PhD Research Report

Studies of the Relative Biological Effectiveness and Biological Dose in Proton and Carbon Ion Therapy

Abstract

Protons and heavier ions have an increased relative biological effectiveness (RBE) compared with photons. While various RBE models are applied clinically in carbon-ion therapy, the RBE in proton therapy is accounted for clinically by applying a constant RBE of 1.1. However, an increasing amount of experimental and clinical data show that the proton RBE varies spatially within the patient. In addition, the existing carbon-ion RBE models give substantially different RBE-weighted dose (often referred to as biological dose) distributions for the same irradiation scenarios. Improvement of the current RBE calculations is therefore crucial to improve the treatment that patients receive. In this thesis, variables that affect the RBE and biological dose models were studied using the FLUKA Monte Carlo code.

In the first part of the work described in this thesis, an experiment at the Oslo Cyclotron Laboratory (OCL) in which cells were irradiated by a low-energy proton beam was implemented in FLUKA (Paper I). The dose and linear energy transfer (LET) (both the dose-averaged LET (LETd) and LET spectra) were estimated in potential cell irradiation positions. The LETd values increased along the beam path up to approximately 40 keV/µm in the distal dose fall-off. The LET spectra became narrower with depth in water. Comparisons with a simulated 80 MeV proton beam showed that the OCL beam had significantly higher LETd values and much narrower LET spectra for the same LETd values. The FLUKA implementation of the OCL beam demonstrated the importance of knowing precise proton-beam characteristics to achieve accurate RBE versus LET data.

In the second part of the work described in the thesis, the RBE model that is applied clinically in carbon-ion therapy in Japan (the microdosimetric kinetic model, MKM) was implemented in FLUKA (Paper II). For the implementation, tables were generated that connected the saturation-corrected dose-mean specific energy to particle type and particle kinetic energy. The FLUKA implementation was then used to study the sensitivity of the MKM to variations in the model parameters (Paper III). The created specific energy tables agreed well with the tables applied clinically in Japan. The relative changes in the biological dose distributions during the sensitivity study were less than the percentage change of a model parameter. In addition, the simultaneous variation of multiple parameters produced smaller impacts on the biological doses in most cases compared with varying parameters separately. The MKM implementation enables conversion from dose distributions obtained with the local effect model (European RBE model) to MKM dose distributions, making direct comparisons with the Japanese clinical carbon-ion data possible.

In the final part of the thesis, the development of a biological dose model that accounted for hypoxia was described for protons and implemented in FLUKA (Paper IV), as well as in a FLUKA-based treatment-planning tool (Paper V). The hypoxia model estimates the biological dose as a function of RBE and oxygen enhancement ratio (OER). The OER is a function of the LET and the partial oxygen pressure (pO2), which was estimated in patients through use of [18F]-EF5 positron emission tomography (PET) images. Areas with low pO2 values were observed in the planning target volume of a head and neck cancer patient, and this resulted in volumes with lower biological dose than prescribed. Treatment plans that were optimised with the hypoxia method had a median biological dose that corresponded with the prescription dose, and physical dose distributions that were increased in the hypoxic areas. The optimisation of treatment plans with the hypoxia model showed good potential to include the OER, as well as the RBE, in treatment planning.

Overall, the work performed for this thesis has contributed to knowledge on the RBE and biological dose calculations in proton and carbon-ion therapy. Monte Carlo studies of an experimental or clinical proton or carbon-ion beam may help to reduce the uncertainties in the RBE and biological dose. Given the increase in the number of proton and carbon-ion facilities worldwide, improvement of the accuracy of RBE calculations to give patients the best possible treatment is more relevant than ever.

What was the motivation for the topic of your PhD work?

The relative biological effectiveness (RBE) makes it possible to utilise treatment protocols from past clinical experience with photons (or particles) in particle therapy, by delivering an RBE-weighted dose to the target area. However, the clinically applied RBE values have large uncertainties, which may lead to increased side effects. Currently, the choice of the most appropriate RBE model for clinical use, especially for proton therapy, is under debate. In my PhD, I have studied RBE models and methods for decreasing the uncertainties in the RBE for both proton and carbon-ion therapy. This has been an especially timely and exciting topic in Bergen during my PhD period, as we are currently planning our first proton centres in Norway.

What were the main findings of your PhD?

First, a low-energy proton beamline, which can be used to study the effects of high linear energy transfer (LET) from protons, was implemented in the FLUKA Monte Carlo (MC) code [1]. This demonstrated that high spatial and dosimetric precision, obtained through accurate MC implementation of a beamline, is essential for correct assessment of the LET during cell irradiation experiments.

Second, the Japanese carbon-ion RBE model (the MKM) was implemented in FLUKA [2], making the direct comparison of the MKM model with the corresponding European RBE model (the LEM) possible (Figure 1). The implementation was used to conduct a sensitivity study of the MKM model parameters [3], which showed that possible uncertainties in the parameters had smaller impacts on the estimated biological dose than the percentage uncertainty in the parameters.

Last, a biological dose calculation method, which accounts for both hypoxia and the RBE, was developed and implemented in FLUKA [4] and in a FLUKA-based treatment planning tool [5]. Underdosage of the tumour volume was seen when no account was taken of hypoxia. However, optimisation of treatment plans with the hypoxia model showed good potential for treatment planning (Figure 2).

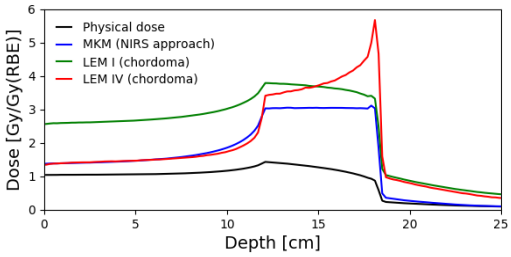

Figure 1: Biological dose in water as computed by the MKM (blue), the LEM I (green) and LEM IV (red). The corresponding physical dose (black) is also shown. The figure is taken from the PhD thesis [6].

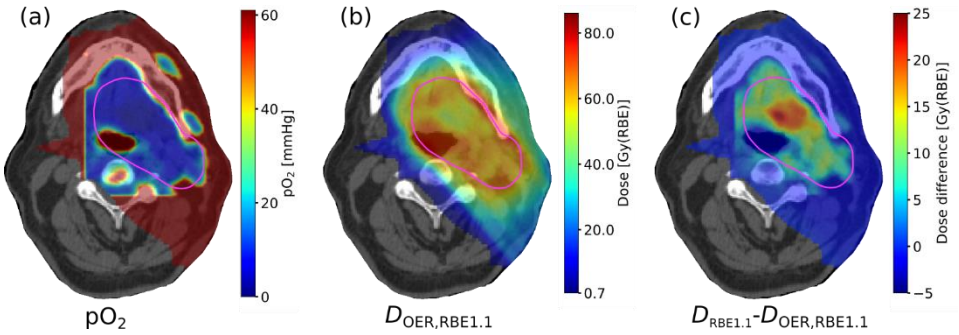

Figure 2: Head and neck cancer patient: partial oxygen pressure (pO2) map (a), biological dose accounting for hypoxia and an RBE of 1.1 (DOER,RBE1.1) (b) and dose difference between DRBE1.1 and DOER,RBE1.1 (c). The planning treatment volume is delineated in pink. The figure is taken from the PhD thesis [6].

Can you comment on the impact of your work to the field?

My PhD work has increased knowledge regarding the RBE and biological dose in proton and carbon-ion therapy. Additionally, it has contributed to scientific research with a thorough implementation of a simulation framework for particle therapy, based on the FLUKA MC code. This powerful research tool will be useful when decisions are made regarding which RBE models should be applied clinically in proton therapy. In addition, part of the implementation is already included in the FLUKA-based workflow for carbon-ion therapy at the particle therapy centre CNAO in Italy.

What was the most challenging part of your PhD?

It was at times hard to stay motivated when time-consuming MC simulations had to be repeated due to small mistakes or bugs. Also, during the final projects, we included the patient partial oxygen pressure (pO2) on a voxel-by-voxel basis in the estimation of the biological dose (Figure 2). This was estimated using [18F]-EF5 PET. However, the estimation of the pO2 from PET images is a challenge and is associated with large uncertainties. To solve this, we adapted a method that is used to estimate the pO2 from [18F]-FMISO PET, by applying [18F]-EF5 PET images of several patients and finding the PET uptake in organs with pO2 values that have been reported in literature.

Who or what inspired you most during your studies?

I was really inspired by the people in my group here in Bergen. The in-depth discussions we had about our projects really helped to solve challenges and to find ways to move forward. I was also inspired by visiting CNAO in Italy and observing the clinical environment at a particle therapy centre. I would definitely like to continue to work with the people in my group, as well as those who work clinically and with research at the Department of Oncology and Medical Physics at Haukeland University Hospital in Bergen.

Will you stay in the field? What are your plans for the future?

I would absolutely like to continue to work with medical physics, but I am not sure yet whether as a postdoctoral researcher or as a clinical medical physicist. I am currently working in a research project at Haukeland University Hospital, Norway, and I am excited to see what the future will bring. I am sure it will be interesting, as Bergen is planning to build its first proton centre soon.

To which institution were you affiliated during your PhD?

I was affiliated with the Department of Physics and Technology, University of Bergen, Norway. The particle therapy group at the University of Bergen focuses mainly on RBE modelling and biological dose calculations, but challenges around range uncertainties also form an active research area. During the last few years, the particle therapy research group at the University of Bergen has grown, both in the number of people there and in the number of collaborators. These include colleagues at other universities and hospitals in Norway, Denmark, Germany, Italy, Finland and the US.

When did you defend your thesis and who was your supervisor?

I defended my thesis on 28 April, 2020. My PhD supervisors were Kristian Smeland Ytre-Hauge (University of Bergen), Andrea Mairani (Heidelberg Ion Therapy Center (HIT) and National Centre for Oncological Hadrontherapy, CNAO) and Camilla Stokkevåg (Haukeland University Hospital and University of Bergen). I really appreciate the time they spent helping me with my project, and I really value all the scientific discussions we have had.

About the author

Tordis Johnsen Dahle received her bachelor's degree in physics in 2012 and Master of Science degree in medical physics in 2014, at the University of Bergen in Norway. After she completed her master's thesis, she worked for one year at the PET centre at Haukeland University Hospital, Norway, before starting her PhD in medical physics at the University of Bergen.

Her research interests are focused on RBE modelling and biological optimisation in proton and carbon-ion therapy. She is currently employed as a temporary researcher at Haukeland University Hospital.

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