Epilepsy Surgery for Pharmacoresistant Temporal Lobe Epilepsy

A Decision Analysis

Hyunmi Choi, MD, MS
Randall L. Sell, ScD
Leslie Lenert, MD, MS
Peter Muennig, MD, MPH
Robert R. Goodman, MD, PhD
Frank G. Gilliam, MD, MPH
John B. Wong, MD

Context Patients with pharmacoresistant epilepsy have increased mortality compared with the general population, but patients with pharmacoresistant temporal lobe epilepsy who meet criteria for surgery and who become seizure-free after anterior temporal lobe resection have reduced excess mortality vs those with persistent seizures.

Objective To quantify the potential survival benefit of anterior temporal lobe resection for patients with pharmacoresistant temporal lobe epilepsy vs continued medical management.

Design Monte Carlo simulation model that incorporates possible surgical complications and seizure status, with 10 000 runs. The model was populated with health-related quality-of-life data obtained directly from patients and data from the medical literature. Insufficient data were available to assess gamma-knife radiosurgery or vagal nerve stimulation.

Main Outcome Measures Life expectancy and quality-adjusted life expectancy.

Results Compared with medical management, anterior temporal lobe resection for a 35-year-old patient with an epileptogenic zone identified in the anterior temporal lobe would increase survival by 5.0 years (95% CI, 2.1-9.2) with surgery preferred in 100% of the simulations. Anterior temporal lobe resection would increase quality-adjusted life expectancy by 7.5 quality-adjusted life-years (95%, CI, −0.8 to 17.4) with surgery preferred in 96.5% of the simulations, primarily due to increased years spent without disabling seizures, thereby reducing seizure-related excess mortality and improving quality of life. The results were robust to sensitivity analyses.

Conclusion The decision analysis model suggests that on average anterior temporal lobe resection should provide substantial gains in life expectancy and quality-adjusted life expectancy for surgically eligible patients with pharmacoresistant temporal lobe epilepsy compared with medical management.

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EPILEPSY ACCOUNTS FOR 1% OF THE global burden of disease due to disability, affecting 0.5% to 1% of the world's population.[1] Despite currently available antiepileptic drugs, 20% to 40% of all patients with epilepsy remain refractory to medical management.[2-5] For such patients, epilepsy surgery still remains underused worldwide.[6-8] Few patients are referred for epilepsy surgery evaluation, and these referrals commonly occur late in the course of their disease, after 20 years of seizures.[9-11] Temporal lobe epilepsy is the most common form of epilepsy[12] and the most likely to be medically refractory.[13]

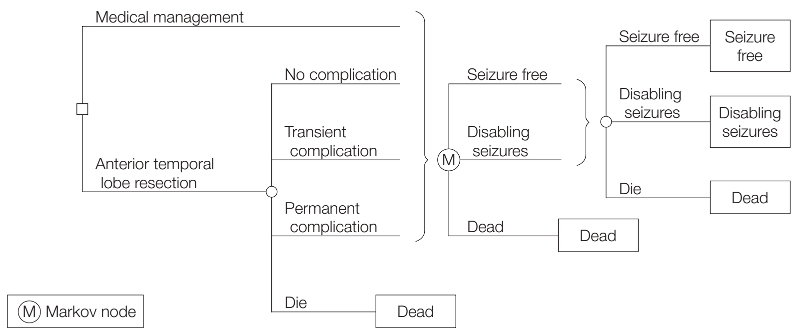
To examine the evidence base for surgery for uncontrolled seizures, in 2003 the Quality Standards Subcommittee of the American Academy of Neurology (AAN) performed a systematic review of the efficacy and safety of anterior temporal lobe resections.[1] Based on 1 randomized trial and 24 observational studies, they found that anterior temporal lobe resection reduced the occurrence of disabling seizures and improved patients' quality of life, with "infrequent morbidity." Furthermore, they speculated that the "greater potential for achieving freedom from disabling seizures offered by surgical treatment, as opposed to continuing pharmacotherapy, may reduce the risks of long-term mortality."

Pharmacoresistant epilepsy has been associated with decreased survival with standardized mortality ratios (SMRs, calculated as observed mortality in patients divided by the expected mortality for a matched general population) as high as 16.[14,15] Patients becoming seizure free after anterior temporal lobe re-

See also pp 2527 and 2548 and Patient Page.

Author Affiliations: Departments of Neurology (Drs Choi and Gilliam) and Neurological Surgery (Dr Goodman), Columbia University, and Department of Health Policy and Management (Dr Muennig), Columbia University Mailman School of Public Health, New York, New York; Department of Community Health and Prevention, Drexel University School of Public Health, Philadelphia, Pennsylvania (Dr Sell); National Center for Public Health Informatics, Centers for Disease Control and Prevention, Atlanta, Georgia (Dr Lenert); and Department of Medicine, Division of Clinical Decision Making, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts (Dr Wong). Dr Gilliam is now with the Department of Neurology, Weill Cornell Medical College, New York, NY.
Corresponding Author: Hyunmi Choi, MD, MS, Columbia Comprehensive Epilepsy Center, The Neurological Institute, 710 W 168th St, Box 210, New York, NY 10032 (hc323@columbia.edu).

Figure 1. Monte Carlo Simulation



The square on the left represents a decision node, representing the choice between surgery and medical management. The circle is a chance node, representing various possible outcomes after surgery including procedure-related operative death, permanent long-term surgical complication, transient short-term surgical complication, or no surgical complication. The brace signifies a subtree that occurs for all branches leading to that brace. Each subtree enters a Markov process, leading to 1 of 3 health states (disabling seizures, seizure free, or dead). The Markov cycle represents time as a single year during which the health state may change. At the end of each branch is a terminal node that indicates the health state in which patients will begin the next 1-year cycle. The probability estimates from the literature in Table 1 determine the likelihood of the chance events.

section have reduced mortality rates relative to patients continuing to have seizures, suggesting potential long-term survival benefit.[16,17] Although ideal, a randomized controlled trial comparing long-term survival with and without surgery is unlikely due to issues with equipoise and difficulty with blinding surgery study participants.[18] The National Institutes of Health–funded, multicenter Early Randomized Surgical Epilepsy Trial,[19] which randomized patients with early intractable temporal lobe epilepsy to surgical or medical therapy, was stopped early because of low enrollment rates. Consequently, we performed a decision analysis using a Monte Carlo simulation model to estimate the effect of anterior temporal lobe resection vs continued medical management on life expectancy and quality-adjusted life expectancy among patients with pharmacoresistant temporal lobe epilepsy.

METHODS

Patient Population

The model considers patients with refractory partial seizures (simple partial, complex partial, secondarily generalized tonic-clonic seizures, or all 3), that are resistant to at least 2 antiepileptic medications. To determine surgical eligibility, an epileptogenic region in the anterior temporal lobe must be identified through diagnostic evaluation including clinical history, electroencephalogram, magnetic resonance imaging, and functional tests (neuropsychological test, single-photon emission computed tomography or positron emission tomography). Mean (SD) age at the time of epilepsy surgery was assumed to be 35 (11) years[9,10,20,21] based on the weighted mean age of surgically treated patients in published studies. Data estimates were based on a systematic search of the medical literature and combined using a random-effects model[22] because of significant heterogeneity among studies ($I^2 > 50\%$).[23] Health-related quality-of-life data were obtained from patients with pharmacoresistant temporal lobe epilepsy.

Decision Analytic Model

The Monte Carlo simulation model[24] (FIGURE 1) considered only the strategies of temporal lobe resection or continued medical management. It included neither gamma-knife radiosurgery because of insufficient data on long-term efficacy and safety nor vagus nerve stimulator because of limited data on effectiveness. Potential surgical complications included mortality, long-term permanent complications (eg, noticeable verbal memory decline, homonymous hemianopsia, or hemiparesis), or short-term transient complications (eg, postoperative infections or depression).[1] Subsequent prognosis for cohorts of 10 000 hypothetically identical patients receiving one option or the other was captured as patients moved among a prespecified set of health states. During each yearly cycle, some patients could develop *disabling seizures*, defined as seizures that impair awareness (ie, complex partial or secondarily generalized seizures)[25] or become *seizure free*, defined as entirely seizure free or having only simple partial seizures that do not affect consciousness (ie, aura). Freedom from disabling seizures is the most commonly used standard seizure outcome classification.[9,25] Regardless of treatment, any year spent with disabling seizures increased mortality and reduced quality of life.

The annual likelihood of moving from one health state to another was modeled using transition probabilities, with the simulation continuing until all patients in the cohort died from epilepsy-related complications, surgical complications, or unrelated causes. The probability of mortality was based on annual age-specific mortality rates obtained from US life tables[26] that were adjusted for additional excess mortality from seizure persistence, relapse, or remission. All analyses were performed using Microsoft Excel 2000 and Decision Maker (WinDM 2007; Tufts Medical Center, Boston, Massachusetts).

Data

TABLE 1 presents the base case data estimates (see eAppendix for details at http://www.jama.com).

One-Year Seizure Outcomes After Temporal Lobe Resection. Although the AAN systematic review of studies published between 1990 and 1999 provided seizure outcomes, it did not specify the follow-up intervals required for estimating transition rates. Our literature search yielded 13 studies published after July 1999 that provided information on seizure outcome following temporal lobe resection[9,10,27-37]; for 1 study, the investigators provided the primary data.[27] From pooling these 13 studies, the baseline probability of being free of disabling seizures a year after anterior temporal lobe resection was assumed to be 71.9% (95% confidence interval [CI], 69.5%-74.3%).

Long-term Seizure Outcomes After Temporal Lobe Resection. Longitudinal studies of patients with anterior temporal lobe resections have shown that the seizure status at 1 year after surgery does not remain stable over subsequent follow-up. Five studies provided long-term data (up to 10 years) based on seizure status 1 year after anterior temporal lobe resection.[21,27,28,32,37] Among patients seizure-free at the end of year 1 following surgery, the annual probability of seizure relapse between years 1 and 5 was 5.6% (95% CI, 2.9%-8.3%) and beyond year 5 was 4.2% (95% CI, 1.6%-6.8%).[21,27,28,32,37] One study found that the likelihood of further relapse for patients seizure free at year 10 was 0%,[27] but given the limited data, we chose to use 4.2% in the base case but explored the effect of this assumption in sensitivity analysis. Similarly, among patients with persistent seizure at the end of year 1 following surgery, the annual probability of becoming seizure free between years 1 and 5 was 5.9% (95% CI, 0.9%-11%) while the probability of becoming seizure free after year 5 was 2.0% (95% CI, 0.2%-7.2%).[27,28]

One-Year Seizure Outcomes After Medical Management. Limited data were available regarding the probability of becoming seizure free with medical management. In the single randomized controlled trial comparing anterior temporal lobe resection vs medical management, the probability of becoming free of disabling seizures at 1 year with continued medical management was 8.0% (95% CI, 0%-16%).[9]

Long-term Seizure Outcomes After Medical Management. As with surgery, seizure status after medical management fluctuates over time. No study exclusively examined the long-term seizure remission and relapse rates among patients with pharmacoresistant temporal lobe epilepsy with medical management, but one study reported these outcomes in intractable epilepsy patients (including 50% of patients with temporal lobe epilepsy).[38] Among patients seizure free at the end of year 1, the annual probability of seizure relapse was 25.4% (95% CI, 10.9%-46.2%). Similarly, among patients with persistent seizures at the end of year 1, the annual probability of becoming seizure free was 4.7% (95% CI, 3.0%-7.0%). By applying the same relative risk reduction as occurred after surgery, we assumed that this probability fell to 1.6% (95% CI, 1.0%-2.3%) beyond year 5.

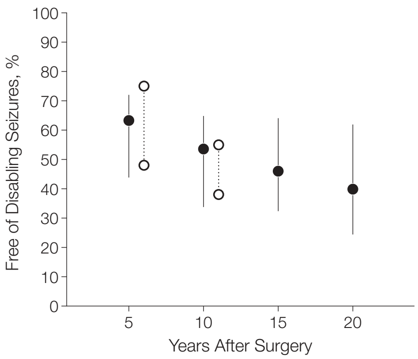
Surgical Morbidity. Adverse surgical complications following anterior temporal lobe resections include neurological deficits (such as noticeable verbal memory decline), postoperative infections, and emotive or behavioral changes (such as depression). Based on the definitions used by the AAN report,[1] we categorized adverse surgical complications as either transient (resolution within 3 months) or permanent. The AAN systematic review[1] identified 7 studies involving 556 patients that allowed classification, with transient complications in 8.0% (95% CI,

Table 1. Base-Case Assumptions and Ranges for Sensitivity Analyses

Variables	Mean (95% Confidence Interval), %	Distribution for Monte Carlo Simulation[a]
Probabilities		
Becoming seizure free during first year		
Medical management[9]	8.0 (0 to 16)	β
Surgery[9,10,27-37]	71.9 (69.5 to 74.3)	Normal
Seizure relapse if seizure free at end of year 1[b]		
Medical management after year 1[38]	25.4 (10.9 to 46.2)	Logit
Surgery		
From years 1-5[21,27,28,32,37]	5.6 (2.9 to 8.3)	Normal
After year 5[21,27,28,32,37]	4.2 (1.6 to 6.8)	Normal
Seizure remission if not seizure free at end of year[b]		
Medical management		
From years 1-5[38]	4.7 (3.0 to 7.0)	Normal
After year 5[38]	1.6 (1.0 to 2.3)	Logit
Surgery		
From years 1 to 5[27,28]	5.9 (0.9 to 11)	Normal
After year 5[27,28]	2.0 (0.2 to 7.2)	Logit
Surgical complications		
Surgical mortality[1]	0.3 (0 to 0.75)	β
Permanent complication[1]	4.0 (2.0 to 6.0)	β
Transient complication[1]	8.0 (6.0 to 10)	β
Standardized mortality ratios		
Seizure free[16,17]	1.11 (0.63 to 1.94)	Log normal
Not seizure free		
Surgery[16,17]	5.64 (3.49 to 9.09)	Log normal
Medical management[39-41]	5.40 (3.96 to 7.37)	Log normal
Preference-Based Quality of Life Scores for Model Health States[c]		
Free of disabling seizures		
Medical management	0.96 (0.84-1.0)	Uniform
Surgery		
No surgical complication	0.97 (0.87-1.0)	Uniform
Permanent complication	0.77 (0.32-1.0)	Uniform
Transient complication	0.96 (0.84-1.0)	Uniform
Not free of disabling seizures		
Medical management	0.75 (0.38 to 1.0)	Uniform
Surgery		
No surgical complication	0.78 (0.41 to 1.0)	Uniform
Permanent complication	0.66 (0.19 to 1.0)	Uniform
Transient complication	0.75 (0.38 to 1.0)	Uniform
Transient surgical complication (days of life deducted)	1.5 (0 to 25.0)	Uniform

[a] Pooled mean (SD) age from literature, 35 (11) years.
[b] Annual probability.
[c] The Monte Carlo analysis used a bootstrap sample for the set of quality-of-life estimates from 1 of the 22 patients assuming a uniform distribution.

Figure 2. Model and Published Seizure-Free Outcomes After Surgery



Comparison of Monte Carlo model predictions for the 5-, 10-, 15-, and 20-year likelihoods of being free of seizures after surgery (solid line with mean and 95% confidence intervals) with the published 5- and 10-year likelihoods (dashed line to display the lowest and highest reported means) of being seizure free after surgery including studies that could not be used in our meta-analysis.[32,33,35]

6.0%-10.0%) and permanent complications in 4.0% (95% CI, 2.0%-6.0%).

Surgical Mortality. No studies reviewed in the AAN report or published subsequently have reported any surgical deaths from temporal lobe resections. However, of the 556 patients, 2 (0.3%) deaths unrelated to surgery occurred within a month of surgery.[1] To bias our model results against surgery and recognize that anesthesia-related deaths may occur, our baseline estimate for operative mortality was 0.3% (95% CI, 0%-0.75%).

Excess Mortality From Epilepsy. Mortality in patients with pharmacoresistant epilepsy exceeds that in the general population.[14,15] Because excess mortality is thought to be epilepsy related, treatments effective in eliminating seizures should reduce excess mortality. For patients seizure-free after temporal lobe resections, studies have reported SMRs of 1.7 (95% CI, 0.35 to 5.0)[16] and of 0 (no deaths).[17] After assuming an SMR of 1.0 for the study with no deaths,[17] the pooled SMR using the random-effects model was 1.11 (95% CI, 0.63-1.94) for seizure-free patients following surgery. In the absence of published data, we assumed an identical SMR for patients who become seizure free with medical management.

For patients with persistent seizures or seizure relapse after surgery, pooling 2 studies yielded an SMR of 5.64 (95% CI, 3.49-9.09).[16,17] Despite a large number of studies examining long-term mortality in patients with intractable epilepsy, no study has examined the specific SMR of patients with pharmacoresistant temporal lobe epilepsy eligible for surgery but treated medically. Therefore, as the closest approximation, combining studies in heterogeneous groups of patients with intractable epilepsy but who had not undergone epilepsy surgery[39-41] yielded an SMR of 5.40 (95% CI, 3.96-7.37).

Preference-Based Quality-of-Life Values. To assess individual preferences for the health outcomes specified in our model, we interviewed patients who had previously undergone temporal lobe resections at our center, using the standard gamble (see eAppendix at http://www.jama.com).[42,43] These preference-based quality-of-life values were then used to adjust life expectancy to yield quality-adjusted life expectancy.

The protocol was approved by the institutional review board at the Columbia University Medical Center. Participants provided written informed consent. Table 1 reports the means and 95% CIs for each health state from 22 patients.

Sensitivity Analyses

In sensitivity analyses, the value of each parameter used in the model was varied over a broad range to determine if the preferred strategy changed. If the preferred strategy changed with variation, we determined the threshold value for that parameter so that for values above the threshold, one strategy would be preferred, while for values below that threshold, the alternative would be preferred. Sensitivity analysis identifies the most influential or important parameters for this analysis, ie, those with thresholds. Table 1 lists the baseline values and the range of values over which we varied that particular parameter.

Our baseline analyses were second-order Monte Carlo simulations in which all parameters were varied simultaneously using normal, log-normal, logit, or β distributions based on 95% CIs.[44,45] Quality-of-life scores were sampled from a uniform distribution. In these analyses, the simulation selected a single-point estimate for each parameter from the respective probability distributions for each evaluation run. Simulations were repeated 10 000 times to yield a mean and 95% CI, incorporating the uncertainty surrounding each variable.

RESULTS

Baseline Analysis

Model predictions of being seizure free 5 years and 10 years after anterior temporal lobe resection were consistent with results from published studies (FIGURE 2). The model suggests that a prototypical surgically eligible 35-year-old patient who would have been medically treated has an average life expectancy of 27.3 years (95% CI, 24.1-30.5) compared with a life expectancy of 44.3 years in the general population. Anterior temporal lobe resection would increase life expectancy by 5.0 years (95% CI, 2.1-9.2) with surgery preferred in 100% of the simulations. Anterior temporal lobe resection would increase quality-adjusted life expectancy by 7.5 (95% CI, −0.8 to 17.4) quality-adjusted life-years (QALYs) with surgery preferred in 96.5% of the quality-of-life simulations (TABLE 2). For a 35-year-old patient, the model suggests that anterior temporal lobe resection increased the number of seizure-free years by 15.0 (95% CI, 9.6-24.6) and reduced the lifetime absolute risk of dying from seizure-related causes by 15% (95% CI, 4.0%-35%)

Sensitivity Analyses

Univariate sensitivity analysis assessed the stability of the model results to alternative assumptions. Table 2 presents the model results for 15- to 75-year-olds with pharmacoresistant temporal lobe epilepsy for fixed ages. Variation of each parameter over the ranges specified in Table 1 did not alter the preferred strategy. When extending variation further to extreme values (eg, 0%-100% for probabilities, 1-10 for SMR, and 0-1 for utilities), medical treatment became preferred for (1) probability of surgical mortality exceeding 24% (baseline, 0.3%), (2) SMR for disabling seizures with medical management falling below 2.3 (baseline, 5.4), (3) annual probability of seizure remission with medical therapy exceeding 79% (baseline, 4.7%), (4) quality of life for "free of disabling seizures after surgery with no complications" falling below 0.58 (baseline, 0.97; 95% CI, 0.87-1.0), and (5) quality of life for "not free of disabling seizures after surgery without complication" falling below 0.30 (baseline, 0.78; 95% CI, 0.41-1; FIGURE 3A-E).

For Figure 3D and E, the quality-of-life estimates that would change the preferred strategy are implausible, falling below the quality of life for all other health states including some that logically should be worse and violating the ordering of health states from the actual patients. No threshold existed for the probability of long-term surgical complication, ranging from 0 to 1 (ie, surgery remained preferred). We also performed a sensitivity analysis in which all utilities were linked in a fixed proportion. Using this approach, medical therapy was preferred only if all surgical quality-of-life estimates were reduced by a relative reduction of at least 24%. In this case, the quality of life of having surgery and being free of seizures would be worse than continued seizures with medical therapy.

To explore potential uncertainty around long-term surgical complications, if the quality of life with long-term complications from surgery were equivalent to being dead (ie, quality of life with permanent complication equals 0), on average surgery would still improve quality-adjusted survival by 6.4 (95% CI, −1.6 to 16.2) QALYs with surgery preferred in 95.2% of the simulations. Extending this analysis further, we performed a 2-way sensitivity analysis to examine jointly the probability of developing a long-term surgical complication along with the quality of life with such a complication (FIGURE 4). Medical therapy becomes preferred for combinations of values with a high likelihood of a long-term surgical complication and a low quality of life with such a complication, eg, 24% likelihood and 0 quality of life (equivalent to death) or 100% likelihood and 0.71 quality of life.

Studies that included data on SMR after surgery were limited to a mean follow-up of 7 years. To explore a nonconstant epilepsy mortality ratio, we assumed a linear decline in the SMR associated with seizures or without seizures to 1.0 (ie, identical to the general population) after 20 years. In this analysis, anterior temporal lobe resection would increase life expectancy by only 1.2 years (95% CI, 0.8-1.5, with surgery preferred in 100% of the simulations) but by 5 QALYs (95% CI, −7.0 to 19.7, with surgery preferred in 90.8% of the simulations) because of fewer years with seizures.

To compare in isolation the effect of long-term surgical morbidity vs seizure-related morbidity on quality of life, we assumed no excess mortality associated with seizures and found that surgery remained preferred by 3.9 (95% CI, −9.0 to 20.4) QALYs (with surgery preferred in 86.3% of the simulations) because patients lived longer (no excess mortality and had more seizure-free years). Two of the baseline assumptions biased our results in favor of medical therapy. If we relaxed those assumptions so that the SMR with seizures following medical therapy equals that with surgical treatment (5.64 instead of 5.40) and if the yearly likelihood of seizure relapse following surgery becomes 0% after 10 years,[27] then the benefit of surgery for a prototypical surgical patient rose to 9.9 years (95% CI, 7.3-13.4, with surgery preferred in 100% of the simulations) and 12.9 QALYs (95% CI, 5.9-22.4, with surgery preferred in 100% of the simulations).

COMMENT

Studies have reported the effectiveness of temporal lobe resection since the 1950s,[46,47] yet a minority of patients are being referred to surgery and those only after an average of 20 years of illness.[9-11,48] For adolescents and young adults, this delay may be particularly significant during a critical period in

Table 2. Expected Outcomes of Decision Analysis

	Age at Surgery, y						
	15	25	35	45	55	65	75
	Life Expectancy, Estimate (95% Confidence Interval), y						
Surgery	48.5 (41.9 to 56.4)	40.3 (34.2 to 47.3)	32.3 (27.0 to 38.5)	24.8 (20.2 to 29.9)	18.2 (14.4 to 22.4)	12.6 (9.6 to 15.9)	8.0 (5.9 to 10.5)
Medical management	43.9 (40.0 to 47.9)	35.6 (32.0 to 39.2)	27.3 (24.1 to 30.5)	19.6 (16.9 to 22.5)	13.2 (11.0 to 15.5)	8.0 (6.4 to 9.8)	4.4 (3.4 to 5.5)
Incremental benefit	4.6 (0.9 to 10.5)	4.7 (1.4 to 9.7)	5.0 (2.1 to 9.2)	5.2 (2.7 to 8.5)	5.0 (3.1 to 7.5)	4.6 (3.0 to 6.4)	3.6 (2.3 to 5.1)
Simulations preferring surgery, %	99.6	99.9	100	100	100	100	100
	Quality-Adjusted Life Expectancy, Estimate (95% Confidence Interval), QALYs						
Surgery	42.1 (24.3 to 53.1)	35.2 (20.9 to 44.6)	28.4 (17.5 to 36.5)	22.1 (14.3 to 28.3)	16.4 (11.1 to 21.1)	11.5 (7.9 to 15.1)	7.4 (5.1 to 9.9)
Medical management	33.8 (12.4 to 43.9)	27.3 (10.2 to 35.6)	20.9 (7.9 to 27.7)	15.2 (5.8 to 20.3)	10.2 (4.0 to 13.8)	6.3 (2.5 to 8.7)	3.4 (1.5 to 4.9)
Incremental benefit	8.3 (−5.5 to 24.8)	7.9 (−3.3 to 21.0)	7.5 (−0.8 to 17.4)	6.9 (1.2 to 14.5)	6.2 (2.4 to 11.3)	5.2 (2.8 to 8.6)	4.0 (2.4 to 6.0)
Simulations preferring surgery, %	92.5	94.0	96.5	99.3	100	100	100

Abbreviation: QALY, quality-adjusted life year.

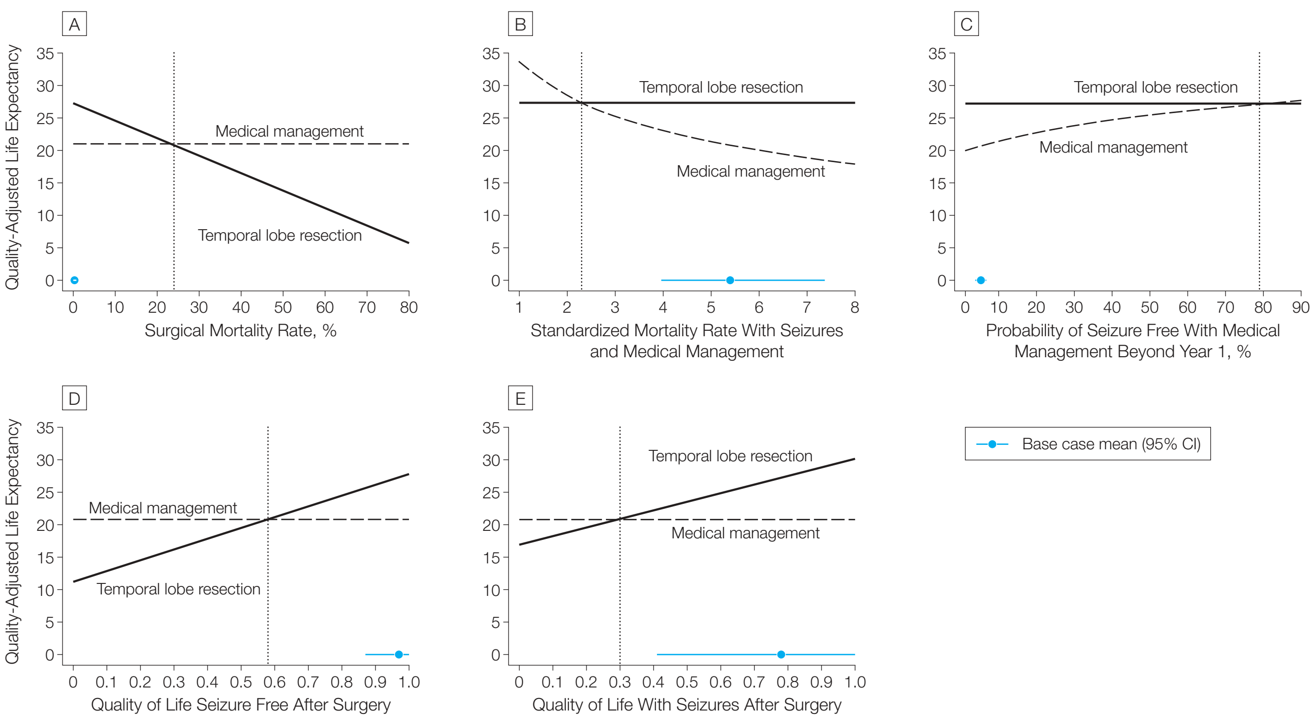
their psychosocial development. Accordingly, a panel of experts systematically reviewed the risks and benefits of anterior temporal lobe resection for pharmacoresistant temporal lobe epilepsy and found that surgery resulted in two-thirds of patients becoming free of disabling seizures with improved overall quality of life. Based on these findings, they recommended that patients with disabling seizures who have failed trials of first-line antiepileptic drugs be referred to an epilepsy surgery center and that appropriate patients who accept its risks and benefits be offered surgery.[1]

Our updated systematic review corroborates their results and extends their findings to quantify the benefits and risks. Our model suggests that anterior temporal lobe resection for patients with pharmacoresistant temporal lobe epilepsy should increase average life expectancy and quality-adjusted life expectancy. When compared with the benefit accrued from other well-accepted medical interventions,[49] the 5.0-year benefit from anterior temporal lobe resection for typical surgically eligible patients (mean age, 35-year-olds) is substantial. For example, eliminating lifelong coronary heart disease mortality in 35-year-old men or women[50] increases life expectancy by 3.1 to 3.3 years and coronary artery bypass grafting or β-blocker use after acute myocardial infarction increases life expectancy by 0.25 to 1.1 years.[51,52]

Inclusion of quality-of-life benefit from being seizure free increases the mean benefit from surgery, but the 95% CI for the quality-of-life gain from surgery includes some negative values for ages 15 through 35 years. This reflected incorporating the preferences of 2 patients who, despite having had good outcomes after surgery, thought that if they had had disabling seizures after surgery, their quality of life would be much worse than having disabling seizures with medical therapy (ie, their quality-of-life estimates for disabling seizures were lower by 0.25 to 0.40 compared with their quality-of-life estimates for disabling seizures after medical management).

In these simulations, the 95% CIs do not reflect individual outcomes but

Figure 3. Sensitivity Analysis of Resection vs Pharmacotherapy for Epilepsy



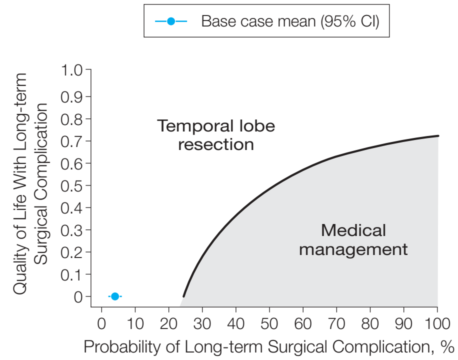
A, Each line represents the quality-adjusted life-years (QALYs) associated with surgery (solid line) or with medical management (dashed line) for 35-year-old patients varying the surgical mortality rate from 0% to 80%. For any particular surgical mortality rate, the higher line is the preferred treatment of choice. The dot indicates the base-case value (0.3%), and the dotted vertical line indicates the threshold (24%) at which temporal lobe resection and medical management are equivalent. Anterior temporal lobe resection is preferred for probabilities below the threshold, and medical management for probabilities above the threshold. B, As the standardized mortality ratio (SMR) of patients with seizures on medical management increases, the benefit of surgery increases. The threshold is 2.3 (base-case, 5.4). Temporal lobe resection is preferred for SMR values above the threshold. C, As the annual probability of becoming seizure free with medical management increases, the benefit of surgery decreases. The threshold is 79% (base-case, 4.7%). Temporal lobe resection is preferred for probabilities below the threshold. D, As the quality of life without seizures following surgery decreases, the benefit of surgery decreases. The threshold is 0.58 (base-case, 0.97). Temporal lobe resection is preferred for values above this threshold. Note that at 0.58, the quality of life with medical management and seizures would be better (0.75) than being seizure free after surgery. E, As the quality of life with disabling seizure after anterior temporal lobe resection decreases, the benefit of surgery decreases. The threshold is 0.30 (base-case, 0.78). Temporal lobe resection is preferred for values above this threshold. Note that this values fall outside of the 95% confidence interval [CI] for patients who have received surgery (0.41-1.0).

rather uncertainty in the model parameters. They should not be interpreted as in a study of hypothesis testing but rather as the range of outcomes. More relevant for interpretation is the percentage of model simulations in which one strategy is preferred over the other. With the quality-of-life simulations, surgery was preferred in more than 92% of the simulations across all ages. For the outcome of life expectancy, surgery was preferred in more than 99% of simulations and the 95% CIs were entirely positive across all ages.

Why then does this discrepancy between clinical practice and recommendations for surgical referral exist? A recent survey of neurologists' views on epilepsy surgery and medically refractory epilepsy[53] found that responding neurologists overestimated the likelihood of surgical complications, with 64% believing that the permanent complication rate exceeded 5%. One-third reported having had a patient with a serious complication after epilepsy surgery, raising the possibility of availability bias, overestimating the likelihood of memorable events because of severity.[54] Neurologists also differed on the definition of drug-refractory epilepsy: 77% required failure of at least 2 different polytherapy trials, 14% required failure of 4 or more, and 19% required failure of all approved drugs. In contrast, in a large cohort study of newly diagnosed patients with epilepsy, only 11% of patients who failed an appropriate first-line antiepileptic drug responded to a second drug and only 3% responded to multiple drugs.[55]

Although the consequence of long-term surgical complication may influence neurologists (perhaps in part due to concerns about errors of commission more so than errors of omission), only when varying both the probability of long-term complication and the quality of life with complications beyond plausible ranges did medical management become preferred. The quality of life and mortality benefit from being seizure free with surgery outweighed the risk of long-term surgical complications. Our analysis suggests that additional research to clarify the likelihood of and the quality of life decrement from long-term complications may help inform patient and physician decision making.

Figure 4. Probability of Long-term Complication After Surgery and the Quality of Life With a Long-term Surgical Complication



The line represents threshold values, so that for combinations of values above the line, surgery is preferred and for those below the line, medical management is preferred. Even if the quality of life with a long-term complication were 0, the probability of a long-term complication would have to exceed 24% (baseline 4%, 95% confidence interval [CI], 2%-6%) for medical management to be preferred.

The most critical parameter affecting survival involved long-term mortality following either treatment. Increased mortality from pharmacoresistant epilepsy typically results from epilepsy-related causes of death such as seizure-induced accidents (eg, drowning or burns), status epilepticus, suicide, and sudden unexpected death in epilepsy.[56,57] In particular, sudden unexpected death in epilepsy comprises the majority of deaths in intractable epilepsy, with a reported incidence of between 2.2 and 9.3 per 1000 patient-years.[17,40,58,59] Two studies have specifically examined late mortality after anterior temporal lobe resection. After stratifying patients on their seizure outcome after surgery, both found that after surgery patients who were free from disabling seizures had mortality rates similar to that of the general population (the 95% CI for SMR included 1), whereas patients with persistence of seizures despite surgery had SMRs ranging from 4.7 to 7.4.[16,17] Combined with the higher likelihood of seizure remission with surgery instead of medical management, this supports the plausibility of improved survival with anterior temporal lobe resection.

However, differences in mortality based on seizure status may not be due to surgery but rather some inherent biological differences due to selection bias so that patients who became seizure free after surgery might have had a lower SMR even without surgery.[15] Indirect evidence linking poor surgical outcome and epilepsy mortality is provided by observational studies. Among patients who had undergone anterior temporal lobe resection, those with advanced age at the time of surgery, longer duration of epilepsy, secondary generalization to tonic-clonic seizures, and absence of hippocampal sclerosis on magnetic resonance imaging scan had a lower likelihood of becoming seizure free.[35,60,61] The presence of secondarily generalized tonic-clonic seizure has also been associated with increased risk of sudden unexpected death.[62] If secondary generalization to tonic-clonic seizures was less common in surgically selected patients than in those treated medically, selection bias could account for lower mortality in the observational studies of patients after surgery. However, in the only randomized controlled trial to date, patients were more likely to become seizure free after surgery and the only death that occurred in that study was from sudden unexpected death in epilepsy of a patient in the medical treatment group.[9]

Our study has some notable limitations. First, the decision model does not consider other interventions such as gamma-knife radiosurgery because of limited information on long-term efficacy and safety[63] or vagus nerve stimulators because of limited data on effectiveness.[64] Second, data in patients with pharmacoresistant temporal lobe epilepsy receiving medical management remain sparse, so our estimates of seizure remission and relapse with medical management beyond the first year included adults with other types of intractable epilepsy. Even so, the sensitivity analyses suggest that anterior temporal lobe resection would remain preferred unless the annual probability of seizure remission beyond year 1 exceeded 79% with medical therapy (baseline, 4.7%).

Third, no study has specifically examined the SMR of patients with temporal lobe seizures who would be eligible for surgery but instead continued medical management. Therefore, we combined the SMRs of pharmacoresistant epilepsy patients (not necessarily temporal lobe epilepsy) who were undergoing surgical evaluation or awaiting surgery, declined surgery, were rejected for surgery based on evaluation, or participated in vagus nerve stimulation trials. The sensitivity analysis suggests that surgery would remain preferred unless the SMR fell below 2.3, a value considerably lower than that found in the literature for pharmacoresistant epilepsy patients.

Fourth, we elicited preference-based quality-of-life estimates from a small group of patients who had previously undergone temporal lobe surgery. This perspective may be a source of bias. Our study assessed these patients' values for hypothetical states in an attempt to minimize bias due to patients' outcomes while taking advantage of their experience with the condition and surgery. There are often systematic differences between the patient perspective and the general population perspective in preference studies, and such differences would likely enhance the value of surgery in analyses. Sensitivity analyses were robust to plausible ranges of utility values. However, when we extended variation of individual utility values further to extreme values, we identified 2 utility thresholds. In addition, we also found that when all surgical utilities were reduced by at least 24%, medical management became preferred. In both of these sensitivity analyses, the postsurgical quality of life of being seizure free would be lower than having seizures with medical treatment and would be inconsistent with the rank ordering of health states from our patients. If eligible patients, indeed, felt this way, then surgery would be inappropriate for them.

Fifth, our model consolidates long-term surgical complications into a single health state, as was done in the AAN practice parameter, so it cannot account in detail for the complex and diverse outcomes that occur in individualized patient-physician decision making, such as potential noticeable verbal memory decline after surgery of temporal lobe seizure focus in the language dominant hemisphere.

Sixth, our study findings are based on model projections, derived mostly from nonrandomized controlled trials and are subject to potential biases and flaws associated with those studies.

Decision analysis is a prescriptive approach to decision making in the face of uncertainty. It explicitly defines alternatives and outcomes, and it quantifies uncertainty to help patients and physicians decide between treatment choices. By linking the probabilities of becoming or remaining seizure free after treatment with seizure-related mortality rates, our decision analysis incorporates the best available data to estimate the long-term survival consequences of pursuing different treatment choices. For patients with pharmacoresistant temporal lobe epilepsy and neurologists, these results provide an additional perspective for comparing the relative benefits of epilepsy surgery vs continued medical management.

Referral of patients in a timely manner is crucial, because factors such as older age at surgery and longer duration of epilepsy are associated with a lower likelihood of becoming seizure-free after anterior temporal lobe resection.[61] Referral to a specialized epilepsy surgery program should be considered when at least 2 appropriate antiepileptic drugs have been tried at maximum tolerable doses and when patients are experiencing disabling partial-onset seizures.[65] At highly specialized epilepsy surgery programs that offer comprehensive diagnostic and treatment services,[66] appropriate patients for consideration of anterior temporal lobe resections include those with interictal or ictal electroencephalogram finding compatible with mesial temporal lobe onset seizure, and atrophy and signal abnormality of hippocampus on brain magnetic resonance imaging scan on the same side as the electroencephalogram onset.[67] Patients with discordant findings require further diagnostic evaluation for accurate localization of the site of seizure origin.

In conclusion, our findings support increased use of anterior temporal lobe resective surgery in appropriate patients.

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Study concept and design: Choi, Sell, Lenert, Muenning, Goodman, Gilliam, Wong.
Acquisition of data: Choi, Lenert.
Analysis and interpretation of data: Choi, Lenert, Muenning, Gilliam, Wong.
Drafting of the manuscript: Choi, Sell, Muenning, Gilliam, Wong.
Critical revision of the manuscript for important intellectual content: Choi, Lenert, Muenning, Goodman, Gilliam, Wong.
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