Original article

Long-term health-related quality of life in drug-resistant temporal lobe epilepsy after anterior temporal lobectomy

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ABSTRACT – Epilepsy surgery is beneficial to patients suffering from drug-resistant temporal lobe epilepsy in the short term, but fewer reports of long-term outcomes have been published. To clarify the long-term outcomes of seizure control and health-related quality of life after epilepsy surgery, we enrolled 48 patients suffering from drug-resistant temporal lobe epilepsy. All of the patients received comprehensive presurgical evaluations, including the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) questionnaire to measure their health-related quality of life. Among the patients, 28 patients received surgery (surgical group) and 20 patients remained under medication (medical group). Eight years later, the seizure frequency and QOLIE-89 were evaluated. The seizure-free rate was much higher in the surgical group (53.6%) than in the medical group (5%), eight years after the initial evaluation. The follow-up QOLIE-89 score was significantly higher in the surgical group than in the medical group. Moreover, the seizure frequency inversely correlated to the QOLIE-89 score, regardless of the treatment group. Our results provide evidence that epilepsy surgery confers benefits with respect to seizure control and health-related quality of life for drug-resistant temporal lobe epilepsy patients based on long-term follow-up.

Key words: temporal lobe epilepsy, drug-resistant epilepsy, anterior temporal lobectomy, epilepsy surgery, seizure outcome, quality of life

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Temporal lobe epilepsy (TLE) is one of the most common drug-resistant epilepsies among adults. Anterior temporal lobectomy (ATL) is an effective treatment for patients suffering from drug-resistant TLE. In addition to the achievement of seizure freedom, an improvement in the health-related quality of life (HRQOL) is another goal of epilepsy surgery. After the development of tools to measure epilepsy-specific HRQOL in the 1990s, HRQOL has become one of

the most important outcome assessments for epilepsy surgery (Vickrey *et al.*, 1992; Devinsky *et al.*, 1995).

In the past two decades, many studies have focused on seizure control and HRQOL after epilepsy surgery. The evidence indicates that epilepsy surgery improves seizure control and HRQOL in the short term (Markand *et al.*, 2000; Wiebe *et al.*, 2001), but the long-term results remain inconclusive. Several studies have explored the long-term effects of epilepsy surgery on seizure control and HRQOL, but the follow-up duration varied from two to ten years (Jones *et al.*, 2002; Helmstaedter *et al.*, 2003). Other studies demonstrated changes in HRQOL over time after surgery, but there has been no data regarding patients who remained under medical treatment for comparison (Spencer *et al.*, 2007; Tanriverdi *et al.*, 2008; Cunha and Oliveira, 2010).

To explore the long-term effects of epilepsy surgery on drug-resistant TLE, we evaluated the seizure frequency and HRQOL in patients receiving surgery preoperatively and eight years after the operation. We also evaluated the same outcome in drug-resistant TLE patients treated with medication at baseline and eight years later.

Patients and Methods

Subjects

We reviewed data from 575 patients who were admitted to the epilepsy monitoring unit (EMU) of the Taipei Veteran General Hospital between September 2000 and May 2003. Eighty-eight adult patients suffering from drug-resistant TLE were admitted for presurgical evaluation. All of the patients received comprehensive presurgical examinations, and the results of the presurgical examinations were discussed at a multidisciplinary seizure conference. It was decided at the conference whether each patient was suitable for surgery. The patients who were not suitable for ATL had features that included bi-temporal foci, psychiatric comorbidity, and a high possibility of speech and memory deficits after surgery. The patients suitable and willing to undergo surgery subsequently received ATL, and the other patients continued on antiepileptic drugs (AEDs). The long-term seizure outcomes of these patients were evaluated in normal neurological clinics by epileptologists, and patients who did not return to the neurological clinics for a regular follow-up were excluded. To investigate the long-term HRQOL outcome, each patient was administered the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) questionnaire from March 2008 to January 2012. A total of 48 patients completed the QOLIE-89 questionnaire and received regular follow-up examinations at neurological clinics.

These patients were further separated into surgical and medical groups, based on their respective treatment. Among the 40 patients who did not receive reassessment, 18 were male, and the average age was 30.28 years old. Seventeen patients received ATL (left/right ATL=9:8) and 23 remained on medication only. There was no significant difference with regards to gender, age, or side of ATL between the groups (chi square test for gender and side of ATL; Mann Whitney U test for age). There were 26 patients who still had regular follow-up in our hospital, but refused to join this study. The social stigma for epilepsy patients in Taiwan might be one of the reasons for hesitating to join the epilepsy-related study (Chung *et al.*, 1995). As for the 14 cases of loss of contact, we were not aware of any further treatment or outcome.

In this study, the patients who were free of disabling seizures during the two years preceding the last follow-up visit were classified as seizure-free (ILAE class I and II). The patients experiencing persistent seizures were further classified as follows: (1) rare seizures: less than once every six months in the medical group and ILAE class III in the surgical group; (2) occasional seizures: less than once per week but more than once every six months in the medical group and ILAE class IV in the surgical group; and (3) frequent seizures: more than once per week in the medical group and ILAE class V and VI in the surgical group.

Presurgical examination

The presurgical laboratory examination included video-EEG telemetry using sphenoidal electrodes, brain MRI, magnetic resonance spectroscopy (MRS), magnetoencephalography (MEG), interictal and postictal single-photon emission computed tomography (SPECT), fluoro-D-glucose positron emission tomography (PET), psychiatric consultation, neuropsychological evaluation, the intracarotid amobarbital test, and HRQOL assessment. The Taiwanese version of the QOLIE-89, a comprehensive self-reporting tool, was used to measure HRQOL in this study (Devinsky *et al.*, 1995; Chen, 2000). The scales of the QOLIE-89 are categorized into four domains, including: mental health, physical health, cognitive distress, and epilepsy-targeted. The overall score could be further calculated as a weighted sum of the scales.

Statistical analysis

The Statistical Package for the Social Sciences was used for statistical analysis. The Chi-square test, the Mann Whitney U test, the Fisher's Exact test, the Wilcoxon signed-rank test, and the Kruskal-Wallis test were used, where appropriate. A two-tailed *p* value of less than 0.05 was considered to be significant.

Table 1. Patient demographics and baseline scores of QOLIE-89.

	Surgical (*n*=28)	Medical (*n*=20)	*p* value
Age at first HRQOL			0.33[a]
Mean ± SD (yr)	29.54 ± 6.94	31.64 ± 7.73	
Range (yr)	18-43	20-44	
Gender			0.15[b]
Male : Female	7 : 21	9 : 11	
Follow-up duration			0.48[a]
Mean ± SD (yr)	8.09 ± 1.31	7.95 ± 0.35	
Range (yr)	5-11	7-8	
Baseline QOLIE-89			
Overall	57.0 ± 13.2	54.8 ± 15.2	0.72[a]
Mental health	59.7 ± 12.7	55.6 ± 18.8	0.46[a]
Physical health	62.8 ± 16.7	54.5 ± 12.5	0.15[a]
Cognitive distress	58.2 ± 18.9	56.8 ± 23.8	0.98[a]
Epilepsy-targeted	47.9 ± 21.1	52.6 ± 16.2	0.38[a]

[a]Mann-Whitney U test; [b]Chi-Square test

Results

Baseline status

A total of 28 patients underwent ATL, while 20 patients remained under medical treatment. The mean follow-up duration was 8.03 years (range: from 5 to 11 years). The demographics of all subjects are provided in *table 1*. There was no statistically significant difference between the two groups with respect to gender (chi-square test), age at evaluation, follow-up duration, or baseline score on the QOLIE-89 (Mann Whitney U test). Sixteen patients had left ATL and 12 had right ATL in the surgical group.

Seizure outcome

At eight years of follow-up, there were 15 patients (53.6%) in the surgical group but only one patient (5%) in the medical group who achieved seizure freedom. The number of seizure-free patients was significantly higher in the surgical group than in the medical group (Fisher's Exact test: *p*<0.01; OR: 21.9). In addition, there were less patients who experienced frequent seizures in the surgical group (11%) than in the medical group (45%); the patients who experienced rare seizures were greater in the surgical group (11%) than in the medical group (0%) (*table 2*).

HRQOL outcome

The changes in QOLIE-89 scores for the surgical and medical groups are shown in *figure 1*. In the sur-gical group, the overall and physical health scores on the QOLIE-89 were significantly improved eight years after ATL (Wilcoxon signed-rank test; *p*=0.038 and 0.003, respectively). For the patients who remained on medical treatment, there was significant worsening eight years later with regards to cognitive distress scores (*p*=0.045) and a trend of decline in the overall, mental health, and epilepsy-target scores on the QOLIE-89 (the physical health score was insignificantly increased). Compared to the medical group, the patients in the surgical group displayed significantly higher scores overall and on the mental health and physical health categories of the QOLIE-89 at eight years of follow-up (Mann Whitney U test; *p*=0.031, 0.011 and 0.025, respectively).

With respect to the relationship between seizure control and HRQOL, the patients experiencing seizure freedom reported much higher overall HRQOL, including all four dimensions of the QOLIE-89, compared to those experiencing persistent seizures, at eight years of follow-up, (Mann Whitney U test; *p*<0.01; *figure 2*). Moreover, the patients exhibiting fewer seizures reported higher overall QOLIE-89 scores, including the mental health, physical health, and epilepsy-targeted categories, at eight years of follow-up (Kruskal-Wallis test; *p*<0.05; *table 2*). An inverse correlation between seizure frequency and QOLIE-89 score was detected regardless of the treatment group.

Discussion

In this study, we have demonstrated that surgery resulted in improved long-term outcome compared

Table 2. Follow-up seizure frequency and HRQOL outcome for the surgical and medical groups

| Seizure Outcome	Seizure freedom	Rare seizures	Occasional seizures	Frequent seizures
Surgical group (n)	15	3	7	3
QOLIE-89 (mean ± SD)				
Overall	71.0 ± 17.7	73.8 ± 14.1	57.5 ± 18.2	43.7 ± 16.2
Mental health	70.0 ± 18.0	73.1 ± 9.0	57.4 ± 13.8	46.2 ± 17.7
Physical health	82.7 ± 20.0	81.0 ± 16.5	65.5 ± 27.8	63.5 ± 14.1
Cognitive distress	66.8 ± 21.1	71.2 ± 22.0	56.8 ± 19.9	38.6 ± 21.0
Epilepsy-targeted	63.9 ± 22.7	69.3 ± 14.3	50.0 ± 22.9	25.6 ± 16.1
Medical group (n)	1	0	10	9
QOLIE-89 (mean ± SD)				
Overall	72.2	NA	53.6 ± 25.6	45.4 ± 20.6
Mental health	73.7	NA	53.3 ± 20.9	42.5 ± 18.4
Physical health	87.7	NA	66.1 ± 22.0	49.6 ± 26.9
Cognitive distress	71.4	NA	44.7 ± 30.8	52.5 ± 27.7
Epilepsy-targeted	55.6	NA	48.7 ± 32.8	38.6 ± 19.2

NA: not available.

to the continuation of medication treatment for drug-resistant TLE. This finding has been demonstrated in two respects. First, the proportion of patients experiencing seizure freedom or rare seizure frequency was higher for those receiving ATL than those continuing to receive AEDs. Second, the score on the QOLIE-89 among the surgically-treated patients was significantly higher eight years after the operation. In contrast, there was a declining trend of the QOLIE-89 score among the medically-treated patients at eight years of follow-up. The higher QOLIE-89 scores among the surgically-treated patients indicated that ATL provided a favourable long-term HRQOL outcome to drug-resistant TLE patients.

For drug-resistant TLE patients without epilepsy surgery, the change in HRQOL over time remains uncertain. To our knowledge, there is no such longitudinal study in the literature, and the results of cross-sectional studies are inconclusive. Some studies indicated that the duration of epilepsy was expected to display a significant negative association with HRQOL (Edefonti *et al.*, 2011), but other studies revealed that the duration of epilepsy did not appear to be associated with HRQOL (Taylor *et al.*, 2011). In the study by Markand *et al.* (2000), the overall, mental health, cognitive distress, and epilepsy-targeted HRQOL domains were not significantly decreased at two years of follow-up. In our study, there was significant worsening in the cognitive distress domain of HRQOL, as well as trends of decline in the overall, mental health, and epilepsy-targeted domains of HRQOL during long-term follow-up. Helmstaedter *et al.* (2003) also demonstrated deterioration in verbal and figural mem-

ory in drug-resistant TLE patients not receiving surgery. These results suggested that HRQOL in the drug-resistant TLE patients might become worse over time, especially with respect to cognition. The formation of hippocampal sclerosis and progressive hippocampal dysfunction in TLE patients could explain part of this mechanism (Marques *et al.*, 2007).

Most previous studies reported benefits in HRQOL after epilepsy surgery, but the extent of improvement varied due to different evaluation methods and follow-up durations. In the study by Vickrey *et al.* (1992), the physical health, mental health and epilepsy-targeted components of HRQOL were significantly higher in surgically-treated patients based on the ESI-55 method during follow-up after five years. Markand *et al.* provided evidence that all four domains of QOLIE-89 were significantly improved after surgery at two years of follow-up, compared to those patients prior to surgery or patients who did not undergo surgery (Markand *et al.*, 2000). In our study, the results revealed that improvement in HRQOL after surgery lasted for a long time, but only in the domains of physical health and mental health (*figure 1*). Compared to the Markand study, the cognitive distress and epilepsy-targeted domains of HRQOL in our study did not significantly improve after surgery. A lower seizure-free rate after long-term follow-up might be one of the possible causes of this difference (de Tisi *et al.*, 2011) (53.6% in our study and 73.6% in the Markand study). This explanation is also supported by the finding that the cognitive distress and epilepsy-targeted domains of HRQOL significantly improved in the seizure-free patients compared to
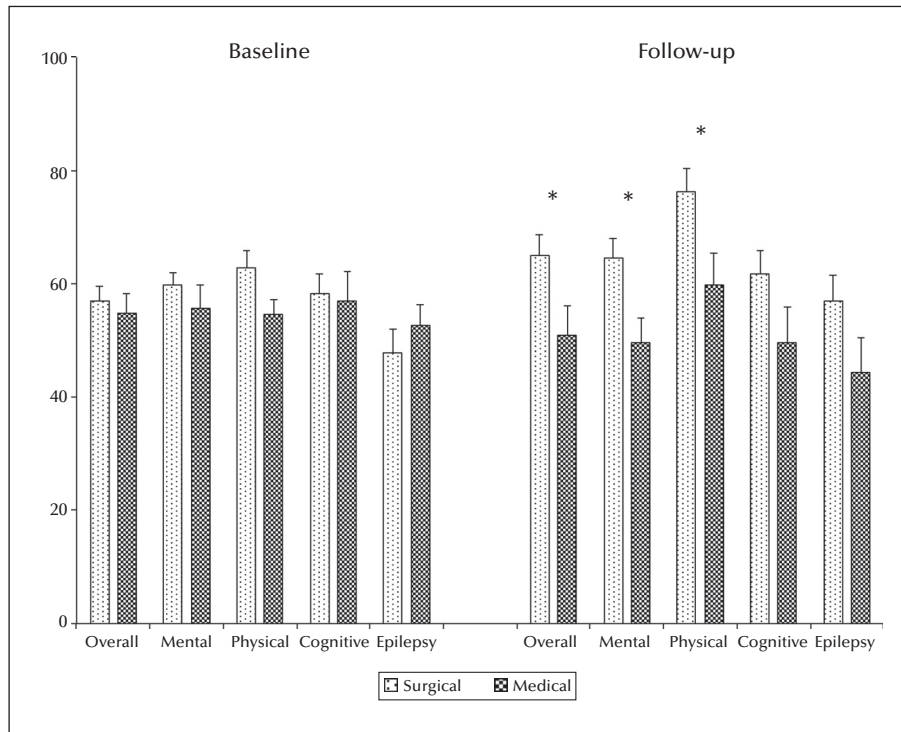
Figure 1. QOLIE-89 scores (overall and of the four dimensions) between the surgical and medical groups at baseline and eight years of follow-up (mean±SE). The overall, mental health, and physical health scores were significantly higher in the surgical group than in the medical group (Mann Whitney U test; $p<0.05$).
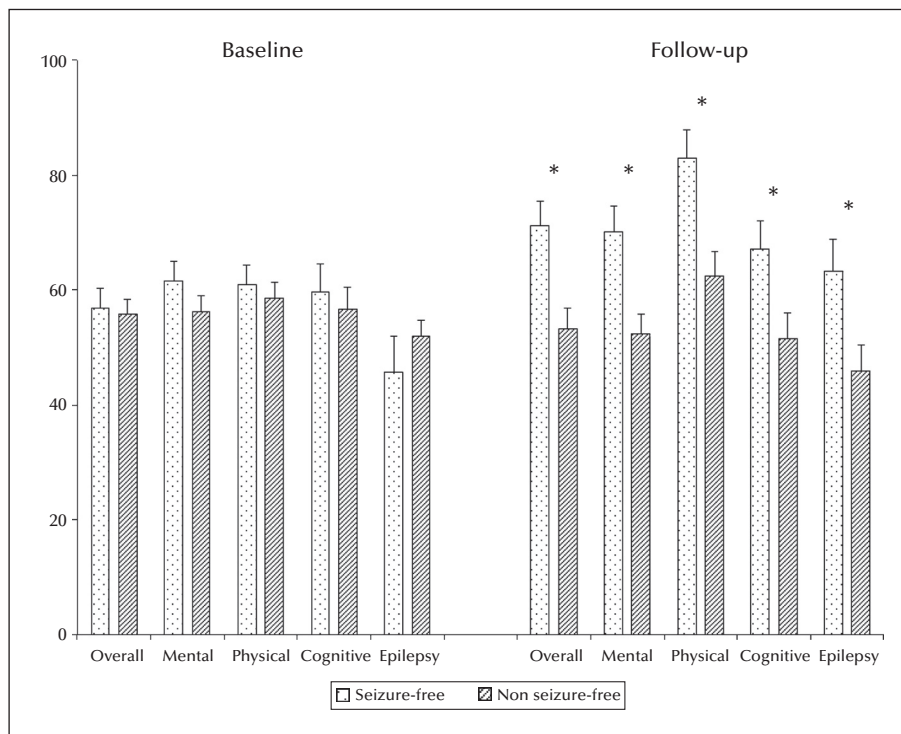
Figure 2. QOLIE-89 scores (overall and of the four dimensions) between patients with and without seizure freedom at baseline and eight years of follow-up (mean±SE). The overall, mental health, physical health, cognitive distress, and epilepsy-targeted scores were significantly higher for seizure-free patients than for patients who still had seizures (Mann Whitney U test; $p<0.05$).

the patients with seizures in this study (*figure 2*). We speculate that the seizure frequency has a greater impact on the cognitive distress and epilepsy-targeted domains than the physical and mental health domains of HRQOL.

Epilepsy surgery is associated with changes in cognition according to side of surgery, duration of postoperative follow-up, and domains of cognitive evaluation (Alpherts *et al.*, 2006; Sherman *et al.*, 2011). The cognitive changes might not be concordant between subjective and objective measurements (Baxendale and Thompson, 2005), and subjective cognitive declines after surgery are common. In our study, we conducted subjective measurement of cognitive function. There were self-reported cognitive declines in the medical group eight years later, but not in the surgical group eight years after surgery. We postulated that the surgical group experienced a stepwise decline following the operation and had eight years to adjust, whilst the medical group continued to decline. However, additional time points would be needed to further investigate the dynamic changes in cognition after epilepsy surgery.

Decreased seizure frequency plays an important role in the improvement of HRQOL. Most studies are in agreement that the most important post-surgical determinant of HRQOL is seizure outcome (Seiam *et al.*, 2011). _ENREF_14Although Spencer *et al.* provided evidence that HRQOL improved regardless of seizure control within six months after surgery, they also found that subsequent improvement in HRQOL over time was dependent on seizure freedom (Spencer *et al.*, 2007). _ENREF_14Our results support the finding that the long-term improvement in all domains of HRQOL is significantly associated with seizure freedom. Moreover, not only the patients in the seizure-free group, but also those in the rare seizure group, achieved favourable HRQOL outcomes (*table 2*). Mohammed *et al.* also demonstrated that the patients classified as postoperative Engel class I (free of disabling seizures) and II (rare disabling seizures) more frequently exhibited HRQOL improvement (Mohammed *et al.*, 2012).

There are, however, limitations to our studies. The patients were not selected randomly, but were retrospectively enrolled using a database. The trajectory of the QOL might be examined more clearly in a prospective long-term study. The number of patients was small because not every patient in the EMU who underwent presurgical evaluation remained in contact with us over the eight-year period. The QOLIE-89 evaluation was performed at only one preoperative point and one postoperative point. Nevertheless, our study provided a simultaneous comparison of HRQOL between the medical and surgical groups, both preoperatively and over the long term postoperatively.

Our results confirm that epilepsy surgery results in improved outcomes with respect to seizure control and HRQOL in drug-resistant TLE patients. The benefits of surgery with respect to seizure control and HRQOL remained profound at eight years of follow-up. The long-term improvement in HRQOL strongly correlated to seizure control. □

Supplementary Data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Which one of the following treatments has the most favourable outcome for patients with drug-resistant temporal lobe epilepsy?

A. Gamma knife radiosurgery
B. Anterior temporal lobectomy
C. Deep brain stimulation
D. Antiepileptic drugs

(2) Which of the following is the most important factor associated with health-related quality of life after surgery in patients with drug-resistant temporal lobe epilepsy?

A. Gender
B. Age
C. Pre-operative seizure frequency
D. Post-operative seizure frequency

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".