CrossMark

Risk Factors for Preoperative Seizures and Loss of Seizure Control in Patients Undergoing Surgery for Metastatic Brain Tumors

Adela Wu[1], Jon D. Weingart[2], Gary L. Gallia[2], Michael Lim[2], Henry Brem[2], Chetan Bettegowda[2], Kaisorn L. Chaichana[2]

■ OBJECTIVE: **Metastatic brain tumors are the most common brain tumors in adults. Patients with metastatic brain tumors have poor prognoses with median survival of 6–12 months. Seizures are a major presenting symptom and cause of morbidity and mortality. In this article, risk factors for the onset of preoperative seizures and postoperative seizure control are examined.**

■ METHODS: **Adult patients who underwent resection of one or more brain metastases at a single institution between 1998 and 2011 were reviewed retrospectively.**

■ RESULTS: **Of 565 patients, 114 (20.2%) patients presented with seizures. Factors independently associated with preoperative seizures were preoperative headaches ($P = 0.044$), cognitive deficits ($P = 0.031$), more than 2 intracranial metastatic tumors ($P = 0.013$), temporal lobe location ($P = 0.031$), occipital lobe location ($P = 0.010$), and bone involvement by tumor ($P = 0.029$). Factors independently associated with loss of seizure control after surgical resection were preoperative seizures ($P = 0.001$), temporal lobe location ($P = 0.037$), lack of postoperative chemotherapy ($P = 0.010$), subtotal resection of tumor ($P = 0.022$), and local recurrence ($P = 0.027$). At last follow-up, the majority of patients (93.8%) were seizure-free. Thirty patients (5.30%) in total had loss of seizure control, and only 8 patients (1.41%) who did not have preoperative seizures presented with new-onset seizures after surgical resection of their metastases.**

■ CONCLUSIONS: **The brain is a common site for metastases from numerous primary cancers, such as breast and lung. The identification of factors associated with onset of preoperative seizures as well as seizure control postoperatively could aid management strategies for patients with metastatic brain tumors. Patients with preoperative seizures who underwent resection tended to have good seizure control after surgery.**

Key words
- Brain tumor
- Cancer
- Engel class
- Metastatic
- Seizures
- Surgery

Abbreviations and Acronyms
AED: Antiepileptic drug
CI: Confidence interval
KPS: Karnofsky Performance Scale
OR: Odds ratio
RPA: Recursive partitioning analysis

From the [1]Johns Hopkins University School of Medicine, Baltimore, Maryland; and [2]Department of Neurosurgery, Neuro-Oncology Outcomes Laboratory, Johns Hopkins University, Baltimore, Maryland, USA

To whom correspondence should be addressed: Kaisorn L. Chaichana, M.D. [E-mail: kaisorn@jhmi.edu]

*Citation: World Neurosurg. (2017) 104:120-128.
http://dx.doi.org/10.1016/j.wneu.2017.05.028*

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

INTRODUCTION

Metastatic brain tumors are among the most common intracranial tumors in adults, with an incidence ranging between 9% and 17% per year.[1,2] Lung, breast, and melanoma comprise up to 75% of the primary cancers that metastasize to the brain.[3] Patients with brain metastases have poor prognoses, with median survival of 6–12 months.[4-6] A major source of morbidity and mortality for patients with metastatic brain tumors is seizures.[7] Seizures occur in approximately 20%–35% of patients with metastatic brain tumors.[7] Seizures are also particularly concerning because antiepileptic drugs (AEDs) can impact quality of life and interfere with chemotherapeutic regimens. Therefore, it is imperative to understand the risk factors for developing preoperative seizures and the factors associated with seizure control. It is especially important for metastatic brain tumors because the presenting primary cancers have a propensity for both local and distal recurrences.[4-6]

The goals of this study are to therefore: 1) characterize the demographic information and epidemiology of preoperative seizures for patients with metastatic brain tumors; 2) identify any risk factors associated with preoperative seizures; 3) determine the effect of surgery on seizure control; and 4) identify any risk factors for loss of seizure control after surgical resection. Our retrospective study includes patients who have received any number of surgical operations for resection of metastatic brain tumors and those who have undergone radiation therapy or chemotherapy in addition to surgery.

MATERIALS AND METHODS

Patient Selection

All adult patients (age >18 years) who underwent surgical resection of one or more intracranial metastases at one institution between 1998 and 2011 were included in this retrospective study. Surgery was pursued for patients who presented with intracranial lesions causing symptoms (i.e., intolerable headaches, weakness, speaking difficulties, vision deficits) or at risk of causing symptoms either from location or swelling. The general goal of surgical resection was to achieve complete resection of the tumor without causing new iatrogenic deficits. Surgery was pursued for multiple metastases when the metastases were easily accessible and/or causing symptoms. Patients advised to undergo surgery typically had at least 3 months of expected survival based on systemic imaging (positron emission tomography, chest/abdomen/pelvis imaging).

Recorded Variables

Clinical and operative notes for each patient were reviewed retrospectively under institutional review board approval. Data collected and recorded included demographic information, primary cancer location, systemic disease, presenting symptoms, comorbidities, perioperative data, radiologic and pathology data, and postoperative clinical follow-up data on seizure characteristics, control, and management. Extent of resection is defined as follows: gross total resection (removal of all visible tumor with no residual tumor on postoperative radiology report), near total resection (removal of all but ≥10% of visible tumor), and subtotal resection (evidence of residual tumor on postoperative radiology report). Karnofsky Performance Scale (KPS) numbers were ascribed during the clinic visit before surgery. In addition, the recursive partitioning analysis (Radiation Therapy Oncology Group recursive partitioning analysis [RPA]) classification, a scale used for prognosis for patients with cancer, was recorded for each patient.[8] Information pertinent to seizures included type and frequency of seizures, types of medications used for the management of seizures, and parameters of seizure control. The Engel Epilepsy Surgery Outcome Scale consists of the following gradations: Class I (seizure-free), Class II (rare disabling seizures), Class III (worthwhile seizure reduction), and Class IV (no worthwhile improvement). Radiologic data included tumor volume, tumor size, and number and location of nonprimary tumors and surgical sites. Primary outcome variables were status of postoperative seizure control and duration of seizure control. Patients with controlled seizures preoperatively were defined as those who did not experience any seizures within the 1 month before surgery with AED use. Uncontrolled seizures included those not suppressed by AEDs when patients experienced one or more seizures in the month before surgery.

Statistical Analysis

All statistical analyses were performed with IBM SPSS Statistics v22.0 (IBM Corp., Armonk, New York, USA) and GraphPad Prism (GraphPad Software, Inc., La Jolla, California, USA). Demographic and summary data were presented as mean ± standard deviation for parametric data and median for nonparametric data. The Student t test was used for comparing parametric data, and the Mann−Whitney U test was used for nonparametric data.

To determine the independent risk factors associated with preoperative presenting seizures and with loss of seizure control after surgery, univariate logistic regression analysis was first performed. Variables associated with seizures in univariate logistic regression ($P < 0.10$) were then inputted into a stepwise multivariate logistic regression analysis. Factors with $P < 0.05$ were considered statistically significant.

Seizure control over time was analyzed with Kaplan-Meier survival curves and log rank analysis. Loss of seizure control was defined as an increased in Engel classification or the presence of new postoperative seizures. All time points were measured from the date of surgery. Univariate proportional hazards regression analysis (Cox) was performed. Variables associated with seizure control in univariate analysis ($P < 0.10$) were then inputted into a stepwise multivariate proportional hazards regression model. The Engel classification was dichotomized for this analysis into Class I (seizure-free) and Class II−IV (retaining seizures). Factors with $P < 0.05$ were considered statistically significant.

RESULTS

Patient Population

Patient demographics are summarized in Table 1. A total of 565 patients underwent at least one surgical resection for metastatic brain tumors, with 114 patients (20.2%) presenting with preoperative seizures. Within the group of patients presenting with seizures, the seizure types included simple partial seizure (62 patients; 55.2%), complex partial seizure (11 patients; 9.65%), and secondary generalized seizure (41 patients; 36.0%). The median number of preoperative seizures among the 114 patients was 1 ± 1.09 (interquartile range 1−2) seizures before surgery. Average age among patients with no presenting seizures was 58 ± 12 years by date of surgery, whereas those with preoperative seizures was 58 ± 12 years ($P = 0.937$). The average age of the 3 patients with uncontrolled seizures was 55 ± 6 years. Of the 565 patients, 266 (47.1%) were men.

The average preoperative KPS was 75, with range of 20−90. A total of 211 patients (37.3%) presented with motor deficits, 59 (10.4%) patients with sensory deficits, 97 (17.2%) patients with language deficits, 124 (21.9%) patients with cognitive deficits, and 106 (18.8%) patients with visual deficits. The primary cancer of origin included adenocarcinoma (161; 28.5%), cancer with squamous features (44; 7.79%) and, more specifically, neuroendocrine (7; 1.23%); non−small cell lung cancer (213; 37.7%); small cell lung cancer (25; 4.42%); breast (80; 14.2%); gastrointestinal cancers including pancreatic, bile duct, stomach, esophagus, small intestine, and liver (50; 8.85%); parotid gland (6; 1.06%); skin (81; 14.3%); renal (41; 7.26%); reproductive organs (18; 3.19%); hematogenous (8; 1.42%); bone (15; 2.65%); bladder (8; 1.42%); genitourinary (49; 8.67%); prostate (7; 1.24%); thyroid (8; 1.42%);

Table 1. Patient Demographic Information for Those Presenting with (114) and without (451) Preoperative Seizures

Characteristics	Preoperative Seizures				*P* Value Associated with Any Seizure
	No Seizures, *n* (%) 451 (79.8)	Any, *n* (%) 114 (20.2)	Controlled, *n* (%) 111 (19.6)	Uncontrolled, *n* (%) 3 (0.53)	
Age, years, mean	58.443 ± 12.34	58.545 ± 12.38	58.629 ± 12.51	55.426 ± 6.16	0.937
Male	218 (38.6)	48 (8.50)	47 (8.32)	1 (0.18)	0.139
Associated symptoms					
Headache	179 (31.7)	29 (5.13)	29 (5.13)	0 (0)	0.003
Motor def	161 (28.5)	50 (8.84)	49 (8.67)	1 (0.18)	0.067
Language def	82 (14.5)	15 (2.65)	15 (2.65)	0 (0)	0.126
Cognitive def	108 (19.1)	16 (2.83)	16 (2.83)	0 (0)	0.013
Sensory def	45 (7.96)	14 (2.48)	13 (2.30)	1 (0.18)	0.286
Visual def	95 (16.8)	11 (1.95)	11 (1.95)	0 (0)	0.003
Type of primary cancer					
Adenocarcinoma	127 (22.5)	34 (6.02)	33 (5.84)	1 (0.18)	0.299
Squamous	34 (6.02)	10 (1.77)	10 (1.77)	0 (0)	0.344
Neuroendo	5 (0.88)	2 (0.35)	2 (0.35)	0 (0)	0.409
NSCLC	161 (28.5)	52 (9.2)	50 (8.84)	2 (0.35)	0.033
Breast	62 (11.0)	18 (3.19)	17 (3.01)	1 (0.18)	0.335
GI	43 (7.61)	7 (1.23)	7 (1.24)	0 (0)	0.170
Skin	75 (13.3)	12 (2.12)	12 (2.12)	0 (0)	0.067
Renal	33 (5.84)	8 (1.41)	8 (1.42)	0 (0)	0.550
Repro	15 (2.65)	3 (5.31)	3 (0.53)	0 (0)	0.492
Heme	7 (1.23)	1 (0.18)	1 (0.18)	0 (0)	0.497
Bone	13 (2.30)	2 (0.35)	2 (0.35)	0 (0)	0.389
Bladder	5 (0.88)	3 (0.53)	3 (0.53)	0 (0)	0.206
Other	5 (0.88)	1 (0.18)	1 (0.18)	0 (0)	0.651
No. met sites	0.975 ± 1.32	0.719 ± 1.22	0.703 ± 1.23	1.33 ± 0.577	0.060
Radiographics					
Tumor size, mean, cm	3.29 ± 1.62	2.81 ± 1.32	2.77 ± 1.29	5.00 ± 1.56	0.005
Tumor location					
Frontal	186 (32.9)	59 (10.4)	57 (10.1)	2 (0.35)	0.028
Parietal	105 (18.6)	41 (7.26)	40 (7.08)	1 (0.18)	0.005
Temporal	86 (15.2)	12 (2.12)	12 (2.12)	0 (0)	0.019
Occipital	88 (15.6)	9 (1.59)	9 (1.59)	0 (0)	0.001
Thalamus	6 (1.06)	0 (0)	—	—	0.257
Skull base	21 (3.71)	1 (0.18)	1 (0.18)	0 (0)	0.053
Seizure type					
Simple partial	—	63 (11.2)	61 (10.8)	2 (0.35)	—
Complex partial	—	11 (1.95)	11 (1.95)	0 (0)	—
Secondary Generalized	—	41 (7.26)	40 (7.08)	1 (0.18)	—

Continues

Table 1. Continued

Characteristics	Preoperative Seizures				*P* Value Associated with Any Seizure
	No Seizures, *n* (%) 451 (79.8)	Any, *n* (%) 114 (20.2)	Controlled, *n* (%) 111 (19.6)	Uncontrolled, *n* (%) 3 (0.53)	
Perioperative outcomes					
Extent of resection					
Gross total	309 (54.7)	89 (15.8)	88 (15.6)	1 (0.18)	0.035
Near total	89 (15.8)	16 (2.83)	15 (2.65)	1 (0.18)	0.176
Subtotal	35 (6.19)	8 (1.42)	7 (1.24)	1 (0.18)	0.478
New deficit					
Motor def	31 (5.49)	17 (3.09)	17 (3.01)	0 (0)	0.007
Language def	12 (2.12)	4 (0.71)	4 (0.71)	0 (0)	0.410
Visual def	11 (1.95)	2 (0.35)	2 (0.35)	0 (0)	0.006
Time to death, mean, months	14.2	12.6	12.5	13.4	0.417
Time to local recurrence, mean, months	10.6	9.95	9.87	12.9	0.763
Time to distal recurrence, mean, months	9.82	9.28	5.73	9.38	0.787

def, deficit; neuroendo, neuroendocrine; NSCLC, non—small cell lung cancer; GI, gastrointestinal; met, metastasis; Heme, hematogenous.

and other cancers (6; 1.06%). The average number of intracranial metastatic sites per patient was 1.73 tumors. The average size of an intracranial tumor was 3.19 ± 1.58 cm^2.

The indications for which patients underwent surgical resection of their brain metastases were for neurologic decline (332; 58.8%), symptoms of mass effect (91; 16.2%), seizure control (47; 8.32%), palliative surgery (22; 3.89%), where not all brain tumors were resected, and for symptoms of hydrocephalus (4; 0.71%). Gross total resection was achieved for 398 patients (70.4%). A total of 105 patients (18.6%) received near total resection, and 43 (7.61%) patients received subtotal resection. Postoperative complications included deep-vein thrombosis (12; 2.12%), pulmonary embolism (12; 2.12%), myocardial infarction (1; 0.18%), pneumonia (7; 1.23%), seizures (14; 2.48%), meningitis (1; 0.18%), surgical-site infections (6; 1.06%), intracranial hemorrhage (14; 2.48%), new motor deficit (48; 8.50%), new language deficit (16; 2.83%), and new vision deficit (13; 2.30%). Sixty-seven patients (11.9%) underwent more than one surgery for removal of metastatic brain tumors, and the number of patients who had multiple intracranial metastases removed was 53 (9.83%). A total of 181 patients (32.0%) received systemic radiation therapy before surgery, and 294 patients (52.0%) received preoperative systemic chemotherapy.

Of note, of the 178 patients presenting with more than one intracranial metastatic tumor, only 53 patients (29.8%) had multiple metastatic brain tumors resected over the course of their follow-up. Seventy-eight patients from this subpopulation (43.8%) with remaining nonsurgical treated brain lesions underwent postoperative brain radiation. Fifty-four patients of this group (30.3%) underwent postoperative chemotherapy.

In total, of the entire cohort, the number of patients who underwent chemotherapy after surgery was 198 (35.0%), whereas 360 patients (63.7%) received brain radiation after surgery, of whom 270 (47.8%) patients underwent whole brain radiation, 186 (32.9%) underwent stereotactic radiation, and 28 (4.95%) received spinal radiation. Significant factors for pursuing postoperative brain radiation management included KPS less than 60 ($P = 0.001$), primary breast cancer ($P = 0.049$), extracranial spread of disease ($P = 0.035$), RPA Class 3A or 3B ($P = 0.001$, $P = 0.047$), presenting with more than one intracranial metastatic tumor ($P = 0.047$), local disease recurrence ($P = 0.001$), and distal disease recurrence ($P = 0.001$).

The average length of hospitalization per patient was 6.33 ± 7.97 days. Of the 565 patients, 429 (75.9%) patients were discharged to home, 128 (22.7%) patients were discharged to rehab, and 8 (1.42%) patients were discharged to hospice. A total of 86 patients (15.2%) had local recurrence of disease with median time to local recurrence of 3.60 months (interquartile range 1.1—9.7). A total of 185 patients (32.7%) had distal occurrence of disease with median time to distal recurrence of 4.3 months (interquartile range 1.3—11.7). In this series, 407 (72.0%) patients died, from systemic cancer, progressive disease, or other medical complications. The median time to death was 6.9 months (interquartile range 2.7—16.9).

Average length of follow-up at the clinical institution was 151 days (interquartile range 42—454). At the time of last follow-up for each patient, 554 patients (98.1%) were Engel Class I, 1 patient (0.18%) was Engel Class II, and 10 patients (1.77%) were Engel Class III.

After surgical resection of brain metastases, 515 patients were discharged with AEDs, including levetiracetam (Keppra), phenytoin (Dilantin), gabapentin (Neurontin), oxcarbazepine (Trileptal), pregabalin (Lyrica), carbamazepine (Tegretol), and lamotrigine (Lamictal). Twenty-four (4.3%) patients were discharged with a combination of 2 or more AEDs. A total of

434 (76.8%) patients were discharged with dexamethasone (Decadron) taper with an average dose of 45 ± 54.6 mg as detailed in the discharge summary. A total of 148 patients (26.2%) were eventually weaned off AEDs.

Patients with Preoperative Seizures

Table 1 summarizes the demographics characteristics of patients with and without preoperative seizures. Patients presenting with preoperative seizures, as compared with those who did not have preoperative seizures, more commonly had headaches ($P = 0.003$), cognitive deficits ($P = 0.013$), and visual deficits ($P = 0.003$), as well as have larger tumors ($P = 0.005$) and non–small cell lung cancer primary disease ($P = 0.033$). As for perioperative outcomes, patients presenting with preoperative seizures were likely to develop new motor ($P = 0.007$) and visual deficits ($P = 0.006$). No other radiologic, pathologic, and clinical data, including time to death or recurrence, were found to be significantly different between the populations of patients with and without preoperative seizures.

Of the patients who presented with preoperative seizures, 110 patients (96.5%) were prescribed AEDs on discharge. Pregabalin/Lyrica was prescribed to 4 patients (3.51%); lamotrigine/Lamictal to 1 patient (0.88%); valproate/Depakote to 1 patient (0.88%); carbamazepine/Tegretol to 7 patients (6.14%); phenytoin/Dilantin to 61 patients (53.5%); and levetiracetam/Keppra to 60 patients (52.6%). Combination AED therapy was used in 103 patients (90.4%).

Factors Associated with Any Preoperative Seizures

The factors associated with preoperative seizures that were significant ($P < 0.10$) in univariate logistic regression analysis included presenting headaches, presence of cognitive deficits, presence of visual deficits, KPS, more than 2 metastatic brain tumor sites, tumor bone involvement, temporal lobe location, occipital lobe location, RPA Class 3, midline shift greater than 5 cm, and tumor size larger than 3 cm at its greatest dimension.

In multivariate analysis, it was determined that the risk factors independently associated with preoperative seizure were presenting headaches (odds ratio [OR] 1.661, 95% confidence interval [CI] 1.014–2.722, $P = 0.044$), presence of presenting cognitive deficits (OR 1.931, 95% CI 1.063–3.508, $P = 0.031$), 2 or more intracranial metastatic tumors (OR 2.040, 95% CI 1.164–3.584, $P = 0.013$), temporal lobe location (OR 1.812, 95% CI 1.027–3.197, $P = 0.031$), occipital lobe location (OR 2.472, 95% CI 1.285–4.755, $P = 0.010$), and bone involvement by tumor (OR 10.765, 95% CI 1.274–65.667, $P = 0.029$) (Table 2). In particular, the patients' general functional condition, as determined by KPS scores, was not associated significantly with the risk of presenting with preoperative seizures after multivariate analysis ($P = 0.515$).

Following the same univariate and multivariate analyses for risk factors significantly associated with uncontrolled preoperative seizures, the following predictors were determined: absence of frontal lobe involvement (OR 12.990, 95% CI 1.391–125.00, $P = 0.027$) and a tumor size greater than 5 cm (OR 9.024, 95% CI 1.191–68.367, $P = 0.033$).

Table 2. Predictors of Preoperative Seizures in Patients with Metastatic Brain Tumors

Variables	Odds Ratio (95% CI)	*P* Values
Associated with any preoperative seizures		
Headaches	1.661 (1.014–2.722)	0.044
Cognitive deficit	1.931 (1.063–3.508)	0.031
>2 metastatic tumors	2.040 (1.164–3.584)	0.013
Temporal lobe location	1.812 (1.027–3.197)	0.031
Occipital lobe location	2.472 (1.285–4.755)	0.010
Bone involvement	10.765 (1.274–65.667)	0.029
Associated with uncontrolled preoperative seizures		
Absence of frontal lobe involvement	12.990 (1.391–125.00)	0.027
Tumor size >5 cm	9.024 (1.191–68.367)	0.033

Factors that were independently associated with any preoperative seizures and with uncontrolled preoperative seizures are shown.
CI, confidence interval.

Seizure Outcomes

Seizure control was recorded for each patient at postoperative clinic visits using the Engel classification scale. Table 3 summarizes the number of patients within each Engel class at 1, 3, 6, 12, and 24 months. At the 1-month postoperative visit, the majority of patients (93.8%) were seizure-free (Engel Class I) with 2.5% of patients experiencing rare seizures (Engel Class II) and 3.7% of patients experiencing seizures but with worthwhile seizure frequency reduction (Engel Class III). No patients had significant amounts of seizures after surgery (Engel Class IV). The majority of patients who continued to be seen at subsequent clinic visits remained Engel Class I at 3 months (88.1%), 6 months (87.8%), 12 months (85.1%), and 24 months (92.9%). The percentage of patients who were Engel Class II was 1.69% at 3 months, 4.88% at 6 months, 0% at 12 months, and 7.14% at 24 months. The percentage of patients who were Engel Class III was 10.2% at 3 months, 7.32% at 6 months, 14.8% at 12 months, and 0% at 24 months. Among the patients who presented with uncontrolled preoperative seizures, 66.7% of the 3 patients passed away or were censored by the 12-month clinic visit, and the remaining patient continued to be seizure-free by the 24-month visit.

The median follow-up time for all patients was 5.03 months (inter-quartile range: 1.40–15.1 months). Figure 1 shows the Kaplan-Meier survival curve for seizure control (defined as maintenance of Engel Class I) in patients who presented with any preoperative seizure compared with patients without preoperative seizures. Log-rank analysis did not yield significant differences between the 2 curves. In addition, the seizure-free percentage of all patients at 1 month was 98.1%; 97.5% at 3 months; 96.7% at 6 months; 96.6% at 12 months; and 98.1% at 24 months. The seizure-free percentage of patients without preoperative seizures was 98.2% at 1 month; 99.6% at 3 months; 98.5% at 6 months; 98.7% at 12 months; and 85.8% at 24 months.

Table 3. Seizure Outcomes for Patients with Metastatic Brain Tumors

	Any Seizures					Controlled Seizures					Uncontrolled Seizures				
Month	1	3	6	12	24	1	3	6	12	24	1	3	6	12	24
No. patients	81	59	41	27	14	78	57	39	26	13	3	2	2	1	1
Engel class															
I	76 (94)	52 (88)	36 (88)	23 (85)	13 (93)	73 (94)	51 (89)	36 (92)	23 (88)	13 (100)	3 (100)	1 (50)	1 (50)	1 (100)	1 (100)
II	2 (2.5)	1 (1.7)	2 (4.9)	0 (0)	1 (7.1)	2 (2.6)	0 (0)	1 (2.6)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)
III	3 (3.7)	6 (10)	3 (7.3)	4 (15)	0 (0)	3 (3.8)	6 (10)	2 (5.1)	3 (11)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)

Seizure status, stratified by preoperative seizure status, at 1, 3, 6, 12, and 24 months after surgery are shown. Values are *n* (%).

Factors Associated with Loss of Seizure Control Postoperatively

Seizures worsened in 30 patients (5.31%), whether patients experienced completely new onset of seizures after their surgery or had worsening seizure control. Seventeen patients (56.7%) of this subgroup had new-onset postoperative seizures, and 13 patients (43.3%) had worsening seizure control after surgery. Six of those patients (75.0%) had experienced local or distal tumor recurrence. Of note, 22 patients requiring postoperative radiotherapy demonstrated loss of seizure control by the time of last follow-up; however, the association was not significant ($P = 0.175$).

The factors associated with loss of seizure control (Engel Class I vs. any other Engel class) that were significant ($P < 0.10$) in univariate logistic regression analysis included African-American race, presence of preoperative seizures, presenting motor deficits, presenting visual deficits, greater than 3 metastatic sites, metastatic brain tumors located in the frontal lobe, temporal lobe, midline shift, subtotal resection of tumor, absence of postoperative chemotherapy, as well as both local and distal disease recurrence. Of note, the general patient condition as denoted by KPS ($P = 0.115$) as well as the use of postoperative AEDs ($P = 0.252$) were not significantly associated with seizure control long-term. In stepwise multivariate analysis, it was determined that the risk factors independently associated with loss of seizure control included presenting preoperative seizures (OR 14.195, 95% CI 5.746–35.066, $P = 0.001$), temporal lobe location (OR 1.180, 95% CI 1.092–1.276, $P = 0.037$), absence of postoperative chemotherapy (OR 6.247, 95% CI 2.554–15.281, $P = 0.010$), local disease recurrence (OR 4.260, 95% CI 1.593–11.338, $P = 0.027$), and subtotal resection of tumor (OR 5.141, 95% CI 1.623–16.281, $P = 0.022$) (Table 4). No other clinical, imaging, or pathologic variables were found to be associated with loss of seizure control in this group of patients.

Tumor and Seizure Recurrence

There were 14 patients (2.47%) who had new-onset postoperative seizures with tumor recurrence. Tumor recurrence was significantly associated with loss of seizure control (OR 35.852, 95% CI 4.089–314.371, $P = 0.001$). Of the patients who developed new-onset seizures, 5 patients (29.4%) had local recurrence of their primary cancer. Nine patients with new-onset postoperative seizures (52.9%) had seizures due to distal recurrence of their primary cancer. Local disease recurrence was associated significantly with worsening seizure control and appearance of new-onset postoperative seizures ($P = 0.027$), whereas distal disease recurrence trended towards but did not achieve significance ($P = 0.071$).

DISCUSSION

Of a group of 565 patients who underwent surgery to resect metastatic brain tumors at one institution, 114 patients (20.2%) presented with preoperative seizures, of whom the vast majority was adequately managed with AEDs (111, 97.3%). Surgical resection leads to good seizure control in patients with metastatic brain tumors. Among patients with preoperative seizures, the majority remained seizure-free over the course of follow-up.

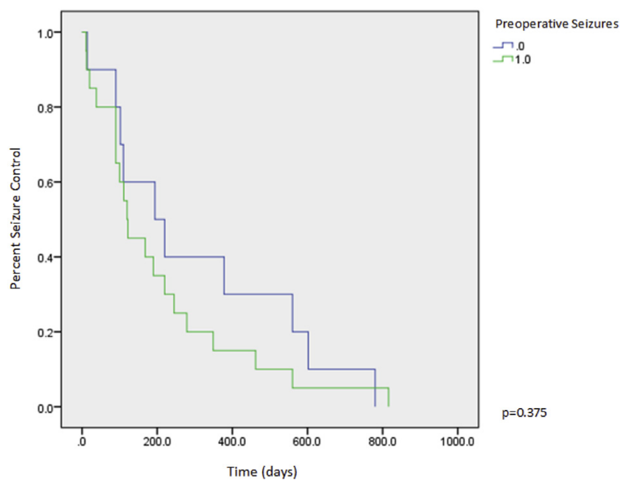

Figure 1. Loss of seizure control in patients presenting with preoperative seizures and patients without preoperative seizures. No significant difference between the time to loss of seizure control, if present, was found between the 2 groups ($P = 0.375$).

Seizures and Metastatic Brain Tumors

Brain metastases are the most common type of brain tumor for adults, with approximately 20%–40% of patients with primary cancers developing brain metastases as their disease progresses.[3,9] Among presenting symptoms, preoperative seizures are common and present in up to 20% of cases of brain metastases.[10]

Identifying significant risk factors for preoperative seizures influences patient care and management. However, there is only a small selection of publications examining associations between incidence of preoperative seizures and patient characteristics for the population of patients suffering from brain metastases. We found several risk factors for preoperative seizures in this population of patients with brain metastases.

Patients presenting with preoperative headaches and cognitive deficits were at increased risk for preoperative seizures as well. Headaches are one of the most common presenting symptoms for patients with brain metastases, accounting for up to 48% of patients with brain tumors.[11] Likewise, as many as two-thirds of patients with cancer with brain metastases suffer from concurrent cognitive deficits.[3,12] The presence of multiple metastases and tumor burden also conferred increased risk for preoperative seizures. According to another study of 109 patients with intracranial metastases from melanoma, having multiple supratentorial metastases and presenting with hemorrhage were significantly associated with seizures.[13]

Our cohort of 565 patients with metastatic brain tumors is one of the largest in existing literature. Other risk factors in our study significantly associated with preoperative seizures following multivariate analysis were preoperative headaches, preoperative cognitive deficits, more than 2 intracranial metastatic tumors, temporal and occipital lobe location for metastases, and bone involvement by tumor. In a group of 650 patients with gliomas, significant risk factors for preoperative seizures included low-grade glioma (Grades I and II), tumor volume $\leq$64 cm^3, age $\leq$60 years, and frontal location for the tumor.[14] The type of primary cancer leading to brain metastases also influences patient outcomes, including tumor control and progression-free survival, although seizure control was not specifically examined in the study of 708 patients.[5] In a separate study of patients with cancer with brain metastases, those with melanoma, lung cancer, and gastrointestinal cancers had a 21%–67% incidence of presenting seizures.[15]

Table 4. Factors That Are Independently Associated with Loss of Seizure Control After Surgical Resection of Metastatic Brain Tumors

Factors*	Odds Ratio (95% CI)	P Values
Preoperative seizures	14.195 (5.746—35.066)	0.001
Subtotal resection	5.141 (1.623—16.281)	0.022
Local disease recurrence	4.260 (1.593—11.338)	0.027
Temporal lobe involvement	1.180 (1.092—1.276)	0.037
Lack of postoperative chemotherapy	6.247 (2.554—15.281)	0.010

CI, confidence interval.
*Associated with loss of seizure control by time of last follow-up.

Seizure Control and Safety of Postoperative Intervention

Seizure control is a critical concern in managing cancer patients' disease progression. In our study, a history of preoperative seizures as well as subtotal resection of tumors led to increased risk of loss of seizure control after surgery. Brain metastases located outside the temporal lobe confer significantly less risk for loss of seizure control, but the administration of postoperative AEDs did not have a significant association with risk for loss of seizure control.

Surgery is effective in establishing seizure control. Patients in our cohort underwent surgery primarily for neurologic decline and the presence of seizures. The vast majority of patients, both with and without the presence of seizures before surgery, were seizure-free at subsequent follow-up visits. There was no significant difference in time to loss of seizure control for patients with and without preoperative seizures, given the large percentage of patients who had adequate seizure control after surgery. Also, 8 (1.77%) of 451 patients who did not present with preoperative seizures developed new-onset seizures after surgery. Given that surgical resection overall significantly improved long-term seizure control for patients with brain metastases, resection of metastatic foci is a critical palliative measure in this patient population.

There are several investigations on whether adjuvant therapies or postoperative AEDs lead to better disease and seizure control. It was found that postoperative chemotherapy was associated with less risk of loss of seizure control in our cohort. However, postoperative radiotherapy, whether stereotactic or whole-brain radiation therapy, was not significantly associated. A meta-analysis of case series focusing on seizure control after surgical resection of supratentorial meningiomas did not determine a significant link between perioperative use of AEDs and new-onset seizures and loss of seizure control.[16] There were no relevant recent studies that examined AEDs or postoperative chemotherapy and seizure control after surgery specifically for patients with metastatic brain tumors. In a study of 50 patients with brain metastases who underwent whole-brain irradiation with a stereotactic radiosurgery boost, 2% of the patient population developed seizures as a treatment effect.[17] Among 258 patients with lung cancer metastatic to the brain, 32 patients (12.4%) developed seizures after Gamma Knife radiosurgery, with leptomeningeal seeding as a significant risk factor for postoperative loss of seizure control.[6] Adjuvant therapy with ^{131}Cs brachytherapy implants after surgery for 24 patients with brain metastases resulted in 4.3% incidence rate for seizures.[18] In a study that compared surgical resection and stereotactic radiosurgery for a single brain metastasis from non–small cell lung cancer, there was a significant survival benefit in the group of patients who underwent surgery, although no data specifically on seizure profiles were presented.[19]

Brain metastases frequently recur, and recurrence of disease and tumor burden is a significant concern for patients with cancer and their caretakers. Numerous adverse complications arise from persistent disease. These include both local and distal recurrences, where the latter occurs when tumors arise outside of previously treated areas including stereotactic radiosurgery.[20] For example, 55.9% of patients with melanoma who had brain metastases experienced regrowth of their intracranial masses after surgical resection.[21] Within our cohort, local tumor recurrence is itself also a significant risk factor for loss of seizure control after surgery, and substantial percentages of the patients with new-onset seizures after surgery had disease recurrence. Specifically, local tumor recurrence was associated with worsening seizure control in both patients who did and did not present with preoperative seizures.

Strengths and Limitations

Metastatic brain tumors are the most common type of intracranial tumor in adults. Frequently, the pathology presents with preoperative seizures, which poorly affect quality of life for up to one fifth of patients with cancer. Many publications discuss the merits of seizure prophylaxis with AEDs as well as medical management and radiosurgery treatment of seizures arising from brain tumors. There is a dearth of literature specifically focusing on seizure epidemiology and management for patients who undergo surgical resection of metastatic brain tumors. The purpose of our study was to examine risk factors for preoperative seizures and loss of seizure control as well as determine whether surgical resection serves as a safe and effective way to control debilitating seizure symptoms for cancer patients with brain metastases. Understanding which patients are at greater risk of presenting with seizures before surgery and at greater risk for poor postoperative seizure control would be useful for patient management, particularly if surgery is being considered as part of the therapy.

Some limitations of this study include its retrospective design and its primary focus on surgical resection. Retrospective chart reviews inherently are subject to numerous biases and cannot identify causation and temporal relationships between risk factors and primary outcomes. To minimize bias, a strict set of inclusion criteria was used to create a patient cohort as uniform as possible, and multivariate regression analyses were used to control for confounding variables. A prospective cohort study would be necessary to gain a more complete understanding of how brain metastases influence the incidence of seizure symptoms and the loss of seizure control. In addition, this study does not investigate the parameters and risk factors involving whole-brain radiation therapy, stereotactic radiosurgery, or medical management for seizures. It is difficult to judge the effectiveness of prophylactic as well as postoperative AEDs, given how few patients in our cohort experienced uncontrolled seizures. In addition, all of the patients in this study underwent surgical resection. No patients were treated with just radiation, and therefore the effects of surgery versus radiation on seizure control were not evaluated. Overall, this study was designed to examine characteristics of patients who presented with seizures as well as to assess the effects of surgical resection on postoperative seizure control.

CONCLUSIONS

Seizures affect a substantial proportion of patients with brain metastases, negatively influencing quality of life. Our study identifies several independent risk factors for preoperative seizures, including preoperative headaches and cognitive deficits, multiple metastases, temporal and occipital tumor locations, and bone involvement by tumor. Significant risk factors for poor seizure control over time include a history of preoperative seizures, temporal lobe tumor location, subtotal surgical resection, lack of postoperative chemotherapy, and local disease recurrence. Overall, our study also shows good seizure control over time associated with surgical resection, because the vast majority of the patient cohort remained seizure-free over the course of follow-up. Given the high prevalence of brain metastases and of seizure symptoms in patients with cancer, understanding how to predict seizures and loss of seizure control is critical and can guide patient management, particularly for patients who undergo surgery for intracranial metastatic tumor resection.

REFERENCES

1. Nayak L, Lee E, Wen P. Epidemiology of brain metastases. *Curr Oncol Rep*. 2012;14:48-54.
2. Takei H, Rouah E, Ishida Y. Brain metastasis: clinical characteristics, pathological findings and molecular subtyping for therapeutic implications. *Brain Tumor Pathol*. 2016;33:1-12.
3. Gallego Perez-Larraya J, Hildebrand J. Brain metastases. *Handb Clin Neurol*. 2014;121:1143-1157.
4. Chaichana KL, Rao K, Gadkaree S, Dangelmajer S, Bettegowda C, Rigamonti D, et al. Factors associated with survival and recurrence for patients undergoing surgery of cerebellar metastases. *Neurol Res*. 2014;36:13-25.
5. Chaichana KL, Gadkaree S, Rao K, Link T, Rigamonti D, Purtell M, et al. Patients undergoing surgery of intracranial metastases have different outcomes based on their primary pathology. *Neurol Res*. 2013;35:1059-1069.
6. Lee MH, Kong D-S, Seol HJ, Nam D-H, Lee J-I. Risk of seizure and its clinical implication in the patients with cerebral metastasis from lung cancer. *Acta Neurochir (Wien)*. 2013;155:1833-1837.
7. Englot DJ, Chang EF, Vecht CJ. Epilepsy and brain tumors. *Handb Clin Neurol*. 2016;134:267-285.

8. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37:745-751.

9. Tsao MN, Lloyd N, Wong RK, Chow E, Rakovitch E, Laperriere N, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev*. 2012:CD003869.

10. Lynam LM, Lyons MK, Drazkowski JF, Sirven JI, Noe KH, Zimmerman RS, et al. Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review. *Clin Neurol Neurosurg*. 2007;109:634-638.

11. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. *Neurology*. 1993;43:1678-1683.

12. Chang EL, Wefel JS, Maor MH, Hassenbusch SJ 3rd, Mahajan A, Lang FF, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery*. 2007;60:277-283 [discussion: 283-284].

13. Goldlust SA, Hsu M, Lassman AB, Panageas KS, Avila EK. Seizure prophylaxis and melanoma brain metastases. *J Neurooncol*. 2012;108:109-114.

14. Skardelly M, Brendle E, Noell S, Behling F, Wuttke TV, Schittenhelm J, et al. Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: a retrospective observational single center study. *Ann Neurol*. 2015;78:917-928.

15. Oberndorfer S, Schmal T, Lahrmann H, Urbanits S, Lindner K, Grisold W. The frequency of seizures in patients with primary brain tumors or cerebral metastases. An evaluation from the Ludwig Boltzmann Institute of Neuro-Oncology and the Department of Neurology, Kaiser Franz Josef Hospital, Vienna. *Wien Klin Wochenschr*. 2002;114:911-916 [in German].

16. Englot DJ, Magill ST, Han SJ, Chang EF, Berger MS, McDermott MW. Seizures in supratentorial meningioma: a systematic review and meta-analysis. *J Neurosurg*. 2016;124:1552-1561.

17. Dincoglan F, Sager O, Gamsiz H, Uysal B, Demiral S, Oysul K, et al. Management of patients with ≥4 brain metastases using stereotactic radiosurgery boost after whole brain irradiation. *Tumori*. 2014;100:302-306.

18. Wernicke AG, Yondorf MZ, Peng L, Trichter S, Nedialkova L, Sabbas A, et al. Phase I/II study of resection and intraoperative cesium-131 radioisotope brachytherapy in patients with newly diagnosed brain metastases. *J Neurosurg*. 2014;121:338-348.

19. Bougie E, Masson-Côté L, Mathieu D. Comparison between surgical resection and stereotactic radiosurgery in patients with a single brain metastasis from non–small cell lung cancer. *World Neurosurg*. 2015;83:900-906.

20. Holt DE, Gill BS, Clump DA, Leeman JE, Burton SA, Amankulor NM, et al. Tumor bed radiosurgery following resection and prior stereotactic radiosurgery for locally persistent brain metastasis. *Front Oncol*. 2015;5:84.

21. Miller D, Zappala V, El Hindy N, Livingstone E, Schadendorf D, Sure U, et al. Intracerebral metastases of malignant melanoma and their recurrences—a clinical analysis. *Clin Neurol Neurosurg*. 2013;115:1721-1728.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 20 February 2017; accepted 4 May 2017

Citation: World Neurosurg. (2017) 104:120-128.
http://dx.doi.org/10.1016/j.wneu.2017.05.028

Journal homepage: ***www.WORLDNEUROSURGERY.org***

Available online: ***www.sciencedirect.com***