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The relative biological effectiveness in particle therapy for clinically relevant endpoints as a function of beam quality

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Abstract

Background

The relative biological effectiveness (RBE) of particle therapy compared to photon radiotherapy is known to be variable but the exact dependencies are still subject to debate. *In vitro* data suggested that the RBE is to a large extend independent of ion type if parametrized by the beam quality Q. This study analyzed the RBE dependence of pre-clinical data on late toxicity with an emphasis on the beam quality.

Material and Methods

Published pre-clinical RBE dose response data of the spinal cord following 1 and 2 fractions of photon and carbon ion irradiation were compiled. The beam quality for each treatment condition was obtained from Monte Carlo simulations. The α_p and β_p parameters of the linear-quadratic (LQ) model were determined from the pre-clinical data and provided as a function of Q. An introduced model proposed α_p to increase linearly with Q and β_p to remain constant. RBE values predicted by the model were compared to the published data.

Results

The α_p parameter was highly correlated with Q ($R^2 = 0.96$) with a linear slope of 0.0188 Gy^{-1} and in excellent agreement with the model prediction (0.0185 Gy^{-1}). No significant variation of β_p with Q was found ($p = 0.317$). RBE and Q were also highly correlated ($R^2 = 0.98$) for 1 and 2 fractions. The (extrapolated) RBE at $Q = 0$ (theoretical photon limit) for 1

and 2 fractions was 1.22 and significantly larger than 1 ($p = 0.004$). The model reproduced the dependence of RBE on fractionation well.

Conclusion

Fraction dose and beam quality Q were sufficient to describe the RBE variability for a late toxicity model within a carbon ion treatment field. The independence of the identified RBE parameters on the ion type suggests the translation of variable (pre-) clinical RBE data from carbon ion to proton therapy.

Introduction

Particle therapy – i.e., carbon ion and, in particular, proton therapy – is increasingly used to treat numerous cancer types given its potential to better spare normal tissue than photon-based radiotherapy. It has, relative to photons, a higher effect on cells quantified by the relative biological effectiveness (RBE). The RBE is defined as the ratio between photon and particle doses resulting in a biological isoeffect. In conventional photon-radiotherapy, dose prescription, fractionation schedules and treatment planning rely on long term experiences from the dose response to photon irradiation, which are usually expressed in terms of tumor- and organ-specific threshold dose levels. The transfer of this established clinical knowledge to particle therapy requires the accurate knowledge of the RBE, since the irradiation dose in particle therapy results from dividing the photon dose by the RBE. The RBE, however, is known to be variable and the exact dependence on potential influencing factors such as tissue type, clinical end point, treatment regimen, but also ion type is still subject to debate. In precise terms, a variable RBE is routinely used for dose prescription and treatment planning in carbon ion therapy, while in current clinical practice, protons are considered to uniformly express a 10% higher biological efficacy than photons. This is in contrast to the recently reported clinical evidence of a variable RBE in proton therapy [1]. Consequently, these treatment planning routines need to be optimized with gaining much more valid (pre-) clinical data especially on late toxicity endpoints of surrounding normal tissues. Towards this aim, it is of high relevance to increase the understanding of RBE in particle therapy, reduce the complex interdependencies associated with the RBE and therewith improve RBE-weighted dose prescription in particle therapy treatment planning.

To appropriately elucidate RBE variations caused by the above mentioned influencing factors, *in vitro* studies comparing dose response of photon to particle irradiation under well controlled experimental conditions are needed [2–5]. Resulting RBE data are usually parametrized by the linear energy transfer (LET), which is a measure of the ionization density caused by the irradiation. A drawback of such a LET parametrization is, however, that it introduces a dependence of RBE on the type of ion irradiation. Our recent analysis of *in vitro* data emphasized the fact that RBE is to a large extend independent of ion type if considered as function of beam quality instead of the LET [6,7]. The translation of such basic understanding is essential for an apparent clinical RBE calculation. To increase robustness of RBE modeling only a small number of clinically accessible input parameters should be included that reflect patient treatment relevant endpoints such as functional organ response to fractionated irradiation. Experimentally, these endpoints can be studied with pre-clinical models, e.g., for late toxicity.

In this study, pre-clinical literature data on dose response of the spinal cord to fractionated photon and carbon ion irradiation were analyzed to identify the essential parameters for an apparent clinical RBE description with special emphasis on the beam quality Q. Furthermore, it was elucidated how to assess the relevant input parameters directly from (pre-) clinical data. An analytical RBE expression based on these parameters was formulated that may also be useful for proton therapy.

Materials and Methods

Pre-clinical literature data

Pre-clinical literature data from a set of experiments on radiation-induced spinal cord injury were compiled for carbon ion and photon irradiation [8–12]. In brief, in all experiments the cervical spinal cord of rats was irradiated using single dose fractions (n = 1) or split dose irradiation (n = 2). The dose values at 50% complication probability, TD_{50}, were determined according to dose-response curves for the development of myelopathy (paresis grade II) within an observation time of 300 days. Irradiation with carbon ions was performed at 6 positions for a 6 cm spread-out Bragg peak (SOBP, LET range 16-99 keV/µm) for n = 1 [10,12] and n = 2 [11]. The RBEs were calculated using TD_{50} values from comparable earlier experimental studies using 15 MV photon irradiation [8,9]. The extracted experimental parameters and RBE data used in the present study are listed in Table 1.The studied late toxicity endpoint of the serially organized spinal cord allows for a well-defined toxicity scoring of a non-transient radiation-induced complication.

Calculation of the beam quality

In this work, the radiation response of ion irradiation was considered as a function of the LET as well as the beam quality Q defined as,

$$Q = \frac{Z^2}{E[\mathrm{MeV/u}]}, \tag{1}$$

with Z and E being the charge and kinetic energy of an ion, respectively. Q is defined to be a dimensionless parameter with E given in units of MeV per nucleon. The beam quality Q parametrizes the shape of the dose distribution deposited around an ion track. More specifically, it directly determines (as a factor) the height of the energy spectrum curve for

the electrons that are produced by an ion track – independently of ion type. A radiation field with a small Q corresponds to a more uniform dose within the area of a cell nucleus while a large Q implies high dose heterogeneity on that level.

The dose, LET, and beam quality Q distributions as a function of depth in water were obtained from Monte-Carlo simulations optimized for carbon ion treatment using SHIELD-HIT12A [13,14]. For this purpose, the same 6 cm SOBP ranging from 70 to 130 mm water-equivalent depth as used for the published irradiation experiments [10–12] was optimized using the treatment planning system TRiP [15]. The resulting treatment plan was imported into the Monte-Carlo tool to simulate particle-resolved energy spectra as function of depth in water. These spectra were used to determine dose-averaged LET and Q values similar as described in [16] using the stopping power routine libdEdx [17]. Simulated dose and LET distributions were compared to those applied for the rat irradiation experiments.

Analysis of the radiation response from fractionated irradiation

In the framework of the linear-quadratic (LQ) model, the dependence of the radiation effect ε is expressed by the linear and quadratic dose-response parameters α and β, respectively [18]. If each successive fraction with dose d in a multidose schedule is equally effective, the effect $\boldsymbol{\varepsilon}$ of n fractions can be expressed as,

$$\varepsilon = \alpha D + \beta d D \,, \tag{2}$$

with the total dose $D = n\,d$. The biological endpoint expressed as 50% complication probability for radiation-induced myelopathy (paresis grade II) within 300 days after irradiation has been assumed as full effect ($\varepsilon = 1$). Then, the equation can be rewritten as,

$$\frac{1}{nd} = \alpha + \beta d \tag{3}$$

The α and β values for the *in vivo* data were obtained from the measured dose values at 50% probability of paresis grade II, TD_{50}, using the graphical method [18]: The reciprocal of the total dose ($1/D$) was plotted against the corresponding dose per fraction d. Assuming a straight line – as suggested by Eq. *(3)* – the intercept on the vertical axis and slope represent α and β, respectively. Additionally, the α/β ratio can be obtained from,

$$\frac{\alpha}{\beta} = \frac{n_1 {d_1}^2 - n_2 {d_2}^2}{n_2 d_2 - n_1 d_1}, \tag{4}$$

using the number of fractions and dose per fraction for two different fractionation regimes resulting in the same effect.

Modeling the dose-response relationship as a function of the beam quality

The LQ parameters α_p and β_p for particle irradiation vary with beam quality. An analysis of *in vitro* cell survival studies using particle irradiation with different ions revealed a linear increase for α_p with Q, while β_p remained approximately constant for the interval $Q < 2.5$ [6,7]. Consequently, the following parametrization,

$$\alpha_p = \alpha(Q) = \alpha_0 + \beta_0 D_L Q\,, \tag{5}$$

$$\beta_p = \beta(Q) \approx \beta_0\,, \tag{6}$$

is used in this study, which results in

$$\frac{\alpha_p}{\beta_p} = \frac{\alpha_0}{\beta_0} + D_L Q\,. \tag{7}$$

The constants α_0 and β_0 represent the limiting LQ parameters for Q approaching zero, which is the theoretical photon limit. They could potentially be approximated by the photon LQ parameters α_X and β_X. The limiting dose,

$$D_{\mathrm{L}} = 1.5\left(\frac{\alpha_0}{\beta_0} + 4.5\ \mathrm{Gy}\right), \tag{8}$$

is a model parameter, which is closely related to the threshold dose, D_{T}, above which the LQ model is assumed to enter into a linear dose response. The relationship,

$$D_{\mathrm{T}} = 1.1\left(\frac{\alpha_X}{\beta_X} + 3.64\ \mathrm{Gy}\right), \tag{9}$$

had been found empirically to match survival data with LEM simulations [19,20].

Determine the RBE as a function of Q

The RBE in particle therapy is defined as the ratio of a reference photon dose, D_{X}, and a particle test irradiation dose, D_{p},

$$\mathrm{RBE} = \left.\frac{D_X}{D_p}\right|_{\mathrm{isoeffect}}, \tag{10}$$

resulting in the same biological effect. For fractionated irradiation with the same number of fractions n for photon and particle irradiation, Eq. *(10)* is reduced by n and the RBE depends solely on the ratio of doses per fraction. The RBE for an endpoint achieved with n fractions of the photon dose d_{X} is then given by,

$$\mathrm{RBE} = \frac{2d_X}{\sqrt{\left(\frac{\alpha_p}{\beta_p}\right)^2 + \frac{4}{n\beta_p}} - \frac{\alpha_p}{\beta_p}}, \tag{11}$$

where the particle fraction dose was replaced by solving Eq. *(3)* for d_p. Removing the dependence on fraction number n and using the model description as proposed in Eqs. *(5)* to *(8)* results in

$$\mathrm{RBE} = \frac{2d_X}{\sqrt{\left(\frac{\alpha_0}{\beta_0} + D_\mathrm{L}Q\right)^2 + 4\frac{d_X}{\beta_0}(\alpha_X + \beta_X d_X)} - \frac{\alpha_0}{\beta_0} - D_\mathrm{L}Q}, \tag{12}$$

which depends on d_X and Q. The equivalent expression for a given particle dose d_p is

$$\mathrm{RBE} = \frac{1}{2d_p}\left(\sqrt{\left(\frac{\alpha_X}{\beta_X}\right)^2 + 4\frac{d_p}{\beta_X}\left(\alpha_0 + \beta_0\left(D_\mathrm{L}Q + d_p\right)\right)} - \frac{\alpha_X}{\beta_X}\right). \tag{13}$$

In the case the parameters α_0 and β_0 can be approximated by the respective photon values α_X and β_X, the RBE expression further simplifies,

$$\mathrm{RBE} = \frac{1}{2d_p}\left(\sqrt{\left(\frac{\alpha_X}{\beta_X}\right)^2 + 4d_p\left(\frac{\alpha_X}{\beta_X} + D_\mathrm{L}Q + d_p\right)} - \frac{\alpha_X}{\beta_X}\right), \tag{14}$$

and the dose response depends only on the photon $\alpha_\mathrm{X}/\beta_\mathrm{X}$ ratio. The dependence of the RBE on the characteristics of the irradiation field (physics) is determined by the dose of the test irradiation per fraction, d_X, and the beam quality Q.

For comparison with the measurements, RBE values for the spinal cord were determined at the 6 positions within the SOBP using the photon irradiation doses d_X for $n = 1$ and $n = 2$ fractions and the RBE formulas in Eqs. *(11)* and *(12)*. For this model, the biological system including the dependence on the considered endpoint (biology) is approximated by α_0 and

β_0. All statistical data analyses were performed using SPSS version 23.0 (IBM Corp.) and for the regression analysis p-values < 0.05 were considered significant.

Results

Simulation of the beam quality in a SOBP

The Monte Carlos simulations of the 6 cm carbon ion SOBP reproduced the depth-dose and depth-LET distributions used for the rat spinal cord irradiation experiments [10–12] well (Fig. 1). From the same simulation, also the beam quality *Q* was obtained by dose-averaging over all primary and secondary particles (similar as for the dose-averaged LET) at each depth position (Fig. 2). The depth dependence of *Q* was correlated to that of the LET. The ratio between *Q* and LET was, however, not constant and increased monotonously with depth toward the distal end of the SOBP. Three depth intervals could be distinguished, between which the *Q* / LET ratio clearly differed: proximal to the SOBP, within the SOBP dose plateau, and in the distal fall-off region. Within each of the first 2 intervals (containing all 6 irradiation positions), the relative change between *Q* and LET was found to be small for the considered carbon ion treatment field.

Analysis of α and β as a function of Q

The parameters α and β (Table 2) were determined from the response to fractionated irradiation with 1 or 2 fractions of photons or carbon ions with different beam qualities *Q* (Fig. 3). The α parameter for carbon ion irradiation increased linearly with *Q* ($R^2 = 0.96$, Fig. 4) and also with LET (not shown). Linear regression (including the photon data) yielded for α a slope (95% confidence limit) of 0.0188 (0.0147 – 0.0230) Gy^{-1} and a constant of 0.0052 (-0.0006 – 0.0111) Gy^{-1}. In contrast, no significant slope was found for the β data ($p = 0.317$). Therefore, β_0 was approximated by the mean value 0.0019 Gy^{-2} (Fig. 4).

For photons, the α/β ratio determined from the 1 and 2 fraction data was 1.2 Gy. Since an earlier analysis of the same photon data pooled with the data for 8 and 16 fractions suggested a higher photon α/β ratio of 2.8 Gy [9], in this study, the α_0/β_0 ratio was approximated as 2 Gy – resembling the value often used clinically for comparable late toxicities in radiotherapy. This resulted in a $\alpha_0 = 0.0038$ Gy^{-1} (product of β_0 and α_0/β_0) and $D_L = 9.75$ Gy [according to Eq. *(6)*]. Consequently, the slope of α with Q was predicted – according to the model [Eq. *(5)*] – by the product $\beta_0 D_L = 0.0185$ Gy^{-1}. This prediction is in remarkable agreement with the slope observed for the experimental α data (0.0188 Gy^{-1}).

RBE analysis and model prediction as a function of Q

The experimental RBE data increased linearly with Q (Fig. 5). Linear regression showed an equally high degree of correlation between RBE and Q ($R^2 = 0.98$) for both fractionation schedules. The slope increased with number of fractions (i.e., decreasing fraction dose) from 0.227 (0.188 – 0.266) to 0.388 (0.319 – 0.456).

The dependence of RBE on fraction dose increased with increasing Q. For $Q \rightarrow 0$ (limit of less densely ionizing high-energy radiation), the RBE seemed to be independent of fractionation. For both fractionation schemes, exactly the same (extrapolated) RBE value of 1.22 was observed for $Q = 0$, which was significantly higher than a RBE of 1 ($p = 0.004$). A RBE of 1 for Q = 0 would have implied isoeffectiveness for high-energy carbon ion and photon irradiation (i.e., $\alpha_0 = \alpha_X$ and $\beta_0 = \beta_X$).

RBE values were calculated with the presented model for 1, 2 and 6 fractions as well as for a photon fraction dose of 2 Gy (Table 3), using the parameters $D_L = 9.75$ Gy, $\alpha_0/\beta_0 = 2$ Gy, and $\beta_0 = 0.0019$ Gy^{-2} derived in the analysis of α and β in the previous section. The model reproduced the dependence on fractionation well (Fig. 5). The overall match with the

experimental data was reasonable. For small Q (especially for $Q < 0.5$, i.e., depths proximal to the SOBP) the model predictions were smaller than the experimental RBE values with a tendency to become larger than the measured RBE data for $Q > 2.5$. While the experimental data could be fitted well with a linear curve, the RBE model showed a slightly upward bended slope.

Discussion

Dependence of RBE on physical parameters

The analyzed organ response to fractionated irradiation in terms of radiation-induced side effects depends on fractionation dose and beam quality Q of the radiation or, in precise terms, on the macroscopic dose and the shape of the microscopic dose distribution on the level of the cell nucleus, respectively. For a carbon ion treatment field, as it was used for the published experimental data, the dose is optimized to be uniform in the treatment volume. The beam quality increases monotonously until the distal edge of the SOBP and can be described as a function of depth. Accordingly, the RBE for late toxicity increases toward the distal end of a particle therapy treatment field as it similarly does the beam quality.

The linear increase of the RBE with the beam quality results primarily from the pronounced linear increase of α with Q. On the other hand, the quadratic term of the LQ model, β, remains approximately constant. The same dependence of RBE and α on Q as well as the weak variation of β, which was observed here for the pre-clinical data, has recently also been noticed in our reanalysis [6,7] of a number of *in vitro* experiments such as [2,3,21]. The consistent outcome of these different *in vivo* and *in vitro* experiments suggests that the observed linear increase of α as well as RBE with Q is a systematic effect. The driving factor for the observed RBE variation is the linear slope of α with Q. It is striking to see that this factor differed less than 2% between the proposed model prediction (based on Q) and the pre-clinical data, even though, the model approach was based on *in vitro* RBE data.

It is important to note, that the simple linear relation between RBE and Q may only hold true in a finite range (approximately $Q \leq 2.5$). For larger Q, the overkill effect might gain

importance, which is known to occur at high LET (for carbon ions typically ≥ 100 keV) leading eventually to a vanishing β and decreasing α [19]. However, the analyzed data demonstrate that in practical terms this Q range is sufficient to cover a clinical treatment field (SOBP).

Dependence of RBE on clinically accessible dose response data

In patient treatment, information on the dose response of clinical relevant endpoints is usually only accessible through the analysis of the response to different doses per fraction. For tumor response, those data can be obtained, e.g., from the analysis of clinical studies with different fractionation schedules. For normal tissue, patient-specific anatomy and treatment plans result inherently in a variation of dose distribution per fraction and among patients within an organ at risk. Those variations can be assessed through an analysis based on normal tissue complication probability models (e.g., for the spinal cord [22]).

The present investigation demonstrates that the LQ model parameters α and β – obtained by fractionation analysis – are in principle sufficient to model pre-clinical RBE. The same approach could also be used to analyze the clinical dose response. The use of such clinically derived data would be an important step to lower the uncertainties associated with RBE predictions that rely on experimental input data only. Additionally, the calculation of RBE from (predictions of) α and β as function of Q – as demonstrated here – has the advantage that the distinct dose-dependence of RBE is taken correctly into account.

It should be noted that the agreement of the modeled and the analyzed experimental data was sensitive to the values used for α_0 and β_0. In particular, a direct approximation by the photon α_X and β_X values [Eq. *(14)*] would lead to a diminished agreement, especially for small Q, with modeled RBE values close to 1. In contrast, for $Q = 0$ (theoretical photon

limit) the experimental RBE values for 1 as well as 2 fractions were significantly larger than 1. This raises the question whether the (frequently used) approach to only use photon α_X and β_X to describe the biology in RBE modeling is sufficient. Determining α_0 and β_0 for modeling RBE directly from ion irradiation appears more robust, since it can be based on a set of data for different Q values. In contrast, for photons (i.e., one fixed Q) only a single pair of parameters can be measured. Therefore, in this study, determining β_0 also relied on β data for carbon ion irradiation.

Disagreement was reported between the predictions by the local effect model (LEM), which is used to determine the RBE for patient treatment with carbon ion therapy in Europe, and the same set of experimental data as considered here [11]. For the comparison, LEM I [20] had been applied with the α and β values as input that are in use for actual patient treatment (α = 0.1 Gy^{-1}, β = 0.05 Gy^{-2}) while for LEM IV [23] values (α = 0.003 Gy^{-1}, β = 0.0015 Gy^{-2}) close to the photon α_X and β_X from the discussed experiments had been used. It remains puzzling, why none of the model approaches was able to satisfyingly predict the experimental outcome. Especially at high ion energies (i.e., in the theoretical photon limit for vanishing Q), the experimental data appeared to be less photon-like than frequently assumed by RBE models. The observed deviations indicate the need for further experimental as well as biophysical modeling studies to improve the reliability of treatment planning software for particle therapy.

The present study was limited by the fact that only published data for 1 and 2 fractions entered the analysis of the experimental α and β parameters. Experimental data for 6 fractions may become available in the near future and serve as a validation data set (cf. Table 3). For carbon ion irradiation, the observed response showed the anticipated systematic behavior (linear increase of α and constant β with Q) as shown in Figs. 3 and 4.

For photon irradiation, the analyzed α/β values appeared to be different whether 1 and 2 or in addition data with 8 and 16 fractions (with the same isoeffect) were considered [9]. It is known that the method used to extract α and β parameters is inefficient to estimate the α/β ratio [24]. Instead of one isoeffective dose point (here TD_{50}) per treatment condition, in a more direct regression approach, the entire experimental dose response curves – if available – should be used.

Pooling RBE data to improve proton therapy

The parameter Q is closely related to a second commonly used parameter for radiation quality, namely the square of the effective ion charge divided by its relativistic velocity, $\left(Z_{\mathrm{eff}}/\left(\frac{v}{c}\right)\right)^2$, which is known to provide a lower dependence of radiation-induced effects on the particle type than the LET [25]. This is in-line with our earlier analysis of *in vitro* cell survival data indicating that experimental α, β, and RBE data were practically independent of the type of ion irradiation (e.g., proton, helium, carbon, neon) when parametrized by Q [6,7]. The present study suggests furthermore that the remarkably simple linear dependence of radiation response on dose and Q also holds true for (pre-) clinical endpoints. Assuming correctness, results from carbon ion irradiation could then be directly transferred to particle therapy with other ions. From a clinical point of view, this would allow for a direct translation of (clinically obtained) RBE data gathered in carbon ion therapy to application in proton therapy. This would be a major step toward improving the simplistic clinical RBE modeling currently in use in proton therapy (constant RBE = 1.1) by profiting from long term clinical experience with a variable RBE in carbon ion therapy. However, that implies that in future α and β as well as RBE will be provided as a function of Q instead of LET, due to the dependence on the type of ion irradiation introduced by LET. Further research

on the dependence of RBE especially under pre-clinical and clinical conditions is mandatory to realize a successful translation of this concept to proton therapy.

In conclusion, we showed for the first time that the fraction dose and beam quality *Q* are sufficient to describe the RBE variability for a late toxicity model and different fractionation schedules within a carbon ion treatment field. The variable RBE could be modeled in a simple way, although, photon dose response data alone were insufficient to explain the considered experimental data. The independence of the relevant RBE parameters on the type of ion irradiation suggests the translation of RBE data from carbon ions to protons to reduce the uncertainties currently associated with radiobiology in proton therapy.

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Tables

Table 1: Experimental literature data for the irradiation of the rat spinal cord compiled based on [8–12].

Depth (mm)	LET (keV/µm)	TD_{50} (Gy)	RBE	TD_{50} (Gy)	RBE
		n = 1		n = 2	
Carbon ion irradiation					
35	16	19.5	1.26	26.7	1.28
65	21	18.4	1.33	24.0	1.43
80	36	17.7	1.39	22.5	1.52
100	45	16.1	1.52	20.1	1.71
120	66	14.6	1.68	17.7	1.94
127	99	13.4	1.83	14.9	2.30
Photon irradiation					
-	-	24.5	-	34.3	-

LET: Linear energy transfer; n: number of fractions; RBE: relative biological effectiveness; TD_{50}: dose at 50% probability of paresis grade II.

Table 2: Simulated beam quality Q at the 6 experimental depths positions of the rat spinal cord as well as α and β parameters extracted from the experimental data and calculated with the presented model approach. For the model, β is assumed to be constant with β = 0.0019 Gy^{-2}.

Depth (mm)	Q	α (Gy^{-1})	β (Gy^{-2})	α/β (Gy)	α (Gy^{-1})	α/β (Gy)
		Experimental data			Model	
Carbon ion irradiation						
35	0.27	0.0074	0.0023	3.3	0.0090	4.7
65	0.36	0.0179	0.0020	9.0	0.0104	5.5
80	0.87	0.0234	0.0019	12.5	0.0199	10.5
100	1.18	0.0292	0.0020	14.3	0.0257	13.5
120	1.94	0.0380	0.0021	18.2	0.0397	20.9
127	2.74	0.0577	0.0013	45.8	0.0546	28.7
Photon irradiation						
-	-	0.00194	0.00159	1.2	0.0038	2.0

Q: beam quality; α, β: linear and quadratic dose response parameters.

Table 3: Modeled RBE values using Eq. *(12)*. The values for 1 and 2 fractions can be compared to the experimental data in Table 1. Extrapolated RBE values are also provided for 6 fractions and a (clinically more relevant) photon fraction dose of 2 Gy.

		d_X (Gy)	24.5	17.2	9.7	2
		n	1	2	6	97
Depth (mm)	*Q*			RBE		
35	0.27		1.18	1.22	1.32	2.11
65	0.36		1.20	1.25	1.37	2.34
80	0.87		1.34	1.45	1.76	4.07
100	1.18		1.43	1.59	2.01	5.16
120	1.94		1.66	1.94	2.69	7.86
127	2.74		1.93	2.35	3.46	10.7

Q: beam quality; d_X: photon fraction dose; *n*: number of fractions; RBE: relative biological effectiveness.

Figures

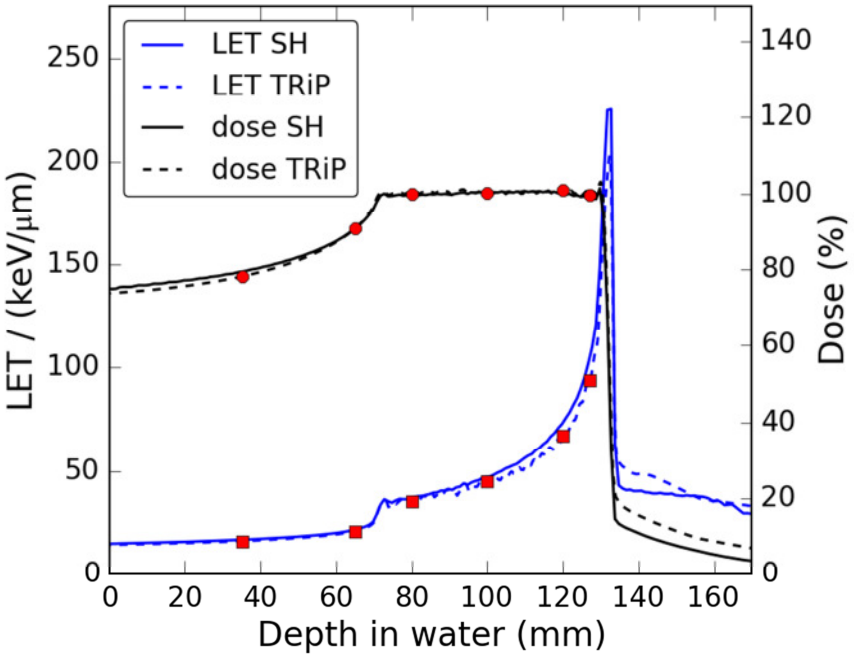

Figure 1: Comparison of the depth-dose (black) and LET (blue) distributions as used in the considered experimental studies [10–12] (dashed lines) and obtained from Monte-Carlo simulations in the present study (solid lines). The treatment positions are indicated by the (red) symbols.

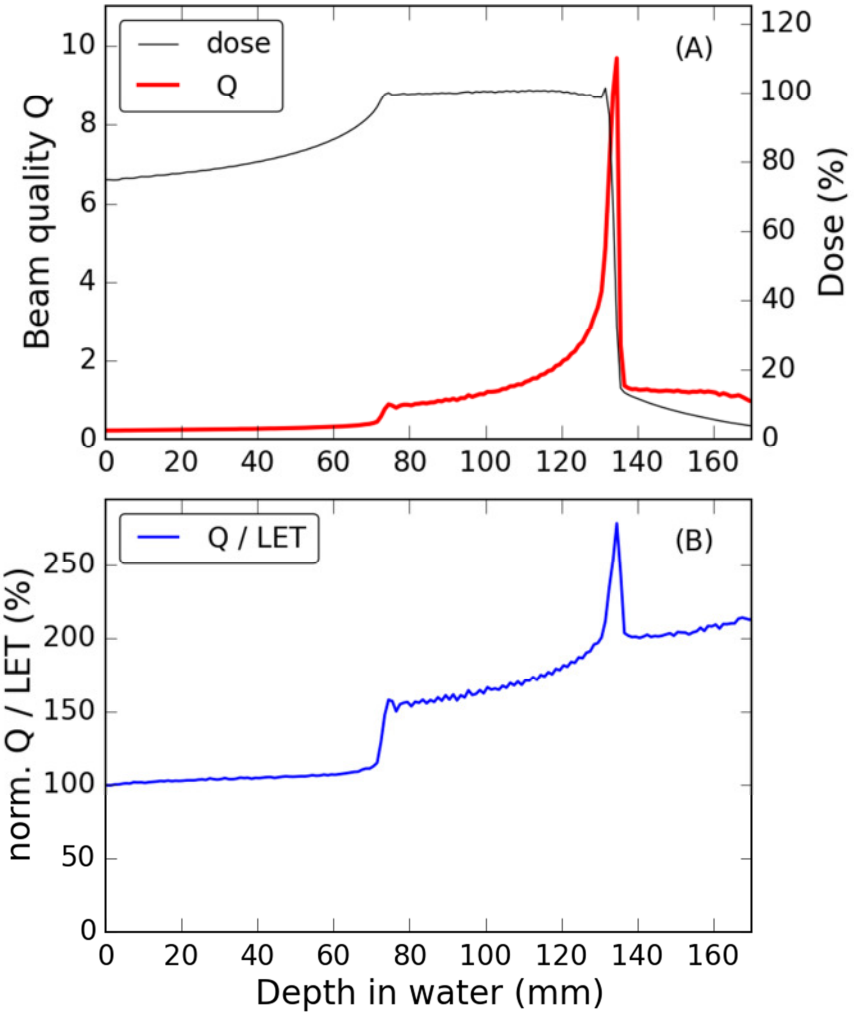

Figure 2: (A) Monte-Carlo simulation of the beam quality *Q* as a function of depth in water compared to the simulated dose. (B) Relative ratio of the beam quality *Q* over the LET normalized to 1 at the depth = 0 mm.

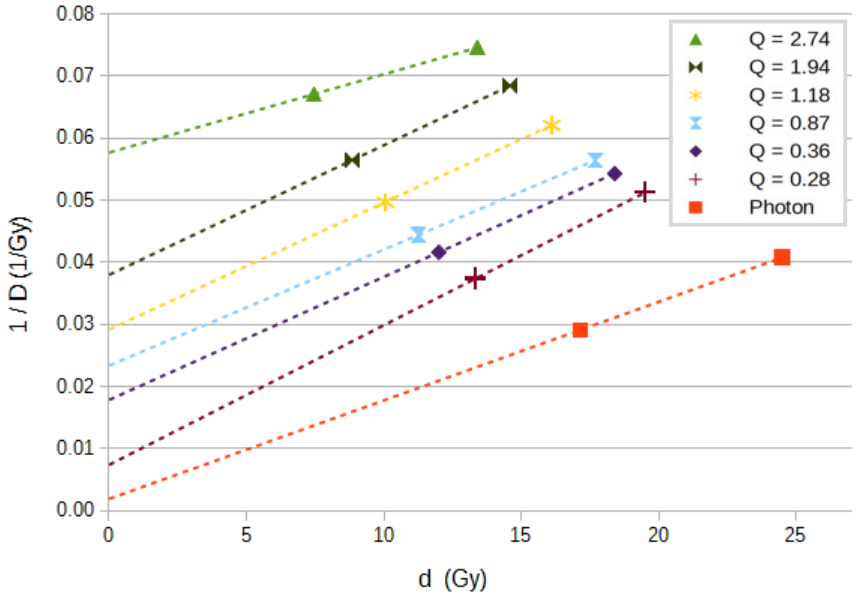

Figure 3: Estimation of α and β [Joiner and van der Kogel 2009] using reciprocal total and fraction doses ($1/D$ and d, respectively) that resulted in 50% paresis grade II after 1 or 2 fractions of photon [8,9] or carbon ion [10–12] irradiation. The intercept with the vertical axis and the slope [cf., Eq. *(3)*] yield approximations for α and β, respectively, which are listed in Table 2 for the different beam qualities Q.

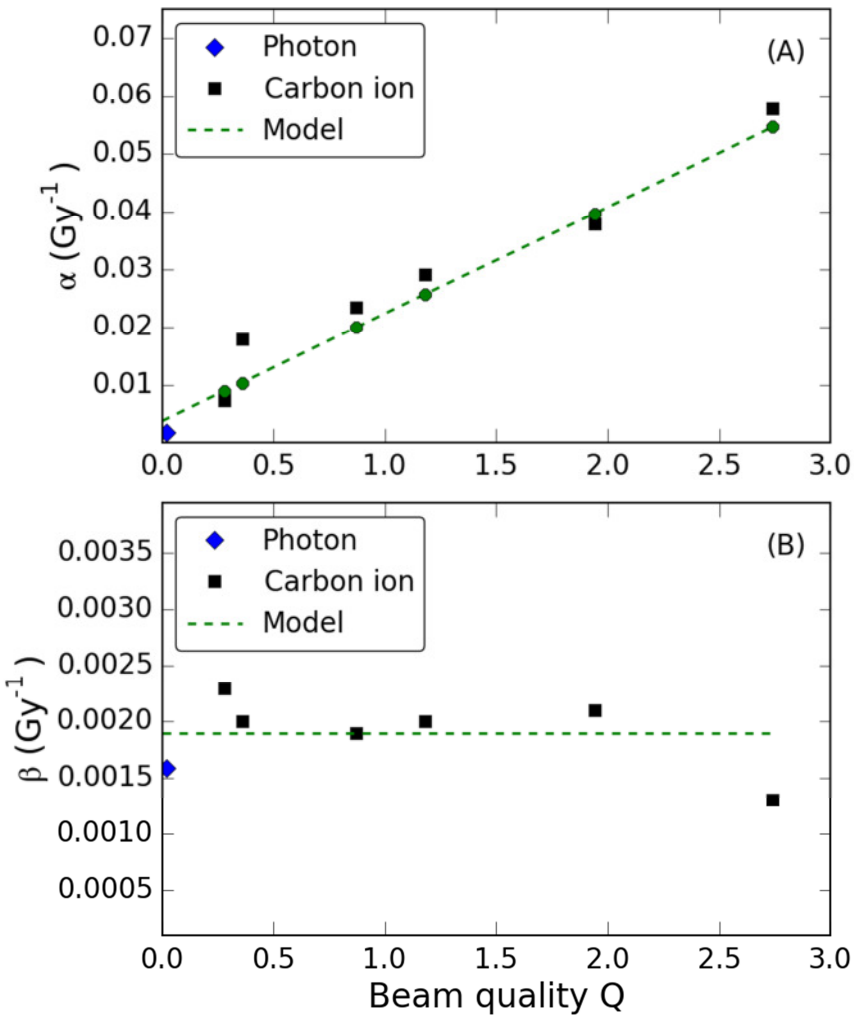

Figure 4: The parameters α and β of the linear quadratic model are shown in (A) and (B), respectively, as a function of the beam quality Q. The experimental data from photon and carbon ion irradiation are compared to the proposed model description.

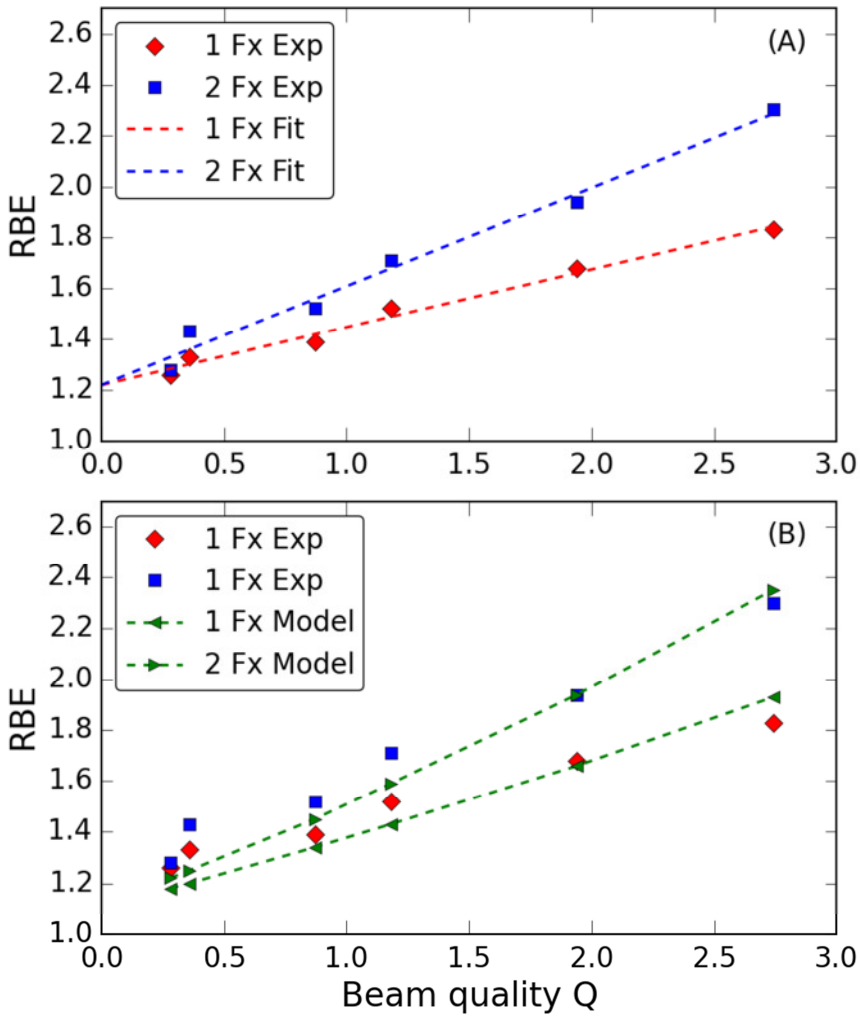

Figure 5: The relative biological effectiveness (RBE) as a function of the beam quality *Q*. Comparison of experimental RBE data for 1 and 2 fractions with (A) linear fits of the experimental data and (B) the proposed RBE model. See text for details.