Long-Term Seizure Outcome in Patients Undergoing Resection of Lesions Detected by Magnetic Resonance Imaging

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Abstract

The long-term efficacy of resective surgery was investigated in patients with lesions detected by magnetic resonance (MR) imaging. Thirty of 47 patients who had undergone lesionectomy between 1987–2001 were followed up by questionnaire. Patients with extratemporal resections outnumbered those with temporal lobe resections. The mean follow-up period was 12.4 ± 3.7 years. Outcomes were graded according to Engel’s criteria, and an arbitrary seizure outcome score was given for quantitative assessment. The mean seizure outcome scores were significantly lower in the early childhood (less than 3 years) onset group than in the late childhood (3 to 15 years) onset group, and significantly lower in the extratemporal resection of the cortical dysplasia group than in the temporal resection and the extratemporal resection of non-cortical dysplasia groups. This study indicated that lesionectomy based on MR imaging findings in patients with intractable epilepsy achieved effective long-term seizure control, and the outcome was related mainly to the pathology of the epileptogenic lesions and the temporal or extratemporal location.

Key words: epilepsy surgery, lesionectomy, extratemporal location, long-term seizure outcome, magnetic resonance imaging

Introduction

Resective epilepsy surgery achieves excellent short-term results, but less has been known about the long-term outcome until recently. Analysis of long-term outcomes after epilepsy surgery is important for the following reasons: Epilepsy is a chronic condition and surgical treatment may have irreversible side effects; some patients who are initially seizure-free can experience late recurrence, whereas others who initially have seizures after surgery may become seizure-free later; information may be obtained about the factors associated with improved postoperative outcomes; and important implications may be identified for patient counseling and postoperative discontinuation of anti-epileptic drugs. Since magnetic resonance (MR) imaging was introduced, few reports have addressed the long-term outcomes, and the rates and predictors of late recurrence in large series of patients undergoing surgery. However, the number of studies of long-term outcome has increased dramatically, and evidence of late seizure recurrence is mounting. Almost all of these studies have been of patients undergoing temporal lobe resections, with few long-term follow-up studies of patients undergoing extratemporal resections.

The present study evaluated the efficacy of resective surgery in patients with lesional epilepsy identified by MR imaging for postoperative long-term seizure control extending for 5 years or more. In our series, patients undergoing extratemporal resections outnumbered those undergoing temporal lobe resections. The preoperative factors associated with long-term efficacy were also investigated.
Materials and Methods

I. Diagnosis of epileptogenic lesions

Our protocol for the diagnosis of epileptogenic lesions amenable to surgical treatment can be applied to both children and adults. Briefly, extensive MR imaging was performed on patients of intractable epilepsy to identify epileptogenic lesions, including volumetric studies of the hippocampus and fluid-attenuated inversion recovery imaging, which has high sensitivity to epileptogenic lesions such as focal gliosis, small and/or low grade tumors, focal dysplastic lesions, cystic lesions, and small hamartomaticus or vascular malformations. Whether or not a lesion identified by MR imaging is an epileptogenic focus can be determined by noninvasive methods, including ictal electroencephalography (EEG) analysis using ambulatory and/or video-EEG recordings. Regional cerebral blood flow and/or metabolism studies were performed using single photon emission computed tomography and/or positron emission tomography. If epileptogenicity was confirmed after repeating these noninvasive studies, craniotomy was scheduled.

Craniotomy was performed under general anesthesia with tracheal intubation. Anesthesia was induced by intravenous administration of thiopental sodium and maintained by inhalation of halothane or sevoflurane combined with nitrous oxide. Based on the findings of preoperative MR imaging and other studies, the lesion and the eloquent area in the brain were identified intraoperatively using inspection, palpation, laser Doppler flowmetry, and B-mode ultrasonography, as well as EEG studies. Intraoperative cortical EEG and/or depth EEG studies with commercially available grid-type and/or needle-type electrodes were used to identify the location and limits of the epileptogenic zone, guide the extent, and assess the completeness of resection. Somatosensory and/or motor evoked potentials were used to localize the primary afferent and/or efferent areas using the same electrodes as those used for EEG.

II. Subjects

The inclusion criteria for the present clinical analysis of long-term outcome of epilepsy surgery were: (i) MR imaging evidence of a lesion but no mass effect and/or contrast enhancement; (ii) resective surgery, in accordance with our protocol, performed by the same neurosurgeon (K.M.); and (iii) postoperative follow up for at least 5 years. Forty-seven patients were identified from among those who underwent surgery between December 1987 and April 2001 at two hospitals, Kyoto University Graduate School of Medicine and Shimane University School of Medicine. These patients received questionnaire surveys by post or telephone regarding postoperative seizure control. Thirty patients who replied to the questionnaire (reply rate 64%) became the subjects of this study.

III. Analysis

Seizure outcome was classified into 4 classes according to the degree of seizure reduction at the most recent follow-up examination, using Engel’s criteria as follows: Class I, free of disabling seizures; Class II, rare disabling seizures, “almost seizure-free”; Class III, worthwhile improvement; and Class IV, no worthwhile improvement. To quantitatively assess postoperative reduction in seizure frequency, the Engel’s grade of seizure outcome was assigned scores as follows: Class I, 5 points; Class II, 3 points; Class III, 1 point; and Class IV, 0 points.

The items in the questionnaire were compared with age at seizure onset and at operation, duration of epilepsy (period between seizure onset and surgery), and clinicopathological features. Factors affecting the long-term clinical outcomes of patients were investigated.

All personal data items were subject to privacy protection procedures. Statistical analysis used the chi-squared test, Mann-Whitney U test, Kruskal-Wallis H test, and Scheffe’s method, and were conducted with Excel 2004 (version 11.2.3; Microsoft, Redmond, Wash., U.S.A.) and SPSS (version 8.0 for Windows; SPSS, Chicago, Ill., U.S.A.) with significance accepted at the 5% level. All values are expressed as the mean ± standard deviation.

Results

I. Patient analysis

The 30 patients (19 males and 11 females) were divided into two groups according to surgical procedure: 11 (5 males, 6 females) who had undergone temporal resection, i.e. resection in the temporal lobe (T group); and 19 (14 males, 5 females) who had undergone extratemporal resection, i.e. resection in the cerebrum other than in the temporal lobe (ExT group). The predominant side of lesionectomy was the right in the T group (right 7, left 4) and the left in the ExT group (right 8, left 10, bilateral 1).

The clinical parameters in the two surgical procedure groups were as follows. The mean follow-up period was 12.4 ± 3.7 years, and was significantly longer in the ExT group (14.2 ± 2.5 years) than in the T group (9.3 ± 3.4 years) (p < 0.001). The mean age at seizure onset was 10.2 ± 11.5 years, and was lower in the ExT group (8.5 ± 9.2 years) than in the

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Table 1 Distribution of patients by Engel’s classification and the mean seizure outcome scores in the groups according to age at seizure onset

<table>
<thead>
<tr>
<th>Age at seizure onset (years)</th>
<th>n</th>
<th>Follow-up period (years)</th>
<th>Engel Class (score)</th>
<th>Mean seizure outcome score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I (5)</td>
<td>II (3)</td>
</tr>
<tr>
<td>Early childhood (≤2)</td>
<td>10</td>
<td>13.6 ± 3.9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Late childhood (3–15)</td>
<td>14</td>
<td>11.9 ± 6.8</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Adult (≥16)</td>
<td>6</td>
<td>11.5 ± 5.3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>12.4 ± 3.7</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

*Statistically significant difference from late childhood onset group (p < 0.01).

The patients were also divided into two groups by age at operation: 8 who received surgery in childhood (less than 16 years) and 22 receiving surgery as adults (16 or more years).

II. Seizure outcomes

Table 1 shows the distribution of patients by Engel’s classification and the mean seizure outcome score in the groups according to age at seizure onset. The mean age at surgery was 21.5 ± 11.2 years, and was lower in the ExT group (19.8 ± 9.6 years) than in the T group (24.3 ± 13.5 years). The mean duration of epilepsy was 11.3 ± 7.0 years, and was almost the same in the T group (11.2 ± 7.6 years) as in the ExT group (11.3 ± 6.9 years).

The patients were divided into three groups according to age at seizure onset. Ten patients had early childhood (less than 3 years of age) onset, 14 had late childhood (3 to 15 years) onset, and 6 had adult (more than 15 years) onset. Patients in the T group were almost evenly distributed over the three seizure onset groups, but less than 20% of patients in the ExT group had adult onset.

The patients were also divided into two groups by age at operation: 8 who received surgery in childhood (less than 16 years) and 22 receiving surgery as adults (16 or more years).

Table 2 lists the histological diagnoses of the epileptogenic lesions. The most prominent histological findings were neuronal loss and gliosis, which was associated with cerebral scarring or porencephaly after head injury, infection, or vascular malformation, or unknown origin. Mesial temporal sclerosis was found in 6 patients, and cortical dysplasia and cryptic angioma in 3 patients each.

This study included only a small number of patients, so seizure outcome was compared between the following three clinicopathological categories, as modified from the previous report,17) into temporal resection (T), extratemporal resection of non-cortical dysplasia (Non-CD exT), and extratemporal resection of cortical dysplasia (CD exT).

Table 3 shows the distributions of patients by Engel’s classification. All 11 patients in the T group, and 14 of the 19 patients in the ExT group had Class I or II outcome. However, 14 of the 15 patients in the Non-CD exT group and none of the 4 patients in the CD exT group had Class I or II outcome. The mean seizure outcome score in the Non-CD exT group (3.93 ± 1.28) was almost the same as that in the T group (4.45 ± 0.93). The mean seizure outcome score in the T group (4.45 ± 0.93) was higher than that in the ExT group (3.21 ± 1.84), although this difference was not statistically significant. The
Table 3 Distributions of patients by Engel’s classification

<table>
<thead>
<tr>
<th>Clinicopathological category</th>
<th>n</th>
<th>Engel Class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>T group</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>ExT group</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Non-CD exT group</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>CD exT group</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>16</td>
</tr>
</tbody>
</table>


mean scores in the T group (4.45 ± 0.93) and the Non-CD exT group (3.93 ± 1.28) were significantly higher than that in the CD exT group (0.5 ± 0.58) (p < 0.001).

Discussion

Valid assessment of the long-term effects of epilepsy surgery presents many problems. The most important factor is the heterogeneity of the subjects, in particular the variability in outcome criteria, including assessment at different periods of follow up, different types of surgery, and different pathologies and etiologies of the epileptogenic lesions. The patient attrition rate, or the rate of loss of contact with patients, also affects the long-term outcome of studies and may be closely related to outcome status, especially for patients with poor outcome after surgery. Such drop-out bias may explain some of the discrepancies between the findings of different studies. Two years is considered the minimum follow-up period necessary for reliable assessment of postoperative seizure resolution and to make predictions about long-term outcome. Only a few reports have examined the outcome of epilepsy surgery after more than 5 years. In the present study, the follow-up period was 5 years or more, with a mean of about 12 years, so is one of the longest reported follow-up periods of patients undergoing epilepsy surgery.

The proportion of patients remaining seizure-free postoperatively for several years shows a progressive decline, although half of the patients who suffered relapse had, at most, one seizure per year. Kindling and maturation of the epileptogenic focus may be involved in the delayed recurrence of seizures. Conversely, 20% of patients who had seizures at 2-year follow up were seizure-free at long-term follow up. This running-down phenomenon, initial disabling seizures followed by freedom from disabling seizures for at least 2 years, may be related to the process of late remission of postoperative seizures.

Predictive factors indicating poor outcome or late recurrence after surgery for epilepsy include the following: Normal pathological findings in resected tissue; absence of discrete abnormalities on preoperative MR imaging; male sex; previous surgery; extratemporal origin of seizures; presence of preoperative generalized tonic-clonic seizures in patients with neocortical epilepsy; and older age at surgery.

In our study, the mean seizure outcome scores in the late childhood onset and adult onset groups were higher than in the early childhood onset group, suggesting that the threshold age of seizure onset that determines the outcome of epilepsy surgery is around 2 years. The higher recurrence rates among younger patients may represent the presence of more diffuse lesions.

The best seizure outcome tends to occur in patients with early presurgical evaluation and early surgery, and lesions identified by presurgical MR imaging. The present study found that the mean seizure outcome score was significantly higher in the adult operation group than in the childhood operation group, possibly because most of the former patients belonged to the T group or the Non-CD exT group, both of which showed good postoperative seizure outcomes.

Both age at operation and duration of epilepsy affect outcome. Children operated on after 6 years of age had no better outcome than children operated on in infancy or at preschool age. Younger age at surgery is a significant and independent predictor and an independent prognostic factor of good surgical outcome. Longer preoperative illness predicts poorer outcome or late recurrence. The duration of preoperative epilepsy is not a reliable predictor of final surgical outcome among patients with medial temporal sclerosis, whereas the duration of epilepsy is inversely and significantly correlated with seizure outcome among patients with extratemporal epilepsy. Secondary epileptogenesis, or kindling, may be responsible for the worse outcome after epilepsy surgery among patients with longer duration of preoperative epilepsy.

Patients undergoing temporal resection of the epileptogenic focus accounted for around 70% to 90% of all series, and patients with extratemporal resection accounted for about 10%. Extratemporal resection was performed in approximately 12% of all cases of adult seizures, but 70% of cases of childhood epilepsy. Our series contained more
patients with extratemporal resection than with temporal lobe resection. One reason is that our patients were treated for lesions detected by MR imaging, which allows better identification of epileptogenic lesions outside the temporal lobe. Another reason is that the majority of our patients had intractable epilepsy of childhood onset, which predominantly originates in the extratemporal region of the cerebrum.

Grading of the patients by Engel's classification showed that reduction in seizure frequency was higher in the T group than in the ExT group, although this difference was not significant. Previously, temporal resection surgery for intractable epilepsy in pediatric patients has almost always given satisfactory long-term results, and patients who have undergone temporal lobe resection tend to have stable Class I seizure outcome.

On the other hand, long-term freedom from seizures is consistently worse after extratemporal surgery and palliative procedures, and recurrent seizures may be more intractable after extratemporal resection than after temporal resection. These findings are consistent with the overall poor outcome after resection in the extratemporal region because of the more extensive and frequently unresectable epileptogenic foci. The reasons for poor outcomes in extratemporal lobe epilepsy remain unclear, although secondary epileptogenesis may be important. The epileptic network in the extratemporal lobe may have a more diffuse recruitment capability, accounting for its stronger ability to use additional neuronal pathways for epileptogenesis with time.

The mean seizure outcome scores in the T group and Non-CD exT group were significantly higher than in the CD exT group, indicating that seizure outcome was excellent in patients in the Non-CD exT group and poor in those in the CD exT group. The type of pathology negatively influences prognosis, and symptomatic seizures associated with cortical dysplasia or tuberous sclerosis in the youngest patients are among the most intractable. Children with acquired epileptogenesis, such as posttraumatic focal gliosis, appeared to have better outcome than those with dysplastic pathologies, such as cortical dysplasia or tuberous sclerosis. Focal cortical dysplasias are a distinct subgroup of malformations of cortical development and have favorable outcomes after resection, but the epileptogenic zone often extends beyond the abnormalities demonstrated by neuroimaging. Improved MR imaging can now visualize subtle and very focal cortical dysplasia, so the differential MR imaging characteristics of the histological subgroups can be established.

These findings reemphasize the importance of including patients with uniform pathological features to avoid the possibility of confounding factors affecting the association of risk factors with outcome.

This study indicated that lesionectomy based on MR imaging findings in patients with intractable epilepsy achieved effective long-term seizure control, and the outcome was related mainly to the pathology of the epileptogenic lesions and the temporal or extratemporal location.

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Commentary

Dr. Moritake et al. report on the long term outcome of epilepsy surgery in 30 patients with lesions detected by MRI studies. Overall they obtained excellent results with Engel class I outcome (absence of disabling seizures) in slightly over 50% of the cases. The authors comment correctly that long term outcome studies are scarce and that a significant proportion of patients have late seizure recurrences. In good agreement with previous reports, patients with early childhood onset seizures and patients with extratemporal epilepsy secondary to cortical dysplasia had a relatively poor prognosis.

This is a valuable study that certainly enriches the literature on long term seizure outcome. The only limitations are the following. Unfortunately the N = 30 is too small to subdivide the different etiologies in subgroups and to analyze outcome according to location, pathology and extension to the epileptogenic zone. It would have been advantageous if the authors could have used the Wieser outcome scale instead of the Engel outcome classification. Engel’s outcome groups are very subjective (e.g. free of “disabling” seizures, “worthwhile” improvement, etc.) and also do not take into account the yearly fluctuation of outcome class. On the other hand, Wieser’s scale clearly identifies objective subgroups (e.g. completely seizure free, 1–3 seizure days per year, etc.) and permits a dynamic follow up after surgery. It is well known that patients with cortical dysplasias who have lesions in the proximity of eloquent cortex need extensive invasive evaluation with depth and/or subdural electrodes to achieve a good outcome. Chronic evaluation with invasive recordings cannot be replaced by intraoperative recordings which only very seldom will permit accurate localization of the epileptogenic zone. The results obtained in this study (all patients with cortical dysplasias had an Engel group III or IV outcome) supports these observations.

As the authors comment in this manuscript, we certainly need more long term studies of epilepsy surgery to better assess prognosis and to define more accurately the factors that influence outcome. Unfortunately, the results obtained in different surgical centers are difficult to compare due to different presurgical evaluation methods, significant differences in surgical techniques, and important differences of the type of patients operated in different epilepsy surgery centers.

Reference


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This study presents a long-term account of the efficacy of resection surgery for refractory epilepsy. Thirty patients out of 47 operated upon were followed from 12 to 3.7 years after lesionectomy for temporal lobe epilepsy and extratemporal resections, based mainly on magnetic resonance (MR) imaging findings.

According to the authors, MR imaging was the predominant diagnostic instrumental means to detect the cortical lesions. However, the eloquent areas were also identified intraoperatively with ECoG, depth electrodes and B-mode ultrasonography, to establish the limits of the epileptogenic zone and guide the extent of resection, associated with somatosensory and/or motor evoked potentials.

This small series (as compared to the larger ones in the literature) contains more patients with extratemporal resections than with temporal ones, which they reasoned are better detected by MR imaging outside the temporal lobe; although they also found poorer results in the first group, since the epileptogenic zone may often extend beyond the MR images. It is our opinion that, in these cases, the image studies should always be complemented by post-resection intraoperative control ECoG or indwelling electrode studies, since simple MR imaging can mislead the surgeon, towards late recurrences of the seizures.

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Greater than five-year follow-up studies of seizure outcome following resective surgery are uncommon, and this retrospective case series report adds to our growing understanding of what can be expected from epilepsy surgery. There are limitations to any study, and this paper is no exception. Potential inaccuracy associated with telephone or mail inquiry, a reply rate of only 64% with associated response bias, and relatively small numbers are recognized and acknowledged by the authors. This reader is a little uneasy with an analytic methodology assigning arbitrary numeric values to ordinal data for statistical purposes. All that being said, however, the reported experience makes a useful contribution.
The effect of age at surgery presumably is to a considerable degree dependent on age of seizure onset (with all its implications regarding the underlying pathophysiological substrate) and epilepsy duration. The findings with dysplasia, consistent with other reports, support an extent of brain involvement and influence for that entity greater than MRI would currently suggest. The long-standing temporal versus extratemporal distinction recognizes the confounding influence of greater potential hippocampal involvement with the former (affecting outcome in opposite directions depending upon whether the resected MRI-lesion is mesial or neocortical), offset by the less stereotyped and perhaps less well understood extratemporal epilepsies.

That lesional epilepsy surgery is highly effective, that its efficacy is durable, and that cortical dysplasia warrants additional attention are valuable lessons for the epilepsy and neurosurgical communities.

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