REVIEW

by

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of the dissertation work of

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on the subject:

"COMPARISON OF GLEASON SCORE FROM PROSTATE BIOPSY AND RADICAL PROSTATECTOMY"

for awarding the educational and scientific degree

"DOCTOR"

In the last decade, the incidence of prostate carcinoma has increased significantly worldwide. According to the World Health Organization, it is the second most common cancer among men, after lung cancer. In Bulgaria, the situation is even more alarming, as prostate cancer ranks first in terms of frequency and fifth in terms of the cause of death from cancer. Prostate carcinoma is gradually becoming a global medico-social problem due to its increasing morbidity and mortality rates and its negative impact on patients' quality of life. This necessitates the

development of new modern diagnostic methods, adequate therapeutic behavior and special public attention.

To a large extent, the reason for the increased incidence is also due to advances in diagnostic methods. Modern advances in genetics, molecular biology, pathoanatomy and immunohistochemistry, as well as innovations in imaging, have greatly contributed to the early detection of prostate carcinoma. Among all diagnostic methods, histological examination plays a leading role. Apart from the fact that, on the one hand, we thus prove the presence of a malignant disease of the prostate, it gives us very important information about the classification of the tumor according to Gleason, and from there and its categorization as high-, moderate- or low-risk, which is important for choosing the most - the effective treatment for each individual patient.

When prostate carcinoma is suspected, histological examination and determination of the Gleason score is sometimes done twice - during the biopsy and after the radical prostatectomy, if we have chosen this method of treatment. What very often puzzles doctors is the high frequency of discrepancy in the determined Gleason score before and after surgery. The aim of Dr. B. Lazarov's dissertation work is to answer this important question by making a comparative analysis of the values of the Gleason score from the prostate biopsy and from the radical prostatectomy, analyzing also its dependence on the main characteristics of the tumor .

From what has been presented so far, it is clear that the searches of Dr. B. Lazarov in this direction are relevant for urological practice. They deserve credit given his enduring interest in the subject and issue. The results of the present study are a valuable scientific source of information and have a proven scientific-practical character.

The dissertation submitted for review is presented in 147 standard typewritten printed pages, which include 52 figures and 40 tables, consecutively arranged in the text. In the abstract, 2 publications related to the dissertation work are indicated. The bibliography includes 155 titles, of which 36 are in Cyrillic and 119 are in Latin, which confirms the author's high awareness of research issues. The bibliography is selected according to the topic of the dissertation work, and the citation of a large percentage of Bulgarian authors is impressive, which deserves a positive evaluation. The work ends with a reference to the contributions, which are five in number. The dissertation is written in a highly professional language and style, but comprehensible and systematic.

The dissertation is structured as follows:

1. Title pages, glossary and table of contents – 3 pages.

2. Introduction - 3 pages.

3. Literature review - 36 pages.

4. Purpose and tasks - 2 pages.

5. Material and method - 16 pages.

6. Results - 56 pages.

7. Discussion – 16 pages.

8. Conclusions - 2 pages.

9. Conclusion - 2 pages.

10. Contributions - 1 page.

11. Book review - 10 pages.

The literature review is composed of 7 subchapters. The first of these examines the epidemiology, incidence and etiology of prostate carcinoma. Epidemiologically, the author states that the incidence is highest in Australia/New Zealand, North America and Northern Europe, and lowest in East, South and Central Asia. It has been noted that mortality rates are higher among men of African descent, intermediate among US white men, and very low among Asians. The morbidity and mortality from prostate cancer in Bulgaria and the USA were compared, and the reasons for the decline in these two indicators in the USA in recent years were highlighted - early diagnosis due to mass PSA screening and the introduction of new, more effective therapies. The etiology of the disease is discussed in detail, highlighting the role of family and racial predisposition, obesity and metabolic syndrome.

In the next sub-chapter, the author examines in detail the modern diagnostic possibilities for early detection of prostate carcinoma. She begins with the role of the digital rectal examination in the detection of this disease, highlighting the reasons why this examination should not be missed - easily applied, can detect carcinoma even with a normal PSA, assesses local status and participates in a large number of nomograms . Further in this subchapter, attention is paid to the study of PSA and PSA screening, stating that there is no strong evidence that overdiagnosis as a result of screening leads to a reduction in overall and tumor-related mortality. A major place in this subchapter is devoted to prostate biopsy. Historically, both methods and different schemes for obtaining histological material are reviewed. The role of mpMRI and the PI-RADS system for improving the diagnosis of prostate carcinoma is highlighted. The three techniques for combining mpMRI with biopsy were considered - at the time of the imaging study, the fusion biopsy, and the so-called cognitive fusion biopsy.

In the next two subsections, attention is paid to the pathoanatomical examination of the material from the biopsy and after radical prostatectomy. They explain the Gleason system, Gleason score and ISUP in detail. The relationship between them is indicated and the types of risk groups are shown in a table. Attention has been paid to the main elements that should be present in the patho-anatomical report – histological variant, degree of differentiation, quantitative description of the tumor, TNM stage and surgical margins.

In the fifth subchapter, Dr. B. Lazarov examines the TNM classification, and the imaging methods that can be used are described in detail.

The next sub-chapter focuses on the treatment of prostate carcinoma, looking at active follow-up with wait and watch, radical prostatectomy, and radiotherapy.

In the last seventh sub-chapter, a critical analysis of all existing literary data related to the discussed problem is made.

The purpose of the dissertation is formulated briefly and clearly. To make a comparative analysis of Gleason score values from prostate biopsy and from radical prostatectomy and to analyze its dependence on basic characteristics of prostate carcinoma. It is precisely defined and corresponds to the title and capabilities of the survey.

The dissertation student sets 7 tasks that are clearly formulated and summarize the accumulated experience in this direction and answer the questions posed in the literature review.

Material and methods

For the period from January 2013 to May 2021, 468 prostatectomies were performed at the Urology Clinic of St. Anna Medical Center - Varna. During the pre-processing of the data, it was found that in a significant number of cases until 2018, information on the Gleason score from the prostate biopsy and/or from the prostatectomy was missing. As a result, the final number of patients available for analysis was 203.

The dissertation student actively participated in the team in the selection, treatment and follow-up of the patients. It provides a detailed description of the technique for performing prostate biopsy, retropubic and laparoscopic prostatectomy.

For data processing, analysis of the obtained results and their graphical presentation, Dr. B. Lazarov uses IBM SPSS version 23, as well as statistical methods, which are generally divided into: descriptive, correlational and those for testing hypotheses.

This allows a complete and comprehensive analysis of the goals and tasks of the dissertation to be carried out and sufficiently reliable information to be obtained.

Chapter "Results" begins with a general description of the study sample. The 203 patients available for analysis were divided into 3 main groups: first group – no change in Gleason score after radical prostatectomy, second group – with an increase in Gleason score after radical prostatectomy (compared to biopsy) and third group – with a decrease in Gleason score after radical prostatectomy (versus biopsy). During the initial analysis of the patients, he found that the two Gleason scores matched in 70 patients - in the rest, the Gleason score after radical prostatectomy either increased or decreased. In the subsequent analysis of the number of patients by year, an increasing trend was observed with each subsequent year, and no statistically significant difference was found in the average age of the patients for the individual years.

Results chapter continues with patients with highly differentiated carcinoma of the prostate by biopsy (HS≤6) - factors pointing to a possible increase in Gleason score after radical prostatectomy. In this subchapter, the dissertation examines the possible influence of age, PSA, PSA density, prostate volume, and prostate nodule palpation in DRI (stage T2) on the observed higher Gleason score after radical prostatectomy.

The next sub-chapter examines the preoperative characteristics of the patients and their relationship to the change in Gleason score after radical prostatectomy. It analyzes in detail: the

change in Gleason score and the age of patients, the change in Gleason score and PSA, the change in Gleason score and prostate volume, the change in Gleason score and PSA density (PSAD-PSA Density), the change in Gleason score in the presence of a palpable nodule in the prostate on rectal examination (stage T2), the change in the Gleason score after surgery and the relationship with the Gleason grade from the biopsy and concludes with an analysis of cases where the same pathologist examined the material from the biopsy and from the surgery, analysis of cases in which biopsy and surgery were performed in the same hospital and change of Gleason score and distribution of patients in risk groups according to EAU.

The next sub-chapter entitled - initial experience with ISUP classification shows ISUP grades from biopsy and how these grades change (or remain) after radical prostatectomy.

The following fifth sub-chapter examines changes in Gleason scores and their relationship to pathoanatomical features (seminal vesicle involvement, extraprostatic tumor development, and presence of lymphatic metastases) found in radical prostatectomy.

In the next subsection, changes in the Gleason score and their significance for biochemical progression-free survival (BPFS) are analyzed. The relationship between biochemical progression-free survival and the values of: PSA, Gleason score, patient belonging to the three risk groups (low, moderate and high risk) defined by EAU and the influence of postoperative pathoanatomic characteristics: presence of extraprostatic tumor growth (pT3a), seminal vesicle invasion (pT3b) and lymphatic metastasis (pN1).

Subchapter seven addresses changes in Gleason score and their relationship to overall survival after radical prostatectomy. After the analysis of the results, a statistically significant relationship was established between the survival of the patients and their belonging to a certain group. The survival of the patients in the first group was the longest, followed by those in the second group, and the survival of the patients in the third group was the lowest.

In the next subsection, the occurrence of metastases after radical prostatectomy in the three groups is analyzed, and in the last ninth chapter, the results of the 16 fusion biopsies performed in the same groups are summarized.

In the chapter "Discussion" the results are discussed by the author in chronological order.

As a first step, the dissertation analyzed patients with highly differentiated prostate carcinoma to identify possible factors that could predict its growth after radical prostatectomy. It examines in detail the influence of: age, PSA, PSA density, prostate volume and palpation of a prostate nodule on DRI.

It then analyzed the various preoperative characteristics of the entire group of patients (not only those with highly differentiated prostate cancer) to detect a possible association with a change in Gleason score (increase or decrease) after surgery. The following characteristics are relevant here: patient age, PSA, prostate volume, PSA density, presence of a palpable prostate nodule, biopsy Gleason score, analysis of cases in which the same pathologist examined biopsy and surgical material, and classification of patients into EAU risk groups (high, moderate and low risk).

Further analysis was done according to the ISUP classification including: whether there was a discrepancy between biopsy and surgery Gleason scores in this classification, and how much there was a correlation between the ISUP grades and the clinical and pathoanatomical characteristics of the patients.

The relationship between survival without biochemical progression and the values of: PSA, Gleason score, postoperative pathoanatomic characteristics - presence of extraprostatic tumor extension (pT3a), seminal vesicle invasion (pT3b) and lymphatic metastasis (pN1) and patient belonging to the three risk groups (low, moderate and high risk) defined by the EAU.

There are 7 conclusions at the end of the dissertation. They present in a synthesized form the enormous work of the dissertation student and are a contribution to urological practice.

1. There is an increasing trend in the number of prostatectomies performed each year. Only in 34.48% of cases there is a coincidence of the Gleason score from the biopsy and from the radical prostatectomy. In the remaining patients there was either an increase in the Gleason score (31.03%) or a decrease (34.48%).

2. In an analysis of patients with highly differentiated prostate carcinoma (Gleason score up to 6 including biopsy), it was found that increased PSA density and small prostate volume were statistically significant prognostic factors for a possible increase in Gleason score after radical prostatectomy.

3. A low biopsy Gleason score is a major risk factor for its subsequent increase after radical prostatectomy.

4. During the analysis of the main perioperative characteristics of the operated patients, the following dependencies were found, pointing to high-risk prostate cancer:

• A statistically significant relationship was found between PSA values and Gleason score (both from the biopsy and after radical prostatectomy) - a higher PSA is a risk factor for the presence of poorly differentiated prostate carcinoma.

• Biopsy Gleason score values were statistically significantly higher in patients with PSA density greater than 0.15 ng/ml/cm3.

• Patients from the preoperative high-risk group according to the EAU classification have more frequent involvement of the seminal vesicles and/or extraprostatic tumor development postoperatively.

5. When analyzing patients using the new ISUP classification (modified Gleason system), a better concordance was found between the result of biopsy and that of surgery (58.97% according to ISUP compared to 41% according to the old system - for highly differentiated carcinomas) . However, even here in 34.62% there is an increase in the degree after the operation. A statistically significant association was also found between biopsy ISUP grades and the presence of pT3a and pT3b stages after surgery with a positive correlation.

6. Biochemical progression-free survival is highest in patients with no change in Gleason score after radical prostatectomy. The time to biochemical progression in patients with an increase in Gleason score postoperatively was not statistically significantly different from that of patients with a decrease. This indicates that biopsy Gleason score also has prognostic value, not only radical prostatectomy Gleason score.

7. When analyzing the survival of the patients, the following dependencies were established: Patients with a Gleason score ≤6 had greater biochemical progression-free survival than patients with a Gleason score ≥7, regardless of whether the Gleason score was determined at biopsy or after surgery.

• Patients with lower PSA have longer biochemical progression-free survival.

• Patients with extraprostatic tumor extension (pT3a), seminal vesicle invasion (pT3b) and lymphatic metastases (pN1) had shorter biochemical progression-free survival.

The scientific contributions of the dissertation work contain the most important points of the work proposed for review and are fully related to medical practice. There are 5 of them:

1. Based on our own clinical material, the cases with a change in the Gleason score were examined, the preoperative characteristics of the patients and the pathoanatomical findings after radical prostatectomy were examined. Patient survival, both overall and biochemical progression-free, was studied, as was the time to metastases. Through uni- and multivariate statistical analysis, a relationship between patient characteristics and Gleason score change after radical prostatectomy was sought.

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

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

4. The new classification according to ISUP (modified Gleason system), which is still little known in Bulgaria, was also used in the analysis of patients. A better concordance was found between the histological result of biopsy and that of surgery compared to the older system.

5. As a practical contribution, the result that in patients with highly differentiated prostate carcinoma (Gleason score up to 6 inclusive) increased PSA density (over 0.15 ng/ml/cm3) and small prostate volume are statistically significant prognostic factors factors for a possible increase in the Gleason score after radical prostatectomy.

CONCLUSION

Dr. Boyan Ivanov Lazarov was born on February 13, 1977 in the city of Varna. In his hometown, he studied at the First Language High School until 1996. He graduated in medicine from the Medical University, Varna in 2002. From 2002 until now, he has been working first as a

resident, and since 2019, as an assistant at the "St. Anna" Medical Center, Varna. He is fluent in English, German and Russian. Since 2005, he has been a member of the European Association of Urology. In 2008, he successfully passed the exam for the European Board of Urology - Fellow of the European Board of Urology. He has a medical, diagnostic and surgical workload. Participates in national and international forums on urology, endourology and oncourology.

By Rector's Order No. R - 109 - 451/28.10.2020, Dr. B. Lazarov was enrolled as a full-time doctoral student at the Department of Surgical Diseases, Faculty of Medicine, Medical University, Varna. Pursuant to the Decision of the Faculty Council of the Faculty of Medicine dated 05.12.2022 and Rector's Order No. R - 109 - 480/14.12.2022, Dr. Boyan Ivanov Lazarov has been appointed as a doctoral student in full-time studies in urology with right of defence. All the requirements of the procedure have been met.

On the basis of the dissertation submitted to me, I can state that the scientific research activity, as well as the professional qualification of Dr. Boyan Lazarov, fully meet the requirements of the regulations for the terms and conditions for acquiring scientific degrees and occupying the scientific and educational degree "doctor" at Medical University - Varna. The indicated own contributions have scientific and applied value for urological practice.

All this gives me a moral reason to recommend to the members of the honorable scientific jury to vote positively and award Dr. Boyan Ivanov Lazarov the educational and scientific degree "Doctor".

01/29/2023

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Reviewer:

(Assoc. Dr. B. Atanasov, MD)