Drug-resistant MTLE is the most common type of epilepsy requiring surgical treatment, with a favorable seizure outcome being achieved in about 60%–75% of patients.\textsuperscript{50,51,64,82,89} Clinically, MTLE is often regarded as a relatively homogeneous syndromic entity, with seizures characterized by typical ictal semiology\textsuperscript{32,96} and EEG findings.\textsuperscript{29,96} However, a variety of MTLE subtypes have been described according to the underlying etiology, with different surgical prognoses.\textsuperscript{47,89,92}

Recent neuropathological classifications of epileptogenic lesions, such as mesial temporal sclerosis (MTS),\textsuperscript{11} granule cell pathology (GCP),\textsuperscript{30} focal cortical dysplasia (FCD),\textsuperscript{12} and epilepsy-associated low-grade tumor (ELGT),\textsuperscript{5,47,54,55,73,74,91} have more precisely defined histopathological features and subtypes, possibly allowing more ac-

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**Seizure outcome in surgically treated drug-resistant mesial temporal lobe epilepsy based on the recent histopathological classifications**

**Clinical article**

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**Object.** The study was performed to investigate the relation between seizure outcome after surgical treatment of mesial temporal lobe epilepsy (MTLE) and pathological findings, classified according to the recently proposed classifications of mesial temporal sclerosis (MTS), granule cell pathology (GCP), focal cortical dysplasia (FCD) and epilepsy-associated low-grade tumors (ELGT).

**Methods.** The authors analyzed data obtained in 120 consecutive cases involving patients presenting with drug-resistant MTLE, who underwent tailored anteromesial temporal lobe resection, and correlated seizure outcome with pathological findings. They identified 5 histopathological groups: Group 1—ELGT; alone or associated with other lesions (30 cases); Group 2—isolated FCD (17 cases); Group 3—MTS, with or without GCP (28 cases); Group 4—MTS associated with FCD, with or without GCP (37 cases); Group 5—other lesions (8 cases).

**Results.** Engel Class I outcome was observed in 83% of patients with ELGT (Class IA in 63%); in 59% of patients with isolated FCD, with FCD Type II showing a better prognosis than FCD Type I; in 82% of patients with isolated MTS (Class IA in 50%), with MTS Type 1a and MTS Type 1b showing a better prognosis than MTS Type 2 and patients with MTS and GCP having better postsurgical results than those with MTS without GCP. Engel Class I outcome was also achieved in 84% of patients with FCD associated with MTS (Engel Class IA in 62%); also in this group MTS 1a and MTS 1b associated with FCD showed a better prognosis than FCD associated with MTS 2. Finally, Engel Class I was also achieved in 2 patients with vascular malformation and in 1 with a temporal pole encephalocele.

**Conclusions.** Patients with MTLE and ELGT, MTS, or MTS associated with FCD showed the best postsurgical seizure outcome (Engel Class I in more than 80% of cases), whereas only 63% of patients with isolated FCD achieved the same type of outcome. Interestingly, the analysis of seizure outcome in histopathological subtypes of FCD and of MTS showed different prognoses in the different pathological subgroups, with worse outcomes for atypical MTS, absence of GCP, and isolated FCD Type I.

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**Key Words** • mesial temporal lobe epilepsy • epilepsy surgery • seizure outcome • hippocampal sclerosis • granule cell pathology • cortical dysplasia • glioneuronal tumor • low-grade tumor

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**Abbreviations used in this paper:** EEG = electroencephalographic; ELGT = epilepsy-associated low-grade tumor; FCD = focal cortical dysplasia; GCP = granule cell pathology; ILAE = International League Against Epilepsy; mMCD = mild malformation of cortical development (microdysgenesis); MTLE = mesial temporal lobe epilepsy; MTS = mesial temporal sclerosis.
accurate clinicopathological correlations and prognostic assessment.

In this study, we analyzed seizure outcome in a population of consecutive patients presenting with drug-resistant MTLE who underwent tailored anteromesial temporal lobe resection after extensive presurgical evaluation without invasive procedures. In particular, we correlated seizure outcome with pathological findings, identified according to the recently proposed classifications of MTS, GCP, FCD, and ELGT.

Methods

We obtained data from the register of the Epilepsy Surgery Centre at the Institute of Neurological Sciences, Bellaria Hospital, Bologna, for all cases in which patients underwent tailored surgery for drug-resistant MTLE between April 2001 and December 2010.

In all cases a detailed clinical history was taken and pathological examination. Electroencephalographic signals were collected by means of noninvasive long-term video-EEG monitoring for seizure recording. Histopathological examination. Immunohistochemistry was performed using a polymer detection system (Ultravision LP Detection System: HRP Polymer, Thermo Scientific). The prediluted antibodies were anti-GFAP (polyclonal), anti-synaptophysin (polyclonal), anti-CD34 (clone QBend/10), and anti–Bel-2 (clone 124). Appropriate positive and negative controls were performed. The Ki 67 (Ventana, clone 30–9, prediluted) labeling index was calculated as the percentage of positive cells per hpf (x400, Zeiss Neofluar 0.25 mm).

All patients were followed up for at least 2 years. Seizure outcome was defined according to the Engel classification.

The surgical planning and procedure were not influenced by neuropsychological findings but relied essentially on antemortem clinical and EEG findings and on MRI data. Functional MRI was performed in all cases. The anterior lateral temporal neocortex was not removed in 1 case, in which the presurgical anatomo-electroclinical data indicated a strictly mesial origin of the epileptogenic zone. In this case (from Group 1, the ELGT group) we performed a trans–superior temporal gyrus approach removing the temporal pole, the tumor (a ganglioglioma) involving the uncus-amygda1a region, and the hippocampal-parahippocampal region. In fact, the most variable part of the surgical procedure regarded the extension of the resection of the lateral neocortex and the length of removed hippocampus. These variables were assessed individually in each case, taking into account anatomo-electroclinical data, boundaries of eloquent cortex in the dominant site, and intraoperative risk factors for hippocampal removal.

Pathological Examination

Hippocampal specimens were dissected along the anterior-posterior axis, and samples from the mid-hippocampal body were chosen for evaluation. Polar temporal specimens were cut perpendicular to the pial surface in 3- to 5-mm sections. Tissue was fixed in 10% buffered formalin and embedded in paraffin. Paraffin sections of 4 μm were serially cut and treated with H & E, Nissl, Kluver, and reticulin staining. In addition, serial 4-μm-thick paraffin sections mounted on precoated slides were processed using standardized automated procedures and antibodies that were prediluted (Ventana Benchmark), with the exception of anti-NeuN (clone A60, dilution 1:500, Chemicon/Millipore Corp.) and anti-IDH1 R132H (clone H09, dilution 1:100, Histoneva, Dianova GmbH) antibodies. Immunohistochemistry was performed using a polymer detection system (Ultravision LP Detection System: HRP Polymer, Thermo Scientific). The prediluted antibodies were anti-GFAP (polyclonal), anti-synaptophysin (polyclonal), anti-CD34 (clone QBend/10), and anti–Bel-2 (clone 124). Appropriate positive and negative controls were performed. The Ki 67 (Ventana, clone 30–9, prediluted) labeling index was calculated as the percentage of positive cells per hpf (x400, Zeiss Neofluar 0.25 mm).

All cases were histologically reviewed according to the WHO classification of tumors of the central nervous system and the more recent classifications for FCD, MTS, and GCP diagnoses.

In 2009, Blümcke et al. elaborated a classification system for GCP recognizing 3 different histological patterns: no GCP (normal granular cell layer); GCP Type 1, characterized by significant cell loss, with a reduced vertical thickness of granular cell layer and/or cell-free gaps in the horizontal direction; GCP Type 2, characterized by broadening of the dentate gyrus granular cell layer or presence of ectopic granule cells in the molecular layer or bilamination of the granular cell layer.

Currently, the status of the dentate gyrus is no longer regarded as an accessory morphological finding, but rather as an additional parameter in predicting seizure and neuropsychological outcome, considering its potential to generate neurospheres from the subgranular zone.

Statistical Analysis

Data are presented as means and ranges. Statistical
Seizure outcome related to pathological findings in TLE surgery

Statistical significance for categorical comparison was determined by the Fisher exact test or eta squared when more than 2 categories were considered. The Mann-Whitney U-test and Kruskal-Wallis test were used for the comparison of continuous variables between 2 or more groups. A p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 16.0.

Results

Data were collected from 120 consecutive cases. All of the patients underwent tailored anteromesial resection for drug-resistant MTLE between April 2001 and December 2010. Fifty-five of the patients were male and 65 were female. Their mean age at epilepsy onset was 14 years (range 6 months–51 years), their mean age at surgery was 33 years (range 3–60 years), and the mean duration of epilepsy was 19 years (range 6 months–51 years). The mean duration of follow-up was 6 years (range 2–11 years). In all but 1 case, the main surgical specimens (hippocampus and temporal pole) were adequate for a proper histopathological evaluation.

On the basis of histopathological findings, we classified the patients into 5 groups as shown in Table 1.

There were no statistically significant differences between any of the groups with respect to age at surgery and epilepsy duration and seizure outcome, although for the ELGT group there was a trend toward worse outcome with older age at surgery and epilepsy duration (p = 0.07).

Seizure Outcome in Relation to Lesion Types

Group 1 (ELGT With or Without Other Lesions). This group included 30 patients (14 male and 16 female, 25% of our series). Their mean age at epilepsy onset was 14 (range 1–51 years), their mean age at surgery was 26 years (range 3–51 years), and the mean duration of epilepsy was 12 years (range 0.5–38 years).

In the whole group, seizure outcome was Engel Class I in 25 patients (Class IA in 19), Engel Class II in 4, and Engel Class IV in 1. The ELGT group included a variety of histological subtypes (Table 2): 13 patients had gangliogliomas (5 of these patients also had FCD IIa, 1 had FCD IIb, 2 had FCD IIIb, and 1 had MTS Type 1a and GCP Type 1); 5 patients had pleomorphic xanthoastrocytoma (associated with FCD IIa in 1 case and with FCD IIIb in another); 3 patients with gangliocytomas (associated with MTS Type 1a and GCP Type 2 in 1 case); 3 patients had dysembryoplastic neuroepithelial tumors (2 also had FCD IIIb); 2 patients had angiocentric gliomas (associated with FCD IIIb in both cases); 1 patient had a papillary glioneuronal tumor; 1 had a melanocytoma (associated with FCD IIIb); 1 had a neurocytoma (associated with FCD IIIb), and 1 had a fibrillary astrocytoma. Interestingly, the association between ELGT and FCD was observed in 53% of patients (16 of 30). In these cases, FCD was Type III in 11 cases and Type II in 5 cases (see Table 3).

Seizure outcome for each histopathological subgroup is reported in Tables 2–4.

### Table 1: Seizure outcome according to lesion type

<table>
<thead>
<tr>
<th>Group</th>
<th>Lesion Type</th>
<th>No. of Pts</th>
<th>Outcome</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>ELGT†</td>
<td>30</td>
<td></td>
<td>25 (83%)</td>
<td>4 (13%)</td>
<td>—</td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IA: 19 (63%)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>isolated FCD</td>
<td>17</td>
<td></td>
<td>10 (59%)</td>
<td>3 (18%)</td>
<td>3 (18%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IA: 8 (47%)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>MTS w/ or w/o GCP</td>
<td>28</td>
<td></td>
<td>23 (82%)</td>
<td>5 (18%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IA: 14 (50%)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>FCD + MTS w/ or w/o GCP</td>
<td>37</td>
<td></td>
<td>31 (84%)</td>
<td>4 (11%)</td>
<td>2 (5%)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IA: 23 (62%)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Group 5‡</td>
<td>vascular lesions§</td>
<td>3</td>
<td></td>
<td>2</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IA: 2</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>temporal pole encephalocele</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IA: 1</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no MTS or FCD</td>
<td>4</td>
<td></td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IIA</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>120</td>
<td></td>
<td>95 (79%)</td>
<td>18 (15%)</td>
<td>5 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class IA: 70 (58%)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* Outcome was assessed using the Engel classification. Abbreviation: Pts = patients.
† Alone or associated with other lesions.
‡ Other lesions.
§ Cavernous angioma or microscopic arteriovenous malformation.
No statistically significant association was found between ELGT type and seizure outcome.

**Group 2 (Isolated FCD).** This group included 17 patients (7 male, 10 female; 14.1% of the series). Their mean age at surgery was 34 years (range 18–45 years); the mean age at seizure onset was 18 years (range 3–41 years), and the mean duration of epilepsy was 16 years (range 1–33 years). Six patients (35%) had FCD Ic and 11 patients (65%) had FCD IIa. Seizure outcome for each histopathological subgroup is illustrated in Table 5. Our data show that 63.6% of patients (7 of 11) with FCD II had Engel Class 1A outcomes, whereas only 16.7% (1 of 6) with FCD I had Engel Class 1A outcomes. We did not find any statistically significant association between FCD type and seizure outcome.

**Group 3 (MTS With or Without GCP).** This group included 28 patients (13 male, 15 female; 23.3% of the series). Their mean age at surgery was 37 years (range 19–54 years), their mean age at seizure onset was 12 years (range 1–31 years), and the mean duration of epilepsy was 24 years (range 4–51 years). Eighteen (64.3%) of these 28 patients had MTS 1a, 5 (17.9%) had MTS 1b, while the remaining 5 patients (17.9%) had MTS 2. Eighteen (64.3%) of these 28 patients had concomitant GCP; in 10 (55.6%) of these 18 cases, a GCP Type 1 picture was present, while in 8 cases (44.4%) a GCP Type 2 picture was observed. In Table 5, seizure outcome for each subgroup is reported. Only 1 (20%) of 5 patients with an atypical pattern of MTS (MTS 2) was seizure free (had an Engel Class IA outcome), while 13 (56.5%) of 23 patients with MTS 1a or MTS 1b achieved complete seizure freedom. With respect to the presence of GCP, we observed that 2 (20%) of 10 patients without GCP had Engel Class IA outcomes, while 12 (67%) of 18 patients with GCP achieved complete seizure freedom. Of the 3 patients with both negative prognostic factors (MTS 2 and no GCP), none achieved complete seizure freedom and 2 had Engel Class II outcomes. Indeed, statistical analysis showed a better outcome in MTS associated with GCP Type 1 than in MTS without GCP (p < 0.05). Comparing the 3 different GCP subtypes, GCP Type 1 showed a better outcome than GCP Type 2 or no GCP (p < 0.005).

**Group 4 (MTS Associated With FCD With or Without GCP).** This group included 37 patients (17 male and 20 female, 30.8% of the total group). Their mean age at seizure onset was 11 years (range 0.5–32 years), the mean duration of drug-resistant epilepsy was long (mean 25 years, range 2–44 years), and their mean age at surgery was 38 (range 2–51 years). The most common histologi-

### TABLE 2: Clinical characteristics and surgical outcome in patients with ELGT (Group 1) stratified by tumor type*

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Pts</th>
<th>Mean Age at Onset (yrs)</th>
<th>Mean Age at Surgery (yrs)</th>
<th>Association w/ FCD</th>
<th>Association w/ MTS</th>
<th>Engel Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>ganglioglioma</td>
<td>13</td>
<td>11</td>
<td>26</td>
<td>8</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>gangliocytoma</td>
<td>3</td>
<td>10</td>
<td>24</td>
<td>—</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>DNET</td>
<td>5</td>
<td>16</td>
<td>22</td>
<td>2</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>PXA</td>
<td>3</td>
<td>17</td>
<td>26</td>
<td>2</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>fibrillary astrocytoma</td>
<td>1</td>
<td>51</td>
<td>51</td>
<td>—</td>
<td>—</td>
<td>II</td>
</tr>
<tr>
<td>melanocytoma</td>
<td>1</td>
<td>11</td>
<td>30</td>
<td>1</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>neurocytoma</td>
<td>1</td>
<td>9</td>
<td>16</td>
<td>1</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>papillary glioneuronal tumor &amp; 1</td>
<td>17</td>
<td>17</td>
<td>34</td>
<td>1</td>
<td>—</td>
<td>I</td>
</tr>
</tbody>
</table>

* DNET = dysembryoplastic neuroepithelial tumor; PXA = pleomorphic xanthoastrocytoma.

### TABLE 3: Seizure outcome in patients with ELGT associated with FCD

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>No. of Pts</th>
<th>Engel Class</th>
<th>Class IA</th>
<th>Class I</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNET + FCD</td>
<td>2 (w/ FCD Iib)</td>
<td>Class IA, 1 Class ID</td>
<td>1 Class IA, 1 Class ID</td>
<td></td>
</tr>
<tr>
<td>gangliogliomas + FCD</td>
<td>8 (w/ FCD Iib, 2 w/ FCD Iic)</td>
<td>6 Class IA, 1 Class IA, 1 Class IIC (FCD Iib, Iia, Iic)</td>
<td>all Class IA, 2 FCD Iib, Class IA, 1 Class Iic</td>
<td></td>
</tr>
<tr>
<td>PXA + FCD</td>
<td>2 (w/ FCD Iib)</td>
<td>1 Class IA, 1 Class IB (FCD Iib, Class IA)</td>
<td>1 Class IA, 1 Class IB</td>
<td></td>
</tr>
<tr>
<td>angiocentric gliomas + FCD</td>
<td>2 (w/ FCD Iib)</td>
<td>1 Class IA, 1 Class ID</td>
<td>1 Class IA, 1 Class ID</td>
<td></td>
</tr>
<tr>
<td>neurocytoma + FCD</td>
<td>1 (FCD Iib)</td>
<td>1 Class IA</td>
<td>1 Class IA</td>
<td></td>
</tr>
<tr>
<td>melanocytoma + FCD</td>
<td>1 (FCD Iib)</td>
<td>1 Class IA</td>
<td>1 Class IA</td>
<td></td>
</tr>
<tr>
<td>all tumors + FCD</td>
<td>16</td>
<td>11 Class IA, 1 Class IB, 1 Class IId, 1 Class IId, 1 Class Iic</td>
<td>68.8%, 81.3%</td>
<td></td>
</tr>
</tbody>
</table>
cal association observed in this series was represented by MTS 1a–FCD IIIa (20 cases, 54.1%), followed by MTS 1b–FCD IIIa (8 cases, 21.6%), MTS 1a–FCD IIa (5 cases, 13.5%), MTS 2–FCD IIa (3 cases, 8.1%), and MTS 2–FCD IIIa (1 case, 2.7%). Thus FCD Type III represents 78.4% of cases (29 of 37), while FCD Type II are 21.6% of cases (8 of 37). Interestingly 22 (59.5%) of the 37 patients of this group had a concomitant GCP, namely GCP Type 1 in 8 cases and GCP Type 2 in 14 cases. For each histopathological subgroup, seizure outcome is illustrated in Table 6. No statistically significant association was found between MTS type, FCD type, or GCP type and seizure outcome.

**Group 5 (Other Lesions).** The remaining 8 cases (6.6%) included 3 cases of vascular lesions (cavernous angioma or arteriovenous malformation, in 2 cases associated with FCD Type IIIc), which resulted in an Engel Class IA outcome in 2 cases and Engel Class II in 1 case; 1 case of temporal pole encephalocele, with excellent outcome (Engel Class 1A); 3 cases in which the hippocampus was normal and the polar temporal cortex showed a mild malformation of cortical development (mMCD); and 1 case in which the hippocampus was not pathologically valuable, due to the unsatisfying condition of the surgical specimen, while polar temporal cortex showed mMCD. No statistical analysis was performed in this group due to the low number of patients and heterogeneity of the lesions.

Regarding treatment failures, the great majority of patients for whom Engel Class IA outcomes were not achieved had Engel Class IB, IC, ID, and II outcomes (see Table 1) with a very low postsurgical seizure frequency. Due to the low chance of recording seizures, no postsurgery long-term video-EEG monitoring was performed in these cases. Five patients had Engel Class III outcomes and 2 had Class IV outcomes. All 5 of these patients underwent postoperative long-term video-EEG monitoring and detailed 3-T MRI studies. The data obtained in the postoperative evaluation suggested that in these patients the failure might be due to incomplete resection of the epileptogenic lesion in order to avoid functional deficit (in 2 patients), incomplete resection of the epileptogenic area (in 3 patients), or incorrect localization of the epileptogenic area (in 2 patients).

**Complications**

No patient died during surgery or the postoperative course. Surgical complications occurred in 6 cases (5%): 2 patients (1.6%) (1 with a subdural hygroma and 1 with sagging of the bone flap) required reoperation. Antibiotic therapy was necessary in 1 patient because of superficial wound infection. Postoperative deep venous thrombosis requiring anticoagulation treatment occurred in 3 cases.

Major neurological postoperative complications occurred in 4 cases (3.3%)—hemiparesis in 1 case (0.8%), hemianopia in 3 cases (2.5%). Two of the 3 patients with hemianopia had a lesion involving the temporomesial optic tract region (a cavernous angioma in 1 case and an ELGT in the other).

Lastly, as a minor neurological complication, transitory nominal aphasia occurred in 5 cases (4.1%). Neuropsychological and psychiatric side effects are not addressed in this study.

**Discussion**

Mesial temporal lobe epilepsy is the most common

### Table 4: Seizure outcome in patients with ELGT without cortical dysplasia

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Pts</th>
<th>Engel Class</th>
<th>Class IA</th>
<th>Class I</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNET</td>
<td>1</td>
<td>Class IA</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>ganglioglioma</td>
<td>5</td>
<td>2 Class IA, 1 Class I, 1 Class II, 1 Class III, 1 Class IVA</td>
<td>60%</td>
<td>78.6%</td>
</tr>
<tr>
<td>gangliocytoma</td>
<td>3</td>
<td>2 Class IA, 1 Class IB</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td>PXA</td>
<td>3</td>
<td>2 Class IA, 1 Class II</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td>fibrillary astrocytoma</td>
<td>1</td>
<td>Class IVb</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>glioneuronal papillary tumor</td>
<td>1</td>
<td>Class IA</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>all tumors</td>
<td>14</td>
<td>8 Class IA, 1 Class IB, 1 Class I, 1 Class II, 1 Class III, 1 Class IVA</td>
<td>51.7%</td>
<td>78.6%</td>
</tr>
</tbody>
</table>

### Table 5: Seizure outcome in Group 2 (patients with isolated FCD) stratified by type and in Group 3 (patients with MTS) stratified by presence of GCP

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>No. of Pts</th>
<th>Engel Class</th>
<th>Class IA</th>
<th>Class I</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCD</td>
<td>17</td>
<td>7 Class IA, 1 Class IB, 1 Class II, 1 Class III, 1 Class IV</td>
<td>63.6%</td>
<td>72.7%</td>
</tr>
<tr>
<td>Type Ila</td>
<td>11</td>
<td>1 Class IA, 1 Class IB, 1 Class II, 1 Class III, 1 Class IV</td>
<td>16.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Type Ic</td>
<td>6</td>
<td>1 Class IA, 1 Class IB, 1 Class II, 1 Class III, 1 Class IV</td>
<td>16.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td>MTS</td>
<td>28</td>
<td>Total</td>
<td>80.7%</td>
<td>72.7%</td>
</tr>
<tr>
<td>w/o GCP</td>
<td>10</td>
<td>2 Class IA, 1 Class IB, 1 Class I, 1 Class II, 1 Class III, 1 Class IV</td>
<td>20%</td>
<td>60%</td>
</tr>
<tr>
<td>w/ GCP</td>
<td>18</td>
<td>12 Class IA, 1 Class IB, 1 Class I, 1 Class II, 1 Class III, 1 Class IV</td>
<td>67%</td>
<td>94%</td>
</tr>
</tbody>
</table>
epilepsy syndrome that is amenable to surgical treatment. The effectiveness, efficacy, and safety of epilepsy surgery for MTLE have been established through one randomized controlled trial, and numerous reports.3,30,31,51,63,64,79,82,83,87,89 The literature provides relatively consistent evidence that common pathogenic mechanisms have been also encountered, whether alone or in association, and it has been shown to considerably improve the reproducibility of the entire group of situations in which FCD can be suggested for ELGT and FCD Type II.61,70 The new classification systems for the main histopathological abnormalities observed in MTLE patients—that is, hippocampal sclerosis, GCP, FCD, and ELGT—have been revised.

In 2011, the new ILAE classification system for FCD introduced, with respect to the previously internationally adopted classification, a third FCD category—FCD Type III—in addition to FCD Type I (for abnormalities in cortical architecture) and FCD Type II (characterized by large and dysmorphic neurons, with or without the presence of balloon cells). Indeed, FCD Type III identifies FCD Type I coexisting with other lesions—hippocampal sclerosis (FCD Type IIIa), epilepsy-associated tumors (FCD Type IIIb), vascular malformations (FCD Type IIIc), or any other lesion acquired during early prenatal or perinatal life (FCD Type IIId). In particular, FCD Type IIIb has been adopted to define cases characterized by the association of FCD Type I with ELGT, supporting therefore the concept that the etiology and pathogenesis of these 2 types of lesions are likely related. It must be pointed out that common pathogenic mechanisms have been also suggested for ELGT and FCD Type II.64,70 The new classification attempts to elaborate a comprehensive view of the entire group of situations in which FCD can be encountered, whether alone or in association, and it has been shown to considerably improve the reproducibility of FCD diagnosis.21 To our knowledge, our study is the first effort to assess the impact of this new classification on surgical practice and prognosis. Thus we have reviewed our series of patients with drug-resistant, surgically treated MTLE, trying to correlate seizure outcome with histopathological findings classified according to the recent proposals.9–12,54,55,73,74,91 In our study, we observed a good seizure outcome, with over 80% of MTLE patients in Engel Class I in the ELGT, MTS, and FCD + MTS groups; the outcome in the isolated FCD group was less satisfying, with only 59% of patients having Class I outcomes.

In the ELGT group, of 25 patients (83%) with Class I outcomes, 19 (63% of the ELGT group) had Class IA outcomes. Four patients (13% of the ELGT group) had Class II outcomes and 1 (3%) had a Class IV outcome. These findings confirm that surgery in MTLE associated with ELGT can achieve optimal results, as previously reported by several studies.7,12,15,16,19,20,23,25,26,35,36,38,41,44,50,55,89,99

All patients with ELGTs had tailored resections to remove the tumor and the epileptogenic zone. In all but 1 of the patients, surgery consisted of removing the tumor (frequently located in the uncus–entorhinal area, amygdala-hippocampal head), the temporal pole, the anterior neocortical lateral cortex, and the hippocampus and parahippocampal gyrus. The anterior temporal neocortex was left in only 1 case, in which the anatomo-electroclinical data indicated a strictly mesial origin of the epileptogenic zone. Temporomesial structures were removed in all cases with ELGT, since it has been extensively demonstrated that the medial temporal lobe, specifically the hippocampus and the entorhinal cortex, have a great epileptogenic potential.15,38,80,94 and that the amount of tissue resected in temporal lobe epilepsy surgery is crucial for surgical success.17,80

In addition, we observed statistically significant differences in a retrospective study comparing seizure outcome in 2 homogeneous series of temporomesial ELGTs, one treated with simple lesionectomy, the other with lesionectomy and tailored resection of the epileptogenic zone; in fact, only 42.8% of those treated by lesionectomy alone were seizure-free (according to the Engel classification) compared with 93% of those who underwent a tailored resection.44 We confirmed these results in a recent retrospective pediatric series.9

The higher effectiveness of an extended resection, beyond the low-grade tumor, might depend on the frequent association of this tumor type with other epileptogenic pathologies, such as the spectrum of cortical dysplasias that might represent the origin of a widespread epileptic network.2

The analysis of outcome in the different types of ELGT found in our patients is significantly limited by the small number of cases in each histopathological subtype;
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Thus we cannot provide clear-cut prognostic information for each of these tumor types. However, examining the larger groups, such as ganglioglioma associated with FCD (8 cases) and pleomorphic xanthoastrocytoma (5 cases), we obtained Engel Class I seizure outcome respectively in 75% of the ganglioglioma and FCD group (6 cases, all with Class IA outcome) and 80% of the pleomorphic xanthoastrocytoma group (4 cases), suggesting that these 2 types of ELGT are probably associated with the best postsurgical seizure outcome. The group of ELGTs, represented mainly by glioneuronal tumors, is currently enlarging not only for the recognition of new, often rare, histotypes but also for the continuous identification of tumors having hybrid or mixed features that suggest the existence of a histological spectrum that can be difficult to categorize.\(^4\),\(^5\),\(^6\),\(^7\),\(^8\),\(^9\),\(^10\) In addition, in our series the association between ELGT and FCD was observed in 53% of cases, confirming previous studies reporting this association in 40%–80% of cases. The new class, FCD Type IIIb, which includes cases with abnormal cortical layering (called FCD Type I when alone) associated with ELGT, has been introduced by the recent ILAE FCD classification.\(^12\) Also in this “mixed” context, as evidenced in cases of isolated FCD (Group 2) below, it can be observed that FCD Type II shows a better postsurgical outcome; for example, the 4 patients (100%) with ganglioglioma and FCD Type Ila all had Engel Class IA outcomes, while only 2 (50%) of 4 patients with ganglioglioma and FCD Type IIIb are completely seizure free. The specific role of each one of these pathological lesions in epileptogenesis is still not well defined.\(^5\),\(^14\),\(^22\),\(^25\),\(^43\),\(^44\),\(^48\),\(^59\),\(^69\),\(^75\) Finally, in our series we found ELGT associated with MTS in 2 cases (10%), in agreement with previous data that reported this association in 2%–25% of cases.\(^14\),\(^16\),\(^86\),\(^98\)

In the setting of ELGT, the distinction among the various subtypes of tumors is essential for predicting the seizure outcome and the oncological behavior. In fact, gangliogliomas and dysembryoplastic neuroepithelial tumors may have pronounced intrinsic epileptogenic properties due to their neuronal and glial components,\(^14\),\(^21\),\(^23\),\(^25\),\(^27\) and their complete removal may lead to seizure freedom. With respect to oncological behavior, ELGTs are usually indolent WHO Grade I lesions, although several reports have demonstrated that gangliogliomas may potentially have an evolving course and may demonstrate malignant transformation.\(^26\),\(^46\),\(^52\),\(^56\),\(^66\),\(^72\) Pleomorphic xanthoastrocytoma can carry a higher risk of early recurrence when it is characterized by numerous mitoses and/or necrosis.\(^39\),\(^40\),\(^68\) Therefore, considering the good prognosis for epilepsy and the possible, although low, risk of malignant transformation, we think that ELGTs should be properly and quickly diagnosed by adequate imaging investigations and considered early for surgical treatment, particularly in young patients, to avoid psychosocial consequences and disability due to long-standing medically intractable seizures.\(^73\),\(^75\),\(^35\),\(^34\),\(^41\),\(^42\),\(^44\),\(^45\),\(^76\),\(^79\)

In our group of 17 patients with isolated FCD, we identified FCD Type Ila in 11 patients, FCD Type Ic in 6 patients. Of the patients with FCD Type Ila, 8 (72.7%) had Class I outcomes, 7 of them (63.6%) of the FCD Ila group had Class IA, whereas considering FCD Type Ic, (Engel Class I outcome was observed in 2 (33.3%) of 6 patients, with only 1 patient (16.6%) having a Class IA outcome. These data, although they should be interpreted with caution due to the small number of patients, seem to suggest a significantly better prognosis for FCD Type II than for FCD Type I.

In our patients with isolated MTS, different histopathological subtypes were identified. Indeed, the latest histopathological classification system for MTS recognizes 2 main groups, MTS Type Ia and Ib, and 2 atypical variants, MTS Type 2 and Type 3. Furthermore, in 2009 a classification system for GCP was elaborated,\(^10\) distinguishing 3 different histological patterns: 1) no GCP (normal granule cell layer); 2) GCP Type 1 (substantial granule cell loss); and 3) GCP Type 2 (architectural abnormalities in the granule cell layer, mainly granule cell dispersion).\(^10\) Analyzing our MTS group as a whole, the seizure outcome was optimal, with Class I outcomes achieved in 82% of cases (although Class Ia in only 50%), whereas the outcome was Class II in the remaining 18%. The various outcome classes were scattered among the different MTS subtypes. Regarding the 14 patients with the best outcome, Engel Class IA was obtained in 11 (61%) of 18 with MTS Ia (with or without GCP), in 2 (40%) of 5 patients with MTS Ib, and in 1 (20%) of 5 patients with MTS 2. Our findings suggest good results after surgery in patients with MTS Ia and MTS Ib, with up to 80% of patients having Engel Class I outcomes. However, when we analyzed cases in which Class IA outcome (complete seizure freedom) was achieved, we found a better outcome for MTS Ia than for MTS Ib (61% vs 40%). Finally, only 1 patient (20%) with MTS 2 had an Engel Class IA outcome, confirming findings in the literature that indicate a worse seizure outcome in this MTS group.\(^11\),\(^92\) Regarding a possible correlation between GCP and seizure outcome, this issue is still under investigation, and the results reported so far are not univocal.\(^20\),\(^24\),\(^57\),\(^61\),\(^62\),\(^92\) In our series we found the different types of GCP (no GCP, GCP 1, GCP 2) associated with the different types of MTS, but for GCP 2 and MTS 2.

Considering the presence of GCP, we observed that 2 (20%) of 10 patients without GCP were in Engel Class IA, while 12 (66.7%) of 18 patients with GCP achieved complete seizure freedom. Focusing on the 3 patients with both negative prognostic factors (MTS 2 and no GCP), none of them achieved complete seizure freedom, but 2 of them had Engel Class II outcomes. These findings indicate better postsurgical results in patients with GCP as compared with those without GCP. The demonstration that a decreased potential to generate neurospheres from the subgranular zone is related to MTS and to alterations of dentate gyrus granule cells, especially in MTS Type Ia and GCP Type 1, suggests the existence of a relationship between dentate gyrus pathology and postsurgical outcome.\(^62\) Indeed, these histological findings may have relevant prognostic implications, regarding either seizure and neuropsychological outcome, in these patients as compared with patients with other epileptogenic lesions (such as FCD, glioneuronal tumors, or vascular lesions).\(^22\),\(^57\),\(^61\),\(^80\),\(^92\)

The association of FCD with MTS was the most common in our series, since it was found in 37 patients.
These cases are now classified as FCD Type IIIa, since the introduction of this class in the 2011 ILAE proposal to diagnose cases of FCD Type I coexisting with hippocampal sclerosis.

In this group, Engel Class I outcome was achieved in 31 cases (84%), with 23 (62%) of them in Engel Class I A. Subgroup analysis by MTS subtype showed that 19 (72%) of 25 and 6 (75%) of 8 patients, respectively, with MTS Ia and MTS Ib associated with FCD, achieved an Engel Class I A outcome, whereas this outcome was observed only in 50% of patients (2 of 4) with MTS 2, again suggesting that patients with MTS I probably have a better seizure outcome after surgery than those with atypical forms of MTS (that is, MTS 2). Interestingly, dividing this population according to the subtypes of FCD, we observed that 87.5% of patients (7 of 8) with FCD Type Ia had Class I outcomes (Class I A in 62.5% [5 of 8]), and 82.8% of patients (24 of 29) with MTS Type III had Class I outcomes (Class I A in 75.9% [22 of 29]). These data suggest that the coexistence of MTS may “mitigate” the worse outcome associated with isolated FCD I as compared with isolated FCD II (see above).

In the group of patients with heterogeneous disorders (3 vascular malformations, 1 temporal pole encephalocoele, and one case difficult to classify due to the inadequacy of the surgical specimen), we obtained Engel Class I outcomes in 3 patients (2 with vascular malformations and the patient with temporal pole encephalocoele had Class I A outcomes) and Engel Class II in the remaining patient, therefore achieving in all of them a clear-cut improvement of their epilepsy.

Our study supports the thesis that pathological substrate represents a significant predictor for seizure recurrence, with rates of Engel Class I outcomes ranging from 59% for patients with isolated FCD to 82%, 83%, and 84%, respectively, for isolated MTS, ELGT, and FCD associated with MTS. These results, as a whole, are in agreement with the majority of data reported in the literature and were obtained with a presurgical evaluation procedure that did not include invasive investigations.

Our neurosurgical complication rate is in line with the pertinent literature, and, also in agreement with literature, over the course of our experience there was an increase of expertise that is mainly reflected in a decrease in perioperative morbidity. A major neurological complication (hemiparesis) occurred at the beginning of our epilepsy surgery program.

To our knowledge, this study represents the largest homogeneous series to date reporting seizure outcomes related to neuropathology in surgically treated drug-resistant MTLE according to the new classification systems of MTS, GCP, FCD, and ELGT. Our findings suggest that different pathological subtypes are associated with different postsurgical seizure outcomes. This implies that surgical failure, that is, seizure recurrence, may occur either because of incomplete resection of the epileptogenic zone or because of an underlying pathological condition with a worse outcome. The epilepsy surgeon should be aware of the relevance of the histopathological assessment and provide adequate specimens for a proper pathological diagnosis. Finally, the recognition of the different subgroups of pathological conditions associated with different seizure outcomes should stimulate the investigation of the specific epileptogenic mechanisms, relating the outcome mainly to the pathological substrate, thus rendering misleading and obsolete the correlation between seizure outcome and site of the focus (temporal, frontal, and so on). This approach is also in agreement with the recent suggestions of the ILAE Commission on Classifications and Terminology to put more emphasis on the underlying pathological substrate in the assessment of postsurgical seizure outcome and in future epilepsy classifications.

In our series such a significant correlation between histopathology and seizure outcome is related to our strict application of the recent histopathological classification of MTS, GCP, FCD, and ELGT. To our knowledge, our study is the first effort to assess how these new histopathological classifications can be related to seizure outcome. Our opinion is that this approach might improve the interpretation of the results and the comprehension of the causes of failures and possibly advance imaging-pathology correlations.

Comments on the Application of the New Histopathological Classification Systems

This study shows that, with the adoption of the more recent neuropathological classification systems, some subgroups of pathological abnormalities with worse outcomes have emerged; they are represented in particular by atypical patterns of MTS, absence of GCP, and presence of isolated FCD Type I. The application of such new classification systems to a large cohort also raises some criticisms.

First, in some of our patients we observed mMCD, but we did not consider this condition in our statistical analysis because very low interobserver and intraobserver reproducibility have been demonstrated for this histological diagnosis. Indeed, the task force has not made an attempt to review this issue critically or to change this classification scheme. However, considering that in the temporal neocortex mMCD could be epileptogenic and that it can affect the diagnosis of FCD Type I, the significance and the features of mMCDs should be clarified.

Second, the new class FCD Type IIIb, which includes cases with abnormal cortical layering associated with ELGTs, has been introduced by the ILAE classification, but in light of the frequent association of FCD Type II with ELGTs and the immunohistochemical evidence of a common pathogenesis linking ELGTs and FCD Type II, the possibility of creating a unifying class also for this kind of FCD should be considered.

Conclusions

Our study indicates that 1) seizure outcome in MTLE is strongly related to the underlying pathology, 2) the epilepsy surgeon must be able to obtain an adequate and appropriately oriented surgical specimen for proper pathological diagnosis, and 3) neuropathological diagnosis must follow and strictly observe an adequate international pathological protocol.
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These conclusions suggest that 1) some failure or recurrence may be related to a pathological substrate with worse outcome on seizure and not to an incomplete epileptogenic zone resection, 2) further studies grouping patients by histological type and subtype are necessary to clearly define the relationship between the cause of epilepsy and seizure outcome and to understand the specific epileptogenic mechanisms involved, and 3) improved pathological and neuroimaging correlations should also be achieved in order to facilitate an early correct diagnosis and correct management that includes an early surgical approach in patients with lesion-related focal epilepsy.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Giulioni. Acquisition of data: Giuliioni, Marucci, Volpi, Riguazzi, Bisulli, Rubboli. Analysis and interpretation of data: Giuliioni, Marucci, Martinoni, Tinuper, Tassinari, Michelucci, Rubboli. Drafting the article: Giuliioni, Mar­t­inoni, Riguazzi, Marliani, Tinuper. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Giuliioni. Statistical analysis: Martinoni. Study supervision: Giuliioni.

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