Journal Pre-proof

Factors Associated with New-Onset Seizures Following Stereotactic Radiosurgery for Newly Diagnosed Brain Metastases

Emily C. Lerner BA , Ethan S. Srinivasan BS ,
Gloria Broadwater MS , Aden P. Haskell-Mendoza MS ,
Ryan M. Edwards BA , David Huie MD ,
Eugene J. Vaios MD MBA , Scott R. Floyd MD PhD ,
Justus D. Adamson PhD , Peter E. Fecci MD PhD

PII: S2452-1094(22)00160-9
DOI: https://doi.org/10.1016/j.adro.2022.101054
Reference: ADRO 101054

To appear in: *Advances in Radiation Oncology*

Received date: 3 March 2022
Accepted date: 10 August 2022

Please cite this article as: Emily C. Lerner BA , Ethan S. Srinivasan BS , Gloria Broadwater MS , Aden P. Haskell-Mendoza MS , Ryan M. Edwards BA , David Huie MD , Eugene J. Vaios MD MBA , Scott R. Floyd MD PhD , Justus D. Adamson PhD , Peter E. Fecci MD PhD , Factors Associated with New-Onset Seizures Following Stereotactic Radiosurgery for Newly Diagnosed Brain Metastases, *Advances in Radiation Oncology* (2022), doi: https://doi.org/10.1016/j.adro.2022.101054

Factors Associated with New-Onset Seizures Following Stereotactic Radiosurgery for Newly Diagnosed Brain Metastases

New-Onset Seizures Following Stereotactic Radiosurgery

Emily C. Lerner, BA[1], Ethan S. Srinivasan, BS[1], Gloria Broadwater, MS,[2], Aden P. Haskell-Mendoza, MS[1], Ryan M. Edwards, BA[1], David Huie, MD[3], Eugene J. Vaios , MD MBA[4], Scott R. Floyd, MD PhD[4,5] , Justus D. Adamson, PhD[5], Peter E. Fecci, MD PhD[3,5]

[1]Duke University School of Medicine, Durham NC, USA
[2]Cancer Statistical Center, Duke Cancer Institute, Durham NC USA
[3]Department of Neurosurgery, Duke University Medical Center, Durham NC, USA
[4]Department of Radiation Oncology, Duke University Medical Center, Durham NC, USA
[5]Duke Center for Brain and Spine Metastasis, Duke University Medical Center, Durham, NC USA

Corresponding Author
Peter E. Fecci MD PhD
Duke University Medical Center
20 Duke Medicine Circle
Durham, NC 27710
E-mail: peter.fecci@duke.edu
Phone: 919-684-3053
Fax: 919-681-9775

Author's Financial Disclosures and Conflicts:
Emily C. Lerner, BA: None
Ethan S. Srinivasan, BS: None
Aden P. Haskell-Mendoza, MS: None
Ryan M. Edwards, BA: None
David Huie, MD: None
Eugene J. Vaios, MD/MBA: None
Gloria Broadwater, MS: None
Scott R. Floyd, MD PhD: None
Justus D. Adamson, PhD: None
Peter E. Fecci, MD PhD: None

Statistical Analysis Author
Gloria Broadwater, MS
Cancer Statistical Center, Duke Cancer Institute
Hock Plaza, 8th Floor
2424 Erwin Rd

Durham, NC 27710
E-mail: gloria.broadwater@duke.edu

Funding:
This manuscript received no funding from any source.

Data Sharing Statement:
Data for this study was collected via retrospective chart review of institutional records and is not available for reuse

Abstract

Introduction

Stereotactic radiosurgery (SRS) is a highly effective therapy for newly diagnosed brain metastases. Prophylactic anti-epileptic drugs are no longer routinely used in current SRS practice, owing to a perceived low overall frequency of new-onset seizures and potential side effects of medications. It is nonetheless desirable to prevent unwanted side effects following SRS. Risk factors for new-onset seizures after SRS have not been well established. As such, we aimed to characterize variables associated with increased seizure risk.

Methods

Patients treated with SRS for newly diagnosed brain metastases between 2013-2016 were retrospectively reviewed at a single institution. Data on baseline demographics, radiation parameters, and clinical courses were collected.

Results

The cohort consisted of 305 patients treated with SRS without prior seizure history. Median age and baseline KPS were 64 years (IQR 55-70) and 80 (IQR 80-90), respectively. Twenty-six (8.5%) patients developed new-onset seizures within 3 months of SRS. There was no association between new-onset seizures and median baseline KPS, prior resection, or prior whole brain radiotherapy.

There were significant differences in the combined total irradiated volume (12.5 vs. 3.7cm^3, $p<0.001$), maximum single lesion volume (8.8 vs. 2.8 cm^3, $p=0.003$), lesion diameter (3.2 vs. 2.0 cm, $p=0.003$), and number of lesions treated (3 vs. 1, $p=0.018$) between patients with and without new-onset seizures, respectively. On multivariate logistic regression, total irradiated volume (OR 1.09 for every 1 cm^3 increase in total volume, CI 1.02-1.17, $p=0.016$) and pre-SRS neurologic symptoms (OR 3.08, 95% CI 1.19-7.99, $p=0.020$) were both significantly correlated with odds of seizures following SRS.

Conclusions

Our data suggest that larger total treatment volume and the presence of focal neurologic deficits at presentation are associated with new-onset seizures within 3 months of SRS. High risk patients undergoing SRS may benefit from counseling or prophylactic anti-seizure therapy.

Abbreviations: SRS: Stereotactic Radiosurgery, Gy: Gray, WBRT: Whole brain radiotherapy, AED: Anti-Epileptic Drugs, KPS: Karnofsky Performance Scale, IQR: Interquartile Range OR: Odds Ratio, NCSLC: non small cell lung cancer, SCLC: small cell lung cancer

Introduction

Stereotactic radiosurgery (SRS) has developed as a staple of brain metastasis treatment since its initial application in the 1980s.[1–3] Broadly, SRS is a highly effective, low morbidity treatment with reported one-year progression-free survival rates ranging from 70-90%.[4–8] The clinical trials from Aoyama *et al.,* Chang *et al*., and Brown *et al.,* demonstrated the efficacy of SRS as a singular first-line therapy with comparable survival outcomes and improved cognitive outcomes across learning and memory metrics relative to whole brain radiotherapy (WBRT).[9,10,11] SRS has since been widely implemented as both a monotherapy and in conjunction with surgical resection. These indications have grown to include patients with multiple brain metastases.[12] Understanding the associated complications of SRS and their contributing factors, particularly as the incidence of brain metastases rises with more effective systemic therapies, is essential for appropriate patient selection, counseling, and risk mitigation.

SRS is generally well tolerated with minimal acute and long-term side effects. Hemorrhage, new sensory or motor deficits, cognitive decline, or seizure are rare, with radiation necrosis representing a relatively uncommon long-term adverse effect. Previous reports suggest an incidence of 12-32% for new neurologic complications, with risk factors including progressing primary cancers, eloquent tumor locations, and lower SRS dosage.[13–16] Some studies suggest that seizures occur in nearly 10% of patients receiving SRS for brain metastases.[13,15] Seizures pose

significant risks of physical injury and even death.[17] Despite the low frequency of seizures, there is little data to guide selection of SRS patients at greatest risk for seizure. Identification of a high-risk cohort could justify prophylactic anti-epileptic drugs (AEDs) or increased steroid doses.[18] The present study is the first to focus specifically on patients with new-onset seizures after SRS for brain metastases, with the intent to characterize predictive factors that could guide future study, intervention, and patient counseling.

Methods

After IRB approval, retrospective chart review was performed on patients treated with SRS for newly diagnosed metastatic intracranial lesions at a single academic institution from 2013-2016. Patients with a history of seizures prior to SRS were excluded. As part of the inclusion criteria, patients who did not experience a post-treatment seizure were followed for a minimum of 3 months. Patients who did not experience seizures and had less than 90 days follow-up were excluded from analysis.

Baseline demographic information was collected through review of clinical documentation, including age, sex, Karnofsky Performance Scale (KPS), prior treatments and clinical course, SRS parameters, and post-treatment course. Clinical seizure activity was defined as any documented seizure within the first 90 days after SRS initial treatment date. Non-seizure neurologic symptoms were defined as focal neurologic deficits such as motor weakness, sensory deficits, or language deficits. Generalized symptoms such as headaches were excluded.

Maximum single lesion diameter and volume as well as total irradiated volume data were obtained for each patient from routine planning documentation for SRS treatment. Patients were grouped by the presence of post-SRS seizures and compared across cohorts.

Statistical Analyses

Patient characteristics are summarized using median, interquartile range (IQR) and range for continuous variables, and categorical descriptors are summarized with frequencies and percentages. Continuous and categorical variables were compared using Wilcoxon rank sum tests and Fisher's exact tests, respectively. Median follow-up time is estimated from date of the patient's first SRS treatment. Univariate logistic regression analysis was used to calculate the odds ratio (OR) associated with neurologic symptoms and total irradiated volume when the outcome was seizure status. It was also used to analyze the association between maximum single lesion diameter and total irradiated volume when the outcome was neurologic symptoms (yes/no). A multivariate logistic regression model tested the significance of total irradiated volume and pre-SRS neurologic symptoms while controlling for maximum single lesion volume, age at SRS, and pre-SRS KPS. P-values less than 0.05 were considered significant. Analyses were conducted using SAS software (Version 9.4; SAS Institute Inc., Cary, NC).

Results

Cohort Demographics and Pre-Treatment Clinical Courses

Data was collected from 435 patients, of whom 42 were excluded due to prior seizure history. Eighty-eight who did not experience seizures post-treatment were excluded due to follow-up times of less than 3 months. Thus, a total of 305 patients met eligibility criteria and were included in the final analysis. The median age was 64 years (55-70) and median follow-up time was 15.3 months

(7.0-37.7). The cohort was 62.0% female with a median baseline KPS of 80-90. Twenty-six (8.5%) patients had new-onset seizures in the 3 months following SRS treatment. Baseline demographics and pre-treatment clinical courses for the overall cohort as well as for patients grouped by those with and without seizures in the first 3 months post-SRS are reported in **Table 1.** There were no significant differences between the seizure and non-seizure groups with respect to gender (57.7% vs. 62.4% female, p=0.68), median age (59 vs. 64, p=0.35), or median pre-treatment KPS score (90 vs. 80, p=0.36). Additionally, there were no significant differences between groups according to prior craniotomy for resection of target lesions (34.6% vs. 24.7%, p=0.35), prior whole brain radiotherapy (7.7% vs. 13.3%, p=0.55), pre-SRS chemotherapy (46.2% vs. 33.7%, p=0.21) or pre-SRS immunotherapy (23.1% vs. 10.4%, p=0.10). New-onset seizures following SRS were associated with the presence of pre-treatment neurologic deficits (69.2% vs. 38.0%, p=0.003).

One hundred and twenty-seven patients (41.6%) were taking steroids prior to SRS. Of these patients, the majority (63.8%) were started for non-seizure neurologic symptoms. Other reasons for starting steroids prior to SRS included asymptomatic prophylaxis (18.9%) and as part of post-craniotomy treatment protocols (13.3%). Similarly, of 39 patients without prior seizure history who were started on AEDs pre-SRS, the reasons cited included post-craniotomy treatment protocol (46.2%), non-seizure neurologic symptoms (23.1%), and asymptomatic prophylaxis (12.8%). Prophylactic AEDs are not routinely prescribed at our institution, though patients initiated on AED's prophylactically at outside hospitals prior to presentation were kept on AEDs. The proportion of patients on prophylactic AEDs immediately following SRS (42.3% vs. 5.7%, p=0.012) was greater in the seizure cohort.

Tumor Characteristics

There were no significant differences between groups with regards to cerebellar (15.4% vs. 34.1%, p=0.077) or brainstem (11.5% vs. 11.1%, p=1.0) involvement, as shown in **Table 1**. Location of the largest treated lesion was not associated with seizure events (p=-.418), although the locations of concomitant intracranial lesions were not able to be assessed and thus may have been confounding. Primary tumor pathologies included non-small cell lung cancer (NSCLC, 52.8%), breast (14.4%), melanoma (14.4%), renal cell carcinoma (RCC, 7.2%), small cell lung cancer (SCLC, 2.3%), and others (8.9%), as shown in **Table 1**. Due to imbalances in sample size across histologies, the relationship between pathology and seizure risk could not be assessed.

Stereotactic Radiosurgery Treatment Variables

The number of metastatic lesions treated with SRS in this cohort ranged from 1-16. New onset seizures were associated with a greater number of treated lesions (3 vs. 1, p=0.018). SRS was delivered in a single fraction for 70.5% of patients with a median prescribed dose of 20Gy. SRS was fractionated for at least one lesion in 29.5% of patients, with all but one treatment plan using 5 fractions at doses of 5 or 5.5 Gy per fraction. The median volume of the largest lesion treated for each patient was 3.1 cm^3 (0.7-11.3 cm^3). Median total irradiated volume per patient was 4.1 cm^3 (1.1-12.8). Results are presented in **Table 2** for the overall cohort, post-SRS seizure group, and post-SRS non-seizure group.

Total irradiated volume per patient was significantly higher in the seizure group as compared with the non-seizure group (12.5 vs. 3.7 cm^3, p<0.001), as was maximum single lesion volume (8.8 vs. 2.8 cm^3 p=0.003), and maximum single lesion diameter (3.2 vs. 2.0 cm, p=0.003). There was also

a significant difference in the use of fractionation (53.8% vs. 27.2%, p=0.007) between those with and without post-SRS seizures. Patients who received fractionated radiation had larger median maximum single lesion volumes (21.0 cm^3 vs. 1.4 cm^3, p<0.001) and total irradiated volumes (22.7 cm^3 vs. 1.9 cm^3, p<0.001). A greater proportion of patients with new-onset seizures also received post-SRS steroids (76.9% vs. 41.2%, p=0.001).

Prior Craniotomy Sub-Group Analysis

We then identified the subset of patients who received pre-SRS craniotomy for sub-group analysis. Seventy-eight patients received prior craniotomy, and comparison of the resultant seizure and non-seizure cohorts is shown in **Table 3**. Among patients who underwent prior craniotomy, there was no difference in age, gender, KPS, number of treated lesions, pre-SRS chemotherapy or immunotherapy, or total radiation dosage between patients with and without seizures. There were significant differences between the two cohorts in total irradiated volume (37.9 cm^3 vs. 19.2 cm^3, p<0.001) and maximum single lesion diameter (4.9 vs 4.0 cm, p=0.048).

Analysis of Factors Associated with Seizure Following Stereotactic Radiosurgery

By univariate logistic regression analysis, total treatment volume (OR 1.04, 95% CI 1.02-1.06, p<0.001) and the presence of pre-SRS neurologic symptoms (OR 3.67, 95% CI 1.54-8.79, p=0.003) were significantly associated with seizure after SRS. In a multivariate model controlling for patient age, baseline KPS score, maximum single lesion volume, total irradiated volume, and the presence of pre-SRS neurologic symptoms, only the presence of pre-SRS neurologic symptoms (OR 3.08, 95% CI 1.19-7.99, p=0.020) and total irradiated volume (OR 1.09, 95% CI 1.02-1.17,

p=0.016) were significantly associated with increased odds of seizure occurring after SRS as shown in **Table 4**.

Discussion

SRS is a critical component of the contemporary brain metastasis treatment paradigm, portending excellent local disease control with relatively minimal post-treatment morbidity.[4–8] Previous work has identified eloquent tumor locations and progressing lesions as key risk factors for new neurologic complications after SRS.[13] A relatively uncommon, though clinically significant complication is the occurrence of seizures. The incidence and risk factors for seizures in the era of modern SRS planning techniques and novel systemic therapies remains unknown. Moreover, patients with and without prior seizure history have not previously been independently analyzed. To our knowledge, this is the first and largest study to examine patients experiencing new-onset seizures after SRS, identifying a unique population that could benefit from anticipatory guidance and prophylactic intervention.

In the analyzed data set, 8.5% of patients without prior seizures were found to experience new-onset clinical seizure activity in the peri-radiosurgery period. This incidence increased to 12.3% when irradiated volumes exceeded 3 cm^3, representing roughly 1 in 8 patients. Key factors significantly associated with these new-onset seizures included pre-SRS focal neurologic deficits, greater maximum single lesion volume and diameter, and greater total irradiated volume. Even after controlling for variables significant on univariate analysis, total irradiated volume remained a significant predictor of post-SRS seizures, with an OR of 1.09 (p=0.02), suggesting a 9% increase

in risk for every 1 cm^3 increase in irradiated volume. Additionally, the presence of pre-SRS neurologic symptoms (OR 3.09, p=0.02) was a significant predictor of post-SRS seizures.

The relationship between new-onset seizures and SRS has not been previously well-defined. Seizures can result from brain metastases independent of treatment, with a reported incidence ranging from 15 to 35%.[20,21] Seizures may be mediated by the underlying disease burden, rather than treatment related effects. Chan *et al*. demonstrated in their 2017 systematic review that seizures are more frequently a presenting symptom, with only a 3% incidence following diagnosis.[15,22] Increased single lesion volume has been previously identified as a risk factor for complications, local treatment failure, and radiation necrosis.[1,2] Similarly, in our study, we report several pre-treatment variables that were predictive of clinical outcomes. Tumor burden and neurologic deficits likely reflect increased disruption of normal brain parenchyma and therefore a reduced seizure threshold. Interestingly, prior craniotomy or previous immunotherapy and chemotherapy was not associated with seizure risk. While tumor-intrinsic factors likely drive risk for new-onset seizures, efforts to mitigate this risk through prophylactic AEDs and steroids, or adjustments in radiation treatment such as fractionation, dose, and treatment heterogeneity, may be appropriate.

Improvements in radiation delivery now enable simultaneous treatment of multiple intracranial lesions with SRS[1]. As the incidence and volume of brain metastases rises with improvements in systemic therapy and clinical outcomes, awareness of the impact of larger treatment volumes on seizure risk is critical for patient management.[12] These findings now define a patient population at increased risk for a typically unpredictable and potentially clinically significant post-treatment

complication. Currently, initiation of AEDs is not routinely indicated for patients without prior seizures undergoing SRS for brain metastases.[1,2] Consideration of short-term pre or post-procedure prophylactic AED or higher steroids doses for at-risk patient populations may be of clinical benefit. Future prospective trials are warranted to validate these findings and the clinical impact of prophylactic measures to mitigate seizure risk.

This study is limited by its retrospective, single institution design. Given the small and imbalanced sample sizes across histologies, reliable conclusions regarding the impact of tumor histology on seizure risk could not be made. Additionally, given the retrospective nature, causation could not be determined between the observed associations with seizure occurrence. Our institutional practice is to use fractionated treatment when lesion size exceeds 2cm [2]. Therefore, the observed association between fractionation and new-onset seizures is likely reflective of lesion size, a proxy for total irradiated volume, which predicted seizure risk on multivariate analysis. Pre-treatment FLAIR volume was also likely simply reflective of lesion size, as these two parameters were correlated upon subgroup analysis of patients with seizure events. These findings further underscore the importance of total disease burden for predicting seizure risk. Notably, a higher proportion of patients on steroids or AEDs immediately after SRS had seizures within the first 3 months post-treatment. These associations are most likely indicative of the presence of focal neurologic deficits warranting treatment, and therefore represent a probable bias of indication rather than an actual causative relationship. Likewise, it was focal neurologic deficits that proved independently associated with seizure events, pre-SRS steroids, and prophylactic AED use.

Importantly, we recognize that some seizure events may not have been documented in medical records either prior to or in the 3 months following SRS, as patients may have received follow up care outside our institution. Nonetheless, the robust findings and large cohort size provide compelling evidence to warrant future prospective investigation.

In conclusion, while SRS is a highly effective first-line therapy for brain metastases, the presence of pre-existing neurologic deficits and great tumor burden are predictive of post-SRS seizures. These findings represent an important addition to the literature guiding clinical management of patients with brain metastases. This is the first study to comprehensively assess risk factors for seizure events using modern radiation techniques and in the era of targeted therapy and immunotherapy. The association of treatment volume, rather than number of brain metastases, is important as the incidence of brain metastases increases and SIMT techniques are adopted in radiation treatment facilities. While seizure events are uncommon, patients undergoing high volume radiosurgery and/or presenting with neurologic deficits would benefit from additional counseling and consideration of prophylactic therapy to reduce seizure risk.

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Citations

1. Sturm V, Kober B, Höver KH, et al. Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. *Int J Radiat Oncol Biol Phys*. 1987;13(2):279-282. doi:10.1016/0360-3016(87)90140-4

2. Greitz T, Lax I, Bergström M, et al. Stereotactic radiation therapy of intracranial lesions. Methodologic aspects. *Acta Radiol Oncol*. 1986;25(2):81-89. doi:10.3109/02841868609136383

3. Alexander E, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. *J Natl Cancer Inst*. 1995;87(1):34-40. doi:10.1093/jnci/87.1.34

4. Pirzkall A, Debus J, Lohr F, et al. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. *JCO*. 1998;16(11):3563-3569. doi:10.1200/JCO.1998.16.11.3563

5. Cho KH, Hall WA, Gerbi BJ, Higgins PD, Bohen M, Clark HB. Patient selection criteria for the treatment of brain metastases with stereotactic radiosurgery. *J Neurooncol*. 1998;40(1):73-86. doi:10.1023/A:1006169109920

6. Sneed PK, Lamborn KR, Forstner JM, et al. Radiosurgery for brain metastases: is whole brain radiotherapy necessary? *International Journal of Radiation Oncology*Biology*Physics*. 1999;43(3):549-558. doi:10.1016/S0360-3016(98)00447-7

7. Varlotto JM, Flickinger JC, Niranjan A, Bhatnagar AK, Kondziolka D, Lunsford LD. Analysis of tumor control and toxicity in patients who have survived at least one year after radiosurgery for brain metastases. *International Journal of Radiation Oncology*Biology*Physics*. 2003;57(2):452-464. doi:10.1016/S0360-3016(03)00568-6

8. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. *International Journal of Radiation Oncology*Biology*Physics*. 2006;64(3):898-903. doi:10.1016/j.ijrobp.2005.08.035

9. 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. *The Lancet Oncology*. 2009;10(11):1037-1044. doi:10.1016/S1470-2045(09)70263-3

10. 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(21):2483-2491. doi:10.1001/jama.295.21.2483

11. 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: A Randomized Clinical Trial. *JAMA*. 2016;316(4):401-409. doi:10.1001/jama.2016.9839

12. Hughes RT, Masters AH, McTyre ER, et al. Initial SRS for Patients With 5 to 15 Brain Metastases: Results of a Multi-Institutional Experience. *Int J Radiat Oncol Biol Phys*. 2019;104(5):1091-1098. doi:10.1016/j.ijrobp.2019.03.052

13. Williams BJ, Suki D, Fox BD, et al. Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications: Clinical article. *Journal of Neurosurgery*. 2009;111(3):439-448. doi:10.3171/2008.11.JNS08984

14. Telera S, Fabi A, Pace A, et al. Radionecrosis induced by stereotactic radiosurgery of brain metastases: results of surgery and outcome of disease. *J Neurooncol*. 2013;113(2):313-325. doi:10.1007/s11060-013-1120-8

15. Yamamoto M, Serizawa T, Higuchi Y, et al. A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores. *International Journal of Radiation Oncology*Biology*Physics*. 2017;99(1):31-40. doi:10.1016/j.ijrobp.2017.04.037

16. Minniti G, Clarke E, Lanzetta G, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol*. 2011;6(1):48. doi:10.1186/1748-717X-6-48

17. Nei M, Bagla R. Seizure-related injury and death. *Curr Neurol Neurosci Rep*. 2007;7(4):335-341. doi:10.1007/s11910-007-0051-1

18. Wali AR, Rennert RC, Wang SG, Chen CC. Evidence-Based Recommendations for Seizure Prophylaxis in Patients with Brain Metastases Undergoing Stereotactic Radiosurgery. *Acta Neurochir Suppl*. 2021;128:51-55. doi:10.1007/978-3-030-69217-9_6

19. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated Volume as a Predictor of Brain Radionecrosis After Linear Accelerator Stereotactic Radiosurgery. *International Journal of Radiation Oncology*Biology*Physics*. 2010;77(4):996-1001. doi:10.1016/j.ijrobp.2009.06.006

20. Ajinkya S, Fox J, Houston P, et al. Seizures in Patients With Metastatic Brain Tumors: Prevalence, Clinical Characteristics, and Features on EEG. *Journal of Clinical Neurophysiology*. 2021;38(2):143-148. doi:10.1097/WNP.0000000000000671

21. Chan V, Sahgal A, Egeto P, Schweizer T, Das S. Incidence of seizure in adult patients with intracranial metastatic disease. *J Neurooncol*. 2017;131(3):619-624. doi:10.1007/s11060-016-2335-2

1. Palmer, J.D., et al., *Single-Isocenter Multitarget Stereotactic Radiosurgery Is Safe and Effective in the Treatment of Multiple Brain Metastases.* Adv Radiat Oncol, 2020. **5**(1): p. 70-76.
2. Shaw, E., 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, 2000. **47**(2): p. 291-8.

	All Patients (305)	Seizure (26)	Non-seizure (279)	p-value
Age, Median (IQR)	64.0 (55.0, 70.0)	59.0 (55.0, 69.0)	64.0 (55.0, 70.0)	0.348
Gender, Female (%)	189 (62.0%)	15 (57.7%)	174 (62.4%)	0.676
KPS pre-SRS, Median (IQR)	80.0 (80.0, 90.0)	90.0 (80.0, 90.0)	80.0 (80.0, 90.0)	0.360
Pre-SRS Neurologic Symptoms	124 (40.7%)	18 (69.2%)	106 (38.0%)	**0.003**
Pre-SRS Steroids	127 (41.6%)	17 (65.4%)	110 (39.4%)	**0.012**
Prior Craniotomy	78 (25.6%)	9 (34.6%)	69 (24.7%)	0.346
Prior WBRT	39 (12.8%)	2 (7.7%)	37 (13.3%)	0.551
Pre-SRS Immunotherapy	35 (11.5%)	6 (23.1%)	29 (10.4%)	0.097
Pre-SRS Chemotherapy	106 (34.8%)	12 (46.2%)	94 (33.7%)	0.205
Cerebellar Involvement	99 (32.5%)	4 (15.4%)	95 (34.1%)	0.077
Brain Stem Involvement	34 (11.1%)	3 (11.5%)	31 (11.1%)	1.0
Location of largest treated lesion				p=0.418
Frontal	100 (32.8%)	8 (30.8%)	92 (33.3%)	
Cerebellum	68 (22.3%)	4 (15.3%)	64 (23.2%)	
Parietal	47 (15.4%)	8 (30.8%)	39 (14.1%)	
Temporal	31 (10.2%)	2 (7.7%)	29 (10.5%)	
Occipital	30 (9.8%)	1 (3.8%)	29 (10.5%)	
Deep	14 (4.6%)	1 (3.8%)	13 (4.7%)	
Brainstem	10 (3.3%)	1 (3.8%)	9 (3.3%)	
Extraaxial	5 (1.6%)	1 (3.8%)	4 (1.4%)	
Histology				
Melanoma	44 (14.4%)	5 (19.2%)	39 (14.0%)	
NSCLC	161 (52.8%)	7 (26.9%)	154 (55.2%)	
RCC	22 (7.2%)	4 (15.4%)	18 (6.5%)	
SCLC	7 (2.3%)	0 (0.0%)	7 (2.5%)	
Breast	44 (14.4%)	5 (19.2%)	39 (14.0%)	
Other	27 (8.9%)	5 (19.2%)	22 (7.9%)	

Table 1: Baseline demographics and pre-treatment clinical courses. SRS = stereotactic radiosurgery; AED = anti-epileptic drug; WBRT = whole brain radiotherapy; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCLC = small cell lung cancer.

Table 2: Stereotactic radiosurgery treatment variables. SRS = stereotactic radiosurgery

	All Patients (305)	**Seizure (26)**	**Non-seizure (279)**	**p-value**
Number of Treated Lesions, Median (Range)	1.0 (1.0, 3.0)	3.0 (1.0, 4.0)	1.0 (1.0, 3.0)	**0.018**
Fractionated Radiation	90 (29.5%)	14 (53.8%)	76 (27.2%)	**0.007**
Total Irradiated Volume (cm^3), Median (IQR)	4.1 (1.1, 12.8)	12.5 (3.6, 37.3)	3.7 (0.9, 11.4)	**<0.001**
Maximum Single Lesion Volume (cm^3), Median (IQR)	3.1 (0.7, 11.3)	8.8 (2.7, 25.9)	2.8 (0.7, 11.2)	**0.003**
Maximum Single Lesion Diameter (cm), Median (IQR)	2.1 (1.3, 3.5)	3.2 (2.0, 4.4)	2.0 (1.3, 3.4)	**0.003**
Steroids Post-SRS	135 (44.3%)	20 (76.9%)	115 (41.2%)	**0.001**
AEDs Post-SRS	27 (8.9%)	11 (42.3%)	16 (5.7%)	**<0.001**

Table 3: Baseline demographics, pre-treatment clinical courses, and radiation variables for patients who received craniotomy prior to stereotactic radiosurgery (SRS)

	All Patients (78)	**Seizure (9)**	**Non-seizure (69)**	**p-value**
Age, Median (IQR)	62.0 (55.0, 69.0)	57.0 (49.0, 63.0)	64.0 (56.0, 69.0)	0.114
Gender, Female (%)	51 (65.4%)	5 (55.6%)	46 (66.7%)	0.711
KPS pre-SRS, Median (IQR)	80.0 (80.0, 90.0)	80.0 (80.0, 90.0)	80.0 (70.0, 90.0)	0.510
Number of Treated Lesions, Median (Range)	1.0 (1.0, 2.0)	1.0 (1.0, 3.0)	1.0 (1.0, 2.0)	0.192
Pre-SRS Immunotherapy	8 (10.3%)	1 (11.1%)	7 (10.1%)	1.0
Pre-SRS Chemotherapy	16 (20.5%)	3 (33.3%)	13 (18.8%)	0.38
Total Irradiated Volume, Median (IQR)	21.7 (11.2, 35.3)	37.9 (33.8, 54.1)	19.2 (11.0, 33.1)	**<0.001**
Maximum Lesion Target Diameter Median, (IQR)	4.2 (3.4, 5.1)	4.9 (4.4, 5.5)	4.0 (3.3, 5.0)	**0.048**

Table 4: Multivariate logistic regression model of variables associated with new-onset post-stereotactic radiosurgery (SRS) seizure. OR = odds ratio; CI = confidence interval; Gy = gray.

Effect	OR (95% CI)	p-value
Total Irradiated Volume	1.09 (1.02-1.17)	**0.016**
Maximum Single Lesion Volume	0.93 (0.86-1.01)	0.100
Pre-SRS KPS	1.04 (0.99-1.09)	0.061
Age at SRS	0.99 (0.95-1.03)	0.611
Pre-SRS Neurologic Symptoms	3.08 (1.19-7.99)	**0.020**