

REFERENCE

from

PROF. DR. MARINCHO IVANOV GEORGIEV, MD, PhD
Department of Urology, Medical University, Sofia

Head of the Clinic of Urology
UMHAT "Alexandrovska", Sofia

on

the dissertation work of **Assoc. Prof. Dr. TOSHO YORDANOV GANEV, MD, PhD**
Assoc. Prof. at the Department of Surgical Diseases, Department of Urology,
Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov", Varna

Head of the Clinic of Urology
MHAT "St. Anna", Varna

on the subject:

**"A MULTIMODAL STRATEGY FOR THE TREATMENT OF HIGH-RISK PROSTATE
CARCINOMA"**

for the award of a scientific degree

"DOCTOR OF SCIENCE"

Pursuant to Order No. R-109-411/27.09.2023 of the Rector of the Medical University, Varna and according to Protocol No. 1 of 03.10.2023 of the Scientific Jury, I have been assigned to prepare a reference on the procedure for acquiring the scientific degree „**Doctor of Sciences**” in the speciality "**Urology**".

Prostate cancer is one of the most common malignant diseases in men, ranking second after bronchial carcinoma. The discovery of biomarkers such as PSA, which are positively correlated with the diagnosis of prostate cancer, greatly support the early diagnosis of this disease. In the late 1980s, with the introduction of PSA testing of men and subsequent biopsies in the USA, the incidence of prostate cancer doubled. A similar increase has been reported in Europe and is a worldwide trend.

The high incidence of prostate cancer worldwide calls for strengthening the existing tools available to identify trends and prevention strategies to reduce the public health impact of this disease in the future. Prostate cancer registries play an important role in the development of research and care for patients with prostate cancer. It is a major source for collecting information on incidence and mortality, disease characteristics, risk factors, quality of care and disparities in access to treatment. Collecting long-term data on this issue improves oncology and outcomes and contributes to improving the quality of life of patients.

From everything that has been said so far, it is clear that the efforts of Assoc. Prof. T. Ganey to devote himself to this problem are relevant for urological practice, and not an end in themselves of the dissertation and deserve a positive evaluation. His long-standing interest in the subject and in-depth scientific research on the problem must be honestly acknowledged.

The dissertation work submitted for review is submitted to 155 non- standard typewritten printed pages, which include 5 tables and 26 figures, black and white and color, arranged in chronological order in the text. The bibliography occupies 42 pages and includes 518 titles. The bibliography made confirms the author's high awareness of the research problem. The dissertation is written in a clear and professional language, showing the active personal attitude of the author on the controversial issues.

The distribution of the material by chapter is as follows:

1. Introduction - 22 pages
2. Literature review - 44 pages
3. Purpose and tasks - 1 page
4. Statistical methods - 33 pages
- 5 . Conclusions - 1 page
- 6 . Scientific contributions - 1 page
- 7 . Scientific publications in connection with the dissertation - 1 page
- 8 . Bibliography - 42 pages

There are 10 scientific publications in connection with the dissertation work, they are noted in the abstract and are from the last 9 years.

In the introduction a serious attempt has been made for thoroughness, detail and comprehensiveness. It is composed of 5 subchapters. Prostate cancer is the second most common malignancy (after lung cancer) in men worldwide. The frequency of prostate cancer increases with age and it is often asymptomatic in the early stages of the disease. In the first 2 subchapters, the epidemiology and etiology of prostate carcinoma are discussed in detail. The author has a serious scientific approach to the interpretation of scientific facts from the studied literature. It provides a multifaceted review of prostate cancer incidence and mortality. When studying the etiology, the patient's age, ethnicity, family history, genetic factors, diet, smoking, etc. are taken into account. In the following subsections, serious attention is paid to prevention and future prospects in patients with prostate carcinoma.

The literature review is professionally done. It consists of 7 subchapters. In the first of them, the main options for therapeutic behavior in a patient with locally advanced carcinoma of the prostate are consistently considered. Serious and in-depth attention is paid to the methods used in medicine for the diagnosis and treatment of prostate cancer - multiparametric MRI, radiation and hormone therapy, radical prostatectomy with extended lymphatic dissection, multimodal therapy and surgical treatment of high-risk prostate cancer. In the second subchapter, Assoc. Prof. T. Ganey describes the guidelines for the treatment of high-risk prostate carcinoma and locally advanced prostate carcinoma. In the third subsection, issues of screening and postoperative complications are addressed. In the fourth sub-chapter, the dissertation explores the problems of accurate diagnosis and discrepancy between the biopsy pathology report and the pathology result of radical prostatectomy. In the following fifth subchapter, the author touches on survival and biochemical progression of PSA. The sixth subchapter discusses extended lymph node dissection in high-risk prostate carcinoma. The seventh subchapter includes an overview of basic therapeutic methods. In it, the author describes achievements in the treatment of prostate carcinoma, summarizes achieved

long-term results, emphasizes the continuous improvement of methods, indicates the indications for choosing treatment, reveals the possibilities of a multidisciplinary approach and patient follow-up.

Everywhere one can see the serious scientific approach of the author in the interpretation of the scientific facts from the studied literature. The literature review is highly informative and balanced. The review is supported by literary sources.

The purpose of the dissertation is formulated briefly and clearly - a finding of the multimodal treatment in high-risk carcinoma of the prostate gland. It largely corresponds to the title of the dissertation work.

The author puts 6 tasks. They summarize his accumulated experience in this direction and answer the questions posed in the literature review.

To process the data, the author used various mathematical and statistical methods - IBM SPSS version 26, Kaplan-Meier method, including Log Rank, ROC curves, etc. This allows the scientific search to be carried out in relation to the goals and tasks and obtaining sufficiently reliable information.

871 patients with prostate cancer from the Clinic of Urology of the "St. Anna", Varna for the period 1996 – 2022 have been investigated. The patients are aged between 48 and 81 years. The author divided the patients into a risk group (491 patients) and a control group (380 patients). Patients in the risk group have higher Gleason score values, higher PSA values, higher disease stage, larger prostate volume and shorter survival period.

The dissertation statistically evaluated factors that determine the high-risk group, as well as their weight in terms of overall survival. Five major predictors of cancer mortality were examined: clinical progression, PSA biochemical progression, disease stage - T3-3+, GS value and PSA values.

There are 7 conclusions at the end of the dissertation. They present the dissertation's work in a synthesized form. The first 2 conclusions are related to mortality and 5-year survival in patients from the risk and control groups according to the treatment. The third conclusion found no statistically significant difference in the time to biochemical progression in the first 5 years for patients in the two groups. The next 3 conclusions are related to the probability of occurrence of biochemical or clinical progression or metastases in the two groups of patients and according to the treatment applied. The final conclusion reveals 5 different survival criteria.

Scientific contributions of the dissertation work are 7 in number in the dissertation work. It has been shown that patients with high-risk prostate cancer need to be treated multimodally. In these patients, it is possible to perform radical prostatectomy in the framework of multimodal treatment, and this approach has a very good cancer-related survival and contributes to the staging of the disease. The author developed prognostic criteria for cancer - related survival of high-risk prostate carcinoma.

CONCLUSION

Assoc. Prof. Tosho Yordanov Ganev was born on November 24, 1963 in Tutrakan. He graduated Medicine in Medical University, Varna in 1993. Between 1994-1999 he was specializing in urology at the Clinic of Urology at the Medical University, Varna. In 1999 he passed the urology specialty exam successfully. In 2009, he defended his dissertation and received the scientific and educational degree "doctor", and in 2013 he was elected as an associate professor at the Department of Surgical Diseases, Department of Urology, Medical University, Varna.

Assoc. Prof. Tosho Yordanov Ganev has a medical, diagnostic and surgical workload. His scientific interests are broad. Speaks fluently Russian and English languages and has computer literacy. He is a member of the Bulgarian Urological Society.

In conclusion, I would like to say that the presented dissertation work of Assoc. Prof. T. Ganev is on an extremely current medical and socially significant topic. It is a qualitative comprehensive scientific summary of the therapeutic options, surgical aspects, follow-up and prognosis in the treatment of high-risk prostate cancer. The number of patients followed is sufficient to draw scientifically based conclusions. The diagnostic and clinical methods used, the large clinical material and the complex approach to their interpretation is a prerequisite for a good mastery of the material and serious contributions of the dissertation on this problem.

I have had the opportunity and the pleasure to personally and closely follow the scientific pursuits and practical activities of Assoc. Prof. T. Ganev over the years. His practical experience and in-depth scientific data processing are proof of the high quality of the presented dissertation work. The specified own contributions have scientific and applied value for urological practice in our country. My assessment is positive, and this gives me a moral reason to recommend the members of the honorable scientific jury to vote positively and award Assoc. Prof. Tosho Yordanov Ganev the scientific degree "**Doctor of Sciences**".

30.10.2023

Sofia

Reviewer:

(Prof. Dr. M. Georgiev, MD, PhD)

