STATEMENT OF ACADEMIC OPINION

on a PhD thesis for obtaining PhD degree

in the field of Higher Education 4. "Natural sciences, mathematics, and computer science", professional field 4.1. "Physical sciences", Sofia University "St. Kliment Ohridski"

The opinion was prepared by: Prof. Eng. Kristina Stanimirova Bliznakova, PhD, Medical University - Varna, in her capacity as member of the scientific jury according to Order No. RD 38-53/26.01.2024. of the Rector of Sofia University.

Dissertation topic: "Methods for dosimetric assessment, optimization and control of radiotherapy plans"

Author of the dissertation: Dimitar Rosenov Penev

I. General description of the presented materials

1. Data on submitted documents

The candidate Dimitar Rosenov Penev has submitted a dissertation on "*Methods for dosimetric assessment, optimization and control of radiation therapy plans*" and an extended abstract, as well as the mandatory tables for the Faculty of Physics from the Regulations for the Terms and Procedures for Acquiring Scientific Degrees and Occupying Academic Positions at Sofia University "St. Kliment Ohridski". The candidate collects 50 points for group of indicators A and 70 points for group of indicators D, according to the regulations of the Faculty of Physics. Further, the candidate collects additionally 7 points from the Additional Requirements of the Faculty of Physics, which results in a total number of 127 points, which is excellent achievement.

Dimitar Penev's dissertation consists of a total of 102 pages, including an Introduction chapter, 6 main chapters, a chapter with scientific contributions and publications, four appendices with Monte Carlo code written in MATLAB and a list of references. The structure of the dissertation and related achievements correspond to the current standards for dissertation work. The dissertation work is well structured, including 29 figures and 3 tables. The abstract is presented in Bulgarian and English and fully reflects the structure and content of the dissertation, emphasizing the most important results and achievements.

The documents submitted by the candidate for the defense correspond to the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria, Regulation for the Implementation of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Terms and Conditions for Acquiring Scientific Degrees and Occupying Academic Positions at Sofia University "St. Kliment Ohridski".

2. Applicant data

Dimitar Penev completed a bachelor's and master's program in medical physics at Sofia University "St. Kliment Ohridski" in 2016 and 2018 respectively. Since 2019, he is a PhD student in the PhD program "Nuclear Physics" at the Atomic Physics department of the same university. Since completing his master's degree, he has participated in prestigious specialized courses to improve his qualifications in the field of radiation therapy.

Dimitar Penev is a leading lecturer in the disciplines "Radiation treatment planning" and "Clinical dosimetry" in English and Bulgarian in the MSc program "Medical Physics" at the Faculty of Physics of Sofia University. His professional path includes an appointment as a physicist at the National Center for Radiobiology and Radiation Protection and currently as a medical physicist at the Radiotherapy Clinic of the University Specialized Hospital for Active Treatment in Oncology in Sofia.

He is a member of the Bulgarian Society of Biomedical Physics and Engineering, as well the author of 5 scientific publications indexed in the scientific database Scopus, and has an h-index of 2. He has participated in 4 scientific forums.

3. General description of the candidate's scientific achievements

Chapter 1 **Introduction** clearly and focusedly introduces the goals of radiotherapy, types and techniques of dosimetric planning. The four objectives of the dissertation work are clearly defined and described.

In Chapter 2 **Dosimetry and dosimetric methods and tools in radiation therapy. Quality assurance**, the dosimetric control procedures used in the medical facility where Dimitar Penev works are considered. This chapter discusses the sources of error that can occur in the administration of radiotherapy to a particular patient. In addition, the important aspect of dosimetric plan feasibility verification is also addressed.

In Chapter 3 **Basic Concepts and Relationships**, the fundamental concepts related to tumor processes and tumor dynamics are examined, as well as various radiobiological models used to evaluate the results of radiation therapy. The response of the cells to x-ray radiation is examined in detail, discussing the processes leading to cell damage and death.

The main models describing the cell response to ionizing radiation are described, including the Single Hit Model, Multi Hit Model, Single Hit – Multi Target Model, Linear-Quadratic Model, as well as the evolution of the models over the years to better describe the cellular response of irradiation. Further, in this chapter, Dimitar Penev presents in detail the five main biological factors that influence radiation therapy. Methods for calculating the tumor control probability (TCP) and their evolution over time, applicable to both population and individual TCP models, are discussed in detail.

In Chapter 4 **Evaluation of Dose-Response Relationships Using TCP Models Using Data from Animal Experiments** Monte Carlo programming codes have been developed that use data from animal experiments to find different values of radiobiological parameters for individual TCP models. This chapter establishes the interrelationship between TCP model parameters. The new finding is the linearity of this interrelationship between the radiobiological parameters α, β and $\log(N_0)$ in the three-

dimensional space. A unique set of TCP parameters can be determined by varying treatment regimens or by combining TCP experiments and cell survival experiments.

The PhD student has developed a MATLAB Monte Carlo code that simulates the processes occurring in the tumor during treatment and subsequently estimates the probability of tumor control under different treatment regimens. This code has been used to analyze data from experiments by other researchers using different fractional irradiation regimes.

Chapter 5 **An opportunity to estimate the range of cellular radiosensitivities for cellular conglomerates with different radiosensitivity** investigates the radiosensitivity of the cells of a heterogeneous tumor by two methods: pseudo-experimental cell survival curves and tumor control probability. The study well demonstrated that the probability of tumor control when irradiating a tumor that is heterogeneous in radiosensitivity depends mainly on the radioresistant component of the cells.

Chapter 6 **Changing the irradiation scheme and influencing the probability of tumor control** is the subject of a theoretical study related to the achievement of tumor control in different fractional regimens, where the same dose per fraction is applied in the same number of fractions, but the time between them (and the total time of therapy) varies. The study included two TCP assessment models that differed in how the tumor was modeled. The advantages of the extended fractional mode over the conventional one are discussed in detail, as well as the conditions under which this advantage was observed using the model of Zaider - Minerbo - Stavreva.

Ruggeri's model confirms the fact that reoxygenation of chronically hypoxic cells does not affect tumor regrowth and at the studied time regimens of radiation therapy. This lack of dependence is well explained very well by calculating and analyzing the survival probability of the different subpopulations of cells: in the oxic state, the chronically hypoxic component of cells, and those in the acutely hypoxic state. The hypothesis that a subpopulation of hypoxic cells controls treatment outcome in relation to TCP has been well proved.

Chapter 7 **Influence of dose uncertainty on the probability of tumor control** presents a theoretical study of deviations in the delivered dose from the reference within wide limits - from 1% to 10%. These cases were analyzed with conventional radiation from Monday to Friday and hypofractionated radiation therapy with a high dose per fraction. The study demonstrated that fractional dose uncertainty plays a significant role in radiotherapy outcome, with a more prominent influence of dose uncertainty observed in radiosurgery radiation mode.

The scientific publications included in the dissertation work are three full-text articles published in journals classified in quartiles Q1 (2 articles) and Q2 (1 article). These publications have been selected taking into account the subject of the dissertation work and represent a significant contribution to the scientific field. They significantly exceed the minimum national requirements, as well as the additional requirements of Sofia University "St. Kliment Ohridski" for obtaining PhD degree in the relevant scientific field and professional direction. Additionally, no cases of plagiarism were

found in the presented dissertation and abstract, as they fully reproduce the original scientific research of the doctoral student.

4. Characteristics and assessment of the candidate's teaching activity

Dimitar Penev delivers lectures and exercises in the discipline "Clinical Dosimetry" for the MSc program of "Medical Physics", at the Faculty of Physics, Sofia University "St. Kliment Ohridski". He is also a leading lecturer of the course "Radiation treatment planning" for MSc program in Medical Physics in English, which takes place within the frame of MODERN A project. The two disciplines are closely related to his area of expertise, giving him the opportunity to share his first-hand practical experience from working in the clinic with future medical physicists.

5. Content analysis of the applicant's scientific and scientific-applied achievements contained in the materials for participation in the competition

Dimitar Penev has declared 4 new scientific and scientific-applied contributions, which are logical and I firmly believe that these contributions are sufficient to acquire a PhD degree.

A new scientific and applied science contribution is the successful validation of the Zaider-Minerbo-Stavreva (ZMS) TCP model, taking into account cells reoxygenation. To this end, data from the animal experiments of Fischer et al. were used to fit the ZMS model. This contribution is of utmost importance, as it represents the main requirement for the use of any scientific-mathematical modeling - prior successful validation with real experimental data.

A new scientific and scientific-applied contribution is also an assessment of the influence of hypoxia on TCP during hypofractionated radiation therapy, using two different TCP models - by Zaider - Minerbo - Stavreva and Ruggeri. This contribution is extremely important for the practice and applications of fractions for better treatment outcome.

Another new, scientific and scientific-applied contribution is the confirmation through the used TCP models that tumor control mainly depends on the death of the most radioresistant tumor cells in the cell conglomerate. This contribution is of extremely practical importance when applying the different therapeutic regimens with the aim of a better outcome of the treatment.

A significant scientific contribution is the demonstrated assessment of the impact of dose uncertainty on the probability of tumor control at different baseline values. The contribution has a scientific-applied aspect by showing the stronger impact of dose uncertainty in radiosurgery radiation modes. It was found that dose uncertainty plays a significant role in treatment outcome and that the smaller the fractions, the larger the doses, the greater the influence of TCP dose uncertainty. The contribution is extremely applicable in practice.

Dimitar Penev has presented 3 publications in journals with a high impact factor such as Eur. Phys. J. Spec. Top (Q2) , Med. Phys. (Q1), Phys. Med. Biol (Q1). In one of them, he is the lead author. Additionally, 4 independent citations were reported. The article in which Dimitar Penev is the lead author was successfully cited by Alexander Jaksic (https://doi.org/10.1140/epjs/s11734-023-00907-4) with sufficient space devoted to the results of the theoretical study related to the study of dose uncertainty on the probability of tumor control. I perceive the research, results and contributions as

an individual work of Dimitar Penev. In addition, he has presented 4 reports at international conferences.

6. Critical notes and recommendations

I have no critical remarks about the dissertation and the work done. Some small remarks are related to the formatting of the equations, which are not consistent throughout the dissertation. Some of the figures, such as Figures 2 and 3, have insufficient resolution. Also, some tables, such as Table 1, are not properly formatted. Some figures are not numbered, such as those on page 47, and the same applies to the equations on page 48. These remarks do not change the overall assessment of the outstanding work presented in the dissertation.

7. Personal impressions of the candidate

I know Dimitar Penev from the course "Computer simulations and models in medical physics", which I lead at the National Center for Radiobiology and Radiation Protection. My impressions of his participation in the exercises, which were related to Monte Carlo techniques in medical imaging and radiation therapy, are excellent.

8. 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 contained in them, **I confirm** that the scientific achievements meet the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria, the Regulation for its Implementation and the corresponding Regulations at Sofia University "St. Kliment Ohridski" for **obtaining PhD degree**. In particular, 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 competition.

I give my **positive** assessment of the dissertation work and express my full support for the awarding of the PhD degree to Dimitar Penev.

II . GENERAL CONCLUSION

Based on the above, **I recommend** the scientific jury to award Dimitar Rosenov Penev the **PhD degree** in the field of Higher Education 4. "Natural sciences, mathematics, and computer science", professional field 4.1. "Physical sciences".

18.04.2024 Prepared by : ....

Varna (Prof. Eng. Kristina Bliznakova, PhD)