

Neurosurgery Concepts

Neurosurgery Concepts: Key perspectives on quality of life in children with spina bifida, cilengitide for the treatment of newly diagnosed glioblastoma, surgery and stereotactic radiosurgery in the management of intracranial metastasis, Gamma Knife radiosurgery in patients with Neurofibromatosis Type 2, patient misconceptions on the diagnosis and treatment of lumbar spondylosisSandi Lam, Gordon Li¹, Gabriel Zada², Panayiotis Pelargos³, Winward Choy⁴, Isaac Yang³, Zachary A. Smith⁴Departments of Neurosurgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, ¹Stanford School of Medicine, ²Keck School of Medicine of University of Southern California, ³University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, ⁴Northwestern University Feinberg School of Medicine, Chicago, IL, USAE-mail: Sandi Lam MD - sandilam@gmail.com; Gordon Li - gordonli@stanford.edu; Gabriel Zada - Gabriel.Zada@med.usc.edu; Panayiotis Pelargos - ppelargo@uci.edu; Winward Choy - winward.choy@northwestern.edu; Isaac Yang MD - iyang@mednet.ucla.edu; *Zachary A. Smith MD - zsmith@nmff.org

*Corresponding author

Received: 19 March 15 Accepted: 21 April 15 Published: 18 June 15

This article may be cited as:Lam S, Li G, Zada G, Pelargos P, Choy W, Yang I, et al. Neurosurgery Concepts: Key perspectives on quality of life in children with spina bifida, cilengitide for the treatment of newly diagnosed glioblastoma, surgery and stereotactic radiosurgery in the management of intracranial metastasis, Gamma Knife radiosurgery in patients with Neurofibromatosis Type 2, patient misconceptions on the diagnosis and treatment of lumbar spondylosis. *Surg Neurol Int* 2015;6:110.Available FREE in open access from: <http://www.surgicalneurologyint.com/text.asp?2015/6/1/110/159075>

Copyright: © 2015 Lam S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Key Words: Cilengitide, lumbar spondylosis, metastasis, Neurofibromatosis Type 2, spina bifida**ASSESSING HEALTH-RELATED QUALITY OF LIFE IN CHILDREN WITH SPINA BIFIDA^[4]****Study Question:** How do chronic health issues of spina bifida affect physical/psychosocial function and pediatric patients' health-related quality of life?

This study aimed to assess the health-related quality of life (HRQOL) in pediatric patients attending a multidisciplinary spina bifida clinic at a tertiary children's hospital in Alabama. Over the span of one calendar year, patients attending the clinic were asked to fill out the Health Utilities Index Mark 3 (HUI3) questionnaire on a prospective basis. The response rate was 159/283 patients (56%). The HUI3 is a validated questionnaire that evaluates eight independent attributes of health: Vision, hearing, speech, cognition, emotion, pain, ambulation, and dexterity, giving an overall multiattribute score.

Patients studied ranged from 5 to 20 years of age, mean 12.6 years. Caregivers responded on behalf of the children, except in 11% who were old enough to fill out their own questionnaires. The largest contributors to lower HRQOL score were the underlying diagnosis and the history of ventriculoperitoneal (VP) shunting. Children with myelomeningocele diagnoses had lower HRQOL scores than patients with closed spinal dysraphism (0.51 vs 0.77, $P < 0.001$), with lower ambulation and cognition domain subscores in the former group. Myelomeningocele**Access this article online****Quick Response Code:****Website:**www.surgicalneurologyint.com**DOI:**

:10.4103/2152-7806.159075

patients with VP shunts had lower HRQOL scores than those without shunts (0.47 vs 0.74, $P < 0.001$), even after taking into account age, history of Chiari II decompression, and number of shunt revisions.

HRQOL scores in this study were not related to insurance type, sex, race, or patient/parent completion of the survey. There was a weak correlation with age, with younger patients having higher HRQOL scores. Bladder function did not impact HRQOL scores, and bowel function weakly correlated with lower scores. The HUI3 is not specific for the spina bifida population, and does not have domains for assessing family involvement, rehabilitation team support, obesity, bowel/bladder function, sexual function, or medical comorbidities, all items which may be important in these patients with complex needs.

Perspective: Spina bifida remains the most common disabling birth defect even with advances in public health and maternal folic acid supplementation. A majority of patients with spina bifida now reach adulthood, with continued complex multidisciplinary health care needs. This study used a general HRQOL survey to evaluate pediatric patients in a multidisciplinary spina bifida clinic and provides a single time-point description. Limitations are apparent with using a general instrument not tailored for spina bifida-specific challenges. While the study cannot elucidate why the presence of VP shunt is associated with lower HRQOL in patients with myelomeningocele, this interesting finding should motivate future directions for research. It is unclear whether the presence of hydrocephalus itself or presence of VP shunt (or a combination of both) leads to the lower HRQOL. The criteria for shunting is evolving in Pediatric Neurosurgery, including concepts of permissive ventriculomegaly and increasing application of endoscopic third ventriculostomy with choroid plexus cauterization. It is essential to follow and study neuropsychological, cognitive, and quality of life outcomes in order to understand how surgical interventions impact patients' lives over time. Further longitudinal studies with spina bifida-specific HRQOL measures are needed to help elucidate best practices for delivering patient-centered care and improving quality of life in this population with chronic care needs.

Summary Written by: Sandi Lam, MD.

CILENGITIDE COMBINED WITH STANDARD TREATMENT FOR PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA WITH METHYLATED MGMT PROMOTER (CENTRIC EORTC 26071-22072 STUDY): A MULTICENTRE, RANDOMIZED, OPEN-LABEL, PHASE 3 TRIAL^[5]

Study Question: Is the addition of cilengitide (a selective $\alpha\beta3$ and $\alpha\beta5$ integrin inhibitor) to temozolomide

and radiotherapy in the treatment of newly diagnosed O6-methylguanine-DNA methyltransferase (MGMT) methylated glioblastoma (GBM) patients beneficial?

A multicenter randomized phase 3 trial was conducted in 146 sites in 25 countries screening 3471 GBM patients. A total of 926 patients had methylated MGMT promotor and of those 545 were randomized 1:1 to either standard chemoradiation versus cilengitide 2000 mg intravenously twice weekly with Temozolomide and radiotherapy. Patients and investigators were unmasked to treatment allocation and outcomes were determined by intention to treat analysis. Maintenance temozolomide was given for up to six cycles, and cilengitide was given for up to 18 months or until disease progression or unacceptable toxic effects. The primary endpoint was overall survival.

There was no significant difference in median overall survival between the two groups. The median overall survival was 26.3 months for both groups. (95% CI 23.8–28.8 in the cilengitide group and 23.9–34.7 in the control group; hazard ratio (HR) 1.02, 95% CI 0.81–1.29, $P = 0.86$). None of the predefined clinical subgroups showed a benefit from cilengitide. There were no toxic effects with cilengitide treatment. The most commonly reported adverse events of grade 3 or worse in the safety population were lymphopenia (31 [12%] in the cilengitide group vs 26 [10%] in the control group), thrombocytopenia (28 [11%] vs 46 [18%]), neutropenia (19 [7%] vs 24 [9%]), leucopenia (18 [7%] vs 20 [8%]), and convulsion (14 [5%] vs 15 [6%]).

Perspective: $\alpha\beta3$ and $\alpha\beta5$ integrins have been found to be overexpressed on GBM. Efforts to inhibit these integrins have been promising in phase 1 and 2 trials. Stupp *et al.* studied this promising target in a large, multicenter, international randomized phase 3 trial. The results demonstrated that cilengitide when given to MGMT methylated GBM patients with chemoradiation does not improve overall survival. Although inhibiting $\alpha\beta3$ and $\alpha\beta5$ integrins may not be effective in treating these patients, there are ongoing efforts to target these overexpressed antigens to either visualize the tumor intraoperatively, or preoperatively by using nuclear imaging techniques.

Summary Written by: Gordon Li, MD.

ESTIMATING THE ADDITIVE BENEFIT OF SURGICAL EXCISION TO STEREOTACTIC RADIOSURGERY IN THE MANAGEMENT OF METASTATIC BRAIN DISEASE^[3]

Study Question: Does the combination of surgical resection with stereotactic radiosurgery (SRS) improve survival and time-to-local recurrence (TTLR) in metastatic brain disease?

The authors^[3] conducted a retrospective analysis of consecutive patients presenting with intracranial metastatic disease with ≤ 4 lesions from a known primary malignancy. Exclusion criteria were any prior treatment to the lesions, including whole brain radiation. They identified 162 patients with a total of 260 metastatic brain lesions. Of these, 49 patients received resection with adjuvant SRS and 113 received SRS alone.

The authors reported that overall survival for complete resection + adjuvant SRS was 14.1 months, incomplete resection + adjuvant SRS was 7.1 months, and SRS alone was 6.9 months ($P = 0.32$, log-rank) and that TTLR for complete resection + adjuvant SRS was 22.5 months, incomplete resection + adjuvant SRS was 6.4 months, and SRS alone was 14.8 months ($P = 0.004$, log-rank). Using stepwise Cox regression analysis, the authors found that TTLR was related to radiation-sensitive pathology (HR = 0.34, $P = 0.001$), treatment volume (HR = 1.078/mL, $P = 0.002$), and complete tumor resection (HR = 0.37, $P = 0.015$), and overall survival was related to age (HR = 1.21/decade, $P = 0.37$), Eastern Cooperative Oncology Group performance score (HR = 1.9, $P = 0.001$), and complete surgical resection (HR = 0.55, $P = 0.01$).

The authors concluded that complete surgical resection + adjuvant SRS improved survival and improved TTLR in comparison with SRS alone. They also reported that incomplete resection + adjuvant SRS did not improve survival or TTLR compared with SRS alone.

Perspective: In this study, the authors use retrospective analysis to examine the value of performing resection with adjuvant SRS in comparison to SRS alone for intracranial metastatic brain tumors. The authors reported that: (i) Complete resection + adjuvant SRS had a nearly 3-fold decrease in TTLR compared with SRS alone; (ii) complete resection + adjuvant SRS increased survival nearly 2-fold over SRS alone; and (iii) incomplete resection + adjuvant SRS has similar or worse outcomes than SRS alone. While Quigley *et al.* acknowledge the limitations of their study, their findings suggest that there needs to be a careful evaluation of the treatment strategies for intracranial metastatic disease. The authors suggest exploring the utility of adding complete surgical resection to SRS therapy.

Summary Written by: Isaac Yang, MD and Panayiotis Pelargos.

GAMMA KNIFE RADIOSURGERY FOR MENINGIOMAS IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 2^[2]

Study Question: What are the outcomes and prognostic factors associated with Gamma Knife

radiosurgery (GKRS) in the management of meningiomas in patients with Neurofibromatosis Type 2?

In this article by Liu *et al.*, the authors report their results following GKRS in 12 patients with Neurofibromatosis Type 2 (NF2). Their institution treated 87 meningiomas in 12 NF2 patients using 24 GKRS procedures over a 14-year interval, and with a median follow-up time of 43 months. The median prescription dose to the tumor margin was 12 Gy. Although the 5-year local tumor control rate was 92%, the distant treatment failure rate was 77%. Local treatment failure occurred in 4 tumors (5%) from 3 GKRS treatments in 3 patients: 3 tumors centrally within the prescription volume and 1 tumor marginally. The median overall survival was 110 months. Predictors for distant treatment failure on multivariate analysis included age and prior number of GKRSs. There were no incidences of malignant transformation. Only grade 1 or 2 toxicity was reported, following 25% of treatments. Local tumor control rates compared with those seen in patients treated via GKRS for sporadic World Health Organization (WHO) grade I meningiomas.

Perspective: This is the first study to report results of GKRS specifically for patients with meningiomas in the setting of NF2. The biological insights derived from this study are that local tumor control is well achieved in NF2 meningiomas, but distal failure patterns resulting in neurological compromise are the major limiting factors to achieving successful long-term outcomes. In addition, despite a concern for transformation to malignant tumors in NF2 meningiomas treated with GKRS, no incidences of malignant transformation were observed. The rates of adverse effects and toxicity were acceptable. All patients with central tumor failure died, likely relating to the aggressive and/or radio-resistant biology of this subset of neoplasms. Despite some limitations in this study, including a relatively short follow-up time, the authors' findings support the role of GKRS for treating meningiomas in NF2 patients. Another effective alternative available in NF2 patients with meningiomas is bevacizumab, which may alter the treatment requirements and indications for offering GKRS to NF2 patients with meningiomas. Longer periods of follow-up from multiinstitutional analyses would help further understand local and distal control/failure patterns and the incidence of malignant transformation.

Summary Written by: Gabriel Zada, MD.

PATIENT MISCONCEPTIONS CONCERNING LUMBAR SPONDYLOSIS DIAGNOSIS AND TREATMENT^[1]

Study Question: What are the misconceptions of patients presenting with back pain at neurosurgery clinic concerning the diagnosis and treatment of lumbar spondylosis?

To assess patient perspectives on lumbar spondylosis, the authors administered a survey comprising multiple choice questions to 121 new patients referred to neurosurgery clinic with chief complaint of back pain in the absence of leg pain. Demographical data was collected for each responder. Two of the questions assessed patients' perceptions on radiographic indications for surgery. A total of 52% and 41% of responders reported that they would be willing to receive surgery if they received abnormal results on either magnetic resonance imaging (MRI) or X-ray, respectively, even in the absence of any clinical symptoms. Answers to these two questions were strongly correlated (<0.0001). Survey results also found that 33% of patients believed that back pain was superior to physical therapy in treating back pain without leg pain, and 17% of patients believed that back injections possessed a greater risk than surgery. Moreover, differences in responses were not significant based on history of prior spine surgery.

Perspective: Assessment of patient outcomes has been increasingly important for quality improvement initiatives within national healthcare reform. Metrics have not only focused on clinical outcomes but also subjective aspects of the patient experience such as patient satisfaction. An understanding of patient expectations and misconceptions is critical as unmet expectations during clinical encounters may diminish patient satisfaction and slow clinical improvement and worsen clinical outcomes. The study found an astonishingly high rate of misconceptions concerning the treatment and diagnosis of lumbar spondylosis. Patients overemphasized the value of radiological studies and indicated that they

would undergo surgery given radiographic abnormalities despite lack of clinical symptoms. Additionally, patients had misconceptions about the efficacy of and safety of surgery versus more conservative management for back pain, regardless of a previous history of spine surgery. While the study was not aimed to elucidate the reasons, which are likely multifactorial, for the discrepancy between patient expectations and medical knowledge regarding the surgical management for back pain, the authors highlight an important opportunity for improved patient education, communication, and management of expectations during evaluation for the surgical management of lumbar spondylosis.

Summary Written by: Dr. Zachary A. Smith, MD and Winward Choy.

REFERENCES

1. Franz EW, Bentley JN, Yee PP, Chang KW, Kendall-Thomas J, Park P, et al. Patient misconceptions concerning lumbar spondylosis diagnosis and treatment. *J Neurosurg Spine* 2015;1-7.
2. Liu A, Kuhn EN, Lucas JT Jr, Laxton AW, Tatter SB, Chan MD. Gamma Knife radiosurgery for meningiomas in patients with neurofibromatosis Type 2. *J Neurosurg* 2015;122:536-42.
3. Quigley MR, Bello N, Jho D, Fuhrer R, Karlovits S, Buchinsky FJ. Estimating the Additive Benefit of Surgical Excision to Stereotactic Radiosurgery in the Management of Metastatic Brain Disease. *Neurosurgery* 2015;76:707-13.
4. Rocque BG, Bishop ER, Scogin MA, Hopson BD, Arynchyna AA, Boddiford CJ, et al. Assessing health-related quality of life in children with spina bifida. *J Neurosurg Pediatr* 2015;15:144-9.
5. Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, Hong K, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1100-8.