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Surgical resection of cavernous angioma located within eloquent brain areas: International survey of the practical management among 19 specialized centers

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ABSTRACT

Purpose: The practical management of cavernous angioma located within eloquent brain area before, during and after surgical resection is poorly documented. We assessed the practical pre-operative, intra-operative, and post-operative management of cavernous angioma located within eloquent brain area.
Method: An online survey composed of 61 items was sent to 26 centers to establish a multicenter international

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Outcome
Return to work

retrospective cohort of adult patients who underwent a surgical resection as the first-line treatment of a supratentorial cavernous angioma located within or close to eloquent brain area.
Results: 272 patients from 19 centers (mean 13.6 ± 16.7 per center) from eight countries were included. The pre-operative management varied significantly between centers and countries regarding the pre-operative functional assessment, the pre-operative epileptological assessment, the first given antiepileptic drug, and the time to surgery. The intra-operative environment varied significantly between centers and countries regarding the use of imaging systems, the use of functional mapping with direct electrostimulations, the extent of resection of the hemosiderin rim, the realization of a post-operative functional assessment, and the time to post-operative functional assessment. The present survey found a post-operative improvement, as compared to pre-operative evaluations, of the functional status, the ability to work, and the seizure control.
Conclusions: We observed a variety of practice between centers and countries regarding the management of cavernous angioma located within eloquent regions. Multicentric prospective studies are required to solve relevant questions regarding the management of cavernous angioma-related seizures, the timing of surgery, and the optimal extent of hemosiderin rim resection.

1. Introduction

Cavernous angioma (CA) is an uncommon neurovascular brain lesion with a prevalence ranging up to 0.9% in the general population [1,2]. Cavernous angioma can be revealed by headaches, neurological and/or cognitive deficits related to an hemorrhagic event (up to 25%), by epileptic seizures (up to 25%), or discovered incidentally on MR examination performed for another reason (up to 50%) [1,3,4]. Epileptic seizures are common events during the natural course of CA and may be drug-resistant. The high likelihood of developing epilepsy after a first seizure, in the presence of CA (5-year risk of epilepsy, 94%), requires antiepileptic drug therapy [3].

Guidelines state that early microsurgical resection is an effective and safe therapy that represents the gold standard first-line treatment for symptomatic CA with inherent risk of bleeding as well as with epileptic seizures [3]. For seizure control purpose, it is suggested that the CA should be completely resected, including, whenever feasible and safe, the surrounding epileptogenic brain tissue that encompasses the hemosiderin rim [5–7]. It is well-recognized that epileptic seizures related to CA arise from the cerebral cortex surrounding the CA and that seizures occur either due to expansion of the lesion and/or to hemorrhagic events. These hemorrhagic events lead to build-up of a hemosiderin ring which is also well-recognized to be epileptogenic. The surgical management of CA located near or within eloquent brain areas is challenging since both a CA-related hemorrhage and the surgery are associated with a high risk of neurological and cognitive deficits. This challenge is even more complex in patients with persistent seizures: resection of CA and peripheral hemosiderin rim should be considered while preserving neurological functions.

Although recommendations for management of CA-related epilepsy exist [3], the pre-operative evaluation is not standardized in the context of patients with a CA located within eloquent brain regions and requiring surgical resection [8–10]. The pre-operative investigation of CA-related epilepsy is very varied, with no cross-center standardization. Investigations include electroencephalography, dedicated visits by an epileptologist, positron emission tomography scanner, single-photon emission computed tomography, and stereo-electroencephalography [10]. Similarly, there is a variety of different intra-operative tools and techniques used by different centers, including intra-operative imaging (ultrasonography, MRI-based neuronavigation, MRI), intra-operative electrophysiological neuromonitoring (electrocorticography, motor evoked potentials, somatosensory evoked potentials), and intra-operative functional brain mapping at the cortical and subcortical levels using direct intra-operative electrostimulations under awake conditions [8,11–13]. The observed variability in pre-operative evaluation, in surgical techniques, and tools underlines the lack of standards.

In this study, we focused on the practical aspects of the surgical management of patients diagnosed with CA located near or within eloquent brain areas to identify points of consensus regarding the current and future best-practice in this field. This will help establish appropriate standards of care for the multidisciplinary treatment of CA.

2. Methods

2.1. Study design

We performed a multicenter international retrospective cohort analysis across all members of the European Low-Grade Glioma Network (ELGGN). Whilst CA are not diffuse low-grade glioma, the ELGGN is a well-established network of professionals with expertise in operating beside eloquent regions and working in units across Europe that also treat CA.

2.2. Setting

The recruitment period spanned from January 1999 to December 2016.

2.3. Data source

The inclusion criteria were: 1) histopathological diagnosis of CA; 2) CA supratentorial location within or close to eloquent brain region, as previously defined according to Sawaya et al [14]; 3) surgical resection as the first-line treatment of the CA; 4) available data regarding pre-operative evaluation; 5) available data regarding intra-operative management; 6) available clinical, imaging, functional data at diagnosis and during follow-up.

2.4. Data collection

Data were obtained from the medical records using a dedicated online form designed for the study. The form contained 61 items (see Supplementary Material 1) divided in pre-operative clinical and imaging findings, pre-operative evaluation, intra-operative management, post-operative clinical and imaging findings, and long-term post-operative follow-up. The form consisted of 25 single-choice items, 17 multiple-choice items, 18 items with quantitative answers, and one item was dedicated to free text answers.

Control of epileptic seizures was classified according to the Engel classification and the outcome classes of the International League Against Epilepsy (ILAE), with Engel Class 1a and ILAE Class I indicating complete seizure freedom [15,16]. Post-operative seizure assessment was made at 2-years from surgery, or sooner if longer-term data was absent.

The data were anonymized at collection and this study received required authorizations (CNIL, 2046650).

2.5. Statistical analysis

Results are expressed as mean ± standard deviation and range for

continuous variables, and as percentages for categorical variables. Some items were not answered by all centers and statistical analyses were performed based on the number of total respondents for each item.

Univariate analyses were carried out using the chi-square test or Fisher's exact tests for comparing categorical variables, and the unpaired *t*-test or Mann–Whitney rank sum test for continuous variables, as appropriate. A p value < 0.05 was considered statistically significant. To assess predictors of seizure and of seizure control, only variables associated at the $p < 0.2$ level in unadjusted analysis were then entered into backward logistic regression models. All statistical analyses were performed using JMP software (version 14.0.0, SAS Institute Inc, Cary, NC, USA).

3. Results

3.1. Baseline information

Twenty-six ELGGN centers were invited to participate and data was received from 19 centers (73%) in eight countries (Fig. 1). The majority of responding teams were based in an academic hospital (n = 15, 79%), whilst three (16%) were based in community hospitals, and one (5%) was located in a private hospital environment. Two hundred and

Table 1
Patients' distribution by participating center and country.

Country	Participating center	n	%
Belgium	Gand, St Lucas Hospital	48	17.6
Germany	Munich, University of Munich - Campus Grosshadern	19	7.0
	Munich, Technical University of Munich School of Medicine	70	25.7
Spain	Madrid, Hospital Universitario Quironsalud	5	1.8
	Santander, Marqués de Valdecilla University Hospital	6	2.2
France	Poitiers, La Milétrie University Hospital	18	6.6
	Paris, Pitié-Salpêtrière University Hospital	8	2.9
	Paris, Sainte-Anne Hospital	7	2.6
	Paris, Lariboisière University Hospital	7	2.6
	Marseille, Clairval Private Hospital	11	4.0
	Montpellier, Gui-de-Chauliac University Hospital	8	2.9
	Nice, Nice University Hospital	1	0.4
	Lille, Roger-Salengro University Hospital	1	0.4
Netherland	Amsterdam, VU University Medical Center	10	3.7
Italy	Milano, Humanitas Hospital	16	5.9
	Brescia, ASST Spedali Civili	8	2.9
	Trente, Azienda Provinciale per i Servizi Sanitari	5	1.8
Sweden	Gothenburg, Sahlgrenska Academy	12	4.4
USA	Chicago, Northwestern Memorial Hospital	12	4.4

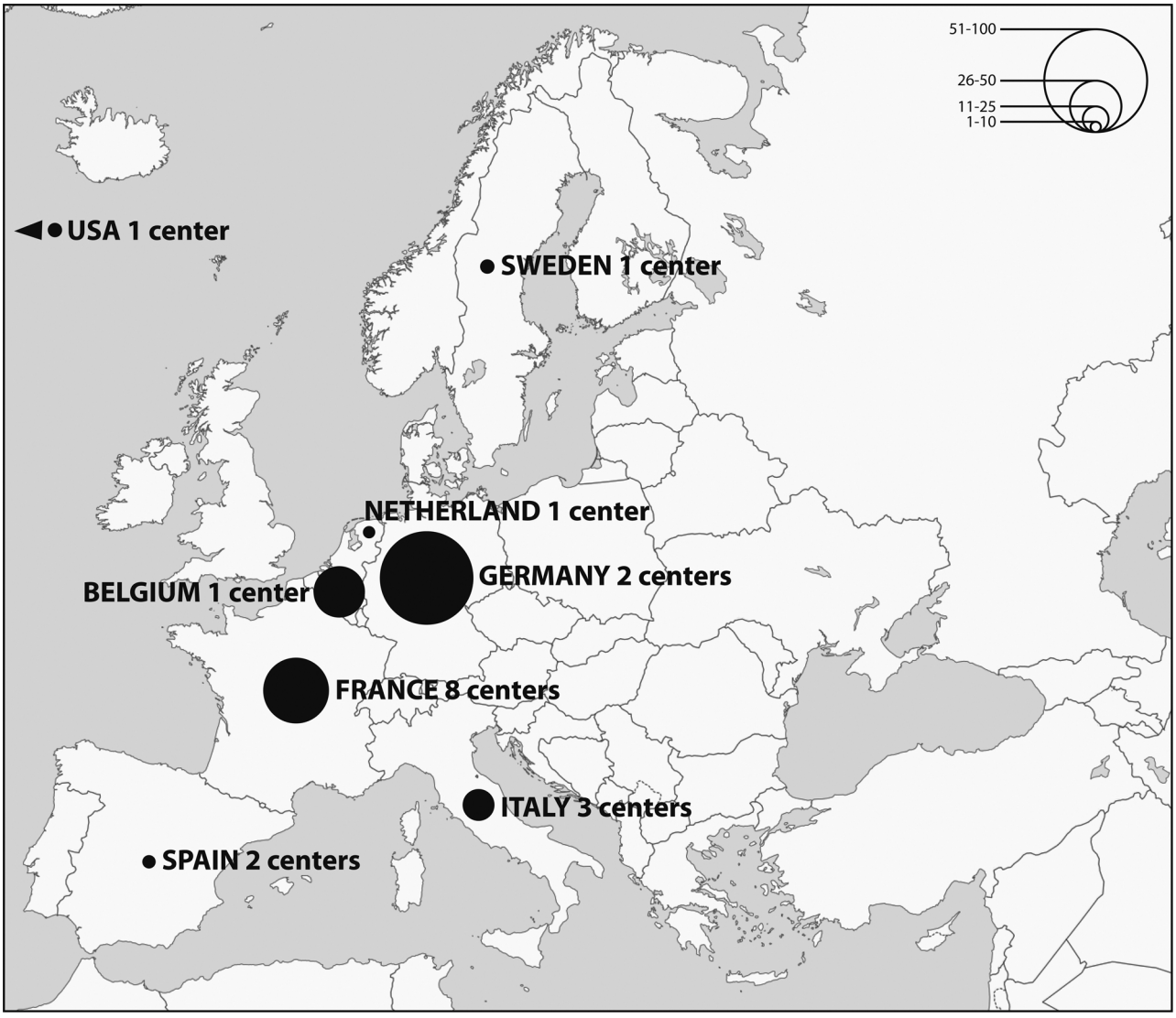

Fig. 1. Range graded proportional circle map of patient's country of origin. Ranges corresponding of circles' size are indicated in the upper-right corner.

Table 2
Main characteristics of the study sample (n = 272).

Parameters	Qualitative	n	%
Clinical characteristics			
Sex	Female	162	59.6
	Male	110	40.4
Past medical history	Previous brain radiotherapy	4	1.5
	Familial cavernomatosis	13	4.8
	Multiple cavernous angioma	27	9.9
Mode of revelation	Seizure	104	38.2
	Hemorrhage	90	33.1
	Seizure and hemorrhage	42	15.4
	Incidental	36	13.2
History of seizure at surgery	Yes	178	65.4
	No	94	34.6
Controlled seizures at surgery	Yes	114	41.9
	No	64	23.5
	No seizure	94	34.6
Focal neurological deficit at surgery	Yes	106	39.0
	No	166	61.0
Karnofsky Perfomance Status at surgery	≤70	28	10.3
	80	38	14.0
	90	98	36.0
	100	95	34.9
Ability to work at surgery	Yes	211	77.6
	No	61	22.4
Number of AED drug at surgery	0	79	29.0
	1	163	59.9
	> 1	30	11.0
Side of the cavernous angioma	Left	169	62.1
	Right	103	37.9
Location of the cavernous angioma	Frontal	95	34.9
	Temporal	58	21.3
	Parietal	48	17.6
	Insular	9	3.3
	Occipital	13	4.8
	Cingular	2	0.7
	Deep-seated	15	5.5
	Multilobar	32	11.8
Presence of a hemosiderin rim*	Yes	219	80.5
	No	53	19.5
Preoperative workup			
Preoperative functional assessment	None	116	42.6
	Cognitive evaluation	27	9.9
	fMRI	9	3.3
	Both cognitive evaluation and fMRI	120	44.1
Preoperative epileptological assessment	None	106	39.0
	EEG only	54	19.9
	Clinical evaluation + EEG	112	41.2
	Epileptogenic zone research∞	12	4.4
Intraoperative findings			
Neurosurgical tools	Imaging system	237	87.1
	Motor/somatosensory evoked potentials	58	21.3
	Electrocorticography	35	12.9
	Direct electrostimulations	158	58.1
Postoperative follow-up			
Resection of both cavernous angioma and hemosiderin rim	Complete	207	76.1
	Partial	65	23.9
Postoperative functional assessment	None	163	59.9
	Cognitive evaluation	43	15.8
	fMRI	0	0.0
	Both cognitive evaluation and fMRI	66	24.3
Epileptic seizure status at last follow-up (in the subgroup of 178 patients with seizures at surgery)	Controlled without AED	56	42.1
	Controlled with one AED	63	47.1
	Controlled with ≥ 2 AED	14	10.8
	Uncontrolled without AED	9	3.3
	Uncontrolled with one AED	23	8.5
	Uncontrolled with ≥ 2 AED	9	3.3
	Unknown	4	2.2
Number of AED at last follow-up	0	149	54.8
	1	100	36.8
	> 1	23	8.5
Karnofsky Perfomance Status at last follow-up	≤70	12	4.4
	80	22	8.1
	90	49	18.0
	100	189	69.5
Ability to work at last follow-up	Yes	241	88.6
	No	31	11.4
Functional worsening at last follow-up	No	237	87.1
	Yes	35	12.9
Quantitative parameters		**Mean**	**SD**
Age at cavernous angioma diagnosis (years)		38.4	15.2
Age at cavernous angioma surgery (years)		40.2	15.1
Time to surgery (months)		16.5	42.8
Cavernous angioma volume (cc)†		3.8	6.8
Hemosiderin rim volume (cc)*		5.0	9.0
Mean duration of surgery (min)		191.1	75.3
Time to post-operative cognitive assessment (months)		3.8	3.6
Mean post-operative follow-up		20.4	25.1

AED: anti-epileptic drug; MRI: Magnetic Resonance Imaging.
∞ PET-Scan, SPECT, SEEG.
† on T1-weighted sequence.
* on T2*-weighted sequence.

seventy-three patients were screened. We excluded one patient (0.4%) from the cohort due to lack of clinical data. A total of 272 cases were available for full analyses with a mean 13.6 ± 16.7 patients (range, 1–70) included per center during the study period. The distribution of patients by participating center and country is detailed in Table 1.

3.2. Clinical and imaging presentation

Clinical and imaging findings of the 272 patients (male, 40.4%) are detailed in Table 2. The mean age at surgery was 40.2 ± 15.1 years (range, 6–80). Concerning the past medical history, four patients (1.5%) had previous brain radiotherapy, 13 patients (4.8%) had a history of familial cavernomatosis, and 27 patients (9.9%) harbored multiple CAs (including nine patients with a history of familial cavernomatosis). The CA was diagnosed following a symptomatic hemorrhage in 132 cases (48.7%), which caused a focal neurological deficit in 85 cases, headaches in 58 cases, and epileptic seizures in 42 cases. The CA was diagnosed following epileptic seizures in 146 cases (53.9%), which included the 42 cases with a seizure related to an acute hemorrhage. The CA was discovered incidentally in 36 cases (13.3%). The mean Karnofsky Performance Status (KPS) was 89.3 ± 11.6 (range, 40–100) with 89.2% of patients with a KPS > 70. 22.7% of patients were unable to work at the time of surgery due to their CA-related condition. At the time of surgery, 178 patients (65.4%) experienced a CA-related epilepsy (unique epileptic seizure in 28.7%, repeated seizures in 36.7%), of whom 64 (36.0%) had uncontrolled epileptic seizures despite one antiepileptic drug in 20.0% of cases and despite two or more antiepileptic drugs in 80.0% of cases. A frontal location of the CA (adjusted Odds Ratio (aOR), 2.82 (95% Confidence Interval (CI), 1.57–5.02), $p < 0.001$) and a temporal location of the CA (aOR, 2.48 (95%CI, 1.29–4.77), $p = 0.006$) were independently associated with epileptic seizures at the time of surgery. The time interval from CA diagnosis to surgery (aOR, 1.04 per unit (months) (95%CI, 1.02–1.07), $p < 0.001$) was the only independent predictor associated

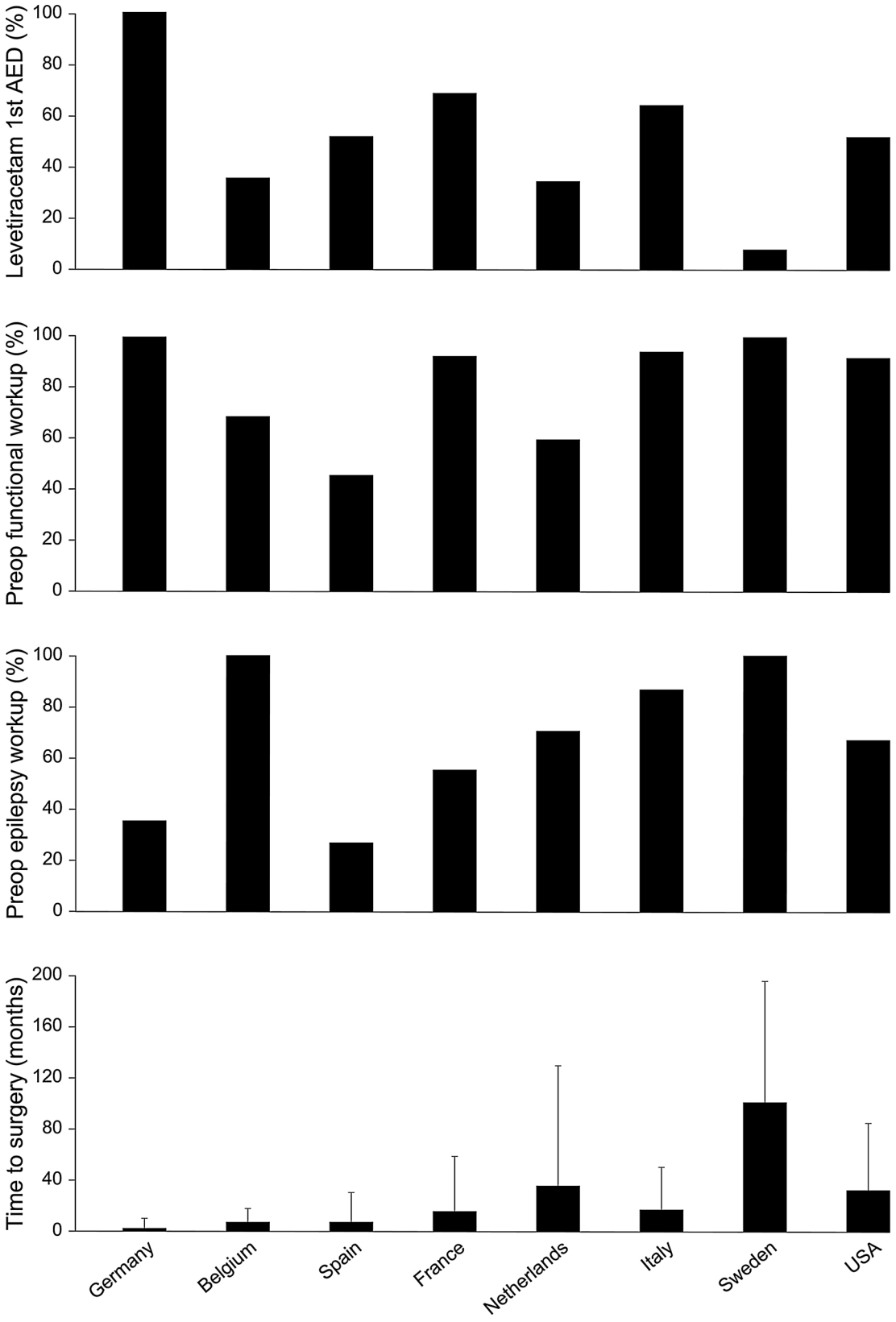

Fig. 2. Distributions of pre-operative characteristics by patient's country of origin. From top to bottom: percentage of Levetiracetam use as the first delivered antiepileptic drug; percentage of realization of a dedicated pre-operative functional workup; percentage of realization of a dedicated pre-operative epilepsy workup; and delay between surgery and diagnosis (months).

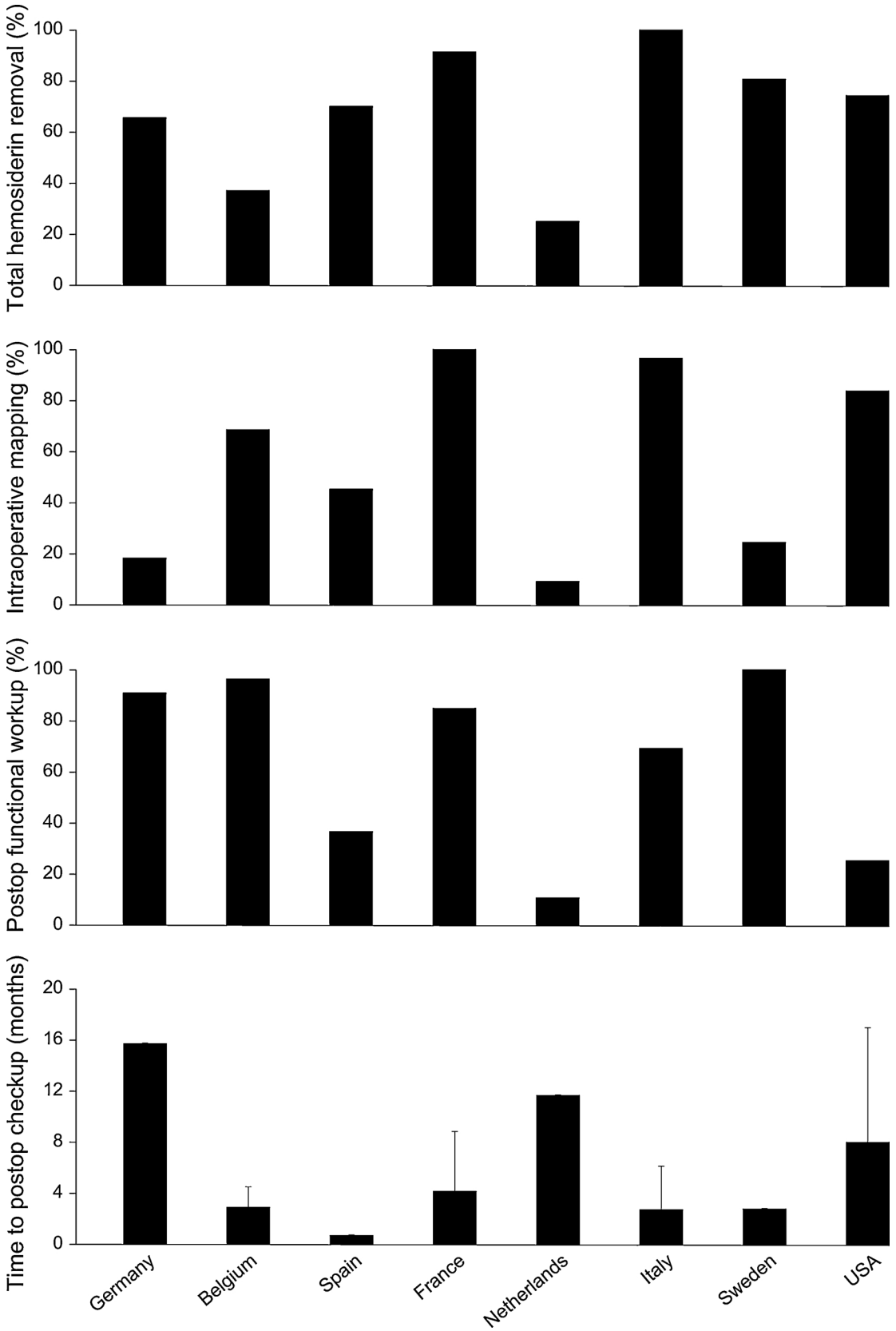

Fig. 3. Distributions of intra-operative and postoperative characteristics by patient's country of origin. From top to bottom: percentage of total resection of peripheral hemosiderin rim: percentage of use of intra-operative mapping (cortico-subcortical functional mapping using direct electrostimulation technique under awake condition or cortical mapping under general anesthesia); percentage of realization of a dedicated postoperative functional workup; and delay between surgery and postoperative functional workup (months).

with uncontrolled epileptic seizures at the time of surgery. The first-line antiepileptic drug varied, with Levetiracetam administered in 64.6% of cases, Valproic Acid administered in 8.5% of cases, Lamotrigine administered in 8.5% of cases, Carbamazepine administered in 7.4% of cases, the remaining 11.0% comprising 10 other antiepileptic drugs. The first-line antiepileptic drug varied significantly by country ($p < 0.001$) but not by center ($p = 0.945$). Giving Levetiracetam as the first-line antiepileptic drug varied significantly by center ($p < 0.001$) and by country ($p < 0.001$) (Fig. 2).

The CAs were mainly located in the left hemisphere (169 patients, 62.1%) and in the frontal lobe (112 patients, 41.2%). The mean CA volume on T1-weighted sequence was 3.8 ± 6.8 cc (range, 0.1–48) and the mean hemosiderin volume beyond CA on T2*-weighted sequence, which was present on 85.5% of cases, was 4.9 ± 0.0 cc (range, 0–64).

3.3. Pre-operative workup

Beyond basic clinical and imaging routine evaluations, pre-operative functional assessment was obtained in 156 patients (57.4%), comprising a cognitive function evaluation only in 17.3%, a functional MRI only in 5.8%, and both a cognitive function evaluation and a functional MRI in 76.9%. The pre-operative functional assessment varied significantly between centers ($p < 0.001$): no evaluation from 0% to 100%, a cognitive function evaluation only from 0% to 91.7%, a functional MRI only from 0% to 50%, and both a cognitive function evaluation and a functional MRI from 0% to 100%. The pre-operative functional assessment varied significantly between countries ($p < 0.001$) (Fig. 2): no evaluation from 0% to 94.4%, a cognitive function evaluation only from 0% to 91.7%, a functional MRI only from 0% to 50%, and both a cognitive function evaluation and a functional MRI from 5.6% to 77.1%.

A dedicated pre-operative epilepsy assessment was organized in 166 patients (61.5%), comprising an electroencephalographic (EEG) evaluation only in 67.5%, and both EEG evaluation and an epilepsy clinical evaluation in 32.5%. A dedicated pre-operative epilepsy assessment was performed more frequently in patients with a history of epileptic seizures at the time of surgery (65.7% Vs. 53.3%, $p = 0.047$) and more frequently in patients with uncontrolled seizures at the time of surgery (65.4% Vs. 57.1%, $p = 0.007$). The pre-operative epilepsy assessment varied significantly between centers (0%–100%, $p < 0.001$), and between countries (27.3%–100%, $p < 0.001$) (Fig. 2). Of note, 12 patients underwent specialized investigation of the epileptogenic zone following the initial epilepsy assessment with, at least one of the following: Positron Emission Tomography scan, Single-Photon Emission Computed Tomogram, and/or Stereo-EEG. The epileptogenic zone assessment varied significantly between centers (0%–27.3%, $p = 0.003$), and between countries (0%–27.3%, $p = 0.012$).

The mean time interval from diagnosis to surgery was 15.5 ± 42.2 months (range, 0–312). The median time to surgery varied significantly between participating centers (from 0 to 30.5 months, $p < 0.001$), and between participating countries (from 1 to 81 months, $p < 0.001$) (Fig. 2). The time interval from diagnosis to surgery was longer in patients with uncontrolled seizures at the time of surgery (mean, 49.2 ± 75.1 months vs. 7.5 ± 15.4 months, $p < 0.001$) and in patients who had a dedicated pre-operative epileptological assessment (mean, 22.9 ± 52.6 months vs. 7.1 ± 18.3 months, $p < 0.001$).

3.4. Intra-operative findings

The mean duration of the surgical procedure was 191.1 ± 75.3 min (range, 65–478). The neurosurgeon used intra-operative imaging and/or navigation in 91.5% - including ultrasound alone in 6.3%, MRI-based neuronavigation alone in 61.6%, and both ultrasonography and MRI-based neuronavigation in 32.1%. Other intra-operative tools included motor and/or somatosensory evoked potentials in 27.0%, intra-operative electrocorticography in 13.5%, and intra-operative functional mapping with direct electrostimulation in 58.1% - including awake craniotomy in 66.5%, with cortical mapping in 88.4% and subcortical mapping in 87.1%. Awake craniotomy was performed according to an asleep-awake-asleep protocol in all centers. The neurosurgical intra-operative setup varied significantly between centers and between countries: the use of intra-operative imaging system varied significantly between centers (0% to 100%, $p < 0.001$), and between countries (10% to 100%, $p < 0.001$), the use of intra-operative functional mapping with direct electrostimulations varied significantly between centers (0% to 100%, $p < 0.001$), and between countries (10% to 100%, $p < 0.001$) (Fig. 3). Of particular interest, when studying the intra-operative functional mapping with direct electrostimulations subgroup, we observed a clear-cut distribution of the use of the awake craniotomy or full anesthetic ("asleep") only condition: all but three centers from two countries used awake craniotomy with direct electrostimulation for all cases for intra-operative functional mapping, with the remaining 3 centers using full general anesthesia only for all their cases.

3.5. Postoperative follow-up

On postoperative imaging, the CA was totally removed in 264 cases (97.8%) and partially resected in the remaining 6 cases (2.2%). The hemosiderin rim was totally removed in 154 cases (71.0%) and partially resected in 63 cases (29.0%), Data was incomplete for two cases. The extent of resection of the CA did not vary significantly between centers ($p = 0.695$) or between countries ($p = 0.244$) but the extent of resection of the hemosiderin rim varied significantly between centers (0%–100%, $p < 0.001$), and between countries (25%–100%, $p < 0.001$) (Fig. 3). A complete removal of the hemosiderin rim was more frequently observed if surgery involved functional brain mapping (76.9% Vs. 63.5%, $p = 0.032$). This was even better when awake craniotomy techniques were used for functional brain mapping (87.8% Vs. 53.8%, $p < 0.001$).

The mean post-operative follow-up was 20.4 ± 25.1 months (range, 0–180), with 72.8%, 57.7%, and 30.5% of patients with a post-operative follow-up at ≥6 months, ≥12 months, and ≥24 months, respectively. At last follow-up, the mean KPS was 94.5 ± 9.5 (range, 50–100) with 95.2% of patients with a KPS > 70, and 11.8% of patients remained unable to work due to their CA-related condition. During the post-operative follow-up, a dedicated functional assessment was organized in 79.4% patients, at a mean 3.8 ± 3.6 post-operative months (range, 1–24). This comprised a cognitive function evaluation alone in 39.4%, and both a cognitive function evaluation and a functional MRI in 60.6%. The post-operative functional assessment varied significantly between centers (0%–100%, $p < 0.001$), and between countries (10%–100%, $p < 0.001$) (Fig. 3).

At last follow-up, of the 178 patients who experienced a CA-related epilepsy at surgery, 133 (74.7%) became seizure-free following surgery, with 56 (31.5%) off all anticonvulsant drugs (Engel Class 1a and ILAE outcome class I), 63 (35.4%) on a single anticonvulsant, and a remaining 14 (7.9%) on two or more anticonvulsants – percentages calculated as percent of overall cohort with pre-operative seizures. Forty-one patients (23.0%) continued to have uncontrolled epilepsy – of these, 9 (5.1%) were not on any anticonvulsant therapy, 23 (12.9%) were on single-drug therapy, and 9 (5.1%) were taking two or more anticonvulsants. Epilepsy seizure control was unknown for 4 patients (2.2%). 82.1% of patients with uncontrolled seizures pre-operatively had a better seizure control post-operatively (from uncontrolled pre-operatively to control post-operatively) when the hemosiderin rim resection was not limited at the cortical level as compared to 66.7% when the hemosiderin rim resection was limited at the cortical level due to the involvement of eloquent cortical areas, without reaching statistical significance ($p = 0.311$). Similarly, 81.8% of patients with uncontrolled seizures pre-operatively had a better seizure control post-operatively (from uncontrolled pre-operatively to control post-operatively) when a

complete resection of the hemosiderin rim was achieved as compared to 71.4% when only a partial resection of the hemosiderin rim was achieved, without reaching statistical significance (p = 0.348). At last follow-up, 71 of the 178 patients who had a diagnosis of CA-related epilepsy at surgery had ≥24 months post-operative follow-up (n = 71). Of these 71 patients, a total of 54 (76.1%) were seizure free, with 18 (25.4%) off all anticonvulsant drug therapy (Engel Class 1a and ILAE outcome class I), 30 (42.3%) on a single anticonvulsant, and a remaining 6 (8.5%) on two or more anticonvulsants. Fourteen patients (19.7%) continued to have uncontrolled epilepsy; of these, 9 (5.1%) were on single-drug therapy, and 6 (8.5%) were taking two or more anticonvulsants. Epilepsy seizure control was unknown for 3 patients (4.2%).

4. Discussion

4.1. Key results

The present study highlights differences in the management across centers and countries and allows several observations to be drawn: 1) the surgical removal of a CA located within or close eloquent brain area is a rare event; 2) there is a varying practice regarding the pre-operative and post-operative functional and epilepsy workups, with a higher frequency of pre- and post-operative functional assessment undertaken in centers that perform functional-based resections using intra-operative brain mapping under awake conditions; 3) there is a varying practice regarding AED therapy management, the first-line AED varies between centers, with Levetiracetam the first-line AED in 64.6% of centers; 4) there is a varying practice regarding the intra-operative management with varying surgical techniques and tools leading to varying surgical goals; 5) the extent of resection of the hemosiderin rim varies between centers and between countries; 6) surgical resection of CA resulted an overall improvement of the functional status and an increase in the number of patients able to work postoperatively as compared to before surgery; and 7) following surgery, there is an improvement in rates of seizure control which appear to be well-maintained at 24-months follow-up.

4.2. Surgical management of a CA located within eloquent brain areas

This multi-center study comprises a large series of 272 cases of CA located within or close to eloquent brain areas (brainstem location excluded). The following outcomes were observed at last follow-up: improved functional independence following surgery (95.2% post-operatively vs. 89.2% pre-operatively); fewer patients unable to work (11.8% post-operatively vs. 22.7% pre-operatively); and an improvement in the rate of epileptic seizure control at last follow-up (74.7% post-operatively vs. 52.8% pre-operatively). No episode of CA-related bleeding was observed post-operatively.

These promising outcomes supports current recommendations that indicate surgery as the first-line treatment for CA with pharmacoresistant seizures and / or inherent risk of bleeding [3,17–19], with thorough counselling about surgical risks [20]. However, in the subgroup of asymptomatic, incidental CA, the surgical decision has to be carefully weighed, balancing the risks (bleeding, seizure, surgical risks) together with the patient's wishes and expectations. Aiming to reduce the surgical risks, intra-operative functional brain mapping with direct electrical stimulation under awake conditions is increasingly proposed for CAs [8,10,11,21]. Given the fact that the awake brain mapping can be easily associated with the other technological resources and surgical tools, including intra-operative MRI, the combination of these approaches seems promising [22]. In addition, patients operated on using awake brain mapping techniques were more frequently assessed with pre- and post-operative cognitive and functional assessments than patients operated upon under full general anesthesia. Such cognitive evaluation is of great importance since it offers an accurate evaluation of the pre- and post-operative patient status, allows a better understanding of neurological and functional impairments, and guides the post-operative rehabilitation [23,24].

4.3. Management of CA-related epileptic seizures

An initial conservative approach is usually favored in the setting of controlled seizures, especially for CA located close to or within eloquent brain areas [3]. Recommendations have been made regarding the choice of which AED therapy should be introduced following epileptic seizures related to an enduring brain lesion [25,26]. The present results emphasized the lack of homogeneity in the first-line AED choice. This may be explained by the particular clinical details of each case, by varying practices among centers, and by varying practice and AED availability during the long period of recruitment. Such heterogeneity also exists for the pre-operative epilepsy assessment. Although detailed pre-operative epilepsy workup was performed more frequently in patients with a history of seizures and with uncontrolled seizures, there was no standardization and no common pre-operative epilepsy workup - some teams performed detailed epilepsy evaluation whereas others did not even perform a pre-operative scalp EEG, in contradiction with guidelines [3]. This finding strongly supports the case for developing practical guidelines regarding AED treatment and pre-operative epilepsy evaluation for each patient with CA-related epilepsy.

In addition, the timing of surgery varied markedly, highlighting varying practices in the decision to propose surgery. One should keep in mind that the duration of the pre-operative epilepsy is a strong risk factor for post-operative uncontrolled seizures in patients harboring a CA-related epilepsy [10,27] and that AED treatment does not address the underlying etiology of epilepsy [28]. This is illustrated in this series, where patients with uncontrolled seizures at the time of surgery had a longer time-interval from diagnosis to surgery than patients with controlled seizures at the time of surgery or without a history of epilepsy. Altogether with the promising post-operative results, early resection of the CA should be proposed for seizure control purposes with careful pre-operative workup. For patients with pharmaco-resistant epilepsy, the workup should also include invasive monitoring [29].

The extent of resection for seizure control purposes is another matter of debate. There is an increasing body of literature supporting the possible positive impact of hemosiderin rim resection in controlling epileptic seizures [5–7,10]. We observed that the extent of resection of the hemosiderin rim varied markedly in this series, suggesting a different philosophy among centers and countries between a pure lesionectomy and an extended resection reaching eloquent boundaries to achieve seizure control. In this way, a complete removal of the hemosiderin rim was observed more frequently when surgery involved intra-operative functional brain mapping, predominantly using the awake craniotomy techniques. This suggests that awake craniotomy should be offered for CA located in or near eloquent brain areas to provide enable to the neurosurgeon to achieve the optimal extent of hemosiderin rim resection [30]. Since preliminary reports suggest that there is no difference in terms of complication rates, functional-based maximal resection of the hemosiderin rim surrounding the CA should be planned for seizure-control purposes [10].

4.4. Generalizability and limitations

This study had several limitations: 1) the retrospective online survey limits the accuracy of the given statements and the representation of a multidisciplinary team cannot be guaranteed, which limits the reliability of the results; 2) participants were not asked to detail how any disagreements were balanced in their own center, precluding analysis of response heterogeneity at the center level; 3) the retrospective data collection design makes recruitment bias possible, and lacks blinding and a control group; 4) although the large number of involved centers (n = 19) and of patients (n = 272) from different countries represent

the major strength of this study, the varying number of patients per center, the low number of patients per center as a mean, and the long period of recruitment with many surgical techniques create difficulties in the determination of common practice; 5) all participating centers are members of the ELGGN with a particular experience in surgical management of brain lesions, and the present results may not necessarily be translated to the whole neurosurgical community; 6) since all patients in this study were treated with surgical resection, we have no data on the long-term natural history of eloquent-region CA managed conservatively and the present study cannot address the specific indications for surgery for CA located in or near eloquent brain areas.

As a consequence, these findings should be interpreted in the light of the exploratory nature of these analyses and should be validated within other prospective large databases. Multi-center studies are required to provide definite answers to clinical relevant questions particularly regarding the management of CA-related seizures, such as the first-line AED, the timing of surgery, the indication of a comprehensive epilepsy evaluation, the extent of the resection encompassing, or not, the hemosiderin rim [9,31].

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Ethical publication statement

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.

Author contribution

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MZ and JP did the data analysis.

MZ, BM, MS, JG, HC, CS, LB, MW, AS, BR, MT, PM, PCWH, GS, LC, EM, SGR, SS, JMG, DF, NR, SK, GH, MW, DC, ER, BN, PM, NY, MR, MCN, CP, VV, HB, LG, FC, CB, AR, ED, HD, and JP did the data interpretation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.03.022

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