1. Introduction

Protons can more effectively produce biological damage as compared to photons, due to differences in the ionization processes between the radiation types (Tommasino and Durante 2015). Comparison of proton and photon treatment plans by the physical dose is therefore not enough. A conversion factor, the relative biological effectiveness (RBE), has been introduced in proton therapy to enable transferring of treatment protocols and experience gathered from γ- and x-ray irradiation (RBE Committee 1963). Clinical proton therapy applies a constant RBE of 1.1, even though the RBE is known to vary with dose, radiation quality and tissue type. These parameters are included in most phenomenological RBE-models for proton therapy, i.e. models based on results from proton beam in vitro experiments (Paganetti 2014).

The phenomenological RBE-models are typically based on the linear quadratic model (LQ-model), which model the dose-response by quantifying the \( \alpha_p \) and \( \beta_p \) parameters (Rørvik et al 2018). The RBE at its maximum
and minimum can be RBE model is then functions described by the variables RBE\textsubscript{max} (=α\textsubscript{p}/α\textsubscript{x}) and RBE\textsubscript{min} (=√β\textsubscript{p}/β\textsubscript{x}) (Schuemann et al 2018). These functions can be dependent on the radiation quality and tissue type, normally represented by the dose-averaged linear energy transfer (LET\textsubscript{d}) and the fractionation sensitivity of the photon radiation ((α/β)\textsubscript{x}), respectively.

The RBE-models agree on an increasing RBE\textsubscript{max} with increasing LET\textsubscript{d}, but the dependency of RBE\textsubscript{min} on LET\textsubscript{d} differ (Rørvik et al 2018). A recent review showed that 7 out of 12 phenomenological models assume a constant RBE\textsubscript{min} (equal to one) for all LET\textsubscript{d} values. However, in the models by Carabe et al (2012), Jones (2015) and Peeler (2016) the RBE\textsubscript{min} increased with increasing LET\textsubscript{d} value, which is in contrast to the models by Belli et al (1997) and McNamara et al (2015), where the RBE\textsubscript{min} decreased with increasing LET\textsubscript{d} (Rørvik et al 2018). The RBE\textsubscript{min} relationships of the analytical biophysical models are also deviating, as shown by Manganaro et al (2017). According to their calculations, the repair–misrepair fixation (RMF) model, the microdosimetric–kinetic model (MKM) and the local effect model (LEM) predict an increasing, a constant and a decreasing relationship with LET, respectively. The differences in the phenomenological models mainly arise from the variations in the experimental data, as the models’ assumptions are freely fitted to the experimental database. Even though all models are based on cell survival experiments, the experiments are not performed in a consistent manner between the experimental groups. They differ both in regard to the experimental setup such as dose range, dose rate and energy spectra and the analysis of the experimental data e.g. regression technique and uncertainty calculations.

A large amount of in vitro data exists for protons, which could be used to investigate different dependencies of the RBE\textsubscript{min} functions. The in vitro data consist of multiple experiments of cell survival from various dose ranges, at a certain LET\textsubscript{d} value, and from which LQ-model parameters are extracted. The experimental setup varies between the different experiments, including dose range, as well as the regression method to determine the α\textsubscript{x} and β\textsubscript{p} parameters from the cell survival data. The fitted LQ-model parameters are highly dependent of the number of data points and the dose range of these points, as shown by Garcia et al (2006) for cells irradiated with photon radiation. Their analysis indicated that including data points with low doses increased the β\textsubscript{p} parameter, as compared to when the regression was restricted to only high doses.

In this study we therefore analysed how the LET\textsubscript{d} dependency of RBE\textsubscript{min} is influenced by the dose range of the proton in vitro experiments. We aimed to determine whether the common assumption of a constant RBE\textsubscript{min} for all LET\textsubscript{d} values holds independently of dose range.

2. Materials and methods

We performed a literature search to find all survival experiments of cells irradiated in vitro by external proton beam therapy (per July 2018). In our work, an experiment was defined as a series of cell survival data from proton irradiations at different dose levels, but with a unique (α/β)\textsubscript{x} value and a single LET\textsubscript{d}. Consequently, each experiment represents a unique cell survival curve, which can be parameterised by fitting the LQ-model to the experimental data points.

We only included experiments executed with monoenergetic beams, as a narrow LET spectra give a better description of the LET range of interest compared to beam with broad LET and energy distributions (Dahle et al 2017). We excluded experiments with LET\textsubscript{d} above 20 keV μm\textsuperscript{-1} from our database due to its limited relevance in clinical treatments. We further restricted our database to cell experiments where the reference experiment had an (α/β)\textsubscript{x} value below 5 Gy. The latter limit the response from early reacting cells with high (α/β)\textsubscript{x} values, as our database then represented late responding tissue. By only focusing on a narrow range of (α/β)\textsubscript{x} values, we avoided the general (α/β)\textsubscript{x} dependency and potentially reduced the data noise. Other established models have included diverse definitions of the (α/β)\textsubscript{x} dependency (Carabe et al 2012, McNamara et al 2015, Peeler 2016).

From each experiment, data points were extracted with WebPlotDigitizer (Rohatgi 2018) from the survival curve figures. The software was used to calibrate the axes and calculate the dose and survival of each individual data point from all experiments. The extraction was restricted to dose versus survival values, omitting potentially reported uncertainty bounds as the uncertainty of the data points were not reported in a concise manner and also lacking in some studies. The LQ-model was subsequently fitted to each extracted proton experiment in MATLAB using linear unweighted regression to the logarithmic survival data, as shown by the LQ-model equations:

\begin{equation}
\ln\left(\frac{S}{S_0}\right) = -\alpha_p D_p - \beta_p D_p^2,
\end{equation}

where \(D_p\) is the physical dose deposited by protons per fraction, \(\frac{S}{S_0}\) is the survival fraction of the radiated cells compared to the reference cells which are not irradiated and α\textsubscript{p} and β\textsubscript{p} are the radiosensitivity parameters of the LQ-model found by the regression. The regression technique was independent of the method applied by the study from which the data was extracted. The obtained LQ-model parameters were therefore compared to the reported values (figure A1). We used the reported LQ-model parameters of the photon experiments, as the data points of the reference experiments were not included in all publications, rendering the refitting of the LQ-model...
difficult (Folkard et al 1989, Prise et al 1990, Schettino et al 2001). From the LQ-model parameters, we found the $RBE_{\text{min}}$ of the experiment by:

$$RBE_{\text{min}} = \beta_p / \beta_x,$$

where $\beta_p$ is our new fitted parameter to the proton data and the $\beta_x$ is the reported parameter of the photon data (Carabe-Fernandez et al 2007). The uncertainties in the $RBE_{\text{min}}$ values were found with the Gauss error propagation principle:

$$\Delta RBE_{\text{min}} = \frac{1}{\sqrt{2 \beta_x}} \sqrt{\frac{\beta_x}{\beta_p} \Delta \beta_p^2 + \frac{\beta_p}{\beta_x} \Delta \beta_x^2}.$$

Further, to investigate the dependence of the $RBE_{\text{min}}$ on the dose range of the experiments, we refitted the LQ-model to multiple subsets of the data points of each experiment by introducing two new variables. The first dose variable, $D_\eta$, is the minimum dose cut-off such that experimental data points lower than this cut-off were excluded. The second variable, $D_\Delta$, described a margin above $D_\eta$ such that the experiment must have a dose point in the interval of $D_\eta$ and $D_\eta + D_\Delta$ to be refitted to the LQ-model. The application of two different $D_\eta$ but identical $D_\Delta$ is shown in figure 1. The $RBE_{\text{min}}$ derived with equation (2) using the refitted $\beta_p$-parameter from those experiments fulfilling the inclusion variables were used to construct a restricted database. To analyse the implication of low dose data (or more importantly, the lack of this data) on the $RBE_{\text{min}}$ function, multiple restricted databases were created by varying the $D_\eta$ from 0 to 2.5 Gy and varying $D_\Delta$ from 0.2 to 0.7 Gy. The upper level of 2.5 Gy was motivated both by the limited amount of available data for higher $D_\eta$ and the most common fraction doses applied in proton therapy.

The $RBE_{\text{min}}$ values were compiled in the restricted databases with the LET$_d$ values of the experiments. Based on the restricted databases, the simplest form for LET$_d$ dependency was explored by the following equation:

$$RBE_{\text{min}} = 1 + c \text{LET}_d,$$

where $c$ is a constant determined from linear regression. Two regression methods were used, as the $c$ value was determined with both unweighted and weighted regression. The inverse of the uncertainty, calculated by equation (3), was used as weights for the weighted regression. With this relationship, a $c$-value significantly different from 0 indicates that $RBE_{\text{min}}$ has a LET$_d$ dependency. We determined the first order $c$ coefficient and its uncertainty by both unweighted and weighted regression.

3. Results

From our literature search, we found 76 experiments, each with a specific survival and dose value and a corresponding LET$_d$ fulfilling our inclusion criteria (Hei et al 1988, Folkard et al 1989, 1996, Prise et al 1990, Belli et al 1993, 1998, Green et al 2001, 2002, Schettino et al 2001, Baggio et al 2002, Schuff et al 2002, Chaudhary et al 2014, Guan et al 2015, Patel et al 2017, Howard et al 2018). This corresponded to in total 529 data points,
which are shown in figure 2. As seen by the histogram in this figure, the data points of the experiments are mainly clustered around integer numbers of Gy and within the dose range of 0.1–10.1 Gy.

The originally reported values of \( \alpha_p \) and \( \beta_p \) and those extracted from our refitting procedure using unweighted regression to the logarithmic data of cell survival are shown in figure A1. The absolute difference between the reported data and refitted data was on average 0.05 (±0.07) Gy\(^{-1}\) for \( \alpha_p \) and 0.02 (±0.04) Gy\(^{-2}\) for the \( \beta_p \) value. In figure 3, the distribution of the \((\alpha/\beta)_{L}\) and LET\(_d\) values of the original (unrestricted) database is shown. As seen, the majority of the cell lines have an \((\alpha/\beta)_{L}\) of 1–4 Gy and the database is dominated by low LET\(_d\) experiments.

The restricted databases from varying \( D_\eta \), but keeping \( D_\Delta \) constant (0.5 Gy), is shown in table 1. In general, the number of included experiments was greatest around \( D_\eta \) of 0.5 to 1.5 Gy. The effect on varying the margin \( D_\Delta \) is shown in table A1, where the number of experiments included in the databases grow as \( D_\Delta \) increased. All experiments included in the restricted database have the lowest dose value between \( D_\eta \) and \( D_\eta + D_\Delta \). By rising either of the two parameters, the mean value of the minimum dose value of the included experiment is naturally increased, as shown by the table A2.

In table 1 and also illustrated by the figure 1, increasing the \( D_\eta \) resulted in a reduction, and thereby potential underestimation, of the \( \beta_p \) parameter. In the example, where a constant \( D_\Delta \) is applied (0.5 Gy), the \( \beta_p \) parameter is reduced by more than 50% for \( D_\eta \) of 1.5 Gy or higher as compared to \( \beta_p \) from the unrestricted experiment. The \( \beta_p \) parameter is relatively stable for \( D_\eta \) values above 1.5 Gy. Most experiments are refitted if a \( D_\eta \) value between 0.5 Gy and 1.5 Gy is applied. The implications for \( \alpha_p \) are smaller and lacking a clear trend.

From the refitted \( \alpha_p \) and \( \beta_p \) parameters the RBE\(_{\text{min}}\) value is found with its uncertainty for every experiment included in our databases. This is exemplified for three restricted databases with a different number of included experiments (figure 4(A) include 34 experiments, figure 4(B) 49 experiments and figure 4(C) 29 experiments). Applying linear regression according to equation (4), we find the regression coefficient, \( c \) to be small but positive for all \( D_\eta \) values. In addition, the \( c \) value is decreasing with increasing \( D_\eta \), which also can be seen in figure 5. Comparing the RBE\(_{\text{min}}\) values found with unweighted regression to the databases with \( D_\Delta = 0.5 \) Gy, we find that a function derived from a database with \( D_\eta = 0 \) Gy will calculate an RBE\(_{\text{min}}\) value between 1.4 ± 0.1 and 2.5 ± 0.2.
in the LET\textsubscript{d} range from 5 to 20 keV \( \mu \text{m}^{-1} \). These values are significantly smaller for a function derived from a database with \( D_\eta = 2 \) Gy, as the same LET\textsubscript{d} range will estimate RBE\textsubscript{min} values between 1.0 \( \pm \) 0.1 and 1.1 \( \pm \) 0.2. Hence, if experiments executed with a higher minimum dose was used for estimating RBE\textsubscript{min} the LET dependency was diminished.

Furthermore, unweighted regression consistently resulted in a stronger dependency on LET\textsubscript{d} for RBE\textsubscript{min}. A \( c \) value equal to 0 corresponds to a constant RBE\textsubscript{min} independent of LET\textsubscript{d}. For unweighted regression this required \( D_\eta > 2.0 \) Gy in combination with a large \( D_\Delta \) and for weighted regression a \( D_\eta > 1.0 \) Gy in combination with as small \( D_\Delta \). Hence, even for weighted regression and inclusion of doses less than 1 Gy, the results indicate the RBE\textsubscript{min} to be significantly higher than the commonly assumed 1 for high LET\textsubscript{d} values.

4. Discussion

Our study revealed a clear correlation between the range of doses included in experiments and the variability of RBE\textsubscript{min} with LET\textsubscript{d}. Only if data from low doses are excluded from the modelling, the assumption that the RBE\textsubscript{min} is constant for all with LET\textsubscript{d} values appears reasonable. When including doses of 1 Gy or less than, our analysis shows a small, but significant, increase in RBE\textsubscript{min} with increasing LET\textsubscript{d}. Experiments consisting of data points only with high doses could therefore estimate a lower \( \beta_p \) parameter compared to experiments including low dose data. This indicates that RBE models which include experiments with high minimum doses could underestimate the RBE.

The sensitivity of low doses for the estimation of the \( \beta_p \) parameter could contribute to the diverging results on the LET\textsubscript{d} dependency for RBE\textsubscript{min} in the literature. As an example, Guan et al (2015) found both the \( \alpha_p \)– and \( \beta_p \) parameters to be nonlinearly increasing with increasing LET\textsubscript{d} value. These experiments included low dose values, with a minimum dose below 0.5 Gy, as compared to other experiments. In contrast, Chaudhary et al
(2014) found the $\beta_p$ parameter to be decreasing with increasing LET$_d$ value, which could be caused by their high the minimum dose of 1.5 Gy in the experiments, as indicated by the three red circles with at 1.5 Gy in figure 1. We hypothesize that the $\beta_p$ values could have been higher, if the experiment included one or more data points with a dose value under 1.5 Gy. Based on our analysis, we therefore recommend that future experiments will be performed with low doses included in the experimental setup, with at least one data point with a dose maximum equal to 1 Gy, preferably lower.

For our analysis, we included the simplest definition of a variable RBE$_{min}$: Variation with a single parameter. However, we cannot exclude more a complex relationship between LET$_d$ and RBE$_{min}$. The definition can be modified to abandon the assumption of RBE$_{min}$ equals 1 at LET$_d$ = 0, by determining the constant from the regression analysis. This was done in the models made by Carabe et al. (2012), McNamara et al. (2015) and Peeler (2016). Further, as previously shown for RBE$_{min}$, the LET relationship might also be non-linear (Peeler 2016). There is however a large variation in the existing data, as seen in figure 4, thus there is no clear non-linear trend. More experimental data and verification of existing models, e.g. the comparison of models to experimental data by Polster et al. (2015) and Mairani et al. (2017), needs to be done to determine which model that give the best representation of the clinical dose response.

Based on the analysis in this work, we recognise that models with an RBE$_{min}$ function with a positive dependency of LET$_d$ could estimate a more precise RBE and should be explored further. As shown in an earlier analysis of phenomenological models (Rørvik et al. 2018), the use of a constant RBE$_{min}$ is inherited from earlier models and not based on quantitative analysis of experimental data. Generally speaking, we recommend that new models should not adapt a constant definition of RBE$_{min}$ without performing statistical analysis of the database. Calculation of the absolute effect of a dose dependent RBE$_{min}$ on RBE estimates have not been performed, as mixing of model functions generally is not recommended.

We chose to focus our RBE$_{min}$ analysis on late responding tissue by excluding cell lines with an $(\alpha/\beta)_x$ value above 5 Gy. This threshold was a compromise between focusing on the late responding tissue, but still having sufficient experiments ($N = 76$) for our regression analysis. Most models are consistent in their definition of the $(\alpha/\beta)_x$ dependency on RBE$_{max}$ with an inversely proportional RBE$_{max}$ with increasing $(\alpha/\beta)_x$. However, the $(\alpha/\beta)_x$ dependency of the RBE$_{min}$ is deviating in previously published models (Rørvik et al. 2018). Carabe et al (2012) used the same inversely proportional definition for RBE$_{min}$ as they did for RBE$_{max}$ however the experimental database only consisted of V-79 cells with a narrow $(\alpha/\beta)_x$ range around 2–3 Gy. McNamara et al (2015) assumed that RBE$_{min}$ is increasing with the square root of $(\alpha/\beta)_x$, while Peeler assumed RBE$_{min}$ to be linear dependent of the $(\alpha/\beta)_x$ value. We did not include an $(\alpha/\beta)_x$, dependency and omitted the issue altogether by analysing a database with a narrow $(\alpha/\beta)_x$, range, mainly between 1 and 4 Gy. We will therefore not postulate if the same effect will be seen for early responding tissue with high $(\alpha/\beta)_x$, values, however, our analysis is of interest in itself, as most organs at risk are regarded as late responding tissue with low $(\alpha/\beta)_x$, values.

Figure 5. The variation of the regression coefficient, $c$ as a function of $D_\eta$ for various $D_\Delta$ values, increasing from subfigure A–F. The reported error bars show one standard deviation of the determination of $c$ from regression.
We introduced a method in our analysis by applying a minimum dose with a margin to construct restricted databases from a major database of existing experiments. The refitting of the database with a low margin value, excludes many experiments from the regression analysis, as seen in table A1. The quality of the regression analysis may therefore be reduced as compared to regression performed on a database constructed with higher margin values. Therefore the found regression coefficients should be interpreted carefully due to the small amount of data. An effect of the low data amount can be seen in figure 5, where the c values fluctuates for $D_\Delta$ values up to 0.5 Gy, while the c values of a $D_\Delta$ of 0.6 Gy or 0.7 Gy monotonically decreases with increasing LET_d value. The fluctuations in the mean values are however smaller than the uncertainty, thus we can assume there is a steady decreasing trend for all $D_\Delta$ values. It should be mentioned that the points in figures 4(E) and (F) are based on overlapping databases, as the interval between the points (0.5 Gy) is smaller than the $D_\Delta$. This will smooth out any oscillations in the dataset. We found 0.5 Gy to be a reasonable size for $D_\Delta$ as a compromise between having enough experiments in the restricted databases but still allowing for separation of the effect from an increasing $D_\eta$. This value of $D_\Delta$ is therefore used in the other examples shown in figures 1 and 4 and table 1.

We analysed and treated $\alpha_p$ and $\beta_p$ as two independent parameters, which is a common practice for LQ-based RBE models (Rørvik et al. 2018). This is however a major approximation, as a change in one of the parameters will be counteracted by the other parameter. The $\alpha_p$ parameter will in general increase when the $\beta_p$ parameters decreases with increasing $D_\eta$ value. An example of this can be seen by the initially steeper curve in figure 1(B) compared to the curve in figure 1(A). Additionally, there is a great variation in the regression fitting techniques used in the different experiments reported in the literature, which further impacts the reported LQ-model parameters. In an attempt to reduce variations from different regression techniques we refitted the LQ-model to the data values with a consistent method for all experiments. Abolfath et al. (2017) also omitted this issue by making a model directly from data values. They used a ‘global-fitting’ method for the LQ-model parameters, by making a regression fit of the LET_d dependent $\alpha_p$ and $\beta_p$ functions in one single regression, instead of treating them independently as we did. The ‘global-fitting’ method is novel and could potentially reproduce the actual response better, however, Abolfath et al. (2017) only adapted the method to two cell lines, independent from each other. It is therefore not directly possible to compare the Abolfath model to our model functions in its current form. The method needs to be developed further to create a general model from multiple cell lines at once.

In a clinical scenario where a patient is treated with a normal fractionated plan, the practical dose range is in between 0 and 2–3 Gy. This is relevant for RBE models, as there should be good correspondence between the experimental data of the model and the clinical usage. Therefore, we advise that the dose region of the RBE models’ background data should be considered relevant in the selection of RBE models. Future RBE models could acknowledge the importance of the dose range of the experiments and adapt inclusion criteria for the experimental database accordingly.

5. Conclusion

Based on a compilation of existing in vitro data with $(\alpha/\beta)_x$ values below 5 Gy, $RBE_{\text{min}}$ was found dependent on LET_d. The small yet significant positive linear correlation of LET_d on $RBE_{\text{min}}$ was visible for databases with minimum experimental doses of 1 Gy or below. If the minimum dose of the cell survival data was set greater than this value, the LET_d dependency was lost and $RBE_{\text{min}}$ become constant. The inclusion of experiments with high minimum dose in phenomenological RBE models could therefore lead to underestimation of the actual proton RBE.

Acknowledgments

This work was funded by Bergen Research Foundation.

Appendix

The value and uncertainty of the $\alpha_p$ and $\beta_p$ parameters of the different experiments are given in figure A1. The refitted values shown are found from a refit to all data points of the experiment, not only a restricted selection of data points with high dose values. The variation of the reported and refitted parameters arises from different fitting techniques, as we only used a linear regression technique. Some articles used the uncertainty in the data in a weighted regression technique. As our database is found from figures, not reported values, this can also explain the difference in figure A1.

By varying $D_\eta$ and $D_\Delta$ values, the number of experiments included in the restricted will also vary, as shown in table A1. The number increases with the width of the dose margin ($D_\Delta$) and is largest for $D_\eta$ between 0.5 and 1.5 Gy. The variation of the parameters also varies the dose values of the included experiments. The actual mean minimum dose is given in table A1.
Table A1. The number of experiments included in the regression of the $RBE_{min}$ of the included experiments.

| $D_\eta$ [Gy] | $D_\Delta$ [Gy] | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 |
|---------------|-----------------|-----|-----|-----|-----|-----|-----|
| 0.0           |                 | 6   | 14  | 22  | 34  | 41  | 45  |
| 0.5           |                 | 27  | 33  | 39  | 61  | 69  | 69  |
| 1.0           |                 | 27  | 36  | 43  | 49  | 55  | 56  |
| 1.5           |                 | 21  | 29  | 34  | 58  | 68  | 69  |
| 2.0           |                 | 20  | 23  | 26  | 29  | 31  | 33  |
| 2.5           |                 | 8   | 11  | 11  | 22  | 31  | 34  |

Table A2. The mean value of the actual minimum dose of the experiments included in the regression of the $RBE_{min}$ of the included experiments.

| $D_\eta$ [Gy] | $D_\Delta$ [Gy] | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 |
|---------------|-----------------|-----|-----|-----|-----|-----|-----|
| 0.0           |                 | 0.13| 0.21| 0.26| 0.33| 0.36| 0.39|
| 0.5           |                 | 0.59| 0.61| 0.65| 0.77| 0.80| 0.80|
| 1.0           |                 | 1.07| 1.12| 1.16| 1.20| 1.23| 1.24|
| 1.5           |                 | 1.6 | 1.62| 1.66| 1.78| 1.82| 1.82|
| 2.0           |                 | 2.06| 2.08| 2.11| 2.15| 2.18| 2.21|
| 2.5           |                 | 2.60| 2.64| 2.64| 2.80| 2.87| 2.89|

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