

To: The chairman of the scientific jury,
By order of the Rector of MU - Varna
№ P-109-411/27.09.2023

STANDPOT

by

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Concerning: I am appointed to present a standpoint regarding the dissertation work:

Multimodal strategy for the treatment of high-risk prostate cancer

For awarding educational and scientific degree "Doctor of Medical Sciences"
of

Assoc. Proff, Dr. Toshko Yordanov Ganev PhD Head of Clinic "Urology"
Hospital "St. Anna", Department of Surgical Diseases, Faculty of Medicine, Head
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Field of higher education: 7. Health and sports, professional field: 7.1. Medicine
Scientific specialty: "Urology"

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Today, thanks to modern diagnostic methods, in 90% of cases, prostate carcinoma in stage T1-T2 is detected. In other patients, due to probably due to genetic disorders, the tumor process develops progressively although it is localized in the organ. In these patients, there is a tendency for biochemical progression, the development of metastases and a rapidly rapid lethal outcome of the disease. The fact is that in the majority of patients with prostate cancer, the disease is slow and can be avoid early surgical intervention and preference is given to monitor the patient, annual staging of the disease, followed by careful waiting, aggressive therapy .

Effective prevention of prostate cancer is the basis for avoiding the development of metastatic, hormoneresistent carcinoma of prosate. Identification with biomarkers such as PSA, immunohistochemical and genetic markers helps to carry out a comprehensive analysis of genetic and epigenetic changes. This information, combined with targeted functional studies, helps to detect indinate signaling pathways that are involved in the progression of prostate cancer.

Knowledge of the problem

The author has made a detailed review of the epidemiology of prostate cancer. He drew attention to the role of genetic and epigenetic factors in the development of prostate cancer. Globally, he evaluates the incidence of prostate mortality, as well as analyzes the pace and development trends of prostate cancer determining the survival of patients at high risk of developing metastatic cancer and biochemical progression, which is the basis of his work to prove the need for multimodal treatment in the group of patients at high risk of disease progression.

The aim of this study is to analyze the multimodal treatment of high-risk prostate cancer by performing a retrospective analysis of dispensary patients on the territory of oncological hospital "Marko Markov" Varna. The study was retrospectively single-centric and included 1,275 patients and treated in St. Anna" in the clinic of urology for the period from 1996 to 2022.

To achieve his goal, the author sets himself six tasks, formulated clearly and comprehensibly and answer the questions posed to determine prognostic criteria determining the survival of treated patients according to biochemical and clinical progression, Gleason score, PSA values, and TNM stage.

The author has shown that patients with newly diagnosed prostate cancer should be considered collectively to find the group of patients with an increased risk of failure in radiotherapy or radical prostatectomy. In this high-risk group, multimodal treatment can give better control of the disease.

It has already been established that at clinical stage T3-T4, the combination of radiotherapy followed by hormone therapy improves survival. Incorporation of adjuvant or neoadjuvant hormone and/or chemotherapy followed by radical prostatectomy and enlarged lymphatic dissection increases survival in these patients. The concept of a multimodal approach to the treatment of prostatic carcinoma in biochemical progression is an interest of many scientists and a number of multi-centric studies have been done especially among groups of newly

diagnosed patients with prostate but locally advanced cancer. These patients represent an intermediate stage between localized and metastatic cancer with a high propensity for biochemical and clinical progression and probable rapid mortality. These are patients in whom intensified treatment is essential to reduce mortality. In them, increasing the dose in radiotherapy, including combination with hormone therapy, supplemented by brachytherapy, show promising results and probably outperforms the method of monotherapy with high-dose telebrachytherapy. Therefore, I believe that the topic of scientific work is relevant not only for our country, but also internationally. The scientific work of Assoc. Prof. Ganev on the multi modal therapy of patients in the group at high risk of biochemical progression of disease.

Structure of the dissertation

The review was prepared on the basis of a dissertation paper in a volume of 150 pages of which 37 references, illustrated with 26 figures, 5 tables and 506 references most of which in the last 10 years. It is structured according to the rules for preparing a dissertation and is moderately balanced as a ratio between the sections. I am pleased to emphasize the maximum visualization of the results with informative figures, tables and graphs. The results have been processed statistically, with the author showing that he is proficient in a wide range of statistical methods to fulfill the purpose of his study. Statistically significant results are well discussed in the autoreferentia and dissertation.

Methodology of the study

The study is single-center, non-interventional retrospective. The analysis is of patients undergoing radical prostatectomy at the Urology Clinic of St. Anna Hospital – Varna. for the period from January 1996 to May 2022 and were followed at for Oncological Diseases "Dr. Marko Markov" in compliance with the generally accepted ethical requirements. The criteria for inclusion in the study were radical prostatectomy, radiotherapy or hormone therapy. Excluded from the study 404 patients who are from other areas and do not have The final analysis was performed on the basis of a sample of 871 patients. Patients were assigned to a control and risk group that included 491 patients with a median age of 67 years. $PSA \geq \leq 17$ stage $\geq \leq T2$ Gleason score sum 4-10 survival ranged between 0-19 years The control group included 380 patients with a median age of 66 years. PSA

10 Gleason score 2-7 survival is up to 25 years. In the second place, survival up to and over 5 years is considered. A statistically significant association was found between patients in the risk group were more likely not to survive 5 years 1.54 times higher than that of patients in the control group. With survival over 5 years, the risk of death in high-risk patients in the first 5 years is 6.6 times higher than the control group. Of interest is the study showing survival until the onset of metastases and then relative to the control group. Of the 143 patients who died in the risk group, 38 began due to clinical progression of the disease. Patients with clinical progression have a 92-fold higher risk of dying from cancer than patients without clinical progression.

The timing of biochemical progression showed that patients in the risk group had a 1.5-fold higher risk of receiving biochemical progression than those of patients in the control group, which was detected by an increase in PSA. Of all the patients studied, 485 died, 89. Of the 140 patients treated with dual therapy, 15 died, and of the patients on triple therapy, which are 345 of them 74 died. A statistically significant relationship was found between type of therapy and mortality. Of the 461 patients in the high-risk dual therapy group, 119 were beers and 342 had triple therapy. All 380 patients in the control group were treated with RP alone.

In the group that survived up to 5 years are 54 patients of whom with dual therapy are 15, and with triple 8 on this indicator there are no significant differences in overall survival. Patients with dual therapy have an overall survival rate that ranges from 1-8 years and with triple therapy the survival is from 0-19 years.

There was no statistically significant difference in survival over 5 years between those treated with dual and triple therapy. In Chapter IX, the author discusses five main causes of cancer mortality. Development of the clinical picture, biochemical progression by increasing the values of PSA, the stage of the disease determined by the Gleason score, the PSA values ≥ 20 .

Found that there was a statistically significant association between GS values and biochemical tumor progression and that the risk of metastasis in GS ≥ 7 patients was 2.5-fold greater than patients with smaller GS.

Characterization and evaluation of dissertation and contributions

The dissertation of Assoc. Ganev is dedicated to the development of a topical topic with important practical application, using an appropriate methodology and the results obtained meet the set goal. From the studies carried out, 8 conclusions were formulated. I accept the formulated 7 contributions of the dissertation. The author, through his dissertation, demonstrates that he has mastered the

methodology of scientific research, that he is able to analyze literature, to pose a scientific problem, to formulate a hypothesis, purpose and tasks of the study, to select and apply the appropriate methods of analysis and to draw correct conclusions. I believe that Assoc.Proff. Ganev did an excellent job in his work. The autoreferate meets the requirements of the Law on the Development of Academic Staff.

Udgement of publications and personal contribution of the dissertant

Ass. Proff. T. Ganev has published the results of his work to the scientific community in Bulgaria. The author is 10 publications related to the topic.

Conclusion

The doctorate of Assoc. Proff. Toshko Ganev PhD on the topic ***Multimodal strategy for the treatment of high-risk prostate cancer*** meets the requirements of the Law on the Development of Academic Staff in the Bulgari Republic.

This is an up-to-date, well-planned and realized scientific work. Therefore, I give my **positive assessment** of the dissertation and take the liberty of calling on the honorable members of the Scientific Jury to also **vote positively** and to award to Assoc. Proff. Toshko Yordanov Ganev educational and scientific degree "**Doctor of Medical Sciences**" in the specialty "Urology" to which I join.

Varna

30.10.2023.

Assoc.Proff. N. Evtimov MD PhD



