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LIST OF ABBREVIATIONS AND DEFINITIONS

RBE=Relative Biological Effectiveness
BED=Biological Effective Dose
LET =linear energy transfer
IMRT= Intensity modulated radiation therapy
GyE=Gray equivalent dose
LEM=Local Effect Model
NT= Normal Tissue
PCP=positively charged particle therapy
LQ= linear quadratic model.
PUBLISHABLE SUMMARY

In the first part of this report a critical analysis of fractionation in particle therapy and related modeling approaches is given. In the second part we discuss examples of treatment plans according to different schemes of fractionation. We present a set of examples we have planned at different fraction sizes with different $\alpha/\beta$ ratio combinations (normal tissue versus tumour) and analyze the results, mainly in terms of dose to normal tissue. The observed dependencies are quite small as compared to photon fractionated plans, but still reveal a few singularities which suggest specific deepening of research. A general trend of plan improvement for smaller fraction size appears. Moreover, the impact of fraction dose in different irradiation approaches is briefly presented and commented.

Fractionation of high LET particle radiotherapy imposes challenges and opportunities to improve and optimise therapeutic index and cost effectiveness, given that hypofractionation, even if applicable in only some clinical situations, will allow greater patient throughput. This can be achieved by further experimental RBE and fractionation programmes, eventually leading to carefully constructed and conducted clinical trials that will appropriately compare particle radiotherapy with low LET radiotherapy alternatives.

There also needs to be greater understanding of the radiobiological principles and new opportunities to calculate isoeffective treatments, by taking into proper account of the underlying complexity. Calculations should include both normal tissues and tumour effects, since they depend on different parameters, and compromises in choice of dose/fractionation are often necessary. Thus, even if most of the computational tools are available, as well as the ideal platform for treatment planning, as here shown, further research is needed to obtain proper BED optimized treatment plans.
PART A –Modeling fractionation in particle radiotherapy

1. Introduction & background radiobiology

Fractionation refers to the splitting of dose into separate treatment ‘fractions’, or treatment sessions. It is of vital importance in radiotherapy since fractionation can be used to change clinical outcomes, or can be used to achieve closely similar outcomes. For example, a greater degree of fractionation of the same total dose reduces most tissue side-effects, whereas the same biological endpoint can be achieved by two very different fractionation schedules provided total dose is changed to accommodate the degree of fractionation used. Time is a further parameter, since the overall treatment duration is related to the number of fractions multiplied by the average inter-fraction interval. Fractionation was often referred to as “time-dose-fractionation”. The role of time will be considered later in this text.

There is a large literature on fractionation of conventional x-ray (photon) based therapy, which varies from relatively simple qualitative considerations to more complex mathematics. The process of fractionation includes variables which are in most situations under medical control: the dose per treatment \( d \), the number of treatments \( n \), the total dose \( D (or n \times d) \) and the overall treatment time \( t \). In general, when \( n \) is increased, \( d \) decreases (to an extent that \( D \) almost always increases) in order to preserve the same bio-effect. This occurs due to sub-lethal radiation damage repair between fractions: the greater the fractionation the greater the opportunity for repair between fractions. It follows that cells which have defects in damage recognition or repair pathways, as found in mutated tumour cells, will be more radiosensitive and less fraction sensitive. Prolongation of \( t \) may also require increases in \( d \) or \( n \), or both, in order to preserve a biological iso-effect such as to match tumour cell repopulation with time in the case of tumours that contain rapidly dividing cells, or normal epithelial tissues that contain rapidly growing cell populations. The relative magnitude of these changes vary in different normal tissues and tumours, depending on their biological properties:

- Slow proliferation states, associated with a high repair capacity, have a high fractionation sensitivity: that is a large change in effect follows a small change in \( d \). These conditions are characterised by a low \( \alpha/\beta \) ratio.
- Fast proliferation states, associated with a lower repair capacity, have a lower fractionation sensitivity: that is a much smaller change in effect follows a small change in \( d \). These conditions are characterised by a high \( \alpha/\beta \) ratio.

Although there have been many attempts to characterise fractionation ‘rules’ in terms of equations, the most successful and widely used model is that of the linear quadratic (LQ) model of radiation effect, which contains \( \alpha \) and \( \beta \) radiosensitivity parameters and for fractionation studies the \( \alpha/\beta \) ratio is important since it is essentially inversely related to fractionation sensitivity, although the terms are sometimes used synonymously.

The term hypofractionation may require clarification: this essentially refers to a shift in fractionation to larger doses per fraction than 2 Gy by using fewer numbers of fractions. The converse is hyperfractionation. These terms can be confusing to some readers. Accelerated fractionation refers to dose schedules which deliver greater than 2 Gy (of conventional radiotherapy photons or x-rays) per day, independently of the number of fractions per day or week.

2. A brief history of fractionation

2.1 Radiobiology

In the meantime, Fowler et al (1963) had confirmed the dominance of dose per fraction in comparison with overall time for experimental pig acute skin reactions and later applied linear quadratic theory, originally an empirical description of the yield of lethal chromosomal events with dose per cell by Douglas Lea, to the study of isoeffective doses (Douglas & Fowler, 1976) using an algebraic reconfiguration of the LQ model in the form of an FE plot (Fractionation Effect).
Linear quadratic effect, \( E \) (or yield of lethal chromosomal aberrations in terms of Lea’s findings), is expressed in fractionated form as:

\[
E = n (\alpha d + \beta d^2)
\]  

[2.1]

It follows that

\[
\frac{1}{D} = \frac{\alpha}{E} + \frac{\beta}{E} d
\]

[2.2]

This transformation to linearity allowed Douglas and Fowler (1976) to study iso-effective doses in their ‘Fe’ (or fractionation effect) plots of \( \frac{I}{D} \) against \( d \). By taking the ratio of the intercept to the slope showed that \( \alpha/\beta \) ratios differed for acute and late effects. They also, importantly showed that \( \alpha/\beta \) values were far higher for fast neutron fractionation experiments, including in pig skin which closely resembles human skin in radiation tolerance. This finding correlated with the fact that increased fractionation does not require as great a change in total dose as in the case of X-rays (photons) to preserve an iso-effect.

Denekamp (1973) showed that the time effect, measured as the additional radiation dose required to maintain an isoeffective skin reaction, was variable and commenced after a finite time delay: mouse skin repopulation is initiated only after the expression of radiation damage and so the concept of acceleration of repopulation in early reacting tissues emerged (Denekamp et al 1974). It is therefore inappropriate to use a power law model for such an effect since the change in isoeffective dose with time requires a variable slope, even on a logarithmic plot. For tumour control, Fowler et al (1974, 1976) described an optimum overall time in an experimental tumour while maintaining a normal tissue (skin) isoeffect, followed by later experiments by Suit and colleagues (1977). This achievement was attributed to effective tumour reoxygenation at the optimum overall time since equally high tumour control was found at much shorter overall times either by the addition of metronidazole (as a hypoxic cell sensitisser), or by using fast neutrons (due to their reduced dependency on oxygen for cell killing, often referred to as a reduced oxygen enhancement ratio). At longer overall times than the optimum time, tumour control was progressively reduced probably due to tumour cell repopulation.

During the 1980s further progress included the detailed analysis of Withers that acute reacting tissues (by then characterised by high \( \alpha/\beta \) values) required little change in total dose with increasing fractionation, whereas late reacting tissues (with low \( \alpha/\beta \) ratios) required more substantial changes in total dose: the form of the relationship, with an asymptotic limit at very small values of \( d \) (large \( n \)) was compatible with LQ theory. Towards the end of the decade several advances occurred, including:

1. Inclusion of a repopulation factor alongside the LQ surviving fraction [by Dale, Fowler, Tucker and Travis. Van den Geijn] in one equation which allowed different fractionation schedules to be compared and allowed Fowler to speculate that clinical outcomes with quite different schedules could be broadly equivalent.

2. Evolution of the LQ model to the Biological Effective Dose concept following the original idea of Barendsen and subsequent important adaptations by Dale and Fowler. This allowed calculation of isoeffective (or equieffective) treatment schedules, ranking of different fractionation schedules, addition of multiple phases of treatment by different radiation modalities or different fractionation patterns, different dose rates [Jones et al (2001), Fowler (2010)] and eventually the inclusion of RBE limits, as originally described by Bewley, in BED equations for high LET radiations [Jones, Carabe-Fernandez and Dale, 2007, Carabe-Fernandez, Jones and Dale, 2008], and which allow a variable or flexible RBE to change with dose per fraction, as will be shown later.

### 2.2 Clinical

Progress in clinical fractionation was made by careful empirical practice and observation. Following the lead of Regaud in France, who used very low dose rate radium applications, Coutard noted that protraction and hyper-fractionation of teletherapy to high total doses produced a substantial reduction in both acute and late effects of therapy while maintaining the desired tumour effect. There emerged several different “schools” of
radiotherapy, separated not just geographically and linguistically but also by differing attitudes to selection of dose per fraction. The French (Coutard, Baclesse, Pierquin, Chassagne) and American schools (Fletcher, Kaplan, Hellman, Suit) had a preference for small fractions over protracted time durations. In Germany and Austria experience was gained in the use of hypofractionation. In the United Kingdom, severe economic constraints in the provision of radiotherapy equipment led to sequential fractionation studies, particularly in Manchester (Patterson) and Edinburgh (McWhirter), where relatively hypofractionated schedules were preferred (2.25-3.5 Gy per fraction).

The advent of megavoltage radiotherapy, with improved depth dosage, led to further and more formal studies, such as the studies at The Hammersmith Hospital (for example those published by Morrison, 1975). There, patients were treated with several total doses, but the overall time remained constant since the number of fractions was fixed at twenty. The results effectively confirmed that small increments in dose per fraction and total dose in twenty fractions caused enhanced toxicity and tumour control. A general trend emerged: Cancer Centres in the North of England, Scotland & Canada (Duncan, Bush, Ryder, Ross, Pointon) favoured daily hypofractionated radiotherapy at 2.5 - 3.3 Gy per fraction in 15 to 20 fractions over 3-4 weeks, while those in the South of England/London (Cade, Smithers, Ledermann, Bloom, Jones) favoured the French/American approach of conventional daily (five fractions per week) doses of 1.8 - 2 Gy given in 30-35 fractions over 6-7 weeks. These prescription differences are very significant, but there was at that time no reliable method for quantification of the effect of variation in overall time, total dose and dose per fraction on the clinical endpoints.

The concept of hyperfractionation combined with acceleration emerged in the early 1980's and followed advances in the understanding of the radiobiology of cell killing, repair processes and repopulation effects. Prospective randomised trials were conducted by the EORTC (pure hyperfractionation to the same total dose and overall time reported by Horiot et al 1992), MRC (hyperfractionated and accelerated to a lower total dose – CHART, reported by Saunders et al 1996), and the North American RTOG (hyperfractionated and partially accelerated - e.g. Fu et al 2000) but long term meta-analysis continues to generate statements of significant improvements in some cancer types e.g. Baujat et al (2010) and Mauguen et al (2012).

Because of persistent economic constraints in the provision of radiotherapy facilities, there remains considerable interest in the use of relatively hypofractionated radiotherapy, especially for delivery of sub-radical doses in an adjuvant setting, such as pre-operative rectal cancer or after wide excision of a primary breast cancer. The UK START breast cancer trial was designed to test daily 2 Gy fractions against larger fraction sizes over the same overall treatment time and which showed broadly equal effects (Hopwood et al 2010).

The assumption that if the same overall treatment time is in the case of the same radiation modality, then the only variable is dose per fraction and number of fractions, seems sound. Yet, for two quite different radiation qualities, this could differ because repair capacity and kinetics will change, along with a greater cell killing effect which may overwhelm acute tissue tolerance and contribute to consequential late effects.

2.3 The power law equations

The relationships between overall treatment time, number of fractions and iso-effective dose have been fitted by power law equations in a variety of clinical situations (Thames & Hendry, 1987). Strandqvist in 1944 considered the influence only of overall time on skin reactions and skin cancer control. This pioneering work ignored the possible effect of variations in dose per fraction and therefore of DNA repair. The separation of the time and fractionation components and the dominant effect of the fractionation exponent evident in the power-law fit given in the equation of Frank Ellis (1969) below, which was based on acute skin effect data, but was inappropriately applied to other tissues:

\[ D = NSD \cdot N^x \cdot T^y \]  [2.3]

Here, \( D \) is the total dose, \( NSD \) the nominal standard dose, \( N \) the number of fractions, \( T \) the overall treatment time, \( x \) and \( y \) are exponents and were the fitted values were 0.22 (6 fractions per week) or 0.24 (five fractions per week) for \( x \) and 0.11 for \( y \). The equation formed the basis of other empirical methods for adjustment of the total dose for changes in overall time or fraction number. Liversage (1971), Fowler (1971), Withers and Peters (1980) argued that there were several deficiencies in this form of model. The logarithmic scaling of the power law models imply that the initial time factor and repair factors are greatest during the early part of...
treatment and that there will be an indefinite increase in the isoeffective dose with increasing fraction number, which are both contrary to biological evidence. There is actually an asymptotic relationship with increasing fraction number \(N\), where further increments in \(N\) do not require such large increases in isoeffective total doses (Withers 1977, 1983). There was also the impossibility of representing single fractions at time zero on double logarithmic plots.

Subsequent clinical experience in post-mastectomy patients (Bates and Peters, 1975) and carefully designed clinical studies (Turesson & Notter 1984 a & b) showed that the equations were appropriate only for early but not late skin and subcutaneous complications. There are greater deviations from the model in other tissues, such as is the CNS, for which the fractionation exponent is much larger (\(x\) is 0.42 in equation 2.1) and the time exponent was only 0.02 (Sheline et al, 1980). Safer, organ-specific power law models, which included larger fraction exponent values, also became available for late reacting tissues, such as lung and kidney.

The power law models eventually correctly emphasised the importance of fraction size on late tissue isoeffects. There was also a considerable error in the allocation of a significant time exponent (derived from acute tissue reactions) if these models were applied to late reacting tissues. Unfortunately, the original idea of the importance of the time factor for tumour control was largely forgotten for many years, particularly because of the assumption that the long human pre-treatment tumour volume doubling times would reflect the repopulation rate during treatment. Subsequent developments of the Ellis relationship, such as the Time Dose Factors of Orton and Ellis (1973) and the Cumulative Radiation Effect of Kirk et al., (1971) were essentially algebraic rearrangements of the Ellis formulation and provide similar predictions (Goitein, 1976). Later developments such as the extremely complex empirically derived models of Orton (1985) and Cohen (1983) are far less valuable than the later, simpler and less empirical Linear Quadratic (LQ) model. In this context, an empirical power law model which contains the wrong time factor for late reacting tissues is actually more dangerous in clinical practice than a biophysical model (such as the LQ) which for late reacting tissue isoeffect calculations completely omits the time factor. This is because of the lack of importance of time in most examples of late tissue damage, except for instances where overall time is very short: short inter-fraction intervals may allow incomplete DNA repair, and excessive dose in a short time may lead to consequential late reactions.

Similar power law models were derived for continuous radiation applications (Trott, 1987). Here, the objections of a variable time exponent for cellular repopulation are not relevant and the time exponent itself represents repair of sublethal DNA damage during radiation exposure. Again, the power law models erroneously predict that the isoeffective dose will rise continuously at extended treatment durations, which is contrary to clinical findings. Power law models were also available for high LET (fast neutron) radiotherapy, as discussed by Bewley, including the concept of a maximum RBE at low dose per fraction and a minimum RBE at far higher doses, but they were not used in fast neutron therapy since only a constant RBE was used. This is of interest since the application of even a partially correct model may well have reduced the toxicity associated with neutron therapy where a fixed rather than a variable RBE (between these two extreme limits) was used. In retrospect, it is perhaps difficult to understand why the British used a constant RBE for fast neutron therapy, despite knowing that RBE varied with dose per fraction. One reason would have been that they were using a hand dose planning technique, rather than computerised dose planning, in those early days: a fixed RBE would be easier to implement. There was also some degree of misplaced confidence that the low energy neutron beams had rapid dose fall off with tissue depth (rather like that from a 250 keV x-ray generator), so that increments in RBE with dose fall off mattered less.

### 2.4 Fractionation in high LET radiation

In comparison with conventional x-ray based fractionation experience, detailed fractionation experiments using high LET radiation have only a 50 year history (for example, Barendsen and Broerse, 1970, Fowler et al 1976). They show reduced dependency on fractionation effects compared with low LET radiations.

Changing radiation quality, quantified by increasing linear energy transfer (LET, measured in kev/\(\mu\)m), from the baseline of photons (or x-rays) in the Compton scattering energy range (defined as low LET, values usually being 1-3 kev/\(\mu\)m), to positively charged particles (PCP) such as protons and ions in their pristine Bragg peaks. Increasing LET, up to around 120 kev/\(\mu\)m in most instances, is associated with an increased relative biological effect (RBE), which is essentially an increased bio-effectiveness. The predominant
increase in RBE with PCP occurs within the Bragg peak region, where particle velocities (and energies) are smaller resulting in more intense LET values. It is also the case that higher values of LET are found with x-rays (or photons) in the lower photoelectric effect energy range (generally speaking x-rays below 70-80 kev, and also with neutrons. RBE is usually defined as the ratio of dose required for the same bio-effect using a low LET radiation compared with one at a higher LET. Symbolically this is represented as

\[ RBE = \frac{d_L}{d_H}, \]  

where the subscripts L and H refer to low and high LET respectively.

Now, when the fractionation schedule changes, the numerator \( d_L \) changes with fractionation to a greater extent than \( d_H \). The low LET numerator dose changes because of repair occurring between fractions, but the denominator \( d_H \) is less susceptible to changes in fractionation. This is because high LET radiations form more clustered, locally complex damage within DNA, which is more difficult or impossible to repair. So, there is lesser repair between fractions in the case of high LET radiations compared with low LET radiations. This must also be understood in terms of the single fraction experiment, where there is no opportunity for repair between fractions. With increasing LET, the \( \alpha \) radiosensitivity parameter increment is proportionately greater than the accompanying much smaller increase in the \( \beta \) parameter: this means that the ratio of \( \alpha_H/\alpha_L \) should always exceed \( \beta_H/\beta_L \). Now since \( \alpha_H/\alpha_L \) is \( \text{RBE}_{\text{max}} \) (the RBE at near zero dose where \( \beta \) related cell kill is negligible) and \( \sqrt{\beta_H/\beta_L} \) is \( \text{RBE}_{\text{min}} \) (the RBE at high dose where \( \beta \) related cell kill predominates). It follows that a reduction in dose per fraction will increase the RBE towards the \( \text{RBE}_{\text{max}} \) limit; conversely as dose increases the RBE will approach the lower \( \text{RBE}_{\text{min}} \) value. It can also be appreciated that the yield of complex lethal chromosomal aberrations per unit dose increases with LET, so the same biological end points can be achieved with lower doses, where \( \alpha \) cell killing mechanism predominates, rather than the \( \beta \) related mechanism. This again means that radiations that have high LET and RBEs will be associated with reduced fractionation sensitivity, since it is the \( \beta \) related damage that is susceptible to sub-lethal damage repair.

This original description of RBE was convenient to radiobiologists, since RBE could be measured from the defining ratio given in equation 2.4, but this allowed RBE to be viewed as being over simplistic, indeed almost of trivial complexity. In fact RBE is a highly complex parameter, depending on multiple variables including particle mass, energy, charge, target volume (and its depth), dose, beam contamination (e.g. with neutrons, \( \gamma \) rays etc) and the radiobiological characteristics of the tissue/tumour being targeted (repair capacity, proliferative status - linked to the low LET \( \alpha/\beta \)).

The importance of fractionation in radiotherapy cannot be doubted because of its clinical impact. Increasing the number of fractions \( n \), along with a reduction in \( d \), inevitably increases \( t \) if, say, only a maximum of 5 fractions a week are to be given: this will allow acute reacting normal tissues (such as epithelial surfaces, skin, oesophagus, intestine) to tolerate radiation treatment better, since the increase in elapsed time will allow more cellular repopulation to occur. Exactly the same will occur with PCP, so that for large treatment volumes containing epithelial surfaces that can repopulate within a month, longer treatment courses tend to be given in order to spare acute effects. The opposite, over intensification of dose in time, can cause very severe acute effects that can lead to so-called ‘consequential’ late effects in tissues, as well as being very unpleasant to the cancer patient.

The situation with late tissue effects is different. In their case, increasing fraction size will have a more deleterious effect for x-rays (photons) than for PCP: the former will require a larger reduction in total dose to maintain an isoeffect, whereas the latter will not require as great a change in total dose and so can be given in fewer fractions.

Late effects and very slow growing tumours generally require no time correction factor, unless treatment is very protracted or if multiple fractions per day (MFD) are used. For MFD, incomplete repair (IR) equations are required, especially for three fractions or more per day. IR is likely to be reduced for high LET radiations compared with low LET radiations, since IR is included within the LQ model by linkage to the \( \beta \) parameter and not the \( \alpha \) parameter which increases to a greater extent than \( \beta \) with LET, as explained previously. Another issue with IR, is fraction duration \( t_i \): difficult to deliver techniques allow short but significant interruptions of treatment, (due to gantry rotation, re-imaging etc). This also applies to some modern photon techniques such as GammaKnife and linear accelerator treatments such as CyberKnife. This is because there
are principally two repair half times: the best estimates remain those in rat spinal cord, namely the first component is fast (half time=0.19 hr) and the second slower (half time =2.16 hr) with close to 50% of damage associated with either form of repair (Pop et al, 2000). It has been shown that many treatments with prolonged $t_f$ values can result in a significant reduction in BED per fraction [J Hopewell, personal communication 2012]. It can be argued that all fractional durations longer than 30 minutes should be recorded for later analysis. Ion beam treatments such as the large 44 Gy-eq single fraction given for early stage lung cancer in Japan can in some instances take over 2 hours to deliver. The intervals of time within a fraction that allow repair to continue between ‘pulses’ of treatment will affect low LET therapy to a greater extent than high LET. Also, tumours and tissues with a high $\alpha/\beta$ are less sensitive to dose rate and incomplete repair effects than their low $\alpha/\beta$ counterparts where extension of $t_f$ produces a greater reduction in BED. More detailed work is required on this topic in the context of particle radiotherapy, using prospective data recorded in the ion beam centres to be eventually correlated with clinical outcomes.

It must always be remembered that a small increment in dose per fraction beyond that prescribed and deposited in normal tissue can lead to enhanced tissue damage due to the non linear effects associated with the LQ model. This has been termed double trouble at 2 Gy per fraction and this effect is enhanced when dose per fraction increases further, when it is called treble (or triple) trouble [Jones et al 2001, Jones, Khaksar and Dale 2000]. It follows that increasing hypofractionation (larger doses per fraction) must be given with caution with respect to dose homogeneity and individual calculations should be done since RBE effects will also complicate this effect, as shown later in this report.

Much could be written here on the economic advantages of hypofractionation: fewer treatments of larger doses per fraction allows greater throughput of patients per year, reduced individual patient costs and inconvenience, with greater utility within society bearing in mind strong competition for finite health care resources. Such potential advantages can only be pursued if outcomes, in terms of tumours controlled and cured along with satisfactory quality of life statistics, either match expectations or can be proven to be superior to other more expensive approaches. The use of adjuvant therapies, either conventional or experimental, must also be considered in the context of fractionation trials, since they may overcome certain disadvantages (e.g. cetuximab on tumour repopulation for longer schedules, new antimetabolites which reduce oxygen consumption and permit rapid tumour reoxygenation prior to short schedules).

Also, it remains to be shown if protons can be delivered in hypofractionated form as safely as carbon ions. It is paradoxical that the majority of patients treated with protons had eye melanomas, treated in 4 large fractions to 52-54 Gy doses, using ‘small fields’. The large and protective volume effect will tend to favour larger fractions for small target volumes as long as non-essential tissues are included in the tumour-normal tissue margin. Our inadequate, but improving, knowledge of the mathematical relationship between normal tissue volume and radio-tolerance may yet provide safer guidelines in the future.

3. The relevant equations and worked examples

3.1 BED equations

Biological Effective Dose (BED) equations expresses the dose in Gy required for a defined biological (or clinical) endpoint when the dose is given in very small fraction sizes. BED essentially acts as a reference dose from which it is possible to calculate the dose required to produce a given bio-effect when using different fractionation schedules. BED is the highest possible dose that can be given to achieve a specified bio-effect. The basic BED principle can also be extended to provide EQD-2 equations, which express the dose required for a defined biological or clinical endpoint when the dose is given in 2 Gy fractions.

Further details of BED are given in the previous ULICE report. In summary, BED is derived from fractionated form of the LQ survival equation, where surviving fraction is expressed as a Poissonian function where the exponent contains the expected number of lethal lesions per cell:

$$SF = e^{-\alpha(d+\beta f^2)}$$

[3.1]

Then, by taking the natural logarithm of each side and multiplying by -1, then dividing by $\alpha$, we obtain
\[ \text{BED} = nd \left( 1 + \frac{d}{\left( \frac{\alpha}{\beta} \right)} \right) \]  

where \( \text{BED} \) replaces \( -\ln(\text{SF})/\alpha \), but which can also be expressed in words as:

\[ \text{BED} = \text{Total Dose} \times \text{Relative Effect}, \]  

or also as in symbols as

\[ \text{BED} = D \left( 1 + \frac{d}{\frac{\alpha}{\beta}} \right), \]  

where \( D \) is the total dose and \( d \) the dose per fraction. \( D \) can be replaced by \( nd \), where \( n \) is the number of fractions.

The function of the \( \alpha/\beta \) ratio is to act as a coefficient which controls the fractionation sensitivity. When fraction size is changed, the resulting total dose needs to be modified in order to provide a constant \( \text{BED} \) (and the same bio-effect). It is important to understand that different tissues and tumours can possess quite different \( \alpha/\beta \) ratios, so that they respond differently to different changes in dose fractionation.

The \( \text{BED} \) equation can be modified for particle radiotherapy (Jones et al 2006, Carabe-Fernandez et al 2007), as

\[ \text{BED} = D_H \left( RBE_{\text{max}} + \frac{RBE_{\text{min}}^2 d_H}{\frac{\alpha}{\beta}} \right) \]  

It can be seen that the \( \alpha/\beta \) ratio used is the same as that for the low LET (x-ray) case and that this parameter will now be less important in influencing the \( \text{BED} \) when \( d_H \) is changed, compared to the standard low LET equation, especially when \( RBE_{\text{max}} \) is large. The percentage \( \text{BED} \) increment with dose per fraction is consequently larger for low LET treatments.

This equation also allows the RBE at any intermediate dose to vary between the \( RBE_{\text{max}} \) and \( RBE_{\text{min}} \) values chosen.

3.2 Converting a specific low LET \( \text{BED} \) fractionation to that for high LET, when the low LET \( \alpha/\beta \) ratio is known, but with no change in overall treatment time.

It is then possible to pursue isoeffect calculations using the equality:

\[ \text{Low LET } \text{BED} = \text{High LET } \text{BED} \]

\[ D_L \left( 1 + \frac{d_L}{\left( \frac{\alpha}{\beta} \right)_L} \right) = D_H \left( RBE_{\text{max}} + \frac{RBE_{\text{min}}^2 d_H}{\frac{\alpha}{\beta}} \right) \]  

The major advantage here is that the \( \alpha/\beta \) ratio used throughout this equality is that of the low LET \( \alpha/\beta \), which are well established for some tissue types e.g. brain and spinal cord, although it is necessary to know the likely values of \( RBE_{\text{max}} \) and \( RBE_{\text{min}} \). In important clinical scenarios these RBE parameters should be sufficiently large to produce conservative values of dose per fraction for the protection of normal tissues with low \( \alpha/\beta \) values, yet sufficiently low in the case of fast growing tumours with large \( \alpha/\beta \) ratios.
Worked example:

It is decided to design a clinical trial which provides the same BED for late brain effects as 60 Gy in 30 fractions of megavoltage x-rays, using either 10 or 15 fractions of carbon ions, which are assumed to have $RBE_{\text{max}}$ values of 6 and $RBE_{\text{min}}$ of 1.25. Find, also, the dose required if given in 2, 3 or 4 Gy fractions. The brain $\alpha/\beta$ is 2 Gy. Compare the results with an assumption that dose is modified by constant RBE factors of (a) 3 and (b) 4, regardless of the magnitude of dose.

The BED for x-rays is:

$$60(1+2/2)=120 \text{ Gy} \ [2]$$

And this BED must now equate with the high LET BED such that

$$120 = n \ d_H \ (RBE_{\text{max}}+RBE_{\text{min}}^2 \ d_H/k), \text{ where } k \text{ is from now on the low LET } \alpha/\beta \text{ ratio.}$$

So, for $n=10$, $d_H=1.65 \text{ Gy}$ and $n=15$, $d_H=1.16 \text{ Gy}$.

If doses ($d_H$) of 2 Gy, 3Gy or 4 Gy fractions are to be given solution of the above equation provides $n=7.9$, 4.79 and 3.29. These are not close to integer values. Rounding off to the nearest fraction would be inappropriate, resulting in under- or over-dosage. Consequently, it is best to use the former approach which calculates the dose per fraction.

Now if the ‘overall RBE’ is a constant at all doses, it has a purely dose modifying function, so that each $d$ term in the BED equation is multiplied by RBE, then we must solve for $d_H$ in :

$$120 = n \ d_H \ (RBE+RBE^2 \ d_H/k), \text{ (or } 120 = n \ d_H \ RBE(1+RBE^2 \ d_H/k),$$

So that for RBE=3, $n=10$, $d_H=1.33 \text{ Gy}$ and $n=15$, $d_H=1.04 \text{ Gy}$,

And for RBE=4, $n=10$, $d_H=1.00 \text{ Gy}$ and $n=15$, $d_H=0.78 \text{ Gy}$.

These results show the critical dependency of the RBE model (fixed versus flexible) for the assumptions used.

3.3 Overall Fractionation differences between low and high LET radiations

Solution of the isoeffect equations given above (equation 3.6 is solved for $d_L$ and the result divided by $d_H$ to provide the RBE at any value of $d_H$) can be used to show how low LET (figure 1) and high LET (figure 2) fractionation influences the total dose required to maintain a tissue isoeffect. The change in total dose with number of fractions (and consequently dose per fraction) is much greater for the low LET megavoltage x-rays. The dependency on tissue $\alpha/\beta$ can also be seen, with a pronounced flattening of the relationship after a few fractions only for the high LET radiation: the change over the first few fractions indicates the shift from reliance on $RBE_{\text{min}}$ for the first few fractions to a greater dependency on $RBE_{\text{max}}$ after that. There appear to be little change in total dose after the 4-6 fraction schedules, with only marginal changes after 10-20 fractions. These modelled examples are typical of the pioneering fast neutron experiments (summarised by Catterall and Bewley 1979, Fowler 1981).

In PCP therapy, it is important to remember that these considerations apply to the high LET part of the beam; fractionation effects corresponding more closely to the low LET will be found where there are only entry beams that are distant from the Bragg peak regions. Thus if, say the skin and rib dose (mainly low LET) determine tolerance for a lung cancer treatment, as is the case in Japan, then fractionation will continue to have an important function. The incidence of rib fractures with large single doses remains of concern and this would probably fall with modest further fractionation since the ribs are not in the very high LET region. 3-D LET, dose and BED plans will ideally be required. LET and dose distributions at any voxel are already available through the ion beam treatment planning system TRiP98 (Kraemer et al. 2000), while the BED can be obtained from the photon equivalent dose through the equation 3.4.

LET based treatment plans have already been generated by Grassberger et al (2011), although in the head region and just for protons, and a similar concept has been recently introduced in TRiP98 (Kraemer et al 2012a).
3.4 Boost doses.

In radiotherapy practice it is often the case that treatment is given in phases, typically beginning with wider field arrangements, often to cover regional lymphatic tissues, but ending with a boost dose to a smaller volume (the tumour itself with appropriate infiltrative margins); with x-ray based IMRT the boost can be given simultaneously with the wider field. Sometimes different radiation modalities are used for each phase: for example the larger initial treatment could be given by megavoltage IMRT, followed by the final phase using protons or ionic beams. As we discussed in the report DJRA 5.5, this possibility has been already introduced in TRiP98 (Kraemer et al. 2012b).
Worked example:

A dose of 45 Gy in 25 fractions delivered by IMRT, is followed by a carbon ion boost, with the aim of giving a total tumour dose equivalent to 70 Gy in 35 fractions of megavoltage x-rays, but preserving a normal tissue isoeffect, equivalent to 40 Gy in 20 fractions. Find the dose per fraction required for a 3, 4 or 5 fraction boost for the same tumour control, but also give the normal tissue BED values for each case. The likely tumour α/β is 4 Gy with RBE_{max} = 4 and RBE_{min} = 1.4; the critical late normal tissue has α/β of 3 Gy and RBE_{max} = 4.7 and RBE_{min} = 1.3 and the most relevant normal tissue volume receives a modal 72% of the IMRT dose and only 42% of the ion beam dose.

The intended total tumour BED is 70 (1+2/4) =105 Gy

The IMRT will provide a tumour BED of 45 (1+1.8/4) =65.25 Gy

The deficit tumour BED to be provided is 105-65.25=39.75 Gy

The allowed total NT BED will be 40 (1+2/3)=66.67 Gy

The IMRT will provide a NT BED of 0.72 45 (1+0.72 1.8/3) =46.40 Gy

For tumour boost dose per fraction find \( d_H \) for n=3, 4 and 5 in:

\[
39.75 = n d_H (RBE_{max}+RBE_{min}^2 d_H/4),
\]

For n=3, then \( d_H=2.53 \) Gy; for n=4, then \( d_H=2.00 \) Gy and if n=5, then \( d_H=1.65 \) Gy

The NT BEDs will be, for each dose per fraction:

\[
0.72 45 (1+0.72 1.8/3) +3\times2.53\times0.42(4.7+1.3^2\times2.53\times0.42/3) = 62.87 \text{ Gy}\]

\[
0.72 45 (1+0.72 1.8/3) +4\times2.00\times0.42 (4.7+1.3^2\times2.00\times0.42/3) = 63.34 \text{ Gy}\]

\[
0.72 45 (1+0.72 1.8/3) +5\times1.65\times0.42 (4.7+1.3^2\times1.65\times0.42/3) = 63.74 \text{ Gy}\]

All of these BED values are below the allowed 66.67 Gy, but it is instructive to note that the lowest NT BED is found for the least number of fractions (and the highest dose per fraction), because of the effective fall of RBE with hypofractionation in this case when using the extreme limits of RBE as parameters.

In other clinical situations, if NT tolerance is exceeded, a BED calculation cannot provide the desired result for both normal tissue and tumour, because their BEDs are separately governed by different α/β and RBE parameters. A compromise in dose selection is necessary and this will require detailed clinical discussion, perhaps accepting increased risks of either recurrence or toxicity, or even a modest amount of each. Typical examples were given in the previous report on unintended treatment interruptions.

3.5 Converting a specific low LET BED fractionation to that for high LET, when the low LET α/β ratio is known, but with a change in overall treatment time.

The equations have been used previously to estimate compensatory doses for unintended treatment interruptions.

\[
BED = D_L \left(1 + \frac{d_L}{\alpha/\beta} \right) - K T_L = D_H \left( RBE_{max} + \frac{RBE_{min}^2 d_H}{\alpha/\beta} \right) - K T_H,
\]

and where \( K \) is the low LET BED dose equivalent of repopulation per day, \( K \) being defined as:

\[
K = \frac{0.693}{\alpha L \omega},
\]

where \( \omega \) is the operative cellular doubling time. \( K \) values are known for some tumour types and are sometimes used along with a lag (or delay) time until the onset of accelerated repopulation. In such cases (usually assumed for squamous cell and transitional cell cancers) the \( T \) values are reduced by the delay time \( T_k \), which is usually assumed to be 21-28 days. It is advantageous that the low LET \( K \) values can be used in
this form, even within the high LET side of the equation, but provided the RBE factors are included within
the BED portion of the equation.

3.6 Alternative approach for isoeffect calculations in the case of two high LET schedules.

For two identical high LET treatments, fractionation iso-effects can be calculated using BED equations that
contain high LET \(\frac{\alpha}{\beta}\) ratios.

Thus for two isoeffective schedules of high LET we have for \(N_1\) factions and \(N_2\) fractions of dose \(d_1\) and \(d_2\)

\[ N_{1H}(\alpha_{H}d_{1H}+\beta_{H}d_{1H}^2) = N_{2H}(\alpha_{H}d_{2H}+\beta_{H}d_{2H}^2) \]  \[3.9\]

It is then permissible to divide throughout by \(\alpha_{H}\) (and not \(\alpha_{L}\), as was previously the case) and obtain

\[ D_{1H}\left(1+\frac{d_{1H}}{\left(\frac{\alpha}{\beta}\right)_{H}}\right) = D_{2H}\left(1+\frac{d_{2H}}{\left(\frac{\alpha}{\beta}\right)_{H}}\right) \]  \[3.10\]

In this case, the two RBE parameters \(RBE_{max}\) and \(RBE_{min}\) are no longer necessary. It would also be possible to
use the single \(R_{C}\) conversion factor, where

\[ R_{C}=RBE_{max}/RBE_{min}^2 \]  \[3.11\]

This is because

\[ \left(\frac{\alpha}{\beta}\right)_{H} = \left(\frac{\alpha_{H}}{\alpha_{L}}\right) \left(\frac{\beta_{H}}{\beta_{L}}\right) \]  \[3.12\]

in the situation of comparing two identical high LET radiations, so that equation 15 would become

\[ D_{1H}\left(1+\frac{d_{1H}}{R_{C}\left(\frac{\alpha}{\beta}\right)_{L}}\right) = D_{2H}\left(1+\frac{d_{2H}}{R_{C}\left(\frac{\alpha}{\beta}\right)_{L}}\right) \]  \[3.13\]

which could also be used in this form along with the time factor corrections, as given below.

For unintended treatment interruptions, the most appropriate time and repopulation correction factors can be
added for the case of tumour isoeffects. This is not necessary for late reacting tissues. The equations are then:

\[ D_{1H}\left(1+\frac{d_{1H}}{\left(\frac{\alpha}{\beta}\right)_{H}}\right) - K_{H}t_{1H} = D_{2H}\left(1+\frac{d_{2H}}{\left(\frac{\alpha}{\beta}\right)_{H}}\right) - K_{H}t_{2H} \]  \[3.14\]

where \(t_1\) and \(t_2\) are the respective overall treatment times for schedule 1 and 2 and \(K_H\) is defined as

\[ K_{H} = \frac{0.693}{\alpha_{H}\omega} \]  \[3.15\]

Compared with the K values for low LET (\(K_L\)), there is little knowledge of \(K_H\) values in the literature. \(K_H\) can
however be found from \(K_L\) by dividing by \(RBE_{max}\) (which is \(\alpha_{H}/\alpha_{L}\)), that is

\[ K_{H} = \frac{K_{L}}{RBE_{max}} \]  \[3.16\]
Some authorities have encouraged total dose RBEs to be used, although with extreme caution (Dasu and Toma-Dasu, 2008), but this approach can lead to confusion and potential errors. It is best to use RBE on a dose per fraction basis, which is consistent with cell survival curve theory and the original definition of RBE by LH Gray. It is recommended that individual dose per fraction RBEs be calculated and then total dose calculated. Where fraction numbers differ between low and high LET schedules this is especially important.

For example, let us suppose that a 10 Gy carbon ion physical dose in 5 fractions produces the same late effect as a 50 Gy in 25 fractions photon dose – what is the RBE?

By taking each of the:

- total doses, the RBE is 50/10=5.
- delivered doses per fraction, the RBE is 2/2, which is absurd.

However, by using the following procedure - based on corrected dose per fraction - a different answer is obtained:

The RBE denominator will be the high LET dose per fraction, which is 2 Gy. The photon dose per fraction, if given in 5 fractions (rather then 25), which would match the same effect as 50 Gy in 25 fractions of photons, assuming a late effect α/β=3 Gy, would be given by \( d \) in the following BED isoeffective doses:

\[
\text{BED (5 fractions, unknown } d) = \text{BED (25 fractions, } d=2) \\
5 \left(1+ \frac{d}{3}\right)=50\left(1+\frac{2}{3}\right)
\]

\( d=5.73 \text{ Gy, which is then used as the numerator of the RBE.} \)

The RBE is then 5.73/2=2.87.

In situations where under- or over-dose has occurred or in calculation of x-ray equivalent schedules the most reasonable estimates of the parameters should be used; clinicians may prefer to use the safest choices, such as a high RBE_{max} in tissues which are highly fraction sensitive for x-rays, such as the central nervous system. The general advice for such calculations in the case of x-rays has been published elsewhere (e.g. Joiner 2004, Jones and Dale, 2008), but the additional effect of RBE must be included if there is any attempt to use (low LET) x-ray tissue tolerances or x-ray tumour control data. The alternative approach is to use only high LET α/β ratios within BED equations where the tolerance and tumour control BED values for the high LET radiation are known. These are subtle but important differences that will be considered in further detail within the ENVISION project.

4. **RBE and dose per fraction**

Early RBE experiments, especially studies using fast neutrons, with RBE values similar to carbon ion therapy, showed that RBE reduced with increasing dose per fraction, leading to potential clinical dangers for small fractions, or higher than expected bio-effects despite high LET dose fall off in normal tissues. Fall off of megavoltage x-ray dose causes a reduction in tissue dose per fraction; but fall off of high LET dose beyond a target volume may be, at least partially, compensated for by a higher RBE.

It is instructive to study figure 3, which shows the relationship between dose per fraction of neutrons and RBE for tissues with different α/β ratios: the overall change in RBE with dose per fraction is much less for biosystems with a high α/β than for those with a low α/β.

This was compiled using parameters derived from a variety of fast neutron experiments *in vivo* and on human cancer cells *in vitro* (Jones et al 2011a). Due to \( RBE_{\text{max}} \) being inversely related to the low LET α/β, and \( RBE_{\text{min}} \) being linearly related to the square root of α/β, there is a crossing over of the RBE values such that biosystems with a low α/β have the highest RBEs at low doses, but the lowest RBE at high doses. If a cell or tissue system does not have a clearly identified α/β ratio then the choice of dose per fraction around the cross over part of the curves would minimise RBE uncertainty.
Figure 3. Plot of RBE against dose per fraction of high LET radiation (based on fast neutron data sets) as in reference [Jones et al 2011]

There are important implications for clinical fractionation here, although these predictions must be better validated by further experimental studies. It is interesting to note that lowering the dose per fraction probably caused more toxicity in late reacting tissues in UK neutron trials. Also, there are suggestions from the Japanese ion beam centres that late side effects may be less prevalent with hypofractionated schedules. Such claims must however be subjected to prospective studies, since at present the hypofractionated regimens have the shortest follow up times and so may show bias. However, these findings are compatible with a hypothesis that the rank order of RBE values can be reversed according to the dose level, as in figure 3. In the case of the brain, with the lowest $\alpha/\beta$ of 2 Gy, this may be important, since the therapeutic ratio might be improved by hypofractionation as long as the brain RBE at large doses would be sufficiently lower than the tumour RBE. This may already explain some excellent outcomes at Heidelberg and GSI for skull base tumours compared with low dose per fraction protons in USA, although the shorter treatment time (<20 days) may also be operative in at least some tumours which may contain more rapidly growing clonogenic cells as may be found after repeated surgery and long intervals of time between the original diagnosis and definitive therapy. In contrast the Swiss PSI centre, has used protons with low dose per fraction and claimed favourable results also, but in their case the use of beam scanning techniques permits a more favourable physical dose distribution. All these results should eventually be subjected to rigorous comparative analysis using the BED with flexible RBE concept.

Major decisions are required in Europe before carbon ion dose per fraction is changed from a relatively fixed dose equivalent of around 3 Gy of photons.

The use of hypofractionation is increasing with newer photon treatments such as Gammaknife and Cyberknife and other robotic guided linear accelerator techniques. The possibility that normal tissue late toxicities would be reduced by using hypofractionated PCP therapy compared to these other photon based techniques, would be a reasonable starting point for clinical trials at some future time, but they would need to be guided by better and more specific data on RBE, leading to improved BED estimates.

Proton radiotherapy also needs some discussion here: the persistent use of a fixed proton RBE of 1.1, based on in vivo and in vitro experiments using rapid assays (Paganetti et al 2002, 2003), with a tendency to high $\alpha/\beta$ values, has a high chance of underestimating RBE values in late reacting tissues and in slowly growing tumours, as well as overestimating RBE in some very rapidly dividing systems such as cancers of childhood: the latter could lead to under-dosage in long fractionated schedules (Jones et al 2012). Scaling of the fast neutron RBE data down to protons can only be a rough estimate of how RBE might change with $\alpha/\beta$, but this is shown in figure 4. The reader is left to contemplate the potential differences compared to an RBE of 1.1, which remains the international world standard (Wambersie et al 2007), especially for $\alpha/\beta$ of 2 Gy (brain and CNS) and other late effects with $\alpha/\beta=3$Gy.
5. Effects of regions of higher and lower dose per fraction relative to the prescribed dose for different fractionation patterns.

The medical prescription refers to a volume of interest, normally the Planning target volume (PTV) where the prescribed dose often refers (e.g. in photon therapy) to the dose at the field intersection or other representative point such that the PTV is allowed to have a variation of dose by as much as -5% to +7%. Normally these percentages (expressed as 95% to 107% of the prescribed dose) do not deviate by these amounts, but with large field sizes and with difficult individual treatment geometry these figures are approached and rarely exceeded.

Homogenisation of dose has become increasingly possible due to intensity modulation in photon therapy and with similar approaches in PCP therapy due to beam scanning and weighting approaches. A deviation in dose will produce a changed biological effect, such that the surviving fraction will be multiplied each fraction; in the case of BED, which is derived as a logarithm, allows the BEds to be added for each fraction. For larger doses per fraction the biological deviation will be more significant, although fewer fractions are then given; for smaller doses per fraction the biological deviation will be smaller but will occur over a larger number of fractions.

Essentially, if $x$ represents the change in dose, then the low and high LET BED will be respectively

$$BED = xD_L \left( 1 + \frac{x d_L}{\left( \frac{\alpha}{\beta} \right)_L} \right)$$ \hspace{1cm} [5.1]$$

$$BED = xD_H \left( RBE_{max} + \frac{RBE_{max}^2 x d_H}{\left( \frac{\alpha}{\beta} \right)_L} \right)$$ \hspace{1cm} [5.2]$$

Where, for example, $x = 0.96$ for 96% of the prescribed dose (of 100%), and 1.05 for 105% of prescribed dose etc.

It is instructive to compare BED values for various values of $x$ in low and high LET radiations, for two tumours or tissues with $\alpha/\beta$=4 Gy and $\alpha/\beta$=8 Gy in Figure 4 (a and b). A non linear effect is apparent,
probably caused by the complexity of PCP radiobiology, where the RBE is inversely related to dose, with RBE ‘crossing-over’ effects (as in figure 3).

These high LET dose changes tend to oppose under-dose (since the BED ratios exceed unity at doses below the prescribed dose) and also protect against overdose (where the ratios are lower than unity), although only partial protection is given.

So, high LET can be considered to be more ‘forgiving’ in these respects. However, when figures 5 (a and b) are looked at closely, it can be seen that the $\alpha/\beta$ values change the order of these BED ratio plots for different fraction numbers, indicating the need for individual calculations of the BEDs in all cases.

Figure 5 (a and b). Ratios of high LET BED to low LET BED are plotted against percentage dose deviation (the factor $x$ expressed as a percentage), for a prescribed dose of 100%, and for different fraction numbers that provide isoeffective tumour control at the prescribed dose level for each fractionation schedule. The colour codes are red=1#, black=4#, blue=10#, grey=20# and green=37#. In figure (a) the tumour $\alpha/\beta$ is 4 Gy and in figure (b) it is 8 Gy.

(5a) 

\[
\alpha/\beta=4 \text{ Gy}
\]

(5b) 

\[
\alpha/\beta=8 \text{ Gy}
\]

It is important to note that the dose gradient across the tumour target volume may be different between an x-ray (photon) plan and a PCP plan, where greater uniformity can be achieved, although this is based on assumptions linking LET and RBE as in the work of Kanai et al in Japan where, from the example of a single field, the distal dose is down-weighted because of the increased LET due to a greater number of Bragg
peaks whereas the proximal part of the target contains more plateau dose regions with lower LET. Ideally, comparison of an averaged BED across the target volume should be used to compare high and low LET target volumes. Failure to do so may allow an advantage for either modality. For example, schematic proton (red line) and x-ray (green curve) dose distributions across a target volume are shown in figure 6. There is a dilemma as to what proton dose should be given to provide the same tumour control: should the proton dose be matched to the calculated average x-ray dose across the volume (as attempted here), rather than be close to the minimum or maximum x-ray dose. Techniques such the uniform equivalent dose of Niemierko (1997) may be of use in this dilemma.

Figure 6: Percentage dose across a planning target volume (PTV) of width 5 cm for protons (red) and x-rays (green).

6. Interpretation of RBE and fractionation effects within the ICRU framework of target volume definitions.

Among the most recent ICRU recommendations of radiation target volumes [8] for the treatment of a primary tumour using proton therapy (and MVRT), for which:

- Gross Tumour Volume (GTV, where tumour is present),
- Clinical Target Volume (CTV, where infiltrating tumour probably occurs), and
- Planning Target Volume (PTV, denoting a wider limit of the prescribed anti-tumour dose, consisting of two components: the internal margin (IM) required for physiological changes such as breathing and changes in GTV, CTV with time; and also SM, the margin required for patient positioning and beam alignment uncertainties.

A further volume (the OTV) – is in the present article defined as being the remainder of the patient outside the PTV. These volumes are shown together in figure 7, with two examples of critical normal tissues that exist either partially in PTV or entirely in OTV; these two differences represent the difficult and the ‘ideal’ treatment scenarios respectively.
Figure 7: Purely schematic diagram of zonal definitions relative to a body outline, where zone 1 is same as GTV, zone 2 is same as PTV, with two examples of organs at risk, OAR 1 which which falls partly within zone 2, and OAR 2 which is entirely in zone 3, which is also shown.

Table 1: Dose status for each zone and likely clinical outcome changes produced by Particle therapy compared with X-ray based therapy, where \( \uparrow \) is an increased dose, = is the ‘equivalent’ dose and \( \downarrow \) is a reduced dose for the CPT.

<table>
<thead>
<tr>
<th>Dose Status</th>
<th>Tumour Control in GTV and {CTV+PTV}</th>
<th>{CTV+PTV} side effects</th>
<th>OTV side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV(\uparrow),{CTV+PTV}(\uparrow), OTV(\downarrow)</td>
<td>much better***</td>
<td>worse*</td>
<td>better^p</td>
</tr>
<tr>
<td>GTV(\uparrow),{CTV+PTV}=, OTV(\downarrow)</td>
<td>better***</td>
<td>equal**</td>
<td>better^p</td>
</tr>
<tr>
<td>GTV=,{CTV+PTV}=, OTV(\downarrow)</td>
<td>equal**</td>
<td>equal **</td>
<td>better^p</td>
</tr>
<tr>
<td>GTV=,{CTV+PTV}↓, OTV(\downarrow)</td>
<td>worse</td>
<td>better^p</td>
<td>better^p</td>
</tr>
</tbody>
</table>

*In some instances reduced doses outside \{CTV+PTV\} may allow better radio-tolerance due to less vascular insufficiency caused by dose in OTV. Also, this condition may be acceptable in a non-essential tissue or for a small volume of essential tissue with little functional change.

**An equal status exists only if dose distributions and RBE are correct.

***Also, in some instances (the radiosensitive tumour classes), tumour control will be very high with x-rays and there will be no gain from dose escalation using any form of radiotherapy.

^p In these cases, a higher than expected RBE in the normal tissues could outweigh the dose advantage and cause equal or worse side effects as for photons/x-rays.

From the table 1, which includes logical conditional statements (essentially a ‘gedankenexperiment’ that is commonly used in theoretical physics but not in medicine), the potential usefulness and limitations of particle therapy can be seen in a useful way for practical guidance and for critical analysis of clinical data sets when these are available. The critical dependency on accurate knowledge of RBE is seen. It is self-evident that particle therapy is most useful in reducing dose to OAR in the OTV (as in column 4 in table 1).
That situation seems relatively simple. Even so, there may be such uncertainty in the RBE used, underestimating the true RBE, that there could be a reversal of the presumed physical dose advantage.

**Taking RBE uncertainty into account**

Where there is uncertainty as to the RBE of tumour or normal tissue, it can be shown that additional ‘safety’ can be introduced by imposing a tougher demand on treatment planning, essentially by increasing the normal tissue constraints. The combined effect of physical dose sparing and RBE can be incorporated in a single equation as an index, $S_I$ (Jones et al 2011, b).

$$S_I = \frac{P_H}{P_L} \times \frac{RBE_{norm}}{RBE_{tum}} \times \frac{(1 \pm \text{Error}_d)}{(1 \pm \text{Error}_z)}$$  \[6.1\]

Where $P_H$ is the physical dose sparing ratio (between normal tissue and tumour, i.e. normal tissue dose/tumour dose) with high LET, $P_L$ the dose sparing ratio achieved with low LET x-ray based techniques, with RBE of the normal and tumour tissue and the error in RBE to normal tissue ($\text{Error}_d$) receiving dose $d$ and the Error in RBE in tumour which receives dose $z$ ($\text{Error}_z$).

**Worked Example of allowing for RBE uncertainty**

Applying 25% errors to the above equation, then

$$S_I = \frac{P_H}{P_L} \times \frac{RBE_{norm}}{RBE_{tum}} \times \frac{(1 + 0.25)}{(1 - 0.25)} = \frac{P_H}{P_L} \times \frac{RBE_{norm}}{RBE_{tum}} \times 1.67$$

Accordingly, it is necessary to improve $P_H$ by 1/1.67=0.6 approximately, in order to maintain the same value $S_I$. If, for example, $P_H$ was 0.7, it must then be 0.7×0.6=0.42, which would be a further challenge to the treatment planning physicist!

The situation is more difficult than the above for important normal tissues (or organ at risk, OAR) that extend into the PTV (in this case $P_H=P_I$ in equation 6.1). For example, consider the optic chiasm (which caries all visual information between the eye and the brain), within the PTV of an adjacent tumour of the skull base, pituitary or supra-sellar region. The dose received by the OAR is then assumed to be the same as the tumour. If the OAR has a higher RBE than the tumour, then the OAR will be susceptible to radiation injury, depending on its tolerance level. The only way of reversing this adverse RBE condition would be to lower BED by changing dose-fractionation. In x-ray (photon) therapy it would be considered standard practice in conventional low LET radiotherapy to use greater fractionation (hyperfractionation). However, high LET treatment hyperfractionation will be associated with a higher RBE; the alternative course of action would be to consider the opposite – hypofractionation, since the RBE may fall. Indeed, the RBEs between the two systems (tumour and OAR may reverse as show previously in figure 3.

**Worked example of fractionation effects for critical normal tissue included in PTV.**

A normal tissue such as optic chiasm with $\alpha/\beta=2$ Gy falls within the PTV of a slow growing tumour with $\alpha/\beta=4$ Gy. Assume tumour RBE limits are 4 and 1.4 respectively, with normal tissue RBE limits of 6 and 1.25. Ideally the tumour should receive a dose equivalent to 72 Gy in 36 fractions of megavoltage x-rays and the tolerance of the chiasm is 50 Gy in 25 fractions with $\alpha/\beta=2$Gy.

Tolerance BED = (50 (1+2/2) = 100 Gy [2]

Intended tumour BED = 72(1+2/4)=108 Gy [4]

The estimated doses per fraction to preserve a tumour isoeffect equivalent to 72 Gy in 36 fractions for 5, 15, 25 and 35 fractions are: 3.71, 1.52, 0.97, and 0.71 Gy. These schedules provide an OAR BED of 165.20, 163.60, 163.08, and 162.82 Gy [2] respectively.

It can be seen that the schedules with fewer fractions (and larger fraction sizes) produce the largest BED values in this case, so that the effect of a fall in RBE with dose per fraction does not ‘rescue’ the problem.
Also, all BED values exceed tolerance. Also, if a lower dose then has to be given (at least to a part of the tumour adjacent to the OAR), it is necessary to check tumour BED values.

Then, for 1, 2, 3, 4, 5 and 6 fractions (considering the case of extreme hypofractionation) we have – to maintain an isoeffect for the normal tissue tolerance level, $d_H$ doses of 8.11, 5.03, 3.74, 3.00, 2.51, and 2.17 Gy respectively. These schedules give tumour BED values of 64.64, 65.10, 65.37, 65.56, 65.69, 65.80 Gy [4] respectively. These are considerably less than the intended value of 102 Gy [4]. It can be seen that, in this example, increasing the number of fractions improves the tumour BED. This is because the tumour $\alpha/\beta$ is larger than the OAR $\alpha/\beta$.

If it is decided to undertreat part of the tumour PTV but accept an higher dose to the chiasm equivalent to 56 Gy in 28 fractions, then we obtain

In 5, 10, 15, 20, 25, 30 and 35 fractions, to preserve this OAR isoeffect the tumour control BED will be 73.50, 73.92, 74.12, 74.23, 74.30, 74.36 and 74.40 Gy [4]. Again it can be seen that increasing fractionation is slightly better for tumour control, but it is interesting to note that the equivalent dose for conventional x-ray tumour control to 74 Gy [4] is 49.33 Gy in 2 Gy fractions.

Alternatively if the number of fractions is further increased to 40, and we accept a reduced tumour BED of say 85 Gy [4], this can be achieved by a dose per fraction of 0.5 Gy, but this gives 127.8 Gy [2] as a late effect BED. Another attempt might be to use 40 fractions to give the expected tolerance level of 100 Gy [2], which requires a dose per fraction of around 0.4 Gy, but then the tumour BED falls to be equivalent to 44.75 Gy in 2 Gy fractions.

So, the therapeutic window is not good and it would be reasonable not to proceed with particle therapy in this instance. In practice, a ‘small amount’ of tumour is sometimes given a reduced BED, sufficient to respect the tolerance of the chiasm.

7. The use of the LQ model with large fraction sizes.

It is known that deviations from the LQ model occur in some cellular systems at doses above 6-8 Gy. Some modellers apply linear models above a certain threshold dose and extrapolate the effect to higher doses. There is no entirely satisfactory method to overcome this. However, it is important to realise that the increasing cell survival slope with dose provided by the LQ model can be considered to be an advantage when assessing normal tissue effects since the LQ inevitably provides the ‘worse case scenario’ and is consequently protective on normal tissues. Deviations from the model matter less for tumour with high $\alpha/\beta$ and for very high LET radiations since the cell survival curves have reduced curvature compared with low LET radiations.

8. Optimisation of fractionation using calculus methods

It is, in principle, possible to study tumour cell kill for an equivalent normal tissue toxicity grading or intensity level. A variety of mathematical techniques could be used such as numerical analysis or, most conveniently, graphical methods. However, relatively simple differential calculus can be used provided the discontinuous fraction number parameter $n$ is replaced by a function of overall time ($t$) and the mean inter-fraction interval ($f$). The approximation

$$t=f(n-1) \quad [8.1]$$

can be used to replace $t$ and then $n$ can be replaced by the normal tissue BED(NT) where

$$BED = n d_H \left( RBE_{\text{max}} d_H + \frac{RBE_{\text{max}}^2 d_H}{k} \right) \quad [8.2]$$

Where, for convenience, $k$ is now the late reacting NT $\alpha/\beta$ ratio, so that
\[ n = \frac{\text{BED}}{d_H \left( RBE_{\text{max}} + \frac{RBE_{\text{min}}^2 d_H}{\alpha / \beta} \right)} \]  

[8.3]

The dose per fraction \( d_H \) will be used as \( d \) from now.

With a repopulation correction factor included we know that

\[
Kt dRBE RBE nd BED_tum - \frac{\alpha}{\beta}_{\text{num}}
\]

\[ [8.4] \]

Then using the replacement given in equation 8.1, we obtain

\[
BED = nd \left( RBE_{\text{max}} + \frac{RBE_{\text{min}}^2 d}{\alpha / \beta}_{\text{num}} \right) - Kt
\]

[8.5]

And then replacing \( n \) by equation 8.3, and defining \( z \) as the tumour dose and \( d \) the normal tissue dose (where \( d = gz \)) which leads to:

\[
BED = \frac{\text{BED(NT)}}{d \left( RBE_{\text{max}} (NT) + \frac{RBE_{\text{min}}^2 (NT)d}{k} \right)} \cdot \frac{\left( RBE_{\text{max}} + \frac{RBE_{\text{min}}^2 d}{\alpha / \beta}_{\text{num}} \right) - Kf \left( \frac{\text{BED(NT)}}{d \left( RBE_{\text{max}} (NT) + \frac{RBE_{\text{min}}^2 (NT)d}{k} \right)} - 1 \right)}{z}
\]

[8.6]

Of course, if the normal tissues receive very low LET radiation, when the RBE factors will be close to unity, we can simplify as

\[
BED = \frac{\text{BED(NT)}}{d \left( 1 + \frac{d}{k} \right)} \cdot \frac{\left( RBE_{\text{max}} + \frac{RBE_{\text{min}}^2 d}{\alpha / \beta}_{\text{num}} \right) - Kf \left( \frac{\text{BED(NT)}}{d \left( 1 + \frac{d}{k} \right)} - 1 \right)}{z}
\]

[8.7]

The normal tissue dose per fraction symbol, \( d \), can in all cases be replaced by \( gz \). Then, a maximum tumour BED (which is proportional to tumour cell kill) while preserving the same normal tissue response occurs only when

\[
\frac{d(BED)}{dz} = 0
\]

[8.8]

This last equation can be solved easily using mathematical software and is, very interestingly, independent of the actual normal tissue BED constraint, but does include the normal tissue \( a/\beta \) (given the symbol \( k \)). Plots of BED in this form show that optimum turnover points are found especially when the normal tissues sparing increases (low \( g \) values) as shown in figure 8.
Figure 8: Plot of tumour BED for an equal late normal tissue isoeffect against tumour dose per fraction using the equations given above and parameters as in previous worked examples.

In these plots it has been assumed that – from empirical data – the $\alpha/\beta$ ratio of the tumour is approximately 50 divided by the tumour cell doubling time and that the low LET $\alpha$ parameter is approximated by $0.03 \times \alpha/\beta_{[\text{tumour}]}$. This gives a reasonably realistic relationship between cell proliferation, fraction sensitivity and cell doubling rates for tentative modelling purposes. In other words, a larger tumour $\alpha/\beta$ is consistent with faster repopulation and greater radiosensitivity and vice versa. The other assumptions made were tumour $RBE_{\text{max}} = 2 + 20/k_{\text{tum}}$, tumour $RBE_{\text{min}} = 0.9 + 0.2 \sqrt{k_{\text{tum}}}$, five fractions a week can only be given, the normal tissue $RBE_{\text{max}}$ is 7 with $RBE_{\text{min}} = 1.2$. It can be seen that there are subtle turnover points between 0 and 5 Gy.

Plots of the estimated optimum $z$ are shown in figure 9, where it can be seen that the required dose per fraction increases with tumour $\alpha/\beta$ (as represented by $k_{\text{tum}}$), due to increased tumour cell proliferation rates, and also increases with improvement of treatment geometry (a lower $g$ value) and vice versa.

For this set of parameters and the other assumptions made, hypofractionation (to very high doses) is predicted to be a better option for conditions of good normal tissue sparing and for more rapidly growing tumours. Such calculations can only be a rough guide and it would be essential to take further measures to ensure excellent results: the aim should always be give the lowest possible normal tissue dose consistent with the highest tumour BED. So, individual calculations will always be required. However, useful trends emerge such as the requirement of a higher dose per fraction for more rapidly growing tumours (with higher $\alpha/\beta$ ratios); the alternative would be to provide twice daily fractions using a lower dose per fraction ($f$ is then shorter, around 0.78 days for say 10 fractions per week).
These interesting findings, however, need verification and testing by in vivo animal experiments, using implanted human tumours, are necessary to search for such effects, as well as careful phase I and II dose fractionation studies. Extrapolation of the interesting dose fractionation results from Japan to Europe in carbon ion therapy is not easy, owing to the different assumptions made in the dose calculations. International uniformity must be encouraged.

A particular problem associated with the calculus method is that parameters used must represent the average values during treatment and cannot easily be changed during treatment. This creates a difficulty with accelerated repopulation, although this is only relevant perhaps to squamous cell cancers (SCC) treated over durations longer than 28 days. Slower growing tumours have less significant repopulation factors and, in any case, ion beam therapy is normally completed well within this time frame. The present author considers it a mistake to assume that there is no repopulation up to 28 days even in SCC, for there is always cellular turnover even if this is at a lower rate.

9. Model variants

Clinicians especially should be aware of two classes of models that can assist with RBE determination, and therefore fractionation issues:

A. Bottom up models: microdosimetry studies, such as the local effect model, based on LET values, together with assumed or measured (the so called low level) sub-cellular and cellular parameters allow prediction of RBE, although remain to be perfected, but will be essential in the future to guide choice of dose, and to deliver the correct dose and so aid treatment planning by application on a voxel to voxel basis etc.

B. Top Down models: these include high level parameters (at the clinical level) such as the BED and $\alpha/\beta$ related work discussed above. They link our present knowledge of clinical radiobiology with fractionation phenomena and can be applied usually in worse case scenarios where it is usually assumed that LET remains high. These are an effective check for the clinician, who should be able to perform such calculations and understand their implications and limitations.

Obtaining a model that contains the entire scale of the problem must remain a future goal. This type of challenge exists in many parts of science, including physics where the separate quantum and gravitational models have yet to be unified in a single framework, despite each model being highly accurate in their own domains. However, there are some realistic assessments of the use of $\alpha/\beta$ to obtain RBE alongside other
microdosimetry related models as in Japan and Germany (Scholz et al 2006, Kasai et al 2011), for example to predict brain RBE using $\alpha/\beta=2$ Gy.

10. Other fractionation contributions

No account of fractionation would be complete without mention of these other important mechanisms that influence fractionation effects. Fractionation is often taught as being dependent on several factors beginning with R, including Radiosensitivity, Repopulation, Reoxygenation, Repair, Reassortment (of the cell cycle). The $\alpha/\beta$ ratios used, if derived from clinical data, probably inherently include all these processes. We have already discussed repair and that $\alpha/\beta$ is the ratio of radiosensitivities, along with the different susceptibility of $\alpha$ and $\beta$ to changes in LET.

Reoxygenation rates are thought to be rapid in most tumours, with perhaps sarcomas, high grade gliomas being exceptions. Much will depend on tumour and vascular supply responsiveness, but there is insufficient knowledge of the rate of reoxygenation in individual tumours at the present time. This key rate can in theory influence the potential outcomes of therapy even in the case of PCP (Dale and Jones, 2007 [see book reference]). A single fraction offers no time for reoxygenation and even two fractions (given daily) will suffer from the fact that the second fraction will contain a greater fraction of hypoxic cells. The minimum time for significant although incomplete reoxygenation might be a week, consistent with 4 fractions given over 4-5 days. A greater number of fractions also might carry an advantage in the case of hypoxia caused by cyclical opening and closing of blood vessels in a tumour, since the volume of tumour treated during a hypoxic phase is expected to be less.

Reassortment of the cell cycle was thought to be important, since high LET radiations exhibit less variation in radiosensitivity in the different phases of the cell cycle and so increasing fractionation would not be so important. This was established for neutron therapy but it is an effect which is mostly seen at low dose; higher doses which produce much lower surviving fractions appear to show less change with cell cycle position (see Catterall and Bewley 1979), presumably since the cell kill then follows the type B ($\beta$-related) cell kill process, which has a lower RBE ($\text{RBE}_{\min}$). Such an effect will apply to both normal tissues and tumours.

The results obtained by Fowler and colleagues, in terms of an improvement in tumour control for x-rays by extending the number of fractions beyond a single fraction were consistent with cell cycle reassortment and reoxygenation, in a tumour where reoxygenation was known to be almost complete in three days after a large single dose. The use of fast neutrons gave just as high a tumour control as the optimum dose per fraction and treatment time even if given in a single fraction because of their reduced dependency on hypoxia and perhaps to a lesser extent on cell cycle position.

Repopulation factors can be used for unintended treatment gap corrections, as discussed previously and included in overall BED calculations for longer treatment schedules. However, since most ion beam treatments do not at present extend beyond a month, this is considered unnecessary in most tumour types. However, the use of ion beams as a boost after IMRT will usually cause treatment time to be more prolonged.

What if radiobiological parameters change during irradiation? We assume that the parameters used in fractionation calculation are the average values during radiotherapy. Where abrupt changes occur it may be necessary to use different forms of mathematics such as summations or series expansions -see appendix A.

The effect of irradiated normal tissue volumes has only been considered briefly above: the precise location of the radiation relative to the 3-D vascular supply of organs may yield further useful data that will permit more selective particle radiotherapy with reduction in normal tissue complications.

Another ‘contribution’ to the effective BED values would be those of chemotherapy, age, surgery etc, which can provide a further increment in cell kill or susceptibility to radiation effects. In principle, these can be represented by a variable BED increment as shown elsewhere (Jones, Dale and Gaya, 2006).

One further issue is malignant induction. It has been argued that the most protective effect of PCP therapy is a reduction in normal tissue cell numbers exposed to radiation, especially since RBE effects can increase the
risk of malignant induction in individual cells. This effectively means that particle radiotherapy should only use the lowest number of treatment fields which meets with the treatment aims and tissue constraints. In principle, fractionation may alter the yield of malignant cells in some hypofractionated cases if the ‘turnover points’ of malignant induction rates are exceeded and cell killing rather than malignant induction then dominates. Much further work is required in this area, although the changes are likely to be small and must be assessed together with any detriments in tumour control or normal tissue side effects that could occur. (Jones 2009, Timlin et al 2011)

PART B - Representative treatment plans for different fractionation schemes

We report here several exemplary particle radiotherapy treatment plans performed for different fractionation schemes and sensitivity ($\alpha/\beta$) scenarios between target and normal tissue.

The plans were optimized with the treatment planning system (TPS) for particles TRiP98 (Kraemer et al. 2000, Kraemer et al. 2012), developed at GSI, using carbon beams, mostly with two opposed fields, for several patient examples.

TRiP98 biological optimization is using the local effect model (LEM) (Scholz et al. 1994, Elsaesser et al. 2010) for producing the initial intrinsic $R_{BE_{max}}$ tables, which are then combined with different models for obtaining the final biological effect of the mixed radiation field (Kraemer and Scholz 2000, Kraemer and Scholz 2006). In the first set of examples the version LEM II (Elsaesser et al 2007) is used. The physical dose calculations were performed with the different algorithms available in the program according to the required accuracy in the different cases.

For all the patient cases, dose profiles as fraction of the planned RBE weighted dose, as well as BED maps are shown, normalized to the BED in the target. For the latter, BED at any voxel are computed according to equation 3.4 from the (RBE weighted) dose cubes $D_{bio}(x,y,z)$, which are output from the program. It is important to note that eq. 3.5, connecting directly the BED to the ion physical dose is only valid for a monoenergetic ion beam where the LET is fixed and arising from a single ion contribution. It is not directly applicable in a mixed beam field, where the RBE contributions of the single beam elements (in particle type and energy) are combined in a complex way as accounted in TRiP98 (see e.g. Kraemer and Scholz 2006).

Dose volume histograms (DVHs) are also provided for each configuration, and for both above mentioned quantities, with several organ at risks (OARs) included, where the different fraction sizes are shown by different linestyles. The fraction sizes were taken consistent to those of the example of section 3.2; the ($\alpha/\beta$) ratios for the target, ($\alpha/\beta)_T$, and for the normal tissue, ($\alpha/\beta)_N$, were chosen in different combinations to map different realistic situations, keeping into account the collection provided in D.JRA5.8 and also according to the available RBE tables in use.

We conclude this section with an overview of the impact of fraction doses on different planning approaches.

1. Head tumours

In figures 10, 11, 12 and 13 we plot the case of a head tumour, with regular shape (cranial example A), irradiated with two opposed lateral fields (180º irradiation angle).

In the first setup (fig.10), with tumour more sensitive than normal tissue, as visible from the DVHs, as well as from the entrance channel isolevels, the dose to normal tissue slightly increases with fraction size, while the BED slightly decreases. In the iso-sensitive configuration (fig.11), instead, BED is constant, as expectable, while the increase in the dose plots is more pronounced. For ($\alpha/\beta)_T < ($\alpha/\beta)_N (fig.12) also the BED start to increase with the fraction size, and for a larger difference of sensitivity (10 to 2, fig.13), the BED increase becomes also relevant.

A similar situation is verifiable in a different patient case, with a more complex tumour shape (patient B, figs 14-15), where we show only two opposite sensitivity configurations ($\alpha/\beta)_T =2$, ($\alpha/\beta)_N=1$ and ($\alpha/\beta)_T =2$, ($\alpha/\beta)_N=3$. The new feature here appearing is that for the BED plots also the target dose conformity is slightly spoiled with increasing fraction size in the first configuration (fig.14).
Figure 10. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a cranial tumour (patient A): \((\alpha/\beta)_{T}=2\text{Gy} \ (\alpha/\beta)_{N}=1\text{Gy}\), prescribed dose from top to bottom: 2, 3, 4 GyRBE.
Figure 11. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a cranial tumour (patient A): \((\alpha/\beta)_T=2\text{Gy}\) \((\alpha/\beta)_N=2\text{Gy}\), prescribed dose from top to bottom: 2, 3, 4 GyRBE
Figure 12. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a cranial tumour (patient A): $(\alpha/\beta)_T=2\,\text{Gy}$ $(\alpha/\beta)_N=3\,\text{Gy}$, prescribed dose from top to bottom: 2, 3, 4 GyRBE
Figure 13. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a cranial tumour (patient A): \((\alpha/\beta)_T=2\text{Gy} \quad (\alpha/\beta)_N=10\text{Gy}\), prescribed dose from top to bottom: 2, 3, 4 GyRBE.
Figure 14. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a cranial tumour (patient B): (α/β)$_T$=2Gy (α/β)$_N$=1Gy, prescribed dose from top to bottom: 2, 3, 4 GyRBE.
Figure 15. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a cranial tumour (patient B): \((\alpha/\beta)_T=2\text{Gy} \ (\alpha/\beta)_N=3\text{Gy}, \text{prescribed dose from top to bottom: 2, 3, 4 GyRBE.} \)
2. Prostate tumours

The prostate tumour cases, being more deep-seated, were planned using the multiple scattering algorithm, which describes the pencil beam with 2 lateral Gaussian profiles.

In figures 16-18 we plot a test (patient C) similar to the above reported for example A-B, with several dose fractions (1,2,3,4 8 GyRBE).

The results are also similar in the trend to the cranial cases, but show sensible differences: In the first case (fig.16), \((\alpha/\beta)_T=2\) Gy \((\alpha/\beta)_N=1\) Gy, the BED in normal tissue (and organs at risk) is more drastically decreasing with the increase of the fraction size, and the dose to normal tissue is also presenting a slight decrease, inversely to what seen in the analogous cranial cases. In the iso-sensitive configuration BED is again almost constant, while the RBE-weighted dose increases. For \((\alpha/\beta)_T=2\) Gy \((\alpha/\beta)_N=3\) Gy, finally, also the BED shows a slight increase with the fraction size.
Figure 16. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a prostate tumour (patient C): $(\alpha/\beta)_T=2\text{Gy}$  $(\alpha/\beta)_N=1\text{Gy}$, prescribed dose from top to bottom: 1, 2, 3, 4, 8 GyRBE.
Figure 17. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a prostate tumour (patient C): \((\alpha/\beta)_T = 2\text{Gy} \quad (\alpha/\beta)_N = 2\text{Gy}\), prescribed dose from top to bottom: 1, 2, 3, 4, 8 GyRBE.
Figure 18. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a prostate tumour (patient C): $(\alpha/\beta)_T=2\text{Gy}$ $(\alpha/\beta)_N=3\text{Gy}$, prescribed dose from top to bottom: 1, 2, 3, 4, 8 GyRBE.
3. Head and Neck tumours

In figures 19-26, finally, we show two patient examples for Head and Neck tumours (D and E). In this case, a part of lateral opposed beams we consider also irradiation with the Marburg set up using oblique nozzle (45° irradiation angle), to evaluate a possible impact from irradiation angle selection.

We present this analysis for two inverse sensitivity scenarios, \((\alpha/\beta)_T=2\) Gy, \((\alpha/\beta)_N=3\) Gy and \((\alpha/\beta)_T=5\) Gy, \((\alpha/\beta)_N=2\) Gy, for 2 fraction doses (2 and 4 GyRBE).

While a general better sparing of the healthy tissue is always evident for the oblique nozzle irradiation as compared to the lateral opposed fields, the impact of fraction doses is very similar, with an almost constant BED and slightly increasing dose in the first set up and a slight decrease of BED in the second.

The only appearing difference is in the dose behaviour in the second setup, which for the oblique irradiation slightly increases and for the lateral one slightly decreases.

![Figure 19. RBE-weighted Dose(left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient D): \((\alpha/\beta)_T=2\) Gy \((\alpha/\beta)_N=3\) Gy; oblique nozzle beams, prescribed dose from top to bottom: 2 and 4 GyRBE.](image-url)
Figure 20. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient D): \( (\alpha/\beta)_T = 5\text{Gy} \) \( (\alpha/\beta)_N = 2\text{Gy} \), oblique nozzle beams, prescribed dose from top to bottom: 2 and 4 GyRBE.
Figure 21. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient D): \( (α/β)_T=2\text{Gy} \ (α/β)_N=3\text{Gy} \), lateral opposed beams, prescribed dose from top to bottom: 2 and 4 GyRBE.
Figure 22. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient D): $(\alpha/\beta)_T=5\text{Gy}$ $(\alpha/\beta)_N=2\text{Gy}$, lateral opposed beams, prescribed dose from top to bottom: 2 and 4 GyRBE.
Figure 23. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient E): $(\alpha/\beta)_T=2\text{Gy}$, $(\alpha/\beta)_N=3\text{Gy}$, oblique nozzle beams, prescribed dose from top to bottom: 2 and 4 GyRBE.
Figure 24. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient E): \((\alpha/\beta)_T=5\text{Gy} \ (\alpha/\beta)_N=2\text{Gy}\), oblique nozzle beams, prescribed dose from top to bottom: 2 and 4 GyRBE.
Figure 25. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient E: $(\alpha/\beta)_R=2\text{Gy} \quad (\alpha/\beta)_T=3\text{Gy}$, lateral opposed beams, prescribed dose from top to bottom: 2 and 4 GyRBE.
4. Impact of fraction dose on plan robustness

We also present here briefly the specific effect of fraction size on different irradiation conditions.

As for robustness, several tests were performed at UNIMAR, partially reported in Jelen et al.2012, to try to elucidate if the fraction size could have a specific impact on a plan robustness, after different type of alterations performed to the irradiation geometry.

In a first set of phantom tests it was evaluated the effect for a drastic alteration due to insertion of a bony heterogeneity (Fig.27). In this case it appear that the lower fraction size has more drastic impact, as a direct consequence of its steeper dose profile.

A similar effect was also investigated on a patient irradiation (prostate, fig. 28) for alteration due to misplacement. This was simulated by recalculation in a presence of a posterior shift of the prostate of 1 cm compensated with isocentre realignment.

In this case the effect of different fraction doses is extremely small, with a very thiny increase in dose to healthy tissue for larger dose fractions (~1%).

Figure 26. RBE-weighted Dose (left) and BED (right) profiles (as fraction of target dose) and DVHs for a head-and-neck tumour (patient E): $\alpha/\beta=5\text{Gy}$ $\alpha/\beta=2\text{Gy}$, lateral opposed beams, prescribed dose from top to bottom: 2 and 4 GyRBE.
Figure 27. Plans optimized in homogeneous phantom (left) and recomputed with bony heterogeneity inserted (right) for prescribed doses 0.5, 1, 3 and 8 GyRBE (top to bottom), on the right panel a collective view of the doses profiles for different fractions.
Figure 28. Plans optimized (left) and recomputed in presence of posterior prostate shift of 10mm and compensated with isocentre realignment (right), for prescribed doses 1.8, 3, and 8 GyRBE (top to bottom).
5. Impact of fraction dose on best particle choice

As initially argued by Brahme 2004 and shown recently by Remmes et al. (2011), the fraction size may play an important role also for the optimal choice of a given particle for irradiation, according to different sensitivity scenarios.

In their study, Remmes et al. after showing quantitatively the known general trend of carbon ion to be more convenient than lower Z particles in radioresistant tumours scenarios, and the inverse effect in opposite configurations, they tested the impact of different fraction doses in normal tissue sparing (fig.29). They used the Microdosimetric Kinetic model (MKM), which has been recently introduced at NIRS in treatment planning, for the biological dose calculations, and considered a passive scanning spread out Bragg peak (4 cm) irradiation.

![Graph showing isoeffective doses for different (α/β)T, (α/β)N combinations](image)

*Figure 29: (Remmes et al. 2011) Isoeffective doses for different \(\frac{\alpha}{\beta}\)T, \(\frac{\alpha}{\beta}\)N combinations, left full surface for a target dose of 2Gy, right for 2 different fraction doses and several ions*

<table>
<thead>
<tr>
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<th>2.2</th>
<th>2.10</th>
<th>10.2</th>
<th>10.10</th>
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<tr>
<td>2 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>1.22</td>
<td>1.22</td>
<td>1.12</td>
<td>1.12</td>
</tr>
<tr>
<td>(^{3})He</td>
<td>1.43</td>
<td>1.50</td>
<td>1.17</td>
<td>1.24</td>
</tr>
<tr>
<td>(^{12})C</td>
<td>1.87</td>
<td>2.26</td>
<td>1.26</td>
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</tr>
<tr>
<td>5 Gy</td>
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</tr>
<tr>
<td>p</td>
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<tr>
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<tr>
<td>(^{12})C</td>
<td>1.34</td>
<td>1.48</td>
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</tbody>
</table>

*Figure 30: (Reinhart et al. 2012) Left Table: Peak (extended target of 4cm) to entrance RBE ratio for different setup \(\frac{\alpha}{\beta}\)N, \(\frac{\alpha}{\beta}\)T and nominal dose fraction size (2 and 5 GyRBE) for different ions. Right, doses to normal tissue*
Their finding is that different fraction sizes just change the absolute values and shrink the differences, but don’t induce any inversion of trend.

However, a similar study was recently initiated also at GSI, for active scanning system and the TRiP98/LEM approach. The preliminary results, reported in Reinhart et al.2012, for an active irradiation of a target with the same size of the SOBP used in Remmes, suggest a more complex behaviour, as a function of particle type, where the lower Z particles may be more advantageous for selected cases even for $\alpha/\beta_T < (\alpha/\beta)_n$ (fig.30).

6. Impact of fraction dose on hypoxia irradiation.

With the new implementation of TRiP98 called TRiP-OER (Scifoni et al. 2013), also extensively discussed in DJRA5.3-4, we recently introduced the specific possibility to irradiate hypoxic tumours by keeping into account heterogeneous intra-tumour sensitivity, induced by regions of different oxygen concentration ($pO_2$).

In that case we cannot anymore consider the RBE-weighted dose as a relevant quantity, since the full biological effect in the target is a combination including also the oxygen enhancement ratio (OER). Thus we focused on an overall effect-based optimization. The new extension, in fact, allows to restore a uniform survival level in the inhomogeneous target.

We now show a simple test of irradiation with different fractionation schemes also in this case.

We considered a phantom composed by 3 different oxygenation levels (see inset of figure 31), irradiated by two opposite fields. The tissue sensitivities are taken consistent to those used for in vitro biological dosimetry experiments with CHO-K1 cells: $\alpha/\beta_T = (\alpha/\beta)_n = 10$. There, a plan optimized disregarding the intratumour inhomogeneity due to hypoxia, would produce a survival profile such as the dotted line in the figure. OER optimized plans through TRiP-OER, instead, will deliver in general more dose in the entrance channels, but will be able to compensate the different increased radioresistences of the different hypoxic compartments.

By accounting for an iso-effect irradiation, we got that 7 fractions of 1.3 GyRBE would lead to the same overall survival effect in the target than a single fraction of 6.5 GyRBE (10%). The two OER-optimized plans are inducing an asymmetric profile in the entrance channels due to the asymmetry of the oxygen concentration in the target. The application of the smaller fractions improve slightly the effect in the normal tissue in the more critical channel.

![Survival level](image)

**Figure 31**: OER optimized plans on a phantom with an heterogeneous tumour, composed by regions at different oxygen concentration ($pO_2$ in the inset) with different fraction sizes, 2 lateral opposed beam. A plan optimized disregarding the hypoxia induced heterogeneity and recomputed on the same phantom is also shown (dotted line).
7. Impact of fraction dose on moving targets irradiation

For completeness we briefly show also the effect of different fractions on moving target irradiation, an issue which is of great importance and is discussed in more detail in WP4. In fact, despite initial promising clinical results on hypofractionation of lung cancer obtained at NIRS (Miyamoto et al. 2007), it was argued that the latter approach would not be generally suitable in connection to motion mitigation approaches.

This problem was investigated at GSI by Woelfelschneider et al. (2012), who assessed the variation of dose coverage (mainly on a DVH level analysis for different fractionation schemes of a moving lung tumour. Calculations were performed with TRiP98, in its 4D extension (Bert et al. 2007). The overall effect was accounted for by summing all the contribution of the different fractions. It is shown that lower fraction numbers produce a less steep profile and a larger uncertainty, thus suggesting a less suitability in treatment of similar tumours (figure 32). On the other hand, while the dose conformity improves substantially, the uncertainty remains considerable also for a high number of fractions.

![Figure 32](image)

**Figure 32. (Woelfelschneider et al. 2012) Whisker-Box plot of DVHs after 1, 5 and 10 fractions, of scanned carbon beam irradiation on a moving lung tumour.**

**CONCLUSIONS**

As expected, from the reported tests we did not see, in general, a remarkable effect of fractionation in particle therapy as it happens for conventional X-ray radiotherapy. Still, significant differences arise for different sensitivity scenarios, suggesting the possibility to reduce the fraction numbers – and then to exploit hypofractionation – just in some cases. Moreover, the full assessment of this effect is not complete at the present time. In particular, the perspective of using a mixed modality irradiation (see DJRA5.5), e.g. photons plus ion boost, where fractionation effects of photons and ions are collectively playing a role, drive efforts of further research for treatment planning oriented to BED assessment and optimization.

Further fractionation tests can be performed for different ions and/or different oxygenation levels, keeping into account more complex processes, resulting in a different target status along the different fractions, such as shrinkage and reoxygenation.

**Summary & Recommendations**

Fractionation of high LET PCP therapy imposes challenges and opportunities to improve and optimise therapeutic index and cost effectiveness, given that hypofractionation, even if applicable in only some clinical situations, will allow greater patient throughput. This can be achieved by further experimental RBE and fractionation programmes, eventually leading to carefully constructed and conducted clinical trials that will compare PCP fairly with low LET radiotherapy alternatives.
There also needs to be greater understanding of the radiobiological principles and new opportunities to calculate isoeffective treatments. The numerical tools for such research are already available, using both bottom up (e.g. micro-dosimetry) and top down (classical radiobiology) modelling techniques. The computational approach may rely on versatile tools like TRiP98. In fact, the presented formalisms may be successfully introduced in the above mentioned treatment planning system.

Fractionation, even of photon (x-ray based therapy) is complex and the further inclusion of changes in radiation quality (RBE), itself dependent on multiple input variables, adds to the complexity. It should also be considered that the growing understanding of radiosensitivity on mechanistic bases, and ways how to modify it, promises not only more accurate prediction of RBE, but even to selectively increase a tumour RBE, e.g. by using radiosensitizers, thus modifying the scenarios presented above. All these will be crucial steps for a maximally safe use of PCP therapy. In the meantime it is desirable to perform in vivo experiments (which reflect human tissue tolerances) to determine the full limits of RBE ($RBE_{\text{max}}$ and $RBE_{\text{min}}$) for a wide range of different values of LET in late reacting tissues such as brain, spinal cord, kidney, lung, heart, bowel, bone etc. This is a major task that will require cooperation across Europe and in the world (not only in cancer therapy, but also in radioprotection etc.).

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Appendix: Series expansions in fractionation

Assume effective dose, or some factor which modifies dose (such as hypoxia), increases each fraction according to a factor \( Q \), where \( f \) is time interval between fractions and \( z \) is the parameter linking \( Q \) with \( f \) as part of an exponential function, with cumulative BEDs being as follows

\[
Q = e^{z \cdot f}
\]

\[
BED = d[1 + d/k] + dQ[1 + \frac{dQ}{k}] + \ldots + dQ^{(n-1)}[1 + \frac{dQ^{(n-1)}}{k}]
\]

\[
BED = d[1 + Q + Q^2 \ldots + Q^{(n-1)}] + \frac{d}{k}[1 + Q^2 + Q^4 \ldots + Q^{(2n-1)}]
\]

\[
\text{series1} = \frac{Q^n - 1}{Q - 1}; \text{series2} = \frac{Q^{2n} - 1}{Q^2 - 1}
\]

\[
BED = d(\text{series1}) + \frac{d}{k}(\text{series2})
\]

as in Dale & Jones (1994), which used a different dose each fraction which depended on a time function related to the tumour shrinkage rate.