Radiotherapy and Oncology 141 (2019) 234–238

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

RBE-weighted doses in target volumes of chordoma and chondrosarcoma patients treated with carbon ion radiotherapy: Comparison of local effect models I and IV

Clarissa Gillmann [a,*], Oliver Jäkel [a,b,c], Christian P. Karger [a,b]

[a] Department of Medical Physics in Radiation Oncology, German Cancer Research Center (DKFZ); [b] National Center for Radiation Research in Oncology (NCRO), Heidelberg Institute for Radiation Oncology (HIRO); and [c] Heidelberg Ion Beam Therapy Center (HIT), Heidelberg University Hospital, Germany

ARTICLE INFO

Article history:
Received 8 May 2019
Received in revised form 30 July 2019
Accepted 9 August 2019
Available online 12 September 2019

Keywords:
Carbon ion radiotherapy
RBE
Local effect model (LEM I vs. LEM IV)
Tumor control probability

ABSTRACT

Background and purpose: To compare the relative biological effectiveness (RBE)-weighted dose distributions in the target volume of chordoma and chondrosarcoma patients when using two different versions of the local effect model (LEM I vs. IV) under identical conditions.

Materials and methods: The patient collective included 59 patients treated with 20 fractions of carbon ion radiotherapy for chordoma and low-grade chondrosarcoma of the skull base at the Helmholtzzentrum für Schwerionenforschung (GSI) in 2002 and 2003. Prescribed doses to the planning target volume (PTV) were 60 ($n = 49$), 66 ($n = 2$) and 70 ($n = 8$) Gy (RBE). The original treatment plans that were initially biologically optimized with LEM I, were now recalculated using LEM IV based on the absorbed dose distributions. The resulting RBE-weighted dose distributions were quantitatively compared to assess the clinical impact of LEM IV relative to LEM I in the target volume.

Results: LEM IV predicts 20–30 Gy (RBE) increased maximum doses as compared to LEM I, while minimum doses are decreased by 2–5 Gy (RBE). Population-based mean and median doses deviated by less than 2 Gy (RBE) between both models.

Conclusions: LEM I and LEM IV-based RBE-weighted doses in the target volume may be significantly different. Replacing the applied model in patient treatments may therefore lead to local over- or underdosages in the tumor. If LEM IV is to be tested clinically, comparisons of the RBE-weighted dose distributions of both models are required for the individual patients to assess whether the LEM IV-plan would also be acceptable and prescribed dose as well as clinical outcome data have to be carefully reassessed.

Carbon ion radiotherapy of tumors of the skull base has gained increasing interest throughout the last two decades. Similar to protons, carbon ions allow for highly conformal irradiation of the tumor while sparing the surrounding normal tissue structures like brain stem, optic nerves and the chiasma due to their "inverted" depth dose profile, the so-called Bragg-peak [1]. An additional rationale for selecting carbon ions results from their higher relative biological effectiveness (RBE) relative to photons and protons, which increases with penetration depth and reaches its maximum at the distal edge of the Bragg-peak [2]. As a consequence, dose distributions are usually prescribed in terms of RBE-weighted rather than absorbed dose. The RBE exhibits a complex dependency on linear energy transfer (LET), fractional dose and tissue type. In treatment planning, the RBE is calculated by biomathematical models, like the mixed beam model [3], the microdosimetric kinetic model [4] or the local effect model (LEM) [5]. The LEM has been clinically introduced at the carbon ion pilot project at the Helmholtz Center for Heavy Ion Research (GSI) in Germany and has subsequently been used also in other carbon ion facilities [6,7].

Clinical studies demonstrated high effectiveness with low toxicity in skull base chordoma and chondrosarcoma suggesting that LEM predicts the RBE with reasonable accuracy [8–11]. On the other hand, studies in the rat spinal cord [12–14] have indicated that the clinically applied version LEM I [5] underestimates the RBE especially at higher LET-values in the SOBP, while the more recent version LEM IV [15] has shown to be more accurate in this region. The question whether LEM I or IV is more accurate in the clinical setting, however, is still investigated as clinical data is scarce.

Schlampp et al investigated temporal lobe reactions in the same patient collective as used in the present study and established a

* Corresponding author at: Department of Medical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany.
E-mail address: c.gillmann@dkfz.de (C. Gillmann).

https://doi.org/10.1016/j.radonc.2019.08.006
0167-8140/

RBE-weighted dose-response curve [16]. Subsequently, Gillmann et al repeated this analysis using the same absorbed dose distributions, applying LEM IV instead of LEM I. As a result, the tolerance doses of the normal brain were shifted by 9.5 and 12.5 Gy (RBE) at the 5% (TD_5) and 50% (TD_{50}) effect levels, [17]. Although this shift was clinically significant, a decision whether LEM I or LEM IV is clinically more accurate was not possible as corresponding photon data is highly uncertain. An analysis in a similar proton-treated patient collective revealed a dose response curve, which was almost identical to that of LEM I, however, a fixed RBE of 1.1 was assumed in this study as it is current clinical standard [18].

These studies were especially sensitive to the highest LET component and much less information is available for planning target volumes (PTV). Using RBE-weighted prescribed doses from photons, protons and carbon ions, Schulz-Ertner analyzed the published 5 year local control rates of chordoma and found a common dose–response curve, however, this curve might be questioned since the underlying patient characteristics between the studies differed considerably and no information on the dose distribution was available [8]. Grün et al. compared the RBE-weighted dose distributions from LEM I and IV in more detail, yet, this study was based on idealized spherical and cubic rather than patient-specific PTVs. As a result, the LEM IV-based RBE-weighted dose was strongly increased at the distal edge but decreased at the center of the target volume leading to a comparable median target dose over all patients [19]. For the individual patient, however, the dose alterations depend strongly on the size and shape of the target volume as well as the number and orientation of the beams.

In this analysis, we apply the same methodology as in Grün et al 2012 [19] to investigate the differences between the LEM I- and LEM IV-based RBE-weighted dose distributions in the PTV based on a real patient collective, which is identical to that of our previous normal tissue studies [16,17]. Special focus is put on the analysis of local over- and under-dosages in the PTV.

Materials and methods

Patient collective

The analyzed patient collective is identical to that studied previously [16,17] and included 59 patients treated with carbon ions for chordoma ($n = 40$) and low-grade chondrosarcoma ($n = 19$) of the skull base at GSI in 2002 and 2003. Prescribed doses to the PTV were 60 ($n = 49$), 66 ($n = 2$) and 70 ($n = 8$) Gy (RBE) delivered in 20 fractions of 3.0, 3.3 and 3.5 Gy (RBE), respectively. 15 fractions were applied to the Planning Target Volume 1 (PTV1) and 5 fractions were applied to a subvolume of the initial PTV (PTV2). Median target volume was 116 cm^3 (range, 24–307 cm^3) for PTV1 and 69 cm^3 (range 14–234 cm^3) for PTV2. Patients were treated with either one ($n = 1$), two ($n = 50$) or three treatment fields ($n = 8$). This well-defined patient collective is still considered representative for today's clinical practice at the Heidelberg Ion Beam Therapy Center (HIT, Germany), where chondrosarcoma patients are treated with a dose of 60 Gy (RBE) ± 5 % and chordoma patients with a dose of 63 Gy (RBE) ± 5 %, both using fractional doses of 3 Gy (RBE) [20].

Dose-volume parameters

Original treatment plans were biologically optimized using LEM I with the treatment planning program TRiP (Treatment Planning for Particles) [21,22]. Based on the resulting fluence distribution, a recalculation of the biological effective dose was performed for each patient, now using LEM IV instead of LEM I. The input parameters for LEM I and LEM IV were chosen according to those established in Grün et al ($\alpha/\beta = 2$ Gy $\alpha = 0.1$ for LEM I, and $\alpha/\beta = 2.45$ Gy, $\alpha = 0.0081$ for LEM IV. $D_t = 30$ for both models) [19]. Prior to evaluation, the resulting total dose distributions were rescaled to a standard fractional dose 2 Gy (RBE) using the linear-quadratic model [23] with the same values of α/β as applied in LEM I and LEM IV, respectively.

From the resulting total RBE-weighted dose distributions, the maximum (Dmax), minimum (Dmin), mean (Dmean) and median (Dmedian) doses together with the dose-volume parameters D2% and D98% (RBE-weighted doses exceeded in 2 % and 98 % of the target volume, respectively) were extracted separately for PTV1 and PTV2.

To analyze the biological effect of the non-uniform RBE-weighted dose distributions in the tumor in terms of cell survival, the equivalent uniform dose (EUD) was calculated according to [24]

$$EUD = -\frac{\alpha}{2\beta} + \sqrt{-\frac{ln(\bar{S})}{\beta} + \left(\frac{\alpha}{2\beta}\right)^2}$$

The mean cell survival in the target volume, $\bar{S}$, was determined from the individual three-dimensional survival distributions calculated by TRiP using the same values of α/β and β as before [19].

Finally, the volumes $V_{90\%}$, $V_{95\%}$ and $V_{107\%}$ (volumes receiving more than 90%, 95% or 107% of the prescribed dose, respectively), were determined for PTV2. As PTV1 received only 75% of the prescribed dose, $V_{67.5\%}$, $V_{71.3\%}$ and $V_{80.3\%}$ were used in this case (75% of the dose levels used for PTV2).

Statistics

Dosimetric parameters were analyzed using the statistics software R [25]. Differences between LEM I and LEM IV were tested with a paired, two-sided Wilcoxon-test and $p < 0.05$ was considered as statistically significant.

Results

Fig. 1 displays the total RBE-weighted dose distributions of LEM I and LEM IV for a patient with a large target volume (patient 1, $Volume_{PTV1} = 247.1$ cm^3) and a patient with a small target volume (patient 2, $Volume_{PTV1} = 47.3$ cm^3). In general, the dose distributions recalculated with LEM IV exhibited large dose gradients along the beam directions. Large tumor volumes received a slightly (∼5 %) reduced dose at the center and an 20–30 % increased dose at the rim of the target. For small targets, the dose was increased over the whole target volume for LEM IV relative to LEM I by at least 10 % at the center and up to 35 % at the rim of the PTV.

Fig. 2 shows the corresponding dose-volume histograms (DVH) of both patients. For patient 1, the maximum doses in PTV1 and PTV2 was increased by 30 % (26 Gy (RBE)). Deviations between median and minimum doses were less than 5 % (2–3 Gy (RBE)). Although median and minimum doses were very similar, a significant over- and underdosage, especially for PTV2, was seen in the DVH. For the patient with the small target volume (patient 2), the DVH-curve of LEM IV is constantly shifted towards higher doses, resulting in 34 % (39 Gy (RBE)) increased maximum doses in PTV1 and PTV2. The median and minimum doses were increased by ∼ 10 % (8 Gy (RBE)) for LEM IV as compared to LEM I.

Table 1 and Fig. 3 summarize the dose-volume parameters for PTV1 and PTV2 calculated by LEM I and LEM IV over all patients. The general trend was very similar for PTV1 and PTV2. LEM IV predicted 20–30 Gy (RBE) increased maximum doses as compared to LEM I, while minimum doses were decreased by 2–5 Gy (RBE). The median increase of D2% was 19 % for PTV1 and 17 % for PTV2, while D98% increased by 5 % for PTV1 and decreased by 7

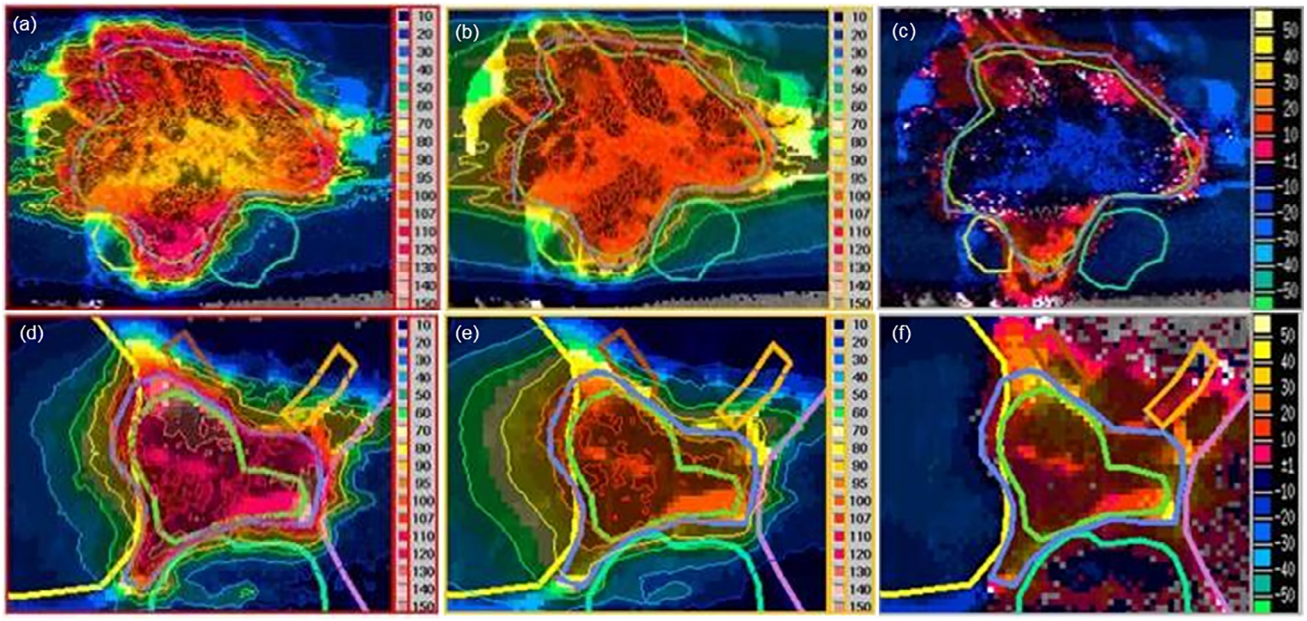

Fig. 1. Comparison of recalculated (LEM IV-based) (a and d) and original (LEM I-based) (b and e) RBE-weighted total dose distributions together with their difference maps (c and f) for a patient with a large (a, b, c) and a patient with a small (d, e, f) target volume. Legends refer to the percentage of the prescribed dose. Volumes of interest: PTV1 (blue), PTV2 (green), brainstem (light green), left temporal lobe (yellow), right temporal lobe (purple), left optical nerve (brown) and right optical nerve (dark yellow).

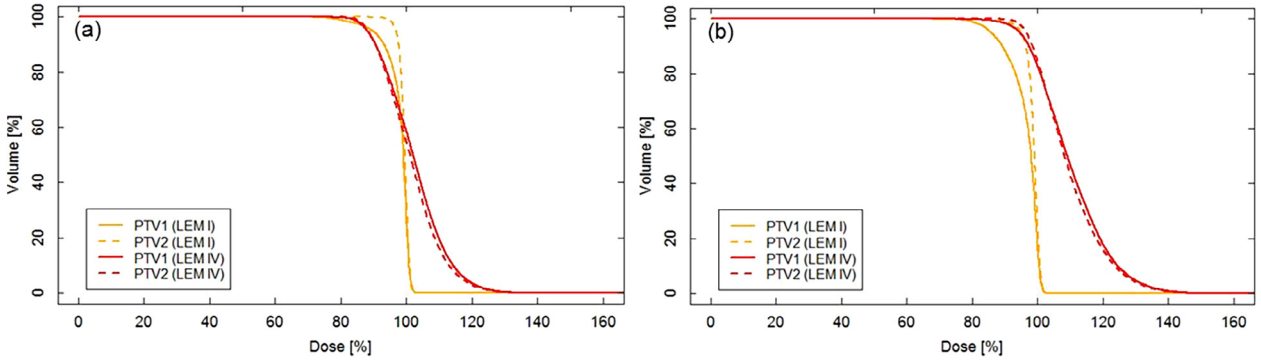

Fig. 2. Comparison of recalculated (LEM IV-based) and original (LEM I-based) dose volume histograms of the total RBE-weighted dose distribution in PTV1 and PTV2 for a patient with a large (a) and a small (b) target volume.

Table 1
Dose-volume histogram parameters of the RBE-weighted total dose distribution calculated by LEM I and LEM IV averaged over all patients.

	Median (25%/75% quantiles)			
	PTV1		PTV2	
	LEM I	LEM IV	LEM I	LEM IV
Dmax [Gy (RBE)]	78.3 (77.7/84.5)	108.2 (104.2/118.4)	78.3 (77.7/83.9)	106.5 (101.8/116.7)
Dmin [Gy (RBE)]	48.5 (42.3/50.7)	46.7 (38.3/49.0)	61.7 (53.1/65.1)	57.2 (52.1/62.3)
D2% [Gy (RBE)]	76.4 (76.2/78.6)	94.1 (89.5/103.4)	76.4 (76.4/77.9)	92.4 (88.6/102.7)
D98% [Gy (RBE)]	57.8 (54.8/62.4)	60.6 (55.8/63.6)	71.3 (70.2/71.9)	66.9 (64.8/74.4)
Dmedian [Gy (RBE)]	74.0 (73.5/74.3)	75.0 (73.3/82.3)	74.6 (74.4/74.7)	75.5 (73.8/83.6)
Dmean [Gy (RBE)]	72.5 (71.4 /73.6)	76.1 (73.1/82.3)	74.3 (74.2/77.4)	76.5 (74.7/83.4)
EUD [Gy (RBE)]	73.1 (72.3/74.1)	77.5 (75.7/84.1)	74.8 (74.7/75.2)	78.4 (76.2/85.8)
V90%(PTV2)/V67.5%(PTV1) [%]	100 (99.6/100.0)	100.0 (99.8/100.0)	99.8 (93.5/98.1)	98.3 (94.7/99.7)
V95%(PTV2)/V71.3%(PTV1)	99.7 (98.5/99.9)	99.9 (99.0/100.0)	96.9 (93.5/98.1)	87.0 (76.8/97.7)
V107%(PTV2)/V80.3%(PTV1) [%]	94.6 (88.2/98.2)	98.1 (94.1/99.4)	0.0 (0.0/0.5)	30.6 (23.0/55.6)

% for PTV2 when replacing LEM I by LEM IV. Population-based mean and median doses deviated by less than 2 Gy (RBE) between both models. EUD was found to be significantly higher for LEM IV as compared to LEM I. The volumes $V_{90\%}$ and $V_{95\%}$ were reduced while $V_{107\%}$ was increased for LEM IV relative to LEM I.

Discussion

For carbon ion radiotherapy, the RBE-weighted dose is associated with significant uncertainties originating from the involved RBE model and its parameters. The aim of the present comparative

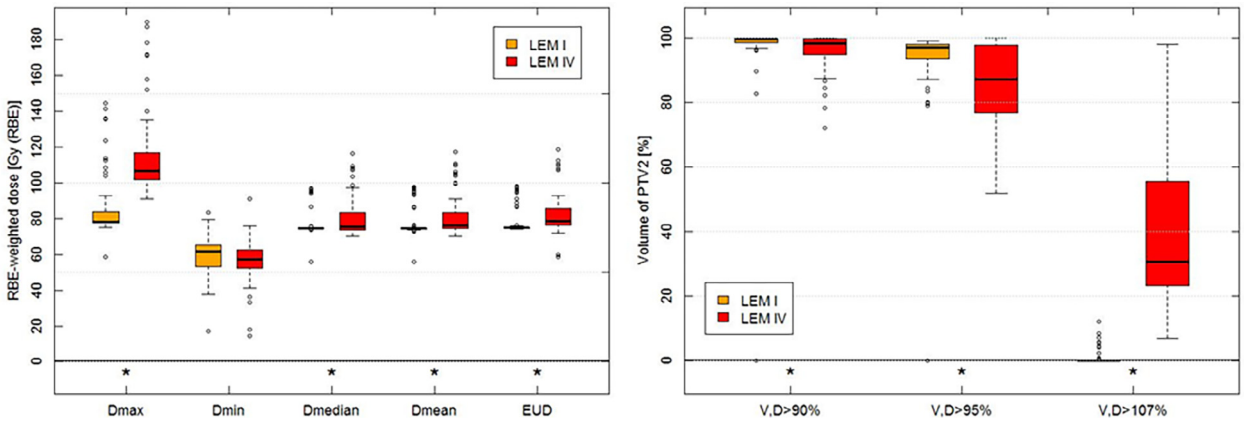

Fig. 3. Comparison of dose-volume parameters for PTV2 determined for LEM I and LEM IV for all patients. (Solid lines: median, boxes: first and third quartiles, whiskers: 5% and 95 % quantiles, circles: outliers) Significant differences between LEM I and LEM IV are indicated by *.

treatment planning study therefore was to analyze the clinical consequences of using a new radiobiological model (LEM IV) by comparing it against the clinically applied model (LEM I) in the tumor volume for the same patient collective. The general findings of this study are very similar to those of Grün et al [19]. However, this study is based on treatment plans of actually treated patients rather than on idealized target geometries and the results may therefore be of higher clinical relevance.

Our treatment plan-based comparison of LEM I and LEM IV revealed major differences in the RBE-weighted dose distributions of individual patients, most strikingly an increase of the maximum doses at the distal edges of the treatment fields by up to 35 % in conjunction with a decrease of the minimum dose at the center of the treatment fields of about 10 %. This observation can be explained by the increase of LET along the beam direction together with the stronger LET-dependence of the RBE in LEM IV as compared to LEM I. The population-based median and mean doses of LEM I and LEM IV agree quite well, however, for the individual patient, this comparison depends strongly on the size of the target volume and the number and orientation of treatment fields. As the high doses at the distal edge of the treatment field receive a higher relative weighting for small target volumes, LEM IV results in significantly higher median and mean doses in these cases as compared to LEM I (see DVHs in Fig. 2 as example).

Both the LEM I and the LEM IV-based dose distributions are based on the same fluence distribution of ions. As the original treatment plan was optimized with LEM I, the LEM IV-based recalculated RBE-weighted dose distribution is highly inhomogeneous due to the different LET-dependence in the model. As in the previous analysis [19] the EUD was used to compare the biological effectiveness of the LEM I and LEM IV-based treatment plans. By construction, the EUD is the RBE-weighted dose that, when uniformly applied to the whole tumor, yields the same expectation value for the number of surviving tumor cells as the original non-uniform irradiation [24].

Although the EUD-concept is often used for such comparisons, it is based on the assumptions of (i) a uniform clonogenic cell density (CCD), and (ii) a uniform radiation sensitivity throughout the target volume. Both may be questioned in the present analysis. Firstly, the highest doses systematically occur at the safety margin of the PTV, which is expected to contain a lower CCD (in case of PTV2) or essentially normal cells (in case of PTV1) and as a result the EUD of LEM IV could be overestimated. Secondly, radiosensitivity-modulating factors like hypoxia may predominantly develop in the core of the tumor leading to a higher number of surviving cells in regions of potentially lower doses. Thirdly, another problem arises from the fact that different values of α and β are used in LEM I and IV and for consistency reasons these values were also used in the calculation of the EUD. While the small difference in α/β has only minor impact on the EUD, the absolute difference in α (and thusβ) influences the EUD significantly. The strong dependence of EUD on α has been analyzed previously McGary et al., who stated that a 25 % change in α can result in an EUD variation of approximately 40 % [26]. For the above reasons, the EUD-values in this study have to be considered with great caution. Finally, it has to be noted that the different α/β-values of LEM I and IV affect also the conversion of the fractionation schedules. This influence, however is <3% and therefore negligible.

In spite of the uncertainties regarding the biological effect in the tumors, our analysis clearly shows highly significant differences in the dose distributions resulting from the use of LEM I and IV. Whether LEM I should be replaced by LEM IV for actual treatments of patients depends critically on the answer to the question, which model describes the RBE for chordoma as well as normal brain tissue more accurately. Regarding the effectiveness in tumors, one important issue is that although the population-based median doses in the target volume are similar for LEM I and LEM IV, the target doses for individual patients may differ quite substantially, depending on individual parameters like the size of the tumor volume.

If LEM IV is assumed to give a correct description of the RBE in the tumor as well as in the normal tissue, our analysis showed that the LEM I-optimized treatment plans would be expected to result in very high RBE-weighted doses at the rim of the target volume for all patients. While this local increase may impact the effectiveness in the tumor only to some degree, it appears likely that the adjacent normal tissue would be affected. Previous analysis of temporal lobe reactions in the same patient collective revealed tolerance doses at the 5% effect level of 68.8 Gy (RBE) for LEM I and 78.3 Gy (RBE) for LEM IV [17]. Although the comparable photon data are lacking, temporal lobe doses around 78 Gy would not be considered acceptable in photon treatments. In a further analysis [18], the LEM I-based dose response curve agreed well with that of a similar analysis in a proton collective, although this analysis was based on a fixed RBE of 1.1, which has recently been questioned [27]. Regarding the lack of severe side effects in normal brain tissue of patients, the potentially high LEM IV-doses might also be compensated by the volume effect due to the very steep dose gradients.

On the other hand, assuming that LEM I predicts the correct RBE, a LEM IV-optimized treatment plan would exhibit significant underdosages at the border of the target volume potentially

leading to compromised control rates. This has to be considered when introducing LEM IV for patients. For this, however, no evidence has been found yet.

Of course, it may also be the case that LEM I and LEM IV are partially correct, depending e.g. on the LET and dose range. Indications for this have been found in preclinical studies in the rat spinal cord [13,14]. Finally, it has to be considered that dose prescription in carbon ion therapy is not completely independent of the applied RBE-model as deficiencies in the RBE-predictions may be compensated to some degree by clinical adjustment of the prescribed dose [2].

Conclusions

LEM I and LEM IV-based RBE-weighted doses in the target volume may be significantly different at the rim as well as at the center of the tumor. Replacing the applied model in patient treatments may therefore lead to local over- and underdosages in the tumor. If LEM IV is to be tested clinically, comparisons of the RBE-weighted dose distributions of both models are required for the individual patients to assess whether the LEM IV-plan would also be acceptable and prescribed dose as well as clinical outcome data have to be carefully reassessed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was supported by Konrad-Adenauer-Stiftung (graduate scholarship) and Helmholtz Gemeinschaft (Virtual Institute Hadron Therapy, VH-VI 303).

References

[1] Suit H, DeLaney T, Goldberg S, et al. Proton vs carbon ion beams in the definitive radiation treatment of cancer patients. Radiother Oncol J Eur Soc Ther Radiol Oncol 2010;95:3–22. https://doi.org/10.1016/j.radonc.2010.01.015.

[2] Karger CP, Peschke P. RBE and related modeling in carbon-ion therapy. Phys Med Biol 2017. https://doi.org/10.1088/1361-6560/aa9102.

[3] Kanai T, Furusawa Y, Fukutsu K, Itsukaichi H, Eguchi-Kasai K, Ohara H. Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. Radiat Res 1997;147:78–85.

[4] Kase Y, Kanai T, Matsumoto Y, et al. Microdosimetric measurements and estimation of human cell survival for heavy-ion beams. Radiat Res 2006;166:629–38. https://doi.org/10.1667/RR0536.1.

[5] Scholz M, Kellerer AM, Kraft-Weyrather W, Kraft G. Computation of cell survival in heavy ion beams for therapy. Radiat Environ Biophys 1997;36:59–66. https://doi.org/10.1007/s004110050055.

[6] Combs SE, Jäkel O, Haberer T, Debus J. Particle therapy at the heidelberg ion therapy center (HIT) – Integrated research-driven university-hospital-based radiation oncology service in Heidelberg, Germany. Radiother Oncol J Eur Soc Ther Radiol Oncol 2010;95:41–4. https://doi.org/10.1016/j.radonc.2010.02.016.

[7] Rossi S. The National Centre for Oncological Hadrontherapy (CNAO): Status and perspectives. Phys Medica PM Int J Devoted Appl Phys Med Biol Off J Ital Assoc Biomed Phys AIFB 2015;31:333–51. https://doi.org/10.1016/j.ejmp.2015.03.001.

[8] Schulz-Ertner D, Karger CP, Feuerhake A, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. Int J Radiat Oncol Biol Phys 2007;68:449–57. https://doi.org/10.1016/j.ijrobp.2006.12.059.

[9] Schulz-Ertner D, Nikoghosyan A, Hof H, et al. Carbon ion radiotherapy of skull base chondrosarcomas. Int J Radiat Oncol Biol Phys 2007;67:171–7. https://doi.org/10.1016/j.ijrobp.2006.08.027.

[10] Uhl M, Mattke M, Welzel T, et al. Highly effective treatment of skull base chordoma with carbon ion irradiation using a raster scan technique in 155 patients: first long-term results. Cancer 2014;120:3410–7. https://doi.org/10.1002/cncr.28877.

[11] Uhl M, Mattke M, Welzel T, et al. High control rate in patients with chondrosarcoma of the skull base after carbon ion therapy: first report of long-term results. Cancer 2014;120:1579–85. https://doi.org/10.1002/cncr.28606.

[12] Karger CP, Peschke P, Sanchez-Brandelik R, Scholz M, Debus J. Radiation tolerance of the rat spinal cord after 6 and 18 fractions of photons and carbon ions: Experimental results and clinical implications. Int J Radiat Oncol 2006;66:1488–97. https://doi.org/10.1016/j.ijrobp.2006.08.045.

[13] Saager M, Glowa C, Peschke P, et al. Split dose carbon ion irradiation of the rat spinal cord: Dependence of the relative biological effectiveness on dose and linear energy transfer. Radiother Oncol J Eur Soc Ther Radiol Oncol 2015;117:358–63. https://doi.org/10.1016/j.radonc.2015.07.006.

[14] Saager M, Glowa C, Peschke P, et al. The relative biological effectiveness of carbon ion irradiations of the rat spinal cord increases linearly with LET up to 99 keV/µm. Acta Oncol Stockh Swed 2016;55:1512–5. https://doi.org/10.1080/0284186X.2016.1250947.

[15] Elsässer T, Weyrather WK, Friedrich T, et al. Quantification of the relative biological effectiveness for ion beam radiotherapy: direct experimental comparison of proton and carbon ion beams and a novel approach for treatment planning. Int J Radiat Oncol 2010;78:1177–83. https://doi.org/10.1016/j.ijrobp.2010.05.014.

[16] Schlampp I, Karger CP, Jäkel O, et al. Temporal lobe reactions after radiotherapy with carbon ions: incidence and estimation of the relative biological effectiveness by the local effect model. Int J Radiat Oncol 2011;80:815–23. https://doi.org/10.1016/j.ijrobp.2010.03.001.

[17] Gillmann C, Jäkel O, Schlampp I, Karger CP. Temporal lobe reactions after carbon ion radiation therapy: comparison of relative biological effectiveness-weighted tolerance doses predicted by local effect models I and IV. Int J Radiat Oncol Biol Phys 2014;88:1136–41. https://doi.org/10.1016/j.ijrobp.2013.12.039.

[18] Gillmann C, Lomax AJ, Weber DC, Jäkel O, Karger CP. Dose-response curves for MRI-detected radiation-induced temporal lobe reactions in patients after proton and carbon ion therapy: Does the same RBE-weighted dose lead to the same biological effect? Radiother Oncol J Eur Soc Ther Radiol Oncol 2018;128:109–14.

[19] Grün R, Friedrich T, Elsässer T, et al. Impact of enhancements in the local effect model (LEM) on the predicted RBE-weighted target dose distribution in carbon ion therapy. Phys Med Biol 2012;57:7261–74. https://doi.org/10.1088/0031-9155/57/22/7261.

[20] Nikoghosyan AV, Karapanagiotou-Schenkel I, Münter MW, Jensen AD, Combs SE, Debus J. Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study. BMC Cancer 2010;10:607. https://doi.org/10.1186/1471-2407-10-607.

[21] Krämer M, Jäkel O, Haberer T, Kraft G, Schardt D, Weber U. Treatment planning for heavy-ion radiotherapy: physical beam model and dose optimization. Phys Med Biol 2000;45:3299–317.

[22] Krämer M, Scholz M. Treatment planning for heavy-ion radiotherapy: calculation and optimization of biologically effective dose. Phys Med Biol 2000;45:3319–30.

[23] Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679–94. https://doi.org/10.1259/0007-1285-62-740-679.

[24] Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. Med Phys 1997;24:103–10.

[25] R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org.

[26] McGary JE, Grant W, Woo SY. Applying the equivalent uniform dose formulation based on the linear-quadratic model to inhomogeneous tumor dose distributions: Caution for analyzing and reporting. J Appl Clin Med Phys 2000;1:126–37. https://doi.org/10.1120/1.1314839.

[27] Paganetti H. Relating proton treatments to photon treatments via the relative biological effectiveness—should we revise current clinical practice? Int J Radiat Oncol 2015;91:892–4. https://doi.org/10.1016/j.ijrobp.2014.11.021.