Original Contribution

PSA AND ITS RELATION TO THE DEGREE OF DIFFERENTIATION OF PROSTATE CANCER

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ABSTRACT
INTRODUCTION: Prostate-specific antigen (PSA) and Gleason score are two of the most important characteristics of prostate cancer. Their complex and ambiguous connection prompted us to examine it in a series of patients operated in our clinic. For the analysis we used the ISUP – grade system according to which the Gleason scores are summed up in 5 grades. METHODS: 195 patients were available for analysis. All patients underwent a transrectal biopsy of the prostate with subsequent radical prostatectomy (either open retropubic or laparoscopic) in the clinic of Urology, MHAT "Saint Anna" – Varna. For PSA, we used the value distribution in three categories: below 10, between 10 and 20 and above 20 ng/ml. RESULTS There was a statistically significant difference in ISUP grades between the PSA categories. This applied to both post-biopsy and postoperative ISUP-grades. The ISUP - grade in the group with PSA < 10 was statistically significantly lower than in the group with PSA >20. DISCUSSION/CONCLUSION: PSA and ISUP grades are related in both analyses, when the ISUP grade is determined after the biopsy and after the radical prostatectomy. This connection is found in spite of possible external influences (presence of benign prostatic hyperplasia together with the tumor).

Key words Gleason score, ISUP grades, radical prostatectomy, prostate biopsy, BPH

INTRODUCTION
Prostate-specific antigen (PSA) and Gleason score (GS) are two of the most important characteristics of prostate cancer (PCa). PSA is produced by the prostatic glands (including the non-tumorous ones) and is elevated in case of PCa. The degree of elevation is to a certain extent connected with the degree of differentiation of the tumor (which is described by the GS). Yet there are many cases when PSA is elevated in patients with big (but benign) prostates. Also sometimes, when PCa is poorly differentiated, PSA can be fairly normal. So, the connection between PSA and GS is not always straightforward which prompted us to examine it in a series of patients operated in our clinic. In the analysis we used the ISUP grade system

according to which GSs are summed up in 5 grades. Also, we used the ISUP grades from the pathological reports after the prostate biopsy and after the radical prostatectomy (RP) since they differ at times.

MATERIALS AND METHODS
195 patients were available for analysis. All patients underwent a transrectal biopsy of the prostate - in some cases, however, the biopsy was performed in another medical institution, not in MHAT "St. Anna" in Varna. All patients included in the study underwent radical prostatectomy at our clinic - either open retropubic or laparoscopic.

The data were analyzed with IBM SPSS version 23. Nonparametric tests (Mann-Whitney U and Kruskal-Wallis H) were used because PSA data do not follow normal distribution and ISUP data are ranked. For PSA, the distribution of values in three groups was used – below 10, between 10 and 20 and above 20 ng/ml.

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RESULTS

1. PSA and postbiopsy ISUP grade

The total number of patients with available PSA and postbiopsy ISUP grade was 195. The preoperative characteristics of the patients are shown on **Table 1.**

Table 1. *Preoperative characteristics of the patients*

	PSA < 10 ng/ml	PSA 10 – 20 ng/ml	PSA > 20 ng/ml
Number of patients	73	79	43
Age years, mean	67.3	68.6	66.8
PSA ng/ml, mean	7.24	14.11	39.89
Prostate volume ml, mean	67.51	61.84	66.28
PSA density, mean	0.12	0.28	0.70
DRE – palpable node Patients/total patients (%)	13/73 (17.81%)	13/79 (16.46%)	8/43 (18.6%)

In the group with PSA<10, there were 73 (37,4%) patients with a mean value of ISUP 1,753 (SD = 1,09) and median 1 (IQR = 1 – 2); in the group with PSA between 10 and 20 there were 79 (40,5%) patients with a mean value of ISUP 2,38 (SD = 1,38) and median 2 (IQR = 1 – 4); in the group with PSA > 20 there were 43 (22,1%) patients with a mean value of ISUP 2,63 (SD = 1,36) and median 2 (IQR = 2 – 4).

2. PSA and postprostatectomy ISUP – grade

The total number of patients with available PSA and postprostatectomy ISUP grade was 191. The other postoperative pathological characteristics of the patients (excluding GS and ISUP - grade) are shown in **Table 2.**

Table 2. *Pathological characteristics of the patients (after radical prostatectomy)*

	PSA < 10 ng/ml	PSA 10 – 20 ng/ml	PSA > 20 ng/ml
Number of patients	69	79	43
Seminal vesicle invasion Patients/all patients (%)	6/69 (8.7%)	11/79 (13.9%)	15/43 (34.9%)
Positive lymph nodes Patients/all patients (%)	2/69 (2.9%)	3/79 (3.8%)	5/43 (11.6%)
Extracapsular extension Patients/all patients (%)	11/69 (15.9%)	26/79 (32.9%)	20/43 (46.5%)

In the group with PSA<10 there were 69 (36,1%) patients with a mean value of ISUP 1,942 (SD = 1,3) and median 1 (IQR = 1 – 2); in the group with PSA between 10 and 20 there were 79 (41,4%) patients with mean value of ISUP 2,29 (SD = 1,43) and median 2 (IQR = 1 – 4); in the group with PSA above 20 there were 43 (22,5%) patients with a mean value of ISUP 2,74 (SD = 1,54) and median 2 (IQR = 1 – 4). Mean values of ISUP - grades in the three PSA – categories are shown on **Figure 1.**
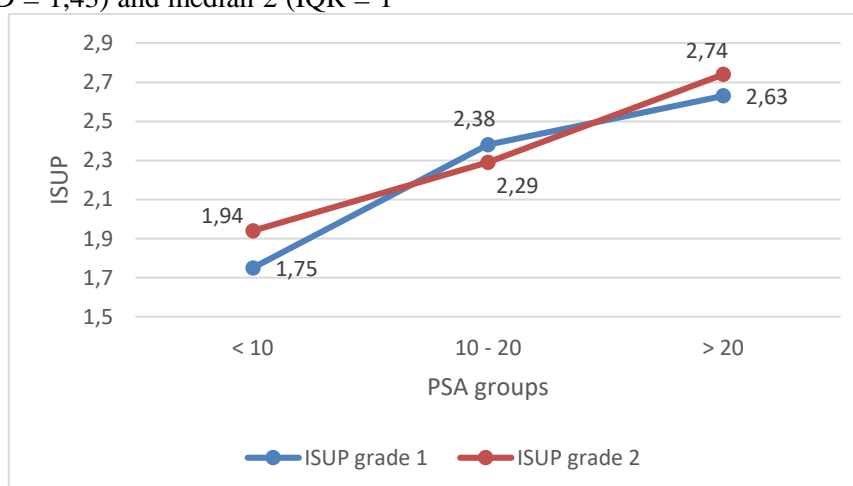
Figure 1. Mean values of ISUP - grades and the PSA – categories; ISUP grade 1 is after the biopsy, ISUP grade 2 is after the radical prostatectomy

There was a statistically significant difference in the ISUP grades between the PSA groups, both after biopsy (test Kruskal Wallis, X^2 = 15,628; p = ,000), and after RP (X^2 = 9,595; p = ,008). When comparing the ISUP grades between the pairs of the PSA groups, it was found that:

- ISUP grade in the group with PSA<10 was statistically significantly lower than the one in the group with PSA between 10 and 20 (test Mann-Whitney U; MWU = 1872,5; p = ,003)- this applied to the ISUP grade after the biopsy, but not to the ISUP grade after RP.
- ISUP grade in the group with PSA<10 was statistically significantly lower than the one in the group with PSA > 20-both for ISUP grade after the biopsy and after RP (test Mann-Whitney U, MWU = 864,000 p = ,000).
- ISUP grade in the group with PSA between 10 and 20 did not differ statistically significantly from those in the group with PSA>20, both for ISUP grade after the biopsy and after the RP (p > ,05).

DISCUSSIONS

PSA is a serine - protease [1] produced by the epithelial cells in the prostate. It is excreted in the semen and its function there is probably connected with coagulation (and subsequent liquefaction) of the semen. The quantity of PSA in blood is million times smaller than in semen – in blood no function is known. PSA is organ-specific but not tumor-specific [2] – it can be elevated in case of urethral instrumentation, infection, PCa and benign prostatic hyperplasia (BPH). The first two conditions can be ruled out relatively easy, but the interaction with BPH remains a problem.

The higher level of PSA is considered a sign of poorly differentiated PCa [3]. The European Association of Urology divides patients into 3 groups (low risk, intermediate and high risk for PSA recurrence) depending on the level of PSA (below 10, between 10 and 20 and above 20 ng/ml). The risk for PSA recurrence is estimated in patients treated with curative intent with either radiotherapy or RP [4, 5]. Still there are a lot of patients with high PSA and well-differentiated PCa, where the PSA elevation is due to another reason.

In our study we examined the connection between PSA and Gleason score – the latter determines the degree of differentiation of PCa. In this study we used the ISUP grades which combine some of the GS grades into 5 grades total. The ISUP grade in the group with PSA < 10 is statistically significantly lower than in the group with PSA > 20 - both for the ISUP grade determined from prostate biopsy and after surgery (radical prostatectomy). So, in spite of possible external influences (presence of BPH together with the tumor) there is a correlation between PSA and the differentiation of PCa.

ISUP stands for International Society of Urological Pathology, the organization responsible for the current recommendations for GS determination. Many patients with PCa have the GS determined twice – after the initial biopsy and after the RP (if they are treated operatively of course). A well-known fact is that the two GSs often do not coincide [6, 7]. That is why we examined the relationship between PSA and cancer differentiation by using both parameters – post-biopsy and post-operative ISUP grade. There were some differences: e.g. the ISUP value in the group with PSA < 10 is statistically significantly lower than that in the group with PSA between 10 and 20 - this applies to the ISUP grade after the biopsy, but not to the ISUP grade after the RP. But otherwise, both ISUP grades show a correlation with the PSA level.

The International Society of Urological Pathology grade system was introduced in 2014 and confirmed in 2019 [8. 9] but it is still not widely accepted in Bulgaria. That is why we used it in our study. The invention of the ISUP grades is actually a consequence of the difference between the two GSs (post-biopsy and post-operative) [10]. In the new grading system, the number of GS grades is reduced to 5. Thus, a discrepancy between the post-biopsy ISUP-grade and the post-operative one appears much more seldom.

The relationship between PSA and the pathological characteristics of PCa is not confined only to the ISUP – grades. The incidence of seminal vesicle invasion, positive lymph nodes and extracapsular extension of the tumor also increases with the rising of PSA **(Table 2).**

CONCLUSIONS

PSA and ISUP grade show a correlation. The highest value of the ISUP grade is in the group

of patients with PSA > 20, and the lowest - in the group of patients with PSA < 10 ng/ml. This applies for both ISUP grades - after the prostate biopsy and after the RP.

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