Epilepsy in the end of life phase of brain tumor patients: a systematic review

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ABSTRACT
Epileptic seizures are common in patients with a primary or secondary malignant brain tumor. However, current knowledge on the occurrence of seizures during the end of life (EOL) phase of brain tumor patients is limited. As symptom management with preservation of quality of life is of major importance for patients with a malignant brain tumor, particularly in the EOL, it is necessary to gain a deeper understanding of seizures and their management during this phase. We performed a systematic review of literature related to epilepsy in the EOL phase of brain tumor patients, based on the e-resources PubMed, Embase and Cinahl. The search yielded 442 unique records, of which 11 articles were eligible for further analysis after applying pre-defined inclusion criteria. Seizures occur relatively frequently in the EOL phase, particularly in patients with high-grade glioma. However, seizure management is often hampered by swallowing difficulties and impaired consciousness. Treatment decisions are largely dependent on expert-opinion, as a standardized approach for treating seizures in the terminal stage of brain tumor patients is still lacking.

INTRODUCTION
Epileptic seizures are a common symptom in patients with a primary or secondary malignant brain tumor. In up to 50% of patients seizures are the presenting sign of a tumor. Tumor type, the location of the tumor and its proximity to the cortical gray matter, influence the chance of developing a seizure. In general, the epileptogenicity of the tumor is inversely correlated with its growth rate. Low-grade gliomas are often most epileptogenic, particularly slow-growing tumors such as gangliogliomas and dysembryoblastic neuroepithelial tumors (DNET), whereas less than 50% of patients with brain metastases and high-grade gliomas (HGGs) have seizures. Antiepileptic drugs (AEDs) as well as tumor-directed treatment may lead to seizure control. However, anticonvulsant treatment may be hampered by pharmacoresistance, side effects and interactions with other drugs or anticancer agents. Eventually, despite AED treatment, more than 30% of patients will be refractory to AED treatment during the course of their disease.

Median survival of patients with a malignant brain tumor varies widely from less than half a year to more than 10 years, depending on tumor type and grade, age, performance status, and, in case of metastases, on the number of cerebral lesions and systemic disease activity. At some point patients will enter the end of life phase, which starts, in our definition, once tumor-directed treatment is no longer deemed meaningful and symptom burden significantly increases. Although the length of the EOL phase in individual cases may range from days to weeks before death, in previous studies it has been confined to the last 3 months prior to death. During this phase, preservation of quality of life by reducing clinical symptoms, such as pain, agitation and seizures, is the mainstay of care. Seizure occurrence at the EOL often leads to rehospitalization and increased Emergency Rooms visits, with an increase in health care economic system costs and worsening of patient’s quality of life. Swallowing difficulties and impaired consciousness in particular can interfere with the regular oral administration of AEDs. In addition to further tumor growth, metabolic disturbances due to organ dysfunction or interactions of AEDs with other drugs, such as antibiotics and neuroleptics, may contribute to an increased risk of seizures in the EOL phase as well. In other words, the context in which a seizure takes place during the EOL may vary considerably among brain tumor patients. A seizure may be the expression of epilepsy, which is defined as the enduring predisposition to generate epileptic seizures and requires the history of at least one seizure. Other patients may have a seizure without having epilepsy, for example in case of an acute symptomatic (or “provoked”) seizure, where a proximate cause is clearly identifiable. Both treating and preventing seizures in the EOL, whether it is in the context of epilepsy or not, are serious challenges. Ongoing seizures may cause
The following study characteristics: publication year, study design, sample size, brain tumor type (primary or secondary malignant brain tumor including subtype), seizure prevalence, time before death evaluated, type of AED treatment and other available data with regard to epilepsy in the EOL phase.

**TABLE 1: Search terms**

<table>
<thead>
<tr>
<th>PubMed</th>
<th>Embase</th>
<th>Cinahl</th>
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</table>

**RESULTS**

Through our search strategy we retrieved 442 unique records, of which 33 were assessed for further eligibility. Of these, 23 were excluded for the following reasons: abstract only (n=11), no seizures described (n=8), no EOL phase described (n=3), reviews (n=3) and full-text unavailable (n=1). One additional study was found after hand-searching the reference lists. The complete selection of articles is outlined in figure 1. All 11 studies that we included for further analysis had a retrospective design. Additional distress for caregivers as well, who already experience a heavy burden of care. As preservation of quality of life is of major importance for patients with a malignant brain tumor as well as their relatives, especially in the EOL, it is necessary to gain a deeper understanding of seizures and their management during this phase.

Current knowledge on the occurrence and treatment of seizures in the EOL phase is limited. In this report we present the results of a systematic review of literature regarding seizures in the EOL phase of brain tumor patients. In particular, we aimed to outline the epidemiology, pathogenesis of seizures, and treatment strategies with regard to the use of AEDs in the EOL phase.
eight studies included chart or database reviews\textsuperscript{20,26-29} and three studies were based on questionnaires.\textsuperscript{30-32} Patient numbers ranged considerably from 29-812 patients.\textsuperscript{20,29} Seven studies focused primarily on patients with an HGG.\textsuperscript{20,27,28,30,31,33-35} Three studies focused on secondary brain tumors\textsuperscript{20,28,29} and one study on brain metastases from lung carcinoma only.\textsuperscript{32} All relevant study characteristics are summarized in table 2.

**Epidemiology of seizures**

Ten studies described the seizure prevalence at some point during the EOL phase (table 2). The prevalence of seizures differed considerably, ranging from 6% to 56%.\textsuperscript{20,26-33} However, the span of time until death that was evaluated varied widely as well. In 6 out of 10 studies a specific period of time before death was analyzed, ranging from 3 days to 3 months.\textsuperscript{20,26,28,29,33,35} One other study reported on the time between referral to a hospice and death, ranging from 1-10 months (mean 3.7 months).\textsuperscript{27} Another study analyzed the time between referral to a palliative care center and death, ranging from 2 to 196 days (mean 42.6 days).\textsuperscript{32} Moreover, one study reported on seizure occurrence anytime during the EOL phase (range 1-294 days; mean 46 days)\textsuperscript{30}, and one study described seizures upon admission to a palliative care unit without a documented time between admission and death.\textsuperscript{31} In two studies that reported on seizures during the last month in 326 consecutive patients (90% HGG), the prevalence varied from 30-37%.\textsuperscript{20,29} Moreover, seizure prevalence appeared to increase towards death in a study evaluating 29 GBM patients in a hospital setting.\textsuperscript{28} A seizure prevalence between 28-38% during the last week was reported in three other studies.\textsuperscript{20,33,35}

Pace et al. reported that of 58 HGG patients with epilepsy in the last month before death, 79% had focal seizures, 18% had generalized seizures and 3% had a status epilepticus. The risk of seizures was higher in patients with a previous history of epilepsy, and only 5% of patients with seizures during the last month had been seizure-free before.\textsuperscript{20} In contrast, Sizoo et al. reported that of 27 HGG patients with epilepsy in the last week before death, 22% had no seizure before the EOL phase.\textsuperscript{35} Moreover, only 9% of patients with previous focal epilepsy experienced focal seizures during the last week before death. Patients with a previous status epilepticus showed a higher prevalence of seizures during the last week before death. No other risk factors for the occurrence of seizures in the last week were found.\textsuperscript{35}

In 55 patients with brain metastases from lung carcinoma 9% had seizures during their stay at a palliative care center (mean 43 days).\textsuperscript{31} In a study of 661 patients with brain metastases and 151 patients with a primary malignant brain tumor referred to a palliative care unit, 6% and 19% reported seizures, respectively.\textsuperscript{31} Similar differences...
### Table 2: Summary of main characteristics of selected articles

<table>
<thead>
<tr>
<th>Article</th>
<th>Study design</th>
<th>Population</th>
<th>Location</th>
<th>Time before death</th>
<th>Seizure prevalence</th>
<th>Additional data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bausewein, 2003&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Retrospective chart review</td>
<td>31 patients 17: glioblastoma multiforme (GBM) 9: grade II astrocytoma 5: other</td>
<td>Palliative care unit, hospital</td>
<td>Last 72 hours</td>
<td>10%</td>
<td>Non-peaceful death due to seizures</td>
</tr>
<tr>
<td>Faithfull, 2005&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Retrospective chart review</td>
<td>39: primary malignant brain tumor</td>
<td>Hospice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oberndorfer, 2008&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Retrospective chart review</td>
<td>29: GBM</td>
<td>Hospital</td>
<td>10-6 weeks 6-2 weeks Last 2 weeks</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Pace, 2009&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Retrospective chart review</td>
<td>169 patients 155: GBM 30: metastases 4: other</td>
<td>At home</td>
<td>Last month</td>
<td>60-34%</td>
<td>Seizure type AED treatment</td>
</tr>
<tr>
<td>Sizoo, 2010&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Retrospective chart review</td>
<td>55: high-grade glioma</td>
<td>Not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ostgathe, 2010&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Retrospective review of database</td>
<td>812 patients 151: primary brain tumor 661: secondary brain tumor</td>
<td>Palliative care unit, hospice, at home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamanaka, 2011&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Retrospective chart review</td>
<td>55: brain metastases from lung cancer</td>
<td>Palliative care center</td>
<td>Anytime during EOL phase, ranging from 1-296 days (median 46 days) Last week</td>
<td>65%</td>
<td>Cause of death</td>
</tr>
<tr>
<td>Flechl, 2013&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Retrospective cohort study, questionnaires</td>
<td>52: GBM</td>
<td>Hospital, at home, hospice, nursing home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace, 2013&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Retrospective review of database</td>
<td>157: high-grade glioma</td>
<td>At home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heese, 2013&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Retrospective cohort study, questionnaires</td>
<td>605 patients 24: grade II astrocytoma 86: grade III astrocytoma 398: GBM</td>
<td>At home, hospital, hospice, nursing home</td>
<td>Last 3 months Last week</td>
<td>52% 38%</td>
<td>Seizure type AED treatment</td>
</tr>
<tr>
<td>Sizoo, 2013&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Retrospective cohort study, questionnaires</td>
<td>92: high-grade glioma</td>
<td>At home, hospital, hospice, nursing home</td>
<td>Last 4 weeks before death n/a Percentage of caregivers satisfied with seizure treatment</td>
<td>29%</td>
<td>Seizure type AED treatment</td>
</tr>
</tbody>
</table>
TABLE 3: List of non-oral antiepileptic drugs that can easily be applied in the out-of-hospital setting

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Drug</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal</td>
<td>Midazolam</td>
<td>27.8mg/ml; 1 spray of 2.5mg in every nostril (total dose of 5mg), if necessary, repeat after 5min</td>
<td>Emergency treatment</td>
</tr>
<tr>
<td>Rectal</td>
<td>Diazepam</td>
<td>10mg, if necessary, repeat after 5min</td>
<td>Emergency treatment</td>
</tr>
<tr>
<td>Buccal</td>
<td>Clonazepam</td>
<td>2-4 times 0.5mg/day, maintenance dose of 4 times 0.5-1.0mg/day, maximum dose of 20mg/day</td>
<td>Prophylactic treatment</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Phenobarbital</td>
<td>100mg; if necessary, repeat after 4-6hours; maintenance dose of 2-4mg/kg</td>
<td>Prophylactic treatment</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Midazolam</td>
<td>Start dose of 10mg, maintenance dose of 15-25mg/hour</td>
<td>Palliative sedation in patients with refractory seizures where other non-oral AEDs have failed</td>
</tr>
</tbody>
</table>

in terms of seizure prevalence during the EOL phase in 30 patients with brain metastases and 135 patients with HGG were found in another study, with 10% versus 34%, respectively. In a study of 55 HGG patients, seizures were thought to be the cause of death in 5% of all patients. In 3% of patients with a malignant brain tumor, death was considered to be non-peaceful due to seizures in the last 72 hours.

Seizure treatment
Three studies described the treatment of epilepsy during the EOL phase. All patients with epilepsy during the course of their disease were on AEDs. However, the use of prophylactic AEDs among patients without seizures before the EOL phase varied widely from none to 88% of patients using prophylactics. No correlation was found between treatment with AEDs and the presence of seizures during the EOL phase.

Regular intake of oral AEDs appeared to be often hampered in the EOL phase, due to swallowing difficulties and/or impaired consciousness. In the last month before death, mild to severe dysphagia was observed in 70% of patients, and 83% had impaired consciousness. 82% of patients were unable to continue oral AEDs until the last days of life, and in 83% of patients the route of AED administration was changed into parenteral use during the EOL phase. Sizoo et al. found that in 29 of 64 patients (45%) AEDs were tapered in the last week before death. In 10 of 29 patients (35%) whose AEDs were tapered, seizures occurred during the last week before death. None of the studies addressed the impact of changes or discontinuation of AEDs on seizure prevalence during the EOL phase. A large study reporting on the caregiver’s perception in 605 glioma patients found that 64% of caregivers thought that epilepsy was treated effectively during the EOL phase.

DISCUSSION
EOL care in patients with a malignant brain tumor is primarily aimed at the reduction of clinical symptoms and relief of suffering, avoiding unnecessary prolongation of dying. Next to a wide range of neurological deficits and cognitive impairments, seizures occur frequently in the EOL phase. Overall, seizures occur in up to 56% of patients. About one third of HGG patients develop seizures during the last month or last week before death, whereas less than 10% of the patients with brain metastases reported seizures during this phase. Possibly, the expansive rather than infiltrative character of brain metastases contributes to a lower seizure burden in this group. It is difficult to characterize the type of seizures that occur in the EOL phase. For example, Pace et al. showed that 46 of 58 patients (79%) had partial seizures, whereas Sizoo et al. showed that 15 of 20 patients (75%) with epilepsy during the last week before death had generalized seizures during the EOL phase. It would be helpful to know which type of seizures are more prevalent, as generalized seizures may require more aggressive treatment compared to seizures of focal origin.

The EOL phase in brain tumor patients is characterized by a rapid progression of neurological and cognitive deficits, which could interfere with adequate seizure treatment. Swallowing difficulties are reported in 10-85% of brain tumors, in particular in patients with HGG in the EOL phase, and can be caused by paresis, apraxia and impaired consciousness. In up to 94% of brain tumor patients progressive confusion or coma are reported in the last days before death. Thus, regular oral AED treatment is hampered in most patients with brain tumor related epilepsy, particularly in the last days before death, leading to a higher risk of seizures.
Besides subtherapeutic drug levels due to inadequate AED intake, several other factors may contribute to the occurrence of seizures during the EOL. Tumor progression itself may lead to an elevated risk of seizures in both patients with and without a history of seizures. In gliomas, abrupt tissue damage causing necrosis and edema, is thought to result in epileptogenicity of the tumor. In rapidly progressive tumors, infiltration of the peritumoral environment may lead to excitability. Metabolic encephalopathy due to electrolyte abnormalities or organ dysfunction may result in an additional seizure risk towards the EOL as well. Serum AED levels may also be affected by interactions with other drugs. For example, corticosteroids may impair the activity of phenytoin through shared pathways of hepatic metabolism. Concomitant use of antipsychotics such as clozapine, or antidepressants, particularly tricyclic antidepressants, may lead to seizures as well, due to a lower seizure threshold. On the other hand, anxiolytics such as benzodiazepines, which are frequently administered in the terminal phase for relief of intractable pain or agitation, may additionally reduce the risk of seizures. The potential role of brain imaging or other diagnostic tools to differentiate between causes of seizures during the EOL, which might subsequently direct treatment, has not been examined in any of these studies.

Where possible, anticonvulsant therapy needs to be continued during the EOL phase, particularly in patients with a higher risk of seizures, such as patients with previous seizures or a status epilepticus during the course of their disease. In patients with a mass effect contributing to the development of seizures, a temporary start or continuation of dexamethasone might be considered. The consequences of discontinuing AEDs in the EOL phase remain largely unknown. Sizoo et al. found that seizures took place in 10 of 29 patients (35%) whose AEDs were tapered during the EOL phase. However, seizures also occur in patients who are on AEDs, suggesting a relative inefficacy of AEDs. Before the EOL phase, the use of prophylaxis in brain tumor patients without a history of seizures is not recommended. Two meta-analyses found insufficient evidence to support prophylactic use of phenobarbital, phenytoin and valproic acid. Prospective data on newer AEDs are unavailable. However, as there are no trials of prophylactic AEDs in the EOL phase of brain tumor patients, it is uncertain whether the benefits of prophylactics outweigh the risks. Therefore, future research should focus on the role of prophylactic anticonvulsant treatment in the EOL phase, particularly in HGG patients. Initially, a study assessing the feasibility of non-oral AEDs in patients who have developed swallowing difficulties towards the EOL would be helpful.

Several studies advocate alternative routes of administration in case patients are unable to continue oral AEDs. The preferred route of non-oral AED administration depends on the place of care in the EOL phase, but also on the availability of AEDs and the physician’s experience with their administration. Achieving seizure control at patient’s preferred place of care is warranted, as it could prevent unnecessary transitions and hospitalization during the EOL. Intravenous administration is used in a clinical setting when a rapid response is needed. In the out-of-hospital setting, intranasal, buccal or rectal administration is more appropriate, as it can easily be applied by the caregiver.

Results from randomized trials analyzing the use of non-oral AEDs in non-oncological patients with epilepsy can be helpful in examining alternative treatment options for brain tumor patients towards the EOL. In comparison with intravenous or rectal diazepam, intranasal midazolam shows a similar efficacy and safety in the acute treatment of seizures. Moreover, caregivers are more satisfied with the use of intranasal midazolam compared to rectal diazepam in treating acute seizures. A meta-analysis by McMullan et al., evaluating three clinical trials, shows that buccal midazolam is superior to rectal diazepam in achieving seizure control. Rectal administration of carbamazepine or valproic acid could contribute to the maintenance of serum levels of orally administered AEDs. However, evidence for rectal use of AEDs that are normally taken orally is limited to a few small prospective studies. Buccal or intranasal clonazepam can be safely applied in the out-of-hospital setting, although evidence for its efficacy is limited as well. Other reports show that intramuscular or subcutaneous phenobarbital in the EOL setting can be effective, as well as repeated use of subcutaneous levetiracetam. In case of unbearable suffering in the EOL phase, for example due to refractory seizures, palliative sedation with benzodiazepines can be initiated. However, it is preferable to restrict the use of palliative sedation in case of epilepsy to those patients in the terminal phase in whom other AED treatment options have failed. A list of non-oral AEDs that can easily be applied in the out-of-hospital setting is outlined in table 3.

There are some limitations of this review. First, as all included studies have a retrospective design, the level of evidence is low according to international classifications. Second, there is a remarkable heterogeneity of study populations in terms of histological diagnosis and place of care. Moreover, as a standardized definition of the EOL phase is lacking, each study used its own time interval prior to death, ranging from days to months. Therefore, comparisons between studies should be interpreted with caution. Third, there is little high quality published data on epilepsy frequency, and seizure management in the EOL phase. Although the highest level of evidence would be achieved by randomized controlled studies, there are serious ethical objections to the randomization of patients with regard to AED treatment in the EOL phase. In
Epilepsy in the EOL phase: a systematic review

In conclusion, seizures occur relatively frequently in the EOL of patients with a malignant brain tumor, particularly in patients with HGG. Treatment decisions are largely dependent on expert-opinion, as a standardized approach for treating seizures in the terminal stage of the disease is lacking. Currently, evidence is too limited to recommend the use of certain AEDs. Prospective studies that take into account the complexity of AED administration during the EOL, should contribute to the development of more targeted seizure treatment.

REFERENCE LIST


(50) Mpimbaza, A, Ndezezi, G, Staelke, S, Rosen-


