Seizures in benign and malignant brain tumors

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Disclosures

None

Learning objectives

- Review the most common types of brain tumors associated with seizures
- Discuss the current guidelines on symptomatic management of seizures in tumors
- Evaluate the effects of antitumor therapy on seizure control

Brain-tumor related epilepsy

- Epilepsy = two or more seizures at least 24h apart, or a single seizure + high risk of recurrent seizures (i.e., abnormal MRI or EEG)
- Drug-resistant epilepsy= failure of two anti-seizure medications (ASMs)
- Risk of epilepsy in CNS tumors
  - low grade gliomas (LGG): 60-100%
  - glioblastomas: 40-60%
  - meningiomas: 20-30%
  - brain metastases: 25%
- 1/3 of patients are drug-resistant

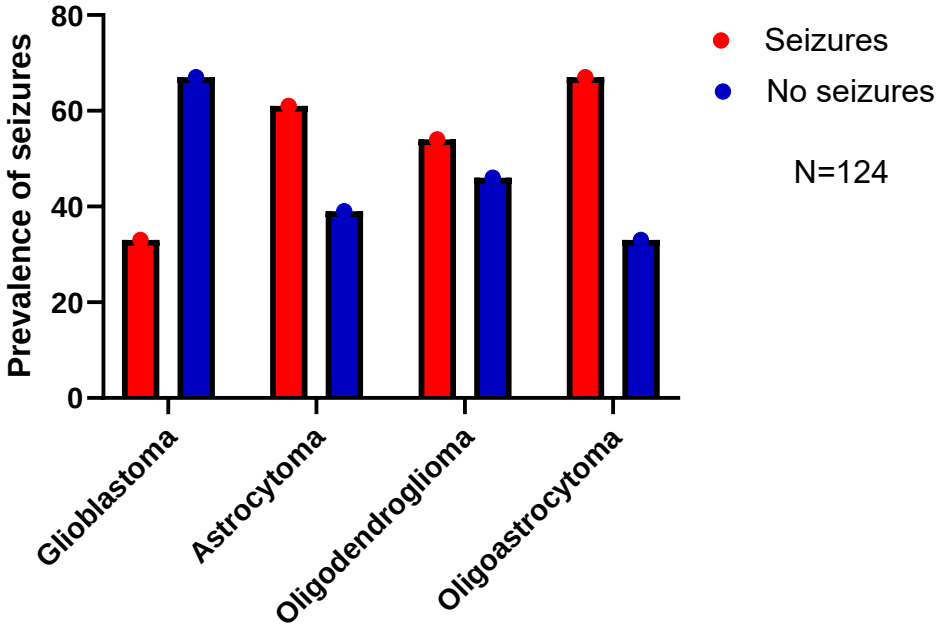
Peters et al, *Neurology* 2024; Fisher et al., *Epilepsia* 2014

Risk factors for seizures

- 30-50% of patients develop seizures at the tumor diagnosis
- 6-45% develop seizures during treatment
- Risk factors:
  - LGG
  - tumor location
    - ✓ superficial cortical location >> subcortical
    - ✓ temporal and insular > frontal region
    - ✓ supratentorial
  - larger tumor size in LGG
  - smaller size in high-grade tumors
  - genetics

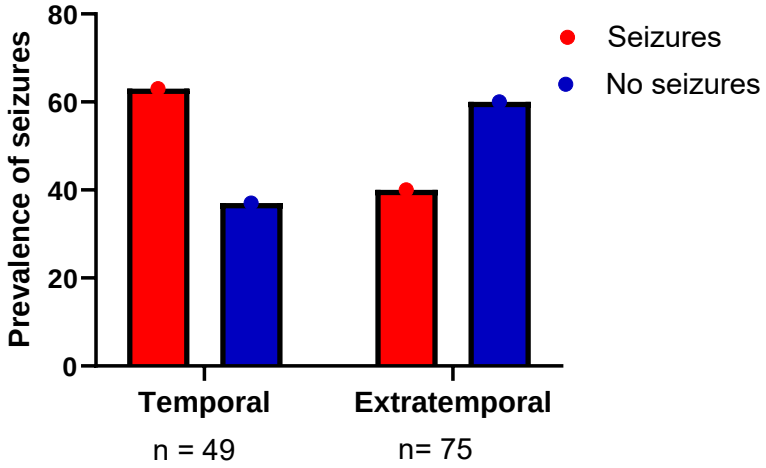
Lee et al., *Arch Neurol* 2010

Tumor histopathology



Lee et al., *Arch Neurol* 2010

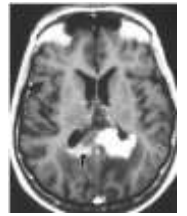
Tumor location and size



- Temporal region: LGG present with more seizures than high-grade gliomas
- Tumor volume correlates with seizure tendency in LGG with a 3% increase per cm^3

Lee et al., *Arch Neurol* 2010

Seizure as the first presentation



- More likely in supratentorial tumors
- Less likely in pericallosal (“butterfly”) high-grade tumors
- Seizure is the only manifestation in many insular tumors:
  - up to 98% of grade II gliomas
  - minimal finings on exam

Lee et al., *Arch Neurol* 2010; Duffau, *J Neurosurg* 2009; Luna et al, *Radiology* 2021

Seizure semiology by tumor location

Frontal lobe
- Simple motor
- Hypermotor
-Speech difficulties
-Gelastic or olfactory

Temporal lobe
- Aura (abdominal, gustatory, olfactory, psychic)
- Visual, autonomic
-Automatisms
- Aphasia

Insular
- Aura (similar to temporal)
- Fear
- Hypersalivation
-Tachy-/bradycardia

Parietal
- Complex visual illusions and hallucinations
-Tonic motor
-Automatisms

Occipital
-Simple visual hallucinations
-Uncontrollable eye movements, nystagmus

Peters et al, *Neurology* 2024

Tumor genetics and seizures

- Presence of mutations in codons 132 and 172 of isocitrate dehydrogenase 1 and 2 (*ICD* 1 and 2)
  - accumulation of glutamate-like metabolites
  - activation of NMDA receptors leading to seizures

Vehcht et al, *The Oncologist*, 2014

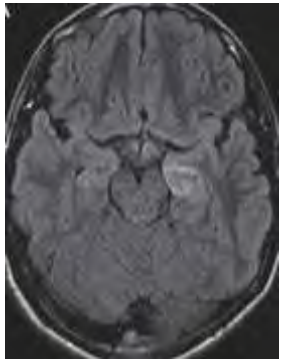
Pathophysiology of seizures in tumors: aberrant glutamate signaling

- Increased expression of glutamate receptors
- Decreased activity of glutamine synthase
- Higher (~100 times!) presence of extracellular glutamate in peri-glioma tissue
- Decreased expression of glutamate transporters
- Changes in GABA metabolism
- Specific mutations *ICD 1* and 2
- Excessive glutamatergic tone results in activation of mTOR and MAPK signaling => cell growth and epileptogenesis

Lange et al., *Cells*, 2021; Vehcht et al, *The Oncologist*, 2014

Epilepsy in pediatric CNS tumors

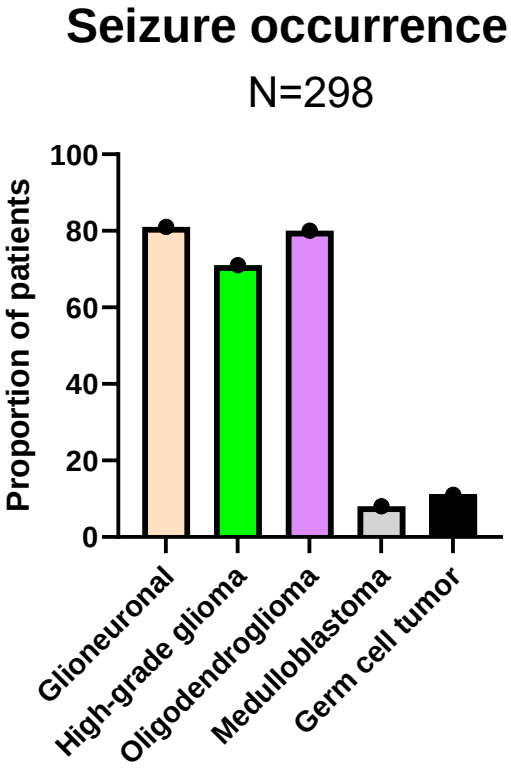
- Occurs in 25-30% of children with tumors
- Seizure as a presenting symptom: ~15%
- Long-term epilepsy associated tumors (LEATs):
  - dysembryoplastic neuroepithelial tumors (DNET), gangliogliomas, oligodendrogliomas
  - can increase overall mortality by a factor of ~5
- Risk factors:
  - cerebral cortex (53%) > midline (18%) > infratentorial (9%)
  - low grade and glioneuronal

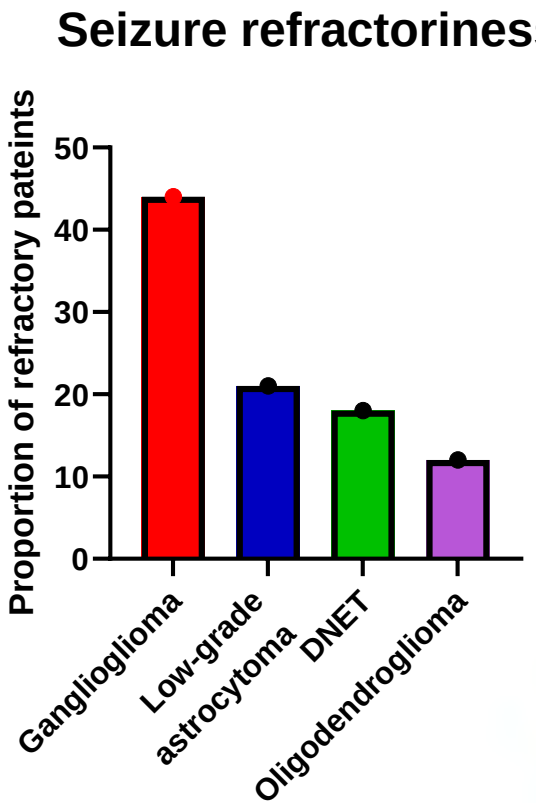


DNET

Fernandez and Loddenkemper *Seizure*, 2017

Seizures by pathology in children





Ulrich et al., *Epilepsia* 2015; Khajavi et al *J Clin Neurol* 1999

Summary

- Seizures commonly herald the diagnosis of CNS tumors (more likely LGG) in adults and children
- LGG are more epileptogenic than high-grade tumors
- Locations in the temporal region (and insula) are more likely to be associated with seizures compared to other locations
- Seizures independently increase mortality in long-term epilepsy associated tumors (LEATs)

Treatment of seizures in CNS tumors

- Initiate after the first seizure
- If left untreated, risk of recurrence is 90% after the second seizure
- Preferred antiseizure medications (ASMs): levetiracetam, valproate* or their combination
  - o also effective in metastatic tumors
  - o valproate and temozolomide has NOT improved survival in GBM
- Next line: lacosamide, lamotrigine, zonisamide
- Topiramate (cognitive slowing), oxcarbazepine (hyponatremia)
- Add-on perampanel: 57% seizure freedom in gliomas
- Enzyme-inducing ASMs (phenobarbital, carbamazepine, phenytoin) can mitigate antitumor effects of chemotherapeutic agents

Peters et al, *Neurology* 2024; Vehcht et al, *The Oncologist*, 2014

Tumor surgery as a tool for seizure control

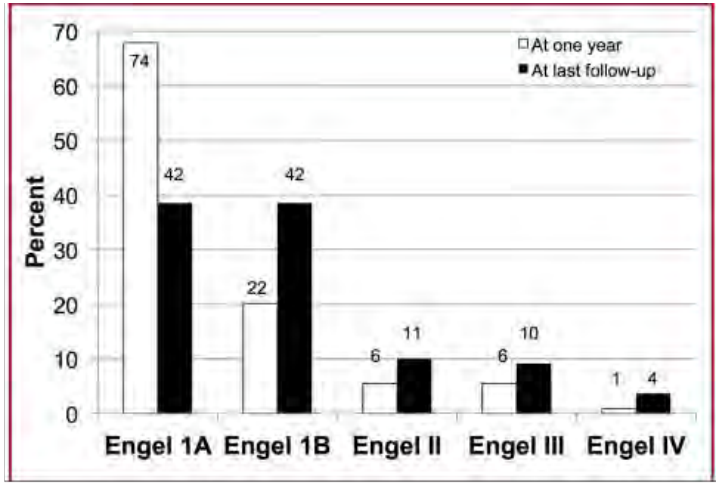
- Most impactful in temporal lobe LGG and other glioneuronal tumors
- Extensive resection (gross total) results in much better seizure control than subtotal or lesionectomy
- Additional benefits:
  - shorter duration of preoperative epilepsy
  - age <18 years
  - use of intracranial EEG
  - ipsilateral hippocampectomy

Englot et al., *Neurosurgery* 2012; Still et al., *Neurosurgery* 2019

Seizure outcomes after glioma resection

Insular gliomas (109 patients)

- 66% were seizure free at 1 year
- greater extent of resection was a predictor of seizure freedom



Wang et al., Neurosurgery 2018

Seizure outcomes after resection of DNET

- Single center: 50 patients
- Median age: 21 years
- Complete resection: 78%
- Additional pathology: focal cortical dysplasia (52%)
- Seizure freedom: 86 and 85% at 1 and 5 years

Chang et al, *J Neurosurgery Pediatr* 2018

Decision to discontinue ASMs

- Often triggered by cognitive or mood symptoms
- In patients without surgery:
  - seizure freedom for > 2 years
  - no history of status epilepticus
  - lack of tumor progression (e.g., LGG)
  - absence of structural injuries (encephalomalacia, radiation necrosis)
  - EEG abnormalities has NOT been found to be a significant predictor for recurrence, except for meningiomas
- In patients who completed surgery
  - no guidelines but can be considered in LGG with extensive resection

Peters et al, *Neurology* 2024

Special considerations in seizure naïve patients with CNS tumors

- ~40% of patients with brain tumors will receive ASM after craniotomy or biopsy
- Most commonly used ASM: levetiracetam
- Patients have no plan for discontinuation
- There is no indication for prophylactic ASMs per the AAN practice guidelines

Glantz et al., *Neurology* 2000

Effects of adjuvant therapy on seizure control

- Controversial findings
- Large retrospective study in LGG (n=1509): no benefits of radiation or chemotherapy for seizures
- Small study in LGG (n=39): temozolomide group achieved better seizure control compared to the group that did not receive this agent
- Few studies reporting benefit of radiation for seizure control

Pallud et al., *Brain* 2014; Sherman *J Neurosurg* 2011; Rogers et al., *Neurology* 1993

Driving

- General driving restrictions:
  - Nebraska and Colorado: no set duration but we limit to 3 months
  - Iowa, North Dakota, Kansas, Oklahoma: 6 months
- Restrict driving if high risk of seizure recurrence
- Also restrict if cognitive impairment, weakness, or impaired vision
- Counsel, if the ASM taper is considered

Summary

- ASMs should be continued in recurrent seizures, tumor progression and short life expectancy
- Discontinuation of ASMs should be guided by tumor histopathology, duration of seizure freedom, disease progression as well as extent of resection
- ASM prophylaxis before and after surgery in seizure-naïve patients is not recommended

Acknowledgements

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