

STANDPOINT

By Prof. Deyan Anakievski, MD, PhD

US Urology, Department of Surgical Diseases, Faculty of Medicine, Medical University - Varna

Concerning: Dissertation work for the award of the ESD "Doctor" to **Boyan Ivanov Lazarov, MD**, a full-time doctoral student in the "Urology" doctoral program, professional direction 7.1. Medicine, enrolled by order No. R-109-451/28.10.2020

By order of the Rector of Medical University - Varna No. R-109-480/14.12.2022 and the decision of the Chairman of the Scientific Jury - Protocol No. 1 of 29.12.2022, I am appointed to present a standpoint regarding the dissertation work of Boyan Ivanov Lazarov, MD on the topic "**Comparison of the Gleason scores from prostate biopsy and from radical prostatectomy**".

The standpoint was prepared according to the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for its Application at the Medical University - Varna.

The dissertation contains a total of 147 pages, including 40 tables and 52 figures. The bibliography includes 155 titles. The presentation is structured correctly, in accordance with the requirements of a scientific study, as follows:

- Introduction – 3 pages
- Literature review - 36 pages
- Aim and tasks - 2 pages
- Materials and method – 16 pages
- Results - 56 pages
- Discussion of results - 16 pages
- Implications – 2 pages
- Contributions – 1 page
- Conclusion – 2 pages
- Publications – 1 page
- Bibliography - 10 pages

The presented PhD Thesis of the dissertation work in volume 64 pages is designed according to generally accepted requirements.

1. Evaluation of the actuality of the topic of the topic. Structure of the study

The topic of the scientific work is suitable for dissertation and current in view of the fact that prostate cancer is the most common non-cutaneous malignant disease in men in Europe and the USA. In Bulgaria, according to data from the National Center for Public Health and Analyzes, 2,606 patients are diagnosed with prostate cancer in 2019 (corresponding to an incidence of 77/100,000 men).

In the introduction to the paper, the candidate presents us with the main problem that he will deal with, namely - the discrepancy between the Gleason score from the prostate biopsy and from the radical prostatectomy, which is a quite common phenomenon. It has implications for patient therapy in two ways:

First, currently a certain proportion of patients prefer active surveillance rather than active treatment of prostate carcinoma – at least in the early stages. If the Gleason score of the biopsy gives an unrealistically low value (well - differentiated tumor), this will lead to an underestimation of the malignant potential of the tumor, possibly delaying the more aggressive treatment required for this type of cancer. Therefore, it is necessary to know the factors that suggest such an unrealistic underestimation of the Gleason score.

Second , there are cases in which the Gleason score after prostatectomy is lower than that after prostate biopsy. The PhD student aims to follow patients' survival to see if this lower Gleason score actually means a more benign cancer or it is an inaccurate result masking a poorly differentiated tumor.

The actual dissertation begins with a literature review that is sufficiently extensive and informative. It focuses on the epidemiology and etiology of prostate cancer. Diagnosis, staging, and treatment of the disease are then sequentially reviewed. A special place (which is directly related to the topic of the dissertation) is devoted to the pathoanatomical examination of the material after prostate biopsy and after radical prostatectomy. Here, the doctoral student correctly draws attention to the many difficulties that practicing pathologists and urologists encounter in the exact determination of the Gleason score, also to the presence (or lack) of positive surgical margins after radical prostatectomy. A critical analysis of the literary data was also made in order to highlight what has been achieved so far (including in the literature in Bulgarian) on the subject.

Chapter three contains the aim and tasks. The aim is clearly formulated - to make a comparative analysis of the Gleason score values from prostate biopsy and from radical prostatectomy and to analyze its dependence on basic characteristics of prostate cancer. The tasks are specific and clear, they correspond to the set aim.

The methodology and clinical material follow, where the doctoral student describes in detail the operative technique used in their clinic. Here the own experience and practice is compared with the techniques recommended by the leading specialists in surgical treatment of prostate cancer (including Bulgarian urologists).

2. Evaluation of results and conclusions

In the fifth chapter, the results of the study are presented, and the discussion of the results is in the following sixth chapter. Numerous statistical methods have been used, both from the field of descriptive statistics and analytical statistical methods in order to detect dependencies between variables. There were 203 patients under study. The tendency to increase the number of prostatectomies performed each year was highlighted. It is interesting that, together with this, the number of cases with extraprostatic extension of the tumor is also increasing - one of the possible explanations is the expansion of the indications for the application of radical prostatectomy.

Patients with well-differentiated carcinoma (Gleason score less than or equal to 6) were initially analyzed in order to identify possible factors that could predict its growth after prostatectomy - according to literature data, it is precisely in these patients that the probability of a discrepancy between the two Gleason scores is greatest. In addition, patients with well-differentiated carcinoma are sometimes referred to less radical treatment methods (active surveillance, watchful waiting) because of the presumed more benign nature of their tumor. The following parameters were analyzed: age, PSA, PSA density, prostate volume - it was found that only increased PSA density (over 0.15 ng/ml/cm^3) and small prostate volume were statistically significant prognostic factors for possible increase in Gleason score after radical prostatectomy.

In the analysis of the entire cohort of patients (and not only those with a well-differentiated tumor), it was found that only a low initial Gleason score (from the biopsy) was a major risk factor for a subsequent increase in the Gleason score after radical prostatectomy. An attempt to solve this problem is the

generalization of low Gleason grades in the ISUP classification (representing a modification of the traditional Gleason system). It is relatively unknown in Bulgaria - here the doctoral student shares his experience in its application in practice.

Not a little attention in the study was also given to the survival of the patients – both the overall and the survival without biochemical progression and also without metastases. In the end, it turns out that patients with no change in the Gleason score after prostatectomy have the longest survival (longer even compared to patients with an improvement in the score after the operation). This indicates that biopsy Gleason score also has independent prognostic value, not only that of radical prostatectomy.

For the dissertation, the doctoral student presents the following scientific publications:

- a. Lazarov BI (2022). Application of the ISUP classification in the analysis of patients with prostate carcinoma. *Clinical Urology*, 2(1), 5 - 9.
- b. Lazarov B, Ganev T, Statelov T, Kosev P (2020). Comparing Gleason score from prostate biopsy and from radical prostatectomy. *Uronet*, 2(2020), 19-20.

3. Evaluation of contributions.

The results and conclusions described so far can ultimately be summarized in the following main contributions:

1. Based on own clinical material, the cases with changes in the Gleason score were studied, the preoperative characteristics of the patients and the pathoanatomical findings after radical prostatectomy were examined. Patient survival was studied - both overall and without biochemical progression, as well as the time to occurrence of metastases. Through univariate and multivariate statistical analysis, a relationship between patient characteristics and Gleason score change after radical prostatectomy was sought.

2. A confirmatory contribution is the result that the Gleason score of the biopsy also has a prognostic value - and not only the Gleason score of the radical prostatectomy. This was established by analyzing the survival of patients with a change in Gleason score after radical prostatectomy.

3. It was also confirmed that a low baseline Gleason score (from the biopsy) is a major risk factor for a subsequent increase in the Gleason score after radical prostatectomy.

4. The new ISUP grade system (modified Gleason system) was also used in the analysis of patients. A better concordance was found between the histological result of the biopsy and that of surgery compared to the older system.

5. As a practical contribution is considered that in patients with well-differentiated prostate cancer (Gleason score up to 6 inclusive) increased PSA density (over 0.15 ng/ml/cm^3) and small prostate volume are statistically significant prognostic factors for a possible increase in Gleason score after radical prostatectomy.

4. Critical notes.

No significant critical remarks can be made to the dissertation work.


5. Conclusion.

In my capacity as a member of the scientific jury, I declare that Boyan Ivanov Lazarov, MD can be awarded the educational and scientific degree "Doctor" for his dissertation work on the topic "Comparison of the Gleason scores from prostate biopsy and from radical prostatectomy".

I am convinced that the other members of the scientific jury will also support my positive vote.

24/01/2023

Varna


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Prof. Deyan Anakievski, MD, PhD