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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 extend 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^{-}

22 ^{1}. 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.

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 biological effect e.g. increased cell killing, 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 – 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 extend 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,

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

6

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 $\boldsymbol{\varepsilon}$ of n fractions can be expressed as,

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

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

7

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,

$$\alpha_p = \alpha(Q) = \alpha_0 + \beta_0 D_\mathrm{L} Q \,, \tag{3}$$

$$\beta_p = \beta(Q) \approx \beta_0 \,, \tag{4}$$

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,

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

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,

$$\text{RBE} = \frac{D_X}{D_p} \bigg|_{\text{isoeffect}}, \tag{6}$$

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,

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

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 Carlos 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 α_0/β_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 $\beta_X = 0.0016$ 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 $D_L = 9.75$ Gy, $\alpha_0/\beta_0 =$

211 2 Gy, and $\beta_0 = 0.0019$ 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 ≤ 120 keV/µm 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/µm) 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 (α_X/β_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}, $\beta = 0.05$ Gy^{-2}) while for LEM IV [27] the applied values ($\alpha = 0.003$ 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 LEMI 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 $\left(Z_{\text{eff}}/\left(\frac{v}{c}\right)\right)^2$, 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.

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425

426   **Tables**

427

428

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	-

429
430   LET: Linear energy transfer; n: number of fractions; RBE: relative biological effectiveness;

431   TD_{50}: dose at 50% probability of paresis grade II.

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

435   based on [10–14].

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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.

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	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**

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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