



Original Contribution

**FACTORS PREDICTING A POSSIBLE INCREASE OF GLEASON SCORE
AFTER RADICAL PROSTATECTOMY IN PATIENTS WITH
WELL-DIFFERENTIATED PROSTATE CANCER**

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ABSTRACT

Introduction The discrepancy between the Gleason score (GS) of the prostate biopsy and those after the radical prostatectomy (RP) is a well-known event. This is important for the patients because some of them, at least initially, prefer active surveillance, not active treatment.

Aim To investigate the factors which can predict a possible increase in GS after RP in patients with well-differentiated ($GS \leq 6$) prostate cancer (PCa).

Methods The patients are divided into three groups. Group 1-GS of the biopsy is equal to those of the RP. Group 2- GS of the biopsy increases after the RP. Group 3- GS of the biopsy decreases after the RP. The information was collected and analyzed using IBM SPSS version 23.

Results The patients available for analysis are 78- 32 patients in group 1, 34 patients in group 2, and 12 patients in group 3. A statistically significant difference in the prostate volumes and PSA density (PSAD) of the patients of the three groups is found.

Discussion According to literature data patients with well-differentiated PCa ($GS \leq 6$) are most likely to have their GS upgraded. That is why we studied several preoperative parameters (age, PSA, PSAD, prostate volume and presence of a palpable nodule in the prostate) in order to find a possible association with a GS-upgrade.

Conclusion Higher PSAD and lower prostate volume are associated with a possible increase in GS. PSA, age, and the presence of a palpable nodule do not demonstrate a difference between the three groups.

Keywords: Gleason score, Biopsy of prostate, Radical prostatectomy,

INTRODUCTION

The contemporary treatment of PCa is multimodal and encompasses different possibilities-ranging from active surveillance and watchful waiting to radical prostatectomy, radiotherapy and hormonal therapy. The main task of the urologist is to classify the PC into different risk groups in order to choose the most appropriate treatment- aggressive enough to eliminate the tumor but, on the other hand, with minimal side effects to the patient. Actually with the systems of tumor classification (including

TNM, Gleason score) we try to predict the future behavior of PCa.

The degree of differentiation of PCa is based on the histological (not cytological) assessment of the tumor according to the Gleason score grading system [1, 2]. But, unlike many other tumors, the grade of PCa is determined twice after the biopsy and after the RP. The discrepancy between the two GSs is a common and well-known event [3-10]. This is important for the patients because some of them, at least initially, prefer active surveillance, not active treatment. So, if the biopsy gives unrealistically low GS (well-differentiated tumor) this will lead to underestimation of the malignant potential of the

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PCa with a possible delay of the aggressive treatment which is necessary for this tumor. That is why we should know the factors which can predict a possible increase in GS after radical prostatectomy in patients with well-differentiated tumors (GS equal or less than 6) from the biopsy.

AIM

The research is based on the patients who has undergone radical prostatectomy in our hospital and presents our experience in the diagnosis and treatment of prostate cancer. We studied several preoperative parameters (age, PSA, PSAD, prostate volume and presence of a palpable nodule in the prostate) in order to find a possible association with a GS-upgrade.

MATERIALS AND METHODS

All the patients have PCa proven with systematic transrectal biopsy of the prostate, performed between 01Jan.2013 and 31May2020. The GS of the biopsy was collected. The patients underwent radical prostatectomy (either open or laparoscopic). The second GS (from the operation) was also collected and compared with the first one. The patients were divided into three groups. Group 1-GS of the biopsy was equal to those of the RP. Group 2- GS of the biopsy

increased after the RP. Group 3- GS of the biopsy decreased after the RP. The information was collected and analyzed using IBM SPSS version 23. Continuous variables with normal distribution are presented by average (mean) and standard deviation (SD). Variables without normal distribution and/or with extreme values are presented with median and interquartile ranges (IQR). The average (mean) of values with normal distribution is compared with ANOVA (for more than two samples). Post Hoc tests are used to compare the means of more than two normally-distributed variables. Non-parametric tests (Mann-Whitney U and Kruskal-Wallis H) are used to compare independent variables without normal distribution and/or category/rank variables. The frequencies of the category variables were compared with non-parametric tests (X² of Pearson).

RESULTS

78 patients with $GS \leq 6$ were identified. The average GS is 5,46 (SD = 1, 00); the median is 6 (IQR = 5 – 6). 32 patients (41%) are in group 1, 34 (43,6%) – in group 2 and 12 (15,4%) in group 3. The characteristics of the patients are shown in **Table 1**.

Table 1. Characteristics of the patients

		All	Group 1	Group 2	Group 3
Number of patients (%)		78	32 (41)	34 (43.6)	12(15.4)
Age(years)	average	66.3	65.6	66	69.5
Preoperative PSA(ng/ml)	average	12.94	13.98	12.76	9.75
Clinical stage (%)	T1c	66 (84.62)	29 (90.63)	26 (76.47)	11 (91.67)
	T2a	4 (5.13)	1 (3.12)	2 (5.88)	1 (8.33)
	T2b	8 (10.25)	2 (6.25)	6 (17.65)	0 (0)
	T2c	0 (0)	0 (0)	0 (0)	0 (0)
Extraprostatic extension (%)		12 (15.38)	4 (12.5)	8 (23.53)	0 (0)
Seminal vesical involvement (%)		6 (7.69)	1 (3.13)	5 (14.71)	0 (0)
Lymph node metastases (%)		2 (2.56)	0 (0)	2 (5.88)	0 (0)
Prostate volume (ml.)	average	68.29	73.51	57.38	83.675
PSA-density (ng/ml/ml)	average	0.25	0.27	0.27	0.11

a. Age

The age of the patients in group 1 ranges between 55 and 76 years with average age 65,6 (SD = 6,28) years; the age of the patients in group 2 ranges between 53 and 78 years with average age 66 (SD = 6,57) years; the age of the patients in group 3 ranges 53 and 78 years with average age 69,5 (SD = 7,21) years. No statistically significant difference in the age of the patients of the three groups was found. (ANOVA, $F = 1,648$; $p = ,199$).

b. PSA

PSA is known in 77 (96,3%) patients with $GS < 7$; 32 from group 1, 33 – from group 2 and 12 – from group 3. In group 1 PSA ranges between 3,09 and 67,87 with average value 13,98 (SD = 13,25); the median is 10 (IQR = 8,4 – 13,8). In group 2 PSA ranges between 4,57 and 30,99 with average value 12,76 (SD = 7,31); the median is 9,6 (IQR = 7,6 – 14,5). In group 3 PSA ranges between 0,9 and 20 with average value 11,24 (SD = 5,54); the median is 9,75 (IQR = 8,1 – 16). No statistically significant difference in the level of PSA in the three groups was found. (Kruskal Wallis test; $X^2 = ,012$; $p = ,994$). Also PSA was divided into three ranges - below 10, 10 – 20 and more than 20. Again no statistically significant

difference in the level of PSA of the patients of the three groups was found. (Kruskal Wallis test; $X^2 = ,943$; $p = ,624$, also $X^2 = 5,853$; $p = ,210$).

c. PSA Density-PSAD

PSAD is available for 63 patients (80,8% of all), 30 patients in group 1, 25 – group 2 and 8 – group 3. In group 1 PSAD ranges between 0,3 and 1,72 with average value 0,27 (SD = 0,367); the median is 0,13 (IQR = 0,1 – 0,34). In group 2 PSAD ranges between 0,06 and 0,81 with average value 0,27 (SD = 0,195); the median is 0,19 (IQR = 0,06 – 0,81). In group 3 PSAD ranges between 0,04 and 0,30 with average value 0,11 (SD = 0,08); the median is 0,095 (IQR = 0,07 – 0,012). A statistically significant difference in the level of PSAD of the patients of the three groups was found (Kruskal Wallis test; $X^2 = 10,656$; $p = ,005$). The difference is statistically significant between group 1 and 2 (MWU = 257,000; $p = ,046$) – PSAD is higher in group 2 compared with group 1. Also statistically significant is the difference in PSAD between group 1 and group 3 (MUW = 64,000; $p = ,045$) and group 2 and group 3 (MWU = 29,000; $p = ,002$). PSAD of the patients in group 3 is lower compared with group 1 and 2. The median values of PSAD are shown in **Figure 1**.

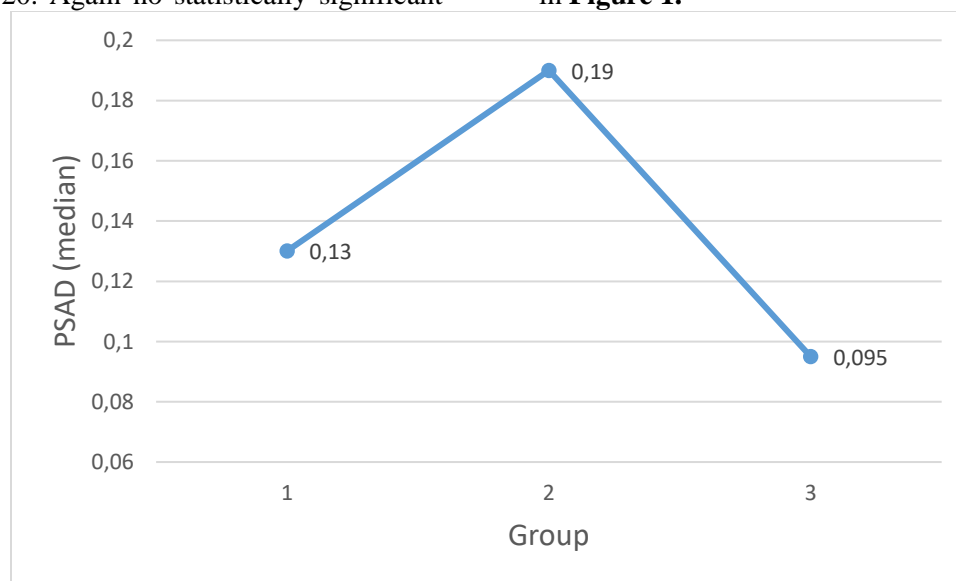


Figure 1. Median values of PSAD in the groups

If PSAD-values are divided into three ranges (below 0,1; 0,1 – 0,15 and more than 0,15) again a statistically significant difference in the level of PSAD of the patients of the three groups is found

($X^2 = 13,710$; $p = ,008$). The difference is found between group 1 and 2 (MWU = 244,5; $p = ,016$) and group 2 and 3 (MWU = 31,5; $p = ,003$).

PSAD of the patients in group 2 is higher compared with group 1 and 3.

d. Prostate volume

Information about the prostate volume (in milliliters) is available for 64 patients (80,8% of all) - 30 from group 1, 26 from group 2 and 8 from group 3. The prostate volume in group 1 ranges between 32,5 and 145,2 with average value 73,51 (SD = 30,135); the median is 85,72 (IQR = 42,3 – 88,5). The prostate volume in group 2 ranges between 21 and 181,1 with average value 57,38 (SD = 36,08); the median is 53,65 (IQR = 34,6 – 64,3). The prostate volume in group 3 ranges

between 22,6 and 164,8 with average value 83,675 (SD = 42,433); the median is 76,35 (IQR = 60,95 – 103,7). A statistically significant difference in the prostate volumes of the patients of the three groups is found (Kruskal Wallis test; $X^2 = 8,213$; $p = ,016$). The difference is statistically significant only between group 1 and group 2 (MWU = 229,000; $p = ,008$) - the prostate volume is smaller in group 2 compared with group 1. No other statistically significant differences are found. The median values of the prostate volume in the groups are shown in **Figure 2**.

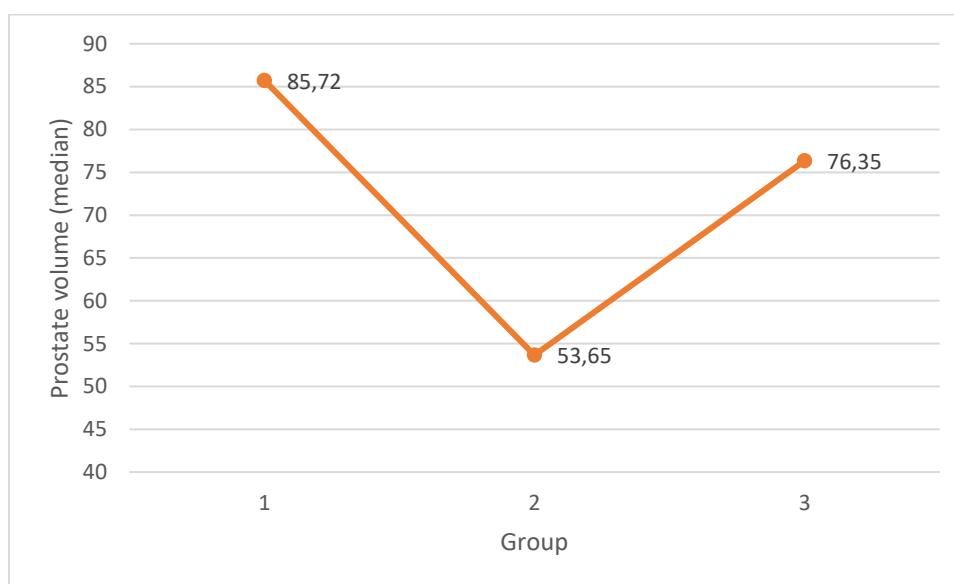


Figure 2. Median values of the prostate volume in the groups

If the values of the prostate volume are divided into three ranges (below 40; 40 – 80 and more than 80) again a statistically significant difference in the level of prostate volume of the patients of the three groups is found ($X^2 = 13,100$; $p = ,001$). The difference is again only between group 1 and group 2 (MWU = 190,000; $p = ,000$) - the prostate volume is smaller in group 2 compared with group 1.

e. Palpable nodule in the prostate (stage T2)

From 78 patients a nodule is palpated in 11 patients (14,1% of all) - 3 patients in group 1, 7 in group 2 and 1 -in group 3. Stage T1 are: 29 patients from group 1, 27 patients from group 2 and 11 patients from group 3. No statistically significant difference between the three groups is

found concerning the presence of a palpable node. ($X^2 = 2,101$; $p = ,350$).

DISCUSSION

In our research we analyzed patients with well-differentiated PCa ($GS \leq 6$) in order to identify possible factors that predict the increase in GS after RP (i.e. belonging of the patients to group 2). According to literature data, these patients are most likely to have their GS upgraded [11]. In addition, patients with well-differentiated PCa are sometimes referred to less urgent treatments (active surveillance) because of the presumed more benign nature of their tumor. Hence

the important practical significance of detecting factors, predicting the increase in GS.

The analyzed patients were divided into 3 groups with equal GS from the biopsy and the RP (group 1), with the upgrade (group 2) and downgrade (group 3) of the GS. This was done for a more complete analysis but actually, our main interest was focused on the differences between groups 1 and 2 - thus the relatively small number of patients in group 3 is of little significance.

We analyzed the following parameters:

a. Age - no statistically significant difference was found in the age of the patients in the three groups. Here, our results differ from the data published so far [12], according to which the advanced age predicts a possible increase in GS after the RP.

b. PSA - no statistically significant difference was found in the PSA values of the patients in the three groups. This result also differs from other publications [12 and 13], according to which the raise in PSA increases the risk of GS-upgrading after RP.

c. PSAD - A statistically significant difference was found in the PSAD of the patients in the three groups. PSAD was higher in the patients in the second group compared with the first group. PSAD in patients in the third group were lower than in patients in the first and second group. The result is consistent with the data from another study [14], which proves that elevated PSAD is an important prognostic sign for possible postoperative increase in GS. Moreover, this conclusion applies only to well-differentiated carcinomas, probably due to lower PSA production from low-grade PCa.

d. Prostate volume - There is a statistically significant difference in the values of prostate volume of patients in the three groups. The difference is statistically significant only between the first and second group - the values of prostate volume are lower in patients of the second group compared to those of the first group. This result is consistent with data from other studies [12, 15 and 16], which demonstrate that a small prostate is more likely to be associated with GS-upgrade after RP.

e. Palpation of a nodule in the prostate - after the introduction of PSA in practice the majority

of patients are in stage T1. However, some of them are in stage T2 - with a palpable nodule in the prostate. There is no statistically significant relationship between patients' distribution into the three groups and the presence of a prostate nodule. That is, the presence of a nodule in the prostate is not a likely sign of worse histology after RP. However, a probable reason for this result may be also the insufficient number of patients in stage T2 preoperatively.

Study limitations

Our study has several limitations. (1) The sample includes patients hospitalized in the urology clinic of St. Anna's University hospital in Varna, Bulgaria during the period January, 2013 and May, 2020 - thus the sample used was relatively small and it is not clear how representative of the general population is. (2) Our results should be interpreted as pertaining to the time period during which the survey was conducted.

CONCLUSION

From the analysis made so far we can draw the following conclusions: higher PSAD and lower prostate volume were associated with possible increase in GS. PSA, age and the presence of a palpable nodule do not demonstrate a difference between the three groups.

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