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ORIGINAL ARTICLE

Surgery in intractable epilepsy—physicians' recommendations and patients' decisions

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Objectives: To identify demographic and clinical variables independently associated with patients' decisions against their physicians' recommendations for resective epilepsy surgery or further scalp video-EEG monitoring (sca-VEM), semi-invasive (sem-) VEM with foramen ovale and/or peg electrodes, and invasive (in-)VEM.

Methods: Consecutive patients, who underwent presurgical assessment with at least one sca-VEM between 2010 and 2014, were included into this retrospective analysis. Multivariate analysis was used to identify independent variables associated with patients' decisions.

Results: Within the study period, 352 patients underwent 544 VEM sessions comprising 451 sca-, 36 sem-, and 57 in-VEMs. Eventually, 96 patients were recommended resective surgery, and 106 were ineligible candidates; 149 patients denied further necessary VEMs; thus, no decision could be made. After sca- or additional sem-VEM, nine out of 51 eligible patients (17.6%) rejected resection. One hundred and ten patients were recommended in-VEM, 52 of those (47.2%) declined. Variables independently associated with rejection of in-VEM comprised intellectual disability (OR 4.721, 95% CI 1.047–21.284), extratemporal focal aware non-motor seizures ("aura") vs. no "aura" (OR 0.338, 95% CI 0.124–0.923), and unilateral or bilateral vs. no MRI lesion (OR 0.248, 95% CI 0.100–0.614 and 0.149, 95% CI 0.027–0.829, respectively).

Conclusions: During and after presurgical evaluation, patients with intractable focal epilepsy declined resections and intracranial EEGs, as recommended by their epileptologists, in almost 20% and 50% of cases. This calls for early and thorough counseling of patients on risks and benefits of epilepsy surgery. Future prospective studies should ask patients in depth for specific reasons why they decline their physicians' recommendations.

KEYWORDS
intracranial EEG, postoperative outcome, presurgical evaluation, seizure focus resection, video-EEG monitoring

1 | INTRODUCTION

In patients with pharmacoresistant focal epilepsy, removal of the seizure focus renders 50% to 65% of cases seizure-free.[1-3] Furthermore, premature mortality is significantly reduced.[4] But still, epilepsy surgery is considerably underused but reasons for this are not entirely clear.[5] One problem is the low referral rate to presurgical evaluation. A recent study from our tertiary epilepsy-center has demonstrated that only one in 10 patients with intractable focal epilepsy was referred, either because the epileptologist did not deem the patient to be a successful candidate or because of patients' decline.[6] After completion of presurgical comprehensive workup including long-term video-EEG monitoring (VEM) with individualized grades of invasiveness, high-resolution cMRI, and neuropsychological testing,[7] patients may be recommended resective surgery, but over the last 30 years, the rate of eligible candidates has been decreasing.[8-10] So far, only few studies have assessed clinical variables independently associated with candidacy for surgery, these comprise male sex, unilateral MRI lesion, and seizure onset in the temporal lobe.[11,12] Surprisingly, after completion of presurgical evaluation, an increasing number of eligible patients decide against their physicians' recommendation for seizure focus resection; in large series from the last years, the rejection rate has risen to 20%.[9-11] If intracranial EEG is necessary, patients' rejection rates are even higher and amount to 35–50%.[8,11,13] The reasons for high rejection rates of resective surgery and invasive EEG procedures are largely unclear.

The aim of the current study was to analyze patients' decision pathways following physicians' recommendations during and after completion of different phases of presurgical assessment for intractable epilepsy. To that end, we sought to identify clinical variables independently associated with patients' decisions against therapeutic or—if necessary—further diagnostic surgical procedures.

2 | METHODS

2.1 | Study overview

We retrospectively analyzed the data of all patients with pharmacoresistant focal epilepsy treated at the Epilepsy-Center Berlin-Brandenburg (Germany) who underwent a least one VEM with scalp electrodes (sca-VEM) assessing eligibility for resective brain surgery in the years 2010 to 2014. Resective surgeries and semi-invasive (sem-) or invasive (in-)VEMs performed in 2015 were considered in this analysis if they had been recommended following VEM at our center in the 5 years before. Patients may have more than one sca-VEM if previous assessments did not allow to draw reliable conclusions, for example, because no seizures were recorded. After the last sca-VEM, patients were either recommended resection of the seizure focus, were identified to be definitely no candidate for resective surgery, or were advised to undergo semi-invasive (sem-) VEM with foramen ovale and/or epidural peg electrodes or invasive (in-)VEM with subdural and/or depth electrodes. After sem-VEM, patients were either candidates for resection or not, or further in-VEM was recommended. In the vast majority of patients who underwent in-VEM, a final recommendation for or against resection could be made. In a next step, we assessed if patients, legal representatives (in case of patients with intellectual disabilities) or parents (in minors) followed the epileptologists' recommendations at the different phases of the evaluation process. The flowchart with recommended and eventually performed VEMs with different grades of invasiveness and resections is presented in Figure 1.

In our clinical routine, the findings of the presurgial evaluation process are discussed at weekly interdisciplinary epilepsy surgery conferences, resulting in consensus-based recommendations on how to proceed. Patients—and usually close family members—are promptly informed of these recommendations. Resective surgery or—if necessary—further diagnostic VEMs are individually explained to the patients considering available data on expected seizure outcome as well as short- and long-term risks.

2.2 | Clinical variables

In all patients, we assessed sex, age at epilepsy onset, age at time of each individual VEM, lifetime number of antiseizure medication (ASM) including current compounds at time of each individual VEM, current or previous depression, intellectual disability, clear lateralizing clinical signs or symptoms with respect to the seizure focus, presence of uni- or bilateral epileptogenic brain MRI pathologies (bilateral neocortical atrophy and previous brain surgery were interpreted as non-epileptogenic), and occurrence of focal aware non-motor seizures, focal impaired awareness seizures, and focal to bilateral tonic–clonic seizures within the last 12 months before each individual VEM. Focal aware non-motor seizures (formerly termed "aura") were differentiated into being likely of temporal (epigastric, psychic, or vegetative sensations) or extratemporal (sensory, visual, acoustic, or unspecific sensations) origin. Data were extracted from patients' paper records and electronic protocols of the epilepsy surgery conferences. In resected patients, seizure outcome was assessed one year after the operation using the Engel classification.[14] Seizure outcome following resections was compared to that in patients without resection—due to either non-eligibility or patients' rejection—1 year after last VEM regardless of grade of invasiveness.

Clinical information was obtained from medical records of a database only, and the need to obtain written, informed consent from each patient is waived by our Institutional Review Board. Patient data were pseudonymized for further analysis and cannot be allocated to individuals. Data were handled under the German and the European data protection act.

2.3 | Statistical analysis

SPSS Statistics 23.0 (IBM, NY, U.S.A) was used to perform all statistical analyses. Variables with continuous data, such as age at

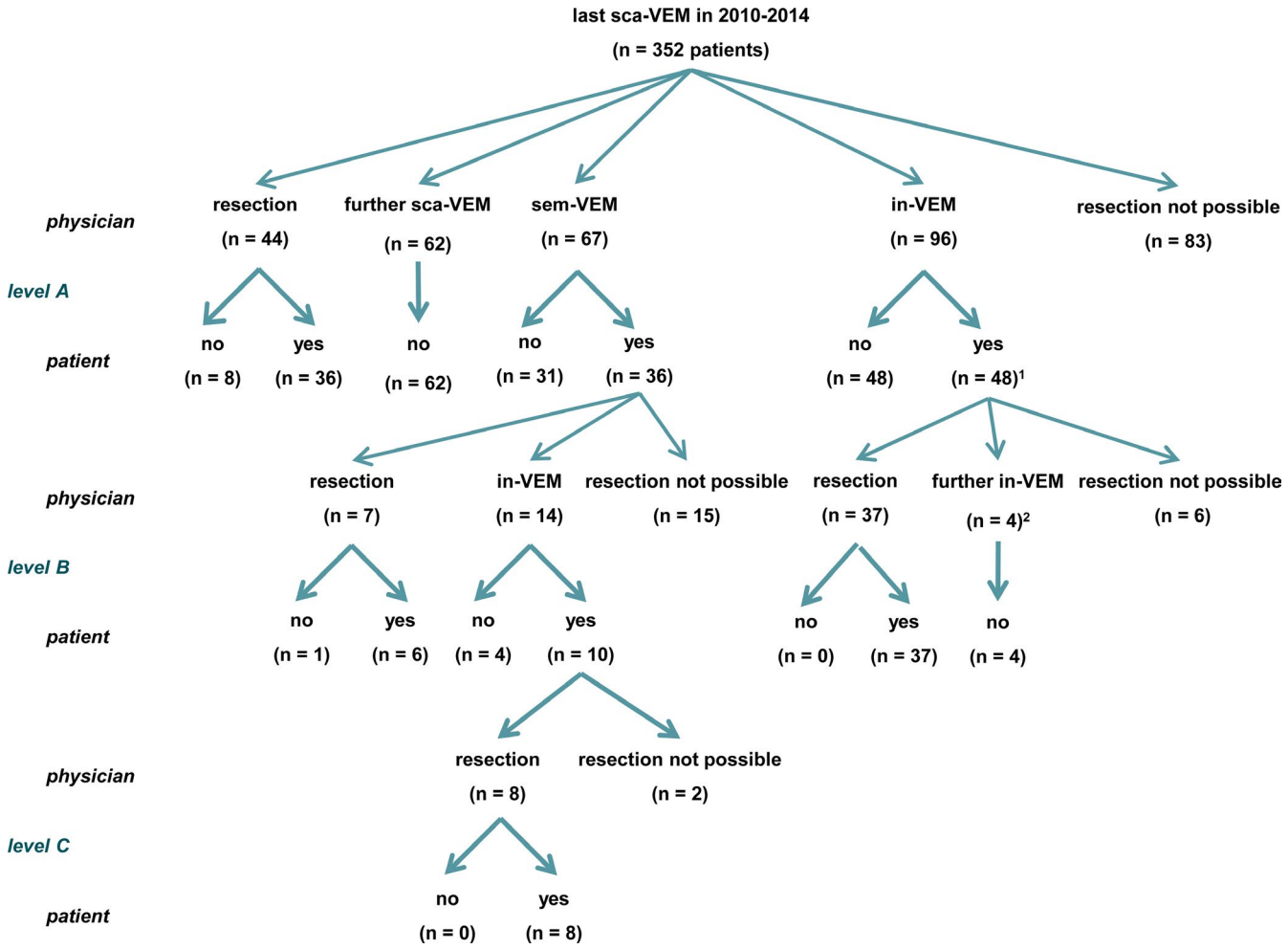

FIGURE 1 Algorithm of decision pathways in consecutive patients with intractable focal epilepsy who underwent at least one presurgical scalp video-EEG monitoring (sca-VEM) between 2010 and 2014 in a tertiary epilepsy-center. On level A to C, physicians' recommendations and patients' decision following recommendations are indicated.[1]One patient who agreed on invasive (in)-VEM (level A) died before the examination was performed; thus, he is not considered on level B.[2]Four patients who underwent in-VEM (level A) required a second in-VEM but all four declined (level B). Sem-VEM, semi-invasive video-EEG monitoring

epilepsy onset, age at examination, and lifetime number of ASM, are presented as median. Categorical variables, such as sex, seizure types, signs of lateralization, current or previous depression, and intellectual disability, are presented binomially with the values "yes" and "no." Focal aware non-motor seizures (temporal, extratemporal, none) and potentially epileptogenic MRI findings (unilateral, bilateral, none) were presented as groups of three different values. All clinical variables were included into multivariate analyses to identify independent predictors for physicians' recommendations for and for patients' decisions against resections or further diagnostic VEMs. Binary logistic regression models were used to calculate odds ratios (inclusion method: stepwise backward; $p < 0.05$ [p in], $p < 0.1$ [p out]; iteration 20; cutoff set at 0.5; constant included). We only assumed significance within the confidence intervals (CI) of 95%.

We used the chi-square test to compare significant differences in excellent seizure outcome (Engel class I) between the three groups, that is, patients with resection and those without resection due to either non-eligibility or patients' rejection. We defined a p-value <0.05 as statistically significant.

3 | RESULTS

3.1 | Study population

We included 352 patients (192 males, 54.5%), with a median age at last sca-VEM of 32 years (range, 4 to 72). Thirty-seven patients were 17 years and younger (10.5%), and five patients were 65 years and older (1.4%). Fifty-two patients (14.8%) had intellectual disabilities. Median age at epilepsy onset was 12 years (range, 0 to 52); median duration of epilepsy at last sca-VEM was 16 years (range, 1 to 65). The last available cMRI (n = 190, 1.5 Tesla; n = 160, 3 Tesla) or cCT (n = 2, MRI not feasible due to metallic clips after previous brain surgery) revealed that epilepsy was structural in 208 cases (58.1%) and

of unknown cause in 144 (40.9%). Specific neuroimaging pathologies are presented in Table 1.

Within the study period, these 352 patients underwent a total of 544 VEM sessions. These comprised 451 examinations with scalp electrodes (sca-VEM, depending on the assumed seizure focus, some of those had additional bilateral sphenoidal electrodes), 36 recordings with foramen ovale and/or peg electrodes (sem-VEM), and 57 assessments with only subdural (n = 53), subdural and depth (n = 2), and only depth electrodes (n = 2) (in-VEM).

3.2 | Physicians' recommendations and patients' decisions after last VEM

Eventually, 96 patients were recommended resective surgery, 44 after sur-, 7 after sem-, and 45 after in-VEM. Another 106 patients were regarded as ineligible candidates, 83 after sur-, 15 after sem-, and 8 after in-VEM (for detailed reasons for non-candidacy, see Table 2). One patient was excluded from the following multivariate analysis due to incomplete data. Variables independently associated with recommendation for resection vs. its rejection after last VEM (any grade of invasiveness) were lifetime number of ASM (OR 0.861, 95% CI 0.767–0.967, p = 0.011), focal aware non-motor seizures arising in the temporal lobe vs. no focal aware non-motor seizures within the previous 12 months (OR 2.705, 95% CI 1.154–6.342, p = 0.022), focal impaired awareness seizures vs. non-occurrence of this seizure type within the previous 12 months (OR 2.511, 95% CI 1.116–5.407, p = 0.019), and unilateral MRI pathology vs. no pathology (OR 5.438, 95% CI 2.440–12.123, p < 0.001) (Table 3).

TABLE 1 Neuroimaging pathologies

Pathology	n = 352
No epileptogenic pathology, n	144 (40.9%)
Normal MRI, n	113 (32.1%)
Neurosurgical scar[a], n	23 (6.5%)
Neocortical atrophy, n	8 (2.3%)
Hippocampal pathology, n	78 (22.1%)
Sclerosis, n	56 (15.9%)
Inhomogeneous signal intensity, n	16 (4.5%)
Atrophy, n	6 (1.7%)
Dual pathology[b], n	7 (2.0%)
Malformation of cortical development, n	44 (12.6%)
Focal cortical dysplasia, n	27 (7.7%)
Heterotopia, n	9 (2.6%)
Polymicrogyria, n	6 (1.7%)
Complex, n	2 (0.6%)
Vascular malformation, n	7 (2.0%)
Acquired lesion, n	50 (14.2%)
Low-grade brain tumor, n	30 (8.5%)
Vascular, n	12 (3.4%)
Traumatic, n	5 (1.4%)
Diffuse scar, n	2 (0.6%)
Post-infectious, n	1 (0.3%)
Cystic lesion, n	3 (0.9%)
Lesion of unknown origin, n	19 (5.4%)

Abbreviations: MRI, magnetic resonance imaging; n, number.

[a]Eleven of those patients had undergone previous resective epilepsy surgery with unsuccessful removal of the epileptogenic zone but no visible epileptogenic lesion in brain MRI.

[b]All patients had hippocampal sclerosis, five patients additional focal cortical dysplasia, one heterotopia, and one a lesion of unknown origin.

One hundred and twenty patients did not experience any or not enough seizures in previous sca-VEMs to draw any conclusions. All these patients were recommended to undergo at least one additional sca-VEM within the next months, but 62 patients (50.8%) decided against (Figure 1, level A). Lifetime number of ASM (OR 0.818; 95% CI 0.703–0.951; p = 0.009) was independently associated with patients' rejection of further sca-VEMs.

After last sca-VEM, 67 patients were recommended sem-VEM with foramen ovale and/or peg electrodes (Figure 1, level A) mostly for the purpose of unequivocal lateralization of the epileptogenic focus in temporal lobe epilepsy; 31 patients (46.2%) decided against this procedure. Patients' rejection of sem-VEM was independently associated with age at last sca-VEM (OR 1.046; 95% CI 1.004–1.090; p = 0.031).

After completion of sca-VEM or sem-VEM, 51 patients were recommended resective surgery (Figure 1, levels A and B). Nine patients (17.6%) decided against seizure focus resection. No variables were identified to be independently associated with those patients who declined surgery.

After last sca-VEM or sem-VEM, 110 patients were recommended in-VEM (94 only subdural electrodes, 7 subdural and depth electrodes, 9 only depth electrodes) (Figure 1, level A and B), mostly for the purpose of delineation of the epileptogenic zone from eloquent cortical structures. Fifty-two patients (47.2%) decided against their physicians' recommendation (40/95 with only subdural electrodes [43.2%], 5/7 with subdural and depth electrodes [66.7%], 7/9 with only depth electrodes [77.8%]). Four of the patients who consented to and eventually underwent in-VEM after sca- or sem-VEM had no seizures during 3 weeks of recording. All of these patients refused a second in-VEM after pondering risks and benefits (one was a minor, none with intellectual disability) but due to their initial decision for in-VEM after sca- or sem-VEM, they were included into the consenting group. One patient died shortly before scheduled in-VEM due to probable SUDEP (sudden unexplained death in epilepsy) and was also included into the consenting group. Variables independently associated with patients' decision against vs. for in-VEM were intellectual disability (OR 4.721, 95% CI 1.047–21.284, p = 0.043), focal aware non-motor seizures arising in extratemporal structures vs. no focal aware non-motor seizures (OR 0.338, 95% CI 0.124–0.923, p = 0.034), and unilateral or bilateral MRI pathology vs. no pathology (OR 0.248, 95% CI 0.100–0.614, p = 0.003 and 0.149, 95% CI 0.027–0.829, p = 0.03, respectively) (Table 4). Thus, lack of intellectual disability, focal aware non-motor seizures which

TABLE 2 Ineligibility for resective surgery after last video-EEG monitoring

Reason for ineligibility	After last sca-VEM *n* = 83	After sem-VEM *n* = 15	After in-VEM *n* = 8	All *n* = 106
Bilateral seizure onset, *n*	36 (43.4%)	11 (73.3%)	1 (12.5%)	48 (45.4%)
No indication for resective surgery, *n*	23 (27.7%)	1 (6.7%)	—	24 (22.6%)
Still unknown epilepsy type after VEM	16	—	—	
Seizure onset contralateral to previous TLR	3	1	—	
Generalized genetic epilepsy	3	—	—	
Exclusively psychogenic non-epileptic seizures, epilepsy well-controlled	1	—	—	
Presumed overlap with eloquent cortex, *n*	9 (10.8%)	—	7 (87.5%)	16 (15.1%)
Low seizure frequency after VEM, *n*	9 (10.8%)	1 (6.7%)	—	10 (9.4%)
Other difficulties complicating diagnostic or resective procedures[a], *n*	6 (7.2%)	2 (13.3%)	—	8 (7.5%)

Abbreviations: in, invasive; *N*, number; sca, scalp; sem, semi-invasive; TLR, temporal lobe resection; VEM, video-EEG monitoring.

[a]Four patients demonstrated uncontrollable behavior during or after seizures in sca-VEM, and thus, injuries during semi-/invasive diagnostic procedures were assumed; in three patients, the epileptogenic focus was inaccessible surgically, one patient was not deemed physically fit enough for brain surgery.

are generated beyond the temporal lobe, and evidence for any MRI lesion guide the patient to rather agree on invasive EEG recording.

3.3 | One-year seizure outcome

Eighty-seven out of 352 patients (24.7%) eventually underwent resective surgery, 158 patients were recommended either direct resection (*n* = 9) or further VEM sessions with various grades of invasiveness (*n* = 149) but declined (44.9%), and 106 patients were ineligible for resective surgery (30.1%). Furthermore, one patient died of probable SUDEP 6 months after last sca-VEM, but prior to scheduled in-VEM (0.3%).

For 288 out of all 352 patients (81.8%), 1-year seizure outcome was available. Fifty-seven out of 81 patients (70.4%) with resection and 1-year follow-up data were free of disabling seizures (Engel class I). Following resective surgery, seizure freedom rate was significantly higher compared to 207 patients with 1-year follow-up data who did not undergo resective surgery due to any reason (27 patients Engel class I, 13.0%; $p < 0.001$). There was no significant difference in Engel class I outcome between non-resected patients who were not eligible (9/83 [10.8%]) and those who were recommended but rejected resection or further necessary VEM (18/124 [14.5%]; $p = 0.443$). Figure 2 depicts 1-year seizure outcomes in the three groups stratified to the four Engel classes.

4 | DISCUSSION

The aim of this retrospective study was to elucidate decision pathways on physicians' and on patients' sides during and after presurgical assessment. To that end, we sought to identify variables associated with candidacy for resection as assessed by physicians and in particular with decisions of patients following physicians' recommendations on seizure focus resection and potentially needed further VEMs. We demonstrated that almost 20% of patients reject resective surgery for intractable focal epilepsy despite successful completion of presurgical evaluation and that almost 50% of patients do not agree on necessary invasive EEG recordings following sca- or sem-VEM; these figures confirm findings from previous large series from other European and North American centers.[8-11,13]

On the physicians' side, recommendation for resection after completion of presurgical assessment was independently associated with low lifetime number of ASM, focal aware non-motor

TABLE 3 Physicians' recommendation for resective surgery vs. rejection after completion of the evaluation process

Variables	Resection recommended (n = 96)	Resection not possible (n = 105)[a]	OR; 95% CI; p-Value
Male sex, n	52 (54.2%)	53 (50.5%)	1.943; 0.965–3.914; p = 0.063
Age at examination, ys (m ± SD)	35.0 ± 12.7	31.8 ± 15.3	0.989; 0.962–1.016; p = 0.442
Age at epilepsy onset, ys (m ± SD)	15.2 ± 10.8	12.5 ± 9.8	1.005; 0.969–1.043; p = 0.772
Lifetime number of ASM, n (m ± SD)	5.6 ± 2.5	6.9 ± 3.7	0.861; 0.767–0.967; p = 0.011
Current or previous depression, n	16 (16.7%)	16 (15.2%)	2.266; 0.998–5.147; p = 0.051
Intellectual disability, n	4 (4.2%)	24 (22.9%)	0.395; 0.108–1.440; p = 0.159
Focal aware non-motor sz.			
None, n	29 (30.2%)	51 (48.6%)	1.000 (reference)
Temporal, n	37 (38.5%)	20 (19.0%)	2.705; 1.154–6.342; p = 0.022
Extratemporal, n	30 (31.3%)	34 (32.4%)	1.408; 0.639–3.101; p = 0.396
Focal impaired awareness sz, n	80 (83.3%)	62 (59.0%)	2.511; 1.116–5.407; p = 0.019
Focal to bilateral tonic–clonic sz, n	52 (54.2%)	59 (56.2%)	1.042; 0.523–2.079; p = 0.906
Clinical signs of lateralization, n	58 (60.4%)	63 (60.0%)	0.994; 0.484–2.042; p = 0.986
Epileptogenic pathology in neuroimaging			
None, n	13 (13.5%)	46 (43.8%)	1.000 (reference)
Unilateral, n	75 (78.1%)	42 (40.0%)	5.438; 2.440–12.123; p = 0.000
Bilateral, n	8 (8.4%)	17 (16.2%)	1.284; 0.404–4.087; p = 0.672

Abbreviations: ASM, antiseizure medication; CI, confidence interval; m, mean; N, number; OR, odds ratio; SD, standard deviation; sz, seizure; ys, years.

[a]In one patient, data were incomplete, and this subject was excluded from multivariate analysis.

seizures arising in the temporal lobe, focal impaired awareness seizures, and unilateral MRI pathology, information all of which are available beforehand. While seizures from temporal lobe structures and unilateral lesions have been described previously to predict candidacy for surgery,[11] low lifetime number of ASM before presurgical assessment may indicate less complex and challenging cases.

On the patients' side, rejection of both further necessary VEMs at all phases of presurgical evaluation and eventually recommended seizure focus resection presents a paramount problem.

In 120 out of 352 patients, sca-VEM did not allow drawing definite conclusions, mostly due to lack of seizures during VEM; therefore, further sca-VEM was required. Half of the patients decided against this recommendation, and—interestingly—low lifetime number of ASM was independently associated with patients' rejection, while—as demonstrated above—this variable increases the likelihood of epileptologists' recommendation for surgery. This finding may be explained by patients' hope that further trials with other ASM may result in seizure freedom or significant relief[15] and that surgery may not be necessary, but studies on responsiveness toward increasing numbers of ASM trials have demonstrated the opposite.[16,17] One may argue that ictal recording is not required in all surgical cases, and that some patients can be offered resection even if they decline further sca-VEM. Indeed, a recent prospective study on patients with unilateral hippocampal sclerosis and compatible seizure semiology has demonstrated similar seizure freedom rates in those with and those without prior ictal VEM.[18] However, the fraction of classical temporal lobe epilepsy with hippocampal sclerosis in surgical programs of European epilepsy centers has decreased from 39% in the 1990s to 20% in the 2010s,[19] and in the current study, 16% of patients had hippocampal sclerosis. Thus, most patients still need ictal VEM prior to surgery.

TABLE 4 Patients decision against vs. for in-VEM after last sca- or sem-VEM

Variables	Decision against in-VEM (*n* = 52)	Decision for in-VEM (*n* = 58)	OR; 95% CI; *p*-Value
Male sex, *n*	29 (55.8%)	31 (53.4%)	1.176; 0.488–2.834; *p* = 0.718
Age at examination, ys (m ± SD)	31.7 ± 13.4	31.7 ± 11.1	0.983; 0.940–1.027; *p* = 0.439
Age at epilepsy onset, ys (m ± SD)	14.8 ± 10.5	14.4 ± 9.6	1.020; 0.977–1.063; *p* = 0.369
Lifetime number of ASM, *n* (m ± SD)	6.4 ± 3.3	5.6 ± 2.4	1.047; 0.887–1.236; *p* = 0.586
Current or previous depression, *n*	12 (23.1%)	12 (20.7%)	1.067; 0.329–3.462; *p* = 0.915
Intellectual disability, *n*	9 (17.3%)	3 (5.2%)	4.721; 1.047–21.284; *p* = 0.043
Focal aware non-motor sz.			
None, *n*	27 (51.9%)	21 (36.2%)	1.000 (reference)
Temporal, *n*	15 (28.8%)	13 (22.4%)	1.311; 0.472–3.640; *p* = 0.603
Extratemporal, *n*	10 (19.2%)	24 (41.4%)	0.338; 0.124–0.923; *p* = 0.034
Focal impaired awareness sz, *n*	32 (61.5%)	39 (67.2%)	0.747; 0.296–1.887; *p* = 0.538
Focal to bilateral tonic–clonic sz, *n*	28 (53.8%)	32 (55.2%)	0.635; 0.268–1.507; *p* = 0.303
Clinical signs of lateralization, *n*	28 (53.8%)	39 (67.2%)	0.750; 0.286–1.970; *p* = 0.560
Epileptogenic pathology in neuroimaging			
None, *n*	27 (51.9%)	14 (24.1%)	1.000 (reference)
Unilateral, *n*	22 (42.3%)	38 (65.5%)	0.248; 0.100–0.614; *p* = 0.003
Bilateral, *n*	3 (5.8%)	6 (10.3%)	0.149; 0.027–0.829; *p* = 0.030

Abbreviations: ASM, antiseizure medication; CI, confidence interval; in, invasive; m, mean; *N*, number; OR, odds ratio; sca, scalp; SD, standard deviation; sem, semi-invasive; sz, seizure; VEM, video-EEG monitoring; ys, years.

In our center, foramen ovale electrodes are inserted bilaterally for lateralization in mesial temporal lobe epilepsies if previous sca-VEM has been inconclusive.[20] As the electrode position is epidural, this approach is termed semi-invasive. Physicians' recommendation for this diagnostic step was also decided against by almost every other patient, and older age as an independently associated variable for rejection may reflect more reluctance toward diagnostic surgical procedures with increasing age.

After sca- and sem-VEM, resection was recommended to 51 patients, and nine of those denied. Likely due to the small number of patients, associations with independent variables could not be identified. Two German studies from the Epilepsy-Centers Bethel and Bonn on trends in epilepsy surgery from the late 1980s to the 2010s have shown that patients' rejection rate of resective surgery after complete workup has increased from 1 to 5% in the earliest period to 20% in the last period observed.[8-10] One possible explanation was that the demonstrated increasing length of consent forms mentioning more possible complications of epilepsy surgery has contributed to growing skepticism in patients.[9] Less invasive surgical approaches for removal of the seizure focus, such as laser ablation, were not available in Germany at the time period studied, but may increase the rate of patients' consent.

One hundred and ten patients (31%) required invasive EEG recording with subdural and/or depth electrodes, which is in line with data from the recent European survey on trends in epilepsy surgery (29%).[19] Patients' rejection rate was almost 50% which is similar to the findings from the National Hospital, London, UK.[13] In the current study, patients' decision against in-VEM after sca- or sem-VEM was independently associated with intellectual disability, lack of focal aware seizures, and lack of uni- or bilateral epileptogenic MRI pathologies. Patients with intellectual disability commonly have legal guardianship, and one can assume that legal caretakers are rather

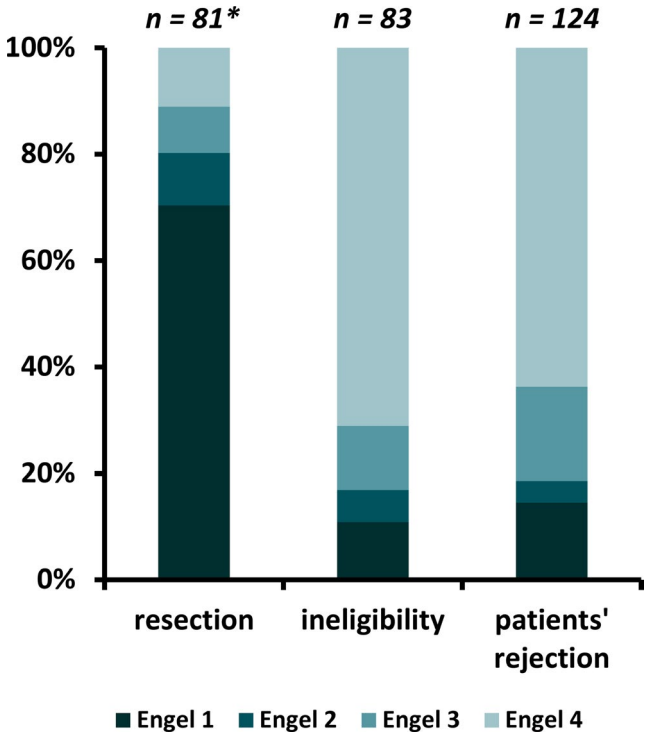

FIGURE 2 Seizure outcome (Engel surgical outcome scale)[14] one year after resection or, in those patients not resected, one year after last video-EEG monitoring (VEM) regardless of grade of invasiveness. Note that patients who were not eligible for resection did not differ from those who were eligible but denied surgery or further necessary VEMs. *In those patients resected, seizure freedom (Engel class 1) was significantly more frequent compared to patients in both groups without resection ($p < 0.001$)

hesitant when it comes to the decision on elective neurosurgery. Presence of brain lesions in preoperative MRI is one of the strongest predictors for seizure freedom after epilepsy surgery.[2] Thus, it is likely that patients without lesions were counseled on reduced chances to become seizure free, and consequently, more patients decided against invasive EEG. We do not have a reliable explanation why lack of focal aware seizures was associated with decline of in-VEM.

In line with most other studies on seizure outcome after epilepsy surgery, seizure freedom rate after one year was 70%. We also assessed seizure outcome in those patients who did not undergo surgery, and seizure freedom rate was similar in those who were not eligible and those who denied resection or necessary further VEMs (11 to 15%). These figures are in line with previous studies from Canada and Israel on non-operated patients reporting seizure freedom rates of 8% 1 year after presurgical evaluation[3] and of 17% after 4 years.[21] These figures indicate that patients who decline VEM at different phases of the diagnostic evaluation process or who decide against eventual resective surgery must be counseled on unfavorable seizure outcome.

This study is limited by its monocentric design, but various data on the population studied, on the procedures employed and rejected by patients, and on the postoperative seizure outcome were comparable to other studies and may allow at least some generalization of our findings. Another major limitation is the retrospective approach which prevented to consider further clinically relevant variables such as detailed frequency of different seizure types, possible unpleasant experiences in previous sca-VEM like seizure cluster or status epilepticus, adverse event burden of antiseizure medication, socioeconomic issues, and details on current psychiatric disorders and on supportive networks. Furthermore, the retrospective approach did not allow assessing concrete reasons why patients decided against resections and further necessary VEMs. To overcome these inherent limitations of a retrospective study and to better understand decision pathways in more detail, a prospective and ideally multicentric study, which also employs qualitative measurements such as personal interviews in particular of patients,[22] is warranted.

In conclusion, the underuse of epilepsy surgery can, at least in part, be explained by high rejection rates of patients during or after presurgical workup; one in five patients declines resective surgery and every other patient decides against recommended VEM at different phases of the presurgical evaluation process. The independent variables associated with patients' declines of necessary further VEMs and resections may help to identify patients "at risk" for such rejections; those patients in particular may be addressed by early and thorough counseling on risks and benefits of resective epilepsy surgery.

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CONFLICT OF INTEREST

MH received speaker's honoraria and/or consultancy fees from Arvelle, Bial, Desitin, Eisai, GW Pharma, UCB, and Zogenix within the last 3 years. UCS holds a consulting agreement with LivaNova Germany for training in vagus nerve stimulation. RD, ABK, HJM, FO and CD did not report any disclosures.

AUTHOR CONTRIBUTIONS

Roman Davids acquired the data, interpreted and analyzed the data, and wrote the manuscript. *Alexander Kowski* interpreted and analyzed the data, and revised the manuscript. *Heinz-Joachim Meencke*, *Frank Oltmanns*, *Christoph Dehnicke*, and *Ulf Schneider* revised the manuscript. *Martin Holtkamp* designed the study, interpreted and analyzed the data, and wrote the manuscript. Open access funding enabled and organized by Projekt DEAL.

DATA AVAILABILITY STATEMENT

Raw data from this study are available for sharing on request.

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