Epilepsy surgery is a widely accepted and effective treatment option for patients with medically drug-resistant epilepsy. A large number of patients suffer from focal, drug-resistant epilepsy associated with benign tumors. Long-term epilepsy-associated tumors (LEATs) are generally slow-growing, low-grade, cortical-based tumors that more often arise in younger patients and, in many cases, show both neuronal and glial differentiation. They may be associated with cortical dysplasia or other neuronal migration abnormalities (40%–80%), and more rarely coexist with hippocampal sclerosis (2%–25%). The predominant tumors in this group are gangliogliomas and dysembryoplastic neuroepithelial tumors (DNTs), often localized in the temporal lobe. Other less common LEATs are low-grade pleomorphic xanthoastrocytomas, papillary glioneuronal tumors, pilocytic astrocytomas, diffuse astrocytomas, oligodendrogliomas, and angiocentric gliomas, which are rarely associated with other lesions.

Most LEATs correspond to WHO Grade I. Although their biological behavior is usually benign, there have been reports of tumor progression or malignant transformation. Furthermore, the focal epilepsy associated with LEATs is extremely responsive to surgical treatment, especially in glioneuronal subtypes; approximately 80% of adult patients in most series become free of seizures after surgery, which is particularly indicated in patients with LEATs for clinical, epileptological, and oncological reasons.

In this study, we retrospectively compared the long-term surgical outcomes in a large population of pediatric patients with childhood onset of epilepsy and a histologically confirmed diagnosis of long-term epilepsy-associated tumors. The authors analyzed long-term seizure outcomes to establish whether the time of surgery and patients’ ages were determinant factors.

METHODS The authors separately investigated several presurgical, surgical, and postsurgical variables in patients operated on before (pediatric group) and after (adult group) the age of 18 years. Patients with <24 months of postsurgical follow-up were excluded from the analysis.

RESULTS The patients who underwent surgery before 18 years of age showed better seizure outcomes than those after 18 years of age (80% vs 53.3% Engel Class Ia outcome, respectively; p < 0.001). Multivariate analysis showed that the only variables significantly associated with seizure freedom were complete resection of the lesion, a shorter duration of epilepsy, and temporal lobe resection.

CONCLUSIONS The findings of this study indicate that pediatric patients are more responsive to epilepsy surgery and that a shorter duration of epilepsy, complete resection, and a temporal lobe localization are determinant factors for a positive seizure outcome.

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KEY WORDS epilepsy surgery; focal symptomatic epilepsy; long-term epilepsy-associated tumors; brain MRI
of the study were to identify possible factors predicting a positive postsurgical outcome and to establish whether the timing of surgery and age of the patient were determinant factors.

Methods

Patient Data

This study received the approval of the local ethical-scientific committee. All patients (or their guardians) gave informed consent for the diagnostic and therapeutic procedures.

By retrospectively searching our clinical database of the 1320 patients operated on between 1996 and 2013, we selected those who met the following criteria: childhood onset of seizures (< 18 years); histological diagnosis of LEAT (isolated or in association with other lesions); and postoperative follow-up > 24 months. Among the selected patients, we separately evaluated those who were operated on before the age of 18 years (pediatric group) and those who were 18 years or older at the time of surgery (adult group).

All of the patients had undergone a presurgical evaluation, which included a thorough clinical history, an accurate description of ictal symptoms and signs, routine electroencephalography (EEG), and brain MRI. In patients with poor anamnestic correlations, scalp video-EEG (V-EEG) monitoring or invasive EEG monitoring (stereo-EEG) was performed. Microsurgical resections (lesionectomy or lesionectomy plus corticectomy) were performed with the aim to remove the epileptogenic zone, according to the anatomo-electroclinical correlations. Sites of resections were defined as temporal, unilobar extratemporal, and multilobar.

The tumors were classified using the revised WHO classification suppression and division into 3 groups: DNTs; gangliogliomas; and other LEATs (pleomorphic xanthoastrocytomas, papillary glioneuronal tumors, pilocytic astrocytomas, teratomas, neurocytomas, astrocytomas, astroblastomas, oligodendrogliomas, oligoastrocytomas, epidermoid cysts, and angiocentric gliomas). The extent of lesion removal (complete or incomplete) was assessed on postoperative brain MR images obtained 3–6 months after surgery.

The clinical, neuroradiological, and histological data of all patients were analyzed, and the postsurgical outcomes (classified according to the Engel classification) at different lengths of follow-up were correlated with possible positive predictive factors.

Statistical Analysis

The continuous variables (age at the time of epilepsy onset and surgery, illness duration, and seizure frequency) are given as median values and interquartile ranges (IQRs). Kaplan-Meier survival curves showing outcomes in the 2 groups during the follow-up period were compared using a log-rank test.

Contingency table analysis was used to evaluate the relationships between all of the clinical categorical variables and Engel Class Ia outcomes, and the independence of the rows and columns was evaluated using Fisher’s exact test. A Mann-Whitney U-test was used to compare continuous variables and Engel Class Ia outcomes.

Multivariate analysis investigated the independent prog-

### TABLE 1. Demographic data and clinical features of 255 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Children (n = 120)</th>
<th>Adults (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of seizure onset, yrs</td>
<td>6.0 (2.0–10.0)</td>
<td>10.0 (5.0–15.0)</td>
</tr>
<tr>
<td></td>
<td>6.6 ± 4.8</td>
<td>9.7 ± 5.7</td>
</tr>
<tr>
<td>Age at time of surgery, yrs</td>
<td>12.0 (7.0–15.0)</td>
<td>28.0 (21.0–37.0)</td>
</tr>
<tr>
<td></td>
<td>11.2 ± 4.7</td>
<td>29.9 ± 9.9</td>
</tr>
<tr>
<td>Epilepsy duration, yrs</td>
<td>4.0 (2.0–7.0)</td>
<td>19.0 (12.0–28.0)</td>
</tr>
<tr>
<td></td>
<td>4.8 ± 4.0</td>
<td>20.3 ± 10.8</td>
</tr>
<tr>
<td>Postop follow-up, mos</td>
<td>93.5 (60.0–142.0)</td>
<td>126.0 (74.0–168.0)</td>
</tr>
<tr>
<td></td>
<td>105.0 ± 54.7</td>
<td>123.6 ± 55.4</td>
</tr>
<tr>
<td>Drug-responsive epilepsy, no. of patients</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Seizure frequency at time of surgery</td>
<td>10.0/mo (0.0–30.0/mo)</td>
<td>8.0/mo (4.0–25.0/mo)</td>
</tr>
<tr>
<td></td>
<td>26.3 ± 39.4/mo</td>
<td>20.8 ± 27.4/mo</td>
</tr>
</tbody>
</table>

Values are expressed as the median (IQR) or mean ± SD unless otherwise specified.

Diagnostic effect of all of the variables significantly associated with Engel Class Ia outcomes at univariate analysis using a stepwise logistic regression model and forward selection. Wald’s statistic was used to test whether the coefficients of the regression equation significantly differed from 0.

IBM SPSS Statistics for Macintosh version 22.0 software was used to perform the analyses, for which a p value ≤ 0.05 was considered significant.

Results

According to the inclusion criteria, a total of 255 patients were selected. One hundred twenty patients operated on were younger than 18 years, and 135 patients were 18 years or older.

Pediatric Population

The 120 children included 77 boys and 43 girls (9.1% of all patients operated on during the study period). The median age of the 120 children was 6.0 years (IQR 2.0–10.0 years) at the time of seizure onset, and 12.0 years (IQR 7.0–15.0 years) at the time of surgery. The median epilepsy duration was 4.0 years (IQR 2.0–7.0 years), and the median postoperative follow-up was 93.5 months (IQR 60.0–142.0 months). Patients’ demographic data and clinical characteristics are reported in Table 1.

Forty-five pediatric patients (37.5%) had anamnestic risk factors for epilepsy (a family history of epilepsy in 18 cases, threatened miscarriage in 6, dystocic delivery in 5, febrile seizures in 4, and head trauma in 2; the remaining 10 patients had ≥ 2 of the same risk factors). Fifteen patients (12.5%) had undergone surgery in other clinics and were referred to our center because of ongoing refractory epilepsy.

All of the patients had brain MRI findings suggesting an LEAT. The anatomical localization was temporal in 72 patients (60%), unilobar extratemporal in 30 patients (25%), and multilobar in 18 patients (15%). Forty-seven patients (39.1%) underwent V-EEG monitoring before surgery, and
the remaining 73 (60.9%) underwent standard interictal EEG. All of the EEG recordings were analyzed during the presurgical evaluation, and anatomo-electro-clinical correlations were established. Eleven patients (9.2%) required intracerebral stereo-EEG monitoring to define the extent of the resection.

The histological findings, surgical procedures, and sites of surgery are reported in Table 2.

### Adult Population

The 135 adults included 78 men and 57 women (10.2% of all patients operated on during the study period). The median age was 10.0 years (IQR 5.0–15.0 years) at the time of seizure onset and 28.0 years (IQR 21.0–37.0 years) at the time of surgery. The median epilepsy duration was 19.0 years (IQR 12.0–28.0 years), and the median postoperative follow-up was 126.0 months (IQR 74.0–168.0 months). Patients’ demographic data and clinical characteristics are reported in Table 1.

Thirty-seven adult patients (27.4%) had anamnestic risk factors for epilepsy (a family history of epilepsy in 16 cases, dystocic delivery in 4, threatened miscarriage in 3, febrile seizures in 2, and head traumas in 2; the remaining had ≥ 2 of the same risk factors). Twenty-one patients (15.6%) had undergone surgery in other clinics (1 patient twice) and were referred to our center because of the persistence of seizures. The 37 adult patients with anamnestic risk factors for epilepsy underwent stereoelectroencephalography (52.6% had undergone surgery in other clinics), and the remaining had ≥ 2 of the same risk factors. Twenty-one patients (15.6%) had undergone surgery in other clinics (1 patient twice) and were referred to our center because of the persistence of seizures.

Brain MRI was positive in all cases: the lesion was temporal in 84 patients (62.2%), unilobar extratemporal in 35 (25.9%), and multilobar in 16 (11.9%). Sixty-six patients (48.9%) underwent V-EEG monitoring before surgery, and the remaining 69 (51.1%) underwent standard interictal EEG. Twenty-seven patients (20%) required stereo-EEG monitoring to define the extent of resection.

The histological findings, surgical procedures, and sites of surgery are reported in Table 2. Figures 1 and 2 show examples of lesionectomy and lesionectomy plus corticectomy, respectively (pre- and postoperatively [upper and lower halves, respectively, of Figs. 1 and 2]).

### Postoperative Outcomes and Factors Predicting a Positive Outcome

In the pediatric group, 96 patients had an Engel Class Ia outcome (80%); in the adult population, 72 patients had an Engel Class Ia outcome (53.3%). Engel Class I as a whole (Ia + Ib + Ic + Id) included 112 children (93.3%) and 104 adults (77%). Kaplan-Meier curves in Fig. 3 show the statistically significant between-group difference (log-rank test p < 0.001).

Antiepileptic drugs (AEDs) were discontinued or reduced in 86 (71.6%) and 16 (13.3%), respectively, of the children, and in 58 (42.9%) and 28 (20.7%), respectively, of the adults. Univariate analysis of the study population as a whole

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**TABLE 2. Histological findings, surgical procedures, and sites of surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Children (%)</th>
<th>No. of Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>120 (34.2)</td>
<td>135 (29.6)</td>
</tr>
<tr>
<td>DNTs</td>
<td>49 (40.8)</td>
<td>71 (52.6)</td>
</tr>
<tr>
<td>GGs</td>
<td>30 (25)</td>
<td>24 (17.8)</td>
</tr>
<tr>
<td>WHO Grade I</td>
<td>101 (84.2)</td>
<td>122 (90.4)</td>
</tr>
<tr>
<td>WHO Grade II</td>
<td>19 (15.8)</td>
<td>13 (9.6)</td>
</tr>
<tr>
<td>Associated FCD (Types I or II)</td>
<td>23 (19.2)</td>
<td>38 (28.1)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>114 (31.7)</td>
<td>24 (17.8)</td>
</tr>
<tr>
<td>Lesionectomy + corticectomy</td>
<td>82 (68.3)</td>
<td>111 (82.2)</td>
</tr>
<tr>
<td>Complete resection</td>
<td>101 (84.2)</td>
<td>127 (94.1)</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>39 (15.8)</td>
<td>8 (5.9)</td>
</tr>
<tr>
<td>Site of surgery</td>
<td>120 (31.7)</td>
<td>135 (29.6)</td>
</tr>
<tr>
<td>Temporal</td>
<td>72 (60)</td>
<td>84 (62.2)</td>
</tr>
<tr>
<td>Extratemporal</td>
<td>30 (25)</td>
<td>35 (25.9)</td>
</tr>
<tr>
<td>Multilobar</td>
<td>18 (15)</td>
<td>16 (11.9)</td>
</tr>
</tbody>
</table>

FCD = focal cortical dysplasia; GG = ganglioglioma.
showed a significant association between an Engel Class Ia outcome and the following variables: complete resection of the anatomical lesion \( (p = 0.005) \); drug-responsive epilepsy \( (p = 0.014) \); a shorter duration of epilepsy \( (p < 0.001) \); a younger age at the time of surgery \( (p < 0.001) \); and less frequent seizures at the time of surgery \( (p = 0.034) \). Engel Class Ia outcomes were also significantly associated with the site of surgery \( (p = 0.044) \): 112 of the 156 patients who underwent temporal lobe surgery (71.8%) are seizure free compared with 37 of the 65 (56.9%) who underwent extratemporal surgery and 19 of the 34 (55.9%) who underwent multilobar surgery. No significant association was found between Engel Class Ia outcomes and age at epilepsy onset, histological subtype, WHO grade, the presence or absence of dysplasia, or the type of surgical procedure (lesionectomy vs lesionectomy plus corticectomy).

A multivariate analysis to investigate the associations between Engel Class Ia outcomes and all of the variables that proved to be significant in the univariate analysis showed only 3 significant associations: complete resection of the lesion \( (OR \ 5.69, 95\% CI 2.28–14.23; p < 0.001) \); a shorter duration of epilepsy \( (OR 0.92, 95\% CI 0.89–0.94; p < 0.001) \); and temporal lobe resection \( (OR 2.28, 95\% CI 1.24–4.18; p = 0.008) \).

**Discussion**

Epilepsy surgery is an effective therapeutic option for patients with LEATs, which are now frequently diagnosed early as a result of the advances made in neuroimaging techniques and increasingly extensive experience in discovering anatomo-electroclinical correlations. Studies of pediatric epilepsy surgery stress the importance of early interventions because of their beneficial effects on seizures and cognitive development. However, it is still not clear when the optimal time is for surgery, as can be seen from the variability in the mean epilepsy durations reported in the literature. Previous systematic reviews have shown that a shorter duration of epilepsy predicts improved seizure outcomes in patients with gangliogliomas and low-grade gliomas. However, the timing of resection has not been found to be predictive in the case of other lesions such as cerebral cavernous malformations or malformations of cortical development. Moreover, a number of studies have found that epilepsy duration is not predictive of a good outcome in patients with temporal lobe epilepsy. It is therefore not surprising that the so-called right time to treat LEATs surgically is still an open and highly debated question.

Another crucial point is the extent of the resection, which is probably essential when considering postsurgical outcomes. Some investigators consider the simple resection of the tumor alone sufficient for good seizure con-
The aims of this retrospective study were to confirm the indication for surgery in patients with LEATs and to establish any factors predicting a positive postsurgical outcome. Children require special care because of the real possibility of giving them a better life and allowing normal development without epilepsy and AEDs. Therefore, we considered a pediatric and an adult population with similar characteristics (childhood-onset epilepsy and an LEAT as the main lesion) separately, and then compared them in an attempt to establish whether a wait-and-see approach was appropriate, using the criterion of postsurgical epileptological outcome.

The main finding of this study is that it is better not to wait in the case of children with LEATs. The postsurgical outcomes in our pediatric group were very positive, with 112 patients (93.3%) in Engel Class I, and 96 (80%) in Engel Class Ia. Furthermore, our results indicated that outcomes were significantly worse when surgery was performed at or after the age of 18 years, with 104 patients (77%) in Engel Class I, and only 72 (53.3%) in Engel Class Ia (log-rank test p < 0.001; Fig. 3).

The reason for the difference is probably related to a lower likelihood of developing drug resistance or to having fewer seizures; however, in any case, the data strongly support the use of early surgery in children with LEATs. From a biological point of view, it seems very difficult to clarify why the patients operated on before the age of 18 years had better postsurgical outcomes. We can only speculate that the pathological networks were created during the years of illness, but clear evidence is still lacking.

Multivariate analysis of the study population as a whole showed that only 3 variables were significantly associated with an Engel Class Ia outcome: a shorter duration of epilepsy (OR 0.92, 95% CI 0.89–0.94; p < 0.001); complete resection of the lesion (OR 5.69, 95% CI 2.28–14.23; p < 0.001); and temporal lobe resection (OR 2.28, 95% CI 1.24–4.18; p = 0.008).

These data indicate that a shorter duration of epilepsy and a temporal lobe localization are determinant factors for a positive outcome. These findings are in line with those of previous studies in adults,2,15,31,39 who generally suffered from epilepsy longer and were therefore more often drug resistant.

A number of studies have analyzed the surgical treatment and epileptological outcomes of children with LEATs,3,15,20,21,27,33 but none of them have allowed any definitive conclusion as to whether lesionectomy alone leads to seizure freedom. We compared lesionectomy with lesionectomy plus corticectomy and did not find any significant differences, but our multivariate analysis showed that complete lesion resection is crucial (OR 5.69, 95% CI 2.28–14.23; p < 0.001). Some studies in small numbers of adults have suggested the importance of complete resection in the case of DNTs,2,10,11,31 and a study of 26 children with DNTs found that short-term outcomes were influenced by an older age at surgery and a longer duration of epilepsy, and that residual tumor is a significant risk factor for poor long-term seizure outcomes.33 It is therefore probable that achieving excellent postsurgical outcomes is due to the combination of the 3 factors revealed by our multivariate analysis.

The advantages of effective early surgical treatment are that it may prevent the drug-induced, developmentally adverse cognitive effects arising from seizure recurrence and prolonged antiepileptic treatment,29 and it may also prevent the (albeit remote) possibility of a long-term malignant transformation.2,26,31 Another favorable effect is the possibility of discontinuing pharmacological treatment6,22,32; AEDs have been discontinued or reduced in 86 (71.6%) and 16 (13.3%), respectively, of the patients in our pediatric group, and in 58 (42.9%) and 28 (20.7%), respectively, of those in the adult group (p < 0.001).

One final aspect to consider is financial. Operating on patients with a shorter duration of illness (particularly children) avoids the need for multiple invasive and non-invasive examinations. As a result of their more definitive diagnoses, V-EEG and stereo-EEG monitoring were needed in 47 (39.1%) and 11 (9.2%) of the patients in our pediatric group, and in 66 (48.9%) and 27 (20%) of those in the adult group. Moreover, the previously mentioned possibility of discontinuing AEDs also reduces the cost of managing patients with epilepsy.

Although to our knowledge it describes one of the largest reported cohorts, one limitation of this study is its retrospective design; a prospective study is probably needed to confirm our findings.

Conclusions

Our findings suggest that childhood LEATs should be removed early to achieve better seizure-freedom rates and, consequently, to improve cognitive development and avoid the (albeit limited) potential risk of tumor progression. Despite the long natural history of LEATs, waiting is not the optimal means of patient management because it precludes children from the chance of a complete cure (sometimes even without drug therapy) and the possibility of completely normal physical, cognitive, and social development.

References

6. Blümcke I, Wiestler OD: Gangliogliomas: an intriguing tu-

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Tassi. Acquisition of data: Pelliccia. Analysis and interpretation of data: Pelliccia, Deleo, Tassi. Drafting the article: all authors. Critically revising the article: Pelliccia, Deleo, Cosu, Tassi. Approved the final version of the manuscript on behalf of all authors: Pelliccia. Statistical analysis: Deleo. Study supervision: Pelliccia, Tassi.

Correspondence

Veronica Pelliccia, Claudio Munari Epilepsy Surgery Centre, Niguarda Hospital, Piazza Ospedale Maggiore 3, Milan 20162, Italy. email: veronica.pelliccia@ospedaleniguarda.it.