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A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

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ABSTRACT

Background Randomized trials of surgery for epilepsy have not been conducted, because of the difficulties involved in designing and implementing feasible studies. The lack of data supporting the therapeutic usefulness of surgery precludes making strong recommendations for patients with epilepsy. We conducted a randomized, controlled trial to assess the efficacy and safety of surgery for temporal-lobe epilepsy.

Methods Eighty patients with temporal-lobe epilepsy were randomly assigned to surgery (40 patients) or treatment with antiepileptic drugs for one year (40 patients). Optimal medical therapy and primary outcomes were assessed by epileptologists who were unaware of the patients' treatment assignments. The primary outcome was freedom from seizures that impair awareness of self and surroundings. Secondary outcomes were the frequency and severity of seizures, the quality of life, disability, and death.

Results At one year, the cumulative proportion of patients who were free of seizures impairing awareness was 58 percent in the surgical group and 8 percent in the medical group ($P < 0.001$). The patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life ($P < 0.001$ for both comparisons) than the patients in the medical group. Four patients (10 percent) had adverse effects of surgery. One patient in the medical group died.

Conclusions In temporal-lobe epilepsy, surgery is superior to prolonged medical therapy. Randomized trials of surgery for epilepsy are feasible and appear to yield precise estimates of treatment effects. (N Engl J Med 2001;345:311-8.)

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EPILEPSY, a serious health problem that affects people of all ages, races, and socioeconomic backgrounds, has a prevalence of 5 to 10 per 1000 population in North America.^{1,2} Epilepsy is the second most common cause of mental health disability, particularly among young adults,³ and accounts for a worldwide burden of illness similar to that of breast cancer in women and lung cancer in men.⁴

Seizures in temporal-lobe epilepsy, which often start in childhood in otherwise healthy persons, occur both as simple partial seizures with preserved awareness of self and surroundings (also known as auras or warnings) and as disabling complex partial seizures in which awareness is impaired. During simple partial seizures, patients commonly experience a variety of psychic, gustatory, olfactory, and autonomic symptoms. During complex partial seizures, patients lose awareness and typically have a motionless stare accompanied by automatisms — stereotyped, repetitive, involuntary movements such as lip smacking, chewing, picking at objects, scratching, and gesturing. Generalized convulsions also occur in a substantial number of patients. Hughlings Jackson's description of Dr. Z's temporal-lobe epilepsy a century ago is a classic in medicine.⁵ Dr. Z's condition thwarted his distinguished academic medical career and culminated in his untimely death.

Recent advances in neuroimaging and surgical techniques have improved the surgical treatment of epilepsy to such an extent that some experts now suggest that physicians should offer surgery early to patients with surgically remediable epileptic syndromes instead

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of waiting for years until multiple anticonvulsant drugs have failed.⁶ Surgery for temporal-lobe epilepsy, one of the most common syndromes,⁷ may not only control seizures but also prevent untimely death.^{6,8} Paradoxically, surgery appears to be grossly underused. It is estimated that only 1500 of the nearly 100,000 eligible patients in the United States undergo such surgical procedures each year.⁹ Many clinicians who care for patients with epilepsy are uncertain about the efficacy and safety of costly surgical procedures¹⁰ and still view surgery as a last resort for patients with intractable epilepsy.⁶

The absence of robust evidence supporting the safety and efficacy of surgery for epilepsy figures prominently among the possible reasons for this view. There have been no randomized, controlled trials. All data derive from case series from disparate centers¹¹ — series that have serious methodologic limitations such as the lack of appropriate controls, the retrospective assembly of cohorts, the unstandardized and unblinded assessment of outcomes, the irregular assessment of negative outcomes and adverse events, and a narrow definition of which outcomes are of interest. Because nonrandomized or inadequately performed trials may unpredictably overestimate or underestimate benefits and risks,^{12,13} developers of practice guidelines for surgery for epilepsy have been unable to make strong recommendations for clinical practice. Finally, comparative studies involving the prospective, longitudinal assessment of the quality of life and psychosocial outcomes have failed to demonstrate a consistent superiority of surgery.^{14,15} We undertook a parallel-group, randomized, controlled trial comparing surgery with medical therapy in patients with temporal-lobe epilepsy.

METHODS

We compared medical treatment with surgical treatment of temporal-lobe epilepsy at the London Health Sciences Centre, University of Western Ontario, Canada, between July 1996 and August 2000. The study reflected the standard of care and was approved by the institutional review board.

After receiving explanations of the diagnosis of temporal-lobe epilepsy, the rationales for medical and surgical treatment, the usual procedures for determining patients' suitability for surgery, and the purpose of the study, all patients whom we enrolled gave written informed consent. At our institution, patients are put on a one-year waiting list before undergoing preoperative investigations. It was explained to patients that randomization results in an equal (50 percent) chance of being assigned to the medical group or to the surgical group. Patients in the medical group were placed on the usual one-year waiting list; then they were admitted for preoperative investigations and, if they were deemed eligible, they underwent surgery within four weeks. The patients in the surgical group underwent preoperative evaluation within 48 hours after randomization and underwent surgery within four weeks if they were deemed eligible. After surgery, they received optimal medical therapy for one year. Patients were told that they could withdraw from the study at any point.

Study Patients

Potential candidates for surgery for temporal-lobe epilepsy whose seizures were poorly controlled with medication were examined by

epileptologists and underwent outpatient electroencephalography (EEG), magnetic resonance imaging (MRI) of the brain (T_1 -weighted axial and coronal, proton-density, T_2 -weighted, and fluid-attenuated inversion-recovery sequences), as well as standardized neuropsychological and psychological assessments.¹⁶ To be eligible, patients had to be at least 16 years old and to have had seizures with strong temporal-lobe semiology¹⁷ for more than one year. The seizures had to have occurred monthly, on average, during the preceding year, despite the use of two or more anticonvulsant drugs, one of which was phenytoin, carbamazepine, or valproic acid. We excluded patients with brain lesions that required urgent surgery and those with progressive central nervous system disorders, active psychosis, pseudoseizures, a full-scale IQ lower than 70, previous surgery for epilepsy, focal extratemporal spikes or slowing on scalp-recorded EEG, or evidence on MRI of extratemporal lesions capable of producing the patient's seizures or of bilateral and equally severe epileptogenic lesions in the temporal lobe.

Two epileptologists who were unaware of the identity of the patient and his or her treatment-group assignment judged the adequacy of medical therapy at each visit by reviewing written clinical information pertaining to the three months since the previous visit. This information included a description of the patient's epilepsy, the type and frequency of seizures, any new seizures or events, the anticonvulsants used previously and the reason for their discontinuation, the anticonvulsants currently being used, their dosages and blood levels, any side effects of the medications, any change in treatment made at the visit and its rationale, and the treatment plan.

Randomization and Interventions

After stratification according to the presence or absence of generalized motor seizures, patients were randomly assigned to surgical or medical treatment. The random assignments were prepared outside the study center and delivered in sealed, opaque, sequentially numbered envelopes.

Patients who were assigned to surgical treatment were admitted to the epilepsy monitoring unit within 48 hours after randomization. The clinical characteristics of seizures were recorded, as were the EEG data obtained with the widely used international 10–20 system of electrode placement as well as mandibular-notch electrodes.¹⁸ The origin of a unilateral or mostly unilateral temporal-lobe seizure was determined by interictal and ictal indexes on the EEG.^{19,20} If the origin of the seizure was unclear, intracranial EEG was performed with the use of bitemporal subdural strips of electrodes and extratemporal electrodes, if needed.²¹ Patients with poor memory function bilaterally or on the side opposite that of the origin of the seizure underwent bilateral intracarotid amobarbital sodium tests. Patients with adequate memory on the side of the origin of the seizure and poor memory function on the contralateral side did not have surgery. Those with seizures originating in one temporal lobe who had consistent data from MRI and neuropsychological tests underwent resection of the anterior temporal lobe within four weeks after randomization (Fig. 1).

One of three neurosurgeons experienced in surgery for epilepsy resected a maximum of 6.0 to 6.5 cm of the anterior lateral nondominant temporal lobe or 4.0 to 4.5 cm of the dominant temporal lobe. The mesial resection included the amygdala and, at a minimum, the anterior 1.0 to 3.0 cm of the hippocampus (most commonly, 4.0 cm).²² Details of the surgical procedure and any perioperative complications were recorded. After the surgery, epileptologists treated patients with the same anticonvulsant drugs they had been receiving before surgery, adjusting the doses to reduce side effects and maintain the necessary serum levels and instructing patients not to decrease their doses of medication during the first nine months after surgery even if they were free of seizures.

Patients assigned to medical treatment were placed on a one-year waiting list for admission to the epilepsy monitoring unit, as is standard practice at our institution. Three epileptologists examined the patients in both the medical and surgical groups every three months, adjusted the doses and combinations of anticonvulsant drugs as dictated by current clinical practice and by patients' levels of tolerance

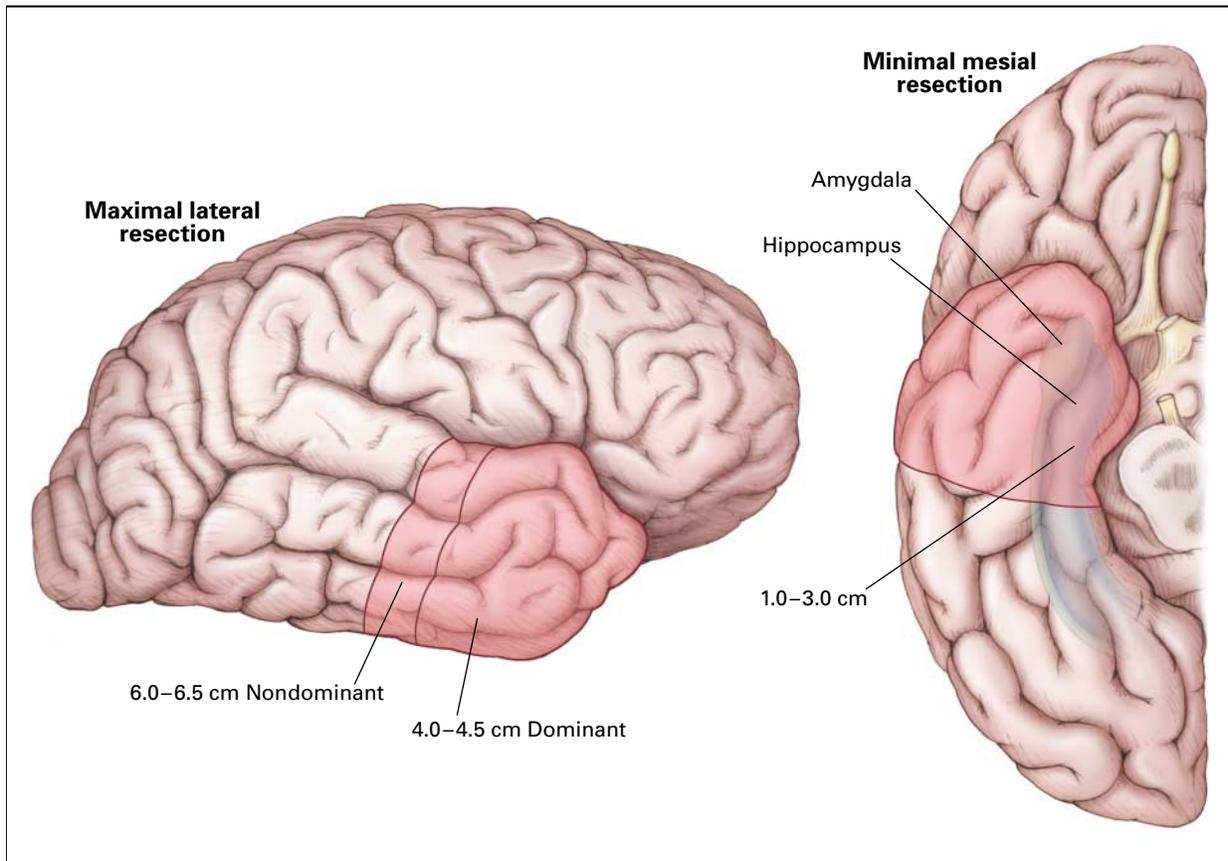


Figure 1. A Typical Surgical Resection for Temporal-Lobe Epilepsy in This Study.

Resection for this condition, in patients not selected according to the cause of the epilepsy, may include resection of up to 6.5 cm of the anterior lateral nondominant temporal lobe and 4.5 cm of the dominant temporal lobe. The mesial resection encompasses the amygdala and a minimum of 1.0 to 3.0 cm of the hippocampus. The extent of the lateral resection may be guided by functional mapping of this area.

and individual requirements,²³ and measured serum anticonvulsant levels when necessary. All patients received similar psychiatric or psychological treatment, as determined by the treating epileptologist and psychologist.

Patients wrote detailed descriptions of all seizure-like events in monthly seizure diaries. Two external epileptologists independently reviewed each diary entry, from which any information identifying the patient had been removed, and reached a consensus on whether or not the event was a seizure. We assessed the severity of seizures and the quality of life with the ictal subscale of the Liverpool Seizure Severity Scale (range of scores, 10 to 48, with higher scores indicating greater severity)²⁴ and the epilepsy-specific Quality of Life in Epilepsy Inventory-89 (QOLIE-89; range of scores, 0 to 100, with higher scores indicating better quality of life),²⁵ respectively. Psychopathology and depression were assessed with the General Health Questionnaire (range of scores, 0 to 28, with higher scores indicating worse health)²⁶ and the depression scale of the Center for Epidemiological Studies (CES-D; range of scores, 0 to 60, with higher scores indicating more depressive symptoms),²⁷ respectively. All of these instruments have demonstrated reliability and validity in assessing patients with epilepsy and were self-administered at base line and at 3, 6, 9, and 12 months. The research coordinator reviewed all the data for completeness and contacted patients for missing responses before the data were double-entered into the study data base.

The primary outcome was freedom from seizures impairing awareness (i.e., complex partial or generalized seizures) at one year. The trial was designed to detect an absolute difference of 34 percent between the proportion of patients in the surgical group who were free of seizures impairing awareness (54 percent) and the portion of those in the medical group who were free of such seizures (20 percent), after correction for the 15 percent of patients in the surgical group who might not be deemed eligible for surgery after they had been assigned to the surgical group.²⁸ These conservative estimates were based on reports from nonrandomized studies. We needed to enroll 40 patients per group in order to detect a difference of this magnitude with 90 percent power at a two-sided significance level of 0.05. With a sample this size, the study had 80 percent power to detect a 10-point (± 15.5 SD) difference between groups in the mean change in the QOLIE-89 global score (20.0 in the surgical group vs. 10.0 in the medical group).²⁹

Statistical Analysis

Data were analyzed according to the intention-to-treat principle. Freedom from seizures was determined on the basis of Kaplan–Meier event-free survival curves. The differences between the groups were evaluated with the log-rank test. Cox proportional-hazards regression was used to assess the effect of any imbalances in the baseline demographic and clinical characteristics of the patients on the

statistical significance of the differences between the groups. The monthly frequency of seizures was categorized as freedom from seizures, the occurrence of auras only, one to four seizures impairing awareness, and five or more such seizures. The cutoff between the last two categories was the median frequency of seizures impairing awareness at base line. For these analyses, seizures were counted starting 1 day after surgery in the patients who underwent surgery and 25 days from the date of randomization in the patients in the medical group and in the patients assigned to the surgical group who did not undergo surgery. The median interval between randomization and surgery was 24 days.

For each patient, we calculated the percentage change in the average monthly frequency of seizures impairing awareness and compared the groups using a median test. The postrandomization QOLIE-89 scores were compared by means of repeated-measures analysis of covariance, with adjustment for base-line scores. We calculated the mean severity of seizures at three-month intervals.

RESULTS

Of 92 patients screened, 86 were eligible; 80 agreed to participate, and 40 were randomly assigned to each group. At base line, there were no imbalances in the important demographic and clinical characteristics of the patients in the two groups, such as age, employment status, level of education, duration of epilepsy, type and frequency of seizures, anticonvulsant drugs used, and MRI findings (Table 1). The patients who were randomly assigned to medical treatment had lower quality-of-life scores at base line than those assigned to surgical treatment.

In the surgical group, six patients had recordings from subdural electrodes, and four patients (10 percent) did not undergo surgery. One declined surgery, two were not deemed eligible for surgery because the results on EEG, MRI, and neuropsychological tests did not agree, and one did not have seizures during the investigations conducted in the hospital. A total of 24 patients had operations on the left side, and 12 had operations on the right side. Two patients (5 percent) underwent a surgical procedure that differed slightly from that specified in the protocol. One underwent a selective amygdalohippocampectomy on the dominant side because of a concern about speech and memory, and one had a more extensive resection that was deemed necessary because of the origin of the seizure as revealed by intracranial EEG.

Four patients had adverse effects of surgery. In one patient, a small thalamic infarct developed, causing sensory abnormalities in the left thigh; in one, the wound became infected; and in two, there was a decline in verbal memory that interfered with the patients' occupations at one year. Asymptomatic, superior subquadrantic visual-field defects occurred in 22 patients in the surgical group (55 percent), as expected. No neurologic abnormalities occurred in the patients in the medical group. Depression occurred in seven patients in the surgical group (18 percent) and eight patients in the medical group (20 percent). Transient psychosis developed in one patient in each group.

No patients were lost to follow-up. There were no crossovers from the medical group to the surgical

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

VARIABLE	MEDICAL GROUP (N=40)	SURGICAL GROUP (N=40)
Age (yr)		
At randomization	34.4±9.9	35.5±9.4
At the onset of seizures	16.2±10.0	14.3±11.7
Female sex (%)	47.5	57.5
Completed high school (%)	75.0	65.0
Current employment status (%)		
Employed or attending school	45.0	45.0
Disability pension related to epilepsy	37.5	35.0
Unemployed	17.5	20.0
History of status epilepticus (%)	12.5	15.0
General Health Questionnaire score†	9.9±8.6	5.8±5.5
QOLIE-89 score‡	52.9±19.2	60.5±15.3
CES-D score§	14.9±9.2	17.2±9.3
Average monthly frequency of seizures impairing awareness in year before randomization		
Median	4.9	5.1
Interquartile range	3.0–14.1	2.4–9.0
No. of antiepileptic drugs used before randomization		
Median	6	6
Interquartile range	4–7	4–8
MRI findings (%)		
Normal	17.5	15.0
Mesial temporal sclerosis	72.5	70.0
Low-grade tumor, cortical dysplasia, or vascular malformation	10.0	15.0

*Plus-minus values are means ±SD. QOLIE-89 denotes the Quality of Life in Epilepsy Inventory-89, CES-D the depression scale of the Center for Epidemiological Studies, and MRI magnetic resonance imaging.

†The range of scores is 0 to 28, with higher scores indicating worse health.

‡The range of scores is 0 to 100, with higher scores indicating better quality of life.

§The range of scores is 0 to 60, with higher scores indicating more depressive symptoms. Scores were available for 32 patients in the medical group and 31 patients in the surgical group.

group. One patient in the medical group died (a sudden, unexplained death) 7.5 months into the study. No deaths occurred in the surgical group.

The anticonvulsants were switched or their doses increased in all patients in the medical group, and in 9 (22 percent) in the surgical group. In the medical group, the anticonvulsant was switched once in 19 patients (48 percent), twice in 9 patients (22 percent), three times in 3 patients (8 percent), and four times in 1 patient (2 percent). All doses of anticonvulsants were increased to therapeutic levels or to the maximal tolerated dose.

The cumulative proportions of patients who were free of seizures impairing awareness at one year were 58 percent in the surgical group and 8 percent in the medical group ($P<0.001$) (Fig. 2A). The proportions who were free of all seizures, including auras, were 38

percent in the surgical group and 3 percent in the medical group ($P < 0.001$) (Fig. 2B). Therefore, only 2 patients (95 percent confidence interval, 1.5 to 3) need to undergo surgery (number needed to treat) to render 1 additional patient free of seizures impairing awareness at one year, and 3 patients (95 percent confidence interval, 2 to 5) must undergo surgery to render 1 additional patient free of all seizures at one year. The benefit of surgery persisted after adjustment for all base-line demographic and clinical characteristics, including the quality of life ($P < 0.001$). Twenty-three of the 36 patients who underwent surgery (64 percent) were free of seizures impairing awareness at one

year, and 15 of these patients (42 percent) were free of all seizures. The median percentage improvement in the monthly frequency of seizures impairing awareness was 100 percent in the surgical group and 34 percent in the medical group ($P < 0.001$). Approximately 15 percent of the patients in the surgical group continued to have one to four seizures impairing awareness per month, and 10 percent had five or more such seizures (Fig. 3). Among the patients with residual seizures, the mean severity of the seizures was similar in the patients in the medical group and in those in the surgical group (Fig. 4).

The quality of life was better among the patients in

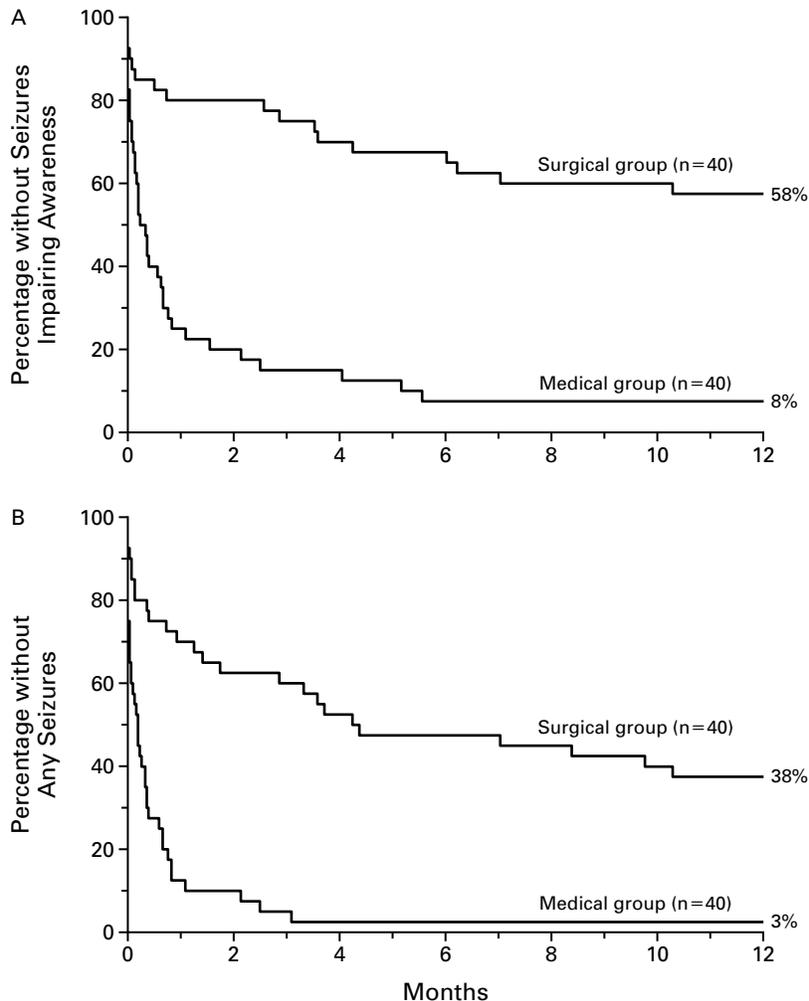


Figure 2. Kaplan–Meier Event-free Survival Curves Comparing the Cumulative Percentages of Patients in the Two Groups Who Were Free of Seizures Impairing Awareness (Complex Partial or Generalized Seizures) (Panel A) and Free of All Seizures (Including Auras) (Panel B).

In both analyses, more patients in the surgical group were free of seizures ($P < 0.001$ by the log-rank test). Follow-up began 1 day after surgery in the surgical group and 25 days after randomization in the medical group.

the surgical group than among those in the medical group ($P < 0.001$), and it improved over time in both groups ($P = 0.003$) (Fig. 5). Although there was a trend toward a higher proportion of patients in the surgical group than in the medical group who were employed or attending school at one year (56.4 percent vs. 38.5 percent), this difference did not achieve statistical significance ($P = 0.11$) (Fig. 6).

DISCUSSION

Our results support the superiority of surgery over medical therapy in terms of the control of seizures, the quality of life, and the rates of employment and school attendance among patients with poorly controlled temporal-lobe epilepsy. The absolute benefit of surgery in terms of the rate of freedom from seizures was large (50 percentage points for seizures impairing awareness and 35 percentage points for all seizures) and precise (confidence intervals were narrow). Our intention-to-treat analysis yielded a rate of freedom from seizures impairing awareness in the surgical group of 58 percent. Although this rate is lower than that found in studies assessing the cumulative freedom from seizures from the time of surgery (69 percent in one study⁸ and 63 percent in another³⁰), the rate of

freedom from seizures among the 36 patients who actually underwent surgery was 64 percent.

Although the assessment of outcomes after the trial is ongoing, the comparisons within the trial were limited to one year after surgery. Investigators disagree about the minimal time needed to determine the long-term seizure-related outcome. On the basis of our past experience²⁰ and that of others,³¹⁻³³ the seizure-related outcome one year after anterior temporal lobectomy seems a reasonable predictor of the subsequent outcome. Significant changes in psychosocial function, employment status, or school attendance may occur more slowly. However, as early as one year after surgery, we observed differences between the groups favoring surgery in terms of the quality of life, employment status, and school attendance. The unexpected death of one patient in the medical group and the absence of deaths in the surgical group support the previous observation of decreased mortality among surgically treated patients.⁸

Surgical morbidity was similar to that reported in case series. Substantial postoperative difficulties with memory developed in 5 percent of our patients and in 1 to 4 percent of those in previous studies.³⁴⁻³⁶ We acknowledge that this complication of surgery is im-

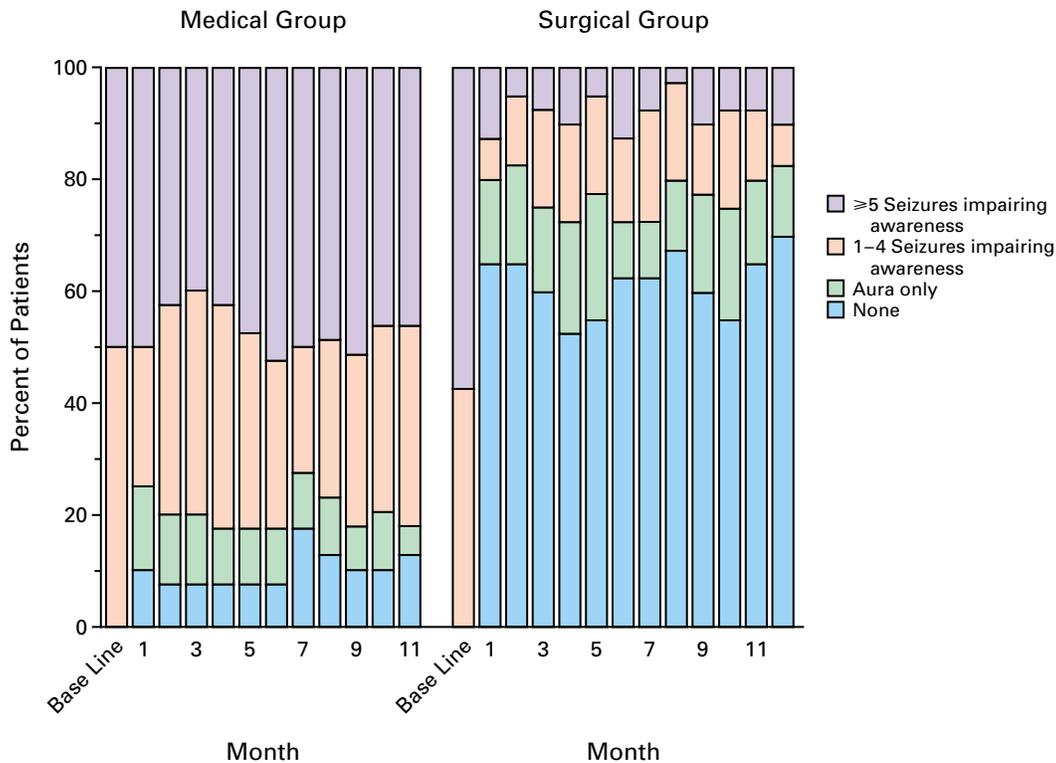
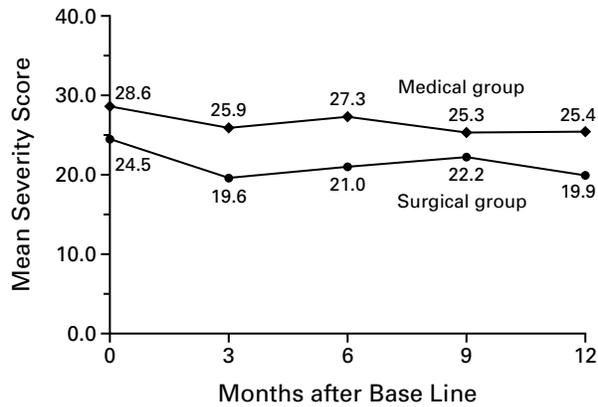


Figure 3. Monthly Rates of Seizures According to Type among Patients in the Medical and Surgical Groups.

Bars represent the percentages of patients in various categories at base line and at monthly intervals after follow-up began (the day after surgery in the surgical group and 25 days after randomization in the medical group). Seizures impairing awareness were complex partial seizures and generalized seizures.



NO. WITH SEIZURES IMPAIRING AWARENESS

Surgical group	17	15	13	14
Medical group	34	34	30	33

Figure 4. Mean Severity of Seizures Impairing Awareness (Complex Partial or Generalized Seizures) in Patients in the Medical and Surgical Groups at Base Line and at Three-Month Intervals Thereafter.

Severity is measured by the ictal subscale of the Liverpool Seizure Severity Scale. The range of scores is 10 to 48, with higher scores indicating greater severity.

portant, but in our opinion, the benefit is worth the risk. Hemiparesis, expected in 2 to 5 percent of patients,³⁶ did not occur in our study. Finally, depression was equally frequent in both groups and was in keeping with published rates.³⁶ The results in the medically treated patients substantiate recent reports indicating a low probability of freedom from seizures (10 percent or less) in patients with temporal-lobe epilepsy⁷ and in those in whom two or more anticonvulsant drugs have previously failed.³⁷

One previous failed attempt at a randomized trial of surgery for epilepsy³⁸ and commentators' emphasis on the difficulties inherent in executing such trials have strengthened the view that they are not feasible.^{14,38} The successful performance of this study demonstrates that randomized, controlled trials of surgery for epilepsy are feasible when the methods are adapted to the specific social and health care context of the patients.

For example, pilot studies revealed that neither the patients nor the clinicians in our center would accept randomization after the investigations in the epilepsy monitoring unit had been completed. Therefore, if skilled epileptologists rated the clinical data and the findings of outpatient investigations as highly likely to indicate a unilateral temporal-lobe origin of seizures, patients were randomly assigned to treatment groups before the inpatient investigations had been conducted. This strategy was successful. Only 10 percent of

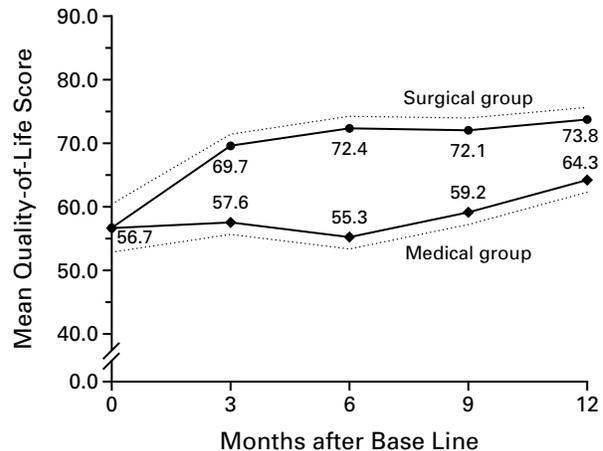


Figure 5. Adjusted and Unadjusted Mean Global Scores on the Quality of Life in Epilepsy Inventory-89.

The range of scores is 0 to 100, with higher scores indicating better quality of life. The adjusted mean scores (solid lines) were calculated by means of repeated-measures analysis of covariance, after base-line differences had been accounted for. Unadjusted scores are represented by dotted lines. The consistently higher scores in the surgical group indicate a better quality of life than that in the medical group during the one year of the study ($P < 0.001$ for the comparison between groups). The quality of life improved in both groups after base line ($P = 0.003$ for the trend for months 3 through 12).

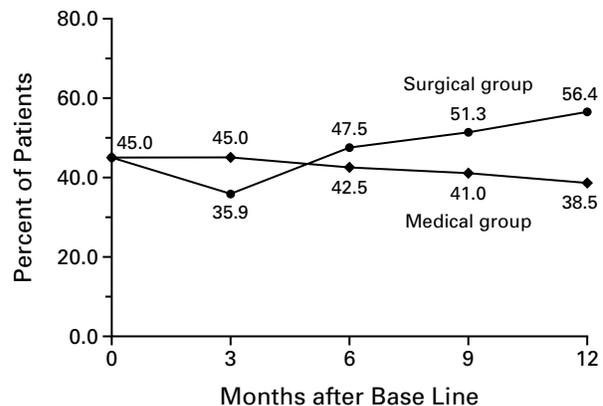


Figure 6. Percentage of Patients in the Medical and Surgical Groups Who Were Employed or Attending School at Base Line and at Three-Month Intervals Thereafter.

An expected transient decrease at three months is seen in the surgical group. More patients in the surgical group were employed or attending school at one year, but the difference was not significant ($P = 0.11$).

the patients assigned to the surgical group did not undergo surgery (fewer than our original estimate of 15 percent), and in only two of the patients assigned to the surgical group (5 percent) was surgery not indicated. Thus, in selected patients with temporal-lobe epilepsy, outpatient investigations may accurately predict decisions regarding surgery.^{39,40}

In summary, this study provides robust and precise estimates of the effectiveness and safety of surgery for patients with temporal-lobe epilepsy from any cause. The results substantiate the belief that prolonged trials of anticonvulsant drugs are futile and support the notion that patients with temporal-lobe epilepsy should be evaluated for surgery in order to preclude unnecessary disability and perhaps even death. However, the trial does not address the question of the optimal timing of surgery, particularly whether early surgery for temporal-lobe epilepsy is superior to medical therapy.⁶

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APPENDIX

Other participants in the study were as follows: *Epileptologists*: J.T. Butler, W.P. McNinis, R.S. McLachlan, G.B. Young; *Neurosurgeons*: A. Parrent, R. Sahjpaul; *Psychologists*: P.A. Derry, M. Harnadek, C. Kubu; *Neuroradiologists*: D.H. Lee, A.J. Fox, D.M. Pelz; *Research administration and data-base personnel*: S. Matijevic, J. DePace, M. Cervinka, B. Gilmore, K. McNeill, H. Casbourn.

REFERENCES

- Hauser WA, Hesdorffer DC. Incidence and prevalence. In: Hauser WA, Hesdorffer DC, eds. *Epilepsy: frequency, causes and consequences*. New York: Demos, 1990:1-51.
- Wiebe S, Bellhouse DR, Fallahay C, Eliasziw M. Burden of epilepsy: the Ontario Health Survey. *Can J Neurol Sci* 1999;26:263-70.
- Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. *Bull World Health Organ* 1994;72:495-509.
- Kale R. Bringing epilepsy out of the shadows. *BMJ* 1997;315:2-3.
- Taylor DC, Marsh SM. Hughlings Jackson's Dr. Z: the paradigm of temporal lobe epilepsy revealed. *J Neurol Neurosurg Psychiatry* 1980;43:758-67.
- Engel J Jr. The timing of surgical intervention for mesial temporal lobe epilepsy: a plan for a randomized clinical trial. *Arch Neurol* 1999;56:1338-41.
- Semah F, Picot MC, Adam C, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256-62.
- Sperling MR, O'Connor MJ, Saykin AJ, Plummer C. Temporal lobectomy for refractory epilepsy. *JAMA* 1996;276:470-5.
- Engel J Jr, Shewmon DA. Overview: who should be considered a surgical candidate? In: Engel J Jr, ed. *Surgical treatment of the epilepsies*. 2nd ed. New York: Raven Press, 1993:23-34.
- National Institutes of Health Consensus Conference: surgery for epilepsy. *JAMA* 1990;264:729-33.
- Engel J Jr, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J Jr, ed. *Surgical treatment of the epilepsies*. 2nd ed. New York: Raven Press, 1993:609-21.
- Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
- Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998;317:1185-90.
- Vickrey BG, Hays RD, Rausch R, et al. Outcomes in 248 patients who had diagnostic evaluations for epilepsy surgery. *Lancet* 1995;346:1445-9.
- McLachlan RS, Rose KJ, Derry PA, Bonnarc C, Blume WT, Girvin JP. Health-related quality of life and seizure control in temporal lobe epilepsy. *Ann Neurol* 1997;41:482-9.
- Miller LA, McLachlan RS, Bouwer MS, Hudson LP, Munoz DG. Amygdalar sclerosis: preoperative indicators and outcome after temporal lobectomy. *J Neurol Neurosurg Psychiatry* 1994;57:1099-105.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389-99.
- Sadler RM, Goodwin J. Multiple electrodes for detecting spikes in partial complex seizures. *Can J Neurol Sci* 1989;16:326-9.
- Blume WT, Borghesi JL, Lemieux JF. Interictal indices of temporal seizure origin. *Ann Neurol* 1993;34:703-9.
- Blume WT, Desai HB, Girvin JP, Lemieux JF. Effectiveness of temporal lobectomy measured by yearly follow-up and multivariate analysis. *J Epilepsy* 1994;7:203-14.
- Blume WT. Principles of clinical investigation of surgical patients. *Int Anesthesiol Clin* 1986;24:47-73.
- Girvin JP. Resection of intracranial lesions under local anesthesia. *Int Anesthesiol Clin* 1986;24:133-55.
- Brodie MJ, Dichter MA. Antiepileptic drugs. *N Engl J Med* 1996;334:168-75. [Erratum, *N Engl J Med* 1996;334:479.]
- Baker GA, Jacoby A, Smith D, Dewey M, Johnson AL, Chadwick D. Quality of life in epilepsy: the Liverpool initiative. In: Trimble MR, Dodson WE, eds. *Epilepsy and quality of life*. New York: Raven Press, 1994:135-50.
- Devinsky O, Cramer JA, eds. Assessing quality of life in epilepsy: development of a new inventory. *Epilepsia* 1993;34:Suppl 4:S1-S44.
- Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med* 1979;9:139-45.
- Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385-401.
- Wiebe S, Gafni A, Blume WT, Girvin JP. An economic evaluation of surgery for temporal lobe epilepsy. *J Epilepsy* 1995;8:227-35.
- Wiebe S, Derry PA, Rose K, McLachlan RS. In search of a minimum clinically important change in epilepsy specific quality of life instruments. *Epilepsia* 1997;38:Suppl 3:83-4. abstract.
- Foldvary N, Nashold B, Mascha E, et al. Seizure outcome after temporal lobectomy for temporal lobe epilepsy: a Kaplan-Meier survival analysis. *Neurology* 2000;54:630-4.
- Ficker DM, So EL, Mosewich RK, Radhakrishnan K, Cascino GD, Shalhough FW. Improvement and deterioration of seizure control during the postsurgical course of epilepsy surgery patients. *Epilepsia* 1999;40:62-7.
- Salanova V, Markand O, Worth R. Longitudinal follow-up in 145 patients with medically refractory temporal lobe epilepsy treated surgically between 1984 and 1995. *Epilepsia* 1999;40:1417-23.
- So EL, Radhakrishnan K, Silbert PL, Cascino GD, Shalhough FW, O'Brien PC. Assessing changes over time in temporal lobectomy: outcome by scoring seizure frequency. *Epilepsy Res* 1997;27:119-25.
- King DW, Flanigin HF, Gallagher BB, et al. Temporal lobectomy for partial complex seizures: evaluation, results, and 1-year follow-up. *Neurology* 1986;36:334-9.
- Walczak TS, Radtke RA, McNamara JO, et al. Anterior temporal lobectomy for complex partial seizures: evaluation, results, and long-term follow-up in 100 cases. *Neurology* 1990;40:413-8.
- Pilcher WH, Roberts DW, Flanigin HF, et al. Complications of epilepsy surgery. In: Engel J Jr, ed. *Surgical treatment of the epilepsies*. 2nd ed. New York: Raven Press, 1993:565-81.
- Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-9.
- Dasheiff RM, Ryan CW, Lave JR. Epilepsy brain surgery: a Pittsburgh perspective. *Seizure* 1994;3:197-207.
- Engel J Jr. When is imaging enough? *Epileptic Disord* 1999;1:249-53.
- Holmes MD, Dodrill CB, Ojemann LM, Ojemann GA. Five-year outcome after epilepsy surgery in nonmonitored and monitored surgical candidates. *Epilepsia* 1996;37:748-52.

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