PART I
Epilepsy and antitumor treatment

2) Seizure outcome after radiotherapy and chemotherapy in glioma patients and its relation with radiological response: a systematic review

3) Seizure reduction in a low-grade glioma: more than a beneficial side effect of temozolomide

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Seizure outcome after radiotherapy and chemotherapy in glioma patients and its relation with radiological response: a systematic review

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ABSTRACT

There is growing evidence that antitumor treatment contributes to better seizure control in low-grade glioma patients. We performed a systematic review of the current literature on seizure outcome after radiotherapy and chemotherapy, and evaluated the association between seizure outcome and radiological response. Twenty-four studies were available, of which 10 described seizure outcome after radiotherapy, and 14 after chemotherapy. All studies demonstrated improvements in seizure outcome after antitumor treatment. Eight studies reporting on imaging response in relation to seizure outcome showed a seizure reduction in a substantial part of patients with stable disease on MRI. Seizure reduction may be therefore be the only noticeable effect of antitumor treatment. Our findings demonstrate the clinical relevance of monitoring seizure outcome after radiotherapy and chemotherapy as well as the potential role of seizure reduction as a complementary marker of tumor response in low-grade glioma patients.

INTRODUCTION

Seizures affect 30-90% of patients with a glioma, and are particularly prevalent in patients with low-grade glioma (LGG). Despite antiepileptic drug (AED) treatment, 15-35% of patients still experiences seizures. Uncontrolled, seizures may result in high morbidity as well as negatively impact quality of life. Therefore, achieving seizure control is an important challenge in the clinical management of LGG.

There is growing evidence that the antitumor treatment itself may lead to better seizure control in LGG patients. Several studies have described a reduction in seizure frequency or seizure freedom after surgery, radiotherapy and chemotherapy, which means a direct clinical benefit for the patient. Furthermore, the effect of antitumor treatment on seizure frequency could be of value in the assessment of tumor response. Currently, tumor response assessment according to the RANO (response assessment in neuro-oncology) criteria is largely based on magnetic resonance imaging (MRI). However, radiological assessment can be rather difficult, particularly after radiotherapy and chemotherapy. In a substantial part of LGG patients, a clinical improvement after non-surgical treatment is not accompanied by an objective radiological response. Thus, in some patients the radiological response does not fully reflect the actual benefit of the treatment. It is therefore of major interest to determine possible complementary outcome measures after antitumor treatment.

With this systematic review we aim to increase the knowledge of the course of epilepsy after antitumor treatment, by giving a comprehensive overview of 1) the existing literature on seizure outcome after radiotherapy and chemotherapy in patients with LGG, and 2) the association between seizure outcome and radiological response after antitumor treatment.

MATERIALS AND METHODS

Search strategy and selection criteria

We performed a literature search, using the electronic resources PubMed and Embase until August 2014. The complete search strategy is outlined in the table 1. The search included a combination of search terms related to ‘glioma’, ‘radiotherapy or chemotherapy’ and ‘seizure outcome’, limited to English language and human studies.

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two authors (JAFK and MK) determined whether the
articles were eligible for inclusion and served as reviewers of the full texts of all selected articles. Inclusion criteria were: (i) adult patients with histologically proven WHO grade II glioma, (ii) treated with radiotherapy (focal fractionated irradiation, stereotactic radiotherapy or brachytherapy) or chemotherapy, (iii) a sample size ≥5. Initial exclusion criteria were: (i) reviews, (ii) abstracts not published as full papers. Additionally, we applied the following exclusion criteria to the remaining articles: (i) no seizure outcome after antitumor treatment reported, (ii) only acute symptomatic seizures described. We searched the reference lists of the selected full text articles to identify additional studies. From the selected articles, we extracted the following data: study design, sample size, demographic and clinical characteristics of the study population, type of radiotherapy or chemotherapy, additional antitumor treatment, time of seizure assessment, and seizure outcome (seizure frequency, seizure reduction, Engel Class and/or seizure freedom). If available, we reported the radiological response in relation to seizure outcome.

**RESULTS**

The search yielded 5590 unique records, of which we assessed 349 full text articles for further eligibility (figure 1). Additionally, we excluded articles for the following reasons: no seizure outcome after radiotherapy or chemotherapy (n=306), only acute symptomatic seizures described (n=19), and studies with children (n=2), and studies with HGG patients only (n=1). Eventually, we included 21 articles and found three additional studies by screening the reference lists of the remaining full text articles. The available 24 studies were categorized into the following three topics: (1) seizure outcome after radiotherapy (10 studies), (2) seizure outcome after chemotherapy (14 studies), and (3) seizure outcome in relation to radiological response (eight studies). All eligible studies are discussed in the context of these three topics in the following sections.

**FIGURE 1: Selection of articles**

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<table>
<thead>
<tr>
<th>Table 1: Search terms</th>
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<tbody>
<tr>
<td><strong>Pubmed</strong></td>
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<td><strong>Embase</strong></td>
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<tr>
<td>(“Brain tumor”exp OR ’glioma’ti,ab OR ’gliomas’ti,ab OR ’glioblastoma’ti,ab OR ’gbm’ti,ab OR ’astrocytoma’ti,ab OR ’oligodendroglioma’ti,ab OR ’brain tumor’ti,ab OR ’brain tumors’ti,ab OR ’brain cancer’ti,ab) AND (’Radiotherapy’exp OR ’radiotherapy’ti,ab OR ’irradiation’ti,ab OR ’radiosurgery’ti,ab OR ’chemotherapy’exp OR ’chemotherapy’ti,ab OR ’temozolomide’ti,ab OR ’pcv’ti,ab OR ’nitrosourea’ti,ab) AND (’outcome’ti,ab OR ’seizure’ti,ab OR ’seizures’ti,ab OR ’epilepsy’ti,ab)</td>
</tr>
</tbody>
</table>

Limit to human and English
Seizure outcome after radiotherapy

The key findings of all 10 studies that described seizure outcome after radiotherapy are outlined in table 2 (page 32).12,23-25,40,41 We found eight patient series12,23-25,37-39,41-43 and one randomized controlled trial.12 The design of one study was unclear.88 However, in all 10 studies seizure data were collected retrospectively. Patients had been treated with focal fractionated irradiation (four studies),12,23-25,37-39 brachytherapy (three studies),88,91-93 or stereotactic radiotherapy (three studies).35,39,42 Five studies included patients with LGG only,27,29,30 three with a WHO grade II or grade III glioma,12,35,36 and two studies included mainly patients with LGGs but also a small group of other, non-glial brain tumors.93,94 In five studies radiotherapy was the first antitumor treatment,12,48,21,88,93 in four studies a proportion of the patient group had previously undergone resection,12,35,88,93 and in one other study previous antitumor treatment was not specified.94 The number of patients in whom seizure outcome was assessed ranged considerably from 5-173 cases. Four studies included both patients with and without a history of epilepsy,12,46,91,93, two other studies included only patients with a history of epilepsy29,30 and four other studies only included patients with medically intractable epilepsy.12,26-28

All studies reported an improved seizure outcome after radiotherapy, however, different seizure outcome measures were used, such as the percentage of patients showing a reduction in seizure frequency, seizure freedom and improved Engel Class. A reduction in seizure frequency, ranging from ≥50% to >75%, was reported in three studies in 72-100% of patients.34,37,39 One study that included WHO II-III glioma patients on a stable AED dose treated with focal fractionated irradiation reported a ≥50% seizure reduction in 72% after 3 months, and in 77% 12 months after radiotherapy. Seizure reduction appeared to be more common in patients with a long history of seizures before the start of radiotherapy.12 One smaller series evaluating seizure outcome after focal radiotherapy reported a >75% seizure reduction in 4/5 patients.12 In a series of 15 patients treated with brachytherapy, all patients showed a reduction in seizure frequency, although the extent of the reduction was not reported.88 In another series of 26 patients treated with Gamma knife radiosurgery in different doses, 66% of patients treated with a high dose reported Engel Class I or II compared to 42% in the low-dose group.99 Seizure freedom was reported in nine articles, ranging from 20% after focal radiotherapy to 80% 6 months after treatment with brachytherapy.88 In one study that compared early versus late radiotherapy in patients with LGG, 59% of patients were seizure free 12 months after treatment in the late radiotherapy group, compared to 75% of patients in the early radiotherapy group.90 Before the start of radiotherapy, there were no differences in the number of patients with controlled seizures between the two groups.90 In a large cohort of 143 patients with LGG treated with stereotactic radiotherapy evaluating seizure outcome 6 weeks post-treatment, the percentage of patients reporting seizures decreased from 70% to 24%.91 Two other studies on brachytherapy reported seizure freedom after 6 months in 80% of patients initially suffering from seizures,91 and after 12 months in 56% of patients.91

Seizure outcome after chemotherapy

In total, 14 studies described seizure outcome after chemotherapy.92-94-96-98 The key findings of all studies are outlined in table 3 (page 34). We found no randomized controlled trials. Seven studies had a prospective non-controlled design,22,35,36,39,41,42 the seven other studies were retrospective,93,94,36,37,39,41,43 of which one study had included a control group of patients with LGG under observation.93 All studies reported patients with diffuse WHO II glioma including astrocytoma, oligoastrocytoma and/or oligodendroglioma. Patients had been treated with either temozolomide (TMZ) (eight studies),93,36,37,39,41,42,45,46 procarbazine-lomustine-vincristine (PCV) (four studies),94,34,35,42 or different types of chemotherapy (either TMZ, PCV, fotemustine, cisplatin or etoposide (two studies).94 In all studies, except one,93 patients had received other antitumor treatment before chemotherapy was administered: in nine studies part of the patients had undergone surgery alone,12,22,24-26,37,39,41,94 in one study radiotherapy alone,94 and in three studies surgery and/or radiotherapy40,41 The number of patients in whom seizure outcome was analyzed ranged from 9-149 subjects. The studies included patients with a history of epilepsy (eight studies),12,22,24-26,37,39,41,43 uncontrolled seizures despite AED treatment (four studies),34,37,40-41 or an unknown seizure status before the start of chemotherapy (two studies).92,93

A reduction in seizure frequency was described in ten of 14 studies, and varied from 48-100%.92,24,41,43-44 Four of these ten studies had defined seizure reduction as a ≥50% reduction in seizure frequency and the six other studies did not specify their definition of a seizure reduction. Of the studies describing seizure reduction, in three studies the timing of seizure assessment was not specified,93,37,39 and in three other studies a seizure reduction was already observed at some point during chemotherapy.93 In the remaining four articles that described seizure frequency, seizures were assessed at fixed intervals (two studies)93,44 or at a specific point in time from the start of chemotherapy (two studies).94 The other four of 14 studies used seizure control or Engel Class as the seizure outcome measure. In these studies, improved seizure control was reported in 30-100% of cases.92,24,41,44

Pace et al. prospectively assessed seizure frequency after every 3 TMZ cycles in patients with progressive LGG and uncontrolled epilepsy. They found a ≥50% seizure
In the only study with a control group, a cohort of 39 patients treated with TMZ was retrospectively compared with 30 patients with LGG under observation. A ≥50% seizure reduction was observed in 59% of the TMZ group in contrast to 13% in the control group. However, when only patients without AED changes were taken into account, seizure reduction was 18% and 0%, respectively.

**Seizure outcome in relation to radiological responses**

We found eight articles in which radiological responses on MRI were described in relation to seizure outcome (Table 4 on page 36). All studies included patients with WHO grade II glioma. Five studies reported on radiological response after TMZ, one study on response after PCV, and two studies on the radiological response after focal irradiation. In six studies data on seizure reduction were available in patients with and without an objective response on MRI.

Four studies that evaluated the response after TMZ applied the revised MacDonald criteria to assess MRI response. In three of these studies patients with and without a response on MRI were compared in terms of seizure reduction. In all three studies, the percentage of patients with a seizure reduction was higher in patients showing an MRI response than in those without. Nevertheless, 21-50% of patients with stable disease on MRI still experienced seizure reduction after TMZ treatment, compared to 29-67% of patients with an objective radiological response. The timing of the response assessment differed considerably between studies, ranging from a single response assessment at a fixed time point to a series of assessments every 3-6 months. One other study on TMZ showed a neurological improvement in 33% of patients with radiologically stable disease (SD), although the precise number of patients with a seizure reduction was not reported.

The only study in PCV-treated patients reported improved seizure control in most patients with a response on MRI, but seizure control in patients without an objective radiological response was not reported.

The largest study on radiological response after radiotherapy analyzing both WHO grade II and III glioma patients, applied the revised MacDonald criteria for LGG as well. At both 3, 6 and 12 months after radiotherapy the percentage of patients with a ≥50% seizure reduction was highest in the group with an objective radiological response, ranging from 78-86%, compared to 64-76% of patients with SD on MRI. In another series of five cases all three patients with a partial response on CT or MRI showed a ≥75% seizure reduction. Of the two remaining patients with radiologically stable disease, one patient had a reduction in seizure frequency.

**DISCUSSION**

All studies that we included in this systematic review demonstrated improvements in the seizure status of patients with LGG after treatment with radiotherapy or chemotherapy. In the largest patient series, ≥50% seizure reduction between 44 and 77% has been reported after focal fractionated irradiation and TMZ chemotherapy. In general, a seizure reduction appeared to be more common in patients with an objective radiological response. However, in all studies that reported on imaging response in relation to seizure outcome, a substantial part of patients with SD reported a seizure reduction as well. These findings underscore the importance of monitoring patient’s seizure status, as a seizure reduction may be the only noticeable effect of antitumor treatment.

Many studies have shown that tumor resection may positively influence seizure outcome in LGG patients. In 13/14 studies on chemotherapy and in 4/10 studies on radiotherapy, part of the included patients underwent previous surgery. Due to a possibly long-term positive effect of tumor resection on seizures, seizure reduction due to radio- or chemotherapy might have been underestimated. Furthermore, the stage of the disease course at the time of analysis differed considerably both between and within the studies.

There are additional limitations of this review, that are mostly inherent to the diversity of studies. In most cases, a clear definition of measures such as seizure control or seizure reduction was lacking. As patient’s seizure status was often not the primary outcome measure, in many of the studies little information was available on both
seizures before the start of antitumor treatment and on seizure outcome. In the subset of studies in which well-defined seizure outcome measures were available, these measures were not consistent. Thus, there is class III evidence at best regarding seizure outcome after antitumor treatment, since most studies had a retrospective nature and were lacking an appropriate control group. In addition, data regarding concomitant AED use were lacking in almost all studies. Apart from three studies in which it was specifically documented that only patients on a stable AED dose were analyzed, a change in AED dose and/or AED type could have underlain the improved seizure outcome. Due to publication bias the true effect of antitumor treatment on epilepsy may be overestimated as well, as a tendency to report only the positive effects of antitumor treatment might be expected. Lastly, we evaluated the effect of different types of irradiation and varying chemotherapy schedules in one review, whereas different regimens may have diverse effects on seizure control.

Altogether, caution in interpreting and comparing the data is necessary.

Nevertheless, our results strongly suggest that radiotherapy as well as chemotherapy have a positive effect on seizure control. In determining the effect of antitumor treatment, gaining insight into seizure outcome is of major clinical importance, as a decrease in seizure burden could contribute to an improvement in patient’s quality of life. However, it should be noted that a reduction in seizure frequency will not necessarily lead to a clinical significant benefit for the patient. In two studies on non-tumor related epilepsy, patients without complete seizure freedom and patients with a >90% seizure reduction reported significantly worse scores on quality of life subscales compared to patients who achieved complete seizure freedom. Moreover, a reduction in generalized seizures may be clinically more relevant than a similar reduction in simple partial seizures. Therefore, seizure outcome measures should preferably be used in combination with other symptom burden or quality of life instruments. Given the wide range of seizure outcome measures that have been applied so far, more uniform measures are highly needed to further determine the clinical relevance of an improved seizure outcome in glioma patients.

Smaller retrospective studies suggest that AED withdrawal might successfully be applied in a selected group of brain tumor patients, for example in case postoperative seizures are absent or in patients with extratemporal located tumors. Reducing AED use in case of seizure control may decrease the risk of drug toxicity and improve neurocognitive functioning. The clinical relevance of keeping track of patient’s seizure status particularly applies to patients with WHO grade II glioma with favorable prognostic features such as a 1p/19q co-deletion, and to patients in whom seizures are the only sign of a tumor. In case antitumor treatment leads to long-term seizure freedom in these patients, reduction or, when possible, withdrawal of AEDs should seriously be considered.

Although the data are scarce, the discrepancies between seizure outcome and the observed radiological response demonstrate that imaging alone does not seem to be fully representative of the effects of antitumor treatment. This is illustrated by the finding that 21-50% of patients with WHO grade II glioma and SD on MRI experienced a seizure reduction after treatment with TMZ. Similar criteria were applied to assess radiological response in these studies, however, two studies used older, probably less sensitive MRI techniques. In a recent study more than 60% of patients with radiologically SD showed a seizure reduction after treatment with radiotherapy. These findings suggest that the observed response on MRI underestimates the benefit of the treatment. Although imaging is a regular part of the follow-up in LGG patients, the relation between imaging response and survival is unclear, and the observed radiological response seems to depend on the timing of the assessment. In patients with grade II or III who underwent radiotherapy for example, the maximum response on MRI was assessed after 3 months. However, in another cohort of 33 patients with a prolonged radiological response after radiotherapy was observed that lasted for years. Similar long-term responses were seen in patients treated with PCV chemotherapy. In a cohort of 149 patients treated with up-front TMZ, the time to maximum response ranged widely from 3 to 30 months (median 12 months). So the imaging responses are regularly delayed, which emphasizes the relevance of a complementary role of seizure outcome in evaluating the effect of antitumor treatment. Interestingly, one of the retrospective studies on seizures after TMZ treatment demonstrated that a seizure reduction after 6 months was an independent prognostic factor for both progression-free as overall survival in patients with LGG, in contrast to the radiological response. Such findings suggest that seizure outcome may even serve as a surrogate marker for tumor response. Of note, this does not necessarily implicate that patient’s seizure status could serve as a general marker for tumor behavior. Although seizures in LGG patients rarely present during a stable course of disease, the association between an increased seizure frequency and tumor recurrence is controversial. Moreover, seizures sometimes occur as an acute complication during antitumor treatment.

The precise molecular biological mechanism through which radiotherapy and chemotherapy contribute to improved seizure control still needs to be clarified. Remarkably, in a cohort of 143 patients treated with stereotactic radiotherapy, a decrease in seizure prevalence was observed already 6 weeks after treatment. A similar early reduction was observed in a patient with medically intractable epilepsy.
treated with TMZ. Together with the fact that seizure frequency reduces in absence of a response on MRI, these observations suggest that improved seizure control after either radiotherapy or chemotherapy cannot be attributed to a reduction in tumor size. Probably, molecular changes in the peritumoral microenvironment directly resulting from antitumor therapy underlie the seizure reduction, although current evidence is limited. TMZ is thought to reduce the intrinsic epileptogenicity of the tumor through a decrease in glutamate levels released from glioma cells. A downregulation of glutamate receptors is also associated with an increased survival in glioma patients treated with TMZ. Other changes in the microenvironment of the tumor might play a role as well, for example regarding the synthesis of neurotransmitters and inhibition of the immune response. After brachytherapy, an increased benzodiazepine receptor density in the brain adjacent to the tumor was found in patients with a significant seizure reduction. In another study a dose-dependent rate of seizure improvement was found after Gamma knife surgery, suggesting that higher radiation doses are possibly more effective in reducing the epileptogenicity of cortical structures around the tumor.

The rate of seizure frequency reduction also appeared to depend on the timing of radiotherapy, although we found contradictory results. Nonetheless, a decrease in tumor size, albeit a small one, could still be the mechanism of action leading to a seizure reduction. After all, the first 25% decrease in the area of the tumor does not qualify for an objective response according to the current RANO criteria. Some patients will therefore be regarded as non-responders, despite a modest reduction in tumor size.

In conclusion, this systematic review demonstrates the improvements in patient’s seizure status that occur after radiotherapy and chemotherapy, as well as the discrepancies between seizure outcome and the radiological response. Improved seizure control implies not only a direct clinical benefit for the patient, but may be a sign that the tumor responds to treatment. Therefore, our findings highlight the importance of using seizure outcome along with radiological response in evaluating the effect of antitumor treatment, particularly in patients with LGG. Given the current lack of high-quality studies, future randomized controlled studies are needed to confirm the positive effect of radiotherapy and chemotherapy on seizure frequency. Preferably, these studies should focus on the additional value of patient’s seizure status and other clinical outcome measures in assessing tumor response, as well as their prognostic significance for survival.
Table 2: Summary of seizure outcome after radiotherapy

<table>
<thead>
<tr>
<th>Article</th>
<th>Study design</th>
<th>Population (baseline)</th>
<th>Additional treatment, n (%)</th>
<th>Time of seizure assessment</th>
<th>Seizure outcome (% of total population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossi et al, 1985&lt;sup&gt;15&lt;/sup&gt;</td>
<td>N/S</td>
<td>Malignant brain tumor and medically intractable epilepsy 15: PA 1 / A 9 / OA 2 / O 2 / AA 2</td>
<td>None</td>
<td>N/S</td>
<td>Reduction in seizure frequency: 15/15 (100%) Seizure freedom: 8/15 (53%)</td>
</tr>
<tr>
<td>Rogers et al, 1993&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>LGG and medically intractable epilepsy 5</td>
<td>None</td>
<td>N/S</td>
<td>&gt;90% seizure reduction: 3/5 (60%) 75-90% seizure reduction: 1/5 (20%) Seizure freedom: 1/5 (20%)</td>
</tr>
<tr>
<td>Scerrati et al, 1994&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Prospective</td>
<td>Grade I/II glioma 36 (34 with history of epilepsy): PA 2 / A 23 / O 11</td>
<td>None</td>
<td>12m after therapy</td>
<td>Seizure freedom: 19/34 (56%)</td>
</tr>
<tr>
<td>Warnke et al, 1997&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>WHO grade II astrocytoma with a history of epilepsy 80; 22 (28%) with seizure freedom</td>
<td>None</td>
<td>3m after therapy</td>
<td>Increase in percentage of patients with: Seizure freedom (from 28% to 68%) Seizure freedom (from 28% to 80%)</td>
</tr>
<tr>
<td>Schrottner et al, 1998&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>Medically intractable tumor epilepsy 26: 17 LGG / 9 other</td>
<td>None</td>
<td>6w after therapy</td>
<td>Decrease in percentage of patients with: - generalized seizures (from 36% to 7%) - focal seizures (34% to 17%)</td>
</tr>
<tr>
<td>Schrottner et al, 2002&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>Mesiotemporal tumor epilepsy 19: LGG 15 / GG 3 / cavernoma 1</td>
<td>None</td>
<td>6m after therapy</td>
<td>Increase in percentage of patients with: Engel class I and II (significant reduction): 11/19 (58%) Engel class III (worthwhile improvement): 7/19 (37%)</td>
</tr>
<tr>
<td>Plathow et al, 2003&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>WHO grade II astrocytoma 143; 52 with general seizures and 49 with focal seizures</td>
<td>None</td>
<td>Resection 10/19 (53%)</td>
<td>Engel class I and II (significant reduction): 11/19 (58%) Engel class III (worthwhile improvement): 7/19 (37%)</td>
</tr>
<tr>
<td>Shankar et al, 2003&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Both retrospective and prospective</td>
<td>Insular low-grade astrocytoma 30 (26 presented with epilepsy)</td>
<td>None</td>
<td>Resection 93/157 (59%)</td>
<td>Engel Class I: 21/30 (20%) Engel Class II: 4/30 (13%) Engel Class III: 1/30 (3%)</td>
</tr>
<tr>
<td>Van den Bent et al, 2005&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Prospective</td>
<td>1) glioma 157: A 78 / OA 25 / O 19 / PA 2 / Grill 20 / other 15 2) glioma 154: A 80 / OA 15 / O 23 / PA 2 / Grill 28 / other 6 (no significant difference in number of patients with seizure control between group 1 and 2)</td>
<td>None</td>
<td>Resection 99/154 (64%)</td>
<td>Seizure freedom: 29/71 (59%)</td>
</tr>
<tr>
<td>Ruda et al, 2013&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>Glioma and medically intractable epilepsy 43: All-III 28 / OAll-III 5 / OII-III 10</td>
<td>None</td>
<td>Resection 29/43 (67%)</td>
<td>≥50% seizure reduction: 31/43 (72%) Seizure freedom: 15/43 (35%) ≥50% seizure reduction: 26/34 (77%) Seizure freedom: 13/34 (38%)</td>
</tr>
</tbody>
</table>

Table 3: Summary of seizure outcome after therapy

<table>
<thead>
<tr>
<th>Article</th>
<th>Study design</th>
<th>Population (baseline)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason et al, 1996</td>
<td>Prospective</td>
<td>Newly diagnosed and recurrent LGG 9 (6 with epilepsy)</td>
<td>PCV</td>
</tr>
<tr>
<td>Soffietti et al, 1998</td>
<td>Prospective</td>
<td>Progressive LGG 26 (23 with epilepsy and/or neurological deficits): OA 9 / O 17</td>
<td>PCV</td>
</tr>
<tr>
<td>Brada et al, 2003</td>
<td>Prospective</td>
<td>Stable or progressive LGG 30 (27 with history of epilepsy): A 17 / OA 2 / O 11</td>
<td>TMZ</td>
</tr>
<tr>
<td>Pace et al, 2003</td>
<td>Prospective</td>
<td>Progressive LGG 43 (31 with uncontrolled epilepsy): A 29 / OA 4 / O 10</td>
<td>TMZ</td>
</tr>
<tr>
<td>Hoang-Xuan et al, 2004</td>
<td>Prospective</td>
<td>Progressive LGG 60: O 29 / OA 11 (seizure status unknown)</td>
<td>TMZ</td>
</tr>
<tr>
<td>Biemond-Ter Stege et al, 2005</td>
<td>Retrospective</td>
<td>O and OA, newly diagnosed or recurrent 21 (20 with epilepsy)</td>
<td>PCV</td>
</tr>
<tr>
<td>Frenay et al, 2009</td>
<td>Retrospective</td>
<td>A 10 (9 with epilepsy, 8 with pharmacoresistant epilepsy)</td>
<td>PCV / F-C-E</td>
</tr>
<tr>
<td>Kaloshi et al, 2007</td>
<td>Retrospective</td>
<td>Progressive LGG 149: O 105 / A-OA 44 (seizure status unknown)</td>
<td>TMZ</td>
</tr>
<tr>
<td>Lebrun et al, 2007</td>
<td>Retrospective</td>
<td>O 33 (24 with epilepsy at tumor presentation)</td>
<td>PCV</td>
</tr>
<tr>
<td>Tosoni et al, 2008</td>
<td>Prospective</td>
<td>Recurrent or progressive LGG 30 (13 with intractable seizures): A 9 / OA 3 / O 18</td>
<td>TMZ</td>
</tr>
<tr>
<td>Taillandier et al, 2009</td>
<td>Retrospective</td>
<td>Insular LGG 21 (20 with epilepsy): A 3 / OA 1 / O 15 / LGG N/S 2</td>
<td>TMZ / PCV / F</td>
</tr>
<tr>
<td>Blonski et al, 2012</td>
<td>Prospective</td>
<td>Unresectable LGG and seizure at tumor presentation 10: A 2 / OA 2 / O 6</td>
<td>Neoadjuvant TMZ</td>
</tr>
<tr>
<td>Sherman et al, 2012</td>
<td>Retrospective</td>
<td>1) LGG and seizure at tumor presentation 39 (10 patients seizure free with AED): A 3 / OA 11 / O 22 / LGG N/S 3</td>
<td>TMZ</td>
</tr>
<tr>
<td>Koekkoek et al, 2014</td>
<td>Retrospective</td>
<td>66 LGG patients with uncontrolled epilepsy: A 43 / OA 9 / O 14</td>
<td>TMZ</td>
</tr>
</tbody>
</table>

LGG: low-grade glioma; A: astrocytoma grade II; OA: oligoastrocytoma grade II; O: oligodendroglioma grade II; PCV: procarbazine, lomustine and vincristine; TMZ: temozolomide; F: fotemustine; C: cisplatin; E: etoposide; N/S: not specified; m: months

Additional treatment, n (%): Time of seizure assessment | Seizure outcome (% of total population)
-------------------------------------------------------------------------------
Resection: 5/9 (56%) | N/S | Improved seizure control: 6/6 (100%)
Resection: 23/26 (88%) | At 4-week intervals during chemotherapy | Improved seizure control: 7/23 (30%) Seizure freedom: 3/23 (9%)
Resection: 12/30 (40%) | During chemotherapy (24 patients completed 12 cycles) | Improvement in seizure frequency: 14/27 (52%)
Resection: 32/43 (74%) | Radiotherapy: 30 (70%) | ≥50% seizure reduction: 15/31 (48%) Seizure freedom: 4/31 (13%) (In patients with previously uncontrolled epilepsy)
Resection: 21/60 (45%) | N/S | Neurological improvement, eg a reduction in seizure frequency: 30/59 (51%)
Radiotherapy: 5/21 (24%) | N/S | Improved seizure control in most of 16 patients showing radiological response to treatment
None | After 2nd course | Seizure reduction: 100% Seizure freedom: 60%
Resection: 68/149 (46%) | Unknown; general follow-up: 30.4m (range 2-70m) | ≥50% seizure reduction: 87/149 (58%)
Resection: 7/33 (21%) | During chemotherapy (mean of 5 courses) | Seizure reduction: 53% Seizure freedom: 31%
Resection: 20/30 (67%) | After beginning of TMZ treatment | Seizure frequency reduction: 8/13 (62%)
Resection: 5/21 (24%) | N/S | Improved Engel Class: 16/20 (80%) Seizure freedom: 8/20 (40%)
Resection: 5/10 (30%) | N/S | Seizure frequency reduction: 9/10 (90%) Seizure freedom: 5/10 (50%)
Resection: 24/39 (62%) | After median of 7 TMZ cycles | ≥50% seizure reduction: 23/39 (59%) ≥50% seizure reduction without AED changes: 7/39 (18%)
Resection: 13/30 (43%) | N/S | ≥50% seizure reduction: 4/30 (13%) ≥50% seizure reduction without AED changes: 0
Resection: 37/66 (56%) | Radiotherapy: 46/66 (70%) | After 6m | ≥50% seizure reduction without AED changes: 29/66 (44%) Seizure freedom: 27/66 (41%)
### Table 4: Summary of radiological responses in relation with seizure outcome

<table>
<thead>
<tr>
<th>Article</th>
<th>Treatment</th>
<th>Time of response assessment</th>
<th>Related seizure outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers et al, 1993&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Focal fractionated irradiation</td>
<td>N/S</td>
<td>Patients with medically intractable epilepsy: 75% seizure reduction in 3 patients with PR and in 1 patient with SD</td>
</tr>
<tr>
<td>Brada et al, 2003&lt;sup&gt;36&lt;/sup&gt;</td>
<td>TMZ</td>
<td>Every 3m in year 1, every 6m in year 2-3; maximum response was assessed after a median of 12-15m</td>
<td>Patients with history of epilepsy: seizure reduction in 10/15 (67%) with response on MRI and in 4/12 (33%) without a response on MRI</td>
</tr>
<tr>
<td>Pace et al, 2003&lt;sup&gt;40&lt;/sup&gt;</td>
<td>TMZ</td>
<td>Every 3 treatment cycles with a median duration of response of 10m</td>
<td>Patients with previously uncontrolled epilepsy: seizure reduction in 8/12 patients (67%) with CR or PR on MRI and in 3/14 patients (21%) with SD on MRI</td>
</tr>
<tr>
<td>Hoang-Xuan et al, 2004&lt;sup&gt;38&lt;/sup&gt;</td>
<td>TMZ</td>
<td>After median follow-up of 14m (range 6-46m)</td>
<td>Neurological improvement (e.g. a seizure reduction) in 12/36 (33%) with stable disease on MRI</td>
</tr>
<tr>
<td>Biemond-Ter Stege et al, 2005&lt;sup&gt;34&lt;/sup&gt;</td>
<td>PCV</td>
<td>N/S</td>
<td>Improved seizure control in most of 16 patients showing radiological response to treatment</td>
</tr>
<tr>
<td>Sherman et al, 2012&lt;sup&gt;39&lt;/sup&gt;</td>
<td>TMZ</td>
<td>N/S</td>
<td>Seizure reduction in 1/23 patients with an MRI response. All other patients with a seizure reduction had SD on MRI.</td>
</tr>
<tr>
<td>Ruda et al, 2015&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Focal fractionated irradiation</td>
<td>After 3m</td>
<td>Seizure reduction in 15/18 (83%) with response on MRI and 16/25 (64%) without a response on MRI.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 6m</td>
<td>Seizure reduction in 12/14 (86%) with response on MRI and 14/20 (70%) without a response on MRI.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 12m</td>
<td>Seizure reduction in 78% with response on MRI and 76% without a response on MRI.</td>
</tr>
<tr>
<td>Koekkoek et al, 2014&lt;sup&gt;40&lt;/sup&gt;</td>
<td>TMZ</td>
<td>After 6m</td>
<td>Seizure reduction in 8/28 (29%) with response on MRI and in 7/34 (21%) without a response on MRI.</td>
</tr>
</tbody>
</table>

CR: complete response; PR: partial response; SD: stable disease; PCV: procarbazine, lomustine and vincristine; TMZ: temozolomide; N/S: not specified; m: months

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