A systematic review of clinical studies on variable proton Relative Biological Effectiveness (RBE)

Abstract

Recently, a number of clinical studies have explored links between possible Relative Biological Effectiveness (RBE) elevations and patient toxicities and/or image changes following proton therapy. Our objective was to perform a systematic review of such studies. We applied a "Problem [RBE], Intervention [Protons], Population [Patients], Outcome [Side effect]" search strategy to the PubMed database. From our search, we retrieved studies which: (a) performed novel voxel-wise analyses of patient effects versus physical dose and LET (n= 13), and (b) compared image changes between proton and photon cohorts with regard to proton RBE (n=9). For each retrieved study, we extracted data regarding: primary tumour type; size of patient cohort; type of image change studied; image-registration method (deformable or rigid); LET calculation method, and statistical methodology. We compared and contrasted their methods in order to discuss the weight of clinical evidence for variable proton RBE. We concluded that clinical evidence for variable proton RBE remains statistically weak at present. Our principal recommendation is that proton centres and clinical trial teams collaborate to standardize follow-up protocols and statistical analysis methods, so that larger patient cohorts can ultimately be considered for RBE analyses.

Introduction

Clinical use of a constant proton Relative Biological Effectiveness (RBE) value of 1.1 began in the late 1970's: 1.1 was a pragmatic average value, determined from skin reactions observed in mice [1]. Yet, at that time, Tepper and his colleagues in Boston remarked: "In those systems where the small intestine were the limiting tissue in a clinical situation, we would assume an RBE of 1.2. As the RBE almost certainly depends on the tissue system studied, further work needs to be performed on a variety of *in-vivo* systems with fractionated radiation and with physical doses per fraction in the clinical range" [1]. Over the decades that have followed, numerous studies have indeed elucidated how proton RBE varies with biological parameters such as cell-type and oxygenation status, and physical parameters such as dose per fraction and linear energy transfer (LET) (although LET estimation can itself be challenging) [2], [3,4]. However, in 2019 a task group of the AAPM concluded that it would be "premature to adopt and recommend a variable RBE model to use clinically" and "in general, use of a constant RBE of 1.1 should be maintained in clinical practice" [5]. The task group also noted that "a potential exception would be the end of range being in a critical structure with known low $\frac{\alpha}{\beta}$… [where] different dose constraints compared to photons may be defined, for example increasing the RBE to 1.2 or 1.3" [5].

Pre-clinical RBE experiments have resulted in a plethora of *in vitro* data on clonogenic survival, demonstrating the local RBE at a certain position within a treatment field, rather than the integral response of tissue [5]. *In vitro* experiments are mostly performed with cells in monolayers, presenting a well-defined, yet very thin, volume along the proton track: these experiments can cover a larger LET range than typical in *in vivo* or in clinical situations, leading to higher maximum RBE values. They also do not fully represent the situation in tissue, where the volume effect plays a great role: *in vivo* the severity of acute and late side effects increases as the volume of normal tissue irradiated is increased [6]. Clonogenic survival may to some extent represent tumour response, but as a surrogate for normal tissue damage, its utility is obviously restricted [7]; further there is a clear deficiency of *in vivo* model data from both tumours and healthy tissue. Despite the deficiencies in the available data, several phenomenological variable RBE models have been developed using various sub-sets of these data (mainly the *in vitro* data). As general

trends, modelled RBEs are highest for tissues with low $(\alpha/\beta)_x$ ratios and low proton doses per fraction [2]. Comparison between the different models shows best agreement in the mid spread out Bragg Peak (SOBP), i.e. the tumour volume, where modelled RBEs also agree with the conservative clinical standard of 1.1 [8]. However, crucially large variations in modelled RBE arise at the distal edge of the SOBP (a region that may fall within normal tissue, in a treatment margin). Given the significant uncertainties in the models and apprehension regarding the relevance of *in vitro* RBE data, it is no surprise variable RBE models have not found their way to the clinic.

In many ways, RBE has become "a thorn in the flesh" of clinical proton therapy. In its infancy, the main application of proton therapy was for ocular tumours, where large proton doses per fraction [9] are likely to limit RBE variation. Yet as clinical application has increasingly focussed on CNS treatments with relatively low proton doses per fraction and low $(\alpha/\beta)_x$ ratios, some clinicians have become mindful that end-of-range elevations in RBE may lead to injury in critical structures, such as the brainstem [10]. Consequently, RBE uncertainties are often considered indirectly/qualitatively (e.g. in the selection of beam configurations [6,7]), with unknown costs to overall plan quality [11]. It has also been speculated that a generic RBE of 1.1 may lead to under-dosage of radiosensitive tumours (with low $\frac{\alpha}{\beta}$ values) such as medulloblastoma [12]. Finally, uncertainties in RBE are likely to hinder our interpretation of proton versus photon clinical trials [13].

As proton treatment centres and clinical trials proliferate worldwide, it can be argued that the onus of exploring variable proton RBE now lies within the clinic rather than the laboratory [14]. As and when they become clinically available, quantitative mitigation strategies such as LET optimization [15]will be associated with dosimetric penalties, such that there is a clear motivation to pursue high quality clinical analyses on the clinical impact (or otherwise) of variable proton RBE. However, as noted above, RBE is likely to be a very local effect, varying over the dose distribution in both tumour and normal tissues. We expect clinical outcomes, such as toxicity or tumour control, to be influenced by a multitude of different factors, including lifestyle and individual patient radiosensitivity. Thus, standard cohort-based approaches to tumour control and normal tissue complication probability modelling, based on patient-level response measures, are unlikely to provide clear data on *in vivo* RBE [16]. The emerging use of

structural and functional imaging for assessment of normal tissue changes after radiotherapy offer a unique opportunity to explore local RBE in the clinical setting, on a voxel-wise scale.

Over recent years a rapidly increasing number of clinical studies have explored (i) links between possible proton RBE elevations and (ii) patient toxicities and/or image changes following proton therapy in varying primary tumour sites. Our objective here was to review and summarise these studies, comparing and contrasting the statistical methods employed, in order to discuss the weight of clinical evidence for variable proton RBE.

Methods

Referring to the PRISMA guidelines [17], we performed a systematic search of the PubMed database. All authors contributed to the design of this search strategy. We used a "Problem [RBE], Intervention [Protons], Population [Patients], Outcome [Side effect]" strategy (please see the Appendix for full details of our search strategy). Results from our search (performed on 25/08/2021) were then automatically filtered to eliminate animal and *in vitro* studies. A 'publication date' filter of 01/01/2014 to 25/08/2021 was applied. This left us with a total of 630 studies. A single reviewer screened the resultant abstracts.

This reviewer manually retrieved studies which:

a) **performed novel voxel-wise analyses of patient effects versus dose and LET (n= 13)**: Peeler [18], Giantsoudi [19], Fossum [20], Roberts [21], Eulitz [22], Bolsi [23], Ödén [24], Wang [19], Bahn [26], Niemierko [27], Yang [28], Skaarup [23], Bertolet [30])[1]. Referred to as 'Group A'.

b) **compared image changes between proton and photon cohorts with regard to proton RBE (n=9)**: Gunther [31] Acharya [32], Bronk [33], Underwood [34], Li [35], Ludmir [36], Song [37], Ritterbusch [38], Zhang [39]. Referred to as 'Group B'.[2]

As clinical concern around variable proton RBE principally relates to normal tissue complications, our search was designed to cover adverse normal tissue side-effects following

[1] A further two studies described methods related to those analyses: Bauer [53], Eulitz [54]
[2] A further two systematic reviews were identified: Lu [55], Mahajan [56]

proton therapy, and their possible links to proton RBE. We did not explicitly search for RBE papers related to tumour control / relapse: such papers were excluded by the initial reviewer.

For each study included, at least two reviewers then worked independently to manually extract data regarding: primary tumour type; size of patient cohort; type of image change studied; image-registration method (deformable or rigid); LET calculation method, and statistical methodology. The reviewers categorised the studies according to the authors' views on whether they had found clinical evidence for variable proton RBE ('yes', 'no' or 'maybe'). All authors discussed the synthesised results, coming to a consensus on final data presentation, discussion thereof and our conclusion.

Results

Table 1 summarises the key details and findings for all 22 clinical studies extracted from the search. The majority report upon fewer than 20 proton patients for their outcome under consideration. Niemierko *et al* [27] analysed the largest cohort: they considered 50 patients with proton-induced effects. Of the 13 'Group A' (voxelised) studies, 10 involved MRI-based analyses of brain tissue, studying contoured regions of image change. Two of the 13 studies considered physician/patient reported toxicities and one considered rib fractures determined from follow-up CT scans. Similarly, the 'Group B' studies were dominated by MRI-based analyses of the brain (7/9). The remaining two studies in 'Group B' considered radiation-induced changes in lung density, determined by quantitative analysis of follow-up CTs. Overall, 6 of the 22 studies conclude that they find evidence for variable proton RBE, 4 of the studies conclude that they find no evidence, with the remaining 12 presenting more nuanced conclusions.

Table 2 provides greater methodological detail for the 'Group A' studies. 11/13 studies used Monte Carlo simulations to determine voxelised values of proton LET (although varying definitions of LET were considered), whereas 2/13 used analytical calculation methods. Analysis methods were highly varied, ranging from qualitative comparisons of RBE hotspots against regions of toxicity to 2-level mixed-effects logistic regression. 5/13 studies applied literature-based models linking proton LET to RBE and/or RBE-weighted dose to relate this to response; while a further 5 used the clinical data to fit their own models of RBE as a function of LET.

Table 3 elaborates on the methodology of the ‘Group B’ studies. Comparisons between proton and photon cohorts were either performed for: patient level effects such as the presence/absence of pseudo-progression (n=6); structure level effects, in this case considering the temporal lobes (n=1); or voxel level image changes (n=2).

Discussion

Clinical reports of variable proton RBE have proliferated in recent years. Our systematic review of the literature returned >20 relevant studies which either analysed LET/RBE on a voxel-wise level ('Group A', n=13) or performed a proton/photon cohort comparison with regard to RBE ('Group B', n=9). Most of the studies report on MRI changes within irradiated brain tissue (17/22). CT-assessed lung density changes and rib fractures (n=3) and physician/patient reported toxicities (n=2) were also considered, although primarily for the proton/photon cohort comparisons. Our systematic search did not consider possible links between tumour control / relapse and proton RBE; for analysis of this topic we recommend Paganetti's excellent review, which further discusses the various *in-vivo* pathways which are likely to underpin RBE variations [40]. It should also be noted that (i) uncertainties in proton radiobiology are entwined with uncertainties in physical dose distributions, such as those stemming from CT number / proton stopping power conversion, and (ii) publication bias may have occurred: the literature may not comprehensively reflect late toxicities observed following proton therapy.

Overall, conclusions regarding evidence for variable RBE from the voxel-wise and cohort comparison studies were mixed: 12/22 studies delivered inconclusive results ("maybes" in Table 1). Six studies concluded that they had found clinical evidence for variable proton RBE, while four studies concluded that they had not.

Limitations in statistical methods

Statistically it is non-trivial to test for the impact or otherwise of variable LET/RBE upon patient/imaging outcomes. The most common statistical method across the studies reviewed was regression analyses to assess the predictive effect of radiotherapy parameters (including modality, dose and LET) on binary outcomes of image change or toxicity. For all of the studies considered, small sample sizes (the maximum sample size being n=50 for Niemierko *et al* [27]*)* limit the authors' ability to draw conclusions: for small samples, estimates from regression models are imprecise and statistical power for significance testing is low. A number of studies attempted to account for potential confounding patient and clinical factors, either in the regression models or by matching patients (in the cohort papers).

Only two of the voxel-wise analysis papers used regression models that allowed for patient-specific radiobiology, via nested or multi-level models (Niemierko *et al* [27]and Skaarup *et*

al [29], respectively). These two studies concluded that they had not found clinical evidence of variable RBE as only dose, not LET, remained significant in their final models. This was in contrast to the conclusions of some other voxel-wise analysis papers that utilised regression modelling. The other statistical approach utilised univariate, non-parametric analyses to compare regions with or without image changes or toxicity, in terms of dose, LET or model-based RBE values. Of these papers only one attempted to account for inter-patient variability (Bertolet *et al* [30]).

Many of the papers in 'Group A' only analysed a subset of patients who exhibited toxicity and/or imaging changes. By pre-selecting patients based on the presence of normal tissue response, these studies may have overestimated any dose and LET effects.

Limitations in models linking LET to biological effect

Use of image changes to assess local effects and examine variable proton RBE, e.g. as consequence of variable LET, is at first glance an attractive preposition. Our review highlights a number of inherent challenges with this approach, however.

Trivially, such analyses depend on an ability to link local treatment parameters (particularly dose and LET) to local tissue response. Tissue deformation during follow-up and non-local effects (e.g. swelling, progressive tissue breakdown) make this link challenging. Bahn *et al* [26] attempted to account for this through their Probability of Lesion Origin (POLO) method: they built their model considering only the smallest 30% of contrast-enhanced brain lesions, hypothesising that all lesions originated from small spots of tissue breakdown. However, to further consider longitudinal effects, closely spaced imaging timepoints, plus deformable registrations coupled with biomechanical modelling may be warranted.

A number of literature-based RBE models (such as those from Wedenberg *et al* [41] and McNamara *et al* [42]) are based on the linear quadratic dose-response and thus consider the impact of voxel-wise dose per fraction in calculating RBE. Logically, for multi-phase treatments RBE weighted doses should be calculated for individual phases and then summed, but methodological detail regarding temporal consideration of LET is rarely reported in published studies. Only one of the papers reviewed here explicitly considered fraction-size effects for both the varied and constant RBE models (Wang *et al* [25] despite this being a well-established consideration in normal tissue response analyses.

As highlighted in Table 2, column 4, a host of different LET calculation and averaging methods were considered by the different groups. For example, studies involved: dose-averaged LET (LET_d), track-averaged LET (LET_t), LET density correction or none, inclusion of various types of secondaries or none. Such variation amongst LET definitions used by different groups is reflected in the systematic review of Kalholm et al [43].We agree with recent calls for the international proton therapy community to harmonize LET reporting [43,44].

Clinical limitations

The studies reported here are also associated with a number of clinical limitations: (i) Since the objective assessment of RBE effects, e.g. by MR imaging, is time-consuming, expensive and still in the exploratory phase, it is not surprising that the number of patients included in the reviewed studies is rather limited. ParticleCare, the joint EORTC and ESTRO European database for collection of generic and site-specific outcome data of patients treated at European particle centres, may serve as a basis for collection of a larger patient cohort [46]. (ii) Moreover, there is neither agreement on the imaging protocols nor on the time-points between the centres working in the field. The studies reviewed here largely utilised structural MRI (particularly T1-w post-contrast images and T2-w FLAIR images), but various forms of functional MRI have been proposed as new means to investigate radiation-induced damage within the brain [47]. Moves towards standardised, quantitative MRI would be beneficial. Three of the studies reviewed here used CT to assess radiation-induced damage to the lungs/ribs. PET has also been considered in the investigation of radiation-induced lung damage [48]. (iii) Image changes may not have clinical consequences for the patients, i.e., patients may be asymptomatic or have changes which resolve over time. Therefore, the correlation of image changes with patients' symptoms needs to be carefully documented and reported. Ideally, patient reported outcomes or functional tests, e.g. neurocognitive function tests, should be considered alongside imaging. (iv) Patients treated with photons may also develop image changes over time. In order to compare to and elucidate the RBE effect in more depth, photon outcome data also need to be assessed meticulously and ideally compared to that collected for protons. (v) The irradiation of certain anatomical substructures (for example the lateral ventricles as considered by Bahn *et al* [26]) is likely to influence overall radiation response. Equally, efficient sparing of normal tissue may override small RBE problems, making them hard to detect. There will be important patient subsets however where the Planning Target Volume (PTV) contains critical tissue, where dose sparing is not

possible. (vi) LET-RBE effects are less likely to be observed in certain clinical settings due to the presence of additional confounding factors, e.g. among paediatric cohorts aging effects are present and the patient population is highly heterogeneous. (vii) Patients with certain primary tumours may be more susceptible to developing radiation injuries after treatment. Therefore, tumour characteristics (including mutational status, e.g. 1p/19q co-deletion and IDH mutation) should also be considered in (multivariate) analyses.

Value of pre-clinical data

From the preclinical side, there is clear evidence of variable RBE, not only from *in vitro* experiments, but also from (a limited set of) *in vivo* experiments [49] [50]. Even though the final call on the clinical impact of variable proton RBE must come from patient datasets, there are still vital data that can obtained from preclinical experiments. As newer clinical data sets on variable proton RBE are tending to emerge from MR-based analyses of brain-irradiated patients, preclinical models could also enable backtranslation of emerging questions. A setup enabling high-precision image-guided proton irradiation of mouse brain sub-volumes developed in Dresden was recently published [51], with late side effects determined by MR scans linked to histology of the mouse brains [52]. Models like these enable questions arising from the clinical studies to be elucidated in *in vivo* follow up studies.

Conclusions

This review indicates that clinical evidence for variable proton RBE remains statistically weak at present. This is perhaps unsurprising due to the lack of large, prospective datasets and difficulties associated with analyzing retrospective, uncontrolled studies. Our principal recommendation is that proton centres and clinical trial teams collaborate to standardize follow-up timepoints, protocols and statistical analysis methods, so that larger patient cohorts can ultimately be considered, prospectively, for RBE analyses. Well-powered animal RBE experiments considering clinically relevant normal tissue effects and doses per fraction could also elucidate this issue.

Further:

- **Tissue type -** when considering variable RBE, we should be mindful of pre-clinical data and modelling that suggest a raised RBE is most likely to occur in CNS tissue, since that has the lowest α/β ratio. The majority of papers reviewed here considered

the brain and we recommend that variable RBE analyses within brain tissue continue to be prioritised.

- **Clinical study types**: a randomised controlled clinical trial to compare two forms of allocation of RBE (variable versus fixed) would be exceedingly difficult to implement. Sample sizes required would be very large (and possibly infeasible). Equipoise would be problematic and/or the analysis would be extremely complex as even for fixed RBE plans, RBE uncertainties are often considered indirectly/qualitatively (e.g. in the selection of beam configurations [6,7]). As paediatric populations are often heterogeneous and affected by growth, they study of adult populations may be more straightforward. Thus we recommend that adult, prospective cohort studies, and photon versus proton clinical trials (where dose-volume effects are carefully considered) are the most relevant study types.

- **Imaging protocols** - Structural MRI within the brain, particularly contrast-enhanced T1w imaging, has underpinned the majority of clinical RBE analyses to date, but functional MR metrics such as diffusion-weighted imaging are also showing promise [47]. To assess radiation-induced damage within the lungs/ribs, CT has also been used. As far as possible, quantitative imaging protocols should be pursued in future studies. Regular imaging timepoints will allow consideration of longitudinal effects and tissue deformation.

- **Statistical analyses** - one of the key points of using an imaging marker for biological effect, other than to capture local variations in RBE, is to increase the number of datapoints available (many thousands per patient), but we recommend (i) that expert statistical advice is sought during study planning and (ii) inter-patient variation should be considered in analyses, e.g. through nested or multi-level models.

- **Physical parameters** - across the studies reviewed, a host of different LET definitions were used. We agree with recent calls for the international proton therapy community to harmonize LET reporting [43,44].

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Appendix: Our full PubMed systematic search method

We utilised a Problem, Intervention, Population, Outcome (PICO) strategy to perform a systematic search of PubMed, as detailed in full in the table below.

Problem	Intervention	Population	Outcome
"relative biological effectiveness"[Title/Abstract] OR "RBE"[Title/Abstract] OR "linear energy transfer"[Title/Abstract] OR "LET"[Title/Abstract] OR "biologic dose"[Title/Abstract] OR "predicting"[Title/Abstract] OR "photon*"[Title/Abstract]	proton*[Title/Abstract]	((Patient*[Title/Abstract]) OR (Subject*[Title/Abstract])) OR (Cohort*[Title/Abstract])	"side effects"[Title/Abstract] OR "adverse"[Title/Abstract] OR "necrosis"[Title/Abstract] OR "lesions"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "imaging change*"[Title/Abstract] OR "image change*"[Title/Abstract] OR "radiographic change*"[Title/Abstract] OR "injury"[Title/Abstract] OR "injuries"[Title/Abstract] OR

			“inflammation”[Title/Abstract] OR "fracture*"[Title/Abstract] OR "pseudoprogression"[Title/Abstract] OR "pseudo-progression"[Title/Abstract] OR "radiation-induced"[Title/Abstract]

The 4 columns added with “AND” gave 922 results.

Limiting with NOT (animals [MeSH Terms] NOT humans [MeSH Terms]) then gave 915 results.

Limiting with NOT ("In Vitro Techniques"[MeSH Terms] OR "Culture Techniques"[MeSH Terms] OR "cells, cultured"[MeSH Terms]) then gave 904 results.

Limiting by date: 2014/01/01 to present [25/08/2021] then gave 630 results. A single reviewer screened these 630 abstracts, as detailed in the main text.