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Determinants of quality of life in patients with refractory focal epilepsy who were not eligible for surgery or who rejected surgery

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ABSTRACT

The aim of the study was to assess the determinants of quality of life (QOL) in adult patients with refractory focal epilepsy who were not eligible for surgery or who rejected surgery after presurgical evaluation. The QOLIE-31, the Hospital Anxiety and Depression Scale and PESOS questionnaire were mailed in 2009 to all adult patients who had been evaluated for suitability for epilepsy surgery between 2001 and 2007 in the Bethel Epilepsy Center and had been deemed not eligible for surgery or had decided against surgery. Questionnaires were sent by post to 359 patients: 172 (47.9%) replied, and of these, 125 patients were eligible for this study. The remaining 47 patients were excluded mainly because they did not fulfill the criteria of refractory epilepsy. Out of the included 125 patients, 106 were considered to be poor surgical candidates for medical reasons, and 19 had decided against surgery. The mean follow-up was 4.1 ± 2.1 years. In the past 6 months, 13.9% of the patients were seizure free, 12 of them (9.6%) were seizure free for one year, 10.7% had 1–2 seizures, 11.5% had 3–5 seizures, 27.0% had one or more seizures a month, 23.0% had one or more seizures a week, and 13.9% had one or more seizures a day. Patient-perceived changes in their seizures since presurgical evaluation were rated by 15.6% of the patients as 'improved significantly', by 28.7% as 'improved', by 46.7% as 'no change', by 6.6% as 'deteriorated' and by 2.5% as 'significantly deteriorated'. Quality of life in patients with refractory epilepsy was much lower compared to operated patients from our center. Multivariate analysis of QOL showed that depression and anxiety are strong predictors but not exclusively. Furthermore, tolerability and efficacy of AEDs are significant predictors of most QOLIE-31 subscales. Employment, seizure frequency, patient-perceived change in their seizures, number of AEDs and the degree of comorbidity appeared as predictors for some aspects of QOL as well. When excluding anxiety and depression, the most important predictors of QOL were tolerability of AEDs and employment. For other aspects of QOL, efficacy of AEDs, gender, number of AEDs, degree of comorbidity and a certificate of disability were additional predictors. The results of the multivariate analysis did not essentially change when seizure-free patients were excluded. *Conclusion*: Quality of life in non-operated patients with refractory epilepsy is significantly lower than in operated patients from the same center. Besides depression and anxiety, patient-rated tolerability and efficacy of AEDs, seizure frequency and employment are the main determinants of QOL.

1. Introduction

Epilepsy remains refractory despite optimal medical therapy in about 30% of patients [1]. Intractable seizures, cognitive decline, increased risk of death and psychosocial dysfunction are the main manifestations of refractory epilepsy [2]. Refractory epilepsy is perceived by patients as life limiting, requiring dependency on others and as an impairment of their QOL [3].

In general, studies reporting QOL in patients with refractory focal epilepsy are rare and have shown great disparity regarding variables used in the analysis. Furthermore, they did not always concur concerning the main determinants of QOL, citing impacting factors such as seizure frequency, seizure freedom, epilepsy-specific factors and psychiatric and psychosocial factors [4–7]. Despite the influence of depression on QOL, several studies did not include data concerning depression or other psychiatric disorders in their analysis [8–10]. Moreover, the studies did not use the same definition of refractory epilepsy [13].

Our aim was to determine the level of QOL and to analyze the influence of epilepsy-specific factors, patient-perceived changes in seizure

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frequency, efficacy and tolerability of AEDs, as well as psychiatric and psychosocial factors in a well-defined large group of patients with refractory focal epilepsy. An additional aim of our study was to compare the QOL of the non-operated patients in this study with the QOL of operated patients in two of our previous studies, using comparable methods [11,12].

2. Patients and methods

2.1. Patients

We retrospectively reviewed all adult patients (≥16 years) referred to our center with the clinical suspicion of refractory focal epilepsy who underwent presurgical evaluation between 2001 and 2007 to determine suitability for epilepsy surgery but who were not operated on, either due to medical reasons or because the patient rejected surgery (n = 359). All patients were followed up for a minimum of two years after presurgical evaluation; the mean follow-up was 4.1 ± 2.1 years. Questionnaires were sent by post to 359 patients in 2009. Whereas 172 patients (47.9%) replied, 187 (52.1%) did not respond, including patients who never received the questionnaire due to incorrect addresses.

2.1.1. Non-responders

The clinical data of non-responders and responders were compared with respect to demographic as well as to epilepsy variables. There were no significant differences regarding gender (responder vs. non-responder: 41.9% vs. 46.3%, exact two-sided Fisher test, $p = 0.46$) or age at monitoring (36.2 ± 14.7 vs. 34.4 ± 12.0 years, two-sided Mann–Whitney test, $p = 0.45$). However, duration of epilepsy was somewhat lower (17.4 ± 13.1 vs. 19.8 ± 13.0 years, $p = 0.035$) in responders. Localization of epilepsy did not differ significantly between groups (temporal: 25.9% vs. 27.1%; frontal: 12.2% vs. 14.9%; local [not specified]: 23.6% vs. 26.3%; all $p > 0.1$).

2.1.2. Responders included in the study

Presurgical evaluation allowed validation of the diagnosis and classification of seizures and syndromes. To ascertain that only patients with refractory focal epilepsy were included, patients were reassessed according to recently published criteria for drug-resistant epilepsy: "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [13]. We assumed 'sustained seizure freedom' when patients were seizure free > 12 months. Following these criteria, 32 patients were excluded because drug resistance could not be confirmed. Furthermore, 15 patients were excluded for the following reasons: no epilepsy (n = 10), only generalized seizures (n = 1), follow-up < 2 years (n = 2), duration of epilepsy < 1 year (n = 1) and mental retardation (n = 1). This left 125 patients included in this analysis whose questionnaires were self-administered, completed at home and returned by post.

The demographic data and clinical characteristics are summarized in Table 1 (for more details, see Table 1A and Table 2A, supplementary material).

Table 1
Sociodemographic and clinical characteristics of the patients.

	Total (n = 125)
Age at seizure onset (years)	17.5 ± 13.2
Duration of epilepsy at follow-up (years)	22.5 ± 13.3
Age at monitoring (years)	36.0 ± 13.8
Duration of follow-up (years)	4.1 ± 2.0
No. of AEDs at follow-up	2.2 ± 0.8
Total no. of AEDs until monitoring	4.7 ± 2.2
Partner (yes)	70 (58.3%)
Regular employment (yes)	37 (30.8%)
MRI finding	
Normal	28 (22.4%)
Lesion	97 (77.6%)
Hippocampus sclerosis	30/97 (30.9%)
Diagnosis of epilepsy syndrome at the time of referral to monitoring	
Temporal epilepsy	52 (41.6%)
Extratemporal epilepsy	36 (28.8%)
Focal epilepsy	37 (29.6%)
Number of AEDs before monitoring	
Two	23 (18.4%)
Three	25 (20.0%)
Four	16 (12.8%)
Five	20 (16.0%)
Six	15 (12.0%)
More than six drugs	26 (20.8%)
Patient-perceived change in seizures since monitoring	
Improved significantly	19 (15.6%)
Improved	35 (28.7%)
Not changed	57 (46.7%)
Deteriorated	8 (6.6%)
Deteriorated significantly	3 (2.5%)
Seizure frequency at follow-up	
No seizures in the past year	12 (9.6%)
No seizures in the past 6 months	17 (13.9%)
1–2 seizures in the past 6 months	13 (10.7%)
3–5 seizures in the past 6 months	14 (11.5%)
One or more seizures a month	33 (27.0%)
One or more seizures a week	28 (23.0%)
One or more seizures a day	17 (13.9%)
Patient-rated efficacy of AEDs	
Very good (no more seizures)	16 (13.8%)
Good (significantly fewer and less serious seizures)	34 (29.3%)
Satisfactory (slightly fewer or slightly lighter seizures)	44 (37.9%)
Unsatisfactory (seizures unchanged, increased or severe)	22 (19.0%)
Patient-rated tolerability of AEDs	
Very good (no side effects)	24 (20.3%)
Good (only minor side effects)	38 (32.2%)
Satisfactory (side effects exist but tolerable)	46 (39.0%)
Unsatisfactory (hardly tolerable side effects)	10 (8.5%)
The Hospital Anxiety and Depression Scale	
HADS anxiety (≥8)	61 (52.1%)
HADS depression (≥8)	45 (39.8%)
HADS anxiety (≥11)	28 (23.9%)
HADS depression (≥11)	24 (21.2%)

2.2. Instruments

2.2.1. Quality of Life in Epilepsy-31 (QOLIE-31)

The QOLIE-31 is an internationally used epilepsy-specific QOL questionnaire whose psychometric properties have been investigated in various studies. The QOLIE-31 is composed of 7 subscales: overall QOL, seizure worry, emotional well-being, energy/fatigue, cognitive and medication effects, and social function. Responses produce seven individual scores (one per subtest) and a total (composite) score. In addition, QOLIE-31 includes a single item that assesses overall health. The raw values of QOLIE-31 are converted to 0–100 scores, higher values reflect better QOL. The total score and the scores for the subscales are calculated according to the QOLIE-31 scoring form. We used the validated German version of the QOLIE-31 [14].

2.2.2. The Hospital Anxiety and Depression Scale (HADS)

The HADS is a widely used instrument to screen emotional disorders of patients in non-psychiatric settings by detecting anxious and depressive states. The HADS contains 14 items and consists of two subscales: anxiety and depression. Each item is rated on a four-point scale, giving maximum scores of 21 for anxiety and depression. Scores of 11 or more on either subscale are considered to be a 'significant' case of psychological morbidity while scores of 8–10 represent 'borderline' and 0–7 'normal'. Optimal balance between sensitivity and specificity for HADS as a screening instrument is achieved most frequently at a cut-off score of 8 for both HADS-A and HADS-D [15].

2.2.3. PESOS questionnaire

The PESOS questionnaire was developed at the Epilepsy Center Bethel in order to assess individual problems that patients with epilepsy have in social and occupational settings and to investigate effects of treatment and counseling on QOL, e.g., impairment by epilepsy and epilepsy-related fears [16]. In this study, we did not report the results of the PESOS regarding the aspects of QOL because reporting these results would exceed the volume of this article. However, the PESOS was used to assess the predictors, e.g., efficacy and tolerability of AEDs, employment status, driving status and comorbidity, in a standardized way.

2.3. Statistical analysis

As the first step, univariate ANOVAs and correlation analyses were performed to investigate the effect of various factors on QOL. Correlation coefficients (r, Pearson correlation coefficient) or 'Eta' was used to describe the effect size of these factors. Eta is closely related to the effect size 'f' of analysis of variance (ANOVA) proposed by Cohen [17]. A small ($f = 0.1$), medium (0.25) or large (0.5) effect size corresponds to Eta values of 0.1, 0.24 and 0.37, respectively. According to Nunnally and Bernstein [18], Eta values > 0.3 can be regarded as 'important'.

In the second step, multivariate analyses were performed in order to identify those factors that had the strongest impact on QOL. Therefore, stepwise regression analyses (forward) were performed using those variables as predictors that were significantly related to QOL in univariate analysis.

The regression analyses were performed using the following predictors:

- Sociodemographic data: sex (m/f) and employment (y/n).
- Seizure related: seizure free > 1 year (y/n), seizure frequency* and patient-perceived change in seizures since presurgical evaluation*.
- Antiepileptic drugs (AEDs): number of AEDs, patient rating of efficacy and tolerability of AEDs*.
- Depression and anxiety (HADS): depression score (< 8 vs. ≥ 8) and anxiety score (< 8 vs. ≥ 8).
- Comorbidity: degree of comorbidity and certificate of disability (y/n).

For tagged predictors (*), details are given in Table 1. Categorical predictors were coded as 'dummy variables' (e.g., employment: yes = 1, no = 0; HADS depression: $< 8 = 0$, $\geq 8 = 1$).

In addition, the regression analyses were performed with and without the predictors, depression and anxiety, and excluding seizure-free patients. The variance inflation factors (VIF) were reported as a check of multicollinearity.

Furthermore, a multivariate analysis adjusted for age, follow-up (time after operation/monitoring) and duration of epilepsy at the time of operation/monitoring was used to compare QOL in non-operated patients and in patients after temporal and extratemporal epilepsy surgery. SPSS for Windows (Version 19.0) was used.

3. Results

3.1. QOL in patients with refractory focal epilepsy at follow-up

The QOLIE-31 total scores and subscale scores for patients with refractory focal epilepsy who were not eligible for surgery or who rejected surgery are shown in Fig. 1. Not surprisingly, QOL in these patients was lower than QOL as measured in two other groups of operated patients from our center [11,12]. The differences are especially pronounced in the epilepsy-related indicators of QOL, i.e., social function, seizure worry, medication effects and in overall health (Fig. 1).

Multivariate analysis of variance of QOLIE-31 scales adjusted for age, duration of follow-up (time after operation/monitoring) and duration of epilepsy at the time of operation/monitoring confirmed a highly significant group effect (non-operated, temporal operation, extratemporal operation, $p < 0.001$). Pairwise comparisons revealed significant differences between non-operated and operated patients (all $p < 0.05$) but no significant differences between the two groups of operated patients (all $p > 0.05$) (see Fig. 1).

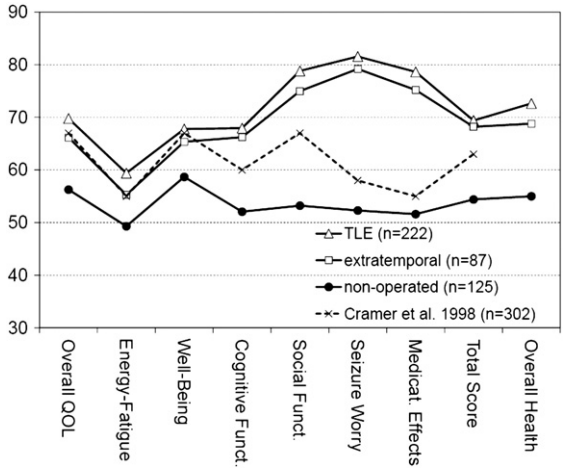

Fig. 1. Mean scores of QOLIE-31 subscales, QOLIE-31 total score and overall health in non-operated patients and operated patients. The figure shows the mean scores of QOLIE-31 subscales, QOLIE-31 total score and overall health in non-operated patients with refractory focal epilepsy ($n = 125$) in patients after extratemporal epilepsy surgery ($n = 87$) and in patients after temporal lobe surgery (TLE, $n = 222$) from our center [11,12]. Pairwise comparisons revealed significant differences between non-operated and operated patients (all $p < 0.05$) but no significant differences between the two groups of operated patients (all $p > 0.05$). The differences were especially pronounced in the epilepsy-related subscales, i.e., social function, seizure worry, medication effects and overall health. For comparison, the corresponding scores of the validation sample ($n = 302$) of the QOLIE-31 [19], which was recruited from 25 American epilepsy centers, are shown. The mean scores of the latter lay between the mean scores of our non-operated and our operated patients.

3.2. Factors correlated with QOL (univariate analysis)

3.2.1. Patients who were not eligible for surgery or who rejected surgery

In our study, 19 patients (15.2%) rejected epilepsy surgery despite an overall good chance of achieving seizure freedom, whereas 106 patients (84.8%) were not eligible surgical candidates for medical reasons (non-lesional (34.9%), non-operable (18.9%), high risk (25.5%), and non-congruent [clinical semiology, EEG findings or imaging produced conflicting localization data] (20.8%)).

The univariate analysis (Table 2) and also the multivariate analysis showed no statistically significant differences in QOL between patients who were not eligible for surgery and those who rejected surgery. This was true for the total score and when comparing the subscales. Therefore, all QOL analyses were henceforth performed for the whole group.

3.2.2. Seizure frequency at follow-up

At the follow-up, the overall seizure freedom rate was 13.9% (17 patients) during the last 6 months and 9.6% (12 patients) in the last year; 1–2 seizures in the last 6 months were reported by 10.7% of the patients, 3–5 seizures by 11.5%, one or more seizures a month by 27.0%, one or more seizures a week by 23.0% and one or more seizures a day by 13.9% (Table 1). Changes in their seizures since presurgical evaluation were rated by 15.6% of the patients as 'improved significantly', by 28.7% as 'improved', by 46.7% as 'no change', by 6.6% as 'deteriorated' and by 2.5% as 'significantly deteriorated' (Table 1). Those patients who reported a subjective improvement in their seizures showed a longer seizure freedom period ($p \leq 0.001$).

Patient-perceived changes of their seizures correlated significantly with 6 of the 8 QOLIE-31 subscales and with the total score (Table 2). Patients who perceived their seizure status as 'improved significantly'

Table 2
Factors related to quality of life — Eta or Pearson correlation coefficients.

Predictor	Overall quality of life	Energy/ fatigue	Well-being	Cognitive function	Social function	Seizure worry	Medication effects	Overall health score	Total QOLIE-31 score	HADS anxiety	HADS depression
Sex (m/f)	**0.19***	0.15	0.16	0.15	**0.19***	0.03	0.07	0.08	**0.19***	0.03	**0.21***
Partner (y/n)	0.10	0.00	0.14	0.10	0.08	0.07	0.06	0.03	0.08	0.01	0.11
Driving a car (y/n)	0.16	0.07	0.02	0.11	**0.35*****	0.09	**0.26****	0.11	**0.20***	0.07	0.05
Employment (y/n)	**0.19***	0.15	0.09	**0.20***	**0.28****	**0.21***	0.09	0.09	**0.26****	0.12	0.12
Age at onset	−0.04	−0.01	−0.01	−0.10	0.06	−0.08	0.04	−0.11	0.00	0.03	0.14
Age at monitoring	0.04	0.06	−0.02	−0.09	0.09	−0.05	0.03	−0.01	0.00	−0.03	−0.01
Age at reply	0.04	0.07	−0.03	−0.10	0.08	−0.08	0.03	−0.01	−0.01	−0.02	−0.01
Epilepsy duration	0.08	0.08	−0.01	0.00	0.04	0.02	−0.01	0.10	0.00	−0.06	−0.15
Seizure free > 1 year (y/n)	0.10	0.09	0.09	0.07	0.15	**0.21***	0.14	0.09	0.14	0.14	0.10
Seizure frequency	**−0.18***	**−0.19***	−0.08	−0.12	**−0.26****	**−0.27****	−0.16	−0.08	**−0.23***	0.10	−0.04
Patient-rated efficacy of AEDs	**−0.23***	−0.17	−0.07	**−0.22***	**−0.34*****	**−0.31****	**−0.31****	**−0.24***	**−0.34*****	0.00	0.02
Number of AEDs	−0.07	−0.04	−0.05	**−0.20***	−0.15	−0.07	−0.06	−0.16	−0.14	0.10	0.13
Patient-rated tolerability of AEDs	**−0.39*****	**−0.51*****	**−0.41*****	**−0.35*****	**−0.35*****	**−0.33*****	**−0.59*****	**−0.47*****	**−0.48*****	**0.23***	**0.33****
Side effects (y/n)	**0.21***	**0.34*****	**0.28****	**0.26****	**0.28****	**0.31****	**0.52*****	**0.36*****	**0.35*****	**0.19***	**0.21***
Comorbidity (y/n)	0.02	0.04	0.01	0.10	0.13	0.10	0.00	0.13	0.06	0.12	0.11
Degree of comorbidity	−0.18	−0.13	−0.16	−0.02	0.00	−0.03	−0.12	**−0.35*****	−0.10	0.12	0.08
Certificate of disability (y/n)	0.16	0.05	0.14	0.12	0.16	0.18	0.09	**0.24****	0.15	0.12	0.12
Surgery denied (y/n)	0.09	0.04	0.10	0.07	0.10	0.07	0.04	0.16	0.09	0.07	0.18
Patient-perceived change in seizures since presurgical evaluation	**−0.24****	**−0.26****	−0.10	−0.14	**−0.24****	−0.17	**−0.22***	**−0.19***	**−0.27****	0.04	−0.03
Depression (HADS ≥ 8)	**0.49*****	**0.47*****	**0.56*****	**0.51*****	**0.57*****	**0.41*****	**0.43*****	**0.51*****	**0.66*****	–	–
Anxiety (HADS ≥ 8)	**0.41*****	**0.45*****	**0.62*****	**0.37*****	**0.41*****	**0.52*****	**0.28****	**0.34*****	**0.55*****	–	–

Note: Pearson correlation coefficient was calculated to describe the correlation between the QOLIE-31 scales (e.g., overall quality of life), HADS scales and continuous variables (e.g., age at onset); Eta coefficient was calculated to describe the association between the different scales and categorical variables (e.g., sex, employment, efficacy of AEDs). Significance of bold: Pearson Correlation or Eta was significant ($p<0.05$).
***=$p<0.001$, **=$p<0.01$, *=$p<0.05$.

had higher scores compared with those who perceived their seizures as 'improved', especially on overall QOL (66.8 ± 23.0 vs. 57.6 ± 18.0), energy/fatigue (62.1 ± 19.9 vs. 48.4 ± 18.5, $p=0.008$), medication effects (78.2 ± 22.9 vs. 47.3 ± 28.9), social function (69.7 ± 30.6 vs. 51.8 ± 24.7) and total QOLIE-31 score (67.0 ± 21.9 vs. 55.5 ± 16.5). Seizure frequency was correlated with 4 subscales and the total score (Table 2). Seizure-free patients (≥1 year) had a significantly higher QOL compared with other patients, in particular when compared with those suffering at least a seizure a day in the following subscales: overall QOL, energy/fatigue, social function, seizure worry and total score.

3.2.3. Efficacy and tolerability of the antiepileptic drugs

Numbers of antiepileptic drugs (AEDs) before monitoring in all patients are summarized in Table 1. The *efficacy of AEDs* was rated as 'very good' (no more seizures) by 13.8% of the patients, as 'good' (significantly fewer and less serious seizures) by 29.3%, as 'satisfactory' (slightly fewer or slightly lighter seizures) by 37.9% and as 'unsatisfactory' (seizures unchanged, increased or severe) by 19.0% of the patients (Table 1). There were significant correlations between efficacy and five of the seven subscales, overall health score and overall score of QOLIE-31 (Table 2). Patients rating the efficacy of AEDs as 'very good' had significantly higher scores than those rating them as 'unsatisfactory'. These differences were significant in overall QOL (67.3 ± 27.4 vs. 54.0 ± 13.7), energy/fatigue (63.0 ± 21.1 vs. 51 ± 16.7), social function (75.0 ± 25.7 vs. 41.3 ± 27.0), seizure worry (73.2 ± 28.2 vs. 46.2 ± 27.1), medication effects (71.3 ± 29.8 vs. 37.1 ± 22.1) and the overall health score (69.1 ± 23.0 vs. 48.9 ± 15.8). Patient-rated efficacy of AEDs and seizure frequency at follow-up were significantly correlated ($r=.55$, $p<.001$).

The *tolerability of AEDs* was rated as 'very good' (no side effects) by 20.3%, as 'good' (only minor side effects) by 32.2%, as 'satisfactory' (side effects exist but tolerable) by 39.0% and as 'unsatisfactory' (hardly tolerable side effects) by 8.5% of the patients (Table 1). Patients who reported a 'very good' tolerability of AEDs (no side effects) showed significantly higher QOL scores than those who reported tolerability as 'unsatisfactory' (hardly tolerable side effects). Tolerability and side effects showed significant correlations with all QOLIE-31 scales (Table 2). These were especially prominent in the following subscales: medication effects (79.9 ± 20.1 vs. 33.1 ± 15.7), energy/fatigue (60.8 ± 15.4 vs. 27.5 ± 8.6), overall health score (69.4 ± 18.3 vs. 38.0 ± 23.9), well-being (68.5 ± 16.7 vs. 40.5 ± 21.0) and total QOLIE-31 score (65.6 ± 13.4 vs. 41.1 ± 11.8).

3.2.4. Anxiety and depression

Of the patients, 52.1% had HADS anxiety scores ≥ 8, and 23.9% had ≥ 11. HADS anxiety scores for all QOLIE-31 scales were highly correlated with QOL (Table 2). HADS depression scores were ≥ 8 for 39.8% of the patients, and 21.2% had a score of ≥ 11. HADS depression scores were highly correlated with all QOLIE-31 scales (Table 2). Using the cut-off HADS ≥ 8, patients with suspected depression or anxiety had significantly lower scores in all QOLIE-31 subscales compared with those without. These differences were most prominent on the following subscales: seizure worry (68.3 ± 9.9 vs. 40.0 ± 26.6), medication effects (61.4 ± 28.4 vs. 45.4 ± 26.1) and social function (66.5 ± 27.2 vs. 43.8 ± 24.2) in the case of suspected anxiety (HADS ≥ 8 vs. HADS < 8) and on social function (67.8 ± 24.8 vs. 35.7 ± 20.2), cognitive function (62.3 ± 19.1 vs. 39.4 ± 19.4) and medication effect (63.8 ± 26.0 vs. 39.1 ± 24.8) in the case of suspected depression (HADS ≥ 8 vs. HADS < 8). Anxiety and depression were not correlated to age, epilepsy duration, seizure freedom, seizure frequency, comorbidity or holding a certificate of disability. On the other hand, gender and patient-rated tolerability and efficacy of AEDs showed a statistically significant but low correlation to depression and anxiety.

3.2.5. Willingness to undergo epilepsy surgery in the future

In answer to the question 'If it were possible in the future to undergo epilepsy surgery, would you make the attempt?', 64 (60.4%) of 106 patients who were not eligible for surgery responded with 'Yes' and 37 patients (34.9%) with 'No'. The question was left unanswered by 5 patients. Among these patients, the 'Yes' responders showed significantly lower QOL compared to 'No' responders on the

following subscales: overall QOL (52.3 ± 17.7 vs. 60.5 ± 21.5), seizure worry (46.3 ± 26.7 vs. 59.4 ± 24.9), medication effects (45.4 ± 26.7 vs. 59.9 ± 30.29), overall health score (49.2 ± 20.4 vs. 61.8 ± 20.6) and total QOLIE-31 score (50.7 ± 17.7 vs. 58.4 ± 18.5).

3.2.6. Other factors correlated to some subscales of QOLIE-31

Employment had a positive effect on overall QOL, cognitive function, social function, seizure worry and total QOLIE-31 score (Table 2). Female patients showed higher scores than males in overall QOL, social function and the total score of QOLIE-31. Driving a car was correlated with a higher total score of QOLIE-31, better social function and fewer side effects ('medication effects'). The degree of comorbidity and holding a certificate of disability had a negative impact on the overall health score. The number of AEDs had an inverse relationship to the subscale 'cognitive function' (Table 2).

3.3. Predictors of QOL (multivariate analysis)

The results of the regression analysis (including depression and anxiety as predictors) showed that depression and anxiety are highly significant predictors of the QOLIE-31 total score and its subscales (Table 3). Patient-rated tolerability of AEDs and efficacy of AEDs were significant predictors of QOL in most of its aspects as well. Moreover, employment, seizure frequency, patient-perceived change in their seizures since presurgical evaluation, number and efficacy of AEDs and the degree of comorbidity were independent predictors of QOL for some QOLIE-31 subscales (Table 3). The results of the second regression analysis (without depression and anxiety as independent variables (Table 4)) showed the ratings of tolerability of AEDs and employment to be the most important predictors of QOL but also not exclusively. Rated efficacy of AEDs, gender, number of AEDs, degree of comorbidity and holding a certificate of disability were predictors of QOL in some aspects (Table 4). The results of the third regression analysis (excluding seizure-free patients) showed the comparable results as the first one with more predictive power to be seen for employment, side effects, efficacy of AEDs and seizure frequency in the last 6 months (Table 3A in Supplementary material).

4. Discussion

4.1. QOL of patients with refractory focal epilepsy compared to operated patients from the same center

Patients who rejected surgery had no significantly different QOL scores compared to those who were not operated for medical reasons. Therefore, the QOL and their predictors were analyzed for the whole group.

Our findings show a significantly lower QOL in patients who were not eligible for surgery or rejected surgery (i.e., the non-operated group) in comparison to two groups from our center who underwent surgery. In this comparison, QOL was controlled for age, duration of follow-up and duration of epilepsy.

When comparing the present non-operated sample of patients with the two operated groups from our center with the validation sample of the QOLIE-31 [19], which was recruited from 25 American epilepsy centers, the scores of the latter lay between our non-operated and our operated patients. Epilepsy centers, as a rule, attract patients who are not seizure free and whose seizures are difficult to treat. Therefore, it can be expected that QOL for these patients is lower than for operated patients who, in most of the cases, are seizure free for several years after surgery yet higher than the QOL in therapy-refractory patients.

4.2. Predictors for QOL in patients with refractory seizures

Our results reveal that depression and anxiety, followed by patient-rated tolerability and effectiveness of AEDS, are the most

Table 3
Results of stepwise regression including depression and anxiety as independent variables.

Predictor	Overall quality of life	Energy/ fatigue	Well-being	Cognitive function	Social function	Seizure worry	Medication effects	Overall health score	Total QOLIE-31 score
Employment (y/n)					9.2* [.16]				4.6* [−.12]
Seizure frequency		−2.4** [−.22]							
Patient-rated efficacy of AEDs				**−5.0* [−.21]**	**−8.5*** [−.29]**	**−6.3** [−.22]**	**−6.7** [−.23]**	**−4.6** [−.22]**	**−4.6*** [−.25]**
Number of AEDs				−4.8* [−.16]					
Patient-rated tolerability of AEDs		**−6.3** [−.32]**	**−4.2** [−.21]**			**−4.9 [−.17]**	**−12.1*** [−.39]**	**−6.4** [−.29]**	**−3.7** [−.19]**
Degree of comorbidity								−3.3* [−.19]	
Patient-perceived change in their seizures since presurgical evaluation	−5.3** [−.25]								
Depression (HADS ≥ 8)	**−12.9*** [−.35]**	**−9.2** [−.25]**	**−12.7*** [−.33]**	**−19.6*** [−.42]**	**−27.0*** [−.47]**	**−11.9* [−.22]**	**−19.7*** [−.34]**	**−17.3*** [−.42]**	**−15.8*** [−.44]**
Anxiety (HADS ≥ 8)	**−12.8*** [−.35]**	**−11.6*** [−.33]**	**−17.0*** [−.46]**	**−10.7** [−.24]**	**−13.3** [−.24]**	**−20.2*** [−.39]**			**−12.3*** [−.35]**
Constant	82.5	74.2	79.1	85.4	81.1	86.2	87.7	84.1	78.0
VIF	1.2	1.3	1.3	1.2	1.2	1.3	1.2	1.2	1.3
n	99	98	97	99	98	97	99	88	94
R	.63	.71	.76	.65	.73	.66	.68	.70	.85
R^2 (corrected)	**.38**	**.48**	**.56**	**.40**	**.51**	**.40**	**.44**	**.46**	**.70**

For each stepwise regression, the unstandardized, standardized regression coefficients [in brackets], significance [*** = p<0.001, ** = p<0.01, *p<0.05], VIF = variance inflation factor; n = number of patients, R = multiple R; R^2 (corrected) = explained variance were reported.
Note: The following example should illustrate the results of the regression analysis for the scale 'overall quality of life'. In this case, the 'overall quality of life' depends only on depression, anxiety and patient-perceived change in seizures since presurgical evaluation.
If a patient had a high HADS depression score ≥ 8 [= 1] and a low HADS anxiety score < 8 [= 0] and reported a clear deterioration in seizures since presurgical evaluation [= 4], then the expected value for 'overall quality of life' was 82.5 (= Constant) − 12.9 × 1 − 12.8 × 0 − 5.3 × 4 = 48.4.
Significance of bold: Predictor was significant (p<0.05) for at least two scales.

Table 4
Results of stepwise regression without depression and anxiety as independent variables.

Predictor	Overall quality of life	Energy/ fatigue	Well-being	Cognitive function	Social function	Seizure worry	Medication effects	Overall health score	Total QOLIE-31 score
Sex (m/f)									7.9* [.20]
Employment (y/n)	**8.0*** **[.21]**	**7.4*** **[.19]**		**10.9*** **[.23]**	**13.2*** **[.22]**				**7.0*** **[.19]**
Patient-rated efficacy of AEDs					**−6.4*** **[−.22]**	**−6.6*** **[−.23]**	**−6.3**** **[−.21]**		**−4.3**** **[−.23]**
Number of AEDs				−5.3* [−.17]					
Patient-rated tolerability of AEDs	**−7.2***** **[−.36]**	**−10.3***** **[−.51]**	**−9.2***** **[−.43]**	**−8.7***** **[−.43]**	**−9.3**** **[−.30]**	**−10.7***** **[−.35]**	**−16.0***** **[−.52]**	**−10.9***** **[−.50]**	**−8.4***** **[−.42]**
Degree of comorbidity								−3.4* [−.19]	
Certificate of disability (y/n)								−8.8* [−.18]	
Constant	64.1	60.8	71.0	72.6	71.4	77.8	83.3	90.3	66.5
VIF	1.0	1.0	1.0	1.0	1.1	1.0	1.0	1.1	1.2
n	109	108	107	109	108	107	109	97	104
R	.41	.54	.43	.47	.48	.46	.60	.60	.62
R^2 (corrected)	**.15**	**.29**	**.18**	**.20**	**.21**	**.20**	**.35**	**.34**	**.36**

For each stepwise regression, the unstandardized, standardized regression coefficients [in brackets], significance [*** = p<0.001, ** = p<0.01, *p<0.05], VIF = variance inflation factor; n = number of patients, R = multiple R; R^2 (corrected) = explained variance were reported.
Note: The following example should illustrate the results of the regression analysis for the scale 'overall quality of life'. In this case, 'overall quality of life' depends only on employment and tolerability of AEDs. If a patient was employed [=1] and reported an 'unsatisfactory' tolerability of AEDs [=4], then the expected value for 'overall quality of life' was 64.1 (=Constant) + 8.0 × 1 − 7.2 × 4 = 43.3.
Significance of bold: Predictor was significant (p<0.05) for at least two scales.

powerful predictors of QOL. This holds for univariate and for multivariate analyses. There are also some effects of employment and of perceived changes in the seizures. In relation to the aforementioned factors, the effects, however, are less consistent and much weaker. The predictors of QOL in refractory patients verified in this study explain up to 70% of the total QOLIE-31 score and 38%–56% of the subscales.

It should be noted that the percentage of patients with high depression scores (21.2%, HADS scores ≥ 11) among our patients with refractory epilepsies was relatively high compared to other studies using the HADS, e.g., Mensah et al. [20]. Our results confirm previous studies showing that depression was the most important predictor of QOL in patients with refractory focal epilepsy [4,20–22] but was not correlated with epilepsy-specific factors. There are, however, also results that do not corroborate these findings [23]. For example, Smith et al. [7] reported a correlation to epilepsy-specific factors, and Szaflarski et al. described an association between depression and epilepsy-specific factors when other psychological variables were removed from the analysis [10]. These divergent results merit further clarification.

Anxiety disorders are the second most frequent psychiatric comorbidity in patients with epilepsy [24]. In agreement with the published data, our results showed that anxiety had a negative impact on all subscales of the QOLIE-31 [21]. In contrast to the depression scores, the rate of patients with high anxiety scores in our patient group (23.9% with HADS scores ≥ 11) was comparable to other studies using the HADS, e.g., Mensah et al. [25]. Moreover, in agreement with published data [25], our results showed that anxiety was not predicted by epilepsy-related variables. These results might indicate that anxiety is a reaction to the diagnosis of epilepsy regardless of the response to medical treatment. Reuber et al. reported that the rate of anxiety disorders did not change over time, neither by surgery nor by medical treatment [26].

In our group, patient-rated efficacy and tolerability of AEDs are important predictors of QOL independent of depression and anxiety. In addition, our results showed that tolerability of AEDs was significantly, but only moderately, correlated with depression and anxiety. This is in agreement with published data regarding tolerability of AEDs [23]. From similar studies, it may be inferred that depression modifies the perception of the effects of seizures and seizure treatment [27].

Several reports showed that the key to improvement of QOL is the degree of seizure control or seizure remission [6]. In contrast, in our study group of patients with refractory seizures, seizure frequency has only a moderate impact in the univariate analysis and nearly no effects in the multivariate analysis. Evidently, patient-rated efficacy of AEDs is a more important predictor than seizure frequency although both are significantly correlated.

One of the drawbacks of previous studies investigating refractory epilepsy is that they included seizure-free patients in the analysis. We avoided this by running a multivariate regression analysis with and without seizure-free patients. By exclusion of seizure-free patients from the analysis, we found that seizure frequency had more impact on the total QOL score but is still limited on most subscales of QOL.

Employment was an important predictor of QOL if all patients were included in the analysis. By excluding seizure-free patients, employment became a more important predictor of QOL in the multivariate analysis. This confirms the importance of employment on QOL, which can improve QOL by raising self-esteem, self-image and independence [28]. Since employment is crucial for normal social health and for improving QOL, occupational rehabilitation should be an essential part of epilepsy monitoring programs, irrespective of whether the patients can be offered surgery [29].

4.3. Predictors of QOL in operated and non-operated patients with refractory seizures

In our earlier study on predictors of QOL after temporal lobe surgery [12], the duration of seizure freedom and severity of side effects of AEDs were the most powerful predictors. However, in that study, depression and anxiety were not addressed. In contrast, the effects of seizure frequency and seizure freedom for > 1 year were only modest in patients with refractory seizures. This is, however, not surprising as the proportion of seizure-free patients > 1 year was very small in our

sample (9.6%), and there were no patients with long-lasting freedom from seizures.

In our study on predictors of QOL after extratemporal epilepsy surgery in adults, duration of seizure freedom, side effects of AEDs and medical comorbidities appeared to be the strongest predictors [11]. A high prevalence of medical comorbidities (more than 40%) is specific for this group. On the other hand, the results on the duration of seizure freedom are in line with those on patients after temporal lobe surgery. Furthermore, the results on side effects concur in all three groups.

4.4. Long-term prognosis of seizures in "refractory epilepsy"

Although all of our patients were evaluated as suffering from drug-resistant epilepsy based on recently published criteria and were considered non-eligible for surgery, or they themselves rejected surgery, about 44% of our patients reported an improvement in their seizures after presurgical evaluation, and about 10% achieved seizure freedom (>1 year). This is in agreement with previously published results which showed that a small proportion becomes seizure free [30]. From this follows the necessity for further clarification of the concepts of drug resistance and refractory epilepsy.

4.5. Limitation of the study

The limitations of this study are the retrospective nature of the study and the relatively high rate of non-responders, which may be due to frustration after monitoring or a loss of hope of being seizure free after surgery.

5. Conclusion

Besides depression and anxiety, the main determinants of QOL in patients with refractory epilepsy were tolerability and efficacy of AEDs and employment. Depression and anxiety were not correlated with epilepsy-specific factors, with the exception of patient-rated tolerability of AEDs. Patient-rated efficacy of AEDs was a more important predictor than seizure frequency. The impact of seizure frequency on QOL increases when we exclude seizure-free patients, but it is still limited. Seizure control, the side effects of AEDs and the burden of depression must all be kept in balance to optimize QOL.

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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