups: Gleason score ≤6 and Gleason score >6. This division was performed according to the biopsy Gleason score and according to the postoperative Gleason score. We compared total prostate-specific antigen, [-2]proPSA, %freePSA, and Prostate Health Index in the subgroups Gleason score ≤6 and Gleason score >6 after biopsy and the definitive score. **Results:** On evaluation of the subgroups created by Gleason score ≤6 and Gleason score >6, we observed agreement between biopsy Gleason score and definitive Gleason score in only 45.3% of cases. Of the calculated biopsy, Gleason score ≤6 and Gleason score >6 subgroups, [-2]proPSA, and Prostate Health Index ($P = .0003$ and $P = .0005$) were statistically significant. Of the definitive Gleason score ≤6 and Gleason score >6 subgroups, Prostate Health Index, [-2]proPSA, %freePSA, and PSA ($P < .0001$, $P < .0001$, $P = .0003$, and $P = .0043$) were statistically significant. The best area under the curve value (0.7496) was achieved by Prostate Health Index when the subgroups were established according to the postoperative Gleason score. **Conclusion:** Prostate Health Index is the best of the tested markers for the categorization of Gleason score 6 tumors and for facilitating the management of patients with prostate cancer. Prostate Health Index can be a helpful marker for indication of active surveillance or radical prostatectomy. Prostate health index can also simplify the decision of whether to perform nerve-sparing radical prostatectomy.

Keywords

prostate health index, prostate-specific antigen, prostate cancer, Gleason score, prostate biopsy, radical prostatectomy

[1] Department of Urology, University Hospital and Faculty of Medicine in Pilsen, Pilsen, Czech Republic
[2] Department of Immunochemistry, University Hospital and Faculty of Medicine in Pilsen, Pilsen, Czech Republic
[3] Department of Pathology, University Hospital and Faculty of Medicine in Pilsen, Pilsen, Czech Republic

Corresponding Author:
Radek Kucera, PhD, Department of Immunochemistry, University Hospital in Pilsen, Dr E. Benese 13, 305 99 Pilsen, Czech Republic.
Email: kucerar@fnplzen.cz

Introduction

The total level of prostate-specific antigen (tPSA) has long been used as a tumor marker for prostate cancer (PC). Total PSA has a limited sensitivity and specificity for PC detection. Its low specificity led to an excessive number of prostate biopsies and unnecessarily high levels of treatment, while its low sensitivity meant a decrease in detection of low-grade PC.[1,2] Especially, at low values, the specificity and sensitivity of tPSA is not sufficient to discriminate patients with aggressive cancers and the others. The introduction of the commercially available [-2]proPSA assay and especially the combined formula called the Prostate Health Index (PHI) in 2010 led to improved clinical PC detection.[3] Nowadays, PHI is Food and Drug Administration approved for using only in the prebiopsy time, but we also focused on the possibility of using it as a tool for better management in patients who undergo radical prostatectomy (RP).

Based on biopsies, the grading system of the Gleason score (GS) has been used since the 1960s as one of the main tools for PC cell assessment. The GS scale can range from 1 to 10. In 2016, the International Society of Urological Pathology (ISUP) revised the PC grading system. Gleason score 6 was included as ISUP grade 1, whereas GS7 is now newly classified as ISUP grade 2 for (3+4), GS7 (4+3) as ISUP grade 3, GS8 as ISUP grade 4, and GS 9-10 as ISUP grade 5.[4,5] The GS is one of the main factors taken into consideration together with the PSA level and imaging techniques when determining a treatment plan. The most sensitive group of patients is that with the GS ≤6. The introduction of another reliable tool which could be taken into consideration for PC aggressiveness assessment would be extremely useful.

One of the largest projects in recent times has been the Multicentric European Study (PROMETHEUS), which confirmed that PHI is one of the strongest predictors of PC which correlates with biopsy GS.[6] The aim of this study was to investigate the PHI as a marker for tumor aggressiveness in prostate biopsy and the optimization of correct indications for treatment options. We focused especially on GS ≤6, which is now considered to be a very-low-risk tumor and in some studies is not even counted as an actual tumor.[7,8]

Materials and Methods

The study was conducted between July 2013 and June 2016. A total of 320 cases were enrolled in this prospective study. The basic characteristics of patient group are summarized in Table 1.

Patients with the biopsy and following RP were included in the study. Nowadays, the indication criteria for the biopsy in our hospital are the following: prostate nodule in transrectal prostate examination, PSA higher than 20 μg/L, and PHI higher than 40. Magnetic resonance imaging is done before each biopsy. Patients who were not able to undergo RP were excluded from this study. The next exclusion criteria were the presence of dutasteride treatment or prior series of biopsy.

All patients underwent a transrectal ultrasound prostate biopsy, and the biopsy GS was specified. Twelve core biopsies were used in all cases. A laparoscopic RP was then performed by our institution and a definitive GS was established using a whole-mount section procedure by an experienced genitourinary pathologist.[9] According to the GS, we divided the group of patients into the 2 subgroups: GS6 and GS>6. This division was made twice: according to the biopsy GS and according to the postoperative (definitive) GS. We compared total PSA, [-2]proPSA, %freePSA, and PHI in the GS6 and GS>6 subgroups created for both biopsy and definitive scores. Blood samples were collected before any kind of treatment or diagnostic prostate procedures were performed. We didn't repeat the total PSA, [-2]proPSA, and %freePSA measurement and PHI calculation before prostatectomy, just compared the PHI to bioptic and definitive GS. Peripheral blood was drawn using VACUETTE Z Serum Sep tubes (Greiner Bio-One, Kremsmünster, Austria) and allowed to clot. Serum was separated within 3 hours of blood collection and analyzed. Total PSA, free PSA (fPSA), and [-2]proPSA were assayed using the ACCESS chemiluminescent kits (Beckman Coulter, Brea, California). The percentage of fPSA and the PHI were calculated using the formulas:

$$\%\text{freePSA} = (\text{fPSA/tPSA}) \times 100 \text{ and}$$

$$\text{PHI} = (-2\text{proPSA/fPSA}) \times \sqrt{\text{tPSA}}.$$

The SAS 9.2 (Statistical Analysis Software release 9.2; SAS Institute Inc, Carry, North Carolina) was used for all statistical analyses. A summary of statistical findings such as median, lower and upper quartile, and minimum and maximum is presented. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) calculated. Cutoff, specificity, sensitivity, positive predictive value (PV+), negative predictive value (PV−), and relative risk for PHI were calculated. The Wilcoxon test was used to compare distributions of values between the groups of patients, and *P* value <.05

Table 1. Basic Characteristics of Patient Group.

Patients		
Male	320 (100%)	
Age		
Median	65 years	
Average	67 years	
Min-Max	45-75 years	
Pathologic stage		
pT		
1c	1 (0.3%)	
2a	47 (14.7%)	
2b	4 (1.2%)	
2c	184 (57.5%)	
3a	47 (14.7%)	
3b	33 (10.4%)	
4	4 (1.2%)	
Biomarker values	Median (Min-Max)	
PSA (μg/L)	8.06 (1.01-55.42)	
%freePSA (%)	10.75 (3.04-32.96)	
proPSA (pg/mL)	18.00 (4.00-304.00)	
PHI (without units)	57.32 (17.04-292.74)	
Gleason Score		
GS	Biopsy Gleason Score	Definitive Gleason Score
GS6	198 (61.9%)	95 (29.7%)
GS7 (3+4)	75 (23.4%)	113 (35.3%)
GS7 (4+3)	18 (5.6%)	58 (18.1%)
GS8	22 (6.9%)	37 (11.6%)
GS9	6 (1.9%)	15 (4.7%)
GS10	1 (0.3%)	2 (0.6%)

Abbreviations: GS, Gleason score; PHI, Prostate Health Index; PSA, prostate-specific antigen.

indicated the statistical significance. The AUC were compared by the nonparametric approach of DeLong *et al* as implemented in SAS proc LOGISTIC as ROCCONTRAST Statement.[10] The study was approved by the local ethical committee on May 3, 2012. Patients signed an informed consent before enrollment into the study.

Results

In our cohort of 320 patients, we observed a different distribution of patients between GS6 and GS>6 when we divided them according to the biopsy or the postoperative histology (Tables 2 and 3). The distribution according to the biopsy was GS6/GS>6 = 198/122, while the postoperative histology showed GS6/GS>6 = 95/225. The same GS was assigned in only 145 (45%) cases. From 198 patients with bioptic GS6 (ISUP grade 1), 112 (57%) had definitive GS>6 (ISUP grade 2 and higher). On the other hand, from 95 patients with definitive GS6 (ISUP grade 1), 9 (10%) patients had a biopsy GS>6 (ISUP grade 2 and higher).

When we evaluated the biomarkers used in this study, [-2]proPSA and PHI ($P = .0003$ and $P = .0005$; Table 2) were found to be statistically significant for distinguishing the biopsy GS6 and GS>6 subgroups. In the distinguishing of definitive GS6 and GS>6 subgroups, PHI, [-2]proPSA, %freePSA, and PSA ($P < .0001$, $P < .0001$, $P = .0003$, and $P = .0043$; Table 3) were statistically significant. We performed ROC analysis and calculated AUC. The ROC curves of the biopsy
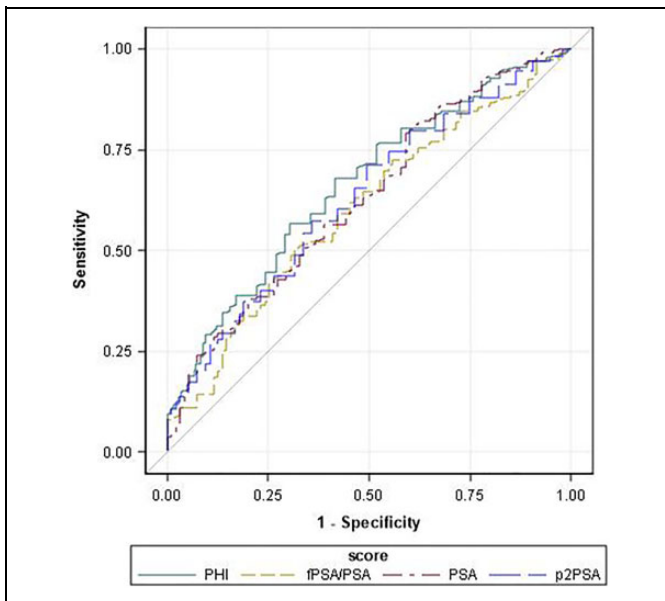
Table 2. Data According to the Biopsy Gleason Score (GS6 vs GS>6).[a]

Biopsy Group	N	Biomarker	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	P Value
GS6	198	PSA	7.74	1.01	55.42	5.89	11.98	.2696
		%freePSA	10.56	3.04	25.45	7.97	14.11	.4360
		proPSA	16.00	4.00	304.00	11.00	23.00	.0003
		PHI	54.34	17.04	292.74	40.71	71.49	.0005
GS>6	122	PSA	8.33	2.07	46.97	6.26	13.58	.2696
		%freePSA	11.25	3.78	32.96	8.31	15.04	.4360
		proPSA	20.00	5.00	129.00	14.00	31.00	.0003
		PHI	63.05	23.85	239.82	48.87	88.03	.0005

Abbreviations: GS, Gleason score; PHI, Prostate Health Index; PSA, prostate-specific antigen.
[a]PSA (μg/L), %freePSA (%), proPSA (pg/mL), PHI (without units).

Table 3. Data According to the Definitive Gleason Score After Radical Prostatectomy (GS6 vs GS>6).[a]

Definitive Group	N	Biomarker	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	P Value
GS6	95	PSA	7.16	1.01	26.46	5.28	9.70	.0003
		%freePSA	12.26	5.26	32.96	8.99	15.71	.0043
		proPSA	14.00	4.00	44.00	10.00	21.00	<.0001
		PHI	43.24	17.04	103.79	35.61	59.45	<.0001
GS>6	225	PSA	8.51	2.72	55.42	6.30	13.42	.0003
		%freePSA	10.06	3.04	26.98	7.58	13.86	.0043
		proPSA	19.00	5.00	304.00	13.00	28.00	<.0001
		PHI	64.28	22.04	292.74	49.45	82.76	<.0001

Abbreviations: GS, Gleason score; PHI, Prostate Health Index; PSA, prostate-specific antigen.
[a]PSA (μg/L), %freePSA (%), proPSA (pg/mL), PHI (without units).

Figure 1. Receiver operating characteristic curves according to the biopsy Gleason score (GS6 vs GS>6). GS indicates Gleason score.
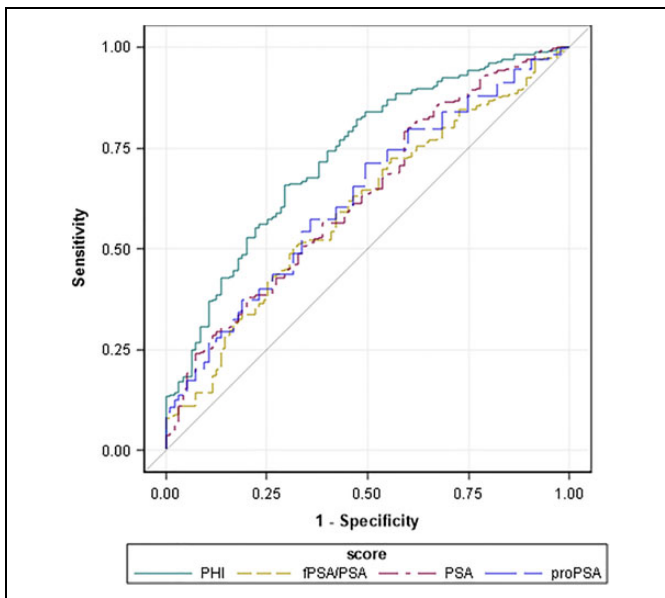

Figure 2. Receiver operating characteristic curves for the definitive Gleason score after radical prostatectomy (GS6 vs GS>6). GS indicates Gleason score.

subgroups are shown in Figure 1. The ROC curves of the definitive subgroups are shown in Figure 2. The best AUC values were achieved by the PHI when the subgroups were established according to the postoperative GS (AUC = 0.7496). The AUC values are summarized in Table 4 including *P* values of the AUC comparison between PHI and other parameters. In the biopsy GS group, *P* values were not significant. In the definitive GS group, the comparison between AUC of PHI versus PSA and PHI versus %freePSA showed statistically significant results (*P* = .0069 and *P* = .0008). Table 5 showed cutoff PHI

based on the postoperative GS. Cutoff PHI = 34 has 95% sensitivity and almost 89% PV−. Cutoff PHI = 38 has 90% sensitivity and almost 84% PV−.

Discussion

It is currently well established that no single biomarker in isolation has the perfect performance characteristics necessary for the detection and risk stratification of PC. The PHI seems to be a simple and inexpensive test for a multivariant approach to PC screening and management. The PHI improves prediction of PC at initial and extended biopsy stages and might distinguish PC from chronic prostatitis while improving prediction of insignificant PC. It can also predict recurrence of the disease after RP.[11]

Sanda and colleagues evaluated PHI in a group of 658 men with PC. The authors reported that PHI improved the prediction of high-grade PC in a group with the range of PSA from 4 to 10 ng/mL. The PHI correlated significantly with the bioptic GS.[12] Lazzeri and collaborators found, in the Multicentric European Study (PROMETHEUS), that [−2]proPSA, a splice variant isoform of tPSA, and its derivatives, %[−2]proPSA and PHI, were significant independent predictors of PC in a high-risk population in men with a positive family history of PC. Other authors reported finding that [-2]proPSA and PHI show a connection with the biopsy GS.[13] Our findings are in accordance with this study. On distinguishing the biopsy GS6 and GS>6 subgroups, [-2]proPSA and PHI (*P* = .0003 and *P* = .0005) were found to be statistically significant (Table 2).

According to the meta-analysis by Wang *et al*, PHI detects prostate carcinoma with a GS ≥ 7 very precisely with an AUC value of 0.90.[14] Our findings are in accordance with the results of this meta-analysis. We chose to separate our group to GS6 and GS>6 because this cutoff leads to treatment decision from active surveillance to RP. Despite we targeted GS6 instead of GS$\geq$7, our results were very similar. The best AUC value and ROC curve were achieved by PHI when the subgroups were established according to the postoperative GS (AUC = 0.7496; Table 4, Figure 2). When comparing the AUC values achieved in discrimination according to the biopsy GS group, we see that addition of the next diagnostic parameters to the tPSA does not statistically significantly increase the differential diagnostic efficiency even we could see some signal that PHI is the best parameter. On the contrary, in discrimination according to the definitive GS group, we can clearly see that the addition of [-2]proPSA and afterward calculation of PHI increase statistically significantly the differential diagnostic ability in distinguishing GS6 and higher than GS6 tumors compared to tPSA and %freePSA (Table 4).

Biopsy has an important place in the guidelines on the diagnosis and staging of PC. The diagnosis of PC depends on histopathological confirmation.[15] However, our data show a very high inaccuracy of prostate biopsy in a comparison between biopsy and definitive GSs. The same GS was assigned in only 145 (45%) cases. It should be noted that there is nearly a 50% chance of distinguishing a higher risk tumor from a low-risk

Table 4. Area Under the Curve According to the Biopsy Gleason Score (GS6 vs GS>6) and Definitive Gleason Score After Radical Prostatectomy (GS6 vs GS>6).

Biopsy Gleason Score			Definitive Gleason Score		
Biomarker	AUC (95% CI)	P Value Versus PHI	Biomarker	AUC, (95% CI)	P Value Versus PHI
PHI	0.6230 (0.5596-0.6865)	NA	PHI	0.7496 (0.6895-0.8096)	NA
proPSA	0.6178 (0.5538-0.6818)	0.8488	proPSA	0.6456 (0.5806-0.7106)	.0630
PSA	0.5368 (0.4705-0.6031)	0.1007	PSA	0.6291 (0.5726-0.6856)	.0069
%freePSA	0.5260 (0.4601-0.5919)	0.0873	%freePSA	0.6018 (0.5349-0.6686)	.0008

Abbreviations: AUC, area under the curve; GS, Gleason score; NA, not applicable; PHI, Prostate Health Index; PSA, prostate-specific antigen.

Table 5. Cutoff PHI Based on the Postoperative Gleason Score (GS6 vs GS>6).

Cutoff PHI	Specificity (%)	Sensitivity (%)	PV+ (%)	PV− (%)	RR
34.36	21.05	95.11	39.85	88.67	3.51
38.46	32.63	90.67	47.69	83.77	2.93

Abbreviations: GS, Gleason score; PHI, Prostate Health Index; PV+, positive predictive value; PV−, negative predictive value; RR, relative risk.

tumor when using only the results of a biopsy. Risk stratification is actually the most important factor taken into consideration when a treatment strategy is being prepared. With the use of our results, we can determine with a much higher probability whether a biopsy GS6 tumor really is in fact a GS6 and can be classified as a low-risk tumor. This classification is crucial for a treatment strategy. A low-risk tumor diagnosis more often allows for the recommendation, for example, of active surveillance instead of a radical surgery procedure.

Currently, active surveillance is an option for low-risk groups of patients. However, selection criteria are not yet fully established, except for the GS which should be GS6 or lower.[16-20] The European Association of Urology (EAU) guidelines in this matter are discussed below. These days, other parameters are studied in great detail to help doctors identify low-risk patients with a higher certainty. Certain recent data show that PSA isoforms, the prostate cancer antigen 3 gene (PCA3) test, transmembrane protease, and certain genomic tests of the prostatic tissue look like promising tools.[20-22] In a recent systematic review on PC biomarkers,[23] PCA3 test has by itself no prognostic value and prognostic value of PHI has been evaluated with the highest level of evidence. In accordance with this review, we showed that PHI can also improve the identification of patients with GS6 tumor.

Another very current question in the treatment of patients with PC is that of which kind of surgery should be used. Doctors decide between RP and nerve-sparing RP. Nerve-sparing surgery during RP has an unquestionable effect on erectile function and postoperative urinary continence.[16] According to the EAU guidelines, nerve-sparing RP can be safely performed in men with low-risk PC. Patients with a high risk of extracapsular disease (category T3, according to the TNM classification of malignant tumors) and with a GS7 or higher in biopsy are clearly contraindicated. Nowadays, nomograms are used for predicting extracapsular extension, and multiparametric magnetic resonance is also helpful in distinguishing low- and high-risk patients.[18] In our study, we tried to establish the cutoff value for PHI based on the postoperative GS to distinguish GS6 and GS>6 tumors. High-grade tumors (GS>6) are contraindicated for active surveillance and nerve-sparing surgery. Therefore, we have to be sure that below the cutoff will be with the highest probability of patients without the presence of the GS>6 tumors. We chose PHI values 34 and 38, respectively (Table 5). When tumor is classified as GS6 and the PHI value is below 34 (38), there is very high probability that really low-grade tumor is present. Our findings are very similar to the National Comprehensive Cancer Network (NCCN) recommendations. The NCCN Guidelines version 1.2018 for Prostate Cancer Early Detection state that men with PSA >3 µg/L and PHI >35 indicate a higher probability of high-grade PC.[24]

According to the results of our study, using PHI in connection with GS, we can better separate which tumors are really GS6 in definitive histology, so we can offer more securely active surveillance or nerve-sparing procedure for the right patient.

Conclusions

Our results demonstrate the high inaccuracy of prostate biopsy in a comparison between biopsy and definitive GS. We tested the panel of the current tumor markers to their ability to distinguish between GS6 and higher than GS6 tumors. The PHI was the best of the tested markers. The PHI can better distinguish GS6 tumors and facilitate decisions for the correct management of patients with PC. The PHI can be a helpful marker for the indication of active surveillance or radical treatment of PC. In cases of active treatment, PHI can also simplify the decision-making process for nerve-sparing RP. Despite the positive experience with the PHI, the searching of the new biomarkers for prostate tumor aggressiveness assessment is still necessary.

Declaration of Conflicting Interests

Funding

ORCID iD

Radek Kucera, PhD http://orcid.org/0000-0002-2739-2302

References

1. Fuchsova R, Topolcan O, Windrichova J, et al. PHI in the early detection of prostate cancer. *Anticancer Res*. 2015;35(9):4855-4857.
2. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med*. 2017;377(2):132-142. doi:10.1056/NEJMoa1615869.
3. Maxeiner A, Kilic E, Matalon J, et al. The prostate health index PHI predicts oncological outcome and biochemical recurrence after radical prostatectomy—analysis in 437 patients. *Oncotarget*. 2017;8(45):79279-79288. doi:10.18632/oncotarget.17476. [Epub ahead of print].
4. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol*. 2016;40(2):244-252. doi:10.1097/PAS.0000000000000530.
5. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol*. 2016;69(3):428-435.
6. Fossati N, Buffi NM, Haese A, et al. Preoperative prostate-specific antigen isoform p2PSA and its derivatives, %p2PSA and prostate health index, predict pathologic outcomes in patients undergoing radical prostatectomy for prostate cancer: results from a Multicentric European Prospective Study. *Eur Urol*. 2016;68(1):132-138.
7. Kulac I, Haffner MC, Yegnasubramanian S, Epstein JI, De Marzo AM. Should Gleason 6 be labeled as cancer? *Curr Opin Urol*. 2015;25(3):238-245.
8. Carter HB, Partin AW, Walsh PC, et al. Gleason Score 6 adenocarcinoma: should it be labeled as cancer? *J Clin Oncol*. 2012;30(35):4294-4296.
9. Pivovarcikova K, Branzovsky J, Bauleth K, et al. Radical prostatectomy—analysis of 191 cases examined using whole-mount section method. *Czech Urol*. 2014;18(1):26-32.
10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.
11. Lepor A, Catalona WJ, Loeb S. The prostate health index: its utility in prostate cancer detection. *Urol Clin North Am*. 2016;43(1):1-6. doi:10.1016/j.ucl.2015.08.001.
12. Sanda M, Wei J, Broyles D, et al. Evaluation of the Prostate Health Index (PHI) for improving prostate cancer detection and identification of clinically significant prostate cancer in the 4 to 10 ng/mL PSA range. In: *Proceedings of American Urological Association Annual Meeting San Diego, Rev Urol*. 2013;15(2).
13. Lazzeri M, Haese A, Abrate A, 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(3):313-321.
14. Wang W, Wang M, Wang L, et al. Diagnostic ability of %p2PSA and prostate health index for aggressive prostate cancer: a meta-analysis. *Sci Rep*. 2014;4:5012.
15. Heidenreich A, Aus G, Bolla M, Joniau S, et al. European Association of Urology. EAU guidelines on prostate cancer. *Eur Urol*. 2008;53(1):68-80.
16. Toren P, Alibhai SM, Matthew A, et al. The effect of nerve-sparing surgery on patient-reported continence post-radical prostatectomy. *Can Urol Assoc J*. 2009;3(6):465-470.
17. Friedersdorff F, Groß B, Maxeiner A, et al. Does the prostate health index depend on tumor volume?—a study on 196 patients after radical prostatectomy. *Int J Mol Sci*. 2017;18(3):488.
18. Beauval JB, Cabarrou B, Gandaglia G, et al. External validation of a nomogram for identification of pathologically favorable disease in intermediate risk prostate cancer patients. *Prostate*. 2017;77(8):928-933. doi:10.1002/pros.23348.
19. Gandaglia G, Schiffmann J, Schlomm T, et al. Identification of pathologically favorable disease in intermediate-risk prostate cancer patients: implications for active surveillance candidates. *Prostate*. 2015;75(13):1484-1491. doi:10.1002/pros.23040.
20. Guazzoni G, Lazzeri M, Nava L, et al. Preoperative prostate-specific antigen isoform p2PSA and its derivatives, %p2PSA and prostate health index, predict pathologic outcomes in patients undergoing radical prostatectomy for prostate cancer. *Eur Urol*. 2012;61(3):455-466.
21. Scattoni V, Lazzeri M, Lughezzani G, et al. Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. *J Urol*. 2013;190(2):496-501.
22. Hendriks RJ, van Oort IM, Schalken JA. Blood-based and urinary prostate cancer biomarkers: a review and comparison of novel biomarkers for detection and treatment decisions. *Prostate Cancer Prostatic Dis*. 2017;20(1):12-19.
23. Lamy PJ, Allory Y, Gauchez AS, et al. Prognostic biomarkers used for localised prostate cancer management: a systematic review [published online ahead of print]. *Eur Urol Focus*. 2017;7(17).
24. National Comprehensive Cancer Network Guidelines Version 1. 2018, Prostate Cancer Early Detection, *National Comprehensive Cancer Network*. 2018. https://www.nccn.org/.