The Henryk Niewodniczański
INSTITUTE OF NUCLEAR PHYSICS
Polish Academy of Sciences
ul. Radzikowskiego 152, 31-342 Kraków, Poland

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Towards incorporation of RBE uncertainty in proton therapy planning systems

Leszek Grzanka[1], Kinga Jeleń, Michael P.R. Waligórski

Abstract

Current arguments concerning the variability of RBE in treatment plans are reviewed and cases are discussed where proton therapy may require the use of treatment planning systems in which a variable RBE is implemented. Novel and recently introduced treatment modalities, such as Proton Arc Therapy, are considered. Risk management following the implementation of a variable RBE in proton therapy planning is also introduced and discussed.

[1] Corresponding author: *Leszek.Grzanka@ifj.edu.pl*

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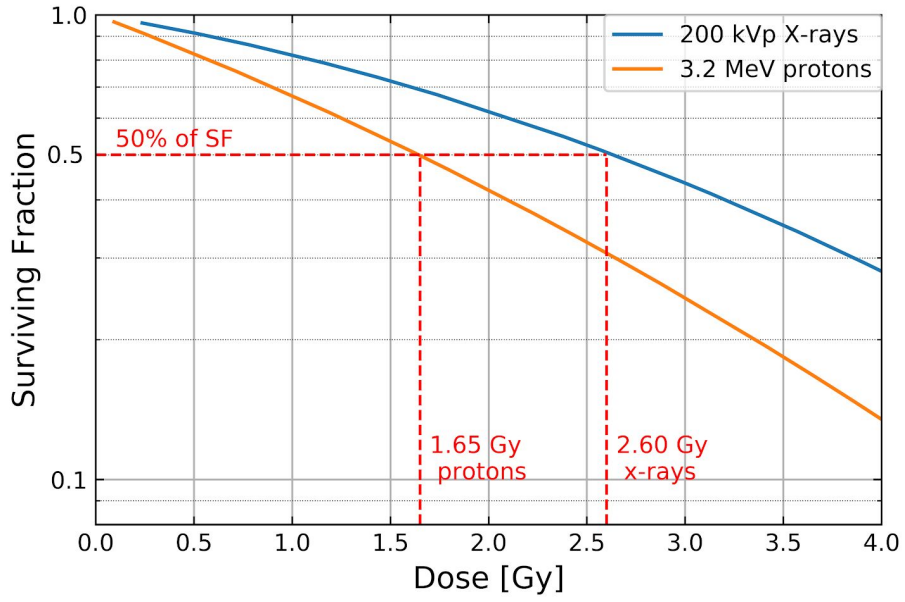
1. Introduction

Compared to standard photon radiotherapy, proton therapy has a great potential due to its advantageous dose distribution. Protons in a beam of a well-specified entrance energy all have a similar range, hence practically no dose is deposited beyond that range. However, the Bragg peak phenomenon occurs over the distal region of the proton beam, resulting in a rapid increase of LET over that region. In terms of radiation biology, the relative biological effectiveness (RBE) of a proton beam is about 1, i.e. it does not differ much from that of a photon beam, except over the Bragg peak region, where RBE may locally increase, in line with the local increase of LET.

Over the last two decades the issue of incorporating proton RBE into proton therapy planning has been hotly debated (McNamara et al. 2019). RBE of a given radiation quality (such as high-LET radiation, e.g. protons) is defined as the ratio of the absorbed dose of a reference beam of photons (typically Co-60 or megavolt X-rays) to the absorbed dose of that radiation modality to produce the same biological effect at a given level.



$$RBE_{0.5} = \frac{D_{x-rays}}{D_{protons}} = \frac{2.60Gy}{1.65Gy} = 1.58$$

Fig 1. The concept of RBE related to cell survival: RBE is a measure of the relative effectiveness of the tested radiation (here - 3.2 MeV protons) in cell killing, against photon reference radiation (here - 200 kVp X-rays) at a given level of effect (here - at 50% survival).

While conceptually rather simple, RBE demonstrates a complicated multifactorial dependence on the type and energy of particles, dose, dose per fraction, degree of oxygenation, cell or tissue type, cell cycle, biological endpoint, and possibly other parameters, as reviewed by Anon and by McDonald (Anon 2008; McDonald 1980). Currently in clinical proton radiotherapy protocols, application of a constant value of RBE = 1.1 is recommended in order to translate physical dose into biological dose (ICRU 2007). Over the recent years, as more proton therapy centres become operational, clinical experience with proton therapy indicates that a constant RBE of 1.1 may be an oversimplification which under certain circumstances may lead to excessive toxicity in critical organs (Ödén et al. 2019). The proton therapy community therefore has a high interest in the debate as to whether or not a variable value of RBE should be applied, and if so, on what radiobiological model should such variable RBE be based on.

The aim of this report is to review the current arguments concerning the variability of RBE in treatment plans and to illustrate cases where proton therapy may require the use of a treatment planning system in which a variable RBE is implemented. Particular attention will be paid to novel and recently introduced treatment modalities, such as Proton Arc Therapy. Risk management following the implementation of a variable RBE in proton therapy planning will also be considered.

2. Derivation of RBE from Cell Survival Data

RBE may be evaluated from experimental *in vitro* cell survival data. Typically, experiments are based on the clonogenic cell survival test, with cell killing as the biological endpoint, as a function of dose. Systematic analysis and a comprehensive database (PIDE) are available, where data from a wide range of experiments have been gathered (Friedrich et al. 2013); (Sørensen et al. 2011)

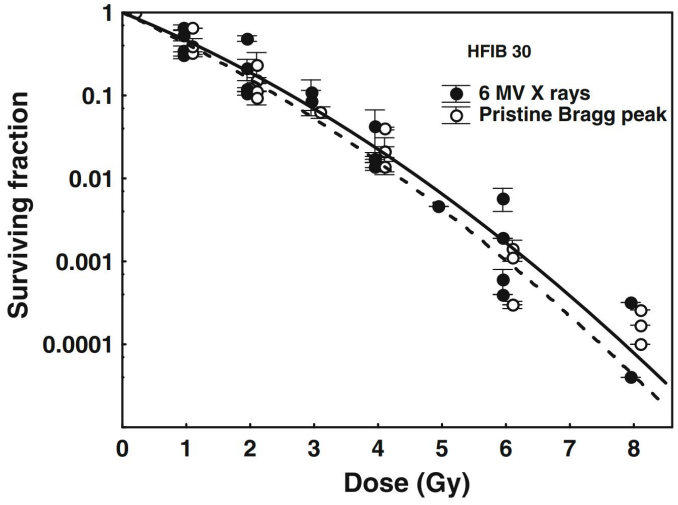


Fig 2. Survival of human skin fibroblasts after irradiation by 6-MV X-rays (solid line and full circles) and by a pristine beam of 60 MeV protons (dashed line and empty circles) around the

maximum of the Bragg peak. Enhancement in cell killing by protons over the Bragg peak region is evident. Circles represent measurements, lines are fits to the linear-quadratic model (Słonina et al. 2014).

The linear-quadratic model providing a simple relationship between cell survival and delivered dose has been extensively used to analyze and predict cellular responses to ionizing radiation (McMahon 2018).

$$S = e^{-\alpha D - \beta D^2} \tag{1}$$

By applying simple mathematical transformations of the above formula and its definition, RBE may be expressed a function of dose and the LQ model parameters representing survival after doses D_p of the tested radiation (protons) and after doses D_x of the reference radiation (X-rays).

$$RBE = \frac{1}{2D_p}\sqrt{\left(\frac{\alpha_x}{\beta_x}\right)^2 + 4D_p\frac{\alpha_x}{\beta_x}\frac{\alpha}{\alpha_x} + 4{D_p}^2\frac{\beta}{\beta_x}} - \frac{\alpha_x}{\beta_x} \tag{2}$$

Most of the available RBE models rely on the LQ model and on the above LQ-based RBE formulation, as summarized in table 1 (Rørvik et al. 2018).

RBE extracted from the experimental data shows a complex pattern of dependences. In general, RBE tends to rise with proton beam penetration depth. When averaged over all cell lines, experimental values of RBE range broadly between values of about 1.0 over the beam entrance region and 1.7 over the distal part of the Spread Out Bragg Peak, SOBP (Paganetti 2014). There are several factors which contribute to the variability of RBE, the most apparent being individual patient radiosensitivity (reflected in cell samples taken from these patients), low statistics of clonogenic assays in *in vitro* studies, or too few repetitions of *in vivo* experiments.

The discussion concerning RBE values in proton therapy is currently based on average values, and does not take into account the variability of individual radiosensitivity in cancer patients. Radiogenomic studies of individual radiosensitivity have demonstrated a considerable variation of individual dose-response curve of skin fibroblasts in a cohort of 152 individuals. The surviving fraction was measured via clonogenic test, where skin fibroblast cells were irradiated with doses of X-rays of up to 4 Gy (Fig 3A). The surviving fraction, SF2, measured after a 2 Gy exposure (the typical fraction dose in radiotherapy) spans between 0.1 and 0.5 (Alsbeih et al. 2016). A broad distribution of SF2 values could imply a large variation of individual RBE dependences if such studies were extended to proton beam irradiation.

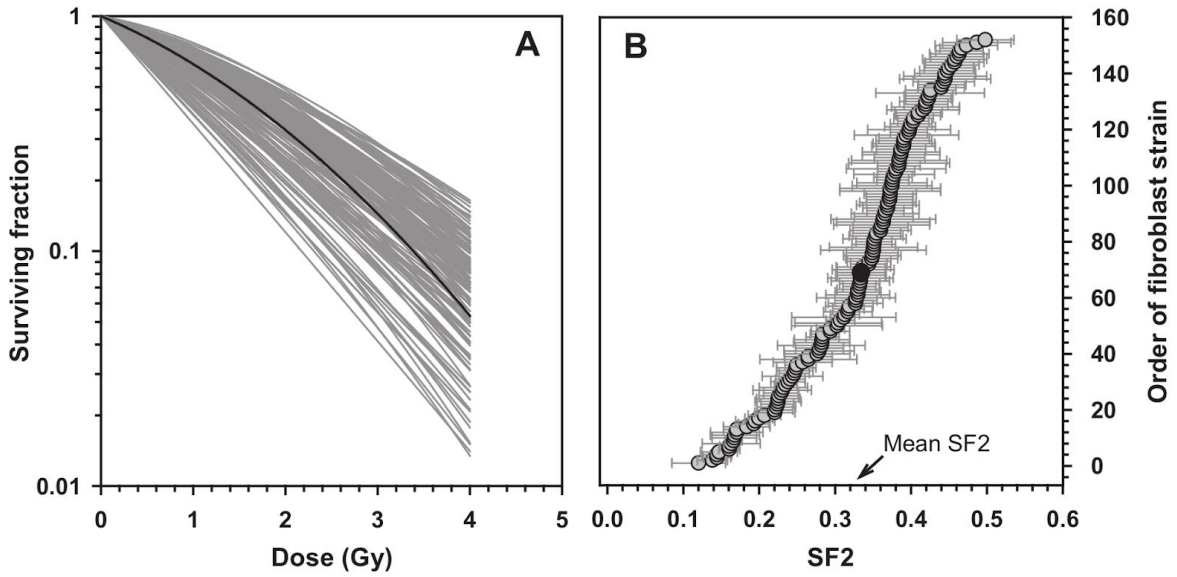


Fig 3. Survival curves of human skin fibroblasts irradiated with 320 kVp X-rays (including 2mm Al filter) for a cohort of 152 individuals. Grey lines depict linear-quadratic fits for each individual sample (strain), while the solid black line represents the mean value (part A). Distribution of survival at 2 Gy (SF2) is shown in part B of the plot, together with surviving fraction error bars. Data points are sorted by increasing SF2 (Alsbeih et al. 2016).

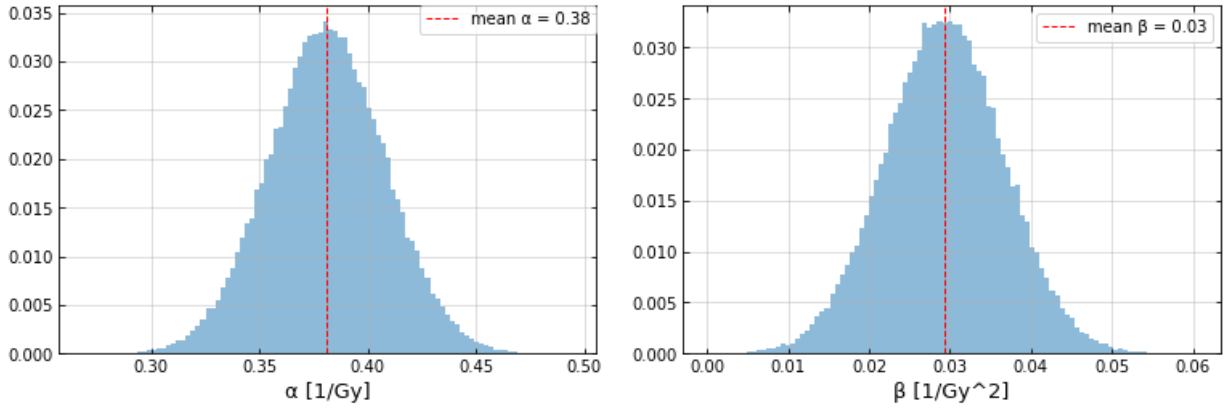


Fig 4. Histograms drawn from distributions of LQ α and β parameters fitted to experimental data points concerning the Chinese hamster V79-753B cell line, irradiated by 3.2 MeV protons (Belli et al. 1998).

Clonogenic tests of cell survival are usually performed with fairly small statistics (often no more than 3-5 measurements at any single dose). This leads to some uncertainty of the measured survival probability, resulting in a broad distribution of values of α and β parameters of the LQ model best fitted to these data, as shown in Fig 4.

3. Clinical Use of Constant RBE and its Rationale

Clinical use of a constant value of RBE (CRBE) recommended by ICRU 78 (ICRU 2007) is based on a conservative approach. The constant value of RBE = 1.1 is derived as an average RBE of several *in-vivo* experiments (Paganetti et al. 2002). This approach is an approximation but it is generally supported by the lack of confidence that the available biological data would justify clinical application of any other proposed approach (Carabe et al. 2012). Despite the recognised elevation of RBE at higher LET values over the distal regions, it is generally considered that this region constitutes only a small fraction of the irradiated volume, hence changes in RBE are not expected to have any major impact on the final treatment outcome.
All clinics offering proton therapy around the globe have adopted the CRBE approach. The variable RBE (VRBE) is accounted for mainly by adjusting the treatment plan in such a manner that the enhanced RBE region is minimized, thus avoiding the consequences of overdosage.

Variable RBE may be responsible for case-reported normal tissue toxicities over the distal parts of proton-irradiated volumes. Radiation-induced brainstem complications and optic nerve disruption has been observed in some patients undergoing proton therapy of intracranial tumours(Ödén et al. 2019)

Ödén et al. provide a detailed discussion of pro and against constant RBE arguments. The main arguments *against* constant RBE may be summarized as follows:

- the RBE value depends on the position in the irradiated volume, dose, LET and tissue type;
- a constant RBE may underestimate or overestimate toxicity (Jones 2017);
- application of constant RBE may lead to development of “hot-spots” in the therapy plan.

4. Variable proton RBE models

Most of the variable RBE (VRBE) models found in the literature are empirical. They are based on experimental data from *in vitro* proton irradiation of various cell lines and typically apply the linear-quadratic (LQ) model, where cell inactivation is the biological endpoint(Rørvik et al. 2018). Mechanism-inspired models are also available, such as the microdosimetric-kinetic-model (MKM), the local effect model (LEM), and the repair-misrepair-fixation (RMF) model. Rørvik et al. published a review of mechanistic models of RBE, the main features of which are given in Table 1. For details, see the original publication (Rørvik et al. 2018).

Model reference	Model abbreviation	Cell lines	Number of data points	RBE_{max} dependencies	RBE_{min} dependencies
Belli *et al* (1997)	BEL	V-79	6	$d(E)$	$d(E)$
Wilkens and Oelfke (2004)	WIL	V-79	19	LET_d	1
Tilly *et al* (2005)	TIL (TIL2/TIL10)	V-79/multiple	7/4	LET_d, $(\alpha/\beta)_x$	1
Chen and Ahmad (2012)	CHE	V-79	14	LET_d	1
Carabe *et al* (2012)	CAR	V-79	44	LET_d, $(\alpha/\beta)_x$	LET_d, $(\alpha/\beta)_x$
Wedenberg *et al* (2013)	WED	Multiple	19 (24)	LET_d, $(\alpha/\beta)_x$	1
Jones (2015b)	JON	Multiple	28 (200)	LET_d, α_x	LET_d, β_x
McNamara *et al* (2015)	MCN	Multiple	285	LET_d, $(\alpha/\beta)_x$	LET_d, $(\alpha/\beta)_x$
Mairani *et al* (2017)	MAI	Multiple	25 (31)	LET_d, $(\alpha/\beta)_x$	1
Rørvik *et al* (2017)	RØR (RØRU/RØRW)	Multiple	85	LET_d, $(\alpha/\beta)_x/d(L)$, $(\alpha/\beta)_x$	1
Peeler (2016)	PLR	Multiple	48	LET_d, $(\alpha/\beta)_x$	LET_d, $(\alpha/\beta)_x$
Frese *et al* (2011)	FRE	Plan-based	0	LET_d, α_x	1
Unkelbach *et al* (2016)	UNK	Plan-based	0	LET_d	LET_d

Table 1. List of relevant mechanism-inspired RBE models, collected by Rørvik et al. (2018)

Another simplified approach is the use of LET-weighted dose (McMahon et al. 2018) which reduces the uncertainty in the α/β factor used in most of the phenomenological models. These models in their basic formulation predict RBE dependences within a single fraction.

In most of these models proton beam quality factoring is considered, typically reduced to dose-weighted linear-energy transfer (LET_D) of protons. Such simplification leads to an issue related to the definition of *LET (Grzanka et al. 2018)*. While losing their kinetic energy, protons not only deliver energy by ionization, but can also trigger nuclear reactions where secondary particles heavier than protons can be emitted. Such particles will have very short ranges (usually < 100μm), due to their low energy (up to a few MeV/nucleon) but a relatively high *LET* (usually > 100keV). The contribution of these secondary particles to RBE and their role in radiobiological modelling is still uncertain and is currently under study (Tommasino & Durante 2015).

5. Treatment Planning Systems for Proton Radiotherapy

Up to now almost 200.000 patients have been treated with protons[2]. Currently, over 80 centres offer proton radiotherapy and 13 are being built or undergo commissioning[3].

A treatment plan prepared using a treatment planning system (TPS) precedes any proton therapy treatment. These medically certified software products are commercially available from several companies, such as RaySearch, Varian (Eclipse), or Siemens (SyngoPT). All TPS products are based on optimization procedures which achieve uniform dose delivery to the

[2] https://www.ptcog.ch/index.php/patient-statistics *(access 12.11.2019)*
[3] https://www.ptcog.ch/index.php/facilities-in-operation *(access 12.11.2019)*

selected volume, while incorporating several dose constraints with respect to neighbouring organs at risk. To achieve high accuracy of dose calculations within limited time constraints, the dose distribution is typically calculated by applying analytical models of individual pencil beams and assuming constant RBE (CRBE). In some prototype systems, such as the research version of RayStation offered by RaySearch Laboratories (Ödén et al. 2017a), some capability is provided to evaluate variable RBE on a standard CRBE plan.

On the other hand, the developed research platforms, such as TOPAS and TRiP98 contain more advanced options to be implemented, allowing, to some extent, the introduction of variable RBE to treatment planning. Within the TRiP98 platform an optimizer has been implemented (Krämer et al. 2000). TOPAS features good support for imaging data and a simplified approach to recalculation of the planned dose (Perl et al. 2012). An essential feature of these platforms is the capability to assess the spatial distribution of LET. Analytical models of the spatial distribution of LET are still rather limited (Wilkens & Oelfke 2003); (Sanchez-Parcerisa et al. 2016); (Wilkens & Oelfke 2003) and have not yet been introduced into any commercial TPS, which hinders the possibility of applying radiobiological modelling within commercial systems. To overcome this issue, Monte-Carlo (MC) calculations of particle transport can be called upon, which require time-consuming tracing of each individual particle trajectory. The advantage of MC-based TPS is however the availability of detailed energy-fluence spectra of all particles created by the interaction of the primary beam ions with the local absorber, whereby derived quantities, such as dose-average LET, can be calculated. These quantities provide the necessary input for VRBE models.

Currently, the most advanced research platform is TOPAS (Perl et al. 2012) which uses Geant4, a state-of-the-art particle transport code. While lacking any inverse optimisation module, it is well-suited for performing forward plan recalculations. TOPAS supports direct readout of patient diagnostic data (CT scans) and treatment plan specifications (DICOM RT files). These may be used to setup a simulation of particle transport. Among the available outcomes of such calculations, the user can choose between dose, LET (track- and dose-weighted for primary and secondary protons), RBE or biological dose (calculated using a selected phenomenological model).

The TRiP98 treatment planning system originates from the early days of carbon ion radiotherapy(Krämer 2009), and was developed at GSI at the time carbon ion therapy was being introduced in Europe. TRiP98 does not apply Monte Carlo particle transport simulation, but relies on pre-calculated energy-spectrum data. The input spectra for TRiP98 can be generated by Monte Carlo particle transport codes such as e.g. SHIELD-HIT12A (Bassler et al. 2014), FLUKA (Böhlen et al. 2014) or TOPAS. An extremely useful feature of TRiP98 is a powerful optimizer which enables non-linear biological optimization using several versions of the LEM model.

To make it easier to script and interface TRiP98 to the DICOM standard, the pytrip98 python package has been developed (Toftegaard et al. 2014), capable of visualising patient CT data, dose distributions and LET overlays. In contrast to commercial products, most of the research

TPS lack any advanced graphical user interfaces (GUI) and require input in the form of scripts or commands. The pytripgui package fills in this gap, enabling users to prepare treatment plans using the TRiP98 package, locally or remotely. Development of open-source tools (including pytrip/pytripgui packages) is supported by the INSPIRE European infrastructure grant.

Direct optimization using variable RBE is feasible (Frese et al. 2011); (Guan et al. 2018); (Sánchez-Parcerisa et al. 2019), but results in large uncertainties of the predicted RBE values.

6. Dealing with RBE uncertainty

Over the recent years several new modes of proton therapy treatment have emerged, such as spot-scanning arc treatment (SPArc) or Grid therapy. SPArc is a novel form of intensity modulated proton therapy, assuming dose delivery with continuous gantry rotation mode and increased number of beams (Li et al. 2019). Due to an efficient optimization planning algorithm SPArc has greater capability to improve the plan robustness and quality (dose lower than 50% in some organs at risk, as compared with proton IMPT). Increase in the number of incident beams leads to areas of elevated LET being smeared out (Fig. 5) alleviating concerns of increased biological effectiveness (Toussaint et al. 2019). Such an approach also results in a decrease in the level of RBE uncertainty, allowing safer and more robust therapy planning.

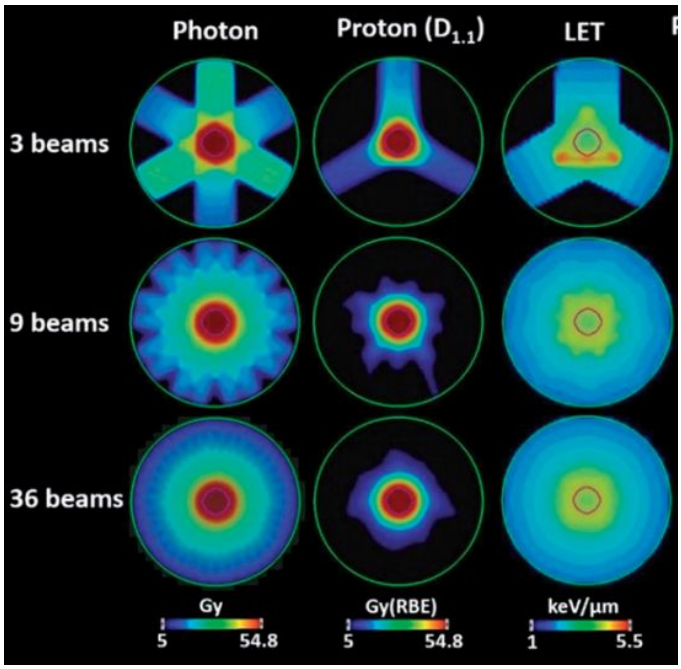


Fig 5. Distributions of photon dose (column 1), proton RBE 1.1 dose (column 2), proton LET distribution (column 3) for three, nine and thirty-six beam plans in a transverse slice of a cylindrical phantom with a central cylindrical target. The elevated LET areas visible in the 3-beam arrangement become smeared out as larger numbers of beams are applied (Toussaint et al. 2019).

Another approach to handle variable RBE is to propagate the underlying uncertainties to the modelled outcomes, in terms of dose and RBE distributions or of DVH and LVH cumulative plots. Statistical techniques such as bootstrapping and Monte-Carlo-based methods are useful tools in radiobiological modelling of such random variables.

A method based on sensitivity analysis of α/β parameters was recently proposed by Ödén (Ödén et al. 2019): 10^4 values of α/β were sampled from a log-normal distribution and used in a calculation of variable RBE models of Wedenberg (Wedenberg et al. 2013) and of McNamara (McNamara et al. 2015). The study also included a large number of scenarios of positioning error propagation. Pseudo-random samples were used to calculate mean values and error bands for DVH, LVH and NTCP. Finally, several plan options were compared, including a clinical plan with constant RBE, with variable RBE and with two or three beams. In the comparison between the plans, not only mean values of DVH were compared but also extents of error bars.

A probabilistic approach to the Wedenberg model may be proposed. The Wedenberg model has one free parameter which is best-fitted against experimental data to a single optimal value. By randomly sampling α and β parameters from joint distributions which reflect the uncertainty and correlation in cell survival data, this single parameter can be replaced by a probability distribution. This in turn leads to a probabilistic version of the model from which a pseudo-random RBE can be sampled, exhibiting a skewed RBE distribution, as shown in Fig 6. This probabilistic approach to the Wedenberg model can then be used to calculate the depth distribution of RBE values, including mean values and confidence intervals, as shown in Fig 7, on which a DVH calculation may be based.

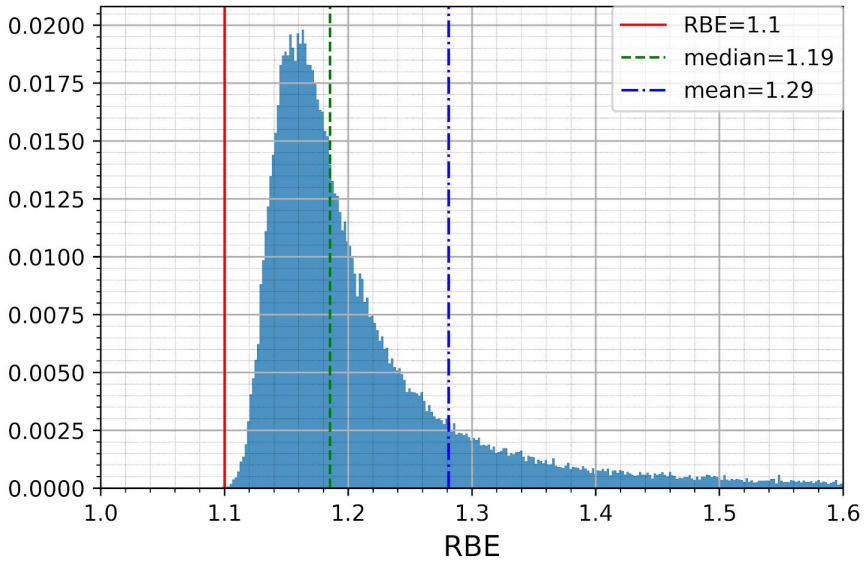


Fig 6. Histogram drawn from the distribution of RBE values for protons of energy 16.7 MeV, dose 2.0 Gy and biological endpoint characterized by α/β = 2.0 Gy in the LQ model.

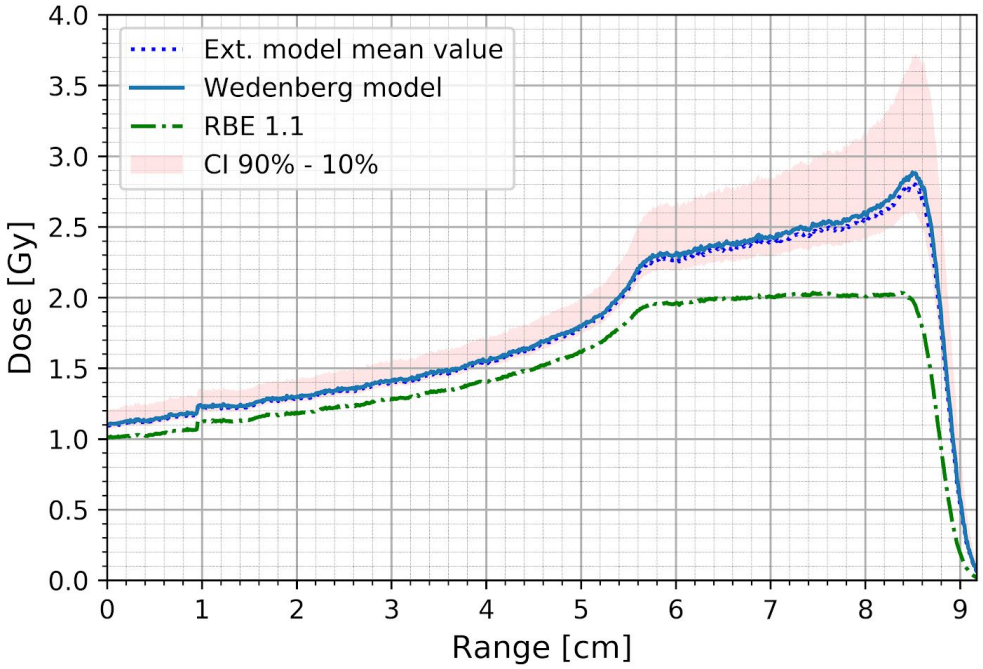


Fig 7. Physical and biological dose [Gy], versus depth, for a proton SOBP, calculated using a probabilistic approach to the Wedenberg model (see text). Blue line represents biological dose from the original Wedenberg model, blue dots represent biological dose from the “probabilistic” Wedenberg model (mean value), green dotted-dashed line represents physical dose multiplied by a constant RBE of 1.1. Red area delineates the 90%-10% confidence intervals in the “probabilistic” Wedenberg model predictions. The biological endpoint is characterized by an α/β ratio of 2.41 Gy in the LQ model.

7. Conclusions

Lack of adequate clinical validation of any variable RBE model imposes **a certain risk in automated application of these models in TPS systems** in a manner similar to that implemented for carbon ions (Lühr et al. 2018).

The likely clinical outcome of introducing a variable RBE has also been of considerable interest in recent dose planning studies. Within these studies the difference between existing plans calculated with a constant RBE and those recalculated using variable RBE models have been quantified, in order to discuss the manner in which such differences may affect dose planning decisions (Rørvik et al. 2018).

The present discussions focus on **mitigating the potential impact of proton RBE uncertainties** in treatment planning decisions, to ensure safe treatment delivery. Potential RBE

mitigation strategies can be categorized into (a) beam angle selection and dose reduction in the distal part, (b) optimization of robustness, and (c) LET optimization. These options have recently been discussed by Lühr et al (Lühr et al. 2018).

Beam angle selection is used in clinical scenarios where certain beam directions are avoided, especially if normal tissues (organs) at risk are positioned close to, or just behind the distal part of the proton beam. Such an approach is widely supported by treatment planners, allowing reduction of LET and of biological dose (according to VRBE models) within certain organs at risk (Fjæra et al. 2017)

Currently, robustness of treatment plans is achieved by the application of range margins and proper beam geometry. Several studies(Ödén et al. 2017b); (Unkelbach et al. 2016) suggest that probabilistic and worst-case optimization may moderate the uncertainties and lead to more robust plans. This would however require a major paradigm shift in the optimization and evaluation routines implemented in treatment planning systems.

Another limitation imposed by optimization algorithms is in including dose-only objectives in the cost function. Therefore an additional factor, allowing redistribution of the high-LET component over the treated volume would limit or minimize regions with a high RBE or move them away from the distal part. The idea of LET painting is not new (Bassler et al. 2010) - it was proposed to overcome the radioresistance of hypoxic regions in heavy-ion radiotherapy.

The increased RBE at the end of the proton tracks leads to the so-called extended biological range. Within current estimates, this increases the VRBE-related range by about 2-4 mm. With improved range monitoring and positioning techniques these estimates may be experimentally verified to supply clinical plans with smaller margins.

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