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# In refractory temporal lobe epilepsy, consider surgery sooner

## ABSTRACT

Despite evidence that surgery for temporal lobe epilepsy is safe and effective, physicians continue to view it as a last resort in people who do not respond to medical therapy. A randomized study in Canada has demonstrated significantly higher rates of freedom from seizures in patients who underwent surgery rather than medical therapy. If we wait too long to rule a patient's epilepsy medically refractory, we increase the patient's risk of morbidity and death, and we miss a window of opportunity to eliminate seizures and permit the patient a full and productive life.

EPILEPSY SURGERY is perhaps the most underused therapy in all of medicine today.

More than 2 million people in the United States have epilepsy—as many women as have breast cancer and as many men as have lung cancer. Of these 2 million people, 400,000 to 600,000 have seizures that are resistant to drug therapy,[1] even with the new antiepileptic medications, and as many as 25% to 50% of those with drug-resistant epilepsy—100,000 to 300,000 patients—may be candidates for epilepsy surgery (ie, they have a small, discrete, area of epileptogenicity that can be safely removed).

Yet a 1990 survey found that only 1,500 surgical procedures for epilepsy were performed in the United States that year.[2] The situation is the same in other industrialized countries and worse in developing countries.[3,4]

Epilepsy affects people of all ages, races, and incomes and impairs their lives substantially.[1,5,6] Uncontrolled seizures carry a significant burden of disease and death.[7,8]

And epilepsy surgery is effective: the cure rates at most centers are 70% to 90% in patients with surgically remediable (but medically refractory) epilepsy syndromes.[9]

Why then do physicians and patients shy away from surgery, even when drug therapy with multiple drugs is unsuccessful?[10] Surgery is expensive and invasive and has an inherent risk of complications. More important, until recently, there has been no randomized, controlled trial comparing surgery with drug therapy.[11]

Such a study has been ethically difficult to design: in view of the high cure rates with surgery it would be unethical to deny a clearly superior treatment to a control group.

Now, however, such a randomized controlled trial has been performed and unequivocally proves the superiority of surgery for medically refractory temporal lobe epilepsy.[12]

It shows that even though surgery carries the risk of complications, avoiding or delaying surgery in patients with medically intractable epilepsy is also fraught with grave risks.

**Epilepsy surgery may be the most underused therapy in medicine**

## EPILEPSY SURGERY STUDY DESIGN

Wiebe and colleagues in London, Ontario, were able to conduct an ethical randomized trial of surgery vs medical therapy (**FIGURE 1**) by taking advantage of what some may consider a weakness of the Canadian health care system: a long (1-year) waiting list for surgery.[12]

### Study population

Patients age 16 years or older with temporal lobe epilepsy were informed about the ratio-

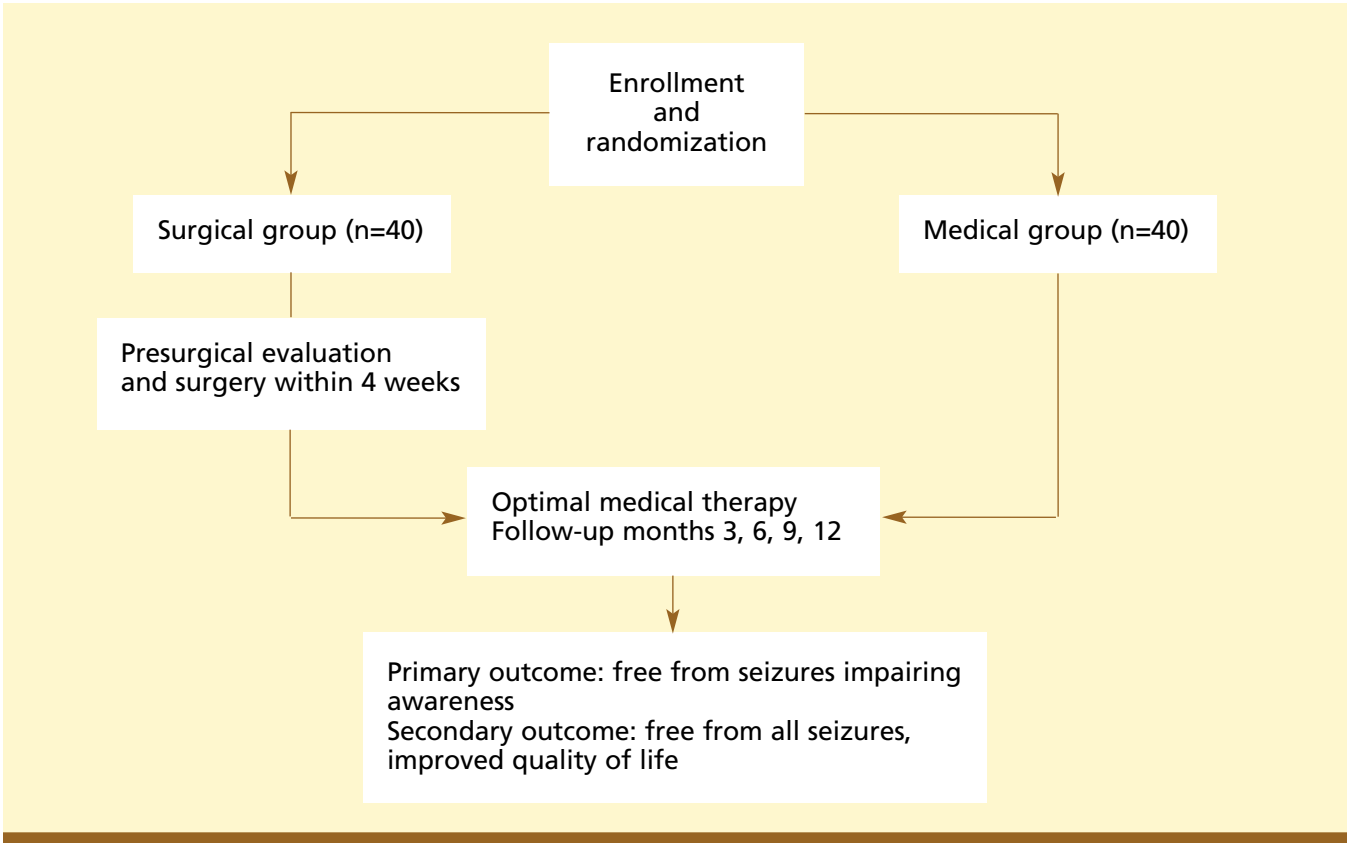


**FIGURE 1.** Schematic design of the Canadian epilepsy surgery trial.[12]

nales for medical and surgical therapy, as well as about the purpose of the study. They were also informed that randomization meant they had a 50% chance of being assigned to receive medical treatment. Written informed consent was obtained from those enrolled.

Patients in the medical group were assigned to the usual 1-year waiting period, at the end of which they were admitted for a presurgical evaluation and offered surgery within 4 weeks if they were eligible.

The patients in the surgical group underwent presurgical evaluation within 48 hours of randomization; then, if eligible, they underwent surgery within 4 weeks.

### Inclusion and exclusion criteria

Patients were eligible only if they had had seizures with strong temporal lobe semiology for more than 1 year that were refractory to two or more anticonvulsant drugs.

Patients were not eligible for the study if they had acute brain lesions requiring urgent surgery, progressive central nervous system disease, previous epilepsy surgery, or evidence of extratemporal disease on electrophysiologic or magnetic resonance imaging (MRI) studies.

### Evaluation and treatment

Before surgery, patients were admitted to an epilepsy monitoring unit, where their seizures were characterized and their electroencephalographic (EEG) data were analyzed. If the surface EEG data were inadequate to locate the source of the seizure, invasive EEG monitoring was carried out. Memory function was assessed by intracarotid amobarbital testing.

Those with seizures originating in one temporal lobe and who had concordant MRI and neuropsychological data underwent anterior temporal lobe resection within 4 weeks after randomization. They then received optimal medical therapy for 1 year.

Two epileptologists who were blinded to

the patients' identities reviewed the adequacy of medical therapy and the status of each patient's seizures at each quarterly follow-up visit by reviewing the written clinical information from the patient's clinic visit. After surgery, the antiepileptic drugs were continued unchanged in therapeutic doses for at least 9 months, even if the patient was seizure-free.

Patients in the medical group were placed on the 1-year waiting list for admission to the epilepsy monitoring unit, according to the medical institution's policies. Both treatment groups were seen every 3 months by epileptologists who tailored each patient's antiseizure drug therapy as needed.

### Outcomes measured

The primary outcome was freedom from seizures impairing awareness at 1 year. The trial was designed to include enough patients (40 in each treatment group) to detect an absolute difference of 34% in this outcome between the groups, with 90% power at a two-sided significance level of 0.05%.

Quality of life after surgery was assessed with the following:

- Liverpool seizure severity scale
- The Quality of Life in Epilepsy inventory
- General health questionnaire
- Center of Epidemiologic Studies depression scale.

Employment status and school attendance were also measured.

Data were analyzed after accounting for any imbalances in demographic and clinical characteristics of the patients that might have affected the statistical significance of the difference between the two groups.

## RESULTS: A MARKED REDUCTION IN SEIZURES

Of 92 patients screened, 86 were eligible, and 80 agreed to participate. Forty patients were assigned to each treatment group. At baseline, the groups were well matched by demographic and clinical characteristics.

**In the surgical group,** 6 patients (15%) needed invasive monitoring with subdural grids, and 4 (10%) did not undergo surgery. One declined surgery, 2 were not found to be good candidates at the completion of their evaluation, and 1 did not have any seizures during the evaluations conducted in the hospital.

Twenty-four patients had operations on the left side and 12 on the right side. Two patients had a surgical procedure that differed slightly from the procedure described in the protocol. One underwent a selective amygdalohippocampectomy due to concerns about speech and memory in the dominant hemisphere,[12] and 1 needed a more extensive temporal resection.

Of 40 patients treated surgically, 4 had surgical complications: 1 had a small thalamic infarct resulting in a sensory deficit in the left thigh, 1 had a wound infection, and 2 had a decline in memory that interfered with their occupations at 1 year. As was expected, because resection involved some fibers that serve visual field function, 22 patients in the surgical group had an asymptomatic superior subquadrantic visual field deficit. This deficit was less than the size of a quadrant and, since patients compensated for it very well, it was not considered clinically important.

Rates of depression were 18% to 20% in both treatment groups.

**In the medical group.** One patient in the medical group died suddenly of an unknown cause 7.5 months into the study. No patients were lost to follow-up, and no patients crossed over from the medical group to the surgical group. All patients in the medical group needed an adjustment or a change in their antiepileptic drugs vs only 22% in the surgical group.

**Number needed to treat.** In the surgical group, 58% were free of seizures impairing awareness at 1 year vs 8% in the medical group ($P < .001$); 38% in the surgical group were free of all seizures including auras vs only 3% in the medical group. Therefore, two patients need to undergo surgery to render one additional patient free of seizures impairing awareness at the end of 1 year, and three patients need to undergo surgery to render one additional patient free of all seizures at 1 year.[12] The severity of persisting seizures was similar in both groups.

**Three patients need to be treated to render one additional patient seizure-free at 1 year**

Quality of life improved in both groups, but at 1 year it was statistically significantly

## Trial data: Surgery beats medical therapy for temporal lobe epilepsy

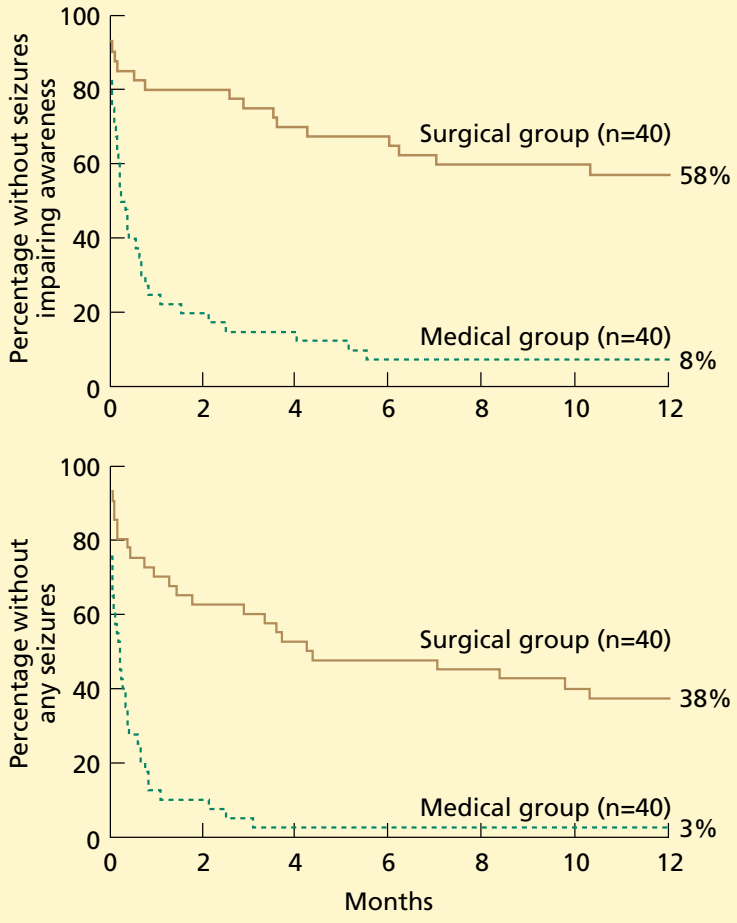


**FIGURE 2.** Kaplan-Meier event-free survival curves comparing the cumulative percentages of patients in the two groups who were free of seizures impairing awareness (top) and free of all seizures (bottom). In both analyses, more patients in the surgical group were free of seizures ($P < .001$).

FROM WIEBE S, BLUME WT, GIRVIN JP, ELIASZIW M. A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY. N ENGL J MED 2001; 345:311–318.

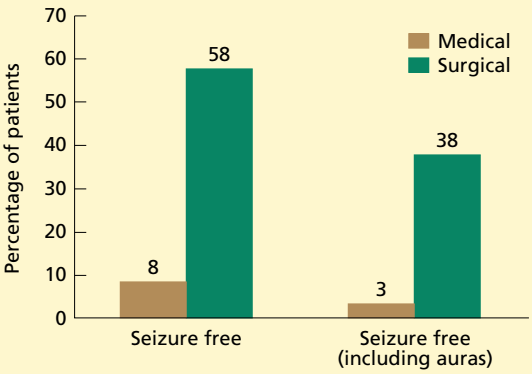


**FIGURE 3.** Comparison of patients in the surgical and medical groups who were free of seizures at 1 year.

DATA FROM WIEBE S, BLUME WT, GIRVIN JP, ELIASZIW M. A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY. N ENGL J MED 2001; 345:311–318.

better in the surgical group than in the medical group. More patients in the surgical group were employed or attending school at 1 year, but the difference did not reach statistical significance.

### TAKE-HOME POINTS FROM THE CANADIAN STUDY

Wiebe et al[12] showed that at 1 year, patients who underwent surgery for temporal lobe epilepsy were more likely to be free of seizures than those who underwent medical therapy (FIGURE 2, FIGURE 3), and their quality of life was better.

### Shortcomings of the study

**Seizure-free rate in surgical patients was comparatively low.** Compared with reports of 70% of surgical patients free of seizures,[13,14] the rate of 58% reported by Wiebe et al may seem low; however, the surgery group included several patients with complicated epilepsy (six needed invasive monitoring studies), which may explain the lower rate of seizure-free outcome. The lower seizure-free rate might also be due to the fact that four of those randomized to the surgical group did not, in fact, undergo surgery.

**Follow-up was limited to 1 year**, which is short for demonstrating the beneficial effects of successful surgery on quality of life and social functioning.[15] Even so, the significantly higher scores on quantitative measure of the quality of life at the end of 1 year, and the trend toward higher rates of employment and school attendance, are meaningful.

### Why the Canadian study is important: The 'no-surgery' approach is also risky

The Canadian randomized, controlled trial is a milestone in several ways:

- It confirms the effectiveness of surgery in

appropriately selected patients with temporal lobe epilepsy

- It indicates that a "no-surgery" approach in patients with medically intractable epilepsy is fraught with risks, the most serious one being the risk of death (sudden unexplained death in epilepsy [SUDEP] or death due to other reasons), as seen with one of the patients in the medical arm.

## A narrow window of opportunity: Surgical evaluation is not a last resort

The study results should prompt physicians to consider surgery not as a last resort, but as a preferred option in patients whose seizures are untreatable with drugs.

There is mounting evidence that drug-resistance can be successfully predicted after only one or two carefully chosen drugs have proven ineffective.[16,17] In a study by Kwan and Brodie,[16] 47% of patients became free of seizures after treatment with the first antiepileptic drug; however, of those who did not become free of seizures with the first drug, only 11% became free of seizures with medical management.

We have evidence to suggest that years of uncontrolled epilepsy lead to cognitive decline.[18] Earlier surgical intervention to eliminate seizures would offer a window of opportunity to allow patients a full and productive life, rather than years of ineffective pharmacotherapy with its consequent toll of time wasted and perhaps an opportunity lost forever. Therefore, consideration for referring a patient for surgical evaluation should be made soon after failure of two drugs.

**Opt for surgery early to take advantage of narrow window of opportunity**

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