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D.5.8 – Table of alpha/beta values depending on initial sensitivity and fractionation scheme

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WP n° and title: WP5 – Adaptive Treatment Planning
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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
PUBLISHABLE SUMMARY

For ion therapy, the choice of an appropriate fractionation scheme is a task that is even more crucial than in conventional radiotherapy. This stems from the change in radiobiological properties of ion fields with penetration depth, with further variations in different irradiated tissues and tumour types.

In order to describe the basis of how to calculate biological effective dose model methods to maintain particle therapy isoeffects, the first part of the report presents a critical collection of $\alpha/\beta$ ratios together with how these important ratios are used within formulae which incorporate the relative biological effect concept for different radiation qualities. In the second part an analysis of compensation for unintended treatment interruptions is reported, with worked examples, leading to the following conclusions:

- It can be appreciated that an individual approach should be used, although formulaic methods can also be devised for precise compensation for either the tumour or the normal tissue isoeffect. However, compromise solutions are inevitably required and individualisation is consequently essential.
- Ideally such corrections should be done by persons who will practice and become used to these approaches, as there are many potential pitfalls.
- It has even been suggested that nation states should organise their own referral system for doing such calculations, although worldwide solutions and more global governance are feasible alternatives in an electronic data age.
- Data collection and sharing is encouraged in order to study and gain further useful information.
CONTENTS AND SPECIFIC DOCUMENT STRUCTURE

Preface

It is hoped that this report will be of benefit, both educationally and practically, as well as lead to further research with better sharing of information in this important area of medicine. The use of mathematics is necessary within the text, but has been kept to a minimum, so that all the relevant disciplines can understand the contents and be able to use the advice provided. References have been kept to the minimum necessary and a good basic knowledge of radiation biology is assumed. Any errors are the sole responsibility of the author.

PART A - The choice of \( \alpha/\beta \) ratio for particle therapies

Background

The \( \alpha/\beta \) ratio is the ratio of the two radiosensitivity parameters in the Linear Quadratic (LQ) model of radiation effect and is expressed in units of Gy. The ratio is

- a relatively robust parameter, especially in the case of late reacting normal tissues
- inversely related to the fraction sensitivity during radiotherapy
- well-characterised for certain classes of tissue and tumours in experimental cell lines, animals and humans.

The \( \alpha/\beta \) ratio probably reflects many cellular processes, such as DNA repair and cell cycle related changes in radiosensitivity and in the case of tumours the extent of hypoxia, although a single \( \alpha/\beta \) value can only represent the average contributions of these processes during therapy. It is an especially useful parameter within Biological Effective Dose (BED) equations \(^{[1-5]}\), which 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 for different fractionation schedules. 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. BED can be separated into two components, \( \alpha/\beta \) ratio forms the biological component of the Relative Effect as in:

\[
BED = \text{Total Dose} \times \text{Relative Effect}, \quad \text{[Eq1]}
\]

which in symbols is

\[
BED = D \left( 1 + \frac{d}{\alpha/\beta} \right), \quad \text{[Eq2]}
\]

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 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 use of \( \alpha/\beta \) ratios in hadrontherapy is more complex, as discussed below.
BED equations have many uses, including the calculation of

- iso-effect (or equi-effect) doses
- compensatory doses after unintended under- or over-dosage
- modified dose-fractionation after unintended treatment interruptions.

BED equations can be adapted for the purposes of charged particle therapy using protons and ions, as well as for drug (Chemotherapy) related effects and for the influence of changes in radiation tolerance due to factors such as age/surgery \[6\].

BED equations are derived from the basic linear quadratic model of radiation effect \[1-5\], by dividing the number of lethal events per cell by the $\alpha$ parameter. Although the BED equation consists of a simple mathematical (quadratic) form, clinical BED calculations require considerable care, especially in the choice of $\alpha/\beta$ ratio used: this applies to both conventional x-ray based megavoltage radiations and charged particle therapy using hadrons.

There are some important rules concerning BED equations:

1. BED’s can be added for different components of an overall treatment given by different types of radiation (e.g. for a treatment combining x-rays and electrons, the overall BED = electron BED + x-ray BED, or for a treatment comprising x-rays and an ion beam boost, then the overall BED=x-ray BED+ ion beam BED).

2. Calculations which involve a specified bio-effect in a given tissue or tumour type should be done only using the same $\alpha/\beta$ ratio; it follows that different $\alpha/\beta$ ratios cannot be used to describe the same bio-effect.

3. It is assumed that the $\alpha/\beta$ ratio reflects an average value during treatment. During a course of radiotherapy lasting 4-8 weeks, the ratio is probably stable in the case of slow growing tumours and slow cell turnover tissues. However, in the case of tissues or fast growing tumours and normal tissues that exhibit real or apparent acceleration of their proliferation rates during treatment, the $\alpha/\beta$ ratio may itself increase; this has been shown to be the case for acute reacting normal epithelial tissues, where $\alpha/\beta$ increases from 5 Gy to 35 Gy from the first few weeks to the sixth week in human and animal skin \[7\].

Some special considerations for particle therapy

In the case of positively charged particle therapy, where linear energy transfer (LET) is greater (the so called high LET radiations) than that of megavoltage x-rays (the low LET radiations), there are several literature reports which attempt to use BED equations which contain $\alpha/\beta$ ratios \[refs\]. The literature can be confusing as this work can still be regarded as being in a developmental stage despite many of the underlying principles being understood around 40 years ago, but before the more widespread utilisation of the LQ model and BED concept. Piecemeal improvements since then have now produced a more coherent framework for iso-effect applications \[8-11\]. Two suggested methods for BED iso-effect calculations in modern hadrontherapy are provided below: these use both low and high LET $\alpha/\beta$ ratios in specific situations, but principally the low LET $\alpha/\beta$ in association with RBE conversion factors. It must be stressed that dose in these calculations refers to the physical dose and not the cobalt equivalent or any other form of RBE weighted dose, unless otherwise stated.
1. **Converting a specific low LET BED to that for high LET, when the low LET α/β ratio is known.**

First, it is necessary to understand some application of limit theory to the basic LQ model. For any isoeffect between low and high LET radiation, that is where

\[ N_L(\alpha_L d_L + \beta_L d_L^2) = N_H(\alpha_H d_H + \beta_H d_H^2) \]  

[Eq3]

Since RBE is defined as the ratio of low LET dose to high LET dose for the same bio-effect, i.e. \(d_L/d_H\), then as \(d\) approaches zero dose (neglecting \(\beta\) terms), RBE is given by \(\alpha_H/\alpha_L\), which is the \(RBEmax\) and at very high dose (neglecting \(\alpha\) terms), RBE approaches a value of \(\sqrt{\beta_H/\beta_L}\), which is called \(RBEmin\).

It follows that

\[ RBEmin = \frac{\beta_H}{\beta_L} \]  

[Eq4]

and so \(\beta_H = RBEmin \times \beta_L\)  

[Eq5]

To obtain the High LET BED, the linear quadratic equation is divided by \(\alpha_L\), the low LET \(\alpha\) parameter. If the biological effect, given in terms of the numbers of lethal lesions per cell is \(E\), then

\[ E = n(\alpha_H d_H + \beta_H d_H^2) \]  

[Eq6]

After dividing by \(\alpha_L\), we obtain

\[ \text{BED} = \frac{E}{\alpha_L} = D_L \left( \frac{\alpha_H}{\alpha_L} + \frac{\beta_H}{\alpha_L} d_H \right) \]  

[Eq7]

From the above equation, using the terms \(RBEmax\) (to replace both \(\alpha\) parameters) and \(RBEmin\) (to replace \(\beta_H\)), we obtain

\[ \text{BED} = D_L \left( \frac{RBEmax}{\beta_L} \left( \frac{\alpha_H}{\beta_L} + \frac{\beta_H}{\beta_L} d_H \right) \right) \]  

[Eq8]

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

\[ \text{BED} = D_L \left( 1 + \frac{d_L}{\sqrt{\beta_L}} \right) - KT_L = D_H \left( RBEmax \times \frac{K}{\sqrt{\beta_L}} + \frac{RBEmax^2 d_H}{\sqrt{\beta_L}} \right) - KT_H \]  

[Eq9]

The major advantage here is that the \(\alpha/\beta\) ratio used throughout this equality is that of the low LET \(\alpha/\beta\), but it is necessary to know the most likely values of \(RBEmax\) and \(RBEmin\).

There is a further advantage of using this system for the purposes of correcting the effects of unintended treatment delays, or where it is thought necessary to do iso-effect calculations where overall time differs for two different dose-fractionation schedules. We can then use, for overall times \(T_L\) and \(T_H\) for the low and high LET schedules respectively:

\[ \text{BED} = D_L \left( 1 + \frac{d_L}{\sqrt{\beta_L}} \right) - KT_L = D_H \left( RBEmax \times \frac{K}{\sqrt{\beta_L}} + \frac{RBEmax^2 d_H}{\sqrt{\beta_L}} \right) - KT_H \]  

[Eq10]

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

\[ K = \frac{0.693}{\alpha_L \omega} \]  

[Eq11]
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.

It should also be noted that the use of \( RBE_{\text{max}} \) and \( RBE_{\text{min}} \) allows the RBE to vary with dose per fraction between these two limits. It is well established that RBE is inversely related to dose per fraction in the case of neutron exposures and the same is probably true for all high LET radiations. However, in the case of proton beam therapy using spread out Bragg peaks the magnitude of the RBE is much reduced and RBE changes with dose per fraction are likely to be more subtle. The use of RBE=1.1 for all tissues and at all proton doses is likely to be wrong, although this assumption used in most proton therapy centres worldwide \(^{[12, 13]} \). The decision to use 1.1 was based on a range of experiments using cell and tissue systems with high \( \alpha/\beta \) ratios and could be highly misleading for application to slow growing tumours and late reacting tissue systems (such as the brain), which have the lowest \( \alpha/\beta \) ratios and show the greatest change in dose required to achieve a given bioeffect when fraction is changed. The later effect must influence the RBE, which is the ratio of dose of the low LET radiation divided by the dose of the high LET radiation. Thus the low LET \( \alpha/\beta \) ratio changes the denominator of RBE.

The relationship between \( (\alpha/\beta)_L \) and \( (\alpha/\beta)_H \) is linked in the following way by the maximum and minimum RBE parameters:

\[
\frac{RBE_{\text{max}}}{RBE_{\text{min}}} = \frac{(\alpha/\beta)_H}{(\alpha/\beta)_L} \quad \text{[Eq12]}
\]

It also follows that \( (\alpha/\beta)_H = \frac{RBE_{\text{max}}}{RBE_{\text{min}}} \cdot (\alpha/\beta)_L \quad \text{[Eq13]} \)

This provides a general method for estimating the \( \alpha/\beta \) for high LET radiations where these are not known. This equation can be further simplified by use of a combined RBE converting factor (\( R_C \)) as

\[
(\alpha/\beta)_H = R_C \cdot (\alpha/\beta)_L \quad \text{[Eq14]}
\]

where \( R_C = \frac{RBE_{\text{max}}}{RBE_{\text{min}}} \). \text{[Eq15]}

Consequently a single number, \( R_C \), can be used to convert low LET \( \alpha/\beta \) to the high LET state. It then follows that

Now the increase in RBE, when dose per fraction is reduced, is mainly due to the increase in repair of sub-lethal damage that occurs in the low LET radiation case. Then, in principle, \( RBE_{\text{max}} \) and \( RBE_{\text{min}} \) may also be governed in part by the low LET \( \alpha/\beta \) ratio, such that a greater change in RBE with dose per fraction occurs in tissues with lower low LET \( \alpha/\beta \) ratios (due to their ability to repair low LET radiation sub-lethal damage more effectively than tissues with higher \( \alpha/\beta \) values). Recent analysis of fast neutron data sets in the UK has shown (for cells and tissues which are not seriously repair deficient) that the \( RBE_{\text{max}} \) and \( RBE_{\text{min}} \) are respectively inversely and directly related to the low LET \( \alpha/\beta \) ratio \(^{[14]} \). \( RBE_{\text{max}} \) appears to be a reciprocal function of the low LET \( \alpha/\beta \) ratio, but \( RBE_{\text{min}} \) is linearly related to the square root of the low LET \( \alpha/\beta \) ratio. In other words, RBE is not only a combination of change in LET and dose (physical), but also is influenced by changes in cell cycling/repair (biological) as reflected in the \( \alpha/\beta \) ratio. This can also be expressed as:
Overall RBE = RBE due to physics(LET) + RBE due to biology($\alpha/\beta$) [Eq16]

The general relationships between $RBE_{\text{max}}$, $RBE_{\text{min}}$ and $RBE_{\text{max}}$, take the following form, where A and C represent the minimum values of $RBE_{\text{max}}$ and $RBE_{\text{min}}$ respectively and B and K are coefficients

$$RBE_{\text{max}} - A + \frac{B}{(\frac{\alpha}{\beta})_{L}}$$  \hspace{1cm} [Eq17]

$$RBE_{\text{min}} - C + K\sqrt{(\frac{\alpha}{\beta})_{L}}$$  \hspace{1cm} [Eq18]

The values of $A, B, C$ and $K$ are available for fast neutrons but remain to be determined for protons and heavier ions. Extending this concept to charged particles should be a research priority, with study of how the basic physics related RBE changes ($A$ and $C$) with LET and obtaining values of the further parameters ($B$ and $K$) and how they change between cells and tissues and with LET and in what way.

It is noted here that the Local Effect Model$^{[15-17]}$, used very effectively in Germany, does incorporate the low LET $\alpha/\beta$ ratio along with a conversion factor based on beam microdosimetry (LET) and mean cellular nuclear volume. It effectively provides an RBE which is related to the low LET $\alpha/\beta$ ratio, and varies with dose per fraction within its accepted range based on in vitro cell survival data and applied successfully in clinical treatments of carbon ions at Darmstadt and Heidelberg using 3 Gy per fraction equivalent dose at the tumour target. The RBE is said to be underestimated by around 10-20%, which ensures that the tumour cell kill will be higher than expected from the stated equivalent dose. It remains to be seen if the model will hold when larger fraction sizes beyond those used to obtain in vitro data are used.

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

Here, in a situation where only the high LET radiosensitivity parameters are known, it is not only possible to use the above approach by using low LET $\alpha/\beta$ ratios coupled by $RBE_{\text{max}}$ and $RBE_{\text{min}}$, but also high LET only parameters.

Thus for two isoeffective schedules of high LET we have for $N_1$ fractions and $N_2$ fractions of dose $d_1$ and $d_2$

$$N_{1H}(\alpha d_{1H} + \beta d_{1H}^2) = N_{2H}(\alpha d_{2H} + \beta d_{2H}^2)$$  \hspace{1cm} [Eq19]

It is then permissible to divide throughout by $\alpha_H$ and obtain

$$D_{1H} \left(1 + \frac{d_{1H}}{R_C(\frac{\alpha}{\beta})_{L}}\right) = D_{2H} \left(1 + \frac{d_{2H}}{R_C(\frac{\alpha}{\beta})_{L}}\right)$$  \hspace{1cm} [Eq20]

Here the $\alpha/\beta$ is that of the high LET parameters (these are less well established in the literature at the present time) but in this case the two RBE parameters $RBE_{\text{max}}$ and $RBE_{\text{min}}$ are no longer necessary. It would also be possible to use the single $R_C$ conversion factor in the situation of comparing two identical high LET radiations, so that equation 15 would become

$$D_{1H} \left(1 + \frac{d_{1H}}{R_C(\frac{\alpha}{\beta})_{L}}\right) = D_{2H} \left(1 + \frac{d_{2H}}{R_C(\frac{\alpha}{\beta})_{L}}\right)$$  \hspace{1cm} [Eq21]
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:

\[ D_{1H} \left( 1 + \frac{\Delta_d}{\Delta_d} \right) - K_H T_{1H} = D_{2H} \left( 1 + \frac{\Delta_d}{\Delta_d} \right) - K_H T_{2H} \]  

[Eq22]

where \( T_1 \) and \( T_2 \) are the respective overall treatment times for schedule 1 and 2 and \( K_H \) is defined as

\[ K_H = \frac{0.698}{\alpha_{H,I}} \]  

[Eq23]

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

\[ K_H = \frac{K_I}{RBE_{max}} \]  

[Eq24]

For \( (\alpha/\beta)_H \) there is little in the way of large scale clinical data for protons and heavier ions, although it is well established that \( \alpha \) values increase with LET to a far greater extent than \( \beta \) values, which results in \( (\alpha/\beta)_H \) being much larger than \( (\alpha/\beta)_L \), as shown in large \textit{in vitro} data sets. It is also possible to infer \( \alpha/\beta \) values from sample clinical data. For example, the Japanese NIRS(Chiba) carbon ion phase 1/2 non-small cell lung cancer studies showed an isoeffective tumour control for 44 Gy-eq in 1 fraction and 60 Gy-eq in 4 fractions given in one week \(^{[17,18]} \), then, the \( (\alpha/\beta)_H \) can be found in the following equation, where an RBE of 2.5 is assumed to convert to physical dose in the middle of the spread out Bragg peak for C ions at NIRS(Chiba).

\[ \frac{44}{2.5 \times (2.5)} \left( \frac{\alpha}{\beta} \right)_H = \frac{60}{2.5} \left( \frac{\alpha}{\beta} \right)_H \]  

from which \( \left( \frac{\alpha}{\beta} \right)_H = 25.9 \) Gy

By repeating this process for patients treated with 1, 4, 9 and 18 fractions to cobalt equivalent Gy total doses of 44 (in one day), 60 (in one week), 72 (in three weeks) and 86 (in six weeks) respectively and allowing for repopulation at an assumed equivalent rate of 0.1 Gy per day between 1 and 3 weeks and of 0.3 Gy per day at times over 28 days. These repopulation rates are in \( K_H \) units and are consequently lower than the \( K_I \) values usually seen. The solutions for are then 25.9, 22.2, 23.9, 15.3, 19.1 and 37.7 Gy when each schedule is compared with another. This provides a mean \( (\alpha/\beta)_H \) of 24 Gy (median 23.1) with a standard error of the mean of 3.3 Gy. This would imply an \( R_C \) value of 2.4 (if the \( (\alpha/\beta)_L \) is 10 Gy). Then, if \( RBE_{min} \) is around 1.3, it follows that \( RBE_{max} \) is around 4.

It can be appreciated from the previous paragraph that changes in total dose are required to compensate for altered dose per fraction even in the case of high LET radiations which have high \((\alpha/\beta)_H \) values. It is only when high LET and very low LET radiations are compared that the fractionation sensitivity of the high LET case is considered to be almost zero in relative terms: this is reflected by the differences in their \( \alpha/\beta \) ratios.

Some recommendations for future work include:

- \( RBE_{max} \) and \( RBE_{min} \) values need to be better established for high LET radiations and linked to specific LET values.
- Specific high LET repopulation dose equivalents are required for different classes of tumours.
• \(\alpha/\beta\) values specific for high LET radiations can be used in some circumstances without RBE when identical high LET radiations are compared, but not for comparing low and high LET schedules, or for calculating a combined BED where low and high LET radiations are used. A library of clinical \((\alpha/\beta)_H\) values must be gathered for protons and ions and would need cooperative international research, although the process has commenced in Germany (GSI, Darmstadt) and should be extended. It will take a long time to establish a comprehensive set of radiobiological parameters specific for hadrontherapy under the circumstances of using only a physical dose, the high LET parameters and no RBE factors. This is a reasonable long term goal which will need to also include the defining of tissue tolerances and expected tumour control rates using such an approach. In the meantime, the use of RBE to convert known tolerance and tumour prescription doses remains the norm. The only alternative is to use data from Japan where dose per fraction has been varied and where good iso-effective dose data are available.

• Users should beware of over reliance on in-vitro \(\alpha\) and \(\beta\) values; these are acquired using ideal cell culture conditions and in only one treatment fraction, which can hardly reflect the conditions in a tumour or normal tissue with all the changes which inevitably occur during fractionated treatment.

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\(_{\text{max}}\) 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 \([19]\), 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 \(\alpha/\beta\) 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.

The low LET \(/\alpha/\beta\) ratios for various tumours can be found in publications by Steele, Wyatt \(et\ al\) and Wigg respectively and the references are given directly near the data ion table form below. It is unfortunate that, because of a general worldwide reduction in radiation research applied to medicine and cancer over the past twenty years that little progress has been made to determine more data from clinical data sets. Despite such setbacks, this remains an important area for research.

From the clinical experience of the present author, who has implemented many forms of the LQ model in clinical situations, it is recommended that a range of \(\alpha/\beta\) values should be modelled. The variation in \(\alpha/\beta\) will normally be greater for tumours than for normal tissues, since the former contain greater genetic and phenotypic heterogeneity. Another issue is that \(\alpha/\beta\) may vary with age and be smaller in younger individuals, consequently making them more fraction sensitive; alternatively an equivalent BED for age can be used. The responsible clinician should ideally be given a choice of a range of solutions to any clinical problem, calculated using a reasonable range of \(\alpha/\beta\) values. It should also be noted that, more recently, the \(\alpha/\beta\) values for human tumours are considered to be lower than those previously established from animal experiments. So, a value of 5-8 Gy may be more reasonable than 10 Gy for many human cancers. Fowler stated that the fractionation effects were far less substantial for tumour \(\alpha/\beta\) greater than 7-8 Gy when compared with normal tissues with values of between 2-4 Gy.

Some normal tissues probably exhibit dual response characteristics where the combined effects of severe acute reactions can make a significant contribution to the late effects; these are termed consequential late reactions. They may be the weighted product of the acute and late reacting \(\alpha/\beta\)
ratios and so can be greater than 3 Gy. An example is rectal damage, often quoted as 4 Gy, but in practical (and conservative) terms assumed to be 3 Gy. There probably are differences in terms of duration of radiation exposure. For the extreme example, the acute exposure of a large single fraction, we should assume the lowest $\alpha/\beta$ value since irradiation takes place in the situation of (relatively) low proliferation. But in the case of a more protracted irradiation, the acute reacting epithelial tissue may increase its own $\alpha/\beta$ ratio with time: this is known to be the case in animal and human skin. Another important issue is that overall treatment time and dose per fraction, taken together, may influence the severity of the acute reaction sufficiently to have an impact on the late reaction \cite{20}. This aspect of clinical radiobiology is relatively neglected in recent times and deserves further attention.

It cannot be overemphasised that $\alpha/\beta$ ratio values in tumours need to be expressed as a function of their degree of de-differentiation, or in other words related to the complexity of genetic disorder, or chaos, within the tumour cell: in other words a choice of a larger value within the accepted range should be considered for poorly differentiated tumours and lower values for the well differentiated state. The $\alpha/\beta$ ratios of normal tissues with respect to their late reacting complications are considered to be more stable so that 2 Gy for central nervous system, and 3 Gy for all other tissues tend to be used.

Obtaining reliable ranges of $K$ values and, where applicable, $T_K$ values for specific tumour and normal tissue classes are also important research aims.

**Data from Applied Radiobiology: Continuous Irradiation and Brachytherapy (D.R. Wigg, Medical Physics Publishing, Madison, Wisconsin. 2008. Page 28. Table 1.3**

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**In Vitro information, pooled data... pg. 215**

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**In Vivo Human Tumours**

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Basic Clinical Radiobiology (Editor GG Steel 2002, Edward Arnold, London) page 135, table 13.1

<table>
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Other analytical techniques have been used for tumours such as glioblastoma where the $\alpha/\beta$ has been estimated to be 9.2 Gy [reference 13].

**Additional References for $\alpha/\beta$ ratios are given here. References for text are given separately at end of document.**


**PART B - Compensation for Unintended Treatment Interruptions**

**Background**

Identification of loss of tumour control with extended overall treatment times were evident in experimental studies and studied using power law equations with respect to treatment time and number of fractions for many years. More serious identification of a clinical problem was made by Withers in 1988. Following this advance, many publications showed a reduction in tumour control by about 1-2% per extended treatment day in the case of squamous cell cancers and rapid repopulation is now a better understood cause of treatment failure [21]. The references for the above
facts can be obtained in the several reports issued by the Royal College of Radiologists [London] [22]. It took a longer time to identify lower control rates with treatment protraction in other forms of cancer, especially those associated with slower tumour cell kinetics such prostate cancer [23]. Further clinical data set analysis is likely to produce further knowledge about other classes of tumour in the future providing funding is made available for this form of scientific activity.

The causes of treatment delays are numerous and include accelerator breakdown, patient illness, severe tissue reactions, chemotherapy complications, transport delays etc. Particle therapy can be especially vulnerable, since treatments in a centre depend only on one accelerator (rather than one per room for x-ray based treatments). For long accelerator or gantry breakdowns, close liaison between the physicist and oncologist is required to discuss alternative treatment approaches such as x-ray IMRT or other focal x-rays based techniques.

The calculations are relatively simple but involve many steps and potential pitfalls [24, 25]. It must be appreciated that exact compensations for either a normal or a tumour tissue isoeffect will lead to a detriment in the other, so it is necessary to provide a range of solutions which can be chosen by the clinician in charge, and - where possible - the views of the patient.

It must be remembered that interruptions occurring early in the treatment course are easier to compensate, for example by working on weekends or by using two well-spaced treatments on some days close to the end of the week. The difficult cases are those interruptions which occur later during the treatment course. A model calculation for a delay in treatment when only part of the treatment was carbon ions has already been published [8] and is reproduced again below. In the case of hadrontherapy, great care is required, especially regarding the units of dose: if calculations involve the true physical dose (for example by conversion from the cobalt equivalent dose) then the answer is in physical dose and any correction would need to be further adjusted to the original units such as cobalt equivalent Gy.

The following two new worked examples are based on (1) pure proton and (2) pure carbon treatments. Protons are used to show how subtle differences in results are found from the two different calculation methods. The values used are not intended to be specific for any particular tumour and the modelling examples are intended to demonstrate general principles.

**Worked example 1**

A proton treatment of 46 Gy-eq in 23 Fractions is prescribed for a paediatric sarcoma affecting the posterior orbit, treating daily five times per week over 31 days; the child does not require anaesthesia but mild sedation. The treatment is interrupted in the fourth week, on the day after 15 fractions had been given and for a duration of 7 days.

Assuming that a simple 1.1 RBE factor has been applied to provide the Gy-eq dose, and that tumour shows constant low rate of repopulation equivalent to 0.3 Gy-eq/day. Then we use standard BED equations since it is assumed that there all doses are convertible by the 1.1 RBE factor. This of course may not be correct, but this assumption is used here and contrasted with a more flexible RBE value using RBE$_{max}$ and RBE$_{min}$ later. We also assume no difference in dose between normal tissue and tumour in this example; readers can calculate different BEDs for different isodose values using the following formula:

\[
BED = xD(1 + x\Delta d/((\alpha/\beta)))
\]  

[Eq1]

Where \(x\) refers to the change in dose and would be 0.6 for a 60% isodose line and 0.35 for a 35% isodose line etc.

*Calculations using fixed RBE value for two different tissue types within PTV.*
Tissue A: Intended PTV contained NT late reacting soft tissue using \(\alpha/\beta=3\) Gy, \(\text{BED}\) is \(46 (1+2/3) = 76.67\) Gy

Tissue B: Intended PTV contained NT late reacting brain/neural tissue using \(\alpha/\beta=2\) Gy, \(\text{BED}\) is \(46 (1+2/2) = 92\) Gy

Tumour: intended tumour \(\text{BED}\), using \(\alpha/\beta=10\) Gy is \(46(1+2/10) - 0.3 \times 38 = 45.90\) Gy

BEDs before interruptions:
- Tissue A: \(30 (1+2/3)=50\) Gy
- Tissue B: \(30 (1+2/2)=60\) Gy
- Tumour: \(30 (1+2/10)=30.3\) Gy

The \(\text{BED}\) deficit is then:-
- Tissue A: \(26.67\) Gy
- Tissue B: \(32\) Gy
- Tumour: \(15.6\) Gy

If uncorrected the tumour \(\text{BED}\) (over \(31+7\) days) would be
\[=46(1+2/10) - 0.3 \times 38 = 43.8\text{ Gy}_{10}.\]

By treating with the same dose per fraction through one weekend, two days can be saved, so tumour \(\text{BED}\) is then
\[=46(1+2/10) - 0.3 \times 36 = 44.4\text{ Gy}_{10}.\]

By treating twice a day for all remaining weekdays treatments (i.e. 8 fractions in four days) the overall time is \(32\) days and \(\text{BED}\) is then
\[=46(1+2/10)-0.3 \times 32=45.6\text{ Gy}_{10}.\]

This seems a good alternative and almost completely restores the \(\text{BED}\), but may not be feasible if twice daily sedation is unacceptable.

Another way forward would be to give additional daily fractions, extending overall time further. If for example we try to give the remaining compensatory dose in one additional fraction of 2 Gy in one extra day after completing the prescribed dose, with all delays we obtain an overall treatment time of around \(39\) days

For \(d=2\) Gy

\[\text{BED}=46(1+2/10) + d(1+d/10) - 0.3 \times 39=45.9\text{ Gy},\]

which is almost the same tumour \(\text{BED}\) as the original prescription, but the NT \(\text{BEDs}\) will then be tissue A \(\text{BED}=80\) Gy and tissue B \(\text{BED}=96\) Gy. These have increased. This additional NT \(\text{BED}\) can be reduced by fractionating the final day of additional treatment into two treatments of 1.1 Gy, so that

\[\text{BED}=46(1+2/10) + 2 \times 1.1(1+1.1/10) - 0.3 \times 39\]

The tumour \(\text{BED}\) is then \(45.94\) Gy; Tissue A=79.67Gy and Tissue B =95.41 Gy. The NT \(\text{BEDs}\) have reduced a little.

Consider what might happen if treatment is hypofractionated and given in only three remaining fractions in order to complete in the same overall treatment time but matched to give the same CNS effect in tissue B (a deficit \(\text{BED}\) of \(32\) Gy).

First, solve \(32 = 3 \times d(1+d/2)\); \(d=3.73\) Gy
Then the tumour BED would then be lower:

\[
\text{BED} = 30 \times (1+\frac{2}{10}) + 3 \times 3.73 \times (1+\frac{3.73}{10}) - 31 \times 0.3 = 42.06 \text{ Gy}_{10}.
\]

This is probably not acceptable, so the alternative method given above would be preferred to maintain reasonable tumour control.

Another approach would be to give twice daily treatment for the entire remainder of treatment. In this way, 16 fractions could be given in 8 further days after the unintended gap, competing treatment in 36 days. For a dose per fraction of 1.15 Gy, we obtain:

The tumour BED would then be:

\[
15 \times 2 \left(1 + \frac{2}{10}\right) + 1.15 \times 16 \left(1 + \frac{1.15}{10}\right) - 36 \times 0.3 = 45.72 \text{ Gy}_{10}.
\]

The Tissue A BED is then:

\[
15 \times 2 \left(1 + \frac{2}{3}\right) + 1.15 \times 16 \left(1 + \frac{1.15}{3}\right) = 75.45 \text{ Gy}_3
\]

and the Tissue B BED is:

\[
15 \times 2 \left(1 + \frac{2}{2}\right) + 1.15 \times 16 \left(1 + \frac{1.15}{2}\right) = 88.98 \text{ Gy}_2.
\]

These BEDs all are slightly below the intended BEDs. It should be noted that these twice daily fractions have not taken into account the possibility of incomplete repair between fractions.

Since the above calculations have been done using a fixed RBE, it should be noted that dose units for the particle therapy are in ‘Equivalent Gy’ rather than Gy.

**Calculations using variable RBE value.**

In this case the actual physical dose of protons must be used along with the RBE\(_{\text{max}}\) and RBE\(_{\text{min}}\).

The 2 Gy fraction was actually calculated from a 1.1 RBE so the actual dose given is 2/1.1=1.82 Gy. If we assume RBE\(_{\text{max}}\)=1.15: RBE\(_{\text{min}}\)=1.05 for tumour, and a higher value of RBE\(_{\text{max}}\)=1.2 for normal tissue and RBE\(_{\text{max}}\)=1.3 for brain tissue, but all have the same RBE\(_{\text{min}}\) (remember that RBE\(_{\text{min}}\) is mainly operative at high dose per fraction and will have little influence on the calculations below), we obtain:

Tissue A: Intended PTV containing normal soft tissue (late-reacting) with \(\alpha/\beta=3\) Gy, the BED is then = 23x1.82 (1.2+1.05⁵×1.82/3)=78.23 Gy\(_3\)

Tissue B: Intended PTV containing late reacting brain/neural tissue with \(\alpha/\beta=2\)Gy, the BED is then = 23x1.82 (1.3+1.05⁵×1.82/2)=96.42Gy\(_2\)

Tumour: intended tumour BED, using \(\alpha/\beta=10\) Gy is 23x1.82(1.15+1.05⁵×1.82/10)-0.3x31=47.24 Gy\(_{10}\)

The BEDs given before interruptions are:

Tissue A: 15x1.82 (1.2+1.05⁵×1.82/3) = 51.02 Gy\(_3\)

Tissue B: 15x1.82 (1.3+1.05⁵×1.82/2) = 62.88 Gy\(_2\)

Tumour: 15x1.82 (1.15+1.05⁵×1.82/10) - 0.3x19 = 31.17 Gy\(_{10}\)

The BED deficit is then:-

Tissue A: 27.21 Gy\(_3\)

Tissue B: 33.54 Gy\(_2\)
Tumour: 16.07 Gy$_{10}$.

If uncorrected the tumour BED (over 31+7 days) would be

\[
\text{BED} = 23 \times 1.82 \times (1.15 + 1.05^2 \times 1.82/10) - 0.3 \times 38 = 45.14 \text{Gy}_{10}
\]

By treating through one weekend, two days can be saved so tumour BED is then

\[
\text{BED} = 23 \times 1.82 \times (1.15 + 1.05^2 \times 1.82/10) - 0.3 \times 36 = 45.74 \text{Gy}_{10}
\]

By treating twice a day for all remaining weekdays treatments (i.e. 8 fractions in four days) the overall time is 32 days and BED is then

\[
\text{BED} = 23 \times 1.82 \times (1.15 + 1.05^2 \times 1.82/10) - 0.3 \times 32 = 46.94 \text{Gy}_{10}
\]

This seems a good alternative but may not be feasible if twice daily sedation is unacceptable.

Another possibility would be to give additional daily fractions, extending overall time further. If, for example, we try to give the remaining compensatory dose in one fraction in one extra day after completing the prescribed course (and the delay), we obtain an overall treatment time of around 39 days, then

\[
\text{BED} = 24 \times 1.82 \times (1.15 + 1.05^2 \times 1.82/10) - 0.3 \times 39 = 47.30 \text{Gy}_{10}
\]

which is almost the same tumour BED as the original prescription, but the NT BEDs will then be

tissue A BED = 81.63 Gy$_3$ and tissue B BED = 100.61 Gy$_2$. These have increased. This additional NT BED can be reduced by fractionating the final days treatment into say two treatments of 1 Gy [physical dose], so that

The tumour BED is then 47.04 Gy$_{10}$; Tissue A BED = 80.89Gy$_3$ and Tissue B BED = 99.42 Gy$_2$.

This appears to be a reasonable compromise.

Consider what might happen if the remaining treatment is hypofractionated and given in only three fractions in order to complete in the same overall treatment time but matched to give the same CNS effect in tissue B (a deficit BED of 33.53 Gy$_2$).

First, solve 33.53 = 3$d(1.3 + 1.05^2 d/2)$; \(d = 3.47 \text{ Gy}\)

Then the tumour BED would be low at

\[
\text{BED} = 15 \times 1.82 \times (1.15 + 1.05^2 \times 1.82/10) + 3 \times 3.47(1 + 3.47/10) - 31 \times 0.3 = 43.58 \text{Gy}_{10}
\]

This is probably not acceptable since the BED is less than the originally intended 47.24 Gy$_{10}$. So, the alternative methods given above would be preferred to maintain reasonable tumour control.

Another possibility would be to use a dose such as 0.98 Gy (physical) twice daily for 8 days, completing treatment in 36 days.

The tumour BED would be:

\[
15 \times 1.82 \times (1.15 + 1.05^2 \times 1.82/10) + 0.98 \times 16(1.15 + 1.05^2 \times 0.98/10) - 0.3 \times 36 = 45.80 \text{Gy}_{10}
\]

The tissue A BED is then:

\[
15 \times 1.82 \times (1.3 + 1.05^2 \times 1.82/3) + 0.98 \times 16(1.3 + 1.05^2 \times 0.98/3) = 75.48 \text{Gy}_3.
\]

And the tissue B BED is then:

\[
15 \times 1.82 \times (1.3 + 1.05^2 \times 1.82/2) - 0.98 \times 16(1.3 + 1.05^2 \times 0.98/2) = 91.73 \text{Gy}_2.
\]

Again, incomplete repair between fractions has not been used in the example, but could be used to further refine the BED.
**Comparison of the two methods**

The fixed and flexible RBE calculations do give different answers when dose per fraction is changed (see Tables 1 and 2). Also, in the case of giving 3 hypofractionated doses as compensation, we have BED values of 42.06 Gy\textsubscript{10} and 43.58 Gy\textsubscript{10} for the fixed and flexible RBE methods respectively. These differences – due to the assumed changes in RBE with dose per fraction - provide a good reason why it might be best to deliver the remaining dose mostly using the same fraction size where possible and using altered fractionation on only a few days, especially those days preceding weekends if there is to be a further break in treatments, since over weekends accumulated incomplete repair will not occur. There is a difficulty in using 2 Gy twice daily for many treatments in acute reacting tissues, since reactions can be made worse. General guidelines for limits of acute reacting tissues have been given by Fowler and colleagues\textsuperscript{20}.

Table 1: BED calculations using two different modelling methods for twice daily fractions of 1.1 Gy-equivalent and 1 Gy (physical) on only one day.

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<th></th>
<th>Fixed RBE</th>
<th>Flexible RBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BED Tumour (Gy\textsubscript{10})</td>
<td>45.94</td>
<td>47.04</td>
</tr>
<tr>
<td>BED Tissue A (Gy\textsubscript{3})</td>
<td>79.67</td>
<td>80.89</td>
</tr>
<tr>
<td>BED Tissue B (Gy\textsubscript{2})</td>
<td>95.41</td>
<td>99.42</td>
</tr>
</tbody>
</table>

Table 2: BED calculations using two different modelling methods for twice daily fractions of 1.15 Gy-equivalent and 0.98 Gy (physical) on eight treatment days, with treatment completion in 36 days.

<table>
<thead>
<tr>
<th></th>
<th>Fixed RBE</th>
<th>Flexible RBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BED Tumour (Gy\textsubscript{10})</td>
<td>45.72</td>
<td>45.80</td>
</tr>
<tr>
<td>BED Tissue A (Gy\textsubscript{3})</td>
<td>75.45</td>
<td>75.48</td>
</tr>
<tr>
<td>BED Tissue B (Gy\textsubscript{2})</td>
<td>88.98</td>
<td>91.73</td>
</tr>
</tbody>
</table>

**Worked example 2**
An ion beam schedule of 64 Gy-eq in 20 fractions over 26 days, is interrupted after 15 fractions, for the entire fourth week and for a further 3 days into the following week (i.e. for 10 days). The tumour being treated is a squamous cell carcinoma of the peripheral bronchial tree. Here we assume a significant change in RBE with dose per fraction and only use the RBE<sub>max</sub> and RBE<sub>min</sub> concepts. There is no spinal cord dose. To simplify the calculations we assume that the dose to lung tissue within the PTV will obliterate all lung function within the PTV; also that a surrounding volume (VLNT) for lung function receives approximately 50% of the prescribed dose and is relevant to the patient’s future wellbeing.

In this example the following assumptions are made:

- RBE for dose conversion = 2.6
- Tumour RBE<sub>max</sub>=3.2
- Normal Tissue (NT) RBE<sub>max</sub>=4
- Tumour and NT RBE<sub>min</sub>=1.2
- Tumour α/β=10 Gy
- NT late reacting NT α/β=3 Gy
- Tumour repopulation is modelled by no repopulation for 21 days followed by a repopulation rate equivalent to 0.9 Gy per day.

The 64 Gy-eq dose is a physical dose of 64/2.6=24.62 Gy and the physical dose per fraction consequently is 24.62/20=1.23 Gy.

Using the flexible RBE model we obtain

Intended tumour BED is given by

\[ 20 \times 1.23 \left(3.2 + \frac{1.2^2 \times 1.23}{10}\right) - 0.9(T-T_k) \]; the final repopulation term is zero since the intended T is less than T<sub>k</sub>, so the BED is 83.08 Gy<sub>10</sub>

The intended NT BED is

\[ 20 \times 1.23 \times 0.5 \left(4 + \frac{1.2^2 \times 1.23 \times 0.5}{3}\right) = 52.83 \text{ Gy}_3 \]

The delivered tumour BED is

\[ 15 \times 1.23 \times 0.5 \left(4 + \frac{1.2^2 \times 1.23 \times 0.5}{3}\right) = 39.62 \text{ Gy}_3 \]

The delivered NT BED is

If it is intended to proceed by either

1. giving the same fraction number (5) over 7 days (that is 10 days longer than intended), but increasing the total dose
2. giving 6 fractions of a lower dose in 3 days (that is 6 days longer) by treating twice daily including on a Saturday.

Then for (1)

(a) if tumour control is to be maintained, we solve:

\[ 20.77 = 5 \, d \left(3.2 + 1.2^2 \, d/10\right) - (36-28) \times 0.9 \]

\[ d = 1.63 \text{ Gy} \]

The normal tissue BED will then have increased to be:
39.62+0.5×5×1.63 (4+1.2²×1.63×0.5/3)=57.52 Gy₃, which has increased from 52.83 Gy₃. This could amount to 5-10% additional complications in the volume of concern if complications increase at 1-2% per Gy. If such a policy were to be followed, it might be appropriate to reduce the dose per fraction to say 1.5 Gy. This would then give a compromised tumour BED of:

62.31+ 5×1.5 (4 + 1.2²×1.5/3) - (36 - 28) 0.9 = 80.73 Gy₁₀ instead of the intended 83.1 Gy₁₀.

Ultimately, it is the oncologist who has to decide which policy to pursue and alter the radiation prescription but since the risks and benefits may have changed, the patient should be informed as to the decision made and, ideally, they should be consulted when it comes to the choice of risks.

For method (2), where 6 fractions are given in three consecutive days (a total of 32 days), we can maintain the same tumour BED by solving for $d$ in:

$$20.77= 5d (3.2+1.2² d/10) - (32-28) 0.9$$

$d = 1.2$ Gy.

Then the normal tissue volume BED increases from the intended 52.83Gy₃ to be

39.62+0.5×5×1.2 (4+1.2²×1.2×0.5/3)=55.06 Gy₃.

The latter option appears more acceptable than the former option 1, although we have not included a small increment for incomplete repair between fractions, which is considered to be small for inter-fraction intervals of 12 hours for only 6 fractions. This exercise has assumed that the RBE operative in the normal tissue is a ‘worse-case’ scenario; at an increasing distance from the target the LET will fall as will the RBE. However, with spread out Bragg peaks the LET remains quite high. Such details are more readily available using specially adapted treatment planning systems [26], but which are beyond the scope of the present article. Again as in the proton case discussed above a lower dose per fraction could be chosen, e.g. 1.15 or 1.18 Gy. In all cases of a lower dose the tumour BED would fall below that intended originally.

As an alternative approach, if $(\alpha/\beta)_H$ is used without RBE values, then it is essential to use $K_H$ and not $K_L$ values. The calculations must then convert the cobalt equivalent Gray (prescribed dose) to the actual physical dose in the equations, which are as follows, assuming an RBE of 2.6 was used for the treatment and that tumour $\alpha/\beta$ was 25 Gy for high LET and 10 Gy for the normal tissue.

Intended tumour BED for a dose per fraction

$$64/2.6 (1+1.23/25)) = 25.83 \text{ Gy}_{25}$$

Delivered tumour BED is $15×1.23 (1+1.23/25)=19.36 \text{ Gy}_{25}$

Intended NT BED = $64×0.5/2.6 (1+1.23×0.5/10)=13.06 \text{ Gy}_{10}$

Delivered NT BED (assuming same RBE is operative) is

$15×1.23×0.5 (1+1.23×0.5/10) =9.79 \text{ Gy}_{10}$

Deficit BED for tumour =6.47 Gy₂₅

Deficit BED for NT = 3.27 Gy₁₀.

To maintain same tumour BED if treating in six fractions over 3 days as in previous example then find $d$ from

$$6.47 = 6d (1+d/25) – (32-28) 0.3,$$ where a 0.3 Gy/day value of $K_H$ is assumed.

Then $d=1.22$ Gy

This results in a total NT BED of 9.79 + 6×1.22×0.5 (1+1.22×0.5/10) = 13.68 Gy₁₀.

which is a small increase on the intended BED of 13.06 Gy₁₀.
Normally such a compromise between the tumour and normal tissue calculation results is accepted.

A further example of an ion beam boost in the context of a treatment gap was published elsewhere \[8\] and is reproduced here as a further example and using different parameters:

**Worked example:** A schedule of 45 Gy in 25 fractions using megavoltage X-rays is to be followed by a highly localised ‘boost’ of 6 Gy in 2 fractions of 3 Gy each, using a high-LET radiation for which \(RBE_{\text{min}} = 1.3\) and \(RBE_{\text{max}} = 8\); these values are assumed to apply for both cancer and normal tissues. There is a delay of seven days in the provision of the boost, due to patient illness. The tumour type is assumed to have a daily repopulation equivalent of 0.6 Gy per day after a lag interval of 25 days during megavoltage x-ray treatment. The normal tissue BED is assumed to be governed by \(\alpha/\beta = 2\) Gy and the tumour \(\alpha/\beta = 10\) Gy.

The intended BED to normal tissue from x-rays = \(45 \times (1+1.8/2) = 85.5\) Gy\(_2\)

The intended BED to any normal tissue that receives the added high-LET boost of 2 fractions of 3 Gy = \(6 \times (8+1.3^2\times3/2) = 63.2\) Gy\(_2\),

so that the total intended maximum BED to same volume of normal tissue = \(85.5 + 63.2 = 148.7\) Gy\(_2\)

The intended BED to tumour by x-rays, \(BED_1= 45 \times (1+1.8/10) = 53.1\) Gy\(_{10}\)

plus the intended BED to tumour by high LET, \(BED_{11} = 6 \times (8+1.3^2 \times 3/10) = 51.04\) Gy\(_{10}\),

so that the total tumour BED is \(104.14\) Gy\(_{10}\) before allowing for repopulation.

The additional seven days of repopulation must be allowed for because of the treatment interruption in providing the boost, which is equivalent to \(0.6 \times 7 = 4.2\) Gy\(_{10}\).

The boost must therefore accommodate the original high-LET BED plus 4.2 Gy,

i.e. \(51.04 + 4.2 = 55.24\) Gy\(_{10}\)

As this is to be given in two fractions, then:

\[2 \times d \times (8+1.3^2 d/10) = 55.24,\]

and the solution for \(d\) is 3.23 Gy/fraction instead of the originally prescribed 3 Gy per fraction given before the treatment gap.

The normal tissue BED will then be

\[2 \times 3.23 \times (8+1.3^2 \times 3.23/2) = 69.31\text{ Gy}_2.\]

Thus the total (low- plus high-LET) normal tissue maximum BED will have increased by 69.31 - 63.2 = 6.11 Gy\(_2\), an increase of 4.1% on an already high BED in the localised boost volume, in order to maintain the same tumour BED. This could cause enhanced tissue side effects.

In practice, a compromise solution such as a dose per fraction of 3.15 Gy instead of 3.23 Gy might be used. This would lead to 67.17 Gy\(_2\) maximum high-LET BED to the normal tissues and 53.75 Gy\(_{10}\) to the tumour.

It must be remembered that there are three overall approaches if it is not possible to complete treatment by giving the same number of fractions in the same overall treatment time. These are:-

1. Treat with same dose per fraction, but extend overall treatment time, possibly increasing the number of fractions. This at least has the potential advantage that the RBE will not change.

2. Treat with larger doses per fraction and complete in same overall treatment time. In this case RBE will decrease since fraction size has increased.
3. Treat with larger number of fractions, but with smaller dose per fraction over a slightly extended treatment time or the same treatment time. In this case RBE will increase since fraction size is smaller. This may have a larger effect in the normal tissues since the maximum RBE is greater in late reacting tissues.

The above examples are meant to serve as a demonstration of how to approach treatment interruption corrections in charged particle therapy for treatments of curative (radical) intent. Similar approaches, with some modifications can be applied to palliative treatments where the endpoint is the relief of symptoms for a reasonable duration [27].

CONCLUSIONS

Summary for unintended treatment gap corrections

- It can be appreciated that an individual approach should be used, although formulaic methods can also be devised for precise compensation for either the tumour or the normal tissue isoeffect. However, compromise solutions are inevitably required and individualisation is consequently essential.
- Ideally such corrections should be done by persons who will practice and become used to these approaches, as there are many potential pitfalls.
- It has even been suggested that nation states should organise their own referral system for doing such calculations, although worldwide solutions and more global governance are feasible alternatives in an electronic data age.
- Data collection and sharing should be encouraged in order to study and gain further useful information.

REFERENCES


