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Radiosurgery vs. Whole Brain Radiotherapy of Multiple Brain Metastases: An Overview of Dosimetric and Biological Perspectives

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Abbreviation: BED: Biologically Effective Dose; **CNS:** Central Nerve System; **CTEP:** Cancer Therapy Evaluation Program; **DVH:** Dose Volume Histograms; **GKRS:** Gamma Knife Radiosurgery; **IDL:** Isodose Line; **LQ:** Linear Quadratic; **NSCLC:** Non-Small Cell Lung Cancer; **RION:** Radiation-Induced Optic Neuropathies; **RTOG:** Radiation Therapy Oncology Group; **SCLC:** Small Cell Lung Cancer; **SFED:** Single Fraction Equivalent Dose; **SRS:** Stereotactic Radiosurgery; **WBRT:** Whole Brain Radiation Therapy

ABSTRACT

Purpose

Treatment option of stereotactic radiosurgery versus whole brain radiotherapy for multiple brain metastases (>10) is an ongoing debate. Detailed dosimetric and biological information are presented in this study to investigate the possible clinical outcomes.

MATERIALS AND METHODS

Nine patients with multiple brain metastases (11–25) underwent stereotactic radiosurgery. Whole brain radiotherapy plans are retrospectively designed with the same MR image set and the same structure set for each patient using the standard opposing lateral beams and fractionation (3 Gy × 10).

Physical doses and biologically effective doses are calculated for each lesion target and the CNS normal tissues and they are compared between whole brain radiotherapy and stereotactic radiosurgery in the context of clinical efficacy and published toxicities.

Results

Tumor biologically effective dose is higher in radiosurgery than in whole brain radiotherapy by factors of 3.2–5.3 in maximum dose and of 2.4–3.1 in mean dose. Biologically effective mean dose in radiosurgery is 1.3–34.3% for normal brain, 0.7–31.6% for brainstem, 0.5–5.7% for chiasm, 0.2–5.7% for optic nerves and 0.6–18.1% for hippocampus of that in whole brain radiotherapy over nine cases presented here. We also presented the dose-volume relationship for normal brain to address the dosimetric concerns in radiosurgery.

Conclusions

Dose-volume metrics presented in this study are essential to understanding the safety and efficacy of whole brain radiotherapy and/or radiosurgery for multiple brain metastases. Whole brain radiotherapy has resulted in higher incidence of radiation-related toxicities than radiosurgery. Even for patients with more than 10 brain metastases, the CNS normal tissues receive significantly lower doses in radiosurgery. Mean normal brain dose in SRS is found to correlate with the total volume of lesions rather than the number of lesions treated.

Keywords: Whole brain radiotherapy; Stereotactic radiosurgery; Multiple brain metastases; Toxicities; Biologically effective dose; Radiation complication

INTRODUCTION

The brain is a common site of metastases for cancer patients. Treatment options for patients with brain metastases are, in part, dependent on the number of lesions. Recently published guidelines [1] recommend Whole Brain Radiation Therapy **(WBRT)** rather than Stereotactic Radiosurgery **(SRS)** for patients with more than 4 lesions, but this is an arbitrary number and there is little evidence- and no level 1evidence- to support a cutoff of 4 lesions as opposed to 5, 10 or more [2-4]. For many institutions, SRS is the preferred treatment for eligible patients with 4 or less CNS lesions for several reasons including the neurocognitive decline noted in patients that have had WBRT [5].

WBRT delivers a fairly uniform dose to the entire brain, usually in 10 or more daily treatments; a common prescription is 30 Gy in 10 fractions to the brain mid plane. SRS delivers tightly

conformal doses to each target lesion in a single fraction with dose (typically 15 Gy or higher) prescribed to a low (50%-70%) isodose surface such that the center of the lesion receives up to twice the prescription dose. Dose delivered in a single fraction has greater biological efficacy than the same dose cumulated over multiple fractions but due to the tight targeting, normal tissues outside a treated lesion receive doses in SRS that drop off fast so are much lower (often <50%) than the prescription.

There are two major concerns about using SRS rather than WBRT for multiple brain metastases. One is that the presence of multiple clinically detectable metastases implies the presence of occult disease that is not addressed by the targeted dose distributions of SRS. The second is that, while for treatments of one or a few lesions, the conformality of the SRS dose distribution makes it safe in terms of normal tissue exposure, as the number of targets increases, overlapping dose from the multiple targets could increase dose to normal structures, particularly normal brain, to a level of clinical concern. Tumor location and overlapping dose are major factors, as well as the number of tumors treated with SRS, that contribute high dose to a particular CNS critical structure.

Studies [6-7] have shown that the cumulative dose to the normal brain is safe for radiosurgery of more than 10 brain metastases with Gamma Knife **(GK)**. However, no publications were found to address the detailed dose metrics for various CNS critical structures in SRS of multiple brain metastases. In light of the debate on the safety and efficacy of SRS versus WBRT, it is essential to understand the dosimetric and biological difference in these two treatment modalities. Our study calculated and compared the physical and biologically effective doses for both treatment targets and the CNS normal tissues in patients with multiple (>10) brain metastases. We use nine cases to demonstrate the fundamental difference in dosimetric and biological results between SRS and WBRT. Some issues related to the normal tissue complications induced by radiation dose-volume effects are raised and discussed in contrast to the current knowledge.

MATERIALS AND METHODS

We present the dosimetric data of nine randomly selected patients with 11 to 25 brain metastases. All patients were treated with Gamma Knife Perfexion unit at Cooper University Hospital. Three of those nine patients have the primary disease of Non-Small Cell Lung Cancer **(NSCLC)**, five of them have breast cancer and one patient has Small Cell Lung Cancer **(SCLC)**; Two patients had WBRT before the current GKRS. The rest had no brain radiation therapy before the current Gamma Knife Radiosurgery **(GKRS)**.

The location of lesions is distributed around every lobe of the brain in each case. Two patients have one lesion located in the pons and another one has one lesion abutting the pons. **Table 1** lists the total number of lesions treated with GKRS, total volume of lesions, median volume, dimension and their ranges. Also included in **Table 1** are the prescription doses and isodose lines. The prescribed doses for individual metastases ranged from 15 Gy to 20 Gy at the 50%–85% Isodose Line **(IDL)**, depending upon the size and location of the lesion.

Table 1: Summary of the characteristics of lesions and prescription doses for the nine cases treated with GKRS at Cooper, including number of lesions, total volume of lesions, median volume, dimension and their ranges as well as the prescription doses and Isodose Lines **(IDL)**.

Target and Dose	Median	Range
No. of Lesions	19	11-25
Total Volume (cc)	9.7	0.3-35.4
Individual Volume (cc)	1.06	0.006-11.23
Individual Dimension (cm)	0.8	0.2-3.6
Prescription Dose (Gy)	18	15-20
Prescription IDL	50%	50%-85%

All the targets and critical structures were delineated by a neurosurgeon based on the high resolution Magnetic Resonance **(MR)** images (voxel size of 1 mm^3) during the Gamma Knife procedure. The MR images together with all the structures were DICOM transferred to the CMS Xio planning system where a WBRT treatment was planned for 30 Gy to isocenter (at the middle of the brain) in 10 fractions with two 6 MV opposing lateral photon beams. All doses were calculated without heterogeneity corrections.

The effect of the number of delivery fractions (N) and dose per fraction on the biological efficacy of a total dose, D, is often described by a theoretical quantity called the Biologically Effective Dose **(BED)**. It has long been observed that dose-per-fraction effects are different for many tumors vs normal tissues as well as for different normal tissues and complication endpoints. Although there are several models for calculating BED, the most widely-used method is the Linear Quadratic **(LQ)** Model [8-9]. The equation for the calculation of BED is given as follows.

(1) $BED_{\alpha/\beta}=D\ (1+(D/N)/(\alpha/\beta))$

In particular, one may use the LQ model to calculate BEDα/β for a chosen fractionation schedule (e.g. 30 Gy in 10 fractions) and compare it to the Single Fraction Equivalent Dose **(SFED)**, the isoeffective dose delivered to the same tissue in a single fraction, by solving the quadratic equation:

(2) $SFED\ (1+SFED/(\alpha/\beta))= BED_{\alpha/\beta}$

Of relevance to the following discussion, the key biological parameter in this calculation is called α/β. The degree to which an effect is sensitive to dose-per-fraction depends inversely on α/β. In our conservative comparison, α/β is assumed to be 1 Gy for normal brain tissues with an increased sensitivity to SRS.

The WBRT dose distribution is quite uniform (<10% variations in our nine cases). If it were completely uniform, a prescription of 30 Gy in 10 fractions would correspond to a tumor BED (assuming α/β=10 Gy) of 39 Gy and a normal tissue BED (assuming α/β=1 Gy), as suggested (29) for some CNS complications, of 120 Gy. For the tumor, the SFED corresponding to 30 Gy/10

fractions is approximately 15.4 Gy while for the normal tissue, it is approximately 10.5 Gy. The dose in an SRS plan is highly inhomogeneous and BED is nonlinearly related to physical dose. The mean BED for a specified structure in SRS is calculated by converting the physical dose of each bin to the individual BED before averaging the volume-weighted BED dose bins over the full DVH.

RESULTS

Figure 1 plots the Dose Volume Histograms **(DVH)** in both SRS and WBRT for the various CNS critical structures for one of our nine cases. Each DVH was calculated with the actual physical dose where SRS was for a single fraction and WBRT for a prescription of 30 Gy in 10 fractions. The brain DVH was calculated for the entire brain that includes the dose to targets. The critical structure normal brain is the entire brain volume with all delineated targets subtracted. (Figure 2) plots the mean normal brain dose in relation to number of lesions and total volume of lesions respectively. Also included in (Figure 2) for the plot of mean brain dose vs total volume of lesions is a power regression curve with the equation of $y = 1.1709x^{0.4503}$ and $R^2 = 0.9788$ (y is the mean dose, x the total volume).Extrapolation of the curve to a total volume of 70.0 cc would result in the mean brain dose of 7.9 Gy.

Table 2 Summarizes the maximum and mean physical dose delivered in the single fraction to the lesions as well as to the critical structures in SRS, and **Table 3** shows the maximum and mean BEDs calculated by the equation (1) for all nine cases. For SRS, different lesions received different prescriptions but for WBRT, the doses differ from a uniform 30 Gy by less than 10%. Using the hypothetical uniform doses for tumor and selected normal tissues in WBRT, the tumor BED is higher for SRS than for WBRT, by factors of 2.4–3.1 in mean dose and of 3.2–5.3 in maximum dose. For normal tissues, the mean BED in SRS are much less than that in WBRT for the normal tissues although the maximum BED for a specific normal tissue can be higher in SRS if there are lesions in proximity.

Table 2: Summary of physical maximum and mean doses in SRS for lesions and some CNS critical structures.

Physical Dose (Gy)	Median Max	Max Range	Median Mean	Mean Range
Lesions	34.9	30.9-40.9	27.3	25.0-30.2
Normal Brain	24.1	22.7-25.9	2.7	0.6-4.8
Brainstem	6.0	2.0-23.9	2.5	0.5-4.6
Chiasm	2.0	0.8-3.0	1.7	0.4-2.1
Rt Optic Nerve	2.0	0.4-3.0	1.2	0.2-2.1
Lt Optic Nerve	2.0	0.3-3.0	1.4	0.2-1.7
RtHippocampus	5.0	2.0-8.0	2.9	0.5-4.1
LtHippocampus	5.0	0.9-11.0	2.1	0.5-3.9

Table 3: Summary of maximum and mean BEDs in SRS for lesions and some CNS critical structures. BED was calculated with α/β of 10 Gy for lesions and with α/β of 1 Gy for the CNS critical structures.

BED (Gy)	Median Max	Max Range	Median Mean	Mean Range
Lesions	157.0	126.0-208.0	102.0	87.5-121.4
Normal Brain	605.0	538.0-696.1	16.6	1.6-41.2
Brainstem	41.7	6.0-595.1	8.8	0.8-37.9
Chiasm	6.0	1.5-12.0	4.6	0.6-6.8
Rt Optic Nerve	6.0	0.6-12.0	2.6	0.3-6.8
Lt Optic Nerve	6.0	0.4-11.9	3.4	0.2-4.5
RtHippocampus	30.0	6.0-72.0	11.6	0.8-21.7
LtHippocampus	29.7	1.7-130.9	6.5	0.7-20.2

Table 2 can also be used to compare SRS maximum and mean physical doses for normal tissues of particular concern in SRS with SFED in WBRT, all of which have a single fraction equivalent uniform dose of about 10.5 Gy. They are the normal brain, the brainstem, the hippocampus, the optic nerves and the optic chiasm. Since WBRT is widely believed to be safe for some of these normal tissues, comparison of SRS doses with these calculated SFEDs might help in setting limits for SRS treatments. The mean normal brain dose is an indicator of whether there might be a serious problem with overlapping dose distributions in SRS. **Table 4** shows the total volumes of normal brain receiving the specified minimum dose from our study in comparison with Yamamoto's study [6], which calculated dose-volume for 80 patients with number of lesions from 10 to 43.

Table 4: Volumes of normal brain expressed as either cc or % that receive the specified minimum dose in SRS from this study and [6].

Study	Unit (cc)	V2	V5	V10	V12	V15	V20
Yamamoto	Median	1105	309	64		24	8
	Range	410–1501	46–1247	13–282		2–77	0–40
Cooper	Median	1029.2	196.7	44.8	34.9	19.0	8.3
	Range	29-1398	7-475	2-128	1-92	0-60	0-28
Unit (% of entire brain)		V2	V5	V10	V12	V15	V20
Cooper	Median	68	11	3	2	1	1
	Range	3-89	1-34	0-9	0-7	0-4	0-2

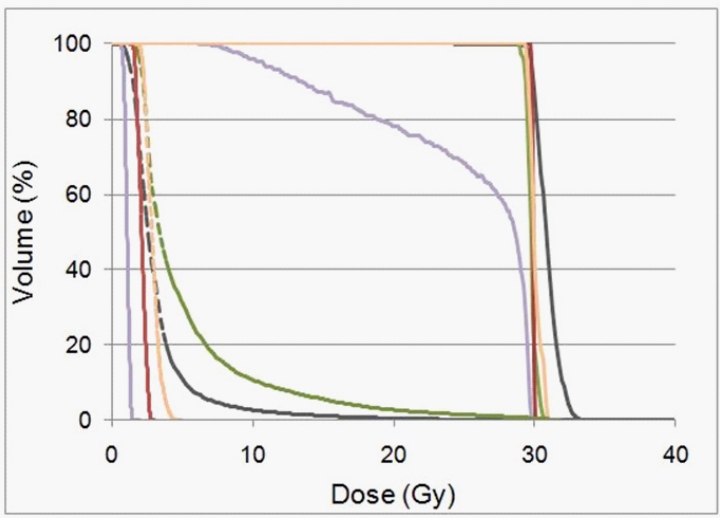

Figure 1: Example of DVH plots (Cases #3) for brain, brainstem, chiasm, optic nerves (right) and hippocampus (right) from both SRS in a single fraction and WBRT in 10 fractions. X axis is physical dose in Gy and Y axis is structure volume in percentage. WBRT plotted as solid line and SRS plotted as dashed line. Black lines are for brain, green for brainstem, burgundy for chiasm, purple for optic nerve and orange for hippocampus.

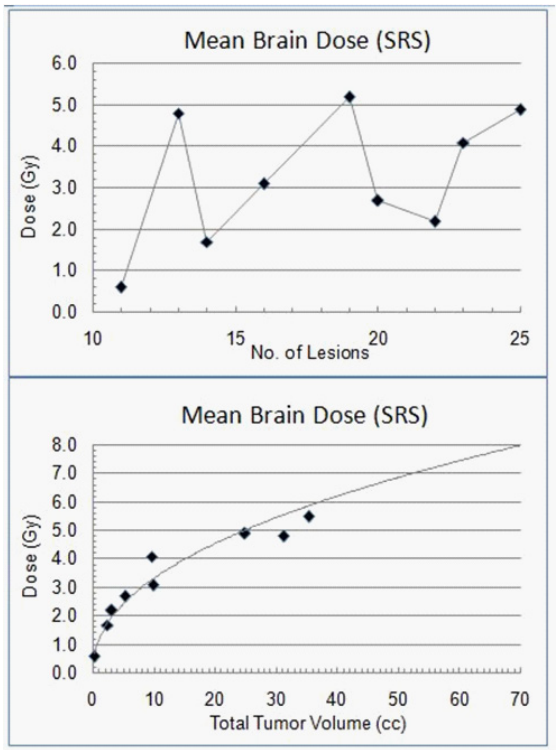

Figure 2: Plots of mean normal brain dose in relation to number of lesions and total volume of lesions respectively.

DISCUSSION

Improved systemic control for patients with metastatic disease makes it likely that more patients will have CNS recurrence and that those with CNS metastatic disease will have an improved survival. This makes treatment of CNS metastatic disease an important clinical issue. The conventional option for patients with multiple (>4) metastases is WBRT while either WBRT or SRS is considered an option for patients with fewer metastatic brain lesions. Nevertheless, dose-volume relationship and the effects on tumor control and normal tissue complications in WBRT and SRS of more than 10 brain metastases have not been fully addressed in the literature.

WBRT produces a rather uniform dose distribution across the entire brain, providing doses to lesions and organs at risk within 10% of prescription. In comparison, SRS delivers a highly non-uniform dose distribution in a single fraction, with the lesions receiving much higher maximum and mean doses and the critical structures receiving much lower doses. Single fraction doses are known to have larger biological effect than equal doses delivered cumulatively, over multiple fractions. This is the reason why patients treated with WBRT alone have a higher chance of subsequent CNS local progression as opposed to patients that are treated with SRS [10].

Base on the review by Mc Tyre et al. [11], more severe radiation-induced complications are observed in WBRT than in SRS. The specific relationship between radiation toxicity and radiation dose for each organ is the subject of extensive studies. Some radiation complications are correlated with low to medium dose to large volume of irradiated tissue; others are correlated with high dose to a small volume. WBRT delivers much higher mean dose (approximately 120 Gy of BED) to CNS normal tissues of interest in comparison to SRS (mean doses typically less than 50 Gy of BED as shown in **Table 3**).

The high mean brain dose is likely related to the higher incidence of radiation-induced complications observed in WBRT as opposed to SRS [11]. The normal brain tissue and the brainstem in SRS can receive fairly high maximum dose to a very small volume around the lesions. Safe treatment that gives high BED to very small (below 1 cc) volumes has been observed in SRS of trigeminal neuralgia and spine [12-13]. The relationship between a low mean dose to large volumes (the bath) and/or a high dose to small sub volumes (the shower), has been demonstrated in animal models of the "bath and shower" effects where the presence of a bath dose as low as 4 Gy was found to reduce the tolerance of a shower dose by as much as 15 Gy [14-16]. These bath and shower radiobiological effects may also be implicitly observed in many clinical paradigms; for example the extremely high brainstem maximum point dose in trigeminal neuralgia treatments may be possible in part because of the negligible bath dose. In whole brain treatments, however, the entire volume of brain and brainstem always receive a bath dose high enough to potentially cause a number of toxicities even without a shower dose. In SRS, the bath doses to the healthy brain and adjacent critical structures are much lower than the WBRT bath doses.

Our data provide a radiobiological rationale for the observations that treatment of multiple CNS metastases with SRS is relatively safe. One of the normal tissues of primary concern when treating multiple lesions with SRS is normal brain. (Figure 3) shows the dose-volume relationship for normal brain based on the Yamamoto's study [6] and our data at Cooper, respectively.

The curve fitting provided the dose-volume relationship as $V(x) = 6355.4x^{-2.098}$ and $R^2 = 0.9722$ from the Yamamoto's dataset and the relationship as $V(x) = 4781.8x^{-2.048}$and $R^2 = 0.9931$ from the Cooper dataset, where V(x) is the normal brain volume receiving the dose >xGy. In our nine cases, the normal brain total Vdose is the sum of separate dose-volumes (individual Vdose) receiving the specified dose for each individual target area with the corresponding target volume subtracted. As a typical example, an individual V12 (the volume receiving > 12 Gy) for a target of 3.3 cc in volume (1.2 cm in dimension) is calculated to be 10.5 cc and 7.2 cc respectively with and without target volume included. Two regression curves agree with each other well, which is consistent with the fast dose fall-off in GKRS.

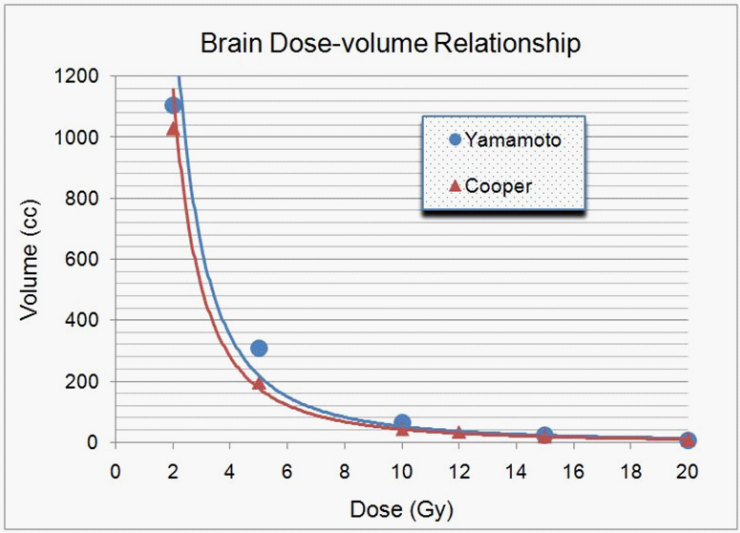

Figure 3: Plots of dose-volume relationship for normal brain dose in radiosurgery based on two datasets in **Table 4.**

The Quantec brain article [17] cites a study [18] in which V12 correlates with symptomatic radiation necrosis and the risk increases significantly from 23% (V12 at 0–5 cc) to 54% (V12 at 10–15 cc). The results of this study, however, appeared as the outliers to others, including RTOG protocol 90-05 [19] and reported clinical outcomes in which an individual normal brain V12 is usually anywhere from a few cc to more than 10 cc but the observed rate of radiation necrosis is as low as a few percent or less. More studies are needed to determine the dose-volume response of symptomatic brain necrosis, especially in the setting of multiple spatially separated high dose volumes.

In terms of other CNS complications, a recent randomized controlled trial [5] suggests that patients treated with SRS plus WBRT are at a greater risk of a significant decline in learning and memory function by 4 months than the group that received SRS alone. This radiation toxicity might be related to the high mean dose to hippocampus [20-21] given by WBRT. Even with treatment of multiple metastases, the mean hippo campal BED is much lower with SRS, which can provide

neurocognitive benefit for SRS (as opposed to WBRT) in these patients. Interestingly, according to the LQ model, the mean SFED in WBRT is approximately 10 Gy but historically, a single fraction of 10 Gy to the whole brain caused 6.7% death within hours of treatment [22]. Many factors are omitted from this simple application of the LQ model to the whole brain, not least of which the concept of damage repair in the time is elapsed between conventional fractions. The brain is an organized structure made up of many types of cells-neurons, glial cells; vasculature- and inter-fraction repair may be a significant feature for some of these cells.

Few Radiation-Induced Optic Neuropathies **(RION)** have been observed in WBRT. Study has found that the mean dose to visual pathway structures is greater for patients with complications vs. those without [23-25] given similar maximum doses. This could be particularly relevant for SRS. A recent literature review [26] found minimal incidence of RION for maximum optic structure doses below 8 Gy in a single fraction, with the incidence rising to 10% for a maximum dose of 12 Gy. Correlation of the risk of RION with other dose-volume metrics, particularly mean dose, is currently unknown.

The LQ model, even including effects such as damage repair and cell repopulation [7-8], is found to deviate from in vitro and animal data for high doses per fraction [27-28]. The deviation seen in some in vitro experiments is more than 20% at greater than 10 Gy per fraction for the calculation of SFED [27-29]. However, the LQ model is reported to describe observed effects well for the lower normal tissue single fraction doses in Table 3. Additionally, the effects of the very different dose distributions for WBRT (uniform) as opposed to SRS (very non-uniform) on complications in multi-functional normal tissues such as the brain and brainstem are not well understood and are beyond the scope of our dose comparisons. The results presented in this study underline the challenges to understanding the biological effects of these two very different but widely used dose distributions. Of note, the LQ model has been widely used clinically to compare the biological effects of different fraction sizes because of its simplicity. However, clinicians should be aware of the uncertainty of the BED and SFED calculations involving hypo fractionation.

From dosimetric and biological perspectives, it is safe to treat patients with more than 10 brain Meta statases with SRS. Peripheral dose to each individual lesion in single fraction is suggested [19] to be 15 Gy to 22 Gy delivered to the 50% isodose line, depending on the size and diagnosis of a lesion (we prefer to treat radio resistant tumor like melanoma and sarcoma to a maximum dose of 22 while other tumors receive a maximum dose of 20 Gy). We recommend keeping the 15 Gy isodose line less than 4 cm in diameter and the 18 Gy isodose line less than 3 cm especially when there is the dose overlap from targets close to each other.

Number of metastases is not always the major dosimetric and biological concern in SRS, because lesion size and location may cause high dose to some CNS critical structures and doses or prescription isodose lines may occasionally have to be adjusted to keep within these constraints. As evident in Figure 2, the mean dose that normal brain would receive in SRS correlates with

the total volume of lesions rather than the number of lesions treated. The mean dose of normal brain may approach8 Gy when the total volume of lesions adds up to 70 cc. More clinical data are needed to refine the regression model observed in **Figure 2**.

CONCLUSIONS

Dosimetric distribution and biological characteristics are significantly different between WBRT and SRS of multiple brain metastases. Based on the maximum and mean BED, SRS is expected to have higher probability of control for the targeted lesions and lower probability of toxicity for many critical structures, especially hippocampus and normal brain.

The biological analysis of this study demonstrates the improved dose to target and the acceptable dose to normal tissues even with more than 10 lesions treated with GKRS. There is evidence that WBRT can potentially lead to more radiation-induced toxicities due to the high mean dose delivered to the CNS normal tissues. Our calculations provided rationale for the potential benefit of SRS in patients with reasonable anticipated survival. We have found that mean normal brain dose in SRS correlates with the total volume of lesions rather than the number of lesions treated. Prospective clinical trials are needed to determine the ultimate efficacy and safety of SRS for multiple brain metastases.

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