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ORIGINAL ARTICLE

Twenty-five years of epilepsy surgery at a Central European comprehensive epilepsy center—Trends in intervention delay and outcomes

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Abstract

Objective: We analyzed trends in patients' characteristics, outcomes, and waiting times over the last 25 years at our epilepsy surgery center situated in Central Europe to highlight possible areas of improvement in our care for patients with drug-resistant epilepsy.

Methods: A total of 704 patients who underwent surgery at the Brno Epilepsy Center were included in the study, 71 of those were children. Patients were separated into three time periods, 1996-2000 (n = 95), 2001-2010 (n = 295) and 2011-2022 (n = 314) based on first evaluation at the center.

Results: The average duration of epilepsy before surgery in adults remained high over the last 25 years (20.1 years from 1996 to 2000, 21.3 from 2001 to 2010, and 21.3 from 2011 to 2020, $P = 0.718$). There has been a decrease in rate of surgeries for temporal lobe epilepsy in the most recent time period (67%—70%—52%, $P < 0.001$). Correspondingly, extratemporal resections have become more frequent with a significant increase in surgeries for focal cortical dysplasia (2%—8%—19%, $P < 0.001$). For resections, better outcomes (ILAE scores 1a-2) have been achieved in extratemporal lesional (0%—21%—61%, $P = 0.01$, at least 2-year follow-up) patients. In temporal lesional patients, outcomes remained unchanged (at least 77% success rate). A longer duration of epilepsy predicted a less favorable outcome for resective procedures ($P = 0.024$) in patients with disease duration of less than 25 years.

Significance: The spectrum of epilepsy surgery is shifting toward nonlesional and extratemporal cases. While success rates of extratemporal resections at our center are getting better, the average duration of epilepsy before surgical intervention is still very long and is not improving. This underscores the need for

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stronger collaboration between epileptologists and outpatient neurologists to ensure prompt and effective treatment for patients with drug-resistant epilepsy.

KEYWORDS

drug-resistant epilepsy, drug-resistant epilepsy epidemiology, drug-resistant epilepsy surgery

JEL CLASSIFICATION

Neurology, Epilepsy, Epilepsy surgery

1 | INTRODUCTION

Drug resistance in epilepsy is commonly defined as the failure of two appropriately chosen anti-seizure drugs to achieve seizure freedom.[1] Eventually, around 30% of patients with epilepsy develop drug resistance[2] and suffer from the consequences of repeated seizures, such as mood disorders, cognitive decline,[3] and risk of sudden death in epilepsy (SUDEP).[4] Additional trials of anti-seizure medication (ASM) prove effective in stopping seizures in less than 3.7% of cases,[5] highlighting the need for other treatment modalities like surgery.

Surgery for drug-resistant epilepsy (DRE) has continuously improved and evolved over the span of the 20th and 21st centuries, pioneered by neurologists and neurosurgeons such as Penfield, Jasper, Talairach, and others.[6] Over the last 30 years, well-designed clinical studies demonstrated effectiveness of epilepsy surgery first in medial temporal lobe epilepsies (MTLE)[7] and later also in extratemporal lesional cases[8] (ie, with a corresponding epileptogenic lesion on brain magnetic resonance imaging) and even nonlesional epilepsies,[9] where the localization of surgical target zone is based on intracranial EEG (electroencephalography) and other advanced diagnostic methods.

Although seizure freedom is always the primary goal in resective surgeries for epilepsy, many patients still see significant benefits even when this goal is not achieved but the surgery results in a significant degree of seizure reduction. Often, there is a marked decrease in the seizures' severity with fewer occurrences of focal to bilateral tonic–clonic seizures (FBTCS)[10] leading to a lower risk of injuries and SUDEP,[4] a lesser degree of cognitive decline,[11] and better quality of life.[12] For patients in whom resective surgery is not possible, palliative treatments such as neurostimulation can be substantially effective.[13]

Today, epilepsy surgery remains steadfast as a treatment of choice for patients with seizures uncontrolled by ASM, even though the spectrum of treated pathologies and patients is changing. The field still faces many challenges, such as long durations of disease before presurgical evaluations,[14] suboptimal results in complex nonlesional cases, and unpredictability of patients' response to palliative treatment modalities like VNS.[15]

Key Points

- Surgeries for temporal lobe epilepsy are decreasing while interventions for extratemporal epilepsy are becoming more common over the last 25 years.
- Surgical outcomes for extratemporal and nonlesional epilepsy patients are steadily improving.
- The duration of drug-resistant epilepsy before surgery in adults is still very long and not showing signs of improvement.

In this study, we investigated the trends in outcomes, delays, and treated epilepsy types in the Brno Epilepsy Center from 1996 until the present. The center started surgically treating patients with epilepsy in 1995, the first VNS implantation took place in 1999. We aimed to capture the evolution of our capabilities in treating patients with DRE, as well as highlight areas of possible improvement in the future.

To our knowledge, this study is the very first one to analyze a complete patient pool in a Central or Eastern European epilepsy surgery center.

2 | METHODS

All patients with available clinical data who have undergone a therapeutic surgical intervention at the Brno Epilepsy Center between January 1996 and October 2022 have been included in this study. Every participant (or their parent/caregiver in case of children and legally incapable patients) signed an informed consent for usage of their anonymized data in research. The exclusion criteria were as follows: (1) The patient has had a prior surgery for epilepsy at another institution, and (2) the main goal of surgery was the resection of a high-grade tumor (eg, a glioblastoma), not necessarily elimination of seizures. Three

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predefined time periods were statistically compared, 1996-2000, 2001-2010, and 2011-2022. Patients were split into these time periods based on the date of the first evaluation at the center.

At our center, selection for epilepsy surgery is contingent upon meeting the criteria for drug-resistant epilepsy, along with the comprehension and acceptance of potential associated risks by the patient or their caregiver. Resective procedures are extended to patients for whom a plausible hypothesis can be formed regarding the location of the epileptogenic zone, and where a resection would not cause significant neurological deficit. In cases where a resective procedure is not possible, or where previous resection has failed and repeat resection is unfeasible, VNS implantation or deep brain stimulation (DBS) are considered as alternative therapeutic approaches.

Patients with an identifiable lesion corresponding with the clinical presentation on presurgical magnetic resonance imaging (MRI) of the brain and electrophysiological investigations were classified as having a lesional epilepsy. According to the histological examination of resected tissue, lesions were classified as follows: (1) hippocampal sclerosis (HS), (2) focal cortical dysplasia (FCD, excluding type III), (3) malformations of cortical development (MCDs) other than FCD, (4) long-term epilepsy-associated tumors (LEATs, eg, gangliogliomas), (5) vascular malformations (eg, cavernomas), (6) postischemic, postinflammatory or post-traumatic changes, and (7) negative for any pathology. FCDs associated with a principal lesion (type III) were included in the subgroups corresponding to the principal lesion (eg, FCD type IIIa as HS and FCD type IIIb as LEAT).

When the presumed epileptogenic zone was in a single lobe, the patients were stratified according to the affected lobe (frontal and temporal). Cases with multiple lesions affecting more than one lobe and/or lesions crossing interlobar boundaries (such as in temporal plus epilepsy) were classified as multilobar.

To score the epilepsy surgery outcomes, we rated patients who have undergone a resection with ILAE epilepsy surgery outcome scale scores 1a-2 (ie, no seizures or only auras after the surgery) as successful.[16] For VNS implantations, success was defined as achieving grades IA-IIB in the McHugh classification (ie, 50% or higher seizure reduction).[17]

Complications arising from treatment were categorized as minor or major. A complication was classified as minor if it was expectable and did not significantly affect the patient's quality of life and/or was transient, such as transient dysphonia after VNS implantation or quadrantanopsia after temporal lobectomy. A complication was classified as major if it resulted in a significant decrease in the patient's quality of life, such as significant hemiparesis, hemianopsia, or the need for repeat surgery.

Only patients with at least 2 years of follow-up were evaluated for their outcomes, the grading occurred at their last available clinical visit. Patients undergoing palliative resective procedures not aimed at seizure freedom (eg, callosotomy) were not assessed for outcomes. In patients who have had more than one therapeutical surgery (eg, repeated resection or DBS implantation after failure of VNS), only results of the first surgery were taken into account.

Patients who underwent presurgical evaluation and surgical intervention during the COVID-19 pandemic from years 2021 to 2022 have been included only in the analysis of epileptogenic zone locations and the histological classification of resected tissue. Due to the short follow-up duration, they were not included in outcomes analysis. These patients were also not included in the analysis of epilepsy duration and length of presurgical evaluation, because these values were altered by a necessary pause in the epilepsy surgery program during the COVID-19 pandemic.

Continuous variables are presented as mean along with standard deviation (SD), categorical variables as total number with corresponding percentage. All statistical analyses were performed using the R software package.[18] For comparisons of means and total counts among the three selected time periods, the chi-squared test was utilized. Linear regression model was used to determine the surgery outcome and epilepsy duration relationship.

3 | RESULTS

A total of 747 patients were evaluated for inclusion in the study. Of these, 704 met the inclusion criteria, and 71 of them were children at the time of surgery. Characteristics of adult patients are summarized in Table 1. The first time period, from 1996 to 2000, included a total of 95 patients, the second, from 2001 to 2010, 295 patients, and the last time period, from 2011 to 2022, 314 patients (both children and adult; Figure S1). The average number of therapeutical surgeries per year was 25.1 (SD = 10.8, repeat surgeries not being considered). The proportion of adult patients treated with VNS as compared with resections remained relatively constant throughout the selected time periods (63% resection vs. 37% VNS from 1996 to 2000, 64% vs. 36% from 2001 to 2010, and 61% vs. 38% from 2011 to 2022, $P = 0.773$).

The interval between diagnosis of epilepsy and surgery has remained similar in the compared time periods ($P = 0.06$), from 1996 to 2000, it was 20.1 years, from 2001 to 2010, it was 21.0 years and from 2011 to 2020, it was 18.4 years. When considering only adult patients, there is no improvement in the presurgical duration of epilepsy ($P = 0.718$), which was

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TABLE 1 Characteristics of adult patients included in the study.

	Total	1996-2000	2001-2010	2011-2022	*P*-value
Number of adult patients	633	95	289	249	
Female, n (%)	307 (48%)	41 (43%)	143 (49%)	123 (49%)	0.528
Age at surgery	34.2 (±11.9)	32.9 (±10)	34.0 (±12)	34.9 (±12.4)	0.541
Duration of epilepsy at surgery in years[a]	21 (±12.6)	20.1 (±11.6)	21.3 (±12.6)	21.3 (±13.1)	0.718
Presurgical evaluation in years[a]	2.3 (±2.9)	2.8 (±3.7)	2.6 (±3.4)	1.7 (±1.6)	0.01
Follow-up length in years	8.6 (±6.5)	16.9 (±6.5)	10.4 (±4.7)	3.3 (±2.7)	
Patients undergoing resection, n (%)	397 (63%)	60 (63%)	185 (64%)	152 (61%)	0.773
Causal lesion on brain MRI, n (%)	411 (65%)	57 (60%)	192 (66%)	162 (65%)	0.498
Localization					
Temporal	396 (63%)	64 (67%)	202 (70%)	130 (52%)	<0.001
Frontal	94 (15%)	20 (21%)	39 (13%)	35 (14%)	0.18
Insular	16 (3%)	1 (1%)	3 (1%)	12 (5%)	0.013
Parietal	16 (3%)	1 (1%)	5 (2%)	10 (4%)	0.148
Occipital	5 (1%)	0	3 (1%)	2 (1%)	0.611
Multilobar	51 (8%)	6 (6%)	15 (5%)	30 (12%)	0.011
Generalized	27 (4%)	3 (3%)	10 (3%)	14 (6%)	0.393
Unknown	28 (4%)	0	12 (4%)	16 (6%)	0.033
Pathology					
HS	173 (44%)	22 (37%)	88 (48%)	63 (41%)	0.33
FCD	44 (11%)	1 (2%)	14 (8%)	29 (19%)	<0.001
Other MCD	18 (5%)	3 (5%)	4 (2%)	11 (7%)	0.304
LEAT	83 (21%)	17 (28%)	45 (24%)	21 (14%)	0.004
Vascular malformation	13 (3%)	3 (5%)	4 (2%)	6 (4%)	0.349
Stroke, trauma, inflammation	15 (4%)	2 (3%)	8 (4%)	5 (3%)	0.804
Negative	51 (13%)	12 (20%)	22 (12%)	17 (11%)	0.918

Abbreviations: FCD, focal cortical dysplasia; HS, hippocampal sclerosis; LEAT, long-term epilepsy-associated tumor; MCD, malformation of cortical development; MRI, magnetic resonance imaging.

[a]Durations of epilepsy and presurgical evaluation were evaluated only until the year 2020.

20.1 years from 1996 to 2000, 21.3 years from 2001 to 2010, and 21.3 years from 2011 to 2020. The duration of the diagnostic process at the center itself (ie, an interval from the first visit to the Brno Epilepsy Center until the surgery) has steadily decreased ($P = <0.001$), from 2.8 years in the first time period to 2.6 years in the second period and finally 1.4 years in the years 2011-2020 (Figure 1; Figure S2). Patients evaluated during the COVID-19 pandemic from 2020 to 2022 were excluded from this analysis, as the epilepsy surgery program had to be paused for several months, impacting the results.

Patients' outcomes were analyzed separately based on the type of surgery. For resective procedures, the success rate was on average 61% from 1996 to 2000, 69% from 2001 to 2010, and 64% from 2011 to 2020, there was no statistically significant difference between these time periods ($P = 0.271$). VNS success rates remained unchanged ($P = 0.105$): 54% from 1996 to 2001, 70% from 2001 to 2010, and 57% from 2011 to 2020.

Outcomes for resective procedures were also assessed separately based on the epilepsy localization and finding of a causal lesion on brain MRI. Specifically for temporal lesional epilepsies, the rate of successful surgeries remained the same in the most recent time period (77% from 1996 to 2000, 80% from 2001 to 2010, and 78% from 2011 to 2020, $P = 0.86$). A similar trend was observed for temporal nonlesional cases (success rate of 50% from 1996 to 2000, 54% from 2001 to 2010, and 42% from 2011 to 2020, $P = 0.796$). Over time, a significantly higher success rate was achieved for extratemporal lesional epilepsies (0% from 1996 to 2000, 18% from 2001 to 2010, and 62% from 2011 to 2020, $P = 0.01$), nonlesional extratemporal cases have shown the least amount of success, although the patient number was low at 16 total (no eligible patients in the 1996-2000 period, 0% success rate from 2001 to 2010 and 14% success rate from 2011 to 2020, $P = 0.598$, Figure 2).

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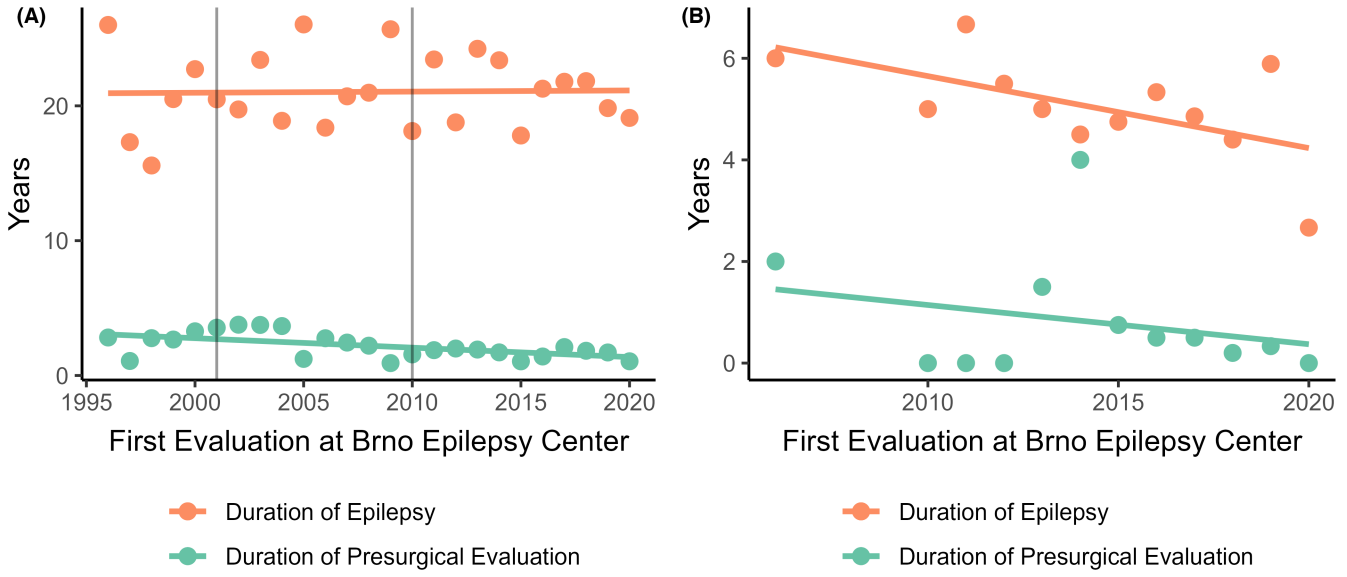
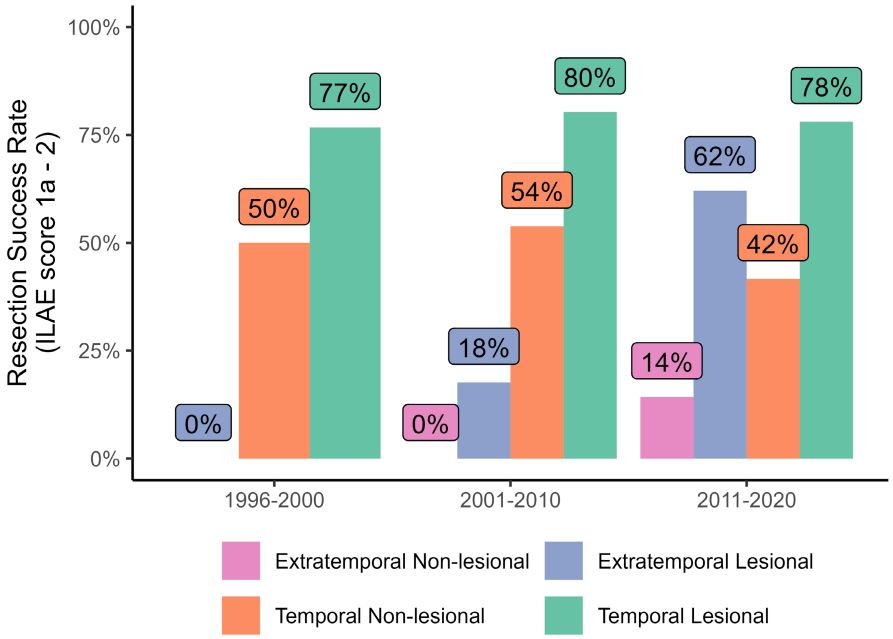


FIGURE 1 Duration of epilepsy before surgical intervention (orange points and line) and the time from first visit to Brno Epilepsy Center until the surgical intervention (green points and line) in adults (A) and children (B). Each point represents an average year count for a specific calendar year. Patients evaluated during the COVID-19 pandemic from 2020 to 2022 were excluded from this analysis.

FIGURE 2 Resection success rates (ie, ILAE scale scores 1a-2) for the major epilepsy types considered for surgery. In the time period from 1996 to 2000, no patients with extratemporal nonlesional epilepsy underwent resective surgery.



At least some seizure reduction is observed in 84% of all patients undergoing a resective procedure (ie, achieving a better than 5 score on the ILAE scale, which equals at least a 50% reduction in seizure frequency). Temporal lobe resections produce clinical improvement in 89% patients overall, 86% from 1996 to 2000, 91% from 2001 to 2010, and 88% from 2011 to 2020 ($P=0.504$). For extratemporal epilepsy patients, this number is somewhat lower at 60% overall, with no patients achieving at least some amelioration of seizures in the 1996-2000 cohort, increasing to 26% from 2001 to 2010 and reaching 81% in the 2011 to 2020 period ($P=<0.001$). In nonlesional cases, 72% of patients experience seizure reduction, staying roughly the same among the studied time periods (83%—79%—62%, $P=0.305$).

Lastly, outcomes in adult patients were analyzed based on the duration of epilepsy prior to surgery. Longer duration of epilepsy did not have a statistically significant impact on the success rate of the interventions, both for resective procedures ($P=0.688$) and VNS implantation ($P=0.39$). Upon exclusion of patients with over 25 years of presurgical epilepsy duration, a statistically significant

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decreasing success rate trend was observed as the disease duration became longer for resective surgeries ($P = 0.024$) but not for VNS implantation ($P = 0.063$, Figure 3).

Over the selected time periods, there has been a clear shift in the spectrum of epilepsies considered for surgical intervention. From 1996 to 2000, 67% of patients have undergone a temporal lobe resection. In the 2001-2010 period, the proportion of temporal lobe resections was almost the same at 68%, decreasing however to just 44% in the most recent time period, while extratemporal resections became more common at 55%. Palliative resection procedures accounted for 5% of cases from 1996 to 2000, 0% from 2001 to 2010, and 1% from 2011 to 2022 (Figure 4A).

The spectrum of epilepsy types treated with VNS has also shifted over the years. 40% of patients undergoing VNS implantation from 1996 to 2000 suffered from temporal lobe epilepsy. This number decreased to 32% from 2001 to 2010 and to just 16% from 2011 to 2022. A similar decrease was observed for frontal lobe epilepsy, going from 37% from 1996 to 2000, to 30% from 2001 to 2010, and to 19% from 2011 to 2022. A rise was observed in the multilobar epilepsy patients (11%—12%—30%) and patients with generalized epilepsy (Figure 4B).

From 1996 to 2000, 40% of patients had a nonlesional epilepsy. From 2001 to 2010, there were 34% patients without a causative lesion on the brain MRI. In the last time period, from 2011 to 2022, 35% of patients were classified as having a nonlesional epilepsy, and this has not differed significantly among the selected time periods ($P = 0.497$). Among the patients undergoing a resection, 20% had nonlesional epilepsy. As expected, this number was higher for the VNS group at 44% of nonlesional cases.

Along with these changes, the spectrum of causative pathologies has also evolved. HS remained the most common cause of surgically remediable epilepsy, accounting for 37% of cases in 1996-2000, 48% in 2001-2010, and 41% in 2011-2022 ($P = 0.06$). The number of patients with FCD rose significantly from 2% in 1996-2000 to 8% in 2001-2010 and finally to 19% in 2011-2022 ($P < 0.001$) and frequency of LEATs dropped from 28% in 1996-2000 to 24% in 2001-2010 and lastly to 14% in 2011-2022 ($P = 0.03$, Figure 4C).

The number of patients undergoing diagnostic intracranial electrode placement has been steadily increasing over the years, from 1996 to 2000, the average number of such procedures per year was 8, increasing to 8.6 per year from 2001 to 2010, and 14.5 per year from 2011 to 2022. This trend is statistically significant ($P < 0.001$; Figure S4).

In total, 9.9% of patients experienced minor (expectable and transient) complications, and 4.0% experienced major (unexpected, significantly affecting patient's quality of life) complications. A total of 2.7% of patients had incurred a permanent neurological deficit. Resection procedures had a higher incidence of complications, with 6.6% of patients experiencing major complications and 11.6% experiencing minor (expectable and transient) complications. Among patients undergoing VNS implantation, 8% experienced minor complications, while no patients experienced major complications. From 1996 to 2000, the overall rate of surgical complications was 19% (3% major, 16% minor). This rate decreased to 13.3% from 2001 to 2010 (4.7% major, 8.5% minor) and 13% from 2011 to 2022 (3.5% major, 9.6% minor, Figure S3). There was no statistically significant difference in the rate of complications across the studied time periods ($P = 0.3$).

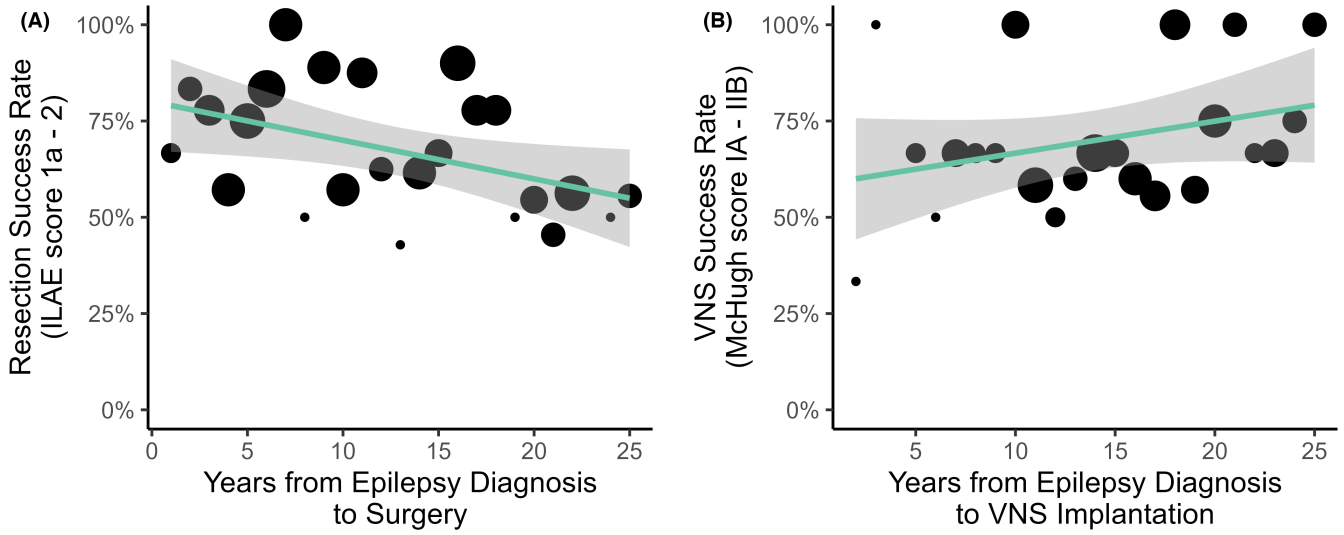

FIGURE 3 Relationship between duration of epilepsy before surgery and resection success rate (ie, ILAE scale scores 1a-2; A) and vagal nerve stimulation success (McHugh scores IA-IIB; B) in patients with disease duration equal or shorter than 25 years. Each point represents a patient group of a single year count of epilepsy duration, the relative size of each point corresponds with the number of patients for that year count. The green trendline was plotted using a linear regression model.

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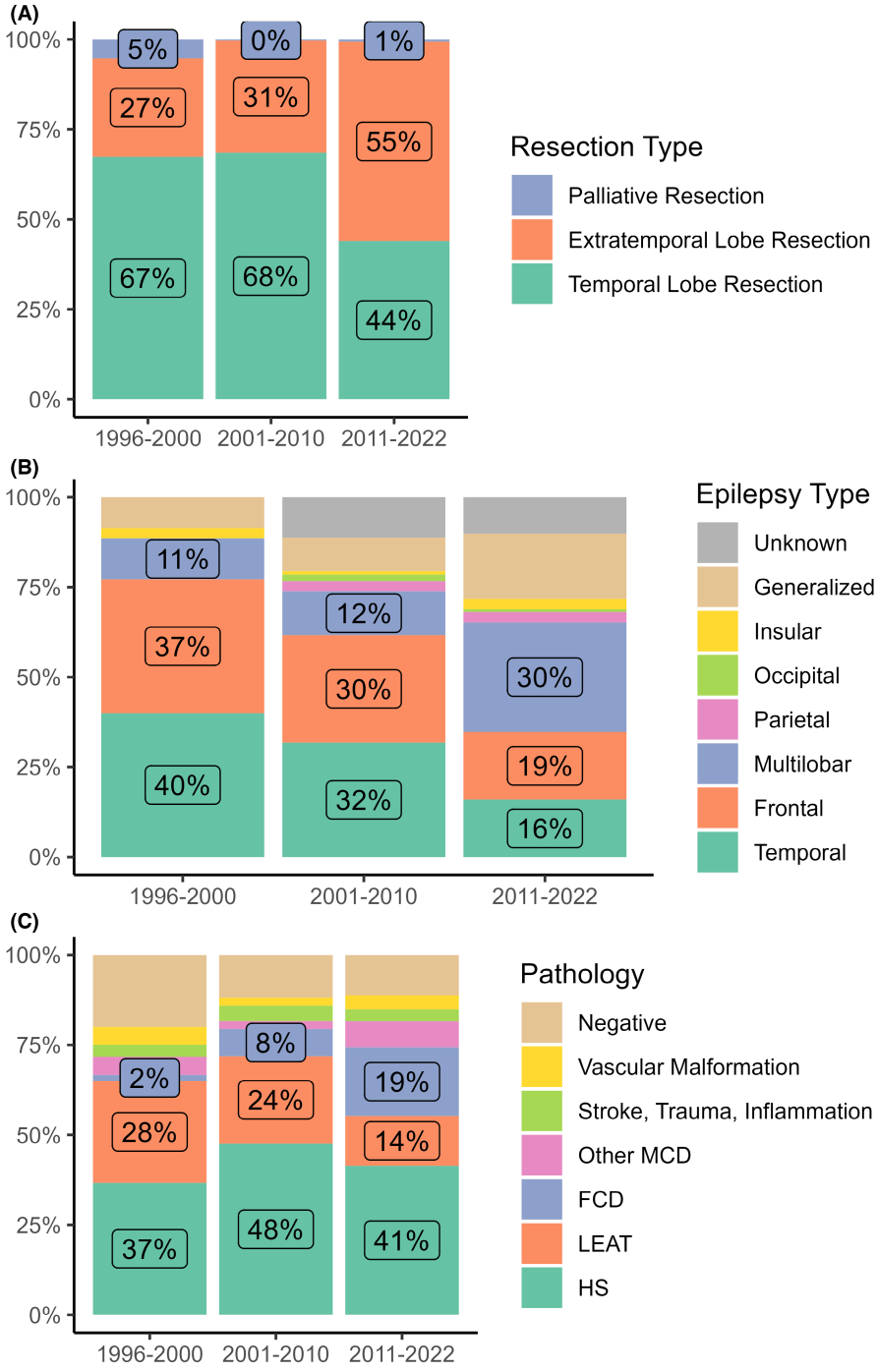

FIGURE 4 (A) Trends in resection types in the selected time periods, showing recent decrease in temporal lobe resections and rise in number of patients undergoing extratemporal resections. (B) Development of epilepsy types in patients with VNS implantation. (C) Rates for pathology types in patients' resected tissue. Note the increase in frequency of malformations of cortical development.

A detailed overview of the specific types of intervention complications can be found in Table S1.

Patients under the age of 19 were analyzed separately, and the summary of this analysis is presented in Table 2. Expectedly, higher rates of extratemporal and generalized epilepsies are seen in children undergoing surgery (73% and 15% respectively). VNS implantation is also more common than in adults, accounting for 62% of the surgical volume. Success rates for resections are encouraging at 63%, while only 43% of children achieve >50% seizure reduction with VNS.

4 | DISCUSSION

While the presurgical diagnostic process at our center has steadily shortened over the years, the duration of epilepsy before surgery has not. Although data are limited, this trend has been observed at numerous epilepsy surgery centers worldwide. For example, the mean waiting time at a Canadian epilepsy surgery center was 16.9 years, while at a Mexican center, it was 18.9 years.[19] A study conducted by Haneef et al[20] revealed no improvement in the mean waiting time at a Californian center, which was

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TABLE 2 Characteristics of pediatric patients (under 19 years of age at the time of surgery) included in the study.

Female; n (%)	34 (48%)
Age at surgery	9.1 (±4.5)
Duration of epilepsy at surgery in years	4.9 (±3.8)
Duration of presurgical evaluation in years	0.5 (±1.2)
Follow-up length in years	4.2 (±3.4)
Patients undergoing resection, n (%)	27 (38%)
Lesion on brain MRI, n (%)	50 (70%)
Localization	
Temporal	8 (11%)
Extratemporal	52 (73%)
Generalized	11 (15%)
Pathology	
MCD	16 (59%)
LEAT	8 (30%)
Negative	3 (11%)
Successful outcome	
Resection[a]	12 (63%)
VNS[b]	15 (43%)

Abbreviations: LEAT, long-term epilepsy-associated tumor; MCD, malformation of cortical development; MRI, magnetic resonance imaging; VNS, vagal nerve stimulation.

[a]Successful outcome for resective procedures was defined as achieving ILAE score 1a-2 with at least 2 years of follow-up.

[b]Successful outcome for VNS implantation was defined as achieving grades IA-IIB in the McHugh classification (ie, 50% or higher seizure reduction) with at least 2 years of follow-up.

17.1 years from 1995 to 1998 and 18.6 years from 2005 to 2008. Another study from a US-based epilepsy surgery center found no difference in presurgical epilepsy duration among three periods from 1996 to 1999, 2000 to 2003, and 2004 to 2007, and the mean durations in this case were 22.6, 22.4, and 21.1 years, respectively ($P = 0.54$).[14] Our findings align with these results, as we recorded a mean duration of 18.4 years from epilepsy diagnosis to therapeutic surgery during the most recent period under review, with no statistically significant improvement over time (20.1 years from 1996 to 2000 and 21.0 years from 2001 to 2010, $P = 0.06$).

Uncovering the reasons for this lack of improvement is not simple, at least two factors are, however, clear contributors: (1) Patients with epilepsy are naturally worried about surgical complications and morbidities,[21] and (2) some outpatient neurologists hesitate with referral to epilepsy surgery centers due to lack of experience with this treatment modality or due to the belief that continued pharmacotherapy may eventually lead to seizure freedom and spare the patient from surgery.[22–24]

More recently, Baud et al conducted a study in which results from a variety of European centers (including ours) were aggregated. The study found a reduction in mean disease duration at surgery by 5.2 years between the periods of 1997-1998 and 2012-2013 (3.5 years when excluding two pediatric centers),[25] indicating that an improvement in this parameter is possible but is not universally achieved.

The number of surgically treated patients with temporal lobe epilepsy has steadily decreased in the last few years. This is probably at least partly due to the fact, that many of the best candidates had already undergone surgery in the past and the pool of these patients is fairly depleted. Also, the prevalence of HS is likely decreasing due to better management of febrile seizures in children.[26] Still, the estimated number of patients with drug-resistant MTLE is much higher than the amount of currently performed surgeries.[27]

Coinciding with this development is a significant rise in the proportion of extratemporal epilepsies being evaluated for surgery.[25] Enabling this trend are modern diagnostic methods, such as 3T MRI, and especially advanced image postprocessing methods,[28] which allow us to correctly identify surgical target zones (eg, FCDs) in these complex cases with much higher confidence.[29] Indeed, in our study, there was a significantly higher proportion of successful outcomes in patients with extratemporal epilepsy in the most recent time period. The results of surgically treated patients with temporal epilepsy have remained similar.

Some authors, therefore, note that the likely reason for the decline in surgical interventions in MTLE/HS lies in a general reduction in referrals to epilepsy surgery centers with temporal lobe epilepsy patients being disproportionately affected compared with extratemporal epilepsies due to recent higher rates of smaller lesion detection (such as FCDs) and an increasing number of extratemporal resections in pediatric patients.[30]

Given this changing landscape in the characteristics of referred patients, achieving total outcomes comparable to previous decades today can be considered a satisfactory result. It is important to mention that surgical treatment of DRE very often leads to a lesser frequency of FBTCS,[10] improves quality of life[12] and reduces the risk of SUDEP,[4] even in patients who do not achieve seizure freedom.

While epilepsy surgery is not risk-free, it is necessary to stress that the long-term dangers of uncompensated epilepsy are often much greater than the those of the surgical intervention. In patients who have not achieved seizure freedom after trialing two ASM, the chance of another drug completely stopping seizures is only 3.7%.[5] These patients clearly benefit from an evaluation at an epilepsy surgery center.

In several previous studies, long duration of epilepsy before resective surgery was associated with worse outcomes.[31] In our patient population, this relationship holds

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true from 1 year to around 25 years of disease duration, where there is a steady decrease in the surgery success rates.

Upon inclusion of all patients undergoing resective procedure (even with over 25 years of disease duration), there appears to be no statistically significant relationship between intervention delay and outcome. We do not have a clear explanation for this trend, although it does not alter the recommendation to operate as soon as possible after establishment of drug resistance, because longer duration of epilepsy is associated with cognitive decline,[32] risk of SUDEP,[4] and other complications.

The success rate for VNS implantation increases with longer disease duration, and we should not therefore be worried about offering VNS to patients with longstanding active epilepsy.

In the most recent studied time period, success rates of resective procedures for nonlesional extratemporal epilepsies at our center have been low. This is a sobering result, especially when all recently evaluated nonlesional epilepsy patients at our center underwent a thorough diagnostic process with intracranial EEG, positron emission tomography (PET), ictal-interictal single-photon emission computed tomography (SPECT) with subtraction coregistered to MRI (SISCOM), and various MRI and PET image postprocessing methods.

Several other groups have reported success rates around the 40% range for resections of nonlesional epilepsies.[9,33,34] We believe that this discrepancy can be, in part, explained by differing risk tolerances among various epilepsy surgery centers, that is, offering surgery only to the most hopeful cases will lead to better outcomes, although some patients who would have benefitted from the procedure can be left out. Also, the previously published studies have analyzed outcomes 1- or 2-year postresection, some patients, however, can experience seizure recurrence even after several years of a seizure-free period. These patients are regarded as not having a successful outcome in our cohort.

Even when patients do not achieve seizure freedom after surgery, many of them experience a very significant reduction in the number and severity of seizures, lower risk of cognitive decline and SUDEP.[4,12] This was the case with our cohort of patients with nonlesional epilepsy, as the majority have achieved a better than 5 ILAE score, leading to a hopefully better quality of life. It is therefore, in our opinion, worthwhile to offer resection even to patients with statistically lower success chances, when this corresponds with their wishes after a thorough discussion and education concerning the procedure's risks and benefits.

Results of resective procedures in children at our center have been encouraging and hold great promise for the future. VNS implantations showed slightly lower success rates than in adults, likely due to a higher prevalence of severe, hard-to-treat pathologies in this patient population, such as developmental and epileptic encephalopathies (DEE). In our clinical experience, many of the children who do not reach the ≥50% seizure reduction threshold after VNS implantation still benefit from the chronic neurostimulation through improvements in quality of life. According to nonvalidated self-reporting questionnaires, there was an improvement in up to 70% of all cases, lower risk of repeat hospital admissions, shortening of disabling seizures and swifter postseizure recovery.

In conclusion, great strides have been made over the last 25 years in our care for patients with DRE. People with extratemporal and/or nonlesional epilepsy now have a better chance than ever to be cured or have a significant improvement in their quality of life with surgery. For those that are not candidates for resection, palliative treatment methods often represent good alternatives. Even with these encouraging results, epilepsy surgery seems underutilized and, unfortunately, many patients still endure seizures for many years or even decades before they are referred to an epilepsy surgery center.

Better cooperation and communication between outpatient neurologists and epilepsy surgery centers is necessary to shorten this period. Ideally, patients should be assessed at a center in several months, not years, after establishing drug resistance. Proper patient education is also of utmost importance, as we should not instill unnecessary fear but also not oversell the possible benefits of surgery. Improvement in these areas will be a main goal in epilepsy surgery over the next decades and, if successful, will have a profoundly positive impact on our patients' health and their lives.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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