Outcome after conservative management or surgical treatment for new-onset epilepsy in cerebral cavernous malformation

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OBJECTIVE The aim of this study was to determine seizure outcome, functional outcome, and the withdrawal of antiepileptic drugs (AEDs) after conservative or surgical treatment of patients with new-onset cavernoma-related epilepsy (CRE).

METHODS The authors conducted a retrospective comparative observational study of 79 consecutive patients, each with a single sporadic cerebral cavernous malformation (CCM) and new-onset CRE.

RESULTS Forty-one patients underwent initial surgery (IS), and 38 patients underwent initial conservative (IC) treatment. Of those in the latter group, 19 underwent delayed surgical (DS) treatment. At the last follow-up, 88%, 32%, and 79% of patients in the respective groups had been seizure free for at least 2 years (International League Against Epilepsy [ILAE] Class 1; IS vs IC, $p < 0.0001$) and 78%, 8%, and 58%, respectively, had been off AEDs (IS vs IC, $p < 0.0001$). The cumulative probability of staying seizure free (ILAE Class 1) during a 5-year period was 73% (mean seizure-free follow-up 49.8 ± 2.7 months, 95% CI 44.4–55.1 months) for the IS group, 22% (mean 31.8 ± 3.6 months, 95% CI 24.8–38.8 months) for the IC group, and 68% (mean 48.6 ± 4.3 months, 95% CI 40.1–57.1 months) for the DS group (IS vs IC $p < 0.001$). Long-term operative morbidity was 3%, and long-term morbidity in the conservatively treated group was also 3%.

CONCLUSIONS Patients with CCM and new-onset CRE who underwent IS treatment showed better results in seizure control and the discontinuation of AEDs than the conservatively treated patients. Operative morbidity was comparable to the morbidity from symptomatic CCM hemorrhage in the conservative group. Half of the patients who started with conservative treatment underwent subsequent surgical treatment; however, a longer duration of epilepsy prior to surgery did not worsen postoperative seizure outcome.

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KEY WORDS epilepsy; cerebral cavernous malformation; surgical treatment

EPILEPTIC seizures are a common manifestation in patients harboring cerebral cavernous malformations (CCMs). They occur in approximately 25% of symptomatic CCM cases.^{4,24} Most patients with a CCM-related first seizure will develop epilepsy within 5 years.¹ Therefore, it is widely accepted that antiepileptic drug (AED) treatment is indicated if the diagnosis of definite or probable cavernoma-related epilepsy (CRE) is confirmed.²⁹ Despite evidence from several large observational studies^{5,6,14,33,36} and systematic reviews^{12,24} that the surgi-

cal treatment of CRE provides excellent seizure control, most authors recommend a conservative therapeutic approach after the initial diagnosis of CRE.²⁹ Subsequently, in cases of a first drug trial failure or the onset of drug-resistant CRE, presurgical evaluation and potential epilepsy surgery are commonly accepted.^{4,29} However, besides the risk of epilepsy, patients with CCM carry the intrinsic risk of symptomatic hemorrhage.^{4,11,20,25,31} Therefore, the management of CRE patients must respect the risks related both to epilepsy and to future CCM hemorrhage. In addi-

ABBREVIATIONS AED = antiepileptic drug; CCM = cerebral cavernous malformation; CRE = cavernoma-related epilepsy; DS = delayed surgical; DVA = developmental venous anomaly; EEG = electroencephalography; IC = initial conservative; ILAE = International League Against Epilepsy; IS = initial surgical; mRS = modified Rankin Scale; NH-FND = nonhemorrhagic focal neurological deficit; SH = symptomatic hemorrhage.

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tion, a negative correlation between preoperative duration of seizures and postoperative seizure outcome has been found in several observational studies,^{6,10,12,14,24,33} arguing for earlier surgical treatment. Furthermore, seizure outcome and functional outcome in patients with new-onset CRE treated conservatively have not been sufficiently studied as yet. Most authors refer to a single retrospective series of 16 patients that lacks specification of epilepsy type and outcome assessment as well as reporting standards for CCM.⁷ More recently, authors have referred to a prospective population-based study¹⁹ comprising 21 cases of new-onset CRE. Unfortunately, the study intermixes epilepsy types and CCM forms (sporadic and familial) and includes a low proportion of lesions localized to the temporal lobe.

Regarding observational studies that report on seizure outcome after surgery, missing or fragmentary data on rates of withdrawal from AEDs and on functional outcome are the most common drawbacks, along with varying definitions of seizure freedom and drug-resistant CRE.³⁴ Beyond that, comparative observational studies are missing or insufficient according to the Centre for Evidence-based Medicine (CEBM) 2011 criteria.²⁸ As regards CRE, only a few observational studies in the literature provide a concurrent control group.^{13,21,27}

According to a report by the Surgical Task Force of the International League Against Epilepsy (ILAE),²⁹ surgical and conservative treatments are both first-line therapeutic options in new-onset CRE; however, given current data, we are unable to counsel patients on which would be the best option, and thus more data are clearly needed. What is the long-term seizure outcome, functional outcome, and successful withdrawal rate of AEDs under conservative or surgical treatment? What is the chance of complete seizure freedom or sustained seizure freedom? What is the risk and what are the risk factors for a first drug trial failure or the onset of drug-resistant CRE under conservative treatment? Does delayed surgical treatment worsen seizure outcome?

To gain a better understanding and to answer these questions, we performed a retrospective observational study of CCM patients with new-onset CRE due to a single sporadic CCM who were admitted to our center and were followed up for at least 3 years according to the ILAE³⁵ and Angioma Alliance² reporting standards. Patients were grouped as follows: immediate (initial) conservative (IC) treatment, immediate (initial) surgical (IS) treatment, and delayed surgical (DS) treatment after failed conservative treatment.

Methods

This study was conducted at the Department of Neurosurgery, University of Duisburg-Essen, Germany, in accordance with all guidelines set forth by the approving institutional review board. It was performed as part of a superordinate observational study on patients with CCM that was registered with the German Clinical Trials Register (<https://www.germanctr.de>) and whose registration no. is DRKS00006020. Informed consent was obtained from each patient. Presurgical epileptological evaluation was performed at the Epilepsy Center Hessen-Marburg,

Department of Neurology, Philipps-University, Marburg, Germany, in some of the patients.

Inclusion Criteria

We searched our CCM database (2002–2011) for patients with a single supratentorial sporadic (no familial history or negative genetic screening) CCM who presented with new-onset epileptic seizures (≤ 3) confirmed to be related to the CCM (definite or probable CRE²⁹) and who started with AED therapy. Further requirements for eligibility were preoperative MRI (contrast enhanced and non-contrast-enhanced T1, T2, and T2* sequences) as well as electroencephalography (EEG) scalp recordings, histological confirmation of the diagnosis (in the case of surgical treatment), and a minimum follow-up of 3 years.

Evaluation of Clinical and Demographic Baseline Data and Follow-Up

Clinical and demographic baseline data were collected through evaluation of patient charts (P.D. and S.N.). Routine clinical follow-up and analysis of seizure outcome and functional outcome in our department for a minimum of 2 years or longer (uninterrupted surveillance) were available in all patients. Some of the patients and/or their general practitioners and/or neurologists were contacted by phone and were asked to provide further information on medical or epileptic seizure history and medication via a standardized telephone questionnaire (P.D. and S.N.). Thus, a complete annual surveillance was retrospectively generated in all patients. A neuroradiologist independently evaluated image data by using the in-house picture archiving and communication system (PACS).

All parameters were assessed according to the reporting standards of CCM research² with a focus on MRI parameters: CCM location (temporal neocortical, temporomesial archicortical, or other; cortical; subcortical), eloquent location (pre- or postcentral gyrus, speech areas, primary visual cortex), CCM size (mm), hemorrhage size (< 5 mm, 5–20 mm, > 20 mm), associated developmental venous anomaly (DVA), epileptic seizure type, AED medication (none, monotherapy, or polytherapy), functional outcome (modified Rankin Scale [mRS]), and seizure outcome (year to year ILAE class³⁵). Because of the available median follow-up of 5 years per person in this study cohort, we quantified completeness of follow-up⁸ data accrued as a proportion of all potential follow-up that could have been obtained to the end of a 5-year follow-up.

Group Assignments

On admission, all patients were similarly counseled regarding potential advantages and risks of initial surgical treatment of the CCM. Generally, resection was offered to all patients, including those with an eloquent location for the lesion. However, conservative treatment was also offered as an option in all cases. After time for consideration, the consultant and the patient jointly decided on the treatment approach. This “policy” was applied with one exception: in CCMs with a large (> 2 cm) associated hemorrhage, surgical treatment was recommended and performed in all cases.

Patients were grouped according to treatment, as follows: immediate (initial) surgical (IS) approach (within 6 months after the onset of CRE), immediate (initial) conservative (IC) approach, and delayed surgical (DS) approach (“failed” conservative approach due to persistent seizures with surgical treatment > 12 months after onset of CRE).

A failed conservative approach was defined as persistent seizures under IC treatment (see definition of “first drug trial failure” below in *Outcome Definitions*). Patients were again consulted regarding surgical treatment. To continue conservative treatment or change into the DS treatment was an individual decision without previously defined criteria (AED schedule, EEG findings, and so forth). However, the minimum duration of conservative treatment attempted in our cohort was 23 months.

Treatment Strategies

Pure lesionectomy or lesionectomy including the hemosiderin rim was performed in all surgical cases. Generally, surgeons intended to remove all hemosiderin deposits (“yellowish tissue”) because of its epileptogenic potential.²³ In highly eloquent lesions (motor strip, speech areas), however, resection of the hemosiderin rim was sometimes limited to spare functional tissue (for example, in the awake surgery setting). Furthermore, routine post-operative MRI was not performed in all patients (47 of 60 surgical patients). Consequently, the complete removal of hemosiderin was not controlled and assured in all patients. No extended resections (mesial resection, standard temporal lobe resection) were performed.

Antiepilepsy drugs were started and withdrawn under the supervision of the attending neurologist without a standardized algorithm. In general, AEDs were withdrawn in cases of seizure freedom for at least 6 months and EEG scalp recordings free of epileptiform potentials. Because of the characteristics of the study cohort, special epileptological presurgical evaluation at an epilepsy center was not routinely performed in all patients. In general, presurgical evaluation included detailed epileptological evaluation and video-EEG monitoring.

Outcome Definitions

Primary outcomes were defined as follows: completely seizure free since treatment start (referred to as ILAE Class 1a; continued seizure freedom during all follow-up years), sustained seizure freedom (seizure free 2 consecutive years with an ILAE Class 1 [this class represents seizure freedom for a specific year]), and AED on/off therapy during the year of last follow-up.

Morbidity was defined as a persistent (> 12 months) decrease of a minimum of 1 point on the mRS score compared with the score on initial presentation.

“First drug trial failure” in the conservative group was defined as 2 successive years of follow-up with an ILAE class > 1 while under AED monotherapy. “Drug-resistant epilepsy” was defined according to the ILAE definition.²²

Statistical Analysis

Statistical analysis was performed using SPSS version

22 (IBM Corp.). Interval-scaled data were expressed as the mean and standard deviation, and nominal data were expressed as the absolute number and valid percent. Data were tested for normal distribution by performing a Shapiro-Wilk test in addition to constructing histograms and Q-Q (quantile-quantile) plots. We used parametric statistics for between-group comparisons for normally distributed data and nonparametric statistics for not normally distributed data. For categorical variables, the chi-square or Fisher’s exact test (expected frequencies < 5) were applied. Outcome end points were compared using relative risk analysis. We performed survival analysis using Kaplan-Meier statistics starting at the time of initial presentation and censoring on the date (computed at the midpoint of the year) of an event (ILAE class > 1) or at the end of the 5-year follow-up if the event did not occur. Therefore, results were right censored. Univariable comparison was performed using the log-rank test. The influence of variables on the occurrence of an event was analyzed using Cox regression. The correlation of independent variables with outcomes was analyzed using Spearman’s rho test. All tests were 2-tailed ($\alpha = 0.05$).

Results

We identified 86 patients meeting the eligibility criteria. Seven patients were lost to follow-up or declined to participate in the study; therefore, 79 patients made up the study cohort, for which there was a total of 526 person-years of follow-up (median 5 years per person, IQR 4–6 years). Overall completeness of follow-up was 83% (IS group 89%, IC group 80%, DS group 78%). Forty-one patients (52%) underwent IS treatment, and 38 (48%) started with conservative treatment. In the latter group, 19 (50%) underwent delayed surgical treatment (Fig. 1 and Table 1).

Seizure Freedom

In the IS, IC, and DS groups, ILAE Class 1a (completely seizure free since treatment start) was attained by 30 (73%), 9 (24%), and 12 (63%) patients, respectively. Differences in attaining ILAE Class 1a between the IS and IC groups ($p < 0.0001$) and the IC and DS groups ($p < 0.05$) were significant. No significant difference was found between the IS and DS groups ($p = 0.5468$). A minimum of 2 years of continuous seizure freedom (ILAE Class 1) at the last follow-up (sustained seizure freedom) was reached in 36 (88%), 12 (32%), and 15 (79%) patients in the IS, IC, and DS groups, respectively. The difference between the IS and IC groups ($p < 0.0001$) and between the IC and DS groups ($p < 0.0005$) were significant. Between the IS and DS groups, no significant difference was found ($p = 0.4165$). Year to year results for follow-up ILAE classes for the groups and inter-group comparisons are featured in Fig. 2 and Table 2. The overall chance of staying seizure free (ILAE Class 1) over 5 years of follow-up after treatment start was 73% (mean seizure-free follow-up 49.8 ± 2.7 months, 95% CI 44.4–55.1 months) for the IS group, 22% (mean 31.8 ± 3.6 months, 95% CI 24.8–38.8 months) for the IC group, and 68% (mean 48.6 ± 4.3 months, 95% CI 40.1–57.1 months) for the DS group. The differences in seizure freedom between the IS and IC groups ($p < 0.001$) were significant, whereas differ-

FIG. 1. Flowchart grouping patients according to the received treatment. Seven patients were not included in the study cohort: 2 patients declined to participate, and 5 were lost to follow-up.

ences between the IS and DS groups ($p = 0.759$) and between the DS and IC groups ($p = 0.13$) were not (Fig. 3).

Cox regression revealed no statistically significant influence on seizure outcome within the different treatment groups among the analyzed variables of age, location of CCM, type of seizure, and size of hemorrhage (see Supplementary Tables).

Antiepileptic Drug Therapy

At the 1-year follow-up, all patients were on AED therapy. At the 3-year follow-up, 18 patients (44%) in the IS group, 26 (81%) in the IC group, and 13 (68%) in the DS

group were on AED therapy. At the last available follow-up, these numbers were 9 (22%), 35 (92%), and 8 (42%), respectively. Antiepileptic drug polytherapy was administered in 0 (0%), 8 (21%), and 3 patients (16%), respectively. From the 2-year follow-up, differences in the discontinuation of AEDs between the IS and IC groups were significant. For the IC and DS groups, a difference in the discontinuation of AEDs was significant at the last available follow-up only (Table 3). The number of “double winners” (ILAE Class 1a and off AEDs) was 29 (71%) in the IS group and 7 (37%) in the DS group. In the IC group, there were 4 (10%) “triple winners” (ILAE Class 1a, off AEDs,

TABLE 1. Baseline clinical characteristics in 79 CCM patients with new-onset epilepsy*

Parameter	All Patients	IS Group	IC Group	DS Group
No. of patients	79	41	38	19
Median age at presentation in yrs	38	39	36	36
Female (%)	38 (48)	18 (44)	20 (53)	9 (47)
Mean duration of epilepsy prior to surgery in mos	NA	2.6 ± 1.7	NA	43 ± 30
Mean no. of seizures prior to inception point ± SD	1.8 ± 0.7	1.8 ± 0.7	1.7 ± 0.7	1.8 ± 0.6 (2.7 ± 1.4)†
Mean follow-up in mos since treatment start ± SD	64 ± 31	69 ± 34	64 ± 48	56 ± 31
Seizure semiology (%)				
Focal	26 (33)	13 (32)	13 (34)	9 (47)
Secondary, generalized	53 (67)	28 (68)	25 (66)	10 (53)
CCM location (%)				
Temporal	43 (54)	19 (46)	24 (63)	12 (63)
Temporomesial	14 (18)	6 (14)	8 (21)	6 (31)
Extratemporal	36 (46)	22 (54)	14 (37)	7 (37)
Cortical involvement‡	71 (90)	38 (93)	36 (95)	16 (84)
Eloquent lesion location	31 (39)	14 (34)	17 (45)	8 (42)
Mean CCM size in mm ± SD	16.3 ± 6.1	17.9 ± 6.0	14.6 ± 5.7	15.2 ± 5.6
Hemorrhage size (%)				
<5 mm	43 (54)	21 (51)	22 (58)	10 (53)
5–20 mm	27 (34)	11 (27)	16 (42)	9 (47)
>20 mm	9 (11)	9 (22)	0 (0)	0 (0)
Associated DVA (%)	32 (40)	11 (27)	21 (55)	4 (21)

NA = not applicable.

* Between-group comparisons revealed no significant differences, apart from CCM size ($p < 0.027$), size of hemorrhage ($p < 0.006$), and association with DVA ($p < 0.011$).

† In parentheses, mean number of seizures during IC treatment approach.

‡ Eight CCMs were located subcortically, all showing cortical hemosiderin deposits.

FIG. 2. Year to year ILAE follow-up classes. Proportion of patients in the 3 groups that scored ILAE Class 1 at each year of follow-up and at the last available follow-up (LAFU). Proportion of patients that stayed completely seizure free during the entire observation period (ILAE Class 1a). Asterisks indicate significant difference (at least $p < 0.05$) compared with the IC group.

TABLE 2. ILAE class over 5 years of follow-up*

Parameter	Group	1-Yr FU	2-Yr FU	3-Yr FU	4-Yr FU	5-Yr FU	LAFU
ILAE class							
1	IS	37 (90)†	36 (88)‡	35 (85)¶	29 (88)¶	22 (88)§	36 (88)†
	IC	19 (50)	19 (51)	18 (56)	14 (56)	7 (43)	14 (36)
	DS	17 (89)§	15 (79)	15 (79)	8 (89)	7 (87)	17 (89)‡
2	IS	2 (5)	1 (2)	0 (0)	1 (3)	1 (4)	1 (2)
	IC	6 (16)	7 (19)	3 (9)	3 (12)	3 (19)	3 (8)
	DS	1 (5)	1 (5)	0 (0)	0 (0)	0 (0)	1 (5)
3	IS	2 (5)	4 (10)	5 (12)	2 (6)	2 (8)	4 (10)
	IC	13 (34)	9 (24)	11 (34)	7 (28)	5 (31)	15 (39)
	DS	1 (5)	3 (15)	4 (21)	1 (11)	1 (12)	1 (5)
4	IS	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)
	IC	0 (0)	1 (3)	1 (3)	1 (4)	1 (6)	2 (5)
	DS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	IS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	IC	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)
	DS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total no.	IS	41	41	41	33	25	41
	IC	38	37	32	25	16	38
	DS	19	19	19	9	8	19

FU = follow-up; LAFU = last available follow-up.

* Values expressed as number (%).

The proportion of patients in the IS or DS group that was seizure free (ILAE Class 1) compared to that in the IC group was significantly different at † $p < 0.0001$, ‡ $p < 0.0005$, § $p < 0.005$, and ¶ $p < 0.05$.

FIG. 3. Chance of achieving complete seizure freedom over 5 years of follow-up after new-onset CRE. Patients underwent IS (solid line), DS (dotted line), or IC (dashed line) treatment.

no surgery). This led to a RR of 6.7 for IS versus IC (95% CI 2.6–17.3, $p < 0.0001$) and a RR of 6 for DS versus IC (95% CI 2.2–16.1, $p < 0.001$). The chance for a first drug trial failure over 5 years of follow-up after treatment start was 45% (95% CI 28%–60%) in the IC group. Among the different variables (lesion location, size of CCM, size of hemorrhage, patient age, type of seizures), only the diagnosis of a CCM-associated DVA correlated with the event of a first drug trial failure (correlation coefficient 0.370, $p < 0.05$; for complete analysis see Supplementary Tables). The risk for developing drug-resistant epilepsy was 16% (95% CI 14%–18%).

Functional Outcome

In the IS and DS groups, 9 patients (15%) had decreased scores by at least 1 point on the mRS at the time of discharge. At the 6-month follow-up, the condition of 4 patients (7%) was still deteriorated. At the 1-year follow-up, 2 patients (3%) still showed a decreased score on the mRS in comparison with the preoperative score; a decrease from an mRS score of 1 to a score of 2 occurred in both patients. At the last follow-up, functional scores remained

unchanged. Overall, long-term operative morbidity (defined as a decrease of a minimum of 1 point on the mRS at the 1-year follow-up) was 3%.

In the complete follow-up period, recurrent symptomatic hemorrhage (SH) or nonhemorrhagic focal neurological deficit (NH-FND) was observed in 3 patients (8%) in the IC group. In 2 patients, the SH or NH-FND occurred without a persistent change on the mRS. In 1 patient (3%), there was a persistent decrease of 2 points on the mRS; therefore, overall cavernoma-related morbidity in the IC group was 3%.

Postoperative Complications

Besides the aforementioned functional outcome results, the following postoperative complications were observed: transient motor deficit (3 [5%] of 60 surgical patients), transient dysphasia (2 [3%] of 60), wound infection (2 [3%] of 60, resolved without revision surgery), and epidural hematoma (1 [2%] of 60, revision surgery performed).

Hemosiderin Resection

In 47 patients, postoperative MRI was available and could be reviewed for hemosiderin remnants (23 personally reviewed by the first author, 24 based on medical reports from outside institutions). In 14 patients, MRI was suggestive of hemosiderin remnants. In 10 cases, the remnants were associated with a postoperative seizure burden. On the other hand, seizures occurred in 2 patients without MRI evidence of hemosiderin remnants. Statistical analysis showed a significant association between hemosiderin remnants and postoperative seizure burden (OR 38.75, 95% CI 6.14–244.23, $p < 0.0001$).

Discussion

This retrospective observational comparative study provides Class III evidence that initial surgical treatment in CCM patients with new-onset CRE seems to be more successful in completely controlling seizures (ILAE Class 1a) than conservative treatment during a 5-year follow-up (73% vs 22%, $p < 0.0001$). Regarding sustained (2 successive years of ILAE Class 1 at last follow-up) seizure freedom, similar results were found (88% vs 32%, respectively, $p < 0.0001$). Sustained seizure freedom is a clinically more robust seizure outcome than the often-used 1-year seizure freedom since AEDs are seldom withdrawn before 2-year seizure freedom in a patient is reached.^{3,19}

TABLE 3. AED medication over 5 years of follow-up*

Variable	Group	1-Yr FU	2-Yr FU	3-Yr FU	4-Yr FU	5-Yr FU	LAFU
On AED	IS	41 (100)	26 (63)†	18 (44)‡	10 (30)†	7 (28)§	9 (22)¶
	IC	38 (100)	35 (92)	26 (81)	19 (86)	14 (88)	35 (92)
	DS	19 (100)	15 (79)	13 (68)	5 (55)	4 (50)	8 (42)¶
Total no.	IS	41	41	41	33	25	41
	IC	38	37	32	25	16	38
	DS	19	19	19	9	8	19

* Values expressed as number (%).

The proportion of patients in the IS or DS group that was on AED treatment compared to that in the IC group was significantly different at † $p < 0.0001$, ‡ $p < 0.0005$, § $p < 0.005$, and ¶ $p < 0.05$.

Furthermore, at the last available follow-up, AED therapy was discontinued significantly more often in patients who had undergone surgical treatment than in those who had received conservative treatment (78% vs 8%, $p < 0.0001$). Patients who underwent surgery had a 6.7 times greater chance (RR 6.7, 95% CI 2.6–17.3, $p < 0.0001$) of staying completely seizure free and finally discontinuing AEDs than the conservatively treated patients. However, we must emphasize that no standardized AED discontinuation protocol was followed in this study. Therefore, differences in AED therapy may, in part, be explained by organizational and medico-legal factors (for example, fear of losing driving permit) rather than medical reasons.

Regarding functional outcome due to surgery-related morbidity or CCM-related morbidity, a worse (sustained over 2 years of follow-up) outcome in surgically treated patients, such as that reported in a recent prospective population-based study,²⁶ was not confirmed in our clinical study. While short-term morbidity (6 months after surgery) was higher in the surgically treated patients than overall morbidity in the conservatively treated group (7% vs 3%, $p = 0.4$), long-term morbidity (12 months after surgery) over the complete follow-up period was similar in both groups (3% vs 3%).

The influence of delayed surgical intervention on seizure outcome, meaning a longer duration of epilepsy and more seizure events prior to surgical treatment, could not be satisfactorily elucidated in this study. This is mainly attributable to the smaller group size and lower completeness of follow-up in the DS group, which hampered statistical analysis. Given the data available, it seems that DS intervention, as compared with IS treatment, does not worsen seizure outcome. However, the superiority in seizure outcome in the DS group compared with that in the conservatively treated group was less significant. Several previous observational studies found a negative correlation between seizure outcome and a longer duration of epilepsy;^{6,10,12,24} however, this finding was not confirmed in the largest multicenter observational study.⁵

While the risks of defined outcome events in CRE under different treatment approaches could be clearly outlined in this study, specific predictors of treatment failure could not be satisfactorily figured out. Among the tested variables, especially the location of CCM (temporal, temporomesial), no significant influence on any of the group results was found. Only the association of the CCM with a DVA showed a (modest) correlation with a first drug trial failure risk. Thus, parameters that may help to select patients for a specific treatment option cannot be proposed based on our results. However, an important finding regarding surgical treatment is that evidence of remnant hemosiderin deposits on postoperative MRI was significantly associated with postoperative seizure burden. This finding accords with data from a recent meta-analysis of 594 patients³⁰ and may actually help to select appropriate candidates for surgical treatment (complete hemosiderin resection possible). On the other hand, it argues for “early” surgical treatment before hemosiderin deposits enlarge in the surrounding brain tissue due to recurrent bleedings in “active” lesions.⁹

The strength of our study was its large sample size of

a specific (new-onset CRE, single CCM, sporadic disease) and clinically most relevant group of patients with CRE, as all previous comparative studies intermixed types of CCM (single, multiple, sporadic, familial) and types of epilepsy (new onset, chronic, intractable). We used well-defined treatment groups and a concurrent control group as well as annual surveillance over a long follow-up period with an acceptable overall completeness of follow-up of 83% ($\geq 85\%$ and prospective study design requested for evidence Level II studies⁸). Based on the Centre for Evidence-based Medicine levels of evidence criteria, the observed differences between the IS and IC groups, as well as, in part, the differences between the DS and IC groups, fulfill the definition of a dramatic effect.¹⁶

The main limitation of this study was the lack of a prospective design and randomization. We did not correct for baseline imbalances, especially for known potential predictors of outcome, as these were not found in between-group comparisons (Table 1). Established risk factors for the development of seizures are supratentorial versus infratentorial localization, cortical involvement versus exclusively subcortical involvement of a supratentorial CCM, and temporomesial versus exclusively neocortical involvement.²⁹ Main seizure outcome predictors are sex, age, seizure type, and duration of epilepsy.²⁹ Size of the CCM was associated with a better 2-year seizure outcome in one study; however, this finding was not confirmed during long-term follow-up.⁵ Despite the balance of the groups, of course the possibility of confounding remains. Generally, smaller group sizes, especially at the end of the follow-up period and because of the number of occurring seizure events and censoring, may lead to an overestimation of the 5-year seizure risks in all groups.

In a previously published systematic review,²⁶ we identified 3 comparative observational studies including more than 20 individuals and available in the English language to put our results in context. One study reported data on CRE exclusively in multiple (familial) CCMs.²¹ Patients with these lesions usually show a less favorable outcome and require a more thorough epileptological workup.²⁹ Furthermore, most of them harbor the familial form of the disease. Therefore, comparison with patients harboring single sporadic CCM with CRE is not constructive. The study by Fernández et al.¹³ revealed no difference in seizure outcome between surgical and medical treatments. However, the authors presented a rather inhomogeneous cohort. The mean preoperative duration of epilepsy was long at 40 months (range 0–376 months). Eight patients had multiple CCMs (4 in each treatment group). Moreover, group size was rather small (26 surgical, 17 medical treatment) and overall follow-up at 5 years was incomplete (32 of 43 patients, not further specified). Additionally, surgical morbidity (27%) was exceptionally high compared with previously reported results.^{10,24} From a methodological point of view, we believe the study to be at risk for bias. In accordance with our results, Noto et al.²⁷ reported better complete seizure control for patients undergoing surgical treatment and a higher proportion of patients that discontinued AED therapy. Although the study included patients with a long observation period (15 years), the data were retrospectively analyzed and the study sample size was

small (31 patients) and included inhomogeneous types of seizures (new-onset and intractable epilepsy). It was also judged to be at high risk for bias.²⁶

Overall, seizure outcome after surgical treatment in our study was better than that in, for example, the observational series of Baumann et al.,⁵ which presented patients with a longer mean duration of epilepsy undergoing lesionectomy (with or without amygdalohippocampectomy), showing only 48%, 43%, and 32% complete postoperative seizure freedom at the 1st, 2nd, and 3rd year of follow-up, respectively. In studies including patients with a short duration of epilepsy or “sporadic seizures,” however, complete postoperative seizure freedom ranged from 84% to 100%.^{6,10,13,33,36}

Unfortunately, data on postoperative AED therapy were not specified in several recent studies.^{5,12,17,32} For patients with their first or first few cavernoma-related seizure(s), AED therapy is recommended as their risk of developing epilepsy is very high.¹ The chance of discontinuing AED therapy, on the other hand, is reported to be rather low.¹³ One aim of surgical therapy, especially in early surgery candidates,²⁹ is therefore to achieve the withdrawal of all AEDs. It is especially important since most patients with CRE are rather young at the onset of seizures, most commonly in the 3rd decade.¹ Older metadata from Moran et al.²⁴ showed overall postoperative withdrawal of AED therapy in 39% of cases at the last follow-up. More recently, Fernández et al. reported 35% and 32% of cases of “nonrefractory” CRE at the 2nd and 5th year of follow-up, respectively.¹³ Specifically reporting on patients with short durations of epilepsy (< 12 months) and few seizures (1–5), Cappabianca et al.⁶ showed a better AED withdrawal rate of 62%.

Postoperative functional outcome data are not specified or are not specified according to reporting standards in most published studies. Persistent “mild neurologic deficits” in 8% of patients,⁵ permanent postoperative neurological deficit in 7%,³³ “complications” (aphasia, monoparesis, hemiparesis) in 13%,³⁶ and postoperative “neurological sequelae” in 27%¹³ were reported in 4 observational studies, indicating rather high operative morbidity. In all other studies cited in our paper, postoperative functional outcome was not further specified.

Conclusions

In summary, we present the largest comparative observational study on CRE including patients who were clinically most relevant. Epilepsy has a significant impact on patient health and quality of life,¹⁸ and AED therapy is not uncommonly associated with adverse effects.¹⁵ Until a randomized controlled trial investigates the effects of surgical and conservative treatment of CRE and provides superior evidence, results from the current study can be helpful in the counseling patients who present with sporadic CCM and new-onset CRE.

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Disclosures

Dr. Rosenow is a consultant for UCB, EISAI, cerbomed, Shire, and Sandoz and has received honoraria for presentations from Novartis, UCB, EISAI, Desitin, and cerbomed.

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Conception and design: Dammann, Mueller, Sure. Acquisition of data: Dammann, Neuschulte, Rosenow. Analysis and interpretation of data: Dammann, Neuschulte, Sure. Drafting the article: Dammann, Wrede, Jabbarli, Menzler, Zhu, Oezkan, Mueller, Forsting, Sure. Critically revising the article: Dammann, Wrede, Jabbarli, Menzler, Zhu, Oezkan, Mueller, Forsting, Rosenow, Sure. Reviewed submitted version of manuscript: Dammann, Wrede, Jabbarli, Neuschulte, Menzler, Zhu, Oezkan, Mueller, Rosenow. Approved the final version of the manuscript on behalf of all authors: Dammann. Statistical analysis: Dammann. Administrative/technical/material support: Dammann, Rosenow. Study supervision: Rosenow, Sure.

Supplemental Information

Online-Only Content

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