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

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Abstract

Purpose: Stereotactic radiosurgery (SRS) is a highly effective therapy for newly diagnosed brain metastases. Prophylactic antiepileptic 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 and Materials: Patients treated with SRS for newly diagnosed brain metastases between 2013 and 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 Karnofsky Performance Scale score were 64 years (interquartile range, 55-70) and 80 (interquartile range, 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 Karnofsky Performance Scale score, prior resection, or prior whole brain radiation therapy. There were significant differences in the combined total irradiated volume (12.5 vs 3.7 cm³, \( P < .001 \)), maximum single lesion volume (8.8 vs 2.8 cm³, \( P = .003 \)), lesion diameter (3.2 vs 2.0 cm, \( P = .003 \)), and number of lesions treated (3 vs 1, \( P = .018 \)) between patients with and without new-onset seizures, respectively. On multivariate logistic regression, total irradiated volume (odds ratio, 1.09 for every 1-cm³ increase in total volume; confidence interval, 1.02-1.17; \( P = .016 \)) and pre-SRS neurologic symptoms (odds ratio, 3.08; 95% confidence interval, 1.19-7.99; \( P = .020 \)) 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 antiseizure therapy.

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Introduction

Stereotactic radiosurgery (SRS) has developed as a staple of brain metastasis treatment since its initial application in the 1980s. Broadly, SRS is a highly effective, low morbidity treatment with reported 1-year progression-free survival rates ranging from 70% to 90%. The clinical trials from Chang et al, Aoyama 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 radiation therapy. 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. 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% to 32% for new neurologic complications, with risk factors including progressing primary cancers, eloquent tumor locations, and lower SRS dosage. Some studies suggest that seizures occur in nearly 10% of patients receiving SRS for brain metastases. Seizures pose significant risks of physical injury and even death. Despite the low frequency of seizures, there is little data to guide selection of patients receiving SRS at greatest risk for seizure. Identification of a high-risk cohort could justify prophylactic antiepileptic drugs (AEDs) or increased steroid doses. 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 and Materials

After institutional review board approval, retrospective chart review was performed on patients treated with SRS for newly diagnosed metastatic intracranial lesions at a single academic institution from 2013 to 2016. Patients with a history of seizures before SRS were excluded. As part of the inclusion criteria, patients who did not experience a posttreatment 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 score (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. Nonepileptic 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 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 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 or 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 <.05 were considered significant. Analyses were conducted using SAS software (version 9.4; SAS Institute Inc, Cary, NC).

Results

Cohort demographics and pretreatment 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 posttreatment 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 to 90. Twenty-six patients (8.5%) had new-onset seizures in the 3 months following SRS treatment. Baseline demographics and pretreatment 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 nonseizure groups with respect to sex (57.7% vs 62.4% female, \( P = .68 \)), median age (59 vs 64, \( P = .35 \)), or median pretreatment KPS score (90 vs 80, \( P = .36 \)). Additionally, there were no significant differences between groups according to prior craniotomy for resection of target lesions (34.6% vs 13.3%, \( P = .35 \)), prior whole brain radiation therapy (7.7% vs 13.3%, \( P = .55 \)), pre-SRS chemotherapy (46.2% vs 33.7%, \( P = .21 \)) or pre-SRS immunotherapy (23.1% vs 10.4%, \( P = .10 \)). New-onset seizures following SRS were associated with the presence of pretreatment neurologic deficits (69.2% vs 38.0%, \( P = .003 \)).

One hundred twenty-seven patients (41.6%) were taking steroids before SRS. Of these patients, the majority (63.8%) were started for nonseizure neurologic symptoms. Other reasons for starting steroids before SRS included asymptomatic prophylaxis (18.9%) and as part of postcraniotomy treatment protocols (13.3%). Similarly, of 39 patients without prior seizure history who were started on AEDs pre-SRS, the reasons cited included postcraniotomy treatment protocol (46.2%), nonseizure neurologic symptoms (23.1%), and asymptomatic prophylaxis (12.8%). Prophylactic AEDs are not routinely prescribed at our institution, though patients initiated on AEDs prophylactically at outside hospitals before presentation were kept on AEDS. The proportion of patients on

| Variable                                      | All patients (n = 305) | Seizure (n = 26) | Nonseizure (n = 279) | \( P \) value |
|-----------------------------------------------|------------------------|------------------|----------------------|--------------|
| Age, median (IQR)                             | 64.0 (55.0, 70.0)      | 59.0 (55.0, 69.0)| 64.0 (55.0, 70.0)    | .348         |
| Female sex, n (%)                             | 189 (62.0)             | 15 (57.7)        | 174 (62.4)           | .676         |
| KPS pre-SRS, median (IQR)                     | 80.0 (80.0, 90.0)      | 90.0 (80.0, 90.0)| 80.0 (80.0, 90.0)    | .360         |
| Pre-SRS neurologic symptoms, n (%)           | 124 (40.7)             | 18 (69.2)        | 106 (38.0)           | .003         |
| Pre-SRS steroids, n (%)                       | 127 (41.6)             | 17 (65.4)        | 110 (39.4)           | .012         |
| Prior craniotomy, n (%)                       | 78 (25.6)              | 9 (34.6)         | 69 (24.7)            | .346         |
| Prior WBRT, n (%)                             | 39 (12.8)              | 2 (7.7)          | 37 (13.3)            | .551         |
| Pre-SRS immunotherapy, n (%)                  | 35 (11.5)              | 6 (23.1)         | 29 (10.4)            | .097         |
| Pre-SRS chemotherapy, n (%)                   | 106 (34.8)             | 12 (46.2)        | 94 (33.7)            | .205         |
| Cerebellar involvement, n (%)                 | 99 (32.5)              | 4 (15.4)         | 95 (34.1)            | .077         |
| Brain stem involvement, n (%)                 | 34 (11.1)              | 3 (11.5)         | 31 (11.1)            | 1.0          |
| Location of largest treated lesion, n (%)     |                        |                  |                      | .418         |
| Frontal                                       | 100 (32.8)             | 8 (30.8)         | 92 (33.3)            |              |
| Cerebellum                                    | 68 (22.3)              | 4 (15.3)         | 64 (22.3)            |              |
| 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)             |              |
| Brain stem                                    | 10 (3.3)               | 1 (3.8)          | 9 (3.3)              |              |
| Extra-axial                                   | 5 (1.6)                | 1 (3.8)          | 4 (1.4)              |              |
| Histology, n (%)                              |                         |                  |                      |              |
| 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)             |              |

Abbreviations: AED = antiepileptic drug; IQR = interquartile range; KPS = Karnofsky Performance Scale score; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCLC = small cell lung cancer; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

Values in boldface are statistically significant.
prophylactic AEDs immediately following SRS (42.3% vs 5.7%, \( P = .012 \)) was greater in the seizure cohort.

### Tumor characteristics

There were no significant differences between groups with regards to cerebellar (15.4% vs 34.1%, \( P = .077 \)) or brain stem (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 (52.8%), breast (14.4%), melanoma (14.4%), renal cell carcinoma (7.2%), small cell lung cancer (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 to 16. New onset seizures were associated with a greater number of treated lesions (3 vs 1, \( P = .018 \)). SRS was delivered in a single fraction for 70.5% of patients with a median prescribed dose of 20 Gy. SRS was fractionated for at least one lesion in 29.5% of patients, with all but 1 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\(^3\)). The median total irradiated volume per patient was 4.1 cm\(^3\) (1.1-12.8 cm\(^3\)). Results are presented in Table 2 for the overall cohort, post-SRS seizure group, and post-SRS nonseizure group.

Total irradiated volume per patient was significantly higher in the seizure group compared with the nonseizure group (12.5 vs 3.7 cm\(^3\), \( P < .001 \)), as was maximum single lesion volume (8.8 vs 2.8 cm\(^3\), \( P = .003 \)), and maximum single lesion diameter (3.2 vs 2.0 cm, \( P = .003 \)). There was also a significant difference in the use of fractionation (53.8% vs 27.2%, \( P = .007 \)) between those with and without post-SRS seizures. Patients who received fractionated radiation had larger median maximum single lesion volumes (21.0 vs 1.4 cm\(^3\), \( P < .001 \)) and total irradiated volumes (22.7 vs 1.9 cm\(^3\), \( P < .001 \)). A greater proportion of patients with new-onset seizures also received post-SRS steroids (76.9% vs 41.2%, \( P = .001 \)).

### Prior craniotomy subgroup analysis

We then identified the subset of patients who received pre-SRS craniotomy for subgroup analysis. Seventy-eight patients received prior craniotomy, and comparison of the resultant seizure and nonseizure cohorts is shown in Table 3. Among patients who underwent prior craniotomy, there were no differences in age, sex, 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 2 cohorts in total irradiated volume (37.9 vs 19.2 cm\(^3\), \( P < .001 \)) and maximum single lesion diameter (4.9 vs 4.0 cm, \( P = .048 \)).

### Analysis of factors associated with seizure following stereotactic radiosurgery

By univariate logistic regression analysis, total treatment volume (OR, 1.04; 95% confidence interval [CI], 1.02-1.06; \( P < .001 \)) and the presence of pre-SRS neurologic symptoms (OR, 3.67; 95% CI, 1.54-8.79; \( P = .003 \)) 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, the risk of new-onset seizures was independent of these factors.

| Variable                                      | All patients (n = 305) | Seizure (n = 26) | Nonseizure (n = 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)       | .018          |
| Fractionated radiation, n (%)                 | 90 (29.5)             | 14 (53.8)        | 76 (27.2)            | .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)      | <.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)      | .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)       | .003          |
| Steroids post-SRS, n (%)                      | 135 (44.3)            | 20 (76.9)        | 115 (41.2)           | .001          |
| AEDs post-SRS, n (%)                          | 27 (8.9)              | 11 (42.3)        | 16 (5.7)             | <.001         |

*Abbreviations: AED = antiepileptic drug; IQR = interquartile range; SRS = stereotactic radiosurgery.
Values in boldface are statistically significant.*
symptoms, only the presence of pre-SRS neurologic symptoms (OR, 3.08; 95% CI, 1.19-7.99; \( P = .020 \)) and total irradiated volume (OR, 1.09; 95% CI, 1.02-1.17; \( P = .016 \)) 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 posttreatment morbidity.\(^4\)\(^5\) 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 \( (P = .02) \), 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; \( P = .02 \)) 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%.\(^{19,20}\) Seizures may be mediated by the underlying disease burden rather than treatment-related effects. Chan et al\(^{20}\) demonstrated in their 2017 systematic review that seizures are more frequently a presenting symptom, with only a 3% incidence following diagnosis. Increased single lesion volume has been previously identified as a risk factor for complications, local treatment failure, and radiation necrosis.\(^2\,\,^3\) Similarly, in our study, we report several pretreatment 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.

### Table 3 Baseline demographics, pretreatment clinical courses, and radiation variables for patients who received craniotomy before stereotactic radiosurgery

| Variable                                      | All patients (n = 78) | Seizure (n = 9) | Nonseizure (n = 69) | \( P \) value |
|------------------------------------------------|----------------------|----------------|---------------------|-------------|
| Age, median (IQR)                              | 62.0 (55.0, 69.0)    | 57.0 (49.0, 63.0) | 64.0 (56.0, 69.0)   | .114        |
| Female sex, n (%)                              | 51 (65.4)            | 5 (55.6)       | 46 (66.7)           | .711        |
| KPS pre-SRS, median (IQR)                      | 80.0 (80.0, 90.0)    | 80.0 (80.0, 90.0) | 80.0 (70.0, 90.0)   | .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)      | .192        |
| Pre-SRS immunotherapy, n (%)                   | 8 (10.3)             | 1 (11.1)       | 7 (10.1)            | 1.0         |
| Pre-SRS chemotherapy, n (%)                    | 16 (20.5)            | 1 (11.1)       | 13 (18.8)           | .38         |
| Total irradiated volume, median (IQR)          | 21.7 (11.2, 35.3)    | 37.9 (33.8, 54.1) | 19.2 (11.0, 33.1)   | \(<.001\)   |
| Maximum lesion target diameter, median (IQR)   | 4.2 (3.4, 5.1)       | 4.9 (4.4, 5.5)  | 4.0 (3.3, 5.0)      | \(.048\)    |

**Abbreviations:** IQR = interquartile range; KPS = Karnofsky Performance Scale score; SRS = stereotactic radiosurgery. Values in boldface are statistically significant.

### Table 4 Multivariate logistic regression model of variables associated with new-onset post—stereotactic radiosurgery seizure

| Effect                          | OR (95% CI)     | \( P \) value |
|---------------------------------|-----------------|---------------|
| Total irradiated volume        | 1.09 (1.02-1.17) | \(.016\)      |
| Maximum single lesion volume   | 0.93 (0.86-1.01) | \(.100\)      |
| Pre-SRS KPS                     | 1.04 (0.99-1.09) | \(.061\)      |
| Age at SRS                      | 0.99 (0.95-1.03) | \(.611\)      |
| Pre-SRS neurologic symptoms    | 3.08 (1.19-7.99) | \(.020\)      |

**Abbreviations:** CI = confidence interval; KPS = Karnofsky Performance Scale score; OR = odds ratio; SRS = stereotactic radiosurgery. Values in boldface are statistically significant.
Improvements in radiation delivery now enable simultaneous treatment of multiple intracranial lesions with SRS.\(^2\) As the incidence and volume of brain metastases rises with improvements in systemic therapy and clinical outcomes, awareness of the effect 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 posttreatment complication. Currently, initiation of AEDs is not routinely indicated for patients without prior seizures undergoing SRS for brain metastases.\(^2,3\) Consideration of short-term pre- or postprocedure 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 effect 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 effect 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 2 cm.\(^3\) 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. Pretreatment fluid-attenuated inversion recovery volume was also likely simply reflective of lesion size, as these 2 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 posttreatment. 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 before 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.

**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 single-isocenter multitarget techniques are adopted in radiation treatment facilities. Although 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.

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