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Critical Review

Clinical Applications of Relative Biological Effectiveness in Carbon Ion Radiation Therapy: Current Status and Consensus Statements

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The exploitation of the high relative biological effectiveness (RBE) of carbon ions is one of the major rationales for their use as a radiation therapy modality. As the RBE depends on many physical and biological factors, biophysical models are used to compute it for the complex radiation fields used in clinical settings. However, the models currently applied in clinics or used to interpret clinical results make different RBE predictions. This creates difficulties for direct comparability of RBE-weighted doses delivered and reported within different approaches. Additional conventions on how these models are applied also differ and further complicate the comparison. Consequently, it is crucial to understand the impact of RBE modeling on the delivered absorbed doses and the reported RBE-weighted doses. Translation concepts between dose prescription systems, that is, the models and the context in which they are used, are needed to exchange treatment protocols between centers with different planning methods and to establish joint clinical studies or meta-studies. Although

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many of these problems are solved for specific cases, a broad perspective is lacking on how to transparently proceed with multiple RBE models and corresponding concepts of RBE-weighted dose.

The present publication is a product of an initiative within the subcommittee on Guidelines in Carbon Ion Radiation Therapy of the Particle Therapy Co-operative group (PTCOG). It aims to (1) raise awareness of the problem; (2) demonstrate the impact of different models used for RBE predictions; (3) provide information on how RBE is currently accounted for; and (4) give an overview of approaches toward the translation of doses. Along this route, we provide several expert consensus statements agreed on by all authors, which provide insights into the complexity of understanding and comparing different dose prescription systems. Despite this complexity, transforming treatment plans between any 2 systems is feasible, opening up novel planning strategies that consider multiple models and paving the way for multi-institutional clinical studies . © 2026 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Introduction

Carbon ion therapy has now been used continuously in clinical routine for >3 decades.[1,2] Besides the characteristic Bragg curve providing an inverted dose profile with respect to photons, the high linear energy transfer (LET) is one of the main rationales for this therapy modality: the high local energy concentration may induce persistent damage in tumor cells, which helps to overcome several sources of radioresistance such as resistant cell cycle phases and tumor hypoxia. As a consequence, carbon ions are more effective at the same absorbed (physical) dose as photon radiation, in particular in the target region. Hence, the absorbed dose given to a voxelized volume is not sufficient to describe the effect. Instead, the enhanced effectiveness has to be accounted for. The conventionally used quantitative measure for this is the relative biological effectiveness (RBE). This is beneficial as it allows a favorable ratio of RBE-weighted (and therefore biologically weighted) dose in the target region, as compared with that in normal tissue, therefore allowing greater normal tissue sparing and a broadening of the therapeutic window. However, RBE has to be thoroughly accounted for in treatment planning. This is a nontrivial task, and given that the RBE depends nonlinearly on both biological and physical factors, an optimization of the RBE-weighted dose is required to properly account for the RBE within a complex radiation field, such as a spread-out Bragg peak (SOBP). For that, usually RBE information for monoenergetic beams within small water layers (often referred to as track segment conditions) is needed as input, which is provided by biophysical models. Pragmatically, these models usually use effects of a reference radiation to predict the effects of the monoenergetic ion radiation, where the effects are expressed within the linear-quadratic (LQ) or linear-quadratic-linear (LQ-L) model,[3] including the linear and quadratic dose-response parameters α and β.

Different approaches have led to mainly 3 classes of models which are nowadays used. These are based on (1) the mixed beam model (MBM),[4-6] using a semiempirical approach based on measured cell survival in different positions of a monochromatic high energetic carbon beam; (2) the microdosimetric kinetic model (MKM)[7,8] which considers microdosimetric distributions among small domains within the cell nucleus; and (iii) the local effect model (LEM)[3,9] exploiting the notion of local dose. The latter 2 models exist in several variants, reflecting improvements and adaptations to specific radiobiological situations. The RBE values are calculated at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, using the modified MKM (mMKM),[10,11] and this procedure was adapted by other facilities mainly in Asia. At most European facilities, the LEM is used in its original formulation, LEM I. Updated versions of the aforementioned models including the oxygen-effect-incorporated stochastic microdosimetric kinetic model,[12] the stochastic and double-stochastic MKM,[13,14] the LEM IV,[15,16] and the Mayo Clinic Florida microdosimetric kinetic model (MCF MKM),[17] take into account further biological effects and claim to be applicable for a broader range of radiation qualities and applications.

The models are applied in combination with certain conventions concerning derived quantities, reference radiation for RBE determination, and assumed model input parameters related to the radiosensitivity of the modeled tissues and the choice of the biological endpoints. Therefore, the approaches used in the clinics differ not only by the chosen model, but also by the way in which the models are used. In the present work, the combination of the biophysical model and the clinical context is referred to as a "dose prescription system," reflecting an integrated approach to determine the RBE in clinical settings. This expression was used in earlier work[18,19] where, however, it was used in a slightly different meaning not fully in line with the strict definition presented here. Because of the different concepts for biological effect–based treatment planning, reported RBE-weighted doses may substantially differ between the dose prescription systems, even if the underlying absorbed dose distributions are similar. This problem was addressed within a dedicated report of the International Commission on Radiation Units and Measurements.[20] However, the complex dependence of RBE predictions on the underlying model and associated conventions still gives rise to confusion, and there are no general strategies and tools for the mutual translation of described doses available, despite many works reporting such conversion, starting from 2 independent initiating publications.[21,22]

In 2024, a PTCOGsubcommittee on guidelines in carbon ion therapy was founded, and as one task group on "clinical applications of RBE," the authors of the present work would like to support further research and help to mature procedures involving multiple RBE models in a clinical context. The goal of this group is to provide information on the problem of intercomparability of dose prescription systems to the community and, in particular, to new facilities and to discuss aspects that play a role in translating doses from one system into another. These aspects will become relevant in particular if further models should be introduced in the future. Likewise, in the scope of making treatment protocols accessible and making joint clinical trials of institutions with different dose prescription systems possible, the problem of multiple coexisting RBE model approaches appears to be of importance. In that context, the task group members suggested statements concerning the properties of RBE and the conversion between dose prescription systems. These statements were then critically discussed and eventually rephrased iteratively to improve clarity. They were kept if consensus was found and dropped otherwise. The thereby derived consensus statements will be outlined in this publication.

This publication is organized as follows: first, we report on consensus statements on properties of RBE. Then, we describe how RBE approaches are used in clinical practice and for evaluation of clinical data. The details in this section reflect the complexity of dealing with multiple RBE approaches and highlight possible hurdles and pitfalls. Based on this, we then give consensus statements on dose translation between the models and associated uncertainties. A discussion section finally shows potential handling routines for the crucial aspects and outlooks for an exploitation of clinical results independent of the applied dose prescription system.

Consensus Statements on Properties of RBE

The statements on which agreement was found are presented below as bullet points in bold face, followed by a brief outline including further remarks. Although we focus here on general properties of RBE, in a section below we extend the list of consensus statements toward aspects of model conversion.

- **The RBE is defined as the ratio of doses for 2 radiation qualities that produce the same effect.**To define the RBE in that way, it must be possible to measure the dose levels leading to the desired effects. If photons are used as reference radiation, the energy spectrum can affect the RBE.
- **The RBE depends on biological parameters such as the selected endpoint and tissue type.** Many biological factors of the exposed tissue may determine the radiation sensitivity. If the impact on radiosensitivity differs for the 2 radiation qualities, these factors also act on the RBE.
- **The RBE depends on physical parameters such as charge (Z) and particle kinetic energy.** As these quantities change along the path of an ion, ions have nonuniform radiobiological properties along their path.
- **The RBE, with reference to photon radiation effects, usually follows a general systematics: RBE increases with decreasing dose per fraction, decreasing α/β ratio, decreasing Z at fixed LET, and increasing LET (up to high LET when it decreases again).** These statements hold for both radiobiological as well as clinical endpoints. In fractionated irradiations, the RBE of subsequent fractions may differ due to changes in biological properties over time. Protons are no exception, as they seem to follow this systematics as well. Notably, RBE may also depend on dose rate. However, dose rate effects are typically stronger for photons than for carbon ions: It is a basic property of ions that sublethal damage interaction is less prominent compared to high-LET particles, where the narrow regions of high energy concentration in ion tracks barely overlap, and the dose rate independent damage interaction within the tracks is pronounced instead.
- **The RBE depends on the oxygen concentrations in the cells or tissues and may depend on further biological factors such as vascularization, cell cycle status, or signaling.** The reason for this dependence is that the response to these factors may depend on the radiation quality of the beam (eg, LET and ion type). Concepts like the oxygen enhancement ratio may help to separately describe the impact of such factors, while in a clinical scenario or in in vivo experiments they might not be known.
- **The RBE for tumor control or normal tissue response may not be derivable directly from radiobiological findings.**Although in radiobiological assays such as clonogenic survival or preclinical experiments with quasi one-dimensional targets (eg rodent spinal cord) a point-like RBE is evaluated, typical clinical response refers to extended organs or tumors. Hence, the aforementioned experiments do not directly reflect RBE values in patients, and accounting for volume effects is needed.

Models of RBE and Their Use: Status of Biological Planning

The dose prescription systems considered in this paper differ in the concepts of the models, their input parameters, and the procedure to predict the RBE used to optimize for a prescribed dose. The models and their implementations are described in detail in the Supplementary Material E1, starting with a brief historical overview, a recall of the model details including their limitations, and the dose calculation

strategies within treatment planning. Formally, the dose prescription systems can be characterized by the models and their input parameters. The MBM includes the cell survival LQ parameters for human salivary gland (HSG) tumor cells for photon radiation α_x and β_x, LET-dependent LQ parameters for carbon ions α_c and β_c, and a scaling factor $F_{clin,\ MBM}$ used to normalize the RBE profile. The mMKM-based dose prescription systems use the LQ parameters in the limit of extremely-low LET α_0 and β_0, the nuclear radius r_n, the radius of microdosimetric domains r_d for HSG cells, and a factor $F_{clin,\ mMKM}$ used for RBE profile normalization. The LEM-based approaches employ the LQ-L parameters for photon radiation α_x and β_x, the dose threshold D_t above which the LQ-like dose response is proposed to continue linearly, and the nuclear radius r_n.

Concepts, quantities, and units

Although the LEM-based approaches determine the RBE in a single step, the procedures developed at NIRS/QST for the MBM/mMKM-based approaches employ a 2-step procedure. In the first step, an in vitro RBE is calculated. Subsequently, the in vitro RBE profile is normalized to a fixed value at a reference point (center of a 60 mm in water carbon SOBP with a maximum energy of 350 MeV/u) using the scaling factor F_{clin}. This is conceptually different from the LEM-based approaches, and therefore also the meaning of "RBE-weighted dose" is not fully clear from the definition[20] but needs a comment: as an overarching expression, "RBE-weighted dose" means a dose relevant for a defined biological or clinical endpoint. A more restricted meaning of "RBE-weighted dose"[20] is that it is the dose which, delivered by the reference radiation quality (typically photons), would result in the same effect as the absorbed dose of the test radiation quality (here carbon ions). The LEM-based approaches use this definition. The MBM/mMKM-based approaches deviate from this definition due to the additional scaling with F_{clin}. Both MBM/mMKM and LEM-based dose prescription systems produce an RBE-weighted dose—although conceptually different. To avoid confusion between the concepts and in line with established nomenclature in the literature, we accordingly distinguish between the so-called "clinical dose" used exclusively for the 2-step procedure including RBE normalization, and RBE-weighted dose used for systems without RBE normalization. We adhere to this wording throughout this work.

In the literature, for both clinical dose and LEM-based RBE-weighted doses, dose values are commonly given in Gy (RBE). Although the International Commission on Radiation Units and Measurements[20] recommends using only Gy for the unit of dose, the informal addition of RBE in parentheses indicates the context of considering the biologically relevant dose instead of the absorbed dose. As this is pragmatic and avoids confusion between absorbed and prescribed doses, we keep the conventional notation using Gy (RBE).

Different models result in different predictions

To demonstrate the impact of model selection, we first consider 1 model for optimization to a specified RBE-weighted or clinical dose, and then use the corresponding absorbed dose to calculate—using another model—its RBE-weighted or clinical dose profile. The value of such "forward calculations" is that one can compare the RBE-weighted or clinical dose profiles predicted with different models for the same absorbed dose profile. In addition to the selection of models, input parameters have to be chosen. If models are conceptually similar, matching parameters can be used. For clinical implementations, standard settings of parameters have been established, which usually do not match from a radiobiological perspective.

Figure 1 shows examples of forward calculations. To consider the impact of the model selection alone, in Figure 1a, we compare a LEM IV optimization to a 2-Gy RBE-weighted dose with predictions of the mMKM using the same linear-quadratic parameters (photons as a reference radiation, no scaling factor). The parameters of both models were used before in the study by Saager et al[23] to simulate the RBE for late effects after rat spinal cord exposure; that is, they were used to simulate the same endpoint and the same data set. In particular, the LQ parameters have been chosen to be identical for both models. The absolute value of the LQ parameters is considerably lower (about a factor ~50) than would be reasonable for clonogenic cell survival studies. The low absolute values are useful in the context of in vivo or clinical endpoints relating to normal tissue, as they in particular suppress the importance of overkill or saturation correction at high LET, which is rather relevant for cellular endpoints. Although overkill correction within the LEM formalism and saturation correction in the mMKM are technically differently implemented, they both lead to a decrease of RBE with LET at very high LET.

Investigating this example in Figure 1a, two important facts become evident: first, a difference in the model prediction exists, as the MKM predicts a substantially higher RBE-weighted dose throughout the SOBP. Second, here this deviation varies between 10% and 20% and is therefore not uniform, but depends on depth and further parameters, as highlighted in the studies by Steinsträter et al[21] and Fossati et al.[22] This is ultimately explained by the RBE-LET gradient of monochromatic beams differing between the models: for moderate doses of carbon ions, LEM I has a shallow increase in RBE with LET (and therefore depth), mMKM is intermediate, and LEM IV shows a stronger gradient.[21,22,24]

When considering a clinical scenario as in Figure 1b, where the mMKM-based dose prescription system as used at NIRS is compared with the LEM I-based dose prescription system, several aspects change. First, the field configuration may be more complex, like 2 opposing fields in the example of prostate irradiation. Second, the used model parameters are different and usually correspond to conventionally chosen values with α/β = 2 Gy for LEM I and HSG

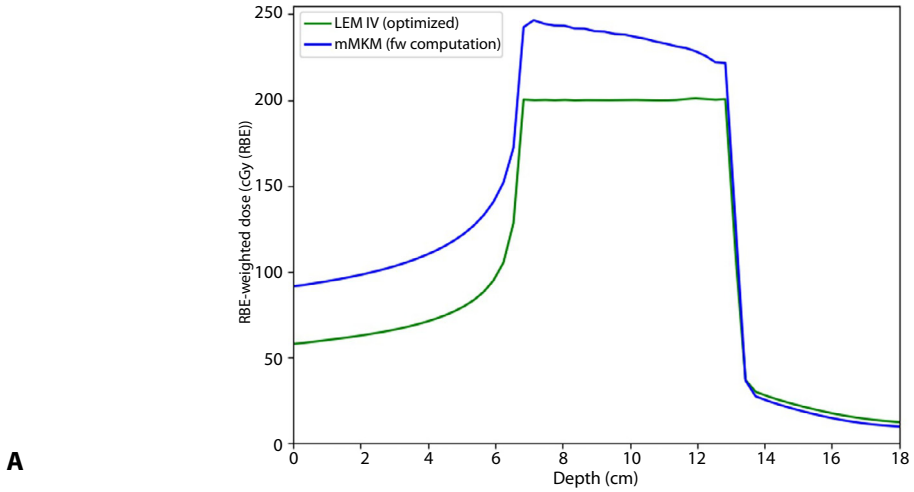


Fig. 1. Examples of different model predictions of RBE-weighted/clinical dose profiles along the beam axis. (a) Comparison of LEM IV (optimized) and mMKM (forward calculation for the same absorbed dose profile) for α/β = 2 Gy (LEM IV parameters: α = 0.003 Gy^{-1}, β = 0.0015 Gy^{-2}, D_t = 22 Gy, r_n = 5 μm; mMKM parameters: α = 0.003 Gy^{-1}, β = 0.0015 Gy^{-2}, r_d = 0.3 μm, r_n = 3.6 μm). (b) Comparison of an optimized treatment plan of a prostate cancer patient (left: 2D representation, right: dose and dose-averaged LET (LET_d) profiles along the beam path through the isocenter) using LEM I and mMKM with the standard parameters of the corresponding dose prescription systems. The plans were optimized to a mMKM-based clinical dose of 57.6 Gy (RBE) and an LEM I-based RBE-weighted dose of 67.2 Gy (RBE) given in 16 fractions. *Abbreviations:* LET = linear energy transfer; LEM = local effect model; mMKM = modified microdosimetric kinetic model; RBE = relative biological effectiveness.

cell parameters (α_0 = 0.172 Gy^{-1} derived from high-LET experiments and β = 0.0615 Gy^{-2})[11,25] for mMKM. Third, for the latter, the scaling factor F_{clin} between the in vitro RBE-weighted dose and clinical dose is applied. In consequence, we here consider not anymore, a comparison of the models alone, but rather of the entire dose prescription system. Moreover, as a biologically oriented planning has to result conventionally in a flat and conformal target dose profile, no identical physical dose profile can be achieved. Instead, one has to determine a best matching physical dose profile. This demonstrates some of the complications and sources of confusion, underlining the need for unambiguous conventions in language and units. In the example, the total dose is shown, and LEM I predicts a higher RBE-weighted dose than the clinical dose predicted by the mMKM system.

For ultimately exploiting RBE modeling in therapy planning, there are many commercial and open-source treatment planning systems available, which can create carbon ion plans using one or several models by either optimizing doses or, for comparisons, performing forward calculations or determining matching absorbed doses. In clinical practice, typically one dose prescription system is used as the

"standard of the institution" to optimize a given RBE-weighted or clinical dose in the target volume, whereas dose constraints for the normal tissue may be considered jointly for multiple models.

Current clinical application of RBE models

In current clinical practice, the LEM I-based dose prescription system[3,9] is predominantly used in Europe and China, and either the MBM-based system[4] or the related mMKM-based system[26] is employed in centers in Japan, China, Taiwan, and Korea. Both systems have proven clinical utility, each with distinct advantages and limitations. Significant differences exist in the dose distributions of treatment plans optimized under 2 models, and neither fully accounts for carbon ion radiation therapy's (CIRT) biological complexity, as they compute equivalent doses with respect to a defined reference radiation for a single endpoint, ignoring tumor and surrounding tissue heterogeneity. As mentioned before, the models are typically used with a standard set of input parameters and conventions. In some cases, however, these are relaxed, and different strategies are attempted. Table 1 provides an overview of which models and associated application conventions are used in the facilities currently operating (December 2025).

Translation between dose prescription systems

For the same patient plan, different dose prescription systems result in different dose constraints concerning irradiated organs at risk. A standardized dose translation is essential for reliable cross-center comparisons, for a unified protocol adoption, and for the optimal planning of multinational trials. For that purpose, the empirical RBE-weighted dose conversion data derived from model comparisons specific to site and histology are used as reported by several investigators.[21,22,27,28] The key procedure is to find an optimized plan with a model whose physical dose profile matches the corresponding plan optimized by another model,[21,22] as outlined in Figure 2. In translating mMKM to LEM I dose prescriptions, conversion factors of 1.04 to 1.15 were found for the considered cases. For example, for head and neck nonsquamous cell carcinomas, a factor of 1.13 is used to convert the prescribed clinical dose from 3.6-3.8 Gy (RBE) to a LEM I-based RBE-weighted dose of 4.1-4.3 Gy (RBE) per fraction, whereas a factor of 1.09 is applied to bone and soft tissue sarcoma prescription doses, converting it from 4.4 Gy (RBE) to 4.8 Gy (RBE) per fraction. These values are used to set clinical goals when evaluating plans. These conversions are dose- and fractionation-specific, adapted for each treatment site and histology as summarized in Table 2, and should be applied with clinical and biological context. Thus, each site and protocol requires individual validation before clinical use. Notably, in all cases in Table 2 the LEM I RBE-weighted doses appear to be somewhat higher than the corresponding MKM clinical doses. However, this systematics is expected to revert for strongly hypofractionated regimens. For example, clinical studies to investigate dose escalation for the treatment of early-stage non-small cell lung cancer at QST/NIRS resulted in a clinical dose of 48 to 50 Gy (RBE) for single-fraction treatment,[29] which translates into 24 to 25 Gy (RBE) using the LEM I-based RBE-weighted dose prescription system with standard parameters (see Fig. 2a). After translation, the absorbed dose profiles are at the same level, but not coincident, again due to the different RBE-LET gradients of the different models. Note that even after matching the absorbed dose profiles, this means that model choice also determines to some extent the LET_d.

Trends toward multimodel application

As all models have limitations, a strategy established within the last few years at some centers is to take multiple model predictions into account: typically, the plan is generated with 1 model and recalculated with another one. Then, the requested model-specific constraints have to be fulfilled by both plans (original and recalculated), imposing a conservative way of acknowledging that we do not know the most suitable model. The strategies are indicated in Table 1 and further outlined below.

The LEM I tends to overestimate the RBE in proximal and mid-target regions and underestimates it, after a conversion from NIRS protocols, near the distal edge of the beam, where LET is highest (>50 keV/μm). The mMKM, alternatively, predicts a more balanced biological effectiveness in these regions, while still high-LET patterns at the field margins can result in elevated effectiveness (c.f. next section). This systematics is a direct consequence of the aforementioned different RBE gradients with respect to depth and LET. As a result, clinical CIRT treatment plans within 3.6 to 4.8 Gy (RBE) per fraction that appear conformal and safe under LEM I may reveal unacceptable hotspots under mMKM at the distal beam edge, as demonstrated in Figure 3. Alternatively, the recalculation of LEM I optimized plans in mMKM may show cold spots where the dose is mostly delivered by the plateau. This can potentially result in underdosage in the center of large tumors, risking potential relapses.[22,28] Due to the dose dependence of translation factors (c.f. Fig. 2), these findings may be different in strongly hypofractionated regimens. Mein et al[30] indicate that the mMKM provides better overall predictions of RBE for carbon ions across varying LET_d regions, while both LEM I and LEM IV achieved optimal accuracy in high-LET_d regions. Although LEM I overestimates the RBE in the low/mid LET_d range, LEM IV largely fixed this systematic deviation. Nevertheless, it underestimates the RBE in the entrance channel regions,[31] although to a much less extent than the overestimation of LEM I, in line with the model limitations considered above. It predicts a pronounced effectivity of high-LET_d distal field patterns, which may be of clinical relevance when critical structures lie adjacent to or

Table 1 Overview of current application of RBE models in carbon ion therapy facilities at operation.

	Main model (reference), parameters	Additional models (reference), parameters	Strategy with additional models
QST/NIRS, Chiba, JP	mMKM (C), standard		
HIT, Heidelberg, DE	LEM I (X), standard	LEM I (X), α_x = 0.2 Gy^{1} or 0.25 Gy^{1} or 0.5 Gy^{1} β_x = 0.05 Gy^{-2} D_t = 30 Gy r_n = 5 μm mMKMx (X), α_0 = 0.05 Gy^{1} β = 0.025 Gy^{-2} r_d = 0.3 μm r_n = 3.6 μm	Strategy 1: - Target: dose calculation using the additional model. - Target: dose calculation using the main model for coverage verification. - OAR: dose constraints with the main model.
SPHIC, Shanghai, CN	LEM I (X), standard	mMKM (C), standard, except F_{clin} = 2.40 (refitted)	Strategy 1: - Target: dose calculation using the main model but adapted to match the dose prescription using the additional model. - OAR: dose constraints with the main model.
MedAustron, Wiener Neustadt, AT	LEM I (X), standard	mMKM (C), standard	Strategy 1: - Target: dose prescription and optimization using main model, dose recalculation using alternative model and dose evaluation using both. - OAR: dose constraints fed to optimizer as per main model and evaluation in both (main and recalculated alternative). If the target coverage or doses to OARs are unsatisfactory as per additional model, the plan is iteratively modified until it is satisfactory in both models.
CNAO, Pavia, IT	LEM I (X), standard	mMKM (C), standard	Strategy 1: - Target: dose calculation using the main model with adapted prescription to match the dose prescription of the additional model. - OAR: dose constraint according to the main model or adapted from the additional model. Strategy 2: - Dose calculation with the additional model, iteratively adapted to satisfy target coverage and OAR constraints according to both models.
i-Rock Kanagawa Cancer Center, Yokohama, JP	mMKM as QST		
East Japan HIC, Yamagata University Hospital, Yamagata, JP	mMKM as QST		
Yonsei Cancer Center, Seoul, KR	mMKM as QST		
Osaka Heavy Ion Therapy Center, Osaka, JP	MBM (X, scanned)		
MIT Marburg, DE	LEM I		

(*Continued*)

Table 1 (*Continued*)

	Main model (reference), parameters	Additional models (reference), parameters	Strategy with additional models
Wuwei Heavy Ion Center, Wuwei, Gansu, CN	MBM (X, passive and scanned)		
Lanzhou Heavy Ion Hospital Campus of Wuwei Heavy Ion Center, Lanzhou, Gansu, CN	MBM (X, passive and scanned)		
Zheijang Cancer Hospital Ion Medical Center, Hangzhou, CN	MBM (X, scanned)		
HIBMC, Hyogo, JP	MBM (X, passive)		
GHMC, Gunma, JP	MBM (X, passive)		
SAGA-HIMAT, Tosu, JP	MBM (X, passive) mMKM as QST for scanning		
Taiwan Veterans General Hospital, Taipei, TW	mMKM as QST		

The table includes the used models as well as additional conventions. Although the "Main model" is the standard approach used for planning in the institutions, additional models may be used for comparison or for specific cases, and the associated strategy is indicated in the table. The RBE evaluation is carried out with respect to photon (X) or carbon ion (C) reference radiation. Model parameters are given explicitly, or as "standard," which is $\{\alpha_x = 0.1\ Gy^{1}, \beta_x = 0.05\ Gy^{-2}, D_t = 30\ Gy, r_n = 5\ \mu m\}$ for the LEM I and $\{\alpha_r = 0.764\ Gy^{1}, \beta_r = 0.0615\ Gy^{-2}, \alpha_0 = 0.172\ Gy^{1}, \beta = 0.0615\ Gy^{-2}, r_d = 0.32\ \mu m, r_n = 3.9\ \mu m, F_{clin} = 2.41\}$ for the mMKM-based dose prescription system. The mMKM using x-rays as reference is termed mMKMx here and in the main text to clearly distinguish it from the QST/NIRS approach. The MBM-based systems use photon parameters $\{\alpha_x = 0.3312\ Gy^{-1}, \beta_x = 0.0593\ Gy^{-2}\}$ for an optimization to 10% survival of HSG cells. However, its implementation may vary between institutions, as the high-LET dose-response reference data depend on the available beam energies and beam delivery mode, as indicated in the table, that is, passive as originally implemented at QST, or scanned.

Abbreviations: AT = Austria; CN = China; CNAO = Centro Nazionale di Adroterapia Oncologica; DE= Germany; GHMC = Gunma University Heavy Ion Medical Center; HIC = Heavy Ion Center; HIT = Heidelberger Ionenstrahl-Therapiezentrum; HIBMC = Hyogo Ion Beam Medical Center; IT = Italy; JP = Japan; KR = Korea; LEM = local effect model; mMKM = modified microdosimetric kinetic model; MBM = Mixed Beam Model; NIRS = National Institute of Radiological Sciences; OAR = organ-at-risk; QST = National Institutes for Quantum Science and Technolgy; RBE = relative biological effectiveness; SAGA-HIMAT = Saga Heavy Ion Medical Accelerator in Tosu; SPHIC = Shanghai Proton and Heavy Ion Center; TW = Taiwan.

within these regions (c.f. section on LET_d below). In the following, we recapitulate how multiple models are jointly exploited in treatment planning at different institutions.

Med Austron: At MedAustron, CIRT treatment plans are routinely optimized under the LEM I, and hypofractionated CIRT plans with dose per fraction between 3.6 Gy (RBE) and 4.8 Gy (RBE) are recalculated and assessed using the mMKM. If the mMKM recalculation reveals a critical organ-at-risk (OARs) overdosage or either unacceptable hotspots or insufficient target dose coverage for targets, the plan is re-optimized in LEM I, adjusting beam angles, spot distribution, or field weighting as needed. Where mMKM is not the primary model used for optimization in TPS, iterative adjustments using LEM I can be the most practical workaround. The single-field plans are more likely to produce mMKM hotspots in distal high-LET regions, which may overlap with healthy normal organs, for example, oral and pharyngeal mucosa in case of lateralized tumors of head and neck. To mitigate this, multifield or opposed-field strategies are preferred, and avoidance of beam stopping in or near critical structures is prioritized by distal spot blocking by "distal patching" or field-specific LET_d control, which allows for better LET_d distribution and dose smoothing.[32,33] Predefined dose constraints based on one model (eg, the MBM/mMKM) are translated into the alternative model (eg, LEM I) and are used as a reference for plan acceptability. For high-dose CTVs, fulfilling mMKM clinical doses $D_{95\%} > 64$ Gy (RBE) for chordoma, $D_{95\%} > 67$ Gy (RBE) for bone and soft tissue sarcomas, and $D_{95\%} > 60.8$ Gy (RBE) for head and neck nonsquamous cell cancers (except sarcomas) and $D_{99.9\%} > 57.6$ Gy (RBE) in HD-CTV is necessary.

CNAO (Centro Nazionale di Adroterapia Oncologica): After 11 years of LEM I-based clinical practice, CNAO currently applies a dual-model optimization strategy for specific treatment protocols based on hypofractionated carbon ion treatments (eg, with a dose per fraction higher than 3 Gy [RBE]), with a slightly different approach compared to MedAustron. For plan approval, compliance with clinical goals such as target dose coverage, conformity, and homogeneity in both dose prescription systems is required, but the optimization starts from mMKM. The plan is then recalculated with LEM I and iteratively reoptimized in mMKM until an optimal solution is found and the clinical goals are fulfilled in both models. Despite applying the required conversion factors, for a uniform RBE-weighted dose distribution, the mMKM models a steeper RBE variation as a function of depth along the beam path than LEM I. Thus,

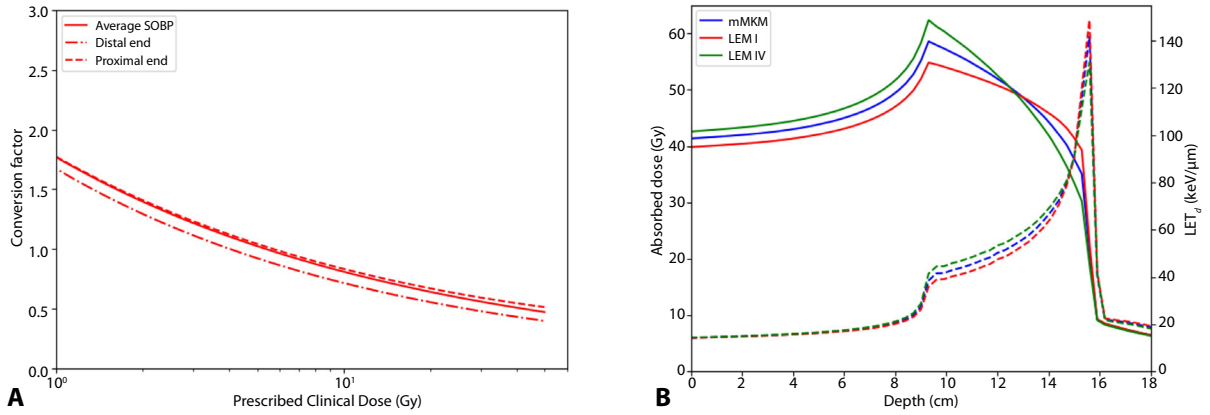


Fig. 2. (a) Conversion factor (LEM I RBE-weighted dose divided by mMKM-based clinical dose) as a function of the mMKM-based clinical dose (taken from Steinsträter et al[21]). Using the standard parameters of the models as used in the clinics, the conversion factors depend on the specific plan features and have been evaluated here for an artificial box-shaped target geometry with SOBP from 160 to 220 mm depth. (b) Absorbed dose and LET_d profiles for optimizations with LEM I (standard parameters, target dose 2 Gy [RBE]), mMKM (standard parameters, target dose 1.25 Gy [RBE]), and LEM IV (α = 0.1 Gy^{-1}, β = 0.05 Gy^{-2}, D_t = 8 Gy, r_n = 5 μm, target dose 1.4 Gy [RBE]) so that absorbed dose profiles match by intersecting in the mid SOBP. The different RBE versus depth gradients of the models become evident. *Abbreviations:* LET_d = dose-averaged linear energy transfer; LEM = local effect model; mMKM = modified microdosimetric kinetic model; RBE = relative biological effectiveness; SOBP = spread-out Bragg peak.

mMKM requests a steeper absorbed dose gradient in the spread-out Bragg peak. A consequence of this behavior is that, when mMKM is applied to an LEM I optimized absorbed dose, inhomogeneities (hot and cold spots) are amplified. Therefore, it was decided to apply mMKM as a principal model for optimization and combine it with the prescription dose conversion, as given in Table 2, for plan approval under the hypothesis that this strategy could facilitate the simultaneous achievement of target RBE-weighted dose homogeneity in both modeling systems.

HIT (Heidelberger Ionenstrahl-Therapiezentrum): Similarly, after 2 decades of using LEM I in Germany at HIT after the GSI pilot trial, new optimization strategies have been investigated using mMKM instead of LEM I. Unlike MedAustron or CNAO, the mMKM version used as a radiobiological model at HIT does not follow exactly the Japanese approach. In fact, at HIT, the mMKM uses photon radiation (mMKMx) as a reference instead of carbon ions, without using the scaling factor F_{clin} that would normalize the RBE profile. One of the main reasons to maintain a photon

Table 2 Clinical doses according to the mMKM dose prescription system and translated LEM I dose prescriptions used in the clinics at MedAustron and CNAO.

Site and histology	Prescription doses	
	Clinical dose using mMKM (NIRS-QST) in Gy (RBE)	RBE-weighted dose using LEM I (MedAustron/CNAO) in Gy (RBE)
Mucosal melanoma	57.6-64	65.6-68.8
Salivary glands malignancies (no elective node irradiation)	57.6-64	65.6-68.8
Bone and soft tissue sarcoma, except skull base chordoma	70.4	70.4-76.8
Skull base chordoma	57.6-60.8	67.2-70.4
Chordoma (non-skull base)	67.2	70.4-73.6
Prostate cancer	51.6 (12 fractions)	57.6 (12 fractions) or 66.4 (16 fractions)
Re-irradiation of recurrent head and neck cancers	48-70.4	65.6-68.8 (16 fr) (MedAustron) 60.0-68.8 (15-16 fr) (CNAO)

All prescription doses are for hypofractionated CIRT schedules of 16 fractions, except for prostate cancers and re-irradiation of recurrent head and neck cancers as indicated explicitly. Notably, the listed conversion doses are used within a clearly defined clinical setting (including field configurations and optimization strategies of the treatment planning system determining the LET distribution), and could be different in other situations.

Abbreviations: CIRT = carbon ion radiation therapy; CNAO = Centro Nazionale di Adroterapia Oncologica; LEM = local effect model; mMKM = modified microdosimetric kinetic model; NIRS = National Institute of Radiological Sciences; QST = National Institutes for Quantum Science and Technolgy; RBE = relative biological effectiveness.

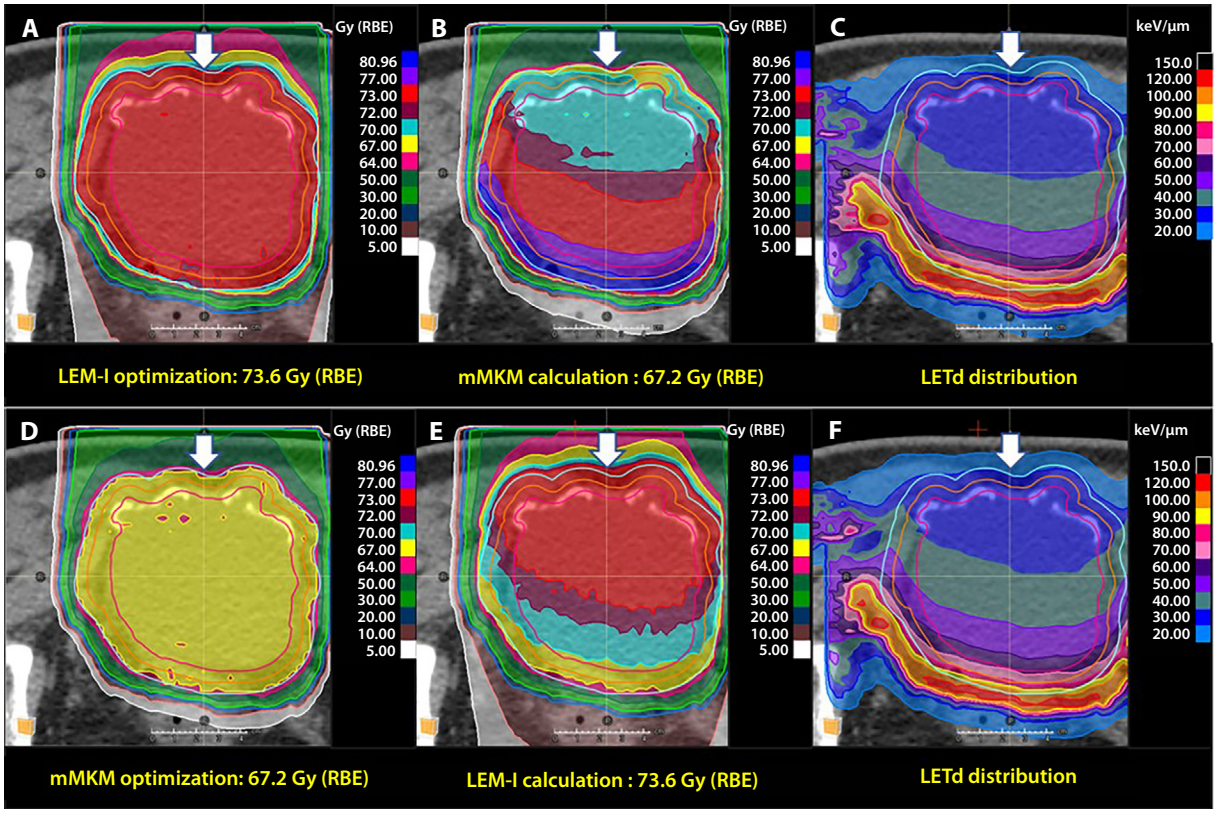


Fig. 3. Single anterior field RBE-weighted dose distribution of a CIRT plan (a) optimized with the LEM I to a dose of 73.6 Gy in 16 fractions (RBE), (b) forward calculation with mMKM, for which the prescribed clinical target dose would be 67.2 Gy (RBE), and (c) the corresponding LET_d distribution in a representative case of sacral chordoma. Conversely, the RBE-weighted dose distribution in the same case (d) optimized with the mMKM to a dose of 67.2 Gy (RBE) in 16 fractions, (e) forward calculation using LEM I, for which the prescribed target dose would be 73.6 Gy (RBE), and the corresponding (f) LET_d distribution. *Abbreviations:* CIRT = carbon ion radiation therapy; LET_d = dose-averaged linear energy transfer; LEM = local effect model; mMKM = modified microdosimetric kinetic model; RBE = relative biological effectiveness.

reference model, as with LEM I, is the possibility to use carbon ions as a sequential boost to a photon or proton plan. Initial investigations for carbon ions with different cell lines were performed comparing LEM I and mMKMx in terms of dose and LET levels,[30] as well as in parallel for helium ions.[34] All helium ion treatments at HIT have been performed using mMKMx, whereas for carbon ions, a transition toward mMKMx is ongoing at HIT for indications such as sacral chordomas and extremity soft tissue sarcomas. The dose prescription and fractionation schedule using mMKMx were kept the same as originally designed at HIT for LEM I. The carbon ion optimization process with mMKMx is an iterative procedure, where the goal is to achieve target coverage in both mMKMx and LEM I while respecting the OAR constraints using LEM I. The plan is first optimized using mMKMx, then recalculated with LEM I to verify OAR constraints, and further adapted using mMKMx to optimize those OARs not meeting constraints (with or without the use of specific artificial help structures in the plan by which the plan can be forced to respect the dose constraints). Ultimately, both the mMKMx plan and its LEM I recalculation are approved for plan release. The transition toward exclusive mMKMx-based calculations for the aforementioned tumor entities will require a better understanding of OAR constraints using mMKMx to avoid unexpected adverse events for patients that were not seen using LEM I.

In summary, in the multimodel approach at CNAO and MedAustron, clinicians carefully assess the final dose distributions using both LEM I and mMKM in parallel, focusing on target coverage and OARs sparing. Some of the translated dose constraints in LEM I for OARs (brainstem, optic nerves, chiasm, and rectum) were validated against clinical outcomes and aligned with Japanese hypofractionated schedules.[35-38] For all centers (including HIT), re-evaluation imaging (typically performed mid-treatment) is also part of the protocol for specific cases, to verify that anatomical changes have not shifted OARs into high-dose, high-LET_d zones. This step reinforces planning reliability and supports adaptive decision making where necessary.

Evaluation and optimization of LET_d

As mentioned previously, LEM I tends to overestimate RBE in normal or moderately hypofractionated regimens, while it underestimates RBE where LET is highest. These 2 effects compensate and lead to smaller differences between the 2 models in high-LET_d regions.[24] In theory, CIRT treatment plans (for both LEM I and mMKM models) that achieve a high RBE-weighted dose but fail to deliver sufficiently high LET across a substantial portion of the tumor may contribute to suboptimal tumor control. This possibility is supported by early clinical findings in pancreatic tumors, sacral chordomas, unresectable chondrosarcomas, locally advanced non-small cell lung cancers, and nonsquamous head and neck cancers.[28,39-41] This highlights the emergent need to incorporate LET penalties in the optimization. Most commonly by use of LET_d in the CIRT planning workflow, in addition to multimodel optimization at least in challenging cases. Alternatively, effects of LET_d on OARs are complex. Although an increased LET_d alone in normal tissues might not significantly increase toxicity, delivering both high LET_d and a high dose to OARs simultaneously could be potentially critical. The recent reports[42-44] demonstrated that severe late toxicities, such as lumbosacral neuropathy, sacral insufficiency fractures, or oro-antral fistula, were observed in cases where OARs were exposed to a high RBE-weighted dose and concurrently high LET_d in a significant volume. These findings are a direct consequence of the distinct RBE gradients of the models in use and underscore the importance of prioritizing biological safety, especially in high-LET_d regions, and suggest incorporating LET_d evaluation along with multi-RBE model-based dose evaluation in clinical workflow.

The use of LET_d-based objective functions in plan optimization can concentrate high-LET_d patterns at the center of the target volume, enhancing targeting of radioresistant and hypoxic regions in a heterogeneous tumor and simultaneously reducing LET_d on adjacent healthy normal tissue. This might result in improved tumor control and minimized toxicities. The other consequence of incorporating LET_d optimization in the planning workflow is that it may decrease the dose difference between the mMKM and LEM I optimized plans, making carbon ion plans more robust against RBE and LET inhomogeneities. However, it should be kept in mind that in a mixed carbon ion field, different plans with different absorbed or RBE-weighted dose distributions and beam designs may result in similar LET_d distributions. The need to consider LET_d to avoid tissue effects at the planning target volume (PTV) margins demonstrates that its action is not fully reflected by the employed RBE models. Moreover, LET_d is not linearly related to RBE for ions and thus not a direct predictor of effectiveness. A high-LET_d distribution alone outside the PTV in the presence of a low absorbed or RBE-weighted dose is unlikely to cause severe normal tissue toxicity. As observed in the evaluation of rectal toxicities and pelvic insufficiency fractures, LET_d alone fails to predict such toxicities.[45,46] Instead, when a high-LET_d pattern outside the PTV with a moderate to high dose is evaluated simultaneously in a significant volume of the organ, it can predict late severe toxicities.[42-44] Including LET_d optimization in treatment planning is hence a pragmatic approach, which, however, requires that clinical priorities are well specified, as a strict combined optimization of robust dose conformity, uniform dose distribution, and improved intratumoral LET_d distribution is not achievable.[47] Although the explicit consideration of LET_d has a clear rationale but also brings along critical issues and is thus being debated, in clinical routine the LET_d distribution is a conventionally considered parameter for treatment plan assessment. In the following, the strategies of including LET_d optimization in treatment planning at different centers are outlined.

NIRS-QST (National Institute of Radiological Sciences - National Institutes for Quantum Science and Technolgy): At NIRS, LET painting in CIRT for nonsquamous head and neck cancer demonstrated significant improvement in the minimum LET_d within tumors (45-59 keV/μm) while maintaining dose coverage.[48] Also, early encouraging tumor response without significantly elevated toxicity was reported.[49]

MedAustron: At MedAustron, to optimize the LET_d distribution in CIRT plans for large pelvic sarcomas and chordomas, techniques such as distal patching or field-specific LET_d control are employed. These methods work by intentionally blocking distal beam spots, thereby shifting the Bragg peaks to the central region of the target. Thereby, the concentration of high-LET_d regions in the tumor center is enhanced while simultaneously LET_d in surrounding OARs is reduced.[32,33] Such a strategy not only improves dose and LET_d distributions, but has shown early encouraging tumor responses in a selected number of large pelvic chordomas and sarcomas at minimal acute toxicity, demonstrating the safety and potential efficacy of LET_d optimization in CIRT (unpublished data).

CNAO: Recently, LET_d optimization was introduced in clinical practice for carbon ion at CNAO, and it is currently applied for sarcomas in the pelvic region (unpublished). Previously, results of a retrospective analysis outlining the suboptimal LET_d distribution were published, potentially entailing suboptimal clinical outcomes.[28] Before clinical implementation, a feasibility study was performed, showing results in agreement with the MedAustron group.[33,50] The maximization of LET_d at the center of the target volume brought along a decrease in the LET_d gradient across the target field and, as a consequence, a decrease in the dose difference between the mMKM and LEM I optimized plans. Indeed, to increase high LET_d in the target, particularly in the gross tumor volume, which often lies at the center of a large CTV, the optimizer chose solutions where Bragg peaks are mainly distributed at the target center, rather than at the edges. This implies that a smaller portion of the target is irradiated with the plateau of the beams. However, such redistribution of Bragg peaks might result in less robust

plans.[50] The safety, robustness, and efficacy of a combined multi-RBE and LET_d-based optimization are currently under evaluation for sacral chordoma patients.

HIT

At HIT, it was also found that optimizing LET_d in the TPS to values around 55 to 65 keV/μm helps to provide similar RBE predictions for LEM I and mMKMx,[51,52] and this approach is now applied for most large targets (outside the head region) when optimizing with LEM I to reach this value range whenever possible or ≥45 to 50 keV/μm, depending the beam arrangements and target size.

To overcome inherent LET_d constraints of carbon ions, multi-ion radiation therapy is being explored in recent years at various centers, which uses unique physical and biological advantages of multiple ions, such as high-LET oxygen and neon ions and low LET Helium, along with carbon ions. Helium ions offer precise treatment by virtue of a decreased lateral scatter effect compared to protons and a smaller fragmentation tail compared to carbon ions, resulting in a smaller distal penumbra. In fact, the peak-to-plateau ratio of the RBE-weighted dose appears to be not inferior to that of carbon ions in typical cases.[53] Additionally, the lower LET of helium ions compared with carbon ions and smaller penumbra compared with protons can potentially offer an increased OAR sparing effect. To effectively target heterogeneous tumors, helium ions can be used near the periphery of the tumor next to healthy normal tissues, while simultaneously delivering higher-LET radiation, such as oxygen, neon, and carbon, to radioresistant, hypoxic regions within the tumor. A multi-ion combination can optimize LET distributions, enhance tumor control, particularly for radioresistant and hypoxic cancers, and minimize normal tissue toxicity.[54,55] A recent in silico study confirmed an improvement in the minimum LET_d values in the PTV using a combination of oxygen, carbon, and neon beams for large (>500 mL) bone and soft tissue sarcomas while simultaneously respecting target dose coverage and dose constraints for OARs.[56] Concerning RBE predictions, multi-ion irradiation requires models that are capable of predicting RBE values for multiple ions. An enhanced application of such treatment strategy thus will have to go along with comprehensive model evaluation.

Consensus Statements on Conversion Between Dose Prescription Systems and Associated Uncertainties

As outlined above, comparing dose levels between different dose prescription systems or translating treatment plans is complex, given the unbalanced concepts and conventions in applied models, model parameters, and clinical implementation. Although there are multiple strategies on how dose translation may be attempted, there are also numerous dependencies to be taken into account, and typical pitfalls to be avoided. In this context, we agreed on the following consensus statements, which may shed some light on the complexity.

- RBE models predict the RBE as a function of particle type, LET spectrum, dose, the biological parameters α/β, the absolute value α, and scaling factor F_{clin}. These quantities consequently have to be accounted for in model translation. A mapping of one dose prescription system to the other can be constructed to establish corresponding prescribed dose values between the 2 systems leading to the same outcome. Notably, in the mMKM-based system, the model-predicted RBE value at a reference point within the SOBP is fixed, while the model-predicted RBE gradient predicts variable RBE values for all other depths. When converting doses between prescription systems, this has to be considered in addition to the above-listed factors impacting RBE.
- The model-predicted RBE depends mainly on (1) the intrinsic model features; (2) the model parameter values; (3) the way the model is implemented in the clinic; and (iv) the physical beam model. Models may be built on microdosimetric scoring of track structure or on amorphous track structure. They may reflect mechanistic processes or are rather empirical to describe the phenomenology of RBE, and may accordingly vary in level of detail. The input parameters which the models use may be related to cells or tissues and different endpoints, for example, early effects, late effects or tumor response. For clinical implementations, several conventions may apply, like a selection of α/β values, an adjustment of the α term (LEM) or a scaling of doses to a reported dose (clinical dose as used in the MBM-based and mMKM-based dose prescription systems). Additionally, for the same dose prescription system, the RBE-weighted or clinical dose also depends to some extent on differences in the beam line characteristics ("physical base data") and dose computation algorithms.
- To convert prescription doses for given clinical results between centers using either different models, model parameters, or ways of clinical implementation, suitable methods are required. This may involve the derivation of dose conversion factors or isoeffective dose/volume constraints. They will depend on irradiation conditions such as single and multiple fields, LET distributions, dose levels, target depths, modulation widths, dose modulations (intensity modulated particle therapy), and pairs of models.
- Model comparison in treatment plans may be conducted in different ways: comparing RBE-weighted/clinical doses for the same absorbed dose distribution, or comparing absorbed dose distributions for equal optimization of RBE-weighted/clinical doses. There are numerous measures to quantify model differences, for example, median or average dose, equivalent uniform

dose, gradients, or dosimetric measures derived from the dose volume histogram.

- There is no unique way of converting prescribed doses of 2 dose prescription systems into each other. For optimized RBE-weighted (or clinical) dose levels, corresponding absorbed dose profiles of any 2 models never coincide in shape. Hence, criteria for best matchings have to be defined. These criteria will also determine how uncertainties propagate into the uncertainty of the converted dose.
- The choice of model parameters that are fixed by initial model optimization can impact dose conversion between models. Some model parameters may be fixed by convention or inspired by measurements. The measured parameters used may differ considerably in their uncertainty. Occasionally, these parameters should be kept fixed to limit the complexity of the analysis. Notably, the decision on which parameters are fixed may depend on multiple factors, such as the request for a minimum number of degrees of freedom in clinical usage, theoretic arguments, or the availability of measured values.
- Physical base data can impact dose conversion between models, but usually less severely than intrinsic model parameters. Most physical data need to be accurately known (eg, dose-depth distributions, lateral profiles, etc.) for reliable treatment planning. The computation of 3D RBE distributions in realistic scenarios may vary depending on whether the calculations are based on monochromatic, trichromatic (NIRS/QST approach), or polychromatic (Monte Carlo transported) pencil beams. In contrast to RBE model parameters, spectra of the mixed radiation field can be measured. For model comparisons, standardization of spectra may be useful. Although these aspects play a second-order role within the field (next to model choice and model parameter choice), they matter in out-of-field regions.
- Model translation procedures may depend on the choice of reference radiation(s). Currently, there are 2 philosophies (independent of model): the clinical dose prescription system considering carbon ions as reference radiation and the RBE-weighted dose prescription system considering photons as reference radiation.
- Isoeffective dose/volume constraints and objectives are affected by the introduction of LET_d-based functions in plan optimization. How LET_d is calculated and used alongside the calculation of dose should be considered, for example, increasing LET_d at the target center may reduce the difference between LEM and MKM-based calculations.
- The different steepnesses of predicted RBE versus depth profiles affect the adaptability of the RBE-weighted dose between models. As an example, when prescribing a uniform dose to the target, if the plan is optimized with MKM, the same absorbed dose generates an almost uniform LEM-based distribution, whose level (eg, median target dose) deviates by the conversion factor. If optimizing for the same prescribed dose with both models, the inhomogeneous absorbed dose profiles will differ by a different factor.

Discussion

Current situation

The elevated RBE is, besides the excellent scattering properties, the main advantage of carbon ion therapy compared with proton therapy. However, a sound understanding of the properties of RBE, its prediction with biophysical models, and its implementation in the clinics is a matter of persistent research over the last decades. The consensus statements on the properties of RBE consider some findings that appear to be elementary for a reasonable clinical RBE modeling and can serve as a guideline for future models that approach this goal.

The models and associated dose prescription systems discussed in this publication all have certain radiobiological limitations (which we did not consider in this work) and require a specific choice of input parameters for their use. Both aspects, as well as assumptions of the model concepts, result in uncertainty of the predictions. From a clinical perspective, this results in a model-inferred uncertainty of dose. Exploring the model limitations is therefore important to understand the clinical impact, in particular in the conversion between dose prescription systems.

In addition to these inherent uncertainties, even for the same delivered absorbed dose profiles, the level of clinical/RBE-weighted doses differs. However, the latter are the reported prescription doses, opening up the problem of intercomparability and translation between dose prescription systems and related clinical outcomes. In this publication, we give a number of consensus statements that may be helpful to understand the complexity of the problem and serve to find reliable routes for translations between these dose prescription systems.

The most fundamental problem in this context is the following: every modification of a dose prescription system (eg, by revised model parameters or by implementing new models) may reflect progress and may overcome prior limitations in predictive capability. At the same time, it will define a new dose metric for the prescribed dose, requiring new dose constraints in treatment planning. In the end, we will have to make clinical decisions as a trade-off between admitting progress in the quality of RBE predictions and the standardization of treatment protocols. Tools using standardized translation procedures will be necessary and helpful to support such delicate decisions. These considerations are intimately related to the question of how to properly report prescribed doses. Given the complexity of the topic, a concise description of the used methods and the type of dose (absorbed, RBE-weighted, clinical, etc.) seems indispensable for proper reporting.[20] However, the aspect of

reporting goes beyond the main focus of the present publication.

We know that all models have limitations, and no unique approach can be selected as the best option in all cases. To soften model limitations and to comply with different available dose prescription systems that make different predictions, 2 strategies evolved during the last years: multimodel-based planning and LET_d homogenization. It was demonstrated that a dual-model planning and evaluation strategy is both feasible and necessary to bridge the differences between dose prescription systems in clinical CIRT. The real impact of multi-RBE model and LET_d evaluation and optimization and their effects on clinical outcomes are under continuous monitoring. To ensure consistency and safety in multinational clinical trials involving CIRT, we recommend that dose prescription and OAR dose constraints should be customized site-specific and should not be employed as nominal values without specific validation. Additionally, LET_d analysis can be considered in the planning process, homogenizing the radiation quality across the SOBP, thereby making differences between dose prescription systems smaller and more uniform as well.

The IPI-trial[57] has highlighted the need for a thorough conversion of prescribed doses when transferring treatment protocols between different dose prescription systems. At a time when strategies for translation were not yet commonly applied, a prostate treatment protocol from NIRS/QST was adapted by optimizing with the LEM I-based dose prescription system directly to the NIRS clinical dose. As the converted RBE-weighted dose actually would be larger than the clinical dose, this led to an underdosage in the PTV. The authors concluded that increasing the assumed α/β parameter in the LEM I-based approach from 2 to 4 Gy would be a pragmatic way to remove the observed inconsistency with clinical data, as this lowers the RBE in the target volume. Alternatively, a similar effect could be achieved by using LEM IV with α/β = 2 Gy. In a subsequent study,[58] it was found that clinical results can also be reproduced accurately by using the mMKM with α/β = 3.1 Gy. As a result, consistency of RBE predictions with clinical data could be obtained with different combinations of models and model parameters. Since the models predict different RBE-LET gradients for the same α/β value, the α/β values had to be adapted for each model to match the observed clinical data. This example demonstrates the importance of thoroughly considering dose translations, predictions of multiple models, as well as the general capabilities and limitations of different models.

Critical aspects and possible future developments

Although we demonstrated the importance of dose translation between different approaches and the corresponding techniques existing for that purpose, pragmatic ways of easily achieving quantitative insights into dose translation are still lacking. Also, so far, no standardized procedure for deriving dose conversion factors has been established. A tool for deriving dose translations between any 2 models for selected reference cases would be very useful and may be used in assessing the capabilities of different models. A further evolution of this concept could consist of a multi-RBE optimization approach, where different RBE models are considered jointly in the plan optimization process. In this way, the process of obtaining a plan compliant with more than one model would be part of the robust inverse planning process.

The strategy to homogenize the biological effectiveness in the PTV by sophisticated LET_d optimization has certain pragmatic benefits, but can also be criticized. It is known that LET_d does not reflect the radiation field nor its biological effectiveness uniquely, as different ions[25] or several spectral compositions even for the same ion species can lead to the same LET_d[59,60] but may be associated with a different biological outcome.[61] In particular for carbon ions, it is known that the LET_d is not a useful surrogate for the RBE.[59,60] Furthermore, if the used RBE model approach would reliably appreciate the effects of the critical high-LET_d patterns in a treatment plan, the optimization process should automatically avoid constellations where LET_d can be a cause of concern. Such model approaches could be improved models not used in the clinic so far, employing the conventional LET (not LET_d) based optimizations, but also could rely on a microdosimetric or nanodosimetric characterization of the radiation field. At this point, there is currently no agreement in the community whether ultimately better RBE models can avoid problems associated with high-LET_d patterns, whether optimizing the LET_d distribution in addition to dose is in general useful, or whether LET_d is the most relevant LET metric.

The models used in CIRT share the property of having a mechanistic underpinning. This allows a radiobiological interpretation of the quantities used within the modeling and brings a certain flexibility in adapting model concepts or input parameters to improve the connection between macroscopic clinical endpoints and cellular damage as the starting point of radiation action. Eventually, such improvements may lead to better RBE predictions. Revised models, such as the oxygen-effect-incorporated stochastic microdosimetric kinetic model,[12] LEM IV,[15,16] and recently developed MCF MKM,[17] have been developed, and both LEM and mMKM are used with different parameter settings, adapting to specific situations (see Table 1). This opens up novel options in both radiobiology and radiation therapy, but also requests thorough validation. Although many publications have addressed this topic, we did not cover the aspect of model validation and testing in the present work, as it is separated from the aspect of clinical integration which we focused on here. It is planned to gather consensus criteria about necessary steps in model validation in the future.

The flexibility of models concerning their input parameters leads to another degree of freedom in therapy planning

that has not been considered to date: the radiobiological response of healthy tissue compared with that of a tumor is often different, characterized by different sensitivity to fractionation. In general, this can be taken into account by including diverse α/β values for different structures in the treatment plan, instead of using a fixed value for all tissues. In a long-term vision, even the use of personalized radiosensitivity parameters could be implemented, if corresponding reliable markers were known. In this context, however, α/β parameters have to be considered effective parameters, reflecting the net responsiveness of tissue, including oxygenation and other biological effects, which may be investigated separately in preclinical studies.

Outlook

In the current advent of numerous new clinical facilities for CIRT in Asia, Europe, and North America, developing or selecting model approaches and implementing them plays a pivotal role in setting up clinical standards in the new facilities and requires thorough initial decisions. It is mandatory to consider that prescription doses and fractionation schemes, as well as OAR dose constraints currently employed in CIRT, are based on clinical experience. Long-term follow-up data on outcome and toxicity exist for patients treated with the established dose prescription systems and play a fundamental role in clinical decision making. More specifically, the dose needed to achieve a high probability of tumor control is based on dose-escalation trials and on results of reported patient series. The dose constraints to be applied to limit toxicity and the evaluation of the magnitude of risk if they are exceeded are also based on reported clinical outcomes. Introducing a new RBE model or a new dose prescription system may have several theoretical advantages but can also limit the applicability of this set of clinical data. Introducing a new RBE/dose prescription system is possible only after a critical evaluation of its impact on these critical parameters. Using dose constraints or prescription doses derived from past experience without a specific effort to adapt them to the new dose prescription system by establishing conversion factors has to be strongly discouraged.

As CIRT expands globally, sharing anonymized clinical and dose-response data across institutions is essential to ensure reproducibility, maintain consistent treatment quality and patient safety, and advance the integration of biological modeling into clinical practice. Future intercontinental collaborations are envisioned to arrive in multi-institutional clinical studies for that purpose. Although a multitude of available and used dose prescription systems complicates the comparability of clinical results and imposes a hurdle for protocol transfer, we have highlighted some aspects that require special attention in that context, and we demonstrated possible translational tools. This may help to overcome these hurdles and even to make use of the coexistence of multiple approaches to reliably predict RBE in clinical practice.

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