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Review Article

Does the uncertainty in relative biological effectiveness affect patient treatment in proton therapy?

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ABSTRACT

Clinical treatment with protons uses the concept of relative biological effectiveness (RBE) to convert the absorbed dose into an RBE-weighted dose that equals the dose for radiotherapy with photons causing the same biological effect. Currently, in proton therapy a constant RBE of 1.1 is generically used. However, empirical data indicate that the RBE is not constant, but increases at the distal edge of the proton beam. This increase in RBE is of concern, as the clinical impact is still unresolved, and clinical studies demonstrating a clinical effect of an increased RBE are emerging.

Within the European Particle Therapy Network (EPTN) work package 6 on radiobiology and RBE, a workshop was held in February 2020 in Manchester with one day of discussion dedicated to the impact of proton RBE in a clinical context. Current data on RBE effects, patient outcome and modelling from experimental as well as clinical studies were presented and discussed. Furthermore, representatives from European clinical proton therapy centres, who were involved in patient treatment, laid out their current clinical practice on how to consider the risk of a variable RBE in their centres. In line with the workshop, this work considers the actual impact of RBE issues on patient care in proton therapy by reviewing preclinical data on the relation between linear energy transfer (LET) and RBE, current clinical data sets on RBE effects in patients, and applied clinical strategies to manage RBE uncertainties. A better understanding of the variability in RBE would allow development of proton treatments which are safer and more effective.

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Compared to photon radiation, proton radiation shows a favourable absorbed dose distribution, which allows for reducing integral dose and sparing of normal tissue. Furthermore, proton radiation has a higher ionisation density than photon radiation resulting in an increased efficiency of cell killing [1]. This efficiency increase is due to an increase in linear energy transfer (LET), the energy deposition per unit of path length, which is a measure of the quality of different types of radiation [1]. The concept of relative biological effectiveness (RBE) has been introduced to account for the increased efficiency of different types of radiation to produce biological effects. RBE is defined as the ratio of a dose from the reference radiation, photons, to a dose from any other radiation quality (such as particles) to produce the same biological effect. Proton treatment in the clinic uses the RBE to convert the absorbed dose to an RBE-weighted dose to describe a response equivalent to photon treatments. This allows long-term clinical experience from photon treatments to be applied to proton therapy.

Proton therapy currently relies on a constant RBE value of 1.1, which is a conceptual constant based on experimental data [1], as recommended worldwide [2]. This factor means that a given

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proton dose is expected to be equivalent to a 10% higher photon dose for all tumours, tissues and organs. The RBE is a complex measure, which is affected by a number of variables such as: tissue type, endpoint, dose per fraction, and LET [3,4]. However, as discussed below, strong evidence exists that the RBE actually varies along the proton beam track. The RBE variation is a universal issue, and applies to all tissues where proton therapy is used. Critical concerns of a constant RBE value includes the limitations of underlying data and the caution that in certain cases RBE can be below 1.1 in the target volume [5]. The central question arising from the variation of the proton RBE is, to what extent, and in what form, it affects patient treatments.

In a proton treatment field, the LET increases with depth along the spread-out Bragg peak (SOBP) with a substantial increase at the very distal edge. The resulting RBE increase adds uncertainty to a treatment plan, as it is currently unclear how the altered RBE translates into clinical impact [6]. This is of critical concern, as the distal edge of the SOBP is likely to be located in the normal tissue surrounding the tumour, or even right in front of an organ at risk (OAR) (Fig. 1). Whether the increase of the RBE towards the distal edge is a clinical issue, or the use of a fixed RBE of 1.1 is an adequate clinical solution is under debate, and there is an increasing awareness of clinical uncertainties in proton therapy arising from RBE issues [2,7–9].

Within the European Particle Therapy Network (EPTN), work package 6 on radiobiology and RBE [10–13], a workshop was held in February 2020 in Manchester, with one day of discussion dedicated to the impact of RBE of protons in a clinical context. The workshop was a revisit of the international expert workshop on the radiobiology of proton therapy held in Dresden in 2016 [6]. Current data on RBE effects, patient outcome and modelling of experimental as well as clinical studies were presented. Furthermore, representatives from European clinical particle centres who were involved in patient treatment laid out their current clinical practice on how to consider the RBE variations in their centres. In line with the workshop, this work considers the impact of RBE issues on patient care in proton therapy by reviewing preclinical data on the LET-dependent RBE, current clinical data sets on RBE effects in patients, and applied clinical strategies to manage RBE uncertainties.

Preclinical foundation

Several in vitro experiments have assessed the RBE of protons in a range of cell lines, e.g. [15], as reviewed in [1,16,17].The range of the in vitro RBE varies with cell line, endpoint and experimental conditions. The RBE is also dependent on the reference radiation, as the biological effect of kV and MV photons differs. For clinical comparison, 6 MV is most suited, but experimentally, kV is often used and in this case, a correction relative to 6 MV is needed [6,18]. While radiation response relies on beam time structure and dose rate [19], the effect of these factors on the RBE requires further investigation [6]. This is also the case for ultra high dose rate, FLASH, with dose rates larger than 40 Gy/s [20]. The increased LET at the distal end of a proton track has been demonstrated to translate into an increased RBE in vitro [14,16,21–23] (Fig. 2A). In most of these studies, the endpoint has been clonogenic survival. Additionally, the level of residual 53BP1 foci and γ-H2AX foci, representing processing of DNA double strand breaks, demonstrates differential DNA damage at the distal edge of the SOBP [24,25]. Within one study, as e.g. from Chaudhary et al, in normal fibroblasts, the RBE in a SOBP ranged from 1.07 (LET of 1.2 keV/µm) to 2.45 (LET of 25.9 keV/µm) [14]. In vitro experiments can cover a larger LET range than what may be obtained in vivo or in clinical situations, leading to higher maximum RBE values. This is due to the conditions of in vitro experiments which are mostly performed with cells in monolayers, presenting a well-defined small sample volume along the proton track, thereby allowing spatial depth sampling of RBE on a sub-millimetre scale. However, this does not represent the situation in tissue, where the volume effect plays a major role, which implies that the severity of acute and late side effects increases as the volume of normal tissue irradiated is increased [26]. The central question is whether the observed in vitro effect translates into a clinical impact and to what degree an RBE increase can be expected to occur in different tissues. To obtain a single LET value in a considered volume, all occurring

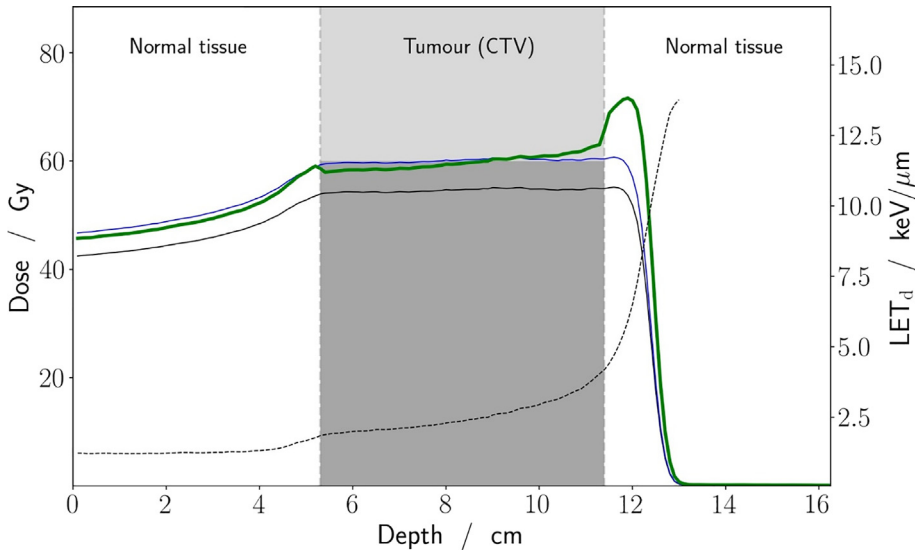

Fig. 1. Absorbed dose (black solid line), RBE-weighted dose with an RBE of 1.1 (blue solid line), and dose-averaged linear energy transfer (LET_d) (dashed line) for a clinical proton treatment field with a prescribed dose of 60 Gy(RBE) in 30 fractions. The calculated variable RBE-weighted dose (bold green line) is the product of absorbed dose and LET-dependent previously published in vitro RBE data [14]. RBE data for tumour and normal cells were applied in the clinical target volume (CTV) and normal tissue, respectively. Note that the difference between RBE-weighted dose assuming an RBE of 1.1 or a variable RBE is small within the tumour target but large at the distal edge, within normal tissue. However, the exact shape of the green RBE-weighted dose curve is uncertain and depends on the differential radiation response between normal and tumour tissues. Modified from [6].

LET values need to be averaged. This can be realised as dose-averaged LET (LET_d) and track-averaged LET (LET_t) by weighting the different LET values according to their contribution to absorbed dose and particle fluence, respectively [27]. Current RBE models are to a great extent based on in vitro data on clonogenic survival [2,28] measuring the local RBE at a certain position within the treatment field rather than the integral response of tissue, and while clonogenic survival may to some extent represent tumour response, as a surrogate for normal tissue damage, it is limited to certain endpoints [29].

In experimental in vivo data for normal tissue endpoints, the RBE of protons has been found to generally be around 1.1, as reviewed in [1,17], while an increased effect in the distal edge of a SOBP has been demonstrated [18,30–32]. To investigate the role of RBE for central nervous system late effects, in vivo experiments have been performed with a well-established rat spinal cord model [30], demonstrating an increase in RBE from 1.13/1.06 (single fraction/split doses) in the entrance part of the beam (LET_d of 1.4 keV/μm) to 1.20/1.12 at the mid SOBP (LET_d of 2.7 keV/μm) and 1.26/1.23 at the distal edge (LET_d of 5.5 keV/μm) (Fig. 2B). The dependence on the dose per fraction is here inconclusive and not in trend with the expectations that the RBE will decrease with increasing fraction dose. This is probably due to the small difference in dose per fraction, high dose values, and the biological uncertainties in the system. Due to the small diameter of the rat spinal cord and the volume-independent response in this model, these RBE-values solely reflect the response to the local beam quality, which is similar to the in vitro data and in contrast to the models mentioned below. Studies of intestinal crypt regeneration and lung tolerance have also been performed [31–33], showing an increased effect of 14% when comparing dose for regenerated crypts in the middle of the SOBP to the end of the SOBP [32], while the RBE for lung toxicity was found to increase by 6% [31]. For these endpoints, the whole body or mouse thorax was irradiated in the middle or at the end of the SOBP. Thus, the irradiated target was covered by around 1.5 cm of the SOBP width, leading to an average RBE over an extended LET interval. Further studies demonstrated that motion during irradiation affected the positioning and hence the outcome of the measurements [34], which underlines the technical challenges in advancing from in vitro to in vivo studies.

In vivo studies are considered an essential transition from 'hypothesis-generating' in vitro data to clinical translation: in vivo models permit simulation of clinical treatments and allow for much more complex biology to be considered. Limited in vivo data have been published on distal edge effects in normal tissue, in part due to the challenging nature of in vivo experiments [35,36], but new models and platforms are evolving [37]. There is a need for more in vivo data in a broad panel of biological models, elucidating how important factors such as fractional dose and tissue type influence the RBE [2,36,38].

For the response in tumours, a range of factors influencing radiosensitivity are known for photon radiation. Relevant biological characteristics of tumours are, e.g., the number of cancer stem-like or clonogenic cells, human papillomavirus status, tumour micro-environmental factors such as hypoxia, and differences in intrinsic radiosensitivity due to DNA-damage response, repair mechanisms and signalling pathways [39]. Differences in tumour radiosensitivity, both within individual tumours as well as between patients, could blur the effect of a variable RBE. However, there are differences to the cellular radiation response caused by photons and protons. Studies in vitro have demonstrated proton radiation-induced DNA double strand breaks (DSBs) to be preferentially repaired by homologous recombination (HR), one of the major DNA repair pathways in DNA-damage response [40–43]. In a recent in vivo study, tumours with HR deficiency due to BRCA1 mutations display an increased radiosensitivity in the Bragg peak as compared to photon radiation, and thereby an increased RBE compared to tumours with a functional HR pathway is expected [44]. These findings point towards the possibility of selecting specifically proton radiosensitive tumours for proton therapy.

Clinical evidence

Challenges in clinical assessment of the radiation response

Despite the observation of a variable proton RBE in experimental in vitro and (to a lesser extent) in vivo settings, the relevant RBE

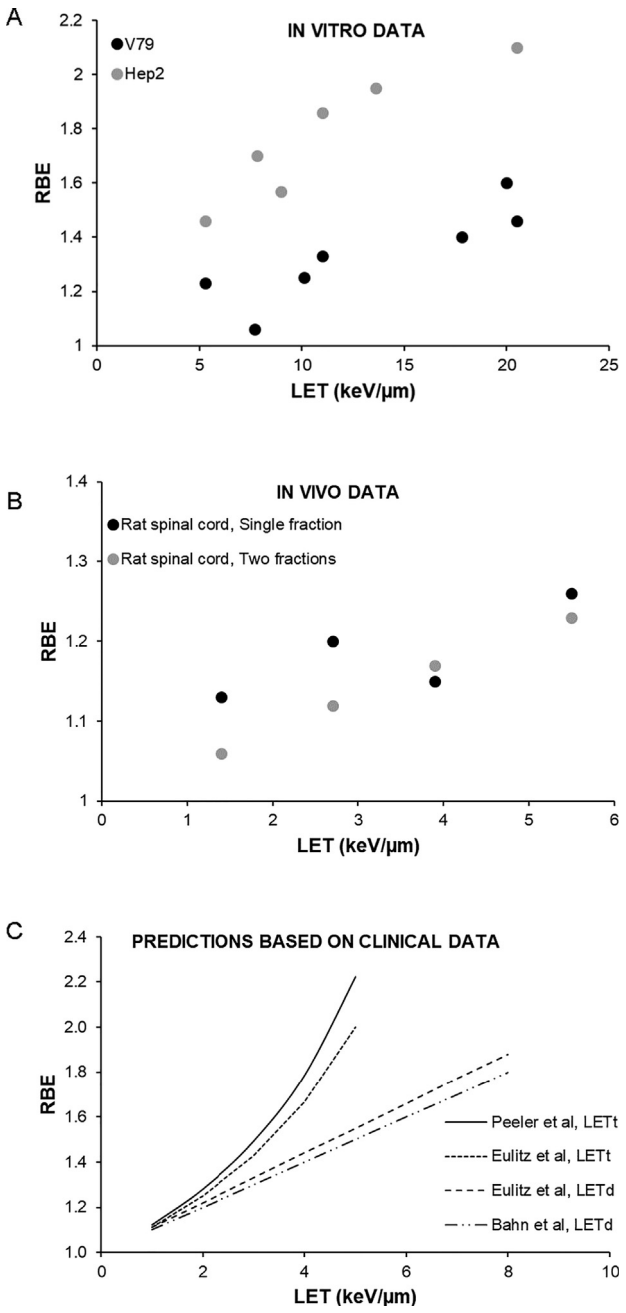

Fig. 2. Examples of previously published empirical data showing a proton RBE-LET dependency. A: In vitro data of RBE for 10% survival fraction from clonogenic assays [22,45,46]. B: In vivo data of RBE for late responding normal tissue [30] C: Clinical data on RBE for normal brain tissue after fractionated proton treatment from retrospective analyses [47–49]. RBE: relative biological effectiveness; LET: linear energy transfer.

for clinical treatment remains imprecisely determined. Obviously, determining RBE in patients is much more difficult and differs in several aspects from well-defined experimental conditions:

- While experiments are designed to induce well-defined biological effects and to systematically test their dependence on relevant parameters, clinical treatments specifically seek to avoid potential risks of elevated radiation effects. Predominantly, this is achieved by generating treatment plans that are robust against range uncertainties. However, as the highest RBE occurs at the distal end of the treatment field, this also results in treatment plans that are more robust against RBE-uncertainties in critical OAR. Thus, the incidence of measurable clinical effects is generally low, which complicates a systematic assessment of radiation tolerance parameters.
- Patient positioning as well as treatment planning results in range and dose uncertainties in patients. Reducing the impact of the uncertainty is one of the priorities in proton treatment planning. This leads to choices of beam setup and optimization parameters, which are also likely reducing the impact of RBE variations. In other words, physically robust treatment plans are likely to be also biologically more robust.
- In contrast to experimental settings, clinical studies observe integral responses of organs or tumours to the whole dose distribution rather than to the local dose. Even if a local response is detected (e.g. by imaging), it may still be entangled with other influencing factors such as volume effects or the LET- and dose-distribution in the entire organ. This prevents determining strictly local RBE-values for comparison with RBE-model predictions.
- In the best - but rather unlikely - case, clinical RBE values may be derived from isoeffective proton and photon treatments. Such an RBE, however, will include the model-predicted RBE-distribution as uncertainty and may also be biased by other factors, e.g. the irradiated volume.
- The inherent heterogeneity of patient cohorts in, e.g., type, volume and location of the tumour, individual radiosensitivity, comorbidities and other risk factors challenges clinical outcome analysis as compared to experiments in highly standardized animal models. Thus, in clinical trials, there is a trade-off between homogeneous patient cohorts and case numbers.

Conditions under which clinical RBE effects are expected

Variable RBE effects can only be observed clinically if the product of absorbed dose and actual RBE is sufficiently high to induce measurable clinical effects [6,35]. In clinical proton treatment plans, however, the highest (modelled) RBE values are typically found at distal field gradients, where the absorbed dose drops-off rapidly (see Fig. 1). Additionally, substantially elevated LET values only occur in a small fraction of the total irradiated volume. Accordingly, variable proton RBE effects will emerge most clearly, and have clinical implications, (i) at locations, where the dose is close to an organ dose threshold and the LET takes elevated values, as well as (ii) in tissues severely affected by localized high doses. Thus, serial organs distal to the beam and directly adjacent to the target volume are at highest risk.

Regarding tumours, providing evidence for a variable RBE based on clinical data is complicated by several factors:

- LET distributions vary only weakly within the clinical target volume (CTV) (Fig. 1) [50] and between patients, typically leading to small modelled elevations of biological effect, with little expected impact on tumour response.
- Inter- and intra-tumour heterogeneity impacts treatment outcome and is likely to obscure the detection of a variable RBE effect in tumours.
- Tumour control primarily depends on cold spots in the dose distribution (typically avoided in the CTV) rather than local RBE-driven dose hot spots.

As a consequence, effects of RBE variation inside the gross tumour volume and CTV are unlikely to be detected. The relevant question is whether the average RBE value for a specific tumour type is significanlty different from the generic value 1.1.

Emerging evidence of a variable RBE for late effects

Despite the aforementioned challenges, recently, a growing number of clinical reports have scrutinized the assumption of a constant clinical RBE of 1.1. They have gathered clinical evidence that the variation of proton RBE also affects patient treatment by carefully separating RBE-related effects from other factors that influence the observed radiation response, such as varying intra-patient radiosensitivity or uncertainties in dose deposition. Primarily, late side effects have been studied. To quantify the variation of RBE, most studies analysed radiation-induced effects observed on patient follow-up imaging and correlated them with dose or dose and LET. At the workshop, authors of four such studies, performed in Dresden, Heidelberg, Boston and Uppsala, gave an update on their work, which are briefly summarized here.

The studies from Dresden and Heidelberg addressed the endpoint of late radiation-induced brain injury (RIBI) following proton treatment for grade 2 and 3 glioma in Dresden, [47] and grade 1 and 2 glioma in Heidelberg, [48]. The RIBI lesions were diagnosed and delineated based on follow-up magnetic resonance imaging (MRI). The findings of the two studies agreed to a large extent. The spatial distribution of RIBI was highly non-uniform. An accumulation of RIBI at the edge of the CTV as well as in the periventricular region (PVR) was observed. RIBI location was significantly associated with dose and dose-average LET_d in voxel-wise logistic regression. In patient-wise analysis, high near-maximum variable RBE-weighted dose correlated with RIBI occurrence. Additionally, both studies consistently found a significant increase in radiosensitivity of the PVR. Considering a different radiation sensitivity within the PVR was crucial to separate and quantify the variable radiation effect caused by the variable RBE. While the similarity of these two studies and the consistency of their results can be considered as a first mutual validation, a dedicated cross-validation of the Dresden and Heidelberg cohorts will follow. The combined results demonstrate the dependence of RBE on LET_d, supporting a variable RBE-model for proton therapy in the brain.

However, the observed interplay between a variable RBE and a spatially varying radiosensitivity complicates the situation in conventional brain tumour treatment planning. In a retrospective replanning study, the Heidelberg authors could show that a redistribution of LET_d can result in an unintended increase in RIBI risk for a particular patient group, when common LET_d averaging methods such as multiple-field plans are used [51]. Their findings underline the importance of a mature treatment planning concept accounting for both variable RBE and radiosensitivity.

A different approach was previously taken in Boston to analyse a chest wall irradiation cohort in which the distal end of the SOBP was in the lung [52]. The study tested the hypothesis that late radiographic changes in the lung after chest wall irradiation with protons or photons would be the same for both cohorts - which would support current RBE practice with a fixed RBE of 1.1. Ten consecutive proton patients with follow-up CT scans were matched with a photon cohort considering age, chemotherapy regimen, disease laterality and implant status. Two parallel analyses were performed: (i) Quantitative Hounsfield Unit changes per unit dose between the pre-treatment and follow-up radiographic images and (ii) qualitative radiographic grading in follow-up CT

scans. Based on the data from the two analyses, the original hypothesis was rejected in favour of stating that late radiographic abnormalities in the lung were greater for the proton cohort, suggesting an end-of-range RBE greater than 1.1 and providing clinical evidence that a fixed proton RBE of 1.1 is inadequate for this endpoint.

Finally, a study from Uppsala investigated the spatial correlation of LET_d and RBE-weighted dosedistributions for intracranial clinical cases with suspected treatment-related toxicity following proton therapy [53]. Normal tissue regions with suspected radiation-induced morphological changes were identified and delineated based on clinical evaluations and MRI during follow-up. The analysis showed that high LET_d and modelled RBE values were spatially correlated with observed toxicity areas, while setup and range uncertainties had a minor impact on the correlation. The study also showed that alternative optimisation strategies could allow for reducing LET_d, RBE-weighted dose and normal tissue complication probabilities, while maintaining an acceptable plan when evaluated against criteria derived from the assumption of a constant RBE = 1.1.

Deriving RBE models directly from clinical data

To parametrize the LET dependence of RBE in patients, the two clinical reports on the late brain lesion endpoint RIBI discussed above approximated an empirical clinical RBE as

$$RBE = 1 + m\ LET \tag{1}$$

from their multivariate logistic regression analyses based on LET_d, resulting in similar values for parameter m of 0.11 μm/keV and 0.10 μm/keV in the Dresden [54,55] and the Heidelberg [48] cohort, respectively.

Earlier, Peeler et al. [49] analysed the voxel-wise induction of early MR image changes in paediatric patients with ependymoma treated with proton therapy. From their data, an approximate RBE for a 50% probability to induce a T2-weighted MR image change in a MR voxel was estimated as

$$RBE = \frac{1}{1 - k\ LET} \tag{2}$$

using track-averaged LET_t and $k = 0.11$ μm/keV. The RBE model in Eq. (2), together with track-averaged LET_t and $k = 0.10$ μm/keV was also used to estimate the RBE variation for radiation-induced necrotic brain voxels observed in contrast-enhanced T1-weighted MR images [47].

These clinically derived RBE models are shown in Fig. 2C. They have in common that they are purely empirical, limited by their missing dependence on dose, derived from image-based brain toxicity studies and lacking a direct comparison to photon data. They do not account for a reduction in RBE with increasing dose per fraction (or vice versa). At a specified dose per fraction these equations will be predictive, but will not apply to a different dose per fraction since RBE has been found to have an inverse relationship with dose per fraction in in vitro data [5]. Note that the two clinical RBE models in Eqs. (1) and (2) result in the same RBE-values for low-LET values. RBE models with more complex equations have been suggested based on the linear-quadratic models [56]. However, for deriving RBE models from clinical data, a simplified equation is more practical.

Current clinical practice

Representatives from six European proton therapy centres (Aarhus, Dresden, Groningen, Manchester, Trento and Uppsala) presented their centres' current clinical practice regarding RBE prescription and RBE mitigation strategies.

All centres were following the current clinical guideline of a constant RBE value of 1.1 compared to photons. No centre had concrete plans to move to, or integrate, a variable RBE calculation as a standard feature in their clinical treatment planning system. At the same time, all centres were applying various measures to counteract the potential clinical impact of variable RBE, although the strategies varied between centres.

In a general approach to decrease clinical uncertainty, the risk of complication by an elevated RBE weighted dose in an OAR at the distal edge is reduced by minimizing range uncertainties. This can be obtained by optimising patient positioning accuracy, e.g., by image guidance. Furthermore, all centres generate robust treatment plans using the strategies described below. In critical cases the robustness is explicitly evaluated under specific error scenarios by analysing tumour coverage and/or dose constraints for selected OARs. However, more advanced methods such as robust treatment plan optimization [57] are not applied to all patients.

All centres actively considered the possibility of clinical impact on OARs from elevated RBE values towards the distal end of the treatment field. A common action of all centres was to take special care in the selection of treatment field arrangements. In particular, centres tried to avoid field angles that result in proton beams stopping in or directly in front of an OAR as much as possible, i.e. remaining mindful of physical range uncertainties and "biological range extension" due to RBE. Otherwise, the relative weight of an unavoidable field stopping in, or in front of, an OAR is decreased by adding more fields. For example, two centres reported on the application of a minimum of three treatment fields spread with at least 30° in between the fields and at maximum one field facing a critical serially-responding OAR.

All centres were equipped to calculate LET and/or variable RBE distributions for treatment plans. In most cases, patient-specific Monte Carlo calculations were performed retrospectively to investigate possible clinical RBE effects or for research purposes. However, for selected cases, patient-specific LET and variable RBE distributions are also calculated to inform clinicians on potential risks during treatment planning. Calculations are performed for various tumour sites, but most commonly for brain cases. In a very small number of individual cases these calculations resulted in plan adaptations.

The use of single field optimisation, rather than multi-field optimisation (MFO), reduces the risk of individual proton 'spots' with very high weighting being delivered to normal tissues. However, in many circumstances the overall quality of the treatment plan is improved by MFO. A similar consideration applies to the use of two phases, rather than a simultaneous integrated boost (SIB), but in some cases the SIB plan can deliver a significantly better dose distribution. In addition, visual inspection of spot maps can avoid unexpected and unwanted dose hot spots or high spot weight. The use of established dose constraints is a useful adjunct in planning and these have been published for central nervous system (CNS) by the EPTN [58].

Finally, future needs and improvements with respect to RBE and its clinical impact were discussed. Participants expressed the need to gain a deeper insight into actual treatment planning practice (in terms of mitigation of potential variable RBE effects) across European proton therapy centres and also worldwide. A consensus on how we might standardize LET calculation was considered highly important, especially in the event that LET-parameterized RBE-models are introduced in the future [27]. In addition, the possibility of calculating LET and RBE within commercial treatment planning systems was requested. Finally, the importance of additional clinical data collection was underlined. Prospective follow-up imaging, performed at regular time points using harmonized protocols, should be given priority.

Discussion

Since the previous international expert workshop on variable proton RBE (Dresden, 2016 [6]), clinical evidence for elevated proton RBEs has mounted. Awareness of the topic has increased and concerns persist about whether using a fixed RBE of 1.1 is the optimal solution for proton therapy. The fact that RBE for protons is variable leads to additional clinical uncertainty and impacts, directly as well as indirectly, the way proton therapy is currently applied in clinical practice. The uncertainty of distal edge-effects and the fear of proton-induced complications result from incomplete knowledge of relevant proton dose–response data and understanding of RBE dependencies in patients. This may lead to a defensive approach in treatment planning for protons meaning that we will not fully utilize the advantageous physical properties of protons.

Making a decision on the optimal use of the RBE for proton therapy requires more data, originating from both experimental studies and clinical cohorts. Efforts must be made to identify, first, the magnitude and extent of RBE variation and, second, those factors that are critical for clinical application. So far, all studies reporting evidence for clinical effects of a variable RBE are considering normal tissue reactions (asymptomatic or symptomatic) - mostly using late-stage imaging changes as endpoint - but for reasons discussed above, not tumour response. Current clinical trials comparing normal tissue toxicities for protons versus photons, plus future studies designed to answer questions about biological differences between the modalities have recently been reviewed and discussed in [59].

Since the EPTN workshop, more clinical studies on RBE effects have emerged, and two studies from Boston on late toxicity have been published. The first study [60] concluded that the increased rib fracture rate seen after proton therapy for breast cancer was probably associated with an increased LET_d leading to an increased RBE at the distal edge of the proton beams. In a second study [61], in a patient cohort with brain tumours or head and neck cancers receiving proton therapy, the authors could not find an association of LET with risk of brain necrosis when adjusted for dose. The authors pointed out that a voxel-based analysis of brain necrosis as an endpoint was difficult owing to uncertainties in the spatial origin of the necrosis, high demands on follow-up imaging quality and timing, inter- and intra-patient variability in radiosensitivity, and the simultaneous effect of dose and LET. Hence, the observation of an expected increase in RBE at the end of range in patients might be obscured by these uncertainties and other confounding factors.

The EPTN workshop held in Manchester in February 2020 highlighted that there is a clinical awareness of the variable RBE in proton therapy, which is incorporated into daily clinical practice at European proton therapy centres. Strategies presented to counteract the risk of RBE dose uncertainty during treatment planning included delivery of more than one field, a focus on placing the distal edge outside an OAR, such as the periventricular region, and the evaluation of LET distributions in treatment plans for individual patients. While these different strategies may be effective in reducing uncertainties and risks associated with a variable RBE, they simultaneously impact proton treatment planning and potentially lead to sub-optimal proton plans with more tissue being affected by additional dose. Certainly, there is a need for further investigation of the impact of RBE uncertainty mitigation strategies, both directly and indirectly, on treatment plan quality. Clinical implementation of a variable RBE model must be considered carefully, as it may be robust planning including a variable RBE implies paying a price e.g. in terms of target coverage. Another possibility is to strive for optimized LET distribution, but to maintain the same absorbed dose.

An important point regarding the clinical datasets for observing an increased RBE effect is that most small volume effects are observed in the CNS, where the level of acceptable complications is particularly low. Therefore, such clinical datasets show very low numbers of serious complications, which makes it, together with the relatively small patient cohorts in PT, difficult to determine accurate RBE values for these toxicities. As an alternative, endpoints with higher incidences can be chosen to better quantify the variability of RBE in patients, although these may be less clinically relevant. Clinical analysis of RBE requires a balance between what data are available for modelling and what endpoints are clinically relevant, and there is a need to find a reasonable compromise. The aforementioned study by Peeler et al. [49] as well as the study from Giantsoudi et al. [62] are good examples on how to handle this dilemma.

Daily variation in patient positioning, anatomy and beam delivery between radiation fractions results in smearing-out of locally elevated LET-values. RBE-weighted dose hotspots observed in treatment planning are reduced by such LET smearing. However, many PT centres are currently working hard to increase treatment precision, for example by introducing advanced imaging and treatment adaptation techniques. Achieving higher physical precision may lead to RBE-weighted dose hotspots being maintained and becoming more clinically relevant in the future.

In order to reach a consensus on whether to implement a variable RBE model, additional knowledge is needed on different levels including:

- From experimental studies:
  - Systematically acquired in vivo data on the LET- and dose-dependence of the RBE in a number of normal tissue models
  - Use of clinically relevant fractional doses
  - Investigation of clinically relevant endpoints
  - Determination of RBE in late versus acute endpoints

- From clinical data sets:
  - Direct comparison of proton to photon response data
  - Additional treatment sites beyond the brain and base of the skull
  - Sophisticated and robust clinical outcome analysis to separate different biological effects from variable RBE
  - Treatment plans archived in a way that allows retrospective data retrieval and analysis based on RBE and LET
  - Joint efforts in collection of outcome data to increase size and homogeneity of cohorts and to improve clinical evidence on variable RBE effects
  - Multi-centre collaboration to validate clinical evidence and develop methods to mitigate variable RBE effects

If an implementation of a variable RBE model is decided, some important factors to consider are:

- To maintain comparability of clinical dose prescription and outcome data between centres, standardization of LET-calculation and the reporting of RBE-weighted dose, including employed model and model-parameters, are required.
- Availability of (robust) RBE-weighted dose optimisation in commercial clinical treatment planning systems in addition to absorbed dose.
- Aim for a consensus RBE model and model parameters across all centres to maintain comparability of clinical prescriptions and outcome data between centres.

These lists are not intended to be comprehensive, but rather to provide guidelines for urgently needed research priorities to further improve proton therapy. The aim of EPTN is to strengthen col-

laborative research and cooperation between European centres and to develop a common research strategy. Ultimately, a better understanding of variable RBE may enable centres to achieve both reduced toxicity in normal tissue and increased efficacy in tumour control, for the benefit of our patients.

Disclosure of interest

None.

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