Neuro-Oncology Practice

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

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Epileptic seizures are common in patients with 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. Because 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 electronic resources PubMed, Embase, and Cinahl. The search yielded 442 unique records, of which 11 articles were eligible for further analysis after applying predefined 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 because a standardized approach for treating seizures in the terminal stage of brain tumor patients is still lacking.

Keywords: brain tumor, end of life, epilepsy, glioma, metastasis.

Epileptic seizures are a common symptom in patients with a primary or secondary malignant brain tumor, and seizures are the presenting sign of a tumor in up to 50% of patients. Tumor type, the location of the tumor, and its proximity to the cortical gray matter influence the chance of developing a seizure.[1–3] In general, the epileptogenicity of the tumor is inversely correlated with its growth rate. Low-grade gliomas are often the most epileptogenic, particularly slow-growing tumors such as gangliogliomas and dysembryoblastic neuroepithelial tumors, whereas fewer than 50% of patients with brain metastases and high-grade gliomas (HGGs) have seizures.[1,4] Antiepileptic drugs (AEDs), as well as tumor-directed treatment, may lead to seizure control.[5–8] However, anticonvulsant treatment may be hampered by pharmacoresistance, side effects, and interactions with other drugs or anticancer agents.[2,9] Eventually, more than 30% of patients will be refractory to AED treatment during the course of their disease despite AED treatment.[10]

Median survival of patients with a malignant brain tumor varies widely from less than 6 months to more than 10 years, depending on tumor type and grade, age, performance status,

and, in cases of metastases, the number of cerebral lesions and systemic disease activity.[11,12] Patients will enter the end of life (EOL) phase at some point, which starts (in our definition) once tumor-directed treatment has been deemed no longer meaningful and symptom burden has increased significantly. Although the length of the EOL phase in individual cases may range from days to weeks before death, it has been confined to the last 3 months prior to death in previous studies.[13,14] During this phase, preservation of quality of life by reducing clinical symptoms, such as pain, agitation, and seizures, is the mainstay of care.[15–17] Seizure occurrence at the EOL often leads to rehospitalization and increased emergency room visits, with an increase in health care economic system costs and worsening of the patient's quality of life.[18] Swallowing difficulties and impaired consciousness, in particular, can interfere with the regular oral administration of AEDs.[19,20] 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 also contribute to an increased risk of seizures in the EOL phase.[21] 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.[22] Other patients may have a seizure without having epilepsy (eg, in the case of an acute symptomatic or provoked seizure) in which a proximate cause is clearly identifiable.[23] Both treatment and prevention of seizures in the EOL, whether in the context of epilepsy or not, are serious challenges. Ongoing seizures may cause additional distress for caregivers as well, who are already experiencing a heavy burden of care.[19,24] Because 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 important to gain a deeper understanding of seizures and their management during this phase.

Current knowledge about 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 regarding the use of AEDs in the EOL phase.

Materials and Methods

Search Strategy

We performed a systematic review of literature in the electronic resources PubMed, Embase, and Cinahl. There were no limits with regard to publication years. We used a combination of 3 search strings related to (i) brain tumors, (ii) epilepsy, and (iii) end of life. The complete search string was as follows and was limited to terms that appeared in the title or abstract: (glioma OR gbm OR glioblastoma OR astrocytoma OR oligodendroglioma OR brain tumor OR brain tumors OR brain tumour OR brain tumours OR brain neoplasm OR brain cancer OR brain metastasis OR brain metastases) AND (epilepsy OR seizures OR convulsion OR anticonvulsant OR antiepileptic OR symptoms) AND (end of life OR palliative OR supportive OR terminal OR dying OR issues) (see online supplementary file).

Selection of Articles

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed.[25] Articles were included when they reported on the epidemiology or treatment of epilepsy in adult brain tumor patients in the EOL phase. We included only peer-reviewed articles that were available full text in English. Case eports and reviews were excluded, as were studies not focusing on the EOL phase. Two authors (J.A.F.K. and L.D.) determined whether the articles were eligible for inclusion after screening title and abstract and served as reviewers of the full texts of all selected and potentially relevant articles. When full-text articles could not be retrieved through electronic resources, we contacted one of the authors to determine if the full text was available. The reference lists of the selected full-text articles were searched manually to identify additional studies. The 2 authors resolved any disagreements by reaching consensus through discussion. From the selected articles, we extracted the following study characteristics: publication year, study design, sample size, brain tumor type (primary or secondary malignant brain tumor including subtype), seizure prevalence, time evaluated before death, type of AED treatment, and other available data with regard to epilepsy in the EOL phase.

Results

Search 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 ($n = 5$), no EOL phase described ($n = 3$), reviews ($n = 3$), and full text unavailable ($n = 1$). One additional study was found after manually searching the reference lists.[26] The complete selection of articles is outlined in Fig. 1.

All 11 studies included for further analysis had a retrospective design,[20,26–35] 8 studies included chart or database reviews,[20,26–32] and 3 studies were based on questionnaires.[33–35] The numbers of cases studied ranged considerably from 29 to 812 patients.[28,31] Seven studies focused primarily on patients with an HGG.[20,27,28,30,33–35] Three studies focused on primary as well as secondary brain tumors,[26,29,31] and one study focused on brain metastases from lung carcinoma only.[32] All relevant study characteristics are summarized in Table 1.
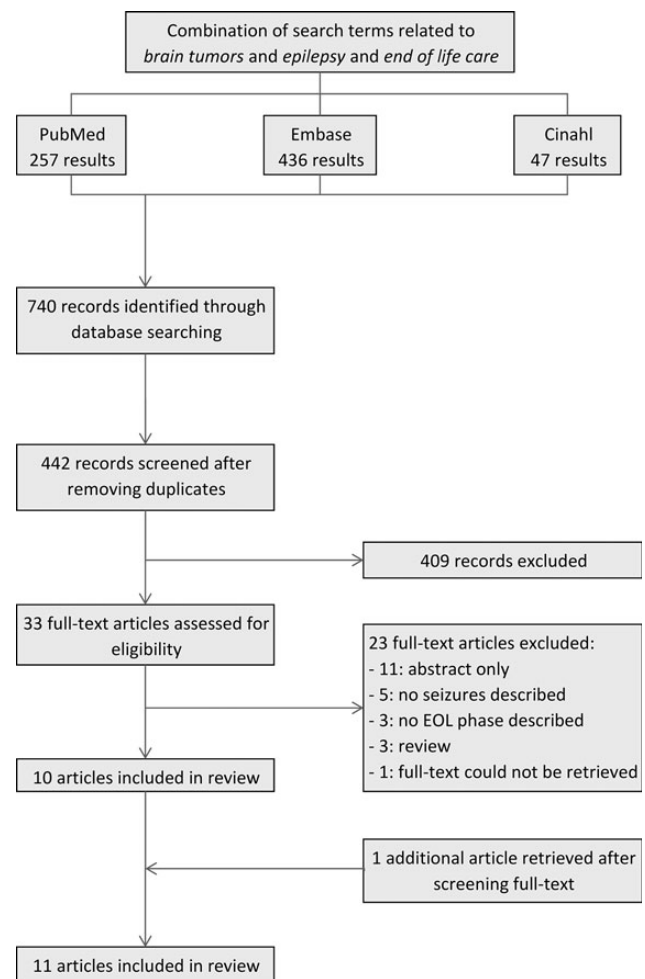

Fig. 1. Identification of articles.

Table 1. Summary of main characteristics of selected articles

Article	Study Design	Population	Location	Time Before Death	Seizure Prevalence	Additional Data
Bausewein, 2003[26]	Retrospective chart review	31 patients: 17 GBM 9 grade II astrocytoma 5 other	Palliative care unit, hospital	Last 72 h	10%	Nonpeaceful death due to seizures
Faithfull, 2005[27]	Retrospective chart review	39 primary malignant brain tumor	Hospice	Time between referral to hospice and death, ranging from 1–10 months with a mean of 3.7 months	56%	
Oberndorfer, 2008[28]	Retrospective chart review	29 GBM	Hospital	6–10 weeks 2–6 weeks Last 2 weeks	21% 28% 50%	
Pace, 2009[29]	Retrospective chart review	169 patients: 135 GBM 30 metastases 4 other	At home	Last month	10%–34%	Seizure type AED treatment
Sizoo, 2010[30]	Retrospective chart review	55 high-grade glioma	Not specified	Anytime during EOL phase, ranging from 1–296 days (median, 46 days) Last week	45% 28%	Cause of death
Ostgathe, 2010[31]	Retrospective review of database	812 patients 151 primary brain tumor 661 secondary brain tumor	Palliative care unit, hospice, at home	Upon admission to palliative care unit	6%–19%	
Yamanaka, 2011[32]	Retrospective chart review	55 brain metastases from lung cancer	Palliative care center	Anytime during stay at palliative care center, ranging from 2–196 days (mean, 42.6 days)	9%	
Flechl, 2013[33]	Retrospective cohort study, questionnaires	52 GBM	Hospital, at home, hospice, nursing home	Last 3 months Last week	52% 38%	
Pace, 2013[20]	Retrospective review of database	157 high-grade glioma	At home	Last month before death	37%	Seizure type AED treatment
Heese, 2013[34]	Retrospective cohort study, questionnaires	605 patients: 74 grade II astrocytoma 86 grade III astrocytoma 398 GBM	At home, hospital, hospice, nursing home	Last 4 weeks before death	n/a	Percentage of caregivers satisfied with seizure treatment
Sizoo, 2013[31]	Retrospective cohort study, questionnaires	92 high-grade glioma	At home, hospital, hospice, nursing home	Last week	29%	Seizure type AED treatment

Abbreviation: GBM, glioblastoma multiforme; n/a, not applicable.

Epidemiology of Seizures

Ten studies described the seizure prevalence at some point during the EOL phase (Table 1). The prevalence of seizures differed considerably, ranging from 6% to 56%,[20,26–33,35] and the time of evaluation before death varied widely as well. In 6 of 10 studies, a specific period of time before death was analyzed, ranging from 3 days to 3 months.[20,26,28,29,33,35] One other study reported the time between referral to a hospice and death, which ranged from 1 to 10 months (mean, 3.7 months).[27] Another study analyzed the time between referral to a palliative care center and death, which ranged from 2 to 196 days (mean, 42.6 days).[32] Moreover, one study reported on seizure occurrence anytime during the EOL phase (range, 1–294 days; mean, 46 days),[30] and one study described seizures upon admission to a palliative care unit without a documented time between admission and death.[31]

In 2 studies that reported on seizures during the last month in 326 consecutive patients (90% HGG), the prevalence varied from 30% to 37%.[20,29] Moreover, seizure prevalence appeared to increase towards death in a study evaluating 29 GBM patients in a hospital setting.[28] A seizure prevalence between 28%–38% during the last week was reported in 3 other studies.[30,33,35]

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.[20] In contrast, Sizoo et al reported that of 27 HGG patients with epilepsy in the last week before death, 22% had no seizures before the EOL phase.[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 were found for the occurrence of seizures in the last week of life.[35]

In 55 patients with brain metastases from lung carcinoma, 9% had seizures during their stay at a palliative care center (mean, 43 days).[32] 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%, respectively, were reported as having had seizures.[31] Similar differences 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.[29]

In a study of 55 HGG patients, seizures were thought to be the cause of death in 5% of all patients.[30] In 3% of patients with a malignant brain tumor, death was considered to be nonpeaceful due to seizures in the last 72 hours.[28]

Seizure Treatment

Three studies described the treatment of epilepsy during the EOL phase.[20,29,35] 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.[20,29,35] No correlation was found between treatment with AEDs and the presence of seizures during the EOL phase.[20]

Regular intake of oral AEDs in the EOL phase appeared to be often hampered by swallowing difficulties and/or impaired consciousness.[13,14] In the last month before death, mild to severe dysphagia was observed in 70% of patients, and 63% had impaired consciousness. Eighty-two percent of patients were unable to continue oral AEDs through the last days of life, and the route of AED administration was changed into parenteral use during the EOL phase for 83% of patients.[20] Sizoo et al found that AEDs were tapered in the last week before death in 29 of 64 (45%) of patients. In 10 of 29 patients (35%) whose AEDs were tapered, seizures occurred during the last week before death.[35] None of the studies addressed the impact of changes or discontinuation of AEDs on seizure prevalence during the EOL phase. A large study (605 glioma patients) reporting on the caregivers' perception found that 64% of caregivers thought epilepsy was treated effectively during the EOL phase.[34]

Discussion

EOL care in patients with a malignant brain tumor is primarily aimed at reducing clinical symptoms, relieving suffering, and avoiding unnecessary prolongation of dying.[36–39] Next to a wide range of neurological deficits and cognitive impairments, seizures occur frequently in the EOL phase.[19,24]

Overall, seizures occur in up to 56% of patients.[26,27] About one-third of HGG patients develop seizures in the last month or last week before death, whereas fewer than ≤10% of patients with brain metastases were reported to have had seizures during this phase.[31,32] Possibly, the expansive, rather than the infiltrative, character of brain metastases contributes to a lower seizure burden in this group.[40] 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.[20,35] It would be helpful to know which type of seizures are more prevalent because generalized seizures may require more aggressive treatment compared with seizures of focal origin.[41]

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.[42] Swallowing difficulties are reported in 10%–85% of brain tumors, particularly 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.[26–31] 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.[20]

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. The abrupt tissue damage in gliomas, which causes necrosis and edema, is thought to result in epileptogenicity of the tumor.[10] In rapidly progressive tumors, infiltration of the peritumoral environment may lead to excitability.[43] Metabolic encephalopathy due to electrolyte abnormalities or organ dysfunction may result in an additional seizure risk towards the EOL as well.[21] 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.[44] Concomitant use of antipsychotics such as clonazepine or antidepressants (particularly tricyclic antidepressants) may lead to seizures as well, due to a lower seizure threshold.[45] 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, was not examined in any of these studies.

Where possible, anticonvulsant therapy needs to be continued during the EOL phase, particularly for patients with a higher risk of seizures such as those with previous seizures or a status epilepticus during the course of their disease.[20,35] 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.[35] However, seizures also occur in patients who are on AEDs, suggesting a relative inefficacy of AEDs.[35] Before the EOL phase, the use of prophylaxis is not recommended for brain tumor patients without a history of seizures.[15,46] Two meta-analyses found insufficient evidence to support prophylactic use of phenobarbital, phenytoin, and valproic acid.[47,48] 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. An initial study to assess the efficacy of non-oral AEDs for patients with swallowing difficulties toward the EOL would be helpful.

Several studies advocate alternative routes of administration when patients are unable to continue oral AEDs.[20,35] The preferred route of nonoral AED administration depends on the location of care in the EOL phase, but also on the availability of AEDs and the physician's experience with their administration.[49] Achieving seizure control at the patient's preferred place of care

is warranted because it could prevent unnecessary transitions and hospitalization during the EOL.[27,28] 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 because as it can easily be administered by the caregiver.[50]

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.[51,52] Moreover, caregivers are more satisfied with the use of intranasal midazolam compared with rectal diazepam in treating acute seizures.[50,53] A meta-analysis by McMullan[54] et al, evaluating 3 clinical trials, shows that buccal midazolam is superior to rectal diazepam in achieving seizure control.[55–57] 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.[50,58] Buccal or intranasal clonazepam can be safely administered in the out-of-hospital setting, although evidence for its efficacy is limited as well.[59] Other reports show that intramuscular or subcutaneous phenobarbital in the EOL setting can be effective, as is repeated use of subcutaneous levetiracetam.[20,60–62] In the case of unbearable suffering in the EOL phase (eg, due to refractory seizures), palliative sedation with benzodiazepines can be initiated. However, it is preferable to restrict the use of palliative sedation for epilepsy to those patients in the terminal phase in whom other AED treatment options have failed.[63,64] A list of non-oral AEDs that can easily be applied in the out-of-hospital setting is outlined in Table 2.

There are some limitations of this review. First, the level of evidence is low according to international classifications because all included studies had a retrospective design. Second, there is a remarkable heterogeneity of study populations in terms of histological diagnosis and place of care. Moreover, because a standardized definition of the EOL phase is lacking, each study used its own time interval prior to death, and these ranged from days to months. Therefore, comparisons between studies should be interpreted with caution. Third, there is a paucity of

Table 2. List of non-oral antiepileptic drugs that can easily be applied in the out-of-hospital setting

Route of Administration	Drug	Dose	Indication
Intranasal	Midazolam	27.8 mg/mL, 1 spray of 2.5 mg in each nostril (total dose 5 mg); if necessary, repeat after 5 min	Emergency treatment
Rectal	Diazepam	10 mg; if necessary, repeat after 5 min	Emergency treatment
Buccal	Clonazepam	2–4 times 0.5 mg/d; maintenance dose 4 times, 0.5–1.0 mg/d; maximum dose 20 mg/d	Prophylactic treatment
Subcutaneous	Phenobarbital	100 mg; if necessary, repeat after 4–6 h; maintenance dose 2–4 mg/kg	Prophylactic treatment
Subcutaneous	Midazolam	Start dose 10 mg; maintenance dose 1.5–2.5 mg/h	Palliative sedation in patients with refractory seizures where other non-oral AEDs have failed.

Abbreviations: d, day; h, hour; min, minute

high-quality published data on the frequency of epilepsy and management of seizures in the EOL phase. Although the highest level of evidence would be achieved by randomized controlled studies, there are serious ethical objections to randomizing patients with regard to AED treatment in the EOL phase. In general, a retrospective study design is well accepted in EOL research and has the advantage of allowing all patients who enter the EOL phase to be identified.[65–67]

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, taking into account the complexity of AED administration during the EOL, should contribute to the development of more targeted seizure treatment.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Practice* (http://nop.oxfordjournals.org/).

Funding

Conflict of interest statement. None declared.

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