

## Resective Epilepsy Surgery and Respective Histopathological Diagnoses: A Retrospective Cohort Study

### Cirurgia de Epilepsia Ressectiva e Respetivos Diagnósticos Histopatológicos: Estudo de Coorte Retrospectivo

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Acta Med Port 2023 Apr;36(4):229-235 ▪ <https://doi.org/10.20344/amp.18712>

#### ABSTRACT

**Introduction:** Over recent decades, brain resection for drug-resistant epilepsy has proven to be a valuable treatment option. The histopathological classification was of paramount value for patient management. The aims of this study were to characterize our resective epilepsy surgical series including the histopathological diagnoses and to understand the differences in clinical practice between two different periods of our epilepsy surgical programme.

**Material and Methods:** We performed a retrospective cohort study, including patients with drug-resistant epilepsy that underwent resective surgery between 1997 and 2021 in the Coimbra University Hospital Centre. Histopathological diagnoses were classified into seven major conventional categories. For comparison purposes, the cohort was divided into two consecutive periods of 12 years.

**Results:** A total of 259 patients were included, from which 228 (88%) were adults at the time of surgery. The median disease duration prior to surgery was 14 (interquartile range 23) years. Fifty-five (21%) patients performed pre-surgical invasive work-up. The temporal lobe was the most frequently operated region (73%). Major and minor post-surgical complications were identified in 21 (8%) patients. A reduction in the number of antiepileptic drugs was possible in 96 (37%) patients after surgery. The most common histopathological diagnosis was hippocampal sclerosis, but among children it was long-term epilepsy associated tumour. Long-term epilepsy associated tumours, hippocampal sclerosis and vascular malformations had the best post-operative outcomes. Malformations of cortical development and glial scars had the worst outcomes. Regarding differences between the two periods, the absolute number of operated patients increased (119 *versus* 140), and the age at surgery was higher in the second period ( $p = 0.04$ ). The number of malformations of cortical development increased ( $p = 0.01$ ), but the number of other tumours ( $p = 0.01$ ) and specimens with no lesion ( $p = 0.03$ ) decreased in the same period.

**Conclusion:** This study is in line with contemporaneous research, reinforcing the previous knowledge on the underlying structural aetiologies, clinical practice, and surgical outcomes over more than two decades of experience. Our data provide realistic expectations about epilepsy surgery and highlight the need for further improvements in diagnosis and treatment paradigm for people with chronic epilepsy.

**Keywords:** Epilepsy/pathology; Epilepsy/surgery; Neurosurgical Procedures

#### RESUMO

**Introdução:** Nas últimas décadas, a cirurgia ressectiva demonstrou ser uma opção valiosa no tratamento da epilepsia farmacorresistente. A classificação histopatológica foi de grande importância na orientação do doente. Os objetivos deste estudo foram caracterizar a nossa série de cirurgia de epilepsia ressectiva incluindo os diagnósticos histopatológicos, e compreender as diferenças na prática clínica entre dois períodos diferentes do programa de cirurgia da epilepsia.

**Material e Métodos:** Realizou-se um estudo de coorte retrospectivo, incluindo doentes com epilepsia farmacorresistente submetidos a cirurgia ressectiva entre 1997 e 2021 no Centro Hospitalar e Universitário de Coimbra. Os diagnósticos histopatológicos foram classificados em sete categorias. Para análise comparativa, a coorte foi dividida em dois períodos consecutivos de 12 anos.

**Resultados:** Um total de 259 doentes foram incluídos, sendo 228 (88%) adultos aquando da cirurgia. A mediana da duração da doença antes da cirurgia foi de 14 (amplitude interquartil 23) anos. Cinquenta e cinco (21%) doentes realizaram investigação invasiva pré-cirúrgica. O lobo temporal foi a região mais frequentemente operada (73%). Complicações pós-cirúrgicas *major* e *minor* foram identificadas em 21 (8%) doentes. Uma redução no número de anti-epilépticos foi observada em 96 (37%) doentes após a cirurgia. O diagnóstico histopatológico mais comum foi a esclerose do hipocampo, mas nas crianças foi o tumor associado a epilepsia de longa duração. Tumores associados a epilepsia de longa duração, esclerose do hipocampo e malformações vasculares tiveram os melhores resultados pós-operatórios. Malformações do desenvolvimento cortical e cicatrizes gliais tiveram os piores resultados. Relativamente às diferenças entre os dois períodos, o número absoluto de doentes operados aumentou (119 *versus* 140), e a idade aquando da cirurgia foi maior no segundo período ( $p = 0,04$ ). O número de malformações do desenvolvimento cortical aumentou

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**Recebido/Received:** 14/06/2022 - **Aceite/Accepted:** 30/08/2022 - **Publicado Online/Published Online:** 15/09/2022 - **Publicado/Publicado:** 03/04/2023

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( $p = 0,01$ ), mas o número de outros tumores ( $p = 0,01$ ) e amostras sem lesão ( $p = 0,03$ ) diminuiu no mesmo período.

**Conclusão:** Este estudo está de acordo com a literatura atual, reforçando o conhecimento prévio sobre as etiologias estruturais, prática clínica e resultados cirúrgicos ao longo de mais de duas décadas de experiência. Os dados analisados fornecem expectativas realistas sobre a cirurgia de epilepsia e destacam a necessidade de melhorias no paradigma de diagnóstico e tratamento destes doentes.

**Palavras-chave:** Epilepsia/cirurgia; Epilepsia/patologia; Procedimentos Neurocirúrgicos

## INTRODUCTION

Resective epilepsy surgery was first introduced in the late 19th century, but the modern approach including electroencephalogram (EEG) was developed in the 1940s.<sup>1,2</sup> Currently, resective epilepsy surgery is an established treatment option for carefully selected drug-resistant focal epilepsies in children and adults, supported by an ever-growing number of surgical series,<sup>3-6</sup> and a few randomized controlled trials.<sup>7-9</sup> Epilepsy surgery has also proved its value in other domains, namely quality of life and productivity.<sup>10,11</sup> Based on the reported results, an early referral to tertiary centres that offer comprehensive evaluation, and surgery, if indicated, has been recommended.<sup>3,12</sup>

Recent progress in the pathologic diagnosis and classification of epileptogenic brain lesions was helpful for clinical correlation, outcome stratification, and patient management.<sup>13</sup> Histopathological diagnosis is an important prognostic factor for outcome of epilepsy surgery.<sup>14</sup> The European Epilepsy Brain Bank (EEBB) was established in 2006 under the direction of the Framework Program of the European Union to standardize histopathological reporting of specimens obtained from epilepsy surgery.<sup>15</sup> International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue<sup>13</sup> and consensus classifications of specimens obtained during epilepsy surgery<sup>16-18</sup> contributed to an improvement in diagnosis reliability.

Over the last few decades, there have been advances in epilepsy knowledge and the practice of epilepsy surgery has been developed and refined.<sup>5,19-21</sup> Previous large studies have analysed the trends in presurgical evaluation and surgical treatment of epilepsy over time, conveying all the experience regarding clinical data, invasive brain recordings, surgical techniques, etiological groups, and outcomes.<sup>3,4,22,23</sup>

With this study, our first goal was to perform a clinical characterization of patients that underwent resective surgical treatment for drug-resistant focal epilepsy at a reference centre in our country, including the respective histopathological findings. Secondly, we analysed the differences in clinical practice between two different periods of our epilepsy surgical programme. Our study provides relevant data on epilepsy surgery practice over more than 20 years of experience, which may contribute to the understanding of how clinical trends evolved over time and also to the improvement of epilepsy care.

## MATERIAL AND METHODS

We performed a retrospective cohort and single-centre study. Patients with a diagnosis of drug-resistant epilepsy, according to the consensus proposal by the *ad hoc* Task Force of the International League Against Epilepsy (ILAE) Commission on Therapeutic Strategies,<sup>24</sup> that underwent resective epilepsy surgery in the Coimbra University Hospital Centre in the period between 1997 and 2021, were included. Before surgery, all patients performed pre-surgical evaluation in the Epilepsy and Sleep Monitoring Unit, with a detailed non-invasive workup and invasive study when necessary. The histopathological diagnoses were executed by an experienced neuropathologist based on light-microscopic inspection of paraffin-embedded tissue stained with haematoxylin and eosin, and additional histochemical stains or immunohistochemical techniques when indicated, according to international recommendations.<sup>13</sup> A histopathological diagnosis of hippocampal sclerosis was assumed as a segmental neuronal cell loss in anatomical sectors of the *cornu ammonis* of the hippocampus, as specified in the consensus classification of the ILAE.<sup>16</sup> Brain tumours were classified according to the 2021 World Health Organization (WHO) classification of tumours of the central nervous system.<sup>25</sup> Focal cortical dysplasia was defined based on the consensus classification system of the ILAE.<sup>17</sup> Histopathological diagnoses were classified into seven major conventional categories [hippocampal sclerosis (HS), malformation of cortical development (MCD), long-term epilepsy associated tumour (LEAT), other non-LEAT tumours (OT), vascular malformation (VM), glial scar (GS), and no lesion].

We included both adults and children (defined as patients whose age was under 18 years of age) with available histopathological diagnoses. A minimal dataset of clinical variables was collected from clinical records, encompassing gender, patient's age at the onset of epilepsy, patient's age at the time of surgery, duration of epilepsy before surgery (with dates rounded to whole year numbers), location of the lesion [frontal, temporal, parietal, occipital, multilobar (including hemispheric)], side of lesion, year of surgery, type of surgery, post-surgical complications, histopathological diagnosis, and post-operative outcomes (evaluated by Engel Classification<sup>26</sup>) at one year ( $n = 257$ ) and three years ( $n = 229$ ) after surgery. For patients that underwent more than one resection, we only included clinical data and histopathological diagnoses from the last surgical procedure.

Descriptive statistics for categorical variables were presented as total number (with corresponding percentage). For quantitative variables, the normality assumption was formally evaluated by the Kolmogorov–Smirnov test or Shapiro-Wilk test, depending on sample size. Variables with normal distribution were described using means [and standard deviations (SD)], whereas non-normally distributed variables were reported using medians [and interquartile ranges (IQR)]. Comparisons between groups were performed with the independent samples t-test, for normally distributed continuous variables, and the Mann-Whitney U test, for non-normally distributed continuous variables. To assess the association between categorical variables the chi-square test was employed. Regarding effect sizes, Cohen's d was applied for independent samples t-test and odds-ratio (OR) for chi-square test. For Mann-Whitney U test, effect size (r) was calculated dividing the z value for the square root of observation number. The descriptive analysis and hypothesis testing were performed using IBM SPSS® Statistics software (version 25).

This study was approved by the Ethics Committee of the local institution. It followed the principles of the Declaration of Helsinki 2013, national legislation for clinical research and good clinical practice norms (ICH-GCP).

## RESULTS

### Total cohort

A total of 259 patients underwent resective surgery. At the time of surgery, 228 (88%) patients were adults and 31 (12%) were children. Demographic and clinical data are summarized in Table 1. The median number of antiepileptic drugs (AEDs) tried prior surgery was three (IQR 2). Fifty-five (21%) patients performed pre-surgical invasive work-up. The operated region was the temporal lobe in 189 (73%) of the patients. Anterior temporal lobectomy with amygdalohippocampectomy (ATL-AH) was the most frequently

performed surgery, in 119 (46%) patients, followed by lesionectomy in 115 (44%) patients. Among the 40 (15%) patients who had two or more surgical resections, OT (25%) and MCD (23%) were the most common conditions. Post-surgical complications were identified in 21 (8%) patients, including major and minor neurological complications in 6% [focal deficits (visual field defects or motor deficit), neuropsychiatric disturbances, memory deficit] and neurosurgical complications in 2% (intracranial haemorrhage, intracranial infection, cerebrospinal fluid leak). The percentage of patients free from seizures dropped from 156 (61%) at one year after surgery to 123 (54%) at three years. A reduction in the number of AEDs was observed in 96 (37%) patients after surgery. In patients with Engel class IA, discontinuation of AEDs was possible in 30 (24%) at latest follow-up.

### Histopathological findings

HS was the most common histopathological finding, occurring in 94 (36%) of the surgical specimens. A second histopathological change (dual pathology) was found in four of these patients. Early seizure onset occurred in this group, with a median age of seven (IQR 14) years. The mean duration of epilepsy before surgery in patients with HS was 28 (SD 13) years, the highest among histological categories. At one year following surgical treatment, 60 (67%) patients were completely seizure-free (Engel's class IA). At three years after surgery, 46 (57%) patients achieved Engel's class IA.

LEATs were the second most common histopathological diagnosis in the cohort, representing 56 (22%) of all specimens, and the most common category considering resective surgery in the paediatric age (n = 15, 48%). Ganglioglioma (GG) was identified in 27 (48%) patients, and dysembryoplastic neuroepithelial tumours (DNT) were diagnosed in 23 (41%) patients. Other entities in the LEAT group were pilocytic astrocytoma, angiocentric glioma, between others.

Table 1 – Clinical data of all patients and according to histopathological categories

	Female no. (%)	Age at onset (years)	Age at surgery (years)	Disease duration (years)	One-year post-operative outcome* no. (%)	Three-years post-operative outcome* no. (%)
All patients	134/259 (52)	14 (IQR 20)	34 (SD 14)	14 (IQR 23)	156/257 (61)	123/229 (54)
HS	59/90 (66)	7 (IQR 14)	39 (SD 11)	28 (SD 13)	60/89 (67)	46/81 (57)
LEAT	22/56 (39)	17 (SD 11)	27 (SD 13)	7 (IQR 11)	41/56 (73)	34/47 (72)
OT	11/34 (32)	32 (SD 17)	37 (SD 15)	3 (IQR 5)	19/34 (56)	16/30 (53)
MCD	18/27 (67)	14 (IQR 22)	28 (SD 14)	10 (IQR 18)	10/26 (38)	8/24 (33)
VM	9/19 (47)	32 (SD 16)	38 (SD 13)	3 (IQR 9)	12/19 (63)	10/16 (63)
GS	3/9 (33)	10 (IQR 15)	36 (SD 16)	19 (SD 15)	1/9 (11)	1/9 (11)
No lesion	10/20 (50)	14 (IQR 11)	32 (SD 12)	16 (SD 10)	10/20 (50)	8/20 (40)

HS: hippocampal sclerosis; MCD: malformation of cortical development; LEAT: long-term epilepsy associated tumour; OT: other tumours; VM: vascular malformation; GS: glial scar  
\* Engel class IA: completely seizure-free since surgery (equivalent to category 1 in the ILAE classification system<sup>11</sup>)

These tumours were located mainly on temporal lobe (n = 43; 77%), followed by frontal lobe (n = 9; 16%). One year after surgery, 41 (73%) patients with LEATs were seizure-free, representing the best postsurgical outcome. Other low-grade non-LEAT tumours were also present in our surgical series (n = 34; 13%), with astrocytoma and oligodendroglioma being the most frequent, with equal frequency (n = 13; 38%). These patients presented one of the shortest disease durations, with a median of three (IQR 5) years before surgery. The rate of seizure freedom at one year and three years after surgery was 56% and 53%, respectively.

MCD were found in only 27 (10%) patients of the whole cohort but represented the second most common category among children (n = 6, 19%). Focal cortical dysplasia (FCD) type II was the most common subtype of malformation, accounting for 16 (59%) cases. Other entities in the MCD category were FCD type I, FCD-not otherwise specified, and hemimegalencephaly. These malformations were most often located in the frontal lobe 13 (48%). Both one-year and three-year postsurgical timepoints presented a low percentage of patients achieving Engel's class IA, 38% and 33% respectively. The outcome was similar considering only FCD type II (38% at one year, and 31% at three years).

VM were identified in 19 (7%) of all specimens. The cavernous angiomas were the most frequent type of VM (n = 16, 84%). The mean age at seizure onset was 32 (SD 16) years, being one of the categories with older patients at disease onset. A favourable post-operative outcome at one year and three years was registered in 63% of the patients. The least frequent category was GS (n = 9; 4%), which presented mainly an extra-temporal topography (56%). The percentage of patients with seizure freedom after surgery was the lowest (11%) of the cohort, representing the histological entity with the worst post-surgical outcome. No specific lesion could be identified or characterized by means of microscopic inspection in 20 (8%) of patients. This included findings of nonspecific reactive gliosis as the only histopathologic abnormality in the neocortex, white matter, or hippocampus. Freedom from seizures one year after surgery occurred in 50% of patients in this category.

### Differences in epilepsy surgery between epochs

For comparison purposes, we divided this retrospective cohort into two consecutive time periods of 12 years (1997 to 2009 *versus* 2010 to 2021) and compared the two epochs (Table 2). The absolute number of operated patients increased, from 119 to 140. The age at seizure onset and disease duration before surgery did not present statistically significant differences between the two periods. However, the mean age at surgery was significantly higher in the second period ( $t = -2.08$ ,  $p = 0.04$ ). Regarding invasive work-up, the number of subdural grids/strips was similar in both

epochs, but the number of stereo-EEG increased in the latter (although not statistically significant). Surgeries involving the temporal lobe were the most frequent in both periods, but extratemporal surgeries were carried out more frequently over the more recent period. Between 1997 and 2009, the most frequent type of surgery was ATL-AH (n = 57, 48%), and between 2010 and 2021 it was lesionectomy (n = 67, 48%). The rate of post-surgical complications remained stable. The number of MCD that underwent resective surgery significantly increased in recent years ( $\chi^2 = 6.83$ ,  $p = 0.01$ ). On the other hand, the OT group ( $\chi^2 = 7.42$ ,  $p = 0.01$ ) and the no lesion group ( $\chi^2 = 5.05$ ,  $p = 0.03$ ) significantly decreased in the same period. There were no significant differences in surgical outcomes between the two periods.

### DISCUSSION

We presented a resective surgery cohort from an active tertiary centre that provides epilepsy surgery to a mixed population of paediatric and adult patients. The presurgical clinical features of our patients with drug-resistant focal epilepsy requiring surgery were in line with previous studies,<sup>4,14,15,27</sup> and did not differ significantly between the two time periods, except for a trend towards an increasing age at surgery. Moreover, the delay from epilepsy onset to surgery exceeded more than 10 years on average (excluding the categories of brain tumours and VM) and remained identical in the different periods. These clinical parameters are relevant for prognosis, since young age at surgery and short duration of epilepsy were associated with more favourable outcomes.<sup>14,28</sup> The gap between evidence and practice with an early underuse of epilepsy surgery has been discussed and several reasons have been presented: epilepsy is a dynamic condition and patients may experience temporary seizure remission with new drugs; difficult access to health care resources; misconceptions about epilepsy surgery leading to under-referral to tertiary centres; overestimation of surgical risks or underestimation of seizure related mortality and morbidity; and depletion of eligible candidates with increasing focus on more complex cases.<sup>1,3,29</sup> The proportion of invasive EEG procedures remained identical, but the proportion of stereotactic studies increased in the most recent epoch. Although surgeries targeting the temporal lobe were the most frequent in both periods, ATL-AH was more prevalent in the former and lesionectomy in the latter. The rate of post-surgical complications was in the range of those previously reported<sup>3,30</sup> and remained stable over time.

Neuropathologic assessment of epilepsy surgery specimens allowed the confirmation of the underlying causes. Unsurprisingly, HS was the most common histopathological diagnosis among adults, a finding consistent with results of current studies.<sup>4,15,27</sup> LEAT was the most common diagnosis among children, which was different from other surgical

**Table 2** – Comparison of clinical data between two epochs (1997 - 2009 versus 2010 - 2021) of resective epilepsy surgery

	1997 - 2009 (n = 119)	2010 - 2021 (n = 140)	Test values	p	Effect size
Female no. (%)	61 (51)	73 (52)	$\chi^2 = 0.02$	0.89	OR = 0.97
Children no. (%)	15 (13)	16 (11)	$\chi^2 = 0.08$	0.77	OR = 1.12
Age at onset (years)	12 (IQR 19)	15 (IQR 24)	U = 6534,00	0.22	r = -0.08
Age at surgery (years)	33 (SD 12)	36 (SD 14)	t = -2.08	<b>0.04</b>	d = -0.26
Disease duration (years)	14 (IQR 20)	14 (IQR 25)	U = 7149,50	0.93	r = -0.01
Invasive workup and surgery					
Subtype icEEG no. (%) $\Delta$	22 (19)	33 (24)	$\chi^2 = 0.99$	0.32	OR = 1.36
Subdural no.	20	23	-	-	-
Depth no.	2	10	-	-	-
Surgery location - Temporal no. (%)	90 (76)	99 (71)	$\chi^2 = 0.79$	0.38	OR = 0.78
Surgery location - Extra-temporal no. (%)	29 (24)	41(29)			
Post-surgical complications no. (%)	10 (8)	11 (8)	$\chi^2 = 0.02$	0.89	OR = 0.94
Histopathological categories					
HS no. (%)	41 (34)	49 (35)	$\chi^2 = 0.01$	0.93	OR = 1.02
LEAT no. (%)	23 (19)	33 (24)	$\chi^2 = 0.68$	0.41	OR = 1.29
OT no. (%)	23 (19)	11 (8)	$\chi^2 = 7.42$	<b>0.01</b>	OR = 0.36
MCD no. (%)	6 (5)	21 (15)	$\chi^2 = 6.83$	<b>0.01</b>	OR = 3.32
VM no. (%)	8 (7)	11 (8)	$\chi^2 = 0.12$	0.73	OR = 1.18
GS no. (%)	3 (3)	6 (4)	$\chi^2 = 0.60$	0.44	OR = 1.73
No lesion no. (%)	14 (12)	6 (4)	$\chi^2 = 5.05$	<b>0.03</b>	OR = 0.34
Post-operative outcome*					
One-year no. (%)	73/119 (61)	83/138 (60)	$\chi^2 = 0.04$	0.84	OR = 0.95
Three-years no. (%)	67/118 (57)	56/111 (50)	$\chi^2 = 0.92$	0.34	OR = 0.78

icEEG: intracranial EEG; HS: hippocampal sclerosis; MCD: malformation of cortical development; LEAT: long-term epilepsy associated tumour; OT: other tumours; VM: vascular malformation; GS: glial scar

\* Engel class IA.

$\Delta$ : Considering only patients that posteriorly underwent resective surgery

Bold values indicate statistical significance at the 0.05 level

series, in which FCD was more frequent.<sup>15,27</sup> FCDs have been reported as being increasingly frequent in series of patients who underwent epilepsy surgery.<sup>3,4,15</sup> Our results supported these studies with a significant increase in the number of surgeries for MCD in the more recent years, probably due to the complexity of these patients. In contrast, the number of OT cases decreased, perhaps because patients with these tumours started to be referred to a specialized team dedicated to the treatment of brain tumours rather than an epilepsy team. No lesion specimens also decreased between epochs, likely related to an improvement in surgical and histological techniques.

Overall, our postsurgical seizure control rates considering all patients and histological subgroups were in accordance with other data reported,<sup>4,15,21</sup> except for MCD and GS which were lower in our study. These patients usually represent more challenging cases, with a predominant extra-temporal location and longer epilepsy duration, which is

known to negatively influence outcomes.<sup>6,14,21</sup> As previously reported,<sup>14,21</sup> the diagnoses of LEATs, HS and VM had the best post-operative outcomes. Interestingly, HS had a good post-surgical outcome despite the longer disease duration. Longer duration of epilepsy was associated with reduced chance of favourable outcomes for all lesions, except for HS.<sup>14</sup> The rationale behind this absence of an effect of duration for patients with HS was not clear.<sup>14</sup> The number of unclassifiable tissue samples was in agreement with other studies,<sup>15</sup> and it does not imply that the resected tissue was functionally normal, since 50% of these patients were seizure-free 12 months after surgery. This was probably related to the inconsistent nature of neurosurgical sampling.<sup>15</sup> No significant difference in the surgical outcomes was detected in the two periods of follow-up. However, there are discrepant results in the literature, with studies reassuring that epilepsy surgery functions in a stable manner on longitudinal evaluation,<sup>4</sup> and others showing improved

postsurgical outcomes in more recent years.<sup>3,5</sup> Our frequency of medication withdrawal after surgery for patients in Engel class IA was similar to previously published intervals.<sup>1,6,21</sup>

Our study has some limitations. First, it is a single-centre study, thus being likely influenced by local policies, available equipment, and referral bias. There was no standardized protocol of patient selection for presurgical evaluation, as in probably most centres. Its retrospective design, with potential imprecisions in data from the 1990s, is another limitation. Also, a few patients were lost to follow-up and some of the most recently operated patients have not yet reached the defined outcome evaluation times, leading to missing values in our dataset.

## CONCLUSION

This study presented an important descriptive and basic inferential statistical analysis of a resective epilepsy surgery cohort, consolidating the previous knowledge on the underlying structural causes, clinical practice, and surgical outcomes over more than two decades of experience. There is still a considerable delay between epilepsy onset and surgery, and the age at surgery increased in the most recent years. Neuropathologic assessment is essential to confirm the aetiology of the epilepsy and the seven histopathological categories presented different post-surgical outcomes. Our data provide realistic expectations about epilepsy sur-

gery and highlight the need for further improvements in the diagnosis and treatment paradigm, leading to a more harmonized approach in epilepsy care.

## AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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