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Overview

The Radiobiology of Proton Therapy: Challenges and Opportunities Around Relative Biological Effectiveness

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Abstract

With the current UK expansion of proton therapy there is a great opportunity for clinical oncologists to develop a translational interest in the associated scientific base and clinical results. In particular, the underpinning controversy regarding the conversion of photon dose to proton dose by the relative biological effectiveness (RBE) must be understood, including its important implications. At the present time, the proton prescribed dose includes an RBE of 1.1 regardless of tissue, tumour and dose fractionation. A body of data has emerged against this pragmatic approach, including a critique of the existing evidence base, due to choice of dose, use of only acute-reacting *in vivo* assays, analysis methods and the reference radiations used to determine the RBE. Modelling systems, based on the best available scientific evidence, and which include the clinically useful biological effective dose (BED) concept, have also been developed to estimate proton RBEs for different dose and linear energy transfer (LET) values. The latter reflect ionisation density, which progressively increases along each proton track. Late-reacting tissues, such as the brain, where $\alpha/\beta = 2$ Gy, show a higher RBE than 1.1 at a low dose per fraction (1.2–1.8 Gy) at LET values used to cover conventional target volumes and can be much higher. RBE changes with tissue depth seem to vary depending on the method of beam delivery used. To reduce unexpected toxicity, which does occasionally follow proton therapy, a more rational approach to RBE allocation, using a variable RBE that depends on dose per fraction and the tissue and tumour radiobiological characteristics such as α/β, is proposed.

Key words: Proton therapy; radiobiology; RBE; radiotherapy treatment planning

Introduction

Radiotherapy is the major treatment modality for around 50% of all cancer treatments internationally and is continuing to go through a rapid phase of technological development. Intensity-modulated radiotherapy, arc therapies, stereotactic therapy, image guidance and, recently, magnetic resonance imaging-linacs all aim to deliver highly conformal beams to maximise tumour dose. For high-energy photon exposures, the high reproducibility and accuracy is driving the rapid testing of stereotactic and hypofractionated treatments combined with novel molecular and immunotargeting strategies [1]. For many years in parallel, proton therapy has been developing based on the physical properties of the Bragg curve. As of the end of 2015, 131 240 patients had been treated across a wide range of tumour types and as of June 2017 there were 62 centres being built or planned internationally, including two National Health Service centres and four private centres in the UK [2]. Carbon ions are also currently used for therapy, but only in a few centres internationally and at a much lower level than protons, with by 2015, 19 376 patients having been treated [2].

All therapeutic interventions have risks and benefits. For new pharmacological agents there is considerable legislation that demands satisfactory preclinical experimental studies before human exposures are allowed; the same is not true for radiation therapy, where the legal emphasis is on quality assurance relating to dose associated with particular techniques. However, radiotherapy evolved pragmatically with its scientific base of radiobiology providing phenomenological support, sometimes

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with useful applications through the use of relatively simple mathematical models. Clinical oncologists will be familiar with how the biological effective dose (BED) and equivalent dose in 2 Gy (EQD-2) concepts have multiple uses and can be used to make radiotherapy much safer, for example dealing with unintended treatment interruptions [3].

Most oncologists consider proton therapy to be an extension of conventional therapy and should be integrated within the present clinical service provisions. This viewpoint is highly desirable for involvement of 'site specialist' oncologists, but the knowledge base of practitioners must be increased to cover the salient physical and radiobiological aspects of proton therapy.

In the context of proton therapy, which is regarded as the most promising modern form of treatment in certain clinical situations, there is a significant body of existing radiobiology research, although it is limited in scope as far as the applicability to human exposures and paucity of information for late normal tissue reactions. Here we consider the challenges and opportunities around protons, focussing on relative biological effectiveness (RBE).

Proton therapy offers delivery of radical treatment doses, often with reduced energy deposition in the body, and avoidance of unnecessary direct radiation doses to many organs due to the Bragg peak effect [1]. There are three potential disadvantages that must be overcome to optimise the safety and effectiveness of their use:

(1) Bragg peak placement inaccuracy due to physical reasons, such as heterogeneous tissue densities, patient movement, daily positioning, and beam delivery-related factors, such as lateral scattering of the beam.
(2) Within Bragg peaks, energy is deposited as clustered rather than sparse ionisation events. This causes more complex DNA damage that is more difficult or impossible for enzymatic DNA repair mechanisms to restore, resulting in enhanced biological effects. These may be advantageous within a cancer, but possibly deleterious for normal tissues in the tumour vicinity and which require to be treated to full or near-full dose to achieve local tumour control.
(3) Currently, the medical prescription of proton therapy dose includes a 10% reduction in dose to all tumours and tissues to compensate for enhanced bio-effectiveness. This correction factor is being challenged, but to understand this issue, it is necessary to be familiar with the physics and biology terms associated with enhanced bio-effectiveness, and how this is modified by physical and biological characteristics.

Underpinning Physics and Radiobiology

Along individual radiation tracks, the closeness of ionisations is expressed by the linear energy transfer (LET), which essentially averages the energy released per micrometre distance and is reported in units of keV per micron. As protons enter the body at high energy and slow down, the ionisation density and, hence, the LET, increases, delivering the characteristic Bragg peak shape.

The other essential definition is that of RBE. It is formally defined as a ratio, and in the context of proton therapy is:

$$RBE = \frac{Dose\ of\ the\ reference\ megavoltage\ photon\ radiation}{Dose\ of\ proton\ therapy}$$

each dose achieving the same specified biological effect.

Protons are typically prescribed to patients at doses where the photon-equivalent RBE-weighted dose (denoted as GyRBE) matches the photon physical dose. As a result, the actual delivered physical proton dose is equal to the physical photon (or X-ray) dose divided by the proton RBE, presently assumed to be 1.1 in all tissues and tumours, irrespective of the dose per fraction. If this 1.1 value is incorrect, the prescribed doses will also be incorrect.

LET and RBE are closely related, with RBE initially increasing approximately linearly with LET. At higher LETs this rate of increase slows and eventually reaches a turning point after which RBE falls, due to energy 'wasting'. The magnitude of the RBE is inversely related to the dose and is also related non-linearly to the intrinsic cellular radiosensitivities (α and β parameters explained below).

In proton therapy, Bragg peaks are 'spread out' to cover the tumour: tissues receive a mixture of Bragg peak (high LET) and non-Bragg peak (low LET) regions, often resulting in average LETs around 1–2 keV/μm in the tumour region, although can be higher and up to 8–10 keV/μm or more, depending on field arrangements and technique used. Pencil beam delivery can result in higher average LETs [4], with perhaps additional bio-effects due to differences in how the protons are modulated compared with passively scattered (wider) beams.

The average LET of conventional megavoltage radiotherapy is around 0.2 keV/μm, which has an immediate implication that the mid-spread out Bragg peak (mid-SOBP) LET may be around six to nine times higher. Another complicating factor is that much of the research on LET and RBE (for protons and other forms of radiation) used low voltage X-ray beams, whose LET was already around 1–1.5 keV/μm and was frequently used to estimated proton RBEs despite introducing the risk of underestimating RBEs.

For further understanding it is necessary to describe the simple, but elegant, mathematical relationship between radiation dose and bio-effectiveness described by the linear quadratic model (see Table 1).

Some general trends have been confirmed from LET-RBE experimental studies that have used a variety of radiation modalities, including fast neutrons (that mainly produce recoil protons), low energy X-rays, alpha particles, carbon and other light ions [4,6–10]. These include the fact that the α parameter increases by more than the β parameter with LET, which leads to the inverse relationship between RBE and dose. At a very low dose per fraction the RBE will be close to the ratio α_H/α_L (often referred to as the RBEmax), whereas at high doses the RBE falls, becoming closer and closer to the ratio $\sqrt{\beta_H}/\sqrt{\beta_L}$ (the RBEmin) [11]. These RBE limits are contained in the BED equation shown in Table 1 and Figure 1.

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