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**BIOLOGY CONTRIBUTION**

# 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

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**Purpose: To present the first direct experimental *in vitro* comparison of the biological effectiveness of range-equivalent protons and carbon ion beams for Chinese hamster ovary cells exposed in a three-dimensional phantom using a pencil beam scanning technique and to compare the experimental data with a novel biophysical model.**
**Methods and Materials: Cell survival was measured in the phantom after irradiation with two opposing fields, thus mimicking the typical patient treatment scenario. The novel biophysical model represents a substantial extension of the local effect model, previously used for treatment planning in carbon ion therapy for more than 400 patients, and potentially can be used to predict effectiveness of all ion species relevant for radiotherapy. A key feature of the new approach is the more sophisticated consideration of spatially correlated damage induced by ion irradiation.**
**Results: The experimental data obtained for Chinese hamster ovary cells clearly demonstrate that higher cell killing is achieved in the target region with carbon ions as compared with protons when the effects in the entrance channel are comparable. The model predictions demonstrate agreement with these experimental data and with data obtained with helium ions under similar conditions. Good agreement is also achieved with relative biological effectiveness values reported in the literature for other cell lines for monoenergetic proton, helium, and carbon ions.**
**Conclusion: Both the experimental data and the new modeling approach are supportive of the advantages of carbon ions as compared with protons for treatment-like field configurations. Because the model predicts the effectiveness for several ion species with similar accuracy, it represents a powerful tool for further optimization and utilization of the potential of ion beams in tumor therapy.** 

**Ion beam therapy, Relative biological effectiveness (RBE), Biophysical model, Treatment planning.**

## INTRODUCTION

As compared with conventional photon beam treatment, ion beam radiotherapy takes advantage of the favorable depth–dose distribution of ions (Bragg curve) expressed by the highest dose deposition deep in the tissue (1–3). On the basis of the advantageous physical properties, proton beam therapy is currently used in several centers in the United States, Europe, and Asia (4–6). Heavier particles exhibit additional advantages due to their increasing relative biological effectiveness (RBE) toward the Bragg peak position (7–9). This provides the rationale for carbon ion therapy, which has proven excellent tumor control and few normal tissue complications (10–12).

A basic parameter in ion beam therapy is the RBE, defined as the ratio of doses of photons and charged particles inducing the same biological effect. The knowledge of the depth-dependent RBE values is crucial for the assessment of the potential clinical advantages of ion beams as compared with protons, for which in general a constant RBE of 1.1 is assumed for clinical applications (4). However, the RBE depends not only on depth, but in a complex way also on other parameters, such as ion charge and energy, dose level, and intrinsic tissue radiosensitivity. Systematic experimental investigation of these dependencies is thus of fundamental importance for the clinical application of ion beams.

Since the experimental determination of RBE values for all clinically relevant combinations of these parameters is

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seemingly unfeasible, biophysical models play an indispensable role to account for these complex dependencies in treatment planning.

In the past, we developed a biophysical model (local effect model, LEM) (13–15), which has been used for treatment planning in the clinical trials at GSI in the past decade (11). Up to now, our main goal was to achieve the highest accuracy for the application of carbon ion beams in the target volume, whereas in the entrance channel and for lighter ions the previous versions of the model overestimate the RBE (15–17). Therefore, to fully exploit the potential advantages of ion beams in tumor therapy, a model is required that is applicable over the whole range of clinically relevant particle beams from protons to oxygen ions in the energy range up to approximately 250 MeV for protons and up to approximately 500 MeV/u for heavier ions like oxygen.

Here, we present our experiments performed at the Heidelberg Ion Therapy (HIT) facility aiming at the first direct radiobiologic comparison of protons and carbon ions using an active beam delivery system. Additionally, we describe the basic concepts for a substantial extension of the LEM, leading to a generally applicable model for biological treatment planning in particle therapy. The experiments described above, as well as literature data, are used as a benchmark for the new modeling approach.

## METHODS AND MATERIALS

### *Cell survival studies*

For the simulation of an irradiation under therapy conditions, a special phantom was constructed that enabled the irradiation of an extended target volume. A container made of acrylic glass with a size of 5 cm × 10 cm × 16 cm and a fixing system at the inner side walls for cell positioning was used to carry plastic slices, which allowed a spatial resolution of 5 mm in beam direction (Fig. 1). Cells were grown as monolayers on 25-cm$^2$ polyethylene slices treated for cell culture attachment (custom product Firma Greiner, Frickenhausen, Germany). Irradiation of the container was performed at room temperature. We used Chinese hamster ovary cells (CHO-K1) grown under standard conditions that were plated 24 h before irradiation (7). For the $^3$He experiments, cells were grown as log-phase cultures. For the proton and carbon irradiation, cells were partially synchronized in S-phase. This synchronization was a consequence of an unexpected delay of the irradiation, thus leading to a higher-than-planned cell density and thus partial synchronization of the cells before reseeding for irradiation. At irradiation time, cells were thus enriched in S-phase and G2-phase (approximately 50% and 20%, respectively) as determined by flow cytometry. Immediately before irradiation, the slices were inserted into the container filled with medium. After irradiation, cells were trypsinized, and cell survival was measured according to standard procedures (7). For proton and carbon irradiation, two independent irradiations were performed. Cell survival for each slice was determined by seeding in triplicate, and error bars were determined from the standard deviation of the total of six replicates for each position.

### *Irradiation*

Proton and carbon ion irradiations were performed at the HIT facility using an active pencil beam scanning technique with energies of 90–120 MeV/u and 175–230 MeV/u for protons and carbon ions, respectively. Irradiation times were approximately 5 min per field and approximately 15 min for a complete two-field irradiation. The capability of this facility to rapidly switch between proton and carbon irradiation allowed comparison of different radiation modalities under identical, precisely defined conditions. The dose levels were 1.5 Gy in the entrance channel for both protons and carbon ions; in the center of target region, doses of 5.3 Gy and 3.9 Gy were applied with protons and carbon ions, respectively.

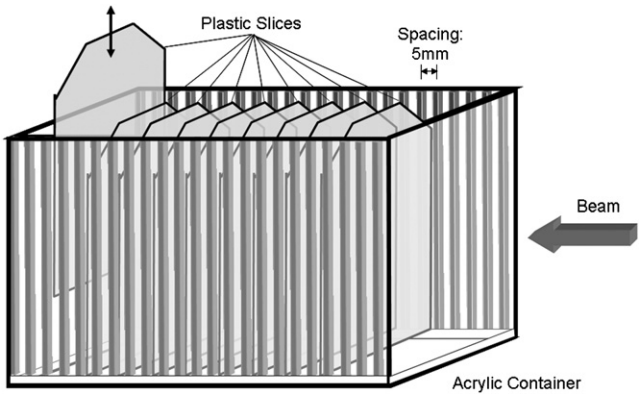


Fig. 1. Schematic view of the acrylic phantom used for the experiments.

Irradiation with $^3$He was performed in the medical cave of the heavy ion synchrotron at GSI using the rasterscan system and active variation of the beam energy in the range from 107 to 138 MeV/u.

The dose levels were 2.5 Gy in the entrance channel and 3.6 Gy in the center of the extended peak. Because of the synchronization of the cells observed in the proton and carbon ion experiments, additional reference survival curves were obtained in experiments performed under similar conditions using an X-ray generator operating at 250 kV and 16 mA; these survival curves are represented by the linear-quadratic parameters given in Fig. 2. For the helium experiments, the standard linear-quadratic parameters characterizing the CHO cells as given in the caption of Fig. 3 were used.

The irradiations were planned by the treatment planning software TRiP98 (18, 19) and optimized to achieve a homogeneous cell survival in the target region, simulating a 4-cm extended target located between 6 and 10 cm water equivalent depth. For the helium experiment, the phantom was irradiated with a single rectangular field. For the proton and carbon experiments, two opposing fields were used to simulate a scenario typical for patient irradiations, using the same extension and depth as for the helium irradiation. For planning the proton and carbon experiments, physical data adapted to the corresponding HIT database (20) were used.

### *LEM: Basics*

The LEM (13–15) aims at deriving the biological effects of ion radiation $E_{ion}$ from the response of cells or tissues to photon radiation, thus efficiently exploiting the large database collected with conventional radiation. The effectiveness of particles is calculated on the basis of the microscopic local dose distribution pattern of ion traversals within the cell nucleus, assuming that equal local doses lead to equal local effects, independent of the radiation quality. Radiation effects due to non-DNA damages are expected to contribute only a little, if at all, and are thus neglected in a first approximation. Typically, the local dose around single ion tracks is determined by an amorphous description of the radial