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Key perspectives on auditory outcomes following radiosurgery for vestibular schwannoma, tumor treating fields for glioblastoma, and a proposed myelopathy score for cervical decompression surgery, intracranial pressure monitoring in diffuse traumatic brain injury

Jonathan H. Sherman, Gordon Li[1], Jin Mo Cho[2], Winward Choy[3,4], Isaac Yang[3], Zachary A. Smith[4]

Department of Neurosurgery, George Washington University School of Medicine and Health Sciences, Washington DC, [1]Department of Neurosurgery, Stanford School of Medicine, California, USA, [2]Department of Neurosurgery, Catholic Kwandong University School of Medicine, Gangneung, South Korea, [3]Department of Neurosurgery, University of California Los Angeles David Geffen School of Medicine, Los Angeles, California, [4]Department of Neurosurgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

E-mail: Jonathan H. Sherman - jsherman@mfa.gwu.edu; Gordon Li - gordonli@stanford.edu; Jin Mo Cho - chojinmo@gmail.com; Winward Choy - winward.choy@northwestern.edu; Isaac Yang - IYang@mednet.ucla.edu; *Zachary A Smith - zachary.smith@northwestern.edu
*Corresponding author

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HEARING SUBCLASSIFICATION MAY PREDICT LONG-TERM AUDITORY OUTCOMES AFTER RADIOSURGERY FOR VESTIBULAR SCHWANNOMA PATIENTS WITH GOOD HEARING[6]

Study Question: In counseling patients with vestibular schwannoma for stereotactic radiosurgery, what is the risk of postoperative hearing loss?

The authors of this study aim to evaluate the risk of post-treatment hearing loss from stereotactic radiosurgery on patients with vestibular schwannoma. Recent literature reports a high rate of tumor control with low morbidity compared to surgical management for these patients. This is especially true for small to moderate size tumors. With the expanding availability of magnetic resonance (MR) imaging, more of these lesions are being identified at a smaller size, commonly prior to symptom onset. There exist reports of good hearing preservation in patients with pre-treatment high level hearing prior to stereotactic radiosurgery (SRS). However, in patients with good hearing, there exists no current subclassification system assessing those patients at increased risk of post-treatment hearing loss.

The authors evaluated 166 patients with Gardiner–Robertson grade I hearing prior to radiosurgery. Patients were subclassified into grade I-A if they displayed no subjective hearing loss and grade I-B if they displayed subjective hearing loss. The grade I-B patients were further subclassified into I-B1 if they displayed a pure tone

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average >10 dB compared with the contralateral ear and I-B2 with a pure tone average <10 dB. There was an even patient distribution with 53 I-A patients, 56 I-B1 patients, and 57 I-B2 patients. The median follow-up for this study was 65 months. The median tumor volume was 0.80 cm^3 and the median tumor margin dose was 12.5 Gy. In this population, 92% displayed stable or regression of the tumor post-treatment, 6% displayed a minor increase in volume, and 2% displayed a progressive increase in volume requiring surgical intervention. The patients displayed an increase in pure tone average of 5, 13.5, and 28 dB for Gardiner–Robertson grade I-A, I-B1, and I-B2, respectively. The median decline in speech discrimination scores was 0, 8, and 40% for Gardiner–Robertson grade I-A, I-B1, and I-B2, respectively ($P < 0.0001$). Gardiner–Robertson grade I hearing was maintained in 87, 43, and 5% of patients and serviceable hearing was maintained in 98, 73, and 33% of patients with pre-treatment grade I-A, grade I-B1, and grade I-B2 hearing, respectively.

Perspective: This study provides data that delineates between patients with Gardiner–Robertson grade I hearing with regard to risk of hearing loss after SRS. By definition, Gardiner–Robertson grade I and II hearing is considered "useful hearing" where the grade I (good) patients display a pure tone average of 0–30 dB and speech discrimination of 70–100%. Grade II (serviceable) hearing is defined as a pure tone average of 30–50 dB and speech discrimination of 50–69%. Prior reports describe good hearing preservation after SRS in patients with good hearing. This study provides evidence that even a minor degree of hearing loss equates to a significant risk of loss of serviceable hearing after treatment. For instance, >25% of patients with a drop in pure tone average of less than 10 dB will lose serviceable hearing in the affected ear following SRS based on this study. With the current availability of MR imaging, many of these lesions are picked up at a small size in patients with minimal symptoms. The clinician must counsel the patients appropriately on the true risks of treatment versus observation. This manuscript provides important information with regard to hearing preservation after SRS. It gives insight in that SRS may not be as benign a procedure as previously indicated, at least with regard to impact on hearing preservation.

Summary written by: Jonathan H. Sherman

MAINTENANCE THERAPY WITH TUMOR-TREATING FIELDS PLUS TEMOZOLOMIDE VS TEMOZOLOMIDE ALONE FOR GLIOBLASTOMA: A RANDOMIZED CLINICAL TRIAL[7]

Study Question: Is the addition of tumor treating fields (TTFields) in combination with temozolomide after standard chemoradiation for newly diagnosed glioblastoma (GBM) patients effective and safe?

TTFields are intermediate frequency (200 kHz), low intensity alternating electric fields that selectively inhibit cell division by physical disruption of molecules involved in mitosis. The electric fields are delivered by a transducer array on a patient's shaved scalp. TTFields has demonstrated promise in the treatment of solid cancers in preclinical models. A multicenter phase 3 international randomized clinical trial was performed. A total of 695 adult GBM patients who had underwent maximal safe resection and did not have any recurrence after standard chemoradiation were randomized 2:1 to either treatment with TTFields and temozolomide versus temozolomide alone. Patients were accrued in 83 centers across the United States, Canada, Europe, Israel, and South Korea between July 2009 and November 2014. Treatment with TTFields was continued continuously (>18 hours a day) via four transducer arrays placed on a shaved scalp and connected to a portable medical device. Temozolomide was given as per standard Stupp protocol 5 days of each 28 day cycle.

Primary endpoint was progression free survival, and overall survival was the secondary end point. Interim analysis was performed on the first 315 patients after 18 months of follow up. A total of 210 patients were randomized to TTFields and Temozolomide and 105 patients received temozolomide alone. Median progression free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9–8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3–5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43–0.89]; $P = 0.001$). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7–25.0 months) in the TTFields plus temozolomide group ($n = 196$) and 15.6 months (95% CI, 13.3–19.1 months) in the temozolomide alone group ($n = 84$) (HR, 0.64 [99.4% CI, 0.42–0.98]; $P = 0.004$).

Perspective: GBM is a heterogeneous and difficult to treat brain cancer. There have been no randomized phase 3 trials that have demonstrated any therapeutic benefit in this patient population since 2005 when Stupp *et al.* demonstrated that the addition of temozolomide to radiation therapy was beneficial in newly diagnosed GBM patients. Although there has been a lot of skepticism regarding TTFields for the treatment of GBM, this trial is the first randomized trial in over 10 years to show an overall survival improvement. Skeptics criticize that the treatment could not be blinded and that we know the more we measure and the closer we follow patients, the better they often do. However, it is hard to explain a statistically significant survival difference of 20.5 versus 15.6 months with this critique. The study was initially

published as interim data, however, due to the data, the accrual was stopped early for a positive study result.

Summary written by: Gordon Li

MYELOPATHIC SIGNS AND FUNCTIONAL OUTCOME FOLLOWING CERVICAL DECOMPRESSION SURGERY: A PROPOSED MYELOPATHY SCORE[5]

Study Question: How do signs of clinical myelopathy change following cervical decompression surgery for cervical spondylotic myelopathy (CSM)? Can a new myelopathy scoring system enhance our ability to predict postoperative functional outcomes?

The authors followed 36 patients after decompressive cervical spine surgery for CSM. Clinical outcome scores, including the modified Japanese Orthopedic Association (m-JOA) score, were used to assess the severity of myelopathy. The authors additionally tracked five "fundamental" signs of myelopathy (Hoffman sign, Babinski reflex, reflexes, proprioception, and clonus). From these fundamental signs, the authors developed a 10-point myelopathy score (MS) with grades of 0–2 for each of these individual five "fundamental" signs. Statistical analyses including Spearman's correlation and paired *t*-test were used to test the strength of correlation between the established mJOA and this newly developed MS scale.

A statistically significant change was found at 1 year for general reflexes, Babinski sign, and proprioception signs (3 of 5). In addition, there was a significant improvement in the mJOA scale score at 1 year compared to the patient's preoperative baseline. The MS score additionally showed a significant degree of improvement at 1 year. As a higher mJOA implies more normal function, there was a negative correlation between postoperative mJOA scale and MS scores (-0.361, $P = 0.031$). Further, in 29 (80.6%) of the 36 patients, there was an improvement in the scores of both scales at 1 year.

Perspective: Clinical improvement following decompressive surgery for CSM may often be incomplete, and commonly recovery occurs slowly over time. There are several myelopathy scales available in the literature, and each uses subjective measures of function. These subjective measures are quite intrinsically linked to a surgeon or patient's impression of progress and symptoms. Thus, objective measures are less commonly employed to assess function.

A new scale that utilizes clinical examination findings, including those intrinsic to the diagnosis of myelopathy, may be of benefit to the clinician. Little is known about the timing of recovery in CSM, and it is not established when clinical examination findings improve. Further, the currently proposed scale evaluates unique outcomes from those currently established (mJOA and Nurick). As such, it may be used as a complementary tool in tandem with established functional outcome scales.

This study evaluates a critical topic in spinal neurosurgery. There are few objective measures of function for postoperative patients with CSM. The exact time course of recovery has not been fully articulated in the literature. In addition, there are no objective tests of clinical function that are commonly used in follow-up. These would likely need to focus on tract-specific injury in CSM, including corticospinal, reticulospinal, and dorsal column injury. These injuries often manifest as weakness, spasticity, and poor proprioception. Exciting recent work in the field has utilized high resolution MRI techniques such as diffusor tensor imaging to quantify spinal tract injury.[4] Furthermore, there is likely an under-recognized vascular insufficiency in these patients. Recent work by Alshareef *et al*. has shown that subclinical compression may lead to anterior spinal artery ischemia to the cord.[1] This current study adds to our growing understanding of how patients recover from CSM, and implies future directions for further investigation.

Summary written by: Zachary A Smith

IS INTRACRANIAL PRESSURE MONITORING OF PATIENTS WITH DIFFUSE TRAUMATIC BRAIN INJURY VALUABLE? AN OBSERVATIONAL MULTICENTER STUDY[8]

Study Question: Is ICP monitoring necessary in patients with severe TBI?

The authors evaluated the effects of intracranial pressure (ICP) monitoring (intraventricular type) using propensity score-matching (PSM) analysis. They retrospectively collected multicenter clinical traumatic brain injury (TBI) data from 48 hospitals for the period between 2012 and 2013. They included severe diffuse TBI patients (Glasgow Coma Scale [GCS] score <9, Marshall class II to IV and age >14), and excluded patients with penetrating brain injury and suspected brain death. The Marshall CT classification is a tool (CT Class I through VI) used to grade the severity of traumatic head injury based on computed tomography (CT) findings. There are no mass lesions in Class I–IV; class I, II, III, IV correspond to no visible pathology on CT, normal cisterns with midline shift of 0–5 mm, compressed cisterns with midline shift of 0–5 mm, and midline shift >5 mm, respectively. They managed patients in accordance with the Brain Trauma Foundation guidelines (2007). Each monitored patient with ICP was matched using a simple 1:1 nearest-neighbor matching algorithm to a patient in

the nonmonitored group who had a similar propensity score. Finally, they compared a total of 129 patients in either the ICP monitored or nonmonitored group. They evaluated the impact of ICP monitoring on the actual outcomes using the matched samples after controlling for independent predictors of the outcomes (6-month mortality and 6-month favorable outcome). Using PSM, the authors showed a significant decrease in the 6-month mortality in the ICP monitoring group. The impact of ICP monitoring was greater in the most severely injured patients (Marshall CT classification IV, GCS score 3–5). Although 6-month favorable outcome was not associated with ICP monitoring in general, ICP monitoring in the more severely injured patients (GCS score 3–5) was associated with 6-month favorable outcome. ICP monitoring of patients with severe TBI was associated with a significant decrease in 6-month mortality, especially in those with GCS scores of 3 to 5 or Marshall CT classification IV.

Perspective: ICP-based treatment is considered as standard care for severe TBI, but this treatment remains controversial. ICP-based treatment can be summarized as follows: monitor ICP if the patients with TBI have a GCS score below 8 with abnormalities on CT scans, and then maintain ICP below 20 mmHg using optimal medical treatment (hyperosmolar therapy, hypertonic saline, hypothermia, etc.). Finally, if the increased ICP is refractory, perform decompressive surgery.

The value of this study lies in evaluating ventricular-type ICP monitoring in patients with severe TBI. Two previous large-scale studies failed to confirm the effect of decompressive craniectomy (DCE) and the efficacy of parenchymal-type ICP monitoring in patients with severe TBI. The DECRA study found that DCE decreased ICP; however, it failed to prove the clinical efficacy of DCE.[3] A study by Chesnut *et al*., which evaluated the efficacy of parenchymal-type ICP monitoring conducted in South America, also failed to show the clinical benefit of parenchymal-type ICP monitoring-based treatment in patients with TBI.[2] This study is a retrospective nonrandomized case-control study. However, the study population is relatively large, matched with a similar population, and statically well-designed. It is well known that ventricular-type ICP is more accurate than parenchymal-type ICP, and can act not only diagnostically but also therapeutically through cerebrospinal fluid (CSF) drainage. Based on personal experience, DCE might not be helpful because of the additional surgical insult to the patient; although it could lower ICP, DCE did not improve the clinical outcome, as illustrated by a previous study. Extraventricular drainage could be an effective treatment option for severe TBI patients because it is a relatively less invasive yet effective treatment option for ICP control. As the author's series, a relatively short period (less than 10 days) of extraventricular drainage did not increase the additional risk of infection. Further study focused on this point is required.

Summary written by: Jin Mo Cho

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Conflicts of interest
There are no conflicts of interest.

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