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100. A Multidisciplinary Approach to Improve Communication Between Pediatric Neurosurgery and Pediatric Nurses: A Team Communication Tool Pilot

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Introduction: Surgical services that work in open admission units often encompass various difficulties with managing their patients related to daily work flow in comparison with traditional medical services. A Neurosurgery Nursing Communication Tool (NNCT) was adapted to the pediatric neurosurgery (NSGY) population to improve team communication and understanding of patient care. There is limited research on rounding tools amongst the multi-disciplinary care team especially NSGY with nurses (RNs).

Methods: This is a prospective cohort study utilizing a pre/post-implementation surveys with RNs on the pediatric unit was distributed to assess perceptions of baseline team communication. Each NNCT was assessed for various data components.

Results: The pre-implementation survey showed that 63% felt their concerns were addressed and 42% feel confident speaking in team rounds. In the first month, there was a NNCT completion rate of 65% with less than 50% of NCCT data completed. Admission diagnoses were only correct on 55.6% of NCCTs. Post implementation surveys showed 85.7% felt it was user friendly. All RNs felt it took less than 5 minutes to complete. 71.4% of RNs felt it has helped to know more about their patient, 81.2% felt their concerns are addressed and 85.7% reported that it has improved communication. There was also an increase of RN confidence. Of RNs surveyed, 71.4% expressed that the NCCT could be helpful for other patients and surgical teams. It found that 72.7% of RNs learn their patient diagnosis from RN report.

Conclusions: By implementing a brief NNCT, there was improved RN confidence and RN understanding of their patient, as well as, improved quality of RN-NCCT perceived communication after a month. This pilot study empathizes that all team members are accountable in patient care and communication. It also demonstrates the need for larger studies with better nursing involvement.

101. Neuroscience Patient Readmissions: Evaluating Prediction Models for Neurosurgical Patients

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Introduction: Readmissions within 30 days of hospitalization are utilized as a quality of care benchmark. We reviewed 30 day hospital readmissions for Neuroscience patients over 4 years at Mayo Clinic.

Methods: We conducted a Mayo Clinic Kern Center for Science of Health Care Delivery retrospective analysis reviewing neurosurgery patients who were readmitted to the hospital within 30 days. The following data points were utilized in the review: age, sex, length of stay, Charlson comorbidity index, ICU stay, elective or urgent surgery, and discharge disposition.

Results: All patients were reviewed from January 2013 to December 2017, totaling 3966 patients that were not readmitted and 295 (6.9%) patients that were unplanned readmissions within 30 days. Factors associated with readmission included: increased length of stay ($p < 0.0001$, mean 5.4 days (SD 6.8) versus 3.8 (SD 4.5), Charlson comorbidity myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease ($p < 0.0001$), dementia ($p < 0.0001$), chronic pulmonary disease ($p < 0.0001$), ulcer, diabetes ($p < 0.0001$), hemiplegia ($p < 0.0001$), moderate or severe renal disease, metastatic solid tumor ($p < 0.0001$), other cancer ($p < 0.0001$), brain/nervous system tumor ($p < 0.0001$), total disease flag count ($p < 0.0001$), ICU stay ($p < 0.0001$), discharge to skilled nursing facility or rehabilitation facility ($p < 0.0001$). Factors without statistical significance included: age, sex, mild liver disease, AIDS, rheumatic disease.

Conclusion: This study has the largest total sample size examining neuroscience patient risk factors for readmission. This data suggests that patients with more comorbidities or decreased functional ability are associated with readmissions. This analysis is the basis for a future a prospective multivariate regression model to quantify readmission risk in neuroscience patients to guide future interventions.

102. Impact of Patient-Controlled Analgesia on Clinical Outcomes after Posterior Lumbar Spinal Fusion Surgery

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Introduction: Optimal post-operative pain control is critical after lumbar fusion surgery. However, there is significant variability in the use of intravenous opioid patient-controlled analgesia (PCA) and little data evaluating its utility compared to multimodal nurse-controlled analgesia (NCA) in this patient population.

Methods: A single institution retrospective review was conducted in patients receiving posterior lumbar fusion for degenerative pathology. Baseline demographics, treatment data, and clinical outcomes were collected. Patients were divided into two cohorts: those treated postoperatively with PCA and NCA. Post-operative numerical rating scale (NRS) pain scores, length of stay, and total opioid consumption were collected. Patients were stratified according to pre-operative opioid consumption as naïve, low (<60 morphine milligram equivalents (MME) daily), high (61-90 MME) or very high (>90 MME).

Results: 240 patients were identified: 62 and 178 in PCA and NCA groups, respectively. PCA patients had higher mean pre-operative opioid consumption compared to the NCA patients (49.2 vs 24.3 MME, $p=0.009$). After stratifying by preoperative opioid consumption, PCA patients had higher 72-hour opioid consumption in all groups. With opioid naïve patients, PCA was associated with higher post-operative NRS scores at 24 and 24-72 hours ($p=0.046$ and 0.023 , respectively) despite greater opioid intake. In the Very High opioid consumption group (>90MME), PCA had increased maximal reported pain scores between 24-72 hours ($p=0.014$) and a greater rate of opioid-related adverse events per patient (0.86 vs 0.43 , $p=0.046$). Pain control and adverse event rates were comparable between PCA and NCA in the middle groups (1-90 MME).

Conclusion: Postoperative PCA utilization is associated with significantly more opioid consumption and equal or worse post-operative pain scores compared to NCA after lumbar spinal fusion surgery, particularly in opioid naïve patients. The increased opioid consumption with PCA may also lead to higher rates of opioid-related adverse events in subsets of patients.

103. Impact of Bracing after Thoracolumbar Spinal Fusion: A Systematic Review

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Introduction: Thoracolumbar fusion is indicated in a variety of spinal pathologies, including trauma, tumor, degenerative disk disease, and scoliosis. However, significant variability exists in the implementation of postoperative orthoses following these procedures. The potential stability conferred by immobilization must be balanced by the potential morbidity and associated discomfort. Limited clinical evidence is available to codify the risks and benefits of bracing following thoracolumbar fusion. Via a systematic review of the literature, this study aims to assess the utility of external fixation of the thoracolumbar spine following fusion procedures.

Methods: A systematic review was performed using Medline. Our search included studies that evaluated the impact of post-operative bracing on complications or quality-of-life following spinal fusion, and was limited to literature published between 1990 and 2018.

Results: Our search identified a total of 1706 publications. Of these, 29 publications evaluated bracing in the post-operative setting. These were subsequently narrowed to only five studies that specifically analyzed postoperative bracing in thoracolumbar patients following spinal fusion. Data extracted from each of the five papers included demographic information, surgical details, complication rates, and a variety of quality of life measures. Mean complication rates, instrumentation failure rates, pseudarthrosis rates, Oswestry Disability indices, visual analog scale Spine Scores, SF-12v2 scores, American Spinal Injury Association impairment scores, and Roland Morris Disability scores, were calculated across bracing and control cohorts and compared using independent samples t-test. Ultimately, thoracolumbar bracing was not found to significantly affect complication rates, or impact postoperative quality of life.

Conclusion: This study does not find any significant effect of postoperative bracing on complication rates or quality-of-life for patients recovering from thoracolumbar fusion. This systematic review was limited by a dearth of available literature, and indicates a need for further exploration of this topic to determine optimal postoperative management of such patients.

104. Multiple Intracranial Aneurysms: Incidence and Risk Factors

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Introduction: Multiple intracranial aneurysms represents 30% of all unruptured intracranial aneurysms, and have been associated with cerebrovascular disorder, familiar history, and previous subarachnoid hemorrhage. Here, we investigated the incidence and risk factors associated with multiple intracranial aneurysms.

Methods: 1404 patients, admitted in Hospital das Clínicas de São Paulo, Brazil, between September 2009 and August 2018, enrolled this study. There were 314 male (22.4%) and 1090 female (77.6%). Diagnosis was performed with digital subtraction angiography. Multiplicity was defined as 2 or more intracranial aneurysms. Individuals characteristics such as sex, age, smoking and hypertension were evaluated.

Results: 512 patients (36.4%) were diagnosed with multiple intracranial aneurysms, accounting for 1362 aneurysms. There was an increased frequency of females with multiple aneurysms ($p < 0.001$, OR= 1.883, 95% CI= 1.386-2.560). Smoking was associated with multiple aneurysms development, as well as advanced age ($p = 0.001$, OR= 1.458, 95% CI= 1.160-1.833, and $p < 0.001$, OR= 1.938, 95% CI= 1.438-2.611, respectively). We observed no significant associations concerning hypertension ($p = 0.702$). Sorting by size, 60.6% had a diameter between 3-10 mm. We observed higher incidence of baby aneurysms (less than 3 mm) in the group of patients with multiple aneurysms, while giant aneurysms (more than 25 mm) were most found in the group of patients with only one aneurysm ($p < 0.001$).

Conclusion: Risk factors to the development of intracranial aneurysms, such as sex, advanced age and smoking, were most found in patients with multiple aneurysms when compared with individuals with only one aneurysm.

105. Patient Protection and Affordable Care Act and Neurosurgery: Neutralizing Bias in Trauma Care?

Robert Wagner Bina (Tucson, AZ), MD; Sara Perotti; Travis Dumont, MD

Introduction: Prior studies have shown potential bias in the surgical treatment of traumatic brain injury patients without insurance. The Patient Protection and Affordable Care Act was passed in 2010. After the enactment of the PPACA, it is unknown if this potential bias persists. This study was undertaken to address this question.

Methods: The Nationwide Inpatient Sample was queried for years 2012-2016. Patients with traumatic intracranial hemorrhage as the primary admitting diagnosis were isolated and compared for surgical treatment and survival relative to patient insurance status. A multivariate analysis including variables of patient gender, age by decade, admission severity score, and teaching hospital status was performed to compare outcome measures between years.

Results: The percentage of uninsured patients declined from 11% to 4% during the queried timeframe. Overall, mortality was 11% for uninsured patients compared with 8% for insured patients. In multivariate analysis, uninsured status was associated with mortality in all years, $p < 0.001$. Multivariate regression analysis suggests an Odds Ratio of 0.82 for surgery in uninsured patients in 2012-2015 ($p < 0.001$) and OR of 0.86 in 2016 ($p < 0.03$).

Conclusion: This analysis supports prior studies that uninsured patients were previously less likely to undergo surgery after admission for traumatic brain hemorrhage compared to insured patients; however, after the enactment of the PPACA, this gap seems to be diminishing. Despite this, mortality rates are higher in uninsured patients.

106. Natural History of Unilateral Moyamoya Progressing to Contralateral Moyamoya

Ephraim W. Church, MD (Stanford, CA); Teresa Bell-Stephens, BSN; Mark Bigder, MD; Gary Steinberg, MD, PhD

Introduction: The natural history of unilateral moyamoya disease remains an enigma in modern vascular neurosurgery. Few, small series with limited follow up have reported relatively high rates of contralateral stenosis progression. We sought to review a large series of unilateral moyamoya patients at our medical center.

Methods: We included all unilateral moyamoya cases treated from 1991 through 2017 and followed at least 1 year. We examined time to contralateral radiographic progression as well as contralateral progression requiring surgery. Using a time to event analysis, we sought to create a prediction model for contralateral progression, including variables such as baseline stenosis, sex, age, syndrome (NF1, Down syndrome, hemoglobinopathy), race, family history, hypertension, hyperlipidemia and smoking history. This study was approved by our IRB.

Results: There were 184 patients treated for unilateral moyamoya. One hundred twenty-nine (70%) were female, and the average age at first surgery was 33 (range 2-68). Average follow up was 5.4 yrs (range 1-22 yrs). Fifteen (8.2%) patients

developed contralateral progression. Seven (3.8%) of these developed progression requiring bypass surgery. A time to event analysis revealed potential predictors of contralateral progression.

Conclusion: Previous series showed relatively high rates of progression in unilateral moyamoya, but these studies were small and long term follow up was not available. Our large series with long term follow up indicates that the rate of progression is lower than previously reported but still warrants yearly non-invasive screening.

107. MR Imaging is Not Reliable for Tumor Presence in Post-Treatment Recurrent High-Grade Glioma

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Introduction: Evaluating for tumor recurrence in post-treatment glioma is a challenge as radiographically appearing contrast-enhancing (CE) regions are a mixture of tumor cells and treatment effect. This study characterizes intratumoral heterogeneity using quantitative digital pathology to correlate intraoperative MRI-localized biopsies with histopathology in the post-treatment setting. These findings are being used to inform a multiparametric radiographic model of intratumoral heterogeneity.

Methods: A retrospective review was performed on adult patients with MRI-localized biopsies obtained during resection for post-treatment recurrent high grade glioma. 46 patients and 133 MRI-localized samples were analyzed (median 2 samples/patient). A histopathological classification was developed to assess each sample for relative abundances of treatment effect and recurrent tumor. Immunohistochemistry (IHC) with SOX2, CD68, and Ki67 was used to validate the classification and further characterize the samples. Slides were digitized and quantified using an automated cell-counting algorithm. IHC quantification was compared across histological groups using ANOVA and paired t-tests.

Results: Of 34 patients with multiple biopsies, 25 (74%) demonstrated heterogeneity (as assessed by histopathological classification). 71/133 (53%) biopsies showed predominantly treatment effect and of those, 40/71 (56%) specimens were CE. 19% (12/62) of non-enhancing specimens contained predominantly recurrent tumor. Cell density was correlated with histopathological classification ($p=2.2e-16$). SOX2 and Ki67 staining were higher in specimens containing predominantly tumor ($p=2.2e-16$, $p=1.269e-14$). CD68 staining was higher in specimens containing substantial treatment effect ($p=1.733e-07$).

Conclusion: This study shows that contrast enhancement is not a reliable predictor of tumor presence in post-treatment recurrent malignant gliomas. A majority of patients demonstrated marked intratumoral heterogeneity, highlighting the difficulty of adequate tumor sampling and diagnostic accuracy in the post-treatment setting. In addition to validating the histological classification, IHC revealed that SOX2 is a useful marker for quantifying tumor burden. These results are being used in the development of radiographic models to map intratumoral heterogeneity.

108. Rear Admiral (Astronaut) Alan Shepard—Ménière's Disease and the Race to the Moon

Patrick David Kelly, MD (Nashville, TN); Richard Menger; Shanik Fernando, MD; Michael Wolf, MD, MS; Anthony Martino, MD

Introduction: On May 5th, 1961 Alan B. Shepard, Jr. piloted the Freedom 7 craft into a suborbital flight to become the first American man in space. His promising astronautical career was soon scuttled by spells of dizziness and tinnitus later diagnosed as Ménière's disease.

Methods: Primary and secondary sources were used in preparation of this historical vignette.

Results: Once diagnosed with Ménière's, Alan Shepard was grounded and relegated to a desk job at NASA; a small chance remained, though, that he might be made flight ready once more if his Ménière's could only be treated. In 1968 William F. House—considered the father of neurotology and a pioneer in surgery for vestibular schwannomas—implanted an endolymphatic-subarachnoid shunt, which at the time was a virtually experimental procedure. Shepard's debilitating Ménière's disease was cured, but not quite in time for him to pilot the doomed Apollo 13 mission; he was reassigned to Apollo 14 and as a result would step foot on the moon on February 5th, 1971.

Conclusion: This historical vignette depicts the tale of how the career trajectories of Alan B. Shepard, Jr. and William F. House—two notable figures in their respective fields—fatefully intersected.

109: How do CRASH and IMPACT Compare to a Machine Learning-Based Prognostic Model from Tanzania?

Cyrus Elahi (El Paso, TX); Thiago Rocha, PhD; Anthony Fuller; Catherine Staton; Joao Vissoci, PhD; Michael Haglund, MD, PhD

Introduction: Health facilities in low and middle income countries (LMICs) could benefit from decision support technologies to reduce time to diagnosis and treatment for patients with traumatic brain injury (TBI). CRASH and IMPACT are robust examples of TBI prognostic models. Despite the strengths of these two models, advanced statistical techniques and improved data quality in LMICs provide an opportunity to develop more accurate, and context specific, prognostic models. We developed a machine learning-based prognostic model using a TBI registry from a hospital in Tanzania. In this study, we compare the performance of our model against CRASH and IMPACT.

Methods: We used the CRASH and IMPACT online risk calculators to generate risk scores for each patient in a TBI registry from a regional referral hospital in Moshi, Tanzania. We compared the discrimination (area under the curve [AUC]) and calibration (agreement between predicted and observed outcomes) for CRASH, IMPACT, and our model. We calculated the AUC using Youden's index and provided the 95% confidence interval (CI). The outcome of interest was unfavorable in-hospital outcome defined as a Glasgow outcome scale score of one, two or three.

Results: We used a 3138 patient TBI registry for the three model comparison. There was an 11% observed unfavorable outcome

rate. The AUC for our model, CRASH and IMPACT was 90.3 (CI: 88.6, 92.1), 85.8 (CI: 83.3, 88.3) and 82.0 (CI: 79.3, 84.7), respectively. The interquartile range for predicted risk scores were 10-36% (median = 16%) for our model, 5-14% (median = 5%) for CRASH, and 15-32% (median = 21%) for IMPACT.

Conclusion: Our model had better discrimination and similar calibration compared to CRASH and IMPACT models. This finding supports the hypothesis that locally derived prognostic models will outperform imported prognostic models. Further work is needed to externally validate our model.

110 The role of lidocaine infusions in cranial surgery

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Introduction: Opioid abuse is a crisis in the United States. Opportunities exist in the perioperative period for alternative modes of analgesia to minimize opioid utilization. The aim of this study is to explore the use of lidocaine infusions in the setting of cranial surgery, with a focus on feasibility and safety.

Methods: Patients who received a lidocaine infusion associated with cranial surgery between 2015 and 2017 were identified through an electronic health record search. Postoperative opioid pain medication consumption in the first and second days were converted into oral morphine milligram equivalents (MME). Non-parametric distributions were compared with the Mann-Whitney U or Wilcoxon signed-rank tests as appropriate.

Results: A total of 55 eligible patients were identified (69.1% female, median age 47, median BMI 30.4). The average length of stay was 4.7 days, with an average ICU length of stay of 1.5 days. The median lidocaine infusion time was 17 hours (IQR: 13-22) in the intraoperative +/- immediate postoperative period, with a median cumulative dosage of 1084 mg (IQR: 785-1703). In the first postoperative day, a median of 60 morphine milligram equivalent (IQR: 34.5-85) was consumed. This declined to 36.5 MME (IQR: 16-70) by the second day ($p=0.016$). There was no difference in the lidocaine infusion duration, total dose, MME at 24 or 48 hours between the sexes or smoking status. No correlation was found between BMI and MME at 24 or 48 hours. Preoperative opioid use was associated with a higher MME in the second (70.0 v 30.5 , $p = 0.009$) but not the first (64.0 v 54.8 , $p = 0.124$) postoperative day. No adverse events or complications related to the lidocaine infusion were identified.

Conclusion: Lidocaine infusions appear to be a promising and safe adjunct in perioperative analgesia for cranial surgery. Future steps include prospective randomized controlled trials.

111. (Re)Defining Success: Relative Seizure Frequency Reduction rather than Absolute Seizure Frequency is a Better Predictor of Patient Reported Quality of Life after Epilepsy Surgery

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Introduction: Success in epilepsy surgery is most commonly judged by post-operative seizure frequency. We wished to identify whether absolute post-operative seizure frequency, absolute reduction in seizure frequency, or relative seizure frequency reduction best predicted patient-reported quality of life after epilepsy surgery.

Methods: We prospectively surveyed patients at outpatient visits to the Cleveland Clinic Epilepsy Center before and after receiving epilepsy surgery (n=550), between 2007 and 2017. The QOL measure of interest was the previously validated Quality of Life in Epilepsy (QOLIE-10) score at the patient's most recent office visit. We used a multivariate linear regression model to predict post-operative QOLIE-10. Variables included in the model included pre-operative QOLIE-10 as well as pre-operative and post-operative depression score (PHQ9), anxiety score (GAD7), absolute seizure frequency, absolute reduction in seizure frequency, relative reduction in seizure frequency, follow-up time, and relevant interaction terms.

Results: For the 550 patients included in the analysis, median follow-up time was 24.7 months (IQR 8.5-54.5). Our model provided good prediction of post-operative QOLIE-10 ($R^2=0.72$, $P<0.001$). Effect tests demonstrated that the most important predictive variables were post-operative PHQ9 ($F=75$, $p<0.001$), pre-operative QOLIE-10 ($F=14$, $p<0.001$), and relative seizure reduction ($F=11$, $p=0.0012$). Absolute seizure reduction, absolute post-operative seizure frequency, and follow-up time did not show statistically significant effects.

Conclusion: Our results demonstrate that patients are likely to report a high quality of life after epilepsy surgery as long as there is a significant relative reduction in their seizure frequency after surgery, even if the absolute seizure frequency reduction is non-zero. Most literature evaluating surgical outcomes in epilepsy uses Engel classification to classify surgical success, which focuses on absolute seizure frequency and ignores patient-reported quality of life outcomes. QOL measures should play a bigger role in the evaluation of surgical outcomes.

112. Using the Neutrophil to Lymphocyte Ratio to Predict Outcomes in Pediatric Patients with Traumatic Brain Injury

Rebekah Kimball (Longwood, FL); Stephanie Eyerly-Webb, PhD; Rachele Solomon, MPH; Elad Shachar; Dean Hertzler, MD; Heather Spader, MD

Introduction: Prognostication for outcomes following pediatric traumatic brain injury (TBI) has traditionally been based upon initial Glasgow Coma Scale (GCS) and other clinical and radiologic indicators. Although the inflammatory cascade following TBI can be both neuroprotective and destructive, inflammatory markers have not been utilized to help predict outcomes in pediatric TBI. This study is the first to utilize the neutrophil-to-lymphocyte ratio (NLR), an inflammatory marker widely utilized in other specialties, to help predict outcomes in pediatric TBI.

Methods: A retrospective review of pediatric patients presenting to our institution with TBI from 2007 to 2017 was performed (n=188, age=0-18 years). Absolute neutrophil count and absolute lymphocyte count on admission and approximately twenty-four and forty-eight hours post-injury were used to calculate NLRs. Data points included GCS on admission, extended Glasgow Outcome Scale (GOS-E) score, and presence of post-traumatic amnesia and/or loss of consciousness. Patients were stratified based on GOS-E score: none to mild disability (GOS-E=1-2), moderate to severe disability (GOS-E=3-6), or vegetative state/death (GOS-E=7-8).

Results: A one-way ANOVA demonstrated statistically significant differences in NLR among patients stratified by GOS-E at 24 hours [$F(2,55)=6.26$, $p=0.004$] and 48 hours [$F(2,24)=7.59$, $p=0.003$]. No significant differences in NLR or neutrophils were observed at any time point based on GCS category or post-traumatic amnesia. Patients who experienced loss of consciousness had a significantly higher NLR on admission ($p=0.013$) and at 24 hours ($p<0.001$) compared to those who did not lose consciousness.

Conclusion: In this study, a higher NLR twenty-four hours post-TBI predicted worse outcomes in pediatric patients. There was no difference based upon admit NLR. This suggests that NLR may be a useful outcome predictor in pediatric TBI as well as a possible future target for therapeutic intervention. Further study is warranted with larger prospective trials, different time points, and alternative inflammation markers.

113. Posterior Vertebral Column Subtraction Osteotomy for the Treatment of Recurrent Tethered Cord Syndrome in Adults: A Prospective Outcome Study

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Introduction: There remains limited data on the safety and efficacy of posterior vertebral column subtraction osteotomy (PVCSO) for the treatment of tethered cord syndrome (TCS). The purpose of this prospective study was to evaluate surgical outcomes following PVCSO in adult patients with a history of failed detethering surgery caused by lipomyelomeningocele.

Methods: From January 2011 to October 2018, select patients were enrolled and treated with PVCSO at Barrow

Neurological Institute and The Johns Hopkins Hospital. Inclusion criteria for surgery were age 18 years and greater, TCS caused by lipomyelomeningocele, history of failed detethering surgery, recurrent symptom progression less than 2 years, and treatment willingness. Herein, all patients undergoing surgery with a one-month minimum follow-up were evaluated.

Results: Twenty patients (mean age: 36 years; sex: 5M/15F) met the inclusion criteria and were evaluated. The average number of previous detethering procedures was 3.7 (range: 1-17). The most common presenting symptom was back pain (95%), followed by urinary incontinence (80%), leg pain (75%), fecal incontinence (55%), sensory abnormalities (50%), and motor deficits (50%). At an average follow-up of 11.2 months (range: 1.8-26 months), symptomatic improvement/resolution was most notable for leg pain (93%), followed by back pain (84%), sensory abnormalities (80%), motor deficits (80%), fecal incontinence (55%), and urinary incontinence (50%). Oswestry Disability Index improved significantly from a mean of 56.1 pre-operatively to 38.4 at end follow-up ($p=0.006$). The mean spinal column height reduction was 23.7 mm (range: 18-28 mm). Three complications were noted, one each for durotomy, wound infection requiring debridement, and new sensory abnormality.

Conclusion: We report the first prospective study on the safety and efficacy of PVCSO in 20 adult patients with a history of failed detethering surgery caused by lipomyelomeningocele. Our results suggest that PVCSO is an attractive alternative, extradural approach that may afford definitive treatment in this subpopulation.

114. The Affordable Care Act and Reimbursement Patterns in Neurosurgery: Analysis of the NERVES survey results

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Introduction: In response to rising national health expenditures the patient protection and affordable care act (ACA) was passed in 2010, with major provisions implemented in 2014. The American Academy of Neurological Surgeons and Congress of Neurological Surgeons stated that the ACA vastly expands the federal governments role and fails to address the shortcomings of the healthcare system. In this study we evaluate trends in neurosurgical reimbursement, productivity and compensation before and after the implementation of the major provisions of the ACA.

Methods: Results from Neurosurgery Executives Resource Value and Education Society (NERVES) surveys were collected, representing data from 2011-2016. Based on the responses from different practice settings across the six years categorized into Before/After 2014, we performed inverse variance-weighted averaging within the frameworks of (a) a one-way ANOVA model with practice setting (Private/Hospital/Academic) as the sub-group factor and (b) a two-way ANOVA model with practice setting and Year (Before/After 2014) as the two sub-group factors. Within these frameworks, we used F-tests to detect any significant difference.

Results: The NERVES survey was distributed to neurosurgery practices in the United States. Response rate ranged from 19.6% to 36%. While median values during a period of average annual GDP-growth of 2.05% for compensation, productivity and reimbursement were lower after the majority of the regulatory changes associated with the ACA were implemented (January 1, 2014) no statistically significant differences were noted within practice type for neurosurgeons in academic, private-practice or hospital-employed groups for annual compensation, annual collections, gross charges, number of annual surgeries performed, total and work RVUs.

Conclusion: Though the ACA has led to significant changes in healthcare, survey data suggests that no statistically significant differences in reimbursement, compensation and productivity have occurred for academic, private-practice, or hospital-employed neurosurgeons since implementation of the major provisions of the ACA.

115. AI-Augmented Diagnosis of Brain Aneurysms from CTA: A Retrospective Study

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Introduction: CTA is the primary non-invasive diagnostic imaging modality for detecting cerebral aneurysms. However, aneurysm diagnosis by CTA can be challenging for clinicians due to lack of experience or subspecialty neuroradiology training, complex neurovascular anatomy, or the labor-intensive nature of identifying aneurysms. We aimed to develop and validate a novel 3D convolutional neural network architecture to automatically detect intracranial aneurysms on CTA and produce location-specific segmentations.

Methods: We retrospectively collected a dataset of 818 CTA head exams from 662 patients with 328 (40.1%) exams containing at least one clinically significant intracranial aneurysm ($>3\text{mm}$) and 490 (59.9%) exams (controls) without intracranial aneurysms between 2003 and 2017 at Stanford University Medical Center. We excluded exams with

hemorrhage, ruptured aneurysm, post-traumatic or infectious pseudoaneurysm, arteriovenous malformation, and any surgical or endovascular hardware. The exams were split into a training set (611 exams, 494 patients) used to train our model, a development set (92 exams, 86 patients) used for model selection, and a test set (115 exams, 82 patients) to evaluate the final model's performance. The ability of the model to augment clinician readers' performance was investigated with a crossover study design involving 8 clinical experts.

Results: Clinical experts augmented with model segmentations had a statistically significant increase in both their micro-average sensitivity and accuracy. The clinical experts'; mean sensitivity increased from 0.831 to 0.890 and mean accuracy increased from 0.893 to 0.932. There was also an increase in inter-rater reliability among clinical experts, with an exact Fleiss' kappa of 0.799 without augmentation and 0.858 with augmentation. The time to diagnosis for each clinical expert decreased on average by 5.96 seconds per case with augmentation.

Conclusion: Our results suggest that segmentation models offer a promising approach for integrating deep learning into the clinical workflow and significantly improving human clinician diagnosis of intracranial aneurysms.

116. Genome-wide association analysis across 16,242 patients identifies an association between the bone morphogenetic protein-6 gene and phenotypic spinal osteoarthritis

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Introduction: The Geisinger MyCode initiative is one of the world's largest biorepositories with integrated longitudinal electronic health record (EHR) linked to genetic data. Currently, approximately 92,000 MyCode participants have high density single nucleotide polymorphism (SNP) array and whole exome sequence data. Leveraging this multimodal dataset, we can identify powerful associations and advance genomics-guided therapies. Spinal conditions account for the third largest United States healthcare expenditure, yet the genetics underlying degenerative spine conditions have not been significantly explored.

Methods: We identified all patients ($n = 3,985$) with an EHR diagnosis of spinal osteoarthritis or spondylosis who had genotype data available as part of our DiscovEHR collaboration with the Regeneron Genetics Center. We also identified 12,257 controls who did not have any diagnosis of osteoarthritis or degeneration. We sought to identify SNPs associated with spinal osteoarthritis or spondylosis using logistic regression in a genome-wide association analysis.

Results: Across the 3,985 cases and 12,257 controls, 39 SNPs demonstrated suggestive association with p -values $< 5 * 10^{-5}$. One SNP (rs9379137) was below the threshold for genome-wide significance ($p = 1.203 * 10^{-8}$). This SNP is located in the coding region of the bone morphogenetic protein-6 (BMP-6) gene. BMP-6 belongs to the transforming growth factor-beta family and has been shown to be involved in bone and cartilage growth.

Conclusion: We describe the use of a massive database of genotypes combined with phenotypic EHR data to identify an association between the BMP-6 gene and the development of spinal osteoarthritis. We are expanding this analysis to the larger 150,000 participant MyCode database. Long-term, we will define precision medicine relationships between the genome and the development of degenerative spinal conditions, as well as identify those patients most likely to respond to surgery and other therapies.

117. Pathological hijacking of the AMPK/HIF1a hypoxia pathway leads to neuronal anaerobic respiration in epilepsy

Alexander Ksendzovsky, MD (Bethesda, MD); Stuart Walbridge, BS; Muzna Bachani, BS; Marcelle Altshuler, BS; Sara Inati, MD; Joseph Steiner, PhD; John Williamson, BS; John Heiss, MD; Jaideep Kapur, MD, PhD; Kareem Zaghloul, MD, PhD

Introduction: Anaerobic respiration, marked by lactate dehydrogenase alpha (LDHA), has recently been found to play an important role in epileptogenesis. However, the metabolic state of excited neurons is unknown. In this study, we demonstrate a switch from aerobic to anaerobic respiration in chronically activated neurons in human and murine models of epilepsy. Using an in vitro epilepsy model, we establish the AMP-activated protein kinase/hypoxia-inducible factor-1a (AMPK/HIF1a) hypoxia pathway as a key regulator leading to increased LDHA expression and anaerobic respiration.

Methods: First, we analyzed human tissue for LDHA expression based on electrographic characteristics of overlying subdural electrodes, as determined during intracranial monitoring (epileptic vs normal cortex). Second, two epilepsy mouse models (pentylenetetrazole (PTZ) and electrical stimulation) were probed for LDHA after seizure development. Finally, a low Mg^{2+} in vitro epilepsy model was developed to elucidate AMPK/HIF1a's role in regulating the metabolic switch from aerobic to anaerobic metabolism.

Results: In human and mouse studies, LDHA expression was significantly upregulated in epileptic neurons. PTZ and electrical stimulation confirmed a positive correlation between seizure frequency and LDHA expression. Treatment of cultured neurons with low Mg²⁺ caused an increase in bursting activity, or in vitro seizures. Neuronal bursting caused depletion of intracellular ATP and subsequent activation of the AMPK/HIF1a pathway through phosphorylation of AMPK. Furthermore, chronic activation of AMPK led to HIF1a and LDHA upregulation and a subsequent switch from an aerobic to a glycolytic cellular phenotype in neurons.

Conclusion: These data suggest that seizures cause a metabolic switch from aerobic to anaerobic respiration in neurons, which occurs through activation of the canonical AMPK/HIF1a hypoxia pathway. To our knowledge this is the first study to demonstrate the metabolic consequences of neuronal over-activation and the key regulatory pathway responsible. We believe our data opens up significant potential for future investigation into mechanisms of epilepsy and new therapeutic targets.

118. Association Between Neurosurgical Volume and Hospital Costs in the United States

James Seungwon Yoon (New Haven, CT); Oliver Tang; Michael Lawton, MD

Introduction: Several studies have documented improved outcomes at high-volume hospitals for neurosurgical procedures. However, the relationship between neurosurgical volume and costs remains poorly understood.

Methods: Using neurosurgery-specific DRG codes, we identified adult neurosurgical admissions in the National Inpatient Sample from 2002 to 2014. We stratified hospitals by annual neurosurgical volume as high-volume (top 20%) or low-volume centers (bottom 80%). We performed survey-weighted analyses to examine the impact of case volume on inpatient costs. Multivariate regression adjusted for patient age, sex, race, insurance, income, severity of illness, length of stay, emergency admission, wage index, hospital ownership, location/teaching status, hospital region, and DRG weights. We created a model for centralization of neurosurgical care, where non-emergency admissions with minor risk of mortality were considered as transfer candidates.

Results: 12,129,029 total admissions underwent neurosurgery from 2002 to 2014, with 59.6% treated at high-volume hospitals. Patients at high-volume centers were more likely to privately insured, present with higher risk of mortality, and undergo higher DRG-weight procedures than those at low-volume centers ($P < 0.001$). High-volume hospital admissions were on average 9% or \$1,791 more expensive than their low-volume counterparts. However, following adjustment for patient, hospital, and case-mix differences, high-volume hospitals were 4.3% less expensive than low-volume centers (\$21,825 vs. \$22,924, $P < 0.01$). If 10% of transfer candidates were rather treated at high-volume centers, we estimate an annual saving of \$192 million, culminating in a total saving of \$2.5 billion.

Conclusion: High-volume institutions appear to have higher costs due to their case-mix of higher patient and procedural severity. After adjusting for this, we found that treating a similar patient at a low-volume hospital would be 4.3% more expensive, suggesting that high-volume hospitals may provide more cost-effective neurosurgical care. Amidst sharply rising medical costs, treatment at high-volume neurosurgical institutions may be a promising strategy to delivering higher value care.

119. Intracranial Gunshot Wounds: Assessment of Morbidity, Mortality, and Surgical Outcomes

Yi-Ren Chen, MD (Stanford, CA); Eli Johnson; Beatrice Ugiliweneza; Maxwell Boakye; Victor Tse

Introduction: Intracranial gunshot wounds (GSW) are often fatal, with most patients dying before intervention can occur. Surgical management, when indicated, results in decreased mortality. However, our knowledge of the outcomes and economic costs of intracranial GSW remains limited.

Methods: We conducted a retrospective analysis using the longitudinal claims Truven MarketScan® database from 2000 to 2016. Mortality was the primary outcome of interest and complications, length of stay and payment were secondary outcomes. Multivariable logistic and linear regression was performed to assess the relationship between age, gender, insurance type and the number of comorbidities to the outcomes measured.

Results: We identified 418 patients (Median age = 26.0y, IQR = 18, 44; 23.4% female) who received craniotomy or craniectomy for intracranial GSW. Mortality occurred in 50 patients (11.96%) and 286 patients (68.42%) experienced complications. The median length of stay was 10 days (IQR = 4; 22days) and cost was \$62,574.00 (IQR = \$28,111.00; \$143,980.00). Increasing age by 1-year increments demonstrated increases in complications (OR = 1.023; 95% CI = 1.007 - 1.038), mortality (OR = 1.023; 95% CI = 1.002 - 1.044), length of stay (RR = 1.01; 95% CI = 1.003 - 1.017) and payment (RR = 1.01; 95% CI = 1.002 - 1.017). When comparing Medicaid to commercial insurance, patients with Medicaid had a longer length of stay (RR = 1.299; 95% CI = 1.049 - 1.608) and less payment (RR = 0.571; 95% CI = 0.454 - 0.718). Finally, increases in the Elixhauser index by 1-comorbidity increments was associated with increased complications (OR = 1.233;

95% CI=1.024 - 1.485), length of stay (RR=1.292; 95% CI=1.188 - 1.405) and payment (RR=1.208; 95% CI=1.104 - 1.322).

Conclusion: Although these findings must be interpreted in the context of the limitations inherent to studies using national administrative data, the current study provides additional insight into the relationship between patient characteristics and outcomes after surgery for intracranial GSW.

120. 3D Ventricular Volume Analysis to Detect Shunt Failure

Siri Sahib Singh Khalsa, MD (Ann Arbor, MI); Jamaal Tarpeh, BS; David Altshuler, MD; Cormac Maher, MD

Introduction: The pre-operative diagnosis of shunt failure typically depends on detecting a difference in ventricular caliber between the current cranial imaging and the most recent well-scan. Patients with hydrocephalus often present with concerns for shunt failure to their local emergency department, which may not have access to previous cranial imaging for comparison. Radiology reports typically describe ventricular caliber in qualitative terms. Thus, a comparison of ventricular caliber by telephone is usually unreliable. We sought to develop and validate a computer program to rigorously measure the 3D ventricular volume on MRI and CT scans to make objective comparisons possible.

Methods: A computer program was developed in Matlab to semi-automatically calculate the 3D volume of cerebrospinal fluid within the entire ventricular system on brain MRI and head CTs, within seconds. A combination of k-means clustering and nearest-neighbor techniques were used for the 3D segmentation. The algorithm was tested on 52 scans from 16 pediatric patients with shunted hydrocephalus. Shunt failure scans confirmed with subsequent shunt exploration were compared to the most recent well-scan. Well-scans were compared to the preceding well-scan for control.

Results: Mean ventricular volume change was +600% +/- 212% for failure-scans and -2.5% +/- 9% for well-scans ($p < 0.01$). A ventricular volume increase cut-off of 20% was 100% sensitive and 89% specific for shunt failure in this cohort.

Conclusion: A computer program was developed to rapidly calculate the volume of the ventricular system on both brain MRIs and head CTs. This method could be used to objectively detect shunt failure between institutions that are not able to share images. This benefit would apply only to patients whose ventricles enlarge during shunt failure. Prospective analysis of a large multi-center cohort will be necessary prior to implementation.

121. Correlation of Language-Eloquent White Matter Pathways with the Course of Language Function in Glioma Patients

Sebastian Ille, MD (Munich, Germany); Lara Engel; Bernhard Meyer, MD; Sandro Krieg

Introduction: As various studies show, damage to white matter pathways leads to permanent functional deficits in a high percentage of patients. Particularly the subcortical language network is complex, and its visualization has a tremendous relevance for neurosurgeons. This pilot study aims to correlate language-eloquent white matter pathways with the course of language function after the resection of left-sided perisylvian gliomas.

Methods: We included patients who underwent resection of highly language-eloquent high- and low-grade gliomas. We performed navigated repetitive transcranial magnetic stimulation (nrTMS)-based tractography via diffusion tensor imaging fiber trackings (DTI FT) preoperatively (PRE-1), postoperatively (POST-1), and at long-term follow-up or tumor recurrence (PRE-2). We separately tracked the inferior fronto-occipital fascicle (IFOF), the frontal aslant tract (FAT), and the superior longitudinal and arcuate fascicle (SLF/AF), and correlated the amount of visualized fibers to the patients' language function at each date.

Results: The changes of nrTMS-based DTI FTs of single white matter pathways correlated with the according status of language function for any of the pathways in 80% of patients and in 19 of 30 single pathway comparisons between PRE-1 and POST-1. Between POST-1 and PRE-2 the nrTMS-based DTI FTs correlated with the status of language function for any of the pathways in all patients and in 24 of 30 single pathway comparisons. Single FT results correlated with the according status of language function at POST-1 in 60%, 70%, and 60% of cases, and with the according status of language function at PRE-2 in 60%, 90%, and 90% of cases for the tracking of the IFOF, FAT, and SLF/AF, respectively.

Conclusion: By the present results we were able to show that nrTMS-based DTI FT of the IFOF, FAT, and SLF/AF correlates with the according status of language function preoperatively, postoperatively, and at long-term follow-up after the resection of left-sided perisylvian gliomas.

122. Pain Management Matters: Demographic Differences in Patient Reported Outcomes

Elizabeth Howell (Durham, NC); Jihad Abdelgadir, MD, MSc; Edmund Ong, PhD; Salma Abdalla, MD, MPH; John Hunting, MPH; Mohamed Diab, MD; C. Rory Goodwin; Padma Gulur, MD; Michael Haglund

Introduction: The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey is utilized nationally to query patient perception of their healthcare across a broad array of domains, such as quality of care, communication, and overall hospital experience. Previous studies have established a correlation between demographic factors - such as race, ethnicity, gender, and socioeconomic status - and patient perception of the adequacy of their pain control. In this study, we examined the link between HCAHPS pain-domain responses and patient demographic variables in order to further characterize this relationship.

Methods: This study included 107,287 records for adult patients discharged from a tertiary university-affiliated hospital between October 2015 and June 2017. Patient responses to HCAHPS pain management questions were collected. Of all records reviewed, 13,026 included responses to at least one HCAHPS pain management question. Systematic statistical analysis was then performed in order to evaluate potential interactions between demographic variables and HCAHPS response rates and types.

Results: Hispanic and Black or African American respondents were more likely to report successful pain control when compared to Not Hispanic and Caucasian/White patients, respectively (ORs 1.60, 1.22). Additionally, among female patients, Black or African American respondents were more likely to have reported positive Staff Helpfulness than Caucasian/White respondents (OR 1.38). Notably, Hispanic and Black/African American patients were each less likely to respond to the HCAHPS pain-domain questions (OR 2.03, 2.74) than other respondents.

Conclusion: Several demographic variables, including race/ethnicity and gender, appear to affect both the rate and type of response to HCAHPS questions centered around adequacy of pain control. Based on the above results, Hispanic and Black/African American patients may underreport negative experiences. Further investigation into this complex relationship is warranted, as demographic biases in HCAHPS responses could potentially undermine the utility of this data to inform healthcare decision-making and practice.

200. Final Results of the HEAT (Hydrogel Endovascular Aneurysm Treatment Trial)

Bernard R. Bendok, MD (Phoenix, AZ), FAANS; Karl Abi-Aad, MD; Jennifer Ward, MBA; Jason Kniss; Mary Jeanne Kwasny; Rami James Aoun, MD, MPH; Tarek El Ahmadieh, MD; Samer Zammar, MD; Salah Aoun, MD; Najib El Tecle, MD; Rudy Rahme, MD; Matthew Welz, MS

Introduction: The Hydrogel Embolic System (HES) coil (Microvention, Aliso Viejo, CA), which is a hydrogel coated platinum coil, was designed to improve packing density and long-term obliteration rates of intracranial aneurysms. The first-generation HES demonstrated lower recurrence rates than bare platinum coils (BPC); however, its use was limited by technical difficulties. A second-generation HES was designed to withstand longer working times and reproduce the ease of use of BPC. The New Generation Hydrogel Endovascular Aneurysm Treatment Trial (HEAT) compares the second-generation HES with BPC in 600 subjects, over a period of 2 years.

Methods: HEAT is a multicenter randomized controlled clinical trial that enrolled subjects 18-75 years of age with 3-14 mm ruptured or unruptured brain aneurysms eligible for endovascular treatment. Randomization occurred in a 1:1 fashion across 46 sites in the US and Canada. Subjects assigned to the Hydrogel arm received 90% second-generation HES, at least. The primary outcome of the study was aneurysm recanalization. Secondary outcomes were initial occlusion, packing density, hemorrhage, retreatment, mortality, and aneurysm recanalization assessed by other scales.

Results: Enrollment began in 2012 and ended in 2016. 86.2% of the 600 enrolled subjects had at least one follow-up angiogram or MRA evaluation. Recanalization rates were 4.4% for HES and 15.4% for BPC ($p < 0.001$). In terms of secondary outcomes, there were no differences in adverse events ($p = 0.498$) mortality ($p = 0.641$), retreatment ($p = 0.162$), and rehemorrhage rates ($p = 0.297$) between both arms.

Conclusion: In the HEAT trial, the second-generation Hydrogel Coil was found to be superior to the bare platinum coil in reducing aneurysm recurrence rates. Adverse events and Clinical outcomes were similar between both arms of the study. The findings of this trial suggest that second-generation hydrogel coils are associated with greater durability of treatment when compared to bare platinum coils without any increase in morbidity.

201. Novel Kilohertz Frequency Neuromodulation For Fiber Selective Blockade Of Sciatic Pain In A Rat Model

William H. Sweet Young Investigator Award

Alexander B. Dru, MD (Gainesville, FL); Lauren Dewberry, BS; Kevin Otto, PhD; Kyle Allen, PhD; Daniel Hoh, MD

Introduction: Pain management for chronic sciatica often results in long-term opioid use leading to dependence, dosage increases, and diminished benefit. Our group previously discovered kilohertz (kHz) frequency modulation (50kHz/3Volts) of the sciatic nerve (SN) eliminates tactile allodynic responses in a validated rat model of sciatic neuropathy, with visual preservation of motor function. Here, we inspect and quantify the selective slow fiber (<5m/s) inhibition observed with the 50kHz/3V modulation.

Methods: A Lewis rat was placed under general anesthesia and right SN exposed. A dual-electrode stimulator cuff was implanted on the proximal SN, recording cuff around the tibial nerve distally (1.9 cm separation), and SN neuromodulator between the cuffs. Compound action potentials (CAPs) were elicited with charge-balanced 500µA/0.1ms biphasic pulses. Frequency-voltage combinations (30-100 kHz in 5 kHz increments at 3, 5, 7, and 9 V peak-to-peak) were applied to the SN during CAP induction. Each trial consisted of 5 CAPs before, 20 CAPs during, and 10 CAPs after neuromodulation. CAPs were recorded on an amplitude-time graph with integrals of peaks corresponding to specific fiber activation.

Results: The integral of the <5m/s combined peak before and during 50kHz/3V modulation was 0.048 and 0.016, respectively, representing 67.0% slow fiber inactivation with preservation of muscle stimulus artifact indicating unblocked motor neurons. The integrals of the 4.7 m/s (slow Aδ fiber) and 1.3 m/s (c fiber) peaks before/during modulation were 0.023/0.007 and 0.025/0.009, representing 69.6% and 64.0% inactivation, respectively.

Conclusion: Sciatic neuromodulation at kilohertz frequency produces rapidly reversible sensory nerve block in a rat model of peripheral neuropathy. Our experiment provides an electrophysiological explanation for the selective muting of downstream-source allodynic discomfort and upstream neuropathy with respect to the neuromodulator location observed in our initial sciatica rat study. This offers additional proof of concept for a pulse generator-sciatic system for durable treatment of painful neuropathy in humans.

202. Trends in Medicare Reimbursement for Neurosurgical Procedures from 2000 to 2018

Kent Richter, BS (Phoenix, AZ); Naresh P. Patel, MD, FAANS; Jack Haglin, BS; Mark Lyons, MD

Introduction: Literature evaluating procedural reimbursements and national financial trends in modern neurosurgery is lacking. A comprehensive understanding of neurosurgical economic trends and financial health is important to ensure the sustained success of the specialty moving forward. This study evaluated monetary trends in Medicare reimbursement rates from 2000 to 2018 for the 10 most common spinal and cranial neurosurgical procedures.

Methods: The Physician Fee Schedule Look-Up Tool from the Centers for Medicare & Medicaid Services was queried for the top 10 most utilized CPT codes in spinal and cranial neurosurgery. Comprehensive reimbursement data was extracted. The raw percent change in Medicare reimbursement rate from 2000 to 2018 was calculated for each procedure and averaged. This was compared to the percent change in the consumer price index over the same time. Data was adjusted for inflation and trend analysis performed. The average annual and the total percentage change in reimbursement were calculated based on these adjusted trends, and the compound annual growth rate was calculated for each procedure.

Results: From 2000 to 2018, the average reimbursement for all procedures decreased by an average of 25.80%. The adjusted reimbursement rate for all procedures decreased by an average of 1.59% each year and experienced an average compound annual growth rate of -1.66%, indicating a steady annual decline in reimbursement when adjusted for inflation.

Conclusion: This is the first study to evaluate comprehensive trends in Medicare reimbursement in neurosurgery. When adjusted for inflation, Medicare reimbursement for all included procedures has steadily decreased from 2000 to 2018, with similar rates of decline observed between cranial and spinal neurosurgery procedures. Increased awareness and consideration of these trends will be important moving forward as continued progress is made to advance agreeable reimbursement models that allow for the sustained future growth of neurosurgery in the United States.

203: The Safety And Efficacy Of Riluzole As A Neuroprotective Therapy In Patients Undergoing Surgical Decompression For Cervical Spondylotic Myelopathy: Results Of The CSM-Protect Trial

Michael G. Fehlings, MD, PhD, FAANS, FRCS (Toronto, Canada); Jetan Badhiwala, MD; Branko Kopjar, MD, PhD; Henry Ahn, MD, PhD; Francis Farhadi, MD, PhD; Christopher Shaffrey, MD; Ahmad Nassr, MD; Praveen Mummaneni, MD; Paul Arnold, MD; Bradley Jacobs, MD; K. Riew, MD; Darrel Brodke, MD

Introduction: Cervical spondylotic myelopathy (CSM) is the leading cause of spinal cord dysfunction. Surgical decompression is effective. Nonetheless, many patients suffer from significant residual disability. Based on preclinical evidence, we hypothesized that the sodium/glutamate blocking drug, riluzole, may enhance clinical outcomes following surgical decompression for CSM.

Methods: In this multi-center, double-blinded, placebo-controlled randomized trial (ClinicalTrials.gov NCT01257828), adults (18-80 years) with moderately-severe CSM (mJOA 8-14) were assigned to surgical decompression plus riluzole (50 mg PO BID for 14 days before surgery and 28 days after surgery) or surgical decompression plus placebo. The primary outcome was change in mJOA score from baseline to 6 months post-operatively. Secondary outcomes included measures of function (Nurick grade), disability (NDI), QOL (SF-36, EQ-5D), neurological function (ASIA scores), grip strength, and pain (VAS). Outcomes were evaluated at enrollment, pre-operative hospital admission, 35 days, 6 months, and 1 year.

Results: Two-hundred and ninety patients were enrolled (n=141 riluzole; n=149 placebo). Mean age was 58.0 ± 10.1 years. Subjects in both trial arms improved in all endpoints for functional status, disability, QOL, neurological function, grip strength, and pain. There was no difference between riluzole and placebo groups in change in mJOA at 6 months (2.45 vs. 2.82, respectively; $P=0.16$) or 1 year. Patients treated with riluzole showed a significantly greater reduction in pain (VAS) at 35 days than those who received placebo; this effect was maintained at 6 months and 1 year ($P<0.05$). There was a strong trend toward superior recovery in ASIA motor score with riluzole versus placebo at 1 year ($P=0.053$).

Conclusion: Adjuvant treatment for 6 weeks peri-operatively with riluzole in the setting of CSM does not enhance functional recovery beyond surgical decompression, which dominates the clinical picture. However, the effects of riluzole in reducing pain in CSM patients are of clinical interest and merit further study.

204. CD200 Inhibition Enhanced the Anti-glioblastoma Effects of Autologous Tumor Vaccination for In Vivo Murine and Canine Glioblastoma models

AANS/CNS Section on Tumors Neuro-Oncology Trainee Award

Truong Do, MD (Minneapolis, MN); Michael Olin, PhD; Elisabet Ampudia-Mesias, MSc; Christopher Pennell, PhD; Zhengming Xiong; Susan Rathe, PhD; David Largaespada, PhD; Aaron Sarver, PhD; Christopher Moertel, MD; G. Elizabeth Pluhar, DVM, PhD; Clark Chen, MD, PhD

Introduction: Previous work demonstrated that CD200 is an immune checkpoint that creates an immuno-suppressive tumor microenvironment for glioblastomas. We investigated whether inhibition of CD200 would enhance the anti-glioblastoma effects of an autologous tumor lysate vaccine using murine and canine animal models.

Methods: CD200-directed peptides were synthesized and tested in murine glioblastoma models as well as spontaneous canine glioma models. C57BL/6 mice pulsed with tumor lysates derived from GL261 glioblastoma model +/- CD200 peptide inhibitors were used for the murine experiments. For canine modeling, 21 dogs with spontaneous gliomas underwent tumor resection. These tumors were processed to generate autologous lysate. Dogs were injected with inhibitory CD200-directed peptides intradermally followed by intradermal injection of autologous lysate. The dogs were monitored both by MRI and physical exam at 4, 8, and 12 months after surgery to assess for tumor recurrence. Survival was compared to historical controls of canines only undergoing autologous lysate injection.

Results: Through structural analysis and systematic mutagenesis of the CD200 receptor, we identified a peptide that potently inhibited CD200 activity. In murine models, CD200 inhibition enhanced antigen specific responses as assayed by interferon- γ production, augmented leukocyte infiltration into the vaccine site, and induced pro-inflammatory cytokine/chemokine production. In the canine spontaneous gliomas, local injection of a canine CD200-directed peptide before delivery of an autologous tumor lysate vaccine prolonged survival relative to historical controls treated with autologous tumor lysate alone (median survivals of 12.7 months and 6.36 months, respectively). MRI analysis of the canine subjects treated with combination CD200 peptide and autologous vaccine revealed increased T2 hyperintensity in the region of the residual tumor, suggesting CD200 inhibition enhanced an anti-tumoral immune response.

Conclusions: These results support CD200 inhibition as a glioblastoma target. Efforts are underway to initiate the first-in-human trial with focus on combining anti-CD200 peptides and autologous tumor vaccination.

205. Targeted Ultra-Small Nanoparticles as a Multi-Modal Platform for Enhanced Drug Delivery to Primary and Metastatic Brain Tumors

[American Brain Tumor Association Young Investigator Award](#)

Rupa Juthani, MD (New York, NY); Brian Madajewski, PhD; Li Zhang, MD; Yoo Barney, PhD; Pei-Ming Chen, PhD; Feng Chen, PhD; Kai Ma, PhD; Michael Overholtzer, PhD; Jason Huse, MD, PhD; Ulrich Weisner, PhD; Michelle Bradbury, MD, PhD; Cameron Brennan, MD

Introduction: Despite breakthroughs in the treatment of solid tumor malignancies, treatment of malignant brain tumors remains stagnant due to variable blood brain barrier (BBB) accumulation, diffusion, and retention (ADR). This study investigates C'dots as a novel vehicle for augmenting CNS drug delivery.

Methods: Ultra-small silica nanoparticles containing Cy5 fluorescent dye (C'dots) were radiolabeled with ^{124}I and conjugated to analogs of the Src inhibitor Dasatinib (Das-NDC) or the EGFR inhibitor gefitinib (Gef-NDC); C'dots were further modified with integrin binding peptide RGD (cRGDY-C'dot) or inert peptide RAD (cRAD-C'dot) for intracranial targeting. Using the RCAS-tv-a murine model of glioblastoma, brain tumor bearing mice (mGBMs) were generated. mGBMs were treated with $45\mu\text{M}$ Das-NDC(^{124}I -cRAD/cRGD-Das-NDC) i.v. and sacrificed at 3 and 96 hours, with concurrent intravital injections of 70kDa FITC-Dextran as a map of BBB breakdown 3 hours prior to sacrifice (PTS), and the nuclear stain Hoechst PTS. Frozen tumor sections were assessed via autoradiography, fluorescence microscopy, and p-S6RP IHC, with quantitative analysis of signal intensities. Mice bearing ECLC26 derived NSCLC flank tumors were treated with daily saline P.O., daily free gefitinib P.O. (150mg/kg), or $15\mu\text{M}$ Gef-NDC i.v. every 3 days and measured daily until tumors exceeded 1.5cm. pEGFR inhibition was evaluated in tumors and in ear clippings as a surrogate for systemic effects.

Results: Integrin targeted cRGD-Das-NDCs demonstrated significantly increased ADR compared to RAD controls, and achieved target inhibition in all treated mGBM tumors. Intermittent dosing of Gef-NDC achieved robust tumor control and survival comparable to daily free gefitinib, with four orders of magnitude reduction in total drug dosing and lack of off-target inhibition.

Conclusion: C'dots present a viable and attractive platform for CNS drug delivery, with a potential to increase therapeutic index while conferring diagnostic PET and intraoperative fluorescence capabilities. ^{89}Zr -RGD-C'dots are concurrently being evaluated in a first-in-human trial of patients with malignant brain tumors.

206. Anti-PD-L1 Immunotherapy Enhances Radiation-induced Abscopal Response in Glioblastoma

[Ronald L. Bittner Award on Brain Tumor Research](#)

Chibawanye Ene, MD, PhD (Seattle, WA); Shannon Kreuser; Miyeon Jung; Ian Parney; Courtney Crane; Eric Holland

Introduction: Immunotherapy for glioblastoma have been largely unsuccessful, in part, because molecular heterogeneity drives selective elimination of only a subset of tumor cells. Therefore, therapeutic success in patients will require achieving an 'abscopal effect' where following focused radiation therapy, non-targeted tumor cells are attacked by the immune system. It remains unclear how glioblastoma respond to focused radiation in terms of failure location and whether immunotherapy could amplify the immune response to tumor outside the radiation field.

Methods: We evaluated patterns of treatment failure and outcomes in glioblastoma patients receiving stereotactic radiosurgery (SRS; N=47). To optimize the abscopal effect, we developed a genetically-engineered mouse model of bilateral glioblastoma. Here, one side of the mouse brain has a tumor treated by focal radiation and the contralateral untreated tumor is used as a readout of abscopal therapeutic efficacy following anti-PD-L1 immunotherapy.

Results: In glioblastoma patients receiving SRS, increasing age (>60 years) as associated with more 'out of field' treatment failure (P=0.036) and poor survival (P=0.001). In mice, we find that focal radiation of one tumor combined with anti-PD-L1 immunotherapy induced an immunological response against tumor cells outside the radiation field and enhanced survival (P<0.05). Significant macrophage and T-cell infiltration occurred in mesenchymal subtype-like tumors (N=6-8 mice per group, P<0.01). In proneural subtype-like tumors, macrophage infiltration alone was associated with 'out of field' tumor regression (N=8 mice per group, P<0.05). In-vitro, treatment of mouse macrophages with anti-PD-L1 antibodies induced significant gene expression changes and enhanced phagocytosis in an ERK-dependent fashion. All 3 commercially available human anti-PD-L1 antibodies also induced ERK signaling with varying efficacies.

Conclusions: Focal radiation combined with anti-PD-L1 therapy induces an immunological response to un-irradiated glioblastoma. We are currently optimizing other treatment combinations that could also be readily assessed in phase I human clinical trials.

207. Surgically Targeted Radiation Therapy: A Prospective Trial in 79 Recurrent, Previously Irradiated Intracranial Neoplasms

Rosenblum-Mahaley Clinical Research Award

Peter Nakaji, MD, FAANS (Phoenix, AZ); Emad Youssef, MD; Christopher Dardis, MD; Kris Smith, MD; Dilini Pinnaduwa, PhD; David Brachman, MD

Introduction: Resection alone is typically insufficient for recurrent previously irradiated intracranial neoplasms and repeat adjuvant external beam radiation treatment (EBRT) is often contraindicated. For these reasons we prospectively evaluated the combination of maximum safe resection (R) and surgically guided collagen tile brachytherapy (TBT) in this cohort of patients.

Methods: From 2/13 to 2/18 recurrent previously irradiated intracranial neoplasms were treated on a single arm, multi-histology study (ClinicalTrials.gov, NCT#03088579). At resection completion biocompatible collagen tiles imbedded with Cs 131 sources were permanently implanted in the operative bed under surgical guidance. The device offset sources from brain surface and delivered 60-80 Gy 5 mm deep to the operative bed. No additional local therapy was given without progression.

Results: 79 recurrent tumors in 74 patients were treated: 40 high grade gliomas (HGG) (10 grade 3, 30 grade 4), 23 meningiomas (1 grade 1, 20 grade 2, 2 grade 3), 12 metastases, and 4 other. Average prior same site surgeries were 2 (range 0-4); median prior EBRT dose 70 Gy. Median age 61 years; 31 females/43 males. Average implantation time was 5 minutes. At median follow-up of 13.4 months (range 1-54.6 mo.), median treatment site local control (LC) was 12 months for HGG, 48.5 months for meningioma, and median time to LC time has not been reached for metastasis. Median overall survival (OS) was 12.0 months for HGG, 49.2 months for meningioma, and 12 months for brain metastasis. Adverse surgical events were wound infection in 2/79 (2.5%), dural closure breakdown in 2/79 (2.5%), and procedure related hematoma in 1/79 (1.3%). Symptomatic radiation brain changes occurred in 6/79 (7.6%) cases, all treated medically.

Conclusion: Surgically targeted tile brachytherapy exhibits good LC and OS with complication rates comparable to existing treatments. This treatment could expand the therapeutic options for this difficult cohort of patients.

208. Modulation of temozolomide dose differentially affects T cell response to immune checkpoint inhibition

Preuss Research Award

Maryam Rahman, MD, FAANS (Gainesville, FL); Aida Karachi, DVM; Changlin Yang, MD, PhD; Farhad Dastmalchi, DVM; Elias Sayour, MD, PhD; Jianping Huang, MD, PhD; Duane Mitchell, MD, PhD

Introduction: Temozolomide has been shown to have both synergistic and negative effects on immune response to different immunotherapy treatment platforms. Therefore, we aimed to determine the immune modulatory effects of temozolomide that would impact response to immune checkpoint inhibition in the treatment of experimental glioblastoma (GBM).

Methods: Immune function and anti-tumor efficacy of immune checkpoint inhibition were tested after treatment with metronomic dose (MD) temozolomide (25mg/kg x 10 days) or standard dose (SD) temozolomide (50 mg/kg x 5 days) in a GL261 and KR158 murine glioma model.

Results: SD temozolomide treatment resulted in an upregulation of markers of T cell exhaustion such as LAG-3 and TIM-3 in lymphocytes which was not seen with MD temozolomide. When temozolomide treatment was combined with PD-1 antibody therapy, MD temozolomide / PD-1 antibody group demonstrated a decrease in exhaustion markers in tumor infiltrating lymphocytes (TILs) that was not observed in the SD temozolomide /PD-1 antibody group. RNA sequencing demonstrated an immune exhaustion phenotype in the intratumoral microenvironment in animals treated with SD TMZ/PD-1 antibody compared to animals treated with MD TMZ/PD-1 antibody. The survival advantage of PD-1 antibody therapy in a murine syngeneic intracranial glioma model was abrogated by adding SD temozolomide to treatment. However, when MD temozolomide was added to PD-1 inhibition it preserved the survival benefit that was seen by PD-1 antibody therapy alone.

Conclusion: The peripheral and intratumoral immune microenvironments are distinctively affected by dose modulation of temozolomide impacting response to immune checkpoint inhibition in GBM. These results demonstrate the importance of thoughtfully modulating host immunity with chemotherapy when combining with immunotherapy.

209. Single Cell Sequencing Identifies Cellular Heterogeneity in Human Microglia

Adam M Young (Cambridge, United Kingdom); Fiona Calvert; Natsuhiko Kumasaka; Andrew Knights; Natalia Murphy; Christopher McMurran; Michael Segel; Peter Hutchinson; Robin Franklin; Daniel Gaffney

Introduction: Microglia the resident immune cells of the brain, rapidly change state in response to their environment. Through development they conform to a number of phenotypes that support homeostasis however, in animal models these are lost with ageing and these cells ultimately support immune function in adults. The study of live human tissue is limited. Here in we present the most comprehensive analysis of human microglia at the single cell level.

Methods: We analysed the RNA expression profiles of over 10,000 individual microglia from 124 patients between 18-87 years of age. Samples were obtained from normal cortex, removed from the surgical tract during a surgical procedure where clinically indicated. Expression quantitative trait locus (QTL) mapping was performed to identify common genetic variants that alter gene expression in primary human microglia and compared available genome wide association studies (GWAS) of neurodegenerative disorders to identify if common variants in microglia were driving neurological disease.

Results: We uncovered seven transcriptionally distinct microglia substates, and characterised how these expression profiles changed with age and with patient type. We found 33 eQTLs that strongly colocalised known neurological disease risk loci.

Conclusion: Our novel and extensive analysis of human microglia has demonstrated for the first time, unique microglia signatures that can be used to better understand microglia function and provides the opportunity to manipulate specific subpopulations in health and disease.

210. Targeting MGMT promoter unmethylated glioblastomas through microRNA delivery

Clark C. Chen, MD, PhD, FAANS (Minneapolis, MN); Valya Ramakirshnan, PhD; Beibei Xu, PhD; Sanjay Dhawan; Jun Ma, MD; Clark Chen, MD, PhD

Introduction: Methyl-Guanine Methyl Transferase (MGMT) promoter unmethylated glioblastomas are intrinsically refractory to concurrent radiation-temozolomide(TMZ) treatment and remain a therapeutic challenge in neuro-oncology. Here we show that miR-603 regulate radiation and TMZ resistance by simultaneously down regulating MGMT expression and suppressing the stem cell state through inhibition of IGF signaling.

Methods: Analysis of clinical glioblastoma specimens, in vitro and in vivo glioblastoma models, immuno-florescent and Western-blot analysis

Results: Orthogonal profiling of miR-603 targets revealed genes which are key components of the Insulin-like Growth Factor (IGF) signaling (IGF1, IGF1R, and IGFBP5), a pathway critical for maintaining the stem-cell state and radiation resistance in glioblastoma as well as MGMT. miR-603 mimic transfection into glioblastoma cells suppressed the expression of the IGF genes as well as MGMT, while miR-603 inhibitor transfection displayed opposite effects. miRNA affinity pull-down and luciferase reporter assay confirmed miR-603 binding to 3' UTR of IGF1, IGF1R, IGFBP5 and MGMT mRNA. Phenotypically, miR-603 suppressed glioblastoma expression of stem-cell markers (SOX2, Musashi, and Nestin), tumorigenicity, as well as radiation resistance. These effects were abolished by exogenous expression or addition of IGF1, suggesting the existence of a miR-603-IGF1 axis that regulate glioblastoma radiation resistance through modulating the transition between stem-cell and non-stem-cell state. In clinical glioblastoma specimens, low expression of miR-603 was associated with poor 6-months progression free survival in patients with MGMT promoter unmethylated glioblastomas. miR-603 injection suppressed MGMT expression and the stem-cell state in mice bearing MGMT promoter unmethylated glioblastomas. Impressively, combination of miR-603 and temozolomide led to cures in <90% of mice bearing MGMT promoter unmethylated glioblastomas.

Conclusion: Our results suggest miR-603 suppresses DNA repair and stem-cell state and plays key roles in glioblastoma therapeutic resistance. As such, miR-603 in combination with temozolomide is a promising therapy for MGMT promoter unmethylated glioblastomas.

211. MicroRNA Nanocells Overcome Therapeutic Resistance in Glioblastoma

Muhammad Babar Khan (Manhasset, NY); Rosamaria Ruggieri, PhD; Nhan Tran, PhD; Jann Sarkaria, MD; Jennifer MacDiarmid, PhD; Himanshu Brahmabhatt, PhD; John Boockvar, MD; Marc Symons, PhD

Introduction: Therapeutic resistance stemming from the presence of multiple cellular genotypes, phenotypes and epigenetic states within the same tumor is a significant impediment towards development of effective therapeutics for

Glioblastoma (GBM). MicroRNAs simultaneously modulate the expression of multiple proteins, potentially counteracting resistance emanating from such intra-tumoral heterogeneity. Our in-silico analysis identified microRNA-34a as a unique microRNA which modulates multiple oncoproteins in GBM.

Methods: Therapeutic effects of microRNA-34a were studied in three primary patient-derived lines (GBM 6, GBM118 and GBM 126, respectively belonging to classical, mesenchymal and proneural subtypes), four established cell lines (T98G, U251, A172, LN229) and two cell lines with acquired resistance to temozolomide (A172-TR, LN229-TR) in vitro. An orthotopic nude mouse model was used for in vivo studies. Nanocells (400 nm diameter) were derived from genetically modified bacteria, provided with a bispecific antibody targeting EGFR and loaded with microRNA-34a. Nanocells were injected intravenously while temozolomide was administered by oral gavage. Treatment response was quantified by measuring tumor growth (qBLI) and animal survival.

Results: GBM cell lines showed variable responses to temozolomide but microRNA 34a inhibited proliferation in all cell lines. Furthermore, microRNA 34a also sensitized multiple tested cell lines to temozolomide (combination index < 0.6 , $p=.03$) and radiation treatment (dose enhancement factor 1.7-2.2, $p=0.02$). PCR arrays confirmed downregulation of multiple therapeutic resistance proteins (shared and unique to different cell lines), and we further validated the direct downregulation of cMET and Bcl-2 protein as a major contributor to therapeutic sensitization. Importantly, we successfully delivered microRNA-34a to orthotopic implanted tumors after systemic intravenous administration and observed significant reduction in tumor growth ($p=0.021$), increased survival ($p<0.001$) with microRNA-34a monotherapy and synergy in combination with temozolomide.

Conclusion: microRNA-34a nanocell therapy has shown promising preclinical data and we are developing this technology for phase I clinical trials for GBM patients.

212. Circulating Tumor Cell Isolation and Analysis Reveals LDHB, NXPH1, and IMMP2L as Genes Associated with Brain Metastasis

Marcus Zachariah, MD (Boston, MA); Richard Ebright; Ben Wittner, PhD; Kira Niederhoffer; John Milner; Brian Nahed, MD; David Ting, MD, PhD; Shyamala Maheswaran, PhD; Daniel Haber, MD, PhD

Introduction: Brain metastasis represents a growing clinical problem. The number of cases of brain metastasis reaching medical attention has nearly doubled over a span of roughly twenty years, with a current estimated cumulative incidence of 10-15% of cancer patients. Recent development of techniques to isolate and study circulating tumor cells (CTCs) provides an unprecedented opportunity to study cancer cells in the act of metastasis.

Methods: Using the CTC iChip, a technology that combines microfluidics, magnetophoresis, and inertial focusing, we isolated circulating tumor cells from the blood of seven patients with widely metastatic breast cancer. These circulating tumor cells were cultured and then engineered to overexpress firefly luciferase and green fluorescent protein.

Subsequently, the cells were stereotactically injected into the right frontal lobe of immunocompromised mice.

Results: CTC lines from all seven patients formed brain tumors after stereotactic injection. Samples from 2/7 patients formed rapidly growing brain tumors that killed 100% of injected mice within 6 weeks. Samples from 2/7 patients form tumors that grew at an intermediate rate, and the remainder formed slowly growing tumors. In all cases, CTC lines formed parenchymal tumors histologically similar to human brain metastases. Samples derived from patients who themselves suffered from brain metastases grew more rapidly after injection into mouse brain. RNA seq was performed and strong growing CTC lines were compared to weak growing CTC lines. LDHB emerged as a gene whose transcription was highly upregulated in strong growing CTC lines. In another experiment, CTCs were isolated directly from widely metastatic breast cancer patients with and without brain metastases. RNA seq was performed directly after CTC isolation. NXPH1 and IMMP2L emerged as genes whose upregulation is associated with brain metastasis.

Conclusion: Analysis of circulating tumor cells reveal LDHB, NXPH1, and IMMP2L as genes associated with brain metastasis.

213. Volumetric Growth Rates of Untreated Vestibular Schwannomas

Zane S. Schnurman, MD (New York, NY); Aya Nakamura, MD; Michelle McQuinn, BA; John Golfinos, MD; Douglas Kondziolka

Introduction: There remains a large discrepancy in vestibular schwannoma (VS) growth expectations among surgeons. These expectations impact clinical decisions, especially concerning intervening or observing. Previous studies of VS natural growth remain limited, mostly confined to linear measurements, often without high resolution, thin-sequence imaging. This study comprehensively assessed tumor growth rates using volumetric measurements.

Methods: 212 treatment-naïve patients diagnosed with unilateral VS between 2012 and 2018 were evaluated. A total of

699 MRIs were assessed, with a range of 2 to 11 MRIs per patient. All MRIs preceded any intervention, with patients subsequently being observed through completion of data analysis (36%) or treated with stereotactic radiosurgery (32%) or microsurgical resection (32%). Tumor volume was measured by summing the products of tumor area outlined by hand in each slice and slice thickness (99% of scans were 1-mm slice thickness or less). A multilevel model was used to assess mean volume change over time. Each tumor was categorized as growing (growth rate >20% per year), fast growing (>100% per year), stable (between -20% and 20% per year), and shrinking (< -20% per year).

Results: The mean VS volumetric growth rate was 33.5% per year (95% CI 26.9% - 40.5%, $p < 0.001$). When assessing the frequencies of individual tumor annual growth rates, 66% demonstrated growth (with 30% fast growing), 33% were stable, and 1% exhibited shrinking. Larger tumors were associated with increased absolute growth, but there was no relationship between tumor size and proportional growth rate.

Conclusion: This study comprehensively assessed VS volumetric growth rates using high-resolution imaging. About one third of the VSs studied remained stable while two thirds exhibited growth (with one third demonstrating a growth rate of more than 100% per year). These findings may inform clinical decisions and contribute to a consensus understanding of tumor behavior.

214. ZEB1-Driven Mesenchymal Transition at the Single Cell Level Promotes Progression during Bevacizumab Treatment of Glioblastoma in A Targetable Manner

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Introduction: Bevacizumab treatment of glioblastoma is limited by transient responses and acquired invasive resistance. We identified biomarkers of therapeutic window closure and upstream regulators whose targeting could prolong the treatment window.

Methods: Using microarrays, we transcriptionally profiled paired patient specimens before and after bevacizumab-resistance and two xenograft models of bevacizumab-resistance. Invasion was assessed using bioengineered 3D models of perivascular and parenchymal tumor invasion. Stem cell enrichment was analyzed by functional stem cell assays. Seahorse extracellular flux analyzer assays were performed for metabolic studies.

CRISPR/Cas9 and honokiol, a natural phenolic compound, were used to target ZEB1 in bevacizumab-resistant cells.

Results: Despite upregulated VEGF-independent pro-angiogenic genes, immunostaining revealed increased hypoxia and decreased vessel density in resistant-xenografts and patient specimens, suggesting tumor growth despite effective therapeutic devascularization. Microarrays revealed dominant mesenchymal subtype gene-signature expression across resistant-xenograft generations and in resistant PDXs, mimicking elevated mesenchymal gene signature that correlated with bevacizumab treatment duration in patient tumors. Single-cell sequencing of bevacizumab-resistant patient specimens revealed these mesenchymal changes, particularly YKL-40 and ZEB1 expression, to arise in early clones with fewer mutations. Serum YKL-40 was elevated in patients with bevacizumab-resistant vs. bevacizumab-naïve glioblastomas ($p < 0.01$). Patient tumor and xenograft microarray analysis revealed ZEB1 to be a potential regulator of this change, with ZEB1 increasing across xenograft generations ($P < 0.001$). Xenograft-derived resistant GBM cells exhibited increased perivascular and parenchymal invasion ($p < 0.001$ and $p < 0.05$), glioma-stem cell enrichment ($p < 0.001$), and increased glycolysis ($p < 0.001$). CRISPR targeting and honokiol treatment of ZEB1 reversed these changes defining resistance with significantly more cell death in bevacizumab-resistant versus bevacizumab-responsive cells in response to honokiol over 72 hours ($p = 0.03-0.001$).

Conclusion: We identified YKL-40 as a biomarker and ZEB1 as a targetable regulator of progression during bevacizumab treatment of glioblastoma. Applying these insights to the clinic could fulfill the promise of anti-angiogenic therapy.

215. MP-Pt(IV): Selective Mitochondrial chemotherapy that sensitizes Glioblastoma to the Stupp Protocol.

David S. Baskin, MD, FAANS, FACS (Houston, TX); David Baskin; Martyn Sharpe, PhD

Introduction: Monoamine oxidase B (MAOB) is highly elevated in glioma1 and converts methyl-tetrahydropyridine (MP-) substrates into the mitochondrially targeted methyl-pyridinium (P+), and can serve as the guidance system for selective mitochondrial chemotherapy.2,3. Our second-generation mitochondrial 'smart bomb', MP-Pt(IV), contains an unreactive 'warhead' that is converted into cis-platin by ascorbate. Glioma MAOB catalyzes the generation of P+-Pt(IV), in vitro and in vivo. Ascorbate reduces the Pt(IV) to cis-platin within mitochondria, damaging mtDNA and respiratory complexes. MP-Pt(IV) greatly improves outcome in intracranial glioma models, especially when coupled to temozolomide (TMZ) radiotherapy.

Methods: Specificity for MAOB was determined using the Amplex Red/HRP assay3. The Hoechst viability assay was used

for in vitro toxicity, and mitochondrial $\Delta\Psi$ was assayed using MitoTracker1. Oxidative stress was measured using MitoSox and H2DCF-AM1-4. Intracranial primary glioma chemoradiotherapy was performed as described previously⁴, and prior to TMZ/2Gy animals received MP-Pt(IV) or vehicle.

Results: Intra-mitochondrial cis-platin is generated from MP-Pt(IV) and levels are dependent on both MAOB activity and ascorbate levels. MP-Pt(IV) is a potent sensitizer of chemoradiotherapy. In mice with untreated xenografts, 50% mortality occurred on day 41 and maximal survival was 90 days. TMZ/2Gy (6-cycles) improved survival 2.6-fold, with 50% surviving 107 days and one mouse surviving to present (day 292). Treatment with MP-Pt(IV) sensitizes intracranial GBM to TMZ, to radiation and to chemoradiotherapy. 50% of animals treated with monotherapeutic MP-Pt(IV) are alive to present. MP-Pt(IV)/TMZ co-therapy provides 100% survival up to present. 66% of those treated with MP-Pt(IV)/TMZ/2Gy are still alive, as are 33% of those treated with MP-Pt(IV)/2Gy.

Conclusion: MP-Pt(IV) is highly effective as a monotherapy in intracranial GBM, and complements Stupp chemoradiotherapy.

References: 1) Sharpe & Baskin. *Oncotarget* 2016; 7:3379. 2) Sharpe, et al., *EBioMedicine* 2015; 2:1122. 3) Sharpe, et al., *ChemMedChem* 2015; 10:621. 4) Sharpe, et al., *Oncotarget* 2018; 9, 23923.

218. Deep-Learning Artificial Intelligence Model for Automated Detection of Cervical Spine Fracture on Computed Tomography (CT) Imaging

[Stewart B. Dunsker, MD Award](#)

Michael Zhang, MD (Stanford, CA); Lily Kim; Robin Cheong; Ben Cohen-Wang; Katie Shpanskaya; Jessica Wetstone; Nidhi Manoj; Pranav Rajpurkar; Kristen Yeom

Introduction: Cervical spine trauma accounts for over 1 million emergency department visits each year in the Northern America. Accurate and timely diagnosis is crucial as delay in intervention may lead to further injury and even paralysis or death. However, detection of cervical spine fractures on computed tomography (CT) scans may be challenging, especially for subtle fractures and adult patients with preexistent degenerative changes. Automated detection model can help clinicians make faster and better decisions in time-critical settings.

Methods: A total of 1347 CT scans obtained at our institution were divided into a training set (990 normal, 222 with fractures) and a validation set (98 normal, 37 with fractures). Manual annotation of all scans containing confirmed cervical fractures were performed by a board-certified neuroradiologist. For the model-building, ResNet-101, a 3D convolutional neural network, was used to extract fracture-related features from each image. With the Feature Pyramid Network architecture, predictions from each image were combined to make a prediction for the entire scan. Focal Loss function penalized high-confidence false predictions, helping the model focus on pertinent features and disregard easier negatives such as the background.

Results: Model performance was measured with Area Under the Receiver Operating Characteristic (AUROC) and Area Under Precision-Recall Curve (AUPRC) metrics, with the expert human annotation serving as the ground truth. Performance was assessed at both the image- (AUROC 0.87, AUPRC 0.52) and scan-level (AUROC 0.85, AUPRC 0.82). Examples of common errors included over-prediction of C2 fractures and under-prediction of fractures in less common locations.

Conclusion: We present the first deep-learning model trained end-to-end to automatically detect fractures in the cervical spine, validated with the largest collection of cervical spine CT scans to our knowledge. The promising performance of our model in predicting cervical fractures is suggestive of its utility in neurosurgical practices for improved diagnostic quality.

219. Annular Closure Reduces Recurrent Herniation and Reoperation in a High-Risk Population Following Lumbar Microdiscectomy: 3-year Data from a Multicenter, Prospective, Randomized Trial

Claudius Thome, MD, IFAANS (Innsbruck, Austria); Javier Fandino, MD; Peter Klassen, MD; Frederic Martens, MD; Annular Closure RCT Study Group

Introduction: Recurrent disc herniation and reoperation are a major concern following lumbar microdiscectomy associated with worse clinical outcomes and greater socioeconomic burden. Patients with large annular defects are known to be at high risk for reherniation. This study aimed at determining whether a bone-anchored annular closure device (ACD) in addition to lumbar microdiscectomy resulted in lower reherniation and reoperation rates plus increased overall success in these patients.

Methods: In this randomized, prospective, multicenter trial primary microdiscectomy patients at 21 sites were randomized

intraoperatively 1:1 to microdiscectomy alone (Control; n=278) or microdiscectomy supplemented with the ACD (n=272). Key inclusion criteria consisted of a minimum of 5mm posterior disc height and an intraoperatively measured annular defect width of 6-10mm. Kaplan-Meier survival analyses were used to evaluate freedom from symptomatic reherniation, reoperation, and severe adverse events (SAEs). Clinical overall success was defined post hoc as freedom from reherniation/reoperation, >15-point improvement in ODI, >20-point improvement in VAS, maintenance of neurological status and freedom from SAEs. Log-rank tests were used for group comparisons.

Results: At 3 years >80% of patients were available for follow-up. Symptomatic reherniations had occurred in 14.8% of the ACD group and 29.5% among Controls ($p<0.0001$). At least one reoperation, for any reason including device complications, was required in 11.0% and 19.3% of patients in the ACD and Control groups, respectively ($p=0.007$). Device- or procedure-related SAEs occurred in 10.0% of ACD patients and 19.3% of Controls ($p=0.002$). 69.9% of ACD patients demonstrated a successful outcome compared to only 55.7% of Controls ($p=0.003$).

Conclusion: The subpopulation of microdiscectomy patients with large annular defects is characterized by a very high risk for reherniation. Adding an ACD at the time of microdiscectomy in these patients significantly lowers the risk of symptomatic recurrence and reoperation plus improves overall clinical success through 3 years of follow-up.

220. Two-Level Cervical Disc Arthroplasty vs. Anterior Cervical Discectomy and Fusion: 10 Year Outcomes of a Prospective, Randomized IDE Clinical Trial

Todd Hopkins Lanman, MD, FAANS (Beverly Hills, CA); Matthew Gornet, MD; Randall Dryer, MD; J. Kenneth Burkus, MD; Scott Hodges, MD; Jeffrey McConnell, MD

Introduction: This paper reports the 10-year results of the Prestige LP FDA trial (clinicaltrials.gov: NCT00637156) comparing the safety and efficacy of Cervical Disc Arthroplasty and ACDF at two contiguous levels.

Methods: 397 patients with two-level radiculopathy and/or myelopathy between C3 and C7 were randomized and treated with investigational CDA (n=209) or control ACDF (n=188). The primary endpoint was Overall Success, a composite variable that included 4 criteria: 1) Neck Disability Index (NDI) improvement of ≥ 15 points, 2) maintenance/improvement in neurological status, 3) no serious adverse events, and 4) no additional surgery.

Results: Patient follow-up at 10 years was 86.0% for investigational and 84.9% for control patients. At 10 years postoperative, the rates of Overall Success, NDI Success and Neurological Success rates demonstrated statistical superiority for CDA over ACDF. At all postoperative time points, NDI, neck and arm pain, and SF-36 score improvements were statistically significant in both groups. NDI and neck pain score improvements achieved statistical superiority for CDA over ACDF at all time points from 2 to 10 years. Rates of serious AEs, serious AEs related to implant/procedure, and secondary surgeries at the index and adjacent levels were statistically lower for CDA than ACDF. The 10-year angular range of motion at the index levels increased by more than 2 degrees in 43.8%, was maintained within 2 degrees in 17.7%, and decreased by more than 2 degrees in 38.5% of CDA patients. The 10-year rates of heterotopic ossification were 20.5% and 19.9% for Grade III and 8.2% and 10.3% for Grade IV at the superior and inferior levels, respectively.

Conclusion: In appropriately selected patients, CDA with the Prestige LP Disc is at least as safe and effective as ACDF for symptomatic cervical DDD at 2 contiguous levels.

221. Awake Endoscopic TLIF vs. Conventional MIS-TLIF: Comparison in Clinically High-Risk Patients

Jang Yoon, MD (Miami, FL); John Paul Kolcun, BS; Michael Wang, MD

Introduction: Endoscopic transforaminal lumbar interbody fusion under conscious sedation (ENDO-TLIF) has been shown to reduce surgical morbidity while achieving clinical outcomes and arthrodesis rates comparable to those of conventional minimally invasive TLIF (MIS-TLIF). In patients with advanced age, obesity, or significant medical co-morbidities, reducing surgical burden and hastening postoperative recovery may have a greater clinical impact than in average patients. We therefore sought to confirm the advantages of the ENDO-TLIF in clinically high-risk patients.

Methods: A consecutive series of 132 patients underwent ENDO-TLIF. A matched cohort of 66 patients underwent conventional MIS-TLIF by the same surgeon. Medical co-morbidity was assessed by the Charlson Co-morbidity Index (CCI). Patients were stratified by advanced age (≥ 70 years), obesity ($\text{BMI} \geq 30$), and significant co-morbidity ($\text{CCI} > 2$). Acute surgical outcomes, including estimated blood loss (EBL), operating time (OR time), and hospital length of stay (LOS), were compared between ENDO-TLIF and MIS-TLIF cohorts.

Results: There were no significant differences in baseline characteristics between cohorts. In patients of advanced age, ENDO-TLIF was associated with reduced EBL (77.0 ± 89.3 vs. 176.9 ± 107.0 mL, $p = 0.001$), OR time (88.6 ± 22.8 vs. 157.4 ± 39.2 min, $p < 0.001$), and LOS (1.7 ± 1.3 vs. 4.4 ± 2.7 days, $p < 0.001$). These effects held in obese patients, with

reduced EBL (88.4 ± 100.9 vs. 148.9 ± 94.0 mL, $p = 0.010$), OR time (82.7 ± 23.3 vs. 182.2 ± 52.1 min, $p < 0.001$), and LOS (1.6 ± 1.0 vs. 3.9 ± 2.4 days, $p < 0.001$), as well as patients with significant co-morbidity, with reduced EBL (77.1 ± 100.4 vs. 131.2 ± 92.9 , $p = 0.03$), OR time (90.1 ± 30.9 vs. 156.9 ± 46.5 , $p = 0.004$), and LOS (1.6 ± 1.1 vs. 3.9 ± 2.7 , $p = 0.002$).

Conclusion: ENDO-TLIF is associated with superior acute surgical outcomes as compared to conventional MIS-TLIF in clinically high-risk patients. Future studies are required to demonstrate generalizability of our results and sustainable clinical and radiographic outcomes over time.

222. Spinal Laser Interstitial Thermal Therapy: Outcomes and Lessons Learned from the First 100 Patients

Brian D. Silber Award

Rafael A. Vega, MD, PhD (Houston, TX); Dhiego de Almedia Bastos, MD; Amol Ghia, MD; Jing Li, MD; Andrew Bishop, MD; Debra Yeboa, MD; Behrang Amini, MD; Ganesh Rao, MD; Laurence Rhines, MD; Claudio Tatsui, MD

Introduction: Spinal laser interstitial thermal therapy (sLITT) is a novel minimally invasive therapeutic modality for the treatment of metastatic epidural spinal cord compression (ESCC). This approach is best used in patients who are poor candidates for larger-scale oncologic spinal surgery and can act synergistically with spinal stereotactic radiosurgery to maximize local control and palliate pain.

Methods: The authors retrospectively reviewed a consecutive series of patients, from 2013 to 2018, with ESCC who were considered to be poor surgical candidates and instead were treated with MRI-guided sLITT. Demographic data, Spine Instability Neoplastic Scale score, degree of epidural compression before and after the procedure, length of hospital stay, progression, need for stabilization, and time to return to oncological treatment were analyzed.

Results: A total of 100 patients with ESCC were treated since the inception of sLITT in 2013 at MD Anderson. Treated levels included 5 cervical, 8 lumbar, and 87 thoracic cases. The majority of preoperative ESCC were high grade with effacement of CSF around the spinal cord. The most common tumor histology was renal cell carcinoma ($n=40$), followed by non-small cell lung carcinoma ($n=10$), hepatocellular carcinoma ($n=6$), and 44 other less common metastasis. Systemic therapy was not interrupted to perform the procedure in any of the cases. Local control was achieved in 83 cases and 17 patients showed eventual progression at follow up. Levels containing motor nerve roots were avoided due to risk of nerve root palsy, which occurred in 3 of the early cases in the lumbar spine.

Conclusions: Clinical data from the first 100 patients demonstrate that sLITT is a safe and viable ablative treatment options for patients with ESCC, and may be considered an alternative to separation surgery for carefully selected patients with lesions in the thoracic spine.

223. Improvement in Sexual Function Following Degenerative Lumbar Spondylolisthesis Surgery

Andrew K. Chan, MD (San Francisco, CA); Praveen Mummaneni, MD; Leslie Robinson; Kai-Ming Fu, MD, PhD; Paul Park, MD; Mohamad Bydon, MD; Mark Shaffrey, MD; Michael Wang, MD; Mohammed Alvi; Jian Guan, MD; Erica Bisson, MD, MPH

Introduction: There is a paucity of investigation on the impact of spondylolisthesis surgery on sexual function. We investigated factors predictive of improved sexual function following surgery.

Methods: This was an analysis of the prospective Quality Outcomes Database registry of surgery for grade 1 degenerative lumbar spondylolisthesis. 221 patients were included who were sexually active and had both baseline and two-year sexual function follow up. Data was collected at baseline and two-year follow up. Sexual function was assessed by Oswestry Disability Index question, "With regards to pain, how would you say your sex life is?" The six, ordinal responses ranged from Normal and causes no extra pain (no dysfunction) to Not sexually active because of pain (most dysfunction). Univariate and multivariate analyses were conducted.

Results: At baseline, 179 (81.0%) patients had sexual dysfunction. Of those with baseline dysfunction, 126 (70.4%) improved in sexual function at two years. Of the 42 patients with no baseline dysfunction, 12 (28.6%) experienced some dysfunction post-operatively. Those receiving fusions ($n=200$) had greater baseline sexual dysfunction (83.5% vs. 57.1% with dysfunction, $p=0.008$) and two-year dysfunction (51.0% vs. 23.8% with dysfunction, $p=0.02$) compared to those receiving decompressions only ($n=21$). Overall, patients improved significantly in sexual function following surgery (baseline 19% vs. post-op 51.6% with no dysfunction, $p<0.001$). Both those receiving fusions (baseline 16.5% vs. post-op 49% with no dysfunction, $p=0.008$) and decompressions only (baseline 42.9% vs. post-op 76.2% with no dysfunction, $p=0.03$) improved significantly at 24 months. In multivariate analyses, leg pain predominant presentation ($OR=7.6$, $95\%CI[1.6-59.7]$, $p=0.02$; reference=back pain), baseline NRS back pain ($OR=1.3$, $95\%CI[1.04-1.6]$, $p=0.02$), and surgeries utilizing MIS techniques ($OR=3.9$, $95\%CI[1.6-10.1]$, $p=0.003$) were associated with improved sexual

function at two-year follow up.

Conclusion: A majority of patients presenting with sexual dysfunction improved following surgery. Both fusion and decompression patients significantly improved their sexual function with spondylolisthesis surgery. Leg pain predominant presentation, magnitude of baseline back pain, and MIS were significant predictors of improved sexual function following spondylolisthesis surgery.

224. Surgery for Potentially Unstable Spinal Metastasis Reduces 90-Day-Admissions

Shashank Gandhi, MD (Manhasset, NY); Shashank Gandhi, MD; Kevin Shah, MD; Daniel Schneider, MD; Maged Ghaly, MD; Ahmad Latefi, DO

Introduction: The Spinal Instability Neoplastic Score (SINS) helps assess the need for surgery for spinal metastatic disease; however, for potentially unstable lesions (SINS 7-12) the benefit is unclear. The role of surgery is palliative to improve quality of life as prognosis is dictated by systemic disease. Therefore, allowing patients to return to daily life while limiting hospitalization is paramount. This study assesses the role of surgery in reducing 90-day-admission for potentially unstable spinal lesions.

Methods: Patients with lesions SINS 7-12 treated for spinal metastatic disease from 2010-2015 retrospectively assessed. Patients were grouped as no surgery or surgery prior to radiotherapy. 90-day-admissions rates after radiotherapy was assessed in each group, along with the impact of the following factors: high grade epidural spinal cord compression (ESCC), radiosensitivity, local control, development of fractures, and hypofractionation.

Results: 61 patients with SINS 7-12 were treated: 44 in no surgery and 17 in surgery prior to radiotherapy. 90-day-admission rates were higher in the nonsurgical group (54.5% vs. 5.9%, $p=0.001$). Spine-pathology related admissions were 18.2% nonsurgical vs. 0% surgical groups. The 1 surgical admission was for ileus. Counterintuitively, ESCC was associated with lower admission (13.3% vs. 50.0%, $p=0.012$); however, is explained as high ESCC correlated to greater likelihood for surgery (58.9% vs. 11.4%, $p<0.001$). Local control did not impact 90-day-admission (48.6% vs. 29.2%, $p=0.131$), nor did tumor radiosensitivity (45.5% vs. 35.8%, $p=0.441$). The development of fractures had higher admission (100% vs 37.9%, $p=0.033$). When controlling for above factors only surgery and development of fractures correlated to reduced 90-day-admission ($p=0.019$ and $p=0.040$). The nonsurgical group had greater fractures (6.82% vs. 0%).

Conclusions: Surgery for potentially unstable metastasis reduces 90-day-admission rates. Development of fractures increases 90-day-admission rates, likely due to pain. Local control does not reduce admission, showing that treatment should focus on quality of life rather than solely tumor control.

225. Use of Polyetheretherketone Interbody Devices for Multi-Level Anterior Cervical Discectomy and Fusion Results in a Three-Fold Higher Rate of Pseudarthrosis Compared to Structural Allograft

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Introduction: Common interbody graft options for anterior cervical discectomy and fusion (ACDF) include: 1) structural allograft and 2) polyetheretherketone (PEEK). PEEK has gained popularity due to its radiolucency and elastic modulus similar to bone. Use of PEEK devices results in higher billing than allograft, which may drive selection. A previous study at our institution found a five-fold higher rate of pseudarthrosis with the use of PEEK devices as opposed to structural allograft in single-level ACDF. Here we follow up those findings with a report on the occurrence of pseudarthrosis of PEEK devices versus structural allograft in patients who underwent multi-level ACDF.

Methods: We retrospectively reviewed 62 consecutive patients who underwent a multi-level ACDF, with at least 1 year of radiographic follow-up. Age, sex, body mass index (BMI), tobacco use, pseudarthrosis, and re-operation rate for pseudarthrosis were collected. Data was analyzed with a Pearson's chi square test.

Results: Of 62 patients, 31 had PEEK implants, and 31 had structural allograft. There were no differences between age, sex, or BMI in the two groups. There were 20/31 (65%) patients with PEEK implants demonstrating radiographic evidence of pseudarthrosis, compared to 6/31 (19%) patients with structural allograft ($p < 0.001$, OR 7.58; CI: 2.39-24.06). Four patients with PEEK implants required re-operation for pseudarthrosis (13%), compared to 0 patients with allograft ($p = 0.014$). There was no difference in tobacco use between the PEEK and allograft groups ($p = 0.154$).

Conclusion: This study reinforces our previous findings on one-level ACDF outcomes, and suggests that the use of PEEK devices in multi-level ACDF also results in a high rate of radiographic pseudarthrosis and need for revision surgery. Surgeons should be aware of these results when deciding on interbody graft options, and reimbursement policies should reflect these discrepancies.

226. Effect of Cage Type on Immediate Post-operative Radiographic Outcomes in Single-level Minimally Invasive Transforaminal Lumbar Interbody Fusion (MI-TLIF)

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Introduction: The type of cage used in MI-TLIF can impact several goals of the procedure, including optimizing disc and foraminal height, interbody fusion, and sagittal balance.

Objective: To assess if cage type has an impact on immediate radiographic outcomes in single-level MI-TLIF.

Method: Segmental Lordosis(SL), Lumbar Lordosis(LL), Posterior Disc Height(PDH) were compared using lateral radiographs obtained pre- and post-operatively. Impact of demographic(age, sex, BMI), pre-operative radiographic(SL, LL, PDH) and operative factors(cage-type, cage-width, cage-position) on radiographic outcomes was assessed.

Results: Of the 154 patients included, 55 received a Static Oblique, 63 a Static Articulating, and 36 an Expandable Articulating cage. There was no significant difference in SL pre-($p=0.389$) or post-operatively($p=0.613$). A difference was seen in change in SL($p=0.023$), with the expandable articulating cage showing the greatest increase, and an improvement from pre- to post-operatively($p=0.033$). A significant difference was seen in change in LL($p=0.050$), with the static oblique and expandable articulating groups maintaining LL($p=0.238$ and $p=0.873$), but the static articulating group showing decrease in LL($p<0.0001$). There was a significant difference in PDH pre- and post-operatively ($p<0.0001$ and $p=0.045$). All three cages increased in PDH($p<0.0001$), with the expandable articulating cage showing the greatest increase ($p=0.009$). Regressions showed that pre-operative SL was the only significant predictor of post-operative SL($p<0.0001$; $R^2=0.418$) and change in SL($p<0.0001$; $R^2=0.247$); pre-operative LL of post-operative LL($p<0.0001$ $R^2=0.609$) and change in LL($p<0.0001$; $R^2=0.227$); and pre-operative PDH of post-operative PDH($p<0.0001$; $R^2=0.360$) and change in PDH($p<0.0001$; $R^2=0.299$). Cage-type, cage-position and cage-width were not significant predictors of radiographic parameters.

Conclusion: Pre-operative radiographic parameters were predictors of post-operative parameters. While the static cages maintained SL, the expandable cage increased SL. The expandable cage had the lowest pre-operative PDH, likely reflective of the expandable technology allowing for cage-insertion even in collapsed disc spaces. The expandable articulating cage demonstrated benefit in increasing SL, maintaining LL and causing the greatest increase in PDH.

227. Use of Artificial Intelligence to Improve Surgical Referrals in Degenerative Lumbar Spine Conditions

[Sanford J. Larson, MD, PhD Award](#)

Nathan Xie (Sydney, Australia); Peter Wilson; Rajesh Reddy

Introduction: The majority of referrals for degenerative lumbar spinal conditions do not lead to surgical intervention.

Stratifying referrals from primary care sources based on likeliness to proceed to surgery would not only expedite care for patients that may benefit from surgical intervention, but also allow non-operative treatments/strategies to be implemented for those who are unlikely to benefit. By identifying clinical and imaging factors associated with progression to surgery, we aimed to develop a Machine Learning model (a branch of Artificial Intelligence) able to calculate the probability that a patient would receive surgery based on these factors.

Methods: We identified 55 factors in the literature associated with surgical progression. All patients presenting with an elective lumbar spine complaint between 2013-2018 at a single Australian Tertiary Hospital ($n=326$) had their medical records reviewed, with data being collected for the potential predictive factors. An Artificial Neural Network (ANN) was constructed, with the outcome being progression to spinal surgery (Yes/No). To compare it with a traditional statistical model, a Logistic Regression (LR) model was created from the same data. These were evaluated on their accuracy, discrimination (Area under ROC Curve (AUC)), and calibration (Hosmer-Lemeshow test (HLT)).

Results: Ten clinical and imaging predictive variables were included as input in the final models. The ANN was able to predict surgical progression with 94.2% accuracy. It also exhibited excellent discriminative ability (AUC = 0.90), with good fit of the data (HLT<0.05). This was superior when compared to the LR model (Accuracy: 87.4%, AUC = 0.86, HLT <0.05).

Conclusion: Both the neural network and regression models predicted surgical progression with a high degree of accuracy. By demonstrating that the operating patterns of single centers can be predicted accurately, the potential for more appropriate/tailored referrals becomes possible, reducing wait-lists and increasing surgical conversion rates.

228. Intraoperative Mixed Reality Holographic Visualization during Spinal Fixation: Early Insights

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Introduction: As surgeons, we operate in a three-dimensional (3D) environment, yet our imaging information is presented in two dimensions. The use of augmented reality (AR) to overlay anatomical models in actual 3D space is an active frontier of cutting-edge innovation. Our team has been working to develop and employ a pipeline for intraoperative AR technology to visualize, interact with, and register holographic projections of patient anatomy during spinal fixation surgery. In this initial stage, we are evaluating clinical feasibility and accuracy of 3D holographic visualization.

Methods: Imaging-based 3D volumes can be generated by two approaches: surface rendering in which the model is derived from a semi-automatic segmentation process of tissue interfaces; or volume rendering where the entire imaging volume is rendered into a 3D model. Using intraoperative O-arm imaging, we used Microsoft HoloLens (Redmond, WA) to compare surface (5 patients) and volume (3 patients) rendering techniques to generate 3D holographic models of patient anatomy. We utilized a custom, radiopaque fiducial system to manually register the models onto the patients.

Results: Surface rendering enabled generation of low density, high fidelity 3D models of posterior bony elements from an intraoperative O-arm scan though required significant model generation times (38+/-11mins). Volume rendering generated rapid, high density, perfect fidelity 3D models (7+/-3mins). However, hologram stability was an issue with the high-density data from this latter approach. In one patient for each group, accuracy measurements were taken after manual registration. Surface rendering achieved a 0.7cm Euclidean distance error while volume rendering achieved 1.1-3.1cm error due to hologram instability and headset parameters.

Conclusion: Though still in early development, intraoperative AR presents a unique opportunity to enhance how surgeons interface with operative anatomy. We are iterating improvements in efficiency of holographic surface renderings, stability of volume renderings, and integrating automated registration to enable feasibility and industry-standard accuracy.

229. A Predictive Model and Nomogram for Predicting Return to Work at 3 Months After Cervical Spine Surgery: An Analysis from the Quality Outcome Database

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Introduction: Neck pain is one of the most common causes of work-loss due to disability. Due to recent changes in healthcare policies, return to work (RTW) has been increasingly prioritized by physicians and hospitals to optimize healthcare delivery. In this manuscript, we utilized a national spine registry to identify clinical factors associated with RTW at 3 months among patients undergoing a cervical spine surgery.

Methods: We queried the Quality-Outcomes-Database registry for preoperatively employed patients undergoing cervical spine surgery for degenerative spine disease. Multiple-imputations were used for missing values and multivariable (MV) logistic regression analysis was employed to identify factors associated with higher odds of returning to work. A nomogram was constructed using the results of the MV model.

Results: A total of 4689 patients were analyzed, of which 82.2 % (n=3854) returned to work at 3-months postoperatively. Among previously employed and working patients, 88.3% (n=3443) patients returned to work compared to 53.3% (n=411) among those who were employed but not working (p<.001). On MV-analysis we found that patients who were less likely to RTW were older (Age>56-65:OR 0.69, 95% CI= 0.57-0.85,p<0.001;>65: OR 0.65, 95%CI= 0.43-0.97,p=0.02), were employed but on leave (OR 0.24, 95%CI: 0.20-0.29,p<0.001), were employed part-time (OR0.56, 95% CI=0.42-0.76, p<0.001), had a heavy (OR 0.42, 95% CI: 0.32- 0.54,p<0.001) or medium (OR 0.59, 95% CI:0.46-0.76,p<0.001) intensity occupation, had worker's compensation (OR0.38, 95%CI:0.28-0.53,p<0.001), had a higher NDI score at baseline (OR 0.60, 95%CI:0.51-0.70,p=0.017), more likely to present with myelopathy (OR 0.52,95%CI:0.42-0.63,p< 0.001) and had more levels fused (3-5 levels:OR 0.46, 95%CI 0.35-0.61,p<0.001). We then constructed a nomogram to predict RTW which was found to have an area under the curve (AUC) of 0.812 and good validity.

Conclusion: Multiple factors are predictive of 3-month RTW following cervical spine surgery including active employment, low-intensity occupation, and non-worker's compensation status.

231. Assessing the Differences in Measurement of Degree of Spondylolisthesis between Supine MRI and Erect X-Ray: An Institutional Analysis of 255 Cases

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Introduction: Degenerative Spondylolisthesis(DS) is the displacement of one vertebral body over the adjacent one secondary to degenerative changes in the vertebral column. While standing and flexion extension X-Rays are preferred for determining listhesis and instability, MRI is often utilized to assess the compression of nerve root or spinal cord. In the present study, we sought to investigate the difference in radiographic measurements of spondylolisthesis between lateral standing X-rays and supine MRI.

Methods: We retrospectively reviewed the records and radiographic images of all cases with a confirmed diagnosis of spondylolisthesis undergoing an operation in 2016. Only those cases with available preoperative X-ray and MRI were selected for review. Primary variable of interest was the degree of slippage as per the Meyerding method, measured independently by 2 reviewers on lateral X-ray and sagittal MRI sections. Agreement between the two reviewers was assessed using the two-way intraclass correlation coefficient (ICC) for slippage percentage and Cohen's Kappa for grade. Agreement of Meyerding grade between the two imaging techniques was assessed using Cohen's Kappa while the slip percentage measured for each technique was compared using a Bland-Altman(BA) plot, mean difference(MD) and one-way ICC.

Results: A total of 255 cases were considered eligible for analysis. ICC between the two reviewers was found to be 0.75(95%CI=0.64-0.83,p<0.001) for X-ray and 0.76(95%CI=0.66-0.83,p<0.001) for MRI showing good agreement. Agreement between X-ray and MRI for grading of spondylolisthesis was found to be poor(Kappa=0.32,p<0.001). BA plot between X-ray and MRI measurements revealed a MD of 4.4%(95% limits of agreement:-10.3%,19.3%) with 5.16% observations outside the limits of agreement and one-way ICC of 0.35 showing poor agreement.

Conclusion: Our results demonstrate the discrepancy of spondylolisthesis grade measurements between weight-bearing X-ray and non-weight-bearing MRI. Careful evaluation of both imaging technique is warranted to determine the final severity of pathology and tailoring of management plan.

232. Long-term Motor Recovery and Functional Outcomes in Patients with Traumatic Central Cord Syndrome

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Introduction: Traumatic central cord syndrome (TCCS) is a clinical diagnosis often described by disproportionately greater upper than lower limb weakness following acute traumatic cervical spinal cord injury (SCI). TCCS has a bimodal distribution and typically occurs in the elderly following low-energy hyperextension neck injuries while it occurs in the younger population as following high-energy neck injuries. Given the increasing aging population, TCCS is expected to become the most common form of traumatic SCI and therefore optimal management strategies for TCCS is imperative. This study aims to elucidate patient, injury, and treatment characteristics associated with long-term motor recovery, functional outcomes, and quality of life in TCCS.

Methods: Three multicenter, international databases including NACTN, NASCIS, and STASCIS were used. Inclusion criteria consisted of patients' 16 years with a diagnosis of TCCS. Advanced regression techniques were applied to evaluate possible predictors of outcomes, including demographics, neurological status, injury characteristics, and management strategies. Functional motor outcomes were measured by the functional independence measure (FIM) scale.

Results: Baseline characteristics assessed included demographics, neurological status, and injury characteristics for the 170 patients meeting inclusion criteria. In the FIM motor-subscore, only 11% of patients were functionally independent. Univariate analysis showed significant improvement in FIM motor-subscore at one-year for initial ASIA motor score (AMS), presence of fracture, time to surgery, initial AIS grade, and Glasgow Coma Scale (GCS) score. A multivariate model including age, baseline AMS, time to surgery, and presence of fracture showed a significant effect of baseline AMS and time to surgery on improvement in functional outcomes.

Conclusion: According to our knowledge, this is the largest study to date suggesting that earlier surgery is correlated with better functional motor outcomes and should be encouraged in the management of TCCS.

233. Predictors of the Best Outcomes Following Minimally Invasive Surgery for Grade 1 Lumbar Spondylolisthesis

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Introduction: The factors driving the best outcomes following minimally invasive surgery (MIS) for grade 1 lumbar spondylolisthesis are not clearly elucidated. This study investigates the factors that drive the best 24-month patient reported outcomes (PRO) following MIS lumbar spondylolisthesis surgery.

Methods: 310 patients from the Quality Outcomes Database (QOD) Lumbar Spondylolisthesis Module underwent surgery for degenerative grade 1 lumbar spondylolisthesis utilizing MIS techniques. Surgeries were classified as MIS if any of the following were involved: MIS laminectomy, MIS pedicle screws, MIS interbody grafts, or percutaneous screws. Baseline and 24-month follow-up parameters were collected. PROs included the Oswestry Disability Index (ODI), numeric rating scale (NRS) Back Pain, NRS Leg Pain, EuroQoL-5D (EQ-5D) Questionnaire, and North American Spine Society (NASS) Satisfaction Questionnaire. Multivariate models were constructed.

Results: The cohort included 233 (75.2%) fusions and 77 (24.8%) decompression only procedures. The mean age was 64.0 ± 11.3 years. The cohort demonstrated significant improvement in ODI, NRS back pain, NRS leg pain, and EQ-5D at 24 months ($p < 0.001$, all relative to baseline). In multivariate analyses, aside from baseline PROs, only three factors were significantly associated with multiple PRO change scores: employment, independent ambulation at presentation, and the addition of fusion to surgery. Employment was associated with superior postoperative ODI (OR=0.002;95%CI[0.0002-0.28]; $p=0.01$), NRS back pain (OR=0.39;95%CI [0.19-0.78]; $p=0.008$), and NASS satisfaction (OR=0.36;95%CI[0.18-0.68]; $p=0.002$). Independent ambulation was associated with superior NRS leg pain (OR=0.34;95%CI[0.12-0.91]; $p=0.03$) and EQ-5D (OR=1.11;95%CI[1.04-1.18]; $p < 0.001$). The addition of a fusion was associated with superior NRS back pain (OR=0.41;95%CI [0.17-0.93]; $p=0.03$) and NASS satisfaction (OR=0.35;95%CI[0.17-0.73]; $p=0.005$). Education was also associated with superior outcomes for a single outcome, ODI (OR=0.002;95%CI[0.0002-0.13]; $p=0.004$).

Conclusion: Multiple factors influence outcomes following lumbar spondylolisthesis surgery. For MIS, preoperative active employment, higher education, independent ambulation at presentation, and fusion surgery were significant predictors of superior outcomes across the domains of disability, back pain, leg pain, quality of life, and satisfaction.

234. The Impact of Osteotomy Grade and Location on Regional and Global Alignment Following Cervical Deformity Surgery

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Introduction: Correction of cervical deformity(CD) often involves different types of osteotomies to address sagittal malalignment. Few studies have investigated the effect of osteotomy grade/location on regional and global alignment outcomes.

Methods: CD was defined: C2-C7 Cobb $>10^\circ$, CL $>10^\circ$, cSVA $>4\text{cm}$, or CBVA $>25^\circ$. Patients were evaluated for level and type of cervical osteotomy. Osteotomy grading used Ames-ISSG Osteotomy Classification: partial facet resection(grade 1), complete facet resection/ponte(2), partial/complete corpectomy(3), uncovertebral joint resection(4), opening wedge(5), closing wedge(6), vertebral column resection(7).

Results: Included: 86 CD patients($61.4 \pm 10.6\text{yrs}$, 66.3%F). A total of 141 osteotomies were performed in the cervical spine; the most common levels were C6(26.2%), C5(24.1%), C7(23.4%), and C4(20.6%). 79 osteotomies were in the thoracic spine; 75% were above T5(commonly T1,T2). 18 major osteotomies were performed(grades 6-7); 50% at T1. Cervical osteotomy patients improved in TS-CL, CL, C2 slope and worsened in T1 slope(25° to 33° , $p < 0.001$) and SVA(9mm to 28mm, $p=0.03$). Upper thoracic osteotomy patients improved in TS-CL, cSVA, C2-T3, C2-T3 SVA and C2 slope(all $p < 0.05$). Lower-thoracic osteotomy patients didn't significantly improve in cervical or global alignment from pre- to post-op, but did trend towards improvement in TS-CL, cSVA, SVA. Minor osteotomies in the upper thoracic spine showed improvement in cSVA(63mm to 49mm, $p=0.022$), C2-T3($p=0.007$), and SVA(-16mm to 27mm, $p < 0.001$). The greatest amount of C2-T3 angular change occurred for patients with major osteotomy at T2(39.1° change), T3(15.7°), C7(16.9°) and T1(13.5°). Upper thoracic major osteotomy patients showed similar pre- to post-operative radiographic changes as patients with 3+ minor osteotomies, though C2-T3 SVA trended towards greater improvement with a major osteotomy(-22.5mm vs +5.9mm, $p=0.058$) due to lever arm effect.

Conclusion: CD patients undergoing cervical and upper thoracic osteotomies showed improvement in TS-CL, C2 slope. In the upper thoracic spine, multiple minor osteotomies or major osteotomy at a single level achieved similar alignment changes. Major osteotomy at T2 had the greatest overall impact in cervicothoracic/global alignment.

235. Correlation between ODI, PROMIS and SF-12 in Minimally Invasive Lumbar Spinal Surgery

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Introduction: As the focus in spine surgery shifts from radiographic to patient-centric outcomes, patient-reported outcomes measures (PROMs) are becoming important. Thus, it is vital to evaluate new outcome measures.

Purpose: To evaluate the correlation between Oswestry Disability Index (ODI), Patient Reported Outcome Measurement Information System Physical Function (PROMIS-PF) and Short Form-12 Physical Health Score (SF-12 PHS) in minimally invasive lumbar surgery.

Methods: PROMs collected pre-operatively and 2 weeks, 6 weeks, 3 months, 6 months and 1 year post-operatively of patients undergoing lumbar surgery were analyzed using Pearson product-moment correlation.

Results: Of the 292 patients included, 158 underwent lumbar decompression and 134 underwent lumbar fusions. ODI decreased from 40.84±19.23 pre-operatively to 16.01±12.84 at 1 year. Similarly, PROMIS-PF and SF-12 PHS improved from 35.51±7.92 to 47.78±11.55 and 32.37±8.38 to 43.35±10.43, respectively. A statistically significant, negative correlation was seen between ODI and PROMIS-PF at all time-points, which was strong pre-operatively ($r=-0.673, n=256, p<0.0001$) and at 2 weeks ($r=-0.715, n=228, p<0.0001$), 6 weeks ($r=-0.779, n=190, p<0.0001$), 3 months ($r=-0.732, n=130, p<0.0001$) and 6 months ($r=-0.685, n=80, p<0.0001$); and moderate at 1 year ($r=-0.517, n=22, p=0.010$). A statistically significant, negative correlation was also seen between SF-12 PHS and ODI at all time-points, which was weak pre-operatively ($r=-0.384, n=287, p<0.0001$), but strong post-operatively (2 weeks: $r=-0.625, n=272, p<0.0001$; 6 weeks: $r=-0.686, n=230, p<0.0001$; 3 months: $r=-0.761, n=171, p<0.0001$; 6 months: $r=-0.789, n=108, p<0.0001$; 1 year: $r=-0.740, n=31, p<0.0001$). There was a statistically significant positive correlation between SF-12 PHS and PROMIS-PF at all time-points, which was weak pre-operatively ($r=0.393, n=255, p<0.0001$); strong at 2 weeks ($r=0.630, n=224, p<0.0001$), 6 weeks ($r=0.676, n=190, p<0.0001$), 3 months ($r=0.781, n=128, p<0.0001$) and 6 months ($r=0.718, n=78, p<0.0001$); and moderate at 1 year ($r=0.548, n=22, p=0.008$).

Conclusions: While ODI and SF-12 have been used for several years, PROMIS is a new outcome measure. Our results show that PROMIS-PF correlates strongly with ODI and SF-12 PHS, thus indicating that PROMIS may be a good surrogate for these legacy measures, as it not only captures disease-specific disability but also reflects the impact on overall physical health. Larger studies are warranted to evaluate the utility and value of this outcome measure in common lumbar spinal conditions.

236. Preoperative Opioids & 1-Year Patient Reported Outcomes After Spine Surgery

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Introduction: Back pain is the most disabling condition worldwide and over half of patients presenting for spine surgery report using opioids. Preoperative dosage has been correlated with poor outcomes, but published studies have not assessed the relationship of both preoperative chronic opioids and opioid dosage with patient reported outcomes. We aim to determine 1-year patient reported outcomes associated with preoperative chronic opioid therapy and high-preoperative opioid dosages in patients undergoing elective spine surgery.

Methods: For patients undergoing elective spine surgery between 2010 and 2017, our prospective institutional spine registry data was linked to opioid prescription data collected from our state's Prescription Drug Monitoring Program to analyze outcomes associated with preoperative chronic opioid therapy and high-preoperative opioid dosage, while adjusting for confounders through multivariable regression analyses. Outcomes included 1-year meaningful improvements in pain, function, and quality of life. Additional outcomes included 1-year satisfaction, return to work, 90-day complications, and postoperative chronic opioid use.

Results: Of 2,128 patients included, preoperative chronic opioid therapy was identified in 21% (Table-1. and Figure-1.) and was associated with significantly higher odds (adjusted odds ratio [95% confidence interval]) of not achieving meaningful improvements at 1-year in extremity pain (aOR:1.5 [1.2-2]), axial pain (aOR:1.7 [1.4-2.2]), function (aOR:1.7 [1.4-2.2]), and quality of life (aOR:1.4 [1.2-1.9]); dissatisfaction (aOR:1.7 [1.3-2.2]); 90-day complications (aOR:2.9 [1.7-4.9]); and postoperative chronic opioid use (aOR:1.5 [1.4-19.7]) (Figure-2.). High-preoperative opioid dosage was only associated with postoperative chronic opioid use (aOR:4.9 [3-7.9]) (Figure-3).

Conclusion: Patients treated with chronic opioids prior to spine surgery are significantly less likely to achieve meaningful improvements at 1-year in pain, function, and quality of life; and less likely to be satisfied at 1-year with higher odds of 90-day complications, regardless of dosage. Both preoperative chronic opioid therapy and high-preoperative dosage are independently associated with postoperative chronic opioid use.

237. Predicting Outcomes after Surgical Decompression for Mild Degenerative Cervical Myelopathy: Moving Beyond the mJOA to Identify Surgical Candidates

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Introduction: Patients with mild degenerative cervical myelopathy (DCM) represent a heterogeneous population, and indications for surgical decompression remain controversial. We sought to dissociate patient phenotypes within the broader population of mild DCM associated with degree of impairment in quality of life (QOL) and surgical outcomes.

Methods: This was a post-hoc analysis of patients with mild DCM (mJOA 15-17) enrolled in the AOSpine CSM-NA/CSM-I studies. A k-means clustering algorithm was applied to baseline SF-36 scores to separate patients into two clusters based on pattern and degree of impairment in QOL. Baseline variables and surgical outcomes were compared between clusters. The primary outcome of interest was change in QOL (SF-36) at 1 year post-surgery compared to baseline. Secondary outcomes included change in mJOA, Nurick grade, NDI, and SF-6D scores. A k-nearest neighbors (kNN) algorithm was used to evaluate the ability to classify patients into the two clusters by significant baseline clinical variables.

Results: One-hundred eighty-five patients were eligible. Two groups were generated by k-means clustering over baseline QOL (SF-36) scores. Cluster 1 'more impaired') had a greater proportion of females (44% vs. 28%, $P=0.029$) and symptoms of neck pain (32% vs. 11%, $P=0.001$), gait difficulty (57% vs. 40%, $P=0.025$), or weakness (75% vs. 59%, $P=0.041$). While baseline mJOA correlated with neither baseline QOL nor outcomes, Cluster 1 was associated with significantly greater improvement in disability (NDI) ($P<0.01$) and QOL (SF-36) ($P<0.05$) scores following surgery. A kNN algorithm could predict cluster classification with 71% accuracy by neck pain, motor symptoms, and gender alone.

Conclusion: We have dissociated a distinct more impaired phenotype of patients with mild DCM, characterized by neck pain, motor symptoms, and female gender, in whom surgical intervention resulted in greater gains. Identification of patient-related predictive factors may help guide surgical decision-making and inform treatment paradigms for mild DCM.

238. Long-term opioid prescription fills in patients undergoing spine surgery

Zachary Sanford (Annapolis, MD); Justin Turcotte, MBA; Haley Taylor; Andrew Broda, BS; Alex Speciale, MD; Chad Patton, MD, MS

Background: Adequate postoperative pain-control in patients undergoing spinal surgery remains a difficult subject of study. Although opioid medications have traditionally been utilized in managing spinal pain, little is known regarding their short and long-term postoperative utilization.

Methods: Retrospective analysis was conducted on a consecutive series of spine surgery patients from May 2014–April 2016 managed by two surgeons at a single high-volume orthopaedic center. Opioid prescription fill data through twenty-four months post-procedure was obtained via Surescripts® (Arlington, VA) with patients subdivided into opioid-naïve [ON] (no opioid prescription fills) or opioid non-naïve [ONN] (≥ 1 opioid prescription fills) within four months prior to surgery. Thirty day preoperative periods were excluded from analysis to control for prescriptions written to bridge therapy prior to surgery as were patients undergoing multiple procedures. Opioid concentrations were converted into morphine milligram equivalents (MME).

Results: 287 patients (194 ON, 93 ONN) were included in this study. Postoperatively, ONN patients' prescription fills decreased from 34% in months 0-3 (MME $\bar{x}$ 3,078) to 14% by 9-12 months (MME $\bar{x}$ 5,715) with no fills in months 21-24. Pain management accounted for the majority of opioids prescribed during the 12-month postoperative period (64%). Conversely, ON patients' percentage of prescription fills increased from 21% in months 0-3 (MME $\bar{x}$ 1,410) to 22% in months 9-12 (MME $\bar{x}$ 2,541), remaining at 29% by months 21-24. Pain management prescribed the majority of total opioids during the 12-months following surgery followed by other specialties and primary care (37%, 27%, 21%).

Conclusion: Our findings suggest spine surgery patients are at risk for ongoing opioid medication use long after surgery, the majority of which are prescribed by non-surgeon providers. Although spine surgery appears to be an effective intervention for reducing opioid dependence among ONN individuals, opportunities exist to reduce postoperative opioid utilization among ON patients through implementation of revised pain management protocols.

239. An approach for efficient brain-wide projection-specific gene transfer

[Philip L. Gildenberg MD Resident Award](#)

Xiaonan (Richard) Sun, MD (Port Washington, NY); Simon Musall, PhD; Anup Khanal; Anne Churchland, PhD

Introduction: The basal ganglia's diverse cognitive and motor functions reflect the large-scale projections to the striatum from all regions of the cerebral cortex. An understanding of cortical computations received by the striatum can reveal how inputs from functionally-unrelated areas are transformed into a unified, coherent output. Importantly, impairments in cortico-striatal connectivity have strong implications in multiple movement and neuropsychiatric disorders. Recent advancements in non-pathogenic viral-mediated gene transfer generated promising vectors for investigating brain-wide circuits. Here, we developed a combinatorial viral strategy in mice for cortex-wide neural activity imaging of the striatum-projecting subpopulation.

Methods: In wild-type mice, we first transduced all neurons to conditionally express the fluorescent calcium indicator protein GCaMP7s through intravenous delivery of a novel capsid variant of adeno-associated virus-9 (AAV-PHP.eB), which efficiently crosses the blood-brain barrier. Next, to specify cortical neurons projecting to the striatum, we performed stereotactic injections of retrograde adeno-associated virus (AAVrg) into the striatum which, by expressing Cre recombinase, activated brain-wide gene expression in striatum-projecting neurons. Finally, mesoscale and microcircuit neural activity imaging were performed with epifluorescence and two-photon microscopy, respectively.

Results: We demonstrate efficient projection-specific cortex-wide AAV-mediated gene transfer in cortico-striatal projection neurons. Neural activity imaging in awake, behaving mice expressing GCaMP7s revealed high signal-to-noise fluorescence changes across multiple brain regions and at the single neuron scale.

Conclusion: We employed an intersectional viral-mediated technique for widespread gene transfer with projection selectivity in mice. While our ongoing efforts focus on the neural representations of perceptual decision-making, this method is generalizable across circuits, species, and disease models. One such example is the interrogation and manipulation of convergent circuits of the cortico-thalamic and cortico-subthalamic networks. Additionally, our viral technique can accelerate circuit-level studies in animal models of neurological disorders. Furthermore, the therapeutic potential of AAV-PHP.eB is positioned to gain significant precision with the ability of network selection.

240. Hierarchical Feature Encoding for Speech Perception in Human Temporal Cortex

Kiefer Forseth (Houston, TX); Patrick Rollo, BA; Nitin Tandon, MD

Introduction: Humans readily precipitate words and meaning from speech, a complex and essential cognitive process that requires the orchestration of a diverse ensemble of neural substrates. These substrates are thought to each contribute unique information (e.g. acoustic, phonetic, lexical, or semantic) to the process of speech perception, but the functional architecture of this intricate cortical system remains controversial. With large-scale human intracranial electrophysiology, we precisely delineate the cascading spatial distribution of hierarchical feature encoding for speech perception.

Methods: Intracranial electrodes (n=18849,103 patients), implanted for the pre-surgical evaluation of epilepsy, furnish direct recordings of human cortex with millimeter spatial and millisecond temporal resolution. Both subdural grid (43 patients) and stereotactic depth (60 patients) electrodes were implanted, providing complementary coverage of superficial and deep cortical structures. Patients were instructed to quickly and accurately articulate the name of common objects cued by short spoken descriptions (a round red fruit). We quantified the engagement of local cortical substrates by gamma (60-120Hz) power and low-frequency (2-15Hz) phase.

Results: We identified a hierarchical speech perception network anchored in bilateral primary auditory cortex. Heschl's gyrus and the transverse temporal sulcus encoded acoustic amplitude in gamma power and acoustic edges in low-frequency phase. The adjacent cortex in planum polare, lateral superior temporal gyrus, and superior temporal sulcus encoded specific phonemic characteristics: place, manner, and voicing of articulation. Lexical encoding was found at superior temporal sulcus and posterior middle temporal gyrus in the language-dominant hemisphere. Finally, semantic features were encoded by a distributed set of substrates in ventral temporal, lateral frontal, and inferior parietal cortex. Importantly, we were able to characterize the dynamic propagation of information from low-level acoustic features to progressively higher-level linguistic representations.

Conclusion: Hierarchical speech features are encoded in a hierarchical cortical network characterized by spreading activation from primary auditory cortex that ultimately recruits widely-distributed regions.

241. Early Experience with Directional DBS Leads in Parkinson's Disease and Essential Tremor Patients

Miriam Mingxuan Shao (Westfield, NJ); Andrea Liss; Yunseo Linda Park; Marisa DiMarzio, BS; Julia Prusik, MPH; Ellie Hobson, RN, BSN; Octavian Adam, MD; Jennifer Durphy, MD; Vishad Sukul, MD; Julie Pilitsis, MD, PhD

Introduction: In the last two years, directional deep brain stimulation (DBS) electrodes have become recently available in the US. Data on real-life experience is limited, and we present our initial experience on incorporating directional DBS into our Parkinson's disease (PD) and essential tremor (ET) patients.

Methods: We compared six-month outcomes between 42 directional and traditional leads implanted in 28 patients. The two cohorts consisted of patients implanted with directional leads and patients implanted with traditional leads. Each cohort included 7 PD patients with stimulation in the bilateral subthalamic nucleus (STN) and 7 ET patients with stimulation in the unilateral ventral intermediate nucleus (VIM) of the thalamus.

Results: Outcomes between groups at six months, as evidenced by medication reductions and motor score improvements, between directional and traditional leads in PD and ET patients were similar. The number of patient visits was the same. Directionality was employed in 1/3 of patients. Notably, the therapeutic window (difference between amplitude when initial symptom relief was obtained and when intolerable side effects appeared) was significantly greater in directional leads in both PD ($p=0.011$) and ET ($p=0.035$) patients. In the STN leads for PD, the windows for directional and traditional leads were $3.1V + 0.2$ and $2.0V + 0.3$, respectively. For VIM leads, windows for directional and traditional leads were $3.1 + 0.4$ and $1.9V + 0.3$, respectively.

Conclusion: Outcomes at 6-month follow-up between directional and traditional leads appear comparable. The therapeutic window of directional leads was significantly larger than that of traditional leads, which suggests increased benefit and programming options. We expect that as we alter workflow associated with the leads, more patients will use directionality, and amplitudes will become lower.

242. Theta Coherence Predicts Risk Taking Behavior

Sarah Kathleen Bourne Bick, MD (Boston, MA); Shaun Patel, PhD; Emad Eskandar, MD

Introduction: Balancing risk and reward is central to our day to day decision making. Inappropriate risk and reward valuation is involved in impulse control disorders such as substance abuse disorders and problem gambling. Anterior cingulate (AC), orbitofrontal cortex (OFC), nucleus accumbens (NAc), and caudate have roles in risk and reward processing. Our objective was to determine how communication between these structures is involved in risk taking behavior, in order to identify neuromodulation strategies for impulse control disorders.

Methods: Six subjects with medically refractory epilepsy who underwent depth electrode placement for seizure localization participated in our study. Local field potentials were recorded from depth electrodes while subjects participated in a gambling task requiring them to place a high or low wager on the outcome of a simulated card game. The card game contained both high risk trials where the chance of winning was 40-60% and low risk trials where the outcome was more predictable. We computed power and coherence in AC, OFC, NAc, and caudate electrodes for different trial and wager types.

Results: In high risk trials, there was a decrease in theta (4-8Hz) power prior to high but not low wagers in AC, OFC, NAc, and caudate. There was increased NAc-caudate coherence, a measure of connectivity, prior to high bets in high but not low risk trials. Conversely, NAc-OFC and OFC-AC coherence was decreased prior to high bets in high risk trials.

Conclusion: Theta coherence between NAc-caudate, NAc-OFC, and OFC-AC predicts risk taking behavior. Increased coherence between NAc and caudate, two structures involved in reward, may indicate increased activation of reward circuitry contributing to high risk decisions, while decreased NAc-OFC and OFC-AC coherence prior to high risk decisions may reflect a decrease in cognitive control. These findings suggest important circuitry to target for neuromodulation for impulse control disorders.

243. Trajectory Analysis for Symptom Response Prediction in Prospective Cohort of Patients with Intractable Obsessive-Compulsive Disorder treated with Gamma Knife Radiosurgical Ventral Capsulotomy

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Introduction: Obsessive-Compulsive Disorder (OCD) is a psychiatric disorder characterized by intrusive obsessions and repetitive compulsions. For some with severe, intractable OCD, Gamma Knife Ventral Capsulotomy (GKVC) is a safe

and efficacious neurosurgical treatment option. While 59% of patients significantly improve with GKVC, our understanding of the predictive validity of the trajectory of patients' early response as well as whether the course of improvement for obsessions and compulsions differ remains limited.

Methods: In this study, we examined the largest known prospective cohort of intractable OCD patients (n=55) treated with GKVC. The primary outcome measure was the Yale-Brown Obsessive Compulsive Score (YBOCS), collected at 6, 12, 24, 36, 48, and 60 months. We analyzed the obsession and compulsion sub-scores separately. We normalized the distributed outcomes with the Blom transform, constructed Parametric and Linear piecewise models, and determined the best fit model using adjusted Bayesian Information Criterion.

Results: Our data show that GKVC reduced obsessions at an increased rate as compared to compulsions in year 1. For both outcomes (obsessions and compulsions), two classes emerged: a majority and minority class. Individuals in the majority classes experience most of their expected 5-year reduction in obsessions and compulsions (82%, 81% respectively) in the first year. However, members of the minority classes, who had more severe impairment at baseline, experienced just over half of their 5-year expected improvement in symptoms (60% obsessions, 65% compulsions) in the first year, with continued improvement beyond year one.

Conclusion: This represents the first trajectory analysis of changes in OCD severity after GKVC and shows that obsessions improve earlier than compulsions. Anterior internal capsule lesions may predominantly affect obsessive behavior, reducing subsequent compulsive drive. Trajectory analysis revealed that most patients will experience continued reduction in symptoms years after GKVC, though the greatest rate of improvement is seen in the first postoperative year.

244. Long-term AADC activity following administration of VY-AADC01 gene therapy using novel intraoperative MRI-monitored intraparenchymal delivery

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Introduction: As Parkinson's disease (PD) progresses, the enzyme AADC, required to convert levodopa to dopamine, is substantially reduced in the putamen, and oral levodopa becomes less effective. Here we report the AADC activity and need for antiparkinsonian medications after administration of VY-AADC01 (an AAV2-AADC gene therapy).

Methods: In this phase 1 trial (PD-1101), 3 cohorts of 5 subjects each with advanced PD and motor fluctuations were administered ascending doses of VY-AADC01 directly into the putamen using intraoperative MRI monitoring; VY-AADC01 concentration and volume increased across cohorts (cohort 1: 8.3×10^{11} vg/mL, up to 450 μ L/putamen; cohort 2: 8.3×10^{11} vg/mL, up to 900 μ L/putamen; cohort 3: 2.6×10^{12} vg/mL, up to 900 μ L/putamen). VY-AADC01 was co-administered with gadoteridol to allow real-time MRI monitoring of the location and volume infused. (18)F-DOPA PET at baseline, month 6 and in an on-going extension study (PD-1104) evaluated dopamine terminal function as an assessment of AADC activity. Daily requirements for antiparkinsonian medications, patient-reported diaries, and clinician assessed endpoints were also collected.

Results: Across cohorts, coverage of the putamen increased from 20.7% in cohort 1, to 33.5% in cohort 2, and 42.3% in cohort 3. Coverage was significantly correlated ($r=0.84$, $p=0.0002$) with (18)F-DOPA PET at 6 months, which was reflected in decreased need for levodopa and other antiparkinsonian medications. Cohort 1: (18)F-DOPA PET increased 13.2%, LED decreased -15.1%; Cohort 2: 56.1% increase and -32.8% decrease, respectively; Cohort 3: 79.3% increase and -42.1% decrease, respectively. Patient diary and clinician assessed data also showed cohort-dependent improvements which were mostly sustained through last follow-up. (18)F-DOPA PET data approximately 3 years post-VY-AADC01 administration will be reported for cohort 1 subjects.

Conclusion: A novel neurosurgical technique using intra-operative MRI to administer VY-AADC01 facilitated increased, targeted coverage of the putamen, resulting in AADC expression and apparent clinical benefit in this Phase 1 trial.

245. Reassessing the Impact of Intraoperative Electrocorticography (ECoG) on Postoperative Outcome of Patients Undergoing Standard Temporal Lobectomy for MRI-negative Temporal Lobe Epilepsy (TLE)

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Introduction: Seizure freedom after surgical resection of MRI-negative TLE ranges from 36-76%. We describe the impact of intraoperative electrocorticography augmented by opioid activation and its effect on seizure outcomes.

Methods: Patients with medically resistant MRI-negative TLE, who had a standardized ECoG at the time of their elective anterior temporal lobectomy (ATL) between 1990 and 2016 were included in this study. Seizure recurrence comprised

the primary outcome of interest and was assessed using Kaplan-Meier and multivariable Cox-Regression analysis plots based on interictal epileptiform discharges (IEDs) distribution recorded on scalp EEG, baseline and opioid induced ECoG and extent of resection.

Results: Of the 1144 ATL performed at our institution between 1990 - 2016, 127 (11.11%) patients (81 females) with MRI-negative TLE were eligible for this study. Patients with complete resection of tissue generating IED recorded on intraoperative ECoG were less likely to have seizure recurrence compared to those with incomplete resection on univariate analysis ($p < 0.05$). No difference was found in seizure recurrence between patients with bilateral independent IEDs and unilateral IEDs ($p = 0.15$), presence or absence of opioid induced epileptiform activation ($p = 0.61$), or completeness of resection of tissue with opioid induced IED on intraoperative ECoG ($p = 0.41$).

Conclusion: We found that incomplete resection of IED-generating tissue on intraoperative ECoG was associated with an increased chance of seizure recurrence. However we found that induction of epileptiform activity with intraoperative opioid activation did not provide useful intraoperative data predictive of improving operative results for temporal lobectomy in MRI-negative epilepsy.

246. Ultra-High Frequency Deep Brain Stimulation at 10,000 Hz Improves Motor Function

Irene Harmsen (Toronto, Canada); Darrin Lee, MD, PhD; Robert Dallapiazza, MD, PhD; Philippe De Vloo, MD, PhD; Robert Chen, MD, MSc; Alfonso Fasano, MD, PhD; Suneil Kalia, MD, PhD; Mojgan Hodaie, MD, MSc; Andres Lozano, MD, PhD

Introduction: Stimulation frequency has been considered a crucial determinant of efficacy in deep brain stimulation (DBS). DBS at frequencies over 250Hz is not currently employed and consensus in the field suggests that higher frequencies are not clinically effective. With the recent demonstration of clinically effective ultra-high frequency (UHF) spinal cord stimulation at 10kHz we tested whether UHF stimulation could also be clinically useful in movement disorder patients with DBS. We evaluated the clinical effects and safety of UHF DBS in patients with subthalamic nucleus (STN) or ventral intermediate thalamic nucleus (VIM) DBS.

Methods: We studied the effects of conventional (130Hz) and UHF stimulation in five patients with Parkinson's disease (PD) with STN DBS and in one patient with essential tremor (ET) with VIM DBS. We compared the clinical benefit and adverse effects of stimulation at various amplitudes either intraoperatively or postoperatively with the electrodes externalized.

Results: Motor performance improved in all six patients with UHF DBS. 10kHz stimulation at amplitudes ≥ 3.0 mA appeared to be as effective as 130Hz in improving motor symptoms (46.2% vs 53.5% motor score reduction, $p = 0.110$, $N = 90$ trials). Interestingly, 10kHz stimulation resulted in fewer stimulation-induced paresthesiae and speech adverse effects than 130Hz stimulation.

Conclusion: Our results indicate that DBS at 10kHz produces clinical benefits in patients with movement disorders. Like 10kHz spinal cord stimulation, 10kHz DBS has the potential to produce clinical benefits while possibly reducing stimulation-induced adverse effects. Further studies will be required to optimize UHF DBS stimulation parameters and to determine its clinical utility.

247. Dynamics of Synchrony in Local Cortical Circuits

Natasha Kharas (Houston, TX); Samantha Debes, BS; Ariana Andrei; Valentin Dragoi, PhD

Introduction: In the cortex, spontaneous fluctuations in neuronal firing are observed at the timescale of milliseconds. Traditionally, synchronized neural activity was characterized as ON and OFF state transitions during sleep, whereas desynchronized activity was viewed as a hallmark of wakefulness. However, recent studies have indicated that ON and OFF states are present during wakefulness, but the prevalence of synchronized activity and its dependence on behavioral state remain unclear.

Methods: To determine this, we recorded single neuron activity and local field potentials using multi-site linear electrodes in non-human primate visual cortex (areas V1 and V4) during task performance or sleep. We employed an unsupervised learning model (hidden Markov model) to identify ON and OFF states in neuronal populations, and measured the frequency of transitions (synchrony) between the two states. Furthermore, we induced ON and OFF state transitions (synchrony) using optogenetic stimulation in one cortical layer to determine whether synchronized fluctuations spread towards adjacent layers.

Results: The number of transitions per second between states (synchrony) was significantly greater in sleep than in wakefulness. We also examined layer-specific activity in the supragranular, granular, and infragranular layers during wakefulness and discovered that synchronized activity was rare across layers. When we optogenetically induced

synchrony to test its spread in the cortex, we observed that the rapid fluctuations in cortical activity caused by light in one cortical layer did not propagate to other layers despite strong inter-layer connectivity.

Conclusion: Our findings indicate that cortical laminar networks operate in a desynchronized mode during wakefulness and switch to synchronized activity during sleep. Interestingly, we demonstrate that induced synchrony remains local and does not propagate across cortical layers during wakefulness. In addition to elucidating the underlying neuronal connectivity of the cortex, our results have implications in understanding and treating aberrant neuronal synchrony in epilepsy and Parkinson's disease in humans.

248. Electrophysiological prognostication of functional cortical integrity after traumatic brain injury

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Introduction: Whether and how consciousness returns after severe traumatic brain injury (TBI) is not clear, mainly due to our lack of understanding of how consciousness arises. Previous studies revealed that correlated activity across a distributed network of cortical cells, the frontoparietal network (FPN), is required for return of consciousness. But data on the transition from coma to wakefulness are sparse. To address this gap, we performed depth electrode recordings of the anterior cingulate gyrus (ACC) and dorsolateral prefrontal cortex (DLPFC) along with simultaneous scalp EEG recording in patients recovering from coma after TBI. We sought to extract predictive electrophysiological biomarkers of regaining consciousness after traumatic brain injury.

Methods: In this study one healthy control (epilepsy) and five comatose traumatic brain injury patients with GCS < 8 and with no major brain structural abnormalities were enrolled. Upon obtaining informed consent by a legally authorized representative, we implanted a seizure monitoring stereotactic (10-contact) depth electrode spanning from DLPFC to ACC. To probe the functional integrity of cortical webs we administered repetitive single-pulse stimulation to ACC and DLPFC (100 μ S, 1 Hz stimulation, 100 reps). Cortico-cortical evoked potentials (CCEPs) were recorded both via the implanted depth electrode and scalp contacts.

Results: We found that recovery of consciousness is associated with increasing amplitude and complexity of CCEPs in DLPFC. While all patients had increased amplitude over time, patients who recovered developed polyphasic, complex waveforms, as measured by zero crossing and permutation entropy ($n = 5$). The patients who did not recover ($n = 2$) had large-amplitude, but simple-waveform CCEP responses.

Conclusion: The characteristics of the evoked responses to electrical stimulation may be a useful surrogate measurement of the integrity of cortical networks required for consciousness. CCEPs potentially be used as an indicator of integrity of cortex to predict outcome after TBI.

249. Theta Power Changes Differentiate Responders versus Non-responders to Long-Term Neural Stimulation for Drug-resistant Epilepsy

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Introduction: The RNS System is the only FDA-approved closed-loop system for drug-resistant epilepsy, comprised of a programmable microprocessor capable of responsive detection and neural stimulation. This device is one of the few treatments available for patients who are ineligible for surgical resection and has a responder rate of 60% at 6 years. Response is currently determined using patient reported outcomes, which are subject to bias and incompleteness. We hypothesize that change in theta power can serve as an objective endpoint for measuring therapeutic response to closed-loop stimulation.

Methods: We reviewed all RNS System intracranial electroencephalography (iEEG) recordings and associated outcomes for patients implanted with the device at UPMC between January 2015 and March 2018. Patients with an Engel classification of $\geq$ II were considered responders. For this analysis, we analyzed only scheduled recordings, we manually validated to contain only baseline brain state activity. We then performed a power-frequency decomposition using Fast-Fourier Transform (FFT) analysis for each recording to obtain the average theta band (4–8 Hz) power. Next, we performed a linear regression of theta power over time to obtain a rate of change for each patient. Finally, we used an unpaired T-test to evaluate change in theta power for responders versus non-responders.

Results: A total of 13,617 iEEG recordings were reviewed for 11 patients, and 7,506 were identified as scheduled recordings containing only baseline activity. The mean length of implantation was 16.6 months. Magnitude of theta power increase is significantly lower in responders versus non-responders ($t = -3.09$; $p = 0.02$).

Conclusion: A small change in theta power was with responder status, while a significantly larger change was associated with non-responder status. This finding may allow physicians to more easily and accurately measure therapeutic response to closed-loop stimulation, resulting in more efficient and appropriate management.

250. Phase 1 Trial of Convection-Enhanced Delivery of Adeno-Associated Virus Encoding Glial Cell Line-Derived Neurotrophic Factor in Patients with Advanced Parkinson's Disease

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Introduction: Parkinson's disease is progressive and presently incurable. GDNF is a neurotrophic factor that prevented the death of dopaminergic neurons in culture and animal models of Parkinson's disease (PD).

Methods: In this Phase 1 clinical trial, 13 adult patients with advanced PD underwent convection-enhanced delivery (CED) of an adeno-associated virus, serotype 2 vector containing glial cell line-derived neurotrophic factor (AAV2-GDNF) to investigate the safety, tolerability, and potential clinical effects of CED of AAV2-GDNF and gadoteridol, a surrogate magnetic resonance imaging (MRI) tracer, into the bilateral putamina (450 μ l per hemisphere). Three escalating dose levels were evaluated: 1) 9 x 10¹⁰vg (6 patients); 2) 3 x 10¹¹vg (6 patients); and 3) 9 x 10¹¹vg (1 patient). Intraoperative MRI was performed during infusions. Pre-operatively, and at 6-12 month intervals post-operatively, Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 assessed motor function and positron emission tomography (PET) scanning with [¹⁸F]DOPA assessed F-DOPA uptake, a sign of presynaptic dopaminergic integrity.

Results: The patients tolerated AAV2-GDNF infusion without short- or long-term clinical or radiographic toxicity. MRI tracked AAV2-GDNF infusion within the bilateral putamina. Average coverage of the putamina was 22%. UPDRS Part 3 assessment scores remained stable throughout the study. Increased [¹⁸F]DOPA uptake in the infused areas was seen bilaterally in 10/13 patients at 6 months (range: 5-274%, median: 36%), and in 12/13 patients at 18 months after infusion (range: 8-130%, median: 54%).

Conclusion: Patients with advanced PD tolerated bilateral CED of AAV2-GDNF without toxicity. Gadoteridol in the infusion solution tracked putaminal AAV2-GDNF distribution. PET findings of increased putaminal [¹⁸F]DOPA uptake suggest a neurotrophic effect on dopaminergic neurons. Based on a satisfactory safety profile, a follow-up clinical trial is planned to increase putaminal coverage and possibly reverse PD progression and signs.

251. Low Frequency Subthalamic Nucleus Stimulation for Verbal Fluency Improvement in Parkinson's Disease

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Introduction: Parkinson's disease (PD) is a common neurodegenerative disorder that results in movement-related dysfunction; however, it often results in cognitive impairment as well. While deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been shown to be effective in improving motor symptoms, cognitive impairment is often not improved and, in some cases, verbal fluency can be impaired. Traditional DBS strategies use high-frequency stimulation (130 Hz), but there is evidence that low frequency theta (5-12 Hz) oscillations are important in learning and memory. We tested the effects of no stimulation, theta stimulation or gamma stimulation on working memory and verbal fluency.

Methods: Nine patients underwent STN DBS implantation for Parkinson's disease and had their leads externalized prior to stage 2 internalization. Each patient underwent a verbal fluency task and spatial working memory binding task. During baseline cognitive testing, STN field potentials were recorded and the individual patients' peak theta frequency was identified during each cognitive task. Patients then underwent no stimulation, peak theta frequency stimulation, and 100 Hz stimulation at either the left ventral STN or left dorsal STN lead during the cognitive tasks. Accuracy was analyzed for the binding task, and vocabulary size was analyzed for verbal fluency.

Results: Peak theta frequency left dorsal stimulation resulted in improvement in the verbal fluency task ($p < 0.01$); however, there was no difference in verbal fluency performance with ventral STN theta stimulation or gamma stimulation ($p = 0.16$). There was no difference on the binding task among the groups (no stimulation, ventral STN theta stimulation, ventral STN gamma stimulation, dorsal STN theta stimulation, dorsal STN gamma stimulation; $p = 0.99$).

Conclusion: Further studies are necessary to determine the effects of low frequency STN stimulation on cognition. Here, we suggest promising evidence that STN theta stimulation may improve verbal fluency.

252. The Effect of Skull Density Ratio on Tremor Improvement and Rates of Adverse Events of MR-Guided Focused Ultrasound Thalamotomy

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Introduction: Magnetic resonance guided focused ultrasound (MRgFUS) thalamotomy has shown to be efficacious in the treatment of Essential Tremor (ET). Skull density ratios (SDR) of less than 0.45 ± 0.05 have previously been thought to be associated with decreased treatment effectiveness and increased rates of adverse events, thereby serving as exclusion criterion for treatment eligibility in some studies. Here, we compared the efficacy and safety of MRgFUS treatment of 189 patients with ET based on an SDR threshold of 0.45.

Methods: Patients treated for ET were divided into two groups: $SDR < 0.45$ and $SDR \geq 0.45$. Efficacy was based on improvement in the Clinical Rating Scale for Tremor (CRST) scores at 1-year follow-up after MRgFUS treatment. Safety was based on rates of the most severe procedure- or thalamotomy-related adverse event reported per patient.

Results: Of the 189 patients treated for ET, 28% had an $SDR < 0.45$. There was no difference in efficacy between groups; 68% of patients with $SDR < 0.45$ demonstrated at least 50% improvement in CRST at 1-year follow-up, compared to 68% of patients with $SDR \geq 0.45$. The group with $SDR < 0.45$ had a lower rate of adverse events compared to the group with $SDR \geq 0.45$ ($P = 0.013$). Additionally, there were no serious adverse events reported in the group with $SDR < 0.45$.

Conclusion: SDR is an indicator of the acoustic transparency of the skull to the ultrasound beam. Usually, lower SDR correlates with higher energy required to reach ablative temperature, but this prediction is not exact. By demonstrating that MRgFUS thalamotomy of some patients with SDR less than 0.45 is beneficial and can be performed without an increase in the rate of adverse events, our analysis presents an opportunity for more patients to access this modality as a feasible, non-invasive therapeutic.

253. A systematic review and meta-analysis of stereo-electroencephalography vs. subdural electrodes for epilepsy surgery

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Introduction: In this systematic review and meta-analysis the authors aimed to compare stereoelectroencephalography (SEEG) and intracranial subdural electrodes (SDE) as investigative measures for invasive monitoring of epileptic seizures prior to surgical resection. The outcomes analyzed in this study include rate of consequent surgery, surgical seizure freedom, overall seizure freedom, and complications of neuromonitoring.

Methods: A literature search was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant articles were identified from 3 electronic databases (MEDLINE, EMBASE, and CENTRAL [Cochrane Central Register of Controlled Trials]) from their inception to January 2018. Random and fixed effects models were used to estimate the overall effect.

Results: Of 11462 screened records, 48 studies met the inclusion criteria and were included in the meta-analysis. These studies reported on 1973 SEEG patients and 2036 SDE patients. Fewer patients who were monitored with SEEG went on to receive resective surgery (WMD -4.7%; 95% CI -5.7 to -3.7%; $p = 0.001$). More patients monitored with SEEG had seizure freedom following their resective surgery (WMD +5.8%; 95% CI 4.7 to 6.9%; $p = 0.001$). Fewer patients monitored with SEEG had mortality (WMD -0.2%; 95% CI -0.3 to -0.1%; $p = 0.001$) and morbidity (WMD -10.6%; 95% CI -11.6 to -9.6%; $p = 0.001$). SEEG and SDE had similar rates of permanent neurological deficits and hemorrhage.

Conclusion: In the comparison between SEEG and SDE neuromonitoring for epilepsy, SEEG analysis resulted in fewer surgical resections yet better seizure freedom outcomes. It is also associated with fewer mortalities and morbidities. Future long-term prospective registries may help clarify further advantages with respect to seizure reduction and cost effectiveness of investigations and treatment. Direct observational or randomized control trials will provide definitive data regarding efficacy and safety profiles of these two investigative methods.

254. Final Electrode Placement Changes from Planned Target Based on Microelectrode Recording Findings in Awake Deep Brain Stimulation Surgery

Gregory Davis, MD (Washington, DC); Jacquelin Arguello, BS; Terrence Patterson, PhD; Zachary Levine, MD

Introduction: Recent studies have shown similar clinical outcomes between patients treated with deep brain stimulation (DBS) under general anesthesia without microelectrode recording (MER) -- "asleep" DBS -- and historical cohorts undergoing "awake" DBS with MER guidance. However, few studies have analyzed coordinate plane trajectory changes adjusted by MER. This study compares targeting accuracy as measured by changes to planned electrode trajectory within all 3 coordinate planes of DBS to the globus pallidus internus (GPi), subthalamic nucleus (STN), and ventral intermediate nucleus (VIM), using awake techniques at a single institution.

Methods: Preoperative 3-T MR images were merged with CT images for planning. Electrode targets were anatomical, based on MR images. A skull-mounted STarFix or NexFrame system was used for electrode placement; all procedures were performed under local anesthesia. MER and test stimulations were utilized to determine final electrode location. Accuracy was assessed by comparing planned electrode location and final location.

Results: 290 electrodes were implanted into 174 patients (130 with Parkinson disease, 34 with essential tremor, and 8 with dystonia). Patients' mean age was 63 ± 12 years. There were 158, 55, and 76 electrodes implanted into the STN, VIM, and GPi, respectively. 1.9%, 3.6%, and 5.3% of STN, VIM, and GPi electrodes, respectively, required changes in the X-Y coordinate plane. There was no significant difference between these observations. There was no significant difference between the accuracy of left and right brain electrodes. 58.9%, 58.2%, and 71.1% of STN, VIM, and GPi electrodes, respectively, required changes in the Z coordinate plane. There was no significant difference between these observations. On average, STN, VIM, and GPi underwent depth changes (in mm) of 0.1 ± 0.9 , -0.3 ± 0.6 , and -0.5 ± 1.0 .

Conclusion: Placement of DBS electrodes using MER and test stimulation results in many changes to final electrode depth. MER remains a consideration when planning DBS electrode placement.

255. Cortical Evoked Potentials Generated By Subthalamic Stimulation: Evidence in Humans for a Motor, Sensory and Auditory Cortical-STN Hyperdirect Pathway

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Introduction: Broad areas of frontal cortex are thought to send axonal projections directly to the subthalamic nucleus (STN). This hyperdirect pathway into the basal ganglia has been implicated in a variety of human behaviors, and its antidromic activation may participate in therapeutic mechanisms of DBS. Miocinovic et al. (2018) recently reported short-latency evoked potentials (EP) recorded over hand motor sensorimotor areas during STN stimulation that provide physiological evidence for the hyperdirect pathway in humans. Here, we determined whether similar EPs generated by STN stimulation could be observed in the opercular cortical regions subserving speech production.

Methods: 11 patients with Parkinson's disease underwent STN DBS surgery and temporary implantation of a 63-contact ECoG strip overlaying regions of premotor, primary motor (M1), primary sensory (S1), and auditory (posterior superior temporal gyrus) cortices. ECoG was recorded during 30 seconds of monopolar stimulation (1Hz, 3mA, 60 μ s) in three locations centered in the dorsolateral STN (center, medial and posterior). Recording locations were determined from either intra-operative CT imaging or fluoroscopy. Trials were aligned, averaged and baseline corrected and EP magnitudes, latencies and locations were identified.

Results: STN stimulation produced EPs in the frontal operculum, M1, S1 and the superior temporal gyrus. EPs were divided into three time bins (1-2, 2-5, or 5-10ms). Throughout all areas, very short latency EPs (median: 1.4, IQR: 1.2-1.5ms) were found consistent with cortico-spinal/cortico-bulbar tract activation, while short (median: 2.7, IQR: 2.6-3.1 ms) and medium latency EPs (median: 5.0, IQR: 4.8-5.6 ms) were found consistent with hyperdirect pathway activation.

Conclusion: Low frequency STN stimulation generated short-latency EPs in cortical areas associated with speech production, consistent with antidromic identification of hyperdirect pathways. The inclusion of peri-sylvian opercular locations in these results adds to limited data suggesting that basal ganglia loops participate in speech perception and production.

256. Clinical Deterministic Tractography of the Dentato-Rubro-Thalamic Tract may Diverge from Intraoperative Microelectrode Recording based Deep Brain Stimulation Lead Placement for Essential Tremor

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Introduction: Diffusion-weighted magnetic resonance imaging (MRI) has shown that the putative target for Essential Tremor (ET), the Ventral Intermediate Nucleus (VIM), may lie along the dentato-rubro-thalamic tract (DRTT). DRTT is perhaps thought to represent the effective clinical target of deep brain stimulation (DBS) for ET. Direct targeting of DRTT is therefore an emerging methodology to replace atlas-based targeting with microelectrode recording (MER). However, current clinical deterministic tractography algorithms are known to be highly dependent on precise seed region selection and even with standardization can be variable. In this study, we evaluate clinical DRT tractography in comparison to MER-based lead placement.

Methods: This is a retrospective analysis of 10 ET patients who underwent DBS (19 hemispheres implanted; 7-10/2018) with intraoperative MER. Fiber tracking was performed using institutionally standardized deterministic tractography (DynaSuite Neuro, InVivo Corp., Germany) on the pre-operative MRI but not used clinically. DRTT axial diameter was measured in the bicommissural plane. Distance from DRTT to implanted lead was measured after co-registration with the immediate post-operative MRI (iPlan Cranial, BrainLab, Germany).

Results: All patients had desired cellularity on MER recordings along the implanted trajectory with intraoperative reduction in tremor on stimulation. Across subjects the mean diameter of DRTT in the bicommissural plane was 7.0 ± 2.6 . However, the range was large, 1.4-14 mm. Within each patient the mean difference in DRTT diameter between two hemispheres was 1.4 ± 1.5 mm. Again, the range was large, 0-4.7 mm. DBS lead was within the DRTT in 4 implanted hemispheres. In the remaining 15 hemispheres, distance from DRTT was 2.1 ± 1.8 mm.

Conclusion: DRT fibers calculated with deterministic tractography were of variable dimensions and not necessarily spatially congruent with DBS lead implantation determined by intraoperative MER and clinical effect. Further investigation into comparative tractography methodology is required prior to utilizing direct targeting of DRTT for lead placement.

257. Comparison of Hospital Costs of SEEG Electrodes and Subdural Grids Using the Value-Driven Outcomes Database

Andrea Brock, MD (Salt Lake City, UT); John Rolston, MD, PhD

Introduction: Invasive seizure monitoring requires stereo-electroencephalography (SEEG) using depth electrodes or placement of subdural grids or strips. While each method has advantages and disadvantages, the method selected is often because of surgeon familiarity and preference. In today's healthcare climate, cost becomes an additional variable when considering potential intervention. The Value-Driven Outcomes (VDO) database was developed at the University of Utah to allow comparisons of hospital cost. In this study, we compare cost drivers for SEEG electrodes and subdural grids.

Methods: All surgeries for SEEG electrodes and subdural grids from 2012 to 2018 by two surgeons at one institution were retrospectively reviewed. Total cost and subcategory cost (as a percentage of the total cost) were calculated for the SEEG electrodes and subdural grids using the VDO database.

Results: Seventy-three patients underwent either SEEG electrode (n=29) or subdural grid (n=44) placement over five years. Subdural grids had a 1.3× higher total cost than the cost of SEEG electrodes, but this difference was not statistically significant (p=0.12). Facility costs were the largest contributor to total cost for both SEEG and subdural grids (55.2% and 59.7%, respectively). Given that facility costs were the largest contributor to total cost, the length of stay (LOS) was calculated for both groups. The average LOS for subdural grids was 10.5 days compared with 6.8 days for SEEG electrodes (p=0.02).

Conclusion: There was no statistical difference in the total cost between SEEG electrodes and subdural grids placed for seizure localization. This was surprising given that facility cost made up the majority of the total cost for both groups and patients who underwent subdural grid placement had a statistically longer hospital stay. Therefore, elucidation of additional cost drivers is needed in an attempt to reduce costs in both groups.

258. Convolutional Neural Networks Classification of Pediatric Refractory Epilepsy with RsMRI Latency Imaging

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Introduction: Pediatric epilepsy affects 0.5-1% of children. 30% of children are refractory to medical anticonvulsant therapy. Interictal epileptiform discharge (IED) found in EEG is a common test for epilepsy. IED, however, is specific (78-98%) but not sensitive (25-56%) for epilepsy. This study aims to analyze convolutional neural network (CNN) classification of pediatric refractory epilepsy using resting-state functional magnetic resonance imaging (rsMRI) data.

Methods: With IRB approval, the rsMRI and anatomical MRI of 63 refractory epilepsy patients, from Washington University and Memorial Hermann Hospital, and 259 healthy control (HC) patients, from the ADHD-200 data set, were collected. Images were transformed to pediatric atlases in Talairach space, and latency maps of the temporal difference between rsMRI and the global mean signal were calculated using voxel-wise cross-covariance. HC voxel-wise mean and standard deviation latency maps were created and were used to calculate latency z-score maps for HC and epilepsy patients. Latency z-score maps were stratified and randomly split into train, validation and test data sets. A CNN model of two convolutional and a fully connected layer was constructed and trained in Tensorflow. CNN hyper-parameters were optimized via grid-search for best validation accuracy and minimized overfitting, determined by difference between train-validation accuracy. Afterward, the model was run using optimized hyper-parameters and test data. Area under the receiver-operating characteristics curve (AUC) was calculated to evaluate the model's ability to classify epilepsy in the test set.

Results: Epilepsy disease state (epilepsy or no epilepsy) was correctly classified in 80% of test patients with an AUC of 0.75 using an optimized CNN model. Model overfitting was minimized but still present.

Conclusion: CNN could classify pediatric epilepsy using rsMRI latency imaging. With further development in model architecture and larger data sets, we hope CNN rsMRI screening could be an adjunct test to diagnose and prognosticate pediatric epilepsy.

259. Exome Sequencing Establishes Dysregulation of Neural Progenitor Cell Fate as a Critical Mechanism in Human Congenital Hydrocephalus

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Introduction: Congenital hydrocephalus (CH), thought to arise from failed cerebrospinal fluid (CSF) homeostasis, is treated with lifelong surgical CSF shunting with substantial morbidity. CH pathogenesis is poorly understood. Our recent genomics study of 180 probands with CH identified four novel CH genes, each implicated in regulating neural stem cell fate (Furey et al., Neuron, 2018). Nonetheless, less than 10 percent of studied cases are solved by these genes.

Methods: To expand our understanding of CH genetics, we doubled the size of our cohort via robust domestic and international collaborations and exome sequenced a total of 361 radiographically confirmed CH probands, including 216 case-parent trios, 14 familial cases, and 2 brain tissue-germ line paired samples.

Results: Exome sequencing revealed multiple new causative mutations in genes we previously identified (e.g., TRIM71 and SMARCC1), along with at least four novel CH genes, each of which is known to regulate ventricular zone NPC cell fate. Strikingly, three of these novel CH genes encode interacting enzymes of a signal transduction pathway targetable with available drugs.

Conclusion: These findings implicate new genes in CH and demonstrate related pathophysiology among sporadic and familial patients. These findings have implications for diagnosis, prognosis, and treatment, and suggest that in a subset of patients the risk of adverse neurodevelopmental outcomes may be unaltered whether or not shunting is performed.

260. Magnetic Resonance-guided Stereotactic Laser Ablation Therapy for the Treatment of Pediatric Epilepsy: A Multi-Institutional Retrospective Study

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Introduction: This study aims to assess the safety and efficacy of magnetic resonance-guided stereotactic laser ablation (SLA) therapy in the treatment of refractory epilepsy in pediatric patients.

Methods: Data from 17 North American centers was retrospectively reviewed. Clinical, technical, and radiographic data for

pediatric patients treated with SLA for a diagnosis of refractory epilepsy from 2008 to present was collected and analyzed.

Results: A total of 195 patients (ages $12.8\text{yr} \pm 5.9\text{yr}$) were included. Treatment locations included cortical (51%), subcortical (11%), mesiotemporal (25%), and hypothalamic (13%). The MRI-guided SLA systems utilized were Visualase in 171 cases and Neuroblate in 24 cases. The goals of the procedures were ablation (134), disconnection (48), or both (13). Median follow-up time was 23.7 months (range 3-71 months). Engel classification was reported for 71.3% patients. Of these patients, 91 (65.5%) had Engel Class I or II, and 48 (34.5%) had Engel Class III or IV at latest follow up. Improvement in targeted seizure type was reported for 82% patients. Subsequent surgery after SLA treatment was not required in 81.5% patients. None of the patients with epilepsy secondary to brain tumors required subsequent surgery after SLA therapy. Complications included: malpositioned catheters (3), intracranial hemorrhage (1), transient neurological deficits (16), permanent neurological deficits (3), worsened neuropsychological testing (1), symptomatic perilesional edema (4), and hydrocephalus (1). Neither the number of laser trajectories or number of lesions created resulted in a significantly increased risk of complications, however, there was an association between higher volumes of the lesion created and the incidence of complications.

Conclusion: SLA is an effective minimally invasive treatment option for pediatric patients with refractory epilepsy and brain tumors although not without risks. A larger volume of data will help define the indications and demonstrate the long-term efficacy and safety profile of this technology in the pediatric population.

261. Long-term survival in patients with primary intracranial germ cell tumors treated with surgery, carboplatin based chemotherapy followed by radiotherapy

Kazuya Motomura (Nagoya, Japan); Atsushi Natsume, MD, PhD; Toshihiko Wakabayashi, MD, PhD

Introduction: In the present study, we performed a retrospective review of patients receiving carboplatin based chemotherapy followed by radiotherapy for newly diagnosed primary intracranial germ cell tumors. In order to identify an optimal germ cell tumor treatment strategy, we evaluated treatment outcomes and toxicity and compliance.

Methods: This study included 110 consecutive patients with newly diagnosed primary intracranial germ cell tumors. The drug doses and administration schedule of carboplatin-etoposide (CARB-VP) were as follows: carboplatin (300 mg/m² daily for 1 days), and etoposide (100 mg/m² on days 1 to 3). Ifosfamide-carboplatin-etoposide (ICE) treatment comprised ifosfamide (1500 mg/m² daily for 3 days), carboplatin (300 mg/m² daily for 1 days), and etoposide (100 mg/m² daily for 3 days). Patients with germinomatous germ cell tumors (pure germinoma or germinoma with STGC) basically receive three cycles of CARB-VP and a total dose of 30Gy whole ventricular radiotherapy. We delivered combination therapy consisting of combined ICE chemotherapy and craniospinal irradiation followed by the complete resection of the residual tumor for nongerminomatous malignant germ cell tumors.

Results: The median follow-up time was 11.0 years (range, 0.5-37.8 years). The 5-year total survival rates of germinomatous and nongerminomatous germ cell tumors were 97.2% and 66.7%, respectively. The 10-year and 20-year total survival rates of germinomatous germ cell tumors were 95.7% and 90.0%, respectively. Adverse events related to carboplatin based chemotherapy are not detected. Furthermore, no treatment-related deaths were observed.

Conclusion: Our treatment with surgery, carboplatin based chemotherapy followed by radiotherapy is effective in treating primary intracranial germ cell tumors, especially in germinomatous group.

262. Dynamic stabilization of the lumbar spine in biomechanic demand individuals: series of 70 military patients

Carlos Roberto Massella junior (São Paulo, Brazil); ROMULO DE ALENCAR ARRAIS MOTA; THAIS DA SILVA MARQUES; RAFAEL DE SOUZA LODUCA; Paulo Porto de Melo

Introduction: Dynamic stabilization is an important spine surgery technique in young patients. There are, however, scarce literature reports about the performance of patients undergoing this type of surgery under extreme physical and biomechanical demands. We report the experience of the Neurosurgery Department of São Paulo Military Area Hospital, Brazilian Army in the surgical management of lumbar spine dynamics stabilization in the military population.

Methods: Retrospective data of all patients at a single tertiary-care military hospital from the Brazilian Army, who underwent operation by the Dynesys (®) technique in the last five years was collected. Data such as age, gender, rank, etiology, tobacco use, number of levels treated, herniated disc removal or only distraction, estimated blood loss, length of hospital stay, pain improvement, complications (including post-operative heterotopic calcifications) time to return to full unrestricted military activities were raised.

Results: In the last five years seventy patients underwent dynamic arthrodesis of the lumbar spine at the São Paulo Military Area Hospital. From this group of patients, 42 (60%) were male and 28 (40%) were female. All active patients

showed significant improvement in Oswestry Low Back Pain Index and 60 returned to unrestricted military activities, 9 returned to restricted activities and only 1 patient, although returning to duty, was able only to perform administrative work.

Conclusion: Dynamic stabilization showed up as an important tool for treating osteo-degenerative disease in the military population. The short hospital stay, safety, preservation of mobility and rapid return to activities make this technique an effective method. It might be an excellent option to treat patients with high biomechanic demands (athletes, military personnel). Preservation of mobility and rapid return to activities make this technique an effective method for them.

263. C1C2 Posterior Fusion for Treatment of Dynamic Compression in Vertebral Artery Dissection in Children: a Case Series

Bruno Perocco Braga (Dallas, TX), MD; Muhammad Janjua, MD; Nancy Rollins, MD; Amy Hogge, MD; Dowling Michael, MD

Introduction: Pediatric ischemic stroke is rare and difficult to diagnose. Vertebral artery dissection has a high recurrence rate and morbidity. Therefore, identifying a cause and establishing a protocol for diagnosis and treatment may improve outcome in children. We present a prospective case series of patients with dynamic compression of the vertebral artery at the site of dissection who underwent treatment by posterior C1C2 fusion.

Methods: From September 2014 to April 2018, nine patients presented with either cerebellar and/or occipital stroke and were found to have unilateral or bilateral dissection at the V3 segment of the vertebral artery. After a period of anticoagulation therapy while on cervical collar and an extensive hematological work-up negative to justify the stroke, they underwent angiogram with rotational maneuver and were found to have total or partial occlusion of the vertebral artery at the site of previous dissection. They all underwent C1C2 posterior fusion as part of their treatment. Other treatment options such as decompression or prolonged anticoagulation with cervical immobilization were not effective or considered but not feasible.

Results: There were 6 male and 3 female patients. Median age was 65.6 months (range 22-121 months). Posterior rib was used as autograft on all patients. On C1, there were 18 lateral mass screws. On C2, there were 12 pedicle screws and 6 pars screws. Median follow-up was 15.5 months (range 3-25 months) and there has been no ischemic event after surgery. Median blood loss was 41.8 mL. Only complication was a superficial wound infection treated with oral antibiotics alone in one patient. There was no need for transfusion, no repositioning of screws, no vascular or neurologic injury.

Conclusion: After following a strict diagnostic and treatment protocol, posterior C1C2 fusion is a safe and effective option for treatment of dynamic compression in vertebral artery dissection in children.

264. Frequent Subgaleal Shunt Taps Results in Improved Two-year Neuro-cognitive Outcomes in Post Hemorrhagic Hydrocephalus

Molly Hubbard, MD (Minneapolis, MN); Leah Kann; Danielle Tran; Sara Ramel, MD; Stephen Haines, MD; Daniel Guillaume, MD

Background: Intraventricular hemorrhage (IVH) in premature infants is a major cause of morbidity in neonates of very low birth weight (<1500g). The incidence of IVH in this cohort of patients has decreased from 50% to about 20% as of 2005, however the incidence of posthemorrhagic hydrocephalus (PHH) continues to be present in 25-50% of patients with IVH and is associated with long-term neurodevelopmental impairment and shown to increase cognitive and psychomotor delay. There is no consensus regarding timing or type of surgical intervention for treatment; with shunt or ventriculosubgaleal shunt (VSGS). We hypothesize that CSF removal with frequent ventricular reservoir taps results in improved two-year neuro-cognitive outcome compared to infrequent taps in premature infants with VSGS for PHH.

Methods: The surgery database containing all records of patients who underwent VSGS at a single institution between 2006-2014 was reviewed, and their birth weight, sex, IVH grade, age at VSGS placement, ventricle size at VSGS placement, maximum/minimum ventricle size, ventricle size at 2 years, number of VSGS taps, volume tapped at each event, cognitive scores at 2 years (Bayley scores) and history of shunt infection/malfunction/seizures were recorded in a secured database.

Results: There were 32 patients, 15 females (47%), with an average birth weight of 808 grams. 18 (56.3%) had grade IV, 9 had grade III hemorrhage, 4 had grade II IVH and one with grade I IVH. 13 patients had their VSGS tapped at least one time. Average ventricular volume had no correlation with Bayley scores at 2 years ($p = 0.489$). Total volume tapped ranged from 2-105.5 cc over the lifetime of the VSGS. In a general linear model, total volume tapped correlated with Bayley scores at 2 years ($p = 0.025$).

Conclusions: Total volume tapped during the lifetime of a VSGS leads to improved Bayley scores at two years of age. Ventricular size did not correlate with outcomes.

265. Postoperative Pain Protocol for Selective Dorsal Rhizotomy

Jeffrey Bejan Hatef, Jr., MD (Columbus, OH); Luke Smith, MD; Giorgio Veneziano; David Martin; Tarun Bhalla; Jeffrey Leonard, MD

Introduction: Selective dorsal rhizotomy (SDR) provides lasting relief of spasticity for children suffering from cerebral palsy, although controlling postoperative pain is challenging. Postoperatively, escalation of therapies to include a patient-controlled analgesia (PCA) pump and intensive care unit (ICU) admission is common. We developed a multi-modal pain management protocol that included intraoperative placement of an epidural catheter. We present the three year results of protocol implementation.

Methods: With IRB approval, all patients undergoing SDR at our institution were identified for review. Hourly pain scores were recorded. Adverse effects of medication, including desaturations, nausea and vomiting, and pruritus were also noted. Thirty nine patients undergoing the procedure with protocolized pain control were compared to seven controls treated with PCAs.

Results: Pain control was satisfactory in both groups, with average pain scores of 1.5 in both groups on postoperative day (POD) zero, decreasing by POD three to 1.1 in the PCA group and 0.5 in the protocol group. No patients under the protocol required admission to ICU; all patients with PCA spent at least one day in the PICU. Desaturations were seen in 16 patients in the protocol group (41%), but none required transfer to the PICU. 42% of PCA patients and 15% of protocol patients required treatment for itch ($p=0.08$). 86% of PCA patients and 46% of protocol patients required treatment for nausea or vomiting ($p=0.05$). Medication requirements for the hospitalization were decreased from 1.1 to 0.28 doses per patient for itch, and from 3 to 1.1 doses per patient for nausea.

Conclusion: Multi-modal analgesia is an excellent alternative to PCA for postoperative pain after SDR. Actual analgesia is comparative to controls without the need for intensive care monitoring. Side effects of high dose opiates were less frequent and required less medication. With the protocol, patients were safely treated on the floor.

266. Newton-2: Randomized, Double-Blind, Placebo-Controlled Study of EG-1962 in Aneurysmal Subarachnoid Hemorrhage

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Introduction: EG-1962 is a sustained-release microparticle formulation of nimodipine administered via an external ventricular drain (EVD) to patients with aneurysmal subarachnoid hemorrhage (aSAH). A randomized, phase 1/2a, dose-escalation study found EG-1962 was safe, well-tolerated and improved outcome. This led to NEWTON-2, a randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of EG-1962 to patients with aSAH, compared to standard of care oral nimodipine.

Methods: Subjects were World Federation of Neurological Surgeons (WFNS) grades 2-4 and had an EVD inserted as standard of care. EG-1962 was administered within 48 hours of aSAH. The primary endpoint was the proportion of subjects with favorable outcome 90 days after aSAH (extended Glasgow outcome scale [eGOS] 6-8). Delayed cerebral ischemia and infarction, use of rescue therapy and safety were evaluated.

Results: The study was halted by the independent data monitoring board after planned interim analysis of 210 subjects (282 randomized) with 90 day outcome found the study was unlikely to achieve its primary endpoint. After 90 day follow-up of all subjects, the proportion with favorable eGOS outcome was 46% (64/138) for EG-1962 and 43% (62/144) for placebo (Odds ratio [OR] 1.09, 95% confidence interval [CI] 0.67-1.77, $p=0.74$). EG-1962 significantly reduced vasospasm (50% [69/138] versus 63% [91/144], $p=0.025$), rescue therapy (27% [37/138] versus 35% [50/144]) and hypotension (7% [9/138] versus 10% [14/144]). Mortality also was lower (7% [10/138] versus 10% [15/144]). Prespecified subgroup analysis suggested efficacy in WFNS 3-4 subjects (46% [32/69] EG-1962 favorable outcome versus 32% [24/75] placebo, OR 1.59, 95% CI 0.98-2.59, $p=0.063$). No safety concerns or imbalance in adverse events were noted that halted the study or precluded further development.

Conclusion: This study found no significant improvement in favorable outcome for EG-1962 compared to standard of care. Favorable outcome was higher in the prespecified WFNS 3-4 subgroup. The safety profile was acceptable.

267. Extracellular RNAs Distinguish Between Stroke Subtypes

M. Yashar S. Kalani, MD (Charlottesville, VA); Kendal Jensen (Charlottesville, VA)

Introduction: Blood-based biomarkers capable of distinguishing between stroke subtypes can greatly aid with the in-field diagnosis of ischemic from hemorrhagic stroke, thereby increasing access to pharmacologic thrombolysis. Combining clinical samples and RNA sequencing we identify blood-based biomarkers predictive of ischemic stroke, spontaneous intraparenchymal hemorrhage and subarachnoid hemorrhage.

Methods: Patients with ischemic stroke, spontaneous intraparenchymal hemorrhage and subarachnoid hemorrhage were recruited at the time of presentation to the hospital. Routine clinical parameters were collected from all patients at admission and at followup. Additionally, we collected blood from a peripheral line at the time of admission. The blood was used to isolate DNA and RNA isolates. The RNA component was subjected to RNA sequencing and analysis to identify markers correlative to stroke subtypes and then validated against a second cohort of samples in a blinded fashion.

Results: Total RNA and small RNA fractions were isolated and subjected to next-generation sequencing using the Illumina platform. We identified 19 differentially expressed RNAs which distinguish between ischemic and hemorrhagic stroke with high fidelity and ability to distinguish between hemorrhage stroke subtypes. The ability to distinguish between ischemic and hemorrhagic stroke had a correlation of 85%.

Conclusion: We identify a high-fidelity blood-based biomarker panel with the ability to distinguish between ischemic and hemorrhagic stroke. This panel has the potential of being clinically tested and refined for the in-field diagnosis of ischemia and exclusion of hemorrhage, thereby increasing access to tPA administration.

268. Identification of novel somatic mutations, excluding KRAS, in adult sporadic arteriovenous malformations of the brain**Cerebrovascular Section Best Basic Scientific Paper**

Jonathan Weyhenmeyer, MD (Indianapolis, IN); Tae-Hwi Schwantes-An, PhD; Aaron Cohen-Gadol, MD, MSc; Brian Williams, MD, MSc; Jesse Savage, MD, PhD

Introduction: The etiology of brain arteriovenous malformations (BAVM) is undefined. Sporadic, congenital, inflammatory, and ischemic models have been proposed. Although the majority of BAVMs are considered sporadic there is minimal scientific evidence to support a specific genetic basis for their formation. The authors hypothesize sporadic BAVMs result from somatic mutation of the cerebral vasculature and utilize whole-exome sequencing (WES) in an effort to identify this change.

Methods: Forty-two patients who underwent surgical resection of non-syndromic BAVMs at a single institution from 2012 through 2017 were included in the study. The discovery cohort consisted of 26 BAVMs with paired blood samples. The validation cohort was comprised of 16 BAVM specimens alone. We performed exome sequencing of genomic DNA isolated from BAVM specimens and leukocyte-enriched fractions of blood. Sequencing data from all cohorts were processed using MuTect2 in order to identify potential sporadic mutations. The catalogue of genes with documented somatic change was tested for enrichment of biological processes using the Gene Ontology (GO) analyses tools.

Results: We identify 22 novel mutations in 13 BAVM patients that were not observed in their corresponding paired blood samples. Mutations in HRNR, ZNF208, ADGRB1, AGAP6, MUC5B, and MUC17 were validated in our unpaired BAVM-alone cohort. Subsequent GO analyses failed to demonstrate statistically relevant enrichment for biological process, cellular component, or molecular functions. In addition, we did not detect a single replicable somatic activating KRAS(chr12:25398284) mutation within our discovery or validation cohorts.

Conclusion: This is the largest WES study of BAVMs to date. There are notable somatic changes within the exome of BAVMs when compared to non-lesional genetic references. However, no single mutation or molecular pathway is ubiquitously appreciated. No replicable KRAS mutations were found. The significance of individual sporadic mutations necessitates further expression studies to elucidate the precise mechanisms non-familial BAVM etiology.

271. Optogenetic Stimulation of Excitatory Motor Cortex Neurons Promotes Functional Recovery after Stroke

Arjun Vivek Pendharkar, MD (Stanford, CA); Sean Harvey, BS; Terrance Chiang, BS; Michelle Cheng, PhD; Gary Steinberg, MD, PhD

Introduction: Post-stroke brain stimulations have been shown to successfully enhance functional recovery. Previously we have demonstrated that optogenetic pan-neuronal stimulations in the ipsilesional primary motor cortex (iM1) promote

functional recovery after stroke, however, the specific neuronal cell types involved (excitatory or inhibitory) remain unclear. Here we use optogenetic techniques to specifically stimulate excitatory neurons in layer V ipsilesional motor cortex and investigate the effects on functional recovery.

Methods: C57BL/6 wild type mice were used (7-9 weeks). Mice underwent stereotaxic surgery to inject AAV1-CAMKIIa-ChR2-eYFP and implant a fiber cannula in the iM1. Six weeks later, all mice were subjected to an intraluminal middle cerebral artery suture occlusion (30 minutes). Optogenetic stimulation began at post-stroke (PD) day 5 and continued until PD14. Sensorimotor tests were used to assess behavioral recovery at PD4, 7 and 14. Mice were sacrificed at PD14 and their brains were processed for immunohistochemistry with CD68 and MAP2 for infarct analysis.

Results: High expression of ChR2-YFP was detected in excitatory neurons of ipsilesional layer V motor cortex.

Optogenetic excitatory stimulations in iM1 resulted in significant forelimb movements. Horizontal rotating beam test demonstrated that iM1-stimulated mice recovered significantly faster than non-stimulated mice in both speed and distance at PD14 after stroke. In particular, iM1-stimulated mice exhibited robust recovery in distance traveled at PD14 ($p=0.01$), with most mice performed similar to pre-stroke baseline. Furthermore, iM1-stimulated mice also exhibited faster regain of body weight loss after stroke. Infarct analysis using immunohistochemistry showed that there was no difference in lesion size between groups.

Conclusion: These data highlight excitatory neurons as key cell type for brain stimulation-induced functional recovery after stroke. Current studies examine the molecular and circuit mechanisms underlying this recovery, including the role of neurotrophins in both the ipsilesional and contralesional sensory and motor cortices.

272. Impact of AVM Location on Language Cortex Right-hemisphere Reorganization: a Voxel-based Lesion-symptom Mapping Study

Xiaofeng Deng (Beijing, China); Yan Zhang; Jizong Zhao

Introduction: Cerebral arteriovenous malformations (AVMs) are congenital malformations, and right-sided dominance of the language cortex is not a rare phenomenon for patients with AVM located in the left language cortex. We tried to use voxel-based lesion-symptom mapping (VLSM) method to depict the location of AVM nidus precisely and to demonstrate the relationship between AVM location and the pattern of language cortex reorganization.

Methods: The authors retrospectively reviewed clinical and imaging data of 70 adult patients with unruptured cerebral AVMs who underwent blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) of language tasks. All patients were right handed, and all lesions were located in the left cerebral hemisphere. Lateralization indexes (LI) of the BOLD signals were calculated for Broca and Wernicke areas separately and were used to reflect the degree of right-sided dominance of the two language areas. VLSM method was applied to study the relationship between AVM location and LI of language task activations.

Results: Statistical analysis revealed that the change of LI of Broca area was significantly associated with lesions located in the inferior frontal gyrus, pre- and post-central gyrus, supramarginal gyrus and middle frontal gyrus. The change of LI of Wernicke area was significantly associated with lesions located in the left superior, middle, inferior and transverse temporal gyrus.

Conclusion: These findings provide new evidence that the language cortex reorganization patterns in AVM patients have anatomic specificity.

273. Minimally Invasive Surgeries for Hypertensive Intracerebral Hemorrhage: Preliminary Results of a Multicenter Randomized Controlled Trial

Xinghua Xu (Beijing, China); Qun Wang, MD; Xiaolei Chen, MD

Introduction: Intracerebral hemorrhage remains a significant cause of morbidity and mortality throughout the world. We tried to investigate whether, and to what extent, endoscopic evacuation and stereotactic aspiration could improve the outcome of supratentorial hypertensive intracerebral hemorrhage (HICH) compared with craniotomy.

Methods: We prospectively recruited patients with supratentorial HICH after the study was ethically approved (S2016-074-01) and registered at ClinicalTrials (NCT02811614). Patients were completely randomized into groups of endoscopic evacuation, stereotactic aspiration, or craniotomy, and received according surgical treatment after an informed consent was signed. The primary outcome was the prognosis estimated using the modified Rankin Scale (mRS) 6 months after ictus. The intent-to-treat analysis was used to compare the prognosis outcome of the three surgical methods. Hematoma clearance rate, operation time, intraoperative blood loss, hemorrhage-related pneumonia and intracranial infection rate were also analyzed.

Results: A total of 113 supratentorial HICH patients were enrolled in this study between June 2016 and June 2017,

including 37 in the endoscopic group, 37 in the drainage group, and 39 in the craniotomy group. Baseline characteristics of patients in each group were balanced. The hematoma clearance rates were 89.8% in the endoscopic group, 51.3% in the drainage group, and 87.6% in the craniotomy group, with statistically significant difference ($P<0.001$). There were also no statistical differences in terms of intracranial infections and in-hospital mortality. Finally, 39% (14/36) patients in the endoscopic group, 37% (13/35) in the drainage group, and 27% (13/35) in the craniotomy group got a good outcome (mRS score 0-2). The mean mRS score were 3.1 in the endoscopic group, 3.2 in the drainage group, and 3.6 in the craniotomy group. The mRS score distribution was statistically different.

Conclusion: Compared to craniotomy, endoscopic evacuation and stereotactic aspiration might enhance the neurological recovery in patients with supratentorial HICH and improve the outcome.

274. Stereotactic Radiosurgery for Pediatric versus Adult Brain Arteriovenous Malformations: A Multicenter Study

Cerebrovascular Section Best Clinical Scientific Paper

Ching-Jen Chen, MD (Charlottesville, VA); Dale Ding, MD; Hideyuki Kano, MD; David Mathieu, MD; Douglas Kondziolka, MD; Rafael Rodriguez-Mercado, MD; Inga Grills, MD; Dade Lunsford, MD; Jason Sheehan, MD, PhD; Gene Barnett, MD; Caleb Feliciano, MD

Introduction: The aim of this international, multicenter retrospective matched cohort study is to directly compare the outcomes after stereotactic radiosurgery (SRS) for brain arteriovenous malformations (AVM) in pediatric vs. adult patients.

Methods: We performed a retrospective review of AVM patients who underwent SRS at eight institutions participating in the International Gamma Knife Research Foundation (IGKRF) from 1977-2014. Patients were categorized into pediatric (<18 years old) and adult (≥ 18 years old) cohorts, and matched in a 1:1 ratio using propensity scores. Favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RIC).

Results: From a total of 2,191 patients who were eligible for inclusion in the overall study cohort, 315 were selected for each of the matched cohorts. There were no significant differences between matched pediatric vs. adult cohorts with respect to the rates of favorable outcome (59% vs. 58%, $p=0.936$), AVM obliteration (62% vs. 63%, $p=0.934$), post-SRS hemorrhage (9% vs. 7%, $p=0.298$), radiologic RIC (26% vs. 26%, $p=0.837$), symptomatic RIC (7% vs. 9%, $p=0.383$), or permanent RIC (2% vs. 3%, $p=0.589$). The all-cause mortality rate was significantly lower in the matched pediatric cohort (3% vs. 10%, $p=0.003$).

Conclusion: The outcomes following SRS for comparable AVMs in pediatric versus adult patients were not found to be appreciably different. SRS remains a reasonable treatment option for appropriately selected pediatric AVM patients, who harbor a high cumulative lifetime hemorrhage risk. Age appears to be a poor predictor of AVM outcomes after SRS.

275. Seizure Outcomes Following Radiosurgery for Cerebral Arteriovenous Malformations: An Updated Systematic Review and Meta-Analysis

Natasha Ironside, MbChB (Rockville, MD); Ching-Jen Chen, MD; Dale Ding; Adeel Ilyas, MD; Jeyan Kumar, MD; Thomas Buell, MD; Davis Taylor, MD; Cheng-Chia Lee, MD; Jason Sheehan, MD, PhD

Introduction: The seizure outcomes for patients with brain arteriovenous malformations (AVM) who undergo intervention with stereotactic radiosurgery (SRS) are incompletely understood. The objective of this study was to determine, in a systematic review and meta-analysis, the rates of seizure control after SRS for patients with AVM-associated seizures and identify predictive factors.

Methods: We performed a systematic review of PubMed and MEDLINE databases from January 1987 to January 2018, in accordance with PRISMA guidelines. Studies reporting post-SRS outcomes data for ≥ 5 patients with AVM-associated seizures were included. The seizure outcomes and factors associated with seizure freedom were evaluated using meta-analysis.

Results: A total of 27 studies, comprising 4,826 patients, met the inclusion criteria for analysis. One or more seizures occurred in 1,456 of 4,826 patients (34.7%, [26.0–43.9%]), and the mean follow-up was 48 $\pm$ 7 months. Seizure control (seizure freedom or seizure improvement) was achieved in 910 of 1,312 patients (73.1% [66.9–78.9%]). Seizure freedom was achieved in 597 of 1,245 patients (55.7% [44.5–66.6%]). Of 259 patients with seizure freedom, cessation of antiepileptic drugs was achieved in 175 patients (67.3% [46.3–85.1%]). AVM obliteration (OR=4.61; $p<0.001$), shorter seizure duration (OR=6.80; $p<0.001$), generalized seizure type (OR=2.27; $p=0.007$), and prior AVM hemorrhage

(OR=5.10; $p<0.001$) were significantly associated with seizure freedom.

Conclusion: SRS affords seizure control to the majority of patients with AVM-associated seizures, and approximately two-thirds of those with seizure freedom are able cease anticonvulsants. Nidal obliteration appears to improve the likelihood of seizure freedom, and thus remains the primary goal of intervention with SRS.

276. Evolution of Open Surgery for Unruptured Intracranial Aneurysms - Less Cases, Increased Difficulty, More Morbidity

Michael Gaub (Tucson, AZ); Bryan Kromenacker; Travis Dumont, MD (Tucson, AZ)

Introduction: The approach to intervention for unruptured intracranial aneurysms (UIAs) remains controversial. Utilization of endovascular techniques for aneurysm repair increased dramatically during the last decade, fueled in part by advances in catheter-based technologies. We sought to analyze recent national trends for electively treated UIAs focusing on pre-existing patient disease burden and intervention modality selection.

Methods: The HCUP-NIS national database was used to identify patients with primary diagnosis codes of unruptured intracranial aneurysm (ICD-9 437.3) between 2000 and 2015. Patients were dichotomized by intervention into endovascular treatment or open surgical treatment. Analysis of pre-existing disease severity characteristics for each group were calculated using the Elixhauser comorbidity index. Complications of combined peri-procedural stroke or death during admission and hospital length of stay were used as primary endpoints for comparison.

Results: The percent of total UIAs treated electively with open approach decreased from more than 95% of cases in 2000 to less than 25% in 2015. Additionally, the rate of primary endpoint complications and length of stay for open cases saw a statistically significant increase during this time ($p<0.05$). Furthermore, the average incoming disease severity for those treated with clipping increased over this interval. Conversely, the relative volume of endovascular cases increased but the rate of complications and average group disease severity decreased.

Conclusion: While the percent by volume of UIAs treated electively with open approach has decreased since 2000, with a concomitant increase in complication rate, the health characteristics of patients treated with surgical clipping show an increase in severity of pre-existing disease burden. Further research into factors contributing to this finding, including potential socioeconomic differences and changes in surgeon experience with open techniques, are needed.

277. Treatment with dimethyl fumarate reduces the formation and rupture of intracranial aneurysms in an elastase mouse model

Mimi Chen (New Orleans, LA); Crissey Pascale, MA; Alejandra Martinez, PhD; Christopher Carr, MD; Devon O'Donnell, BS; Aaron Dumont, MD

Introduction: Oxidative stress and chronic inflammation in arterial walls have been implicated in intracranial aneurysm (IA) formation and rupture. Dimethyl fumarate (DMF), an oral fumaric acid ester, exhibits immunomodulatory properties, partly via activation of the Nrf2 pathway, which reduces oxidative stress by inducing the antioxidant response element (ARE). This study evaluated the effects of DMF on the inflammatory response to TNF- α treatment in vitro, and in mice using an elastase aneurysm model.

Methods: Vascular smooth muscle cells (VSMC) were treated with TNF- α (50 ng/ml) and/or DMF (20 μ M, 50 μ M, 75 μ M and 100 μ M) for 24 hrs. Gene and protein expression for cytokines and smooth muscle cells markers were then evaluated using real-time RT-PCR and a Bio-Plex Immunoassay, respectively. Annexin V-FITC apoptosis detection assay was used to detect cell death by flow cytometry. Aneurysms were induced in C57BL/6 mice using a well-established elastase model. The mice were then treated with either DMF at 100mg/kg/day P.O. or vehicle (1% carboxymethylcellulose) for two weeks. At the conclusion of the study, the circles of Willis were harvested for gene expression analysis.

Results: DMF treatment protected VSMCs from TNF- α induced inflammation as demonstrated by its downregulation of cytokines and upregulation of Nrf2 and smooth muscle cell markers. Moreover, at higher doses, DMF inhibited the pro-proliferative action of TNF- α by increasing apoptosis which protected the cells from necroptosis. In mice, DMF treatment significantly decreased the incidence of aneurysm formation and rupture with increased Nrf2 levels in the cerebrovasculature.

Conclusion: DMF demonstrated a neuroprotective effect in a murine IA model that may be mediated by the activation of the Nrf2 pathway with a resultant inhibition of oxidative stress, inflammation, and fibrosis in the cerebrovasculature. This suggests a potential role for DMF as a rescue therapy for patients at risk for formation and rupture of IAs.

278. Craniocervical and Posterior Fossa Dimensions Can Affect Need for Decompressive Craniectomy In Posterior Fossa Hemorrhage

Ethan Allen Neufeld (Salt Lake City, UT); Sarah Menacho, MD; Lubdha Shah, MD

Introduction: Posterior fossa hemorrhage (PFH) may require decompressive craniectomy due to hydrocephalus and/or herniation. Literature shows that hematomata >3 cm have higher likelihood of surgery, which is indicated for evidence of herniation or declining GCS. No evaluation of the effect of craniocervical junction (CCJ) and PF dimensions on the need for surgery exists. We evaluated validated CCJ/PF measurements in patients with PFH and correlated these measurements with need for decompression.

Methods: CT/MR examinations performed on adults with primary presentation of PFH were found. Cases with an underlying mass or concurrent supratentorial pathology were excluded. Hemorrhage size was measured in three dimensions and averaged. PF dimensions measured included: McRae's, clival line, Twining's, internal occipital protuberance to opisthion distance (IOP-OP), tentorium diameter, and transverse diameter of the PF. Chart review for management details, blood pressure, use of anticoagulation, and patient disposition was performed. Values of the craniectomy group and non-surgical, surviving group were compared using two tailed t-test.

Results: 29 non-surgical and 19 surgical cases were included. Statistically significant difference between hematoma diameter of the surgical (4.6 cm) and non-surgical cases (2.9 cm) was found ($P<.001$). Product of the clival length, Twining's, and transverse diameter was calculated. Statistically significant difference between mean of this measurement of the surgical (296.02 cm³) and non-surgical cases (328.66 cm³) was found ($P=.02$). A scaled score was made by dividing hematoma diameter by PF volume and multiplying by 1000. Statistically significant difference in the mean of scores of the non-surgical and surgical patients was found ($P<.001$). No non-surgical patient scored >14. No surgical patient scored <11.

Conclusion: Our data indicates that smaller PF volumes were more likely to require surgery as determined by clinical standards, independent of hemorrhage size. Our data suggests that patients with scores <11 may be managed conservatively while those scoring >14 will likely require surgery.

279. Astaxanthin inhibits NLRP3 inflammasome signaling through sirtuin 1 after experimental subarachnoid hemorrhage

Xiangsheng Zhang (Nanjing, China); Yue Lu; Chunhua Hang

Introduction: Inflammation contributes greatly to the development of early brain injury (EBI) after subarachnoid hemorrhage (SAH). However, the anti-inflammatory effects of astaxanthin (ATX) and the underlying molecular mechanisms are not fully elucidated. The nod-like receptor pyrin domain-containing 3 (NLRP3) inflammasome involves in and plays an important role in EBI pathogenesis after SAH. In addition, the NLRP3 inflammasome signaling can be modulated by sirtuin 1 (SIRT1) activation, which is also implicated in the pathophysiology of SAH. The current study was conducted to investigate whether ATX could inhibit SIRT1-mediated NLRP3 inflammasome activation and the subsequent brain injury after SAH.

Methods: A prechiasmatic cistern SAH model was conducted in vivo experiments. In vitro, neuron-microglia co-cultures were exposed to oxyhemoglobin to mimic SAH. SIRT1-specific inhibitor sirtinol was exploited to study the underlying neuroprotection mechanisms of ATX. Neurological scores and brain water content were recorded. Immunofluorescence staining, enzyme-linked immunosorbent assays, real-time PCR analysis, and Western blotting were performed to detect NLRP3 inflammasome signaling pathway and SIRT1 activation. Neuronal degeneration was determined by lactate dehydrogenase assay and TUNEL staining.

Results: Our data showed that NLRP3 inflammasome was significantly activated in the cerebral cortex after SAH, with consequent increases in the inflammatory response. Treatment with ATX could significantly suppress the NLRP3 inflammasome signaling and the subsequent inflammatory damage after SAH. ATX administration also significantly inhibited caspase-1-mediated pyroptosis and caspase-3-dependent apoptosis both in vivo and in vitro. Additionally, ATX treatment activated SIRT1 expression after SAH, whereas SIRT1-specific inhibitor sirtinol evidently inhibited ATX-induced SIRT1 expression and induced NLRP3 inflammasome activation. Sirtinol pretreatment also reversed the beneficial effects of ATX against SAH and exacerbated brain damage after SAH.

Conclusion: These results suggested that ATX could ameliorate inflammatory damage and the subsequent brain injury after SAH by suppression NLRP3 inflammasome signaling pathway, which might be modulated by SIRT1 activation.

280. Mechanical Cisternal Occlusion Causes Glymphatic Dysfunction and Increased AQP-4, Iba1 Expression Following Subarachnoid Hemorrhage

Zoe Teton (Portland, OR); Tristan Stani, MD; Justin Cetas, MD, PhD

Introduction: The discovery of the glymphatic system was one of the most momentous in brain physiology in recent years and the implications of its existence are only just beginning to be realized. For the neurosurgeon, this is nowhere more apparent than in the study of subarachnoid hemorrhage (SAH). Glymphatic channels are lined with aquaporin-4 and it is the expression and polarization of these water channels that dictate the level and direction of CSF flow within them. When these channels are disrupted, fluid dynamics are effected in ways that are not yet fully understood. We used a model of cisternal microbead injections to reproduce the glymphatic dysfunction following SAH that stems purely from mechanical blockade.

Methods: Three treatment groups--aCSF, autologous blood, and microbeads--were administered into the prechiasmatic cistern of adult male rats. Glymphatic flow was assessed by injecting 20 μ l of Evans Blue dye into the cisterna magna and then surface fluorescence intensity was recorded. Sagittal brain slices were stained and secondary antibody fluorescence signal was quantified regionally. Degree of AQP-4 depolarization was measured as previously described.

Results: Microbead and SAH groups showed comparable acute glymphatic dysfunction beginning at 1 hour. In both of these groups, AQP-4 and GFAP fluorescence intensity peaked at 24 hours and then decreased, whereas Iba1 peaked at 96 hours. SAH and Beads groups showed significantly increased ventricular volumes and markedly increased AQP-4 depolarization as compared to aCSF controls.

Conclusion: Mechanical cisternal occlusion with microbeads produces glymphatic dysfunction comparable to that following SAH. In both cases, Aquaporin-4, GFAP and IBA-1 are upregulated, consistent with a progressive inflammatory response, while increased ventricular volumes and AQP-4 depolarization suggest disrupted fluid dynamics. Further study is warranted into both glymphatic dysfunction and into AQP-4 and Iba1 as therapeutic targets in SAH.

281. SIRT1 Activity is Critical for Hypoxic Conditioning-Induced Neurovascular Protection in Subarachnoid Hemorrhage (SAH)

Jin Vivian Lee, BA (Saint Louis, MO); Deepti Diwan, PhD; Jane Yuan, BA; Julian Clarke, BA; Ananth Vellimana, MD; Gregory Zipfel, MD

Introduction: Delayed cerebral ischemia (DCI) is the most preventable cause of poor outcomes after subarachnoid hemorrhage (SAH). However, the pathophysiology of DCI after SAH is poorly understood. This knowledge gap may explain the lack of existing therapies for DCI prevention. Previously, our lab has shown that hypoxic postconditioning (HPostC) after SAH protects against several vascular hallmarks of DCI, including vasospasm and microvascular thrombosis (MVT), and improves neurological function. However, this novel treatment paradigm has limited translational potential. In search of druggable molecular targets, we recently found a critical role for SIRT1 activation in HPostC.

Methods: First, the causal role of SIRT1 in HPostC-induced DCI protection was investigated. Wild-type mice were treated with SIRT1 inhibitor, EX527, or vehicle and HPostC (8% O₂ for 2h) or normoxia after surgery. Global SIRT1 knockout mice were treated with HPostC after SAH or sham. Second, the extent of neuroprotection mediated by SIRT1 was tested by treating wild-type mice with a SIRT1 activator, resveratrol, or vehicle after SAH or sham surgery. Transgenic mice with SIRT1 global overexpression were subjected to SAH or sham surgery. Neurological function was assessed every 24h. Vasospasm and MVT were analyzed 72h after SAH. Vasospasm of middle cerebral artery diameter was assessed by ROX-SE blood vessel staining. MVT was quantified by counting fibrinogen-positive immunoreactive vessels. SIRT1 mRNA and protein expression were assessed in brain lysates by qPCR and Western blot, respectively.

Results: HPostC after SAH augments SIRT1 mRNA and protein expression. Pharmacologic inhibition and genetic deletion of SIRT1 block HPostC-induced protection against vasospasm, MVT, and neurological deficits following SAH. Pharmacologic activation and global overexpression of SIRT1 reduce the DCI-related outcomes.

Conclusion: SIRT1 activity is critical and sufficient for inducing HPostC-induced protection against DCI-related outcomes after SAH. Our findings suggest a new therapeutic target to prevent DCI and may help to elucidate its pathophysiology.

282. Risk Factors For Clinically Significant Vasospasm Following Traumatic Brain Injury

ThinkFirst Injury Prevention Award

Ryan McCormack, MD; Nicholas King, BS; Huimahn Choi, MD; Ryan Kitagawa, MD (Houston, TX)

Introduction: The risk factors for clinically significant post traumatic vasospasm (PTV) are poorly described. This study characterizes these risk factors to allow for improved screening and prevention of delayed cerebral ischemia after traumatic brain injury (TBI).

Methods: A retrospective chart review of TBI patients for an urban level I trauma center between 2014 and 2018 was performed. Our patient cohort included patients with medically-refractive vasospasm requiring angiogram intervention, patients with medically-responsive vasospasm identified by angiogram, and matched (age, date within 1 year of injury, and mechanism of injury) control patients without clinical PTV. Patients with potentially confounding vascular injuries were excluded. Univariate general linear modeling was utilized to identify significant categories with cross validation by one-way ANOVA with post-hoc testing.

Results: Of the 10,392 patients screened, a total of 552 patients were reviewed in detail. 52 patients required intervention for medically-refractive PTV, 26 patients had medically-responsive vasospasm present on angiogram not requiring intervention, and 474 patients that did not have clinical vasospasm were used as case matched controls. Our analysis demonstrated that a lower admission Glasgow Coma Scale (GCS) score, subarachnoid hemorrhage (SAH), amphetamines or marijuana use, and admission arterial blood gas base deficit (BD) each contributed to an increase in risk of vasospasm. When medically-refractory and responsive vasospasm were compared, fever, SAH involving multiple lobes, cocaine use, elevated intracranial pressure, and hypertonic saline use were more common in medically refractive PTV. Within the medically-refractory group, 20/52 developed strokes during hospital course.

Conclusions: Our study is the largest cohort to date of angiogram verified PTV with a matched population. We demonstrate that the following factors are associated with PTV: low GCS, BD, subarachnoid hemorrhage, and drug use (amphetamines, marijuana, and cocaine). Further directions will include modeling with a prospective analysis to validate our model for prediction of PTV.

283. Blunt Cerebrovascular Injury in Pediatric Trauma: A National Database Study

Dominic Harris, MD; Andrew Carlson, MD (Albuquerque, NM)

Introduction: The incidence of blunt cerebrovascular injury (BCVI) has not been well characterized in the pediatric population. Our objective is to describe the incidence, patient characteristics, and risk factors for pediatric patients with cerebrovascular injuries.

Methods: We collect data from the Kids' Inpatient Database (KID), a nationally representative database of pediatric admissions, for years 2000, 2003, 2006, 2009, and 2012.

Results: Among 644,399 admissions for blunt trauma, 2,150 were associated with BCVI, an incidence of 0.33 percent. The incidence of BCVI nearly doubled from 0.24 percent in 2000 to 0.49 percent in 2012. Patients ages 4 to 13 were less likely to have BCVI compared to patients in the youngest (0-3 years) and oldest age groups including adolescents (14-17 years) and young adults (18-20 years). In multivariate analysis, mechanism of injury was not associated with increased risk of vascular injury. BCVIs were associated with cervical (adjusted odds ratio [aOR] 4.6, 95% confidence interval [CI] 3.8-5.5), skull-base (aOR 3.0, 95% CI 2.5-3.6), clavicular (aOR 1.4, 95% CI 1.1-1.8), and facial fractures (aOR 1.3, 95% CI 1.0-1.5), as well as intracranial hemorrhage (aOR 2.7, 95% CI 2.2-3.2) and traumatic brain injury (aOR 2.0, 95% CI 1.7-2.4). Among pediatric patients with BCVI, 37.4 percent had an ischemic infarct and in-hospital mortality was 12.7 percent.

Conclusion: The incidence of BCVI in pediatric population is increasing, likely due to increased use of screening. Patients in both the oldest and youngest age groups are most at risk for BCVI. Risk factors include the presence of cervical, facial, clavicular, and skull-base fractures. Diagnosed BCVI is associated with a relatively high incidence of stroke with increased morbidity and mortality. Screening in high risk pediatric patients and treatment with anti-platelet or anticoagulation is likely reasonable, taking into consideration other injuries.

284. No Increase in Neurodegenerative Proteinopathy Following TBI in Military Services Members: A Preliminary Study Demonstrating Absence of CTE pathology

Arushi Tripathy (Kalamazoo, MI); Ashley Shade; Brittany Erskine; Kristi Bailey; George Perry; Rudy Castellani

Introduction: It is presently unknown whether military service members are at risk for CTE pathology or neurodegenerative proteinopathies such as Alzheimer's disease (AD), due to TBI, with or without blast. Studies are mixed with respect to mild TBI, although an increased risk of clinical AD with moderate and severe TBI is more consistently demonstrated. However, no studies to date demonstrate a longitudinal progression from traumatic brain injury to autopsy neuropathology. We therefore studied veterans for proteinopathy, as it relates to military service and TBI history.

Methods: In this cross-sectional survey of autopsy neuropathology in former military service members, brain specimens from 21 former military services members were examined. Next-of-kin consented to donation and research. Proteinopathy burden (Braak staging, and modified CERAD score) was compared to age-matched controls.

Results: 20 out of 21 decedents were male, with a mean age of 66.2 (range 32-94). 14 had a history of psychiatric problems; 10 had a history of PTSD specifically. 5 had neurological problems including stroke and seizure. One subject had early onset AD. 4 subjects had a history of TBI and 3 had a history of blast exposure. Neuropathological examination showed variable age-related proteinopathy, ranging from Alzheimer disease neuropathologic change A0B1C0 to A3B3C3 by NIA-AA 2012 consensus guidelines. None of the cases showed changes specific for CTE pathology. There was no relationship between p-tau burden (Braak stage) or amyloid- β burden (modified CERAD plaque score) and TBI, blast exposure, or psychiatric signs. P-tau in the amygdala showed no correlation with PTSD history.

Conclusion: These preliminary studies argue against the assertion that military service represents a risk for CTE pathology or neurodegenerative proteinopathy. More research is needed to study the relationship, if any, between TBI and neurodegenerative proteinopathy.

286. Exosomes generated from mesenchymal stem cells cultured under 3D conditions promote recovery after traumatic brain injury in rats

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Introduction: Multipotent human bone marrow-derived mesenchymal stem cells (hMSCs) improve functional outcome after experimental traumatic brain injury (TBI). The present study was designed to investigate whether systemic administration of cell-free exosomes generated from hMSCs cultured in 2-dimensional (2D) conventional conditions or in 3-dimensional (3D) collagen scaffolds also promote functional recovery and neurovascular remodeling in rats after TBI.

Methods: Adult male Wistar rats were subjected to TBI induced by controlled cortical impact; 24 hours later tail vein injections of exosomes derived from hMSCs cultured under 2D or 3D conditions or an equal number of liposomes (control) were performed (n=8/group). The Morris water maze (MWM) test, neurological severity scores (NSS) and footfault tests were employed to evaluate cognitive and sensorimotor functional recovery. Animals were sacrificed at 35 days after TBI and histological and immunohistochemical analyses were performed

Results: Compared with liposome-treated control, exosome-treatments significantly improved spatial learning measured by the MWM as well as sensorimotor functional recovery measured by the NSS and footfault tests ($p < 0.05$). Exosome treatments significantly increased the number of newborn endothelial cells (angiogenesis) in the lesion boundary zone and dentate gyrus, and significantly increased the number of newborn neurons in the dentate gyrus. Exosome treatments also reduced neuroinflammation. Exosomes cultured in 3D scaffolds provided better outcome in spatial learning than exosomes cultured in the 2D condition.

Conclusion: Exosomes generated from hMSCs significantly improve functional recovery in rats after TBI, at least in part, by promoting endogenous angiogenesis and neurogenesis and reducing neuroinflammation. Also, culturing the exosomes under 3D conditions enhances their functional efficacy. Thus, exosomes can be a novel cell-free therapy for TBI.

287. Avoiding Antiplatelet Reversal in Non-Operative Intracranial Hemorrhages: Functional Outcomes of Guideline-Based Practice

Courtney Pendleton, MD (Philadelphia, PA); Christine Hammer, MD; Erika Dillard, MD, PhD; Ariya Mobaraki; Trinava Roy; Syed Shah; Jack Jallo, MD, PhD

Introduction: Historically, standard of care was to reverse antiplatelet medications in all patients presenting with intracranial hemorrhages, regardless of demonstrated hemorrhage expansion or need for neurosurgical procedures. In 2016, the Neurocritical Care Society and Society of Critical Care Medicine issued joint guidelines for reversal of antiplatelet agents in intracranial hemorrhages. We present an analysis of a single-institution experience with pre- and post-guideline management.

Methods: Retrospective cohort analysis from 2016-2018 was done for a single tertiary academic referral center using ICD9/ICD10 codes. Included patients had use of antiplatelet agent and two head CTs available to evaluate hemorrhage expansion. Exclusion criteria: patients <18 years old, pregnant, with a hematologic disorder, or aneurysmal subarachnoid hemorrhage. The primary outcome was modified Rankin score (mRS) at time of discharge and time of last follow-up.

Results: 225 patients were included with an average age of 64.3 years. 62.5% received no reversal of antiplatelet medications in the absence of hemorrhage expansion or need for neurosurgical procedure. 37.5% received platelet transfusions for reversal of antiplatelet medications. The mRS at follow-up did not significantly differ between these two groups ($p < 0.08$).

Conclusion: We reviewed clinical outcomes for patients with non-operative intracranial hemorrhages receiving pre- and post-guideline management of antiplatelet medications. The mRS between these two groups at the time of discharge, and at the time of last follow-up, did not differ significantly. This suggests that in addition to minimizing adverse events associated with blood product transfusion, post-guideline management may lead to equivalent functional outcomes in a large single-institution experience.

288. Immediate Head CT Following Emergency Craniotomy or Craniectomy for Acute Trauma: Is it Beneficial?

Christian Joaquin (Vallejo, CA); Kevin Yoo, MD; Gail Tominaga, MD; Imad Dandan, MD; Fady Nasrallah, MD; Gary Schwendig, MD; Marc Sedwitz, MD; Sanjay Ghosh, MD; Scott Leary, MD; Jeffrey Schweitzer, MD; Vikram Udani, MD; Frank Coufal, MD

Introduction: There is no neurosurgical standard of care of when a follow-up head CT (HCT) should be performed following craniotomy/craniectomy (Crani) for acute trauma injury (ATI). When patients require a second Crani based on a delayed post-op HCT, there is always a question of whether the new HCT findings could have been detected earlier. Our hypothesis is that a HCT performed immediately after Crani will allow earlier detection of intracranial lesions requiring further surgery, thereby preventing delay of potentially clinically significant treatment.

Methods: All trauma patients requiring emergency Crani for ATI at one Level II Trauma Center over 3 years were taken from the operating room directly to the CT scan for an immediate post-operative HCT. The Neurosurgeon reviewed the HCT while the patient was in the CT scanner and determined if the patient needed to return to the OR for a second Crani. Protocol violators were those that did not have an immediate head CT following Crani.

Results: A total of 114 Crani patients with 13 excluded and 22 protocol resulting in a study population of 79 patients. There were 10 repeat Crani procedures performed on 8 patients based on the immediate post-op HCT results. Two patients required a third Crani after their second immediate post-op HCT. In the end, 10.1% of patients went back to the OR for at least 1 repeat Crani following an immediate post-op HCT. Looked at differently, 12.3% of the immediate post-op HCT group revealed findings that were deemed by our Neurosurgeons to repeat a Crani.

Conclusion: Significant surgical findings were identified in 12.3% of all immediate post-op head CT scans prompting re-operation. Immediate post-op HCT following Crani for ATI may be warranted to detect ongoing or new intracranial hemorrhage requiring multiple Crani's to avoid delays in management and progression of brain injury.

289. Early Versus Late Pharmacologic Thromboprophylaxis In Traumatic Intracranial Hemorrhage: A Systematic Review And Meta-Analysis.

Mohammed Ali Alvi, MD (Rochester, MN); Victor Lu, MD, MS

Introduction: Traumatic brain injury (TBI) presents a significant morbidity and mortality risk, with part of that make-up due to the increased risk of venous thromboembolic (VTE) events as a consequence of prolonged immobilization and

systemic hypercoagulability and also of intracranial hemorrhage (ICH). Studies have shown that pharmacologic thromboprophylaxis (PTP) initiated within 72 hours after computed-tomography (CT) demonstrated stabilization of ICH does not increase progression risk. The aim of this study was to investigate if the incidence of thromboembolic events in traumatic ICH is impacted by the timing of PTP.

Methods: The search strategy was designed around the PICOS (Population, Intervention, Comparator, Outcome, Study) question format. The definition of early was study dependent; however it was limited to within 72 hours or less of admission. PTP could be achieved with either UFH or LMWH. The primary outcomes of interest included incidence of hemorrhagic progression and VTE events during the course of while secondary outcomes included specific incidences of deep vein thrombosis (DVT), pulmonary embolism (PE), and mortality.

Results: Eleven retrospective studies consisting of 5036 cases were considered eligible for this study; of these, 2 studies defined early as <24-hrs of admission, 3 studies as <48-hrs, and 6 studies as < 72-hrs of admission. Meta-analysis indicated that there was a statistically significant difference between early and late PTP in incidence of overall VTE, favoring early PTP (OR 0.58;95%CI 0.38-0.87; I²=39.5%; P=0.008); DVT, favoring early PTP (OR 0.49;95%CI 0.35-0.70; I²=19.4%; P<0.001); and PE, favoring early PTP (OR 0.54;95%CI 0.30-0.92; I²=0.0%;p=0.022). No differences were observed in incidence of hemorrhagic progression and other secondary outcomes.

Conclusion: Our results indicate that compared to late-PTP, early-PTP does not augment the risk of adverse thromboembolic events following TBI when administered up to 72 hours from admission, and may even confer a more favorable VTE profile.

290. Evaluating Topical Vancomycin to Reduce Surgical-Site Infections in Craniotomies: Interim Analysis of a Randomized Controlled Trial

Diana Tang Ruan (New York, NY); Sophie Ulene; Brandon Christophe; Alison Clarke; E. Connolly, MD

Introduction: Surgical site infections (SSIs) following craniotomy procedures are associated with worse outcomes and higher costs. Application of topical vancomycin prior to wound closure has decreased SSI rates in spine, cardiac, and ophthalmologic procedures, while minimizing systemic exposure to vancomycin. Here, we assess the efficacy of topical vancomycin in reducing SSIs in craniotomy patients.

Methods: As of August 1st, 2018, 970 craniotomy patients at New York Presbyterian-Columbia and Cornell were enrolled and 758 interviewed in this ongoing multi-center, patient-blinded randomized controlled trial. Subjects were randomized to Cohort I, which received IV cefazolin, or to Cohort II, which received IV cefazolin and 2 g topical vancomycin. Follow-up phone interviews were conducted to screen for SSIs within 30 and 90-days post-operation (POD). Primary outcomes were defined as antibiotic prescription for suspected SSI (probable) or positive skin culture with/without SSI-related hospital readmission (confirmed).

Results: Among 378 Cohort I subjects (50.1%) interviewed at POD 30, SSI rates were 1.85% probable and 0.8% confirmed. The 367 Cohort II patients (49.9%) interviewed at POD 30 had rates of 0.53% probable and 1.1% confirmed (RR 1.05; 0.27, 4.19, p=0.9399; NNT=1,775). Of 123 Cohort I subjects (50.6%) interviewed at POD 90, SSI rates were 0.8% probable and 0.8% confirmed. Among the 120 Cohort II subjects (49.4%) interviewed at POD 90, SSI rates were 0% probable and 0.8% confirmed SSIs (RR 1.03; 0.06, 16.20, p=0.986; NNT=4,920).

Conclusion: Both POD 30 and 90 follow-up data show no significant difference in confirmed SSIs between the two cohorts, which may be attributable to low baseline infection rates at the study sites relative to centers included in published literature. While the trial is ongoing, initial analysis suggests a larger cohort and greater site diversity may be necessary to observe a significant decrease in craniotomy SSIs following prophylactic application of topical vancomycin.

291. Enhanced Documentation and Accurate Coding with the Introduction of a Standardized Neurosurgery History and Physical Template

[*Louise Eisenhardt Travel Scholarship*](#)

Laila Malani Mohammad, MD (Albuquerque, NM); Kristopher Kimmell, MD; Rebecca Coffman; Christopher Taylor, MD

Introduction: Proper documentation is the cornerstone of good patient care and also vital to proper coding and billing.

Most neurosurgical patients are considered high complexity, requiring complex decision making and communication.

Proper documentation enhances provider communication and also ensures appropriate level of billing. Our hypothesis was that the introduction of a dedicated neurosurgery history and physical template (NHPT) would improve documentation and coding for neurosurgical patients.

Methods: Retrospective study of neurosurgical patients at the University of New Mexico, who received a history and

physical (H&P) for an initial inpatient admission from July 2015 to July 2016. A standardized electronic health records (EHR)-based NHPT was introduced in December 2015. Data collected included types of documentation (typed, dictated, dynamic documentation without template, or NHPT), initial coding level (1, 2, or 3), and ultimate coding level based on review by professional coder. Inpatient consult notes and clinic notes were not included in the analysis due to different billing criteria..

Results: In July of 2015, before the introduction of the NHPT, 7/30 (23.33%) of inpatient neurosurgery H&Ps were a level 1, compared to 3/61 (4.92%) in July of 2016, a decrease of 79% ($p = 0.008$). Prior to the NHPT, the most common causes for down-coding were inadequate documentation, including a lack of complete review of systems or comprehensive physical exam. As the use of the NHPT increased in popularity, the percentage of level 1 coding decreased. No notes that used the NHPT were down-coded for missing elements, and 193/193 (100%) resulted in a level 3. After the implementation of the NPHT, the average billed note increased by 10%.

Conclusion: Introduction of an EHR-based standardized history and physical template enhanced documentation and resulted in more accurate coding and charges for complex neurosurgical patients.

292. Opportunity for Improvement in Quality and Value: A National Analysis of First Year Post Spinal Cord Injury

Remi A. Kessler (New York, NY); Raj Shrivastava, MD; Sabrina Chen, BA; Deborah Benzil, MD

Introduction: Spinal cord injury (SCI) is a devastating disturbance to motor, autonomic and sensory function, with impact on quality-of-life and functional-status. In the US, there are 17,000 cases of SCI annually. Over one-third of patients will be rehospitalized annually following injury, with a 22-day mean length-of-stay and costs \$769,000-1,060,000. Healthcare costs in the post-acute phase is dependent on injury severity and age at injury. The goal of this study is to analyze the causes of SCI rehospitalization in the first-year post injury and to use this analysis to design interventions to reduce expenditures across the care continuum.

Methods: This study uses a retrospective cohort design including all patients sustaining SCI between 1972-2017. SCI was defined as an acute traumatic lesion of spinal canal neural elements resulting in sensory and/or motor deficit. Exclusion criteria consisted of in-hospital mortality from acute injury or within the first six months post-injury. Data was drawn from National SCI Statistical Center, which is a US prospective longitudinal multi-center study capturing SCI patients' healthcare data. It is the largest SCI database worldwide.

Results: A total of 32,720 patients met inclusion criteria. The male-female breakdown was 80.6% (N=26,365) versus 19.4% (N=6,355). The average age at injury was 35. Vehicular causes and falls were the leading causes of injury (42.2%, 22.4%). Survival at 1-year was 95.4% and 10-years was 82.40%. Analysis of 30-day readmission in 2,904 patients with complete data revealed that genitourinary system diseases were the leading cause of rehospitalization (47.3%), followed by skin pathology (18.7%). Other causes included respiratory, digestive, circulatory and musculoskeletal diseases.

Conclusion: This study suggests that relatively simple interventions to prevent serious urinary-tract-infections and integumentary disruption could dramatically reduce rehospitalization and costs for SCI patients. Further detailed analysis of this large database will likely yield additional critical information to design better post-hospitalization care.

293. Simulating Costs for Episode-Based Bundled Payments for Cranial Neurosurgical Procedures

Zachary Adam Medress, MD (Stanford, CA); Beatrice Ugiliweneza; Jonathon Parker, MD, PhD; Dengzhi Wang, MS; Eric Burton, MD; Shiao Woo, MD; Maxwell Boakye; Stephen Skirboll, MD

Introduction: Episode-based bundled payments were introduced by Medicare in 2013 as the Bundled Care Improvement Initiative (BPCI) in order to improve care coordination and cost efficiency. BPCI has been implemented for orthopedic, cardiac, and spine procedures, but has not yet been applied to cranial neurosurgical procedures. We project the cost of episode-based bundled payments for cranial neurosurgical procedures.

Methods: We performed a large retrospective observational study using the MarketScan administrative database to project bundled payment costs for common cranial neurosurgical procedures. Operations were classified into four groups: Craniotomy for unruptured aneurysm, craniotomy for meningioma, craniotomy for malignant glioma, and craniotomy for metastasis. We project 30-, 60-, and 90-day bundle payments for each category, and analyze the contributions of post-discharge costs to total bundle payments at each time point.

Results: We identified 15,276 procedures that met our inclusion criteria. We observed significant variability between groups, with 90-day bundle projected costs ranging from \$58,200 for craniotomy for meningioma to \$102,073 for craniotomy for malignant glioma. We also found significant variability in projected bundled payments within each class of operation. On average, payment for the index hospitalization accounted for 85% of projected costs for a 30-day bundle

and 70.5% of projected costs for a 90-day bundle. Multivariate analysis showed that medical comorbidities, adjuvant therapies, and payer status significantly contributed to projected cranial bundle costs.

Conclusion: For the first time in our knowledge, we report projected costs of 30-, 60-, and 90-day episode-based bundled payments for common elective vascular and tumor cranial operations. As previously identified in the orthopedic literature, there is significant cost variability in total bundle payments within each cranial procedure. Compared to spine and orthopedic procedures, post-discharge costs significantly impact total bundle payments in cranial neurosurgery. We believe projected bundle costs will inform future health policy in cranial neurosurgery.

294. Disparities in Discharge Destination by Insurance Payer Group After Posterior Cervical Decompression and Instrumented Fusion

Daniel J Snyder (New York, NY); Daniel Snyder, BS; Jonathan Rasouli, MD; Sean Neifert, BS; Jonathan Gal, MD; Brian Deutsch, BS; Robert Rothrock, MD; John Caridi, MD

Introduction: Posterior cervical decompression and fusion (PCDF) is the treatment of choice for degenerative cervical radiculopathy and myelopathy refractory to medical management. Despite numerous studies examining patient-specific risk factors for outcomes after PCDF, questions remain about whether socioeconomic differences are risk factors themselves. Our goal was to investigate the effect of insurance status on episode-based outcomes for patients undergoing PCDF.

Methods: All PCDF cases between 2008-2016 were obtained from a single institution. Demographic, comorbidity, and outcomes data were collected. Five cohorts were created by insurance status: commercial, Medicare, Medicaid, managed care, and uninsured. Groups were compared using bivariate analysis. Multivariate models were also created including age, sex, ASA status, and Elixhauser score for the following outcomes: in-hospital complication, LOS, ICU stay, post-acute care (PAC) discharge, unplanned readmission and ER visit within 30- and 90-days.

Results: A total of 1,137 patients underwent PCDF during the study period: commercial (n=217), managed care (n=492), Medicaid (n=63), Medicare (n=360), and uninsured (n=5). Patients in the Medicaid cohort had higher ASA designations than those in the commercial cohort. When compared to the commercial cohort, Medicaid patients were more likely to have an ICU stay (25.4% vs. 12.4%, p=0.01) and an ER visit within 90 days (14.3% vs. 4.2%, p=0.004); these differences failed to retain significance in multivariate analyses. Patients with Medicaid had a higher frequency of PAC discharge (38.1% vs. 18.0%, p=0.0008), and a higher likelihood of PAC discharge (OR=2.4, 95% CI: 1.1 - 5.7; p=0.009). No other outcomes differed significantly between cohorts.

Conclusion: Our findings show an association between Medicaid insurance status and PAC facility discharge after PCDF, even after adjusting for clinical characteristics. Recent literature suggests that PAC facility discharge may predispose patients to adverse events postdischarge, and future literature should investigate the reasons behind differential rates of PAC discharge for Medicaid patients.

295. Cost of Hospitalization for Stroke in a Low-Middle Income Country: Findings from a Public Tertiary Hospital in the Philippines

Best International Abstract Award

Abdelsimar Tan Omar (Manila, Philippines); Jose Danilo Diestro; Robert Joseph Sarmiento; Clare Angeli Enriquez; Lennie Lynn De Castillo; Beverly Ho; Kathleen Joy Khu; Jose Leonard Pascual

Introduction: Determining the cost of hospitalization for acute stroke is important for the appropriate allocation of resources and the analysis of interventions for cost effectiveness. The objective of this study was to determine the total cost of hospitalization for acute stroke in a tertiary public hospital in the Philippines and identify the factors influencing cost.

Methods: The study was a retrospective review of medical and billing records of the hospital. Adult patients admitted for acute stroke between June 2017 to October 2017 were included in the analysis. After the mean cost of stroke was determined, multivariable logistic regression analysis was done to determine demographic and clinical characteristics that were predictive of stroke cost.

Results: A total of 509 patient records were analyzed. The mean cost of stroke was 32,798.07 PHP (609.43 USD). Independent determinants of increased cost include stroke type (hemorrhagic stroke (p=0.001) and subarachnoid hemorrhage (p=0.001)), younger age (p=0.001), infection (p<0.001), length of hospital stay (p<0.001) and mechanical ventilation (p=0.001). The cost of hospitalization was higher than the fixed reimbursement rates provided by the National Health Insurance Program for all types of stroke except ischemic stroke.

Conclusion: The study provided current data on the cost of hospitalization for acute stroke in a public tertiary hospital in the Philippines. Stroke type, age, presence of infection, length of hospital stay, and need for mechanical ventilation were independent predictors of cost.

296. Spinal Surgical Risk Calculator Utilizing Machine Learning Techniques

James Edward Towner, MD (Rochester, NY); Viet-Duy Nguyen; Yan Li, PhD; Jiebo Luo, PhD; Yan Li, MD, PhD

Introduction: Accurate pre-surgical risk prediction and stratification potentially has value in informing perioperative decision making for physicians and patients. We sought to develop a spine surgery specific tool to examine risk factors associated with the following: days from operation to death, hospital admission >30 days, any reoperation, unplanned reoperation, any hospital readmission, or unplanned hospital readmission.

Methods: Multicenter, prospectively collected data from the American College of Surgeons National Surgical Quality Improvement Program database was used to examine fifty risk factors from over 2,000,000 patient records using machine learning techniques. Computational procedural terminology codes were used to define specific spine surgical interventions. If any risk factors had 20% missing data, we excluded the patients with missing data. If missing data for any risk factor was higher than 80%, we excluded the entire risk factor from analysis. Fifty out of sixty-five risk factors satisfied this requirement and were used in the analysis. Management of imbalanced data was handled with upsampling (centroid cluster technique) and downsampling (synthetic minority over-sampling technique) methods. 10-fold cross-validation was utilized to evaluate the system with the dataset divided in an 8:1:1 ratio of training set: validation set: test set.

Results: Gradient boosting techniques (XGBoost) and ensemble learning technique (random forest) performed better than regression methods (logistic regression technique). Our system achieved >90% accuracy for predicting every outcome which had sufficient data for analysis.

Conclusion: Using machine learning techniques, we developed a spine specific surgical risk calculator with potential to predict the days from operation to death, hospital admission >30 days, reoperation, and hospital readmission.

297. The Long Term Financial Impacts of a Decision to Pursue a Neurosurgical Career

Ian Andrew Eisenberg (Tenafly, NJ); Shabbar Danish, MD; Thomas Prusa, PhD

Introduction: We examine the income and wealth consequences of a neurosurgeon's delayed entry into the workforce. Our analysis focuses on the financial trajectories of a variety of career paths for a college age student and examines the effects of subsidized medical education.

Methods: We characterized the schooling and training for multiple career paths. We computed income, student debt, and return on savings for each possible career path. We used data from the BLS, Forbes and the AAMC, and utilized benchmark economic variables in our analysis. We compared the age at which a neurosurgeon breaks even with alternative careers in terms of the present day value of cumulative earnings.

Results: Neurosurgical careers match the cumulative income of MBA careers between their mid-30's to mid-40's. However a neurosurgeon's net worth does not match that of MBA-healthcare and MBA-finance tracks until ages 45 and 51 respectively. Neurosurgeons who pursue a year of research will match the wealth of the MBA-healthcare track at age 53 and never match the wealth of the MBA-finance track. If both research and fellowship are pursued, a neurosurgeon will never match the wealth of either MBA track. Subsidized medical education has little to no effect on lifetime income and wealth.

Conclusion: The analysis shows neurosurgeons do not match the income or wealth accumulation of high pay alternative careers until their early-50's, if ever. The time and cost of a neurosurgeon's education and training delays their ability to build wealth. Even when the cost of medical education is subsidized, there is little effect on wealth and income. This analysis suggests that the decision to pursue a career in neurosurgery requires extreme patience, as the economic returns will not be realized for several decades, if ever.

298. Staining Functional and Non-functional Pituitary Adenomas: A Review to Establish a Clinical Trial Protocol.

M. Maher Hulou (Lexington, KY); M. Hulou, MD; Justin Fraser, MD

Background: We aim to review the literature on chemical and immunohistochemical pituitary adenoma staining after resection to understand its role and potential predictive value.

Methods: 365 articles related to pituitary adenoma and staining were reviewed. Information on histological studies, protocols and outcomes was extracted.

Results: 16 papers were included, which encompassed 2,107 surgical specimens. Stains included TSH, FSH, LH, GH, prolactin, Ki-67, cyclin D1, and MGMT. One study found that 3% of pituitary adenomas stained positive for TSH, of which approximately 85% were nonfunctional. Most TSH-staining adenomas were plurihormonal, particularly costaining with GH. Two studies investigated the relationship between LH/FSH stains and pituitary tumors: Recurrence rates in LH positive group seem to be higher for non-functional pituitary adenomas (NFPAs) with large tumor volume and preoperative cavernous sinus invasion. Tumor recurrence rates were significantly higher for NPFAs that were positive for LH. Re-operation rate, but not recurrence rate, was higher in patients with positive FSH. Eight papers reported on Ki-67 which seems to have a role in predicting invasion and acromegaly control with octreotide; however, the correlation between Ki-67 and tumor size or recurrence is still controversial among the 8 studies. One study found that acromegalics with tumors that stain for prolactin and GH have a significantly higher aggressive clinical presentation. Expression of cyclin D1 in pituitary tumors was found to be related to cell proliferation, recurrence, and metastatic potential in one paper and nuclear cyclin D1 expression seems to be a good marker of aggressive behavior in pituitary tumors.

Conclusion: There is a paucity of literature correlating pituitary adenoma pathological staining to outcomes. Furthermore, there is no uniformity with regard to staining protocols after resection. Published studies do suggest a role for hormonal stains, reflecting a need for further long-term and prospective evaluation.

299. Annual Meeting Involvement and Research Productivity of AANS Medical Student Chapters**Byron Cone Pevehouse Young Neurosurgeons Award**

Debraj Mukherjee, MD (Baltimore, MD); Prateek Agarwal; Michael Ivan, MD

Introduction: The Young Neurosurgeons Committee (YNC) under AANS established a program in 2014 that allowed individual medical schools to create AANS Medical Student Chapters. The purpose of this study was to assess the professional, educational, and research activities of these chapters.

Methods: Data on membership, AANS annual meeting attendance, and research output were collected and analyzed from chapter annual reports from 2014-2018.

Results: The total number of AANS Medical Student Chapters increased rapidly from 12 chapters in 2014 to 109 chapters in 2018 (2015: 39, 2016: 60, 2017: 85). The mean number of members per chapter has remained relatively constant around 35, but the mean number of chapter members attending the AANS annual meeting has increased from 2014 to 2018 (2014–2015: 1.25, 2015–2016: 1.48, 2016–2017: 1.19, 2017–2018: 1.67). Abstracts submitted, abstracts accepted, and total publications authored by chapters have fluctuated considerably with means over the past four years of 1.89, 1.67, and 9.26, respectively. During the 2017-2018 academic year, chapters from “top 20 medical schools” (U.S. News) attended the annual meeting in greater numbers (mean 3.00, $p = 0.0078$), submitted more abstracts (mean 4.20, $p < 0.001$), had more abstracts accepted (mean 3.00, $p = 0.0017$), and authored more publications (mean 21.55, $p = 0.0026$) relative to chapters from other schools. This finding was also true for chapters with “top 20” neurosurgery residency programs by reputation (Doximity) [mean attending meeting 3.09, $p = 0.0041$; mean abstracts submitted 4.30, $p < 0.001$; mean abstracts accepted 3.70, $p < 0.001$; mean publications 20.55, $p = 0.0062$] compared with chapters with lower ranked residency programs.

Conclusion: Since their inception, AANS Medical Student Chapters have increased in number significantly and demonstrated substantial research productivity and involvement in organized neurosurgery, particularly chapters from highly ranked medical schools and residency programs.

300. Predictors of Fast Shunt Failure in Pediatric Hydrocephalus, a Hydrocephalus Clinical Research Network (HCRN) study

Jason Scott Hauptman, MD PhD (Seattle, WA); John Kestle, MD; Jay Riva-Cambrin, MD; Sam Browd, MD, PhD; Abhaya Kulkarni, MD, PhD; Curtis Rozelle, MD, PhD; William Whitehead; Robert Naftel, MD; Jonathan Pindrik, MD; David Limbrick, MD, PhD; James Drake, MD; Jay Wellons

Introduction: Little is understood about the subgroup of children who undergo multiple shunt revisions in a short period of time. The goal of this study is to identify the children in the registry who have experienced rapid shunt failures (<30 days after shunt operation) and compare them to a matched cohort.

Methods: We limited this analysis to subjects in the HCRN cohort who have had a shunt placement in the registry and have had at least one subsequent shunt revision prior to 1/1/18. A multivariate logistic regression model was used to determine if there is a difference between procedures that failed within 30 days (fast failure), within 7 days (ultra-fast failure) and procedures that failed after 30 days. We examined the effects of etiology, age at initial shunt placement, presence of slit-ventricles on imaging at revision, ventricular enlargement on imaging at revision, and history of fast failures.

Results: A total of 3,310 shunt operations were evaluated in the clean cohort, of which 1,121 were primary shunt placements and 2,189 were shunt revisions. For primary shunt placements, the mean age at the time of shunt placement was 0.3 years [0.1, 1.2]. The etiologies of hydrocephalus included post-IVH secondary to prematurity (24.1%), myelomeningocele (16.9%), aqueductal stenosis (8.6%), and other (50.5%). For revisions, the mean age at the time of revision was 1.8 years [0.6, 4.9]. Of these patients, 43 (2.0%) were identified by the surgeon as having slit ventricle syndrome, and 1222 (55.8%) had ventricular enlargement noted at the time of failure. Multivariate logistic regression revealed that etiology was an independent predictor of fast failures ($p < 0.001$) and both age at the time of procedure ($p = 0.01$) and etiology ($p = 0.009$) were predictors of ultra-fast failures.

Conclusion: Age at shunt placement and etiology of hydrocephalus are significant predictors of rapid shunt failures in children.

301. Using Resting-State Electrocorticography to Demonstrate Cortical Regions Important in Sensory-Motor Integration

Ai Phuong S Tong (Lynnwood, WA); Kurt Weaver, PhD; Andrew Ko, MD; Jeff Ojemann

Introduction: Neuroprosthetics can improve functionality for amputees because they can be controlled by the intact mind independent of peripheral integrity. However, movement requires integration of sensory feedback and motor planning, which is difficult to map with task-based experiments with limb loss. *Objective*-compare neural activity during a tactile task and at rest to determine if resting-state coupling localizes integration centers where sensory and motor information converge. Areas of parietal cortex are activated during tasks that require sensory-motor integration. *Hypothesis*-these areas exhibit increased phase-amplitude coupling (PAC) and correlation with sensory or motor regions at rest because these regions communicate for a functional purpose.

Methods: We used epilepsy monitoring procedures used to identify seizure onset zones. We recorded brain activity from five patients at Harborview Medical Center using 8-x-8 electrocorticography grids during rest and a tactile task in which the patient responds to light touch. PAC, a measure of neural coupling, was used to identify information flow between parietal cortex and other regions. Bootstrapping identified statistically significant interactions.

Results: There was a significantly increased proportion of above average response time, $>265 \pm 23$ ms, when touch occurred during peaks of 8-12 Hz (alpha band) waveforms within posterior parietal cortex (PPC) ($P < 0.05$). Significant average PAC occurred at rest between the phase of intraparietal sulcus (IPS), bordering PPC, and amplitude of somatosensory (S1) and frontal eye field (FEF) ($Z\text{-score} > 1.645$). IPS activity is not correlated with S1 at rest.

Conclusion: Slower response during greater alpha band activity in the PPC indicates it modulates sensory-motor integration during motor response. IPS-FEF coupling is consistent with previously reported resting-state networks. IPS-S1 coupling at rest also suggests information sharing between these two regions. Overall, parietal regions involved in motor control may be identified by resting-state coupling patterns, offering a more reliable biomarker to localize targets for neuroprosthetic feedback.

304. Clinical and Patient Satisfaction Outcomes after Partial Sensory Rhizotomy for Refractory Trigeminal Neuralgia Among MS Patients

Mark Gregory Bigder, MD (Thunder Bay, Canada), FAANS; Sandeep Krishnan, MD, MSc; E. Francis Cook; Anthony Kaufmann, MD, MSc

Introduction: MS related trigeminal neuralgia is associated with high recurrence and retreatment rates. Optimal treatment and role for partial sensory rhizotomy (PSR) for MS-TN remains to be determined.

Methods: We analyzed time to treatment failure (TTF) after PSR (n=14) versus prior procedures (n=53) among MS-TN patients. Kaplan-Meier curves and Log-Rank tests were utilized to compare BNI pain scores and TTF after PSR vs prior procedures using the same patient cohort as their own control group. Subsequent analysis compared TTF after PSR to prior procedures among a second cohort of MS-TN patients not undergoing PSR.

Results: TTF was significantly longer after partial sensory rhizotomy compared to prior procedures among the PSR cohort ($p<0.0001$) with median TTF of 79 vs 10 months respectively. Similarly, there was a longer TTF after PSR compared to prior procedures among the MS-TN cohort with median TTF 79 vs 16 months respectively ($p<0.001$). PSR resulted in a higher proportion of excellent pain scores when compared to prior procedures in the MS-TN cohort (77% vs 29%, $p<0.001$).

Conclusion: TTF was significantly longer following PSR compared to prior procedures in MS-TN patients. Additionally, a higher proportion of patients achieved excellent BNI pain scores after PSR.

305. Intraoperative Ketamine May Increase Risk of Post-Operative Delirium After Complex Spinal Fusion (≥ 5 Levels) for Adult Deformity Correction: A Single Institutional Study of 138 Patients

Aladine Abdalla Elsamadicy, BE, MD (New Haven, CT); Aladine Elsamadicy, MD; Lefko Charalambous; Joaquin Camara-Quintana; Isaac Freedman, MPH; Nicolas Drysdale; Adam Kundishora, MD; Muhammad Abd-El-Barr, MD, PhD; Isaac Karikari; Syed Adil

Introduction: For complex surgery, intraoperative ketamine administration is readily used to reduce post-operative pain. However, there have been a few studies suggesting that intraoperative ketamine may have deleterious effects and impact post-operative delirium. Therefore, we sought to identify the impact that intraoperative ketamine has on post-operative after complex spinal surgery involving ≥ 5 level fusions.

Methods: The medical records of 138 adult (≥ 18 years old) spine deformity patients undergoing elective, primary complex spinal fusion (≥ 5 level) for deformity correction at a major academic institution from 2005 to 2015 were reviewed. We identified 98 (71.0%) who had intraoperative ketamine administration and 40 (29%) who did not (Ketamine-Use: n=98; No-Ketamine: n=40). Patient demographics, comorbidities, intra- and post-operative complication rates were collected for each patient. The primary outcome investigated in this study was the rate of post-operative delirium. A multivariate nominal-logistic regression analysis was used to determine the independent association between intraoperative ketamine and post-operative delirium.

Results: Patient demographics and comorbidities were similar between both cohorts, including age, gender, and BMI. The median number of fusion levels operated, length of surgery, estimated blood loss, and proportion of patients requiring blood transfusions were similar between both cohorts. Postoperative complication profile was similar between the cohorts, except for the Ketamine-Use cohort having significantly higher proportion of patients experiencing delirium (Ketamine-Use: 14.3% vs. No-Ketamine: 2.6%, $p=0.047$) and a lower 30-day unplanned readmission rate (Ketamine-Use: 9.2% vs. No-Ketamine: 25.0%, $p=0.014$). In a multivariate nominal-logistic regression analysis, intraoperative Ketamine-Use was independently associated with post-operative delirium [OR: 9.475, 95% CI (1.026, 87.508), $p=0.047$].

Conclusion: Our study suggests that the intraoperative use of ketamine may increase the risk of post-operative delirium. Further studies are necessary to understand the physiological effect intraoperative ketamine has on patients undergoing complex spinal fusions in order to better overall patient care and reduce healthcare resources.

306. Preoperative Greater Occipital Nerve Block Correlates with Improved Postoperative Outcomes in Chiari Decompressive Surgery

Adam Kundishora, MD (New Haven, CT); Richard Zhu, MD; Jacky Yeung, MD; Kristopher Kahle, MD, PhD; Michael DiLuna, MD

Introduction: Patients with Chiari-I malformation (CM-1) suffer from posterior headaches that are commonly treated with posterior fossa decompression. However, a subset of patients have incompletely treated or even refractory headaches

postoperatively. This retrospective analysis investigates the effect of preoperative greater occipital nerve blocks (GONB) on postoperative pain and long-term headache resolution.

Methods: We retrospectively reviewed the charts of all patients who underwent posterior fossa decompression for CM-1 between the years of 2013 and 2016. Patients were grouped into one of three categories: no GONB, GONB with local anesthetic only (GONB-L) and GONB with local anesthetic and steroids (GONB-LS). Primary outcomes were postoperative opioid consumption, time to transition from IV to PO opioid use, length of stay (LOS), and long-term headache control.

Results: 37 Adults were reviewed, of which 22 received some form of GONB. Postoperative opioid consumption was lower for patients who received GONB-LS ($p = 0.001$), as was time to transition to P.O. medication only ($p = 0.003$). At one-month follow up, headache resolution was better among patients who received preoperative GONB-L or GONB-LS as opposed to no GONB.

Conclusion: Patients who undergo posterior fossa decompression for Chiari-I malformation associated headaches have lower opioid requirements and improved rates of headache freedom at one-month follow up if they receive preoperative GONB.

307. What is the Impact of Spine Surgery on Opioid Use? A Systematic Review and Meta-Analysis

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Introduction: There is an alarming, unprecedented increase in mortality and morbidity associated with use of opioids nationwide. Previous studies estimate prescription opioid use contributes to more than 40% of opioid related death. Spine patients are specially at risk due to chronic pain. In this systematic review and meta-analysis, we aim to estimate the proportion of chronic opioid users after cervical fusions, lumbar fusions, and non-fusion spine surgeries.

Methods: In accordance with PRISMA and MOOSE guidelines we searched the following electronic databases: PubMed, Embase, and Web of Science. Articles were eligible if they included data on opioid use three months after spine surgery. In addition, a reference and citation analysis was conducted as well as a data quality assessment. We calculated proportion and odds ratios using a mixed effect model. We classified those using opioids at three months or later after surgery as chronic opioid users. **Results:** There were a total of 11 studies including 12,895 spine patients: 659 non-fusion, 10,378 lumbar fusion and 1858 cervical fusion patients. The overall proportion of chronic opioid users was 34%. The proportion of chronic use among non-fusion patients was 30%, among lumbar fusion patients was 41%, while among cervical fusion patients was 23%. Patients that were using opioids prior to surgery were 40% more likely to use opioids more than 3 months after surgery, OR: 1.40 (95% CI: 1.16 - 1.63).

Conclusion: The current study suggests that the prevalence of prolonged opioid use after surgery is very high. While further studies are necessary to characterize the risk factors for prolonged use after surgery, surgeons will need to devise multidisciplinary strategies to optimize opioid use prior to surgery and plan for successful postoperative opioid wean.

308. High-Cervical Targeted Drug Delivery for Anesthesia Dolorosa

John Sheehy, MD (Phoenix, AZ); Zaman Mirzadeh, MD, PhD

Introduction: Anesthesia dolorosa, or painful numbness, is a dreaded complication in the management of trigeminal neuralgia resulting from trigeminal nerve deafferentation following surgical procedures that often damage the nerve. Anesthesia dolorosa is notoriously difficult to treat. Here we present our experience with two patients suffering from anesthesia dolorosa treated with high-cervical intrathecal targeted drug delivery.

Methods: Both patients underwent trial placement of an externalized intrathecal catheter with the tip at C1. After positive responses to periodic test boluses of a bupivacaine and fentanyl combination over 2 days during an inpatient stay, the patients returned to the operating room for catheter internalization and pump implantation. Quality of life assessments, including the Brief Pain Inventory, were completed before and after surgery.

Results: Both patients were adult women who had developed unilateral anesthesia dolorosa following treatment for ipsilateral trigeminal neuralgia. Patient one had undergone a microvascular decompression and two gamma knife radiosurgery treatments, while patient two had undergone two microvascular decompressions. Both patients experienced substantial periodic pain relief in accordance with their pump-based dosing schedule, including periods of pain freedom for patient one. With regard to the lowest pain level experienced over a 24 hour period, patient one improved from 3/10 pre-operatively to 0/10 post-operatively, while patient two improved from 9/10 to 4/10. Both patients

continued to improve with further dose optimization after surgery.

Conclusion: High-cervical targeted drug delivery is a neuromodulation strategy that can provide meaningful relief in patients with *anesthesia dolorosa*.

309. Pilot Safety Trial of Extended Release Liposomal Bupivacaine (Exparel) for Postoperative Analgesia in the Adult and Pediatric Neurosurgical Population

David Rafael Santiago-Dieppa, MD (San Diego, CA); Carlos Sanchez, MD; Arvin Wali, MD, MAS; Joel Martin, MD; Jeffrey Steinberg, MD; Rishi Parikh, MD; Reid Hoshide, MD, MPH; David Gonda, MD; Michael Levy, MD, PhD

Introduction: Liposomal bupivacaine (LB, EXPAREL) is an extended release amide local anesthetic that is FDA-approved for single-dose surgical site infiltration in adults. The efficacy of LB has been demonstrated in 3 multi-center, randomized, double-blind, placebo-controlled studies evaluating bunionectomy, hemorrhoidectomy, and brachial plexus nerve block for shoulder arthroplasty or rotator cuff repair. Given the efficacy of LB, off-label use has expanded to include additional surgical sites and populations including children. However, there are no published studies regarding the safety of this drug in pediatric or adult neurosurgical patients. Furthermore, the safety of using LB in cases where durotomy is required is unknown.

Methods: Institutional use of this drug was approved by Rady Children's Hospital of San Diego. We performed a retrospective observational study of all neurosurgical patients who received this drug at the time of surgery. The primary outcome was occurrence of adverse events. LB (13.3 mg/ml) was administered at a dose of 0.3 ml/kg and admixed with 0.6 ml/kg of 0.25% bupivacaine. For cases that required durotomy LB was injected prior to incision to ensure no contact with the central nervous system.

Results: 14 patients (7 males and 7 females) ranging in age from 2-26 received surgical site infiltration of LB. Cases included supratentorial craniotomy (2), spinal cord tumor (2), Chiari decompression (4), tethered cord release (3), and lumbar decompression and/or instrumented fusion. There were no neurologic, cardiovascular, respiratory, or allergic events observed. **Conclusion:** Use of LB proved to be safe and was not associated with any adverse events. LB may play an important role in the management of postoperative neurosurgical pain. Larger randomized prospective trials should be performed in order to further evaluate the safety and efficacy of this drug in the neu

310. Evaluating the Impact of Initial Prescription on Long-Term Opioid Utilization Following Discectomy and Laminectomy Surgery.

Anna K Wright (Seattle, WA); Sikora Matt; Jean-Christophe Leveque, MD

Background: Long-term opioid use in spine surgery is associated with higher healthcare utilization and worse postoperative outcomes. The impact of prescribing practices at discharge and optimal prescription dose remain poorly understood. The goal of this study was to determine whether prescribing practices at discharge are associated with opioid dependence in patients undergoing discectomy or laminectomy procedures for degenerative (non-deformity) indications.

Methods: A query of an administrative database was conducted to identify all patients undergoing discectomy or laminectomy procedures at our high volume tertiary referral center between 2006 and 2016. For patients included in the analysis, opioid prescription data on admission and discharge was manually abstracted from the electronic health record, including opioid type, frequency, route, and dose; and converted to daily Morphine Equivalent Dose (MED) values. We defined opioid dependence as having a consecutive narcotic prescription lasting for at least 90 days in the 12 months following spine surgery.

Results: Of the 819 total patients, 499 (60.9%) patients had an active opioid prescription before surgery. Postoperatively, 813 (99.3%) received at least one narcotic prescription within a week of index surgery, and 162 (19.8%) continued with sustained opioid use in the 12 months following surgery. In adjusted analysis, patients with opioid dependence had a higher incidence of preoperative depression ($p = 0.012$) and preoperative opioid use ($p < 0.001$), as well as a higher frequency of benzodiazepine prescriptions ($p = 0.009$), and discharge MED value exceeding 120 mg/d ($p = 0.013$).

Conclusion: This is the first study to test for an association between MED values prescribed at discharge and sustained opioid use after spine surgery. In addition to previously reported risk factors, discharge prescription dose exceeding 120mg/d is independently associated with opioid dependence following spine surgery.

311. Outcomes Using an Spinal Cord Stimulation Device Capable of Delivering Combination Therapy (Simultaneous or Sequential) and Advanced Waveforms/Field Shapes

Clark Metzger (Pensacola, FL); M. Blake Hammond, PA; Stephen Pyles, MD; Anthony Berg, MD; Romanth Waghmarae, MD; James North, MD; Yu Pei, MPA; Roshini Jain, MS

Introduction: Developing all in one spinal cord stimulation (SCS) systems with capability for multiple types of neurostimulation paradigms will likely empower patients to identify the best treatment approach suitable for their own needs. As these advanced SCS systems become available, it will important to evaluate their use and associated patient outcomes. We aimed to assess real-world outcomes using a new SCS system designed to offer patients the capability of combination therapy (simultaneous or sequential) and waveform automation.

Methods: This is a consecutive, multi-center case-series of patients treated with a newly designed SCS system (Precision Spectra WaveWriter, Boston Scientific) capable of combination therapy (either sequential or simultaneous), multiple waveforms and advanced field shapes, and waveform automation for the treatment of low back and/or leg pain. Data collection includes: 1) Baseline characteristics: demographics, medical history; pain diagnosis 2) procedural information: lead configuration, programming parameters; and 3) pre- and post- implant numerical rating scale pain intensities (0-10 NRS). Statistical analyses were prospectively defined.

Results: To date, 217 patients have been analyzed. A statistically significant improvement in overall targeted pain scores (NRS) at last follow-up was reported (Baseline NRS: 7.5; at last follow-up [96.6 ± 80.9 days] NRS: 2.4; $p < 0.0001$). Thirty-nine percent of all patients indicated >80% pain relief at their last follow-up. Twenty-two percent (48 of 217) of all patients reported being pain free (NRS = 0) at last follow-up. Additional and updated data of this on-going study will be presented.

Conclusion: Given the overall diversity of etiologies and experiences associated with chronic pain, the SCS-implanted patient population may particularly benefit from devices with considerable adaptability providing for individualized treatment customization. Results from this real-world cohort demonstrate significant improvement in overall pain with use of a recently introduced SCS system capable of providing combination therapy and multiple waveforms/field shapes.

313. Clinical Outcomes Following Linac-Based Radiosurgery For Trigeminal Neuralgia

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Introduction: We reviewed clinical outcomes and complications following frame-based versus frameless stereotactic radiosurgery using a linear accelerator (linac) based treatment device, with radiation collimated using 4mm versus 5mm diameter cones in patients with medically refractory, intractable TN.

Methods: We performed a retrospective review of all patients who underwent stereotactic radiosurgery for TN at our institution between 1996 and 2018. The Barrow Neurological Institute (BNI) pain score was used to evaluate pain relief.

Results: A total of 282 patients were identified. Their mean age at the time of radiosurgery was 68.1 years (range, 24.3 – 95.5 years). A total of 119 (42.2%) patients underwent radiation collimated by 4mm cones, whereas 5mm cones were used in the remaining 163 (57.8%) patients. Overall, frameless stereotaxy was used in 112 (39.7%) patients. Following radiosurgery, 67.5% of patients in the 5mm group experienced complete pain relief (BNI I), compared to 40.3% in the 4mm group ($p < 0.005$). A complete pain relief was achieved in 42.0% of cases in the frameless group, and in 65.3% in the frame-based group ($p < 0.005$). Overall, mean latency to initial pain relief was 1.1 months. Pain recurrence occurred overall in 15.6% of cases. A higher frequency of pain recurrence was present in the 4mm and the frameless group (28.6%) ($p < 0.005$). Side effects of SRS treatment included permanent facial hypoesthesia in 5% ($n=14$), hyperesthesia/paresthesia in 2.5% ($n=7$), dry eye syndrome in 1.8% ($n=5$) and deafferentation pain in 5.7% ($n=16$).

Conclusion: Frameless SRS with a 5mm collimator, is a feasible treatment for TN. Despite the risk of spillage-related brainstem adverse effects of larger collimator size, confirmed our results, that a 5mm collimator is superior to 4mm collimator size in terms of pain relief, with no increase in long-term side effects.

314. Randomized Crossover Trial Comparing Burst and Tonic Spinal Cord Stimulation: Burst Stimulation Decreases Pain Catastrophizing

Miriam Mingxuan Shao (Westfield, NJ); Michael Gillogly, RN; Andrea Liss; Marisa DiMarzio, BS; Philip Yeung, MD; Julia Prusik, MPH; Julie Pilitsis, MD, PhD

Introduction: Burst spinal cord stimulation (SCS) has emerged as a technology that is novel in its stimulation of the nervous system's natural burst firing patterns. It shows promise in offering better pain outcomes than tonic stimulation, particularly in patients who prefer paresthesia-free pain relief. In this prospective, randomized, crossover study, we compared the effects of burst and tonic SCS on pain outcomes and quantitative sensory testing (QST) with patients serving as their own controls.

Methods: Fifteen patients implanted with devices capable of tonic and burst SCS completed pain outcome assessments without SCS, after four weeks of tonic SCS, and after four weeks of burst SCS. Whether burst or tonic SCS was administered first was randomized for each patient. Pain outcomes were assessed using the Numerical Rating Scale (NRS), McGill Pain Questionnaire (MPQ), Oswestry Disability Index (ODI), Pain Catastrophizing Scale (PCS), Beck Depression Inventory (BDI), Insomnia Severity Scale (ISS), Epworth Sleep Scale (ESS), and QST.

Results: Patients diagnosed with failed back surgery syndrome and neuropathic pain were included in this study. The mean patient age was 60.3 ± 3.1 and included 6 males/9 females. Compared to no stimulation, burst SCS significantly improved outcomes for PCS-total ($p=0.024$), PCS-rumination ($p=0.015$), PCS-helplessness ($p=0.027$), NRS-average ($p=0.023$) and NRS-worst-during-week ($p=0.021$). Compared to tonic stimulation, burst stimulation significantly improved NRS-average ($p=0.032$) and showed a trend towards improving ODI scores ($p=0.062$).

Conclusion: Burst SCS significantly improved PCS compared to no stimulation. Burst SCS decreased average NRS and showed a tendency towards improving disability compared to tonic SCS. Our observation that burst SCS did not significantly alter patients' ratings for QST but did for PCS, which has been associated with pain's affective component, supports earlier studies suggesting that burst SCS effects on pain's medial pathways may distinguish it from tonic SCS.

315. Complications associated with opioids for pain management in the post-operative period for lumbar and cervical spinal fusions: a single institution retrospective analysis

Ramneek Dhillon (Toledo, OH); Nicholas Henkel, BA; Giana Dawod, BS; David Botschner, BA; Brian Potocnik; Azedine Medhkour, MD; Harsh Desai; Thomas Papadimos, MD

Introduction: With the recent opioid crisis, healthcare professionals have worked to increase consciousness with regards to managing pain. Within a neurosurgical context, pain management for post-operative patients who have undergone cervical or lumbar spinal fusions is a major point of care. The CDC's 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes shows that dosages at or above 50 morphine milligram equivalents (MME)/day increases the risk for overdose by at least 2x. To date, no single-center studies in the U.S. have examined the consequences associated with both cervical and lumbar spinal fusions.

Methods: We undertook a retrospective, IRB approved analysis of patients who underwent anterior cervical discectomy and fusion (ACDF), a posterior cervical discectomy and fusion (PCDF), or a lumbar discectomy and fusion (LDF) at the University of Toledo Medical Center.

Results: Total cohort of patients from 2012 to 2016 is 836. For the cervical patient data examined thus far, a positive correlation exists between morphine equivalent dose (MED)/day and whether opioids at discharge were necessary for pain management ($\bar{x} = 50.48$; $p = 0.007$). For lumbar patients examined thus far, long-term pain management was necessary more often than for cervical patients ($p < 0.001$). Additionally, lumbar patients were found to have more complications ($p = 0.011$). The length of stay and average MED was significantly higher for patients who were given opioids to take home compared to those who were not. ($p = 0.001$).

Conclusion: A positive correlation exists between administration of opioids for acute pain management and the need to manage postoperative pain with additional opioids. This finding, at a local level, reiterates the potential risk for opioid abuse in the spinal fusion patient population, corroborating the findings of the CDC. This warrants further assessment and continued analysis towards potential treatment options to mitigate such risk.

316. Retrograde implantation of paddle lead spinal cord stimulator at C1-C2: Technique and outcome analysis in an Institutional series

Tanmoy Kumar Maiti, MD (Cleveland, OH); Andre Machado, MD; Sean Nagel, MD; Leonardo Frizon, MD; Jianning Shao, MD; Nathan Radakovich, MD

Introduction: The percutaneous cylindrical lead or anterograde paddle lead placement in cervical region can be challenging, especially with a previous surgery via posterior approach. Retrograde insertion of paddle lead can be excellent option in this scenario. However, the literature is scarce. We aim to analyze the patients who were treated with cervical paddle lead in our institute. To the best of our knowledge, this is the largest report ever described.

Methods: Forty-two patients were included in this series. Twenty-two patients (out of thirty) showed >50% pain relief during trial (7-14 days). Another twelve patients had previously effective percutaneous leads. Finally, a total of 34 patients underwent permanent paddle lead placement (cervical spondylosis with failed neck surgery =13, CRPS=17, cranial=2, other=2). Risk factors for unsuccessful trial; duration of efficacy, and complications after successful placement have been analyzed. Surgical technique included subperiosteal dissection at C1 and C2, drilling of upper border, and occasional cut of lower border of posterior arch of C1. A complete laminotomy/ laminectomy was never performed. After achieving adequate exposure, the paddle lead was then passed in a rostrocaudal fashion, under direct visualization. SSEP was monitored for all.

Results: There were no appreciable difference in demographic features, indications, duration of symptoms and pain character in unsuccessful candidates ($p>0.1$). Efficacy decreased with time in 62.5% cases. 1-year, 2-year, and 5-year revision free survival were 83.3%, 66.67%, and 50%. Health quality indexes such as PHQ-9, PDI, EQ-5D index, and GAD-7 showed improvement for both cervical spondylosis and CRPS patients at 3-month, 6-month, and one-year follow-up. No patient experienced neurological deterioration. Two patients had Infection requiring removal of IPG and re-implantation

Conclusion: Retrograde paddle electrode placement across C1-C2 is a safe procedure with excellent pain relief. Long-term follow-up is required for wider adoption.

317. The first chordotomy and the personal dynamics of Drs. Spiller, Martin and Frazier

Vesalius Award

C. Michael Honey, MD (Winnipeg, Canada), MD; Christopher Honey, MD; Alan Rheume, BSc

Introduction: January 19, 1911, Dr. Edward Martin made a midline incision in the back of Iguatz Yokua. The procedure would be the first 'chordotomy' ever performed on a patient. This paper is the story of the people behind that operation. Who conceived of the idea to cut the spinal cord to relieve pain? Who dared to perform the operation?

Methods: A comprehensive literature and archive review was preformed in order to piece together the story of the first ever chordotomy.

Results: The genius behind the idea of chordotomy was Dr. William G. Spiller. He was Professor of Neuropathology at the University of Pennsylvania and ran a neurology service at the Philadelphia General Hospital. He had completed medical school at UPenn in 1892 with distinction. His classmate and friend, Charles Harrison Frazier, would embark on a career in neurological surgery at his suggestion and become a founding member and President of the AANS. Why a general surgeon (Martin), who often mocked Spiller, performed the first chordotomy rather than his gifted neurosurgical friend remains a topic for speculation.

Conclusion: Though Martin preformed the initial chordotomy, Frazier would be the one responsible for popularizing the technique in America. At a meeting of the Philadelphia Neurological Society less than a year later, Frazier was reported to have said, "When surgeons first began operating upon the brain, there was general outcry against experimenting upon so delicate an organ. But this feeling was gradually overcome and in the like manner, must surgeons get away from the attitude of "hands off" concerning the spinal column". His textbook *Surgery of the Spine and Spinal Cord* published in 1918 had a chapter devoted to Chordotomy. In it, he reported that his experience with three cases 'substantiated in the most gratifying way all that Spiller anticipated'

318. Wilder Penfield and Edward Archibald: Historical Examination of Successful Mentoring Principles in Neurosurgery

Evgenii Belykh (Irkutsk, Russian Federation); Xiaochun Zhao; Claudio Cavallo; Sirin Gandhi, MD; Leandro Borba Moreira, MD; Daniel Valli, MD; Ali Tayebi Meybodi; Aqib Zehri; Richard Leblanc, MD; Mark Preul, MD

In 1927 Edward Archibald the father of chest surgery recommended to McGill University to establish a sub-department in neurosurgery and to hire a full-time neurosurgeon. Archibald contacted his colleagues in New York who recommended Wilder Penfield at Columbia Presbyterian Hospital. Archibald met Penfield in New York and observed his neurosurgical procedure. Archibald invited Penfield to Montreal and transitioning neurosurgical cases to Penfield. Archibald envisioned the hub of neurosurgery would be transferred from Boston to Montreal through scholarly activity in histology, physiology, and experimental procedures in neurosurgery directed by Penfield, while Penfield envisioned Montreal to be suitable headquarters dedicated to neuroscience and patient care. When Boston City Hospital offered Penfield to organize a neurosurgical service from cross-town rival Cushing, Archibald prudently advised Penfield that taking such a position would engender enmity and would not lead to a productive neurosurgical career. Archibald worked diligently to meet Penfield's requests. Penfield accepted the offer, performing his first neurosurgical operation on October 18, 1928 in Montreal. With Archibald's assistance, Penfield secured a foothold in Montreal to pursue founding an institute for scientific study and treatment for neurological disorders that Archibald initiated. Yet the underlying story reflects a more intimate, respectful, supportive, and even humorous relationship between two men. Penfield's dream happened because of a powerful combination of shared vision and mentoring. We explored this unique history using the Penfield-Osler and Cushing Archives and long correspondence (over 100 letters) between Archibald and Penfield, aided by Archibald-Cushing material. Archibald and Penfield displayed the mutual trust, insight, energy, support, confidence, wisdom, and personal concern that are integral for success in and out of a professional relationship. Penfield and Archibald's relationship should stand as a model for principles of mentoring in neurosurgery, and allowed for progress of the professionalization, practice and science of neurosurgery in North America.

319. Dr. Jose Manuel Rodriguez Delgado: Inventor, Neuroscientist, Bullfighter

Zachary S. Hubbard, MD (Charleston, SC); Fraser Henderson Jr, MD; Jeffrey Wessell, DO; Alejandro Spiotta (Charleston, SC)

Introduction: Jose Delgado was born on a farm in Ronda, Spain in 1915. He attended Medical School in Madrid in 1933 and after a brief stint in the military as a medical corpsman, he began research on neurophysiology in the early 1940s.

Methods: He experimented with electrodes for brain implantation while working at the Ramon y Cajal Center in Madrid. Motivated by his curiosity to delineate the mysteries of the brain, he refined techniques developed by Swiss professor Hess who later went on to win the Nobel Prize for his works. Improving the electrodes pioneered by Hess, Delgado increased the number of electrodes from one to seven, which he would leave implanted for up to years at a time.

Results: As he dove deeper into research on primates, he began to feel short of instruments needed to conduct his experiments. Meanwhile, he discovered that there was intensive research on the brain being conducted in the United States. It was at this time that he was offered a scholarship to Yale University. Here, he published on human electrode implantation.

Conclusion: In the summer of 1964 an experiment was conducted that shocked the nation and demonstrated the power and capability of manipulation of the mind through implantation. Dr. Jose Manuel Rodriguez Delgado stood facing a bull in Cordoba, Spain. Armed with a red cape and a radio transmitter, Dr. Delgado provoked the bull to charge. The electrodes placed in the caudate nucleus of the bulls brain the day before had worked exactly as Dr. Delgado had anticipated. Reports of the experiment could be found in countless newspapers across the world, including The New York Times who called the event the most spectacular demonstration ever performed of the deliberate modification of animal behavior through external control of the brain.

320. Dr. Dwight Parkinson: Neurosurgical Pioneer of the Canadian Prairies

Andrew A. Ajisebutu (Winnipeg, Canada); Marc Del Bigio, MD, PhD, FRCPC; Michael West; Demitre Serletis

Introduction: In 1950, Dr. Dwight Parkinson (1916-2005) was the first qualified neurosurgeon to arrive in Winnipeg, Manitoba, at a time when there was not another neurosurgeon for over a thousand miles. He played a monumental role in developing one of the earliest neurosurgical training programs in Western Canada.

Methods: Using published materials (including online resources), hospital archives and interviews with former trainees and

colleagues, we have conducted a comprehensive and systematic historical review of Parkinson's formative years, his development of the Section of Neurosurgery at the University of Manitoba, his neurosurgical achievements and his wide-reaching impact and legacy.

Results: Parkinson was a pioneering neurosurgeon who went on to serve as the first President of the Canadian Neurosurgical Society, in 1965. He was the epitome of the skull base neurosurgeon, a subspecialty in its infancy at the time to which he contributed a detailed neuroanatomical body of work on the lateral sellar compartment (housing the parasellar venous plexus -- a term he emphasized as more accurate than 'cavernous sinus'). During his career, Parkinson made seminal contributions in the management of cerebrovascular disease, in addition to offering new insights on cerebral concussion.

Conclusion: Parkinson's steadfast philosophy towards neurosurgical excellence and resident education laid a cornerstone for the development of neurosurgery and the neurosciences in Manitoba, marking him a key figure in Canadian neurosurgery. This updated biographic synopsis offers new insights into the personal and professional exploits of this remarkable, and at times strictly disciplinarian, neurosurgeon-anatomist.

321. The Life of Ambroise Paré Spared by Hiding in a Clothes Closet. A Historical Vignette

Bruno Splavski, MD (Zagreb, Croatia); Kenan Arnautovic, MD; Kresimir Rotim, MD

Ambroise Paré was an illustrious surgeon of the Renaissance whose ideas, books and practical endeavors revolutionized surgery. He promoted medical empiricism and established a platform for evidence-based medicine that will define future anatomy and surgery. Therefore, he is considered a father of modern surgery and precursor of neuroscience. Ambroise Paré was born in the French province in 1510 to the humble family. At an early age he became a barber-surgeon and surgical student at the Hotel Dieu hospital in Paris. The experience he gained there enabled him to become a military surgeon making many innovations considering wound management, arteries ligation to prevent hemorrhaging during limb amputations, but also war head injury. His scientific publications were written in his native French what made them widely accessible. He insisted that a surgeon should operate on gently to reduce pain and to improve the outcome. Although he served four successive French monarchs at the royal Court, his prolonged career was also concerned with care for the wounded, sick and poor what made him famous. His professional vocation and his personal life were burdened by unrewarding political circumstances and religious prejudice. Purges organized by non-tolerant Catholic fanatics endangered his physical existence since he was a Huguenot (Reformed Protestant) by faith. However, his life was saved by hiding in a clothes closet during the St. Bartholomew's Day Massacre in 1572. In this paper, we discuss the scientific achievements, professional career and personal life of Ambroise Paré in the light of religious intolerance of his times.

322. Hippocrates: a less known period of his life

Theofanis Giannis (LARISA, Greece); Thanasis Paschalis; Gail Rosseau; Konstantinos Fountas

Introduction: Hippocrates of Kos is traditionally considered to be the father of modern medicine. His contribution to the world was prodigious, regarding the transition from the ancient years' superstitions about diseases to the establishment of medicine as a science. Although there is a large body of studies about Hippocrates' early life, the last and most productive from scientific standpoint part of it remains less explored.

Methods: A thorough review of the pertinent Greek and English literature was performed, in order to lighten Hippocrates' last days of life in Larissa, Greece. Furthermore, local and regional records and sources were included in our current communication.

Results: Hippocrates was a committed reformer of the way people thought about the concepts of disease, diagnosis, and treatment, while he served with devotion his noble vision until the end of his life. Hippocrates travelled and practiced medicine in many places including Kos, Thrace, Thessaly, and the Asia Minor. The purpose of his journeys was primarily to observe the influence of people's lifestyle and climate particularities into their health, as well as to describe the endemic diseases of each place. There are many references that Hippocrates' tomb could be found a few kilometers outside the city of Larissa, at least until the beginning of the 19th century. The tomb was surrounded at that time by graves of known locals. The strongest witness is provided by a local physician in 1857, who describes the discovery of a sarcophagus with a few ancient coins, a snake-shaped chain, and a tombstone with Hippocrates name on it, but without having any signs of human remains in it.

Conclusion: Hippocrates spent his most productive period of his life in Larissa, Thessaly serving with great devotion his vision until his death, in c. 370 BC. He inherited his legacy to the world.

323. A History of the Jannetta Procedure

Anthony M. Kaufmann, MD (Winnipeg, Canada); Angela Price, MD

Introduction: Jannetta, assigned to prosect cranial nerves specimens for dental students while a neurosurgery resident, in 1965, identified the portio intermedius of the trigeminal nerve. He proposed preservation of these sensory fibers may avoid complete facial numbness, and together with Robert Rand developed a sub-temporal trans-tentorial approach for selective rhizotomy for trigeminal neuralgia. Such rash surgery, utilizing an operating microscope, was then forbidden at their UCLA center, so they collaborated with John Alksne to perform the first surgery at Harbour General Hospital. Upon visualizing the trigeminal nerve, Jannetta was surprised to see a pulsating artery compressing the nerve and said That's the cause of the tic. He also hypothesized that alleviating the observed vascular cross-compression may be curative.

Methods: A few months later, while assessing a patient with hemifacial spasm, Jannetta had the epiphany this was the same disease process as TN but instead affecting the facial nerve. The patient consented to what would become Jannetta's first MVD procedure. As the senior faculty members who had forbidden such surgery were away, the supervising neurosurgeon, Paul Crandall, granted the approval to perform the surgery and assisted. Through a retromastoid approach in sitting position and utilizing the operating microscope, Jannetta identified and alleviated the culprit neurovascular compression with a resulting cure.

Results: Jannetta presented his neurovascular compression theory and operative findings to the neurosurgical patriarchy of the time. Elders of the field were generally not inclined to accept the bold speculations of an untested neurosurgeon, and were often determined to discredit the new cure of the old diseases.

Conclusion: Over decades of refining his surgical technique, documenting the outcomes and enduring the skepticism he often faced, Jannetta's theory and his MVD procedure withstood critical analysis and have become recognized as one the great discoveries and advances in Neurosurgery and Medicine.

324. Dr. John A Jane Sr. (1931 – 2015): A quintessential "General" Neurosurgeon who treated "Superman"

Tanmoy Kumar Maiti, MD (Cleveland, OH); Jamal McClendon, MD; Bernard Bendok, MD; Chandan Krishna, MD; Devi Patra, MD

Introduction: Dr. John A Jane Sr. had contributed enormously in the field of Neurosurgery.

Biography and training: Born in Chicago, he completed his medical degree, and Neurosurgical residency, and PhD at the University of Chicago in 1952-1967. During training, he worked with Paul Bucy, Oscar Sugar, and Wilder Penfield, among others. After 4-year-stint in Case Western University, at the age of 37 years, he joined University of Virginia as Professor and Chairman, and served in same post till 2006. A General Neurosurgeon and "team-man" Dr. Jane was a skilled General neurosurgeon. With Plastic surgery, he made significant contribution in correction of craniosynostosis (Pi procedure). He documented one of the initial descriptions of supraorbital craniotomy. With ENT surgeons he expertized in treating Esthesioneuroblastomas. Association with endocrinology led to establishment of the distinguished Pituitary Center. Editor of JNS. He became a member of the Editorial Board of JNS in 1984. Subsequently, he succeeded Dr. Sundt as editor (1992-2013). He established the *JNS:Spine* and *JNS:Pediatrics*.

Recognition and awards: Dr. Jane served as the director of the ABNS, and president of SNS. Among several national and international awards, Lifetime Achievement Award from the American Cleft Palate-Craniofacial Association (1999), Cushing Medal (2004), CNS Founder's Laurel Award (2005), and the Governor's Public Service Award for Career Achievement (2014) worth special mention.

Most famous case: In 1995, actor Christopher Reeve famous for his role as Superman suffered a complex fracture of upper cervical spine, after thrown from his horse. Dr. Jane's team fused his C1 and C2 in a successful attempt to prevent further damage to his spinal cord.

Conclusion: Dr. John was a pioneer, with his surgical excellence and visionary leadership. His son, Dr. John A Jane Jr., a neurosurgeon in University of Virginia is successfully continuing his legacy.

325. Watt Weems Eagle (1898-1980) and the History of Eagle Syndrome

Rimal Hanif Dossani, MD (Shreveport, LA); Rimal Dossani, MD; Anan Rmilah, MD; Brian Willis, MD

Introduction: Watt Weems Eagle (1898-1980) was an American otolaryngologist who first described Eagle syndrome, a rare clinical entity that presents with a triad of dysphagia, cervical pain, and foreign-body sensation in the throat. The aim of this study is to present a historical vignette on Eagle's life and on the syndrome that became eponymous with his name.

Methods: We performed interviews of Eagle's colleagues to obtain biographical information. We then performed a literature search on PubMed Central to identify all historical manuscripts authored by Dr. Eagle.

Results: Watt Weems Eagle was born in Statesville, North Carolina, in 1898. He obtained his medical degree and completed a residency in otolaryngology at Johns Hopkins. At Duke, Eagle served as the first chief of the ENT division from 1930-1949. In several publications published in the late 1930s, Eagle was the first to systematically describe the clinical syndrome and surgical treatment for elongated styloid processes, and this syndrome has since been associated with his name. The classical form presents with persistent unilateral pharyngeal pain worsened by swallowing. The vascular form, which is of interest to neurosurgeons, is characterized by compression of the internal carotid artery by an elongated styloid process.

Conclusion: Watt Eagle was an outstanding American surgeon and otolaryngologist who spent the majority of his career at Duke Medical Center. He is known for defining Eagle syndrome, a rare clinical entity with a constellation of neuropathic and vaso-occlusive symptomatology caused by abnormal elongation or angulation of the styloid process.

328. Brain Iron Deposition After Ferumoxytol-enhanced MRI: A Study of Porcine and Pediatric Brains

Lily H. Kim (Mountain View, CA); Michael Iv, MD; Ashok Theruvath, MD; Laura Pisani, PhD; Olga Lenkov, PhD; Heiki Daldrop-Link, MD, PhD; Gerald Grant, MD; Samuel Cheshier, MD, PhD; Kristen Yeom, MD; Katie Shpanskaya, BS

Introduction: Use of ferumoxytol (Fe) as an intravascular contrast agent for magnetic resonance imaging (MRI) has shown robust performance in presurgical evaluation of arteriovenous malformations. While it is known that gadolinium as a contrast agent deposits in the brain, iron oxide nanoparticle distribution in the brain after intravenous injection remains unknown. In this study, we investigated if there is any intracranial iron deposition after multiple ferumoxytol administrations.

Methods: We conducted a retrospective study of 9 pigs and 12 pediatric patients (7 females, 5 males) who received Fe (5 and 3 mg/kg, respectively). Inclusion criteria were: whole porcine brains with ex-vivo T2* (T2 star) MRI at 7 Tesla; patients with at least two Fe-enhanced T2* MRIs at 3 Tesla. Quantitative T2* values were extracted from caudate, lentiform, dentate, thalami, globus pallidus, putamen, and substantia nigra. Pearson correlation was used to evaluate Fe dose relative to R2* and susceptibility values.

Results: In pigs, there was no significant difference in R2* of Fe-exposed brain versus controls. In humans, R2* and susceptibility in all brain regions did not significantly differ from baseline ($P>0.05$), except for increased R2* in the dentate ($P=0.013$) and globus pallidus ($P=0.019$) at follow-up MRI (mean follow-up 14.67 months). However, this was not dose-dependent.

Conclusion: No significant differences were found in R2* and susceptibility values in porcine and human brains after Fe-enhanced MRIs except for slightly increased R2* in the dentate and globus pallidus in humans at follow-up, suggesting that exogenous Fe administration results in minimal brain iron deposition. Given high performance of Fe as an intravascular contrast agent with potentially less risk for permanent brain deposition compared to gadolinium, Fe may be a useful alternative intravascular MRI contrast agent for neurosurgical evaluation of vascular lesions.

329. One Hundred Years of Innovation: Deep Learning for Automatic Detection of Brain Ventricular Volume in a Multi-Institutional Study

Jennifer Lauren Quon, MD (Stanford, CA); Lily Kim, BA; Michelle Han, BS; Edward Lee, PhD; Samuel Cheshier, MD, PhD; John Kestle, MD, PhD; Robert Lober, MD, PhD; Kristen Yeom, MD; Michael Taylor, MD, PhD; Gerald Grant, MD; Michael Edwards, MD

Introduction: This year marks the centennial of the development of ventriculography by Walter Dandy in 1918. Significant strides have since been made in neuroimaging, and visualization of the ventricles has become routine in hydrocephalus management. However, we lack a readily available method to measure ventricular volume in clinical settings. Management of hydrocephalus is further complicated by the paucity of data on normal ventricular development and volumetric changes that occur with intracranial pathologies. We conducted a multi-institutional study to develop a deep-learning model designed to automatically detect ventricular volume.

Methods: Six hundred pediatric brain magnetic resonance images (MRIs) (400 normal, 200 hydrocephalus) were divided into training ($n=420$), validation ($n=90$), and testing ($n=90$) datasets. All normal scans were obtained from patients between the ages of 0 and 18 evaluated at our institution between 2011-2017. The hydrocephalus cohort was selected among patients with posterior fossa tumors who had radiologic evidence of ventriculomegaly. Scans from this cohort included 50 MRIs from our institution and 150 from three outside academic centers. Expert segmentation of the ventricles was performed on all T2-weighted and thin-slice T1-weighted spoiled gradient recalled acquisition in the

steady state (SPGR) scans. Our encoder-decoder convolutional neural network architecture consisted of a UNet with a pre-trained ResNet50 encoder.

Results: Manual segmentation served as the ground truth for ventricle delineation. True ventricular volume was based on SPGR sequences. Dice score for model performance was 0.8699 for automatic segmentation of ventricle volume for T2-weighted sequences. Predicted ventricular volume was, on average, within 8% of the manually determined volume.

Conclusion: In this multi-institutional study, we present a deep learning model that automatically segments ventricles and outputs volumetric information. This clinically applicable and externally validated tool may enhance our current understanding of ventricular development and facilitate accurate ventricular volumetric measurement in the clinical setting.

330. In vivo Treatment of Progressive Congenital Hydrocephalus via Drug Inhibition of mTOR

Tyrone DeSpenza (New Haven, CT); Stephanie Getz; Sheng Chih Jin; Jinhui Zhang; Wei Wang; Murat Gunel; Bryan Luikart; Duy Phan; August Allocco; Carol Nelson-Williams; Richard Lifton; Kristopher Kahle

Introduction: Congenital hydrocephalus (CH) is a morbid, heterogeneous disorder treated mainly with surgical shunting. A personalized medical approach could enhance therapeutic options for patients. We have found loss-of-function de novo mutations in PTEN, which over-activate downstream mTOR signaling, to cause multiple cases of sporadic CH. We hypothesized that drug inhibition of mTOR signaling in PTEN-mutated hydrocephalus could represent a feasible non-surgical treatment strategy for CH.

Methods: We conditionally knocked out PTEN in C57BL/6J mice using Cre-LoxP recombination in fluorescently labeled neural progenitor cells. Kaplan-Meier survival curves were constructed for PTEN KO and their WT, control littermates. Rapamycin was injected intraperitoneally in PTEN KO and WT mice daily from postnatal (P) day 10-22. PTEN KO and WT mice brains were sectioned, immunostained, and imaged with confocal microscopy to assess for ventricular size.

Results: PTEN KO resulted in fully penetrant, fatal hydrocephalus with a median survival of P17.5. The Kaplan Meier survival analysis showed that WT animals (n=41) survived significantly longer than PTEN animals (n=10) ($p<.0001$). Rapamycin was able to fully rescue the fatal hydrocephalus phenotype (n=8) by inhibition of mTOR ($p<.0001$).

Conclusion: Conditional PTEN KO in neural progenitor cells in mice caused fatal hydrocephalus that was rescued by pharmacological inhibition of the mTOR pathway with Rapamycin. These results show that dysregulated neural progenitor cell fate is involved in the pathogenesis of CH, and suggest a novel treatment paradigm that may be adopted into clinical trials in a subset of CH patients that harbor PTEN mutations.

331. Pediatric Lumbar Puncture Pressures do not Correlate with Intracranial Pressures Measured via Intraparenchymal Wire

Christina Sarris, MD (Phoenix, AZ); Tyler Cole, MD; Ruth Bristol, MD

Introduction: Lumbar puncture has long been considered a reliable method of measuring intracranial pressure. The development of the intraparenchymal pressure monitor calls the accuracy of those measurements into question. The effects of general anesthesia on LP opening pressures should not be underestimated. The flurane anesthetics, ketamine, patient's BMI, and elevated end-tidal CO₂ have all been found to increase ICP.

Methods: An IRB-approved retrospective review of all patients who had undergone ICP wire placement and also had prior LP opening pressure measurements between 2012 and 2017 was carried out.

Results: 25 patients met inclusion criteria. The majority of patients were undergoing workup for chronic headache or idiopathic intracranial hypertension. Preoperative LP opening pressures were recorded in cm H₂O and converted to mm Hg for comparative analysis. Mean LP opening pressure was 29.6 cm H₂O, or 21.9 mmHg (Range 16-37 mmHg). Intraoperative mean ICP measured via wire was 13.2 mmHg (Range 6-26 mmHg), and postoperative mean ICP measured via wire was 8.1 mmHg (Range -2.5 to 18.5 mmHg). Results of a paired t-test demonstrated that both LP opening pressures and intraoperative ICP measurements were significantly higher by 14 and 5 points, respectively, compared to postoperative ICP measurements ($p<0.001$). End-tidal CO₂ was not found to significantly correlate with intraoperative ICP ($p=0.515$).

Conclusion: Lumbar puncture pressure was not an accurate measurement of intracranial pressure in our series. As physicians often incorrectly use mmHg and cm H₂O interchangeably, the discrepancy in using cm H₂O for lumbar puncture and using mmHg for ICP should be accounted for by conversion to the same units for comparison. Anesthetic protocols should avoid inhalational agents and ketamine. Interventions, such as shunting, cranial vault remodeling, or medication management, should be undertaken with caution if LP opening pressure measurement is the only available estimate of ICP.

332. Pediatric Brain Arteriovenous Malformation Unfavorable Hemorrhage Risk: Extrapolation to a Morphologic Model

Li Ma (Beijing, China); Zongze Li, MD; Yuanli Zhao, MD

Introduction: Children with brain arteriovenous malformations (bAVM) are at risk of life-threatening hemorrhage contributing to unfavorable neurological deficit in their early lives. Our aim was to propose a classification system predicting the unfavorable hemorrhage in children with bAVM.

Methods: We identified all consecutive children admitted to our institution for bAVMs between July 2009 and August 2015. A hemorrhage event was defined as unfavorable when it is life-threatening (requiring emergent invasive intervention) or with post-hemorrhage mRS >3. The effects of demographic characteristics and bAVM morphology on unfavorable hemorrhage risk were studied using univariate and multivariable regression analyses, followed by discrimination analysis using area under the receiver operating curve (AUROC) and 5-fold cross validation.

Results:

A total of 162 pediatric bAVM cases were identified, unfavorable hemorrhage occurred in 49 (30.2%). Periventricular nidus location (HR, 4.46; 95%CI, 1.93-10.31; $P < 0.001$), non-temporal lobe location (HR, 2.72; 95%CI, 1.20-6.15; $P = 0.02$) and long pial draining vein (HR, 3.26; 95%CI, 1.53-6.97; $P = 0.002$) were independent predictors of an earlier unfavorable hemorrhage in pediatric bAVMs. We further classified the bAVM into three types: Type I, periventricular and non-temporal location (Ia, deep location; Ib, superficial location); Type II, with long pial draining vein and non-periventricular or temporal location; Type III, non-periventricular or temporal location without long draining vein. Predictive accuracy of this classification for unfavorable hemorrhage was assessed with AUROC of 0.77 (95% CI 0.69-0.85) and remained stable after cross validation.

Conclusion: A morphologic model based on nidus location and venous drainage might predict unfavorable hemorrhage in children with bAVM.

333. Correlation between Involvement in Specific Sports and Lifetime Risk of Developing a Traumatic Brain Injury in Young Students Athletes.

Clementine Koa Affana (Roseau, Dominica)

Introduction: Pediatric concussions have become a major health concern with a 71% increase in diagnoses in children ages 10 to 19. With the long-term cognitive effects of repeated concussions, assessing the lifetime risk of students athletes of developing a concussion is crucial. Our goal was to assess if there was an association between past history of concussions and involvement in specific sports.

Methods: As part of a larger sports concussion study, student athletes at 6 area high schools and 1 college (ages 12 to 23) in Minneapolis completed a demographic survey which involved the preliminary portion of the Boston Assessment of Traumatic Brain Injury - Lifetime (BAT-L). Sports included football, soccer, hockey, volleyball, tennis, cross country and swimming. The survey provided a detailed assessment of past TBI episodes (timeline, severity and symptoms duration).

Results: 222 subjects completed the survey (mean age of 16.27), 61.3% of those were males. 54 (26.1%) reported having had at least one concussion in the past. Males were more likely to have had a past history of concussion than females (30.1% vs 15.5%), older subjects reported more concussions (32.1% in those 18 or older and 19.1% were younger than 18). The most common causes of past concussions were sports (77%) followed by falls (9%) and motor vehicle accidents (5%). Other causes accounted for 9% of past concussions. Football and soccer players had more reported episodes compared to other sports (football: 12, soccer: 15, volleyball: 3, hockey: 1, tennis: 0, cross-country: 0, swimming: 0), and soccer players reported having had multiple episodes of concussion in their lifetime compared to other sports.

Conclusion: Preliminary data demonstrates that older students athletes that play football are more likely to have experienced multiple concussions in their lifetime. Efforts should be made to reinforce preventive measures at earlier stages of sports involvement.

334. Topical Vancomycin for Surgical Prophylaxis in Pediatric Craniofacial Surgeries

Allen L. Ho, MD (Stanford, CA); Jyodi Mohole; John Cannon; Arjun Pendharkar; Eric Sussman; Samuel Cheshier; Gerald Grant

Introduction: The application of topical vancomycin to surgical wounds has been demonstrated to be safe and effective for reducing surgical site infections (SSIs) following spine surgery in both adults and children, however, there are no studies of its efficacy in reducing SSIs in craniofacial surgery. SSIs are one of the most common complications following craniofacial surgery. The complexity of craniofacial procedures, use of grafts and implants, long operative durations and larger surgical wounds all contribute to the heightened risk of SSIs in pediatric craniofacial cases.

Methods: A retrospective review of all pediatric craniofacial procedures performed between 5/2014-12/2017 at a single children's hospital was conducted to examine SSI rates between patients receiving topical vancomycin and a historical control group. The treatment group received topical vancomycin irrigation prior to wound closure. An ad-hoc cost analysis was performed to determine the cost-savings associated with topical vancomycin use.

Results: A total of 132 craniofacial procedures were performed during the study period, with 50 cases in the control group and 82 cases in the vancomycin group. Overall, SSI rate was 3.03%. Use of topical vancomycin irrigation led to a significant reduction in SSIs (4/50 SSI or 8.0% in control group vs 0/82 or 0% in vancomycin group, $P=0.04$). No adverse events were observed with topical vancomycin use. The potential cost-savings associated with the use of topical vancomycin as SSI prophylaxis in this study was \$102,152.

Conclusion: Addition of topical vancomycin irrigation as routine surgical infection prophylaxis can be an effective and low-cost method for reducing SSI in pediatric craniofacial surgery.

335. Endoscope-assisted hemispherotomy: preliminary results in nine patients

Kathryn Wagner, MD (Houston, TX); kathryn wagner; Vijay Ravindra, MD; Sandi Lam, MD

Introduction: Hemispherectomy has is an effective surgical treatment of intractable epilepsy in appropriately selected patients. Historically an open procedure with significant morbidity, endoscopic approaches to hemispheric disconnection have been pursued in efforts to minimize exposure and associated complications. We have previously described the development and implementation of the endoscopic-assisted hemispherectomy at Texas Children's Hospital (TCH). Here we present the preliminary results of this technique.

Methods: Data was prospectively collected on pediatric patients undergoing hemispherectomy at TCH. Patient candidacy for endoscopic hemispherectomy was the consensus of a multi-disciplinary epilepsy team, and all procedures were performed by the senior faculty who implemented the procedure at TCH. Full disconnection of the hemispheres was performed using the endoscopic-assisted technique previously described. Patient characteristics, perioperative data, clinical course, outcomes, complications, and seizure freedom rates were reviewed. Patient who have a minimum of three months follow up were included in this review.

Results: Nine patients aged two months to 16 years underwent endoscopic hemispherotomy from 11/2017-7/2018 with subsequent follow up. Diagnoses included perinatal stroke, intraventricular hemorrhage of prematurity, polymicrogyria, and cortical dysplasia. Estimated blood loss ranged from 30-200cc, and operative time ranged from three to eight hours, with duration correlating with complexity of pathologic anatomy. There were no intraoperative or perioperative complications. All patients remain seizure free at last follow up, and 22% patients have required cerebrospinal fluid shunt to date. When compared to a historical open craniotomy cohort at our institution, endoscopic patients had lower estimated blood loss.

Conclusion: Endoscopic hemispherotomy can be safely implemented in clinical practice with early outcomes similar to standard open procedures. Our short-term seizure freedom rate is 100%, and rates of postoperative hydrocephalus requiring shunts are similar to those published regardless of surgical technique. Larger series and long term data is needed to compare novel endoscopic techniques to current open procedures.

336. Surveillance of Residual Pediatric Brain Arteriovenous Malformations Using Ferumoxytol-based ASL and SPGR Magnetic Resonance Series

Yuhao Huang (Stanford, CA); Timothy Singer; Michael Iv; Bryan Lanzman; James Stadler III; Jia Wang; Gerald Grant; Samuel Cheshier; Kristen Yeom

Introduction: Pediatric patients with intracranial arteriovenous malformations (AVMs) undergo digital subtraction angiography (DSA) for surveillance following surgical intervention. However, DSA carries substantial radiation risk,

particularly for the pediatric population. We evaluated whether magnetic resonance (MR) with ferumoxytol contrast can be used to surveil residual AVM.

Methods: A retrospective cohort was assembled for children treated with AVM from 2014 to 2016 who underwent surveillance by DSA and ferumoxytol-based MR imaging. Arterial spin labeling (ASL) and spoiled gradient recalled acquisition (SPGR) were the MR series used. Two radiologists blinded to DSA results independently assessed MR scans for residual AVM and lesion evolution. Diagnostic confidence was examined using a Likert scale. Sensitivity, specificity, and inter-modality reliability were determined with DSA as the gold standard. Radiation exposure was calculated as total dose area product (TDAP), total air kerma (TAK) and peak air kerma (PAK).

Results: Fifteen patients were included in this study (mean: 11 years, range: 3-17). The average time between the first surveillance DSA and subsequent MR was 17 days (SD: 98). Inter-modality agreement was excellent between SPGR and DSA ($k = 0.848$, $p < 0.001$), but poor between ASL and DSA ($k = 0.393$, $p = 0.014$). Sensitivity and specificity of SPGR and ASL in diagnosing AVM were 92% and 100%, 72% and 100%, respectively. Radiologists reported greater diagnostic confidence with ferumoxytol-based MR versus standard MR. On average, patients received two DSA studies during surveillance. Per DSA, radiation for TDAP, TAK and PAK was 58,632 mGy.cm² (95% CI: 38,570 - 78,693), 562 mGy (95% CI: 378 - 747), and 310 mGy (95% CI: 209 - 411), respectively. Two surveillance DSA studies constitute 56% of the 2Gy safety threshold (95% CI: 38-75%).

Conclusion: Ferumoxytol-based MR performed similarly to DSA for AVM surveillance in the pediatric population and can be considered an equal alternative.

337. Risk of venous thromboembolism for a busy pediatric neurosurgical service: a retrospective 25-year institutional experience

Mason Anthony Brown (Milwaukee, WI); Daniel Fulkerson, MD

Introduction: Venous thromboembolism (VTE) refers to both deep venous thrombosis (DVT) and pulmonary embolism (PE). The risk of VTE in adult neurosurgical patients is thoroughly studied, and multiple quality measures have been implemented to reduce the morbidity and mortality of this potentially preventable complication. However, the incidence and risk of VTE within a pediatric neurosurgical population is not well-defined. This study was undertaken to retrospectively analyze the incidence and specific risk factors of VTE in patients evaluated by a pediatric neurosurgery service over a 25-year period.

Methods: A retrospective review of electronic medical records was performed for 9149 hospitalizations (admissions or consultations) of 6355 unique patients evaluated by the pediatric neurosurgery service at Riley Hospital for Children (Indianapolis, IN) from 1990-2014. There were 6769 elective procedure admissions and 2380 trauma evaluations.

Results: VTE was diagnosed in 19 (0.21%) hospitalizations in 18 (0.28%) unique patients. All DVTs were diagnosed via Doppler ultrasound and all PEs were identified via CT angiography. Anatomic clot locations included: 8 (0.09%) lower extremity DVT, 9 (0.10%) upper extremity DVT, and 3 (0.03%) PE. One (0.01%) patient developed a DVT and subsequent PE during the same admission, and 3 (0.03%) patients developed multiple DVTs during the same admission. Of the hospitalizations with VTE, 13 (68.42%) had some route of venous line placement prior to diagnosis.

Conclusion: A VTE was diagnosed in 19 of 9149 (0.21%) hospitalizations evaluated by a single-institution pediatric neurosurgical service over 25 years. This represents the experience of a broad, comprehensive pediatric neurosurgical population. Our data suggests that the risk of VTE in hospitalized pediatric patients is substantially lower than reported levels in adult neurosurgical patients.

338. In Vitro Modeling of IVH of Prematurity Mirrors the In Vivo Inflammatory Response

Brian Snyder, MD (Lexington, KY); Danielle Goulding; R. Vogel; Brandon Miller, MD, PhD

Introduction: An unfortunate consequence of preterm birth is neonatal intraventricular hemorrhage. This extravascular hemorrhage is frequently associated with periventricular leukomalacia. Our group hypothesizes that neuroinflammation, in particular activated microglia/macrophages, mediates this ultimate white matter loss.

Methods: Mixed cortical cultures were obtained from post natal day two rats and allowed to expand. Microglia were isolated and exposed to different concentrations of hemoglobin. Nine different inflammatory cytokines were measured by using a meso-scale detection ELISA. We then co-cultured oligodendrocyte progenitor cells with microglia to test the possibility of hemoglobin-induced microglial OPC death. Cells were stained with IB4, a microglial marker, and NG2, a marker of immature oligodendrocytes. An in vivo model of neonatal IVH using rat pups was used to measure cytokine production and oxidative stress within the whole brain.

Results: Numerous proinflammatory cytokines including TNF- and CXCL1 are significantly elevated in microglia exposed

to hemoglobin. The cytokine profile is consistent with a M1 or pro-inflammatory macrophage response. This inflammatory profile in vitro mirrors the cytokine profile seen in our in vivo model of intraventricular hemorrhage. Oxidative stress is present throughout the brain after IVH, and occurs after the initial inflammatory response. Analysis of OPC survival in response to hemoglobin alone and hemoglobin-activated microglia is in progress.

Conclusion: Our rodent model of neonatal IVH induces a proinflammatory cytokine profile that mirrors our in vivo model of intraventricular hemorrhage of prematurity. Upon analysis of our OPC survival data we will be able to deduce whether or not hemoglobin induced microglia or hemoglobin alone kills oligodendrocyte progenitor cells. This in vitro model of IVH-induced PVL may be useful for future mechanistic and therapeutic studies.

339. Perivascular Stasis of Intraventricularly Injected Macromolecules as a Hallmark of Hydrocephalus: Experimental Study Using POMGnT1 Knockout Mice

Satish Krishnamurthy, MD (Manlius, NY), FAANS; Jie Li, MD; Haiya Hu, PhD

Introduction: Pathogenesis of hydrocephalus is not clearly understood. Brain is permeable to water and we have shown that infusion of hyperosmolar dextrans into the ventricles is sufficient to cause hydrocephalus. Therefore, water influx into the ventricles is secondary to the presence of macromolecules in the ventricles. Macromolecules infused into the ventricles were distributed widely in the brain parenchyma especially in the perivascular region and cleared into the blood. There is delayed clearance in kaolin-induced hydrocephalus with stasis of the macromolecules in the perivascular region. Present study was undertaken to determine whether these changes are present in a genetic mouse model of hydrocephalus.

Methods: POMGnT1 knockout (genes involved in protein glycosylation) mice results in congenital muscular dystrophy is associated with hydrocephalus. Ventricular volumes of the knockout mice (n=6) and wild type mice (n=5) were compared by calculations using histopathology sections utilizing ImageJ software. Next, 15µl of FITC 10KD dextran (FITCDex) was injected into brain lateral ventricle of knockout mice (n=3 at 30 and n=11 at 60 min) and wild type mice (n=3 at 30 and n=13 at 60 min). Histopathology was performed to determine if there was perivascular stasis.

Results: Ventricular volume was larger (0.15 µl) in knockout mice as compared to the wild type mice (0.04 µl *P<0.05). (Graph 1 and Fig1). FITCDex particles were not distributed through the entire brain parenchyma at 30 mins in knockout like it was in the wild type mice. FITCDex particles clearance was delayed at 30 and 60 mins in the knockout mice as compared to wild type mice (Fig. 2 and Fig 3).

Conclusion: Perivascular stasis suggestive of delayed clearance of macromolecules from the ventricles is a pathognomonic feature of hydrocephalus. Future studies of the impaired transport mechanism in this genetically mutated mouse might offer clues to finding a pharmacological cure of hydrocephalus.

340. The Effect of Proteins and Temperature on Certas and Hakim Valves Function

Riccardo Serra (Baltimore, MD); Noah Leviton Gorelick; Riccardo Serra, MD; Arba Cecilia; Rajiv Iyer, MD; Betty Tyler; Mark Gregory Luciano; Henry Brem, MD

Introduction: While both differential pressure and resistance valves have been used alone and in combination to regulate flow in shunting, the resultant flow is not well understood. In our benchtop gravity-flow system, here using Certas+ and Hakim valves with Siphoguard, we vary protein content, temperature and pressure in diurnal simulations of upright and supine conditions to evaluate CSF flow rate and variability.

Methods: Saline and Human CSF were tested for 2 consecutive trials of 30 days each. CSF was collected from patients through an IRB-approved protocol and filtered, protein concentration was adjusted to 500 mg/dl. Hourly measurements of ICP, temperature and flow output collected for both upright and supine positions of the Certas and Hakim valves, thereby varying resistance and ball valve engagement. Flow rates were calculated and plotted using set valve resistances (3 Certas+ at 2, 3 Hakim valves at 50) allowing for comparison between saline and high-protein CSF, and temperature (25° and 37° C).

Results: Protein effect: when tested supine with high-protein CSF at 37° C, Certas+ valves went from 37 ml/hr to 27 ml/hr (37% increase, p=0.01), compared to protein-free saline, with no increase seen in the upright position. Hakim valve supine flow increased (52 ml/hr Vs 38 ml/hr, 36.8%, p=0.07) and upright positions (27 ml/hr Vs 22 ml/hr, 22%, p=0.02). Temperature effect: With higher temperature valves showed a increased CSF flow rates when the temperature was raised, 20% (p=0.004) and 55%, (p=0.001). in Hakim and Certas+ valves, respectively.

Conclusion: CSF (with protein) and temperature interact to increase the flow rate and variability through valve systems. These effects are different in different ball valves constructs and especially different comparing ball valve to resistance regulation. Further, these changes are in the range that have potential clinical impact.

341. Targeting The CSF1/CSF1R Axis is an Effective Treatment Strategy for Malignant Meningiomas

AANS/CNS Section on Tumors Skull Base Award

Jacky Yeung, MD (New Haven, CT); Danielle Miyagishima, BS; Miguel Sanmamed, MD, PhD; Ti Badri, MS; Jennifer Moliterno, MD; Joseph Piepmeier, MD; Murat Gunel, MD; Lieping Chen, MD, PhD

Introduction: While most meningiomas are benign and surgical resection can be curative, there are a small group of patients with recurrent and malignant forms of the tumor that have limited surgical and chemotherapeutic options. Our initial results using RNA deconvolution revealed M2 immunosuppressive macrophages as the most prevalent immune cell type in human meningiomas. We hypothesized that targeting macrophages in meningiomas would be an effective treatment strategy.

Methods: We targeted the CSF1/CSF1R axis, an important regulator of macrophage phenotype, using a pre-clinical immunocompetent murine model for malignant meningioma (Yale/INSERM collaboration). FVB Mice were injected in the flank subcutaneously with 106 tumor cells. The mice were treated with 200 µg of monoclonal antibodies targeting CSF1 or CSF1R i.p. twice weekly at 1 week post-implantation. Immunohistochemistry were used to analyze the immune cell infiltration. RNA-seq was performed to identify changes in gene expression in the tumor microenvironment after treatment.

Results: Immunohistochemistry identified an abundance of myeloid cells, a paucity of T cells, and low PD-L1 expression in our model of murine meningiomas. We found that anti-CSF1 antibody (5A1) treatment significantly abrogates the growth of murine meningiomas and increased T cell infiltration into the tumor microenvironment. Similarly, anti-CSF1R antibody (AFS98) treatment exerted significant CD8-dependent anti-tumor effect in vivo without changing F4/80+ tissue macrophage abundance. Treatment with anti-CSF1R antibody, but not anti-PD-1 antibody, effectively slowed the growths of early (day 7) and late (day 30) meningiomas. GO analysis using RNA-seq data revealed differentially expressed gene sets related to immune and inflammatory responses.

Conclusion: Our findings demonstrate that anti-CSF1/CSF1R antibody treatment effectively suppresses tumor growth in a preclinical murine malignant meningioma model that is resistant to anti-PD-1 antibody therapy. The current data provides strong rationale for future human clinical trial.

342. Genetic variation of recurrent low-grade and high-grade meningiomas is associated with clinical outcomes and progression-free survival: An analysis of 150 meningiomas with complete genomic sequencing

Integra Foundation Award

Joshua N. Loewenstern (New York, NY); Will Shuman; Remi Kessler; Karan Kohli; Margaret Pain, MD; Melissa Umphlett, MD; Robert Sebra, PhD; Michael Donovan, MD, PhD; Joshua Bederson, MD; Mary Fowkes, MD, PhD; Raj Shrivastava, MD

Introduction: While most resected low-grade meningiomas will not recur, there exists a significant population of more aggressive recurrent low-grade and atypical/anaplastic meningiomas that are likely to recur after surgical resection, leading to increased morbidity, re-operation, and decreased survival. However, few studies have investigated genetic risk factors driving meningioma recurrence. The present study aimed to identify key driver mutations that are associated with post-resection outcomes.

Methods: 150 consecutively resected recurrent low-grade (WHO grade I, n=32) and high-grade (WHO grade II/III, n=118) meningiomas with adequate biopsy specimens from 2007-2016 underwent complete genomic sequencing and assessed for driver mutations. Genetic variants were correlated with post-operative clinical outcomes including tumor recurrence, functional status, and progression-free survival (PFS).

Results: The most common driver mutations identified included ARID1A, CDKN2A, NF1, NF2, NOTCH3, PTCH1, and SMARCB1, which combined were present in 55% of meningiomas. Tumors with a NOTCH3 driver mutation had decreased PFS (HR=1.95, p=0.047). Further, tumors without a known driver mutation had improved PFS relative to those with at least 1 identified driver mutation (p=0.042), but those with multiple driver mutations did not differ from those with 1 mutation (p=0.75). Meningiomas with a NF2 mutation were associated with larger tumor size (p=0.039) and correlated with higher mitotic proliferation on histopathological examination (p=0.003).

Conclusion: Genetic variants involved in intercellular signaling, cell differentiation, and cytoskeletal integrity like NOTCH3 and NF2 may be especially predictive of recurrence risk and tumor proliferation. Identification of driver mutations associated with recurrence and post-operative outcomes is an important step in targeted molecular treatment of tumors refractory to resection and radiation.

343. Genetic Signatures of Skull Base Chordoma Progression after Surgery and Radiation

Georgios Andrea Zenonos, MD (Miami, FL); Ahmed Jorge, MS; Andrew Venteicher, MD, PhD; Benita Valappil, MS; Juan Fernandez-Miranda, MD; Carl Snyderman, MD; Eric Wang, MD; William LaFramboise, PhD; Paul Gardner, MD

Introduction: The genetic aberrancies driving recurrent skull base chordomas after surgery and radiation are poorly understood. Deciphering these processes may be key in developing targeted therapies for tumors that fail the standard of care.

Methods: To minimize the background genetic noise of inter-subject variability, we sought to study the progression of genetic signatures in the same patients with skull base chordomas, each undergoing the sequence of primary tumor resection, radiation, tumor progression, and recurrent tumor resection. Whole-exome sequencing was performed on 16 samples: five primary tumors and their six recurrences (one patient had two recurrences), along with matched peripheral blood. Germline and tumor-specific mutations (single nucleotide variations, insertions/deletions, and copy number variations) were called using established pipelines for each patient's blood, primary and recurrent tumor(s) samples. The data were then curated for potentially deleterious mutations employing a battery of algorithms (ACMG designation and effect, and 14-Variant Effect Predictor scores). The genetic aberrancies unique to the transition of primary to recurrent tumors were determined, and studied using a series of gene set enrichment analysis tools (GSEA, DAVID, IPA, CPDB, and Reactome).

Results: Three-hundred and ninety-eight genes were exclusively affected in recurrent tumors, either by copy number variations, or potentially deleterious point mutations and insertions/deletions. Gene set enrichment analysis integrated these results into several potentially actionable pathways, such as Neurotrophin-signaling (FDR=1.52e-4), EGF-signaling (FDR=1.01e-3), mTOR-signaling (FDR=2.74e-3), ErbB-signaling (FDR=3.76e-3), Jak2-signaling (FDR=7.57e-3), and ATF2-signaling (FDR=7.57 e-3). Additionally, a number of other cancer-related and immunologic signatures, as well as cytoskeleton-related processes were enriched with an FDR<0.01.

Conclusion: We have identified genetic signatures uniquely characterizing the progression of primary skull base chordomas to recurrent tumors after surgery and radiation. Many of the affected pathways are potentially actionable, and could guide targeted therapy investigations for these challenging tumors.

344. Results of a Prospective Multicenter Controlled Study Comparing Pituitary Gland Hormone Outcomes of Microscopic versus Fully Endoscopic Transsphenoidal Surgery for Nonfunctioning Pituitary Adenomas

Andrew Scott Little, MD (Phoenix, AZ), FAANS; TRANSSPHER Study Group

Introduction: Many surgeons have adopted fully endoscopic over microscopic transsphenoidal surgery for pituitary tumors, although no high-quality evidence demonstrates superior patient outcomes with endoscopic surgery. Previously, we presented an analysis of extent of tumor resection from a multicenter prospective study, which demonstrated that these techniques yielded similar gross total tumor resection rates. In this abstract, we present the comparative pituitary gland endocrine outcomes.

Methods: Adrenal, thyroid, gonadal, and posterior gland function were evaluated before and 6 months after surgery using standard endocrine laboratory testing. Results were centrally adjudicated.

Results: Seven pituitary centers and 15 surgeons participated. 260 patients were enrolled (82 with microscopic procedures, 177 with endoscopic procedures, 1 cancelled surgery). Baseline patient tumor characteristics were similar between groups. A new deficiency of at least one hormone axis was noted in 19 of 67 patients (28.4%) in the microscopic cohort and 14 of 145 patients (9.7%) in the endoscopic cohort ($P<0.001$; OR, 3.7; 95% CI, 1.7-7.7). Improvement in at least one hormone axis was noted in 12 of 50 patients (24.0%) in the microscopic group and 20 of 93 patients (21.5%) in the endoscopic group ($P=0.83$; OR, 1.2; 95% CI, 0.5-2.7). Increased rates of new adrenal insufficiency (11 of 59 patients [18.6%] vs. 4 of 135 patients [3.0%]; $P<0.001$; OR, 7.5; 95% CI, 2.5-22.1) and diabetes insipidus (7 of 79 patients [8.9%] vs. 4 of 166 patients [2.4%]; $P=0.04$; OR, 3.9; 95% CI, 1.2-12.2) were observed in the microscopic cohort compared with the endoscopic cohort. Rates of individual hormone axis recovery were similar between groups ($P<0.30$) for all evaluated pituitary hormone axes. Individual surgeon effects will be presented.

Conclusion: The endoscopic technique was associated with lower rates of new postoperative adrenal insufficiency and diabetes insipidus. We hypothesize that the superior view provided by the endoscopic technique facilitates gland preservation.

345. Decreased Function of Isoprenylcysteine Carboxymethyltransferase Function Results in Increased Sensitivity to Chemoradiation

David Altshuler, MD (Ann Arbor, MI); Vivek Yadav; Maria Ventosa; Padma Kadiyala; Patrick Dunn; Maria Castro; Pedro Lowenstein

Introduction: Oligodendroglioma is an indolent, chemosensitive glioma characterized by 1p/19q co-deletion. This loss of genetic information may be responsible for its unique treatment sensitivity. Our preliminary data suggests a role for the 1p gene, isoprenylcysteine carboxymethyltransferase (ICMT). ICMT is the only enzyme to methylate prenylcysteine substrates and has broad influence on lamin A function in the nucleus. We hypothesized that ICMT may be responsible for the treatment sensitivity of oligodendroglioma.

Methods: An in vivo brain tumor model was established in ICMT knock-down transgenic mice whereby subventricular zone cells of neonates were transfected with oncogenic plasmids and a transposase to generate a tumor, recapitulating de novo glial oncogenesis. A Kaplan-Meier analysis was performed for mice treated with CCNU chemotherapy grouped according to ICMT expression levels from low to high by genotype (hypomorphic, heteromorphic, or wildtype). Procarbazine, carmustine, vincristine (PCV) and radiosensitivity assays were performed in vitro in cells with and without ICMT inhibition. The impact on lamin A function was characterized by immunofluorescence.

Results: There was a significant difference in the median survival of CCNU-treated transgenic mice by ICMT genotype. Hypomorphic mice had the longest median survival (91 ± 29 days, $n=9$) compared to heteromorphs (78 ± 19 , $n=14$) and wildtype (72 ± 44 , $n=16$). In vitro, cells with ICMT inhibited demonstrated increased sensitivity to PCV and radiation. Lamin A immunofluorescence revealed disrupted nuclear membranes in ICMT-inhibited cells, suggesting potential increased sensitivity to DNA damaging agents.

Conclusion: The 1p/19q co-deletion that is a characteristic of oligodendroglioma may be related to its unique treatment sensitivity. Preliminary in vivo and in vitro data implicate ICMT as a gene on chromosome 1p that may play an important role. Further characterization of the involved molecular mechanisms may lead to novel therapeutic strategies that exploit associated vulnerabilities in oligodendroglioma and other glial neoplasms.

346 Immune Monitoring with CyTOF in Peptide Vaccine Therapy for Low-Grade Glioma

Maryam Shahin (Dayton, OH); Neil Almeida, BA; Diego Carrera, MD; Erin Simonds, PhD; Payal Watchmaker, PhD; Hideho Okada, MD, PhD

Low-grade gliomas are slow-growing primary brain tumors with potential to recur or progress to higher-grade tumors with a phenotype resistant to chemoradiation. Immunotherapy in the form of peptide vaccines poses a unique advantage, with the goal of eliciting an antigen-specific T cell response which could overcome current challenges in treating low-grade glioma. Currently, there is an ongoing clinical trial at UCSF (NCT02924038) which aims to use a cocktail of 11 glioma-associated peptides (IMA950 Vaccine Peptide) in patients with low-grade glioma. To assess anti-tumor response in low-grade glioma bearing patients undergoing peptide vaccine clinical trials, we aimed to develop an immune monitoring platform for high dimensional cellular analysis using mass cytometry (CyTOF). Peptide-MHC tetramers are tagged with heavy metal labels and used in combination with 30 different antibody markers to allow detailed phenotypic analysis of peptide-reactive T cells. After optimization of our protocol for tetramerization of biotinylated peptide-MHC monomers to avidin-fluorophore, we validated our protocol by comparing the NIH H3.3K27M tetramer and our H3.3K27M tetramer tested against cells transduced to express the H3.3K27M T cell receptor (Jurkat76CD8+siTCR+). Post validation, we stimulated human leukocyte antigen (HLA)-A2+ healthy donor derived PBMCs with two IMA950 peptides (FABP7 and BCAN) in vitro. Using the appropriate tetramer, we successfully identified FABP7 and BCAN reactive T cells and tetramerized our H3.3K27M peptide-MHC monomers to metals for utilization in a CyTOF platform. We developed a tetramer protocol which can identify specific T cell reactive populations that may be found in patients undergoing IMA950 Vaccine Peptide therapy and conjugated tetramers to metals for CyTOF. Next, we plan to tetramerize IMA950 Vaccine Peptide-MHC monomers to metals for utilization in a CyTOF platform to enable immune monitoring in patients. Furthermore, we aim to isolate peptide reactive T cell populations that stain with appropriate tetramer and sequence the T cell receptor.

347. Development and validation of an individualized predictor of meningioma recurrence

Farshad Nassiri, MD (Toronto, Ontario, Canada); Yasin Mamatjan; Suganth Suppiah; Jetan Badhiwala; Olli Saarela; Laila Poisson; Houtan Noushmehr; Felix Sahm; Andreas von Deimling; Kenneth Aldape; Gelareh Zadeh

Introduction: Difficulties in predicting recurrence risk for individual patients with meningioma using current classification systems limits appropriate selection of patients who may benefit from adjuvant therapy to delay recurrence. Recent data suggests the utility of DNA methylation as a clinically-relevant biomarker. We aimed to develop and validate a combined molecular and clinical predictor of recurrence for individual patients with meningiomas.

Methods: In this multi-centre study, DNA methylation profiles from 486 meningioma tumors were used to develop and validate a predictor of 5-year recurrence-free-survival (RFS). Cox modelling was used to select features for model generation in a training cohort (N=228 patients) which was then applied to three independent validation cohorts (N=54; N=140; N=64 patients). Penalized-Cox modeling was used to generate a 5-year meningioma recurrence score based on a nomogram that integrated the methylome-based predictor with prognostic clinical factors.

Results: The methylome-based predictor of 5-year RFS performed favourably compared to a grade-based predictor when tested using the three validation cohorts ($\Delta\text{AUC} = 0.10$, 95%CI 0.03 – 0.018) and was independently associated with RFS after adjusting for tumour grade, extent of resection and burden of copy number alterations (EOR; HR 3.6, 95%CI 1.8 – 7.2, $P < 0.001$). A nomogram combining the methylome-predictor with clinical factors demonstrated greater accuracy than a nomogram using clinical factors alone in two independent validation cohorts ($\Delta\text{AUC} = 0.20$ and $\Delta\text{AUC} = 0.22\%$) with an overall accuracy of approximately 87% and resulted in two different risk groups with distinct recurrence patterns (HR 7.7, 95%CI 5.3 – 11.1, $P < 0.001$) and clinical implications.

Conclusion: The tools developed and validated in this study provide important prognostic information not captured by previously established clinical and molecular factors that could be used to individualize decisions regarding the need for adjuvant radiation therapy versus observation alone in patients with meningiomas.

348. Tumor-Specific Super-Enhancers Span Multiple Novel Therapeutic Targets in Meningioma

Bradley King (La Jolla, CA); Briana Prager; Harish Vasudevan, MD, PhD; Derrick Lee; David Raleigh, MD, PhD; Jeremy Rich, MD

Introduction: Treatment of meningiomas, the most common primary brain tumor, is confounded by genetic heterogeneity and difficulty in targeting known tumorigenic drivers. At present, no effective medical therapies exist for atypical or malignant meningiomas. The present work better characterizes the super-enhancer landscape in high-grade and recurrent meningiomas to identify critical regulators of cellular function and unmask new therapeutic targets.

Methods: H3K27Ac ChIP-seq was performed on 33 primary meningioma samples and three early-passage arachnoid granulation cell lines to identify enhancers. Tumor-specific super-enhancers were identified by subtracting super-enhancers present in normal tissue. In vitro studies utilizing CRISPR knockouts or pharmacologic inhibition of pathways of interest were performed to determine whether identified targets influence meningioma cell viability.

Results: Analysis of the enhancer landscape identified 1490 super-enhancers, 1104 of which were tumor-specific, and clustering revealed grade-specific subgroups. Disrupting selected pathways impaired cell survival across a panel of five meningioma cell lines to a significantly greater degree than in arachnoid granulation cells. Small-molecule inhibition of the most sensitive gene product yielded a 10-fold more potent response in meningioma, resulting in 90% cell death at 1 μM concentration.

Conclusion: Characterization of the enhancer landscape revealed novel therapeutic targets in meningioma. Our in vitro results warrant further investigation to assess the efficacy of targeted treatment on inhibiting tumor growth and progression in animal models.

349. Cost-effectiveness of Endoscopic versus Microscopic Transsphenoidal Surgery for Pituitary Adenomas

Ankush Chandra (San Francisco, CA); Harsh Wadhwa, BS; Jonathan Rick, BS; Ishan Kanungo, BS; Ivan El-Sayed, MD; Lewis Blevins, MD; Manish Aghi, MD, PhD

Introduction: Transsphenoidal surgery is the gold standard for treating most pituitary tumors and can be performed using microscopic (MTS) or endoscopic (ETS) approaches. We compared the economic burden and cost-effectiveness of the two approaches.

Methods: Retrospective review of patients with pituitary adenomas (2007-2013) undergoing surgical resection at our institution and corresponding in-patient hospital cost.

Results: Of 192 patients (median age=47.2; females=54.2%), ninety (46.8%) underwent ETS while 102 (53.2%) underwent MTS. All ETS were done with OHNS assistance while MTS were done solely by neurosurgeons. Temporal trends revealed a gradual increase in the number of endoscopic surgeries, with 4.43 more cases every year ($R^2=0.88$, $p=0.002$), while there was a gradual decline in the number of microscopic surgeries by 1.2 cases per year ($R^2=0.35$, $p=0.032$). Tumor characteristics were similar between both cohorts. The endoscopic cohort had lower total in-patient hospital costs compared to the microscopic cohort (\$26,805 versus \$37,371, $p=0.001$). Categorical analysis revealed that ETS patients had lower room/board (\$7,328.48 versus \$9,866.27, $p=0.01$) and operative costs (\$7,035.27 versus \$9,129.61, $p=0.02$) than MTS patients, while cost associated with labs, imaging, in-hospital pharmacy, pathology or any inpatient treatments were similar in both groups. Postoperatively, the endoscopic cohort had shorter hospital stays versus microscopic patients (2.1 days versus 2.8 days; $p=0.02$). Progression-free survival (4.6 years vs 4.1 years, $p=0.04$) and QALY scores (3.7 vs 3.21, $p=0.026$) were significantly better for endoscopic patients than microscopic patients. The incremental cost per QALY was \$21,563 lower for the endoscopic approach.

Conclusion: ETS was associated with lower hospital costs despite involving dual specialty co-surgeries, shorter stay in the hospital, and better QALY scores and progression-free survival. Multi-institutional validation of these findings could offer valuable information to centers considering transitioning to endoscopic approaches and could justify multidisciplinary co-surgeries to insurance payors who may inaccurately perceive these procedures to be costlier.

400. Trepanation of the Outer Table as a Treatment for Scalping Injuries on the American Frontier

Nicholas James Brandmeir, MD (Morgantown, WV); Grant Judy

Introduction: Traumatic scalp injuries that involve a circumferential injury and devascularization/avulsion of the scalp represent complex surgical problems. These cases are often managed at level I trauma centers with a multi-disciplinary team consisting of trauma, plastic, and neurological surgery. The historical example of scalp-taking along the American frontier presented a unique medical challenge where many these complex wounds were treated by surgeons with minimal resources, even for that era. We examine the historical development and propagation of a novel technique for the treatment of these wounds.

Methods: A literature review was conducted on the history of scalping along the American frontier as well as medical treatments available. Primary sources and accounts as well as historical articles were reviewed for descriptions of surgical procedures used to treat scalping injuries.

Results: French surgeon Augustin Bellosté published his technique for trepanation of the outer table in the early post-injury phase in 1696. His method spread to the Netherlands, where it is found in the teachings of Boerhaave. From there it spread to Scottish surgeons, some of whom traveled to America. By the middle and end of the 18th century the technique was applied widely across the frontier from Ft. Pitt to Tennessee.

Conclusion: Trepanation of the outer table is an effective technique for the treatment of circumferential avulsions of the scalp that remains relevant today. It was applied successfully over a wide area of the American frontier until the closing of the frontier in the late 19th century.

401. Spreading Depolarization as a Measure of Cerebral Autoregulation in the Neuro-ICU

Chanju Fritch, BS (Albuquerque, NM); Adarsh Vangala, BS; Fares Qeadan, PhD; Bill Shuttleworth, PhD; Andrew Carlson

Introduction: Recovery from acute neurologic injury (traumatic brain injury (TBI), stroke, and subarachnoid hemorrhage (SAH)) is often complicated by secondary injury, which can significantly influence a patient's outcome. Cerebral autoregulation and its disturbance are known factors for vulnerability to these secondary injuries. Cortical spreading depolarization (SD) is recognized to occur commonly after acute neurologic injury and is likely induced in regions of metabolic instability. We hypothesize that SD may be in regions of impaired autoregulation and may be a surrogate measure for autoregulatory disturbance.

Methods: Adult patients undergoing clinically indicated triggered craniotomy were prospectively enrolled in an observational study of factors affecting SD. A subdural electrode was placed at the time of surgery and monitored for SD. MAP and CBF data were collected in a time locked multiparametric monitoring system (Moberg CNS). Physiology data was gathered in 1m intervals, filtered for spurious values, and re-binned into 20 min sections. Probability of SD was plotted versus falling MAP. Loss of autoregulation (defined as correlation of CBF and MAP > 0.7) was then also tested for association with SD.

Results: A total of 31 patients were enrolled. Per 1mmHg of MAP increase, SD occurrence probability changed by 0.955 (95%CI=.944-.966) with a $p<.0001$. Dichotomized odds of SD for MAP less than 90mmHg demonstrated OR of 2.717 (95%CI 1.979-3.730) compared to MAP values above 90. Furthermore, the odds of SD were significantly increased with

loss of autoregulation (OR=2.238, 95%CI=1.044-4.800).

Conclusion: These data confirm that risk of SD increases with lower MAP, with a strong inflection point around 90mmHg. Significant association of SD with loss of autoregulation suggests that SD may reflect autoregulatory instability, either globally, or focally in regions that would not be detected by standard global measures such as PRx. These results have potential implications in monitoring and prevention of secondary brain injury.

402. Evidence of CNS Response to Pembrolizumab for Leptomeningeal Carcinomatosis at a Single Cell Resolution

Journal of Neuro-Oncology Award

Christopher Alvarez-Breckenridge, MD (Boston, MA); Christopher Alvarez-Breckenridge; Sanjay Prakadan; Anita Giobbie-Hurder; Donald Lawrence; Kevin Oh; Elizabeth Gerstner; Daniel Cahill; Alex Shalek; Scott Carter; Ryan Sullivan; Priscilla Brastianos

Introduction: Approximately 8% of patients with cancer develop leptomeningeal carcinomatosis (LMD). LMD is associated with approximately 4 week median survival and limited treatment options. We performed single cell RNA sequencing of CSF from longitudinally collected patients enrolled in a phase II study of the PD-1 inhibitor pembrolizumab in LMD (NCT02886585) in order to identify cellular states and genetic programs associated with response to immune checkpoint blockade.

Methods: The primary endpoint is the rate of overall survival at 3 months (OS3). A Simon two-stage design was used to compare a null hypothesis OS3 of 18% against an alternative of 43%. Serial CSF, blood samples and tumor samples were collected to elucidate the genomic and transcriptional determinants of response to immunotherapy in CNS lesions.

Results: Eighteen patients were accrued and the median follow-up of patients still alive was 6.8 months (range: 2.2 to 7.6 months). At the time of data retrieval, 11 patients (61%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing of tissue samples and cell-free DNA from CSF and blood, as well as single-cell RNA sequencing of CSF, were carried out to decipher tumor evolution, track immune cell recruitment, and identify biomarkers of response. Analysis of 7877 tumor and immune cells across 6 patients demonstrated patient-specific tumor clustering and evidence of T cell and antigen presenting cells recruited to the CSF following pembrolizumab treatment. Genetic and transcriptomic differences of tumor and immune cells within the CSF were detected longitudinally during therapy and in patients that reached OS3 compared with those that did not.

Conclusion: Pembrolizumab has activity in LMD and single cell sequencing of CSF provides a window in which to monitor the evolution of the tumor and immune microenvironment in response to immune checkpoint blockade.

403. Sensory nerve action potential recordings in low frequency focused ultrasound modulation of common peroneal nerve injury in vivo

Julie G. Pilitsis, MD, PhD, FAANS (Albany, NY); Abigail Hellman, BA; Teresa Maietta, BS; Julia Nalwalk, MS; Paul Neubauer, BSE; Harini Byraju; Damian Shin, PhD; Emery Williams, PhD; Clif Burdette, PhD

Neuromodulation is typically electrical; we examine an alternative, pulsed low-intensity focused ultrasound(FUS). Effects of FUS modulation on peripheral nerves have been shown in situ, yet no similar work has been performed in vivo.

Previously we showed increased mechanical thresholds 5 days post FUS treatment without histological damage. Here we measure the downstream effects of dorsal root ganglia(DRG)FUS. We induced common peroneal nerve injuries(CPNI) in male Sprague-Dawley rats(200-300g). After one week, we utilized Von Frey Fibers(VFF) to confirm allodynia. External ring electrodes were placed around the knee cap and the base of the ankle with electrode gel as recording and reference electrodes. An invasive stimulating electrode was placed in muscle adjacent to the sciatic nerve. 8W of pulsed FUS was delivered for 3min at a frequency of 38 Hz and pulse width of 90µs. Sensory nerve action potentials(SNAPs) were recorded at baseline and every 5min for 60min after FUS. SNAPs were obtained with a data acquisition system coupled to a noise suppressor and digitized at 1KHz through a low pass filter to 100Hz. Latency and amplitude were calculated. Animals had allodynia following CPNI measured through VFF. VFF normalized 24 hours after FUS ($p<0.001$; $n=7$). FUS resulted in significantly increased latencies in the sciatic nerve immediately after FUS.

Latencies remained significantly increased for 25min, ($p=0.01$; $n=7$). They returned to baseline at 50min. No changes in amplitude were noted. We are the first to demonstrate the effects of pulsed FUS of the DRG on peripheral nerves in vivo. Prior work is limited to in situ findings that show FUS temporarily blocks tissue it targets. Downstream and upstream effects have not been documented. We present an iterative step in bringing pulsed FUS to the clinic for treatment of chronic pain.

404. Optimal Spinal Cord Stimulation Parameter Settings to Restore Volitional Movement after Motor-complete Spinal Cord Injury

David Darrow, MD (Minneapolis, MN); David Balser, MD; Ann Parr, MD, PhD; Uzma Samadani, MD, PhD; Aaron Phillips; Andrei Krassioukov, MD, PhD; Andy Lamperski, PhD; Theoden Netoff, PhD

Introduction: Spinal cord stimulation has now been shown to restore some volitional movement and autonomic function in patients with motor-complete spinal cord injury, but little has been done to evaluate the millions of possible frequency, pulse width, and amplitude parameter settings. The E-STAND trial was designed to efficiently and systematically evaluate the parameter space for optimal restoration of volitional movement and autonomic function through novel, remotely-collected quantitative and qualitative assessments.

Methods: Seven patients have been enrolled in the E-STAND trial and undergone implantation of SCS to restore volitional movement after motor-complete SCI. Ages range from 28 to 60 and time since injury ranges from 2 years to 15 years. Remotely-collected daily survey and daily task data was modeled monthly using a probit response function over frequency and pulse width. Bayesian optimization was performed to find the most important settings each month.

Results: All patients had restoration of some volitional movement. Probit response surfaces demonstrate that some variability exists across the most optimal settings for restoration of volitional movement with peaks ranging from 24 Hz to 40 Hz while pulse width preference ranges from 350 to 450 us. When compared to the evaluated parameter space, there is significant overall preference for frequencies between 30 and 40 Hz ($p < 1e10$) compared with higher settings. Colinear results were found for optimal settings for restoration of posture but not restoration of autonomic function.

Conclusion: Using a novel probit response surface and Bayesian optimization for setting selection, the optimal ranges for SCS parameters is actually quite narrow (30Hz, 350 to 450 us), though individual preferences vary slightly. This significant finding will enable further research into the effect of SCS on restoration of volitional movement and aid computational modeling efforts to optimize electrode configuration.

405. New Care Pathway to Decrease the Length of Stay and Costs of Single Level Lumbar Fusion

[Robert Florin Award](#)

Samer Zammar, MD (Hershey, PA); Brian Anderson; George Reiter, MD; Abraham Schlauderaff, MD

Introduction: Single level lumbar fusion is a procedure associated with relatively narrow set of indications. It requires multiple surgical steps and exploits the use of implanted hardware. The patient usually requires an inpatient stay and utilizes multiple hospital services including radiology, physical therapy and rehabilitation medicine. The authors implemented a new perioperative pathway for these patients in an attempt to decrease the length of stay (LOS) of patients undergoing single level lumbar fusion.

Methods: Data collected from Time-Driven Activity-Based Costing was used to develop a multidisciplinary perioperative pathway with an aim to optimize the stay for our single level spinal fusion patients. The pathway involved changes in the consent process, the review of usual hospital course, and setting patients expectation in the pre-op visit. On an inpatient level, the process engaged the surgery, immediate post-op care, pain medications, and rehabilitation evaluation. Finally, the pathway involved the outpatient therapy and rehab stay in the postoperative setting. The authors compared patient populations before and after the implementation of this new protocol. The primary outcome was the LOS and the secondary outcome was the cost changes.

Results: The average LOS of patients decreased significantly from 4.1 days to 3.2 days and there was an average of \$1,271 cost savings per case after the care pathway was implemented. The total reduced cost from the new LOS was \$121K. The new contribution margin from additional capacity was \$728K. This resulted in an overall cost reduction to \$849K. **Conclusion:** The new implemented multidisciplinary perioperative pathway significantly decreased the LOS and the total costs for patients with single level lumbar fusion without affecting the quality of care. This new pathway merits the discussion in other surgical indications due to its potential beneficial effects to the patient and the hospital.

406. Visual improvement after carotid endarterectomy is associated with the increased chorioretinal blood flow confirmed by laser speckled flowgraphy

Shinsuke Yoshida (Kawagoe, Japan); Soichi Oya; Masamichi Endo; Tsukasa Tsuchiya; Takumi Nakamura; Masahiro Indo; Masaaki Shojima; Toru Matsui

Introduction: It is well known that cervical internal carotid artery (cICA) stenosis can cause ipsilateral amaurosis fugax. Apart from this acute clinical problem, however, the visual impairment of chronic retinal ischemia due to cICA stenosis remains to be elucidated. In this study, we investigated whether the increased chorioretinal blood flow (CRBF) renders the improvement chronic visual deficit improves after carotid endarterectomy (CEA).

Methods: We prospectively enrolled patients who underwent CEA from 2015 to 2018. We measured the CRBF by laser speckled flowgraphy (LSFG) before and after CEA, and analyzed the relationship of the increase of CRBF and postoperative visual recovery. Visual recovery was assessed by subjective improvement and quantitative visual acuity measurement using CSV1000 (Vector Vision). The CRBF approximated by Mean Blur Ratio (MBR) was calculated in the papillary vascular and tissue area by LSFG.

Results: The MBR measured in 41 consecutive patients who had CEA. The ipsilateral MBR were 33.5 ± 8.0 in the vascular area and 10.3 ± 2.2 in the tissue area before surgery, significantly increased to 38.2 ± 9.4 and 11.5 ± 3.4 after surgery ($p=0.0005$, $p=0.002$). As for visual function, the ipsilateral additional value of CSV1000 was 15.3 ± 7.0 , and significantly improved to 18.2 ± 6.7 ($p=0.006$). 23 patients (56.1%) reported subjective visual improvement, which was more frequently observed in patients with the improvement of CRBF ($p=0.009$). Increased CRBF of affected papillary tissue area after CEA was significantly associated with visual acuity improvement measured by CSV-1000 ($p=0.018$).

Conclusion: CEA for cICA stenosis increases the CRBF. Postoperative subjective and objective visual improvement was significantly associated with the increase of CRBF. Based on our results, CEA might contribute to restoring the chronic visual deficit in patients with cICA stenosis that cannot otherwise be explained by ophthalmological diseases.

407. Gender-Pay Equity in Academic Neurosurgery at United States Public Universities

Kathryn Kearns (Charlottesville, VA); Ching-Jen Chen, MD; M. Yashar Kalani, MD, PhD; Mark Shaffrey, MD; Min Park, MD

Introduction: We investigated any potential association between gender and salary and identified factors associated with salary, among academic neurosurgeons in public institutions across the US.

Methods: This is a cross-sectional study of publicly-available data for the 2016-17 fiscal years of institutions from the AANS Neurosurgical Residency Training Program Directory. Neurosurgical faculty from public, academic institutions within the US with publicly available data in accordance with the Freedom of Information Act were included. The reported total annual salary (US dollars [US\$]) was used in the analysis. Differences in demographics, training, and appointments were compared between male and female neurosurgeons. Predictors of salary were identified using univariable and non-imputed and multiply-imputed multivariable models.

Results: 460 faculty members were examined (female $n=34$; male $n=426$). Total annual salaries were comparable between male and female neurosurgeons. Female neurosurgeons were more likely to be younger ($p=0.001$), to have had completed training recently ($p=0.003$), to have had fellowship training ($p=0.011$), and to have lower h-indices ($p=0.003$) compared to male neurosurgeons. Male and female neurosurgeons differed in academic ranks ($p=0.035$) and specialties ($p=0.038$). Practice in the Midwest ($\alpha\beta=-US\$337,516.7$, $p=0.002$), South ($\alpha\beta=-US\$302,500.5$, $p=0.003$), and West ($\alpha\beta=-US\$276,848.8$, $p=0.005$) were independent predictors of lower total annual salary in reference to practice in the East. Chair position ($\alpha\beta=US\$174,180.3$, $p=0.019$) and associate professor rank ($\alpha\beta=US\$126,633.4$, $p=0.037$) in reference to assistant professor rank were independent predictors of higher total annual salary. Gender was not a significant predictor of total annual salary.

Conclusion: Total annual salaries were not different between male and female neurosurgeons in public, academic institutions in the US. Furthermore, gender was not a significant predictor of total annual salary. This study is applicable only to public institutions with Freedom of Information Act reporting requirements. These results may serve as encouragement to women who aspire to pursue a career in academic neurosurgery.

408. Liquid Biopsy for Detection of Histone H3 Mutations in Pediatric Diffuse Midline Gliomas

Columbia Softball Pediatric Award

Amanda Muhs Saratsis, MD (Chicago, IL); Erin Bonner, BS; Eshini Panditharatna, PhD; Daphne Li, MD; Julia Pantalone, BA; Tina Huang, MS; Rishi Lulla; Carl Koschmann, MD; Javad Nazarian, PhD; Amanda Saratsis, MD

Introduction: Pediatric diffuse midline glioma (DMG) is a highly morbid tumor not amenable to surgical resection.

Mutations in histone H3 encoding genes occur in 80% of cases, and portend a worse clinical prognosis. We previously detected H3 mutations in circulating tumor DNA (ctDNA) in CSF derived from children with DMG and high grade glioma. Here, we describe a more sensitive and specific approach for H3 mutation detection and quantification in plasma and CSF with low starting [ctDNA], with validation performed across multiple centers.

Methods: Plasma (n= 7) and CSF (n=4) specimens were collected at diagnosis and submitted for ddPCR. H3 mutation status was assessed by calculating mutation allelic frequency (MAF, mutant/mutant + wild type droplet counts). To validate our approach, CSF from patients who received tumor biopsies (n=8) and one healthy control was also analyzed, with H3 mutation status determined via tissue sequencing (H3K27M n=5, H3WT n=4). Isolated ctDNA was pre-amplified using sequence-specific primers, then analyzed using RainDance and BioRad ddPCR workflows with custom primers and fluorescent LNA probes. Primers and probes were validated using DNA from H3K27M mutant and wild-type pediatric glioma cell lines.

Results: Thermal gradient analysis identified optimal annealing temperatures of 50.7°C-52.1°C for H3 K27M mutant and H3 WT probes, and 58°C for primers. 83.5 copies of H3.3K27M DNA/uL was detected with 1.0 ng loaded DNA, and 7.66 copies of H3.3K27M DNA/uL for 0.01 ng loaded DNA derived from mutant glioma cell lines. H3.3K27M mutations were robustly detected using ctDNA isolated from as little as 1 mL plasma or 500µL CSF.

Conclusions: We demonstrate the utility of liquid biopsy for identifying H3K27M mutations in plasma and CSF with low starting [DNA], representing a rapid, minimally invasive method for diagnosis and therapeutic monitoring of pediatric brain tumors. ddPCR of additional pediatric glioma liquid biopsy specimens is currently underway.

409. Utility of a Near-Infrared Light Device (NIRD) in Detecting Subdural (SDH) and Epidural (EDH) Hematomas: An Effectiveness Trial Toward Using a NIRD for Neurosurgical Triaging in Low and Middle-Income Countries (LMICs):

Young Neurosurgeons Medical Student Abstract Award

Robert M. Gramer (Toronto, Canada); Anthony Fuller; Lexie Yang, PhD; Donna Niedzwiecki, PhD; Carmelo Graffagnino, MD; Beth Perry, BS; Michael Haglund, MD, PhD

Introduction. The World Health Organization estimates that more than 10 million people sustain traumatic brain injury (TBI) resulting in death or significant irreversible deficits annually, the majority occurring in low and middle-income countries (LMICs). When subdural (SDH) and/or epidural (EDH) hematomas occur, the limited availability of computer tomography (CT) in these TBI-laden areas frequently impedes life-saving neurosurgical decompression. As neurosurgical infrastructure in LMICs continues to expand, a reliable, accessible, cost-effective solution to detect and localize such bleeds is imperative.

Methods. 500 consecutive patients presenting to Duke University Hospital Emergency Department with confirmed or suspected head trauma who received a head CT scan were included in this study. Within thirty-minutes of the initial head CT scan, an examiner, blinded to the result, scanned each patient's cranium with a near-infrared device (NIRD), interrogating frontal, temporal, parietal, and occipital quadrants bilaterally. A difference in optical density $>|.20|$ was considered a positive result, indicative of an intracranial bleed. For all NIRD-positive patients who underwent subsequent CT scans, serial NIRD measurements were collected. **Results:** 104 patients had an intracranial bleed(s). For all patients with CT-proven bleeds, irrespective of size, initial NIRD scans localized the bleed to the appropriate quadrant with a sensitivity of 86% and specificity of 96% compared to CT scan. For extra-axial bleeds $>3.5\text{ml}$, sensitivity and specificity were 94% and 96%, respectively. For longitudinal serial rescans with the NIRD, sensitivity was 89% (<4 days from injury: sensitivity=99%) and specificity was 96%.

Conclusion: These data demonstrate that a NIRD is both highly sensitive and specific in diagnosing intracranial bleeds. For all patients who required craniectomy or craniotomy, the device demonstrated 100% sensitivity. With these results, we intend to initiate a feasibility trial in Uganda using a NIRD to diagnose SDH/EDH and inform neurosurgical care where our group, DGNN, is working to build neurosurgical capacity.

410. Germline mutations in sporadic brain arteriovenous malformations*Hao Li; (beijing, China)*

Introduction: Brain arteriovenous malformations (AVMs) are defined as an abnormal tangle of blood vessels located in the brain with an annual risk of intracranial hemorrhage of 2%–4%. The underlying genetic causes of sporadic brain AVMs are still not clear. This study was to identify de novo germline mutation in sporadic brain AVM.

Methods: We have enrolled a total of 22 patients diagnosed with sporadic brain AVMs and their phenotypically normal parents. Then we extracted DNA from their peripheral blood and performed whole-exome sequencing (WES) of the 22 trios. De novo germline variants-calling and annotation were proceeded by SAVI software.

Results: We identified two de novo germline heterozygous variants in two patients, including ENG c.360+1G>A and EXPH5 c.3331A>T. The ENG c.360+1G>A has been established as a pathogenic variant related with hereditary hemorrhagic telangiectasia (HHT) and c.3331A>T is a stop-gained variant which is highly devastating to the gene function.

Conclusion: Our study highlights ENG and EXPH5 germline mutations might be the genetic causes for sporadic brain AVMs which needs further investigation.

411. Cortical Vein Opacification for Risk Stratification in Anterior Circulation Endovascular Thrombectomy*Haydn Hoffman, MD (Syracuse, NY); Robert Ziechmann, MD; Grahame Gould, MD*

Introduction: Endovascular thrombectomy (EVT) is standard of care for acute ischemic stroke due to anterior circulation large vessel occlusion (ACLVO). There is continued interest in identifying factors that predict a favorable outcome after EVT, especially ones that are available to smaller hospitals with fewer resources. We sought to compare the predictive values of two different scoring systems for evaluating venous collateral circulation.

Methods: A retrospective review of all patients who underwent EVT for ACLVO at a single institution over the past 10 years was performed. Those who underwent pre-procedural computed tomography angiography (CTA) were selected. The Cortical Vein Opacification Score (COVES) and Prognostic Evaluation Based on Cortical Vein Score Difference in Stroke (PRECISE) score were calculated from each patient's CTA. Our primary outcome of interest was the Modified Rankin Scale (mRS) score at 90 days.

Results: A total of 109 patients were included in the study. The average age was 67.9 years and the median NIHSS on presentation was 15. The mean time to reperfusion was 6.3 hours and TICI 2B or 3 reperfusion was achieved in 76.1% of cases. A favorable COVES score was significantly associated with a favorable (mRS 0 – 2) outcome (OR: 4.39; 95% CI 1.82 – 10.58), while a favorable PRECISE score was not (OR: 1.54; 95% CI 0.65 – 3.66). Based on the Receiver Operating Characteristic (ROC) analysis, the COVES score had a sensitivity of 72.4%, specificity of 68.6%, and AUC of 0.778. The PRECISE score had a sensitivity of 70.7%, specificity of 64.7%, and AUC of 0.718.

Conclusion: Adequate cortical venous collateral circulation, as defined by a favorable COVES score, is associated with favorable neurologic outcomes at 90 days. Based on our cohort, this measure has greater sensitivity and specificity for predicting outcome than the PRECISE score.

412. Time course of metabolomics in cerebrospinal fluid after aneurysmal subarachnoid hemorrhage*Ondra Petr, M.D. (Innsbruck, Austria); Wingi Ho, MD; Alice Görke, MD; Herbert Oberacher, PhD; Christian Freyschlag, MD; Claudia Unterhofer, MD; Claudius Thome, MD*

Introduction: The aim of this study is the investigation of metabolite levels in cerebrospinal fluid (CSF) in their time-dependent course after aneurysmal subarachnoid hemorrhage (aSAH) and their comparison with CSF of patients harboring unruptured intracranial aneurysms.

Methods: Eighty CSF samples of 16 patients have been analyzed. The study population included patients undergoing endovascular/microsurgical treatment of ruptured intracranial aneurysm (n=8) which were investigated for 10 days after aSAH. Control samples were collected during elective aneurysm surgery (n=8). The CSF samples were consecutively collected with EVD placement/intraoperatively, 6 hours later, and daily thereafter (day 1-10). The endogenous metabolites were analyzed with a targeted quantitative and quality controlled metabolomics approach using the AbsoluteIDQ® p180 Kit.

Results: Numerous alterations of amino acid (AA) levels were detected within the first hours after bleeding. The highest mean concentrations occurred one week after aSAH. AA levels were continuously increasing over time starting 6 hours after aSAH. Taurine concentration was highest briefly after aSAH starting to decrease already 6 hours postoperatively.

The levels of sphingomyelins/phosphatidylcholines/lysophosphatidylcholines/fatty acids were highly elevated on day 0 and decreased over the next several days to concentrations comparable to the control group. Carnitine concentrations were decreased after SAH, while they recovered within the next day. The Fischer ratio was lowest right after SAH and recovered within 7 days.

Conclusion: AA demonstrated increased CSF levels overtime and often differed from patients without SAH. There was a peak concentration of structural AA within the first 6 hours after aneurysm treatment. Time-dependent alterations of CSF metabolites and compounds may elucidate pathophysiological processes after aSAH providing biomarkers evaluable in laboratory routine without additional invasive methods.

413. Microsurgical Treatment of Intracranial Aneurysms after Failure of Flow Diversion: A Multicenter Case Series and Review

Rabih G. Tawk, MD, FAANS (Jacksonville, FL); Nnenna Mbabuikwe, MD; Justin Mascitelli, MD; Adib Abila, MD; Edward Duckworth, MD; Peter Kan, MD; Mohamed Muneer, MD; Clemens Schirmer, MD; Fady Charbel, MD; Michael Lawton, MD; Evandro de Olivera; Rabih Tawk, MD

Introduction: Flow diversion has become increasingly popular for treatment of cerebral aneurysms over the last few years. There have been an increasing number of patients with aneurysms who failed flow diversion with a paucity of literature on salvage microsurgical treatment of these challenging cases. This review focuses on the microsurgical treatment of intracranial aneurysms in the event of failure of flow diversion.

Methods: A retrospective review of databases at 7 tertiary care centers was conducted from January 2011 to June 2018. Eleven cases with intracranial aneurysms that failed treatment with flow diversion and required microsurgical bailout treatment were identified and included in this analysis. We also conducted a literature review on this topic over the same period of time.

Results: The series included 11 patients (7 women and 4 men) with a mean age of 55 years. The rationale for surgery was aneurysm rupture 1/11, mass effect from the aneurysm 4/11, or persistent aneurysm filling 6/11. Nine aneurysms were located on the anterior circulation, and 2 were located on the posterior circulation (1 fusiform vertebrobasilar aneurysm and 1 giant basilar trunk aneurysm). Time of rescue surgery ranged from 6 weeks to 3 years. Patients were treated with microsurgical clipping of the aneurysm in 5/11 (one with STA-MCA bypass), aneurysm trapping in 3/11, decompression of aneurysm fundus for relief of mass effect from the aneurysm on adjacent structures in 2/11, and proximal ligation of the ICA with double barrel STA-MCA bypass in 1/11.

Conclusions: Aneurysms that fail flow diversion present a variety of unique and challenging management situations and they will likely be encountered with increased frequency given the popularity of flow diversion. Microsurgical bailout options require an individualized care that is tailored to the underlying pathology, patient characteristics, and surgical expertise.

414. An endovascular assisted non-occlusive cerebral bypass - a technical feasibility study in a rabbit model.

Alexander Spiessberger (Zurich, Switzerland); Fabio Strange; Basil Grueter; Stefan Wanderer; Michael Diepers; Luca Remonda; Javier Fandino; Javier Anon; Serge Marbacher

Introduction: Temporary parent vessel occlusion to establish a high flow interpositional bypass carries the risk of infarcts. Therefore we investigated the feasibility of a novel technique to establish a high-flow bypass without temporary parent vessel occlusion to lower the risk of ischemic complications. A novel endovascular device was developed and utilized to allow for a dry arteriotomy while the central blood flow in the parent vessel is maintained, potentially reducing the risk of ischemic complications.

Methods: In ten New Zealand white rabbits, a carotid artery side to end anastomosis was performed under partial parent vessel occlusion with a novel endovascular balloon device. Intraoperative angiography, postoperative neurologic assessments and postoperative MRI/MRA were performed to evaluate the feasibility and safety of the novel technique.

Results: A patent anastomosis was established in 10 of 10 animals; three procedure-related complications occurred. No postoperative focal neurologic deficits were observed. MRI/MRA findings include no infarcts: bypass patency in 50% of animals.

Conclusion: We demonstrated the feasibility of an endovascular, assisted non-occlusive high flow bypass. Future refinement of the device and technique in an animal model is necessary to lower complication rate and increase patency rates.

415. Lymphopenia and Bone Marrow T-cell Sequestration Accompanying Stroke are Mediated by T-cell S1P1 Loss

Cosette DeChant (Durham, NC); Pakawat Chongsathidkiet, MD; Daniel Wilkinson, PhD; Haichen Wang, MD; Hanna Kemeny; Jessica Waibl Polania; Xiuyu Cui; Daniel Laskowitz, MD; Peter Fecci, MD, PhD (Durham, NC)

Introduction: Sequestration of T-cells in bone marrow is a phenomenon recently characterized by our group in the setting of intracranial tumors, regardless of histology. It is accompanied by lymphopenia and lymphoid organ regression and is mediated by loss of S1P1 receptor from the T-cell surface. We now reveal that this phenomenon is not unique to tumors, but accompanies additional intracranial pathologies, most notably stroke.

Methods: Blood, bone marrow, and spleens were collected from mice at day 2, 5, 7 or 14 following stroke via MCA occlusion or sham surgery and analyzed by flow cytometry. T-cell S1P1 levels were assessed, as were T-cell counts in each compartment. S1P1 receptor stabilization was achieved with a knock-in model in which receptor internalization is inhibited.

Results: Following stroke, T-cells accumulated in the bone marrow of injured mice. T-cell numbers peaked at day 7 post-stroke before returning to normal by day 14. Bone marrow accumulation was accompanied by transient lymphopenia and splenic involution following stroke. T-cells in the bone marrow yielded decreased levels of S1P1 on their surface. Conversely, mice with genetically stabilized T-cell S1P1 prove protected against sequestration, lymphopenia, and splenic regression following stroke.

Conclusion: Bone marrow T-cell sequestration occurs transiently following stroke and is mediated by the S1P-S1P1 axis. This may prove to be an adaptive mechanism to limit intracranial inflammation following an initial insult. Better understanding of this phenomenon may uncover a novel mechanism of immune privilege and allow for therapeutic modulation in the setting of stroke, brain tumor, and other types of intracranial injury.

416. Feasibility of Robotic Assisted Neurovascular Interventions Initial Experience in Flow Model and Pig

Gavin W. Britz, MD (Houston, TX), FAANS; Gavin Britz; Johnny Tomas; Alan Lunsden, MD

Background: Despite advances in robotic-assisted technology for cardiac and peripheral vascular interventions, a robotic-assisted platform for neurovascular intervention is not yet available. Objective: The goal of this preclinical study was to evaluate the feasibility of the CorPath GRX robotic-assisted platform (Corindus Inc., Waltham, MA, USA) for neurovascular interventions.

Methods: The robotic system was tested for its ability to accurately navigate a variety of common neurovascular instruments in an in vitro flow model and in a live, anesthetized pigs, under conditions and following procedures appropriate for clinical intervention. An access catheter was introduced manually at the equivalent of the common carotid artery in both models. Endovascular wires and catheters were navigated through the external and internal carotid artery and posterior cerebral vasculature under robotic assistance using 0.014 in guidewires, 2.4F/1.7F microcatheters, bare-metal stents, and embolic coils. This allowed the surgeon to robotically coil aneurysms in a porcine model and flow model, place stents and perform stent assisted coiling in a porcine model and flow model, embolize AVMS using Onyx and place stent retrievers.

Results: All procedures in both the flow and pig models, including navigation, wiring, and deployment of the stent, and coils, onyx embolization were performed successfully with no technical complications. There was no evidence of extravasation, dissection, thrombosis, or other vascular injury when angiography was compared before and after the live-animal procedure. Videos will be provided demonstrating technical success.

Conclusion: This is the first study in the world to demonstrate that use of a robotic-assisted platform that is feasible for intracranial neurovascular intervention. The robotic system was successful at navigating and deploying the small-gauge instruments specific to neurovascular procedures. Given the potential benefits of robotic-assisted surgery for the patient and the surgeon, further investigation is warranted for this indication.

417. High Throughput Metabolite Profiling Identifies Plasma Taurine as a Biomarker of Functional Outcome After Aneurysmal Subarachnoid Hemorrhage

Christopher James Stapleton, MD (Chicago, IL); Hannah Irvine; Zoe Wolcott; Aman Patel, MD; Jonathan Rosand, MD, MSc; William Kimberly, MD, PhD

Introduction: Metabolites reflect changes associated with disease conditions and metabolite profiling (metabolomics) can identify candidate biomarkers for disease and potentially uncover pathways for intervention.

Methods: We performed high throughput metabolite profiling across a broad spectrum of chemical classes (173 metabolites) on plasma samples taken from 191 patients with aneurysmal subarachnoid hemorrhage (aSAH). Samples were drawn at 3 time points following ictus: 0-5, 6-10, and 11-14 days. Univariate and logistic regression analyses were performed to examine the relation of each metabolite and multiple clinical variables with short- and long-term functional outcomes (modified Rankin Scale, mRS).

Results: A good functional outcome (mRS 0-2) was found in 38.7% and 61.6% of patients at discharge and 90 days, respectively, following aSAH. Age, World Federation of Neurological Surgeons (WFNS) grade, modified Fisher grade, hydrocephalus, and vasospasm were all significantly associated with discharge and 90-day functional outcomes. Plasma concentrations of the amino acid taurine from samples collected between days 0-5 after aSAH were elevated by 120.0% ($P = 0.0005$) and 128.3% ($P < 0.0001$) in patients with good discharge and 90-day functional outcomes, respectively. A similar statistical result was noted with samples collected between days 6-10, but not days 11-14, after aSAH. Logistic regression demonstrated that taurine was a significant predictor of functional outcome at 90 days ($P = 0.0043$; OR 2.9, 95% CI: 1.36%-6.93%), but not at discharge ($P = 0.1225$), even after adjusting for other factors that influence outcome, including age, WFNS grade, modified Fisher grade, hydrocephalus, and vasospasm.

Conclusion: Elevated plasma taurine levels following aSAH predict a good 90-day functional outcome. While experimental evidence in animals suggests this effect may be mediated through down-regulation of pro-inflammatory mediators such as TNF- α , IL-1 β , IL-6, and NF- κ B, additional studies are required to validate this hypothesis in humans.

418. Influence of Clinical Parameters on the Efficacy of Immune Checkpoint Inhibitors in Patients with Non-Small Cell Lung Cancer Brain Metastases (NSCLCBM)

Adam Lauko (Cleveland Heights, OH); Bicky Thapa, MD; Baha'eddin Muhsen, MD; Hamid Borghei-Razavi, MD; Samuel Chao, MD; John Suh, MD; Nathan Pennell, MD; Manmeet Ahluwalia, MD

Introduction: Non-small cell lung cancer brain metastases (NSCLCBM) patients have a dismal prognosis. Advances in immune checkpoint inhibitors (ICI) have changed outcomes dramatically in a subset of patients, although limited information exists on the impact of ICI in patients with NSCLCBM.

Methods: We reviewed 107 NSCLCBM (2012-2018) patients treated at our tertiary care center. Inclusion criteria for analysis was at least 2 cycles of ICI therapy after diagnosis of NSCLCBM and one or greater follow-up MRI. Overall survival (OS) and progression-free survival (PFS) were calculated from the start of ICI therapy to date of death, progression or last follow up. Objective response rate (ORR) was determined using a modified Resist criteria. Kaplan-Meier curves were used to estimate survival and were analyzed using the Wilcoxon test.

Results: Median age at diagnosis of NSCLCBM was 62 years (39-81) and the median KPS was 90. 86 patient received Nivolumab monotherapy, 7 Atezolizumab, 12 Pembrolizumab, and 3 patients received Nivolumab plus one other ICI. 99 patients received SRS ranging from 1-8 treatments. Only 2 patients received ICI alone and 22 patients underwent surgical resection. 19 patients received oral steroids at within the first 28 days of ICI (median prednisone equivalent dose of 27 mg). Patients with upfront steroid use had a median PFS of 127 days vs 290 days in patients without upfront steroids (p -value .015). CBC at the start of ICI was available for 87 patients and neutrophil to lymphocyte ratios (NLR) were calculated. Patients with NLR at the start of ICI above 5 ($n=33$) had an overall survival of 337 days compared to 558 days when NLR was below 5 (p -value .038).

Conclusion: Patients on steroids at the time of initiation or within first 28 days of ICI and NLR of greater than 5 have worse outcomes in NSCLCBM treated with ICI.

419. Immunomodulating Effect of a LiverX Receptor Agonist (LXR-623) and Its Synergistic Effect With Anti-PD-1 Antibodies Against Chordomas in an NSG-SGM3-BLT Humanized Mouse Model

Wataru Ishida, MD (Baltimore, MD); Alexander Perdomo-Pantoja, MD; Betty Tyler, BS; Michael Lim, MD; Timothy Witham, MD; Sheng-fu Lo, MD

Introduction: We previously established a humanized mouse model of chordomas, which allowed us to investigate the interaction between human chordomas and human immune cells in vivo. This model is particularly useful for investigating in vivo efficacy of immunotherapy against rare cancers such as chordomas, where murine equivalents are currently unavailable. We sought to use this model to study synergism between PD-1 blockade and LXR-623, a synthetic agonist of liverX receptors, a class of anti-neoplastic agents disrupting cancer cholesterol metabolism.

Methods: To reconstitute the immune system, 24 NSG-SGM3 mice were engrafted with human fetal thymus and hematopoietic stem cells, whose HLA-types were partially-matched with those of the U-CH1 chordoma cell lines. The animals were divided into the four groups ($n=6$ for each): control (isotype Abs), anti-PD-1 Abs monotherapy

(anti-human-PD-1-Abs (Clone: J116), 10 mg/kg, 3 times/week for 4 weeks, i.p.), LXR-623 monotherapy (isotype Abs + LXR-623 100mg/kg, daily for 4 weeks, i.p), and the combinatorial treatment (anti-human-PD-1 Abs + LXR-623). One week after treatment, each animal was sacrificed for downstream experiments. Anti-tumor activity was monitored via tumor size and flow cytometric analyses of tumor-infiltrating lymphocytes (TILs), using the following Abs: anti-mouse-CD45, anti-human-CD3, anti-human-CD4, anti-human-CD8, anti-human-CD11b, anti-human-CD14, anti-human-CD33, anti-human-CD45, anti-human-PD-1, and anti-human-FoxP3.

Results: The synergistic inhibitory effect of LXR-623 and anti-PD1-Abs against chordomas was observed as evidenced by synergistic tumor volume reduction in the combinatorial group ($p < 0.05$ for each intergroup comparison except between control versus mono-LXR-623). In the TIL analysis, the combinatorial group exhibited highest in human CD8+CD3+ cells and lowest human PD-1+CD8+CD3+ cells and human CD14-CD11b+CD33+ cells.

Conclusion: Our data suggest the synergism between LXR-623 and checkpoint inhibition potentially via reduction in CD14-CD11b+CD33+ (myeloid-derived suppressor cells) in the chordoma microenvironment. We are currently conducting multiplex-cytokine analysis including TGF-beta, IFN-gamma, and IL-2 as well as multiplex-immunohistochemistry (CD3, CD8, CD11b, CD33, PD-L1, Brachyury).

420. Homogenous Aggressive and Indolent Subgroups of Atypical Meningiomas Identified using Oncogenic Signatures

Alexander Landry (Toronto, Canada); Zsolt Zador, MD, PhD; Ashirbani Saha, PhD; Michael Cusimano, MD, PhD

Introduction: Meningiomas are the most common adult brain tumours. Prognostication and clinical management are heavily influenced by histopathological grade, which ranges from more indolent grade 1 to highly aggressive grade 3. Atypical (grade 2) meningiomas are notoriously ambiguous, with a five year recurrence rate of approximately 50%. We sought to subcategorize these tumours into a group with low recurrence and another with high recurrence based on their genetic similarity to grade 1 or 3 tumours.

Methods: We first identified co-expressed gene modules within a cohort of 212 meningiomas from 6 independent cohorts using established techniques. Module expression levels were used to cluster tumours using a two-centroid fuzzy C-means algorithm. Inputs were selected to maximize the average separation between grades 1 and 3 based on a cost function. Hard thresholding (80% probability) of both centroids yielded indolent (grade 1-dominant centroid) and aggressive (grade 3-dominant centroid) atypical subgroups. Available recurrence rates were evaluated with a chi-square test, and overall genetic landscapes were compared by correlating median module expression levels.

Results: Our approach succeeded in reclassifying 33/46 atypical meningiomas as either indolent (14/46) or aggressive (19/46). Recurrence rates were significantly higher in the latter (8/11 vs 0/9, $p < 0.005$). Concordantly, there was no significant difference between recurrence rates of these atypical subgroups and their adjacent grade (1 or 3). Additionally, module expression levels exhibited significant positive correlations between the atypical subgroups and their adjacent grades, but not between each other. Similarly, we show that the genetic separation of grades 1 and 3 is similar to that of atypical subgroups.

Conclusion: In this study, we have reclassified most atypical-grade meningiomas as indolent or aggressive, with concordant recurrence rates and gene expression profiles. These findings support a shift towards a new nomenclature relevant for their clinical management as well as clinical trial design and interpretation.

421. Reliability of Fluorescein-assisted Stereotactic Brain Biopsies in Predicting Conclusive Tissue Diagnosis

Edin Nevzati, MD v; Grégoire Chatain, MD; Kevin Lillehei, MD; David Ormond, MD

Introduction: Fluorescence-based tumor resection has developed into a standard of care in the treatment of malignant brain tumors, facilitating differentiation between tumor and brain parenchyma. Although relying on the same technology, fluorescence-assisted stereotactic brain biopsies are not uniformly performed across neurosurgical institutions. Intraoperative specimen collection rather relies on neuropathological interpretation of fresh frozen samples. The purpose of this study was to assess the reliability of fluorescein sodium in predicting conclusive tissue diagnosis in stereotactically harvested brain lesion biopsies, and to assess its specificity with contrast enhancing and non-enhancing MRI lesions.

Methods: A total of 19 patients were included in the study, consisting of 14-contrast enhancing and 5 non-enhancing lesions on preoperative MRI-scan. All patients received 3mg/kg fluorescein sodium during anesthesia induction. Biopsy specimens were observed and photographed using a microscope-integrated fluorescent module prior to histopathological analysis. Two observers reviewed the photographs blindly and independently in a retrospective fashion. Fluorescence status was confirmed with location-concordant histopathological results and correlated with

contrast-enhancement on imaging.

Results: Out of 19 biopsies, permanent pathology revealed tumor in 15 samples. Fifteen fluorescing specimens were location-concordant with histopathological results (sensitivity 100%, specificity 75%, positive predictive value 75%). Of 19 specimens, 13 fluorescing biopsies were also contrast-enhancing on MRI (sensitivity 93%, specificity 40%, positive predictive value 81%). Interestingly, of 4 non-enhancing lesions biopsied, fluorescein correctly identified tumor tissue in two fluorescing samples while the two non-fluorescing tissues were negative for neoplasia on pathology. The interobserver agreement for fluorescing status was good ($k=0.77$).

Conclusion: Fluorescein-assisted stereotactic brain biopsies demonstrate high sensitivity in predicting conclusive tumor pathology in contrast-enhancing MRI lesions. Considering the low side effect profile of fluorescein sodium, this surgical adjunct may be considered for routine use to enhance accuracy and safety in stereotactic brain biopsies.

422. Nanoscale Epitope Uncovering and De-crowding Using Expansion Microscopy of Normal Human and Glioma Tissues

Pablo Valdes Quevedo, MD (Boston, MA); Khalid Shah, PhD; Edward Boyden, PhD; E Chiocca, MD, PhD

Introduction: Imaging of cellular structures at the nanoscale level requires use of complex pioneering super-resolution microscopy methods. Most diffraction limited microscopy methods, modern super-resolution methods and expansion microscopy (ExM), are reliant on immunostaining methodologies. 'Hidden' tissue epitopes require unmasking by means of antigen retrieval techniques which are limited in that they leave sterically hindered structures inaccessible, leaving epitopes masked, limiting our understanding of the complex molecular composition of tissues. We present a form of ExM, multiplex ExM (multiExM), that enables epitope unmasking, de-crowding, and multiplexed post-expansion immunostaining of a broad range of normal human brain and brain tumors

Methods: We developed multiExM as a technology for: treating clinical samples with Acryloyl-X to anchor proteins, embedding in a swellable polymer, chemically treating tissues enabling protein denaturation with epitope preservation, and expanding 4x in deionized water. Clinical formalin-fixed paraffin-embedded normal human brain and glioma samples underwent immunostaining both prior to and following gel embedding. Samples were imaged using super-resolution imaging and conventional confocal microscopy. Rigid and non-rigid registration of images was performed and image analysis performed to measure tissue isotropy and quantify epitope unmasking with in house MATLAB software.

Results: MultiExM treated tissues maintained excellent isotropy following expansion; and enabled epitope uncovering of neuronal, oligodendrocytic and astrocytic structures in normal brain, as well as 'hidden' structures in tumor cells and infiltrating activated microglia; and multiplexing to >15 simultaneous targets including visualization of the complex perivascular niche, blood brain barrier, and tumor tunneling micro- and nano-tubes with mitochondrial cargo.

Conclusion: We describe multiExM, a method for embedding tissues in a swellable polymer to enable multiplexed immunostaining of unmasked epitopes for nanoscale resolution imaging using diffraction limited microscopes. MultiExM enables processing of clinical samples of normal and diseased human brain to visualized nanoscale structures previously inaccessible to clinicians and researchers.

423. siRNA-mediated Knockdown of Multiple Enzymatic Targets for Potentiation of 5-Aminolevulinic Acid Fluorescence

Alexa Semonche (Somerset, NJ); Ana Pascoini, BS; Daniel Eichberg, MD; Ashish Shah, MD; Javier Figueroa, MD; Ricardo Komotar, MD; Michael Ivan

Introduction: 5-aminolevulinic acid (5-ALA) has recently gained FDA approval for clinical use in gliomas; it enhances visualization during resection and photodynamic therapy (PDT), a more novel treatment option. Previous studies have shown that the amount of protoporphyrin IX (PPIX) accumulation from 5-ALA correlates with the extent of tumor cell killing by PDT. Therefore we sought to manipulate enzymes involved in the metabolism or export of PPIX from patient-derived glioblastoma stem cell lines (PDGSC) following treatment with 5-ALA as a potential way to increase the efficacy of 5-ALA-based PDT for treatment of glioblastoma (GBM) tumors. This process may also improve the sensitivity of fluorescence-guided resection with 5-ALA.

Methods: GBM tumor samples obtained intraoperatively were used to establish PDGSC. Cells were transfected with either scramble siRNA, siRNA against ABCG2, siRNA against FECH, or a combination of siRNA against ABCG2 and FECH. Non-transfected cells served as a control. Cells were incubated in 5-ALA following transfection. Flow cytometry measurements of median fluorescence intensity (MFI) of PPIX served as a correlate of intracellular PPIX accumulation. MFI was compared across transfection conditions.

Results: 10 patient-derived primary PDGSCs were established. There was a significant difference in PPIX fluorescence following 5-ALA exposure across cell lines, demonstrating variability within GBM. All cell lines showed a dose and time dependent response to 5-ALA. After co-transfection with siRNA against ABCG2 and FECH, PPIX fluorescence increased ($P < 0.01$) compared to siRNA control and siRNA against ABCG2 and ferrochelatase alone ($P < 0.05$). Transfection with scramble siRNA did not increase PPIX fluorescence ($P = 0.63$).

Conclusion: PDGSCs vary significantly regarding PPIX levels and fluorescence following 5-ALA treatment. Greater PPIX fluorescence following incubation with 5-ALA may sensitize tumor cells to 5-ALA-based PDT therapy and improve visualization during intraoperative resection of GBM. A multiple knockdown approach may improve tumor fluorescence after 5-ALA treatment.

424. Receptor Tyrosine Kinase Gene Amplification is Predictive of Intraoperative Seizures during Glioma Resection with Functional Mapping

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Introduction: Intraoperative seizure during craniotomy with functional mapping is a common complication that impedes optimal tumor resection and results in significant morbidity. The relationship between genetic mutations in glioma and the incidence of intraoperative seizure has not been well-characterized.

Methods: We queried our institutional database for patients with brain tumors who underwent surgical resection with intraoperative functional mapping between 2005 and 2017. Basic clinicopathologic characteristics including the status of the following genes were recorded: IDH1/2, PIK3CA, BRAF, KRAS, AKT1, EGFR, PDGFRA, MET, MGMT, and 1p/19q. Relationships between gene alterations and intraoperative seizure were evaluated using chi-square as well as two-sample t-test and logistic multivariate analyses.

Results: 416 patients met criteria for inclusion, of which 98 (24%) experienced an intraoperative seizure. Patients with a history of preoperative seizure and those treated with anti-epileptic drugs (AEDs) prior to surgery were less likely to have intraoperative seizures (history: OR = 0.61 (0.38 – 0.96), $c^2(1) = 4.65$, $p = 0.03$; AED load: OR = 0.46 (0.26-0.80), $c^2(1) = 7.64$, $p = 0.01$). In a univariate analysis of genetic markers, amplification of genes encoding receptor tyrosine kinases (RTKs) were specifically identified as a positive predictor of seizure (OR = 5.47 (1.22-24.47), $c^2(1) = 5.98$, $p = 0.01$). In multivariate analyses considering RTK status, AED use, and either World Health Organization (WHO) 2007 tumor grade or modern WHO 2016 tumor groups, we found that amplification of the RTK proto-oncogene, MET, was most predictive of intraoperative seizure ($p < 0.05$).

Conclusion: This study describes a previously unreported association between genetic alterations in RTKs and intraoperative seizures during glioma resection with functional mapping. Future models estimating intraoperative seizure risk may be enhanced by inclusion of genetic criteria.

425. Contralateral Extra-Axial Hematoma after Decompressive Hemicraniectomy: Description and Incidence in a Consecutive Trauma Series

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Introduction: Decompressive hemicraniectomy is a common neurosurgical procedure performed for severe traumatic brain injury. This operation is occasionally complicated by development of contralateral extra-axial hematoma. Here we review the outcomes of patients with contralateral extra-axial hematomas after decompressive hemicraniectomy in a consecutive trauma series.

Methods: Retrospective review was conducted to identify all adult and pediatric patients undergoing emergent hemicraniectomies between May 2015 and April 2018. Patients without traumatic pathologies, including stroke and spontaneous hemorrhage, were excluded. Imaging was reviewed to identify patients with a postoperative contralateral extra-axial hematoma defined as either a new hematoma at least 5mm in thickness or a progressive hematoma increased by at least 5mm in thickness. Fisher exact test was used to compare categorical variables.

Results: Of 154 patients, 11 (7.1%) did not receive post-operative imaging due to peri-operative mortality. Of 143 patients receiving postoperative imaging, 12 (8.4%) developed postoperative contralateral hematomas, which were subdural in 11 cases and epidural in 1 case. Eight of these hematomas were not present on preoperative scan, and four were enlarging hematomas. All patients with contralateral subdural hematomas either died ($n=8$) or were neurologically devastated at last follow up (GCS <8 , $n=3$). Contralateral hemicraniectomy was performed in four cases, including the

three patients who were discharged with GCS<8. Patients receiving contralateral hemicraniectomy were more likely to survive in a vegetative state (75% versus 0%, $p=0.02$). The patient with contralateral epidural hematoma underwent evacuation via contralateral craniotomy and recovered.

Conclusion: In this series of patients receiving hemicraniectomy after traumatic brain injury, the rate of new or progressive contralateral extra-axial hematoma was 8.4%. Predictive factors for this complication remain elusive. Hemicraniectomy may increase the rate of survival without meaningful recovery for patients with contralateral subdural hematomas. These data may guide decision making for this unfortunate complication.

426. The Effect of Supplementation of Vitamin D in Neurocritical Care Patients with Hypovitaminosis D: A Randomized Clinical Trial

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Hypothesis: Hypovitaminosis D is prevalent in neurocritical care patients but the potential to replenish vitamin D and improve patient outcome has not been investigated.

Methods: A single-center, double-blinded, placebo-controlled clinical trial was performed from October 2016 until April 2018, where emergently admitted neurocritical care patients with vitamin D deficiency (≤ 20 ng/ml) were randomized (1:1) to receive vitamin D3 supplementation (cholecalciferol, 540,000 IU) or placebo. Hospital length-of-stay (LOS) was the primary outcome.

Results: Patients were treated with vitamin D3 ($n=134$) or placebo ($n=133$) (mean age 54.0 ± 17.2 years, 56.9% male, 77.2% White). After an interim analysis suggested a low conditional power for outcome difference (predictive power: 0.2), the trial was halted. For as-treated patients, no significant difference in hospital LOS was seen between vitamin D3 and placebo groups (10.4 ± 14.5 vs. 9.1 ± 7.9 days, $p=.4$). Vitamin D3 supplementation significantly improved repeat serum levels compared with placebo (20.8 ± 9.3 vs. 12.8 ± 4.8 ng/ml, $p<.001$) without adverse side effects. There were no differences in intensive care unit length of stay (5.8 ± 7.5 vs. 5.4 ± 6.4 days, $p=.4$), mortality within 30 days (8.2% vs. 9.8%, $p=.7$), sepsis (1.5% vs. 2.3%, $p=.6$), pneumonia (11.9% vs. 10.5%, $p=.7$), urinary tract infection (6.7% vs. 4.5%, $p=.4$), or deep vein thrombosis (6.0% vs. 2.3%, $p=.1$) between vitamin D3 vs. placebo groups. The most common disposition for patients was home (38.8% vs. 44.4%) followed by rehabilitation (32.1% vs. 21.1%) for vitamin D3 vs. placebo ($p=.2$). No subgroups could be identified by exclusion of length of stay outliers or segregation by Glasgow Coma Scale score, SAPS II score, or severe vitamin D deficiency (≤ 10 ng/ml).

Conclusion: Despite studies showing vitamin D can help predict prognosis, supplementation in vitamin D-deficient neurocritical care patients did not result in an appreciable improvement in outcomes and likely does not play a role in acute clinical recovery.

427. Secondary Analysis and Proposed Validation of a Predictive Model for MVC Outcomes

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Introduction: Motor vehicle collisions (MVC) remain a significant injury mechanism in the modern United States, each year accounting for up to 40,000 deaths and almost one-third of emergency department visits. We recently generated computer models to predict clinically significant outcomes in MVC patients using machine-learning tools. We have further assessed our model's performance and propose a prospective trial for external validation.

Methods: We queried two prospectively-maintained databases at our institution's free-standing Level 1 trauma center: i) The American College of Surgeons National Trauma Data Bank (local sample), and ii) an in-house clinical research database. De-identified case records were included for all vehicle occupants who presented after MVC. Patients were categorized by mortality and hospital admission. We trained a convolutional neural network (CNN) to predict mortality and hospital length of stay (LOS).

Results: A total of 17,088 cases met criteria for inclusion. Our CNN-derived model predicted mortality at presentation with a 96.8% sensitivity, 92.7% specificity, 92.8% PPV, 96.7% NPV, and an overall 98% AUROC from age, GCS, and injury severity score (ISS) alone. In the sub-group of 16,287 cases who survived and were admitted, our model predicted eventual mortality with 92.1% sensitivity, 90.1% specificity, 90.2% PPV, 92.0% NPV, and an overall 97% AUROC, from age, GCS, ISS, and time to admission alone. Our model predicted overall LOS in these patients with a mean absolute error of ± 4.23 days from the same variables. This accuracy reached ± 2.23 days when analysis was restricted to patients with LOS below the 95% percentile. Model accuracy remained high when testing-group patients were stratified by age and sex.

Conclusion: Our CNN-derived models predict clinical outcomes following MVC trauma with high accuracy. We propose a prospective multi-center trial to further refine and validate this tool.

428. Perfusion-Dependent Impairment of Cerebral Autoregulation in Malignant Hemispheric Stroke

Nils Hecht (Berlin, Germany); Max Schrammel; Sebastian Major; Jens Dreier; Peter Vajkoczy; Johannes Woitzik

Introduction: Regional loss of cerebral autoregulation (CA) has been shown to play a key role in secondary brain damage attributable to edema formation and infarct progression in malignant hemispheric stroke (MHS). However, it remains unclear to what extent CA impairment depends on the regional perfusion level within the affected hemisphere. Therefore, in the present study we performed a spatial-temporal assessment of CA in patients undergoing decompressive hemicraniectomy (DC) for treatment of MHS.

Methods: In 24 patients undergoing DC, autoregulation over the affected hemisphere was intraoperatively assessed by continuous cortical perfusion mapping by Laser Speckle Imaging (LSI) and mean arterial blood pressure (MAP) monitoring. Regions of interest (ROIs) were positioned within the color-coded LSI perfusion map and LSI-specific cortical perfusion was calculated within the infarcted and non-infarcted cortex. Cortical perfusion was normalized to 100% and six levels of cortical perfusion were defined (0-20%, 20-40%, 40-60%, 60-80%, 80-100% and >100%). Means, standard deviations and confidence intervals (CI) of the cortical perfusion level, MAP and the interaction of both variables during a 20-minute monitoring period were estimated with a linear random slope model and Pearson correlation analysis.

Results: For each perfusion level, n=578 ROIs were analyzed across all hemispheres. Pearson correlation analysis showed significantly less autoregulation impairment in non-infarcted tissue (>100%: $r=0.36$) than in tissue with critically reduced cortical perfusion (20-40%: $r=0.67$; 40-60%: $r=0.68$; 60-80%: $r=0.68$; $*p<0.05$). Further, linear cortical perfusion changes per mmHg MAP were significantly greater in areas with critically reduced perfusion (40-60%: 0.42% per mmHg and 60-80%: 0.46% per mmHg) compared to non-infarcted (>100%: 0.22% per mmHg) or infarcted (0-20%: 0.29% per mmHg) areas ($*p<0.001$).

Conclusion: Spatial identification of regions with penumbral perfusion patterns may be critical for effectively targeting CA as a strategy to prevent secondary neurologic injury in patients suffering MHS.

429. Post-operative Imaging. When We Need It And When We Don't. A Prospective Algorithm Based Study

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Introduction: Necessity and timing of early post-operative imaging have been the debate of many studies. Despite the consensus that early post-operative imaging does not change patient management, these exams are still performed routinely. To our knowledge this is the first prospective study related to post-operative imaging.

Methods: The study design was an algorithm based prospective single blinded single center study. The algorithm has pre, peri and post-operative considerations among them are estimated pathology type, device placement and post-operative neurological change. When the algorithm stated there was no need for post-op imaging, scans were performed but the treating team was blinded to them, and patient management was conducted based on clinical exams only. An uninvolved neuroradiologist and neurosurgeon reviewed all the scans for safety reasons. The primary objective was to assess the necessity of early post-op imaging in the asymptomatic patient. The secondary goal was to verify accuracy of the algorithm with less than 5% failure.

Results: A hundred and three patients were enrolled, 88 remained asymptomatic, and 15 became symptomatic post-operatively. One percent of the asymptomatic and 53% of the symptomatic patients had pathologic post-op imaging (the difference was statistically significant). In the asymptomatic group neither medical nor surgical treatment modifications were made post-operatively. Additionally, there was no need to remove the blinding for the surgical team for any of the patients. To the contrary, 20% of the symptomatic patients returned to the operating room because of imaging and neurologic findings. The goal of less than a 5% algorithm failure was reached with statistical significance.

Conclusion: In the asymptomatic post-operative patient when imaging isn't utilized for oncological, device placement verification or similar reasons, it is unnecessary and does not change the management of these patients.

430. Clinical outcomes following spine surgery for traumatic injury in the octogenarian population

Michael Gigliotti (Pittsburgh, PA); Gordon Mao, MD; Nestor Tomycz, MD; Daniel Altman, MD; Frances Philp

Introduction: The octogenarian population has more than doubled in the developing world since 1985. In an aging population, physiologic changes lead to a reduced ability to withstand traumatic injury, leading to an increase in traumatic and unintentional injury. Specifically, unintentional injury has risen to rank third in morbidity and mortality in the United States. Although multiple studies have increasingly found comparable outcomes in elective spinal surgery cases in the octogenarian population, there is a lack of outcome data in relation to emergent spinal trauma surgery.

Methods: Patients with both radiographic and clinical evidence of acute traumatic spine injury after trauma were reviewed utilizing an institutional trauma survey to determine patient demographics and outcome data in a population of patients aged 80 years and older.

Results: 39 patients underwent surgical intervention for acute spinal trauma in patients aged 80 years and older. There were 25 cases of cervical spine and 14 cases of thoracolumbar spine surgical intervention. Falls were the number one cause of acute spinal injury (31/39, 71%). Major respiratory disorders were the most common post-operative adverse event (12/39, 31%). Five patients experienced either superficial wound dehiscence, fascial dehiscence, superficial infection, and delayed wound erosion. Patients were either discharged to home (10.5%), inpatient rehabilitation, (38.5%), skilled nursing facilities (17.9%), or long-term care facilities (17.9%). Post-operative mortality rate was 10.3%.

Conclusion: Although the octogenarian population has increased risk for post-operative events after acute spinal injuries, surgical intervention may be worthwhile in the elderly population. While direct surgical complication rates are not higher, medical risks are significantly higher following surgery.

431. The Management and Outcomes of Isolated Interhemispheric Subdural Hematomas Associated with Falx Syndrome

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Introduction: Large interhemispheric subdural hematomas (iSDH) causing falx syndrome are rare and a paucity of data exists regarding the outcomes after contemporary management of iSDH. There is a general consensus among neurosurgeons that large iSDH with neurologic deficit represent a particular challenge to treat with generally poor outcomes. As such, radiographic and clinical outcomes after surgical and nonsurgical management of iSDH bear further study.

Methods: A prospectively-collected, single-institution trauma database was searched for patients with traumatic iSDH causing falx syndrome from 2008 to 2018. Demographic and radiographic information, clinical and radiologic outcomes and post-treatment complications were collected and tallied. They subsequently dichotomized patients by management strategy to evaluate clinical outcome and 30-day survival.

Results: 25 patients (0.4% of all intracranial injuries, 0.05% of all trauma patients) of average age 73.4 years with iSDH and falx syndrome represented the study cohort. Most patients (23 of 25, 92%) were taking anticoagulants or antiplatelet medications. 19 patients underwent craniotomy for iSDH evacuation, and 17 (89.5%) had improvement or resolution of motor deficits post-operatively. There were no instances of venous infarction, re-accumulation, or infection. In total, 9 of 25 patients (36%) died within 30 days, including 6 of 19 (32%) who underwent craniotomy. Patients who died were significantly more likely to experience in-hospital neurologic deterioration prior to surgery (67% vs 15%, $p=0.046$) and were more likely to be comatose prior to surgery (23% vs 100%, $p=0.0031$). The median mRS of surgical patients who survived ($n=13$) was 1 at 22.1 months.

Conclusion: Interhemispheric subdural hematomas associated with falx syndrome can be evacuated safely and effectively, and prompt surgical evacuation prior to neurologic deterioration may improve outcomes. In this experience, craniotomy for iSDH evacuation proved to be a low-risk strategy that was associated with generally good outcomes, though appropriately-selected patients may fare well without evacuation.

432. Neurosurgery Resident Surgical Experience in Pediatric Cases

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Introduction: The purpose of this study is to identify the national trends in neurosurgical resident exposure to pediatric procedures and to subsequently evaluate how these operative experiences correlate with the minimum requirements set forth by the ACGME.

Methods: ACGME resident case logs from residents graduating between 2013 and 2017 were retrospectively reviewed. These reports were analyzed to determine trends in resident operative experience in pediatric procedures. The number of cases performed by residents were compared to the required minimums set by the ACGME within each pediatric surgical category. A linear regression analysis was utilized to analyze the change in cases performed over the study period.

Results: A mean of 98.78 procedures were performed for each of the 877 residents graduating between 2013 and 2017. The total number of pediatric procedures declined at a rate of 1.74 cases/year ($r^2=0.77$). Spine and CSF diversion procedures decreased at rates of 1.93 ($r^2=0.70$) and 1.20 ($r^2=0.70$) cases/year respectively. The number of trauma and brain tumor cases were shown to have increased at rates of 1.02 ($r^2=0.86$) and 0.32 ($r^2=0.69$) cases/year respectively. There was also a trend of increasing cases logged as lead resident surgeons by 12.85 cases/year ($r^2=0.99$). The number of cases performed by the average graduating resident was also higher than the minimums required by the ACGME; residents, on average, performed three times the required minimum number of pediatric cases.

Conclusion: Neurosurgical residents reported decreasing overall case volumes for pediatric neurosurgery cases from 2013 to 2017. Despite this downward trend, the number of cases logged vastly exceeded ACGME requirements and there was an increasing trend of case logged as lead resident surgeons, indicating that residents are nevertheless graduating with substantial pediatric neurosurgical exposure.

433. Rates of In-Hospital Failure for Endoscopic Third Ventriculostomy (ETV) compared to Shunting in Post-Hemorrhagic Hydrocephalus of Prematurity (PHHP)

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Introduction: ETV has shown promise as a means of treating PHHP in an effort to prevent lifelong shunt dependence in neonates. However, there is limited data regarding in-hospital failure rates and the factors contributing to their potential failure.

Methods: We performed a retrospective analysis of the Nationwide Inpatient Sample (NIS) between 2004-2014. Patients < 1 year of age with an ICD-9-CM diagnosis code indicating IVH of prematurity (772.1x) and an ICD-9-CM procedure code indicating an ETV (02.2 and 02.22) or a shunt (02.3x) were included. Univariate analysis was used to test covariates predictive of in-hospital failure, time to failure and crossover to shunt or ETV after failure. Interaction and confounding were assessed through stratification and relevant expansion covariates. Factors predictive in univariate analysis ($p<0.20$) were entered into a backwards elimination multivariate logistic regression analysis. P-values of ≤ 0.05 were considered statistically significant.

Results: 9,325 patients with PHHP were identified in the NIS from 2004-2014. Patients shunted as an initial treatment had significantly decreased risk of failure compared to those who underwent an ETV (OR .366, 95% CI .318 to .422, $p < 0.0001$). There were no significant differences in time to failure between the two groups. ~92% of ETVs that failed were shunted after the first failure and those who were shunted as an initial treatment were much less likely to undergo ETV if they failed (OR 1.56, 95% CI .12 to .202, $p < 0.0001$). Both ETV and shunts were more likely to fail in patients with respiratory distress syndrome and perinatal infections were predictive of shunt failure but not ETV. Grade of IVH was not predictive of failure in either group.

Conclusion: Although ETV can be effective in treating PHHP, it has a much higher initial failure rate than shunts, and should thus be chosen based on a multifactorial approach.

434. Experimental in-vitro shunt valve studies and computerized modeling demonstrate cerebrospinal fluid overdrainage under physiologic conditions

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Introduction: There have been few improvements on modern shunt technology since John Holder introduced the modern silicon valve. There is growing evidence that most shunted patients are subjected to cerebrospinal fluid (CSF) overdrainage, which is hypothesized to cause proximal shunt obstructions and headaches. The present study is aimed at better understanding why valves are afflicted by supra-normal CSF flow rates under physiologic conditions.

Methods: Using models constructed in MatLab®, invasive ICP recordings from patient monitoring, and experimental data obtained from a sophisticated benchtop valve testing apparatus CSF flow rates were predicted under physiologic conditions. Models were based upon manufacture reported valve performance and experimental data obtained through in-vitro testing. Real-time patient ICP monitoring data were used to inform physiologic parameters.

Results: Modeling and in-vitro valve experiments demonstrate shunts are susceptible to CSF overdrainage in the upright

position due to gravity-dependent siphoning. When intracranial pressure pulsations related to cardiac cycle or changes in systemic venous pressure (i.e. valsava) are additionally considered, shunt valves have increased susceptibility to CSF overdrainage in both the upright and supine positions.

Conclusion: Modern CSF shunts are subjected to overdrainage in both the supine and upright positions. A better understanding of physiologic changes in ICP and CSF flow through shunts may better inform patient counseling and guide technological development of new valve designs.

435. Staged MR-Guided Laser Interstitial Thermal Therapy for Hypothalamic Hamartoma: Analysis of Ablation Volumes and Morphological Considerations

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Introduction: Hypothalamic hamartomas (HH) are a challenging pathology that cause gelastic seizures. Magnetic Resonance Imaging-guided Laser Interstitial Thermal Therapy (MRgLITT) offers a safe and effective treatment for HHs via a minimally invasive technique. In this study, we analyzed radiographic data and reconstructed volumetric imaging to determine how clinical outcome correlates to residual tumor volume and surgical strategy.

Methods: Clinical and radiographic information was retrospectively reviewed of 58 pediatric patients who underwent MRgLITT for HH with at least 6 months of follow-up. MR imaging was volumetrically reconstructed to analyze the impact of hamartoma and ablation volumes on outcome. Primary outcome measure was freedom from gelastic seizures.

Results: Eighty-one percent of patients were completely free of gelastic seizures at last follow-up; of 22 patients with secondary non-gelastic epilepsy, 15 were free of additional seizures. Post-operative complication rate was low. There was no significant difference in gelastic seizure outcome related to pre- or post-operative hamartoma size. Residual hamartoma percentage in those free of gelastic seizures was 43% compared to 71% in those with continued seizures ($p=0.021$). Larger hamartomas required multiple ablations to achieve seizure freedom.

Conclusion: This large series of patients confirms the safety and efficacy of MRgLITT for pediatric HH and describes morphological considerations that predict success. Our data suggests that complete ablation of the lesion is not necessary, and that the focus should be on appropriate disconnection of the epileptogenic network. We have found that a staged approach to hamartoma ablation allows adequate disconnection of the hamartoma while mitigating risk to surrounding structures.

436. Network Disconnection: An Early Predictor of Seizure Freedom After Surgery

Elliot G Neal (Tampa, FL); Long Di; Stephanie Maciver; Fernando Vale

Introduction Network connectivity patterns vary between epileptic patients with similar clinical presentation. These differences may contribute to why some patients with epilepsy fail surgical resection. In our previous work, patient-specific networks were mapped without prior knowledge of epileptogenic zones. We hypothesized that seizure freedom depends on surgical disconnection of this specific network.

Methods Scalp EEG and resting state fMRI (rsfMRI) were acquired for fourteen patients undergoing surgery for mesial temporal lobe epilepsy (mTLE). The epileptogenic zone was localized using a forward cortical dipole model and inverse Bayesian reconstruction. rsfMRI data was used to map regions functionally correlated with the epileptogenic zone, which represented the putative epilepsy network. Network connectivity was measured pre- and post-operatively (three months). Network connectivity was also measured in age matched control patients.

Results: The network model was validated by overlaying epilepsy networks on healthy control patients. Network connectivity was significantly higher in the patients with mTLE compared to the healthy control patients ($p<0.05$). After one year, eight patients were seizure-free after surgery and six were not. In the seizure free patients, the epilepsy network was significantly more disconnected than in patients with seizure recurrence (66% vs. 35%) ($p<0.05$). ROC curve analysis revealed that networks with greater than 46% disconnection predicted seizure free outcomes with 100% specificity and 64% sensitivity (AUC = 0.804).

Conclusions: We showed that network disconnection may be a reliable non-invasive test for seizure freedom after surgery. These data were generated from non-invasive data available at any comprehensive epilepsy center. This prognostic test was conducted at three months post-op, much sooner than the one year normally required to classify seizure freedom. Early prediction of outcomes helps patients and doctors alike in executing treatment plans. Future studies will investigate why degree of disconnection varies despite similar surgical techniques.

437. Comparative Study of Open Surgical Callosotomy and Laser Interstitial Thermal Therapy (LITT) in Pediatrics

Muhammad Burhan Ud Din Janjua, MD (Dallas, TX); Alison Dolce, MD; Angela Price, MD

Introduction: Corpus callosotomy has been efficacious for patients with multifocal refractory epilepsy or secondarily generalizable seizures, and drop attacks (atonic or tonic). Given the morbidity of the open procedure, there has been an increasing trend to seek the alternative treatment options. MR-guided Laser Interstitial Thermal Therapy is a minimally invasive surgical option for ablation of epileptogenic foci. To date, there is no comparative study; therefore authors report their results from open corpus callosotomy (OCC) and Laser Interstitial Thermal Therapy (LITT).

Methods: All patients operated with either open surgical callosotomy or LITT from Jan 2005 to Jun 2018 were reviewed at a single center. Patient demographics, presurgical seizure burden, operative variables, postoperative outcome, complications, revision operation, steroid use, disposition to rehab facility/home, and overall recovery from seizure burden were recorded.

Results: 20 patients male to female ratio of 4:1 with mean age of 10 years {OCC versus LITT, (9.2 vs. 11.6)} were operated for medically refractory epilepsy. 6 (30%) patients underwent LITT procedure. When compared with OCC cohort, statistically significant decrease in EBL ($p < 0.003$), and decreasing trend towards LOS ($p < 0.149$) was observed in LITT cohort {mean $\pm$ SEM, (50.71 $\pm$ 8.40 vs. 7 $\pm$ 3.41), and (6.07 $\pm$ 0.44 vs. 4.50 $\pm$ 1.18)}. Reported follow-up (in months) for OCC cohort was 87.64, and for LITT was 6.91. In OCC cohort 9 (64%) patients were transferred to inpatient rehab facility while, all LITT patients were discharged home postoperatively. Interestingly, 10 (71%) patients in OCC, and 5 (83%) in LITT cohort documented recovery from seizure burden.

Conclusion: The concept of treatment of multiple epileptogenic foci in children using LITT has been relatively recent. Corpus callosotomy using LITT is a novel alternative procedure to conventional open surgical approach with significant decrease in EBL, and LOS. When compared to OCC, LITT offers quicker recovery, almost complete cure from drop seizures, and final disposition to home.

438. Anterior Cingulate Electrographic Activity associated with Recovery after Severe Traumatic Brain Injury

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Introduction: Outcomes after severe TBI remain disappointing. The reasons some patients improve and some do not remain poorly understood, however the anterior cingulate cortex (ACC) has been identified as a key player in coordinating conscious activity within the frontal lobe. Despite this there have been few studies that employ depth electrodes to monitor activity of the ACC in patients who have experienced sustained loss of consciousness - such as in extended coma following severe TBI. We therefore analyzed ACC signals to look for markers of recovery of consciousness. In this study, electrophysiologic recording of the ACC and prefrontal cortex (PFC) was performed and the spectral features of patients who recovered versus deteriorated were examined.

Methods: Depth electrodes for post-traumatic epilepsy monitoring were implanted in patients arriving comatose ($n = 4$, defined as GCS < 8) at Stony Brook University Hospital following TBI. ECoG data was collected and 15min blocks of baseline data were bipolar re-referenced, and spectral decomposition using pwelch was performed to obtain the power spectral density of baseline neural activity in ACC and PFC.

Results: In patients who recovered consciousness (patients 1, 2, 4), ACC recordings showed steady increase in power density of the beta (14-40 Hz) range relative to the theta (5-8 Hz). However in patients who failed to recover (patient 3), the beta:theta power ratio decreased. Furthermore, the PSDs in the ACC of patients who recovered were notably punctuated by alpha, beta, and theta peaks, while the PSD of our patient who deteriorated showed smoother 1/f-type activity. In patient #4, PFC activity failed to capture peaks associated with recovery, whereas these peaks were revealed by electrodes located in the CC.

Conclusion: The ACC exhibits spectral features that are distinct from the frontal lobe. Based on our preliminary study, time-frequency characteristics may serve as valuable prognostic guides for clinical decision making.

439. The Effect of Gamma Knife Radiosurgery on Large Posterior Fossa Metastases (LPFM) and the associated peritumoral edema and 4th ventricle volume

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Introduction: Gamma Knife Radiosurgery (GKRS) as monotherapy is often avoided for the treatment of large (≥ 2 cm) posterior fossa brain metastasis (LPFM) based on a theoretical risk of increased peritumoral edema (PTE) and associated compression of the 4th ventricle (4V) related to the treatment.

Methods: A single center, IRB approved, retrospective review of LPFM treated with GKRS from 2009-2017 was performed. Brainlab® iPlan software was used to evaluate the tumor, 4V and PTE volumes at initial treatment and all subsequent follow-ups. Statistical analysis was performed using Wilcoxon Signed Rank test and McNemar test.

Results: Results We identified 49 lesions in 47 consecutive patients; 55% males, median age 61.5 years, median KPS was 90 at the time of GKRS. Median number of LPFM and overall brain metastases was 1 and 2.5 respectively. The median overall tumor, PTE, and 4V volumes at diagnosis were 5.37 cm³, 17.11 cm³, 1.23 cm³ respectively with a median study follow-up of 7.28 months (range 1.87-56.23). At first follow-up, 2 months post treatment, median tumor volume decreased by 54.04 % [range -96.95, 48.69] ($p < 0.001$), median PTE decreased by 55.66 % [range -99.92, 143.36] ($p < 0.001$) and 4V increased (23.89 [range -50.16, 545.76] p 0.31). No patient required surgical intervention, external ventricular drainage or shunting between treatment and first follow-up. Post treatment, 65.95 % receive our routine steroid taper, 4.25% received no steroids and 29.78% required prolonged steroid treatment.

Conclusions: Patients with LPFM treated with GKRS had in a significant reduction in tumor size and PTE ($p < 0.001$) and marked opening of the 4V post treatment. This study suggests that GKRS was well tolerated and can be considered in the management of LPFM especially in patients for whom surgery is contraindicated.

442. Management of Intraoperative High Impedance Levels During Placement of Deep Brain Stimulating Electrodes

Mark K. Lyons, MD, FAANS, FACS (Phoenix, AZ); Naresh Patel, MD; Matthew Neal, MD

Introduction: Deep brain stimulation (DBS) is a well-established treatment for medically refractory Parkinsons disease (PD), essential tremor (ET) and dystonia. The expansion of DBS to dozens of other clinical conditions continues to rapidly grow globally. A critical component of the success of these procedures depends significantly on the reliability and durability of devices implanted. Immediate feedback during surgery often gives the surgeon and patient a sense of confidence of long term success. When impedances are found to be elevated during the implantation of the DBS leads, appropriate trouble shooting measures are critical.

Methods: We present the case of a 73 male undergoing awake subthalamic DBS with microelectrode recordings for severe PD. Once the optimal trajectory and depth were ascertained the permanent DBS electrode was placed. High impedances were recorded. Troubleshooting procedures were performed and were all negative as to the cause of the values. Correct impedance levels of the DBS electrode was confirmed with extracranial testing, but continued high values were found again with intracranial positioning of the electrode. The electrode was replaced with identical results.

Results: A postoperative computerized tomography (CT) scan confirmed a small amount of intracranial air surrounding all of the contacts. The patient went on to outpatient programming with excellent clinical results and normal electrode impedances three weeks following surgery.

Conclusions: The presence of pneumocephalus surrounding the electrode contacts may explain such readings in the absence of any other causes, especially when the impedance values in saline are normal. Intraoperative imaging may be very helpful in confirming pneumocephalus as the cause of the high impedance recordings and give the surgical team confidence that the electrode is good and programming will be successful.

443. Mutant IDH-induced LDHA Expression in Peritumoral Cortex as a Mechanism for Tumor Related Epilepsy

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Introduction: Although incidence of seizures in patients with low-grade, IDH-mutated, brain tumors reaches 80-90%, the pathogenesis of seizures remains unknown. Recent data from epilepsy patients implicate changes in neuronal metabolism and upregulation of lactate dehydrogenase A (LDHA) as a potential contributor to epileptogenesis. We

present clinical implications and experimental data that suggest LDHA upregulation as a mechanism for tumor-related epilepsy (TRE).

Methods: Five patients with WHO grade II-III IDH1-mutated gliomas who presented with seizures underwent subdural electrode placement for extraoperative electroencephalography (EEG) to define normal cortex, tumor, peritumoral epileptogenic cortex, and eloquent cortex, followed by resection of tumor and epileptogenic zone. Based on EEG findings, we separated the resected tissue and stained via immunohistochemistry for mutated IDH1 (R132H) and LDHA.

Results: All patients underwent successful resection of tumor and associated epileptogenic cortex. Mean age was 33 years, with 4 males and 2 females. There was no change in mean Karnofsky performance status (KPS) with 80 pre- and postoperatively. Engel outcome was 1a in 4 patients (80%) and 1b in one patient (20%) with 6-month follow-up, compared to 70% postoperative seizure freedom in the literature. Immunohistochemistry revealed elevated LDHA in epileptogenic peritumoral cortex compared to non-epileptic cortex and tumor tissue. IDH staining showed expected mutated IDH1 within tumor and decreased mutated IDH1 in peritumoral cortex.

Conclusion: Our series demonstrates invasive EEG monitoring for tumor related epilepsy can safely facilitate mapping of epileptogenic and eloquent cortex in the setting of TRE. Given the differential expression of mutated IDH1 and LDHA in our patients, we hypothesize a neuronal switch from aerobic to anaerobic respiration may be an underlying mechanism of TRE. Furthermore, given the sharp interface between mutated IDH1 and LDHA staining seen in our specimens, an interaction between peritumoral neurons and IDH1 mutated glial cells is possibly responsible for this metabolic change.

444. Discrete States and Interactive Networks in the Cortical Dynamics of Speech Production

Kiefer Forseth (Houston, TX); Aram Giahi-Saravani, PhD; Xaq Pitkow, PhD; Nitin Tandon

Introduction: Speech production involves an integrated multistage process that seamlessly translates conceptual representations in the brain to an articulatory plan. Evaluating this progression of states requires combining high-resolution recordings with an analytic approach to model discrete neural states. We used Hidden Markov Models (HMMs) to resolve trial-by-trial state transition sequences in distributed networks derived from a large-scale electrocorticographic dataset.

Methods: Intracranial electrodes (n=20321,123 patients), including both surface grid electrodes and penetrating stereotactic depth electrodes, were implanted for the evaluation of epilepsy. Patients performed picture naming of common objects. A surface-based mixed-effects multilevel analysis of broadband gamma activity in the language-dominant hemisphere was used to identify loci with significant activity. This revealed 9 regions of interest: early visual cortex, fusiform gyrus, intraparietal sulcus, supplementary motor area, anterior insula, inferior frontal gyrus, subcentral gyrus, early auditory cortex, and superior temporal gyrus.

Results: First, we resolved state dynamics in the global naming network: early visual cortex, fusiform gyrus, inferior frontal gyrus, subcentral gyrus, and superior temporal gyrus. This overview captured 3 network states: a fixed length initial state corresponding to visual processing, a variable-length second state driven primarily by activity in the mid fusiform and inferior frontal gyri, and a third state during overt articulation dominated by activity in ventral sensorimotor cortex and superior temporal gyrus. Critically, the second state is consistent with the variable demands - semantic, lexical, and phonological - for each stimulus. Second, we further elucidated the network dynamics of this second state by focusing on a perisylvian sub-network corresponding to the generation of motor and auditory plans in language production. In contrast to the temporally discrete states observed in the overall network, this sub-network revealed a high-degree of state-switching specific to language planning.

Conclusion: Our work pairs large-scale electrocorticography with sophisticated analyses to answer long-standing questions about language production.

445. Convolutional Neural Networks for Detection of Parkinsonian Motor Impairment

David Liu (Providence, RI); Minkyu Ahn, PhD; Shane Lee, PhD; Peter Lauro, BS; Erin Schaeffer, BS; Daniel Amaya, BS; Umer Akbar, MD; Wael Asaad, MD, PhD

Introduction: We sought to identify the neural signatures of fluctuating symptoms in Parkinson's Disease (PD) using a convolutional neural network (CNN) trained to classify motor performance on short timescales using neural activity recorded from the subthalamic nucleus (STN). Specifically, we determined whether CNNs could identify nonlinear features in the STN local field potential (LFP) spectrogram that could predict a patient's symptomatic state.

Methods: We recorded STN LFPs in 22 PD patients undergoing DBS surgery as they performed a target-tracking task. LFP recordings were processed into 3-second, 1-200 Hz spectral images with 250ms slide. Images were labeled as either from a low or high symptomatic state using a multidimensional symptom score calculated from task

performance. 4-layer CNNs with spectrotemporal pooling, dropout, and batch normalization were trained on each patient's data. Training was performed on NVIDIA Titan V GPUs with 10-fold cross validation and a new 90/10 training/validation split on each fold, evaluated by the maximum validation accuracy metric. Performance was compared to classification obtained using a linear method (support vector machine).

Results: The average accuracy classifying 3-second movement epochs as high- vs. low-symptomatic was 0.759 ± 0.040 was across all patients, with accuracies ranging from 0.690-0.864. The CNN outperformed the support vector machine on 20 out of 22 patients (paired t-test; $p < 0.001$). Activation filters in convolutional layers showed that CNNs utilized nonlinear features for classification, such as chirps and coherence.

Conclusion: Our results demonstrate that CNNs can classify short-timescale Parkinsonian symptoms, likely by utilizing nonlinear features of a spectrogram. Identification of biomarkers underlying Parkinsonian motor impairment as well as control algorithms for closed-loop DBS may therefore benefit from this approach. Additional data, such as higher-order neural features, including phase and cross-frequency coupling, and further optimization of CNN architecture may yield even higher accuracy and higher temporal resolution.

446. Efficacy and Mechanisms of Novel Patterns of Deep Brain Stimulation (DBS): Preclinical Studies in the MPTP Non-human Primate Model of Parkinson's Disease

Felipe Branco de Paiva (Cleveland, OH); Brett Campbell; Hugh Chan, PhD; Luke Dotson; Andre Machado, MD, PhD; Ken Baker, PhD

Introduction: Deep brain stimulation (DBS) is a well-established treatment for late-stage Parkinson's disease (PD) that entails delivering isochronal, continuous high-frequency electrical stimulation to deep brain targets. While effective, traditional DBS' efficacy can be limited by both motor and non-motor side effects. Novel DBS paradigms, including coordinated reset (CR) DBS, are being explored in an effort to improve both the safety and efficacy profile of DBS treatment. Here, we will summarize our efforts, using a chronically instrumented non-human primate (NHP) model of PD, to evaluate the motor and electrophysiological effects of novel DBS paradigms.

Methods: Three NHPs have been implanted unilaterally with a directional DBS lead targeting the subthalamic nucleus (STN) and rendered parkinsonian using intracarotid injections of the neurotoxin, MPTP. One was further instrumented with chronic recording arrays across the motor cortex and sensorimotor thalamic and pallidal sub-regions. DBS efficacy and physiological effects are evaluated using a randomized block design.

Results: Our preliminary data support the potential of CR DBS to improve parkinsonian motor signs, with therapeutic efficacy outlasting cessation of DBS by up to ten days. The study design presented will enable us to confirm and extend those findings, while exploring potentially mechanistic changes in neural activity across the cortico-striato-pallido-thalamo-cortical (CSPTC) circuit.

Conclusion: Although the effects of CR DBS are well described using computational models of the CSPTC circuit, there is limited data from animal models and humans to support the translational value of this or other novel DBS paradigms. The model established as part of this work will enable serial, longitudinal studies of the physiological and behavioral effects of these newer paradigms that hold promise for limiting the cognitive, affective, and sensorimotor side effects of DBS.

447. Correlation between Calcium Channel Imaging and Local Field Potential Power Increases in the Nucleus Accumbens in Mice prior to Approach to Food Reward

Bina Wasunga Kakusa (Stanford, CA); Hemmings Wu; Boris Heifets; Robert Malenka; Casey Halpern

Introduction: Non-compliant feeding behavior is one of the strongest contributors to the obesity epidemic, for which about 50% of patients exhibit binge-eating behavior. Local field potential (LFP) is an essential source of real-time, in vivo, neural information that may serve as a biomarker for pathological impulsivity. To gain a better biophysiological understanding of this potential biomarker, we record LFP signals and simultaneous in vivo calcium imaging (fiber photometry) in the nucleus accumbens (NAc) in a mouse model of binge-eating behavior.

Methods: AAV-hSyn-GCaMP-6f virus injection, followed by optetrode (one optic fiber surrounded by four platinum/iridium electrodes) implantation was performed in the left NAc in 6 mice (male C57-BL6, age 8-10 weeks). They were then put on a limited high-fat (HF) exposure protocol known to induce binge eating. NAc LFP and fiber photometry signals were recorded simultaneously during HF consumption.

Results: Analysis was performed on epoched trials zeroed at onset of HF-related activity, defined as approach behavior to the HF food source. Frequency-normalized power spectrograms demonstrated prominent 1-4Hz (delta-band) LFP activity in the 2 seconds prior to HF-related activity. The photometry signal ($\Delta F/F$) increased gradually starting, on

average, 2-seconds prior to HF-related activity, and peaking at 1-second after activity onset. Further, multiple regression analysis indicated that $\Delta F/F$ significant explained more of the variance in LFP-delta power activity as opposed to the remaining frequency bands ($R^2=.20$, $p < 0.0001$). Analysis replicated on randomly selected trial epochs outside of the HF-related periods lacked increased $\Delta F/F$ activity and showed decreased correlation of delta-band LFP and $\Delta F/F$.

Conclusion: NAc delta oscillation is highly associated with transients in the fiber photometry signals. This suggests that the NAc delta biomarker during binge-like behavior may result in NAc neuronal activation that could be used to guide closed-loop neuromodulation such as responsive neurostimulation.

448. Novel Inter-Trial Resting State Network Analysis can Reliably Predict Learning and Performance of a Cognitive Reaction Time Task

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Introduction: The network substrates of rapid learning and dynamic cognitive performance remain ill-defined. Current neurophysiological correlates primarily arise from task-dependent (intra-trial) behavioral epochs. Resting states such as inter-trial periods, display distributed and reproducible spontaneous activity. The relationship of these inter-trial resting states (ITRSs) to learning and subsequent cognitive performance is less known. Utilizing new techniques from graph theory and network science we have developed an approach to analyze short-time scale network metrics during ITRS epochs while subjects perform a simple temporal expectancy reaction time (RT) task. We hypothesize that salient network features could encode information regarding the ability to rapidly learn or dynamically perform this fundamental task.

Methods: We analyzed eighteen epilepsy patients who underwent stereotactic electroencephalography (sEEG). Behaviorally we defined over-trial learning by a negative linear correlation of RT over time and single-trial performance by respective RT. We performed dynamic network analysis during ITRS in the 500ms prior to the start of each trial. We analyzed high gamma (70-100Hz) and broad theta (3-12Hz) frequency dependent network strength (netStr) and nodal communicability (Qexp). We used linear regression and machine learning to create subject-specific classification of over-trial learning and single-trial performance.

Results: Across all subjects ($n=18$) we found that increasing ITRS HG netStr was specifically and strongly correlated with degree of over-trial learning ($r=0.82$, $R^2=0.67$, $p=3.3 \times 10^{-5}$; Theta netStr $r=0.0$, $R^2=0.0$, $p=0.9$). Dichotomously, strong prediction of dynamic single-trial performance was driven by ITRS theta band nodal Qexp (median AUC=0.71, $p=1.1 \times 10^{-4}$ vs. chance) outperforming HG netStr prediction (median AUC=0.58, difference $p=0.03$).

Conclusion: Surprisingly, across subjects we find that differential network metrics in the inter-trial resting state can strongly predict individual subject learning rate and dynamic single-trial performance. These findings may support the potential for one day utilizing a network brain-computer-interface (nBCI) for closed-loop control of a learning and dynamic cognitive prosthetic.

449 Neural Substrates of Audiovisual Speech Perception Measured with iEEG

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Introduction: Perceiving speech is one of our most important human abilities and uses information from both the visual and auditory modalities. We examined perceptual and neural responses to words in which the mouth movements of visual speech precede the auditory speech sounds ("mouth-leading") and to words in which auditory speech sounds precede perceptible mouth movements ("voice-leading").

Methods: Mouth-leading and voice-leading words were presented in audiovisual (AV) and auditory-only (A) formats to healthy controls ($n = 80$) and epilepsy patients ($n = 8$) implanted with intracranial electrodes. We measured the high-frequency broadband activity (75-150 Hz) in a window from 0 ms to 500 ms after auditory speech onset in 34 electrodes over the posterior superior temporal gyrus (pSTG).

Results: For the behavioral experiment only, auditory noise was added to increase the importance of visual speech. Comprehension performance was better for audiovisual than auditory-only words, reflecting the utility of the visual modality in understanding noisy speech. This improvement was significantly greater for mouth-leading words (15% improvement, from 2% to 17%) than for voice-leading words (8% improvement, from 10% to 18%; $p=10^{-9}$ from linear mixed-effects model). Electrodes placed on the pSTG responded strongly to all words. A weaker response was observed for audiovisual compared to auditory-only words, with a significantly greater decrease for mouth-leading words (29%; 129%A vs 100%AV) than voice-leading words (4%; 114%A vs 110% AV; $p=0.001$).

Conclusion: Our results suggest that multisensory integration in speech perception is strongly dependent on the speech content: we saw differences in both perception and neural responses between mouth-leading and voice-leading words. Our results are consistent with a predictive coding model in which the visual speech information available prior to auditory speech onset in mouth-leading words allows for more accurate recognition of these words with less computational burden, resulting in reduced responses in pSTG.

450. Magnetic Resonance guided Laser Interstitial Thermal Therapy (MRgLITT) vs Stereotactic Radiosurgery (SRS) for Medically Intractable Temporal Lobe Epilepsy (TLE) : A Systematic Review and Meta-Analysis of Seizure Outcomes and Complications

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Introduction: Magnetic Resonance guided Laser Interstitial Thermal Therapy (MRgLITT) and Stereotactic Radiosurgery (SRS) are two emerging minimally invasive procedures being increasingly employed for surgical intervention among cases of medically intractable Temporal Lobe Epilepsy (TLE). To date, there have been no comparative analyses of these two procedures. In the current study, we have made an effort to synthesize pooled data from existing studies to present a systematic review and meta-analysis of seizure and clinical outcomes of the two procedures among patients with TLE.

Methods: PICO (Population, Intervention, Comparator and Outcome) approach and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines were followed to perform an indirect meta-analysis of seizure and clinical outcomes between MRgLITT and SRS. Only studies reporting outcomes for patients with TLE were included in the current review.

Results: A total of 19 studies were included in the final analysis, giving a total of 415 TLE patients, of which 9 studies were on MRgLITT with a total of 250 patients (60%) while 10 studies were on SRS with a total of 165 patients (40%). We found that the overall seizure freedom rate was comparable between the two procedures, (MRgLITT 50%, 95% CI 44-56% vs SRS 42%, 95% CI 27-59%, $p=0.39$). Similarly, among cases with lesional pathologies only, the seizure freedom rate was found to be comparable between the two procedures (MRgLITT 62%, 95% CI 48-74% vs SRS 50%, 95% CI 37-64%, $p=0.23$). Compared to SRS, MRgLITT was found to be associated with lower complication (MRgLITT 20%, 95% CI 14-26% vs SRS 32%, 95% CI 20-46%, $p=0.06$) but similar reoperation (15%, 95% CI 9-22% vs 27%, 95% CI 12-46%, $p=0.31$) rates.

Conclusion: Our results show that LITT and SRS may have equivalent outcomes in terms of seizure freedom, complication rate and reoperations

452. Embolization of Middle Meningeal Artery for Chronic Subdural Hematomas: A Systematic Review and Meta-Analysis

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Introduction: Embolization of middle meningeal artery (MMA) has been proposed as a potential treatment for chronic subdural hematomas (cSDH) by cutting off the blood supply to the subdural membrane, preventing microhemorrhages, and enabling hematoma resorption. We sought to investigate its safety and efficacy in the treatment of recurrent and newly-diagnosed cSDHs.

Methods: A systematic review of the literature was performed searching multiple databases for reports on the treatment of cSDHs with embolization of MMA. Outcomes investigated included procedure-related complications, mortality, rate of hematoma recurrence, and rate of rescue surgery after embolization. The odds of recurrence after embolization were compared between recurrent and newly-diagnosed cSDHs.

Results: A total of 11 studies were included, involving 128 patients and 136 cSDHs. All patients had successful embolization of the frontal and parietal branches of the MMA. Mean age was 70 years (± 6.2 years) and 70% of patients (89) were males. Forty percent of patients (48) were taking antiplatelets or anticoagulants. Mean hematoma size was 19mm (± 1.8 mm). The rate of procedure-related complications was 1.4% (95% CI, 0.5% - 3.4%). There were no neurological complications or mortalities. Seventy-eight (57%) hematomas were treated upfront with MMA embolization and 58 (43%) were treated with embolization after one or more recurrences from drainage. The rate of recurrence was similar in both groups 1.2% and 3.4%, respectively (odds ratio of recurrence, 0.36; 95% CI 0.03 – 4.11, $p=0.41$) during a mean follow up of 5.1 months (± 2.5 months). The rate of rescue evacuation after embolization was 0.7% (95% CI, 0.002% - 1.4%).

Conclusion: Our systematic reviewed showed that treatment of cSDHs with embolization of the MMA is extremely safe

with low rates of morbidity and no mortalities. We also found that MMA embolization was effective not only for newly-diagnosed cSDH but also for recurrent cSDHs. A prospective, randomized study is warranted.

453. Tau Phenotyping of Chronic Traumatic Encephalopathy Recapitulates Aging-Related Processes

John Arena (Philadelphia, PA); Victoria Johnson; Edward Lee; Josephine Fullerton; John Trojanowski; William Stewart; Douglas Smith

Introduction: Traumatic brain injury (TBI) is recognized as a risk factor for neurodegenerative disease, including chronic traumatic encephalopathy (CTE), where accumulation of pathologic tau protein within neurons and astrocytes at the depths of cortical sulci has been described as a potentially distinguishing neuropathologic feature. However, it is unknown whether the tau species in CTE are distinct from other neurodegenerative diseases. Here we performed tau phenotyping and mapping in post-mortem cases of CTE for comparison with well-characterized pathologies, including Alzheimer's disease (AD), primary tauopathies and aging-related tau astrogliopathy (ARTAG).

Methods: From the Glasgow TBI Archive and the Penn Neurodegenerative Disease Brain Bank, cases were selected as: athletes with history of repetitive mild TBI and long-term survivors of single severe TBI with CTE pathology (n=8); uninjured controls with ARTAG (n=6); AD (n=2); and primary tauopathies (n=3). Immunohistochemistry was performed to determine tau phenotypes using antibodies to phosphoepitopes (PHF1, CP13, AT100, pS262), microtubule-binding repeat domains (3R, 4R), truncation (Tau-C3) and AD-conformation selective tau (GT-7, GT-38). Additionally, maps of neuronal and astroglial tau pathologies were generated to evaluate cortical distributions.

Results: TBI-associated astroglial pathology was comprised of 4R tau-positive thorn-shaped astrocytes concentrated at the depths of cortical sulci, identical in both morphology and immunoreactivity profile to those of ARTAG. In contrast, neurofibrillary tangles (NFTs) were comprised of both 3R and 4R tau, with post-translational modifications and conformations consistent with AD and aging controls. Interestingly, in contrast with current descriptions of CTE, our data show astrocytes but not NFTs preferentially concentrate towards the depths of sulci.

Conclusion: Here we demonstrate that neuronal and astroglial tau phenotypes in CTE are indistinguishable from AD and aging-associated pathologies. Additionally, the distinctive distribution of sulcal depth pathology in CTE appears primarily astroglial. These findings underscore the need for further characterization to determine whether CTE is a distinct neuropathological entity.

454 Impaired performance in smooth pursuit and anti-saccades tasks in patients after mild traumatic brain injury

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Introduction: Visual dysfunction is a common sequela following mild traumatic brain injury (mTBI). Impaired eye movements may not be easily detected on examination. Eye tracking tools have been increasingly utilised in recent years to detect these subtle changes in ocular motility. The purpose of this study was to assess the impact of mTBI on oculomotor movements using an eye tracking tool.

Methods: Patients with mTBI (n = 25) and healthy controls (n = 25) were recruited and assessed for oculomotor performance in clockwise smooth pursuit and horizontal anti-saccades tasks using an eye tracking tool. In three trials of smooth pursuit task, participants were instructed to trace a stimulus (red dot) as it moved in a clockwise direction. In the horizontal anti-saccades task, participants were asked to look in the opposite direction of the stimulus (red dot) with reference to a fixation cross.

Results: In the smooth pursuit task, mTBI patients made more eye position errors than healthy controls (Z-score_{mTBI} -0.37 ± 0.47 versus Z-score_{HC} 0.15 ± 0.76 , $p = 0.006$). The minimum bounding circle radius was larger in patients than healthy controls (16.1 ± 1.7 cm versus 15.1 ± 1.3 cm, $p = 0.025$). In the horizontal anti-saccades task, there were no differences in the number of directional errors and anti-saccades latency. However, the directional error latency in response time (0.30 ± 0.09 secs versus 0.21 ± 0.11 secs, $p = 0.005$) and correction time were longer in mTBI patients (0.28 ± 0.26 secs versus 0.15 ± 0.09 secs, $p = 0.032$).

Conclusion: Compared to healthy controls, patients with mTBI demonstrated impaired performance in smooth pursuit and longer directional error latency and correction time in executing horizontal anti-saccades. These abnormalities were detected with an eye tracking tool, which may have clinical applications in the future.

455. Expressions of Eotaxin-3, Interleukin-5 and Eosinophil-Derived Neurotoxin in Chronic Subdural Hematoma Fluids

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Introduction: Eosinophils induce inflammation by releasing cytokines and cytotoxic granule proteins. Infiltration of eosinophilic granulocytes occurs in the outer membrane of chronic subdural hematomas (CSDHs). Eosinophils play an important role in the growth of CSDHs. However, the manner in which eosinophils accumulate within CSDH fluid remains undetermined. In the current study, we assessed the expression of eosinophil chemoattractants in CSDH fluids according to the growth stage of the CSDHs and examined the correlation between the two.

Methods: CSDH fluids were obtained from 38 patients during trepanation surgery. Ecalectin, eotaxin-3, interleukin-5 (IL-5) and eosinophil-derived neurotoxin (EDN) concentrations were measured using ELISA kits. For use as controls, serum samples were collected from five healthy adults, and cerebrospinal fluid (CSF) samples were collected from five adults with unruptured aneurysms. The percentage of eosinophils (%eosinophil) in the CSDH fluids was calculated using Giemsa staining.

Results: The concentrations of ecalectin, eotaxin-3, IL-5 and EDN were nearly equivalent in the serum and CSF samples; however, their concentrations were high in the CSDH fluids. In particular, the ecalectin and EDN levels in the CSDH fluids were significantly higher than those in the serum and CSF. The levels of eotaxin-3, IL-5, EDN and %eosinophil were significantly higher in the laminar type of CSDH, while that of ecalectin was not. The correlations between eotaxin-3 and IL-5, IL-5 and EDN, and EDN and %eosinophil were statistically significant ($p < 0.01$).

Conclusion: Our data suggest that eotaxin-3 is a chemoattractant of eosinophils. IL-5 induces the activation of eosinophils following the degranulation of EDN into CSDH fluids. These factors may serve as novel therapeutic targets for managing CSDH.

456. Summary Analysis of Patients with Cortical Spreading Depolarizations (CSD) from CSD² Trial (CSD in Chronic Subdural Hematoma (cSDH) Patients after evacuation)

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Introduction: Most patients who undergo chronic subdural hematoma (cSDH) evacuation recover with a straightforward course. There is a subset of patients who do not improve or even worsen after evacuation. We hypothesize that worsening in some cases may be related to temporary brain dysfunction caused by cortical spreading depolarizations (CSD).

Methods: Prospective observational study of 40 patients who underwent cSDH evacuation. At the time of surgery, a 1x6 subdural electrode strip was placed on the cortex parallel to the drain. CSD was scored using standard criteria of propagating DC shift, with associated depression of high frequency electrocorticography (ECog) activity.

Results: Definite CSD occurred in 6/40 subjects (15%). There were no statistical differences in demographics between the populations, including age, gender, subdural characteristics, or pre-operative presentation. 4/6 subjects (67%) had resolution of their pre-operative symptoms. A clinical EEG was ordered in 2/6 subjects (33%), with no findings of seizures or epileptiform activity. One subject's new deficit was observed 40 hours following the appearance of the first CSD, after the electrode strip was removed. The other subject, with clinical deterioration, had fluent speech immediately post-operatively but had documented aphasia 28 hours later, as reported by nursing. This correlated precisely with the first spreading depolarization seen on the patient's electrode recording. The patient continued to have both aphasia and the presence of CSD until the removal of the strip electrode.

Conclusion: This is the first observation of CSD occurring after cSDH evacuation, at a rate of 15%, in our series. One subject demonstrated delayed clinical deterioration after the electrode had been removed, and another subject demonstrated a time-locked clinical deterioration that correlated precisely with their first CSD. This data supports our hypothesis that CSD may be responsible for some cases of protracted recovery. This may represent a new therapeutic target in these patients.

457. Accuracy of a wearable mixed-reality holographic computer for guiding transcranial puncture for the treatment of spontaneous intracerebral hemorrhage: a prospective, randomized, single-center study

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Introduction: Freehand transcranial puncture and drainage based on anatomical surface landmarks is one of the common operations for the treatment of spontaneous intracerebral hemorrhage (SICH). However, it often faces the problem that the target is deep and the catheter positioning is experience-dependent. The goal of this study was to explore the accuracy of using a wearable mixed-reality holographic computer to guide transcranial puncture for the treatment of SICH.

Methods: 41 SICH patients who needed transcranial puncture were enrolled into this prospective, randomized, single-center study. 20 patients were randomized into the hologram-guided transcranial puncture group (group A), and 21 into the freehand group (group B). Pre- and postoperative CT scanning were performed routinely for every patient. Surgical plan including model reconstruction and trajectory calculation for group A was completed based on preoperative CT. By wearing a Microsoft HoloLens, the neurosurgeon was able to visualize the surgical plan and perform transcranial puncture by keeping aligned with the holographic trajectory. The accuracy of the hologram-guided technique were evaluated by comparing the operation time, number of passes, and target deviation between the 2 groups.

Results: Hologram visualization were achieved in all the cases of group A. The mean operation time of group A was 37.44 ± 12.53 mins, compared with 54.38 ± 15.35 mins in group B ($p < 0.01$). The average number of passes was 1.12 ± 0.47 in group A, compared with 2.52 ± 0.66 in group B ($p < 0.01$). The mean target deviation was 5.47 ± 2.08 mm in group A and 13.14 ± 0.38 mm in group B ($p < 0.01$).

Conclusion: This study demonstrates the use of a wearable mixed-reality holographic computer to successfully perform hologram-guided transcranial puncture for the treatment of SICH. The authors also provide preliminary confirmation of the accuracy of this hologram-guided technique.

458. Neurosurgical Outcomes for Traumatic Brain Injury Patients in Uganda

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Introduction: Neurosurgical outcomes studies in low- and middle-income countries (LMICs) are limited despite global health efforts to increase availability of neurosurgical services. This study evaluates long-term outcomes of traumatic brain injury (TBI) patients presenting to Mulago National Referral Hospital (MNRH) neurosurgery ward in Uganda.

Methods: A prospective database of 1274 TBI patients presenting to MNRH from 2014-2015 was reviewed for in-patient clinical data. Patients available for follow-up were reached through phone survey in the participant's language.

Results: Of 1274 adult patients, 302 (23.7%) died in-patient with higher mortality rates amongst patients with increased age and lower admission Glasgow Coma Scale (GCS) score. These patients were also less likely to have received surgical treatment. Of the 972 discharged patients, 591 (61%) patients were available at follow-up, of whom 53 (9%) were deceased. Median survival was 18.6 months and 5 months for patients alive and deceased at follow-up, respectively. Deceased patients were more likely to be older, have needed a tracheostomy in-patient, have had lower admission and discharge GCS, and had a longer median length of stay. Patient age (HR: 1.03, 95% CI: 1.009-1.05), in-patient tracheostomy (HR: 4.38; 1.05-16.7) and discharge GCS (HR: 0.71, 0.53-0.94) remained significant predictors of survival time in multivariate analyses. There were no differences in outcomes based on surgical interventions. Only 63.8% of the surviving patients followed-up with a health care provider after their initial hospitalization. Patients with moderate to severe disability were more likely to seek follow-up care compared to those in recovery ($p < .0001$).

Conclusion: Age, tracheostomy placement, and discharge GCS were significant predictors of survival, whereas surgical intervention was not. Further research efforts are needed to track patient outcomes and validate the beneficial impact of global health efforts in neurosurgery. This study establishes a baseline for ongoing tracking of head trauma outcomes in Uganda.

459. Mortality Prediction for Civilian Cerebral Gunshot Wounds: A Decision-Tree Model Based on a Single Trauma Center

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Introduction: Gunshot wound (GSW) remains one of the most lethal forms of head trauma. The lack of clear guidelines for managing civilian gunshot wounds complicates the surgical decision making process. We present a clinically applicable decision-tree model based on 15-year data from our level 1 trauma center.

Methods: We retrospectively reviewed 95 consecutive patients who presented with cerebral GSWs between 2003 and 2018. Patients were divided into two cohorts based on survival status. Clinical information captured in our trauma database, EMR, and relevant imaging scans was reviewed for each patient. A decision-tree model was constructed based on variables showing statistically significant differences ($P=0.05$) between two groups on chi-square test.

Results: After excluding patients who died at arrival and/or did not undergo brain imaging, 54 patients with radiologically confirmed intracranial injury were included. Survivors (53.7%) and non-survivors (46.3%) had similar average age and gender distribution. Non-survivors were significantly more likely to have self-inflicted ($P=0.049$) and perforating (entry and exit wound), as opposed to penetrating (entry wound only), injuries ($P=0.02$). Bi-hemispheric and posterior fossa involvement, cerebral herniation, and intraventricular hemorrhage (IVH) were the radiologic features more commonly present in patients who expired. Based on the decision-tree, in patients with Glasgow Coma Scale (GCS) >8 , penetrating injury limited to a single hemisphere predicted survival. When initial GCS was 8 or lower, all patients with absent pupillary response failed to survive. Among patients with pupillary response, lack of 1) posterior fossa involvement, 2) cerebral herniation, 3) bi-hemispheric injury, and 4) IVH, was associated with survival.

Conclusion: We present a decision-tree model to help neurosurgeons identify surgical candidates with favorable prognosis based on readily available clinical and radiological information in a time-sensitive setting. Further validation of the model in a large patient setting is recommended.

460. Efficacy of Seizure Prophylaxis Following Complicated Mild Traumatic Brain Injury: A Retrospective Pilot Study

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Introduction: Complicated mild TBI (mTBI) is defined as GCS 13-15 with a head CT demonstrating a traumatic intracranial lesion (hemorrhage/contusion/edema) or depressed skull fracture. Studies investigating the necessity/efficacy of seizure prophylaxis following complicated mTBI to prevent post-traumatic seizures (PTS) are limited and guidelines for antiepileptic drug (AED) administration in these patients are lacking. We examined PTS incidence following complicated mTBI in patients that either received, or did not receive, seizure prophylaxis.

Methods: A Level 1 trauma center database was retrospectively reviewed to identify consecutive subjects aged 15+ years that presented with complicated mTBI between Apr-Dec 2016. Exclusion criteria included a history of seizures; prior or penetrating TBI; neurological decline to GCS <13 ; need for invasive neurosurgical intervention. Demographic data was collected and prophylactic AED administration information was obtained, including AED type/dose/duration. Medical records were queried to determine the incidence of early/late PTS from in-hospital events and on follow-up. Data was analyzed using unpaired Student's t, Fisher's exact, or Chi square tests, as appropriate.

Results: 86 consecutive complicated mTBI patients (mean age 58.7 $\pm$ 2.3y, 62% male, mean GCS 14.8 $\pm$ 0.1) were included in our cohort. 79.1% of patients received prophylactic AEDs, median AED duration was 8 days (range 1-98). There were no in-hospital PTS (0/86, 0%). For patients with 7+ days follow-up ($n=62$), the incidence of early PTS was 1.9% (1/52) in the AED group and 10.0% (1/10) in the no AED group ($P=0.30$). There were 3 late PTS in both the AED/no AED groups (4.4% versus 16.7%) ($P=0.10$). Overall PTS incidence was 8.1% (7/86).

Conclusion: No patients in our cohort had an immediate PTS during their initial hospital visit. The early PTS rate was low (3.2%), but there was a non-trivial incidence of late PTS (8.1%). The incidence of both early/late PTS trended lower in patients that received prophylactic AEDs immediately after injury.

461. Cerebral Blood Flow Augmentation Using a Novel Intracranial Pulsating Balloon Pump in a Swine Model of Elevated ICP

Omer Doron, MD (Holon, Israel)

Introduction: Augmenting brain perfusion or reducing intracranial pressure (ICP) dose is the end target of many therapies in the neuro-critical care unit. Many present therapies rely on aggressive systemic interventions that may lead to untoward effects. Previous studies have used a cardiac-gated intracranial balloon pump (ICBP) to model hydrocephalus or to flatten the ICP waveform. We sought to optimize ICBP activation parameters to improve cerebral physiological parameters in a swine model of raised ICP.

Methods: We developed an ECG-gated intracranial balloon pump in which volume, timing, and duty cycle of balloon inflation could be altered. We studied the ICBP in a swine model of elevated ICP attained by continuous intracranial fluid infusion with continuous monitoring of systemic and cerebral physiological parameters. We defined two specific protocols of ICBP activation.

Results: We studied 11 swine, three of which were studied to define the optimal timing, volume, and duty-cycle of balloon inflation. Eight swine were studied with two defined protocols at baseline and with ICP gradually raised to a mean of 30.5 mmHg. ICBP activation caused a consistent modification of the ICP waveform. Balloon activation Protocol A led to a consistent elevation in CBF (8% to 25% above baseline, $p < 0.00001$). A second protocol (Protocol B) resulted in a modest reduction of ICP over time (8% to 11%, $p < 0.0001$) at all ICP levels. Neither protocols significantly affected systemic physiological parameters.

Conclusion: Our preliminary results indicate that optimized protocols of ICBP activation may have beneficial effects on cerebral physiological parameters, with minimal effect on systemic parameters. Further studies are warranted to explore whether ICBP protocols may be of clinical benefit in patients with brain injuries with increased ICP.

462. Leukemia Inhibitory Factor in Mouse Model for Pediatric Traumatic Brain Injury

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Introduction: Traumatic brain injuries (TBI) affect 1.7 million patients each year. Most cases of pediatric TBI are diffuse, closed-head injuries (CHI), resulting in cognitive and behavioral problems. Previously findings from our lab found that mice haplodeficient in leukemia inhibitory factor (LIF) sustain greater damage after CHI. We hypothesize that intranasally administered LIF will reduce brain injury when provided after a CHI.

Methods: Juvenile wild-type CD1 mice were administered blunt, closed-head injuries to the parietal lobe. There were three groups (sham, vehicle, and experimental). Experimental and vehicle mice were administered intranasal LIF and water, respectively, starting 4 hours after the injury followed by 6 subsequent intranasal administrations at 12 hour intervals. Sham mice underwent surgery and were sutured without administering a closed-head injury. Behavior outcomes were determined with the modified neurological severity score (mNSS), average time spent traversing an inclined beam, and mean hang time in the four-limb wire test. Western blots and immunofluorescence were performed for Caspase 6 cleaved tubulin, GFAP, Iba-1 and MBP.

Results: There was a statistically significant difference in mNSS between groups as determined by the nonparametric Kruskal-Wallis test ($H(2)=8.70$, $p < 0.05$), with the vehicle group demonstrating the highest scores. There was a trend towards reduced time on the inclined beam for the experimental group. There was no statistically significant difference between groups by average hang time in the four-limb wire test. Axonal damage, as assessed by caspase 6 cleaved tubulin, appeared diminished and there was a trend for reduced white matter astrogliosis in the LIF-treated group, but no change in the microglial response compared to intranasal vehicle treated mice.

Conclusion: These data demonstrate that intranasal LIF treatment is viable as a therapeutic, as it has the potential to preserve axonal conductance and abate glial responses as manifested by improved behavioral outcomes after pediatric traumatic brain injury.

463. The matrix Gla protein (MGP) rs1800801 is associated with first year recurrence of ischemic stroke in Caucasians

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Introduction: Recurrent ischemic stroke is associated with increased morbidity and mortality. The matrix gamma-carboxyglutamic acid Gla protein (MGP) is an extracellular matrix protein involved in the inhibition of vascular calcification. The MGP rs1800801 single nucleotide polymorphism (SNP) specifically is associated with recurrent ischemic stroke. Here, we explored the relationship between this SNP and recurrence of ischemic stroke within one year in a Northeastern Pennsylvania cohort.

Methods: We retrospectively reviewed a cohort of Caucasian acute ischemic stroke patients admitted between 10/2009 and 12/2016 who enrolled in a system-wide exome sequencing program at a large healthcare system in Northeastern Pennsylvania. Patients admitted in 2016 were assessed for recurrent strokes until 12/2017. We then compared the rs1800801 SNP in patients with recurrent stroke within one year against those without recurrent stroke.

Results: 1,068 patients had ischemic stroke and exome sequencing completed, deeming them eligible for inclusion. 79 (7.4%) patients had recurrent ischemic events. Multivariable analysis suggested hypercoagulability (OR = 3.563, 95% CI 1.504 – 8.443, $p = 0.004$), prior stroke (OR 9.694, 95% CI 5.793 – 16.224, $p \leq 0.001$), and the AA genotype of SNP rs1800801 (OR = 2.408, 95% CI 1.079 – 4.389, $p = 0.004$) were independently associated with recurrent stroke within one year. Family history of stroke shows a positive trend towards recurrent stroke (OR = 1.698, 95% CI 0.988 – 2.916, $p = 0.055$).

Conclusion: The AA genotype of the rs1800801 SNP is independently associated with recurrent ischemic stroke within one year among Northeastern Pennsylvania Caucasians. Although risk of recurrence is still undetermined in subgroups of Caucasians, these findings may contribute to the development of preventative measures for patients with high risk genetic profile for recurrent ischemic stroke.

464. Comparison of Readmission to Index vs Non-index Hospitals after Mechanical Thrombectomy in Stroke Patients

Kristina Shkirkova (Los Angeles, CA); Michelle Connor; Krista Lamorie-Foote; Arati Patel; Qinghai Liu; Li Ding; Nerses Sanossain; Frank Attenello; William Mack

Introduction: Stroke systems of care typically employ a spoke-and-hub model, with few centers performing mechanical thrombectomy (MT) compared to a large number of stroke-receiving centers. This system design offers high-level, centralized treatment to a large number of patients, and relies on suitable postoperative care for at local/ regional hospitals.

Methods: This study leveraged a population-based, national sample of stroke patients undergoing MT from the National Readmissions Database from 2010 to 2014. Descriptive and dichotomized analyses were performed to determine patient and hospital level factors that influenced 90-day readmissions to index and non-index hospitals. Regression models were used to assess for differences in mortality, complications, subsequent readmissions, and failure to rescue between patients readmitted to index and non-index hospitals.

Results: During the study period, 2111 stroke patients were treated with MT, of whom 534 (25.3%) were readmitted within 90 days. The most frequent reasons for readmission were: septicemia (5.93%), atrial fibrillation (4.78%), and cerebral artery occlusion with infarct (4.78%). Among readmitted patients, 387 (74%) were readmitted to index hospital and 136 (26%) to non-index hospital. On multivariable logistic regression analysis, non-index hospital readmission was not independently associated with mortality ($p=0.22$), major complications ($p=0.07$), neurological complications ($p=0.38$), second readmission ($p=0.82$), or failure to rescue ($p=0.5$).

Conclusion: Approximately one-fourth of stroke patients treated with mechanical thrombectomy were readmitted within 90 days, one quarter of whom were readmitted to non-index hospitals. Readmission to non-index hospital was not associated with mortality or increased complication rates. In a spoke-and-hub treatment model it is important that follow up care for a specialized procedure can be performed effectively at a vast number of non-index hospitals that cover a large geographic area.

465. Treatment of Cerebral Aneurysms in the Post-ISAT Era: Trends and Outcomes

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Introduction: Following the ISUIA and ISAT studies, the paradigm for treatment of cerebral aneurysms shifted from open surgical clipping to endovascular embolization as primary therapy in many cases. While this trend has been widely acknowledged, outcome data and large-scale treatment patterns have not been reported in recent years.

Methods: The National Inpatient Sample from 2004-2014 was reviewed. Aneurysmal Subarachnoid hemorrhage (aSAH) and unruptured aneurysm (UA) discharges were identified along with treatment given, surgical clipping or endovascular repair. Time trend plots were created. Following Shapiro-Wilks normality confirmation, linear and logistic regression estimated significant yearly changes in treatments. $P \leq 0.05$ considered significant (SAS 9.4).

Results: A total of 397,540 SAH and 387,353 UA discharges were reviewed. There was a significant yearly increase in SAH (+732, $p=0.014$) and UA (+2550, $p<0.0001$) discharges (2004 vs. 2014; SAH 33423 vs 40000; unruptured 21711 vs 44575). For aSAH treatment, yearly discharges after clipping decreased (-287, $p=0.0001$) and increased for endovascular treatment (+366, $p=0.0005$) (2004 vs. 2014; aSAH-clipping 6854 vs 3435; aSAH-endovascular 4083 vs 7740). For treated UA, yearly discharges for clipping remained stable and increased for endovascular therapy (+615, $p<0.0001$) (2004 vs. 2014; UA-clipping 3672 vs 3745; UA-endovascular 4083 vs 9705). Over time, inpatient mortality decreased for both clipped ($p<0.0001$) and endovascularly treated ($p<0.0001$) aSAH (2004 vs. 2014 mortality rates; aSAH-clipped 13% vs 11.7%; SAH-endovascular 15.8% vs. 12.7%). Mortality rates for clipped UA decreased over time ($p<0.0001$) and did not change for endovascular treated UA (2004 vs. 2014 mortality rates; UA-clipped 1.57% vs 0.40%; UA-endovascular 0.59% vs. 0.52%). Length of stay decreased for UA and not ruptured aneurysms. **Conclusion:** Patients with ruptured and unruptured aneurysms are increasingly treated with endovascular therapy over clipping. Mortality rates of ruptured aneurysms is improving regardless of treatment; whereas, mortality in unruptured aneurysms is only improving for surgical clipping.

466. Are Nationwide Inpatient Sample database studies for Cerebral Aneurysm Over-Rated? Critical Analysis and Systematic Review

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Introduction: There has been a surge in the number of Nationwide Inpatient Sample (NIS) database studies. These studies have attracted publication in high impact journals. There is a discrepancy in the outcome endpoints of these studies in relation to the actual disease pathology. Objective of our study was to critically assess the viability of these studies in relation to Cerebral Aneurysms and provide relative reliability and extrapolation to neurosurgical patient population.

Methods: We conducted a literature search from Jan 1995 to December 2017 using a standard PRISM criteria and databases including Pubmed, Google Scholar, EMBASE, and Cochrane. After screening, thirty-one studies were selected for critical analysis. Critical appraisal chart was formulated using modification of RECORD, STROBE and JAMA-Surgery Checklist.

Results: Aneurysmal sub-arachnoid hemorrhage outcomes have been reported and compared across different treatment groups without controlling for WFNS/Fisher Grade, vasospasm, IVH, aneurysm location/size/morphology in all the studies reporting 'outcome'. Ultra-early interventional studies are misleading in the setting of aneurysmal rupture which don't control for transfer status (only available for 2 years in NIS database). External validation points for assessing the outcomes cannot compare to what the model of standardized randomized or prospective studies have provided so far. Missing data analysis is a statistical tool which again represents extreme heterogeneity in the data analysis for its valid extrapolation to the neurosurgical population. 74 % of the studies were published in high impact factor neurosurgery journals (Impact Factor >3). The mean lag between the year of publication and the years studied was 7.5 years (90 months).

Conclusion: NIS database studies looking at Cerebral Aneurysms typically lag behind 7.5 years. Majority of the studies were published in top two neurosurgical journals. Lack of significant external validation and significant heterogeneity in the missing data analysis raises serious questions in universal extrapolation of these studies.

467. Magnetic Resonance Vessel Wall Imaging in Human Intracranial Aneurysms: A Histological Analysis

Joseph Scott Hudson (Iowa City, IA); Mario Zanaty, MD; Daichi Nakagawa, MD; David Kung, MD; Pascal Jabbour, MD; Edgar Samaniego, MD, MS; David Hasan, MD

Introduction: The clinical significance of magnetic resonance vessel wall enhancement in intracranial aneurysms (IA) remains ill defined. In this report, we describe the histological analysis of resected human IAs which underwent MR-VWI.

Methods: Consecutive IA patients undergoing microsurgical clipping were included. Patients received a 3T MRI T1 black blood sequence (Siemens Stryka, Munich, Germany) scan preoperatively. Three independent neuroradiologists reviewed the films. IAs were classified into an avidly enhancing category or no/mild enhancement category. IA wall tissue was harvested during microsurgical clipping. Tissue was fixed in paraffin and stained with hematoxylin/eosin and elastochrome for histological analysis. Immunohistochemical quantification of infiltrating macrophages was performed as previously described by Hasan et al. (2012, Stroke).

Results: 5 patients were classified as Avidly Enhancing (AE), whereas 5 patients were classified as "No or Mild Enhancement" (NME). Measurement of wall thickness from the operatively resected IA tissue revealed AE IA tissue had a higher average thickness than NME IA tissue ($412.0 \pm 78.6 \mu\text{m}$ vs $218.0 \pm 67.6 \mu\text{m}$, $P=0.003$). Semi-quantitative analysis for IA wall macrophage infiltration revealed a higher average level of infiltration within the resected AE IA tissue when compared with NME IA tissue (2.6 ± 0.5 vs 1.4 ± 0.5 , $P=0.048$). Microscopic inspection of the histologically prepared IA tissue revealed NME IA tissue to be relatively hypocellular, whereas AE IA tissue was hypercellular. Both groups of resected IA tissue were deficient in elastin. Intra-operatively, AE IAs were thick and yellow walled while NME IAs were thin walled and transparent.

Conclusion: Prior studies have associated macrophage infiltration and inflammatory degeneration with aneurysm rupture, yet it remains unclear whether thick enhancing (inflamed) walls or thin (acellular) walls are more prone to rupture. Future studies should prospectively investigate whether the presence or absence of IA-wall enhancement is associated with an increased risk of IA rupture.

468. Microglia Activation in a Mouse Model of Chronic Cerebral Hypoperfusion

Michelle Connor (Los Angeles, CA); Kristina Shkirkova; Krista Lamorie-Foote; Arati Patel; Qinghai Liu; William Mack

Introduction: Chronic cerebral hypoperfusion (CCH) is a known mediator of vascular dementia and small vessel ischemic disease. Murine bilateral carotid artery stenosis (BCAS), an experimental model of CCH, results in blood-brain barrier breakdown, inflammation, oxidative stress, white matter injury, and behavioral deficits. The mechanism by which these changes occur, however, has yet to be established. The aim of this study was to examine microglia activation in response to CCH, as a potential mechanism for the CNS damage seen in this model.

Methods: Mice underwent either BCAS (n=9) or sham (n=9) surgery. Mice were anesthetized, common carotid arteries were exposed through a midline cervical incision, and microcoils were placed around each carotid artery. Sham-operated mice underwent the same procedure, but without placement of microcoils. After 30 days, mice were sacrificed. Reactive microglia were identified by immunohistochemical staining for Iba-1. Under resting conditions, microglia are ramified with small cell bodies and extensive branching processes. When activated, microglia adopt an amoeboid morphology characterized by an enlarged cell body and thickened, retracted processes. The ratio of cell body size to dendritic process size was quantified to evaluate for these morphological changes, with higher ratios indicating a more amoeboid, and thus activated, morphology.

Results: Reactive microglia cell count [$p<0.05$] and microglial cell body size to dendritic process size ratio [$p<0.05$] were significantly greater in the corpus callosum of BCAS mice when compared to sham controls.

Conclusion: Microglia become activated in the corpus callosum following CCH. This inflammatory response likely contributes to the white matter damage and behavioral deficits evident in this model. These findings suggest microglia and inflammatory microvascular failure as important targets for further mechanistic study in the pathophysiology of white matter ischemic injury.

469. Predictive Factors of Incomplete Aneurysm Occlusion after Endovascular Treatment with the Pipeline Embolization Device

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Introduction: The Pipeline Embolization Device (PED) is a routine choice for the endovascular treatment of select intracranial aneurysms. Its success is based on the high rates of aneurysm occlusion, followed by practically non-existent relapse risk if occlusion occurs. Therefore, identification of patient factors predictive of incomplete occlusion on last angiographic follow-up is critical to its success.

Methods: A multi-center retrospective cohort analysis was conducted on consecutive patients treated with PED at 3 academic institutions in the United States. Patients with angiographic follow-up assessing the degree of aneurysm occlusion were selected to identify the factors associated with incomplete occlusion.

Results: Among all 3 participating institutions we identified a total of 523 PED placement procedures. Three hundred and ninety-five of these (75.5%) had radiographic follow-up and were included in this analysis (age median 58 years; female-to-male ratio 4.4:1). Complete occlusion (Raymond-Roy class I) was noted in 68.6% of cases, while incomplete occlusion (Raymond-Roy class II or III) at last follow-up was identified in 31.4% after a median of 6 months. After accounting for factor collinearity and confounding, multivariate analysis identified older age (≥ 70 years; OR=3.07, 95% CI 1.77-5.32, $P<0.001$), higher maximal diameter (≥ 15 mm; OR=3.33, CI 1.65-6.71, $P=0.001$) and fusiform morphology (OR=3.04, CI 1.56-7.42, $P=0.002$) to be independently associated with higher rates of incomplete occlusion on last follow-up.

Conclusion: In this study we provide validation of previous findings that age, aneurysm diameter and fusiform morphology are associated with incomplete aneurysm occlusion after PED placement. Such predictive factors can be utilized to guide individualized treatment selection and counseling in cerebrovascular neurosurgical patients. Furthermore, these results provide a clinical background for research on the biologic factors affecting endothelialization of the PED.

470. Stereotactic Laser Ablation for Brain Tumors: Lessons Learned from 240 Cases Over the Past Decade

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Introduction: Stereotactic laser ablation (SLA) is a novel, minimally invasive alternative to surgical resection for intracranial lesions, especially in patients with poor functional status and tumors close in proximity to eloquent structures. However, this technique is not uniformly optimal for all patients. As one of the first institutions to adopt this technology, we present a comprehensive case series detailing the evolution of patient selection, surgical trends, and lessons learned over the past decade in the largest patient cohort on SLA treatment in brain tumors to date.

Methods: Retrospective review was performed on 240 patients with various brain tumors treated with SLA. Extensive data on patient demographics, surgical and tumor characteristics, temporary (resolved within 6 months) and permanent complications, and follow-up data were collected. Consecutive patients were categorized into two time periods (2011-2014, 102 patients; 2015-2018, 138 patients), and statistical analysis was performed for both time periods.

Results: Initially, SLA was predominantly utilized for upfront and recurrent gliomas (76.64%); recently, however, there has been a marked increase in SLA usage for metastases and radiation necrosis following radiosurgery failure (25 combined cases --> 58 combined cases; 23.4% --> 42.65%). Additionally, there is a trend against SLA usage for large tumors (diameter > 4cm, 15.65% --> 9.57%) due to poorer outcomes associated with these lesions. Surgically, advances in SLA technology led to shorter operation times (6.25 hours --> 3.6 hours) and better separation between tracts and the hyperthermic field, ultimately resulting in fewer temporary (39.17% --> 30.1%) and permanent (13.3% --> 7.5%) postoperative deficits. Lastly, better patient selection resulted in a lower mortality rate (4.17% --> 0.83%).

Conclusion: Our study shows that the evolution of SLA usage at a single institution led to better patient selection and maturation of surgical planning, ultimately resulting in fewer complications and better outcomes.

471. Vorinostat for Hemangioblastomas in Germline Missense von Hippel-Lindau Disease: A Phase 0 Clinical Trial

Panagiotis Mastorakos, MD PhD (Bethesda, MD); Jacqueline Boyle; Konstantinos Floros; Russell Lonser; Prashant Chittiboina

Introduction: Von Hippel-Lindau disease (VHL) is a tumor suppressor syndrome with a propensity for multiple central nervous system (CNS) hemangioblastomas. Current standard of care is surgical resection which is linked to significant morbidity and mortality. Normally, VHL protein (pVHL) marks hypoxia inducible factor 1a (HIF1a) for degradation by E3 ligase activity. In VHL disease, mutations lead to decreased pVHL activity, elevated HIF1a signaling, and tumorigenesis. With germline missense mutations, mutated pVHL retains activity, but is rapidly degraded via chaperonin (Hsp90) binding. Histone deacetylase inhibitors (HDACIs), such as Vorinostat, can restore pVHL levels by decreasing the affinity of Hsp90 to misfolded pVHL. In pre-clinical models, HDACI-mediated pVHL stabilization can significantly attenuate tumor growth. We aimed to determine whether vorinostat can safely reduce degradation of mutant VHL protein in VHL patients with germline missense mutations.

Methods: We enrolled seven germline missense VHL patients with symptomatic CNS hemangioblastomas. The subjects received 400 mg of Vorinostat by mouth daily for seven days prior to surgery and subsequently underwent surgical resection. Tissue samples were analysed using qPCR, Western blot analysis and immunohistochemistry.

Results: Vorinostat was well tolerated by all patients. pVHL levels in resected hemangioblastomas were significantly higher following Vorinostat administration compared to control specimens with no change in the mRNA levels.

Conclusion: Vorinostat is well tolerated by patients with symptomatic CNS hemangioblastomas in the setting of germline missense VHL disease and results in stabilization of mutated pVHL protein. These results suggest that Vorinostat may be a promising treatment for patients with a missense germline mutation and constitute an example of how deep understanding of the pathogenesis of a disease can lead to development of personalized treatments.

472. Sarcosine promotes trafficking of dendritic cells to draining lymph nodes and improves efficacy of a vaccine strategy for the treatment of brain tumors via CX3CL1

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Introduction: We have previously demonstrated that increasing dendritic cell (DC) migration after DC vaccination improves survival in patient with glioblastoma (GBM). In this study, we hypothesized that a novel metabolite, sarcosine, would increase DC migration and outcomes in the treatment of brain tumors.

Methods: Human and murine dendritic cells were cultured from peripheral blood mononuclear cells (PBMCs) as previously described. Cells were loaded with sarcosine by adding sarcosine to the media and electroporating cells. Migration was measured in vitro, in vivo and murine tumor models were utilized to test efficacy of sarcosine loaded and control DC vaccines. The mechanism of sarcosine on migration was tested using PCR and blocking antibodies.

Results: Human and murine DCs loaded with sarcosine did not have changes in cell phenotype, cell cycle or cell growth. Both human and murine DCs demonstrated significantly increased migration in vitro when loaded with sarcosine. In vivo, sarcosine loaded DCs had significantly increased homing to the local lymph nodes and to the spleen within 48 hours of vaccination compared to control DCs. Intracranial and flank tumor bearing animals had improved tumor control and survival when treated with sarcosine loaded DCs compared to control DCs. PCR analysis revealed an upregulation of CX3CL1 in sarcosine loaded cells. When human or murine DCs loaded with sarcosine were exposed to CX3CL1 blocking antibody, their increased migration was abrogated.

Conclusion: Sarcosine increases the migration of DCs via the CX3CL1 pathway. This increase in DC migration also results in a more robust anti-tumor immune response and better tumor control in a murine brain tumor model. Sarcosine is non toxic to murine and human DCs. Further studies in human subjects are necessary to determine the utility of this treatment platform.

473. Receptor discordance in breast cancer brain metastases: incidence and survival outcomes**Brainlab Neurosurgery Award**

Alexander Frans Christiaan Hulsbergen (Utrecht, Netherlands); An Claes, MD, PhD; Vasileios Kavouridis, MD; Claudine Nogarede; Ali Ansaripour, BS; Nancy Lin, MD; Timothy Smith; Joost Verhoeff, MD, PhD; Marike Broekman

Introduction: Brain metastases (BMs) in breast cancer can differ from the primary tumor in terms of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression. The aim of this study was to describe the frequency of this receptor discordance and assess its impact on survival outcomes.

Methods: An international multi-center cohort of patients who underwent neurosurgical resection for breast cancer BMs was created. Data were retrospectively collected on ER, PR and HER2 expression in primary tumors and BMs. Multivariable Cox Proportional Hazards Model was used to assess effects of discordance on survival outcomes.

Results: Across four institutions, 167 patients were included, and 149 (89.2%) had data available on all receptors. Discordance in any receptor occurred in 49 (32.9%) of patients. Receptor-specific discordance rates were 27/165 (16.3%) for ER, 33/159 (20.8) for PR, and 16/156 (10.3%) for HER2. Discordance, in particular loss of receptor expression, was highly correlated with worse overall survival after adjusting for patient age and receptor profile of the BM (HR = 2.45; CI = 1.53 – 3.39; p = 0.0002).

Conclusion: Breast cancer BMs frequently display a different ER, PR and HER2 expression when compared to their primary tumors, and this discordance is prognostically unfavorable. Our results highlight a benefit of obtaining BM tissue in this patient population.

474. Radiographic Trends in Cerebral Metastases Treated with Gamma Knife Radiosurgery: Indicators for Early Intervention for Post-Gamma Knife Failures**Leksell Radiosurgery Award**

Arthur Carminucci, MD (Newark, NJ); Sabrina Zeller, BS; Shabbar Danish, MD

Introduction: Recurrence following Gamma Knife (GK) radiosurgery treatment of cerebral metastases is not uncommon. Recurrence can represent recurrent tumor or radiation necrosis. The radiographic response to GK treatment is variable with some tumors remaining stable, some decreasing in size, some increasing in size, while some may show a combination of all three. For recurrences, which demonstrate progression on MRI imaging, the question to intervene with additional surgical or radiation therapy and the timing of such intervention is debatable. In this study, we retrospectively reviewed surveillance MRIs of post-GK cerebral metastases to determine if radiographic trends are a predictor of infield progression.

Methods: Retrospective review of cerebral metastases treated with GK radiosurgery with at least 2 consecutive post-GK MRI scans.

Results: 297 cerebral metastases were treated with GK radiosurgery. Median length of follow-up was 21 months (3-105.2). Local control rate 82.5%. Sixty-nine metastasis demonstrated radiographic progression on 1 follow-up MRI scan. Of those 52 (75.4%) demonstrated continued progression and/or need for surgical intervention on follow-up imaging, while 17 (27.9%) stabilized or regressed. For post-GK metastases demonstrating progression on two consecutive MRI scans, 87.8% (n=36) of lesions continued to progress; whereas, only 12.2% (n=5) demonstrated stabilization or regression. 100% (n=28) of metastasis with radiographic progression on 3+ consecutive MRIs went on to need further intervention.

Conclusion: Approximately, one third of post-gk metastasis demonstrating progression on the first surveillance MRI will stabilize or regress. However once radiographic progression is demonstrated on 2 consecutive scans, 87.8% will ultimately progress; suggesting need for further intervention at this time point. Early intervention before infield recurrence increases in size or patients require high-dose steroids maybe beneficial.

475. Human Adipose-derived Mesenchymal Stem Cell Immunomodulation of Microglia in Glioblastoma

Adip G. Bhargav (Rochester, MN); Rawan Al-Kharboosh; Cesar Garcia; Alfredo Quiñones-Hinojosa, MD

Introduction: Targeting Brain Tumor Initiating Cells (BTICs) implicated in recurrence and treatment resistance of Glioblastoma (GBM) is a tremendous therapeutic challenge. Furthermore, tumor-supportive myeloid cells create a hostile tumor environment that contributes to refractory disease. Human Adipose-derived Mesenchymal Stem Cells

(hAMSCs) are promising delivery vehicles of anti-GBM cargo that can target BTICs. However, the immunomodulatory effects and interaction of hAMSCs with the GBM stroma remain unclear. Here, we present data on the hAMSC-microglia interaction and implications for BTIC targeting.

Methods: hAMSCs were harvested, isolated, and purified from patient lipoaspirates while primary, patient-derived GBM tissue was used to isolate BTICs. hAMSCs were allowed to condition media for 48 hours, after which, media containing secreted, soluble factors was filtered and used for experiments to assess: 1) polarization of microglia via flow cytometry and 2) migration to determine tropism of hAMSCs via transwell assay. Gene expression was analyzed to dissect hAMSC-microglia interaction in the context of GBM. Appropriate 1-way ANOVA analysis was used to examine experimental findings.

Results: hAMSCs preferentially migrated to anti-inflammatory, tumor-supportive, polarized microglia. Furthermore, hAMSCs polarized microglia to a pro-inflammatory, tumor-suppressive phenotype as measured by CXCR4/CD206 expression. Infiltrating microglia are known to secrete IL-4 in the tumor stroma; however, there was no loss in stemness and no risk of oncogenicity with hAMSCs exposure to IL-4. In the presence of BTICs, hAMSCs reduced BTIC stem markers, proliferation, and sphere-forming capacity. Finally, hAMSC treatment of microglia increased endogenous microglial expression of BMP4, a potent anti-glioma protein.

Conclusion: hAMSC—microglia interactions suggest a site-specific immunomodulatory role for hAMSC therapy in GBM. hAMSCs preferentially target microglia and promote a tumor-suppressive microglial phenotype. Thus, hAMSCs can work both directly and indirectly by suppressing BTIC oncogenicity and promoting a pro-inflammatory immune phenotype, respectively. These results suggest hAMSCs play a dual role in suppressing GBM.

476. Tenascin-C as a Biomarker of Tumorigenesis and Treatment Response in Pediatric Diffuse Midline Glioma

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Introduction: Pediatric diffuse midline glioma (DMG) and high-grade glioma (HGG) are the most morbid pediatric cancers. Tenascin-C (TNC) is an extracellular matrix glycoprotein that mediates cell-cell and cell-matrix interactions during central nervous system development. Our group recently found TNC overexpression in pediatric HGG and DMG CSF, tissue and cell lines. Here, we describe effects of modulated TNC expression in vitro and in vivo on HGG and DMG tumorigenesis.

Methods: The effects of altered TNC expression in pediatric DMG (n=7), supratentorial HGG (n=3) cell lines were evaluated and compared to normal human astrocytes (n=1) and human stem cells (n=1) as controls. Lentiviral-mediated TNC shRNA and cDNA transfection was performed, and efficacy confirmed by qPCR and western blot. Cell proliferation, migration, adhesion, and viability were assessed. Comparative whole transcriptome analysis (RNA-Seq, Illumina Platform) was performed to determine effects of altered TNC on global gene expression in vitro (Ingenuity Pathways Analysis).

Results: TNC knockdown was associated with decreased cell proliferation and migration in vitro, reversed with exogenous TNC administration, and differed by endogenous TNC expression, ACVR1 and histone H3 mutation status. TNC cDNA transfection increased tumor proliferative and migratory cell capacity. Functional pathways analysis implicated targetable signaling pathways associated with altered TNC expression, and suggest TNC may serve as a biomarker of EZH2 and BRD inhibition. Tumor formation was confirmed in mouse xenografts via bioluminescence imaging, with comparative analysis of tumor growth and animal survival currently underway.

Conclusion: Our findings suggest TNC expression levels are affected by ACVR1 and H3F3A mutation status, change in response to molecularly targeted therapies, and may contribute to DIPG tumorigenicity through activation of PDGF and VEGF signaling. In vitro studies animal xenografts are underway. Overall, these data suggest TNC may serve as a disease biomarker and potential therapeutic target for pediatric DMG.

477. A Novel Bioinformatics Approach to Estimate Hazard in Pediatric High Grade Glioma

Greg Schwing (Detroit, MI); Marc Moisi, MD; Chindo Hicks, PhD

Introduction: Cox-nnet is an Artificial Neural Network that performs Cox (Proportional Hazards) Regression. The neural network learns through training, optimizing, and testing to find hidden connections between variables to estimate hazard.

Methods: The combined mRNA Expression z-Scores from Affymetrix arrays, Agilent arrays, and RNASeq of Mackay et al. 2018 were retrieved from pedcbioportal.org. The inclusion criteria were reporting of the following clinical covariates - Diagnosis, WHO Grade, Tumor location, Gender, Age, Censored Survival, and Histone subtype. The Samples meeting inclusion criteria (n=162) were analyzed with Cox-nnet, using the expression z-scores of 8,540 genes and clinical

covariates as inputs.

Results: The Kaplan-Meier curves generated by partitioning the test set above and below estimated median log hazard ratio (MLHR = 0.04) were statistically significant by log-rank test (Chisq= 7.4 on 1 degrees of freedom, p= 0.006). The five most important clinical covariates (weight given in parentheses) were WHO Grade (0.078), Histone 3.3 K27M mutation (0.025), Wild-Type Histone (0.0156), Hemispheric (0.009), and Midline (0.008). The five most important genes were those encoding for Perforin-1 (0.674), Neuropeptide-Y (0.498), DRC11 Antibody (0.280), Serine Protease 3 (0.280), and Zinc-Alpha-2-Glycoprotein-1 (0.222). The three most important pathways were Hepatic Fibrosis (2.021); Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis (1.848); and Axonal Guidance Signaling (1.617). The pHGG-specific pathways were Glioblastoma Multiforme Signaling (0.785), Glioma Invasiveness Signaling (0.449), and Embryonic Stem Cell Pluripotency (0.630).

Conclusion: The predictive model was strong, as indicated by the significant log-rank test. Of the top five genes, four were either immunologic or CNS-related. Only one, Zinc-Alpha-2-Glycoprotein-1, was tumorigenic. The pathways followed a similar trend. This partially explains the difficulty in treating pHGG. Most of the important features are either immunologic, a field in the early stages of drug development, or related to the underlying CNS physiology, which could be devastating to disrupt.

478. Targeting Immunostimulatory Pathways in Combination with Checkpoint Blockade Improves Survival in Murine Glioma

Karolina Woroniecka (Durham, NC); Cosette Dechant; Kristen Rhodin; Pakawat Chongsathidkiet, MD; Daniel Wilkerson, PhD; Xiuyu Cui, MS; Peter Fecci, MD, PhD

Background: The success of checkpoint monotherapy against glioblastoma (GBM) has been disappointing. Anti-PD-1 strategies may be hampered by poor baseline T-cell activation, as well as by severe T-cell exhaustion, both characterized by our group. Identifying high levels of 41BB on GBM-infiltrating T-cells (TIL), we combined PD-1 blockade with a 4-1BB agonist, with the aim of pre-activating T-cells and licensing efficacy for checkpoint blockade.

Methods: 4-1BB expression was characterized on TIL isolated from human and murine brain tumors. Mice were implanted intracranially or subcutaneously with glioma (CT2A), lung carcinoma (LLC), melanoma (B16F10), or breast carcinoma (E0771). Subsequently, mice received intraperitoneal injections with 4-1BB agonist antibody, PD-1 antagonist antibody, or the combination. Effects of a CD8 depleting antibody were also assessed, and survival was compared. Flow cytometry was used to characterize TIL number and, function, as well as expression of exhaustion-associated alternative checkpoints following treatment.

Results: Our data revealed that 4-1BB is a viable target on GBM TILs. 4-1BB is frequently expressed on CD8+ TIL in human GBM, and highly expressed on TIL within murine glioma when compared to other tumors. In murine glioma, 4-1BB agonism and PD-1 blockade demonstrated an additive survival benefit in a CD8 T-cell-dependent manner. The combination decreased T-cell exhaustion and improved T-cell functionality. This strategy, surprisingly, proved most successful against glioma, in a manner correlating with 4-1BB expression on TILs.

Conclusions: Poor T-cell activation and severe T-cell exhaustion both prove to be limiting factors for checkpoint blockade in the intracranial environment. 4-1BB agonism obviates these limitations and produces long-term survival in murine glioma. These results may guide personalized treatment strategies employing 4-1BB agonism to improve responses to checkpoint blockade in patients with GBM.

479. Utility of the Modified Frailty Index in the Risk Stratification of Patients Undergoing Brain Tumor Resection

Nikita (New York, NY); Scott Zuckerman, MD; Blaine Stannard; Eric Sussman, MD; Constantinos Hadjipanayis, MD, PhD; Joseph Cheng, MD, MS

Introduction: The modified frailty index (mFI) is a key measure of frailty based on demographics and is associated with complications in surgical cohorts, but has very limited validation in neurosurgery. The purpose of this study was to explore the relationship between the mFI and multiple postoperative outcomes in patients undergoing craniotomies for brain tumor resection as well as compare the mFI with other commonly used preoperative scores.

Methods: CPT codes were applied to the 2008-2014 National Surgical Quality Improvement (NSQIP) database in order to identify all patients undergoing craniotomy for the resection of primary and secondary intracranial lesions. American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI), and mFI were computed for each patient. A binary logistic regression model was used to explore the relationship between these variables and postoperative outcomes including mortality, major complications (Clavien IV), minor complications, and hospital length of stay (LOS). Other significant variables such as demographics, operative time, body mass index (BMI), and tumor location were

controlled for in each model. The c-statistic was computed to assess the predictive capacity of the regression models.

Results: A total of 17,815 patients were identified. Of these, 587 (3.3%) died within 30 days of surgery. After controlling for confounders, the mFI was an independent predictor of mortality (OR=14.5, $P<0.001$), major adverse events (OR=2.38, $P=0.034$), minor complications (OR=9.33, $P<0.001$), and prolonged LOS (OR=21.5, $P<0.001$). Patients' CCI scores were significantly associated with mortality, but not other outcomes. The c-statistic values for the models were 0.79, 0.66, 0.761, and 0.711, respectively.

Conclusion: The mFI may be a valuable tool for risk stratification in brain tumor resection and provided superior discriminatory capacity compared to CCI and ASA scores. By combining key chronic conditions, past health events, and functional status, the mFI may better identify patients at risk for adverse outcomes.

480. Neutrophil-to-Lymphocyte Ratio Predicts Overall Survival After Laser Induced Thermal Therapy in Glioblastoma Patients

Javier Figueroa, MD, PhD (Miami, FL); Alexa Semonche, BS; Stephanie Magoon; Ashish Shah, MD; Ricardo Komotar, MD; Michael Ivan, MD

Introduction: Laser-induced thermotherapy (LITT) offers a minimally-invasive treatment option for glioblastomas (GBM) which are relatively small or in eloquent areas. While laser ablation for malignant gliomas is known to be safe and effective, the role of the subsequent immune response is not well established. In this study we analyze the prognostic potential of edema volume and acute inflammation, quantified as neutrophil-to-lymphocyte ratio (NLR), in predicting response to treatment and length of survival.

Methods: Twenty-one patients were identified with new or recurrent glioblastomas that were determined to be candidates for LITT. Laser ablation was performed using standard solid tumor protocol for treatment volume, intensity and duration. Edema volume was quantified using follow-up MRI imaging, while retrospective chart review was performed to calculate NLR and survival.

Results: In patients treated with LITT for GBM, peritumoral edema volumes did not significantly change post-operatively ($p > 0.200$), while NLR significantly increased ($p = 0.0002$). The degree of NLR increase correlated with longer overall survivals, and ROC analysis demonstrated an area under the curve of 0.827 ($p = 0.112$). A delta-NLR cutoff of 7.0 results in positive and negative predictive values of 78% and 75%, respectively, in predicting overall survival > 1 year. Patients with with delta-NLR > 7.0 lived significantly longer than those with delta-NLR < 7.0 , median survival 440 days compared to 239 days ($p = 0.0297$).

Conclusion: Here we show that monitoring the inflammatory response after LITT therapy in GBM patients offers a prognostic tool to determine treatment efficacy and overall survival.

481. Toca 511 and 5-FC in Combination with Metronomic Cyclophosphamide Reduces Treg Cells and Enhances Therapy Efficacy in a Preclinical Murine Model

Tiffany T Montellano (San Diego, CA); Sophie Viaud, PhD; Daniel Mendoza; Maria Rodriguez-Aguirre; Harry Gruber, MD; Douglas Jolly, PhD; Derek Ostertag, PhD

Introduction: Toca 511 (vocimagene amiretrorepvec) is an investigational, conditionally lytic, retroviral replicating vector that selectively infects cancer cells due to their high mitotic index and immune-suppressed tumor microenvironment. Toca 511 stably delivers optimized yeast cytosine deaminase (CD) that converts subsequent Toca FC (an investigational, extended-release version of 5-fluorocytosine [5-FC]) into 5-fluorouracil (5-FU). 5-FU kills infected dividing cancer cells and, in preclinical models, local immunosuppressive myeloid cells, stimulating anti-tumor immunity. Patients with recurrent high grade gliomas treated with a local injection of Toca 511 followed by treatment with Toca FC have shown prolonged survival and durable complete responses (median duration of follow-up for response: 37.4+ months); responses were delayed in onset, consistent with an immunological mechanism. These data led to a phase III trial (NCT02414165). To improve therapy, we implemented a novel preclinical system to model submaximal infections and investigate combination treatments such as with metronomic cyclophosphamide for its immuno-stimulatory and antiangiogenic properties.

Methods: Naive B6C3F1 mice were implanted in the flank with a mouse glioma cell line Tu-2449SQ that has been adapted to grow subcutaneously. In order to control Toca 511 spread, tumor cells previously transduced with Toca 511 or a sister vector that expresses GFP (Green Fluorescent Protein) instead of CD, were admixed at various percentages as Toca 511 does not readily infect cells already infected with the GFP virus.

Results: We show a tumor control benefit when metronomic cyclophosphamide is combined with 5-FC with only 10% of tumor cells infected with Toca 511, which is associated with a significant depletion of peripheral Treg and increase in

CD8+ T cells in the peripheral blood.

Conclusion: These data demonstrate that Toca 511 and 5-FC therapy can be combined with metronomic chemotherapeutics like cyclophosphamide to enhance efficacy in preclinical models and may help design future clinical development.

482. Super-Selective Intra-Arterial Cerebral Infusion Bevacizumab for Treatment of Newly Diagnosed Glioblastoma: Phase I/II Clinical Trial Early Results

Nitesh Vijay Patel, MD (Bloomfield, NJ); Lukas Faltings, BA; Tamika Wong, MPH; Sherese Fralin, NP; Ashley Ray, NP; Mona Li, BA; Rafael Ortiz, MD; David Langer, MD; John Boockvar, MD

Introduction: Glioblastoma multiforme (GBM) has a 2-year survival of 26.5%. The perivascular cancer stem cell (CSC) niche is of high-interest and pre-clinical evidence suggests bevacizumab depletes this niche. We explore intra-arterial (IA) bevacizumab in patients with newly diagnosed GBM.

Methods: An open-label, single-arm, non-randomized trial enrolled patients with newly diagnosed GBM. Lesions had an endovascularly accessible arterial supply and location limiting significant resection. Mannitol (20%, 12.5 mL) opened the BBB and IA bevacizumab was delivered (15 mg/kg; 1 mL/s). On Day 0, patients underwent either biopsy or subtotal resection. At approximately day 30, a single dose of IA bevacizumab was given followed by standard radiation and oral temozolomide (TMZ) for 42 days. At day 72, a 1 month rest period was started; at approximately day 100, maintenance oral TMZ was started (150-200 mg/m²; 5 days on / 23 days off x 6-12 months). At days 120 and 210, repeat IA bevacizumab was delivered. Overall survival (OS) and progression free survival (PFS) were computed and adverse events (AE) were recorded.

Results: Fourteen patients were analyzed. Average age was 57+13 with equal males/females. Eleven completed all three IA treatments; the remaining 3 completed 2 of 3 treatments but further treatment was stopped due to progression or AE. Median OS was 38.2 months (92.3% survival at 1 year; 51.3% at 3 years). Median PFS was 29.5 months (62.2% PFS at 1 year; 31.2% at 3 years). Adverse events included seizures (2), deep venous thrombosis (3), pulmonary embolus (1), and intracranial hemorrhage (1); all managed non-operatively with full recovery to baseline.

Conclusions: Delivery of IA bevacizumab is safe and may be particularly effective for the CSC niche. Our findings suggest IA bevacizumab may be a useful adjunct as OS and PFS are significantly longer in this cohort relative to comparable series in the literature.

483. Intraoperative Near-Infrared Imaging Accurately Detects Abnormal Intracranial Tissue

Steve Cho (Philadelphia, PA); Bhavya Khanuga, BS; Love Buch, BS; John Lee

Introduction: We previously described a novel technique using the near-infrared (NIR) fluorophore indocyanine-green (ICG) for intraoperative visualization of brain tumors. This technique, termed Second-Window-ICG (SWIG), takes advantage of ICG's accumulation in tissue with enhanced endothelial permeability to detect neoplastic regions. Despite its high sensitivity for neoplastic tissue, prior analysis demonstrated low specificity and positive-predictive-value. Since necrosis and inflammation result in damage to the intracranial vasculature endothelium, we investigated the utility of SWIG in intraoperative visualization of these abnormal changes.

Methods: For this IRB-approved study, patients with high-grade gliomas (HGG) or brain metastases were enrolled and 5mg/kg ICG was administered intravenously 24-hours preoperatively. Intraoperatively, NIR imaging of the tumor and post-resection margins was performed using a dedicated NIR-exoscope. The mean signal-to-background-ratios (SBRs) were calculated for all patients and the Mann-Whitney test was used to compare these values in different subgroups of patients.

Results: 74 patients (19 untreated metastases, 31 untreated HGG, 10 previously-treated metastases, and 14 previously-treated HGG) were enrolled. Of the 24 patients with prior surgical/radiation treatment, 4 patients displayed necrosis, inflammation, and/or treatment-effect without neoplasm. Despite differences in pathology, all specimens exhibited gadolinium-enhancement and strong ICG-fluorescence. The mean SBR of the gross tumor specimens in-vivo (n=70) was 6.81 ± 2.33 (mean $\pm$ SD). The mean SBR in-vivo for patients with abnormal tissue but no tumor (n=4) was 8.16 ± 4.49 . No significant difference was observed between the two groups using the nonparametric t-test ($p=0.94$). Furthermore, 14 out of 38 gross glioblastoma specimens contained necrosis with tumor. No significant difference was observed in the mean SBRs between specimens with necrosis+tumor (6.69 ± 2.90) and those with tumor alone (7.34 ± 1.93 , $p=0.64$). Overall, the sensitivity of SWIG for abnormal tissue detection was 100%.

Conclusions: Intraoperative NIR imaging with SWIG, although an accurate indicator of abnormal tissue, currently cannot distinguish neoplasm from necrosis, inflammation and/or treatment-effect.

484. Can Sonography Replace Electromyography and Nerve Conduction Velocity in Carpal Tunnel Syndrome?

[AANS International Travel Scholarship](#)

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Purpose of the Study: To justify the efficacy of the ultrasonography (US) in the diagnosis of carpal tunnel syndrome (CTS) in the postoperative follow-up in comparison to electrodiagnostic tests [electromyography (EMG) and nerve conduction velocity (NCV)].

Patients and Methods: One hundred CTS patients were documented through clinically, electrophysiologically, and intraoperatively grading by using the Tuncali grading system (TGS), in Mansoura University Hospital, Insurance Hospital, and EL Ahrar. All patients were evaluated pre and postoperatively by both the gold standard invasive electrodiagnostic (EMG, NCV) and the new noninvasive US tests.

Results: All of the 100 CTS cases (24 men, 76 women) showed improvement in pain after releasing incisions (TGS grades 2 and 3). The CTS diagnosis by electrodiagnostic (EMG and NCV) were 90 positive and 10 negative. However, by the US were 86 positive and 14 negative. Six months after surgery, electrodiagnostic tests (EMG and NCV) had improved in 74% of cases, but with US, it showed improvement in the cross-sectional area (CSA) swelling of median nerve after three weeks in 64 CTS cases (64%). The sensitivity and the specificities were 90% and 79.2% for NCV respectively while for the US were 86% and 77.4% respectively.

Conclusion: US showed improvement of morphological criteria (within 3 weeks) than the betterment of the function by electrodiagnostic (after 6 months) in the postoperative follow-up of CTS cases. Therefore, US examination for CTS can possibly be done without the need for other invasive investigations. Keywords: Carpal tunnel syndrome; electromyography; median nerve; ultrasonography; nerve conduction velocity.

485. The Incremental Value of Magnetic Resonance Neurography for the Neurosurgeon

Hamilton Cole Newhart (Little Rock, AR); John Patterson, BS; Arun Gunasekaran, BS; Tarun Pandey, MD; Manoj Kumar, MD; Noojan Kazemi, MD

Introduction: When attempting to visualize and diagnose neurological lesions involving peripheral nerves and spine, conventional MRI can identify large structural neural problems, but is inadequate for distinguishing nerves tissue from soft tissue. Magnetic Resonance Neurography (MRN) is an evolving imaging modality that can visualize peripheral nerves including spinal nerve roots in great detail when compared to traditional MRI. Alterations in signal intensity, fascicular pattern, continuity and size can be detected with MRN. Although MRN has been described, few have addressed the additional value of MRN in assisting management of challenging cases, specifically for neurosurgeons and spine surgeons. It is still underutilized in neurosurgery, and our paper highlights specific categories of disease where MRN can significantly impact clinical and surgical decision making.

Methods: We performed a retrospective review of 206 (129 female, 77 male) cases where MRN was used for preoperative or postoperative evaluation. The impact of MRN (compared to standard MRI or CT) was determined through correlation with clinical information and specific categories were identified.

Results: MRN lead to a significant change in diagnosis or care of 44 patients (21.4% -27 female, 17 male). Through further analysis of those cases, we identified five diagnostic categories out of the 44 patients, which included: Trauma (13.6%- 6 patients), Post-surgical evaluation (11.4%- 5 patients), Compressive/Degenerative conditions (15.9%- 7 patients), Tumors (29.5%- 13 patients), and Neuritis/Inflammation (29.5%- 13 patients). We have selected representative cases from each category to discuss the specific radiographic findings that can be seen on MRN imaging.

Conclusion: MRN has proven to be a valuable tool for the neurosurgeon when utilized for the variety pathologic conditions listed in this poster. We advocate for further widespread use of MRN, which can significantly lower the socioeconomic burden of many diseases that can be difficult to treat and detect with traditional radiographic methodology.

486. Predictors of pectoralis major functional outcomes following intercostal nerve transfers after brachial plexus nerve root injury: an analysis of 161 patients

Mark A. Attiah, MD (Los Angeles, CA); Anil Bhatia; Justin Brown

Introduction: Brachial plexus injuries frequently lead to weakness in the pectoralis major muscle, yet very few studies have examined functional recovery in this muscle after reconstructive surgery. Restoring function to the pectoralis muscle allows for shoulder flexion and internal rotation of the arm, which can significantly improve quality of life. This study aimed to identify clinical predictors of pectoralis muscle strength recovery in a cohort of patients with brachial plexus injury and pectoralis muscle weakness who underwent intercostal nerve transfer surgery.

Methods: We retrospectively analyzed prospective data of 161 patients who suffered pectoralis weakness from brachial plexus injury and subsequently underwent nerve transfer using a single intercostal nerve at a single institution between 1995-2017 by an experienced surgeon. Outcomes in pectoralis strength were classified according to manual muscle testing (M0-M5). Multivariable regression was performed to identify predictors of good outcome, defined as M3 to M5.

Results: A total of 161 patients were identified who underwent reconstructive surgery. 70 (44%) patients had poor outcome (M0-2). 90 (56%) had a good outcome. Factors associated with a good outcome in our model were age (OR 0.95; $P = 0.02$), follow up time (OR 1.11; $P < 0.001$), time interval between injury and surgery (OR 0.83; $P = 0.005$), and injury location (0.026; $P = 0.03$). Sex and sidedness of injury were non-significant.

Conclusion: Loss of shoulder flexion and internal rotation from brachial plexus injury and pectoralis weakness may be improved with intercostal nerve transfer procedures in well-selected patients. Younger age, adequate follow up length, shorter interval before surgical exploration, and injury location may positively influence motor outcome.

487. Modern wartime peripheral nerve injury: a review

Zachary S. Hubbard, MD (Charleston, SC); Fraser Henderson Jr, MD; Jeffrey Wessell; Alejandro Spiotta, MD

Introduction: The management of peripheral nerve injury (PNI) has a rich history involving military conflict. Military technologies have evolved over time, creating new injury patterns and necessitating the need for adjustment in medical and surgical management. Conflicts provide great advances in the surgical management of neurosurgical conditions, with lessons that extend into the civilian sector. The majority of the available military literature on this subject consists of retrospective case series and case reports. The aim of this study was to perform a systematic review of the available evidence on the treatment of peripheral nerve surgery in military conflict.

Methods: A PubMed database search was performed to identify literature with military and civilian focus from 1980-2018. Combinations of the following phrases that describe PNI in the military setting were used (peripheral nerve, injury, wartime, military, combat, brachial plexus, sciatic) to conduct the search.

Results: Our PubMed search yielded 356 articles for screening. Following application of our inclusion criteria, this was narrowed down to 16 articles (all retrospective studies). Table 1 summarizes 15 studies summarizes the patient demographics. The mean age was 27.7 and 97.8 of patients were male. 6 of the studies focused on the War on Terror, 5 on the Yugoslav Wars, 3 on the Iran-Iraq conflict, and 1 on the Croatian Civil War. The most common mechanism of injury was explosion (68.1%) followed by gunshot wound (32.9%). Surgeries were completed from 3 weeks to 5 months. Nerve grafts were employed in 70% of cases. Successful or good outcome was achieved in 65.1% of cases.

Conclusions: Peripheral nerve injury is common in the military setting. Successful outcomes are accomplished in the majority of patients, despite significant collateral bone, vascular, and soft tissue injury. Nerve grafting is the most common technique for peripheral nerve repair following combat injury.

488. Posterior Lumbar/Sacral Nerve Root Stimulation for Treatment of Chronic Foot and/or Ankle Pain

Stephen Pyles, MD (Ocala, FL); Kristen Lechleiter, MS; Lilly Chen, MD; Roshini Jain, MS

Introduction: Chronic focal pain relief has been reported using Dorsal Root Ganglion (DRG) stimulation. However, a high incidence of adverse events associated with this technique has now been documented. Effective treatment of groin and pelvic pain using stimulation with leads over the L1 dorsal nerve root has previously been reported. We therefore evaluated outcomes of proximal dorsal somatic nerve root stimulation as an alternative method for treatment of chronic foot/ankle pain.

Methods: This is a single-center, case-series evaluating patients with chronic foot/ankle pain diagnosed with Complex Regional Pain Syndrome or Diabetic/non-Diabetic peripheral neuropathy (N=9). Patients were implanted with a neurostimulator capable of anatomically-guided (3D) neural targeting (3DNT, Precision Spectra, Boston Scientific).

Using a previously described technique, leads were placed antegrade through the sacral hiatus within a range of L5-S1 (Alo KM., et al. *Neuromodulation*. 1999 Jan;2(1):23-31).

Results: A 6.3-point reduction in NRS ($p < 0.0001$) was reported at mean last follow-up duration=315.6 days. Fifty-five percent (5/9) of patients reported 91-100% improvement in their pain and 44% (4/9) reported no pain (NRS=0) at last follow up. Additionally, >75% (7/9) of patients reported NRS $\leq$ 1, 56% preferred standard rate and 44% preferred higher rate stimulation. Additional and updated data is planned for presentation.

Conclusion: DRG stimulation may be associated with additional risks in addition to a more complex procedure. This small case-series demonstrates that neurostimulation within the L5-S1 range using 3DNT is a viable option to treat focal foot/ankle pain.