Surgical Treatment of Extratemporal Epilepsy: Results and Prognostic Factors

Daniel Delev, MD[*‡]
Bernhard Oehl, MD[*]
Bernhard J. Steinhoff, MD[§]
Julia Nakagawa, MD[*‡]
Christian Scheiwe, MD[*‡]
Andreas Schulze-Bonhage, MD[‡¶]
Josef Zentner, MD[*‡]

[*]Department of Neurosurgery, Medical Center—University of Freiburg, Frieburg, Germany; [‡]Faculty of Medicine, University of Freiburg, Freiburg, Germany; [§]Epilepsy Center Kork, Kehl-Kork, Germany; [¶]Freiburg Epilepsy Center, Department of Neurosurgery, Medical Center—University of Freiburg, Freiburg, Germany

Portions of this work were presented in abstract form at the 67th Jahrestagung der deutschen Gesellschaft für Neurochirurgie (DGNC), Frankfurt, Germany, June 12 to 15, 2016.

Correspondence:
Daniel Delev, MD,
Department of Neurosurgery,
University of Freiburg,
University Medical Center,
Frieburg, Germany.
E-mail: daniel.delev@uniklinik-freiburg.de

Received, July 28, 2017.
Accepted, March 4, 2018.

BACKGROUND: Surgery is a widely accepted option for the treatment of pharmacoresistant epilepsies of extratemporal origin.

OBJECTIVE: To analyze clinical and epileptological results and to provide prognostic factors influencing seizure outcome.

METHODS: This retrospective single-center study comprises a consecutive series of 383 patients, most of whom had an identifiable lesion on MRI, who underwent resective surgery for extratemporal epilepsy. Data including diagnostic modalities, surgical treatment, histopathology, prognostic factors, and epileptological outcome were analyzed.

RESULTS: Resective procedures were located as follows: frontal (n = 183), parietal (n = 44), occipital (n = 24), and insular (n = 24). In 108 cases resection included more than 1 lobe. Histopathological evaluation revealed focal cortical dysplasias (n = 178), tumors (n = 110), cavernomas (n = 27), gliosis (n = 42), and nonspecific findings (n = 36). A distinct epileptogenic lesion was detected in 338 (88.7%) patients. After a mean follow-up of 54 mo, 227 (62.5%) patients remained free from disabling seizures (Engel class I), and 178 (49%) were completely seizure free (Engel class Ia). There was no perioperative mortality. Permanent morbidity was encountered in 46 cases (11.8%). The following predictors were significantly associated with excellent seizure outcome (Engel I): lesion visible on magnetic resonance imaging (MRI; $P = .02$), noneloquent location ($P = .01$), complete resection of the lesion ($P = .001$), absence of epileptic activity postoperatively ($P = .001$), circumscribed histological findings ($P = .001$), lower age at surgery ($P = .008$), and shorter duration of epilepsy ($P = .02$).

CONCLUSION: Surgical treatment of extratemporal epilepsy provides satisfying epileptological results with an acceptable morbidity. Best results can be achieved in younger patients with circumscribed MRI lesions, which can be resected completely.

KEY WORDS: Extratemporal lobe epilepsy, Surgical treatment, Long-term outcome, Prognostic factors

Neurosurgery 0:1–11, 2018 DOI:10.1093/neuros/nyy099 www.neurosurgery-online.com

Epilepsy is one of the most common neurological disorders, affecting more than 50 million people worldwide.[1] Around one-third of all epilepsy patients present with drug-resistant seizures, leading to decreased life expectancy, impaired quality of life, and devastating socioeconomic consequences.[2,3] Among those, approximately 70% are diagnosed with temporal lobe epilepsy (TLE), whereas the remaining 30% are characterized by extratemporal lobe epilepsy seizures (ETLE, extratemporal lobe epilepsy). The ratio of temporal to extratemporal resections reflects primarily differences in the epileptogenic potential of different brain areas. However, it also reflects the difficulties

ABBREVIATIONS: CI, confidence interval; **DNTs,** dysembryoplastic neuroepithelial tumors; **ECoG,** electrocorticography; **ETPs,** epilepsy-typical potentials; **ETLE,** extratemporal lobe epilepsy; **FCD,** focal cortical dysplasia; **fMRI,** functional magnetic resonance imaging; **LEAT,** long-term epilepsy associated tumors; **MRI,** magnetic resonance imaging; **OR,** odds ratio; **PET,** positron emission tomography; **SMA,** supplementary motor area; **SPECT,** single photon emission computed tomography; **TLE,** temporal lobe epilepsy

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encountered to define the epileptogenic zone in extratemporal epileptogenesis.[4]

ETLE includes a variety of epileptogenic syndromes, which can arise from any region of the cerebral cortex outside of the temporal lobe.[5] Even if the zone of seizure onset can be exactly identified, the ictogenic network may be more widespread, thus preventing the proper definition of resection boundaries. Further problems restricting surgical treatment refer to the involvement of eloquent cortical areas.[6,7] In these cases, there is a dilemma between the 2 major goals of surgery, seizure control, and preservation of functional integrity, which should be critically discussed with the affected patients.[8,9]

Recent advances in noninvasive techniques such as epilepsy specific magnetic resonance imaging (MRI) protocols including postprocessing analysis, single photon emission computed tomography (SPECT) and positron emission tomography (PET) have improved the diagnostic tools of ETLE, facilitating surgical treatment.[10-12] Nevertheless, in many cases invasive diagnostic work-up, including implantation of depth, subdural strip or grid electrodes may be necessary to define the epileptogenic zone.[13,14] Moreover, the intraoperative use of electrocorticography (ECoG) may provide important information concerning interictal activity, modifying the extent of planned resection.[15]

Despite all of these technical advances and developments, epileptological results of surgical treatment of ETLE are not as favorable as in TLE and many efforts are done to identify prognostic factors, helping to define those patients, who can be expected to benefit most from resective surgery.[16-20] The present study reports a consecutive series of 383 patients, who underwent resective surgery for ETLE. Main goals were to present long-term seizure outcome dependent on localization of resection and histopathological findings, and to present prognostic factors in terms of seizure control. Moreover, we describe 2 models of preoperative and postoperative available variables, which can help to identify the subgroup of patients most suitable for surgical treatment.

TABLE 1. Demographic and Clinical Features

	n	%
	Demographics	
Sex		
Male	225	58.5
Female	158	41.5
Duration of epilepsy (yr)	12.7 (+/–12, range 0-52)	
Age at seizure onset (yr)	13.5 (+/–13, range 0-69)	
Age at surgery (yr)	24.3 (+/–15.6, range 0-77)	
FU (mo)	54.2 (+/–45, range 3-214)	
	Clinical features	
Side		
Left	188	49.1
Right	195	50.9
Localization		
Eloquent	229	59.8
Noneloequent	154	40.2
Invasive EEG		
Depth electrodes	31	26%
Subdural grids	77	64%
Subdural stripes	92	76%
Extent of resection		
Complete	210	65.6
Partial	110	34.4
Seizure outcome		
Engel I	227	62.5
Engel II-IV	136	37.5

METHODS

Patient Cohort

This is a single-center retrospective study. A total of 1668 patients underwent surgery for drug-resistant epilepsy from 1997 until 2015. Among them, there were 383 extratemporal resections (Table 1). Data were evaluated from patients' charts and regular outpatient visits. Informed consent was obtained according to the Declaration of Helsinki. The study was approved by the local ethics committee.

Preoperative Evaluation

All patients were submitted to presurgical assessment undergoing a standard protocol[21] comprising clinical, neuroradiological, neuropsychological, and EEG-data in 4 cooperating Epilepsy Centers. All 4 epilepsy centers share the same criteria and all decisions are taken monthly during an interdisciplinary meeting, attended by all epilepsy centers. All preoperative images were acquired in 1 of the 4 cooperating centers and reviewed during the interdisciplinary epilepsy conference. The preoperative imaging corresponded to specific epilepsy MRI protocols as described elsewhere.[22,23] Invasive diagnostics were performed in 120 patients (31%). Depth electrodes were implanted in 31 patients, strip electrodes in 77 cases, and grid electrodes in 92 patients (61 patients received more than 1 type of electrode). The decisions for invasive diagnostics were individually based and discussed during the interdisciplinary epilepsy conference. Criteria for invasive diagnostics included: (1) patients, in whom the epileptogenic zone could not be localized or lateralized precisely or if there was a discrepancy between the results of surface EEG, seizure semiology, and radiological findings; (2) patients with MRI-negative epilepsy; and (3) patients, in whom a functional mapping of the eloquent cortex was required. If a deep-seated focus was suspected depth electrodes were usually preferred for localizing the epileptogenic zone. However, depth electrodes were less suitable for a broad covering of the neocortical surface or mapping of functionally eloquent cortex. For this purpose, subdural strip or grid electrodes were applied. EEG evaluation was performed according to guidelines described elsewhere.[24] Functional mapping of eloquent cortex was done in 72 patients. In addition, intraoperative ECoG was used in 74 (19.3%) patients, including the following indications: (1) tailoring of the resection in spread epileptogenic lesions, or (2) in lesions encroaching upon eloquent areas, and (3) in cases, where the epileptogenic zone could not be well-defined.

Surgical Procedures

Resective procedures were located as follows: frontal (n = 183), parietal (n = 44), occipital (n = 24), and insular (n = 24). Resection

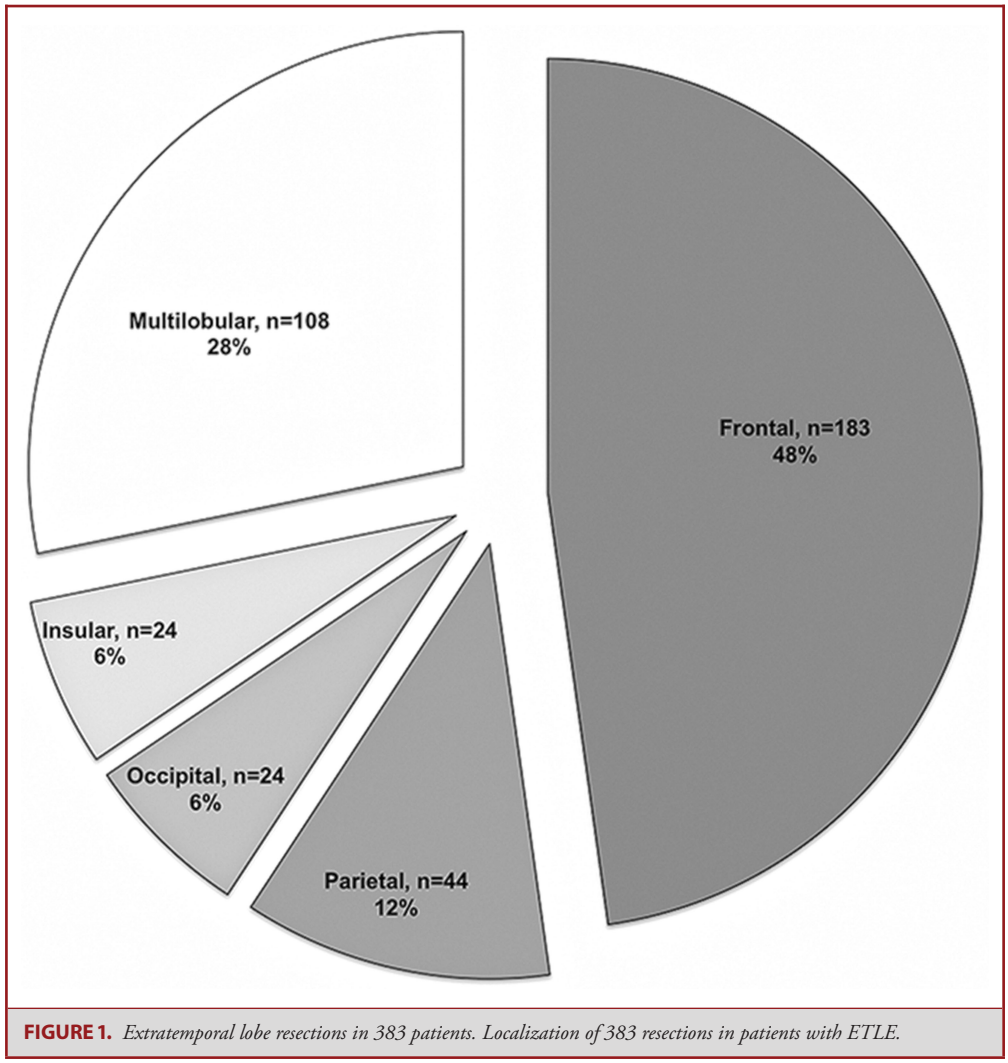

FIGURE 1. *Extratemporal lobe resections in 383 patients. Localization of 383 resections in patients with ETLE.*

included more than 1 lobe in 108 patients (Figure 1). Reoperations due to recurrent seizures were performed in 49 patients: 26 of them showed incomplete lesionectomy after first surgery, 5 patients revealed recurrent tumors, and in 13 patients an additional epileptogenic focus was identified. Frontal and parietal lobectomy were guided by standard anatomic landmarks sparing the motor and sensory cortex as well as the frontal speech areas on the dominant side. Lobectomy was the procedure of choice when all or most parts of the lobe were involved in the epileptogenic zone. Extended lesionectomy was performed in cases with localized seizure origin and MRI detectable lesion. The resection aimed at the complete removal of the epileptogenic zone, including the whole superficial cortex adjacent to the pia. The extent of the resection (complete vs not-complete) was evaluated according to the postoperative MRI.

Eloquent cortical areas were designated according to the classification reported by Chang et al[25] and included the rolandic cortex (pre- and postcentral gyrus), the supplementary motor area (SMA), insula, primary visual cortex as well as the areas of Broca and Wernicke. Surgical resection encroaching upon eloquent cortex was done in 229 patients. Except for the SMA, the resection was performed in these cases by emptying the gyri, leaving intact the pial banks. The central rolandic area was resected up to an extent of 3 cm above the Sylvian fissure, sparing the hand area and leaving intact the central arteries and veins. Most of the operations were performed by the senior author (J.Z.). Some of the pediatric patients were operated by a second surgeon under the supervision of the senior author.

Histopathological Findings

All specimens were reviewed by 2 neuropathologists. Histopathological findings included 4 main groups: focal cortical dysplasia (FCD), neoplasms, vascular lesions, and other nonspecific histhopathological abnormalities. FCD was classified according to Palmini et al,[26] distinguishing FCD type I and type II. At present, the clinicopathological ILAE classification of FCD[27] is used in our institution. Neoplasms were divided in glial tumors (astrocytomas, oligoastrocytomas, and oligodendrogliomas) and neuroepithelial tumors (gangliogliomas and dysembryoplastic neuroepithelial tumors [DNTs]). Tumors were classified

according to the World Health Organization classification.[28] Unspecific histhopathological abnormalities included gliosis, scars, and others. Gangliogliomas, DNTs, and cavernomas were summarized as circumscribed lesions, as they are well defined both on MR-imaging and from intraoperative aspect. In contrast, gliomas, scars and especially FCDs usually show less defined borders (both on MRI and intraoperatively) and were therefore classified as noncircumscribed.

Postoperative Evaluation

Postoperative follow-up included clinical visits at 3, 6, and 12 mo after surgery. Further outpatient visits usually followed in annual intervals. Standardized telephone interviews, which included questions regarding seizure frequency, overall status, and antiepileptic drug medication, were performed for patients with follow-up <12 mo. Last available outcome was used for the analysis. Antiepileptic drugs were tapered according to the epileptologists' recommendations.[29,30] Complete follow-up data (>3 mo) were obtained from 363 patients. Mean follow-up was 54 mo (range 3-214 mo, ±45 mo). Twenty patients were lost for follow-up. Seizure outcome was evaluated according to the Engel classification.[31]

Statistics

Statistical analysis was performed for the whole cohort using the chi-square test for the categorical variables. Fisher's exact test was used if sample sizes were <5, and the Wilcoxon test was used for comparison of nonparametric values. All tests were 2-sided, and a *P*-value below .05 was considered statistically significant. Multiple comparison correction was performed according to the Benjamini–Hochberg false discovery rate.

Two different models were created and tested by multivariate binary logistic regression analysis designating Engel class I outcome as a dependent variable. Model I (preoperative available variables) investigated patients' characteristics known prior to surgery and thus can be helpful during the preoperative consulting of the patients. The following variables were included: duration of seizure disorder, age at surgery, use of invasive EEG, spatial relationship between seizure focus and eloquent cortical areas, visibility of a lesion on MRI, and localization of the resection (frontal, parietal, occipital, insular, and multilobular). Model II (postoperative available variables) included: presence of postoperative epilepsy-typical potentials (ETPs) on EEG, use of intraoperative ECoG, completeness of resection according to postoperative MRI (MRI negative cases were excluded), and type of histology (circumscribed or noncircumscribed). For all analyses, the SPSS Software (Released 2010, IBM SPSS Statistics for Windows, Version 19.0. IBM Corp, Armonk, New York) was used.

RESULTS

Clinical Findings

There were 225 (59%) males and 158 (41%) females. Mean age at seizure onset was 13.5 yr (median 9 yr, ±13 yr, range 0-69 yr). Seizure onset was earliest in patients with FCD (mean 6.1 yr) and latest in patients with glial tumors (mean 27.2 yr). Mean duration of epilepsy was 12.7 yr (median 9.1 yr, ±12 yr, range 0-52 yr). Patients with FCD were operated later (mean duration of epilepsy 14.8 yr) as compared to patients with glial tumors (mean duration of epilepsy 6.2 yr). Mean age at surgery was 24.3 yr (median 20 mo, ±15 mo, range 0-77 mo).

Histopathological Findings

Detailed description of histopathological findings is given in Table 2. FCD was found in 178 patients (46.5%) followed by glial tumors (n = 56; 14.6%), glioneuronal tumors (DNT and GG; n = 44; 11.5%), gliosis (n = 42; 11%), and cavernomas (n = 27; 7.0%). FCD was the most common histopathological finding in multilobular (n = 67; 62%) and frontal (n = 85; 46.4%) resections. FCD type I was found in 47 patients (26%) and FCD type II in 91 patients (51%). The FCD characterization was not available in the remaining 40 patients. In contrast, histopathological findings after insular resections revealed in most cases glial tumors (n = 15; 62.5%).

Preoperative Diagnostics

Table 3 provides an overview on noninvasive and invasive diagnostic modalities and their localizing value. MRI was performed in almost all patients (n = 381; 99.9%), and the majority of patients (n = 338; 88.7%) showed a distinct lesion. The localizing accuracy for identifying the epileptogenic area was 71.2% (99/139) with PET and 69.6% (39/56) with SPECT (Table 3A). Preoperative fMRT was done in 145 (38.0%). Invasive EEG (iEEG) was performed in 120 (31.0%), including 84 patients with resections nearby eloquent cortex areas, 36 patients with nonlesional epilepsy and 17 patients with discrepancies between different noninvasive diagnostics. Intraoperative ECoG was used in 74 (19.3%) patients (Table 3B).

TABLE 2. Histopathological Findings and Localization of Resection

	Frontal N (%)	Parietal N (%)	Occipital N (%)	Insular N (%)	Multilobular N (%)	Total N (%)
FCD	85 (46.4)	12 (27.3)	10 (42.7)	4 (16.7)	67 (62.0)	178 (46.5)
Glial tumor	24 (13.1)	7 (15.9)	1 (4.2)	15 (62.5)	9 (8.3)	56 (14.6)
DNT, GG	21 (11.5)	8 (18.2)	4 (16.6)	1 (4.2)	10 (9.3)	44 (11.5)
Cavernoma	16 (8.7)	3 (6.8)	2 (8.3)	3 (12.5)	3 (2.8)	27 (7.0)
Gliosis	23 (12.6)	6 (13.6)	3 (12.5)	0 (0.0)	10 (9.3)	42 (11.0)
Other	14 (7.7)	8 (18.2)	4 (16.7)	1 (4.2)	9 (2.3)	36 (9.4)
Total	183 (100.0)	44 (100.0)	24 (100.0)	24 (100.0)	108 (100.0)	383 (100.0)

TABLE 3. Noninvasive (A) and Invasive (B) Diagnostic Modalities

	Frontal		Parietal		Occipital		Insular		Multilobular		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
A. Noninvasive preoperative diagnostics and localizing value												
MRI	182	100	44	100	24	100	24	100	107	100	381	100
Lesion visible	156	87.3	38	86.4	22	91.7	23	95.8	99	92.5	338	88.7
PET	70	100	15	100	4	100	3	100	47	100	139	100
Localizing value	47	67.0	12	80.0	3	75.0	0	0.0	37	78.7	99	71.2
SPECT	21	100	8	100	3	100	3	100	21	100	56	100
Localizing value	15	71.0	5	62.5	2	66.6	1	33.3	16	76.1	39	69.6
B. Diagnostic modalities and localization of resection												
Invasive EEG	64	35.0	14	32.0	4	16.0	2	9.0	36	34.0	120	31.0
ECoG	39	21.3	7	15.9	7	29.2	0	0.0	21	19.4	74	19.3
fMRT	79	43.3	11	25.0	7	29.0	9	37.0	39	29.0	145	38.0

TABLE 4. Seizure Outcome and Localization of Resection

	Frontal N (%)	Parietal N (%)	Occipital N (%)	Insular N (%)	Multilobular N (%)	Total N (%)	Total (FU > 12mo) N (%)
Engel I	111 (65.0)	30 (71.4)	14 (61.0)	12 (52.2)	60 (58.8)	227 (62.5)	209 (62.9)
Engel Ia	85 (49.4)	26 (62.0)	9 (39.0)	11 (47.8)	47 (51.0)	178 (49.0)	162 (48.5)
Engel II	27 (15.7)	3 (7.1)	4 (17.4)	4 (17.6)	13 (12.6)	51 (14.0)	46 (13.8)
Engel III	20 (11.6)	7 (16.7)	1 (4.6)	2 (8.7)	9 (8.7)	39 (10.7)	39 (11.7)
Engel IV	14 (8.7)	2 (4.8)	4 (17.4)	5 (21.7)	21 (19.7)	46 (12.7)	40 (12.0)
Total	172 (100.0)	42 (100.0)	23 (100.0)	23 (100.0)	103 (100.0)	363 (100.0)	334 (92.0)

Seizure Outcome

Seizure outcome of the total group and in relation to the localization of resection is presented in Table 4. At last follow-up, a total of 227 patients (62.5%) were free from disabling seizures (Engel I), and 178 (49.0%) were completely seizure free (Engel Ia). Most favorable epileptological results were achieved in patients with frontal and parietal resections (Engel I 65.0% and 71.4%, respectively), whereas insular resections showed less favorable results (Engel I 52.2%). Overall seizure outcome remained stable over the observation time with Engel I in approximately 60% of the patients at 3-, 5-, and 10-yr follow-up (Figure 2). With respect to histopathology, most favorable seizure outcome was achieved in patients with cavernomas and glioneuronal tumors (gangliogliomas and DNTs) with 89% and 85% seizure-free (Engel I) patients, respectively (Figure 3). Among the MRI-negative patients with available epileptological outcome (n = 36), 16 patients (44%) became seizure free (Engel I) after surgery.

Figure 4 shows a forest plot representing different variables and their relation to seizure outcome. Younger age (<18 yr) and shorter duration of epilepsy (<10 yr) were associated with a higher chance to become seizure free after surgery. Resections performed more distantly from eloquent cortical areas ($P = .02$, odds ratio [OR] = 1.7, confidence interval [CI] = 1.1-2.7) and patients with circumscribed histopathological findings ($P < .01$, OR = 3.6, CI = 1.8-7.3) were associated with improved seizure outcome. The use of iEEG did not influence seizure outcome ($P = .4$). However, patients in whom no persistent spikes were seen on ECoG were significantly more frequently assigned to Engel class I ($P = .03$).

Operative Complications

There was no perioperative mortality. Postoperative neurological deficits such as hemiparesis and aphasia were observed in 76 patients (20%), and surgical complications such as deep vein thrombosis, wound infections, and meningitis in 38 patients (9%). However, most of these complications resolved completely during the further postoperative course. Thus, permanent neurological morbidity was encountered in 41 patients (10.8%), and mainly referred to mild dysphasia, hemiparesis, or visual field deficit. Among the 41 patients with permanent neurological morbidity, 16 (4%) had unexpected deficits—hemiparesis (n = 6), dysphasia (n = 6), hemianopia (n = 3), and dysphasia and hemiparesis (n = 1). Permanent surgical morbidity was seen in 5 patients (1.0%): 4 patients needed VP-shunt due to postoperative hydrocephalus and 1 patient was reoperated due to subdural empyema.

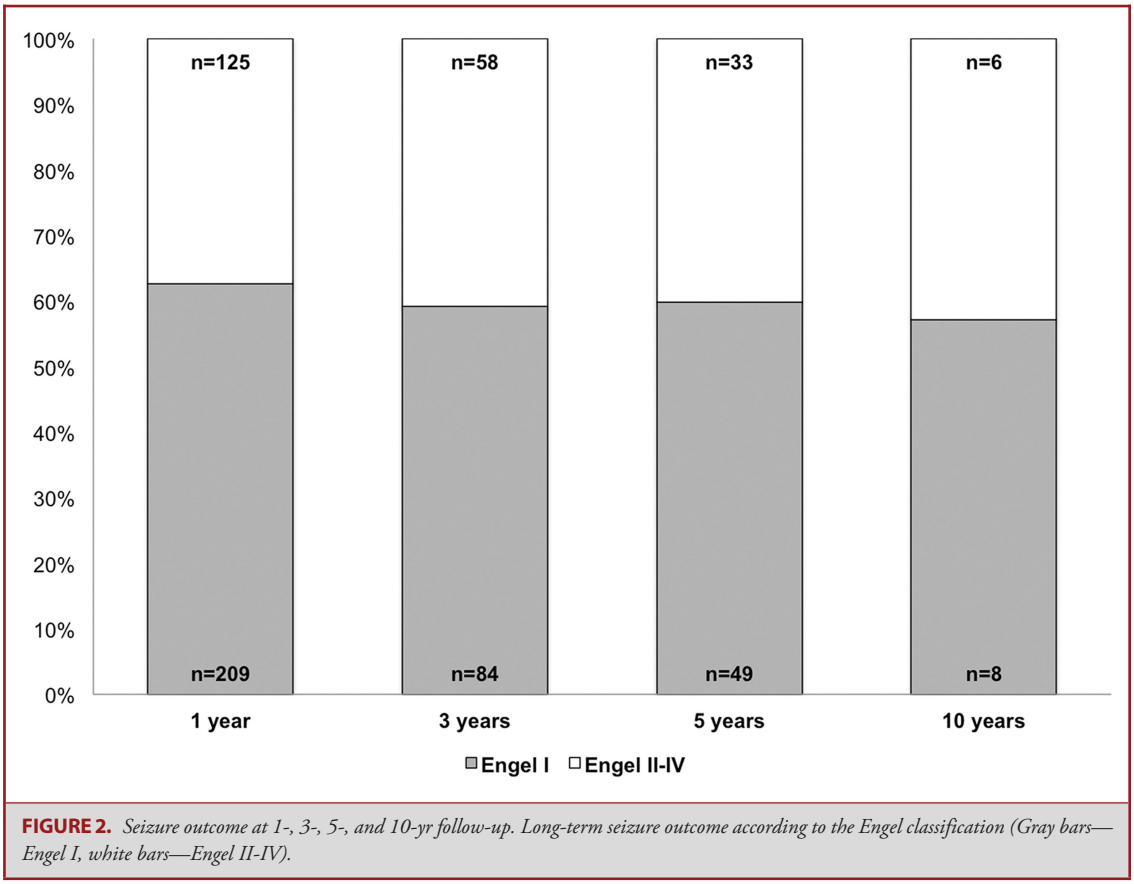

FIGURE 2. *Seizure outcome at 1-, 3-, 5-, and 10-yr follow-up. Long-term seizure outcome according to the Engel classification (Gray bars—Engel I, white bars—Engel II-IV).*

Prognostic Factors

Table 5 shows multivariate analysis of preoperative (Model I) and postoperative (Model II) available prognostic factors associated with Engel class I outcome. Model I (preoperative variables) revealed 3 variables as independent prognostic factors associated with Engel class I outcome: age at surgery <18 *yr* (P = .04, OR = 1.7, CI = 1.1-2.8), lesion on MRI (P = .03, OR = 2.3, CI = 1.1-5.2) and noneloquent localization of epileptogenic lesion (P = .01, OR = 1.9, CI = 1.2-3.1; Table 5A). Model II (postoperative variables) showed the following prognostic factors to be associated with favorable seizure outcome (Engel I): complete resection of the epileptogenic lesion (P < .01, OR = 5.4, CI = 2.9-9.9) and absence of postoperative epilepsy typical potentials (ETPs; P < .01, OR = 7.1, CI = 3.7-13.4; Table 5B).

DISCUSSION

Surgical treatment of extratemporal epilepsies remains challenging due to difficulties in localizing the epileptogenic focus, identifying the appropriate borders of the surgical resection, and the close relationship of the epileptogenic zone to areas of high functionality.[4,32] Meanwhile, developments in presurgical diagnostics based on multimodal data acquisition from SPECT, PET, and functional magnetic resonance imaging (fMRI) have improved the detection rate of epileptogenic foci. However, there is still some uncertainty with respect to the selection of surgical candidates who can be expected to benefit most from surgery.

Surgical Aspects

Most procedures performed for extratemporal epilepsies are frontal resections.[32] In our series, 48% of all operations referred to the frontal lobe, while parietal, occipital, and insular resections accounted for 24% of the procedures. Extended lesionectomy including resection of the epileptogenic zone[4] was the most common procedure performed in 66% of our patients. However, it seems to be noteworthy that multilobectomies accounted for 28% of all extratemporal procedures in our series, mainly referring to the parieto-occipital area, while extratemporal resections including more than one lobe have been found to range between 12% and 22% in the literature.[33]

Special attention should be paid to resections of highly vascularized areas as well as of epileptogenic zones around areas of high functionality, where surgery should be performed in a subpial manner by emptying the gyri leaving intact pial banks, in order to preserve all arteries and major veins. According to our experience, even the primary motor cortex can be safely resected in this way up

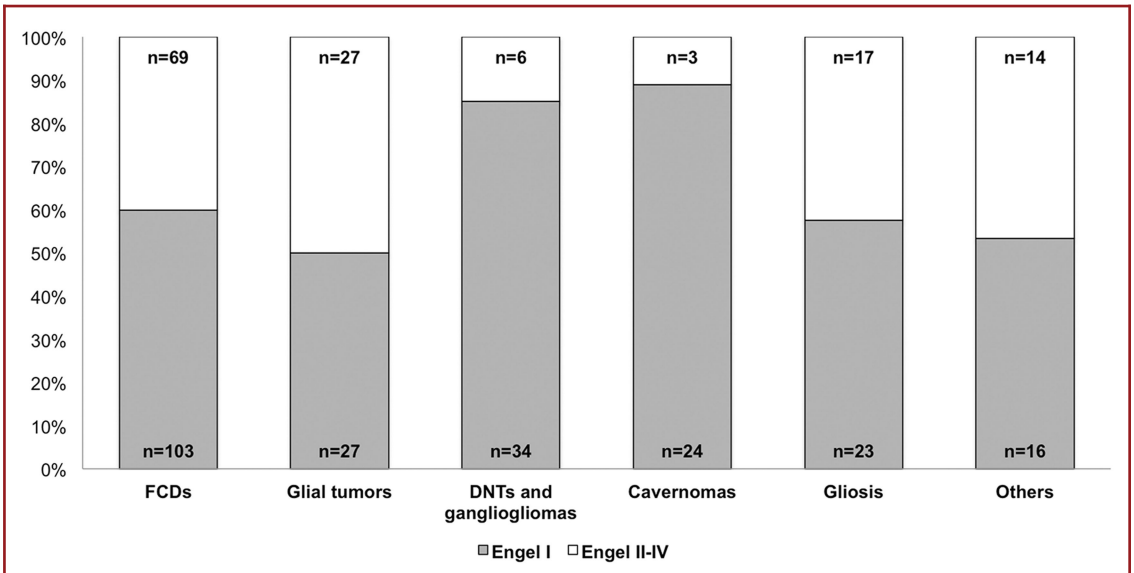

FIGURE 3. *Seizure outcome and histopathological findings. Seizure outcome (Gray bars—Engel I, white bars—Engel II-IV) according to the different histopathological findings.*

to 3.0 cm above the Sylvian fissure sparing the motor hand area. This is particularly true since these resections are only followed by a transient facial paresis, which resolves completely within a few days. If a frontal epileptogenic zone extends to the insula, this area can be removed from a frontal approach dissecting between the basal ganglia and the Sylvian vessels. Otherwise, the transsylvian or—in particular on the nondominant side—the transcortical approach through the frontal opercula can be used to treat insular epilepsies.[52] Neuronavigation can be used both to plan the surgical approach and define the resection area. Functional MRI and intraoperative electrophysiological mapping and monitoring facilitate resections around speech, motor, and insular areas. In particular, subdural electrodes implanted to define the epileptogenic zone can be used to delineate areas of high functionality. In such cases, where the epileptogenic zone encroaches upon areas of high functionality, iEEG is indispensable and cannot be easily substituted by fMRI. We observed that the rate of subdural grid and stripe electrodes decreased from 81% to 64%, while the rate of depth electrodes increased from 3% to 24% during the last 10 yr of our epilepsy surgical program. This represents somehow the increasing utility of depth electrodes being suitable for both detection of the epileptogenic zone and mapping of eloquent subcortical areas.

Complications

Detailed and accurate knowledge of complications is of paramount importance both for counseling surgical candidates during the decision-making process as well as to develop strategies to avoid these risks. However, comparison between the reported complication rates is difficult due to different surgical techniques, pathologies, and cohorts (children/adults) encountered in the respective series. In addition, many of the observed risks (eg, quadrantanopia, cognitive, and psychiatric disorders) are partially evaluated as inevitable side effects and partially as complications.

In their overview, Hader et al[34] reported temporary morbidity caused by surgical and neurological complications in 16.0% and permanent morbidity in 6.2% of the cases. The complication rate was higher in extratemporal location as compared to temporal resections with a perioperative mortality of 1.2% in extratemporal resections.[34] Permanent morbidity of extratemporal procedures varies in different series between 3% and 43%.[7,35-37] In our series there was no perioperative death. Permanent morbidity due to surgical and neurological complications was 10.8%. This number is similar to others reporting a permanent morbidity of 10% to 15%.[5,16,33] It should be considered that in our series surgical resections encroached upon areas of high functionality in almost two-thirds of the cases. Thus, the complication rate seems to be acceptable.

Histopathological Aspects

FCD is one of the most common histopathological findings after extratemporal resections especially in children and adolescents.[38] In our series, FCD accounted for 46.5% of all histopathological findings followed by tumors, gliosis, and cavernomas. Although the seizure onset was much earlier in patients with FCD compared to those with tumors, cavernomas, or gliosis,[38] patients with FCD were operated often later and presented with a longer lasting epilepsy compared to patients with other histopathological findings. This observation can be explained by difficulties in diagnosis and MRI visualization of FCD. While FCD type II

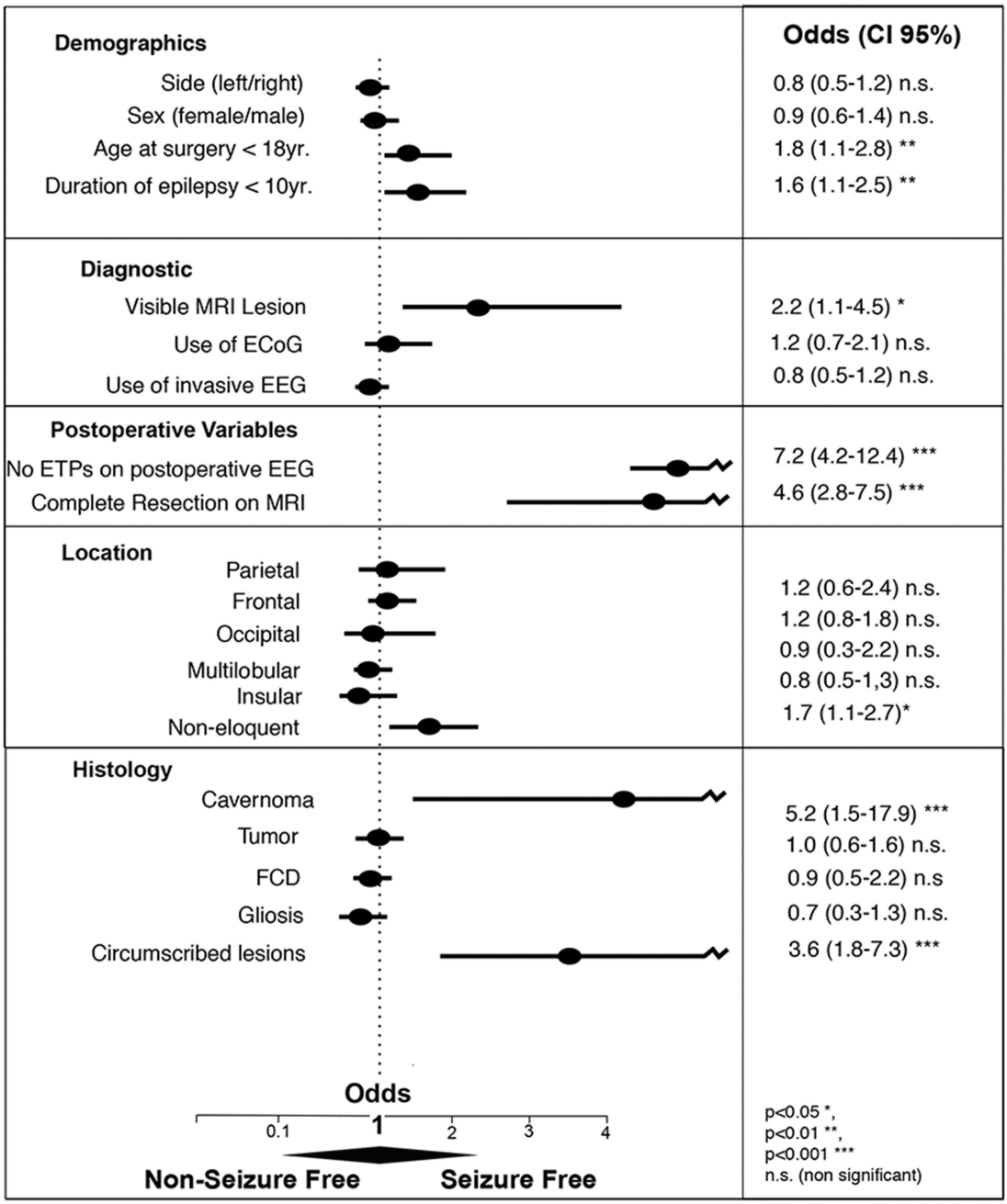

FIGURE 4. *Favorable (seizure free) vs unfavorable (nonseizure free) outcome dependent on different variables. Forest plot showing different variables and their relation to the seizure outcome. The black ovals show calculated odd ratios with the corresponding 95% CI (black lines) after chi-quadrat test. Variables located on the right side of the dashed line were associated with favorable seizure outcome; variables on the left side were associated with poor seizure outcome. Significant P-values are marked with asterisk (*).*

TABLE 5. Multivariate Analysis of Preoperative (A, Model I) and Postoperative (B, Model II) Prognostic Factors

Variable	OR	CI	*P*-value
A. Multivariate analysis of preoperative variables (Model I)			
Age at surgery <18yr	1.6	1.1-2.8	.04*
Duration of epilepsy <10yr	1.3	0.7-2.1	.28
Invasive diagnostics	1.2	0.7-2.1	.47
Lesion on MRI	2.3	1.1-5.1	.04*
Location of the lesion	1.0	0.9-1.2	.53
Noneloquent location	1.9	1.2-3.2	.01*
B. Multivariate analysis of postoperative variables (Model II)			
Absence of postoperative ETPs	7.1	3.7-13.4	<.01*
Intraoperative ECoG	0.7	0.3-1.6	.54
Circumscribed lesions	1.9	0.8-4.2	.12
Complete resection of lesion	5.4	2.9-9.9	<.01*

Significant *P*-values are marked with asterisk (*).

is characterized by gray-matter blurring and a white-matter tail, MRI visualization of other FCD types is difficult. Therefore, it may be necessary to repeat diagnostics especially in children and adolescents with a pharmacoresistant epilepsy, in whom the initial MRI is negative.[53]

We observed gangliogliomas and DNTs in approximately 10% of the patients. These tumors belong to the group of long-term epilepsy associated tumors (LEAT).[38-40] With LEAT the surgeon has to keep not only epileptological but also oncological aims in mind when planning the surgery. Despite of their benign character, LEAT may in rare instances become malignant, and it would be a mistake to argue that they do not need to be removed at all, or they should be observed for a long period. From an oncological point of view, a totally removed ganglioglioma or DNT has much lower chance to recur and then to become malignant in the later course.

Seizure Outcome

Various data for seizure outcome after extratemporal resections are available in the literature. McIntosh et al[41] reported initial seizure freedom in 40.7% of their patients, which dropped to 14.7% 5 yr postoperatively. Controversially, Hanáková et al,[16] D'Argenzio,[42] and Elsharkawy et al[43] reported relatively stable Engel I rates over years of approximately 50% in adults and children. In our series, 62.2% of the patients were seizure free (Engel I), which is comparable with a meta-analysis reported by Tellez-Zenteno et al[44] and slightly better compared to other series.[16,18,45,46] Engel I outcome after frontal and parietal resections in our cohort was 65% and 71%, respectively, whereas other studies reported Engel I outcome ranging from 45.1% to 57.5%.[47,48-50] Epileptological results reported by Binder et al[51] and Yang et al[52] for occipital resections with 69% and 71% Engel I outcome, respectively, and by von Lehe et al[36] for insular resections with 62% Engel I outcome, were slightly better compared to our results with 61% seizure-free patients after occipital and 52% seizure-free patients after insular resections. Engel I outcome in MRI-negative patients was with 44%, slightly better than the results by Noe et al[53] and Tellez-Zenteno et al[44], who reported Engel I rates of 38% and 33%, respectively.

Pre- and Postoperative Prognostic Factors

Most prognostic factors with respect to seizure outcome after surgery of ETLE described so far include complete resection of the lesion, short duration of epilepsy, younger age at surgery, and circumscribed histopathological findings.[41-43,47,54] In addition to these factors, a larger distance of the epileptogenic zone to eloquent cortex was associated with a more favorable outcome (Engel I), although the localization of resection (frontal, parietal, occipital, insular, or multilobular) did not significantly influence seizure outcome.

Multivariate analysis comprised 2 models. Model I included clinical characteristics available prior to resection, thus contributing to identify patients who can be expected to benefit most from surgery. Three independent variables were found to influence seizure outcome: younger age at surgery (<18 yr), visible lesion on MRI and distant relationship between epileptogenic lesion and eloquent cortex. Model II concentrated on variables available after surgery. Complete resection of the lesion and absence of postoperative ETPs was associated with favorable outcome. While univariate analysis showed a direct relationship of circumscribed histopathology with Engel class I outcome, this finding could not be confirmed by the multivariate analysis, implying the greater impact of the complete resection on seizure outcome as compared to the histopathological findings.

Limitations

Our study has some imitations as well. Firstly, this is a single-center cohort study without clear denominator, which could lead to a relevant bias in terms of patient selection. Data analysis was performed retrospectively. Moreover, the sample size in some

subgroups may limit proper analysis by false-positive associations or confounder effects. However, due to the standardized diagnostic and surgical procedures, long follow-up, large patient number, and low drop-out rate this retrospective series still provides valuable information. Nevertheless, the main goal of future investigations should be the generation of prospective data by defining primary endpoints like seizure outcome, quality of life, and social integration after surgical treatment thus providing data with stronger evidence.

CONCLUSION

Despite numerous challenges, surgical treatment of extratemporal lobe epilepsies is successful and provides satisfying epileptological results with an acceptable morbidity. Younger patients with visible lesions distant from eloquent cortex that can be resected completely form the subgroup with the best chance for long-term seizure control.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Sander JW, Shorvon SD. Epidemiology of the epilepsies. *J Neurol Neurosurg Psychiatr*. 1996;61(5):433-443.
2. Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. *Epilepsia*. 1997;38(3):353-362.
3. Baker GA, Nashef L, van Hout BA. Current issues in the management of epilepsy: the impact of frequent seizures on cost of illness, quality of life, and mortality. *Epilepsia*. 1997;38(suppl 1):S1-S8.
4. Roper SN. Surgical treatment of the extratemporal epilepsies. *Epilepsia*. 2009;50(suppl 8):69-74.
5. Elsharkawy AE, Pannek H, Schulz R, et al. Outcome of extratemporal epilepsy surgery experience of a single center. *Neurosurgery*. 2008;63(3):516-526.
6. Oliveira RS, Santos MV, Terra VC, Sakamoto AC, Machado HR. Tailored resections for intractable rolandic cortex epilepsy in children: a single-center experience with 48 consecutive cases. *Childs Nerv Syst*. 2011;27(5):779-785.
7. Behdad A, Limbrick DD, Jr, Epilepsy surgery in children with seizures arising from the rolandic cortex. *Epilepsia*. 2009;50(6):1450-1461.
8. Delev D, Send K, Wagner J, et al. Epilepsy surgery of the rolandic and immediate perirolandic cortex: surgical outcome and prognostic factors. *Epilepsia*. 2014;55(10):1585-1593.
9. Otsubo H, Chitoku S, Ochi A, et al. Malignant rolandic-sylvian epilepsy in children: diagnosis, treatment, and outcomes. *Neurology*. 2001;57(4):590-596.
10. Ansari SF, Tubbs RS, Terry CL, Cohen-Gadol AA. Surgery for extratemporal nonlesional epilepsy in adults: an outcome meta-analysis. *Acta Neurochir*. 2010;152(8):1299-1305.
11. Kim S, Mountz JM. SPECT imaging of epilepsy: an overview and comparison with F-18 FDG PET. *Int J Mol Imaging*. 2011;2011(10):1-9.
12. Pardoe H, Kuzniecky R. Advanced imaging techniques in the diagnosis of nonlesional epilepsy: MRI, MRS, PET, and SPECT. *Epilepsy Curr*. 2014;14(3):121-124.
13. Cardinale F, Cossu M, Castana L, et al. Stereoelectroencephalography. *Neurosurgery*. 2013;72(3):353-366.
14. Shah A, Mittal S. Invasive electroencephalography monitoring: indications and presurgical planning. *Ann Indian Acad Neurol*. 2014;17(5):89.
15. Greiner HM, Horn PS, Tenney JR, et al. Preresection intraoperative electrocorticography (ECoG) abnormalities predict seizure-onset zone and outcome in pediatric epilepsy surgery. *Epilepsia*. 2016;57(4):582-589.
16. Hanáková P, Brázdil M, Novák Z, et al. Long-term outcome and predictors of resective surgery prognosis in patients with refractory extratemporal epilepsy. *Seizure*. 2014;23(4):266-273.
17. Hardy SG, Miller JW, Holmes MD, et al. Factors predicting outcome of surgery for intractable epilepsy with pathologically verified mesial temporal sclerosis. *Epilepsia*. 2003;44(4):565-568.
18. Englot DJ, Breshears JD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after resective surgery for extra-temporal lobe epilepsy in pediatric patients. *J Neurosurg Pediatr*. 2013;12(2):126-133.
19. Englot DJ, Berger MS, Barbaro NM, Chang EF. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. *Epilepsia*. 2012;53(1):51-57.
20. Englot DJ, Han SJ, Berger MS, Barbaro NM, Chang EF. Extent of surgical resection predicts seizure freedom in low-grade temporal lobe brain tumors. *Neurosurgery*. 2012;70(4):921-928.
21. Kral T, Clusmann H, Urbach J, et al. Preoperative evaluation for epilepsy surgery (Bonn algorithm). *Zentralbl Neurochir*. 2002;63(03):106-110.
22. Wellmer J, Quesada CM, Rothe L, Elger CE, Bien CG, Urbach H. Proposal for a magnetic resonance imaging protocol for the detection of epileptogenic lesions at early outpatient stages. *Epilepsia*. 2013;54(11):1977-1987.
23. Oertzen von J, Urbach H, Jungbluth S, et al. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *J Neurol Neurosurg Psychiatr*. 2002;73(6):643-647.
24. Rosenow F, Bast T, Czech T, et al. Revised version of quality guidelines for presurgical epilepsy evaluation and surgical epilepsy therapy issued by the Austrian, German, and Swiss working group on presurgical epilepsy diagnosis and operative epilepsy treatment. *Epilepsia*. 2016;57(8):1215-1220.
25. Chang EF, Clark A, Smith JS, et al. Functional mapping–guided resection of low-grade gliomas in eloquent areas of the brain: improvement of long-term survival. *J Neurosurg*. 2011;114(3):566-573.
26. Palmini A, Najm I, Avanzini G, et al. Terminology and classification of the cortical dysplasias. *Neurology*. 2004;62(6 suppl 3):S2-S8.
27. Blumcke I, Thom M, Aronica E, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia*. 2011;52(1):158-174.
28. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. *Brain Pathol*. 1993;3(3):255-268.
29. Tellez-Zenteno JF, Ronquillo LH, Jetté N, et al. Discontinuation of antiepileptic drugs after successful epilepsy surgery. A Canadian survey. *Epilepsy Res*. 2012;102(1-2):23-33.
30. Schmidt D. Time to withdraw AEDs after successful epilepsy surgery. *Lancet Neurol*. 2012;11(9):745-746.
31. Wieser HG, Blume WT, Fish D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia.* 2001;42(2):282-286.
32. Bauer S, Hamer HM. Extratemporal Epilepsies. In: Vallar, G, Coslett, HB (eds). Handbook of Clinical Neurology. Vol 107. 1st ed. Amsterdam: Elsevier; 2012:241-256. doi:10.1016/B978-0-444-52898-8.00015-X.
33. Sarkis RA, Jehi L, Najm IM, Kotagal P, Bingaman WE. Seizure outcomes following multilobar epilepsy surgery. *Epilepsia*. 2012;53(1):44-50.
34. Hader WJ, Tellez-Zenteno J, Metcalfe A, et al. Complications of epilepsy surgery-a systematic review of focal surgical resections and invasive EEG monitoring. *Epilepsia*. 2013;54(5):840-847.
35. Behrens E, Schramm J, Zentner J, König R. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. *Neurosurgery*. 1997;41(1):1-10.
36. Lehe von M, Wellmer J, Urbach H, Schramm J, Elger CE, Clusmann H. Insular lesionectomy for refractory epilepsy: management and outcome. *Brain*. 2008;132(4):1048-1056.
37. Benifla M, Sala F, Jane J, Jr, et al. Neurosurgical management of intractable rolandic epilepsy in children: role of resection in eloquent cortex. *J Neurosurg Pediatr*. 2009;4(3):199-216.
38. Blumcke I, Aronica E, Urbach H, Alexopoulos A, González-Martínez JA. A neuropathology-based approach to epilepsy surgery in brain tumors and proposal for a new terminology use for long-term epilepsy-associated brain tumors. *Acta Neuropathol*. 2014;128(1):39-54.
39. Zentner J, Hufnagel A, Wolf HK, et al. Surgical treatment of neoplasms associated with medically intractable epilepsy. *Neurosurgery*. 1997;41(2):378-387.

40. Luyken C, Blumcke I, Fimmers R, et al. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. *Epilepsia*. 2003;44(6):822-830.
41. McIntosh AM, Averill CA, Kalnins RM, et al. Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery. *Epilepsia*. 2012;53(6):970-978.
42. D'Argenzio L, Colonnelli MC, Harrison S, et al. Cognitive outcome after extratemporal epilepsy surgery in childhood. *Epilepsia*. 2011;52(11):1966-1972.
43. Elsharkawy AE, Thorbecke R, Ebner A, May TW. Determinants of quality of life in patients with refractory focal epilepsy who were not eligible for surgery or who rejected surgery. *Epilepsy Behav*. 2012;24(2):249-255.
44. Tellez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res*. 2010;89(2-3):310-318.
45. Engel J, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy. *Epilepsia*. 2003;44(6):741-751.
46. Zentner J, Hufnagel A, Ostertun B, et al. Surgical treatment of extratemporal epilepsy: clinical, radiologic, and histopathologic findings in 60 patients. *Epilepsia*. 1996;37(11):1072-1080.
47. Englot DJ, Wang DD, Rolston JD, Shih TT, Chang EF. Rates and predictors of long-term seizure freedom after frontal lobe epilepsy surgery: a systematic review and meta-analysis. *J Neurosurg*. 2012;116(5):1042-1048.
48. Schramm J, Kral T, Kurthen M, Blumcke I. Surgery to treat focal frontal lobe epilepsy in adults. *Neurosurgery*. 2002;51(3):644-655.
49. Jeha LE, Najm I, Bingaman W, Dinner D, Widdess-Walsh P, Lüders H. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain*. 2007;130(2):574-584.
50. Binder DK, Podlogar M, Clusmann H, et al. Surgical treatment of parietal lobe epilepsy. *J Neurosurg*. 2009;110(6):1170-1178.
51. Binder DK, Lehe von M, Kral T, et al. Surgical treatment of occipital lobe epilepsy. *J Neurosurg*. 2008;109(1):57-69.
52. Yang P-F, Jia Y-Z, Lin Q, et al. Intractable occipital lobe epilepsy: clinical characteristics, surgical treatment, and a systematic review of the literature. *Acta Neurochir*. 2015;157(1):63-75.
53. Noe K. Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. *JAMA Neurol*. 2013:70(8):1003-1008. doi:10.1001/jamaneurol.2013.209.
54. Englot DJ, Berger MS, Barbaro NM, Chang EF. Predictors of seizure freedom after resection of supratentorial low-grade gliomas. *J Neurosurg*. 2011;115(2):240-244.

COMMENTS

This is an impressively large case series of surgery for extratemporal lobe epilepsies. Level 1 evidence in epilepsy surgery is scarce, and only present for surgery of temporal lobe epilepsy. Thus, other scientific approaches have to take this role for other types of focal epilepsies. This series describes a "state of the art" from the reported period 1997–2015. Reporting large cohorts still makes sense, even if no striking novelty can be derived. However, such reports provide the reader with reliable information on what has been possible, and what has not been achievable over a defined period of time. This has clear relevance for decision making today: inclusion criteria and results are not very specific, but they mirror the reality we face while taking care for patients undergoing epilepsy surgery, thus they represent an aspect of "truth".

The results of this series are better compared to older series, reflecting improvements in diagnostics, but also in safety of neurosurgical treatment. On the other hand, the immanent limitations of resective surgery, especially in eloquent brain areas, are still limits to be respected. Epilepsy outcome was good and as expected a seizure-free rate of about 60% could be reached. Three hundred eighty-three consecutive patients were included. Due to the large number, numbers for frontal (183), parietal (44), occipital (24), and insular (24) epilepsies seem representative, whereas other numbers, for example the rate of invasive monitoring (31%) and intraoperative electrocorticography (19%) are more related to center policies.

A retrospective cohort study like this has clearly its limitations, but the content shows high quality of interdisciplinary care, and even more important, it's useful to share this vast experience.

Hans Clusmann
Aachen, Germany

In this retrospective series, the authors evaluated 383 cases of extra-temporal epilepsy treated surgically at a single center over 18 years to determine clinical factors associated with seizure outcome. They found that the overall complication rate was 11.8%, and 49% of patients were Engel 1a at an average of 54 months postoperatively. Multivariate analysis revealed that visible lesions, non-eloquent location, absence of postoperative seizures, circumscribed pathology, patient age, and epilepsy duration all correlated with better seizure outcome. They conclude that extra-temporal epilepsy responds well to surgical treatment with acceptable morbidity and good seizure outcome.

The efficacy of surgical treatment for extra-temporal epilepsy is confirmed by the excellent follow-up in this large case series, although the patient population evaluated in the study is heterogeneous with a wide variety of lesions, locations, and presentations, which makes it somewhat difficult to generalize the findings. The diagnostic and surgical practices described are standard, and the predictors of good outcome are generally not modifiable. Nevertheless, the findings in this study demonstrate that surgery in patients with extra-temporal epilepsy is associated with a favorable seizure and complication profile.

Jonathan P. Miller
Cleveland, Ohio