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Epilepsy surgery related to pediatric brain tumors: Miami Children's Hospital experience

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OBJECT Pediatric brain tumors may be associated with medically intractable epilepsy for which surgery is indicated. The authors sought to evaluate the efficacy of epilepsy surgery for seizure control in pediatric patients with brain tumors.

METHODS The authors performed a retrospective review of consecutive patients undergoing resective epilepsy surgery related to pediatric brain tumors at Miami Children's Hospital between June 1986 and June 2014. Time-to-event analysis for seizure recurrence was performed; an "event" was defined as any seizures that occurred following resective epilepsy surgery, not including seizures and auras in the 1st postoperative week. The authors analyzed several preoperative variables to determine their suitability to predict seizure recurrence following surgery.

RESULTS Eighty-four patients (47 males) with a mean age (± standard deviation) of 8.7 ± 5.5 years (range 0.5–21.6 years) were included. The study included 39 (46%) patients with gliomas, 20 (24%) with dysembryoplastic neuroepithelial tumors (DNETs), 14 (17%) with gangliogliomas, and 11 (13%) with other etiologies. Among the patients with gliomas, 18 were classified with low-grade glioma, 5 had oligodendroglioma, 6 had uncategorized astrocytoma, 3 had pilocytic astrocytoma, 3 had pleomorphic xanthoastrocytoma, 3 had glioblastoma, and 1 had gliomatosis cerebri. Seventy-nine (94.0%) resections were guided by intraoperative electrocorticography (ECoG).

The mean time (± standard deviation) to seizure recurrence was 81.8 ± 6.3 months. Engel Class I outcome was achieved in 66 (78%) and 63 (75%) patients at 1 and 2 years' follow-up, respectively. Patients with ganglioglioma demonstrated the highest probability of long-term seizure freedom, followed by patients with DNETs and gliomas. In univariate analyses, temporal location (HR 1.75, 95% CI 0.26–1.27, p = 0.171) and completeness of resection (HR 1.69, 95% CI 0.77–3.74, p = 0.191) demonstrated a trend toward a longer duration of seizure freedom.

CONCLUSIONS ECoG-guided epilepsy surgery for pediatric patients with brain tumors is highly effective. Tumors located in the temporal lobe and those in which a complete ECoG-guided resection is performed may result in a greater likelihood of long-term seizure freedom.

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KEY WORDS resective epilepsy surgery; pediatric brain tumor; seizure freedom; time to event; oncology

Pediatric brain tumors are commonly associated with seizures. These tumors are often low-grade lesions such as dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas, and low-grade gliomas (LGGs). While DNETs and gangliogliomas almost exclusively present with seizures, gliomas may also produce focal neurological deficits secondary to mass effect and cerebral edema. The most common locations for brain tumors causing epilepsy are in the temporal lobe and the perirolandic region.[19] Surgery can be offered to these patients, even to those with tumors in eloquent brain regions, with the aid of modern tools such as stereotaxy, the intraoperative microscope, intraoperative ultrasound, the ultrasonic aspirator, evoked potentials, and advanced functional neuroimaging.

A retrospective observational study by Alsemari et al. found that resective epilepsy surgery in benign central nervous system tumors results in 73.4% and 66.5% seizure freedom at 1 and 5 years postoperatively, respectively.[1] In a cohort of adult patients with epileptic seizures associated with diffuse LGGs, the extent of resection (subtotal vs total) has also been shown to be independently predic-

ABBREVIATIONS AED = antiepileptic drug; DNET = dysembryoplastic neuroepithelial tumor; ECoG = electrocorticography; EEG = electroencephalography; ETANTR = embryonal tumor with abundant neuropil and true rosettes; EZ = epileptogenic zone; FCD = focal cortical dysplasia; LGG = low-grade glioma; TTE = time to event.

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tive of seizure freedom.[15] Likewise, in a small cohort of pediatric patients with brain tumor–associated epilepsy who were treated by lesionectomy only, an Engel Class I outcome was achieved in all 10 patients who underwent a gross-total resection and in all 4 patients who underwent a subtotal resection of the tumor.[10]

Controversy exists regarding the need for electrocorticography (ECoG)–guided resections to identify and resect additional seizure foci compared with a lesionectomy-only approach.[4] Tandon and Esquenazi compared a retrospective surgical cohort of patients who had epilepsy related to a brain neoplasm (who underwent an epilepsy resection) to those with tumoral epilepsy (who underwent an oncological resection).[19] In the first group ECoG-tailored resections were performed in 6 of the 13 patients and Engel Class I outcomes were achieved in 12 patients (92.3%); the second group underwent maximal lesionectomy and Engel Class I outcomes were achieved in 18 (94.7%) of 19 patients.[19] However, it is important to note that the patients who underwent an oncological resection often had a higher-grade tumor that may have been associated with a more benign course of epilepsy.

The aim of the present study was to report our experience with seizure outcomes following resective epilepsy surgery in pediatric patients with brain tumors at the Miami Children's Hospital. Our secondary goals were to assess the efficacy of epilepsy surgery associated with various underlying pathologies and hypothesize potential predictors of seizure outcome.

Methods

Study Design and Patient Population

We performed a single-center, retrospective, observational cohort study to describe the efficacy of epilepsy surgery in pediatric patients with brain tumors. The population of interest consisted of consecutive children with medically intractable epilepsy (defined as ongoing seizures after treatment with at least 2 antiepileptic drugs [AEDs] and beginning a third AED at the time of epilepsy surgery referral and workup) related to a pediatric brain tumor who underwent a resection primarily for epilepsy and, in certain cases, for an oncological indication at Miami Children's Hospital from June 1986 to June 2014.

Seizure Outcome

We assessed seizure outcomes using a time-to-event (TTE) Kaplan-Meier analysis.[5,6,9] An event was defined as the occurrence of any seizures or auras other than those that occurred in the 1st postoperative week. We also excluded reactive seizures and those attributable to poor AED compliance or weaning of an AED. TTE analysis has several advantages over a yes/no seizure recurrence approach: 1) The analysis takes into account the changing seizure status and the variability in follow-up duration, and therefore increasing our sample size (patients with a short follow-up period can be included in this model); 2) the TTE analysis approach places a positive value in delay of seizure recurrence; 3) using Cox regression analysis allows us to examine the influence of various patient-level covariates on seizure outcome; and 4) TTE analysis is statistically more powerful than the yes/no approach. However, the main disadvantage of this approach is that it will fail to account for the "running down phenomenon" (gradual decline of seizures over several months or years until seizure freedom is achieved following surgery).[5,17] We also collected data using the Engel classification of seizure outcomes, but these data were not used for statistical analysis.[7]

Setting and Exposure of Interest

This study took place at Miami Children's Hospital in Miami, Florida, which is a regional and international referral center for pediatric epilepsy. This is a high-volume academic center for epilepsy surgery currently staffed by 5 epileptologists, 3 neurosurgeons, and 3 neuroradiologists. We reviewed a web-based database that was prospectively maintained by an experienced senior epileptologist (I.M.). This database is updated in real time during epilepsy surgery conference or immediately following surgery.

The variables extracted from the database include demographic data (patient age at the onset of seizures, patient sex, duration of epilepsy, patient age at the time of surgery) as well as other factors that may plausibly predict seizure outcome. These additional factors include focality of video electroencephalography (EEG), invasive EEG implantation, use of ECoG-tailored resection, extent of resection (lesionectomy only vs lesionectomy plus), pathology, completeness of resection of the epileptogenic zone (EZ), as well as outcome data such as seizure outcome, length of follow-up, time to seizure recurrence, tumor recurrence, and, when available, mortality related to the tumor.

Surgical Procedure, Indication for ECoG, and Completeness of Resection

Resective surgery was aimed at gross-total resection of the tumor when possible and resection of the EZ as defined by chronic invasive EEG or intraoperative ECoG. In our practice, chronic invasive EEG monitoring is done by implanting subdural grid, strip, and/or depth electrodes. These electrodes were used to determine the presumed extent of the EZ (when noninvasive evaluation and/or ECoG was not sufficiently localizing) and/or for brain mapping (when adjacent eloquent brain areas were involved). Given the minimal additional risk associated with ECoG, we used it in all cases when available in order to better delineate the EZ. We evaluated the electrocorticographic images for a qualitative change, specifically seeking an area of maximum abnormality and determining whether there was a sharp demarcation of this abnormality. The abnormalities that we evaluated on ECoG were ictal recordings (when present), frequent spike(s) and wave formation, and discontinuous burst suppression. We never left tumor or the presumed EZ behind unless the resection involved eloquent cortex. In addition, we never left behind focal cortical dysplasia (FCD) unless it extended into eloquent cortex. Completeness of resection was defined by the surgeon's ability to resect both the entire tumor, which was also confirmed by postoperative MRI, and the EZ, which was localized based on prior workup and supplemented with invasive acute or chronic EEG data, when available. We used ECoG to define the surgical margins by identifying the irritative zone or continuous epileptic discharges and including it in our resection. Resections were "incomplete" when we were limited

by eloquent cortex. Regions of eloquent cortex were determined using presurgical stereotactic functional MRI and supplemented by intraoperative evoked potentials, when used. Completeness of resection was determined by the attending epileptologist and neurosurgeon for each particular case and was recorded prospectively.

Statistical Analysis

We presented the raw data using descriptive statistics. For continuous variables, we presented means, standard deviations, and ranges. For categorical data, we presented frequencies and percentages. We used a log transformation for non–normally distributed quantitative variables and removed any variable with less than 20 observations. We performed univariate Cox regression analysis to identify potential predictors of seizure outcome. Kaplan-Meier curves were created to graph the overall time-to–seizure recurrence function and for other categorical potential predictors of outcome. Since this was a hypothesis-generating exercise, we accepted any variable with a p value of less than 0.20 as a potential predictor of outcome. All statistics were performed in IBM SPSS Statistics version 20.

This study was approved by and compliant with the institutional review board at Miami Children's Hospital.

Results

From June 1986 to June 2014, 84 pediatric patients (47 males) underwent a craniotomy for an epilepsy resection of a brain tumor that was performed by 3 surgeons at Miami Children's Hospital (Table 1). At a minimum, all patients underwent a preoperative evaluation by the multidisciplinary epilepsy team, MRI, and video EEG. Seventy-nine (94.0%) of the resections were ECoG-guided. The mean age (± standard deviation) at surgery was 8.7 ± 5.5 years (range 0.5–21.6 years). Seizure frequency, which was calculated using available data from 80 patients, was daily in 40 (50.0%) patients, weekly in 25 (31.3%) patients, and monthly or less frequently in 15 (18.8%) patients. The study included 39 (46.4%) patients with gliomas, 20 (23.8%) with DNETs, 14 (16.7%) with gangliogliomas, and 11 (13.1%) with other etiologies.

TTE analysis is depicted in Fig. 1. The mean time to seizure recurrence following surgery was 81.8 ± 6.3 months. Seizure freedom was achieved in 66 (78%) and 63 (75%) patients at 1 and 2 years' follow-up, respectively. An Engel Class I outcome was achieved in 75%, 77%, 71%, and 56% of patients at 1, 2, 5, and 10 years, respectively (Fig. 2). We performed 43 (51.2%) temporal, 18 (21.4%) frontal, 9 (10.7%) parietal, 1 (1.2%) occipital, and 13 (15.5%) multilobar resections. Of these resections, 55 (65.5%) were lesionectomies, 16 (19.0%) were lobectomies, and 13 (15.5%) were multilobar resections. Patients with gangliogliomas demonstrated the highest probability of long-term seizure freedom, followed by patients with DNETs and gliomas (Fig. 3A). In univariate analyses, temporal location (HR 1.75, 95% CI 0.26–1.27, p = 0.171; Fig. 3B) and completeness of resection (HR 1.69, 95% CI 0.77–3.74, p = 0.191; Fig. 3C) demonstrated a trend toward a longer duration of seizure freedom (Table 2). We performed 55 lesionectomy-only and 29 lesionectomy-plus resections (Fig. 3D), and there was no statistically significant difference in seizure outcomes between the 2 resection types. There were 9 patients who experienced tumor recurrences: 3 with ganglioglioma, 2 with glioblastoma, 1 with gliomatosis cerebri, 1 with oligodendroglioma, 1 with DNET, and 1 with embryonal tumor with abundant neuropil and true rosettes (ETANTR). Three (2 glioblastoma, 1 ETANTR) of these tumor recurrences led to death.

TABLE 1. Summary of patient characteristics

Characteristic	Frequency (%)
Sex	
Female	37 (44.0)
Male	47 (56.0)
Invasive EEG implantation*	
No	62 (75.6)
Yes	20 (24.4)
ECoG†	
No	2 (2.5)
Yes	79 (97.5)
Completeness of resection‡	
Incomplete	27 (32.5)
Complete	56 (67.5)

* Data were only available for 82 of the 84 patients.
† Data were only available for 81 of the 84 patients.
‡ Data were only available for 83 of the 84 patients.

Complications

In this consecutive patient series, for which there were available data from 83 patients, there were 5 (6.0%) complications including 3 (3.9%) postoperative ischemic strokes and 2 (2.6%) postoperative infections. Perioperative blood transfusions were not recorded prospectively in our database.

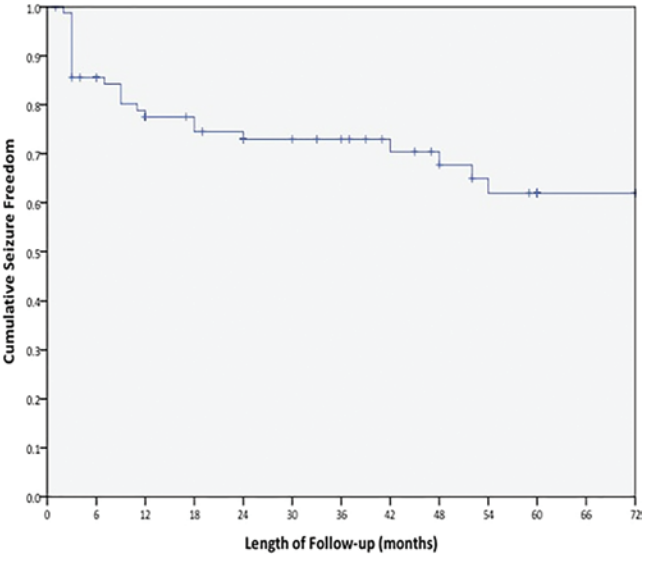

FIG. 1. Kaplan-Meier curves for seizure freedom. Graphs demonstrate cumulative seizure freedom over the follow-up period after epilepsy surgery for pediatric patients with brain tumors. Figure is available in color online only.

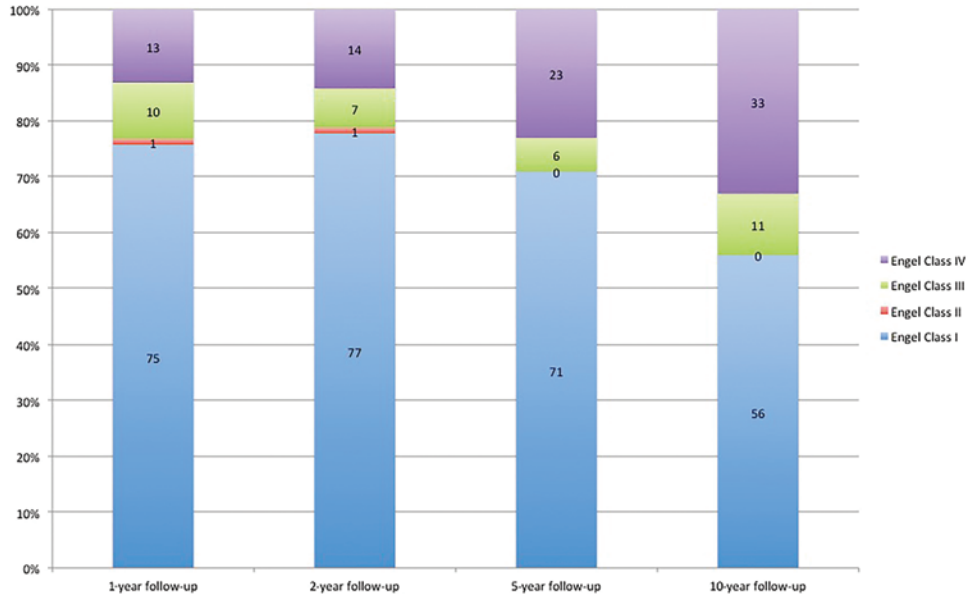

FIG. 2. Engel classification of seizure outcomes. Cluster bar charts demonstrate percentage of patients experiencing Engel Class I–IV outcomes at 1, 2, 5, and 10 years following surgery, respectively. Figure is available in color online only.

Discussion

In this single-center, 3-surgeon series, an excellent rate of seizure freedom was achieved in a consecutive series of children with epilepsy related to brain tumor. This outcome is comparable to those in other published series.[1,4,10,11,19] Although we were not adequately powered to determine the efficacy of epilepsy surgery by pathology, patients with gangliogliomas achieved better results than those with DNETs or gliomas. Interestingly, although gangliogliomas may be associated with cortical dysplasia more commonly than DNETs, the epileptogenicity may be independent from the co-occurring cortical dysplasia.[3,18] Completeness of resection and temporal location of resection may be predictors of favorable seizure outcomes.

As we used ECoG almost routinely, we are unable to draw conclusions on the added utility, if any, of an ECoG-tailored resection compared with a lesionectomy-only approach in extratemporal epilepsy, which also has excellent results.[2,12,14] ECoG utility depends on several important factors: 1) whether there are abnormal findings (often ECoG can be normal because of anesthesia effects); 2) the nature of the ECoG abnormalities (irritative zone, deficit zone, or continuous epileptic discharges); and 3) whether these abnormalities are resected or not. It is important to remember that in the setting of tumoral epilepsy, recurrence of seizure activity following lesionectomy may be due to the presence of dual pathology (gliosis, hippocampal sclerosis, or cortical dysplasia).[8] In these cases, the EZ may not be contiguous with the tumor.

Disadvantages of ECoG-Guided Resections

ECoG can add to the cost, personnel, and duration of a resection. However, with increased familiarity, the length of the procedure is increased by only 15–30 minutes. It is exceedingly rare to have ictal findings on ECoG; therefore, resection margins are frequently determined using brief recordings of interictal data.[16] Most importantly, it is unclear what the significance of the irritative zone is with respect to the need for resection. Many studies of ECoG in the literature are retrospective with a small number of patients. This makes drawing firm conclusions challenging.

Generalizability of Study Results

Generalizability of the results of this study to other centers must be made cautiously. Given that this study was performed at a high-volume referral center, our results may not be similar to those obtained elsewhere. Further limitations of this study include its retrospective methodology (our conclusions are only valid to the extent of the accuracy of our data), the involvement of trainees, and the reported experience of only 3 surgeons.

Study Strengths

The strengths of this study are as follows: 1) This is a relatively large series of consecutive pediatric patients with medically intractable epilepsy related to a brain neoplasm; 2) TTE analysis of outcomes was used, enhancing the statistical power to identify patient-level covariates that may predict seizure outcomes; and 3) although the study was performed retrospectively, the data were collected prospectively and entered into a database by an experienced epileptologist.

Study Limitations

There are several important limitations to this study. First, this is a single-center series, limiting generalizability. Second, TTE analysis may result in overly pessimistic seizure outcome estimates, as a patient who experiences the running-down phenomenon would be ascertained as having a poor seizure outcome despite eventually becoming seizure free. To the extent that this occurs, the internal

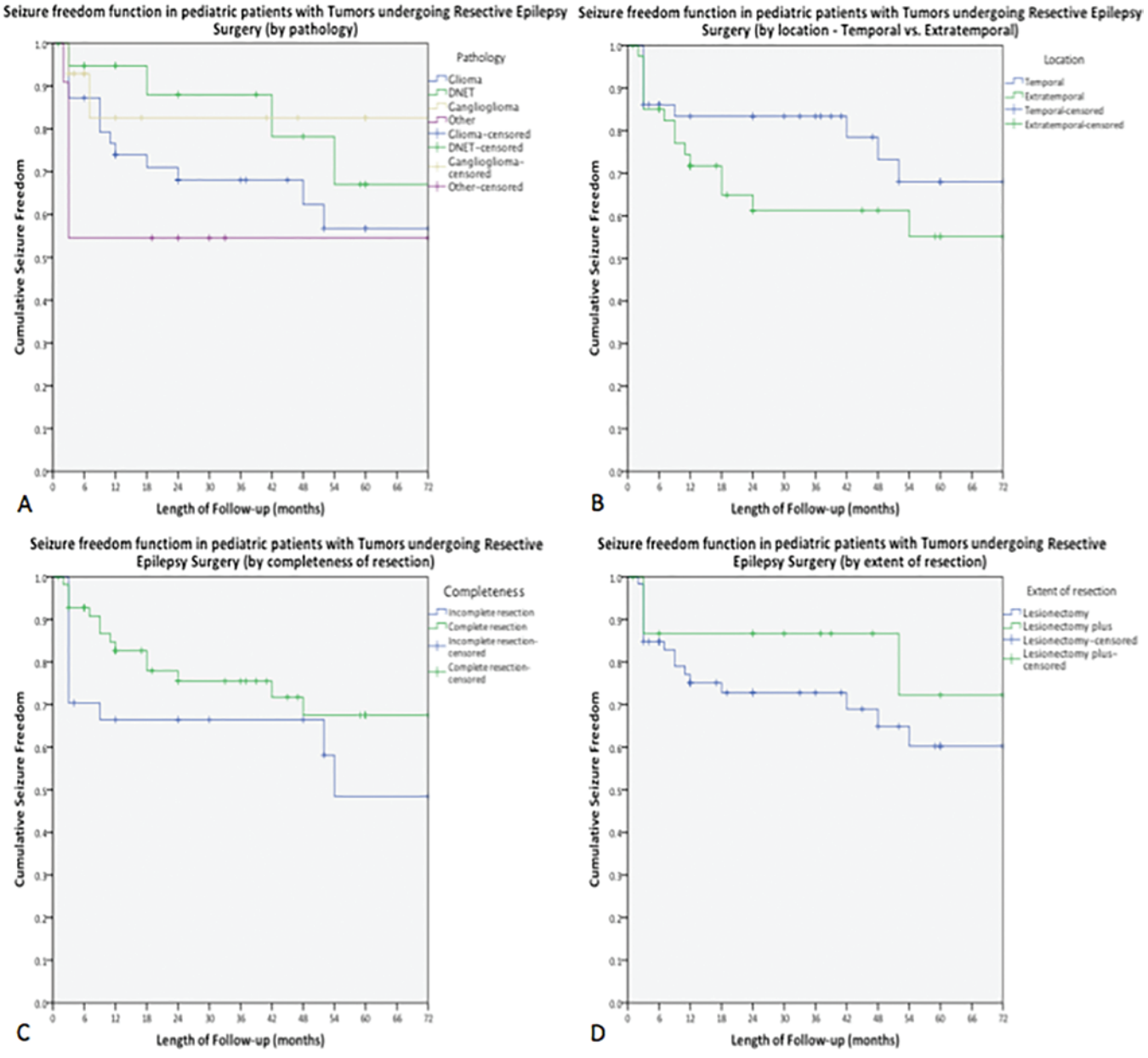

FIG. 3. Kaplan-Meier curves for seizure freedom. Graphs demonstrate cumulative seizure freedom over the follow-up period after epilepsy surgery for pediatric brain tumors by pathology **(A)**, location **(B)**, completeness of resection **(C)**, and extent of resection **(D)**. Figure is available in color online only.

validity of this study is compromised. However, it is also important that seizure recurrence following surgery is not equated with a poor surgical result. Although seizure freedom is an important predictor of improved health-related quality of life,[13] significant improvements in seizure frequency and severity can also lead to an improved health-related quality of life; however, this was not studied here. Third, there are probably other predictors of seizure outcomes that were not investigated. Fourth, we did not prospectively track the cases in which ECoG altered our preoperative resection strategy. This information was also not available retrospectively. Therefore, it is unclear whether ECoG-assisted resections offered any additional efficacy compared with a lesionectomy-only approach.

Future Research Questions Related to ECoG

Although excellent outcomes can be achieved through both epilepsy surgery and an oncological resection, several questions remain and could be the focus of future studies: 1) What are the indications for ECoG-guided epilepsy resections? 2) How often is the presurgical EZ hypothesis altered following intraoperative ECoG? 3) Is there prognostic utility in postresection ECoG recording; that is, is a normal postresective ECoG study or are certain types of postresective spikes predictive of seizure outcome? 4) Is the histopathological diagnosis of ECoG-guided resection of nontumoral cortex consistent with FCD or is it normal? 5) What is the cost-effectiveness of ECoG-guided resec-

TABLE 2. Univariate Cox regression analysis of predictive factors for seizure outcomes in pediatric patients with brain tumors undergoing resective epilepsy surgery

Characteristic	HR	95% CI	p Value
Lower $\log_{10}$ (age at seizure onset)	1.490	0.786–2.825	0.222
Log_{10} (age at surgery)	1.166	0.434–3.133	0.761
Duration of seizures	1.057	0.960–1.163	0.259
Nonfocal/multifocal EEG (vs focal EEG)	1.767	0.594–5.263	0.306
No invasive EEG implantation	1.845	0.814–4.184	0.142*
Complete resection of EZ (vs incomplete resection of EZ)	1.694	0.768–3.735	0.191*
Temporal resection (vs extratemporal resection)	1.748	0.256–1.274	0.171*
Resection greater than the lesion (vs lesionectomy only)	1.742	0.512–5.923	0.374

* Statistically significant.

tions given the excellent outcomes that can be achieved with a lesionectomy-only approach?

Conclusions

In this study, we were able to establish the high efficacy of and low risk associated with a consistent approach of ECoG-guided surgery in brain-tumor related epilepsy in a relatively large cohort of children. In addition, using a data-driven approach, we were able to identify completeness of resection and temporal location as potential surgery-related predictors of seizure outcomes. We find ECoG to be a useful tool in the armamentarium of the epilepsy surgeon in defining surgical margins of the EZ. We advocate tailoring the extent of resection to the individual patient with careful consideration of proximity to eloquent area and the patient's functional state. However, there are many centers that perform a lesionectomy only and still report excellent outcomes. Large, multicenter, prospective, appropriately powered studies are required to determine the efficacy of epilepsy surgery in various pediatric brain tumors and to better define the indication for and utility of ECoG in guiding resections.

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Disclosure

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: Fallah, Weil. Acquisition of data: Fallah, Weil, Sur. Analysis and interpretation of data: Fallah, Miller, Jayakar, Bhatia, Ragheb. Drafting the article: Fallah. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fallah. Statistical analysis: Fallah. Study supervision: Morrison, Bhatia, Ragheb.

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