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The physical separation between the LET associated with the ultimate relative biological effect (RBE) and the maximum LET in a proton or ion beam

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Abstract

Purpose: To identify the relative positions of the ultimate RBE, at a LET value of LET_U (where the LET-RBE turnover point occurs independently of dose), and of the maximum LET (LET_M) for a range of ions from protons to Iron ions. Methods: For a range of relativistic velocities (β), the kinetic energies, LET values and ranges for each ion are obtained using SRIM software. For protons and helium ions, the LET changes with β are plotted and LET_M is compared with LET_U. For all the ions studied the residual ranges of particles at LET_U and LET_M are subtracted to provide the physical separation (S) between LET_U and LET_M. Results: Graphical methods are used to show the above parameters for protons and helium ions. For all the ions studied, LET_U occurs at kinetic energies which are higher than those at LET_M, so the ultimate maximal RBE occurs proximal to the Bragg peak for individual particles and not beyond it, as is commonly supposed. The distance S, between LET_U and LET_M, appears to increase linearly with the atomic charge value Z. Conclusions: For the lighter elements, from Argon and Iron, larger S values of several centimetres occur, which may have implications not only in any proposed therapeutic beams but also at very low doses encountered in radiation protection where the few cells that are irradiated will typically be traversed by a single particle.

Introduction

A recent publication presented the kinematics associated with specific values of linear energy transfer (LET) for maximum biological cell-killing efficiency, designated as LET_U, for the lighter elements in their ionic form [1]. The existence of a unique LET_U value, based on previous publications [2], for each ionic species is contrary to previously assumptions where a common LET_U value was assumed [1]. There are many implications that emerge due to the new paradigm, some of which are considered further in the present article. Of special concern is the comparison of the LET_U values with those of LET_M (defined as the maximum LET value of individual particles in the beam, situated at the Bragg peak itself, and for the present tentative purposes assumed to be unaffected by the process of straggling). Published experimental data sets almost invariably show only LET and RBE values in isolation, without any reference to the position of the LET-RBE turnover points within the geometry of the Bragg peak. The LET_U points must exist at a lower LET value than the maximum LET, as evidenced by the classical LET-RBE data sets which show a turnover in LET-RBE at LET_U, with diminishing RBE values with further increases in LET. The maximum possible LET values for each ion exist where energy (E) release at a particle traversal distance x is expressed as dE/dx, with the highest LET occurring at the Bragg peak, as seen in the familiar plots of dE/dx with respect to depth in a medium [3, 4] and can be found numerically using the SRIM software [5].

The present paper will show the LET-RBE relationships and the LET_U positions for the range of ions considered in the previous report [1], and will further investigate the relationships between the position of
the maximum possible RBE (obtained from published experimental data sets) and the maximum LET (LET\textsubscript{M}) at the Bragg peak itself for individual particles. This is important, since a sufficiently large difference in the position of maximum dose deposition and RBE could have implications for therapeutic ion beams, as well as in radioprotection.

**Methods**

The LET\textsubscript{U} values for fully ionised protons, deuterium, carbon, silicon, neon, argon and iron obtained in the previous publication [1] are used to plot the LET-RBE relationships by using the simplified equations used for data fitting purposes in the appendix of the same publication. These are consequently all based on the slopes and curves of cell survival based RBE data sets, the slopes being the linear ascent of RBE with LET until LET\textsubscript{U} is reached, and the curves are those fitted for the LET-RBE relationship beyond LET\textsubscript{U}, and given in that publication [1]. No specialised or modelled LET-RBE estimations are used in this paper. They resemble the plots previously published by Jones[2], presented as a simple energy efficiency model, but with updated LET\textsubscript{U} values and have a greater number of elemental ions. In that paper plots of experimental data sets and the model were presented and which showed good agreement, but in the present report only the actual experimental data fitted parameters were used along with extant data points.

Since RBE must be 1.0 at the LET of the reference radiation, the linear slope \( m \) towards the LET\textsubscript{U} value will be the ratio of the maximum RBE (at any specified dose or cellular surviving fraction) divided by LET\textsubscript{U}. A small correction can be introduced to include the reference radiation LET value (LET\textsubscript{C}, which is normally between 0.2 and 0.6 keV.\mu m\textsuperscript{-1} for megavoltage photons but could be higher for low voltage photons at 1 keV.\mu m\textsuperscript{-1} or above), but the megavoltage values are small compared to LET\textsubscript{U}, so no correction is used in this analysis.

It was also shown that \( \text{LET}_{U} = \frac{k}{\sqrt{m}} \), where \( k \) is a parameter that controls the displacement of the reciprocal relationship between LET and RBE beyond the LET\textsubscript{U} position in the previous publication appendix [1].

It follows that \( k = mL^2 \). The overall LET-RBE relationship can then be plotted for each ion by finding \( m \) and \( k \) for each specific value of LET\textsubscript{U}.

The SRIM software package [5] provided estimates of LET for specified values of particle kinetic energy for each ion in liquid water. First, changes in relativistic velocities (\( \beta = \frac{v}{c} \)) were used to find the particle kinetic energy, which is \( m c^2 \left( \frac{1}{\sqrt{1 - \beta^2}} - 1 \right) \), where \( m \) is here the mass, followed by application for the SRIM software to obtain the LET (or stopping power) in keV.\mu m\textsuperscript{-1}.

To estimate the physical separation in distances of centimetres, the SRIM software was used to determine the particle ranges for particles with kinetic energies at the LET\textsubscript{U} and LET\textsubscript{M} positions. It then follows that:

\[
\text{Range LET}_{U} - \text{Range LET}_{M} = \text{physical separation distance}.
\]

**Results**

The data-based LET-RBE relationships for each of the representative ions are shown in figure 1, where the linear rise of RBE with LET reaches a unique peak for each ion at LET\textsubscript{U}, followed by a longer curve where the RBE is progressively reduced. In the case of the ‘heavier’ ions under consideration these curves extend to large LET values.

Figure 2 contains the graphics which show the proton KE (kinetic energy), LET and RBE plotted against \( \beta \). The beam direction is from right to left in these displays. The rise in RBE to its maximum value at
LET_U does not coincide with the maximum LET value (LET_M), which occurs at a larger value of LET situated at the Bragg peak itself. The LET_U is at 30.4 keV·μm⁻¹, but the LET_M is around 85 keV·μm⁻¹.

For helium ions, a similar separation of LET_U and LET_M is seen in figure 3, where the LET_U is around 121 keV·μm⁻¹, but the LET_M occurs near a value of 200 keV·μm⁻¹.

For all the ions under consideration, the values of LET_U and LET_M are plotted in figure 4. The difference between LET_U and LET_M becomes progressively greater for increasing values of atomic number, Z, the increase being apparently linear with a gradient of 182.3 per unit Z between Helium and Iron, but between protons and helium there is an increment of around 141 keV·μm⁻¹ for unit change in Z.

The graphical relationship between residual ranges and LET for each ion species considered are shown in figure 5, where comparison is made with a typical living cell thickness. It can be seen from the solid vertical lines which indicate the ranges at LET_U and the dotted vertical lines for LET_M that the separation distances (S) will increase to be several cm for ions with Z values above Argon and as much as 5.78 cm in the case of Iron. These distances estimated for water density. Additional information, including particle energies and ranges for LET_U and LET_M for each ion are provided in table 1.
Discussion

The findings of this study suggest that the highest RBEs occur at LET values which are found proximal to the Bragg peak where the maximum LET (LET_M) of the particle occurs. The numerical difference between the two LET values under consideration (LET_U and LET_M) increases with Z number.

Individual mono-energetic ions have been considered and these will result in very sharp ‘pristine’
Bragg peaks which are narrow and contain large energy changes over short distances. The familiar Bethe—Bloch equations require modifications at low energies [4, 5]. Recent simulations show precipitous falls in LET and energy near the end of range for protons [4]. The SRIM calculations are based on theoretical models fitted to a large number of experimental data and take into account the reduction in effective charge at low energies [5]. The process of straggling in a medium, and the use of an energy spectrum, will both tend to reduce these marked changes. For practical therapeutic beams, range straggling of the particles with reduction in particle velocities will result in a lower average LET at the broad measured Bragg peak due to the resulting energy spread and will be dependent on the initial particle energy range.

The phenomenon of overkill (that is a reduction in RBE values), which commences at LET values greater than LETU, is discussed elsewhere [1], but it needs to be briefly mentioned here. For high LET particles and in particular beyond LETU where the LET rises sharply, the resulting ionisation clustering is known not only to result in DNA double-strand breaks (DSB), but also in complex forms of DSB (which include additional damage, such as strand breaks and/or base damage, with a few base pairs) over and above the level required to prevent repair with high fidelity [6]. Additionally, high-LET charged particles produce correlations on DNA damage along the path of an individual particle over larger scales corresponding to the packing of DNA (e.g. nucleosomes, chromatin fibre and chromosome territories) within the cell nucleus. The proximity of these correlated sites of damage (which increases with increasing LET) increases the probability of miss-repair through pairwise interactions; as a result the probability and complexity of the resulting chromosomal rearrangements increases with LET and associated lethality of these events, which can include multiple lethal events within individual cells [6]. Also it must be remembered that as LET increases the number of particles traversing the cell for a given dose decreases. So the increasing complexity of clustered damage at sites of DNA damage is associated with a decrease in the number of these sites for a given dose.

The local ionisation density is not only dependent on LET, but also on the range of the emerging delta-electrons. For any given LET, the maximum energy and therefore range of delta-electrons increases with increasing mass of the particle, resulting in a local decrease in ionisation density close to the track and therefore a reduction in the complexity of DNA damage produced. The maximum range of delta-electrons for protons, carbon ions and iron ions at the LETU associated with maximum RBE for cell killing correspond to approximately 0.1 μm, 13 μm and 5.7 mm respectively. However the majority of interactions will occur very much closer to the particle track than this.

Interpretation of experimental radiobiology data can also be problematic for several reasons. Many studies are performed using high energy beams which are subsequently degraded to the required energy. As a consequence of range straggling and nuclear fragmentation this can result in cells being irradiated with a distribution of energies and LETs. Additionally there may be a significant variation in LET across the traversed cell for studies using low atomic number particles (e.g. protons, helium ions) close to LETU where the residual range is close to the dimensions of a cell.

It is often stated that the highest RBEs occur beyond the Bragg peak, but this may not be the case, although it is true that the highest RBEs occur towards the end of range of a spread out Bragg peak (SOBP), which is well shown in publications by Paganetti [7]. However, it remains to be seen if any physical separation between LETU and LETM would have any impact on the RBE distribution in relation to the geometry of the spread-out Bragg peak (SOBP). This should be a topic for further research using simulations and experiments. Such experiments are complex and require detailed consideration and technique. For example, Grün et al [8], showed that for a carbon ion SOBP for a target from 70 mm to 130 mm depth, the dose-averaged LET increasing from approximately 24 keV.μm⁻¹ to 180 keV.μm⁻¹ across the SOBP rising to a maximum of approximately 195 keV.μm⁻¹ just beyond it. These dose-averaged LET values are significantly lower than the LETM value for carbon of 977 keV.μm⁻¹ as a result of range straggling and fragmentation. Significant range straggling can also be important for high energy mono-energetic beams (e.g. 13 mm for a 225 MeV proton beam) where at the measured peak dose along the beam path (at the Bragg peak) is a result energy deposition by particles with a broad range of energies and LETs. For example, for a pristine carbon ion beam at around 72 mm, the LET at the Bragg peak is approximately 110 keV.μm⁻¹ but rises to approximately 300 keV.μm⁻¹ at a depth of 75 mm [8]. Therefore, as a result of increasing loss in particle numbers beyond the dose peak and the associated increase in the average LET of the remaining low energy particles, the RBE can remain high and could increase. This is illustrated by the variation in RBE with depth for salivary gland cells at 50% survival for 12C ions by Li et al [9]. Interesting this group also observed an additional enhancement in RBE at and beyond the peak, when radioactive 12C was used with a similar depth dose distribution, as a result of the subsequent production of short ranged, high-LET α-particles and protons at the terminus of the original beam. As a result, care must be taken when comparing biological effects from monoenergetic particles incident on the cells, with experiments with the same average LET, especially as the spectra of particles is dependent on the setup used. Indeed the calculations of Grün et al [8], show that dose-averaged LET is not a good predictor for RBE where there is a broad LET distribution.
as observed in a SOBP, due to nonlinearity of the RBE and LET relationship at high LET values. There are important implications for advanced treatment planning systems in that the LET-RBE profile can in principle be mapped onto spread out Bragg peaks at specific tissue depths [10].

A further consideration concerns the choice of the optimum therapeutic ion: should the maximum RBE be as close as possible to the Bragg peak or not? Protons would be the best option if such proximity offers advantages in treatment planning. It is at the Bragg peak that the highest dose is found and it would appear reasonable to suggest that the least separation between maximum dose (and maximum LET) and the maximum RBE might be the best choice for therapy. However, the results suggest that there would be no significant clinical effects due to the separation of LET_U and LET_M for ions up to carbon, since the distances fall considerably below 1 mm, which represents the best available spatial accuracy in radiotherapy.

Further complications and distortion of the above findings may occur with nuclear fragmentation effects, which are found in heavier ions and are of significance in carbon ion therapy [11], although there is currently no evidence of this process being detrimental in terms of clinical outcomes. Nuclear fragmentation has not been included in the present study on the basis that it is localised at lower energies with a tail of mainly Low LET γ rays in the forward direction. More sophisticated simulations and experiments would be required to determine the importance of nuclear fragmentation and this is a topic for further research for carbon and heavier ions.

For doses associated with therapeutic cancer therapy exposures within clinical target volumes, all cells are typically traversed by multiple particle tracks. However, for high-LET particles this is often not the case for the much lower doses associated with more remotely situated normal tissues.

Also, there are many situations encountered in radiation protection, where only a small fraction of cells will be traversed by a single track, often with many of the cells not being exposed to the primary particle track. In this situation it is often useful to consider the effectiveness of a single particle traversal of cells, where the peak in effectiveness will typically be at a lower particle energy (with higher LET) than that for maximum RBE (at LET_U) but closer to LET_M [12]. Here, not only will be dose to the cell be greatest, but the number/density of correlated DNA damage sites along the track will also be maximal, along with the degree of complexity of damage at the site. Therefore, for the assessment of risk associated with typical low dose exposure to charged particles, either in therapy or radioprotection, the separation of LET_U and LET_M may also be an important consideration.

Conclusions

The maximum possible RBE is predicted to occur at LET values below that of the maximum LET in ionic beams, and so occurs proximal to the Bragg peak for individual particles when electronic interactions are studied. There may be important differences for heavier ions due to additional nuclear fragmentation effects. The location differences between these two important LET values increases in a linear manner with Z, but for ions up to carbon the distances between the two maxima are too small to influence therapeutic beam placements when compared to the standard accuracy tolerances of radiotherapy, but for higher Z values there are larger differences which may be of importance in radioprotection or if therapeutic beams were to be used.

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Declarations

None

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