Scientific Article

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

Matthew D. Riina, BS,a Cassandra K. Stambaugh, PhD,b and Kathryn E. Huber, MD, PhDb,*

aTufts University School of Medicine and bDepartment of Radiation Oncology, Tufts Medical Center, Boston, Massachusetts

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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 (D100), maximum dose to 40% of the volume (D40), and maximum point dose (Dmax, 0.03 cm3) were obtained for the unilateral and bilateral hippocampi and compared between plans with 4 to 9 and ≥10 lesions. The rate at which plans met hippocampal dose constraints (D100 ≤ 4.21 Gy, D40 ≤ 4.50 Gy, and Dmax ≤ 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 ≥10 lesions were associated with significantly greater median bilateral mean dose (1.0 vs 2.0, P = .001), D100 (0.4 vs 0.8, P = .003), D40 (0.9 vs 1.9, P = .001), and Dmax (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 ≥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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* Corresponding author: Kathryn E. Huber, MD, PhD; E-mail: khuber@tuftsmedicalcenter.org

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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.** 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.** 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 ≥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 ≥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 ≤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
cancha. 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.

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

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 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 $D_{\text{mean}}$, $D_{\text{100}}$, $D_{\text{40}}$, and $D_{\text{max}}$ ($P = .001$, .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 $D_{\text{max}} > 6.65$ Gy in at least 1
hippocampus, and 1 plan failed owing to both $D_{\text{max}} > 6.65$ 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 $\geq 10$ 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, $r_{\text{min}}$ 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 $r_{\text{min}}$ 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 $\geq 10$ 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 $D_{\text{max}}$ due to 1 PTV, decreases were seen in $D_{\text{mean}}$, $D_{100}$, 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 $r_{\text{min}}$ and the frequency with which original GK-SRS plans successfully spared the hippocampi is detailed in Table 4. Plans with $\geq 10$ brain metastases were associated with a significantly reduced $r_{\text{min}}$ compared with those with 4 to 9 (median 6.3 mm vs 19.8 mm, $P = .0003$). Additionally, more of such plans had $r_{\text{min}} \leq 5$ 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 1  Hippocampal dosimetry for original GK-SRS plans designed without consideration of the hippocampi

|                      | Left hippocampus |                      | Right hippocampus |                      | Bilateral hippocampus |                      |
|----------------------|------------------|---------------------|-------------------|---------------------|-----------------------|---------------------|
|                      | 4-9 metastases (n = 60) | $\geq 10$ metastases (n = 15) |                      | 4-9 metastases (n = 60) | $\geq 10$ metastases (n = 15) |                      |
| $D_{\text{mean}}$, Gy | 1.0 (0.6-1.9)   | 1.7 (1.5-3.1)   | $.001$             | 0.9 (0.6-1.7)   | 2.0 (1.6-2.4)   | $.002$             |
| $D_{100}$, Gy       | 0.6 (0.3-0.9)   | 0.9 (0.7-1.9)   | $.003$             | 0.4 (0.3-0.7)   | 0.8 (0.6-1.3)   | $.004$             |
| $D_{40}$, Gy        | 1.0 (0.6-1.8)   | 1.8 (1.4-3.3)   | $.001$             | 0.8 (0.6-1.8)   | 1.9 (1.5-2.2)   | $.003$             |
| $D_{\text{max}}$, Gy| 1.5 (1.0-2.7)   | 4.0 (2.4-4.8)   | $.001$             | 1.5 (0.9-3.0)   | 4.2 (3.0-5.7)   | $.0003$            |
| Plans meeting hippocampal constraints (%) | 58 (97) | 15 (100)   | $.638$             | 58 (97) | 12 (80)   | $.052$             |

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

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

|                      | 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, \( \text{cm}^3 \) | 2.7 (0.8-5.7)                                       | 2.5 (1.2-4.2)                                     | .853   |
| PTV of closest metastasis, \( \text{cm}^3 \) | 0.3 (0.05-2.5)                                      | 0.6 (0.2-1.2)                                     | .966   |
| \( r_{\text{min}} \), 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, \( \text{cm}^3 \) | 2.2 (1.2-4.4)                                       | 6.1 (5.7-9.2)                                    | .048   |
| PTV of Closest Metastasis, \( \text{cm}^3 \) | 0.02 (0.02-0.06)                                     | 0.1 (0.07-0.6)                                   | .734   |
| \( r_{\text{min}} \), 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. \( r_{\text{min}} \) = 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 \( r_{\text{min}} \) at which an original plan failed to meet hippocampal constraints was 6.3 mm, and the smallest value of \( r_{\text{min}} \) in our cohort was 1.2 mm. Original plans with \( r_{\text{min}} \leq 5 \) mm less frequently met hippocampal constraints than those with \( r_{\text{min}} > 5 \) mm (67% vs 97%, \( P = .003; \) odds ratio 0.07; 95% CI, 0.01-0.4). This difference was exacerbated when \( r_{\text{min}} \) was \( \leq 3.5 \) 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 \( r_{\text{min}} = 6.3 \) 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.ado.2019.10.003](https://doi.org/10.1016/j.ado.2019.10.003).)
0.005-0.2). As all plans met hippocampal constraints after replanning, \( r_{\text{min}} \) had no effect on the feasibility of hippocampal-sparing. A representative original and replanned GK-SRS plan for a short \( r_{\text{min}} \) 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. 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 \( \geq 10 \) 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 \( D_{\text{max}} \) 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.
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 \( r_{\text{min}} \geq 10 \) 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 \( r_{\text{min}} \) can still spare the hippocampi. Though an \( r_{\text{min}} \) of 5 mm has been the cutoff for HA-WBRT, the majority of GK-SRS plans with \( r_{\text{min}} \leq 5 \) 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 \( r_{\text{min}} \leq 5 \) mm who are therefore ineligible for HA-WBRT.

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

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**Figure 2** T1-weighted axial, sagittal, and coronal magnetic resonance images of an original and hippocampal-sparing (HS) Gamma Knife stereotactic radiosurgery plan with \( r_{\text{min}} = 1.8 \) 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.)
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 \( \geq 10 \) 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 (\( \geq 5 \) 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 \( \leq 60 \) 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} \( \leq 5 \) 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 \( \geq 10 \) 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 \( \geq 10 \) brain metastases or lesions located \( \leq 5 \) 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 \( \geq 10 \) lesions are present and when lesions are located in close proximity to the hippocampus. 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.

### References

1. Kazda T, Jancek R, Pospisil P, et al. Why and how to spare the hippocampus during brain radiotherapy: The developing role of hippocampal avoidance in cranial radiotherapy. *Radiat Oncol*. 2014; 9:139.
2. Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med*. 1998;4:1313.
3. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. *Nat Med*. 2002;8:955.
4. Yoneoka Y, Sato M, Akiyama K, Sano K, Fujii Y, Tanaka R. An experimental study of radiation-induced cognitive dysfunction in an adult rat model. *Br J Radiol*. 1999;72:1196-1201.
5. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): A phase II multi-institutional trial. *J Clin Oncol*. 2014;32:3810-3816.
6. Gondi V, Pugh S, Brown PD, et al. Significant preservation of neurocognitive function (NCF) and patient-reported symptoms with hippocampal avoidance (HA) during whole-brain radiotherapy (WBRT) for brain metastases: Final results of the NRG Oncology CC001. *Int J Radiat Oncol Biol Phys*. 2019;105:S12.
7. National Comprehensive Cancer Network. Central Nervous System Cancers (Version 1.2019). Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed July 5, 2019.
8. Sahgal A, Ruschin M, Ma L, Verbakel W, Larson D, Brown PD. Stereotactic radiosurgery alone for multiple brain metastases? A
review of clinical and technical issues. Neuro Oncol. 2017;19:ii2-ii15.
9. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA. 2006;295:2483-2491.
10. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases. JAMA. 2016;316:401-409.
11. Chang WS, Kim HY, Chang JW, Park YG, Chang JH. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: Is stereotactic radiosurgery effective for multiple brain metastases? J Neurosurg. 2010;113:73-78.
12. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. Lancet Oncol. 2009;10:1037-1044.
13. Grandhi R, Kondziolka D, Panczykowski D, et al. Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases. J Neurosurg. 2012;117:237-245.
14. Limon D, McSherry F, Herndon J, et al. Single fraction stereotactic radiosurgery for multiple brain metastases. Adv Radiat Oncol. 2017;2:555-563.
15. Mohammadi AM, Recinos PF, Barnett GH, et al. Role of Gamma Knife surgery in patients with 5 or more brain metastases. J Neurosurg. 2012;117:5-12.
16. Salvetti DJ, Nagaraja TG, McNeill IT, Xu Z, Sheehan J. Gamma Knife surgery for the treatment of 5 to 15 metastases to the brain. J Neurosurg. 2013;118:1250-1257.
17. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): A multi-institutional prospective observational study. Lancet Oncol. 2014;15:387-395.
18. NIH National Library of Medicine. Stereotactic radiosurgery compared with hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine for 5-15 brain metastases. Available at: https://clinicaltrials.gov/ct2/show/NCT03550391. Accessed July 19, 2019.
19. Roberge D, Brown P, Mason W, et al. CMET-48. CE7 Canadian Clinical Trials Group / Alliance For Clinical Trials In Oncology. A phase III trial of stereotactic radiosurgery compared with whole brain radiotherapy (WBRT) for 5–15 brain metastases. Neuro Oncol. 2017;19:vi49-vi49.
20. Zhang J, Antone J, Li J, et al. Hippocampal-sparing and target volume coverage in treating 3 to 10 brain metastases: A comparison of Gamma Knife, single-isocenter VMAT, CyberKnife, and TomoTherapy stereotactic radiosurgery. Pract Radiat Oncol. 2017;7:183-189.
21. Birer SR, Olson AC, Adamson J, et al. Hippocampal dose from stereotactic radiosurgery for 4 to 10 brain metastases: Risk factors, feasibility of dose reduction via re-optimization, and patient outcomes. Med Dosim. 2017;42:310-316.
22. Chang JS, Ma L, Barani IJ, McDermott MW, Sneed PK, Larson DA. Hippocampal radiosurgery with radiosurgery for multiple intracranial targets: The rationale for proactive beam shaping. Technol Cancer Res Treat. 2016;15:555-559.
23. Nguyen TK, Sahgal A, Detsky J, et al. Single-fraction stereotactic radiosurgery vs. hippocampal-avoidance whole brain radiotherapy for patients with 10-30 brain metastases: A dosimetric analysis. Int J Radiat Oncol Biol Phys. 2019;105:394-399.
24. Gondi V, Tome WA, Rowley H, Mehta MP. Hippocampal contouring: A contouring atlas for RTOG 0933. Available at: https://www.rtog.org/Corelab/ContouringAtlases/HippocampalSparing.aspx. Accessed June 17, 2019.
25. NRG Oncology. NRG-CC003: A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer. September 2015. https://www.nrgoncology.org/. Accessed June 1, 2019.
26. NRG Oncology. NRG-CC001: A Randomized Phase III Trial of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients with Brain Metastases. August 2016. https://www.nrgoncology.org/. Accessed June 1, 2019.
27. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys. 2012;83:e487-e493.
28. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. 7th ed. Philadelphia, PA: Wolters Kluwer; 2012.
29. Stanley J, Breitman K, Dunscombe P, Spencer DP, Lau H. Evaluation of stereotactic radiosurgery conformity indices for 170 target volumes in patients with brain metastases. J Appl Clin Med Phys. 2011;12:245-253.
30. Song CW, Kim M-S, Cho LC, Dusenberg K, Sperduto PW. Radiobiological basis of SBRT and SRS. Int J Clin Oncol. 2014;19:570-578.