Purpose: Proton radiotherapy is rapidly becoming a standard treatment option for cancer. However, even though experimental data show an increase of the relative biological effectiveness (RBE) with depth, particularly at the distal end of the treatment field, a generic RBE of 1.1 is currently used in proton radiotherapy. This discrepancy might affect the effective penetration depth of the proton beam and thus the dose to the surrounding tissue and organs at risk. The purpose of this study was thus to analyze the impact of a tissue and dose dependent RBE of protons on the effective range of the proton beam in comparison to the range based on a constant RBE of 1.1.

Methods: Factors influencing the biologically effective proton range were systematically analyzed by means of treatment planning studies using the Local Effect Model (LEM IV) and the treatment planning software TRiP98. Special emphasis was put on the comparison of passive and active range modulation techniques.

Results: Beam energy, tissue type, and dose level significantly affected the biological extension of the treatment field at the distal edge. Up to 4 mm increased penetration depth as compared to the depth based on a constant RBE of 1.1. The extension of the biologically effective range strongly depends on the initial proton energy used for the most distal layer of the field and correlates with the width of the distal penumbra. Thus, the range extension, in general, was more pronounced for passive as compared to active range modulation systems, whereas the maximum RBE was higher for active systems.

Conclusions: The analysis showed that the physical characteristics of the proton beam in terms of the width of the distal penumbra have a great impact on the RBE gradient and thus also the biologically effective penetration depth of the beam. © 2013 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4824321]

Key words: proton radiotherapy, biologically effective range, RBE, LEM, treatment planning, distal penumbra

1. INTRODUCTION

Proton beam therapy is becoming a clinical standard treatment procedure in radiotherapy for specific types of cancer which are difficult to treat with surgery or conventional radiotherapy with photons. Protons are known for their superior depth dose profile compared to x-rays, and their tissue sparing effects make them particularly suitable for tumors located close to critical structures. The biological effectiveness of protons in tissue has been shown to be on average very similar to that of x-rays for in vivo endpoints and most of their path which is why a constant relative biological effectiveness (RBE) of 1.1 is used in clinical practice. Nevertheless, in vitro studies show that even protons have an increased RBE at the end of their range, which significantly exceeds 1.1 depending on the tissue type. There are only
few experiments which determined a RBE at the distal end of the extended Bragg peak, but nearly all showed an increase, which clearly exceeds 1.1. This increase of the RBE can be explained by the sharply increasing linear energy transfer (LET) at the distal edge of the spread-out Bragg peak (SOBP), which consequently leads to an extension of the effective proton range as described, e.g., by Larsson and Kihlman,11 Sweet et al.,12 and Robertson et al.4 The major deviation from a constant RBE of 1.1 thus occurs at the distal field end and strongest in the distal edge of the Bragg peak. The resulting biological extension can be of special concern for organs at risk (OAR) located close to treated tumors, especially if the beam is directed toward the critical structure. Moreover, as in general for high-LET radiation, the tissue type and dose level are expected to have significant impact on the RBE and thus also on the extension of the effective range as also shown by Carabe et al.13

The Local Effect Model (LEM) in its recently published version (LEM IV) (Refs. 14 and 15) has shown to be suitable to predict tissue and energy dependent RBE values not only for carbon ions but also for protons and other clinically relevant ions. In the present work, we thus use the LEM IV for a systematic analysis of the factors influencing the biological range extension. We first analyze the impact of the biological characteristic of a given tissue and physical parameters such as dose, dimension, and depth of the SOBP on the extension of the effective range. Special attention is then turned to the influence of the physical beam characteristics on the biological extension and the subsequent systematics by comparing different beam delivery methods, i.e., active and passive beam delivery. We finally discuss the potential impact of these factors in clinical cases, where the range extension might be of concern for the dose delivered to the surrounding tissue.

2. MATERIALS AND METHODS

2.A. Treatment planning

To investigate the biologically effective range of protons, idealized target geometries (cubes) placed in a simulated water phantom were used to facilitate the systematic analysis. The cubic volume has a fixed lateral dimension of 50 × 50 mm² but varies in its dimension along the beam axis. Treatment plans consisted of only one field to most clearly illustrate the range extension. The treatment planning system TRiP98 was used to optimize the physical dose distribution.16–18

As proton treatments can utilize active or passive range modulation, both modalities were simulated. For active range modulation,19 the primary beam energy was varied in order to shift the Bragg peaks in depth, for example, used at the Heidelberg Ion-Beam Therapy Center (HIT). For passive range modulation, a range shifter was simulated. With the range shifter modulation, only single primary proton energies are used and polymethyl methacrylate (PMMA) plates are positioned in between the beam exit window and target area to degrade the beam energy and shift the Bragg peak in depth.20 Note that with active range modulation the energies used depend on the location and dimension of the target volume whereas the passive range modulation uses one fixed energy. We thus simulated typical energies used in proton beam therapy with the passive modality, i.e., 160 and 235 MeV as well as monoenergetic beams from 71 to 220 MeV. However, the details of the beam characteristic at different institutions are expected to be accelerator and beam line dependent, and thus the analysis presented here mainly focuses on the general aspects of the range modulation technique rather than a detailed facility-dependent beam description.

Note that within this paper the terms “active” and “passive” only refer to the range modulation technique. Concerning the lateral extension of the treatment field for both range modulation modalities, a spot scanning technique via horizontal and vertical deflection of the beam was simulated. The dose levels were chosen from 1 to 10 Gy absorbed dose to cover the whole clinically relevant range of dose prescriptions including hypofractionation.

2.B. RBE data

Biological optimization with TRiP98 requests RBE input data, which are calculated with the LEM. The basic principle of the LEM is to derive the biological effectiveness of ion beam radiation from a combination of the known dose response curve for photon radiation with the description of the microscopic dose deposition pattern of individual particle tracks.14,21–23 For the prediction of the RBE, the latest version of the LEM (LEM IV) was used, which has been shown in a previous publication14 to predict the RBE over a wide range of particles from protons to carbon ions with sufficient accuracy. The LEM can be used to precalculate RBE values for all projectiles from protons to neon in the energy range from 0.1 to 1000 MeV/u, which characterize the RBE for the initial slope of the dose response curves and are stored in a so-called “RBE-table”. These precalculated values are used as input for the TRiP98 treatment planning system, which determines actual RBE values based on the mixed composition of the radiation field and the dose in each voxel of the treatment volume.17,24

The biological input parameters of the LEM are the parameters α_y, β_y, and D_t describing the photon dose-response curves according to a modified linear-quadratic model. This modification is characterized by a transition to a linear shape for doses larger than D_t,21 which is consistent with the linear-quadratic-linear model as proposed by Astrahan25 with

\[
S(D) = \begin{cases} 
    e^{-(x + y D^2)} & \text{for } D < D_t, \\
    e^{-(x + y D^2 + s_{max}(D - D_t))} & \text{for } D \geq D_t,
\end{cases}
\]

where \(s_{max} = \alpha_y + 2\beta_y D_t\) is the maximum slope of the photon dose response curve for doses larger than \(D_t\). All other parameters of the LEM are kept constant and were chosen as described in Elsässer et al.14

In a first step, it was demonstrated that the combination of LEM and TRiP98 actually allows to accurately predict the variation of RBE along the SOBP for proton beams. Therefore, the model predictions were validated by comparison...
with two sets of experimental RBE data obtained for different cell lines with significantly different sensitivities. Tang et al.\textsuperscript{7} measured the RBE for survival of Chinese hamster ovary (CHO) cells exposed to doses of 1, 2, 4, 6, and 8 Gy and at different depth positions of 2, 10, 18, and 23 mm, using a 65 MeV proton beam to produce a SOBP with about 17.5 mm extension located between approximately 10 and 27.5 mm depth. As input parameters for the model calculations, the photon parameters obtained with Cs-137 gamma rays given in Tang et al.\textsuperscript{7} together with a $D_i$ of 13 Gy for the RBE table AB6.5 (Table I) were used.

Bettega et al.\textsuperscript{8} determined the RBE for the survival of SCC25 cells derived from human squamous cell carcinoma of the tongue in a 65 MeV modulated proton beam of 15 mm extension. The corresponding photon input parameters, as given in Bettega et al.\textsuperscript{8} for Co-60 gamma rays, together with a $D_i$ of 15 Gy, were used for the RBE table AB47.5 (Table I). For the two simulated SOBP, a bolus of 5.9 mm was used to adapt the position of the Bragg peak in depth; this accounts for facility- and beam line specific details not taken into account in this simulation study.

For the systematic studies regarding the biological range extension, two different RBE tables were used (Table I). The RBE tables describe two hypothetical cell or tissue types with an $\alpha_p/\beta_p$-ratio of 2 Gy (AB2), characteristic for rather radiosensitive late responding cell or tissue types, and with an $\alpha_p/\beta_p$-ratio of 10 Gy (AB10), characteristic for rather radioresistant early responding cell or tissue types.\textsuperscript{26} The parameter settings are typical for in vitro cell survival assays, where a change of the $\alpha_p/\beta_p$-ratio usually goes along with a change of $\alpha_p$ rather than of $\beta_p$. The parameter $D_i$ was adapted according to an empirical approximated linear relation between $\alpha_p/\beta_p$-ratio and $D_i$. This relation was found empirically when using the LEM over a huge set of experimental cell survival data.\textsuperscript{27}

### Table I. Input parameters for the RBE tables.

<table>
<thead>
<tr>
<th>RBE table</th>
<th>$\alpha_p$ (Gy$^{-1}$)</th>
<th>$\beta_p$ (Gy$^{-2}$)</th>
<th>$\alpha_p/\beta_p$ (Gy)</th>
<th>$D_i$ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB6.5$^a$</td>
<td>0.16</td>
<td>0.0246</td>
<td>6.5</td>
<td>13</td>
</tr>
<tr>
<td>AB47.5</td>
<td>0.57</td>
<td>0.012</td>
<td>47.5</td>
<td>15</td>
</tr>
<tr>
<td>AB2</td>
<td>0.1</td>
<td>0.05</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>AB10</td>
<td>0.5</td>
<td>0.05</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

$^a$AB is the abbreviation for the photon $\alpha_p/\beta_p$-ratio with the number representing its value.

2.C. Determination of the biologically effective range

The biological range extension was quantified by taking into account the RBE predicted by the LEM IV for different dose-levels and biological endpoints described by the $\alpha_p/\beta_p$-ratio. As a reference dose distribution, we optimized a physical absorbed dose and calculated the corresponding RBE-weighted dose with constant RBE of 1.1; the depth where the RBE-weighted dose decreased to 80% of the prescribed RBE-weighted dose, i.e., $d_{80}^\text{RBE} = 0.8 \cdot d_{\text{prescribed}}^\text{RBE}$ was used to determine the corresponding biologically effective range $R_{80}^\text{RBE}$. The 80% isodose $d_{80}$ was chosen according to considerations of Gottschalk\textsuperscript{28} where it was stated that the distal $d_{80}$ is a well suited value to describe the range of the proton beam since it is independent of the energy spread of a certain beam and reflects the mean projected range of the protons.\textsuperscript{28,13} Figure 1(a) schematically shows the biological range extension due to a variable RBE with depth indicated by the green line segment.

In analogy to the reference value, the biologically effective range in the case of a variable RBE, $R_{80}^\text{RBE}$, was also determined from the position where the RBE-weighted dose decreases to the reference value of $d_{\text{varRBE}} = d_{80}^\text{RBE} = 0.8 \cdot d_{\text{prescribed}}^\text{RBE}$ as defined above for the case of constant RBE. The biological extension, i.e., the difference in biological range predicted by the LEM IV as compared to the case of a constant RBE is then calculated as $R_{\text{varRBE}} - R_{80}^\text{RBE}$.

The biological extensions were determined for the RBE tables AB2 and AB10 (Table I) together with all the previously described settings and field arrangements. Moreover, the biological extension was determined for monoenergetic...
Bragg peaks ranging from 71 to 220 MeV optimized to different dose levels and covering penetration depths from approximately 50 to 300 mm. For the monoenergetic Bragg peaks, the peak defines the dose level and the $R_{\text{diff}}^{80}$ is determined as described above.

Furthermore, the influence of the width of the 80/20 distal penumbra of the Bragg peak on the biological extension was investigated. The width is defined as the difference in penetration depth from the 80% isodose (percentage of the prescribed dose) to the 20% isodose.\(^2\) Note that the symbols in Figs. 3–6 correspond to simulated data points and the corresponding lines are empirical best-fit-curves to the data points with the aim to guide the eye. Figure 1(b) demonstrates the difference in the width of the distal edge of the Bragg peak using different energies to modulate the SOBP. Due to momentum spread and range straggling effects (scattering and range modulation components in the nozzle), which are more prominent for higher energies, the 80/20 distal penumbra increases with increasing energy.\(^29\)

Finally, the RBE at the position of the maximum RBE-weighted dose was evaluated to investigate the correlation with the width of the 80/20 distal penumbra. The RBE at maximum RBE-weighted dose was chosen because it is a measure for the highest effect in the tissue. To choose the maximum RBE would be not suitable since the RBE further increases throughout the distal penumbra and is highest for infinitesimal doses which go along with high uncertainties. The ranges $R_{c_{\text{RBE}}}^{80}$ and $R_{var_{\text{RBE}}}^{80}$ were determined along the central axis of the beam using TRiP98.

### 3. RESULTS

#### 3.A. Comparison with experimental RBE measurements along depth

Figure 2(a) shows the RBE measurements reported by Tang et al.\(^7\) with CHO cells in different depths for 1, 2, 4, 6, and 8 Gy, respectively. The model predictions based on the RBE table AB6.5 are in accordance with the experimentally observed RBE within the SOBP; the RBE is slightly underestimated by the model in the entrance region.

Figure 2(b) shows the RBE measurements reported by Bettega et al.\(^8\) with the SCC25 cell line in different depth positions including the declining edge for 2, 5, and 7 Gy, respectively. The RBE prediction is based on the RBE-table AB47.5 for a 65 MeV modulated proton beam. Only a minor dose dependence, but still a strong increase of RBE at the declining edge, is observed.

Since in both cases a good agreement of the model predictions and experimental data was observed, the accuracy of the model was considered to be sufficient for the systematic analysis described in Secs. 3.B and 3.C.

#### 3.B. The biologically effective range

We systematically analyzed the impact of the increased RBE of low energetic protons on the extension of the effective range considering various physical and biological parameters:

- The dose level
- The extension and position in depth of the target volume
- The range modulation technique (active and passive)
- The tissue type as characterized by the $\alpha/\beta$-ratio for photon irradiation.

Figure 3 shows the biological range extension dependent on the dose for target volumes all having the same proximal end (a) and target volumes all having the same distal end but differing in their depth dimension (b). The calculation was performed using the active range modulation method with different energies to cover the target volume. Independent from the dimension of the SOBP, only minor differences are observed when the distal end of the spread out Bragg peak is positioned at the same depth. In contrast, target geometries of
FIG. 3. Dose dependent biological range difference $R_{\text{diff}}^{80}$ for different target depth dimensions from 20 to 100 mm for active beam modulation with same proximal end at 50 mm but different $R_{\text{cRBE}}^{80}$ (a) and same $R_{\text{cRBE}}^{80}$ at 152 mm but different proximal end (b). The solid symbols correspond to an $\alpha/\beta_{\gamma}$-ratio of 2 Gy and the open symbols to an $\alpha/\beta_{\gamma}$-ratio of 10 Gy, in (b) the curves lie on top of each other. Note that here and in subsequent figures the symbols represent the simulated data points and the lines are empirical best fit-curves to the data points with the aim to guide the eye.

For passive range modulation, a bolus was simulated to shift the proximal end of the SOBP to the same position in depth when using different energies. As shown in Fig. 4, the biological extension is largely different when comparing the different initial energies of 160 (a) and 235 MeV (b). The solid symbols correspond to an $\alpha/\beta_{\gamma}$-ratio of 2 Gy and the open symbols to an $\alpha/\beta_{\gamma}$-ratio of 10 Gy. Note that the curves for the different dimensions lie on top of each other.

The fact that the biological extension of the beam does not depend on the extension of the target volume, but seems to primarily depend on the initial energy indicates that the biological range extension is mainly determined by the width of the 80/20 distal penumbra. We thus analyzed the correlation of the biological extension with the width of the 80/20 distal penumbra using monoenergetic Bragg peaks with different initial energies ranging from 71 to 220 MeV.

Figure 5(a) illustrates the biological range extension dependent on the 80/20 distal penumbra. Variation of the distal penumbra is achieved by variation of the energy from 71 to 220 MeV, and with increasing energy an increase of the distal penumbra is observed due to a more pronounced range straggling. The increasing distal penumbra is connected to an increased extension of the biologically effective range, which is most pronounced for low doses, low $\alpha_{\gamma}/\beta_{\gamma}$-ratios, and high energies as used for deep seated tumors, i.e., 235 MeV, where range differences exceeding 4 mm are observed [Fig. 4(b)]. The extension of the biologically effective range emerges due to a competition between the decreasing dose and increasing...
FIG. 5. Biological range difference (a) and RBE at maximum RBE weighted dose (b) vs the distal penumbra for different physical dose levels of 1, 3, 6, and 10 Gy. The data points represent the distal penumbra for energies from 71 to 220 MeV. The solid symbols correspond to an $\alpha/\beta_\gamma$-ratio of 2 Gy and the open symbols to an $\alpha/\beta_\gamma$-ratio of 10 Gy.

RBE. Decreasing initial energy accompanies a steeper dose penumbra and leads to a higher LET and thus maximum RBE at the distal part of the SOBP [Fig. 5(b)]. Simultaneously, the LET gradient in the distal penumbra of the dose distribution becomes steeper and covers a smaller region in depth, and correspondingly the biological range extension becomes less pronounced [Fig. 5(a)]. Figure 5 thus demonstrates that the RBE at maximum RBE-weighted dose is anticorrelated with the width of the 80/20 distal penumbra, whereas the biological range extension correlates with the 80/20 distal penumbra.

3.C. Influence of the reference isodose

The range of the proton beam is a matter of definition. In the clinical routine, the range of the proton beam in water is defined at the distal 90% isodose. In this study, the 80% isodose is used as reference for the biological range extension. The 80% isodose is a good compromise to describe the biological spread of the beam since it reflects the extension of the high dose region at the distal end as well as for the physical properties. Figure 6 shows the influence of the isodose level used for the proton range definition on the biological range extension with different reference isodoses from 90% to 20%. The choice of the reference isodose matters mainly for small doses where the largest deviations are observed in the predicted biological range difference between the reference isodoses.

4. DISCUSSION

4.A. Relevance of a variable RBE

With the increasing interest in protons as a promising treatment modality for cancer radiotherapy, an accurate prediction of the increased biological effectiveness and assessment of the associated uncertainties becomes important. Two aspects especially have to be considered here:

- The increased RBE-weighted dose observed at the distal end of the SOBP
- The extension of the RBE-weighted depth-dose profile due to the rise of RBE in the distal penumbra.

Due to the competition between increasing RBE with depth and decreasing dose, the position of the maximum RBE-weighted dose and maximum RBE typically do not coincide; the maximum RBE-weighted dose is reached close to the end of the SOBP, whereas the maximum RBE is found beyond that position at low doses in the penumbra region of the dose distribution.

Experiments which focus on the measurement of RBE along the proton SOBP typically aim at the determination of the maximum RBE-weighted dose, since this is of particular interest with respect to constraints concerning the tolerance of normal tissues located close to the distal end of the treatment field. Many in vitro experiments indicate a rise of RBE at the distal end significantly above the clinically used value of 1.1. However, the experimentally determined RBE in the distal edge is associated with large uncertainties since the
measurement is very difficult due to the steep dose and LET gradient.

Because of uncertainties in the systematic description of this increased RBE, e.g., in terms of dose level and tissue characteristics, a detailed depth dependence is currently not taken into account in clinical practice. Instead, situations are avoided where an increased RBE could lead to unacceptable high normal tissue doses, and consequently the potential advantages of proton beams cannot be fully exploited yet. Therefore, there is a clear need to make progress in the detailed analysis of the factors influencing the RBE in proton beams and to take them into account in treatment planning. Biophysical models are valuable in that respect because they allow extrapolation to situations that are difficult to exploit experimentally. However, thorough validation of a model by means of available experimental data is of course required before it can be used for this extrapolation.

4.B. Validation of the LEM for proton irradiation

For the analysis presented here, we used the LEM IV that has been demonstrated to accurately predict the biological effectiveness of protons for a typical clinical treatment scenario. However, a more detailed analysis is desirable to further validate the model with respect to the dependencies of RBE on the depth position in the SOBP, the dose level and the cell or tissue type under consideration. We have thus compared the model prediction along the SOBP to two data sets reported by Tang et al. and Bettega et al. for CHO and SCC25 cells, respectively.

For both cellular systems, in general a very good agreement between model prediction and experimental data has been achieved for different dose levels and different positions within the SOBP. In the entrance region, the LEM somewhat underestimates the RBE in the case of CHO cells. This might be traced back to the contribution of secondary recoil protons induced in the target material, which are not taken into account in the current version of the treatment planning system. Other studies have shown that this contribution could lead to about 8% higher RBE values in the entrance region. In contrast to CHO cells, for SCC25 good agreement is also observed in the entrance region. However, because of the generally lower RBE values for SCC25 as compared to CHO cells, this cell system might not be sufficiently sensitive to detect this subtle difference. Anyhow, the observed underestimation of the RBE in the entrance channel has no influence on the agreement of the RBE prediction in the distal end and penumbra and thus is not of concern for the estimated biological range extension.

4.C. Impact of dose and tissue type on the biological range extension

Because of its good agreement with measured RBE values, the LEM is suitable to analyze in detail the extension of the biologically effective range that results from a variable RBE as compared to a constant RBE value of 1.1. In general, according to the LEM prediction the extension is expected to be more pronounced for tissues characterized by a low $\alpha_\gamma/\beta_\gamma$-ratio as compared to tissues with a high $\alpha_\gamma/\beta_\gamma$-ratio. The difference is most significant at low doses and gets smaller with increasing dose. We did not focus on the sensitivity of the threshold dose $D_t$ since we adapted the parameter according to an empirical relation between the $\alpha_\gamma/\beta_\gamma$-ratio and $D_t$ found by Friedrich et al. Apparently, a variation of $D_t$ accompanies a RBE variation which also influences the biological range extension. However, in the case of protons, the RBE is rather robust for a $D_t$ variation and the main determinant for the RBE remains the $\alpha_\gamma/\beta_\gamma$-ratio.

These general trends are in line with the results recently published by Carabe et al. They also analyzed the biological range extension, but used another empirical model for the calculation of RBE values and a different evaluation method for the biological range difference based on the differences becoming apparent in the dose-volume histogram (DVH). However, this evaluation method is not too different from the central axis approach we used due to the fact that we as well as Carabe et al. consider idealized target geometries (cubes) in our analysis. We thus expect no differences since deviations in the DVH are only due to the biological range extension at the distal end. Their results also indicate a dose dependence of the range extension, although this dose dependence seems significantly less pronounced as in our case. Similarly, Carabe et al. also demonstrate a tissue dependence of the range extension, where for small $\alpha_\gamma/\beta_\gamma$-ratios the range extension is much more pronounced than for high $\alpha_\gamma/\beta_\gamma$-ratios. However, in this case, the results reported by Carabe et al. differ not only quantitatively but also qualitatively from our results. Whereas in our analysis for all situations an increased extension as compared to the assumption of a constant RBE is found, in the analysis of Carabe et al. in general negative extensions are found for higher $\alpha_\gamma/\beta_\gamma$-ratios, indicating that the corresponding RBE values in the distal penumbra are smaller than the reference value of 1.1. This is in contrast to our case, where RBE values always higher than 1.1 are predicted for all combinations of dose levels and $\alpha_\gamma/\beta_\gamma$-ratios that were analyzed.

Since the predicted extension obviously significantly depends on the model that is used for the RBE calculations, a detailed conceptual comparison of the different models and their underlying assumptions would be highly desirable. Although this detailed discussion would be beyond the scope of the present paper, we would like to address the main aspects that are likely to contribute most to the differences observed between the two models. For the LEM, according to the track structure properties, the minimum RBE value predicted for low LET protons is 1 [the slightly lower value of 0.97 observed in Fig. 2(b) for the very sensitive SCC25 cells is considered to be insignificant with respect to the magnitude and range of RBE values discussed here]. In contrast, the parameterization used by Carabe et al. allows for RBE values substantially below 1 at low LET and in particular for higher $\alpha_\gamma/\beta_\gamma$-ratios; the limiting value for LET $\to$ 0 is reported to be 0.843. This difference is likely due to the fact that actually the RBE-LET relationship is not exactly linear in the LET range up to 20 keV/μm. The LEM predicts a vanishing
slope for the RBE-LET dependence in the limit of LET → 0, but then shows an overproportional increase toward the high LET values. A linear fit to such a bended curve would typically show an underestimation of the RBE at very low and high LET values, but an overestimation at intermediate LET values. A more thorough comparison to experimental data would however be required to analyze this aspect in detail. Furthermore, if for a given proton energy the LEM predicts RBE values greater than 1, the RBE values in general decrease with increasing dose. In contrast, although details depend on the LET and \( \alpha_\gamma/\beta_\gamma \)-ratios, according to the parameterization used by Carabe et al.\(^{13} \) the maximum RBE values observed at low doses (RBE\(_{\text{max}}\)) can be smaller than the minimum RBE values (RBE\(_{\text{min}}\)) that represent the RBE values for \( D \rightarrow \infty \). This corresponds to an inverted dose dependence of RBE as compared to the LEM prediction. Taken together, although the general trends like increase of RBE with increasing LET and decreasing \( \alpha_\gamma/\beta_\gamma \)-ratio are similarly predicted by both approaches, the RBE values along a SOBP might be systematically shifted in the model used by Carabe et al.\(^{13} \) as a consequence of the above mentioned quantitative differences, and might show an inverted dose dependence of RBE for low LET values.

4.D. Impact of the dose gradient at the distal penumbra on the biological range extension

In our analysis, we showed that for different range modulation techniques significantly different range extensions are expected, and that these variations can be traced back to the gradient in the distal penumbra of the dose distribution. To our knowledge, this aspect has not been addressed in detail by other studies so far; they mainly focus on the maximum RBE-weighted dose in the distal edge and the consequential overdosage, which are of concern for the nearby OARs.\(^{3, 39} \) Nevertheless, the impact, e.g., of the full-width at half maximum (FWHM) of the proton peak on RBE effects in general has been recognized, but not been specifically analyzed in terms of the dose gradient at the distal penumbra. For example, Paganetti et al.\(^{31} \) reported about the anticorrelation between the RBE\(_{\text{max}}\) (ratio of initial slopes, \( \alpha_1/\alpha_\gamma \)) at the maximum dose of pristine Bragg peaks for different beam energies and their corresponding FWHM. Surprisingly, although no supporting details are presented in this paper, the authors conclude that the biological extension “increases with decreasing initial proton energy,” which is in contrast to our results. Furthermore, Paganetti and Schmitz\(^{40} \) discuss the influence of beam modulation techniques on dose and RBE in proton radiation therapy. They show that the RBE gradient becomes less pronounced with increasing initial proton energy, but the aspect of range extension is not addressed in their paper.

In that respect, it might be important to emphasize that lower overall RBE values do not necessarily lead to a less pronounced biological extension of the SOBP. Instead, the range extension critically depends on the balance between increase of RBE and the dose gradient at the distal penumbra, as schematically illustrated in Fig. 7. If the dose gradient and with that the LET gradient is high, this results in comparably large RBE values. However, even a correspondingly large vertical shift of the depth-dose curve resulting from the high RBE values will not lead to a large longitudinal shift because of the high dose gradient. In contrast, for a shallower distal penumbra, the corresponding RBE values might be lower, but due to the inclination of the distal penumbra even a comparably small vertical shift can lead to a more pronounced longitudinal shift. This effect is, moreover, independent on the model used to predict the RBE.

Consequently, the biological range extension is also affected by the beam delivery method. In active range modulation techniques, in general, lower initial energies are used, leading to a higher gradient of the distal penumbra. This results in a high maximum RBE at the distal edge, but a smaller biological range extension. In contrast, passive range modulation techniques use higher initial energies, leading to a shallower gradient of the distal penumbra. In this case, smaller maximum RBE values but a more significant biological extension is expected. Nevertheless, it is primarily the resulting gradient that determines the biological extension, but not the exact technique that is used to generate the SOBP.

According to these considerations, the increased RBE of protons at the distal end shows up in any case, either as a comparably high RBE at the distal end of the SOBP or a large biological extension. Appropriate choice of the radiation modality allows shifting between these two options, but there seems to be no possibility to completely avoid the impact of RBE effects.

Moreover, the extension is expected to affect not only the distal penumbra, but also the lateral penumbra. However, it is expected that in the lateral direction the dose dependence of RBE is more important, whereas the contribution of the increase of LET is less pronounced, although the detailed
balance between these effects will also depend on the position in depth.

4.E. Clinical impact of the biological range extension

Range uncertainties represent a major reason to avoid field configurations that point in the direction of a critical organ behind the target volume, although particularly in this configuration the specific advantages of particle beams could be exploited. In order to account for these uncertainties, at present in many proton facilities 3.5% of the proton range plus extra additional 1–3 mm is used as an extra margin. In case of prostate treatments with proton ranges of approximately 15 cm, this corresponds to more than 5 mm extra range and for anterior-oriented fields would deliver high dose to the anterior rectal wall. Up to now, mainly physical aspects are considered in the estimation of these range uncertainties. According to the analysis presented here, extensions of up to about 4 mm have to be taken into account resulting from the increased RBE at the distal part of the SOBP, depending on the dose level and tissue characteristic under consideration.

Johansson showed for the irradiation of hypopharyngeal carcinoma where they positioned the distal penumbra just before the spinal cord that the effective dose to the spinal cord with a variable RBE increased by a factor of 1.5 compared to the case where a constant RBE of 1.1 was chosen or only the physical dose was regarded. Even though the critical dose level was not exceeded, one should be aware that not only a larger part of the surrounding tissue is affected but also the integral dose to this volume is much higher than expected as discussed also by Jones et al. Special caution is thus needed for pediatric patients where the same dose affects an even larger relative fraction of the surrounding tissue compared to adult patients.

The impact of range uncertainties and extensions has been also addressed by Gensheimer et al., using MRI measurements, they were able to directly determine the biologically effective range in patients treated with proton beams. They reported an average overshoot of the proton beam in the lumbar spine of 1.9 mm (0.8–3.1 mm). They attributed a small part of the overshoot to the increased RBE in the distal edge but assumed that the overshoot should be less than 1 mm based on the study of Paganetti et al.—because the higher beam energy causes a more gradual dose falloff.

However, according to the discussion above, we come to the opposite conclusion, namely, that the overshoot should increase with increasing energy precisely because of the more gradual penumbra. The biological extension predicted by the LEM IV is dependent on the pristine energy used and would be between 1.6–3 mm for 235 MeV and 1.1–1.8 mm for 160 MeV and a RBE-weighted dose (RBE = 1.1) of 2 Gy (RBE) at the 50% isodose, depending on the radiosensitivity of the tissue type. These values are significantly larger than the maximum value of 1 mm as estimated by Gensheimer et al.; they could thus explain the discrepancy between the overshoot that according to the authors could be attributed to misregistration of the MRI and CT images and the overshoot actually measured in the patients.

5. CONCLUSION

The RBE predictions of the LEM for protons together with the treatment planning software TRiP98 showed to be consistent with experimental data and thus represent a useful tool to describe the variable RBE along the treated volume. It was demonstrated in this study that the biologically effective range of proton beams is strongly dependent on physical properties of the beam as well as on dose and the biological properties of the tissue irradiated and can lead to up to 4 mm extension of the SOBP in extreme situations. In general, the extension is more pronounced for shallow as compared to steep gradients of the dose in the distal penumbra for a given dose level and tissue type.

ACKNOWLEDGMENTS

Work is part of HGS-HIRe. The authors are grateful to John Eley for careful reading and suggestions to the paper.