Variance-based sensitivity analysis for uncertainties in proton therapy: A framework to assess the effect of simultaneous uncertainties in range, positioning, and RBE model predictions on RBE-weighted dose distributions

Jan Hofmaier
Department of Radiation Oncology, University Hospital, LMU Munich, Munich 81377, Germany

George Dedes
Department of Medical Physics, Faculty of Physics, LMU Munich, Garching b. Munich 85748, Germany

David J. Carlson
Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA 19104, USA

Katia Parodi
Department of Medical Physics, Faculty of Physics, LMU Munich, Garching b. Munich 85748, Germany

Claus Belka
Department of Radiation Oncology, University Hospital, LMU Munich, Munich 81377, Germany

German Cancer Consortium (DKTK), Munich 81377, Germany

Florian Kamp
Department of Radiation Oncology, University Hospital, LMU Munich, Munich 81377, Germany

(Received 12 August 2019; revised 20 October 2020; accepted for publication 11 November 2020; published 18 December 2020)

Purpose: Treatment plans in proton therapy are more sensitive to uncertainties than in conventional photon therapy. In addition to setup uncertainties, proton therapy is affected by uncertainties in proton range and relative biological effectiveness (RBE). While to date a constant RBE of 1.1 is commonly assumed, the actual RBE is known to increase toward the distal end of the spread-out Bragg peak. Several models for variable RBE predictions exist. We present a framework to evaluate the combined impact and interactions of setup, range, and RBE uncertainties in a comprehensive, variance-based sensitivity analysis (SA).

Material and methods: The variance-based SA requires a large number ($10^4$–$10^5$) of RBE-weighted dose (RWD) calculations. Based on a particle therapy extension of the research treatment planning system CERR we implemented a fast, graphics processing unit (GPU) accelerated pencil beam modeling of patient and range shifts. For RBE predictions, two biological models were included: The mechanistic repair-misrepair-fixation (RMF) model and the phenomenological Wedenberg model. All input parameters (patient position, proton range, RBE model parameters) are sampled simultaneously within their assumed probability distributions. Statistical formalisms rank the input parameters according to their influence on the overall uncertainty of RBE-weighted dose–volume histogram (RW-DVH) quantiles and the RWD in every voxel, resulting in relative, normalized sensitivity indices ($S = 0$: noninfluential input, $S = 1$: only influential input). Results are visualized as RW-DVHs with error bars and sensitivity maps.

Results and conclusions: The approach is demonstrated for two representative brain tumor cases and a prostate case. The full SA including $\sim 3 \times 10^4$ RWD calculations took 39, 11, and 55 min, respectively. Range uncertainty was an important contribution to overall uncertainty at the distal end of the target, while the relatively smaller uncertainty inside the target was governed by biological uncertainties. Consequently, the uncertainty of the RW-DVH quantile $D_{98}$ for the target was governed by range uncertainty while the uncertainty of the mean target dose was dominated by the biological parameters. The SA framework is a powerful and flexible tool to evaluate uncertainty in RWD distributions and DVH quantities, taking into account physical and RBE uncertainties and their interactions. The additional information might help to prioritize research efforts to reduce physical and RBE uncertainties and could also have implications for future approaches to biologically robust planning and optimization. © 2020 The Authors. Medical Physics published by Wiley Periodicals LLC on behalf of American Association of Physicists in Medicine. [https://doi.org/10.1002/mp.14596]

Key words: proton therapy, range uncertainty, relative biological effectiveness, sensitivity analysis, uncertainty analysis
1. INTRODUCTION

Treatment plans in proton therapy are more prone to uncertainties than in photon therapy. In addition to setup uncertainty, which is also relevant for treatment with photons, proton beams are affected by range uncertainties. Furthermore, the relative biological effectiveness (RBE) of proton beams needs to be taken into account and additional sources of uncertainty are introduced through the conversion of physical to RBE-weighted dose (RWD). Since uncertainties in the actually delivered RWD may give rise to unanticipated normal tissue toxicities or local treatment failure and may impede the intercomparability of different radiation modalities (photons, protons, heavier ions) in clinical studies, a well-founded understanding of the magnitude of the overall uncertainty and the impact and interactions of the different sources of uncertainty is crucial. To enable the comparison of different planning strategies (e.g., beam arrangements) with regard to these uncertainties,1–4 no method for the systematic assessment of the combined impact and interactions of setup, range, and biological uncertainties has been presented so far. When multiple sources of uncertainty are combined, the analysis is typically restricted to range and motion.8,9 A possible way to deal with these uncertainties in intensity-modulated proton therapy (IMPT) is robust optimization. Up to now, robustness approaches are also mostly restricted to setup and range uncertainties and do not explicitly consider biological modeling. If at all, linear energy transfer (LET) is considered as a surrogate of biological effect.10,11 Therefore, a better understanding of uncertainty in biological modeling in combination with setup and range uncertainties is needed to enable biologically robust planning. Furthermore, quantifying the relative impact of setup, range and RBE uncertainty on the overall uncertainty of clinically relevant dose metrics could help to prioritize research efforts aiming at reducing the individual uncertainties and improve cost-effectiveness in radiotherapy.

The technique of global, variance-based sensitivity analysis (SA) is a method to evaluate the influence of the uncertainty in various input factors on the output of a quantitative model.12 Compared to local methods, such as derivative-based approaches, regression analysis, or the isolated treatment of the different input factors (one factor at a time approaches), this technique has the advantage of exploring the entire input space by varying all input factors simultaneously, which allows to take into account also interactions between multiple input factors.13 While the alternative techniques mentioned have their limitations in the case of nonlinear models, global, variance-based SA is a model-independent approach and is applicable for any probability distribution of the input factors. In the field of medical physics, this technique has so far only been applied to RBE modeling of carbon ion therapy, excluding range and setup uncertainties and to nuclear medicine, in order to assess the impact of interpatient variability on organ dose estimates.16

In this feasibility study, we present a framework to apply the technique of global, variance-based SA to uncertainties in proton therapy, explicitly modeling RBE, range, and setup errors.

2. MATERIALS AND METHODS

2.A. Global variance-based sensitivity analysis

Global variance-based SA is a method to estimate the relative influence of the k input factors \( X = (x_1, x_2, \ldots, x_k) \) on the output \( Y \) of a model \( f \):

\[
Y = f(X) \tag{1}
\]

The function \( f \) can be decomposed into terms of increasing dimensionality whose mean is zero, that is:

\[
f = f_0 + \sum_{l=1}^{k} f_l(x_l) + \sum_{l=1}^{k} \sum_{m=l+1}^{k} f_{lm}(x_l, x_m) + \ldots + f_{1,2,\ldots,k}(x_1, x_2, \ldots, x_k) \tag{2}
\]

where for all \( p = 1, \ldots, s \)

\[
\int f_{1,2,\ldots,k}(x_1, \ldots, x_s) dx_p = 0 \tag{3}
\]

Sobol proved that then all summands in equation (2) are orthogonal.17 The variance in \( Y \) can be decomposed

\[
V(Y) = \sum_{l=1}^{k} V_l + \sum_{l=1}^{k} \sum_{m=l+1}^{k} V_{lm} + \ldots + V_{1,2,\ldots,k} \tag{4}
\]

where

\[
V_l = V(f_l) = V(E(Y|X_l)) \tag{5}
\]

The expectation value \( E(Y|X_l) \) is hereby calculated over all possible values of all input factors except for \( X_l \), which is kept fixed. The higher order terms are

\[
V_{lm} = V(f_{lm}) = V[E(Y|X_l, X_m)] - V_l - V_m \tag{6}
\]

and so on. The first- and second-order sensitivity indices introduced by Sobol’ are defined as:

\[
S_l = \frac{V_l}{V(Y)} \tag{7}
\]

\[
S_{lm} = \frac{V_{lm}}{V(Y)} \tag{8}
\]

Higher order terms are defined in an analogous fashion. Monte Carlo estimates for all sensitivity indices can be calculated without the need to know an explicit form of \( f \) or any of the terms in the expansion in Eq. (2). Due to the normalization to the overall variance, the Sobol’ indices are normalized to 1. Since the number of sensitivity indices is \((2^k - 1)\) for \( k \) input factors, making interpretation of the results very difficult, total effects \( ST_l \) are introduced.18 For the input factor \( l \) they are defined as the sum of all terms of any order containing \( l \):
\[ ST_l = S_l + \sum_{m \neq l}^k S_{lm} + \ldots + S_{1\ldots k} \]  

when only first order and total effects for each input factor are considered, the number of indices is reduced to \(2k\). First order and total effects allow for an intuitive interpretation: \(S_l\) is the average fraction by which the overall variance would be reduced if input factor \(l\) could be fixed anywhere in its range, \(ST_l\) is the average fraction of the overall variance that would remain if all input factors except for \(l\) could be fixed within their respective range. \(ST_l = 0\) is the necessary and sufficient condition for input \(l\) being noninfluential. By examining the difference, \((ST_l - S_l)\), the impact of interaction terms involving input factor \(l\) can be characterized. If \((ST_l - S_l) = 0\), interactions with input factor \(l\) do not contribute to overall variance.

Saltelli\(^{19}\) proposed an efficient method for direct Monte Carlo calculation of \(S_l\) and \(ST_l\), without the need to calculate all the interaction terms, which has also been used in this paper.

In this approach, \(S_l\) and \(ST_l\) are estimated via:

\[
S_l = \frac{1}{N} \sum_{m=1}^{N} \frac{f(B)^{m} - f(A)^{m}}{V(Y)}
\]

\[
ST_l = \frac{1}{N} \sum_{m=1}^{N} \left( f(A)^{m} - f(A^{(0)})^{m} \right)^2 / V(Y)
\]

where \(A\) and \(B\) are independently sampled input matrices of \(N\) input vectors (size: \(N \times k\)). The matrix \(A^{(0)}\) is equal to matrix \(A\), except for column \(l\), which is taken from \(B\). \((A)^{m}\) and \((B)^{m}\) are the \(m\)-th rows of \(A\) and \(B\), respectively. The total number of model evaluations in this approach is \(N \cdot (k + 2)\). \(N\) has to be chosen sufficiently large for Eqs. (10) and (11) to converge.

A faster convergence of Eqs. (10) and (11) is achieved when the input parameters are sampled from quasi-random, low-discrepancy sequences.\(^{19}\) In our implementation, we used the Sobol’ sequence\(^ {20,21}\) as suggested by Saltelli.

In our application of the concept, the model \(f\) will correspond to an RWD distribution calculation including a calculation of RBE-weighted dose volume histograms (RWD-DVHs), the input vector \(X\) will contain isocenter shifts in three spatial dimensions, relative and absolute range shifts as well as biological model parameters. The output \(Y\) will include the dose in every voxel and RWD-DVH quantiles for structures of interest. Since for the variance-based SA the model needs to be evaluated approximately \(10^3\)–\(10^5\) times, a fast RWD calculation for any set of \(X\) from the input space is required. To achieve this, a GPU-based RWD calculation was implemented based on a particle extension of the research treatment planning system CERR.\(^ {22-26}\) To model the physical uncertainties, the following approximations were made: The proton beams were assumed to be nondivergent, and patient deformations and rotations were excluded. Range uncertainty was modeled as a relative and an absolute range shift, which was applied to all spots of the same beam equally. A detailed description of the implementation can be found in Appendices A and B.

In clinical routine, a constant RBE of 1.1 is commonly assumed. However, there is evidence from in \(\textit{vitro}\) experiments that RBE is dependent on dose, biological endpoint, and proton energy and there is an ongoing debate if the current clinical practice needs to be revised.\(^ {27-29}\) For variable RBE prediction, two biological models are currently implemented: the mechanistic repair-misrepair-fixation (RMF) model,\(^ {29,30}\) which uses double strand break (DSB) yields from a Monte Carlo Damage simulation (MCDS)\(^ {31}\) and the phenomenological Wedenberg model.\(^ {32}\) Both models provide a method to calculate radiosensitivity parameters of the linear quadratic (LQ) model, \(\alpha\) and \(\beta\), and have the advantage that they can be executed very fast for changed model and x-ray reference radiosensitivity parameters. For the RMF model, the DSB yield \(\Sigma\) and the x-ray reference parameters \(\alpha_X/\beta_X\) were treated as uncertain; details on the implementation can be found in Appendix C.1. For the Wedenberg model, x-ray reference parameters \(\alpha_X/\beta_X\), the fit parameter \(q\) and the model assumption \(\beta_p = \beta_X\) were treated as uncertain. Details on the implementation can be found in Appendix C.2.

### 2.B. Application to patient cases

The framework was applied to two brain tumor patient cases. The evaluation of an additional prostate case can be found in the supplementary material S1. In both brain tumor cases the clinical target volume (CTV) was overlapping with the optic nerve and in close proximity to the brain stem. For patient 1, the CTV partially overlapped with the optic chiasm while for patient 2 the chiasm was almost completely within the CTV. The CTV of patient 1 had a larger volume with a size of 15.2 cm\(^3\), for patient 2 it was 4.7 cm\(^3\). Planning target volumes were created using an isotropic CTV-to-PTV margin of 3 mm. The plan for patient 1 consisted of two PBS beams from 60° and 135°, the plan for patient 2 of two opposing PBS beams from 90° and 270°. Both plans were optimized for a fraction RWD of 1.8 Gy (RBE), where a constant RBE of 1.1 was assumed. The total prescribed RWD was 54 Gy (RBE) in both cases. In the plan optimization, the total \(D_{3\%}\) for adjacent and overlapping OARs (chiasm, optic nerves, brain stem) was constrained to be smaller or equal to 54 Gy (RBE). In each plan, the two beams were optimized independently to deliver a homogeneous dose distribution to the target (single field uniform dose (SFUD) concept). Sensitivity analyses of the resulting plans were performed using the RMF and the Wedenberg model. All input parameter uncertainties were assumed to follow normal distributions truncated to two standard deviations (\(\sigma\)). The following \(\sigma\) were used:

- 1 mm for patient shifts in \(X\), \(Y\), and \(Z\) direction\(^ {33}\)
- 3% for relative range uncertainty\(^ {1}(R_{rel})\)
- 1 mm absolute range uncertainty\(^ {1}(R_{1\text{abs}}, R_{2\text{abs}}\text{ for beam numbers }1,2,\ldots)\)
10% for the x-ray reference radiosensitivity parameters (\(\alpha_X/\beta_X\))
15% for the parameter \(q\) of the Wedenberg model
10% for \(\beta_p\) in the Wedenberg model
5% for the DSB yield \(\Sigma\) used in the RMF model

These assumptions are not definitive and might differ between tumor sites (e.g., in the abdomen a larger setup error than 1 mm might be adequate) or CT acquisition (e.g., in case a dual-energy CT is used for stopping power determination a smaller relative range uncertainty might be reasonable). To model a possible higher uncertainty in the x-ray reference sensitivity parameters in organs at risk (e.g., the chiasm), an additional calculation was performed where \(\alpha_X/\beta_X\) was assumed to be uniformly distributed over the interval 1.5 to 10 Gy. All other input uncertainties remained unchanged. For the CTV and the chiasm, the overall uncertainty of all RW-DVH quantities was visualized by plotting the RW-DVH with its respective 95% and 68% confidence intervals. For selected quantities of (CTV \(D_{98\%}\), CTV \(D_{95\%}\), brain stem \(D_{2\%}\), optic nerve \(D_{2\%}\), and chiasm \(D_{2\%}\)), first order and total effect sensitivity indices were calculated. Additionally, the first-order sensitivity for the RBE-weighted dose was calculated on a voxelwise basis and visualized as sensitivity map.

To demonstrate the application of the framework to a prostate case, an additional evaluation of such a plan can be found in supplementary material S1.

3. RESULTS

A fast modeling of patient shifts, range shifts and changes in biological parameters was implemented which allows the calculation of RWD distributions for arbitrary sets of these input parameters from the input space. The simultaneous variation of all input parameters allows to model interactions of different sources of uncertainty and to perform a global, variance-based SA. Here the results for the two brain tumor cases are shown, the results for the prostate case can be found in the supplementary material S1.

On a computer with 16 CPU cores (Intel Xeon E5-2690 @ 2.90 GHz), 192 GB RAM and two Nvidia Tesla K80 GPUs the full SA including \(\sim 3 \times 10^4\) RWD calculations was performed in 39 min for patient 1 and 11 min for patient 2.

Figure 1 shows the convergence of the first-order indices and total effects for selected DVH quantities, a representative voxel at the center of the PTV and a representative voxel in the high LET region for patient 1. \(N\) refers to the number of rows of the input matrices used for the Saltelli estimator for \(S_i\) and \(ST_i\) described above, the actual number of RWD calculations performed is \(N \cdot (k + 2)\), with the number of input factors \(k\).

3.2. DVH quantities

Figures 2 and 3 show the RW-DVH of the CTV and the chiasm for patients 1 and 2, respectively. The proton treatment plan was optimized on 1.8 Gy(RBE) in tumor assuming a constant RBE of 1.1. Then the SA was performed with both biological models assuming a spatially constant \(\alpha_X/\beta_X = 2\) Gy (\(\alpha_X = 0.1\) Gy \(^{-1}\) and \(\beta_X = 0.05\) Gy \(^{-2}\)). For each model, the treatment plans were recalculated \(\sim 3 \times 10^4\) times, randomly varying patient position, proton range and RBE model parameters within their assumed uncertainties. To quantify the overall uncertainty, 95% and 68% confidence intervals were calculated empirically from the resulting RW-DVHs and visualized in Figs. 2 and 3. As expected, a higher RBE than 1.1 is predicted for both biological models. The same calculation was in addition also applied to an RWD calculation assuming a constant RBE of 1.1, including only range and setup uncertainties. The resulting RW-DVH is plotted for comparison. For both patients, a larger overall uncertainty was observed for the variable RBE models with their respective uncertainties included. For example, the expectation value for the mean RWD to the CTV for patient 1 was 2.04\(\pm 0.10\) Gy(RBE), 2.03\(\pm 0.14\) Gy(RBE) and 1.77\(\pm 0.04\) Gy (RBE) for the RMF model, the Wedenberg model and a constant RBE of 1.1, respectively (the reported ranges are the 95% confidence intervals.). For patient 2, the mean RWD to the CTV was 2.01\(\pm 0.22\) Gy(RBE), 2.00\(\pm 0.16\) Gy(RBE) and 1.75\(\pm 0.14\) Gy(RBE) for the RMF model, the Wedenberg model and a constant RBE of 1.1, respectively. For the chiasm, the D\(_2\) for patient 1 was 2.23\(\pm 0.23\) Gy(RBE) and 2.17\(\pm 0.18\) Gy(RBE) for the RMF model and the Wedenberg model, respectively, when an \(\alpha_X/\beta_X = 2\) Gy with a standard deviation of 10% was assumed. In the calculation with the large \(\alpha_X/\beta_X\) variation it was 2.09\(\pm 0.28\) Gy(RBE) (RMF) and 1.98\(\pm 0.26\) Gy(RBE) (Wedenberg). For patient 2, a chiasm D\(_2\) of 2.12\(\pm 0.25\) Gy(RBE) and 2.09\(\pm 0.17\) Gy(RBE) was observed for RMF and Wedenberg, respectively, when an \(\alpha_X/\beta_X = 2\) Gy with a standard deviation of 10% was assumed. 2.01\(\pm 0.26\) Gy(RBE) (RMF) and 1.93\(\pm 0.24\) Gy(RBE) (Wedenberg) was found for the D\(_2\) in the calculation with the large \(\alpha_X/\beta_X\) variation.

For selected clinically relevant RW-DVH quantiles, the confidence intervals in Figs. 2 and 3 are broken down to the impact of the different uncertainties in terms of \(S_i\) and \(ST_i\) in Fig. 4. All plots show results of the calculation with \(\alpha_X/\beta_X = 2\) Gy and a standard deviation of 10%. SA results are color-coded for both patients and both RBE models. For most quantiles, the differences between the \(S_i\) and \(ST_i\) are small, indicating a low impact of interaction terms on the overall uncertainty. For range uncertainty, however, interactions often do play a role. For example, for the D\(_2\) of the right optic nerve for patient 2 [Figs. 4(c) and 4(d)] \(ST_i\) is considerably larger than \(S_i\) both for the relative range uncertainty (\(R_{\text{rel}}\)) for both biological models (\(ST_{\text{rel}} = 0.56, S_{\text{rel}} = 0.26\) for the RMF model and \(ST_{\text{rel}} = 0.54, S_{\text{rel}} = 0.28\) for the Wedenberg model, respectively) and for shifts in Y and Z direction (\(ST_Y = 0.03, S_Y = 0.18, ST_Z = 0.25, S_Z = 0.45\) for the RMF model and \(ST_Y = 0.07, S_Y = 0.20, ST_Z = 0.26, S_Z = 0.44\) for the Wedenberg model, respectively). This suggests that, in this plan, a relevant fraction of the overall D\(_2\) uncertainty for the right optic nerve is attributable to interaction between setup and range uncertainty. Biological
uncertainty generally was driven by $DSB\Sigma$ for the RMF model and by $q$ and $\beta_p$ for the Wedenberg model and the most important contribution to the CTV $D_{50}(e.g.,$ for patient 2: $S_{DSB\Sigma} = 0.75, ST_{DSB\Sigma} = 0.77$ for the RMF model and $S_q = 0.42, S_{\beta_p} = 0.23, ST_q = 0.43, ST_{\beta_p} = 0.23$ for the Wedenberg model, respectively). In both models, the relative impact of the x-ray reference parameters $\alpha_X = \beta_X$ was very low in comparison (e.g., for the CTV $D_{50}$ for patient 2: $S_{(\alpha/\beta)_X} < 0.01, ST_{(\alpha/\beta)_X} < 0.01$ for the RMF model and $S_{(\alpha/\beta)_X} = 0.02, ST_{(\alpha/\beta)_X} = 0.02$ the Wedenberg model, respectively). Biological uncertainty was also the most important contribution to the chiasm $D_2$ for patient 1 ($S_{DSB\Sigma} = 0.78$ for the RMF model and $S_q = 0.41$ and $S_{\beta_p} = 0.14$ for the Wedenberg model). The relative range uncertainty $R_{rel}$ was an important input factor for many investigated DHV quantiles with the exception of the $D_{50}$ of the CTV and the $D_2$ of the brain stem for patient two, which due to its position lateral to the two opposing beams from $90^\circ$ and $270^\circ$ was not affected by range shifts. For this parameter, the most relevant contribution to overall uncertainty is observable for a patient shift in $Y$ direction ($S_Y = 0.71$ for the RMF model and $S_Y = 0.69$ for the Wedenberg model, respectively).

3.B. Voxelwise SA

The result of the voxel-based SA assuming $\alpha_X/\beta_X = 2$ Gy with a standard deviation of 10 % for patient 1 is shown in Fig. 5 for the RMF model and in Fig. 6 for the Wedenberg model. Nominal RWD distribution, the local standard deviation as a measure of local uncertainty and the dose-weighted LET distribution are shown in the first row. SA maps report the contribution of the input uncertainties to the local variance for every voxel, indicating the spatial changes of the impact of different uncertainties. The largest uncertainties are observed at the distal end of the beams, were they are governed by $R_{rel}$. The impact of the absolute range uncertainties $R_{1\text{abs}}$ and $R_{2\text{abs}}$ is small in comparison, as well as the uncertainty in the x-ray reference parameters $\alpha_X/\beta_X$. In the CTV and in the entrance plateaus, the biological input factors $\beta_p$ for the Wedenberg and $DSB\Sigma$ for the RMF model are the most important contributions, where the overall uncertainty is generally lower than at the distal ends of the beams.

4. DISCUSSION

The presented framework is, to the best of our knowledge, the first implementation of a tool for variance-based sensitivity analysis of the combined impact of setup, range and RBE uncertainties in proton therapy, including also their interactions. Additionally to the numerical calculation of confidence intervals for the RBE-weighted dose in every voxel and RW-DVH quantiles, it allows to break down the overall uncertainty to the impact of the different sources of uncertainty. This complimentary sensitivity information has not yet been reported or used in proton therapy. The computation times were below 40 min which is extremely fast given the recalculation of $\sim 3 \times 10^4$
treatment plans per SA execution for patient 1. For patient 2, which has a considerably smaller CTV the simulation time was even shorter. This was expected, since both the number of treated voxels (due to the restriction to the 2 cm expansion of the target volume) and the number of PBS spots increase with the target volume and therefore the number of entries in the $ij$-matrices increase. The quick convergence of the sensitivity indices suggests that actually a much smaller number of about $N = 500$ would already be sufficient. Since the calculation time scales linearly with the number of dose calculations, this would mean a reduction by 80%, to well below 10 minutes for patient 1 and to less than 2 and a half minutes for patient 2. The SA was performed for RW-DVH quantiles and the RWD in every voxel of interest. Further plan quality metrics based on the RWD distribution such as equivalent uniform dose, homogeneity index, conformity index, tumor control, and normal-tissue complication probabilities and others could be included at very little extra computational cost. An alternative approach to modeling uncertainties was proposed by Bangert et al., who introduced analytical probabilistic modeling (APM), a technique to propagate setup and range uncertainties through a pencil beam dose calculation via analytical integration to calculate expectation values and variances for dose distribution and other plan quality indicators. Wieser et al. used APM to investigate the influence of setup and range uncertainties on RWD distributions, however, uncertainties in the biological modeling itself were not considered in their work. Note that both works do not include the possibility to determine sensitivity values. Perkó et al. used an alternative approach to sensitivity analysis using polynomial chaos expansion, but also did not consider uncertainties in RBE modeling.

4.A. Potential applications

The current performance of the SA framework is sufficient to be forward calculated for the clinical evaluation of proton treatment plans. In such a setting, the additional uncertainty and sensitivity information could support the decision for or against a treatment plan and help to find the optimal compromise. Forward calculation of the SA could also be used in planning studies for the systematic assessment of the impact of setup, range, and RBE uncertainty on clinically relevant dosimetric parameters in proton therapy. The information which type of uncertainty is dominating the overall uncertainty could help to prioritize research attempts to reduce the uncertainties. In this regard, higher cost effectiveness could be achieved by concentrating on the dominant contributions.
FIG. 3. RW-DVHs for the CTV and the chiasm for a plan optimized for a constant RBE of 1.1 for patient 2. The uncertainty analysis was performed by recalculating the dose using the RMF (a and d) and the Wedenberg model (b and e) including range, setup, and RBE uncertainty. Panels (c) and (f) show the RW-DVHs for a constant RBE of 1.1 including only range and setup uncertainty. Panels (g) and (h) show the variation of the RW-DVH of the chiasm including range, setup, and RBE uncertainty when $\alpha_X/\beta_X$ is varied over the larger interval from 1.5 to 10 Gy for comparison. 68% and 95% confidence intervals of the RW-DVHs are visualized by the shaded areas. “Nominal” refers to a forward calculation in the respective model with all input factors fixed to their nominal value. The solid line shows the expectation value of the DVH. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. First-order sensitivities and total effects for selected DVH quantiles of the CTV, brain stem, the optic nerves, and the chiasm for both patients and both RBE models in the calculation with $\alpha_X/\beta_X = 2$ Gy with a standard deviation of 10%. The empirical standard deviations of the respective quantile are also reported. [Color figure can be viewed at wileyonlinelibrary.com]
to overall uncertainty. Another possible application of the SA framework could be the systematic comparison of proton treatment plans to evaluate, for example, different robust planning concepts.\textsuperscript{10,11} This would allow to determine the residual uncertainty of RW-DVH quantiles of interest for these plans and analyze the sources of this uncertainty using the sensitivity indices.

4.B. Limitations

Current limitations of our SA framework include the restriction to rigid patient shifts, excluding rotations. Deformations are not explicitly modeled, either, although some nonrigid changes (such as weight loss and filling of air cavities with fluid) are modeled by the employed heuristic model.
of absolute range uncertainties. However, considerable deformations of the patients’ anatomy cannot be modeled. Furthermore, the method does not yet cover all possible types of uncertainties. Additional uncertainties exist in radiotherapy planning and delivery, which are not included in our approach, for example, inter- and intraobserver delineation variability. In this work, a pencil beam algorithm based on precalculated Geant4 simulated data in water was used. Although Monte Carlo algorithms are known to be more accurate than pencil beam algorithms, the necessary high number of RWD calculations cannot be achieved with a Monte Carlo algorithm in reasonable time. The accuracy of pencil beam algorithms is known to decrease in regions with high tissue heterogeneity, therefore, results obtained with the
SA framework using the current pencil beam algorithm will be less reliable in such cases.

Having a good assumption of the underlying uncertainties in the input factors is crucial for the execution of the SA. Unfortunately, these uncertainties can be difficult to estimate, in particular for the biological parameters. For example, a 95% confidence interval of about ±18% was reported for $q$ as a fit parameter over various in-vitro experiments, which corresponds to standard deviation of 9% for normal distributed data. To account for additional uncertainties related to the transfer from in-vitro data to the clinic, a standard deviation of 15% was assumed for $q$. The 5% standard deviation for DSB $\Sigma$ in the RMF model was based on reasoning about the underlying Monte Carlo simulation of DSB induction. However, these should be considered rather rough estimates of the actual uncertainty. Therefore, we did not aim at comparing the RBE prediction uncertainties of the two models. The objective is to show the flexibility of the approach with regard to the used biological model. It should also be kept in mind that the variance-based SA gives information about the variability, that is, the precision of the output, but does not give any information about the accuracy of a model. This means, for instance, that a higher robustness of an RBE model against uncertainties in its input parameters does not imply a higher accuracy.

In our analysis, the impact of the x-ray reference parameter $\alpha_X/\beta_X$ on the overall RWD variability was low compared to the other biological parameters when the RWD of a single fraction was calculated, even when $\alpha_X/\beta_X$ was varied over the large interval from 1.5 to 10 Gy. This means that the used RBE models are rather robust against $\alpha_X/\beta_X$ variability. It should be stressed, however, that this does not include fractionation effects.

### 4.C. Outlook

In this first analysis we applied the SA framework to proton therapy. The application to other charged particle types, such as helium or carbon ions could be achieved in the same way. Given that for these heavier ions the RBE is generally expected to be higher than for protons, a systematic assessment of uncertainty might be even more important in these cases.

Given the present performance of our SA framework, also future applications in robust plan optimization itself are imaginable if the execution of the variance-based SA can be further accelerated. While the framework is currently limited to the forward evaluation of proton treatment plans since the code still takes too long to be executed during optimization (for our patient cases from a few minutes to more than half an hour), the quick convergence of the sensitivity indices suggests that a considerable reduction of the number of model evaluations is feasible. In addition, the sensitivity analysis could be restricted to regions of interest with respect to plan robustness. The use of multiple, high-end GPUs with more memory for this highly parallelizable code is also expected to significantly improve the performance. All this might accelerate the estimation of the sensitivity indices to a point where they can be evaluated during optimization. To date, most robust optimization approaches do not include RBE variability. If at all, RBE is only considered indirectly using LET as a surrogate. While it is in theory possible to fully compensate for setup and range uncertainty (although at the cost of additional dose to normal tissue), this is not the case for RBE uncertainty. Although RBE uncertainty can be reduced by avoiding excessive LET hot spots, it cannot be fully eliminated by shaping the physical dose distribution. Explicit inclusion of RBE uncertainty would therefore lead to an inevitably larger overall uncertainty, rendering current robust optimization approaches insufficient.

The complimentary sensitivity information has the potential to overcome these limitations since it allows introducing additional SA-based cost functions into the optimization. For example, one could use SA-based cost functions ensuring, for example, $ST_{X,Z}(D_{95\%\_CTV})<5\%$ and $ST_{R_{rel\_D}}(D_{95\%\_CTV})<5\%$ while allowing for larger sensitivity values in the biological inputs. By using the total effects also interactions between physical and RBE uncertainties are taken into account. Once the necessary performance for the execution of the variance-based SA during inverse planning is achieved, this will allow a systematic approach to physically and biologically robust IMPT planning. The consecutive step should then be followed by an evaluation of clinically relevant scenarios with focus on achievable improvements in proton therapy planning.

### 5. CONCLUSIONS

A framework for global, variance-based sensitivity analysis of proton therapy treatment plans has been implemented and demonstrated for two different variable RBE models. It is a powerful and flexible tool to assess the combined impact and interactions of positioning, range, and RBE uncertainties. Besides resulting overall uncertainties, the method provides quantitative information on the relative impact of the different input factors, which might have implications for future biologically robust IMPT planning.

### ACKNOWLEDGMENT

This project was supported by the DFG grant KA 4346/1-1 and the DFG Cluster of Excellence Munich Center for Advanced Photonics (MAP). Open access funding enabled and organized by ProjektDEAL.

### CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

### APPENDIX A

The following paragraphs describe how the individual sources of uncertainty are modeled.
A. MODELING OF PATIENT TRANSFORMATIONS

In the particle extension of CERR, the dose calculation is performed as follows:

$$D_{ij} = PD_E \cdot \frac{1}{2\pi \cdot \sigma_E^2} \cdot \exp \left( -\frac{r_{ij}^2}{2 \cdot \sigma_E^2} \right) \cdot RD_{ij}$$

where $PD_E$ and $\sigma_E^2$ are precalculated look-up tables for the depth-dose-curve and the lateral dose spread in water for incident proton energy $E_i$ in water, $RD_{ij}$ denotes the radiological depth on the central beam axis of the $j$-th spot at the depth of the $i$-th voxel, and $r_{ij}$ is the distance of the $i$-th voxel to the central beam axis of the $j$-th spot. The lookup tables $PD_E$ and $\sigma_E^2$ were precalculated in water using the Monte Carlo algorithm Geant4 for all relevant incident energies (50 to 260 MeV in steps of 1 MeV) assuming generic, mono-energetic beams.

Once the $D_{ij}$ matrix is obtained, the dose in the $i$-th voxel can be calculated as:

$$d_i = \sum_j D_{ij} \omega_j$$

With a vector containing the pencil beam scanning (PBS) spot weights $\omega_j$. Therefore, the full dose vector can be obtained by a matrix-vector multiplication. In the particle extension of CERR, this is used for treatment plan optimization: Eq. (A2) is evaluated repeatedly to find the optimal weight vector. Throughout the entire optimization, $D_{ij}$, which contains all geometric information, is kept constant.

In order to recalculate treatment plans for a changed geometry, a fast way to generate the changed influence matrix is required. To achieve this, the following approximations are made: First, nondivergent beams are assumed, which is equivalent to assuming that the source is far away from the patient. The second approximation is that no patient deformations occur and the third that only rigid translations (isocenter shifts) are modeled, excluding rotations.

Then, $r_{ij}$ and $RD_{ij}$ in Eq. (A1) have to be replaced in order to reflect a patient shift. When $r_{ij}$ is expressed in a two-dimensional Cartesian coordinate with axes perpendicular to the beam (i.e., a beams-eye-view (BEV) coordinate system):

$$r_{ij}^2 = x_{ij}^2 + y_{ij}^2$$

The changes to the lateral offsets $x_{ij}$ and $y_{ij}$ caused by a rigid patient shift are then, in the approximation of nondivergent beams, the projection of the shift onto these axes:

$$x_{ij} = x_{ij} + \Delta x(\phi_n)$$

$$y_{ij} = y_{ij} + \Delta y(\phi_n)$$

where $x_{ij}'$ and $y_{ij}'$ denote the updated lateral offsets, which, for a given patient shift and in the approximation of nondivergent beams, only depend on the gantry angle $\phi_n$ of the beam $n$, making the computation very efficient for large $ij$-matrices.
C.1. RMF model

The repair-misrepair-fixation (RMF) model was introduced by Carlson et al.29 In our implementation, it uses estimates from a Monte Carlo damage simulation (MCDS)31 to link \( \alpha_p \) and \( \beta_p \) to double strand break (DSB) yields.30 For a given particle type and energy, these are calculated as:

\[
\alpha_p = \frac{\Sigma}{\Sigma} \left[ \alpha_x + 2 \beta_x \left( \sum \bar{z}_f - \sum \bar{z}_{FX} \right) \right] \quad (A7)
\]

\[
\sqrt{\beta_p} = \sqrt{\beta_x} \cdot \frac{\Sigma}{\Sigma} \quad (A8)
\]

where \( \alpha_x \) and \( \beta_x \) are the reference x-ray reference radiosensitivity parameters, \( \Sigma \) and \( \Sigma_X \) are the DSB yields for the particle (defined as the initial number of DSB per Gray per giga base pair Gy\(^{-1}\)Gbp\(^{-1}\)) and reference radiation of a Co-60 source, respectively; and \( \bar{z}_f \) and \( \bar{z}_{FX} \) denote the frequency-mean specific energy. The default RMF model settings were used for the predictions. The model does not require any fit to experimental data. The MCDS software version 3.10A with default settings (cell model does not require any fit to experimental data. The RMF model settings were used for the predictions. The model does not require any fit to experimental data. The MCDS software version 3.10A with default settings (cell nucleus diameter 5 \( \mu \)m) was used to calculate DSB yields and the frequency-mean specific energy for all relevant proton energies. The DSB yields and frequency-mean specific energy were used as inputs for the RMF model as previously demonstrated by Carlson et al.,29 Frese et al.30 and Kamp et al.25

A rapid implementation25,26 of this model in the \( ij \)-formalism for carbon ions has already been used for a variance-based SA of biological uncertainties by Kamp et al.15 and for RWD optimization by Guan et al.40. We use a similar approach. To obtain \( \alpha_{p,ij} \) and \( \beta_{p,ij} \) (the radiosensitivity parameters for the dose contribution of the \( j \)-th voxel to the \( i \)-th voxel), Eqs. (A7) and (A8) need to be integrated against the fluence spectrum \( \Phi_j \) and the stopping power \( SP(E) \), which are both a function of the particle energy \( E \). By simulating the fluence spectra using Geant4 as described above, precalculated, tabulated data for the resulting integrals can be obtained.

Integration of Eqs. (A7) and (A8) against the fluence spectrum \( \Phi_j \) and the stopping power \( SP(E) \) yields:

\[
\alpha_{p,ij} = \alpha_{ij} \frac{\int_0^\infty \Phi_j(E) \cdot SP(E) \, dE}{\int_0^\infty \Phi_j(E) \cdot SP(E) \, dE} + \int_0^\infty 2 \beta_{X,ij} \cdot \sum \Phi_j(E) \cdot SP(E) \, dE - \int_0^\infty 2 \beta_{X,ij} \cdot \sum \bar{z}_{FX} \cdot \Phi_j(E) \cdot SP(E) \, dE \quad (A9)
\]

\[
\sqrt{\beta_{p,ij}} = \sqrt{\beta_{X,ij}} \cdot \frac{\int_0^\infty \Phi_j(E) \cdot SP(E) \, dE}{\int_0^\infty \Phi_j(E) \cdot SP(E) \, dE} \quad (A10)
\]

By introducing precalculated constants for the integrals:

\[
\frac{\int_0^\infty \Phi_j(E) \cdot SP(E) \, dE}{\int_0^\infty \Phi_j(E) \cdot SP(E) \, dE} = C_{1,ij} \quad (A11)
\]

\[
\frac{\int_0^\infty 2 \cdot \Phi_j(E) \cdot \Phi_j(E) \cdot SP(E) \, dE}{\int_0^\infty \Phi_j(E) \cdot SP(E) \, dE} = C_{2,ij} \quad (A12)
\]

equations (A9) and (A10) can be written as:

\[
\alpha_{p,ij} = \alpha_{X,ij} \cdot C_{1,ij} + \beta_{X,ij} \cdot C_{2,ij} - 2 \beta_{X,ij} \cdot \bar{z}_{FX} \cdot C_{1,ij} = \left( \alpha_{X,ij} - 2 \beta_{X,ij} \cdot \bar{z}_{FX} \right) \cdot C_{1,ij} \cdot \beta_{X,ij} \cdot C_{2,ij} \quad (A13)
\]

\[
\sqrt{\beta_{p,ij}} = \sqrt{\beta_{X,ij}} \cdot C_{1,ij} \quad (A14)
\]

This reparametrization is very closely related to the one used by Kamp et al.,26 who used the two reparametrization constants \( C_{1,ij} \) and \( C_{2,ij} \). While in our case \( C_{1,ij} \) is defined in exactly the same way, note that our \( C_{2,ij} \) is related to \( C_{2,ij} \) via:

\[
C_{2,ij} = C_{2,ij} - 2 \cdot \bar{z}_{FX} \cdot C_{1,ij} \quad (A15)
\]

The precalculated tables \( C_1 \) and \( C_2^* \) are referenced with the radiological depth and the corresponding incident proton energy to obtain \( C_{1,ij} \) and \( C_{2,ij}^* \):

\[
C_{1,ij} = C_{1,E_j}(RD_{ij}) \quad (A16)
\]

\[
C_{2,ij}^* = C_{2,E_j}(RD_{ij}) \quad (A17)
\]

To model biological uncertainty in the RMF model, we will treat \( \Sigma \) as uncertain and apply a relative variation \( \frac{\Delta \Sigma}{\Sigma} \). Under the assumption, that this variation is independent of the energy, \( C_{1,ij} \) depends linearly on \( \frac{\Delta \Sigma}{\Sigma} \). For \( C_{2,ij}^* \), there is a quadratic dependence. Therefore, Eqs. (A13) and (A14) become:

\[
\alpha_{p,ij} \left( \frac{\Delta \Sigma}{\Sigma} \right) = \left( \alpha_{X,ij} - 2 \beta_{X,ij} \cdot \bar{z}_{FX} \right) \cdot C_{1,ij} \cdot \left( 1 + \frac{\Delta \Sigma}{\Sigma} \right) + \beta_{X,ij} \cdot C_{2,ij} \cdot \left( 1 + \frac{\Delta \Sigma}{\Sigma} \right)^2 \quad (A18)
\]

\[
\sqrt{\beta_{p,ij}} \cdot \left( \frac{\Delta \Sigma}{\Sigma} \right) = \sqrt{\beta_{X,ij}} \cdot C_{1,ij} \cdot \left( 1 + \frac{\Delta \Sigma}{\Sigma} \right) \quad (A19)
\]

C.2. Wedenigen model

In the Wedenigen model,32 \( \alpha_p \) is assumed to depend on the x-ray reference radiosensitivity parameter and increase linearly with the linear energy transfer (LET):

\[
\frac{\alpha_{p,ij}}{\alpha_{ij}} = 1 + q \cdot \frac{LET_{ij}}{LET_{ij}} \quad (A20)
\]

where \( q = 0.434 \text{ Gy}^{-1} \text{ mm}^{-1} \) is obtained from a fit to in-vitro cell survival data and \( LET_{ij} \) is the LET contribution of the \( j \)-th PBS spot to the \( i \)-th voxel. It is obtained by referencing precalculated depth-LET tables for the incident proton energies \( E_j \) with the radiological depth \( RD_{ij} \).
\[
LET_{ij} = LET_{E_i}(RD_{iq}) \tag{A21}
\]

where \(LET_{E_i}\) contains MC calculated data for the dose-weighted LET in water simulated using Geant4 as described above. \(\beta_p\) is assumed to be equal to the reference value:

\[
\frac{\beta_{p,ij}}{\beta_{X,ij}} = 1 \tag{A22}
\]

To include uncertainty in this model, both \(q\) and \(\beta_{p,ij}\) were treated as uncertain:

\[
q' = q \left(1 + \frac{\Delta q}{q}\right) \tag{A23}
\]

\[
\beta_{p,ij}' = \beta_{p,ij} \left(1 + \frac{\Delta \beta_p}{\beta_{p,ij}}\right) \tag{A24}
\]

For both RBE models, \(\alpha_{i,j}\) and \(\sqrt{\beta_{p,ij}}\) for the \(i\)-th voxel can then be calculated as dose-weighted sums in the \(ij\)-formalism\(^1\):

\[
\alpha_{p,j} = \frac{1}{d_{ij}} \sum \alpha_{p,ij} \cdot D_{ij} \cdot \omega_j \tag{A25}
\]

\[
\sqrt{\beta_{p,j}} = \frac{1}{d_{ij}} \sum \sqrt{\beta_{p,ij}} \cdot D_{ij} \cdot \omega_j \tag{A26}
\]

Then, the RBE is calculated using the formula:

\[
RBE_i(\alpha_{x,i}, \beta_{X,i}, \alpha_{p,i}, \beta_{p,i}, d) = \frac{-\alpha_{x,i} + \sqrt{\alpha_{x,i}^2 + 4\beta_{X,i} \cdot (\alpha_{p,i} + \beta_{p,i} \cdot d)}}{2\beta_{X,i} \cdot d} \tag{A27}
\]

\(RBE_i(\alpha_{x,i}, \beta_{X,i}, \alpha_{p,i}, \beta_{p,i}, d)\) reduces to \(RBE_i(\alpha_{x,i}/\beta_{X,i}, q, d)\) for the Wedenig model and to \(RBE_i(\alpha_{x,i}/\beta_{X,i}, \text{LET}_{i, q}, d)\) for the RMF model, therefore the uncertainty in the x-ray reference parameters can be treated by varying one parameter, the fraction \(\alpha_{X,i}/\beta_{X,i}\).

A convenient property of the \(ij\)-formalism is that the RWD calculation can be restricted to arbitrary subgroups regions of interest to reduce memory usage. In our calculations we typically restricted the RWD calculation to a 2 cm expansion of the CTV and all OARs for whom the DVH quantities were included in the SA (optic nerves, chiasm, brain stem).

\(^{1}\)Author to whom correspondence should be addressed. Electronic mail: jan.hofmaier@med.uni-muenchen.de; Telephone: 00498944007644.

REFERENCES

1. Paganielli H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol. 2012;57:R99–R117.

2. Schuennann J, Dowdell S, Grassberger C, Min CH, Paganielli H. Site-specific range uncertainties caused by dose calculation algorithms for proton therapy. Phys Med Biol. 2014;59:4007–4031.

3. Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 1: the potential effects of calculated uncertainties. Phys Med Biol. 2008;53:1027–1042.

4. Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fracture and interfraction motions. Phys Med Biol. 2008;53:1043–1056.

5. Paganielli H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. Phys Med Biol. 2014;59:R419–R472.

6. Mohan R, Feeler CR, Guan F, Bronk L, Cao W, Grosshans DR. Radiobiological issues in proton therapy. Acta Oncol (Madr). 2017;56:1367–1373.

7. Paganielli H. Proton relative biological effectiveness-uncertainties and opportunities. Int J Part Ther. 2018;5:2–14.

8. Bangert M, Hennig P, Oelke U. Analytical probabilistic modeling for radiation therapy treatment planning. Phys Med Biol. 2013;58:5401–5419.

9. Perkó Z, van der Voort SR, van de Water S, Hartman CMH, Hoogeman M, Lathouwers D. Fast and accurate sensitivity analysis of IMPT treatment plans using Polynomial Chaos Expansion. Med Phys Biol. 2016;61:4646–4664.

10. Unkelbach J, Alber M, Bangert M, et al. Robust radiotherapy planning. Phys Med Biol. 2018;63:22TR02.

11. Unkelbach J, Paganielli H. Robust proton treatment planning: physical and biological optimization. Semin Radiat Oncol. 2018;28:88–96.

12. Sobol IM. Global sensitivity indices for nonlinear mathematical models and their Monte Carlo estimates. Math Comput Simul. 2001;55:271–280.

13. Borgonovo E, Plischke E. Sensitivity analysis: a review of recent advances. Eur J Oper Res. 2016;248:869–887.

14. Kamp F, Brüningk S, Cabal G, Mairani A, Parodi K, Wilkens JJ. Variance-based sensitivity analysis of biological uncertainties in carbon ion therapy. Phys Medica. 2014;30:583–587.

15. Kamp F, Wilkens JJ. Application of variance-based uncertainty and sensitivity analysis to biological modeling in carbon ion treatment plans. Med Phys. 2019;46:437–447.

16. Zvereva A, Kamp F, Schlattli H, Zankl M, Parodi K. Impact of interpatient variability on organ dose estimates according to MIRD schema: uncertainty and variance-based sensitivity analysis. Med Phys. 2018;45:3391–3403.

17. Sobol IM. Sensitivity estimates for nonlinear mathematical models. Model Comput Exp. 1993;1:407–414.

18. Homma T, Saltelli A. Importance measures in global sensitivity analysis of nonlinear models. Reliab Eng Syst Saf. 1996;52:1–17.

19. Saltelli A, Annoni P, Azzini I, Campolongo F, Ratto M, Tarantola S. Variance based sensitivity analysis of model output. Design and estimator for the total sensitivity index. Comput Phys Commun. 2010;181:295–270.

20. Sobol IM. On the distribution of points in a cube and the approximate evaluation of integrals. USSR Comput Math Math Phys. 1967;7:86–112.

21. Sobol I, Turchaninov V, Levitan Y, Shukhman B. Quasi-random sequence generators. Ipm zak; 1992:30.

22. Deasy JO, Blanco AI, Clark VH. CERR: a computational environment for radiotherapy research. Med Phys. 2003;30:979–985.

23. Schell S, Wilkens JJ. Advanced treatment planning methods for efficient radiation therapy with laser accelerated proton and ion beams. Med Phys. 2010;37:5330–5340.

24. Brüningk SC, Kamp F, Wilkens JJ. EUD-based biological optimization for carbon ion therapy. Med Phys. 2015;42:6248–6257.

25. Kamp F, Cabal G, Mairani A, Parodi K, Wilkens JJ, Carlson DJ. Fast biological modeling for voxel-based heavy ion treatment planning using the mechanistic repair-misrepair-fixation model and nuclear fragment spectra. Int J Radiat Oncol Biol Phys. 2015;93:557–568.

26. Kamp F, Carlson DJ, Wilkens JJ. Rapid implementation of the repair-misrepair-fixation (RMF) model facilitating online adaptation of radiosensitivity parameters in ion therapy. Phys Med Biol. 2017;62:N285–N296.

27. Lühr A, von Neubeck C, Pawelke J, et al. “Radiobiology of proton therapy”: results of an international expert workshop. Radiother Oncol. 2018;128:56–67.

28. Paganielli H, Blakesly E, Carabe-Fernandez A, et al. Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy. Med Phys. 2019;46:e53–e78.

29. Carlson DJ, Stewart RD, Semenenko VA, Sandison GA. Combined use of Monte Carlo DNA damage simulations and deterministic repair
models to examine putative mechanisms of cell killing. *Radiat Res* 2008;169:447–459.

30. Frese MC, Yu VK, Stewart RD, Carlson DJ. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. *Int J Radiat Oncol Biol Phys* 2012;83:442–450.

31. Stewart RD, Yu VK, Georgakilas AG, Koumenis C, Park JH, Carlson DJ. Effects of radiation quality and oxygen on clustered DNA lesions and cell death. *Radiat Res*. 2011;176:587–602.

32. Wedenberg M, Lind BK, Härdermark B. A model for the relative biological effectiveness of protons: the tissue specific parameter $\alpha/\beta$ of photons is a predictor for the sensitivity to LET changes. *Acta Oncol (Madr)*. 2013;52:580–588.

33. Mesías MC, Boda-Heggemann J, Thoelking J, Lohr F, Wenz F, Wertz H. Quantification and assessment of interfraction setup errors based on cone beam CT and determination of safety margins for radiotherapy. *PLoS One*. 2016;11:e0150326.

34. Wohlfahrt P, Möhler C, Stützer K, Greilich S, Richter C. Dual-energy CT based proton range prediction in head and pelvic tumor patients. *Radiother Oncol*. 2017;125:526–533.

35. Schulz-Ertner D, Karger CP, Feuerhake A, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. *Int J Radiat Oncol Biol Phys*. 2007;68:449–457.

36. Wieser HP, Hennig P, Wahl N, Bangert M. Analytical probabilistic modeling of RBE-weighted dose for ion therapy. *Phys Med Biol*. 2017;62:8959–8982.

37. Semenenko VA, Stewart RD. A fast Monte Carlo algorithm to simulate the spectrum of DNA damages formed by ionizing radiation. *Radiat Res*. 2004;161:451–457.

38. Unkelbach J, Bortfeld T, Martin BC, Soukup M. Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning. *Med Phys*. 2009;36:149–163.

39. Taasti VT, Bäumer C, Dahlgren CV, et al. Inter-centre variability of CT-based stopping-power prediction in particle therapy: survey-based evaluation. *Phys Imaging Radiat Oncol*. 2018;6:25–30.

40. Guan F, Geng C, Carlson DJ, et al. A mechanistic relative biological effectiveness model-based biological dose optimization for charged particle radiobiology studies. *Phys Med Biol*. 2018;64:015008.

41. Wilkens JJ, Oelfke U. Fast multifield optimization of the biological effect in ion therapy. *Phys Med Biol*. 2006;51:3127–3140.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Application of the SA framework to an additional prostate case.