THE EFFECT OF THE GLEASON SCORE CHANGE ON BIOCHEMICAL PROGRESSION-FREE SURVIVAL

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ABSTRACT

INTRODUCTION: The degree of differentiation of prostate cancer is evaluated by the Gleason score (GS). Patients who undergo radical prostatectomy (RP) have their GS determined twice—first, during the biopsy, and second, after the RP. The two GSs often differ.

AIM: We have studied how the change of GS affects biochemical progression-free survival (BPFS) of the patients.

MATERIALS AND METHODS: 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. Pearson's chi square test, Mann-Whitney U test, and the Kaplan-Meier test were used to evaluate the difference in the BPFS in the three groups.

RESULTS: The patients available for analysis were 111—42 patients in Group 1, 40 patients in Group 2, and 29 patients in Group 3. A significantly better survival was proven for the patients in Group 1 compared with Groups 2 and 3.

DISCUSSION: Group 2 had the worst prognosis expected—here the GS increased. We proved that Group 3 also had bad prognosis although here the GS improved. Group 1 had the best prognosis.

CONCLUSION: The likely explanation of these differences in BPFS is that the GS from the needle biopsy also has prognostic significance which is in accordance with the literature data analyzed in the text.

Keywords: *Gleason score, biopsy of prostate, radical prostatectomy, biochemical progression-free survival*

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INTRODUCTION

Prostate cancer presents as heterogeneous disease with widely varying survival among the affected patients. Urologists constantly try to develop predicting tools with which to guess the expected behavior of the tumor in a certain patient. One of the most important characteristics of prostate cancer is the degree of differentiation evaluated by the Gleason score (GS). Patients who undergo radical prostectomy (RP)

have their GS determined twice—first, during the biopsy, and second, after the RP. These scores sometimes differ (1). Traditionally the GS of the RP is expected to be more accurate because the whole prostate can be examined—not just separate cores. If this is true, then patients with decreasing GS after the RP will have a good prognosis. Nevertheless, there are data (2,3) that patients without changes in GS after RP actually have the best prognosis—not the patients with a decrease.

AIM

We analyzed the operated patients in our hospital (St. Anna Hospital, Varna). We tried to check if downgrading of GS after RP improves survival or not. Patients undergoing RP are considered to have life expectancy of at least 10–15 years. The assessment of the overall survival of such patients is quite difficult. That is why we examined the biochemical progression-free survival (BPFS) of the patients in order to evaluate the significance of the GS change.

MATERIALS AND METHODS

All the patients had prostate cancer proven with systematic transrectal biopsy of the prostate, performed between 01 January 2013 and 31 May 2020. Patients with targeted biopsy of the prostate (MRI-guided) were not included. The GS of the biopsy was collected. The patients underwent RP (either open or laparoscopic). Patients with pre- or postoperative hormonal or radiotherapy were excluded. 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 decreases after the RP. Information about the BPFS of the patients was collected and analyzed using IBM SPSS version 23. Non-parametric statistical methods were used: Pearson's chi square test, Mann-Whitney U test, Kaplan-Meier test.

RESULTS

The patients available for analysis were 111. The characteristics of the study population are shown in Table 1. A total of 42 patients (or 37.8%) were in Group 1, 40 patients (or 36%)—in Group 2, and 29 patients (or 26.2%)—in Group 3. The GSs of the groups (after the biopsy and after the RP) are shown in Fig. 1 and 2. In Group 1, 16 patients were with biochemical progression (38.1% of the patients in this group). Time to biochemical progression ranged from 1 to 51 months, average 18.9 months, the median is 15.5 months {IQR (interquartile range) =4.0–31.0)}. In Group 2 there were 26 patients with biochemical progression (65% of the patients in this group). Time to biochemical progression ranged from 1 to 22 months, average 5.6 months, the median is 2.5 months (IQR=1.0–10.0). In Group 3 there were 10 patients with biochemical progression (34.5% of the patients in this group). Time to biochemical progression ranged from 1 to 24 months, average 7.0 months, the median is 2.5

Table 1. Characteristics of study population.

		All	Group 1	Group 2	Group 3
Number of patients (%)		111	42 (37.8)	40 (36)	29 (26.2)
Age (years)	average	67.9	67.8	67.7	68.4
Preoperative PSA (ng/mL)	average	17.87	19.08	19.86	13.4
Clinical stage (%)	T1c	88 (79.28)	37 (88.10)	28 (70)	23 (79.31)
	T2a	6 (5.41)	1 (2.38)	3 (7.5)	2 (6.90)
	T2b	9 (8.11)	2 (4.76)	6 (15)	1 (3.45)
	T2c	8 (7.20)	2 (4.76)	3 (7.5)	3 (10.34)
Extraprostatic extension (%)		35 (31.53)	14 (33.33)	13 (32.50)	8 (27.59)
Seminal vesical involvement (%)		17 (15.32)	3 (7.14)	9 (22.50)	5 (17.24)
Lymph node metastases (%)		8 (7.21)	3 (7.14)	5 (12.5)	0 (0)
Prostate volume (mL)	average	68.31	70.56	64.12	70.44
PSA density (ng/mL/mL)	average	0.28	0.31	0.30	0.21

months (IQR=1.0–12.0). The average time to biochemical progression is shown in Fig. 3.

A statistically significant correlation was found between the time to biochemical progression and the three groups (X^2=7.938; p=.019). In Group 2 the time to biochemical progression (average 5.6 months) was significantly shorter than the time in Group 1 (average 18.9 months): Mann-Whitney U test, MWU=105.000; **p**=.007. In Group 3 the time to biochemical progression (average 7.0 months) was also significantly shorter than the time in Group 1 (MWU=42.500; p=.047). Between Group 2 and Group 3 there was no statistically significant difference in the time to biochemical progression (MWU=129,500; p=.986). The probability of a patient in Group 2 developing biochemical progression was 3 times higher compared with that of a patient in Group 1 (OR=3.018; 95%CI=1.227–7.423; p=.015). The probability of a patient in Group 3 developing biochemical progression was 2 times higher compared with that of a patient in Group 1 (OR=2.073; 95%CI=1.135–3.787; p=.012).

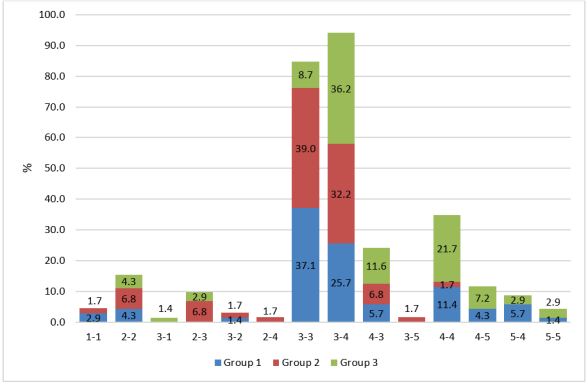

Fig. 1. Gleason scores of the groups after the biopsy.

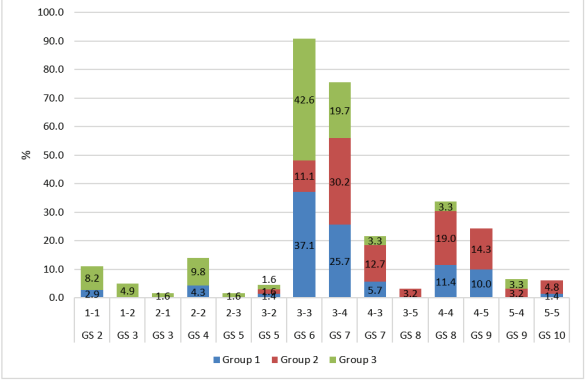

Fig. 2. Gleason scores of the groups after the radical prostatectomy.

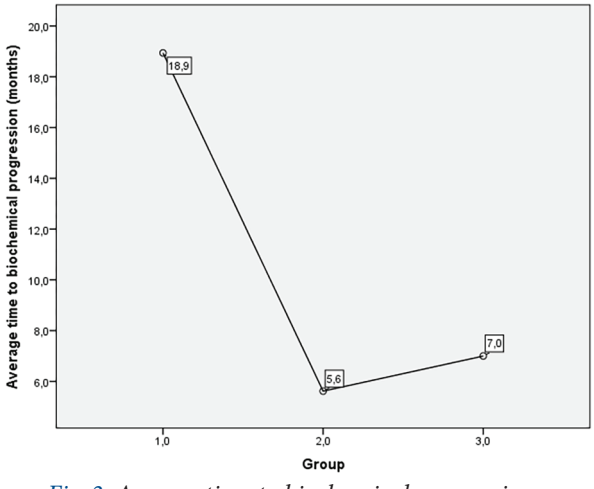

Fig. 3. Average time to biochemical progression.

The Kaplan-Meier survival analysis is shown in Fig. 4. It demonstrates a significantly better survival of the patients in Group 1 compared with Groups 2 and 3. (Kaplan-Meier log rank test (Mantel-Cox); X^2=10.785; p=.005).

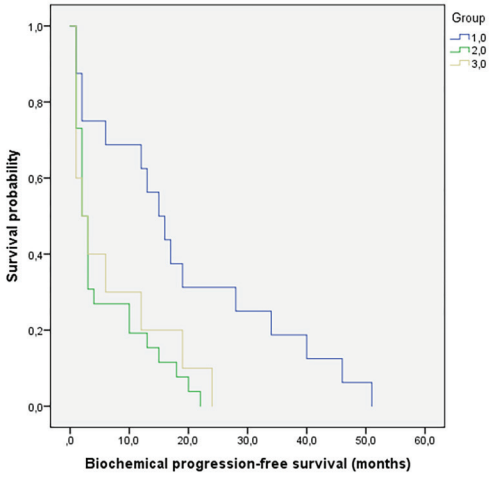

Fig. 4. Kaplan-Meier survival analysis.

DISCUSSION

Prostate cancer is the second most common cancer in men (4). After the introduction of PSA, most of the tumors are discovered in an early stage and hence there are many different treatment options. The treatment depends on the disease stage and on the risk assessment of the cancer. The pathological characteristics of the tumor are among the most important elements of this risk assessment—it

is done according to the Gleason grading system. In patients who have undergone radical prostatectomy, the GS is examined twice—after the biopsy and after the operation. A well-known fact is that the two GSs very often do not coincide (5–23). Many investigators are concerned with the fact that after RP the GS can increase. This is of course important because some patients are treated with deferred treatment—either active surveillance or watchful waiting. If their GS is underestimated during the biopsy this may have negative impact on the survival of the patients. That is why investigators try to find factors which may suggest underestimation of the GS from the biopsy (24–28).

When the GS decreases after the RP, the prognosis seems quite favorable because the postoperative pathological report is considered more accurate. This concept was challenged by Nicholas J. Fitzsimons et al. (3) who examined the BPFS and compared it with biopsy and postprostatectomy GSs. They prove that higher biopsy GS were positively associated with biochemical progression (log rank $p<0.001$). Even after adjusting for multiple pathological characteristics, including postprostatectomy GS, the association between higher biopsy GS and progression was little changed, in that men with biopsy Gleason 3 + 4 and 4 + 3 or greater were significantly more likely to experience progression ($p=0.001$ and <0.001, respectively). When stratified by postprostatectomy GS, higher biopsy GS were associated with an increased risk of biochemical progression in each postprostatectomy GS category (log rank $p\leq0.007$).

This hypothesis was further examined by Michael Muntener, Jonathan I. Epstein, David J. Hernandez, Mark L. Gonzalgo, Leslie Mangold, Elizabeth Humphreys, Patrick C. Walsh, Alan W. Partin, and Matthew E. Nielsen (2). The main idea in their article is that the needle biopsy has also prognostic significance—patients with low GS from the biopsy have better prognosis than patients with high GS. In the latter group are also found patients with high GS from the biopsy, which was later downgraded after the RP. In this scenario the BPFR is still worse than in patients who have low GS from the biopsy and RP. We can assume that in such situations a less differentiated tumor was found with the biopsy which later was missed by the postoperative pathological analysis. Potential explanatory hypotheses are: pathology error, borderline cases, sampling error (in which a minor component of tumor in the RP is sampled in the needle biopsy).

In the same article, the authors examine the situation when the biopsy GS increases after RP. Patients with the same GS from the biopsy and the RP (for example, 3 + 4) were compared with patients with initially lower GS from the biopsy. In this case the patients with the upgrading had better BPFS. The authors believe that this reflects an increase in the precision of describing the relative amounts of tumor with a given Gleason pattern in a given case. For example, a patient with biopsy GS 3 + 3 may likely have a greater proportion of pattern 3 in their prostate, despite their ultimate GS 3 + 4, than the patient with postoperative GS 3 + 4 who initially had pattern 4 detected on biopsy. In our patients we did not find such association between the BPFS and the upgrading of the GS—Group 2 had worse prognosis compared with Group 1.

While examining the survival of our patients, we tried to find how the BPFS corresponded to the change of GS. We divided the patents into three groups (equal GS, upgraded, and downgraded GS) and compared it with the BPFS of the patients. The fact that Group 2 had the worst prognosis was to some extent obvious and expected—here the GS increased (although, as mentioned above, the conclusion of Muentener M et al. is more nuanced). Less obvious was the fact that Group 3 also had bad prognosis although here the GS improved after the RP. The likely explanation is the aforementioned idea that the GS from the needle biopsy also has prognostic significance.

In our opinion the fact that targeted biopsies (MRI-guided fusion biopsy of the prostate) are not included in the study is not a limitation—to some extent it can be considered an advantage. According to contemporary data the targeted biopsy predicts the final GS better (29). This means that even the „inaccurate" systematic biopsy probably has prognostic significance. Then the prognostic significance of the targeted biopsy is expected to be much better.

An important limitation of our study is the relatively small number of patients available for analysis. This precludes us from dividing the patients into separate groups according to the GS, which was

done in the complex analyses by the other groups. Still the difference in BPFS of our patients was visible and we tried to find a possible explanation for this phenomenon.

Very interesting is the question of whether the GS of the biopsy is worth implementing in practice. Obviously it depends to some extent on which parameters will be included in the designed prognostic nomograms. A possible answer is found in a research conducted by Boorjian SA et al., from Mayo Clinic, Minnesota, USA (30). The authors admit that increasing the biopsy GS was significantly associated with systemic progression in patients with pathological 3 + 4 and 8 to 10 cancer. It was also an independent predictor of death from prostate cancer in patients with pathological GS 3 + 4 tumors. However, adding biopsy GS to the institutional post operational GS, PSA, seminal vesicle and margin status scoring algorithm minimally increased the concordance statistic for the association of that algorithm with cancer-specific mortality from 0.827 to 0.842—the number of analyzed patients was 8054. Unfortunately, as mentioned above, we did not have enough patients to prove or deny such statements.

CONCLUSION

The downgrading or upgrading of GS after the RP is a frequent event. We proved that it is also associated with differences in BPFS—it is longest when the GS does not change, much shorter when the GS increases or decreases after the operation. The likely explanation is that the GS of the biopsy has prognostic significance as well.

Statements

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by the Commission for Scientific Research Ethics at the Medical University of Varna (Approval No. 102).

Conflict of Interest: The authors have no conflicts of interest to declare.

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Data Availability Statement: All data analyzed during this study are available in the hospital database of St. Anna Hospital, Varna. Further enquiries can be directed to the corresponding author.

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