Improving the Accuracy of Biologically Effective Dose Estimates, from a Previously Published Study, After Radiosurgery for Acoustic Neuromas

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■ OBJECTIVE: **To recalculate biological effective dose values (BED) for radio-surgical treatments of acoustic neuroma from a previous study. BEDs values were previously overestimated by only using beam-on times in calculations, so excluding the important beam-off-times (when deoxyribonucleic acid repair continues) which contribute to the overall treatment time. Simple BED estimations using a mono-exponential approximation may not always be appropriate but if used should include overall treatment time.**

■ METHODS: **Time intervals between isocenters were estimated. These were especially important for the Gamma Knife Model 4C cases since manual changes significantly increase overall treatment times. Individual treatment parameters, such as iso-center number, beam-on-time, and beam-off-time, were then used to calculate BED values using a more appropriate bi-exponential model that includes fast and slow components of DNA damage repair over a wider time range.**

■ RESULTS: **The revised BED estimates differed significantly from previously published values. The overestimates of BED, obtained using beam-on-time only, varied from 0%—40.3%. BED subclasses, each with a BED range of 5 $Gy_{2.47}$, indicated that revised values were consistently reduced when compared with originally quoted values, especially for 4C compared with Perfexion cases. Furthermore, subdivision of 4C cases by collimator number further emphasized the impact of scheduled gap times on BED. Further analysis demonstrated important limitations of the mono-exponential model. Target volume was a major confounding factor in the interpretation of the results of this study.**

■ CONCLUSIONS: **BED values should be estimated by including beam-on and beam-off times. Suggestions are provided for more accurate BED estimations in future studies.**

INTRODUCTION

The recent publication by Villafuerte et al.[1] considered the impact of the large variations in the treatment time taken to deliver a given physical dose in Leksell Gamma Knife (GK) radiosurgery (SRS) for acoustic neuromas, given in a single treatment session. The published Biological Effective Dose (BED) estimates were obtained using a very simplified but convenient method, but which may not be accurate over a wide range of overall treatment times.[2] In addition, the study highlighted concerns about the way in which the BED method

Key words
- Acoustic neuroma
- Biologically effective dose
- Brain oedema
- Radiation volume related effects
- Radiosurgery
- Vestibular schwannoma

Abbreviations and Acronyms
APS: Automatic positioning system
BED: Biological effective dose
CI: Confidence interval
DNA: Deoxyribonucleic acid
GK: Gamma Knife
HR: Hazard ratio
LF: Local tumor failure
LQ: Linear quadratic
SRS: Radiosurgery

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has been applied more generally in radiosurgery. This has led to a further more detailed re-evaluation of the BED values for the cases included in this study with a view to obtaining a better understanding of the different approaches and to increase BED estimation accuracy.

BED equations have been used in conventional radiotherapy for over 35 years, with long established rules,[3] which are also applicable and must also be respected in SRS. It originally arose from the linear quadratic (LQ) model of radiation effect, itself based respectively on cell damage yields with increasing dose, fundamental dosimetry, and enzymatic repair considerations.[4-7] Essentially, radiation lethal effects occur due to an accumulation of single-hit (simultaneous) and double-hit (nonsimultaneous) ionizing events, the latter type being subject to time modification, since enzymatic repair can with time reduce the probability of a second hit in the same microlocation. This leads to the concept of sublethal damage (i.e., the presence of only a single hit when 2 are necessary), which will diminish with time due to repair, but could be compounded to lethal damage if a second hit should occur. To account for repair occurring during and between continuous radiation exposures, time-dependent incomplete repair of sublethal damage equations were developed[8] and with inclusion of the Barendsen's mathematical transformation[9] of the LQ model in the BED concept by Dale[10] and Thames.[11] The advantage of BED was that the 2 coefficients of the single and double hit were combined in a single identifiable parameter (the α/β ratio) and with considerable simplification of the mathematics, which led to clinical applications in radiotherapy from the late 1980's onward.[3,12] It is axiomatic that all time intervals which occur during any single treatment must be accounted for, since enzymatic deoxyribonucleic acid (DNA) repair is a continuous process. Thus, the total or overall treatment time of a single SRS treatment must be used rather than the beam-on-time only. The Jones and Hopewell BED analysis method[2] fully respected these rules and the more sophisticated equations (such as that termed A9) included both, beam-on and the beam−off-times, the sum of the time between isocenters and any additional time-gaps occurring for any other reason.

In the publication by Villafuerte et al,.[1] only the readily available beam-on-time was used to estimate BED, and some lengthy periods of beam-off-time between isocenters were not taken into account. In this re-evaluation the overall or total treatment time, from the beginning of radiation exposure with the start of the delivery of the first isocenter to the end of irradiation with the final isocenter, inclusive of the estimated setup gap times between isocenters was used in the calculation, as originally specified for the method used,[2] thus respecting all well-established fundamental radiobiology evidence.

The reduction in BED, as a function of increasing overall treatment time, is due to the repair of sublethal radiation damage that takes place over the entire period over which the radiation dose is delivered, and this is inclusive of any scheduled (set-up gaps) or unscheduled interruptions in the treatment delivery. The sublethal damage enzymatic repair processes[13,14] have characteristic repair rates.

The initial approach developed to calculate the BED, for multiple isocenter treatments, also involved very extensive computer time and additional software to be run in conjunction with a research version of GammaPlan© (Elekta AB).[15,16] Simplistically, this enabled the physical dose matrix, for each isocenter within a volume of interest, to be exported from retrospective patient treatment plans. BED values were then calculated on a voxel-by-voxel basis, taking into account the dose prescription on a given isosurface for each voxel. These BED values varied, even for the same physical dose, in the same patient treatment, and thus the BED was expressed as the mean and the associated range for a given prescription dose.[15,16] An added advantage was that the BED matrix could be reimported back into GammaPlan© and thus physical and BED isosurfaces could be compared.

In order to avoid the requirement for specialist software, which was not commercially available, the need for extensive computation and in order to make the approach more generally usable to the radiosurgical community, some simplifications were subsequently proposed.[2] One approach averaged the dose per isocenter contributing to a given physical prescription dose and also importantly also averaged the gap times between isocenters, inclusive of any unscheduled gaps in treatment, where again, repair will continue to occur. For centers where the full details of the individual gaps times were not available this required the provision of reasonable estimates. The simplified method of estimating the BED[2] used the same repair and tissue sensitivity parameters as used previously for the voxel-by-voxel approach.[15,16] These were originally derived from the studies of Pop et al.[17] for normal central nervous system tissue.

The initial modification of the original detailed voxel-by-voxel approach[15,16] required the use of a relatively complex equation, referenced as Equation A9 in that publication.[2] Then, as a further "first order" simplification, A9 BED values were fitted by either a simple mono-exponential or a linear function with respect to overall treatment time for doses in the range of 8−25 Gy, where the individual equations for each dose were listed in Table 1 of that publication.[2] The use of such a simplification was originally intended to be the simplest and quickest way to estimate whether there was a significant change in BED which might require a change in prescription dose, although such a change in dose should only be estimated using more detailed equations. These simplistic equations are associated with the original α/β ratio and repair parameters used for the A9 BED calculations. They are also dependent both on the use of overall total treatment time and the range of treatment times used for the original derivations, namely 25−130 minutes. For overall treatment times above and below these values the Table 1 approach[2] will progressively underestimate BED values. The intercept or extrapolation number given for each Table 1 equation[2] provides the upper estimate of the BED (at zero time) for each dose, e.g., for 12 Gy an upper estimate of 65.37 $Gy_{2.47}$, from the expression 65.37 $e^{-0.0032T}$, where T is the overall treatment time in minutes and the subscript associated with the units of BED (Gy) indicates the

α/β ratio used in the original A9 BED calculations. This BED value is lower than the value of 70.3 $Gy_{2.47}$ obtained for the same dose, delivered close to instantaneously, calculated using the basic LQ BED equation

$$BED = D\left[1 + \frac{D}{\alpha/\beta}\right]$$

which does not contain a repair function, implying no repair over the period of exposure. Again, the subscript associated with the units of BED (Gy) indicates the α/β ratio used in the BED calculations.

The recent publication[1] that used the simplified mono-exponential equations, as initially proposed by Jones and Hopewell[2] to estimate the BED values, set out to determine if this correlated with local control and normal tissue toxicity in the SRS treatment of acoustic neuromas. The study population included patients treated with either the Leksell GK 4C or Perfexion (Elekta AB, Stockholm, Sweden). However, as indicated initially, instead of using the overall treatment time in the calculations, requiring an estimation of the total beam-off-times between isocenters, only the available beam-on-time was used. This lead to overestimated BED values for each case, unless the treatment involved only a single isocenter (with no gaps in the treatment). Moreover, the level of overestimation is likely to be variable because of the inclusion of both 4C and Perfexion cases in this study. Scheduled gap times between isocenters are relatively short for Perfexion cases, the total beam-off-time will depend on the isocenter number. However, the impact for 4C cases will be greater for although timings, using the automatic positioning system (APS) are relatively short, those associated with collimator or gamma angle changes are significantly longer. All gaps are relatively long when the 4C is used in Trunnion Mode.

The purpose of the present investigation was to re-evaluate the distribution of cases by BED values by a) using a bi-exponential model rather than the simplified mono-exponential model and b) incorporating best estimates of the beam-off-time for the cases included in the original study[1] paying particular attention to the differences between those treated with the different GK models. Attention also focused on the use of the 4C where a variable number of larger manual isocenter gap changes may be interspersed with those using the APS system. These evaluations also lead to an investigation highlighting the importance of the target volume as a confounding factor for studies investigating adverse reactions.

MATERIALS AND METHODS

This collaborative reanalysis was approved by the University Health Network Research Ethics Board (21–6148). A total of 615 of the original 617 acoustic neuromas, treated at Princess Margaret Cancer Centre, University Health Network, Toronto,[1] included within the original study, were available for the present re-evaluation. Of these 605 were treated with a prescription dose of 12 Gy, 10 others with either 10 or 11 Gy. The breakdown of the cases of acoustic neuroma according to the mode of treatment is given in **Table 1**, overall 337 lesions were treated with GK Perfexion and 278 using the 4C. Since the "overall treatment time" is to a significant extent influenced by the time taken to make the longer manual collimator changes using the 4C GK these cases were further subdivided into the number of different-sized collimators used, with the majority requiring a single change. A small group of 10 lesions were treated, at least in part, using the machine in Trunnion Mode. To avoid any potential misunderstanding, as the appropriate interpretation of the term "overall treatment time" a detailed description of its derivation for a 4 isocenter treatment is given in **Figure 1**, where the implications for the inclusion of any unscheduled gap in treatment, which also has implications for repair, is also included.

Table 1. Distribution of Acoustic Neuroma Treatments According to Delivery Mode, Either Using the Perfexion or 4C GK, the Latter Being Further Subdivided by the Number of Collimators Used Because These Represent Lengthy Manual Changes

Gamma Knife Model	Total Cases	Dose (Gy) 12	11	10
Perfexion	337	335	2	0
4C All	278	271	6	1
1 collimator	43	43	0	0
2 collimators	175	171	3	1
3 collimators	49	47	2	0
4 collimators	1	1	0	0
Trunnion	10	9	1	0

While no detailed documentation was available to indicate the exact intervals between isocenters the records of the shot sequences delivered and information from other centers where details of the timing of automated changes had been measured allowed an estimate of the larger gap sizes in the treatment sequences used. This was supported by the senior radiographer responsible for treatment delivery over the period when the 4C was used (Tamerou Messeret: personal communication). Based on these available sources of information the average time for a collimator change was estimated to be 20 minutes and a separate Gamma Angle change to be 15 minutes. The average estimated isocenter change time for the machine operating in the Trunnion Mode was 11 minutes, a value obtained directly, from a group of 4 cases, with more precise timing information. The isocenter changes carried out using the APS system of the 4C were timed as an average of 0.52 minutes (Lee Walton: personal communication). Calculations based on fully documented treatment plans for the Perfexion indicate the average isocenter change time to be 0.06 minutes. These timings, along with the fully documented beam-on-time, were used for the revised calculation of the BED. The average estimated 20 minutes for a 4C collimator change and 11 minutes for a Trunnion Mode change are longer than the calculated average for the UK GK Centre, Sheffield, where values of 13 minutes and 6 minutes were calculated, respectively for the treatment of acoustic neuromas (Hopewell et al.—unpublished data). Alternatively, Graffeo et al.[18] estimated an average gaps time of 5 minutes for Acromegaly cases, which they always treated in Trunnion Mode using the 4C and older versions of GK. While it is possible to make reasonable estimates of scheduled gaps in

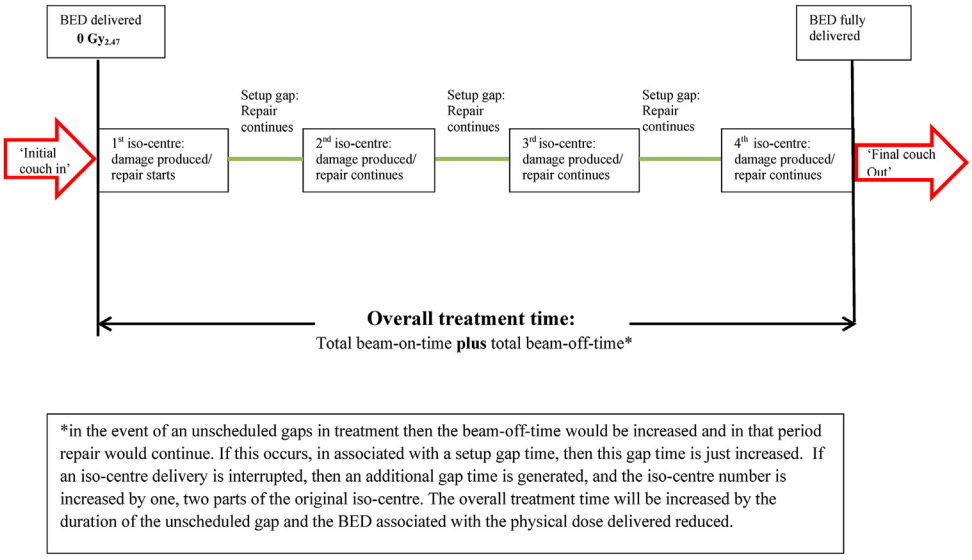

Figure 1. Diagrammatic illustration of the timings needed to derive the overall treatment time, for a 4 isocenter treatment, from the start of the initial irradiation delivery from the beginning of the dose delivery from the first isocentret to the end of dose delivery from the last isocenter. Damage is produced over the beam-on-time while repair of sublethal DNA damages occurs over the whole of the overall treatment time.

treatments using the different types of GK, unscheduled gaps can also have a significant effect on calculated BED values.[19] It is not believed that unscheduled gaps had a significant influence on the cases included in the present study.

The equation used to estimate the BED in the original publication[1] for lesions treated with 12 Gy was

$$BED = 65.37\, e^{-0.0032T}$$

where "T" represents the "overall treatment time" and not the "beam-on-time only" as originally used.[1] Comparable equations, based on the use of the beam-on-time only, do not exist, since this would ignore the repair that takes place in the gaps between the different isocenters.

A subsequent observation was that even the beam-on-times, used to make the original estimates of the BED, included those with treatment times outside the range initially used to establish the Table 1 style equations,[2] namely 25–130 minutes, thus adding an additional uncertainty factor in relation to the original BED estimates.[1] The beam-on-times ranged from 6.49 to 150 minutes, the lower value representing a single isocenter treatment. The overall treatment times, inclusive of the estimated beam-off-time between isocenters, ranged from 6.49 to 179.8 minutes. This correction further increased the time range outside that was originally recommended for the use of the mono-exponential approximation. The most appropriate equation for the full range of overall treatment times was the bi-exponential equation A9 from the publication by Jones and Hopewell.[2] BED values were calculated using a purpose-designed calculator (Moore et al.; in preparation) using either the estimated average gap time between isocenters (g) for individual cases or for the assumption that the gap time was zero (g = 0), in order to demonstrate the overestimate of the BED associated with the incorrect use of beam-on-time only.

A reanalysis of clinical outcomes was also carried out using the revised A9 BED values, which appropriately involved the use of the "overall treatment time," in relation to the local tumor failure (LF) using a proportional hazards model to calculate a LF-specific hazard ratio (HR), with the revised A9 BED values as a continuous variable. Radiological edema (by lesion) and symptomatic edema (by patient) were modeled using logistic regression, again using the revised A9 BED values as a continuous variable. Statistical analyses of clinical outcomes were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Differences Between Beam-On-Time and Total or Overall Treatment Time

A simple plot of all the values of the appropriately estimated overall treatment times and the originally used beam-on-times are, for the acoustic neuromas treated in the present study are given in Figure 2. Clearly, irrespective of whether the beam-on-time or estimated overall treatment time was used, many cases in this study were outside the time range originally used for the development of the mono-exponential approximation, linked to the simplified Table 1 style equations, namely 25–130 minutes, published previously.[2] The shift in values associated with the estimation of the overall treatment time, as opposed to the use of beam-on-time, is greatest for cases treated with the 4C, that include either one or more scheduled manual collimator changes, in association with the use of APS. The most marked change was

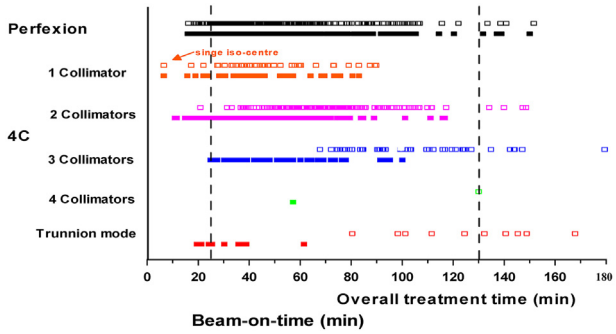

Figure 2. Variation in the beam-on-time (*closed symbols*) and overall treatment time (*open symbols*) for all cases of acoustic neuroma treated either with the 4C or Perfexion GK. The differences were relatively small for the Perfexion cases, indicating the small gap times between isocenters. Using 4C this difference varies according to the treatment configuration, being largest when operated at least in part using Trunnion Mode and smallest when only a single collimator was used. The difference between the overall treatment time and beam-on-time was very highly significant for all groups, even for the Perfexion subgroup with the smallest differences ($P < 0.0001$ based on 2 tailed *t*-test). The times were only identical for a single isocenter treatment, no setup gaps. Vertical lines indicate range of overall treatment times originally used to derive the simplified Table 1 style equation.[2] Using the Wilcoxon signed rank test the differences in the beam-on-time and overall treatment was statistically significant ($P < 0.01$).

in the 10 cases treated, at least in part, in the Trunnion Mode. This shift is illustrated in a plot of the original beam-on-times against the overall treatment times (Figure 3). Other than the single lesion, treated with a single isocenter using the 4C GK and a number of the Perfexion cases, treated with a few isocenters in a short time period, there was no parity between the 2 definitions of treatment time. The disparity, between the estimated overall treatment time and the originally used beam-on-time only was greatest for 4C cases and is clearly related to the number of collimators used, a reflection of the total beam-off-time that was not taken into account in the original analysis.[1]

Calculation of BED Using the Overall Treatment Time

Given the range of overall treatment times, indicated above, the most appropriate equation to calculate BED values is the bi-exponential A9 equation.[2] The variation in BED as a function of the overall treatment time for cases treated with the 4C and Perfexion are given separately in Figure 4. There is a comparable bi-exponential relationship between the BED and overall treatment time for both data sets, originating from an upper value of 70.3 $Gy_{2.47}$ for a physical dose of 12 Gy. This is the maximum values applicable for a dose of 12 Gy, when the dose is nominally delivered instantaneously, such that there is not time for any repair of sublethal damage over the period of exposure. This declines to a minimum value of 40.3 $Gy_{2.47}$ for an overall treatment time of 179.8 minutes.

In addition, for both data sets, a mono-exponential approximation was applied to data points with overall treatment times in the range 25–130 minutes, the approximation originally applied to derive the simpler Table 1 style equations.[2] Similar mono-exponential fits were obtained for both data sets, consistent with the extrapolation/intercept number of 65.37 $Gy_{2.47}$ in the original Table 1 equation[2] for 12 Gy. This again is the maximum BED value for this particular dose, since it is associated with a nominal instantaneous exposure. The negative, mono-exponential slope, based on this approximation for the Perfexion cases, was slightly steeper than that found for the 4C cases. However, this was not statistically significant ($P > 0.1$) and both were consistent with that quoted negative single exponential parameter in the Table 1 equation.[2] The minimal differences reflect the distribution of cases in the 2 data sets. Perfexion cases were more distributed to shorter overall treatment times than was the case for those treated using the older machine. For overall treatment times below 25 minutes this Table 1 derived approach to determining BED values, progressively underestimated the A9 BED values, as highlighted previously.[2] Similar inaccuracies occur for much longer treatment times, indicating again a further limitation of the use of this simplified approach.

In order to compare the originally estimated BED values using Table 1 equations,[2] using only the beam-on-time with those calculated using the more complex A9 equation incorporating both the beam-off and beam-on-times into the overall treatment time the cases were divided into subgroups, each with a range of 5 $Gy_{2.47}$. For all cases (Figure 5A) the original estimated BED distribution showed a distinct peak for BED values in the range <60–>55 $Gy_{2.47}$. When the estimated overall treatment time was used, values were reduced and were spread more widely, reflecting the reduction in BED that is associated with the inclusion of the variable beam-off-time into the calculations. These differences in BED values were significantly reduced when the overall treatment time is used (Wilcoxon signed rank test,

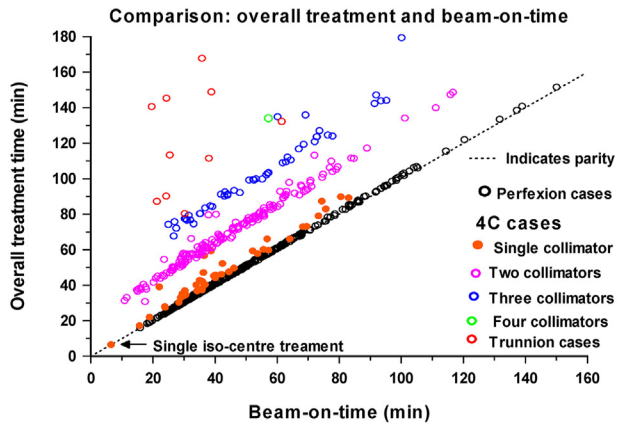

Figure 3. Comparison of overall treatment times and the beam-on-times (ignoring scheduled gaps in treatment between isocenters) for all acoustic neuromas treated with either the 4C or Perfexion GK. Parity between the 2 expressions of times was only seen for a single isocenter treatment and for Perfexion cases treated with a few isocenters (no or minimal gap times). The use of longer beam-on-times in association with Perfexion is usually associated with increased treatment complexity and hence an increased contribution of scheduled gap times to the overall treatment time. The shift of the cases treated using 4C is really dominated by the longer manual changes for collimator changes and is greatest for cases treated in Trunnion Mode.

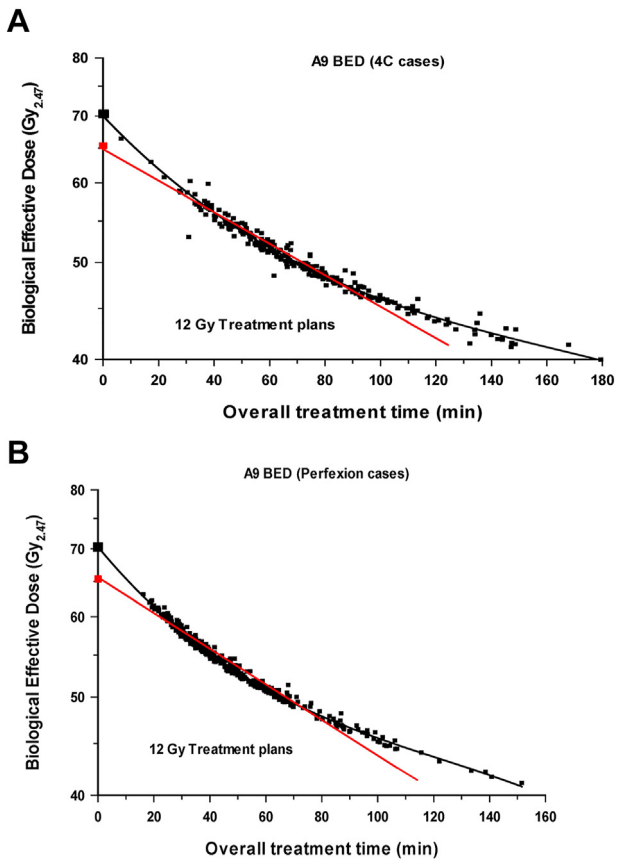

Figure 4. Shows the variation in BED values (log scale), calculated using the A9[2] equation (*black curve*), as a function of the overall treatment time (inclusive of the intervals between isocenters) using either the 4C (**A**) or Perfexion (**B**) GK. Both 'full' data sets could be fitted using a bi-exponential function. A mono-exponential fit (*red line*) has also been applied to data points over the range 25–130 minutes, as was applied in Jones and Hopewell.[2] These fits are compatible with an extrapolation number of 65. 37 $Gy_{2.47}$, for a 12 Gy Table 1 equation. The mon-exponential slope was slightly steeper for the fit to Perfexion cases. This was largely related to relatively shorter overall treatment times in the Perfexion series.

z-val = −21.08, $P < 0.01$). In this respect, as anticipated, the impact in terms of the downward shift of values was greater for the 4C cases compared with those treated using Perfexion (Figures 5B and C). Although a further subdivision of 4C cases was associated with smaller numbers it is still possible to see the effects of introducing a single and a double collimator change when compared with cases treated using a single collimator in APS mode (Figure 6A, B and C).

In order to evaluate the impact of the use of beam-on-time versus the overall treatment time and to avoid any confounding effects associated with the use of a mono-exponential approximation, BED values were also calculated using equation A9 but with the average gap time artificially set to zero, in effect now just taking into account the beam-on-time. Other than a single 4C case treated with a single isocenter the use of the overall treatment time is always associated with lower BED values (Figure 7). The greatest disparity is seen for the 10 cases, treated at least in part in Trunnion Mode and the smallest disparity in the large group of cases treated using Perfexion where the average scheduled gap time is short, at 0.06 minutes.

The percentage overestimate of the calculated BED value associated with ignoring the beam-off-time in the calculation, when only the beam-on-time is used, is illustrated Figure 8. For Trunnion cases the error was in the range 20%–40%, while for the use of a single collimator and the APS system for the 4C GK the error ranges from 0%–8%. Use of 2 or 3 collimators produced an intermediate range of errors, as indicated in Figure 8. The relative absolute errors in BED values associated with the use of Perfexion and the beam-on-time only are small, <2% (Figure 8). However, a change in the rank ordering of cases by BED value is seen when using the BED values derived using beam-on-time only compared with the overall treatment time, which may be clinically significant when comparing treatment outcomes between tumors treated.

For this evaluation, all the cases were ranked, 1–337, according to the A9 BED value calculated using the beam-on-time only. In this situation, as the case ranging number increases this was always associated with a progressive decline in the quoted BED value, as predefined by the ranking order approach adopted (Figure 9A). To illustrate the change, when the overall treatment time was used to calculate the A9 BED value, the correctly revised A9 BED values were also plotted but using the same ranking as before. Now the A9 BED values do not decline in order, as the original ranking number increased, clearly indicating a different ranking is associated with the introduction of the beam-off-time into the BED calculations. The discrepancies in the ranking of A9 BED values calculated using only the beam-on-time, as opposed the overall treatment time, are shown in Figure 9B, highlighting a total of 257 (76.3%) miss-ranked cases, and a maximal ranking error of 55 positions. For a number of ranking changes, the revised BED value is seen to fall markedly, with a subsequent decrease in the BED value and hence an increase in the original ranking number, indicating that the new BED values are no longer progressively decline using the original ranking numbers that are based on beam-off-time only in the BED calculations. It is relatively easy to include an estimated average gap time, e.g., 0.06 min, for Perfexion GK treatments and thus ranking errors of this type would simply be avoided.

Impact of Changes in the Timing of Manual Collimator Gap Changes or Isocenter Changes (Trunnion Mode) Using the 4C GK Based on the A9 BED Values

As indicated earlier, different operating procedures in different Centers could potentially influence the average timing of manual procedures for 4C and earlier GK models. The estimated timing of collimator and Trunnion Mode changes in the present cohort of cases are large when compared with other centers where estimates or measurements have been made.[18] In order to investigate the impact of this further, 4C cases receiving a prescription dose of 12 Gy, using 2, 3, or 4 (single case) collimators, plus those treated in pure Trunnion Mode (6 cases) were re-evaluated (Figure 10). The mean increase in BED associated with a reduction of 7 minutes (from 20 to 13 minutes) in the estimated collimator change time was 2.06%, 3.35%, and 3.9% for a single, double,

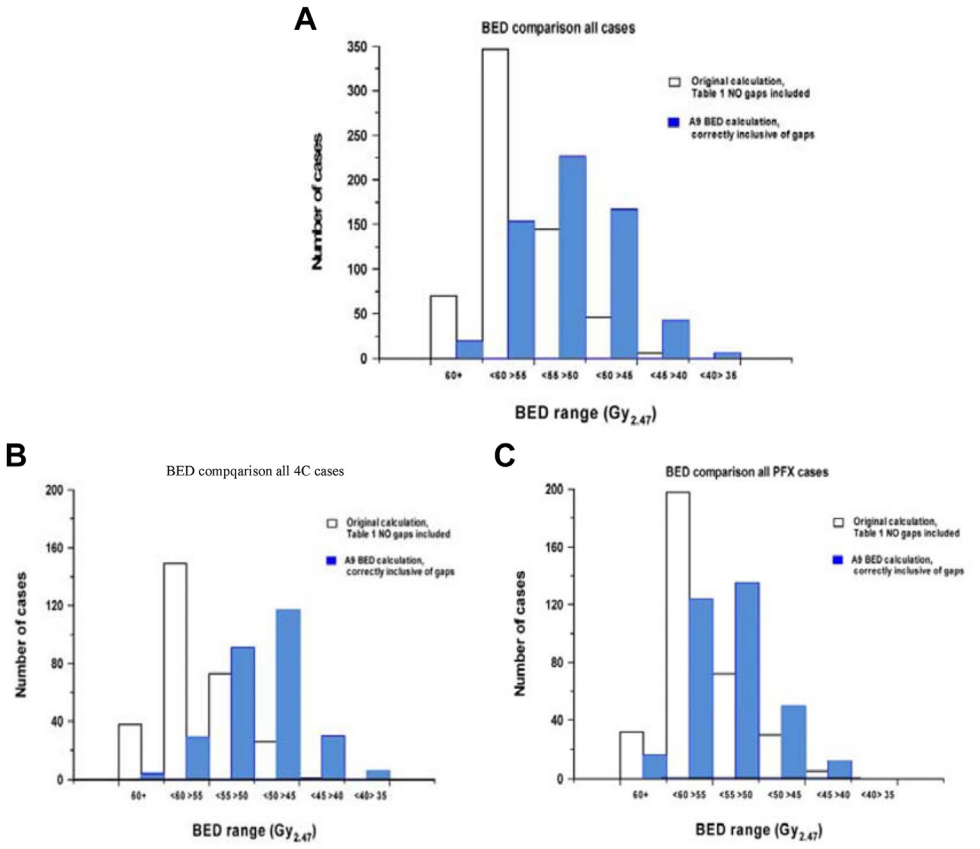

Figure 5. Comparison of the distribution of all cases by BED range, based on either the previously published[1] values estimated using the mono-exponential Table 1 style equations[2] based inappropriately on the use of beam-on-time only, and a re-evaluation using equation A9 in association with the overall treatment time, based on estimates of the beam-off-time. For all cases and with no allowance for the gaps between isocenters the majority of cases had a BED in the range >55−< 60 $Gy_{2.47}$. The introduction of estimated gap times, between isocenters, to derive overall treatment times resulted in a variable reduction in BED values (**A**). This reduction was greater for 4C (**B**) than Perfexion cases (**C**). The difference tween the BED values calculated using equation A9 (inclusive of gap times) and as estimated originally using the Table 1 equation.[1] The difference in BED values is statistically significant for each of the plots ($P < 0.01$) based on the Wilcoxon signed-rank test.

and triple collimator changes, respectively. When operated in Trunnion Mode, the effects of reducing the time for the isocenter change from the original 11 minutes down to 6 minutes resulted in around a 9% increase in the estimated A9 BED values.

Effect on Treatment Outcomes

Based on the previous publication[1] 3 clinical endpoints were selected for further investigation, namely tumor progression, radiographic edema alone, or in combination with symptoms requiring medication. The percentage incidence of each of these outcomes, as a function of the mean BED, are given in **Table 2** along with the mean target size associated with the different BED groups for those cases treated with 12 Gy. The incidence of tumor progression was low, under 10%, so a high probability of tumor control was observed with a median time of 5 years' follow-up. There was no significant relationship between BED and the incidence of progression, on that shallow part of the control probability curve. The univariate local failure-specific hazard ratio for A9 BED (per $Gy_{2.47}$) was 0.97 (95% confidence interval [CI] 0.90−1.04, $P = 0.35$). Even after adjustment for tumor characteristics (cyst), indication for SRS (salvage treatment), this still remained statistically insignificant based on multivariate regression for local failure (adjusted HR 1.00, 95% CI 0.92−1.09, $P = 0.98$).

In terms of the complication rates, the risk data suggested an increase, particularly in relation to radiographically diagnosed edema, is associated with the A9 BED grouping, being 0% in the >60 $Gy_{2.47}$ grouping and 35% in the <45 $Gy_{2.47}$ grouping for all cases. Taken at face value, this implies a negative BED-effect relationship which is clearly counterintuitive. However, the reduction in the mean BED, associated with these groups, is subject to an important confounding factor, the volume of the original target. There is a clear indication that larger target

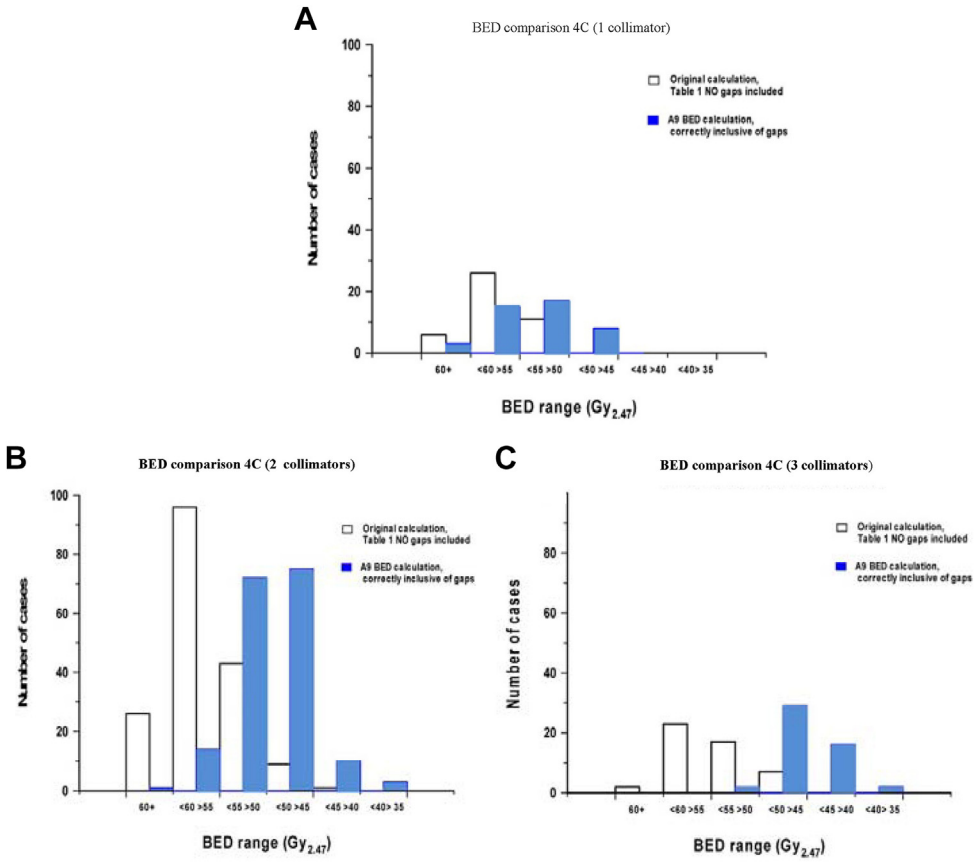

Figure 6. Extension of the data given in Figure 4 to illustrate the reduction in BED values associated with progressively increasing the beam-off-time with the introduction of 1 (**B**) or 2 manual collimator (**C**) changes, compared with no manual changes using a single collimator (**A**). The difference between the original Table 1 BED estimates and those calculated using the A9 equation (inclusive of the gaps between iso-centres) were statistically significant; reference Figure 4.

volumes were associated with lower BED values. In this respect it is interesting that the relationship between the BED and the original target volume fell more rapidly for the 4C GK cases than for the Perfexion cases (Figure 11). Using the older machine type, the development of a treatment plan for a larger-sized target will generally require more collimators of different diameters leading to longer total treatment times and hence will be associated with a lower BED values when compared with a similar volume treated using Perfexion. The BED subgroup with the largest incidence of radiographic edema was the one that received <45 $Gy_{2.47}$, namely $54.45 \pm 15.02\%$ for Perfexion cases (Table 2). This incidence, was significantly higher ($P < 0.05$), over twice that of the comparable 4C subgroup (i.e., $23.33 \pm 7.72\%$). This Perfexion subgroup was also associated with a significantly higher ($P < 0.02$) mean target volume, than the comparable 4C group. However, the mean BED values for these 2 subgroups, were not significantly different; pointing to the dominant importance of the target volume for this adverse effect. Moreover, when the A9 BED values were considered in multivariable logistic regression analysis, after adjustment for patient sex, prior surgery, tumor volume, tumor diameter, BED was not associated with radiologic edema (odds ratio 1.03 per Gy, 95% CI 0.98–1.09, $P = 0.29$). For symptomatic edema, after adjustment for tumor volume, BED was again not associated with symptomatic edema (odds ratio 0.98, 95% CI 0.92–1.05, $P = 0.59$). Nearly all cases treated in this study received a 12 Gy prescription dose; a few received either 11 or 10 Gy. There was no indication these dose reductions were associated with unusually large lesions.

The potential impact of additional variables, such as prior external beam radiotherapy and prior surgery, were also examined. However, the number of cases involved was small and the interval between the 2 different procedures also varied. No significant impact on clinical outcomes was observed (data not shown).

DISCUSSION

The present re-evaluation of the original BED estimates, for a large series of acoustic neuromas treated with either the 4C or Perfexion, given in the earlier publication by Villafuerte et al.[1] has

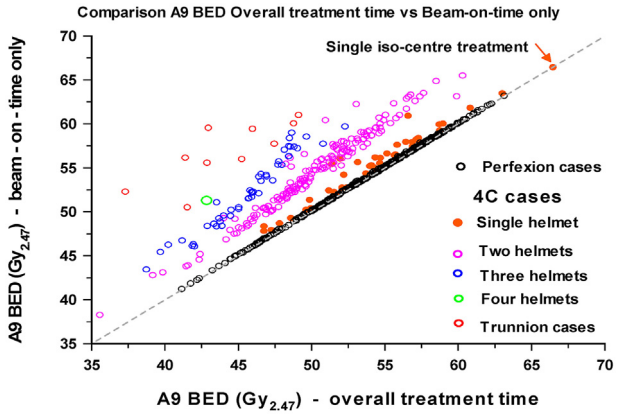

Figure 7. Comparison of BED values calculated using the A9 equation[2] without the inclusion of estimated intervals between isocenters (beam-on-time) and correctly using the overall treatment time (inclusive of the estimated gaps times between isocenters. The lack of an allowance for repair in the gaps between isocenters results in an overestimation of the true BED value.

highlighted important issues as to the need to correctly interpret the methods based on the well-established radiobiological principles previously listed in the Introduction above, and originally published in the context of radiosurgery by Jones and Hopewell.[2] This work included the use of some simplified mono-exponential equations derived from this approach, the Table 1 equations,[2] rather than the bi-exponential A9 equation. These simplified equations, which are easy to use, allowed first order estimates of the BED to be made simply based on knowledge of the physical dose and the overall treatment time, but as indicated previously are subject to significant limitations, all of which were also identified in the original methods paper.[2]

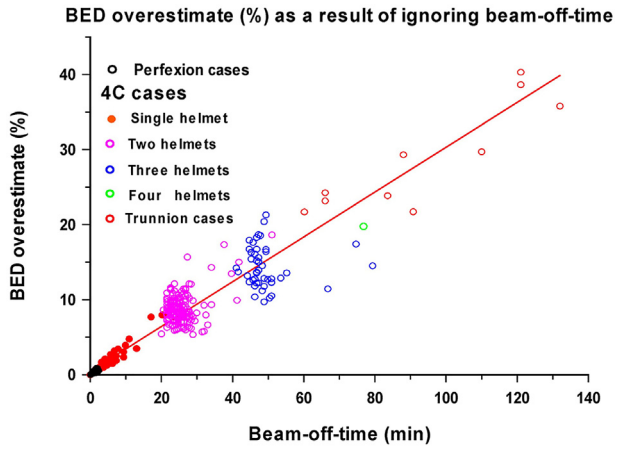

Figure 8. Shows the percentage overestimate of all BED values resulting from the use of the beam-on-time alone, thus ignoring the scheduled beam-off-time between isocenters, as a function of that beam-off-time. The largest beam-off-times were associated with the use of the 4C GK in Trunnion Mode.

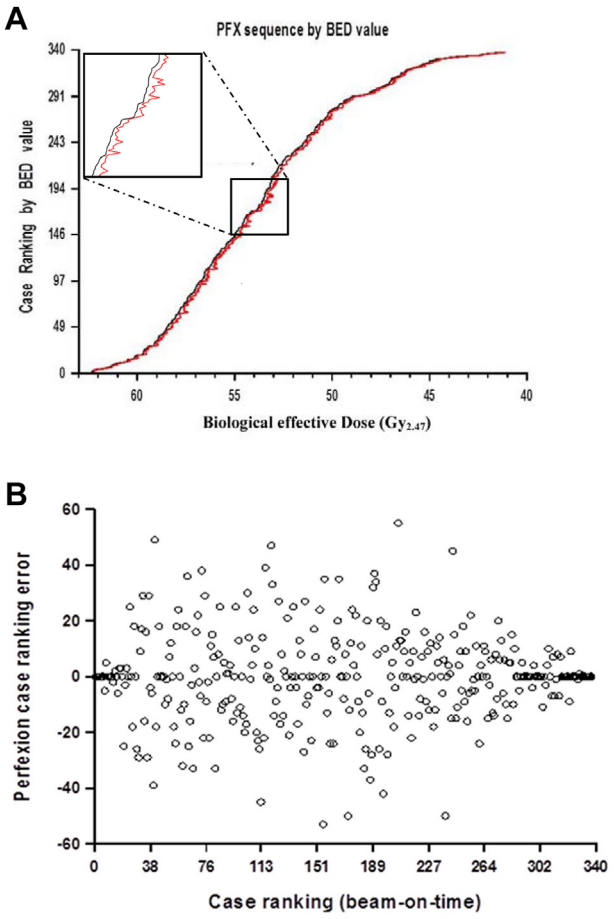

Figure 9. (**A**) Ranking of Perfexion cases (1—337) by decreasing BED values, as calculated using the A9 equation,[2] however, failing to take account of the scheduled time intervals between the different isocenters, i.e., using beam-on-time only (*black line*—the ranking number always goes up as the BED value declines). Using the same ranking, applied to cases, but now with A9 BED values calculated correctly, by also including the isocenter gap times, the BED values no longer descend progressively with the original ranking number. This indicates a change in the sequence of cases when using the initial ranking number, based on beam-on-time only, thus ignoring the small but variable number of gaps between isocenters (*red line*). (**B**) Ranking errors are shown with respect to ranking A9 BED values using beam-on-time in descending order. The case ranking error denotes the positional ranking change when ranking A9 BED values using overall treatment time in descending order.

Of overriding importance, irrespective of which of the 2 methods are used was the need to use the overall treatment time, namely the beam-on-time plus the total set-up time between all isocenters, the beam-off-time. This is because, as pointed out previously,[20] 'repair of sublethal radiation damage begins at the start of irradiation and thus the longer the treatment time, inclusive of both scheduled and unscheduled gaps, when repair of sublethal damage continues to occur but when no additional damage is produced, the lower the biological effectiveness of any given dose'. Comparable to the statements in Jones and Hopewell,[2] namely the equations given are applicable provided

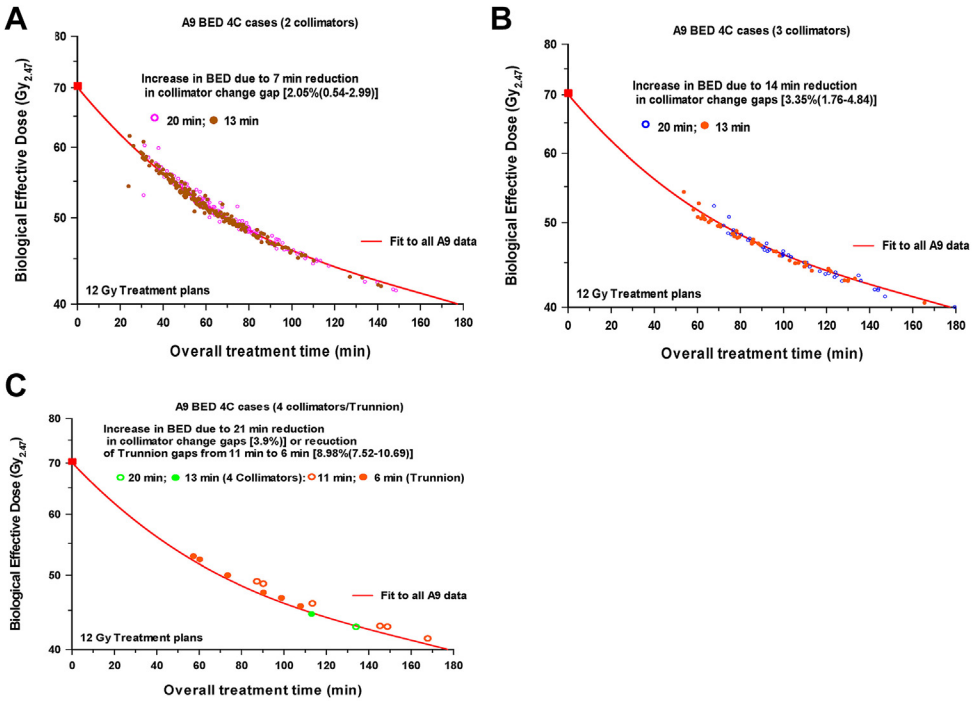

Figure 10. Effects of shortening the overall treatment times for using the 4C Gamma Knife by either a reduction of the estimated time allowed for a collimator change from the original 20 minutes down to 13 minutes and the isocenter change time from the original estimated 11 minutes down to 6 minutes. This involved a reduction in overall treatment time of 7 minutes for 1 collimator change (**A**) and 14 minutes for the use of 3 collimators (**B**). A 4 collimator case (21-minute reduction) and the results for 6 pure Trunnion Mode cases are plotted separately (**C**).

the "beam-on" and "beam-off" times were known. The overall treatment duration, allowing for repair during each radiation exposure and in the nonexposure intervals between each of a variable number of isocenters. Moreover, earlier publications using the voxel-by-voxel approach to calculate the BED have also emphasized the need to use the overall treatment time (inclusive of the beam-off-time).[15,16] Indeed the initial publication, illustrating the application of the BED concept to radiosurgery,[21] illustrated the impact of changing the average gap time between isocenters for the Model B GK from 8 to 6 minutes and more significantly the impact of the greatly reduced gap time with use of Perfexion for the same shot sequence, namely the same beam-on-time.

In the direct comparison of individual treatments, BED values, calculated using the bi-exponential A9 equation, the disparity in BED values obtained using the beam-on-time, as opposed to the correct overall treatment time, was very much dependent on the treatment and equipment use. In particular, for 4C cases the number of collimator helmets and the use of the APS versus Trunnion Mode, for which some gap times had to be estimated. The failure to include the estimated beam-off-time in the equations resulted in a 0%–40.3% overestimate of the real BED value. This is the difference between treatment given as a single isocenter treatment and multiple large gaps between isocenters when the GK was used in Trunnion Mode. Differences in shot and collimator change times between different centers also impact the BED values calculated.

For lesions treated with Perfexion, the impact of only using the beam-on-time, on the BED values calculated, using the A9 equation were small, comparable to the physical dose uncertainty in GammaPlan. However, a comparison of treatments using the A9 calculations using the equation correctly, inclusive of gap times, will still always give lower BED values than when using only the beam-on-time. The difference was associated with the number of isocenter gaps associated with the treatment. In this series, the ranking of cases by beam-on-time BED values, indicated a change in ranking relative to the improved calculation involving the overall treatment time with an estimated average beam-off time of 0.06 minutes between isocenters.

The original publication[1] of the results for the present cases used the simplified Table 1 mono-exponential equations[2] to estimate the BED using beam-on-time only. However, those equations were originally derived using the overall treatment time as the correct input. An additional limitation was the overall treatment time range applicable for the use of Table 1 should be between 25–130 minutes. This is because, as used here, a mono-exponential relationship was approximated to A9 BED values to obtain these simplistic equations. The overall relationship between A9 values and overall treatment time is more complex because the A9 equation included a fast as well as a slow

Table 2. Percentage Incidence (±SE) of Tumour Progression and Radiographic Oedema Which May be Asymptomatic or Symptomatic Requiring Medication as a Function of Both the A9 BED (Based on the Overall Treatment Time) and Mean Target Volume (12 Gy Prescriptions Doses Only)

BED Range ($Gy_{2.47}$)	Sample Size	Distribution (%)	Mean A9 BED ($Gy_{2.47}$)	Mean Target Volume (cc)	Tumour Progression (%)	Radiographic Oedema (%)	+ Symptomatic (%)
All Cases							
60+	20	3.3	61.495 ± 0.329	0.635 ± 0.154	5.0 ± 4.87	0.0 ± 0.0	0.0 ± 0.0
<60 >55	153	25.2	57.197 ± 0.106	1.484 ± 0.146	6. 54 ± 2.0	11.1 ± 2.54	4.58 ± 1.69
<55 >50	226	37.3	52.523 ± 0.093	2.264 ± 0.147	2.65 ± 1.07	19.6 ± 2.5	7.9 6 ± 1.8
<50 >45	166	27.4	47.782 ± 0.109	3.046 ± 0.176	5.42 ± 1.76	20.5 ± 3.1	10.84 ± 2.41
< 45	41	6.8	43.079 ± 0.204	5.099 ± 0.378	2.14 ± 2.1	35.0 ± 7.5	9.76 ± 4.63
4C cases							
60+	4	1.5	62.638 ± 1.4	1.265 ± 0.568	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
<60 >55	29	10.7	56.846 ± 1.213	1.296 ± 0.276	10.34 ± 5.65	13.79 ± 6.4	6.9 ± 4.71
<55 >50	91	33.6	52.433 ± 0.141	1.575 ± 0.175	1.2 ± 1.14	17.58 ± 3.99	7.7 ± 2.79
<50 >45	117	43.2	47.878 ± 0.128	2.577 ± 0.174	5.13 ± 2.04	15.38 ± 3.34	5.98 ± 2.19
< 45	30	11.0	42.939 ± 0.232	4.534 ± 0.4	10.0 ± 5.48	23.33 ± 7.72	16.67 ± 6.8
PFX cases							
60+	16	4.8	61.209 ± 0.215	0.4775 ± 0.115	6.25 ± 0.05	0.0 ± 0.0	0.0 ± 0.0
<60 >55	124	37.0	57.279 ± 0.119	1.529 ± 0.168	5.65 ± 2.07	10.48 ± 2.75	4.03 ± 1.77
<55 >50	135	40.3	52.584 ± 0.124	2.729 ± 0.207	3.7 ± 1.62	20.74 ± 3.49	8.15 ± 2.35
<50 >45	49	14.6	47.553 ± 0.206	4.166 ± 0.4	6.12 ± 3.42	34.69 ± 6.8	22.45 ± 5.96
< 45	11	3.3	43.461 ± 0.415	6.641 ± 0.748	0.0 ± 0.0	54.45 ± 15.02	9.09 ± 8.67

component of repair of sublethal damage (a bi-exponential function). Thus its application to the present data set, even if applied correctly, would not have been totally accurate. BED values estimated above and below the original stipulated overall treatment time range, using this approach, would be underestimated, relative to the use of the A9 equation. This effect was noted in the original methods paper[2] and is implicit in the extrapolation numbers (i.e., the intercept values) in the equations provided for the different physical doses. Also implied in the original modelling publication was that the Table 1 style mono-exponential approximations would also be dependent on the study population used to derive the simplistic equations to estimate the BED. Evidence for this was also obtained for this in the present study, where there was a minor but insignificant change in the mono-exponential parameter obtained from the A9 values, over the time range 25–130 minutes, for the 4C versus Perfexion cases. This can simply be explained by the different distribution of cases over this time range in the 2 groups of cases as was indicated as being likely to be the case in the original publication.[2]

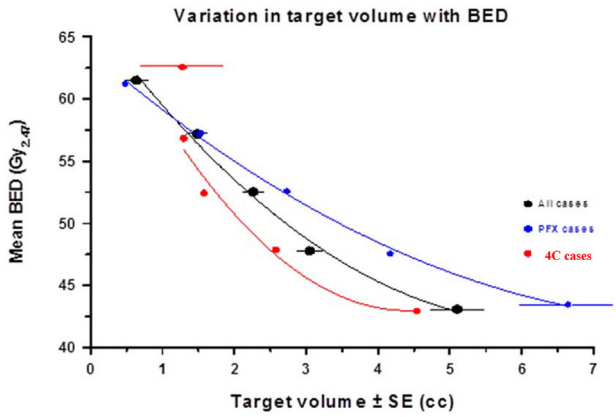

Figure 11. Variation in BED with target volume. The BED declines as a function of the target volume, due to the increased complexity and time taken to treat larger volumes. In this respect the decline in BED with volume is greater for the 4C Gamma Knife due to the added contribution made to the overall treatment time by the beam-off-time.

The original publication by Villafuerte et al.[1] is not the only publication to use the Table 1 estimates of the BED or the A9 calculations of BED, as originally described.[2] Indeed in a number of publications the actual equations used are not actually given, although the use of Jones and Hopewell[2] is alluded to. For authors, reviewers, and editors it should be an essential requirement that the actual equations and any assumptions associated with the use of the prescribed method are clearly indicated in the manuscript. These assumptions would include any estimates of the scheduled gaps between isocenters, to enable an estimate of the overall treatment time,

as was carried out in the present study, because some of these may depend on the procedures used. If authors use the more complex A9 equation from Jones and Hopewell,[2] this should be associated with a statement of the α/β ratios and the repair half times used. An α/β value of 2.47 Gy with fast and slow repair half-times of 0.19 and 2.16 h are implicit in the BED estimates obtained using Table 1 equations[2] correctly.

Table 3 lists a series of recent publications where the degree to which this essential information is given is limited or unclear. In the majority of these publications only the beam-on-time is used in the calculation of BED, even though this is not in agreement with the fully justified requirement to use overall treatment time in the original methodology publication.[2] The removal of what can be a very variable "beam-off-time" from the calculations can only imply that it was considered that NO repair occurs over this time period and that the impact of time on the BED was restricted to repair only occurring over periods of radiation exposure. However, no evidence is provided to support this assumption. Indeed such evidence does not exist; in fact the reverse is true because studies with variable gaps between multiple radiation exposures have been used in the past[29-31] to establish the kinetics of repair of sub-lethal damage. The most recent of these publications[31] included data with variable gaps between doses and also variable dose-rates. The parameters obtained, for this enzyme based DNA repair process, were comparable to those proposed by Pop et al.[17] using variable continuous exposure times. Thus repair does take place in the beam-off-time and cannot be arbitrarily ignored, simply because the essential data has not been collected in a number of centers. Two of these publications also evaluate BED values for cases with acoustic neuromas. In the study by Berger et al.[27] it has been confirmed, in a personal communication, that the Table 1 approach was used; the equation used for a dose of 12.5 Gy was obtained by extrapolation from the available equations for 12 and 13 Gy, was consistent with the predictions from Jones and Hopewell,[2] namely,

$$BED = 70.52\ e^{-0.00325T}$$

therefore, an upper BED estimate of 70.52 $Gy_{2.47}$, for an instantaneous exposure, is applicable for this dose using this approach. The BED values quoted in the publication are consistent with the above equation. The publications for the same target by Tuleasca et al,.[25] involved a prescription dose of 12 Gy. The paper states that BED values were calculated using similar approaches, as proposed by Jones and Hopewell,[2] but no details are given. However, a reference to the limitations of the mono-exponential fit strongly suggests that a Table 1 equation[2] was used. However, a BED range 73.9–54.1 $Gy_{2.47}$, for treatments delivered over 7.3 to 101.8 minutes, is not consistent with the present findings and those of Berger,[27] suggesting an error in the calculations. However, without the essential information on the equation used, no conclusive judgement can be made. Both publications[26,27] had the same limitation of only using the "beam-on-time" in the calculations for Perfexion cases.

Studies involving the treatment of Cushing disease[24] or arteriovenous malformation (AVM's),[25] which also failed to give information on the equations also only used the beam-on-time

Table 3. A Summary of SRS BED Clinical Studies in the Literature Including Conclusions and Calculation/Estimation Methods Used

Author, Year (Indication)	Conclusion	Was BED Calculation Method Stated?	BED Method Used	Calculation or Estimate?	Was Overall Treatment Time as Opposed to Beam-On-Time Used?
Tuleasca et al. 2019 (TN)[22]	BED a better predictor of Hypoesthesia than physical dose.	Yes	Full bi-exponential equation for single iso-centre treatment	Calculation	Yes
Graffeo et al. 2020 (Pituitary)[18]	BED a better predictor of hormone	Yes	Jones & Hopewell Table 1	Estimation	Yes for U, B and C cases
Nesvick et al. 2021 (AVM)[23]	BED a better predictor of AVM occlusion	Yes	Jones & Hopewell Table 1	Estimation	Yes for U, B and C cases
Balossier et al. 2021 (Cushings)[24]	BED a 'potential' predictor of remission rates	No	Jones & Hopewell Table 1: not applicable for all doses used	?	No
Tuleasca et al. 2021 (AVM)[25]	BED the strongest predictor of obliteration	No	Not stated	Estimation	No
Tuleasca et al. 2021 (VS.)[26]	BED a better predictor of tumour shrinkage	No	BED values not compatible with the dose used	Estimation	No
Berger et al. 2022 (VS.)[27]	BED a better predictor of hearing deterioration	Correct reference not given	Jones & Hopewell Table 1: with interpolation (K Bernstein, personal communication)	Estimation	No
Huo et al. 2022 (Meningioma)[28]	BED is a predictor of local control	Yes	Jones & Hopewell Table 1	Estimation	No

SRS, radiosurgery; BED, biologically effective dose.
Improving the accuracy of BED estimates, from a previously published study, after radiosurgery for acoustic neuromas.

in the calculations. However, in this instance either all cases[24] or a significant number of cases,[25] involved the use of the Model C GK and hence the potentially significant, variable impact, of the effect of the beam-off-time was ignored. This will result in a variable, unknown, overestimate of BED values, irrespective of which approach was used to calculate/estimate the BED values. The publication by Balossier et al.[24] also involved the use of a higher dose than those provided by the simple Table 1 approach and thus, if used, details as to how those equations were derived should ideally be provided.

Two sets of analyses from the Mayo Clinic[18,23] used the Table 1 style equations[2] with the inclusion of estimated time gaps using the older GK models. However, no such adjustment was made for the Perfexion cases. In addition, the restrictions in overall treatment time range were not taken into account. The most recent publication from the Toronto group[17] involving the treatment of meningioma, also only used the beam-on-time to estimate BED values using Table 1 equations.[2]

In this re-evaluation, using the overall treatment time and A9 BED values, the data originally presented by Villafuerte et al.[1] continued to show that BED was not associated with LF, radiologic edema, or symptomatic edema. Careful consideration of BED, with clinical outcomes, must therefore also consider confounding factors such as tumor volume. Thus, the impact of the target volume on BED values was also investigated as a potential confounding factor; large volumes tend to be associated with more complex and hence potentially longer overall treatment times. The results of this investigation supported the hypothesis since lower BED values were associated with larger volumes, the decline in BED with volume being more marked for 4C cases because more complex treatments were also associated with a more marked escalation of the overall treatment time and hence a decline in BED values. Thus this is a potential confounding factor in the interpretation of SRS data in relation to BED. Radiologic or symptomatic edema, was reported to occur more frequently following the treatment of larger volume tumors in the original publication.[1] This is equally the case in the present re-evaluation, based on the 12 Gy cases alone, even though as a consequence of the more complex treatments, this was associated with a decline in the BED with volume. This would suggest that had cases been treated to achieve an iso-BED level then the rise in radiologic or symptomatic edema, with volume would have been even greater. The relationship between the incidence/severity of adverse effects, in particular for small volumes/field dimension, is well established from animal studies.[32] The original publication[1] suggested that local failure was more frequent in larger diameter tumors. Based on the present subgrouping of patients by BED values, which was associated with a decrease in BED with an increase in the target volume, no significant BED or volume-related effect could be demonstrated. However, overall levels of local failure were very low, making the detection of significant change either by BED or target volume difficult.

CONCLUSION

The present re-evaluation of the BED values given in a previous publication[1] has demonstrated the essential requirement to always use the overall treatment time in either the direct or estimated calculation of BED values, because of the impact of variable beam-off-time intervals associated with any GK treatment. While it may be standard SRS practice to record beam-on-time, use of this parameter should not be used in isolation as BED values will be over-estimated by variable amounts. It is recommended that GK centers record the overall treatment time (beam-on and beam-off times including scheduled/setup gaps and unscheduled gaps). The significance of recording unscheduled gaps, where repair of DNA damage continues, needs to be emphasized in the SRS community. The significant impact of a single 15-minute unscheduled gap on BED values has recently been demonstrated for Perfexion cases of acoustic neuroma treated with either 12 or 13 Gy.[19]

Reasonable estimates of the beam-off-time must be included if the full records are not available, such records are essential if the effects of unscheduled gaps in treatment, which also impact BED values, are to be included.[19] The Table 1 style equations[2] do allow a rapid estimate of BED values if used appropriately, but the limits need to be fully recognized along with the recognition that the inherent α/β ratio and repair parameters cannot be changed. The simplified BED equation, A9, represents the most convenient alternative option, even though its use is more complex. In this respect, it is planned to publish details of further developments associated with the use of the A9 approach and this will include an application which will calculate BED values on the input of a number of basic treatment parameters (Moore et al.—in preparation). This will also relate the A9 findings to those obtained using the more detailed voxel-by-voxel approach to the calculation of BED.[15,16]

Revision of the original study,[1] using corrected BED values also highlights the importance of being aware that target volume can be a major confounding factor in the interpretation of the results of SRS studies.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

John W. Hopewell: Conceptualization, Methodology, Investigation, Writing — original draft, Writing — review & editing, Final edit. **Joshua Moore:** Investigation, Formal analysis, Writing — review & editing, Approve final manuscript. **Conrad J. Villafuerte:** Writing — review & editing, Approved final manuscript. **Ian Paddick:** Conceptualization, Methodology, Investigation, Writing — review & editing, Approve final manuscript. **Bleddyn Jones:** Conceptualization, Methodology, Investigation, Writing — review & editing, Approve final manuscript. **Mark A. Hill:** Administrative support, Writing — review & editing, Approved final manuscript. **Derek S. Tsang:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing — review & editing, Approved final manuscript.

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