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Scientific Article

Hippocampal Dosimetry and the Necessity of Hippocampal-Sparing in Gamma Knife Stereotactic Radiosurgery for Extensive Brain Metastases

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Abstract

Purpose: To characterize hippocampal dosimetry in Gamma Knife stereotactic radiosurgery (GK-SRS) for extensive brain metastases and evaluate the need for hippocampal-sparing in GK-SRS treatment planning.

Methods and Materials: We reviewed 75 GK-SRS plans for the treatment of 4 to 30 brain metastases generated without consideration of the hippocampi. The mean dose, maximum dose to 100% of the volume (D_{100}), maximum dose to 40% of the volume (D_{40}), and maximum point dose (D_{max}, 0.03 cm^3) were obtained for the unilateral and bilateral hippocampi and compared between plans with 4 to 9 and $\geq$10 lesions. The rate at which plans met hippocampal dose constraints ($D_{100} \leq$ 4.21 Gy, $D_{40} \leq$ 4.50 Gy, and $D_{max} \leq$ 6.65 Gy) was compared between groups, and each was examined for risk factors associated with excessive hippocampal dosing. For plans that exceeded constraints, we attempted replanning to spare the hippocampi.

Results: Compared with those for the treatment of 4 to 9 brain metastases, GK-SRS plans with $\geq$10 lesions were associated with significantly greater median bilateral mean dose (1.0 vs 2.0, $P = .001$), D_{100} (0.4 vs 0.8, $P = .003$), D_{40} (0.9 vs 1.9, $P = .001$), and D_{max} (2.0 vs 4.9, $P = .0005$). These plans also less frequently met hippocampal constraints, with this difference trending toward significance (80% vs 93%; $P = .1382$; odds ratio 0.29; 95% CI, 0.06-1.4). Risk factors for exceeding constraints included greater total disease volume and closer approach of the nearest metastasis to the hippocampi, both of which depended upon the number of metastases present. Seven plans failed to meet constraints and were successfully replanned to spare the hippocampi with minimal increases in treatment time and without compromise to target coverage or conformity.

Conclusions: Patients with extensive brain metastases treated with GK-SRS are at increased risk for excessive hippocampal dosing when $\geq$10 lesions are present or when lesions are in close proximity to the hippocampi and may benefit from hippocampal-avoidant treatment planning.

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Introduction

Irradiation of the hippocampal stem cell compartment has long been purported to be the pathologic mechanism underlying the neurocognitive decline seen after whole-brain radiation therapy (WBRT) for brain metastases.[1-4] Although historically this hypothesis has been based only on preclinical models, the single-arm, phase 2 trial Radiation Therapy Oncology Group (RTOG) 0933 was the first to demonstrate that limiting dosing to the hippocampus through hippocampal-avoidant WBRT (HA-WBRT) leads to less neurocognitive decline than conventional technique, with these findings being confirmed by its newly concluded phase 3 contemporary: NRG CC001.[5,6] It is therefore reasonable to expect that transition to more conformal modalities such as stereotactic radiosurgery (SRS) may further decrease hippocampal dosing and better preserve neurocognitive function.

Until recently, concern for local and regional recurrence of brain metastases has reserved SRS for patients with a limited number of lesions (1-3) or for salvage after WBRT.[7] However, substantial evidence has amassed in support of SRS as a single-modality treatment for more extensive brain metastases ($\geq$4) with many prospective and retrospective studies demonstrating that overall survival is noninferior to WBRT, including in cohorts with a mean lesion quantity >10.[8-17] Additionally, in a prospective observational study of patients with 1 to 10 brain metastases and a total disease volume of $\leq$15 cm^3, Yamamoto et al showed that lesion quantity is not predictive of overall survival when controlling for total intracranial disease burden, although application of these findings to greater total disease volumes remains to be examined.[17] In response to the mounting evidence, use of SRS to treat extensive brain metastases has grown, and widespread acceptance of this practice is pending based on the results of the ongoing Canadian Cancer Trials Group CE7 trial directly comparing outcomes of SRS and HA-WBRT + memantine in patients with 5 to 15 brain metastases.[18,19]

Multiple SRS modalities have previously been shown to be capable of achieving hippocampal dose levels lower than those seen in HA-WBRT in the treatment of extensive brain metastases, often without the need for purposeful hippocampal-avoidance.[20-23] Additionally, in a comparison of 4 SRS modalities, Zhang et al showed that frame-based technologies such as Gamma Knife (GK-SRS) lead to more dramatic dose fall off and lower hippocampal dosing when treating 3 to 10 brain metastases.[20] Such evidence suggests that GK-SRS is a favorable option for patients with lesions located in close proximity to the hippocampi, the most commonly cited risk factor for excessive hippocampal dosing in SRS.[21,22]

However, hippocampal dosimetry and the necessity of hippocampal-sparing in GK-SRS for extensive brain metastases are incompletely characterized. To date, only 2 studies have evaluated patients with 10 or more brain metastases treated with GK-SRS, neither including cases where lesions were located within 5 mm of the hippocampi (the zone of ineligibility for HA-WBRT).[22,23] Therefore, the goal of this study was to provide the largest and most comprehensive case series to date evaluating hippocampal dosimetry and the role of hippocampal-sparing in single-fraction GK-SRS for the treatment of extensive brain metastases. We evaluated the comparative hippocampal dosimetry of plans for the treatment of $\geq$10 and 4 to 9 brain metastases, seeking to characterize risk factors for increased hippocampal dosing and identify patients who may benefit from GK-SRS with purposeful hippocampal-sparing.

Methods and Materials

This study was approved by our institutional review board and adhered to the Declaration of Helsinki.

By retrospective review of institutional records, we identified all GK-SRS plans for the treatment of 4 to 30 brain metastases at our urban tertiary care center between January 2008 and June 2019. To be included in this study, plans were required to have been generated based on magnetic resonance (MR) imaging or a fusion of computed tomography simulation and MR imaging. If a single patient was treated for $\geq$4 brain metastases on multiple occasions, each plan was included independently. Demographic and clinical data were obtained from institutional electronic medical records.

Original GK-SRS treatments were planned using Leskell GammaPlan TPS (v10.1.1, Elekta AB, Stockholm, Sweden) for treatment on a Leskell Gamma Knife (Elekta AB, Stockholm, Sweden) Perfexion or 4C. On the day of treatment, all patients underwent MR imaging on a 1.5T Philips (Koninklijke Philips NV, Amsterdam, Netherlands) scanner with images acquired in 1-mm slices. The treating physicians contoured metastases on T1-weighted, gadolinium-enhanced MR images, and the gross volume of each lesion served as the planning target volume (PTV) without expansion. Target grid sizes of 0.5 to 2.5 mm were used, and lesions in close proximity were treated in the same dose calculation matrix. Prescriptions to targets were as follows: lesions $\leq$2.0 cm in greatest diameter received 20 Gy, lesions 2.1-3.0 cm in greatest diameter received 18 Gy, and lesions 3.1-4.0 cm in greatest diameter or located in regions of eloquent cortex received 14 to 16 Gy. The most frequent prescription isodose line was 50% (range, 40%-70%), and a higher line was selected when lesions were in close proximity to critical structures such as the brain stem, optics, or

cochlea. No original plans were generated with consideration of the hippocampi. For original plans, shots were placed manually, and inverse planning was used as needed to refine PTV coverage and improve conformity. Minimum acceptable PTV coverage with the prescription dose was 95%. Sector blocking was used as needed.

Analysis of GK-SRS plans was performed using GammaPlan, and PTV contours were preserved from original treatments. Hippocampi were contoured per the RTOG 0933 atlas without expansion, and contours were approved by an American Board of Radiology–certified radiation oncologist.[24]

Definitions for dosimetry parameters mirrored those of NRG CC001 and 003, the most contemporary applications of the RTOG 0933 hippocampal-avoidance protocol.[25,26] For each hippocampus we obtained the mean dose (D_{mean}), maximum dose delivered to 100% of the volume (D_{100}), maximum dose to 40% of the volume (D_{40}), and maximum point dose (D_{max}, 0.03 cm^3).

Constraints on acceptable hippocampal dosing were obtained from the protocols of NRG CC001 and CC003 and a previous study by Gondi et al.[25-27] Constraints were converted to a single-fraction scheme using equivalent doses in 2 Gy fractions with an α/β of 2.[20,21,23,28] Hippocampal constraints for single-fraction GK-SRS were $D_{100} \leq 4.21$ Gy, $D_{40} \leq 4.50$ Gy, and $D_{max} \leq 6.65$ Gy. Successful hippocampal-sparing was defined as meeting all constraints in both the unilateral and bilateral hippocampi.

To assess potential risk factors for exceeding constraints, we followed the principles of the protocol of Birer et al by recording for each patient: the total number of lesions treated, total intracranial disease volume (total PTV), and the closest approach of a metastasis to either hippocampus in the x, y, and z dimensions (r_{min}).[21] We also recorded the volume of said closest metastasis and the prescription and maximum doses for that PTV.[21]

Plans exceeding any hippocampal dose constraint were then replanned to intentionally spare the hippocampi. All replanning was conducted for treatment on a Leskell Gamma Knife Perfexion and focused primarily on the lesion closest to the hippocampus, as contribution from other PTVs was negligible. To ensure no unacceptable compromises after replanning, we compared the coverage of the total PTV and mean Paddick conformity index (CI) of individual lesions between original and new plans by the Wilcoxon signed-rank test. The Paddick CI was defined as $\frac{(TV_{PIV})^2}{(TV \times V_{RI})}$ where TV is the PTV, V_{RI} is the volume receiving the prescription isodose, and TV_{PIV} is the volume of the PTV receiving the prescription isodose.[29] As the planning of highly conformal targets was associated with increased treatment time, we did not seek to reduce hippocampal dosing further once constraints were met. All treatment times were standardized to a dose rate of 3.000 Gy/min.

Statistical analysis was conducted with SPSS (v25; SPSS, Inc, Chicago, IL, USA). Except as noted, all continuous data were compared by the Mann–Whitney *U* test and all categorical data by Fisher exact test.

Patients were grouped by number of brain metastases (4-9 and ≥10), and unilateral and bilateral hippocampal D_{mean}, D_{40}, D_{100}, and D_{max} were compared. We also assessed the frequency at which each hippocampus and the bilateral hippocampi met constraints. Risk factors for exceeding hippocampal constraints were compared between plans that did and did not meet them.

Because patients with $r_{min} \leq 5$ mm are ineligible for HA-WBRT, we sought to determine the frequency at which GK-SRS plans with lesions located ≤5 mm from the hippocampi met constraints, both with and without replanning. We conducted the same assessment at $r_{min} \leq 3.5$ mm that was qualitatively identified to be the point at which a greater proportion of plans failed to meet constraints.

Results

Demographics

Eighty-three GK-SRS plans for the treatment of 4 to 30 brain metastases were identified. Eight plans with intrahippocampal lesions were excluded. The median subject age of the included plans was 60 years, and 44 (59%) were from female patients. The median PTV for an individual metastasis was 0.09 cm^3 (interquartile range [IQR] 0.02 cm^3-0.35 cm^3), and the median total PTV for 1 patient was 2.7 cm^3 (IQR 0.97 cm^3-5.5 cm^3). Sixty plans (80%) were for the treatment of 4 to 9 brain metastases, and 15 (20%) were for ≥10. Plans for the treatment of ≥10 metastases contained 10 to 24 lesions (median 12, IQR 11-15). The median volume of a single hippocampus was 2.4 cm^3 (IQR 2.1 cm^3-2.7 cm^3).

Hippocampal dosimetry

Hippocampal dosimetry for original GK-SRS plans is shown in Table 1. Compared with plans for the treatment of 4 to 9 brain metastases, plans for the treatment of ≥10 were associated with a significantly higher bilateral D_{mean}, D_{100}, D_{40}, and D_{max} ($P = .001$, .003, .001, and .0005, respectively) and less frequently met hippocampal constraints, with this difference trending toward significance (80% vs 93%, $P = .1382$; odds ratio 0.29; 95% CI, 0.06-1.4).

Seven plans failed to meet at least 1 hippocampal constraint, 3 of which contained ≥10 lesions. Six plans failed only owing to $D_{max} > 6.65$ Gy in at least 1

Table 1 Hippocampal dosimetry for original GK-SRS plans designed without consideration of the hippocampi

	Left hippocampus		
	4-9 metastases (n = 60)	≥10 metastases (n = 15)	*P*
D_{mean}, Gy	1.0 (0.6-1.9)	1.7 (1.5-3.1)	.001
D_{100}, Gy	0.6 (0.3-0.9)	0.9 (0.7-1.9)	.003
D_{40}, Gy	1.0 (0.6-1.8)	1.8 (1.4-3.3)	.001
D_{max}, Gy	1.5 (1.0-2.7)	4.0 (2.4-4.8)	.001
Plans meeting hippocampal constraints (%)	58 (97)	15 (100)	.638
	Right hippocampus		
	4-9 metastases (n = 60)	≥10 metastases (n = 15)	*P*
D_{mean}, Gy	0.9 (0.6-1.7)	2.0 (1.6-2.4)	.002
D_{100}, Gy	0.4 (0.3-0.7)	0.8 (0.6-1.3)	.004
D_{40}, Gy	0.8 (0.6-1.8)	1.9 (1.5-2.2)	.003
D_{max}, Gy	1.5 (0.9-3.0)	4.2 (3.0-5.7)	.0003
Plans meeting hippocampal constraints (%)	58 (97)	12 (80)	.052
	Bilateral hippocampi		
	4-9 metastases (n = 60)	≥10 metastases (n = 15)	*P*
D_{mean}, Gy	1.0 (0.6-1.8)	2.0 (1.6-2.6)	.001
D_{100}, Gy	0.4 (0.2-0.7)	0.8 (0.5-1.1)	.003
D_{40}, Gy	0.9 (0.7-1.8)	1.9 (1.5-2.6)	.001
D_{max}, Gy	2.0 (1.1-4.5)	4.9 (4.0-5.8)	.0005
Plans meeting hippocampal constraints (%)	56 (93)	12 (80)	.1382

Abbreviation: GK-SRS = Gamma Knife stereotactic radiosurgery.
Note: All continuous data are reported as median (interquartile range). *P* values for comparisons of continuous data were obtained from the Mann–Whitney *U* test and those for comparisons of categorical data from Fisher exact test.

hippocampus, and 1 plan failed owing to both $D_{max} >$ 6.65 Gy and $D_{40} >$ 4.50 Gy in the same unilateral hippocampus. Bilateral D_{40} of the latter plan met constraints. No plans failed owing only to unilateral or bilateral $D_{40} >$ 4.50 Gy, and no plans had unilateral or bilateral $D_{100} >$ 4.21 Gy.

Risk factors for GK-SRS plans exceeding hippocampal constraints

A summary of the risk factors analyzed for their contribution to exceeding hippocampal constraints is shown in Table 2. For patients with ≥10 metastases, increased total PTV was the only risk factor identified as significantly different between plans that met constraints and those that did not (median 2.2 cm^3 vs 6.1 cm^3, $P =$ .048). However, r_{min} was also reduced in those plans that exceeded constraints, and this difference trended toward significance (median 9.1 mm vs 3.2 mm, $P =$ .101). The small quantity of plans that failed to meet constraints prohibited multivariate analysis.

In patients with 4 to 9 brain metastases, only a reduced r_{min} was associated with plans exceeding hippocampal constraints (median 20.5 mm vs 3.9 mm, $P =$ .004), with no difference in total PTV observed (median 2.7 cm^3 vs 2.5 cm^3, $P =$ .853).

Comparison of original and replanned GK-SRS plans

The 7 original GK-SRS plans failing to meet hippocampal constraints were successfully replanned to spare the hippocampi, including the 3 with ≥10 brain metastases, an example of which is shown in Figure 1. A comparison of original and replanned GK-SRS plans is shown in Table 3. Despite replanning focusing only on reducing excessive D_{max} due to 1 PTV, decreases were seen in D_{mean}, D_{100}, and D_{40} in most patients. Replanning was associated with a median increase in treatment time of 8 minutes (IQR 4-16 minutes) and no change in PTV coverage or mean CI ($P =$ 1.000 for both measures).

Association between closest approach and hippocampal-sparing

The association between r_{min} and the frequency with which original GK-SRS plans successfully spared the hippocampi is detailed in Table 4.

Plans with ≥10 brain metastases were associated with a significantly reduced r_{min} compared with those with 4 to 9 (median 6.3 mm vs 19.8 mm, $P =$ .0003). Additionally, more of such plans had $r_{min} \leq 5$ mm (47% vs 13%, $P =$ .008; odds ratio 5.7; 95% CI, 1.6-20.0), making them more likely to be ineligible for HA-WBRT.[25,26]

Table 2 Evaluation of risk factors for exceeding hippocampal constraints in original GK-SRS plans

	4-9 brain metastases		
	Plans not exceeding hippocampal constraints (n = 56)	Plans exceeding hippocampal constraints (n = 4)	*P*
Number of metastases	5.0 (4.0-6.0)	5.0 (4.0-6.3)	.943
Total PTV, cm^3	2.7 (0.8-5.7)	2.5 (1.2-4.2)	.853
PTV of closest metastasis, cm^3	0.3 (0.05-2.5)	0.6 (0.2-1.2)	.966
r_{min}, mm	20.5 (16.0-26.9)	3.9 (1.8-6.2)	.001
Prescribed dose to closest PTV, Gy	18.0 (16-18)	18.0 (17-18.5)	.943
Maximum dose to closest PTV, Gy	36.0 (32.1-36.1)	36.0 (34.0-37.1)	.989
	≥10 brain metastases		
	Plans not exceeding hippocampal constraints (n = 12)	Plans exceeding hippocampal constraints (n = 3)	*P*
Number of metastases	13.5 (11-15.5)	11 (11-12)	.448
Total PTV, cm^3	2.2 (1.2-4.4)	6.1 (5.7-9.2)	.048
PTV of Closest Metastasis, cm^3	0.02 (0.02-0.06)	0.1 (0.07-0.6)	.734
r_{min}, mm	9.1 (3.7-11.5)	3.2 (2.2-4.8)	.101
Prescribed dose to closest PTV, Gy	18.0 (17.5-18.0)	18.0 (16.5-19.0)	.945
Maximum dose to closest PTV, Gy	34.0 (30.1-36.1)	36.0 (33.0-40.3)	.633

Abbreviations: GK-SRS = Gamma Knife stereotactic radiosurgery; PTV = planning target volume. r_{min} = closest approach of a metastasis to either hippocampus in the x, y, and z dimensions.
Note: All data are reported as median (interquartile range). All statistical analysis was performed by the Mann–Whitney *U* test.

The greatest r_{min} at which an original plan failed to meet hippocampal constraints was 6.3 mm, and the smallest value of r_{min} in our cohort was 1.2 mm. Original plans with $r_{min} \leq 5$ mm less frequently met hippocampal constraints than those with $r_{min} > 5$ mm (67% vs 97%, $P = .003$; odds ratio 0.07; 95% CI, 0.01-0.4). This difference was exacerbated when r_{min} was ≤3.5 mm (50% vs 97%, $P = .0004$; odds ratio 0.03; 95% CI,

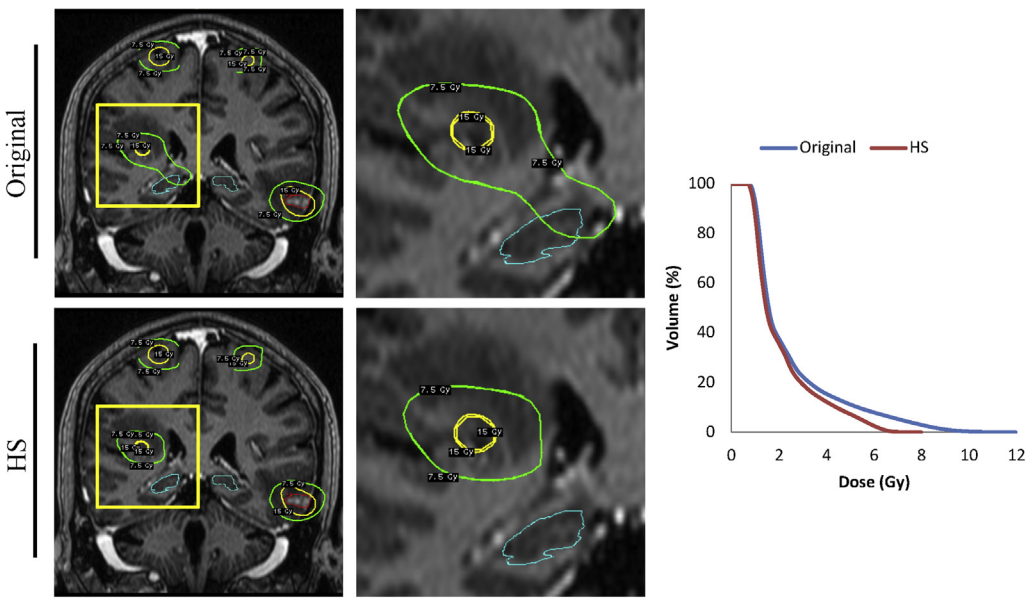

Figure 1 T1-weighted coronal magnetic resonance images of an original and hippocampal-sparing (HS) Gamma Knife stereotactic radiosurgery plan for the treatment of 11 brain metastases with r_{min} = 6.3 mm shown at 2 magnifications alongside the associated dose-volume histogram of the right hippocampus. Red contour = planning target volume; cyan contours = hippocampi; yellow isodose curve = 15 Gy (prescription isodose); green isodose curve = 7.5 Gy. (A color version of this figure is available at https://doi.org/10.1016/j.adro.2019.10.003.)

Table 3 Comparison of bilateral hippocampal dosimetry in original and replanned, hippocampal-sparing GK-SRS plans

	1	2	3	4	5	6	7	Median (IQR)
D_{max}, Gy								
Original	9.8	7.6	9.2	7.9	7.4	11.2	8.7	8.6 (7.7-9.5)
HS	6.2	6.3	6.4	6.0	6.4	6.6	6.6	6.4 (6.3-6.5)
D_{40}, Gy								
Original	1.6	3.8	2.3	2.3	1.8	2.6	3.3	2.3 (2.1-3.0)
HS	1.4	1.5	2.2	2.3	1.8	2.0	3.0	2.0 (1.6-2.3)
D_{100}, Gy								
Original	0.5	1.6	0.7	1.0	0.3	0.5	1.1	0.7 (0.5-1.1)
HS	0.5	1.2	0.7	1.0	0.4	0.2	1.4	0.7 (0.5-1.1)
D_{mean}, Gy								
Original	1.7	3.8	2.5	2.4	1.8	2.5	3.3	2.5 (2.1-2.9)
HS	1.6	3.1	2.3	2.4	1.8	1.9	2.9	2.3 (1.9-2.7)
Treatment time, min								
Original	206	119	123	110	85	75	77	110 (81-121)
HS	209	127	139	112	90	98	92	112 (95-133)
ΔTime	+3	+8	+16	+2	+5	+23	+15	+8 (4-16)
Total PTV coverage, %								
Original	99.8	100	99.9	100	100	100	100	100 (100-100)
HS	99.8	100	100	100	100	100	100	100 (100-100)
Mean CI								
Original	0.14	0.37	0.25	0.28	0.16	0.37	0.66	0.33 (0.21-0.37)
HS	0.14	0.41	0.25	0.28	0.16	0.44	0.66	0.35 (0.21-0.43)

Abbreviations: CI = conformity index; GK-SRS = Gamma Knife stereotactic radiosurgery; HS = hippocampal-sparing; IQR = interquartile range; PTV = planning target volume; ΔTime = change in treatment time
Note: Treatment time was calculated at a dose rate of 3.000 Gy/min.

0.005-0.2). As all plans met hippocampal constraints after replanning, r_{min} had no effect on the feasibility of hippocampal-sparing. A representative original and replanned GK-SRS plan for a short r_{min} is shown in Figure 2.

Discussion

Hippocampal-sparing during radiation therapy for brain metastases has been shown in multiple randomized trials to improve posttreatment neurocognitive function and quality of life and is now commonly incorporated into WBRT treatment planning.[5,6] However, the literature examining hippocampal dosing from SRS is incomplete. Therefore, we sought to provide a comprehensive characterization of hippocampal dosimetry resulting from GK-SRS treatment of extensive brain metastases and evaluate the need for hippocampal-sparing in GK-SRS treatment planning.

Results of our case series illustrate that the majority of GK-SRS plans for the treatment of extensive brain metastases do not result in hippocampal dosing above thresholds linked to adverse neurocognitive outcomes. However, compared with plans for the treatment of 4 to 9 brain metastases, plans for the treatment of ≥10 were associated with increased hippocampal dosing and showed a trend toward greater frequency of failing to meet hippocampal dose constraints. Therefore, these patients may be at increased risk for compromised neurocognitive function if the hippocampi are not purposefully spared.

In analyzing the cause(s) of GK-SRS plans failing to meet hippocampal constraints, an excessive D_{max} was identified as the predominant mechanism, demonstrating that excessive hippocampal dosing in GK-SRS tends to be localized to a small region of a single hippocampus

Table 4 r_{min} and the feasibility of hippocampal sparing in plans with 4 or more brain metastases

$r_{min,\ mm}$ (n)	>5.0 (60)	≤5.0 (15)	≤3.5 (10)
Original GK-SRS plans meeting hippocampal constraints (%)	58 (97)	10 (67)	5 (50)
Hippocampal-sparing GK-SRS plans meeting hippocampal constraints (%)	60 (100)	15 (100)	10 (100)

Abbreviation: GK-SRS = Gamma Knife stereotactic radiosurgery. r_{min} = closest approach of a metastasis to either hippocampus in the x, y, and z dimensions.

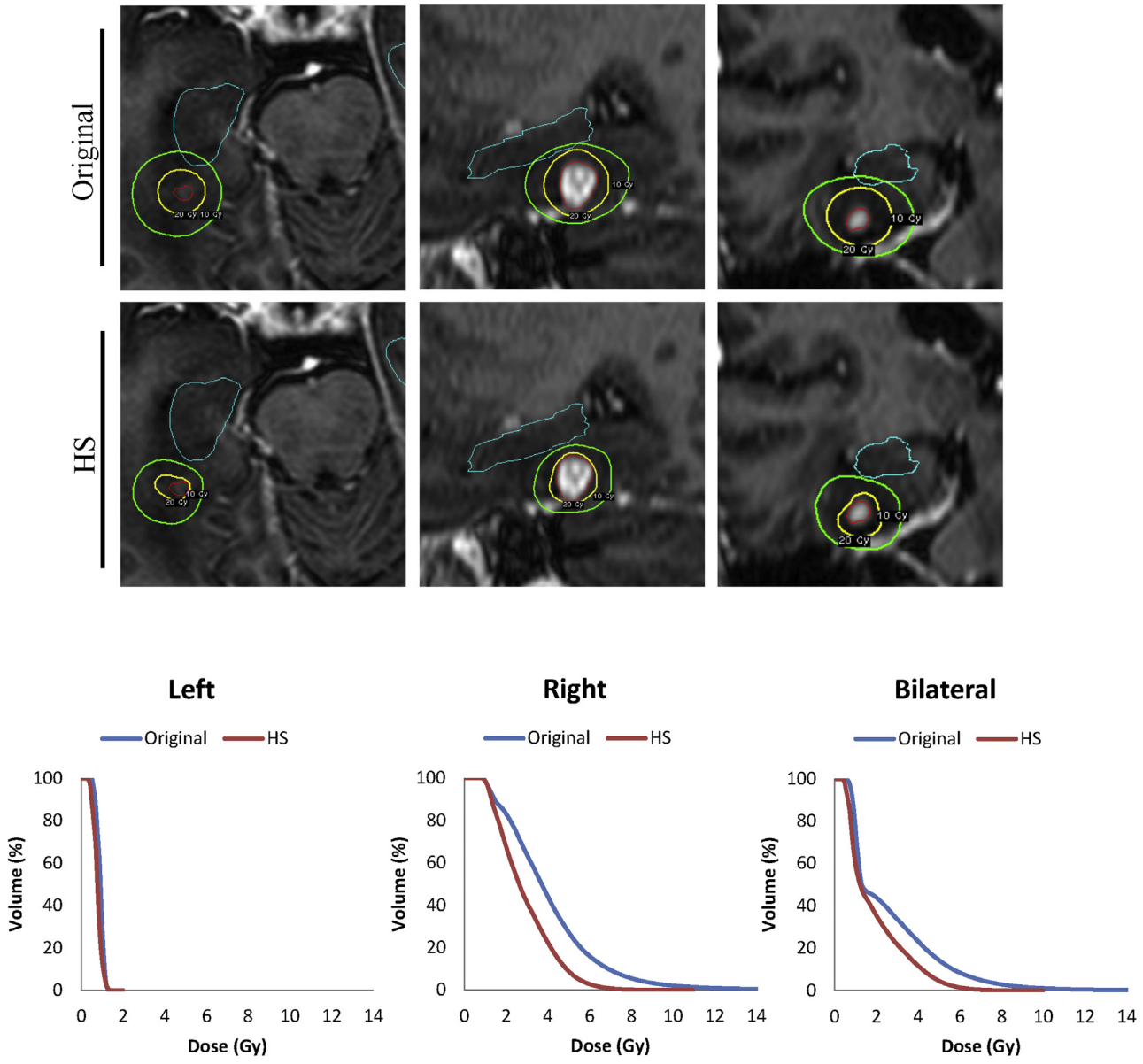

Figure 2 T1-weighted axial, sagittal, and coronal magnetic resonance images of an original and hippocampal-sparing (HS) Gamma Knife stereotactic radiosurgery plan with r_{min} = 1.8 mm shown alongside the associated hippocampal dose-volume histograms. Red contour = planning target volume; cyan contours = hippocampi; yellow isodose curve = 20 Gy (prescription isodose); green isodose curve = 10 Gy. (A color version of this figure is available at https://doi.org/10.1016/j.adro.2019.10.003.)

located in close proximity to a treated metastasis. Additionally, plans that failed to meet hippocampal constraints, regardless of lesion quantity, were associated with a closer approach of the nearest metastasis to the hippocampi. Together, these findings suggest that the increased rate of excessive hippocampal dosing observed in plans with ≥10 lesions is a consequence of not only more targets but also a higher probability of a lesion being in close proximity to the hippocampi.

Despite the importance of closest approach as a risk factor for increased hippocampal dosing, our findings also show that plans with a small r_{min} can still spare the hippocampi. Though an r_{min} of 5 mm has been the cutoff for HA-WBRT, the majority of GK-SRS plans with $r_{min} \leq 5$ mm met hippocampal constraints without purposeful replanning (67%) and all met constraints after hippocampal-sparing.[23-26] GK-SRS may therefore represent a favorable option for hippocampal-sparing radiation therapy in patients with 4 to 30 brain metastases and $r_{min} \leq 5$ mm who are therefore ineligible for HA-WBRT.

An important caveat, however, is that 33% of original plans with $r_{min} \leq 5$ mm failed to meet hippocampal constraints, a proportion that grew with decreasing r_{min} and was reduced when $r_{min} > 5$ mm, with no plans beyond r_{min} = 6.3 mm exceeding constraints. As

replanning of all of such plans to spare the hippocampi was successful, patients with r_{min} of approximately 6.0 mm or less would benefit from consideration of hippocampal dosing during GK-SRS treatment planning.

Interestingly, total PTV, the only other risk factor identified as contributing to exceeding hippocampal constraints in patients with ≥10 brain metastases, was not identified as a risk factor with 4 to 9 brain metastases. This contrasts the findings of Birer et al, who described that, in SRS delivered by volumetric modulated arc therapy, total PTV was significantly increased in plans for the treatment of 4 to 10 brain metastases that failed to meet hippocampal constraints.[21] Therefore, GK-SRS, even without hippocampal-sparing, may be a more appropriate modality for preserving neurocognitive function in patients with 4 to 9 brain metastases and a larger total intracranial disease volume (≥5 cm^3), a speculation supported by our work and that of Zhang et al.[20]

An important consideration in the planning of highly conformal GK-SRS treatments is increased treatment time. A similar study by Chang et al demonstrated that although more extensive replanning can reduce hippocampal dosing further than in our work, this is associated with significant increases in treatment time.[22] As any advantages to reducing hippocampal dosing further below constraints have yet to be described, such extensive replanning may be unfavorable when considering the practicality of subjecting patients to extreme treatment times. Should future evidence dictate hippocampal dosing be reduced further, an alternative approach described by Nguyen et al is to spread single-fraction treatment across multiple days with treatment time ≤60 minutes/d, a procedure that could be combined with hippocampal-sparing to yield a practical approach to hippocampal dose reduction.[23]

Although our work did not examine clinical outcomes, the ongoing CE7 study randomizing patients between HA-WBRT + memantine and SRS for the treatment of 5 to 15 brain metastases will provide the first comparison of these treatments in terms of survival and neurocognitive function. This will also be the first HA-WBRT protocol to include patients with r_{min} ≤5 mm; however, hippocampal-sparing is not being employed in the SRS arm. As we have demonstrated that patients with $r_{min} \leq 5$ mm or ≥10 brain metastases may require purposeful hippocampal-avoidance to meet dose constraints, future trials should consider incorporation of hippocampal-sparing SRS.

As with any study, ours is not without its limitations. All of the limitations associated with a single-institution, retrospective study are present in our work. Additionally, although our hippocampal constraints were derived from those validated clinically in WBRT, their applicability to GK-SRS is unknown. The use of the linear-quadratic model to predict toxicity after SRS has limitations, and therefore our dose constraints bear such limitations.[21,30] Data from the CE7 trial will assist in the development of clinically validated hippocampal constraints for SRS.

To the best of our knowledge, this work represents the largest case series to date evaluating hippocampal dosimetry from SRS in patients with extensive brain metastases. This is also the most comprehensive of such studies, identifying patients with ≥10 brain metastases or lesions located ≤5 mm from the hippocampi as standing to benefit from hippocampal-sparing SRS. We hope this work will provide a foundation for evaluating the clinical outcomes of hippocampal dosimetry in SRS and, in the interim, encourage the consideration of hippocampal-avoidance in GK-SRS treatment planning.

Conclusions

In patients with extensive brain metastases treated with GK-SRS, hippocampal dose constraints are more often exceeded when ≥10 lesions are present and when lesions are located in close proximity to the hippocampi. Because implementing hippocampal-sparing in GK-SRS is both feasible and practical, patients with identifiable risk factors for exceeding dose constraints should have treatment plans generated with consideration of the hippocampi. To fully understand the role of hippocampal-sparing in GK-SRS for extensive brain metastases, future studies should directly evaluate the association between hippocampal dosimetry and neurocognitive outcomes.

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