Total target volume is a better predictor of whole brain dose from gamma stereotactic radiosurgery than the number, shape, or location of the lesions

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Purpose: To assess the hypothesis that the volume of whole brain that receives a certain dose level is primarily dependent on the treated volume rather than on the number, shape, or location of the lesions. This would help a physician validate the suitability of GammaKnife[®] based stereotactic radiosurgery (GKSr) prior to treatment.

Methods: Simulation studies were performed to establish the hypothesis for both oblong and spherical shaped lesions of various numbers and sizes. Forty patients who underwent GKSr [mean age of 54 years (range 7–80), mean number of lesions of 2.5 (range 1–6), and mean lesion volume of 4.4 cm³ (range 0.02–22.2 cm³)] were also studied retrospectively. Following recommendations of QUANTEC, the volume of brain irradiated by the 12 Gy (VB12) isodose line was measured and a power-law based relation is proposed here for estimating VB12 from the known tumor volume and the prescription dose.

Results: In the simulation study on oblong, spherical, and multiple lesions, the volume of brain irradiated by 50%, 10%, and 1% of maximum dose was found to have linear, linear, and exponentially increasing dependence on the volume of the treated region, respectively. In the retrospective study on 40 GKSr patients, a similar relationship was found to predict the brain dose with a Spearman correlation coefficient >0.9 . In both the studies, the volume of brain irradiated by a certain dose level does not have a statistically significant relationship ($p \geq 0.05$) with the number, shape, or position of the lesions. The measured VB12 agrees with calculation to within 1.7%.

Conclusions: The results from the simulation and the retrospective clinical studies indicate that the volume of whole brain that receives a certain percentage of the maximum dose is primarily dependent on the treated volume and less on the number, shape, and location of the lesions. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4818825>]

Key words: gamma knife, brain dose, lesion volume, stereotactic radiosurgery

1. INTRODUCTION

Gamma radiosurgery (Leksell Gamma Knife, Sweden) is used to perform stereotactic radiosurgery on intracranial lesions based on magnetic resonance imaging (MRI).^{1–4} When assessing a patient's suitability for GammaKnife[®] based stereotactic radiosurgery (GKSr) a common limitation is considered to be the maximum number of brain lesions that can be treated. Radiation Therapy Oncology Group 95–08 suggests that one to three lesions are suitable for treatment using radiosurgery and whole brain radiation,⁵ while others have treated more than three brain lesions with no increase in the number of radiation-related complications.^{6–8} Whole brain radiation is used as adjuvant therapy with GKSr either prophylactically, when there is suspicion of occult disease, or when there are considered to be too many lesions for GKSr alone.

Herein, we seek to develop a framework by which the contribution of dose to the whole brain can be assessed, prospectively. This is motivated by a need to assess the suitability

of GKSr for patients with multiple brain metastases, as well as to provide enhanced guidance on the number or types of lesions that can be treated. In conducting this study, we discovered that GKSr brain dose depends primarily on the volume of the brain lesions and not on their number, shape, and location. Precedence to this exists in a study by Kim *et al.* and other groups who have shown a correlation between overall survival and total tumor volume.^{9–12} In this study, we are attempting to show the independence of brain dose not only on the number of lesions,¹³ but also on their shape and location.

The QUANTEC report states that the incidence of radiation necrosis and asymptomatic radiological changes to the brain is higher in GKSr treatment if the volume of brain receiving 12 Gy (VB12) exceeds 5–10 cm³.¹⁴ Despite cautions regarding data extrapolation and outcomes from multiple centers, the report ultimately recommends VB12 as the recommended method of reporting the dose to brain in GKSr. A study on 73 arteriovenous malformation patients proves a strong association between radiation injury in linear

accelerator based radiosurgery and VB12 for $VB12 > 28 \text{ cm}^3$, a volume tolerance level higher than that of QUANTEC.¹⁵ Herein, we present a methodology that can be used to prospectively assess the VB12 for patients being considered for GKSR.

2. METHODS AND MATERIALS

2.A. Management of the reporting accuracy of the maximum whole brain dose

All data presented herein were collected using a Gamma Knife Perfexion treatment unit and GammaPlan treatment planning software, version 10.1. Early on in this study, we discovered that the maximum whole brain dose reported by the GammaPlan software was inconsistent in the following context.

The whole brain was contoured as a single, large structure that includes the white and gray matter, typically with a volume of 1500 cm^3 . Separately, a smaller ($4\text{--}10 \text{ cm}^3$) dose calculation matrix was defined in which the shot was placed and the prescription isodose lines were set. We discovered an inconsistency between the maximum brain dose reported in the whole brain structure versus the target matrix structure. The description of our management of this discrepancy follows.

In a simulation study on the precise positional dependence of the shot placement on the brain dose, a single shot of size 4, 8, or 16 mm diameter was placed in the MRI of the brain. A prescription dose of 20 Gy was assigned to the 50% isodose line, resulting in a known maximum dose of 40 Gy. The shot was translated in steps of 1 mm, along the three axes, independently. A whole brain structure was created by contouring the outer extent of the brain parenchyma on a single patient's MRI scan. The volume of the whole brain structure in this case was 1546 cm^3 . In addition, a target matrix was created with dose grid spacing of 1.0 mm that encompassed the immediate, 50% isodose volume.

In the Gamma Plan software all nontarget volumetric dose measurements are calculated from a uniform $31 \times 31 \times 31$ dose grid encompassing the volume and then extrapolated 5 times to a $155 \times 155 \times 155$ dose grid. In order to cover the whole brain volume of 1500 cm^3 (approximately), the dose sampling grid resolution is 3–4 mm. In moving the shot along each of the three axes, the maximum brain dose was found to have a dependence on the location of the shot. We hypothesized that this was due to the usage of a sparse dose grid that encompasses the whole brain volume. Due to the very small and sharp dose distribution, it is likely that the maximum dose point is “missed” when sampling the dose grid.

While the higher isodose lines (i.e., 25% and higher) showed a large positional dependence within the dose grid, we conjectured that the lower isodose lines have less dependence on the position of the shot. In order to test this, a single 4 mm shot was placed at one such location where the maximum brain dose equals the maximum target dose and the shot was moved along the three axes, independently. The spatial

dependence in the volume of brain irradiated (VBI) by various isodose lines was recorded.

2.B. Simulation study of the relative location of two shots

Two shots of the same size (4, 8, or 16 mm) were placed in a target near the center of the brain volume. The two shots were given a prescription dose of 20 Gy to the 50% isodose line and equally weighted. Initially the two shots were placed at the same location and the separation increased in steps of 0.2 up to 1 cm and then in steps of 1 up to 10 cm. As the separation increased, the spatial dose distribution transforms from a single sphere to a dumbbell shape, before becoming two separate spheres. At each separation, the VBI of the lower isodose lines was recorded and plotted as a function of the shot separation.

2.C. Simulation study of the lesion shape

Multiple shots of the same size (4, 8, or 16 mm) were placed along the anterior–posterior axis at equal separation to mimic an oblong lesion. The number of shots was increased in steps of 1, starting from 1 until the target length was reached. The separation between the shots was increased in uniform steps to ensure that the 50% isodose line appeared as a straight line on visual inspection, representing a theoretical dose distribution for an oblong lesion, as shown in Fig. 1(a). As outlined in Table I, the spacing used was 4, 6, and 10 mm for 4, 8, and 16 mm shots, respectively. The number of shots that could be accommodated within a target grid depends on the spacing between the shots. A single target grid could be covered from end to end by either seventeen 4 mm shots, eleven 8 mm shots, or seven 16 mm shots in such a way that the resulting 50% isodose lines were uniform and oblong. These data were used to test our hypothesis that there is a direct correlation between the VBI of lower isodose lines and the volume of target irradiated (VTI) by the 50% isodose line (VT50%). In order to study the dependence of brain dose on the shape of the lesion, a correlation study was performed between VT50% and the aspect ratio of the lesion which is defined as the ratio of minimum to maximum dimensions of the lesion along the three axes. Likewise, a correlation study was performed between VT50% and the number of lesions.

FIG. 1. Shape of the 50% isodose line in the simulated (a) oblong lesion and (b) spherical lesion studies. In (c), multiple lesions were spread throughout the whole brain and calculated using three dose grids.

TABLE I. Details of the simulated lesion geometry, shot size, number of shots, mean separation between shots (mm), shot weight, and orientation of the 50% isodose line in space.

Geometry	Shot size (mm)	# Shots	Mean separation between shots (mm)	Shot weight	Orientation
Oblong lesion	4	1–17	4	1	AP
	8	1–11	6	1	AP
	16	1–7	10	1	AP
Spherical lesion	4	$3 \times 3 \times 3 = 27$	1, 2, 3, 4	1	3D
	8	$3 \times 3 \times 3 = 27$	1, 2, 3, 4, 5, 6	1	3D
	16	$3 \times 3 \times 3 = 27$	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	1	3D
Multiple lesions	4	1–10	3 ± 4.6 cm	1	Separated
	8	1–10	3 ± 4.6 cm	1	Separated
	16	1–10	3 ± 4.6 cm	1	Separated

2.D. Spherical lesion simulation study

Twenty-seven shots of the same size (4, 8, or 16 mm) were placed in a $3 \times 3 \times 3$ grid in a dose grid near the center of the brain to mimic a single large lesion. The resulting 50% isodose line possessed an approximately spherical shape and represented the spatial dose distribution for a spherical lesion, as shown in Fig. 1(b). The separation between the shots was increased in steps of 1 mm, starting from 1 mm, until the 50% isodose lines started to bend visually. The largest separation between 4, 8, and 16 mm shots were 4, 6, and 10 mm, respectively, as outlined in Table I. These data were used to test our hypothesis that direct correlation exists between the VBI of the lower isodose lines and VT50%.

2.E. Multiple lesion simulation study

In order to simulate multiple brain lesions, one to ten shots using the same collimator size (i.e., 4, 8, or 16 mm) were distributed throughout the brain using three target matrices, as shown in Fig. 1(c). The three targets were placed in the cerebellum, right temporal lobe (bordering the frontal lobe), and left temporal lobe (bordering the frontal lobe) and were given up to four, three, and three, shots, respectively. The VBI was recorded as a function of VT50%. The mean separation between any two shots was 3 ± 4.6 cm, representing up to ten lesions distributed throughout the brain, as described in Table I. Our hypothesis of the existence of a direct correlation between the VBI by the lower isodose lines and VT50% was tested using these data.

2.F. Clinical study

The institutional review board approved the present retrospective clinical study. Forty patients were chosen retrospectively in order to test the hypothesis that there is a monotonic relationship between the VBI of the lower isodose lines and VT50%. The patient characteristics are shown in Table II. The 40 patients include 8 with arteriovenous malformation and 2 with trigeminal neuralgia. In all our clinical cases, the lesions are contained within the boundaries of the whole brain structure and no case was considered that had any portion of lesion outside the brain contour. The treatment plans

were developed by two different physicists who were trained at different centers and had different levels of experience. In all the cases, planning techniques used were variable, but appropriate weighting, number, and size of shots were used. All plans were reviewed and approved by a radiation oncologist and neurosurgeon. Care was taken during the brain contouring to include it all the way to the brain stem. For the 40 cases, the mean volume of brain is 1482 ± 123 cm³ (range: 1252–1724 cm³). We performed a correlation study between the VT50% and VBI by the lower isodose lines.

2.G. Toxicity scoring in clinical study

We propose a mathematical fitting method for computing VB12 prospectively. The global maximum brain dose is taken as the largest of the maximum tumor dose (in Gy) for all the individual lesions. The 12 Gy volume determines the X% isodose line where $X = \{12 \text{ Gy/global maximum brain dose (in Gy)}\} \times 100$. We propose a power-law relationship between VB12 and X:

$$\text{VB12} = \text{VT50\%} \times \left(\frac{X}{50}\right)^{-\alpha}, \quad (1)$$

where α is the fitting parameter of the power-law relationship and VT50% equals the sum of volumes of individual lesion covered by 50% isodose line of the global maximum dose. A value for α is computed for each patient using the above formula. Analyzing all the patient data, a mean value for α was estimated. Using the mean value of α , VB12 is recalculated for each patient and is compared with the measured value of VB12.

TABLE II. Patient and tumor characteristics.

Characteristic	Value (or mean)	Range
No. of patients studied	40	
Male	17	
Female	23	
Age at diagnosis (yr)	54	7–80
Mean no. of lesions at presentation	2.5	1–6
Mean lesion volume at presentation (cm ³)	4.4	0.02–22.2

3. RESULTS

3.A. Management of the reporting accuracy of the maximum whole brain dose

In this study, we noted a spatially periodic dependence on the maximum brain dose. For a single 4, 8, or 16 mm shot, the maximum reported brain dose oscillates between two values with a periodicity of 3, 6, and 10 mm along any of the three axes, respectively. For given Rx dose = 20 Gy to 50% isodose line, the maximum reported brain dose ranged between 28 and 40 Gy for a 4 mm shot. Figure 2(a) shows such a periodic dependence of the maximum reported brain dose when a 4 mm shot is moved along the superior–inferior axis in steps of 1 mm for given Rx dose = 20 Gy to 50% isodose line.

When a shot is placed at one such maximum brain dose location and moved along the three axes separately, the volume of brain irradiated to a given isodose level showed dependence on the location of the shot. The brain volume irradiated by 1%, 5%, 10%, 25%, 37.5%, and 50% isodose lines is shown in Fig. 2(b). The VBI-1% and VBI-10% isodose lines have a standard deviation of less than 5%, thereby showing less dependence on the location of the shot. In contrast, the higher isodose lines showed an increasing error in the maximum reported dose. As such, in subsequent data analysis, we confined our whole brain dose analysis to the 1% and 10% isodose lines in order to assure whole brain dose reporting accuracy of better than 5%. Note that this discrepancy is only evident when the maximum dose is reported using the large, whole brain structure volume. Alternatively, the maximum dose reported using the much smaller, and therefore geometrically fine “target” grid, was found to have no signif-

FIG. 2. (a) Measured maximum brain dose (Gy) when a 4 mm shot was displaced along the superior–inferior axis, in steps of 1 mm. Note that the Rx dose of 20 Gy was prescribed to the 50% isodose line. (b). Volume of brain (mm^3) covered by 1%, 5%, 10%, 25%, 37.5%, and 50% isodose lines, when a 4 mm shot was displaced in steps of 1 mm along the anterior–posterior axes.

icant positional dependence and was assumed to be constant and accurate.

3.B. Simulation studies of relative location, shape, size, and spatial distribution

The behavior of the dosimetric indices as a function of relative separation is shown in Figs. 3(a)–3(c). The data show that VB50%, VB10%, and VB1% increase gradually initially and level off with increasing shot separation for 4, 8, and 16 mm shots, respectively. At increasing separation between the two shots, the VB50% approached twice the volume of 50% isodose line of a single shot, thereby, showing the independence of shots.

The simulation study data are shown collectively in Figs. 4(a)–4(c). These data demonstrate that VB50%, VB10%, and VB1% have statistically significant relationships with VT50%, but the shape, number, and location of lesions are not significantly related.

FIG. 3. Volume of brain (cm^3) covered by 1%, 10%, and 50% isodose lines as a function of the separation between dual shots of size (a) 4 mm, (b) 8 mm, and (c) 16 mm, respectively.

FIG. 4. Volume of the brain (cm^3) covered by (a) 50%, (b) 10%, and (c) 1% isodose lines as a function of the volume of the target (cm^3) covered by the 50% isodose line. This simulation study includes oblong, single spherical, and multiple spherical lesions. An exponential curve fit is shown with 95% confidence intervals. The wide data range for the multiple lesions at $\text{VT50\%} = 4$ and 9 cm^3 is characteristic of the fact that the upper data points were created with multiple, 8 mm lesions, while the lower data points were created with one to two, 16 mm lesions.

The dependence of $\text{VB50\%}$, $\text{VB10\%}$, and $\text{VB1\%}$ on $\text{VT50\%}$ was tested for the oblong and spherical lesion as well as multiple lesions. $\text{VB50\%}$ and $\text{VB10\%}$ are linearly related with $\text{VT50\%}$ ($\text{VB50\%} = 0.94 \times \text{VT50\%}$ and $\text{VB10\%} = 13.56 \times \text{VT50\%}$), while $\text{VB1\%}$ has an exponential relation with $\text{VT50\%}$ ($\text{VB1\%} = 1266 - 1198.8 \times \exp(-0.5 \times \text{VT50\%})$). $\text{VB50\%}$, $\text{VB10\%}$, and $\text{VB1\%}$ were found to have strong correlation with $\text{VT50\%}$ with Spearman correlation coefficients of 0.98, 0.99, and 0.94, respectively. The corresponding p -values derived from a Student's t test were all $< 1 \times 10^{-4}$. Regarding the relationship between the aspect ratio and number of lesions with $\text{VT50\%}$, the Spearman correlation coefficients were 0.08, 0.19 and p -values were 0.47 and 0.08, respectively. The data derived using multiple metastases have wide variation in $\text{VB1\%}$ at $\text{VT50\%}$ values of 4 and 9 cm^3 as indicated in Fig. 4(c). The high data points were de-

FIG. 5. Volume of the brain (cm^3) covered by (a) 50%, (b) 10%, and (c) 1% isodose lines as a function of the volume of target (cm^3) covered by 50% isodose lines, in the clinical study.

rived from five to ten, 8 mm lesions, whereas the low data points were derived from one to two, 16 mm lesions.

3.C. Clinical study

Figures 5(a)–5(c) show the dependence of $\text{VB50\%}$, $\text{VB10\%}$, and $\text{VB1\%}$ with $\text{VT50\%}$, respectively. The parameters of the linear and the exponentially increasing function of the respective graphs are $\text{VB50\%} = 0.91 \times \text{VT50\%}$, $\text{VB10\%} = 10.69 \times \text{VT50\%}$, and $\text{VB1\%} = 1185.3 - 1073.1 \times \exp(-0.4 \times \text{VT50\%})$. This study demonstrated a strong correlation with Spearman correlation coefficients of 0.99, 0.97, and 0.89, respectively. The corresponding p -values from a Student's t test were all $< 1 \times 10^{-4}$. In contrast, the relationship between the number of lesions and $\text{VT50\%}$ had a Spearman correlation coefficient of -0.1 and the p -value was 0.53. For the 17 clinical cases with a single lesion, the relationship between the aspect ratio and $\text{VT50\%}$ had a Spearman correlation coefficient of -0.5 and p -value of 0.04. These clinical

FIG. 6. Plot of the measured, calculated, and the difference in V12Gy of brain (cm^3) for the 40 patients in the clinical study, as a function of volume of target (cm^3) covered by 50% isodose line.

data demonstrate that VB50%, VB10%, and VB1% have statistically significant dependence on VT50%, but not on the number of lesions. There is a weak correlation between the VT50% and the aspect ratio of lesions in the clinical study.

3.D. Toxicity scoring in clinical study

The mean value of α for the 40 patients included in this study was 1.5. The measured VB12 of brain agrees with the calculated value of VB12 (using $\alpha = 1.5$) to within 1.7%. The data are shown in Fig. 6.

4. DISCUSSION

The data provided above describe a correlation between the total volume of all target lesions and lower isodose lines such as VB12, and VB10%. However, to emphasize this point we reanalyzed certain data from the simulation study (i.e., the multiple metastases study) and the clinical data. Figures 7(a) and 7(b) display the VB10% as a function of total treatment volume (i.e., VT50%) and as a function of the number

FIG. 8. Data from the retrospective clinical study show that the volume of lower isodose lines (VB10% and VB12Gy) is independent of the number of lesions, and that this volume has large variation for any given number of lesions.

of discrete lesions, respectively. In addition, the lack of such a correlation with the number of metastases was noted in the clinical study. Figure 8 shows VB10% and V12 as a function of the number of lesions in the clinical study. Both data sets illustrate a lack of reliable correlation with the number of lesions. As such, it is logical to conclude that the total treatment volume, rather than the number of lesions, should be used to predict brain dose or suitability for Gamma Knife treatment.

Review of the data presented in Fig. 4 suggests that superior curve fitting might be achieved if the data were separated between single and multiple metastases for the very low isodose lines such as VB1%. We chose not to do this in this study considering the clinical context. For example, a typical dose prescription is 48.0 Gy, and 1% of this would therefore be 48.0 cGy. This dose level is likely to be clinically insignificant within the context of the patient population to be treated. Further, use of the curve that was fit using all of the data would yield an expected absolute brain volume of approximately 1250 cm^3 , as opposed to the total brain volume of 1546 cm^3 . A clinician using this data would conclude that 80% of the brain received a dose of 48.0 cGy as opposed to 100%, and would likely not change his or her clinical judgment based on this difference.

The data demonstrate that the volume of brain irradiated by certain isodose lines depends primarily on the sum of the volume of treated lesions, and not on their number, shape, or

FIG. 7. Analysis of the multiple lesion part of the simulation study: (a) Plot showing the correlation between the brain volume irradiated by the 10% isodose line and the target volume irradiated by the 50% isodose line. (b) Plot showing the lack of correlation between the brain volume irradiated by the 10% isodose line and the number of shots used to cover the target. The three distinct groups of data points correspond to data derived using 4, 8, and 16 mm shots.

location. This can be incorporated into the clinical decision making process in determining the suitability of GKSR for a specific patient. Total lesion volume can be estimated *a priori* using pretreatment MRI. This could be accomplished by contouring the lesion structures and assuming that their volume is treated to the 50% of maximum isodose line. Using this total volume, the expected value of VT50% and VB12 can be estimated.

It is uncertain whether these results may be applicable to treatment of more than ten lesions. In the simulation study on various shapes, oblong lesions were created with up to seventeen 4 mm shots, eleven 8 mm shots, or seven 16 mm shots. The restriction in this part of the simulation study is in placing as many shots as possible within the target grid such that the 50% isodose line is uniform and oblong. It seems plausible that these data could be extrapolated to more than ten lesions, but the validity of doing so is not established.

Future work may focus on collecting data from multiple clinical sites in order to assess the robustness of these conclusions when different planning techniques are involved. In addition, it would be of benefit to extend the VB12 analysis to more lesions, since some sites treat ten or more lesions in a single GKSR session. The clinical data that are available in our clinic were limited to a maximum of six lesions.

5. CONCLUSIONS

This study provides insight into the relationship between the brain dose and the prescription lesion dose–volume in GKSR. The simulation and the clinical data demonstrate that the volume of brain irradiated by 50%, 10%, and 1% of maximum dose is statistically significantly related to VT50%, but the shape, number, and location of lesions are not significantly related. We presented an empirical model that is capable of predicting the VB12, given the anticipated treatment volume and prescription dose. The total treatment volume, rather than the number, shape, and location of lesions should be used as selection criteria for GKSR.

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