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FULL-LENGTH ORIGINAL RESEARCH

Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery

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Summary

Purpose: We aimed to assess long-term seizure outcome and risk factors for seizure recurrence in a cohort of patients who have undergone extratemporal resection for management of refractory seizures.

Methods: Eighty-one patients underwent extratemporal resection at Austin Health, Melbourne, Australia (1991–2004). Seizure recurrence was any postoperative disabling seizure (complex partial seizure [CPS] ± secondary generalization). Multivariate Cox proportional hazards regression models examined potential preoperative and perioperative risk factors and the risk associated with early postoperative seizures (≤28 days postsurgery). The change between preoperative and postoperative seizure frequency was also measured.

Key Findings: Median follow-up was 10.3 years (range 1–17.7). The probabilities of freedom from disabling seizures (on or off antiepileptic medication) were 40.7% (95% confidence interval [CI] 30–51) at 1 month, 23.5% (95% CI 15–33) at 1 year, and 14.7% (95% CI 8–23) at 5 years postoperative. Reduction of disabling seizures to at least 20% of preoperative frequency was attained by 57% of patients at 5 postoperative years. Of the preoperative/perioperative factors, focal cortical dysplasia (FCD) type I (hazard ratio [HR] 1.90, 95% CI 1.08–3.34, p = 0.025) and incomplete resection (HR 1.71, 95% CI 1.06–2.76, p = 0.028) were independent recurrence risks. After surgery, an early postoperative seizure was the only factor associated with higher risk (HR 4.28 [2.42–7.57], p = 0.00).

Significance: Distinction between subtypes of focal cortical dysplasia, which can be made using magnetic resonance imaging (MRI) criteria, may be useful for preoperative prognostication. Early seizures after surgery are not benign and may be markers of factors that contribute to seizure recurrence. Most patients achieve substantial reduction in seizure frequency. Further study of the significance of this reduction in terms of surgical "success" or otherwise is required.

KEY WORDS: Resection, Recurrence, Focal cortical dysplasia, Balloon cells, Neighborhood seizures.

Outcome after extratemporal resection (defined as resection outside the temporal lobe) has not been as well studied as outcome after anterior temporal lobectomy, and there are few long-term data that are relevant to seizure outcome after this procedure (Tellez-Zenteno et al., 2005; Jeha et al., 2007; Jehi et al., 2009). The identification of risk factors for poor outcome after extratemporal resection for refractory seizures is important for preoperative and postoperative counseling and management.

We aimed to examine seizure outcome and to identify risk factors in a cohort of patients who had undergone extratemporal resection at Austin Health, Australia. We included the entire cohort, with an examination of the effect of site of surgery and years of surgery. Other variables to be examined included histopathology and completeness of resection, as these have been noted as important risk factors for postoperative seizure recurrence in some previous studies (Jeha et al., 2007; Elsharkawy et al., 2008a; Kim et al., 2010). An additional potential risk factor for poor outcome is the occurrence of early seizures (neighborhood/acute seizures) soon after surgery. Although previously discounted as portending poor outcome, recent data suggest that they do predict seizure recurrence after temporal lobectomy (Park et al., 2002; Radhakrishnan et al., 2003; McIntosh et al., 2005; Tezer et al., 2008; Buckingham et al., 2010), and

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perhaps after extratemporal surgery (Mani et al., 2006; Jeha et al., 2007). These and several other potential risk factors were examined using long-term outcome data.

Methods

Subjects

Included were patients who underwent extratemporal resection at the Comprehensive Epilepsy Program at Austin Health, Australia between 1991 and 2004. This cut-off date provided outcome data of at least 5 years. Excluded were eight patients who had previous epilepsy surgery (temporal lobe surgery, n = 6; corpus callosotomy, n = 1; cortical transection, n = 1). This resulted in a study cohort of n = 81.

Preoperative evaluation and surgery

Presurgical evaluation comprised video–electroencephalography (EEG) monitoring, magnetic resonance imaging (MRI) (0.3T prior to 1993 and 1.5T from 1993), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and neuropsychological testing to localize seizure focus. Patients with difficult to localize seizures underwent intracranial electrode placement and monitoring. Details of surgery are included in the Supporting Information.

Outcome data were collected from medical records and communications from treating doctors. Patients who underwent surgery before 1997 were interviewed by telephone if no follow-up data were available for at least 2 years before the date the records were reviewed. Patients who underwent surgery from1997 onward (n = 49) had routine follow-up via the Comprehensive Epilepsy Program at 3–6 month intervals until 2 postoperative years. After this time we conducted a telephone interview if patients had not had medical follow-up for 2 years or more. In cases where additional information was required to clarify data (such as date of recurrence), we requested information from patients, their relatives, or treating doctors.

Histopathology diagnosis

One neuropathologist (RMK) reported all operative specimens. The resected specimens of cerebral tissue were fixed in buffered formalin solution before examination and subsequent serial slicing. Most or all of the tissue was submitted for histologic examination. Histologic diagnosis was in all cases primarily made on examination of hematoxylin and eosin sections, with special stains such as Luxol fast blue and/or immunohistochemical stains used as an adjunct in some cases.

All original histopathology reports were reviewed by the neuropathologist for the current study. When reports contained terminology that was superseded or unclear (n = 21), the original operative specimens were reexamined. All assessment was made blind to outcome.

Histopathology findings were classified as:

1. Lesion, defined as ganglioglioma/other tumor, dysembryoplastic neuroepithelial tumor (DNET), vascular malformations (VMs), and nonneoplastic cystic lesions. Both DNET and ganglioglioma may be associated with cortical dysplasia but were not classified as double pathology (as in the recent International League Against Epilepsy (ILAE) classification of focal cortical dysplasias (Blumcke et al., 2011).
2. Acquired insult (i.e., traumatic injury or ischemic injury)
3. ''Cortical dysplasia,'' which was divided according to the recent ILAE classification of focal cortical dysplasias (Blumcke et al., 2011) into focal cortical dysplasia (FCD) type I (abnormal cortical layering) or FCD type II (disrupted cortical lamination and cytologic abnormalities). Within FCD type II, the presence of balloon cells (FCD type IIb) or absence (FCD type IIa) was noted. The balloon cell dysplasia group included specimens with cortical neuronal disarray, variable numbers of enlarged dysmorphic neurons, and large cells predominantly in the subjacent white matter with nuclei of neuronal type and abundant pale antigenically variable eccentric cytoplasm (Blumcke et al., 2011).
4. Nonspecific pathology, where changes noted were subtle and unable to be otherwise classified, or were of questionable significance (e.g., increased perivascular spaces, gliosis).

The patients with a cortical lesion outside the area of resection were then denoted as a separate group in the histopathology analyses (see item 3 in the section Extent of resection of cortical abnormality below).

Details about type of abnormality as seen on preoperative MRI were not included in the analysis, as the time span covered by the cohort meant that many early MR scans were suboptimal by current standards used to define abnormality type. However, most were of sufficient quality to identify whether an abnormality was present, and this enabled assessment of the extent of resection. Only six cases had negative MR scans but positive histopathology. These comprised: FCD type I, n = 4; FCD type II, n = 1; acquired insult, n = 1.

Extent of resection of cortical abnormality

All available postoperative MRI scans were assessed by one neuroradiologist (LAM). Preoperative and postoperative MRI scans were compared to assess resection extent as accurately as possible. In cases where one or both of the preoperative or postoperative scans were missing, all available radiologic evidence, including the original reports, were reviewed. The extent of resection was classified as:

1. Complete resection of the cortical lesion thought to be responsible for seizure generation, this included cases where only white matter abnormality or gliosis remained
2. Partial resection of the lesion
3. A cortical abnormality located outside the resection, thought to be capable of seizure generation (''extraresection abnormality'')

4 Nonspecific preoperative findings
5 Unable to ascertain due to scan quality or missing information

One patient had genetic testing undertaken some time after surgery and was found to have Ring Chromosome 20 syndrome. This case was coded with the ''extraresection abnormality'' group.

Other potential risk factors

We examined the effect of year of surgery on outcome to account for differences in technology and other changes over the time span of this cohort. This variable was analyzed as a continuous variable, and was also divided into two groups for analysis by dividing cases at the median value.

The risk associated with the presence of preoperative secondary generalized seizures was also examined by coding cases as positive if these events had occurred within the 3 years prior to surgery (McIntosh et al., 2004), or if medical records indicated they had occurred relatively recently. One patient who had experienced therapy-resistant epilepticus partialis continua over a period of 7 weeks before surgery was coded together with the secondary generalized cases. Age at surgery and duration of preoperative epilepsy were also examined as potential risk factors for recurrence. Each variable was split into two groups for analysis by dividing cases at the median value. A variable for the use of preoperative intracranial electrodes was also included in the analysis. All variable assessments were made blind to outcome.

Summary of postoperative seizure outcome

The probability of remaining free of disabling seizures (complex partial seizure [CPS] ± secondary generalization) was calculated using Kaplan-Meier survival analysis. Patients remained in the analysis from time of surgery until the first postoperative seizure or last follow-up for patients who remained seizure-free.

We also examined postoperative change in seizure frequency. Postoperative disabling seizure frequency was calculated as a percentage of preoperative frequency. Medical records were not sufficiently specific to include seizure types in the comparison. Calculations were undertaken at two time points. The first was in the fifth postoperative year (from fourth to fifth postoperative anniversary). The fifth year was selected as it was expected all cases would have a minimum of 5 years of follow-up, and assessment of outcome over the same postoperative period in each patient would be facilitated. The second assessment of outcome was at last follow-up.

Tapering or cessation of AEDs was not included as a risk factor in these analyses due to the small number of patients who were likely candidates (e.g., seizure-free at two postoperative years) for medication reduction. Supporting Information contains further details.

Analysis of risk factors for postoperative seizure recurrence

Analysis 1: examination of preoperative and operative risk factors for recurrence

This first step aimed to assess preoperative and operative risk factors for seizure recurrence. Pathology and extent of resection were included in this first analysis because although they are not known definitively before surgery, modern preoperative neuroimaging provides data that allow these factors to be considered in preoperative prognostication.

A multivariate analysis was conducted using Cox proportional hazard regression. For this analysis, seizure recurrence was represented by the first disabling seizure (CPS ± secondary generalization) after surgery. Entry into the multivariate regression was determined by preliminary univariate analysis of each variable; the threshold for inclusion in the multivariate analysis was $p \leq 0.10$ for at least one subset of a variable.

Analysis 2: risk associated with early postoperative seizures

We also aimed to examine the risk of subsequent recurrence associated with seizures that occur soon after surgery (early postoperative/neighborhood seizures). This variable was not included in the first analysis (above) because these seizures occur after surgery and therefore are an entirely unknown factor that cannot be considered in preoperative prognostication.

For this analysis, all seizures in the first 28 days postsurgery were recoded as ''early seizures'' according to the ILAE proposal (Wieser et al., 2001). Early seizures were analyzed as a risk factor for subsequent recurrence using univariate Cox regression, with the presence of early seizures as a time-dependant covariate. This is appropriate for events that occur after the start of the analysis (i.e., after surgery). Subsequent seizure recurrence was represented by a disabling seizure that occurred from day 29 onward.

Analysis 3: risk associated with all significant variables

We then planned a multivariate analysis including the variables found to be significant risk factors in the first analysis together with the presence or absence of early postoperative seizures.

In the multivariate analyses, results were considered statistically significant at the 5% level.

In some cases, specific dates for seizures were not given and estimated dates (midpoint between the two appointments) were used (McIntosh et al., 2004; Jehi et al., 2010). In all cases the relationship of early seizures to subsequent seizures was correct. However, the calculation of times in the summary statistics should be viewed as a close estimate.

This study was approved by the Austin Health Research Ethics Committee.

Results

Thirty-eight cases (47%) were male. Median follow-up postsurgery was 10.3 years (interquartile range [IQR] 6.3–12.5, range 1–17.7). Eight cases had <5 years follow-up; all were deceased before the 5-year postoperative anniversary. Five of these eight cases had >3 years follow-up at the time of death. All cases had current follow-up (within 2 years); none were lost to follow-up.

Median age at surgery was 27.5 years (IQR 21–38), range 4–60 years. Twelve cases were <16 years old at surgery. The median duration of preoperative epilepsy was 15.9 years. Forty-eight percent of cases had a left-sided resection. Fourteen patients experienced complications related to surgery, n = 9 were anticipated preoperatively due to the location of the surgery. Details are available in the Supporting information. Histopathology comprised: lesions, n = 14; acquired insult, n = 12; FCD type I, n = 18; FCD type II, n = 25 (type IIa, n = 0; FCD type IIb, n = 25); nonspecific findings, n = 5 and extraresection abnormality n = 7.

All patients remained on a routine antiepileptic drug (AED) protocol for the first 2 years after surgery. Ten of the 81 patients had discontinued and remained off their AEDs by last follow-up. Nine of these patients had remained seizure-free at last follow-up, and one experienced a couple of provoked seizures and undetermined events but had not recommenced AEDs.

At total of 10 patients were deceased at last follow-up. There were three possible Sudden Unexpected Death in Epilepsy (SUDEP): one patient died from postoperative complications after the fourth surgical procedure and two were deceased because of recurrence of tumor (glioblastoma, oligoastrocytoma; in both these cases surgery was undertaken to control refractory seizures). Two patients committed suicide and two died of other non–epilepsy-related causes. At the time of death only one patient had remained seizure-free from surgery.

Summary of postoperative seizure outcome

At the time of last follow-up, 70 of 81 cases had experienced a seizure at some time after surgery. The probabilities of freedom from any disabling seizure for the entire cohort were 40.7% (95% CI 30–51) at 1 month, 32.1% (95% CI 22–42) at 3 months postsurgery, 23.5% (95% CI 15–33) at 1 year, and 14.7% (95% CI 8–23) at 5 years (Fig. 1).

We examined seizure outcome including postoperative change in seizure frequency at 5 years postoperative and at the time of last follow-up.

Before surgery frequent daily seizures were common; 34% of patients had seizures 1–4 times a day and 18% had >5 seizures a day. In the fifth postoperative year after surgery, a reduction of at least half the preoperative seizure frequency was experienced by 61% of patients. Major improvement in seizure frequency (<20% of preoperative frequency) was experienced by 56% of the patients (Table 1).

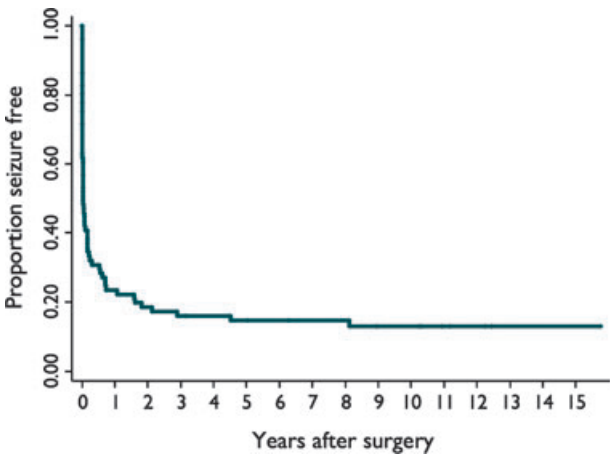

Figure 1.
Probability of seizure freedom after extratemporal resection.
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Table 1. Seizure outcome at five postoperative years

Postoperative seizure outcome[a]	N	%
Major improvement postsurgery		56
Seizure-free from surgery	11	14
Seizures but seizure-free during fifth year	19	24
<10% of preoperative frequency	8	10
10–19% of preoperative frequency	7	9
Some/no improvement postsurgery		37
20–49% of preoperative frequency	4	5
50–99% of preoperative frequency	2	2
Same as preoperative	9	11
More than preoperative	2	2
Reoperation before/during fifth year	13	16
Deceased before/during fifth year[b]	6	7

[a]During fifth year after surgery, seizure-free = free from disabling seizures.
[b]Seizure-free, n = 1; SUDEP (sudden unexpected death in epilepsy), n = 3; tumor recurrence, n = 2; not epilepsy related, n = 1.

Outcome at last follow-up was also assessed, including details for patients who underwent repeat surgery (Table 2). After one surgical procedure, a reduction of at least half the preoperative seizure frequency was attained by 64% of the total patients. Fifty-two percent had a seizure frequency of <20% of preoperative frequency. Twenty-two percent were seizure-free for at least 2 years prior to last follow-up and an additional five patients experienced at least 2 years seizure freedom over the time of follow-up but had seizures recur. Twenty percent of patients had repeat surgery due to unsatisfactory seizure control following their first operation.

The second surgical procedure added an additional 12% who attained a reduced seizure frequency of <20% preoperative by last follow-up. Five of these were seizure-free in the 2 years prior. An additional five cases experienced at least 2 years seizure freedom at some time after

Table 2. Seizure outcome over the 2 years before last follow-up[a]

Outcome at last follow-up (median follow-up 10.3 years)	N (%)
Patients who underwent one operation	65 (80)
Seizure-free from surgery[b1]	11 (14)
Seizure-free for ≥2 years prior to last follow-up[b1]	18 (22)
<10% of preoperative frequency[b1] (≤3 seizure per year, n = 3)	10 (12)
10–19% of preoperative frequency[b1]	3 (4)
20–49% of preoperative frequency[b3]	10 (12)
50–99% of preoperative frequency	4 (5)
Same as preoperative	4 (5)
More than preoperative	1 (1)
Seizures but frequency unable to be assessed[b2]	4 (5)
Patients who underwent repeat surgery	16 (20)
Seizure-free for ≥2 years before last follow-up	5
<10% of preoperative frequency (≤3 seizure per year, n = 2)	3
10–19% of preoperative frequency	2
20–49% of preoperative frequency	3
50–99% of preoperative frequency[b1]	2
Seizures but frequency unable to be assessed	1

[a]Three deceased prior to 2 years postoperative.
[b]Number deceased in each subgroup.

Table 3. Preliminary analysis of potential risk factors for postoperative seizure recurrence

Risk factor	N	HR (95% CI)	p-Value
Site of resection			
Frontal	49	Reference	
Parietal	18	1.51 (0.86–2.66)	0.15
Occipital	8	0.53 (0.21–1.35)	0.19
Multilobe	6	0.93 (0.39–2.19)	0.86
Histopathology			
FCD type II	25	Reference	
FCD type I	18	2.00 (1.04–3.83)	0.04
Tumor/DNET/VM[a]	14	0.99 (0.49–2.02)	0.99
Acquired insult	12	1.11 (0.52–2.37)	0.78
Nonspecific	5	1.14 (0.43–3.04)	0.79
Extraresection abnormality[b]	7	0.79 (0.30–2.09)	0.63
Extent of resection			
Incomplete resection	38	Reference	
Complete resection	17	0.53 (0.28–0.99)	0.05
Extraresection abnormality[b]	7	0.49 (0.19–1.27)	0.14
NAD preoperative[c]	10	0.63 (0.30–1.32)	0.22
No information[d]	9	0.61 (0.28–1.32)	0.21
Intracranial electrodes			
No	55	Reference	
Yes	26	1.36 (0.86–2.22)	0.22
Preoperative secondary generalized seizure[e]			
Yes	62	Reference	
No	19	1.32 (0.72–2.37)	0.36
Year of surgery[+]			
1991–1997	42	Reference	
1998–2004	39	1.24 (0.77–1.98)	0.37

[a]Tumor, n = 8; DNET, n = 3; VM, n = 2; cyst, n = 1.
[b]Extraresection abnormality noted on MRI. Cases comprised: frontal/parietal FCD type II occipital abnormality (pathology = ischemia), additional lesions (probable traumatic injury), Ring 20 Syndrome identified postoperative (pathology = nonspecific), focal cortical abnormality outside the resection area ×2 cases (probable dysplasia). These last two cases were identified on re-review of MRIs.
[c]Six cases NAD on MRI but positive histopathology: FCD type I, n = 4; FCD type II, n = 1; acquired insult, n = 1.
[d]Preoperative scan missing or quality too poor to be useful. Histopathology: FCD type I, n = 2; FCD type II, n = 3; lesion, n = 3; acquired insult, n = 1; nonspecific, n = 1.
[e]Includes n = 1 case with epilepticus partialis continua.
[+]Year of surgery also analyzed as a continuous variable, p = 0.43.

their second operation but had seizures recur. Of the patients that underwent repeat surgery, 15 had one additional procedure and one patient had three additional procedures (this patient died following postoperative complications). Histopathology comprised seven cases with FCD type I, three cases with FCD type II, two with lesions, one case with acquired insult, and three cases with an abnormality outside the resection.

Risk factors for seizure recurrence

Analysis 1: preoperative and operative risk factors for recurrence

Preliminary analysis of potential risk factors for seizure recurrence was undertaken using univariate Cox regression (Table 3). The largest risk groups were used as the reference group. The variables of age at surgery (p = 0.64), duration of preoperative epilepsy (p = 0.96), and side of surgery (p = 0.71) showed no effect and were not included in the table.

There was no effect for preoperative secondary generalized seizures, use of intracranial electrodes before surgery, or year of surgery. Patients with FCD type I had a significantly higher hazard for recurrence compared to patients with FCD type II. Those who had complete resection had borderline lower recurrence compared to those who had incomplete resection. The Supporting information provides the probabilities of seizure-free outcome for pathology and extent of resection.

Multivariate analysis. Multivariate regression was then undertaken including pathology and extent of resection, the two variables that met the threshold for inclusion in multivariate analysis. The pathology groups ''Tumor/DNET/VM'' and ''Acquired insult'' were combined, as their hazard rates were similar and they did not contribute to the results as separate groups. Similarly, extent of resection was combined into three groups: those with incomplete resection, those with complete resection, and other. Reference groups for the analysis were changed so that the subgroups with the greatest risk on the preliminary analyses were used as the reference (Table 4).

When compared to patients with FCD type I, those with FCD type II had a lower hazard for recurrence (after adjustment for extent of resection). Patients with tumor/acquired

Table 4. Multivariate analysis of risk factors for seizure recurrence*

Risk factor	HR (95% CI)	p-Value
Histopathology		
FCD type I	Reference	
FCD type II	0.47 (0.24–0.91)	0.02
Tumor/DNET/VM/insult	0.56 (0.29–1.07)	0.08
Nonspecific	0.76 (0.25–2.31)	0.63
Extraresection abnormality	0.51 (0.17–1.57)	0.24
Extent of resection		
Incomplete resection	Reference	
Complete resection	0.53 (0.28–1.01)	0.06
Other	0.55 (0.29–1.08)	0.08

*Proportional hazards, p = 0.71.

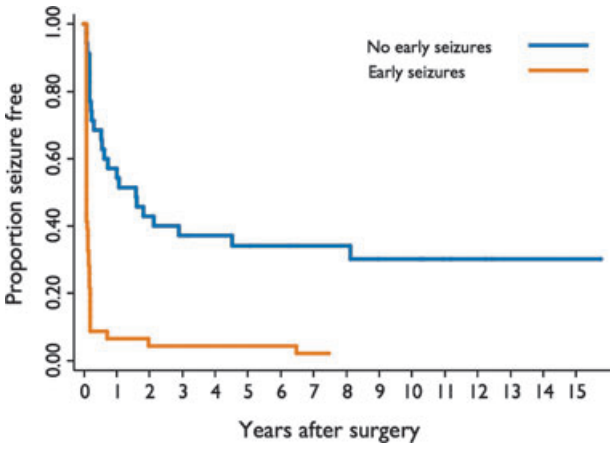

Figure 2.
Kaplan-Meier survival analysis plotting the first seizure after postoperative day 28 for patients who had early seizures (lower orange line) versus those who had no early seizures.
Epilepsia © ILAE

insult had a borderline lower hazard. Patients who had a complete resection had a borderline lower hazard compared to those with incomplete resection but failed to reach significance, possibly due to small numbers in the group.

The model in Table 4 was rationalized further by combining all histopathology other than FCD type I in one group. The resection variable was rationalized by combining patients in the complete resection group and ''other'' group. The combinations of these groups were based on the similar hazard rates of the subgroups. The resulting analysis indicated that FCD type I (HR 1.90, 95% CI 1.08–3.34, p = 0.025) and incomplete resection (HR 1.71, 95% CI 1.06–2.76, p = 0.028) were independent risk factors for seizure recurrence when compared with other groups combined. The interaction term for the two variables was not significant (p = 0.94). This indicates that the effect of one of the variables did not vary with the level of the other variable (i.e., the effect of extent of resection did not vary according to the pathology group, and so on).

Analysis 2: examination of the risk associated with early postoperative seizures

Forty-six cases (57%) had seizures in the first 28 postoperative days (early seizures). Of these, 14 cases had a seizure in the first 2 days postsurgery, 17 in days 3–7, and 15 cases had their first seizure within days 8–28 postsurgery. Subsequent seizure recurrence after the first 28 days was experienced by all but one (45 of 46) of the cases with an early seizure.

Univariate analysis confirmed that the occurrence of early seizures is associated with an increased hazard for subsequent recurrence (HR 4.42; 95% CI 2.57–7.58). The probability of remaining seizure-free after day 28 according to the occurrence of early seizures is plotted in Fig. 2. Patterns of recurrence demonstrate that most patients with early seizures experience further seizures almost immediately after the end of the first 28 days postoperatively.

Cases with FCD type I were more likely to be represented in the early seizure group (FCD type I, 33% [n = 15] in cases with early seizures vs. 9% [n = 3] in cases with no early seizures; $\chi^2_1 = 6.7$, p = 0.01). Patients with incomplete resection were also more common in the group with early seizures (incomplete resection, 61% [n = 21] in cases with early seizures vs. 29% [n = 10] in cases with no early seizures; $\chi^2_1 = 8.3$, p = 0.004).

Table 5. Multivariate analysis of risk factors for seizure recurrence*

Risk factor	HR (95% CI)	p-Value
Early seizures		
No	Reference	
Yes	4.28 (2.42–7.57)	0.00
Histopathology		
Other pathology	Reference	
FCD type I	1.54 (0.87–2.42)	0.14
Extent of resection		
Complete resection and other	Reference	
Incomplete resection	0.98 (0.59–1.63)	0.95

*Proportional hazards, p = 0.21.

Analysis 3: analysis of risk for all variables

Analysis 3 comprised a multivariate regression including the variables shown to have a significant relationship with recurrence in analysis 1, together with the presence or absence of early seizures (Table 5).

The risk associated with early seizures showed little change after adjustment for the effects of the other variables. After adjustment for the effect of early seizures, histopathology and extent of resection did not have a significant effect. Analysis with histopathology and extent of resection in their original subgroups did not result in any additional significant findings.

The interaction terms for early seizure × histopathology (p = 0.4) and early seizure × extent of resection (p = 0.9) were not significant. This indicates that the effect of resection or pathology did not vary according to the level of the variable for early seizures (i.e., whether early seizures occurred or not), although the numbers in some of these subgroups were small.

The occurrence of early seizures was a very good prognostic indicator of later recurrence. All but one of the 46 patients who experienced an early seizure had later recurrence. As such, the investigation of other risk factors for patients who experienced early seizures, such as timing or type of early seizures, was not warranted.

Discussion

This study measured the risk of seizure recurrence after extratemporal resection in three steps. The first analysis assessed the risk associated with preoperative and operative factors. In this analysis the occurrence of any disabling postoperative seizure was assessed as a recurrence. In common with a number of other studies (Zentner et al., 1996; Janszky et al., 2006; Yun et al., 2006; Jeha et al., 2007; Elsharkawy et al., 2008b; Kim et al., 2010; Wagner et al., 2011), we found that the extent of resection was an independent risk factor for seizure recurrence. We also found that the presence of FCD type I was an independent risk factor for recurrence.

There are few published data regarding outcome for subtypes of cortical dysplasia, as studies often group all types of dysplasia together due to small numbers (Lawson et al., 2005). Our study found that cases with FCD type I have a lower seizure-free outcome compared to cases with FCD type II, all of which had FCD type IIb (with balloon cells). Kral et al. (2003) found that patients with dysplasia including balloon cells had better outcome than patients with other dysplasias; our data are concordant with this finding. We are unable to comment on outcome for patients with FCD type IIa (no balloon cells), as they did not appear in our sample. Little is known about the frequency of subtypes type IIa and type IIb in adult epilepsy extratemporal surgery cohorts unselected for histopathology findings. We note that the frequency of FCD type IIa is also small (0–13%) in the few publications comprising predominantly adult cohorts with FCD subgroups (Tassi et al., 2002; Fauser et al., 2004; Siegel et al., 2006; Kral et al., 2007; Lee et al., 2008), most of which were mixed extratemporal and temporal lobe surgeries.

Our findings suggest that that FCD type IIb (with balloon cells) has a hazard similar to the group with tumor/acquired insult and other reasonably discrete pathologies. Lawson et al. (2005) noted that dysplasia with balloon cells (CDT-BC) has relatively well-demarcated margins on histopathology. The hypothesis that FCD type IIb is a relatively discrete abnormality may account for the better postsurgical seizure-free outcome that we found for patients with this pathology. It has also been suggested that dysplasia with balloon cells is associated with increased epileptogenicity on clinical and electrocorticographic measures (Rosenow et al., 1998; Kim et al., 2011).

The findings of this analysis may be helpful in formulating preoperative prognosis. We used the most accurate measures of extent of resection and histopathology available in this cohort where surgery spanned 13 years. Our findings are relevant to contemporary preoperative prognostication, as current imaging allows most gross pathologies to be accurately identified and assessment of resection to be made before surgery. The consensus classification of focal cortical dysplasia (Blumcke et al., 2011) notes several MRI appearances that contribute to differentiation of dysplasia with balloon cells, including a ''transmantle'' signal change (extending from the cortex to the lateral ventricular surface) (Barkovich et al., 1997) that is almost exclusively associated with FCD type IIb (Blumcke et al., 2011). Further research into the identification and surgical outcome of dysplasia subtypes would contribute to patient counseling and management.

We did not find a significant effect for year of surgery, suggesting differences in technology over time have not had a significant effect on outcome. This is probably because we used recently reviewed histology rather than MRI findings, the utility of which may vary according to the technology available at the time. In contrast to some other studies (Kral et al., 2003; Janszky et al., 2006; Jeha et al., 2007; Lee et al., 2008; Tellez-Zenteno et al., 2010), we did not find a higher risk for cases with normal histopathology or extraresection abnormality. Our numbers in these groups are small (n = 5 and n = 7, respectively) and further analysis using larger numbers is required.

Early seizures (during the first 28 days after surgery) are strongly associated with subsequent recurrence (analysis 2). In fact, 45 of 46 patients who experienced early seizures went on to have subsequent seizures. This suggests that early seizures should not be considered as benign events or excluded when assessment of seizure outcome is conducted. Our findings concur with Jeha et al. (2007), and add to growing evidence of the poor prognosis associated with these so-called ''neighborhood seizures'' after temporal and extratemporal surgery. Figure 2 demonstrates a pattern of rapid recurrence among those who experience early seizures, suggesting that a residual epileptogenic zone may contribute to these events.

Although histopathology and extent of resection were important preoperative and perioperative prognostic factors; neither showed an effect after adjustment for early postoperative seizures (analysis 3). This suggests that after surgery, the occurrence of early seizures is an effective prognostic indicator for later recurrence in this extratemporal surgery group. Rather than being a cause of subsequent recurrence in themselves, it is likely that early seizures are a very

efficient marker of the combination of factors (including pathology and resection) that contribute to seizure recurrence after extratemporal resection (Jeha et al., 2007). Early seizures may represent these risk factors more accurately than other measures, at least in historical cohorts. This may account for the lack of effect of resection extent or histopathology in this final analysis.

We have not formally examined the effect of postoperative AED withdrawal on seizure recurrence in this study. Determination of the risk associated with this factor remains difficult given the small number of studies that have examined this issue and the fact that patients who attempt medication withdrawal are highly selected.

Our study demonstrates low probabilities of complete seizure freedom in this cohort, with 15% (95% CI 8–23) seizure-free at 5 postoperative years. It should be noted that complete seizure freedom is a ''harsh'' measure; 57% of cases had a major benefit at 5 years (<20% preoperative frequency). Published seizure-free outcomes from extratemporal surgery vary widely. In a meta-analysis by Tellez-Zenteno et al. (2005), the pooled percent seizure-free was 27–46% seizure-free. They noted the highly heterogeneous nature of the data, with reports of seizure freedom among seven studies of frontal lobe resections ranging from 9–80% seizure-free. Even in the case of a standardized procedure such as anterior temporal lobectomy, comparisons of seizure freedom are difficult given the variety of methodologies and classifications in use (McIntosh et al., 2001; Tellez-Zenteno et al., 2005). Comparisons are, therefore, particularly problematic for nonstandardized extratemporal resections, where the proximity of functional cortex to the seizure focus and the diffuse and widespread nature of the abnormalities create additional difficulties for surgery.

Arguably, in these circumstances, it is the selection of surgical candidates that plays a major role in outcome differences between centers. Selection is likely to depend on the availability of technology and the degree of complexity that each center finds acceptable. Surgical centers that operate on more complex cases are likely to have lower outright seizure-free results. In these cases, the concordance of preoperative seizure outcome prognostication with postoperative results may be a useful measure of outcome.

Although we have not formally examined this issue, the complex nature of the presenting epilepsy is reflected in the prognosis offered to patients who are considering this surgery at our center. Broadly speaking, patients are given a prognosis of between 40% and 60% chance of seizure freedom or improvement in seizure status. Our findings indicate that 52–56% of patients have a postoperative seizure frequency that is <20% of the preoperative frequency. Despite the fact that continued seizures preclude attainment of a driver's license and affect other activities, this outcome should be seen in the context of both the severity of the preoperative epilepsy and the expectations of the patients. A previous study of ours found that the outlook for patients who experience seizures after epilepsy surgery is not uniformly negative, with some individuals expressing satisfaction with outcome in cases where substantial improvement in seizure status had occurred (Shirbin et al., 2009). The authors of another study (Derry & Wiebe, 2000) have noted that ''failure'' of epilepsy surgery is a judgment based on preoperative expectations. Further examination of these issues including impact on quality of life would contribute to the understanding of postsurgical outcome (Tracy et al., 2007), particularly in situations where individuals have severe complex epilepsy and surgery does not offer a high likelihood of seizure freedom.

In conclusion, postsurgical seizure outcome among those who have undergone extratemporal resection for treatment of refractory seizures is a complex issue affected by a number of factors. Our study of this extratemporal cohort indicates that incomplete resection and FCD type I are independent risk factors for seizures after surgery. Our data suggest that the identification of dysplasia subtypes may be advantageous in terms of surgical planning and management. Early seizures after surgery are associated with recurrence, adding to the growing data that suggests they should not be discounted as benign events. These seizures are probably efficient markers of the combinations of factors that contribute to poor outcome after extratemporal surgery. Despite the difficulties associated with extratemporal resection, most patients achieve notable reduction in seizures. These data may be of use when counseling patients before surgery.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Details of surgery.

Data S2. AED withdrawal.

Data S3. Complications related to surgery.

Data S4. Probabilities of seizure freedom at the first postoperative year.

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