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Abbreviations: BED – biological effective dose; GK – Gamma knife; TN – Trigeminal Neuralgia; SRS – Stereotactic Radio-surgery; CDR – Calibration dose rate; AVM - arterial-venous malformations; CNS – Central nervous system; HDR – high calibration dose rate; LDR – low calibration dose rate

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ABSTRACT

OBJECTIVES How variations of treatment time affect the safety/efficacy of Gamma Knife (GK) radiosurgery is a matter of considerable debate. Due to the relative simplicity of treatment planning for trigeminal neuralgia (TN) this question has been addressed in a group of these patients. Using the concept of biologically effective dose (BED) the effect of the two key variables, dose and treatment time have been taken into account.

METHODS A retrospective analysis was carried out on 408 TN cases, treated between 1997 and 2010. Treatment involved the use of a single 4 mm iso-center. If conditions allowed, the iso-center was placed at a median distance of 7.5 mm from the emergence of the trigeminal nerve from the brain stem. Effects were assessed in terms of the incidence of the complication, hypoesthesia, or in terms of efficacy, the incidence of 'pain free' after 30 days and at 1 and 2 years. These responses were evaluated with respect to both the physical dose and the biological effective dose (BED), the latter using a bi-exponential repair model.

RESULTS Re-evaluation showed that the prescription doses, at the 100% iso-dose, varied between 75 and 97.9 Gy, delivered over 25 - 135 min. The relationship between physical dose and the incidence of hypoesthesia was not significant; the overall incidence being approximately 20%. However, there was a clear relationship between BED and the incidence of hypoesthesia, the incidence increasing from < 5% after a BED of ~1800 $Gy_{2.47}$ to 42% after ~2600 $Gy_{2.47}$. Efficacy, in terms of freedom from pain, was approximately 90%, irrespective of the BED (1550-2600 $Gy_{2.47}$) at 1 and 2 years. There was a suggestion from the data that 'pain free' status developed more slowly at lower BED values.

CONCLUSION These results strongly suggest that safety/efficacy may be better achieved by prescribing a specific BED instead of a physical dose. A dose/time to BED conversion table has been prepared to enable iso-BED prescriptions. This finding may dramatically change dose-planning strategies in the future. This concept needs to be validated in other indications where more complex dose-planning is required.

INTRODUCTION

Gamma Knife (GK) Radiosurgery is an effective treatment for trigeminal neuralgia (TN), advocated in numerous patient series, including the reporting of long and very-long term results.[17,23,24,31] The results of a prospective clinical trial,[16] established the minimum effective dose for TN of 70 Gy for GK treatments. Recently, the International Stereotactic Radiosurgery Society review paper considered the maximum dose to be 90 Gy.[23] Several other factors could also play a role in the safety and efficacy of SRS for classical TN. The time taken to deliver any given SRS treatment, using a GK, varies significantly. For example, the total treatment time of SRS for TN, which by virtue of the use of a single iso-center is likely to give the smallest variation possible, by a factor of ~ 4. However, where multiple iso-centers are used this may vary by a factor of up to 10.

There are multiple factors that lead to this variability. Historically, the decay of the Cobalt-60 sources, with a half-life of 5.26 years, has been considered a major factor. For comparable treatment plans, the beam-on time will become progressively longer with time such that, by one half-life, the beam-on time would double. However, the introduction of progressive plugging/sector blocking would have the same effect. In addition, collimator factors and individual patient geometry will also affect the beam-on time. Time gaps in treatment may be scheduled or unscheduled, although this is less likely in the case of the treatment of TN where treatments are most frequently given as a single continuous exposure. Then clearly, for a given prescription dose, the source activity, the degree of beam/sector blocking and patient geometry are the only factors that influence the duration of the total treatment time for TN.

The GK calibration dose rate (CDR) has recently been indicated to play a role in the safety and efficacy of SRS for TN.[1,2] In addition, Lee et al[18] suggested treatment with a CDR of > 2 Gy/min produces an earlier and more long-lasting pain relief, with a lower recurrence rate, than a CDR of < 2 Gy/min, in a series of 133 patients treated with the same prescription dose of 80 Gy.

Retrospective analysis of SRS data has frequently resulted in confounding results. For cranial nerves,[15] morbidity was reported to be higher in those that were treated in shorter times with new sources compared with those treated in a longer time with older sources, an effect that was said to be related to the CDR. In contrast, a multi-variate analysis of the complications associated with the treatment of arterial-venous malformations (AVMs) found no such correlation,[8] although there are many more treatment variables in patients treated for

the closure of AVMs. However, it was also suggested, in the same publication, that a smaller number of iso-centers may increase the efficacy of a given prescription dose.[8] Clearly the use of fewer iso-centers will result in fewer repositioning gaps, which with the older models of Gamma Knife would have also greatly reduced the overall treatment time.

The CDR, a physical measurement in a standard phantom, is not the same as the dose-rate in tissue in an individual patient. This is because this 'in patient' parameter not only depends on the activity of the sources (CDR) but also on the collimator(s) used, the individual patient geometry and the degree of plugging/sector blocking, which vary for a fixed CDR. The dose-rate in an individual patient, at the prescription iso-dose, depends on the prescription dose and the total treatment time, both of which vary.

It has been long been recognized that the biological effectiveness of a given physical radiation dose, in tissue, declines as a function of increasing exposure time. This was classically illustrated by cell survival studies where different doses are delivered at fixed dose-rates.[3] However, in a recent study a range of doses have been delivered over fixed times.[12] This more directly mimicking the SRS situation where the target is irradiated simultaneously at different dose-rates e.g. the dose-rate at the 50% iso-dose is half that at the 100% iso-dose, because treatment to all areas is given in a fixed time. The effect of a range of doses was shown to be progressively reduced with increasing exposure times. Thus doses needed to be increased to maintain the same level of effect (cell survival). Comparable effects have been seen in CNS tissue.[22]

The importance of the two variables, treatment time and dose, can only be evaluated appropriately using the concept of biologically effective dose (BED) where the impact of the changes in treatment time can be taken into account for the different doses prescribed.[14,21] The purpose of the present study was to evaluate whether this parameter would be of help in the evaluation of the safety and efficacy of SRS for TN. This was investigated in a large historical cohort of patients treated using the GK for classical TN. Due to the variety of radiation doses used in this cohort of cases, the use of minimal and/or extensive use of plugging or sector blocking, the effect of large variations in BED could be investigated. This was expressed in terms of three measures of safety and efficacy: pain free incidence (acutely, at 30 days), maintenance of pain relief at 1 and 2 years, and the overall incidence of hypoesthesia. The bias associated with confounding factors was also considered.

MATERIALS AND METHODS

Type of study

A retrospective analysis has been carried out on a historical cohort of cases presenting with intractable classical TN, treated between 1997 and 2010, using GK (Elekta Instrument, AB, Sweden) based SRS.

Patient population

Previously, clinical parameters were carefully studied for a cohort of 497 patients with more than one year of follow-up.[25,26,27] In order to analyse a more homogeneous cohort of TN cases, in strict relation to the radiation treatment, cases related to compression of the mega-dolicho-basilar artery,[28] multiple sclerosis[29] or those that had had a previous GK procedure,[30] were excluded from the present analysis, as these could change the radio-sensitivity of the trigeminal nerve. Thus a total of 408 patients were selected for the present study to examine the influence of either the total physical dose or its modification, as a consequence of the variation in treatment time, expressed as the BED.

Radiation treatment technique

From August 1997 until March 2000 the Model B GK was exclusively used for 104 (25.5%) cases. The Model C, introduced in May 2000 was then used to treat a further 133 (32.6%) cases. This was replaced by a Model 4C in September 2006 to which a Perfexion® was added in February 2007. Up until November 2010, these machines were used to treat 153 (37.5%) and 18 (4.4%) cases, respectively. Over this period the use of Perfexion® was intentionally avoided, as it does not allow individual beam blocking.

TN treatments at the Marseille University Hospital involve the use of an anterior target position (the retrogasserian target). This meant that the iso-center was placed at a median distance of approximately 7.5 mm from the emergence of the trigeminal nerve from the brain stem, if anatomical conditions allowed. In the treatment planning process, a dose of 90 Gy was initially prescribed, at the 100% iso-dose. Beam blocking (‘plugging’) was then used, depending on the maximum dose received by a 10 mm^3 volume of the brainstem. It was intended that if this dose exceeded 15 Gy, the prescription dose was usually reduced, initially to 85 Gy, or further down to 80 or 75 Gy. Beam blocking was finally applied to further decrease the dose to the brain stem if required.

In the initial years covered by the present study a change was introduced to the output factor of the 4 mm collimator, namely from 0.80 to 0.87,[10] although this change has not been

appropriately acknowledged in many retrospective studies.[1] For the purposes of the present study a retrospective analysis of the treatment plans was carried out, this revealed that two different output factors were used for the 4 mm collimator of the Models B and C GK, despite using the same collimator system on both machines. This change was adopted when the Gamma Knife was upgraded to the Model C in May 2000. As a consequence, treatments delivered to 104 cases with the Model B were given a dose that was higher than prescribed, by a factor of 0.87/0.80, or nearly 9%.

Treatments were divided into two sub-groups; those using 20 or less plugs vs those with greater than 20 plugs. Plugging affects the shape of the iso-dose and hence the length of nerve irradiated, 20 plugs indicates that just under 10% of total irradiation beams were blocked, which changes the diameter of the 50% iso-dose of the 4mm collimator by ~ 0.3mm, or 5% of its diameter. This variation in iso-dose shape was less than that associated with the anatomical variations between patients and was considered negligible. Patients with zero to ≤ 20 plugs were classified as 'unplugged', those with more than 20 plugs were considered 'plugged'. The average number of plugs in this latter group was 37.2 (median 34, range 21 – 96 plugs).

Calculation of biologically effective dose (BED)

For Gamma Knife SRS single continuous exposures the BED is calculated using the equation:

$$\mathrm{BED} = D_T + \frac{1}{\alpha/\beta}\left[\frac{\varphi(\Xi,\mu_1) + c\varphi(\Xi,\mu_2)}{1+c}\right] D_T^{\,2}$$

where D_T represents the total physical prescription dose, at the 100% iso-dose, given as a single continuous exposure. The same equation can also be applied to calculate the BED for the physical doses on any other physical iso-surface. The α/β ratio is a tissue specific constant and in this study a value of 2.47 Gy has been used as applicable for a nerve originating from the brain stem (CNS white matter). The term $\varphi(\Xi,\mu)$ is a complex function of the protocol and the repair rates; the effects of dose-rate and the exposure time are mediated via this function, the full definition of which can be found elsewhere.[20] The parameters 'μ_1' and 'μ_2' represent two sublethal radiation damage repair rates that are associated with protracted exposures and 'c' the partition coefficient of the slower component ('μ_1' > 'μ_2'). It should be noted that the absolute partitioning between the two repair processes 'μ_1' and 'μ_2' is 1.0/[1+c] and c/[1+c], respectively. Experiments in the rat spinal cord were used to derive the values of

the repair kinetic parameters for normal CNS white matter.[2] Half-times for the repair of sublethal irradiation damage of 0.19 h ($\ln 2/\mu_2$) and 2.16 h ($\ln 2/\mu_1$); partition coefficient 'c' (0.98), were obtained from these studies with an associated α/β ratio of 2.47 Gy. The units associated with BED values are also Gray as modulated by the value of the α/β ratio used in the calculations, and hence is designated by the units $Gy_{2.47}$ so as not to be confused with the unit of physical dose, which is a measure of absorbed energy in tissue.

Data analysis

A retrospective study of this type is always associated with concerns as to the introduction of bias from likely confounding factors.[4,5] When assessing the risk of hypoesthesia in relation to SRS only hypoesthesia in the absence of subsequent procedures, including further SRS using the GK can be included. Patients without previous hypoesthesia that developed the condition after a further intervention, due to failure of the primary treatment were thus considered as lost to follow-up for toxicity. The degree of beam blocking is also a potential confounding factor in relation to the risk of toxicity, due to the so called "Flickinger effect".[9] The presently quoted 100% prescription dose can, at best, be considered to be a surrogate for an, as yet unknown, actual physical dose/biologically effective dose at some critical distance along the nerve from the current reference point. Thus cases treated were divided into two sub-groups; those using 20 or less plugs and those with greater than 20. To investigate the bias associated with plugging the analysis compared all patients with those with ≤ 20 plugs.

Subsequent surgery, and its timing, either as a result of the failure of the initial GK treatment or as a consequence of relapse was also considered as a confounding factor in the evaluation of the pain free status of patients acutely (30 days) and at 1 and 2 years after SRS. Evaluated was the time at which patients reported being pain free and in those where treatment failed the subsequent date of further surgery. For those that responded, but subsequently relapsed there was, particularly in the first year, further investigations undertaken to determine the likelihood as to whether this relapse was either transient or permanent, as this impacted on the pain free incidence at 1 and 2 years after SRS.

Physical dose and BED related changes in the incidence of hypoesthesia and pain free rates, acutely and at 1 and 2 years after radiosurgery were evaluated, where appropriate using weighted probit analysis [35,36] and associated software (SAS System, v8). Probit analysis allows the proportional weighting of groups according to their size, which is essential to ensure unwanted bias, particularly from small outlying groups.

In this model the physical dose/BED (D) is a continuous variable. It is assumed that the initial rate of change in effect (E) with D is S, and that S decreases in proportion to D, representing a progressive saturation effect controlled by the constant k, so that

$$dE/dD = S - kD$$

Integration of both sides and rearrangement leads to

$$E = S/k(1 - \text{Exp}[-kD])$$

where S/k represents the maximum possible 'plateau' value of E and D is the physical dose but may be substituted by BED, in which case the values of S and k will differ. Equations of this form are commonly used in all the physical sciences, including biomedical applications in classical pharmacokinetics.[11]

RESULTS

Re-evaluation of prescribed physical dose and calculation of biologically effective dose (BED)

The original planned physical doses prescribed in this cohort of patients were 70 to 90 Gy. Re-evaluation of these physical doses, based on the adoption of the change in the 4 mm collimator factor, resulted in a revised dose range of 76.1 - 97.9Gy. The numbers of cases treated with the different prescription doses are shown in Table 1. Relatively few cases were treated with a prescription dose of 75 Gy and 76.1 Gy and thus physical dose-effect relationships can only be meaningfully be evaluated for doses $\geq$ 80 Gy.

The variation in BED, as a function of the physical prescription dose and the treatment time are given in Figure 1. The line for each physical dose represents the full range of BED values for that specific physical dose, with the open symbols representing the actual range of values for cases treated using $\leq$ 20 plugs, while the solid symbols represent those cases with >20 plugs. The highest BED value was 2665.5 $Gy_{2.47}$ (90 Gy in 26.95 min), the lowest 1539.4 $Gy_{2.47}$ (75 Gy in 61.87 min). This represents a 75.0% variation in BED in this patient population compared with a 30.5% variation in the physical dose. By way of an example, this indicates that 80 Gy in 30 min is approximately equivalent to either 85 Gy in 50 min; 87 Gy in 60 min or 97.9 Gy in 120 min.

The patient population was subdivided into 8 groups, each with a BED range of 142.5 $Gy_{2.47}$ (Table 1). The numbers of cases in the two lowest BED grouping were low, largely representing the few cases treated with the two lower doses, 75 and 76.1 Gy and a few cases in the 80 Gy prescription group, where treatment times were protracted because of extensive plugging.

Dose and BED related changes in the incidence of hypoesthesia onset after SRS

The physical dose-related changes in the incidence of hypoesthesia are shown in Figure 2A. Evaluation using probit analysis suggests a slight trend in the relationship between the incidence of hypoesthesia and the physical prescription dose, however, this trend was not statistically significant and 95% confidence intervals could not be calculated. A direct comparison of the two of the larger groups (80Gy and 97.9Gy) showed no significant difference in hypoesthesia (13.3 ± 6.2% and 22.2 ± 6.9% respectively).

Due to paucity of data in 3 of the 4 lower dose groups there was insufficient evidence to indicate that plugging (>20 up to a maximum of 96 plugs) had any effect on the incidence of hypoesthesia.

For the evaluation of the incidence of hypoesthesia, as a function of BED, the response relationship was initially examined for cases that were 'unplugged' and this result was compared with the evaluation of all cases, irrespective of the level of plugging. The results of these two analyses are illustrated in Figure 2B, data points are plotted as the mid-point in the 8 BED ranges identified in Table 1.

For BED values in the range 1535 – 1962.6 $Gy_{2.47}$ no 'unplugged' cases of hypoesthesia were found. However, the number of cases with ≤ 20 plugs was small, representing 1, 1 and 4 cases, respectively, for the 3 lowest BED groups. Above these values there was a progressive increase in the incidence of hypoesthesia with increasing BED, such that in the highest group (2535.5 – 2675 $Gy_{2.47}$) the incidence was ~ 45% (compared with ~ 5% for a BED of ~ 1820 $Gy_{2.47}$). A clearly defined BED-effect relationship was obtained with associated 95% confidence intervals. When cases were included with > 20 plugs a BED effect relationship was still obtained, slightly less steep, but not significantly different from that obtained for the initial evaluation. However, the 95% confidence intervals were very wide (excluded for clarity). The underlying reason for this difference was the high incidence of hypoesthesia in the lower BED groups associated with extensive plugging (34 – 96 plugs), as described above. The incidence of hypoesthesia, in the higher BED ranges, did not differ significantly in the two approaches to the analysis.

Based on the BED effect curve given in Figure 3, for 'unplugged cases' it is possible to determine the BED values associated with differing levels of effect, namely those associated with either a ~ 5, 10, 20% or 40% incidence of hypoesthesia; 1820, 2105 2390 and 2600 $Gy_{2.47}$, respectively. The physical dose and treatment time combinations that are

equivalent to these BED values are obtained from Figure 1 and plotted in Figure 3, which in effect provides a basis for a 'look up table' enabling a user to prescribe a physical dose, given in a particular treatment time to achieve iso-BED values associated with ~5 and ~10% incidences of hypoesthesia (Table 2). The critical question arising; is there a significant increase in the long term pain free rates associated with this escalation in BED?

Changes in the incidence of acute and long-term pain free rates in relation to BED

The time to the onset of pain relief after SRS varied, occurring as early as the day of irradiation out to 180 days. Only 21 patients in this cohort were classified as non-responders. These patients opted for a further interventional procedure but at different times after the initial SRS. In six cases the timing of the additional procedure was 8 – 149 days, well within the time range normally associated with the loss of pain. As these six cases could have potentially responded, they were classified as lost to follow up to prevent an under estimate of the response to SRS. The remaining 15 cases were classified as true non-responders to SRS following a further intervention after 200 days to 12.9 years.

There was an initial group of 22 responders that experienced an apparent relapse within the first 12 months, in 10 this relapse occurred within 6 months. These cases did not opt for a further intervention and on closer examination it was found that 16 (72.7%) of these cases only experienced a transient relapse and were pain free at 1 year.

There was another cohort of 26 cases that also showed an apparent relapse in the first 12 months (13 within 6 months), but these opted for an additional procedure. By analogy it is estimated that in the majority of these cases ((72.7% of 26 = 19 cases) this relapse would only have been transient and only a small number would have been permanent (7 cases). All these cases were excluded from the present analysis since the nature (transient/permanent) could not be identified.

In the longer term, of those that showed an initial response, that then relapsed and opted for a further intervention, this was carried out at intervals from 12.1 – 117.4 months after SRS (47 cases). The date of relapse was not given in the database, only the time of the intervention. Since the time between treatment failure and any further intervention has been shown to vary very considerably, these cases have also had to be excluded from the analysis to avoid bias.

Based on these observations the acute (30 day) pain free incidence was first assessed as a function of both the BED and the physical prescription dose (Figure 4 A and B). Using probit analysis a trend was found using both approaches, the incidence of 'pain free' rose

from ~ 60% for the lowest to ~80% for the highest BED group/physical dose. However, these trends were not statistically significant.

In an alternative approach both data sets were fitted using a saturation model, assuming the effect reaches a plateau after a given BED/physical dose. For BED a plateau indicating a pain free incidence of ~ 80 % was found for cases in the range 1677.5 – 2676 $Gy_{2.47}$ (Figure 4A). Efficacy in the lowest BED range (1535- 1677.5 $Gy_{2.47}$) was approximately half this value (43%). However, the number of cases in this BED group and the next grouping are low (7 cases each), which reduces the confidence that can be put on these values.

For physical dose (Figure 4B), a plateau of pain free incidence at ~ 75% was obtained for a dose > 80 Gy. However, the interpretation of the incidence at lower doses is difficult because 3 of the 4 lowest doses are associated with only 2- 5 cases (Table 1) making further evaluation difficult. Since the incidence of hypoesthesia was closely correlated with BED and not physical dose, the key parameter on which to assess the pain free incidence has to be BED in order to establish any therapeutic ratio.

The BED related changes in the incidence of 'pain free' at 1 and 2 years after irradiation are given in Figure 5A and 5B, respectively, where a comparison is made with the acute response. At both time periods, there was no significant variation in the pain free incidence with BED; at 1 year the average incidence was a little over 90% and at 2 years a little under but over none of the BED ranges was the change significant. The effects of plugging were also investigated. Of the 3 unplugged cases in the 1535- 1677.5 $Gy_{2.47}$ grouping the pain free incidence was 66.7 ± 27.2%, an incidence that was not significantly different from that of the total group. For all other BED groups the pain free incidence was not significantly different from that for all cases, irrespective of the degree of plugging, e.g. 1820 - 1962.5 $Gy_{2.47}$ grouping, 94.4 ±5.4%.

Based on these findings it would suggest that an effective therapeutic ratio for the treatment of TN would be a dose/treatment time combination associated with a BED in the range 1820 - 1962.5 $Gy_{2.47}$, associated with a long term pain free incidence of 90% with a low risk (< 10%) of developing hypoesthesia. BED values higher than this are not associated with a higher probability of pain control but are associated with an increasing risk of complications.

DISCUSSION

The results from the re-evaluation of physical dose in the present investigation suggest the need for caution in the interpretation of the results of other analysis based on physical dose, particular cases recruited in the period before the 4 mm collimator factor changed from 0.80 to 0.87.[10] Studies involving the Models U and B Gamma Knife may under-report the physical dose prescribed. In the present study, the revised variation in the prescription dose was 30% (75 – 97.9 Gy). This was associated with an even larger (75%) variation in the BED (1536 – 2675 $Gy_{2.47}$). This indicates the impact of the wide variation in the overall treatment time. This is not just a function of the Gamma Knife CDR, a phantom measurement, but variations in the degree of plugging/sector blocking along with individual patient geometry.

The prescription dose and overall treatment time, as quantified using BED, had a marked impact on the incidence of hypoesthesia, increasing from low incidence in the lowest BED groups to a little over 40% at BED values of 2535.5- 2675 $Gy_{2.47}$, for 'unplugged' cases. Extensive plugging had an impact on the incidence of hypoesthesia at low BED values, but this was not statistically significant. This is likely to be related to the change in the length of nerve irradiated ('Flickinger Effect'[9]). However, as only a small number of cases were involved, the impact on the BED-effect relationship was not significant. Other studies have identified plugging as a factor associated with adverse results[19]. A fixed prescription dose of 90 Gy was used to compare 'no plugging' with 'plugging'. The incidence of trigeminal dysfunction was significantly higher in the plugged group. Mild trigeminal dysfunction increased from 18% to 49%, with plugging, while bothersome dysfunction increased from 1.6% to 10%. Treatment times were not provided for this study and hence it is not possible to compare the two groups more appropriately on the basis of BED.

Plugging/sector blocking is used to reduce the radiation dose to the brain stem which is also an area of controversy in the treatment of TN. In the present study, most doses to the brain stem were less than 15 Gy to the first 10 mm^3. This physical dose will also be subject to the influence of changes in the overall treatment time and when delivered in 20 min (the shortest treatment time in the present study), would be associated with a BED of 90.4 $Gy_{2.47}$. With a progressive increase in the treatment time the BED will decrease progressively e.g. to 85.0, 74.1 and 62.7 $Gy_{2.47}$, for treatments over 30, 60 and 120 min. respectively.

Another analysis,[15] reported the incidence of complications to be higher in those that were treated in shorter times with new sources, an effect that was said to be related to the CDR. However, no details of other potential confounding factors were given. Recently Lee et al,[18] reported on cases treated with a fixed prescription dose of 80 Gy and a CDR which declined from 2.95 to 1.26 Gy/min (no plugs). Complication rates (numbness) in this study were said to be low (< 10%) but no specific values were given. From the data provided to the authors (Lee, personal communication) individual treatment times ranged from 29.3 – 68.9 min. Thus the range of BED values can be calculated, 1695 – 2080 $Gy_{2.47}$. In general terms the individual BED values correlated with the trend of changes in CDR, although this does not account for individual changes in patient geometry, and there is not a linear relationship between CDR and BED. Cases were subdivided into 2 equally sized groups of 61 cases using a threshold CDR of 2 Gy/min, which corresponded to a BED of 1900 $Gy_{2.47}$ and the incidence of numbness calculated for each group. These two data points have been added to those from the present study in Figure 6, where only data points based on groups of > 20 cases are plotted. This additional data was remarkably consistent with the current study and the BED-effect curve fitted is not significantly different from that based on the present data alone (Figure 3), although 95% confidence intervals are now reduced.

This significant BED-effect relationship, contrasts markedly with the relationship between the incidence of hypoesthesia and physical prescription dose where no significant relationship was found. All that could be deduced was that the average incidence of this complication was just over 20%, independent of the physical prescription dose.

In one additional study[1], increased facial sensory dysfunction was reported in an HDR group (19.3%) of patients compared to a LDR group (14.5%). The authors again assessed this on the basis of the CDR, although they did quote the range of exposure times associated with the fixed prescription dose of 80 Gy. A collimator factor of 0.8 was used, for patients treated between 1994 and 2005, the period over which there was debate about the output factor for the 4 mm collimator, which increased from 0.80 to 0.87.[10] Thus it is likely that the actual prescription dose was higher, 87 Gy. Thus for total treatment times ranging from 26.7 to 95.1 min a range of BED could be calculated. The highest values were 2478 $Gy_{2.47}$, the lowest 1816 $Gy_{2.47}$. The BED value of the threshold, corresponding to a CDR of 2.02 Gy/min, between the two subgroups, depends on the treatment time, which is a function of the individual patient geometry. This was estimated to be 52 min (range 49.2 – 54.8 min), thus the threshold BED value would be of the order of 2150 $Gy_{2.47}$ (range 2122 - 2180 $Gy_{2.47}$). Thus the dysfunction incidence values related to the two CDR's grouping can be

approximately assigned to different ranges of BED values. The incidences of complications quoted are remarkably consistent with the data plotted in Figure 6, which in themselves are also suggestive of a higher dose having been delivered.

Pain relief was reported from as early as the day of treatment up to 6 months. With such a marked spread of latency times the underlying mechanisms of acute and longer term effects are likely to be different. The acute effect, is likely to be related to the development of edema, with the delayed changes being a function of a delayed progressive degenerative process, to a lesser degree than that associated with the clinical expression of hypoesthesia. The presence of a transient relapse in some cases, mostly in the first 6 months, tends to support this view. This then begs the question at what time after SRS should the benefits of the procedure be considered to be at a maximum? This is important if there is a wish to avoid premature further intervention. The present data would suggest that a period of approximately 9-10 months be allowed to determine the maximum effectiveness of SRS and to avoid further early intervention unless this was considered clinically desirable.

The evaluation of pain free status after 30 days, demonstrated that the maximum effectiveness of SRS was not expressed at this time. There was a trend for both the prescription dose and BED to show a very small increase in effectiveness as they escalated, however, this was not significant. A saturation model provided a more appropriate fit to the data, with the degree of effectiveness saturating at a little below 80% by day 30, for BED values of 1677.5 – 2995 $Gy_{2.47}$. The incidence for the lowest BED range was approximately half this plateau value, but the group size was small (7 cases). A similar trend was seen for an evaluation based on the physical prescription dose but this was only after a combination of the data for the two lowest dose groups, when again the group sizes were very small. Lee et al[18] also claimed a small reduction in efficacy at 30 days, with in effect increasing treatment time, as the CDR declined. Efficacy in this instance was based on results expressed in terms of a percentage change in pain, using a rigorous scoring. The approximate BED range used in that study was towards the lower end of those in the present study and thus the results are to an extent comparable. However, the results are illustrated as a linear regression evaluation of efficacy vs CDR without data points. Thus a trend towards a saturation effect cannot be judged, especially since BED is not linearly related to the CDR.

The pain free incidence at 12 months increased to ~ 90%, indicative of the significant numbers of late responders. The incidence plateaued as a function of the BED value, because of saturation effects. Arai et al[1] also found that the proportion of patients failing SRS was of the order of 9% with no difference between the LDR and HDR groups, where the estimated

BED range was small compared with the present study. In contrast, Lee et al[18] reported a greater proportion of cases showing recurrence of pain, using a scoring system, for those that received a low (< 2 Gy/min) vs a high (> 2 Gy/min) CDR related treatment (or a BED threshold of 1900 $Gy_{2.47}$). As these results are based on the scoring of individual patients it is difficult to directly compare with the other approaches of assessing pain relief.

One further study[2] analyzed the importance of both CDR and treatment time on the control rate or the degree of pain relief and concluded there was no individual association with either. However, as discussed previously,[13] this paper involved treatments where the CDR decreased from 3.63 to 2.0 Gy/min and treatment times increased from approximately 30 – 55 min. Moreover, examination of the individual treatment times showed that the first patients were treated with 80 Gy, in approximately 30 min and the final patients with 90 Gy in about 55 min. It was concluded[13], using the BED equation used in the present study, that the dose escalation used over the period, approximately compensated for the progressive increase in treatment time. In the original publication[2] the authors also claimed that irrespective of the prescription dose (80, 85 or 90 Gy) the BED did not vary with CRD. However, these calculations were based on a totally inappropriate BED equation and a single repair parameter half time of 6.5 h, for which no evidence was provided.

From the present study it was deduced that for BED values between 1900 $Gy_{2.47}$ and 2675 $Gy_{2.47}$ there is no significant variation in the long term incidence of pain control. However, in terms of hypoesthesia this is not the case because after a BED of 2105 $Gy_{2.47}$ the incidence increased rapidly from a value of ~10%, to over 40%. This indicates the presence of a therapeutic window where a high incidence of pain control can be achieved with a low risk of complications. The relationship between the radiation dose and treatment time for differing levels of iso-effect are illustrated in Figure 3. However, given the good level of pain control it would be difficult to justify a hypoesthesia rate in excess of 10%. The relationship between dose and treatment time for BED values of 1820 and 2105 $Gy_{2.47}$ have been further evaluated and listed in Table 2. This ‘look up’ table enables the prescription of iso-BED treatments, by looking up the in-patient dose rate on the day of treatment and choosing the corresponding prescription dose. The calculated prescription doses and corresponding treatment time can be approximately verified using Figure 3. Treatment times of around 21 min are possible for GK but shorter times many be achieved by linac based procedures. However, caution is recommended since the dose distributions between the two techniques may vary significantly and are outside the scope of the present study.

CONCLUSIONS

The key strength of this study has been the consideration of the major variables in any treatment rather than just a single variable e.g. CDR or physical dose. Limitations were those commonly associated with any retrospective study of this type, namely potential bias, although as indicated, efforts have been made to minimise these.

Consequently the present results indicate that safety/efficacy in SRS for TN may be best be achieved by prescribing a specific BED instead of a physical dose. These findings suggest that an effective therapeutic ratio for the treatment of TN would be for dose/treatment time combination associated with a BED in the range 1820 - 1962.5 $Gy_{2.47}$. This would be associated with a long term pain free incidence of 90% and a low risk (< 10%) of developing hypoesthesia. BED values higher than this are not associated with a higher probability of pain control but are associated with an increasing risk of complications.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Table 1: Number of patients treated with either the nine different 100% prescription doses or the associated subdivision into 8 biological effective dose (BED) ranges available for analysis in this historical cohort study. The range of BED values calculated enabled cases to be subdivided into groups that covered a fixed BED range of 142.5 $Gy_{2.47}$

Prescription dose (Gy)	**75.0**	**76.1***	**80.0**	**81.6***	**85.0**	**87.0***	**90.0**	**92.4***	**97.9***
No. cases	5	2	37	4	117	40	145	8	50
BED range ($Gy_{2.47}$)	**1535/ 1677.5**	**1677.5/ 1820**	**1820/ 1962.5**	**1962.5/ 2105**	**2105/ 2247.5**	**2247.5/ 2390**	**2390/ 2535.5**	**2535.5/ 2675**	
No. cases	**7**	**7**	**25**	**86**	**61**	**88**	**111**	**23**	

*indicates cases treated using the Model B GK, with doses of 70, 75, 80, 85 and 90 Gy, with collimator factor correction of 0.87/0.80. For explanation see text.

Table 2. Calculated prescription dose/treatment time combinations required to give iso-BED treatment of 1820 and 2105 $Gy_{2.47}$, a hypoesthesia incidence of ~ 5 and 10%, respectively. The in-patient dose rates at 100% isodose associated with the dose/treatment time combinations are the provided for convenience to look up of acceptable combinations (see Figure 3).

Time/dose prescription for a BED of 1820 $Gy_{2.47}$			**Time/dose prescription for a BED of 2105 $Gy_{2.47}$**		
Time (min)	**Dose (Gy)**	**In-patient dose rate (Gy/min)**	**Time (min)**	**Doses (Gy)**	**In-patient dose rate (Gy/min)**
30	**75**	2.5	11	75	6.82
34	**76**	2.24	14	76	5.43
40	**77**	1.93	17	77	4.53
43	**78**	1.81	**21**	**78**	3.71
48	**79**	1.65	**24**	**79**	3.29
54	**80**	1.48	**28**	**80**	2.86
56	**81**	1.45	**31**	**81**	2.61
63	**82**	1.3	**35**	**82**	2.34
69	**83**	1.2	**39**	**83**	2.13
75	**84**	1.12	**43**	**84**	1.95
82	**85**	1.04	**47**	**85**	1.81
88	**86**	0.98	**52**	**86**	1.65
95	**87**	0.92	**57**	**87**	1.53
102	**88**	0.86	**62**	**88**	1.42
109	**89**	0.82	**67**	**89**	1.33
117	**90**	0.77	**73**	**90**	1.23
125	**91**	0.73	**78**	**91**	1.17
134	**92**	0.69	**84**	**92**	1.1
142	**93**	0.65	**90**	**93**	1.03
151	**94**	0.62	**97**	**94**	0.97
163	95	0.58	**103**	**95**	0.92
170	96	0.56	**110**	**96**	0.87
179	97	0.54	**118**	**97**	0.82
190	98	0.52	**125**	**98**	0.78
200	99	0.5	**132**	**99**	0.75
210	100	0.48	**140**	**100**	0.71

Indicated likely impractical limits to treatments involving a GK

Figure Legends

Figure 1: Variation in the biologically effective dose (BED) as a function of the overall treatment time taken to deliver a range of prescription doses from 75 – 97.9 Gy, to the trigeminal nerve (100% iso-dose). The open symbols represent the maximum range of values of BED for each dose associated with cases treated as 'unplugged' (≤ 20 plugs), while the solid symbols represent the range for 'plugged' cases (> 20 plugs).

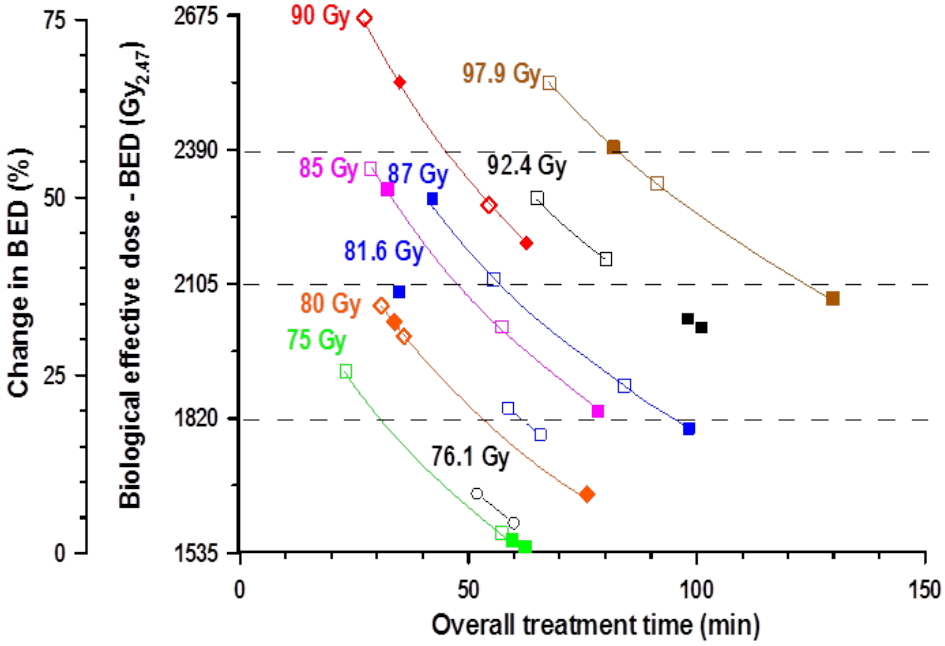
Figure 2: Plot of the incidence of hypoesthesia as a function of the physical prescription dose (A) and BED (B). The use of the probit model indicated a trend in the response for higher physical doses but the difference was not statistically significant. The average incidence of hypoesthesia was ~ 20%. BED related changes in the incidence of hypoesthesia for all cases and those where there were ≤ 20 plug (unplugged). The BED effect curve for unplugged cases is given (—) ± 95% confidence interval (– –) along with the BED effect based on all cases (—). Data points are plotted ± SEM.

Figure 3: The relationship between the physical radiation dose to the 100% prescription is-dose to the trigeminal nerve and the overall treatment time, for different BED values that are associated with differing incidences of hypoesthesia, as obtained from the BED effect curve in Fig 3 for cases treated using ≤ 20 plugs.

Figure 4: BED (A) and physical dose (B) related changes in the incidence of patients being pain free 30 days after GKS. The data were either fitted using probit analysis (– – -) or a saturation effect model (—). For further explanation see the text. Incidence values given ± SEM.

Figure 5: BED related changes in pain free incidence at either 1 year (A) or 2 years (B) after GKS. The results at both times compared with the acute (30 day) pain free incidence. Error bars indicate ± SEM.

Figure 6: BED related changes in the incidence of hypoesthesia (numbness) for groups which included > 20 cases. When the addition data of from Lee et al (■, person al communication) were included the fit, the curve is not different from the use of current data alone (■). BED estimates, derived from Arai et al.[1] are also plotted for comparison, for further explanation see text. Values indicate ± SEM, the 95% confidence intervals are indicated (- – –).



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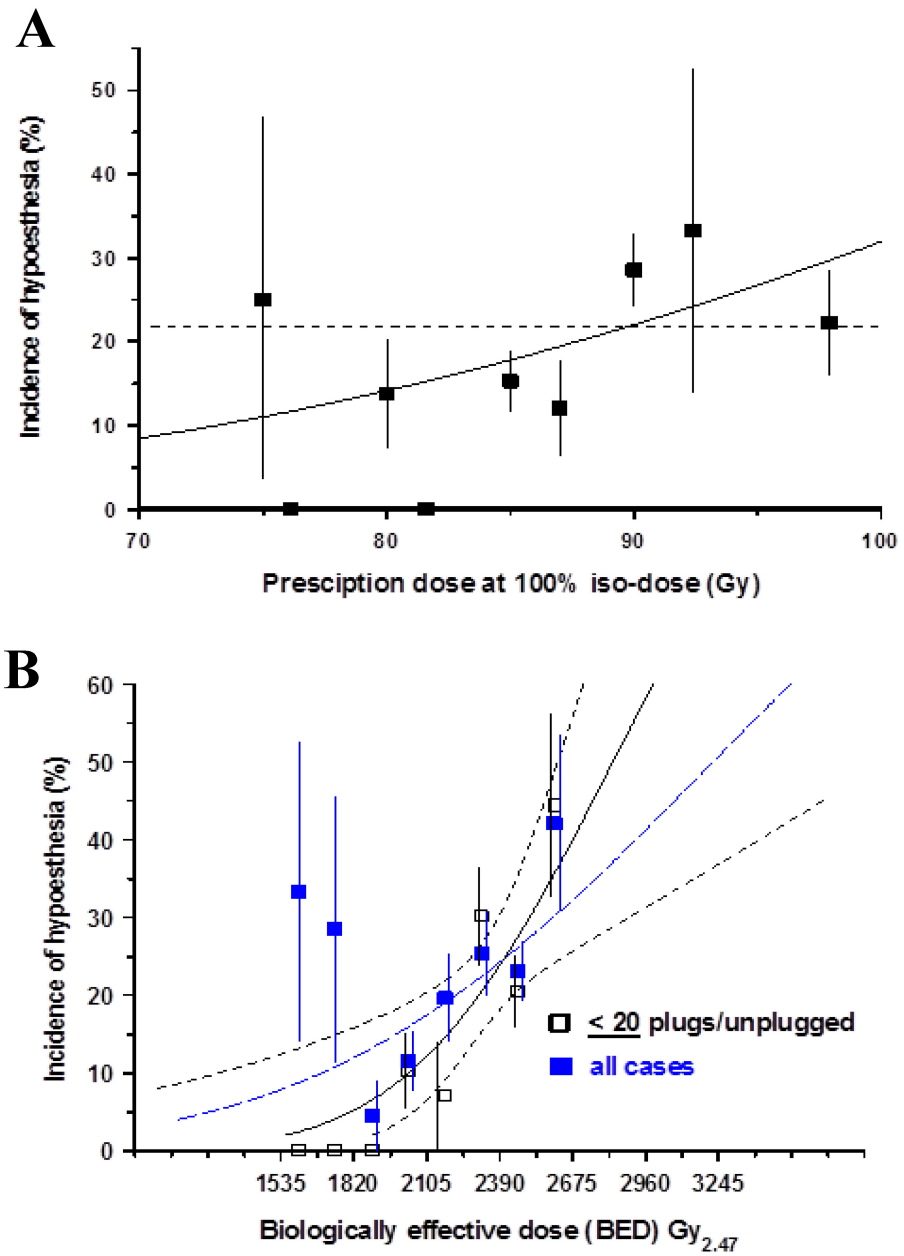

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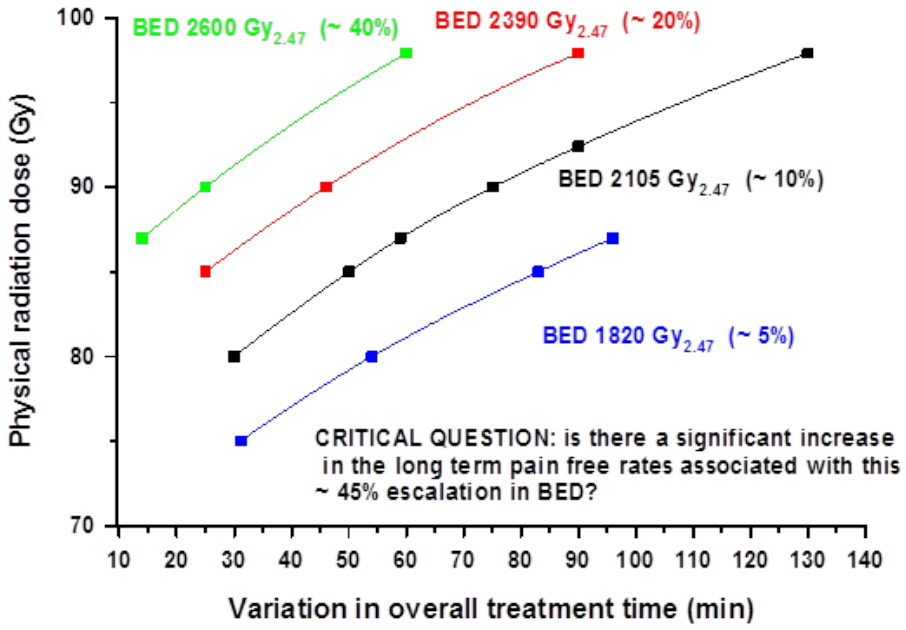

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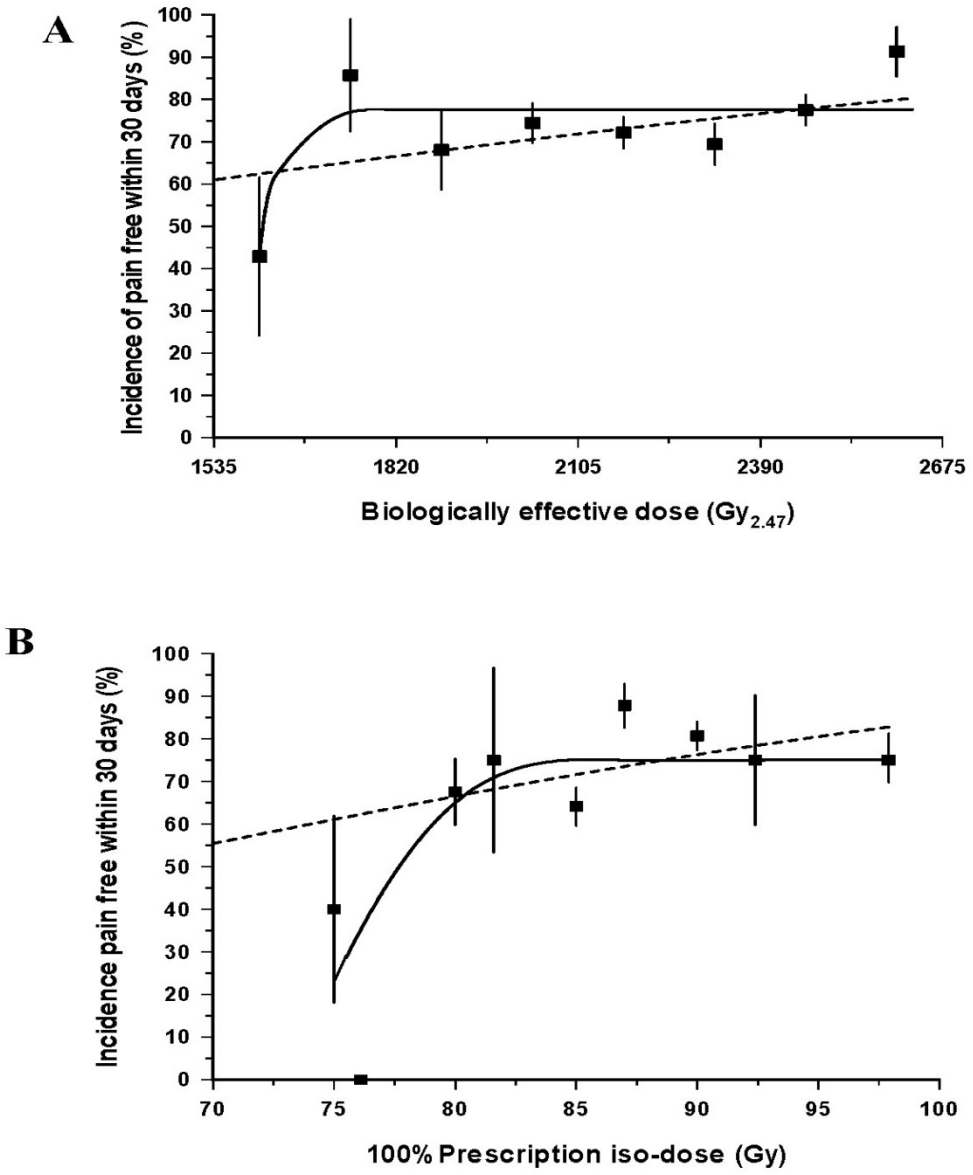

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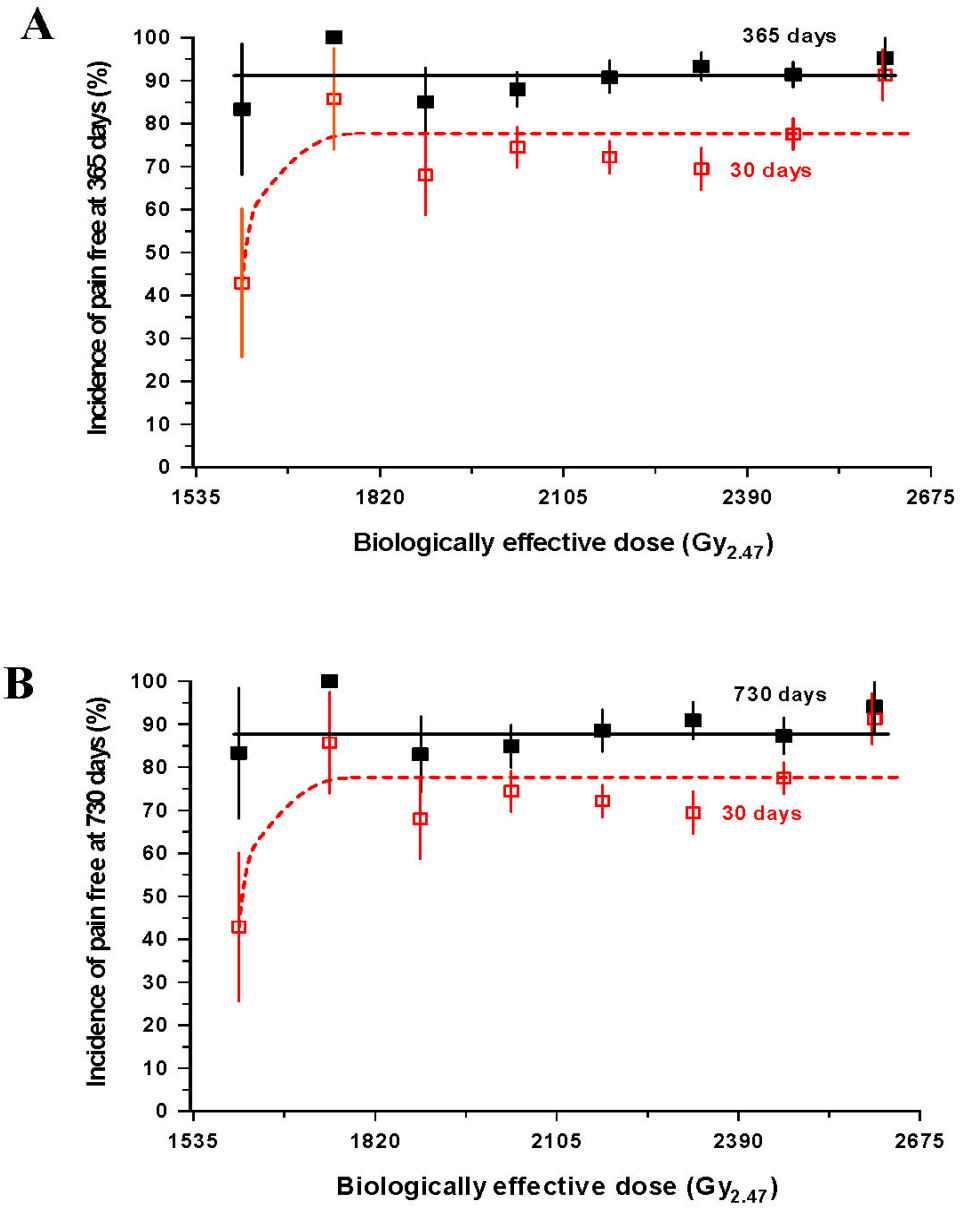

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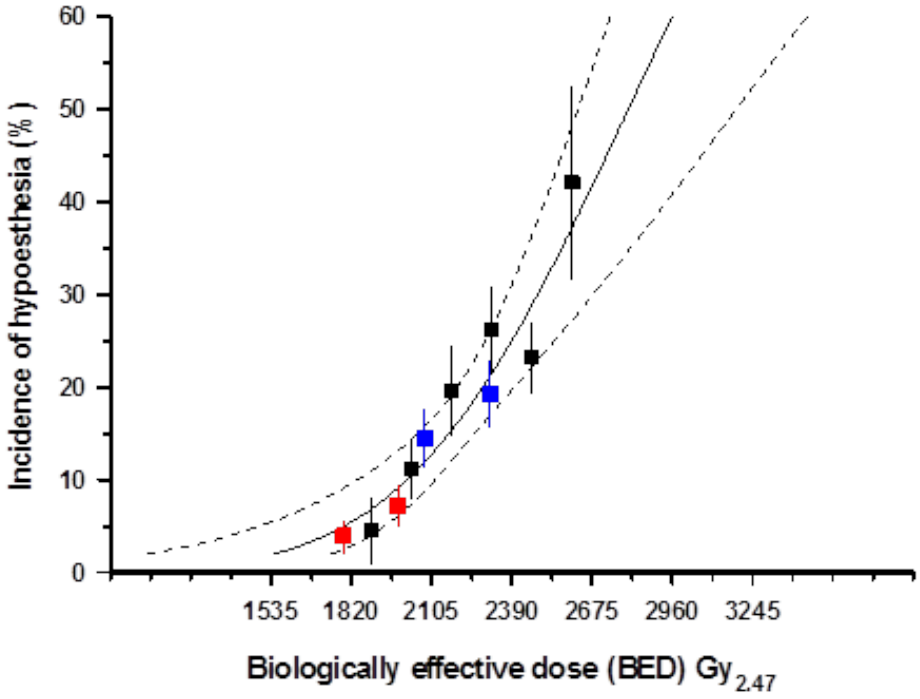

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References

1. Arai Y, Kano H, Lunsford LD, et al. Does the Gamma Knife dose rate affect outcomes in radiosurgery for trigeminal neuralgia? J Neurosurg 2010;113 (Suppl):168-171.
2. Balamucki CJ, Stieber VW, Ellis TL, et al: Does dose rate affect efficacy? The outcomes of 256 gamma knife surgery procedures for trigeminal neuralgia and other types of facial pain as they relate to the half-life of cobalt. J Neurosurg 2006;105: 730-735.
3. Bedford JS, Mitchell JB: Dose-rate effects in synchronous mammalian cells in culture. Radiat Res 1973;54:3216-327.
4. Deeks JJ, Dinnes J, D'Amico R, et al: International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group: Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:iii-x,1-173.
5. Ergina PL, Cook JA, Blazeby JM, et al: Challenges in evaluating surgical innovation. Lancet 2009;374:1097-1104.
6. Finney DJ: The adjustment for a natural response rate in probit analysis. Ann Appl Biol 1949;36:187-195.
7. Finney DJ, Stevens WL: A table for the calculation of working probits and weights in probit analysis. Biometrika 1948;35:191-201.
8. Flickinger JC, Kondziolka D, Pollock BE, et al: Complications from arteriovenous malformation radiosurgery: multivariate analysis and risk modelling. Int J Radiat Oncol Biol Phys 1997;38:485-490.
9. Flickinger JC, Pollock BE, Kondziolka D, et al: Does increased nerve length within the treatment volume improve trigeminal neuralgia radiosurgery? A prospective double-blind, randomized study. Int J Radiat Oncol Biol Phys 51:449-454, 2001.
10. Goetsch SJ, 4-mm Gamma Knife helmet factor. Int J Radiat Oncol Biol Phys 2002; 54:300–301.
11. Goldstein A, Aronow L, Kalman SM, The Time Course of Drug action: The Plateau Principle. In: Principles of Drug Action (Chapter 4) 1968, pp 295-305, Harper and Row, New York, INT 32-02306.
12. Hallgren S, Hill MA, Thompson JM, et al: Effects of variations in overall treatment time on the clonogenic survival of V79-4 cells: Implications for radiosurgery. J Radiosurg SBRT 2019; 6;1-9.
13. Hopewell JW, Millar WT, Lindquist C: Radiobiological principles: their application to gamma knife therapy. Prog Neurol Surg 2012;25:39-54.
14. Hopewell, J.W., Millar, W.T., Lindquist, C, et al: Application of the concept of biologically effective dose (BED) to patients with Vestibular Schwannomas treated by radiosurgery. J Radiosurg SBRT 2013;2:259-271.
15. Kondziolka D, Lunsford LD, Maitz A et al: Radiobiologic considerations in gamma knife radiosurgery. Prog Neurol Surg 1998;14:21-38.
16. Kondziolka D, Lunsford LD, Flickinger JC, et al: Stereotactic radiosurgery for trigeminal neuralgia: a multi-institutional study using the gamma unit. J Neurosurg 1996;84:940-945.

17. Kondziolka D, Zorro O, Lobato-Polo J, et al: Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg 2010;112:758-765.
18. Lee JY, Sandhu S, Miller D, et al: Alonso-Basanta M: Higher dose rate Gamma Knife radiosurgery may provide earlier and longer-lasting pain relief for patients with trigeminal neuralgia. J Neurosurg 2015;123:961-968.
19. Massager N, Nissim O, Murata N, , et al: Effect of beam channel plugging on the outcome of gamma knife radiosurgery for trigeminal neuralgia. Int J Radiat Oncol Biol Phys 2006;65:1200-1205.
20. Millar WT, Canney PA: Derivation and application of equations describing the effects of fractionated protracted irradiation, based on multiple and incomplete repair processes. Part I. Derivation of equations. Int J Radiat Biol 1993;64:275-291.
21. Millar WT, Hopewell JW, Paddick I, , et al: The role of the concept of biologically effective dose (BED) in treatment planning in radiosurgery. Physica Medica: Eur J Med Phys 2015;31:627-633.
22. Pop LA, Millar WT, van der Plas M, et al: Radiation tolerance of rat spinal cord to pulsed dose rate (PDR-) brachytherapy: the impact of differences in temporal dose distribution. Radiother Oncol 2000;55:301-315.
23. Régis J, Carron R, Tuleasca C, et al: Distal radiosurgical targeting for trigeminal neuralgia. In: Controversies in Stereotactic Radiosurgery: Best Evidence Recommendations. Sheehan JP, Gerszten PC (eds). Thieme MedOne (New York) 2014; pp 120-130.
24. Régis J, Tuleasca C, Resseguier N, et al: Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. J Neurosurg 124:1079-1087,2016.
25. Régis J, Tuleasca C, Resseguier N, et al: Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: A 497-patient historical cohort study. J Neurosurg 2016,124:1079-1087.
26. Régis J, Tuleasca C, Resseguier N, et al: The Very Long-Term Outcome of Radiosurgery for Classical Trigeminal Neuralgia. Stereotact Funct Neurosurg 2016; 94:24-32.
27. Tuleasca C, Carron R, Resseguier N, et al: Patterns of pain-free response in 497 cases of classic trigeminal neuralgia treated with Gamma Knife surgery and followed up for least 1 year. J Neurosurg 2012;117(Suppl):181-818.
28. Tuleasca C, Carron R, Resseguier N, et al: Trigeminal neuralgia related to megadolichobasilar artery compression: a prospective series of twenty-nine patients treated with gamma knife surgery, with more than one year of follow-up. Stereotact Funct Neurosurg 2014;92:170-177.
29. Tuleasca C, Carron R, Resseguier N, et al: Multiple sclerosis-related trigeminal neuralgia: a prospective series of 43 patients treated with gamma knife surgery with more than one year of follow-up. Stereotact Funct Neurosurg 2014;92:203-210.
30. Tuleasca C, Carron R, Resseguier N, et al: Repeat Gamma Knife surgery for recurrent trigeminal neuralgia: long-term outcomes and systematic review. J Neurosurg 2014;21(Suppl): 210-221.

31. Young B, Shivazad A, Kryscio RJ, et al: Long-term outcome of high-dose gamma knife surgery in treatment of trigeminal neuralgia. J Neurosurg 2013;119:1166-1175.