Seizure: European Journal of Epilepsy 70 (2019) 30–37

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Review

An overview of anti-epileptic therapy management of patients with malignant tumors of the brain undergoing radiation therapy

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ARTICLE INFO

Keywords:
Brain tumor
Glioma
Glioblastoma multiforme
Brain metastases
Seizure
Anti-epileptic drugs
Anticonvulsant drugs
Surgery
External beam radiotherapy
Radiation
Stereotactic radiosurgery

ABSTRACT

As our surgical, radiation, chemotherapeutic and supportive therapies for brain malignancies improve, and overall survival is prolonged, appropriate symptom management in this patient population becomes increasingly important. This review summarizes the published literature and current practice patterns regarding prophylactic and perioperative anti-epileptic drug use. As a wide range of anti-epileptic drugs is now available to providers, evidence guiding appropriate anticonvulsant choice is reviewed. A particular focus of this article is radiation therapy for brain malignancies. Toxicities and seizure risk associated with cranial irradiation will be discussed. Epilepsy management in patients undergoing radiation for gliomas, glioblastoma multiforme, and brain metastases will be addressed. An emerging but inconsistent body of evidence, reviewed here, indicates that anti-epileptic medications may increase radiosensitivity, and therefore improve clinical outcomes, specifically in glioblastoma multiforme patients.

1. Introduction

Seizures are the most common symptomatology among patients with malignancies of the brain, with reported rates of 15–95%. Seizures are often the initial manifestation of an intracranial malignancy, though 20–45% of patients will develop seizures later in the course of their disease [1–13]. The underlying pathophysiology of epilepsy among brain tumor patients is multifactorial and incompletely understood, but likely included physical and biochemical changes in the surrounding neural tissue. Proposed mechanisms include edema, increased intracranial pressure, changes in synaptic vesicles, neuronal migration, intercellular communication, angiogenesis, and neurotransmitter concentrations [1,2,14–19]. Tumor location and histology are drivers of seizure incidence. Supratentorial tumors, especially with superficial locations within the cortical gray matter, are more epileptogenic. Temporal, frontal, parietal or insular lesions are likely to induce seizures, whereas lesions in the occipital lobe, brainstem, or cerebellum rarely do. With regard to histology, the incidence of seizures is inversely correlated with degree of malignancy, with higher seizure incidence in low grade glioma (LGG) patients compared to patients with high grade glioma (HGG), glioblastoma multiforme (GBM) or brain metastases [2,4–6,8,9,12,13,15,16,18–21].

Optimal seizure management is of great importance in this patient population, as there is abundant evidence that seizure burden negatively affects neurocognitive functioning and quality of life (QoL), especially for those already afflicted by a cranial malignancy. Seizures themselves represent a loss of control for the patient, and a distressing manifestation of their underlying disease. Additionally, seizures can be associated with social stigma, job restrictions, and limitations in daily activities. Poorly controlled seizures can cause significant morbidity, as they can lead to aspiration, edema or injury [1,4,6,9,13,15,18,20–23]. An important aspect of optimal management of these patients is an understanding of the appropriate use of anti-epileptic drugs (AEDs), especially in conjunction with other treatment modalities. Management of seizures in brain tumor patients carry unique challenges, including that tumor-induced seizures are often refractory to medical management, there is potential for interaction between AEDs and chemotherapeutic agents, and there is risk of enhanced toxicity [1–3,17,23]. There

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https://doi.org/10.1016/j.seizure.2019.06.019
Received 5 April 2019; Received in revised form 28 May 2019; Accepted 12 June 2019

is compelling evidence of increased AED toxicity among CNS tumor patients relative to other epilepsy patients, with rates of adverse events of 20–40% [2,3,16,20,24–28]. The underlying cause of this observation is not well elucidated, but could be related to cerebral abnormalities, or to interactions with other cancer treatments, such as chemotherapy, radiotherapy (RT) or steroids [3,16,20]. Cutaneous adverse effects (AEs), including severe reactions, are especially common among brain tumor patients receiving AEDs [2,3,16,24,25]. Further, many AEDs impair cognitive functioning, and patients with existing brain damage due to cranial tumors, or to surgical resection, chemotherapy, or RT, may be especially prone to this sequela [1,2,13].

Many patients with malignancies of the brain will require RT at some point in their treatment course, whether definitively, adjuvantly, or in a palliative setting. Since radiation oncologists see patients, potentially for weeks during RT, as well as in follow-up, it is important that they have an understanding of AED management in this patient population. This review will discuss the existing literature regarding AED use among patient with cranial malignancies, especially in the context of RT. Prophylactic and perioperative AED use, choice of AED, AED withdrawal and general principles of RT and seizure risk will be discussed. Further, AED management in patients with gliomas, GBM, and brain metastases will be specifically addressed.

2. Prophylaxis & perioperative management

There is expert consensus that when a brain tumor patient presents with a first seizure, AED initiation is appropriate, given the high recurrence risk in patients with structural cranial pathology. Among seizure-free patients with brain tumors, approximately 10–20% will eventually develop seizures, so the question has arisen of whether AED therapy should be initiated prophylactically has arisen. For many years, seizure prevention with anticonvulsants was considered effective, and prophylactic AED use was routine. This practice was based upon little compelling evidence, and more recently, prophylactic AED therapy in this population has become controversial [1–3,8,9,27–30]. Several prospective randomized control trials (RCTs) and meta-analyses have failed to demonstrate any significant reduction in first-seizure rate or seizure-free survival with prophylactic AED use for brain tumor patients [1,3,9,24,29,31–33].

The American Academy of Neurology (AAN) does not advise routine AED prophylaxis for patients with newly diagnosed cranial tumors. This recommendation is based upon data from four RCTs, eight cohort studies and a meta-analysis of the four RCTs. The AAN concluded that long-term AED prophylaxis is not effective, as it does not reduce seizure frequency in this population [3,24,27]. Two subsequent meta-analyses confirmed the lack of benefit conferred by prophylactic AED use [33,34]. Similarly, in 2010 the Association of Neurological Surgeons/ Congress of Neurological Surgeons clinical practice guidelines discouraged routine AED prophylaxis for brain tumor patients, as it does not decrease subsequent seizure risk or affect overall survival (OS) [12,27].

For brain tumor patients, the perioperative period, especially the first 48 h, confers increased seizure risk, with incidence following craniotomy historically cited as 10–25% [1,8,11,19,36]. As a result, prophylactic AEDs are often prescribed, though the literature guiding anticonvulsant use in the perioperative setting is sparse [2,10,11,18,28,35]. Unfortunately, many of the studies addressing this clinical question include patients with a variety of diagnoses, or combine patients who undergo resection and those who do not. Of the handful of more recent studies specifically evaluating AED prophylaxis in brain tumor patients during the perioperative period, seizure incidence was less than 10%. In the setting of such low risk, especially compared to the rates cited historically, the practice of prophylactic AED use in the perioperative period is questioned by some authors [11,36]. Generally, there is agreement, including from the AAN, that if AEDs are initiated perioperatively, they should be withdrawn after one week [1,3,24].

A limitation of the data regarding prophylactic and perioperative AED use is that it is based upon studies predominantly employing traditional AEDs, especially phenytoin (PHT) and phenobarbital (PB). For example, the twelve studies that form the basis of the AAN guidelines evaluated PHT, PB, and valproic acid (VPA) [24]. A comparable level of evidence for the newer AEDs is lacking. Despite the evidence that AED prophylaxis should not be routinely used for brain tumor patients, studies demonstrate that the majority of providers continue this practice [9,10,27,37–39]. Guidelines regarding perioperative AED use are also often not followed. A Canadian retrospective study of malignant glioma patients undergoing surgical resection found that 40% of seizure-free patients were treated with prophylactic AEDs, and almost three quarters remained on treatment beyond one week post-operatively [10].

It is critical for radiation oncologists to familiarize themselves with the existing literature regarding prophylactic AED use in patients with cranial malignancies. Generally, prophylactic AED use should be discouraged, and for patients being seen post-operatively, tapering of AEDs should be discussed with the patient, as well as with their neurosurgeon. While these recommendations apply generally, for the patients at highest seizure risk, AED prophylaxis may be warranted, and individualized treatment decisions are required [16,28,40].

3. Choice of anti-epilectic therapy

There are few large prospective or Phase III studies of brain tumors patients upon which to base the choice of anticonvulsant. The evidence to date consists of retrospective studies or prospective case series of heterogeneous populations, and evidence-based guidelines regarding AED choice in this patient population are lacking [1–3,5,8,12,16,18,21,23,27]. A recent meta-analysis by the Cochrane collaboration determined that there is a lack of strong evidence to guide AED choice for the management of seizures in brain tumor patients [15]. Ultimately, the choice is often based upon physician experience and preference. Many patients and disease characteristics must be considered, including age, sex, seizure type, liver and kidney function, comorbidities, concurrently administered drugs, cost, and convenience of dosing and monitoring [3,7,8,18–20,23,41].

Generally, seizures in brain tumor patients are managed similarly to partial seizures in adult epilepsy patients [3,15]. Based upon evidence from meta-analyses and RCTs, the International League Against Epilepsy (ILAE) guidelines recommend levetiracetam (LEV), carbamazepine (CMZ), PHT, and zonisamide as level A, VPA as level B, and gabapentin (GPT), lamotrigine, oxcarbazepine (OX), PB, topiramate (TPM), and vigabatrin as level C AEDs [15]. Specifically for brain tumor patients, there is consensus among neuro-oncologists that enzyme-inducing AEDs (EIAEDs), including PB, CMZ, and PHT, should be avoided [1,3,8,12,15–17,19]. Commonly used AEDs in this patient population include VPA, lamotrigine, LEV, OX, TPM, and GPT [3]. Overall, the AEDs for which there is evidence specifically in brain tumor patients include LEV and VPA, with numerous authors recommending LEV as first line [2,3,5,8,12,16,19,21,37,41–45]. Advantages of LEV include a wide spectrum of anticonvulsant effects, excellent tolerability, low potential for drug interaction, affordability, rapid onset of action, no blood level monitoring, and availability of oral and intravenous formulations [4,5,21]. Other agents, such as tiagabine, pregabalin, and lacosamide, are utilized as add-on treatment, as there is sparse data regarding their use in brain tumor patients [3]. Lacosamide is a newer, third generation AED approved by the Food and Drug Administration as add-on therapy for partial-onset seizures. Lacosamide may be particularly useful in CNS tumor patients, as it has twice daily dosing, low protein binding, is a non-EIAED, and has a favorable AE profile [15,23,46]. As an add-on therapy, lacosamide shows a 50% seizure reduction in 40–66% of patients, as well as 31–43% rate of FFS [46–48].

As with all kinds of epilepsy, it is advisable to first attempt AED monotherapy [4]. If freedom from seizure (FFS) is attained, but intolerable AEs occur, monotherapy with an alternative AED with distinct toxicity profile should be attempted. If partial seizure control is attained with an initial AED at full dose, a subsequent monotherapy can be employed. If this strategy fails, polytherapy can be attempted, as different AEDs have different mechanisms of action and may improve efficacy when combined [2,4,8,18]. For example, there is evidence that the combination of LEV and VPA can act synergistically, with favorable tolerability [1,2,16].

When patients with CNS tumors attain FFS, the question arises of when AED withdrawal is appropriate. There are no robust RCTs addressing this, and clinical decision-making is based upon experience in other epilepsy patients and retrospective data. Generally, withdrawal is only considered in seizure-free patients, with completely treated cranial lesions, and anticipated long OS. If the epileptogenic source remains, relapse risk is high, so AED withdrawal is avoided in patients with incompletely treated tumors [3,20].

4. Radiation and seizure risk

Cranial RT can cause pathologic changes in the brain, including demyelination, axonal loss, gliosis, and vascular changes, which can subsequently cause edema. As a result, RT, whether WBRT, partial brain RT or SRS, can exacerbate existing epilepsy, or cause *de novo* seizures. Seizure is an established acute toxicity of cranial RT, often secondary to edema in the treated area. It is also well-documented that seizures can manifest as chronic RT toxicity, months to years after treatment, often as a consequence of radiation necrosis [2,15,49–52]. In patients already prescribed AEDs, radiation oncologists must be mindful of the acute increase in seizure risk associated with RT, especially when considering the timing of AED taper or withdrawal. Patients undergoing RT should be informed of this potential AE, and counseled to contact their physician in case of symptoms of seizure during or following RT.

4.1. Dexamethasone

Patients with intracranial tumors are often prescribed steroids, most commonly dexamethasone, to reduce intracranial edema and resultant neurological symptoms. It is important to note that dexamethasone can transiently increase PHT levels through competitive protein binding, but can also decrease PHT levels by increasing hepatic metabolism [2,51]. For patients receiving PHT, increased seizure frequency has been reported with co-administration of dexamethasone, and toxic levels of PHT can occur with dexamethasone withdrawal [27]. Radiation oncologists are often the providers who initiate, manage, and taper steroids for brain tumor patients. It is vital that they are cognizant of this potential drug interaction, and that patients on PHT requiring dexamethasone or other steroids are carefully monitored in conjunction with a neurologist or neuro-oncologist.

4.2. Erythema multiforme, stevens-johnson syndrome, and toxic epidermal necrolysis

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are a spectrum of severe, immunologic, cutaneous reactions. Clinically, they consist of diffuse erythema, rash, subepidermal edema, and formation of necrotic or hemorrhagic bullae of the skin and mucous membranes. Some controversy exists regarding the distinction between EM, SJS, and TEN, but most physicians now consider these reactions to represent the same process along a spectrum of severities. SJS and TEN are very rare, with an estimated incidence of 0.4–1.4 cases per million annually. EM, SJS, and TEN are associated with considerable morbidity and potentially mortality. With modern management of TEN, mortality rates as high as 30% have been reported. There are many potential triggers for EM, SJS, and TEN, including infections, collagen vascular disease, malignancy or medications. EM, SJS or TEN induced by AEDs has been widely reported in the literature [53–58].

Literature has emerged linking concurrent cranial RT and AED use to the development of EM, SJS or TEN. There is compelling evidence that the trigger is the combination of RT and AED use, rather than either factor alone. There are no reported cases of EM, SJS or TEN with RT as the only inciting factor, the severity of skin reaction observed is beyond what is usually encountered secondary to radiation dermatitis, and in all published cases, the cutaneous reactions began coincident with radiation fields, then subsequently generalized. In cases where a drug was thought to be responsible for the reaction, rather than RT, subsequent use of the drug failed to induce EM, SJS or TEN. Similarly, there have been cases of EM, SJS or TEN where prior or subsequent RT was pursued without concurrent AED, without symptom recurrence. Overall, cases of EM, SJS or TEN with RT as an inciting factor are exceedingly rare. Though literature is scarce, generally EM, SJS or TEN occur approximately three to four weeks after the start of RT, with median time to development of 25 days. No relationship has been reported between severity of reaction and RT dose, drug dose, or underlying pathology of the treated lesion; there is no known age or gender predilection [53–58].

Although rare, given the morbidity of EM, SJS or TEN, when possible AEDs which have not been associated with this reaction should be prescribed in patients planned to undergo cranial RT. CMZ, OX, PHT, and PB have all been associated with severe cutaneous reactions in the context of RT, whereas LEV is not known to produce EM, SJS or TEN, alone or in combination with cranial RT [2,3,26,54,55,57]. If cranial RT patients are receiving concurrent AEDs, any cutaneous toxicity during or after RT must be evaluated promptly. At the first suspicion of EM, SJS or TEN, AED and RT should be discontinued and medical management should be initiated [55]. Radiation oncologists delivering cranial RT for patients on AEDs should counsel patients on the importance of notifying their physician if they develop any significant dermatologic symptoms.

5. Glioma

Seizures are the most common symptom among patients with gliomas, occurring in 60–80% of LGG patients and 25–60% of HGG patients. In fact, seizures are the most common presenting symptom in this population. Seizures are more common among younger patients, those with lower grade malignancies, and for tumors with an oligodendroglial component or isocitrate dehydrogenase (IDH-1) mutation [1,2,8,16,18–22,24,51,59,60]. There is no high-quality evidence to guide AED choice in this patient population, but LEV is the AED with the strongest evidence, and is generally considered first line. Numerous studies have evaluated LEV for glioma patients and reported FFS in 65–91%, and at least 50% seizure reduction in up to 100% of patients [3,16,18,21,44,45,61–64]. Additionally, there is some evidence that LEV may improve verbal memory and cognitive functioning in glioma patients [16,18,26]. There is also evidence supporting the use of VPA for glioma patients, with reported FFS rates of 30–78% [16,18,21,65].

Lacosamide is a newer AED which is increasingly being used in this patient population as an add-on treatment [22]. In a study of 71 patients managed with lacosamide as an add-on treatment, at least 75% experienced seizure reduction of 50% or more, and almost half achieved FFS [23]. Maschio et al. evaluated a small series of glioma patients and reported at least 50% seizure reduction in 36% and FFS in an additional 49% [48]. In a study by Saria et al. of brain tumor patients, predominantly gliomas, 54% of patients had at least 50% seizure reduction [49]. Recently, a study of patients with primary intracranial tumors, predominantly gliomas, managed with lacosamide after failure of other AEDs, reported reduced seizure frequency by at least 50% in 66% of patients and FFS in 31% [47].

Table 1
Studies evaluating the role of radiotherapy in seizure reduction for glioma patients.

Author, Year	N	Pathology	RT	Outcomes
Rogers et al., 1993 [72]	5	LG Astrocytoma	EBRT	Reduction in seizure > 90%: 60% Reduction in seizure 75-90%: 20% FFS: 20%
Scerrati et al., 1994 [68]	36	LGG	Interstitial brachytherapy ± EBRT	FFS: 56%
Warnke et al., 1997 [59]	80	Grade II Astrocytoma	Interstitial brachytherapy	FFS: 79%
Schrottner et al., 1998 [70]	26	Majority LGG	Gamma Knife SRS	Engel class I/II (significant reduction): 54% Engel class III (worthwhile improvement): 17%
Schrottner et al., 2002 [71]	19	Majority LGG	Gamma Knife SRS	Engel class I/II: 58% Engel class III: 37%
Plathow et al., 2003 [75]	143	Grade II Astrocytoma	Fractionated SRS	Generalized seizures reduced 36% to 7% Focal seizures reduced 34% to 17%
Shankar et al., 2003 [69]	30	Insular Grade II Astrocytoma	RT, unspecified	Engel class I/II: 83% Engel class III: 3%
Van den Bent et al., 2005 [73]	311	LGG and HGG	EBRT	Immediate RT, FFS: 75% Delayed RT, FFS: 59%
Kahlenberg et al., 2012 [74]	73	LGG	RT, unspecified	Statistically significant reduction in seizure frequency with RT
Ruda et al., 2013 [60]	43	LGG and HGG	EBRT	Reduction in seizure frequency ≥50%: 76%

AEDs, surgical resection, and adjuvant chemotherapy and RT are employed in the management of gliomas. In LGG following surgical resection, depending upon risk factors, patients can undergo adjuvant RT, or observation, with RT reserved for recurrence. For HGG patients, standard of care includes adjuvant chemotherapy and RT following maximal safe resection. As with any cranial irradiation, RT for glioma treatment can acutely increase seizure incidence [1,16,38,66,67]. There is no evidence that this risk is sufficient to warrant prophylactic AED usage. However, this potential acute toxicity, and the seizure risk factors outlined above, should be considered by radiation oncologists contemplating initiating prophylactic AED use, or, conversely, AED taper or withdrawal. There is compelling evidence that in glioma patients, RT significantly improves seizure incidence following treatment. Retrospective studies of LGG patients managed with RT indicate 50% seizure reduction in 56–77% of patients, and FFS in 38–80% [18,59,60,68–71]. Table 1 summarizes the key trials evaluating the effect of RT on seizure rates in glioma patients. In a study of low grade (LG) astrocytoma patients, external beam RT (EBRT) was associated with 90% or greater reduction in seizure frequency in three of five patients at one year, and only one patient had no seizure response [72]. In a study of 80 patients with Grade II astrocytoma managed with interstitial brachytherapy, 40% of patients attained FFS at three months and at six months, only 21% of patients had refractory seizures. In fact, RT was more effective at seizure reduction than AED use [59].

In the European Organisation for Research and Treatment of Cancer (EORTC) 22845 trial, a large, multi-institutional prospective RCT of 311 LGG patients, immediate post-operative RT improved seizure control, with 25% seizure incidence, compared to 41% for patients randomized to observation [66,73]. A recent retrospective study reported that RT was a prognostic factor for seizure control in 73 LGG patients [74]. Ruda et al. recently completed a retrospective study of 43 glioma patients with epilepsy managed with EBRT. They reported FFS in 32% of patients at one year, ≥50% reduction in seizure frequency in 72% of patients at three months and in 76% of patients at one year. In this study, no difference was observed with regard to seizure control with early RT or RT delayed until tumor progression [16,60]. It is interesting to note that Ruda et al. and Kahlenberg et al. observed reduction in seizure incidence even in the absence of radiographic tumor response, implying that RT may have direct effects on epileptogenesis [3,60,75]. Further prospective studies are necessary to determine the role of RT in the management of seizures in glioma patients.

For glioma patients successfully completing cranial RT, and being seen in routine follow-up, the question of AED withdrawal arises. In LGG patients with complete tumor treatment, after a two year seizure free interval, taper and withdrawal of AED can be considered. The seizure risk factors for glioma patients, discussed above, can be considered in making this decision. Though many patients do experience prolonged OS, the infiltrative nature of gliomas is such that in most patients, recurrences eventually occur. Therefore, there is a risk for recurrent seizures, and AED withdrawal must be approached cautiously [16,21,76].

6. Glioblastoma multiforme

GBM is the most common primary malignant brain tumor in adults. Estimates of seizure prevalence among GBM patients range from 30 to 60%, with one third of patients presenting with seizure, and an additional one third developing seizures during the course of their illness. Older patients and those with larger tumors are less likely to present with seizures. Patients with tumors of the frontal lobe, temporal lobe, and insula have higher seizure incidence, as do those with IDH1 mutations and p53 overexpression. There is evidence of higher seizure incidence in GBM progressing from lower grade gliomas, compared to *de novo* GBM [1,2,16,18,20,22,77,78]. The standard treatment for GBM consists of maximal safe resection, followed by concurrent RT and temozolomide (TMZ), and adjuvant TMZ, as established by the landmark Stupp trial [81,82]. The diagnosis of GBM confers a dismal prognosis, with median OS of 14–18 months, even with treatment. Unfortunately, efforts at improving OS have had only modest success. GBM recurs most commonly within the high dose RT field, or at its margin, leading to the suggestion that perhaps outcomes could be improved if the efficacy of RT were increased [79,81–88].

VPA is commonly chosen in the management of GBM patients with epilepsy, with the best evidence supporting this anticonvulsant [3,8,16,20,79]. In a Dutch study of GBM patients treated with surgery and concurrent chemoradiotherapy (CRT), FFS was achieved in 41% of patients taking VPA, 43.3% among those receiving LEV, and 76.6% receiving a combination [3,65]. There is some concern that VPA may induce or aggravate hematologic toxicity, especially thrombocytopenia, in a dose-dependent manner. This may be especially pronounced in combination with chemotherapy, including TMZ and nitrosureas, commonly used for GBM [3,16,17,42,43]. However, a recent study of 104 GBM patients undergoing the Stupp regimen and receiving LEV or VPA did not demonstrate significant differences in rates of hematologic toxicities between the two AEDs [16,80]. Given the short OS associated with GBM, withdrawal of AEDs in this patient population is not generally recommended [17,67].

6.1. Radiosensitizing effects of AED

Recently, in vitro and in vivo evidence has emerged suggesting that AEDs may themselves have anti-tumor effects, and act synergistically with other treatment modalities, such as chemotherapy or RT [79,83–85,89]. This effect has been most thoroughly investigated with VPA in GBM. The mechanism of action of VPA includes histone deacetylase (HDAC) inhibition, and in vitro experiments have shown that HDAC inhibition can increase tumor cell radiosensitivity in a variety of malignant cell lines, while protecting normal tissues [78,83–87,89–92]. The mechanism of action for this radiosensitization is thought to be through interference with repair of DNA double strand breaks. Additionally, HDAC inhibition may induce apoptosis and autophagy, halt cell cycle progression, cause growth arrest, and interfere with angiogenesis, metastasis, differentiation, and senescence [78,79,85,87,89–92].

VPA can act as a radiosensitizer specifically to glioma cells, but as a neuroprotector to healthy neural tissues [78,83–92]. In experiments with healthy neural cell lines, exposure to VPA decreased RT-induced apoptosis and cell death [91]. In experiments with glioma cell lines, investigators have demonstrated decreased cell growth and colony formation with VPA, and additively impaired growth with the combination of VPA, TMZ, and RT [85,90,91,93]. This trend is not universally observed. Eckert et al. exposed GBM cell lines and spheroids to TMZ and RT, with or without VPA, assessed colony formation and clonogenic survival and did not observe a significant sensitizing effect of VPA [88]. This discordant finding highlights the importance of the exact protocols and cell lines employed. Studies in animal models have supported the role of VPA as a radiosensitizing agent for glial cells and a radioprotector for normal neural tissues. There is reduced spinal cord and hippocampal injury induced by RT in rats and mice exposed to VPA before and during RT [83,91]. Also, using mouse and rat models, experimenters have shown increased radiosensitivity, delayed glial tumor growth and improved OS using VPA concurrent with RT, compared to VPA alone [88,91,93].

6.2. VPA in GBM

There is some evidence that GBM patients receiving VPA concurrently with chemotherapy and RT may have better disease-related outcomes [7,16,20,79,87,91]. A retrospective subgroup analysis of the Stupp trial evaluated the association between AED use and OS among 573 patients. On multivariate analysis, for patients receiving concurrent RT and TMZ, VPA use was associated with a three month improvement in OS [41]. Numerous additional retrospective studies have shown significant prolongation of OS in GBM patients receiving VPA, with reported improvements ranging from three to twelve months [16,42,65,78,83,84,87,91,94]. Further, a prospective study of GBM patients showed progression free survival (PFS) of ten months and OS of 29 months when VPA was combined with the Stupp regimen [84]. In contrast, a retrospective study by Berendsen et al. did not find an OS advantage with the use of VPA in 647 GBM patients, though, in this study not all patients received the complete Stupp regimen [78]. Similarly, a meta-analysis of 1800 GBM patients managed with surgery and CRT from 4 RCTs (AVAGlio, NCT00943826; CENTRIC, NCT00689221; CORE, NCT00813943; Radiation Therapy Oncology Group 0825, NCT00884741), did not demonstrate improved OS with VPA treatment [7]. An even more modern meta-analysis of the existing literature on the effect of VPA on OS in GBM patients was published in 2018. The study included 2181 GBM patients from seven retrospective studies, and found that VPA statistically significantly improved OS by 2.4 months. This effect was most apparent in older studies and for younger patients [79]. Table 2 summarizes some relevant publications that have explored the impact of VPA on OS among GBM patients. Unfortunately, all of these studies are retrospective in nature. The issue of the clinical impact of concurrent VPA use for GBM patients undergoing treatment warrants further investigation, and a prospective trial would be required to address this question definitively.

The anti-tumor effects of other AEDs have also been investigated in GBM patients, though the literature is sparse and conclusions are heterogeneous [79]. In a retrospective study of 620 GBM patients, those receiving EIAEDs had increased PFS and OS compared to those not receiving EIAEDs [20,95]. Conversely, a study of 168 GBM patients managed with surgery, and adjuvant chemotherapy found that use of EIAEDs was associated with worse OS compared to patients receiving non-EIAEDs, mostly VPA [42]. In a small, retrospective study, it was demonstrated that LEV improved OS in GBM patients receiving TMZ [87]. The meta-analysis of GBM patients treated with CRT by Happold et al. referenced above also evaluated the effect of LEV. Unfortunately, this study failed to find an association between LEV use and OS or PFS [7]. A Norwegian retrospective cohort study of 1263 GBM patients identified by national registry concluded that none of the six AEDs evaluated, VPA, LEV, CMZ, OX, lamotrigine or PHT, significantly affected OS [96].

7. Brain metastases

Appropriate management of secondary CNS malignancies is of great clinical importance, as intracranial metastases are common, with estimated incidence of 8–14 per 100,000 people. Approximately 20–40% of cancer patients will ultimately develop brain metastases, which are the most common intracranial malignancy [4,28,51,97]. Further, management of intracranial metastases is of growing importance, as the incidence of brain metastases is increasing. This is partially attributable to increased utilization and quality of diagnostic imaging. Additionally, improved systemic therapies are controlling metastatic disease, but are not as effective intracranially, secondary to the blood-brain barrier.

Seizures are common among patients with brain metastases, especially with increasing burden of disease [5]. The most common malignancies causing intracranial metastases are lung (20%), melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal (1.8%) [28,51]. Reported rates of seizures among patients with brain metastases range from 13 to 48%, and vary widely depending upon histology [1,2,4,5,8,18,20,28]. Patients with intracranial metastases from melanoma are at especially increased risk of seizure, with reported rates as high as 67% [5,13,20,28]. This may be related to their tendency to be cortical and hemorrhagic [28]. Among lung cancer patients, 29–48% develop seizure, compared to 16–33% of breast cancer patients, and 21% of those with gastrointestinal malignancies [5,18,20,51].

There are no RCTs guiding AED choice in brain metastasis patients, but as with other intracranial tumors, non-EIAEDs are preferred and there is evidence for good efficacy of LEV [18,28,45]. In a retrospective study of brain metastases patients managed with LEV monotherapy or add-on, seizure frequency was reduced by at least 50% in all patients, and 77% of patients experienced FFS [61]. Maschio et al. investigated the use of three newer AEDs, LEV, OX, and TPM, in 38 patients with brain metastases and noted that all three agents had good efficacy, with significant reduction in seizure frequency [5]. In patients with brain metastases whose lesions have been successfully treated with surgery or RT, and who remain seizure-free, some experts recommend gradual AED taper and withdrawal three to six months after treatment [17].

For many decades, whole brain RT (WBRT) represented the standard of care in palliative management of patients with brain metastases [30,98]. As with any cranial RT, WBRT can acutely increase seizure risk or exacerbate existing epilepsy. Reported seizure incidence in the first weeks after WBRT is 10–15% [41,49]. Wong et al. retrospectively analyzed seizure rates before and after WBRT in 129 patients with brain metastases. The rate of seizures at baseline was 11% and following WBRT, 10% reported reduced and 11% reported worsened seizure burden [99]. Stereotactic radiosurgery (SRS) is a RT technique specifically developed to deliver high doses of very conformal radiation in one to five fractions to intracranial lesions, with minimal dose delivered to surrounding healthy tissues [97,98].

In recent decades SRS, alone or in conjunction with WBRT, has been increasingly used in the management of brain metastases, as it confers good local control and a favorable AED profile [15,30,98,100–102].

Table 2
Studies evaluating the role of VPA in OS for GBM patients.

Author, Year	N	VPA comparison	Outcome
Weller et al., 2011 [41]	573	VPA vs. EI-AED	With VPA, improved OS vs. EI-AED (HR 0.69; 95% CI 0.53–0.90)
		VPA vs. no AED	With VPA, improved OS vs. no AED (HR 0.67; 95% CI 0.49–0.93)
Guthrie et al., 2012 [94]	236	VPA vs. no AED	With VPA, longer OS vs. no AED (Mantel–Cox log-rank test 17.506, $p < 0.001$)
		VPA vs. other AED	With VPA, longer OS vs. other AEDs (Mantel–Cox log-rank test 5.303, $p < 0.02$)
Barker et al., 2013 [83]	544	VPA vs. other AED	With VPA, median OS 23.9 months vs. 15.2 months with other AED, (p = 0.26)
Kerkhof et al., 2013 [65]	165	VPA vs. no VPA	With VPA, median OS 69 weeks vs. 61 weeks without (HR 0.63; 95% CI 0.43–0.92, p = 0.016)
Redjal et al., 2016 [111]	224	VPA vs. other AED	With VPA, 28% decrease in HR of death (p = 0.031), 28% decrease in HR of progression or death (p = 0.015), in dose dependent manner
Berendsen et al., 2016 [78]	212	VPA vs. no VPA	With VPA. median OS 13.8 months vs. 12.7 months without (HR 0.90; 95% CI 0.62-1.29, p = 0.55)

Because SRS delivers high radiation dose to target lesions and some surrounding neurological tissue, it can also induce seizure, albeit at low rates. The literature establishing the seizure risk associated with SRS is sparse, and interpretation of the data is complicated by the heterogeneity of studies with regard to patient diagnoses, baseline AED use, seizure severity, follow up period and prior intracranial treatments. Various studies of patients undergoing intracranial SRS report acute seizure risk of 0–21% [15,49,98,100,101,103–105]. Seizures within two days of SRS occur in approximately 5% of patients [106]. The reported risk of severe seizure ranges from 2.7 to 8.7% [98,101,105].

Many studies have reported seizure incidence among patients undergoing SRS, and a few larger and more methodologically sound studies will be highlighted; Table 3 provides a summary of this literature. In a study by Werner-Wasik et al., among 78 patients treated with SRS for intracranial lesions, including benign, malignant, primary, and metastatic tumors, 8% developed seizures within two weeks [100]. A prospective study was conducted at MD Anderson Cancer Center of 273 patients receiving SRS for one to two brain metastases for which they had not previously received RT or surgery. The onset of new seizures was the most common AE observed, seen in 13% of cases. Among patients who developed seizure, 46% were severe [101]. Meisner et al. followed 93 patients with 142 brain metastases managed with SRS, with approximately half receiving SRS alone, thirteen receiving SRS and WBRT and 34 treated with SRS following prior WBRT. Ten patients experienced seizures within three months of SRS, but six of these also had radiographic evidence of disease progression [107]. There is some indication in the literature that lesion location correlates with seizure risk following SRS, with lesions of eloquent cortex, especially primary motor or somatosensory cortex, conferring increased risk [15,97,101,102]. Seizure rates among patients with motor cortex metastases treated with SRS have been reported as high as 67% [101,102]. There is no compelling evidence supporting prophylactic AED usage prior to WBRT or SRS for brain metastases.

Arvold et al. conducted an internet-based survey of 161 U.S. radiation oncologists specializing in CNS treatment, evaluating their prophylactic AED use in the context of SRS. Of the radiation oncologists queried, 79% “rarely” or “never” prescribed prophylactic AEDs. Fewer than 10% of respondents recommended AEDs “always” or “usually.” For those who did recommend AED use, their recommended duration of use was < 1 week, 1–2 weeks, and > 2 weeks for 35, 25, and 41%, respectively. Most of these radiation oncologists estimated the seizure risk in the context of SRS to be 5% or less. Overall, there is marked variability among radiation oncologists in their AED prescribing practices for patients undergoing SRS. This heterogeneity is not surprising given the lack of guidelines addressing this clinical question, and the varying seizure risk estimates in the published literature [15]. However, it may be worthwhile to consider prophylactic AED administration in the highest risk patients based upon histology and location. Additionally, these risk factors should guide decisions regarding AED taper or withdrawal. The appropriate use of AEDs in the context of SRS is an area that warrants more research, especially of a randomized, prospective nature.

8. Conclusion

In conclusion, seizures are common among patients with CNS malignancies, and significantly affect QoL, so their appropriate management is of great clinical significance. There are many anticonvulsants available, and the appropriate choice of AED must consider patient and disease characteristics. AED choice is largely based upon clinician preference, without strong randomized or prospective evidence. However, there appears to be consensus that newer AEDs should be preferentially employed for intracranial tumor patients, with the strongest evidence for LEV monotherapy. Brain tumor patients are at high risk for AEs from AEDs or for drug interactions, and should be carefully monitored. Based upon existing evidence, prophylactic AED use should be avoided in this patient population, except perhaps for patients with significant seizure risk. AEDs can be used perioperatively,

Table 3
Studies evaluating seizure risk following SRS in brain metastasis patients.

Author, Year	N	Population	Seizure incidence	Follow-up period
Loeffler et al., 1990 [109]	44	Varied, including brain metastases	6%	≤24 hours
Alexander et al., 1995 [97]	248	Brain metastases	4%	≤2 days
Gelblum et al., 1998 [102]	47	CNS tumors, 89% brain metastases	21%	≤3 months
Lavine et al., 1999 [[108]]	45	Melanoma brain metastases	9%	≤1 day
Werner-Wasik et al., 1999 [100]	78	Varied, 24% brain metastases	8%	≤2 weeks
Kondziolka et al., 2005 [110]	104	Brain metastases	3% (WBRT + SRS) 3% (SRS only)	
Manon et al., 2005 [105]	31	Brain metastases (renal cell carcinoma, melanoma, sarcoma)	3%	
Aoyama et al., 2006 [98]	132	Brain metastases	2% (WBRT + SRS) 6% (SRS only)	3 months
Williams et al., 2009 [101]	273 (316 lesions)	Brain metastases	3% of lesions	≤30 days
Chang et al., 2009 [30]	58	Brain metastases	4% Grade 3+ (WBRT + SRS) 0% (SRS only)	≤4 months
Meisner et al., 2010 [107]	93 (142 lesions)	Brain metastases	11%	≤3 months

but should be tapered or stopped after one week. Cranial RT itself can temporarily increase risk, but overall seizure risk is low, and prophylactic AED use is not necessary for most patients. Cranial RT sometimes necessitates use of steroids, and PHT levels should be carefully monitored if dexamethasone is used concurrently. Additionally, cranial RT concurrent with some AEDs can induce severe cutaneous adverse effects, and monitoring for these should be vigilant. For gliomas, the strongest evidence supports LEV monotherapy. There is also compelling evidence for decreased seizure risk following treatment with RT. For GBM patients, VPA is often the AED of choice, though drug interactions and hematologic toxicities can occur. There is increasing but inconclusive evidence regarding potential synergistic anti-tumor effect of RT and VPA. For patients with brain metastases, LEV is also an effective and well-tolerated anti-convulsant. Both WBRT and SRS in the management of brain metastases can acutely increase seizure risk, especially for lesions of eloquent cortex, though there is no evidence supporting routine prophylactic AED use during RT.

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