



Editorial

Relative Biological Effect/Linear Energy Transfer in Proton Beam Therapy: A Primer

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Proton beam therapy is a rapidly developing tool in cancer treatment. This educational piece will outline the key physical, biological and clinical parameters that give a basic understanding of the radiobiology of proton therapy (Figure 1). In particular, it will focus on the important parameters of linear energy transfer (LET) and relative biological effectiveness (RBE).

Proton versus Photon Physical Characteristics

Radiotherapy is based on the concept of delivering a physical dose, in the form of ionising radiation, to cause a biological response. We know that the main target for damage is cellular DNA. High energy photons are used globally for radiotherapy. They are indirectly ionising particles, which means that the photons interact to produce secondary electrons, which then impart dose to the medium. At the photon energies used for external beam radiotherapy (≥ 6 MV) the dominant interaction is Compton scattering, where incoming photons eject an atomic electron [1]. By contrast, protons are directly ionising particles and predominantly interact with atomic electrons through multiple coulomb scattering. The mass advantage of the protons means that little energy is lost by the proton during an interaction but with the sheer number of interactions the proton loses energy with depth in the patient [2]. As the energy decreases, the velocity of the proton decreases and the number of interactions increases, consequently increasing the local dose deposition. The dose deposited increases steeply in a short distance at the end of the

protons' range with a sharp fall-off beyond the peak. This dose distribution with depth is known as the Bragg curve.

Proton therapy is comparatively expensive to deliver relative to linac-based photons [3]; however, the difference in interactions results in a preferential dose distribution that has the potential to reduce the dose to normal tissues relative to optimal photon delivery. We know that protons are radiobiologically more effective than photons; the quantification of this difference is a current active area of research [4].

Absorbed Dose

Absorbed dose is defined as the mean energy imparted by ionising radiation to matter of mass m in a finite volume v . The unit of absorbed dose is the gray (Gy), where 1 Gy is equivalent to 1 joule per kilogram (J/kg).

Linear Energy Transfer

LET is defined as the average energy locally imparted to the absorbing medium by a charged particle of specified energy traversing a given distance of the medium. It is most typically expressed in units of kiloelectronvolts per micrometre (keV/ μm). As with dose, LET increases with depth for protons, with the maximum just beyond the Bragg peak.

Relative Biological Effectiveness

RBE is defined as the ratio of dose required to produce the same biological effect between a radiation beam (often charged particles) and a reference radiation, usually defined as 250 kVp X-rays or ^{60}Co γ -rays (RBE = 1). RBE depends on the conditions under which the effect is measured [5].

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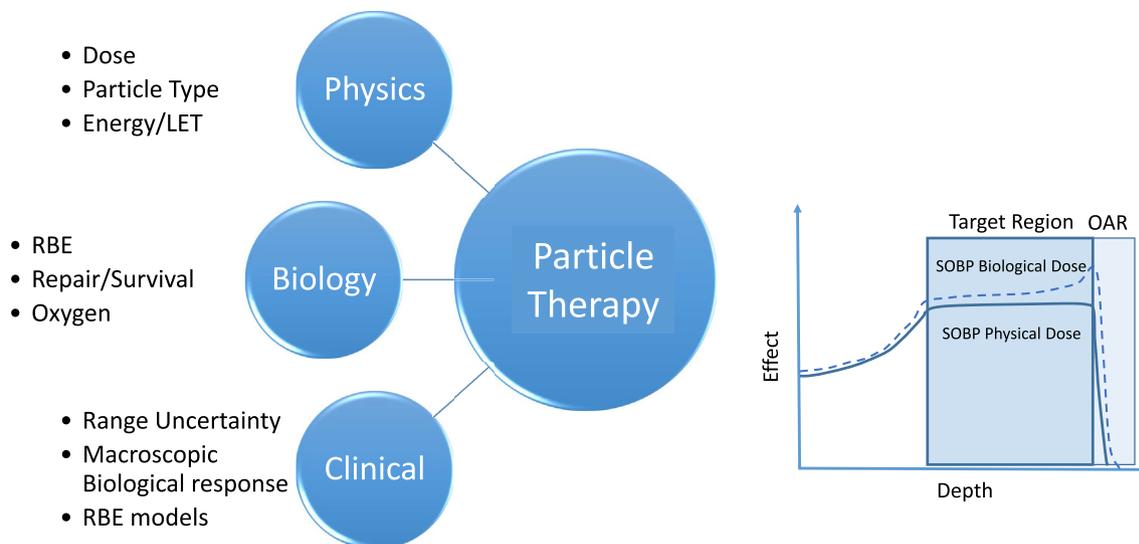


Fig 1. Schematic of key physical, biological and clinical issues associated with proton beam therapy delivery. An idealised spread out Bragg peak (SOBP) is shown with an example of the difference between physical and biological dose with depth.

Experimental evidence has shown that RBE is related to LET, increasing towards the end of the range of a proton, in and just slightly beyond the Bragg peak. Although clinically a constant value of 1.1 is used to relate proton dosimetry to the biological effect, this is an oversimplification for both tumour and normal tissue responses [6].

Photons versus Protons Biological Characteristics

The increased ionisation density of particles relative to photons (i.e. increased LET), leads to more densely ionising clusters of energy interacting with cells and, in particular, with the nuclear DNA, leading to a high probability of clusters of DNA damage being produced locally on the DNA. These can consist of multiple DNA lesions, such as base damage, single-strand breaks, double-strand breaks and crosslinks as part of what is termed clustered (or complex) DNA damage [7]. This damage is thought to be more difficult to repair and with increasing LET more double-strand breaks are left unrepaired and have a higher probability of leading to cell death. This leads to an increased RBE for cell killing with increasing LET, typically up to a maximum value (dependent on ion species) beyond which energy then becomes wasted (overkill effect). RBE, however, is dependent on many additional factors, such as dose, dose rate and individual radiosensitivity. Oxygen is also a major modifier of response that is LET dependent. For low LET radiations, such as X-rays and γ -rays, regions of tumour that are hypoxic (at reduced oxygen) are more radioresistant. Oxygen rapidly converts radicals produced after irradiation to damaging peroxyradicals, which are the precursors of DNA damage. In the absence of oxygen, cells are about three times more radioresistant. This is measured in clonogenic survival assays as an oxygen enhancement ratio. This is defined as the ratio of the radiation dose under anoxic conditions to

produce a given effect relative to the radiation dose under fully oxygenated conditions to produce the same effect. The oxygen enhancement ratio also decreases with increasing LET, making ion beams more effective against hypoxic tumours.

Calculating Relative Biological Effectiveness – Cell Survival Curve

RBE is found experimentally by plotting the cell survival curves for a single cell line comparing the survival fraction using the reference beam and the particle beam. The dose required to produce a specific survival is compared. These measurements are sensitive to a large number of experimental factors, including the choice of reference beam, the cell line, the choice of survival fraction and dose rate [5].

The review article by Paganetti [5] that collated pre-clinical data found the RBE to be 1.1 at the entrance of the beam, 1.3 at the distal edge and 1.7 in the distal fall-off region. It also noted the large variation in experimental set-up and the large uncertainty in the derived values.

Current Data for Protons – Models

Mathematical models relating physical dose to relative biological effect are numerous and remain largely unvalidated. Models based on the linear–quadratic model are widely cited when considering proton beams [8–11]. It is beyond the remit to describe in full each implementation but generally each model requires the dose averaged LET and α/β value of the tissue (photons). The models have been fitted to mostly preclinical data to derive the relevant parameter values. Due to variation between models, papers often present results for two or three models.

In general, the models describe an increase in RBE with LET and an increase in RBE for low α/β values. It should be

noted that most preclinical data do not include dose points in the range of interest for clinical radiotherapy, i.e. ≤ 2 Gy per fraction, and rarely include fractionated data.

Heavy Ions

This article has considered the LET/RBE from the perspective of protons as they have now become part of UK radiotherapy. However, internationally, heavier ions, most commonly ^{12}C , have been used, particularly in Japan and Germany [12]. In the case of heavy ions, a variable RBE with depth is included in treatment planning [13]. As such the physical dose is reduced in regions where the RBE increases. Due to the higher LET than protons, significant biological advantages occur, particularly for the treatment of radio-resistant tumours. Given the importance of the underlying biology, a range of mechanistic models have also been developed to define RBE relationships for different ions (see [14] for a review).

Clinical Proton Beams

For the delivery of clinical spot-scanning proton beams, overlapping pencil-width beams of different energies (and hence range) are raster scanned into the patient to produce a spread out Bragg peak (SOBP) covering the tumour volume at depth (Figure 1). The proton beam range has a small inherent uncertainty resulting from the calibration curve required to translate Computed Tomography (CT) Hounsfield units to proton stopping powers. Uncertainty in patient positioning and changes over the course of treatment will further blur the dose distribution compared with the well-controlled preclinical environment. As individual organs are complex functional units of different cell types, the assays of individual cell lines may not be relevant. Additionally, dose distributions to organs at risk (OAR) are intentionally heterogeneous and therefore complex to characterise. The ability to calculate LET and RBE at a voxel-wise level is emerging and subsequently the potential for LET-based treatment plan optimisation. It has been shown that the distribution of high RBE regions may well be outside the clinical target volume and within adjacent OAR. However, despite the comprehensive data indicating that the RBE is variable, to date clinical practice has steadfastly used the value of 1.1. This has been due to (i) uncertainty in knowing the correct value to use in the clinical setting, (ii) the inability to include variable RBE in commercial treatment planning systems and, perhaps most influentially, (iii) limited clinical evidence of an enhanced RBE at the distal edge of a clinically delivered SOBP [15].

The way forward is to consider the potential consequences of variable RBE while remaining mindful of the uncertainties. The American Association of Physicists in Medicine released Task Group Report 256 earlier this year [4]. This report focuses on how to move forward in the knowledge that a constant value of 1.1 may not be the

optimal approach but states that ‘it is premature to adopt and recommend a variable RBE model to use clinically’.

Until LET and RBE information becomes available and is widely implemented in commercial treatment planning systems, it is important to consider the potential implications when designing and reviewing proton therapy treatment plans. The most widely discussed scenario is where an OAR abuts the target volume and a beam is placed so that the distal edge of the SOBP sits at the border of the two. In an ideal case this situation would be avoided by considering alternative beam placement, but this is not always achievable, for example where tumours are in close proximity to the brainstem. If field-specific optimisation is used, it may be possible to limit the weighting of spots adjacent to or overlapping the OAR using additional structures defining the overlap region or by decreasing the dosimetric constraint. The assessment of treatment plan robustness, that is inherent to the proton treatment planning process, will indicate the level of uncertainty in the physical dose to the region of concern.

Summary

Understanding the relationship between LET and RBE is important for improved strategies of clinical delivery that can mitigate uncertainties with the use of proton and other ion beams.

Conflict of Interest

The authors declare no conflicts of interest.

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