EUD-based biological optimization for carbon ion therapy

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Purpose: Treatment planning for carbon ion therapy requires an accurate modeling of the biological response of each tissue to estimate the clinical outcome of a treatment. The relative biological effectiveness (RBE) accounts for this biological response on a cellular level but does not refer to the actual impact on the organ as a whole. For photon therapy, the concept of equivalent uniform dose (EUD) represents a simple model to take the organ response into account, yet so far no formulation of EUD has been reported that is suitable to carbon ion therapy. The authors introduce the concept of an equivalent uniform effect (EUE) that is directly applicable to both ion and photon therapies and exemplarily implemented it as a basis for biological treatment plan optimization for carbon ion therapy.

Methods: In addition to a classical EUD concept, which calculates a generalized mean over the RBE-weighted dose distribution, the authors propose the EUE to simplify the optimization process of carbon ion therapy plans. The EUE is defined as the biologically equivalent uniform effect that yields the same probability of injury as the inhomogeneous effect distribution in an organ. Its mathematical formulation is based on the generalized mean effect using an effect-volume parameter to account for different organ architectures and is thus independent of a reference radiation. For both EUD concepts, quadratic and logistic objective functions are implemented into a research treatment planning system. A flexible implementation allows choosing for each structure between biological effect constraints per voxel and EUD constraints per structure. Exemplary treatment plans are calculated for a head-and-neck patient for multiple combinations of objective functions and optimization parameters.

Results: Treatment plans optimized using an EUE-based objective function were comparable to those optimized with an RBE-weighted EUD-based approach. In agreement with previous results from photon therapy, the optimization by biological objective functions resulted in slightly superior treatment plans in terms of final EUD for the organs at risk (OARs) compared to voxel-based optimization approaches. This observation was made independent of the underlying objective function metric. An absolute gain in OAR sparing was observed for quadratic objective functions, whereas intersecting DVHs were found for logistic approaches. Even for considerable under- or overestimations of the used effect- or dose–volume parameters during the optimization, treatment plans were obtained that were of similar quality as the results of a voxel-based optimization.

Conclusions: EUD-based optimization with either of the presented concepts can successfully be applied to treatment plan optimization. This makes EUE-based optimization for carbon ion therapy a useful tool to optimize more specifically in the sense of biological outcome while voxel-to-voxel variations of the biological effectiveness are still properly accounted for. This may be advantageous in terms of computational cost during treatment plan optimization but also enables a straightforward comparison of different fractionation schemes or treatment modalities.

Key words: equivalent uniform dose (EUD), biological optimization, carbon ion therapy, treatment planning

1. INTRODUCTION

Ionizing radiation offers the opportunity to treat cancer in regions of the body which are inaccessible to other treatment modalities as surgery or chemotherapy. On its way to the tumor, radiation inevitably strikes healthy tissue and it is the goal of radiation therapy treatment planning to locally irradiate the tumor without causing major damage to the adjacent normal tissue and organs at risk (OARs).

Presently, for inverse treatment planning, the biological response of an organ that results in a particular treatment outcome is summarized in terms of the delivered dose. However, the delivered physical dose is only a surrogate for complex biological processes taking place after the irradiation of
an organ. Whereas on a cellular level it is possible to quantify the biological effectiveness of a treatment in terms of cell survival by *in vitro* experiments, the modeling of the whole organ response and its impact on the patient are still subject of current research. The most prominent examples for biological models are the equivalent uniform dose (EUD), the normal tissue complication probability (NTCP), and the tumor control probability (TCP). These models have been applied for treatment plan evaluation as well as inverse treatment plan optimization for photon therapy which is then referred to as "biological optimization." 

In the case of particle therapy, the physical dose distribution alone is not sufficient to predict the treatment outcome. It is essential to take the local biological effectiveness of the radiation into account for treatment planning. Up to date, this has been done on a cellular level by weighting the physical dose by the relative biological effectiveness (RBE) of the radiation with respect to photon irradiation. For the patient, however, the biological response of each organ as a whole is important. A first step toward a realistic modeling of radiation effects in an OAR is the concept of EUD which has been introduced for photon therapy. The EUD corresponds to the uniformly given dose that yields the same biological outcome as the actual inhomogeneous dose distribution.

In this paper, two methods to apply the concept of EUD to carbon ion therapy are presented and used as treatment planning objective for OARs. We demonstrate differences between treatment plans resulting from biological objective functions and the common voxel-based optimization routines. The question of uncertainties in the biological parameters is addressed as well in the last part of the paper.

### 2. METHODS

#### 2.A. EUD calculation for photon therapy

In 1998, Niemierko suggested a phenomenological description of EUD for photon therapy which can equally be applied to tumors and normal tissues. Here, the EUD equals the generalized mean of the nonuniform dose distribution in a structure of interest,

\[
\text{EUD} = \left( \frac{1}{N} \sum_{i=1}^{N} D_i^a \right)^{\frac{1}{a}}.
\]  

(1)

In this expression, the number of voxels is denoted by \( N \), \( D_i \) is the physical dose in voxel \( i \), and the exponent \( a \), the inverse Lyman parameter, indicates the dose–volume response of the respective structure. This exponent is specific for each tumor or OAR and accounts for a biological weighting of the dose distribution. For tumors, \( a \) takes large negative values drawing the EUD value to the minimum of the distribution, while normal tissues display a positive exponent greater than one. Depending on the organ architecture, i.e., its degree of serialism and parallelism, \( a \) ranks between unity (purely parallel organs) and infinity (purely serial organs) attributing a value between the arithmetic mean and the maximum of the dose distribution to the EUD.

#### 2.B. Biophysical modeling for carbon ion therapy

The RBE provides a mathematical framework to compare different treatment modalities. It refers to the isoeffective ratio of the dose deposited by a reference radiation to that of carbon ion irradiation in one fraction, \( d_p \) (with \( p \) standing for particle). In the context of the linear quadratic (LQ) model, the RBE can be calculated using the LQ-parameters \( \alpha_p \) and \( \beta_p \) for particles and \( \alpha_X \) and \( \beta_X \) for the reference radiation (x-rays),

\[
\text{RBE} = \frac{-\alpha_X + \sqrt{\alpha_X^2 - 4\beta_X(\alpha_p d_p + \beta_p d_p^2)}}{2\beta_X d_p}. \tag{2}
\]

The induced cellular damage, and thus the LQ-model parameters, strongly depends on the linear energy transfer of the respective radiation. The parameters \( \alpha_p \) and \( \beta_p \) for each ion type and energy level are estimated from biological modeling approaches, e.g., the local effect model (LEM).

For an accurate modeling of both, the delivered physical dose and the biological effectiveness of a carbon ion beam, it is essential to consider its specific fragment and energy spectrum. For a multienergetic beam of energies \( E \), constituted of a range of fragments \( Z, \alpha_p \) and \( \beta_p \) at each voxel \( i \) in a patient are the dose averaged sum of the contributions from each pristine Bragg peak.

\[
\alpha_p(i) = \sum \int_0^\infty \alpha(Z,E) \cdot \Phi(i,Z,E) \cdot S_p(Z,E) dE.
\]  

(3)

\[
\sqrt{\beta_p(i)} = \frac{\sum \int_0^\infty \sqrt{\beta(Z,E)} \cdot \Phi(i,Z,E) \cdot S_p(Z,E) dE}{\sum \int_0^\infty \Phi(i,Z,E) \cdot S_p(Z,E) dE}.
\]  

(4)

Here, \( S_p(Z,E) \) refers to the stopping power and the fragment spectra are denoted by \( \Phi(Z,E) \). Using this representation of the LQ-model parameters, the RBE as given in Eq. (2) varies across the volume of interest and is thus in the following denoted as \( \text{RBE}_i \), the RBE in voxel \( i \).

#### 2.C. EUD formulations for carbon ion therapy

A straightforward implementation of an EUD concept for carbon ion therapy is the application of photon EUD formula (1) to the RBE-weighted dose distribution,

\[
\text{EUD}_{\text{RBE}} = \left( \frac{1}{N} \sum_{i=1}^{N} (d_p \cdot \text{RBE}_i)^a \right)^{\frac{1}{a}}. \tag{5}
\]

In this approach, the dose–volume parameter \( a \) refers to the same parameter obtained from clinical studies with photon irradiation. Although the concept of \( \text{EUD}_{\text{RBE}} \) represents a valid implementation of the EUD concept to carbon ion therapy, it may not be ideal for an application to treatment plan optimization. A formulation of EUD that can be applied directly to ion therapy and that is independent of RBE would be preferable to reduce the number of biological parameters and the overall complexity of the formulation leading to a potential computational advantage.
In the context of the LQ-model, the surviving fraction of clonogenic cells in a tumor, SF, is solely determined by the biological effect $\epsilon$, which can be calculated for each voxel $i$,

$$\text{SF}(\epsilon) = e^{-\epsilon} \quad \text{with} \quad \epsilon_i = \alpha_p d_P + \beta_p d_P^2. \quad (6)$$

Wilkins and Oelfke proposed an optimization of the biological effect rather than the RBE-weighted dose. Following this concept, we take the generalized mean over the effect distribution, $\{\epsilon_i\}$, as an alternative to the concept of EUD$_{RBE}$. The obtained quantity is denoted as the equivalent uniform effect (EUE) and refers to the uniform biological effect that yields the same degree of injury/number of surviving clonogenes as the inhomogeneous effect distribution,

$$\text{EUE} = \left( \frac{1}{N} \sum_{i=1}^{N} \epsilon_i^{a'} \right)^{1/a'} \quad (7)$$

The exponent $a'$ denotes the effect-volume parameter of the organ under study which differs from the inverse Lyman parameter $a$ applied in Eq. (5). Yet, the overall mathematical characteristics of the generalized mean are preserved in the EUE concept leading to small positive effect-volume parameters for parallel OARs, large values for serial OARs, and negative parameters for tumors.

The effect-volume parameter may be derived by numerically solving the following equation that calculates the EUE as the biological effect of a homogeneous irradiation with the RBE-weighted dose EUD$_{RBE}$ according to the LQ formalism.

$$\text{EUE} = \alpha X \cdot \text{EUD}_{RBE} + \beta X \cdot \text{EUD}_{RBE}^2 \quad (8)$$

In addition to Eq. (8), for tumors, the effect-volume parameter can be estimated in a mechanistic approach similar to that proposed by Søvik et al. for photon EUD calculations. Under the assumption of independent, uniformly distributed clonogenes, a homogeneous biological effect EUE yields the same number of surviving clonogenes as the nonuniform effect distribution. In the context of the LQ-model, it is possible to equalize the surviving fractions to obtain a phenomenological formulation of EUE, independent of a dose–volume parameter,

$$\text{SF}(\text{EUE}) = \text{SF}(\{\epsilon_i\}). \quad (9)$$

By substituting the EUE with Eq. (7), an equation is obtained that can be solved numerically for $a'$,

$$\left( \frac{1}{N} \sum_{i=1}^{N} \epsilon_i^{a'} \right)^{1/a'} = -\ln \left( \frac{1}{N} \sum_{i=1}^{N} e^{-\epsilon_i} \right) \Rightarrow a'. \quad (10)$$

The presented expressions of $a'$ [Eqs. (8) and (10)] both depend on the underlying dose statistics, i.e., the shape of the differential dose–volume histogram, and biological parameters $\alpha$ and $\beta$. Since the actual dose distribution is unknown prior to the treatment plan optimization, it requires some experience to estimate the values of $a'$ in a meaningful way to use the EUE during the optimization process. Yet, even if the “correct” effect-volume parameters are not known during the optimization, the treatment planner may as well use estimated, fictitious values for $a'$ to steer the optimization in the intended direction.

### 2.D. Integration into 3D treatment planning system

Recently, Schell et al. upgraded the research treatment planning platform CERR (Computational Environment for Radiation Research) to feature proton therapy treatment planning. We extended their work to enable 3D treatment plan optimization for carbon ion therapy. For this, the implementation of beam fragmentation and biological modeling follows closely the methods described by Kamp et al. for 1D planning. Here, the Monte Carlo code FLUKA was used to generate the ion fragmentation spectra that are further applied for the biological modeling. The respective particle parameters, $\alpha_p$ and $\beta_p$, are provided as tabulated data sets calculated by a LEM1 (Ref. 15) implementation by INFN and I-SEE (available at http://totlxl.to.infn.it/lem/).

To test the applicability of EUD-based treatment plan optimization, a dedicated tool has been integrated into the platform featuring the objective functions given in Sec. 2.E. The implementation has been carried out using the MATLAB (The MathWorks, Inc.) function fmincon with the interior-point algorithm which is part of the MATLAB optimization toolbox. First derivatives were provided to the optimizer, whereas the Hessians were approximated by the L-BFGS-algorithm as an available option of fmincon. Besides the default options, the maximum number of function evaluations was limited to 1000 and the minimum first order optimality was set to $10^{-10}$ to ensure a convergence of the optimization.

### 2.E. Implemented objective functions

For carbon ion therapy, instead of optimizing the physical dose, either the RBE-weighted dose or the biological effect is optimized to take the enhanced biological effectiveness of the radiation into account. In this paper, all voxel-based objective functions refer to an optimization of the biological effect $\epsilon$.

In conventional, voxel-based treatment planning systems, quadratic objective functions are the standard implementation. These functions sum up the squared difference between the effect $\epsilon_i$ in each voxel $i$ of a structure $T$ and its prescribed minimum or maximum values $\epsilon_{\text{min}}$ and $\epsilon_{\text{max}}$. Penalty factors $p_{\text{min}}$ and $p_{\text{max}}$ that are normalized to the number of voxel per structure, $N_T$, make it possible to rank optimization objectives according to user-defined priorities,

$$P_{\text{SQ,vox}}(\{\epsilon_i\}) = \sum_{i \in T} \left[ p_{\text{min}} \cdot (\epsilon_{\text{min}} - \epsilon_i)_{+}^2 + p_{\text{max}} \cdot (\epsilon_i - \epsilon_{\text{max}})_{+}^2 \right]. \quad (11)$$

The plus operator $[.]_+$ ensures that only unsatisfied objectives contribute to the objective function score. This implies that the combination of penalty factors and prescribed dose objectives has to be defined carefully to optimize the dose distribution in multiple structures to the best achievable extend.

EUD-based optimizations implemented for photon therapy on the other hand have been introduced by Wu et al. in terms...
of logistic objective functions.\(^\text{22}\)

\[
F_{\text{LS, str}}^T(\text{EUD}) = \ln \left( \frac{1}{1 + \left( \frac{d_{\text{min}}}{\text{EUD}} \right)^{p_{\text{min}}}} \right) + \ln \left( \frac{1}{1 + \left( \frac{d_{\text{max}}}{\text{EUD}} \right)^{p_{\text{max}}}} \right).
\]

(12)

In contrast to quadratic objective functions, here the relative deviation from prescribed parameters is considered. Moreover, an objective will always contribute to the objective function score even if the prescribed criteria are met. Solely, the slope of the function decreases with increasing agreement between actual and yielded EUD values.

Consequently, even for identical penalty factors, \(F_{\text{SQ}}\) and \(F_{\text{LS}}\) will emphasize different optimization criteria (compare Fig. 1). To draw a meaningful comparison of EUD- and voxel-based optimization approaches, we thus restrict this comparison to treatment plans optimized by the same objective function. Therefore, in addition to the functions given in Eqs. (11) and (12), we implemented a quadratic objective function for EUD optimization, \(F_{\text{SQ, str}}^T\), as well as the logistic, voxel-based objective function \(F_{\text{LS, vox}}^T\).

\[
F_{\text{SQ, str}}^T(\text{EUD}) = p_{\text{min}} \cdot (d_{\text{min}} - \text{EUD})^2 + p_{\text{max}} \cdot (\text{EUD} - d_{\text{max}})^2,
\]

(13)

\[
F_{\text{LS, vox}}^T(\{\epsilon_i\}) = \sum_{i \in T} \ln \left( \frac{1}{1 + \left( \frac{d_{\text{min}}}{\epsilon_i} \right)^{p_{\text{min}}}} \right) + \sum_{i \in T} \ln \left( \frac{1}{1 + \left( \frac{d_{\text{max}}}{\epsilon_i} \right)^{p_{\text{max}}}} \right).
\]

(14)

In the following, the variable EUD in the structure-based objective functions, \(F_{\text{SQ, str}}^T\) and \(F_{\text{LS, str}}^T\), is replaced either by EUD\(_{\text{RBE}}\) or EUE as defined in Eqs. (5) and (7). The prescribed minimum and maximum parameters are replaced by respective RBE-weighted dose or biological effect prescriptions.

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**Fig. 1.** Objective functions \(F_{\text{LS, str}}\) (solid line) and \(F_{\text{SQ, str}}\) (dashed line) according to Eqs. (12) and (13) as a function of \(d_{\text{max}}/\text{EUD}\) for equivalent penalty factors \(p_{\text{max}} = 150\) and \(p_{\text{max}} = 0\).

**Fig. 2.** Transversal CT slice of the head-and-neck patient. Indicated are the PTV, the 1 cm margin \(M\), the eyes, and the optic nerves ON.

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### 2.F. Studied patient

Carbon ion irradiation produces very conformal dose distributions. Only OARs close to the planning target volume (PTV) are of concern for a biological treatment plan optimization. The studied patient was a head-and-neck case with several OARs located directly adjacent to the PTV. Figure 2 gives an overview of the patient geometry. In this study, the optic nerves, the right eye, as well as a 1 cm margin \((M)\) of brain tissue around the PTV were considered. For treatment planning, two beams from 0° and 90°, a lateral beam spot distance of 3 mm, and a lateral beam size full width at half maximum of 0.14 cm (in air on the patient surface) were used. Concerning the biological modeling for treatment planning, parameters for chordoma cells, \(\alpha_X = 0.1 \text{ Gy}^{-1}\) and \(\beta_X = 0.05 \text{ Gy}^{-2}\) were assigned across all volumes of interest as these parameters are used in clinical routine.\(^\text{21,24}\)

### 2.G. Calculated treatment plans

For photon therapy, in several cases, a superior OAR sparing was reported for EUD-based treatment plan optimization compared to voxel-based optimization approaches.\(^\text{4,5,25–28}\) To test this observation for carbon ion therapy, we compared treatment plans optimized via voxel- and EUD-based objective function contributions for the OARs. To ensure a reasonable comparison of treatment plans solely on the basis of different dose distributions in the OARs, the competing plans were optimized using the same objective function metric. The objective function by itself has a great impact on the optimization result and the speed of convergence.

All treatment plans displayed consistent dose distributions in the PTV and the PTV margin. OAR sparing under the
condition of unfavorable PTV coverage or dose homogeneity would make the overall benefit of such a treatment plan questionable.

In detail, plans were calculated by a logistic, voxel-based optimization ($F_1$), logistic, EUD$_{RBE}$-based optimization ($F_2$), a quadratic, voxel-based optimization ($F_3$), a quadratic, EUD$_{RBE}$-based optimization ($F_4$), and a logistic, EUE-based optimization ($F_5$). The mathematical formulations of $F_1$–$F_5$ are listed in Table I with their respective optimization parameters.

The PTV and the PTV margin $M$ were always optimized on a voxel basis ($F_{LS,vox}$ and $F_{SQ,vox}$) with adjusted sets of penalty factors to account for the different contribution of EUD- and voxel-based objective function terms. To ensure an optimal coverage of the PTV, two minimum (100% and 95%) and maximum (100% and 105%) dose objectives were applied to this structure for quadratic objective functions $F_3$ and $F_4$, whereas a single objective was sufficient for logistic optimizations ($F_1$, $F_2$, and $F_5$).

The prescribed RBE-weighted dose in the PTV was 2.2 Gy (RBE) per fraction (in the following denoted as 100%) and all EUD values were calculated for a dose–volume parameter of $d_{PTV} = -50$. The prescribed maximum doses per fraction of the OARs were selected to yield a NTCP of 1% for an irradiation of 32 fractions. Biological reference data for the dose–volume parameters and EUD prescriptions were taken from the work of Luxton et al. The PTV margin was treated as brain tissue ($a_M = 4$); for the eye, the data for retina [$a_{ON} = 5$, $d_{max} = 1.1$ Gy (RBE) per fraction] was used, and the optic nerves (ON) were optimized for $a_{ON} = 4$ and $d_{max} = 1.3$ Gy (RBE) per fraction.

3. RESULTS

3.A. Comparison of EUD- and voxel-based optimization

3.A.1. Logistic objective functions

In the context of logistic objective functions, the treatment plans resulting from an optimization using the objective functions $F_1$ and $F_2$ are compared. An exemplary slice of the 3D physical dose, RBE, and RBE-weighted dose distribution of the treatment plan optimized by $F_1$ is shown in Fig. 3. Treatment plans were analyzed regarding the final EUD$_{RBE}$ in the OARs (see Table II) and the corresponding DVHs that are shown in Fig. 4(a).

For all OARs, the DVHs of the voxel- and EUD-optimized treatment plans intersect. The EUD-based optimization yielded a slight increase in the volume fraction receiving higher doses in favor of an enhanced sparing in the intermediate and low dose regime. Regarding the calculated EUDs, the prescribed RBE-weighted dose in the PTV was 2.2 Gy (RBE) per fraction (in the following denoted as 100%) and all EUD values were calculated for a dose–volume parameter of $d_{PTV} = -50$. The prescribed maximum doses per fraction of the OARs were selected to yield a NTCP of 1% for an irradiation of 32 fractions. Biological reference data for the dose–volume parameters and EUD prescriptions were taken from the work of Luxton et al. The PTV margin was treated as brain tissue ($a_M = 4$); for the eye, the data for retina [$a_{ON} = 5$, $d_{max} = 1.1$ Gy (RBE) per fraction] was used, and the optic nerves (ON) were optimized for $a_{ON} = 4$ and $d_{max} = 1.3$ Gy (RBE) per fraction.

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Table I. Objective functions $F$, penalty factors $p$, maximum dose objectives $d_{max}$, and minimum dose objective $d_{min}$ in the PTV, the PTV margin $M$, and the OARs. For the PTV, the same penalty factors are used to penalize under- and overdosage.

| $F$ | $\mathbf{PTV}$ | $\mathbf{M}$ | $\mathbf{OARs}$ | $\mathbf{M}$ | $\mathbf{PTV}$ | $\mathbf{PTV}$ |
|-----|----------------|---------------|----------------|---------------|----------------|----------------|
| $F_1 = \sum_{T \in \{PTV, M, OARs\}} F_{LS,vox}^{T}$ | 150 | 3 | 0.6 | 100 | 105 | 95 |
| $F_2 = \sum_{T \in \{PTV, M\}} F_{LS,vox}^{T} + \sum_{T \in \{OARs\}} F_{LS,ur}^{T}(EUD_{RBE})$ | 150 | 1 | 1 | 100 | 105 | 95 |
| $F_3 = \sum_{T \in \{PTV, M, OARs\}} F_{SQ,vox}^{T}$ | 150, 10 | 5 | 0.5 | 82 | 105, 100 | 95, 100 |
| $F_4 = \sum_{T \in \{PTV, M\}} F_{SQ,vox}^{T} + \sum_{T \in \{OARs\}} F_{SQ,ur}^{T}(EUD_{RBE})$ | 300, 20 | 5 | 0.1 | 77 | 105, 100 | 95, 100 |
| $F_5 = \sum_{T \in \{PTV, M\}} F_{LS,vox}^{T} + \sum_{T \in \{OARs\}} F_{LS,ur}^{T}(EUE)$ | 150 | 1 | 1 | 100 | 105 | 95 |

![Fig. 3](image-url) Transversal slice of the treatment plan optimized by $F_1$. Shown are the physical dose (a), the RBE (b), and the RBE-weighted dose (c) distributions with delineated OARs and PTV as indicated in Fig. 3.
values, the sparing of the OARs is improved in the sense of a decreased EUD$_{RBE}$ for EUD-based optimization. In general, the overall absolute dose difference is relatively small and ranges in the order of a few per cent for all studied OARs. The optic nerves receive an EUD$_{RBE}$ of 72.4% (left optic nerve) and 78.2% (right optic nerve) in the EUD-optimized plan, whereas the comparable plan optimized on a voxel-basis yielded 75.6% and 79.7%, respectively. For the right eye, the EUD$_{RBE}$ is reduced by 1.8% in the optimization with $F_2$ compared $F_1$.

### 3.A.2. Quadratic objective functions

Figure 4(b) illustrates the DVHs obtained from optimizations using the quadratic objective functions $F_3$ and $F_4$. The quadratic, EUD-based optimization resulted in an absolute gain in OAR sparing in the intermediate dose regime compared to the voxel-based optimization. Consequently, the EUD-optimized treatment plan yielded a decreased EUD$_{RBE}$ in the OARs (compare Table II). The EUD$_{RBE}$ values after EUD- (voxel-)based optimization were 71.9% (73.3%) for the right optic nerve, 69.1% (71.0%) for the left optic nerve, and 57.3% (58.2%) for the right eye.

### 3.B. Optimizing EUD$_{RBE}$ and EUE

Treatment plans resulting from EUD$_{RBE}$ and EUE-based optimizations for the OARs were compared. The respective objective functions were $F_2$ and $F_3$ in the context of logistic objective functions. For an optimization of EUE, the effect-volume parameters $a_{ON} = 3.25$ and $a_{REye} = 3.8$ were used. The resulting DVHs and EUD$_{RBE}$ values are displayed in Fig. 5 and Table II.

Independent of the used EUD calculation approach, the optimization yielded equivalent treatment plans in terms of final EUD$_{RBE}$ and absolute dose distributions. Considering the less complex formulation via the equivalent uniform effect, it seems reasonable to favor this concept over the EUD$_{RBE}$ for treatment plan optimization. Solely the definition and

### Table II. Resulting EUD$_{RBE}$ values for optimizations with objective functions $F_1$ to $F_5$ in the PTV margin ($M$), the left optic nerve (LON), the right optic nerve (RON), and the right eye (REye). All values are relative to 2.2 Gy (RBE) $= 100\%$.

| $F_n$ | $M$ (%) | LON (%) | RON (%) | REye (%) |
|------|---------|---------|---------|----------|
| 1    | 65.7    | 75.6    | 79.7    | 60.7     |
| 2    | 65.1    | 72.4    | 78.2    | 58.9     |
| 3    | 66.0    | 71.0    | 73.2    | 58.2     |
| 4    | 65.8    | 69.1    | 71.9    | 57.3     |
| 5    | 65.3    | 72.3    | 78.1    | 58.8     |

![Fig. 4. Dose–volume histograms for a head-and-neck treatment plan using (a) logistic and (b) quadratic objective functions. Solid lines indicate voxel-based objective functions ($F_1$ and $F_3$), dashed lines represent EUD-based criteria ($F_2$ and $F_4$). On the abscissa, 100% $\pm$ 2.2 Gy (RBE).](image)

![Fig. 5. DVHs of the RBE-weighted dose distributions in the OARs optimized with $F_2$ (solid lines) and $F_3$ (dashed lines). On the abscissa, 100% $\pm$ 2.2 Gy (RBE).](image)
uncertainty of the applied effect-volume parameters remain to be discussed.

3.C. Influence of the dose–volume parameter on the optimization outcome

We restrict the following discussion to logistic objective functions. To study the impact of the dose–volume parameters on the optimization outcome, 20 treatment plans were optimized using $F_2$ for artificial dose–volume parameters $a_{\text{opt}}$ ranging from unity to 50 for the right eye. In addition to this OAR, only the PTV and the PTV margin $M$ were considered in the optimization. The ratio of penalty factors was 150:1:1 (PTV:$M$:OAR).

The difference $\Delta$ in the resulting $\text{EUD}_{\text{RBE}}$ after EUD- and voxel-based optimization is analyzed as a function of the dose–volume parameter. Results are given in % referring to the difference relative to the prescribed dose to the PTV, $D_{\text{pres},\text{PTV}}$.

$$\Delta = \frac{\text{EUD}_{F_2}(a) - \text{EUD}_{F_2}(a_{\text{opt}})}{D_{\text{pres},\text{PTV}}}.$$  

(15)

The quantity $\text{EUD}_{F_2}(a)$ refers to the $\text{EUD}_{\text{RBE}}$ which is calculated with a dose–volume parameter $a$ for a dose distribution obtained from an optimization using an objective function $F_2$. Figure 6 shows the resulting plots for the PTV and the OAR. For the OAR, the same dose–volume parameter is applied during the optimization and for the final EUD calculation ($a_{\text{opt}} = a$), for the PTV, all EUD values are calculated with $a_{\text{PTV}} = -50$.

For all treatment plans, the PTV dose distributions remained comparable ($\Delta_{\text{PTV}} \approx 0$) and the EUD-based optimization yielded a decreased $\text{EUD}_{\text{RBE}}$ with respect to the voxel-based optimization in the OAR ($\Delta_{\text{OAR}} < 0$). It is observed that for logistic objective functions, the gain in OAR sparing is higher for serial structures ($a \gg 1$) than for parallel OARs ($a \approx 1$).

As the dose–volume and thus also the effect-volume parameters are still subject to large uncertainties, it is of interest how uncertainties in $a_{\text{opt}}$ influence the optimization outcome. Since the mathematical characteristics of the generalized mean are the same for $\text{EUD}_{\text{RBE}}$ and EUE, the following analysis was carried out only for a variation of the dose–volume parameter $a_{\text{opt}}$ used in $\text{EUD}_{\text{RBE}}$-based optimizations. The obtained results are transferable to an optimization of EUE with uncertain effect-volume parameters $a'_{\text{opt}}$.

For each of the 20 treatment plans, the $\text{EUD}_{\text{RBE}}$ values of the right eye are recalculated with dose–volume parameters between 1 and 50. On the basis of this dataset, it is possible to interpolate $\text{EUD}_{\text{RBE}}$ values that are calculated with a dose–volume parameter $a$ from a distribution that was optimized using an arbitrary parameter $a_{\text{opt}}$ between 1 and 50. The relative difference $\delta$ in $\text{EUD}_{\text{RBE}}$ between treatment plans optimized for $\text{EUD}_{\text{RBE}}$ using the correct dose–volume parameter ($a_{\text{opt}} = a$) and those calculated with either a too small or too large parameter ($a_{\text{opt}} = \tilde{a}$) was analyzed,

$$\delta(a) = \frac{\text{EUD}_{F_2}(a_{\text{opt}}) - \text{EUD}_{F_2}(a)}{D_{\text{pres},\text{PTV}}}.$$  

(16)

Figure 7 shows $\delta$ for the right eye as a function of the actual dose–volume parameter $a$ for 30%, 50%, and 80% under- and overestimation of the dose–volume parameter used in the optimization.

The resulting relative differences in final $\text{EUD}_{\text{RBE}}$ in the OAR were relatively small ($\delta < 2\%$) also for considerable under- and overestimations of $a_{\text{opt}}$. This implies that even in the presence of high uncertainties in the optimization parameters, EUD-based optimization results in most cases still in a superior $\text{EUD}_{\text{RBE}}$ than treatment plans optimized on a voxel basis ($\delta(a) < \Delta(a)$). Yet, it is notable that a considerable underestimation of the dose–volume parameter will result in a greater deviation in final $\text{EUD}_{\text{RBE}}$ than an overestimation of the
parameter to the same extent. The final $EUD_{\text{RBE}}$ of serial-parallel OARs ($3 < a < 10$) shows a stronger correlation to potential variations in $a_{\text{eq}}$ than purely parallel or rather serial OARs.

4. DISCUSSION

In this article, we introduced two novel EUD formulations to enable biological treatment plan optimization for carbon ion therapy. Differences between the used objective functions and their impact on the optimization outcome as well as the impact of uncertainties of the optimization parameters were evaluated.

It was shown that the proposed concepts are applicable to treatment plan optimization. Whereas the $EUD_{\text{RBE}}$ may be considered an extension of the well known gEUD formalism by A. Niemierko, the EUE represents a concept that could replace the gEUD formalism and generalizes the application for different treatment modalities. In this article, we proposed two concepts to enable biological optimization for carbon ion treatment planning for the first time.

In agreement with previous observations for EUD-based optimization for photon therapy, EUD-based optimization for carbon ion therapy resulted in a superior OAR sparing in terms of $EUD_{\text{RBE}}$ for comparable PTV dose distributions, independent of the underlying objective function metric. The absolute gain in OAR sparing was relatively small due to the high conformity of carbon ion treatment plans. Only OARs that are directly adjacent to the PTV will profit considerably from a biological optimization approach. Due to the physical characteristics of carbon ion beams in combination with a precise beam delivery, e.g., by active scanning, it is possible to sculpture the dose distribution with fine and individual details. These technical advances make it possible to deliver fine-tuned dose distributions enabling a gain in OAR sparing through treatment plans, which are optimal in a biological sense.

The reduction in $EUD_{\text{RBE}}$ in the OARs was due to different criteria depending on the applied objective function metric. This observation stresses the importance of considering the used objective function metric when comparing different treatment plans. For logistic objective functions, the DVHs for the OARs from EUD- and voxel-based optimizations intersect, whereas a quadratic EUD-objective function yielded a reduction of the level of low and intermediate doses for the same OAR. This may be explained by the fact that the ways of searching in the solution space differ for the two objective functions: The logistic voxel-based optimization reduces the overall mean dose in the respective OAR as all voxels contribute to the objective function value at any time. Therefore, especially serial OARs, which are sensitive to the maximum rather than the mean dose, profit from EUD-optimized treatment plans in the context of logistic objective functions.

For quadratic objective functions, the improvement in $EUD_{\text{RBE}}$ is achieved by a steepening of the dose gradient in the intermediate dose regime. Due to the plus operator [compare Eq. (11)], voxels receiving doses that meet an objective do not contribute to the objective function. The optimization is driven by the maximum of the distribution, whereas intermediate dose levels are not optimized with this kind of voxel-based objective function. The EUD on the other hand is improved by lowering the overall dose received by an OAR. Thus, the EUD-based optimization takes all voxel of an OAR into account as long as the overall EUD exceeds the prescribed maximum dose. It would therefore be expected that rather parallel OARs profit more from EUD-based optimization in the context of quadratic objective functions. Yet, this hypothesis is difficult to prove since a variation of the dose–volume parameter of the OARs during the optimization strongly influences the PTV dose distribution. The penalty factors and prescribed maximum objectives would have to be adjusted very carefully in a long trial-and-error process for each variation of the dose–volume parameter to yield comparable PTV dose distributions.

Finally, it should be noted that independent of the used objective function, i.e., logistic or quadratic, voxel- or EUD-based, the available solution spaces should be equivalent. Solely, the way of steering the optimization in the desired direction is different. It should indeed be possible to find a treatment plan of equivalent OAR sparing by voxel-based optimization in a longer trial-and-error process of defining the desired optimization parameters. With a single dose objective, however, a dose distribution that is optimal in a biological sense is difficult to find with voxel-based optimization routines.

We demonstrated that both $EUD_{\text{RBE}}$ and EUE-based objective functions yield identical treatment plans for matching biological parameters. The EUE requires less biological parameters than $EUD_{\text{RBE}}$ since it is a formulation that is independent of a reference radiation but is applied directly to the effect distribution. Thus, EUE-based objective functions comprise a considerably less complex formulation which makes the optimization procedure computationally less expensive. Moreover, the comparison of different fractionation schemes is straightforward for calculated EUE values due to the additivity of the biological effect. However, currently no values have been derived from clinical data for the introduced effect-volume parameter, but it may be estimated form the respective dose–volume parameters. Since this method only provides an estimate of the parameter, we addressed the impact of uncertainties of the dose–volume parameter on the optimization outcome to prove that the concept is still applicable.

It was shown that even in the presence of considerable uncertainties up to 80% in the dose–volume parameters, EUD-based optimization still resulted in treatment plans, which were favorable over or equal to plans optimized on a voxel basis. The characteristics of carbon ion (RBE-weighted) dose distributions may explain these observations. With carbon ions, it is possible to achieve very steep dose gradients leading to highly inhomogeneous dose distributions in an OAR that is directly adjacent to the target. Without violating the target coverage, the possibilities of limiting the absolute maximum of the distribution are small. Thus, an increase of the dose–volume parameter beyond $a \approx 10$ will not lead to significant changes in the high dose–volume fraction of the overall dose distribution. Therefore, the relative difference in $EUD_{\text{RBE}}$ is very small if overestimated dose–volume parameters are used in the
optimization for rather serial OARs. An overestimation of the dose–volume parameter during an EUD-based optimization may thus only lead to a decreased plan quality for rather parallel OARs.

An underestimation of the parameter, on the other hand, will draw the emphasis of the optimization closer to the mean of the distribution. A reduction of the mean dose in an OAR that is located in the gradient region of the dose distribution is achieved by steepening the dose fall off. As carbon ion beams display very steep dose gradients, an increment of the dose gradient implies a compromise in target coverage. The observation that some treatment plans yielded a superior EUD_{RBE} when optimized by overestimated dose–volume parameters (\( \delta > 0 \) in Fig. 7) may be explained by a minimal decreased treatment plan quality in the PTV for the respective plans in favor of lowering the dose in the OAR.

In order to lower the mean dose in a structure, all dose levels are taken into account. A reduced volume fraction receiving lower or intermediate doses can compensate small hotspots in the organ. For nonpurely parallel OARs, these high dose–volume fractions will greatly influence the EUD value leading to a reduced plan quality in terms of final EUD_{RBE} for large underestimations of the dose–volume parameter during the optimization.

In general, a false estimation of the dose–volume parameter has the greatest impact for an OAR, which is neither rather serial nor rather parallel (3 < a < 10). Here, the interplay of maximum and mean of the distribution is the most important and both under- and overestimations of the dose–volume parameters increase the final EUD_{RBE}. For such OARs, it is therefore important to define the dose–volume parameters with more accuracy if it is to be used for treatment planning.

Keeping the above discussion in mind, it is justified to claim the applicability of EUE-based optimization even in the presence of uncertainties in the effect-volume parameters. It is feasible to use estimated parameters to steer the optimization in the desired direction. Considering that also the dose–volume parameters are subject to large uncertainties and directed at a single endpoint, also EUD_{RBE}-based optimizations only provide a steering of the optimization toward a biologically more meaningful dose distribution. The EUE is therefore considered as the favorable metric for comparing inhomogeneous dose distributions, independent of the applied treatment modality, but specifically for ion beam therapy applications.

5. CONCLUSION

We presented two possible concepts, the EUE and the EUD_{RBE}, to transfer the concept of EUD to carbon ion therapy. Both concepts were implemented in a treatment planning system for different objective functions and used for structure-based treatment plan optimization for OARs. It was possible to reproduce the observations made for EUD-based optimization of photon therapy plans, i.e., to relate the optimization closer to the biological response of the respective organ as a whole leading to a superior sparing of the OARs in terms of final EUD_{RBE}. The presented EUE formalism is directly applicable to various treatment modalities and is considered a favorable alternative to the classical gEUD concept.

Moreover, we showed that an over- or underestimation of the dose–volume parameters during the optimization resulted only in minor deviations of the final EUD_{RBE}. Structure-based optimization may be considered a promising tool for carbon ion therapy treatment planning in the future—even in the presence of relatively large uncertainties in the used biological parameters.

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