ACTA ONCOLOGICA
2020, VOL. 59, NO. 10, 1151–1156
https://doi.org/10.1080/0284186X.2020.1826573

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS

Check for updates

RBE for proton radiation therapy – a Nordic view in the international perspective

Iuliana Toma-Dasu[a,b], Alexandru Dasu[c,d], Anne Vestergaard[e], Petra Witt Nyström[c,e] and Håkan Nyström[c]

[a]Department of Physics, Medical Radiation Physics, Stockholm University, Stockholm, Sweden; [b]Department of Oncology and Pathology, Medical Radiation Physics, Karolinska Institutet, Stockholm, Sweden; [c]The Skandion Clinic, Uppsala, Sweden; [d]Medical Radiation Sciences, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; [e]Danish Centre for Particle Therapy, Aarhus, Denmark

ABSTRACT

Background: This paper presents an insight into the critical discussions and the current strategies of the Nordic countries for handling the variable proton relative biological effectiveness (RBE) as presented at The Nordic Collaborative Workshop for Particle Therapy that took place at the Skandion Clinic on 14th and 15th of November 2019.

Material and methods: In the current clinical practice at the two proton centres in operation at the date, Skandion Clinic, and the Danish Centre for Particle Therapy, a constant proton RBE of 1.1 is applied. The potentially increased effectiveness at the end of the particle range is however considered at the stage of treatment planning at both places based on empirical observations and knowledge. More elaborated strategies to evaluate the plans and mitigate the problem are intensely investigated internationally as well at the two centres. They involve the calculation of the dose-averaged linear energy transfer (LET_d) values and the assessment of their distributions corroborated with the distribution of the dose and the location of the critical clinical structures.

Results: Methods and tools for LET_d calculations are under different stages of development as well as models to account for the variation of the RBE with LET_d, dose per fraction, and type of tissue. The way they are currently used for evaluation and optimisation of the plans and their robustness are summarised. A critical but not exhaustive discussion of their potential future implementation in the clinical practice is also presented.

Conclusions: The need for collaboration between the clinical proton centres in establishing common platforms and perspectives for treatment planning evaluation and optimisation is highlighted as well as the need of close interaction with the research academic groups that could offer a complementary perspective and actively help developing methods and tools for clinical implementation of the more complex metrics for considering the variable effectiveness of the proton beams.

ARTICLE HISTORY
Received 9 July 2020
Accepted 16 September 2020

KEYWORDS
Proton therapy; RBE; Skandion Clinic; Danish Centre for Particle Therapy

Introduction

The number of centres dedicated to proton therapy has seen a steady increase in the past decade [1] and the trend is likely to continue in the coming years as more facilities are under construction [2]. This rising trend is the result of the favourable dose distributions that could potentially be achieved with protons [3] and the increased availability of clinically-dedicated technology from several vendors. Two Nordic centres have already opened their doors for patients, the Skandion Clinic, the Swedish national facility for proton radiotherapy, in August 2015 and the Danish Centre for Particle Therapy in January 2019, while two more proton centres are under construction in Oslo and Bergen in Norway and will become operational by 2024.

Nevertheless, as the number of patients treated with protons is still quite small in comparison to those treated with photons, clinical practice is still largely based on the experience gained from photon therapy. The current practice for dose prescription in proton radiation therapy is to use standard dose levels from photon radiation therapy modified with a suitable factor that accounts for the potentially different biological effectiveness of protons due to differences in dose deposition relative to photons. The currently used value for the proton relative biological effectiveness (RBE) is 1.1 following the recommendations of the International Commission on Radiation Units (ICRU) [4]. Several reasons have been brought up for the clinical approach of using a single value for the RBE, including the desirability of a unique value for the relative biological effectiveness that will ease comparisons between centres of proton therapy and computation limitations of treatment planning systems that did not allow the incorporation of complex models in addition to the fact

CONTACT Iuliana Toma-Dasu iuliana.livia.dasu@ki.se Medical Radiation Physics, Karolinska University Hospital, Solna, Visiongatan 48A-44 (P9:02) Box 260, S-171 76 Stockholm, Sweden

that clinical evidence of a variable proton RBE is still rather scarce. This approach has however been questioned in the light of the findings of experimental studies showing a more complex dependence of the RBE of protons on tissue type, dose, and energy of the protons [5–6]. Thus, the general relationship indicates that the RBE increases with the increasing stopping power of the particles, and hence with decreasing the energy of the protons, as well as with decreasing the deposited dose. There is also a general tissue dependence that modulates the relationship with particle energy and deposited dose. It is interesting to note that for other particles used therapeutically like carbon ions, several models have been proposed and implemented clinically to account for the complex variation of their relative biological effectiveness [7–9]. Radiobiological models based on experimental studies to account for the variable proton RBE [10–13] have been developed in parallel with computational tools in the treatment planning systems (TPS) allowing for the calculation of the dose-averaged LET (LET_d) values in addition to the absorbed dose. These new models and hereby tools have facilitated a number of *in silico* planning studies aiming at assessing the clinical implications of the simplified application of a constant RBE value of 1.1 or assuming a more complex RBE variation [14–16]. Such information can be useful both for the evaluation of the treatment plans and in the selection of patients for proton therapy.

The current paradigm of a constant proton RBE of 1.1 has started to be questioned by several individual research groups [5,17–19] and also by larger associations and organisations such as the European Particle Therapy Network (ETPN) group – a task force of the European Society for Radiotherapy & Oncology (ESTRO) – and the American Association of Physicists in Medicine (AAPM). Thus, within the EPTN initiative, there is a dedicated working group to the radiobiology of proton therapy aiming at creating the network and the infrastructure for systematic, large-scale experiments and theoretical modelling studies to investigate the proton RBE dependence on both biological and physical parameters. Similarly, AAPM has established a task group (TG-256) on the investigation of the relative biological effectiveness of protons that produced a comprehensive report recently published [20]. Aligning therefore to these initiatives, the Nordic proton community dedicated a group discussion at the most recent meeting at the Nordic Collaborative Workshop for Particle Therapy that took place at the Skandion Clinic in Uppsala on the 14th and 15th of November 2019. This paper presents a short background and an insight into the critical discussions and the current strategies of the Nordic proton facilities for handling the variable proton RBE and the future plans formulated at this meeting.

Nordic strategies for accounting for the potentially variable RBE

Until now

The biological end-of-range effects have not been entirely ignored in the past and experienced planners know to avoid stopping a beam just before an organ at risk. While not specifically Nordic, the use of several fields with a certain minimum angular separation has been a typical rule of thumb to mitigate the expected effects at the end of the proton range. In the process of plan evaluation, assessment of potential areas of enhanced LET_d in regions close to organs at risk and with a certain dose level is a common approach and can be facilitated by, for example, looking at the dose distributions from each field individually or to extract line doses over critical areas. Furthermore, the networking and exchange of experiences from other proton clinics has been essential, as well as the experience from The Svedberg Laboratory, Uppsala, Sweden.

Present

The above simple rules have been important but they are perceived as too rudimentary, in particular for complicated cases such as craniopharyngiomas and skull base sarcomas [21], but also for cases where organs-at-risk close to the end of the proton range are unavoidable, such as the heart in breast cases [22]. A more advanced approach to evaluate the possible end-of-track effects in treatment planning is to take a combination of LET_d and dose into account. LET_d has the obvious advantage to be a physical quantity, possible to calculate with reasonable accuracy. Although there is no simple and unique relation between cell kill, dose, and LET_d, there is a consensus that there is an approximately linear relationship between LET_d and RBE [20]. As a tool to compare different planning approaches and to estimate the possible risk for different field orientations, LET_d calculations constitute a valuable addition to a strict dose calculation. Possibilities for LET_d calculations are getting increasingly available both in commercial TPS and in dedicated software packages such as FRoG [23].

The strategy currently employed at the Danish Centre for Particle Therapy accounting for the potentially detrimental effects of proton plans optimised under the assumption of a constant 1.1 RBE is based on the observed relationship between LET_d and RBE. For tumours close to the brainstem and treated to prescribed doses at or above 54 Gy, the distal edge in the brainstem is only allowed for one out of the minimum three fields. In selected cases, the distribution of proton LET_d values at the voxel level is calculated using FRoG [23] and the presence of elevated LET_d in critical normal tissue is evaluated. If it is obvious that there is more than one beam having a distal edge in the brainstem, a correction of the beam arrangement would be considered by adjusting beam angles to avoid several beams having the distal edge in the same area according to recommendations from the National Cancer Institute Workshop on Proton Therapy for Children [24].

The strategy utilised by The Skandion Clinic for handling the proton RBE has been built around common recommendations and research results. Thus, dose prescription is currently performed both in physical dose, as well in RBE-weighted dose, assuming the ICRU-recommended value of 1.1 for protons [4]. Although the planning practice has been evolving along the time, most plans employ at least two fields to mitigate end-of-range effects and RBE uncertainties and non-coplanar solutions are considered for plans with three fields or more. While an RBE of 1.1 is routinely used for evaluating the expected effects of the increased effectiveness of the protons, for cases with organs at risk doses close to tolerances or with dose hotspots, additional evaluation is performed assuming an RBE of 1.2 or higher for the normal tissues [25] to implicitly increase the protection for the critical normal tissues in these situations. In selected cases with unexplained toxicity, more advanced analyses have been retrospectively performed based on calculations of LET_d at voxel level combined with several RBE models [26], taking advantage of the underlying calculation and prescription in physical dose.

Future

Present approaches are based on a combination of LET and dose [27–29]. If just a simple product of LET and dose is used, an obvious limitation would be the over-pronunciation of the LET-effect relying on the multiplication of the two quantities [30]. Hence, a high value could be caused by the increase of only one of the factors which might not by itself be correlated with the effect. Other approaches are therefore also considered based on the estimation of RBE as a function of dose, LET and type of tissue [31–33].

The general conclusions and recommendations of the recent AAPM TG-256 report [20] are to maintain the 1.1 RBE value for the optimisation and the evaluation of proton treatment plans, specifying, however, that particular clinical scenarios might warrant a change in current practice. With respect to the target, the conclusion of TG-256 was that the use of RBE = 1.1 at 2 Gy is not entirely unreasonable under the presumption that RBE values should be chosen conservatively to avoid under dosage of the target. Caution is however recommended for small SOBP widths and/or low α/β where the average RBE could be higher. Concerning the normal tissue, since the slope of the NTCP curve is expected to be steeper compared to the tumour control probability (TCP) slope, meaning that RBE uncertainties are even more critical for NTCP, special attention should be paid to normal tissues and organs prone to be affected by hot spots in the region close to or beyond the distal end of the SOBP, such as the brainstem, spinal cord, or optic nerves. The importance of accurate identification of the factors, including the variable RBE, that might affect the accurate estimation of the NTCP values is particularly high in the case of following the Dutch model for patient selection to proton radiotherapy based on ΔNTCP calculations [34]. The AAPM TG-256 report further suggests that different maximum dose constraints may be adopted for these tissues.

The frequently quoted AAPM TG-256 report is generally regarded as reflecting the international perspective on the RBE for proton therapy and the concerns raised in this report pose questions regarding the current clinical considerations of the potential consequences of a variable proton RBE. More specifically the questions could be formulated as such: '*Should the proton plans optimised for a 1.1 RBE be evaluated considering also the LET distribution and/or the variable RBE distribution before the final clinical approval?*' and '*What strategies could be employed to mitigate the effect of the LET/RBE hotspots under the variable RBE assumptions?*'.

The approach proposed in Sweden for the evaluation of the plans is described in the work by Ödén et al. [26] building on the development of a framework for the inclusion of a variable RBE into treatment planning evaluation [31,35]. Thus, clinical treatment plans are assessed from the robustness point of view by recalculating them for comprehensive error scenarios regarding the patient setup and the range of protons and subsequently evaluated using a constant RBE = 1.1 and variable RBE models. Using the Monte Carlo dose and LET_d calculation engine in a research version of RayStation v6 (RaySearch Laboratories AB, Stockholm, Sweden), this method for treatment planning evaluation was proven to predict average RBE values around 1.3, thus substantially higher RBE-weighted doses and potentially higher NTCPs for three patients treated at The Skandion Clinic that presented suspected treatment-related toxicities following proton therapy [26]. Alternative plans can also be made to decrease the RBE in the normal tissue by reducing the LET_d while maintaining the physical target dose. The proton track-end optimisation method developed by Traneus and Ödén was proposed for the re-optimisation of the plans [36] and led to considerable reductions in the LET_d and RBE, and thus to potential lower levels of NTCP compared to the clinical plans without compromising the physical target dose. Although most of the work was focussed on the impact of the variable RBE on the OARs, the effect on the target and the potential to be included in the optimisation of the plans for increasing the tumour control have also been considered [35,37].

The actual impact of accounting for a variable proton RBE on daily clinical decision making is planned to be investigated in the near future in a collaborative workshop.

Discussion

The investigation of the potential clinical implications of a variable RBE in proton therapy has seen increased interest as the number of clinical proton facilities has also increased. Several approaches are available making use of the various facets of the issue as given by LET distributions or by the RBE distributions predicted by the various models proposed in the literature. This is illustrated by the complementary approaches adopted at the Danish Centre for Particle Therapy and at the Skandion Clinic. Both approaches indicate that the predicted differences from a variable RBE for protons as compared to a generic value could be significant and that LET or RBE distributions should be taken into account for the evaluation of the proton plans. Nevertheless, the approaches need to go through a process of validation to account for the associated and, in many cases, overlapping uncertainties as well as to establish the necessary correlations with clinical results needed for evaluations as well as for later optimisations accounting for such distributions.

The uncertainties associated with the experimental determination of RBE are well known, however, a recent multicentric study conducted within the frame of the Infrastructure in Proton International Research (INSPIRE) project has shown significant uncertainties in calculating the RBE-driving LET [38]. These results indicate on one hand a need for standardisation of calculation of LET_d distributions in various systems, and on the other, a need for quality control of the LET_d calculations that mirrors the need for quality controls of the dose calculations. Prospective validation studies would have to continue and predictions of the various models or approaches will have to be compared to the growing body of clinical and experimental evidence.

For the purpose of plan evaluation and comparison, treatment planning systems need to produce and store information about the distributions of measurable physical quantities like dose and LET and also to incorporate several RBE models that could be used for effect predictions and treatment plan evaluation [39]. Scripting options for the user can offer additional flexibility to test future models. These tools will allow the continuous upgrade of models and eventually the clinical validation of relevant models and approaches.

A consistent and thorough database of prospectively collected data, including tumour-related efficacy, toxicity both in short and long-term, as well as comorbidity and other patient-related data, is essential for further insights into the question of variable RBE and also for validating NTCP models. Thus, regarding the availability and the quality of clinical data required for a potential validation of the RBE models one could mention an ongoing European initiative for a common European database (https://project.eortc.org/e2-radiate/) as a tool to harmonise data collection and get access to big data for evaluation.

It has to be mentioned that the proposed approach of multi-model evaluation will not replace the current standard of practice for clinical acceptance of plans, but rather will augment it with knowledge from other models of radiobiological effectiveness of protons. Furthermore, the parallel evaluation of plans would continue to build specific knowledge for proton therapy. Indeed, storing measurable physical quantities from proton plans that is not linked to any particular RBE model, will allow future correlations with radiobiological effects in a parallel approach to the current practice of converting doses from photon therapy. Nevertheless, the additional knowledge from multi-model evaluations has the potential to alter clinical decisions with respect to target coverage and OAR burden and it will be the responsibility of the clinicians to evaluate the implications and to ensure proper prioritisation of dosimetric criteria.

Incorporation of multiple RBE models into treatment planning systems will also offer the possibility to optimise plans according to one model or another, irrespective of the model that will be used for final plan evaluation and approval, similar to the multicriteria optimisation approach that only recently entered clinical practice. The ultimate approach would be to include RBE modelling in a strategy of robust optimisation from which proton plans will become available to be evaluated according to the standard practice, for example, using a fixed value for the RBE as currently recommended or with another RBE model, but having the intrinsic robustness to inter-model variations.

Nevertheless, it should be stressed that both Nordic approaches are based on calculations on the dose and LET_d distributions. Limitations of analytical algorithms for proton dose calculations have started to be recognised [40] and Monte Carlo algorithms are increasingly recommended for better accuracy. These are indeed more demanding in terms of computational capacity, but the conditions improve by the increased implementation of faster calculations [23]. Similarly, uncertainties in calculating LET have also been shown to lead to rather large differences in reported values [38]. The possible combination of uncertainties in the dose and LET for RBE calculation poses increased requirements for the proper benchmarking of the calculation algorithms, as well as inter-centre comparison. It is therefore expected that regular cheques of LET and RBE calculation will be added to future quality assurance programs for treatment planning systems, as well as for future clinical studies in proton radiotherapy. These will face the same challenges that are relevant for the quality control of dose distributions that are destined for three-dimensional geometries in heterogeneous media, while verification is often performed in two-dimensional geometries in the homogeneous media. Possible improvements could be achieved from independent dose and LET_d calculation engines that will go through a separate validation and control, removing the need for individual validation [41]. In this respect, Monte Carlo calculation appears to be the most useful tool to calculate LET_d, while microdosimetric methods could be a promising way to benchmark how different MC based engines can accurately predict LET_d distributions [42–44]. Both Nordic proton therapy centres will collaborate in the future, together with other centres, to further explore the uncertainties in calculating and reporting the LET distributions from clinical plans. Far from being hindrances in further development in proton therapy, they open good opportunities for regional and international cooperation.

It should be mentioned that even if proton-only knowledge of prescription and tolerance doses will become the norm in the future, there will still be interest in RBE models that will allow comparisons with photon therapy, either for comparisons between clinics and also in the utmost scenario of treatment individualisation, when the clinicians will have to decide whether proton therapy or photon therapy will bring the most benefit for individual patients.

Conclusions

The Nordic Collaborative Workshop for Particle Therapy critically scrutinised the current practice for proton treatment planning based on a constant value of 1.1 for proton RBE in light of the continuously accumulating clinical experience as well as the novel research findings highlighting the importance of regional collaboration aligned with the international perspective, concluding that (i) simple empirical rules to mitigate the end of range effect, such as using a reasonable number of fields, are important, (ii) such rules are sometimes not enough and visualisation of the LET_d distribution or calculation of RBE from validated models are necessary and (iii) multi-centre collaboration will be essential to develop and validate more advanced methods to mitigate the end of range RBE uncertainties.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was financially supported by the European Union's H2020 Research and Innovation Programme under Grant Agreement Number [730983].

ORCID

Alexandru Dasu http://orcid.org/0000-0001-8171-2541

References

[1] PTCOG. Facilities in operation [Internet]. Villigen (Switzerland): Particle Therapy Co-Operative Group; 2020 [cited 2020 June 30]. Available from: https://www.ptcog.ch/index.php/facilities-in-operation
[2] PTCOG. Facilities under construction [Internet]. Villigen (Switzerland): Particle Therapy Co-Operative Group; 2020 [cited 2020 June 30]. Available from: https://www.ptcog.ch/index.php/facilities-under-construction
[3] Suit H, DeLaney T, Goldberg S, et al. Proton vs carbon ion beams in the definitive radiation treatment of cancer patients. Radiother Oncol. 2010;95:3–22.
[4] ICRU. Prescribing, recording, and reporting proton-beam therapy. Bethesda (MD): International Commission on Radiation Units and Measurements; 2007. (ICRU Report 78).
[5] Dasu A, Toma-Dasu I. Impact of variable RBE on proton fractionation. Med Phys. 2013;40:011705.
[6] Paganetti 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.
[7] Hawkins RB. A microdosimetric-kinetic model of cell death from exposure to ionizing radiation of any LET, with experimental and clinical applications. Int J Radiat Biol. 1996;69:739–755.
[8] Scholz M, Kellerer AM, Kraft-Weyrather W, et al. Computation of cell survival in heavy ion beams for therapy. The model and its approximation. Radiat Environ Biophys. 1997;36:59–66.
[9] Antonovic L, Brahme A, Furusawa Y, et al. Radiobiological description of the LET dependence of the cell survival of oxic and anoxic cells irradiated by carbon ions. J Radiat Res. 2013;54:18–26.
[10] Carabe-Fernandez A, Dale RG, Jones B. The incorporation of the concept of minimum RBE (RBE_{min}) into the linear-quadratic model and the potential for improved radiobiological analysis of high-LET treatments. Int J Radiat Biol. 2007;83(1):27–39.
[11] Wedenberg M, Lind BK, Hardemark 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. 2013;52(3):580–588.
[12] McNamara AL, Schuemann J, Paganetti H. A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published in vitro cell survival data. Phys Med Biol. 2015;60:8399–8416.
[13] Rorvik E, Thornqvist S, Stokkevag CH, et al. A phenomenological biological dose model for proton therapy based on linear energy transfer spectra. Med Phys. 2017;44:2586–2594.
[14] Wedenberg M, Toma-Dasu I. Disregarding RBE variation in treatment plan comparison may lead to bias in favor of proton plans. Med Phys. 2014;41:091706.
[15] Ödén J, Toma-Dasu I, Eriksson K, et al. The influence of breathing motion and a variable relative biological effectiveness in proton therapy of left-sided breast cancer. Acta Oncol. 2017;56(11):1428–1436.
[16] Pedersen J, Petersen JBB, Stokkevag CH, et al. Biological dose and complication probabilities for the rectum and bladder based on linear energy transfer distributions in spot scanning proton therapy of prostate cancer. Acta Oncol. 2017;56(11):1413–1419.
[17] Tilly N, Johansson J, Isacsson U, et al. The influence of RBE variations in a clinical proton treatment plan for a hypopharynx cancer. Phys Med Biol. 2005;50(12):2765–2777.
[18] Mohan R, Peeler CR, Guan F, et al. Radiobiological issues in proton therapy. Acta Oncol. 2017;56(11):1367–1373.
[19] Willers H, Allen A, Grosshans D, et al. Toward a variable RBE for proton beam therapy. Radiother Oncol. 2018;128(1):68–75.
[20] Paganetti H, Blakely 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(3):e53–e78.
[21] Gutierrez A, Rompokos V, Li K, et al. The impact of proton LET/RBE modeling and robustness analysis on base-of-skull and pediatric craniopharyngioma proton plans relative to VMAT. Acta Oncol. 2019;58(12):1765–1774.
[22] Wang CC, McNamara AL, Shin J, et al. End-of-range radiobiological effect on rib fractures in patients receiving proton therapy for breast cancer. Int J Radiat Oncol Biol Phys. 2020;107(3):449–454.
[23] Kopp B, Jensen MF, Mein S, et al. FRoG: an independent dose and LET_d prediction tool for proton therapy at ProBeam® facilities. Med Phys. 2020. DOI:10.1002/mp.14417
[24] Haas-Kogan D, Indelicato D, Paganetti H, et al. National Cancer Institute workshop on proton therapy for children: considerations regarding brainstem injury. Int J Radiat Oncol Biol Phys. 2018;101:152–168.
[25] Jones B. Towards achieving the full clinical potential of proton therapy by inclusion of LET and RBE models. Cancers. 2015;7(1):460–480.
[26] Ödén J, Toma-Dasu I, Witt-Nyström P, et al. Spatial correlation of linear energy transfer and relative biological effectiveness with suspected treatment-related toxicities following proton therapy for intracranial tumors. Med Phys. 2020;47(2):342–351.
[27] Unkelbach J, Botas P, Giantsoudi D, et al. Reoptimization of intensity modulated proton therapy plans based on linear energy transfer. Int J Radiat Oncol Biol Phys. 2016;96(5):1097–1106.
[28] Fjaera LF, Li Z, Ytre-Hauge KS, et al. Linear energy transfer distributions in the brainstem depending on tumour location in intensity-modulated proton therapy of paediatric cancer. Acta Oncol. 2017;56(6):763–768.
[29] Toussaint L, Indelicato DJ, Holgersen KS, et al. Towards proton arc therapy: physical and biologically equivalent doses with increasing number of beams in pediatric brain irradiation. Acta Oncol. 2019;58(10):1451–1456.
[30] McMahon SJ, Paganetti H, Prise KM. LET-weighted doses effectively reduce biological variability in proton radiotherapy planning. Phys Med Biol. 2018;63(22):225009.
[31] Ödén J, Eriksson K, Toma-Dasu I. Incorporation of relative biological effectiveness uncertainties into proton plan robustness evaluation. Acta Oncol. 2017;56(6):769–778.
[32] Sanchez-Parcerisa D, Lopez-Aguirre M, Dolcet Llerena A, et al. MultiRBE: treatment planning for protons with selective radiobiological effectiveness. Med Phys. 2019;46(9):4276–4284.

[33] Resch AF, Landry G, Kamp F, et al. Quantification of the uncertainties of a biological model and their impact on variable RBE proton treatment plan optimization. Phys Med. 2017;36:91–102.

[34] Langendijk JA, Lambin P, De Ruysscher D, et al. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol. 2013; 107(3):267–273.

[35] Ödén J, Eriksson K, Toma-Dasu I. Inclusion of a variable RBE into proton and photon plan comparison for various fractionation schedules in prostate radiation therapy. Med Phys. 2017;44(3):810–822.

[36] Traneus E, Ödén J. Introducing proton track-end objectives in intensity modulated proton therapy optimization to reduce linear energy transfer and relative biological effectiveness in critical structures. Int J Radiat Oncol Biol Phys. 2019;103(3):747–757.

[37] Fager M, Toma-Dasu I, Kirk M, et al. Linear energy transfer painting with proton therapy: a means of reducing radiation doses with equivalent clinical effectiveness. Int J Radiat Oncol Biol Phys. 2015;91(5):1057–1064.

[38] Ödén J, Hahn C, Vestergaard A, et al. INSPIRE: A multi-centric study to harmonize linear energy transfer (LET) calculations for biological assessments of proton therapy plans. [Abstract] Joint AAPM/COMP Meeting 2020 WE-B-TRACK 3–3.

[39] Nystrom H, Jensen MF, Nystrom PW. Treatment planning for proton therapy: what is needed in the next 10 years? Br J Radiol. 2020;93(1107):20190304.

[40] Saini J, Maes D, Egan A, et al. Dosimetric evaluation of a commercial proton spot scanning Monte-Carlo dose algorithm: comparisons against measurements and simulations. Phys Med Biol. 2017;62(19):7659–7681.

[41] Wagenaar D, Tran LT, Meijers A, et al. Validation of linear energy transfer computed in a Monte Carlo dose engine of a commercial treatment planning system. Phys Med Biol. 2020; 65(2):025006.

[42] Newpower M, Patel D, Bronk L, et al. Using the proton energy spectrum and microdosimetry to model proton relative biological effectiveness. Int J Radiat Oncol Biol Phys. 2019;104(2):316–324.

[43] Bertolet A, Baratto-Roldán A, Cortés-Giraldo MA, et al. Segment-averaged LET concept and analytical calculation from microdosimetric quantities in proton radiation therapy. Med Phys. 2019; 46(9):4204–4214.

[44] Bertolet A, Cortés-Giraldo MA, Souris K, et al. Calculation of clinical dose distributions in proton therapy from microdosimetry. Med Phys. 2019;46(12):5816–5823.