Practical Radiobiology for Proton Therapy Planning

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Practical Radiobiology for Proton Therapy Planning

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This book is dedicated to Dr O C A Scott, MD (Cantab) FRCR, who inspired so many scientists and clinicians, gave freely of his ideas and was such a generous benefactor.

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Preface

This book is intended to cover the principles concerning the advantages and potential pitfalls that occur in proton therapy, especially its radiobiological modelling applications. For these to be understood, it is essential to present summaries of radiotherapy, radiobiology, clinical radiobiological modelling for conventional radiotherapy techniques as well as for protons and other ion beams. Radiobiological modelling has proved useful in radiotherapy, especially in situations where departures from protocols occur for a variety of reasons such as unintended treatment interruptions, errors in treatment delivery, dose rate effect applications, comparisons of different techniques, dose fractionation schedules, re-treatments and even in clinical trial design. These techniques, if suitably adapted, are capable of producing similar insights and practical guidelines in proton and other forms of ion beam therapy. The optimisation of proton and ion beams is essential since there is considerable 'competition' from the more advanced forms of megavoltage photon-based radiotherapy, which allows fewer and highly focused treatments to be given as well as being more economical.

The use of relatively simple mathematics and some very basic worked examples are included within the text, but have been kept to a minimum, so that *all the relevant disciplines* can understand the principles, and then use the historical content and advice provided to develop the subject further. A basic knowledge of radiation biology is assumed, and references have been kept to the minimum necessary. The parameters chosen for exploratory modelling and illustrative purposes may require modification and further input for more specific clinical applications. Any errors are the sole responsibility of the author. There is inevitably some degree of repetition where this is considered essential.

The mainstay approach has been to use the biological effective dose (BED) concept based on the linear-quadratic (LQ) model of radiation effect. In recent years it has been possible to assess the BED values of charged particle therapies such as protons and light ions by incorporation of the maximum and minimum limits of the relative biological effect (RBE), which accounts for the increasing complexity of DNA damage and the increasing proportion of non-repairable damage that occurs when the linear energy transfer (LET) of a radiation is increased. Typically LET increases within the Bragg peak region for charged particles, with resultant increments in the RBE, but the RBE reduces with increasing dose and also at very high LET values, but it is important to realise that different biosystems will have quite different RBE values. The topic of the RBE remains controversial, although it is being increasingly understood, and there are several models that attempt to link LET with the RBE, many of which use formidable mathematics. In contrast, this book addresses how to achieve this by using relatively simple mathematics. Such a simpler approach can be understood by physicians, physicists and biologists. More complex approaches can be limited in their usefulness due to excessive and/or restrictive assumptions and the limits of what can be known. Simpler models,

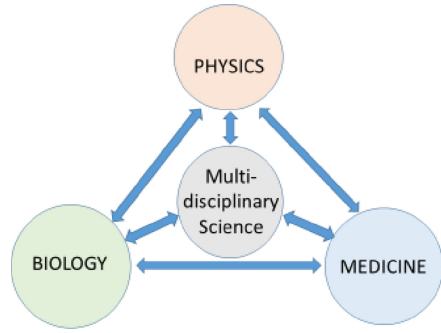

Figure 1. The central multi-disciplinary role, which must include a modelling component.

although they always require caveats, are capable of providing useful qualitative and quantitative understanding of the basic principles that govern clinical outcomes.

This subject is very multidisciplinary, and is based on a triangular arrangement with physics, medicine and biology forming the apices of an isosceles triangle (figure 1). The decisive middle ground has to be covered by individuals who have sufficient knowledge and experience of all three disciplines. A basic knowledge of these three subjects and the inter-disciplinary subject of radiation biology is assumed, along with basic aspects of particle therapy such as the Bragg peak effect, and the characteristics of the spread out Bragg peak and how this may be achieved. The author is minded that the text should be reasonably understood by members of all these disciplines, although additional reading will be required from review articles and textbooks to supplement cross-disciplinary understanding. Also, each primary discipline is divided into a spectrum of further specialisation groups: physicists are split into fundamental particle physicists, accelerator or detector physicists and their medical physicist colleagues; in biology there are purely molecular biologists (biochemists) concerned with *in vitro* work, biophysicists (physiologists), pharmacologists and zoologists, some concerned with *in vivo* animal testing; within the faculties of medicine, the knowledge base is spread over anatomy, all forms of pathophysiology, oncology, surgery, patient management as well as a broad interest in epidemiology. Also, many non-biologically trained physicists have had a very significant influence in advancing radiobiology and, given the added complexities of charged particle physics, their continued involvement will be essential to understanding particle therapy and its associated radiobiology.

With all these facets in mind, it is necessary to write sympathetically for the non-specialist, but furnish sufficient detail regarding many necessary fundamental aspects across these topics, while providing more detailed information for the practitioner or researcher in this field. For reasons of space and economy, it has been necessary to omit the classical graphs and diagrams associated with the basic sciences, but these can be found in standard textbooks. In most instances, since most readers of this book will be familiar with them, the brief qualitative descriptions and definitions provided will act as an aide memoire.

The medical decision makers of the future in particle therapy will need broad scientific backgrounds, excellent clinical and oncological training, and be able to appreciate the strengths and weaknesses of the available mathematical models that link the clinical, biological and physical parameters, and which can be used to protect the patient against over or under-dosage. Modelling is a necessary way of quantitative communication between the three apices already referred to, in the important multidisciplinary centre-ground, complementing rational verbal or written approaches. In essence, this must be kept sufficiently simple in order for all disciplines to interact.

Considerable practice is necessary to become familiar and competent in this subject. The calculations may appear to be deceptively easy, as only knowledge of some higher school mathematics is necessary, and this can be aided by computer software systems such as Mathematica, Matlab and Maple. However, some of the clinically based calculations are quite protracted, with many more pitfalls (due to the RBE, LET, etc) than for similar calculations in the case of photon-based treatments.

There are many who regard particle therapy as just a seamless extension of photon-based radiotherapy. This is certainly useful in terms of departmental organisation within a hospital structure, to ensure good patient access and to capitalise on site-specialist knowledge of the oncologist in terms of detailed regional anatomy and indications for therapy. However, owing to the added complexity of particle therapy, there is an essential need to educate and train all the sub-disciplines involved in treatment delivery and patient management in order to inform them of the strengths and weaknesses of particle therapy, and by knowing these to continually search for better, highly optimised therapy.

Depending on the background of the reader, it is not necessary to read the whole of the book. Chapter 1 provides the essential physics background mostly for the benefit of biologists and clinicians, but includes the importance of the choice of the reference radiation in RBE studies as well as the different ways in which LET is expressed, and introduces the potentially important parameter of inter-track distance. In chapter 2, the basis of radiobiological modelling is introduced, with formulations for conventional megavoltage photon radiotherapy and for particle therapy, including low and high dose, dose rate variations and the useful BED concept. Chapters 3 and 4 have been written for persons who have little or no previous experience of radiotherapy, with discussion of the essential medical aspects of treatment planning, including the influence of surgery and other factors on tissue viability. Some of the key historical developments in radiotherapy are covered in chapter 5, as well as what has been learned from extensive basic and clinical research using fast neutrons for modern applications with charged particles. Chapter 6 considers dose-fractionation effects in photon and particle therapy, with some worked examples. The rationale for using a variable as opposed to the conventional constant RBE in proton therapy is provided in chapter 7. This is followed by the description of a relatively simple 'energy efficiency' model for estimation of the RBE values for any ion beam in chapter 8. More specific applications in proton therapy are given in chapter 9, with some tables that suggested tentative RBE allocations for variable values of LET in different classes of tissues and tumours. The correction of

unintended treatment interruptions for high LET treatments, with worked examples, is described in chapter 10, which also includes formulations for assessing re-treatment doses in the central nervous system. Chapter 11 considers the radiobiological correction of Bragg peak placement errors, resulting in deviations in both LET and dose. Chapter 12 contains further possible future developments to improve our overall understanding and especially to obtain more accurate modelling parameters, as well as methods of assessing the potential impact of concomitant drug sensitisation with high LET radiations.

It is hoped that this book will not only improve the safety and effectiveness of particle therapies, but also inspire further research and enquiry.

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Glossary of terms and symbols

α, the radiosensitivity coefficient of the LQ model per unit dose, in units of Gy^{-1}.

α_L, refers to α for the low LET condition when high and low LET qualities are being compared.

α_H, refers to α for the high LET condition when high and low LET qualities are being compared.

α_U, the ultimate value of α at the turnover point of the LET–RBE relationship.

Similarly, β is the radiosensitivity coefficient of the LQ model per unit dose squared, in units of Gy^{-2}.

β_L, β_H, and β_U refer to the same specifications as for α.

α/β, this important ratio, which has units of Gy, determines the dose per fraction sensitivity in an inverse sense, such that low values (2–3 Gy) show large dose per fraction sensitivity, but high values denote low dose per fraction sensitivity (those above 7 Gy).

$(\alpha/\beta)_L$, refers to the low LET ratio in situations where low and high LET radiation qualities are being compared.

$(\alpha/\beta)_H$, refers to the high LET ratio in situations where low and high LET radiation qualities are being compared.

RBE, defined as the ratio of dose for low LET (the control or reference) radiation divided by the dose of the high LET test radiation in order to achieve the same specified bio-effect.

$RBE_{max,}$ the limiting value of RBE at very low dose (approaching zero dose) for any specified high LET radiation when compared with a low LET radiation.

RBE_{min}, the asymptotic limiting value of RBE at very high dose for any specified high LET radiation when compared with a low LET radiation.

RBE_C, an intermediate value of the RBE where the following conditions apply: $R_{max}/R^2_{min} = (\alpha/\beta)_H/(\alpha/\beta)_L$.

LET, the linear energy transfer parameter defined as the energy release per unit length of track in the track plane expressed in units of keV μm^{-1}. Further definitions are given in chapter 1.

LET_U, the value of LET at the turnover point of the LET–RBE relationship.

LET_C, the value of LET of the low LET control radiation quality.

LET_x, any specified value of LET for the test high LET radiation.

N, the number of dose fractions in a treatment course (or schedule).

d, the dose per fraction in units of Gy, D is the total dose (or $n \times d$).

E, the negative logarithm of the surviving fraction, often referred to as the log cell kill, which is proportional to the surviving fraction.

SF, the surviving fraction of cells in an experiment.

g, the ratio of a specified normal tissue dose divided by the tumour dose.

S, a formulation for combining the g factor with the uncertainties of knowledge regarding the most appropriate RBE value in normal tissues and tumour.

BED, the biological effective dose, in units of Gy, which expresses the dose required to achieve a specific bio-effect if given in ultra-small dose fractions, and represents a ceiling of dose that can be used for comparative purposes.

ω, the average cellular doubling time during radiation.

K, the BED equivalent of cellular repopulation expressed as Gy day^{-1}.

T_K, the lag time, in days, that may occur before cellular repopulation is manifest.

f, refers to the mean inter-fraction interval (days). For example, if five treatments per week are given $f = 7$ days/$(5 - 1) = 7/4 = 1.75$ days.

Z, the nuclear charge.

z, the tumour dose if the normal tissue dose is specified as d.

μ_F, the DNA repair rate constant for the fast component of repair.

μ_S, the DNA repair rate constant for the slow component of repair.

h, the incomplete repair parameter for closely spaced treatments.

Fluence refers to the number of radiation tracks crossing a specified area.

KERMA refers to the kinetic energy released per unit mass (J Kg^{-1}).

Absorbed dose refers to the energy absorbed in a specified mass (J Kg^{-1}).

Radiation quality refers to the LET of a radiation at a specified energy.

Author biography

Bleddyn Jones

Bleddyn Jones studied Medicine at Cambridge (with some mathematics), followed by clinical and post-graduate training at Guy's, St Thomas, St Bartholomew's and The Royal London Hospitals. He also studied Radiobiology (University of London) before commencing Clinical Oncology training, subsequently holding Consultant and Academic appointments in Clatterbridge, Hammersmith, and Birmingham. He later became Professor of Clinical Radiobiology in Oxford, where his research concentrated on developing mathematical models of particle therapy, as well as other difficult aspects of radiotherapy such as re-treatments and radiosurgery. This was an extension of his previous applied radiobiology work in reducing toxicity following Gynaecological Brachytherapy, initially using models developed by Professor RG Dale, with whom he collaborated extensively over many years.