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Comparison of two biologically effective dose calculation models applied to single fraction stereotactic radiosurgery

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ABSTRACT

Background: Recent studies suggest strong correlations between Biologically Effective Doses (BED) and single fraction stereotactic radiosurgery treatment outcomes, as demonstrated for vestibular schwannomas (VS), arterio-venous malformations and pituitary adenomas. The BEDs calculated in these studies consider an uniform dose delivery where the spatio-temporal aspects of dose delivery were neglected.
Purpose: The aim of the study is to quantify the discrepancies between the BED values calculated with a simplified model of uniform dose delivery against the more complex model that incorporates the temporo-spatial incrementation of dose delivery and the bi-exponential effect of the sub-lethal damage repair.
Methods: A software tool that computes the BED distributions based on individual isocenter dose matrices extracted from the GammaPlan (Elekta) treatment planning was developed. Two cohorts 5 VS and 5 jugular foramen schwannoma cases of various tumor volumes and isocenter number were utilized to benchmark the method. Their BEDs covering 98% of tumor volumes were compared against those determined with the uniform delivery model.
Results: The BEDs covering 98% of the tumor volumes as calculated with both models show an approximately linear dependency with the treatment time. For all studied cases, the uniform delivery model overestimates the BEDs calculated with the full spatio-temporal delivery model. This discrepancy seems to accentuate with the tumor volume and treatment complexity.
Conclusions: Despite their resemblance, the BED distributions provide a plethora of BED measures more suitable to characterize clinical outcomes than the unique peripheral BED value calculated with the simplified model of uniform dose delivery.

1. Introduction

Stereotactic radiosurgery (SRS) is a well-established radiation treatment modality [1] in which a significant radiation dose is delivered with sub-millimeter accuracy to control and eradicate either benign or malignant conditions. To date, there are several platforms capable of delivering SRS treatments, among which the most commonly used are the Gamma Knife [2] (GK, Elekta AB, Sweden), the CyberKnife [3,4] (CK, Accuray Inc, CA, USA), diverse C-arm Linac platforms [1], and more recently the Zap-X [5] (Zap Surgical Systems Inc, CA, USA). Common to all these delivery platforms is that the desired dose distribution is delivered either by the sequential overlap of the individual isocentric shots (GK), or by the sequential delivery of partially overlapping beams in the remaining SRS platforms. Therefore, there is a specific temporo-spatial pattern of dose delivery characteristic to each of the aforementioned radiation delivery equipment.

Variations in the temporal pattern of dose delivery have been shown to radiobiologically affect the response of mammalian cells to radiation, by means of clonogenic survival experiments by Bedford [6] and Hallgren [7] and by in vivo assessment of clinical end-points like paralysis [8] or tumor growth delay [9]. This effect is mainly attributed to the sublethal repair processes, which are activated immediately after the radiation starts being delivered [6,10–13]. According to Millar and Canney [14], who originally developed a biphasic cellular repair model,

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the magnitude of the repair processes is shown to depend on two tissue specific repair half-lives, one short of about 10–15 min and one long, lasting as much as up to four to five hours. Utilizing this model, Canney and Millar [15] examined the potential implications of the biphasic repair processes upon the use of multiple field treatments used in conventionally fractionated clinical practice. Their findings have been derived using the concept of biologically effective dose (BED) applied to either instantaneous dose delivery or conversely, the more realistic fractionated treatments that allowed a specific amount of time between radiation field delivery. They concluded that on average, about 66 % of the total repairable sub-lethal damage will be repaired in the shorter phase.

Over the past decade there has been a growing interest in developing methods for calculating BED distributions or simplified model BED approaches with the purpose of enabling clinical correlations between tumor control probabilities and/or treatment complications with the factors impacting the overall BED.

In a series of papers that aimed at calculating the BED distributions for Vestibular Schwannoma (VS) cases utilizing the GK platform, Hopewell et al. [16], Millar et al. [17], Klinge et al. [18], and Moutsatsos et al. [19] for the CK, concluded that the BED values decline as treatment times increase. The mechanism implied by this decline is the result of sub-lethal damage repair that accumulates with treatment time. Of note is their evaluation of the patients treated on the GK B-model, where the treatment times are significantly prolonged when collimator helmets are changed, and hence much lower BEDs. Another finding regards the approximately 10 % BED variation for the voxels belonging to the same physical prescription isodose surface [16–19]. This can be explained by the differential dose rate under which these voxels are accumulating the physical dose throughout the treatment and may have an important clinical consequence: the target BED coverage may be lower than what the planner expected when prescribing a certain physical dose. Although pioneering, the authors [16–19] inferred no clinical correlations or recommendations to the studied pathology (VS) in terms of tumor control or toxicity.

Recent clinical literature [20–24] suggests in some studies a strong correlation between the peripheral BED and clinical outcomes. However, such BED values reflect only the unique value of the peripheral dose covering the intended treated volume and do not offer any insights on how the BED is distributed inside targets. The BEDs calculated for these studies considered an uniform photon fluence delivery where the spatial aspects of dose delivery were neglected. Most of those studies employed the Lea and Catcheside [25] and further improved by Jones and Hopewell [14] BED calculation model, with bi-exponential repair rate for the sublethal damage repair. Moreover, tools to extract dose rate distributions on per beam basis from the clinical treatment planning systems to perform the calculations of the BED distributions were and are not readily available.

The current work aims at assessing the potential discrepancies between the simplified, uniform delivery BED model proposed by Jones and Hopewell [14] and an in-home developed software tool capable of calculating the BED distributions from the dose files generated by the GammaPlan. The newly developed tool considers the full aspects of spatio-temporal aspects of dose delivery as described by Millar and Canney [14]. The approach is currently using the GammaPlan (Elekta Instruments, AB, Sweden) DICOM* generated files, but it is easily adaptable for any other radiation delivery technology. The method necessitated an innovative workaround for the extraction of GammaPlan individual isocenter dose distribution files needed for calculating the BED distributions.

2. Methods and materials

2.1. Patient Cohort and treatment planning

The present study was performed upon two series of five patients with vestibular schwannoma (VS) and jugular foramen schwannoma (JFS) respectively, treated between 2010 and 2019 at our institution. The VS series included grade Koos I (intracanalicular) cases, with tumor volumes spanning from 0.01 to 0.32 cc. Given their small tumor volumes (TV) the number of isocenters (shots) utilized in their treatment plans ranged from 2 to 6. The jugular foramen series TVs are much larger (0.649 to 7.3 cc) and the number of shots varied between 14 and 41.

All patients underwent computer tomography (CT) and magnetic resonance imaging (MRI) after the application of the Leksell frame G type (Elekta Instruments, AB, Sweden). Tumor volumes together with organs at risk (OARs), particularly the cochlea, were outlined in the GammaPlan by neurosurgeons. The physical dose prescription was 12 Gy for all cases. The corresponding treatment plans counted from two to forty-one isocenters and were delivered by the Perfexion model (2010–2016) and subsequently by the ICON model (2016–2019).

2.2. Data extraction from the GammaPlan

The data needed for the BED calculation with the bi-exponential repair model developed by Millar and Canney [14] involves the extraction of the dose matrices corresponding to the physical dose distributions for each of the delivered isocentric shots, and their corresponding delivery times. The overall process flowchart is summarized in Fig. 1.

To this end, the delivered treatment is copied into a “new” plan for which the same 12 Gy prescription dose is kept. This “new” plan has the same dose distribution as the original, delivered one, only the treatment times of the isocenters are updated to reflect the exponential decay of the Co^{60} sources. The treatment times of the shots in the originally delivered plans are recorded. To extract each isocenter dose distribution, all shot weights are brought to zero except that of interest, for which the weight is set to 1. Subsequently, the prescription dose for the selected shot is increased until the treatment time equals the same shot treatment time recorded from the originally delivered plan. The prescription isodose level is kept intact.

The DICOM RT Dose file corresponding to the shot is exported and its name is indexed with the shot number. The procedure is repeated for each of the isocenters. An instance of the DICOM structures file (RTSS) and RT Plan is obtained along with the full set of the DICOM CT dataset. The original shot durations of the delivered plan are also recorded and are going to be utilized for the BED calculations.

2.3. Calculation of the BED distribution

The BED distributions are calculated by an in-home built software developed on the MATLAB platform (The MathWorks, Inc. (2022). MATLAB version: 9.13.0 (R2023b). Accessed: January 01, 2023. Available: https://www.mathworks.com) and named BED Constructor (BEDC). BEDC is capable of loading patient specific CT image sets and reading the above-mentioned DICOM files.

The BED model utilized in our calculations was developed by Millar and Canney [14] and further revised by Pop et al. [8]. Each delivered shot is considered as a separate sub-fraction. The time gaps between shots, albeit very short, are also included as incomplete repair intervals. The time gaps between shots are considered three seconds, on both Perfexion and ICON models. The biphasic exponential model has two components: a fast one with a repair half-time $T^f_{1/2} = 11.4$ min and a slow one $T^s_{1/2} = 129.6$ min. These repair times are reflected into the repair coefficients $\mu_f = \frac{ln2}{T_{1/2}^f} = 0.0608 min^{-1}$ and $\mu_s = \frac{ln2}{T_{1/2}^s} = 0.0053 min^{-1}$. Each voxel of the BED matrix is calculated according to the formula:

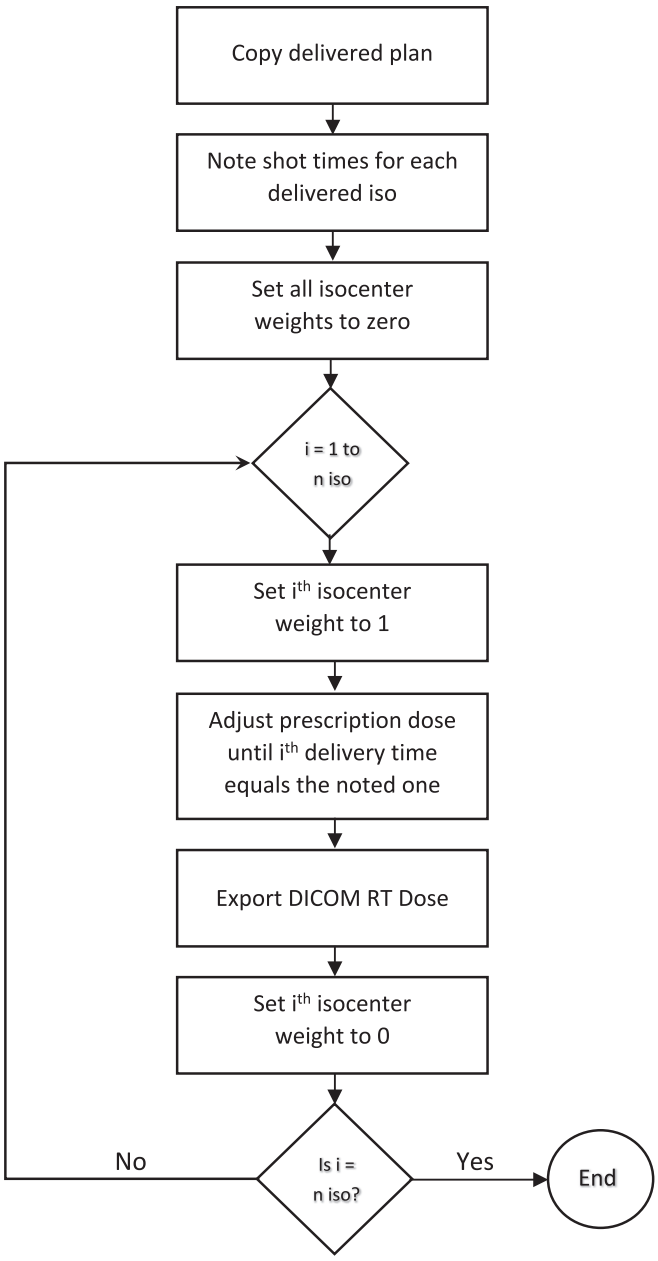

Fig. 1. Flowchart of the GammaPlan isocenter-specific dose extraction process.

$$BED = D_T + \frac{1}{\alpha/\beta}\cdot\left[\frac{\Phi\left(\Xi,\mu_f\right) + c\cdot\Phi(\Xi,\mu_s)}{1+c}\right]\sum_{i=1}^{N_{shots}} d_i^2 \quad (1)$$

where D_T is the total dose delivered during the treatment, N_{shots} is the total number of isocenters (shots), d_i^2 is the matrix corresponding to the squared dose distribution for each shot. The ratio $\alpha/\beta = 2.47$ Gy quantifies the tumor (VS) and brain tissue radiosensitivities. The BED formula contains the terms $\Phi\left(\Xi,\mu_f\right)$ and $\Phi(\Xi,\mu_s)$ that are functions specific to the irradiation protocol and repair rates and are described by Miller and Canney [14] and Pop et al [8].

2.4. BED calculation with the uniform dose delivery model

The second model for the BED calculation makes the assumption that the photon fluence delivered throughout the treatment is constant such as all shots would be delivered simultaneously in the space domain. Each delivered shot is of the same size and duration. The model was proposed by Jones and Hopewell [14] and was utilized in most publications that assessed clinical outcomes relative to BED. It should be noted that the BED uniform delivery model does not imply that the BED is uniform within the tumor volume, but as described in equation (2) below, it is proportional to the dose and modulated by the time-dependent sub-lethal damage repair factors.

$$BED = c\bullet nd\left(1+\left(\frac{nd}{\alpha/\beta}-\frac{d}{\alpha/\beta}\right)\bullet f\left(\mu_f T\right)+\frac{d}{\alpha/\beta}\bullet f\left(\mu_f t\right)\right)+(1-c)\bullet nd\left(1+\left(\frac{nd}{\alpha/\beta}-\frac{d}{\alpha/\beta}\right)\bullet f(\mu_s T)+\frac{d}{\alpha/\beta}\bullet f(\mu_s t)\right) \quad (2)$$

The formalism assumes that the overall physical dose is delivered in n subfractions of equal dose d, where t is the delivery time for each shot and T is the overall treatment time, including the gaps between the shots. The functions $f\left(\mu_f T\right)$ and $f\left(\mu_{fs} T\right)$ model the exponential sub-lethal damage repair rates and like in the previous case depend on the fast and slow half-time repair constants μ_f and μ_s, respectively. c is called the partition coefficient that weighs the proportion of the slow and fast repair mechanisms. We utilized for c a value of 0.5 in both models. All the other parameters were kept the same as in the model for the BEDC distribution calculations. The above-described simplified BED calculation model was implemented into an Excel Worksheet where any physical isodose can be converted into a BED value, according to (2).

It is important to note here that the uniform delivery model can also be utilized to calculate a 3D BED distribution. The BED distribution will have the same appearance as the absorbed dose distribution, with the corresponding absolute dose levels converted into BEDs according formula (2).

3. Results

3.1. Dose check

Each set of solitary isocenter dose distributions generated by the GammaPlan (GP) was loaded and summed up in the BEDC and the result was compared to the total delivered dose in the original plan. The originally delivered dose distribution was exported as a DICOM RT DOSE file from the GammaPlan. Fig. 2 shows the BEDC-summed (thin lines) and the GP original dose distributions (thick lines) for one 0.248 cc VS case, for which 12 Gy was prescribed to the 50 % isodose line. One can observe a slight difference between the two isodose sets, one of potential reasons being the rounding error introduced when the prescription dose is entered in the GammaPlan to generate the individual shot dose distribution. GammaPlan allows only one decimal for the input of the prescription dose and thus, the corresponding isocenter delivery time cannot be identically matched to the one in the copied, "new" plan. Another factor contributing to the discrepancy may be related to the interpolations occurring within BEDC.

3.2. BED calculation and BED distributions

The bi-exponential model for BED calculation described in section 2.3 uses the individual dose distributions loaded for each isocenter. The special functions $\Phi\left(\Xi,\mu_f\right)$ and $\Phi(\Xi,\mu_s)$ are the two exponential terms that describe the fast and slow repair rates, and their values depend on the succession of the isocenters and their respective treatment times. The treatment times utilized for the chosen cases are those derived from the original, delivered plans.

Fig. 3 shows the BED distributions for the axial, coronal and sagittal planes for the same vestibular schwannoma case number 2, for which the physical dose was computed and displayed in Fig. 2.

The BED statistics for all 10 VS and JFS cases in this study are shown

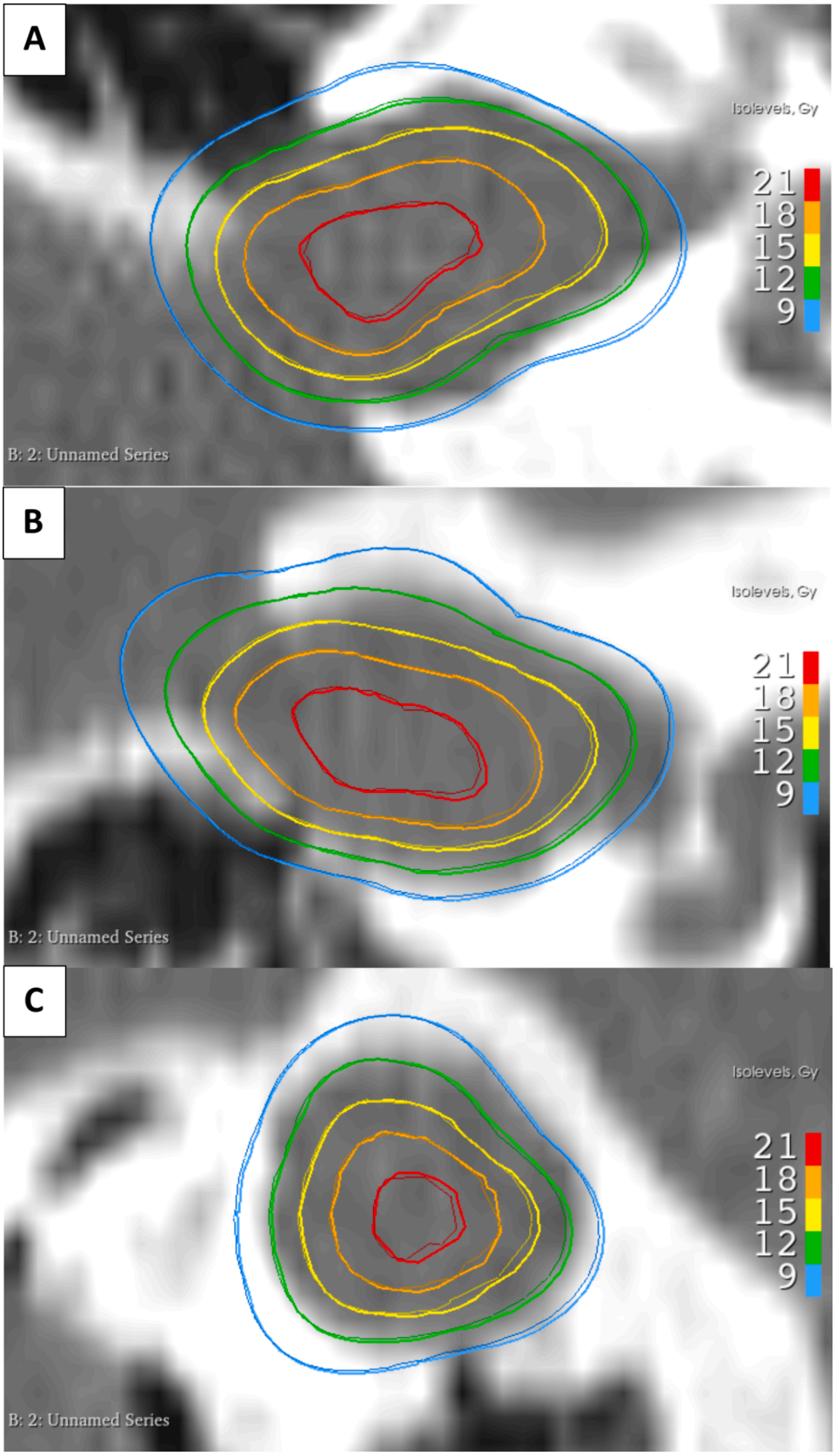

Fig. 2. Axial (A), Coronal (B) and Sagittal (C) dose distributions showing the GammaPlan-calculated plan (thick and light-colored lines) and the summed, individual-isocenter dose distributions extracted with the proposed method (thin and darker shaded lines).

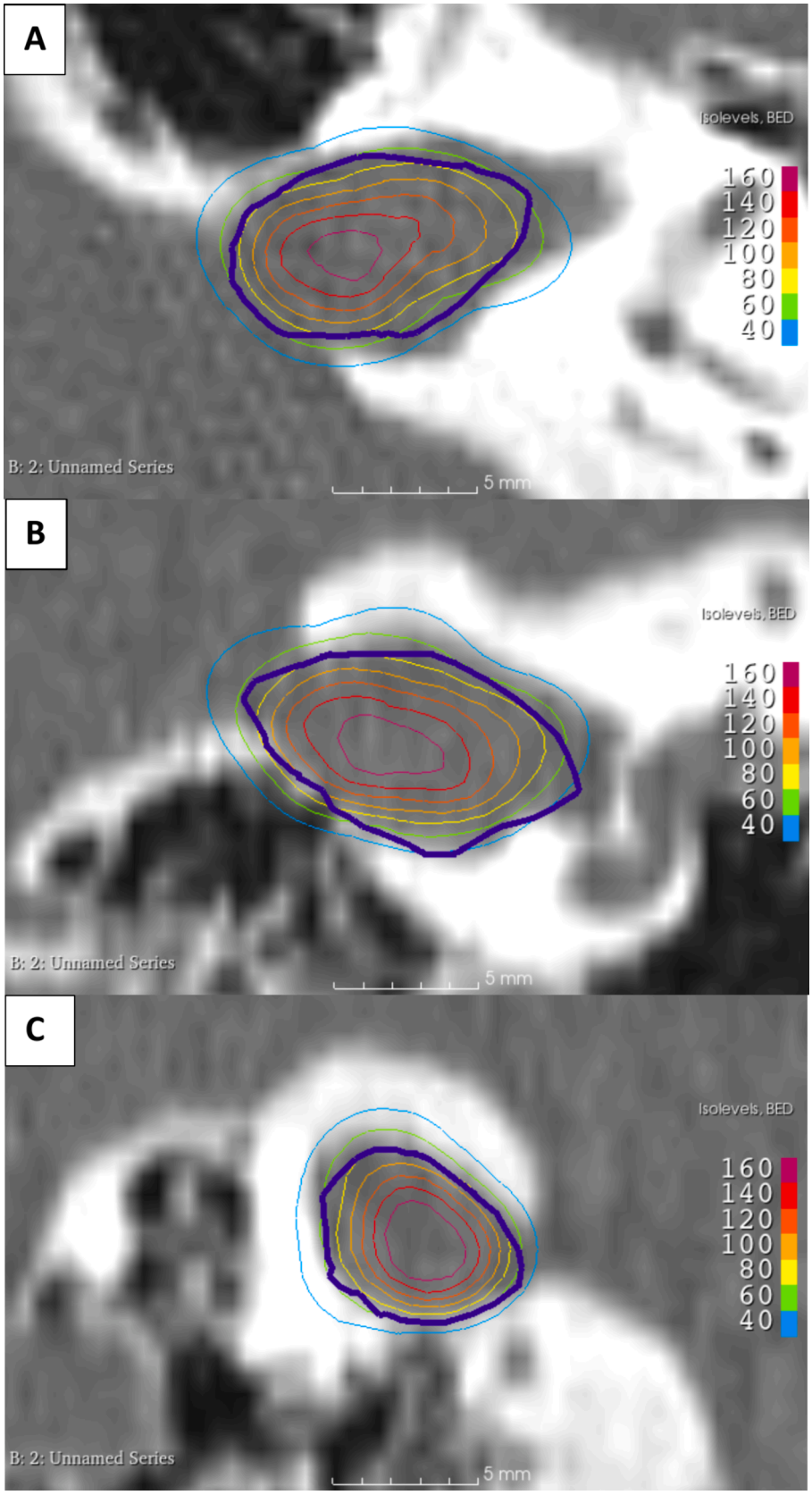

Fig. 3. Axial (A), Coronal (B) and Sagittal (C) BED distributions for the Vestibular Schwannoma case number 2 calculated with BEDC. The thick purple line represents the outline of the tumor volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in Table 1. As an example for case number 2, the marginal BED covering 98 % of the TV is 55.98 $Gy_{2.47}$ and the maximum BED is 199.17 $Gy_{2.47}$. The $BED_{98\%}$ is selected here as a representative parameter because in our clinic we aim at prescribing the therapeutic dose at the 98 % coverage of the tumor volume. The reference dose rate at the time of delivery was 2.703 Gy/min. The overall beam-on time was 31.5 min for a physical prescription dose was 12 Gy to the 50 % isodose.

In Table 1 we observe a significant deviation of the BED value covering 98 % of the tumor volume for case number 1 against the average values for the rest of the patients. Tumor volume for the VS case 1 is the smallest among all the cases. As a result, even using the 4 mm collimator for planning, the 12 Gy prescription isodose is far from being conformal. Under these circumstances, the physical dose covering 98 % of the tumor volume is 12.88 Gy, 7 % higher than the intended 12 Gy.

3.3. BED comparison: full modulated fluence vs. uniform fluence

The simplified BED calculation model proposed by Jones and Hopewell [26], where each shot is of the same duration and dose was implemented into an Excel Worksheet. Here only a certain physical isodose can be converted at a time into a BED value, according to formula (2) detailed in section 2.4. The model incorporates the biphasic sub-lethal damage repair. In order to illustrate the BED distribution differences between the two models we calculated with formula (2) several BED values that would match *iso*-BED levels calculated with the BEDC.

The results are displayed in Fig. 4, where it appears that the uniform dose delivery model *iso*-BED lines (the thinner lines) encompass the *iso*-BED lines determined with the BEDC, meaning that the first model overestimates the BEDs calculated with BEDC. The lower *iso*-BED lines follow closely one another while the discrepancies between the higher *iso*-BED lines accentuate. The maximum BED values are 208.9 $Gy_{2.47}$ for the uniform dose delivery model while the BEDC calculated maximum is 199.2 $Gy_{2.47}$, a 4.9 % difference for the VS case number 2.

For the rest of the cases, we evaluated the BED differences just for one single isodose. The physical isodose converted into BED is the $D_{98\%}$ (the dose covering 98 % of the TV), as this dose is clinically relevant in our clinic for the desired tumor coverage. For each case the $D_{98\%}$ was extracted from the GammaPlan (Table 2, column 4). The time gap between the shots was 0.05 min. (3 s) as in the calculation with BEDC. Table 2 incorporates the BEDC and uniform delivery $BED_{2.47}$ in columns five and six and their respective percent difference in column seven.

In both calculations, the repair half-times, alpha/beta ratios and partition coefficients were identical. The $BED_{2.47}$ ratios obtained with the two methods reveal that for all the cases, the uniform delivery overestimates the BEDC calculated values. The average discrepancy of uniform delivery vs. BEDC calculated for all the cases is +6.3 %. If one calculates the discrepancies separately for the VS cases and JFS series one obtains +5.27 % vs. +7.31 % respectively, suggesting that the errors accentuate for larger tumor values and number of isocenters used in the treatment plans. It may be possible that in the latter case the BED values corresponding to the hypothetical isodose surface covering 98% of the tumor volume have a larger spread, skewed towards lower values.

Fig. 5 shows the plot of the $BED_{D98\%}$ values as a function of the total treatment time. As expected, there is a clear trend that indicates that as the total treatment time increases, the BED values become smaller. A linear regression fitting procedure indicates a negative slope dependency of the $BED_{D98\%}$ with the total treatment time T in both models. The intercepts of the fitted lines at T = 0, corresponding to the instantaneous dose delivery are 67.37 $Gy_{2.47}$ for the uniform delivery model and 64.57 $Gy_{2.4}$ for the BEDC model. If one compares these values to the instantaneous BED value of 70.83 $Gy_{2.47}$ corresponding to the 12.05 Gy (the average of $D_{98\%}$ in Table 2, column 4), then the percentage differences would be −4.9 % and −8.8 %, respectively. A value of −6% was reported by Moutsatsos et al. [19] in case of VS treated to the 13 Gy prescription isodose line with the Cyberknife. Jones and Hopewell [14] reported a difference of −7%.

3.4. BED histograms and model validation

The BED distributions created for the VSs cases resemble those already published in the literature [17,18]. BED distributions are characterized by extremely high gradients and heterogeneity. To graphically illustrate the volumetric distribution of the BED within the tumor volume, the BEDC was equipped with the capability of computing the BED Volume Histograms (BEDVH). Fig. 6 depicts the BEDVHs for the VS case 2 for which both uniform dose delivery and BEDC calculated BED histograms were calculated. As expected and confirmed from the calculations presented in the previous section, the histogram for the uniform dose delivery model is shifted towards higher BED values compared to the BEDC. A special characteristic of the BEDVH that we encountered for all the studied cases is the long tail of the histogram. Unlike the absorbed dose DVHs (thin dotted line in Fig. 6), the BEDVHs display a significant BED heterogeneity within the tumor volume. If for a typical GK case the natural physical prescription isodose line is 50%, in the case of the BEDs, the corresponding prescription BED drops to approximately 27 % of the maximum BED, like patient 2 depicted in Fig. 6. A similar BED ratio of 31 % was observed by Millar et al. [17]. The same publication also calculated a frequency distribution of the BED values corresponding to the voxels receiving the 12 Gy prescription dose, with peak frequency centered at 45.5 $Gy_{2.47}$. This comes in line with the BEDVH plot in Fig. 6, where a 45 $Gy_{2.47}$ corresponds to tumor coverage of approximately 99 %.

4. Discussion

The purpose of this work was to explore the equivalency of two BED calculation models currently utilized by several researchers to adapt prescription doses as a function of treatment time in order to achieve biological *iso*-effective treatments in terms of tumor control in SRS. It

Table 1
Absorbed dose statistical figures (Mean, Min, Max and $D_{98\%}$ and the corresponding relevant BED statistical measures ($BED_{2.47}$ Min., Max., Mean and $BED_{98\%}$) for the five Vestibular Schwannoma cases (1–5) and five Jugular Foramen schwannomas (6–10).

	Tvol (cc)	No Iso	Dprscr (Gy)	Isodose (%)	Mean Dose (Gy)	Min Dose (Gy)	Max Dose (Gy)	$D_{98\%}$ (Gy)	BED Mean ($Gy_{2.47}$)	BED Min ($Gy_{2.47}$)	BED Max ($Gy_{2.47}$)	BED98% ($Gy_{2.47}$)
1	0.062	3	12	60	16.1	10.2	20.0	12.88	100.32	45.05	147.10	65.74
2	0.254	6	12	50	16.5	7.4	24.0	11.97	102.19	34.97	199.17	55.98
3	0.223	6	12	50	16.7	10.8	24.0	12.12	107.81	45.54	201.43	57.59
4	0.126	5	12	60	15.2	10.3	20.0	11.55	85.99	43.37	136.06	54.12
5	0.074	2	12	62	16.3	10.0	19.4	12.05	97.24	38.38	129.11	52.61
6	0.649	14	12	50	15.9	10.5	24.0	11.85	84.76	37.53	172.12	48.30
7	2.120	21	12	50	17.3	10.5	24.0	12.06	93.44	39.58	171.94	51.39
8	7.300	19	12	50	16.9	9.8	24.0	11.8	92.76	34.56	178.36	45.66
9	3.980	31	12	50	16.6	10.4	24.0	12.1	88.9	36.47	169.86	49.45
10	3.740	41	12	55	16.6	10.3	21.8	12.37	81.98	36.10	135.36	49.02

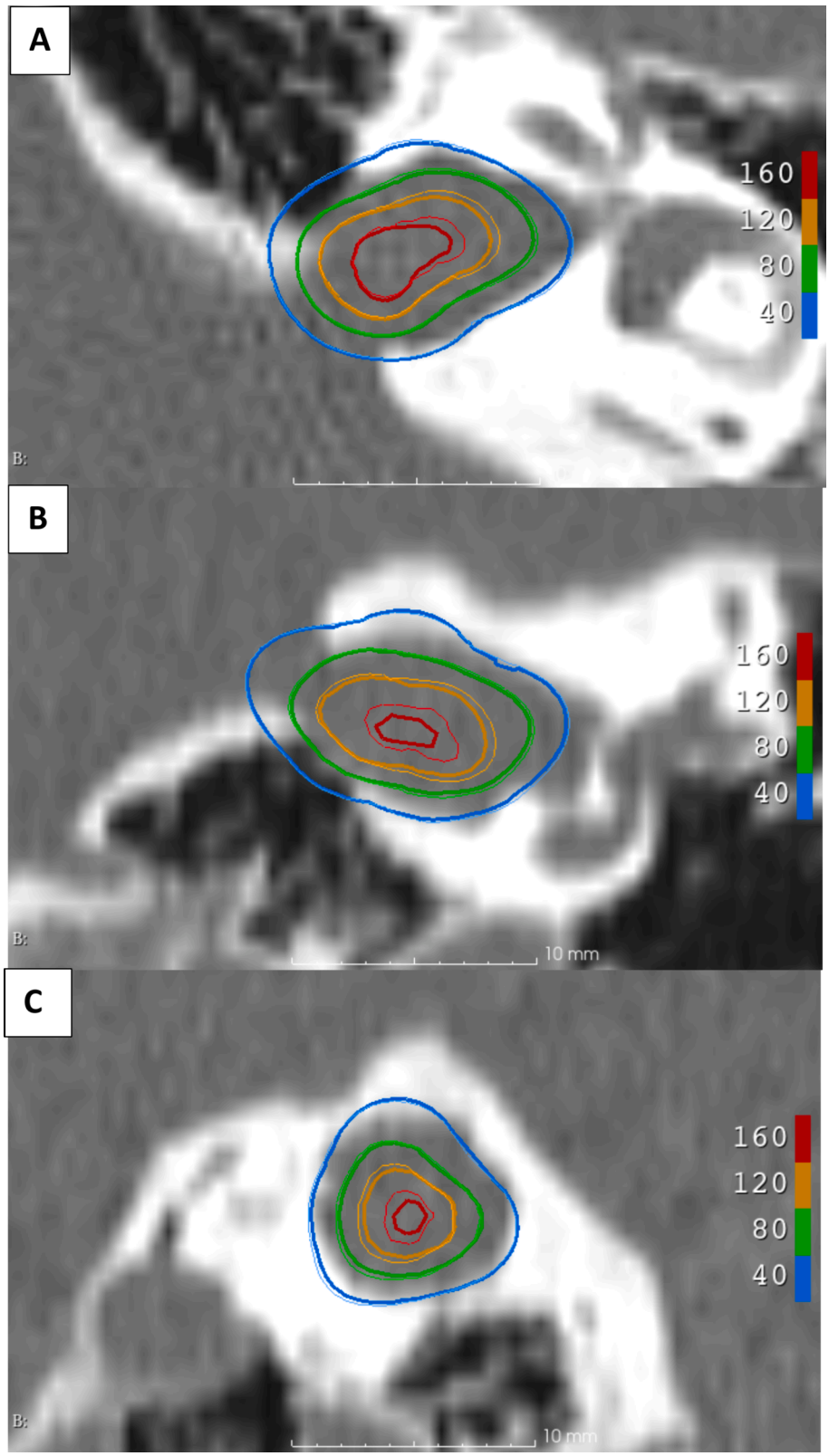

Fig. 4. Axial (A), Coronal (B) and Sagittal (C) BED distributions for the Vestibular Schwannoma case number 2 calculated with BEDC (thick and darker shade lines) and the uniform dose delivery model (thin and lighter shade lines).

was once again validated with our ten schwannoma cases that the relationship between the BED and the treatment time can be modelled as being approximately linear. This was also advocated previously by Jones and Hopewell [14] who utilized the BED distributions calculated by Millar et al [14] and compared the minimum, average and maximum BEDs corresponding to the voxels belonging to the prescription isodose surface with the BEDs obtained with a simplified model.

The spectrum of the BED values for the voxels of a certain physical

Table 2
BEDs calculated as uniform delivery overestimate by up to 10% those derived from the sequentially delivered isocenters.

Patient	N iso	Tx time (min)	$D_{98\%}$(Gy)	BEDC BED $_{98\ \%}$ ($Gy_{2.47}$)	Uniform $BED_{98\%}$ ($Gy_{2.47}$)	Uniform/ BEDC (%)
1	3	24.54	12.67	65.74	67.27	102.3 %
2	6	31.43	11.97	55.98	57.95	103.5 %
3	6	22.27	12.04	57.59	61.22	106.3 %
4	5	24.52	11.62	54.12	56.99	105.3 %
5	2	24.77	12.05	52.61	57.28	108.9 %
6	14	56.90	11.85	48.30	50.55	104.6 %
7	21	42.5	12.06	51.39	54.56	106.2 %
8	19	63.2	11.8	45.66	48.84	107.0 %
9	31	44.85	12.1	49.45	54.03	109.3 %
10	41	55.8	12.37	49.02	53.67	109.5 %

iso-surface is a very useful demonstrative concept to show the effect of spatio-temporal pattern of dose delivery, but it may have little clinical significance. It may be confusing in a clinical workflow which BED measure to consider significant for prescription: that derived from mean BED of the voxels corresponding to the prescription isodose, or maybe the minimum? In this respect we propose a volumetric approach and suggest that the $BED_{98\%}$ (in our clinic the TV coverage of 98% is the goal) may be a more suitable measure to characterize the biologic effectiveness of a certain physical dose distribution. One could hypothesize that the $BED_{98\%}$ would correspond to a "virtual" physical dose covering the same volume of the target volume. If that physical dose is used to re-calculate the BED utilizing the simple, uniform delivery model we obtain discrepancies averaging 6.3 % for all the studied cases spanning tumor volumes from 0.062 to 7.30 cc and number of isocenters from 2 to 41. Further investigation should be dedicated to exploring if this difference is solely a cause of the chosen BED calculation model or if our hypothesis overestimates the true "$D_{98\%}$".

Most of the clinical studies [16–18] that infer correlations between the BED and clinical outcomes use the simplified, uniform delivery model proposed by Jones and Hopewell [14]. In this respect, only the peripheral BED is calculated. This approach may be sufficient for the functional SRS cases like trigeminal neuralgia or tremor, where only one shot is utilized and therefore, there should be no difference between the two models. There is anecdotical information that some clinics already started adapting the prescription physical dose to match a certain therapeutic BED. As shown in our investigation, for more complex cases one would expect larger BED differences between models and therefore a full calculation of BED distribution may be more accurate and clinically relevant. Moreover, having access to the BED distributions would allow the computation of all statistical BED measures like minimum, mean, maximum, integral BEDs, which in turn may prove useful correlators in retrospective studies.

One limitation of this study is related to the accuracy of the used radiobiological parameters, where the brain tissue α/β ratio was also assigned to the VS tumors, altogether with the slow and fast sub-lethal half-time repair rates. These values were derived form rat spinal cord experiments performed by Pop et al [8], which had as end-point radionecrosis obtained following various single dose exposures at different dose rates. As explained in studies by Hopewell et al. [16] and Millar et al [14] this data represents to date the best available for central nervous system, but may not fit closely the biology of the VS tumor which is known to be histologically heterogeneous and with various degrees of vascularization.

A number of prior publications reported the utilization of individual shot dose matrices for the purpose of determining the real distribution of BEDs in case of single fraction SRS by means of GK. All the above projects involved the usage of research versions of the GammaPlan treatment planning workstations, specifically adapted for the extraction of the individual isocenter dose distributions. The data needed for our project of BED calculation was extracted from the clinical version of the GammaPlan workstation, using a workaround that allowed us to generate dose distributions for each individual isocenter. The workaround was applied to patients already treated and thus, additional time and effort was needed to adjust the data for the sources decay. The process of data extraction is quite tedious as it may take up to 1–2 min to

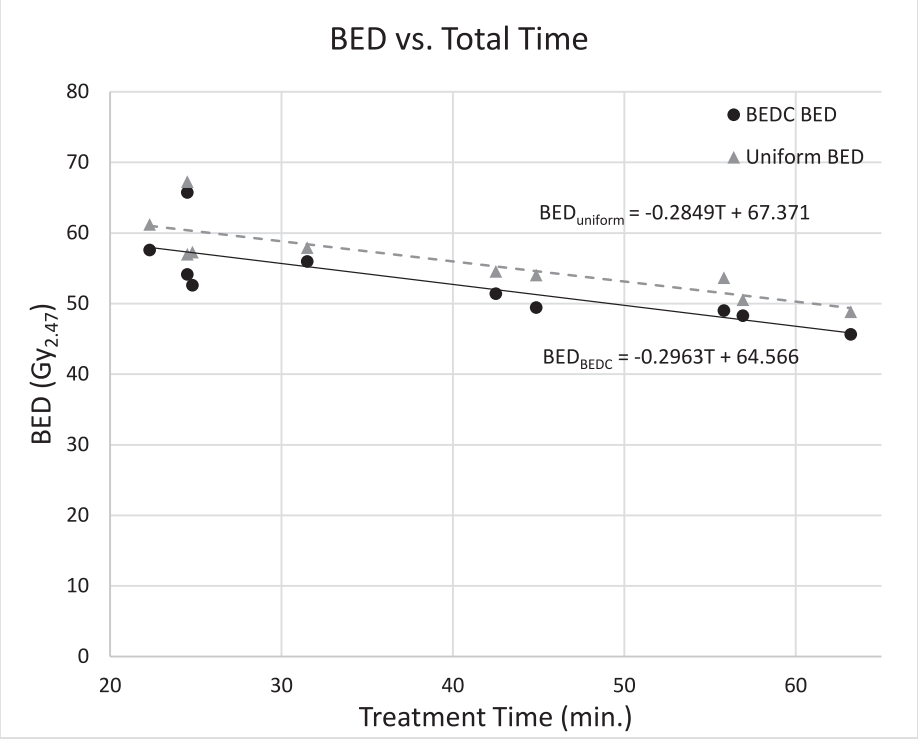

Fig. 5. BED $D_{98\%}$ for the two models plotted as a function of total treatment time T for the 5 VS and 5 JFS cases.

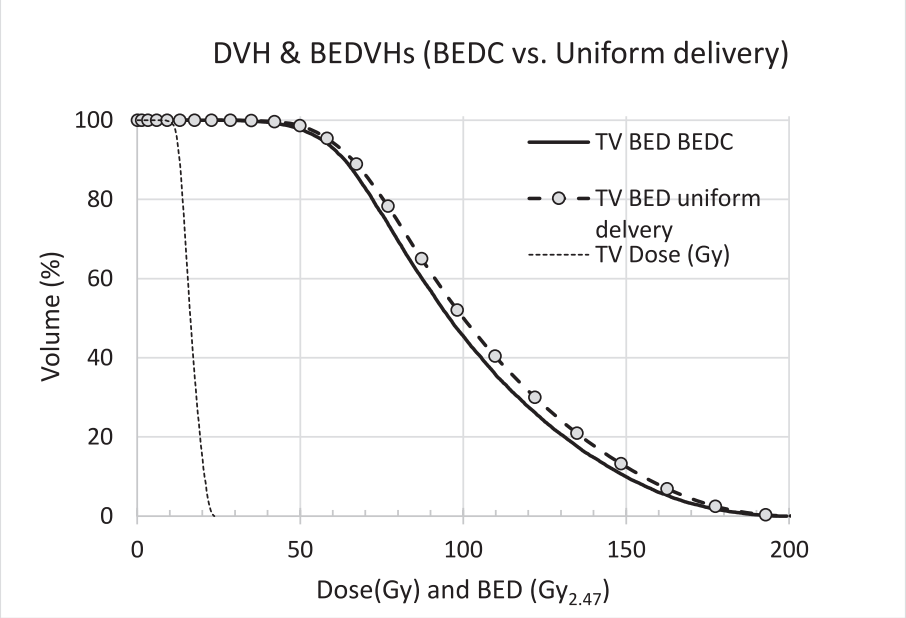

Fig. 6. BED Volume Histogram for the six isocenter Vestibular Schwannoma case number 2.

extract the DICOM RTDOSE file for a single isocenter. This process is acceptable for treatment plans with a small number of shots (maybe up to 10–15) but can grow into a very tedious routine for plans generated by the Lightning inverse planning module of the GammaPlan, that produces 40–50 isocenter solutions. For this kind of cases, automation would be necessary. Given the growing interest of the SRS community in investigating the effects of BED on the clinical outcomes it may be useful for the user to have access to the individual shot dose matrices in a more user-friendly manner.

One of the main findings of this study is that the simplified, uniform dose delivery model overestimates the BED distributions calculated with full spatio-temporal photon fluence modulation. The discrepancies range from 2.3 % to 9.5 %. The average discrepancy is larger for JFS cases, characterized by bigger volumes and longer treatment times. One possible recommendation stemming from this observation would be to exercise caution in choosing the BED calculation model for those treatment platforms necessitating longer delivery times.

The BED calculation method described herein is also applicable to other treatment modalities. Moutsatsos et al. [19] applied the same methodology for a series of vestibular schwannomas treated with the Cyberknife and concluded that the delivered dose distributions must be resolved in the temporal domain to enable BED estimations accounting for the sublethal DNA repair occurring within the treatment session. The treatment times ranged between 15 to 45 min. for a prescription of 13 Gy dose. Moutsatsos et al. concluded that a loss of almost 20% compared to the acute exposure is associated for the CK treatment associated with the delivery of 13 Gy in 35 min. They also suggested that the simpler Lea-Catcheside BED model could be applied, but made no estimations on the differences between the two models. It is notable in their work the cumulative evolution of the BEDC-like calculated BED and the instantaneous BED. For treatment times shorter than 15 min the two curves are almost overlapped, with increasing divergence as the treatment times increase.

With the advancement of image guidance on Linacs, VMAT stereotactic treatments of vestibular schwannomas or other kind of pathologies were also reported [26]. The authors planned the VS and pituitary adenoma cases with three noncoplanar arcs of 6MV FFF beams (1400 MU/min dose rate) for which the total delivery time of the treatment ranged 3–7 min. Considering that the DNA sub-lethal damage repair short half-time is around 11 min, it appears that the effect of repair might be minimal, and therefore BED calculations could safely be performed using the simple Lea-Catcheside model, or even considering the instantaneous delivery BED formula. For treatment times of around 10 – 15 min, as reported by other authors, the Lea-Catcheside model (uniform dose delivery) for BED calculation should be accurate, provided that setup times between arcs are also included.

Comparison of BED data for treatments delivered on different radiotherapy platforms should be interpreted with caution for several reasons: first, the treatment plans are generated using different, proprietary dose calculation algorithms and as a result, the dose discrepancies might also affect the BED calculation accuracy. Secondly, absolute BED comparative analysis or inter-platform treatment efficacy should carefully consider the relevant physical dose variations and the possible range of biological parameters before bio-efficacy of a certain SRS treatment scheme or fractionation is claimed.

5. Conclusions

Our findings reveal that the peripheral BED values calculated with a simplified model follow the same descending pattern with the overall increase in the total treatment time as for the case of an in-home developed software tool that considers the spatio-temporal aspects of dose delivery. The discrepancies between the two models average 6% for a series of ten schwannoma cases when $BED_{98\%}$, a newly proposed measure of peripheral BED quantification is considered. The difference may prove meaningful in the context of reporting clinical results based on BEDs calculated with different models. The peripheral BED is not the ultimate measure to infer clinical correlations on the treatment's outcomes, as the BED volume histograms indicate elevated heterogeneity. It is thus the time to assess the effect of this heterogeneity on the clinical outcomes and therefore, a tool that fully accounts for the spatio-temporal aspects of dose delivery becomes a necessity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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