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The influence of tumor zone origin and growth dominant pattern in prostate cancer patients on urine PCA3 levels in the context of ISUP postoperative class

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Abstract

Introduction. Prostate cancer (PCa) is a common and relevant disease, especially in developed countries (8, 22). Radical prostatectomy (RP) remains the gold standard for the treatment of localized PCa (9, 10, 16). However, research findings often show conflicting results regarding the potential dividends in patients that choose this option. A recent meta-analysis demonstrated that the greatest benefits were observed in the high-risk group of PCa patients (4). Therefore, the identification of this contingent of patients is highly relevant. Biomarkers remain promising in this context (1, 12). In particular, PCA3, the use of which is actively discussed, taking into account the heterogeneity of the research results (5, 11. 13, 18). In our opinion, this can be associated with the studies designs.
Objectives. In this work, we tried to evaluate the relationship between the PCa patients urine PCA3 levels and the tumor dominant growth pattern (TDGP) according to the tumor zone origin (TZO) in the context of the postoperative ISUP class (ISUP-GG). Materials and methods. The inclusion criteria were the presence of results: urine PCA3, total PSA, prostate MRI, ISUP-GG. The study included 130 participants, that were divided into subgroups depending on the TZO and TDGP: aPCa (anterior), aPZ-PCa (anterior, peripheral zone) and pPZ-PCa (posterior, peripheral zone). Results. The zones of origin of tumors according to the division into subgroups determined on the basis of MRI were confirmed by the results of patho-histological conclusion. A statistically significant difference between the study subgroups was observed only in PCA3 levels. The PSA level was significantly different only between the aPZ-PCa and pPZ-PCa groups. Based on the results of Spearman's rank correlation analysis, a statistically significant positive relationship between the level of PCA3 and ISUP-GG was obtained in the pPZ-PCa group. Conclusions. It is probably worth taking into account the TZO and TDGP of PCa when PCA3 urine levels is interpreted. Further research is needed.

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Introduction

Prostate cancer (PCa) is a common and urgent problem, especially in developed countries [1, 8, 17, 22]. RP remains the gold standard for the localized PCa treatment [2, 16, 10]. However, research findings often show conflicting results regarding the likely dividends of performing RP. So, a recent MET-analysis demonstrated the greatest benefits in a high-risk group of PCa patients who underwent RP [3, 4]. Therefore, it is highly relevant to identify this contingent of patients. Biomarkers remain promising in this context [1, 5,12]. In particular, PCA3, which diagnostic usefulness is actively discussed [6-10, 11, 18, 13, 5[. Such heterogeneity results, in our opinion, are related to the research design, in which no subgroups according to tumor zonal origin (TZO) and growth dominant pattern (TGDP) PCa were made.

Objectives

In this work, we tried to evaluate the relationship between the PCa patients' urine PCA3 levels and the tumor dominant growth pattern (TDGP) according to the tumor zone origin (TZO) in the context of the postoperative ISUP class (ISUP-GG).

Materials and Methods

The study included 130 participants with verified PCa who underwent extraperitoneoscopic RP. The inclusion criteria were: presence of the results of following tests - urine PCA3 level, total PSA, prostate MRI, ISUP-GG. The study did not include patients who had severe sub-compensated conditions due to chronic and systemic diseases, taking finasteride or surgical interventions due to prostate diseases. The general patient's data are shown in Table 1. All patients were divided into subgroups depending on the TZO and TGDP PCa on anterior peripheral zone (aPZ-PCa), posterior peripheral zone (pPZ-PCa) and transition zone (TZ-PCa). The latter were identified with MRI (Figure 1, 2, 3) and confirmed by the postoperative patho-morphological conclusion. The Mann-Whitney U Test was used for analyze the differences between the studied parameters. To determine the relationships between the analyzed parameters, the non-parametric method of Spearman rank order correlations was used. MedCalc's free statistical calculators was used for analysis [21].

Table 1. The general clinical patient's data

Me (Q1; Q3)	**PCa (n=130)**
Age, years	66 (63; 71)
T-stage	2 (2; 3)
ISUP-G	3 (2; 4)
PIRADS	4 (4; 5)
PSA, ng/ml	11,1 (7,05; 17,6)
PCA3	57,4 (29,2; 73,2)

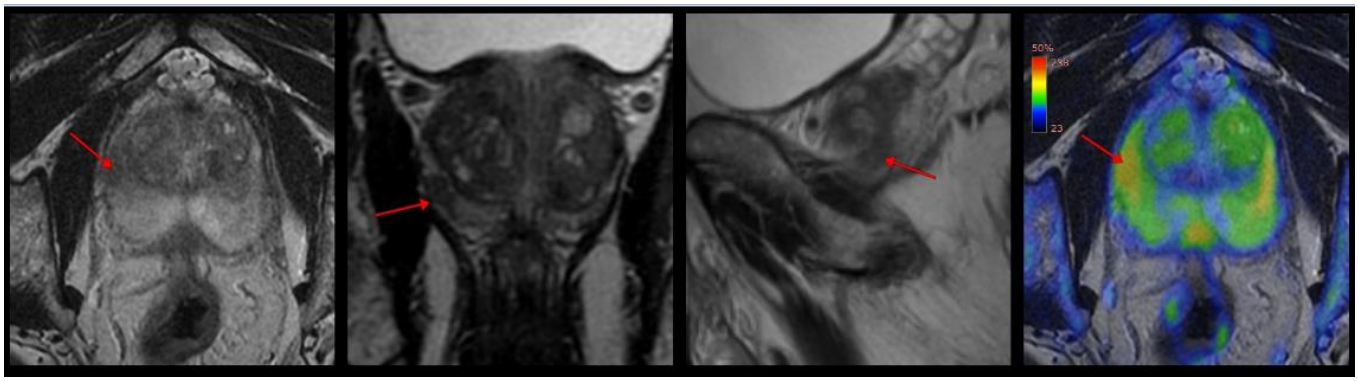

Figure 1. MRI of the anterior peripheral zone PCa

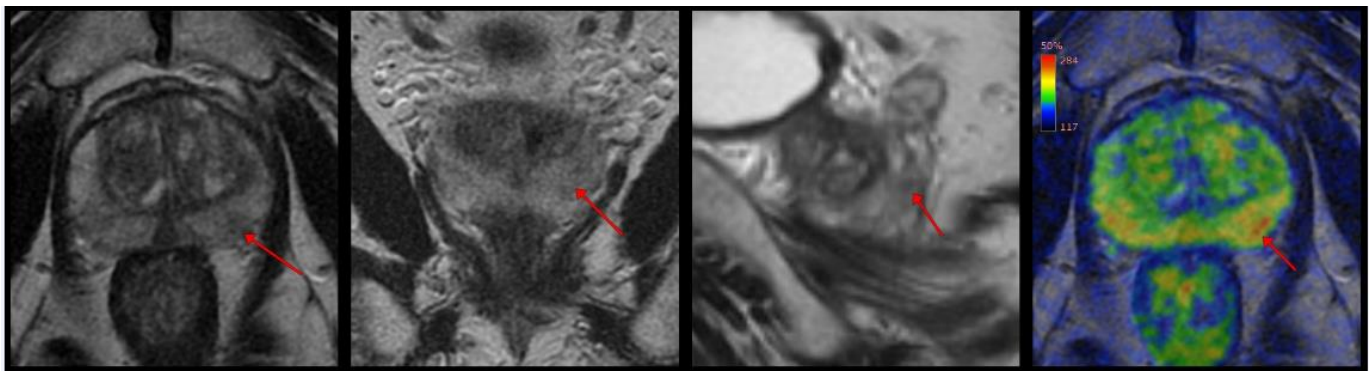

Figure 2. MRI of the posterior peripheral zone PCa

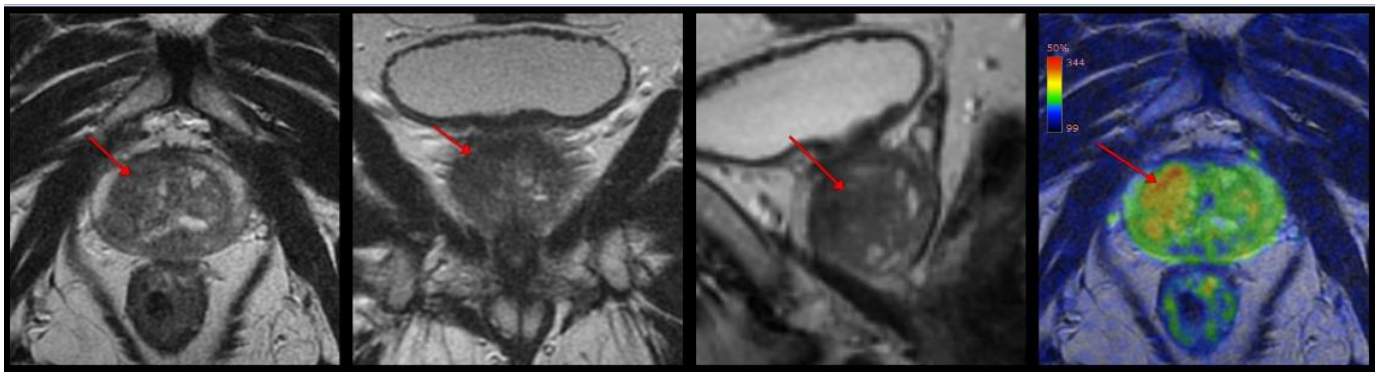

Figure 3. MRI of the tranzitional zone PCa

Results

MRI identification of the TZO and GDP demonstrated no differences with the results of postoperative patho-morphological conclusion. The levels of research parameters among subgroups of aPCa, aPZ-PCa and pPZ-PCa, as well as statistically significant differences are shown in Table 2. As can be seen from the results, statistically significant differences were observed only in the PCA3 levels (Figure 4, 5). Statistically significant differences in subgroups were observed only in the PCA3 levels. As showed in Figure 1 and 2, only pPZ-PCa showed statistically reliable ($p<0,001$) differences with aPCa and aPZ-PCa. According to the Spearman's rank correlation results, statistically significant ($p < 0.05$) strong positive relationship (r - 0.71) between the PCA3 level and ISUP-G was obtained in pPZ-PCa group (Table 3).

Discussion

PCA3 is well known biomarker, which routinely used for PCa diagnosis [5, 1]. Although PCA3 has demonstrated its high specificity for PCa, as well as significant association between the PCA3 urine levels and Gleason score [3], the diagnostic utility of the latter remains controversial [2, 13, 11]. We share the colleague's opinion that such results may be related to the studies design which did not assess PCA3 levels according to the TZO and TGDP [6, 20]. There are proven differences between TZ and PZ PCa [23, 19]. Moreover, the AUA recommends additional division of PZ-PCa into anterior and posterior TDGP [7]. In our opinion, additional factor for a such heterogeneous results may be the specificity of urine collection for PCA3 analysis [15]. Probably, PCA3 urine levels in patients with anterior GDP PCa may be doubtful, due to their location and specificity of the TZ-PCa. Therefore, in our study, we tried to evaluate the dependence of PCA3 urine levels in PCa patients depending on TZO and TGDP. All statistical analysis in this work was based on postoperative pathology-morphological conclusion. Since the ISUP-G often differs from biopsy result. So, a recent study [14] found a 67% increase in the ISUP class compared to preoperative results. Which, on the one hand, is an advantage of this research design, and on the other, a certain limitation. The strong correlation bond presence between the postoperative ISUP-GG and patients PCA3 levels of pPZ-PCa allows us to consider wider PCA3 test use in this group. The main limitation, in our opinion, is the low number of the T1 stage patients.

Table 2. The levels of research parameters among subgroups of aPCa, aPZ-PCa and pPZ-PCa.

Me (Q1; Q3)	aPCa (n=50)	aPZ-PCa (n=31)	pPZ-PCa (n=80)	U (50; 80)	Z (50; 80)	U (31; 80)	Z (31; 80)
Age	67,5 (64; 72)	66 (64; 69)	65 (62; 70,5)	1665,0	-1,60074	1195,0	-0,29249
ISUP-G	3 (2; 3)	3 (2; 3)	3 (2; 4)	1708,5	1,39257	1099,0	0,92349
PSA	12 (7; 19,6)	16 (9,8; 24,8)	11,1 (7; 16,8)	1824,0	-0,83985	822,0	-2,74418*
PIRADS	4 (4; 5)	4 (4; 5)	4 (4; 5)	1840,5	0,76089	1201,50	0,24977
PCA3	28 (14,5; 51,1)	40,5 (14,9; 57,6)	68,3 (55,9; 89,8)	498,0	7,18539*	390,0	5,58366*

* Correlations significant at p <0.05

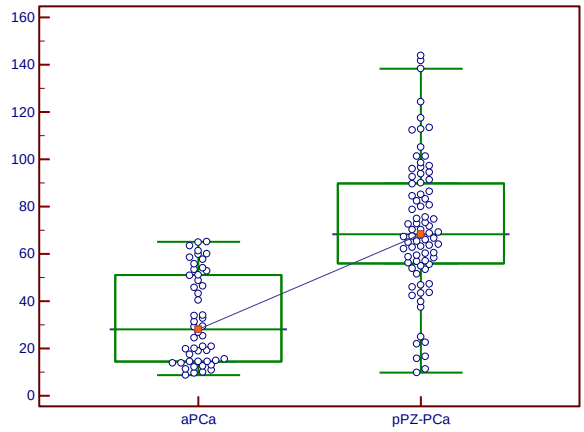

Figure 4. Difference in PCA3 levels between aPCa and pPZ-PCa group (p<0.001).

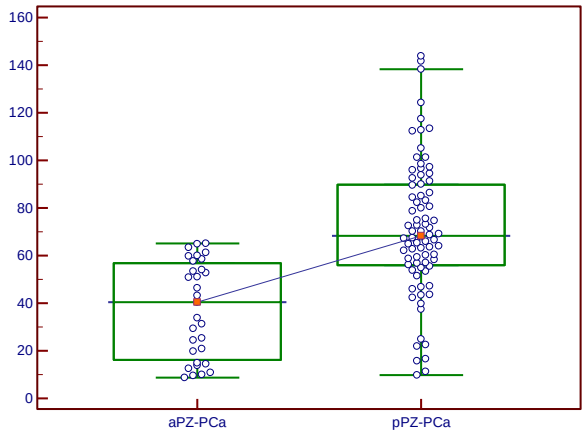

Figure 5. Difference in PCA3 levels between aPZ-PCa and pPZ-PCa group (p<0.001).

Table 3. Spearman Rank Order Correlations in pPZ-PCa patients.

Parameter	Age	ISUP	PSA	PIRADS	PCA3
Age	1,0	0,4*	0,16	0,07	0,24*
ISUP	0,4*	1,0	0,24*	0,32*	0,71*
PSA	0,16	0,24*	1,0	0,05	0,15
PIRADS	0,07	0,32*	0,05	1,0	0,19
PCA3	0,24*	0,71*	0,15	0,19	1,0

*Correlations significant at p <0,05

Conclusion

It is essential to consider the zone of prostate cancer growth when interpreting PCA3 urine levels. Additional research is warranted to further investigate this relationship.

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