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Factors associated with preoperative and postoperative seizures in patients undergoing resection of brain metastases

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OBJECTIVE Epileptic seizures are a common and potentially devastating complication of metastatic brain tumors. Although tumor-related seizures have been described in previous case series, most studies have focused on primary brain tumors and have not differentiated between different types of cerebral metastases. The authors analyzed a large surgical cohort of patients with brain metastases to examine risk factors associated with preoperative and postoperative seizures and to better understand the seizure risk factors of metastatic brain tumors.

METHODS Patients who underwent resection of a brain metastasis at the University of California, San Francisco (UCSF), were retrospectively reviewed. Patients included in the study were ≥ 18 years of age, required resection of a brain metastasis, and were treated at UCSF. Primary cancers included melanoma, non–small cell lung adenocarcinoma, breast adenocarcinoma, colorectal adenocarcinoma, esophageal adenocarcinoma, gastric adenocarcinoma, renal cell carcinoma, urothelial carcinoma, ovarian carcinoma, cervical squamous cell carcinoma, and endometrial adenocarcinoma. Patients were evaluated for primary cancer type and seizure occurrence, as well as need for use of antiepileptic drugs preoperatively, at time of discharge, and at 6 months postoperatively. Additionally, Engel classification scores were assigned to those patients who initially presented with seizures preoperatively. Univariate and multivariate regression analyses were used to assess the association of tumor type with preoperative seizures.

RESULTS Data were retrospectively analyzed for 348 consecutive patients who underwent surgical treatment of brain metastases between 1998 and 2019. The cohort had a mean age of 60 years at the time of surgery and was 59% female. The mean and median follow-up durations after the date of surgery for the cohort were 22 months and 10.8 months, respectively. In univariate analysis, frontal lobe location ($p = 0.05$), melanoma ($p = 0.02$), *KRAS* mutation in lung carcinoma ($p = 0.04$), intratumoral hemorrhage ($p = 0.04$), and prior radiotherapy ($p = 0.04$) were associated with seizure presentation. Postoperative checkpoint inhibitor use ($p = 0.002$), prior radiotherapy ($p = 0.05$), older age ($p = 0.002$), distant CNS progression ($p = 0.004$), and parietal lobe tumor location ($p = 0.002$) were associated with seizures at 6 months postoperatively. The final multivariate model confirmed the independent effects of tumor location in the frontal lobe and presence of intratumoral hemorrhage as predictors of preoperative seizures, and checkpoint inhibitor use and parietal lobe location were identified as significant predictors of seizures at 6 months postoperatively.

CONCLUSIONS Within this surgical cohort of patients with brain metastases, seizures were seen in almost a quarter of patients preoperatively. Frontal lobe metastases and hemorrhagic tumors were associated with higher risk of preoperative seizures, whereas checkpoint inhibitor use and parietal lobe tumors appeared to be associated with seizures at 6 months postoperatively. Future research should focus on the effect of metastatic lesion–targeting therapeutic interventions on seizure control in these patients.

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KEYWORDS brain metastases; epilepsy; metastasis; brain tumor; seizure; checkpoint inhibitor; surgery; oncology; metastatic cancer

ABBREVIATIONS AED = antiepileptic drug; NSCLC = non–small cell lung carcinoma; UCSF = University of California, San Francisco.

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EPILEPTIC seizures are a frequent and potentially devastating complication of metastatic brain tumors.[1–3] The reported prevalence of seizures in patients with brain metastases ranges between 10% and 35%. This is lower than the incidence of seizures in patients with gliomas (55%–75%), and similar to that of patients with supratentorial meningiomas (10%–50%). Brain tumor–related epilepsy can lead to transient neurological deficits, mood disturbances, and cognitive deterioration in affected patients.[4,5] Given the impact seizures can have on patient quality of life, inquiry into seizure rates, predictors of seizure occurrence, and likelihood of seizure freedom is needed for patients with brain metastases.[2,5]

Seizures associated with brain metastases have been understudied in comparison with other brain tumor types.[1,2,6] Prior studies of tumor-related seizures have focused on primary rather than metastatic brain tumors and have failed to differentiate seizure risk according to primary cancer type. There is currently a paucity of data regarding what factors predispose patients to epileptic seizures at presentation, as well as which tumor types, treatment factors, and tumor locations are more frequently associated with seizures in the patient population with brain metastases.[1,3] Furthermore, it is unclear if novel adjuvant checkpoint inhibitor therapy, which has been demonstrated to improve brain metastasis control, influences seizure risk.[7–10]

The goal of this study was to identify rates of seizures in patients with surgically treated brain metastases, as well as patient, treatment, and tumor factors associated with preoperative and postoperative seizures. We also examined whether checkpoint inhibitor therapy, which induces an inflammatory response, was associated with higher rates of seizures. These data may help to better delineate factors that influence seizure risk among patients with metastatic brain tumors, as well as to identify at-risk patients who may benefit from increased duration of antiepileptic drug (AED) therapy.

Methods

Study Design

This retrospective cohort study was conducted at an academic medical center. After obtaining approval from the IRB of the University of California, San Francisco (UCSF), the UCSF tumor registry was searched for adult patients who underwent resection of 1 or more brain metastases between 1998 and 2019. Inclusion criteria were patients who 1) were aged 18 years or older at the time of surgery, 2) had brain metastases diagnosed with a known primary cancer type, 3) underwent surgery for resection of 1 or more brain metastases, 4) had pathology-confirmed malignant tissue present at the time of surgery, and 5) had an electronic medical record with imaging data and documentation of clinical outcomes. Patients were excluded if 1) only their brain metastases were biopsied and 2) if pathology demonstrated no viable tumor. In total, 348 patients met the inclusion criteria.

Patients were evaluated for demographic variables, primary tumor characteristics, seizure occurrence, and AED use at multiple time points. In addition, Engel classification scores at last follow-up were assigned to those patients who presented with seizures. Univariate and multivariate regression analyses were used to test the effects of the studied variables on seizure presentation and outcome.

Patient Cohort

A retrospectively generated database of patients with surgically treated metastatic brain tumors at UCSF, as described above, was analyzed. All tumors were diagnosed and further characterized on the basis of findings on brain MRI. The radiological studies were reviewed independently by neuroradiologists on the basis of the findings on the original images and coded by using predefined database forms. The included morphological variables included tumor volume, tumor location within the brain, and tumor spread.

The collected clinical variables included primary tumor type and treatment modalities applied to the tumors. Use of radiotherapy and checkpoint inhibitors was determined on the basis of clinical decision-making by a multidisciplinary team of neurosurgeons, neuro-oncologists, and radiation oncologists. Demographic variables (age and sex) were obtained retrospectively from patient charts.

AEDs were initiated under the care of a neurologist or neurosurgeon, either at our institution or at an outside institution before referral. Levetiracetam was the standard drug that was started owing to ease of administration, limited interactions with other drugs, and relative affordability. In most cases, patients with new seizures were started on levetiracetam unless referred from an outside neurologist and already receiving an AED, in which case the previously prescribed AED was continued. For patients with preoperative seizures, AEDs were typically continued indefinitely. For patients who did not experience preoperative seizures, AEDs were continued for 1–3 months after surgery depending on the judgment of the treating neurologist and neurosurgeon, with the majority of patients stopping AEDs at 1 month after surgery.

Many patients received initial evaluation and treatment at a referring center. Thus, the results of electroencephalography were often unavailable for review. Patients were referred to our center for definitive tumor treatment (typically before seizures were refractory to medications), so referral to a level 4 epilepsy program was unnecessary. Engel class was determined on the basis of the clinical course gleaned from the medical notes.

Statistical Analysis

Univariate and multivariate logistic regression models (level of significance $p \leq 0.05$) were used to test the effects of clinical, demographic, and morphological characteristics on seizures at initial presentation in patients with metastatic brain tumors. Only supratentorial tumors were included in the initial and downstream regression analyses. All significant variables on univariate analysis were included in the final multivariate model. Patient age (years), tumor volume (cubic centimeters), number of tumors, time to surgery (days), and length of follow-up (months) were analyzed as continuous variables. Survival differences between patient cohorts were tested using the Gehan-Bres-

TABLE 1. Demographic, tumor, and clinical characteristics of the cohort

Characteristic	Value
Demographic	
Age at surgery, yrs	60 ± 11
Sex	
Male	141 (40.5)
Female	207 (59.5)
Tumor	
Primary cancer type	
NSCLC	118 (33.9)
Melanoma	92 (26.4)
Breast adenocarcinoma	82 (23.6)
Gastrointestinal	28 (8.0)
Esophageal	8 (2.3)
Gastric	4 (1.1)
Colorectal	16 (4.6)
Gynecological	12 (3.4)
Ovarian	6 (1.7)
Endometrial	3 (0.9)
Cervical squamous cell carcinoma	3 (0.9)
Renal cell carcinoma	13 (3.7)
Urothelial carcinoma	12 (3.4)
Tumor laterality	
Rt	186 (53.4)
Lt	162 (46.5)
Tumor location	
Frontal	108 (31)
Perirolandic	29 (27)*
Parietal	66 (19)
Temporal	47 (13.5)
Occipital	41 (11.8)
Cerebellar	79 (22.7)
Intraventricular	4 (1.1)
Insular	3 (0.9)
Total no. of brain metastases at surgery	3 ± 2.7
Surgical tumor vol, cm^3	21.9 ± 17.8
Hemorrhage w/in surgical tumor	146 (42)
Tumor progression	
Local	85 (24.4)
Distant	178 (51.1)
Clinical	
Resection status	
Gross total	269 (77.3)
Subtotal	79 (22.7)
Radiotherapy prior to surgery	80 (23)
Postop radiotherapy	225 (64.7)
Radiation necrosis	79 (22.7)
Checkpoint inhibitor use	
Prior	18 (5.2)
Postop	61 (17.5)
Clinical (*continued*)	
Anticonvulsant use	
Preop	209 (60)
Levetiracetam	189 (90)†
Phenytoin	12 (5.7)†
Lamotrigine	5 (2.4)†
Divalproex sodium	2 (1)†
Lacosamide	1 (0.47)†
Postop at 6 mos	149 (42.8)
Levetiracetam	134 (90)‡
Phenytoin	13 (8.7)‡
Carbamazepine	2 (1.3)‡
Lacosamide	2 (1.3)‡
Phenobarbital	1 (0.67)‡
Topiramate	1 (0.67)‡
Valproic acid	1 (0.67)‡

Values are shown as number (percent) or mean ± SD.
* Percent of patients with frontal tumors is shown.
† Percent of patients who received preoperative anticonvulsants is shown.
‡ Percent of patients who received postoperative anticonvulsants at 6 months is shown.

low-Wilcoxon test. All statistical analyses were performed using R version 3.5.1 (The R Foundation), and graphs were created with GraphPad Prism (GraphPad Software, Inc.).

Results

Cohort Composition and Follow-Up

Data were retrospectively analyzed for 348 consecutive patients who underwent surgical treatment of brain metastases between 1998 and 2019. A comprehensive list of demographic, clinical, and tumor characteristics is shown in Table 1. The cohort had a mean age of 60 years at time of surgery and was 59% female and 41% male. The mean and median follow-up durations after the date of surgery for the cohort were 22 months and 10.8 months, respectively. Regarding the primary tumor types, 118 (33.9%) patients had non–small cell lung carcinoma (NSCLC), 92 (26.4%) melanoma, 82 (23.6%) breast adenocarcinoma, 28 (8.0%) gastrointestinal cancers, 13 (3.7%) renal cell carcinoma, 12 (3.4%) gynecological cancers, and 12 (3.4%) urothelial carcinoma. The median surgically resected tumor volume at time of surgery was 15.4 cm^3, 46.5% of lesions were left sided, and the most frequent tumor location was within the frontal lobe (31%). Radiation necrosis occurred in 79 (22.7%) tumors postoperatively. At the time of surgery, the median total number of brain metastases present was 2.

Rates of Seizure and AED Use

Overall, 84 (24%) patients with brain metastases experienced seizures prior to operation. At 6 months postop-

TABLE 2. Clinical variables tested for associations with preoperative seizures

Variable*	OR (95% CI)	p Value
Primary cancer		
Melanoma	1.8 (1.1–3.1)	0.02
BRAF mutation	0.74 (0.3–1.8)	0.52
NSCLC	0.58 (0.32–1.0)	0.06
EGFR mutation	0.64 (0.03–3.9)	0.69
KRAS mutation	3.9 (1.0–14.0)	0.04
Renal cell carcinoma	0.94 (0.21–3.2)	0.97
Gastrointestinal	0.81 (0.29–2.0)	0.66
Urothelial	0.66 (0.03–8.1)	0.99
Gynecological	2.3 (0.68–7.5)	0.16
Breast carcinoma	1.1 (0.59–4.1)	0.81
Clinical & demographic variables		
Male (vs female)	1.2 (0.74–2.0)	0.42
Prior hemorrhage	1.7 (1.0–2.7)	0.04†
Prior systemic checkpoint inhibitor treatment	1.4 (0.9–2.9)	0.08
Age	0.98 (0.96–1.0)	0.09
Time to surgery (days)	0.99 (0.99–1.0)	0.11
Systemic disease	1.0 (0.6–1.7)	0.99
Prior radiotherapy	1.8 (1.0–3.1)	0.04
Total no. of metastases	1.1 (0.95–1.2)	0.55
Multiple metastases	1.4 (0.84–2.2)	0.21
Tumor vol (cm^3)	1.7 (0.9–1.1)	0.32
Tumor location		
Lt side (vs rt side)	1.2 (0.72–1.9)	0.50
Frontal	1.9 (1.1–3.2)	0.05†
Parietal	1.7 (0.95–3.1)	0.07
Occipital	1.6 (0.77–3.3)	0.18
Temporal	0.5 (0.2–1.0)	0.07

* All continuous variables were tested for associations with 1.0-unit increases.
† Significant ($p \leq 0.05$) in the final multivariate model.

eratively, 40 (11.4%) patients were experiencing seizures. Among these, 22 patients (55%) had experienced preoperative seizures. There was a higher incidence of seizures in patients with multiple metastases compared with those with a single metastasis, both preoperatively (26% vs 18%, respectively) and postoperatively at 6 months (12% vs 7%). Regarding AED use, 209 patients (60%) received preoperative treatment and 149 (42.8%) were receiving treatment at 6-month follow-up. Regarding Engel classification scores at the time of last follow-up among patients who experienced preoperative seizures, 48 were categorized as Engel class I (free of disabling seizures), 16 Engel class II (rare disabling seizures), 12 Engel class III (worthwhile improvement), and 8 Engel class IV (no worthwhile improvement). Overall, tumor treatments (including resection, radiotherapy, and medical therapy) together with AED administration resulted in a favorable (Engel class I or II) seizure outcome in 74% of patients 6 months postoperatively and in 76% at last follow-up. In univariate regression analysis, no associations between Engel class and tumor type or location were found.

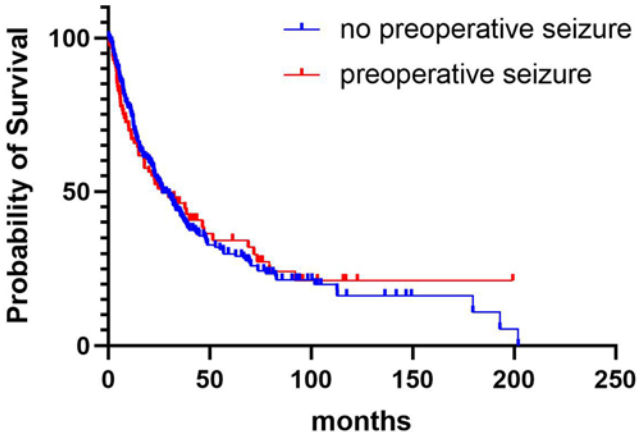

FIG. 1. Survival of patients with and without preoperative seizures from the time of diagnosis of brain metastases. Figure is available in color online only.

Factors Associated With Preoperative Seizures

In univariate analysis, frontal lobe location ($p = 0.05$), melanoma ($p = 0.02$), *KRAS* mutation in lung carcinoma ($p = 0.04$), intratumoral hemorrhage ($p = 0.04$), and prior radiotherapy ($p = 0.04$) were associated with seizure presentation. No factor was associated with decreased seizure risk, although a trend was noted in patients with NSCLC metastases ($p = 0.06$). By using a comprehensive list of clinical, demographic, and morphological variables (Table 2), the multivariate model confirmed the independent effects of tumor location in the frontal lobe and presence of intratumoral hemorrhage as predictors of preoperative seizures (Table 2). No independent associations were found with tumor volume, number of tumors, tumor type, or other anatomical tumor location. There was no difference in overall survival from the time of surgery between those patients who experienced preoperative seizures and those who did not ($p = 0.6$) (Fig. 1).

Factors Associated With Postoperative Seizures

In univariate regression analysis, postoperative checkpoint inhibitor use ($p = 0.002$), prior radiotherapy ($p = 0.05$), older age ($p = 0.002$), presence of multiple metastases ($p = 0.01$), distant CNS progression ($p = 0.004$), and parietal lobe tumor location (42% of which were dominant) ($p = 0.002$) predicted postoperative seizure occurrence. Multivariate analysis confirmed checkpoint inhibitor use and parietal lobe location (independent of dominance or extent of resection) as significant predictors of seizures at 6 months postoperatively (Table 3).

Discussion

Seizures due to brain metastases carry significant morbidity.[1,5,11] Quality of life is worse in patients with seizures than in the general population but is near normal when seizures are well controlled.[5,12] A thorough understanding

TABLE 3. Clinical variables tested for associations with seizures at 6 months postoperatively

Variable	OR (95% CI)	p Value
Primary cancer		
Melanoma	1.1 (0.5–2.2)	0.89
BRAF mutation	0.98 (0.4–3.7)	0.98
NSCLC	0.62 (0.5–1.8)	0.28
EGFR mutation	0.98 (0.4–9.9)	0.94
KRAS mutation	1.1 (0.1–6.9)	0.94
Renal cell carcinoma	0.69 (0.04–3.9)	0.63
Gastrointestinal	1.45 (0.63–4.1)	0.52
Urothelial	0.84 (0.02–6.9)	0.99
Gynecological	2.9 (0.17–5.0)	0.21
Breast carcinoma	1.3 (0.6–2.7)	0.49
Clinical & demographic variables		
Male (vs female)	0.79 (0.38–1.6)	0.51
Postop systemic checkpoint inhibitor treatment	2.7 (1.2–4.9)	0.004†
Age	0.95 (0.93–0.98)	0.002
Time to surgery (days)	0.99 (0.99–1.0)	0.28
Gross-total resection	1.1 (0.5–2.7)	0.75
Systemic disease	1.1 (0.51–2.1)	0.35
Prior radiotherapy	2.0 (0.98–4.1)	0.05
Postop radiotherapy	1.5 (0.68–3.4)	0.36
Local progression	1.7 (0.80–3.4)	0.16
Distant progression	2.2 (1.1–4.8)	0.04
Length of follow-up	1.0 (0.99–1.0)	0.365
No. of metastases	1.0 (0.98–1.1)	0.125
Presence of multiple metastases	2.4 (1.2–5.2)	0.02
Tumor vol (cm^3)	1.2 (0.9–1.7)	0.86
Tumor location		
Lt side	1.8 (0.9–3.5)	0.11
Frontal	1.3 (0.61–2.5)	0.522
Parietal	3.2 (1.5–6.7)	0.002†
Occipital	1.2 (0.37–3.0)	0.79
Temporal	0.14 (0.01–0.65)	0.05

* All continuous variables were tested for associations with 1.0-unit increases.
† Significant ($p \leq 0.05$) in the final multivariate model.

of the rates and predictors of seizures, as well as the likelihood of seizure freedom after treatment, is therefore critical for clinicians who treat patients with metastatic brain tumors. Despite this, few current studies have focused on solely brain metastasis–related seizures. Existing studies have primarily examined the frequency of seizures in relation to tumor types and characteristics and have failed to control for several important variables that may affect epileptogenesis.[1,13] In the aforementioned studies, several associations between brain metastases and epileptic seizures have been described.[1–3,6,14] Previous reports have described epileptogenic associations with melanoma, NSCLC, multiple metastatic lesions, radiotherapy, and location in the frontal and temporal lobes.[1,2,6,11,15,16] A summary of previous reports that examined seizure risk in patients with metastatic brain tumors is shown in Table 4.

In this study, preoperative seizures were seen in almost one-quarter of patients, and postoperative seizures occurred in roughly 10% of patients by 6 months postoperatively (55% of these patients experienced preoperative seizures) despite resection and adjuvant therapy. Another main objective of this study was to identify risk factors associated with preoperative seizures. By using univariate regression analysis, we found that frontal lobe location, melanoma tumors, *KRAS* mutations in NSCLC, hemorrhage, and prior radiotherapy were associated with preoperative seizures. The final multivariate regression model confirmed the independent effects of frontal lobe location and intratumoral hemorrhage at 6 months postoperatively.

Additionally, we aimed to identify factors associated with persistent seizures after surgery. At 6 months postoperatively, checkpoint inhibitor use, preoperative radiotherapy, distant progression, and tumor location in the parietal lobe predicted seizures. The final multivariate regression model confirmed the independent effects of checkpoint inhibitor use and parietal lobe location at 6 months postoperatively.

Our findings are consistent with those of studies that have shown a higher prevalence of epilepsy in patients with metastatic tumors in the frontal lobe. A similar trend has been described for other types of brain tumor in the frontal lobe, as well as for noncancerous lesions in the frontal lobe.[5,17–20] It is unclear why patients with frontal lobe lesions may be more likely to present with seizures. Although inherent factors such as the circuitry of the frontal lobe may predispose patients to seizures, it is also pos-

TABLE 4. Summary of previous studies that classified seizure risk in patients with metastatic brain tumors

Authors & Year*	No. of Patients	Incidence of Seizures (%)	Notable Brain Metastasis–Seizure Associations
Wolpert et al., 2020[3]	799	28	Single brain metastasis & tumoral hemorrhage in nonoperative tumors; supratentorial tumors & lung adenocarcinoma tumors in preop patients; supratentorial tumors & incomplete resection in postoperative patients
Ajinkya et al., 2021[13]	187	29.4	Melanoma & hemorrhagic brain metastases
Lamda et al., 2021[16]	1453	11.6	Melanoma, >4 brain metastases, brain metastases in a high-risk location, & lack of local-directed brain therapy
Oberndorfer et al., 2002[6]	470	24	Melanoma, lung adenocarcinoma, & gastrointestinal brain metastases
Lynam et al., 2007[14]	35	34	NSCLC

* All studies were retrospective reviews of clinical charts.

sible that tumors in this region are less likely to encroach on an eloquent cortex and are thus more likely to exist undetected until a seizure occurs.[5,19]

Additionally, the association between hemorrhagic tumor and seizures is consistent with the results of prior studies. Excitation of neural tissue by blood products is a frequent occurrence in many entities known to cause seizures.[21,22] Numerous mechanisms for the epileptogenic effect of blood on the brain parenchyma have been proposed, such as downstream signaling effects caused by albumin and a more direct effect of heme or iron on neurons.[23,24] This association may explain why melanoma, a metastatic tumor that was associated with hemorrhage and seizures in a previous series, was associated with seizures on univariate but not multivariate regression.[11]

KRAS-mutant lung carcinoma was associated with preoperative seizures. This finding has not been reported in any prior studies. KRAS and MAP-K pathway alterations have been reported as genetic and oncological causes of epilepsy, although it is unknown whether any downstream signaling effect from KRAS leads to this epileptogenic effect. Overall, the epileptogenic impact of different tumor mutations has been largely understudied.[25,26] NSCLC has been reportedly associated with both increased and decreased risk of seizures.[2,3,6,15,16] Variable mutation profiles may explain this dichotomy. Overall, this is an area that warrants further study with a larger cohort of lung cancer patients.

To our knowledge, this is the first association described between checkpoint inhibitor use and postoperative seizures in patients with resected brain metastases. Previous reports have indicated potential links between metastatic brain tumors treated with checkpoint inhibitors and seizures, although these links were noted in a limited number of patients and have not undergone any significant statistical testing.[27] Although no clear underlying mechanism has been identified, several hypotheses regarding why checkpoint inhibitors may increase seizure risk have been previously described. Increased immune cell infiltration may generate an inflammatory microenvironment with increased perilesional edema and release of proconvulsive cytokines.[27,28] Additionally, epileptic seizures may be caused by autoantibody-mediated autoimmune encephalitis.[29,30] Either of these potential mechanisms would explain why seizures in the setting of checkpoint inhibitor use often respond more favorably to steroids than to traditional AEDs.[27] Although this finding was significant on multivariate regression analysis, it should be noted that the majority of patients who were prescribed checkpoint inhibitors had either melanoma or NSCLC. This is a potential limitation of the generalizability of this finding.

The association of parietal lobe tumors with postoperative seizures is somewhat challenging to explain. Although parietal lobe tumors have been linked to seizures in prior studies, there is no obvious reason why tumors in this region should be more epileptogenic 6 months postoperatively than cortical and temporal lobe tumors, which traditionally have been more associated with seizures.[5,6,31–33] Other studies have shown less successful control of postoperative seizures in patients with primary brain tumors of the parietal lobe, as well as in those with primary parietal lobe epilepsy, although the explanations for these findings were largely speculative.[34,35] Investigators concluded that additional diagnostic tools, including imaging and neuromonitoring, may be key to achieving satisfactory seizure outcomes of parietal lobe surgery.[32,34,35] The current study suggests that failure to obtain gross-total resection is not the reason for worse outcomes in patients with parietal metastases. Surgery on the parietal lobe may be more likely to lead to injury, inflammation, or edema in adjacent white matter, thereby leading to epileptiform changes.[31,32] Alternatively, patients with parietal lobe lesions may experience cognitive dysfunction, which ultimately affects their ability to take their AEDs.[36] Regardless of the causative mechanism, this correlation warrants further study in future reports.

Interestingly, there was no association between tumor volume and seizures, and no significant differences in the numbers of metastases were observed between patients who did or did not present with seizures. Additionally, no association was found between radiation necrosis and postoperative seizures at 6 months. No associations between seizure and any primary cancer type were found with the multivariate model, although findings on univariate regression were identified. Finally, extent of resection had no impact on seizure outcomes at 6 months postoperatively. These data contrast with those of studies that found associations between seizure outcomes and extent of tumor resection and radiation necrosis, as well as with tumor number, size, and type and both increased and decreased risk of seizures.[1,3,6,33]

No difference in survival was found between those patients who experienced preoperative seizures and those who did not. This finding contrasts with data from several studies that reported increased survival in patients with primary brain tumors and preoperative seizures.[37–39] A likely explanation for this difference is that patients with seizures due to a metastatic lesion may have an overall cranial or systemic tumor burden that exceeds any benefit conferred by a seizure, thereby leading to earlier discovery of a tumor.[40,41]

The treatment of metastatic brain tumors continues to evolve, with the decision regarding surgical treatment influenced by extent of disease, presence of neurological symptoms, and the quality-of-life goals of the patient. This study, like most other tumor treatment series, suggests that a substantial number of patients with metastatic brain metastases continue to have seizures despite taking seizure medications.[1,3,13] Validation of our findings in larger prospective studies could enable a personalized precision medicine approach to AED treatments for patients with brain metastases who are undergoing surgery. For example, future studies should address whether patients at risk for residual postoperative seizures (but with reasonable life expectancy and quality of life) should undergo resections that incorporate electrophysiological recording to allow for treatment of adjacent epileptogenic tissue.[4,5,13] Additionally, it may be prudent for patients who require checkpoint inhibitors to be provided with AEDs in advance.

This study should be interpreted in the context of several limitations. This was a retrospective analysis of patients

from a single high-volume treatment center. As such, this study was not designed to determine whether the observed risk factors are causal. In addition, the retrospective nature of the study predisposed it to recall bias. We examined a cohort over 11 years, which carries the advantage of capturing a larger and more representative patient sample. However, although the natural course of brain metastases and seizures has probably not changed over this time, the diagnostic and surgical guidelines may have. This must be considered when interpreting our results regarding postoperative seizures. The cohort that presented with seizures, although derived from a large group, was not large enough to provide adequate power to assess tumor or treatment subgroups. Additionally, several demographic and morphological variables that likely modified the threshold for seizures were unavailable in the database of medical records included in this study. These variables included demographic factors (e.g., family history of seizures, medications known to provoke seizures) and pathologic factors such as presence of cortical hemosiderin deposits, acute or chronic edema, and gliosis.

Conclusions

Although metastatic and primary brain tumors share some of the risk factors of preoperative and postoperative seizures, their risk factor profiles do not entirely overlap. Patients with metastatic tumors in the frontal lobe and hemorrhagic brain metastases are more likely to experience seizures preoperatively. Additionally, metastatic brain tumors in the parietal lobe and the use of checkpoint inhibitors were associated with seizures at 6 months postoperatively. These findings should be explored further in clinical studies focused on seizure control in these patients. Hopefully, the results of this study can be used to improve the quality of life of patients with metastatic brain tumors.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Aghi, JH Garcia, Morshed, Chung. Acquisition of data: JH Garcia, Morshed, Chung, Millares Chavez, Sudhakar, Saggi, Avalos, Gallagher. Analysis and interpretation of data: JH Garcia, Morshed, Daras. Drafting the article: JH Garcia. Critically revising the article: Aghi, JH Garcia, Morshed, Young, PA Garcia. Reviewed submitted version of manuscript: Aghi, JH Garcia, Morshed, Sudhakar, Saggi, Avalos, Gallagher, Young, Daras, McDermott, PA Garcia, Chang. Approved the final version of the manuscript on behalf of all authors: Aghi. Statistical analysis: JH Garcia. Administrative/technical/material support: McDermott, Chang.

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