

To the Chairman of the Scientific Jury,
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of the Rector of the Medical University - Varna
On your Protocol No. 1/ of 22.12.2022

REVIEW

from

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On the dissertation work of Dr. Boyan Ivanov Lazarov, on the topic:

**"Comparison of Gleason score from prostate biopsy and from radical
prostatectomy"**

for the awarding of a scientific educational degree "Doctor"

Prostate carcinoma is the second most common malignant tumor in men over 40 after lung carcinoma. Its first description was made by the English surgeon John Hunter of Arden 600 years ago. It affects 21% of men in Western Europe. In Bulgaria, it ranks second in terms of mortality among men. Treatment of this socially significant disease is diverse, from active follow-up to multidisciplinary combined treatment. A decision on the most suitable behavior for the patient is

sometimes difficult and depends on a number of factors, the most important of which is the degree of malignancy of the tumor. Everything said so far emphasizes that the topic of Dr. Lazarov's work is significant, important and current.

The dissertation work for obtaining the scientific educational degree "Doctor" on the topic: "Comparison of Gleason score from prostate biopsy and from radical prostatectomy" developed by Dr. Boyan Lazarov is the result of the long-term experience of the Clinic of Urology at the Medical University of Varna in the diagnosis and surgical treatment of carcinoma of the prostate gland. The presented scientific work contains 147 pages and is illustrated with 40 figures and tables for which there is no available numbering. The bibliography includes 155 titles. It is noteworthy that the articles of are divided into those in Cyrillic and Latin, and their ratio cannot be estimated.

The structure of the dissertation corresponds to modern requirements and contains all the necessary sections.

The literature overview is detailed in content and covers the etiology, epidemiology, diagnosis, staging and treatment of prostate carcinoma in a volume of 36 pages. Particular attention is paid to the pathoanatomical examination from the preoperative biopsy examination and from the final, postoperative examination of the prostate gland. In the last part of this chapter, a critical analysis of the known literary data in the Bulgarian and foreign language modern medical literature is made. This creates a basis for developing the thesis of the scholar's research. Prostate carcinoma is a heterogeneous disease, in the assessment of which many factors must be taken into account, the most important of which is the final histological grade of malignancy - Gleason score (GS). According to the scientific data, Dr. Lazarov found a frequent discrepancy in the preliminary and final histological GS. The increase in GS after radical prostatectomy (RP) is very concerning because it indicates that the malignant potential of the tumor may be underestimated by biopsy. The PhD student reports that the factors that can lead us to a possible increase in GS after RP are not clear. Through research and analysis of his own clinical experience, he looks for evidence supporting (or rejecting) the stated controversial claims.

The goal set by Dr. Boyan Lazarov in the development of the **dissertation is to make a comparative analysis of the Gleason score values from prostate biopsy and from radical prostatectomy and to analyze its dependence on the main characteristics of prostate carcinoma.** The formulated goal is general and versatile.

For the realization of this goal, Dr. Lazarov sets himself seven tasks in order to prove his thesis. They are quite generally formulated, including data from chapter material of the study. The number of assigned tasks is sufficient to justify the main thesis of the dissertation work.

In the chapter **material and method** of the study, Dr. Lazarov presents systematized and summarized clinical and statistical results of the study of 203 patients with carcinoma of the prostate gland. All patients were operated on at the Urology Clinic at the "St. Anna" - Varna from January 2013 to May 2021. Data on survival and progression of the disease from the oncology clinic "Marko Markov" - Varna were also used.

The author presents in detail the technique of performing a biopsy, the complications that have arisen, and the steps taken to manage them. The biopsies and histological examinations were carried out at St. Anna Medical University, as well as in other medical institutions. This implies heterogeneity and subjectivity of the obtained results, since the evaluation of the preparations was performed by different pathoanatomists. The following is a detailed description of the steps of the retropubic and laparoscopic extraperitoneal radical prostatectomy operative technique used. Finally, the author presents the statistical methods used to process the data.

The results obtained are presented in the next chapter. The number of patients operated on by year, the demographic data of the patients, the changes in the values of GS have been examined in detail. Dr. Lazarov describes and discusses the factors that can lead to an increase in postoperative GS: age, PSA, PSA density, prostate volume, palpation of a nodule on rectal douching. The preoperative characteristics of the patients and their relationship with the change of GS after RP were examined. No relationship was established between age, the

presence of a palpable nodule on rectal douching and changes in GS. A statistically significant difference in the change of GS, Dr. Lazarov found in the groups with a high density of PSA and with a small volume of the prostate gland.

Particularly important and valuable are the data from the analysis of 190 patients, when the same pathologist and in the same hospital examined the material from the biopsy and from the permanent specimen after the operation of the prostate gland. A statistically significant difference is found for the probability of a change in GS from lower to higher.

Of interest are **the results** of changes in GC and survival of patients without biochemical progression. A statistically significant relationship was established between patients with an increase in GS and the occurrence of biochemical progression. Another important result was a statistically significant difference in the occurrence of progression in patients with a preoperative PSA above 17 ng/ml and also for patients with a postoperative $GS \geq 7$. A survival analysis of patients with pT3b, pN1 and pT3a showed that they have prognostic significance in terms of biochemical progression-free survival.

In the **discussion section**, the statistical results obtained and the conclusions drawn are synthesized and compared with the data from publications on the topic. The PhD student concluded that his initial experience with the new ISUP classification (a modification of the traditional Gleason system) showed better concordance between the histological result of biopsy and that after RP. Finally, Dr. Lazarov critically examines some limitations of the study, which shows self-criticism and a clear idea of the state of the problem under consideration.

The next section includes the formulation of **conclusions**, which, after the analysis of the obtained results, give in a synthesized form the conclusions regarding the significance of comparing the Gleason score from prostate biopsy and from radical prostatectomy, the most important of which are:

- Only in 34.48% of cases there is a coincidence of GS from the biopsy and from the radical prostatectomy
- In patients with GS up to 6 from biopsy, increased PSA density and small

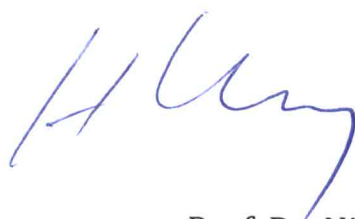
prostate volume were statistically significant prognostic factors for increased GS after RP.

- Low biopsy GS is a major risk factor for its subsequent increase after radical prostatectomy.
- Biopsy HS values were statistically significantly higher in patients with PSA density greater than 0.15 ng/ml/cm³.
- When analyzing patients using the new ISUP (modified Gleason system) classification, better concordance was found between the result of biopsy and that of surgery
- Biochemical progression-free survival after RP is highest in patients with no change in GS

In the **contributions** chapter, Dr. Lazarov formulated five scientific contributions of a scientific-practical and confirmatory nature, with which I agree.

In **conclusion**, I can say that Dr. Boyan Lazarov's dissertation on "Comparison of Gleason score from prostate biopsy and from radical prostatectomy" is properly structured and written in an academically sound style with a marked scientific-applied contribution. The scientific value of the dissertation gives me reason to recommend to the respected scientific jury to award Dr. Boyan Ivanov Lazarov the educational and scientific degree "Doctor".

28.01. 2023
sincerely:



Yours

Prof. Dr. Nikolay Kolev, MD