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The Radiobiology of Proton Therapy: Challenges and Opportunities to Overcome RBE-related Problems

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With the current worldwide expansion of proton therapy, there is a great opportunity for clinical radiation oncologists and physicists to develop an interest in the associated scientific base and clinical results. In particular, the continuing 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. There is also considerable evidence from fast neutron experiments which are relevant some aspects of proton therapy, because neutrons cause most of their ionisation by producing recoil protons. Relatively simple mathematical 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 (or other ion beam) RBEs for different doses and linear energy transfer (LET) values. LET is a measure of radiation ionisation density which progressively increases along each proton track. Late reacting tissues such as the brain, where β = 2 Gy, show a substantially higher RBE than 1.1 at low dose per fraction (1.2-1.8 Gy), for LET values which are used to cover conventional target volumes, but can be much higher, especially at the ends of spread out Bragg peak or scanned beams. RBE changes with tissue depth appear to vary depending on the method of beam delivery used, and may also reflect the beam fluence, which is related to the particle inter-track distance.
To reduce unexpected toxicity, which does occasionally follow proton therapy, a more rational approach to RBE allocation, using a variable RBE which depends on dose per fraction and the tissue and tumour radiobiological characteristics such as β is proposed. Such an approach should make proton therapy safer and more effective.

Primary author: JONES, Bleddyn (University of Oxford)