Оригінальні дослідження. Урологія та гінекологія

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PCA3 score prognostic value for identifying postoperative ISUP grades 4–5 in localized peripheral zone prostate cancer with a posterior tumor growth dominant pattern

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At present, the identification of high-risk groups of localized prostate cancer (PCa) is highly relevant. Our previous research demonstrated that prostate cancer antigen 3 (PCA3) scores depend on the tumor zone of origin (TZO) and the tumor growth dominant pattern (TGDP).

The aim: to assess the prognostic value of PCA3 score for identifying postoperative 4–5 grade group according to the International Society of Urological Pathology 2014 (ISUP) classification in patients with localized peripheral zone prostate cancer with posterior TGDP (pPZ-PCa).

Materials and methods. PCA3 scores and correlations were assessed and compared in different PCa patient groups and subgroups based on TZO, TGDP, and ISUP grade. Receiver operating characteristic curve (ROC) analysis was used to evaluate the diagnostic significance of the model and determine the optimal PCA3 score cutoff for identifying ISUP 4–5.

Results. The PCA3 scores showed a significant ($p < 0.01$) positive correlation ($r = 0.71$) with ISUP grade in pPZ-PCa. PCA3 scores differed significantly ($p < 0.01$) between ISUP 1–3 and 4–5 pPZ-PCa subgroups. ROC analysis demonstrated excellent performance with an AUC of 0.98 (95% CI: 0.95–0.99) for identifying ISUP 4–5 pPZ-PCa.

Conclusions. PCA3 scores demonstrated prognostic value for identifying postoperative ISUP 4–5 in pPZ-PCa.

The study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee for all participants. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: PCA3, prostate cancer, peripheral zone prostate cancer, prostate cancer tumor dominant growth pattern, ISUP.

Прогностична цінність рівнів РСА3 для ідентифікації післяопераційного класу ISUP 4–5 у пацієнтів із локалізованим раком периферичної зони передміхурової залози із заднім домінантним патерном росту пухлини

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На сьогодні ідентифікація груп високого ризику локалізованого раку передміхурової залози (РСа) зберігає свою високу актуальність. Результати наших попередніх досліджень засвідчили залежність рівнів Антигену раку простати 3 (РСА3) від зони походження пухлини (TZO) та характеру домінантного росту пухлини (TGDP).

Мета: оцінити прогностичне значення рівнів РСА3 для ідентифікації післяопераційного класу 4–5 згідно з класифікацією Міжнародного товариства урологічної патології 2014 (ISUP) у пацієнтів із локалізованим раком периферичної зони передміхурової залози із заднім домінантним патерном росту пухлини (pPZ-PCa).

Матеріали та методи. Рівні РСА3 та кореляції оцінено та порівняно в різних групах та підгрупах пацієнтів із PCa залежно від TZO, TGDP та класу ISUP. Для оцінки діагностичної значущості отриманої моделі та вибору оптимальних критеріїв рівнів РСА3 для ідентифікації ISUP 4–5 pPZ-PCa використано аналіз кривої характеристики оператора приймача (ROC).

Результати. Констатовано вірогідну (p<0,01) позитивну кореляцію (r=0,71) між рівнем РСА3 та класом ISUP у pPZ-PCa. Показники РСА3 достовірно відрізнялися (p<0,01) між 1–3 та у 4–5 ISUP pPZ-PCa. ROC-аналіз засвідчив відмінну модель AUC=0,98 (95% CI: 0,95–0,99) для визначення ISUP 4–5 pPZ-PCa.

Висновки. Рівні РСА3 продемонстрували діагностичну цінність для ідентифікації післяопераційного класу ISUP 4–5 у pPZ-PCa.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної у роботі установи. На проведення досліджень отримано інформовану згоду пацієнтів.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: РСА3, рак передміхурової залози, рак периферичної зони передміхурової залози, домінантний тип росту раку передміхурової залози, ISUP 4–5.

Introduction

Prostate cancer (PCa) is a significant health concern, particularly in developed countries [3,9,18,25]. Radical prostatectomy (RP) offers good oncological and functional outcomes for localized PCa [10,11,17]. Identifying high-risk patients is crucial, as they have a significantly higher risk of PCa-specific mortality [5]. Biomarkers have shown promise in this regard [1,12,23]. Prostate cancer antigen 3 (PCA3) is a well-known urinary biomarker for PCa [14], but its use remains debated due to heterogeneous research results [1,2,3,6,12–15,19,24]. We hypothesize that this heterogeneity may be related to study designs that do not differentiate between tumor zone origin (TZO) and dominant growth pattern (TGDP). Our previous work [21] demonstrated differences in PCA3 urine levels based on TZO and TGDP, prompting further investigation into PCA3's utility.

The aim: to assess the prognostic value of the PCA3 score for identifying postoperative 4–5 grade according to the International Society of Urological Pathology 2014 (ISUP) classification in patients with localized peripheral zone prostate cancer with posterior TGDP (pPZ-PCa).

Materials and methods of the study

The study included 130 patients with localized PCa categorized by TZO and TGDP: anterior peripheral zone (aPZ-PCa, n=31), posterior peripheral zone (pPZ-PCa, n=80), and transition zone (TZ-PCa, n=19), who underwent extraperitoneoscopic RP (ERP). TZO and TGDP were identified using MRI and confirmed by postoperative pathological examination according to the ISUP grading system. pPZ-PCa patients were further divided into ISUP grade 1–3 (n=51) and 4–5 (n=29) subgroups. Control groups consisted of 40 healthy volunteers (HV), 40 patients with benign prostatic hyperplasia (BPH), and 40 with chronic prostatitis (CP). All 250 participants were free of severe systemic disease and had not used finasteride. Inclusion criteria for the PCa group were: urine PCA3 level, total PSA, prostate MRI, ISUP grade, and postoperative pathological confirmation of TZO and TGDP. Inclusion criteria for control groups were: urine PCA3 level, total PSA, prostate MRI, verified CP or BPH diagnosis, and no evidence of PCa during 2 years of follow-up.

Numerical data are presented as median (Me), lower quartile (LQ), and upper quartile (UQ). The Mann–Whitney U test was used to compare quantitative variables between independent groups, where p represents the probability of rejecting the null hypothesis. The Spearman rank correlation was used to assess relationships between variables. ROC analysis was performed to evaluate the diagnostic performance of the model and determine the optimal PCA3 score cutoff. AUC values were interpreted as: 0.9–1.0 – excellent, 0.8–0.9 – very good, 0.7–0.8 – good, 0.6–0.7 – average, and 0.5–0.6 – unsatisfactory. Statistical significance for AUC=0.5 was set at $p<0.001$. Statistical significance for AUC=0.5 was set at $p<0.001$. AUC values are reported with 95% confidence intervals (CI). The optimal cutoff (OC) was chosen to maximize the balance between sensitivity (Se) and specificity (Sp), positive predictive value (+PV), negative predictive value (-PV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR) were calculated. MedCalc and STATISTICA 10 were used for statistical analysis.

The study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee for all participants. The informed consent of the patient was obtained for conducting the studies.

Results of the study

MRI identification of TZO and TGDP showed high concordance with postoperative pathological findings. General data for the control groups (CP, BPH, and HV) are presented in Table 1.

Table 1
General data of the control groups

Parameters, Me (LQ; UQ)	HV n=40	CP n=40	BPH n=40	Total n=120
Age, years	64 (58; 72.5)	63 (55.5; 72.5)	68.5 (61.5; 74.5)	65 (58.5; 73.5)
PSA, ng/ml	5.7 (4.5; 6.8)	8.3 (6; 9.95)	9.9 (7.4; 13.8)	7.3 (5.4; 9.9)
PCA3	7.95 (4.7; 12.7)	17.7 (12.7; 24.9)	27.2 (12.3; 40.3)	15 (8.5; 25.7)

Table 2
General data of the PCa patients

Parameters, Me (LQ; UQ)	PCa n=130	aPCa n=50	aPZ-PCa n=31	pPZ-PCa n=80
Age, years	66 (63; 71)	67.5 (64; 72)	66 (64; 69)	65 (62; 70.5)
T-stage	2c (2a; 3b)	2c (2a; 3b)	2c (2a; 3b)	2c (2a; 3b)
ISUP	3 (2; 4)	3 (2; 3)	3 (2; 3)	3 (2; 4)
PIRADS	4 (4; 5)	4 (4; 5)	4 (4; 5)	4 (4; 5)
PSA, ng/ml	11.1 (7.1; 17.6)	12 (7; 19.6)	16 (9.8; 24.8)	11.1 (7.1; 16.8)
PCA3	57.4 (29.2; 73.2)	28 (14.5; 51.1)	40.5 (14.9; 57.6)	68.3 (55.9; 89.8)

Higher PCA3 scores, as well as PSA levels, were observed in the CP and BPH groups, consistent with previous reports [1,4,21]. No statistically significant difference was observed in participants' ages. General data for the PCa patients are presented in Table 2.

No statistically significant differences were found in age, T-stage, or PIRADS scores between the aPCa, aPZ-PCa, and pPZ-PCa groups. PSA levels differed significantly only between aPZ-PCa and pPZ-PCa, $U[80;31]=822$, $p<0.01$. PCA3 scores were significantly higher in pPZ-PCa compared to aPCa, $U[80;50]=498$, $p<0.01$. Moreover, a statistically significant difference was present between pPZ-PCa and aPZ-PCa $U[80;31]=390$, $p<0.01$. Lower PCA3 scores in the aPCa group may be influenced by the presence of TZ-PCa. The PCA3 test methodology may also contribute to the observed differences between the aPZ- and pPZ-PCa groups.

Spearman's rank correlation analysis in the pPZ-PCa group demonstrated a strong, statistically significant ($p<0.01$) positive correlation between PCA3 scores and ISUP grade ($r=0.71$) (Fig. 1).
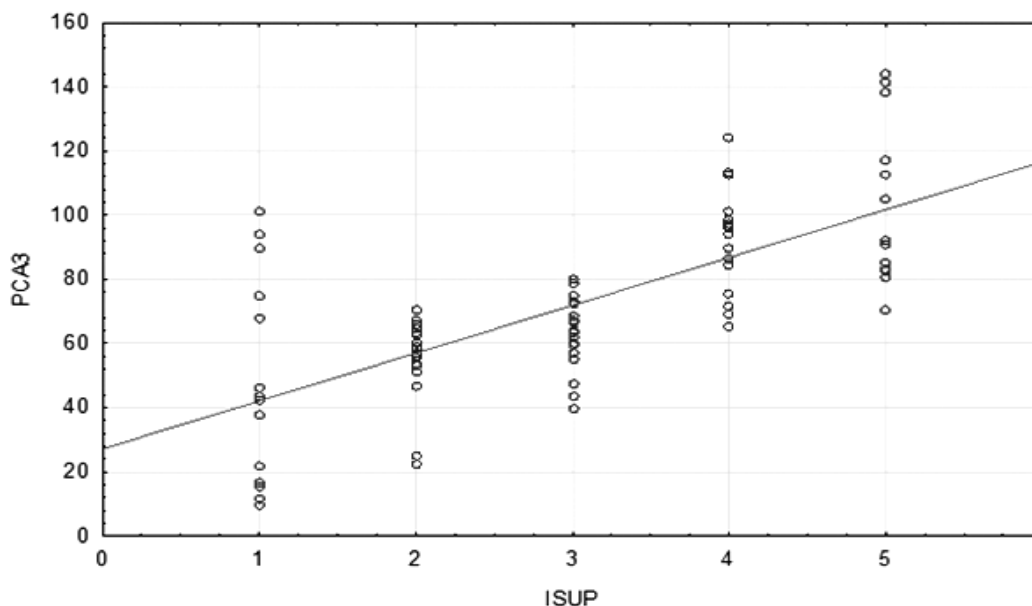
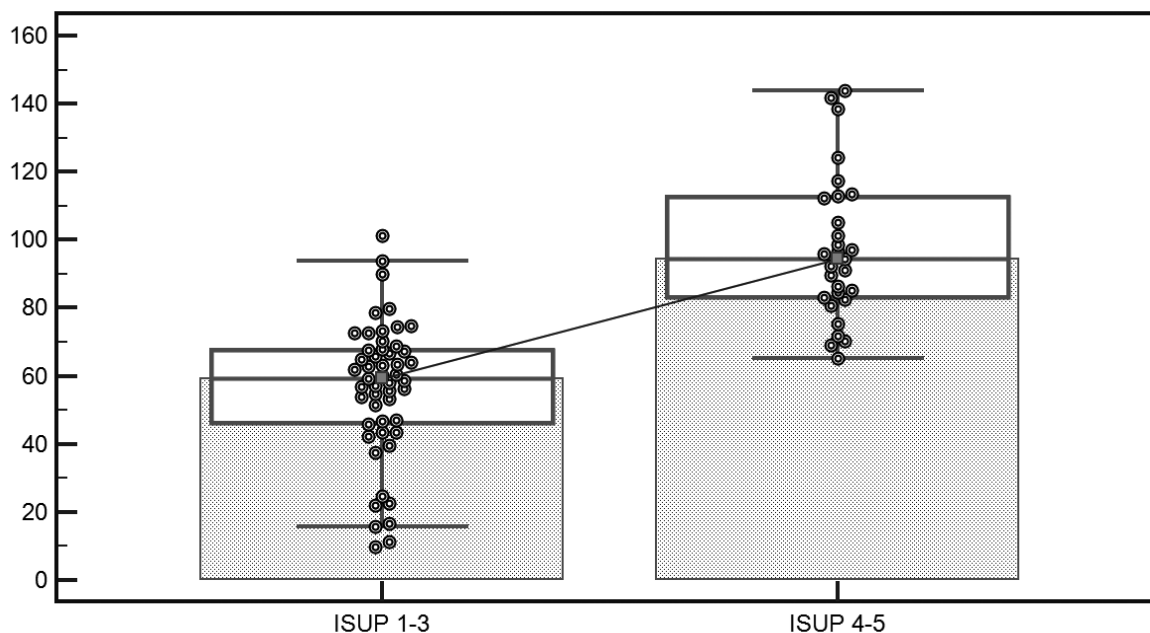**Fig. 1.** Correlation between PCA3 score and ISUP grade in pPZ-PCa (p<0.01)

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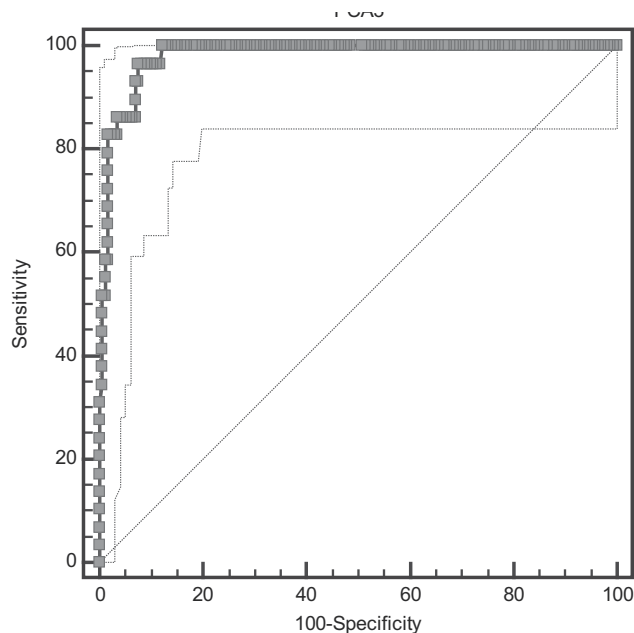**Fig. 2.** PCA3 scores in different ISUP subgroups pPZ-PCa, (p<0.01)

Fig. 3. PCA3 scores ROC analysis for ISUP 4–5 subgroup pPZ-PCa (p<0.01)

These findings prompted further subgroup analysis of ISUP 1–3 vs. 4–5 within the pPZ-PCa group. General data for these subgroups are presented in Table 3.

The subgroups were similar in PSA, PIRADS, and T-stage, with no statistically significant differences observed in the Mann–Whitney U test. There was a trend toward higher T-stage in the ISUP 4–5 subgroup, but this difference was not statistically significant. The age difference between subgroups was a limitation of this analysis (p<0.01). The Mann-Whitney U test revealed a statistically significant difference in PCA3 scores between the subgroups. The median PCA3 score in the ISUP 4–5 subgroup was 37.1% higher than in the ISUP 1–3 subgroup, U[51;29]=83.5, p<0.01 (Fig. 2).

These results led to a ROC analysis to evaluate the AUC model and identify an OC for ISUP 4–5 pPZ-PCa. The AUC model demonstrated excellent performance in identifying ISUP 4–5 pPZ-PCa (Table 4).

The AUC for ISUP 4–5 pPZ-PCa was 0.98 (95% CI: 0.95–0.99, p<0.001). The PCA3 OC was >65.4, with

Table 3

ISUP subgroups comparison in pPZ-PCa

Parameters Me (LQ; UQ)	pPZ-PCa		U	p
	1–3 ISUP, n=51	4–5 ISUP, n=29		
Age, years	64 (61; 67)	68 (64; 72)	451	<0.01
pT-stage	2c (2a; 2c)	2c (2c; 3b)	580.5	0.11
PIRADS	4 (4; 5)	4 (4; 5)	579.5	0.11
PSA, ng/ml	10.7 (7.1; 14.1)	12.9 (7.9; 19.9)	586.5	0.13
PCA3	59.4 (45.9; 67.8)	94.4 (83.2; 112.4)	83.5	<0.01

Table 4

PCA3 scores ROC analysis for ISUP 4-5 subgroup pPZ-PCa

AUC 95% CI	p	OC	Se 95% CI	Sp 95% CI	+LR 95% CI	-LR 95% CI	+PV 95% CI	-PV 95% CI
0.98 [0.95-0.99]	<0.001	>65.4	96.6 [82.2-99.9]	88.3 (82.5-92.7)	8.3 [5.4-12.5]	0.04 [0.01-0.3]	58.3 [43-72.5]	99.3 [96.4-100]

96.6% sensitivity (95% CI: 82.2–99.9) and 88.3% specificity (95% CI: 82.5–92.7) (Fig. 3).

The +LR was 8.3 (95% CI: 5.4–12.5), and the -LR was 0.04 (95% CI: 0.01–0.3). The -PV was very high at 99.3% (95% CI: 96.4–100), indicating that a negative PCA3 test almost certainly rules out ISUP 4–5 pPZ-PCa. However, the +PV was lower at 58.3% (95% CI: 43–72.5), suggesting the need for further investigation to confirm a positive result. These values may be useful as a prognostic tool for identifying postoperative ISUP 4–5 in patients with pPZ-PCa.

Discussion

Identifying and treating localized PCa remains a significant challenge. PCA3 is a widely used biomarker in PCa patients, primarily for identifying candidates for primary or repeat prostate biopsy [1,2,6,14,19,20]. While PCA3 scores have shown a significant association with biopsy Gleason score [4,13], its use is debated due to heterogeneous research results [1–3,6,12–15,19,24].

One potential reason for this heterogeneity is the specificity of the PCA3 test. Urine collection after DRE can increase the validity of results from 80% to over 98% [16]. In our opinion, this may affect PCA3 scores in PCa patients with anterior TGDP. Especially in the TZ-PCa cases, which have anterior TGDP and distinct features compared to PZ-PCa [7,8,22,23,26].

J.A. Sinnott et al. (2015) found that zonal differences in normal tissue persist in tumor tissue and that these differences are associated with Gleason score, emphasizing the importance of considering TZO in biomarker research [23]. Moreover, Fine et al. [7] recommend to separate aPZ and pPZ-PCa in studies.

Another factor influencing PCA3 scores may be the increase in ISUP grade after surgery compared to preoperative biopsy results. A recent study by Liss et al. [15] demonstrated a 67% ISUP upgrade after surgery. We hypothesize these factors may contribute to the controversial diagnostic utility of the PCA3 test that was described previously [2,6,13,14].

Our results suggest the potential use of the PCA3 urine test for identifying ISUP 4–5 pPZ-PCa. The high -PV is particularly noteworthy, making PCA3 a valuable tool for ruling out 4–5 ISUP pPZ-PCa. However, the moderate +PV highlights the need for confirmatory testing following a positive PCA3 result. The narrower confidence intervals around the AUC for 4–5 ISUP pPZ-PCa suggest a more precise estimate of the test's discriminative ability for this outcome. We believe that differentiating between TZO and TGDP may improve the diagnostic accuracy of the PCA3 urine test. This reinforces the idea that PCA3 is a useful marker for more aggressive prostate cancer, at least in pPZ-PCa. Considering the findings of Falagario et al. [5], this may be beneficial for patients considering RP.

The small sample size and the age imbalance between ISUP 1–3 and 4–5 subgroups are limitations of this study. The study's findings need to be validated in larger, multi-center studies with more diverse patient populations. This will ensure the generalizability of the results.

Conclusion

PCA3 scores showed prognostic value for identification postoperative ISUP 4–5 pPZ-PCa. This finding underscores the potential of PCA3 as a tool for refining risk stratification and guiding personalized management strategies in this specific subgroup of PCa patients. Our findings emphasize the importance of considering TZO and TGDP when evaluating the clinical utility of PCA3. Moving forward, there is a need for further investigations to validate our findings in larger, multi-center studies with more diverse patient populations.

No conflict of interests was declared by the authors.

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