REVIEW

of a dissertation

for awarding the educational and scientific degree "doctor "

in the professional area 4.1. Physical sciences,

defense procedure at the Faculty of Physics

of Sofia University "St. Kliment Ohridski"

This review was prepared by Prof. Jenia Nachkova Vassileva, PhD, in her capacity as a member of the scientific jury, according to the Order No. RD 38-53/26.01.2024 of the Rector of Sofia University "St. Kliment Ohridski".

Dissertation topic: METHODS FOR DOSIMETRIC ASSESSMENT, OPTIMIZATION AND CONTROL OF RADIOTHERAPY PLANS

Author: DIMITAR ROSENOV PENEV
Academic supervisor: Prof. Dobromir S. Pressyanov, Ph.D., D.Sc.
Scientific consultant: Pavel Stavrev, Ph.D

I. GENERAL DESCRIPTION OF SUBMITTED MATERIALS

1. Submitted documents

The PhD candidate Dimitar Penev has submitted a dissertation thesis, an abstract in Bulgarian and in English, as well as an author's reference for the contribution nature of the works with a comparative table according to the requirements of the Regulation for the conditions and procedures for acquiring scientific degrees and holding academic positions at Sofia University. A curriculum vitae, a copy of the MSc diploma with the professional qualification "Master of Medical Physics" from Sofia University, a declaration of authorship and copies of the main publications on the dissertation work are also presented.

The defense documents submitted by the candidate correspond to the requirements of the Bulgarian lows and regulations, as well as the Regulation for the conditions and procedures for acquiring scientific degrees and holding academic positions at Sofia University.

2. Information about the PhD candidate

Dimitar Penev holds a bachelor's degree in medical physics (awarded 2016) and a master's degree in medical physics (awarded 2018) from the Sofia University "St. Kliment Ohridski". Since 2019 he

has been enrolled as a PhD student at the Department of Atomic Physics of the Sofia University, in the professional field of Physical Sciences, doctoral program "Nuclear Physics".

From 2017 to 2018 he worked as a physicist at the Radiation Protection in Medical ExposureLaboratory at the National Center for Radiobiology and Radiation Protection, and from 2018 to present he has been working as a medical physicist at the Clinical Dosimetry and Radiation Protection Laboratory at the Clinic of Radiation Therapy of the Specialized University Hospital for Active Oncology Treatment in Sofia. The candidate continues his professional development through thematic courses in Bulgaria and abroad, including a course on radiotherapy planning and related activities.

The candidate is a lecturer and tutor in the course on Clinical dosimetry (Physics in radiotherapy) for MSc students in Medical Physics at the Faculty of Physics of the Sofia University, as well as a lecturer in the course in English on Radiation treatment planning for MSc students Medical Physics (in English) under the MODERN-A project.

Dimitar Penev's scientific interest in the field of radiobiological modeling dates back in his university education, including the topic of the master's thesis defended with honors in 2018.

3. General characteristics of the candidate's scientific achievements

The dissertation is devoted to the very current topic of the integration of radiobiological knowledge for increasing the effectiveness of radiation therapy - a method based on the destruction or slowing of tumor growth by irradiation with high doses of ionizing radiation of different types and energies. Modern radiation therapy is one of the fastest growing and most technological medical specialties, in which variation of sources is used - radioactive sources, X-ray tubes and accelerators of electrons, protons and other heavy nuclei, as well as a variety of accompanying methods and equipment for diagnostics imaging and image guidance, computer systems for ttreatment planning and dosimetry equipment. This also determines the interdisciplinary nature of radiation therapy, in which medical physicists play an essential role. The development of radiation therapy technologies, modalities and methods is aimed at improving the accuracy of dose delivery in the tumor, while keeping dose to surrounding normal tissues as low as possible. For this purpose, a variety of percutaneous and brachytherapy techniques are developed and applied, which are selected according to the characteristics of the patient and the tumor. The dissertation discusses the current techniques of conformal, intensity-modulated (IMRT, VMAT) radiation therapy, as well as different approaches to dose fractionation - conventional with a large number of fractions with a dose per fraction between 1.5 to 4 Gy, and stereotactic or radiosurgery (SRS and SBRT) , with a small number of fractions with

a dose per fraction of 6 to 30 Gy (hypofractionation). The goal is to increase the effectiveness of the radiation treatment outcome – a high probability of local tumor control and an increased chance of cancer cure, while reducing the risk of unwanted complications in normal tissues and other side effects. Even small deviations of the delivered radiation dose from the optimal evidence-based prescribed dose can compromise the clinical outcome. All this determines the importance of the candidate's research and the contributions of the dissertation.

The dissertation presents the results of efforts to optimize the radiation treatment plan and increase the effectiveness of the outcome of percutaneous radiation treatment with high-energy photons from a linear accelerator, by applying radiobiological models to estimate the tumor control probability (TCP) and integrating them into the therapeutic plan . In my opinion, this is how the goal of the dissertation work could be defined, and the goals formulated at the end of the first chapter of the dissertation are rather the tasks for achieving this goal.

As his first objective (task), the candidate defines tracking the progress of radiobiological models for the assessment of TCP and normal tissue complication probability (NTCP). This is essentially a study of the state of the problem and a review of the scientific literature, which cannot be the goal of the dissertation, but a mandatory condition on the basis of which the goal and tasks are formulated. The first objective (task) could be refined to match the work done and reported as an achievement, namely – creating computer models based on theoretical models for TCP and verifying them by comparing the results of their application with published experimental data. The other three objectives (tasks) formulated by the candidate have been fulfilled and properly presented as contributions: the influence of hypoxia on TCP during hypofractionated irradiation has been investigated and evaluated and it has been confirmed that tumor control depends mostly on the death of the most radioresistant tumor cells in the cell conglomerate; the effect of different intervals between irradiations on the probability of tumor control was investigated and the effect of tumor dose uncertainty on the probability of tumor control was analysed.

The results of the dissertation work have been published in three original scientific publications in the journals Physics in Medicine & Biology (2018), Medical Physic (2021) and The European Physics Journal Special Topics (2023), in two of which the candidate is a co-author, and in one he is the lead author. The results have also been presented at scientific forums, with two extended abstracts of the reports published in the journal Physica Medica and two in Radiotherapy and Oncology.

The abstract presents well the main parts of the dissertation, with an emphasis on the description of work done and the achievements.

4. Analysis of the dissertation content and of the scientific and applied achievements

The dissertation is structured in ten chapters and is presented in a total of 102 pages, 27 figures, three tables and four appendices. It also includes 130 references, which are were properly cited in the literature review and in the analysis of the own results. The reference list includes the three scientific publications of the candidate that are presented in Chapter 8 with the scientific contributions and publications related to the dissertation work and should not appear in the list of references.

The structure of the work is untypical for a dissertational that hampers reading and makes it difficult to distinguish the own work from the literature review on the discussed issues. The first three chapters are essentially an overview of the subject. They briefly but clearly discuss the goals and methods of radiation therapy, types of radiation therapy, and dosimetric planning techniques. The different methods of fractionation – conventional radiotherapy and stereotactic (radiosurgery) – are defined, which are the subject of study and comparison in the dissertation in terms of the tumor control probability. The second chapter presents the purpose and content of procedures for dose calibration of radiotherapy equipment and quality assurance at all stages of radiotherapy, with an emphasis on dosimetric planning and criteria for verifying the accuracy of the realized dose distribution compared to the planned one, which is also investigated in the dissertation. In the third chapter, the basic concepts related to the processes taking place in the tumor and tumor dynamics and the radiobiological models used to evaluate the result of radiation therapy are introduced. The thesis would have been easier to read if these three parts had been united and more clearly separated from the methods used to achieve the objective of the work and the results of the implementation of the defined tasks.

The presentation of the own work carried out by the candidate begins in the fourth chapter, and its individual stages are presented sequentially in the next four chapters of the dissertation (from the fourth to the seventh).

The fourth chapter is key to the dissertation, as it presents the existing theoretical radiobiological TCP models and discusses the biological and geometrical parameters affecting the dose-response curve. An essential part in this chapter is the presentation of the results of the radiobiological modeling done by the candidate using Monte Carlo codes developed by him, as well as their validation. For this purpose, a comparison was made with the results of the analytical calculations based on the theoretical models and with the published experimental data from the in vivo studies of Fischer et al. with laboratory mice irradiated with seven different fractionation regimens, and from the in vitro experiment of Tarnawski et al. with mega colonies of two cell types irradiated with three dose

fractionation regimens. Despite the detailed discussion of the results in the text, the end of the chapter lacks summary conclusions on this task.

In the shorter fifth chapter, which is presented on three pages, the cellular radiosensitivity of a heterogeneous tumor composed of two subpopulations of cells – hypoxic (radioresistant) and oxygenated (radiosensitive) – was investigated by two methods – pseudo-experimental cell survival curves and TCP. It is concluded that the probability of tumor control when irradiating a heterogeneous tumor depends entirely on its hypoxic subpopulation of cells, even if it is the smallest.

In the sixth chapter, the influence of the radiation scheme on the probability of tumor control was investigated, applying two theoretical models that take into account the reoxygenation of tumor cells - the Zaider-Minerbo-Stavreva (ZMS) model and the Ruggieri-Nahum (RN) model. Different SBRT fractionation regimens, proposed in several clinical trials and differing in the interval between fractions and total radiation time, were compared. The applicability of the developed computer codes for simulating the parameters of the radiobiological model and for choosing the radiation scheme in order to achieve maximum tumor control is shown. It is again confirmed that hypoxic cells in the tumor determine treatment outcome in terms of TCP.

Chapter seven explores and discusses the impact and components of dose uncertainty on the probability of tumor control. With the help of a developed computer code, a theoretical study of TCP was carried out, taking into account the reoxygenation process. 10,000 scenarios were run, simulating a normal distribution around the target (true) dose value with deviations between 1 and 10%, and at different fractionation regimes for conventional and hypofractionated radiotherapy (SBRT). It has been shown that hyporactionated irradiation with high doses per fraction requires less dose uncertainty to achieve the desired tumor control. This requires the application of stricter accuracy criteria, quality assurance procedures, and verification of treatment plans prior to their application to the patient.

5. Critical notes and recommendations

The presented dissertation work has indisputable scientific and scientific-applied contributions. The work is sufficient in volume and is based on a thorough knowledge of the theory of the radiobiological effects of photon radiation on different types of tumor cells and healthy tissues, as well as the factors that determine and modify these effects. A good knowledge of the analytical models of the tumor control probability is demonstrated, which, together with the normal tissue complication probability, allow to objectively optimize the radiation parameters and increase the effectiveness of radiation therapy. The candidate applies successfully Monte Carlo computer modeling methods, and verifies

the developed codes by comparing radiobiological models with published experimental results. All simulated exposure situations are taken from real clinical research studies or from routine clinical practice, which increases the value of the dissertation. The set objectives are fulfilled, and the contributions are correctly formulated. I do not detect any plagiarism in the work.

My remarks are mainly about the structure and style of the dissertation work. As I have already pointed out, typical for such a work structural elements are absent, such as literature review, material and methods, results, discussion and conclusions. The absence of a summary and conclusions from the tasks performed makes it difficult to assess the contributions to be sought in the text.

Reading is also hampered by the abundance of stylistic and grammatical errors, as well as terminological inaccuracies and lack of systematicity in the terms used in Bulgarian. I will give just a few examples: On page 4, the quantity "dose", D, is introduced, instead of the correct term "absorbed dose". Needless to say, page 18 discusses radiation weighting factors for different types of ionizing radiation, since this quantity was introduced by the International Commission on Radiological Protection (ICRP) for radiation protection purposes to describe stochastic effects, which are not discussed in the dissertation. For the purposes of radiobiological consideration in radiotherapy, it is sufficient to discuss the quantity relative biological effectiveness (RBE). Pages 6 and 7 refer to "quality assurance of dosimetry equipment", although meaningfully the text discusses quality assurance of radiotherapy equipment. On page 9, the abbreviations TCP and NTCP are used for the first time without explanation, which appears later in the text. The term "cell killing" is not used with the proper Bulgarian term. On page 74 there is a discussion about calibration and radiation output of the "radiation machine" instead of the correct terms "radiation equipment" and "dosimetric calibration". In places, foreign words for "response", "distribution" or “reporting” are used instead of the proper Bulgarian terms. It is not clear why the quote from Ruggieri et al. on page 17 is in English.

The indicated inaccuracies are not related to the essence of the scientific work and do not change my assessment of its value and its scientific and scientific-applied contributions.

I recommend candidate to continue his research on this important for clinical radiotherapy practice and very current topic, by applying the developed methods to the modeling of the NTCP function and the optimization of the irradiation plan, simultaneously considering the parameters modifying TCP and NTCP. I hope that he will also continue his specialization in the clinical specialty "Medical Radiological Physics" with the subsequent acquisition of the qualification " Medical Physics Expert", which are a prerequisite for independent clinical work and for his full academic involvement in the education and training of qualified medical physicists.

6. Conclusion

After having familiarized myself with the presented dissertation work, abstract and other materials, and based on the analysis of their significance and the scientific and scientific-applied contributions, I **confirm** that the scientific achievements meet the requirements of the respective Bulgarian low and regulations, as well as the procedures and criteria of Sofia University for awarding the educational and scientific degree "doctor". The candidate satisfies the minimum national requirements in the professional field and no plagiarism has been found in the dissertation, abstract and scientific works submitted for the defence.

I give my **positive assessment** of the dissertation work.

II. GENERAL CONCLUSION

Based on the above, I recommend the scientific jury to award to Dimitar Rosenov Penev the educational and scientific degree "doctor" in professional area 4.1. Physical sciences.

18 April 2024 г. Reviewer: 

Prof. Jenia Vassileva, PhD