Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence

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Summary

There is little information available relevant to long-term seizure outcome after anterior temporal lobectomy, particularly at extended postoperative periods. The aim of this study was an in-depth examination of patterns of longitudinal outcome and potential risk factors for seizure recurrence after lobectomy, utilizing a large patient sample with long follow-up. Included were 325 patients who underwent anterior temporal lobectomy between 1978 and 1998 (mean follow-up 9.6 ± 4.2 years). Retrospective data were analysed using survival analysis and multivariate regression with Cox proportional hazard models. The probability of complete seizure freedom at 2 years post-surgery was 55.3% [95% confidence interval (CI) 50–61]; at 5 years, 47.7% (95% CI 42–53); and at 10 postoperative years it was 41% (95% CI 36–48). Patients with discrete abnormalities preoperatively (i.e. lesions and hippocampal sclerosis) had a significantly higher probability of seizure freedom than patients without obvious abnormality. The latter group had a pattern of recurrence similar to that in patients with lesions outside the area of excision. After adjustment for preoperative pathology, only the presence of preoperative secondarily generalized seizures had a significant association with recurrence [occasional preoperative generalized seizures, hazard ratio (HR) 1.6, 95% CI 1.1–2.3; frequent seizures, HR 2.0, 95% CI 1.4–2.9 compared with absence of preoperative generalized seizures]. Duration of preoperative epilepsy, age of seizure onset and age at surgery did not have an effect on outcome. Patients with two seizure-free postoperative years had a 74% (95% CI 66–81) probability of seizure freedom by 10 postoperative years. This late seizure recurrence was not associated with any identified risk factors. Specifically, patients with hippocampal sclerosis were not at higher risk. Surprisingly, complete discontinuation of anti-epileptic drugs (AEDs) after two postoperative years was not associated with an increased risk of recurrence (HR 1.03, 95% CI 0.5–2.1). This may be because selection of patients for AED discontinuation is biased towards those individuals perceived as ‘low risk’. The results of this study indicate that the lack of an obvious abnormality or the presence of diffuse pathology, and preoperative secondarily generalized seizures are risk factors for recurrence after surgery. Late recurrence after initial seizure freedom is not a rare event; risk factors specific to this phenomenon are as yet unidentified.

Keywords: epilepsy surgery; temporal lobe; seizure outcome; recurrence

Abbreviations: AEDs = anti-epileptic drugs; CI = confidence interval; DNET = dysembryoplastic neuroepithelial tumour; FTL = foreign tissue lesion; HR = hazard ratio; HS = hippocampal sclerosis; IQR = interquartile range

Introduction

Anterior temporal lobectomy is now well established as effective in patients with medically refractory temporal lobe epilepsy (Wiebe et al., 2001). Most current studies of seizure outcome after anterior temporal lobectomy tend to have short follow-up and use cross-sectional methods of analysis. As a result, there are few data relevant to long-term outcome patterns...
and few studies that have examined risk factors for recurrence using longitudinal methods (McIntosh et al., 2001). Further understanding of these issues is essential for pre- and postoperative counselling of patients and long-term postoperative management.

Data from the small number of studies with longitudinal outcome beyond two postoperative years indicate that the outcome pattern is an initial rapid decrease in the proportion of seizure-free cases followed by a slower decrease for at least several years afterwards (Berkovic et al., 1995; Wyler et al., 1995; Sperling et al., 1996; Foldvary et al., 2000; Yoon et al., 2003). The purpose of this current study was to use extended follow-up data and a large surgical cohort to examine long-term postoperative seizure outcome. In particular, we aimed to assess seizure freedom at extended periods of follow-up, and measure the frequency of late seizure recurrence after a period of initial seizure freedom; the latter is of particular importance as many patients regard themselves as ‘cured’ after one or two postoperative years without seizures.

We also aimed to examine long-term seizure freedom and late recurrence with respect to preoperative pathology and a number of risk factors for seizure recurrence. Specifically, we tested whether age of seizure onset, age at surgery, duration of epilepsy and the presence of generalized preoperative seizures were associated with long-term postoperative seizure outcome and late recurrence. These factors were included because of contradictory findings from previous studies (as discussed in McIntosh et al., 2001). Additionally, the use of univariate analyses in many previous studies means that associations between the variables frequently are not taken into account (McIntosh et al., 2001). In this study, the effects of these variables were analysed using multivariate analysis, including adjustment for preoperative pathology.

One of the most obvious potential risks for seizure recurrence after surgery is discontinuation of anti-epileptic drugs (AEDs). This issue is highly pertinent, as patients commonly cite the hope of AED discontinuation as a reason for undergoing epilepsy surgery (Wilson et al., 1998). Yet there is limited information about the risks of seizure recurrence posed by AED discontinuation. Therefore, we also aimed to investigate AED discontinuation as a potential risk factor for seizures after surgery.

Large long-term surgical cohorts with systematic follow-up are the optimal resource for studying these long-term seizure outcome patterns. One issue that is closely associated with long-term follow-up but rarely addressed is the evolution of technological, procedural and diagnostic sophistication over the span of these cohorts (McIntosh et al., 2001). For example, many studies utilize histopathology ‘diagnoses’ made at the time of surgery. In some cases, these may be misleading due to the presence of inadvertent misclassifications related to less sophisticated technologies (i.e. undiagnosed extratemporal lesions), or incomplete histological specimens due to surgical techniques such as suction extraction. The design of this study takes these issues into account.

Methods

Subjects

Three hundred and sixty patients underwent standard anterior temporal lobectomy at the Comprehensive Epilepsy Program, Austin Health between January 1, 1978 and December 31, 1998 (the term ‘temporal lobectomy’ as used herein denotes anterior temporal lobectomy described below). The preoperative evaluation and surgical procedure have been described previously (Berkovic et al., 1995). Surgery was performed by or under the direction of one of three surgeons. Over the period of the study, the surgical technique was modified somewhat to restrict the amount of neocortex resected. A standardized procedure involved a 3.5–5.5 cm resection including hippocampus and lateral amygdala. Lesionectomy without hippocampal resection was performed for cases where the lesion was remote from a normal appearing hippocampus.

Excluded from this study were eight cases that had undergone previous seizure surgery and 27 cases with insufficient evidence on either MRI or histopathology to establish preoperative pathology. Seizure outcome was studied for the remaining cohort of 325 patients (including the 135 patients studied in Berkovic et al., 1995).

Follow-up

Follow-up for patients who underwent temporal lobectomy after 1986 (n = 285) has been described previously (Berkovic et al., 1995). Follow-up is conducted second yearly by telephone for patients who had not had contact with Austin Health in the previous 2 years. Patients prior to 1986 who had not remained patients at Austin Health were contacted by telephone, and seizure history since last follow-up was reviewed.

Preoperative pathology groups

‘Best evidence’ pathology diagnosis

The method of coding preoperative pathology attempted to take into account the evolution of technology and reflect the actual preoperative pathology as closely as possible. All available information, including the reports of pre- and postoperative investigations at Austin Health and reports from treating neurologists, were reviewed. All histopathology specimens were reviewed systematically by one neuropathologist, and coded as for our previous study (Berkovic et al., 1995). Histopathology and ‘best evidence’ classifications were performed blinded to outcome.

The decision as to the ‘best evidence’ preoperative pathology was accomplished as follows. For cases where the postoperative specimen included the hippocampus, and pre- and postoperative MRI reports were concordant with histopathology, then histopathology findings were used to classify ‘best evidence’ preoperative pathology. Cases where pathology was insufficient or not concordant with MRI reports were treated as follows. (i) Where the hippocampal specimen was insufficient to judge the presence of hippocampal sclerosis (HS) accurately (n = 38), the preoperative MRI scan was reviewed (Jackson et al., 1990). ‘Best evidence’ preoperative pathology was then decided in conjunction with the histopathology results. (ii) In cases where histopathology and MRI reports gave conflicting or unclear information, preoperative and postoperative scans (where available) were reviewed blind by a neuroradiologist and a decision as to ‘best evidence’ pathology was made (by S.B and A.M.). If the scans were unavailable, a decision was made from all available data.

For example, if the patient lacked an interpretable hippocampal specimen due to complete suction removal but had unequivocal HS on
MRI, ‘best evidence’ pathology was coded as HS. Likewise, patients who had no major abnormalities in the histopathology but were noted to have an extratemporal lesion on a later review of the preoperative MRI or a more recent postoperative MRI were coded as a ‘distant lesion’ case.

‘Best evidence’ pathology was coded as: (i) foreign tissue lesions (FTLs) comprising: vascular malformations, tumours, dysplastic leptomeningeal tumour and cysts; (ii) HS; (iii) ‘other’ focal temporal lobe lesions, i.e. dysplasia and other lesions large enough to be seen macroscopically (e.g. post-traumatic gliosis) (Berkovic et al., 1995); (iv) ‘normal’ temporal lobe including hippocampus; ‘normal’ was a general term, used to denote cases with histological abnormalities that were mild and generally diffuse (e.g. microdysgenesia) or cases with MRI findings of minor global atrophy, or extratemporal lesions judged as non-epileptogenic (e.g. small areas of increased white matter signal); and (v) cases where a potentially epileptogenic lesion was present outside the area of excision were classified as ‘distant lesion’ cases (heterotopia, tumours, obvious dysplastic lesions or contralateral hippocampal sclerosis).

Histopathology with adjustment for era of surgery
The above approach introduced a potential for bias, as some early patients had no preoperative MRI, and postoperative reinvestigation information was not available for all patients (i.e. those who had not experienced seizure recurrence did not usually have reinvestigations). Therefore, a second analysis was undertaken using histopathology results alone, including a statistical adjustment for the era of surgery. This adjustment was a way of accounting for the changes in technology and knowledge over the years, and the effect these may have had on the accuracy of localization.

For the purpose of this analysis, three groups spanning a roughly equal number of surgery years were coded. These comprised cases from 1979 to 1985, 1986 to 1991 and 1992 to 1998. This grouping also roughly reflected the ‘eras’ in preoperative investigations available to the Comprehensive Epilepsy Program cohort. Preoperative MRI (0.3 T) became routine from 1986, and 99mTc HMPAO SPECT (single photon computed tomography) became available shortly afterwards. In late 1992, interictal [18F]fluorodeoxyglucose (FDG) PET became a routine preoperative investigation, and a 1.5 T MRI scanner was used from early 1993.

Risk factors for recurrence
Potential risk factors for recurrence included in this analysis were age at onset, duration of preoperative epilepsy, age at surgery, the presence of preoperative secondarily generalized seizures and postoperative discontinuation of AED. The presence of postoperative aura/simple partial seizures was not assessed as a risk factor in this analysis because the complex nature of such an analysis requires a separate study.

Age at onset, duration of preoperative epilepsy, age at surgery and preoperative secondarily generalized seizures
Data for these variables were extracted from the patients’ medical files. Variables were collected and coded blinded to outcome. Age at onset was defined as the onset of any afebrile seizures.

In terms of preoperative generalized seizures, patients were coded as having had at the time of preoperative admission: (i) no preoperative secondarily generalized seizures (excluding initial seizure at time of diagnosis and at time of drug withdrawal); (ii) previous secondarily generalized seizures but none for at least 3 years (including those who claimed none for ‘a few years’); (iii) occasional secondarily generalized seizures (no more than two per year average) at the time of preoperative admission; and (iv) frequent secondarily generalized seizures.

The terms ‘convulsions’ or ‘tonic-clonic’ seizures in patient files were accepted as evidence of secondarily generalized seizures.

Discontinuation of AEDs
The protocol at Austin Health is that patients remain on AEDs for a minimum of 2 years after surgery. Tapering and eventual discontinuation of AEDs is tailored to the individual; all patients progress through an extended period of AED taper before finally ceasing medication.

Information regarding AED discontinuation was obtained from medical records. Where medical records indicated that discontinuation occurred between two appointments or follow-up contacts, the date of AED discontinuation was taken as the mid-point of this time period. This period of time was usually a few months, and rarely longer than 1 year. Cases where this time period was longer than 1 year were excluded from analyses if the calculation of time from AED discontinuation to exit from analysis was a factor.

It was not possible to code drug discontinuation and remain blinded to outcome, as the medical notes tended to include reports on both. However, each variable was coded separately from the other and on a different occasion.

Missed AED doses
We could not make an unbiased assessment of poor AED compliance as a risk factor for recurrence. This was because of the strong possibility that non-compliance was not reported unless it was associated with a seizure. Therefore, non-compliance was not considered in this analysis, and seizures associated with missed doses were coded as drug withdrawal seizures (see ‘Outcome’ section below).

Outcome
Patients were classified as seizure free or not seizure free. The seizure-free group included those who experienced auras (simple partial seizures only), ‘neighbourhood’ seizures (1 month post-surgery) (Commission on Neurosurgery of the International League against Epilepsy, 2001) and drug withdrawal seizures (except in cases outlined in the following section). This agrees with Engel’s outcome classification Class I a), b) and d) (Engel et al., 1993). Drug withdrawal seizures were identified as seizures that occurred within 7 days of abrupt AED discontinuation or a substantial drop in medication, gastrointestinal upset severe enough to suspect failure to absorb medication, or low medication levels proven on a blood test.

Where medical records indicated that a seizure recurrence occurred between two appointments or follow-up contacts, the date of the seizure was estimated using the same approach outlined above for the date of AED discontinuation. Late seizure recurrence was nominated as seizures after two postoperative years. In some analyses, recurrence after one seizure-free year was also calculated. Outcome had already been coded blind for a prior study (McIntosh et al., 1999).
Outcome for analyses related to AED discontinuation following a period of taper
The issue of drug withdrawal seizures required special consideration for analyses related to outcome after AED discontinuation. Only two patients were noted to have experienced (‘convulsive’) seizures in close proximity to the last dose of AEDs after a tapered reduction. These events were coded as drug withdrawal seizures, which according to the Engel classification (Engel et al., 1993) allows them to remain as Class I or ‘seizure free’. However, due to the potential implications of these two cases for the analyses of AED discontinuation, the ‘drug withdrawal’ seizures were recoded as a ‘seizure recurrence’ (i.e. not seizure free) for the purposes of this analysis alone.

Statistics
Kaplan–Meier ‘survival’ analysis was used to calculate the probability of seizure freedom and late seizure recurrence. Statistical significance was tested using the log-rank test and comparison of 95% confidence intervals (CIs).

Potential risk factors for recurrence were examined using Cox proportional hazards models. Variables significant at the 10% level in preliminary univariate analyses were included in the multivariate Cox proportional hazards regression models. Cox regression was also used to adjust for era of surgery when analysing outcome according to histopathology findings.

Discontinuation of AEDs was analysed as a time-dependent variable using Cox regression. This is the preferred approach for variables that change their values during the observation time (i.e. after surgery). The analysis was restricted to patients who were seizure free at two postoperative years, as the protocol at Austin Health is to maintain medication for at least 2 years post-surgery. As is the case for the preoperative variables, this method takes into account the time to seizure recurrence when comparing the ‘survival’ experience of patients who had ceased AEDs with those who had not.

The proportional hazards assumption associated with Cox regression was tested and no significant violations were found (data not shown). Results were considered statistically significant at the 5% level.

Results
Among the 325 temporal lobectomies, 145 had right-sided surgery. There were 18 deaths in the series. There was no operative mortality; causes of death were: sudden unexplained death in epilepsy (SUDEP) (n = 11), suicide (n = 4), accident (n = 2) and an unrelated medical condition (n = 1). All but two deceased patients had seizure recurrence before death.

Mean postoperative follow-up from surgery was 9.6 ± 4.2 years [0.7–23 years; interquartile range (IQR) 6.6–12.3]. Only five patients had follow-up of <2 years (four deceased and one lost to follow-up). Only 11 patients (3.4%) were lost to follow-up. Patients who were deceased or lost to follow-up contributed data up to their last follow-up date. Follow-up was current to January 1, 2001.

Long-term seizure outcome
Seizure recurrence after surgery occurred in 190 patients. Amongst the sample as a whole, the probability of seizure freedom dropped to 78.5% in the first 3 months after surgery, and to 67.4% by 6 months. This was followed by a 2.7–5.6% drop in seizure-free probability per year until 5 years, with a slower attrition after this. At one postoperative year, the probability of seizure freedom was 60.9% (95% CI 55–66), and at two postoperative years it was 55.3% (95% CI 50–61). At 5 years, the probability was 47.7% (95% CI 42–53), and at 10 years 41% (95% CI 36–48) and at 15 years 36.8 (95% CI 30–44).

The identity of the surgeon did not have a significant effect on outcome (univariate log rank test P = 0.7).

Seizure outcome according to preoperative pathology
‘Best evidence’ pathology diagnosis
This comprised FTLs n = 51 (11 with co-existent HS), HS n = 201, ‘normal’ temporal lobe n = 33, ‘other’ n = 16 (three with co-existent HS) and ‘distant lesion’ n = 24.

FTLs comprised vascular malformations (n = 11), astrocytoma/oligodendromas (n = 6), gangliogliomas (n = 15), DNETs (n = 16) and cysts (n = 3). Of those in the ‘distant lesion’ group, 10 patients had a malformation of cortical development, one had a ganglioglioma, one had a DNET, two had a gliotic lesion, two had an uncharacterized lesion, six had bilateral HS and two had other abnormalities. The ‘distant lesions’ were ipsilateral in 13, contralateral in one and bilateral in 10 patients (including those with bilateral HS). Three patients had co-existent HS (excluding those with bilateral HS).

In 48 patients, the ‘best evidence’ pathology diagnosis (using all available evidence) differed from the histopathology (using temporal specimens alone). Most of the changes in ‘diagnosis’ occurred amongst the group with a ‘normal’ temporal lobe.

Kaplan–Meier estimates of the probability of long-term seizure freedom for the ‘best evidence’ preoperative pathology groups were calculated (Fig. 1).

Figure 1 illustrates a higher probability of seizure freedom for patients in the FTL and HS groups compared with the patients in the other three groups. Amongst those with FTLs, four patients had incompletely excised lesions; three of these experienced seizure recurrence. All individuals with a ‘distant lesion’ experienced seizures, although one patient (with moderately extensive polymicrogyria) was seizure free for 15 years before recurrence. The lower three curves in Fig. 1 are very similar, and the steep drop in survival estimates indicates that seizures tended to recur quickly amongst these patients. Seizure recurrences after 2 years were seen in all groups. The flattening of curves at extended follow-up periods is related to smaller numbers in these groups at this time. Seizure-free estimates are provided in more detail in Table 1. CIs for the FTL and HS groups overlap at each time point, indicating that outcome does not differ significantly. The difference in overall outcome estimates (‘survival functions’)
between patients with FTLs and HS is of borderline significance (log-rank test \( P = 0.054 \)). There is a statistically significant difference in estimates of seizure freedom between patients with lesions and HS compared with those in the other groups, as indicated by discrete CIs. The wide CIs for the smaller groups in the extended follow-up periods indicate that these survival estimates are less reliable.

Analyses of outcome according to histopathology after adjustment for era of surgery

This next analysis examined outcome according to the (temporal lobe) histopathology findings alone. In other words, additional information (such as a later MRI scan) was not taken into account. To account for the changes in technology and knowledge over the years, statistical adjustments were made for ‘era of surgery’. This approach provided an alternative to the ‘best evidence’ pathology diagnosis (above).

Histopathology groups comprised FTLs \( n = 51 \), HS \( n = 191 \), ‘normal’ temporal lobe \( n = 68 \) and ‘other’ \( n = 15 \). Of these cases, \( n = 35 \) in the ‘normal’ group and \( n = 3 \) in the ‘other’ group lacked sufficient tissue to assess the hippocampus for sclerosis and were excluded from this analysis. Era of surgery comprised 1979–1985 \( n = 25 \), 1986–1991 \( n = 128 \) and 1992–1998 \( n = 134 \).

Kaplan–Meier estimates of long-term outcome according to histopathology produced results that differed no more than 3% from the estimates produced using ‘best evidence’ pathology and are not presented in detail. Cox regression calculated the hazard of recurrence for the histopathology group, after adjustment for era of surgery. The HS group was used as the reference group. When compared with patients with HS, patients with lesions had a lower hazard of recurrence, of borderline statistical significance [hazard ratio (HR) 0.62; 95% CI 0.38–1.00, \( P = 0.051 \)]. Patients with ‘other’ pathology or ‘normal’ findings had a hazard of recurrence at least three times greater than patients with HS (HR 3.03; 95% CI 1.9–4.7, \( P = 0.00 \) and HR 3.36; 95% CI 1.8–6.3, \( P = 0.00 \), respectively).

Era of surgery did not have a significant effect on outcome in either a univariate (\( P = 0.67 \)) or a multivariate (Cox) regression. When era of surgery was added to the regression, there were negligible changes in hazard rates for histopathology, indicating that confounding of the two variables did not occur.

As results for both approaches to pathology categorization were similar, further analysis was undertaken using ‘best evidence’ pathology only.

Analyses of risk factors for recurrence in long-term outcome

As the distant lesion group was comprised of cases that were clearly not unilateral temporal lobe cases (see ‘Best evidence pathology diagnosis’), they were dropped from this analysis. This resulted in a sample of \( n = 301 \).

Descriptive data pertaining to AED discontinuation

Ninety-four patients (31%) had stopped taking their AEDs by the date of last follow-up. Data relevant to AED discontinuation were missing on four patients. All patients who stopped taking their medication were seizure free from surgery at the time that AEDs were discontinued (one patient experienced a single ‘drug withdrawal seizure’ when one of two AEDs was discontinued). Median time until medication discontinuation was 3.6 years after surgery (IQR 2.5–5.7; range 0.34–15.2). Eleven cases stopped taking their medication prior to 2 years post-surgery. Of these 11, all but two remained seizure free after cessation. Eighty-three patients discontinued medication...
<table>
<thead>
<tr>
<th>Years post-surgery</th>
<th>Foreign tissue lesion (n = 51)</th>
<th>Hippocampal sclerosis (n = 201)</th>
<th>‘Normal’ pathology (n = 33)</th>
<th>Other (n = 16)</th>
<th>Distant lesion (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases remaining in analysis</td>
<td>Probability seizure free (%)</td>
<td>95% CI</td>
<td>Cases remaining in analysis</td>
<td>Probability seizure free (%)</td>
</tr>
<tr>
<td>1 year</td>
<td>40</td>
<td>78.4</td>
<td>64.5–87.4</td>
<td>135</td>
<td>67.7</td>
</tr>
<tr>
<td>2 years</td>
<td>38</td>
<td>76.4</td>
<td>62.2–85.9</td>
<td>124</td>
<td>62.2</td>
</tr>
<tr>
<td>5 years</td>
<td>35</td>
<td>72.4</td>
<td>57.9–82.6</td>
<td>95</td>
<td>54.2</td>
</tr>
<tr>
<td>10 years</td>
<td>13</td>
<td>59.6</td>
<td>43.7–72.4</td>
<td>38</td>
<td>47.0</td>
</tr>
<tr>
<td>15 years</td>
<td>3</td>
<td>51.1</td>
<td>30.2–68.6</td>
<td>7</td>
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</tr>
</tbody>
</table>
after two postoperative years; 13 (15.7%) experienced seizures by last follow-up (log-test P = 0.92). Further analysis of AED discontinuation was restricted to the analysis of outcome after two postoperative years (see late seizure recurrence).

Univariate analyses of risk factors for recurrence
Variables of interest in this analysis were age at onset, duration of preoperative epilepsy, age at surgery and the presence of preoperative secondarily generalized seizures. Preliminary analyses (not shown) indicated that age at onset, age at surgery and duration of epilepsy appeared to exert a non-linear effect on the hazard. Therefore, analysis was undertaken with the variables divided into two categories at the median value.

Using univariate Cox regression procedures, a longer duration of epilepsy, later age at surgery and the presence of secondarily generalized seizures had statistically significant associations with poor outcome (Table 2). Age at surgery and duration of preoperative epilepsy were correlated (r = 0.64, P = 0.00). Age of onset had no effect and was not considered further in this analysis.

Outcome for the ‘previous’ category of the ‘generalized seizure’ variable was not significantly different from outcome for those with no secondarily generalized seizures. Therefore, these two groups were combined.

Multivariate regression analysis
After adjustment for ‘best evidence’ preoperative pathology, the presence of preoperative generalized seizures had a significant association with postoperative seizure recurrence (Table 3). The age at surgery and duration of preoperative epilepsy failed to attain statistical significance. Testing confirmed that ‘duration’ and ‘age at surgery’ could be removed from the model with no significant impact (log partial likelihood ratio test P = 0.25). The final model is presented below (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of epilepsy (range 1.6–51.4; IQR 12.0–25.4)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤18.5 years n = 151</td>
<td>1.08</td>
<td>0.64</td>
<td>0.59–2.03</td>
</tr>
<tr>
<td>&gt;18.5 years n = 150</td>
<td>1.38</td>
<td>0.04</td>
<td>1.01–1.87</td>
</tr>
<tr>
<td>Age at surgery (range 6.7–58.8; IQR 21.3–37.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤29.5 years n = 154</td>
<td>1.5</td>
<td>0.01</td>
<td>1.09–2.03</td>
</tr>
<tr>
<td>&gt;29.5 years n = 147</td>
<td>1.08</td>
<td>0.64</td>
<td>0.79–1.46</td>
</tr>
<tr>
<td>Age at onset (range 0.25–40; IQR 3–16)</td>
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</tr>
<tr>
<td>≤8 years n = 151</td>
<td>1.08</td>
<td>0.64</td>
<td>0.79–1.46</td>
</tr>
<tr>
<td>&gt;8 years n = 150</td>
<td>1.38</td>
<td>0.04</td>
<td>1.01–1.87</td>
</tr>
<tr>
<td>Preoperative secondarily generalized seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None n = 147</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous n = 14</td>
<td>1.22</td>
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</tr>
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<td>Occasional n = 75</td>
<td>1.60</td>
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<td>1.11–2.34</td>
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<tr>
<td>Frequent n = 65</td>
<td>1.96</td>
<td>0.00</td>
<td>1.34–2.86</td>
</tr>
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</table>

Post hoc comparison
We were interested in whether the borderline statistically significant difference between the FTL group and the HS group changed when the presence of secondarily generalized seizures was taken into account. In the FTL group, 32% of patients had experienced recent preoperative generalized seizures, compared with 49% in the HS group. The unadjusted hazard for patients with FTLs compared with those with HS was HR 0.63, 95% CI 0.39–1.02, P = 0.06. Comparison with the adjusted ratio in Table 3 indicates that the borderline difference between the two groups is no longer present after adjustment for the presence of generalized seizures.

Late seizure recurrence
Kaplan–Meier estimates of seizure freedom for all patients (including those with ‘distant lesions’) who were seizure free for 1 year (n = 188) and for 2 years (n = 178) following surgery were calculated (Table 4). The two sets of estimates are provided to allow comparison with other reports.

The estimates above differ by ~5% between the two sets. The probability is that one-quarter of patients who are seizure free after 2 years experience at least one seizure during the subsequent year, while the two groups is no longer present after adjustment for the presence of generalized seizures.

Table 2 Results of univariate analyses for pre-operative variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR*</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Best evidence’ pathology</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HS n = 210</td>
<td>Reference</td>
<td></td>
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</tr>
<tr>
<td>FTL n = 51</td>
<td>0.71</td>
<td>0.18</td>
<td>0.18</td>
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<tr>
<td>‘Normal’ n = 33</td>
<td>3.18</td>
<td>0.71</td>
<td>0.00</td>
</tr>
<tr>
<td>‘Other’ n = 16</td>
<td>3.11</td>
<td>0.90</td>
<td>0.00</td>
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<tr>
<td>Preoperative secondarily generalized seizures</td>
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<td></td>
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</tr>
<tr>
<td>Absent/previous n = 161</td>
<td>Reference</td>
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<td></td>
</tr>
<tr>
<td>Occasional n = 75</td>
<td>1.60</td>
<td>0.30</td>
<td>0.01</td>
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<tr>
<td>Frequent n = 65</td>
<td>2.03</td>
<td>0.39</td>
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</tbody>
</table>

Log partial likelihood ratio test P = 0.0000. *HR after adjustment for the other variable in the model.
Ten years after surgery, the probability was 78% (95% CI 58.7–89.1) for those with FTLs, and 75.6% (95% CI 65.5–83.1) for those with HS (the ‘normal’ group was too small to assess). CIs for all groups overlap at each time interval, indicating that the differences between the groups are not statistically significant.

**Analyses of risk factors for late recurrence**

The total sample was n = 170 (excluding the ‘other’ and distant lesion group). The association of age of onset, duration of epilepsy, age at surgery and secondarily generalized seizures with seizure recurrence (in patients seizure free for two postoperative years) was examined. These variables failed to reach statistical significance in the univariate analyses (Table 5).

**Discontinuation of AEDs and seizure outcome**

The examination of outcome after drug discontinuation included 157 patients. We included all those who were seizure free for 2 years, minus n = 3 with missing AED data and n = 9 who had ceased medication prior to 2 years (the other n = 2 who ceased AEDs prior to 2 years had already been excluded from this analysis because they were not seizure free at two postoperative years). Details of AED discontinuation are contained in Table 6.

Medication was discontinued in 24 out of 34 patients with FTL, 56 out of 116 with HS and three out of seven with ‘normal’ findings. Discontinuation was more common amongst individuals with preoperative lesions. Of those patients who continued AEDs and experienced seizure recurrence, 42% had undertaken some reduction of AED dosage.

Survival analysis of the probability of seizure freedom from the date of AED discontinuation was undertaken (Table 7). Eight patients where the precise date of AED discontinuation was unknown and estimates of the date were made within a time period longer than 1 year (see Methods) were dropped in order to minimize inaccuracy. For comparison, seizure-free probabilities for patients who had not ceased medications and were seizure free for two postoperative years were also calculated.

Table 7 shows that seizure-free probabilities remained fairly high in both groups; the differences between the groups were not significant at any time (as shown by overlapping CIs throughout the analysis). Amongst those who experienced
seizures after AED discontinuation, the median time from discontinuation to seizure was 11 months (IQR 0.5–1.46 years; range 3 days to 6.7 years; these values are estimations in some cases).

Univariate Cox analysis confirmed that AED discontinuation (analysed as a time-dependent variable) was not associated with a greater risk of seizure recurrence (HR 1.03, 95% CI 0.5–2.1) when compared with outcome for those who remained on medications. Adjustments for era of surgery had a negligible impact on the hazard rate (log partial likelihood ratio test \( P = 0.81 \)), indicating that the findings were not confounded by year of surgery. Multivariate analysis, including AED continuation together with ‘best evidence pathology’, age at onset of preoperative seizures, duration of epilepsy, age at surgery and preoperative secondarily generalized seizures did not result in any significant effects (data not shown).

Discussion

Long-term seizure outcome after temporal lobectomy

For the sample as a whole, the likelihood of remaining seizure free by 1 year post-surgery was 61%, and at two postoperative years it was 55%. The period of greatest risk for seizure recurrence was within the first 6 months after surgery, with a continued slow but steady decrease thereafter up to at least 15 years after surgery. These results are very consistent with other recent longitudinal studies (Sperling et al., 1996; Foldvary et al., 2000; Wiebe et al., 2001; Yoon et al., 2003). The recurrences noted in this current study were not directly related to missed AED doses or a decrease of AEDs, as seizures proximate to these events were excluded from the analysis. It is possible that the slow attrition of the seizure freedom pattern continues after 15 years; however, the numbers in this study were not sufficient to analyse outcome at these longer times. Clearly, some patients have extended periods of seizure freedom prior to recurrence.

Sixteen of the 18 patients who were deceased had experienced seizure recurrence. This is in agreement with other studies that indicate that continuing seizures are associated with an increased risk of death (Sperling et al., 1999; Salanova et al., 2002).

Seizure outcome according to preoperative pathology

Outcome for the FTL and the HS group

As in our previous study (Berkovic et al., 1995), patients with FTLs and HS had a better outcome than those in other pathology groups. There was a borderline trend towards better outcome amongst those with FTLs compared with those with HS. However, in this current study, the difference between the two groups was reduced after adjustment for the presence of preoperative generalized seizures. The higher percentage of generalized seizures amongst those with HS may be an indicator of heterogeneous seizure mechanisms amongst this group.

Outcome for the ‘normal’ and ‘other’ group

In past studies, the examination of outcome for patients with no obvious temporal abnormality has been hampered by the inadvertent inclusion of patients with abnormalities located elsewhere. In this study, the exclusion of cases with incomplete specimens and reclassification of mislocalized distant lesions ensured that our ‘normal’ temporal lobe group was as close to ‘normal’ as possible, given available information and by current standards of imaging and pathological examination. Patients in both the ‘normal’ and ‘other’ groups had a poor outcome. It is striking that the outcome and pattern of rapid recurrence seen in these groups (Fig. 1) are very similar to the pattern seen amongst patients with a distant lesion. Future improvements in imaging technology and knowledge may increase the identification of distant lesions among cases currently considered to have no abnormal pathology. It is tempting to speculate that this group may also comprise a number of epileptogenic mechanisms that are as yet not recognized or understood. For this reason, further in-depth examination of this group using other methods such as functional imaging and genetic analysis is of interest.
Patients in the ‘other’ group may also have an epileptogenic zone extending outside the area of resection. The diffuse or widespread nature of the migrational/developmental or traumatic abnormalities that comprise this group makes this hypothesis likely.

**Outcome for the distant lesion group**
The expected poor outcome results for this group may have been biased by the fact that the individuals who underwent postoperative reinvestigations were those who experienced recurrent seizures. While it is unlikely that epileptogenic lesions outside the area of resection would be found in seizure-free individuals, the fact that one patient was seizure free for 15 years before recurrence suggests this possibility cannot be ruled out.

**Risk factors for recurrence in long-term outcome**
*Secondarily generalized seizures*
The presence of preoperative secondarily generalized seizures near the time of surgery was associated with seizure recurrence after temporal lobectomy. One may speculate that these seizures are a manifestation of a more widespread epileptogenic zone of secondary epileptogenesis. Occasional generalized seizures up to the time of surgery were accompanied by a lower hazard compared with frequent seizures at the time of surgery, but outcome for these two subgroups was not significantly different.

Individuals who at the time of surgery reported that they had experienced generalized seizures >3 years previously (‘previous seizures’) did not appear to have a poorer outcome compared with those who had no generalized seizures, or generalized seizures with epilepsy onset or drug withdrawal only. This may be because the ‘previous seizure’ group was small, or because reports of past generalized seizures reflected earlier periods of instability during the adjustment of AEDs.

**Age at surgery, duration of preoperative epilepsy and age at onset**
Age at surgery and duration of epilepsy had a significant effect on univariate analysis. This reflects the findings of a number of other studies (Erba et al., 1992; Blume et al., 1994; Salanova et al., 1994; Specht et al., 1997; Ficker et al., 1999; Jeong et al., 1999). However, most cited studies did not make statistical adjustments for other factors (McIntosh et al., 2001). The results of the regression analysis undertaken in this study showed that after preoperative pathology and generalized seizures were taken into account, the age at surgery and duration of epilepsy had no effect on outcome.

The significance in univariate analysis but lack of significance in multivariate analysis may reflect an association of these variables with the development of generalized seizures. This is a biologically plausible explanation for the variable ‘duration of epilepsy’, as seizures may evolve and become more complex over time in some patients (French et al., 1993; Wieser et al., 1993). The variable ‘age at surgery’ may be implicated with generalized seizures due to its independence with duration of preoperative epilepsy.

The age of onset was not found to be associated with seizure recurrence after surgery. This is in agreement with other studies (Abou-Khalil et al., 1993; Mathern et al., 1995; Berg et al., 1998; Radhakrishnan et al., 1998; Ficker et al., 1999; Jeong et al., 1999; Kilpatrick et al., 1999).

**Late seizure recurrence**
The probability of recurrence in patients who were seizure free for one postoperative year was 17% by 5 years and 30% by 10 years after surgery. Yoon et al. (2003), using the same methodology and a similar sample size, noted slightly higher attrition (28% at 5 years and 44% at 10 years). The higher percentage in Yoon et al. (2003) may be related to the inclusion of patients who underwent extratemporal surgery, or the inclusion of drug withdrawal seizures in the analysis. Both studies underscore that late recurrence is not uncommon.

The likelihood that patients who were seizure free for two postoperative years would experience recurrence was 14% by 5 years after surgery. This is similar to a number of other studies, where late recurrence was found in 10–15% of patients (Elwes et al., 1991; Blume et al., 1994) although others have found a lower late of attrition, with 5 or 6% affected (Sperling et al., 1996; Foldvary et al., 2000) by 5 years. A quarter of patients who were seizure free for two postoperative years experienced a recurrence by 10 postoperative years.

**Late recurrence according to preoperative pathology groups**
Late seizures occurred in all pathology groups. In the FTL group, late seizure recurrence occurred in 22% by 10 postoperative years. Eliashiv et al. (1997) found a similar result, with recurrences of ~25% between 2 and 11 years post-surgery. In contrast, another study (Kirkpatrick et al., 1993) found that all FTL cases that experienced seizure recurrence did so before the end of the first postoperative year. However, 87% in the cohort had DNETs. In this current study, patients with DNETs who had recurrence also tended to do so soon after surgery (data not shown).

Amongst those with HS, late recurrence occurred in 24% by 10 postoperative years. Yoon et al. (2003) found that 38% of patients with mesial temporal sclerosis relapsed after one seizure-free year, although seizure-free probabilities at specific times were not given.

In our earlier report with a mean follow-up of 3.7 years (Berkovic et al., 1995), late recurrence after 30 months appeared to be restricted to patients with HS. Data from this current study (that includes all our earlier cases) do not confirm this initial trend. This concurs with Yoon et al. (2003), who found that amongst those with temporal resection only, patients...
with and without HS had a similar risk of relapse after one seizure-free year. Yoon et al. (2003) also noted that the absence of abnormal pathology was a risk factor for late recurrence. Figure 2 in this study shows a trend towards higher late recurrence in the ‘normal’ group, although the numbers were small in this group, possibly contributing to the lack of statistical significance.

In our previous study, the lack of late recurrences amongst the lesion and ‘normal’ groups was probably related to the smaller numbers in these groups at that time. One feature of the Kaplan–Meier survival curve is the long horizontal lines at extended follow-up times. This may indicate a core group of ‘cured’ patients, but often occurs because only a few individuals remain in the study at these times (Matthews and Farewell, 1996; Hosmer and Lemeshow, 1999). As the patient numbers were increased for this current study, more cases of late recurrence were accumulated.

**Analysis of risk factors for late recurrence**

The age at onset, age at surgery, duration of epilepsy and presence of preoperative secondarily generalized seizures did not have an effect on late seizure recurrence. This concurs with Yoon et al. (2003).

**Discontinuation of AEDs**

Complete cessation of medication amongst patients seizure free for 2 years does not appear to be associated with an increased risk of seizure recurrence. This differs from the findings of Schiller et al. (2000), where patients who discontinued AEDs were found to have a significantly higher risk of recurrence. It is possible that the protocol and approach to AED withdrawal differs between surgical centres, and this may account for the differences in findings. Additionally, there is a slight difference in the balance of preoperative pathology between the cohorts, which may have contributed to the differences (the cohort of Schiller et al. had a higher percentage of patients without abnormalities and a few patients with extra-temporal resections).

The findings in our current study may be related to the selection of patients for AED discontinuation. This is likely to be heavily biased towards individuals who appear to the clinician to be ‘low risk’. Patients who have postoperative auras, withdrawal seizures with missed medication, or who display behaviour that may increase the risk of seizures may be less likely to be selected for AED withdrawal. Neither do the patients who experience a seizure during the tapering of medication proceed to discontinuation, as they are dropped from these analyses when the seizure occurs. Interestingly, despite this selection, a significantly lower risk of recurrence is not seen amongst this group either (as shown by the HR and the fact that the ‘survival’ probabilities are not significantly different at any point). It can be hypothesized that the relatively stable seizure status seen in patients who remained in the analysis after two postoperative years is the major contributing factor to the findings, over-riding any effect of medication changes.

It is also possible that the focus on outcome after discontinuation of AEDs fails to ‘capture’ the most important period of risk related to medication changes. For example, tapering of AEDs after surgery may be the first time patients are exposed to relatively low doses for many years, and this is arguably a period of greater risk than the transition from a very low dose of AED to no medication. Forty percent of patients in the analysis who did not completely discontinue medications and experienced seizures had some tapering of AEDs. Often, rationalization of AEDs occurs in the first year or so after surgery, which is the time most recurrences have been shown to occur.

Additionally, other factors such as the number and type of postoperative medications and missed AED doses may have a mediating effect and should be investigated further. Postoperative medications and missed AED doses are potentially important variables that may indicate persistent post-surgical epileptogenesis. These phenomena may be a risk factor for complex partial seizures generally, but may also have particular implications for AED withdrawal. It is likely that when auras or drug withdrawal seizures manifest during AED reduction, the process of AED withdrawal is altered (i.e. AED dosage may be held steady for prolonged periods or increased). The association of AED reduction with outcome is complicated; further analyses and, ideally, prospective controlled studies are required.

**Determinants of late seizure recurrence**

The risk factors for late recurrence are obscure. Hypothetically, seizure recurrence that occurs many years after surgery may be associated with risk factors that are different from those associated with early seizure recurrence. One of the issues associated with analysis of late recurrence is lack of a clear cut-off between late and early seizures. The arbitrary designation of 1 or 2 years as the point of division may not adequately delineate the groups, if in fact there is an actual division to be made.

**Year of surgery and diagnostic changes**

**Changes to preoperative pathology ‘diagnosis’**

This study has attempted to deal with the changes that occur in original preoperative pathology diagnoses when further, more up to date evidence becomes available. Such changes serve as a reminder that current accepted diagnoses are also likely to evolve over time. Unfortunately, because of practical restrictions, not all the evidence available used the most modern of technology (i.e. some scans were performed on earlier machines). The issue of revision of diagnosis is pertinent to other studies that use long-term surgical cohorts; the fact that most changes were in the ‘normal’ group is of particular note.

**The effect of era of surgery**

Changes in technology, investigation and treatment protocols over the years spanned by these long-term cohorts will
continue to be an issue for outcome studies. In this study, we managed this issue by using two alternative approaches to preoperative pathology diagnosis. The ‘best evidence’ approach is restricted by a reliance on retrospective records and the fact that recent reinvestigation of all patients is not feasible. However, it does supply the most accurate ‘diagnosis’ using available information. Histopathology with adjustment for era of surgery offers an alternative approach. Further discussion of methodological approaches aimed at managing this issue may be of benefit to outcome research.

Interestingly, the era of surgery did not have an effect on outcome either as an independent variable or as a confounder for histopathology. This finding is supported by Yoon et al. (2003) who also studied outcome for a surgical cohort that covered a similar period of time. These data differ from the findings of other studies (Engel, 1993; McIntosh et al., 2001) where earlier cohorts had lower seizure freedom compared with later cohorts. However, these studies used a cross-section approach to data analysis. That method does not take into account the fact that an earlier cohort will have had more years in which to accumulate late recurrences. An explanation for the current findings is that the improvements in localization approaches to data analysis. That method does not take into account the fact that an earlier cohort will have had more years in which to accumulate late recurrences. An explanation for the current findings is that the improvements in localization techniques have resulted in surgery for difficult cases who previously would have not been considered, i.e. cases with diffuse lesions or epilepsy that is difficult to localize.

**Clinical implications of these findings**

These data will inform preoperative decision making and pre- and postoperative patient counselling, rehabilitation and management. Preoperatively, careful examination should be made of patients with no obvious abnormality to ensure an extra-temporal focus is not present. Those with no obvious abnormality or ‘other’ pathology have a poorer outcome after surgery and can be counselled accordingly. The presence of generalized seizures as a risk factor for recurrence can also be discussed. A prolonged postoperative seizure-free period does not guarantee ongoing seizure freedom.

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