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Modeling *in vivo* relative biological effectiveness in particle therapy for clinically relevant endpoints

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1 **Modeling *in vivo* relative biological effectiveness in particle therapy for**

2 **clinically relevant endpoints**

3

4

5 **Abstract**

6 *Background*

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

12 *Material and Methods*

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

20 *Results*

21 The α_p parameter was highly correlated with Q ($R^2 = 0.96$) with a linear slope of 0.019 Gy^{-1} .
22 No significant variation of β_p with Q was found. RBE and Q were also highly correlated
23 ($R^2 = 0.98$) for one and two fractions. The (extrapolated) RBE at $Q = 0$ (theoretical photon

24 limit) for one and two fractions was 1.22 and significantly larger than 1 ($p = 0.004$). The
25 model reproduced the dependence of RBE on fractionation well.

26 *Conclusion*

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

31 **Introduction**

32 Particle therapy – i.e., carbon ion and, in particular, proton therapy – is increasingly used to
33 treat numerous cancer types given its potential to better spare normal tissue than photon-
34 based radiotherapy. It has, relative to photons, a higher biological effect e.g. increased cell
35 killing, quantified by the relative biological effectiveness (RBE). The RBE is defined as
36 the ratio between photon and particle doses resulting in a biological isoeffect. In
37 conventional photon-radiotherapy, dose prescription, fractionation schedules and treatment
38 planning rely on long term experiences from the dose response to photon irradiation, which
39 are usually expressed in terms of tumor- and organ-specific threshold dose levels. The
40 transfer of this established clinical knowledge to particle therapy requires the accurate
41 knowledge of the RBE, since the irradiation dose in particle therapy results from dividing
42 the photon dose by the RBE.

43 The RBE, however, is known to be variable and the exact dependence on potential
44 influencing factors such as tissue type, clinical end point, treatment regimen, but also ion
45 type is still subject to debate. In precise terms, a variable RBE is routinely used for dose
46 prescription and treatment planning in carbon ion therapy, while in current clinical
47 practice, protons are considered to uniformly express a 10% higher biological efficacy than
48 photons. This is in contrast to the recently reported clinical evidence of a variable RBE in
49 proton therapy [1]. Consequently, these treatment planning routines need to be optimized
50 with gaining much more valid (pre-) clinical data especially on late toxicity endpoints of
51 surrounding normal tissues. Towards this aim, it is of high relevance to increase the
52 understanding of RBE in particle therapy, reduce the complex interdependencies associated
53 with the RBE and therewith improve RBE-weighted dose prescription in particle therapy
54 treatment planning – as recently discussed for proton therapy [2–4].

55

56 To appropriately elucidate RBE variations caused by the above mentioned influencing
57 factors, *in vitro* studies comparing dose response of photon to particle irradiation under
58 well controlled experimental conditions are needed [5–8]. Resulting RBE data are usually
59 parametrized by the linear energy transfer (LET), which is a measure of the ionization
60 density caused by the irradiation. A drawback of such a LET parametrization is, however,
61 that it introduces a dependence of RBE on the type of ion irradiation. Our recent analysis
62 of *in vitro* data emphasized the fact that RBE is to a large extent independent of ion type if
63 considered as function of beam quality instead of the LET [9]. The translation of such
64 basic understanding is essential for an apparent clinical RBE calculation. To increase
65 robustness of RBE modeling only a small number of clinically accessible input parameters
66 should be included that reflect patient treatment relevant endpoints such as functional
67 organ response to fractionated irradiation. Experimentally, these endpoints can be studied
68 with pre-clinical models, e.g., for late toxicity.

69

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

76

77 **Materials and Methods**

78 ***Pre-clinical literature data***

79 Pre-clinical literature data from a set of experiments on radiation-induced spinal cord
80 injury were compiled for carbon ion and photon irradiation [10–14]. In brief, in all
81 experiments the cervical spinal cord of rats was irradiated using single dose fractions ($n =$
82 1) or split dose irradiation ($n = 2$). The dose values at 50% complication probability, TD_{50} ,
83 were determined according to dose-response curves for the development of myelopathy
84 (paresis grade II) within an observation time of 300 days. Irradiation with carbon ions was
85 performed at six positions for a 6 cm spread-out Bragg peak (SOBP, dose-averaged LET
86 range 16-99 keV/ μm) for $n = 1$ [12,14] and $n = 2$ [13]. The RBEs were calculated using
87 TD_{50} values from comparable earlier experimental studies using 15 MV photon irradiation
88 [10,11]. The extracted experimental parameters and RBE data used in the present study are
89 listed in Table 1. The studied late toxicity endpoint of the serially organized spinal cord
90 allowed for a well-defined toxicity scoring of a non-transient radiation-induced
91 complication.

92

93 ***Calculation of the beam quality***

94 In this work, the radiation response of ion irradiation was considered as a function of the
95 dose-averaged LET – which will only be denoted as LET throughout the manuscript – as
96 well as the dose-averaged beam quality Q defined as,

$$Q = \frac{Z^2}{E}, \quad (1)$$

97 with Z and E being the charge and kinetic energy of an ion, respectively. In this work, Q
98 was defined to be a dimensionless parameter and E had to be given in units of MeV per

99 nucleon. The beam quality Q parametrizes the shape of the dose distribution deposited
100 around an ion track. More specifically, it directly determines (as a factor) the height of the
101 energy spectrum curve for the electrons that are produced by an ion track – independently
102 of ion type. A radiation field with a small Q corresponds to a more uniform dose within the
103 area of a cell nucleus while a large Q implies high dose heterogeneity on that level.
104 The dose, LET, and beam quality Q distributions as a function of depth in water were
105 obtained from Monte-Carlo simulations optimized for carbon ion treatment using
106 SHIELD-HIT12A [15,16]. For this purpose, the same 6 cm SOBP ranging from 70 to 130
107 mm water-equivalent depth as used for the published irradiation experiments [12–14] was
108 optimized using the treatment planning system TRiP [17]. The resulting treatment plan was
109 imported into the Monte-Carlo tool to simulate particle-resolved energy spectra as function
110 of depth in water. These spectra were used to determine dose-averaged LET and Q values
111 similar as described in [18] using the stopping power routine libdEdx [19]. Simulated dose
112 and LET distributions were compared to those applied for the rat irradiation experiments.

113

114 ***Analysis of the radiation response from fractionated irradiation***

115 In the framework of the linear-quadratic (LQ) model, the dependence of the radiation effect
116 ϵ is expressed by the linear and quadratic dose-response parameters α and β , respectively
117 [20]. If each successive fraction with dose d in a multidose schedule is equally effective,
118 the effect ϵ of n fractions can be expressed as,

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

119 with the total dose $D = n d$. The biological endpoint expressed as 50% complication
120 probability for radiation-induced myelopathy (paresis grade II) within 300 days after

121 irradiation has been assumed as full effect ($\varepsilon = 1$) as suggested in [20]. The α and β values
122 for the *in vivo* data were obtained using the graphical method [20] both for photon
123 irradiation and each of the six carbon ion treatment positions as described in more detail in
124 the Supplementary Materials.

125 ***Modeling the dose response and RBE***

126 The LQ parameters α_p and β_p for particle irradiation vary with beam quality. An analysis of
127 *in vitro* cell survival studies using particle irradiation with different ions suggested a linear
128 increase for α_p with Q , while β_p remained approximately constant for the interval $Q < 2.5$
129 [9]. In this study, the simple parametrization,

$$\alpha_p = \alpha(Q) = \alpha_0 + \beta_0 D_L Q, \quad (3)$$

$$\beta_p = \beta(Q) \approx \beta_0, \quad (4)$$

130 was used which was found to be useful to describe previously analyzed *in vitro* data (not
131 shown here). It is motivated by the local effect assumption combined with the LQ model as
132 used, e.g., in the local effect model (LEM) [21] and the microdosimetric-kinetic model
133 (MKM) [22], which are both in use for patient treatment with carbon ion therapy.

134 The constants α_0 and β_0 represent the limiting LQ parameters for Q approaching zero,
135 which is the theoretical photon limit. They could potentially be approximated by the
136 photon LQ parameters α_x and β_x . The limiting dose D_L is a model parameter, which is
137 assumed to depend on the biological system but to be independent of ion type. It is
138 conceptually related to the threshold dose, D_T , above which the LQ model is assumed to
139 enter into a linear dose response again. Following the local effect approximation, the
140 increase of biological effectiveness (assuming the validity of the LQ model) results from

141 the inhomogeneous dose distribution irradiation on the cellular level of particle. However,
 142 this increase of effect is then limited to local doses up to values around the threshold dose
 143 D_T , i.e., a higher D_T may result in a higher D_L . The relationship,

$$D_T = 1.1 \left(\frac{\alpha_X}{\beta_X} + 3.64 \text{ Gy} \right), \quad (5)$$

144 had been found empirically to match survival data with LEM simulations [21,23], which
 145 only depends on the photon α_X/β_X ratio.

146

147 The RBE in particle therapy is defined as the ratio of a reference photon dose, D_X , and a
 148 particle test irradiation dose, D_p ,

$$\text{RBE} = \frac{D_X}{D_p} \Big|_{\text{isoeffect}}, \quad (6)$$

149 resulting in the same biological effect. For fractionated irradiation with the same number of
 150 fractions n for photon and particle irradiation, Eq. (6) is reduced by n and the RBE depends
 151 solely on the ratio of doses per fraction. The RBE for an endpoint achieved with n
 152 fractions (i.e., $\varepsilon = 1$ after n fractions) of the photon dose d_X and proton dose $d_p =$

153 $\frac{1}{2\beta_p} \left(\sqrt{\alpha_p^2 + \frac{4\beta_p}{n}} - \alpha_p \right)$ – obtained by solving Eq. (2) for d_p – is given by,

$$\text{RBE} = \frac{2d_X}{\sqrt{\left(\frac{\alpha_p}{\beta_p}\right)^2 + \frac{4}{n\beta_p}} - \frac{\alpha_p}{\beta_p}}. \quad (7)$$

154 Removing the dependence on fraction number n and using the model description as
 155 proposed in Eqs. (3) and (4) results in

$$\text{RBE} = \frac{2d_x}{\sqrt{\left(\frac{\alpha_0}{\beta_0} + D_L Q\right)^2 + 4\frac{d_x}{\beta_0}(\alpha_x + \beta_x d_x) - \left(\frac{\alpha_0}{\beta_0} + D_L Q\right)}}. \quad (8)$$

156 For this model, the dependence of the RBE on the characteristics of the irradiation field
 157 (physics) is determined by the dose of the reference irradiation per fraction, d_x , and the
 158 beam quality Q . The dependence on the biological system including the considered
 159 endpoint (biology) is approximated by α_0 , β_0 and D_L .

160 In the case the parameters α_0 and β_0 can be approximated by the respective photon values
 161 α_x and β_x , the RBE expression further simplifies,

$$\text{RBE} = \frac{2d_x}{\frac{\alpha_x}{\beta_x} \left(\sqrt{\text{RBE}_Q^2 + \left(1 + 2\frac{\beta_x}{\alpha_x} d_x\right)^2} - 1 - \text{RBE}_Q \right)}, \quad (9)$$

162 with $\text{RBE}_Q = 1 + \frac{\beta_x}{\alpha_x} D_L Q$. Then the dependence of RBE on the biology is parametrized
 163 only by the photon α_x/β_x ratio and D_L .

164 For comparison with the measurements, modeled RBE values for the spinal cord were
 165 determined at the six positions within the SOBP using the photon irradiation doses d_x for n
 166 = 1 and $n = 2$ fractions and the RBE model given in Eq. (8). The α_0/β_0 ratio was
 167 approximated as 2 Gy – resembling the value often used clinically for comparable late
 168 toxicities in radiotherapy. All statistical data analyses were performed using SPSS version
 169 23.0 (IBM Corp.) and for the regression analysis p -values < 0.05 were considered
 170 significant.

171

172

173 **Results**

174 ***Simulation of the beam quality in a SOBP***

175 The Monte Carlo simulations of the 6 cm carbon ion SOBP reproduced the depth-dose
176 and depth-LET distributions used for the rat spinal cord irradiation experiments well (Fig.
177 1). The ranges of the SOBPs differed by less than 0.3 mm and the relative dose differences
178 were well below 1% for all but the most proximal irradiation position (about 1%). The
179 relative difference in LET increased toward the distal edge of the SOBP with the high LET
180 gradient ranging between about 1% and 6%. The ratio between beam quality Q and LET
181 was correlated but not constant and increased monotonously with depth toward the distal
182 end of the SOBP (Fig. 2). Three depth intervals could be distinguished, between which the
183 Q / LET ratio clearly differed: proximal to the SOBP, within the SOBP dose plateau, and in
184 the distal fall-off region. Within each of the first two intervals (containing all six irradiation
185 positions), the relative change between Q and LET was found to be small for the
186 considered carbon ion treatment field.

187

188 ***Analysis of α and β as a function of Q***

189 All α and β values obtained from the analysis of the experimental data are listed in Table 2.
190 The α parameter for carbon ion irradiation increased linearly with Q ($R^2 = 0.96$, Fig. 3) and
191 also with LET (Fig. S2 in Supplementary Material). Linear regression (including the
192 photon data) yielded for α a slope (95% confidence limit) of 0.019 (0.015 – 0.023) Gy^{-1}
193 and a constant of 0.0052 (-0.0006 – 0.0111) Gy^{-1} . In contrast, no significant slope was
194 found for the β data. Therefore, β_0 was approximated by the mean value 0.0019 Gy^{-2} (Fig.
195 3). This resulted in the values 9.9 Gy and 0.0038 Gy^{-1} for the model parameters D_L
196 (product of β_0 and the slope of α_p) and α_0 (product of β_0 and $\alpha_0/\beta_0 = 2$ Gy). For photons,

197 the α/β ratio determined from the one and two fraction data was 1.2 Gy with $\alpha_x = 0.0019$
198 and $\beta_x = 0.0016 \text{ Gy}^{-2}$.

199

200 ***RBE analysis and model prediction as a function of Q***

201 The experimental RBE data increased linearly with Q (Fig. 4). Linear regression showed
202 an equally high degree of correlation between RBE and Q ($R^2 = 0.98$) for both
203 fractionation schedules. The slope increased with number of fractions (i.e., decreasing
204 fraction dose) from 0.23 (0.19 – 0.27) to 0.39 (0.32 – 0.46).

205 The dependence of RBE on fraction dose increased with increasing Q. For $Q \rightarrow 0$ (limit of
206 less densely ionizing high-energy radiation), both fractionation schemes showed the same
207 (extrapolated) RBE value of 1.22 at $Q = 0$, which was significantly higher than a RBE of 1
208 ($p = 0.004$).

209 RBE values were calculated with the presented model for one, two and six fractions as well
210 as for a photon fraction dose of 2 Gy (Table 3), using the parameters $D_L = 9.75 \text{ Gy}$, $\alpha_0/\beta_0 =$
211 2 Gy , and $\beta_0 = 0.0019 \text{ Gy}^{-2}$ (cf. previous section). The model reproduced the dependence
212 on fractionation well (Fig. 4). The overall match with the experimental data was
213 reasonable. For small Q (especially for $Q < 0.5$, i.e., depths proximal to the SOBP) the
214 model predictions were smaller than the experimental RBE values with a tendency to
215 become larger than the measured RBE data for $Q > 2.5$. While the experimental data could
216 be fitted well with a linear curve, the RBE model showed a slightly upward bended slope.

217 **Discussion**

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

227 The linear increase of the RBE with the beam quality results primarily from the
228 pronounced linear increase of α with Q . On the other hand, the quadratic term of the LQ
229 model, β , remains approximately constant. The same dependence of RBE and α on Q as
230 well as the weak variation of β , which was observed here for the pre-clinical data, has
231 recently also been noticed in our reanalysis [9] of a number of *in vitro* experiments such as
232 [5,6,24]. The consistent outcome of these different *in vivo* and *in vitro* experiments
233 suggests that the observed linear increase of α as well as RBE with Q is a systematic effect.
234 The driving factor for the observed RBE variation is the linear slope of α with Q .

235 It is important to note, that the simple linear relation between RBE and Q may only hold
236 true in a finite range (approximately $Q \leq 2.5$ corresponding to $LET \leq 120$ keV/ μ m for
237 carbon ions). For larger Q , the overkill effect might gain importance, which is known to
238 occur at high LET (for carbon ions typically > 100 keV/ μ m) leading eventually to a
239 vanishing β and decreasing α [23]. The analyzed data demonstrate that in practical terms
240 this Q range is sufficient to cover the proximal 95% of the considered carbon treatment

241 field (SOBP). However, in clinical situations, it might be that parts of the remaining distal
242 fall-off region are placed inside an organ at risk. There, the use of the proposed model
243 could become problematic since it might estimate too large RBE values. Then the observed
244 toxicity would be lower than estimated, i.e., the model prediction had to be considered as
245 conservative estimate. While this has to be clarified based on experimental data it has to be
246 acknowledged that performing pre-clinical experiments and dose-response modeling
247 around the distal dose fall-off of the SOBP is challenging, also due to various uncertainties,
248 such as the range uncertainty.

249

250 In patient treatment, information on the dose response of clinical relevant endpoints is
251 usually only accessible through the analysis of the response to different doses per fraction.
252 For tumor response, those data can be obtained, e.g., from the analysis of clinical studies
253 with different fractionation schedules. For normal tissue, patient-specific anatomy and
254 treatment plans result inherently in a variation of dose distribution per fraction and among
255 patients within an organ at risk. Those variations can be assessed through an analysis based
256 on normal tissue complication probability models (e.g., for the spinal cord [25]).

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

264

265 It should be noted that the agreement of the modeled and the analyzed experimental data
266 was sensitive to the values used for α_0 and β_0 . In particular, a direct approximation by the
267 photon α_x and β_x values [Eq. (9)] that were obtained here ($\alpha_x/\beta_x = 1.2$ Gy) would have led
268 to a diminished agreement, in particular, for small Q with modeled RBE values close to 1.
269 While the experimental RBE values for one as well as two fractions extrapolated to $Q = 0$
270 (theoretical photon limit) were significantly larger than 1, RBE results compatible with 1
271 for $Q = 0$ would have implied isoeffectiveness for high-energy carbon ion and photon
272 irradiation (i.e., $\alpha_0 = \alpha_x$ and $\beta_0 = \beta_x$). On the other hand, the analysis of *in vitro* RBE data
273 for different cell lines irradiated with carbon ions [9] and protons [26] suggested that RBE
274 for particle irradiation in the limit $Q = 0$ might be compatible with a RBE of 1. An earlier
275 analysis of the same photon data pooled with data for eight and 16 fractions suggested a
276 higher photon α_x/β_x ratio of 2.8 Gy [11].

277 Disagreement was reported between the predictions by the LEM, which is used to
278 determine the RBE for patient treatment with carbon ion therapy in Europe, and the same
279 set of experimental data as considered here [13]. For the comparison, LEM I [21] had been
280 applied with the α and β values as input that are in use for actual patient treatment ($\alpha = 0.1$
281 Gy^{-1} , $\beta = 0.05 \text{ Gy}^{-2}$) while for LEM IV [27] the applied values ($\alpha = 0.003 \text{ Gy}^{-1}$, $\beta = 0.0015$
282 Gy^{-2}) were close to the photon α_x and β_x that were obtained in the present study. LEM I
283 fitted best at the lowest Q (LET = 16 keV/ μm) and deviated progressively toward higher
284 LET values while LEM IV agreed best at the highest Q (LET = 99 keV/ μm) and showed
285 increasing deviations below. While the measured increase of RBE with LET could neither
286 be fully described by LEM I nor by LEM IV, the systematic increase of the fractionation
287 dependence of the RBE at higher LET values was better described by LEM IV. The
288 observed deviations in this and earlier studies indicate the need for further experimental as

289 well as biophysical modeling studies to improve the reliability of treatment planning
290 software for particle therapy.

291

292 The present study of the experimental α and β parameters was limited by the fact that only
293 published data for one and two fractions were available for the analysis. Determining a
294 straight line from two experimental data points results in great uncertainties which
295 propagate to the extracted parameters – specially, in the extrapolation to derive α as the
296 intersection of the vertical axis. With only two points the straight line is given by default
297 and the uncertainties are large. It is also known that the method used to extract α and β
298 parameters is inefficient to estimate the α/β ratio [28]. Instead of one isoeffective dose
299 point (here TD_{50}) per treatment condition, in a more direct regression approach, the entire
300 experimental dose response curves – if available – should be used. However, the obtained
301 α and β values fully reproduced all experimental RBE data using Eq. (7), i.e., no modeling.
302 Experimental data for six fractions may become available in the near future and serve as a
303 validation data set (cf. Table 3). For carbon ion irradiation, the observed response showed
304 the anticipated systematic behavior (linear increase of α and constant β with Q) as shown
305 in Fig. 3. For photon irradiation, the analyzed α/β values appeared to be different whether
306 one and two or in addition data with eight and 16 fractions (with the same isoeffect) were
307 considered [11].

308

309 The parameter Q is closely related to a second commonly used parameter for radiation
310 quality, namely the square of the effective ion charge divided by its relativistic velocity,
311 $(Z_{\text{eff}}/(v/c))^2$, which is known to provide a lower dependence of radiation-induced effects on
312 the particle type than the LET [29]. This is in-line with our earlier analysis of *in vitro* cell

313 survival data indicating that experimental α , β , and RBE data were practically independent
314 of the type of ion irradiation (e.g., proton, helium, carbon, neon) when parametrized by Q
315 [9]. The present study suggests furthermore that the remarkably simple linear dependence
316 of radiation response on dose and Q also holds true for (pre-) clinical endpoints. Assuming
317 correctness, results from carbon ion irradiation could then be directly transferred to particle
318 therapy with other ions. From a clinical point of view, this would allow for a direct
319 translation of (clinically obtained) RBE data gathered in carbon ion therapy to application
320 in proton therapy. This would be a major step toward improving the simplistic clinical RBE
321 modeling currently in use in proton therapy (constant RBE = 1.1) by profiting from long
322 term clinical experience with a variable RBE in carbon ion therapy. However, that implies
323 that in future α and β as well as RBE will be provided as a function of Q instead of LET,
324 due to the dependence on the type of ion irradiation introduced by LET. Such an approach
325 would also imply the need for extrapolation of carbon ion RBE data (here obtained for $Q \geq$
326 0.25) down to smaller values of $Q \leq 0.25$ (i.e., proton energies ≥ 4 MeV), which are
327 typically found in a proton SOBP. The applicability of such an extrapolation needs to be
328 proven prior to application. Therefore, further research on the dependence of RBE,
329 especially under pre-clinical and clinical conditions, is mandatory to realize a successful
330 translation of this concept to proton therapy.

331

332 In conclusion, we showed for the first time that the fraction dose and beam quality Q are
333 sufficient to describe the RBE variability for a late toxicity model and different
334 fractionation schedules within a carbon ion treatment field. The variable RBE could be
335 modeled in a simple way, although, photon dose response data alone were insufficient to
336 explain the considered experimental data. The independence of the relevant RBE

337 parameters on the type of ion irradiation suggests the translation of RBE data from carbon
338 ions to protons to reduce the uncertainties currently associated with radiobiology in proton
339 therapy.

340

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343 providing treatment plans that had been used in the analyzed rat irradiation experiments.

344

345

346

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348

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- 425

426 **Tables**

427

428

| Depth | LET | TD ₅₀ | RBE | TD ₅₀ | RBE |
|------------------------|----------|------------------|-------|------------------|------|
| (mm) | (keV/μm) | (Gy) | | (Gy) | |
| 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 | - |

429

430 LET: Linear energy transfer; n: number of fractions; RBE: relative biological effectiveness;

431 TD₅₀: dose at 50% probability of paresis grade II.

432

433

434 Table 1: Experimental literature data for the irradiation of the rat spinal cord compiled

435 based on [10–14].

436

437

438

439
440

| 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 |

441

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

443

444

445 Table 2: Simulated beam quality Q at the six experimental depths positions of the rat spinal

446 cord as well as α and β parameters extracted from the experimental data and calculated

447 with the presented model approach. For the model, β is assumed to be constant with $\beta =$

448 0.0019 Gy⁻².

449

450

451

452

453

454

| | | 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 | |

455

456 Q : beam quality; d_x : photon fraction dose; n : number of fractions; RBE: relative biological
457 effectiveness.

458

459 Table 3: Modeled RBE values using Eq. (8). The values for 1 and 2 fractions can be
460 compared to the experimental data in Table 1. Extrapolated RBE values are also provided
461 for six fractions and a (clinically more relevant) photon fraction dose of 2 Gy.

462

463

464 **Figures**

465

466

467 Figure 1: Comparison of the depth-dose (black) and LET (blue) distributions as used in the
468 considered experimental studies [12–14] (dashed lines) based on TRiP and obtained from
469 SHIELD-HIT (SH) Monte-Carlo simulations in the present study (solid lines). The
470 treatment positions are indicated by the (red) symbols on the experimental dose (circles)
471 and LET (squares) curve.

472

473

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

477

478

479 Figure 3: The parameters α and β of the linear quadratic model are shown in (A) and (B),
480 respectively, as a function of the beam quality Q . The experimental data from photon and
481 carbon ion irradiation are compared to the proposed model description.

482

483

484 Figure 4: The relative biological effectiveness (RBE) as a function of the beam quality Q .
485 Comparison of experimental RBE data for 1 and 2 fractions with (A) linear fits of the
486 experimental data and (B) the proposed RBE model. See text for details.

487