REVIEW

of a PhD thesis
for the educational and scientific degree "PhD"
in professional field 4.1. Physical Sciences, DP "Nuclear Physics",
under the procedure for defence at the Faculty of Physics
of Sofia University "St. Kliment Ohridski" (SU)

The review was prepared by Assoc. Prof. Dr. Desislava Zvezdomirova Kostova-Lefterova, National Cardiology Hospital, MU-Pleven, as a member of the scientific jury, according to the Order № RD 38-53/ 26.01.2024 of the Rector of Sofia University.

Thesis topic: 'Methods for dosimetric evaluation, optimization and control of radiotherapy plans'
Author of the PhD thesis: Dimitar Rosenov Penev

I. General description of the submitted materials

1. Details of the submitted documents

The candidate Dimitar Rosenov Penev has submitted a PhD thesis and an Abstract, as well as the obligatory tables for the Faculty of Physics from the Rules and Regulations of the University of St. Kliment Ohridski. There are also 6 other documents (reference to the scientific contributions of the PhD thesis, reference to the citations of the publications, list of publications and participation in scientific forums, copies of publications, CV of the author, declaration of authorship and copy of the Master's degree) supporting the candidate's achievements.

Note: The author's reference provided for the contributions of the works of Dimitar Rosenov Penev is not a real reference for the scientific contributions of the PhD thesis, but is a comparative table with recommended requirements of the FPh.

The documents presented by the candidate in the defence comply with the requirements of the Law on the Acquisition of Scientific Degrees and Academic Positions at the Sofia University "St. Kliment Ohridski".

The PhD dissertation is written in 85 pages of main part and 102 pages in total, including 8 pages of bibliography, 4 appendices of 8 pages and 1 page of acknowledgements. The thesis is richly illustrated - it contains 27 figures, some with several separate parts. The number of tables is 3. The

list of references used includes 130 titles, and these are not arranged according to the BNS standard but in order of appearance in the text.

The abstract of Mr. Penev's Ph.D. thesis meets the requirements and reflects accurately and completely its content, main developments and scientific and applied achievements.

2. Candidate details

Dimitar Rosenov Penev graduated from the Nature and Mathematics High School "Acad. Nikola Obreshkov", Razgrad. He graduated in 2011. In 2016, he graduated with a Bachelor's degree in Medical Physics from Sofia University "St. Kliment Ohridski", and in 2018 - Master of Science in Medical Physics. Since 2019 he is a PhD student at Sofia University in the professional field of Physical Sciences, PhD program "Nuclear Physics" at the Department of Atomic Physics. He started his professional development in 2017 as a physicist at the Laboratory "Radiation Protection in Medical Exposure", National Center for Radiobiology and Radiation Protection. Since 2018, he has been working as a medical physicist at the Laboratory of Clinical Dosimetry and Radiation Protection at the Clinic of Radiotherapy at the University Specialized Hospital for Active Treatment in Oncology, Sofia. He specializes in three courses related to his work as a medical physicist in the field of radiotherapy. He is a member of BSBPE. His research work and interests are in the field of radiobiological modelling, testing of TCP and NTCP models and the impact of dose uncertainty on treatment outcome, as well as the effect of different irradiation schedules on the probability of achieving tumour control.

3. General description of the candidate's scientific achievements

The relevance of Dimitar Rosenov Penev's dissertation work is indisputable - the methods for dosimetric evaluation, optimization and control of radiotherapy plans are essential for the accurate implementation of radiotherapy plans. The cancer treatment is one of the challenges in modern medicine. Dosimetry in radiotherapy and quality assurance are part of the tasks of the medical physicist.

The PhD student does not formulate one goal and tasks to achieve it, but defines 5 different goals, which I would rather define as tasks to achieve the main goal. Mr. Penev traces the progress of the various radiobiological models used to estimate the probability of tumor control and the probability of damage to normal tissue. The PhD student discusses in detail the mechanisms of cell damage and their incorporation into the radiobiological models themselves. Another of the objectives thus defined is related to the study of the application of radiobiological models to assess the impact of hypoxia in hypofractionated radiotherapy. In this thesis, the influence of different intervals between irradiations on the probability of tumor control and the influence of the uncertainty of the delivered dose to the tumor on the probability of tumor control are investigated.

Due to the lack of a clear structure of the proposed PhD thesis, in which the methods and materials as well as results, discussion and conclusions are defined in one place, it is extremely difficult to clearly trace Dimitar Penev's personal contribution in the text. The PhD student merges his additional developments and analyses with the literature review and current developments on the set objectives. Conclusions are not clearly drawn throughout the text.

Dimitar Penev discusses theoretically how uncertainties in the delivered dose affect the outcome of radiotherapy and the likelihood of tumour control. In Section 4. 1, Mr. Penev describes a code he developed that uses a "creeping" Monte Carlo method that searches for different values of the radiobiological parameters (N0 (initial cell number), α, and β (α is associated with a double-strand break from a single particle, while β is related to two-strand breakage by two separate particles)) that lead to identical values for the geometric D50 and γ50 (with a given tolerance ΔD50 and Δγ50) (the dose producing a 50% probability of replication and a population mean standard deviation of 50D). The dissertation concludes that the relationship between TCP model parameters (probability of tumor control, TCP) is expected, but the linearity of this relationship between α, β, and log(N0) in 3D space is a new finding. A similar linear relationship was found in the population model of Webb and Nahum, where different pairs of parameters αmean and ln(N) lead to identical values of D50. A unique set of TCP parameters can be determined by varying the treatment regimes to produce a range of TCP curves or by combining TCP and cell survival experiments. Additionally, a parameter that accounts for repopulation is included in the analysis.Разработен е втори „пълзящ“ Монте Карло метод [предоставен в Приложение 1], чрез който се търсят в параметричното пространство всички комбинации от параметри, които биха довели до идентични стойности на D_{50} и γ_{50} и респективно TCP, но за различни стойности на параметъра на репопулация.

Section 4.2 and 4.3 present analyses of the Fischer & Moulder data and the Tarnawski et al. To simulate the processes occurring in the tumour during treatment and subsequently assess the likelihood of tumour control under different treatment regimens, the PhD student proposes a Monte Carlo code written in Matlab and presented in Appendix 2. Mr. Penev first models the radiation-induced cell death process, followed by the processes of birth and natural (non-radiation) cell death, and for each cell surviving a fraction of irradiation from the total course of treatment - are compared to the time between the realized fraction and the next such fraction.

In Section 5, the PhD student investigates the cellular radiosensitivity of a heterogeneous tumour using two methods - pseudo-experimental cell survival curves and tumour control probability. The conclusion reached is that the probability of tumor control when irradiating a tumor heterogeneous in radiosensitivity depends entirely on the radiosensitive component of cells, even though it is the most abundant. Another conclusion is that the tumor can be viewed as a single-component in radiosensitivity - assuming one effective parameter value, αeff.

Section 6 presents a theoretical study related to clinical results from a study by Alite et al. in which tumor control is reported to be achieved with different SBRT regimens: conventional - 1-5 fractions implemented on consecutive days (Saturday and Sunday - rest), and extended - 1-5 fractions

implemented in a Monday-Wednesday-Friday schedule (Saturday and Sunday - rest). In their paper, Alite et al. reported that -SBRT therapy in five fractions delivered on non-consecutive days resulted in better local control and similar toxicity compared to irradiation on five consecutive days, a claim that is fully supported by the experimental data of van Putten, Fowler JF et al. and Fischer et al. [106]. For this purpose, the PhD student used two TCP models in which the reoxygenation of cells during the course of radiation treatment was taken into account.

The first model considers fractionated radiotherapy with arbitrary time intervals between fractions (formula 45) and accounting for tumor cell reoxygenation. It is assumed that reoxygenation causes simultaneous resensitization (change in radiosensitivity) of tumor cells located in a hypoxic state. It is concluded that higher values of αm for a given value of α0 is in favor of the prolonged regimens over the short one, since thus in most cases (depending on the value of the parameter b) the shorter treatment time is not sufficient for the radiosensitivity to reach its maximum value and thus to have the full advantage of the resensitization itself. Low values of b indicate slow resensitization. At the same time, prolonged regimes have no advantage at high values of the repopulation rate (λ), but it should be kept in mind that a high repopulation rate is not very likely when cells are in a hypoxic state.При вторият модел се оценяват различните режими на фракциониране при SBRT техника на облъчване, модел на Ruggieri-Nahum (RN).

In this TCP model, the tumor is viewed as a conglomerate of cells with different radiosensitivities and accordingly divided into three groups - oxygenated cells, acutely hypoxic cells and chronically hypoxic cells. Each of these sub-populations of cells is characterized by its own values of the parameters determining their radiosensitivity, α and β, involved in the LQ pattern of cell killing. In Appendix 3, Mr. Penev presents the formulas for calculating the average number of surviving oxy cells, acutely hypoxic cells, chronically hypoxic cells, and chronically hypoxic cells converted to oxy cells after n number of irradiations. The influence of the subpopulation of cells in the oxy state on the probability of tumor control was also investigated. Again, it is confirmed that the subpopulation of hypoxic cells (the most resistant) controls the treatment outcome in terms of TCP.

Section 7 theoretically investigates the impact of dose uncertainty on the probability of tumor control. Dose delivery to the tumor has uncertainty due to device-related factors, such as - calibration of the radiotherapy machine (machine flow rate, field profiles), position of the multileaf collimator (MLC) "leaf" at any time during the procedure (applies to intensity modulated techniques - IMRT, VMAT), computational algorithms of the scheduling system. Uncertainties related to the human factor are the correct delineation of the planned target volume (PTV) and critical organs (OAR), the movement of the tumor and critical organs during irradiation, the position of the machine mass, the immobilization means, the correct matching of the 3D image obtained by CBCT (Cone Beam Computed Tomography) immediately before irradiation, with that of the CT scanner, on which the 3D image is prepared the dosimetry plan itself. The uncertainty with which the ionisation chambers used in the measurements associated with the commissioning of the radiotherapy equipment and in the subsequent periodic quality control and calibration are calibrated is known. The Ph.D. student

developed a program written in Matlab and presented in Appendix 4 that considers cases of deviations of delivered dose from the reference (prescribed) dose over a wide range, from 1% to 10%. The conclusion of the study is that uncertainty in fraction dose is essential to the outcome of radiotherapy (in TCP terms). A more pronounced influence of dose uncertainty was observed in SBRT radiation regimens (with high fraction doses), necessitating the application of more stringent criteria. The largest deviations in TCP are observed for TCP values in the range of 30%-70%, due to the fact that these TCP values fall in the steepest part of the curve and even small deviations in dose lead to large changes in TCP value.

The scientific publications included in the PhD thesis fully comply with the minimum national requirements (according to Art. 2b, par. 2 and 3 of the Law on Research and Development) and with the additional requirements of St. Kliment Ohridski" for the acquisition of the educational and scientific degree " PhD". Two of the publications are in international journals falling in quartile Q1 and one in quartile Q2. Additionally, the PhD student has participated with 4 papers in international conferences where the results were presented. Dimitar Rosenov Penev, declares that the submitted dissertation on "Methods for dosimetric evaluation, optimization and control of radiotherapy plans" for obtaining the PhD degree in the professional field 4.1 Physical Sciences, PhD programme "Nuclear Physics", is an original work and the attached documents are reliable. It also declares that this thesis has not been submitted to any other institution for the award of the degree of PhD.

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

- Dimitar Penev's teaching activity is related to:
- - lectures and exercises on "Clinical Dosimetry" for Master students of the specialty "Medical Physics", at the Faculty of Physics, Sofia University "St. Physics and Physical Therapy, Department of Physics, Medical Physics Department, Sofia University;
- lectures on "Radiation treatment planning" to master students of the specialty "Medical Physics in English", at the Faculty of Physics, Sofia University 'St. Kliment Ohridski', under the MODERN-A project.

5. A substantive analysis of the applicant's scientific and applied achievements contained in the application materials

The scientific and applied contributions of this PhD thesis are:

-Successful fitting of the animal experimental data of Fischer et al. with the ZMS model accounting for cellular reoxygenation, thus verifying the model.

-Evaluation of the impact of hypoxia on TCP in hypofractionated radiotherapy using two different TCP models, TCPZMS and TCPRN.

-Through the TCP models used, it is confirmed that tumor control mainly depends on the death of the most radiation resistant tumor cells in the cell conglomerate.

-Evaluation of the impact of dose uncertainty on the probability of tumor control at different baseline values of this uncertainty.

In the course of the PhD thesis research, papers have been published where the PhD student is co-author on two papers and first author on one. The results have been presented in 4 papers at international conferences.

6. Critical remarks and recommendations

I would point to the disorganized structure of the PhD thesis as a major criticism. Proper structuring of the PhD thesis would facilitate its reading and use: Introduction; Literature review, which should clearly emphasize the relevance of the problem; Purpose (main purpose) and the tasks to achieve it; Methods and Materials; Results of the tasks; Discussion of the tasks and clearly drawn Conclusions.

7. Personal impressions of the candidate

I do not know Dimitar Penev well enough to present my personal impressions of him, but following his professional development and scientific developments, I see in his face a consistent and diligent young scientist with great potential for further developments and research in the field of radiotherapy. This is the first successfully defended PhD thesis by a medical physicist in the field of radiotherapy in many years, which in itself is a very great achievement and I welcome the motivation of the PhD candidate for the development and his desire to develop academically in the field of radiotherapy.

8. Conclusion

Having read the submitted PhD thesis, Author's abstract and other materials, and based on the analysis of their significance and the scientific and applied contributions contained therein, I confirm that the scientific achievements meet the requirements of the Law on Research and Development and the Regulations for its application and the relevant Regulations of the University of St. Kliment Ohridski" for the acquisition of the educational and scientific degree " PhD". In particular, the candidate satisfies the minimum national requirements in the professional field and no plagiarism has been found in the PhD thesis, Abstract and scientific papers submitted for the competition.

I give my positive evaluation of the PhD thesis.

II. GENERAL CONCLUSION

On the above basis, I recommend the Scientific Jury to award the degree of PhD in the professional field 4.1. Physical Sciences, DP "Nuclear Physics" of Sofia University "St.

17.04.2024 г. Reviewer: .....

(assoc. prof. Desislava Kostova-Lefterova, PhD)