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.**

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

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

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%);