The BIANCA Biophysical Model

Subjects: Others | Biophysics | Oncology
Contributor: Francesca Ballarini

Cancer ion therapy is constantly growing, thanks to its increased precision and, for heavy ions, its increased biological effectiveness (RBE) with respect to conventional photon therapy. The complex dependence of RBE on many factors demands for biophysical modelling. Up to now only the Local Effect Model (LEM), the Microdosimetric Kinetic Model (MKM) and the "mixed-beam" model are used in clinics. In this work the BIANCA biophysical model, after extensive benchmarking *in vitro*, was applied to develop a database predicting cell survival for different ions, energies and doses. Following interface with the FLUKA Monte Carlo transport code, for the first time BIANCA was benchmarked against *in vivo* data obtained by C-ion or proton irradiation of the rat spinal cord. The latter is a well-established model for CNS (Central Nervous System) late effects, which in turn are the main dose-limiting factor for head-and-neck tumors. Furthermore, these data have been considered to validate the LEM version applied in clinics. Although further benchmarking is desirable, the agreement between simulations and data suggests that BIANCA can predict RBE for C-ion or proton treatment of head-and-neck tumors. In particular, the agreement with proton data may be relevant if the current assumption of a constant proton RBE of 1.1 is revised. This work provides the bases for future benchmarking against patient data, as well as the development of other databases for specific tumor types and/or normal tissues.

Keywords: head-and-neck tumors ; ion beam radiotherapy ; relative biological effectiveness (RBE) ; RBE models ; carbon ions ; protons ; Monte Carlo simulations

1. Introduction

Cancer ion-beam therapy is spreading more and more worldwide, with more than 220,000 patients treated and more than 100 facilities in operation by the end of 2019. While most patients have been irradiated with protons, about 28,000 have been treated with C-ions (www.ptcog.ch).

Due to the high dose localization in the Spread-Out Bragg Peak (SOBP) region, radiotherapy treatments with charged particles like protons or carbon ions are characterized by a highly conformal dose distribution in the tumor. Furthermore, heavy ions like carbon possess a higher biological effectiveness within the SOBP. This is thought to be due to a higher level of DNA damage clustering, which is less likely to be repaired. This is an advantage especially for patients with radioresistant tumors, like head-and-neck tumors.

2. RBE

As a consequence, the RBE variation along the beam needs to be known as precisely as possible. This is especially true if the dose is delivered by an active beam scanning technique as employed at CNAO in Pavia (Italy) and HIT in Heidelberg (Germany) because the RBE has to be predicted for each point in the treatment field.

The RBE is a complex quantity depending not only on radiation quality (that is, particle type and Linear Energy Transfer, or LET), but also on the considered effect level and thus fractional dose: in general, higher survival levels imply higher RBE values, and *vice versa*. In addition, more radioresistant cells, which in general have a lower α/β ratio, tend to show higher RBE values with respect to more radiosensitive cells, which are characterized by a higher α/β ratio.

Therefore, predicting RBE for heavy ions requires appropriate models. Currently, only three models are applied in clinics: the Local Effect Model (LEM) in Europe and Shanghai (China) e.g., [1][2].the Microdosimetric Kinetic Model (MKM) e.g., [3] and the "mixed-beam" model e.g., [4] in Japan. The LEM was first applied to tumors of the skull base, considering late reactions of the central nervous system (CNS) as the main endpoint; indeed, late effects in the CNS are the main dose-limiting factor for head-and-neck tumors. Since data on CNS radiation tolerance in patients are scarce, animal studies are necessary.

Although absolute dose values obtained in such studies may not be directly transferable to patient cases, relative values such as the RBE and its dependence on treatment parameters may be more applicable. The rat spinal cord is known as a well-established model to investigate CNS late effects [5][6], and it has been applied to measure RBE values for C-ion therapy e.g., [5][7][8][9] and protons [10]. These are the main in vivo data that have been used to benchmark the clinically employed LEM version (LEM I), but also the more recent version LEM IV [2].

In the present work, the BIANCA (BIophysical ANalysis of Cell death and chromosome Aberrations) biophysical model, after extensive in vitro validation e.g., [11][12][13], was applied to establish a radiobiological database (i.e., alpha and beta cell survival parameters as a function of particle type and energy). The model was then tested against available rat spinal cord data for carbon ion and proton irradiations. Using the FLUKA Monte Carlo transport code, e.g. [14], which is used at HIT in Heidelberg (Germany) and CNAO in Pavia (Italy) for treatment plan verification/re-calculation, the RBE was predicted for the experimental settings and compared to experimental data.

Although further benchmarking is desirable, the agreement between simulations and data suggests that BIANCA can predict RBE for C-ion or proton treatment of head-and-neck tumors; in particular, the agreement with proton data may be relevant if the current assumption of a constant proton RBE of 1.1 is revised. This work therefore provides the bases for future benchmarking against patient data, as well as the development of other databases for specific tumor types and/or normal tissues.

References

1. Scholz M, Kellerer AM, Kraft-Weyrather W, Kraft G.; Computation of cell survival in heavy ion beams for therapy. The model and its approximation . *Radiat. Environ. Biophys.* **1997**, *36*, 59-66, .
2. Elsässer T, Weyrather WK, Friedrich T, Durante M, Iancu G, Krämer M, Kragl G, Brons S, Winter M, Weber KJ, Scholz M.; Quantification of the relative biological effectiveness for ion beam radiotherapy: direct experimental comparison of proton and carbon ion beams and a novel approach for treatment planning. *Int. J. Radiat. Oncol. Biol. Phys.* **2010**, *78*, 1177-83, .
3. Inaniwa T, Furukawa T, Kase Y, Matsufuji N, Toshito T, Matsumoto Y, Furusawa Y, Noda K.; Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model . *Phys. Med. Biol.* **2010**, *55*, 6721-37, .
4. Kanai T, Furusawa Y, Fukutsu K, Itsukaichi H, Eguchi-Kasai K, Ohara H.; Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy . *Radiat. Res.* **1997**, *147*, 78-85, .
5. Karger CP, Peschke P, Sanchez-Brandelik R, Scholz M, Debus J.; Radiation tolerance of the rat spinal cord after 6 and 18 fractions of photons and carbon ions: Experimental results and clinical implications . *Int. J. Radiat. Oncol. Biol. Phys.* **2006**, *66*, 1488-1497, .
6. van der Kogel AJ, Barendsen GW.; Late effects of spinal cord irradiation with 300 kV X rays and 15 MeV neutrons . *Br. J. Radiol.* **1974**, *47*, 393-8, .
7. Saager M, Glowa C, Peschke P, Brons S, Scholz M, Huber PE, Debus J, Karger CP.; Carbon ion irradiation of the rat spinal cord: dependence of the relative biological effectiveness on linear energy transfer . *Int. J. Radiat. Oncol. Biol. Phys.* **2014**, *90*, 63-70, .
8. Saager M, Glowa C, Peschke P, Brons S, Grün R, Scholz M, Huber PE, Debus J, Karger CP.; Split dose carbon ion irradiation of the rat spinal cord: Dependence of the relative biological effectiveness on dose and linear energy transfer . *Radiother. Oncol.* **2015,** , *117,* , 358-63, .
9. Saager M, Glowa C, Peschke P, Brons S, Grün R, Scholz M, Huber PE, Debus J, Karger CP.; The relative biological effectiveness of carbon ion irradiations of the rat spinal cord increases linearly with LET up to 99 keV/μm . *Acta Oncol.* **2016**, *55*, 1512-1515, .
10. Saager M, Peschke P, Brons S, Debus J, Karger CP.; Determination of the proton RBE in the rat spinal cord: Is there an increase towards the end of the spread-out Bragg peak? . *Radiother. Oncol.* **2018,** , *128,* , 115-120, .
11. Carante MP, Aimè C, Tello Cajiao JJ, Ballarini F.; BIANCA, a biophysical model of cell survival and chromosome damage by protons, C-ions and He-ions at energies and doses used in hadrontherapy . *Phys. Med. Biol.* **2018**, *63*, 075007, .
12. Carante MP, Tello Cajiao JJ, Ballarini F.; Predicting biological effects along hadrontherapy dose profiles by the BIANCA biophysical model . *Radiat. Prot. Dosim.* **2019,** , *183,* , 111–115, .
13. Carante MP, Aricò G, Ferrari A, Kozlowska K, Mairani A, Ballarini F.; First benchmarking of the BIANCA model for cell survival predictions in a clinical hadron therapy scenario . *Phys. Med. Biol.* **2019**, *64/21*, 215008, .

14. Battistoni G, Bauer J, Boehlen TT, Cerutti F, Chin MPW, Dos Santos Augusto R, Ferrari A, Ortega PG, Kozłowska W, Magro G, Mairani A, Parodi K, Sala PR, Schoofs P, Tessonnier T, Vlachoudis V.; The FLUKA Code: An Accurate Simulation Tool for Particle Therapy. *Front. Oncol.* **2016**, *6*, 116, .