

REVIEW

by Prof. Krasimir Yanev, MD, PhD

Department of Urology,

Faculty of Medicine, Medical University - Sofia

Clinic of Urology, UMBAL "Alexandrovska", Sofia

Concerning: Dissertation work for the award of the scientific degree "Doctor of Sciences" to Assoc. Prof. Tosho Yordanov Ganev, MD, PhD in the field of higher education 7. Health care and sports, professional direction 7.1. Medicine.

By decision of the Chairman of the Scientific Jury - Protocol No. 1 of 03.10.2023, I have been assigned to present a review of the dissertation work of Assoc. Prof. Tosho Yordanov Ganev, MD, PhD on the topic "**A MULTIMODAL STRATEGY FOR THE TREATMENT OF HIGH-RISK PROSTATE CANCER**".

The review was prepared according to the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria.

The dissertation contains a total of 152 standard typewritten pages, illustrated with 26 figures and 5 tables. The bibliography includes 518 titles. The presentation is structured correctly, in accordance with the requirements of a scientific study, as follows:

- Introduction – 1 page
- Literature review - 70 pages
- Aim and tasks - 2 pages
- Material and methods – 2 pages
- Results and Discussion – 33 pages
- Conclusions - 1 page
- Contributions – 1 page
- Publications – 1 page
- Bibliography - 40 pages

The presented PhD Thesis of the dissertation work in volume 77 pages is designed according to generally accepted requirements.

1. Assessment of the topicality of the topic, analysis of the studied sample.

The topic of the scientific work is suitable for dissertation and relevant in view of the fact that the modern treatment of oncological diseases (including the prostate cancer) is usually multi-staged and includes many methods and steps.

The dissertation begins with a literature review, which is sufficiently extensive. It focuses on the epidemiology of prostate cancer, outlining the problem groups of patients by race and nationality. Here, the doctoral student presents in detail the possible etiological factors, including the current from a practical point of view, the question of the impact of diet on the probability of developing prostate cancer.

The aim and objectives of the dissertation work follow. The goal is clearly formulated - to analyze multimodal treatment in high-risk prostate cancer. The tasks set are specific and clear, they correspond to the set goal.

Further, the doctoral student describes in detail the statistical methods used. The available clinical material in the form of summaries and operative protocols from the "St. Anna-Varna" Hospital is also presented - the analysis was performed on the basis of a sample of 871 patients, which is a significant number for our country. The subsequent follow-up of those operated for at least five years is especially valuable. The analyzed patients are divided into two large groups: risk group - here are included high-risk and/or locally advanced prostate cancer according to the definition of the European Association of Urology; control group - includes low- and moderate-risk patients. The applied therapies are summarized as dual therapy - includes radical prostatectomy and adjuvant hormonal therapy and triple therapy - radical prostatectomy and adjuvant radio- and hormonal therapy.

2. Evaluation of the results.

The next chapter presents the results of the study. The overall survival of patients in the risk group was lower than that in the control group; similar results were obtained when analyzing cancer-specific survival, clinical and biochemical progression-free survival. This confirms the importance of accurately determining the degree of malignancy of prostate cancer which, as we know, can have many faces and manifestations - from extremely malignant and rapidly progressing to a slow-growing tumor.

The following is an analysis of the influence of adjuvant therapy (hormonal therapy with or without radiotherapy) on the survival of patients from the risk group. Available data show that survival (overall, cancer-specific, metastases-free and biochemical progression-free survival) does not differ statistically significantly between patients on double and triple therapy. These results are in line with the recommendations of the European Association of Urology that adjuvant treatment of high-risk prostate cancer should be individualized and tailored to the stage of the disease in each specific patient, and not applied universally and indiscriminately.

Finally, some predictors of prostate cancer mortality were outlined through detailed statistical analysis. Here again, the importance of the main parameters characterizing high-risk prostate carcinoma is emphasized – this includes clinical progression (that is, the appearance of metastases); PSA progression postoperatively; disease stage T3–4; Gleason score value >7 and PSA values >20.

3. Publications related to the dissertation work

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

1. Lazarov B, Ganev T, Mircheva I. The effect of the Gleason score change on biochemical progression-free survival. *Scripta Scientifica Medica*. 2022;54(2):18–24.
2. Lazarov B, Ganev T. The Impact of Gleason Score from the Biopsy and from the Radical Prostate- Ctomy on the Biochemical Progression- Free Survival. *J IMAB*. 2022;28(4):4720–3.
3. Ganev T, Dulgerov V, Abushev I, Nankova M, Genova M. Primary adenocarcinoma of the urethra in a woman. *MD*. 2017;14(4):80–1.
4. Dulgerov V, Nankova M, Ganev T, Markova S. Spontaneous atraumatic rupture of a kidney. *MD*. 2018;15(4):80–1
5. Evtimov N, Ganev T, Zhelezov M. The role of periprostatic adipose tissue NGF & BDNF in prostate carcinoma. *Urology*. 2014;20(4):93–8.
6. Evtimov N, Ganev T, Petkova L, Hinev A, Stamboliyski V. Retrospective analysis of patients after radical cystoprostatectomy for bladder carcinoma. *Urology*. 2015;21(4):80-3.

7. Evtimov N, Ganev T, Stamboliyski V, Petkova L. Complications when choosing a laparoscopic operative technique. *Urology*. 2015;21(2):36–8.
8. Kosev P, Ruseva Zh, Ganev T. Approach to patients with HPV infection in childhood. A clinical case from practice. *General medicine*. 2021;23(3):41–4.
9. Nankova MP, Ganev TY, Chusova YM, Dulgerov VY. Bladder cancer during pregnancy. *Science through the prism of time*. 2017;8(8):127–30.

4. Evaluation of contributions

The contributions of the dissertation can be summarized as follows:

1. A retrospective study was conducted of 871 patients operated for prostate cancer at the Urology Clinic of the "St. Anna" Hospital.
2. Statistical analysis and processing of the obtained results was carried out.
3. The multimodal treatment of high-risk prostate cancer was analyzed.
4. Prognostic criteria for cancer-specific survival of high-risk prostate cancer were developed.
5. It was proven that patients with high-risk prostate cancer need to be treated multimodally.
6. It was proven that in patients with high-risk prostate cancer, radical prostatectomy is possible and should be performed, within the framework of multimodal treatment - with very good cancer-specific survival.
7. It was proven that radical prostatectomy in high-risk and/or locally advanced prostate cancer should be performed with the aim of accurate staging and reduction of tumor burden as the operation is part of multimodal therapy.

5. Critical notes

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

6. Conclusion

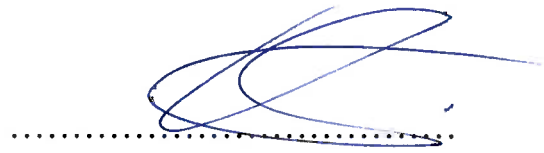
In my capacity as a member of the scientific jury, I declare that Assoc. Prof. Tosho Yordanov Ganev, MD, PhD can be awarded the scientific degree "Doctor

of Sciences" for his dissertation work on the topic "**A MULTIMODAL STRATEGY FOR THE TREATMENT OF HIGH-RISK PROSTATE CANCER**".

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

19.10.2023

Sofia



Prof. Krasimir Yanev, MD, PhD