

# Biological implications of whole-brain radiotherapy versus stereotactic radiosurgery of multiple brain metastases

## Clinical article

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**Object.** The efficacy and safety of treatment with whole-brain radiotherapy (WBRT) or with stereotactic radiosurgery (SRS) for multiple brain metastases (> 10) are topics of ongoing debate. This study presents detailed dosimetric and biological information to investigate the possible clinical outcomes of these 2 modalities.

**Methods.** Five patients with multiple brain metastases (n = 11–23) underwent SRS. Whole-brain radiotherapy plans were 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 radiation doses and biologically effective doses (BEDs) in WBRT and SRS were calculated for each lesion target and for the normal brain tissues for comparison of the 2 modalities in the context of clinical efficacy and published toxicities.

**Results.** The BEDs targeted to the tumor were higher in SRS than in WBRT by factors ranging from 2.4- to 3.0-fold for the mean dose and from 3.2- to 5.3-fold for the maximum dose. In the 5 patients, mean BEDs in SRS (calculated as percentages of BEDs in WBRT) were 1.3%–34.3% for normal brain tissue, 0.7%–31.6% for the brainstem, 0.5%–5.7% for the chiasm, 0.2%–5.7% for optic nerves, and 0.6%–18.1% for the hippocampus.

**Conclusions.** The dose-volume metrics presented in this study were essential to understanding the safety and efficacy of WBRT and SRS for multiple brain metastases. Whole-brain radiotherapy results in a higher incidence of radiation-related toxicities than SRS. Even in patients with > 10 brain metastases, the normal CNS tissues receive significantly lower doses in SRS. The mean normal brain dose in SRS correlated with the total volume of the lesions rather than with the number of lesions treated.

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**KEY WORDS** • multiple brain metastases • whole-brain radiotherapy • stereotactic radiosurgery • toxicities • biologically effective dose • radiation complication • oncology

THE brain is a common site of metastases in cancer patients. Treatment options for patients with brain metastases are, in part, dependent on the number of lesions. Recently published guidelines<sup>25</sup> recommend whole-brain radiation therapy (WBRT) rather than stereotactic radiosurgery (SRS) for patients with more than 4 lesions. However, this is an arbitrary number, and there is little evidence—and no Level 1 evidence—to support a

cutoff of 4 lesions rather than a higher lesion number for SRS treatment.<sup>7,9,24</sup> For many institutions, SRS is the preferred treatment for eligible patients with 4 or fewer brain lesions for several reasons, including the neurocognitive decline noted in patients that have had WBRT.<sup>3</sup>

Whole-brain radiotherapy delivers a fairly uniform radiation dose to the entire brain, usually in 10 or more daily treatments; a common prescription is 30 Gy in 10 fractions to the brain midplane. Stereotactic radiosurgery delivers tightly conformal doses to each target lesion in a single fraction, with doses (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. A dose delivered in a single fraction has a greater biological efficacy than the same dose cumulated over multiple frac-

*Abbreviations used in this paper:* BED = biologically effective dose; DVH = dose-volume histogram; GKS = Gamma Knife surgery; IDL = isodose line; LQ = linear-quadratic; RION = radiation-induced optic neuropathy; SFED = single-fraction equivalent dose; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

## WBRT vs SRS for multiple brain metastases

tions. Because of the tight targeting in SRS, normal tissues outside a treated lesion receive radiation doses that drop off fast, so the doses the tissues receive are much lower (often less than 50%) than the prescribed dose.

There are 2 major concerns about using SRS rather than WBRT for treating 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 1 or a few lesions the conformality of the SRS dose distribution makes this modality safe in terms of normal tissue exposure, an increase in the number of targeted lesions may increase radiation exposure to normal brain tissues to a level of clinical concern, because of overlapping doses targeting the multiple lesions. Tumor location and overlapping doses are major factors, as are the number of tumors treated with SRS, contributing a high dose to a critical CNS structure.

Previous studies have shown that the cumulative dose to the normal brain is safe for SRS of > 10 brain metastases with Gamma Knife.<sup>29,30</sup> However, no reports were found to address the detailed dose metrics for various critical CNS structures in SRS of multiple brain metastases. In light of the debate on the safety and efficacy of SRS versus WBRT, it was essential to understand the dosimetric and biological differences in these 2 treatment modalities. Our study calculated and compared the physical and biologically effective doses (BEDs) for both treatment targets and for the normal CNS tissues in patients with > 10 brain metastases. We used 5 representative cases to demonstrate the fundamental differences in dosimetric and biological outcomes between SRS and WBRT. Some issues related to the normal tissue complications induced by radiation dose-volume effects are raised and are discussed in the context of the current knowledge of the efficacy and safety of the 2 treatment modalities.

### Methods

This study was approved by the Cooper Health System Internal Review Board. We examined the dosimetric data of 5 patients who had undergone simultaneous treatment for > 10 brain metastases at our institution. All of the patients were treated with a Gamma Knife Perfexion (Elekta) unit at Cooper University Hospital. The primary disease of Patient 1 was non-small cell lung cancer; of Patient 2, breast cancer; of Patient 3, small cell lung cancer; and of both Patients 4 and 5, breast cancer. Patients 1, 2, and 5 had not undergone brain radiation therapy before the current Gamma Knife surgery (GKS), and both Patients 3 and 4 had undergone WBRT before the GKS.

In all cases, lesions were distributed around every lobe of the brain. Patient 3 had 1 lesion located in the pons, and Patient 5 had 1 lesion abutting the pons. Table 1 lists the total number of lesions and total volume of lesions treated with GKS, along with median tumor volumes, dimensions, and their ranges. Also included in Table 1 are the prescription doses and isodose lines (IDLs) for each patient. The prescribed doses for individual metastases ranged from 16 Gy to 20 Gy at the 50%–85% IDL, depending on the size and location of the lesion.

All of the targets and critical structures were delineated by a neurosurgeon on the basis of the high-resolution MRI scans (that is, a voxel size of 1 mm<sup>3</sup>) during the Gamma Knife procedure. The MRI scans, together with all of the structures, were transferred according to Digital Imaging and Communications in Medicine standards to the CMS Xio planning system (Elekta), where a WBRT treatment was planned for 30 Gy to the 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, the BED. It has long been observed that dose-per-fraction effects for many tumors are different from those for normal tissues as well as for different normal tissues and for complication endpoints. Although several models can calculate the BED, the most widely used method is the linear-quadratic (LQ) model.<sup>5,11</sup> The equation for the calculation of BED is given as follows:

$$\text{BED}_{\alpha/\beta} = D \left( 1 + (D/N)/(\alpha/\beta) \right) \quad [\text{Eq. 1}]$$

In particular, one may use the LQ model to calculate the  $\text{BED}_{\alpha/\beta}$  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 following quadratic equation:

$$\text{SFED} (1 + \text{SFED}/(\alpha/\beta)) = \text{BED}_{\alpha/\beta} \quad [\text{Eq. 2}]$$

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

### Results

Figure 1 shows the dose-volume histograms (DVHs) in both SRS and WBRT for the various critical CNS structures for 2 of the 5 patients. 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 including the dose to targets was calculated for the entire brain. The normal critical brain structure is the entire brain volume with all delineated targets subtracted. Figure 2 shows the relationships of the mean dose delivered in SRS to normal brain tissues with the number and the total volume of lesions. Included in the plot of mean dose versus the total volume of lesions is a power regression curve; extrapolation of the curve to a total lesion volume of 50.0 cm<sup>3</sup> resulted in a mean dose to the brain of 6.9 Gy in SRS.

Table 2 summarizes the maximum and mean physical doses delivered in the single fraction of SRS to the lesions as well as to the critical structures for each patient. Table 3 shows the maximum and mean BEDs calculated by Eq. 1 for each patient's SRS treatment. For SRS, different lesions received different prescriptions, but for WBRT, the doses differed from a uniform 30 Gy by

TABLE 1: Characteristics of the lesions and prescription doses for each patient treated with GKS\*

Characteristic	Patient No. (range)				
	1	2	3	4	5
no. of lesions	11	13	16	20	23
total tumor vol in cm <sup>3</sup>	0.3	31.2	9.9	5.3	9.7
median tumor vol in cm <sup>3</sup>	0.02 (0.006–0.05)	1.65 (0.02–10.54)	0.21 (0.02–1.65)	0.11 (0.01–1.49)	0.2 (0.01–2.26)
median dimension in cm	0.4 (0.3–0.6)	1.2 (0.3–3.4)	1.0 (0.3–1.8)	0.6 (0.2–1.5)	0.8 (0.4–1.7)
median Rx dose in Gy	20.0 (20–20)	16.0 (15–18)	18.0 (16–20)	18.0 (15–18)	20.0 (18–20)
median max dose in Gy	30.8 (23.5–40.0)	35.7 (30.0–36.0)	36.0 (26.7–40.0)	36.0 (22.5–36.0)	40.0 (30.8–40.0)
median Rx IDL in %	65 (50–85)	50 (50–50)	50 (50–60)	50 (50–80)	50 (50–65)

\* Rx = prescription.

less than 10%. Using the hypothetical uniform doses for tumor and selected normal tissues in WBRT, the tumor BED was higher for SRS than for WBRT: 2.4- to 3.0-fold higher for the mean dose and 3.2- to 5.3-fold higher for the maximum dose. For normal tissues, the mean BED in SRS was much lower 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 nearby, such as in the brainstem in Patients 3 and 5. In the 5 patients, the mean BEDs in SRS (calculated as percentages of the BED in WBRT, that is, 120 Gy) were 1.3%–34.3% for normal brain tissue, 0.7%–31.6% for the brainstem, 0.5%–5.7% for the chiasm, 0.2%–5.7% for optic nerves, and 0.6%–18.1% for the hippocampus.

The WBRT dose distribution was quite uniform (< 10% variations in our 5 cases). If it were completely uniform, a prescription of 30 Gy in 10 fractions would correspond to a tumor BED (assuming  $\alpha/\beta = 10$  Gy) of 39 Gy and a normal tissue BED (assuming  $\alpha/\beta = 1$  Gy) of 120 Gy, as suggested for some CNS complications.<sup>19</sup> For the tumor, the SFED corresponding to 30 Gy in 10 fractions was approximately 15.4 Gy, while for the normal tissue, it was approximately 10.5 Gy. The dose in an SRS plan is highly heterogeneous, and the 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 DVHs.

Table 2 compares SRS maximum and mean physical doses for normal tissues of particular concern in SRS with SFED in WBRT, all of which had a single-fraction equivalent uniform dose of about 10.5 Gy. These tissues included the normal brain, brainstem, hippocampus, optic nerves, and 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.

## Discussion

Improved systemic control of cancers for patients with metastatic disease makes it likely that more of these patients will have tumor recurrence in the CNS and that

they will have improved survival. This makes treatment of CNS metastatic disease an important clinical issue. The conventional option for patients with multiple (that is, > 4) brain metastases is WBRT, and either WBRT or SRS is considered an option for patients with few metastatic brain lesions. Nevertheless, dose-volume relationships and their effects on tumor control and toxicity on normal tissues in WBRT and SRS of > 10 brain metastases have not been fully addressed in the literature.

Whole-brain radiotherapy produces a rather uniform radiation dose distribution across the entire brain, providing doses to lesions and risk organs within 10% of the prescribed dose. In comparison, SRS delivers a highly nonuniform dose distribution in a single fraction in which the lesions receive much higher maximum and mean doses, and the critical brain structures receive much lower doses. Single-fraction doses are known to have a larger biological effect than equal doses delivered cumulatively over multiple fractions. This is the reason why patients treated with WBRT alone have a higher risk of subsequent local disease progression in the CNS than patients who are treated with SRS.<sup>1</sup>

Table 4 lists the potential toxicities of WBRT and SRS, graded on the basis of symptoms according to the common toxicity criteria of the Cancer Therapy Evaluation Program for brain injury (<http://ctep.cancer.gov/reporting/ctc.html>). As described in a recent review,<sup>17</sup> most of the potential toxicities are mild, moderate, or asymptomatic (Grades 1 or 2), but some may need intervention because of the risk of causing disability or even death (Grades 3–5). According to McTyre and colleagues, more severe radiation-induced complications are observed in WBRT than in SRS.<sup>17</sup> The specific relationship between radiation toxicity and radiation dose for each organ is the subject of extensive studies. Some radiation complications are positively correlated with a low-to-medium dose to a large volume of irradiated tissue, whereas others are positively correlated with a high dose to a small tissue volume. Whole-brain radiotherapy delivers a much higher mean dose (approximately 120 Gy of BED) to normal CNS tissues of interest than SRS does (as shown in Table 3, mean BEDs with SRS are typically lower than 50 Gy).

The likely reason for the higher incidence of radiation-induced complications in WBRT than in SRS is that WBRT delivers a higher mean dose to the brain than SRS

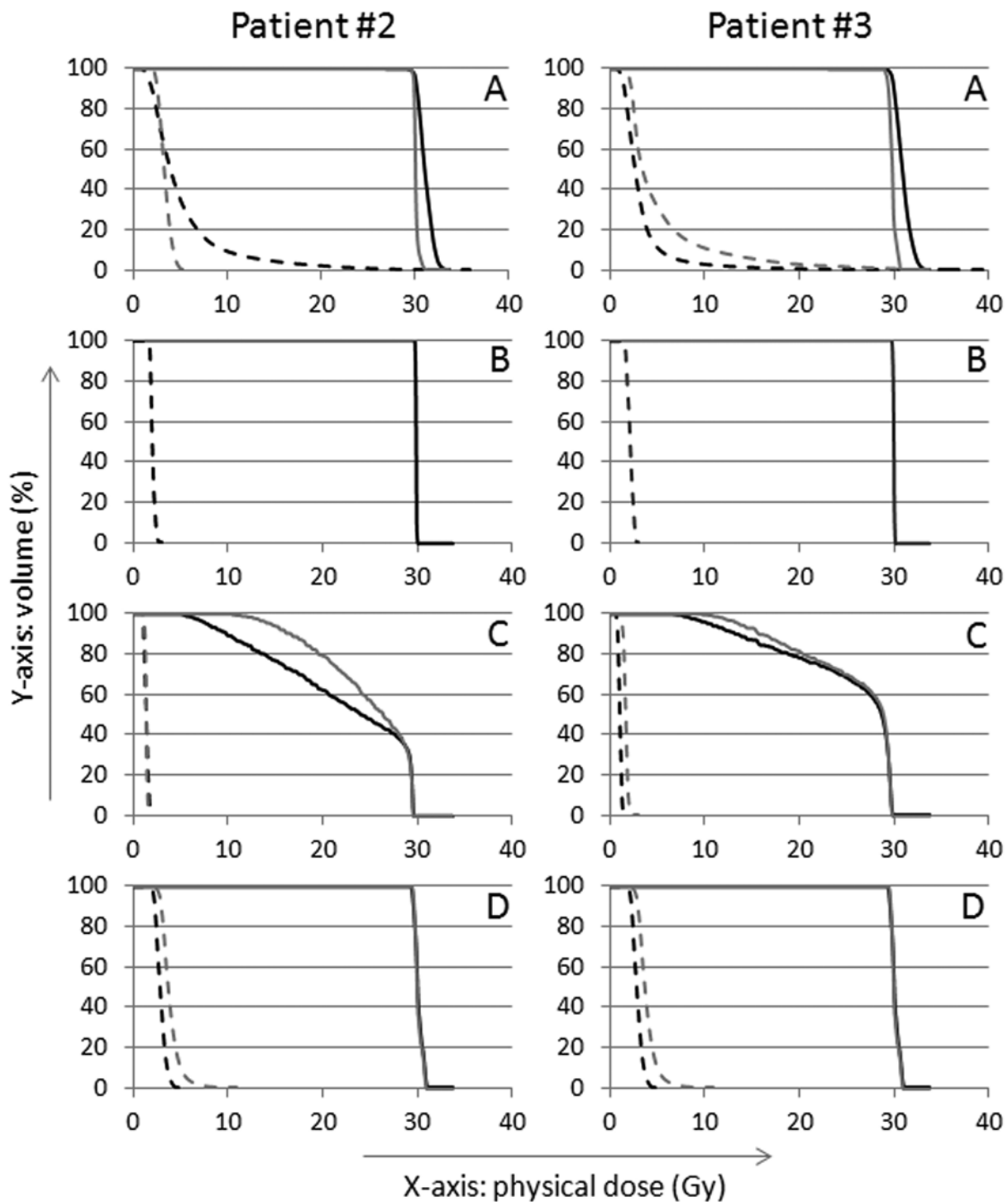
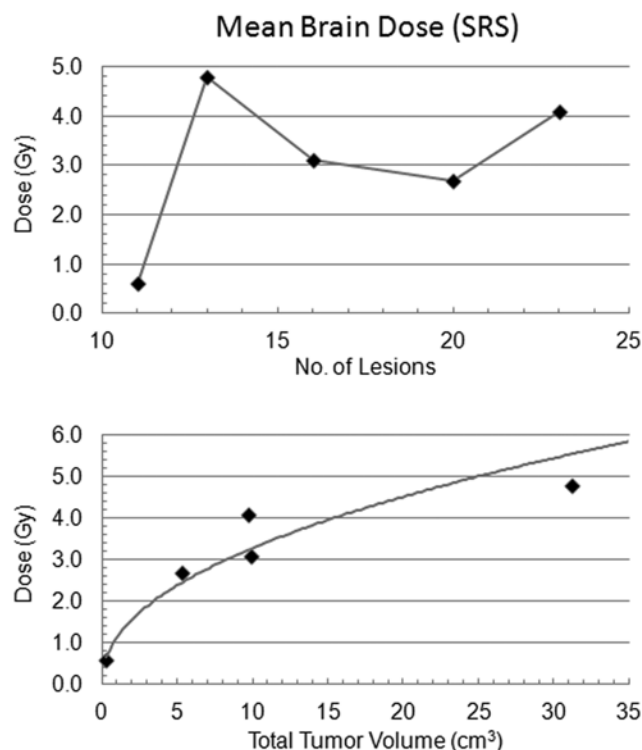


FIG. 1. Dose-volume histograms for Patients 2 and 3. Values for WBRT and SRS are plotted as solid and dashed lines, respectively. The plots represent the brain (black lines) and brainstem (gray lines) (A), chiasm (B), optic nerves (right nerve black lines and left nerve gray lines, C), and hippocampus (right black lines and left gray lines, D) from SRS in a single fraction and from WBRT in 10 fractions.

does.<sup>17</sup> In SRS, the normal brain tissues and the brainstem can tolerate fairly high maximum doses to a very small tissue volume around the lesions. Safe treatment that delivers a high BED to very small (< 1 cm<sup>3</sup>) volumes has been observed in SRS of trigeminal neuralgia and spine.<sup>4,28</sup> In

animal models of the so-called “bath-and-shower” effect, radiobiological relationships between a low mean dose to large volumes (the “bath”) and a high dose to small subvolumes (the “shower”) have been demonstrated in which the presence of a bath dose of as low as 4 Gy reduces





**Fig. 2.** Plots of the mean dose in SRS to normal brain tissues relative to the number of lesions (**upper**) and the total lesion volume (**lower**; the curve shows a power regression with the equation  $y = 1.1399x^{0.46}$  [ $y$  is the mean dose and  $x$  the total volume;  $R^2 = 0.9786$ ]).

the tolerance of a shower dose by as much as 15 Gy.<sup>2,20,26</sup> 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 treatments of trigeminal neuralgia may be possible in part because of the negligible bath dose.

In whole-brain treatments, the entire volumes 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 those of WBRT. The bath-and-shower effect may also underlie the differences in biological outcomes between maximum dose and mean dose. Studies have reported that, given similar maximum doses, the mean dose to visual pathway structures was greater for patients with complications than for those without.<sup>6,10,15</sup> Interestingly, few radiation-induced optic neuropathies (RIONs) have been observed in WBRT, even though optic structures receive high mean doses. However, the SRS clinic has seen a different paradigm. A literature review found that the incidence of RIONs was negligible for maximum doses to the optic structures below 8 Gy in a single fraction, rising to 10% for a maximum dose of 12 Gy.<sup>16</sup> A recent study by Pollock et al.<sup>21</sup> shows for 133 Gamma Knife cases of parasellar tumors that the median volumes of optic nerve receiving maximum doses of 8 Gy, 10 Gy, or 12 Gy are fairly small (15.8, 1.6, or 0.1 mm<sup>3</sup>, respectively), and that the dose falls to 4–6 Gy a few millimeters outside the prescription IDL. The understanding of the correlation of the risk of RION with dose-volume metrics, particularly with the mean dose, is currently incomplete.

Our data provide a radiobiological rationale for the

**TABLE 2: Maximum and mean physical doses delivered by SRS to lesions and to critical CNS structures**

Tissue	Patient No.				
	1	2	3	4	5
<b>max dose (Gy)</b>					
lesions*	30.9 (23.9–40.9)	34.9 (30.9–36.9)	36.9 (27.9–40.9)	32.9 (22.9–36.9)	40.9 (36.9–40.9)
normal brain	23.3	22.7	25.1	25.1	24.1
brainstem	2.0	6.0	20.1	4.0	22.9
chiasm	0.8	3.0	3.0	2.0	3.0
rt optic nerve	0.4	2.0	3.0	0.8	3.0
lt optic nerve	0.3	2.0	3.0	2.0	3.0
rt hippocampus	2.0	7.0	5.0	3.0	6.0
lt hippocampus	0.9	5.0	11.0	4.0	4.0
<b>mean dose (Gy)</b>					
lesions*	27.3 (22.8–32.7)	26.0 (21.8–34.3)	27.3 (21.3–34.5)	27.0 (21.7–31.4)	29.7 (27.0–32.7)
normal brain	0.6	4.8	3.1	2.7	4.1
brainstem	0.5	3.4	4.6	1.6	2.8
chiasm	0.4	2.0	2.1	1.4	1.8
rt optic nerve	0.2	1.4	2.1	0.6	1.8
lt optic nerve	0.2	1.4	1.7	0.7	1.5
rt hippocampus	0.5	4.1	2.9	1.4	2.6
lt hippocampus	0.5	3.6	3.9	1.9	2.0

\* Indicated are the means (ranges) of maximum and mean doses to the lesions.

TABLE 3: Maximum and mean BEDs delivered by SRS to lesions and to critical CNS structures\*

Tissue	Patient No.					SD
	1	2	3	4	5	
max BED (Gy)						
lesions	126 (81–208)	157 (126–173)	173 (106–208)	141 (75–173)	208 (126–208)	31.6
normal brain	566	538	655	655	605	52.4
brainstem	6.0	41.7	424.1	19.9	547.3	257.7
chiasm	1.5	11.9	11.9	6.0	11.9	4.7
rt optic nerve	0.6	6.0	11.9	1.6	11.9	5.4
lt optic nerve	0.4	6.0	11.9	6.0	11.9	4.8
rt hippocampus	6.0	55.6	29.7	11.9	41.7	20.6
lt hippocampus	1.7	29.7	130.9	19.9	9.8	52.8
mean BED (Gy)						
lesions	102 (75–140)	94 (69–152)	102 (67–154)	100 (69–130)	118 (99–139)	8.9
normal brain	1.6	41.2	18.9	15.0	29.5	15.0
brainstem	0.8	15.4	37.9	4.4	13.1	14.5
chiasm	0.6	6.3	6.8	3.3	5.2	2.5
rt optic nerve	0.3	3.5	6.8	0.9	5.3	2.8
lt optic nerve	0.2	3.5	4.5	1.2	3.8	1.8
rt hippocampus	0.8	21.7	11.6	3.6	19.9	9.4
lt hippocampus	0.7	16.5	20.2	6.0	6.2	8.1

\* The BED was calculated with an  $\alpha/\beta$  of 10 Gy for lesions and with an  $\alpha/\beta$  of 1 Gy for the critical CNS structures. Numbers in parentheses are the range.

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 the normal brain. Table 5 shows the total volumes of normal brain receiving the specified minimum dose in our study in comparison with those of Yamamoto et al.,<sup>29</sup> which calculated dose volumes for 80 patients whose lesions ranged in number from 10 to 43. In our 5 patients, the total dose volume to the normal brain was the sum of separate dose volumes receiving the specified dose for each individual target area with the corresponding target volume subtracted. As a typical example, an individual V12 (the brain volume receiving > 12 Gy) for a target of 3.3 cm<sup>3</sup> in volume (1.2 cm in dimension) is calculated to be 10.5 cm<sup>3</sup> and 7.2 cm<sup>3</sup> with and without target volume included, respectively. Our Patient 1 experienced radiation exposure of volumes of normal brain that were lower than the volume range in the study by Yamamoto and colleagues because this patient had a very small total lesion volume and higher prescription IDLs. The exposed volumes in the other 4 patients were within the range reported by Yamamoto et al.<sup>29</sup>

The Quantec brain article<sup>14</sup> cites a study<sup>13</sup> in which the V12 correlated with symptomatic radiation necrosis and in which the risk of necrosis increased significantly from 23% (V12 at 0–5 cm<sup>3</sup>) to 54% (V12 at 10–15 cm<sup>3</sup>). The results of this study, however, appear to be outliers relative to those reported by others, including the Radiation Therapy Oncology Group protocol 90-05.<sup>23</sup> These studies have reported clinical outcomes in which the V12 of an individual normal brain usually ranges from a few cubic centimeters to more than 10 cm<sup>3</sup>, but the observed rate of radiation necrosis is only a few percent or lower.

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.

A recent randomized controlled trial suggests that patients treated with SRS plus WBRT are at a greater risk of a significant decline in learning and memory function 4 months after the treatment than patients who received SRS alone.<sup>5</sup> This radiation toxicity might be related to the high mean dose delivered to the hippocampus in WBRT.<sup>18,22</sup> Even with treatment of multiple metastases, the mean hippocampal BED is much lower with SRS, which therefore provides better neurocognitive benefits than 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.<sup>8</sup> Many factors are omitted from this simple application of the LQ model to the whole brain, not least of which is the concept of damage repair in the time elapsed between conventional fractions. The brain is an organized structure made up of many cell types, including neurons and glial cells, and vasculature and interfraction repair may be a significant feature of some of these cells.

The LQ model, even when accounting for effects such as damage repair and cell repopulation,<sup>5,30</sup> deviates from in vitro and animal data for high doses per fraction.<sup>19,27</sup> This deviation is observed in some in vitro experiments and reaches more than 20% for the calculation of SFED at doses greater than 10 Gy per fraction.<sup>12,19,27</sup> However, the LQ model is reported to describe observed effects well for the lower normal tissue single-fraction doses in Table 3. In addition, the effects of the large differences in the dose distributions between WBRT (uniform) and

**TABLE 4: Summary of potential complications associated with WBRT or SRS with grades according to the CTEP criteria\***

Toxicity	CTEP Grade	
	WBRT	SRS
<b>acute (1st days to wks)</b>		
fatigue	1	1
nausea	2	2
vomiting	2	2
cerebral edema	1, 2, 3	1, 2, 3
decreased appetite	2	NA
alopecia	2	NA
dermatitis	2	NA
encephalopathy	4	NA
cerebral herniation	5	NA
headache	NA	2
<b>early delayed (1st wks to mos)</b>		
fatigue	1	1
somnolence	3	NA
neurocognitive deficits	3	NA
neurological symptoms	3	NA
somnolence syndrome	4	NA
neurological dysfunction	4	NA
cerebral edema	NA	1, 2, 3
<b>late (after 90 days)</b>		
radiation necrosis	1, 4	1, 4
leukoencephalopathy	4	NA
neurocognitive degeneration	4	NA
moyamoya syndrome	4	NA

\* Complications were assessed according to the review by McTyrre et al.<sup>17</sup> CTEP = Cancer Therapy Evaluation Program; NA = not available.

SRS (very nonuniform) on complications in multifunctional 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 the understanding of the biological effects of these 2 very different but widely used dose distributions. Of note, because of its simplicity, the LQ model has been widely used clinically to compare the biological effects of different fraction sizes. However, clinicians should be aware of the uncertainty of the BED and SFED calculations involving hypofractionation.

From both dosimetric and biological perspectives, it is safe to treat patients with more than 10 brain metastases with SRS. The peripheral dose to each individual lesion in a single fraction is suggested to be 15–22 Gy delivered to the 50% IDL,<sup>23</sup> depending on the size and diagnosis of a lesion (we prefer to treat radioresistant tumors, such as melanoma and sarcoma to a maximum dose of 22 Gy, while other tumors receive a maximum dose of 20 Gy). We recommend keeping the 15 Gy IDL to less than 4 cm in diameter and the 18 Gy IDL to less than 3 cm, especially when there is the dose overlap due to closely adjacent targets.

The number of metastases is not always the major dosimetric concern in SRS, because both the size and the location of a lesion may be the causes for high radiation doses to critical brain structures. Moreover, doses or prescription IDLs may have to be occasionally adjusted to keep within the above constraints. As is evident in Fig. 2, the mean dose that normal brain tissues would receive in SRS correlates with the total volume of the lesions rather than the number of lesions treated. The normal brain may get a mean dose of about 7 Gy when the total volume of lesions reaches 50 cm<sup>3</sup>. More clinical data are needed to refine the regression model observed in Fig. 2.

There are a few limitations of this work. The study

**TABLE 5: Volumes of normal brain receiving the specified minimum dose in SRS from this study and from the study by Yamamoto et al.**

Patient No.	Total Dose Vol (V) in Gy to the Normal Brain					
	V2	V5	V10	V12	V15	V20
<b>vol (cm<sup>3</sup>)</b>						
Yamamoto et al.*	1105 (410–1501)	309 (46–1247)	64 (13–282)	NC	24 (2–77)	8 (0–40)
1	29.4	6.6	1.5	0.9	0.4	0.1
2	1227.3	474.9	127.7	92.0	59.6	27.8
3	1095.2	168.9	43.0	29.8	18.0	7.6
4	760.1	110.9	26.5	18.2	10.5	3.7
5	1213.5	311.1	66.8	45.8	28.6	13.9
<b>percentage of total brain vol</b>						
<b>present study</b>						
1	2.5	0.6	0.1	0.1	0.0	0.0
2	88.3	34.2	9.2	6.6	4.3	2.0
3	68.0	10.5	2.7	1.9	1.1	0.5
4	54.7	8.0	1.9	1.3	0.8	0.3
5	88.6	22.7	4.9	3.3	2.1	1.0

\* Numbers in parentheses indicate range. NC = not calculated.

was retrospective, and the 5 cases presented were chosen because they were the only patients with more than 10 brain metastases treated at our institution. Specific clinical criteria would have to be determined for the inclusion of patients in the future, particularly for prospective studies of outcomes. Nevertheless, the dosimetric data and the results of our analysis of the 5 cases are quite representative of the differences between WBRT and SRS. However, more cases with a greater variety of lesion sizes and locations might yield additional information about the expected range of critical organ doses. The limitation of using the LQ model to compare the BED between conventional fractionation and single fraction was discussed here and in other studies.

## Conclusions

Whole-brain radiotherapy and SRS for treatment of multiple brain metastases significantly differ in dosimetric and biological characteristics. On the basis of maximum and mean BED, SRS is expected to provide better control of the targeted lesions and to have lower toxicity to many critical structures, especially the hippocampus and other normal brain tissues.

The biological analysis of this study demonstrated that SRS improves dose delivery to the target and delivers an acceptable radiation dose to normal tissues, even when more than 10 lesions are treated with GKS. Evidence suggests that WBRT can lead to more radiation-induced toxicities because of the high mean dose delivered to the normal CNS tissues. Our calculations provided a rationale for the potential benefit of SRS in patients with reasonable anticipated survival. We have found that, in SRS, the mean dose to the normal brain correlates with the total volume of lesions rather than with the number of lesions treated. Ultimately, prospective clinical trials are needed to determine the efficacy and safety of SRS for multiple brain metastases.

## Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Xue. Acquisition of data: Xue, Kubicek, Goldman. Analysis and interpretation of data: Xue, Kubicek, Grimm, Yorke. Drafting the article: Xue, Kubicek, Grimm, Yorke. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Xue. Statistical analysis: Xue, Yorke. Administrative/technical/material support: LaCouture, Chen, Goldman.

## Reference

1. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial 363. **Lancet** **363**:1665–1672, 2004
2. Bijl HP, van Luijk P, Coppes RP, Schippers JM, Konings AW, van der Kogel AJ: Unexpected changes of rat cervical spinal cord tolerance caused by inhomogeneous dose distributions. **Int J Radiat Oncol Biol Phys** **57**:274–281, 2003

3. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. **Lancet Oncol** **10**:1037–1044, 2009
4. Daly ME, Choi CY, Gibbs IC, Adler JR Jr, Chang SD, Lieberman RE, et al: Tolerance of the spinal cord to stereotactic radiosurgery: insights from hemangioblastomas. **Int J Radiat Oncol Biol Phys** **80**:213–220, 2011
5. Hall EJ, Giaccia AJ: **Radiobiology for the Radiologist**, ed 7. Philadelphia: Lippincott Williams & Wilkins, 2012
6. Flickinger JC, Kondziolka D, Lunsford LD: Radiobiological analysis of tissue responses following radiosurgery. **Technol Cancer Res Treat** **2**:87–92, 2003
7. Grandhi R, Kondziolka D, Panczykowski D, Monaco EA III, Kano H, Niranjana A, et al: Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases. Clinical article. **J Neurosurg** **117**:237–245, 2012
8. Hinde WA, DeTrana FA III, Lee MS, Hendrickson FR: Large dose increment irradiation in treatment of cerebral metastases. **Cancer** **26**:138–141, 1970
9. Hunter GK, Suh JH, Reuther AM, Vogelbaum MA, Barnett GH, Angelov L, et al: Treatment of five or more brain metastases with stereotactic radiosurgery. **Int J Radiat Oncol Biol Phys** **83**:1394–1398, 2012
10. Jiang GL, Tucker SL, Guttenberger R, Peters LJ, Morrison WH, Garden AS, et al: Radiation-induced injury to the visual pathway. **Radiother Oncol** **30**:17–25, 1994
11. Joiner M, Kogel AVD (eds): **Basic Clinical Radiobiology**, ed 4. London: Hodder Arnold, 2009
12. Kirkpatrick JP, Meyer JJ, Marks LB: The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. **Semin Radiat Oncol** **18**:240–243, 2008
13. Korytko T, Radivoyevitch T, Colussi V, Wessels BW, Pillai K, Maciunas RJ, et al: 12 Gy gamma knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. **Int J Radiat Oncol Biol Phys** **64**:419–424, 2006
14. Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE, et al: Radiation dose-volume effects in the brain. **Int J Radiat Oncol Biol Phys** **76** (3 Suppl):S20–S27, 2010
15. Martel MK, Sandler HM, Cornblath WT, Marsh LH, Hazuka MB, Roa WH, et al: Dose-volume complication analysis for visual pathway structures of patients with advanced paranasal sinus tumors. **Int J Radiat Oncol Biol Phys** **38**:273–284, 1997
16. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J: Radiation dose-volume effects of optic nerves and chiasm. **Int J Radiat Oncol Biol Phys** **76** (3 Suppl):S28–S35, 2010
17. McTyre E, Scott J, Chinnaiyan P: Whole brain radiotherapy for brain metastasis. **Surg Neurol Int** **4** (Suppl 4):S236–S244, 2013
18. Merchant TE, Kiehna EN, Li C, Shukla H, Sengupta S, Xiong X, et al: Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumors including medulloblastoma. **Int J Radiat Oncol Biol Phys** **65**:210–221, 2006
19. Park C, Papiez L, Zhang S, Story M, Timmerman RD: Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. **Int J Radiat Oncol Biol Phys** **70**:847–852, 2008
20. Philippon ME, Pop LA, Visser AG, Peeters WJ, van der Kogel AJ: Bath and shower effect in spinal cord: the effect of time interval. **Int J Radiat Oncol Biol Phys** **73**:514–522, 2009
21. Pollock BE, Link MJ, Leavitt JA, Stafford SL: Dose-volume analysis of radiation-induced optic neuropathy after single-



- fraction stereotactic radiosurgery. *Neurosurgery* [epub ahead of print], 2014
22. Radiation Therapy Oncology Group: **RTOG-0933. A Phase II Trial of Hippocampal Avoidance During Whole Brain Radiotherapy for Brain Metastases.** (<http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0933>) [Accessed August 6, 2014]
  23. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* **47**:291–298, 2000
  24. Sheehan J, Schlesinger D: Editorial. Ten brain metastases. *J Neurosurg* **117**:234–236, 2012
  25. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al: Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* **2**:210–225, 2012
  26. van Luijk P, Faber H, Schippers JM, Brandenburg S, Langendijk JA, Meertens H, et al: Bath and shower effects in the rat parotid gland explain increased relative risk of parotid gland dysfunction after intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* **74**:1002–1005, 2009
  27. Wang JZ, Huang Z, Lo SS, Yuh WT, Mayr NA: A generalized linear-quadratic model for radiosurgery, stereotactic body radiation therapy, and high-dose rate brachytherapy. *Sci Transl Med* **2**:39ra48, 2010
  28. Xue J, Goldman HW, Grimm J, LaCouture T, Chen Y, Hughes L, et al: Dose-volume effects on brainstem dose tolerance in radiosurgery. Clinical article. *J Neurosurg* **117** Suppl: 189–196, 2012
  29. Yamamoto M, Ide M, Nishio Si, Urakawa Y: Gamma Knife radiosurgery for numerous brain metastases: is this a safe treatment? *Int J Radiat Oncol Biol Phys* **53**:1279–1283, 2002
  30. Yang CC, Ting J, Wu X, Markoe A: Dose volume histogram analysis of the gamma knife radiosurgery treating twenty-five metastatic intracranial tumors. *Stereotact Funct Neurosurg* **70** (Suppl 1):41–49, 1998

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