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PUSHING THE FRONTIERS OF RADIOBIOLOGY: A SPECIAL FEATURE IN MEMORY OF SIR OLIVER SCOTT AND PROFESSOR JACK FOWLER: FULL PAPER

Modelling the influence of treatment time on the biological effectiveness of single radiosurgery treatments: derivation of “protective” dose modification factors

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Objective: To provide simpler models for adjusting total dose to compensate for significant variations in central nervous system radiosurgical treatment times, which vary and will influence treatment bioeffectiveness. At present, no allowance is made for time variations. A framework of simpler equations would allow radiosurgical outcomes to be analysed with respect to treatment time, and a system for dose adjustments between radioisotope and linac-based techniques with different treatment durations.

Methods: The standard biological effective dose (BED) equations for fractionated and protracted radiations have been combined, using biexponential DNA repair kinetics, to provide the following equation:

$$BED = x \cdot nd \left(1 + \left(\frac{nd}{k} - \frac{d}{k} \right) f(\mu_1 T) + \frac{d}{k} f(\mu_1 t) \right) + (1-x) \cdot nd \left(1 + \left(\frac{nd}{k} - \frac{d}{k} \right) f(\mu_2 T) + \frac{d}{k} f(\mu_2 t) \right)$$

for “n” isocentres (or subfractions), each treated to a variable dose “d” in time “t”, the overall time-being, T, μ_1 , μ_2 , are fast and slow repair rate coefficients, with partition factors of x and (1-x), respectively and k is the alpha/beta ratio, with $f(\mu T)$ being the function that summates sublethal damage repair. Thus, repair during the period of irradiation and in the time interval between each isocentre can be taken into account. Simpler monoexponential and linear models are also used.

Results: The results obtained using simpler models are compared with those obtained using more complex retrospective Gamma Knife BED treatment planning by Millar et al. (2015) in a group of 23 patients on a 13 Gy physical isodose surface. The above equation provides a BED value around 3% above their minimum values, 4% below their average value and 10% below their maximum BED values. Changes in isocentre numbers used, due to treatment plan complexity, can influence total treatment time, producing variations in the BED-time data: instead of a unique curve for each “n” value, in aggregate form the data (ranging from around 20 to 140 min treatment times) can be fitted by monoexponential time functions and further approximated to a linear function for more rapid estimations. Worked examples show how dose can then be tailored to the expected treatment times in order to obtain isoeffective treatments for central nervous system tissues.

Conclusion: The models allow better analysis of radiosurgical treatment time data and guidance to the choice of dose to match the overall time. Although this study is based on Gamma Knife treatments, in principle the methods will also apply to any radiosurgical technique, so that dose-time compensations can be made between differing techniques.

Advances in knowledge: The new BED equation-based framework is relevant to analyse and optimise radiosurgical treatments.

INTRODUCTION

In any radiation treatment, the physician prescribes the total prescription dose, the number of treatment sessions

(frequently in one treatment session in the case of radiosurgery), and in the case of multiple treatment sessions the overall treatment time. These are sometimes referred

to as the controllable parameters. In radiosurgery, for a given prescription dose, the actual treatment duration can vary very significantly, from approximately 0.25 to over 2.5 h depending on treatment complexity, tumour volume, number of isocentres used and other causes of interruption such as gantry repositioning with Linacs, plugging times for Cobalt-60 systems, or for patient non-compliance-related issues. In addition, the natural decay of the activity of the Cobalt-60 sources will have an additional influence in the protraction of treatment times in the case of Gamma Knife radiosurgery. It was perhaps inevitable that pioneering Gamma Knife prescribed doses were also used in the more recently developed linac-based techniques such as Cyber Knife, VMAT etc. despite the more rapid dose delivery. Also, the evolution of Gamma Knife equipment has also lead to shorter treatment times, although the treatment dose protocols have not been lowered to compensate for the general shortening of treatment times.

Treatment time will vary because of technique, the precise condition being treated and treatment complexity and so, it is inevitable that the average dose rate also varies substantially within an individual patient, due to the dose ranges provided by the selected dose gradient, each dose being divided by the treatment time to provide the dose rate. Moreover, at any specific location within a patient the actual tissue dose rate will vary because of its location relative to a given isocentre while it is being treated, but will always be 0 in the time period between isocentres repositioning or while different arc angles are achieved in the case of linac rotational techniques. This dose rate distribution in the tissues of a patient is totally different from the calibration dose rate of any treatment machine (used for quality assurance purposes), which is defined by the dose rate for a fixed geometry and will only vary with radiation source decay in the case of isotopes such as Cobalt-60.

Both dose, dose rate and any interruptions of treatment, scheduled or unscheduled, will determine the overall treatment time and will collectively change the radiation biological effectiveness of the treatment, not only for the desired therapeutic effect but also for the relevant degree of normal tissue functional outcomes. The evidence for changes in bioeffectiveness with dose rate, for dose rates between of 10 Gy min^{-1} and 0.3 Gy h^{-1} is considerable, from both *in vitro* and *in vivo* experimental and clinical data sets, and can be represented by standard radiobiological equations.¹⁻³ The above dose rate effects appears to exist for all repair competent cells or tissues exposed to low linear energy transfer radiations, as conventionally used in radiotherapy and radiosurgery.

There are also very important clinical examples where a reluctance to compensate for the dose rate effect, defended on the basis of steep, protective dose gradients (as in radiosurgery), did result in enhanced and sometimes severe patient morbidities. For example, in the treatment of head and neck cancer, higher dose rate iridium implants, over the range $0.3\text{--}0.9 \text{ Gy h}^{-1}$, resulted in higher necrosis rates but improved tumour control.⁴ Similarly, in the treatment of gynaecological cancer, the increase in dose rate possible by using Caesium sources of $1.5\text{--}1.8 \text{ Gy h}^{-1}$, rather than $0.4\text{--}0.5 \text{ Gy h}^{-1}$, when used with no change in the total dose

prescription, resulted in markedly increased serious toxicity in many treatment centres.⁵⁻⁷ However, in one treatment centre, use of BED equations inclusive of the dose rate and treatment time,⁸⁻¹¹ reduced serious toxicity to low levels while maintaining tumour control in the highest quartile of a UK-wide audit.¹² This was achieved very efficiently in most instances by referring to printed tables that contained suggested changes in total dose to match 10, 20 and 30% shifts in dose rate away from a standard dose rate of 1 Gy h^{-1} . This was made possible by estimating dose rates and biologically effective dose (BED) values in the most relevant adjacent normal tissues, as demarcated by the treating clinician. It should be noted that these tissues did not necessarily occupy the same isodose surface as the prescription isodose.

Although radiosurgery is given at higher dose rates than in the above examples, treatment times are still variable and thus, the general dose rate principle still applies: even modest changes in treatment time will influence the amount of DNA damage repaired by enzymatic systems, which operate under first-order kinetics (repairing the same proportion of sublethal damage in a fixed time regardless of dose), and are characterised by the appropriate repair half-time(s). The longer the overall treatment time, the greater the opportunity for repair over the period of exposure, with and without gaps in treatment, and so the biological effectiveness of a given radiation dose delivered becomes progressively reduced compared with shorter treatment times.

This study provides a simpler method of calculating changes in the total dose required to compensate for changes in treatment duration than those published previously¹³⁻¹⁵ for Gamma Knife treatments. The dose modification factors can be normalised to a reference BED for a radiosurgery treatment given over 1 h using only one isocentre. The time-dose modification equations and guidelines provided can be used for actual treatments and for retrospective data analysis that includes treatment duration changes, as described below. There is a pressing need to analyse radiosurgical outcomes with respect to changes in treatment time. In principle, the equations given below will also be applicable in linac-based radiosurgical techniques provided the "beam-on" and "beam-off" times are known. There is particular concern that relatively short duration modern linac-based techniques and the newer (and faster) versions of Gamma Knife applications have been used without changing the original Gamma Knife prescribed doses that were associated with longer treatment times.

METHODS AND MATERIALS

The standard dose rate equation for the repair of sublethally radiation damaged, DNA repair, are used with the best available central nervous system (CNS) repair half-times fitted using a two component model with repair half-times that are fast (12 min) and slow (2.2 h) in approximately equal proportions,¹⁶ and with an α/β ratio of 2.47 Gy for the endpoint of radionecrosis. The method uses the (BED) concept,^{3,17} which allows isoeffective dose calculations that include the effect of changes in the overall treatment duration, allowing for repair during each radiation exposure and in the non-exposure intervals between each of a variable number of isocentres (or subfractions), as illustrated in

appendix A. The change in BED or the isoeffective total physical dose required with increasing treatment durations, within the time-range typical for radiosurgery, can then be estimated.

A comparison has been made of the results achieved using this simpler approach with those obtained using the more extensive model published in 2015¹⁵ and extended to 23 patients treated for an acoustic neuroma and where different numbers of isocentres were used and the repair functions summated according to the precise times for which each isocentre was used. For each patient, the BED values were calculated for all voxels in a $31 \times 31 \times 31$ matrix in the region of interest. From these individual patient data, the BED value for all voxels on the 13 Gy isosurface (± 0.02 Gy) were extracted, so that minimum, average and maximum values BED value were obtained for that specific physical dose. The treatment times of each patient, with their isocentre numbers, were used to estimate the BED using equation A9 and the results compared with those obtained by the method of Millar et al,¹⁵ both numerically and graphically. Simpler fitting of the entire BED data set was achieved using least squares methods using Mathematica (Wolfram) Software on equations of the following form: biexponential ($BED = A e^{-at} + B e^{-bt}$), monoexponential ($BED = C e^{-a t}$) and linear ($BED = C - at$) functions, where C is the intercept at zero time, while a and b are arbitrary time coefficients. The monoexponential function fit (because the value of the exponent obtained was small) was converted to a further linear model in the form of $BED = C(1 - at)$, which described a constant fractional reduction in BED with time. The same analysis was applied to the data set of treatment times and isocentre numbers for 13 Gy prescriptions generated by applying equation A9 to produce BED values.

The concept of equivalent dose, delivered almost instantaneously, is also provided for in the appendix and will be used to provide a reference to facilitate calculations of dose reduction factors in the worked examples.

RESULTS

In general, the biological effectiveness of a given physical dose falls with increasing treatment time. It follows that, in order to obtain the same bioeffectiveness, the physical dose will need to be increased with protraction of the treatment time. Conversely, dose will need to be reduced in order to maintain isoeffectiveness when treatment times are reduced. The equivalent instantaneous dose values for a range of prescription doses, up to 25 Gy, for differing treatment times (20–140 min) are plotted in Figure 1. It can be seen that the effectiveness, expressed in terms of equivalent instantaneous dose of the intended (or prescribed) treatment dose, is effectively reduced with increasing protraction of the total treatment time, since that equivalent single instantaneous dose reduces with increase in treatment time. For example, a prescribed dose of 25 Gy if delivered in 20 min is equivalent to an instantaneous dose of 23 Gy, but reduces to just above an 18 Gy equivalent instantaneous dose if the same dose were to be given in 140 min. Likewise, a prescribed dose of 13 Gy (given in 20 min) is equivalent to an equivalent instantaneous dose of 12 Gy and reduces to an equivalent instantaneous dose of just above 9 Gy if given in 140 min. However, in reality instantaneous doses

Figure 1. Plot of the variation in equivalent instantaneous dose changing with prescribed dose due to variations in the treatment time.

cannot be delivered in radiosurgery and thus for a given dose delivered in a specified time, the equivalent dose will need to be increased if treatment times are extended or decreased if treatment times are shorted relative to the reference overall treatment time.

The BED value for any particular treatment can be estimated for different prescribed doses, as is shown in Figure 2, in this instance for a specified 13 isocentres (or subfractions denoted by the symbol N) and a total treatment that is represented by 98% “beam-on” time (2% of the total treatment time is representative of the interval between isocentres in such cases). This represents a hypothetical situation since in reality for a given number of isocentres the gap time is approximately constant, depending on the Gamma Knife model, and treatment times vary because of the complexity of the treatment and device related factors (Co-60 activity changes with time and the degree of blocking of sectors for the Gamma Knife, or gantry rotation times with clinical linear accelerators).

The effect of changes in the value of N (the number of isocentres/subfractions) used on the value of BED is shown in Figure 3, which has been calculated using an average time interval of 6 min between each isocentre where no exposure is given. It can be seen that there is a marked change in BED with increasing total treatment time and it must be understood that for any practical data set where times and numbers of isocentres (N) were varied, the data points would fall on separate isocentre-specific curves, and so, show variation in the BED value obtained with time. This must be remembered for the clinical data used below.

The clinical data set contains a range of different isocentre numbers, ranging from 2, (delivered in 29.6 min) to 13 (delivered in 129.6 min), all data are analysed for voxels on the 13 Gy physical isodose. The results for this data set, calculated using the model developed by Millar et al¹⁵ are plotted in Figure 4. BED estimates are shown as the maximum, average and minimum which all decline with increasing total treatment time, there is also a

Figure 2. Variation in BED estimates for RS treatments with increasing total treatment times, using 13 isocentres/subfractions ($N = 13$) where the beam-on time (t) represents 98% of the total treatment time (T). BED, biologically effective dose; RS, radiosurgery.

trend for the number of isocentres used to increase as a function of time, treatments becoming progressively more complex. The results obtained using the newly proposed model are also plotted (red points), and provide single values for each patient between the average and the minimum BED values obtained by Millar et al.¹⁵ The average (and medians in parenthesis) values of the ratios of the BED estimates obtained using the present model and the minimum, average and maximum BEDs estimated by Millar et al.¹⁵ are: -3% (-3%), +4% (+3%) and +10% (+10%) respectively. Thus, the values for the presently proposed model fall within the range of the more complex modelling of Millar et al.¹⁵ The frequency distribution of the number of isocentres and the influence of isocentre number on treatment time in the present study are shown in Figures 5 and 6 respectively.

Figure 3. Variation in BED with overall treatment time using the proposed model, with variation of parameter N (number of isocentres/subfractions), where the average elapsed "beam-off" time between each isocentre treatment is 6 min while delivering a dose of 13 Gy. BED, biologically effective dose.

Figure 4. (a, b) Variation in BED values for different treatment times in 23 acoustic neuroma patients treated to 13 Gy at the prescription isosurface, showing comparison of the data points for the maximum (grey), average (black) and minimum (blue) BED values calculated by the method of Millar et al.,¹⁵ compared with the red data points obtained from equation A9, and fitted (a) by the simpler monoexponential model proposed in this paper, and (b) are all fitted by the linear approximation, using the same colour codes respectively. The fitted functions for each subset are: maximum BED = $76.88e^{-0.002T}$; average BED = $76.31e^{-0.003T}$; minimum BED = $72.04e^{-0.003T}$. The proposed simpler model is represented by $75.67e^{-0.003T}$. Since the exponent time coefficients are small, these may be further approximated as BED = $76.88(1-0.002T)$, BED = $76.31(1-0.003T)$ and BED = $72.04(1-0.003T)$ for the maximum, average and minimum BED values respectively, while the simplified linear model provides BED = $75.67(1-0.003T)$. BED, biologically effective dose.

By applying the new model (equation A9), using the same frequency distribution of isocentres shown in Figure 5, but for a range of different prescribed doses (8–25 Gy), the resulting data can be further approximated to a monoexponential function fitting over a limited range of overall treatment times, as already illustrated for the dose of 13 Gy in Figure 4a,b. The actual monoexponential linear fits for each total dose given in a single treatment session are listed in

Figure 5. Bar chart showing frequencies of isocentre numbers used to treat to the 13 Gy isodose surface (data from reference).¹⁵

Table 1, and the individual curves are shown in Figure 7. It is important to understand that the apparent reduction of a biphasic time equation to a monoexponential form (as shown in Figure 4a) occurs mainly because the data set does not contain times below 23 min, so that the fitted functions cannot include the initial steepest part of the overall time-dependent curve. The biphasic nature of repair is also obscured by a noticeable gap in the data between 95 and 120 min; heterogeneity of isocentre number and averaging processes will also tend to obscure the subtlety of the time-dependent relationship. It is of interest to note that attempted fitting of biexponential equations (of the form referred to in “Methods and materials” section) to the data sets in some instances produced negative parameters for the slower repair component, even if the intercept value was set to be the BED equivalent of 13 Gy delivered in an instantaneous fraction (a BED of 81.42 Gy_{2.47}), so were rejected in favour of the monoexponential equations (which also had R^2 values of over 0.99) and the linear equations ($R^2 = 0.71$ –0.95).

Practical estimated dose modification factors for any dose rate compensation are given in Table 2, where the results have all been normalised to 1 h plans for the special case of using one isocentre. This is an arbitrary reference time point, chosen for convenience, but it is reasonably close to the mean treatment time of 64 min in the present clinical series, and is assumed to represent a typical

Figure 6. Plot of number of isocentres and the overall treatment time required to deliver a total dose of 13 Gy.

Table 1. Linear fitting parameters for the same distribution of isocentres as for the data presented in Figure 4, for different prescribed doses in a single treatment session

Dose (Gy)	Monoexponential Fit	Simplified linear fit
8	$31.65 e^{-0.0029T}$	31.65 (1–0.0029T)
9	$38.95 e^{-0.0030T}$	38.95 (1–0.0030T)
10	$47.01 e^{-0.0031T}$	47.01 (1–0.0031T)
11	$55.82 e^{-0.0032T}$	55.82 (1–0.0032T)
12	$65.37 e^{-0.0032T}$	65.37 (1–0.0032T)
13	$75.67 e^{-0.0033T}$	75.67 (1–0.0033T)
14	$86.72 e^{-0.0033T}$	86.72 (1–0.0033T)
15	$98.51 e^{-0.0034T}$	98.51 (1–0.0034T)
16	$111.06 e^{-0.0034T}$	111.06 (1–0.0034T)
17	$124.35 e^{-0.0035T}$	124.35 (1–0.0035T)
18	$138.39 e^{-0.0035T}$	138.39 (1–0.0035T)
19	$153.18 e^{-0.0035T}$	153.18 (1–0.0035T)
20	$168.71 e^{-0.0036T}$	168.71 (1–0.0036T)
21	$184.99 e^{-0.0036T}$	184.99 (1–0.0036T)
22	$202.03 e^{-0.0036T}$	202.03 (1–0.0036T)
23	$219.81 e^{-0.0036T}$	219.81 (1–0.0036T)
24	$238.33 e^{-0.0037T}$	238.33 (1–0.0037T)
25	$257.61 e^{-0.0037T}$	257.61 (1–0.0037T)

The actual plots for the monoexponential fit are shown in Figure 7. The goodness of fit p -values are around 0.89 for the entire monoexponential column and 0.66 for the simplified linear fit for doses of 8–19 Gy, but is 0.42 for higher doses (Kolmogorov–Smirnov Test).

treatment time during the development of radiosurgery and thus reflected what became clinically acceptable. The special case of treating only a single isocentre can be used as a first approximation for more complex plans. It can be seen that the treatment

Figure 7. BED plots of each mono-exponential equation given in Table 1 for time intervals between 20 and 130 min, assuming the same distribution of iso-centre numbers as shown in (Figures 4 and 5). BED, biologically effective dose.

Table 2. Dose and time correction factors for different prescribed total doses (D) and treatment time duration (T), rounded to two decimal places and normalised to a 1 h treatment time for a single isocentre treatment, obtained using equation A8 and the standard BED equation

	<i>D</i> = 10 (Gy)	<i>D</i> = 12.5	<i>D</i> = 15	<i>D</i> = 17.5	<i>D</i> = 20	<i>D</i> = 22.5	<i>D</i> = 25
T = 20 (min)	0.90	0.90	0.90	0.90	0.89	0.89	0.89
T = 30	0.93	0.93	0.93	0.93	0.93	0.93	0.92
T = 40	0.96	0.96	0.95	0.95	0.95	0.95	0.95
T = 50	0.98	0.98	0.98	0.98	0.98	0.98	0.98
T = 60	1	1	1	1	1	1	1
T = 70	1.02	1.02	1.02	1.02	1.02	1.02	1.02
T = 80	1.03	1.04	1.04	1.04	1.04	1.04	1.04
T = 90	1.05	1.05	1.05	1.05	1.06	1.06	1.06
T = 100	1.06	1.07	1.07	1.07	1.07	1.07	1.07
T = 110	1.08	1.08	1.08	1.08	1.09	1.09	1.09
T = 120	1.09	1.09	1.10	1.10	1.10	1.10	1.10
T = 130	1.10	1.11	1.12	1.11	1.11	1.11	1.12
T = 140	1.11	1.12	1.12	1.12	1.13	1.13	1.13

The first column refers to the time to give the specified dose using the standard technique without compensation for the change in treatment time (T in min). The suggested treatment time will be the specified dose multiplied by the correction factor and given in a time which is the specified time multiplied by the correction factor. For example, for an isoeffect to 20 Gy in 1 h, if the expected treatment time is 30 min, then the suggested dose would be $20 \times 0.93 = 18.6$ Gy and given in a time of $30 \times 0.93 = 27.9$ min.

time is capable of influencing clinical outcomes, especially if the treatment delivered is close to the tolerance dose for radio-necrosis, where each unit rise in dose may typically produce 1–3% increases in effect, depending on the position and shape of the BED or physical dose response curve.¹⁷ These values will change for treatments which use larger numbers of isocentres but only if there is a significant “beam-off” time. Alternatively, the continuous functions for the dose required to maintain an isoeffect of 13 Gy in 1 h are shown in Figure 3, and where the number of isocentre/subfractions used are varied. It can be seen that for the case of faster treatments due to reduced intervals between the isocentre/subfractions, there is considerably reduced variation due to the use of a greater number of isocentre related subfractions.

In general, there will be a positive correlation between the number of isocentres used and the treatment time, although there is considerable superimposed variation (Figure 6) due to additional causes of treatment interruptions such as patient discomfort or other technical reasons, although in the past these have not been well recorded and none were assumed to have occurred in the 23 cases evaluated.

The influence of isocentre number on the ratio of the maximum BED calculated by Millar et al¹⁵ and that of the present model (Equation A9) is shown in Figure 8. This can be fitted by an overall linear relationship, although there is much variation and the distribution is skewed, the average value of the ratio being 1.12 (median 1.10, standard deviation 0.05).

It must be fully understood that the use of the simpler linear and monoexponential functions, on account of their rapidity

and convenience, should only be used within the data range used to obtain these fits. Inaccuracies inevitably occur at shorter and longer times, as is clearly illustrated in Figure 9. The significance of the initial fast component of repair is clearly indicated by the fit obtained using equation A8, since the extrapolation of the curve to zero time gives a BED value close to the calculate instantaneous BED of 81.42 Gy_{2.47}, however, the fit appears to be less good to the data in the 20–80 min range. Both the monoexponential and linear functions, over this time range, appear to be give similar fits, although extrapolation outside this range to time values below 20 min would

Figure 8. Relationship between the number of isocentres used to deliver 13 Gy and the maximum BED calculated by Millar et al¹⁵ divided by the present model estimated (using equation A8), with linear fit provided by $1 + 0.0162N$, where *N* is the number of isocentres used. BED, biologically effective dose.

Figure 9. Illustration of the likely inaccuracies using linear and mono-exponential model fitting at short and longer times and outside the range of the clinical data used for the simpler model fitting of the data. The data points are the average BED values obtained reference,¹⁵ with superimposed fitted functions using (a) equation 9—the black curve, (b) a linear fit of $76.31(1-0.0028T)$ —the solid grey line and (c) the mono-exponential fit provided by $76.31e^{-0.0028T}$ —the hatched grey curve. Note that the intercept BED, which is an instantaneously delivered dose for a dose of 13 Gy using $\alpha/\beta = 2.47$ Gy is 81.42 Gy_{2.47}. Extrapolation beyond the actual data set results in a serious under estimate this value. The linear model also becomes less accurate at longer treatment times.

lead to an underestimate of the isoeffective BED (since the instantaneous BED estimate is around 76 Gy_{2.47}). The linear fit also underestimates the BED for treatment times longer than 90 min.

Two worked examples are given in [Supplementary Material 1](#), which use the equivalent dose concept.

DISCUSSION

It has been shown in the present paper that the dose rate effect can be critically important in the safe practice of both radiotherapy and radiosurgery and should be taken into account establishing treatment prescriptions. In surgical parlance, it is the reverse of the enhanced complication effect expected after increasing the duration of any operative procedure. In practical radiotherapeutics, it would be necessary to estimate the treatment time (to say within 2–5 min in view of the fastest repair half-time) and then adjust the prescribed treatment dose using the correction factors proposed in the publication. This requires increased liaison between the responsible physician and physicist, as well as reasonably accurate information regarding beam-off times to deliver the required number of monitor units and dose. This may require information from a library of past simulations using humanoid phantoms, or adaptation of the treatment planning software for this specific purpose.

The dose modification factors can also be used to analyse clinical results more rationally, by converting the prescribed dose into an “effective dose” modified by time, by multiplication of the given physical dose by the correction factor (as determined by the dose

and operative time as in [Table 1](#)). This will allow better correlation of total dose and time with observed clinical effects which is especially important in adapting dose prescriptions between different radiosurgical techniques. There are inevitable caveats: the models in some cases are dependent on linear quadratic theory and the DNA repair rate parameters used and their relative proportions. These parameters are derived from central nervous tissue radionecrosis data, and so could be different in other normal tissues. For the simplest equations, the linear and simple exponential fits are derived from Gamma Knife treatments, but they will also, in principle, apply to linac-based treatments providing the precise beam-off and beam-on times are known. Although linac-based treatments are faster, there may be redundancy due to resetting of beam angles, increasing complexity and interruptions due to patient discomfort or machine breakdown can also occur. It must also be noted that the equations presented can be modified for higher linear energy transfer radiations such as protons and light ions, in accordance with operative RBE values. These can be found elsewhere.¹⁶

The associated mathematics for correcting for the dose rate related effect can appear daunting to physicians, especially when two half-times of repair are considered, as well as the influence of treatment interruptions. For example, the mathematics associated with pulsed brachytherapy is formidable. However, it is not necessary to master the entire process, since simplification of the mathematics can be used to provide a reasonable degrees of accuracy, and table based corrections can be applied. All those concerned with radiosurgery, using the Gamma Knife and/or modern linac-based techniques the CNS or elsewhere in the body, should familiarise themselves with the clinical importance of the dose rate effect and be able to change the prescription dose appropriately. The new model proposed gives a rapid estimation of a working value of the BED which can be related to those obtained using a more extensive approach used by Millar et al.¹⁵ It could be used as a secondary check to the more complex system or used alone for the purposes of correcting the total dose for the treatment duration in order to maintain isoeffective normal tissue end points, but also may similarly apply to the required therapeutic effect.

The intended target tissue may vary from situations like trigeminal neuralgia, neurofibromas and arteriovenous malformations, as well as other neurological or metastatic tumours, and more recently non-CNS targets for total ablative or cancer therapy. These may vary in the degree in which the dose rate effect is operative. Whatever the target, the response of the surrounding normal brain tissue will be dose rate dependent.

Should the therapeutic effectiveness be very high, it is possible that a small reduction of dose rate may not make much difference, due to the shape of the dose response curve, although the use of each therapeutic indication needs careful analysis, and for each type of radiotherapy. Should there be a reduction in effectiveness with increasing treatment time when the same dose is given, then serious consideration should be given to increasing the dose. At the same time, should normal tissue sequelae be significantly enhanced by reducing the treatment time, then dose reduction should also be considered.

One practical and interim suggestion, which may “fail safe” and not be too dependent on the modelling predictions, would be to implement 50% of the changes indicated. For example, if in a certain situation, the model suggested a dose of X instead of Y , then a dose of $(X+Y)/2$ could be used. In this way, improvements in the therapeutic ratio may be possible without taking excessive risks by complete application of the model estimation, which must contain some uncertainties.

The new modelling approach taken is economical in terms of computing, since only 4–5 lines of code are required, while providing reasonable estimates when compared with more complex systems that require more extensive programming. This becomes apparent when the more elaborate equations for incomplete repair of pulsed radiation are visualised, with the added complexity of biphasic or other forms of repair.^{3,13,18,19} It is also evident that when the number of isocentres/subfraction number exceeds 7–8, there is little difference in the changes in total dose with time, as they then approximate reasonably closely to the continuous repair function as in equation A3. In the case of treatments with 13 Gy, the monoexponential or linear fits to the data could be used as a rapid check on the estimated BED, and Table 2 can be used as an initial guide as to whether a more sophisticated time correction is necessary.

There has also been discussion elsewhere about the radiobiological basis of radiosurgery. For example, based on studies with a transplanted Walker 256 carcinomas model, Song et al²⁰ argued that the benefits of SBRT and RS could be explained by a selective effect of large doses on the tumour vasculature and that the linear quadratic model had limited usefulness in these types of treatment. This conclusion has been correctly and justifiably challenged.²¹ A high dose exposure in the studies of Song et al²⁰ was seen as being uniform, continuous and a relatively acute exposure. This is totally unlike the non-uniform, and often protracted exposures encountered in radiosurgery, and there was no investigation of the effects of dose protraction or of intermittent exposures. Other studies with implanted Lewis Lung tumours used the regrowth delay assay, the magnitude of which is certainly related to clonogenic tumour cell survival,²² have shown that protraction of a dose of 18 Gy over 30 or 60 min progressively results in a loss of efficacy relative to an 18 Gy acute exposure given in 11.5 min. Dose escalation would be required to compensate for dose protraction to obtain an isoeffective tumour response. Song et al²⁰ also claim support for their hypothesis by a comparison of the effects of a large single dose of 20 Gy with fractionated exposure to either four or eight daily doses of 5 Gy or 2.5 Gy, respectively, to the same total dose of 20 Gy. It is to be expected that eight fractions of 2.5 Gy, in particular, was less biologically effective for the vascular parameter than the 20 Gy single dose because these two schedules cannot be biologically equivalent. The change in the amount of repair of sublethal damage, as a consequence of dose fractionation or from treatment protraction, is a corner stone of any radiation treatment. Increasing dose fractionation for a fixed total dose or with dose protraction always results in a loss of bioeffectiveness in terms of tissues responses. It should not be forgotten that repair of sublethal radiation damage is a universal phenomenon in cells

and tissues, apart from the exceptions of repair deficient mutant cells and with the use of high linear energy transfer conditions that occur in the Bragg peak of charge particle therapy with protons and heavy ion beams.

The models described in the present paper rely on the validity of the linear quadratic model of radiation effect, which may show greater linearity at high dose in some circumstances, although the statistics of estimating survival fraction become worse at high dose and also the diminution of the β -related cell kill with more protracted exposures required to deliver a higher dose. The utility of the LQ model in providing safe limits for avoiding radionecrosis in spinal cord tissue over a large range of dose fractionation schedules, with suggested methods for incorporating a transition to linearity with increasing dose in BED equations are presented by Jones and Dale in the same volume of this special edition.²³

There needs to be greater discussion of this topic and consensus decisions taken by informed specialists and patient representatives. The model can be presented for clinical use in different ways, by suggesting modified dose or percentages by which dose should be reduced or increased relative to a standard time (which could be, *e.g.* 30–60 min) by agreement. Firstly, Table 2 should be consulted to give a first order approximation (the equations given in Table 1 are derived from the specific Gamma Knife data set used, and may not be as accurate for other techniques). If this suggests a time-dose correction is required, then the generic equation Equation A9 should be used with the isocentre number, or beforehand the simpler monoexponential fits provided the treatment time is not shorter than around 20 min. Dose with time adjustments can then be made, with estimation of the possible maximum dose from the differences found between the results obtained using equation A8 and the BED values obtained by Millar et al.¹⁵ In highly complex situations, Millar et al¹⁵ method may be necessary, but even then it is important to check the results by means of the simpler approaches.

After detailed discussion, if there is equipoise regarding whether to change therapeutic protocols, it may be appropriate to proceed with randomised control studies where such a modelled approach is tested against the conventional constancy of total dose regardless of overall treatment time. Then, with sufficient statistical power by means of cooperative studies, definitive answers to these vexing questions would be obtained and treatment policy changed accordingly.

CONCLUSION

The suggested framework of simpler equations would allow radiosurgical outcome time-dependency to be analysed, guide clinical decision-making and provide a system for dose adjustments between radioisotope and linac-based techniques that can vary markedly in treatment duration.

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APPENDIX A

Derivation of equation to include repair of sublethal damage during radio-surgical treatment and to include incomplete repair between iso-centres (different sub fractions) and on-going repair of sublethal radiation damage over the duration of each exposure.

The derivation relies on an induction method, and is initially described for simplicity using only a single repair process and printing space considerations. It is later extended to two repair processes, by using the following well-established classical equations [3] for the situations below:

- (1) When a dose D is delivered as a single fraction in a short time of a few seconds or minutes (with insufficient time for any repair to occur over the period of exposure), where for convenience the α/β ratio is replaced by k , then:

$$BED = D \left(1 + \frac{D}{k} \right) \quad [A1]$$

this can also be represented by n fractions of dose d (where $D = nd$) provided there is no time separation between the n fractions, essentially a continuous exposure, as

$$BED = nd \left(1 + \frac{nd}{k} \right) \quad [A2]$$

- (2) If this dose is given over a more extended overall treatment time T , where R is the reduced dose rate and $D = RT$, then

$$BED = RT \left(1 + \frac{RTf(\mu T)}{k} \right) \quad [A3]$$

where the function $f(\mu T)$ represents the increasing repair of sub-lethal damage with treatment time and contains the repair coefficient (μ) as

$$f(\mu T) = \frac{2}{\mu T} \left(1 - \frac{(1 - e^{-\mu T})}{\mu T} \right) \quad [A4]$$

Since repair is an exponential process, the half-time of repair (T_{half}) is related to μ as

$$T_{half} = \frac{0.693}{\mu} \quad [A5]$$

It is important to recognise that the expression $f(\mu T)$ has an upper limiting value of 1 when T approaches zero, and if T is very long, relative to the half-time of repair, that the expression tends towards zero.

- (3) For n iso-centres/sub fractions of dose d , each separated by an interval of time that allows for the near complete repair of sub-lethal damage between fractions (conventional daily dose fractionation), then equation A2 above is modified to be:

$$BED = nd \left(1 + \frac{d}{k} \right) \quad [A6]$$

This is the standard BED equation used for conventionally fractionated radiotherapy and it can be noted that the second term within the brackets refers to the quadratic portion of cell kill in the linear quadratic model, which has changed from nd/k (equation A2) to d/k in equation A6.

The relationship between the entire treatment duration T and t , the mean sub fraction time, is given by $T = nt + (n-1)g$, where g is the inactive time between each iso-centre treatment of duration t . It then follows that

$$t = \frac{T - g(n-1)}{n}$$

A close inspection of equations A1, A2, A3 and A6 reveals that the transition between A2 and A6 represents the influence of incomplete sub-lethal damage repair between fractions (represented by the numerical difference between nd/k and d/k), where each d represents the dose to each iso-centre/sub fraction associated with a single radio-surgical treatment session. This transition (between equations A2 and A6) will be time-related and governed by the sub-lethal damage repair function given in equation A4, which operates for the duration of the entire

treatment (T) on the difference in the quadratic-related damage, that is between nd/k (A2) and d/k (A6) so that:

$$BED = nd \left(1 + \left(\frac{nd}{k} - \frac{d}{k} \right) f(\mu T) \right) \quad [A7]$$

This accounts for the change in the proportion of sub-lethal damage that will contribute to cell lethality that occurs, with the time *between* the n iso-centres/sub fractions, over overall time T . It assumes that each sub fraction was delivered in a short time, t , which then neglects any repair during the treatment “beam-on” time. Now if t is sufficiently long for significant repair to occur during the ‘beam on’ time, then a further allowance must be made to include the $\frac{d}{k}f(\mu t)$ term, leading to:

$$BED = nd \left(1 + \left(\frac{nd}{k} - \frac{d}{k} \right) f(\mu T) + \frac{d}{k} f(\mu t) \right) \quad [A8]$$

This equation now includes repair during and between sub fractions associated with a radio-surgical procedure, although it is important to test its range limits where T approaches zero or if T is very long, as well as the limits of t approaching 0, and where t is close to T (where T is either very short or long relative to the half time for repair). These are taken in turn:

- (1) As $T \rightarrow 0$, (and so $t \rightarrow 0$), and each of $f(\mu T)$ and $f(\mu t) = 1$,

Then BED approximates to $BED = nd(1 + \frac{d}{k})$, the same as equation A2, which is also the case of the large single fraction of dose D given in A1.

- (2) As T becomes very large, then $f(\mu T)$ approaches 0, and if t is small (and $f(\mu t)=1$), then $BED = nd(1 + \frac{d}{k})$, which is the standard BED equation already given as equation A6.

- (3) Also, as T becomes large, with $f(\mu T)$ approaching 0, and if t is also large (so $f(\mu t) \rightarrow 0$), then $BED = nd(1 + 0)$, or simply D (or RT). This condition is the same as equation A3 when T is large, since the BED is then the same as the total dose or the product RT .

Thus, equation A8 reverts to standard expressions at all of the appropriate limits. However, equation A8 only assumes that each sub fraction is of the same size and duration, this is **not** the case for the different iso-centres/sub fractions used in any radio-surgical treatment, where different dose weightings will inevitably occur in the treatment planning process. This issue is, to a limited degree, overcome by the averaging processes that are inherent in the current model estimation of a single overall BED for a particular treatment planned using a given cumulative total physical dose. The method used previously by Millar et al¹⁵ was to estimate separate BED values for each voxel the target structure or region of interest, taking the contribution from each iso-centre/ r sub fraction. For each voxel receiving the individual BED would depend on the dose and the dose prescription, an effect of differently iso-centres weighting to that voxel which will always exist, such information could be reimported back into GammaPlan[®] (or equivalent linac-based software) to produce iso-BED plans compare with the original physical dose plan. In the present analysis the range of BED values for voxels receiving a specific total physical dose have been averaged for all such voxels although maximum and minimum values are also recorded.

Equation A8 can be extended for biphasic CNS repair, with its fast and slow repair components, using the parameters proposed by Pop et al¹⁷ and where x is used to represent the partition of the fast (x) and slow ($1-x$) mechanisms, with the use of $f(\mu_1 T)$, and $f(\mu_2 T)$, for fast and slow repair half times respectively, as:

$$BED = x.nd \left(1 + \left(\frac{nd}{k} - \frac{d}{k} \right) f(\mu_1 T) + \frac{d}{k} f(\mu_1 t) \right) + (1-x).nd \left(1 + \left(\frac{nd}{k} - \frac{d}{k} \right) f(\mu_2 T) + \frac{d}{k} f(\mu_2 t) \right), \quad [A9]$$

Equations A8 and A9 estimate the overall BED based on the simplification that there is no differential dose weighting of iso-centres.

The more comprehensive system of Millar et al¹⁵ may be indicated with BED estimates for specific small regions if retrospectively there is specific concern about either under or over dosing at a particular region of the treatment or for a full BED approach, but in many situations the averaged BED could be a reasonable guide to bio-effectiveness until full BED treatment planning is adopted.

This approach simplifies the original partitioning, designated $1/[1+c]$ and $c/[1+c]$, where the partition coefficient $c=0.98$, as proposed by Millar et al¹⁵.

The new simpler model not only applies to the sub-lethal damage repair function as for a continuous radiation, but to the difference between a single session and multiple session treatment to the same total dose, as well as compensating for the actual duration of each sub fraction delivered in time T with the total beam on time being $n \times t$.

Application of changes in dose and time to match an iso-effect for a reference dose and time.

Because of the difficulties posed by obtaining solutions to multiple transcendental equations containing the variable of time, the following method is suggested.

The reference BED (or BED_{REF}), given in a time of 60 min, is found for low LET radiations by using the complex methods in Millar et al,¹⁵ or by use of equation A9, or by the simpler mono-exponential or linear methods given above. Then an equivalent dose given in zero time, in this case $_{REF0}d_{eq}$, is obtained by solving the equation

$$BED_{REF} = _{REF0}d_{eq}(1 + _{REF0}d_{eq}/k), \quad [A10]$$

The same procedure is also applied to the proposed treatment (using the same dose but in a different overall time, so the BED proposed treatment (or $_pBED$) is also obtained using equation A9, or by the simpler linear method given above. Then the equivalent dose at zero time, in this case $_p0d_{eq}$, is obtained by solving

$$_pBED = _p0d_{eq}(1 + _p0d_{eq}/k), \quad [A11]$$

Now the ratio of the two equivalent doses given in zero time will be preserved at any longer value of time (as can be seen in Figure 2), which can easily be proved. This is because each $_p0d_{eq}$ will be influenced by the same time-related parameters, whatever model is being used. It is also important to change only the 'beam-on-time' within equation A9. This can be adjusted easily by considering that the overall time T can be expressed as:

$$T = nt_f + (n-1)t_0 \quad [A12]$$

where t_0 is the beam-off time between sub fractions (or iso-centres) and t_f is the time taken to deliver each sub fraction (or iso-centre), which is easily rearranged as

$$t_f = \frac{T - t_0(n-1)}{n} \quad [A13]$$