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Introduction To Particle Therapy

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President's conference paper

The case for particle therapy

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Abstract. Among the most important decisions facing the British Government regarding the treatment of cancer in the National Health Service (NHS) is the purchase of charged particle therapy (CPT) centres. CPT is different from conventional radiotherapy: the dose is deposited far more selectively in Bragg Peaks by either protons or "heavy" ions, such as carbon. In this way, it is possible to "dose paint" targets, voxel by voxel, with far less dose to surrounding tissues than with X-ray techniques. At present the UK possesses a 62 MeV cyclotron proton facility at Clatterbridge (Wirral), which provides therapy for intraocular cancers such as melanoma; for deeper situated cancers in the pelvis, chest etc., much higher energies, over 200 MeV are required from a synchrotron facility. There is an impressive expansion in particle beam therapy (PBT) centres worldwide, since they offer good prospects of improved quality of life with enhanced cancer cures in situations where conventional therapy is limited due to radioresistance or by the close proximity of critical normal tissues. There is a threat to UK Oncology, since it is anticipated that several thousand British patients may require referral abroad for therapy; this would severely disrupt their multidisciplinary management and require demanding logistical support.

The benefits of an increase in charged particle therapy (CPT) centres in the UK would be not only for children and young adults with cancer, where a reduced risk of radiation induced malignancy is predicted, but also in older patients where it is necessary to avoid abnormal tissues such as an enlarged heart/restricted lung irradiation and where artificial (metallic) joints may cause difficulties in the use of conventional radiotherapy techniques. The results of phase I and II clinical studies are extremely encouraging. The UK must obtain at least one CPT centre with protons/ions in order to conduct research and development; it is suggested that quality adjusted life years should be used to assess outcomes. It is anticipated that the UK might eventually require 7–8 such centres in 10–15 years from now. In the meantime, healthcare purchasers and providers need to put in place mechanisms and personnel for patient referrals abroad, as well as the establishment of UK CPT facilities.

Background

The connection between subatomic particles and health delivery improvements may seem rather tenuous, but the narrative begins in 1879, when J J Thompson discovered the negatively charged electron in Cambridge, and Aneurin Bevan was born in Wales. The subsequent discoveries of the positively charged proton (a term coined by Ernest Rutherford in 1920) and the uncharged neutron by James Chadwick in 1931, confirmed the pre-eminence of our science. Bevan, with similar precision of thought, digested the wide recommendations of the Beveridge Report (1942) and transformed most of its principles to practical achievements, including the National Health Service Act of Parliament (1946) and the inception of the service in 1948. Subsequently, Britain was at the forefront of practical applications of physics and engineering developments in cancer therapy until the early 1990s, when the reorganized NHS became disadvantaged in terms of expensive technological acquisition.

Dr R D Errington related the history of cyclotron radiotherapy at the BIR President's Day conference in 2003. He detailed how the initial promising results obtained with neutron therapy at The Hammersmith Hospital were not subsequently confirmed in randomized trials at Edinburgh and at the Clatterbridge facility [1, 2], which produced neutrons that matched a 5 MeV X-ray beam. The latter facility was converted to produce protons on the recommendation of the late Prof. Arthur Jones of St. Bartholomew's Hospital. This enabled patients with choroidal melanoma of the eye to receive radical radiotherapy using protons; this technique was the first example of three-dimensional (3D) radiotherapy in the UK. Over 1400 patients have by now received this therapy with a local control rate of 98% – an outstanding achievement within British medicine [3].

Past attempts to obtain a higher energy facility in the UK

Since 1992, Clatterbridge, Oxford and the National Physical Laboratory at Daresbury (near Warrington) have all unsuccessfully attempted to obtain a higher energy CPT facility [4]. All these bids were rejected because of perceived lack of clinical support, intermittent beam availability, the lack of clinical trial evidence, the recommendation that a facility should be sited in a University Hospital campus and perhaps mostly, the expected high initial costs incurred at a time when NHS reforms discouraged large-scale projects, even the provision of new (replacement) linear accelerators.

More recently, there has emerged a more collective response from clinical oncologists and medical physicists who appreciate that obtaining a CPT facility is essential

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for the advancement of radiation oncology standards in the UK. The Royal College of Radiologists (RCR), British Institute of Radiology (BIR) and Institute of Physics and Engineering in Medicine (IPEM) for example all support the case for a CPT facility. Recent improvements in the quality of cancer imaging and the availability of industrially produced turnkey facilities, has allowed the question to be carefully re-considered and better understood, particularly in relation to the rapid expansion in CPT facilities abroad.

Technical aspects

The velocity of heavy charged particles (electrons are considered to be light) is reduced as they traverse deeper through tissues. The interaction probability to cause ionization increases as the velocity falls, so that a peak of dose occurs at a depth proportional to the energy imparted to each particle. William Bragg, a British physicist, described this phenomenon over 100 years ago [5]. The so called Bragg peak can be "spread out" to achieve a plateau of uniform dose that covers a target by use of rotating range-shifting modulators of variable thickness. In the past, passively scattered beams were used in this way to provide wide circular or rectangular beams with spread out Bragg peaks (Figure 1). More recently, the spot scanning method allows smaller beams to deposit their peaks within individual voxel targets defined by good imaging techniques: by the use of "wobbler" magnets and particle energy selection, the raster scanning system allows cancer bearing voxels (defined by *x, y, z*, co-ordinates), to be "dose painted".

The Bragg peak position will depend on the initial energy imparted to the particles as well as their mass and charge; the Bethe-Bloch equation contains all the necessary parameters. It can be seen from Figure 2 that the range for clinical use should be at least 200 MeV in the case of protons; higher energies – up to 400 Mev – for carbon ions.

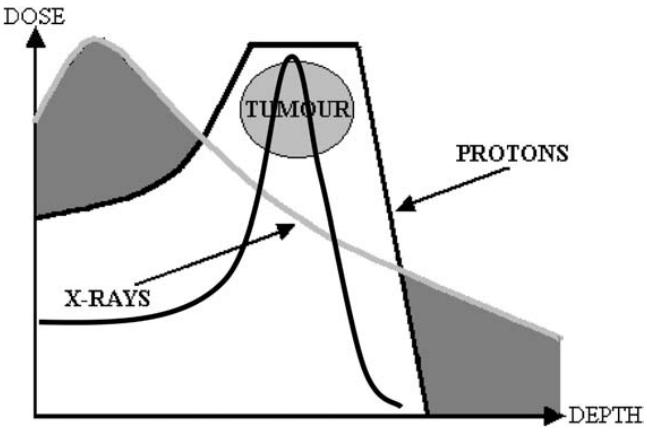

Figure 1. Schematic depth dose diagram of a proton beam Bragg peak, the spread out Bragg peak and a megavoltage X-ray beam (modified from Suit et al [12]). The grey shaded areas indicate the extent of dose reduction within normal tissues situated proximal and distal to the tumour target.

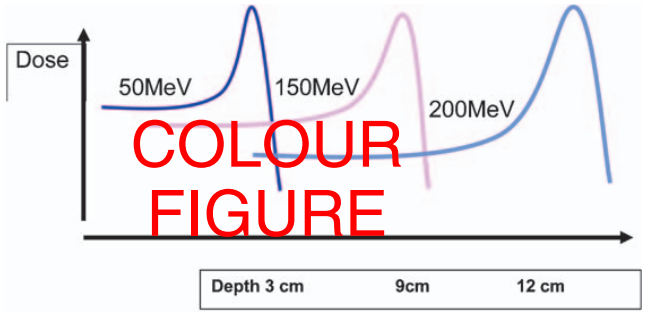

Figure 2. Approximate depth dose positions of partially spread out Bragg peaks for protons of different energies.

Gantries and robots

Within treatment rooms there are options for beam arrangements. The simplest approach is to have either fixed horizontal or vertical beams, or a combination of the two for the simplest treatments. An isocentric rotating gantry is required for more complex geometrical problems. These consist of large cylindrical rotating structures that contain the beam bending magnets: they weigh 100 tonnes for protons and 200 tonnes for ions and require movement with 1 mm precision of beam placement. Future engineering innovations may reduce the tonnage and costs. Robotic treatment couches are desirable in order to rapidly position the patient at predetermined angles relative to the beams; they may also transport patients in fixed positions from image guided or other localization devices in the treatment rooms to the actual treatment location. Radiographers may feel sensitive about robotics, but it will always be the radiographer who commands the robot and remotely monitors their performance.

Typical centre

The typical layout of a centre is illustrated in Figure 3. The particles are injected from a small linear accelerator and further accelerated to higher energies around the synchrotron, then extracted and delivered selectively to different rooms; the beam switching time between rooms is

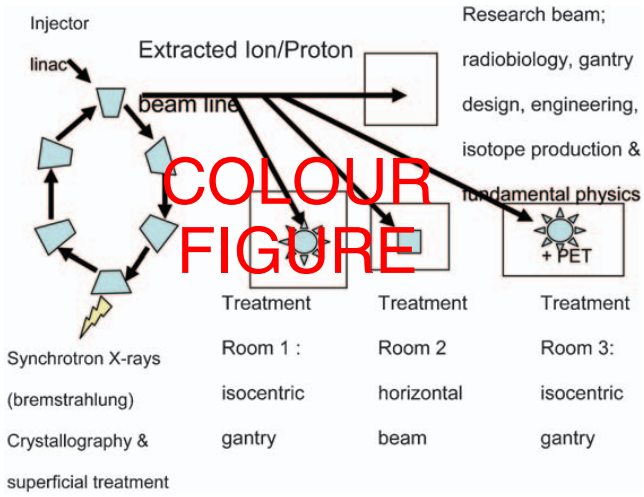

Figure 3. A schematic diagram of a synchrotron treatment centre.

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as short as 10–20 s. A high throughput of patients can be achieved by efficient placement and preparation of patient position in advance of the beam availability in each room. Larger synchrotrons can deliver carbon ions or protons. Some rooms may be equipped with positron emission tomography (PET) scanning facilities and other image guided devices. The overall arrangement is quite different from standard radiotherapy departments where there is a linear accelerator in each treatment room. For more detailed plans see various chapters in Supplement 2 of *Radiotherapy & Oncology* (volume 73), 2004 [10].

The dose distribution advantages

Many authors have made important contributions by means of comparative dose distributions using X-rays and protons, which are summarized elsewhere [6, 7]. The essential principles may be better realised by inspection of relatively simple depth dose diagrams as seen in Figure 4. In Figure 4A, the spread out Bragg peak (SOBP) is seen from a single beam entering from the left hand side. In contrast, the X-ray fall off of dose is pseudo-exponential as shown in Figure 4D. When two opposed fields are used there is uniform dosage in the case of X-rays (as in Figure 4E), whereas for particles there is a preferential dose deposition where the SOBPs coincide, as in Figure 4B. For three intersecting beams, there is now some degree of selectivity for X-rays as seen in Figure 4F, but the ratios of dose in the centre to that near the surface is considerably better for the particles as shown in Figure 4C.

Inspection of axial views of three intersecting beams, as in Figure 5, shows the different dose distributions achievable. These figures can be normalized to give the same dose in the central region, with resulting lower peripheral doses for particles. The absence of dose in one direction beyond the target is striking – this arrangement may be used to reduce exposure to critical structures such as rectum, spinal cord, etc. Rotation of the beams may also be used to avoid beam traversion through, or scattered

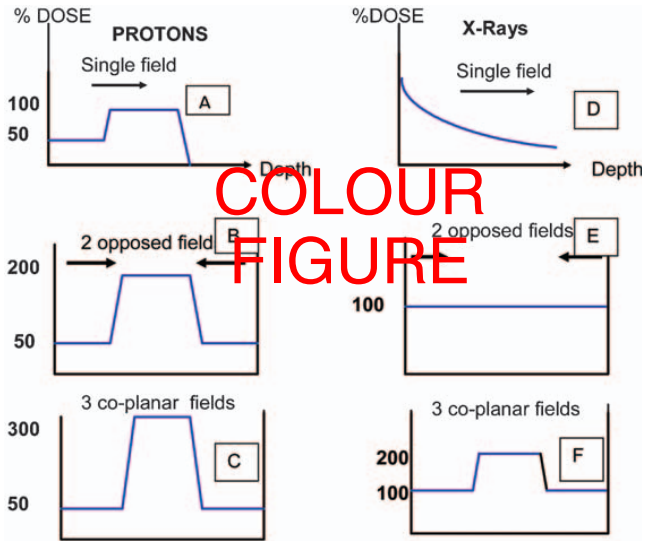

Figure 4. (A–C) Schematic diagrams of protons and (D–F) X-ray percentage depth dose distributions for three simple field arrangements. [1]

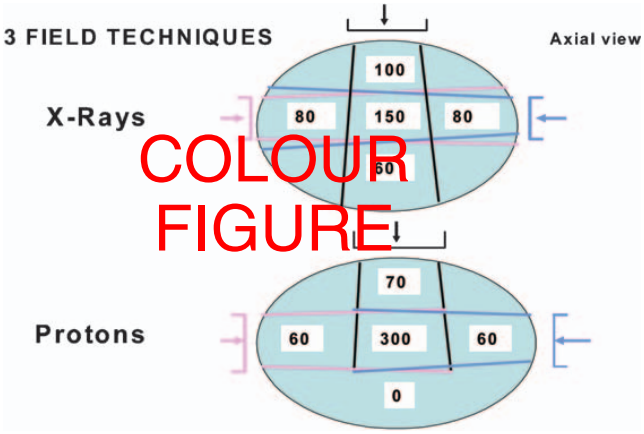

Figure 5. (a,b). Axial views of simplified schematic dose distributions for three field coplanar techniques using X-rays and protons.

radiation from metal prostheses, which cause dose uncertainties in treatment planning.

The reduction in the so called integral dose, which is an assessment of dose to wider volumes within a patient, is considerable – proton beams generally reduce this by 50% and frequently by more in some cases [7]. This effect alone should reduce the risk of second cancer formation [8], which may be enhanced with the use of some modern linear accelerator based techniques such as intensity-modulated radiotherapy (IMRT), where there is a "dose bath" effect due to increased integral dose. Not only is the risk of second cancers reduced, but also substantial reductions occur in dose commitment to organs that are sensitive to radiation, *e.g.* kidneys, eyes, lung, heart, and parts of the nervous system. Low doses to substantial proportions of these organs can cause functional problems. For example, consider the treatment plans shown in Figure 6, where multiple field IMRT is compared with single field spot scanning protons. Whilst the target volume is covered equally well with both techniques, the dose bath effect is readily seen for IMRT, with significant dose to spinal cord and kidneys; the proton plan effectively spares these critical organs. Even a tissue such as bone is highly relevant: bone marrow cell production is not supported at doses above 30 Gy and longer term effects include osteoporosis, micro-fractures and fractures; in practice, low backache is not infrequent following pelvic radiotherapy, and bone density changes, revealed by MRI, are seen to exactly correspond to the beam portals used.

For a wide variety of cancers the advantages of the improved dose distributions should provide substantial improvements in the quality of life where normal tissue doses are reduced and improved cure potential when tumour dose is increased. These are considered in further detail in Table 1, although the generic reduction of second malignancy is not included.

Meticulous studies in Japan, using carbon ions, with respiratory movement gating compensation, have shown two extremely important results. They are:

(1) Cure of small peripheral screen detected lung cancers in a single exposure and without loss of lung function; similar cure rates can be achieved by surgery, but with inevitable loss of lung function [9].

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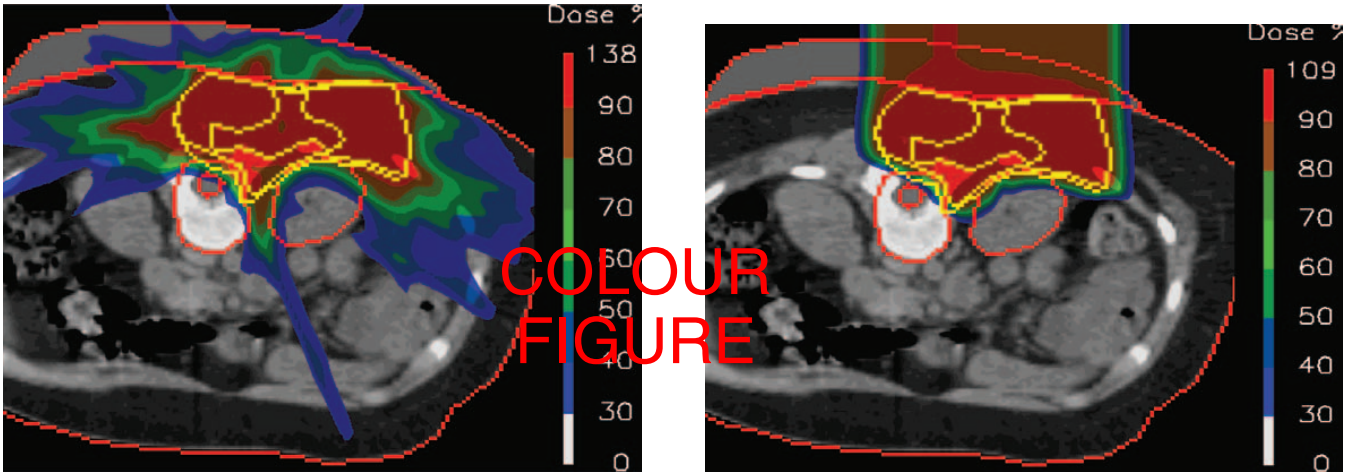

(a) (b)

Figure 6. (a, b) Comparative dose distributions for IMRT and protons for a recurrent sarcoma in a young 12 yearold boy (reproduced by kind permission of Dr A Lomax, PSI, Switzerland and Prof. P Hoskins, Editor of Clinical Oncology).

Table 1. The advantages of charged particle therapy (CPT) in a range of anatomical situations

Cancer bearing region	Advantage of CPT
Breast	Avoid irradiation of heart, lung and brachial plexus
Head and neck	Reduced dose to spinal cord, salivary glands, eyes, bone and brain
Pelvis (*e.g.* prostate, bladder, rectum)	Reduced irradiation of bone, sparing of organs such as bladder, rectum; large sarcomas are safely treated without sacral plexus damage
Gynaecological system	As in pelvis, but also improved dose to lateral parametrium, better distribution for vulvar cancers; can be used where brachytherapy not feasible; field extension to para-aortic region with less toxicity
Limbs	Reduced lymphoedema and deformities
Lung	Better preservation of lung and heart function
Liver/pancreas	Marked reduction in acute effects, can safely dose escalate for radio-resistant cancers, *e.g.* hepatoma, cholangiocarcinoma
Paraspinal/para-aortic	Sparing of small bowel, spine and kidneys
CNS	Reduction of irradiation to sensitive structures such as hypothalamus, pituitary, reduced risk of stroke
	Reduction of collateral irradiation to tissues outside the CNS, *e.g.* all tissues anterior to spine and reduced irradiation of appendages *e.g.* external auditory apparatus and eye, etc.

(2) Cure of patients with primary liver cancers treated in four exposures; again similar rates of cure can be achieved following surgery but with considerable morbidity and some mortality [10].

These results suggest that radiotherapy might eventually replace radical surgery in deeply situated anatomical locations. The risks and costs of radical surgery are likely to increase with time in an ageing population. In addition, these results confirm previous theoretical predictions based on radiobiological modelling that as dose is better localized to the target and markedly reduced in a wider range of surrounding tissues, the principles of fractionation become less important [11]. Thus treatment can be delivered in far fewer exposures; the economics of CPT then become more favourable. In addition, the treatment is more elegant, involves fewer beams and is potentially less liable to errors made in treatment delivery.

Owing to space constraints it is only possible to show a limited number of treatment plans. Figure 7 shows the advantages of a four field proton plan which could be used to treat a hepatoma or cholangiocarcinoma. The colour wash dose distribution shows how restricted the dose is to target; this spares the patient of acute side effects of nausea, vomiting and severe malaise which occur with X-ray traversion of the stomach, duodenum and liver.

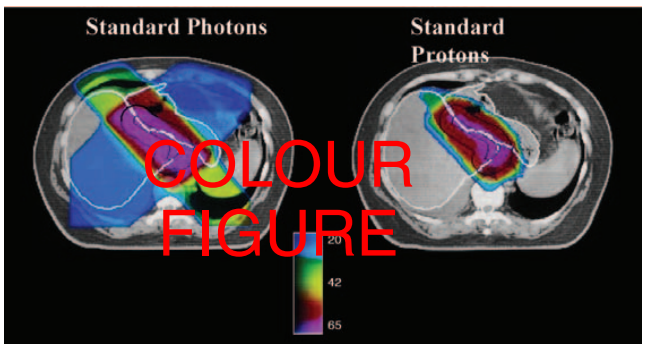

Figure 7. Comparisons of dose distributions for a 4 field X-ray (photon) plan and a proton plan for treatment of hepatocellular cancer (courtesy of Dr J Munzenrider, Northwest Proton Therapy Centre, Boston, USA).

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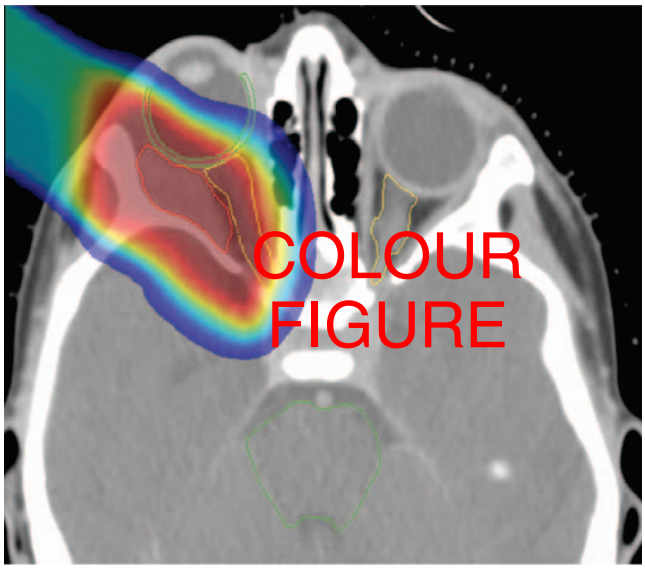

Figure 8. An example of a single field application of protons to treat a posterior orbital cancer (courtesy of Dr J Munzenrider, Northwest Proton Therapy Centre, Boston, USA). The colours denote different dose levels with red being the full prescribed dose, with fall off to the limits of the beam.

The next example (Figure 8) shows how the brain and other bony structures in the head and neck can be spared due to the sheer elegance of a single field proton approach to treat cancers in the posterior orbit, such as lachrymal gland cancer or rhabdomyosarcoma. To obtain equivalent uniformity of dose across the target region, at least 2 or 3 X-ray fields would be required, with resultant exit doses into the brain.

The existing evidence base

The clinical evidence base consists of phase I/II dose escalation studies. There are no randomized control trials that compare CPT with conventional radiotherapies [6], although there are randomized phase II "dose searching" studies. One example is the randomization between 72 Gy and 78 Gy cobalt Gray equivalent (CGE) for skull base chordomas at Massachussets General. Some international authorities consider that randomized studies that compare conventional X-ray therapy with protons are not justified because of the advantageous dose distributions for the latter [12]. Whereas this may be true for skull base tumours and in hepatic cancers, there must be greater justification elsewhere, *e.g.* the comparison of IMRT/implants with protons in prostate cancer. Whether phase III studies (comparisons with conventional radiotherapy) will be performed remains to be seen: some authorities consider that such research would be unethical [12]. It is inevitable that randomized comparisons of CPT against radical surgery will have to be done for small screen detected cancers in deeply situated tissues (see below).

Misconceptions

It is not surprising that misconceptions abound when referring to CPT. Comparisons are often made with neutrons due to their production from similar sophisticated equipment. It must be remembered that neutrons are neutral particles and consequently do not have Bragg peak characteristics: the additional toxicity seen with neutron therapy was due to the higher relative biological effect (RBE) and high integral doses.

Precision is another issue: are protons and ions too precise? Certainly, the dose can be painted onto any safe volume, so that tumour margins can be fully respected. There is no reason why, in certain tumours, one cannot do wide initial volumes, shrinking down to smaller targets with increasing dose; protons could be used with three definite dose volume regions, *e.g.* 55 Gy, 65 Gy and 75 Gy volumes defined around a target simultaneously.

Many Oncologists assume that the advantages are only seen in tumours such as skull base chordomas. It must be realised that such tumours were treated because of poor results with conventional therapy and with limited proton beam time coupled with relatively low energy beams that precluded treatment of deeper structures. Greater beam availability has allowed testing of CPT in a wider variety of tumours in different locations.

Added value for science research and teaching

A clinical facility could also be used for radionuclide production: the particles can activate stable elements to become radioactive, with applications in healthcare and industry. Overnight production allows income generating use of short-lived radionuclide on the following day.

Synchrotron radiation, essentially mono-energetic bremstrahlung emitted when the particles are deviated by magnets, can be used for X-ray crystallography studies. Particle micro-beam analysis of solid state and biological material can also be pursued, *e.g.* intracellular diagnostic capacity at nanometre levels, testing of materials for their resistance to cosmic rays prior to space flights. A detailed case is presently being written by the Engineering and Physical Sciences Research Council (EPSRC) Medical Applications of Ion Beams Network.

Contributions from molecular biology

The vast expansion in knowledge gained by research in molecular biology applied to oncology will inevitably result in more reliable early diagnosis of cancer. Screening of a population by "PCR (polymerase chain reaction) amplification" techniques and proteomic techniques should detect aberrant DNA and protein products from quite small cancers in body fluids. Further gene specific or target protein imaging using sophisticated forms of PET scanning may be sufficient to confirm the presence of small cancers in deeply situated organs. Image guided biopsies may also be necessary in some cases. These approaches are probably more practical than the more distant Holy Grail of cancer cure following the application of such approaches. This is not to say that such approaches will not be useful, particularly in modifying cancer growth patterns and metastatic potential; but when used alone, molecular approaches may be doomed to failure because of the capacity of a cancer to produce further mutations and to bypass metabolic blockade even when multiple approaches are used. However, the reliable earlier diagnosis of cancer would create a high demand for

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surgery and radiotherapy, particularly highly focal forms of radiotherapy that enable a high localized dose to be delivered with good sparing of normal tissues, as in CPT. The decisive clinical trials of the future may be those that compare CPT with surgery, particularly in sites where the latter has a high morbidity, mortality and cost, *e.g.* hepatic, pancreatic and renal surgery.

Contributions from medical oncology

The reduction of exit dose radiation to skeletal regions that contain active bone marrow will reduce the risk of severe neutropenia and the morbidity and mortality that follow septicaemia. Thus CPT radiotherapy may be combined with more aggressive chemotherapy regimens. In addition, the risk of subsequent organ failure on exposure to certain classes of radiotherapy may be reduced. For example, the cochlear sparing associated with medulloblastoma proton-therapy is likely to reduce the high tone deafness associated with the use of Cis-platinum treatment [13]; the risk of renal failure may be reduced when using protons instead of IMRT to treat the para-aortic nodes in metastatic or advanced local cervix cancers. Also, the risk of severe cardiomyopathy may be reduced – even in the case of later exposure to anthracycline drugs – if the heart has not been exposed to significant radiation dose by use of CPT, *e.g.* in the case of left sided breast cancer. There is clearly a wide prospectus for research with a major input from Medical Oncologists with an interest in radiotherapy in this important area of Oncology.

Contributions from surgery

The increasing future role of radiotherapy in small volume deep-seated cancers has already been mentioned. For larger cancers, volume reduction using surgery may still be desirable, as might the concept of ''improving treatment geometry'' by selective resection and restoring a finite space between tumour and critical normal tissues. Prolonged surgery will always reduce tissue tolerance owing to accumulated vascular damage. Decisions regarding operability, the extent of surgery and the necessary dose of radiation will always need careful consideration according to circumstances. The possibility of pre-operative CPT in some situations would be useful: in Massachusetts General Hospital there is already some experience of pre-operative proton therapy to paraspinal bone tumours in order to reduce the potential for brachytherapy catheter implantation of tumour cells when radio-iodine seed implants are made into the adjacent bone situated distally to the tumour. There is clearly considerable scope for research in the degree to which surgery and CPT can be combined.

Research and development: quality adjusted survival end points

There is increasing disquiet that very large trials are required to detect small incremental changes in outcomes, with a tendency to favour patient survival as the primary end point, possibly with inclusion of some separate quality of life study. This stance is not unreasonable for comparisons of chemotherapy schedules, where severe acute toxicity is life threatening and influences survival. Such approaches are far from ideal for the assessment of new radiation techniques where subtle long-term differences in a wide spectrum of tissues are more relevant. Newer forms of trial assessment will probably be necessary. One such approach is considered here. In a computer generated survival curve with only 100 patients in each treatment arm, with a survival advantage of $\sim$10% for CPT *c.f.* X-rays, the p-value exceeds 0.05 using the log-rank test ($p>0.05$). The side effect profiles (graded in four categories according to ascending severity) show subtle improvements with CPT, although when tested using a contingency table the Chi-squared statistic shows a non significant trend ($p>0.05$) because of the low numbers in each category. But when survival is adjusted by using the toxicity grade factor F defined as $(5\text{-}x)/5$, where x is the toxicity grade, the quality adjusted survival (F times the actual survival) becomes highly significant ($p<0.0001$). More work is required to justify and encourage these approaches, but the potential advantages in terms of cost and rapidity of obtaining results with a greater number of trial arms containing different doses/treatment combinations are readily apparent from the example given. Such a novel approach could be used within CPT studies.

The threat to British oncology

If the UK will not invest sufficiently rapidly in CPT facilities, there is a real risk of there being between 5000 and 12 000 patients who will require or demand therapy abroad in around 10 years from now [14]. These estimates were arrived at using the logistic equation to simulate supply and demand with best and worst case scenarios for overall capacity to accept UK referrals abroad. Treatment abroad would undoubtedly cause severe disruption of multidisciplinary cancer care as well as anticipated social and linguistic problems. In terms of staff retention, there is a risk that many British physicists, radiographers and oncologists might be attracted to work abroad. Also, the UK clinical trial portfolio may not contain state of the art radiotherapy and consequently our trials may become irrelevant and ignored elsewhere in the world.

Costs

It has become politically incorrect to mention costs in medical circles, although cost effectiveness is deemed respectable and quotable. Such restrictive criteria are, for example, accepted by *The British Medical Journal* for its publications. One cannot escape the fact that the costs for synchrotron commissioning are large, of the order of £70–100 million depending upon the specifications for protons and the more expensive ions and how many large gantries are required. Some consideration has already been given to cost benefit and patient demand in Switzerland, Sweden, France and Austria [15–18]. Cost benefit will be most accurately measured prospectively within clinical trials. The costs charged will vary with the number of exposures: presently around £12 000 for 4 exposures at Clatterbridge; but with some economies of scale and improved throughput one can envisage CPT therapy for around £8000–25 000 per year, depending on the

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fractionation used; this is less than the cost of renal dialysis necessary to keep a patient alive for 1 year and compares favourably with the cost of prolonged radical surgery.

A single UK centre should recoup its own initial and running costs within 6 years providing it can treat 2500 patients by its third year of operation. However, the UK would depend on a multitude of healthcare purchasing agreements – a most unsatisfactory system for the provision of complex healthcare. Definitive cancer treatment using radiation should be separated from these cumbersome procedures, with a clear assurance that all British patients with a diagnosis of cancer will receive equal access to more complex therapy where necessary.

Dr Neil Burnet has estimated from Swedish data (Burnet N, personal communication) that the proportion of total cancer care costs spent on radiotherapy would increase from the present 5% to be 6% if 15% of all radiotherapy is given by protons [18]. This is likely to be cost effective in the long term because of the reduced side effects and compares well with the present expenditure on cytotoxic chemotherapy, which accounts for around 12% of total cancer care.

It remains unclear as to how funding can be achieved without a high level political decision. Even the new Foundation NHS Trusts cannot borrow the necessary monies to enable CPT. Our NHS needs better structures that can arrange finance, whether public or private: perhaps a return to regional and supraregional systems for cancer care?

Logistics for a National Centre

The NHS has developed impressive Cancer Networks as part of its Cancer Plan, and CPT will need to be imaginatively superimposed on this framework. These existing networks are essential to ensure equity of access for CPT. Each local Network should form the basis of referral to special multidisciplinary team (MDT) meetings concerned with CPT. When a clinical indication is identified, then appropriate dose planning assessments are necessary: this might be achieved by electronic transfer of data to a national reference centre which itself might be virtual, *i.e.* it can be envisaged that all cases of tumour type X might be independently assessed in City A, and for tumour type Y in City B as for the physical appropriateness of IMRT or CPT. The referring city could also plan with the two modalities and confer with the national CPT centre. Encouragement for physicists and oncologists to attend a National Centre on a rotational or frequent basis, *e.g.* for specific MDT and treatment planning meetings, should also be encouraged. A national service will need to have strong links with other centres abroad for the treatment of rare conditions.

Logistics for referral abroad

The prospect of referring hundreds or thousands of patients abroad is daunting. The time taken to asses and counsel, and to send all diagnostic information away is significant. There is an immediate need for full time staff devoted to these logistics, with attention to transfer funding for provision of appropriate care abroad. British staff should be put in place to support patients and families whilst abroad and also to promote training in how to deliver CPT. Eventually, the number of treatment facilities in the UK should become appropriate to meet the needs of the British people. However, UK healthcare planners should urgently apply themselves to these problems and produce appropriate plans that meet the most likely short and long-term requirements.

Politics/Government/Research Councils and Charities

CPT needs to be fully researched, with major UK participation. At least one high-energy UK CPT facility should be established to conduct clinical research and trials, with equitable patient referral via the Cancer Networks. The immediate questions for the UK authorities are ''when'' and ''how many facilities'' do we need? These important decisions confront the UK Government for future cancer care, and must be judged in the context of the proposed increase investment in the scientific base of this country [19]. The concept of joined up working across the various Research Councils (EPSRC, MRC, Accelerator Science, N-Tech), and linked to the major cancer charities (Cancer Research UK) should allow the UK to further develop the technology that underpins the most sophisticated form of radiation therapy against cancer. It would be tragic to wait until public awareness forces the issue. Bevan, an astute politician and cancer sufferer, would surely have sensed that the NHS should possess the weapon of particle radiotherapy within its arsenal against cancer, in the same way as he bravely supported an independent nuclear deterrent. He wanted only the best for the British people and so should we.

Acknowledgments

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Short communiction

Calculation of high-LET radiotherapy dose required for compensation of overall treatment time extensions

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Abstract. A method is presented that allows biological effective dose (BED) equations to be used to calculate compensatory doses for treatment time extensions when high-LET (linear energy transfer) radiotherapy schedules are used. The principles involved are the same as those for low-LET radiations, but incorporate two relative biological effectiveness (RBE) factors, RBE_{MAX} and RBE_{MIN}, which represent the RBE at very low and very high fraction doses, respectively, with the actual RBE changing between these extremes. The method has the advantage that low-LET α/β ratios and low-LET daily dose-equivalent repopulation factors are used in the calculations. The daily dose repopulation equivalents and increments in dose per fraction in the case of high LET radiotherapy are smaller than those for low LET.

The loss of tumour control following an extension in treatment duration can, in principle, be overcome by increasing the total dose after the extension. This can be achieved – as well as our assumptions allow – by calculating the dose per day (d_c) that should compensate for the additional tumour cell repopulation. The magnitude of d_c can be estimated from a logical extension of the linear-quadratic (LQ) model of radiation effect through consideration of the biologically effective dose (BED) concept [1–4]. Dale et al [5] have stressed that the compensatory dose per day is normally expressed in BED Gy units, which are those that pertain for a specific tumour α/β ratio and from this the actual physical dose (d_c) can be separately calculated. There are some additional subtleties in the case of high-LET radiotherapy because additional RBE (relative biological effectiveness) correction factors need to be included. The general mathematical approach is that originally followed by Bewley [6] for high LET radiations, but is now adapted to the LQ model and the BED concept in particular, such that the use of the Cobalt equivalent Gy concept is avoided.

Methods

RBE is conventionally defined as the ratio of the dose per fraction of the low LET radiation to the dose per fraction of the high LET radiation, so that it is usually greater than 1, as in:

$$\mathrm{RBE} = \frac{d_L}{d_H} \tag{1}$$

As shown in Appendix A, RBE is maximized at low dose to a value given as RBE_{max}, where:

$$RBE_{Max} = \frac{\alpha_H}{\alpha_L} \tag{2}$$

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Similarly, from Appendix A, at very high dose RBE approaches an asymptotic minimum value (RBE_{min}), where:

$$RBE_{\min} = \sqrt{\frac{\beta_H}{\beta_L}} \tag{3}$$

Consequently, where RBE_{min} is significantly greater than unity and in contradiction with the conventional assumption first put forward in the Theory of Dual Radiation Action by Kellerer and Rossi [7], it follows that $\beta_H > \beta_L$. Also, the high-LET β parameter can be expressed in terms of the low-LET β value and the RBE_{Min}, at high dose per fraction, *i.e.*:

$$\beta_H = (RBE_{Min})^2 \beta_L \tag{4}$$

These Equations (2–4) are used to form BED equations for high LET radiations as shown in Appendix B.

Next we consider how to compensate for a practical problem using the standard BED equations for low LET radiations and also the newly derived equation for the high LET BED (BED_H):

$$BED_H = N_H d_H \left[RBE_{\max} + \frac{RBE_{\min}^2 d_H}{\left(\frac{\alpha_L}{\beta_L}\right)} \right] \tag{5}$$

where N is the number of fractions, d the dose per fraction and (α_L/β_L) is the low LET α/β ratio. The repopulation equivalent equations are also given in Appendix B: essentially, the repopulation terms in the high LET equations are the same as for low LET.

Worked example

A schedule of 45 Gy in 25 fractions using megavoltage X-rays is to be followed by a highly localized ''boost'' of 6 Gy in 2 fractions of 3 Gy each, using a high-LET radiation for which $RBE_{min}=1.3$ and $RBE_{max}=8$; these values are assumed to apply for both cancer and normal

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tissues. There is a delay of 7 days in the provision of the boost, due to patient illness. The tumour type is assumed to have a daily repopulation equivalent of 0.6 Gy per day after a lag interval of 25 days during megavoltage X-ray treatment. The normal tissue BED is assumed to be governed by $\alpha/\beta=2$ Gy and the tumour $\alpha/\beta=10$ Gy.

The intended BED to normal tissue from X-rays$=45\times(1+1.8/2)=85.5$ Gy_2.

The intended BED to any normal tissue that receives the added high-LET boost of 2 fractions of 3 Gy$=6\times(8+1.3^2\times3/2)=63.2$ Gy_2, so that the total intended maximum BED to same volume of normal tissue$=85.5+63.2=148.7$ Gy_2.

The intended BED to tumour by X-rays, $BED_L=45\times(1+1.8/10)=53.1$ Gy_{10}, plus the intended BED to tumour by high LET, $BED_H=6\times(8+1.3^2\ 3/10)=51.04$ Gy_{10}, so that the total tumour BED is 104.14 Gy_{10} before allowing for repopulation.

The additional 7 days of repopulation must be allowed for because of the treatment interruption in providing the boost, which is equivalent to $0.6\times7=4.2$ Gy_{10}.

The boost must therefore accommodate the original high-LET BED plus 4.2 Gy, *i.e.* $51.04+4.2=55.24$ Gy_{10}.

As this is to be given in two fractions, then: $2\times d\times(8+1.3^2d/10)=55.24$, and the solution for d is 3.23 Gy/fraction instead of the originally prescribed 3 Gy per fraction, prescribed before the treatment gap had occurred.

The normal tissue BED will then be: $2\times3.23\times(8+1.3^2\times3.23/2)=69.31$ Gy_2.

Thus the total (low- plus high-LET) normal tissue maximum BED will have increased by $69.31-63.2=6.11$ Gy_2, an increase of 4.1% on an already high BED in the localized boost volume, in order to maintain the same tumour BED. This could cause enhanced tissue side effects.

In practice a compromise solution such as a dose per fraction of 3.15 Gy instead of 3.23 Gy might be used. This would lead to 67.17 Gy_2 maximum high-LET BED to the normal tissues and 53.75 Gy_{10} to the tumour.

A plot of the calculated compensatory dose per day, given as a single fraction, for high-LET radiations is shown in Figure 1. It can be seen that the α/β ratio has little influence on the value of the compensatory dose, with marginal differences only if α/β is very low and when K is large. This result is dominated by the RBE_{max} value, since small fractional doses are operational – *e.g.* for a K value of 1 Gy per day the equivalent high LET dose per day is 0.12 Gy per day which is close to the ratio $1/RBE_{max}=1/8$ $(=1.25)$. It needs to be stressed that these calculated doses, which are single fraction equivalents, must not be used as additional doses added to the prescribed dose per fraction; to be correctly incorporated the method used in the worked example should be followed to adjust the dose per fraction.

Discussion

As in the case of low-LET radiations, extension of treatment time can cause significant dilemmas to the radiation oncologist. Gaps occurring later in the treatment are particularly difficult to compensate for since an extension to the prescribed treatment time becomes unavoidable [4]. Compensations for overall treatment

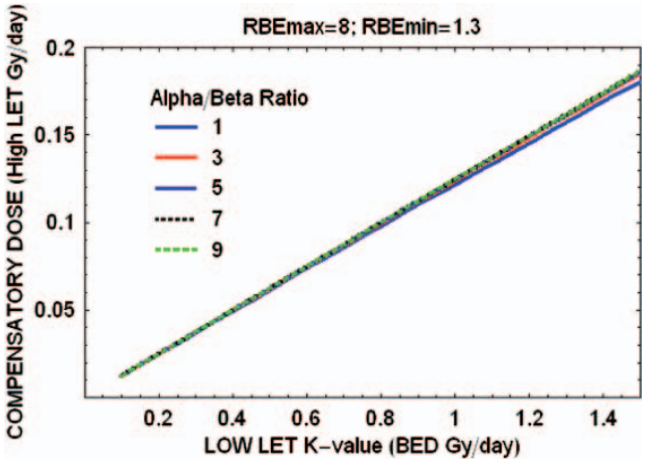

Figure 1. Relationship between low linear energy transfer (LET) K value and the calculated single fraction compensatory dose per day for a high LET radiation with relative biological effectiveness $(RBE)_{Max}=8$ and $RBE_{Min}=1.3$, with variation of the α/β ratio, obtained using Equation (B10) (given in Appendix B).

time extensions typically involve a compromise between delivery of a higher BED to normal tissues and a reduced BED to tumour, or the same BED to tumour and an even higher BED to normal tissues. The incorporation of RBE within BED equations has enabled the calculation of estimated compensatory doses for high LET radiations.

The use of a fixed RBE weighting factors is an alternative approach. Although approved in international definitions, this method will under estimate RBE at low doses per fraction and over estimate RBE at high doses per fraction. In contrast, the use of RBE_{max} and RBE_{min} overrides this potential problem. The RBE_{max} dominates the effective RBE at low dose per fraction, whereas RBE_{min} dominates the RBE at large doses per fraction. We have used these two RBE parameters because of the increasing use of large fraction sizes in high LET radiotherapy [8].

The actual high LET daily dose correction factors are much lower than the K value doses, as are the increments in dose per fraction required when compared with those required in low LET radiotherapy.

These aspects should be additionally considered in situations where protraction of relatively high LET radiotherapy occurs, *e.g.* radioiodine seed implants and in the case of hadrontherapy, for instance using ion beam or neutron radiotherapy schedules. For high-energy proton beams with significant spread out Bragg peaks, the correction factors will be much smaller, since the average RBE for protons is only around 1.1, although the refinement of a variable RBE with dose per fraction might lead to better results [9, 10]. In the case of ions beams, treatments are hypofractionated [8, 11], varying from 1 fraction to 20 fractions with treatment times of up to 1 month, but these times – apart from the single fraction case – could be extended for a variety of reasons such as patient illness, synchrotron breakdown etc.

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authors are members of the EPSRC-funded medical applications of ion beams network. BJ and RGD are Hon. Professors at the University of Caen as part of the ASCLEPIOS project, part of the French National Hadrontherapy Project.

Appendix A

To obtain RBE terms

RBEs are derived by intercomparing the single doses (low- and high-LET) required to obtain a given iso-effect. Since only single doses are involved there is no need to consider the repopulation effect, *i.e.* the iso-effect equation is simply:

$$\alpha_L d_L + \beta_L d_L^2 = \alpha_H d_H + \beta_H d_H^2 \quad \text{(A1)}$$

At near-zero doses the quadratic dose terms become negligible and:

$$\alpha_L d_L = \alpha_H d_H \quad \text{(A2)}$$

Leading to:

$$RBE \rightarrow RBE_{\max} = \frac{d_L}{d_H} = \frac{\alpha_H}{\alpha_L} \quad \text{(A3)}$$

Similarly, at exceedingly high doses, the quadratic terms dominate, *i.e.*:

$$\beta_L d_L^2 = \beta_H d_H^2 \quad \text{(A4)}$$

and:

$$RBE \rightarrow RBE_{\min} = \frac{d_L}{d_H} = \sqrt{\frac{\beta_H}{\beta_L}} \quad \text{(A5)}$$

Appendix B

To obtain high LET BED equations

The standard linear quadratic equation for the low LET surviving fraction (SF) with compensation for cellular repopulation is:

$$SF = e^{-\alpha_L N_L d_L - \beta_L N_L d_L^2 + \frac{0.693(T - T_{DEL})}{T_{EFF}}} \quad \text{(B1)}$$

where α_L and β_L are the low LET radiosensitivity parameters, N_L is the number of low LET fractions of dose d_L, T is the overall treatment time in days, T_{DEL} is the delay time in days before which repopulation becomes significant and is optional according to tumour type and T_{EFF} is the effective cellular doubling time in days.

For high LET radiations the surviving fraction expression is changed to be:

$$SF = e^{-\alpha_H N_H d_L - \beta_H N_H d_H^2 + \frac{0.693(T - T_{DEL})}{T_{EFF}}} \quad \text{(B2)}$$

where the subscripts are changed to H in order to refer to high LET radiations. Next, taking the natural logarithm of each side and multiply by -1 to, respectively, obtain from Equations (B1) and (B2) the log cell kills designated by E_L and E_H:

$$E_L = \alpha_L N_L d_L + \beta_L N_L d_L^2 - \frac{0.693(T_L - T_{DEL})}{T_{EFF}} \quad \text{(B3)}$$

$$E_H = \alpha_H N_H d_H + \beta_H N_H d_H^2 - \frac{0.693(T_L - T_{DEL})}{T_{EFF}} \quad \text{(B4)}$$

Assume that Equations (B3) and (B4) refer to the same biological effect.

To obtain the BED, divide each equation by α_L, the low LET radiosensitivity parameter, then, for Low LET, the BED is:

$$BED = \frac{E_L}{\alpha_L} = N_L d_L \left[1 + \frac{d_L}{\left(\frac{\alpha_L}{\beta_L}\right)}\right] - K(T_L - T_{DEL}) \quad \text{(B5)}$$

and where $K\left(= \frac{0.693}{\alpha_L Teff}\right)$ is the daily dose equivalent for repopulation in units of BED Gy per day.

The High LET BED is also obtained by dividing by the low LET α_L parameter to give

$$BED = \frac{E_H}{\alpha_L} = N_H d_H \left[\frac{\alpha_H}{\alpha_L} + \frac{\beta_H d_H}{\alpha_L}\right] - K(T_L - T_{DEL}) \quad \text{(B6)}$$

Replacement of the high LET radiosensitivity parameters in Equation (B6) with RBE_{max} and RBE_{min} – as given in Equations (2–4) in the main text – results in:

$$BED_H = N_H d_H \left[RBE_{\max} + \frac{RBE_{\min}^2 d_H}{\frac{\alpha_L}{\beta_L}}\right] - K(T_H - T_{DEL}) \quad \text{(B7)}$$

For calculations involving overall treatment time variations and compensation of unintended treatment interruptions, the same low- LET daily BED dose equivalent values (K) are used in both cases.

The first component of the right hand side of Equation (B7) represents the BED which must be delivered to offset the effect of T_H days-worth of repopulation, as quantified by the second (subtractive) factor. Equating these two components we obtain:

$$N_H d_H \left[RBE_{\max} + \frac{RBE_{\min}^2 d_H}{\left(\frac{\alpha_L}{\beta_L}\right)}\right] = K(T_H - T_{DEL}) \quad \text{(B8)}$$

Once the time-point (T_{DEL}) is passed, the BED-equivalent of repopulation for each additional day (for which $T_H - T_{DEL} = 1$) is found by setting $N_H = 1$ in Equation (B8). On rearrangement, this leads to:

$$K = d_H \left[RBE_{\max} + \frac{RBE_{\min}^2 d_H}{\left(\frac{\alpha_L}{\beta_L}\right)}\right] \quad \text{(B9)}$$

In Equation (B9) the repopulation term K is expressed as an equivalent BED dose per day. The actual (physical) dose per day (d_c) – given as a single fraction – required to compensate for repopulation is the solution for d_H in Equation (B9), *i.e.*:

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$$d_c = \frac{-RBE_{\max} + \sqrt{RBE_{\max}^2 + \frac{4KRBE_{\min}^2}{\left(\frac{\alpha}{\beta}\right)_L}}}{2\frac{RBE_{\min}^2}{\left(\frac{\alpha}{\beta}\right)_L}} \qquad \text{(B10)}$$

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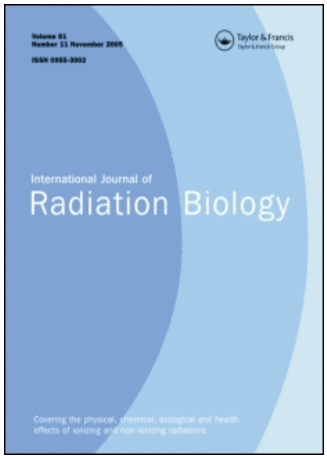

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The incorporation of the concept of minimum RBE (RBE_{min}) into the linear-quadratic model and the potential for improved radiobiological analysis of high-LET treatments

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The incorporation of the concept of minimum RBE (RBE_{min}) into the linear-quadratic model and the potential for improved radiobiological analysis of high-LET treatments

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Abstract

Purpose: The formulation of relative biological effectiveness (RBE) for high linear energy transfer (high-LET) radiation treatments is revisited. The effects of changed production of sub-lethal damage with varying LET is now considered via the RBE_{min} concept, where RBE_{min} represents the lower limit to which RBE tends at high doses per fraction.

Materials and methods: An existing linear-quadratic formulation for calculating RBE variations with fractional dose for high-LET radiations is modified to incorporate the twin concepts of RBE_{max} (which represents the value of RBE at an effective dose-per-fraction of 0 Gy) and RBE_{min}.

Results: Fits of the model to data showed RBE_{min} values in the range of 0.1 – 2.27. In all cases the raw data was a better statistical fit to the model which included RBE_{min}, although this was only very highly significant in one case. In the case of the mouse oesophagus it is shown that, if change in the β-radiosensitivity coefficient with LET is considered as trivial, an underestimation $>5\%$ in RBE can be expected at X-ray doses of 2 Gy/fraction if RBE_{min} is not considered. To ensure that the results were not biased by the statistical method used to obtain the parameter values relevant to this analysis (i.e., using fraction-size effect or Fe-plots), an alternative method was used which provided very similar correlation with the data.

Conclusions: If the production of sublethal damage is considered independent of LET, there will be a risk that non-corrected evaluation of RBE will lead to an over- or under-estimate of RBE at low doses per fractions (the clinically relevant region).

Keywords: *High-LET radiotherapy, RBE, isoeffective fractionation schedules, acute and late reacting tissue, neutrons*

Introduction

The theory of dual radiation action (TDRA) (Kellerer & Rossi 1972) predicts that high linear energy transfer (high-LET) radiation increases the linear (α) component of radiation damage, while the quadratic (β) component remains unchanged. As a consequence it is to be expected that, as fractional dose size decreases, the relative biological effectiveness (RBE) tends asymptotically to an intrinsic maximum value and which is the ratio of the initial slopes at zero dose of the associated cell-survival curves relating to the high-LET radiation in question and the reference (low-LET) radiation (Dale & Jones 1999). Similarly, the TDRA prediction of β being independent of radiation quality will mean that RBE tends to unity at very high doses. However, this latter point has been found not to be the case for a number of systems and radiation qualities.

The analysis of experimental data (especially that relating to ultrasoft X-rays) using the TDRA model has shown that the assumption that β is constant can lead to very unsatisfactory prediction of biological effectiveness (Goodhead 1977). The conclusion is that the initial hypothesis of the TDRA is not valid and also that β should change as a function of LET, i.e., $\beta_H \neq \beta_L$. Alternative mechanistic models have been proposed which allow for the variability of β on the basis of a LET-dependant saturable sub-lethal damage repair process.

This article presents an extension of an earlier radiobiological model developed by this group (Dale & Jones 1999) and introduces a new concept

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($RBE_{\min}$) within the linear-quadratic (LQ) model, which is defined as:

$$RBE_{\min} = \sqrt{\frac{\beta_H}{\beta_L}} \tag{1}$$

An experimental method is also proposed to search for the existence of the $RBE_{\min}$ parameter which, together with $RBE_{\max}$, should provide a better description of the overall shape of the curve of RBE versus dose.

Methods and materials

RBE and fractionated irradiation

Under the LQ formulation, a given high-LET fraction dose (d_H) will produce the same effect as a given low-LET dose (d_L) only if:

$$\alpha_L d_L + \beta_L d_L^2 = \alpha_H d_H + \beta_H d_H^2 \tag{2}$$

But, taking into account that $\alpha_H = \alpha_L RBE_{\max}$ and $\beta_H = \beta_L RBE_{\min}^2$ (the latter being the new assumption), and dividing both sides of the resultant equation by β_L, we arrive at:

$$(\alpha/\beta)_L d_L + d_L^2 = (\alpha/\beta)_L RBE_{\max}\, d_H + RBE_{\min}^2\, d_H^2 \tag{3}$$

Dividing both sides of Equation 3 by d_H, and noting that $d_H = (d_L/RBE)$, Equation 3 can be re-written purely in terms of low-LET parameters, as follows:

$$(\alpha/\beta)_L RBE + RBE d_L = (\alpha/\beta)_L RBE_{\max} + RBE_{\min}^2 \frac{d_L}{RBE} \tag{4}$$

Solving Equation 4 for positive values of RBE:

$$RBE = \frac{(\alpha/\beta)_L RBE_{\max} + \sqrt{(\alpha/\beta)_L^2 RBE_{\max}^2 + 4 d_L RBE_{\min}^2 ((\alpha/\beta)_L + d_L)}}{2((\alpha/\beta)_L + d_L)} \tag{5}$$

Equation 5 describes RBE as a function of changing low-LET dose per fraction and is similar in form to an earlier equation (Dale & Jones 1999) but which did not allow for non-constancy of β with changing LET and therefore did not include the $RBE_{\min}$ factor in the final term, i.e.,

$$RBE = \frac{(\alpha/\beta)_L RBE_{\max} + \sqrt{(\alpha/\beta)_L^2 RBE_{\max}^2 + 4 d_L ((\alpha/\beta)_L + d_L)}}{2((\alpha/\beta)_L + d_L)} \tag{6}$$

This previous version was conceived as being adequate for low doses per fraction (or high surviving fraction) since β mediated damage is then relatively small compared with α mediated damage. One relevant point of Equation 5 is that RBE is entirely determined by low-LET parameters, $(\alpha/\beta)_L$ and d_L which, for a range of tissues, are more extensively tabulated. In Equation 5, as $d_L \to 0$ Gy, $RBE \to RBE_{\max}$, which is also the case for the earlier formulation. However, as $d_L \to \infty$Gy, $RBE \to RBE_{\min}$, rather that unity.

Modification of BED equations to allow for RBE effects and calculation of relevant parameters

$RBE_{\max}$ and $RBE_{\min}$ are respectively the ratios of α and $\sqrt{\beta}$ as normally measured directly from survival curves. The measurement of these parameters is relatively easier in *in-vitro* experiments but, even then, the determination of both parameters from simple regression analysis applied to survival data is error prone. The only parameters used when specifying a patient treatment are the total dose and the dose per fraction, generally chosen to achieve the highest tumour control probability (TCP) while keeping the normal tissue complication probability (NTCP) as low as possible. Generic values of (α/β) ratios for each individual tissue included in the treatment field can usually be assumed. The question then would be if there is any way of obtaining $RBE_{\max}$ and $RBE_{\min}$ values from the parameters commonly used clinically, i.e., number of fractions (n), total dose (TD) and (α/β) ratios for the irradiated tissues.

These three parameters are related together by the Biologically Effective Dose (BED) concept. BED is defined as the theoretical total physical dose required for a given biological effect with a fractionated regime consisting of an infinite number of fractions of infinitesimally small doses and in the absence of repopulation. For low-LET radiations, the BED is formulated as (Joiner & Bentzen 2002):

$$BED_L = \frac{E_L}{\alpha_L} = n_L d_L \left(1 + \frac{d_L}{(\alpha/\beta)_L}\right) \tag{7}$$

For high-LET radiations the "$1+\cdots$" term is simply changed to "$RBE_{\max}+\cdots$" (Dale & Jones 1999), i.e.,

$$BED_H = n_H d_H \left(RBE_{\max} + \frac{d_H}{(\alpha/\beta)_L}\right) \tag{8}$$

Equations 7 and 8 may be derived from the respective equations which define "effect" (E) in a fractionated treatment. Taking that same methodology a

stage further and incorporating Equation 1 leads to the following sequence:

$$\begin{aligned} & n_L\left(\alpha_L d_L + \beta_L d_L^2\right) = n_H\left(\alpha_H d_H + \beta_H d_H^2\right) \\ & \Rightarrow n_L d_L\left(1 + \frac{d_L}{(\alpha/\beta)_L}\right) = \\ & \quad = n_H\left(RBE_{\max} d_H + \left(\frac{\beta_H}{\alpha_L}\right) d_H^2\right) \\ & \quad = n_H\left(RBE_{\max} d_H + \left(\frac{\beta_L RBE_{\min}^2}{\alpha_L}\right) d_H^2\right) \\ & \quad = n_H\left(RBE_{\max} d_H + RBE_{\min}^2 \frac{d_H^2}{(\alpha/\beta)_L}\right) \end{aligned} \quad (9)$$

This identity indicates that the BED for high-LET radiations [earlier written as Equation 8] should be more comprehensively defined as:

$$BED_H = n_H d_H\left(RBE_{\max} + RBE_{\min}^2 \frac{d_H}{(\alpha/\beta)_L}\right) \quad (10)$$

Equation 10 provides a tool with which to compare treatments carried out using radiations of different quality. The fact that Equation 10 has been formulated in terms of $(\alpha/\beta)_L$ is convenient as this means the low- and high-LET BEDs are each being expressed in the same biological dose units and may therefore be directly compared, one with another.

Isoeffective low- and high-LET treatments must therefore comply by definition with the condition,

$$BED_L = BED_H \quad (11)$$

Equations 7 and 10 as applied to fractionation schedules corresponding to isoeffective low- and high-LET treatments can be respectively rewritten as,

$$\begin{aligned} BED_L = n_L d_L\left(1 + \frac{d_L}{(\alpha/\beta)_L}\right) \Rightarrow \\ \frac{1}{D_L} = \frac{1}{BED} + \frac{1}{(\alpha/\beta)_L BED} d_L \end{aligned} \quad (12)$$

$$\begin{aligned} BED_H = n_H d_H\left(RBE_{\max} + \frac{RBE_{\min}^2 d_H}{(\alpha/\beta)_L}\right) \Rightarrow \\ \frac{1}{D_H} = \frac{RBE_{\max}}{BED} + \frac{RBE_{\min}^2}{(\alpha/\beta)_L BED} d_H \end{aligned} \quad (13)$$

where the notation has been simplified to $BED = BED_L = BED_H$.

Equation 12 is the formulation proposed by Fowler (1989) for use in deriving the (α/β) ratios of tissues treated with isoeffective low-LET fractionated regimes, via the so-called fraction-size effect or 'Fe-plots', which are plots of Y = reciprocal total dose against X = dose-per-fraction. Reciprocal total dose is the same as reciprocal BED only when dose-per-fraction tends to zero, as defined by Barendsen (1982a) for Extrapolated Total Dose (ETD) before it was renamed BED by Fowler (1989). From the intersection of the low-LET Fe-plot on the vertical axis we obtain the reciprocal of the BED associated with the given end point. Knowing the slope of the line, the BED is then used to derive the (α/β) ratio of the tissue. Using Equation 13 the corresponding Fe-plot is derived from the high-LET doses required to achieve the same biological end point. The intersection value and the slope, used in conjunction with the values for BED and (α/β) derived from the low-LET data, allow $RBE_{\max}$ and $RBE_{\min}$ to be derived. Comparing Equations 12 and 13 it is clear that the high-LET slope differs from that for low-LET by a factor of $RBE_{\min}^2$. Thus, Fe-plots showing little or no change in slope indicate that $RBE_{\min} \sim 1$, whereas high-LET slopes which are greater or less than the low-LET slopes respectively indicate $RBE_{\min} > 1$ or < 1.

Testing of the model against measured data

Mice LD_{50} after oesophagus injury

To illustrate the operation of the above method to calculate $RBE_{\max}$ and $RBE_{\min}$, it will first be used to derive the RBE for the mouse oesophageal endpoint of LD_{50} in 10–40 days (animals which survive this period may die later from radiation pneumonitis) after irradiation of the thorax with 250 kVp X-rays and d(16)Be neutrons. Endpoint doses are available for single doses, two fractions in 24 h, five fractions in 4 days and 10 fractions in 11 days (Hornsey & Field 1979). Figure 1 shows the resultant Fe-plots.

From the X-ray slope and intersection point the derived BED and (α/β) are:

$$\begin{aligned} BED = \frac{1}{0.0112} = 89.54\ Gy \Rightarrow \\ (\alpha/\beta)_L = \frac{1}{BED \cdot 0.007} = \frac{0.0112}{0.007} = 16.25\ Gy \end{aligned}$$

Therefore, from the Fe-plot corresponding to the fast neutrons, the subsequently derived $RBE_{\max}$ and $RBE_{\min}$ are:

$$\begin{aligned} RBE_{\max} = 89.54 \times 0.0341 = 3.05 \Rightarrow \\ RBE_{\min} = \sqrt{BED \times (\alpha/\beta)_L \times 0.0036} = 2.28 \end{aligned}$$

Substituting the values obtained for $(\alpha/\beta)_L$, $RBE_{\max}$ and $RBE_{\min}$ into Equation 5, the resultant

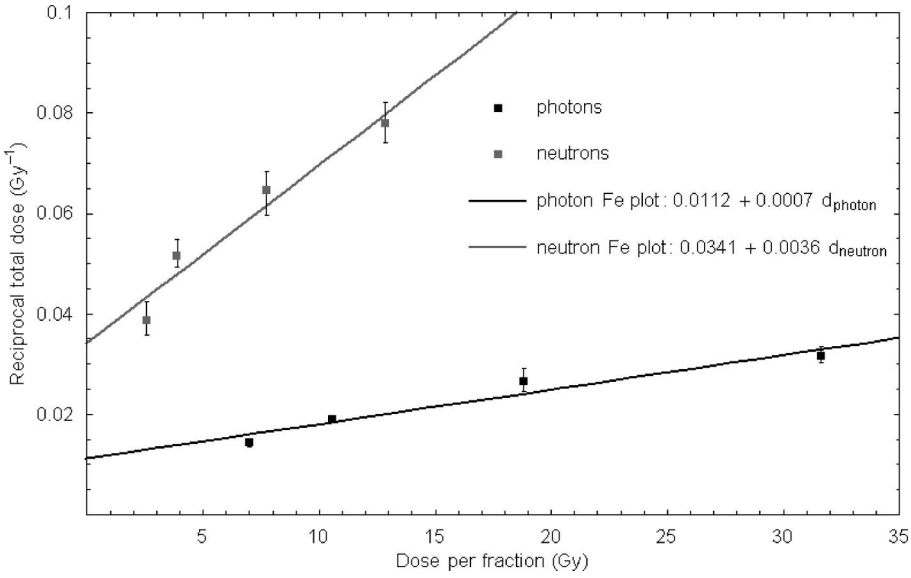

Figure 1. Fe-plots for LD_{50} due to oesophagus injury in TO mice after irradiations with X-rays and fast neutrons. Data from Hornsey and Field (1979).

expression for RBE as a function of the X-ray dose per fraction is:

$$RBE = \frac{49.58 + \sqrt{2458.69 + 336.48 d_L + 20.71 d_L^2}}{32.49 + 2 d_L} \quad (14)$$

The resultant RBE curve from Equation 14, along with the original data points, is shown in Figure 2.

The black trace corresponds to the RBE obtained when using RBE_{max} and RBE_{min} in Equation 5, while the grey line corresponds to the RBE obtained without using the concept of RBE_{min} [i.e., that obtained via Equation 6). The RBE difference (ΔRBE) obtained between the two lines at 2 Gy per fraction is 5.2%. This difference is due to the large value of RBE_{min} and which reflects the values of RBE at very large doses per fraction reported by Hornsey and Field (1979). The black squares in Figure 2 are the original data points and it is clear that the curve incorporating the RBE_{min} concept provides an altogether better fit to the data.

Renal damage in mice after fast neutron irradiation

Stewart et al. (1984) reported RBE values for the renal damage of mice irradiated with 3 MeV neutrons based on early and late endpoints of reduction of haematocrit in the kidney to a 40% level (22 weeks) and ethylenediaminetetraacetic acid (EDTA) clearance of 3% retention (28 weeks), respectively. The resultant parameters from the Fe-plot analysis are summarized in Table I and the RBE curves obtained from Equation 5 for each endpoint are shown in Figure 3.

Very little difference was found between considering and not considering RBE_{min} in the RBE equation (see Table I), primarily because the fitted RBE_{min} value is ~ 1. Figure 3 suggests that, up to around 25 Gy of X-ray dose, the RBE for early renal damage effects is higher than for late effects.

The data assessed in Figure 3 employed X-ray doses per fraction in the range 4.7 – 14.4 Gy. In a separate study, Joiner and Johns (1987) investigated the same range of fractional dose sizes for mouse renal damage, but used 1, 2, 5 and 10 fractions and also included 10 fractions plus a ''top-up'' dose of neutrons in order to measure RBE in the lower X-ray dose range of 0.75 – 3.0 Gy per fraction. This ''top-up'' data however has not been included in the present analysis in order to maintain the correspondence with the previous experiments and also to avoid including any low-dose hypersensitivity effects which might be produced by X-rays at very low doses per fraction. Also, RBE has been calculated at different levels of functional effect in order to reproduce the method used by Joiner and Johns. The resultant RBE_{max} and RBE_{min} calculated for these levels are shown in Table I. The value of RBE_{max} and (α/β) calculated here are 15.85 and 2.23 Gy respectively, these values being in accordance with the values proposed by Joiner and Johns (see bracketed values in Table I). The fitted RBE versus dose-per-fraction curves are shown in Figure 4.

Colo-rectal injury in mice

Terry et al. (1983a, 1983b) studied the RBE of early- and late-effects in colo-rectal normal tissue after

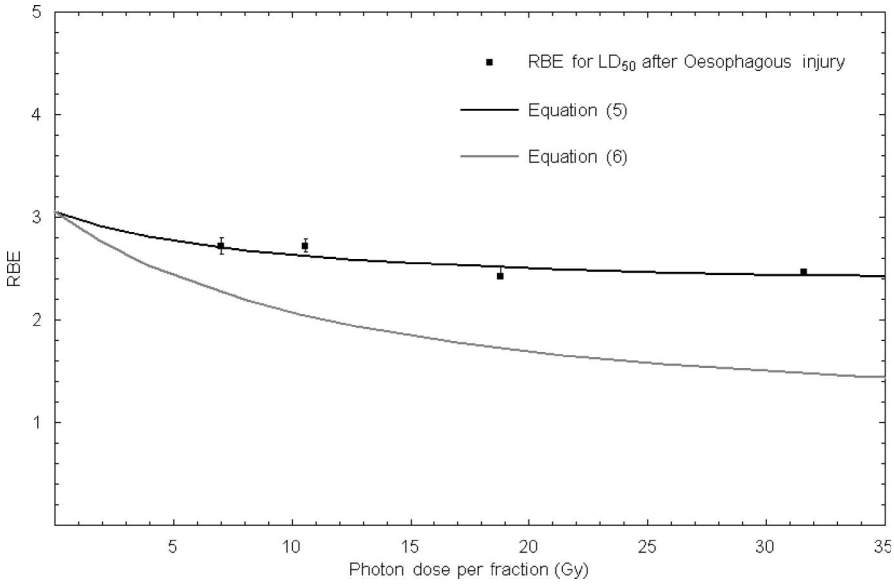

Figure 2. Data points show the RBE variation with dose derived from the data plotted in Figure 1. The black line is derived from Equation 5 and incorporates a fitted value of $RBE_{\min}$ whilst the grey line assumes that $RBE_{\min}$ is unity. The better match of the measured data to the former is apparent.

Table I. Relevant radiobiological parameters obtained from Equations 12 and 13 for the different end-points selected. The values in round brackets correspond to the published values. In the final two columns are listed the two-tailed t and (in square brackets) the associated p values of the fit of the data points to the two alternative models [Weatherbum (1962)]. For all of the data analysed the complex model (i.e., that including both $RBE_{\max}$ and $RBE_{\min}$) provides the better statistical fit, although only in the case of oesophagus LD50 data is the fit very highly significant.

End point	$\left(\alpha/\beta\right)_L$ [Gy]	BED_L (d→0 Gy) [Gy]	$RBE_{\max}$	$RBE_{\min}$	t [$p_{\text{two-tailed}}$] ($RBE_{\min}$, $RBE_{\max}$)	t [$p_{\text{two-tailed}}$] ($RBE_{\max}$)
LD_{50} – Oesophagus injury (Hornsey & Field 1979)	16.24	89.54	3.05	2.27	0.1348 [0.9013]	6.4745 [0.0075]
40% Residual Haematocrit (Stewart et al. 1984)	1.15	178.65	26.33	1.19	0.1678 [0.8774]	0.3223 [0.7684]
3% Residual EDTA (Stewart et al. 1984)	1.22	183.74	20.58	1.35	0.6348 [0.5706]	6.2033 [0.0084]
Mouse kidney (Joiner & Johns 1987)	2.23 (3.04 ± 0.35)	115.48	15.85 (11.65 ± 0.69)	0.73	0.4029 [0.6898]	0.9594 [0.3450]
Mouse skin injury (Joiner et al. 1983)	17.42 (43.6)	60.69	5.35 (7.2)	0.41	1.1813 [0.2486]	1.9109 [0.0675]
Colo-rectal injury (Nadir body weight) (Terry et al. 1983b)	12.33 (13.07)	70.50 (67.11)	7.04 (8.5)	0.47	0.7401 [0.4688]	3.4067 [0.0031]
Colo-rectal injury (Peak body weight) (Terry et al. 1983b)	7.38 (9.21)	82.10 (85.47)	6.84 (5.7)	0	1.0803 [0.3012]	2.2668 [0.0427]
LD_{50} – Colo-rectal injury (2 months) (Terry et al. 1983)	28.69 (28.63)	76.68 (76.92)	5.7 (5.7)	1.46	0.0925 [0.9321]	0.5223 [0.6376]
LD_{50} – Colo-rectal injury (15 months) (Terry et al. 1983)	3.11 (3.12)	108.24 (107.87)	12.56 (12.70)	0.41	0.2503 [0.8185]	1.2076 [0.3137]
BR × 1.1 – Lung injury (28 weeks) (Parkins et al. 1985)	2.93 (2.9)	50.04	7.63	0.58	0.5920 [0.5755]	1.0587 [0.3304]
BR × 1.1 – Lung injury (68 weeks) (Parkins et al. 1985)	2.14 (2.1)	54.11	9.22	0.10	0.8678 [0.4188]	2.9749 [0.0248]
LD_{50} – Lung injury (28 weeks) (Parkins et al. 1985)	5.95 (4.5)	38.51	5.19	0.99	0.7143 [0.5018]	0.6987 [0.5190]
LD_{50} – Lung injury (68 weeks) (Parkins et al. 1985)	2.32 (2.15)	56.18	8.62	0.72	0.5789 [0.5837]	1.9497 [0.0991]
Desquamation – Pig skin injury (Hopewell et al. 1988)	15.17	79.05	3.46 (2.75)	0.71	0.0227 [0.9827]	0.5692 [0.5938]
Necrosis – Pig skin injury (Hopewell et al. 1988)	5.25	101.27	4.26 (4.32 ± 0.39)	0.91	0.3146 [0.7657]	0.4138 [0.6962]

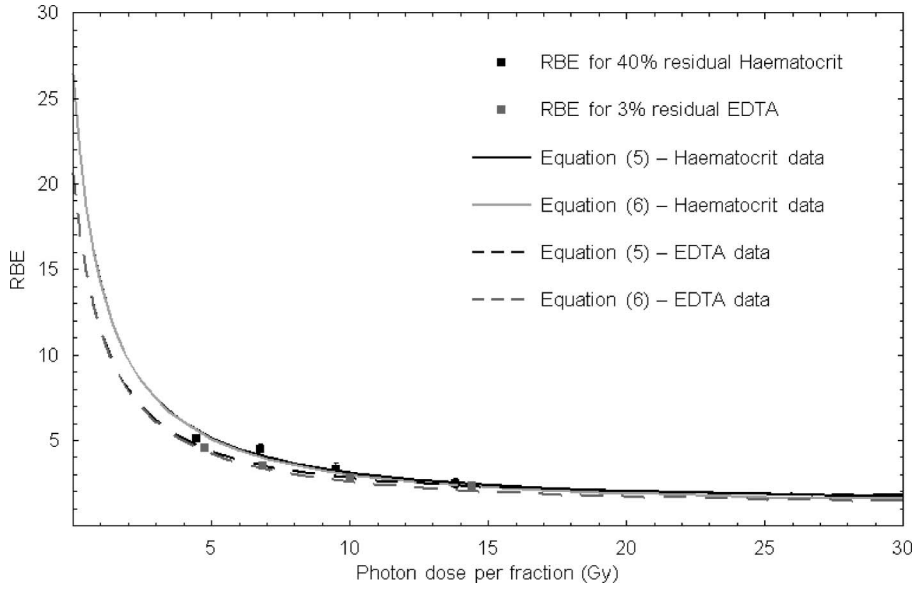

Figure 3. RBE versus dose curves for Haematocrit reduction to 40% level (early reaction – 22 weeks) and 3% ethylenediaminetetraacetic acid retention (late reaction – 28 weeks) for mice kidney after being irradiated with X-rays and fast neutrons. The fitted curves (respectively black and grey) are derived from Equation 5. Data from Stewart et al. (1984).

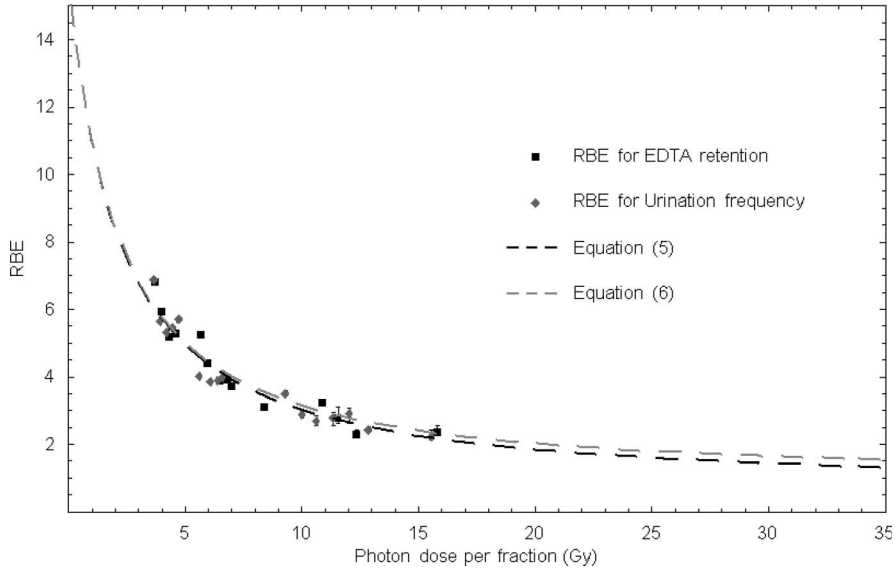

Figure 4. RBE versus dose curves corresponding to mouse kidney damage for X-rays and fast neutrons. The black squares are the data points obtained from the ethylenediaminetetraacetic acid clearance experiments, while the grey diamonds represent the data extracted from the urination frequency experiments. The black line corresponds to the RBE-fitted curve which includes RBE_{min}, whilst the grey line corresponds to the calculation without taking RBE_{min} into account. Data from Joiner and Johns (1987).

irradiation of mice with ^{137}Cs gamma-rays and fast neutrons. The end points used were:

- Body weight: The weight lost shortly after irradiation and the maximum body weight regained were both studied as a function of radiation dose. The nadir in weight occurred between 11 and 17 days (early effect), and the maximum body weight was achieved at 4 – 7 months after irradiation (late effect).
- Lethality: The proportion of surviving animals was assessed sequentially at monthly intervals up to 16 months after irradiation. The lethal total dose required to kill 50% of the mice population (LD_{50}) values were obtained at 15 days and 15 months after irradiation with both γ-rays and neutrons.

Table I summarizes the results obtained from the present analysis and the results determined by Terry et al. The associated RBE curves to the relevant end

point (with and without the $RBE_{\min}$ concept) are presented in Figures 5 and 6.

In both Figures major differences are only noted at doses-per-fraction larger than 10 Gy. A notable feature in Figure 6 however, is the existence of a certain threshold dose/fraction ($\approx$5 Gy) above which the late-reacting RBE is lower than that for the acute response. As the fractionation response of most tumours is similar to that of acute-responding normal tissues then this divergence in RBE values might have important implications for therapy. To avoid more damage to the normal tissue than tumour, the doses/fraction required would have to be >5 Gy, as lower doses would infer a higher RBE for normal tissues and higher toxicity. It is also interesting to notice how the difference between the early and late effects tend to increase for any given dose per fraction when $RBE_{\min}$ is included in Equation 5.

Damage to mouse lung

Parkins et al. (1985) measured lung damage after exposing the thorax of CBA/Ht male mice to 240 kVp X-rays and 3 MeV neutrons. The end points used were increase of breathing rate (by a factor 1.1 with respect the normal rate) and lethality (LD_{50}). The RBE curves for these are respectively presented in Figures 7 and 8.

In Figure 7, the RBE curves associated with increased breathing rates at early and late stages of the experiment shows a distinction between the cases corresponding to inclusion or non-inclusion of $RBE_{\min}$ in Equation 5. The largest difference is observed in the late effects, but this difference is significant only at high doses per fractions. The implication is that treatment with neutrons would be beneficial only if the doses per fraction were larger than $\sim$3 Gy. It is clear from the p values in Table I that a better fit to the RBE points is achieved when considering $RBE_{\min}$ in Equation 5. That can be seen from the points at higher doses per fractions and which lay well under the early- and late-RBE curves which do not include $RBE_{\min}$.

In Figure 8 the same difference between considering and not considering $RBE_{\min}$ is observed in the case of late end points but it is not as great in the case of early end points, for which the associated RBE curves are almost perfectly coincident. Adverse therapeutic index is likely at fractional dose less than about 4 Gy.

Acute skin reactions in:

- *Pig skin*. Hopewell et al. (1988) exposed pig skin to different fractionated doses of 250 kV X-rays and d(42)Be neutrons in order to investigate the respective early and late end-point RBE of pig skin desquamation and necrosis. The data from that study are presented in Figure 9, together with the RBE curves derived using the present analysis. Small differences between inclusion and non-inclusion of $RBE_{\min}$ are apparent at higher fractional doses. A positive therapeutic

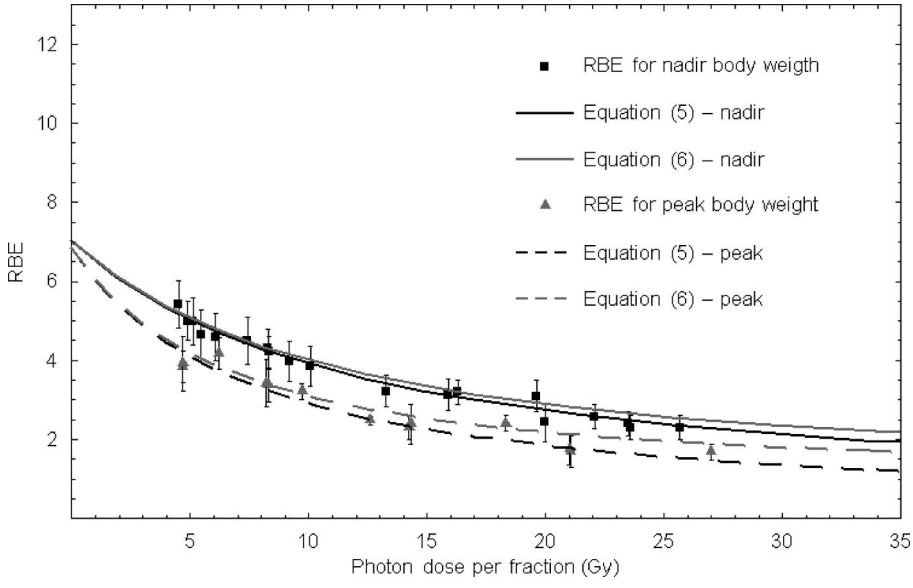

Figure 5. RBE versus dose curves for changes in body weight as a consequence of colo-rectal damage after pelvic irradiation. The black squares represent the data points for the lower limit of body weight attained, while the grey triangles are for the higher limit. The biggest differences between the predicted curves obtained from Equation 5 and 6 are noticeable at doses per fraction > 10 Gy. According to this figure, the use of neutron is contraindicated as the RBE for early effects is higher than for late effects at any given dose per fraction. Data from Terry et al. (1983a, 1983b).

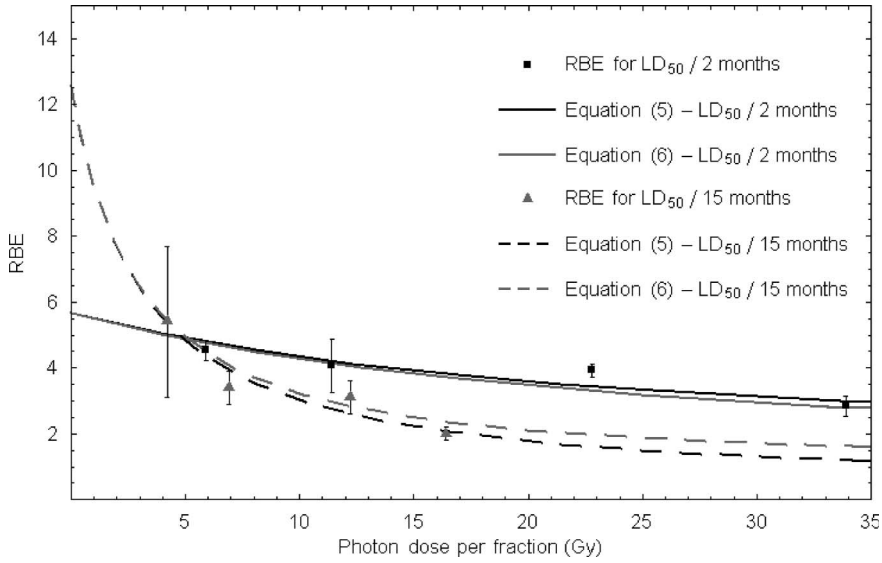

Figure 6. RBE versus dose for LD_{50} following colo-rectal damage. Squares correspond to data for early effects while triangles correspond to late effects. The solid lines are fitted to the former data and the dotted lines to the latter. The data impliess that favourable disposition of the RBE effect (assuming that tumours would behave similarly to the acute effects) is achievable only above 5 Gy. Data from Terry et al. (1983a, 1983b).

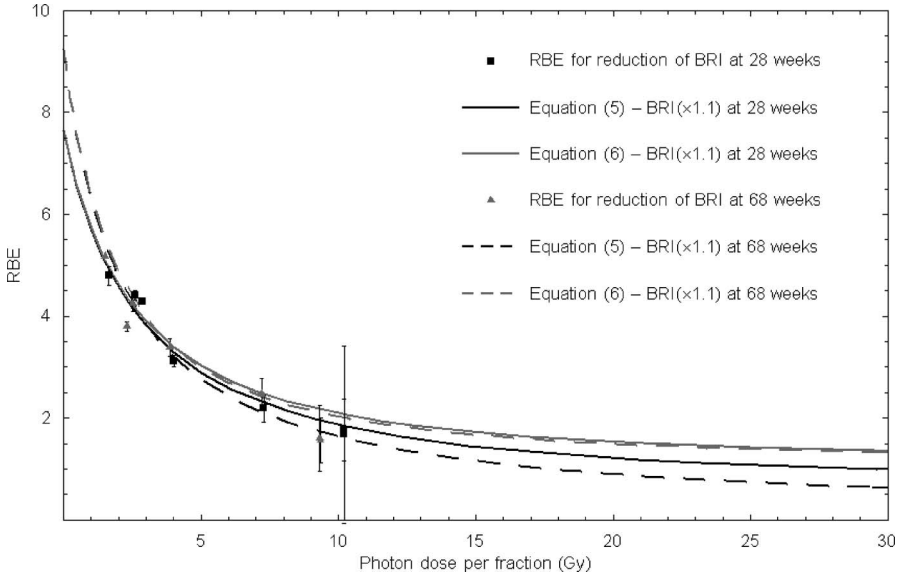

Figure 7. RBE versus dose for increased breath rate by a factor of 1.1 following exposure of whole mouse thorax to X-rays and neutrons. Squares correspond to early (28 weeks) data endpoint while triangles correspond to late (68 weeks) endpoint. Data from Parkins et al. (1985).

ratio will only be valid for doses greater than $\sim$2 Gy.

- *Mouse skin*. Other useful data on normal tissue effects was produced by Joiner et al. (1983) using neutrons from the 4 MV van de Graaf accelerator at the Gray Laboratory. Two different experiments were performed, one where single, two or five equal fractions were delivered daily, and a repeat experiment that included 9 equal fractions, the dose being delivered twice per day with an inter-fraction interval of at least 6 h. The data analysis and curve fitting was performed slightly differently in this case in order to reproduce the method used by Joiner. The RBE were calculated for different skin reaction levels from 0.8–2.4, the resultant RBE_{max} and RBE_{min} values being as listed in Table I and the RBE curve fits being shown in Figure 10.

For comparison purposes, we have included the RBE curves for EDTA retention shown in Figure 4.

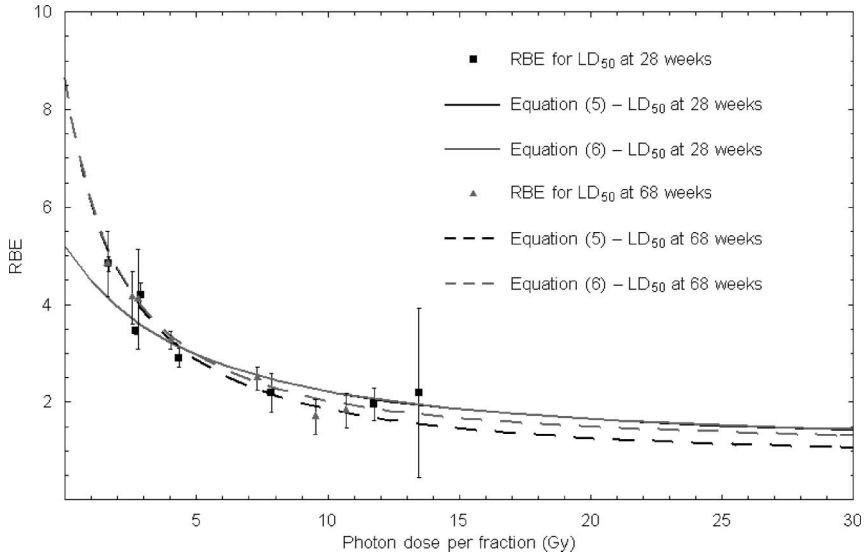

Figure 8. RBE versus dose for LD_{50} determinations following exposure to X-rays and neutrons of whole mouse thorax. Squares correspond to early (28 weeks) end point while triangles correspond to late (68 weeks) end point. Data from Parkins et al. (1985).

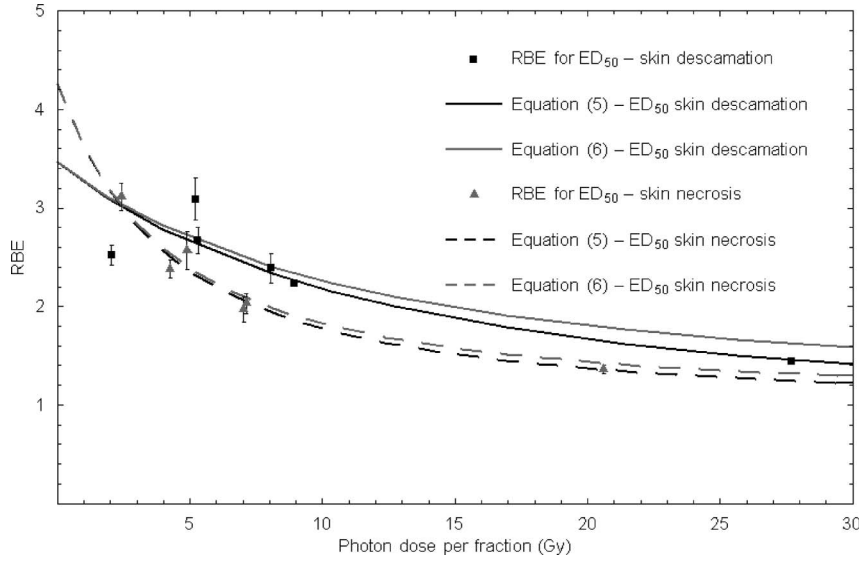

Figure 9. ED_{50} after exposure to X-rays and neutrons of pig skin. Squares correspond to early end point (desquamation) while triangles correspond to late end point (necrosis). Data from Hopewell et al. (1988).

This shows that in these circumstances, a positive therapeutic ratio can only be achieved at doses higher than $\sim$7 Gy.

Overall results and comparison with predicted values

Figures 6 to 10 show a general agreement of a higher RBE for late effects at the levels of dose per fraction conventionally used in clinical radiotherapy. Although these results are not conclusive, they corroborate earlier suggestions that the reason for adversity when using neutrons is a consequence of the greater impact they have on normal tissues at lower fractional doses. The Hammersmith neutron trials in the 1970s (Catterall & Bewley 1979) are often considered to be disappointing because, although the tumour control in advanced head and neck cancer increased by a factor of four (from 12/62 to 54/71; Catterall 1989), so did the late complications (from 4–17%), the latter figure being considered unacceptably high and adding to the general impression that neutron therapy failed to match expectations. The Edinburgh neutron trials used lower fractional doses but failed to indicate an improved therapeutic ratio (Duncan 1994).

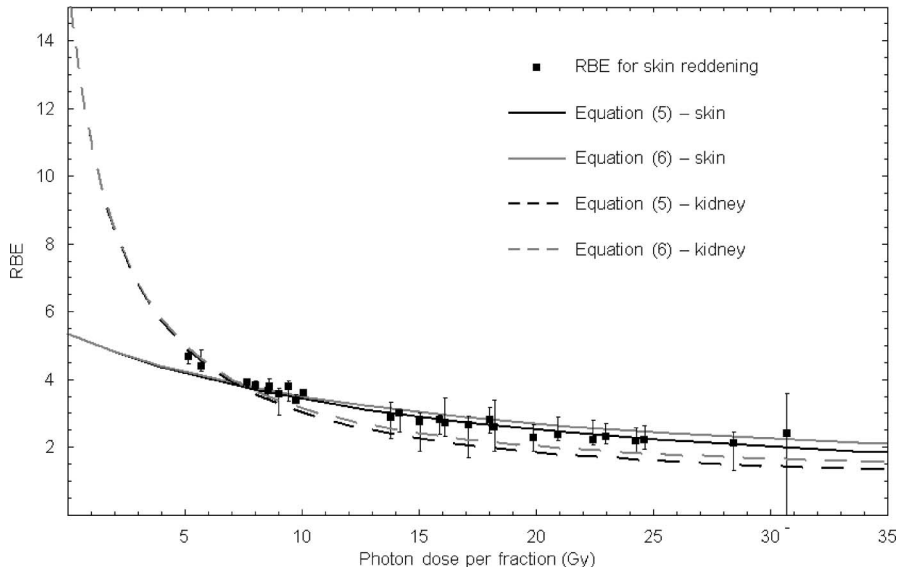

Figure 10. RBE versus dose corresponding to mice skin exposed to X-rays and fast neutrons. The back boxes represent the data obtained from the experiment using one, two or five daily fractions; the grey triangles represent the data extracted from the second experiment which included up to 9 fractions. The black solid line corresponds to the RBE fitted curve which includes RBE_{min}, while the grey solid line corresponds to the calculation without taking RBE_{min} into account. Data from Joiner et al. (1983).

Table I summarizes the results obtained from the present analysis and compares them with the measured data points. In the final two columns are listed the two-tailed t and (in square brackets) the associated p values of the fit of the data points to the two alternative models. For all of the data analysed the complex model (i.e., that including both RBE_{max} and RBE_{min}) provides the better statistical fit, although only in the case of oesophagus LD50 data is the fit very highly significant.

For this particular tissue, the difference in RBE at a dose per fraction of 2 Gy of X-rays between the two traces shown in Figure 2 is 5.15%. In the rest of the tissues analysed $\Delta RBE|_{2Gy}$ is minimal. However, it is interesting to notice how the presence of RBE_{min} in Equation 5 makes a bigger change to the RBE of late effects than to those of the early effects. In all the cases analysed, the RBE late effect changes are smaller when RBE_{min} is taken into account. This means that, if the RBE curves for early and late effects cross over at some point, the dose-per-fraction at which they cross could be shifted towards lower doses, which ultimately would affect the lower limiting dose required to achieve a positive therapeutic ratio. Conversely, had the RBE changes for late effects been larger when considering RBE_{min} in Equation 5, the crossing point between early and late reaction curves would have shifted to higher doses-per-fraction. It is still not clear why, or in what cases, the RBE_{min} correction increases the change in RBE in some cases and decreases it in others. The present authors are investigating this effect using data produced with other tissues and radiation qualities.

Discussion

A method is proposed for calculating RBE values using the assumption that the main radiosensitivity parameters describing the LQ model, α and β, are *both* susceptible to change with changing LET. As indicated in a previous paper (Dale & Jones 1999), several authors have shown experimentally that the β-values for some cell lines appear to be LET-dependent (Kellerer & Rossi 1972, Goodhead 1988, Stenerlöw et al. 1995). As discussed here, a consequence of that is the requirement to consider two intrinsic RBE values (RBE_{max} and RBE_{min}) for every cell line and which, as demonstrated in Figure 2, could have an important impact in calculating the relative effectiveness of a given high-LET dose. In order to obtain a high TCP while keeping an NTCP as low as possible, it is essential in radiotherapy to keep the normal tissue dose well below its tolerance limit. This principle is valid whatever the radiation type is used and Figures 6 – 10 suggest that neutrons may produce more damage in normal tissue than in tumour for the doses per fraction normally used in radiotherapy. This might be an indication of the reasons why the UK neutron trial experience was disappointing although, perhaps, any radiobiological shortcomings may well have been exacerbated by a poorly-penetrating and heterogeneous neutron beam.

Several points arise from this analysis. Most of the cases reviewed do not show a tremendous difference between the plots produced with and without the RBE_{min} included in Equation 5 and, even then, the difference is noticed only at high fractional doses. However, the fact that, in the oesophagus case in particular, there is a significant difference suggests that the RBE_{min} might well be a parameter that must be more generally taken into account to avoid the risk of underestimating RBE at low fractional doses, particularly in critical organs. It follows then that the general consensus of considering β independent of LET might be inappropriate for some high-LET radiotherapy. One advantage of our revised model is that it does not require any additional clinical data from isoeffect or other studies and it therefore can serve to increase the clinical utility of BED/RBE iso-effect formulations, the potential usefulness of which were first identified by Barendsen (1982a). The overall variation of β with LET is in any case likely to be small and this *may* explain why derived RBE_{min} values, as seen from Table I, are both greater and less than unity (the majority being in the latter category). In addition to the possibility of a systematic dependence of β on LET there are a number of other influences which may affect the magnitude of the observed variations, e.g., measurement imprecision, variable radiosensitivity, breakdown of the LQ model at high doses, etc., and the finding of β-values either side of unity does mean that experimental imprecision and/or modelling limitations cannot be ruled out.

There is also the issue of the statistical significance of the raw data. Although Fe-plots have been used for many years to estimate the (α/β) parameter (e.g., Douglas & Fowler 1976), several authors have commented on the statistical shortcomings of this method (Tucker 1984, de Boer 1988, Taylor & Kim 1989). Some of these criticisms are: (i) The method derives the (α/β) parameter via a two-stage (indirect) analysis, (Fischer & Fischer 1977, Herring 1980); and (ii) the method tends to be biased in its estimation of (α/β) as a consequence of the uncertainty in both, the independent and the dependent variables (d and 1/TD respectively). This double uncertainty precludes the use of linear regression analysis [which may be applied only if the experimental uncertainty is restricted to the values of the ordinate (de Boer 1988)] and forces the use of non-linear analysis (Tucker 1984). However, Fe-plots do use clinically relevant data (dose per fraction and iso-effective total doses) and link it with BED, a parameter of widely recognized value and which is very helpful when comparing isoeffective treatments. de Boer (1988) proposed a method based again on a linear least-square fit of data presented as a TD vs. d·TD plot, which provided values of E/α and (α/β) very similar to those derived from non-linear

Table II. Relevant radiobiological parameters obtained when applying de Boer's method.

End point	$\left(\alpha/\beta\right)_L$ [Gy]	BED_L (d→0 Gy) [Gy]	RBE_{max}	RBE_{min}	t [p] (RBE_{min}, RBE_{max})	t [p] (RBE_{max})
LD_{50} – Oesophagus injury (Hornsey & Field 1979)	14.87	94.38	3.10	2.28	0.0576 [0.9579]	6.5641 [0.0072]
40% Residual Haematocrit (Stewart et al. 1984)	1.47	145.07	21.23	1.02	0.6676 [0.5521]	0.7155 [0.5960]
3% Residual EDTA (Stewart et al. 1984)	1.17	190.84	21.30	1.25	3.4072 [0.0422]	5.7134 [0.0106]
Mouse skin injury (Joiner et al. 1983)	46.21	45.27	4.12	0.17	24.29 [0.8098]	0.0264 [0.9790]
Mouse kidney (Joiner & Johns 1987)	29.18	36.27	5.06	0.15	0.2429 [0.8098]	0.0264 [0.9791]
LD_{50} – Colo-rectal injury (2 months) (Terry et al. 1983)	34.39	72.04	5.35	1.52	0.0583 [0.9571]	0.8018 [0.4813]
LD_{50} – Colo-rectal injury (15 months) (Terry et al. 1983)	5.49	73.95	8.54	0.17	0.4031 [0.7139]	0.4677 [0.6719]
BR × 1.1 – Lung injury (28 weeks) (Parkins et al. 1985)	3.19	47.82	7.29	0.32	0.7726 [0.4691]	0.9916 [0.3697]
BR × 1.1 – Lung injury (68 weeks) (Parkins et al. 1985)	3.61	39.55	6.74	0.07	0.1283 [0.9021]	0.1771 [0.2837]
LD_{50} – Lung injury (28 weeks) (Parkins et al. 1985)	5.81	39.33	5.31	0.40	1.5105 [0.1817]	0.4634 [0.6594]
LD_{50} – Lung injury (68 weeks) (Parkins et al. 1985)	3.11	47.12	7.22	0.43	2.1008 [0.0804]	0.7342 [0.4905]
Desquamation – Pig skin injury (Hopewell et al. 1988)	17.72	75.54	3.29	0.17	0.7262 [0.5002]	0.3454 [0.7438]
Necrosis – Pig skin injury (Hopewell et al. 1988)	5.42	100.1	4.21	0.39	3.2473 [0.0228]	0.4723 [0.6566]

statistical methods. Table II shows the result of using the de Boer method to reassess the Fe-derived parameters listed in Table I. No significant variations are observed, suggesting that the use of Fe-plots is justified in this analysis.

A final comment needs to be made on the use of Equation 5 to obtain isoeffective fractionation schemes between high- and low-LET radiotherapy. The equation provides a first estimate of the RBE as a function of low-LET parameters, thus making it simpler to use clinically, but a number of adjustments might in future need to be made to this equation. Ideally, Equation 5 should be extended to consider the different RBE effects produced by the γ-contamination typically existing in a neutron beam since the equation is presently not designed for mixed-LET beams. It is highly likely that the neutron beams used in the experiments considered in this article possessed low-LET photon contamination. However, the applications discussed here, and the consequent clinical implications, do not require such resolution since, at this preliminary level, empirical correlations to ''whole beams'' are being assessed.

For those treatments where a mixture of radiation types is required it will be necessary to consider the dependency of RBE with LET. In a previous paper (Dale & Jones 1999), the Microdosimetric-Kinetic (MK) model (Hawkins 2003) was suggested as providing a good explanation of this dependency. However, the MK model itself leads to the implication that β is independent of LET. Thus, from what has been suggested in this paper, the philosophy embodied within the MK model itself may need to be reconsidered. In clinical practice, Equation 5 can be used as the first approach to finding the 'clinical RBE' (Barendsen [1982b], Wambersie [1999]) and then later readjusted as the result of clinical experience (e.g., dose escalation phase I studies) built up from treatments using that particular high-LET.

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