Scientific Article

How Does the Number of Brain Metastases Correlate With Normal Brain Exposure in Single-Isocenter Multitarget Multifraction Stereotactic Radiosurgery

Dandan Zheng, PhD,* Jihyung Yoon, PhD, Hyunuk Jung, PhD, Olga Maria Dona Lemus, PhD, Lang Gou, Yuwei Zhou, Kenneth Y. Usuki, MD, Sara Hardy, MD, and Michael T. Milano, MD, PhD

Department of Radiation Oncology, University of Rochester Medical Center, Rochester, New York

Purpose: To investigate the relationship between normal brain exposure in LINAC-based single-isocenter multitarget multifraction stereotactic radiosurgery or stereotactic radiation therapy (SRT) and the number or volume of treated brain metastases, especially for high numbers of metastases.

Methods and Materials: A cohort of 44 SRT patients with 709 brain metastases was studied. Renormalizing to a uniform prescription of 27 Gy in 3 fractions, normal brain dose volume indices, including V23 Gy (volume receiving >23 Gy), V18 Gy (volume receiving >18 Gy), and mean dose, were evaluated on these plans against the number and the total volume of targets for each plan. To compare with exposures from whole-brain radiation therapy (WBRT), the SRT dose distributions were converted to equivalent dose in 3 Gy fractions (EQD3) using an alpha-beta ratio of 2 Gy.

Results: With increasing number of targets and increasing total target volume, normal brain exposures to dose ≥18 Gy increases, and so does the mean normal brain dose. The factors of the number of targets and the total target volume are both significant, although the number of targets has a larger effect on the mean normal brain dose and the total target volume has a larger effect on V23 Gy and V18 Gy. The EQD3 mean normal brain dose with SRT planning is lower than conventional WBRT. On the other hand, SRT results in higher hot spot (ie, maximum dose outside of tumor) EQD3 dose than WBRT.

Conclusions: Based on clinical SRT plans, our study provides information on correlations between normal brain exposure and the number and total volume of targets. As SRT becomes more greatly used for patients with increasingly extensive brain metastases, more clinical data on outcomes and toxicities is necessary to better define the normal brain dose constraints for high-exposure cases and to optimize the SRT management for those patients.

Introduction

Stereotactic radiosurgery (SRS) has become a standard-of-care treatment modality for patients with brain metastases, offering accurate, focused radiation delivery to target lesions, and sparing normal brain tissue and

other critical organs at risk, during a shortened (relative to whole brain radiation therapy [WBRT]) treatment course.[1] In recent years, there has been a paradigm shift in the management of brain metastases, with an increasing preference for SRS compared with WBRT.[2,3] Although SRS had been most commonly delivered in 1 fraction to patients with 1 or a few (generally ≤4) brain metastases, modern SRS applications use single- or multi-fractionated (generally 3-5 fractions) schedules, with the treatment of one, a few or many brain metastases.[4-6]

The highest number of brain metastases treated with SRS/stereotactic radiation therapy (SRT) has steadily increased both from literature reports and in clinical practice, from 4 to 15, >20, >30, and to >40.[7-13] In our clinic, the maximum number of metastases treated in one SRS/SRT plan has steadily risen to >40. And recently, a 3-fraction SRT course was planned for a patient with over 150 brain metastases, although the patient did not ultimately receive treatment due to comorbidity. However, because the complexity of SRS/SRT treatment planning escalates with the growing number of brain metastases, ensuring effective tumor control while minimizing normal brain tissue toxicity becomes increasingly challenging. As the number of metastases increases, treatment planning becomes increasingly intricate due to the potential overlap of isodose lines from individual targets, even with single-isocenter techniques that use dynamic conformal arcs (DCA) or volume-modulated arc therapy (VMAT). Consequently, the merging of these isodose lines can result in a sharp escalation of the normal brain tissue dose, potentially increasing the risks of toxicity and compromising the therapeutic ratio. Additionally, the proximity of metastatic lesions to one another can impact the effectiveness of SRS/SRT, raising concerns about the adequacy of tumor coverage and control when planning for large numbers of lesions.

Constraining normal brain dose in SRS/SRT is important because excessive dose may lead to cognitive defects and/or brain necrosis.[14] Addressing the optimal management of multiple brain metastases and effective SRS/SRT treatment planning therefore necessitates consideration of the impact of a number of lesions and total target volume on normal brain exposure. Especially for SRS/SRT cases treating a high number of brain metastases, current understanding of the impact on normal brain exposure and its clinical implications is scarce. The information is vital for efforts to strike an optimal balance between achieving tumor control and mitigating potential adverse effects on normal brain tissue.

In this work, we aim to delve into the intricate landscape of SRS/SRT treatment planning for patients with multiple brain metastases based on a cohort of our clinical SRT patients. We explore the relationship between the total number and the total volume of brain metastatic targets and the normal brain tissue dose. This investigation endeavors to provide valuable insights for the ongoing evolution of management for multiple brain metastases.

Methods and Materials

Study cohort and characteristics

Approved by our Institutional Human Subjects Review Board, treatment plans from consecutive patients who received SRS/SRT treatments for brain metastasis at our clinic from November 2021 to May 2023 were queried. The inclusion criteria are patients receiving SRT with a single-isocenter plan treating 5 or more metastases during this timeframe, and plans prescribing all targets to the same dose level in 3 fractions as this is the most common fractionation scheme used in our department for this type of treatments. Exclusion criteria therefore are multiple dose levels in a plan (for example some targets close to organs at risk are prescribed to a lower dose than the rest of targets) or other fractionations (single and 5-fraction SRS are also occasionally used in our practice, but those cases were excluded due to the small numbers).

All patients were simulated with our SRS protocol using a GE LightSpeed RT 16 CT scanner (GE Healthcare) with a slice thickness of 1.25 mm. Gross tumor volumes were delineated on high-resolution brain MRIs with a slice thickness of 1 mm or less registered to the planning computed tomography. Majority of cases applied a 1 mm margin to generate the planning target volume (PTV), and margins of 0.5 and 1.5 mm were also sometimes used. Majority of these cases were planned using the DCA technique in the Brain-Lab Multiple Metastases Elements module (BrainLab), and the rest were planned using single-isocenter VMAT in Varian Eclipse (Varian Medical Systems). All plans were delivered with the Varian Edge with high-definition multileaf collimators (Varian Medical Systems) using the 6 MV flattening-filter-free mode. All plans are single-isocenter treating all targets, with the isocenter location optimized to leverage the finer leaves for more targets and to reduce the rotation arm in image guided localization. However, no efforts were made to guarantee, such as by splitting into multiple isocenters, that the finer leaves were always used for all targets. The majority of cases had a prescription of 27 Gy in 3 fractions (27 Gy/3 fractions), and 24 Gy in 3 fractions (24 Gy/3 fractions), and 21 Gy in 3 fractions (21 Gy/3 fractions) were used for other cases. Per our institutional guidelines based on existing clinical literature,[2,3,15,16] the maximally allowed dose within targets for SRS/SRT plans was 150% of prescription dose, and the plans were normalized such that 95% of the PTV would receive at least the prescription dose. Dose calculation used volumetric Monte Carlo when planned with Elements or Acuros External Beam when planned with Eclipse. Detailed patient and planning characteristics are listed in Table 1.

Table 1   Patient and case characteristics

Characteristic	Count
Total no. of patients	44
Total no, of lesions	709
No. of lesions per patient	Median, 13 (range, 5-41)
Prescription	
27 Gy/3 fxs	31 (70%)
24 Gy/3 fxs	11 (25%)
21 Gy/3 fxs	2 (5%)
GTV/PTV margin	
0.5 mm	63 (9%)
1 mm	564 (79%)
1.5 mm	82 (12%)
Planning technique	
MME DCA plan	31 (70%)
Eclipse VMAT plan	13 (30%)

Abbreviations: DCA = dynamic conformal arcs; fxs = fractions; GTV = gross tumor volume; MME = multiple metastases elements; PTV = planning target volume; VMAT = volume-modulated arc therapy.

Data collection and analysis

For data collection and analysis, treatment plans with a prescription of 24 Gy/3 fractions, or 21 Gy/3 fractions were renormalized to 27 Gy/3 fractions, and those with a 27 Gy/3 fractions prescription were kept unchanged. The nomalization is so that the normal brain exposure can be compared among all cases on a common ground of a 27 Gy/3 fractions prescription. From each plan, the following data were collected: the total number of targets, the total PTV, the volume of normal brain tissues (defined as nongross tumor volumes brain tissues) receiving at least 23 Gy (V23 Gy), the volume of normal brain tissues receiving at least 18 Gy (V18 Gy), and the mean normal brain dose.

The impacts of the total number of targets and the total PTV on the normal brain dose metrics were depicted with scatter plots, and the correlations were analyzed with linear regression. To visualize normal brain dose's potential codependency on the total number of targets and the total PTV, 3-dimensional scatter plots were used.

Comparison with normal brain exposure in WBRT

As a naïve comparison of normal brain exposure between SRT and WBRT, dose distributions of a sample set of patient plans were converted to equivalent dose in 3-Gy fractions (EQD3) using an alpha-beta ratio of 2 Gy[17,18] to compare SRT dose-distributions optimally to standard WBRT of 30 Gy in 10 fractions. The conversion was carried out in Velocity (Varian Medical Systems). For this analysis, the original clinical prescriptions were used (because the prescribed dose may have accounted for anticipated brain exposure and therefore best reflects clinical practice) and renormalization was not performed (different from the analyses described in *Data collection and analysis*). The volume of normal brain tissue receiving at least 110%, 150%, 200%, and 250% of 30 Gy (ie, WBRT dosage) was collected, in addition to the mean and maximum normal brain EQD3 doses.

Results

From a total of 302 queried patients, 44 patients met the inclusion criteria and were included for analysis. Single-isocenter SRT was planned for these patients, with each plan treating 5 to 41 lesions (median, 13) as listed in Table 1.

Physical dose to normal brain

As one would expect, normal brain exposure rises with increasing number of lesions and with increasing total PTV. We use a few sample cases to illustrate this in Fig. 1. The dose distributions of 3 different patients are depicted in Fig. 1, with the lesion and normal brain characteristics of these patients listed in Table 2 with more details. Cases 1 and 2 both have the same number of metastases (5), but case 2 resulted in higher normal brain doses because of one large lesion that accounted for the increased total PTV. Although case 3 has lower total PTV than case 2, case 3 resulted in higher normal brain dose because of the much higher number of lesions. The number of lesions versus total PTV more greatly affects lower dose spread, as can be observed from the larger difference of V18 Gy than V23 Gy between case 2 and 3.

For the entire studied cohort, positive correlation was observed between normal brain tissue exposure and number of targets or total target volume. Figure 2 plots the relationship of normal brain V23 Gy and V18 Gy against the number of targets (a) and against the total PTV (b). The linear correlation coefficient (CC) is also displayed in the figure. Linear correlation was lower for the number of targets (CC of 0.40 for V23 Gy and 0.55 for V18 Gy) than for the total PTV (CC of 0.88 for V23 Gy and 0.80 for V18 Gy). To visualize the normal brain exposure's codependence on these 2 variables, 2 3-dimensional scatter plots are shown in Fig. 3 with linear regression.

Similarly, normal brain mean dose was also observed to increase with increasing number of targets or increasing total PTV, as shown in Fig. 4, but the linear
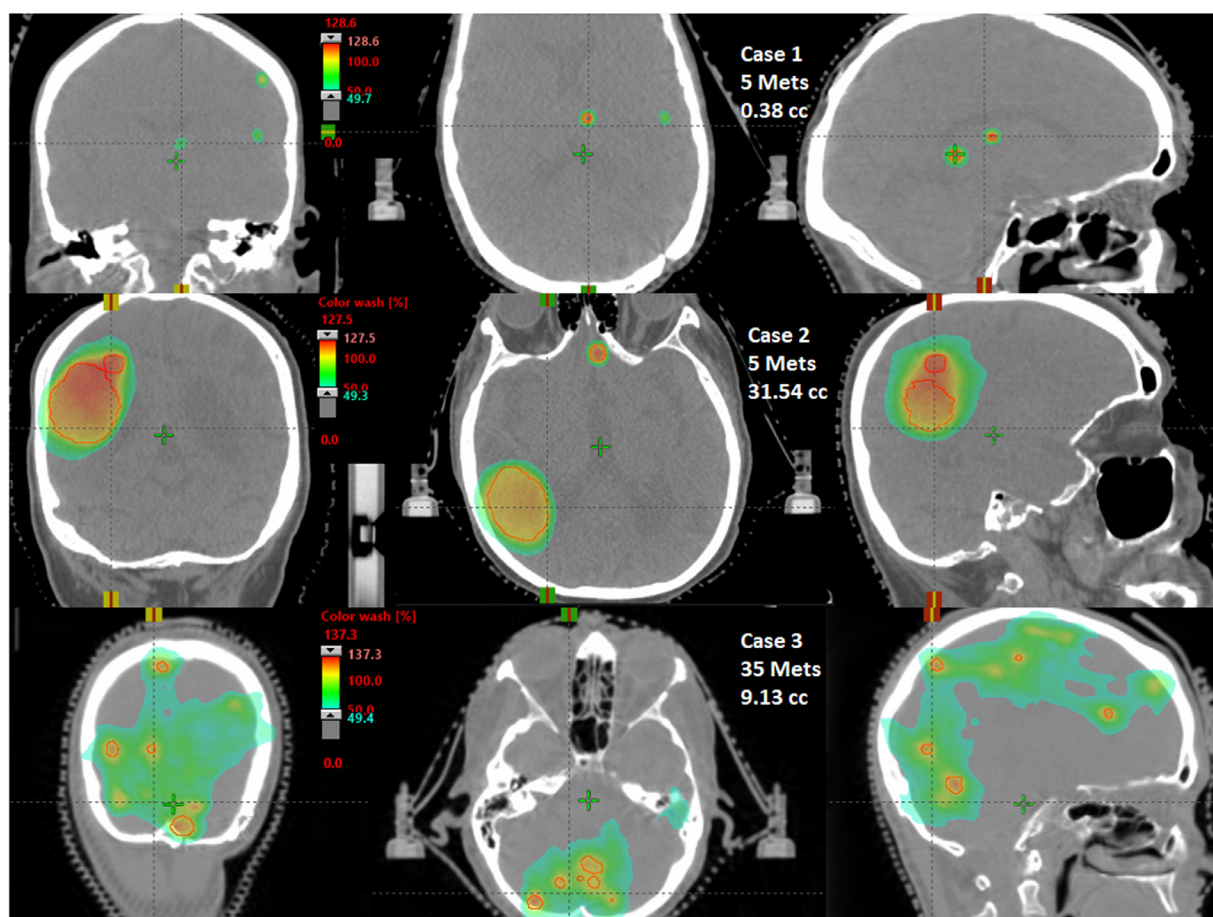
Figure 1 Dose distributions for 3 example cases, with 5, 5, and 35 metastases, respectively. Dose is displayed in color wash and the planning target volumes are shown in the red contours.

Table 2   Target and normal brain dose statistics of the 3 example cases from Fig. 1

	No. of Mets	Total PTV (cc)	V23 Gy (cc)	V18 Gy (cc)	Mean normal brain dose (Gy)
Case 1	5	0.38	0.86	1.72	0.8
Case 2	5	31.54	24.50	41.15	4.1
Case 3	35	9.13	26.64	114.91	11.9
Abbreviation: PTV = planning target volume.					

correlation was lower, with CC of 0.84 and 0.54 for the number of targets and for the total PTV, respectively.

EQD3 to normal brain and key organs at risk

The 3 example cases shown in Fig. 1 were converted to EQD3 with their original clinical prescription, assuming an alpha-beta ratio of 2 Gy for normal brain tissue. For these cases, the mean normal brain EQD3 dose in these SRT cases was from 0.5 to 12.8 Gy, considerably lower than the 30 Gy prescription dose in WBRT (for which the mean normal brain dose would generally range from slightly less to slightly greater than 30 Gy depending on how dose was prescribed and planned) for all cases. On the other hand, looking at the hot spot dose exposures, such as V33 Gy-EQD3 at the 110% of the WBRT prescription level, normal brain at this dose level was from 1.2 to 36.8 cc for the SRT plans, affected by both the original prescription dose and the extent of the brain metastases. These and other details of the resultant normal brain tissue EQD3 exposures are described in Table 3. The maximum EQD3 doses to the optical apparatus (eyes, lens, optical nerves, and chiasm) and to the brain stem are also listed. As expected, the dose to these organs at risk (OARs) is more dependent on the specific locations of tumors in a case than on the number or total volume of tumors in that case.
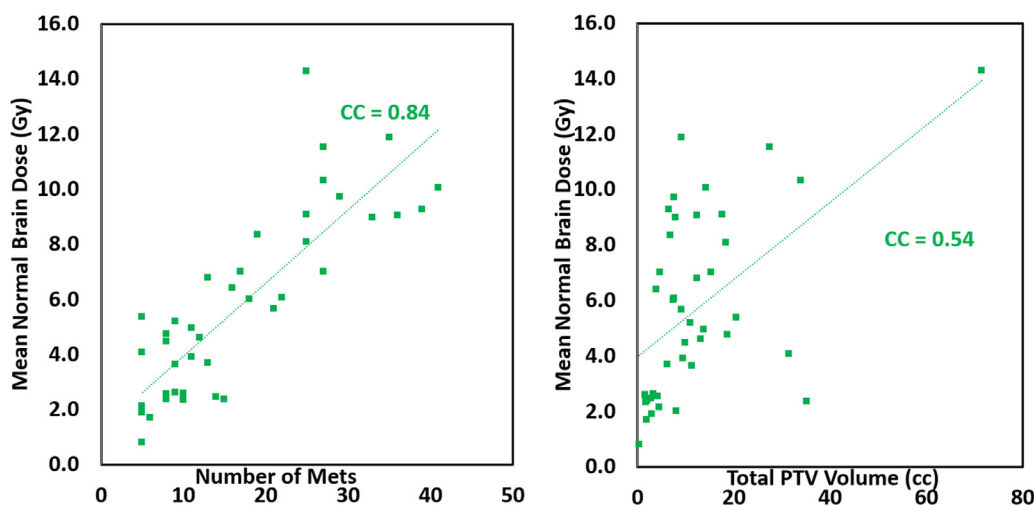
Figure 2   Normal brain tissue V23 Gy and V18 Gy was plotted for the entire cohort against: (a) the number of targets; and (b) the total planning target volume. The V23 Gy and V18 Gy both increase with (a) the number of targets, having linear correlation coefficient (CC) = 0.40 and 0.55, respectively; they also increase with (b) the total planning target volume, having higher CC = 0.88 and 0.80, respectively. *Abbreviation:* PTV = planning target volume.
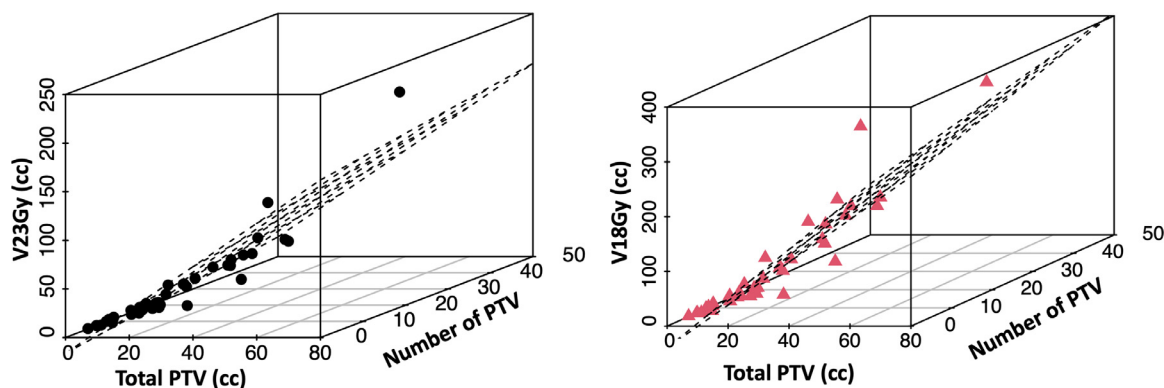

Figure 3   A 3-dimensional scatter plot to show the codependence of normal brain V23 Gy (left) and V18 Gy (right) on the number of targets and the total planning target volume. A linear regression plane is also displayed with dotted lines. *Abbreviation:* PTV = planning target volume.

Discussion

SRS/SRT has emerged as an important tool in managing multiple brain metastases due to its effective local control while minimizing damage to surrounding normal brain tissue. Improved systemic control for patients with metastatic cancers, together with the technological advancements in SRS/SRT to accurately and efficiently treating multiple targets at once, has increased the utilization of SRS/SRT in managing large numbers of brain metastases as opposed to using conventional WBRT. With these changes and the shift in using SRS/SRT for more and more extensive brain metastases, it has become increasingly important to gain a good understanding on how normal brain exposure is affected by the number and volume of metastases to be treated, because excessive normal brain exposure can lead to

clinical toxicities such as cognitive defects or brain necrosis.[14]

To gain insights into this, in our study a cohort of 44 patients with single-isocenter SRT plans each treating 5 to 41 metastases were analyzed. This is, to our knowledge, the first effort to systematically investigate the relationship using clinical data of a large sample size (44 patients, 709 metastases) and with cases extending to high numbers of metastases. Normal brain exposure was found to positively correlate with the number of targets and with the total PTV, with linear CC from 0.4 to almost 0.9. As shown in our example cases in Fig. 1 and Table 2, the total number of targets has a bigger effect on increasing the lower dose spread compared with the higher dose spread, as can be seen from the larger V18 Gy and mean normal brain dose differences between case 2 and case 3 than from the V23 Gy difference. This makes intuitive sense
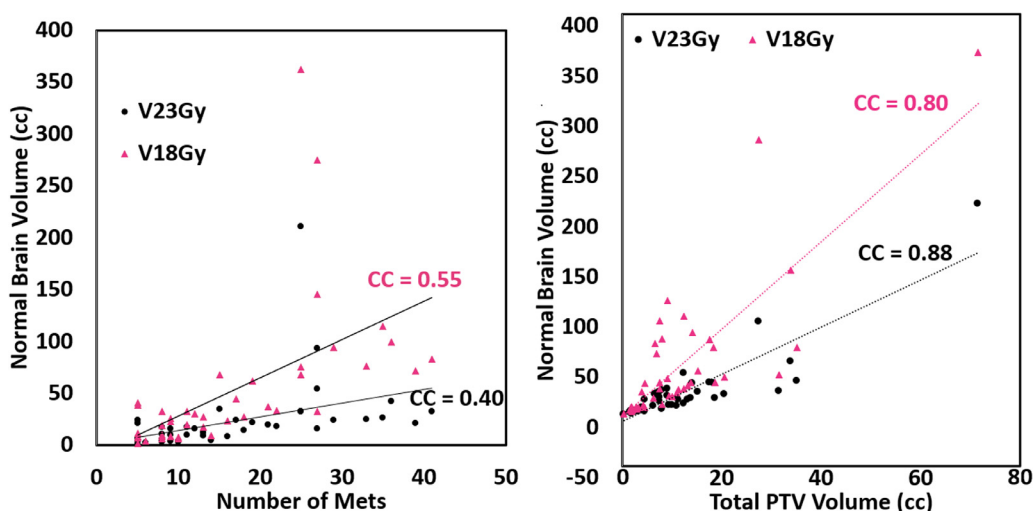
Figure 4   Mean normal brain dose was plotted for the entire cohort against: (a) the number of targets; and (b) the total planning target volume. Mean normal brain dose increases with the number of targets and with the total planning target volume, with a linear correlation coefficient (CC) = 0.84 and 0.54, respectively. *Abbreviation:* PTV = planning target volume.

Table 3   Original prescription and converted EQD3 dose to the normal brain, optical apparatus, and brain stem for the 3 example cases shown in Fig. 1

	Case 1	Case 2	Case 3
No. of Mets	5	5	35
Total PTV (cc)	0.38	31.54	9.13
Clinical Rx	8 Gy × 3 = 24 Gy	9 Gy × 3 = 27 Gy	8 Gy × 3 = 24 Gy
V_{NB}33 Gy (110%) EQD3 (cc)	1.2	35.3	36.8
V_{NB}45 Gy (150%) EQD3 (cc)	0.7	23.9	11.8
V_{NB}60 Gy (200%) EQD3 (cc)	0.2	12.7	1.1
V_{NB}75 Gy (250%) EQD3 (cc)	0	3.8	0
Max EQD3 NB (Gy)	74.8	92.2	75
Mean EQD3 NB (Gy)	0.5	4.3	12.8
Max EQD3 optical apparatus (Gy)	1.1	2.5	8.0
Max EQD3 brain stem (Gy)	18.3	2.0	35.8
Abbreviations: EQD3 = equivalent dose in 3 Gy fractions; NB = normal brain; PTV = planning target volume.			

because as the number of targets increase, the low dose clouds from individual targets start to smear into each other before the high dose clouds do. The total PTV volume shows a higher correlation with V18 Gy and V23 Gy than the number of targets. However, the latter shows a higher correlation with mean normal brain dose.

A prior study by Xue et al compared the biologically effective dose between SRS and WBRT using 5 multiple-metastasis cases.[19] They found, with power regression, that the mean normal brain dose in SRS better correlated with the total tumor volume than with the total number of metastases. In our series, the linear correlation was somewhat higher with the total number of metastases than the total PTV for V23 Gy, V18 Gy, and mean normal

brain dose. In addition to a much larger sample size and an expanded set of investigated dose volume metrics in our series, the different finding might have also stemmed from the different regressions used in these 2 studies. In our study we intentionally used the simplest linear regression, although more complex regression models such as exponential regression or power regression could result in better fit. The choice was made for robustness consideration, as there were certain heterogeneity factors in our data set described in Table 1 that could confound the data, such as 2 different treatment planning systems and techniques used, and the variation in target margin among the targets. Also, their study included only the number of metastases from 11 to 23, which is a smaller

range than our data. Nevertheless, reasonably strong correlations identified with the simple linear regression from our large cohort of clinical cases shed light on the effects of metastasis count and volume on the resultant SRS/SRT normal brain exposure. Our results could also be potentially useful as a nomogram or in more complex fashions to improve plan consistency and quality if used in knowledge-based planning automation for SRS/SRT of brain metastases.

To optimize patient outcomes from SRS/SRT while minimizing potential risks, many studies have investigated normal brain dose constraints for brain SRS/SRT based on existing clinical data.[16,18,20,21] For example, V12 Gy for single fraction SRS[21] and V23 Gy and V18 Gy for 3-fraction SRT[16] are frequently used normal brain dose volume metrics for toxicity evaluation and minimization in SRS/SRT. Although toxicity guidelines are well established in these reports on the lower volume end, for example a V12 Gy of 5, 10, and 15 cc corresponding to a 10%, 15%, and 20% of toxicity risk for symptomatic necrosis in single-fraction SRS respectively, the toxicity risks on higher exposure volumes have been less studied or reported. With the increasing utilization of SRS/SRT in managing higher numbers of brain metastases, more clinical data will potentially accumulate, eventually leading to guidelines on the higher volume end. In the interim, to gain insights into understanding the biologic implications of the higher normal brain exposure, we calculated EQD3 of the example cases to draw parallels between these SRT cases and WBRT. Similar to what was concluded by the 5-case parallel-planning study,[19] our analysis also found that the mean normal brain EQD3 in SRT is considerably lower than in conventional WBRT. Although not included in the study analysis, we also calculated the normal brain dose and EQD3 for the case with over 150 targets that we planned but not treated. Even for this extreme case, the mean EQD3 for normal brain is still lower, at 23.6 Gy, than that of 30 Gy prescription in conventional WBRT. The classical analogy comparing SRS/SRT and WBRT is shower versus bath, with SRS/SRT showering higher dose to focused target areas while WBRT gives a lower dose bath to the entire brain. At the same time, as the number and volume of targets increase in SRS/SRT, the high dose spillage into the normal tissue also smears and adds up to an increasing volume. As shown in Table 3, the maximum normal brain EQD3 dose of these cases much surpasses the conventional limit of 107% hotspot in WBRT.[22] At an EQD3 hotspot dose level of 110% of WBRT prescription dose, the SRT plan of the 3 example cases recorded 1.2 to 36.8 cc of normal brain tissue, influenced by the metastasis volume and number as well as SRS prescription. And the maximum EQD3 normal brain dose was 74.8 to 92.2 Gy for these cases, primarily influenced by the SRT prescription. Another finding of our study is that in SRS/SRT, the total PTV volume is more influential for the shower dose

(higher correlations with V23 Gy and V18 Gy) and the number of targets is more influential for the bath dose (higher correlation with mean normal brain dose). Besides the normal brain, there are also many other OARs to consider in SRS/SRT planning such as the optical apparatus (eyes, lens, optical nerves, and chiasm) and the brain stem. The doses to the OARs are separately considered and constrained in treatment planning. However, the dose to these OARs is more dependent on the specific locations of tumors (the distance between a tumor and an OAR) in a case than on the number or total volume of tumors in that case. As shown in Table 3, the maximum EQD3 to these OARs may therefore be lower or higher than would be received in the WBRT, depending on the case.

A few limitations should be noted for our study. There are some heterogeneities in our data, such as DCA versus VMAT techniques or different margin values, that could confound the dosimetric results. However, because such high-number-target cases are relatively rare leading to the limited total number of cases, we chose to perform aggregated analyses instead of subgroup analyses. There are also limitations on the biologic dose analysis. The linear quadratic model sustaining the biologic dose analysis relies on clinical data validated only with smaller fractional dose, and its application in SRS/SRT has not been fully established.[17,23-25] In general, the application in SRS/SRT with fractional doses higher than 10 Gy is debatable as such high doses are hypothesized to cause additional cell killing beyond double strand DNA breaks theorized in the linear quadratic model, such as vascular damage and immune responses.[17,26-28] Nevertheless, because our cohort was treated with 3-fraction SRT with fractional doses from 7 to 9 Gy, the analysis was relatively more acceptable than for single-fraction SRS data. Additionally, although we used an alpha beta ratio of 2 that is commonly accepted for brain tissue,[17,18] it is a simplification and there is always uncertainty associated with the model and the selected parameters. Furthermore, the normal tissue dose from SRS/SRT is dependent on the planning and delivery approach. Our study only analyzed plans treated with single-isocenter plans. As the number of tumors increases, single-isocenter plans, especially those using DCA, may become increasingly susceptible to multileaf collimator island blocking and intermediate dose fall-off problems. With more segments, VMAT plans are generally more robust; therefore, in our cohort, VMAT tends to be used for cases with higher number of tumors or those with closely collocated tumors. Nevertheless, studies have shown that a dual-isocenter approach would further improve the dose conformity and reduce dose to the normal brain, compared with the single-isocenter approach.[11,29] Also, our study analyzed normal brain dose for SRS/SRT on standard LINAC, and the dose is also dependent on the machine type and might be different for SRS/SRT on specialty machines such as GammaKnife and CyberKnife.[30]

Although our primitive biologic dose analysis is informative, there are also many questions left to answer. Clinical outcome data are needed to better understand whether the shower (hot spot normal brain dose) or the bath (mean normal brain dose) plays a larger role in leading to brain toxicity. Despite the progression of using SRS/SRT over WBRT to manage patients with increasingly higher number of brain metastases, the reported toxicity of SRS/SRT remains to be low.[2,5,16,31-33] Furthermore, there have also been increasing evidence that supports taking the necessary risk of radiation necrosis to achieve durable control of brain metastases.[20] For brain metastases of certain histology such as melanoma where WBRT has limited efficacy and considerable neurocognitive toxicity, SRS/SRT in combination with targeted agents and immunotherapy present a preferred treatment option.[34-37] As such, the dose volume and the biologic dose results from our study will provide useful information to planners and clinicians for their SRS/SRT practice in multiple brain metastases, and support the accumulation of more clinical and outcome data to further optimize this important treatment modality for brain metastases.

Conclusion

The correlation was investigated between normal brain exposure and the number or volume of metastases treated with single-isocenter SRT for multiple brain metastases on cases treating over 5 metastases. Increasing number or volume of metastases increases the normal brain exposure, with mean normal brain equivalent dose still lower than WBRT but hot spot equivalent dose higher than WBRT. The study results shed light on how the number of metastases correlate with normal brain exposure in SRS/SRT. Clinical outcome data are warranted to further correlate dose with clinical outcomes, to optimize SRS/SRT for managing high numbers of brain metastases.

Disclosures

The authors have no relevant conflicts of interest to report.

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