Oral Presentations

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501. Inspired by Harvey Cushing: The Illinois Neuropsychiatric Institute

Daniel Meier Birk, MD; James Stone, MD; Sepideh Amin-Hanjani, MD; Fady Charbel, MD (Chicago, IL)

Introduction: The last time the Chicago Cubs won the World Series was in 1908 at the West Side Grounds. That land was sold to the state for an academic hospital, and in 1939, ground was broken at the site of the clubhouse for the Illinois Neuropsychiatric Institute (NPI). We review the history of the NPI and explore its ties to Harvey Cushing, himself a competitive baseball player.

Methods: The archives of the NPI and historical documents were reviewed.

Results: Eric Oldberg, the last chief resident to run Cushing's service in Boston, joined the University of Illinois at Chicago in 1931. It was during his tenure as Chairman of Neurology and Neurosurgery, that the NPI was built as the first institute in North America to house Neurosurgery, Neurology and Psychiatry departments. The art-deco building was designed as an architectural tribute to the neurosciences. Oldberg was the founder, and he recruited a neuroscience dream team to the NPI, including Percival Bailey. Cushing hired Bailey to create a histological laboratory for brain tumors at the Peter Bent Brigham Hospital; Cushing and Bailey's influential monograph on tumors of the glioma group, published in 1926, ultimately led to today's WHO brain tumor classification system. Amongst his achievements at the NPI, Bailey pioneered anterior temporal lobectomy for psychomotor epilepsy.

Conclusion: The NPI was the first multi-specialty neuroscience institute in the country. Its founding leadership had a track record of close associations with Harvey Cushing, and, like Cushing, sought to advance the field of Neurosurgery through cross-specialty research and practice.

502. Blood-brain Barrier Disruption and Endothelial Cell Gene Expression after Experimental Subarachnoid Hemorrhage

Michael Tso, MD; Paul Turgeon, MSc; Bert Bosche, MD; Jinglu Ai, MD, PhD; Philip Marsden, MD; R. Loch Macdonald, MD, PhD (Toronto, Canada)

Introduction: Over the last 25 years, clinical trials have largely failed to provide new effective drug therapies for patients with subarachnoid hemorrhage (SAH). The pathophysiology of SAH is complex and includes blood-brain barrier (BBB) disruption. Interrogating the gene expression profiles of brain endothelial cells (BECs) in SAH may help determine new therapeutic targets.

Methods: SAH was induced in Tg(Tie2GFP)287Sato/J mice using the prechiasmatic blood injection model. Two hours prior to transcardial perfusion at 24h and 48h, mice were injected with cadaverine dye intraperitoneally. Whole brain imaging and confocal microscopy of coronal brain slices were performed. BECs from SAH and sham FVB mice were isolated by mechanical and enzymatic tissue dissociation followed by sequential magnetic-based sorting with myelin depletion, CD45 (leukocyte marker) depletion,

then CD31 (EC marker) enrichment. Total RNA extracted from BECs was linearly amplified and hybridized to Affymetrix Mouse Gene 2.0 ST Arrays.

Results: BBB disruption, as evidenced by cadaverine dye extravasation, was present after SAH and was higher at 24h compared to 48h. Using the 24h time-point, BECs were successfully isolated, with >90% of cells confirmed to have EC identity on flow cytometry (CD45-CD31+). These cells were also significantly enriched for EC-related genes such as Cdh5, Icam2, Nos3 and Pecam1. Microarray results will provide a list of genes that are significantly upregulated or downregulated in BECs after SAH, requiring further validation studies.

Conclusion: BBB disruption is greater at 24h than at 48h in an experimental SAH model. This study is the first to provide whole genome expression profiling of freshly-isolated BECs derived from an SAH animal model. Thereby, our findings may open new translational and clinical research avenues aimed at improving SAH clinical outcomes.

Additional Information: MT is the NREF Cerebrovascular Section Research Fellow for 2013–2014. *This study received NREF funding.*

504. Quality of Life Outcomes Following Surgical Management of Coexistent Parkinson's Disease and Cervical Spondylotic Myelopathy

Roy Xiao; Jacob Miller, BS; Daniel Lubelski, MD; Jay Alberts, PhD; Thomas Mroz, MD; Edward Benzel, MD; Ajit Krishnaney, MD; Andre Machado, MD, PhD (Cleveland Heights, OH)

Introduction: No studies have investigated the outcomes of surgery for patients with coexisting Parkinson's disease (PD) and cervical spondylotic myelopathy (CSM). The purpose of this study was to characterize the quality of life (QOL) outcomes of patients with PD and CSM following decompression.

Methods: A matched cohort-controlled retrospective review of patients diagnosed with PD and CSM undergoing decompression between 1/2009 and 12/2014 at a tertiary-care institution was conducted. QOL was measured by the EuroQol 5-Dimensions (EQ-5D), Pain Disability Questionnaire (PDQ), and Patient Health Questionnaire-9 (PHQ-9). Multivariable regression was used to identify predictors of QOL outcomes.

Results: Eleven PD patients were matched to 44 controls. Mean age was 65 for both groups. PD and control patients were followed postoperatively for 12.4 and 13.4 months, respectively. No significant differences in preoperative QOL were observed between groups. While controls experienced significant postoperative improvements in all three QOL measures, PD patients only improved in PDQ (-19.7 , $p=0.01$). PD patients experienced inferior postoperative QOL compared to controls in EQ-5D (0.526 v. 0.707 , $p=0.01$) and PDQ (80.7 v. 51.4 , $p=0.03$). Only 18% of PD patients achieved EQ-5D minimal clinically important difference (MCID), compared to 57% of controls ($p=0.04$). Multivariable regression revealed PD as a predictor of decreased improvement in EQ-5D ($\beta=-0.09$, $p=0.04$).

Conclusion: PD patients experienced significant reduction in pain following decompression. However, PD was identified as a

significant independent predictor of diminished improvement in EQ-5D, with no significant improvement in QOL following decompression.

505. The History of Therapeutic Hypothermia and its Use in Neurosurgery

Michael Bohl, MD; Nikolay Martirosyan, MD; Zachary Killeen, BS; Hasan Zaidi, MD; Nicholas Theodore, MD; Mark Preul, MD (Phoenix, AZ)

For millennia, accounts of hypothermic patients surviving typically fatal circumstances piqued the interest of physicians, prompting many to perform early investigations of hypothermic physiology. In 1650, for example, a 22-year-old woman in Oxford suffered a 30-minute execution by hanging on a notably cold and wet day, but was found breathing hours later when her casket was opened by Thomas Willis in a medical school dissection laboratory. News of her recovery inspired pioneers such as John Hunter to perform the first complete and methodical experiments on life in a hypothermic state. Hunter's work helped spark a scientific revolution in Europe that witnessed the overthrow of centuries-old dogma that volitional movement was created by hydraulic nerves filling muscle bladders with cerebrospinal fluid, and replaced this theory with animal electricity. Central to this paradigm shift was Giovanni Aldini, whose public attempts to reanimate the hypothermic bodies of executed criminals not only inspired tremendous scientific debate, but also influenced a young Mary Shelley to write her novel *Frankenstein*. Neurosurgeon Temple Fay introduced hypothermia to modern medicine with human trials on systemic and focal cooling, though his work was derailed after Nazi physicians in Dachau used his results to justify their infamous experiments on prisoners of war. In the latter half of the 20th-century hypothermic cerebrovascular arrest was introduced to neurosurgical operating rooms. The ebb and flow of neurosurgical interest in hypothermia that has since persisted reflects our continuing struggle to achieve the neuro-protective benefits of cooling while minimizing the systemic side effects. Despite an overwhelming history demonstrating the potential of hypothermia, clinical trials from the last 50 years have failed to show a convincing benefit. This comprehensive historical analysis of technology and technique provides a context needed to consider the current status of clinical hypothermia research, and the best future direction for this field.

506. A Systematic Review of Conduits used for Peripheral Nerve Regeneration

Tina Ramineni (Albany, NY)

Introduction: Three non-autologous materials are approved for treatment of critical nerve gaps: Type I collagen, polycaprolactone (PCL), and polyglycolic acid (PGA) polymers. Although biodegradable conduits have proven most effective in peripheral nerve regeneration, head to head comparisons of such conduit materials are lacking. Thus, we performed a systematic review of these conduits using a rat sciatic model to find the most effective.

Methods: A systematic review was conducted on July 25th, 2014 using the following databases: [PubMed, Web of Science, Cochrane, ClinicalTrials.gov, SciFinder/Chemical Abstracts]. The article search was limited to articles written in English and published during or after 1985. 12 articles were chosen which fit all selection criteria. Electrophysiological and histological data, including twitch force, CMAP latency and amplitude and myelinated axon count were collected for each article.

Results: Our study shows collagen to be the most widely used conduit followed by PGA and polyesters/co-polyesters. Collagen had positive histological and electrophysiological outcomes in the majority of studies. Specifically, collagen conduits had the highest CMAP amplitudes, nerve conduction velocities (NCV), axon counts and twitch forces.

Conclusion: Our review shows collagen to have regenerative capacity comparable to the gold standard, while PGA and polymers and copolymers yield more conflicting data. These results are in concordance with prior research, affirming the efficacy of collagen in peripheral nerve regeneration.

507. Mid-Term Follow-up in a North American Cohort with Moyamoya Disease

Jose Porras; Wuyang Yang, MD; Justin Caplan, MD; Geoffrey Colby, MD, PhD; Alexander Coon, MD; Rafael Tamargo, MD; Edward Ahn, MD; Judy Huang, MD (Baltimore, MD)

Introduction: Moyamoya disease (MMD) is prevalent in populations of Asian origin, but rarely reported in other ethnicities. The present study seeks to characterize MMD and evaluate the effectiveness of intervention or conservative treatment at a single East Coast referral center.

Methods: We performed a retrospective review of MMD patients treated from 2000–2015. Baseline information was collected and analyzed on a per-hemisphere basis. Survival analysis of a TIA/stroke-free period at follow-up after treatment was determined using multivariate Cox regression analysis.

Results: Sixty-four patients with 126 affected hemispheres were evaluated. Average age at first presentation was 25.43 ± 20.78 years, with 76.6% (n=49) being female. The majority of patients were White (n=28, 43.8%), followed by Black (n=19, 29.7%), Asian (n=9, 14.1%), and Other (n=8, 12.5%). Of 79 surgically-treated hemispheres, 7 underwent direct bypass, 57 indirect, and 15 combined. There were more males ($p < 0.001$) in the treated group (35.4%) than the conservative group (4.3%). The treated group had significantly more baseline cognitive dysfunction ($p = 0.048$), and more baseline speech disturbance with borderline significance ($p = 0.066$). During an average follow-up of 6.19 (0.09–29.07) years, risk of ipsilateral TIA/stroke ($p = 0.340$) and mRS ($p = 0.828$) was similar across the two treatment groups, with the treated group reporting fewer headaches ($p = 0.003$) and visual disturbances ($p = 0.039$). Survival analysis revealed that only hypertension ($p = 0.018$) was associated with earlier onset of follow-up TIA/stroke after adjusting for other variables. Overall annual risk of TIA/stroke in a 5-year period is 4.8%.

Conclusion: Our study, comprised predominantly of White and Black patients, suggests that hypertension is associated with follow-up TIA/stroke. Surgical treatment provided better outcomes than conservative treatment despite more severe presenting symptoms. Annual risk of follow-up TIA/stroke is 4.8%.

508. Glioma-infiltrating iAPCs mediate T cell recruitment to and activation in the tumor microenvironment

Joseph Paul Antonios; Horacio Soto, MS; Joey Orpilla, BS; Namjo Shin; Richard Everson, MD; Robert Prins, PhD; Linda Liau, MD, PhD (Los Angeles, CA)

Introduction: Tumor lysate-pulsed dendritic cell vaccination has shown efficacy in promoting an immune response in the resected glioma patient treatment setting. However, cure rates are elusive when tumors are well established. We hypothesized that a mechanism of immune regulation exists in the tumor setting; specifically,

suppression is dominantly mediated via the PD-1/PD-L1 mechanism by tumor-infiltrating immunosuppressive antigen presenting cells (iAPCs).

Methods: To test this hypothesis, we co-cultured T cells with murine glioma in the presence of iAPCs derived from C57BL/6 DC vaccine-treated mice with/without inhibition of the PD-1/PD-L1. T cell cytotoxicity in vitro was then assessed using the xCelligence impedance analysis system. To examine these mechanisms in an in vivo setting, we intracranially implanted mice with GL261 glioma and treated with DC vaccination +/- PD-1 mAb blockade or a small molecule inhibitor of CSF-1R (PLX-3397, Plexxicon) and overall survival was quantified.

Results: We characterized the tumor infiltrate induced by DC vaccination and showed that there existed a PD-L1+ population of heterogeneous myeloid-lineage cells. This inhibitory antigen-presenting cell (iAPC) population significantly reduced T cell cytotoxicity in in vitro assays; blockade of PD-L1 on these cells recovered T cell cytotoxicity against tumor. In our in vivo model, PD-1 mAb blockade in combination with tumor lysate-pulsed DC vaccination induced a highly significant survival benefit to tumor-bearing mice. Treatment with PLX-3397, in conjunction with DC vaccination, additionally improved the survival benefit beyond that of adjuvant PD-1 mAb blockade.

Conclusion: These findings suggest that an anti-tumor immune response targeted towards glioma is dependent on blockade of iAPC function within the tumor microenvironment.

509. Use of Vancomycin Powder for Surgical Prophylaxis Following Craniotomy

Allen Ho, MD; Vinod Ravikumar, BS; Eric Sussman, MD; Arjun Pendharkar, MD; Gordon Li, MD (Stanford, CA)

Introduction: Surgical site infections constitute a significant burden to patients and institutions, with approximately \$3.3 billion in annual costs. Topical vancomycin powder is known to be effective at reducing postoperative infection rates, but has not been widely utilized in craniotomies. The goal of this high-power study is to determine whether there is utility in applying intrawound vancomycin powder to reduce infections in craniotomies/craniectomies.

Methods: This is a retrospective pre and post-intervention study that included patients from July, 2011 to October, 2015 undergoing craniotomy or craniectomy. All patients received the standard of care during procedures, including pre- and post-operative intravenous antibiotic prophylaxis. Patients in the experimental group were treated with 1g of powdered vancomycin evenly distributed over the bone or dura. Operation duration, steroid use, and various risk factors (age, male sex, BMI, etc.) were evaluated. Statistical analysis assessed for significant differences in pre- and post-vancomycin powder cohorts.

Results: 304 patients were studied in which 201 were in the pre-intervention control cohort and 103 were in the post-intervention cohort. Vancomycin use correlated with 100% reduced incidence ($p < 0.05$) of surgical site infections (0% infection rate) compared with the standard prophylactic antibiotics (3.5% infection rate). Our calculated number needed to treat was 32 patients in order to prevent an additional infection. In our cost effectiveness analysis based on published data on additional costs associated with infection, use of vancomycin powder in our cohort amounted to a \$445.68 cost savings per patient. Experimental and control cohorts were well-matched, with no significance found in risk factors between the two groups.

Conclusion: Powdered vancomycin use in the setting of craniotomies/craniectomies correlates with a reduced SSI rate, and is likely to improve patient outcomes and reduce healthcare expenditures.

510. Replacing hand-injections with power-injections during neuroendovascular procedures reduces radiation dosage by 3-fold to physicians/trainees

Jason Anthony Liew; Henry Keenan, BA; Stephen Sandwell, MD; Dushyant Damania; Nancy Kung; Jennifer Ortega; Frederic Mis, PhD; Babak Jahromi, MD, PhD (Rochester, NY)

Introduction: As neuroendovascular procedures increase in prevalence, exposure to ionizing radiation is a growing concern for the operating team. We investigated the effectiveness of power injector usage in reducing the operating team's radiation exposure in the setting of a teaching hospital.

Methods: We reviewed 172 endovascular procedures performed between December 2014 and May 2015. A collar dosimeter badge (InstadoseTM) was worn by the attending physician (endovascular neurosurgeon) and trainee (neurosurgery resident) for every procedure. Total radiation dosage, Dose Area Product (DAP), Cumulative Air Kerma (CAK), and total fluoroscopy time for the attending and resident physicians were recorded for each procedure. Power injector usage varied depending on surgeon discretion. Physician radiation exposure was then compared between power-injector and hand-injection procedures. Statistical analysis was performed using JMP 12.0.0.

Results: Mean attending physician radiation dosage for procedures utilizing a power-injector for contrast injection were approximately three-fold lower than for hand-injection procedures ($0.009 \text{ mSv} \pm 0.003$ versus $0.033 \text{ mSv} \pm 0.005$ per procedure, $p < 0.0001$). Similar results were found for resident physicians ($0.004 \text{ mSv} \pm 0.001$ versus $0.013 \text{ mSv} \pm 0.002$, $p = 0.002$). There was no significant difference in mean fluoroscopy time, DAP, CAK, and complication rates between neuroendovascular procedures utilizing power injection versus hand injection.

Conclusion: Our data suggests that using power injection for contrast injection during neuroendovascular procedures dramatically reduces radiation exposure to both attending and resident physicians. This has significant implications for both risk reduction in long-term practitioners of neuroendovascular surgery, and obligations towards trainees expected to participate in such procedures within teaching institutions.

511. Acid Ceramidase Inhibitors: A De Novo Drug Target and a New Class of Drug Capable of Killing Glioblastoma Cancer Stem Cells With High Efficiency

Ninh Doan, MD; Shamma Mirza, PhD; Wade Mueller, MD (Milwaukee, WI)

Introduction: Glioblastoma (GBM) is still the most common, malignant primary cancer of the central nervous system with a low life expectancy. No therapy has been developed to target glioma cancer stem cells. Identifying biomarkers associated with survival will enable the design of a de novo therapy aiming at improving survival.

Methods: GBM tumor tissues collected at the time of tissue resection and snap frozen in liquid nitrogen and stored at -80°C at the Medical College of Wisconsin. Pathology was performed by the Department of Pathology. Samples underwent tandem mass spectral (LC-MS/MS) analysis and protein identification and quantification by spectral counting analysis. Findings were confirmed by Western blot. Survival studies were done by MTT assay using ASAHI inhibitors against U87 and 3 different patient-derived GBM cancer stem cell lines.

Results: We investigated the correlation with survivals of more than 600 proteins using patient GBM tissues. A de novo biomarker

named acid ceramidase (ASAHI) was, for the first time in GBM, found to have a significant negative correlation with survival. The Western blot study revealed a significant upward trending of ASAH1 levels in patients with a lower overall survival. Strikingly, U87 cells, and 3 different patient-derived GBM cancer stem cell lines were efficiently killed by 3 different known ASAH1 inhibitors.

Conclusion: This study has discovered both ASAH1 as a de novo GBM drug target and a new class of drug to treat GBM. To our knowledge, these are first small-molecule drugs demonstrated to be highly effective against GBM cancer stem cells. Among these 3 known inhibitors of ASAH1, carmofur, which is capable of crossing the blood-brain barrier, is commonly used in Japan for the treatment of colorectal cancers. As such, patients with GBM can potentially receive immediate benefits from this new class of drug.

512. Tetanus-Diphtheria Recall Responses and Chemokine CCL3 Delivery Enhance Migration and Efficacy of Dendritic Cell Vaccines

Kristen A. Batich; Luis Sanchez Perez; Gary Archer, PhD; Elizabeth Reap, PhD; Smita Nair, PhD; Denise Lally-Goss; Sharon McGehee-Norman; Beth Perry, RN; James Herndon II, PhD; Duane Mitchell, MD, PhD; John Sampson, MD, PhD (Durham, NC)

Introduction: Efficacy of dendritic cell (DC) vaccines for glioblastoma (GBM) is limited by suboptimal migration to vaccine site-draining lymph nodes (VDLNs). We assessed the impact of DC migration on clinical outcomes by randomizing patients with primary GBM to two vaccine site pre-conditioning strategies, unpulsed DCs or tetanus-diphtheria (Td) toxoid as a recall antigen prior to DC therapy.

Methods: Lymph node homing of ¹¹¹Indium-labeled DCs using SPECT/CT imaging was evaluated in patients, along with progression-free survival (PFS) and overall survival (OS). Transgenic mouse models were used to determine mechanisms underlying effects of Td recall responses and adjuvant CCL3 on vaccine efficacy.

Results: Patients given Td pre-conditioning as a recall antigen showed increased DC migration ($p=0.04$) and increased OS ($p=0.013$) compared to controls. Td recall elicited a significant fold increase in serum CCL3 ($p=0.031$). In mice, Td recall resulted in localized CCL3 production that was dependent on prior Td immunity ($p=0.0001$) and abrogated by host depletion of CD4⁺ T cells ($p=0.0001$). Td pre-conditioned Ccl3^{-/-} mice demonstrated accelerated tumor growth comparable to controls, yet antitumor immunity was recovered with provision of Td-activated CD4⁺ T cells and exogenous CCL3 ($p=0.044$). In patients, serum CCL3 levels following Td recall were associated with OS (Spearman $r=0.61$, $p=0.038$). In mice, recombinant CCL3 delivery with Td recall showed an additive effect on increasing DC migration to VDLNs and operated in a dose-dependent manner ($p=0.029$).

Conclusion: Td pre-conditioning as a recall antigen increased lymph node homing of DC vaccines, which was associated with increased PFS and OS in patients with primary GBM. In patients, CCL3 induction following Td recall was associated with OS. In mice, adjuvant CCL3 delivery was a potent adjuvant for enhancing DC vaccine migration and efficacy.

513. Across the spectrum of total lumbar disk replacement: 12 yrs experience in Calgary

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Introduction: Modern lumbar total disk replacement (TDR) has been used in clinical practice for over 20 years, but limited clinical data on results in North America exists outside of the large FDA IDE studies.

Methods: All patients either had a single-level TDR, a two-level TDR or a hybrid-lumbar construct (TDR and ALIF) implanted between 2003-2015 by a single surgeon. We prospectively collected 23 variables including but not limited to: type of prostheses, clinical pain duration, LE radicular pain, BMI, VAS-LE, VAS-back, BMI, and ODI. We analyzed 2 primary endpoints: 1) composite indicator of clinical outcomes and complications and 2) reoperation rate. We conducted a multivariate analysis via the random forest method. Logistical regression was applied to qualify relationship between variables.

Results: We had 119 single-level, 34 two-level and 56 hybrid to review in the database. For each respective category, 68%/58%/77% had excellent results defined >50% improvement in both VAS and ODI as well as no complications and no reoperation. 20%/24%/18% had good results defined as >25% improvement in both VAS and ODI or any complication/reoperation despite >50% improvement. Reoperation rate was 1% for all-causes. Multivariate-analysis revealed 5 variable associated with prediction of an excellent outcome: M6-implant (OR 5.45), Prodisc-implant (OR 3.44), high BMI (OR 1.13), clinical pain duration > 10 years (OR 1.07), and LE radicular pain (OR 0.39).

Conclusion: Success rates comparable to the large FDA IDE studies are achievable in clinical practice. In strictly selected patients, lumbar TDR provide long term relief of back pain in a majority of cases.

514. Reoperation and Readmission after Clipping of Unruptured Intracranial Aneurysms: A National Surgical Quality Improvement Program Analysis

Hormuzdiyar Dasenbrock, MD; Robert Rudy, BS; William Gormley, MD, MPH; Timothy Smith; M. Aziz-Sultan, MD; Rose Du, MD, PhD (Boston, MA)

Introduction: Although reoperation and readmission are important quality metrics, this is the first national study to evaluate the reasons and predictors of unplanned reoperation and readmission after craniotomy for clipping of an unruptured aneurysm.

Methods: Patients who underwent craniotomy for microsurgical clipping of an unruptured aneurysm were extracted from the prospective National Surgical Quality Improvement Program registry (2011–2013). Multivariable logistic regression with forward selection evaluated independent predictors of unplanned thirty-day reoperation and readmission. Predictors screened included patient age, sex, comorbidities, American Society of Anesthesiologists class, functional status, aneurysm location, preoperative laboratory values, and postoperative complications.

Results: Among the 383 patients evaluated, 5.2% ($n=20$) underwent a reoperation at a median of 8.5 (IQR: 3-18) days postoperatively. The most common reoperations were tracheostomy (25%), ventricular shunt placement (20%), decompressive hemicraniectomy (10%), and craniotomy for hematoma evacuation (10%). Independent predictors of an unplanned reoperation were age greater than 65 years and longer operative time ($p\leq 0.04$). Readmission

occurred in 5.9% (n=22) of patients at a median of 15.5 (IQR: 8.5–21.5) days postoperatively. The most common reasons for readmission were hydrocephalus, seizures, and headache (all 18.2%). Unplanned readmission was independently associated with dependent functional status, morbid obesity, a hematologic comorbidity, preoperative renal insufficiency and hypoalbuminemia ($p \leq 0.02$).

Conclusion: In this national analysis, patients aged greater than 65 years, with a dependent functional status, morbid obesity, a hematologic comorbidity, renal disease, and hypoalbuminemia had significantly higher odds of unplanned reoperation or readmission. This highlights patients who may be at risk of adverse events after clipping of unruptured cerebral aneurysms.

515. Effects of Physical Exercise Following Ischemic Stroke: Too Early is Not a Good Thing

Hajra Khan; Xiaokun Geng; Jose Rafols; Yuchuan Ding (Windsor, Canada)

Introduction: Accumulating evidence has shown that physical rehabilitation post-stroke may reduce morbidity. The extents of these benefits, however, appear to be contingent upon the initiation time of exercise. The specific role of initiation time and the corresponding mechanisms that influence brain repair processes have yet to be thoroughly investigated. In this study, we assessed the hypothesis that very early exercise increases the risk of cell injury by stimulating lactic acidosis and reactive oxygen species (ROS) activation.

Methods: Adult male Sprague-Dawley rats were subjected to middle cerebral artery occlusion for 2 hours and were randomly assigned to 4 training groups: 1) non-exercise, 2) Rota-rod exercise, initiated very early (at 6 h of reperfusion), 3) early (at 24 h), and 4) relatively late (at day 3) post-stroke. Brain injury was determined by cell apoptosis 24 hours after exercise. Brain oxidative metabolism was determined by levels of NADH, ATP and ROS immediately after exercise, while lactic acidosis was also obtained at the same time point.

Results: Apoptotic cell death was significantly ($p < 0.05$) increased in the 6 h but not 24 h exercise group compared to the stroke group without exercise. Apoptosis decreased in the 3 day exercise group compared to the non-exercise stroke group ($p < 0.05$). This exacerbated injury at the very early stage (6 h) was associated with increased lactate levels ($p < 0.05$), although decreased levels ($p < 0.05$) of NADH and ATP were observed in all exercise groups. ROS production was significantly enhanced by early but not late (3 days) exercise.

Conclusion: Lactic acidosis and ROS generation were enhanced by post-stroke exercise, if conducted too early. Early exercise may lose its benefits and diminish long-term functional recovery after stroke. Our results provide a basis for future investigation to reveal a more comprehensive understanding of the time-sensitive exercise effects in post-stroke rehabilitation.

516. Transitional Care Services: A Quality and Safety Process Improvement Program in Neurosurgery

Faith C. Robertson, B.S.; Jessica Logsdon; Sandra Yan; Siobhan Raftery; Timothy Smith; Hormuzdiyar Dasenbrock, MD; William Gormley, MD, MPH (Boston, MA)

Introduction: Few programs have examined the utility of transitional care services for surgical patients in optimizing hospital discharge and enhancing post-discharge surveillance.

Methods: The Department of Neurosurgery at the Brigham &

Women's Hospital established a transitional care program designed to decrease length of stay, improve discharge efficiency, and reduce readmissions. The program emphasized patient education, primarily through a 30-minute exit-consultation with a trained discharge nurse. Patients also received a pre-admission hospitalization overview, anticipated discharge date, daily inpatient contact with the transitional care team, 24-hour advance notice of discharge, in-hospital prescription filling, and a phone call 48-hours post-discharge. Intervention and control patients treated by five neurosurgeons were accrued from elective cases discharged to home; controls were matched by age, sex, and operation. Outcomes were evaluated by multivariable regression.

Results: The program enrolled 416 patients from 2013 to 2015. The intervention significantly reduced length of stay (median 53, interquartile range (IQR) 34–77 hours versus median 57, IQR 36–101 hours among controls, decreased by 17.02%, 95% confidence interval (CI): 9.95–24.10%, $p < 0.001$), increased the proportion of patients with early discharge (40% compared to 18%; odds ratio (OR): 3.13, 95% CI 2.27–4.30, $p < 0.001$), and decreased readmissions (2.5% versus 5.9%; OR: 0.41, 95% CI 0.19–0.88, $p = 0.02$). Subgroup analyses of patients who received the complete or partial intervention revealed that the exit interview was critical for early discharge and readmission reduction.

Conclusion: This transitional care program decreased length of stay and reduced readmission rates after elective neurosurgery, which emphasizes the importance of patient education and surveillance at and after hospital discharge.

518. Prospective Outcomes Evaluation of a Novel Zero-Profile Device for Three- and Four-Level Anterior Cervical Discectomies and Fusion

Peter C. Gerszten, MD, MPH, FAANS; Erin Paschel (Pittsburgh, PA)

Introduction: Anterior cervical discectomy and fusion (ACDF) is a well accepted treatment option for patients with cervical spine disease. Three- and 4-level discectomies are known to be associated with a higher complication rate and lower fusion rate than single level surgery. The role of zero-profile devices in multi-level ACDF is poorly documented. This study was performed to evaluate zero-profile fixation for 3- and 4-level ACDF.

Methods: Twenty-two patients underwent ACDF (C3 to T1) using the Optio-CTM zero profile system (Zimmer Spine). The device is a unique PEEK interbody spacer connected to a titanium plate cover that allows for a load-sharing interface. The variable angle screws prevent stress shielding. This also allows for segmental fixation without a supplemental plate while conforming to patient anatomy. Radiographic fusion was assessed at 3 months. Outcomes were assessed using SF-12 PCS and MCS, VAS pain, and NDI.

Results: There were 18 men and 4 women. Mean age was 61 years; range 41–75 years. The primary indication for surgery was radiculopathy in 12 cases, myelopathy in 6 cases, and both in 4 cases. Clinical improvement was statistically significant for the entire cohort. There were no cases of persistent dysphagia, vocal cord injury, or pseudoarthrosis. Clinical outcome was found to be independent of number of levels fused, smoking, primary indication, age, and sex.

Conclusion: This study found zero-profile instrumentation to be associated with excellent clinical outcomes in patients who underwent 3- and 4-level ACDF. Zero-profile segmental fixation devices should be considered over plates for patients requiring multi-level anterior cervical fusion surgery.

519. Telemedicine in Neurosurgery: Welcome to the Future

Marianne Beare, RN NP; James Ecklund, MD (Falls Church, VA)

Introduction: Telemedicine is a growing technology in medicine. We describe a telemedicine program, initiated in the United States military while many active duty neurosurgeons were deployed to Iraq and Afghanistan. This program has been expanded to civilian practice for increased access to care, and increased access to care, and increased convenience for the patient and surgeon. There is also a valuable international role for the use of telemedicine in neurosurgery in countries without adequate neurosurgical manpower. Expansion of such telemedicine services could facilitate residency training programs, and large international outreach, and promote world-wide access to neurosurgical patient care.

Methods: The present status of telemedicine in our neurosurgical department is presented. A detailed, easily replicated template is described, based on our initiation of a neurosurgical telemedicine program in metropolitan Washington, D. C. Details pertaining to the required equipment and personnel are outlined. Patient response to the program is documented.

Results: The analysis of our telemedicine program indicates that patient satisfaction, cost containment, and surgical case volume all benefit from the provision of neurosurgical tele-services.

Conclusion: Utilization of telemedicine can expand the reach of neurosurgical expertise, locally, regionally, nationally and internationally. The experience of one program in metropolitan Washington, D. C. provides an example of how telemedicine in neurosurgery may be successful throughout the United States and beyond. A neurosurgical telemedicine program allows for equal access to academic medical centers in rural and urban areas as well as internationally, in countries with challenges for transportation to neurosurgical services.

600. Immune responses and clinical outcome after glioma-associated antigen vaccination in children with recurrent low-grade gliomas

Columbia Charity Softball Award

Ian F. Pollack, MD, FAANS; Regina Jakacki, MD; Lisa Butterfield, PhD; Ronald Hamilton, MD; Ashok Panigrahy, MD; Daniel Normolle, PhD; Angela Connelly, BS; Sharon DiBridge, BS; Gary Mason, MD; Theresa Whiteside, PhD; Hideho Okada, MD, PhD (Pittsburgh, PA)

Introduction: Low-grade gliomas (LGG) are the most common childhood brain tumors. Although resection is curative for well-circumscribed superficial lesions, tumors that are infiltrative or arise from deep structures are challenging, and prone to recurrences leading to cumulative morbidity. Accordingly, new treatment approaches are needed. Having identified a panel of glioma-associated antigens (GAAs) overexpressed in these tumors, we initiated a novel pilot trial of vaccinations with peptides for GAA epitopes in HLA-A2+ children with recurrent LGG that had progressed after <2 prior regimens.

Methods: Peptide epitopes for three GAAs (EphA2, IL13Ra2, survivin) were emulsified in Montanide-ISA-51 and administered subcutaneously adjacent to intramuscular injections of poly-ICLC every 3 weeks for 8 courses, followed by booster vaccines every 6 weeks. Primary endpoints were safety and T-lymphocyte responses against GAA epitopes. Treatment response was evaluated clinically and by magnetic resonance imaging.

Results: Fourteen children were enrolled. Other than grade 3

urticaria in one child, no regimen-limiting toxicity was encountered. Vaccination induced immunoreactivity to at least one vaccine-targeted antigen in all 11 evaluable patients: to IL13Ra2 in 3, EphA2 in 10, and survivin in 3. One child with a metastatic LGG had asymptomatic pseudoprogression 6 weeks after starting vaccination, and subsequently had dramatic disease regression with <75% shrinkage of the primary tumor and regression of all metastatic disease, persisting <52 months. Three other children had sustained partial responses, ongoing at 41 and 27 and 6 months, and one had a transient response. A trend was noted between ELISPOT response and progression-free survival. Patients with positive ELISPOT responses to two or more antigens were more likely to have objective responses than those responding to a single antigen ($p = 0.03$, Fisher's exact test).

Conclusion: GAA peptide vaccination in children with recurrent LGGs is well tolerated, with preliminary evidence of immunological and clinical activity.

601 "Awake" MIS TLIF without general anesthesia: Initial clinical and radiographic results with one-year follow-up

Michael Y. Wang, MD, FAANS; Herb Chang, MD (North Miami, FL)

Introduction: One of the goals of minimally invasive surgery (MIS) has been to speed the recovery following surgery. In this cases series we utilized an endoscopic technique for interbody fusion combined with percutaneous screws to obviate the need for complete general anesthesia.

Methods: The first 10 consecutive patients treated with minimum one-year follow-up were included in this series. The patients were all treated using endoscopic access through Kambin's triangle to allow for neural decompression, discectomy, endplate preparation, and interbody fusion. This was followed by percutaneous pedicle screw and connecting rod placement using liposomal bupivacaine for long-acting analgesia. No narcotics or regional anesthetics were used during surgery.

Results: All patients underwent surgery successfully without conversion to open surgery. The average age was 62.2 years. All patients had severe disc height collapse and 60% had a Grade I spondylolisthesis. The mean operative time was 113.5 minutes, and blood loss was 65 cc. Hospital length of stay was 1.4 nights. There were no intraoperative or postoperative complications. Preoperative vs. final clinical metrics demonstrated that the ODI improved from an average of 42.0 to 13.3, and the SF-36 PCS improved from 47.6 to 49.7. The EQ-5D improved from 10.7 to 14.2. There were no cases of nonunion identified radiographically on follow-up imaging.

Conclusion: Endoscopic fusion under conscious sedation may represent a feasible alternative to traditional lumbar spine fusion in select patients. Larger clinical series are necessary to validate that clinical improvements are sustained and that arthrodesis rates are successful when compared with open surgery. This initial clinical series demonstrates the possible utility of this procedure.

602. Stability of latency and topology in functional networks of the human neocortex

Kareem Zaghloul, MD, PhD; Julio Chapeton; Sara Inati (Bethesda, MD)

Introduction: Complex network analysis and graph theory provide powerful tools in both the study of epilepsy and normal cognitive function. Perhaps the most important step in analyzing

brain connectivity, however, is the initial construction of functional networks. Here, we use mutual information to construct stable functional networks of the human cortex based on electrocorticographic data acquired from epileptic patients undergoing seizure monitoring.

Methods: We calculate the average mutual information between voltage traces from pairs of electrodes for a range of time lags, which allows us to extract the strength, latency, and direction of the connection between each electrode pair. For each patient we construct networks using short time blocks collected over several days in order to examine the temporal evolution of these networks. We compare the connectivity at different time points by calculating measures of similarity between adjacency matrices and by comparing topological metrics.

Results: We found extracted network connectivity that is stable over time scales ranging from minutes to days. Notably, connections between electrode pairs that persisted over multiple time blocks had latencies that were significantly preserved across different days. We tracked the latency and direction of stable and causal connections and compared these functional connections to the known dynamic evolution of cortical activity.

Conclusion: Previous studies have suggested that functional connectivity can change dynamically in a matter of seconds. Our results, however, suggest that cortical regions exhibit functional relationships that are remarkably stable and that persist over much longer time scales.

603. Rehemorrhage and Recurrence Rates of Small ACOM Aneurysms post Embolization

Nina Moore, MD; Min Lang, MS; Mark Bain, MD (Cleveland, OH)

Introduction: Anterior circulation aneurysms at our institution are being treated both with open clipping and endovascular coil embolization. From our experience, despite the reported natural history increased risk of anterior circulation aneurysms rupturing above 7mm in diameter, we have encountered a fair amount of ACOM aneurysms rupturing below 7mm in diameter. We looked at retreatment and hemorrhage outcomes for patients treated with endovascular embolization in aneurysms less than 7mm at our institution.

Methods: An IRB approved retrospective analysis of all aneurysms treated endovascularly between 2007 and 2015 was performed. We examined 500 patients, 54 of which were ACOM aneurysms. These patients were evaluated for initial hemorrhage on presentation, treatment strategy, residual aneurysm post treatment, recurrence and re-hemorrhage rates.

Results: 32 ACOMs were less than 7mm in diameter. 12 were discovered when ruptured and 20 were unruptured initially. 9, 5, 9, and 1 underwent coiling, stent assisted coiling, balloon assisted coiling, and balloon/stent assisted coiling, respectively. Of the 32 aneurysms less than 7mm treated via embolization, 7 had residual aneurysm, 8 recurred, 5 were retreated, 2 had intraoperative rupture and 4 re-hemorrhaged.

Conclusion: Small ACOM aneurysms may have a higher rupture risk than other anterior circulation aneurysms which may encourage treatment of smaller aneurysms. Smaller ACOM aneurysms may be more amenable to open clipping as they may be more difficult to treat endovascularly initially given the difficulty in placing enough coils to fully embolize the aneurysm while still doing so safely.

604. ReACT: A Randomized Phase II Study of Rindopepimut (CDX-110) plus Bevacizumab in Relapsed Glioblastoma

National Brain Tumor Society Mahaley Award

John H. Sampson, MD, PhD, FAANS; Annick Desjardins; James Schuster; David Tran; Karen Fink; Louis Nabors; Gordon Li; Daniela Bota; Rimas Lukas; Lynn Ashby; David Reardon (Durham, NC)

Introduction: EGFRvIII, an EGFR deletion driver mutation, is associated with poor long-term survival in glioblastoma (GB). The investigational vaccine rindopepimut consists of an EGFRvIII-specific peptide sequence conjugated to keyhole limpet hemocyanin (KLH), delivered intradermally with GM-CSF. Three phase II studies in newly diagnosed, resected, EGFRvIII+ GB demonstrated encouraging progression-free survival (PFS), overall survival (OS) and safety.

Methods: In the Phase II ReACT study, 73 bevacizumab (BV)-naïve pts in 1st or 2nd relapse with EGFRvIII+ GB were randomized 1:1 to BV plus double-blinded injection of rindopepimut or control (KLH). Endpoints: 6-month PFS (PFS6; primary; target $\alpha=0.2$ by 1-sided chi-square test), objective response rate (ORR), PFS, OS and safety.

Results: Primary rindopepimut toxicity is Grade 1-2 injection site reaction. For rindopepimut+BV vs. KLH+BV (per centralized review; RANO criteria): PFS6=28% (10/36) vs. 16% (6/37) ($p=0.116$); ORR=30% (9/30) vs. 18% (6/34). Cessation of steroids >6 months: 33% (6/18) vs. 0%. Median (95% CI) OS=11.6 (10.0, 16.2) vs. 9.3 (7.1, 11.3) months (HR=0.57 [0.33, 0.98], $p=0.039$). OS analyses adjusted for various prognostic factors consistently favor rindopepimut. Rindopepimut induced robust anti-EGFRvIII titers (1:12,800-1:6,553,600) in 80% of pts. Antibodies, predominantly IgG1 isotype, mediate killing of EGFRvIII+ tumor cells through ADCC and CDC in vitro. Within the rindopepimut arm, peak titer ($\geq 1:12,800$ at any time) and rapid titer generation ($\geq 1:12,800$ by Day 57) were associated with prolonged OS (HR=0.16, $p<0.0001$ and HR=0.59, $p=0.182$, respectively). Survival follow-up continues.

Conclusion: Rindopepimut induces potent EGFRvIII-specific immune response and tumor regression, and appears to significantly prolong survival when administered with BV, in pts with relapsed GB.

605. Cognitive Decline with Whole Brain Radiotherapy after Radiosurgery for Metastases

Leksell Radiosurgery Award

Anthony L. Asher, MD, FAANS, FACS; Paul Brown; Karla Ballman; Elana Farace; Jane Cerhan; S. Keith Anderson; Xiomara Carrero; Fred Barker II; Richard Deming; Stuart Burri; Cynthia Menard (Charlotte, NC)

Introduction: Whole brain radiotherapy (WBRT) significantly improves tumor control in the brain after radiosurgery, yet the role of WBRT remains controversial due to concerns regarding cognitive risks.

Methods: Patients with one-three brain metastases were randomized to radiosurgery alone or radiosurgery plus WBRT, and underwent cognitive testing before and after treatment. Primary endpoint was cognitive deterioration (decline >1 SD from baseline in at least one cognitive test at 3 months).

Results: 213 patients were enrolled. Cognitive deterioration at 3 months was more frequent after radiosurgery plus WBRT vs. radiosurgery alone (91.7% vs. 63.5%, $p < 0.001$). Patients receiv-

ing WBRT experienced more deterioration in immediate memory (30.4% vs. 8.2%, $p = 0.004$), delayed memory (51.1% vs. 19.7%, $p < 0.001$), and verbal fluency (18.6% vs. 1.9%, $p = 0.010$). There was greater deterioration in QOL at 3 months with WBRT, notably functional well-being ($p = 0.006$) and overall QOL ($p = 0.001$). Intracranial tumor control at 3 months was 93.7% with WBRT vs. 75.3% with radiosurgery alone ($p < 0.001$). Median OS was 7.4 months for radiosurgery plus WBRT vs. 10.4 for radiosurgery (HR=1.02, $p = 0.920$). For long-term survivors, cognitive deterioration was more frequent after radiosurgery plus WBRT at 3 months (94.1% vs. 45.5%, $p = 0.007$); no differences were observed in quality of life and functional independence.

Conclusion: Decline in immediate/delayed memory and verbal fluency as well as QOL at 3 months were more frequent with the addition of WBRT to radiosurgery. Adjuvant WBRT did not improve OS despite improved intracranial tumor control. Long-term survivors receiving WBRT also had more cognitive decline.

606. Activated Wnt signaling for the therapeutic targeting of treatment-refractory medulloblastoma stem cells

Branavan Manoranjan; Sujeivan Mahendram; David Bakhshinyan; Michelle Kameda-Smith; Chitra Venugopal; Bradley Doble; Sheila Singh (Toronto, Canada)

Young Neurosurgeons Abstract Award

Introduction: Brain tumors represent the leading cause of childhood cancer mortality, of which medulloblastoma (MB) is the most frequent malignant pediatric brain tumour. Current molecular subgroups of MB recognize distinct disease entities of which activated Wnt signaling (monosomy 6, exon 3 mutations in CTNNB1, and a Wnt gene signature) is associated with a distinct subgroup and the best overall outcome. In contrast, only non-Wnt MBs are characterized by metastatic disease, increased rate of recurrence, and poor overall survivorship.

Methods: Given the excellent clinical outcome in patients with Wnt-driven MB, we aimed to convert treatment-resistant MB subgroups into an ostensibly benign tumor through selective targeting by small molecule Wnt agonists (Wnt3A), GSK3 inhibitors (CHIR99021), and transgenic lines containing a stabilized beta-catenin mutant.

Results: Activated Wnt signaling resulted in decreased in vitro self-renewal and promoted differentiation within primary human MB stem cells. The clinical relevance of these findings were demonstrated with an in vivo survival advantage in human-mouse xenografts containing orthotopic injections of cells with a stabilized beta-catenin mutant representative of constitutively active Wnt signaling. Xenografts generated from Wnt-activated tumors were much smaller in size, maintained a much lower rate of proliferation, and reduction in key MB stem cell self-renewal genes (Bmi1, Sox2, Msi1, FoxG1).

Conclusion: Our work establishes activated Wnt signaling as a novel treatment paradigm in childhood MB, while providing evidence for the context-specific tumor suppressive function of the canonical Wnt pathway.

607. Intravenous Toca 511 Delivery Leads to Viral DNA in Resected High Grade Glioma (HGG)

Steven N. Kalkanis, MD, FAANS; Michael Vogelbaum, MD, PhD; Daniela Bota, MD, PhD; Derek Ostertag, PhD; Oscar Diego; Douglas Jolly, PhD; Jamey Skillings, MD; Kader Yagiz; Joan Robbins, PhD; Alice Chu; Timothy Cloughesy, MD (Detroit, MI)

Introduction: Recurrent HGG remains resistant to therapy with survival ranging from 7.2–9.2 months. An ongoing Phase 1 study (NCT01985256) using retroviral replicating vector (RRV), Toca 511 with oral Toca FC is evaluating the highest tolerated doses and viral pharmacokinetics. Resected tumor is evaluated for presence of virus and transgene.

Methods: Toca 511 doses administered over 1 or 3 day to 9.4×10^9 TU IV/day for 5 days and to 1.2×10^9 TU injected intracranially are followed by Toca FC at 300 mg/kg/day for 7 days.

Results: Tumor samples have demonstrated presence of viral DNA signal in a dose dependent manner with 10/14 (71%) detectable overall of which 7/9 (78%) were in subjects treated with 3 day delivery. Quantifiable viral DNA was found in 6/14 (43%) overall of which 5/9 (56%) was in the 3 day IV cohort. Expression of yeast CD transgene was detectable by IHC. Five weeks after Toca 511 injection, viral RNA could not be detected in blood above the lower quantification limit. As of September 18 2015, all but one subject remain alive with a maximum follow-up of 15.4 months (median follow-up 6.2 months). Based on 11 subjects evaluated by independent radiology review, 1 was reported radiologically to have an unconfirmed CR (with an unrelated stroke) and 2 to have stable disease. Safety data to date shows good tolerability with low grade pyrexia ($n=2$, 18.2%) and related SAEs of cerebral cyst and also vasogenic edema.

Conclusion: This study confirms successful gene transduction following IV delivery of Toca 511.

608. Clinical profiles of 132 cases of intracranial germ cell tumors of the iGCT Consortium

Hirokazu Takami, MD; Shintaro Fukushima, MD, PhD; Kohei Fukuoka, MD; Yoshitaka Narita, MD, PhD; Ryo Nishikawa, MD, PhD; Masao Matsutani, MD, PhD; Koichi Ichimura, MD, PhD (Tokyo, Japan)

Introduction: The Intracranial Germ Cell Tumor Genome Analysis (iGCT) Consortium was established in 2011 to facilitate investigation into the biology and their clinical association in central nervous system germ cell tumors (CNS GCT). Here we present an integrated analysis on the clinical characteristics in relation to genomic data.

Methods: A total of 132 cases (male 117, female 15) were selected for the study. The median age was 16 y.o. in male and 20 y.o. in female. A central pathological review determined 73 pure germinoma, 23 mixed germinoma, 30 non-germinomatous GCT (NGGCT) and 6 others.

Results: Eight cases were under 5 years old, and all had teratoma component except one (YST). Five/ten-year progression-free survival of pure germinoma, mixed germinoma and NGGCTs were 81.0/66.9, 67.5/60.8, and 82.6/64.3 %, respectively; 5/10-year overall survival being 86.4/78.4, 70.3/57.1, and 82.9/66.9 %. Germinoma cases which occurred in neurohypophyseal or pineal regions had significantly longer PFS compared with those outside such predilection areas ($p = 0.004$). Mixed germinoma which harbor a choriocarcinoma component had a significant tendency to occur outside neurohypophyseal or pineal regions ($p = 0.005$). Cases which had an immature teratoma component were significantly younger than those without ($p = 0.007$). No female case ($n=14$) had MAPK pathway mutations, contrasted by a high mutation rate (51.3 %) in male. Serum or CSF hormonal values were available in 120 cases. Elevated AFP was seen in 28 cases and many (8) had a YST component; however mature and immature teratoma cases were also included in 5 cases each. For HCG elevation, 11 cases were found, and one cases of pure germinoma was included. These suggest that elevated hormonal values cannot necessarily lead to the diagnosis

of malignant GCTs and has the possibility of pure germinoma or mature teratoma.

Conclusion: It is imperative to further the integrated analyses of clinical and genomic data in order to clarify the treatment targets.

609. Toca 511 Followed by Toca FC in Subjects with Recurrent High Grade Glioma (HGG)

Manish K. Aghi, MD, PhD, FAANS; Michael Vogelbaum, MD, PhD; Timothy Cloughesy, MD; Santosh Kesari, MD, PhD; Jana Portnow, MD; Derek Ostertag, PhD; Mary Rose Keller, PhD; Alice Chu; Jamey Skillings, MD; George Kaptain, MD (San Francisco, CA)

Introduction: Recurrent HGG remains deadly with survival ranging from 7.2–9.2 months. Viral infection and killing of tumor cells stimulates antitumor immune responses pre-clinically. An ongoing escalating-dose Phase 1 study (NCT 01156584) using a retroviral replicating vector, Toca 511, with oral Toca FC (extended-release 5-FC) is evaluating safety and efficacy.

Methods: Toca 511 is given by 3 different delivery methods: intratumoral (IT) with biopsy needle, IT using real-time MRI guidance/CED, and intravenous (IV). Toca FC is administered for 7 days in monthly cycles starting 4 weeks after injection. Forty-five subjects have been treated (39 efficacy evaluable—received both Toca 511 IT and Toca FC).

Results: Toca 511 doses have been increased to 1.5×10^9 TU IT or 4.6×10^9 TU IV $\times 3$ days and Toca FC doses to 300 mg/kg/day for 7 days have been safe and well tolerated with no DLTs. Related grade ≥ 3 adverse events for Toca 511 and Toca FC are infrequent (4.4%, 5.0%) and no subjects have discontinued Toca FC for toxicity. Median overall survival is improved ($p=0.0249$) using the biopsy needle (13.8 months, 95%CI 7.1, 22.2, $N=21$ vs 7.9 months, 95%CI 4.4, 13.0, $N=18$ using CED). In multivariate analysis biopsy needle delivery, grade 3, recurrences ≤ 2 , and male gender are associated with improved survival. Independent radiology review demonstrated 1 PR (2.6%), 2 unconfirmed PRs (5.1%) and 12 SD (30.8%).

Conclusion: This study confirms the feasibility and safety of transcranial delivery of RRV without resection. Survival with IT biopsy needle compares favorably to historical data.

610. Single cell analysis of long non-coding RNAs in the developing human neocortex and brain tumors

Daniel A. Lim, MD PhD, FAANS ; Siyuan Liu; Tomasz Nowakowski; Alex Pollen; Jan Lui; Max Horlbeck; Frank Attenello; Jonathan Weissman; Arnold Kriegstein; Aaron Diaz (San Francisco, CA)

Introduction: Long non-coding RNAs (lncRNAs) comprise a diverse class of transcripts that can regulate molecular and cellular processes in brain development and disease. lncRNAs exhibit cell type- and tissue-specific expression, but little is known about the expression and function of lncRNAs in the developing human brain.

Methods: Here, we deeply profiled lncRNAs from polyadenylated and total RNA obtained from human neocortex at different stages of development and integrated this resource to analyze the transcriptomes of single cells. To test lncRNA function, we used CRISPR technologies to regulate lncRNA expression in brain tumor cells.

Results: While lncRNAs were generally detected at low levels in bulk tissues, single cell transcriptomics revealed that many lncRNAs are abundantly expressed in individual cells and are cell type-specific. Furthermore, we used CRISPR technologies to show that a specific lncRNA enriched in radial glia but detected

at low abundance in tissues, regulates cell proliferation of human glioblastoma.

Conclusion: The discrete and abundant expression of lncRNAs among individual cells has important implications for their biological function, utility for distinguishing neural cell types, and the development of lncRNAs as brain tumor diagnostics and therapeutics.

611. Cortical plasticity of motor-eloquent areas measured by navigated transcranial magnetic stimulation in glioma patients

Sandro Krieg, MD; Neal Conway; Noemie Wildschütz; Tobias Moser; Lucia Bulubas; Nico Sollmann, MD; Jamil Sabih, MD; Noriko Tanigawa; Bernhard Meyer, MD (Munich, Germany)

Introduction: Better understanding of the mechanisms behind cerebral plasticity, coupled with non-invasive detection of its presence, harbors a huge potential to improve glioma therapy. This study's aim was to demonstrate the frequency of plastic reshaping, find clues to the patterns behind it, and prove it can be recognized non-invasively using navigated transcranial stimulation (nTMS).

Methods: We used nTMS to map cortical motor representation in 22 patients with gliomas affecting the precentral gyrus immediately pre-op, and 3–42 months post-op. Location changes of the primary motor area, defined as hotspots and map centers of gravity, were measured.

Results: Spatial normalization and analysis showed an average primary motor area shift of 4.7 ± 0.8 mm standard error of the mean (SEM) on the mediolateral axis, and 9.7 ± 1.5 mm SEM on the anteroposterior axis. Motor-eloquent points tended to shift towards the resection cavity by 4.5 ± 3.6 mm SEM if the lesion was anterior to the Rolandic region and by 2.6 ± 3.4 mm SEM if it was located more posteriorly. Overall, 8 out of 16 (50%) high-grade and 3 out of 6 (50%) low-grade glioma patients showed a functional shift of over 10 mm at the cortical surface level.

Conclusions: The data from this yet small series show impressively that cortical functional reorganization occurs quite frequently. Moreover, nTMS is shown to detect such plastic reorganization non-invasively. However, since tumor- and deficit-related subgroups might show different patterns, multicentric analysis of a larger cohort seems compulsory. This provides further motivation to join our newly founded multicentric international study group.

612. Biological subtypes and survival outcomes in breast cancer patients with brain metastases: a 406 patients clinical series

Dhiego Bastos, MD; Marcos Vinícius Maldaun, MD; Sujit Prabhu, MD; Sergio Listik, MD; Jeffrey Weinberg, MD; Dima Suki, PhD; Frederick Lang, MD; Paulo Henrique de Aguiar, MD; Raymond Sawaya, MD (Campinas, Brazil)

Introduction: Breast cancer is the major source of brain metastasis in women. There is recognition that breast cancer is a collection of heterogeneous diseases divided in subtypes based on combined molecular features such as hormonal receptors (HR) and HER2 status. We aimed to study clinical differences among biological subtypes.

Methods: Retrospective study with 406 consecutive patients with BM from BC from the Department of Neurosurgery of the MD Anderson Cancer Center from 1997 to 2014. Subtypes were classified as luminal A (HR+/HER2-), luminal B (HR+/HER2+), HER2 (HR-/HER2+), and basal (HR-/HER2-). End points were time to development of brain metastasis (TDBM), brain metastasis free survival (BMFS) and overall survival (OS). Univariate and multivariate cox proportional hazard regression models were used.

Results: In Luminal A, TDBM was 41 months; 58 months for Luminal B; 30 months for HER2; 27 months for Basal ($p<0.001$). BMFS was 9 months for Luminal A; 24 months for Luminal B; 9 months for HER2; and 7 months for Basal ($p=0.06$). For Luminal A, the OS was 20 months, for Luminal B was 22 months, for HER2 was 24 months; and Basal was 9 months ($p<0.001$). In multivariate analyses Basal subtype showed lower OS compared with others subtypes with a hazard ratio of 1.9 ($p<0.001$).

Conclusion: HR and HER2 are the most significant biomarkers that drive BC behavior, including BM. Study of breast cancer heterogeneity among patients is important for understanding the biologic basis of the disease, for planning future clinical investigation of novel therapeutics, and for personalized medicine

613. Galectin-3 mediates glioma-induced immunosuppression through expansion of regulatory T cells

Leonel Ampie; Winward Choy, BA; Jonathan Lamano, MS; Orin Bloch, MD (Bronx, NY)

Introduction: Glioblastoma (GBM) is known to induce immunosuppression through expansion of intratumoral and circulating regulatory T-cells (Tregs). The tumor-derived factors responsible for this phenotypic shift remain undefined. We investigated the role of Galectin-3, a carbohydrate-binding lectin involved in fibrosis and inflammation, in expansion of Tregs in GBM.

Methods: Conditioned media from primary ($n=8$) and established ($n=1$) glioma cell lines were analyzed for Galectin-3 secretion by ELISA. Cell lysates were analyzed for intracellular Galectin-3 via immunoblotting and localization was confirmed by immunohistochemistry of GBM tissue. Healthy control lymphocytes were activated with anti-CD3/CD28 and recombinant Galectin-3, with assessment of lymphocyte phenotype by flow cytometry on day 3 of incubation. Treg fraction (CD4+/CD25+/FoxP3+) and cell surface immune-checkpoint induction were analyzed.

Results: Four of eight primary patient cell lines secreted varying levels of Galectin-3 ranging from 0.2-1.7ng/mL. The established cell line (U87) also produced Galectin-3 (2.77ng/mL). Results were verified via immunoblotting for intracellular protein, which correlated with secretion by ELISA. Stimulation of healthy lymphocytes with 1ug/ml Galectin-3 resulted in increased Treg expansion compared to unstimulated controls (30% vs. 14.2%, $p=0.0002$). Analysis of immune checkpoints on CD4+ cells revealed an increase in LAG-3 expression with Galectin-3 stimulation compared to unstimulated controls (30% vs. 22.8%, $p=0.0014$).

Conclusion: For the first time, we demonstrate that Galectin-3 can induce Treg expansion and LAG-3 expression on CD4+ cells. We also demonstrate that Galectin-3 is secreted by a subset of GBM tumors, contributing to the immunosuppressive environment observed in patients. Our data suggests that Galectin-3 may be a novel target for immunomodulation in GBM.

614. Delayed Clearance of Neural Stem Cells Enhances Migration to Glioma Xenografts After Intranasal Delivery

Drew Allan Spencer, MD; Dou Yu, PhD; Ramin Morshed; Yu Han; Lingjiao Zhang; Maciej Lesniak, MD; Irina Balyasnikova, PhD (Maywood, IL)

Introduction: Glioblastoma multiforme has limited clinical treatment options due to its privileged intracranial location and inherent biology. Intranasal stem cell therapy has previously been investigated in GBM models, showing promising efficacy via tumor-targeted oncolytic virus delivery. However, the efficiency

of tumor-tropic migration by stem cells along this unique passage is yet to be optimized. We hypothesize that the olfactory epithelium covering the cribriform plate serves as a major barrier to the intracranial migration of therapeutic stem cells, limiting delivery of therapeutic payload.

Methods: We aimed to enhance the migratory capacity of therapeutic human neural stem cells (NSCs) toward intracranial GBM xenografts via reversible strategies: 1) biomaterial-facilitated NSC resistance to intranasal clearance; 2) pharmacological intervention to circumvent the barrier function of the olfactory epithelium. First, biocompatible Tisseel was co-administered with NSCs to antagonize clearance by nasal epithelial cilia. Second, experimental animals were pre-treated (48 hours before intranasal NSC therapy) with methimazole, an antithyroid medication with reversible olfactory epithelial toxicity.

Results: Methimazole pre-treatment significantly improved NSC migration to intracranial tumors based on live animal bioluminescence imaging, histology, and immunocytochemical staining of the sagittal sections of brains and cribriform plate areas. The resultant migratory advantage improved therapeutic delivery and animal survival after intranasal delivery of NSCs carrying oncolytic virus to the GBM xenografts.

Conclusion: Our work demonstrates enhanced intracranial migration and therapeutic benefit after intranasal NSC delivery using reversible biomaterial and pharmacological interventions. This modality therefore carries significant potential for clinical translation, and is a promising topic of future study and optimization.

615. Re-evaluation of the relevance of Simpson grading system and recurrence-free survival after surgery for World Health Organization grade I meningiomas

Anil Nanda, MD, MPH, FAANS, FACS; Shyamal Bir, MD, PhD; Tanmoy Maiti, MCh; Subhas Konar, MCh; Bharat Guthikonda, MD (Shreveport, LA)

Objective: Recent report on surgical resection of meningioma challenged the relevance of the Simpson resection grading system as a predictor for recurrence of WHO grade I meningiomas. The authors reviewed their experience of surgical resection of WHO grade I meningiomas and assessed the association between extent of resection, evaluated by the Simpson grade, and recurrence-free survival (RFS) of patients after meningioma surgery.

Methods: Clinical and radiological information of 458 patients with WHO grade I meningiomas who underwent surgery at over the past 20 years, were retrospectively reviewed. Simpson and Shinshu grading scales were used to evaluate the extent of surgical resection. Statistical analysis was conducted using Kaplan-Meier curves and Cox proportional-hazards regression.

Results: Overall tumor recurrence rates for Simpson grades I, II, III and IV of resection were 5%, 22%, 31% and 35% respectively. After Cox regression analysis, Simpson grade I/extensive resection was revealed as a significant predictor of RFS ($p=0.003$). Patients undergoing Simpson grade I and II resections showed significant increase in RFS compared to patients undergoing grades III and IV resection ($p=0.005$). The extent of resection had a significant effect on recurrence rates for both skull base ($p=0.047$) and convexity ($p=0.012$) meningiomas. Female gender and Karnofsky performance score (KPS) >70 were also identified as independent predictors of RFS after resection of WHO grade I meningiomas.

Conclusion: Contrary to recent report, in our cohort of patients, a significant association was noted between the extent of resection and rates of tumor recurrence. In our experience the Simpson grading system maintains its relevance and prognostic value and can serve an important role for patient education. Even though complete

tumor resection is the goal, it should be tailored to each patient depending on the risks and surgical morbidity.

616. An extent of resection threshold for seizure freedom in low grade glioma patients

David Shuo Xu, MD; Nader Sanai, MD (Phoenix, AZ)

Introduction: Seizures are the most common presenting symptom of newly-diagnosed WHO grade II gliomas (LGG) and impair quality of life. Although gross total resection of LGG is associated with better seizure control, it remains unclear whether an extent of resection 'threshold' exists for long-term seizure control. Specifically, what proportion of FLAIR-positive tissue in newly-diagnosed LGG patients must be removed to improve achieve Engel Class I seizure-freedom?

Methods: We identified 128 consecutive newly-diagnosed LGG patients who presented with seizures and were treated at the Barrow Neurological Institute from 2001 to 2011. Patients were then dichotomized into those who were seizure free post-operatively and those who were not. Univariate analysis included the chi-squared test and the Mann-Whitney U test, and a multivariate logistic regression analysis was performed. To determine a threshold of EOR that optimizes seizure freedom, a receiver operating characteristic curve (ROC) was plotted.

Results: At 6 months post-operatively, 105 (82.0%) patients were seizure-free (Engel Class I), while 23 (17.9%) patients were Engel Class II-IV. Univariate analysis found pre-operative KPS, time from diagnosis to surgery, type of seizure, and EOR to be statistically significant. After multivariate analysis, only EOR was found to be a significant predictor of seizure freedom. When plotted on an ROC curve, an EOR of 80% was found to have the highest sensitivity and lowest false-positive rate on both manual inspection and derivation of manual concordance.

Conclusion: For low-grade glioma patients presenting with seizures, a stepwise improvement in both the proportion of seizure-free patients, as well as the durability of their seizure freedom, was observed beyond an 80% EOR threshold. Interestingly, this putative EOR seizure-freedom threshold closely approximates that reported for survival benefit in newly-diagnosed hemispheric LGGs, suggesting that a minimum level of radiographic tumor burden is necessary for both disease and symptomatic progression.

617. Use of an anti-viral drug, Ribavirin, as an anti-glioblastoma therapeutic

Francesco Volpin; Joshua Casaos; Antonella Mangraviti, MD; Tarik Lott; Raphael Felder; Mitchell Rock; Shazia Dharssi; Henry Brem, MD; Betty Tyler; Nicolas Skuli (Baltimore, MD)

Introduction: Ribavirin, an anti-viral molecule primarily used for hepatitis C treatment that inhibits eukaryotic initiation factor eIF4e, has shown anti-cancer effects on breast cancer and acute myeloid leukemia. Since improvements in therapeutic options for patients with glioblastoma (GBM), a grade IV astrocytoma, are necessary, we hypothesized that Ribavirin could affect GBM cell growth both in vitro and in vivo.

Methods: Various GBM cell lines (U87, SF767, LN18, 9L, T98G, F98, 1113, GB1A)- rodent and human- were plated and the effects of Ribavirin on cell proliferation, cytotoxicity, migration and adhesion, and cell cycle arrest and apoptosis analysis via flow cytometry were analyzed. Ribavirin was also tested in vivo, both alone and in combination with current standardized treatments. Intact or immunodeficient rodents orthotopically implanted with rodent or human

GBM tumors, respectively, were treated with systemically delivered Ribavirin and a Kaplan-Meier curve was generated.

Results: We demonstrate that Ribavirin decreases GBM cell proliferation, migration and adhesion, while inducing cell cycle arrest, apoptosis and cell death in vitro for all GBM cell lines tested. We also demonstrate that Ribavirin treatment in combination with temozolomide and radiation therapy induces a synergistic anti-tumoral response in GBM cells through increased cell death in vitro. Ribavirin treatment in vivo significantly improved survival of rats and nude mice orthotopically implanted with 9L tumors ($p=0.00264$) or GB1A cells ($p=0.0002$), respectively.

Conclusion: Ribavirin represents a potential new therapeutic option for the treatment of GBM and may enhance the cytotoxic effects of temozolomide and/or radiotherapy.

618. Systematical analysis of the value of 5-ALA induced fluorescence in brain metastases: experience in 98 patients

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Introduction: Incomplete resection of brain metastases is not uncommon resulting in a worsened patient prognosis. One important cause for incomplete resection is insufficient intraoperative identification of brain metastasis tissue especially in subtypes with a diffuse infiltrative growth pattern. The value of 5-aminolevulinic acid (5-ALA) for visualization of brain metastases remains unclear. The aim of our study was thus to systematically analyze the value of 5-ALA in a large series of brain metastases.

Methods: 5-ALA was administered in 98 patients that were surgically treated for a brain metastasis. By using a modified neurosurgical microscope, the tumor fluorescence status (strong, vague or negative) and fluorescence homogeneity (homogeneous or heterogeneous) was analyzed. After tumor removal, the resection cavity was checked for fluorescence.

Results: Fluorescence (strong: 19; vague: 36) was observed in 55/98 metastases (55%), whereas no fluorescence was found in 44/98 metastases (45%). The fluorescence pattern was homogeneous in 19/36 (53%) and heterogeneous in 17/36 (47%) analyzed fluorescing metastases. Interestingly, the surrounding brain tissue of the resection cavity showed fluorescence in 38/58 (66%) analyzed tumors. While 5/8 (66%) metastases from melanoma showed no fluorescence, all metastases (100%) from renal cell carcinomas revealed fluorescence.

Conclusion: In this largest series to date, we found 5-ALA induced fluorescence in approximately half of the patients with brain metastases. Metastases from specific primary tumors such as renal cell carcinomas demonstrated particular high rates of fluorescence. The significance of fluorescing surrounding brain tissue and its impact on recurrence has to be clarified in future.

619. Development of a Preoperative Predictive Model for Intra- or Peri-operative Major Complications with High Accuracy Validated with 558 ASD Patients

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Introduction: Operative management of ASD patients has high complication rates, and it remains unknown whether baseline

patient characteristics and surgical plans may predict early complications (intraop and periop fewer than 6wk). Development of a preoperative predictive model can aid in patient counseling, decision making, and surgical planning.

Methods: Inclusion criteria: age $\geq$ 18, ASD. 45 variables were included in training of the model and included demographic data, comorbidities, surgical variables, baseline HRQOL, and coronal and sagittal radiographic parameters. Patients were grouped as either having at least 1 major intra- or periop complication (COMP) or not (NOCOMP). An ensemble of decision trees was constructed using the C5.0 algorithm with 5 different bootstrapped models. Internal validation was accomplished via a 70:30 data split for training and testing each model, respectively. Overall accuracy, and the area under a receiver operator characteristic curve (AUC) were calculated.

Results: 558 patients were included, NOCOMP:410(73.5%), COMP:148 (26.5%). Overall model accuracy was 87.6% correct with an AUC of 0.89 indicating a very good model fit. 20 variables were determined to be the top predictors (importance $\geq$ 0.90) and included (in decreasing importance): age, leg pain, ODI, #decompression levels, #interbody fusion levels, PCS, SRS-Schwab coronal curve type, CCI, SRS Activity, T1PA, ASA grade, presence of osteoporosis, PT, SVA, primary vs revision, SRS pain, SRS total, use of BMP, use of iliac crest graft, and PI-LL.

Conclusion: A successful model (87% accuracy, 0.89 AUC) was built predicting major intra- or periop complications. This model can provide the foundation toward improved education and point-of-care decision making for patients undergoing ASD surgery.

620. Predictive Value of Intraoperative Neurophysiological Monitoring in Patients with Normal and Abnormal Baseline Recordings during Spine Surgery

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Introduction: We sought to delineate if having baseline deficits on preoperative recordings increased the predictive value of detecting a new neurodeficit with intraoperative neurophysiological monitoring.

Methods: Analysis of a consecutive series of patients who underwent spine surgery with neurophysiological monitoring during a 3-year period at a university hospital. Sensitivity and specificity were determined using Bayesian techniques. There were 1652 (65.3%) patients with abnormal baseline recordings and 2530 (60.5%) patients with normal baseline recordings. Impact of length of surgery & of variables including age, sex, BMI, DM, HTN, CAD, CVD & history of smoking, on the development of a new neurodeficit was defined.

Results: Seventy (4.2%) & 53 (2.1%) new neurodeficits occurred in patients with abnormal & normal baseline recordings respectively. The OR for developing a new neurodeficit in patients with pre-operative abnormal readings was 2.06 (p0.001, CI95% 1.42%–3.02%). Intraoperative monitoring had a sensitivity of 17% and specificity of 89% in predicting a postoperative neurodeficit in patients with abnormal baseline recordings. In patients with normal baseline recordings this sensitivity and specificity increased to 24.5% and 92.2%, but this was not statistically significant (p=0.35). Neither the length of surgery nor did any analyzed patient related variable have a statistically significant impact on the development of a new neurodeficit.

Conclusion: The odds of developing a new neurodeficit are higher in patients with abnormal baseline recordings. Normal baseline recordings do not increase the sensitivity and specificity of the IOM to predict a new neurodeficit.

621. Manual Muscle Test at C5 palsy onset predicts the likelihood of and time to C5 palsy resolution

Stewart B. Dunsker, MD Award

Mohamad Bydon, MD; Mohamed Macki, MD; Ridwan Alam, BS; Panagiotis Kerezoudis; Ziya Gokaslan; Ali Bydon (Rochester, MN)

Introduction: The primary objective of this study was to identify time to and prognostic factors of C5 palsy resolution.

Methods: All patients over a seven-year period who experienced C5 palsy following a posterior decompression and instrumented fusion surgery were retrospectively reviewed. C5 palsy resolution was defined as a recovery of deltoid muscle function equal to or greater than the preoperative condition as defined by the MMT.

Results: Of the 511 patients who met the selection criteria, 8.6% (n = 44) experienced C5 palsy. MMT information was available for 43 patients: 81.4% (n = 35) had full resolution from their condition. Of the 35 patients who resolved, the median MMT score at onset was 3-. Following a discrete-time proportional hazards model, the hazards of C5 palsy resolution increased by 19% for every 1-grade increase in MMT score at symptom onset (HR=1.19, P=0.005). Moreover, males displayed a 71% lower hazard of resolution than females (HR=0.29, P=0.003). Following an adjusted Kaplan-Meier analysis, the median time to C5 palsy resolution was between 6 months and 1 year. In a multiple linear regression, a lower MMT score at the onset of C5 palsy predicted a longer time to C5 palsy resolution (coefficient=-0.19, P=0.003). Time to C5 palsy onset was not statistically associated with hazards of palsy resolution (P=0.381) or time to resolution (P=0.121).

Conclusion: A higher MMT score at the onset of C5 palsy statistically significantly predicted a higher chance of resolution and a shorter recovery time. In addition, female gender was also associated with a higher hazard of resolution.

622. A Multicenter Prospective Randomized Controlled Clinical Trial to Evaluate the Effectiveness and Safety of a Standalone Percutaneous Interspinous Spacer Versus Decompressive Surgery in Degenerative Lumbar Spinal Stenosis with Neurogenic Intermittent Claud

Bernhard Meyer, MD; Jean Charles LeHuec, MD (Munich, Germany)

Introduction: The objective of this study is to show that a percutaneous IPD is safe and non-inferior to SDS in patients suffering from Degenerative Lumbar Spinal Stenosis with NIC (Neurogenic Intermittent Claudication).

(Multicenter international RCT, NTC00905359)

Methods: 163 patients (mean age 65 $\pm$ 11 years, 51% female) were randomized to IPD or SDS group and followed until 24 months. Physical function, symptom severity and patient satisfaction were assessed by Zurich Claudication Questionnaire (ZCQ) until 24 months. Leg, buttock/groin and back pain were assessed by VAS scores. SF-36v2 questionnaire was used to assess quality of life.

Results: ZCQ physical function mean change from baseline to 12 months (primary outcome variable) decreased equally and without statistically significant difference for both groups (-32 $\pm$ 32%, -37 $\pm$ 23%, p=0.158) and was stable after 24 months. As for secondary outcomes the IPD group showed shorter surgical time and less blood loss (24 $\pm$ 11 minutes and 6 $\pm$ 10 ml, p < 0.001) compared to the SDS group (70 $\pm$ 39 minutes and 157 $\pm$ 145 ml, p<0.001). Symptom severity improved in both groups equally (-31 $\pm$ 27%, -36 $\pm$ 25%, p=0.140, CI -4, +14). VAS leg pain score improved with 59% for the

IPD and 66% for the SDS group from baseline to 24 months follow-up. SF-36 v2 physical and mental score improved equally for both treatment groups. Re-operations at index level occurred in 18 % in the IPD group and in 11 % in the SDS group.

Conclusion: This confirms two recent RCTs. IPDs as well as open decompression achieve both equally satisfying results for NIC with an advantage in some secondary outcomes for IPDs. The excessively higher reoperation rate for IPDs could not be confirmed in this study, which opens a window of indication in a subset of patients with NIC, i.e. those with cardiac or other comorbidities.

623. Clinical Outcomes Following Surgical Management of Coexistent Parkinson's Disease and Cervical Spondylotic Myelopathy

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Introduction: Distinguishing the causes of weakness, imbalance, and gait instability in patients with coexisting Parkinson's disease (PD) and cervical spondylotic myelopathy (CSM) is a diagnostic and therapeutic challenge due to symptomatic similarities. To date, no study has reported outcomes following decompression in patients with coexisting PD and CSM. The present study is the first to report outcomes following decompression for patients with coexisting PD and CSM.

Methods: A retrospective matched cohort study of all patients with coexisting PD and CSM undergoing cervical decompression at a tertiary-care center between January 1996 and December 2014 was conducted. PD patients were matched to patients with CSM alone by age, gender, ASA classification, and operative parameters. Myelopathy was assessed by Nurick and modified Japanese Orthopaedic Association (mJOA) scales. Multivariable regression identified predictors of change in mJOA and relief of myelopathic symptoms.

Results: Twenty-one matched pairs were included. Symptoms improved postoperatively in both groups; however, back pain, radiculopathy, and bowel/bladder dysfunction persisted in PD patients. PD patients experienced poorer improvement in both Nurick (0.0 vs. -1.0, $p < 0.01$) and mJOA (0.9 vs. 2.5, $p < 0.01$) scores. Multivariable regression identified PD as a significant independent predictor of decreased improvement in mJOA ($\beta = -0.93$, $p < 0.01$), failure to achieve a minimal clinically important difference in change in mJOA (OR 0.55, $p = 0.02$) and failure to experience relief of myelopathic symptoms (OR 0.14, $p = 0.02$).

Conclusion: This study is the first to characterize outcomes following cervical decompression in patients with coexisting PD and CSM. PD patients experienced symptomatic improvement, but significantly less improvement in myelopathy compared to controls.

624. Risk factors for 30-day re-operation and 90-day readmission: Analysis from the National Neurosurgery Quality and Outcomes Database Lumbar Spine Registry

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Introduction: To use a prospective, longitudinal, multi-center outcome registry of patients undergoing surgery for lumbar degenerative disease to assess the incidence and risk factors of 30-day re-operation and 90-day readmission.

Methods: The N2QOD lumbar spine registry was analyzed. Multivariate binomial regression analysis was performed to identify

risk factors for 30-day re-operation and 90-day readmission. A sub-analysis of patients with Medicare coverage 65 years and older were compared to patients younger than 65 years-old with Medicare coverage. Continuous variables were compared using unpaired t-tests, and proportions were compared using Fisher's exact test.

Results: 9,852 patients were identified. The 30-day re-operation rate for Medicare patients was 2.5% and 1.8% for privately insured patients ($p < 0.01$). Multivariate analysis revealed that prolonged operative time was an independent risk factor for re-operation within 30 days.

The 90-day readmission rate for Medicare patients was 8.2% and 5.1% private insurance patients ($p < 0.0001$). Multivariate analysis demonstrated that Medicare insurance was associated with higher readmission rates (vs private insurance, OR 1.43, 95% CI 1.17-1.76). Higher ASA grade (OR 1.46 per grade, 95% CI 1.25-1.70) and history of depression (OR 1.27, 95% CI 1.04-1.54) were independent risk factors for readmission.

Medicare patients less than 65 years-old were significantly higher rates of 30-day re-operation and 90-day readmission. They had a higher BMI ($P < 0.01$) and higher rates of depression ($P < 0.0001$).

Conclusion: In this analysis of a large prospective, multi-center registry of patients undergoing lumbar surgery, multivariate analysis revealed that the 30-day re-operation rates were similar for Medicare and private insurance patients. The 90-day readmission rates were higher in Medicare beneficiaries, individuals with higher ASA grades and patients with a history of depression. Medicare patients less than 65 years-old constituted a subgroup who were significantly more likely to be re-operated within 30 days and to be readmitted within 90 days.

625. Survival and Clinical Outcomes in Patients with Metastatic Epidural Spinal Cord Compression: Results from the AOSpine Prospective Multi-Centre Study of 142 patients

Michael G. Fehlings, MD, PhD, FAANS, FRCS; Anick Nater, MD; Lindsay Tetreault; Branko Kopjar; Paul Arnold, MD; Mark Dekutoski, MD; Joel Finkelstein, MD; Charles Fisher, MD; John France, MD; Ziya Gokaslan, MD; Eric Massicotte, MD (Toronto, Canada)

Introduction: Although surgery is being increasingly used in patients with Metastatic Epidural Spinal Cord Compression (MESCC) as a complementary strategy to radiation and chemotherapy, the impact of surgery on quality of life (QoL) is not well established. This study aimed to prospectively evaluate survival, neurological, functional, and QoL outcomes in MESCC patients undergoing operative management.

Methods: A total of 142 surgically treated patients with a single symptomatic MESCC lesion enrolled in a prospective North American multi-center study were followed for 12 months. Clinical data, such as Brief Pain Inventory (BPI), ASIA, SF-36, Oswestry Disability Index (ODI), and EQ-5D scores, were obtained both pre- and post-operatively.

Results: The median survival was 7.7 months. The 30-day and 12-month mortality rates were 9% and 62%, respectively. Six weeks post-operatively, ambulatory status ($p = 0.02$) and bladder control ($p = 0.03$) were significantly improved. Overall, 67.5% of ASIA B, C, or D patients gained at least 1 grade after surgery, 25% remained stable, and 7.5% deteriorated. ODI, EQ-5D, BPI scores were significantly improved at each follow-up ($p \leq 0.01$). SF-36 scores were generally higher after surgery for mental and physical components, and for all domains except energy/fatigue. The incidence of wound complications was 10% and 2 patients required a second surgery (screw malposition and epidural hematoma).

Conclusion: Surgical intervention, as a complementary adjunct to radiation and chemotherapy, provides immediate and sustained

improvement in pain, neurological, functional, and QoL outcomes with acceptable risks in patients with a focal symptomatic MESCC lesion.

626. Impact of Functional Status of Patient on Satisfaction with Surgery 12-months after Elective Spine Surgery for Lumbar Degenerative Disease

Silky Chotai, MD; Matthew McGirt, MD; Clinton Devin; Mohamad Bydon, MD; Kristin Archer; Kevin Foley, MD; Meic Schmidt, MD; Steve Glassman, MD; Jack Knightly; Anthony Asher, MD; N2QOD Investigator group (Nashville, TN)

Introduction: In this era of value-based reforms, the quality of care is measured by patient-reported outcomes (PROs) and patients' perception of overall care. The impact of baseline and 12-month Oswestry disability index (ODI) on satisfaction with surgery is not well documented. In this analysis, we determine the impact of functional status of the patient on satisfaction with surgery.

Methods: Patients undergoing spine surgery for degenerative lumbar disease were entered into prospective multi-center registry (N2QOD). Baseline and 12-months follow-up ODI was recorded. Satisfaction was measured using North American Spine Society (NASS) satisfaction questionnaire. Previously published values of minimal clinically important difference (MCID) for ODI:14.9 was used. Univariable and multivariable analysis were conducted to determine impact of baseline and 12-month ODI on satisfaction.

Results: 64% (n=2768) of total 4302 patients reported that surgery met their expectations at 12-month follow-up. Compared to patients that were less satisfied, patients in whom surgery met their expectations had lower disability at 12-month (14 ± 15 vs. 32 ± 17 vs. 46 ± 18 , $P < 0.001$). Patients with mild baseline disability had lower change scores at 12-month (6.5 ± 11.01) compared to those with severe disability (33.2 ± 23.5) and bed-ridden patients (46.8 ± 27.03) ($P < 0.001$). The proportion of patients achieving MCID was lower in those with mild (35%) and moderate disability (69%) compared to severe disability (77%) and bed-ridden (91%). However, the patients with severe disability at baseline were less satisfied compared to those with mild disability (53% vs. 76%, $P < 0.001$). Multivariable proportional odds logistic regression analysis, controlling for baseline variables, for a fixed baseline ODI score a bigger change score is required to achieve better satisfaction.

Conclusion: Functional status of the patient at 12-month following surgery had a significant impact on satisfaction. Patients with higher baseline ODI achieved higher change scores; however they were not as satisfied. Satisfaction should not be used as a sole yardstick to measure outcomes and quality of care after spine surgery. Clinically significant functional outcomes including 12-month ODI scores and change scores should be utilized to report and promote quality of spine care.

627. Understanding effect of minimally invasive fusion technologies on outcomes after elective lumbar fusion: Analysis of N2QOD registry

Scott Parker, MD; Matthew McGirt, MD; Praveen Mummaneni, MD; Jack Knightly, MD; Deborah Pfortmiller, PhD; Kevin Foley, MD; Anthony Asher, MD (Nashville, TN)

Introduction: While several smaller studies have suggested minimally invasive surgery (MIS) technologies decrease surgical morbidity and reduce hospital stay, evidence to suggest patient-reported outcome benefits remain lacking.

Methods: We analyzed N2QOD aggregate dataset (2010–2014)

to identify one- and two-level lumbar fusion procedures performed for lumbar stenosis and/or spondylolisthesis with 12-month follow-up. Peri-operative and one-year outcomes were compared between cases performed with MIS enabling versus traditional open technologies before and after propensity matching.

Results: 467 (24%) patients underwent elective lumbar fusion utilizing MIS enabling technologies while 1,480 (76%) were performed utilizing traditional open technologies. MIS patients were healthier (ASA grade, $p < 0.001$), more frequently had private insurance ($p = 0.002$), and less frequently underwent two-level fusion ($p < 0.001$). MIS was associated with reduced blood loss ($p < 0.001$), 0.7 day reduction in mean length of hospital stay ($p = 0.001$), and 5% reduced need for post-discharge inpatient rehabilitation ($p < 0.001$); but, equivalent 90-day safety measures. After propensity matching, MIS remained associated with reduced blood loss and length of stay, with equivalent outcomes in all other 90-day safety measures. In both unadjusted and propensity matched comparison, MIS and open technologies were associated with equivalent return to work, patient-reported pain, physical disability, and quality of life at 3- and 12-month follow-up.

Conclusion: Regardless of approach, lumbar fusion was associated with significant and sustained improvements in all measured health domains. When utilized in everyday care by a wide spectrum of spine surgeons, use of MIS technologies was associated with reduced intra-operative blood loss but only a half-day reduction in mean length of hospital stay. MIS was not associated with improved peri-operative safety measures or 12-month outcomes.

628. Postoperative Anterior Cervical Infection: A Multi-institutional Retrospective Database Review of the Incidence and Management

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Introduction: The versatility of the anterior cervical discectomy and fusion (ACDF) has become one of the most commonly performed spinal surgeries. Postoperative surgical site infection (SSI) has been frequently reported in posterior approach spinal surgery while limited guidance is available in the literature for the management of SSI after ACDFs.

Methods: A retrospective multi-center case-series study was conducted involving twenty one high-volume surgical centers from the AOSpine North America Clinical Research Network. Medical records for 17,625 patients who received cervical spine surgery (levels from C2 to C7) between January 1, 2005 to December 31, 2011, inclusive, were reviewed to identify the occurrence of 21 pre-defined treatment complications. Patients who had undergone an ACDF were identified in the database and reviewed for the occurrence of postoperative anterior cervical infections.

Results: A total of 8887 patients were identified from a retrospective database analysis of 17 centers providing data for postoperative anterior cervical infections (17/23, 74% response rate). A total of 6 postoperative infections after ACDF were identified for a mean rate of 0.07% (range 0–0.39%). The mean age of patients identified was 57.5 (std=11.6, 66.7% female). The mean BMI was 22.02. Of the total infections, half were smokers ($n=3$). Two patients presented with myelopathy and three presented with radiculopathic-type complaints. The mean length of stay was 4.7 days. All patients were treated aggressively with surgery for management of this complication, with improvement in all patients. There were no mortalities.

Conclusion: The incidence of postoperative infection in anterior cervical discectomy and fusion is exceedingly low. The manage-

ment has historically been urgent irrigation and debridement of the surgical site. However, due to the rarity of this occurrence, guidance for management is limited to retrospective series.

629. Spinal Fusion for Scheuermann's Kyphosis in Adolescents: An Analysis of the Kids' Inpatient Database

Kavelin Rumalla; Chester Yarbrough, MD; Ian Dorward, MD (Kansas City, MO)

Introduction: The surgical management of Scheuermann's Kyphosis (SK) remains controversial. National trends and complications associated with spinal fusion surgery for SK in adolescents have not been recently reported.

Methods: We queried the Kids' Inpatient Database (available every 3 years) from 2003 to 2012 to identify all hospitalizations (age<10) involving spinal fusion in patients with a diagnosis of SK. Trends in patient characteristics, operative management, and in-hospital outcomes were analyzed. Multivariable logistic regression was used to identify independent predictors of complications.

Results: A total of 1,028 cases were identified. The rate of posterior approaches for spinal fusion (PSF) increased from 60.2% to 94.4% ($P<0.0001$) from 2003 to 2012, while the rate of combined anterior release and posterior fusion (AR/PSF) decreased from 39.8% to 5.6% ($P<0.0001$). The use of bone morphogenetic protein-2 (BMP) increased from less than 1% in 2003 to 18.2% in 2009 and then decreased to 7.6% in 2012. Significant downtrends in complication rate (17.5% to 8.5%, $P=0.016$) and mean length of stay (6.71 days to 5.80 days, $P<0.0001$) were demonstrated over this time period. These improvements were accompanied by a significant increase in mean inflation-adjusted hospital costs (\$50,698 to \$66,351, $P<0.0001$). Factors independently increasing the odds of a complication included comorbidity score (OR: 1.43, 95% CI: 1.16-1.75), AR/PSF approach (OR: 3.32, 95% CI: 2.00-5.50), and BMP use (OR: 2.18, 95% CI: 1.20-3.97).

Conclusion: Our results suggest that the surgical management of SK has trended towards more posterior-only approaches, with a simultaneous increase in cost but a decrease in complications and LOS.

630. Predictors of Quality of Life Outcomes Following Kyphoplasty and Vertebroplasty

Jaes Christian Jones; Jacob Miller, BS; Nicolas Thompson, MS; Dattanand Sudarshana, BS; Thomas Mroz, MD; Edward Benzel, MD (Cleveland, OH)

Introduction: In 2009, two randomized-controlled trials demonstrated no improvement in pain following vertebral augmentation compared with sham surgery. However, a recent randomized trial demonstrated significant pain relief following vertebroplasty compared to controls. Accordingly, we sought to identify factors that may predict favorable pain-related quality of life (QOL) outcomes following vertebral augmentation surgery.

Methods: All patients who underwent kyphoplasty or vertebroplasty at a single institution from 2010–2015 with available prospectively-collected QOL data were included. The PDQ instrument was used to measure pain-related QOL—higher scores indicate greater pain. Multivariable linear regression was used to identify predictors of postoperative PDQ score. 13 candidate predictors were selected a priori: age, gender, smoking history, history of coronary artery disease, depression, and/or diabetes, operative time, location (thoracic, lumbar), time from fracture to surgery, BMI, prior spine surgery, and indication (metastases, osteoporosis/osteopenia, other).

Results: For each additional operative hour, postoperative PDQ

scores increased by 7.6 ($p<0.001$). For each 10-year increase in age, postoperative PDQ scores decreased by 8.2 ($p=0.003$). For each doubling time from fracture to surgery, post-operative PDQ scores increased by 3.6 ($P = 0.036$). Finally, patients with osteoporosis/osteopenia had significantly higher postoperative PDQ scores (19.0 points, $p=0.013$) compared to those with metastatic lesions.

Conclusion: Variables associated with worse postoperative PDQ scores included longer operative duration, younger age, longer interval from fracture to surgery, osteoporosis/osteopenia rather than metastasis, and history of depression. These clinically-relevant predictors may permit identification of patients who may benefit from vertebral augmentation, as well as guide timing of therapy.

631. Comparison of early and late complications after minimally invasive and hybrid adult spinal deformity surgery

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Introduction: This study compares outcomes and complications (COMP) of circumferentially minimally invasive surgery (CMIS) and hybrid surgery (HYB; MIS lateral and open posterior) for treatment of ASD.

Methods: A multicenter retrospective database of ASD patient complications reported as early (eCOMP) <30 days or late (lCOMP) >30 days from surgery. Unpaired t-test and Mann Whitney U used to assess differences between groups.

Results: Of 426 patients, 190 with minimum of 2 year follow-up included for analysis, 104 CMIS and HYB 86. CMIS had significantly less ($p<0.001$) EBL and OR compared to HYB (1584 v.481cc; 681 v 427 min). Radiographic and clinical parameters similar between groups. A mean 4.7 levels fused in CMIS and 8.2 in HYB ($p<0.001$). CMIS had significantly lower rate early major (13.5% v 29.1%, $p=0.007$) and minor complications (9.6% v 36%, $p<0.001$). Minor lCOMP occurred 4.8% of CMIS, 9.3% HYB ($p=0.175$). Major lCOMP 9.6% CMIS and 15.1% HYB ($p=0.175$). Within entire study population, occurrence of an eCOMP (major or minor) resulted in significantly higher ODI at 2 years (table 1). Stratifying by approach, only CMIS major eCOMP had significantly higher ODI at 2 years (41.9 v 27.2, $p=0.023$) vs. no COMP.

Conclusion: Both approaches resulted in patients with satisfactory clinical and radiographic results. Although CMIS had significantly fewer COMP compared to HYB, the occurrence of a major eCOMP in CMIS left patients more disabled at 2 years than those without an eCOMP. Furthermore we found that patients with an eCOMP had worse ODI at 2 years.

632. Predictive Model for Return to Work after Elective Surgery for Lumbar Degenerative Disease: An Analysis from National Neurosurgery Quality Outcomes Database Registry

Silky Chotai, MD; Matthew McGirt, MD; Clinton Devin, MD; Mohamad Bydon, MD; Kristin Archer, MD; Kevin Foley, MD; Meic Schmidt, MD; Steven Glassman, MD; Jack Knightly, MD; Anthony Asher, MD; N2QOD Investigator group (Nashville, TN)

Introduction: Current costs associated with spine care are unsustainable. The productivity loss and time away from work in gainfully employed patients contributes greatly to the financial burden. Therefore, it is vital to identify the factors associated with returning to work after lumbar spine surgery. We present a predictive model

of ability to return to work (RTW) after lumbar spine surgery for degenerative disease.

Methods: Patients undergoing spine surgery for degenerative lumbar disease were entered into prospective multi-center registry (N2QOD). Patients that were employed preoperatively and completed 3-month follow-up were included in the analysis. The time to return to work defined as the period between operation time and date of returning to work. A multivariable Cox proportional hazards regression model, including an array of preoperative factors, was fitted for RTW.

Results: 82.5% of total 3467 patients returned to work within one-year postoperatively. The performance measure of our model (c-index) was 0.71. The risk-adjusted likelihood of RTW within 3-months was higher in patients with higher education level compared to those with less than high school level education. Female patients (HR=0.82, CI=0.76–0.89), African-American versus white race (HR=0.68, CI=0.57–0.81), history of diabetes (HR=0.86, CI=0.75–0.98), preoperative non-ambulatory (HR=0.46, CI=0.23–0.91), dominant back pain as presenting symptom (HR=0.88, CI=0.79–0.99), symptom duration greater than 3-months (HR=0.83, CI=0.75–0.92), higher ASA grades (HR=0.73, CI=0.62–0.85), those employed preoperatively but were not working (HR=0.49, CI=0.44–0.55), those occupied with heavy manual labor (HR=0.52, CI=0.46–0.59) and on workman's compensation (HR=0.41, CI=0.32–0.51) had a lower likelihood of RTW. Patients undergoing fusion compared to those undergoing decompression alone for the diagnosis of disc herniation (HR=0.49, CI=0.35–0.69), recurrent disc herniation (HR=0.42, CI=0.27–0.65), and stenosis (HR=0.48, CI=0.36–0.64) had lower likelihood of RTW within 3-months after surgery.

Conclusion: We identified the predictors of returning to work after lumbar spine surgery. Early identification and discussion with patients regarding the probability of RTW, based on these predictors, has the potential in promoting patient, payers and employers to have realistic expectations for returning to work after surgery resulting in improved patient satisfaction and potential health care savings.

633. Diffusion tensor imaging in a large series of CSM patients correlates with long-term functional outcome

Hesham Soliman, MD, MSc.; Avinash Rao; Shekar Kurpad, MD, PhD; Brian Schmit; Marjorie Wang, MD; Matt Budde (Wauwatosa, WI)

Objective: We investigated the correlation between Fractional Anisotropy (FA) of the high cervical cord and functional recovery in a large group of patients who underwent surgery for CSM and were followed for 2 years.

Methods: CSM patients received diffusion tensor imaging (DTI) scans pre-operatively. FA values of the whole cord at C1-C2 and the level of maximal compression (LMC) were calculated on axial images from these scans. Functional status was measured using the modified Japanese Orthopedic Association (mJOA) scale pre-operatively, and at 3, 6, 12, and 24 months. Correlation between FA and the mJOA assessments was performed using linear regression analysis. Control scans were also performed to compare FA values at the high cervical cord and at the LMC against a normal population using two-sample t-tests.

Results: Forty four patients underwent surgery for CSM and were compared to 24 controls. FA was lower in the surgical candidates at both the high cervical cord (0.56 vs 0.61, $p=0.000002$) and at the LMC (0.51 vs 0.57, $p=0.00004$). FA at the LMC was found to have a positive correlation with pre-operative mJOA ($mJOA=9.94*FA+8.43$, $p=0.048$). Additionally, there was a persistent trend throughout the post-operative follow-up showing an

inverse relationship between pre-operative FA and post-operative improvement in mJOA. This was most significant at 12 months post-operation ($\Delta mJOA = -20.49*FA + 11.14$, $p=0.003$).

Conclusions: In the largest longitudinal study of this kind so far, FA shows promise as a biomarker for predicting improvement following decompressive surgery for myelopathy. With further study, it could be used as an objective measure of functional status in CSM and provide a concrete basis with which to discuss expected recovery patterns in patients following decompressive surgery.

634. Combining Biological Therapy with Deep Brain Stimulation for the Treatment of Parkinson's Disease

Craig van Horne, MD PhD, FAANS; Jorge Quintero, PhD; John Slevin, MD; Julie Gurwell; Greg Gerhardt, PhD (Lexington, KY)

Introduction: We are investigating a strategy that couples a biological therapy with DBS surgery in an attempt to deliver neurotrophic factors to areas of the brain affected in PD. We are implanting autologous sural nerve grafts containing Schwann cells, which are known to release growth factors including GDNF, NGF, BDNF, and NT-3. We describe our ongoing clinical trials examining the safety and feasibility of this approach in PD patients undergoing DBS surgery.

Methods: Multi-stage, DBS surgery targeting the subthalamic nucleus or internal globus pallidus was performed using standard procedures. A 5mm section of sural nerve was excised, stripped of the epineurium, cut into 1mm pieces, and unilaterally delivered into the area of the substantia nigra or nucleus basalis of Meynert after DBS electrode implantation. Multiple clinical assessments, including UPDRS profiles, were performed at scheduled time points up to 24 months. Adverse events were continuously monitored.

Results: Our 1-year Phase I study (NCT01833364) of 8 participants found that 6 of 8 participants showed a lower UPDRS III motor score than at baseline (25.5 ± 16.8 at 12 months vs. 32.5 ± 9.8 at baseline; Mean $\pm$ SD, N=8) representing more than a moderate clinically important difference (Shulman et al. 2010). We have begun a follow-up, open-label, two-year study of safety and feasibility (NCT02369003) that expands the location of DBS electrodes placement and the graft target. Grafts have been delivered to the substantia nigra (n=10) and to the nucleus basalis of Meynert (n=1). Immediate post-operative MRIs did not indicate evidence of abnormality. Adverse event profiles for the two studies were comparable to standard DBS surgery.

Conclusions: Initial results from two clinical trials indicate a potentially safe and feasible means of delivering biological therapy at the time of DBS surgery.

635. Cortical-basal ganglia loop interactions during movement revealed through intracranial recordings in Parkinson's disease subjects

Ahmad Alhourani; Anna Korzeniewska, PhD; Efsthios Kondylis, BS; Witold Lipski, PhD; Thomas Wozny, BS; Nathan Crone, MD; Donald Crammond, PhD; Robert Richardson, MD, PhD (Pittsburgh, PA)

Introduction: Pathological oscillatory changes in broadband gamma frequencies have been described both in the subthalamic nucleus (STN) and cortex of subjects with Parkinson's disease (PD), but casual relationships between neural activity in these structures is unknown. Using intracranial local field potential (LFP) recordings, we employed Event-Related Causality (ERC) techniques to explore these interactions.

Methods: LFPs were recorded simultaneously from STN and sensorimotor cortex while PD subjects (n=5) performed an incentivized, bimanual handgrip task, during implantation of DBS leads. Using the gamma frequency band between 70-150 Hz (high gamma), ERC was calculated by constructing a multivariate autoregressive model based on the signal of interest from M1, S1 and STN channels. A false discovery rate correction of 5% was applied.

Results: Causal interactions between neuronal population activity in the STN and sensorimotor cortex were demonstrated. Cortical high gamma power modulated high gamma power in the STN, prior to and during movement, suggesting that cortical neural activity drives STN activity in that epoch. In contrast, high gamma power in the STN modulated cortical high gamma power at the termination of movement, suggesting that STN neural activity influences cortical activity most strongly during the arrest of movement.

Conclusion: The directionality of causal interactions across the basal ganglia-cortical motor loop is specific to different phases of motor planning and execution. These novel data highlight the value of intraoperative recordings in movement disorders patients for furthering our understanding of activity within the cortical-basal ganglia network and for informing interpretation of existing models of basal ganglia function.

636. Producing Artificial Sensation through Cortical Stimulation in Humans

Philip L. Gildenberg MD Resident Award

Daniel Kramer, MD; Brian Lee, MD, PhD; David Brown, BS; Tatyana Dobrova, BS; Christian Klaes, PhD; Richard Andersen, PhD; Charles Liu, MD, PhD (Los Angeles, CA)

Introduction: The restoration of sensation has vast implications following the loss of functional control. This is a proof of concept study aimed at generating artificial sensation through cortical stimulation in humans.

Methods: Two epilepsy patients undergoing implantation of cortical electrodes for the purpose of seizure localization were implanted with a 64-channel, mini-subdural grid over the hand area of primary sensory cortex. Using parameter ranges established in standard cortical mapping for epilepsy surgery, the hand area was stimulated using the mini-subdural grid. Subsequently, several target acquisition tasks were performed. Subjects passed their hand over objects until the correct target was found, at which point stimulation through the mini-subdural grid was applied to assess if the subjects were able to reliably interpret this signal as sensory feedback to locate the target.

Results: First, the hand was mapped, revealing multiple distinct sensory areas which were consistently identified 100% of the time. Second, stimulation parameters were altered independently, however only a change in intensity was reported by the patient. Finally a two target, four target, and three by three directional grid of targets (to establish a directional correct answer such as diagonal) were tested with 50 trials each. Accuracy by both subjects on all three trials was 100%. No adverse events were encountered.

Conclusion: This proof of concept study suggests that safe stimulation can produce three adjustable variables through artificial stimulation; topographic location, on/off discrimination, and intensity of signal were all 100% accurate.

637. Multimodal use of MEG in epilepsy surgery: slow waves, spikes, and functional connectivity

Dario J. Englot, MD, PhD; John Rolston, MD, PhD; Doris Wang, MD, PhD; Heidi Kirsch, MD; Srikantan Nagarajan, PhD; Edward Chang, MD (San Francisco, CA)

Introduction: Potential uses of magnetoencephalography (MEG) to help noninvasively identify the epileptogenic zone (EZ) in epilepsy surgery and predict seizure outcome include: i) epileptic spike localization, ii) slow wave lateralization, and iii) measurements of resting-state functional connectivity. This is the first study to evaluate multimodal MEG techniques to aid the presurgical evaluation of patients with intractable focal epilepsy.

Methods: We studied 132 focal epilepsy patients who received MEG followed by resection at our institution (follow-up mean = 3.6 years). Interictal spike mapping was performed using dipole source modelling, and MEG/EEG recordings were evaluated for prominent asymmetric slowing (1-4 Hz). In 61 adults without invasive lesions, functional connectivity maps were generated.

Results: Interictal spikes were modelled in 78% of 132 patients, and among those with successful modelling, MEG findings were concordant/specific to the region of resection in 66% of patients. Whereas 85% of patients with concordant/specific MEG spikes became seizure-free, this outcome was achieved by only 37% of individuals with non-specific or discordant MEG spikes ($\chi^2 = 26.4$, $p < 0.001$). Asymmetric large-amplitude slowing was observed on interictal MEG recordings in 16% of 132 patients, and lateralized to the EZ in all but one (95%) patient. MEG was significantly more sensitive for asymmetric slowing than EEG, as lateralized EEG slowing was only present in 52% of individuals with MEG slowing, and none of the patients without MEG slowing had asymmetric EEG slowing ($\chi^2 = 63.4$, $p < 0.001$). Finally, patients with increased regional functional connectivity within the resection site were more likely to achieve post-operative seizure freedom (88%) than those with neutral (64% seizure free) or decreased (48% seizure free) connectivity ($p < 0.02$, chi-square).

Conclusion: Multimodal use of MEG offers a novel and valuable approach for noninvasive localization of the EZ and prediction of seizure outcome in epilepsy surgery.

638. GABA-A Receptor $\alpha 1$ and $\alpha 3$ Subunit Density and Cellular Localization in the Human Parkinsonian Brain

Joshua Miles Diamond; M. Lopes, MD; William Elias, MD; Laura Jansen, MD, PhD (Charlottesville, VA)

Introduction: The pathophysiology of Parkinson's disease remains poorly understood. An improved understanding of the neurochemistry of the pallidum could aid in the development of treatment strategies. An increase in expression of the $\alpha 1$ subunit of the GABA-A receptor has been observed in the globus pallidus of humans with Huntington's disease. Subunit expression in the basal ganglia of PD has not been studied. The objective of this study was to determine whether differences exist in expression of GABA-A receptor $\alpha 1$ and $\alpha 3$ subunits in human parkinsonian patients as compared to controls.

Methods: Immunohistochemical studies were performed on post-autopsy tissue samples from the globus pallidus of three patients with idiopathic PD and on five nonparkinsonian, age-matched controls.

Results: Expression of both $\alpha 1$ and $\alpha 3$ subunits was significantly decreased in parkinsonian patients as compared to controls, in both the GPe and GPi. We found two distinct populations of neurons in the globus pallidus: large projection neurons and small interneu-

rons. While the large neurons expressed both $\alpha 1$ and $\alpha 3$ subunits, small interneurons expressed $\alpha 3$ only.

Conclusions and relevance: Our results shed light on the pathophysiology of PD, and could inform future treatments. Reduced $\alpha 1$ and $\alpha 3$ expression in the GPe may represent a compensatory response to excess local GABA levels. However, reduced GABA-A receptor expression in the GPi may actually serve to worsen symptoms. A potential therapy might act to increase $\alpha 1$ activity in the GPi, thus reducing the excess thalamic inhibition seen in PD. The subpopulation of $\alpha 3$ -positive interneurons could also serve as a therapeutic target. Since local circuit interneurons tend to be inhibitory, activating these interneurons could suppress the activity of large projection neurons within that same nucleus. Activating local interneurons in the GPi, then, would also reduce forward inhibition of the thalamus.

639. A Method for Connectivity Guided Targeting of the Subcallosal Cingulate Region

Evangelia Tsolaki; Nader Pouratian (Beverly Hills, CA)

Introduction: Clinical outcomes for deep brain stimulation (DBS) of the subcallosal cingulate (SC) for treatment resistant depression (TRD) depend on the structural connectivity of the targeted region. Our goal is to develop a method for identifying the optimal region within the SC region on a patient specific based on structural connectivity.

Methods: Preoperative MR diffusion tensor and postoperative CT imaging of the brain were acquired in two patients with TRD who underwent bilateral DBS implantation in SC. We used FSL to evaluate the voxel-wise probabilistic connectivity with each of four patient-specific targets (ventral striatum, cingulum, and bilateral prefrontal cortex) and thereby derive the sub-region with the highest joint probability of connectivity to all 4 targets. Concordance of probabilistic connectivity maps and postoperative lead positioning was compared to clinical outcomes.

Results: The seed-based classification identified distinct probabilistic maps to each target. Joint probabilities identified clusters with the highest connectivity probability with all 4 patient-specific targets. CT fusion confirmed that leads traverse this voxel cluster. The subject with closer spatial correlation between DBS contact and the cluster of interest demonstrated greater clinical response to DBS.

Conclusion: This report provides preliminary results about the effectiveness of SC DBS targeting based on joint probabilistic connectivity maps, providing a tomographic maps that could be used in an intuitive fashion for DBS surgical planning, potentially improving the accuracy and efficacy of DBS.

640. Creation of a Novel Ultrahigh-Resolution 3-D Atlas of the Basal Ganglia and Thalamus for Neurosurgery

Abbas F. Sadikot, MD, PhD, FAANS; Ayca Alyinkaya, MD; Claude Lepage, PhD; Alan Evans, PhD (Montreal, Canada)

Introduction: Current cytoarchitectonic brain atlases registered to MRIs can enhance boundary identification, but are restricted by low-resolution, stereotactic discordance in different planes, and lack of well-validated protocols for atlas to patient-MRI registration. To overcome these limitations we created a high-resolution 3-D segmented atlas of the basal ganglia and thalamus, from the first ultrahigh-resolution cytoarchitectonic atlas of the human brain (BigBrain, Amunts et al, Science, 2013). We determined surgical utility by evaluating atlas positions of electrophysiologically-verified DBS electrodes.

Methods: Merker-stained 20 μ m-thick coronal sections were digitized at ultrahigh-resolution (10 μ m) thru the entire healthy brain of a 65-year-old man. A segmented atlas of the basal ganglia and thalamus was created (180 nuclei/tracts) by analyzing 1/20 of 2440 coronal sections. The atlas was registered to standard reference MRIs (MNI-152, ADNI), and to DBS patient MRIs using a combination of intensity and gradient based cross-correlation methods, and non-linear MRI image matching algorithms.

Results: We created the first interactive segmented 3-D atlas of the basal ganglia and thalamus, also containing cytoarchitectonic information reformatable in virtually any plane. MRI-atlas registration was validated by: 1) A volume-of-overlap analysis suggesting <95% voxel overlap between segmented nuclei (thalamus, striatum, GPi) in MRIs and the atlas 2) Demonstrating DBS positions verified by electrophysiology in Parkinson's disease (n=22) or Essential Tremor (n=10) had at least one contact in the subthalamic nucleus (14/16 leads), ventrolateral thalamus (13/14) or pedunculopontine nucleus (2/2), or in close proximity (3/32, <2mm).

Conclusion: This is the highest resolution 3-D volumetric segmented atlas of the human basal ganglia and thalamus. It provides a digital tool for augmented visualization of subcortical nuclei in neurosurgery and neuroscience. Results so far suggest excellent MRI-atlas registration in PD and ET. However, registration may be more challenging with more severe atrophy or deformation, and must be critically evaluated in each case.

641. Hippocampal functional connectivity disruption in Mesial Temporal Lobe Epilepsy captured using Magnetoencephalography

Ahmad Alhourani; Thomas Wozny, BS; Zachary Jessen, BS; Efsthios Kondylis, BS; Ajay Niranjani, MD, MBA; Avniel Ghuman, PhD; Robert Richardson, MD, PhD (Pittsburgh, PA)

Introduction: Structural imaging often does not reveal pathology within the hippocampus of subjects with mesial temporal lobe epilepsy (MTLE). In contrast, magnetoencephalography (MEG) may be sensitive to alterations in hippocampal network connectivity. We developed a novel method using MEG to demonstrate functional connectivity of the hippocampus in normal subjects and in those with MTLE.

Methods: 15 healthy controls and 22 subjects with unilateral MTLE (11 left, 11 right) underwent 5 minutes of non-task, eyes-open recordings using a 306-sensor MEG. A deep brain activity model was used to account for subcortical regions in modeling the source activity. The source signals were bandpass filtered into the canonical delta (1–4Hz), theta (4–8Hz), alpha (8–12 Hz) and beta (13–30 Hz) frequency bands and transformed using the Hilbert transform. Functional connectivity was estimated using the phase locking value (PLV) across a 2 minute period. Permutation testing was used to test for significance for intrahippocampal connectivity.

Results: In normal subjects, the hippocampus was found to be highly connected to the prefrontal cortex, parietal and temporal lobes. In comparison to MTLE subjects, decreased connectivity to these regions was observed in both frequencies. In subjects with left-sided onset, intrahippocampal connectivity was greater on the side of seizure onset, while in subjects with onset on either side, contralateral intrahippocampal connectivity was decreased, compared to the same side in controls.

Conclusion: Global and intra-hippocampal connectivity contralateral to the side of seizure onset are decreased in MTLE. Recovery of this functional connectivity may relate to improvements in cognition following temporal lobectomy.

642. Lactate Dehydrogenase Marks a Metabolic Switch in Epileptic Neurons

Roger Murayi; Alex Ksendzovsky, MD; Sara Inati, MD; Kareem Zaghoul (Bethesda, MD)

Introduction: Lactate dehydrogenase (LDH) plays a critical role in anaerobic metabolism, and recent studies in mouse models have demonstrated that LDH mediates changes in neuronal membrane potential and epileptic activity. Aberrant activity of LDH-A specifically in astrocytes has been hypothesized to disrupt the astrocyte-neuron lactate shuttle and to contribute to epileptogenesis. Here, we demonstrate neuronal up-regulation of LDH-A, previously undescribed, in epileptic tissue. Our data suggest that LDH-A expression is dynamic and specific to epileptic neurons and provide insight into the role of metabolism in epileptogenesis.

Methods: We analyzed temporal lobe, amygdala, and hippocampal tissue collected from 12 patients who underwent anterior temporal lobectomy for refractory epilepsy. We collected tissue from one patient based on electrographic characteristics of the overlying subdural electrodes, as determined during intracranial monitoring (ictal, interictal, normal, slow-wave, hippocampus and amygdala). We conducted immunohistochemistry (IHC), immunofluorescence and real-time PCR to probe for metabolic enzyme transcription and expression.

Results: IHC of temporal cortex, amygdala and hippocampus revealed a statistically significant up-regulation of LDH-A in neurons of epileptogenic hippocampus when compared to histologically normal temporal cortex, where LDH-A stained predominantly within astrocytes. PCR confirmed LDH-A mRNA up-regulation in epileptic hippocampal tissue. In contrast, pyruvate dehydrogenase, a downstream enzyme responsible for aerobic metabolism, demonstrated a significant decrease in IHC staining within neurons of epileptic tissue. Immunofluorescence of tissue selected based on electrographic properties confirmed neuronal LDH-A up-regulation in hippocampus and ictal onset zone neurons when compared with electrographically silent cortex.

Conclusion: Our data demonstrate an increase in LDH-A transcription and enzyme expression, and a coordinated decrease in PDH expression, in epileptic neurons. Taken together these data suggest that molecular mechanisms underlying focal epilepsy may be related to a metabolic switch from neuronal aerobic to anaerobic metabolism.

643. Mapping Synaptic Pathology and Aberrant Mesoscale Connectivity in Human Epileptic Hippocampus

Robert Mark Richardson, MD PhD, FAANS; Ahmad Alhourani, MD; Michael Modo, PhD; Kenneth Fish, PhD (Pittsburgh, PA)

Introduction: Remarkably little is known about the synaptic organization of the hippocampus in humans, despite the large societal impact of temporal lobe epilepsy. Methodological constraints in studying tissue from humans with epilepsy have limited interpretation of historical findings, as previous studies have relied primarily on morphological characterization using single label immunohistochemistry.

Methods: Tissue sections were obtained from en bloc resections of the hippocampus (n=5) in patients with intractable epilepsy and compared to age-matched post-mortem controls (n=5). A post-image capture intensity/morphological segmentation and classification platform was combined with quintuple-label fluorescence confocal microscopy for the bouton-level evaluation of GABAergic synapses in the dentate gyrus. One additional en bloc resection was subjected to ex vivo high-resolution multi-parametric 11.7T MR imaging with microtractography and coregistered immunohistochemistry.

Results: Quintuple-labeling enabled the identification and char-

acterization of perisomatic GABAergic boutons on the soma of dentate neurons, via simultaneous visualization of parvalbumin, two isoforms of glutamic acid decarboxylase (GAD65/GAD67), and vesicular GABA transporter. Qualitative assessment suggested that profound functional reorganization of perisomatic synapses of axo-axonic and basket cells onto dentate granule neurons occurs in both sclerotic and nonsclerotic epileptic hippocampi. Quantitative data will be presented. Separately, MR imaging data demonstrated that aberrant connections within regions of the hippocampus may be detectable via mesoscale tractography.

Conclusion: The study of en bloc hippocampal resections from epilepsy patients is significantly underdeveloped. The demonstration of these novel molecular and mesoscale imaging techniques highlights the potential of this work to greatly inform our understanding of the organization of the normal and diseased human hippocampus.

644. Evidence for Interregional Oscillatory Phase Relationships Mediating Seizure Dynamics: Towards Novel Anti-epileptic Stimulation Therapies

Thomas A Wozny; Witold Lipski, PhD; Ahmad Alhourani, MD; Efsthios Kondylis, BSE; Scott Stanslaski; Jon Giftakis; Robert Richardson, MD, PhD (Pittsburgh, PA)

Introduction: Neuronal oscillations reflect rhythmic fluctuations in the excitability of neuronal populations and have been extensively studied in epilepsy. Since certain phases of an oscillation correspond to either relative excitation or inhibition of the local population, we hypothesize that particular interregional phase relationships facilitate, while others suppress, the generalization of focal onset seizures.

Methods: One rhesus macaque with idiopathic epilepsy was implanted with clinical deep brain stimulation leads in the bilateral hippocampi, connected to a sensing-enabled pulse-generator. Periods of interictal activity (<2.5 hrs total) and seizures (n=27) were recorded on the implanted device. Inter-hippocampal phase coherence was computed across a range of frequencies (1–150Hz). Seizures were aligned by their onset, and their coherence values were compared to interictal values to find periods of consistent changes in inter-hippocampal coherence across seizures.

Results: All seizures began in the right and spread to the left hippocampus. Three periods of increased inter-hippocampal phase coherence were observed during seizures: 1) low-frequency coherence at seizure onset 2) high-frequency coherence during the middle of the seizure 3) a return to low-frequency coherence at seizure termination. All three periods of increased coherence displayed consistent inter-hippocampal phase differences across seizures with each time period exhibiting a preference for a different phase.

Conclusion: These novel data suggest that different patterns of increased phase coherence are associated with different stages of seizure evolution, and that particular interregional phase differences may either facilitate or inhibit ictal activity. In ongoing work, we are investigating the effects of phase-specific hippocampal stimulation on coherence and seizure suppression.

645. Volumetric Trends Associated with MRI-Guided Laser Induced Thermal Therapy (LITT) in Mesial Temporal Sclerosis

Arthur Carminucci, MD; Nitesh Patel, MD; Neil Majmundar, MD; Shabbar Danish, MD (Newark, NJ)

Introduction: MRI-guided laser induced thermal therapy (MRgLITT) is a minimally invasive procedure for the treatment of refractory epilepsy in patients with mesial temporal sclerosis (MTS). Limited data exists on the post-ablation volumetric trends associated with the procedure.

Methods: Seven patients with MST underwent stereotactic amygdalohippocampectomy using the LITT procedure. Two independent raters computed ablation volumes at the following: pre-ablation (PreA), immediate post-ablation (IPA), 24 hours post-ablation (24PA), first follow-up post-ablation (FPA), and greater than 3 months follow-up post-ablation (<3MPA), using OsiriX DICOM Viewer. Statistical trends in post-ablation volumes were determined for the time points. Additionally, the student's t-test was utilized for inter-rater reliability.

Results: The mean initial volume of the amygdalohippocampal complex measured 2.36 cm^3 ($p=0.7$). Post-ablation volumes peaked at the IPA time point (5.54 cm^3) and were significantly larger when compared to the PreA (2.65 cm^3), 24PA (3.50 cm^3), FPA (3.20 cm^3), and <3MPA (2.42 cm^3) time points. ($p<0.04$) (Fig.1). The average volume increase [95% CI] for the IPA, 24PA, FPA, and <3MPA were 218% [145–290%], 137% [97–177%], 121% [71%–170%], and 68% [51–84%] respectively. There was no statistical difference between the 24PA, FPA, and <3MPA time points ($p<0.08$). There was no difference in inter-rater reliability among the time points.

Conclusion: MRgLITT for stereotactic amygdalohippocampectomy produces a maximal increase in post-ablation volume immediately following the procedure, which decreases and stabilizes at 24 hours post-procedure and beyond 3 months follow-up. We recommend post-ablation volume assessments be made at least 24 hours post-MRgLITT.

646. Modeling Healthcare Expenditures associated with Implantable Neurostimulation for Headache Disorders

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Introduction: Chronic daily headache is a considerable source of morbidity for patients and also carries an enormous economic burden. Patients who fail standard medication regimens lack well-defined therapies, and neurostimulation is an emerging option for these patients. The purpose of this study was to analyze the cost utility of implantable neurostimulation for treatment of headache.

Methods: We utilized the Thompson Reuters Marketscan Database to identify individuals diagnosed with headache disorders who underwent percutaneous neurostimulation. Healthcare expenditures for individuals who subsequently received permanent, surgically implanted neurostimulatory devices were compared to those who did not. Only individuals who sought implantable neurostimulation were included to account for headache severity. The cohorts were adjusted for comorbidity and prior headache-related expenses. Costs were modeled longitudinally using a generalized estimating equation.

Results: A total of 579 patients who underwent percutaneous trial of neurostimulation were included, of which 324 (55.96%) converted to permanent neurostimulation within one year. Unadjusted expenditures were greater for patients who underwent conversion to the permanent neurostimulation device, as expected. Costs grew at a

lower rate for patients who converted to permanent device implantation. Cost neutrality for patients receiving the permanent device was reached in less than five years after the enrollment date.

Conclusions: Our study suggests that implantable neurostimulation reduces healthcare expenditures within a relatively short time period in patients with severe refractory headache.

647. Electromagnetic tracking of severe tremor motion kinetics

Seth F. Oliveria, MD, PhD; Kelly Foote; Frank Bova (Gainesville, FL)

Introduction: Severe, intractable tremors are often composed of multiple components. In particular, there is often an underlying oscillatory component that may respond to Deep Brain Stimulation (DBS) therapy, and an ataxic component that is unlikely to improve after DBS. These can be difficult to differentiate clinically, which makes surgical decision making difficult.

Methods: We used electromagnetic tracking to measure symptomatic upper extremity tremor in patients undergoing DBS therapy for severe, intractable tremor. Tremor kinetics were recorded from the finger, wrist, elbow and shoulder during finger-nose-finger and spiral drawing tasks either before and after DBS placement or in the DBS-on and DBS-off states after surgery. After the data were de-trended and fast Fourier transforms were applied, power spectra were generated to identify voluntary, ataxic and oscillatory tremor components of the performed tasks.

Results: Spectral analysis of upper extremity tremor kinetics can readily distinguish low frequency ($< 1 \text{ Hz}$) motion from high frequency non-voluntary ($< 1 \text{ Hz}$) motion. Further analysis of the non-voluntary motion can distinguish oscillatory tremor from coexisting non-oscillatory ataxic movement. Together these findings were used to determine the relative contribution of non-oscillatory motion for each individual before and after deep brain stimulation.

Conclusion: Electromagnetic tracking of severe upper extremity tremor can be used distinguish coexisting ataxia from oscillatory tremor. This can be helpful when evaluating and counseling patients with complex tremor that may experience only a limited response to DBS therapy.

648. Tractography-defined VIM nucleus: comparison of deterministic and probabilistic methods

Francesco Sammartino; Vibhor Krishna, MD; Nicolas Kon Kam King; Andres Lozano; Mojgan Hodaie (Toronto, ON, Canada)

Introduction: VIM thalamus is a common target for functional procedures on tremor. The gold standard for targeting is indirect targeting and MER. We previously developed a methodology that uses deterministic tractography to do thalamus parcellation and we validated the results using a probabilistic tractography algorithm.

Methods: 3T (GE, Signa) DTI and structural T1 imaging from 6 patient candidates to VIM thalamotomy or DBS for tremor were analyzed as part of a previous study. Briefly after preprocessing, deterministic tractography was carried using StealthViz software (Medtronic Inc.) following a methodology previously developed by our group. A 3D object corresponding to the 4 voxels in the center of the parcellated VIM nucleus was then created and exported as overlay on the 3DT1 sequence. Its coordinates were then used as a seed for FSL probtrackx. The tractography results were then transformed in T1 space for comparison.

Results: The output from probtrackx as overlay in T1 space was analyzed. For each of the 6 patients it was possible to identify con-

nectivity between the seed mask and the motor/premotor area as well as the ipsilateral and contralateral dentate nucleus, thus confirming the previous findings. It was always possible to identify the dento-rubro-thalamic tract contralateral component in all our subjects.

Conclusion: In this comparison study it is shown as the deterministic tractography algorithm, though displaying a lower degree of connectivity between the target rois, it was at the end more suitable for targeting in a clinical setting. The main advantages of the streamline tractography are the faster analysis and display of results as compared to the FSL ball&stick model. In a ideal research setting it could be reasonable to integrate both tractography approaches to gain reliable results, although this could be considerably time consuming and can add another level of complexity when studying structural connectivity between different brain regions.

649. Melodic Music Enhances Synchronization of Neuronal Firing Patterns in the Subthalamic Nucleus During Awake DBS Surgery in a Patient with Parkinson's Disease

Rebecca Achey; Darlene Lobel, MD; Damir Janigro, PhD (Cleveland Heights, OH)

Introduction: Music therapy reduces motor symptoms of Parkinson's disease (PD). However, the physiologic basis for this has not been described. Previously, we demonstrated that melodic music decreases neuronal firing frequency in the thalamus during deep brain stimulation (DBS). To better elucidate the mechanism by which music affects motor symptoms, we examined the effect of melodic versus rhythmic music on neuronal activity in the thalamus and subthalamic nucleus (STN) using microelectrode recording (MER).

Methods: A PD patient undergoing DBS listened to a melodic piece, Beethoven's op. 7, and a rhythmic piece, Ligeti's Grand Macabre, during MER in the thalamus and STN. Stable neuronal units were isolated from three electrodes, spaced 2 mm apart. One minute music clips were interspersed with 15 seconds of silence. Neuronal activity from each electrode and synchronicity of neuronal firing across adjacent electrodes was analyzed using pCLAMP and OriginLab software.

Results: In the STN, melodic music increased neuronal synchronization by 40% while rhythmic music decreased synchronization by 20%. Both melodic and rhythmic music decreased neuronal firing frequency (melodic: $52.7 \text{ Hz} \pm 1.43$ vs preceding silence: 62.1 ± 2.85 ; rhythmic: $65.1 \pm .99$ vs 74 ± 1.99 , $P < .001$ for both). In contrast, thalamic neurons responded to both pieces with increased followed by decreased synchronization.

Conclusion: Melodic music enhanced neuronal firing synchronization in the STN of an awake patient undergoing DBS. This suggests that music and DBS may share similar mechanisms to reduce motor symptoms of PD. Future studies will correlate music's effect on neuronal firing patterns during DBS with post-operative changes in motor and non-motor outcomes.

650. Interstitial directional high intensity ultrasound in a 6-hydroxydopamine lesioned rodent model of Parkinson's disease

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Introduction: In the past, pallidotomy was used for the treatment of Parkinson's Disease (PD); however in the late 1990s, this treat-

ment was largely replaced by deep brain stimulation. The advent of MR guided HIFU has caused a resurgence in interest in lesioning for movement and psychiatric disorders.

Methods: Rats were lesioned in the right medial forebrain bundle using an injection of 6-hydroxydopamine. Parkinsonian phenotype was established behaviorally, and rats were assessed at baseline for quantitative measurements of gait, locomotive activity, and balance. Animals were then lesioned using HIU applicators for thermal therapy at the target location. Ablation zone was calculated post-operatively.

Results: We first demonstrated that a HIU device can be placed and applied in naive animals. Following this, seven PD animals underwent HIU treatment, and three underwent behavioral testing before and following (24h, 72h, 5 days) HIU treatment. HIU settings were adjusted for the survival of PD animals and edema only occurred at higher voltage. No significant changes were noted from baseline to 5 days following HIU treatment in parkinsonian symptoms, gait, locomotion or anxiety, though step test results marginally improved.

Conclusion: We have demonstrated that interstitial HIU can be used in a PD rodent model, and have established that survival rates in PD rats are higher at lower wattage. HIU can be safely administered and we will next develop a HIU device fitted for use in rodent brain to evaluate efficacy with more accurate delivery.

651. The iSys1® Roboter Reduces Entry and Target Point Errors in Navigation-Guided Frameless Stereotactic Implantation of Depth Electrodes in Patients with Therapy-Refractory Epilepsy

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Introduction: Recently, a novel technique for a navigation-guided frameless stereotactic approach for the placement of depth electrodes in epilepsy patients has been published by our group. It uses a bone fixated guide (GIDE) for stereotactic drilling, screwing of a fixation bolt and implantation of the electrode. To further improve the accuracy of this technique, we implemented the iSys1® robot, which avoids the need for a manual alignment of the Vertek® articulate biopsy arm along the trajectory.

Methods: Twelve patients (6 male, 6 female) with an overall of 70 electrodes (30 left, 40 right) have been included in the study. The mean length of the planned trajectories was $47.9 \pm 23.2 \text{ mm}$ ($19.0 - 100.3 \text{ mm}$). All procedures were performed with the neuronavigation system Medtronic S7® and the Synergy Cranial version 2.2 software and the iSys® robot.

Results: The mean target alignment error before and after insertion of the percutaneous bolt as measured intraoperatively by neuronavigation was 0.06 mm ($0-0.2 \text{ mm}$) and 0.32 mm ($0-1 \text{ mm}$), respectively, resulting in a mean setup stability of 0.26 mm ($0-0.9 \text{ mm}$). Digital reconstruction of the postoperative CT scans showed a mean real error at the entry point of $1.45 \text{ mm} \pm 0.78$ ($0-3.4 \text{ mm}$) and at the target point of $1.78 \text{ mm} \pm 1.06$ ($0.4-6.7 \text{ mm}$). Compared to our data obtained from the manual technique, the mean real error at the entry point could be reduced by almost 60% from $3.5 \pm 1.4 \text{ mm}$ to $1.45 \pm 0.78 \text{ mm}$. Furthermore, the mean real error at the target point was reduced by almost 40% from $3.0 \pm 1.9 \text{ mm}$ to $1.78 \pm 1.06 \text{ mm}$.

Conclusion: The iSys1 robot is an accurate, versatile and easy-to-use tool for the frameless stereotactic navigation-guided placement of depth electrodes.

652. Long Term Hemorrhagic Risk in Pediatric Arteriovenous Malformation (AVM) Patients

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Introduction: Compared to the general population, the specific natural history of pediatric arteriovenous malformations (AVMs) is less well understood. Furthermore, few pediatric studies have compared post-treatment hemorrhagic risk and functional outcome across different treatment modalities. We aim to elucidate these points in this study.

Methods: We retrospectively reviewed all AVM patients age <18 years admitted to Johns Hopkins Hospital from 1990–2013. The natural history of AVM was assessed by hemorrhagic risk during the observation period. For treated patients, the observation period was defined as the interval between diagnosis and treatment. Post-treatment hemorrhagic risk and functional outcomes were also assessed.

Results: A total of 124 pediatric AVM patients were evaluated, and ninety patients (72.6%) were retained through follow-up. Average age was 13.2±3.8 years, with follow-up period of 9.92 years. Overall obliteration rate was 44.2% with radiosurgery at 34.7%. Thirteen patients were conservatively managed. Annual hemorrhagic risk during the observation period was 0.9%. Post-treatment risk by treatment modalities was: surgery±embolization (0.0%), radiosurgery±embolization (0.8%), embolization alone (2.8%), surgery+radiosurgery±embolization (3.5%) and observation (0.8%). Significantly higher risk of post-treatment hemorrhage was observed for patients with hemorrhagic presentation ($p=0.039$) in multivariate Cox regression analysis. Seizure presentation, frontal lobe location, non-headache presentation, and treatment modality were significantly associated with increased risk of poor functional outcomes.

Conclusion: The natural history of hemorrhage in pediatric AVM patients was 0.9% per year. Surgical resection remained the optimal management for hemorrhage control and preservation of functional outcome in pediatric AVMs. AVM obliteration is the goal of treatment, especially for patients with ruptured presentation, to prevent further hemorrhages in later life.

653. Verbal and Visual Memory Functioning In Children with Chiari Type 1

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Introduction: Allen and colleagues (2014) recently documented subtle cognitive deficits in a small sample of adults with Chiari Malformation Type 1 (CM 1) following decompression surgery. At present, only case studies and small cohorts (Dunn et al., 2014) have been presented investigating cognition in children with CM 1. The present study attempted to identify the memory profile in the largest cohort of children with CM 1.

Methods: 73 children, mean age of 11 (range 6–17 years) consecutively recruited at a university based surgery clinic completed standardized neuropsychological measures of verbal learning and memory [California Verbal Learning Test-Children's Version (CVLT-C)] and incidental visual learning and memory [Rey Complex Figure Test and Recognition Trial (RCFT)]. Performances were compared to normative references, with means, percentages and T tests calculated using SPSS-22.

Results: On the verbal memory measure, total free recall was in the average range [$T=51.5$ (11.1)], as was delayed free recall [$T=50.7$ (11.5)] and recognition performances [$T=52.9$ (9.9)] compared to age peers. In contrast, individuals with CM Type 1 displayed mildly impaired incidental free recall of visual material [$T=40.1$ (11.1)] and delayed free recall [$T=38.9$ (10.9)] with average recognition memory skills [$T=46.8$ (12.6)]. This was mediated by constructional deficits.

Conclusion: Children with CM Type 1 displayed subtle visual retrieval based memory difficulties, yet intact verbal memory processing. This is consistent with prior data indicating a role of the cerebellum in visual attention, memory and planning. Further research into the cognitive and emotional functioning associated with childhood onset Chiari Malformation Type 1 is warranted based on recent survey results in adults, the vulnerability of the cerebellum during development and implications in other developmental disorders (e.g. autism).

654. Differential contributions of syrinx size and tonsil position to presence and magnitude of scoliosis in Chiari I malformation

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Introduction: Scoliosis in the setting of Chiari I malformation (CM) with or without syrinx has not yet been well defined. Specifically the relationship between radiologic syrinx characteristics and tonsil position with the presence or magnitude of scoliosis is unclear.

Methods: All patients with CM (tonsil position ≥ 5 mm below the foramen magnum) were identified from 13,928 consecutive individuals undergoing brain or cervical spine imaging over an 11-year interval. Imaging features such as width, cranial and caudal extent and length of syrinx, tonsil position, and degree of largest curve were recorded.

Results: 509 patients with CM were identified. 117 had a syrinx (≥ 3 mm in width), 114 had scoliosis (cobb angle ≥ 10 degrees) and 72 patients had both syrinx and scoliosis. In patients with CM and syrinx, there was no difference in tonsil position according to presence of scoliosis. Patients with scoliosis had wider (8.6 vs. 6.4 mm, $p<0.01$) and longer (9.7 vs. 6 levels, $p<0.001$) syrinxes. When controlling for age, sex, tonsil position, length, width and cranial extent of syrinx, only syrinx length was independently associated with the presence of scoliosis ($p<0.01$). However only tonsil position was independently associated with degree of curve ($p<0.05$) after controlling for age, sex, and width, length and cranial extent of syrinx. For patients with CM, syrinx and scoliosis, tonsil position correlated with curve magnitude ($p<0.05$), but there was no correlation for patients with CM and scoliosis without a syrinx ($p=0.78$).

Conclusion: In CM patients, syrinx length, but not tonsil position, is independently associated with scoliosis. Conversely, tonsil position is independently associated with degree of greatest curve, but syrinx length and width are not. There may be different pathophysiological processes at play for the presence and degree of scoliosis in patients with CM.

655. Comparison of Posterior Fossa Volumes and Clinical Outcomes After Chiari I Decompression

Siri Sahib Singh Khalsa, MD; Alan Siu, MD; Justin Cappuzzo, BS; Robert Keating (Ann Arbor, MI)

Introduction: The purpose of this study is to determine whether a larger volume change of the posterior cranial fossa (PCF) after

Chiari I (CM1) decompression correlates with improved clinical outcomes. Most studies have been limited by two-dimensional quantitative methods, while more current 3D methodologies necessitate time-intensive manual segmentation. We thus sought to develop a more automated tool to calculate 3D PCF volumes, and correlate with outcomes.

Methods: A semi-automated segmentation program was developed, and used to compare the pre and postoperative volumes of the PCF and the CSF spaces (prepontine cistern, fourth ventricle, and cisterna magna) in CM1 patients. Volume changes were correlated with symptomatic improvements in headache, tonsillar descent, cervicomedullary kinking, and overall surgical success.

Results: A total of 42 patients were included in this study. The mean percentage increase in PCF volume was significantly greater in patients who had clinical improvement vs. no improvement in headache (5.89% vs. 1.54%, $p < 0.05$) and tonsillar descent (6.52% vs. 2.57%, $p < 0.05$), and overall clinical success was associated with a larger post-operative PCF volume increase ($p < 0.05$). These clinical improvements were also significantly associated with a larger increase in the volume of cisterna magna ($p < 0.05$).

Conclusion: A greater increase in the post-operative PCF volume, and specifically an increase in the cisterna magna volume, was associated with clinical improvements in headache and tonsillar descent.

656. Long-term Reliability of Neuroendoscopic Aquelectomy in Idiopathic Aquelectomy related Hydrocephalus

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Introduction: Endoscopic aquelectomy (AP) was considered to be an alternative approach compared to endoscopic third ventriculostomy (ETV) in hydrocephalus related to idiopathic aquelectomy stenosis in the end of the 1990s. After promising preliminary reports, little is known about the long-term efficacy of AP.

Methods: The authors report their long-term results of AP for the treatment of idiopathic aquelectomy stenosis.

Results: 20 patients (14f, 6m, mean age 41.7 years, range from 0.5 to 67 years) were treated at our institution between 1996 and 2002. Two patients were lost to follow-up. One patient died 6 months after aquelectomy, but not related to the procedure itself. Mean follow-up for 17 patients was 107.5 months. Clinically relevant aquelectomy reclosure was observed in 11 patients after a mean follow up of 53.4 months. All of them underwent an ETV, 5 combined with a re-AP. All re-AP's remained unsuccessful during further follow-up. In 6 other patients, MRI revealed aquelectomy stenosis after a mean follow up of 91.9 months. No patient who underwent an ETV required further surgical intervention.

Conclusion: Our study indicates a high risk of AP failure in the treatment of idiopathic aquelectomy stenosis. Aquelectomy reclosure/stenosis occurred in 17 (85%) patients during long-term follow up, whereas no sufficient long term follow-up was available for 3 (15%) patients. ETV should be the procedure of first choice to treat idiopathic aquelectomy stenosis. AP remains reserved for a limited number of patients, when ETV is not feasible, but should then be combined with stenting to avoid reclosure of the aqueduct.

657. The Thoracolumbar Injury Classification and Severity Score in Children: A Validity Study

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Introduction: There are multiple classification systems for injuries of the thoracolumbar spine. The more recent Thoracolumbar Injury Classification and Severity Score (TLICS) has been shown to be a valid and reliable tool for adult patients. We aim to assess the validity of the TLICS system in pediatric patients.

Methods: A retrospective review of the medical records was completed for pediatric patients with acute, traumatic thoracolumbar fractures at two Level 1 trauma centers. A TLICS score was calculated for each patient using computed tomography and magnetic resonance images, along with the neurologic examination recorded in the patient's medical record. TLICS scores were compared with the type of treatment received.

Results: TLICS calculations were completed for 166 patients. The average patient age was 11.1 (± 4.2) years. Males represented 55.7% of patients. Eighty-two percent of patients were white. The most common mechanisms of injury were motor vehicle accident (41.3%), fall (31.7%), sports related (10.8%), and ATV accident (7.8%). The mean TLICS score was 2.98 (± 2.87). When a score of greater than or equal to 4 was considered indicative of the need for surgical treatment, TLICS correctly predicted the treatment modality in 84.9% of cases, with a positive predictive value of 64.8% and a negative predictive value of 94.6%. The scoring system had a specificity of 84.8% and a sensitivity of 85.4%.

Conclusion: The TLICS system demonstrates satisfactory validity for selecting thoracolumbar injury treatment in pediatric patients, in addition to clinical judgment.

658. Stereotactic Laser Ablation in the Management of Lesional Frontal Lobe Epilepsy in Children

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Introduction: MRI-guided laser thermal ablation is a relatively new stereotactic surgical technique. Results of surgical removal of epileptiform lesions of the frontal lobe are often suboptimal, and may cause significant morbidity. We hypothesized that the laser ablation technique would provide good seizure control and decreased post-surgical morbidity.

Methods: Our epilepsy database was reviewed from June 2013 to present. Only patients with at least 6 months follow-up were included in the analysis. All patients had pre-surgical workup consistent with seizures originating from the frontal lobe. Most had depth or subdural electrode placement for confirmation. Laser applicator probes were stereotactically placed in the operating room, and ablations were performed in the MRI suite. All patients were evaluated for surgical outcome (Engel class) and morbidity.

Results: 30 of 122 patients undergoing intracranial procedures had laser ablations. 8 of 30 (26.67%) had focal frontal ablations. 7 patients had lesions consistent with dysplasia (2 with tuberous sclerosis), and one with benign glioma. Depth electrodes were placed in 6 patients (one also had subdural grids). 7 patients were Engel Class Ia and one patient class 3a outcomes. One patient had temporary foot weakness after surgery. No patient to date had neuropsychological sequelae.

Conclusion: MRI-guided laser thermal ablation appears to be

effective for children with lesional frontal lobe epilepsy. Seizure outcome is equivalent or better than resective surgery although longer term follow-up is required. Laser ablation may therefore be an effective alternative to traditional resection for treating seizures induced by frontal lesions while providing decreased risk of physical and neuropsychological deficits.

659. Altered glial precursor cell (GPC) specification leads to neonatal hydrocephalus in a Bardet-Biedel Syndrome (Bbs1) knockout mouse model.

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Introduction: Hydrocephalus is a neurodevelopmental disorder with an estimated prevalence of 1 in 1000 live births.¹ BBS is an autosomal recessive human disorder with impaired cilia, and 25% of human patients present with ventriculomegaly and clinical signs of hydrocephalus.³ Hydrocephalus is fully penetrant in mice with conditional knockout of the Bbs1 gene.³ Our lab recently demonstrated that NG2+PDGFR- α OPCs in Bbs1 mutant mice develop neonatal hydrocephalus, uncovering a possible mechanism for this disease in humans.³ In this study, we show that a novel set of GPCs markers are significantly altered in Bbs1 mutant mice, suggesting that abnormalities in GPC development can lead to hydrocephalus.

Methods: Using Cre-LoxP recombination, we conditionally knocked out the BBS1 gene in our Bbs1flox/flox mice during GPC specification. Bbs1 wild type and mutant mouse brains were sectioned and immunostained at various developmental time points during oligodendroglialogenesis. GPC developmental markers were quantified with confocal analysis and immunocytochemistry. Statistical analysis was then performed to compare these markers across genotypes.

Results: We identified a set of GPC developmental markers that were temporally and spatially regulated in the genesis of neonatal hydrocephalus and that differed significantly between Bbs1 conditional knockout mice and their littermate controls. These markers implicate gliogenesis as a key developmental step in regulating hydrocephalus.

Conclusion: Our results demonstrate that GPC maturation and lineage specification are involved in the genesis of hydrocephalus in our BBS1 mouse model. Future studies will be focused on the molecular and cellular mechanisms governing GPC development in hydrocephalus.

660. The Effect of the Xiao Procedure on Bladder Volume and Quality of Life: Results of a RCT

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Introduction: Our group previously reported a lack of efficacy of the Xiao procedure for producing functional voiding, continence or reproducible bladder contractions. Here we report more detailed results regarding the effect of the Xiao procedure on bladder volume and contractility.

Methods: A randomized, prospective, double blinded trial was initiated in March 2009, enrolling children with spina bifida with neurogenic bladder dysfunction who were scheduled for spinal cord detethering for the usual indications. At the time of detethering, patients were randomized between two arms of the study: half of the patients underwent a standard spinal cord detethering procedure

alone and half underwent detethering plus the Xiao procedure. Patients, families and study investigators were all blinded to the treatment arm during their 3 year follow-up. .

Results: Twenty patients were enrolled in the study: 10 undergoing only spinal cord detethering and the other 10 undergoing the Xiao procedure in addition to standard spinal cord detethering. While the Xiao procedure did not result in improved continence, controlled voiding or reproducible bladder contractions, patients who underwent the Xiao procedure in addition to spinal cord detethering were more likely to experience an improvement in their quality of life and they had a more sustained increase in bladder volume after surgery.

Conclusions: The Xiao procedure did not result in controlled urination or continence in patients undergoing spinal cord detethering, but their quality of life was improved compared to controls, possibly the result of increased bladder volumes related to spinal nerve root sectioning.

661. In Vitro Analysis of Tenascin-C Expression in Pediatric Brainstem Glioma

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Introduction: Diffuse intrinsic pontine glioma (DIPG) is a highly morbid pediatric brainstem tumor. Tenascin-C (TNC) is an extracellular matrix protein associated with NOTCH pathway activation, and is expressed during normal brain development by oligodendroglial cells (OPCs), the purported DIPG cell of origin. We previously reported TNC overexpression in DIPG tissue and CSF, associated with Histone H3K27M mutation. We therefore investigated the pattern and effect of TNC expression using pediatric glioma primary cell lines.

Methods: TNC expression was evaluated in H3K27M mutant DIPG (n=2) and H3K27 wild type pediatric glioma cell lines (n=5). Cell lines were modified to evaluate effects of altered TNC expression on proliferation, migration and differentiation in vitro. H3K27 methylation, CD133, BMI, and NOTCH-1 expression was also evaluated in tumor cell lines and tissue specimens.

Results: TNC was detected in pediatric glioma primary cell lines (n=6), but did not correlate with K27M mutation or WHO grade. Decreased H3K27 and TNC promoter methylation was observed in H3K27M mutant tumors relative to wild-type. Tumor-specific TNC expression was confirmed in DIPG tissue specimens (n=22) compared to normal controls (n=16). Overexpression of TNC was associated with altered differentiation, proliferation and migration.

Conclusions: Here, we report the pattern and effect of TNC expression in pediatric brainstem glioma (DIPG) in vitro. Our findings suggest TNC may play a role in maintaining stem-like features in OPCs, possibly contributing to brainstem gliomagenesis. Further in vitro and in vivo studies exploring the mechanism of overexpression and effects of targeting TNC expression in DIPG are planned.

662. Intra-arterial Chemotherapy for Retinoblastoma: Safety, Efficacy, Technical Nuances, and Lessons Learnt from 450 Consecutive Cases

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Introduction: Preliminary experience with intra-arterial chemotherapy (IAC) has shown promising results in the treatment of advanced and medically refractory retinoblastoma. We assess the safety and efficacy of IAC in the largest series of patients with retinoblastoma to date.

Methods: A total of 450 IAC procedures were performed between June 2010 and June 2015. Each patient was scheduled for 1-7 cycles of IAC at monthly intervals, and the number of cycles was based on the tumor response. Our technique consists of catheterization of the ostium of the ophthalmic artery only, followed by superselective injection of melphalan, topotecan, and/or carboplatin in a pulsatile fashion over 30 minutes. Data on procedural safety was prospectively recorded.

Results: Several important technical and protocol refinements have been made over the study period to address evolving challenges. The technical success rate was 99%. There were 4 overall complications (0.89%): 2 internal carotid artery spasms during cannulation, 1 tiny infarct on magnetic resonance imaging, and 1 femoral artery thrombosis requiring 48h of intravenous heparin. None of these complications left permanent morbidity. No patients developed retroperitoneal hematoma, internal carotid artery dissection, or intracranial hemorrhage. After IAC with a mean follow-up of 19 months, globe salvage was achieved in 72% of primary-treated cases and in 62% of secondary-treated cases. Over the past 3 years, the combined incidence of ophthalmic, retinal, and choroidal vascular ischemia was reduced to 1%. There were no instances of metastasis, secondary tumor, or death.

Conclusion: Intra-arterial chemotherapy is a novel technique in the management of retinoblastoma that provides remarkably high rates of globe salvage. Technical complications are usually benign and uncommon (<1%). A proper operative technique is crucial to maximize the efficacy of chemotherapy and minimize its toxicity. Intra-arterial chemotherapy holds promise for thousands of infants and young children around the globe suffering from retinoblastoma.

663. Location-based algorithmic approach for surgical treatment of complex middle cerebral artery aneurysms

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Introduction: Complex aneurysms of the middle cerebral artery (MCA) not amenable to endovascular or clipping techniques may require a bypass when outflow arteries are compromised by the aneurysm occlusion. Various bypass techniques, both extracranial-to-intracranial (EC-IC) and intracranial-to-intracranial (IC-IC), are available, and bypass selection can be confusing. An algorithmic approach to classify these lesions and determine an optimal bypass strategy has not been established.

Methods: The prospectively maintained database of vascular neurosurgery at our institution was queried for MCA aneurysms treated with bypass. Aneurysms were classified as pre-bifurcation, bifurcation, and post-bifurcation. Patient records, operative notes, imaging studies, and outcomes were analyzed retrospectively.

Results: During a seventeen-year period, 30 patients with complex MCA aneurysms required a total of 33 bypasses. 8 MCA aneurysms were pre-bifurcation, 5 were at the MCA bifurcation, and 17 were post-bifurcation MCA. Bypasses included: 10 low-flow EC-IC bypasses using the superficial temporal artery; 5 high-flow EC-IC bypass using the cervical carotid artery as a donor; 3 reimplantations; 8 reanastomoses; 3 in situ bypasses with side-to-side anastomosis; and 4 IC-IC bypasses with interposition grafts. For pre-bifurcation aneurysms, incorporation of lenticulostriate arteries in the aneurysm was the most important factor dictating aneurysm obliteration and bypass strategy. The obliteration strategy (trapping

vs. parent artery occlusion) affected selection of bypass the most for bifurcation and post-bifurcation aneurysms. There was no operative mortality, and 90% of patients experienced good outcome.

Conclusion: MCA aneurysm location relative to the MCA bifurcation and the aneurysm obliteration technique dictate bypass selection. The proposed algorithms may guide the selection of the optimal bypass from the many EC-IC and IC-IC bypass options that are possible with these aneurysms. Good patient outcomes can be expected when bypass techniques are applied to these complex aneurysms.

664. Pituitary dysfunction after aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis

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Introduction: The prevalence of hypothalamic-pituitary dysfunction after aneurysmal subarachnoid hemorrhage has not been precisely determined and conflicting results have been reported in the literature. Timing of hormonal evaluation after the event and differences in endocrine tests and thresholds may explain this variability. Our goal was to perform a systematic review and meta-analysis investigating the prevalence of pituitary insufficiency after aneurysmal subarachnoid hemorrhage, and to focus on basal serum and dynamic test differences.

Methods: The prevalence of pituitary dysfunction was quantified at 3–6 months and >6 months after aneurysmal subarachnoid hemorrhage. Proportions were transformed with the logit transformation. A subgroup analysis was performed focusing on the differences in outcome between basal serum and dynamic tests for the diagnosis of growth hormone deficiency and secondary adrenal insufficiency.

Results: Overall prevalence of hypopituitarism differed considerably between studies, ranging from 0.05–0.45 in studies performed between 3–6 months after the event, and from 0–0.55 in long-term studies (>6 months), with pooled frequencies of 0.31 (95% CI: 0.22–0.43) and 0.25 (95% CI: 0.16–0.36), respectively. Pooled frequency of growth hormone deficiency (GHD) at 3–6 months was 0.14 (95% CI: 0.08–0.24). At >6 months, GHD prevalence was 0.19 (95% CI 0.13–0.26) overall, but ranged from 0.15 (95% CI 0.06–0.33) with the insulin tolerance test to 0.25 (95% CI 0.015–0.36) using the GHRH-Arginine test.

Conclusion: Hypopituitarism is a common complication in patients with aneurysmal subarachnoid hemorrhage, with growth hormone deficiency being the most prevalent diagnosis. We showed that variations in prevalence rates in the literature are partly due to methodological differences among pituitary function tests.

665. Thrombotic complications during aneurysm coiling: Use and indications of Abciximab

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Introduction: Abciximab is used for the treatment of thromboembolism occurring during endovascular procedures, however the experience with intra-arterial infusion is limited. The objective is to evaluate the safety and effectiveness of this drug for the treatment of coiling complications.

Methods: From an aneurysm coiling database of 441 patients, patients treated with intra-arterial abciximab due to thrombotic

complications were selected for analysis. Patient were classified either as non-ruptured aneurysm for elective coiling or presenting with subarachnoid hemorrhage. Indication for using abciximab was thrombotic complication during coiling, seen as flow delay or complete occlusion of the parent vessel in procedural check angiograms. They all had pre- and post-procedure cerebral angiography performed at our institution as part of routine work-up. Success rate was based on recanalization seen on cerebral angiography. Complications of using abciximab were reported.

Results: 35 of 441 coiling patients had a thrombotic complication. 13 of them were treated using intra-arterial infusion of abciximab and were recruited. 2 of 13 patients were male and age range was 49-70 years old. 6 patients presented with sub-arachnoid haemorrhage.

84 % of patients had at least partial recanalization, while 38 % experienced complete recanalization of the parent vessel. 45 % of patients had complications, none severe. 2 patients had aneurysm recanalization, 3 distal migration of thrombus and 1 had haemorrhage (non ruptured aneurysm).

Conclusion: Success rates of intra-arterial abciximab (ReoPro) infusions seem to be not quite optimum, in spite of being considered a safer alternative, it does have potential risks, including hemorrhage, distal thromboembolism and aneurysm recanalization.

666. Long Term Outcome of Moyamoya Patients Post Revascularization Surgery

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Introduction: Long-term outcomes of moyamoya disease (MMD) patients post revascularization are not well-documented. With one of the largest cohorts of treated MMD patients, we investigated their long-term physical, functional and social well-being.

Methods: Single institution, combined MMD database and questionnaire study.

From 1991–2014, 1307 revascularization procedures (1170 direct bypass, 137 indirect bypass) were performed in 772 patients. We received and analyzed 316 completed patient questionnaires.

Results: 548 females and 224 males, mean age 32 years (range 1–68). We performed 344 revascularizations in 197 pediatric patients (73% direct bypasses), and 963 revascularizations in 572 adults (96% direct bypasses).

With a mean follow-up of 7 years (0–25 years), there were 23 deaths, 5 within 30 days postoperatively, and 4 who had died from stroke at long-term follow-up. The other 14 deaths were non-MMD related. Of the returned questionnaires, 222 patients reported preoperative headache and 182 (82%) of these experienced post-revascularization improvement in their headaches. 101 patients had preoperative hypertension, and postoperatively anti-hypertensives were either discontinued (18) or the dosage reduced (47). 79% (251/316) of patients remained employed or in school at long-term follow up. Excluding children and adults with learning difficulties, 87% (237/273) are self-caring and 75% (204/273) are living independently. Overall, 83% of patients had excellent outcomes (mRS 0–1) at long-term follow up. A limitation of the study is that 41% of the patients responded to the questionnaire, and it's possible this may affect the data. Further telephone or clinic visit followup is being performed on the additional patients.

Conclusion: Headache and hypertension could be the presenting symptoms in some MMD patients, as subgroups experienced improvement postoperatively. About 80% of MMD patients have had excellent long-term physical, social, and functional outcomes post revascularization, with up to 25 years of follow up.

667. Clipping of Previously Coiled Cerebral Aneurysms: Efficacy, Safety and Predictors in a Cohort of 111 Patients

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Introduction: With the increasing number of aneurysms treated with coiling, more recurrences are being encountered. The aim of this study is to evaluate the efficacy and safety of microsurgical clipping in the treatment of recurrent, previously coiled cerebral aneurysms.

Methods: 111 patients with recurrent aneurysms who were managed with clipping between January 2002 and October 2014 were identified. The rates of aneurysm occlusion, re-treatment, complications and good clinical outcome were determined. Univariate and multivariate logistic regression were performed to identify factors associated with these outcomes.

Results: Mean patient age was 50.5 years. Mean aneurysm size was 7 mm. Mean follow-up was 22 months. Complete aneurysm occlusion was achieved in 97.3% of aneurysms (108/111). 1.8% of patients had a recurrence after clipping (2/111). Re-treatment was required in 4.5% of patients after clipping (5/111). Major complications were observed in 8% and mortality in 2.7%. 90% of patients had a good clinical outcome. Aneurysm size (OR=1.4, p=0.009, 95% CI: 1.08-1.7) and location in the posterior circulation were significantly associated with higher complications. All patients who had coil extraction had a post-operative stroke (3 patients). Aneurysm size (OR=1.2, P=0.025, 95% CI: 1.02-1.45) and higher number of interventions prior to clipping (OR=5.3, P=0.019, 95% CI: 1.3–21.4) were significant predictors of poor outcome. Size <7mm (p=0.018) was a significant predictor of incomplete obliteration and re-treatment.

Conclusion: Surgical clipping is safe and effective in treating recurrent previously coiled aneurysms. Aneurysm size, location and number of previous coiling procedures are important factors to consider in the management of these aneurysms.

668. A Prospective Pilot Study of Intraparenchymal & Intravenous Cerebral Pressure Assessment During Venous Sinus Stenting

Robert M. Starke, MD; Kenneth Liu, MD; Christopher Durst, MD; R. Webster Crowley, MD; Tony Wang, MD; Dale Ding, MD; Steven Newman, MD (Charlottesville, VA)

Introduction: Pseudotumor cerebri may cause visual alterations and blindness as a result of increased intracranial pressure (ICP). Venous stenosis has been identified in select patients leading to stenting as a potential treatment. Therapeutic effects on global ICP remains unclear and ophthalmological, neurological, and radiographic outcomes are incompletely defined.

Methods: Patients failing medical therapy were prospectively followed in this pilot study. Ophthalmologic examinations were assessed (acuity, funduscopy, OCT, visual fields), and patients with venous sinus stenosis on MRA proceeded to cerebral angiography, venography with assessment of pressure gradient, and ICP monitor placement. Patients with elevated ICPs and pressure gradient across venous stenosis received stenting.

Results: All patients had elevated maximum venous pressure (39.5±14.9), gradient across venous stenosis (30.0±13.2) and ICPs (42.2±15.9). Following stenting, all patients had resolution of their venous pressure gradient and stenosis. Patients had an immediate decrease in ICP immediately following stenting (17.0±8.3), which

further decreased overnight (mean 8 ± 4.2). All patients had subjective and objective improvement following stenting and all but one had objective and subjective improvement during follow-up (mean 16.1 months; 12-27.1). Two patients developed stent-adjacent stenosis with significant pressure gradients; retreatment abolished the stenosis and gradient. Patients presenting with papilledema had resolution as demonstrated on fundoscopic imaging and OCT and improvement on visual field testing. Patients presenting with optic atrophy had optic nerve thinning on follow-up OCT, but improvement in visual field testing.

Conclusion: For select patients with pseudotumor and venous stenosis with elevated pressure gradient and ICPs, venous stenting results in immediate resolution of the venous pressure gradient, reduction in ICP, and functional, neurological, and ophthalmological improvement. As pseudotumor patients are at risk of stent-adjacent stenosis, further prospective follow-up is necessary to determine long-term outcomes and gain an understanding of venous stenosis as a primary or secondary pathological process behind elevated ICP.

669. Balloon Test Occlusion of the ICA: Venous Phase Delay Does Not Predict SPECT Result

Samir Sur, MD; Brian Snelling, MD; Racheal Wolfson, BS; Sudheer Ambekar, MD; Dileep Yavagal, MD; Mohamed Elhammady, MD; Eric Peterson, MD (Miami, FL)

Introduction: Balloon test occlusion (BTO) of the internal carotid artery (ICA) is commonly used to predict feasibility of carotid sacrifice in the management of certain neoplastic and vascular diseases. Technetium-99m Single Photon Emission Computed Tomography (SPECT), is routinely performed to increase the sensitivity of BTO in predicting delayed ischemic complications. The purpose of this study is to evaluate whether venous phase delay predicts SPECT results during BTO of the ICA.

Methods: We obtained IRB approval to review the medical records of consecutive patients who underwent BTO between April 2008 to April 2014. Patients who underwent successful clinical and angiographic BTO followed by SPECT imaging were included. The difference in onset between the venous phase of each hemisphere was determined independently by two physicians and compared with stratified, qualitative assessment of the SPECT imaging performed by our radiologists.

Results: A total of 57 patients met inclusion criteria. Twenty-seven patients showed no evidence of ischemia on SPECT imaging while 30 showed evidence of hypoperfusion. The average venous delay was 0.68s (range: 0-3s) and 0.96s (range: 0-3s) respectively. Two-sample t-test demonstrated no significant difference between the two groups ($p=0.24$). Further stratification of patients demonstrating hypoperfusion on SPECT (mild vs moderate-to-severe) did not yield any correlation with venous phase delay by ANOVA ($p=0.22$). Comparison between extreme groups (no hypoperfusion vs moderate-to-severe) by t-test did not yield a significant difference ($p=0.14$).

Conclusions: Our results demonstrate a lack of correlation between observed venous phase delay and SPECT results in our series of patients undergoing BTO of the internal carotid artery. These results underscore the importance of a patient-specific approach to management and utilization of multiple diagnostic modalities in patients being considered for carotid sacrifice. Further data and analyses are needed to better determine correlation of angiographic findings and SPECT results with clinical outcomes.

670. Clinical Factors Affecting Cognitive Function after Carotid Revascularization: A Multivariate Analysis

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Introduction: It is still unclear through which mechanisms cognitive function is impaired in patients with carotid stenosis. This study was aimed to clarify the predictors of cognitive dysfunction in carotid stenosis and of its recovery after carotid revascularization.

Methods: This prospective study included 129 patients with carotid stenosis who underwent carotid endarterectomy (CEA, $n=45$) or carotid artery stenting (CAS, $n=84$). There were 116 men and 13 women (mean age: 71 years). Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was employed to assess cognitive function before, one week and three months after CEA/CAS. Using [123I]-IMP-SPECT, cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to acetazolamide were quantitatively measured before CEA/CAS. Multivariate analysis was performed to evaluate the predictors to affect cognitive function in them.

Results: Before CEA/CAS, total RBANS score in 62 patients was significant lower than the age-matched controls. Total RBANS scores significantly improved in 17 patients at one week, in 71 patients at three months after CEA/CAS. Multiple regression analysis demonstrated that high-grade stenosis ($P=0.017$), cerebral infarction ($P=0.016$), and blood flow decline ($P<0.001$) independently predicted cognitive impairment. The absence of DWI-positive lesions ($P<0.001$) and CAS ($P<0.001$) significantly correlated with recovery of cognitive function one week after CEA/CAS, but only preoperative decline of CVR ($P=0.033$) predicted it three month after CEA/CAS.

Conclusion: These findings strongly suggest that high-grade carotid stenosis and persistent ischemia impairs cognitive function. CEA/CAS improves cognitive function and the beneficial effects are most notable in poor CVR patients.

671. Complications in Endovascular Neurosurgery: Critical Analysis and Classification

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Introduction: Complications are used to measure quality; endovascular neurosurgery lacks common definitions for complications. Additionally, complications may not always negatively affect outcome and remain unreported. We critically review our interventions and propose a classification of endovascular complications into four categories: mechanical, technical, judgment errors, and adverse incidents.

Methods: This single center review of endovascular interventions performed from September 2013 to August 2015 included all patients with no exclusion criteria. Complications were analyzed and defined by a senior endovascular neurosurgeon. A descriptive analysis was performed to calculate the overall incidence of complications and for each category.

Results: Two hundred and seventy-five endovascular interventions were performed from September 2013 to August 2015 in 245 patients (65% were female, mean age 55 years, range 0.5-92 years). In total, 40 complications occurred in 39 patients (15%); most commonly during treatment of intracranial aneurysms 24/40 (60%). Mechanical complications occurred in 8/40 (20%) [device deployment, catheter, or closure device failure], technical complications in

11/40 (27.5%) [failure to deploy flow diverter, unintended embolization, air emboli, retroperitoneal hemorrhage, dissection], judgment errors in 9/40 (22.5%) [patient or equipment selection], and adverse incidents in 12/40 patients (30%) [groin hematoma, hemorrhagic or thromboembolic complications]. Only 12/40 complications (30%) resulted in new neurological deficits, vessel injury requiring surgery, or blood transfusion.

Conclusions: We have critically reviewed a series of consecutive interventions and propose an endovascular specific classification system of complications with four categories: mechanical, technical, judgment errors, and adverse incidents. This provides a framework for future studies and quality improvement in endovascular neurosurgery.

672. Cavernous Sinus Dural Arteriovenous Fistulas: The Role of Stereotactic Radiosurgery

Shao-Ching Chen; Cheng-Chia Lee; Hsiu-Mei Wu (New Taipei City, Taiwan)

Introduction: Stereotactic radiosurgery for low-flow cavernous sinus dural arteriovenous fistulas (CS DAVFs) has had excellent results and few complications. We present a retrospective analysis of data acquired during a 22-year period from 230 CS DAVF cases.

Methods: Three hundred and forty-five patients with intracranial DAVFs at various locations and grades underwent GKS between 1993 and 2015. Of these patients, 230 (66.7%) DAVFs were located within cavernous sinus. The prescribed margin dose for CS DAVFs was 17.2Gy in 68.2 isodose line. The mean follow-up time is 26.4 (range: 12.0–200.3) months. There are 175 patients (76.1%) underwent regular follow-up in our clinic.

Results: Complete regression occurred in 118 patients (67.4%), and partial regression occurred in 57 patients (32.6%). The clinical symptoms and signs were improved in 167 patients (95.4%). The recovery interval was 3.7 months in average. However, some complications may happen unanticipated. Twenty-three patients had thrombosis of superior ophthalmic vein (SOV thrombosis), which caused further transient ocular congestion (9.1%), transient visual deterioration (4.3%), and permanent visual impairment (1.3%). New onset cranial nerve palsy was found in 6 patients (2.6%). Intracerebral hemorrhage was noted in 2 patients. One mortality was due to cerebellar infarction.

Conclusion: The study emphasized the role of the GKS in treatment of low-flow CS DAVF. The clinical symptoms were improved in months (3.7 months in average), and the obliteration rate of DAVFs can achieve around 67.4% in long-term follow-up (24.6 months) with acceptable complications. We also closely observed the paradoxical worsening of ocular and visual symptoms with SOV thrombosis, which is the main complications after GKS. The hemodynamic study after GKS for CS DAVFs, and the management for SOV thrombosis need further investigation.

673. Impact of Surgeon Experience and Timing of Intervention Among 454 Consecutively Treated Brainstem Cavernous Malformations

Hasan Aqdas Zaidi, MD; Michael Mooney, MD; Michael Levitt, MD; Alexander Dru, MD; Adib Abl, MD; Robert Spetzler, MD (Phoenix, AZ)

Introduction: Brainstem cavernous malformations (BSCMs) are angiographically occult lesions with a propensity to hemorrhage. The impact of surgeon experience on clinical outcomes is currently unknown given the relative rarity of this pathology and timing of surgical intervention remains controversial.

Methods: Consecutive adult patients (≥ 18 years old) with surgically treated BSCM between 1985-2014 were retrospectively reviewed.

Results: A total of 454 patients (397 adult, 57 pediatric) were treated during the study period. Among adult patients, 40% were male with a clinical follow-up of 35.45 ± 44.48 months; 31.5% of these patients underwent resection in the acute setting (< 6 wks of hemorrhage). Postoperatively, 205 patients (52%) had resolution of some or all preoperative symptoms whereas 140 patients (35%) experienced new permanent postoperative deficits at last follow-up. On univariate analysis, a higher proportion of patients treated within 6 weeks of hemorrhage trended towards an improved GOS ($p = .06$). On multivariate analysis, preoperative size of BSCM negatively predicted good outcome ($OR = 0.65$, $p = .002$) and patients treated within 6 weeks of hemorrhage experienced improved clinical outcomes ($OR = 1.73$, $p = 0.028$). Furthermore, a sub-group analysis indicated that among patients with an admit GOS < 3 , a significantly higher proportion of the recent cases (post-2007) achieved a good outcome in comparison to early cases (100% versus 64%, $p = .017$) by the same surgeon.

Conclusion: Favorable symptom resolution can be achieved in a carefully selected group of patients. Overall, patients surgically treated acutely benefit most from surgical intervention, and surgeon experience is directly related to clinical outcomes.

674. Surgery within the Context of Global Health: the World Health Organization's Critical Role

Walter D. Johnson, MD, FAANS(L), FACS (Redlands, CA)

Introduction: The role of surgery within the context of global public health has only begun to emerge. The core issues are: the enormous global unmet need—lack of access and competent providers; positive overall societal economic impact, but often with catastrophic hardship to patients and families; novel methods of surgical training and task-shifting; and increasing political will through diverse organizations, Ministries of Health, and the World Health Organization (WHO). These adjoined influences culminated in recent passage of World Health Assembly Resolution 68.15: Strengthening emergency and essential surgical care and anaesthesia as a component of universal health coverage.

Methods: Review of current developments in WHO Emergency and Essential Surgical Care Programme (EESC)

Results: WHO EESC is currently developing a roadmap towards implementation of the resolution, which includes provisions for advocacy and funding development; access and integration of services; data collection, monitoring & evaluation; essential medicines and supplies; and training, competency and credentialing. Other efforts include a Global Initiative for EESC, quality and patient safety initiatives, eLearning platforms, health economic programmes, and both internal and external bridge-building.

Conclusion: With escalating momentum derived from the Resolution and two recent, key academic contributions (World Bank's DCP3 Essential Surgery and Lancet Commission on Global Surgery), it is a critical time to merge our influence toward that goal of providing adequate access to surgical services wherever and for whomever those services are indispensable, whether in Africa or surgical deserts of North America, through cost mechanisms supported by sustainable funding sources and without devastating economic consequences.

675. Cx43 function blocking antibody improves outcome and reduces secondary expansion in traumatic spinal cord injury (SCI)

DePuy Synthes Spinal Cord Injury Award

Asif Maknojia, MD; Shane Sprague; Manuel Riquelme, PhD; Sumin Gu, PhD; Viktor Bartanusz, MD, PhD; Jean Jiang, PhD; Naomi Sayre, PhD (San Antonio, TX)

Introduction: Connexin 43 (Cx43), a gap junction protein with abundant plasma membrane expression on astrocytes, forms hemichannels and pathological opening of the hemichannels has been implicated in propagating secondary SCI. We used a proprietary antibody to inhibit Cx43 hemichannels, and tested whether SCI damage decreased after treatment.

Methods: C57BL/6 male mice underwent T10-12 laminectomies and were injured using a pneumatic impactor. Mice were randomized into 3 groups: Cx43+SCI (n=5), IgG+SCI (n=3), vehicle+SCI (n=2). Drugs were administered 30 minutes after injury. The Basso Mouse Scale (BMS) and accelerating rotarod were used up to 6 weeks after injury to assess functional recovery in mice with BMS score of 0-3 at 6 hours after injury. Immunohistochemistry was performed to assess tissue pathology. Statistically significant differences was measured using one-way ANOVA followed by Tukey's HSD.

Results: At six weeks post injury, anti-Cx43 treated mice achieved a mean BMS score of 7.8 (SD 1.68) compared to 1.3 (SD 1.04) in the control IgG group (p<0.01). Anti-Cx43 mice regained 80% of their pre SCI ability to spend time on accelerating rotarod as opposed to 25% in the control IgG group (p<0.05). Spinal cords assessed for astrogliosis 2 days after SCI showed a 2.5 fold increase of GFAP immunolabeling in IgG treated mice compared to sham mice (p=0.019, n=3). This increase was not observed in the anti-Cx43 mice.

Conclusion: Mice treated with Cx43 antibody show improved functional recovery and reduced gliosis compared to IgG treated mice. These results confirm Cx43 hemichannels are a viable therapeutic target for traumatic SCI.

676. Timing of Cranioplasty: A 10 Year Single Center Analysis of 754 patients

DePuy Synthes Resident Craniofacial Award

Ryan Patrick Morton, MD; I. Abecassis, MD; Josiah Hanson, BS; Jason Barber, MS; Mimi Chen; John Nerva, MD; Samuel Emerson, MD, PhD; Chibawanye Ene, MD, PhD; Michael Levitt, MD; Michelle Chowdhary, MD; Andrew Ko, MD (Seattle, WA)

Introduction: Despite their technical simplicity, cranioplasty procedures harbor high reported morbidity rates. We report the largest study to date on complications after cranioplasty, focusing specifically on the ideal timing of the operation.

Methods: We retrospectively reviewed all cranioplasties performed at Harborview Medical Center over the past 10.75 years.

Results: We performed 754 cranioplasties over 10.75 years. Sixty-percent were male with an average follow up of 533 days. Thirty-day mortality was 0.26% (n=2, both due to post-operative epidural hematoma). The morbidity was 22.7% including infection necessitating explanation of the flap (6.6%), post-operative hydrocephalus requiring a shunt (5.7%), resorption of flap (4.5%), seizure (3.4%), post-operative hematoma requiring evacuation (0.9%), and other (1.6%) When evaluating complication rates against the timing of the cranioplasty we found infection was significantly higher if when the cranioplasty was performed <14 days from original decom-

pression (p=0.007). Hydrocephalus was statistically less common in patients whose cranioplasty was performed after 90 days (p<0.0005); however new onset seizure only occurred in patients who received their cranioplasty <90 days. The resorption rate was lowest when the cranioplasty was performed within 15-30 days from the original decompression (overall p=0.035) and was also statistically influenced by patient age. The hazard ratio for resorption decreased by 33% per increase of 10 years of age (p=0.001).

Conclusions: The ideal timing for cranioplasty remains controversial but our data suggests that performing the procedure between 2 and 4 weeks helps minimize infection, seizure, and resorption, while waiting <90 days minimizes hydrocephalus but significantly increases risk of seizure.

677. Anterior Surgery of hard and soft Cervical disc

Mohamed Shabaan Mahmoud Mohamed, MD (Beniseuf, Egypt, Arab Rep.)

Introduction: Cervical anterior discectomy of hard and soft Cervical disc Complaining from neck pain and radiculopathy by using microscopic anterior discectomy with drill and Cervical cage fusion. Comparing the result of hard and soft Cervical disc surgery, regarding operative time hospital stay and relieving of symptoms

Methods: 21 patients diagnosed with cervical spondylosis by MRI cervical spine. They were treated with complete anterior cervical discectomy Overall 14 soft disc and 7 hard disc. 14 single, 4 two level, and 3 three level. The levels of surgery Include ten C5-6, nine C6-7, and Two C4-5.

Results: The median age of all patients was 42 years old . Duration of surgery range from three hours in soft disc to 6 hours in hard disc. Hospital stay range from 2 to 3 days. patients underwent postoperative assessment three weeks and 3, 6 months. Neck and arm pain significantly improved immediately in soft disc and delayed up to three months in hard discs. Sensory deficit improved gradually with no recurrence or associated complications .

Conclusion: The result of soft and hard discs surgery by anterior microscopic discectomy using drill with cervical cage show no difference except hard disc required long operative time and long hospital stay with more conservative treatment postoperative. Patient with multiple level surgery show similar result as single level surgery.

678. Treatment with N-acetyl-seryl-aspartyl-lysyl-proline Improves Functional Recovery in Rats after Traumatic Brain Injury

Asim Mahmood, MD, FAANS; Yanlu Zhang, MD; Ye Xiong, MD, PhD; Michael Chopp, PhD (Detroit, MI)

Introduction: N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is a naturally occurring multifunctional tetrapeptide, which has shown neuroprotective effects in ischemic stroke models. This study was designed to test the hypothesis that AcSDKP treatment provides neuroprotection and improves functional recovery in rats after traumatic brain injury (TBI).

Methods: Adult male Wistar rats (n=8) were injured with controlled cortical impact (CCI) and treated with AcSDKP suspended in 0.01N acetic acid (vehicle). Control group (n=8) were treated with vehicle only after CCI. AcSDKP (0.8 mg/kg/day) or vehicle was administered subcutaneously starting at 1 hour post injury and continuously for 3 days through an osmotic minipump. Sensorimotor function and spatial learning were assessed using a modified neurological severity score (mNSS) and Morris water maze (MWM)

tests, respectively. Animals were sacrificed 35 days after injury and brain sections processed to assess lesion volume, hippocampal cell loss, neurogenesis and dendritic spine remodeling after AcSDKP treatment.

Results: AcSDKP treatment initiated 1 hour post injury significantly improved sensorimotor functional recovery (mNSS, $p<0.05$) and spatial learning (MWM, $p<0.05$). Histological analysis revealed that AcSDKP treatment reduced cortical lesion volume by 30% ($p<0.05$), decreased hippocampal cell loss ($p<0.05$), and enhanced neurogenesis and the number of dendritic spine in the injured hippocampus ($p<0.05$).

Conclusion: AcSDKP treatment initiated 1 hour post injury provides neuroprotection and neurorestoration after TBI, indicating that this small tetrapeptide has promising therapeutic potential for treatment of TBI. These data warrant further investigation of the optimal dose and therapeutic window of AcSDKP treatment for TBI and the associated underlying mechanisms.

679. Potential Use of an Artificial Spinal Cord in the Treatment of Spinal Cord Injury

Assad A. Mazhari, MD, FAANS(L) ; Harini Sundararaghavan, PhD; Taania Girgla; Radhika Sharma; Tonya Whitehead; Richard Honablu; Tanvee Jain; Rohit Bollineni; Jay Meythaler; Jean Peduzzi (Bloomfield Hills, MI)

Introduction: An effective treatment for severe spinal cord injury has yet to be found. An artificial spinal cord (Artificial SC) mimicking the normal cytoarchitecture of the spinal cord was evaluated in an animal model. The Artificial SC replaces damaged neurons and glia and encourages the growth of ascending and descending axons while preventing scar formation.

Methods: Twelve adult male inbred Lewis rats were randomly assigned to 1 of 3 groups: 1). Sham surgery - laminectomy only; 2). Spinal cord segment removal and hyaluronic acid (HA) hydrogel graft; 3). Spinal cord segment removal and Artificial SC graft consisting of a central layer of olfactory neural progenitor cells on electron spun fibers surrounded by 2 layers of electrospun fibers with opposing gradients of beads that slowly release neurotrophic factors (GDNF or BDNF) in a hydrogel containing olfactory ensheathing cells to myelinate and chondroitinase ABC to prevent scar formation. Rats were evaluated using the BBB test, inclined plane, beam and Hargreaves and data were analyzed using ANOVA and student t-tests.

Results: Laminectomy-only rats reached presurgery scores in all tests in 2 weeks. Group 3 (Artificial SC) performed better than Group 2 (Hydrogel) in the BBB, inclined plane, and beam tests but significance was only reached with the BBB locomotor test ($p<0.001$).

Conclusion: Our first attempts at creating and evaluating an Artificial SC resulted in encouraging results. This construct will form a platform for further modifications to improve the treatment of severe spinal cord injury. Clinical translation will be facilitated by using autologous olfactory cells and components already FDA approved.

680. Intramedullary lesion length on MRI is a predictor of outcome in cervical spinal cord injury

Bizhan Aarabi, MD, FAANS, FACS; Charles Sansur, MD; David Ibrahimi, MD; Noori Akhtar-Danesh, MD; Cara Diaz, CRNP; Jennifer Massetti, CRNP; Marc Simard, MD; David Hersch, MD; Elizabeth Le, MD (Baltimore, MD)

Introduction: The EM-SCI and SCIMS studies indicate that natural recovery in cervical spinal cord injury (SCI) is more robust than previously thought. We sought to further investigate indicators of grade conversion following cervical SCI.

Methods: AIS grade conversion over a 6 months period was studied in 100 patients with SCI.

Results: Mean age was 39.5, injury severity score (ISS) 31 and ASIA motor score (AMS) 17.1. AIS grade was A in 52 patients, B in 29 and C in 19. Surgical decompression was an average of 17.6 hours following trauma. Complete decompression was verified by MRI in 73 patients. Intramedullary lesion length (IMLL) on post-operative MRI measured 72.8 millimeters, and hemorrhage at the injury epicenter was noted in 71 patients. Grade conversion took place in 26.9% of AIS grade A patients, 65.5% of AIS grade B, and 78.9% of AIS grade C. There was a relationship between AIS grade conversion and ISS ($P<0.01$), morphology ($P<0.01$), admission AIS grade ($P<0.001$), extent of decompression ($P<0.001$), presence of intramedullary hemorrhage ($P<0.001$), AMS ($P<0.0001$) and IMLL ($P<0.0001$). When analyzed by a multiple logistic regression, IMLL was the only significant indicator of AIS grade conversion (odds ratio 0.950, 95% CI 0.931-0.969). Thus, for 1-mm and 10-mm increases in IMLL, one expects to see 5% and 40% decreases, respectively, in the odds of AIS grade conversion. Demographic, timing; technique; and extent of decompression had no effect on AIS grade conversion.

Conclusion: In cervical SCI, length of spinal cord swelling (IMLL) on postoperative MRI had a significant relationship with grade conversion.

681. Concussion symptomatology, symptom resolution time, and return to play time in youth, high school, and college American football athletes

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Introduction: Little research has examined concussion across the youth and adolescent spectrum. Our objective was to compare sport-related concussion outcomes, including symptomatology, symptom resolution, and return to participation, in youth, high school and collegiate football athletes.

Methods: Data were collected by athletic trainers from 2012-2014. The Youth Football Surveillance System included over 3,000 youth football athletes aged 5-14 years from 118 teams providing 310 team-seasons. The National Athletic Treatment, Injury and Outcomes Network program included 96 secondary school football programs providing 184 team-seasons. The National Collegiate Athletic Association Injury Surveillance Program included 34 college football programs providing 71 team-seasons. Average number of symptoms, prevalence of each symptom, and the proportion of concussions that had long symptom resolution or return to play times was calculated. Differences among levels of competition were examined with analysis of variance (ANOVA) tests and injury proportion ratios (IPRs) with 95% Confidence Intervals (CI).

Results: A total of 1,429 concussions with an average 5.48 (SD=3.06) symptoms were reported. Across all levels, 7.7% had a long symptom resolution time and 15.3% resulted in a long return to play time. Compared to youth, a higher number of concussion symptoms were reported in high school (Difference: 0.84; 95%CI: 0.25, 1.43) and college (Difference: 0.79; 95%CI: 0.15, 1.44). The proportion of concussions with long symptom resolution time in high school was larger than that of college (IPR=2.55; 95%CI: 1.54, 4.24) and youth (IPR=3.84; 95%CI: 1.58, 9.31). Compared to college, the proportion of concussions with long return to play time

was larger in youth (IPR=2.34; 95%CI: 1.44, 3.82) and high school (IPR=2.85; 95%CI: 1.95, 4.19).

Conclusions: Differences in concussion-related outcomes existed by level of competition and may be attributable to level-specific variations in concussion-related policies/protocols, athlete training management, and athlete disclosure. Further study is warranted to further explore such differences.

682. Early Venous Thromboembolism Chemoprophylaxis in Combat Related Penetrating Brain Injury

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Introduction: Traumatic Brain Injury (TBI) is independently associated with deep vein thrombosis and pulmonary embolism (DVT/PE). Based upon numerous studies of civilian closed head injury, the Brain Trauma Foundation recommends venous thromboembolism chemoprophylaxis (VTC) in severe TBI. There have been no studies to date examining this practice in penetrating brain injury (PBI).

Methods: The Kandahar Airfield neurosurgery service managed over 900 consults January 2010–March 2013. 156 patients were US active-duty members; 80 of these suffered PBI, 13 of whom were excluded because they presented with frankly non-survivable CNS injury, or died during initial resuscitation from other causes. This is a retrospective analysis of the remaining 67 US active-duty PBI patients, examining the safety and efficacy of early VTC with respect to worsened intracranial hematoma (ICH) and DVT/PE.

Results: 32 patients received early VTC (intervention), 35 did not (control). Mean time to first dose was 24 hours. 29 received LMWH, 3 UFH. 52 had blast mechanism PBI, 15 had gunshot wounds to the head. The incidence of worsened ICH was 16% in the intervention group and 17% amongst the controls, with the relative risk approaching one (RR=0.91, 95% CI 0.31–2.7). The incidence of DVT/PE was 12% in the intervention group, and 17% in the controls, for absolute risk reduction of 5% and number needed to treat to prevent one DVT/PE of 22; however, this was not statistically significant (RR=0.73, 95% CI 0.23–2.4).

Conclusion: Early VTC was safe in this population with regards to worsened ICH. The data suggest early VTC may be efficacious for preventing DVT/PE, though not statistically significantly. This is the first study to examine early VTC in PBI, and though the results are non-generalizable (military trauma, mostly blast mechanism) there is no other data available to guide practice.

683. CSF HMGB1 Level as a Potential Predictive and Prognostic Biomarker for Neurosurgery Patients with Ventricular Drain

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Introduction: High-mobility group box 1 (HMGB1) is a ubiquitous nuclear protein that is passively released from damaged cells, and actively released from immune cells. Previous studies report that it in part reflects the degree of necrosis and apoptosis present after brain injuries and contributes to cell death and neurological morbidity. In this study, we assessed the predictive and prognostic value of cerebrospinal fluid (CSF) HMGB1 in comparison with traditional biomarkers.

Methods: The CSF samples were collected from patients with

normal pressure hydrocephalus (NPH) (n=3), subarachnoid hemorrhage (SAH) (n=6), and brain tumor (n=4) who had the clinical need for a ventricular or lumbar drain. NPH patients served as a control population. HMGB1, S100b, interleukin-6 (IL-6) and interleukin-1 β (IL-1 β) levels were determined at four time intervals (0–24 h, 25–48 h, 49–72 h, and 73–97 h) using enzyme-linked immunosorbent assay (ELISA).

Results: In the patients with SAH and brain tumor, HMGB1 (P = 0.002), S100b (P = 0.003), IL-6 (P = 0.013) and IL-1 β (P = 0.031) were significantly increased on the first day (0–24h) compared to the NPH patients. CSF HMGB1 correlated significantly with S100b, IL-6 and IL-1 β (R = 0.681, 0.711, and 0.697, respectively).

Conclusions: There was a significant correlation between CSF HMGB1 levels and the other reported biomarkers for brain damage. These results suggest that HMGB1 might play an important role in predicting the prognosis of neurosurgical patients and encourage further investigation.

684. Serum Procalcitonin Level and Infection in Neurosurgical Intensive Care Unit (NICU) Patients

Lauren Elana Rotman, MD; Gustavo Chagoya, MD; Matthew Davis, MD; James Markert, MD (Birmingham, AL)

Introduction: Procalcitonin, a blood stream inflammatory biomarker, has shown to be useful in the early diagnosis of sepsis in critically ill patients. To date, procalcitonin levels have primarily been studied in medical and surgical intensive care unit patients. This study aimed to further our understanding of procalcitonin levels in NICU patients with a specific focus on patients found to have normal procalcitonin levels.

Methods: An IRB approved retrospective study of all neurosurgical patients admitted to the University of Alabama Hospital NICU who had normal procalcitonin levels (<2.0 ng/ml) drawn between November 1, 2012 and November 2014 was conducted. Subjects were categorized as true negative (TN) or false negative (FN) based on microbiology results and clinical signs of infection. Statistical analysis was performed using JMP Pro 12.0.1 software.

Results: 139 patients met inclusion criteria (59% female, 41% male). 70 were categorized as FN and 69 TN. Comparison between these cohorts (FN vs TN) revealed no difference in average age (58.7 vs 57.14, p=0.30) or gender (28.06% vs 30.94% female, p=0.43). Temperature and white blood count were not independently associated with the accuracy of procalcitonin values (p=0.19, p=0.53). Longer NICU stay and meeting SIRS criteria was predictive of falsely low procalcitonin levels (p<0.001, p<0.0001).

Conclusion: An approximately 25% chance of falsely normal procalcitonin levels was evident in our review of 139 NICU patients. This emphasizes the importance of both cautious interpretation of procalcitonin levels in neurosurgical patients and the need for further investigation to assist in broadening our understanding of procalcitonin levels in this population.

685. Propensity Score Analysis of the Impact of Decompressive Craniectomy on Outcomes Following Traumatic Brain Injury

Venkatakrishna Rajajee, MD; Deepak Agrawal; Krishnan Raghavendran, MD; Douglas Schaubel, PhD; Mahesh Misra (Ann Arbor, MI)

Introduction: The impact of Decompressive Craniectomy (DC) on outcomes following Traumatic Brain Injury (TBI) is not clear. Our objective was to determine the impact of DC on outcomes following TBI, and to examine the impact of secondary DC, performed specifically for refractory intracranial hypertension.

Methods: The data source was a TBI registry with prospective data-entry at a high-volume referral center. Severe TBI (Glasgow Coma Scale <9) patients >12yrs old in a 2-year period meeting Brain Trauma Foundation criteria for Intracranial Pressure Monitoring (ICPM) were included. Actual use of ICPM was at the discretion of the attending neurosurgeon. Outcomes of interest were in-hospital mortality and poor 6-month functional outcome (Glasgow Outcome Scale, GOS <3). A propensity and prognostic score based analysis was utilized. Covariates included clinical and imaging predictors of outcome. Subgroup analysis was performed in patients who underwent secondary DC on the basis of ICPM.

Results: Of 1345 patients meeting criteria, 589(44%) underwent DC. In-hospital mortality was 35% (471/1345). Poor 6-month outcome occurred in 161 (35%) of 454 survivors with follow-up available. DC was associated with a 6.5% ($p=0.004$) increase in probability of in-hospital death and a 3.9% ($p=0.04$) increase in poor 6-month outcome. In the subgroup of patients who underwent secondary DC ($n=497$) there was no significant difference in the probability of in-hospital death ($p=0.11$) or poor 6-month outcome ($p=0.758$).

Conclusion: The use of DC following severe TBI was associated with an increased probability of in-hospital mortality and poor 6-month functional outcome, except in the subgroup of patients who underwent secondary DC on the basis of ICPM.

686. Blood alcohol level does not affect coagulopathy measured via thromboelastography in the setting of traumatic intracranial hemorrhage

Abigail Justine Rao, MD; Amber Laurie, MS; Rochelle Fu, PhD; Kelly Fair, MD; Tori Lennox, MD; Ronald Barbosa, MD; Susan Rowell, MD (Portland, OR)

Introduction: Progression of traumatic intracranial hemorrhage (ICH) is associated with increased morbidity and is associated with coagulopathy, though data is mixed. We previously showed that alcohol use is associated with hypocoagulability based on thromboelastogram (TEG) in male volunteers. This analysis tests whether blood alcohol level at ED admission is associated with coagulopathy measured via TEG and clinical outcomes in trauma patients.

Methods: We conducted a prospective observational study in patients with traumatic ICH at a level 1 trauma center. Progression of ICH was defined as $\geq 33\%$ increase in volume, presence of a new lesion, or by radiologist interpretation. Univariate analyses were performed to compare baseline clinical characteristics and TEG values between alcohol-positive versus alcohol-negative patients and between legal (≤ 0.08) versus illegal (< 0.08) levels of alcohol. Linear regression was used to assess for a relationship between TEG and blood alcohol levels within alcohol-positive patients. A logistic regression model was used to assess for a relationship between blood alcohol levels and clinical outcomes.

Results: 167 patients met entry criteria, of which 54.4% showed progression and 36.5% were alcohol positive. Blood alcohol status and levels were not related to TEG values, with the exception that increasing alcohol levels were associated with prolonged R time at 48 hours after admission ($p=0.04$). Alcohol status or levels was not associated with differences in progression of ICH, need for neurosurgical procedure, or mortality.

Conclusion: Blood alcohol is not associated with coagulopathy measured via TEG or clinical outcomes. Further investigation of the role of alcohol in the morbidity of TBI is warranted.

687. The Negative Impact of Anemia on Outcome from Traumatic Brain Injury

Simon Anthony Martin; Jenna Diaz, BS; Bin Ge, MA; Greg Petroski, PhD; Stephen Barnes, MD; Norman Litofsky, MD (Columbia, MO)

Introduction: Anemia's impact on outcome from traumatic brain injury (TBI) is controversial. We hypothesized TBI patient outcomes with concomitant anemia would be worse than without anemia, and investigated anemia effects on TBI considering hemoglobin sampling times, threshold values, gender and transfusion.

Methods: Patients from 2009–2013 with non-penetrating TBI, head Abbreviated Injury Scale (AIS) <3, and abnormal head CT findings were reviewed. Relationships between initial hemoglobin and lowest hemoglobin during hospitalization threshold values of <7, <8, <9, and <10 g/dl were related to follow-up Glasgow Outcome Score within one-year. A duration effect of anemia was investigated using area-under-the-curve analysis.

Results: Of 939 patients (mean age 46.75, 66.1% male gender) meeting inclusion criteria, initial and first hemoglobin were significant predictors of poor outcome ($p<0.0001$). Every 1g/dL higher hemoglobin value had a 33% good outcome increase. More severe anemia levels were associated with lower GCS, higher head AIS, and higher ISS ($p<0.0001$). Anemic patients had more surgery and blood transfusions ($p<0.0001$). Anemia duration did not appear to impact outcomes. Female patients had worse outcomes for initial hemoglobin between 7 and 8 g/dL ($p<0.05$). Blood transfusion was associated with poorer outcome at hemoglobin levels <9 and <10 g/dl ($p<0.05$), but not at more severe anemia levels.

Conclusion: TBI patient outcomes are worse with concomitant anemia. While anemic patients have more severe injuries, initial hemoglobin and lowest hemoglobin are independent factors affecting outcome. Female patients may be more susceptible to more severe anemia levels. These findings indicate packed red cell transfusion is appropriate with hemoglobin <8g/dl.

688. Does the Open Payments Database Provide Sunshine on Neurosurgery?

Byron Cone Pevehouse Young Neurosurgeons Award

Maya Babu, MD, MBA; Robert Heary, MD; Brian Nahed, MD, MSc (Rochester, MN)

Introduction: The Open Payments Database (OPD) was launched by the Centers for Medicare & Medicaid Services in 2014 as a result of the Affordable Care Act. Through this online searchable database, the public can explore physician-industry interactions. Many of these payments have garnered high-profile media attention and are viewed with skepticism by the public. These value transfers include research activity, textbooks, and educational seminars. There is no published literature on the database for neurosurgeons.

Methods: We searched 4.3 million records in 2013 and 11.41 million records in 2014 for board certified neurosurgeons verified by the American Board of Neurological Surgery. The time queried included all available records in the OPD from 2013 and 2014. Given the significant number of files explored, we used Delimit software to condense the data, Microsoft Access for all database queries, and STATA to perform descriptive analyses.

Results: Of the 1607 physicians identified as neurosurgeons within the OPD in 2013, 1210 were neurosurgeons and 397 were incorrectly identified as neurosurgeons. Of the entire OPD in 2013, there were 3073 board certified neurosurgeons with approximately 63,787 attributed records. Of the 1841 physicians identified as

neurosurgeons within the OPD in 2014, 1465 were neurosurgeons and 376 were incorrectly identified as neurosurgeons. Of the entire OPD in 2014, there were 3424 board certified neurosurgeons with approximately 160,193 attributed records. The total payments to neurosurgeons in 2013 was \$33,000,432.05; in 2014 it was \$92,265,680.31.

Conclusions: The Open Payments Database details physician interactions with industry but suffers from multiple inaccuracies and a lack of appropriate context for value transfers. While seemingly benign, publicly availing inaccurate information through a searchable governmental website that can be accessed by patients and journalists alike has the potential to tarnish individual neurosurgeons and undermine professional credibility.

689. From Bench to Bedside: NIH Funding for Neurosurgeons from 1991-2015

Journal of Neuro-Oncology Award

Arman Jahangiri; Patrick Flanigan, BS; Maxine Arnush; Sarah Choi, BS; Alvin Chou; Nima Emami, BS; Ruby Kuang; Albert Truong, BS; Mitchel Berger, MD; Manish Aghi, MD, PhD (San Francisco, CA)

Introduction: Neurosurgeons have long played an important role in advancing medicine through research, funding of which is historically linked to the NIH. We defined variables associated with neurosurgical NIH funding, prevalence of funded topics by neurosurgical subspecialty, and temporal trends in NIH neurosurgical funding.

Methods: Retrospective review of NIH funded AANS members, assessed using NIH Reporter (<http://report.nih.gov/>) from 1991-2015.

Results: We followed 6,515 neurosurgeons over 24 years, including 6,124 (94%) MDs and 406 (6%) MDPHs. NIH grant(s) were awarded to 391 (6%) neurosurgeons. The average total funded years per neurosurgeon was 12.5 years (range=1-85). A higher percentage of MD-PhDs were NIH funded than MDs (5%=297 vs. 22%=91; $P<.0001$). Commonest grants were R01 (n=128/33%), K08 (n=69/18%), F32 (n=60/15%), M01 (n=50/13%), and R21 (n=39/10%). For training grants, 30% of F32 recipients transitioned to K08s (18%) and/or R01s(18%), and 38% of K08 recipients transitioned to R01s. Of NIH funded neurosurgeons, 32 (8%) transitioned to funded clinical trial(s). Funded neurosurgical subspecialties included neuro-oncology (33%), functional/epilepsy (32%), cerebrovascular (17%), trauma (10%), and spine (6%). Dividing our 24-year period in halves, F32s were granted equally ($P=0.4$), K08s decreased by 50% ($P<0.03$) while funded R01s increased by 50% ($P=0.0006$).

Conclusion: The decrease in K08 funding and plateau in F32 funding suggests that the upward trend in R01s awarded to neurosurgeons during the last 24 years will be difficult to maintain and underscores the importance of continued selection and mentorship of neurosurgeons capable of impacting patient care through research, including the MDPHs we noted to be particularly successful at procuring funding.

690. Association Between Baseline Affective Disorders and 30-Day Readmission Rates in Patients Undergoing Elective Spine Surgery

Robert Florin Resident Award

Owoicho Adogwa, MD; Aladine Elsamadicy, BE; Joseph Cheng, MD, MS; Carlos Bagley, MD (Durham, NC)

Introduction: In 2013, the Centers for Medicare and Medicaid Services implemented a policy that penalizes hospitals for “excessive” all-cause hospital readmissions within 30-days after discharge from index hospitalization. Accordingly, there is a growing understanding of the prevalence and impact of affective disorders on perception of health status in patients’ undergoing elective spine surgery. However, there role in early readmission is unclear. The aim of this study is to investigate the influence of psychiatric comorbidities on 30-day all-cause readmissions following elective spine surgery.

Methods: The medical records of 400 patients undergoing elective spine surgery at a major academic medical center were reviewed, of which 107 patients had comprehensive 1- & 2-year patient reported outcomes data. We identified all unplanned readmissions within 30 days of discharge. Prevalence of affective disorders such as depression and anxiety were also assessed. We hypothesized that psychological disorders, such as depression and anxiety, are independently associated with an increased risk of 30-day readmission after elective spine surgery. All-cause readmissions within 30-days of discharge was the primary outcome variable.

Results: Baseline characteristics were similar between both groups, Table 1. Approximately 6% of patients were readmitted within 30-days of discharge. The rate of readmission was 3-fold greater for individuals with a psychiatric comorbidity compared with those without a psychiatric comorbidity (10.34% vs 3.84%, $p=0.03$). In a univariate analysis, race, BMI, gender, patient-age, smoking, diabetes and fusion levels were associated with increased 30-day readmission rates. However, in a multivariate logistic regression model, depression was an independent predictor of readmission within 30-days of discharge, Table 2. Additionally, there were no significant differences in baseline, one- and two-year patient reported outcomes measures between both groups, Table 3.

Conclusion: Psychological disorders like depression and anxiety are independently associated with higher all cause 30-day readmission rates after elective spine surgery. Future interventions to reduce readmission should consider adding mental health components.

691. Remote, Continuous Monitoring of Patient Mobility after Discharge: A Marker for 30-Day Readmission

Trae Robison; R. Widemon, BS; Blake Taylor, BS; Brandon Christophe, BA; E. Connolly, MD

Introduction: Thirty day hospital readmission has become a major focus of the American health care reform initiative over the past few years. With readmission rates from 5-15% for neurosurgical procedures, it is of particular concern for the specialty. In order to better identify and support patients who are at risk for readmission, we employed the use of a common mobile health technology to monitor patient movement and rate of readmission.

Methods: The movement of postoperative neurosurgical patients was monitored via smartphone connected accelerometer (Fitbit®) for 30 days after discharge. The device worn on the patient’s ankle where it most accurately measures the number of patient steps and level of activity. The device was returned via a provided, prepaid mailer after the study period was completed.

Results: Of the 69 subjects enrolled, 6 were readmitted within 30 days. The 63 patients who were not readmitted averaged 2316 steps per day as compared to 537 for the 6 who were ($p=.006$). Trends also showed on average that patients who steadily improved increased their number of steps per day, while the steps for the readmitted patients declined.

Conclusion: Results show that patients who go on to be readmitted exhibit less activity as detected by the Fitbit accelerometer than the non-readmitted patients. Using the inexpensive Fitbit technology, a feasible and scalable home monitoring system is possible for postoperative neurosurgical patients. With as close to real-time surveillance as possible, the remote activity tracking may allow for early intervention and the ability to improve 30-day readmission rates as well as overall quality of care.

692. The Impact of Inter-Facility Transfers on Patient Outcomes for Surgically Managed Aneurysmal Subarachnoid Hemorrhage

Brandon Allan McCutcheon, MD; Brian Hirshman, MS; Scott Nomura, BS; Jennifer Padwal, BS; Logan Marcus, MD, MS; Bob Carter, MD, PhD (Rochester, MN)

Introduction: While increased hospital volume is associated with improved outcomes in aneurysmal subarachnoid hemorrhage (aSAH), the effect of patient transfer from a low-volume to high-volume facility remains unclear. This relationship has significant implications for health-systems organization and triage; especially given potential concerns about delays associated with time-to-transfer.

Methods: Patients who underwent coiling or clipping for aSAH from 1999 to 2009 were identified using the California Office of Statewide Health Planning and Development longitudinal database. The interaction between transfer status and hospital volume was evaluated with respect to adverse discharge disposition and in-hospital mortality using multivariable logistic regression analysis.

Results: 10,044 aSAH cases were observed in primary analysis. 4,017 (40.0%) were at high volume centers (≥ 30 cases/year), and 3,028 (30.1%) involved inter-facility transfer. Multivariable analysis controlled for: patient demographics, comorbidities, transfer status, clipping versus coiling, hospital location, and year. Patients directly admitted to a high volume hospital (OR 0.62, 95% CI 0.52 to 0.73) and patients transferred to a high volume center (OR 0.50, 95% CI 0.41 to 0.62) experienced a significant reduction in the odds of mortality relative to patients admitted directly to low-volume centers. Similar results were seen for adverse discharge disposition. Results were replicated in a secondary confirmatory dataset.

Conclusion: Inter-hospital transfer from a low to high volume hospital was associated with a significant reduction in the odds of mortality and adverse discharge in aSAH patients. This observation may guide health-systems organization.

693. Hospital Acquired Infection Reduction Using a Multidisciplinary, Data-Driven Approach

John Joseph Knightly, MD, FAANS; John Halperin, MD, PhD; Edward Zampella, MD; Sharon Ninni, RN; Bonnie Weiss, RN; Charlene Ruggerio; Dorian Prasek, RN; Ann Richards; Iris Verdi, RN (Morristown, NJ)

Introduction: Neuro ICU patients are at high risk of hospital acquired infections (HAIs)—which contribute to excess morbidity, mortality and resource consumption. We implemented a multidisciplinary performance improvement program focusing on reduction

in catheter associated urinary tract infections (CAUTIs), ventilator associated pneumonias (VAPs) and surgical site infections (SSIs).

Methods: Nosocomial infection marker (NIM®; December 2010 to May 2014) and National Healthcare Safety Network (NHSN) data (2012 to current) on all neurosurgery patients at a single center with approximately 3,000 neurosurgery discharges/year were reviewed, tracking SSI's and NeuroICU CAUTIs and VAP's. HAI rates were calculated before and after interventions, and reviewed at all department QI meetings.

Results: SSIs: There was no SSI clustering by personnel, location, equipment, type of procedure or patient diagnosis or demographics. With implementation of chlorhexidine showers and operating room environmental changes, SSIs decreased from 3.0% of cranial and 1.5% of spinal neurosurgery cases to 0.4% and 0.5% respectively.

VAPs: On preliminary analysis frequency of transports for CTs correlated with respiratory ($p=0.0049$) and urinary ($p<0.001$) NIM®s. Use of a mobile CT scanner decreased transports by approximately half. Concomitantly VAP's decreased from 4.6/1,000 ICU patient-days to 1.7. CAUTIs: NeuroICU nurses were re-educated in optimal aseptic bladder catheter insertion and maintenance technique; we implemented a new simplified kit and the Ann Arbor criteria for appropriate use of indwelling catheters, including daily review of patients' need for catheterization. Foley catheter use decreased by a third and CAUTIs decreased from 17/1,000 ICU patient days to 6.7/1,000. Over 18 months, HAIs decreased from 8.5% to 3.5% of neurosurgical patients.

Conclusions: Combining a multidisciplinary team approach with rigorous analysis of objective data we decreased HAIs 60% over 18 months. Key drivers were decreased patient transport from the ICU for imaging, improved use of urinary catheters, and institution of pre-operative chlorhexidine showers.

694. The Impact of Commercial Health Plan Prior Authorization Programs on the Utilization of Services for Low Back Pain

Paul Park, MD, FAANS; Robert Goodman; Corey Powell, PhD (Ann Arbor, MI)

Introduction: Low back pain (LBP) is prevalent. Concern exists that spinal fusion is over-utilized for LBP. The study's purpose was to evaluate the impact of a health plan's prior authorization (PA) programs on use and cost for LBP in a non-Medicare population by assessing changes in pre-surgical non-operative care; lumbar fusion trends; and overall back surgery rates. The PA programs require mandatory physiatrist consultation before allowing referral for surgical consultation, with subsequent additional LBP surgery PA.

Methods: Data from a health maintenance organization (HMO) with commercial membership averaging <500,000 annually was reviewed. Patients analyzed included HMO commercial members aged 18–65 years, and a subset of 501 members who underwent lumbar fusion during the period 1-1-2008 through 12-31-2013. Annual rates of lumbar fusion was trended over 6 years. Standardized costs for LBP-related services was assessed.

Results: After initiation of the physiatrist PA in December 2010, lumbar fusions decreased from 76.27/100,000 in 2010 to 62.63/100,000 in 2011. However, there were subsequent increases to 64.24/100,000 and 73.84/100,000 in years 2012 and 2013, respectively. For members who had lumbar fusion, there were increased per-member, pre-surgical costs of \$2,233 with the physiatrist PA and an additional \$1,370 with implementation of the LBP surgery PA (March 2013). Spinal injections (23.2%) and inpatient admissions (18.5%) were the two greatest contributors to the overall increase in pre-surgical costs. The physiatrist and LBP surgery PA programs were also associated with lengthening of LBP episodes ending in surgery by 309 and 198 days, respectively.

Conclusion: Mandatory referral to a physiatrist prior to surgical evaluation did not result in persistent reduction in lumbar fusions. Instead, these programs were associated with the unintended consequence of increased costs from more non-operative care for only a transitory change in the lumbar fusion rate, likely from delays due to the introduction of both PA programs.

695. Effect of 90-day Complications on Cost-utility following Lumbar Decompression with and without Fusion for Degenerative Spine Disease

Scott Parker, MD; Silky Chotai, MD; Ahilan Sivaganesan, MD; John Sielatyski, MD; Clinton Devin, MD; Matthew McGirt, MD (Nashville, TN)

Introduction: Understanding the effect of complications on cost and effectiveness of surgery is vital to understanding its overall impact. We evaluated effect of complications on cost-utility after lumbar decompression with/without fusion.

Methods: 407 consecutive patients undergoing elective surgery for degenerative lumbar pathology were enrolled into prospective longitudinal registry. PROs were recorded at baseline, 3-months, 12-months, and 24-months post-operatively: ODI, NRS-back and leg pain (BP, LP), EQ-5D. Two-year back-related medical resource utilization, missed work, and health-state values (quality-adjusted life years [QALYs]) were assessed. Two-year resource use (direct cost) and patient/caregiver workday losses (indirect cost) were calculated. Mean total (direct+indirect) 2-year cost/QALY gained was assessed. Patients were stratified into cohorts based on whether a 90-day major complication had occurred (surgical site infection, hardware failure, neurological deficit, pulmonary embolism, hematoma, MI).

Results: There was significant mean improvement in pain, disability, and quality of life for total cohort 2-years post-operatively ($p<0.0001$). Total 24-month cost was significantly lower in patients without vs. with complication for decompression alone ($\$16,133 \pm 8,008$ vs. $\$21,322 \pm 9,029$, $p=0.09$) and decompression + fusion ($\$37,674 \pm 11,686$ vs. $\$40,825 \pm 11,570$, $p=0.03$). QALY gained at 24-months was similar in patients without/with complication for decompression alone (0.68 ± 0.70 vs. 0.72 ± 0.63 , $p=0.81$) and decompression + fusion (0.59 ± 0.60 vs. 0.46 ± 0.60 , $p=0.21$). Cost/QALY gained was reduced in patients without vs. with complication for decompression alone ($\$23,725/\text{QALY}$ vs. $\$29,614/\text{QALY}$, $p=0.05$) and decompression + fusion ($\$63,854/\text{QALY}$ gain vs. $\$88,750/\text{QALY}$, $p=0.11$).

Conclusion: Lumbar surgery provided significant improvement in pain, disability, and quality of life at 24-months regardless of occurrence of 90-day complication. Occurrence of complication resulted in significantly increased cost at 24-months. Cost-utility was $\$5,889$ higher after decompression alone and $\$24,896$ higher after decompression + fusion. Measures focused on prevention of complications will improve value of spine surgery.

696. Influence of Insurance Status on Survival of Adults with Glioblastoma Multiforme (GBM): A Population Based Study

Xiaoming Rong; Wuyang Yang, MD; Tomas Garson-Muvdi, MD; Justin Caplan, MD; Michael Lim, MD; Judy Huang, MD (Guangzhou, China)

Introduction: The impact of insurance status on survival time of glioblastoma multiforme (GBM) patients has not been described. We aim to clarify the association between insurance status and survival of GBM patients.

Methods: This is a cohort study utilizing data from the

Surveillance, Epidemiology, and End Results (SEER) Program. We included adult patients (age ≥ 18 years) with GBM as the primary diagnosis from the years 2007–2012 in SEER dataset. The primary outcome of this study was GBM-related survival. A survival analysis between insurance status and GBM related death was performed using multivariate Cox regression analysis. Demographic and clinical variables were included to adjust for confounding effects.

Results: Among the 13665 adult patients in our study cohort, 558 (4.1%) were uninsured, 1516 (11.1%) had Medicaid coverage, and 11591 (84.8%) had non-Medicaid insurance. Compared with patients who were uninsured, insured patients were more likely to be older, female, white, married, and with smaller tumor size. Multivariate Cox regression showed that older age ($\text{HR}=1.04$, $p<0.001$), male ($\text{HR}=1.08$, $p<0.001$) and large tumor ($\text{HR}=1.23$, $p<0.001$) were independent risk factors for shortened survival of GBM, while non-Medicaid insurance ($\text{HR}=0.89$, $p=0.039$), radiotherapy ($\text{HR}=0.40$, $p<0.001$) and married status ($\text{HR}=0.86$, $p<0.001$) indicated a better outcome. We discovered an overall yearly improvement of survival in patients diagnosed from 2007–2011 ($p<0.001$). This trend was also found in non-Medicaid insured patients ($p<0.001$), but not in uninsured patients or Medicaid-insured patients.

Conclusion: Variations existed in insurance status within the GBM population. Non-Medicaid insurance suggested longer survival compared to uninsured patients in GBM population. GBM patients with non-Medicaid insurance sustain a significant yearly survival gain compared to uninsured and Medicaid-insured patients.

697. An Assessment of Data and Methodology of Online “Surgeon Scorecards”

Linda Xu, MD; Amy Li, BA; Christian Swinney, BA; Maya Babu, MD, MBA; Anand Veeravagu, MD; Stacey Wolfe, MD; Brian Nahed, MD; John Ratliff, MD (Stanford, CA)

Introduction: Recently, two surgeon rating websites (Consumers’ Checkbook and ProPublica) were published to allow the public to compare surgeons amongst their colleagues by surgical volume and complication rates. In neurosurgery and orthopedic surgery, procedures evaluated included cervical and lumbar spine, hip, and knee procedures.

Methods: We examined the methodology of each website. We queried each online tool for reports for spine neurosurgeons and spine or joint orthopedic surgeons amongst the top hospitals in the United States as represented by a national consumer publication ranking system within these respective fields.

Results: A search of 510 surgeons showed that only 28% and 56% surgeon data was represented on Consumers’ Checklist and ProPublica respectively. Of the surgeons with data, 17% were quoted to have high complication rates, 12% with lower volume than other surgeons, and 77% had a 3 out of a 5 star rating. There was no significant correlation found between the number of stars a surgeon receives on Consumers’ Checklist and his adjusted complication rate on ProPublica ($p=0.79$).

Conclusion: When looking at each website’s methodology, neither site assessed complication occurrence, but rather readmissions or prolonged length-of-stay with limited or no risk adjustments. A substantial number of surgeons from top-ranked hospitals have no ratings on either site, or have data that suggests they are low volume surgeons or have higher complication rates, with no correlation between surgeon grading between sites. Given the significant methodological issues, incomplete data, and lack of appropriate risk stratification of patients, the featured websites may provide erroneous information to the public.

698. The Predictive Performance of the American College of Surgeons Universal Risk Calculator in Neurosurgical Patients

Sasha Vaziri, MD; Jacob Wilson, BS; Tyler Carney, BS; Joseph Abbatematteo; Paul Kubilis, MS; Daniel Hoh, MD (Gainesville, FL)

Introduction: The current era in healthcare prioritizes patient safety as a metric for evaluating physician performance. In addition, patient centered surgical risk assessment is one measure currently reported to the Physician Quality Reporting System. Surgical risk calculators are potentially valuable predictive tools for post-operative complications, and may assist in patient shared decision-making to appropriately risk stratify. The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Universal Surgical Risk Calculator is an online decision-support tool that uses patient characteristics to estimate risk of adverse post-operative events. Further validation of this risk calculator in the neurosurgical population is needed; the objective of this study was to assess the predictive performance of the ACS NSQIP Surgical Risk Calculator in neurosurgical patients treated at a tertiary center.

Methods: A single-center retrospective review of 1033 neurosurgical patients from 1/2012 and 5/2015 was performed. Cases reviewed were limited to those with a single neurosurgical CPT code. Individual patient characteristics were entered into the NSQIP calculator. Predicted complications were compared to actual occurrences identified through chart review and administrative quality coding data. Statistical models were used to assess predictive performance of risk scores.

Results: No significant differences were found in the prevalence of predicted versus observed mortality, serious complications, any complications, return to OR, and surgical site infection (SSI). However, the NSQIP had poor predictive performance in our population for serious complications (c-stat=0.76, R2=0.18 [0.12–0.25]), any complication (c-stat=0.74, R2=0.17 [0.10–0.24]), return to OR (c-stat=0.68, R2=0.08 [0.003–0.16]), SSI (c-stat=0.56, R2=–0.02 [–0.07–0.05]), discharge disposition (c-stat=0.79, R2=0.13 [0.02–0.25]). The NSQIP calculator demonstrated predictive accuracy for post-operative mortality (c-stat=0.932, R2=0.38 [0.32–0.46]).

Conclusion: This study illustrates the importance of validating universal risk calculators in specialty specific surgical populations. The ACS NSQIP Universal Risk Calculator may be used as a decision support tool for neurosurgical informed consent with respect to predicted mortality.

700. Safety, Tolerability, Pharmacokinetics and Efficacy of Intraventricular Sustained Release Nimodipine (EG-1962) for Subarachnoid Hemorrhage

R. Loch Macdonald, MD, PhD, FAANS; Daniel Hänggi, MD; Nima Etmnan, MD, PhD; Stephan Mayer; Francois Aldrich; Michael Diringer, MD; Hans Steiger, MD; Brian Hoh, MD; J Mocco, MD; Poul Strange, MD, PhD; Herb Faleck, DO (Toronto, Canada)

Introduction: Treatments for aneurysmal subarachnoid hemorrhage (aSAH) remain limited. EG-1962 is a sustained release formulation of nimodipine for intraventricular delivery in order to avoid dose-limiting hypotension common with systemic administration. We conducted a phase 1/2a multicenter, controlled, randomized, openlabel, dose escalation study to determine the maximum tolerated dose (MTD) and assess safety, tolerability, pharmacokinetics and efficacy at 90 days on the extended Glasgow outcome scale (GOSE)

of a single intraventricular dose of EG-1962 (www.clinicaltrials.gov Identifier: NCT01893190).

Methods: Subjects with aSAH repaired by clipping or coiling were randomized within 60 hours of aSAH to EG-1962 or oral nimodipine if they were World Federation of Neurological Surgeons grade 2 to 4 and had a ventricular catheter. Cohorts of 12 subjects received 100, 200, 400, 600, 800 or 1200 mg EG-1962 (9 per cohort) or oral nimodipine (3 per cohort).

Results: The MTD was 800 mg EG-1962. Plasma nimodipine concentrations with EG-1962 were sustained for 21 days and increased in a dose-dependent fashion. Cerebrospinal fluid nimodipine concentrations with EG-1962 were orders of magnitude higher than in plasma or with oral nimodipine. There was one serious adverse event related to EG-1962 and two EG-1962 dose limiting toxicities; all were without clinical sequelae. There was no EG-1962-related hypotension versus hypotension in 17% (3/18) with oral nimodipine. Favorable outcome (GOSE 6–8) was achieved in 27 of 45 (60%) EG-1962 subjects (5/9 with 100, 6/9 with 200, 7/9 with 400, 4/9 with 600, 5/9 with 800 mg) and 5/18 (28%) oral nimodipine subjects. Delayed cerebral ischemia (15/45 [33%] EG-1962 versus 11/18 [61%] oral nimodipine) and rescue therapy (11/45 [24%] versus 10/18 [56%]) were reduced in EG-1962 subjects.

Conclusion: Intraventricular EG-1962 was safe and tolerable to 800 mg, associated with sustained, dose-dependent nimodipine plasma concentrations, improved clinical outcome and reduced delayed cerebral ischemia and rescue therapy after aSAH.

701. CMV-targeted Dendritic Cell Vaccines Increase Survival for Randomized Patients with Glioblastoma in Successive Trials

Stryker Neuro-Oncology Award

Kristen A. Batich; Elizabeth Reap, PhD; Gary Archer, PhD; Luis Sanchez Perez, PhD; Pam Norberg, BS; Robert Schmittling, BS; Weihua Xie, MS; James Herndon II, PhD; Patrick Healy, MS; Duane Mitchell, MD, PhD; John Sampson, MD, PhD (Durham, NC)

Introduction: Cytomegalovirus (CMV) antigens are expressed in a high proportion of glioblastomas (GBMs) and could serve as tumor-specific targets for immunotherapy.

Methods: In a randomized and blinded trial, patients with primary GBM received standard radiation and temozolomide (TMZ) (200 mg/m² x 5 days) combined with a dendritic cell (DC) vaccine pulsed with mRNA encoding the CMV antigen pp65 and vaccine site pre-conditioning consisting of either tetanus-diphtheria (Td) toxoid or unpulsed DCs. In a subsequent single arm Phase II trial, patients received dose-intensified TMZ (100 mg/m² x 21 days) and pp65-DCs admixed with GM-CSF. Both trials assessed immunogenicity by pp65-specific ELISpot, progression-free survival (PFS), and overall survival (OS).

Results: Patients receiving pp65-DCs and Td pre-conditioning showed a significant increase in both PFS and OS (p=0.013; median PFS=15.4 months; median OS=25.7 months) compared to patients receiving unpulsed DCs who had median PFS and OS of 10.8 and 18.5 months, respectively. Three censored patients from the Td cohort did not progress and were alive at the time of survival analysis (<41.1 months). The survival benefit of pp65 DC vaccines was confirmed in a second trial, wherein patients given pp65-DCs demonstrated increased pp65-specific immune responses (p=0.0186). PFS and OS were also significantly increased (median PFS=25.3 months, CI95: 11.0–undefined; median OS=41.1 months, CI95: 21.6–undefined). Four of 11 patients remain progression-free at 59–64 months from diagnosis. For both trials, there was no trend across prognostic factors (age, KPS, IDH-1/2 mutation, and MGMT promoter methylation) that could provide a more favorable outcome.

Conclusion: In two separate trials, including one blinded and randomized trial, targeting CMV in GBM significantly increased patient survival and generated potent immune responses compared to controls. CMV pp65-DC vaccines have now been associated with superior OS rates in multiple trials, fortifying the rationale for CMV targeting and long-term survival in other studies.

702. Incidence of Position Related Neuropraxia in 4489 Consecutive Patients Undergoing Spine Surgery. Role of SSEP Monitoring?

Sanford J. Larson, MD, PhD Award

Gurpreet Surinder Gandhoke, MD; Jaspreet Kaur; Parthasarathy Thirumala; Zachary Tempel; Jeffrey Balzer; Donald Crammond; William Donaldson; David Okonkwo; Adam Kanter (Pittsburgh, PA)

Introduction: No large database study exists looking at the incidence of peripheral nerve injury from positioning during spine surgery.

Methods: Records of 4489 consecutive patients undergoing spine surgery at a university hospital were reviewed. Incidence of peripheral nerve injury from positioning among these patients is reported. IOM changes related to arm and leg positioning and their sensitivity and specificity predicting the development of a new position related peripheral nerve injury is calculated. Impact of length of surgery & of variables including age, sex, BMI, DM, HTN, CAD, CVD & history of smoking, on the development of a new peripheral nerve injury was defined.

Results: Positions were, arms abducted and flexed at the elbow, n=2904 (64.7%), arms tucked at the side, n=1570 (35%), and the Lateral position, n=15 (0.3%). Thirteen out of 4489 (0.29 %, CI95% 0.15-0.49%) patients developed a new positioning related peripheral nerve deficit. Seven (54%) developed meralgia paresthetica, 6 (46%) developed ulnar neuropathy. Seventy-two (1.6%) patients developed IOM changes from positioning and all these patients underwent a repositioning maneuver. One of these 72 (1.3%) developed a new position related nerve deficit. Of the 4417 (98.4%) patients who did not develop position related IOM changes 12 (0.3%) developed a new position related nerve deficit. Sensitivity of IOM to detect a new position related nerve deficit was 7.69% and, the specificity was 98.41%. The positive predictive value was 1.39% (CI95% 0.04-7.5%) and the negative predictive value 99.73% (CI95% 99.53-99.86%). Neither the length of surgery nor did any analyzed patient related variable have a statistically significant impact on the development of a new neuropraxia.

Conclusion: The incidence of a new position related nerve deficit in spine surgery was 0.29%. IOM has high specificity and poor sensitivity in detecting a positioning related nerve deficit.

703. Orthoxenograft Rodent Model for Evaluation of Malignant Peripheral Nerve Sheath Tumors and Preliminary Results of Tumor Response to IL-13 Conjugated Liposomal Doxorubicin

Russell A. Payne, MD; Elias Rizk, MD, MS; Kimberly Harbaugh, MD; Becky Webb, BS; James Connor, PhD; Achuthamangalam Madhankumar, PhD; Oliver Mrowczynski, MS (Hershey, PA)

Introduction: Treatment of malignant peripheral nerve sheath tumors is poor without any effective systemic therapies having been

established. MPNSTs express the IL13Ra2 receptor which is an ideal target for therapies. Development of a reproducible and cost effective animal model on which novel treatments can be tested is imperative. We present a orthoxenograph animal model utilizing intraneural sciatic nerve injection of a MPNST tumor cell line expressing luciferase and the results of IL-13 conjugated liposomal doxorubicin on tumor growth.

Methods: Tumor cells from a MPNST cell line expressing IL13Ra2 receptor were transfected to express luciferase. The sciatic nerves of six mice were injected with 50,000 cells/5ml. Tumor growth was confirmed using in vitro imaging system (IVIS). The mice were then divided into control and treatment groups. Those within the treatment group received either non-targeted liposomal doxorubicin (2 mice) or targeted (IL-13 conjugated) liposomal doxorubicin. Tumor size was then monitored using in vitro imaging.

Results: In vitro imaging of the mice identified progressively increasing bioluminescent signal within the injected hindlimb of all mice. Visual inspection revealed a firm, immobile mass within the hindlimb along the course of the sciatic nerve. Gross examination of the sacrificed mice revealed tumor within the sciatic nerve of all injected specimens. Close inspection revealed that the tumor did emanate from the sciatic nerve and weighed between 1.5-3.0 grams. Histopathological evaluation revealed intraneural proliferation of tumor with avid immunofluorescence staining of IL13Ra2 receptor confirming presence of tumor.

Conclusion: We present a novel animal model for evaluating treatment of MPNSTs. Unlike previous models which have relied on subcutaneous injection of tumor cells, we have developed a reliable and realistic animal model in which the tumor principally grows within, and emanates from, the injected sciatic nerve. This model allows for accurate evaluation of new therapies developed to combat MPNSTs.

704. Deep Temporal Nerve Transfer for Facial Reanimation - A Cadaveric Dissection Study

Walavan Sivakumar, MD; Mark Mahan, MD; Justin Brown, MD (Salt Lake City, UT)

Introduction: Facial nerve palsy is a disabling condition that may arise from a variety of injuries or insults and may occur at any point along the nerve or its intracerebral origin. We have started investigating the deep temporal branches of the motor division of the trigeminal nerve as a possible donor for neural reconstruction of the temporal branches of the facial nerve for the restoration of active blink and periorbital facial expression. We attempted to identify surgical landmarks that would allow for consistent identification of the appropriate temporal branches.

Methods: Formalin-fixed hemifaces were dissected to identify landmarks for the deep temporal branches and the tension-free coaptation lengths.

Results: Ten hemifaces were dissected. The middle deep temporal nerve was able to be consistently identified on the deep side of the temporalis, within 14 to 22 mm posterior to the jugal point of the zygoma. The posterior deep temporal nerve was identified 20 to 28 mm posterior to the jugal point. From a lateral approach through the temporalis, the middle deep temporal nerve could be directly coapted to facial temporal branches in all specimens.

Conclusion: The middle deep temporal branches can be readily identified and utilized for facial reanimation. As there are multiple branches, selective use of a single branch can potentially occur without risk of profound denervation atrophy. This technique has been used in one patient with a history of facial palsy due to brainstem cavernoma. There was successful reanimation of the orbicularis oculi muscle with independent activation.

705. Ultrasound Evaluation of Traumatic Peripheral Nerve Injuries

Michel Klot, MD, FAANS; Ashley Hastings-Robinson, BA; Sabrina Lee, PhD; Thomas Grant, DO; Thomas Gallagher, MD; Siddhartha Sikdar, PhD; Imran Omar, MD; Kevin Blount, MD (Chicago, IL)

Introduction: A major diagnostic challenge in treating traumatic peripheral nerve injuries is to distinguish axonometric from neurotmetic grades of injury, since the former can recover on their own while the latter require a surgical intervention and repair. Current treatment protocols mandate performing serial clinical exams and electrodiagnostic studies to look for evidence of functional recovery and muscle reinnervation respectively. MR neurography using diffusion tensor imaging (DTI) protocols is showing promise in visualizing axons both in normal and injured nerves showing axonal degeneration and regeneration. We are studying various ultrasound protocols to determine whether this less expensive and more available imaging modality can also be used to distinguish axonometric from neurotmetic grades of nerve injury.

Methods: Patients with severe traumatic peripheral nerve injuries producing complete axonal degeneration were evaluated with serial clinical exams, electrodiagnostic studies, MR neurography, and ultrasound studies using both standard and elastography protocols. Ultrasound imaging was performed with the focus on looking at differences in nerve containing axons, severely damaged nerve not containing axons following axonal degeneration, and repaired nerve containing regenerating axons. Ultrasound findings were correlated with evidence of recovery as shown by functional improvement on clinical exam, muscle reinnervation on EMG studies, and findings on MR DTI studies.

Results: Our preliminary findings show that ultrasound imaging can detect differences in nerve with and without axons. Specifically, distal damaged nerve following degeneration of axons shows evidence of increased stiffness as compared to more normal nerve with axons proximal to the site of traumatic injury.

Conclusion: Ultrasound using both standard and elastography protocols shows promise in distinguishing severe nerve injuries that can recover through axonal regeneration (axonometric grade) from the more severe types of injury (neurotmetic grade) that cannot recover without a surgical intervention and repair.

706. The Anconeus Epitrochlearis Muscle may Protect against Development of Cubital Tunnel Syndrome

Thomas J. Wilson, MD; R. Shane Tubbs, PhD; Lynda Yang, MD, PhD (Ypsilanti, MI)

Introduction: The anconeus epitrochlearis muscle is an anatomic variant replacing Osborne's ligament to form the roof of the cubital tunnel that has historically been seen as a cause of ulnar nerve entrapment and potential indication for surgical intervention. Instead, we hypothesize that presence of an anconeus epitrochlearis decreases the risk of cubital tunnel syndrome.

Methods: This retrospective cohort study used patients undergoing ulnar nerve decompression as the experimental group and asymptomatic individuals from the published literature as the control group. Primary outcome of interest was presence of an anconeus epitrochlearis. Standard statistical methods were used.

Results: 9 (5.4%) of 168 patients who underwent decompression of the ulnar nerve for cubital tunnel syndrome had an anconeus epitrochlearis present. Of 634 asymptomatic individuals, an anconeus epitrochlearis was present in 98 (15.5%) individuals. An anconeus epitrochlearis was present significantly less frequently in

symptomatic patients than in asymptomatic individuals ($p < 0.001$). Among patients undergoing surgical decompression, an anconeus epitrochlearis was associated with symptoms in the dominant arm ($p = 0.037$).

Conclusion: An anconeus epitrochlearis was present significantly less often in patients with cubital tunnel syndrome than in asymptomatic controls. We hypothesize that the mechanism of protection may be that this muscle decreases rigidity of the entrance into the cubital tunnel. While in specific instances the anconeus epitrochlearis may be a point of ulnar nerve compression, we believe our data support the concept that the mere presence of an anconeus epitrochlearis should not be seen as an indication for surgical exploration.

707. Intraoperative Imaging in Traumatic Peripheral Nerve Lesions: Correlating Histologic Cross-Sections with High Resolution Ultrasound

Stephen Shelby Burks, MD; Iahn Cajigas, MD, PhD; Jean Jose, DO; Allan Levi, MD, PhD (Miami, FL)

Introduction: Advanced imaging plays an important role in the diagnosis and management of traumatic peripheral nerve lesions in continuity. Recently intraoperative ultrasound (US) has been used as a guide during surgery. This allows one to better identify scarred tissue without disrupting normal, healthy tissue. The objective of this work is to correlate histologic cross-sections from nerve samples taken at the time of surgery with axial, high-resolution ultrasound images at similar locations. Illustrate fascicular and neuroma anatomy with both US and histologic sections. Validate this important tool for intraoperative guidance in nerve surgery.

Methods: Three subjects undergoing nerve repair procedures after traumatic nerve injuries were enrolled prospectively. US images captured at the time of surgery were later matched with gross-anatomical cross-sections and fascicular anatomy compared across modalities.

Results: In cases 1 and 3 neuromatous tissue spanned the entire cross-sections of the common peroneal and upper trunk of brachial plexus, respectively. In case 2 only a portion of the sciatic nerve was involved with neuroma, thus Nerve Action Potentials (NAPs) were elicited distal to the lesion. Ultrasound clearly aided in minimizing the disruption of healthy neuronal tissue.

Conclusion: Intraoperative US correlates well with anatomical sections removed at the time of surgery. This report serves to highlight the role of US and validate its use in peripheral nerve surgery.

708. An International, Randomized, Controlled Trial of Focused Ultrasound Thalamotomy for Essential Tremor

William Jeffrey Elias, MD, FAANS; Nir Lipsman, MD; Howard Eisenberg, MD; Michael Schwartz, MD; Pejman Ghanouni, MD; Ryder Gwinn, MD; Travis Tierney, MD; Rees Cosgrove, MD; Takaomi Taira, MD, PhD; William Ondo, MD; Jin Woo Chang, MD, PhD (Charlottesville, VA)

Introduction: Recent advance shave allowed ultrasound to be transmitted with precision through the human skull. Pilot studies suggest that MR guided focused ultrasound can be used to successfully generate stereotactic thalamic lesions. We present the one year results of a double-blinded, randomized, controlled trial of FUS thalamotomy for essential tremor.

Methods: Seventy-six patients with essential tremor were randomized 3:1 to receive a unilateral focused ultrasound thalamotomy or a sham procedure. Tremor (CRST) and quality of life (QUEST) measures were obtained at baseline, 3, 6, and 12 months. Safety was

determined by monitoring adverse events throughout the study period. All tremor assessments were videotaped and then rated by an independent core lab of neurologists not involved in the procedures.

Results: Contralateral hand tremor, the primary endpoint, was improved by 49% at 3 months (18.1 ± 4.81 to 9.55 ± 5.06) compared to sham procedures (16.00 ± 4.42 to 15.75 ± 4.90) and the effect was durable at one year (10.89 ± 4.86). Similarly, functional measures of disability and quality of life were statistically improved whereas there was no change in the sham cohort. There were two serious adverse events in the treatment group: persistent sensory loss from the thalamotomy procedure and an unrelated TIA.

Conclusion: Focused ultrasound can be delivered effectively through the skull to make precise ablations deep in the brain. MR guided focused ultrasound thalamotomy improves hand tremor in ET with an acceptable safety profile. Additional studies are needed to determine the long term durability of the treatment.

709. Design and development of a novel, fast, extensive intra-operative registration technique of optical machine vision to pre-operative imaging for cranial and spinal neurosurgical procedures: clinical feasibility and comparison with existing neuronavigation

Raphael Jakubovic, Daipayan Guha, MD; Michael Lu; Shaurya Gupta; David Cadotte, MD, PhD; Chris Heyn, MD, PhD; Peter Howard, MD; Todd Mainprize, MD; Albert Yee, MD; Yang Victor (Toronto, Canada)

Introduction: Surface anatomy based localization of neurosurgical targets is used in planning appropriate skin incisions, minimizing exposure, and optimizing surgical corridors. Computer-assisted frameless stereotactic navigation is standard for most cranial procedures requiring localization of deeper structures, and is employed in spinal procedures. With pre- and/or intraoperative imaging for navigation, there are workflow limitations including setup time, ease of registration, and ability to account for tissue movement between imaging and navigation.

Methods: A novel structured-light-illumination machine vision system was developed for cranial and spinal neuronavigation. 118 patients undergoing craniotomy or spinal procedures requiring stereotactic neuronavigation were enrolled with thin-slice preoperative imaging. Intraoperative patient registrations were performed using the system and compared to existing neuronavigation (Medtronic StealthStation, O-arm, Stryker Navigation). Navigation data was compared to post-operative imaging, where detectable implants' positions were measured on 3D reconstructions and absolute deviations determined.

Results: The system provided surgical exposure maps for automatic registration using fast (<3 sec) iterative closest point algorithm, despite extensive datasets (mean 25,000 points/cranial, 1,500 points/vertebra). Time from optical imaging to navigation was 46 ± 39 sec, statistically faster than existing cranial (111 ± 81 sec) and spinal (254 ± 192 sec) navigation systems' setup time. Cranial registrations on scalp and face showed absolute error of 2.08 ± 3.05 mm (axial). Lamina spinal registrations showed absolute error of 1.73 ± 1.34 mm (axial) and 1.22 ± 0.98 mm (sagittal). There is no statistically significant difference in absolute positional measurement error between machine vision system and existing neuronavigation techniques.

Conclusions: Optical machine vision is faster and comparably accurate for cranial and spinal neuronavigation. Rapid structured-light-illumination allows efficient initial and repeat registrations with minimal workflow interruptions.

710. Cortical Networks High Frequency EEG Activity Patterns in Patients Undergoing Epilepsy Surgery

Farid Hamzei-Sichani, MD; Michael Sperling, MD; Stefan Fuertinger; Ashwini Sharan, MD; Kristina Simonyan, MD, PhD (New York, NY)

Introduction: Cortical high-frequency oscillations (100–500 Hz) play a critical role in the pathogenesis of epilepsy; however, whether they represent a true epileptogenic process remains largely unknown. We examined the dynamical transitions of functional brain networks at different high frequency bands in order to determine their spatio-temporal characteristics underlying epileptic seizures.

Methods: We used high-resolution intracranial electroencephalographic recordings and graph theoretical analysis to identify the community structure of cortical brain networks at different frequency bands at rest and during multiple seizure episodes in patients with intractable epilepsy. All patients underwent chronic, video-monitored subdural iEEG recordings for localization of an epileptogenic zone prior to surgical resection.

Results: Neural networks at all examined frequencies showed temporally stable nodal community architecture during rest in all patients. During seizure periods, high frequency networks showed a significant breakdown of their community structure, which was characterized by an emergence of numerous small nodal communities or modules not limited to the seizure foci and encompassing the entire network. Such network disorganization manifesting as modular breakdown was observed on average 211 sec before the onset of clinical seizure and extended on average 187 sec after the end of the seizure. Gamma networks were characterized by stable community dynamics during resting and seizure periods.

Conclusion: Our findings suggest that the modular breakdown of high frequency networks represents a distinct functional pathology that underlies epileptogenesis and corresponds to a cortical state of highest propensity to generate seizures. As such, pathological network-HFO may facilitate the development of novel biomarkers for epileptogenesis.

712. Interhemispheric parietal connectivity is associated with improved functional recovery following MCA stroke in the cynomolgus macaque

Douglas James Cook, MD, FAANS; Joseph Nashed, PhD; Gallivan Jason, PhD; Coverdale Nicole, PhD; St. Amand Tim, PhD (Kingston, Canada)

Background: Stroke is a leading cause of death and disability worldwide. There is high variability in degree and rate of recovery following stroke. Stroke location is a key determinant of recovery. In the cynomolgus macaque model of MCA stroke we have previously shown that functional outcomes are improved with preservation of parietal cortex independent of total stroke volume. Parietal areas are intimately involved in processing sensorimotor information related to vision, reaching and grasp. We hypothesize that preservation of parietal cortex and parietal connectivity following MCAO is associated with improved post-stroke recovery following MCAO.

Methods: Twelve cynomolgus macaques underwent transient 90-minute MCAO. Perfusion, Diffusion, DTI and T2-MRI images were obtained following MCAO occlusion and at 48 h and 30 d. Total stroke volume and regional stroke volumes in premotor (PM), primary sensory cortex (S1), primary motor cortex (M1), and all parietal regions were quantified. Neurobehavioural outcomes were evaluated using the Non-Human Primate Stroke Scale (NHPSS). Animals were dichotomized into good and poor recovery by 30 d NHPSS (< 8 denotes poor recovery).

Results: Comparisons between the good and poor recovery groups showed no difference in penumbra (PWI-DWI) and stroke core volume at baseline and no difference in total stroke volume at 48h and 30 days (both $P < 0.05$). Functional connectivity maps 30 days post-stroke demonstrated connections between inter-hemispheric parietal regions in animals with good recovery. There were no differences in intra-parietal connectivity maps. DTI and connectivity maps with extra-parietal cortical regions demonstrate that preservation of input and output tracts are associated with improved outcomes.

Conclusions: We conclude that inter-parietal connectivity is associated with improved motor recovery following MCA stroke in the cynomolgus macaque. Preservation of ipsi-lesional parietal input and output tracts is associated with improved stroke recovery independent of intra-parietal connectivity. These results may guide future targeting of neuromodulation for stroke recovery.

713. Gamma Knife radiosurgical capsulotomy for obsessive compulsive disorder

Selcuk Peker, MD, Peker; Meltem Yilmaz; Meric Sengoz; Nazan Ulku; Kultegin Ogel (Istanbul, Turkey)

Introduction: Obsessive-compulsive disorder (OCD) is an anxiety disorder in which people have recurring, unwanted thoughts, ideas or sensations (obsessions) that make them feel driven to do something repetitively (compulsions). In this study, Gamma Knife radiosurgical capsulotomy was evaluated for refractory OCD patients.

Methods: Ten (6 male and 4 female) medically intractable OCD patients underwent bilateral anterior capsulotomy from 2007 to 2015 were retrospectively reviewed in this study. All patients were preoperatively confirmed as having severe OCD by one psychiatrist and one psychologist. Psychologist recorded Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. Gamma Knife radiosurgery (GKRS) was performed to targets of the bilateral anterior capsule. A single 4-mm isocenter was used for both left and right side for first 2 patients and 2 4-mm shots were used to irradiate for each target for 8 patients. The mean maximum dose 140 Gy (range 140–150 Gy) were delivered. The median age was 32 (range 26–43). The median follow-up was 9 months (range 6–97 months). At the time of the GKRS the median Y-BOCS score was 38 (range 25–40). Neuroimaging studies at 6 months after GKRS were performed for all patients.

Results: The median Y-BOCS score was 16 (range 0–32) at the last follow-up, 8 (80%) patients showed clinical improvement; One (10%) patient was reported as OCD symptoms free, significant improvement was recorded for 6 (60%) patients, mild improvement was seen for 1 patients. The remaining 2 (20%) patients notified as no improvement yet. There were T2 signal changes between before and 6 months after treatment. No adverse clinical effects were noted in this series.

Conclusion: Gamma Knife radiosurgical capsulotomy may be effective treatment option for the medically refractory OCD patients for the improvements of the quality of life. Further studies are needed in order to see late effects.

714. Expression Levels of Cortical Genes are Associated with Seizure Outcome Following Temporal Lobectomy

Jesse Michael Skoch, MD; Matthew Gallek, PhD; Tracy Ansay, MD; Martin Weinand, MD (Cincinnati, OH)

Introduction: Whole genome analyses were performed to test the

hypothesis that temporal cortical gene expression differs between patients rendered seizure-free and non-seizure-free following anterior temporal lobectomy with amygdalohippocampectomy (TL/AH). Four genes not previously associated with epilepsy were found to predict a seizure-free outcome when expression levels were relatively down-regulated.

Methods: Twenty-four patients underwent TL/AH to treat medically intractable seizures of temporal lobe origin (mean age 36 years, mean follow up 42 months). RNA was isolated from the lateral temporal cortex and gene expression analysis was performed on Affymetrix chips. Whole genome data were analyzed for prognostic value for seizure-free outcome following TL/AH by logistic regression ($\alpha < 0.05$, < 0.90 area under the receiver operating characteristic curve (AUC)). A leave-out analysis to assess for outliers that could skew results eliminated no probes.

Results: Gene expression associated with seizure-free outcome included relative down-regulation of Zinc-Finger 852 (ZNF852) ($p < 0.000001$, AUC=0.958), CUB (Complement, uEGF, Bmp1) Domain Containing Protein 2 (CDCP2) ($p < 0.001$, AUC=0.941), Proline-rich Transmembrane Protein 1 (PRRT1) ($p < 0.001$, AUC=0.916), and Hypothetical LOC440200 (FLJ41170) ($p < 0.001$, AUC=0.908).

Conclusion: This study suggests a predictive value in temporal cortical gene expression for seizure outcome after TL/AH. Four genes were found to be associated with seizure-free outcome after TL/AH when their levels were relatively down-regulated. None of these genes currently have well defined functional roles, and none have been previously tied to epilepsy. Future prospective investigation of these or other genes in blood leukocytes and cell-free RNA is underway and could establish novel biomarkers predictive of seizure outcome following TL/AH.

715. Deep Brain Stimulation Targeting the Zona Incerta Modulates Eye Movements in Humans

Omar Khan Bangash; Arosha Dissanayake, MBBS; Shirley Knight; John Murray; Megan Thorburn; Nova Thani, MBBS; Arul Bala; Rick Stell, MBBS; Christopher Lind (Perth, Australia)

Introduction: The posterior subthalamic area (PSA) centred on the zona incerta (ZI) is an investigational target for therapeutic deep brain stimulation (DBS). Animal evidence indicates the ZI may play a role in saccadic eye movements via a GABAergic incerto-collicular pathway. PSA DBS for Parkinson's disease (PD) and essential tremor (ET) provided an opportunity to test this hypothesis in humans and characterise its effects on saccades.

Methods: Sixteen patients (PD=12, ET=4) underwent DBS under general anaesthesia using the MRI-directed implantable guide tube technique. Active electrode positions were confirmed at the caudal ZI. Eye movements were tested using electro-oculography (EOG) in the medicated state pre and post-operatively on a horizontal predictive task subtending 30°. Post-operative assessments consisted of microlesion (ML) and high frequency stimulation (HFS: frequency = 130Hz, up to 3 volts) conditions. A two-way analysis of variance (ANOVA) was performed with $\alpha = 0.05$.

Results: PSA HFS leads to significant reduction in first saccade amplitude by 10.4% (95% CI 8.68–12.2) and 12.6 % (95% CI 10.0–15.9) in the PD and ET groups respectively. With HFS peak velocity was reduced by 14.7% (95% CI 11.7–17.6) in the PD and 27.7% (95% CI 23.7–31.7) in the ET group. HFS lead to PD patients performing 21% (95% CI 16–26) and ET patients 31 % (95% CI 19–38) more saccadic steps to reach the target.

Conclusion: PSA DBS in patients with PD and ET leads to hypometric, slowed saccades with an increase in the number of steps taken to reach the target. Given the location of the active

contacts, the GABAergic incerto-collicular pathway is likely to be responsible. This is the first evidence for its existence in humans. Furthermore these findings suggest patients undergoing PSA DBS may have impaired saccadic performance which requires further investigation.

716. The Effects of Mechanical and Thermal Stimuli on Local Field Potentials in Parkinson's Disease Patients

Julie G. Pilitsis, MD, PhD, FAANS; Abigail Belasen, BSc; Julia Prusik, BS; Youngwon Youn, BA; Brant Lai, BA; Adolfo Ramirez-Zamora, MD; Brian Kaszuba; Lucy Gee, BS; Khizer Rizvi, BS; Philip Yeung, BS; Damian Shin, PhD (Albany, NY)

Background: Chronic pain is a major, debilitating symptom of Parkinson's disease (PD). Although deep brain stimulation (DBS) has been shown to improve pain outcomes in patients who have received DBS for motor symptoms, the mechanisms underlying this phenomenon are unclear. Microelectrode recording (MER) routinely performed at our center for DBS allows us to measure both single neuronal unit activity and local field potentials (LFPs).

Objective: We examine changes in LFPs in the STN, globus pallidus interna (Gpi), and globus pallidus externa (Gpe) following exposure with mechanical or thermal stimulus.

Methods: Sensory thresholds were determined pre-operatively using quantitative sensory testing (QST). Based on these data, patients were exposed to stimuli at detection and pain thresholds in the region where they have pain or in the contralateral lumbar region in patients without pain.

Results: When compared to a baseline recording, heat pain increased Gpe low beta activity.

Discussion: Mechanical stimuli result in changes in STN LFPs while heat sensation/pain alter Gpi/Gpe activity. These findings imply basal ganglia involvement in sensory perception and provide insight into differential roles of STN and pallidal structures. Understanding how LFPs are altered during the sensory symptoms of PD has important implications for analgesic therapy and closed-loop DBS systems.

717. Transient Elevation of Brain Temperature Could Serve as a Surrogate Marker of Cortical Spreading Depolarization

ThinkFirst Injury Prevention Award

Chunyan Li; Raj K. Narayan, MD (Manhasset, NY)

Introduction: Cortical spreading depolarization (CSD) is a pathophysiological phenomenon that can interrupt cortical brain function. This phenomenon is receiving much attention at present as a possible cause of secondary damage after traumatic brain injury. Previous studies have shown that CSD can significantly affect regional cerebral blood flow, brain tissue oxygen, and cerebral metabolism. However, the interplay of CSD and brain temperature has received little attention. We hypothesized that brain temperature may be correlated with CSD.

Methods: 21 male Sprague-Dawley rats were used in these studies. A craniotomy to implant the neural probe was made in the right hemisphere (0.8 mm2; ML: +2 to +3 mm; AP: -2 to -3 mm; DV: -4.5 mm). A small burr-hole was drilled on the same side 3 mm anterior to the probe to induce CSD with needle pricks. 1-channel alternating-current electrocorticography (AC-ECOG) and 2-channel temperature signals were simultaneously recorded.

Results: CSD wave was identified by negative shift of direct-current (DC) potential (3.4 ± 1.5 mV; 86.27 ± 19.27 s) and tran-

sient suppression of AC-ECOG. During CSD, brain temperature increased transiently. The surface temperature experienced a higher (0.25 ± 0.07 vs. 0.076 ± 0.015 °C) and faster (84.54 ± 19.27 vs. 179.14 ± 6.28 s) elevation than deep brain temperature. The sensitivity of the temperature to CSD amplitude was 0.0829 ± 0.0271 °C/mV. The durations of CSD and brain surface temperature elevation were closely matched (86.27 ± 17.83 vs. 84.54 ± 19.27 sec).

Conclusions: Our experimental data suggest that transient brain surface temperature elevation might serve as a useful surrogate marker of CSD and could provide a useful adjunct or alternative to DC-ECOG recordings to track CSD.

718. Participation in pre-high school football and later life neurological, neuroradiological, and neuropsychological findings: A study of 45 retired NFL players

Scott Zuckerman, MD; Gary Solomon, PhD; Andrew Kuhn, BS; Ira Casson, MD; David Viano; Mark Lovell, PhD; Allen Sills, MD (Nashville, TN)

Introduction: A recent study found that an earlier age of first exposure (AFE) to tackle football was associated with long-term neurocognitive impairment in retired NFL players. Our objective was to assess the association among number of years of exposure to pre-high school tackle football (PreYOE) and neuroradiological, neurological, and neuropsychological outcome measures in a different sample of retired NFL players.

Methods: Forty-five former NFL players were included in this study. All participants prospectively completed an extensive history, neurologic examination, brain MRI, and a comprehensive battery of neuropsychological tests. To measure the associations between PreYOE to tackle football and these outcome measures, multiple regression models were utilized, while controlling for several covariates.

Results: After applying a Bonferroni correction for multiple comparisons, none of the neurologic, neuroradiologic, or neuropsychological outcome measures yielded a significant relationship with PreYOE. A second Bonferroni-corrected analysis of a subset of these athletes with self-reported learning disability yielded no significant relationships on paper and pencil neurocognitive tests, but did result in a positive association between learning disability and computerized indices of visual-motor speed and reaction time.

Conclusions: The current study failed to replicate the results of a prior study, which concluded that an earlier AFE to tackle football may result in long-term neurocognitive deficit. In 45 retired NFL athletes, we found no associations between PreYOE to tackle football and neuroradiological, neurological, and neuropsychological outcome measures.

719. Serum biomarkers as predictor of long term outcome in severe traumatic brain injury

Amol Raheja, MBBS; Sumit Sinha; Neha Samson; Sanjeev Bhoi; Arul Selvi; Pushpa Sharma; Bhawani Sharma (Salt Lake City, UT)

Introduction: There has been increased interest in the potential importance of biochemical parameters as predictors of outcome in sTBI.

Methods: Out of 107 sTBI patients randomised for placebo controlled phase II trial of progesterone with or without hypothermia, we serially analysed serum biomarkers (S100-B, GFAP, NSE, TNF α , IL-6, Eg and Pg) using sandwich ELISA at admission and day7 for 86 patients, irrespective of assigned group. Their long term predictive value on dichotomised GOS, FIM and survival sta-

tus at 6 and 12 months was analysed using adjusted binary logistic regression model and receiver-operating characteristic curve.

Results: Favourable GOS at 1 year was predicted by higher admission IL-6 above 108.36 pg/ml and day 7-Pg levels above 3.15 ng/ml. Unfavourable GOS at 1 year was predicted by higher day 7-GFAP levels above 9.50 ng/ml. Survivors at 1 year had significantly higher day 7-Pg levels above 3.15 ng/ml. Non-survivors at 1 year had significantly higher day 7-GFAP serum levels above 11.14 ng/ml and day 7-IL-6 serum levels above 71.26 pg/ml. In multivariate analysis, independent predictors at 1 year were serum levels of day 7-Pg (favourable GOS; OR 3.24, CI=1.5-7; $p = .003$ and survival; OR 2, CI = 1.2-3.5; $p = .01$), admission IL-6 (favourable GOS; OR 1.04, CI = 1.00-1.08; $p = .04$) and day 7-GFAP (favourable GOS; OR 0.79, CI = 0.65-0.95; $p = .01$ and survival; OR 0.80, CI = 0.66-0.96; $p = .01$).

Conclusion: Serial Pg, GFAP and IL-6 monitoring could aid in prognosticating patients with acute sTBI.

720. Beneficial Effect of Faster Cooling Elicited by Combination of TRPV1 Agonist (Dihydrocapsaicin) and Mild Physical Hypothermia in Ischemia/Reperfusion Injury

Kaiyin Liu; Jun Zhang; Yunxia Duan; Xunming Ji, MD, PhD; Murali Guthikonda, MD; Yuchuan Ding, MD, PhD (Detroit, MI)

Introduction: Pharmacological hypothermia (PH) with various agents has been investigated. The time window after stroke is important to successful rescue of neurons. However, drawbacks of PH and physical cooling are the long time and large doses needed to achieve neuroprotective hypothermia. Transient Receptor Potential Vanilloid (TRPV) 1 receptor and its agonist dihydrocapsaicin (DHC) have been reported to induce hypothermia and exert neuroprotective effects in animal stroke models. It is proposed that TRPV1 agonism plays a thermoregulatory role in possibly reducing thermoregulatory set-point at the peripheral thermosensors and at the pre-optic anterior hypothalamus. Hypothesis: The combination therapy of physical cooling and PH may achieve faster cooling rates by increasing heat loss and decreasing heat generation.

Methods: Sprague Dawley rats were subjected to 2 h middle cerebral artery occlusion (MCAO) and followed by 24 h of reperfusion. Ischemic rats in each group ($n=8$) received either: no treatment, mild hypothermia, low DHC (0.5 mg/kg), high DHC (1.5 mg/kg) or combination (low DHC plus hypothermia). Treatments lasted for 3 h. Rate to target hypothermia (31C) onset was measured. Infarct volume was determined using triphenyl tetrazolium chloride (TTC) staining.

Results: Temperature decrease rate at which groups was determined as 0.1C/min for hypothermia, 0.06C/min for low DHC, 0.07C/min for high DHC and 0.2C/min for combination. The combination treatment was 3 times faster ($p<0.05$) than low and high DHC groups, while 2 times faster ($p<0.05$) than mild hypothermia. Infarct volume was largely and significantly reduced by combination therapy (19.2%), as compared to no treatment (49.5%), mild hypothermia only (50.0%), low DHC (36.6%), and high DHC (39.9%) groups.

Conclusion: Combination of physical hypothermia and DHC elicited a faster reduction of body temperature and strong neuroprotection as compared to single treatments. This novel therapy may provide better opportunity for ischemic brain to reach therapeutic hypothermia temperature.

721. Amyloid Deposition after TBI Correlates with Cognitive Deficits and Symptom Worsening

Joshua Gatson; Cari Stebbins, MS; Joseph Kilianski, MD; Ramon Diaz-Arrastia, MD; Christopher Madden, MD; Joseph Minei, MD; Hunt Batjer, MD (Dallas, TX)

Introduction: Traumatic brain injury (TBI) is a risk factor for Alzheimer's disease (AD). The primary objective of this case-series study was to conduct early 18F-AV-45 (florbetapir F18) positron emission tomography (PET) imaging in mild-to-moderate TBI subjects after injury to determine if amyloid plaque load predicts cognitive deficits.

Methods: Serial florbetapir F18 PET imaging was conducted in 7 individuals with a mild or moderate TBI (as indicated by their Glasgow Coma Scale [GCS] score between 13 and 15) at day 14 and at 12 months after injury. Of the 7 subjects that were tested, only one had a moderate TBI. Amyloid plaque levels were measured in the cerebral cortex of each individual. To screen for cognitive deficits, the symbol match test was administered at 12 months after TBI.

Results: At day 14 after injury, compared to healthy controls, the mild and moderate TBI subjects ($N=7$) had a 10% increase in amyloid plaque load within the cerebral cortex. When stratified by cognitive outcomes, at day 14 after injury, the subjects with poor outcomes ($n=3$) experienced a 20% and 13% increase in brain amyloid compared to healthy controls and TBI subjects with good outcomes, respectively. With respect to cognition, at 12 months after injury, the subjects with poor outcomes exhibited a negative correlation ($r = -0.71$) between amyloid plaque load and cognitive performance. Also, a positive correlation ($r = +0.78$) was detected between increased brain amyloid load and symptom scores at 12 months.

Conclusion: In conclusion, individuals with early, substantial increases in brain amyloid experience poor outcomes in the form of memory dysfunction and heightened symptoms (memory deficits, headaches, difficulty concentrating, etc.) at 12 months post-injury. Data presented here suggests that florbetapir F18 PET imaging may be a sensitive biomarker for predicting outcomes within the mild and moderate TBI population.

722. Acute Effects of Human Protein S Administration after Traumatic Brain Injury in Mice

Quoc-Bao D. Nguyen; Jing Tong; Timothy Robinson; Xiaowei Wang; Jason Huang (Temple, TX)

Introduction: Protein-S functions in the regulation of coagulation, inflammation, and apoptosis. Any single activity of protein-S or combinations thereof could potentially confer neuroprotective effects following traumatic brain injury (TBI).

Methods: A controlled cortical impact (CCI) mouse model was used to study the effects of protein-S administration on TBI. Ten to fifteen minutes after CCI, mice were injected with either a single dose of protein-S or phosphate buffered saline as a control. Fine motor coordination abilities of injured and sham-operated animals were evaluated by beam-walk-testing. Lesion volumes were calculated following Nissl staining. Markers of inflammation were assayed by immunohistochemistry.

Results: Twenty-four hours after CCI, the group treated with protein-S had approximately 56% better limb movement than control (beam-walk-test, T-test, $P<0.05$). Histology and immunohistochemistry revealed brains treated with protein-S had less lesion area and edema than control. Less CD11b+neutrophils were found in deep brain structures of protein-S group compared to control. In the treated group, the number of cells displaying activated caspase-3 and bcl-2 (marker and regulator of apoptosis respectively) signifi-

cantly decreased ($P<0.001$), while aquaporin-4 mRNA expression increased.

Conclusion: Our results suggest that intravenous protein-S treatment immediately (10–15 minutes) after CCI is beneficial for reducing the degree of injury and protecting early neurological function during the first 24 hours. In particular, protein-S potentially could protect against secondary injury following TBI by limiting early edema and inflammatory reactions mediated through a reduction in apoptosis and infiltration of leukocytes and macrophages. In addition, protein-S could regulate aquaporin-4 expression and thereby eliminate edema after TBI.

723. Using Diffusion Tensor Imaging as a Tool to Characterize Brainstem White Matter Track Injury

Theresa Williamson, MD; Amanda Rabinowitz, PhD; Elizabeth Wilde, PhD (Durham, NC)

Introduction: A challenge in mild traumatic brain injury (mTBI) is that its mechanism, diffuse axonal injury (DAI), is invisible to standard neuroimaging. Diffusion tensor imaging (DTI) is a modality thought to reflect white matter integrity. In this study we examined DTI metrics in three brainstem tracks in relation to mTBI diagnosis, cognitive performance, and concussion symptoms.

Methods: 66 adolescents and young adults (12–30 years) with mTBI and 36 demographically-matched uninjured controls underwent neuroimaging and neuropsychological assessment including the symbol-digit modalities test and Rivermead post-concussion symptoms questionnaire. DTI acquisition occurred on the day of injury. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were calculated for the following regions of interest: left and right cerebral peduncles (LCP & RCP) and medial lemniscus (ML). General linear modelling and correlation analyses were used to examine relationships between DTI metrics and demographics, mTBI diagnosis, and outcome measures.

Results: Diagnosis of mTBI was related to increased ADC in the ML ($F(2)=3.5$, $p=0.0335$). Within the mTBI group, concussion symptoms correlated with FA in the ML ($\rho=-0.37$, $p=0.003$) and LCP ($\rho=-0.34$, $p=0.008$) and ADC in the LCP ($\rho=0.31$, $p=0.014$) and RCP ($\rho=0.33$, $p=0.0098$). FA in the ML significantly correlated with duration of loss of consciousness ($\rho=-0.26$, $p=0.0372$).

Conclusion: DTI measures of brainstem white matter integrity distinguished mTBI patients from uninjured controls. Measures of brainstem injury were related to loss of consciousness and symptom severity. Findings suggest that DTI is a useful tool for examining DAI injury following mTBI.

724. Efficacy of edaravone, a free radical scavenger, on early brain injury after experimental subarachnoid hemorrhage. Early brain injury (EBI), which consists of neuronal apoptosis and vasogenic edema has recently been recognized as an important factor affecting outcome.

Masato Naraoka; Naoya Matsuda; Norihito Shimamura; Hiroki Ohkuma (Hiroaki, Japan)

Introduction: Early brain injury (EBI), which consists of neuronal apoptosis and vasogenic edema has recently been recognized as an important factor affecting delayed cerebral ischemia (DCI) and outcome after aneurysmal subarachnoid hemorrhage (SAH). Oxidative stress has been pointed out to be one of the factors inducing EBI. The aim of this study was to investigate whether administration of edaravone could ameliorate EBI using experimental SAH.

Methods: Male SD (400–450g) rats were subjected to SAH using

a modified endovascular perforation model with tungsten wire and guide tube. Edaravone (3.0mg/kg) was administered intraperitoneally at the time of SAH production. Twenty-four hours after SAH, the brain was taken, apoptosis of neuronal cells was evaluated by ELISA analysis of caspase 3 and TUNEL stain analysis, brain edema was evaluated by brain water content, and disruption of blood brain barrier (BBB) was investigated by Evan's blue content and ELISA analysis of MMP-9. Neurological state was evaluated 12 and 24 hours after SAH. Parameters were compared among the sham group, SAH group, and SAH-edaravone group.

Results: Apoptosis observed in the SAH group by TUNEL staining and caspase 3 ELISA, and apoptosis was significantly prevented by edaravone administration. Brain edema, BBB disruption, and MMP-9 were observed in the SAH group also suppressed in the SAH-edaravone group. However, statistically significant differences were not seen in the SAH-edaravone group compared to the SAH group. Neurological status was improved in the SAH-edaravone group, but not significantly differences among SAH, SAH-edaravone, and sham group.

Conclusion: This study indicated some efficacy of edaravone for EBI after SAH. It suggested that oxidative stress is one of the important factors inducing EBI and that edaravone administration has some usefulness for severe clinical grade patients with aneurysmal SAH.

725. Early Trigeminal Nerve Stimulation Reduces Brain Edema and Lesion Volumes Following Traumatic Brain Injury

Eugene Golanov; Chunyan Li, PhD; Gavin Britz, MD; Raj Narayan, MD (Houston, TX)

Introduction: Excitation of the trigeminal nerve has been reported to trigger an endogenous neuroprotective mechanism, the diving response. Recently, we have demonstrated that trigeminal nerve stimulation (TNS) is effective in attenuating the consequences of traumatic brain injury (TBI) by decreasing lesion volumes, suppressing inflammation and improving motor behavior. Here, we studied the effect of TNS at different time points after TBI in a rat model.

Methods: Controlled cortical impact (CCI) model was used to create severe TBI in male Sprague-Dawley rats ($n=6-8$ /group). Animals were divided into four groups: sham-animals; TBI-animals; TBI-animals with TNS immediate and 1 hour after the TBI. Electrical stimulation of the trigeminal nerves was performed by introducing two needles subcutaneously bilaterally along an imaginary line connecting the ear and eye. Rectangular cathodal pulses (0.5 ms, 10 V) were delivered at 25 Hz, continuously for 60 minutes. Brain edema (wet-dry-weight method) and lesion volumes (cresyl violet staining) were measured 24 hours after TBI.

Results: CCI produced brain lesions (0 vs 11.65 ± 1.26 mm³; $n=6$, $p<0.05$; sham vs. TBI) accompanied by brain edema ($77.2 \pm 0.6\%$ vs. $82.9 \pm 0.8\%$; $n=8$, $p<0.05$; sham vs. TBI). In the TNS groups, TNS decreased brain water content from 7% (no TNS) to 4.3%, compared to 6% after 1-hour delayed TBI ($80.5 \pm 0.5\%$ vs. $81.8 \pm 0.7\%$; $n=8$, $p<0.05$). Lesion volumes decreased by 26% after immediate stimulation compared to 19% following delayed TNS (7.0 ± 1.03 vs. 9.47 ± 2.04 mm³; $n=6$, $p<0.05$).

Conclusion: Trigeminal nerve stimulation reduced lesion size and edema after TBI. Immediate stimulation exerted more powerful effect than stimulation 1-hour after the TBI.

726. IDH Mutant Gliomas Escape Natural Killer Cell Immune Surveillance Through Downregulation of NKG2D Ligands

Ronald L. Bittner Award on Brain Tumor Research

Christopher Paul Deibert, MD; Zel Zhang, BA; Aparna Rao, PhD; Paola Grandi, PhD; Nduka Amankulor, MD (Pittsburgh, PA)

Background: Mutations in isocitrate dehydrogenases (IDH) are genetic drivers of a large subset of diffuse low grade gliomas and secondary glioblastoma. It is unknown how IDH mutant gliomas escape immune surveillance and whether epigenetic reprogramming caused by IDH mutations contributes to immune escape.

Methods: NKG2D ligands expression levels and NK cell-mediated lysis were measured in IDH mutant and wild-type patient-derived glioma cell lines and in genetically engineered astrocytes. We then assessed the impact of hypomethylating agent Decitabine as a potential NK sensitizing agent in IDH mutant cells.

Results: IDHmut astrocytes demonstrated a 5-fold reduction in gene expression for the NKG2D ligands ULBP1, ULBP2 and ULBP3 compared to IDHwt astrocytes. Five of five IDH mutant glioma cell lines tested exhibited significantly lower expression of NKG2D ligands compared with IDH wild-type cells. Additionally, IDH mutant astrocytes were significantly resistant to NK cell-mediated lysis. In patient derived lines, co-culture with NK cells and IDHmut demonstrated a 3.62% specific lysis compared to 24.13% in IDHwt lines. Blockade of NK cell NKG2D decreased cell percent specific lysis from 10.4% in isotype controls to 3.37%. Treatment with Decitabine restored NKG2D ligand expression and doubled NK-mediated lysis in IDH mutant cells in an NKG2D-dependent manner.

Conclusions: Here we demonstrate a novel, reversible mechanism for immune evasion in IDH mutant glioma cell lines. IDH mutant glioma cells are resistant to NK cell-mediated cytotoxicity in a NKG2D dependent fashion. Epigenetic therapy with Decitabine increases expression of NKG2DLs and may sensitize IDH mutant gliomas to NK cell immune surveillance.

727. A Prospective, Randomized Control Trial for Lumbar Drain Placement after Endoscopic Endonasal Skull Base Surgery

Synthes Skull Base Award

Nathan T. Zwagerman, MD; Samuel Shin; Georgios Zenonos; Eric Wang; Juan Fernandez-Miranda; Carl Snyderman; Paul Gardner (Pittsburgh, PA)

Introduction: CSF leaks remain a complication after endoscopic endonasal surgery. In this study, subjects were randomized to receive an immediate postoperative lumbar drain or not with comparison of postoperative leak rates.

Methods: The study randomized patients to lumbar drainage or no drain following reconstruction. The inclusion criteria included: 1) extensive arachnoid dissection, 2) dissection into a ventricle or cistern, or 3) dural defect greater than 1cm². Demographic data, tumor location, defect size, and leak rates were collected. The study was approved by the Institutional Review Board. (PRO010030258)

Results: The trial was stopped early (170 patients) due to a significant difference in CSF leak rate between the experimental (drain) and control (no drain) groups. No significant differences were found in the demographic measures between the two groups with an average age of 51.2 years (19–86) and BMI of 31.1. The most significant variable for postoperative leak was not having a drain ($p < 0.011$). A difference in leak rate was found based upon the tumor

location (anterior, posterior, suprasellar) ($p < 0.021$). However, when a drain was employed, tumor location was not a significant factor in post-op leak ($p < 0.507$). Defect size was noted to be larger in the group with leaks compared to the control group (6.86 cm² v. 2.78 cm², $p < 0.076$). Thirty-six patients had anterior pathology (olfactory groove or planum). The leak rate was 10% with and 35% without a drain ($p < 0.11$). Fifty patients had posterior pathology (clival). The leak rate was 13% with and 30% without a drain. ($p < 0.12$). Finally, 85 patients had suprasellar lesions. The leak rate was 4.7% with and 9.5% without a drain ($p < 0.43$).

Conclusions: For patients undergoing endoscopic endonasal skull base surgery, lumbar drain placement lowers the rate of postoperative CSF leak. The impact seems to be greatest in patients with large anterior or posterior cranial base defects.

728. Increased Survival when Combining BRAF Inhibitors and Stereotactic Radiosurgery in Patients with Melanoma Brain Metastases

Amparo Myrelle Wolf; Sayyad Zia, MD; Rashik Verma; Anna Pavlick, MD; Melissa Wilson, MD, PhD; Joshua Silverman, MD, PhD; Douglas Kondziolka, MD (London, Canada)

Introduction: The purpose of the study was to evaluate the impact of BRAF inhibitors on survival outcomes in patients receiving stereotactic radiosurgery (SRS) for melanoma brain metastases.

Methods: We prospectively collected treatment parameters and outcomes for 80 patients with melanoma brain metastases who underwent SRS. Thirty-five patients harbored the BRAF mutation (BRAF-M) and 45 patients did not (BRAF-WT). Univariate and multivariate analyses were performed to identify predictors of overall survival.

Results: The median overall survival from first SRS procedure was 6.7 months, 11.2 months if treated with a BRAF inhibitor and 4.5 months for BRAF-WT. Actuarial survival rates for BRAF-M patients on an inhibitor were 54% at 6 months and 41% at 12 months after radiosurgery. In contrast, BRAF-WT had overall survival rates of 28% at 6 months and 19% at 12 months. Overall survival was extended for patients on a BRAF inhibitor at or after the first SRS. The median time to intracranial progression was 3.9 months on a BRAF inhibitor and 1.7 months without. The local control rate for all treated tumors was 92.5%, with no difference based on BRAF status. Patients with higher KPS, fewer treated metastases, controlled systemic disease, RPA Class I and BRAF-M patients had extended overall survival.

Conclusions: Patients with BRAF-M treated with both SRS and BRAF inhibitors, at or after SRS, have increased overall survival. As patients live longer as a result of more effective systemic and local therapies, close surveillance and early management of intracranial disease with SRS will become increasingly important.

729. Safety and Activity of Nivolumab ± Ipilimumab in Recurrent Glioblastoma: Updated Results From CHECKMATE-143

John H. Sampson, MD, PhD, FAANS; Antonio Omuro; Gordana Vlahovic; Solmaz Sahebjam; Joachim Baehring; David Hafler; Alfredo Voloschin; Robert Latek; Timothy Cloughesy; Michael Lim; David Reardon (Durham, NC)

Introduction: Following progression after first-line therapies, patients with glioblastoma (GBM) have a poor prognosis. Immune checkpoint inhibitors have shown antitumor activity in patients with several types of solid tumors and also in preclinical glioma models.

The phase 1 portion of CHECKMATE-143 was designed to evaluate the safety and tolerability of nivolumab, a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 immune checkpoint pathway, as monotherapy and in combination with ipilimumab, a monoclonal antibody that inhibits cytotoxic T-lymphocyte antigen-4, in patients with a first recurrence of GBM. All patients in Cohort 1 had prior surgical resection, radiation, and temozolomide but were bevacizumab-naïve. Median age was 57 years (range: 37–73), and Karnofsky performance status was ≥ 70 . Preliminary results from the study, presented previously, showed nivolumab monotherapy 3 mg/kg was well tolerated in patients with recurrent GBM, with no reported treatment-related grade 3–4 adverse events (AEs). Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg was associated with a higher incidence of treatment-related grade 3 (n=7/10) and 4 AEs (n=2/10). Histopathology and neuroimaging detected antitumor activity within the tumor site, and preliminary overall survival (OS) at 9 months was 6/10 for both the monotherapy and combination arms.

Methods: Patients (n=20) were randomized 1:1 to receive nivolumab 3 mg/kg every 2 weeks (Q2W) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks followed by nivolumab 3 mg/kg Q2W. The primary endpoint was safety/tolerability.

Results: This report will provide updated follow-up data including safety and OS at 12 months.

730. Laser-Induced Thermal Therapy in Treatment of Recurrent Intracranial Metastatic Disease post-Stereotactic Radiosurgery

Daria Krivosheya, MD; Ganesh Rao, MD; Sujit Prabhu, MD (London, Canada)

Introduction: Effective control of intracranial metastases improves patient survival and quality of life. Laser-induced thermal therapy (LITT) is a novel technique for the treatment of recurrent intracranial metastases or radiation necrosis. At present, little evidence exists demonstrating the effectiveness of this technique for treatment of intracranial metastases.

Methods: We retrospectively reviewed patients who underwent LITT treatment for recurrent brain metastases post-stereotactic radiosurgery (SRS). We categorized treatment response by measuring the volume of each lesion before the treatment and at 1, 3, and 6 months.

Results: We identified 27 patients with 38 intracranial lesions who met study criteria. The median lesion size treated was 4.3 cc (range: 1.1–19.9 cc). Treated lesions included melanoma (N=12, 32%), breast (N=10, 26%), lung (N=9, 24%), and other (N=7, 18%) metastases. There were no perioperative complications, and 85% of patients were discharged within two days after surgery. At one-month follow-up, all lesions increased or remained unchanged in size. Whereas, at 6 months, 30 (79%) lesions remained stable or decreased in size. Of the eight (21%) lesions that failed treatment, five (63%) were melanomas. Lesions that failed treatment had a median volume of 8.3 cc (range: 1.2–12.4 cc), significantly larger than lesions that responded to treatment (median of 3.6 cc, range: 1.1–11.0 cc, p=0.03).

Conclusion: LITT represents an effective treatment modality for recurrent metastatic brain lesions that have progressed post-SRS. Patients tolerated the procedure well, and the treatment response depends on tumor histology and pre-treatment lesion size.

731. Prospective Evaluation of Molecular Prognostication Indices for Clival Chordomas, and Their Natural History in Recurrent Tumors

Georgios Zenonos, MD; Kenan Alkhalili, MD; Nathan Zwagerman, MD; David Panczykowski, MD; Yue-Fang Chang, PhD; Mary Koutourousiou, MD; Juan Fernandez-Miranda, MD; Eric Wang, MD; Carl Snyderman, MD; Paul Gardner, MD (Pittsburgh, PA)

Background: Molecular prognostication for clival chordomas remains rudimentary, limiting our ability to guide management.

Methods: We prospectively evaluated 92 clival chordomas with Fluorescent In Situ Hybridization for 1p36 and 9p21(p16) deletions, as well cellular proliferation with Ki-67 immunohistochemistry. Radiographic Progression Free Survival after Surgery (RPFSS), and Radiation (RPFSR) were calculated using Kaplan-Meier curves, and the Cox Proportional Hazard Model was used to calculate Hazard Ratios (HR) for each percentile increase in the molecular indices. Twenty-eight patients had multiple resections (2–5) because of recurrences, and the evolution their tumors' molecular profile was followed over time in correlation with other clinical variables.

Results: After a median follow-up of 45 months, we found that each percentile increase in tumor cells with homozygous 9p21(p16) deletion (HR=1.03; p=0.001), 1p36 deletion (HR=1.01; p=0.012), 1p hyperploidy (HR=1.02; p=0.018), and Ki-67 staining (HR=1.07; p=0.001) was predictive of a shorter RPFSS. Increasing percentages of cells with homozygous 9p21(p16) deletions (HR=1.03; p<0.001), and Ki67 (HR=1.05; p=0.001) were also predictive of a shorter RPFSR.

Over recurrences, 9p21/1p36 deletions and 1p hyperploidy were roughly equally divided between no change, increasing, and decreasing. The Ki-67 remained unchanged in 72% of tumors, but increasing age correlated with increases in Ki-67 over recurrences (r=0.479; p=0.038). Changes in one marker did not usually correlate with changes in others. Prior irradiation did not affect changes in 9p21 deletions, 1p36 deletions, or 1p hyperploidy, but inversely correlated with increases in Ki-67 over 5% (r ϕ =-0.392; p=0.029). Time between recurrences, gender, and chondroid chordomas did not correlate with changes.

Conclusion: Our study suggests a number of molecular indices as promising predictors of clival chordoma outcomes that could prove useful adjuncts to clinical decision-making. Repeated testing with each resection is warranted as these markers can change over time. During the intermediate term studied, radiation did not appear to have a detrimental effect on the tumor's biology based on our molecular profile, and may be beneficial in terms of cellular proliferation (Ki-67).

732. Navigated Transcranial Magnetic Stimulation Motor Cortex Mapping Improves Outcome in Glioblastoma Surgery: a controlled observational Study

Thomas Picht; Dietmar Frey; Stefan Thieme; Stefan Kliesch; Peter Vajkoczy (Berlin, Germany)

Introduction: The authors report on a controlled observational study designed to isolate the additive impact of preoperative navigated transcranial magnetic stimulation (nTMS) on surgical outcome in glioblastoma treatment in or near motor eloquent locations by comparison to a concurrent control group.

Methods: The trial data is derived from a large university hospital with a differential availability of its nTMS mapping service at its two campuses. 127 glioblastomas were operated with intraoperative mapping and monitoring of motor function (IOM) between 2012

and 2014. Of these, 93 underwent preoperative nTMS and nTMS-based DTI evaluation (nTMS & IOM group), 34 did receive standard DTI tracking but not TMS mapping solely for organizational reasons (IOM-only). Both cohorts did not differ in their biometric variables and were operated on by the same group of surgeons. Key end-points: a) amount of postoperative residual tumor volume b) functional outcome at three months c) progression free survival.

Results: The average residual tumor volume was significantly ($p < .05$) smaller in the nTMS & IOM cohort (5.9 ml; SD 8.4; range 0–25.2) than in the IOM-only arm (9.6 ml; SD 17.2; range 0–77.9). With respect to motor outcome 13% of patients in the nTMS & IOM and 15% in the IOM-only arm had a new or increased permanent motor deficit. An average increase of 3.4 month in progression-free survival was observed in the TMS & IOM group (8.4 month; SD 4.1; range 1–16) compared to the “non-TMS group” (11.8 month; SD 7.8; range 0–25).

Conclusion: This study demonstrates for the first time that the improved surgical outcomes after the implementation of nTMS are indeed caused by the additional functional data provided by presurgical nTMS and nTMS-based DTI. The data also confirm that less residual tumor volume after glioblastoma surgery leads to an increase in progression free survival.

733. Postoperative CSF Diversion Following Intraventricular Tumor Resection is Preventable

Christina Sarris, MD; Lynn Ashby, MD; Steven Coons, MD; Nader Sanai, MD (Phoenix, AZ)

Introduction: Following microsurgical resection of an intraventricular tumor, it remains unclear which features predispose adult patients to CSF diversion. Operative approach, tumor histology, extent of resection, and intraventricular blood have all been previously postulated as causative factors. Here, we review the largest single-center experience with intraventricular tumor surgery to identify the at-risk population for eventual CSF diversion.

Methods: One-hundred consecutive adult patients with intraventricular tumors were treated at the Barrow Neurological Institute from 2009 to 2015. All patients underwent open microsurgical resection. Patients with colloid cysts were excluded.

Results: The most common diagnosis was ependymoma (43%), followed by central neurocytoma (19%), and glioma (13%). Median tumor volume was 16.1 cm³ (range, 0.5–281.1 cm³) and median clinical follow-up was 1.6 years. Tumors were primarily located within the fourth ventricle (44%) or lateral ventricle (34%). 36% of patients had ventriculomegaly at presentation. Postoperatively, radiographic presence of intraventricular hemorrhage (IVH) was identified in 30 cases (30%), of which 14 (47%) demonstrated an IVH score of 2 or greater. In total, 26 patients (26%) required CSF diversion within a median 14-day interval following resection. In a multivariate Cox proportional hazards analysis, extent of postoperative IVH was the single most predictive risk-factor for CSF diversion ($p < 0.01$). Importantly, neither preoperative ventriculomegaly nor hydrocephalus were independent predictors.

Conclusion: Our findings suggest that postoperative hydrocephalus following intraventricular tumor resection is a preventable outcome and largely predicated on surgical technique. Although tumor volume and histology are also associated with CSF diversion, the single most predictive risk-factor was postoperative IVH. Interestingly, our data corroborate the importance of operative strategy and execution, as avoidance of trans-cortical corridors and subtotal resection were also significant predictors of CSF diversion rates.

734. Morbidity and Mortality of Meningioma Resection Increases in Octogenarians

Integra Foundation Award

Jeremy Steinberger, MD; Nathan Lee, BA; Parth Kothari, BA; Ahmed Awad, MD; Christopher Sarkiss, MD; Eric Oermann, MD; John Caridi, MD; Raj Shrivastava, MD (New York, NY)

Introduction: Large scale studies examining the effect of age on outcomes after meningioma surgery have not been performed to date. This study utilizes a large national database to assess the impact of age in adults undergoing surgery for meningioma.

Methods: Patients were identified by CPT code in the NSQIP database. Univariate analysis was performed to compare demographics, comorbidities, and postoperative complications in patients of different ages. Multivariate step-wise logistic regression was performed on each complication that demonstrated significant association with age in the univariate comparison.

Results: 1,568 patients were identified in the database. On univariate analysis, patients under 50 had overall complication rates of 17.9%, while patients 71–80 had rates of 29.6% and patients above 80 had rates of 31.2% ($p < 0.0001$). Specifically, patients in the 71–80 group and <80 group had higher rates of pulmonary complications, deep venous thromboses/pulmonary embolisms, and urinary tract infections. Patients under 50 had a length of stay greater than 5 days 32.3% of the time, while patients 71–80 and <80 had rates were 49.2% and 64.5%, respectively ($p < 0.0001$). Age had a significant impact on mortality. Patients under 50 had a 30-day mortality rate of 0.7%, while patients 71–80 had mortality rates of 2.5% and patients <80 had mortality rates of 8.6% ($p < 0.0001$). On multivariate analysis, patients greater than 80 were at higher risk of overall complications (Adjusted OR 2.37, 95% CI 1.30–4.36, $p = 0.015$) and prolonged length of stay (Adjusted OR 3.154, 95% CI 1.78–5.58, $p = 0.0002$). Death within 30 days was greater than 15 times higher in patients <80 than the younger groups (Adjusted OR 15.7, 95% CI 3.03–81.0, $p < 0.0001$).

Conclusion: In evaluating the effect of age in 1,568 patients undergoing meningioma surgery, 80 years old seems to be the statistical cut off for significantly increased morbidity and mortality.

735. Subarachnoid Hemorrhage Acutely Induces Spreading Depolarizations and Cortical Infarction

DePuy Synthes Cerebrovascular Section Resident/Fellow Award

Bryan Krueger, MD; Jonathan York, MD; Jason Hinzman, PhD; Jens Dreier, MD; Mario Zuccarello, MD; Jed Hartings, PhD (Cincinnati, OH)

Introduction: Spreading depolarizations (SDs) are associated with delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage (SAH) and may also contribute to early brain injury (EBI). Here we investigated the occurrence of SD and infarction following experimental induction of cortical SAH in the swine brain.

Methods: Twenty-one swine were anesthetized, mechanically ventilated and monitored. Following craniotomy over right frontal cortex, fresh arterial blood (2 cc) was injected through a 25-gauge needle into subarachnoid space ($n = 17$). In other animals ($n = 4$), blood was clotted ex vivo and injected (1 cc) into sulcus. A subdural electrode strip (5-cm length) was placed spanning the injection site. At 6 hr post-SAH after sacrifice, 3T MRI scans were obtained and brains were sliced and stained with TTC. Quantitative PCR and Western blots were performed on tissue remote from the injection site.

Results: Spontaneous SD occurred in 13/17 (76%) animals with successful subarachnoid location of fresh blood injection: 7 (41%) had clusters (<12 SD), 6 (35%) had sporadic SD (=6), and 4 (24%) had no SD. Post-mortem studies showed that ischemic cortical lesions were present adjacent to clots in 85% (6/7) of animals with SD clusters, but only 20% (2/10) of animals with sporadic or no SD (Fisher's exact, $p < 0.02$). Subarachnoid injection of clotted blood resulted in SD clusters and adjacent cortical infarcts in 3 animals, but no SD and no infarct in a fourth. In cortex remote from the injection site, cyclooxygenase-2 mRNA and protein were significantly upregulated 5-fold (< 0.001) in hemispheres with SD clusters.

Conclusion: Accumulation of subarachnoid blood is sufficient to acutely trigger repetitive SDs, which are both a mechanism and marker for cortical infarction. This may explain the early peak of SD activity after clinical SAH (<24 hr) and suggests therapeutic treatment of SD may mitigate EBI.

736. Intraventricular Transplantation of Autologous Bone Marrow Mesenchymal Stem Cell in Hemorrhagic Stroke

AANS International Travel Scholarship

Asra Al Fauzi, MD, IFAANS; Nur Suroto (Surabaya, Indonesia)

Introduction: Stroke is one of the most devastating diseases and a leading cause of death and disability in the world with further impact to emotional and economical problems. This research mainly to investigate the role of intraventricular transplantation using bone marrow mesenchymal stem cell in stroke patients. .

Methods: This study was a one group (eight patient) pre and post test design. Subjects were selected from supratentorial hemorrhagic stroke patients after six months treatment with stable neurological deficits with NIHSS of 5–25. Clinical outcomes were measured using NIHSS scale six months after transplantation. Bone marrow was aspirated taken from the same patient under aseptic conditions and expansion of MSC took 3–4 weeks. All patients were administered a mean of 20×10^6 cells intraventricularly.

Results: The result showed improvement of NIHSS score in five patients after treatment and the rest were in the same condition. No important adverse events derived from transplant or surgery observed during 6 months follow up.

Conclusion: Our study demonstrate that bone marrow mesenchymal stem cell can be transplanted intraventricularly with excellent tolerance and without complications. Stem cell transplantation aiming to restore function in stroke is safe and feasible. Further randomized controlled trials are needed to evaluate its efficacy.

737. Evolution of Treatment and a Detailed Analysis of Obliteration, Recurrence, and Clinical Outcomes in an Endovascular Library of 260 Dural Arteriovenous Fistulas

Bradley Gross, MD; Felipe Albuquerque, MD; Karam Moon, MD; Cameron McDougall, MD (Phoenix, AZ)

Introduction: The intriguing anatomy of cerebral dural arteriovenous fistulas (dAVFs) lends itself to treatment creativity that has catalyzed the evolution of their endovascular management. Despite the preponderance of technical reports and small series describing their treatment, only few reports exist for a substantial series of patients.

Methods: We reviewed our endovascular database from 1995–October 2015 for patients harboring cranial dAVFs treated initially with endovascularly. We extracted background, angio-

graphic, detailed treatment and follow-up data, evaluating obliteration rates, complication rates, recurrence rates and symptomatic resolution rates.

Results: Our analysis included 251 patients with 260 distinct dAVFs. Since the introduction of Onyx, the initial occlusion rate increased from 60% to 76% ($p = 0.01$). In addition, a significantly greater number of dAVFs were occluded via transarterial only approaches (43% vs 23%, $p = 0.002$) and even via a single arterial pedicle (29% vs 11%, $p = 0.002$). Among patients with dAVFs without cortical venous drainage (CVD) with pulsatile tinnitus, resolution after treatment was seen in 59% of cases, improvement in 20% and persistence in 21% over a mean follow-up period of 3 years. Among patients with dAVFs without CVD with ocular symptoms, resolution after treatment was seen in 48% of cases, improvement in 30% and persistence/worsening in 22% over a mean follow-up period of 2 years. The overall complication rate was 8% with permanent complications occurring in 3% of cases. Of 110 patients undergoing angiographic follow-up of initially angiographically-occluded dAVFs, 3 had new apparent radiographic residual/recurrence (3%).

Conclusion: Endovascular treatment of dAVFs is associated with high rates of obliteration and symptomatic improvement. The introduction of Onyx has significantly improved obliteration rates and broadened the spectrum of endovascular-accessible lesions.

738. Multistaged Volumetric Management of Large Arteriovenous Malformations

Hideyuki Kano, MD, PhD; Craig Lehecky, MD, PhD; John Flickinger, MD; Kyung-Jae Park, MD, PhD; Huai-che Yang, MD; Ajay Niranjana, MCh, MBA; Edward Monaco, MD, PhD; L. Dade Lunsford, MD (Pittsburgh, PA)

Introduction: To define the long-term outcomes and risks of staged stereotactic radiosurgery (SRS) for symptomatic large volume arteriovenous malformations (AVMs) unsuitable for surgery.

Methods: In 1992, we prospectively began to stage anatomic components in order to deliver higher single doses to AVMs > 10 cc in volume. Sixty patients with such AVMs underwent volume staged SRS. Twenty-four patients (40%) had a prior hemorrhage and 25 patients (42%) underwent prior embolization. The median interval between the first stage SRS and the second stage SRS was 4.5 months (3–14 months). The median target volume was 11.6 cc (4.0–26 cc) in the first stage SRS and 10.1 cc (2.8–33.7 cc) in the second stage SRS. The median margin dose was 16 Gy (13–18 Gy) for both SRS stages.

Results: After 2 to 4 SRS procedures AVM total obliteration was confirmed in 22 patients at a median follow-up of 76 months (0.4–215 months). The total obliteration rate after staged and repeat SRS were 21% at 5 years, 44% at 7 years, and 64% at 10 years. Twenty-four patients underwent additional SRS after initially staged SRS at a median interval of 61 months (33–113 months). Thirteen patients bled after staged SRS and six died. Four of 24 patients who underwent repeat SRS bled after repeat SRS and died. The cumulative rates of AVM hemorrhage after SRS were 5.0% at 1 year, 8.7% at 2 years, 12.6% at 5 years and 33.9% at 10 years. Symptomatic adverse radiation effects (ARE) were detected in 13%. No patient died due to ARE.

Conclusion: Prospective volume staged SRS for large AVMs has potential benefit but often requires 3–4 procedures spread over time. In the future prospective volume staged SRS followed by embolization (to reduce flow, obliterate fistulas, and occlude associated aneurysms) may further reduce the risk of hemorrhage.

739. The long-term outcome of 331 patients with moyamoya disease in a single center of China

Zhao Jizong; Xingju Liu, MD (Beijing, China)

Introduction: To describe the long-term outcome of 331 patients with moyamoya disease in a single center.

Methods: 331 patients with MMD in our hospital were retrospectively reviewed. All the patients had at least 1 year follow-up. The following events were included: transient ischemic attack, new infarction, and hemorrhage. Kaplan-Meier stroke risk was calculated.

Results: Of the 331 patients, the initial symptom of presentation was ischemia in 227, hemorrhage in 104. Sixty patients who received conservative management were hemorrhagic MMD. The remaining 271 patients underwent neurosurgical revascularization procedures, including 94 indirect bypass and 177 STA-MCA bypass. Rebleeding and mortality rates in hemorrhagic MMD (n=104) were higher than the rate in ischemic MMD (n=227) (26.9% versus 2.2%, $P < 0.001$; 4.8% versus 0.4% $P < 0.05$). Twenty-five of 60 (41.6%) conservatively treated patients and eight of 271 (2.9%) surgically treated patients experienced rebleeding events, significant different in the Kaplan-Meier curve of rebleeding analysis ($P < 0.01$). The improvement of perfusion was found in 164 of 224 (73.2%) surgically patients at 1 month after discharge. Among the 104 hemorrhagic patients, rebleeding attacks were observed in 25 patients in the nonsurgical group (n=60) and 3 patients in the surgical group (41.6% versus 6.8% OR 9.7; 95% CI 2.7–35.0, $P < 0.01$).

Conclusion: Hemorrhagic MMD had a much higher rate of rebleeding and poorer prognosis than ischemic type. Surgical revascularizations can improve cerebral perfusion and have positive impact to prevent rebleeding in hemorrhagic MMD.

740. Aneurysms with Persistent Filling after Failed Treatment with the Pipeline Embolization Device

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Introduction: The Pipeline Embolization Device (PED) has become a valuable option in the treatment of cerebral aneurysms. Although failures with PED treatment have been reported, the characteristics and course of these aneurysms remains a topic of uncertainty.

Methods: Electronic medical records and imaging studies were reviewed for all patients treated with the PED between June 2010 and December 2014 to identify patient and aneurysm characteristics of those with residual aneurysm filling after PED treatment.

Results: 50 aneurysms with residual filling were identified. This represents 14.3% of all cases treated. The mean patient age in this population was 58.7 years. The mean aneurysm size was 10 mm±7mm. 9 aneurysms were fusiform in shape (18%). Of the aneurysms with residual filling, there were 19 carotid ophthalmic (CO) aneurysms (16.5% of all CO aneurysms treated), 10 other paraclinoid aneurysms (13.9% of all paraclinoid aneurysms), 8 posterior communicating artery (PCOM) aneurysms (20% of all PCOM aneurysms), 6 cavernous internal carotid artery (ICA) aneurysms (10.9% of all cavernous ICA aneurysms), 4 vertebro-basilar (VB) aneurysms (15.4% of all VB aneurysms) and 3 middle cerebral artery (MCA) aneurysms (25% of all MCA aneurysms). 11 patients had placement of more than one PED (22%) with a mean number of devices of 1.28/case. 10 aneurysms were previously treated (20%),

6 of them with a prior stent placement (12%). 16 patients underwent re-treatment (32%) while 34 did not undergo re-treatment (68%), had continued angiograms, or non-invasive imaging.

Conclusion: While PEDs can allow for treatment of large broad-necked aneurysms with high efficacy, treatment failures do occur (14.3%). Aneurysm size, shape and previous treatment may influence treatment outcomes.

741. Long-term persistent aneurysm patency after treatment with the pipeline embolization device

Visish Srinivasan, MD; Edward Duckworth, MD; Nnenna Mbabuike, MD; Maxim Mokin, MD, PhD; Bartley Mitchell, MD, PhD; Vin Ban, BS; Ajit Puri, MD; Babu Welch, MD; Rabih Tawk, MD; Mandy Binning, MD; Peter Kan, MD (Houston, TX)

Introduction: The Pipeline Embolization Device (PED) was approved by the U.S. Food and Drug Administration for the treatment of intracranial aneurysms from the petrous to the superior hypophyseal segment of the internal carotid artery. However, since its approval, its use for treatment of intracranial aneurysms in other locations and non-side wall aneurysms has grown tremendously.

Methods: A multi-institutional registry was created with patients with aneurysms meeting the following criteria: 1) treatment with PED, with or without adjunctive or prior treatment; 2) minimum of 12 months of angiographic and clinical followup, and 3) aneurysms incorporating an end vessel with no distal collaterals.

Results: A cohort of 15 patients with 16 cerebral aneurysms was identified. The cohort included 8 posterior communicating artery aneurysms, 5 ophthalmic aneurysms, 1 superior cerebellar artery aneurysm, 1 anterior inferior cerebellar artery aneurysm, and 2 middle cerebral artery aneurysms. All 16 aneurysms remained patent with minimal change at last angiographic followup and all end vessels remain patent with no stenosis.

Conclusion: Based on our observation, we do not recommend the use of flow diverter for treatment of this subset of cerebral aneurysms. It appears not only to be ineffective for meaningful aneurysm occlusion, but it also limits or precludes future surgical and intrasaccular treatment options.

742. Patency of the Posterior Communicating Artery Following Treatment with the Pipeline Embolization Device

Pascal Marcel Jabbour, MD, FAANS; Badih Daou, MD; Edison Valle, MD; Nohra Chalouhi, MD; Robert Starke, MD; Stavropoula Tjoumakaris, MD; David Hasan, MD; Robert Rosenwasser, MD; Pascal Jabbour, MD (Philadelphia, PA)

Introduction: The Pipeline Embolization Device (PED) has become an effective treatment strategy for some cerebral aneurysms. Concerns regarding the patency of branch arteries have been raised. Our objective is to assess the patency of the posterior communicating artery (PCOM) following treatment of PCOM aneurysms using the PED.

Methods: All patients with PCOM aneurysms treated with the PED who had angiographic follow-up were retrospectively identified. The patency of the PCOM at follow-up was evaluated by two authors not involved in the intervention. Univariate and multivariate analyses were performed to identify factors associated with (1) PCOM patency versus no or diminished flow and (2) PCOM patency and diminished flow versus PCOM occlusion.

Results: 30 patients were included with an angiographic follow-up of 6 months. Aneurysm obliteration rate was achieved in 26 patients (86.7%). The PCOM was patent in 7 patients (23.3%),

had diminished flow in 7 patients (23.3%) and was occluded in 16 patients (53.3%). In univariate analysis of outcome (1), there was a trend for aneurysms with incomplete occlusion, aneurysms not previously treated, presence of a fetal PCOM and artery coming from the aneurysm for higher odds of PCOM remaining patent. In univariate and multivariate analysis of factors associated with outcome (2), fetal PCOM and presence of artery coming from the aneurysm were associated with the PCOM artery remaining open $\pm$ diminished flow. No patients had symptoms related to PCOM occlusion.

Conclusion: Occlusion and diminished flow through the PCOM artery is common following PED treatment. However, it is clinically insignificant in most cases.

743. Intracranial Hemorrhage After Glue Embolization of Cerebral Arteriovenous Malformations: A Systematic Review and Meta-Analysis

Hormuzdiyar Dasenbrock, MD; Yusuf Subat, BA; Bradley Gross, MD; Rose Du, MD, PhD; M. Aziz-Sultan, MD (Boston, MA)

Introduction: Although peri-procedural intracranial hemorrhage is a major complication of embolization of cerebral arteriovenous malformations (AVMs), this is the first meta-analysis to analyze the rate and predictors of this complication.

Methods: PubMed, Embase, and Web of Science were queried for studies published between 1990-2015 reporting the peri-procedural hemorrhage of cerebral AVMs treated with glue embolization. Random effects meta-analysis evaluated the pooled hemorrhage rate of flow-related hemorrhage, those attributed to alterations in hemodynamics, and total hemorrhage. Univariable meta-regression evaluated the association of hemorrhage with patient age, Spetzler-Martin grade, year of study, embolizate, and intent of treatment.

Results: A total of 75 studies with 6,792 patients were included. The total hemorrhage rate was 5.3% (95% confidence interval (CI): 4.3–6.6%); the mortality and morbidity rates associated with hemorrhage were 19.6% (95% CI: 13.6–25.6%) and 53.9% (95% CI: 40.1–66.9%), respectively. Additionally, the rate of flow-related hemorrhage was 4.1% (95% CI: 3.3–4.8%). Studies with pre-surgical intent reported a 4.7% (95% CI: 2.2–7.1%) rate of total hemorrhage, compared to 8.2% (95% CI: 3.3–13.1%) in studies with curative intent. Meta-regression found a trend towards a higher rate of total hemorrhage in AVMs treated with curative intent ($p=0.08$), but no associations were seen with patient age, Spetzler-Martin Grade, or embolizate; meta-regression did not reveal any significant associations with flow-related hemorrhage.

Conclusion: In this meta-analysis, intracranial hemorrhage occurred in 5.3% of embolizations and was associated with significant mortality and morbidity. No significant predictors of hemorrhage were discerned in meta-regression, suggesting that all patients are at risk of this major complication.

744. Changes in Pulsatility and Resistance Indices of Cerebral Arteriovenous Malformation Feeder Arteries after Embolization and Surgery

Louise Eisenhardt Traveling Scholarship

Sophia F. Shakur, MD; Sepideh Amin-Hanjani, MD; Mohamed Abouelleil, BS; Victor Aletich, MD; Fady Charbel, MD; Ali Alaraj, MD (Chicago, IL)

Introduction: Embolization reduces flow in cerebral arteriovenous malformations (AVMs) before surgical resection, but changes in pulsatility and resistance indices (PI, RI) are unknown. Here, we

measure PI, RI in AVM arterial feeders pre- and post-embolization/surgery.

Methods: Records of patients who underwent AVM embolization and surgical resection at our institution between 2007-2014 and had PI, RI, and flows obtained using quantitative magnetic resonance angiography were retrospectively reviewed. $PI = [(systolic - diastolic \text{ flow velocity}) / \text{mean flow velocity}]$ and $RI = [(systolic - diastolic \text{ flow velocity}) / \text{systolic flow velocity}]$. Hemodynamic parameters were compared between the feeder and contralateral artery pre- and post-embolization/surgery.

Results: 32 patients with 48 feeder arteries underwent embolization (mean 1.3 sessions). Another 32 patients with 49 feeder arteries had surgery with/without preoperative embolization. Before any treatment, flow volume rate and mean, systolic, diastolic flow velocities were significantly higher in feeders versus contralateral counterparts ($P < 0.001$ for each parameter), and PI, RI were significantly lower in feeder compared to contralateral vessels ($P = 0.003, 0.002$). After embolization, mean, systolic, and diastolic flow velocities increased significantly ($P = 0.02, 0.01, 0.01$, respectively), but PI, RI did not change significantly ($P = 0.53, 0.31$). However, after surgery mean, systolic, and diastolic flow velocities within feeders decreased significantly ($P = 0.001, 0.002, 0.001$, respectively) and PI, RI normalized to match the indices of their contralateral counterparts ($P = 0.46, 0.46$).

Conclusion: Following partial AVM embolization, PI, RI are unchanged and flow velocities in feeder arteries increase significantly likely due to redistribution of flow through residual nidus. Complete surgical resection results in normalization of PI, RI and a concomitant decrease in flow velocities.

800. Antagonism of Wnk/Hsn2 kinase ameliorates neuropathic pain by reducing maladaptive KCC2 inhibitory phosphorylation after nerve injury

William H. Sweet Young Investigator Award

Kristopher Kahle; Jean-François Schmouh; Valérie Lavastre; Alban Latremoliere; Jinwei Zhang; Nick Andrews; Patrick A. Dion; JingJing Duan; Clifford J. Woolf; Perrine Inquimbert; Guy A. Rouleau (New Haven, CT)

Introduction: Neuropathic pain is a major clinical problem inadequately treated with available pharmacology. The study of rare Mendelian diseases can identify key regulatory nodes in complex physiological pathways, revealing unexpected drug targets relevant for more common diseases. WNK1/HSN2 is a kinase mutated in hereditary sensory and autonomic neuropathy type II (HSANII), featuring congenital insensitivity to pain, but the function of this kinase and the mechanism by which it causes disease is unknown.

Methods: Using cre recombinase technology, we have generated and characterized the first knockout mouse targeting Wnk1/Hsn2 (Wnk1Hsn2/Hsn2) using a multidisciplinary approach including mouse genetics, electrophysiology, biochemistry. We also explored the role of this signaling pathway in models of neuropathic pain associated with inflammation and peripheral nerve injury.

Results: WNK1/HSN2 kinase contributes to a maladaptive decrease in KCC2 cotransporter activity and loss of GABA inhibition in the spared nerve injury (SNI) model of neuropathic pain by increasing KCC2 inhibitory phosphorylation at Thr906/Thr1007. Antagonizing WNK1/HSN2 signaling by genetic knockout or pharmacological inhibition reduces SNI-induced cold allodynia and mechanical hyperalgesia by converting KCC2-dependent depolarizing GABA-evoked responses to hyperpolarizing, inhibitory responses. Compared to humans with disease-causing mutations resulting in WNK1/HSN2 truncation with an intact kinase domain,

Wnk1Hsn2/Hsn2 mice with complete WNK1/HSN2 isoform depletion exhibit only a mild distal loss of thermal sensitivity without other apparent central or peripheral nervous system defects.

Conclusion: These data reveal novel mechanistic insight and a compelling target for neuropathic pain. The restricted expression profile, lack of other neurological phenotypes when deleted, and protective effect of Wnk1/Hsn2 inhibition in the development of neuropathic pain make WNK1/HSN2 a compelling and potentially druggable kinase target worthy of further exploration.

801. Cellular architecture of human IDH1-mutant gliomas revealed using single-cell RNA sequencing

Preuss Research Award

Andrew Venteicher, MD, PhD; Itay Tirosh, PhD; Christine Hebert, BS; Leah Escalante, BS; Brian Nahed, MD; William Curry, MD; Robert Martuza, MD; Daniel Cahill, MD, PhD; Aviv Regev, PhD; Mario Suva, MD, PhD (Boston, MA)

Introduction: Heterogeneity among tumor cells within human glioma underlie their ability resist chemotherapy and radiation, ultimately leading to tumor recurrence. Mounting evidence indicates that rarer subpopulations of tumor cells are endowed with stem-like properties, which are capable of resisting chemoradiation, proliferating, and causing more aggressive, recurrent tumors. Characterizing these rarer glioma stem-like populations has been difficult due to their elusive nature.

Methods: We have optimized a technique to isolate single tumor cells for RNA sequencing from primary human gliomas at time of resection in consented patients. We perform sensitive reverse transcriptase and amplification from each isolated cell, and to date we have profiled the transcriptome from over several thousand cells purified from IDH1-mutant gliomas. Using computational analysis, we searched for tumor subpopulations based on gene expression profile within IDH1-mutant gliomas.

Results: Comparing the gene expression profiles of tumor cells derived from IDH1-mutant gliomas demonstrates that a majority of tumor cells are differentiated along two specialized glial programs. Surprisingly, a third rarer subpopulation of tumor cells was also detected that express a distinct stem-like program. Consistently, cellular proliferation was restricted to this stem-like subpopulation, consistent with the existence of a stem-like compartment that is solely responsible for fueling growth of IDH1-mutant gliomas in humans. The expression signature shared among these glioma stem-like cells mirrors the signature from normal fetal neurodevelopment, suggesting that features of a neurodevelopmental program are co-opted to support the growth and maintenance of human gliomas.

Conclusion: Single cell transcriptome analysis in IDH1-mutant gliomas reveals three distinct subpopulations of tumor cells: two dominant populations of specialized glial-like cells and a third rarer stem/progenitor-like subpopulation capable of cellular proliferation. These results provide unprecedented insight into the cellular composition of IDH1-mutant gliomas with critical implications for disease management.

802. Spine Stereotactic Radiosurgery with Concurrent Tyrosine Kinase Inhibitors for Metastatic Renal Cell Carcinoma

Jacob A Miller; Ehsan Balagamwala, MD; Lilyana Angelov, MD; John Suh, MD; Brian Rini, MD; Jorge Garcia, MD; Manmeet Ahluwalia, MD; Samuel Chao, MD (Cleveland, OH)

Introduction: With the introduction of anti-angiogenic tyrosine kinase inhibitors (TKIs), systemic control of metastatic renal cell carcinoma (mRCC) has substantially improved. The second most common site of metastasis in mRCC is the spine. As a radioresistant histology, spine stereotactic radiosurgery (SRS) has emerged to control metastases. In laboratory models, strong evidence exists for a synergistic relationship between TKIs and SRS. However, controlled studies have yet to demonstrate a corresponding clinical benefit.

Methods: An institutional retrospectively-collected database was queried for patients undergoing spine SRS for mRCC. Patients were divided into one of four cohorts: A) SRS with concurrent first-line TKIs; B) chemotherapy-naïve patients; C) patients who had failed first-line chemotherapy undergoing SRS with concurrent TKIs; D) patients who had failed first-line chemotherapy undergoing SRS without concurrent TKIs. The primary outcome variable was radiographic control. Cox proportional hazards modeling was used to control for confounding differences among cohorts.

Results: 151 consecutive treatments (100 patients) for mRCC were identified. At 12 months, actuarial radiographic failure was lowest (8%) among patients treated with concurrent first-line TKIs, compared with 25–31% in cohorts B-D. No grade ≥ 3 toxicities occurred among patients receiving concurrent therapy. After adjusting for confounding, patients treated with concurrent first-line TKIs failed less rapidly (HR 0.16, $p < 0.01$) than patients in other cohorts.

Conclusion: In the present investigation, we observed a significant and independent radiographic control benefit with the addition of first-line TKIs to SRS. These results have significant implications in the oligometastatic setting, and support laboratory evidence of an interaction between SRS and TKIs.

803. Characterising the temporal evolution of ICP and cerebrovascular reactivity after severe traumatic brain injury

Best International Abstract Award

Hadie Adams; Joseph Donnelly, MD; Angelos Koliass, MD; Peter Smielewski; Virginia Newcombe; Peter Hutchinson; Marek Czosnyka (Cambridge, United Kingdom)

Introduction: Large cohort traumatic brain injury (TBI) studies have shown that intracranial pressure (ICP) and the pressure reactivity index (PRx) are independently associated with patient outcome. However, how these parameters evolve over the course of the intensive care stay and whether this evolution has any prognostic importance is not well studied.

Methods: ICP and PRx were monitored in 573 severe TBI patients in a regional neuro-critical care unit. Data were calculated in 12h epochs for the first 168h (7 days) referenced from the time of ictus. Data were stratified by the presence of diffuse TBI (dTBI) or space occupying lesions (SOL) as well as fatal or non-fatal outcome at 6 months post-injury. Mixed linear modelling was used to assess change of ICP and PRx over time to detect differences in mortality.

Results: Mean ICP peaked between 24 and 36h after ictus, but only in those who died. The difference in mean ICP between those with fatal and non-fatal outcome was only significant for the first 120h after ictus (all $p < 0.05$). For PRx, those with fatal outcome also had higher (more impaired) PRx throughout the whole first 168h

after ictus (all $p < 0.05$). The separation of ICP & PRx was greatest in the first 72h after ictus. Also, mean differences of ICP and PRx between the outcomes groups were more pronounced in those with dTBI than those with SOL.

Conclusion: In this cohort of 573 TBI patients with high resolution physiologic data, both ICP and PRx display a distinctive temporal evolution. Importantly, early ICP and PRx allow for the clearest prognostic delineation. The optimal thresholds, prognostic significance and clinical correlations of ICP and PRx are likely to be time dependent. Prognostic and therapeutic applications of ICP and PRx should therefore account for their temporal evolution.

804. 30-Day Re-admission After Spine Surgery: An Analysis of 1400 Consecutive Spine Surgery Patients

Owoicho Adogwa, MD; Aladine Elsamadicy, BE; Jing Han, BA; Joseph Cheng, MD, MS; Carlos Bagley, MD (Durham, NC)

Introduction: Early readmissions after spine surgery is being used as a proxy for quality of care. One-fifth of patients are rehospitalized within 30 days after spine surgery, and more than one-third within 90 days. Nearly 60% of these readmissions are unplanned, which translates into billions of dollars in hospital payments. However, there is a paucity of data investigating the cause of early readmission after elective spine surgery.

Methods: 1400 patients undergoing elective spine surgery at Duke University Hospital between 2008 and 2010 were included in the study. We identified all unplanned readmissions within 30 days of discharge. Unplanned readmissions were defined to have occurred as a result of either a surgical or a nonsurgical complication. Patient's records were reviewed to determine the cause of readmission and the length of hospital stay.

Results: A total of 132 (9.42%) unplanned early readmissions were identified. The mean $\pm$ SD age was 58.58 ± 15.12 years, Table 1. Lumbar decompression and fusion was the most common procedure, Table 2. The most common causes for readmission were infection or a concern for infection (34.84%) and pain (19.70%), and 26.51% of readmissions required a return to the operating room. The mean $\pm$ SD number of days from discharge to readmission was 9.80 ± 7.87 days and the average length of hospital stay for the readmissions was 7.49 days. The majority of patients that were readmitted presented to the emergency department from home (57.98%) while 25.21% were readmitted from a skilled nursing facility, Table 3.

Conclusion: Our study suggests that infection and refractory pain in patients that underwent lumbar decompression with fusions were the most common primary reasons for unplanned readmission.

805. Thermal Flow Detection Improves Diagnostic Accuracy of Shunt Malfunction: Prospective, Multicenter, Operator-Blinded Study

David M. Frim, MD, PhD, FAANS, FACS; Joseph Madsen, MD; Tehnaz Boyle, MD, PhD; Mark Neuman, MD, MPH; Gregory Heuer, MD; Joseph Zorc, MD; Mandeep Tamber, MD, PhD; Robert Hickey, MD; Julie Leonard, MD, MPH; James Chamberlain, MD; Joseph Piatt, MD (Chicago, IL)

Introduction: We evaluated the diagnostic value of ShuntCheck® thermal flow detection in ventriculoperitoneal shunts to determine whether ShuntCheck plus neuroimaging improved diagnostic precision over imaging alone.

Methods: Thermal flow detection and neuroimaging were obtained in 263 symptomatic patients <29 years at ten centers. Clinicians, blinded to the results of the ShuntCheck, recorded

whether radiographic studies showed ventricular enlargement, and whether surgery was performed within one week. The positive and negative predictive values (PPV and NPV) of imaging-alone, and ShuntCheck-plus-imaging, were calculated. Before imaging, patients were classified by an Attending physician as Unlikely or Somewhat/Likely to require surgery.

Results: Imaging-alone had PPV of 71.0% (44/62 cases, 95% C.I. 58.7–80.8%). ShuntCheck, when concordant and positive (flow-not-confirmed, ventricular enlargement) showed PPV of 88.6% (39/44, 95% C.I. 76–95%). Of 91 patients with both studies negative (flow-confirmed, no ventricular enlargement), none had surgery (NPV 100%, 95% C.I. 95.9–100.0%). For imaging-alone, the NPV was 92.5% (186/201, 95% C.I. 88.1–95.4%). The improvement in PPV of 17.7% (95% C.I. 8.1–27.2%) and NPV of 7.46% (95% C.I. 3.83–11.1%) is significant. The 91 concordant negative patients had 25 admissions for observation, 5 lumbar punctures, 3 shunt taps, and 2 radionuclide flow studies—but no shunt revisions. Of the 56% of patients clinically pre-designated Unlikely to require surgery, 91% indeed did not. ShuntCheck (NPV 100%) was not inferior to neuroimaging (NPV 97.6%) in confirming this clinical judgment (risk difference 2.3%; 95% C.I., 0.997 to 1.052).

Conclusion: The combination of neuroimaging and ShuntCheck improves shunt malfunction diagnostic accuracy and may diminish the need for hospital admission or additional testing. ShuntCheck was not inferior to neuroimaging for ruling out shunt malfunction in children assessed as unlikely to require surgery and may obviate the need for neuroimaging among these patients. Support: NIH-NINDS R44NS067772.

806. Comparison of Effectiveness of Occipital Nerve Stimulation Frequency in Treating Allodynia in Rodent Migraine Model

Shannon Wang Clark, MD; Lalit Venkatesan, PhD; David Boorman, MS; Nathan Fried, PhD; Ashwini Sharan, MD; Melanie Elliott, PhD; Michael Oshinsky, PhD (Philadelphia, PA)

Introduction: A translational rat model of episodic migraine was used to compare the effectiveness of different tonic ONS frequencies in treating trigeminal allodynia.

Methods: Twelve Sprague-Dawley rats with spontaneous trigeminal allodynia were implanted with miniaturized paddle leads over the occipital nerves along with the pulse generator battery. ONS (2, 20, 40, 60, 100, 200, or 500Hz; 200 μ s, 80% motor threshold) was delivered for 5hours/day (STIM OFF otherwise) using a randomized block design. Periorbital thresholds were assessed using von Frey filaments (VFF) at baseline, and for 0.25, 0.5, 1, 2, 3, 4, & 5hours of stimulation. Rats were characterized as hypersensitive when VFF ≤ 4 g, or as non-sensitive (responders) when VFF ≥ 6 g. Generalized Estimating Equations were used to test for statistical significance.

Results: Overall, ONS significantly improved VFF thresholds compared to baseline ($p < 0.005$), and significant interaction effects ($p = 0.003$) were observed between STIM ON time and stimulation frequency. After 5 hours of stimulation, 200 Hz was significantly better in increasing VFF thresholds ($p < 0.001$) compared to all other followed by 100Hz. The 2 Hz stimulation frequency was significantly inferior ($p < 0.001$) than all other frequencies and was not therapeutic. A significantly greater proportion ($p = 0.007$) of rats (75%) responded to 500 Hz stimulation at the 1 hour assessment. After 5 hours, 85% of the rats responded to 100 and 200 Hz stimulation, compared to 75% responding to 40, 60 and 500 Hz stimulation ($p = 0.56$). Stimulation frequencies of 2Hz resulted in a significantly lower ($p = 0.002$) proportion of responders 8%, followed by 20Hz with 58% ($p = 0.31$).

Conclusion: This acute study identified 200 Hz as being more

effective in inducing a therapeutic outcome compared to standardly used stimulation frequencies (3-130Hz). Response to ONS seems to improve over several hours, and this delayed response should be taken into account while optimizing device programming in a clinical setting.

807. Rate of Peri-Operative Neurological Complications after Surgery for Cervical Spinal Cord Stimulation

Andrew K. Chan, MD; Ethan Winkler, MD, PhD; Line Jacques, MD (San Francisco, CA)

Introduction: Cervical spinal cord stimulation (cSCS) is used to treat pain of the cervical region and upper extremities. Case reports and small series have shown a relatively low risk of complication after cSCS, with only two reported cases of peri-operative spinal cord injury in the literature. Catastrophic cSCS-associated spinal cord injury remains a concern as a result of under-reporting. To aid in pre-operative counseling, it is necessary to establish a minimum rate of spinal cord injury and surgical complication following cSCS.

Methods: The NIS is a stratified sample of 20% of all patient discharges from non-federal hospitals in the United States. We identified discharges with a primary procedure code for spinal cord stimulation (ICD-9 03.93) associated with a primary diagnosis of cervical pathology from 2002–2011. We analyzed short-term safety outcomes including the presence of spinal cord injury and neurological, medical, and general peri-operative complications and compared outcomes using univariate analysis.

Results: Between 2002 and 2011, there were 2,053 discharges for cSCS. The spinal cord injury rate was 0.5%. The rate of any neurological, medical, and any general peri-operative complication was 1.1%, 1.4%, and 11.7%, respectively. There were no deaths.

Conclusion: In the largest series of cSCS, the risk of spinal cord injury was higher than previously reported (0.5%). Nonetheless, this procedure remains relatively safe, and physicians may utilize this data to support the safety of cSCS in an appropriately selected patient population. This may become a key treatment option in an increasingly opioid dependent, aging population.

808. Intravenous Acetaminophen for Pain Control following Supratentorial Craniotomy - A Randomized, Double-Blinded, Placebo-Controlled Trial

Walavan Sivakumar, MD; Paul House, MD; Michael Jensen, BS; Julie Martinez; Nancy Duncan; Craig Kilburg, MD; Safdar Ansari, MD; Robert Hoesch, MD, PhD; Jay Riva-Cambrin, MD (Salt Lake City, UT)

Introduction: Acute pain control following cranial surgery is challenging. Prior research has shown that post-craniotomy patients experience inadequate pain control. The use of oral medications can be delayed secondary to postoperative nausea and the use of narcotics can impair the evaluation of brain function. Few nonnarcotic intravenous (IV) analgesics exist. We present the final results of the first prospective study evaluating the use of IV acetaminophen in post-craniotomy patients.

Methods: We conducted a randomized, double-blinded, placebo-controlled investigation with 204 patients completing the trial. Adults undergoing elective, supratentorial craniotomies were randomized into two groups. The experimental group received 1000mg/100mL IV acetaminophen every 8 hours for 48 hours. The placebo group received 100mL 0.9% normal-saline. Both groups were also treated with a standardized pain control algorithm. The study was powered to detect a 30% difference in the primary out-

come measure; narcotic consumption (morphine equivalents) at 24 and 48-hours after surgery.

Results: No significant differences were found in narcotic consumption between groups at either time-point (morphine equivalents at 24/48 hours were $84.3 \pm 7.2/123.5 \pm 10.5$ versus $85.5 \pm 6.4/134.2 \pm 11.3$, respectively). No adverse effects were reported. Although a secondary measure, patients treated with IV acetaminophen reported predicted pain scores 0.71 and 0.96 points lower at 24 and 48 hours ($p=0.03/0.01$), respectively.

Conclusion: Patients who received postoperative IV acetaminophen after craniotomy did not have significantly decreased narcotic consumption but did experience better pain control after surgery. The drug was well tolerated and safe in this patient population.

809. Resistance to Cerebrospinal Fluid Outflow as Diagnostic Marker of Spontaneous Cerebrospinal Fluid Leakage

Jürgen Beck; Christian Fung, MD; Christian Ulrich, MD; Michael Fiechter, MD; Jens Fichtner, MD; Pasquale Mordasini, MD; Werner Z'Graggen, MD; Jan Gralla, MD; Andreas Raabe, MD (Bern, Switzerland)

Introduction: Spinal cerebrospinal fluid (CSF) leakage causes spontaneous intracranial hypotension (SIH). This study assessed CSF dynamics via lumbar infusion testing in patients with or without proven spinal CSF leak.

Methods: This analysis included all consecutive patients with SIH treated from January 2012 to February 2015. The gold standard for proven CSF leak was extrathecal contrast accumulation after intrathecal contrast application in spinal MRI, myelography or post-myelography-CT. Computerized lumbar infusion testing (constant rate 2 ml/min) was performed to analyze lumbar pressure at baseline (opening pressure) and at plateau, as well as pulse amplitude, CSF outflow resistance (RCSF), craniospinal elastance, and pressure volume index.

Results: Thirty-one patients completed clinical imaging and lumbar infusion testing, and were included in the final analysis. Comparison of the 14 patients with proven CSF leakage with the 17 patients without leakage showed statistically significantly lower lumbar opening (5.26 vs 11.77mmHg, $p<0.001$), plateau pressure (16.11 vs 32.06mmHg, $p<0.001$), and RCSF (1.97 vs 11.78 mmHg/ml/min, $p<0.001$), respectively. Sensitivity, specificity, and positive and negative predictive values for RCSF cutoff of ≤ 5 mmHg/ml/min were 0.86, 1.0, 1.0, and 0.89 (AUC of 0.96) respectively. Median pressure volume index was higher (26.43 vs. 20.93ml, $p=0.003$), and baseline (0.18 vs. 0.38mmHg, $p=0.017$) and plateau (1.03 vs. 2.80mmHg, $p<0.001$) pulse amplitudes were lower in patients with proven leakage.

Conclusion: Lumbar infusion testing captures a distinct pattern of CSF dynamics associated with spinal CSF leak. RCSF assessed by the computerized lumbar infusion test has higher diagnostic accuracy than lumbar opening pressure. We suggest inclusion of RCSF in the diagnostic criteria for SIH.

810. Low Back Pain Relief with a New 32-Contact Surgical Lead Using a Neural Targeting Algorithm

Nitzan Mekel-Bobrov, PhD; Julie Pilitsis, MD, PhD; Giancarlo Barolat, MD; Joshua Rosenow, MD; James Brennan, MD; Alexander Bailey, MD; Jeffrey Epstein, MD; Blake Hammond, PA; Clark Metzger, MD; Dai Huynh, PhD; Kristen Lechleiter, MS (Valencia, CA)

Introduction: A new 32-contact surgical lead that couples multi-

ple independent current control (MICC) with an anatomically-based 3-dimensional targeting algorithm allows for customization of stimulus field shape and position via patient-specific programming. This advance may allow for sustained low back and leg pain relief with improved success and patient satisfaction.

Methods: We present results of an ongoing multi-center, consecutive, observational study of a new 32-contact surgical lead, using the Precision Spectra SCS System (Boston Scientific Corporation). We examine data from up to 100 subjects, including medical history, procedural information, pain reduction as measured by numeric rating scale (NRS) scores, disability, and quality of life out to 1 year post-implant.

Results: Analysis of 25 subjects at 6 months post-implant showed a mean reduction of 5.0 points from 7.7 (baseline) to 2.7 in overall pain (0–10 NRS). In severe pain subjects (NRS < 8), a mean reduction of 5.8 points from 8.7 (baseline) to 2.9 in overall pain was found. In subjects reporting low back pain only, a mean pain intensity reduction from 7.8 (baseline) to 1.6 was determined. Of these, 89% of subjects showed $\geq 50\%$ back pain reduction. Also, activities of daily living (ADLs) improved and prescribed pain medications decreased in a majority of subjects (83% and 67%, respectively).

Conclusion: Analysis of 25 subjects at 6 months post-implant: demonstrated the following: Significant reduction in overall and back pain - 89% of subjects showed $\geq 50\%$ back pain reduction - Improvement in activities of daily living and reduction in pain medications. Additional clinical and secondary outcomes data from up to 100 patients out to 1 year post-implant will be presented.

811. Cervical Spinal Cord Stimulation: Outcomes with Percutaneous and Paddle Leads

Stephane Owusu-Sarpong; Sameah Haider, BS; Maria Peris-Celda; Meghan Wilock; Julia Prusik, BS; Julie Pilitsis, MD, PhD (Albany, NY)

Background: Spinal cord stimulation (SCS) has been a valuable resource for treatment of chronic, nonmalignant pain that persists in the face of maximal medical management. A recent study demonstrated efficacy of cervical SCS in a multi center registry. In our single center study, we delve into patient specifics, explore outcomes with percutaneous versus paddle leads, and examine impact of patient symptomatology.

Objectives: To examine outcomes using paddle and percutaneous cervical spinal cord stimulators for treating post-laminectomy syndrome (PLS), complex regional pain syndrome (CRPS), and neuropathic pain.

Methods: We retrospectively evaluated our prospectively collected data on patients who underwent cervical SCS via Visual Analogue Scale (VAS), McGill Pain Questionnaire (MPQ), Oswestry Disability Index (ODI), and Beck Depression Inventory (BDI). Patients completed this battery pre-operatively, at 6 months and at one year. Data were analyzed via repeated measures ANOVA and Independent T-tests.

Results: In our 20 patients, the diagnosis was PLS (15%), CRPS (20%), and neuropathic pain (65 %). There were 8 men and 12 women. Mean age was 48 ± 8.6 . Two people had isolated radicular pain, four had axial pain alone, three had radicular and axial pain, and eleven had extremity pain. At both 6 months and 1 year, we saw significant improvements in VAS scores ($p=0.021$; $p=0.047$). ODI score also improved at 1 year ($p=0.009$). At both 6 months and 1 year, patients with percutaneous leads had significantly less disability on ODI ($p=0.016$; 0.034). There was no difference in any other outcome measure based on type of lead. Diagnosis did not correlate with any measure of outcome.

Discussion: We demonstrate that neck and arm pain can be

improved with cervical SCS at six month and one-year follow-ups. Both percutaneous and paddle implants have benefit. We tend to place percutaneous leads for radicular pain and retrograde C1-2 paddles for axial pain.

812. Management of Basilar Invagination—A Historical Perspective

Vesalius Award

Abhidha Harshad Shah, MS, MD (Mumbai, India)

Introduction: For a long time basilar invagination remained an anatomic and radiological curiosity and it is only in recent years that this entity has entered the realm of clinical neurosurgery.

Methods: The terms basilar invagination and platybasia were used interchangeably causing confusion in diagnosis and management. Basilar invagination has been defined as a prolapse of the vertebral column into the spinal cord. Platybasia is defined as an abnormal obtuse angle between the anterior skull base and the clivus. The author reviews the existing literature and summarizes the historical and modern perspectives in the management of basilar invagination.

Results: From radiological curiosities, the subject of basilar invagination is now viewed as eminently treatable. The more pronounced understanding of subject has taken place in the last three decades when on the basis of understanding of the biomechanical subtleties the treatment paradigm has remarkably altered. From surgery that involved decompression of the region, stabilization and realignment now form the basis of treatment.

Conclusion: As the understanding of basilar invagination has evolved it appears that mechanical instability is the cause and craniovertebral re-alignment and atlantoaxial fixation is the current management of this anomaly.

813. The evolution of Charles Elsberg's philosophy of spine surgery and the contemporary setting for his novel, innovative, revolutionary 1916 text

Nikolay L. Martirosyan, MD; Evgenii Belykh, MD; Alessandro Carotenuto, MD; Arpan Patel, MD; M. Yashar Kalani, MD, PhD; Nicholas Theodore, MD; Mark Preul, MD (Tucson, AZ)

Charles Elsberg is regarded as the father of modern spine surgery. While there have been several short biographies, none have traced the evolution of his philosophy of spinal surgery, nor have they put his seminal textbook devoted singularly to spine surgery within the context of the developing professionalization of neurosurgery. Contemporary to Cushing and Krause and preceding Dandy, he worked during a period of the rapidly evolving professionalization of neurosurgery. Elsberg furthered his surgical training with von Mikulicz-Radecki in Breslau, who was pioneering operating techniques, procedures, and tools. This influenced his views on spinal surgery, as most comprehensive literature on this matter before 1912 was translated from German, and there was little systematic consideration for spinal disease, much less surgical approach or cure. Elsberg's formative years span the early 1910s, when his experience and knowledge of spinal cord trauma and tumors markedly increased. His writing was exploratory and innovative, yet objective in stance, since there was little advanced opinion. The first significant contribution in the eventual subspecialty of spinal cord surgery came in the form of a new surgical theory, explained in his 1910 paper, The Extrusion of Intraspinal Tumors. Compared to concurrent multi-volume works containing sections on spine

surgery (von Bergmann, Krause, and Wollbey (Keen)), Elsberg's 1916 book solely on spine surgery, *Diseases of the Spinal Cord and its Membranes*, demonstrates a uniquely American, modern style of surgical instruction, with a plethora of illustrations, a tradition initiated by Krause and Cushing. Elsberg revolutionized spine surgery and he evolved also, especially in the 1920s. His contributions to neurosurgery's emerging professionalization, instructive textbooks and easy explanations opened the enigma of spine disease, obscure to the general surgeon, and provided clear, enlightening teaching aids based on personal experience tempered with introspection for the next generations of spinal and neurological surgeons.

814 Standards of Care (SsC) in the Union Army: Case Studies of Head Injuries during the American Civil War

William C. Hanigan, MD, PhD, FAANS(L) (Jackson, MS)

Introduction: Following passage of a medical reform bill by Congress in early 1862 the Union Army, under leadership of William Hammond and Jonathan Letterman, began a series of improvements in casualty evacuation and hospital arrangements with an establishment of a surgical meritocracy. Using contemporary surgical guidelines and case reports of 20 head injuries this report argues that Union military surgeons eventually practiced in experienced surgical groups that followed established SsC.

Methods: Case reports abstracted from the Medical and Surgical History of the War of the Rebellion. SsC derived from contemporary surgical textbooks.

Results: Twenty casualties received treatment in division or general hospitals from 1862 through 1864; two were Confederate POWs. Nineteen casualties sustained GSWs. Surgical intervention with anesthesia consisted of trephination or bone removal. Expectant treatment usually involved cold water dressings. Frequent second opinions stressed expertise and accountability. There were thirteen fatalities. Eight fatalities and five survivors underwent surgery. Autopsies were inconclusive or corroborated treatment plans in five of six cases. SsC were not met in two fatalities; one of these underwent surgery. Two cases met SsC which saved their lives. The remaining cases met SsC without changes in expected outcomes. Details of two cases will be discussed.

Conclusion: Results indicated that casualties under federal care with survivable head injuries could expect prompt evacuation, competent surgical treatment and follow-up that conformed to contemporary recommendations. Case fatality rates remained formidable but these novel military arrangements provided an organizational framework for changes in military and civil surgery in the late 19th century.

815. "Pepper Pot": Percival Bailey and Harvey Cushing

Jeffrey Paul Mullin, MD; Heather Fuhrman; Chris Sloffer, MD (Shaker Heights, OH)

Percival Bailey was a Chicago neurosurgeon, neuropathologist, neurophysiologist, neurologist, and psychiatrist, and an important scientific contributor to each of those areas. He was a polymath whose interests ranged far beyond the neurosciences. An active member of the Chicago Literary Club, he was a dedicated attendee of their weekly Monday meetings, served several times as a Club officer, and as its president for the 1954–55 year. He frequently presented papers to that club. Later in life, Bailey published a collection of these essays on a variety of topics in a book entitled, *Up from Little Egypt*, a reference to his origins in a poor, rural part of Illinois. Notably, a 1953 essay presented to the Literary Club

was omitted from this publication. Pepper Pot described Bailey's sometimes tumultuous relationship with Harvey Cushing, with whom Bailey studied, worked, and published on several occasions. Because his portrait of Cushing was critical in some respects, Bailey sent the paper to Cushing's daughters prior to publication. The Cushing family not only did not support its publication, but threatened Bailey with legal action, should he publish the paper. Though advised such a suit was unlikely to be successful, Bailey did not publish the essay. We review that essay and Bailey's experiences with Cushing. In reviewing this paper, one learns a great deal about both Bailey and Cushing, each an icon of neurosurgery. Bailey praised and admired Cushing greatly, but also described that, while gifted and influential, he was imperfect. Dr. Cushing was, in fact, a human being—oh, how human.

816. The Raney Brothers and the Invention of the Raney Clips

Vin Shen Ban, MA, MB, BChir, MRCS; Christopher Madden, MD; Ankur Patel, MD; Hunt Batjer, MD (Dallas, TX)

Introduction: The Raney clip has been instrumental in hemostasis control, allowing for cranial neurosurgery to be performed in its current form today. From the early days of Cushing's pneumatic tourniquet to the introduction of hemostats that have reduced craniotomies from two-day to one-day procedures, the Raney clip has withstood the test of time. However, little is known about its origins and its inventors.

Methods: An interview was conducted with Aidan Raney Jr, MD (son of Aidan Raney, MD and nephew of Rupert Raney, MD) and records were obtained from University of Southern California's (USC) Department of Neurosurgery.

Results: Rupert B. Raney (1900–1959) and Aidan A. Raney (1911–2002) were born in Loogootee, Indiana. They attended Creighton University School of Medicine prior to embarking on residencies in General Surgery. Rupert was influential in sparking Aidan's interest in neurosurgery, and they were both residents at the LA County General Hospital (USC). The Raney brothers were avid inventors, spending hours together in their workshop developing instruments for surgery. Perhaps their most famous invention was the Raney clip. Realizing its impact and wishing for the public to benefit from it, they decided against filing for a patent. Besides the Raney clip, the brothers also improved on pneumatic and electric power units, enabling their use to power surgical bone drills and significantly reduce the time and effort required to perform a craniotomy.

Conclusion: Inventions in neurosurgery such as the Raney clip have revolutionized the field of Neurosurgery. Raney clips have also been used in cardiothoracic surgery, emergency medicine and pediatric surgery. The Raney brothers and their Raney clips are excellent examples of Neurosurgery Leading the Way.

817. Percival Bailey, Renaissance Man and Early Chicago Neurosurgeon

Heather Augusta Alberta Fuhrman; Jeffrey Mullin, MD; Chris Sloffer, MD (Cleveland Heights, OH)

Percival Bailey had tremendous impact on the world of neurosurgery, and neuroscience, in general. Rising from a poor, rural area of southern Illinois, he eventually worked with notable mentors worldwide. He was engaged with, and made important contributions to, almost every aspect of neuroscience, from neuroanatomy and neuropathology to clinical neurology, neurosurgery, and psychiatry. Bailey was multilingual, and published in the German and French literature, in addition to his work in English. He was chairman of

neurosurgery at the University of Chicago, and helped to develop that institution's training program. Bailey molded the disarray and confusion over brain tumors into a systematic, categorical classification based on pathological and histological samples, correlated with clinical histories. His books, *Intracranial Tumors and Tumors of the Glioma Group*, are masterworks. He identified medulloblastomas for the first time and, with Cushing, coined the term hemangioblastoma. Bailey delved into extensive investigations with his assistant and first trainee, Paul Bucy, including confirmation that oligodendrogliomas are derived from oligodendroglia. Bailey's contributions as an intellectual, and as a psychiatrist, must not be underestimated. He trained with Pierre Janet at the Salpêtrière. He ultimately was the director of the Illinois Neuropsychiatric Institute and of the Illinois State Psychopathic Institute. He was a vocal critic of Freud and ultimately published a monograph, *Sigmund, The Unserene*. Percival Bailey was a polymath, a pioneer, and a neuroscientist in the broadest sense of the term. His contributions were many, and he must not be forgotten.

818. The Nonsurgical Sketches of Harvey Cushing

Chris S. Karas, MD, FAANS (Columbus, OH)

Introduction: Much has been written regarding the surgical expertise of Harvey Cushing. His scholarly and clinical volumes are wrought with legendary and detailed anatomical and surgical sketches. Less known, however, is his nonsurgical artistry, finely displayed in his own accounts of his time in Europe and at war.

Methods: A literature search was performed which included journals, manuscripts, and limited publications authored by Dr. Cushing. Some of these primary resources are available for viewing at the special collections section of the Cleveland Public Library and were studied on site. Nonsurgical sketches were compiled and contextualized.

Results: Dr. Cushing's nonsurgical sketches encompass a wide variety of subject matter from botany to architecture as well as landscapes and mundane (as he refers to them) scenes depicting the people and happenings of everyday life. The attention to detail in the renderings of his imagined hospital compound on the Boston Commons or in the water color depictions of European dress are reminiscent of his surgical illustrations. His understanding of three dimensional space and contrasting are apparent throughout.

Conclusion: Even a cursory examination of the nonsurgical sketches of Harvey Cushing is fascinating to one interested in the sometimes symbiotic and sometimes conflicted relationship between the clinical and ordinary contemplations of a physician. The sketches are a visual mantra reminding us that even the father of modern neurosurgery was brought to playful fascination by a dog chasing sheep or a friend laden with vacation trinkets.

819. William Edward Gallie (1882–1959): Father of the Gallie Wiring Technique for Atlantoaxial Arthrodesis

Rimal Hanif Dossani, MD; Jai Thakur, MD; Anil Nanda (Shreveport, LA)

Introduction: Dr. William Edward Gallie (1882-1959) invented the first wiring technique for atlantoaxial arthrodesis. We present a historical vignette on Gallie's life and chronicle his contributions to neurosurgery.

Methods: We searched for articles authored by Gallie on PubMed and reviewed historical manuscripts for details about his life and his surgical contributions.

Results: In 1882, Gallie was born in Barrie, a small city in Ontario, Canada. In 1929, he became Chair of Surgery at Toronto General Hospital. As Chair, he encouraged Dr. William Keith to pursue training in pediatric neurosurgery in Chicago and London. Keith founded the pediatric neurosurgery service at Sick Kids in Toronto in 1935 and became one of the pioneers of pediatric neurosurgery. Prior to 1929, there was no formal surgical training for young surgeons in Canada. Gallie organized a program for postgraduate training in surgery, a course his students popularized as the Gallie Course in Surgery. Gallie invented a wiring technique that involves passing a steel wire underneath the posterior arch of C1 and the spinous process of C2 to secure an H-shaped iliac crest bone graft to facilitate atlantoaxial arthrodesis. His other key contribution was his discovery of fascia lata grafting for surgical closure of abdominal hernias.

Conclusions: Gallie's wiring technique was an inspiration to other surgeons who later modified his technique. As Chair, he created the postgraduate surgical training curriculum in Canada and facilitated the growth of the specialty of neurosurgery.

820. Transtentorial herniation, the neurosurgeons blight: A historical sketch and future directions

Brian D. Sindelar, MD; James Stone, MD; Julian Bailes, MD (Gainesville, FL)

Introduction: We will discuss the history of transtentorial herniation, current modalities of assessment, and their pitfalls.

Methods: A systematic review of the literature dating to the late 18th century in regards to our knowledge of transtentorial herniation, pathophysiology of ICP elevation, anatomical differences that buffer ICP elevations preventing herniation, and current tools for assessment of herniation.

Results: In the late 1800's, Hill appreciated that an intracranial mass is prone to temporal lobe displacement and brainstem compression. Clinically, the patient was noted to develop a unilateral and unreactive pupil, worsening lethargy, and subsequent coma. This was coined as herniation and secondarily found to be associated with midbrain and pontine hemorrhages on post-mortem pathological examination by Meyer et. al in 1920. Since that date, we have made full strides in understanding the pathophysiology, different types, and buffering systems for cerebral herniation. With the advent of neuroimaging, various groups, like Fisher and Ropper, began to look at levels of shift and how this correlated with patient's symptoms. This knowledge of cerebral herniation has allowed us to place greater emphasis on different tools for evaluation of herniation like clinical exam, imaging modalities, and ICP monitors. In this presentation, we will review further the history, clinical neuroanatomy, and pathophysiology of herniation. We will then discuss the current tools, mentioned above, used and then review the limitations to these various modalities, specifically ICP monitoring.

Conclusion: Dramatic medical advancements in this population have been seen for various measures; yet, little to no progress has been made in the practicality of real-time monitoring for earlier warning of brain herniation. Only through our knowledge of cerebral herniation and limitations to current modalities, will we become better able to address the need for a real time, continuous monitoring tool.

821. The History of Neurosurgical Training: Where We Were, Where We Are, and Where Are We Going

A. Nimer Amr, MD; Alf Giese, MD, PhD (Mainz, Germany)

Introduction: Surgical education in general has only recently began to evolve from the century-old Halstedian model. We explore the history of neurosurgical training, from the pre-Halstedian era, to Halsted, the Flexner Report, Cushing, Dandy, and the latter part of the 20th century, to current paradigms in neurosurgical training, and discuss possible trends in the future of surgical education with special reference to modern paradigms in education theory.

Methods: We performed an exhaustive search of the Ovid MEDLINE and Pubmed databases, as well as the historical literature in German and English on the subject of surgical education with particular reference to neurosurgical training. We furthermore researched the state of neurosurgical training today in North America and Europe, and investigated the use of modern education theory in current neurosurgical training programmes.

Results: The history of neurosurgical training is a rich one, and is intertwined and inseparable from the history of neurosurgery as a whole. Even in the early eras of Cushing and Dandy, conflicting educational philosophies existed that resulted in heterogeneous neurosurgical programmes. National and supranational neurosurgical societies have tried with varying degrees of success to unify neurosurgical training in their respective jurisdictions. There are few departments that currently incorporate modern education theory in their training programmes.

Conclusion: In order to understand and improve the state of neurosurgical training today, it is important to recognize the history and evolution of neurosurgical education. We present the history of neurosurgical training, its current state, and possible future trends in tune with modern education theory.

822. From Bench to Bedside: Results of a Phase I trial using a Notch inhibitor for Glioblastoma

American Brain Tumor Association Young Investigator Award

Viviane S. Tabar, MD, FAANS; Ran Xu, MD; Antonio Omuro, MD (New York, NY)

Introduction: This is the first report of the results of a Phase I trial of a Notch inhibitor (RO4929097) in combination with standard of care therapy in malignant gliomas (MG). The study is designed as a proof-of-concept and based on data developed in the lab using human tumor explants.

Methods: 21 patients with newly-diagnosed MG received RO4929097 in three dosages (10, 15 and 20 mg) combined with temozolomide (TMZ) and radiotherapy (RT). Primary objectives were determining the maximum tolerated dose, toxicities and pharmacokinetics. The study design allowed for exploratory studies characterizing in human effects of RO4929097, including evaluation of tumor and brain drug penetration, neuro-imaging parameters and effects on the Notch pathway and cancer stem cells. Analyzed surgical specimens were differentially sampled from areas with and without blood-brain barrier disruption.

Results: Treatment was well tolerated and no dose-limiting toxicities were observed. Immunohistochemistry of treated tumors showed a decrease in proliferation (Ki-67: 27.7% to 13.6%; n=7), and in expression of the notch receptor (NICD) by tumor cells (21.9% to 5.1%), and blood vessels (67.6% to 30.0%). Organotypic explant cultures of study patients revealed a decrease in proliferation, viability, and CD133+ cell population with treatment. Perfusion MRI demonstrated a significant decrease in relative plasma volume, from 9.34%

to 3.92% after drug exposure (n=8). Upon recurrence, tumors exhibited a switch from Notch- to VEGF-dependent angiogenesis, suggesting a potential for combination therapy with anti-VEGF agents.

Conclusion: The combination of RO4929097 with TMZ and RT in newly-diagnosed malignant glioma is safe and well tolerated; the drug has variable blood brain barrier penetration with some evidence of target modulation, including inhibition of the Notch pathway and CSC population, and evidence of anti-angiogenesis. Lab data performed on fresh tumor tissue was predictive of treatment response.

823. BRAF alteration status and the histone H3F3A gene K27M mutation segregate spinal cord astrocytoma histology

Brian D. Silber Award

Ganesh Mani Shankar, MD; Matthew Meyerson, MD, PhD; Jay Loeffler, MD; Jeffrey Wisoff, MD; Priscilla Brastianos, MD; John Shin, MD; Ann-Christine Duhaime, MD; Michael Taylor, MD, PhD; David Louis, MD; Daniel Cahill, MD, PhD; William Curry, MD (Boston, MA)

Introduction: Intramedullary spinal cord neoplasms represent 2-4% of central nervous system tumors, of which astrocytic gliomas represent 80%. Histologic grading can be challenging in spinal cord astrocytomas because of the often relatively small samples obtained at the time of the surgical procedure. To address the hypothesis that genomic alterations could segregate spinal cord astrocytoma histologic grades, we performed sequencing of cancer-related genes in a cohort of 17 tumors.

Methods: Spinal cord astrocytomas from children and adults were obtained as formalin-fixed, paraffin-embedded (FFPE) specimens from Massachusetts General Hospital, the University of Toronto, and New York University. Targeted sequencing of 560 cancer related genes and 39 translocation events was performed on DNA extracted from these specimens. Data was analyzed for somatic nucleotide variants, copy number changes and rearrangement analysis.

Results: The most recurrent findings in Grade I spinal cord astrocytomas were a BRAF-K1AA1549 translocation (n=4/10) and BRAF copy number gain (n=5/10). WHO grade II astrocytomas were similarly characterized by alterations involved in the MAPK-ERK or PI3K pathways, including BRAF amplification (n=2/3). In addition, we observed that all four Grade III and IV astrocytomas in the discovery cohort shared the H3F3A K27M mutation. Further targeted Sanger sequencing of H3F3A was performed in five additional specimens and revealed the K27M mutation in 2/3 spinal Grade IV astrocytomas and 0/2 Grade I astrocytomas.

Conclusion: The findings described here represent the first genomic characterization of spinal cord astrocytomas. In summary, our observations indicate that BRAF alterations and histone H3F3A K27M mutations are grade-related features of spinal cord astrocytomas that should enter routine initial evaluation of spinal cord gliomas and provide a potential foundation for adjuvant therapeutic strategies.

824. "Cure" of Intracranial Metastases of less than 100 mm³ Treated by Stereotactic Radiosurgery

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Introduction: Our purpose was to determine if there is a threshold tumor volume and maximal diameter below which local control

(LC) rates of intracranial metastases after stereotactic radiosurgery (SRS) approaches 100%.

Methods: Using a prospective registry of patients with brain metastases having undergone SRS, we identified 200 patients with 1223 tumors treated between 2013-2014. Median follow-up time was 8 months (max, 39 months). The median tumor volume was 90mm³ (1-21000mm³) and median maximal diameter was 6mm (1.5-45mm). The prescription tumor margin dose was a median of 18 Gy (10-20 Gy). Patients had non-small cell lung cancer (96), melanoma (40), breast cancer (35) and others (29).

Results: 29 of 1223 tumors demonstrated local progression, at a median time of 6.2 months. LC at 1 and 2 years was 100% for intracranial metastases that were less than 100mm³ in volume or 6mm in maximal diameter. The 1-year LC was 99% for tumors below 250mm³ or 8mm in diameter and 98% for tumors below 350mm³ or 10mm. LC was independent of histology. For failures, the median tumor volume was 390mm³ and maximal diameter 12.4mm.

Conclusions: The incidence of brain metastases is increasing with more effective systemic therapies. 100% local control after SRS can be achieved for tumors up to 100mm³ or 6mm in maximal diameter. This places impetus on early and routine MRI screening of patients with metastatic cancers, in order to prevent the development of larger, symptomatic tumors known to be associated with poorer outcomes. Routine screening is not part of the current care of most cancers.

825. Indications and efficacy of Gamma Knife stereotactic radiosurgery for recurrent glioblastoma: two decades of institutional experience

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Introduction: Treatment of recurrent glioblastoma remains heterogeneous and institution dependent. The role of stereotactic radiosurgery (SRS) for this indication, along with the radionecrosis risk in this setting remain unclear. Larger studies are needed to help inform proper target patient profiles, efficacy and anticipated complications.

Methods: We retrospectively analyzed recurrent glioblastoma patients who underwent Gamma Knife SRS between 1991-2013 at a single academic medical center. We used the partitioning deletion/substitution/addition (partDSA) decision tree algorithm to identify potential predictor covariate cut points followed by Kaplan-Meier and proportional hazards modeling to identify factors associated with post-SRS survival.

Results: 176 glioblastoma patients with median age of 53.9 years underwent SRS a median of 8.8 months after initial diagnosis. 75% had one treatment target (range=1-6) and median target volume and prescription were 6.8 cm³ (range 0.3-39.0) and 16.0 Gy (range 10-20), respectively. Median overall survival was 10.6 months (range 1.4-157.6 months) following SRS. Kaplan-Meier and multivariate modeling revealed that younger age at SRS and longer interval between original surgery and SRS are significantly associated with improved post-SRS survival. 46 patients (26%) underwent craniotomy a mean of 6.6 months after SRS with 63% showing radionecrosis or mixed tumor and necrosis versus 35% showing purely recurrent tumor. The necrosis/mixed group had lower mean isodose prescription compared to the tumor group (16.2 vs. 17.8 Gy, p=0.0031) and larger mean total treatment volume (10.0 vs. 5.4 cm³, p=0.0091).

Conclusion: We have prepared, to our knowledge, the largest

retrospective series studying the outcomes of Gamma Knife for the treatment of recurrent glioblastoma. We conclude that Gamma Knife may benefit a subset of focally recurrent glioblastoma patients, particularly those who are younger with smaller recurrences. Higher prescriptions are associated with improved post-SRS survival and do not seem to have greater risk of symptomatic treatment effect.

826. Stereotactic Radiosurgery for Jugular Foramen Schwannomas: An International Multicenter Study

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Introduction: For some jugular foramen schwannomas complete surgical resection is possible, but it may be associated with significant morbidity. Stereotactic radiosurgery (SRS) is a minimally invasive alternative or adjunct to microsurgery for jugular foramen schwannomas. Patients with neurofibromatosis were excluded in this study. We reviewed clinical and imaging outcomes of SRS for jugular foramen schwannomas.

Methods: Seven participating centers of the International Gamma Knife Research Foundation (IGKRF) identified 77 patients underwent SRS between 1990 and 2013. Thirty-five patients had prior microsurgical resection and all patients suffered from various cranial neuropathies. The median interval between previous surgery and SRS was 16 months (range, 0.5-144 months). Seventy-four patients had preexisting cranial nerve symptoms and signs. The median tumor volume was 4.2 cc (0.8-22.6 cc) and median margin dose was 13 Gy (10-18 Gy).

Results: The median follow-up was 50 months (6-266 months). Tumors regressed in 38 patients, remained stable in 30 and progressed in nine. The progression-free survival was 93% at 3 years, 89% at 5 years, and 86% at 10 years. Preexisting cranial neuropathies improved in 20 patients (27%), remained stable in 46 (60%), and worsened in 11 (14%) after SRS. The improvement rate of cranial nerve deficits after SRS was 15% at 1 year, 21% at 2 years, 23% at 3 years, and 30% at 5 years. Symptomatic adverse radiation effects occurred in six patients (8%) at a median of 6 months (4-38 months). Five patients required repeat SRS at a median of 54 months (44-128 months). Three patients underwent surgical resection at a median of 12 months after SRS (8-16 months).

Conclusion: Stereotactic radiosurgery proved to be a safe and effective management for newly diagnosed or residual jugular foramen schwannomas. Long-term tumor control rates and stability or improvement in cranial nerve function was confirmed."

827. Recovery Room Cortisol Predicts Long-term Glucocorticoid Need after Transsphenoidal Surgery for Pituitary Tumors

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Introduction: Accurate assessment of the need for glucocorticoid therapy is essential after transsphenoidal surgery (TSS) for pituitary tumors. Agreement on the best test to use in the early post-operative setting is lacking. We aimed to examine recovery room (RR) cortisol as a predictor of long-term need for glucocorticoids.

Methods: We retrospectively studied 149 patients that underwent

TSS for pituitary tumors between January 2007 and December 2014. Pathological tumor diagnoses were confirmed. Endocrinologists assessed the need for glucocorticoid supplementation using a standardized protocol 4–12 weeks after TSS. We extracted data on preoperative, RR, day 1–3 post-TSS morning serum cortisol (MSC), and follow-up MSC. We reported areas under the receiver operating characteristic curve (AUC) and diagnostic measures for different cortisol measures. We also conducted a logistic regression to identify the most predictive variables.

Results: Eighteen patients required glucocorticoid supplementation at follow-up. RR cortisol was the most accurate measurement in the early post-operative period (AUC [95% confidence interval {CI}], 0.92 [0.85–0.99]; $p < 0.001$), followed by day 1, 2, and 3 post-TSS MSC, respectively. A threshold RR cortisol of 26.97 $\mu\text{g/dL}$ (744.0 nmol/L) had 90.9% sensitivity and 73.7% specificity, while 27.46 $\mu\text{g/dL}$ (757.5 nmol/L) had 100% sensitivity and 70.0% specificity. The logistic regression identified RR cortisol as the sole significant predictor (odds ratio [CI], 0.36 [0.18–0.71] for every 3.62 $\mu\text{g/dL}$ [100 nmol/L] increase; $p = 0.0033$).

Conclusion: The RR cortisol is highly accurate in predicting long-term glucocorticoid supplementation and may be the best early post-operative measure. Future larger studies should validate these findings and derive optimal RR cortisol threshold values.

828. Magnetic Resonance-Guided Laser Ablation for Postradiosurgery Metastatic Recurrence or Radiation Necrosis

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Introduction: In patients who have previously undergone radiosurgery for metastatic brain tumors, enhancing lesions that demonstrate progression are often tumor recurrence or radiation necrosis. Magnetic resonance-guided laser-induced thermal therapy (LITT) continues to gain momentum as a minimally-invasive treatment option for postradiosurgery recurrence or radiation necrosis. We report the largest prospective series with longest follow-up to date of LITT for the treatment of recurrent enhancing lesions after radiosurgery for brain metastases.

Methods: Patients with recurrent metastatic intracranial tumors or radiation necrosis who had previously undergone radiosurgery and had a Karnofsky performance status of >70 were eligible for LITT. The primary endpoint was local control using MR scans at intervals of >4 weeks. Radiographic outcomes were followed prospectively until death or local recurrence.

Results: 30 patients (age range 46–90 years) who underwent 40 LITT procedures for 39 enhancing lesions were available for follow-up. The mean pre-procedure lesion size measured 3.5 cm^3 (range 0.23–10.52 cm^3). On average, there were 3.0 ablations per treatment (range 1–5) with 76.5 mm depth to target (range 56–123.5 mm), ablation dose of 10.9 watts (range 8.25–15 watts), and total ablation time of 5.0 minutes (range 0.65–12 minutes). At a median follow-up of 42.7 weeks post-procedure (range 4.9–181.9 weeks), local control was 76.9% (30 of 39 lesions), median radiographic progression-free survival was 22.7 weeks (range 2.1–181.9 weeks), and overall survival at 6, 12, 18, and 24 months was 83.3%, 46.9%, 23.3%, and 13.3% respectively.

Conclusion: LITT is an effective treatment for local control of recurrent metastatic brain disease that has failed radiosurgery.

829. Pre- and post-operative factors associated with seizure in 1039 patients with supratentorial meningioma

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Introduction: Meningiomas often present with seizures, however, the factors that predict seizures pre- and post-operatively in meningioma patients is under-studied. Here, we evaluated a large single-center cohort to evaluate for factors associated with pre- and post-operative seizures in patients with supratentorial meningioma.

Methods: A retrospective review was conducted of 1039 subjects who underwent surgical resection of supratentorial meningioma from January 1991–March 2014. Univariate and multivariate logistic regression were performed to identify variables significantly associated with pre-operative and post-operative seizures both in the immediate post-op period and after discharge.

Results: Pre-operative seizures occurred in 225 (22.6%) subjects. At 5 years post-op, the probability of being completely seizure free was 62.2% among subjects who had a pre-op seizure and 89.9% among subjects who did not have a pre-op seizure. Of 121 subjects who experienced a pre-op or early post-op seizure and who had 1 year or more of followup, 74.4% achieved eventual Engel I seizure freedom. Multivariate analysis identified male gender (OR: 1.48), WHO grade II/III (OR: 1.77), non-skull-base location (OR: 2.73), and presence of $\geq 1\text{cm}$ of peritumoral edema (OR: 4.35) to be significant predictors of pre-operative seizures. Headache (OR: 0.48) and cranial nerve deficit (OR: 0.36) as presenting symptoms were associated with lower risk of pre-operative seizures. Multivariate analysis of early post-operative seizures found that non-skull-base location (OR: 2.16) and weakness on presentation (OR: 3.04) were significant predictors of early post-operative seizures. Finally, multivariate Cox regression revealed presence of pre-operative seizure to be the single significant predictor of post-op seizure (RR: 2.89).

Conclusion: In a large series of patients undergoing meningioma resection, male gender, WHO Grade II/III tumors, non-skull base location and peri-tumoral edema were associated with increased risk of pre-operative seizures, and non-skull base location and weakness on presentation were associated with increased risk of post-operative seizures.

830. Intra-Arterial Chemotherapy for Retinoblastoma: Five-Year Experience and Discussion of Technical Nuances

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Introduction: Selective catheterization of the ophthalmic artery for intra-arterial (IA) delivery of chemotherapeutic agents has rapidly become standard treatment for advanced cases of retinoblastoma (RB) as globe salvage therapy. It is likely to become first line therapy for many presentations of RB as the efficacy and safety of this approach is demonstrated in various patient cohorts. Here, we present our single-institution series of IA chemotherapy for RB with a focus on alternative access and technical considerations.

Methods: We retrospectively reviewed our series of consecutive patients undergoing intra-arterial chemotherapy for RB over a 5 year period between January 2009 and December 2014. All patients presented with vitreous seeding (Reese-Ellsworth Grade Vb) and both patients treated primarily and as secondary therapy after systemic chemotherapy were included. Enucleation rate, method of access, and complications were recorded.

Results: Seventy-six eyes in 65 patients were treated in total.

Overall globe salvage rate was 74% (n=56) and 86% (n=31) in eyes treated primarily with IA therapy (n=36). In total, there were 328 treatment sessions for an average of 5 sessions per patient. In 5% (n=17) of treatments, the middle meningeal artery was cannulated in order to deliver the chemotherapy. Among these patients, the salvage rate was 67%. There were no deaths. One procedure was aborted due to bronchospasm and bradycardia which subsequently resolved.

Conclusion: Intra-arterial chemotherapy delivery for retinoblastoma is an increasingly utilized therapy and we present our institutional 5-year experience here. We demonstrate high globe salvage rates even among patients with complex arterial supply to their tumor.

831. Investigating a thickened pituitary stalk in children: A retrospective review and prospective treatment paradigm

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Introduction: A thickened pituitary stalk (TPS) is a nonspecific finding on magnetic resonance imaging (MRI) with a wide differential diagnosis, ranging from idiopathic to neoplastic processes. Treatment of TPS may be time sensitive for neoplasia. We reviewed our institutional experience while creating a treatment paradigm.

Methods: This is a single institution retrospective IRB approved review of the electronic medical record and radiology database by ICD-9 codes and keyword queries from 2000–2015. MRI's were reviewed by neuroradiology and neurosurgery. Patient, endocrine and radiographic data were collected for analysis.

Results: We identified 97 patients with TPS. Fifty patients had isolated TPS in the absence of systemic Langerhans cell histiocytosis (LCH) or obvious tumor. Median age at presentation = 12.4 years (Range: 2.9–18 yrs) with female predominance. Median follow-up = 3.6 years. Patients presenting with diabetes insipidus (DI, n=12) were more likely to have a neoplastic process ($P<0.001$). Six developed neoplasia, including germ cell tumor (n=2), LCH (n=3) and low-grade glioma (n=1). Four of these had concurrent anterior pituitary dysfunction (APD) at presentation, such that all patients with DI and APD had neoplasms ($p<0.001$). Of the 38 patients without DI, 2 developed LCH during the follow up period. Patients with neoplasms had significantly thicker stalks (5.8mm vs 3.6mm, $p<0.001$).

Conclusion: Patients with TPS without DI are unlikely to develop a neoplastic process. A thicker stalk, DI, and DI with APD are indicators of neoplastic processes, requiring close surveillance and often a biopsy in the absence of other laboratory and radiographic predictors of disease.

832. Complication Avoidance in Minimally Invasive Endoscopic Craniosynostosis Surgery

Hal S. Meltzer, MD, FAANS; Cecilia Dalle-ore; Monisha Dilip; Joyce McIntyre; Reid Hoshide; Mark Calayag; Amanda Gosman; Steven Cohen (San Diego, CA)

Introduction: The authors review their 15 year single institution experience in the endoscopic treatment of non-syndromic craniosynostosis with an emphasis on complication avoidance including postoperative care.

Methods: A retrospective chart review was carried out on all patients undergoing endoscopic, minimally invasive surgery for non-syndromic craniosynostosis at Rady Children's Hospital from 2000-2015. All patients were operated on by a single neurosurgeon in collaboration with two plastic and reconstructive surgeons as part of our institution's craniofacial team.

Results: 200 patients were identified as having undergone minimally invasive endoscopic surgery for non-syndromic craniosynostosis from 2000–2015. There were 135 boys and 65 girls. The average age at surgery was 4.3 months. The average operative and anesthesia times were 63 and 106 minutes respectively. The average estimated blood loss was 36cc. There were no identified episodes of air embolism or operative deaths. 195 patients were admitted to the standard surgical ward where the average length of stay was 1.5 days. 5 patients were admitted to an intensive care unit (ICU) ward. Four of these patients had preexisting medical conditions which the team had identified pre-operatively as necessitating post-operative ICU admission.

Conclusion: In the endoscopic treatment of non-syndromic craniosynostosis, significant complications were avoided while allowing for post-operative care for the vast majority of infants on a standard surgical ward. ICU care was primarily limited to medically fragile patients identified pre-operatively.

833. Correlating Prenatal Imaging Findings of Fetal Ventriculomegaly with the Need for Surgical Intervention at Birth

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Introduction: Our objective was to determine which prenatal imaging measurement best predicts the need for cerebrospinal fluid (CSF) diversion at birth.

Methods: We retrospectively reviewed medical records of fetuses screened for hydrocephalus from January, 2011 to December, 2014. Prenatal measurements on ultrasound and/or MRI included head circumference (HC), biparietal diameter (BPD), and lateral ventricle (LV) width. Patients requiring CSF diversion within 12 weeks of birth were compared to those who did not using Wilcoxon Rank Sum Test. Receiver operating characteristic (ROC) analysis was used to evaluate threshold values.

Results: 50 of 1,303 screened patients had ventriculomegaly. 33 patients had open neural tube defects, 6 had aqueductal stenosis, and 11 had hydrocephalus of miscellaneous causes or unknown etiology. 31 patients required CSF diversion within 12 weeks after birth. Mean LV width (mm) during the entire pregnancy was greater for the surgery group than the non-surgery group (19.9 ± 4.8 vs. 14.1 ± 8.6 ; $p = 0.014$). Largest LV width between 28–32 weeks was also greater for the surgery group (26.8 ± 16.9 vs 17.4 ± 6.6 mm; $p = 0.047$). Neither BPD nor HC showed differences between the groups. A LV of 15mm predicted the need for a diversion procedure with a sensitivity of 0.91 and specificity of 0.43.

Conclusion: LV width is the prenatal imaging measurement that best predicts the need for postnatal CSF diversion. Awareness of this finding will facilitate accurate prenatal counseling when a fetus is diagnosed with ventriculomegaly.

834. Bmi1 is a Therapeutic Target in Recurrent Medulloblastoma

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Introduction: Current clinical trials for recurrent medulloblastoma (MB) patients who no longer respond to risk-adapted therapy are based on genomic profiles of primary, treatment-naïve tumors.

These approaches will provide limited clinical benefit for patients since recurrent metastatic MBs are highly genetically divergent from their primary tumor. Our experimental approach defines a tractable target, the epigenetic regulator Bmi1, which characterizes recurrent MB.

Methods: Through comparative gene expression and functional stem cell profiling of primary and recurrent MB, combined with functional gene knockdown and patient-derived xenograft model studies, we show that Bmi1 defines a treatment-refractory cell population that is uniquely targetable by a novel class of small molecule inhibitors.

Results: By undertaking gene expression analyses and stem cell assays on primary and matched-recurrent Group 3 MB samples, we have identified Bmi1 as a key regulator of self-renewal to drive treatment failure. When administered to mice xenografted with patient tumors, oral delivery of Bmi1 inhibitors to mice results in significant reduction in tumor burden and increased mouse survival, without neurotoxicity.

Conclusion: We show that Bmi1 is a novel therapeutic target for the treatment of recurrent human Group 3 MB, a tumor that often presents with metastasis for which there is virtually no treatment option as children are limited to palliation. Through a strategic targeted analysis of a conserved Bmi1-regulated transcriptional network in primary and matched-recurrent Group 3 MBs, we have identified compounds that inhibit self-renewal and metastatic disease, offering a means to selectively eradicate the evolving clonal populations that dynamically drive tumor maintenance and relapse. As Group 3 MB is uniformly fatal at recurrence, with no current or planned trials of targeted therapy; an efficacious targeted agent would be rapidly transitioned to clinical trials.

835. Hydrocephalus Clinical Research Network (HCRN) Shunt Infection Protocol Implementation Across Pediatric Neurosurgery—A Cross-Sectional Survey

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Introduction: There is uncertainty regarding how frequently standardized peri-operative protocols, such as the HCRN shunt infection protocol, are being incorporated into contemporary pediatric neurosurgical practice, and whether barriers to the implementation of such protocols exist within various practice environments.

Methods: A survey instrument assessing current practice relating to peri-operative strategies designed to minimize the incidence of shunt infection, as well as items identifying potential surgeon- or institution-level barriers to implementation of standardized peri-operative protocols, was designed using Delphi methodology and administered to Pediatric Section members.

Results: Of 51 respondents, 47% reported using the peri-operative HCRN shunt infection protocol. Protocol adoption was associated with increasing agreement with the statement “the incidence of shunt infection can be improved at my institution” ($p=0.02$), with trends towards protocol adoption observed in those practicing at stand-alone children’s hospitals ($p=0.10$) and those who feel that HCRN results are generalizable to their practice ($p=0.10$). Significant heterogeneity relating to peri-operative interventions designed to minimize shunt infection incidence was documented. The lack of a team approach in the operating room appears to be an important institutional barrier to the implementation of standardized peri-operative protocols.

Conclusion: Despite being published for several years, the HCRN

shunt infection protocol is currently implemented by less than half of responding surgeons. There is significant practice variation with respect to peri-operative measures designed to prevent shunt infection, and, although barriers to the implementation of standardized protocols do exist, our community is receptive to standardization and quality improvement initiatives going forward.

836. Overdrainage-Related Ventricular Tissue is a Significant Cause of Proximal Shunt Obstruction

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Introduction: Prospective studies of ventricular shunts demonstrate a staggering failure rate of 50% after two years. The majority of shunt malfunctions are due to proximal ventricular catheter obstruction. According to the literature and surveys of North-American pediatric neurosurgeons, obstructions are most often attributed to in-growth of choroid plexus and/or reactive cellular aggregation. Here, we report overdrainage-related evagination of ventricular wall tissue as a significant, if not primary cause of proximal shunt obstruction.

Methods: A retrospective review was completed on patients undergoing shunt revision surgery between 2008 to 2015, identifying all cases in which endoscopic documentation of ventricular tissue in-growth was reported in the senior author’s surgical notes. Detailed clinical, radiographic, histological and surgical findings were examined.

Results: Forty-one patients (13 adults, 28 children) underwent 69 endoscopic shunt revision procedures that revealed in-growth of ventricular wall tissue into the catheter tip orifices, producing partial, complete, or intermittent shunt obstructions. Choroid plexus was involved in only three cases. Real-time endoscopic evidence shows outgrowths of ventricular wall tissue at various stages of evolution forming secondary to siphoning into the catheter.

Conclusion: Ventricular wall tissue is a significant cause of proximal shunt obstruction, which appears to be related to siphoning of surrounding tissue into the ventricular catheter, and CSF overdrainage as a primary mechanism. We will discuss the impact of these observations on our understanding of the pathophysiology of shunt malfunction and treatment options.

837. Lumbar-Peritoneal Shunting in Hydrocephalus: Preventing Chiari Malformations and Decreasing Shunt Revisions

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Introduction: Lumbar-peritoneal shunts (LPS) are considered disadvantageous due to tendency to overshunt, difficulty in access to tap/revise, risk of subdural hematoma formation, and progressive cerebellar tonsillar herniation with overdrainage reported in up to 70% of cases. However, the use of horizontal-vertical valves (HV) and our minimal exposure technique have minimized these complications, particularly the incidence of Chiari malformation (CM) and proximal revisions.

Methods: We performed a retrospective analysis of all patients treated with a LPS at the Children’s Hospital of Michigan. One-hundred-forty-four pediatric patients with hydrocephalus were treated with LPS from 1997–2015 (Follow-up range: 8-months to 8-years). Most common cause of hydrocephalus was congenital hydrocephalus of prematurity (32%). In patients with slit-ventricles

from chronically treated hydrocephalus or repeated shunt malfunctions from proximal catheter obstruction, lumbar drain was inserted to assess candidacy for LPS conversion. Age at insertion/conversion to LPS ranged from 1-42 years.

Results: 27% of patients (n=39) underwent initial shunting with LPS; 73% (n=105) were converted to LPS from VPS. Nineteen patients had CMs: 16/19 patients had documented CMs prior to LPS and 3/19 patients did not have MR prior to shunting but were found to have CM on routine subsequent MR. No progression was noted on follow-up MR in these patients. Therefore, no patients had LPS-induced acquired-CM. No patients developed subdural hematomas. Proximal catheter malfunction rate decreased from 4.9 prior to conversion to 1.7.

Conclusion: Contrary to accepted ideology, use of LPS does not significantly increase the risk of cerebellar tonsillar herniation when using HV valves. Conversion to LPS significantly reduces the number of proximal malfunctions in patients with chronically-treated hydrocephalus, minimizing acute symptoms of shunt malfunction and improving patient outcomes and satisfaction.

838. Prenatal injury impairs cortical myelination and executive function in a preclinical rat model

Jesse Lee Winer, MD; Lindsay Chan; Jessica Van Sweringen; Lauren Jantzie; Shenandoah Robinson (Brookline, MA)

Introduction: Preterm birth is a global problem with significant social and economic impact, as 175,000 survivors born before 32 weeks annually suffer from cognitive deficits. Gray matter myelin is implicated in cognition. We hypothesized that prenatal injury would damage gray matter myelination and impair cognitive function.

Methods: On embryonic day 18, pregnant dams underwent laparotomy with transient uterine artery occlusion and intra-amniotic lipopolysaccharide injection (TSHIplusLPS). Rats were born at term, and juveniles underwent touch-screen operant platform testing of visual discrimination (VD) and cognitive flexibility (reversal). Black gold staining was performed to analyze myelin and qPCR to assess mRNA. P-value below 0.05 was considered significant.

Results: At postnatal day 15, myelin-debris spheroids were increased in cortex from TSHIplusLPS animals compared to shams (n=3-4, p=0.007), concomitant with decreased myrf transcription factor mRNA levels (n=7-8, p=0.02). These pathological changes were less prominent in white matter. Touchscreen testing revealed sham (n=6) and TSHIplusLPS (n=18) animals have intact VD, however TSHIplusLPS animals demonstrate significant impairment in VD reversal. During reversal TSHIplusLPS animals commit significantly more errors (p=0.03) and exhibit more perseveration (p=0.008), consistent with impaired cognitive flexibility and reduced executive function.

Conclusion: For the first time in an animal model of perinatal brain injury, we demonstrate impaired executive function using a touch-screen platform, a highly translatable method of reliable cognitive testing also used in humans. Impaired cognition correlates with regional susceptibility to injury, specifically, gray matter myelin loss. Only through deciphering molecular mechanisms of impaired cognition can we potentially restore cognitive abilities with novel therapeutic strategies.

839. Creation of Novel Hi-Fidelity Patient-Specific 3D Printed Models for Simulation of Minimally Invasive Neurosurgery

Roberta Rehder, MD; Peter Weinstock, MD, PhD; Sanjay Prahbu, MD; Alan Cohen, MD (Boston, MA)

Introduction: Rapid advances in optics and miniaturization have opened the door to the field of Minimally Invasive Neurosurgery. In selected cases, minimally invasive procedures can enhance operative exposure, reduce trauma to the brain and expedite patient recovery. However, such techniques are not risk-free. Conventional methods for training in these techniques are ineffective. Using 3D printing technology, we have developed patient-specific models of non-communicating hydrocephalus for the simulation of endoscopic third ventriculostomy. The models are highly realistic, reusable, reliable and cost-effective.

Methods: Our 3D models were designed with realistic intraventricular landmarks, including the foramen of Monro, choroid plexus, septal and thalamostriate veins, mammillary bodies and third ventricular floor. Lifelike vascular pulsation and CSF flow were incorporated. A simulation-based training protocol was developed and neurosurgery residents were enrolled in the course in our Minimally Invasive Neurosurgery laboratory.

Results: Participants assessed the trainer's face and content validity. Two neurosurgeons blindly evaluated the subjects' performance based the Objective Structured Assessment of Technical Skills for Surgery scale. Preliminary data suggest that this is a powerful tool to improve the acquisition of technical skills in Minimally Invasive Neurosurgery.

Conclusion: We have developed novel hi-fidelity patient-specific 3D printed models for training in Minimally Invasive Neurosurgery, using a structured curriculum. This technology has the potential to transform the teaching and practice of Minimally Invasive Neurosurgery, and, possibly, of all aspects of neurosurgery. This initiative is ideally suited to complement residency education and enhance operative performance through simulation-based training.

840. Development of Validated Computer Based Preoperative Predictive Model for PJF or Clinically Significant PJK

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Introduction: PJF and PJK are significant complications. Specific drivers behind their development remain unclear. This study attempts to develop a preoperative predictive model to identify patients at risk to develop PJF or PJK.

Methods: Inclusion criteria: age ≥ 18 , ASD, ≥ 4 levels fused. Variables included: demographics, primary/revision, use of 3-column osteotomy, UIV/LIV levels, anchor(screw/hooks), # levels fused, baseline sagittal radiographs (PT, PI, PI-LL, TK, and SVA). PJF defined as requiring revision for PJK, and PJK defined as increase from baseline of PJK $<20^\circ$ and deterioration by at least 1 SRS-Schwab sagittal modifier grade from 6wks postop. An ensemble of decision trees were constructed using the C5.0 algorithm with 5 different bootstrapped models, and internally validated via a 70:30 data split for training and testing. Accuracy and the area under a receiver operator characteristic curve (AUC) were calculated. Final model utilized 13 preop variables.

Results: 510 patients were included, with 357 for model training and 153 as testing targets (PJF:37, PJK:102). Overall model accuracy was 86.3% with AUC of 0.89 indicating a good model fit.

The 6 strongest (importance ≥ 0.95) predictors were (% target): age (<64 yrs, 41.4%), PI-LL ($<48.7^\circ$, 35.6%), UIV (T10–L3, 35.1%), SVA ($<13.5^\circ$, 32.5%), LIV (sacroiliac, 31.6%), and UIV Type (screws, 29.8%). If a patient met these criteria, they had a 66.7% chance of developing PJF or PJK with deterioration of sagittal alignment.

Conclusion: A successful model was built predicting either PJF or clinically significant PJK. This model can set the groundwork for preop point-of-care decision-making, risk stratification, and need for prophylactic strategies for ASD surgery.

841. Surgical Resection of Intradural Extramedullary Spinal Tumors: Patient Reported Outcomes and Minimum Clinically Important Difference

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Introduction: Patient-reported outcomes (PROs) metrics are vital in establishing the value of spine care. There is limited availability of prospective, quality studies reporting PROs among patients undergoing surgery for intradural extramedullary (IDEM) tumors. We sought to determine relative validity, responsiveness and minimum clinically important difference (MCID) thresholds in this unique a group of patients.

Methods: Patients enrolled in a single center, prospective, longitudinal registry were analyzed. Baseline, post-operative 3-months, and 12-month PROs were recorded: Oswestry Disability Index (ODI) or Neck disability Index (NDI), EuroQol-5D (EQ-5D), Short-form-12 item health survey (SF-12), numeric rating scale pain scores (NRS), and North American Spine Society (NASS) satisfaction questionnaire. Responders were defined as those who achieved level of improvement 1 or 2 on health transition index (HTI) of SF-36. Receiver-operating characteristic curves were generated to assess validity of PROs. Responsiveness was defined as the difference between standardized response means (SRMs) in responders vs. non-responders. MCID thresholds were derived using previously reported minimal detectable change (MDC) approach.

Results: Total 40 tumors were resected via an open, posterior approach. A significant improvement across all PROs at 3-months and 12-months follow-up was noted. 86% of patients were able to return-to-work and 85% were satisfied with surgery. The derived MCID thresholds were: 13.9 points for ODI/NDI, 0.14 quality adjusted life years for EQ-5D, 2.8 points for SF-12PCS and 10.7 points for SF-12MCS, 1.9 points for back/neck pain, and 1.8 points for leg/arm pain. SF-12 PCS was the most accurate discriminator of meaningful improvement (AUC-0.83) and most responsive (SRM-1.36) to postoperative improvement. EQ-5D, ODI/NDI, NRS-BP and LP were all accurate discriminator (AUC-0.7-0.8) and responsive measures (0.97–0.67) of meaningful postoperative improvement. SF-12MCS was neither a valid discriminator (AUC-0.48) nor a responsive measure (SRM:-1.5) of outcome.

Conclusion: Surgical resection of IDEM tumors provides significant and sustained improvement in PROs at 12-month following surgery. This is the first comprehensive study that provides validated PROs, clinically meaningful thresholds, satisfaction and return to work in these relatively rare spine tumors.

842. Graft Subsidence as a Predictor of Revision Surgery Following Stand-Alone Lateral Lumbar Interbody Fusion

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Introduction: Lateral lumbar interbody fusion (LLIF) is a less invasive option for a variety of spinal conditions especially for high-risk patient populations. The LLIF complication profile has been thoroughly described in the literature and is unique to the procedure. The LLIF is routinely performed in a stand-alone fashion, which may lead to radiographic subsidence of the graft. However, the clinical effect of subsidence remains unclear.

Methods: Retrospective review of patients who underwent stand-alone LLIF over four years. 297 patients were included. Imaging studies were examined for graft subsidence. Subsidence of 0–25% was grade 0, 25–50% grade 1, 50–75% grade 2 and $>75\%$ grade 3. Additional variables included: levels fused, DEXA T-score, BMI and routine demographic information. The data were analyzed using univariate and multivariate regression analysis.

Results: 34 patients (11.4%) had radiographic evidence of subsidence. 18 (6.1%) of these patients required revision surgery. Mean subsidence grade for patients requiring revision surgery was 2.44 compared to 0.94 for those without revision surgery ($p<0.01$). All revision surgery patients had high-grade subsidence. Seven patients (38.9%) suffered a vertebral body fracture. High-grade subsidence was a significant predictor of need for revision surgery ($p<0.05$; OR 12, 95% CI 1.29–13.6), while age, BMI, T-score and number of levels were not.

Conclusion: More than half of the patients in our single institution that developed severe subsidence following stand-alone LLIF required revision surgery. It may be advantageous to place supplementary instrumentation, either up-front or immediately after the presentation of high-grade subsidence to circumvent negative clinical sequelae.

843. Effect of Obesity on Cost and Effectiveness after Decompression with and without Fusion for Degenerative Lumbar Disease

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Introduction: Obese patients have greater co-morbidities and risk of complications, which may decrease cost-effectiveness for surgery compared to non-obese patients.

Methods: Patients undergoing elective decompression with/without fusion for degenerative lumbar pathology were enrolled into prospective longitudinal registry. Patients were defined as obese for BMI ≥ 35 . Patient-reported outcome measures (PROs) were recorded at baseline, 3-months, 12-months and 24-months postoperatively. One and two-year back-related medical resource utilization, missed work, and health state values were assessed. Resource use (direct cost) and patient/caregiver workday losses (indirect cost) were assessed to determine total cost. Mean total cost/QALY gained after surgery was assessed in obese and non-obese.

Results: 339 patients were included. There was significant improvement in pain, disability, and general health for both cohorts 2-years postoperatively ($p<0.001$). At one year, total cost was similar in obese and non-obese groups after decompression alone ($p=0.37$) and decompression+fusion ($p=0.37$). One-year QALYs gained were similar for obese vs. non-obese after decompression alone (0.45 vs. 0.32, $p=0.24$) and decompression+fusion (0.27 vs. 0.36, $p=0.24$).

At one-year, non-obese vs. obese had higher cost/QALY after decompression alone (\$43,596 vs. \$34,973, $p=0.09$), but lower cost/QALY after decompression+fusion (\$92,288 vs. \$127,886, $p=0.07$). At two years, total cost, mean QALY gained, and cost/QALY gained were similar for both cohorts after decompression alone and decompression+fusion.

Conclusion: Surgery for degenerative lumbar disease provided significant, cost-effective improvement for obese patients. At one year, cost/QALY was lower in the obese group after decompression alone, but higher after decompression+fusion as compared with non-obese. At two years these differences began to equalize; the long-term cost/QALY after both decompression alone and decompression+fusion was similar between obese and non-obese patients.

844. Is Preoperative Duration of Symptoms a Significant Predictor of Functional Status and Quality of Life Outcomes in Patients Undergoing Surgery for the Treatment of Degenerative Cervical Myelopathy?

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Introduction: Longstanding compression of the spinal cord in patients with degenerative cervical myelopathy (DCM) may result in irreversible neural tissue damage. This study aims to analyze whether a longer duration of symptoms influences surgical outcomes and to determine the optimal timing for decompressive surgery.

Methods: Three hundred and fifty patients with symptomatic DCM were prospectively enrolled in either the CSM-North America or International study at 12 sites in North America. For each patient, pre- and post-operative functional status were evaluated at 12-months using the mJOA. Duration of symptoms was dichotomized into a short and long group at several cut-offs. An iterative mixed model analytic approach procedure was used to evaluate differences in change scores on the mJOA between duration groups in 1-month increments.

Results: Our cohort consisted of 201 men and 149 women, with a mean duration of symptoms of 25.71 ± 36.68 months. In unadjusted analysis, patients with a duration of symptoms shorter than 4 months had significantly better functional outcomes based on the mJOA ($p=0.04$) than patients with a longer duration of symptoms (<4 months). On average, patients with <4 months symptom duration improved by 3.71 on the mJOA, whereas those with a duration ≥ 4 months only exhibited a 2.96 mean gain, difference of 0.75 (95% C.I. 0.03 to 1.47). Twelve months was identified as the next important cut-off beyond which patients had a significantly worse outcomes on the mJOA. In adjusted model, patients with <12 months symptom duration improved by 3.37 on the mJOA, whereas those with a duration 12 months or longer exhibited a 2.85 mean gain, difference of 0.52 (95% C.I. 0.01 to 1.03).

Conclusion: Patients who are operated on within 4 months of symptom presentation have better mJOA outcomes. It is recommended that patients with DCM are diagnosed in a timely fashion and referred early for surgical consultation.

845. Total en bloc spondylectomy outcomes for primary malignant tumors of the lumbar spine

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Introduction: Total En Bloc Spondylectomy (TES) at the lumbar spine is relatively uncommon, given that most spinal tumors present in the thoracic region and the surgical challenge associated with the unique anatomy of the lumbar spine—proximity of lumbar plexus, iliopsoas muscle, major vessels, and bowel.

Methods: A retrospective review of neurosurgical patients undergoing lumbar TES for primary aggressive/malignant tumors at a single institution between 2004 and 2014 was performed. Patient characteristics, tumor characteristics (primary pathology, Enneking stage, and Tomita Type), and surgical data were ascertained from clinical notes. Outcomes included perioperative complication rates, reoperation rates for instrumentation failure/pseudoarthrosis, disease-free survival, and overall survival.

Results: A total of 21 patients were identified and followed for an average of 51 months (range 6–117 months). The most common primary histology was chordoma in 52.4% of cases, followed by sarcoma in 19%. The perioperative complication rate was 61.9%, and the most common complication was wound infection in 23.8% of cases. Eight patients (38.1%) required reoperation for instrumentation failure/pseudoarthrosis on average 26 months after index spondylectomy; this rate was not significantly different for single vs. multi-level spondylectomy ($p=0.346$). The 5-year disease-free survival was 66.5% and the 5-year overall survival was 82%. There were no significant differences in disease-free survival and overall survival based on tumor pathology, Enneking stage, or Tomita Type by the log rank tests.

Conclusion: Although the perioperative complication rate and instrumentation failure rate after total en bloc spondylectomy is considerably high, this technique may provide a high disease-free and overall survival rate for patients with primary malignant and locally aggressive tumors of the lumbar spine.

846. Natural History of Odontoid Pseudoarthrosis managed Non-Operatively

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Introduction: While the goal of treatment of type II odontoid fracture is bony union, some advocate continued non-surgical management of minimally symptomatic older patients who have fibrous union or minimal fracture motion. The risk of this strategy is unknown.

Methods: This is a retrospective study of 74 consecutive adults with type II odontoid fracture initially managed non-surgically; particular attention was paid to patients who had orthosis removal despite absent bony fusion. The medical record was reviewed for clinical and radiographic findings at all encounters. Patients were also contacted by telephone.

Results: Of seventy-four patients managed non-surgically; 32 (43.2%) proceeded to bony fusion, 7 (9.5%) were treated surgically for persistent instability, and 35 (47.3%) had orthosis removal despite odontoid non-union on imaging. The last group had a median follow-up of 39.2 months, with 20 of 35 patients followed until death. Of these patients, one patient (2.9%) chose delayed surgical fusion despite being asymptomatic, because of his young age and active lifestyle; one patient (2.9%) had progressive myelopathy;

and one patient developed gait instability, and urinary incontinence, but did not undergo work-up for myelopathy. Chi square test found no association of tobacco use, persistent neck pain, spinal canal diameter, or flexion-extension motion <2mm with treatment failure, defined as the development of symptoms or delayed surgery.

Conclusion: Orthosis removal despite fracture non-union may be reasonable in carefully selected patients with high surgical risk. Patients should be counseled about the possibility of delayed myelopathy. Larger studies might identify risk factors for deterioration.

847. Risk factors for venous thromboembolism in patients undergoing spinal surgery

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Introduction: Patients undergoing spinal surgery are at risk for developing venous thromboembolism (VTE). We sought to identify risk factors for VTE in these patients.

Methods: The American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) database for years 2006-2010 was reviewed for patients undergoing spinal surgery, based on Current Procedural Terminology (CPT) codes. Clinical factors were analyzed to identify associations with VTE.

Results: 22,434 patients who underwent spinal surgery were identified. The rate of VTE in the cohort was 1.1% (pulmonary embolism (PE) 0.4%; deep vein thrombosis (DVT) 0.8%). Multivariate binary logistic regression analysis found twelve factors associated with VTE. Pre-operative factors included dependent functional status, paraplegia, quadriplegia, disseminated cancer, inpatient, hypertension, history of transient ischemic attacks, sepsis, and African American race. Operative factors included surgery time <4 hours, emergent case, and ASA class 3-5. A risk score was developed based on the number of factors present in each patient. Patients with a score of ≥ 7 had a 100-fold increased risk of developing VTE compared to patients with a score of 0. The receiver operating characteristic (ROC) curve of the risk score generated an area under the curve of 0.756 (95%, CI 0.726-0.787).

Conclusions: Spinal surgery patients' risk of developing VTE is informed by race, pre-operative co-morbidities, and operative characteristics. A risk score based on these factors predicts VTE rates. Many of these risks can be identified prior to surgery. Future VTE protocols should focus on prevention in these predisposed patients.

848. Efficacy of i-Factor™ Bone Graft versus Autograft in ACDF: Prospective Randomized FDA IDE Study Results

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Introduction: i-Factor™ Bone Graft (i-Factor) is a composite bone substitute consisting of P-15™; synthetic collagen fragment adsorbed onto anorganic bone mineral, suspended in an inert biocompatible hydrogel carrier. P-15™ has demonstrated fusion efficacy in dental, orthopedic, and non-human applications. We conducted a prospective, randomized, controlled, parallel, single-blinded non-inferiority multicenter pivotal IDE trial to investigate efficacy and safety of i-Factor compared to local autograft in single-level anterior cervical discectomy and fusion (ACDF) for cervical radiculopathy.

Methods: Patients randomly received either autograft (N=154) or i-Factor (N=165) in a cortical ring allograft. Success was defined as non-inferiority in fusion, Neck Disability Index (NDI) and Neurological Success endpoints, and similar adverse events profile at 12 months.

Results: At 12 months, both i-Factor and autograft subjects demonstrated a high fusion rate (88.97% and 85.82%, respectively, non-inferiority $p=0.0004$), significant improvements in NDI (28.75 and 27.40, respectively, non-inferiority $p<0.0001$) and high Neurological Success rate (93.71% and 93.01%, respectively, non-inferiority $p<0.0001$). Rate of adverse events was similar (83.64% and 82.47% in i-Factor and autograft groups, respectively, $p=0.8814$). Overall Success rate (fusion, NDI, Neurological Success and Safety Success) was higher in i-Factor subjects compared to autograft subjects (68.75% and 56.94%, respectively, $p=0.0382$). Improvements in VAS pain and SF-36v2 scores were clinically relevant and similar between groups. 81.4% of patients in both groups reported good or excellent Odom's outcomes.

Conclusion: i-Factor has met all four FDA mandated non-inferiority success criteria and has demonstrated safety and efficacy in single-level ACDF for cervical radiculopathy. i-Factor and autograft groups demonstrated significant post-surgical improvement and high fusion rates.

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