Levetiracetam Monotherapy Good First-Line Choice for Seizures

Efficacy and Safety of Levetiracetam in Patients With Glioma: A Clinical Prospective Study.
Rosati A, Buttolo L, et al:

Arch Neurol 2010; 67 (March): 343-346

Levetiracetam is safe and efficacious in treating all epileptic seizure types in glioma patients.

**Background:** Approximately 30% of patients with newly diagnosed glioma will present with epilepsy. While levetiracetam is not FDA-approved for monotherapy, it does have many advantages over other anticonvulsants such as the lack of activation of hepatic enzymes and the absence of interaction with other drugs as well as its lack of life-threatening effects.

**Objective:** To assess the safety and efficacy of levetiracetam monotherapy in patients newly diagnosed with brain glioma of all grades.

**Design:** Prospective single-center study with a mean follow-up of 13 months.

**Participants/Methods:** 176 consecutive patients newly diagnosed with brain glioma were enrolled. The median age was 59 years and women represented 43% of the total. Of 176 patients, 82 (13 with low-grade, 69 with high-grade gliomas) were diagnosed with epilepsy. Levetiracetam was given to all 82 patients and the dose was increased to until the seizures were controlled (up to 4000 mg/day). If monotherapy was not sufficient, oxcarbazepine, topiramate, or valproic acid were added. Drug-resistant patients all had a high-grade glioma.

**Results:** 75 of 82 patients treated with levetiracetam alone became seizure free. Two of these patients had to be switched to another anticonvulsant because of side effects. Forty-nine patients were controlled with a regular dose of levetiracetam (1500 to 3000 mg/day). In the other 23 patients, a dose of 3000 to 4000 mg/day was necessary to achieve seizure control. The major side effects of levetiracetam alone and in combination included diarrhea and visual hallucinations. No metabolic anomalies were noted.

**Conclusions:** These results suggest that levetiracetam might be a good first choice monotherapy in patients with all types of seizures secondary to brain glioma.

**Reviewer's Comments:** As a first-line monotherapy, levetiracetam has many advantages over other FDA-approved drugs including benign side effects, a proven efficacy, and the absence of known drug interactions. Ideally, a study involving a direct comparison with other anticonvulsants should be designed. A key question is whether there is an indication to continue levetiracetam beyond the first postoperative week when it is given prophylactically (ie, to patients without seizures) at the time of surgery. I would suggest not in light of the level 1 evidence against this practice with other anticonvulsants. Finally, the mechanism of action of levetiracetam might involve direct effects on glial cells, and possibly glioma cells, ranging from GABA release, as well as anti-inflammatory and antioxidant properties as now reported in several preclinical studies. (Reviewer-Luc Jasmin, MD).

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Keywords: Seizures, Primary Brain Tumor, Antiepileptic Drugs, Side Effects, Prospective Study

Print Tag: Refer to original journal article
Is Radiosurgery for Large Meningiomas Riskier Than Resective Surgery?

Radiosurgery for Large-Volume (>10 cm³) Benign Meningiomas.
Bledsoe JM, Link MJ, et al:

J Neurosurg 2010; 112 (May): 951-956

Whereas radiosurgery is relatively safe for patients with large-volume skull base meningiomas, resection should remain the primary disease management for the majority of patients with large-volume supratentorial meningiomas.

Background: Large meningiomas can be difficult to remove completely, and residual tumors are often treated with radiosurgery. However, radiosurgery is being considered for more patients with larger meningiomas, particularly of the skull base. Primary radiosurgery treatment raises the issues of radiation risk with high doses, or substandard treatment with lower doses.

Objective: To determine whether radiosurgery can be effective with such large lesions, and at what risk.

Design/Methods: The authors retrospectively reviewed the records of 116 patients treated with the Gamma Knife between 1990 and 2007 for benign meningiomas, with an average tumor volume of 17.5 cm³ (10 to 48 cm³). Average tumor margin dose was 15.1 Gy, with mean follow-up of 70.1 months (minimum 12 months) and imaging at 6-, 12-, and then 24-month intervals. Growth was considered to be present at >2 mm of enlargement.

Results: Two of 10 patients’ deaths were from tumor-related causes. Overall, 4% had tumor progression including at the margins of treatment at a median of 40 months. The “in-field” 3- and 7-year control rates were 100% and 98%, respectively. Six percent had symptomatic edema; 23% developed complications at a median 7 months, with 7% being major and 16% minor. Complications included seizure, hemiparesis, trigeminal dysfunction, headache, diplopia, and cerebral infarction. There were no patients with symptomatic brainstem edema. There was a significant predilection for complications with supratentorial tumors (44% vs 18%) compared with skull base tumors. There was a positive correlation between treatment volume and complication risk.

Conclusions/Discussion: Reports of small tumor volumes treated with radiosurgery show 95% tumor control. Larger tumor volume is a factor that is generally associated with a lower rate of control. This study showed excellent control rates of 92% at 7 years with complications in 7%; more common for supratentorial tumors. Morbidity associated with stereotactic radiosurgery (SRS) for supratentorial large benign meningiomas is higher than literature data on the risks of resection of these tumors. The authors recommend surgical treatment for larger supratentorial meningiomas whenever feasible if the average tumor diameter is >2.5 cm (103 cm³ volume). The authors have more of a positive recommendation for SRS for skull base meningiomas. They extend this recommendation to postop residual tumor if it is a Grade II or III, or if there is documented Grade I tumor enlargement.

Reviewer's Comments: This work further defines the role of radiosurgery in the treatment of larger meningiomas. The complication rate data presented are very useful in guiding consideration of options with patients. (Reviewer-Paul L. Penar, MD).

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Keywords: Radiosurgery, Meningioma, Large Lesions, Radiation Dosage

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Decompressive craniectomy not only lowers intracranial pressure but also improves average brain oxygen and may prevent secondary injury.

**Background:** Increased intracranial pressure (ICP) can cause brain ischemia and lead to secondary injury. Multimodality monitoring, which includes measurement of brain oxygen, is more and more used to optimize severe traumatic brain injury (TBI) management. It has shown that brain oxygen <20 mm Hg after severe TBI is associated with poor outcome.

**Objective:** To examine whether decompressive craniectomy (DC) to treat elevated ICP reduces the cumulative ischemic burden (CIB) of the brain and the therapeutic intensity level (TIL) that is needed to control ICP.

**Design:** Retrospective cohort study.

**Participants/Methods:** 10 severe TBI patients (mean age, 31.4 ± 14.2 years) who had continuous brain oxygen monitoring before and after delayed DC were retrospectively identified. Patients were managed according to the brain trauma foundation guidelines for the management of severe TBI. The CIB was defined as the total time spent with brain oxygen levels <20 mm Hg. Brain hypoxia was classified in 3 groups: brain oxygen between 15 to 20, 10 to 15, and 0 to 10 mm Hg. Therapeutic intensity was assessed by calculating the therapeutic intensity level every 12 hours. Points were given for 6 categories: hyperventilation, pressor administration, hyperosmolar therapy, ventricular drainage, paralysis, and sedation. The maximal score is 18.

**Results:** DC was performed on average 2.8 days after admission. ICP was immediately reduced. There were significantly less episodes of low brain oxygen after DC and the therapeutic intensity level decreased significantly as well.

**Conclusions:** These results suggest that a DC for increased ICP can reduce episodes of low brain oxygen after severe TBI and possibly lower the likelihood of secondary injury.

**Reviewer's Comments:** This article uses 2 very neat ideas to demonstrate the effect of DC: therapeutic intensity level and cumulative ischemic burden. Although over a 4-year time frame only 10 subjects could be identified, the authors showed convincing data that DC lowered ICP but also decreased brain hypoxia. One of the limitations is that brain oxygen measurements are only local and do not reflect the oxygenation status of the whole brain. Also the classification of brain hypoxia into mild, moderate, and severe seems arbitrary and the clinical significance of such is not explained. All in all, this is an important contribution to the TBI literature. In the future it may help us to better understand when to take patients with severe TBI and high ICP to the operating department. Maybe not only ICP but also longer episodes with low brain oxygen could be the trigger. Further experience with multimodality monitoring will tell. (Reviewer-Martina Stippler, MD).

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Keywords: Brain Oxygen, Severe Traumatic Brain Injury, Therapeutic Intensity Levels

Print Tag: Refer to original journal article
Front or Back in Postlaminectomy Cervical Kyphosis?

The Long-Term Results of Anterior Surgical Reconstruction in Patients With Postlaminectomy Cervical Kyphosis.

Park Y, Riew KD, Cho W:

Spine J 2010; 10 (May): 380-387

Combined cervical corpectomy and discectomy alone achieves good results in correcting postlaminectomy cervical kyphosis.

**Background:** Postlaminectomy kyphosis of the cervical spine is a difficult condition to treat. The exposed cord posteriorly, progressive kyphosis, segmental instability, and possible remaining anterior compression have to be taken into consideration when making an operative decision. Anterior corpectomy alone results in 2 halves of the spine connected only by soft tissues. Stand-alone anterior corpectomy has an unacceptable complication and graft failure rate.

**Objective:** To determine the long-term results and outcomes of anterior surgical treatment alone for patients with postlaminectomy cervical kyphosis.

**Design:** Retrospective review of prospectively collected data in an academic institution.

**Participants/Methods:** The sample comprises 23 patients who underwent anterior multilevel cervical hybrid decompression for the treatment of postlaminectomy kyphosis from August 1995 to October 2006. Hybrid decompression is described by the authors as a combination of 1- or 2-level anterior cervical corpectomy and 1- to 3-level cervical discectomy. Pain, kyphosis angles, neurological status, and fusion were evaluated preoperative, postoperative, and at last follow-up.

**Results:** The mean follow-up ranged from 24 to 120 months. The average preoperative kyphosis of 20.9° was significantly improved to a lordosis of 14.0°. Preoperative pain and neurological status were significantly improved at the last follow-up. Solid fusion was confirmed by CT scan at about 4 months. There were 7 (30.4%) complications: 4 (14.3%) of them were graft-related.

**Conclusions:** The data suggest that multilevel anterior surgical treatment using a combination of corpectomy and discectomy yields acceptable clinical and neurological improvement and effective correction of cervical kyphosis.

**Reviewer's Comments:** Acknowledging the limitation of a single-center case series, the authors could show that a combination of anterior cervical discectomy and corpectomy is superior to anterior corpectomy without posterior fusion. However, the use of bone morphogenetic protein (BMP) off-label in some cases needs to be taken into consideration. It would be informative if the authors had commented more on the use of BMP. Seroma and edema are common with the use of BMP and can lead to serious troubles in anterior spine procedures. However, the authors did not have that experience. The proposed hybrid approach is less morbid than a combined anterior-posterior approach. It would be helpful to know whether the overall outcome is comparable. (Reviewer-Martina Stippler, MD).

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Keywords: Cervical Spine Deformity, Kyphosis, Anterior Surgical Treatment, Complications

Print Tag: Refer to original journal article
MRI diffusion tensor imaging fractional anisotropy changes might be caused by dilatation of the ventricles causing pressure and damage to adjacent white matter, with distortion of fibers or increased or decreased fiber density.

**Background:** Tests to confirm the clinical impression of normal pressure hydrocephalus (NPH) are often inconclusive. It would be beneficial to have definitive imaging to support the diagnosis. MRI diffusion tensor imaging (DTI) of white matter tracks might serve that purpose.

**Objective:** To investigate DTI parameters in patients with chronic idiopathic hydrocephalus to evaluate microstructural changes of brain tissue caused by chronic ventricular dilatation.

**Participants/Methods:** The authors report on 11 patients who fulfilled clinical criteria for NPH as well as 10 healthy control subjects, and performed DTI, quantitated with fractional anisotropy (FA) and mean diffusivity (MD). The hypothesis was that microstructural changes occur in periventricular gait control structures (corticospinal tract [CST] and corpus callosum) with NPH. The details of these techniques are given in the paper. Regions of interest (ROIs) were placed in the white matter by the investigators either along the CST or the corpus callosum. A second automated method known as tract-based spatial statistics (TBSS) was also used to cross-validate the findings and minimize bias with the ROI method. The diagnosis of NPH was based on clinical history and physical examination and all patients had typical "magnetic gait." All showed moderate ventricular dilatation out of proportion to sulcal enlargement. Six patients were excluded on suspicion of secondary hydrocephalus.

**Results:** By ROI methods, the patients with NPH had higher MD values in the periventricular corticospinal tract and corpus callosum, and higher FA values in the CST, but lower than normal in the corpus callosum. These findings in the CST on 2 measures correlated with the severity of the gait disturbance. The TBSS method detected significant differences of MD between patients and controls only in the corpus callosum. They found a correlation between DTI diffusivity change in the corticospinal tract and clinical parameters.

**Conclusions:** DTI FA changes might be caused by dilatation of the ventricles causing pressure and damage to adjacent white matter, with distortion of fibers or increased or decreased fiber density. Increased DTI MD in the CST might support chronic tissue damage or increased interstitial water content due to transependymal water diffusion.

**Reviewer’s Comments:** The most significant limitation of this study is that MRI findings, derived through a laborious analysis, correlated well with a clinical exam -- information that is simpler to obtain than a detailed MRI analysis. The DTI findings are no more diagnostic than exam. Also, this paper describes a group of patients who had a clinical diagnosis of NPH and did not receive follow-up with regard to their response to shunting. Therefore, we cannot know that they actually had the entity known as NPH, with a positive response to shunting. This information certainly is interesting but does not get us closer to a noninvasive diagnosis of adult idiopathic normal pressure hydrocephalus unless it can be correlated with outcome. (Reviewer-Paul L. Penar, MD).

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Keywords: Chronic Hydrocephalus, Diffusion Tensor Imaging

Print Tag: Refer to original journal article
Arachnoid cysts are common incidental findings on intracranial imaging in pediatric patients. An older age at the time of presentation is associated with a lack of clinical or imaging changes over time.

**Background:** The prevalence and natural history of arachnoid cysts in children are not well defined. This is the largest pediatric MR imaging series to date.

**Objective:** To study a large consecutive series of children undergoing MR imaging to better define both the MR imaging-demonstrated prevalence and behavior of these lesions over time.

**Design/Methods:** The authors retrospectively reviewed the electronic records of all patients aged ≤18 years who had undergone brain MRI in their institution from 1997 to 2008.

**Results:** 11,738 children underwent MRI in the studied period; 309 arachnoid cysts were identified (2.6% prevalence rate), diagnosed at a mean of 6.4 years. Prevalence didn't vary among age groups but peaked at ages 1 and 5 years at 3.8% and 4.6%, respectively. Overall, it was higher in males (2:1). Almost half of the cysts were in the middle fossa. Here, 45% were on the left, 27% were on the right side, and 28% were in the midline. Cysts in the posterior fossa had a greater number of midline cysts. Anterior fossa and quadrigeminal plate cysts were positively correlated with the presence or development of symptoms and surgical treatment whereas posterior fossa cysts were negatively associated. Mean cyst size was 3.0 x 2.7 x 3.0 cm; males had larger cysts than females. A larger initial cyst size was associated with the presence or development of symptoms and a recommendation for surgical treatment. Twenty-one of 309 patients with arachnoid cysts underwent surgical treatment. In total, 111 patients with arachnoid cysts thought to be asymptomatic at the time of diagnosis were not offered surgery and were followed for a mean of 3.5 ± 2.7 years (range, 5 months to 16.5 years). Eleven cysts increased in size, 13 decreased, and 87 remained stable. Three of 11 subjects with enlarging cysts developed new symptoms and had surgery. All 3 were initially diagnosed in the first year of life and had surgery at no more than 2.5 years of age. A younger age at presentation was significantly associated with cyst enlargement and the need for surgery whereas no patient aged >4 years at time of initial diagnosis had cyst enlargement, experienced new symptoms, or underwent surgical treatment.

**Conclusions:** According to the authors, "Arachnoid cysts are common incidental findings on intracranial imaging in pediatric patients. An older age at the time of presentation is associated with a lack of clinical or imaging changes over time."

**Reviewer's Comments:** Arachnoid cysts are relatively common and with the advent of MRI, more patients are referred to the neurosurgeon for evaluation. Younger patients have less clear symptoms and together with the always concerning question of whether the cognitive development may be impaired if not treated, surgical recommendations can be challenging. In general, the cysts are not immediate life-threatening conditions, but it is for those few that may need surgery that early intervention may influence the cognitive prognosis. This article adds valuable information that can be used on decision making. (Reviewer-Amir Kershenovich, MD).
Cervical arthroplasty and anterior cervical discectomy with fusion appear to have comparable outcomes 2 years following surgery.

**Objective:** To conduct a meta-analysis of clinical trials comparing the effectiveness of cervical arthroplasty versus cervical fusion for treating symptomatic cervical radiculopathy from cervical disc herniation.

**Design/Methods:** A comprehensive literature search was conducted including all published abstracts and manuscripts until February 9, 2009. Surgical trials comparing cervical arthroplasty versus cervical fusion for treating single-level cervical disc herniation with radiculopathy (but not myelopathy) were included in a meta-analysis. The visual analog score (VAS) of the arm, VAS of the neck, physical composite score of the Short Form 36 (SF-36), as well as adverse events including re-operation for cervical spondylosis were evaluated.

**Results:** 9 clinical studies (6 published randomized controlled trials [RCTs] and 3 oral abstract presentations of RCTs) with 1533 total patients were included for meta-analysis. Overall, 1165 randomized patients had satisfactory follow-up (12 or 24 months). Pooled data at 1 year demonstrated superior VAS arm and neck pain scores favoring arthroplasty. In addition, pooled SF-36 physical composite scores and mental composite score scores favored arthroplasty. At 2-year follow-up, both procedures had comparable scores except that the neck disability index scores in the arthroplasty group were superior, although they were not significantly different at 1 year.

**Conclusions:** Cervical arthroplasty and anterior cervical discectomy with fusion appear to have comparable outcomes 2 years following surgery. Patient bias is suggested as a possible contributor to the benefit observed using several outcome measures following arthroplasty at 1 year.

**Reviewer's Comments:** The authors have used sophisticated statistical methodology to combine the results of several trials that have compared the effectiveness of cervical arthroplasty versus cervical fusion for treating single-level cervical disc herniation and radiculopathy. The authors conclude that despite significant differences favoring cervical arthroplasty in pooled data at 1 year, there is "no justification for cervical disc prostheses in clinical practice." This is a strong statement that is not supported by the very evidence these authors presented. The authors suggest in their discussion that the evidence supporting the development of adjacent level disease in the cervical spine following fusion is "currently the subject of debate." This is certainly true. The authors have dismissed the pooled 12-month data that favored arthroplasty and have suggested that the data could otherwise be accounted for by patient or surgeon bias. The authors further conclude that "cervical disc prosthesis for a single-level herniated disc cannot be recommended" because of their higher costs, although no economic analysis was included in their study. The authors have highlighted an important topic -- adjacent level disease following cervical fusion. The authors propose patient bias as the explanation for the results of the meta-analysis favoring arthroplasty. Author (and investigator) bias is another factor that future studies should continue to address and avoid. (Reviewer-Zoher Ghogawala, MD).

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**Keywords:** Arthroplasty, Cervical Spine, Cervical Fusion, Meta-Analysis

**Print Tag:** Refer to original journal article
Can Resection of Aneurysm, Perifocal Gliosis Cure Seizures?

Primary Epileptogenic Unruptured Intracranial Aneurysms: Incidence and Effect of Treatment on Epilepsy.

Hänggi D, Winkler PA, Steiger HJ:

Neurosurgery 2010; 66 (June): 1161-1165

Resection of the aneurysm as well as the perifocal gliosis may cure the seizures observed with these so called epileptogenic aneurysms.

**Background:** Vascular lesions such as arteriovenous malformations and cavernomas often present with seizures. Epilepsy may infrequently be observed as a result of subarachnoid hemorrhage or ischemic stroke in association with a cerebral aneurysm.

**Objective:** To determine characteristics of epileptogenic aneurysms and to evaluate antiepileptic treatment strategies in this setting.

**Design:** Retrospective study.

**Methods:** The study was based on data accumulated over a 16-year period in centers in Munich and Dusseldorf, Germany. All patients presenting to these institutions with unruptured intracranial aneurysms were included. Aneurysmal rupture was verified by history, symptomatology, physical examination, magnetic resonance imaging, and spinal tap in equivocal cases, and excluded preoperatively.

**Results:** There were 347 unruptured intracranial aneurysms. Nine patients with 10 intracranial aneurysms presented with seizures. Location of these aneurysms was distal internal carotid artery (ICA) in 3 patients, proximal middle cerebral artery (MCA) in 2, bilateral proximal MCA in 1, distal MCA in 1, anterior communicating artery in 1, and pericallosal artery in 1. The 3 patients with ICA aneurysms had generalized seizures corroborated on electroencephalogram (EEG). These aneurysms were 15 to 20 mm in maximal diameter and appeared to be in close association with the parahippocampal gyrus and amygdala on MRI with evidence of perifocal gliosis. The patient with bilateral proximal MCA aneurysms experienced a generalized seizure as well with an abnormal EEG. The right MCA aneurysm measured 15 mm and was associated with extensive perifocal gliosis on MRI. A patient with a giant left proximal MCA aneurysm experienced sudden transient amnesia and had a nonspecific EEG. These symptoms were attributed to either transient ischemic attacks or seizures. The aneurysm was associated with marked surrounding gliosis on MRI. Two patients with a right proximal MCA aneurysm measuring 8 and 17 mm, respectively, had psychic auras that could not be attributed to any other cause and these were therefore deemed seizure activity. Their EEG was abnormal but did not demonstrate any epileptiform changes. MRI again showed perianeurysmal gliosis in both. The patient with the pericallosal aneurysm had 1 short generalized seizure, whereas the patient with the anterior communicating artery aneurysm had temporary expressive aphasia nonspecific in nature. Both patients had normal EEGs but with no epileptiform changes; no MRI findings were available. The authors noted that the feature linking nongiant aneurysms and seizures in this series is the close contact between the aneurysm and the mediotemporal lobe.

**Conclusions:** Resection of the aneurysm as well as the perifocal gliosis may cure seizures.

**Reviewer's Comments:** In this study, some of the reported symptoms may have been confounded with TIAs/or vice versa; therefore, under/overestimating the true incidence of epileptogenic aneurysms. Regardless, while surgical resection seems to provide seizure control, it would be interesting to assess whether endovascular therapy can do so as well. (Reviewer-Ziad A. Hage, MD).

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Keywords: Cerebral Aneurysm, Epilepsy, Symptomatic Aneurysm, Unruptured Aneurysm

Print Tag: Refer to original journal article
Patients intubated for combativeness are more likely to have neurological deficits, as well as other complications.

**Background:** Combative trauma patients are frequently intubated for safety and obtaining diagnostic studies. Intubation can be associated with complications, and sedatives and paralytic agents can cloud neurological assessment.

**Objective:** To determine if trauma patients intubated for combativeness instead of medical necessity have more complications and longer lengths of stay (LOS).

**Design:** Retrospective single institution case-control series.

**Methods:** Patient data from a computerized trauma data registry of all trauma alerts or consults (4740 patients) between January 2001 and July 2004 were grouped into intubated before hospital admission for documented combativeness (group 1), Injury Severity Score (ISS) <15 intubated for medical necessity prior to hospital admission (group 3), and unintubated patients matched to group 1 by age, sex, and ISS at 2:1 ratio (group 2). Patients were intubated using a rapid sequence protocol. Data collected included demographics, ISS, hospital LOS, discharge disposition, adverse outcomes, comorbidities, emergency department medications administered, physical restraint use, ventilator and weaning time, head or lung injury, and discharge neurological deficit.

**Results:** Group 1 (34 patients), group 2 (67), and group 3 (58) had similar age, sex, and ISS, helicopter transport, and alcohol intoxication. Drug intoxication (tetrahydrocannabinol or cocaine) was more common in group 1. Initial mean Glasgow Coma Scale score was higher in group 2 (14.7) than in group 1 (12.6) or group 3 (8.1). Overall, 29.4% of group 1 patients were sedated and 44.1% were physically restrained prior to intubation. Oxygen saturation was similar in groups 1 and 2. Neurological deficits at discharge were more common in group 1 (33%) than group 2 (6%) or group 3 (8.1). Overall, 29.4% of group 1 patients were sedated and 44.1% were physically restrained prior to intubation. Oxygen saturation was similar in groups 1 and 2. Neurological deficits at discharge were more common in group 1 (33%) than group 2 (6%), but head injury frequency defined by ICD-9 code was comparable (50% vs 37%). Pneumonia was more common in group 1 (29%) than in group 2 (6%). Fewer group 1 patients were discharged home than group 2 and LOS was longer in group 1 (7.3 days) than group 2 (4.2 days). More sedation was required in group 1 than group 2. Group 1 and 3 had no differences in LOS, ventilator days, pneumonia, discharge status, or neurologic deficit, although head injury was more common in group 1 (50%) than group 3 (22%).

**Conclusions:** Intubation for combativeness alone is associated with increased LOS, pneumonia, and sedative medication use, as well as reduced home discharge. Increasing sedative medications in the emergency department may reduce intubation requirements.

**Reviewer's Comments:** This study's results support the notion that patients intubated for combativeness have a more difficult hospital course than similar unintubated patients. Combative patients have more significant neurological injuries, which may account for the combativeness. Neurosurgeons should carefully assess these patients, even if CT scans are normal; recommending MRI evaluation may be appropriate. Judicious pharmacological control of combativeness is appropriate; prompt efforts to wean ventilator support should follow when intubation is required. (Reviewer-N. Scott Litofsky, MD).

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Keywords: Trauma, Intubation, Psychiatric, Combativeness, Pneumonia

Print Tag: Refer to original journal article
Lab Data Reflect Tumor Behavior in Pediatric Patients

Clinical Outcome in Pediatric Glial and Embryonal Brain Tumors Correlates With In Vitro Multi-Passageable Neurosphere Formation.

Panosyan EH, Laks DR, et al:

Pediatr Blood Cancer 2010; June 29 (): epub ahead of print

In vitro neurosphere formation predicts the clinical course of pediatric glial and embryonal neoplasms.

Background: Pediatric-derived brain tumor cells can form repeatedly passageable cells (neurospheres) with stemness properties of self-renewal, multipotency, expression of neural stem cell-associated genes, and in vivo tumorigenicity. These cells, few in number in any tumor, are thought to be responsible for tumor progression and therapy resistance. The clinical relevance of these cells is not certain in pediatric brain tumors. Objective: To determine whether the study of neurospheres derived from pediatric brain tumors is clinically relevant.

Design: Single-institution case cohort study.

Participants/Methods: Brain tumors resected from patients aged <21 years were cultured using standard neural stem cell techniques. Neurospheres from the cultures were dissociated and passaged every 7 to 21 days. Cultures maintained for at least 3 passages were considered to be capable of renewable neurosphere formation. Clinical data, including time to survival (TTS), time to progression, tumor histopathology, and Ki67 immunostaining were analyzed for the full cohort of patients and for subpopulations of glial, embryonal, and mixed glioneuronal tumors.

Results: 21 of 56 tumors (12 mixed glioneuronal, 18 low-grade glioma, 12 high-grade glioma, and 14 embryonal) formed renewable neurosphere cultures. Neurosphere formation correlated with younger patient age, greater proportion of high-grade lesions, and higher median Ki67. Overall, 34% of supratentorial and 43% of infratentorial tumors formed renewable neurospheres. Neurosphere formation occurred in 33% of glioneuronal tumors, 17% low-grade tumors, 50% high-grade glial tumors, and 57% embryonal tumors. A total of 57.7% of subtotally resected tumors formed neurospheres compared to 20% of gross total resected tumors. Follow-up data were available on 51 patients. Neurosphere formation was associated with risk of patient death and tumor progression, respectively, of 16.6x and 9.94x for all tumors, 5.06x and 6.62x for glial tumors, >10x and >10x for embryonal tumors, and >10x and >10x for medulloblastomas. All patients without neurosphere formation had progression-free survival >5 years. Neurosphere formation was predictive of survival and progression when adjusted for age, gender, Ki67, and treatment.

Conclusions: In vitro neurosphere formation predicts the clinical course of pediatric glial and embryonal brain tumors independent of established prognostic indicators. Multi-passage neurosphere formation is a robust and comprehensive neurobiological tool for preclinical brain tumor research.

Reviewer’s Comments: The discovery of neural progenitor stem cells and associated neurosphere formation has revolutionized clinical and basic neurosciences over the last 2 decades. Their implications for brain tumor biology and neural transplantation are immense. This study shows that isolation of tumor stem cells and subsequently cultured neurospheres from pediatric tumors has significant predictive capabilities of tumor behavior and patient prognosis, the small number of tumors notwithstanding. Further research regarding these cell populations may yield new targets for treatment that can alter current patient outcomes. (Reviewer-N. Scott Litofsky, MD).

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Keywords: Brain Tumors, Cancer Biology, CNS Tumors, Neuro-Oncology, Outcomes Research

Print Tag: Refer to original journal article