Epilepsia, **47**(11):1865–1869, 2006
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Assessment of the Long-term Effects of Epilepsy Surgery with Three Different Reference Groups

*Christian G. Bien, *†Andreas Schulze-Bonhage, *Bettina M. Soeder, ‡Johannes Schramm, *Christian E. Elger, and *§Henning Tiemeier

*University of Bonn, Department of Epileptology, Bonn, Germany; †University of Freiburg, Epilepsy Unit, Freiburg, Germany; ‡University of Bonn, Department of Neurosurgery, Bonn, Germany; and §Erasmus Medical Center, Department of Epidemiology and Biostatistics, Rotterdam, The Netherlands

Summary: *Purpose:* It is difficult to validly assess the long-term effect of epilepsy surgery. Here, this is attempted by comparing the outcome of surgically treated pharmacoresistant epilepsy patients to three different nonoperated comparison groups regarding seizure control, antiepilepsy drug (AED) usage, and health related quality of life (QOL).

Methods: One hundred thirty-one operated patients (group 1, mean follow-up since presurgical assessment 6.9 years), 105 patients awaiting presurgical assessment (group 2, mean follow-up after assignment to waiting list 0.8 years), 99 patients considered to be presurgical candidates who chose to withdraw from waiting for presurgical assessment (group 3, mean follow-up after assignment to waiting list 5.5 years), and 49 patients who were not deemed to be eligible for surgery after comprehensive assessment (group 4, mean follow-up since presurgical assessment 6.5 years) were studied. The patients completed a questionnaire on seizures, AED usage, and QOL (ESI-55).

Results: The surgical patients had a better outcome than all three comparison groups regarding seizure frequency, seizure freedom rate, and number of AEDs used. They scored higher than groups 2, 3, and 4 on 7/11, 6/11, and 3/11 ESI-55 domains, respectively.

Conclusions: The superior long-term outcome of the operated patients was most marked if compared to the patients awaiting surgery. This is compatible with the assumption that patients present for presurgical candidacy selection and assessment at a "nadir" of their disease course. After several years, a regression to the mean occurs which reduces (but does not abolish) the differences between nonoperated and operated patients.
Key Words: Epilepsy surgery—Long-term outcome—Quality of life—Seizure outcome—Seizure control.

Epilepsy surgery has become accepted as an effective treatment for patients with medically refractory epilepsy. The only prospective randomized controlled trial over a 1 year period demonstrated the superiority of surgical compared to conservative treatment in all mentioned domains (Wiebe et al., 2001). Due to ethical constraints it is unlikely that the long-term effects of epilepsy surgery will ever be determined by a randomized controlled trial (Dasheiff et al., 1994). These long-term effects must be judged with observational data. A recent meta-analysis concluded that the long-term effect of epilepsy surgery on seizure freedom is similar to its short term consequences. However, well-controlled studies were too rare for a valid assessment of the postsurgical outcome (Tellez-Zenteno et al., 2005). Seizure freedom rates decline during the first years after surgery (Wieser et al., 2003; Schmidt et al., 2004). Conversely, a recent study reported that patients with inoperable epilepsy may have a better outcome than expected: 21% of nonoperated patients were seizure free at a mean follow-up period of 4.4 years (Selwa et al., 2003).

The few available long-term outcome studies including health related quality of life (QOL) (Baker and Jacoby, 2000) compared operated patients to patients awaiting surgery (Gilliam et al., 1999) or not eligible for surgical treatment (Vickrey et al., 1995; McLachlan et al., 1997). These studies demonstrated—at different degrees—superior outcomes in operated patients. However, the results could be biased: The reference patients had not (or not yet) received the treatment they expected, i.e., epilepsy surgery. Patients' expectations may strongly influence self-reported outcome variables (Wilson et al., 1998; Wilson et al., 1999; Carr et al., 2001).

The present study was designed to study the long-term effects of epilepsy surgery using three comparison groups: a "short-term" group awaiting presurgical assessment, and two "long-term groups": one that was not offered surgery and one group of patients that opted out of

Accepted June 12, 2006.
Address correspondence and reprint requests to Dr. Christian G. Bien, University of Bonn, Department of Epileptology, Sigmund-Freud-Str. 25 53105 Bonn, Germany. E-mail: christian.bien@ukb.uni-bonn.de
doi: 10.1111/j.1528-1167.2006.00813.x

undergoing presurgical evaluation after completing outpatient assessment, i.e., a novel comparison group without recent disappointment and without expectations of an intervention.

PATIENTS AND METHODS

From the database of patients of the Bonn Epilepsy center, four groups of patients were selected as described below. A questionnaire with the German version of the Epilepsy Surgery Inventory (ESI)-55 (Vickrey et al., 1992) together with a cash allowance equivalent to 10 US-$ was sent to the patients of groups 1, 3, and 4; patients of group 2 received the questionnaire during a visit to the outpatient department on day 1 of their formal presurgical assessment on the ward. The total number of patients allocated to a group minus those in which the present address was unknown minus those who underwent surgery elsewhere (four in group 3 and one in group 4) were considered eligible. The response rate was calculated as the percentage of eligible patients returning the questionnaire after completion of the majority of items.

Group 1: Pharmacoresistant epilepsy patients (use of at least two antiepilepsy drugs [AEDs] which had not lead to seizure freedom or had achieved this aim only at the cost of intolerable side effects) treated by resective interventions over an 11-year period and remaining in continuous postsurgical care at our center during a minimum follow up of 1 year.

Group 2: All outpatients identified as "presurgical candidates" (based on semiological, electrophysiological, or neuroradiological features concordant with the assumption of a single operable focus) over a period of 7 months.

Group 3: All outpatients identified as "presurgical candidates" over an 11-year period who opted not to undergo presurgical assessment.

Group 4: All patients not eligible for epilepsy surgery after presurgical assessment, but otherwise fulfilling the same criteria as the patients in group 1 (minimum follow-up after presurgical assessment 1 year).

Baseline data were collected from the patients' records.

Statistical tests: We compared the groups with *t*-test, Mann-Whitney test, χ^2 test, and ANCOVA where appropriate.

RESULTS

Three hundred eighty-four patients were studied. Of the 175 eligible patients in group 1, 131 patients responded (response rate 75%). Eighty-four percent of the patients underwent surgery in the temporal lobe, 12% in the frontal lobe, and 4% in other lobes. Six patients underwent a second surgical procedure extending the previous one. In group 2, the number of eligible patients was 115, 105 responded (91%). A total of 194 patients were assigned to group 3. Of those, 146 met our criteria, and 99 responded (68%). Most frequent reasons for withdrawal were: fear for adverse effects of surgery (77%), improvement of seizure frequency by recent AED therapy (60%), not expecting surgical success (59%). Sixty-five patients were assigned to group 4, of which 49 responded (75%). The reasons for refusing surgical treatment were: focus not identified (47%), multiple foci (19%), unacceptable

TABLE 1. *Characteristics of subjects at baseline and at follow-up (time of questionnaire)*

	Surgical group (N = 131)	Awaiting presurgical assessment (N = 105)	Withdrew from waiting for presurgical assessment (N = 99)	Surgery denied after presurgical assessment (N = 49)
At baseline				
Age, yr, (SD)	31.1 (10.6)	35.8** (10.5)	31.9 (10.2)	36.6* (13.1)
Gender, female, %	47	44	56	55
Primary education only, %	44	69***	55	57
Seizure frequency per month				
Mean (SD)	23.7 (35.9)	15.0 (35.9)	37.9 (76.4)	32.4 (65.4)
Median (interquartile range)	10 (20.3)	5 (9.5)	10 (26)	5 (11.3)
Seizure free last year, %	2	3	1	0
No. of AEDs (SD)	2.1 (0.8)	2.2 (0.9)	2.2 (0.9)	2.1 (1.1)
At follow-up				
Follow-up time[a] in years: mean (SD)	6.9 (2.7)	0.8*** (1.2)	5.5*** (1.6)	6.5 (2.3)
Seizure frequency per month:				
Mean (SD)	3.4 (9.9)	11.2 *** (28.6)	6.1*** (9.6)	5.1*** (8.6)
Median (interquartile range)	0 (1)	3.8 (6.6)	3 (7.0)	2 (6.8)
Seizure free during last year,%	52	5***	14***	24***
No. of AEDs: mean (SD)	1.5 (1.2)	2.2*** (0.9)	2.3*** (1.0)	2.4*** (1.1)

SD, standard deviation; AEDs, antiepilepsy drugs;

[a]Groups 1 and 4: since start of presurgical assessment; groups 2 and 3: since assignment to waiting list. p values are in comparison to surgical group: *p < 0.05, **p < 0.01, ***p < 0.001—calculated with χ^2, Student's *t*–test, or Mann–Whitney test as appropriate. The number of subjects in a group vary per outcome category due to missing information (< 5 %).

TABLE 2. *Comparison of ESI-55 values at follow-up of the surgical and the reference groups*

	Surgical group (N = 131)	Awaiting presurgical assessment (N = 105)		Withdrew from waiting for presurgical assessment (N = 99)		Surgery denied after presurgical assessment (N = 49)	
	Mean	Mean	Adj. diff. (95% CI)	Mean	Adj. diff. (95% CI)	Mean	Adj. diff. (95% CI)
General							
Health perception	78.6	66.8***	−11.4 (−15.3, −7.5)	71.6***	−6.7 (−10.5, −2.9)	72.1*	−5.3 (−10.1, −0.5)
Energy/fatigue	68.5	62.4*	−5.6 (−10.4, −0.8)	63.3*	−4.7 (−9.4, −0.1)	66.0	−1.8 (−7.7, 4.1)
Overall quality of life	70.0	59.2***	−9.5 (−14.1, −4.8)	64.8	−4.5 (−9.0, 0.1)	64.1	−4.2 (−10.0, 1.6)
Social functioning	83.2	72.9***	−10.4 (−15.9, −4.7)	75.7**	−7.4 (−12.8, −2.0)	79.9	−3.2 (−10.2, 3.7)
Mental							
Emotional well-being	71.5	72.1	0.5 (−3.7, 5.0)	70.9	−0.6 (−4.8, 3.7)	74.9	3.4 (−2.0, 8.8)
Cognitive function	74.4	66.1**	−8.1 (−12.9, −3.2)	72.4	−2.0 (−6.7, 2.7)	64.1**	−8.5 (−14.5, −2.4)
Role limitations due to emotional problems	88.7	85.8	−2.6 (−7.3, 2.1)	82.9*	−5.2 (−9.8, −0.6)	86.8	−0.6 (−6.3, 5.3)
Role limitations due to memory problems	90.5	86.3	−3.6 (−7.9, 0.7)	87.6	−2.7 (−6.9, 1.5)	90.9	1.7 (−3.7, 7.0)
Physical							
Physical function	95.0	88.1***	−6.1 (−9.5, −2.7)	88.6***	−5.9 (−9.2, −2.6)	88.0*	−5.3 (−9.5, −1.1)
Role limitations due to physical problems	88.1	82.1*	−5.6 (−10.3, −1.0)	82.4*	−5.4 (−9.9, −0.8)	82.3	−4.0 (−9.7, 1.8)
Pain (freedom from)	82.0	78.6	−3.3 (−9.3, 2.6)	80.2	−1.5 (−7.3, 4.2)	77.5	−2.4 (−9.8, 5.1)
"Overall score"	82.1	76.2***	5.4 (−8.8, −2.1)	77.5**	4.2 (−7.5, −1.0)	78.0	2.6 (−6.7, 1.6)

Adj. diff., adjusted differences; CI, confidence intervals. The table gives unadjusted means. Differences were calculated with ANCOVA adjusted for age, gender, and education. p values are in comparison to surgical group: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. The number of subjects in a group vary per outcome category due to missing information (<5%).

neurological or neuropsychological risks (16%), or more than one reason (18%).

At baseline, the comparison groups did not differ from the surgical group with regard to gender distribution and seizure frequency. However, the group 2 patients were older than those of group 1 and more often had primary education only. Follow-up period was shorter in groups 2 and 3 compared to group 1 (Table 1). The operated patients showed a superior outcome compared to all three comparison groups with regard to seizure frequency, seizure freedom rate during the previous year, and number of AEDs. The surgical patients' mean "overall QOL score" was superior to the mean scores of the groups 2 and 3, but not of group 4. On most QOL domains, the surgical group scored highest. Group 2 scored significantly lower in seven, group 3 in six domains, and group 4 in only three out of 11 domains (Table 2). Table 3 shows that seizure freedom is strongly associated with better QOL in all four groups. With one exception, the QOL scores of seizure free patients were higher than those of patients who were not seizure free. The differences did not always reach significance because numbers in these within group comparisons were smaller.

DISCUSSION

In this study, seizure and AED outcome of the surgically treated patients was significantly more favorable than in three comparison groups. However, in the two nonoperated long-term comparison groups 3 and 4, a high number of patients became seizure free (14% and 24%) which confirms a similar previous observation (Selwa et al., 2003). Consequently, the most marked difference was observed in the comparison between surgically treated patients and the short-term reference patients still awaiting presurgical assessment. As seizure freedom corresponded strongly to QOL it comes as no surprise that the latter group also had the lowest scores on all but three of the eleven ESI-55 domains. QOL scores of the long-term comparison patients were only moderately reduced as compared to the operated patients. Especially group 4, in whom surgery was denied, did not differ from the operated cases in the majority of QOL domains. This group, however, was relatively small and we may not have had enough power to detect differences. Overall, our results are concordant to those of previous studies using the ESI-55 and in part had similar comparison groups (Vickrey et al., 1995; McLachlan et al., 1997).

The observations may be interpreted as follows: Patients with pharmacoresistant epilepsies present to a tertiary epilepsy center at a "nadir" of their disease course in terms of seizure frequency and QOL. The group undergoing epilepsy surgery has the best long term outcome. After a similar period of time, a considerable proportion of patients choosing not to use the surgical option and—even more so—patients in whom surgical treatment was refused after presurgical assessment seem to "catch up" with the operated patients. This can be interpreted as regression to the mean caused by the natural history of the disease or optimized AED treatment (whereas the seizure freedom rate in the operated group may decrease over time). Indeed, the relatively high percentage of seizure-free patients in

TABLE 3. *ESI-55 values at follow-up of the surgical and reference groups stratified by seizure freedom*

	Surgical group (N = 131)		Awaiting presurgical assessment (N = 105)		Withdrew from waiting for presurgical assessment (N = 99)		Surgery denied after presurgical assessment (N = 49)	
	Seizure free (N = 68) Adj. mean (SE)	Not seizure free (N = 63) Adj. mean (SE)	Seizure free (N = 5) Adj. mean (SE)	Not seizure free (N = 100) Adj. mean (SE)	Seizure free (N = 14) Adj. mean (SE)	Not seizure free (N = 85) Adj. mean (SE)	Seizure free (N = 12) Adj. mean (SE)	Not seizure free (N = 37) Adj. mean (SE)
General								
Health perception	83.5 (1.6)	72.7*** (1.7)	85.8 (5.8)	65.8** (1.4)	86.7 (3.6)	69.1*** (1.4)	86.8 (4.0)	68.2*** (2.2)
Energy/fatigue	72.7 (2.1)	63.2** (2.2)	77.7 (8.4)	62.0 (1.8)	65.9 (4.6)	63.0 (1.9)	78.0 (5.1)	61.9** (2.8)
Overall quality of life	73.9 (2.0)	64.2** (2.1)	70.3 (7.3)	59.8 (1.8)	80.1 (4.5)	62.2*** (1.8)	75.5 (5.0)	61.3* (2.8)
Social functioning	88.1 (2.5)	77.9** (2.5)	87.3 (8.9)	72.1 (2.2)	88.6 (5.4)	73.6* (2.2)	91.7 (6.0)	75.9* (3.4)
Mental								
Emotional well-being	75.6 (1.9)	67.0** (2.0)	86.0 (6.9)	71.4* (1.7)	75.5 (4.2)	70.2 (1.7)	83.8 (4.7)	71.9* (2.6)
Cognitive function	77.6 (2.1)	70.5* (2.2)	78.4 (7.7)	65.3 (1.9)	84.5 (4.7)	70.1** (1.9)	75.2 (5.2)	62.3* (2.9)
Role limitations due to emotional problems	90.9 (2.1)	85.4 (2.2)	98.0 (7.5)	85.0 (1.8)	88.0 (4.6)	82.3 (1.9)	93.9 (5.1)	85.6 (2.9)
Role limitations due to memory problems	92.1 (1.9)	88.1 (2.0)	100.0 (6.9)	85.7* (1.7)	98.2 (4.2)	85.6** (1.7)	94.0 (4.7)	90.8 (2.6)
Physical								
Physical function	96.3 (1.5)	92.6 (1.6)	86.0 (5.5)	88.5 (1.3)	92.9 (3.4)	87.8 (1.4)	92.2 (3.7)	88.2 (2.1)
Role limitations due to physical problems	92.0 (2.1)	83.1** (2.1)	88.2 (7.4)	81.8 (1.8)	87.5 (4.5)	81.5 (1.8)	94.5 (5.0)	80.2* (2.8)
Pain (freedom from)	85.1 (2.7)	77.9 (2.7)	83.5 (9.6)	78.2 (2.3)	82.8 (5.6)	79.7 (2.4)	95.4 (6.5)	74.0* (3.7)
"Overall score"	85.4 (1.5)	77.8*** (1.5)	87.1 (5.2)	75.7* (1.3)	85.3 (3.2)	76.2** (1.3)	88.4 (3.6)	76.0** (2.0)

Adj. mean, adjusted mean; SE, standard error. The means were calculated with ANCOVA adjusted for age, gender, and education. The number of subjects in a group vary per outcome category due to missing information (<5%).

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

the long-term comparison groups could be a consequence of the new drugs introduced during the last 10 years. It is also possible that patients awaiting presurgical assessment rate their QOL lower to "justify" their decision for this procedure and a possible brain operation.

All differences must be interpreted with some caution as the groups have not been randomized and the follow-up time differs due to the nature of this observational study. Moreover, it is possible that the differences between the surgical group and the long-term comparison groups were attenuated due to selection bias, because we cannot rule out that the nonresponders in groups 3 and 4 had a worse outcome. However, even if all those patients had seizures at follow-up, the percentage of seizure-free patients would be higher in these groups than in those awaiting surgery. Another systematical error may be caused by a potential difference between the types of epilepsies in the four groups. This possibility is inherent in the nature of this study and its patient groups. The differences between baseline seizure frequencies may point towards such group divergences.

To conclude, the data presented here confirm that epilepsy surgery at a specialized center is the approach of choice in suitable patients with pharmacoresistant focal epilepsy. Even patients in continuous care of a tertiary center have no more than a 24% chance of becoming seizure free after several years, whereas this is more than double in those undergoing surgery. However, comparing operated patients to those awaiting interventions may overestimate the effect of surgery. There is some evidence that patients with pharmacoresistant epilepsy awaiting presurgical assessment may be at a low point of seizure control and QOL. This effect is apparently not present in long-term patients. Comparisons with these may thus give a more realistic view of the benefits of epilepsy surgery.

Acknowledgment: The authors thank Fabian Bien for assistance with the data collection.

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