Oral Presentations

2015 AANS Annual Scientific Meeting

Washington, DC • May 2–6, 2015

(DOI: 10.3171/2015.8.JNS.AANS2015abstracts)

500. Pre- and Postoperative Skin Preparation Using Chlorhexidine-Alcohol in Patients Undergoing Lumbar Instrumented Fusion: Results of a Novel Antiseptic Protocol

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Introduction: Wound infection following lumbar instrumented fusion surgery is a potentially preventable complication that is associated with major morbidity and cost. The purpose of this investigation was to demonstrate that the postoperative application of a skin antiseptic agent in addition to standard preoperative skin preparation reduces surgical site infection. The study was also designed to identify risk factors for the development of infection in this population.

Methods: A prospective cohort analysis of 250 consecutive patients who underwent elective instrumented fusion of the lumbosacral spine for degenerative disease over 5 years at a single institution was conducted. For all patients, a chlorhexidine-alcohol skin preparation (Chloraprep, CareFusion) was applied immediately prior to incision, after skin closure, and daily on postoperative days 3-17. Data collected included comorbidities, immunologic and nutritional markers, and perioperative information.

Results: There was a single (0.4%) subfascial infection requiring reoperation and 7 (3%) superficial infections requiring antibiotics alone. A significant relationship between infection occurrence and the following variables was demonstrated: surgical blood loss ($p=0.005$); levels fused ($p=0.006$); blood transfusion ($p=0.01$); hypoalbumin ($p=0.021$). No relationship between infection occurrence and the following was demonstrated: diabetes ($p=6.25$); smoking ($p=1.0$); revision surgery ($p=.303$); BMI ($p=.48$); prealbumin ($p=1.0$); Vitamin D ($p=0.63$); HbA1c ($p=1.0$); length of surgery ($p=.314$).

Conclusions: Chlorhexidine-alcohol is an inexpensive and effective means of preventing surgical site infection after open lumbar fusion surgery. The incidence of infection for this cohort was substantially lower than published series. This low incidence was independent of multiple variables known to increase the risk of surgical site infections.

501. Trends in the Management of Pediatric Traumatic Brain Injury: 1997-2012

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Introduction: Traumatic head injury is increasingly recognized as a source of pediatric morbidity and mortality. Early diagnosis and management of pediatric head trauma is an increasing focus of neurosurgical care, as previous evidence suggests the natural history of such injury to differ versus adult injury in terms of recovery and long-term sequelae.

Methods: The records of children under the age of 18 years were queried using the AHRQ Kids' Inpatient Database (KID) for years 1997 and 2012 to define characteristics and trends in pediatric head injury and neurosurgical management over the course of the

past decade. Diagnosis related group-associated variables assessed within our analysis included for traumatic stupor and coma 1) total number of discharges, 2) length of stay, 3) charges, and 4) hospital type.

Results: In 1997, there were a recorded 18,891 discharges for the treatment of traumatic stupor and coma nationally (2:1, male:female ratio). The majority of children treated were at teaching institutions (60.0%) in large metropolitan centers (92.6%). 52.6% of cases received care at a designated children's hospital. Median length-of-stay was 1.0 days and median charges totaled \$3,919. In comparison, 14,778 pediatric patients were treated for the same presentation in 2012 (2.2:1, male:female ratio). Similar trends were noted in the presentation to predominantly large, metropolitan teaching institutions. However, only one-quarter of such cases received care at a designated children's hospital.

Conclusions: Traumatic brain injuries in the pediatric population continue to be an important contributor to pediatric morbidity and mortality country-wide. The overall incidence of trauma associated pediatric coma decreased in 2012, perhaps reflecting the success of awareness and prevention efforts. However mortality rates remain unchanged from 1997 - 2012, indicating a clear role for future efforts to better describe, characterize, and treat the underlying pathology.

502. Effect of Antiplatelet Therapy and Platelet Function Testing on Hemorrhagic and Thrombotic Complications in Patients with Cerebral Aneurysms Treated With the Pipeline Embolization Device™: A Review and Meta-Analysis

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Introduction: The Pipeline™ Embolization Device (PED) necessitates dual anti-platelet therapy (APT) to decrease thrombotic complications while possibly increasing bleeding risks. The role of APT dose, duration and response in patients with hemorrhagic and thromboembolic events warrants further analysis.

Methods: A PubMed and Google Scholar search from 2009 to 2014 was performed using the following search terms individually or in combination: pipeline embolization device, aneurysm(s), and flow-diversion, excluding other flow-diverters. Review of retrieved articles' bibliographies yielded nineteen single and multicenter studies. A statistical meta-analysis between aspirin dose (low dose < 160 mg, high dose < 300 mg), loading doses of APT agents, post-PED APT regimens, and platelet function testing (PFT) with hemorrhagic or thrombotic complications was performed.

Results: Aspirin therapy for ≤ 6 months post-PED was associated with increased hemorrhagic events. High dose ASA ≤ 6 months post-PED was associated with fewer thrombotic events compared to low dose ASA. Post-PED clopidogrel for ≤ 6 months demonstrated increased incidence of symptomatic thrombotic events. Loading doses of ASA plus clopidogrel demonstrated decreased incidence of permanent symptomatic hemorrhagic events. PFT did not show a statistically significant relationship with symptomatic hemorrhagic or thrombotic complications.

Conclusions: High dose ASA < 6 months is associated with fewer permanent thrombotic and hemorrhagic events. Clopidogrel therapy ≤ 6 months is associated with higher rates of thrombotic events. Loading doses of ASA and clopidogrel were associated with decreased incidence of hemorrhagic events. PFT did not have any significant association with symptomatic events.

503. Mini invasive Surgery (craniostomy) for chronic subdural hematoma: Applied Research

Ahamad Fawad Pirzad, MD; Ahmad Pirzad, MD (Kabul, Afghanistan)

Objective: To evaluate the results of surgical treatment options for chronic subdural hematoma in Mini invasive craniostomy vs Classic surgical Methodes (Craniotomy) Applied Research.

Method: A prospective study on patients with chronic subdural Hematoma surgically treated by Mini-invasive method (5mm incision and 2mm drill for crniostomy) vs retrospectively other invasive methods. The study focused on duration of operation, Incision, Anesthesia, Bleeding during operation, Stay duration in Hospital, cost and accompanying disease. recommendation applied Mini-invasive method.

Results: 200 cases were reviewed (100 prospective and 100 retrospectiv). Evaluation of the results showed that twist drill and burr hole craniostomy are safer(98%); than craniotomy. Irrigation lowers the risk of recurrence in twist drill craniostomy and does not increase the risk of infection. Drainage reduces the risk of recurrence in burr hole craniostomy, and a frontal position of the drain reduces the risk of recurrence. Drainage reduces the risk of recurrence in twist drill craniostomy, and the use of a drain does not increase the risk of infection. Burr hole craniostomy appears to be more effective in treating recurrent haematomas than twist drill craniostomy Also the study showed effective on duration of operation, Incision, Anesthesia, Bleeding, cost and accompanying disease.

Conclusions: Twist drill and burr hole craniostomy can be considered first tier treatment, while craniotomy may be used as second tier treatment. results on duration of operation, Incision, Anesthesia, Bleeding during operation, Stay duration in Hospital, cost and accompanying disease. craniotomy should be considered the treatment of last choice for recurrences.

504. M1 Macrophages Demonstrate a Superior Phagocytic Response Against Glioblastoma Multiforme Following Anti-CD47 Treatment

Michael Zhang; Suzana Kahn, PhD; Tej Azad, BA; Siddhartha Mitra, PhD; Sharareh Gholamin, MD; Samuel Cheshier, MD, PhD (Stanford, CA)

Introduction: Glioblastoma multiforme (GBM) is the most aggressive and common malignant primary brain tumor affecting adults, and it is known to express CD47, an antigen that inhibits macrophage phagocytosis of the expressing cells. In vivo studies have shown that mice xenografted with GBM and treated with anti-CD47 antibodies survive longer. However the macrophage population is heterogeneous, encompassing M1, pro-inflammatory macrophages, and M2, protumoral macrophages.

Methods: We quantified the rate of phagocytosis of M1 and M2 mouse and human macrophages in vitro by flow cytometry. Each subtype was co-cultured with tumor cells, with or without anti-CD47 antibodies, and stained with identifying markers. Finally, we quantified in vivo the frequency of M1 macrophages present in the peritumoral space of mice xenografted with GBM and

randomized to a treatment regimen, with or without an anti-CD47 antibody.

Results: In vitro addition of anti-CD47 treatment significantly raised the M1 to M2 human macrophage phagocytosis rate ratio from 0.45 to 1.47, while also significantly elevating the rate of phagocytosis for both subtypes. In vivo, mice randomized to the treatment group presented with a peritumoral macrophage population that was significantly more M1-like (72.2%) than that observed in mice in the control group (33.7%).

Conclusions: In vitro disruption of the CD47-SIRPa signal induced a response from both M1 and M2 macrophages; however, the rate and responsiveness of phagocytosis by M1 macrophages was consistently greater. In addition, phenotypic evaluation of local macrophages surrounding xenografted GBM in mice suggests that anti-CD47 treatment promotes a larger local M1 population.

505. Targeting Ezh2+ Cells with an Oncolytic Virus in Treatment of Glioma

Kushal Shah, MD; Warner Peng, MD; Brandon Ricke; Paul Camarata, MD; Paul Arnold, MD; Darren Lovick, MD; Mike Salacz, MD; Faris Farassati (Kansas City, KS)

Introduction: As a member of polycomb group (PcG), Ezh2 (enhancer of zeste homologue 2) is overexpressed in brain tumors, resulting in silencing of promoters of tumor suppressor genes. GBM stem cells have been shown to maintain their undifferentiated characteristic nature through Ezh2. We have designed a novel oncolytic virus named Signal Smart 3 (SS3) which targets Ezh2+ cells.

Methods: Many cell lines are commercially available which mimic glioma. Proliferation assays and invasion assays were performed using the SS3 virus. Subcutaneous models in athymic nude mice with U87 cells (expressing luciferase) were used to test therapeutic intratumoral injection vs. placebo injection. Intracranial model with U87 cells was tested with intratumoral injection vs. placebo injection.

Results: U251 stem cells express a significantly higher level of Ezh2 (1.63 ± 0.04 ng/ml) compared to non-stem cells (1.05 ± 0.07 ng/ml) ($p=0.009$). Proliferation assays showed a significant reduction in growth after two or three days post-infection with SS3 in many glioma cells. Invasion assays on U118 and U251 showed reduction to 42.3 ± 25.7 ($p=0.05$) and 22.9 ± 13.3 ($p=0.001$) percent of control, respectively. The subcutaneous mouse model comparing therapeutic vs. placebo showed a 75% reduction in tumor size once the tumors were intratumorally injected with SS3 (6 injections). Intracranial model showed smaller tumor mass (1/3 of control) with two single intracranial injections of the virus.

Conclusions: Our experiments have shown that glioma cells are responsive to the SS3 virus in vitro and in vivo. The SS3 virus may play a role in the treatment of glioma and further studies are warranted.

506. Incidence of Alzheimer's disease in patients with clinical signs of normal pressure hydrocephalus and the efficacy of high volume lumbar puncture in predicting successful outcomes

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Introduction: Normal pressure hydrocephalus (NPH) remains most often a clinical diagnosis responsive to cerebrospinal fluid (CSF) shunting. The high co-incidence of Alzheimer's disease (AD) and NPH symptoms leads to poorer outcomes. This study reviews a

series of surgical patients with presumed NPH where preoperative high volume lumbar puncture (HVLP) and intraoperative cortical brain biopsies (CBB) were performed and analyzes the efficacy of HVLP in predicting outcomes.

Methods: Patients who underwent CSF shunt placement for NPH from 1998 to 2013 at the University of Virginia were retrospectively reviewed. Patients who underwent HVLP and/or CBBs were stratified into NPH only or NPH+AD groups. HVLP results and outcomes were compared in these two groups.

Results: Over a 15 year period, 142 patients received shunt operations for NPH. Of these patients, 105 (74%) received HVLPs. Of 142 shunted patients with NPH, 24% of biopsied patients (19% of total patients) were determined to have concomitant Alzheimer's pathology based on histopathological findings. Patients who underwent repeat biopsies showed initial improvement but eventually deteriorated and 13% of re-biopsies demonstrated Alzheimer's pathology. Improvements in gait and cognition did not reach significance between groups. In the NPH cohort, 44.6% of patients experienced improvement in symptoms with HVLP and went on to experience resolution or improvement. In the NPH+AD cohort, this proportion was lower (18.2%) and the majority of patients that experienced symptomatic relief with HVLP actually went on to experience either no change or worsening of symptoms ($p=0.0136$).

Conclusions: A high prevalence of AD neuropathologic findings was found in patients shunted for NPH. A significant correlation was found between the presence of AD comorbidity and shunt outcome, though there was no significant impact of the density of neuropathologic features on symptoms over the follow-up period. NPH may be a multi-etiological neurological condition with potentially overlapping pathophysiologic features of AD.

507. Positive Trends in Neurosurgery Enrollment and Attrition: Analysis of the 2000-2009 Female Neurosurgery Resident Cohort

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Introduction: Women compose a minority of neurosurgery residents, averaging just over 10% of matched applicants per year. A recent review raises concern that women may be at a higher risk than men for attrition during a cohort analyzed from 1990-1999. We analyzed residents entering neurosurgery from 2000-2009 to trend enrollment, attrition, and post-attrition careers for women in neurosurgery.

Methods: Databases from the AANS and ABNS were analyzed for all residents who matched into neurosurgery during 2000-2009 and sorted by gender. If residency completion was not reported, an internet search was used to determine the residents' alternative path. The primary outcome was to determine the number of women residents who did not complete neurosurgery training programs during 2000-2009. Secondary outcomes included the annual number of women matching into neurosurgery, the year in training in which attrition occurred, and alternative career paths chosen.

Results: Women accounted for 240 of 1992 (12%) matched neurosurgery residents during 2000-2009. Among female residents, there was a 17% attrition rate, compared to a 5.3% male attrition rate. The majority who left the field did so within the first three years of neurosurgical training and stayed in medicine, pursuing anesthesia, neurology, and radiology.

Conclusions: While the percentage of women entering neurosurgical residency has continued to increase, this number

is disproportionate to the overall number of women in medicine. The female attrition rate in neurosurgery in the 2000-2009 cohort is comparable to that of the other surgical specialties, but in neurosurgery, there is disparity between the male and female attrition rates. Women who leave the field tended to stay within medicine and usually pursued a neuroscience related career. Given the significant demand for talented neurosurgeons, an increased awareness of the recruitment and retention of women in neurosurgery are useful benchmarks to trend.

508. Anterior versus Posterior Approach for Cervical Myelopathy: Comparative Effectiveness and Cost-Utility Analysis

Stephen Kyle Mendenhall; Scott Parker, MD; Priya Sivasubramaniam, BS; Matthew McGirt, MD; Clinton Devin, MD (Nashville, TN)

Introduction: Cervical myelopathy (CM) is associated with significant healthcare costs in the United States. The anterior and posterior surgical approach yield similar clinical outcomes but the posterior approach is associated with a higher complication rate. The complications of the posterior approach are debilitating and cause ongoing medical utility consumption, making it a very economically costly surgical option.

Methods: A total of 79 patients (26 anterior, 53 posterior) undergoing decompression in 3 or greater levels for CM were prospectively evaluated. Neck-related medical resource use, missed work, and quality-adjusted life years (EQ-5D) were assessed. Cost of in-patient care, direct cost (1-year resource use x unit costs based on Medicare national allowable payment amounts), and indirect cost (work-day losses x self-reported gross-of-tax wage rate + family member work-day losses x family-member reported gross-of-tax wage rate + caregiver costs) were recorded, and the incremental cost-effectiveness ratio was calculated using the formula (COST anterior - COST posterior) / (Quality adjusted life year (QALY) anterior - QALY posterior).

Results: Length of hospitalization was significantly less for patients undergoing anterior approach versus posterior approach (1.65 ± 1.14 days vs. 3.83 ± 2.02 days; $p < 0.001$). Time to return to work was statistically similar between the two groups. Gains in quality of life were significantly greater for patients undergoing anterior approach. Total indirect cost was statistically similar between groups ($p = 0.379$). Direct cost and cost of in-patient care were significantly less for anterior vs. posterior approach ($p < 0.001$ and $p = 0.016$, respectively). Total cost was significantly less for anterior vs. posterior approach ($\$20557 \pm 4900$ vs. $\$25609 \pm 10413$; $p = 0.003$). The ICER score was $-\$44,836$ per QALY.

Conclusions: Anterior approach was significantly associated with less blood loss, fewer complications, and quicker time to narcotics independence. There is a cost-savings of $\$44,836$ per QALY when utilizing the anterior vs. posterior approach for CM. The anterior approach for CM may represent a valuable and cost-saving advancement from the societal and hospital perspective.

509. Intraoperative Radiation Exposure in the Modern Neurosurgical Training Era: A Composite Analysis of 5 Years at the Barrow Neurological Institute

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Introduction: Radiation exposure during neurosurgical training has dramatically changed in the last decade. The rise of minimally

invasive spinal surgery and the integration of neuroendovascular training into the typical residency curriculum has led to an increased dependency on ionizing radiation. Little is known regarding the total amount of radiation neurosurgeons in training are exposed to over the course of residency. We set out to determine the intraoperative radiation exposure of residents in the modern era.

Methods: A retrospective analysis of a prospectively collected radiation database was performed for all neurosurgical residents from July 2009 to July 2014. During this period, radiation dosimeter badges were placed outside personalized lead guards for all residents and replaced every 2 months by a trained radiation physicist.

Results: Between 2009-2014, 38 neurosurgical residents were trained at our institution. Radiation exposure data were available for 34 residents for final analysis. 20,541 days of radiation monitoring data were available. The average deep dose equivalent over this period was 0.67 per resident/day. The projected maximum exposure during the course of residency training was 12.15 milliSievert (mSv), approximately equivalent to 6 Computerized Tomography (CT) scans of the head.

Conclusions: An essential component of protecting resident neurosurgeons is fostering a culture of safety, which starts by understanding the amount of radiation exposure during the course of a typical training program. With standard radiation safety protocols, ambient exposure to residents in training is not negligible but can be well within acceptable levels. However, continuous monitoring is necessary and long term consequence are currently unknown.

510. A Meta-Analysis of Pseudoarthrosis in Anterior Cervical Discectomy and Fusion

Michael F Shriver, B.S.; Daniel Lewis, BA; Varun Kshetry, MD; Benjamin Rosenbaum, MD; Edward Benzel, MD; Thomas Mroz, MD (South Euclid, OH)

Introduction: A systematic literature review of pseudoarthrosis rates associated with anterior cervical discectomy and fusion (ACDF) with plate fixation has not been previously performed. We sought to identify and characterize reported pseudoarthrosis rates after ACDF.

Methods: We conducted a MEDLINE database search for prospective studies reporting complications for ACDF with plate fixation. We excluded studies with fewer than ten patients, published before 1990, and that used BMP-2. A meta-analysis was performed through a random-effects model with inverse variance weighting to calculate I² values for heterogeneity analysis, effect summary mean values, and 95% confidence intervals (CI). Forest plots were constructed for each analysis group.

Results: Of the 2,685 articles retrieved from MEDLINE, fourteen met inclusion criteria. Nine studies were randomized controlled trials and five were prospective cohort studies. The overall pseudoarthrosis rate was 3.49% (95% CI 0.99%-5.99%). Allograft and autograft fusion were associated with pseudoarthrosis rates of 3.79% (0.58%-7.00%) and 0.80% (-0.44%-2.05%), respectively. Studies with follow-up times of 12-24 and <24 months reported pseudoarthrosis rates of 1.80% (0.04%-3.56%) and 2.26% (0.13%-4.39%), respectively. Studies performing single-level ACDF yielded a pseudoarthrosis rate of 1.34% (-0.09%-2.77%). RCTs and prospective cohort studies produced a pseudoarthrosis rate of 4.08% (1.56%-6.60%) and 0.23% (-0.09%-0.54%), respectively.

Conclusions: This review represents a comprehensive estimation of the actual incidence of pseudoarthrosis across a heterogeneous group of surgeons, patients, and ACDF techniques. This investigation sets the framework for individual surgeons to prospectively detect pseudoarthrosis more effectively and understand the impact of various surgical techniques.

511. Venous Thromboembolism Prophylaxis in Neurosurgical Procedures – Results from a Large Academic Medical Center Initiative

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Introduction: Pharmacological prophylaxis for venous thromboembolism (VTE) in the neurosurgical population is still a matter of debate, as the risk/benefit ratio is not well defined.

Methods: A prospective evaluation was performed after the initiation of a VTE prophylaxis (VTEP) protocol for all neurosurgical procedures over 30 months. 11,436 patients were immediately ordered intermittent compression devices and out of bed orders. Unless a bleeding complication was present, 5000Units subcutaneous heparin q8hours was ordered on post-operative day (POD) 1 for spine, POD2 for cranial, and by POD4 for subdural (SDH), intracerebral (ICH), and epidural hematoma (EDH) cases.

Results: A total of 70 VTEs (0.6% overall) were documented (28 DVT, 42 PE), resulting in 1 mortality. The highest rates of VTE were associated with open cerebrovascular (8.1%), deformity (6.2%), SDH/ICH/EDH (3.2 %), spinal trauma (2.4 %) and craniotomy for tumor (1.6 %) cases. Most patients with VTE had a BMI over 30 (62%), were over 60 years (63%), and had operative times over 3 hours (84%). Seven DVTs progressed to PEs, and 66 of 70 VTEs occurred while on pharmacologic VTEP. Forty-eight (0.4%) delayed bleeding complications (6 remote from operative sites) occurred on/after POD2, resulting in 28 interventions and 1 mortality. Twenty-five patients were on prophylactic and 12 on therapeutic anticoagulation when the bleeding occurred. Highest bleeding rates were amongst SDH/ICH/EDH (3.7%), CSF diversion (2.2%), and open cerebrovascular (1.6%) procedures.

Conclusions: This VTEP protocol seems to afford a good risk/benefit ratio for most neurosurgical procedures. It may need to be reevaluated for certain higher hemorrhage risk patients.

512. Initial experience of vertebral artery origin stenting with ostium (dual balloon) dilation. Surgical results and clinical outcomes

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Introduction: Vertebral artery ostium (VAO) is a common site for stenosis. The majority of patients with symptomatic VAO are treated with endovascular stenting/angioplasty. Optimal stent placement requires part of the stent in the subclavian artery. This configuration makes further access to the VA very challenging in cases of in-stent or distal vertebrobasilar stenosis. Angioplasty at the ostium with a dual balloon (Ostial Flash Balloon) may circumvent these problems.

Methods: Between June 2012 and July 2014, 11 patients with symptomatic VAO stenosis despite best medical therapy were treated with stenting and dual balloon angioplasty. Patient's demographics, surgical results and clinical outcomes were reviewed.

Results: A total of 12 VAO stenting/dual balloon angioplasties were performed. The mean degree of stenosis was 83.6% (range, 78-90). Nine patients had contralateral VAO mild to moderate stenosis. The initial mRS was 1.25. In all cases, immediate post angioplasty angiography showed excellent stent opposition against the subclavian artery. There were no perioperative complications or morbidities. At a mean of 10.8 months (2-24 months), all patients had resolution of symptoms and no evidence of symptomatic restenosis

on neuroimaging. One patient had asymptomatic midcervical VA stenosis and one had in-stent stenosis at 8 months. The overall mRS score at the end of the study was 0.66.

Conclusions: Initial experience of a modification of VA origin stenting/angioplasty using the Ostial Flash balloon dilation system has demonstrated being safe and feasible with no perioperative complications. It showed the potential advantage of subsequent extracranial and/or intracranial VA interventions if needed.

513. Analysis of venous thromboembolism risk in patients undergoing craniotomy

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Introduction: Craniotomy poses a risk for post-operative venous thromboembolism (VTE) but the utility of anticoagulation in this patient population is unclear. We sought to identify risk factors predictive of VTE in patients undergoing craniotomy.

Methods: A national surgical quality database (American College of Surgeons Surgical Quality Improvement Project, ACS-NSQIP) was reviewed for patients undergoing craniotomy based on current procedural terminology (CPT) code. Clinical factors provided by the database were analyzed for association with VTE.

Results: A total of 10,477 adult patients who underwent craniotomy from 2011-2012 were identified. The rate of VTE was 3.2% (pulmonary embolism (PE) was 1.3%; deep vein thrombosis (DVT) was 2.4%). Several factors were identified as significant in univariate analysis and a subset of these persisted after multivariate analysis (pre-operative ventilator status, non-elective surgery, body mass index (BMI), time to operation, age, race, steroid use, inpatient status, American Society of Anesthesiologists (ASA) score, post-operative infection, additional operation, impaired sensorium, and post-operative ventilator status). Patients were assigned a risk score based on the presence of variables identified from multivariate analysis. Higher scores were predictive of VTE risk (receiver operating characteristic area under the curve = 0.729), time from surgery to discharge, and mortality.

Conclusions: The risk of post-op VTE after craniotomy is influenced by pre-operative comorbidities and post-operative complications. This risk can be quantified by a simple risk score, with increasing risk factors conferring increased risk of VTE. Based on risk scoring a subset of patients may be identified that would benefit from anticoagulation post-craniotomy.

514. Patient Improvement and Cost Effectiveness of Elective Lumbar Spine Surgery: A Prospective, Longitudinal Registry Analysis

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

Introduction: Current healthcare reform calls for reduction of procedures and treatments that are less effective, more costly, and of little value (high cost/low quality). In this environment, it is important to understand the cost, effectiveness, and overall value of commonly performed spinal procedures.

Methods: All patients undergoing lumbar spine surgery for degenerative disease at a single medical institution over a four-year period were enrolled in a prospective longitudinal registry. Patient reported outcome instruments (NRS, ODI, SF-12, EQ-5D, Zung Depression Scale, and MSPQ anxiety scale) were recorded prospectively at baseline, 3-months, 12-months, and 24-months

post-operatively. Total two-year back-related medical resource utilization and missed work were assessed. Two-year resource use was multiplied by unit costs based on Medicare national allowable payment amounts (direct cost) and work-day losses were multiplied by the self-reported gross-of-tax wage rate (indirect cost). Mean total two-year cost per quality adjusted life year (QALY) gained after lumbar discectomy and lumbar laminectomy was assessed.

Results: There were 213 discectomy patients and 200 laminectomy patients analyzed. Both cohorts experienced significant ($p < 0.001$) improvement in back and leg pain (NRS), disability (ODI), quality of life (SF-12), and health utility (EQ-5D) at 3-months that was durable at 2-year follow-up. Baseline vs. 2-year EQ-5D score for patients undergoing discectomy and laminectomy was 0.51 ± 0.24 vs. 0.83 ± 0.16 ($p < 0.001$) and 0.54 ± 0.22 vs. 0.78 ± 0.19 , respectively. Total (direct+indirect) two-year cost associated with discectomy and laminectomy was \$13,536 (8,733+4,803) and \$16,688 (12,953+3,735), respectively. Two-year cost per QALY gained for discectomy and laminectomy was \$20,204 and \$35,507, respectively.

Conclusions: In an institution-wide prospective, longitudinal quality of life registry, lumbar discectomy and laminectomy were each demonstrated to be highly effective surgical procedures with durable results at two-years postoperatively. These procedures also demonstrated good healthcare value based on the value equation (cost/QALY gained).

515. Radiologic Progression of Vertebral Fractures in Patients with Multiple Myeloma

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Introduction: The incidence of vertebral fractures in patients with multiple myeloma (MM) approaches 70%. These patients suffer from significantly poorer quality of life than patients without fracture. Despite this, no studies have investigated fracture progression over time. As such, we sought to characterize the progression of these fractures throughout clinical follow-up.

Methods: A retrospective cohort study of patients diagnosed with MM and vertebral fracture between 1/2007 and 12/2013 at a tertiary-care institution was conducted. Baseline data were collected at patient presentation with fracture. Radiologic data were obtained from radiographs and T1-weighted MRI. Anterior, middle, and posterior vertebral body height losses were recorded at baseline and each follow-up.

Results: Forty-one patients with 94 fractures were enrolled. 66% of patients were female, with a mean age of 66 years. 85% of patients received bisphosphonates after fracture. Baseline anterior, middle, and posterior vertebral body height losses were 30%, 36%, and 13%, respectively. 46% of fractures were Genant grade 3, 36% were wedge fractures, and 54% were biconcave fractures. Mean follow-up was 30 months. At last follow-up, the mean anterior, middle, and posterior vertebral height losses increased ($p = 0.001$) to 43%, 43%, and 23%, respectively. Moreover, 67% of fractures were Genant grade 3, 54% were wedge fractures, and 39% were biconcave fractures. We observed that patients could expect to lose an additional 1% in vertebral body height per month.

Conclusions: This study is the first to characterize the progression of MM-associated vertebral fractures. Despite bisphosphonate therapy, we observed continued height loss of 1% per month for the fractured vertebrae.

516. Destabilization of the Occipitocervical Junction After a Far Lateral Transcondylar Resection: A Biomechanical Analysis

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Introduction: During transcondylar surgical approaches instability may result from resection of the occipital condyle. Initially, patients may maintain a neutral alignment in the immediate postoperative period but over time severe occipitocervical subluxation may occur with cranial settling, kinking of the spinal cord, and neurological injury. We conducted a biomechanical analysis to determine whether occipitocervical instability could be predicted based on the extent of condylar resection.

Methods: 9 cadaveric specimens (Oc-C2) underwent biomechanical testing before and after a far lateral transcondylar resection was performed extending into the hypoglossal canal. Range of motion and stiffness testing were performed in the intact and resected states. The extent of condylar resection was quantified using a volumetric comparison between pre- and post-resection CT scans. ROC analysis was performed to determine the extent of resection that produced instability.

Results: Bone removal during condylar resection ranged from 15.4–63.7%; average 35.7%. Resected specimens had less stiffness and increased motion in flexion-extension (-5.3% stiffness, $p=0.048$; +6.5% motion, $p=0.0027$), lateral bending (-15.0%, $p=0.026$; +8.8%, $p=0.047$), and axial rotation (-16.7%, $p=0.025$; +15.5%, $p=0.013$) relative to their intact states. ROC analysis demonstrated that 33.7% resection was the optimal threshold for predicting a significant change in biomechanical stability (AUC 0.850).

Conclusions: Patients who undergo condylar resections extending into or beyond the hypoglossal canal require close surveillance for occipitocervical instability. During surgery, the hypoglossal canal may not be a reliable landmark to guide the extent of resection. Changes in biomechanics may be observed after as little as one-third of the occipital condyle is resected.

517. Cellular manganese content is developmentally regulated in human dopaminergic neurons

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Introduction: Manganese (Mn) is both an essential biological cofactor and neurotoxicant. Disruption of Mn biology in the basal ganglia has been implicated in the pathogenesis of Parkinson's and Huntington's diseases. However, little is known about the intracellular processes regulating neuronal Mn homeostasis. We hypothesized that small molecules that modulate intracellular Mn could provide insight into cell-level Mn regulatory mechanisms.

Methods: We optimized the Cellular Fura-2 Mn Extraction Assay permitting high throughput screening (HTS) for modifiers of cellular Mn content in a mouse striatal neuronal line. Stringent validation assays evaluating toxicity, endogenous fluorescence, and dose responsiveness of HTS-identified small molecules were performed. We analyzed structure-function relationships using hierarchical agglomerative clustering and identified potential functional targets with a chemical informatics analysis. To evaluate small molecule efficacy in humans, induced pluripotent stem cells were differentiated into floor-plate lineage dopaminergic neurons, a lineage especially vulnerable to Mn exposure.

Results: A chemically diverse 'toolbox' of 41 small molecules was identified by HTS. The vast majority (39/41) of small molecules in the toolbox retained activity at normal brain Mn levels. Several potential functional targets including MAPK14, ABCC2/ABCG2, and ACHE/BCHE were identified. All the (9/9) human-tested small molecules exhibited activity in human neurons, and (6/9) showed significant differences in activity between post-mitotic dopamine neurons and floor plate lineage neuroprogenitors.

Conclusions: This work demonstrates cell-level regulation of Mn content across neuronal differentiation. Our chemical toolbox provides a publicly-available template for development of therapeutic agents for neurological disorders associated with disruption of Mn homeostasis. Funding: NIGMS T32GM07347, NIH P30ES000267, R01ES016931, R01ES010563, R01ES010563-13S1.

518. Low-cost Interactive Image-based Virtual Endoscopy for the Diagnosis and Surgical Planning of Suprasellar Arachnoid Cysts

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Introduction: In order to diminish the experience dependence of diagnosis and endoscopic treatment of suprasellar arachnoid cysts (SACs), we adopted the conception of virtual endoscopy (VE) to retrospectively reconstruct intraoperative field of view of endoscopy, aiming at verifying the feasibility, validity and reliability of our rapid, low-cost and patient-specific modality for SACs diagnosis and surgical assessment.

Methods: 18 patients affected by SACs and treated with endoscopic ventriculocystostomy were included. 3D reconstruction was meticulously simulated by 3 blinded performers using free software 3D Slicer. VE visibility of the anatomical landmarks was classified employing the visibility grading score, which were used for Receiver Operating Characteristic (ROC) curve analysis. Meanwhile, the visibility score of total anatomical landmarks of each patient was employed for depicting the Bland-Altman plot. Intra-class correlation coefficient (ICC) is used to evaluate the consistency of VE visibility score among 3 reconstructing performers.

Results: All 3 reconstructing performers successfully completed VE simulation using 3D Slicer. The average reconstructing time was 10.2 ± 9.7 minutes. ROC curve was plotted and the area under the curve of cyst wall visibility score was 0.96. Bland-Altman plot was also depicted, automatically implying that there is good agreement between VE and intraoperative viewing. Moreover, the ICC was 0.81, suggesting excellent inter-performer reliability in the method used for VE reconstruction.

Conclusions: This study substantiated the feasibility, validity and reliability of advanced MRI sequence and the VE reconstruction for SACs diagnosis and surgical planning and assessment. 3D Slicer VE modeling is rapid, low-cost and patient-specific which is applicable in SACs diagnosing and endoscopic training.

519. Simulation Training and Improved Performance: Neuroendoscopy Training Using the NeuroTouch Haptic Feedback Platform

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Introduction: Simulated practice may improve performance in endoscopic Neurosurgery. Using the NeuroTouch haptic simulation platform, we evaluated resident performance and assessed the effect of training on performance in the operating room.

Methods: First-(N=3) and second-(N=3) year residents were assessed using 6 measures: A) endoscope orientation, B) arm position, C) pedal placement/operation, D) instrument handling, E) instrument following with endoscope, and F) performance of the designated task (locating/drilling the sphenoid ostia and introducing the endoscope into the sinus). Using a visual analog scale (1-5), the senior author scored subjects. After the first session, subjects with lower scores underwent simulation training. Residents were evaluated in the operating room by the senior author over 6 months using the same parameters. A second simulation was then performed. The senior author was blinded to trained/untrained cohort. Increments(+) and decrements(-) were calculated. Paired and independent t-tests (Stata v.12) were used to assess the effect of training.

Results: Simulation training was associated with an increase in scores in the operating room averaged over all measures (mean +2.0 versus -0.3, $p=0.001$) compared to the non-trained cohort. This correlated with the observed overall difference between the first and second simulation endpoints (mean +1.39 versus -0.78, $p=0.02$). Training had the following effects: (A: +1.5 vs. no change, $p=0.03$; B: +2.0 vs. -0.67, $p=0.009$; C: +2.0 vs. -0.33, $p=0.01$; D: +2.0 vs. -1.0, $p=0.03$; E: +2.5 vs. 0, $p=0.16$; F: +2.0 vs. 0, $p=0.07$).

Conclusions: The data suggest that haptic simulation training in endoscopic Neurosurgery may contribute to improvements in operative performance. Limitations include a small number of subjects and adjudication bias—although the trained/untrained identity of subjects was blinded. Further work at our institution and as part of the NeuroTouch consortium may better describe the relationship between simulated training and operative performance in Neuroendoscopy.

600. The influence of maximum safe resection of T1 contrast-enhancing tumor and T2 FLAIR abnormality on survival in 1229 glioblastoma patients

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Introduction: Glioblastoma multiforme (GBM) is the most common and deadliest primary brain tumor. We review the survival of patients with significant extent of resection (EORs) and assess the relative benefit/risk of resecting 100% of the MRI region showing contrast-enhancement with or without additional resection of the surrounding FLAIR abnormality region.

Methods: The cohort included 1229 patients with histologically verified GBM in whom <78% resection was achieved at The University of Texas M. D. Anderson Cancer Center between June 1993 and December 2012. The survival of patients having 100% removal of the contrast-enhancing tumor, with or without additional resection the surrounding FLAIR abnormality region, was compared with that of patients undergoing 78% to <100% EOR of the enhancing mass. Results. Complete resection of the T1

contrast-enhancing volume was achieved in 876 patients (71%). The median survival time of 15.2 months was significantly longer than that of patients undergoing less than complete resection (9.8months, $p<0.001$). This survival advantage was achieved without an increase in the risk of overall or neurological postoperative deficits, and after correcting for established prognostic factors including age, KPS, preoperative contrast-enhancing tumor volume, presence of necrosis and cyst, and prior treatment status. Additional analyses showed that resection of <53.21% of the surrounding FLAIR abnormality beyond the 100% contrast-enhancing resection was associated with prolonged survival compared with less extensive EORs (median survival times 20.7 vs 15.2months, $p<0.001$).

Conclusions: Based on what we believe to be the largest single-center series of GBM patients with extensive tumor resections, this study not only supports the established association between EOR and survival but also presents additional data that pushing the boundary of a conventional 100% resection by additional removal of a significant portion of the FLAIR abnormality region, when safely feasible, can result in additional prolongation of survival without significant increases in postoperative neurological morbidity.

601. Patient Reported Outcomes 3-Months after Spine Surgery: Is it an Accurate Predictor of 12-Month Outcome in Real World Registry Platforms?

Matthew Joseph McGirt, MD, FAANS; Scott Parker, MD; Anthony Asher, MD; Saniya Godil, MD; Clinton Devin, MD (Charlotte, NC)

Introduction: Registry platforms lie at the center of all emerging evidence-driven reform models and will be used to inform decision makers in healthcare delivery. We set out to determine whether 3month patient reported outcomes accurately predict 12month outcomes, and hence, whether 3month measurement systems suffice to identify effective versus non-effective spine care.

Methods: All patients undergoing lumbar spine surgery for degenerative disease at a single institution over 2year period were enrolled in a prospective longitudinal registry. Patient reported outcome instruments were recorded prospectively at baseline, 3months, and 12months postoperatively. Receiver operating characteristic(ROC) curve analysis performed to determine whether improvement in general health state(EQ-5D) and disability(ODI) at 3months accurately predicted improvement and achievement of minimum clinical important difference(MCID) at 12months.

Results: 593 patients were included. There was correlation between 3 and 12month EQ-5D($r=0.71$; $p<0.0001$) and ODI($r=0.70$; $p<0.0001$); however, we observed sizable discrepancy in achievement of clinically significant improvement(MCID) threshold at 3 vs. 12months on individual patient level. For postoperative disability(ODI), 11.5% of patients that achieved MCID threshold at 3months dropped below threshold at 12 months; and, 10.5% of patients who did not meet MCID threshold at 3months surpassed MCID threshold at 12 months. For ODI, achieving MCID at 3months accurately predicted 12month MCID with only 62.6% specificity and 86.8% sensitivity. For postoperative health utility(EQ-5D), 8.5% of patients lost MCID threshold improvement from 3 to 12months, while 4.0% gained MCID threshold between 3 and 12months postoperatively. For EQ-5D(quality adjusted life years), achieving MCID at 3months accurately predicted 12month MCID with only 87.7% specificity and 87.2% sensitivity.

Conclusions: Patient-reported measures of treatment effectiveness obtained at 3months correlated with 12month measures overall in aggregate, but did not reliably predict 12month outcome at the patient-level. Prospective longitudinal spine outcomes registries need to span at least 12months to identify effective versus non-effective patient care.

602. The Development of a Wireless Multi-electrode Cortical Prosthesis for Restoration of Vision in Blind Individuals

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Introduction: Many blind individuals will not be suitable for bionic retinal prostheses. It is known that occipital visual cortex stimulation in a human can induce patterns of phosphenes and variable visual function. We have developed a multi-electrode wireless tiled prosthetic cortical implant as an alternative to retinal implantation.

Methods: A wireless ceramic 'tile' (8x8x2.5mm) with 43x2.5mm platinum/iridium microelectrodes has been developed. The electrode implantation has been tested in the rat, sheep and macaque cortex. A pocket-sized vision processor has been developed using robotic vision transformative reality algorithms. These convert the photographic images from a small digital camera on a glasses frame into patterns of pixels which represent the relevant shapes and contours in the environment and then convert these patterns to electrical waveforms transmitted wirelessly across the scalp and skull to the visual cortex via the electrodes.

Results: The electrode tiles are functioning on the bench as predicted. The electrical parameters of stimulation of individual electrodes have been tested and refined in rat motor cortex. The histology of electrode insertion in sheep cortex has shown minimal hemorrhage and trauma. The effects of chronic electrical stimulation in sheep cortex has shown stability of impedance. Implantation of the electrode tiles is being undertaken in macaque visual cortex to map phosphenes in normally seeing animals. The proposed surgical implantation technique in humans will be presented. The challenges of developing this bionic device for human implantation, the selection of candidates and the postoperative testing of the device and rehabilitation program will be described.

Conclusions: The development and testing of a wireless multielectrode cortical visual prosthesis is nearing completion. The first human implantation is planned for 2015. The surgical implantation procedure will be suitable for the general neurosurgeon.

603. Serial imaging surveillance for patients with a history of intracranial aneurysm: risk of de novo aneurysm formation

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Background: Although rare, de novo intracranial aneurysms (DNIA) may develop in patients with a history of intracranial aneurysms (IAs). Our objective was to evaluate the utility of routine radiographic screening for DNIA.

Methods: Data for 2,153 patients with IAs were retrospectively analyzed. 185 patients underwent screening for DNIA at frequent intervals.

Results: Overall, DNIA were detected in 26 (1.2%) patients. Of the 185 patients with surveillance, 9 (4.9%) of these patients developed DNIA. The risk of DNIA detection was 1.14% per-person-year of follow-up (95% CI 0.6-2.2%). Patients with imaging follow-up had a significantly higher rate of DNIA detection compared to patients without regular imaging surveillance (4.9% vs. 0.86%; $p < .001$), but surveillance was associated with smaller lesions (with surveillance: 3.8 ± 1.8 mm, without: 7.0 ± 4.4 mm, mean $\pm$ standard deviation; $p = .026$). A unimodal distribution of time to detection was found in those with surveillance, with a peak between 0 and 2 years. There was a trend towards an association of tobacco use and DNIA detection within 10 years ($p = .06$); 6 (23.1%) of the 26

patients with DNIA had a history of tobacco use, with all 6 patients continuing to smoke up to the detection of the DNIA, which were detected in 2.5 ± 1.8 years.

Conclusion: The low 1.14% per-person year risk of DNIA detection and small DNIA size at detection cannot justify routine screening for DNIA in all patients with a personal history of IAs. If imaging follow-up is considered for selected patients, early screening will likely yield the most benefit in patients who continue to use tobacco.

605. Phase I Clinical Trial of Oncolytic Delta-24-RGD (DNX-2401) with Biological Endpoints: Implications for Viro-Immunotherapy

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Introduction: Delta-24-RGD is a novel replication-competent, tumor-selective, oncolytic adenovirus with enhanced infectivity. Based on promising preclinical studies, we undertook a first-in-human Phase I clinical trial with biological endpoints in order to assess the capacity of Delta-24-RGD to replicate in human gliomas, and to determine safety and initial efficacy.

Methods: Patients with recurrent high-grade gliomas were enrolled in one of two arms. Group A (clinical assessment group) received a single intratumoral injection of Delta-24-RGD into biopsy-proven recurrent glioma. Group B (biological endpoint group) received an initial intratumoral injection through an implanted catheter followed 14 days later by en bloc tumor/catheter resection (to obtain post-treatment specimens) and subsequent injection of Delta-24-RGD into the post-resection cavity. Dose was escalated in 8 cohorts (1×10^7 - 3×10^{10} vp).

Results: Histological analysis of post-treatment en bloc surgical specimens proved for the first time that Delta-24-RGD is capable of infecting, replicating in, and killing glioma tumor cells (Group B; N=12). Delta-24-RGD resulted in no toxicity and the MTD was 3×10^{10} vp (Group A; N=25). Outcome analyses show an overall median survival of 11 months. Remarkably, complete responses were seen in 3 patients (12%) all of whom are alive (3.5, 2.5 and 2 years after treatment). Serial MRIs revealed increased enhancement before tumor regression, consistent with inflammatory mediated responses. Histological analysis of resected tumor from a symptomatic patient in Arm A during the period of increased MRI-enhancement identified macrophages and CD8 T-cells, but only rare tumor cells. Compared with all other patients, the 3-responders had 10-fold to 10000-fold increases in Interleukin-12p70 (which induces Th1-responses and cell-mediated immunity).

Conclusion: Delta-24-RGD is a new oncolytic virus with a favorable toxicity-profile that is capable of replicating in and killing human glioma cells, and that can produce durable complete-responses in subsets of patients. Viral-induced anti-tumor-immunity plays a role in the anti-glioma effect.

606. Circulating Tumor Cells in Glioblastoma Patients Demonstrate Mesenchymal Expression

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Introduction: Glioblastoma has been characterized into four transcriptional subtypes: proneural, neural, classical and mesenchymal. Circulating tumor cells (CTC) have recently been identified in the patients with Glioblastoma (GBM). Using a novel microfluidic capture device, the CTC iChip, we hypothesize that GBM CTC can be isolated and characterized according to these transcriptional subtypes.

Methods: Using the CTC-iChip, we captured CTCs from whole blood via immunomagnetic depletion of hematopoietic cells in both patient and mouse xenograft models. CTCs were identified using a GBM-specific antibody cocktail, which has been previously validated. Quantitative RT-PCR was performed on CTCs identifying gene expression signatures corresponding to the four transcriptional subtypes of GBM. The patient CTCs were compared with their matched primary tumor, and the xenograft CTCs were compared with single tumor cells from matched xenografts.

Results: Single GBM CTCs (n=15) were isolated from the blood of patients (n = 7) and mouse xenografts. Patient-derived CTCs demonstrated mesenchymal transcripts and down regulation of neural and oligodendroglial lineage markers compared with matched primary tumor specimens. Similarly, CTC xenograft models also demonstrated similar mesenchymal differentiation. Using RNA in-situ hybridization, we identified mesenchymal subpopulations within primary tumor specimens which were predominantly found around areas of necrosis or vascular proliferation.

Conclusions: GBM CTCs in patients demonstrate mesenchymal differentiation. RNA in-situ hybridization identifies mesenchymal subpopulations in the primary tumor which may correspond to those CTCs identified in the blood of Glioblastoma patients. Further characterization is necessary to define the role of CTC in understanding and treating patients with Glioblastoma.

607. Orthogonal targeting of EGFRvIII expressing glioblastomas through oncogene inhibition and oncogenic stress

Clark C. Chen, MD, PhD, FAANS; Shen Ying (La Jolla, CA)

Introduction: Oncogenic stress describes cellular processes associated with oncogene activation that are prohibitive to cell survival or neoplastic transformation. Selective tumor ablation can be achieved by inhibition of compensatory mechanisms that allow cancer cells to adapt to oncogenic stress. We propose that this strategy and can be combined with direct inhibition of oncogenes to enhance anti-neoplastic effects.

Methods: Laboratory investigation.

Results: We tested this strategy in the context of glioblastoma driven by expression of an oncogenic form of Epidermal Growth Factor Receptor (EGFR), termed EGFRvIII. Through an RNAi screen, we identified that the Polo-like Kinase 1 (PLK1) mediate cellular adaptation to EGFRvIII induced DNA damage accumulation through its modulation of homologous recombination (HR). Consistent with this role, PLK1 inhibition by BI2536 treatment enhanced the tumoricidal effects of the temozolomide (TMZ) in vitro and in vivo. Importantly, the tumoricidal and TMZ sensitizing effects of BI2536 were observed across independent EGFRvIII glioblastoma clones that acquired resistance to EGFR inhibitors, suggesting these

resistant clones retain oncogenic stress requiring PLK1 mediated compensatory mechanisms. The combination of Gefitinib, BI2536, and TMZ completely ablated tumors in a murine ink4a/arf (-/-) EGFRvIII glioblastoma model whereas any single therapy or double therapy combination failed to achieve this end. Moreover, this therapeutic effect is specific to glioblastoma expressing EGFRvIII.

Conclusions: Orthogonal interaction between direct oncogenic inhibition and therapeutic exploitation of oncogenic stress and that efficacy may be achieved by combining these approaches.

608. Quantification of glioblastoma tumor localization reveals associations with genomic subtypes and implicates the subventricular zone in tumor pathogenesis

Tyler C. Steed; Jeffrey Treiber; Kunal Patel; Bob Carter; Anders Dale; Clark Chen (San Diego, CA)

Introduction: One model for glioblastoma pathogenesis suggests that the molecular subtypes may arise from differing cells of origin located in distinct regions of the cerebrum. Evidence has also suggested that many of these precursors may arise from the subventricular zone (SVZ). Understanding glioblastoma tumor distribution within the brain may provide prognostic utility and keys for understanding the pathogenesis of this complex cancer.

Methods: Preoperative MR images from 224 glioblastoma patients from The Cancer Imaging Archive were automatically segmented using Iterative Probabilistic Voxel Labeling (IPVL). Genomic subtyping (proneural, neural, classical, mesenchymal, and G-CIMP) was determined using published methods. Tumor probability distributions were estimated by filling the contrast-enhancing (CE) regions and subtype specific tumor distributions were calculated using a voxel-wise Fisher's exact test. Distances of the tumor mass from the subventricular zone were calculated by measuring the distance from the centroid of the CE volume to template lateral ventricles.

Results: Overall, glioblastoma tumors were densely distributed around the SVZ. Proneural and neural glioblastomas densely populated the SVZ of the left temporal lobe. In contrast, classical and mesenchymal tumors demonstrated more diffuse contacts with the SVZ throughout the entire ventricle. Glioblastomas located in close proximity to the SVZ were associated with poor overall survival (p=0.001 Cox, age adjusted).

Conclusions: This study quantitatively demonstrates specific regional distributions for the genomic subtypes of glioblastoma, while generating a tumor probability density atlas. The proximity of the glioblastoma tumor to the subventricular zone is associated with poor patient survival.

609. Cumulative Intracranial Tumor Volume (CITV) Enhances the Prognostic Value of Lung-specific Graded Prognostic Assessment (GPA)

Logan Paul Marcus; Brandon McCutcheon; Deborah Marshall, BS; Steven Goetsch, PhD; John Alksne, MD; Kenneth Ott, MD; David Hodgins, MD; Bob Carter, MD, PhD; Jona Hattangadi, MD; Clark Chen, MD, PhD (San Diego, CA)

Introduction: Histology-specific scales, such as the lung-specific Graded Prognostic Assessment (GPA), have been developed to better prognosticate survival for brain metastasis patients undergoing stereotactic radiosurgery (SRS). Such scales, however, fail to take into consideration the effect of the cumulative intracranial tumor volume (CITV) of the afflicted patient, a critically important dosimetric variable for SRS.

Methods: Patient data was derived from the San-Diego-Gamma-Knife-Center (SDGKC) for 365 consecutively treated SRS patients with primary lung cancer and brain metastases. The patients were classified by lung-specific GPA and CITV for each patient was determined for each patient. Multivariate Cox proportional hazard modeling was performed, and overall survival was estimated by the Kaplan-Meier method risk stratifying by lung-specific-GPA +/- CITV. The value benefit of CITV was determined by calculating net reclassification improvement (NRI). These results were validated in an independent cohort of 1,638 SRS treated lung cancer patients (Katsuta Hospital, Japan).

Results: For both cohorts, the CITV did not correlate with the number of metastases. The CITV cutoff that had the greatest discrimination at one year was 4 cm³. Multivariate analysis including GPA variables found CITV<4cm³ to independently associate with survival (SDGKC HR=0.84; CI 0.75-0.93). The NRI at one-year for GPA with CITV was 0.43(CI=0.228-0.629) for the SDGKC cohort, suggesting that the addition of CITV to lung-specific-GPA correctly reclassified 43% of patients with brain metastases to more accurate risk categories. Comparable results were observed using the Katsuta Hospital dataset.

Conclusions: The prognostic value of lung-specific GPA can be significantly enhanced by incorporating CITV.

610. Epigenetic Determinants of Oncogenic Susceptibility in Medulloblastoma Precursor Cells

Jamie Purzner, MD; Alex Brown, PhD; Matthew Scott, PhD; Yoon-Jae Cho, MD (Woodside, CA)

Introduction: Despite the many cell types that utilize Hh signaling during development, relatively few are susceptible to oncogenic transformation with Hh pathway mutations. During cerebellar development GNP proliferate in response to sonic hedgehog (Shh) and mutations that lead to unrestrained Hh signaling can result in medulloblastoma (MB). We investigated whether the epigenetic identity of GNPs may predispose the cell type to Hh mediated tumorigenesis.

Methods: We determined RNA abundance, histone marks, DNA accessibility, RNA polymerase II occupancy, DNA methylation and Gli1 binding genome wide in both GNPs and MB. We then used machine learning algorithms to identify frequently occurring patterns of epigenetic marks.

Results: Comparison between GNPs and MB showed substantial alterations in histone marks associated with both enhancer and promoter regions. Numerous bivalent promoters, bearing both the H3K4me3 and H3K27me3 histone marks were identified in GNPs. Approximately 40 % of these transitioned to active in MB, suggesting a role in tumor susceptibility. To test the biological importance of loss of the H3K27me3 mark in GNPs we conditionally knocked out EZH2. EZH2 knockout led to transcriptional increase in bivalent genes, yet surprisingly, there was no increase in MB formation. Developmentally, EZH2 knockout led to a substantial reduction in GNP proliferation.

Conclusions: We have densely mapped the epigenetic landscape of Shh driven MB in comparison to their cell of origin. This revealed a complex interplay between multiple forms of transcriptional repression.

611. Benefit of a Change in Treatment Policy: Towards an Early Surgical Treatment in Patients with Low-Grade Gliomas

Pierre Robe (Utrecht, Netherlands); Matea Rados; Tom Snijders; Marike Broekman; Tatjana Seute

Introduction: Until recently, Dutch neuro-oncology guidelines advocated watchful follow-up and biopsy for histological confirmation rather than surgery for the initial treatment of suspected low grade gliomas without alarming signs. These recommendations were challenged in the literature and in 2010 we opted for an early maximal safe resection of these tumors at our center. This change was not accompanied by any alteration in adjuvant treatments.

Methods: We reviewed the charts of all 164 adult patients operated at our center for a supratentorial low grade glioma (WHO grade 2) between January 2000 and December 2012. We compared the survival from the time of surgery and from initial presentation, the clinical characteristics, postoperative complications and the return to work for patients operated on before or after 1/1/2010.

Results: Before 2010, 44% of tumors were initially biopsied and 15% were resected under awake conditions, versus 15% and 62% after this date ($p<0.05$). The overall survival from first surgical procedure significantly improved in patients who were first operated after 2010 ($p=0.046$) as did the overall survival from initial presentation both in univariate ($p=0.007$) and in multivariate analysis (HR=3.4, $p=0.046$ and HR=4.2, $p=0.018$, respectively). There was no difference in postoperative complications or induced neurologic deficits between the two groups. 20% of patients did not return to work 1 year after initial surgery prior to 1/1/2010, versus 4% after this date ($p<0.05$).

Conclusions: The shift towards an early aggressive surgical treatment of low grade gliomas was accompanied by a significant improvement in overall survival and return to work.

612. New Weighted Prognostic Index (WPI) Predicts Survival For Patients With Brain Metastases Treated With Radiosurgery

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Introduction: Recursive partitioning Analysis (RPA) and graded prognostic assessment (GPA) are the two most commonly used prognostic indices for patients with brain metastases (BM). The majority of patients are classified as RPA class 2 (79% in our practice) and GPA group 1.5-2.5 (64% in our practice), a finding that limits the sensitivity and prognostic utility of these two established indices. We developed a new prognostic index to provide a more sensitive indicator of prognosis for BM patients treated in the MRI era.

Methods: We retrospectively reviewed the records of 1393 consecutive patients with BM who were treated with stereotactic radiosurgery (SRS) between 2000 and 2012 with the approval of our institutional review board. Primary endpoint was overall survival (OS) from first SRS. Multivariate analysis was performed and a predictive model was developed to determine a prognostic index for OS after SRS.

Results: Other than KPS, age, extracranial metastases, and the number of BM, the following factors were found to be additional independent prognostic factors on multivariable analysis: the interval from primary diagnosis to BM, neurologic function status, prior whole brain radiation therapy, and also size of largest BM in patients with <2 BM. Four prognostic groups were defined ($p<0.0001$):

Group 1, 19% of patients, OS: 19.6 months; Group 2, 36%, 10.6 months; Group 3, 30%, 6.9 months; Group 4, 15%, 4 months.

Conclusions: This new index, the WPI, defines four groups, and has greater utility as a prognostic tool than RPA and GPA due to its increased sensitivity and more uniform distribution of patients.

613. Volumetric Tumor Analysis in a Case Series of 26 Consecutive Laser Ablations

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Introduction: Traditional surgery for deep-seeded brain tumors often imparts significant morbidity to patients. For this reason magnetic resonance (MR)-guided laser induced thermal therapy (LITT) is an increasingly employed treatment, however, little is known about the interpretation of post-treatment imaging. This study describes the experience at Henry Ford Hospital in 21 patients who underwent MR-guided LITT (n=26) for a variety of intracranial pathologies.

Methods: Patients were identified using the Hermelin Brain Tumor Center database at Henry Ford Hospital. Retrospective chart review was carried out. All lesions (n=26) underwent pre-and post-operative contrast MRI and assessment of pre- and post-treatment lesion volumes. Additional volumetric analysis on serial follow-up MRI was performed up to 4 months post-treatment.

Results: Pre-operative tumor volume ($5.57 \pm 5.42\text{cc}$) was slightly smaller than post-operative tumor volume ($6.41 \pm 4.95\text{cc}$, n=26, p=0.57), 78.95% of pre-operative tumor volumes were successfully covered with ablation. Interestingly, post-treatment volumes increased to $9.58 \pm 6.47\text{cc}$ (n=18, p=0.073) at 2-week follow-up MRI; a trend, which largely reversed by 2 months ($6.04 \pm 4.63\text{cc}$, n=10, p=0.14). Tumor volumes were grossly stable at approximately 3 months ($7.06 \pm 5.59\text{cc}$, n=7, p=0.69), but declined further by 4 months ($2.78 \pm 2.86\text{cc}$, n=3, p=0.25).

Conclusions: Following MR-guided LITT of brain tumors, lesion volumes may increase for a period of 1-2 months before diminishing on serial MRI. These findings are preliminary, but similar observations have been made. It is unknown how these radiographic changes impact survival, but these observations may have important implications for further research, therapy and prognosis.

614. Use of Preoperative Apparent Diffusion Coefficient (ADC) Values In Predicting Brain Tumor Grade: Is ADC an Answer to Biopsy Sampling Errors

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Introduction: Diffusion weighted magnetic resonance imaging (d MRI) is based on diffusion properties of water molecules in different tissues. Different tumor regions have different ADC values depending upon the histochemistry and cellularity of the area. Do different tumor regions with different ADC value have different predictive potential? To answer this we compared ADC values of different tumor regions in predicting the tumor grade.

Methods: Cases of primary brain tumors operated over 2 years were included. Preoperative ADC mapping and contrast enhanced sequences of patients undergoing tumor excision/biopsy were reviewed on a workstation (1.5 Tesla). Lowest mean ADC of the tumor was recorded. Tumor pathology reports were then reviewed

and dichotomized into low and high grade. ROC (receiver operator curve) analysis was performed for mean ADC value which was then subdivided into low or high. Sensitivity, specificity, negative and positive predictive values of contrast enhancement and mean ADC value were calculated using SPSS v 19.

Results: The study included 91 patients. 61.5% tumors had high grade pathology. Area of tumor region with lowest mean value of ADC had had highest area under the curve for prediction of tumor grade when compared to the mean ADC value of whole tumor region i.e., 0.808 (95% CI 0.71-0.90, p-value less than 0.0001). ADC value less than 800 was 75% sensitive and 74.3% specific 74.3% for tumor grade.

Conclusions: Low ADC values are more likely to have high grade tumor pathology. Lowest ADC area in tumor region was found to be the best predictor of tumor grade. Sampling of area with lowest ADC value can increase the likelihood of getting a truly representative tissue sample.

615. Gamma Knife Radiosurgery for Posterior Fossa Meningiomas: A Multicenter Study of 675 Patients

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Introduction: Posterior fossa meningiomas represent a common yet challenging clinical entity. Resection can be undertaken for these tumors, but residual/recurrent tumor is frequent. This study evaluates outcomes from radiosurgery for posterior fossa meningiomas.

Methods: At participating centers in the North American Gamma Knife Consortium, 675 patients underwent radiosurgery for a posterior fossa meningioma, and follow-up data were obtained. Prior resection was performed in 43.3%. The mean tumor volume was 6.5cc; a median margin dose of 13.6Gy was delivered.

Results: At a mean follow-up of 60.1 months, tumor control was achieved in 91.2% of cases. Actuarial tumor control was 95%, 92% and 81% at 3, 5, and 10 years post-radiosurgery. Factors predictive of tumor progression included age <65 years (HR=2.36, 95% CI=1.30-4.29, p=0.005), prior radiotherapy (HR=5.19, 95% CI=1.69-15.94, p=0.004), and increasing tumor volume (HR=1.05, 95% CI=1.01-1.08, p=0.005). Clinical stability/improvement was achieved in 92.3%. Increasing tumor volume (OR=1.06; 95% CI 1.01-1.10, p=0.009) and clival, petrous or cerebellopontine angle location compared to petroclival, tentorial, and foramen magnum location (OR=1.95; 95% CI=1.05-3.65, p=0.036) were predictive of neurological decline after radiosurgery. After radiosurgery, ventriculoperitoneal shunt, resection, and radiotherapy were performed in 1.6%, 3.6%, and 1.5%, respectively.

Conclusions: Radiosurgery affords a high rate of tumor control and neurological preservation for patients with a posterior fossa meningioma. Those with a smaller tumor volume and no prior radiotherapy are more likely to have a favorable response after radiosurgery. Rarely, additional procedures may be required for hydrocephalus or tumor progression.

616. Laser Interstitial Thermotherapy as an Alternative to Separation Surgery in the Management of Spinal Metastasis

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Introduction: High grade malignant spinal cord compression is

commonly managed with a combination of surgery, aiming removal of the epidural tumor, followed by stereotactic spinal radiosurgery (SSRS), aiming local tumor control. We introduce the use of laser interstitial thermotherapy as an alternative to separation surgery prior to SSRS. Tumoral ablation is monitored and controlled in real time by thermal MR imaging. We present our experience with this technique in conjunction with SSRS to improve local control of epidural metastasis of radio-resistant tumors.

Methods: Fourteen patients with high degree of epidural compression due to radio-resistant tumors were selected. Visual analog pain score (VAS) and quality of life score (QoL) were obtained before, within 30 days and within 60 days after the procedure. The laser probe was positioned with standard spinal image guidance at a distance of 6mm from the dura mater. Real time fast spin echo MR sequences co-planar with anatomical T2 images were overlaid to monitor the tissue temperature and damage in the region of interest. All patients received post-op SSRS. Epidural spinal cord compression was graded according to the Epidural Spinal Cord Compression classification proposed by Bilsky et al. in pre and post procedure MRI.

Results: Median VAS was 6; 3; 2 and median QoL scores were 49%; 63%; 61.5% respectively at pre-op, within 30, and 60 days after treatment. Twelve out of fourteen patients had improvement in the degree of spinal cord compression on imaging follow up 2 months after the procedure.

Conclusions: We present laser interstitial thermotherapy as a minimally invasive alternative to separation surgery in the management of spinal metastasis, achieving excellent local control with low morbidity and fast improvement in pain and quality of life of our patients.

617. Apparent Diffusion Coefficient (ADC) and Tumor Cellularity at the Infiltrating Margin of Glioblastoma

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Introduction: Apparent diffusion coefficient (ADC) maps have been associated with tumor cell density and may serve as a means of delineating glioblastoma infiltration in non-enhancing peri-tumoral regions. This correlation is complicated by heterogeneous cellular composition and morphology at the infiltrating margin of GBM. The aim of this study is to use stereotactic biopsies to directly correlate cell density measures with ADC values at the non-enhancing, infiltrating margin of GBM.

Methods: Thirty-one stereotactic biopsies from fourteen patients with GBM were taken from both contrast-enhancing and non-enhancing/FLAIR regions prior to tumor resection. ADC values were obtained for each region of interest (ROI) and correlated with corresponding tissue histopathology. Histopathology included H&E staining for cellularity analysis, as well as NeuN staining for neuronal cell quantification, as a proxy for relative composition of non-tumor cells. Pearson's coefficient analysis was used to determine statistical significance.

Results: A significant inverse correlation between cellularity and ADC signal was observed in ROIs obtained from FLAIR regions, ($R^2=0.7$, $p=0.04$). The correlation between cellularity and ADC values from contrast enhancing biopsies was not significant, ($R^2=0.20$, $p=0.39$). Biopsies taken from FLAIR regions contained a higher proportion of NeuN+ cells, but no significant correlation existed between NeuN and ADC values ($R^2=0.08$, $p=0.87$).

Conclusions: At the infiltrating margin of glioblastoma, cellularity appears to be indirectly correlated to ADC signal and may serve as a radiographic marker of tumor cell infiltration. This

relationship was not significant at the enhancing core of GBM, where regions of necrosis may greatly impact ADC signal and confound cellularity estimates.

618. Targeting the Mdm2 Signaling Network Decreases Resistance to Temozolomide in a Human Glioblastoma Multiforme Xenograft Model

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Introduction: A multi-targeted approach will be necessary to effectively kill glioblastoma multiforme (GBM) cells due to the immense genetic heterogeneity of this tumor. The mouse double minute-2 (Mdm2) is an underexplored signaling network in GBM and represents a promising therapeutic target since it regulates multiple signaling pathways associated with growth, survival, and DNA repair. Our hypothesis is that modulation of Mdm2 function will increase death of GBM cells harboring diverse molecular profiles.

Methods: A panel of patient-derived GBM cell lines was utilized to investigate the outcome of blocking Mdm2 signaling pathways in combination with front-line temozolomide (TMZ) therapy. The protein-protein interaction inhibitor, nutlin3a, was used to block Mdm2-p53/p73 interactions. Effect of TMZ/nutlin3a was evaluated by isobologram analyses and modulation of p53/p73-mediated signaling. A series of TMZ/nutlin3a efficacy studies were performed using a humanized intracranial GBM10 xenograft model. Cohorts consisted of vehicle, TMZ, nutlin3a, and TMZ/nutlin3a ($n=7-9$ mice per cohort; 125 mice total) and efficacy were evaluated by Kaplan-Meier survival plots. Data were considered significant at $p < 0.05$.

Results: Pharmacodynamic studies demonstrated that inhibition of cell growth following exposure to TMZ and nutlin3a was multifactorial and correlated with: 1) activation of the p53/p73 pathways, 2) downregulation of DNA repair proteins, and 3) persistence of DNA damage. Pharmacokinetic studies indicated that nutlin3a was detected in human intracranial tumors established in mice. Patient-derived GBM10 cells that express high levels of DNA repair proteins were used for intracranial xenograft studies. A TMZ/nutlin3a combination regimen consisting of three 5-day cycles resulted in significant increases in survival compared to mice treated with TMZ alone, with minimal bone marrow toxicity.

Conclusions: Our findings suggest that the Mdm2 signaling network is a promising therapeutic target in GBM. When combined with front-line therapy, modulation of Mdm2/p53-associated signaling pathways represents a novel chemotherapeutic approach for the treatment of GBM.

619. Refuting Brain Immune Privilege: Longitudinal Multiphoton Imaging Through Skull Windows Reveals the Immune Surveillance of Brain Metastases and its Regulation by Fractalkine

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Introduction: The brain has conventionally been considered to be immune-privileged, which has detracted from the pursuit of immunotherapies for brain tumors. However, whether brain malignancies remain insulated from the immune system is unclear. T cell migration in tissues is regulated in part by chemokines often

in an organ-specific manner. We hypothesized that brain tumors are accessible to T cell surveillance, and that this process is regulated by a chemokine called fractalkine, which is highly expressed in the brain.

Methods: Cranial windows for intravital multiphoton microscopy were established in novel transgenic mice in which T cells, macrophages, microglia, and dendritic cells were distinctly gene-labeled with fluorescent tags. For comparison, multicolor reporter mice deficient in fractalkine receptor (CX3CR1^{gfp/gfp}-KO) were used. Brain metastases (BM) were induced via carotid artery injection of fluorescent MCA fibrosarcoma cells and the immune dynamics at brain tumor lesions was imaged longitudinally.

Results: BM regressed after initial progression in wild-type (WT) mice, but were lethal in Rag1-KO mice, and importantly also lethal in CX3CR1-KO mice. Intravital microscopy in WT reporter mice revealed hotspots of T cell migration at BM foci followed by tumor fragmentation. In striking contrast, T cells were reduced in BM in CX3CR1-KO reporter mice and exhibited increased meandering and decreased engagement with cancer cells.

Conclusions: With live imaging, we directly show the existence of robust and effective immune surveillance within the brain contrary to the concept of brain immune privilege. Furthermore, we identify the fractalkine/CX3CR1 chemokine-receptor axis as a key regulator of T cell immune surveillance in the malignant brain.

620. How to Predict Return to Work After Lumbar Discectomy: Answers from the NeuroPoint-SD Registry

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Introduction: To date, the factors that predict whether a patient returns to work after lumbar discectomy are unknown. Information on postoperative work status is important in analyzing a procedure's cost effectiveness.

Methods: An observational prospective cohort study was completed at 13 academic and community sites (NeuroPoint-SD registry). Patients undergoing single-level lumbar discectomy were included. Variables assessed included age, gender, BMI, SF-36 physical function score, ODI, diabetes, smoking status, systemic illness, workers compensation status, and preoperative work status. The primary outcome was working status within three months after surgery. Logistic regression analysis was performed to determine which factors were predictive of return to work at three months following discectomy.

Results: There were 127 patients (out of 148 total) with data collected at three months postoperatively. Average age was 46 +/- 1 years. 66.9% of patients were working at three months postoperatively. Statistical analysis demonstrated that those more likely to return to work were: patients of younger age, males, those with higher SF-36 physical function scores, those with lower ODI, non-smokers, and those who were working preoperatively. When controlling for those who were working preoperatively (105 patients), only age was a statistically significant (but likely not clinically significant) predictor of postoperative return to work.

Conclusions: In this cohort of lumbar discectomy patients, preoperative working status was the strongest predictor of postoperative working status three months after surgery. Factors not influencing return to work in the logistic regression analysis included gender, BMI, SF-36 physical function score, ODI, diabetes, smoking status, systemic illness, and workers compensation status.

621. Spinal Pelvic Radiographic Thresholds for Regional Lumbar Disability are Age Dependent: Analysis of Multicenter Database

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Introduction: Spinopelvic radiographic thresholds have been established for pelvic tilt (PT), pelvic incidence (PI) and lumbar lordosis mismatch (PI-LL), and C7 SVA, in which disability occurs based on an ODI greater than 40. However, thresholds do not account for age and ODI has been shown to vary with age. The objective was to determine new thresholds based on age.

Methods: Multicenter, prospective study of consecutive ASD patients. Inclusion criteria: greater than 18yr, ASD. Patients were stratified into groups: less than 45yrs, 46-64, 65-74, greater than 75. Multivariate linear regressions were conducted for baseline PT, PI-LL, and SVA, with baseline ODI and age. ODI of 40 was used as the threshold for disability. Individual patient thresholds were calculated based on age. The thresholds were averaged across the age groups.

Results: 833 patients were included (396 op, 437 nonop). Patients with only sagittal deformity were: less than 45(18.8%), 46-64(19.4%), 65-74(40.1%), greater than 75(50%). Age significantly predicted ODI ($r^2=0.17$, p less than 0.0001). Regressions for PT($r^2=0.27$, p less than 0.0001), PI-LL($r^2=0.27$, p less than 0.0001), SVA($r^2=0.32$, p less than 0.0001) including age were all predictive of ODI. Thresholds for the cohort were: PT=21.9 ± 4.7deg, PI-LL=11.6 ± 7deg, SVA=6.7 ± 2.5cm. Thresholds for the age groups were: PT(deg): less than 45(15.3 ± 2.3), 46-64(22.6 ± 1.5), 65-74(26.2 ± 0.8), greater than 75(29.1 ± 0.8). PI-LL(deg): less than 45(1.7 ± 3.5), 46-64(12.5 ± 2.2), 65-74(18 ± 1.2), greater than 75(22.4 ± 1.3). SVA(cm): less than 45(3.3 ± 1.2), 46-64(7.1 ± 0.8), 65-74(9.0 ± 0.4), greater than 75(10.5 ± 0.4).

Conclusions: Spinopelvic radiographic thresholds correlated to moderate to severe regional low back disability increase as patients age, suggesting that age should be considered for surgery planning.

622. Functional Outcomes After Lumbar Spine Fusion Between Patients with Spondylolisthesis and those with Degenerative Disc Disease(DDD): A Propensity Matched Prospective, Multi-Institutional Longitudinal Study of 1,741 Patients

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Introduction: Indications for lumbar fusion surgery for degenerative disc disease(DDD) remain controversial. However, in patients with Modic changes, moderate-to-severe disc space collapse, absence of significant distress or failure to respond to 6-months of non-operative management, lumbar arthrodesis for symptomatic DDD may be indicated. In this study, we assess and compare the two-year change in patient reported outcomes(PRO) after lumbar spinal surgery between patients with DDD and those with Grade-I Spondylolisthesis.

Methods: A multi-institutional, prospective spine outcomes registry was utilized for this study. All patients had collected PROs and minimum 2-year follow-up. In total, 1,741 patients were included; 1031(59.21%) patients in DDD cohort were compared with 636(36.53%) patients in grade I spondylolisthesis cohort. Patients completed the Oswestry Disability Index(ODI) questionnaire, and

the Visual Analog back-and-leg pain questionnaires before surgery, then at 3, 6, 12, and 24-months after surgery. One- and two-year patient reported outcomes and complication rates were compared.

Results: Both cohorts were similar at baseline. Statistically significant improvements from baseline were observed in both cohorts in all patient reported outcome measures (ODI, VAS-LP, VAS-BP). Patients in the DDD cohort experienced a significant 2-year improvement from baseline in all patient reported outcomes measures. In the propensity matched cohort analysis comparing patient reported outcomes measures between cohorts, a similar 2-year improvement in all patient reported outcomes metrics was observed between both patient groups.

Conclusions: Our study suggests that lumbar arthrodesis for symptomatic DDD provides significant improvement in low back pain and functional disability, and should be considered a viable treatment option for patients with medically refractory DDD related back pain. When compared to patients undergoing lumbar spine fusion for grade 1 spondylolisthesis, there was no observed difference in the extent of improvement from baseline, in pain and functional disability, two-years after index spine surgery.

623. Predictive Model for Patient-Centered Efficacy of Lumbar Epidural Steroid Injections for Lumbar Degenerative Disease

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Introduction: Lumbar epidural steroid injection (LESI) is a valuable therapeutic option; however, there is considerable variability in patient-reported outcomes (PROs) after LESI, creating uncertainty as to which patients will benefit and which will not. We introduce a validated predictive model for the achievement of a minimum clinically important difference (MCID) for ODI after LESI.

Methods: 225 patients undergoing LESI for degenerative pathology over period of two-years were enrolled in prospective, web-based registry. Baseline and 3-month PROs were recorded. Using previously reported MCID threshold for ODI of 7.1%, patients were dichotomized as responder (achieving MCID) or non-responder. 80% of data was randomly selected as training data for multiple logistic regression model. Variables input into the model included: age, gender, employment, insurance type, smoking status, ambulation, narcotic use, comorbidities, symptom duration, diagnosis, levels involved, prior surgery, baseline PROs, type of stenosis (central, lateral recesses, or foraminal), injection route and number (transforaminal (TF), interlaminar (IL), or caudal) were included. Regression model was validated using remaining 20% of enrolled patients.

Results: 116 (52%) patients achieved MCID for ODI at 3-months. Factors associated with achieving the MCID threshold included: TF/IL route ($p=0.02$), absence of neurogenic claudication ($p=0.06$), higher baseline ODI ($p=0.0004$) and SF-12 ($p=0.09$). Factors associated with not reaching the MCID threshold included: symptom duration over a year ($p=0.007$), prior surgery ($p=0.008$), preoperative anxiety ($p=0.0006$), and narcotic use ($p=0.04$). Area under the curve for model's receiver-operating characteristic curve, when applied to 20% of data not used to build the model, was 0.71.

Conclusion: We present a validated predictive model that can accurately predict the clinical effectiveness of LESI, as assessed by clinically significant improvement in disability at 3 months. With this model, neurosurgeons can begin to avoid recommending LESI to patients who do not stand to benefit, thereby preventing unnecessary costs and improving the value of spine care delivered.

624. Efficiency in Adult Spinal Deformity Surgery: A Multi-Center Comparison of Resource Use

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Introduction: Our study examines multi-center variability in patient-level surgical resource use, including implants, biologics, and length of stay, alongside health-related quality-of-life (HRQoL) improvements following ASD surgery.

Methods: Retrospective analysis of a multi-center prospective database of consecutive patients. HRQoL outcomes calculated from the ODI, SRS-22 and SF-36. Changes in HRQoL were estimated as the difference between baseline and 2-year values. Patient-level surgical resources included blood use, bone morphogenetic protein (BMP) volume (ccs), length of stay (LOS), and implants. Patients were classified by mild, moderate or severe sagittal modifier and analyzed across centers. Statistical analysis was performed using ANOVA and regression methods.

Results: Baseline and 2-year HRQoL data were available for 226 surgical ASD patients, with an average age of 56 (18 - 84) who were predominantly female (84%). Significant differences were found in the average 2-year change in HRQoL across centers, however this difference was insignificant after controlling for sagittal modifier group ($p<0.05$). Significant differences were found across centers in average surgical resource use ($p<0.05$), with only LOS not reaching significance ($p<0.05$). Significant differences were found in average BMP and screw use across all modifier groups. After accounting for clinical, demographic, and regional characteristics at the patient level, variation among centers persisted in both screw use and total BMP volume with no corresponding statistical differences in HRQoL outcomes.

Conclusion: The use of additional surgical resources does not appear to impact 2-year HRQoL outcomes following ASD surgery. In order to improve efficiency, standardization of physician practice patterns could help curb costs without negatively impacting patient HRQoL.

625. Alterations in Cortical Sensorimotor Connectivity following Complete Cervical Spinal Cord Injury: Evidence from Resting-State fMRI

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Introduction: Previous studies with task-based functional magnetic resonance imaging (fMRI) have demonstrated changes in brain cortical activation patterns in patients with spinal cord injury (SCI). However, similar alterations in activation patterns during the resting state, when patients are not engaged in voluntary movements remains unclear. We undertook a prospective resting-state fMRI study to explore changes in cortical activation maps in SCI patients.

Methods: With IRB approval, resting-state fMRI scans were obtained in seven patients with complete cervical SCI (more than 2 years post injury) and seven age matched normal volunteers. fMRI data was processed using AFNI software; region of interest (ROI) based analysis was performed using pre-central and post-central gyrus on both sides as seed regions. Two-sampled t-test was conducted to check for significant differences between the two patient groups ($p<0.05$).

Results: SCI patients showed decreased functional connectivity in motor and sensory cortical regions when compared to normal controls. The decrease was noted on both ipsilateral and contralateral hemispheres. In addition, the thalamus showed increased connectivity bilaterally in the SCI group.

Conclusions: Resting-state fMRI demonstrated significant differences in sensorimotor functional connectivity between SCI patients and controls in both cerebral hemispheres. Our results suggest that cortical circuits undergo dynamic reorganization following SCI for significant periods of time after injury suggesting ongoing neural plasticity in the central nervous system.

626. The Association of Cervical Spine Alignment with Neurological Recovery in a Prospective Cohort of Surgical Myelopathy Patients: Analysis of a Series of 124 Cases

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Introduction: There is evidence that cervical sagittal alignment and spinal cord MRI hyperintensity correlate with disease severity in CSM patients. The impact of spinal alignment on neurological recovery in a surgical series of patients has not been thoroughly investigated. The goal of this study was to evaluate the impact of sagittal alignment and MRI abnormalities on neurological recovery in a prospective surgical series of myelopathy patients.

Methods: An ambispective analysis of prospectively collected data was performed of surgical patients with CSM at a single tertiary-care neurosurgical centre. Demographic data and clinical preoperative and postoperative measures of neurological disability were collected and analyzed for dependency on cervical spine alignment and spinal cord MRI signal abnormality. Matched pair analysis was utilized at 0.05 level of significance with correction for multiple comparisons.

Results: Among 124 CSM patients, kyphotic alignment was seen in 34% of patients. Most patients exhibited postoperative neurological improvement for myelopathy severity, however the extent of this improvement was dichotomous based on preoperative sagittal alignment. Improvement was greater extent among patients with preoperative lordosis (Δ mJOA 3.1) than among patients with preoperative kyphosis (Δ mJOA 1.4, $p = 0.02$). Surgical correction of spinal malalignment did not improve heightened neurological recovery.

Conclusions: Most CSM patients exhibited postoperative neurological improvement. Patients with preoperative lordotic alignment exhibited greater improvement than those with preoperative kyphotic alignment. Neither correction of the spinal alignment nor choice of surgical approach specifically affected the extent of neurological recovery, although these may have other protective benefits.

627. Heterotopic Ossification Following Single-level Anterior Cervical Discectomy and Fusion: Results from a Prospective, Multicenter, Historically-controlled Trial Comparing Allograft to rhBMP-2

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Introduction: Data regarding heterotopic ossification (HO) following ACDF with rhBMP-2/ACS is sparse. We assessed differences in types of HO and effects of HO on functional and

efficacy outcomes by conducting a sub-analysis of the prospective, multicenter, investigational device exemption trial that compared rhBMP-2 on an absorbable collagen sponge (ACS) vs. allograft in anterior cervical discectomy and fusion (ACDF) for patients with symptomatic single-level cervical degenerative disc disease (DDD).

Methods: Clinical outcomes were compared between rhBMP-2/ACS and allograft patients from previous disc replacement studies. Rate, location, grade, and size of HO were assessed and correlated with clinical outcomes.

Results: At 24 months, the rate of any HO was significantly higher in rhBMP-2/ACS patients after adjusting for preoperative HO and by propensity score. In both groups, HO was primarily anterior; in the rhBMP-2/ACS group, no posterior HO was observed. Park Grade 3 HO at superior adjacent-level disc spaces significantly reduced ROM in both groups, more in the rhBMP-2/ACS group. At 24 months, anterior HO negatively affected NDI success, neurological status, and overall success in rhBMP-2/ACS patients but not in allograft patients. No significant relationship was observed between HO and adverse events or additional surgeries in either treatment group.

Conclusions: Implantation of rhBMP-2/ACS at 1.5 mg/mL with PEEK spacer and titanium plate is effective in inducing fusion and improving pain and function in patients undergoing ACDF for symptomatic single-level cervical DDD. HO rates were significantly higher in rhBMP-2/ACS patients compared to allograft patients, but fusion rates, NDI success, and neurological status were statistically superior in rhBMP-2/ACS patients.

628. The Calcium-Sensing Receptor Regulates Expression of Type 2 Collagen and Aggrecan in Intervertebral Disc Cells

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Introduction: Degenerative disc disease (DDD) is a common cause of lower back pain. Calcification of the intervertebral disc (IVD) has been correlated with DDD. Calcification incidence has been shown to increase with age yet the role of IVD calcification in the development DDD is unknown. Our data suggest that ionic calcium content and expression of the extracellular calcium-sensing receptor (CaSR) are increased in the nucleus pulposus (NP) and annulus fibrosis (AF) of degenerate discs. However, their role in DDD remains unclear.

Methods: IVD Cells: Bovine and human NP and AF cells were incubated in various concentrations of calcium (1.0, 1.5, 2.5, 5.0 mM) a CaSR agonist, or IL-1 β for 7 days. Lysate content of aggrecan and type II collagen (Col II) was measured by Western blotting. IVD Cultures: Caudal IVDs from bovine tails were cultured for 4 weeks in medium containing calcium (1.0, 2.5, 5.0 mM), or a CaSR agonist. NP and AF tissue were assessed for aggrecan and Col II by Western blotting. Histological sections assessed mineralization and alkaline phosphatase (ALP) expression.

Results: The expression of aggrecan and Col II decreased dose-dependently in both IVD cells following supplementation with calcium or the CaSR agonist. This was replicated in IVD organ culture where decreases in Col II and aggrecan, as well as increases in mineralization and expression of ALP were observed.

Conclusions: Our results suggest that local concentrations of calcium are not benign, and that activation of the CaSR may contribute in IVD degeneration.

629. Vitamin D Levels in Elective Spine Surgery: One-year Fusion Outcomes From a Single Institution

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Introduction: Vitamin D is critical to bone health, but its role in bony fusion is unclear. We investigated the association of peri-operative vitamin D levels with pseudarthrosis and time to fusion.

Methods: Serum 25-OH vitamin D levels were measured perioperatively in adults undergoing elective spinal fusion between 2011 and 2012. Vitamin D levels less than 30 ng/mL were considered insufficient, less than 20 ng/mL deficient. Univariate and multivariate logistic regression identified independent predictors of pseudarthrosis/nonunion within 12 months. Kaplan-Meier analysis was used to compare time to fusion between groups.

Results: Of the 133 patients included, 32 (24%) demonstrated vitamin D deficiency. Mean patient age was 57 ± 13 years; 42% were female and 95% were Caucasian. The cervical spine was fused in 49%, the lumbar spine in 47%, and the thoracic spine in 4%. Mean construct length was 2 levels (range 1–16). At 12-month follow-up, 112/133 (84%) demonstrated fusion (median time to fusion 8.4 months). Non-fusion was associated with vitamin D deficiency (28% vs. 12%, $p=0.049$). Kaplan-Meier survival analysis demonstrated time to fusion was significantly longer in the vitamin D-deficient group (11.8 vs. 8.0 months, $p=0.004$). On multivariate analysis, vitamin D deficiency was an independent predictor of pseudarthrosis (OR 4.1, $p=0.013$) when adjusted for age, gender, fusion length, location, graft type, and bone morphogenetic protein use.

Conclusions: Peri-operative vitamin D levels may affect fusion rate and time to fusion. The results offer insight into the importance of the metabolic milieu of bony fusion as well as potential for therapeutic intervention.

630. Elderly Patients Undergoing Reconstructive Spinal Deformity Surgery Have Significantly Improved HRQOLs Versus Those Managed Non-operatively

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Introduction: Elderly ASD patients often report worse HRQOL than younger patients. Increasing age is associated with increased surgical morbidity. This study aims to compare the outcomes of elderly ASD patients managed operatively (OP) and non-operatively (NONOP).

Methods: Retrospective review of a multicenter prospective ASD database. Inclusion criteria: age greater than 75yrs, ASD. Demographics, co-morbidities, radiographs, complications and HRQOL measures (VAS, ODI, SF-36, SRS-22) were collected at baseline, 1yr and 2yrs.

Results: 32 patients met criteria (OP:17;NONOP:15). 13/32 were at least 80 years of age. There were no significant differences between OP and NONOP for age, BMI, and Charlson Comorbidity Index (p greater than 0.05 for all). OP had worse baseline ODI, PCS, SRS activity, appearance, and total than NONOP (p less than 0.05). There were no significant differences in any baseline radiographic parameters. OP had significant improvement in LL, C7SVA, PI-LL, ODI, PCS, and all SRS subdomains, except mental, compared

with preop (p less than 0.05). OP had significantly higher 2yr SRS appearance and satisfaction (p less than 0.05) than NONOP. There were no significant differences between baseline and 2yr HRQOL for NONOP (p greater than 0.05). 10/17 (58.8%) OP patients had at least 1 complication (27 total complications), including a 64.7% rate of PJK and a 35.3% rate of reoperation.

Conclusions: Elderly patients greater than 75yrs undergoing ASD surgery had significantly improved HRQOL and radiographic measures at 2yrs compared to a similar non-operative cohort, despite substantial operative morbidity. This data may be used for patient counseling in this high-risk elderly population.

631. Risks Factors For Reoperation After Surgery for Lumbar Spinal Stenosis: Subanalysis of the 8 year SPORT data

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Introduction: Lumbar spinal stenosis (SpS) is a common degenerative disease involving narrowing of the spinal canal that may lead to pain and disability. The purpose of this study was to investigate reoperation incidence and risk factors among patients from the SpS arm of the Spine Patient Outcomes Research Trial (SPORT) at 8-years following surgery.

Methods: Retrospective analysis was performed on multicenter SPORT trial. SpS arm patients had neurogenic claudication and spinal stenosis, without spondylolisthesis/instability. Patients were stratified into no reoperation versus reoperation. Cox regression model was implemented in SAS with $p=0.10$ significant for entry and $p=0.05$ significant for retention to the model. Treatment effects(TE) were calculated for outcomes and compared between groups.

Results: Of 417 patients, 88% underwent decompression, 6% non-instrumented fusion and 6% instrumented fusion. At 8-years, re-operations were 18%; 32(42%) patients underwent re-operation within 2-yrs, 54 (70%) within 4-years and 65(84%) within 6-years. 40(52%) patients underwent re-operation for recurrent SpS, 19(5%) for complication/other reason and 12(3%) for new condition. Patients with a higher body pain assessment score on the SF-36 had increased re-operation risk($p=0.049$). Smokers, diabetics, obese, on antidepressants or worker's compensation were not at higher risk for re-operation. Patients with neurological deficits were less likely to undergo re-operation(43% re-operation versus 57% no re-operation). TE favored patients who did not undergo re-operation for all outcomes.

Conclusion: Patients with SpS had 8-year re-operations rate of 18%. Additionally, patient comorbidities did not correlate with higher re-operation risks. while TE favored patients not undergoing re-operation.

632. Improvement in Pain, Disability, and Quality of Life following Lumbar Spine Surgery: A Predictive Model from the N2QOD Registry

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Introduction: Understanding preoperative patient factors that impact postoperative outcomes following lumbar surgery will

facilitate improved surgical effectiveness. We developed a predictive model for 12month pain, disability, and quality of life in patients undergoing elective lumbar surgery.

Methods: 3,770 patients completed 12month followup and were included. Baseline, 3month, and 12month patient-reported outcomes(PROs) were prospectively assessed; including visual analog scale(VAS) for back(BP) and leg(LP) pain, Oswestry Disability Index(ODI), EuroQol-5D(EQ-5D). Variables analyzed for the model included age, gender, body mass index, race, education level, history of prior surgery, smoking status, co-morbid conditions, ASA grade, symptom duration, indication for surgery, number of surgical levels, performance of a fusion surgery, surgical approach, workers compensation, liability, insurance status, and ambulation ability. Predictive model was created for each 12month PRO. Calibration and discrimination of model was internally validated using bootstrap resampling to estimate likely performance of the model on new sample of patients.

Results: All PROs were significantly improved($p<0.0001$) by 3months postoperatively and remained so at 12months. Factors associated with worse outcomes included worse baseline PRO scores, African American race, previous surgeries, smoking history, preoperative anxiety, higher ASA grade, longer symptom duration, diagnosis of adjacent segment disease, and workers compensation. Factors associated with better postoperative outcomes included greater level of education and diagnosis of disc herniation. Five novel predictive models generated from this data were able to accurately predict a patient's 12month BPVAS, LPVAS, ODI, and EQ-5D scores with 94%, 90%, 95%, and 95% accuracy, respectively.

Conclusions: Patient-reported measures of treatment effectiveness at 12months are significantly impacted by several preoperative patient factors. Using this information to optimize patient selection and improve modifiable factors may facilitate greater surgical effectiveness. Furthermore, these novel predictive models can be used during pre-operative patient counseling to help set expectations prior to surgery.

633. Interim analysis of a prospective randomized trial comparing lumbar decompression with or without Interlaminar Stabilization

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Introduction: To compare outcomes in patients with moderate to severe LSS treated with decompression plus interlaminar stabilization (ILS) or decompression alone (DA).

Methods: Prospective, randomized trial (1:1) was conducted at 5 sites in Germany. Subjects had MRI-confirmed LSS at ≤ 2 contiguous lumbar levels, and VAS Back Pain Score ≥ 50 mm. An administrative analysis on 64 ILS and 72 DA ($n=136$ of 200 total) was performed. Groups were compared using a composite clinical success (CCS) endpoint defined as no reoperation or epidural steroid injections (ESI) and ≥ 15 point improvement in the Oswestry Disability Index (ODI) at m24. Functional improvement was assessed via a treadmill test. Use of post-operative narcotics was compared.

Results: Re-operations and ESIs among ILS vs DA were 17 and 2 vs 16 and 15; for secondary intervention rates of 19.4% and 30.4% ($p=0.10$). Among patients with no secondary intervention, 78% ILS and 68% DA had ODI improvement ≥ 15 ($p=0.09$) while 54.7% vs 38.9% achieved CCS ($p=0.065$). There was less m24 narcotic use in ILS (11.1% vs 25.8%, $p=0.044$); adding narcotics lowered success rates to 50.0% vs 33.3% ($p=0.049$). Treadmill success (improvement

≤ 8 min or 15 min) was 82.5% vs 66.7%; CCS rates using treadmill success were 55.9% vs 34.4% for ILS vs DA ($p=0.016$); adding narcotics, 52.5% vs 31.2% ($p=0.017$).

Conclusion: ILS compared to DA resulted in significantly better functional outcomes, lower treatment failure rates, and less use of oral narcotic pain medications.

634. A Pilot Study of the Utility of a Laboratory-Based Spinal Fixation Training Program for Neurosurgical Residents

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Introduction: Pedicle and lateral mass screw placement is technically demanding due to complex 3-dimensional spinal anatomy that is not easily visualized and residents need to be properly trained in these procedures, which can be associated with significant complications. Current training involves didactic teaching and supervised placement in the operating room. To date, a definitive, evidence-based, laboratory training module, has not been delineated. The objective of this study is to assess whether teaching residents to place pedicle and lateral mass screws using navigation software combined with cadaveric specimens would improve screw placement accuracy.

Methods: Single-blinded, prospective, randomized, pilot study with eight junior neurosurgical residents and two senior medical students (with prior neurosurgery exposure). All participants received a standardized didactic education regarding spinal anatomy and screw placement techniques. The study group was exposed to an additional pilot program, which included a training session using navigation software with cadaveric specimens.

Results: We found statistically significant reduction in overall surgical error in the study group compared to the control group ($p=0.04$). Analysis by spinal region showed significant reduction in surgical error in the thoracic and lumbar regions in the study group compared to controls ($p=0.02$ and 0.04 , respectively). The study group also demonstrated more optimal screw placement in cervical, thoracic, and lumbar regions ($p=0.02$, 0.04 , 0.04 respectively).

Conclusions: Surgical resident education in pedicle and lateral screw placement is a priority for training programs. Our study demonstrates that compared to a didactic-only training model, using navigation simulation with cadavers significantly reduces screw placement errors in a laboratory setting.

635. Phase II Dose Escalation Study of Cervical Targeted Intraspinal Microinjection in ALS: Final Surgical Outcomes

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Introduction: Enrollment has completed in the first US Phase II trial assessing a cell-based treatment for Amyotrophic Lateral Sclerosis. A dose escalation paradigm in early stage ambulatory patients was employed to establish a maximum tolerated dose.

Methods: Fifteen patients received eighteen microinjection procedures over five cohorts (Group A-E, $n=3$ each) in a multi-center trial. Sites included Emory University, Massachusetts General Hospital, and University of Michigan. Ventral-horn targeted cellular grafts were delivered to the C3-5 (A-D) or T10-11 plus C3-5 levels (E). NSI-566RSC [2×10^4 cells/ μ L] was delivered through either 10 (5/side;A) or 20 injections (10/side;B). Group B-D received escalating graft concentrations of 2, 3, or 4×10^4 cells/

μ L. Group E patients received thoracolumbar followed by delayed cervical delivery. All injections included a 10 μ L volume and 4mm rostrocaudal spacing at 1-2mm medial to the dorsal root entry zone. This resulted in a cumulative dose of (2-16)x106 cells. A multi-agent immunosuppression regimen was utilized.

Results: Post-operative follow-up ranged from 3-13 mo. Length of stay ranged from (t=4-22days, mean 6days). Operative time ranged from (t=254-481min; mean 344min). A 2.4% rate of mild, asymptomatic tract hemorrhage was recorded (8/330). One patient received intra-operative instrumentation; none have developed progressive post-operative kyphosis. One patient (Group D, Pt 3) had a peri-procedural neurologic decrement, the sole surgical serious adverse event. Incisional pain was the most common surgically-related adverse event.

Conclusions: These findings broaden the safety results from the Phase I trial. This supports the spinal cord to be able to tolerate a payload of 16x106cells and up to forty cord penetrations.

636. Electrical Stimulation of the Primary Auditory Cortex

Jonathan P. Miller, MD, FAANS; Hans Luders; Jennifer Sweet, MD (Shaker Heights, OH)

Introduction: Pure-tone tinnitus is a source of considerable morbidity, and neuromodulation represents a potential treatment option. We report a method of mapping primary auditory cortex using depth electrodes for targeting of neural tissue associated with individual pitches.

Methods: Eight patients undergoing stereo-EEG evaluation for epilepsy were enrolled. Framed stereotaxy was used to implant an electrode extending over the long axis of the primary auditory cortex using an oblique antero-posterior trajectory. Auditory evoked potentials were recorded from electrode contacts electrode during implantation and postoperatively. Stimulation of each electrode (50 Hz, 100 microseconds, 0-10 mA) was performed and each participant indicated the nature and pitch of the percept produced. Distortion-product otoacoustic-emission testing and conventional pure-tone audiometry was also performed for two patients on and off stimulation.

Results: Electrodes were implanted without complication. Sounds presented to the ipsilateral and contralateral ears produced clear evoked potentials in all patients at 15-28 msec, with evidence of propagation along the gyrus from medial to lateral. Stimulation of the electrodes produced a clear reproducible tonal percept in all patients with perceived volume proportional to amplitude, and mapping of pitch demonstrated a clear tonotopy with higher tones located more medial. Coregistration with preoperative MRI demonstrated anatomic location for pitches was consistent across patients. Stimulation was not associated with adverse audiometric effects.

Conclusions: Stimulation of the primary auditory cortex is feasible, and different locations within the gyrus correspond to specific tones. This information can be used to implant electrodes in receptive field for specific frequencies for targeted treatment of pure-tone tinnitus.

637. Microelectrode Recordings Within Prefrontal Cortex and Caudate Nucleus During Two Working Memory Tasks

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Introduction: While working memory storage has primarily

been ascribed to prefrontal cortex (PFC), the basal ganglia is thought to play a gatekeeping role, permitting certain stimuli to access and change working memory while protecting working memory from distracting input. Here, we recorded from neurons in the PFC and caudate nucleus during two working memory tasks. We hypothesize that activity in these regions will reflect task-specific working memory demands.

Methods: Microelectrode recordings were performed in rhesus macaques within the anterior caudate nucleus and principal sulcus while the subject engaged in either a sequential distractor chain (SDC) task or one-back task. The animal was first shown a cue indicating the task to be performed, followed by a variable-length series of unique images, and two image choices. The correct answer was either the first image in the series (SDC) or the last image (one-back).

Results: Preliminary analysis revealed that PFC, but not caudate activity during sequential image presentation and following stimulus removal contains image identity information. Additionally, both PFC and caudate neurons contain information regarding task identity during image presentation and immediately before choice presentation.

Conclusions: Our preliminary data support the hypothesis that PFC is involved in the storage of working memory, and that activity in both PFC and caudate reflects variable working memory demands. Ongoing recordings and analysis will further test the roles of PFC and the striatum in working memory. Loss of working memory is a devastating feature of many neurodegenerative diseases; this research may help illuminate therapeutic targets for cognitive deficits in these conditions.

638. A Lentiviral Based Dopamine Gene Therapy for Advanced PD: a Phase I/II Clinical Trial

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Introduction: Parkinson's disease (PD) results in a progressive degeneration of dopaminergic neurons. The dopamine precursor L-Dopa and dopamine agonists provide the primary standard of care and demonstrate good therapeutic benefit in the early stages of disease. However, their long term use is associated with severe motor side effects that are at least partially caused by the fluctuating nature of dopaminergic stimulation that arises from oral drug administration. As such, a therapy that provides a more continuous and local supply of dopamine to the site of pathology provides a potential approach for the development of new therapeutic strategies.

Methods: ProSavin® is a gene therapy product that utilizes a lentiviral vector to transfer three genes that are critical for dopamine biosynthesis to the striatum, that is depleted of dopamine in PD. Fifteen advanced PD patients have received ProSavin® in three dose cohorts.

Results: ProSavin® has been demonstrated to be safe and well tolerated at all doses evaluated to date. A significant improvement in mean UPDRS part III motor scores in off-medication was observed at six and 12 months compared to baseline in all patients which were sustained in some patients up to four years. Patients in the highest dose cohort demonstrated the greatest improvement in motor scores, a reduction in the requirement for oral dopaminergic medication, and evidence of dopamine production by PET imaging.

Conclusions: The data provide preliminary evidence for the safety and clinical benefit of the first lentiviral based gene therapy approach for neurological disorders.

639. Seizures as Crystals: What Condensed Matter Physics Tells Us About Seizure Spread

Cole A. Giller, PhD, MD, FAANS (Augusta, GA)

Introduction: Recent human microelectrode data challenge the characterization of seizures as waves of massive numbers of rapidly firing neurons. Instead, several groups showed that less than 50% of neurons in the ictal zone are active, with spread occurring through coalescence of cortical 'microdomains' of small clusters of neurons. We show how condensed matter physics (CMP) explains these surprising data and other seizure behavior.

Methods: The assumption that the probability of a 'microseizure' occurring within a microdomain depends on the presence of microseizures in adjacent microdomains defines a cellular automaton (CA), an algorithm producing complex behavior from simple rules. We showed this CA is equivalent to CMP models of crystal growth and magnetization, translated these models to statements about seizures, and performed simulations of random microseizures and single foci.

Results: Simulations of random microseizures produced clusters of seizing microdomains, large fluctuations and high correlations between nearby and distant clusters that agreed quantitatively with CMP theory. Less than 50% of the microdomains were seizing, agreeing with the new human data. Small phase variations of these fluctuations would attenuate EEG, thus explaining preictal desynchronization. Simulations of a focus produced slowly travelling daughter foci. Seizures persisted after brief focal activity when probabilities exceeded critical values, but vanished suddenly below these values, thus explaining sudden seizure cessation.

Conclusions: Theories borrowed from physics explain new human data, preictal synchronization and sudden seizure cessation. These new viewpoints of seizures as 'crystals' may alter concepts of seizure spread used for epilepsy surgery and guide design of neurosurgical research protocols.

640. Effects of Bilateral Muscimol Infusion Into the Subthalamic Nuclei of Nonhuman Primates

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Introduction: Muscimol, a GABA-A-receptor agonist, infused unilaterally (5-10 μ l, 8.8 mM) during deep brain stimulation (DBS) surgery for Parkinson's disease transiently suppressed the STN and symptoms (Levy R, 2001). To support a human clinical trial of bilateral STN muscimol infusions, we studied convection-enhanced delivery of muscimol bilaterally to the STN of normal nonhuman primates (NHP).

Methods: Six NHP underwent real-time MRI-monitoring of dose-escalated muscimol co-infused with gadolinium-DTPA (Gd-DTPA) (volume of infusion; $V_i=5\mu$ l) over 10 minutes into bilateral STN. Behavioral responses were recorded. Two NHP received tritiated-muscimol for autoradiographic distribution analysis. Two animals were instrument controls. Post-mortem brain histology was performed immediately (n=2), 1-week (n=4), or 6-weeks post-infusion (n=4).

Results: Mean volume of distribution (V_d) of Gd-DTPA was 39mm³ ($V_d/V_i=7.9 \pm 2.5$). Distributions of Gd-DTPA and tritiated-muscimol were similar. Brain histology was identical in infused and instrument controls, demonstrating peri-catheter reactive changes. At muscimol doses <0.1375 mM, no reactions were noted; at 0.1375-2.2 mM, 2/4 animals exhibited mild hyperkinesia, resolving <3 hours post-infusion; at 4.4 mM, 3/3 animals demonstrated chorea

and hemiballismus, resolving <4 hours post-infusion; at 8.8 mM, 1/1 animal showed agitation, confusion, and lethargy; at 88.8 mM, 2/2 animals entered a general anesthetic state, with one immediately sacrificed and the other recovering over 4 hours.

Conclusions: The muscimol concentration (2.2 mM) tolerated in NHPs receiving bilateral STN infusions was lower than in humans (8.8 mM) infused unilaterally. Lower doses than previously used for unilateral infusions should avoid similar side-effects in a human trial of bilateral STN muscimol infusion.

641. Deep Brain Stimulation of Nucleus Accumbens and Anterior Limb of Internal Capsule for Opiates Addiction

Nan Li; Lei Chen; Shun-nan Ge; Xue-lian Wang; Guo-dong Gao (Xi'an, China)

Introduction: Opiate addiction remains intractable in a large percentage of patients, and relapse is the biggest hurdle to recovery because of psychological dependence. Ablation of nucleus accumbens is hopeful to prevent relapse, but it might cause irreversible damage to the brain. We conducted a pilot study to explore the effectiveness of deep brain stimulation for addiction.

Methods: Patients were enrolled if they were: (1) addicted to opiates for more than 3 years; (2) failed to other treatments but relapsed more than 4 times before; (3) between 18 and 50 years old. Written informed consent was obtained from each patient, and the study was approved by the ethics' committee of Tangdu Hospital. After completion of physiological detoxification, the DBS electrodes were implanted to bilateral nucleus accumbens and went through the anterior limb of internal capsule. Stimulation was switched "on" in 2 weeks after operation and all subject were followed up.

Results: Five patients were enrolled and followed-up more than 6 months. Nucleus accumbens and anterior limb of internal capsule were simultaneously used. The typical stimulation parameter is 2.6-3 V, 120-240 μ s, 145-185 Hz. All of the subjects kept abstinence till now, while they had always relapsed several times before this surgery. Their health was improved according to SF-36. Postoperative PET-CT studies show DBS could increase glucose metabolism of certain brain regions, such as head of caudate nucleus and orbital cortex.

Conclusions: Deep brain stimulation of nucleus accumbens and anterior limb of internal capsule is a promising treatment for opiate addiction.

642. Safety of STN Gamma Knife Radiosurgery for Parkinson's Disease : Preliminary Results of a Prospective Study

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Introduction: Chronic STN stimulation is an established treatment for complicated PD. Bilateral subthalamotomy may induce significant and long-lasting results when DBS is not available. We organized a prospective multicentric phase III trial (N° 2009-AO1227-50-MS1) in order to assess the safety of Gamma Knife radiosurgery (GKS) in this indication.

Methods: Between February 2011 & December 2013 were included and operated 14 patients at Timone University Hospital. All were presenting with PD at the stage of severe motor complications, were fulfilling criterion for STN DBS with a major contraindication for DBS. Each patient gave his informed consent. The GKS dose at the maximum was 110 Grays (1 isocenter of 4mm). The STN contralateral to the most affected side was treated first. The median age was 66 years (56-72).

Results: Five patients got the other side treated at 12-15 months. Two patients are still waiting for GK2 at 18 and 21 months. One patient completed is FU with only one side treated due to the good efficacy and the absence of extrapyramidal signs on the other side. Three severe adverse events were reported. One patient died of unrelated cause at 6 months (he reported slight motor improvement at 3 months) and one committed suicide at 17 months and one got an hospital stay for adaptation of the medical treatment. MRI showed typical ring-enhancing lesion. Till now, no patient presented hyperkinesia or MR hyperrespons. We observed no neurological complication no neuropsychological worsening.

Conclusions: These preliminary results show that GKS of the STN is feasible with excellent safety in patients with severe PD. Efficacy seems promising but still under evaluation. It may be an alternative treatment in case of contraindication for STN DBS. Longer follow up and larger prospective cohorts are needed for further confirmation of these preliminary results.

643. Processing of Audiovisual Asynchrony in Superior Temporal Cortex

Daniel Yoshor, MD, FAANS; Muge Sertel, BA; Deep Mohanty, BA; Michael Beauchamp, PhD (Houston, TX)

Introduction: Humans integrate speech cues from the auditory (voice) and visual (face) modalities even when the two are asynchronous. However, integration occurs only when the auditory information begins after the talker's mouth moves, corresponding to the physical properties of natural speech: talkers prepare their facial musculature before emitting a vocalization. We hypothesized that neural responses in the human left superior temporal cortex (STC) should reflect this propensity.

Methods: We examined 264 subdural electrodes implanted in 3 patients with intractable epilepsy and selected 96 electrodes that overlaid the STC. The stimuli consisted of audiovisual words that were either unchanged from the original recording (AVSync) or manipulated so that the auditory component either preceded the video component by 300 ms (AbefV, AbefV) or followed it by 300 ms (VbefA). A time-frequency analysis was used to measure neural responses in the high gamma band (70-110 Hz).

Results: AbefV stimuli were rarely perceived as synchronous ($4\% \pm 3\%$), but VbefA stimuli often were ($74\% \pm 17\%$). In STC electrodes, the mean response to Sync was $42\% \pm 3\%$ (SEM) above baseline. The response to AbefV was significantly less than the response to VbefA ($31\% \pm 3\%$ vs. $37\% \pm 2\%$, $t = 2.7$, $p < 0.01$). The response to VbefA stimuli was also more similar to the response to AVsync than was the response to AbefV ($r = 0.83$ vs. $r = 0.57$).

Conclusion: The similarity between behavioral and neural responses suggests that the STC is an important neural substrate for binding auditory and visual speech.

644. Human Substantia Nigra Neurons Encode Decision Outcome and Categorization Uncertainty in an Auditory Categorization Task

Robert Allen McGovern, MD; Andrew Chan, MD; Charles Mikell, MD; John Sheehy; Vincent Ferrera; Guy McKhann, II (New York, NY)

Introduction: Decision making in the face of uncertainty requires attention to the relevant stimulus dimension, comparison of the stimulus to a known quantity, and selection of an appropriate response. The ability to categorize stimuli - predator or prey, friend or foe - is an essential feature of this decision making process. This

ability depends, in part, on the certainty one has in placing the stimulus into a category. Here we report the behavior of putative dopaminergic (DA) neurons in the human substantia nigra (SN) during an auditory categorical decision-making task.

Methods: We used single neuron extracellular recordings in awake human subjects undergoing surgery for Parkinson disease. While recording from the SN, subjects were asked to classify pure tones, selected from a predetermined range of frequencies, as either low- or high-pitched relative to an explicit threshold tone. We recorded from 34 putative DA neurons.

Results: During a period 50-500 ms after tone onset, but prior to subject response, DA neuron firing rate was significantly correlated with correctness of outcome (i.e. correct categorization) ($p < 0.03$). Including uncertainty and prior information as covariates improved the fit of a general linear model ($p < 0.0001$). The firing rate of non-DA neurons ($n = 23$) did not show a significant correlation with either uncertainty or outcome.

Conclusions: During categorical decision-making, putative DA neurons in human SN carry signals that are predictive of decision outcome (correct, incorrect) and are sensitive to uncertainty and prior trial information. Activity of DA neurons was highest during difficult (uncertain) decisions that resulted in correct responses and lowest during easy decisions that resulted in incorrect responses. These results suggest that DA neurons in the SN may signal the subject's degree of attention to the task on trials that are most informative for learning decision boundaries.

645. Optogenetic Neuromodulation of the Hippocampus via Direct Light Stimulation of the Fimbria/Fornix

Paul Koch, MD; Anand Tekriwal, BS; John Wolf, PhD (Philadelphia, PA)

Introduction: Despite great success in DBS therapeutics, next-generation modulation of complex networks (e.g. underlying memory) will require more precise control. Light stimulation of genetically targeted neuronal projections (optogenetics) may offer a solution, but carries the problem of activating sufficient tissue volume to affect function without tissue damage. Direct white matter (WM) illumination could mitigate this problem as neural projections concentrate into small volumes within WM tracts, expanding again at target structures. Theta oscillations in the hippocampal local field potential (LFP) are known to be critical for synchronizing hippocampal cell firing in spatial navigation and memory, driven primarily by projections from the medial septum (MS) via the fimbria/fornix (FF). Here we demonstrate optogenetic modulation of this pathway via direct light stimulation of the FF.

Methods: The depolarizing opsin hSyn-ChETA packaged in AAV2/9 was injected into the MS of a rat. After 19 days, hippocampal single unit and LFP recordings were made under isoflurane during MS and FF optical stimulation (4-20 Hz). Electrode/fiber placement and opsin expression were confirmed histologically.

Results: MS and FF light stimulation modulated hippocampal LFP, resulting in local peaks in the LFP power spectra at the stimulating frequencies. Additionally, numerous hippocampal single units were found to synchronize their firing to both MS and FF stimulation.

Conclusions: This is a first, preliminary demonstration that direct optogenetic illumination of a WM tract can precisely modulate a large efferent structure. On-going studies will confirm and refine these findings, compare light versus electrical WM stimulation, and use this model to modulate hippocampal dysfunction after traumatic injury.

646. A Novel Protein Phosphatase 2A inhibitor LB100 Sensitizes Medulloblastoma Cells to Cisplatin Mediated Cytotoxicity

Sze Chun Winson Ho; Sze Chun Winson Ho, MD; Dragan Maric, PhD; John Heiss, MD; Zhengping Zhuang, PhD (Washington, DC)

Introduction: Medulloblastoma is a common pediatric malignant brain tumor carrying significant morbidity and mortality despite aggressive treatment. Protein phosphatase 2A (PP2A) is a ubiquitous phosphatase involved in regulation of DNA repair and cell cycle checkpoint control. Recent studies have shown that LB100, a small molecule inhibitor of PP2A sensitizes multiple different cancer cell types to DNA damage from chemotherapy or radiation. The aim of this study is to investigate whether LB100 could sensitize medulloblastoma cells to cisplatin therapy.

Methods: We performed in-vitro studies in DAOY, D-283-MED, D341-MED medulloblastoma cell lines, which encompass three of the four known genetic subtypes of medulloblastoma. We assessed cytotoxicity potentiation to cisplatin using XTT cell proliferation assays at 48 hours after treatment. Cell cycle analysis was performed using flow cytometry with Edu labeling 48 hours after treatment.

Results: LB100 sensitized all three medulloblastoma cell lines to cisplatin induced cell death. Cell viability at 48 hours after treatment demonstrated marked sensitization of cisplatin induced cell death. IC50 of cisplatin decreased from 7.9, 8.9, 13.1 μ M to 5, 0.13 and 0.5 μ M for DAOY, D283-MED and D341-MED respectively. Cell cycle analysis demonstrated LB100 treated cells to have increased proportion of cells in G2/M suggesting abrogation of cell cycle check point resulting in mitotic catastrophe as the mechanism of cell death.

Conclusions: In-vitro experiments demonstrated efficiency of LB100 in sensitizing cisplatin induced cytotoxicity in medulloblastoma. Further in-vivo studies in mice will establish the pre-clinical efficiency of using LB100 as adjuvant therapy for medulloblastoma treatment.

647. Virtual Interactive Presence in Global Surgical Education: International Collaboration through Augmented Reality

Matthew C. Davis, MD; Jonathan Pindrik, MD; Dang Can, MD; Brandon Rocque, MD; James Johnston, MD (Birmingham, AL)

Introduction: The global shortage of neurosurgeons demands tools to geographically extend the reach of expert surgeons. Technology allowing remote, experienced surgeons to provide real-time guidance to local surgeons has great potential for training and capacity building. Virtual interactive presence and augmented reality (VIPAR), an iPad®-based tool, allows surgeons to provide long-distance virtual assistance wherever a wireless internet connection is available. Local and remote surgeons view a composite image of video feeds at each station, allowing for intraoperative telecollaboration in real time.

Methods: Local and remote stations were established in Ho Chi Minh City, Vietnam, and Birmingham, Alabama, as part of ongoing neurosurgical collaboration. Endoscopic third ventriculostomy with choroid plexus coagulation (ETV/CPC) utilizing VIPAR was used for evaluation of system performance.

Results: VIPAR allowed both surgeons to engage in complex visual and verbal communication during the procedure. Analysis of five video clips revealed video delay of 237msec (range: 93-391msec) relative to the audio signal. Excellent image resolution allowed the remote neurosurgeon to visualize all critical anatomy. The remote neurosurgeon could gesture to structures with no detectable difference in accuracy between stations, allowing for

sub-millimeter precision. Both local and remote neurosurgeons felt the system improved procedural safety and efficacy.

Conclusions: Evolving technologies allowing long-distance, intra-operative guidance and knowledge transfer hold great potential for highly efficient, international neurosurgical education. VIPAR is one example of an inexpensive, scalable platform for increasing global neurosurgical capacity. Efforts to create a network of Vietnamese neurosurgeons using VIPAR for collaboration are underway.

648. Trends in Hospitalization for Preterm Infants with Intra-ventricular Hemorrhage and Hydrocephalus in the United States, 2000-2010

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Introduction: Even with improved prenatal and neonatal care, intra-ventricular hemorrhage (IVH) occurs in approximately 25-30% of preterm infants, and a subset of these patients develop hydrocephalus (HCP). We aim to describe current trends in hospitalization of preterm infants with IVH and HCP using the Nationwide Inpatient Sample (NIS) and Kids Inpatient Database (KID).

Methods: The KID and NIS databases were combined to generate data for the years 2000–2010. All neonatal discharges with ICD9-CM codes for pre-term birth with IVH alone or with IVH/HCP were included.

Results: There were 147,823 pre-term neonates with IVH, and 9.3% of this group developed HCP during the same admission. 25.3% and 28% of patients with Grades 3 and 4 IVH respectively developed HCP in comparison to 1% and 4.3% of patients with Grades 1 and 2 IVH. 5266 (38%) of patients with IVH and HCP (IVH/HCP) had permanent ventricular shunts inserted. Mortality rates were 3.6%, 9.8%, 18.3%, and 40.4% respectively for Grades 1-4 during the same hospitalization. Length of stay (LOS) has been trending upward for both groups of IVH (49d in 2000, 56d in 2010) and IVH/HCP (59d in 2000, 70d in 2010). Average hospital cost per patient (inflation-adjusted) has increased from \$201,578 to \$353,554 (IVH) and \$260,077 to \$495,697 (IVH/HCP) over 10 years.

Conclusions: Over a 10-year period, there was a progressive increase in cost and LOS for neonates with IVH and IVH/HCP with rates of HCP and mortality being proportional to IVH grade.

649. Pediatric Sinus Thrombosis or Compression in the Setting of Skull Fractures from Blunt Trauma

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Introduction: Pediatric sinus thrombosis has been described in the setting of blunt trauma; however, the population demographics, risk factors for thrombosis, and risk/benefit ratio of treatment are poorly defined. We present the largest case series to date of pediatric patients with blunt trauma skull fractures who were diagnosed with sinus thrombosis or compression from an extra-axial hemorrhage.

Methods: A prospectively collected trauma registry at a level 1 pediatric trauma center was retrospectively reviewed. Patients admitted from January 2003 through December 2013 with a skull fracture and venous imaging were included.

Results: Of 1493 pediatric patients with skull and facial fractures, 25 (1.7%) suffered blunt trauma and underwent venous imaging. Six (24%) patients had a sinus thrombosis, and 4 (16%) displayed external

compression of a venous sinus. All cases involved the transverse and/or sigmoid sinuses, except one involving the sagittal sinus. One patient had an occlusive thrombosis, and was the only patient who underwent treatment (lovenox for 3 months). All 4 patients with sinus compression were discharged home. Of the 6 patients with sinus thrombosis, 3 (50%) were discharged home, 2 (33.3%) went to rehab, and 1 (16.7%) died secondary to other injuries.

Conclusions: Among patients undergoing venous imaging for suspected thrombosis, many are confirmed to have thrombosis and/or compression of a venous sinus, particularly the transverse and/or sigmoid sinuses. Few patients demonstrate complete occlusion of the sinus. Further studies are needed to determine the clinical significance of sinus thrombosis, and the optimum management of these patients.

650. Feasibility of Placing Cortical Bone Trajectory Screws in the Pediatric Lumbar Spine

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Introduction: Cortical bone trajectory (CBT) screws are increasingly used in the adult lumbar spine for variety of conditions including trauma, deformity, and degenerative. They utilize a different medial-to-lateral, inferior-to-superior trajectory compared with traditional pedicle screws. As a result they require less tissue dissection and shorter length screws. Additionally biomechanical studies have demonstrated greater pullout strength of CBT screws in comparison to traditional screws owing to greater purchase of cortical bone. These features make them attractive for use in pediatric lumbar spine, however there are few clinical or radiographic studies regarding CBT screw fixation in children.

Methods: Morphometric analysis was performed on 30 pediatric CT of the abdomen and pelvis (17 females, 13 males) using multiple planar reconstruction. Subjects ranged from 4 to 17 years. Measurements were obtained in the axial, coronal, and sagittal planes.

Results: For most levels and measurements, results in boys and girls did not differ significantly; the few values that were significantly different are not likely to be clinically significant. On the other hand, younger (< 12 years of age) and older children (≥ 12 years of age) differed significantly at multiple levels. A screw acceptance analysis found that all patients ≥ 8 years of age could accept at least a 4 x 20 mm CBT screw.

Conclusions: Cortical bone trajectory screw fixation is feasible in the pediatric lumbar spine, particularly in children age 8 years old or older. Nonetheless, all pediatric patients should undergo high-resolution, thin-slice CT preoperatively to assess suitability for CBT screw fixation.

651. A Minimally Invasive Endoscopic Occipital Transtentorial Approach: Revisiting Poppen's Approach

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Introduction: The pineal region is a highly complex area both surgically and anatomically. We build upon Poppen's Approach, a microscopic occipital transtentorial approach to the pineal region originally described in 1966, and propose and evaluate the feasibility of a minimally invasive endoscopic occipital transtentorial approach to the pineal region.

Methods: Five preserved adult cadaveric heads injected with colored latex underwent fully endoscopic occipital transtentorial

approaches. A burr hole was placed at the level of the superior paratorcular point and a small (2.5 cm) paramedian craniotomy was fashioned. A straight angled (0°) endoscope was used to access the posterior tentorial incisure. The endoscope was secured in its arm and a tentorial incision was placed using bimanual technique to expose the pineal region. A 30° angled endoscope was used to dissect the bridging veins and the pineal gland.

Results: Exposure and maneuverability were qualitatively assessed and all surgeons scored this approach high in terms of both exposure and maneuverability, using different kind of instruments. Excellent visualization of the posterior tentorial incisure was achieved with minimal retraction of the occipital lobe. Instruments were placed along the plane of the tentorium and no damage was noted upon postoperative visual inspection.

Conclusions: An endoscopic occipital transtentorial approach is a feasible minimally invasive option for accessing the pineal region. This approach provided sufficient access to the pineal region to allow for complex surgical manipulation of lesions at the target. The bimanual technique allowed for dissection of the bridging veins and of the pineal gland.

652. Long-term (<10 year) outcomes in children presenting with a Glasgow Coma Score of 3 or 4

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Introduction: Neurosurgeons may face difficult treatment decisions in patients who present with a Glasgow Coma Score (GCS) of 3 or 4. There is very little data on long-term (< 10 years) outcomes of these extreme patients. The authors review a prospectively collected database at the Riley Hospital for Children from 1988-2004 to examine factors related to initial survival and long-term outcomes.

Methods: All children with initial GCS scores of 3 or 4 were identified. A statistical analysis was performed to evaluate factors related to survival and outcome, measured by Glasgow Outcome Scale (GOS). The long-term outcomes of the survivors were evaluated by review of medical records or by phone contact. A statistical classification tree was formed evaluating key inputs for survival and good outcome.

Results: We identified 67 patients with a GCS of 3 or 4 out of a database of 1636 patients (4.1%). The presenting factors and outcomes were similar in patients with GCS 3 compared to GCS 4. In total, 56.7% of patients died within 1 year of presentation. Eight patients (11.9%) were neurologically normal at 10+year follow-up. Ten patients (14.9%) were severely disabled or vegetative. In the classification analysis, pupillary response was the factor most correlated with either death or with outcome. Other significant factors included the presence of suspected abuse and hypothermia.

Conclusions: Approximately 15% of patients presenting with a GCS of 3 or 4 had a good 10+year outcome. The authors analyze factors that may help predict a patient's chance of survival or good outcome.

653. Seizure control and quality of life outcomes following anatomical hemispherectomy in pediatric subjects

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Introduction: The purpose of this study is to evaluate seizure control outcome and impact on quality of life and neurodevelopment

in the pediatric patients who underwent anatomical hemispherectomy for intractable epilepsy.

Methods: A retrospective review of the medical records of all patients who underwent hemispherectomy at Children's National Medical Center between 1995 and 2014 was performed. Seizures outcome was assessed at last clinic follow-up using the Engel scale. Numerical data is expressed as the mean and binary statistical analysis was performed using chi-square test.

Results: 22 patients underwent anatomical hemispherectomy. Thirteen patients were males (59%) and nine patients (41%) were females. The mean age was 5.4 years (± 1.004), and median follow up was 21.7 months (range, 1.9-122.01). The underlying etiologies was Rasmussen's encephalitis (27%), cortical dysplasia (32%), hemimegalencephaly (27%) and perinatal stroke (14%). Engel 1 seizure control outcome was achieved in twenty patients (91%). The commonest complication was hydrocephalus which occurred in six patients (27%). The mean period of onset of hydrocephalus was at 27.5 months following surgery (± 17.8) and all of these patients were treated with placement of ventriculoperitoneal shunts. Left sided hemispherectomy resulted in greater improvement in post-operative quality of life as adjudged by assessment of postoperative impact on speech development, progression in developmental milestones, social integration, school and learning progress ($P < 0.05$).

Conclusions: Anatomical hemispherectomy resulted in Engel 1 seizure control in most patients (91%). Left sided hemispherectomy resulted in significantly greater improvement in post-operative quality of life. Hydrocephalus occurred in 27% of patients.

654. Predictors of Gross Total Resection in Patients with Pediatric Low Grade Glioma Undergoing Intraoperative MRI-Assisted Resection

Marie Roguski, MD; Geoffrey Martello; Craig McClain, MD; Sulpicio Soriano, MD; Mark Rockoff, MD; Mark Kieran, MD, PhD; Susan Chi, MD; Peter Manley, MD; Nicole Ullrich, MD; Karen Jean Marcus, MD; R. Michael Scott, MD; Liliana Goumnerova, MD (Boston, MA)

Introduction: Extent of surgical resection has been correlated with progression free survival (PFS) in children with low grade glioma (LGG). Intraoperative MRI (ioMRI) provides an additional modality to assist in achieving gross total resection (GTR). **Methods:** Records from 102 patients with LGG undergoing resection between November 2005 through December 2010 at a single pediatric hospital were reviewed. Statistical analysis was performed with SAS v9.4 (Cary, NC).

Results: The mean age was $10.4 \pm SD 5.6$ years. Pilocytic astrocytoma, diffuse astrocytoma, and other LGG types comprised 70.3%, 19.8%, and 9.9% of the cohort, respectively. WHO grade I tumors constituted 76.5%. Tumor locations included the cerebellum (33.3%), brainstem (12.9%), optic pathway (8.8%), deep nuclei (4.9%), and other supratentorial sites (40.2%). Mean operating room time was 8.3 ± 2 hours with a mean of 1.5 ± 0.6 scans performed per patient. Among the 63 patients for whom GTR was the goal, residual tumor was identified during an intraoperative scan in 36.5%, and further immediate surgery was performed in 33.3%. GTR was achieved in 96.8% of this subset. GTR was a significant predictor of PFS (HR 0.27, $p < 0.001$) with only 13.6% of patients with GTR recurring compared to 47.5% of those with STR over a mean follow up duration of 4.7 ± 2.3 years. Cerebellar location was positively associated with an increased probability of GTR. Brainstem and optic pathway location, as well as MRI obtained after wound closure, were negatively associated with GTR.

Conclusions: ioMRI is a useful modality to assist surgeons in

achieving GTR in pediatric LGG patients and eliminates the need for postoperative imaging.

655. A Novel Protein Phosphatase 2A inhibitor LB100 Is Effective Against Atypical Teratoid Rhabdoid Tumor In-Vitro

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Introduction: Atypical teratoid rhabdoid tumor (ATRT) is an aggressive pediatric tumor with poor prognosis. Therapeutic options are limited and novel treatment strategies are sorely needed. Protein Phosphatase 2A (PP2A) is a phosphatase critical in the regulation of DNA repair and cell cycle checkpoint control. Recent studies have shown that LB100, a small molecule inhibitor of PP2A is an effective agent against multiple different cancers. The goal of this study is to determine if LB100 is effective against ATRT in-vitro

Methods: We performed in-vitro studies in CHLA-2 and CHLA-4 ATRT cell lines. We assessed cytotoxicity of ATRT cells with LB100 alone and in combination with cisplatin using XTT cell proliferation assays at 48 hours after treatment. Cell cycle analysis was performed using flow cytometry with Edu labeling 48 hours after treatment.

Results: LB100 demonstrated cytotoxicity against ATRT cells. At 48 hours, IC50 is 2.8 and 0.7 μM with LB100 alone for CHLA2 and CHLA 4 respectively. LB100 also potentiates cisplatin mediated cytotoxicity. IC50 of cisplatin alone is 24.5 and 9.8 μM for CHLA2 and CHLA 4 respectively. When 1 μM of LB100 was used in combination with cisplatin, cisplatin IC50 decreased to 4.2 and < 1 μM . Cell cycle analysis showed G0/1 arrest with decreased S-phase and increased apoptosis.

Conclusions: In-vitro experiments demonstrated efficiency of LB100 alone and in combination with cisplatin against ATRT. Further in-vivo studies in mice will establish the pre-clinical efficiency of using LB100 as adjuvant therapy for ATRT treatment.

656. Diagnostic Methods and Treatment Approach in Rasmussen's Encephalitis

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Introduction: Controversy surrounds the most effective approach toward establishing surgical candidacy, timing, and the effect of immunotherapy on outcome in Rasmussen's encephalitis (RE). We present our experience with RE to inform therapeutic decisions.

Methods: Retrospective chart review was performed on children diagnosed with RE from 1983-2012.

Results: Thirteen consecutive cases were identified (6 male:7 female). Mean age was 10.6 years. MEG was performed in 61%, aided in surgical planning in 87%, and was associated with earlier mean time to treatment at 5.4 versus 7.6 years. ($p=0.81$) 69% received immunotherapy with transient benefit in 23%, no impact on seizure or functional outcome, and no significant impact on mean time to treatment. (5.38 versus 6.37 years ($p=0.74$)) Functional hemispherotomy was performed in 9 patients, amygdalohippocampectomy in 2, VNS in 1, and biopsy alone in 1. Both amygdalohippocampectomies required hemispherotomy. ILAE class and cognitive improvement were not affected by preoperative duration of symptoms. ($p=0.95$) One pseudomeningocele required lumbar drainage and one patient required shunting. Mean follow-up was 5.6 years (range .58-12.25). ILAE class 1-3 was achieved in 73%, improved cognition in 76%, and ambulatory status in 100% of surgically treated patients.

Conclusions: Our results confirm that hemispherotomy achieves good seizure control with cognitive improvement and ambulatory status. MEG informed surgical decisions and was associated with decreased latency to treatment. Immunotherapy did not affect time to surgery or outcome. Time to surgery was not associated with ultimate ILAE class or cognitive outcome, suggesting that hemispherotomy can be offered in older children with expectations of good seizure and functional outcomes.

657. Prospective, Multidisciplinary Recording of Perioperative Errors in Cerebrovascular Surgery: Is error in the eye of the beholder?

Suzanne Marie Michalak; John Rolston; Michael Lawton (Wilson, NC)

Introduction: Surgery requires coordination of multiple team members, each playing a vital role in mitigating errors. Previous studies have focused on eliciting errors only from the attending surgeon, likely missing events observed by others.

Methods: Surveys were administered to the attending surgeon, resident, anesthesiologist, and nursing staff following each case; participants were instructed to record any deviation from optimal course.

Results: Errors were recorded in 93.5% of 31 cases, with each case having an average of 3.0 ± 2.1 errors. Technical errors were most common (24.5%), followed by communication (22.4%), management/judgment (16.0%), and equipment errors (11.7%). Residents reported the most errors (52.1%), followed by nurses (31.9%), the attending (26.6%), and anesthesiologists (14.9%). Attending surgeons and residents were most likely to report technical errors (52% and 30.6%, respectively), while anesthesiologists reported primarily anesthesia errors (36%), and nurses, communication errors (50%). Using only surveys completed by the attending surgeon, as in prior studies, would have missed 72% of equipment errors, 90% of anesthesia and communication errors, and all nursing errors. Furthermore, we would have concluded that errors occurred in 45.2% of cases (rather than 93.5%) and delays in 3.2% of cases, instead of the 74.2% calculated using data from four team members.

Conclusion: This study is unique in eliciting error reporting from multiple members of the operating team and showing that perioperative error rates vary based on whom you ask. These results emphasize that only by understanding every perspective can we begin to efficiently prevent errors, improve patient care and safety, and decrease delays.

658. Blunt Cerebrovascular Injury: A Retrospective Review and Novel Classification System

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Introduction: Blunt cerebrovascular injury (BCVI) accounts for 1% of blunt trauma admissions. Early treatment can decrease the stroke risk by 20-50%, but the incidence of stroke or death remains 7-18%. The complication risks of anticoagulation and antiplatelet agents must be weighed against the stroke prevention benefits. The Denver criteria categorizes BCVI by grade I through V based on the injury type and severity, but this system may not fully characterize this disease.

Methods: A retrospective review was performed of all BCVI cases from 2009 through 2014. Our treatment protocol included antiplatelet agents within 24 hours of injury or 48 hours of stable head imaging if intracranial hemorrhage was present. The patient

demographics, imaging, injury type and Denver classification, interventions, and complications were reviewed.

Results: 342 BCVI patients were identified. 262 (77%) patients received antiplatelet agents, 17 (5%) received anticoagulants, and 10 (2.9%) underwent endovascular intervention. There were 33 (9.6%) strokes and 45 (13%) deaths. The stroke incidence was 1.9% for grade I, 11.9% for grade II, 7.3% for grade III, and 20.9% for grade IV. Vertebral artery injuries and carotid artery injuries had a stroke rate of 7.7% and 10.9% respectively. A novel classification system to supplement the Denver criteria was created and separates injuries into vertebral and carotid lesions, intracranial and extracranial arterial damage, and the presence or absence of dissection related subarachnoid hemorrhage.

Conclusions: Despite aggressive treatment of these lesions with antiplatelet agents, our stroke and death rate remains 9.6% and 13% respectively. The highest stroke rate was found for grade II and grade IV lesions, especially for anterior circulation injuries. We propose a novel supplementary grading system in an attempt to initiate stroke prevention earlier than our current protocol. A prospective study utilizing a treatment protocol based on our new system is ongoing.

659. Patency of ICA Branch Vessels Adjacent to Aneurysms Treated with Pipeline Embolization Devices

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Introduction: Pipeline embolization devices (PEDs) were originally approved for treatment of ICA aneurysms proximal to the posterior communicating artery origin. The indications for PED use have since been expanded for aneurysms in other locations. Thus far, limited data exists regarding the patency of branch vessels adjacent to aneurysms that are covered by PEDs.

Methods: Records of all patients (N=119) who underwent PED treatment between 2009 and 2013 were analyzed. Patency of ICA branch vessels (ophthalmic, PCOM, anterior choroidal, ACA, anterior temporal arteries) was evaluated by DSA immediately after coverage by PEDs and at approximately six months follow-up. All patients also underwent clinical evaluation during this period.

Results: Of 119 cases, we identified 78 patients with branch vessel coverage by PEDs. Immediately after PED deployment, all branch vessels were patent. At follow up only the ophthalmic artery (4 of 71 cases, 5.6%) and PCOM artery (7 of 19 cases, 36.8%) had evidence of occlusion. None of the anterior choroidal vessels (0 of 19 cases), ACAs (0 of 3 cases) or anterior temporal artery (0 of 1 cases) showed evidence of occlusion. There were no adverse clinical consequences noted from ophthalmic artery or PCOM occlusion in the follow-up period.

Conclusions: PED deployment can result in occlusion of branch vessels (ophthalmic and PCOM) that have collateral blood flow. Terminal branch vessels (particularly anterior choroidal) remain patent despite PED coverage likely from a pressure gradient that promotes flow. We conclude PEDs are safe for treatment of ICA aneurysms despite their effect on some branch vessels.

660. The Influence of Operator Experience on Complications: Analysis from the IntrePED Registry

Richard Wiley Williamson, Jr., MD; Ricardo Hanel, MD, PhD (Phoenix, AZ)

Introduction: The Pipeline Embolization Device (PED,

Covidien) is a flow-diverting stent effective in treating certain intracranial aneurysms. Previous data suggests that the operator's experience influences the complication rate. Here we present the effect of operator experience on complications in the IntrePED (International Retrospective Study of Pipeline Embolization Device) registry.

Methods: A total of 793 patients were enrolled in the registry. Operator experience was divided according to the number of patients that operator treated. Group 1 included operators who treated 1-20 patients; group 2, 21-40 patients; and group 3, <40 patients. Major neurological complications included major stroke, major hemorrhage, or neurological death. The rate of major neurological complications was compared between the groups using Pearson's chi square test.

Results: Neurological complication rate was 8.4% with a mortality rate of 3.8%. 339(43%) patients were treated by operators in group 1, 247(31%) treated by operators in group 2, and 207(26%) treated by operators in group 3. There was no significant difference in the rate of major hemorrhage between the groups (2.7%vs2.8%vs1.5%, $p=0.42$). There was a trend towards significance in the rate of major stroke between the groups, (5.6%vs5.7%vs1.9%, $p=0.07$). There was a significant difference in the rate of neurological death between the groups (5.3%vs3.2%vs1.9%, $p=0.04$).

Conclusions: This analysis demonstrates the effect of operator experience on complication rates in the IntrePED registry. There was a significant reduction in the rate of neurologic death in the hands of operators who treated more than 40 patients in the registry.

661. The Pipeline Embolization Device is Associated with an Increased Rate of Delayed FLAIR Lesions.

Mina Gamal Safain, MD; Marie Roguski, MD, MPH; Robert Heller, MD; Adel Malek, MD, PhD (Boston, MA)

Introduction: Flow diversion utilizing the PED is reported as a safe treatment of aneurysms. Complete aneurysm occlusion, however, occurs in a delayed fashion with continued flow across the aneurysm neck. We hypothesized that this continued flow may impart a higher rate of delayed FLAIR lesions on follow-up MRI studies.

Methods: All patients undergoing aneurysm treatment with the PED from October 2011-February 2014 and a comparison group of patients undergoing Neuroform-mediated embolization between May 2006 and April 2013 were studied. Patients' charts, endovascular procedure notes, and MRI imaging were reviewed. MRIs were assessed for the presence of newly occurring DWI and FLAIR lesions at multiple times. Additionally, a DWI or FLAIR burden was calculated by totaling the maximal diameter of each lesion into one value.

Results: 41 Pipeline and 78 Neuroform patients were studied. Pipeline patients were more likely to have new ipsilateral FLAIR lesions compared to Neuroform patients at all time points studied (30.6% vs 7.2% of patients at T=2 and 34.5% vs 6.2% at T=4). The mean FLAIR burden was also significantly increased for Pipeline patients (10.1 vs 0.7mm at T= 2 and 8.8 vs 1.9mm at T=4). No delayed ipsilateral hemorrhages occurred in this cohort.

Conclusions: The PED is associated with increased rate of delayed and de-novo FLAIR lesions. The etiology and clinical effect of these lesions is unknown but they may aid in explaining the higher incidence of delayed ipsilateral hemorrhage after PED deployment.

662. A long-Term Study of Durability and Risk Factors for Aneurysm Recurrence after Clip Ligation

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Introduction: This study was undertaken to evaluate the durability of microsurgical clip ligation, to identify risk factors for recurrence, and to validate the need for long-term follow-up imaging.

Methods: A retrospective review of medical records identified 616 consecutive patients (156 males, 460 females; mean age 48.4+/-12.4; range 6-90 years) who underwent microsurgical clip ligation and follow-up imaging for greater than one year after discharge between 1990 and 2010 at our institution. Of a total of 919 aneurysms, 727 underwent surgical clip ligation for their ruptured and unruptured aneurysms. Late follow-up angiographic imaging was obtained at a mean of 7.2 years+/-4.7 years post-discharge (median 5.7 years; range 1-22 years).

Results: Of these patients, late follow up angiography revealed only two recurrent aneurysms (0.35%) out of 571 clipped aneurysms without residua after their initial operation. Of the 45 (7.3%) known residual aneurysms after clip ligation based on postoperative imaging, 9 aneurysms (20%) regrew of which 4 required treatments. Two recurrent aneurysms underwent endovascular coiling, one underwent endovascular stent assisted coiling, and one aneurysm underwent repeat clip ligation. The average time to recurrence was 6.1 years (range 1.2-15.3 years). None of the recurrences was due to broken or delayed displacement of clips; there were no aneurysmal hemorrhages related to recurrent aneurysms. De novo aneurysm formation occurred in 9 patients (1.4%) of which 6 (66.7%) presented with multiple aneurysms.

Conclusions: This is the largest study to date with the longest follow-up data that confirms the long-term efficacy of aneurysm clip ligation. There still exist an approximate 1.8% chance of recurrence for all aneurysms and a significant risk of 2.7% per year for regrowth of residual aneurysms. These findings strongly support the necessity for continued follow-up, late angiographic imaging, and potential need for further intervention for residual aneurysms after clip ligation.

663. Protocolized Emergency Treatment of Ruptured Intracranial Aneurysms to Reduce In-hospital Rebleeding and Improve Clinical Outcomes

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Introduction: As recurrent hemorrhage can occur anytime after SAH, the present authors adopted a 24-hour-a-day protocolized emergency treatment strategy for patients with a ruptured aneurysm. The incidence of in-hospital rebleeding and clinical outcomes were investigated and compared with those from previous years when using a broadly defined early (< 3 days of SAH) treatment.

Methods: A total of 442 patients were managed using a protocolized emergency treatment strategy (Period A), while 423 patients were managed with a strategy of broadly defined early treatment (Period B). Propensity score matching (PSM) was used to adjust the differences in age, gender, modified Fisher grade, WFNS clinical grade at admission, size and location of a ruptured aneurysm, treatment modality (clipping/coiling), and time interval from SAH to admission between the two periods.

Results: During Period A, the endovascular coiling and surgical clipping were started at a median time from admission of 2.9 hours and 3.1 hours, respectively. After PSM, Group A showed a significantly reduced incidence of in-hospital rebleeding (2.1% versus 7.4%, $p = 0.003$) and higher proportion of patients with a favorable clinical outcome (mRS 0-3) (87.9% versus 79.7%, $p = 0.008$). In particular, the good-grade patients in Group A experienced significantly less in-hospital rebleeding (1.7% versus 5.7%, $p = 0.018$) and better clinical outcomes (93.8% versus 87.7%, $p = 0.021$) than the good-grade patients in Group B.

Conclusions: Patients with a ruptured aneurysm may benefit from a strategy of emergency application of clipping or coiling due to the reduced incidence of recurrent bleeding and improved clinical outcomes.

664. CYP2C19 and CES1 Polymorphisms and Efficacy of Clopidogrel and Aspirin Dual Antiplatelet Therapy in Patients with Symptomatic Intracranial Atherosclerotic Disease

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Introduction: Symptomatic intracranial atherosclerotic disease (ICAD) has a high risk of recurrent stroke. Genetic polymorphisms (SNPs) in CYP2C19 and CES1 are associated with adverse outcomes in cardiovascular patients, but have not been studied in ICAD. We studied CYP2C19 and CES1 SNPs in symptomatic ICAD patients.

Methods: At three centers, genotype testing for CYP2C19 *2, *3, *8, *17, and CES1 G143E was performed on symptomatic ICAD patients taking clopidogrel and aspirin. Multiple logistic regression was performed to assess the association of these SNPs with the primary endpoint which was a composite of TIA, stroke, myocardial infarction, or death within 12 months of initiating clopidogrel.

Results: 234 patients were separately analyzed by treatment: percutaneous transluminal angioplasty/stenting (PTAS) ($n=45$) and medical ($n=189$). The primary endpoint occurred in 31% of PTAS and 47% of medical patients. After adjusting for covariates, variant allele of CES1 G143E was nominally associated with higher odds of primary endpoint in the medical group compared to wild-type homozygotes (OR 10.71, 95% CI 1.23-93.62, $P=0.032$). There were no CES1 G143E variant carriers in the PTAS group. There was no association between CYP2C19 variants and the primary endpoint in either the medical or the PTAS groups.

Conclusions: This is the first study examining genetic variants and their effects in symptomatic ICAD. CES1 G143E polymorphism was nominally associated with the primary endpoint in symptomatic ICAD patients. However, the direction of the association was opposite of what is expected based on the function of this SNP. This may reflect an incomplete understanding of CES1 genetic variation, and warrants further investigations.

665. The Impact of Body Habitus on the Outcomes after Aneurysmal Subarachnoid Hemorrhage

Hormuzdiyar Dasenbrock, MD; Rose Du, MD, PhD (Boston, MA)

Introduction: This is the first national study to evaluate the impact of body habitus on the outcomes of patients with aneurysmal subarachnoid hemorrhage.

Methods: Data from the Nationwide Inpatient Sample

(2002-2010) were retrospectively extracted. Patients were included who had subarachnoid hemorrhage and underwent aneurysm repair. Multivariate logistic regression analyses were performed to calculate the adjusted odds of in-hospital mortality and a non-routine hospital discharge for obese patients (with a body mass index between 30.0 kg/m² and 40.0 kg/m²) and morbidly obese patients (with a body mass index greater than 40.0 kg/m²) compared to non-obese patients. The odds of undergoing tracheostomy, gastrostomy, or ventricular shunting were also evaluated. All analyses were adjusted for differences in patient age, gender, co-morbidities, treatment modality, ventriculostomy, mechanical ventilation, intraparenchymal hemorrhage, as well as hospital volume, bed size, and teaching status.

Results: 18,104 hospital admissions were examined; . Neither obese (OR: 0.82, 95% CI: 0.59, 1.13) nor morbidly obese (OR: 0.84, 95% CI: 0.56, 1.27) patients had significantly different adjusted odds of in-hospital death, compared to non-obese patients. Additionally, the likelihood of undergoing tracheostomy, gastrostomy, or ventricular shunting did not vary based on body habitus. Morbidly obese patients (OR: 1.46, 95% CI: 1.08, 1.97) had an increased adjusted odds of non-routine hospital discharge.

Conclusions: In this nationwide study evaluating patients with subarachnoid hemorrhage, morbidly obese patients were found to have higher rates of nonroutine hospital discharge, but no differences in in-hospital mortality was seen by body habitus.

666. Effect of Prior Embolization on Adverse Radiation Effects Following Stereotactic Radiosurgery for Cerebral Arteriovenous Malformations: A Matched Cohort Analysis

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Introduction: The aim of this matched, case-control study is to determine the effect of prior embolization on the incidences of radiation-induced changes (RIC), latency period hemorrhage, and cyst formation following stereotactic radiosurgery (SRS) for cerebral arteriovenous malformations (AVM).

Methods: We evaluated a prospective database of AVM patients treated with SRS. AVMs which underwent intervention with combined embolization and SRS (case cohort) were matched to AVMs treated with SRS alone (control cohort) based on patient, AVM, and SRS characteristics. RICs were perinidal T2-weighted hyperintensities on MRI. The rates of post-radiosurgery RIC, hemorrhage, and cyst formation were compared.

Results: The matching process yielded 242 patients in each cohort. In the case cohort, the actuarial rates of RIC at 1, 2, and 5 years were 20%, 35%, and 42%, respectively. In the control cohort, the actuarial rates of RIC at 1, 2, and 5 years were 36%, 47%, and 52%, respectively. RIC rates were significantly lower in the case cohort ($P=0.003$, log-rank test). Independent predictors of RIC in the multivariate analysis were the lack of prior embolization ($P=0.009$) and fewer draining veins ($P=0.011$). Symptomatic RIC was also significantly less frequent in the case cohort (6% vs 15%, $P=0.003$), although the incidences of permanent RIC ($p=1.000$), latency period hemorrhage ($P=0.769$), and post-SRS cyst formation ($P=0.760$) were similar.

Conclusions: Embolization appears to confer protection against RIC, although it does not appreciably alter the risk of latency period hemorrhage or post-SRS cyst formation. These findings suggest an improved risk to benefit profile for combined embolization and SRS than previously reported.

667. Natural history of unruptured intracranial aneurysms. Single institutional cohort study

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Introduction: Natural history of unruptured intracranial saccular aneurysm (UIA) is still unclear and management strategy is not well defined.

Methods: From January 2003 through December 2012, we enrolled patients with unruptured intracranial aneurysms in our institution. 2244 patients with 2905 UIAs were eligible for analysis and 1968 UIAs were conservatively managed. Precise morphological evaluation was maintained by Three-dimensional computed tomography angiography, digital subtraction angiography or MRA.

Results: The mean follow up duration was 7479 aneurysm-years and 59 lost follow up. During observation, 56 UIAs ruptured resulting in a 0.76% rupture rate per year and 39 were smaller than 7mm. Annual rupture rate in size 5-6mm was 3.1% (CI 1.9-4.9). Prior history of subarachnoid hemorrhage (SAH) (HR 4.12, 95% CI, 1.77-9.61), cerebral hemorrhage (HR 8.22, 95% CI 1.14-59.45), IC-posterior communication and posterior circulation location, size, and daughter sac were significant independent predictors for aneurysm rupture. Mean initial clinic visit-rupture interval was 790 days and 29 out of 56 patients (52%) were severely disabled or died after bleeding.

Conclusions: Small/single aneurysms can be rupture in Japanese population. The aneurysms 5-6mm or more in diameter may need therapeutic intervention.

668. The Pipeline Embolization Device: Complications, Midterm Occlusion Rates, and Outcomes in 300 consecutive Cases

Nohra Chalouhi, MD; Badih Daou; Guilherme Barros; Mario Zanaty; Stavropoula Tjoumakaris; Richard Dalyai; Robert Rosenwasser; Pascal Jabbour (Philadelphia, PA)

Introduction: Flow diverters have emerged as a promising treatment option for intracranial aneurysms. The safety and efficacy of these devices remain under investigation. We present the largest experience to date with the pipeline embolization device (PED).

Methods: The study includes 300 consecutive patients who underwent PED treatment at a single institution between May 2011 and July 2014. Data on procedural safety was prospectively recorded at our institution. Clinically significant complications are reported both in the perioperative period and through follow-up.

Results: Aneurysm size was 9.7 mm on average. Aneurysm morphology was saccular in 84% and fusiform/dissecting in 16%. Seventeen aneurysms were treated in the setting of SAH. The mean number of devices used was 1.3, and this number significantly decreased from 1.9 early in the study period to 1.1 in the last year ($p < 0.05$). Overall complications occurred in 6% which included a 3.7% hemorrhagic complication rate and a 2.3% thromboembolic complication rate. Among several factors significantly associated with complications were a higher number of PEDs deployed and the early discontinuation of dual antiplatelet therapy. Treatment in the setting of SAH was not associated with increased morbidity. At follow-up, favorable outcomes were noted in 95% of the patients. The mortality rate directly related to PED treatment was 1.3%. At follow-up (mean, 13 months), 77% of aneurysms were completely occluded (100%), 12% were near-completely occluded, and only 11% remained incompletely occluded. The occlusion rate did

not differ with the number of devices deployed. No patient had aneurysm recurrence.

Conclusions: Treatment of ruptured and unruptured aneurysms is associated with an excellent safety efficacy-profile at large cerebrovascular centers. Several key factors associated with complications/outcome are discussed. Compliance with prolonged dual antiplatelet therapy is crucial for avoidance of complications. Using a single PED decreases the complications and provides equally high occlusion rates.

669. Reduction of Intraparenchymal Pressure after Porcine Acute Spinal Cord Contusion Injury by Neuro-Spinal Scaffold Implantation

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Introduction: Spinal cord injury (SCI) causes acute hemorrhage, edema, and spinal cord swelling. Elevated intraparenchymal pressure (IPP) promotes ischemia by reducing the net perfusion pressure. InVivo Therapeutics is developing a novel neuro-spinal scaffold that is in an IDE clinical trial and is implanted via a myelotomy at the contusion epicenter. The neuro-spinal scaffold serves as a locus for appositional healing and decreased cyst formation and spared white matter in rodents. The objective of this study was to measure IPP at the contusion epicenter before, during, and after surgical implantation of the investigational neuro-spinal scaffold in a porcine model.

Methods: T10 severe contusion injuries were created in Gottingen pigs ($n=2$) with a weight drop apparatus. At 24 hrs, a 0.3 mm diameter intraparenchymal pressure catheter was placed at the injury epicenter. Pressures were monitored throughout the surgical procedure which included durotomy, piodotomy, myelotomy, scaffold implantation, approximation of the pia, and expansion duraplasty.

Results: Intraparenchymal pressures in both animals were elevated (mean: 25.0 mmHg) at 24 hrs compared to normal values (11.5 mmHg). Surgical decompression via myelotomy, scaffold implantation, and expansion duraplasty resulted in decreased IPP in both animals (mean: 10.4 mmHg) to physiologically normal levels.

Conclusions: The surgical approach to the implantation of the neuro-spinal scaffold provides the benefit of reduction of IPP to physiological levels. Additional studies are underway to study the evolution of IPP increases in the porcine contusion model and to determine the association between reduced IPP and spinal cord blood flow. Raised IPP may be an important component of secondary injury in SCI.

670. The Use of Anticoagulants and Antiplatelet Agents before Removal of EVDs – How Safe is It?

Catherine Ann Miller, MD; Ramachandra Tummala, MD (Minneapolis, MN)

Introduction: External ventricular drains (EVDs) are both a therapeutic and diagnostic tool used everyday by neurosurgeons. Hemorrhage is a common complication of EVD placement and has recently been recognized to occur more frequently than originally believed. There is also risk of hemorrhage with removal of an EVD, which has not been well described. No universal recommendations exist regarding timing of anticoagulants and/or antiplatelet agents before removal of an EVD. We investigated the affect of anticoagulants and antiplatelet agents on hemorrhage caused by removal of an EVD.

Methods: After obtaining IRB approval, a database was created to include all patients who required EVD placement from March 2008 to June 2014 at our institution. A retrospective chart review was completed and all imaging was reviewed for evidence of hemorrhage on placement and removal of an EVD.

Results: 479 EVDs were placed in 370 patients during the designated time period. Hemorrhage occurred in 94 patients (19.6%) on placement with an average volume of $1.32 \pm 4.50\text{cm}^3$, while 55 patients (11.5%) had hemorrhage on EVD removal, with an average volume of $8.28 \pm 20.32\text{cm}^3$. Anticoagulants or antiplatelet agents were started in 147 high risk patients (30.7%) prior to EVD removal. Imaging was performed on 239 patients after removal, with hemorrhage in 18 ($10.98 \pm 26.0\text{cm}^3$) of the high risk group and 37 ($6.94 \pm 17.2\text{cm}^3$) in the normal group, OR 0.849 (CI 0.4487-1.083, $P = 0.616$).

Conclusions: Multiple studies have investigated hemorrhage related to EVD placement with rates varying from 0-42%, while very few studies have described hemorrhage secondary to EVD removal. The risk factors associated with EVD removal have not been investigated. We found no correlation between the use of anticoagulants and/or antiplatelet agents and an increased risk of hemorrhage on EVD removal.

671. Non-invasive intracranial pressure monitoring in a hospital-wide setting. Challenges met.

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Introduction: Current intracranial pressure (ICP) monitoring, such as the external ventricular drain and the intracranial pressure bolt, are invasive, require calibration, often have to be revised, and may be a source of infection; furthermore, bolts are MRI incompatible and/or create signal artifacts during imaging. For these reasons, non-invasive ICP (nICP) monitoring for application at the bedside in a hospital-wide setting can be a valuable modality in the management of critically ill patients. Our group has recently developed a model-based approach to the non-invasive, continuous, patient-specific and calibration-free estimation of ICP (Kashif et al. *Science Transl. Med.* 4(129):129ra44, 2012). One important challenge lay in the ability to utilize the patient information from the bedside monitors to feed into the nICP algorithm system.

Methods: A laptop-based data acquisition system was developed to capture waveforms from critical care monitors at the Boston Medical Center. Simulated patient signals were used to feed the system. LabVIEW (NI) was used for graphic user interface design.

Results: The system is able to connect to the bedside monitors and collect, display and analyze data streams in real-time in parallel and non-invasive way. The system can collect up to 14 different waveforms, including ECG, SpO₂, arterial blood pressure and respiration, and archive patient data. Real-time arterial blood pressure and transcranial doppler data can be obtained to estimate nICP values. The developed data-acquisition infrastructure can also be used to collect high-resolution bedside monitoring data longitudinally for extended periods of time for neurocritical care studies.

Conclusions: The bedside system described allows real time acquisition, processing and database archiving of waveforms from neurocritical care patients. In a hospital setting, obtaining patient data in parallel, without interfering with patient care, is challenging but possible. The system will improve the performance of the nICP estimation algorithm and, improve the reliability of nICP monitoring.

672. A meta-analysis of spinal surgical site infection and vancomycin powder

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Objective: Surgical site infection (SSI) is a serious and costly complication of spinal surgery. There have been several conflicting reports on the use of intrawound vancomycin powder in decreasing SSI in spine surgery.

Methods: A comprehensive search of multiple electronic databases and bibliographies was conducted to identify clinical studies that evaluated the rates of SSI with and without the use of intrawound vancomycin powder in spine surgery. Independent reviewers extracted data and graded the quality of each paper that met inclusion criteria. A random effects meta-analysis was then performed.

Results: Our search identified 8 retrospective cohort studies (level III evidence) and one randomized controlled trial (level II). There were 2,424 cases and 95 infections in the control group (3.9%) and 2,368 cases and 28 infections (1.1%) in the treatment group, yielding a pooled ARR and RRR of 2.8% and 72%, respectively. The meta-analysis revealed the use of vancomycin powder to be protective in preventing SSI (RR=0.30, 95% CI 0.14-0.67, $p < 0.011$). The number needed to treat (NNT) to prevent one SSI was 36. A subgroup analysis found that patients who had implants had a reduced risk of SSI with vancomycin powder ($p = 0.023$), compared to those who had non-instrumented spinal operations ($p = 0.226$).

Conclusion: This meta-analysis suggests that the use of vancomycin powder may be protective against SSI in open spinal surgery; however, the exact population in which it should be used is not clear. This benefit may be most appreciated in higher-risk populations or in facilities with a high baseline rate of infection.

673. Effects of cranioplasty in cerebral blood flow

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Introduction: Cranial vault defects may be related with neurological deficits that can be associated with changes in cerebral hemodynamics. Our goal was to evaluate if cerebral blood flow (CBF) increases after cranioplasty using computed tomography perfusion (CTP).

Methods: We prospectively evaluated patients with bone defect after decompressive craniectomy (DC) with CTP before and after cranioplasty. We performed neurological examination and evaluation of prognostic scales (mRs, MMSE and Barthel index) before and after six months.

Results: We evaluated 30 patients, 15 (50%) with DC related to TBI and the remainder due to cerebrovascular disease. We have verified that CBF ranging from $24.13 \pm 6.3 \text{ ml/100g / min}$ (mean and SD) to $22.63 \pm 8.2 \text{ ml/100g / min}$ (mean and SD) $p = 0.315$ on the bone defect side, and $27.75 \pm 6.21 \text{ ml/100g / min}$ (mean and SD) to $26.23 \pm 5.73 \text{ ml/100g / min}$ (mean and SD) $p = 0.242$ in the normal side. The mean transit time (MTT) showed reduced values in both hemispheres, being significant ($p = 0.02$) on the defect side. We also observed that there was significant improvement in all neurological parameters.

Conclusion: Although all literature report increased CBF after cranioplasty, and correlate this finding with clinical improvement, we observed that the best parameter to assess hemodynamics

condition for these patients is MTT. After cranioplasty could occur a down regulation of the cerebral autoregulation curve, allowing suitable neuronal function with lower CBF.

674. Is Lateral Stabilization Enough In Thoracolumbar Burst Fracture Reconstruction? A Biomechanical Investigation.

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Introduction: Traditional reconstruction for burst fractures involves columnar support with posterior fixation at one or two levels cephalad/caudad; however it can be stabilized in various ways.

Methods: Six human spines (T11-L3) were tested on a six-degrees-of-freedom simulator enabling unconstrained motion (ROM) at ± 6 N·m in flexion-extension (FE), lateral bending (LB) and axial rotation (AR) following a simulated burst fracture at L1. Expandable corpectomy spacers with/without integrated screws (Fi)/ (F) (FORTIFY® Integrated/FORTIFY® Globus Medical, Audubon, PA) were tested with different endplate sizes (21x23mm, 22x40-50mm) using a lateral approach. Posterior fixation via bilateral pedicle screws and rods (PI) were used one level above/below the burst fracture. Lateral plate (LP) fixation was tested. Devices were tested in following order: 1) Pre-operative; 2) Fi21x23; 3) Fi21x23+PI; 4) F21x23+PI+LP; 5) F21x23+LP; 6) F22x40-50+LP; 7) F22x40-50+PI+LP; 8) Fi22x40-50+PI; 9) Fi22x40-50.

Results: In FE and AR, lateral fixation constructs showed no significant difference in stability compared to intact. In LB, F22x40-50+LP showed a significant increase in stability relative to intact, but no other construct without PI reached significance. In FE and LB, circumferential constructs were significantly more stable than intact. In AR, no construct showed significant differences in motion in comparison to the intact condition.

Conclusions: Constructs without supplemental posterior fixation were the least stable of all tested constructs in all bending modes. Circumferential fixation provided higher stability in FE and LB than lateral fixation constructs and intact. Axial rotation showed no significant differences in any construct compared to the intact state.

675. Succinate Administered Focally Enters the Brain TCA Cycle and Ameliorates Lactate/Pyruvate Ratio in TBI Patients

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Introduction: Following traumatic brain injury (TBI), complex cerebral processes include energy perturbations. Correlating with unfavourable outcome, high brain extracellular lactate/pyruvate (L/P) ratio suggests high glycolytic activity: glucose converted to pyruvate generating a low ATP yield, then lactate dehydrogenase (LDH) converts pyruvate plus NADH to lactate plus NAD⁺, allowing more glycolysis. We investigated whether focal administration of succinate, a tricarboxylic acid (TCA) cycle intermediate that interacts directly with the mitochondrial electron transport chain, could improve brain energy metabolism.

Methods: We used microdialysis to perfuse disodium 2,3-13C2 succinate (12 mmol/L) for 24h into 6 sedated TBI patients' brains and simultaneously collected the microdialysates for analysis (NMR and ISCUSflex).

Results: Products of 2,3-13C2 succinate were 2,3-13C2 malate and 2,3-13C2 glutamine indicating TCA cycle metabolism, and 2,3-13C2 lactate suggesting TCA cycle spinout of pyruvate (by malic enzyme or phosphoenolpyruvate carboxykinase and pyruvate kinase) then LDH-mediated conversion to lactate. Compared with baseline, succinate perfusion improved brain chemistry: lower L/P ratio (due to higher pyruvate), lower glutamate, and better glucose utilisation.

Conclusions: Succinate perfusion improved brain chemistry. Lower L/P ratio suggests better cellular redox whereby NADH is recycled to NAD⁺ by mitochondrial shuttles (malate-aspartate and/or glycerol 3-phosphate), diminishing need for LDH conversion of pyruvate to lactate. Lower glutamate concentration may also be due to the malate-aspartate shuttle. Whether these improvements translate into better ATP status for the brain will be investigated.

676. Complications after Decompressive Craniectomy and Cranioplasty: Incidence, Surgical strategies, Effects on 30 days Mortality and Outcome

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Introduction: Effectiveness of decompressive craniectomy from being established. On the counterpart, the rate of complications following this procedure is incredibly high and raises doubt on the real benefits of this surgical treatment. Only few papers focused attention on a thorough analysis of complications role in short term mortality and global outcome in patients undergoing decompression and cranioplasty

Methods: We retrospectively analyzed a series of 393 patients treated by decompressive craniectomy at our Institution in a 11-years time interval. Factors considered as potentially affecting the development of complications after decompression included: craniectomy modality, duration of surgery, age, conditions at presentation (pupils/GCS), time from admission to surgery. A full list of complications observed was compiled. Flap conditions at presentation, post-craniectomy GOS and time from decompression to cranioplasty were the leading parameters considered before cranioplasty as predictors of complications development. The impact of complications on outcome was statistically evaluated by uni and multivariate analysis.

Results: Only the 7% of patients undergoing decompression and the 32% receiving cranioplasty were complications free. Malignant brain swelling was statistically relevant on short term mortality in craniectomized patients and it was considered as an indicator of bad patient selection. No other complications affected outcome in a statistically significant way. Hydrocephalus and bflap resorption were the only complications with a statistically significant impact on prognosis. Epidural haematoma, CSF leaks, Bone infection, rebleeding, were all considered uninfluent on outcome, even though this might be due to their development in low-GCS and GOS patients.

Conclusions: The range of complications after decompressive craniectomy and cranioplasty is quite wide and their incidence is relevant. Nonetheless, prompt complication observation and treatment seems to be more important than complication development in terms of patient outcome.

677. A New Device for the Continuous Monitoring of Cerebral Edema

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

Introduction: The currently available clinical tools for estimating brain edema (CT and MRI) only provide intermittent information. Based on the correlation between thermal conductivity and water content, we postulated that a flow microsensor that we have developed could estimate brain water content.

Methods: In vitro experiments were performed in agar-glycerol-water mixtures with different water contents (69-89%). In vivo studies were performed 14 adult male Sprague Dawley rats that were randomly divided into Control Group (n=3) and TBI Group (n=5 for sensor recording, n=6 for wet-dry method). Stereotaxic surgical techniques were used to unilaterally A calibrated sensor was implanted into the neocortex. The controlled cortical impact (CCI) method was used to produce traumatic brain injury. Control Group rats underwent an identical surgery but no TBI.

Results: In vitro: Measured thermal conductivity from agar-glycerol-water mixtures with different water contents was well correlated with actual water content ($R^2 = 0.983$, SD less than 0.063%). In vivo: In the Control Group (n=3), data from the sensor showed no obvious change in brain water content ($77.9 \pm 0.37\%$) for the first 24 hours after craniotomy. In the TBI group (n=5), brain water content rapidly increased after 30 minutes ($78.8 \pm 0.24\%$) and reached the first peak at the sixth hour after the injury ($81.6 \pm 0.46\%$). Brain water content measured by the wet-dry method at 30 minutes ($79.2 \pm 0.21\%$) and 24 hours ($81.7 \pm 0.57\%$) after CCI was slightly higher to, but not significantly different from the sensor readings.

Conclusions: This study shows that thermal conductivity measured with a microsensor correlated well with actual water content in vitro. Furthermore, in vivo measurements in the rat CCI model showed that the microsensor can track brain edema development in real time. Such monitoring has the potential to substantially improve the care of severely brain-injured patients.

678. Traumatic Lung Injury and Multiple Organ Trauma Effects on Traumatic Brain Injury Patients

Justin Baum; Azedine Medhkour, MD; Kavir Shah, MD; Pouya Entezami; Delia Mekus (Milford, OH)

Introduction: The purpose of this study was to retrospectively evaluate patients treated for traumatic brain injuries (TBI) in an effort to determine how multiple organ trauma (MOT) and lung injuries sustained at the time of initial injury affect outcome.

Methods: A single institution retrospective review of all patients diagnosed with TBI at a level I trauma center from 2000-2009 was conducted. Clinical outcome was based on Glasgow Outcome Scale (GOS) at hospital discharge. The highest abbreviated injury scores (AIS) were recorded for head and chest regions. TBI with $ISS \geq 30$ was defined as MOT. Lung injury was defined as presence of pulmonary contusions, pneumothorax, rib fractures, or diaphragmatic rupture proven by radiologic studies. Regression analysis adjusting for age and gender was conducted on each variable independently using SPSS 21.

Results: There were 301 patients reviewed. Majority of patients were male (76%), average age was 45y (16-94), average GCS was 7, and 69.5% had severe TBI ($GCS < 9$). MOT was identified in 123 patients (41%) and mean ISS was 28.5. Seventy-five patients (25%) had poor outcome. Regression analysis indicated GCS ($OR = 0.90$, $p = 0.001$), ISS ($OR = 1.03$, $p = 0.005$), MOT ($OR = 2.0$, $p = 0.014$), and

head AIS ($OR = 2.63$, $p < 0.001$) as significant predictors of poor outcome ($GOS \leq 2$). Neither lung injury incidence nor lung AIS were significant predictors of outcome.

Conclusions: While multiple organ trauma and head injury severity are significant predictors of outcome, lung injury incidence and lung injury severity are not. Simultaneous lung injuries sustained during initial TBI will not significantly affect outcome if treated appropriately.

679. Hyaluronic Acid Hydrogel Reduces Scarring in Spinal Cord Injury

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Introduction: Spinal cord injury occurs in 2 phases. Initial trauma is followed by inflammation leading to fibrous scar tissue and glial scarring. Scarring causes further axon death around and above the injury. A reduction in secondary injury could lead to functional improvement.

Methods: Hyaluronic acid (HA) hydrogels were made by crosslinking thiolated HA with poly (ethylene glycol)- diacrylate. Hydrogels of varying polymer concentrations were placed in hemisectioned spinal cords of 54 Sprague-Dawley rats. At 8 or 16 weeks animals were euthanized and perfused. Samples were stained using hematoxylin and eosin, neurofilament stain (neurons and axons), silver stain (disrupted axons), glial fibrillary acidic protein stain (astrocytes), and IBA1 stain (mononuclear cells). Animals were tested for limb function using the Basso-Beattie-Bresnahan locomotor score.

Results: Histology revealed decrease in disorganized scar tissue in and above the lesion site in HA hydrogel animals and a decrease in cavitation. Immunohistochemistry revealed retention of axons and neurons above the lesion, decreased axon degradation, and lowered mononuclear cell presence in the hydrogel compared to the control ($P < 0.05$). Importantly, HA hydrogel tissues showed axon alignment near the lesion, while control samples showed axon disorganization. Reactive astrocytes were present in both samples. HA treated animals showed more intact red nucleus neurons compared to controls ($P < 0.05$). Axons were not present in the gel cavity. Locomotor function was not significantly different but trended positively.

Conclusions: Hyaluronic acid hydrogel protected the spinal cord from inflammation and reduced the secondary injury. The reduction of disorganized scar tissue and retention of neurons near and above the lesion is important for future regenerative efforts.

680. Comparative Study of Outcome Measures and Analysis Methods for Traumatic Brain Injury Trials

Aziz Alali, MD; Darcy Vavrek; Jason Barber, MS; Sureyya Dikmen, PhD; Avery Nathens; Nancy Temkin, PhD (Ottawa, Canada)

Objective: Composite measures of functional and cognitive performance have been proposed as theoretically better alternatives to the Extended Glasgow Outcome Scale (GOSE) as the primary outcome for traumatic brain injury (TBI) trials. We conducted a study to compare three sets of outcome measures for phase III TBI trials: GOSE and a composite outcome of functional and cognitive metrics.

Methods: Using data from a recent randomized trial, we simulated multiple treatment effects (10%, 7.5%, 5% relative risk reduction) across multiple outcome measures. We generated 10,000

samples via bootstrapping for each treatment effect (each with $n=800$ patients). For each sample, the null hypothesis was tested using a suite of statistical techniques. We computed the percentage of bootstrapped samples where the null hypothesis was rejected to estimate the power of detecting a treatment effect for each outcome measure and analytic technique. We estimated the corresponding Type-I error by analyzing the dataset with 0% treatment effect.

Results: GOSE analyzed using the sliding dichotomy method offered higher power across all treatment effects (e.g., 97.1% power to detect 10% treatment effect across 10,000 bootstrap samples, each sample with $n=800$) than the composite outcome measure, regardless of the statistical technique used to analyze the composite outcome. Increasing the baseline prognostic groups from 3 to 10 in the sliding dichotomy method further increased the power to detect a treatment effect. Analyzing GOSE using the conventional fixed dichotomization method provided the overall lowest power. All the statistical techniques used to analyze the outcome measures of interest had low rates of type I error ($<5\%$).

Conclusion: GOSE can offer higher statistical power to detect a treatment effect than composite measures of functional and cognitive performance, assuming similar relative risk reduction across all component measures. The superior power was demonstrated when GOSE data were analyzed using the sliding dichotomy method.

681. The Use of Apparent Diffusion Coefficient Values to Predict Outcome in Patients with Traumatic Brain Injury

Daria Krivosheya; Godefroy Hardy-St Pierre, MD; Brian Young, MD; Sandrine de Ribaupierre, MD (London, Canada)

Introduction: Traumatic brain injury (TBI) is a major cause of mortality and morbidity worldwide. There are no tools available at present to reliably predict patient outcome in cases of severe TBI. Apparent diffusion coefficient (ADC), a quantitative measurement of water diffusion in the brain, has been suggested to represent the degree of diffuse axonal injury and thus be used to predict neurological outcome. To date, the results of the use of ADC in trauma patients have been mixed. The goal of our study is to determine whether ADC values extracted from MRI scans obtained within 96 hours after injury can predict patient outcome.

Methods: We used our trauma patient database at London Health Sciences Center to identify patients with head trauma admitted between 2007 and 2014 that had an MRI brain performed within 96 hours of injury. The diffusion sequences were then reviewed and the ADC values determined at pre-defined areas of subcortical white matter. The resultant ADC values were then correlated with patient outcomes and somatosensory evoked potentials (SSEPs).

Results: Our preliminary data indicates that there is a significant difference in ADC values in temporal subcortical white matter between patients with good outcomes and patients who did poorly. All patients with good outcomes had normal SSEPs.

Conclusions: Subcortical white matter ADC values obtained within 96 hours after injury may help predict outcome in patients with TBI.

682. Exosomes derived from mesenchymal stromal cells improve functional recovery and enhance neurovascular plasticity in rats after traumatic brain injury

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

Introduction: Transplanted multipotent mesenchymal stromal

cells (MSCs) improve functional recovery in rats after traumatic brain injury (TBI). In this project we test a novel hypothesis that systemic administration of cell-free exosomes generated from MSCs also promotes functional recovery and enhances neurovascular remodeling in rats after TBI.

Methods: Adult male Wistar rats were subjected to TBI by controlled cortical impact (CCI) followed by tail vein injection of 100 μ g protein of exosomes derived from MSCs or an equal volume of vehicle phosphate-buffered saline ($n=8$ /group) 24 hours later. To evaluate functional recovery, Morris water maze (MWM), neurological severity scores (NSS) and footfault tests were performed. Animals were sacrificed at 35 days after TBI. Histopathological and immunohistochemical analyses were performed for measurements of lesion volume and neurovascular remodeling (angiogenesis and neurogenesis).

Results: Compared with saline-treated controls, exosome-treated TBI rats showed significant improvement in spatial learning measured by the MWM test ($p < 0.05$), and sensorimotor functional recovery measured by NSS and footfault tests ($p < 0.05$). Exosome treatment significantly increased angiogenesis in the lesion boundary zone and dentate gyrus ($p < 0.05$) as well as significantly increased neurogenesis in the dentate gyrus ($p < 0.05$).

Conclusions: We, for the first time, demonstrate that MSC-generated exosomes effectively improve functional recovery, at least in part, by promoting endogenous angiogenesis and neurogenesis in rats after TBI. Thus, MSC-generated exosomes may provide a novel cell-free therapy for TBI and possibly other neurological diseases.

683. Dexamethasone Treatment to Prevent Surgery for Chronic Subdural Hematoma: A Retrospective Study and Cost Analysis

Jonathan David Dvorak, B.S. in Biology; Robert James; Hilal Kanaan (Weddington, NC)

Introduction: Chronic Subdural Hematomas (CSDH) are a disease entity that tends to affect elderly patients on anticoagulants. Neurosurgeons have employed short courses of steroids in mildly symptomatic CSDH patients in order to avoid surgery. We administered Dexamethasone to minimally symptomatic CSDH patients and assessed neurologic and radiologic outcomes and additionally performed a cost-analysis.

Methods: A retrospective review was performed of 39 patients treated with Dexamethasone (4 mg T.I.D; 7-10 days) for CSDH between August 2011 and April 2014. 27 Patients met inclusion criteria including pre-existing CSDH, follow-up imaging studies performed, and anticoagulation therapies discontinued at time of treatment.

Results: Median Modified Rankin Scale (mRS) for the group at time of treatment decreased from 2 to 1 at last follow-up visit. Patients presenting with a single complaint (headache, weakness, gait abnormality, cognitive dysfunction) had better mRS outcomes than those with multiple complaints (91.7% vs. 80% improvement). 12 patients (44.4%) received a second Dexamethasone treatment and 3 patients (11.1%) ultimately received surgery. All patients who avoided surgery had a mean decrease in maximal hematoma thickness by at least 50% in Computed Tomography studies. Cost analysis indicates an estimated savings of \$1,260,000 in medical care by treating 24 of 27 patients conservatively with medical management. This is a projected savings of \$52,600 per patient treated with Dexamethasone.

Conclusions: A Short course of Dexamethasone administration for minimally symptomatic Chronic Subdural Hematomas is an effective and safe treatment option. This provides a low cost, conservative management alternative for these patients in an outpatient setting.

683. Endoscopic approach to tumors of the third ventricle. Technical considerations for use of solid or flexible systems.

Assem Mounir Abdel Latif; Tarek Lotfy; Mark Souweidane (Cairo, Egypt)

Introduction: With the myriad of endoscopic options available for management of third ventricular lesions, come certain technical points pertinent to preoperative evaluation and operative decision-making. Of these, authors wished to evaluate lesion size, consistency, location within third ventricle, presence of hydrocephalus and the intended goal of surgery.

Methods: Twenty one patients have been treated by 2 senior authors (TL, MMS) in 2 institutions with prospective data maintenance.

Results: Of the 21 patients, 13 had anterior lesions, 7 had posterior and 1 had a lesion spanning third ventricle length. Median lesion size was 20mm (5-60mm) with 61.9% cystic lesions, 14.2% solid and 23.8% partly solid and cystic tumors. Hydrocephalus was found in 90.5% with mean FOR 0.439 and Evan's ratio 0.36. Goal of endoscopic intervention was cyst decompression in 42.9%, cyst/tumor excision in 19%, cyst decompression and solid lesion biopsy in 14.3%. Target achievement was 95.2% (20/21) with concomitant CSF diversion in 61.2% of cases. Subclinical fornix injury occurred in 9.5% (n=2). Flexible endoscopy was used in 3 patients with posterior lesions due to difficulty of solid lens navigation. These patients had significantly less hydrocephalus evidenced by FOR and Evan's difference (p= 0.028 and 0.039 respectively) and significantly smaller third ventricular width (p=0.0007).

Conclusions: Endoscopy remains a valid option for intraventricular lesions especially of the third ventricle. Hydrocephalus and third ventricular width affect the ease of procedure. In difficult cases, flexible endoscopy provides safe access with good achievement of limited objectives (cyst fenestration/biopsy).

726. Somatic Mutations in SUZ12 in Malignant Peripheral Nerve Sheath Tumors

Chetan Bettegowda, MD; Ming Zang, PhD; Yuxuan Wang; Kevin McMahon, PhD; Allan Belzberg, MD; Kaisorn Chaichana, MD; Gary Gallia; Ziya Gokaslan; Jean-Paul Wolinsky; Ken Kinzler, PhD; Nickolas Papadopoulos, PhD; Bert Vogelstein, MD (Baltimore, MD)

Introduction: Neurofibromatosis 1 is a hereditary syndrome characterized by the development of numerous benign neurofibromas, a small subset of which progress to malignant peripheral nerve sheath tumors (MPNSTs). The genetic basis for malignant transformation is incompletely understood.

Methods: To better understand the genetic basis for MPNSTs, we performed genome-wide or targeted sequencing on 50 cases. In addition, we performed targeted sequencing on matched neurofibromas from 11 cases to identify genetic factors specific for MPNST development. To test the functional significance of mutations identified in the epigenetic machinery, we performed immunohistochemistry to evaluate H3K27 trimethylation.

Results: Sixteen MPNSTs but none of the neurofibromas tested were found to have somatic mutations in the chromatin modifying gene SUZ12. In tumors without SUZ12 alterations, we identified frequent somatic mutations in other members of the polycomb repressor complex 2 (PRC2), including EED, EZH2, and CHD4. In all cases tested, SUZ12 mutation resulted in abrogation of protein expression and loss of H3K27 trimethylation, a downstream target of SUZ12, suggesting that the alterations were inactivating protein function.

Conclusions: Our results suggest that SUZ12 and other members of the PRC2 complex, which is a central regulator of cellular epigenetic machinery, play a critical role in the transformation of benign neurofibromas into MPNSTs.

727. Progesterone for Severe Traumatic Brain Injury: Results of the SyNAPSe Multinational Trial

Raj K. Narayan, MD, FAANS; Brett Skolnick, PhD; Andrew Maas, MD, PhD; Roland van der Hoop, MD, PhD; Thomas MacAllister, PhD; John Ward, MD; Neta Nelson; Nino Stocchetti, MD; For SyNAPSe Trial Investigators (Manhasset, NY)

Introduction: Numerous experimental animal studies have supported the pharmacological use of progesterone for traumatic brain injury (TBI). In addition, two single-center phase II trials suggested that this effect was present in humans. The SyNAPSe trial was therefore initiated to confirm the clinical efficacy and safety of progesterone in a large prospective, randomized, multi-center, Phase III trial.

Methods: 1195 subjects, 16 years of age or older with severe TBI (GCS 3-8 with at least one reactive pupil) were randomized to receive progesterone or placebo within 8 hours of injury and continued for 120 hours. The Glasgow Outcome Score (GOS) at 6 months was the primary efficacy endpoint with a variety of secondary endpoints including mortality and the extended GOS.

Results: A proportional odds analysis was used with covariate adjustments for baseline characteristics including age, GCS motor score, pupillary response, Marshall classification and geographic region. No treatment effect of progesterone was found (OR: 0.96; CI: 0.77-1.18). Unfavorable outcome on the GOS was 49.5% for placebo and 49.6% for progesterone. No safety concerns were noted.

Conclusions: In contrast to the robust experimental and early clinical studies, progesterone showed no clinical benefit in patients with severe TBI. The failure to demonstrate clinical effects with many promising therapeutics over the past years mandates a careful reassessment of the criteria that should be met before advancing a drug for further clinical development. In addition, mechanistic targeting, better classification and the use of early surrogate endpoints, if identified, could allow for more sensitive, efficient and inexpensive trials in TBI.

728. Validation of a System Designed to Predict Recanalization After All Types of Endovascular Treatment of Intracranial Aneurysms in 1,543 Patients from Five Institutions

Christopher S. Ogilvy, MD, FAANS; Michelle Chua; Matthew Fusco, MD; Christoph Griessenauer, MD; Mark Harrigan, MD; Ashish Sonig, MD; Adnan Siddiqui, MD, PhD; Michael Avery, MD; Alim Mitha, MD; Jorma Shores; Brian Hoh, MD; Ajith Thomas, MD (Boston, MA)

Introduction: With increasing utilization of endovascular techniques in the treatment of ruptured and unruptured aneurysms, the issue of obliteration efficacy has become increasingly important. There is strong evidence that patients have a better understanding of risk if outcomes are presented numerically. We have previously reported the Aneurysm Recanalization Stratification Scale which uses accessible predictors including aneurysm-specific factors (size, rupture, intraluminal thrombosis) and treatment-related features (treatment modality and immediate angiographic result) to predict retreatment risk following endovascular therapy.

Methods: External validity of the Aneurysm Recanalization Stratification Scale was assessed in independent cohorts from four

centers in the United States and Canada where endovascular and open neurovascular procedures are performed and in a multicenter cohort of 1,543 patients. Probability of retreatment stratified by risk score was derived for each center and the combined multicenter cohort.

Results: Despite moderate variability in retreatment rate among centers (29.5%, 9.9%, 9.6%, 26.3%, 19.7%, and 18.3%), the Aneurysm Recanalization Stratification Scale demonstrated good predictive value with C-statistics of 0.799, 0.943, 0.780, 0.695, 0.755, and 0.719 for each center and the combined cohort respectively. Probability of retreatment stratified by risk score for the combined cohort is as follows: -2, 4.9%; -1, 5.7%; 0, 5.8%; 1, 13.1%; 2, 19.2%; 3, 34.9%; 4, 32.7%; 5, 73.2%; 6, 89.5%; 7, 100.0%.

Conclusions: Surgical decision-making and patient-centered informed consent require comprehensive and accessible information on treatment efficacy. The Aneurysm Recanalization Stratification Scale is a valid prognostic index. This is the first comprehensive model that has been developed to quantitatively predict retreatment risk following endovascular therapy.

729. Longer Delays from Pain Diagnosis to Spinal Cord Stimulation Result in Higher Post-Implant Healthcare Utilization

Frank William Petraglia III; Alexander Kent, PhD; Nirav Dalal; Edward Karst, MS; Ashwini Sharan, MD; Peter Staats, MD, MBA; Shivanand Lad, MD, PhD (Durham, NC)

Introduction: The long-term therapeutic efficacy of spinal cord stimulation (SCS) has been reported to decrease with longer delay times from chronic pain diagnosis to SCS implantation. The objective of this analysis was to determine the impact of this pain-to-SCS procedure time on patients' post-implant healthcare utilization.

Methods: A retrospective analysis was performed using the Truven Health MarketScan® Database analyzing patients' claims data from April 2008 through March 2013. The predictor variable was the time from the first diagnosis of chronic pain to permanent SCS implant. Using multivariate regression, we studied the impact of pain-to-SCS procedure time on healthcare utilization in the first year post-implant.

Results: A total of 753 patients met inclusion criteria, with a median pain-to-procedure time of 1.36 years (Q1: 0.84, Q3: 1.91). For every one-year increase in pain-to-procedure time, the odds increased by 47% for being in the high inpatient/outpatient medical expenditures group (defined using the third tercile: \$4,255-359,084) over the low group (first tercile: \$0-650). The odds increased by 50% for being in the high opioid prescriptions group (9-58 prescriptions) over the low group (0-1). The odds increased by 53% and 61%, respectively, for being in the high office visits (7-77) or hospital visits (2-28) group over the low office visits (0-2) or hospital visits (0) group.

Conclusions: We found that healthcare utilization in the first year following SCS implantation increased with longer delays from pain-to-SCS procedure time. These results suggest that considering SCS earlier in the care continuum may reduce the economic healthcare burden of patients with chronic pain.

746. Exceptional Response of Papillary Craniopharyngioma to Targeted Therapy

Priscilla Kaliopi Brastianos; Ganesh Shankar, MD; Corey Gill; Amaro Taylor-Weiner; David Panka, PhD; Ryan Sullivan, MD; David Louis, MD; Sandro Santagata, MD, PhD; Daniel Cahill, MD, PhD; William Curry, MD; Frederick Barker, MD (Boston, MA)

Introduction: Craniopharyngiomas cause significant deficits

through mass effect at presentation and are associated with high morbidity after treatment with surgery and radiation. We recently reported that BRAF V600E is the principal oncogenic driver in papillary craniopharyngioma: 96% of these tumors harbor this mutation, for which effective drug treatment has been developed in metastatic melanoma.

Methods: We treated a patient with a multiply-recurrent papillary craniopharyngioma known to harbor the V600E BRAF mutation using the BRAF inhibitor, dabrafenib, and the MEK inhibitor trametinib. To detect V600E mutant DNA in peripheral blood, we used an assay recently described for detecting this mutation in melanoma and thyroid cancer patients. Whole exome sequencing was performed on pre- and post-treatment tumor samples.

Results: After 38 days of treatment with targeted therapy, there was an 85% volumetric reduction in the enhancing tumor mass, from an initial volume of 9.5cc to 1.5cc after treatment. A small associated tumor cyst also reduced in volume, from 0.6cc to 0.1cc. Whole exome sequencing found no new treatment-acquired mutations that could mediate tumor escape from MAPK pathway inhibition. We also detected circulating BRAF V600E in the patient's blood at several times during treatment, at levels significantly elevated above normal controls.

Conclusions: We demonstrate the first response of a craniopharyngioma to rationally chosen targeted drug therapy, as well as the presence of circulating tumor-specific DNA harboring the mutation necessary for tumor sensitivity to these drugs. These findings suggest that clinical trials of these drugs in papillary craniopharyngiomas are urgently needed.

700. The Arc-Quadrant Principle of Stereotaxis: Used, Forgotten, Rediscovered and Inspired by Warfare

Cole A. Giller, PhD, MD, FAANS (Augusta, GA)

Introduction: The principle of arc-quadrant stereotaxis was introduced by Leksell in 1949. Its history, however, began more than 50 years earlier, motivated by the need to localize bullet fragments. We trace this principle from its development in 1897.

Methods: Sources included: articles regarding the device of Contremoulins (1897-1898); authoritative texts and articles regarding foreign bodies (1916-1938); Leksell's autobiography; biographies of Contremoulins and Hirtz; and published comments regarding Leksell. A Hirtz compass owned by this writer was used to clarify its operation.

Results: Shortly after X-rays were discovered, Contremoulins and Remy announced their technique for localizing foreign bodies. A portable 'compass', registered to facial tattoos, held a pointer sliding along an arc as it identified a target localized by wires strung between the X-ray sources and the object's image. Two patients were successfully treated. The inventors were celebrated in the literature and awarded the prestigious Montyon prize. Contremoulins later became an important figure in French radiology. Further development led to the popular Hirtz compass, used extensively in WWI and included in multinational textbooks. These devices were then abandoned for simpler procedures, forgotten, and scarcely mentioned after 1920. Leksell later commented that the emphasis for his arc-quadrant frame arose in part from his experiences with gunshot wounds during the Winter War between Finland and Russia.

Conclusions: Over a period of 50 years, the arc-quadrant method was developed, extensively used, forgotten and then rediscovered. Each stage of its development was motivated by the surgical need to localize bullet fragments.

701. Sir Hugh Cairns - Cushing's Most Enduring Resident

James L. Stone, MD, FAANS, FACS; Vimal Patel, PhD; Julian Bailes, MD (Chicago, IL)

Introduction: The Oxford scholar Sir Hugh Cairns (1896-1952) had superb presence and a charismatic personality. An exacting planner with remarkable work capacity, he inspired the right people to accomplish lofty plans. A favorite resident (1926-1927) of Harvey Cushing whose career he closely emulated, Cairns was the first British surgeon fully limited to neurosurgery and led a massive medical school renovation at Oxford. Cairns World War II (WWII) military leadership resulted in monumental progress in triage, surgical care, and outcome from head injury.

Methods: We reviewed Cairns publications, biographical material, and information on physicist Hylas Holbourn (1907-1962) selected to work on helmet development and theoretical biomechanics of brain injury. We interviewed neuropathologist Sabina Strich, a co-worker of Cairns and Holbourn.

Results: Cairns team opened a Military Head Injuries Hospital, the first spinal cord injury center and rehabilitation hospitals. The results were WWII advances in head injury management and elucidation of the role of damaging angular shear forces in brain injury. His innovations—mandated motorcycle helmets, helmet design, mobile neurosurgical units providing definitive care of injuries near battle zones, and introduction of penicillin in civilians and the military—saved thousands of lives.

Conclusions: Cushing residents advanced operative techniques, progress within medical schools, and neurosurgical organizations. Cairns did likewise, but implemented monumental WWII life saving advances to include helmets; mobile army surgical hospitals (MASH units); the first neurological injury centers; and stimulated a generation neurosurgeons in neurotrauma treatment. The Cairns/Holbourn biomechanical theories contributing to concussion and diffuse brain injury remain influential to the present time.

702. Dr. Louise Eisenhardt: Protégé to Harvey Cushing and Pioneer for Women in Neurosurgery

Thana Theofanis, MD; Pascal Jabbour, MD; Robert Rosenwasser, MD; Stavropoula Tjoumakaris, MD (Philadelphia, PA)

Introduction: Through her work with Harvey Cushing, Dr. Louise Eisenhardt contributed a wealth of data on intracranial tumors to the neurosurgical community. Furthermore, she is one of the first women to become established as a leader in neurosurgery.

Methods: A review of historical texts and articles was performed, to study the life of Dr. Louise Eisenhardt and her career in Neurosurgery.

Results: Dr. Louise Eisenhardt began working as Cushing's editorial assistant in 1915. In 1921, she enrolled at Tufts University School of Medicine. She graduated in 1925 with the highest scholastic record ever attained while simultaneously continuing her work for Cushing. After an internship at the New England Hospital for Women and Children, she joined Cushing as a Junior Associate in Surgery. Eisenhardt became an essential authority in the operating room, known for meticulous record keeping in her infamous black book and made diagnoses of tumors and tissues as Cushing removed them. Eisenhardt also became the first managing editor of the *Journal of Neurosurgery* (JNS) and first female President of the AANS. During her tenure with the JNS she logged her first 14 years of editorial decisions, establishing a peer-review process with the highest level of integrity.

Conclusions: Dr. Louise Eisenhardt reaped tremendous success as a result of documenting accurate observations and honest reporting of findings. During her time as President of the AANS

and Managing Editor of JNS, she established herself as a true role model of the work ethic and professionalism required to succeed in Neurosurgery.

703. History and Evolution of Endovascular Neurosurgery

Ahmed Cheema, MD; Phillip Bonney, BS; Andrew Conner, MD; Chad Glenn, MD; Sam Safavi-Abbasi; Bradley Bohnstedt, MD (Oklahoma City, OK)

Introduction: Endovascular treatments for neurological pathologies have evolved over time and are now a mainstay of our practices. We review the evolution of endovascular as a field.

Methods: We performed a literature review regarding the development of the endovascular concept to the present.

Results: Since the first successful intravenous access by Major in 1662, major advances have been made to access vessels as means of resuscitation, treatment and diagnosis of pathologies. The concept of having controlled physiological response to foreign agents introduced intravenously or intra-arterially has lead to efforts as early as in 18th century to coagulate aneurysms using heated needles directly introduced into the sac. The astute observation by Moore in 1864 of fibrin clot around a bullet wound and earlier experiments by Phillip in canine models in 1832 further progressed these thoughts to find ways of controlling the extent of inflammation and obliteration response. These radical views were not entertained originally based upon poor results. The parallel evolution of technologies including arterial access by Hurter (1912) and Stadie (1919) and earlier discovery of X-rays (1895) lead to first successful angiogram by Moniz (1926). Furthermore, the Seldinger technique (1951), angioplasty by Dotter (1969), detachable balloons by Serbiniko (1974) and detachable coils by Guglielmi (1990) have put forward the endovascular route of treating cerebral pathologies upfront as genuine treatment options.

Conclusions: Endovascular access and therapies have evolved significantly over time. The ongoing technological advances have put forward the endovascular method as a major treatment modality in neurosurgery.

704. Joseph Warren: A Discussion of his Life and Analysis of his Death

Ryan Holland; Victor Sabourin; Chirag Gandhi, MD; Peter Carmel, MD; Charles Prestigiacomo, MD (East Brunswick, NJ)

Introduction: On June 17, 1775, troops from Great Britain met those from the Thirteen Colonies at the Battle of Bunker Hill. Among those soldiers was Joseph Warren, a medical doctor and political activist. He earned fame by holding several public offices and writing newspaper articles that supported the colonies' fight against a perceived oppressive government. Although it was known soon after the battle that Warren had died at Bunker Hill, the details of his injury and last living moments remained a mystery.

Methods: Biographies, contemporary sources, and pictures of Warren's skull were analyzed in order to describe his life and get an accurate depiction of his death.

Results: Almost immediately after Bunker Hill, rumors and lore spread about Dr. Warren. There were differing stories on where he was shot and his level of activity afterwards. After being discovered by Paul Revere, Warren's bullet-laden skull provided insight into how he was killed defending the country he loved. The smaller gunshot wound in the skull's left maxilla and larger one in the right occiput suggests that Warren was shot facing his shooter and died instantly after an intracranial injury.

Conclusions: Joseph Warren was not shot in the forehead nor the back of the head as was originally reported. He also died instantly and therefore gave no final speech to his men before his death. If not for his untimely death, Warren would have played an influential role as Major General of the Continental Army and in the future of the young country.

705. Russell Meyers (1904-1999): Pioneer of Functional and Ultrasonic Neurosurgery

Taylor John Abel, MD; Timothy Walch, PhD; Matthew Howard, MD (Iowa City, IA)

Introduction: Advances in functional neurosurgery, including neuromodulation and more recently ultrasonic ablation of the basal ganglia, have improved life for patients with debilitating movement disorders. What is little known, however, is that both of these neurosurgical advances have their origin in the pioneering work of Russell Meyers, whose contributions we document in this paper.

Methods: To study the life and contributions of Russell Meyers, we reviewed his published work and professional correspondence in addition to documents held by the Department of Neurosurgery at the University of Iowa.

Results: Meyers received his neurosurgical training at hospitals in New York City. In 1939, a chance encounter with a young woman with damaged bilateral ventral striata convinced Meyers that the caudate could be lesioned to treat parkinsonism without disrupting consciousness. Shortly thereafter, he performed the first caudate resection for postencephalitic parkinsonism. In 1946, Meyers became the first Chairman of Neurosurgery at the State University of Iowa, which led to the mentoring of 8 faculty members and 18 residents during his tenure. Through collaboration with the Fry brothers at the University of Illinois, Meyers performed the first stereotactic ultrasonic ablations of deep brain structures to treat choreoathetosis, dystonia, intractable pain, and hypothalamic hamartoma. Meyers left academic neurosurgery in 1963 for reasons that are incompletely understood, but he continued clinical neurosurgery work for several more decades.

Conclusions: Despite his early departure from academics, Meyers' contributions to neurosurgery provided a legacy that has improved the lives of many movement disorder patients.

706. Spine trauma evolution in 20th century by "Chance", "Howland" & Jefferson: British Revolution in Medicine

Jai Deep Thakur, MD; Richard Menger, MD; Osama Ahmed, MD; Matthew Hefner, MD; Anil Nanda, MD (Shreveport, LA)

Introduction: Even though the concepts of spinal cord injury originated in 3000 BC under the Egyptian Empire, the spine trauma and its management was relatively slow to sprout. The understanding of spine trauma gained its full throttle in Europe in the 20th century with 'World War' playing the necessary evil. Neurosurgeons encounter Jefferson, Chance and Howland fractures commonly, however, history of these eponymous names is a literature to be unlocked.

Methods: Literature search using historical database, Cochrane, Google scholar and Pubmed was done.

Results: Sir Geoffrey Jefferson (1886-1961) pioneering neurosurgeon obtained his MBBS from Manchester University, England in 1909. Only a decade later he published his cases describing the atlas fractures and penetrating traumas only to find him being elected as a Fellow of the Royal Society. George Quentin Chance, also a Manchester based British physician has

been considered an eminent radiologist in his time. His notations and observations lead to greater understanding of spine trauma and associated biomechanics. He described the eponymous fracture in 1948. It was actually EA Nicoll who used the term Chance Fracture. Sir Frank Wild Holdsworth (1904-1969) renowned British orthopedist laid strong foundation in the rehabilitation of spinal injuries under the aegis of the Miners' Welfare Commission. Holdsworth Fracture we all know was published as "Fractures, dislocations, and fracture-dislocations of the spine in the *Journal of Bone and Joint Surgery*, February 1963.

Conclusion: This abstract discusses the journey of these physicians and associates the radiating growth in spine trauma during the past century.

707. The Surgical Treatment of Head Injury in the Continental Army

Manan Shah, BA; Victor M. Sabourin, B.A.; Frederick Yick, BA; Chirag Gandhi, MD; Charles Prestigiacomo, MD (Clifton, NJ)

Introduction: The American Revolution was a gruesome war and during that time, the treatment of traumatic head injury as well as the origins of American neurosurgery in the 18th century were elucidated. The Continental Army's surgical manual was titled Plain Concise Practical Remarks on the Treatment of Wounds and Fractures first published in 1775 by Dr. John Jones. This manual, which is reviewed here, explains the different types of cranial injuries understood at that time and the relevant surgical treatments.

Methods: Review and classification of head injury during the Revolutionary War according to Plain Concise Practical Remarks on the Treatment of Wounds and Fractures.

Results: Scalp injuries included incisions, punctures, lacerations, and contusions. Large incisions were treated with sutures and bandages. Punctures were surgically drained if there was a fluid collection, otherwise they would be treated as incisions. Lacerations could have pericranial detachment and were treated by re-approximating skin edges and sutured. Concussions were sometimes examined for intracranial injury and subsequently trephined if necessary. Depressed and undepressed fractures of the skull were usually treated with trephination and hematoma evacuation if visible. If no hematoma was found, the surgeon would divide the dura. Trephination was a complicated and potentially lifesaving surgical technique used during the Revolutionary War for the treatment of acute head injury.

Conclusions: Management of head injury during the Revolution was well defined by Dr. John Jones in his surgical manual. This work can therefore be considered as one of the earliest examples of American neurosurgical literature.

708. Unsung Hero: Donald Darrow Matson's Legacy in Pediatric Neurosurgery

Roberta Rehder; Subash Lohani, MD (Boston, MA); Alan R. Cohen, MD, FACS, FAAP, FAANS

Introduction: Donald Matson, whose life was cut short by catastrophic illness, made seminal contributions to pediatric neurosurgery and is considered one of its founding fathers. Here we discuss his extraordinary career, emphasizing his scholarly accomplishments along with little known vignettes about his personal life.

Methods: Retrospective review of archival records from Boston Children's Hospital.

Results: Matson was born in 1913, the youngest of four sons

of an army colonel. He graduated from Harvard Medical School in 1939 and did his neurosurgical training with Franc Ingraham, who founded the field of pediatric neurosurgery in 1929. Matson's training was interrupted by WWII, where he served as a neurosurgeon under General Elliot Cutler. He returned as Ingraham's partner. He was a gifted technical surgeon. With, Ingraham, he published *The Neurosurgery of Infancy and Childhood* in 1954- the first pediatric neurosurgery textbook in the world. He served on the ABNS, the *Journal of Neurosurgery*, and became President of the AANS. But Matson was unable to preside at his meeting of the AANS, set in Cleveland in 1969 to mark the 100th anniversary of Cushing's birth. Matson contracted Jacob-Creutzfeldt disease, which ended his life later that year.

Conclusions: Matson has been under-recognized for his role as a founding father of pediatric neurosurgery. Upon Ingraham's death in 1965, Matson assumed the chairmanship of neurosurgery at Boston Children's Hospital and the Brigham. In 1968 he became the first Ingraham Professor at Harvard Medical School. Sadly, he died a year later at age 55, surviving his mentor by only four years.

709. Early Craniometry as a Predecessor to Neurosurgical Stereotaxis

Demitre Serletis, MD, PhD, FRCSC, FAANS; T. Glenn Pait (Little Rock, AR)

Introduction: Craniometry refers to early cranial measurements used for the accurate correlation of external skull landmarks to specific brain regions. Largely drawing on methods from the newly-emerging fields of physical anthropology and phrenology in the late 19th and early 20th centuries, basic mathematical concepts were combined with simplistic mechanical tools, leading to the first known attempts at craniocerebral topography.

Methods: We present here a comprehensive and systematic historical review of the most popular craniometric techniques and tools developed prior to the advent of modern-day stereotactic techniques, for the purposes of craniocerebral measurement and target localization.

Results: Our methodological description of early craniometric techniques covers the contributions from early physical anthropology, phrenology (i.e. cranioscopy) and the 'school' of cortical localization. The subsequent advent of surgical craniometry sought to define fixed coordinates along the cranium on the basis of external, measurable landmarks that were linked to the underlying cerebral topography.

Conclusions: The pre-imaging epoch of craniometry, and the creativity and ingenuity used to solve the challenge of reproducibly and reliably accessing a specific target in the brain, laid the foundation for sophisticated advances in modern-day neurosurgical stereotactic techniques.

710. The Original Cushing Society: A Historical Review of the Senior Society's First 6 Meetings

Analiz Rodriguez, MD PhD; Ann Liu, BS; Aravind Somasundaram, BS; Donald Quest, MD; Stephen Tatter (Winston Salem, NC)

Introduction: The Society of Neurological Surgeons (SNS), founded in 1920, is the oldest neurosurgical society. The founding members were prominent leaders of American neurosurgery and met bi-annually. Initial meetings were forums to observe and discuss new surgeries.

Methods: The Society of Neurological Surgeons collection was reviewed at the Dorothy Carpenter Archives of Wake Forest

University. The membership, meeting notes, publication records, and Dr. Cushing's correspondences from 1920 to 1922 were reviewed.

Results: During the first six meetings of the SNS, surgical cases from the areas of cranial trauma, epilepsy, spinal cord tumors, brain tumors, pituitary tumor, trigeminal neuralgia and cerebellar tumors were discussed. Publications from the members during that time included articles on the use of hypertonic saline, trigeminal neuralgia, brachial plexus injuries, management of head injury, spinal cord tumors, cervical spine trauma, and intracranial hemorrhage in the newborn. A summative table of the cases and publications of the SNS members are presented. The members also had invited lectures by other specialists (i.e. neurology, ophthalmology, radiology, pathology) typifying the interdisciplinary nature of neurosurgical practice. The meetings served as a forum to build consensus on neurosurgical treatment methods. Cases that ultimately changed the practice of neurosurgery at that time will be profiled.

Conclusions: The SNS began as a traveling club of neurosurgical leaders who learned from each other's clinical experience to mold this burgeoning new field. However, the members made an impact on how neurosurgery was practiced nationally. The SNS remains a premier society that continues to educate the neurosurgeons of tomorrow.

711. A Chest Surgeon in a Neurosurgery Photo: the Influence of Edward Archibald on Early 20th Century Neurosurgery

Mark C. Preul, MD; Aqib Zehri, BS; Ali Elhadi, MD; Evgenii Belykh, MD; Ting Lei, MD; Richard Leblanc, MD (Phoenix, AZ)

Introduction: Edward Archibald, regarded as the father of thoracic surgery in America, was also Canada's first real neurosurgeon and crucially inspired the Montreal Neurological Institute. We sought to provide an examination of Archibald's profound contributions to the development, professionalization, and practice of neurosurgery. In the early 20th century, neurosurgery evolving: procedures performed by general surgeons, who either trained themselves or learned through collaborations with neurologists. Neurosurgical practice at Montreal's Royal Victoria Hospital developed in similar fashion, although Archibald was sent off for neurology training with Gowers and neurosurgery training with Horsley. Archibald's neurosurgical monograph in Bryant and Buck's *American Practice of Surgery, Surgical Affections and Wounds of the Head* was published in 1908, the same year as Cushing's monograph in Keen's *System of Surgery*. These monographs revolutionized neurosurgical instruction, being singularly influential for a decade. Whether or not deserving, Cushing's work was hailed, recognized as the first real modern neurosurgical guide. However, careful reading of Archibald's work reveals a longer, more illustrated, more systematically organized and comprehensible work aimed at educating regarding surgery of the brain to perform common neurosurgical procedures written in step-by- step fashion. Even though dedicated to chest surgery, his early career was cast around a neurosurgical need that he accepted as benefiting patients and for the good of McGill. Archibald is recognized for his altruistic passion for recruiting arguably Canada's two most famous physicians nearly in the same year: Wilder Penfield and Norman Bethune. Although Cushing and Sachs did not want general surgeons who fancied themselves as also neurosurgeons to join the Neurosurgical Club, the Society of Neurological Surgeons, Cushing recruited Archibald into the society. Archibald figures prominently, although unrecognized to many neurosurgeons in a 1922 photograph of the earliest members of the society. His endeavors and contributions are part of neurosurgery's important legacy.

712. Intrathecal Resiniferatoxin for Intractable Cancer Pain

John D. Heiss, MD, FAANS; Michael Iadarola, PhD; Amina Oughourli, BSN; Fredric Cantor; Bryan Jones, MD; Michael Royal; Andrew Mannes, MD (Bethesda, MD)

Introduction: Resiniferatoxin (RTX) is a small organic compound and agonist of the transient receptor potential cation channel, subfamily V1 (TRPV1). TRPV1 is highly-expressed on primary afferent (C and A-delta) neurons and superficial dorsal horn interneurons that transmit pain and temperature sensation. RTX induces rapid excitotoxic programmed cell death of these neurons. After intrathecal RTX treatment, companion dogs with lower limb cancer increased their mobility, suggesting pain relief.

Methods: An open-label, single-site (NIH) phase I clinical trial of ascending IT RTX doses in cancer patients with severe, medically-refractory pain is ongoing. RTX is administered via spinal catheter and under general anesthesia. Patients are awakened, observed overnight, and discharged to home. NRS pain scores, BPI pain interference items, quality of life, thermal sensitivity, opioid use and spontaneous adverse reactions are measured before and at defined intervals after RTX administration. A pilot study and two 3-person dose cohorts have been completed.

Results: Pilot study patients experienced variable amounts of pain relief. In the two higher dose cohorts, most patients improved with overall average worst pain intensity decreasing 20% and the 7 BPI pain interference items decreasing 1.6 point at the 2 week time point. The 2 patients with pain-limited mobility improved substantially (wheelchair or bed-bound to walking) after RTX. Reduced thermal sensitivity accompanied pain relief, consistent with the TRPV1 mechanism, but no other sensory or motor changes occurred. No DLTs were identified.

Conclusions: These preliminary findings suggest that IT RTX can produce significant pain reduction in patients with persistent cancer-related chronic pain. Additional dose cohorts are planned.

713. Clinical Paresthesia Atlas Illustrates Likelihood of Coverage Based on Spinal Cord Stimulation Electrode Location

Alexander Taghva, MD; Paul Underwood, RN; Edward Karst (Mission Viejo, CA)

Introduction: Therapeutic success of spinal cord stimulation (SCS) and paresthesia coverage depends on proper lead placement with regard to spinal level, as different levels provide different patterns of coverage. While some published data exist, no definitive "atlas" correlating perceived patient paresthesia locations with spinal level of electrode placement has been developed with contemporary SCS systems.

Methods: The St. Jude Medical EMPOWER study was a prospective, non-randomized, outcomes-oriented study of patients considered for percutaneous or paddle-lead SCS systems. Patient evaluation, SCS device programming, spinal x-rays, and paresthesia maps were recorded at time of permanent implant and at 3, 6 and 12 month follow-up visits. Paresthesia maps consisted of a 106-segment visual diagram completed by the patient at the visit. X-ray locations of each SCS lead electrode were reviewed and tallied by a single neurosurgeon while blinded to paresthesia location. Active cathodes on stimulation programs utilized at the time of paresthesia map collection were correlated with corresponding lead electrode X-ray locations to develop level-specific paresthesia maps.

Results: The study enrolled 636 candidates for SCS at 31 investigational sites between August 2009 and February 2013. There were 565 patients who had trials, with 408 permanent systems implanted (183 percutaneous, 225 paddle). Follow-up data were

available at 3 months (329 patients), 6 months (286 patients), and 12 months (213 patients). Paresthesia maps corresponding to active cathodes from T6-L1 were generated. Differential coverage of low back, legs, feet as well as unwanted lateral stimulation was evaluated. In addition, a relational database, graphical user interface, and other related tools were designed and implemented (by the lead author) for data manipulation and querying.

Conclusions: The spinal cord stimulation atlas may provide a clinically valuable tool for SCS implantation as well as a source for data-driven research.

714. Low Back Pain Relief and Patient-Specific Programming Optimization with a new 32-Contact Spinal Cord Stimulation (SCS) Surgical Lead

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Introduction: Spinal cord stimulation (SCS) has become standard in treating lumbosacral radiculopathy, with reports of up to 70% leg-pain relief (Stidd et al. 2014). Historically, however, SCS has been more challenging for low-back pain, attributed to less representation of the back within dorsal columns, resulting in less availability to superficial stimulation (Oakley, 2006). It has been postulated recently that advances in surgical leads and programming capabilities would result in increasingly effective low-back pain relief (Kinfe et al., 2012). The best example of this is the recently introduced 32-contact surgical lead. Coupled with 32-contact multiple independent current control and anatomically-based stimulation targeting algorithms, this lead allows for patient-specific programming optimization previously not possible.

Methods: We present here a multi-center consecutive case-series of our early experience with the new 32-contact surgical lead, using Spectra and Illumina 3D programming. We examine data from 20 patients across 5 centers, including medical history, procedural information, pain reduction, and disability, and quality of life.

Results: Clinical outcomes from 20 patients will be presented out to 3 months post-implant. Additionally, in-depth analysis of stimulation parameters and patient-specific optimization will be presented, including multivariate correlation with baseline patient characteristics.

Conclusions: Effective treatment of low-back pain has long been challenging. New developments in SCS technology may offer previously unavailable options for low-back pain patients. Data presented here is intended to begin a discourse on the potential of new surgical leads and programming algorithms to fully address the needs of these patients.

715. Longitudinal Study of Pain and Functional Abilities in Chiari 1 Malformation and Syringomyelia

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Introduction: To characterize disease burden and response to treatment of Chiari I Malformation and of syringomyelia we are conducting a longitudinal prospective study of pain and function in symptomatic patients with CM1 alone (CM1-A), CM1 with syringomyelia (CM1-S), and syringomyelia alone (S-A).

Methods: Based on baseline clinical and MRI evaluations, 56 patients with CM1-A (12), CM1-S (16), or S-A (28) were selected for operative treatment (N=30) or observation (N=26). Test scales administered at baseline and 1 year follow up included: a Numerical

Rating Scale of pain severity (NRS), Karnofsky Performance Status Scale (KPS), Motor Functional Independence Measure (FIM-M), Ambulatory Scale (AS), McCormick Clinical Functional Classification (MC), and the American Spinal Injury Association motor grading scale (ASIA).

Results: For the entire patient group, KPS and NRS ($p=0.0001$) inversely correlated. KPS and ASIA and FIM-M and NRS correlated less strongly. At Baseline, the Surgery group had lower function (KPS 73 ± 14) than the Observation group (87 ± 11). All Test Scale measurements at Baseline and at the 1 year visit were similar except for KPS which improved significantly ($p=0.002$). Within the patient groups, operated and non-operated patients had similar changes in Baseline and 1 year test scale measurements except for patients with CM1-A, in whom KPS improved more in non-operated than operated patients ($p=0.0473$). Persisting pain due to headache was related to cervical muscle spasm.

Conclusions: The favorable course of the operative and non-operative groups confirms that the criteria for recommending surgery or observation were appropriate and that surgical intervention halted progression.

716. Systematic Review of the Diagnostic Implications of MR Imaging in Trigeminal Neuralgia

David Darrow, MD; Heidi Johng; Coridon Quinn, MD; Stephen Haines, MD (Minneapolis, MN)

Introduction: Current diagnosis of idiopathic trigeminal neuralgia (ITN) is based upon clinical features as defined by the International Headache Society (IHS). Neurovascular compression (NVC) is significantly associated with presentation and has been reported in 80-90% of patients indicated for surgical microvascular decompression (MVD). While MVD directly corrects NVC, therapeutic advantages requires the presence of NVC confirmed by imaging. MRI has proven to be highly sensitive and specific in MVD candidates both clinically and surgically. However, many studies were performed without blinding and only correlated MRI with surgical findings. The aim of this study was to systematically review all available evidence regarding use of imaging in MVD to determine sensitivity and specificity for the diagnosis of ITN via identification of NVC via MRI.

Methods: An electronic search was done via MEDLINE for studies that prospectively investigated neurovascular compression in a blinded fashion with a reference standard of clinic ITN. For each study, methodological quality was assessed by QUADAS-2, and overall sensitivity and specificity was calculated along with stratified values for MRI technology and sequences.

Results: A total of 228 studies were reviewed for contribution to the systematic review. Of these studies, 18 used blinded radiological readings, meeting our designated criteria.

Conclusions: There are few studies that evaluate the utility of MRI in blindly confirming the diagnosis of NVC in ITN. Subsequent to our review, we designed a randomized and blinded study to evaluate the sensitivity and specificity as well as the interobserver kappa scores while taking into account evolving resolution and technology in MRI.

717. Impact of Tailoring Spinal Cord Stimulation Therapy on Clinical Outcomes

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Introduction: Spinal cord stimulation (SCS) systems can be tailored to treat patient-specific chronic pain characteristics. The objective of this work was to determine the impact of investigator-based patient tailoring of SCS on patients' clinical outcomes.

Methods: An analysis was designed using data from the St. Jude Medical EMP3OWERTM prospective, multi-center, post-market study. The extent of physician variation in permanent SCS placement was based on characteristics such as number, type, and location of leads implanted and used to calculate the fraction of unlike comparison (UC) score. The UC score serves as a measure of physician variability and tailoring of the procedure between patients. Clinical outcomes were evaluated at 3, 6, and 12 months post-implant.

Results: 407 patients were implanted with a permanent SCS device, with follow-up data available for 355 patients across 40 sites. A 10% absolute increase in the UC score for percutaneous leads was correlated with a 47% increase in the odds of having reduced opioid usage at 6 months ($p=0.009$). For paddle leads, a 10% increase in UC score was correlated to a 78% increase in the odds of having reduced opioid usage at 12 months ($p=0.03$).

Conclusions: These results suggest that investigator tailoring of SCS system characteristics including lead type and location have a significant impact on SCS clinical outcomes. Greater variation in both percutaneous and paddle SCS system characteristics by investigators generally corresponded to improved clinical outcomes at 6 and 12 months. These improved outcomes may be a consequence of matching SCS characteristics to patients' specific disease states and pain patterns.

718. When Trigeminal Neuralgia Is Associated with Skull Base Meningiomas

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Introduction: To evaluate the incidence and management of patients with trigeminal neuralgia (TN) associated with skull base meningiomas.

Methods: From our 27 year Gamma Knife® stereotactic radiosurgery (SRS) data base registry we identified 553 patients with skull base meningiomas. Fifty-two patients had medically refractory tumor-associated TN. SRS was the initial tumor management. The median duration between pain onset and SRS was 12 months (1-181 months). The median tumor volume was 5.4 cc (1.0-28.6 cc) and median margin dose was 13 Gy (11-18 Gy). The follow-up interval was 11-185 months (median, 65 months).

Results: TN was reported in 29 (11%) of 272 cavernous sinus meningiomas, 15 (9%) of 168 petroclival meningiomas, and eight (11%) of 74 cerebellopontine angle meningiomas. The probability of favorable pain relief (BNI grade I-IIIb) was 25% at 1 year, 39% at 3 years, and 43% at 5 years. A shorter pain history was associated with shorter interval until favorable pain relief after SRS (continuous data: $p=0.043$). The 5 year pain control rate was 54% in patients with < 1 year pain compared to 23% in patients whose pain history was < 1 year ($p=0.025$). Three patients (6%) had tumor progression and 32 (62%) had tumor regression. Tumor regression was not associated

with pain relief ($p=0.275$). Three patients had persistent pain despite delayed surgical resection.

Conclusions: Approximately 10% of patients with skull base meningiomas also suffer from TN. SRS provided tumor control in most patients but pain control proved more problematic. Continued medical management was needed in most patients.

719. Intraoperative Neurophysiological Monitoring for Lateralization and Programming in Spinal Cord Stimulation

Steven G Roth; Steven Lange, BS; Chris Fama; Jessica Haller; Michael Briotte; Steven Panicioli; Priscilla DeLaCruz, BS; Meghan Wilock, PA; Julie Pilitsis, MD, PhD (Ellicott City, MD)

Introduction: Accurate placement of the lead is critical for spinal cord stimulation (SCS) efficacy. Awake placement, the traditional gold standard, is often difficult and occasionally contraindicated. The use of intraoperative neurophysiological monitoring (IOM) is a proposed alternative; however the technique lacks thorough prospective evaluation. This study prospectively analyzes the use of IOM to lateralize placement. Additionally, we retrospectively assess whether IOM can predict stimulation contacts in use at 6 month follow-up.

Methods: 72 patients were implanted with SCS using electromyography (EMG) and somatosensory evoked potential (SSEP) collision studies to verify lead placement. IOM data were compared with contacts that demonstrated the greatest utility in alleviating pain as determined by device interrogation at 6 month follow-up.

Results: 58 patients had complete datasets for analysis. With EMG, we were able to lateralize the lead with 86.7% success. Using SSEP collision studies, we were able to lateralize the lead with 64.0% success. Leads were repositioned in 30.0% of cases as a result of IOM data. The contacts used intraoperatively for EMG had a sensitivity of 82.2%, a specificity of 18.2%, a positive predictive value of 87.0%, and a negative predictive value of 13.3% for predicting contacts in use at 6 months.

Conclusions: These data suggest that IOM is a viable method of verifying SCS placement. Additionally, EMG may be useful to help streamline device programming by predicting the ideal contacts in many cases.

720. Role of Plasma Membrane Calcium ATPase 2 (PMCA2) in Nociceptive Processing in the Spinal Cord

Veronika Khariv; Wei Dong; Robert Heary; Stella Elkabes (Newark, NJ)

Introduction: PMCA2 is a calcium extrusion pump expressed primarily in neurons of the spinal cord (SC) and brain. It plays an important role in ventral horn motor neuron function and viability. However, its role in sensory neurons of the dorsal horn and contribution to central nociceptive processing remains undefined.

Methods: Thermal sensitivity was assessed by the hotplate paw withdrawal test. Western blots evaluated protein levels in the dorsal horn. A SC contusion injury (50 kdynes) was induced in PMCA2^{+/+} and PMCA2^{-/-} mice at thoracic T8 level using the Infinite Horizon Impactor. ANOVA and t-test were used for statistical analysis.

Results: Naive, PMCA2^{+/+} mice ($n=17$) show reduced sensitivity to a thermal stimulus with a 33% increase in paw withdrawal latency compared to PMCA2^{+/+} ($n=12$) littermates ($t(27)=3.60$; $p=0.001$). Decreased thermal sensitivity was also observed in PMCA2^{-/-} mice sustaining SCI ($F(1,15)=12.29$; $p=0.003$; $n=8-9$). Since GABAergic, NMDA receptor, and metabotropic glutamate

receptor (mGluR)-expressing neurons contribute to mechanisms of nociception, protein levels in the dorsal horn were quantified. No significant differences were observed in NMDAR2B or GAD levels. Surprisingly, mGluR1 levels were significantly increased by 86% in the dorsal horn of PMCA2^{+/+} mice ($t(11)=3.64$; $p=0.004$; $n=5-8$).

Conclusion: These findings suggest that PMCA2 plays a role in nociception. Although a reduction in PMCA2 causes specific perturbations in the dorsal horn exemplified by increased mGluR1, it remains to be determined whether and how the culmination of such changes results in reduced nociception.

721. Repeat Radiosurgery for Recurrent Trigeminal Neuralgia

Corbin Andrew Helis, BS; John Lucas, Jr.; J. Bourland, PhD; Michael Chan, MD; Stephen Tatter, MD, PhD; Adrian Laxton, MD (Winston-Salem, NC)

Introduction: Repeat gamma knife radiosurgery (GKRS) is an established option for patients whose trigeminal neuralgia (TN) has recurred after initial GKRS. Predictive factors for response to repeat GKRS are not established. This study aimed to report the outcomes of patients who have undergone repeated GKRS for trigeminal neuralgia at a single institution and determine factors that predict good outcomes.

Methods: Between 1999 and 2013, 152 patients have undergone repeat GKRS at Wake Forest, 125 of whom were available for long term follow up. A retrospective chart review and telephone interviews were conducted to determine background medical history, dosimetric data, outcomes, and adverse effects.

Results: 84% of patients achieved at least BNI IIIb pain relief, with 46% achieving BNI I. The 1, 3, and 5 year rates of BNI I pain relief were 63%, 50%, and 37% respectively. The 1, 3, and 5 year rates of BNI IIIb or better pain relief were 74%, 59%, and 46% respectively. One patient experienced bothersome numbness and two developed anesthesia dolorosa. The dominant predictive factors for pain relief were facial numbness after the first GKRS and a positive pain response to the first GKRS.

Conclusion: Repeat GKRS is an effective method of treating recurrent trigeminal neuralgia. Patients who have facial numbness after the first treatment and a positive pain response to the first GKRS are significantly more likely to respond well to the second treatment.

722. A Randomized, Prospective, Double Blinded Surgical Trial of a Somatic to Autonomic Intradural Nerve Anastomosis (Xiao Procedure) in Children with Neurogenic Bladder Undergoing Spinal Cord Detethering

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Introduction: Xiao et al have reported 67% to 86% success in the establishment of voluntary voiding in patients with neurogenic bladder dysfunction, purportedly the result of the establishment of a skin-CNS-bladder reflex arc created by an intradural somatic to autonomic lumbosacral nerve anastomosis. We designed a study to more rigorously analyze this novel procedure, which has generated great enthusiasm among patients and their physicians, as a possible transformative new procedure to allow voluntary voiding with neurogenic bladder dysfunction.

Methods: Twenty children with spina bifida undergoing spinal

cord detethering surgery were randomized between two arms: half of the patients underwent a standard detethering procedure, with the other half undergoing detethering plus the Xiao procedure. Patients, families and health care providers, who were blinded to the treatment arm, analyzed motor and sensory function, ADLs and bladder function before surgery and at 3, 6, 9, 12, 24 and 36 months after surgery using extensive questionnaires, physical examinations and detailed urodynamic studies.

Results: All 20 patients completed the 3-year follow-up evaluation period. No child in either group had a reproducible, reliable and useful ability to initiate normal voiding at their three-year follow-up. Early results of over 1,000 clinical outcome data points per patient will be summarized.

Conclusions: This rigorous evaluation of the Xiao procedure failed to produce reliable and reproducible improvements in bladder function or voluntary voiding in children with spina bifida when compared to patients who underwent a standard spinal cord detethering procedure.

723. Neural Placode Tissue Derived from Myelomeningocele Repair Serves as a Viable Source of Oligodendrocyte Progenitor Cells

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Introduction: Central nervous system injury remains a leading cause of permanent functional compromise. Despite evidence suggesting potential for restoration of neurological function through cell-based repopulation across a number of clinical applications, successful efforts through the use of primary tissue, embryonic stem cells, and induced pluripotent stem cells remain thus far limited. Recent evidence suggests the tendency of neural stem cells to reside adjacent to ependymal-lined surfaces along the central nervous system axis. Given such neuroanatomical correlation and regenerative capacity in fetal development, we assessed neural placode tissue as a potentially novel source of neural stem and progenitor cells.

Methods: Nonfunctional neural placode tissue was harvested from infants (n=3) during the surgical repair of myelomeningocele and subsequently further analyzed by in vitro studies, flow cytometry, and immunofluorescence. To assess lineage potential, neural placode-derived neurospheres were subjected to differential media conditions. Through assessment of PDGFR α and CD15 cell marker expression, Sox2+Olig2+ putative oligodendrocyte progenitor cells (OPCs) were successfully isolated.

Results: PDGFR α hiCD15hi cell populations demonstrated the highest rate of self-renewal capacity and multipotency of cell progeny. Immunofluorescence of neural placode-derived neurospheres demonstrated preferential expression of oligodendrocyte progenitor marker, CNPase, whereas differentiation to neurons and astrocytes was also noted, albeit to a limited degree.

Conclusions: Neural placode tissue contains multipotent progenitors that are preferentially biased towards oligodendrocyte progenitor cell differentiation and presents a novel source of such cells for use in the treatment of a variety of pediatric and adult neurologic disease, including spinal cord injury, multiple sclerosis, and metabolic leukoencephalopathies.

724. Supraclavicular donor nerve graft: A better way to repair neonatal brachial plexus palsy

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Introduction: Neonatal brachial plexus injuries often result in long-term disability for affected children. Historically, sural nerve donor grafts have been used for repair of the injured brachial plexus, requiring a separate incision for harvest. Utilization of donor nerve within the field of dissection (brachial plexus neurolysis) potentially offers reduced morbidity/larger donor graft. Long-term functional outcome of supraclavicular sensory nerve donor graft was compared to previously used sural grafts for reconstruction of neonatal brachial plexus injuries.

Methods: A retrospective chart review of patients with neonatal brachial plexus injuries undergoing surgery at Children's National Medical Center (1998 to 2014) was performed. Motor outcome was assessed by manual muscle testing (MMT grading).

Results: Over 15 years, 54 infants underwent brachial plexus reconstruction. 29 patients were male (54%) and 25 patients females (46%). Median age at surgery was 10.4 months (5.5-22.9), follow-up 27 months (6.8-181). The right side was involved 64%, left side 36%. A change in technique (past 3 years) led to 17/54 patients (31%) having supraclavicular nerve used as donor graft. One year follow-up demonstrated superior improvement for muscle strength when the supraclavicular nerve was used as donor graft. Improvement was seen in the deltoid, triceps, biceps muscles at 570.3%, 91%, 218% respectively for the supraclavicular graft compared to 262.9%, 67.4%, 119.2% for the sural nerve. Total muscle improvement was 570.3% for supraclavicular nerve graft compared to 262.9% for sural (P=0.002).

Conclusions: The use of a supraclavicular sensory nerve for grafting brachial plexus injuries offers a single incision, more graft material and has demonstrated an improved outcome in motor strength at one year and is now our standard approach.

725. Development and Validation of a Pediatric Occipitocervical Junction Finite Element Model: A Biomechanical Comparison

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Introduction: Recent biomechanical data from pediatric cadaveric specimens have enabled a better understanding of the flexion/extension range of motion (ROM) of the developing spine. Using this information, we developed a validated finite element (FE) model of the pediatric occipitocervical (Oc-C1-C2) complex for simulating the biomechanical effects of traumatic injury at the occipitocervical junction.

Methods: A FE model of the normal pediatric Oc-C1-C2 complex was created using Amira, ANSA, and FEBio software. Initially, adult ligament and cartilage material properties were used to create a model that simulated normal physiologic motion in flexion/extension. To account for the ligamentous laxity and increased motion present in children, the material properties of individual ligaments and cartilage were iteratively decreased until the ROMs predicted by the FE model were within one standard deviation of the ROMs from published experimental data.

Results: Flexion/extension ROMs were within one standard deviation of previously reported biomechanical data of children when cartilage and ligament properties were reduced to 10% of adult values. Experimentally measured ROMs were 19.8 +/- 9.68

degrees (flexion), 20.3 +/- 7.71 degrees (extension), and 40.2 +/- 10.5 degrees (total). The ROMs predicted by our model were 23.5 degrees (flexion), 16.4 degrees (extension), and 39.9 degrees (total), respectively.

Conclusions: We have developed a validated FE model of the pediatric Oc-C1-C2 complex that accurately predicts flexion/extension ROMs. Future studies will investigate the contribution of specific tissue structures on occipitocervical stability. Other directions include injury simulation and stability studies, with particular emphasis on atlanto-occipital dislocation.

725. Comparison of Pediatric NSQIP and KID database reports of perioperative complications in craniostomosis surgery

Yimo Lin; I-Wen Pan, PhD; Jill Gouvion; Thomas Luerssen, MD; Sandi Lam (Chicago, IL)

Introduction: The Pediatric NSQIP is a quality improvement/outcomes database collected by clinical reviewers; the Kids' Inpatient Database (KID) is a national administrative database. This study aims to ascertain the accuracy of clinical representation in large datasets by comparing the incidence of perioperative complications after craniostomosis surgery reported in the two databases.

Methods: Craniostomosis surgeries were identified by CPT codes in the Pediatric NSQIP database and by ICD-9 codes in KID over 12 months (year 2012). Perioperative complications were identified by pre-defined event variables in NSQIP and by ICD-9 codes in KID.

Results: A total of 572 cases (NSQIP) and 2620 cases (KID) of craniostomosis surgery were identified in 2012. The demographics were similar- mean (SD) age: 1.31 (1.9) years NSQIP, 1.12 (2.3) years KID, 31% female (NSQIP), 33% female (KID). Rates of wound disruption (0.5% NSQIP, 0.3% KID), ischemic/hemorrhagic stroke (0.2% NSQIP, 0.3% KID), convulsions (0.4% NSQIP, 0.7% KID), cardiac events (0.4% NSQIP, 0.4% KID), pulmonary events (0.5% NSQIP, 0.3% KID), infection (0.9% NSQIP, 0.2% KID) and sepsis (0.2% NSQIP, 1.6% KID) were low and similar between the two databases. The incidence of transfusion/hemorrhage was higher in NSQIP (68%) than in KID (36%).

Conclusions: Perioperative complication rates in Pediatric NSQIP and KID associated with craniostomosis surgery in children were generally similar, with notable variation in transfusion events. This discrepancy may be due to confounding differences in the studied populations or under-reporting in the KID due to limitations in the structure of administrative data.

730. Timing of Complications and Unplanned Readmission after Spinal Procedures in High-Volume Medical Centers in New York State

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Introduction: Reducing preventable hospital readmission after discharge has become a priority in current healthcare quality improvement efforts. In spinal neurosurgery, readmissions are frequently due to infectious complications (eg. surgical-site infections), hardware malfunction, and medical (eg. cardiac) complications. The timing of these causes of readmission, however, has not been well characterized. Knowledge of the timing may allow for targeted intervention so as to reduce readmission.

Methods: We conducted a longitudinal study of spinal neurosurgery cases from 2009-2012 using the New York Statewide Planning And Research Cooperative System (SPARCS), which collects patient-level details for nearly every hospital admission and discharge within the state of New York. Patients were initially admitted to the top-10 highest volume hospitals and then readmitted to any hospital within New York. The primary ICD-9 diagnostic code on readmission was used to determine the cause of readmission, and median time to readmission was calculated. Planned readmissions were excluded.

Results: Of the 37,682 patients admitted for a spinal procedure, 2,459 (6.52%) were readmitted within 30 days, and the overall median time between discharge and readmission was 10 days (IQR: 13). Early causes of readmission were new-onset neurological symptoms (median of 8 days) and venous thromboembolism (8.5 days). Somewhat later causes were medical complications (10 days), hardware complications (10.5 days), and infection (11 days).

Conclusion: Readmission after spinal neurosurgery tends to occur between the first and second weeks after discharge, and the causes of readmission occur at slightly different, yet predictable times. Our results suggest that one approach to reducing readmission rates may be by improving early follow-up that focuses on detecting these specific complications.

731. Measures of Surgical Effectiveness One-Year After Lumbar Spine Surgery Accurately Predict Two-Year Outcomes.

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Introduction: In light of Patient Protection and Affordable Care Act, there has been a shift toward critical analyses of quality and longitudinal assessment of subjective and objective outcomes after lumbar spine surgery. However, obtaining longitudinal outcomes for patients', 24-months after spine surgery remains a challenge. The aim of this study was to assess whether 12-month measures of treatment effectiveness accurately predict long-term outcomes(24-months).

Methods: A multi-institutional, prospective spine outcomes registry was utilized for this study. All patients had collected outcome measures and a minimum 2-year follow-up. Patient reported outcomes instruments (ODI,SF-36,VAS-BP/VAS-LP) were completed before surgery, then at 3, 6, 12, and 24-months after. The Health Transition Index of SF-36 was used to determine the 1- and 2-year Minimum Clinical Important Difference (MCID), and logistic Regression modeling was performed to determine whether 12-month measures of treatment effectiveness accurately predict long-term outcomes (24-months)

Results: The study group included 1506 patients(ALIF: 300 patients, TLIF: 606 patients , XLIF: 600 patients). There was a significant correlation between 12- and 24-month ODI ($r=0.82$; $p<0.0001$), SF-36 PCS ($r=0.89$; $p<0.0001$), VAS-BP($r=0.90$; $p<0.0001$) and VAS-LP($r=0.85$; $p<0.0001$). For ALIF cohort, patients achieving MCID thresholds for ODI at 12-months were 13 fold more likely to achieve MCID at 24-months. Similarly, for TLIF and XLIF cohorts, patients achieving MCID thresholds for ODI at 12-months were 13-fold and 14-fold more likely to achieve MCID at 24-months, respectively. Outcome measures obtained at 12-months post-operatively are highly predictive of 24-month outcomes, independent of surgical procedure.

Conclusions: In a multi-institutional prospective study, patient centered measures of surgical effectiveness obtained at 12-months adequately predict long-term(24-months) outcomes after lumbar spine surgery. Patients achieving MCID at 1-year were more likely

to report meaningful and durable improvement at 24 months; suggesting that 12-months time-point is sufficient to identify effective versus non-effective patient care.

732. The Influence of Spinopelvic Alignment on Development of Symptomatic Adjacent Level Disease Following Single Level Transforaminal Lumbar Interbody Fusion (TLIF)

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Introduction: The annual incidence of developing symptomatic adjacent level disease (ALD) following lumbar fusion surgery ranges from 0.6 to 3.9%. Sagittal malalignment may contribute to the development of symptomatic ALD. We describe the relationship between spinopelvic parameters and symptomatic ALD requiring revision surgery following single-level transforaminal lumbar interbody fusion (TLIF).

Methods: Patients who underwent a single-level TLIF at either L4/5 or L5/S1 at our institution for between July 2006 and December 2012 were analyzed for pelvic tilt (PT), sacral slope (SS), pelvic incidence (PI), lumbar lordosis (LL), and PI-LL mismatch. Univariate and multivariate logistic regression analysis was used to compare spinopelvic parameters of patients who required revision surgery for symptomatic ALD against those who did not. The sensitivities and specificities for symptomatic ALD requiring surgery were based on preoperative values of PT < 24° and pelvic mismatch < 12°.

Results: 159 patients met inclusion criteria. Multivariate logistic regression analysis found preoperative PI-LL mismatch (OR: 1.25 CI: 95% (1.16, 1.33) $p < 0.0001$), postoperative PI-LL mismatch (OR: 1.40 CI: 95% (1.27, 1.54) $p < 0.0001$), and postoperative change in LL (OR: 0.96, CI: 95% (0.92, 1.0) $p = 0.39$) to be statistically-significant independent predictors of symptomatic ALD requiring revision surgery. The sensitivity and specificity of PI-LL mismatch < 12° for symptomatic ALD requiring surgery were 81.82% and 86.54%. The positive predictive value for a postoperative PI-LL mismatch = 12° was 79.0%; the area under the receiver operating characteristic (ROC) curve was 0.92.

Conclusions: Abnormal preoperative spinopelvic parameters and persistent mismatch are associated with higher rates of symptomatic ALD requiring surgery following a single-level TLIF. Postoperative PI-LL mismatch was the strongest predictor. Accounting for spinopelvic parameters in the preoperative period may improve outcome following single-level TLIF.

733. Studying Mesenchymal Stem Cell Survival and Proliferation in Lumbar Posterolateral Spinal Fusion via a Murine Model

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Introduction: Clinically, bone marrow aspirate has been successfully used alongside various grafting materials to augment spinal fusion. Little is known about the survival and proliferation of these transplanted cells or how much they contribute to bone formation compared to host cells from adjacent decorticated bone. Insights into these cellular dynamics will yield a deeper understanding of the biological processes underlying spinal fusion and allow for evaluation and development of fusion therapies that reduce rates of pseudoarthrosis.

Methods: Forty FVB/NJ mice underwent posterolateral lumbar

spinal fusion surgery with one of 4 fusion grafts: syngeneic iliac crest bone (n=10), Vitoss® bone-matrix alone (n=10), Vitoss® bone-matrix with syngeneic bone marrow cells (2.5 x 10⁶ cell/side) (n = 10), or Vitoss® bone-matrix with transgenic luciferase-expressing syngeneic bone marrow cells (2.5x10⁶ cell/side) (n=10). Bone marrow cells were isolated from the long bones of either syngeneic FVB/NJ mice or syngeneic FVB mice which constitutively express the luciferase gene (FVB-Tg(CAG-luc,-GFP) L2G85Chco/J mice). In vivo survival, distribution and proliferation of transplanted luciferase-expressing cells were monitored via bioluminescence imaging over 8 weeks. Spinal fusion was assessed 4, 6 and 8 weeks post-surgery via microCT imaging. The number of donor vs. host cells within the fusion mass was evaluated via immunohistochemistry.

Results: Bioluminescence imaging data demonstrated an increasing signal from 24 hours to 2 weeks post-surgery, thus indicating cellular proliferation. Bioluminescence decreased between weeks 4 and 8 suggesting a loss of transplanted cells within the fusion mass at later time points. Correlations with histology and microCT imaging of the fusion mass are currently under analysis.

Conclusions: We have demonstrated a novel murine model which enables non-invasive in vivo monitoring of transplanted luciferase-expressing bone marrow cells following spinal fusion surgery. Future applications of this model include the assessment of therapeutics for improving spinal fusion.

734. Endplate Coverage Correlates with Heterotopic Ossification in One- and Two-Level Cervical TDR Patients

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Introduction: While cervical total disc replacement (cTDR) may lead to heterotopic ossification (HO), the etiology of HO is not fully understood. At 5 years post-operation, we examine whether the occurrence of HO is related to cTDR prosthesis endplate coverage.

Methods: A prospective, randomized, controlled clinical trial comparing cTDR and ACDF with 389 subjects receiving cTDR at one or two contiguous levels. Endplate coverage was measured as the ratio of the anteroposterior length of the contacting endplate to the anteroposterior length of the prosthesis for both the superior and inferior aspect of the prosthesis. Grades 3 and 4 HO were considered clinically relevant.

Results: At 5 years, the median HO grade was grade 2. Endplate coverage and HO grade were significantly related; less endplate coverage correlated to a higher HO grade ($p < 0.05$). The median endplate coverage was significantly larger for one-level patients with HO grades 0, 1, and 2 ($p < 0.01$). Two-level cTDR patients with HO grades 0, 1, and 2 also demonstrated higher endplate coverage, although not significant. No significant correlations were observed between HO grade and NDI, VAS neck pain, and SF-12 PCS scores.

Conclusions: Five-year results show a significant relationship between HO and endplate coverage of the prosthesis for one and two-level cTDR treatment. Patients with HO grades 3 and 4 did not correlate with a worse clinical outcome. Results suggest proper sizing of the prosthesis to the endplate may mitigate HO as an adverse event following cTDR treatment at one or two levels.

735. Patient demographics, insurance status, and race predict morbidity and mortality after spinal cord injury.

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Ammar Hawasli, MD; Michael Kelly, MD; Michael Kelly, MD; Ian Dorward, MD; Paul Santiago, MD; Neill Wright, MD; Wilson Zachary Ray, MD (Islamabad, Pakistan)

Introduction: Health-care disparities among preventable diseases have been an ongoing public health problem. Since trauma does not rely on the same infrastructure observed for preventable diseases, less disparity based on demographics and socioeconomic status may result. In this study, we reviewed all spinal cord injury (SCI) admissions to a level I tertiary referral center to analyze factors affecting outcome from SCI.

Methods: 795 all SCI patients between 2003 and 2013 were reviewed. Diagnosis, demographics, race, insurance status, comorbidities, complications, outcomes, and readmissions were collected. Payor status and race were evaluated with univariate and multivariate analysis while linear regression was used to analyze length of stay (LOS), ICU-LOS, age and BMI with respect to 30 day and 1 year readmission rates.

Results: 248 women (32%) and 511 men (68%) with an average age of 40.9 years and an average BMI of 26.7 were diagnosed with SCI. Payor status did not affect LOS, ICU-LOS, or perioperative complications. However, payor status was a significant predictor of readmission within 30 days of discharge ($p < 0.005$). Medicare (17.4%) and Medicaid (24.5%) showed higher rates of readmission than commercial insurance (13%), self-funded (7.8%), workers compensation (4.7%), and military patients (0%). Medicaid versus others shows a significant higher rate of readmission (Odds ratio: 2.1, 95% confidence interval 1.32-3.34). Univariate analysis identified the following significant predictors for 30 day readmission: race, LOS, ICU-LOS, and diabetes. 22.8% of African-Americans were readmitted, versus 12.3% of other patients (Odds ratio: 2.2, 95% confidence interval 1.36-3.27, $p < 0.001$).

Conclusion: Payor status does not affect in-hospital parameters of patient care during initial management of SCI. Patients with Medicaid and Medicare show higher rates of 30 day readmission, as do African-Americans. The effect of race on readmission is multifactorial, and is explained by the increased rate of Medicaid coverage in African-Americans in our institutions catchment area.

736. Lack of Evidence for Publication Bias in Industry Funded Clinical Trials of Degenerative Diseases of the Spine

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Introduction: Previous studies have demonstrated a propensity for positive results in industry funded clinical trials as compared to their non-industry funded counterparts. Reasons for excessive positive results amongst industry funded trials may include investigator bias in the study performance, inappropriate study designs, fraudulent manipulation of the data or a publication bias.

Methods: We reviewed all clinical trials registered at clinicaltrials.gov relating to degenerative diseases of the spine as categorized under seven specific medical subject heading (MeSH) terms (back pain, spinal stenosis, spondylolisthesis, spondylolysis, spondylosis, failed back surgery, intervertebral disc degeneration) and with statuses of completed or terminated. These collected studies were categorized as having, or not having, industry funding. Published results for these studies were then sought within Pubmed and Google Scholar.

Results: One-hundred sixty-one clinical trials, registered between January 1999 and September 2014, met criteria. One hundred eighteen of these trials had industry funding and forty three did not. Of those with industry funding, forty three (37%) had identifiable results. Of those without industry funding, eighteen (42%) had identifiable results.

Conclusions: There was no difference in the rates of publication of results from clinical trials of degenerative diseases of the spine no matter the funding source.

737. Genetic Mechanisms of Recurrence in Glioblastoma Delineated by RNA Sequencing

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Introduction: Despite advancements in the treatment of glioblastoma multiforme (GBM), mean survival continues to be around 15 months with most patients developing recurrence. The goal of this study was to evaluate a clinically relevant mouse model and treatment scheme to recapitulate and analyze tumor recurrence in GBM.

Methods: Cultured, patient-derived primary GBM-neurosphere cells were dissociated and implanted intracranially into athymic nude mice. Tumor volume was measured regularly with MRI (9.4T). Mice were randomized into treatment groups with combinations of radiation (IR) and temozolomide (TMZ) once their tumor volume reached 20-30mm³. Samples were collected pre-treatment and post-recurrence using a novel MRI-guided biopsy technique. The tumors were analyzed using whole genome RNA sequencing and validation using biochemical studies to delineate genomic basis for treatment resistance. To confirm the therapeutic resistant phenotype of recurrent tumors, pre-treatment and post-treatment tumors were implanted into immunodeficient mice.

Results: Despite an initial response with TMZ/IR, all animals had recurrence towards the end of treatment. Pre-treatment and post-treatment (recurrence) samples were analyzed with RNAseq. Genes involved in cell adhesion, neuronal differentiation/development and cellular morphogenesis were dominant in the upregulated clusters. Transcriptome profiling revealed that TMZ/IR resistance might be related to an upregulation of a network of genes within the mesenchymal signature and downregulation of genes involved in cell death. It is conceivable that as tumors develop TMZ/IR resistance, tumor cells would acquire capability to avoid cell death.

Conclusions: We have developed a novel recurrence model of GBM and used an MRI-based stereotactic biopsy technique with RNAseq to genetically compare paired pre-treatment and recurrent GBMs.

738. Divergence of Intratumoral T Cell Repertoires Reflects Gene Expression in the Glioma Microenvironment

Jennifer Sung Sims; Boris Grinshpun; Timothy Ung; Justin Neira; Yaping Feng, PhD; Jorge Samanamud; Peter Sims, PhD; Peter Canoll, MD, PhD; Yufeng Shen, PhD; Jeffrey Bruce, MD (New York, NY)

Introduction: Local and systemic immunosuppression are characteristic of advanced glioblastoma (GBM) but not low-grade glioma (LGG). While glioma immunotherapy has revolutionary potential, the relationship between tumor progression and potentiation of anti-tumor responses is complex, leading to unpredictable and sub-clinical responses even in successful trials.

Methods: We sequenced pan-repertoire libraries of the T cell receptor (TCR) A and B chains from tumor-infiltrating lymphocytes (TILs) in cryofrozen tissue and peripheral blood of three LGG, seven GBM, and two non-glioma patients. We developed a computational pipeline for correcting sequencing error, and measured diversity

(Shannon entropy) for each library and the divergence between paired TIL and peripheral libraries (Jensen-Shannon divergence metric, JSM).

Results: We calculated the amino acid-dependent divergence between TIL and blood repertoires, suggestive of antigen-specific drive. In LGG, the TIL repertoire diverged from the blood with a major contribution from amino acid identity, while in GBM, the antigen-binding component of divergence was variable. The degree of antigen-specific divergence was correlated with high tumor tissue expression of monocyte/microglial genes promoting T cell maturation and suppressing inflammation, and anti-correlated with genes representing the inflammatory response and suppression of adaptive immune functions.

Conclusions: Antigen-driven TCR divergence of the TIL population from peripheral blood, which differs between high and low-grade gliomas, correlates with two distinct, monocyte/microglia functional profiles suggestive of immune function. Identifying distinct states of microenvironmental immune gene expression may inform and predict the relative impact of systemic and local interventions on anti-tumor T cell activity, allowing tailoring of such immunotherapies for glioma patients.

739. Proton Radiation Therapy is Associated with Decreased Incidence of Radiation-induced Necrosis in IDH-mutant Gliomas

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Introduction: Radiation therapy remains the standard-of-care therapy for patients with low-grade gliomas. Issues of late adverse effects of cancer therapy become increasingly relevant in long-term survivors, such as IDH1-mutant glioma patients, and delayed complications remain challenging to patient management. Proton beam radiation can effectively target tumor while reducing the dose to surrounding healthy tissues. We therefore hypothesized that proton therapy could be associated with a decreased rate of central nervous system complications in long-term survivors, such as IDH1-mutant glioma patients, when compared with patients treated with standard radiation therapy.

Methods: We retrospectively examined a cohort of 139 IDH1-mutant glioma patients treated with either proton or photon radiotherapy in regard to frequency of surgically proven tissue necrosis based on type and dosing of radiation. Univariate and multivariate statistical analysis and Fisher's exact two-tailed tests were performed to compare outcomes.

Results: Within the cohort, 59 patients underwent surgical re-resection; 14 (26%) had been treated with proton therapy while 45 (74%) had received photon therapy. Median time-to-2nd-surgery was 48.30 and 52.23 months in the photon- and proton-group, respectively ($p=NS$). Radiation necrosis was identified in 17 cases (28.81%), only one of which had received proton-therapy ($p=0.0242$). This association remained significant when controlling for tumor grade, patient age and total radiation dose.

Conclusions: Proton therapy, when compared to photon therapy, is associated with a significantly lower incidence of subsequent radiation necrosis in IDH1-mutant glioma patients. Proton radiation may be a less toxic upfront treatment option for IDH1-mutant glioma patients, most notable in long-term survivors.

740. Surgeon Volume Impacts Cost of Care in Pituitary Surgery

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Introduction: Surgeon volume and experience affect complications and length of stay. We examined the relationship between surgeon volume and variation in hospital cost and charges across New York State for transsphenoidal pituitary surgery.

Methods: Using the HCUP State Inpatient Database for New York, we performed surgeon volume-cost analysis on pituitary tumor surgery from 2008 to 2011. All patients underwent elective pituitary tumor surgery and were discharged to home or self-care. Surgeons who performed less than 20 cases per year were compared to surgeons who performed 20 or more cases per year on hospital charges, costs, cost-to-charge ratios, and length of stay (LOS).

Results: 1,803 transsphenoidal pituitary tumor surgeries were performed in New York State. Patient mean age was 50.7 years (54% female). Median hospital charge and cost for surgeons with less than 20 cases per year was \$47,800 and \$15,600, respectively. Median hospital charge and cost of surgeons with 20 or more cases per year was \$28,200 and \$10,500. The cost-to-charge ratios for surgeons with less than 20 cases per year were lower than that of surgeons with 20 or more cases per year, suggesting charge inflation. Median LOS for surgeons with less than 20 cases per year and surgeons with 20 or more cases per year were 3 days and 2 days, respectively.

Conclusions: Within New York State, experienced pituitary neurosurgeons demonstrated decreased hospital charges, costs, and length of stay. These data suggest that patients with pituitary tumors (a highly portable disease) should be considered for referral to high volume surgeons to promote high value, effective care.

741. Chromosomal aberrations in atypical and anaplastic meningiomas

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Objective: Analysis of 22q, 18p11, 1p32 and 14q32 deletions in grade II and Grade III meningiomas and their correlation with tumor grade and recurrence.

Methods: 50 cases of Grade II and Grade III meningiomas were analysed with fluorescence in situ hybridization (FISH) technique with locus specific probes. Types of aberrations and deletions were analysed and correlated with the tumor status.

Results: There was a statistically significant increase in deletions in recurrences when compared to primary surgeries. The mean mitotic index was higher in patients with deletions. Patients with 18p deletions tended to occur in younger patients and had a significant association with sheeting. 22q deletions were associated with hypercellular tumors. 1p, 14q and 1p14q codeletion had a significant association with mitosis ≥ 7 .

Conclusion: This is a first study analysing deletions of all these four sites for deletions using FISH technique. Recurrent tumors and tumors with tendency to recur have a higher frequency of deletions. Further studies in larger sets of patients' alongwith clinical correlation would help in categorising patients with high risk of recurrence and guide clinical management.

742. Visualizing Brain Tumor Infiltration With Stimulated Raman Scattering Microscopy

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Introduction: Differentiating tumor from normal brain remains a central challenge in neurosurgical oncology. Numerous techniques have been proposed as solutions. We recently reported the use of Stimulated Raman Scattering (SRS) microscopy, a non-destructive, label-free optical method, for brain tumor imaging in animal models. Here we evaluate the performance of SRS microscopy to detect brain tumor infiltration in neurosurgical patients.

Methods: With IRB approval, 60 fresh biopsies (17 from 3 anterior temporal lobectomy patients as controls and 43 biopsies from 18 central nervous system (CNS) tumor patients) were collected, placed fresh into saline-loaded chambers, and imaged first with SRS then with H&E microscopy. Protein:lipid Raman signal ratio, cellularity and axonal density were quantified in SRS images using Image J and MATLAB software. Quantified imaging data from 1477 fields of view were analyzed via a quasi likelihood approach with a generalized additive model (GAM) to generate a classifier to predict tumor infiltration.

Results: SRS microscopy accurately depicts histoarchitectural features of normal brain and CNS tumors. While protein:lipid intensity ratio, cellularity and axonal density have limited predictive ability for detecting tumor, a classifier incorporating all variables is 97.5% sensitive and 98.5% specific for detecting tumor. H&E microscopy verified that SRS could accurately detect tumor, even in tissue up to 1cm away from grossly visible tumor margins.

Conclusions: SRS microscopy reveals diagnostic features of tumor-infiltrated and non-infiltrated brain and accurately detects tumor infiltration, even in tissue appearing grossly normal. Future work is warranted to determine how SRS microscopy can be applied for surgical guidance.

743. Increased Robo--Slit Signaling in Glioblastoma

Andrew E. Sloan, MD, FAANS; Amber Kerstetter-Fogle, PhD; David Bonda, BA (Cleveland, OH)

Introduction: Glioblastomas (GBM) account for 54.3% of newly diagnosed glioma in the United States each year. Their rapid growth and invasion into neuronal parenchyma renders them devastating, with median survival ranging between 12-15 months and limited treatment options at recurrence. We hypothesized that the Slit-Robo signaling pathway is involved in GBM invasion.

Methods: We reviewed various databases and performed PCR and western blot of members of the Robo-Slit family members from GBM samples obtained from our IRB approved biorepository.

Results: Analysis of the NCI Rembrandt database indicates poorer survival among glioma patients overexpressing the Robo2 gene (17.1 months versus 37.4 months; $p=1.42E-4$), and recent publications in other cancers suggest Robo1- Slit2 expression is increased in other types of recurrent cancer. In tissue samples from 6 GBM and 3 control patients, we found a 19.8-fold increase in Robo2 relative protein density as well as a 101-fold increase in Robo2 mRNA expression in GBM compared to controls ($p<0.001$). Slit1 and Slit 2 also demonstrated co-localization in a majority of tumor cells. . Robo-Slit signaling in cell populations from distinct geographic regions of each tumor, obtained using stereotactic image-guided biopsies of preselected tumor regions revealed significant differences in Robo/Slit levels in areas of objectively defined regions on MRI ($p<0.01$).

Conclusions: These data suggest a complex and heterogeneous tumor microenvironment and implicates Robo-Slit axis signaling in GBM invasion. These findings implicate the Robo-Slit axis as a potentially attractive therapeutic target.

744. Impact of GBM Microenvironment on Expression Profile of Bone Marrow Derived Progenitor Cells

Gelareh M. Zadeh, MD; Kelly Burrell (Toronto, Canada)

Introduction: We have recently shown that bone marrow derived cells (BMDC) provide a distinct tumor region dependent contribution to Glioblastoma Multiforme (GBM) neovascularization. The influence of GBM microenvironment on modulation and expression of cytokines by BMDC however remains unknown. Here we establish the differential expression profile of BMDC as a consequence of recruitment and interaction with GBM microenvironment and in response to radiation (RTx) and anti-angiogenic therapy (AATx).

Methods: Chimeric mice with reconstituted green-fluorescent bone marrow were used to create intracranial GBM xenografts, by implanting red fluorescent glioma stem cells or U87 into the frontal lobes. Subsequently, BMDC recruited to the GBM were isolated from the GBM cells using FACS during GBM growth, and following treatment (RTx/AATx). RNA was extracted from both FACS-purified BMDC and GBM cells, and mRNA and miRNA array analyses were performed. We compared the expression profiles to systemic BMDC derived from control mice.

Results: BMDCs were found to exhibit significant plasticity and altered their expression profiles based on stage of GBM growth and in response to therapy. TGF β was significantly upregulated in BMDCs following recruitment to GBMs, with a compensatory increase in expression of IL6,4,8 by GBM cells. BMDC up-regulate cytokines, IFNG, CXCL and TNF pathways, and transcriptional regulators, SMAD2, all of which are able to influence the tumor microenvironment. BMDCs also prove to express angiogenic factors and angiomiRs, with a distinct differential expression pattern based on stage of GBM growth and in response to therapy.

Conclusions: We demonstrate that a significant cross-talk exists between BMDC in the tumor microenvironment and GBM cells. There is a distinct angiogenic and invasive profile of BMDC once recruited to the GBM. Furthermore, recruited BMDC provide a source of angiogenic factors, that are differentially expressed based on the stage of GBM growth and in response to therapy.

745. Biopsy versus Laser Interstitial Thermal Therapy: Early Outcomes in Glioblastoma.

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Introduction: Glioblastoma not amenable to surgical resection undergo biopsy followed by concurrent chemo-radiation (CRT) and adjuvant temozolomide. There is limited data on outcomes of these patients. We evaluated the outcomes of these patients in the temozolomide era and the role of laser interstitial thermal therapy (LITT).

Methods: With IRB approval, the Cleveland Clinic's database was used to identify newly diagnosed glioblastoma that were not amenable to surgical resection from January 2004 to July 2014 treated with CRT+temozolomide (RT 30-60Gy). The primary outcomes were progression-free (PFS) and overall survival (OS), measured from the date of surgery. All LITT patients' tumors were

<5.5 cm (longest diameter) and therefore outcome comparisons were restricted to such tumors. The Wilcoxon rank sum test and logrank test were used for data analysis.

Results: 116 patients were included in the study; 105 underwent biopsy and 11 underwent LITT. Median PFS and OS for the whole cohort was 5.3 and 17.4 months respectively. Median age at diagnosis was 61 years (range, 18-81) in the biopsy group and 57 years (33-74) in the LITT group. Median PFS in patients who underwent biopsy (n=30) with CRT-temozolomide was 6.4 months vs. 28.3 months for patients who underwent laser neuro-ablation with LITT (n=5) and CRT-temozolomide (p=0.005). Median OS was 16.5 months (biopsy only) vs. not reached, p=0.02. Conclusion: Patients with glioblastoma that are not amenable to surgical resection have comparatively good outcomes when treated with LITT laser ablation and CRT-temozolomide. A prospective study with LITT in this patient population is needed.

815. A prospective phase II clinical trial of 5-aminolevulinic acid to correlate intraoperative fluorescence intensity with histologic cellularity

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Introduction: Due to paucity of studies, a phase II clinical trial was undertaken to correlate the intensity of 5-aminolevulinic acid (ALA) fluorescence with degree of tumor cellularity during resection of high grade gliomas.

Methods: A single-center, single arm, phase II clinical trial of ALA fluorescence-guided resection of high grade gliomas was held from August 2010 to February 2014. Biopsies were graded on a 4 point scale (0-none to 3-highest) based on ALA fluorescence intensity by the neurosurgeon and independently based on tumor cellularity by a neuropathologist. Outcome of interest was the correlation of ALA fluorescence intensity to tumor cellularity and adverse events.

Results: A total of 211 biopsies from 59 patients were included: 79.7% glioblastoma. ALA intensity 3 correlated with tumor presence 97.4% of cases and ALA intensity 0 correlated with tumor absence 93.0% of cases. For all tumor types, glioblastoma, high grade, and recurrent tumors, ALA fluorescence intensity 3 correlated strongly with cellularity grade 3; correlation coefficients were 0.65, 0.66, 0.65, and 0.62, respectively. Specificity and PPV of ALA intensity 3–cellularity grade 3 match ranged from 95% to 100% and 86% to 100%, respectively. In samples without tumor, 35.4% had ALA fluorescence. Of those, 90.9% contained reactive astrocytes and atypical cells; 8.1% were normal brain. In non-fluorescent samples, 62.3% had tumor cells present. ALA associated complication was 1.7%.

Conclusions: ALA demonstrated high PPV and NPV, and ALA intensity 3 correlated strongly with cellularity grade 3. However, even in the absence of tumor cells, reactive changes including inflammation may lead to ALA fluorescence.

816. Subacute MRI Abnormalities Correlate with Microglial Activation in a Clinically Relevant Model of Mild Repetitive Brain Injury

Jesse Lee Winer, MD; Jacqueline Berglass, BA; Jianhua Qiu, PhD; Justin Berkner, BS; William Meehan, MD; Rebekah Mannix, MD, MPH; Shenandoah Robinson, MD; Lauren Jantzie, PhD (Los Angeles, CA)

Introduction: Repetitive mild traumatic brain injury (rmTBI) is

associated with chronic neurological deficits. Advancement of novel treatments and current management are hampered by limited ability to stratify patients in the subacute injury phase. We hypothesize that advanced magnetic resonance imaging (MRI) techniques can identify microstructural abnormalities that correlate with subacute and chronic microgliosis.

Methods: With IACUC approval, 2 month-old mice were anesthetized and randomized to undergo injury (7 concussive injuries from 54g bolt dropped 28 inches over 9 days) or sham (anesthesia only). One week later, brains were collected for 4.7T MRI or immunohistochemistry with stereological estimates. Observers blinded to injury status performed quantification. Differences were compared with t test with p < 0.05 significant.

Results: RmTBI causes chronic inflammation and functional deficits without MRI abnormalities at 6 months, and deficits dissipate with prolongation of inter-injury interval. Here signs of subacute inflammation, including excess Iba1-positive microglia and CD68-positive activated microglia were present in hippocampus and white matter fimbria of rmTBI mice compared to shams (n = 6 to 7, all p < 0.01). Following rmTBI axial diffusivity was reduced in white matter and thalamus by 19% (n = 2). Mean diffusivity was increased in the cortex. MRI results with prolonged inter-injury intervals are pending.

Conclusions: We found the subacute inflammatory burden correlates with MRI abnormalities. If subacute MRI following rmTBI correlates with total cumulative injury burden, then patients with rmTBI could be stratified. Those most prone to chronic deficits could receive novel interventions, and potential efficacy could be identified more effectively.

817. Nonelective Decompression for Central Cord Syndrome: The economics and outcomes

Christopher Storey, MD; Jai Thakur, MD; Anil Nanda, MD, MPH (Shreveport, LA)

Introduction: Central cord syndrome is the most common form of incomplete spinal cord injury. Many modalities are used to treat the disease process including hypertensive therapy, steroids, and surgical decompression.

Methods: Using the national inpatient sample (NIS) database, we looked at patients from 2005-2010. ICD-9 codes, 952.03 and 952.08, were used to identify patients with central cord syndrome. The ICD-9 codes, 03.0, 03.09, 80.5, 80.50, 80.51 were used to identify patients who were surgically decompressed. All elective admissions were filtered out. ANOVA and Kruskal-Wallis test on SPSS was used.

Results: 3143 patients who were admitted on a nonelective basis for central cord syndrome. 874 patients had surgical decompression during admission. Surgical patients were significantly younger 57 years vs 59 years (p=0.001). Length of stay and total charges for admission were also significantly longer, 9 vs 12 days (p<0.001), and higher, \$64,387 vs \$120,000 (p<0.001) for surgical patients. No significant difference was seen in discharge disposition. Early surgical intervention did not show any significant improved outcome over conservative management. Patients that had surgery in delayed fashion had poorer discharge disposition, longer stays, and higher total charges than both conservative management and early surgery.

Conclusions: Surgery for central cord syndrome does not offer significant benefit during a nonelective admission. If a patient can be decompressed acutely, it does not provide any immediate benefits but possible could offer quicker recovery with therapy. If a patient has multiple comorbidities that would delay surgery, it is likely not in patients' best interests to operate during that admission.

818. Can The Mutant Huntingtin Gene Product Spread From Cell to Cell: Evidence From Neuronal Allografts in Huntington's Disease Patients

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Introduction: Huntington's disease (HD) is caused by a genetically encoded pathological protein (mutant huntingtin (mHtt)), which is thought to exert its effects in a cell-autonomous manner where degeneration occurs within individual cells that carry the aberrant gene. Here, we investigated the hypothesis that mHtt (like pathogenic protein species involved in other neurodegenerative conditions) is capable of spreading within cerebral tissue.

Methods: The brains of four patients with HD who received genetically unrelated fetal neural allografts at least a decade earlier were examined post-mortem. The presence of mHtt aggregates within the grafted tissue was confirmed using an array of techniques including microscopy (brightfield, fluorescence and electron), western immunoblotting and infrared spectroscopy, and a number of different antibodies targeting different epitopes of mHtt aggregates.

Results: A number of mHtt protein aggregates were located within intracerebral allografts of striatal tissue in three of these HD patients. No grafts survived in the fourth transplant recipient. The mHtt+ aggregates were observed in the extracellular matrix of the genetically unrelated transplanted tissue while in the host brain they were localized in neurons, neuropil, extracellular matrix and blood vessels. In addition, peripheral immune cells in separate HD patients contained mHtt. There are thus a number of non cell-autonomous mechanisms which could explain these observations including transsynaptic propagation as well as hematogenous transport of mHtt, among others.

Conclusions: We have demonstrated, for the first time, the presence of mHtt in genetically normal and unrelated allografted neural tissue transplanted into the brains of HD patients. These observations raise questions on the importance of non-cell autonomous mechanisms of protein spread in genetic disorders of the CNS, and further provide new targets for the development of therapeutic strategies.

819. Efficacy of Tranexamic Acid to Reduce Blood Loss in Open Calvarial Vault Remodeling Surgery for Craniosynostosis

Ruth E. Bristol, MD, FAANS; Nicole Hooft, MD; Davinder Singh, MD; Rosemarie Serrone, MD; Stephen Beals, MD; David Shafron, MD; Edward Joganic, MD (Phoenix, AZ)

Introduction: It is well known that craniosynostosis surgery is associated with significant blood loss. Recently, tranexamic acid (TXA) has been used in attempts to reduce blood loss and transfusion requirements in patients undergoing calvarial vault remodeling. This has been well studied in pediatric orthopedic and cardiovascular surgery. However, in craniosynostosis surgery these studies have provided mixed results and the efficacy of tranexamic acid in open calvarial vault remodeling for craniosynostosis still needs to be further investigated.

Methods: We retrospectively reviewed 81 patients with craniosynostosis who underwent either bifrontal or biparietal-occipital calvarial vault remodeling before institution of a TXA administration protocol (non-TXA group) and 36 patients after institution of the TXA protocol (TXA group). Variables tracked included: total intraoperative blood transfused, post-operative blood transfused and estimated blood loss (EBL).

Results: Patients who received TXA required significantly less total blood transfusion during their operation; 258cc TXA group vs 390 cc non-TXA ($p=0.009$). Patients who received TXA required no blood transfusions postoperatively, compared to the non-TXA group who received an average of 78cc postoperatively ($p=1.25E-05$). EBL was also lower in the patients receiving TXA, 260cc in the TXA group vs 410cc non-TXA ($p=0.26$). All patients underwent transfusion intraoperatively, as per our institutional preference to transfuse early for open calvarial vault surgery.

Conclusions: Intraoperative TXA administration reduced blood transfusion requirements, as well as EBL, in patients undergoing open calvarial vault remodeling. There were no adverse events related to TXA administration. Incorporation of TXA with other blood preservation protocols may further reduce transfusion rates.

820. Football's Crisis of 1905: An Examination of the Neurological Injuries and Events that Inspired Roosevelt to Save Lives and America's Sport

Ali Elhadi, MD; Nicholas Theodore, MD; Peter Nakaji, MD; Robert Spetzler, MD; Mark Preul, MD (Phoenix, AZ)

Although football is cheered by millions of viewers, the AANS, NFL, NCAA, among others, have launched significant efforts concentrating on the sport's devastating delayed and acute neurological effects. After over a century of reforms, the game is safer. Modern spectators view a radically changed game from the 1880s-1900s when football brutality and violence were hallmarks. Bone crushing injuries were common; spectators often witnessed disabling severe, or even fatal, neurological injuries. The 1905 Gridiron Crisis marked a turning point in college football when violence became unbearable; the public seizing on an already significant anti-football sentiment. Harvard almost abolished football, Columbia actually did, several other universities were to follow if not for the efforts of President Theodore Roosevelt. Game structure was lax: most colleges had their own rules; protective gear was minimal and not mandatory; strategies for inflicting intentional injuries far being banned, were cheered; crowds were an intimate part of the field. Spine and skull fractures, cerebral hemorrhages, severe concussions and other severe neurological injuries happened regularly. Acting nearly on his own, Roosevelt intervened, believing that football should help young men build a healthy and strong character rather than promote violence and hostility. An outdoor games and athletics proponent, he launched a campaign against brutality in football, personally ensuring that leaders of rules committee began reforms to eliminate violence. In this study we reviewed primary archival sources to detail the neurological injuries that occurred during the 1905 college football season and the actions of a president that literally saved the game.

1287. Comparison of Peripheral Nerve Axonal Area Differences in Central and Peripheral Zones of Injured and Repaired Nerves

Jacob Thayer; Ji-Gheng Yan, MD, PhD; Lin-Ling Yan, MD; Michael Agresti; Robert Havlik, MD (Milwaukee, WI)

Introduction: Histological analysis remains a cornerstone approach for the investigation of peripheral nerve regeneration. This study investigates a newly recognized histological difference between peripheral zones and central zones within regenerating nerve trunks. The purpose was to determine if nerve axonal area (NXA) in regenerating peripheral nerves differs within central and peripheral areas, when viewed in cross section.

Methods: Fourteen rats were divided into two groups, and subjected to different injuries to the right sciatic nerve. Group 1: Transection injury with immediate repair. Group 2: Crush injury without any treatment. The left sciatic nerve was left uninjured and served as a control in each rat. Following 4 weeks of recovery, nerve trunk cross-sections were prepared. Computerized techniques were then employed to divide nerve sections into central and peripheral zones and calculate corresponding NXA values for subsequent statistical analysis.

Results: NXA of injured nerves was greater within peripheral compared to central zones, independent of injury type ($P < 0.05$). No statistically significant difference existed between 2 control groups.

Conclusions: Nerve axonal area (NXA) in regenerating peripheral nerves was greater in peripheral zones than within central zones. This finding may be due to less central intraneural pressure and better blood supply within peripheral zones. This finding suggests that the epineurium and perineurium should be partially opened in the injured or repaired nerve segment to improve nerve regeneration outcomes.

800. Inside Intramural Thrombus Formation with Inflammatory Reactions is Relevant to the Rupture of Cerebral Aneurysms

Yusuke Shimoda; Naoki Nakayama; Masaaki Hokari; Takeo Abumiya; Hideo Shichinohe; Ken Kazumata; Kiyohiro Houkin (Sapporo, Japan)

Introduction: Although recent researches on cerebral aneurysms (CAs) have been performed with the hydrodynamic or the molecular biological technique, the mechanisms of rupture are not fully understood. The aim of this study is to assess the mechanism by a comparison between ruptured and un-ruptured CAs with histopathological and electron-microscopic analysis.

Methods: We analyzed 33 CAs (24 ruptured, 9 un-ruptured) collected surgically after neck clipping. As for the ruptured CAs, we operated them within 24 hours from the onset. HE staining, Elastica Masson staining, PTAH staining, and CD68 immunohistochemical staining were performed with paraffin sections. Morphological analysis with Scanning Electron Microscopy (SEM) was performed with 6 CAs (3 ruptured, 3 un-ruptured).

Results: The common histopathological finding in both ruptured and un-ruptured CAs was that the aneurysmal wall consisted mostly of thick collagen layer without normal internal elastic lamina and media. The characteristic histopathological finding in ruptured CAs was inside intramural thrombus formation with infiltration of CD68 positive cells at the rupture point. The common SEM finding in both ruptured and un-ruptured CAs was the denudation of endothelial cells and the exposure of a subendothelial amorphous or a fibrous surface. The characteristic SEM finding in ruptured CAs was the cluster formation of thick fibrin fibers with incorporation of macrophages and platelets.

Conclusions: While the endothelial denudation, the disappearance of internal elastic lamina and media, and the predominance of collagen layer in the aneurysmal wall were common in both ruptured and un-ruptured CAs, inside intramural thrombus formation with inflammatory reactions was characteristic only in ruptured CAs. This result suggests that thrombo-inflammatory reactions in CAs may act as a trigger for ruptures.

801. A Rapid Blood Test for in Field Early Detection of Stroke

Melissa A. Bradley-Whitman, Ph.D.; Bert Lynn, PhD; Creed Pettigrew, MD, MPH; Justin Fraser, MD; Mark Lovell, PhD (Lexington, KY)

Introduction: Rapid identification of patients suffering from ischemic stroke is needed to exclude stroke-mimicking conditions and to enhance patient triage. We recently developed a blood-based point-of-care lateral flow device (LFD) that allows for sensitive and rapid quantification of a neuron specific Ca²⁺ sensor protein that is rapidly released into blood following an ischemic event.

Methods: Transgenic (Tg) rats overexpressing the tumor necrosis factor-alpha (TNF α) were subjected to either suture occlusion of the middle cerebral artery for 1 hr or sham surgery. Arterial blood was sampled prior to occlusion (baseline), immediately following occlusion, and 15 min and 24 hr post-reperfusion. Serum levels of the Ca²⁺ sensor protein were normalized to pre-injury levels and compared to sham-surgery animals. Brain infarct volumes were measured 24 hrs post-injury. In translational experiments, serum samples procured from patients (n = 4) 6 hr after an ischemic stroke were compared to serum obtained from normal control patients (n = 4).

Results: Serum levels of the Ca²⁺ sensor protein in rats were significantly ($p \leq 0.05$) elevated 15 min and 24 hr post-reperfusion compared to baseline measures. Serum levels of the Ca²⁺ sensor protein was significantly elevated in ischemic rats 24 hr post injury compared to sham surgery rats. Levels of the Ca²⁺ sensor protein measured at 15 min post-reperfusion were positively correlated with infarct volume measured at 24 hr ($r = 0.788$; $p = 0.007$). Levels of the Ca²⁺ sensor protein were significantly ($p \leq 0.05$) elevated in ischemic stroke patients compared to normal control patients.

Conclusions: Elevation of the Ca²⁺ sensor protein after stroke is highly conserved between rodent models of stroke and human stroke patients. Our LFD provides rapid quantification of the Ca²⁺ sensor protein levels, which correlate to extent of injury, positively detect stroke compared to controls, and may accelerate ischemic stroke detection.

802. Effects of Remote Ischemic Conditioning on Subarachnoid Hemorrhage Outcomes

Azim N Laiwalla, MS; Yinn Cher Ooi, MD; Mark Connolly, BS; Raymond Liou, BS; Nestor Gonzalez, MD (Los Angeles, CA)

Introduction: Remote ischemic conditioning (RIC) is a powerful endogenous response to sublethal episodes of ischemia, which can protect against severe ischemic insult at a distant site. While RIC has been found to be effective in the cardiovascular system, the role of RIC for cerebral protection remains unclear. We hypothesize that RIC is an effective prophylactic treatment for delayed ischemic neurological deficit after aneurysmal subarachnoid hemorrhage (aSAH), leading to improved outcomes.

Methods: The neurologic outcome (modified Rankin scale [mRS]) of patients enrolled in a prospective trial (RIPC) was measured. Matched controls were identified from an institutional aSAH registry. Study patients underwent up to 4 RIC sessions of the lower limb, consisting of 4 five-minute cycles per session performed over non-consecutive days. Both groups received current standard of care for the management of aSAH. The occurrences of vasospasm and stroke were recorded. Good outcome was defined as a mRS of 0-2.

Results: 21 RIPC patients, age 22-76y (mean: 51y, SD: 12.7), 14 females (66.7%), and 59 matched controls, age 20-77y (mean 52y, SD: 12.2), 41 females (69.5%). There was no significant

difference in age, gender, aneurysm location, clipping vs coiling, vasospasm, or H&H grades between the groups. RIC was found to be an independent predictor for good outcome (OR: 6.89; 95% CI: 1.50-39.9). RIC also showed a non-significant trend towards lower incidence of stroke (28.6% vs 47.5%).

Conclusion: Lower limb RIC led to improved clinical outcomes and a trend towards lower incidence of strokes in patients with aSAH.

803. Parietal area 5 preservation determines motor recovery in a gyrencephalic non-human primate model of MCA stroke

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Introduction: Parietal area 5 (PA5) integrates sensorimotor information related to reaching and grasp. PA5 lies in the MCA watershed distribution of the macaque brain and is inconsistently infarcted following MCA occlusion (MCAO). We hypothesize that preservation of PA5 is associated with improved post-stroke experiential motor recovery, independent of total infarct size.

Methods: Fourteen cynomolgus macaques underwent transient 90-minute MCAO. Perfusion, DWI, T2-MRI were obtained during occlusion, 48h, and 30d following MCAO. Total stroke volume and regional stroke volumes in premotor, primary sensory (S1), primary motor (M1), parietal, and PA5 cortices were quantified. Post-stroke neurobehavioural outcomes were evaluated serially using Non-Human Primate Stroke Scale (NHPSS).

Results: Animals were dichotomized by 30d-NHPSS score into good (NHPSS less-than 9, n=8) and poor recovery (NHPSS greater-than 8, n=6). Comparisons showed no differences in baseline penumbra (PWI-DWI) and stroke core volumes or in total stroke volume at 48h and 30d. PA5 stroke volume was equivalent at 48h, but significantly decreased at 30d (4.1mL vs 5.2mL, $P=0.02$) in good recovery. Correlation analysis using the complete cohort showed that at 48h post-MCAO, total and PA5 infarct volume did not correlate with NHPSS (n=14, $R^2=0.1$, $P=0.28$ and $R^2=0.02$, $P=0.62$ respectively). At 30d however, PA5 stroke volume on T2-MRI positively correlated with NHPSS scores ($R^2=0.58$, $P=0.01$). This relationship was not seen with any other area or total stroke volume. Functional connectivity maps generated 30d post-stroke confirmed strong connections between ipsilateral M1, S1, and PA5 nodes in good recovery animals.

Conclusions: These data support the notion that PA5 plays a key role in motor recovery following MCA stroke. Future mechanistic research focused on PA5-dependent motor recovery may lead to novel neurorestorative/neuromodulatory therapies.

804. Differential expression levels of Collagen 1A2, Tissue inhibitor of metalloproteinase 4 and Cathepsin B in intracranial aneurysms and their clinico-radiological correlation

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Introduction: The aim of this study was to evaluate the expression level of differentially expressed genes which include Collagen 1A2 (COL1A2), Tissue inhibitor of metalloproteinase 4 (TIMP4) and Cathepsin B (CTSB) when compared to the normal artery of these genes in Intracranial aneurysms (IA) and their correlation between the various clinico-radiological factors.

Methods: The mRNA level was studied in twenty three aneurysmal walls and 19 superficial temporal arteries (STA)

harvested from 23 patients undergoing clipping of intracranial aneurysms, by real time polymerase chain reaction (RT-PCR) method.

Results: The TIMP4 gene is 3.23 times under-expressed in the aneurysmal sac compared to superficial temporal artery on an average. The mean fold change of CTSB gene between the aneurysm sample and the STA sample was 31.47 ± 39.01 (range- 4.99 to 138.09). There was significant positive correlation of TIMP4 expression level and the aneurysm size ($p=0.008$ for maximum diameter of aneurysm and $p=0.012$ for fundus of aneurysm). There was significant negative correlation between TIMP4 expression and the systolic blood pressure at admission ($p=0.005$). There was statistically significant association between hydrocephalus at presentation and post-operative neurological deficits and the CTSB expression. The mean fold change of CTSB of patients who had pre-operative hydrocephalus in the CT scan at admission was 56.16 and that of the patients who did not have hydrocephalus at presentation was 13.51 ($p=0.008$).

Conclusion: This study is the first of its kind in which a direct correlation with the clinico-radiological features has been performed and needs further clinical validation.

805. Decreased Cerebral Blood Flow in the Central Core of Malignant MCA Stroke in Patients Submitted to Decompressive Craniectomy is Associated with Late Recovery of Consciousness

Robson Amorim, MD; Edson Shu; Almir Andrade; Gabriel Gattas; Wellington Paiva; Manoel Teixeira (Sao Paulo, Brazil)

Introduction: The phenomenon of brain extrusion occurs after decompressive craniotomy (DC) in patients with malignant middle cerebral artery (MCA) stroke is a common event, but with uncertain impact on prognosis. In order to determine the impact of severity of ischemia on the occurrence of cerebral extrusion and prognosis, we investigated the central region of infarction by TC perfusion.

Methods: We evaluated patients with ischemic stroke and indication of DC. Preoperative hemodynamic parameters such as mean transit time (MTT), cerebral blood volume (CBV) and cerebral blood flow (CBF) were studied. The primary outcome measure was the association between hemodynamic values in the central region of the infarct and the evolution to brain extrusion. Secondary outcomes were evaluated: recovery of consciousness within 7 days, modified Rankin scale after 6 months, which was dichotomized into favorable (0-3) and unfavorable (4-6); fatal outcome within 1 month and 6 months. To compare the MTT, CBF and CBV values in the central region of the infarct with outcomes, we used the Student t test for paired two-tailed. To assess correlation between variables Spearman's test was used.

Results: 33 patients were included. Patients who recovery consciousness after 7 days had significantly lower preoperative CBF ($p=0.03$). Also, there was a tendency to worse prognosis in patients with lower CBF: mortality in 1 month (2.8 mL/100g/min vs 7.4 mL/100g/min, $p=0.059$); mortality in 6 months (3.9 mL/100g/min vs 8 mL/100g/min, $p=0.08$); unfavorable outcome (4.5 mL/100g/min vs 9.1 mL/100g/min, $p=0.07$). Also, there was a negative association between hyperdense MCA and CBF (coef -0.52, $p=0.004$), and midline shift in 48-72h after DC and CBF (coef -0.69, $p=0.01$).

Conclusions: Decreased CBF in the central core of the infarction determines a lower chance of consciousness recovery within 7 days and, possibly, is associated to all outcomes assessed in this study.

806. Cognitive Outcome and Hemodynamic Changes 3 months after Carotid Endarterectomy in Primary Stroke Prevention

Jiri Fiedler, MUDr., Ph.D.; Tomas Mrhalek; Michal Vavrečka; Jiri Kubale; Marek Preiss; Iva Stuchlikova (Budweis, Czech Republic)

Introduction: The effect of carotid endarterectomy (CEA) on cognition is unclear. The aim of the observational study is to assess institutional results of CEA for asymptomatic stenosis.

Methods: Inclusion criteria: tight ICA stenosis confirmed by CT angiography. Exclusion of ipsi and contralateral stenosis of M1, A1, A2 and P3 segments more than 60%. Absence of hemispheric or ocular symptomatology from carotid territory of operated carotid stenosis at least for 6 months and exclusion of silent ischemia with MR. Ability to undergo MR and neurocognitive testing. All patients underwent standard micro CEA with supraselective shunting. Flow volumes from both sides of Willisian arteries were obtained and simple ratio for each artery was calculated. RBANS and Trail Making Test were used. The difference between preoperative and postoperative values was tested using Wilcoxon nonparametric test (one and two tailed) and nonparametric Spearman's rank correlation.

Results: 11 patients took part in study 3 – 10/2013. Postoperative external carotid artery occlusion was recorded in one case. Within the overall score of RBANS battery, the improvement was detected postoperatively ($Z=-1.61$ $p=0.05$), which correlated with the change of blood flow in ACA2. When analyzing subtests, the correlation between flow change in ACA2 and test of immediate memory ($p=0.01$) was detected. Improvement in test of visuospatial skills ($p=0.02$) and test of language ($p=0.02$) correlated with the improvement of blood flow in MCA.

Conclusions: The improvement in RBANS was related to flow change in ACA2. Improvement in MCA flow was associated with improvement in attention and executive functions.

807. The Role of Lymphocytes in the Pathogenesis and Rupture of Intracranial Aneurysm

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Introduction: Intracranial aneurysm (IA) pathogenesis is driven by chronic inflammation. Lymphocyte infiltration has been associated with aneurysm formation and rupture in human tissue specimens, however it is unknown whether these cells play a causative role. The present project investigated the contribution of lymphocytes to aneurysm formation and rupture.

Methods: IAs were induced in three groups of mice using an established model involving hypertension and stereotactic elastase injection: healthy C57BL/6 ($n = 15$), Rag1 knockout mice (do not produce mature B- or T-cells, $n = 12$), and Rag1 knockouts reconstituted with lymphocytes collected from healthy C57BL/6 donors ($n = 7$). Rates of aneurysm formation and rupture were measured over a two-week period, and aneurysm tissue specimens were collected.

Results: Reconstitution of lymphocytes in the third group was confirmed at the end point via flow cytometry for CD3 and CD19 ($p = 0.004$). Rates of aneurysm formation were approximately 60%, and were not significantly different between the three groups. Rates of rupture in animals forming aneurysms were significantly lower in the Rag1 knockouts (50%) than either the C57BL/6 group (100%) or the Rag1 reconstituted group (75%, $p = 0.040$).

Conclusions: The results of this experiment suggest that lymphocytes may not play a part in the initial formation of IAs, but that they are an important component of the inflammatory processes

underlying aneurysm progression to rupture. Further work could reveal therapeutic targets for preventing aneurysmal subarachnoid hemorrhage by elucidating the mechanism behind this relationship.

808. Effect of Prior Embolization and Nidus Angioarchitecture on Obliteration Following Stereotactic Radiosurgery for Cerebral Arteriovenous Malformations: A Matched Cohort Analysis

Eric Karl Oermann, MD; Dale Ding, MD; Chun-Po Yen, MD; Robert Starke, MD, MSc; Joshua Bederson, MD; Douglas Kondziolka, MD, MSc; Jason Sheehan, MD, PhD (New York, NY)

Introduction: The aim of this matched, case-control study is to determine the effect of prior embolization and nidus angioarchitecture on obliteration following stereotactic radiosurgery (SRS) for cerebral arteriovenous malformations (AVM).

Methods: We evaluated a prospective AVM SRS database and stratified patients based on prior embolization. AVMs treated with embolization and SRS (case cohort) were matched to AVMs treated with SRS alone (control cohort), based on patient, AVM, and SRS characteristics. Nidus angioarchitecture was defined by the number of major feeding arteries and draining veins. Cox-regression analysis was performed to determine predictors of obliteration.

Results: The matching process yielded 242 patients in each cohort. The cumulative obliteration rate for all patients was 57%. In the case cohort, the actuarial obliteration rates at 3, 5, and 10 years were 19%, 31%, and 49%, respectively. In the control cohort, the actuarial obliteration rates at 3, 5, and 10 years were 26%, 48%, and 64%, respectively. Obliteration rates were significantly lower in the case cohort ($p=0.003$, log-rank test). Independent predictors of obliteration in the multivariate analysis were fewer feeding arteries ($P=0.006$), fewer draining veins ($P<0.001$), and radiologic evidence of radiation-induced changes ($p=0.016$). Embolization was not significant in the multivariate model for obliteration ($p=0.744$).

Conclusions: Our findings suggest that analyses of the effect of prior AVM embolization on obliteration rates following SRS may be confounded by the angioarchitectural complexity of the nidus, which appears to inversely correlate with obliteration. This may warrant a re-evaluation of the role of combined embolization and SRS in the multimodality management of AVMs.

809. The Myth of Restenosis after Carotid Angioplasty and Stenting

Karam Moon, MD; Felipe Albuquerque, MD; Azam Ahmed, MD; Michael Levitt, MD; M. Kalani, MD, PhD; Cameron McDougall, MD (Phoenix, AZ)

Introduction: Carotid endarterectomy and stenting have been shown to have similar safety and efficacy in CREST. Restenosis rates after endovascular treatment are highly variable in the literature and risk factors for this pathology are poorly understood.

Methods: The authors reviewed all patients undergoing carotid artery stenting (CAS) between 1995 and 2010. Symptomatic and asymptomatic patients were selected based on NASCET and ACAS criteria. Risk factors, indications, rates of technical success, intraoperative and perioperative complications, restenosis ($<70\%$) rate, and clinical outcomes were evaluated.

Results: A total of 156 patients met inclusion criteria, but 35 were lost to follow-up, leaving 121 patients with 134 vessels treated. Ninety-seven (72.4%) lesions were symptomatic. Indications for stent placement included patients who were poor surgical candidates,

prior endarterectomy, prior radiation, study randomization, acute occlusions, tandem stenosis, high bifurcation, and contralateral laryngeal nerve palsy. Procedures were technically successful in all but one case. Intraoperative and peri-operative stroke occurred in 4 patients (3.0%). Mean follow-up was 38 months (range 1 to 204 months). Thirteen patients (9.7%) developed restenosis greater than 70%. Of these, 9(69.2%) were hostile neck carotids that had undergone prior radiation or endarterectomy. Amongst atherosclerotic lesions, the rate of severe restenosis was 5/80(6.3%) and symptomatic restenosis only 1/80(1.2%).

Conclusions: The rate of restenosis after carotid stent placement is low and compares favorably to that of endarterectomy, especially when considering only high-grade or symptomatic cases. Patients who undergo stenting after radiation or endarterectomy are at higher risk for restenosis than those with atherosclerotic lesions.

810. The Angular Approach of the Median Nerve to the Carpal Tunnel and its Importance in Preventing Nerve Injury

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Introduction: A thorough understanding of anatomy is critical for successful carpal tunnel release. Most texts depict the median nerve (MN) as taking a course parallel to the long axis of the forearm. We present evidence showing that the MN actually takes an angular approach to the carpal tunnel and discuss its clinical significance.

Methods: The wrist width and the distance from the radial wrist to the MN were recorded on cadaveric dissections. Also, the distance between the wrist crease and where the MN first becomes visible from under the muscles of the forearm was measured. Finally, the angle between the MN and flexor carpi radialis (FCR) tendon was measured using ImageJ.

Results: The ratio of the MN to radial wrist distance divided by wrist width revealed an average value of 0.49(R) and 0.48(L) indicating that the nerve was usually located just radial to midline. The distance between the wrist crease and the MN's appearance was 34.2mm(R) and 34.8mm(L). The average angle between the MN and the FCR tendon was found to be 13.0°(R) and 14.6°(L) and varied from 0-33°. Notably, 6 of 76 forearms measured (7.9%) showed an angle of greater than 20°. The PL was absent in 14 of the 76 wrists (18.4%).

Conclusions: This previously undescribed angular approach of the MN to the carpal tunnel puts the nerve at risk when instruments are passed longitudinally across the wrist. Our findings will assist clinicians in preventing nerve injury when performing both open and endoscopic carpal tunnel release.

811. Diffusion Tensor Imaging of an Innovative Technique for Peripheral Nerve Repair

David C Riley; Richard Boyer, BS; Nathaniel Kelm, BS; R Shack, MD; Wesley Thayer, MD, PhD (Nashville, TN)

Introduction: Presently, the most reliable methods for peripheral nerve repair depend on microsutures, nerve conduits, and/or autologous nerve grafts. However, even with these techniques functional recovery depends on a lengthy process that involves axonal outgrowth, which occurs at a rate of 1-3 mm/day. Polyethylene-glycol (PEG) has proven the ability to improve behavioral outcomes in animal models immediately following nerve transection. We hypothesized that this technique could restore

axonal continuity as assessed by high-resolution diffusion tensor imaging.

Methods: Bilateral rat sciatic nerves were transected and repaired in 6 animals using standard microsurgical techniques. Experimental animals received Plasmalyte-A, 1% methylene blue, PEG, and Lactated Ringers; control animals did not receive PEG. Electrophysiological recordings were acquired pre-injury and post-repair. High-resolution diffusion tensor images were obtained using diffusion-weighted spin-echo acquisitions at 4.7-tesla.

Results: We found that PEG-fused nerves had restored axonal continuity immediately following application of PEG. 83% (5/6) of PEG-fused nerves had restored compound action potential (CAP) function, while 0% (0/6) of control animals showed returned CAP function. Additionally, diffusion tensor tractography displayed a significantly increased ($p<0.01$) number of axonal tracts through the repair site in PEG-fused nerves. Furthermore, fractional anisotropy was increased at the injury sites of PEG-fused nerves compared to control nerves.

Conclusions: These findings suggest that PEG-fused nerves immediately restore axonal continuity. We believe that this novel nerve fusion technique may produce a change in the clinical management of traumatic injuries to peripheral nerves. Additionally, high-resolution diffusion tensor imaging is a promising tool for future diagnosis and tracking of traumatic nerve injuries.

812. Magnetic Resonance Diffusion Tensor Imaging Can Visualize Nerve Fibers and Their Relationship to Peripheral Nerve Tumors

Tene A. Cage, MD; Anuradha Rao, MD; Stephanie Hou, MD; Michel Klot, MD, PhD; Esther Yuh, MD, PhD; Cynthia Chin, MD (San Francisco, CA)

Introduction: The majority of growing and/or symptomatic peripheral nerve tumors are schwannomas and neurofibromas. They are almost always benign and can usually be fully surgically resected while sparing motor and sensory function if approached with the proper expertise and techniques. Intraoperative electrophysiological stimulation and recording techniques allow the surgeon to map the surface of the tumor in an effort to identify and thereby avoid damaging functioning nerve fibers. Recently, magnetic resonance diffusion tensor imaging (MR DTI) techniques have permitted the visualization of axons, due to their anisotropic properties, in peripheral nerves.

Methods: MR DTI data and intraoperative data were collected prospectively for seven patients with peripheral nerve tumors that were surgically resected. We compared preoperative identification of nerve fiber location in relation to the surface of the nerve tumor as seen on MR DTI studies with their intraoperative localization using electrophysiological stimulation and recordings.

Results: We found good correlation between nerve fiber location seen on MR DTI and anatomic nerve fiber location seen intraoperatively. MR DTI demonstrated 85.7% sensitivity, 92.9% specificity, 92% positive predictive value and 87% negative predictive value in determining the relationship of nerve fibers relative to the tumor.

Conclusions: We conclude that preoperative MR DTI techniques are extremely reliable as an imaging modality and are very useful in helping the peripheral nerve surgeon to both determine the risks involved in resecting a nerve tumor as well as in planning the safest surgical approach.

814. Novel Clinical Techniques for Repairing Peripheral Nerve Gaps

Emil Antonio Pastrana-Ramirez, MD; Damien Kuffler, PhD (Carolina, PR)

Introduction: Sensory nerve grafts, restore good neurological function only for nerve gaps <2 cm, repairs performed <2 months post trauma, and patients <20 years of age

Methods: We tested 3 novel techniques: (1) A nerve graft bridged within a collagen tube filled with pure fibrin; (2) nerve gaps bridged with a sensory nerve graft inside a collagen tube filled with autologous PRP; and (3) nerve gaps bridged with a collagen tube filled with autologous PRP.

Results: Technique #1 induced 100% motor and sensory function in spite of a 6 cm long radial nerve gap repaired 4 months post trauma. Technique #2 restored sensory function to 100% and motor to 93% of nerves in spite of gaps from 4-16 cm in length (ave. 6.5 cm), repairs performed 0.3-3 years post-trauma (ave. 1.8 years), and patients 23-50 years of age (ave. 36). Technique #3 restored sensory function to 100% and motor function to 88% of patients in spite of gaps 2-12 cm in length (ave. 6.2), surgeries delayed 0.5- 3.25 years of age (ave. 1.6), and patients 24-58 years of age (ave. 34).

Conclusions: These data indicate each of these techniques restores neurological function under conditions where sensory nerve gaps are not effective. Further studies are required to determine whether these techniques can be improved to induce even more extensive neurological recovery.

821. WFNS Rabat Reference Center for Training African Neurosurgeons A Successful Experience to Build Neurosurgery in Sub-Saharan Africa

Abdeslam El Khamlichi, MD (Rabat, Morocco)

Introduction: The ratio of neurosurgeons in Sub-Saharan Africa (SSA) is 1/7 M (personal survey, 1998). The majority of African neurosurgeons (AN) trained abroad had not come back home. In 2001, the WFNS took the initiative to create a regional training center to train AN in their environment, to avoid a brain drain, and reduce the cost of training.

Methods: The creation of a regional training center in Morocco, where the training program in neurosurgery and local authorities supported all facilities. The WFNS Foundation was established to provide for scholarships and basic equipment. A cooperation agreement was signed in 2005 between Rabat University and the WFNS.

Results: Over 12 years (2002-2014), 39 trainees had been enrolled in the basic training program. They came from 15 SSAC. Among these trainees, 12 have already finished their training. 5 are finishing by the end of 2014, and 23 are under training. All of them share the same training program with Moroccan residents. Since 2010, 4 to 6 applicants enroll in the Center every year. As CME, since 2007, one course and one workshop are organized every year in Rabat, gathering up to 80-120 AN. The program of each course includes presentations to assess the work of young neurosurgeons already back home. Today, the success of the Center is underlined by the number of collaborative institutions, the number of trainees granted by their national institutions, and the results achieved by the young neurosurgeons when they return.

Conclusions: The best way to build neurosurgery in SSA is to support local or regional training, because its contribution to neurosurgery development in the country is far better than training abroad. However, the latter is needed for a short period, to allow

African neurosurgeons trained locally to be exposed to all aspects of modern neurosurgery.

822. The practice of cranial neurosurgery and the malpractice liability environment in the United States

Kimon Bekelis, MD; Symeon Missios; Kendrew Wong; Todd MacKenzie; David Roberts (Lebanon, NH)

Introduction: The potential imbalance between malpractice liability cost and quality of care has been an issue of debate. We investigated the association of malpractice liability with unfavorable outcomes and increased hospitalization charges in cranial neurosurgery.

Methods: We performed a retrospective cohort study involving patients who underwent cranial neurosurgical procedures from 2005-2010 and were registered in the National Inpatient Sample (NIS) database. We used data from the National Practitioner Data Bank (NPDB) from 2005 to 2010 to create measures of volume and size of malpractice claim payments. The association of the latter with state-level mortality, length of stay (LOS), and hospitalization charges for cranial neurosurgery was investigated.

Results: During the study period, there were 297,222 patients (mean age 53.5 years, with 71.4% females) who underwent cranial neurosurgical procedures, and were registered in NIS. In a multivariable regression, higher number of claims per physician in a state was associated with increased ln-transformed hospitalization charges (OR 1.55; 95% CI, 1.47 to 1.63). On the contrary, there was no association with mortality (OR 23.84; 95% CI, 0.55 to 1040) or LOS (OR 0.91; 95% CI, -0.05 to 1.88). The size of the awarded claims demonstrated similar relationships. The average claims payment size (ln-transformed) (Pearson's rho=0.435, P=0.01) demonstrated a positive correlation with the risk-adjusted hospitalization charges but did not demonstrate a correlation with mortality or LOS.

Conclusions: In the present national study, aggressive malpractice environment was not correlated with mortality but was associated with higher hospitalization charges after cranial neurosurgery. In view of the impact of malpractice on the economics of healthcare, the need to regulate the medical litigation system becomes a priority.

823. Patient Demographics, Payer Type, and Hospital Status Predict Postoperative Outcomes in Patients Undergoing Transsphenoidal Pituitary Surgery

Gabriel Zada, MD; Andrew Platt; Diana Jin; John Carmichael; Steven Cen; William Mack (Los Angeles, CA)

Introduction: Socioeconomic and hospital metrics may predict post-operative complications, length of stay, and hospital charges following surgical treatment for pituitary adenomas (PAs). We assessed various demographic/hospital variables and their relation to transsphenoidal surgical outcomes.

Methods: Longitudinal hospital inpatient data from the 2002-2010 HCUP/NIS database was analyzed for endocrine and non-endocrine complications, mortality, hospital charges, and length of stay following transsphenoidal operations for PAs. Patient predictors including race/payer status, and hospital predictors including transsphenoidal volume and teaching status, were tested using univariate and multivariate analyses.

Results: From 2002-2010, 71,892 transsphenoidal surgeries performed on 71,245 total PA admissions were analyzed. Medicaid patients had an increased rate of mortality (RR=2.31;p=0.03) compared to privately insured patients. With regard to endocrine complications,

African-Americans had increased risk ($RR=1.15;p=0.02$) compared to white patients, and Medicaid patients had increased risk ($RR=1.18;p=0.02$) compared to privately insured patients. Increased hospital charges were noted in African American ($RR=1.25;p<0.01$) and Hispanic patients ($RR=1.34;p<0.01$). Increased hospital charges were also noted in Medicare patients ($RR=1.20;p=0.01$) and Medicaid patients ($RR=1.28;p<0.01$) compared to privately insured patients. Decreased hospital charges were identified in patients treated at teaching hospitals ($RR=0.82;p<0.01$). Patients treated at high volume transsphenoidal hospitals had decreased length of stay ($RR=0.73;p<0.01$), lower hospital charges ($RR=0.77;p<0.01$), and decreased total complications ($RR=0.85;p=0.04$), endocrine complications ($RR=0.75;p<0.01$), and electrolyte abnormalities ($RR=0.67;p<0.01$).

Conclusion: Race and payer status remain significant predictors of endocrine complications, mortality, hospital charges and length of stay. Teaching hospitals and high-volume transsphenoidal centers provide higher value care in the surgical treatment of PAs.

824. Cost Benefit Estimates of the Use of Topical Vancomycin to Prevent Surgical Site Infection After Craniotomy

Kalil G Abdullah, MD; Mark Attiah, BS; Ashwin Ramayya, PhD; Andrew Richardson, PhD; Timothy Lucas, MD, PhD (Philadelphia, PA)

Introduction: Topical vancomycin powder has been shown to be effective in reducing surgical site infections after spinal and cranial surgery. The ability to reduce cranial wound infections has important cost implications for neurosurgeons and the healthcare system at large.

Methods: Seventy five previously presented control patients who underwent craniotomy were compared to 75 patients who underwent craniotomy with application of topical vancomycin. The infection rates in each group were then extrapolated to the number of craniotomies during one year at our hospital. Cost valuations were performed for all admission and operative modifiers to determine overall cost estimates for revision craniotomy after surgical site infection. The cost of repeat craniotomy was multiplied by the number of modeled infections per year in both groups. Differences in cost were then calculated.

Results: The overall infection rate in the control group was 6.7% vs. 1.3% in the vancomycin group. There were 931 craniotomies during the same fiscal year. The cost of a revision craniotomy for infection at our institution is \$24,853. The total estimated cost of all infections assuming a 6.7% infection rate was \$1,555,255. The infection cost in the vancomycin group was \$323,934, with an overall cost reduction of \$1,231,321. The cost saving to a department performing 1000 craniotomies annually would be \$1,500,000 to \$2,000,000 depending on individual costs for craniotomy revision.

Conclusions: The use of topical vancomycin during craniotomy to prevent surgical site infections has substantial cost implications in our patient series. While this study is limited by small sample size, further research can and should be done to better interpret the generalizability of this data.

825. Clinical Utility and Cost-Effectiveness of Routine Post-operative Head CTs in Elective Aneurysm Clippings

Corinna C. Zygourakis, MD; Ethan Winkler, MD, PhD; Lawrence Pitts, MD, PhD; Lisa Hannegan; James Kahn, MD, MPH; Michael Lawton, MD, MPH (San Francisco, CA)

Introduction: Post-operative head CTs are performed routinely at our institution on all patients after elective aneurysm clippings.

Our goal was to determine how often these scans influence medical management and whether their routine use is cost-effective.

Methods: We reviewed the medical records and accounting database for 304 patients who underwent elective aneurysm clippings by one surgeon (MTL) from 2010-2014 at the University of California, San Francisco.

Results: Post-operative CT findings influenced management in 3.6% of cases. They led to permissive hypertension in 4 patients for possible ischemia, administration of mannitol for edema and high-flow oxygen for pneumocephalus in 2 patients each, seizure prophylaxis in 1 patient, plavix re-adjustment in 1 patient, and take-back to the operating room for epidural hematoma evacuation in 1 patient. If we stratify patients on the basis of post-operative neurologic exam, the CT scan altered management in 1%, 5%, and 9% of patients with no new neurologic deficits, a non-focal exam, and focal deficits, respectively. The average total hospital cost of treating our elective aneurysm patients was \$72,227 (+/- 53,966), and the cost of a non-contrast head CT was \$289. In a neurologically intact patient, we needed to perform 99 head CTs and spend \$28,611 in order to obtain 1 head CT that influenced medical management.

Conclusions: Although there are no clear guidelines, the large number needed to treat and high cost of CT scans suggest that careful neurologic monitoring may be more clinically and cost-effective than routine post-operative CT scans in the neurologically intact elective aneurysm patient.

826. Quantifying Variability within Spinal Surgery Using A Novel CPT-based Procedure Categorization Method

Daniel Refai, MD; Griffin Richard Baum, MD; Scott Boden, MD (Atlanta, GA)

Introduction: Our goals were to identify components of care responsible for cost-variability and to identify a method of quantitating inter-group variability between surgeons performing spine surgery. We hypothesized that a novel CPT-based procedure categorization would more reliably identify inter-group variability and quantify cost-variability within spinal surgery.

Methods: Using an administrative database, we retrospectively analyzed 3,538 patients who underwent surgical spine procedures within our hospital system using DRGs. We then analyzed 2,891 patients who had CPT-related data. Using the generalized linear model of regression, procedures were analyzed by cost center to reveal areas of highest cost-variability. Then, case-matched cohorts were used to evaluate the inter-group variability based on DRGs and CPT-based procedure categories.

Results: Based on DRGs, we observed 66% of cost-variability to originate within the OR. DRGs have high inter-group variability due to the heterogeneity of procedures they contain. The 13 spine-related DRGs were characterized into 31 CPT-based procedure categories, which decreased inter-group variability by 25%. A sub-group analysis of CPT-based procedures with high inter-group variability revealed that up to 66.5% of the variance can be attributed to surgeon decision-making within the OR, specifically costs of implants or instrumentation.

Conclusions: Variability among surgeons performing the same procedure suggests opportunity for cost-reduction and value-improvement. DRGs are not useful to assess inter-surgeon variability. Using our CPT-based procedure categorization, we found most cost-variance occurs within the OR based on surgeon decision-making. Surgeons and institutions must work together to control non-evidence based cost-variability to maximize the value of spine surgery.

827. Neurosurgery and Tort Reform: A Systematic Review of the Role of Damage Caps

Jacob Richard Lepard, MD; Beverly Walters, MD; Curtis Rozzelle, MD (Birmingham, AL)

Introduction: Over the past 40 years there have been three major medical malpractice crises, with the most recent occurring from 2001-2003. Some factors that have been found to contribute to development of a malpractice crisis are elevated insurance premiums, high claim rates, increasing indemnity payments, and lack of access to high-risk specialties. The purpose of this study is to determine if tort reform in the form of damage caps are capable of influencing these four contributing factors.

Methods: Multiple online databases (Pubmed, Scopus, EMBASE, and JSTOR) were queried using the key words malpractice AND damage caps for articles from 2000-2014. A total of 96 abstracts were screened for inclusion and exclusion criteria. Of these, 22 articles were reviewed in full and another seven were excluded for either study design or poor quality of data. The remaining fifteen articles were evaluated and relevant data was extracted.

Results: A total of six studies were found showing good evidence that the presence of non-economic damage caps influenced the regional supply of physicians. Additionally three studies associated damage caps with decreased frequency of claims and three studies found an association with decreased frequency as well as severity of jury awards. Lastly, three studies were able to show that damage caps have an effect on malpractice premiums.

Conclusions: There is good evidence in the literature showing that total and non-economic damage caps have the potential to help prevent a future malpractice crisis. It is important for Neurosurgeons to be informed and continually advocate for effective reform measures.

828. Cost-Effectiveness Comparison between Transforaminal and Lateral Lumbar Interbody Fusions Using the Incremental Cost-Effectiveness Ratio

Gurpreet Surinder Gandhoke, MD; Han Moe Shin; Yue Fang Chang; Zachary Tempel; Peter Gerszten; David Okonkwo; Adam Kanter (Pittsburgh, PA)

Introduction: We compared costs associated with transforaminal lumbar interbody fusion (TLIF) and lateral lumbar interbody fusion (LLIF) by calculating the incremental cost-effectiveness ratio (ICER). We also calculated the thresholds for Minimum Clinically Important Difference and Minimum Cost Effective Difference for patient-reported outcome measures at 2-year follow-up.

Methods: Forty-five patients who underwent single level TLIF and 29 patients who underwent single level stand-alone LLIF for degenerative spondylosis with low back and leg pain were included. All costs from diagnosis through 2-year postsurgical follow up were available from a comprehensive single center data bank within a unified hospital system. Total cost to the third-party payor for all spine-related medical resource use from the time of diagnosis through 2 years was recorded. QALYs were calculated from EQ5D.

Results: Statistically significant improvements were observed at 2 year follow up for both TLIF and LLIF utilizing SF36PCS, ODI, VAS BP, VAS LP and EQ5D. ICER calculations revealed similar mean cumulative QALYs gained at the 2-year interval (0.67 for TLIF and 0.60 for LLIF; $p=0.331$). Mean total cost of care following TLIF and LLIF were \$53,038 and \$55,464, respectively; ($p=0.960$). MCED thresholds with an anchor of $<\$50,000/\text{QALY}$ were higher than MCID thresholds (calculated using the Health Transition Index anchor) for all patient-reported

outcome measures. Total mean cost and EQ5D were statistically equivalent between the 2 treatment groups.

Conclusions: Transforaminal lumbar interbody fusion (TLIF) and lateral lumbar interbody fusion (LLIF) produced equivalent 2-year patient outcomes at an equivalent cost effectiveness profile.

829. Predictors of Unplanned Readmission in Cranial Neurosurgery: A Nationwide Analysis of Patient-Specific Risk Factors

Blake E. Taylor; Geoffrey Appelboom, MD, PhD; Brett Youngerman, MD; Robert McGovern, MD; Bryan Lieber, BA; E. Connolly, Jr., MD, FACS (New York, NY)

Introduction: Reducing the rate of early hospital readmission has become a priority in recent healthcare quality improvement policy to reduce costs and patient morbidity. Since Centers for Medicare and Medicaid Services began using the rate of unplanned 30-day readmission as a factor in hospital reimbursement, there has been increased attention to identifying patients at high risk of readmission. This data is lacking, however, in cranial neurosurgery.

Methods: Using the national, prospectively-collected American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2006-2012, we compared patient demographic (eg. age, sex) and clinical (eg. comorbidities, in-hospital variables, complications) characteristics between those readmitted and not readmitted. After an initial univariate analysis, a multivariate model was then constructed using significant characteristics from the univariate analysis ($p<0.05$) with binary logistic regression. Exclusion criteria included planned readmissions and death <30 days postoperatively.

Results: Of the 4,303 cases identified, 497 (11.6%) were readmitted within 30 days postoperatively. Independent predictors of readmission were a history of severe COPD (OR=1.57; $p=0.046$), perioperative sepsis (OR:1.92; $p=0.014$), septic shock (OR:3.21; $p=0.008$), and prolonged hospitalization (OR:1.02; $p<0.001$). Of postoperative complications, predictors were surgical-site infections (OR:16.5, $p<0.001$) and venous thromboembolism (OR:3.29, $p<0.001$). Factors including age, cardiac conditions, operative time, pneumonia, and urinary tract infections did not reach significance.

Conclusions: We provide one of the first analyses of nationwide data determining independent predictors of readmission after cranial neurosurgery. Our results suggest that readmission rates may be lowered by improving postoperative care focused on detecting infectious complications and venous thromboembolism, and follow-up care of patients with chronic conditions such as COPD.

830. Socioeconomic Disparities in Nontraumatic Subdural Hematoma Outcome

Briana Prager; Benjamin Rosenbaum, MD (Cleveland, OH)

Introduction: The incidence of nontraumatic subdural hematoma (SDH) has been increasing consistently, and thus the number of deaths is rising despite a slow decline in mortality. However, disparities in outcome and their relationship to socioeconomic status remain poorly characterized. We therefore sought to analyze the contribution of several socioeconomic factors to mortality following nontraumatic SDH.

Methods: A retrospective analysis was performed using the Nationwide Inpatient Sample (NIS) database from 1988 to 2011 to acquire data on all nontraumatic SDH hospitalizations during that period. Contributing factors were analyzed using multivariable

logistic regression to obtain odds ratios (OR) at a significance level of $p < 0.05$.

Results: In contrast to previously reported decreased odds of mortality for non-white race, we identified confounding by the older average age of the white patient population, which masked an increased risk of death for African Americans. Furthermore, self-pay was significantly associated with emergent admission (OR=1.66; 95% CI 1.59-1.73), while private insurance was protective (OR=0.86; 95% CI 0.84-0.87). Additional factors significantly associated with increased mortality include older age, female gender, emergency admission, absence of surgical intervention and Elixhauser comorbidity index < 3 .

Conclusions: This is the first study to assess socioeconomic disparities in nontraumatic SDH outcome. These results demonstrate a previously unknown increased mortality for African Americans and an increased likelihood of emergent admission for non-private payers. These data suggest the need for further assessment of the impediments to early identification or presentation of nontraumatic SDH related to insurance as well as the factors underlying racial disparities in mortality.

831. Effect of Closed Continuous Lumbar Drainage on Treatment of Postoperative Intracranial Infection: A Retrospective Analysis of 2127 Cases

Xue-Song Liu, MD; Chao You; Yuekang Zhang; Xuhui Hui (Chengdu, China)

Introduction: Postoperative intracranial infection are considered more severe than any other infection acquired in the hospital environment, which can result in high death rates, longer hospital stay, and higher hospital costs. To address this issue, the authors performed the traditional antibiotic therapy assisted by closed lumbar drainage on some patients, and the other patients only underwent traditional therapy. The data of this two group cases were analyzed retrospectively.

Methods: The medical records of 2127 patients who developed postoperative intracranial infection in the department of Neurosurgery in West China Hospital during 1995-2013 were reviewed. The outcomes of prognosis and medical economics were compared and analyzed between the two different groups.

Results: The diagnosis of postoperative intracranial infection was confirmed by clinical symptoms and laboratory findings in 2127 patients (1007 male and 1120 female, mean age 47.6 years). The traditional antibiotic therapy strategy was performed in 1176 patients (Group one). The same strategy assisted by closed lumbar drainage was performed in the other 951 patients (Group two). The mean duration of the drainage was 12.9 days. The mean duration of positive result of CSF bacterial culture convert to negative were 31.7 days and 15.8 days respectively. Induced by the infection, the rates of reoperation were 7.3% and 3.4% respectively. The mean hospital costs for treatment of intracranial infection were 3867 dollars and 1735 dollars. The mortality of these two groups was 15.2% and 6.1%. The morbidity of neurological dysfunction was 21.8% and 9.4%. All of these outcomes are statistically significant ($P < 0.05$).

Conclusions: Since the closed lumbar drainage can accelerate the CSF circulation and the evacuation of contaminative CSF, the traditional antibiotic therapy assisted by this method can contribute to shorter hospital stay lower hospital cost lower morbidity and lower mortality.

832. Memory Task-specific Encoding by Neuronal Networks in the Human Hippocampus

Mark R. Witcher, MD; Adrian Laxton, MD; Daniel Couture, MD; Gautam Popli, MBBS; Myriam Sollman, PhD; Cheryl Sexton, MS; Sam Deadwyler, PhD; Robert Hampson, PhD (Winston Salem, NC)

Introduction: Epilepsy patients undergoing intracranial monitoring for seizure localization provide an excellent model to study discharge patterns of single neurons within the mesial temporal lobe during memory tasks. Animal models have shown that discharge patterns of CA3 neuronal populations influence the discharge of CA1 neurons. We therefore hypothesized that human hippocampal neurons have regionally and temporally specific and interrelated discharge patterns which contribute to task specific memory formation and retrieval.

Methods: Seven adult epilepsy patients undergoing implantation of hippocampal electrodes (Ad-Tech, Racine, WI) for seizure localization were enrolled. Consent was obtained for study participation. Electrodes were stereotactically (BrainLab, Westchester, IL) implanted into the CA3 and CA1 hippocampal subfields. Placement was confirmed using postoperative high resolution 3T MRI. Single unit neuronal activity was isolated via extracellular action potential waveform identification and recorded (Plexon, Dallas, TX; Blackrock Microsystems, Salt Lake City, UT) Neurocognitive experiments consisted of visual object-oriented and spatial-oriented stimuli within Delayed-Match-to-Sample type tasks (e.g. DMS & PAL CANTAB tasks, and custom-written object/spatial DMS tasks).

Results: Hippocampal neurons exhibited differential firing rate increases to behavioral events within both object-oriented and spatial-oriented tasks. Specific CA3 and CA1 firing rate changes were identified which related to anterior and posterior hippocampal locations as well as differences in event-related encoding between the object and spatial tasks.

Conclusions: Hippocampal neurons exhibited the same differential encoding and correlation to successful versus failed memory performance as shown in prior rodent and nonhuman primate studies. These findings support the utility of this model for the eventual development and testing of a human memory prosthetic.

833. Laser Interstitial Thermal Therapy: Lessons Learned

Rachel Pruitt, BS; Alexander Gamble, DO; Ashesh Mehta, MD, PhD; Michael Schulder, MD (Manhasset, NY)

Introduction: Complications of laser interstitial thermal therapy (LITT) are seemingly underreported. We discuss how we have modified our technique in the context of technical and treatment-related complications.

Methods: Saline-cooled laser probes (Medtronic Visualase, Houston TX) were inserted using intraoperative MRI (iMRI) (5 patients), frameless stereotaxy (FS, in 2), or frame-based in 28. LITT was done in a 1.5 Tesla diagnostic MRI (dMRI). 35 patients were treated, 15 with brain tumors, 1 with a filum terminale ependymoma, 15 with mesial temporal lobe epilepsy (MTLE), and 4 with hypothalamic hamartomas (HH).

Results: Laser misplacement occurred in two patients; in one FS was used for tumor targeting, and in one with MTLE, the laser was suboptimally placed when an alignment rod was not inserted beforehand. No other patients with a stereotactic frame sustained laser misplacement. Two MTLE patients had hemorrhage from laser insertion, one with a superior quadrantanopsia, and one was asymptomatic. Four patients had complications from the LITT treatment itself. Two with brain tumors developed deficits

from laser hyperthermia, one affecting the brainstem, and another the primary motor cortex. The patient with the filum terminale ependymoma developed a paraparesis postoperatively. In one patient with glioblastoma, treatment was aborted when the saline coolant flow ceased and the laser tip overheated.

Conclusions: Complications of LITT can result from laser misplacement, laser insertion, and laser treatment. Our lessons learned include: 1) A stereotactic frame provides optimal laser placement; 2) In patients where a long laser placement is needed, an alignment rod should be inserted before the laser; 3) Preoperative CTA with MR fusion can be used to avoid vascular injury; 4) Critical structures should not be treated with the full hyperthermia dose to minimize the risk of neurological complications; 5) Intraspinal LITT should be used with caution; and 6) Saline coolant flow must remain continuous.

834. Use of Dual Lead Thalamic DBS to Treat Severe Multiple Sclerosis Tremor

Seth F. Oliveria, MD PhD; Michael Okun, MD; Kelly Foote, MD (Gainesville, FL)

Introduction: Surgical treatment of severe multiple sclerosis tremor has proven more difficult than for essential or parkinsonian tremor; lesioning and DBS for this condition have had mixed and often disappointing results.

Methods: 12 patients with refractory MS tremor all underwent ipsilateral VIM and VOA-VOP DBS and were randomized to initial Vim On or VOA-VOP On stimulation. Blinded assessment was performed at 3 months with the tremor rating scale score (TRS) and quality of life measures. After this all patients had both leads activated and optimized, then returned for a six month evaluation of all conditions (On VIM, On VOA-VOP, both On, and both Off). The primary outcome measure of the study was 3 and 6 month TRS compared to preoperative baseline TRS. Mood and neuropsychiatric batteries were performed to assess procedure safety.

Results: VIM and VOA-VOP DBS significantly improved multiple sclerosis tremor TRS at 6 months compared to baseline. Tremor improvement was significantly greater with co-activation of VIM and VO than with both stimulators off. However, neither VIM nor VO stimulation was superior to the other in this study. The most frequent side effects were headache, slowed or slurred speech and fatigue. The only serious adverse event that occurred in more than one participant was change in mental status, and this occurred in only 2 participants.

Conclusion: Dual lead VIM and VOA-VOP DBS therapy is generally safe and efficacious for refractory MS tremor.

835. Intracranial Electrophysiologic Responses to Visual Naming in the Human Anterior Temporal Lobe

Taylor John Abel, MD; Ariane Rhone; Timothy Ando; Kirill Nourski; Hiroto Kawasaki; Hiroyuki Oya; Matthew Howard, III; Daniel Tranel (Iowa City, IA)

Introduction: Naming famous faces is a fundamental human ability often impaired in patients with left temporal lobe epilepsy and also after resection of the left anterior temporal lobe (ATL) for epilepsy. The purpose of this study was to characterize the electrophysiologic responses of the human ATL during naming.

Methods: 10 patients undergoing implantation of electrodes for seizure localization, with dense electrode coverage of the ATL, were the subjects for this study. Patients named 50 distinct pictures

(presented for 1s each) of several (3 or more) famous people and hand held tools. Electrocorticographic (ECoG) responses were recorded. Event-related band power (ERBP) was measured for each ATL recording site and associated sensory cortex when available (e.g. fusiform gyrus; FG).

Results: Picture naming resulted in increased high frequency (30-150 Hz) power in FG that preceded responses from ATL cortex. Both the right and left ATL (in separate subjects) demonstrated robust and focal increases in beta band power during person and tool naming. Person and tool naming responses co-localized to the same cortical sites on the ventrolateral ATL.

Conclusions: Our findings demonstrate that visual naming of people and tools is associated with robust and localized increases in beta band power in both the left and right ATL. Measurement of visual naming responses may provide the groundwork for future mapping modalities to localize eloquent cortex in the ATL.

836. Complete Sub-Sylvian Resection of the Insula in Peri-Insular Hemispherotomy: Technique, Complications, and Epilepsy Outcome

Brent Randle O'Neill, MD FAANS; Marie McKinnon, MS; James Reszczenski, BS; Michael Handler, MD (Aurora, CO)

Introduction: Hemispherotomy is an operation designed to treat intractable epilepsy by disconnecting or removing the cortex of a pathologic hemisphere. A number of techniques have been described to accomplish this but none have thoroughly addressed disconnection or resection of the insula.

Methods: A retrospective chart review was undertaken to compare peri-insular hemispherotomy without insular resection to peri-insular hemispherotomy with complete insular resection by sub-Sylvian technique. Sub-Sylvian insular resection consists of direct aspiration of the insular grey matter beneath the Sylvian arachnoid. This Sylvian arachnoid and middle cerebral artery (MCA) branches are progressively elevated from posterior to anterior and superior to inferior until the insula is completely resected. The MCA trunk is then ligated allowing en-bloc removal of the Sylvian arachnoid and overlying frontal and temporal lobe tissue.

Results: Between 2003 and 2013, 75 patients underwent hemispheric surgery for epilepsy at a large pediatric hospital. 32 had peri-insular hemispherotomy without formal resection of the insula, all prior to 2010. 40 patients had peri-insular hemispherotomy with sub-Sylvian insular resection. Three had another technique (excluded). The insular resection group trended toward better seizure outcome at one year post-operatively (83% vs 75% seizure free) and fewer complications (25% vs 44%). Neither of these differences is statistically significant. The rate of hydrocephalus was identical between the two groups. The sub-Sylvian group had shorter operative times and lower volume of blood transfusion.

Conclusions: Sub-Sylvian insular resection is a safe adjunct to peri-insular hemispherotomy that may improve seizure outcome.

837. Changes in Subthalamic Nucleus Local Field Potentials Following Administration of Levodopa in Patients with Parkinson's Disease

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Introduction: Levodopa and deep brain stimulation (DBS) of the subthalamic nucleus (STN) are commonly used in the management of Parkinson's disease (PD). Local field potentials (LFP) recorded

from DBS electrodes have demonstrated a decline in beta and increase in gamma band power in the STN during the on state, and are under investigation for informing closed-loop DBS devices. In this study, we evaluated the LFP-based temporal relationship of levodopa administration and the clinical on state.

Methods: LFPs were recorded in seven PD patients who underwent STN DBS placement. LFPs were recorded with 1024 Hz and 16 bit A/D resolution for 36 hours. Patients were recorded continuously for 30 minutes before medication intake through 30 minutes after the on state began.

Results: Analysis of LFPs revealed baseline beta (11-30 Hz) activity within STN prior to levodopa administration. Following levodopa administration, beta activity suppressed on average 36.3 minutes (SD=18.6) and gamma (70-90 Hz) activity increased 28.5 minutes (SD = 13.5) before the on state. Compared to the off state, beta energy decreased by 47.1% (SD = 34.4) and gamma increased by 102.4% (SD = 93.4) during the on state. There was a trend for a decline in beta power preceding gamma power rise by 15.5 minutes ($p=0.059$).

Conclusions: LFPs recorded in STN undergo reproducible changes following levodopa administration. There is a trend for beta suppression preceding gamma enhancement, and both precede the on state. The clinical effect of levodopa is temporally related to electrophysiological changes in STN. Both beta and gamma band changes serve as neuromarkers for patient on state.

838. Motor-Related Neuronal Activity in the Nucleus Ventralis Intermedius of the Thalamus

David Segar, BS; Shane Lee, PhD; Stephanie Jones, PhD; Wael Asaad, MD, PhD (Providence, RI)

Introduction: The ventral intermediate nucleus of the thalamus (VIM), a key link between the cerebellum and the sensorimotor cortex, has long been a neuromodulatory target for pathologic tremor. Stimulation of VIM can dramatically reduce tremor in these patients; however, the underlying mechanisms by which VIM modulates motor output are poorly understood.

Methods: We obtained VIM single-neuron recordings from three essential tremor patients during DBS surgery. We asked patients to execute a jump-target task to assess neuronal responses to movement direction and movement error-correction. Subjects performed an 8-direction center-out task where on some trials the target jumped to an expected or unexpected new location just after movement onset. Waveforms surpassing a voltage threshold were sampled at 40 kHz and sorted off-line using principal components. Behavioral data was aligned with electrode recordings using digital time codes. All data was analyzed in Matlab.

Results: Each neuron was tested for task-related responsiveness by comparing baseline firing rates to firing rates cued to particular task-related events. Of 36 neurons recorded, 18 neurons responded to at least one task-related visual cue or motor event. Eleven neurons exhibited classical directional tuning. A notable subgroup of 2 neurons responded only to the appearance of a jumped target and the associated movement correction.

Conclusions: VIM neurons were actively engaged by this joystick movement task, and many were tuned to the direction of movement. Several also selectively responded to corrections of movement, supporting a role for the VIM in conveying alterations in motor plans from the cerebellum to the cortex.

839. Human Subthalamic Nucleus and Prefrontal Cortex Demonstrate Increased Coherence During Behavioral Adaptations to Conflict and Errors

Baltazar Antonio Zavala; Huiling Tan, PhD; Peter Brown; Kareem Zaghloul (Washington, DC)

Introduction: There is growing evidence that the subthalamic nucleus (STN), which is the most common target for deep brain stimulation (DBS), plays a crucial role in altering the dynamics of decision-making in the human brain. Previous studies have suggested that the STN prevents impulsive responses by synchronizing its theta (4-8 Hz) activity to that of the prefrontal cortex during conflict. Here, we examined whether coordinated activity between the prefrontal cortex and STN local field potential and spiking activity modulates across trial adaptations based on performance or difficulty.

Methods: We simultaneously captured STN single-unit spiking, STN local field potentials, and prefrontal cortex electrocorticography during DBS surgery as patients performed sensory-motor tasks involving conflict and errors.

Results: During trials that followed an error or high levels of conflict, we found slower response times and increased theta band phase synchrony between the prefrontal cortex and the STN. When conflict was present in the previous trial, the theta band synchrony occurred following presentation of a fixation cue. When an error had occurred in the previous trial, however, we found increased synchrony during the decision period. We found that the extent of theta band synchrony was related to the salience of the errors.

Conclusions: Our results suggest that prefrontal-STN communication plays an important role in adapting strategies for subsequent performance. These networks may be disrupted by DBS, which may underlie some of the cognitive side effects observed following DBS. Thus optimal DBS therapy should aim to selectively suppress pathological STN activity while preserving physiological communication.

840. Cellular Mechanisms Underlying the Use of Striatal Stimulation for the Treatment of Traumatic Brain Injury

Anna L. Huguenard; Husam Katnani, PhD; Emad Eskandar, MD, MBA (Boston, MA)

Introduction: The therapeutic benefit of deep brain stimulation (DBS) has expanded into many indications including traumatic brain injury (TBI). A previous study in the Eskandar Lab demonstrated that DBS in the ventral striatum improves performance of task learning in a rodent model of TBI. Whole genome analysis (WGA) demonstrated increased expression of neuroproliferation, neuroplasticity, and neuroprotection genes. This project further examined immunohistochemical markers in those categories.

Methods: Mice underwent a unilateral controlled cortical impact injury and were implanted with sham or stimulating electrodes targeted to the ventral striatum. At 2, 5, 7, or 14 days after stimulation, brains were extracted for immunohistochemical analysis. Regions evaluated included: hippocampus, anterior rostral migrating stream (RMS), striatum (STR), subventricular zone (SVZ), and perilesional space (PLS). Three categories of markers were studied based on WGA: neuroproliferation (BrdU, NeuN, DoubleCortin, and GFAP), cell migration and plasticity (MARCKS and GAP43), and cell injury, scarring, or death (Caspase 3, Ox-42, and FluoroJade-B).

Results: Animals treated with DBS showed increased markers of neuroproliferation, with more co-labeled BrdU+/NeuN+ and BrdU+/DoubleCortin cells in the SVZ, RMS, and PLS. MARCKS and

GAP43 expression was also increased, demonstrating augmented mechanisms of neuroplasticity. Markers of cell death and axonal injury such as Caspase 3, Ox-42, and FluorJade-B were decreased demonstrating an attenuation of the deleterious effects involved in post-injury gliosis and axonal degeneration.

Conclusions: We found that following TBI, animals treated with DBS showed increased markers of neuroproliferation, neuroplasticity, and neuroprotection. These findings begin to elucidate the cellular mechanisms underlying the therapeutic benefit of DBS following brain injury.

841. Whole Transcriptome Analysis of Nucleus Accumbens Deep Brain Stimulation in a Rodent Traumatic Brain Injury Model

Joshua Paul Aronson, MD; Husam Katnani, PhD; Anna Huguenard, BS; Emad Eskandar, MD (Boston, MA)

Introduction: Recovery after traumatic brain injury (TBI) depends on restoration of neuronal cellular and network function. We have previously demonstrated intermittent stimulation of the nucleus accumbens (NAcc) enhances learning after controlled cortical impact, restoring spatial learning performance to that of uninjured controls. We sought to identify mechanisms underlying this finding. We utilized whole transcriptome analysis (RNA-seq) to study changes in gene transcription across brain regions after TBI and stimulation.

Methods: Nine C57BL/6 were utilized for RNA-seq (three 'control' uninjured, injured/unstimulated 'sham', and injured/stimulated 'stim'). Mice underwent right parietal craniotomy, with six undergoing controlled cortical impact over the hippocampus. Electrodes were implanted in the ipsilateral NAcc. Stim animals received high frequency biphasic stimulation. Animals were euthanized and 1 mm³ sections of right NAcc, left NAcc, left hippocampus, and left ventromedial prefrontal cortex were resected. Tissue was digested and mRNA was isolated. RNA-seq was run on pooled samples. Ingenuity Pathway Analysis was used to identify expression changes in relevant pathways. An additional six mice were used for immunohistochemical analysis.

Results: Whole transcriptome analysis identified changes in dopamine signaling, apoptosis and inflammatory pathways, glutamate signaling, synaptic plasticity, and neuronal growth and migration in the ipsilateral NAcc of stimulated compared to sham mice as well as in sham compared with uninjured control mice. In the contralateral hippocampus, expression changes in neurogenesis pathways were identified. Immunohistochemical analysis supported enhanced neurogenesis along the rostral migratory stream and hippocampus.

Conclusions: Our whole transcriptome analysis in a TBI model treated with DBS advances understanding of the mechanisms underlying the benefits of DBS to augment normal recovery processes. Our findings indicate that DBS after TBI causes upregulation of genes associated with neurotransmitter release, neuronal proliferation, and neuroprotection. These results elucidate the function and mechanisms of DBS as a viable therapy to enhance recovery of deficits following brain injury.

842. Mechanism of Activation of Mitogen-activated Protein Kinases

Masahiro Aoyama; Koji Osuka, MD, PhD; Nobuteru Usuda, MD, PhD; Masakazu Takayasu, MD, PhD (Nagakute, Japan)

Introduction: In a 2014 AANS meeting, we reported that

mitogen-activated protein kinase (MAPK) is activated and expressed in chronic subdural hematoma (CSDH) outer membrane. Previous studies have shown that growth factors and inflammatory cytokines activate the MAPK cascade. In this study, we further examined whether CSDH fluid activates major MAPKs in cultured endothelial cells and fibroblasts in vitro.

Methods: Cultured endothelial cells and fibroblasts were incubated with medium containing CSDH fluid, which was obtained during trepanation surgery. Cells incubated with medium only were used as a control. Protein lysates were prepared in harvested cells at 5, 15, and 60 min. Expression of MEK, phosphorylated (p)-MEK, ERK, p-ERK, p38, p-p38, JNK, p-JNK, and actin was examined by western blotting. Furthermore, to investigate whether CSDH fluid induces MEK activation in these cultured cells, we tested the effects of antibodies directed against interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF).

Results: Expression of p-MEK and p-ERK in endothelial cells and fibroblasts was significantly induced immediately after treatment with CSDH fluid, while p-p38 and p-JNK were significantly induced in endothelial cells 60 min after treatment, but not in fibroblasts. Activation of MEK was significantly inhibited by pretreatment with IL-6 and VEGF antibodies in endothelial cells, but not in fibroblasts.

Conclusions: Regulation of activation of MAPKs by CSDH fluid might be different between endothelial cells and fibroblasts. IL-6 and VEGF might activate the MEK/ERK pathway in endothelial cells, which could be associated with neovascularization in CSDH outer membrane. These MAPK pathways could become novel targets for treatment of CSDHs.

843. Evolution of T2 hyperintensity on Magnetic Resonance Imaging (MRI) Following Spinal Cord Injury in Professional Athletes

Joseph Charles Maroon, MD, FAANS(L); Zachary Tempel, MD; Jeffrey Bost, PA-C (Pittsburgh, PA)

Introduction: The evaluation and management of contact sport athletes with spinal cord T2 MRI hyperintensity is challenging. Although T2 hyperintensity is evidence of cord trauma in the short-term, the long-term pathophysiologic and prognostic value of this finding is poorly understood. With complete recovery of neurological function it is unclear whether unresolved T2 hyperintensity is significant in return-to-play (RTP) recommendations.

Methods: Retrospective chart review of five professional contact sport athletes with cervical cord injuries associated with T2 hyperintensity on MRI was collected between 2007 - 2014. Pertinent demographic data: age, height, weight, sport and position played, radiographs and MRI studies. Long-term outcomes evaluations: symptoms, examination, MRI results, surgical interventions, RTP recommendations and long-term outcome.

Results: Four NFL players and one professional wrestler all had resolution of signs and symptoms of neurapraxia at initial surgical evaluation. Initial MRI showed congenitally small cervical canal(1) and multilevel spondylosis/stenosis and prominent disc herniation at level of T2 hyperintensity(4). The signal abnormalities were seen at C3/4(3), C4 mid-vertebral body(1) and C5/6(1). Four athletes had single-level ACDF, and one no surgery. Serial MRI imaging (range:6-36 months, ave.13) showed T2 hyperintensity completely resolved(1), partially(3) and unchanged(1). Based on authors RTP criteria all athletes were released to return their sport. Two athletes retired and one is waiting to resume play. Two athletes returned to play have not suffered additional episodes of neurapraxia or cervical spine complications at 18(1) and 36(1) months.

Discussion: T2 hyperintensity is often used as contraindication

to RTP in contact sport athletes despite being symptom-free, normal examination and no spinal instability. This review provides support that resolution of symptoms and normal neurologic function with a stable spine should be considered in determining RTP criteria despite a persistent MRI T2 hyperintensity.

844. Impact of Invasive Intracranial Pressure Monitoring on Outcomes following Severe Traumatic Brain Injury

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

Introduction: While a recent clinical trial (BEST-TRIPS) demonstrated no improvement in outcomes with invasive Intracranial Pressure (ICP) monitoring (ICPM) following severe Traumatic Brain Injury (TBI), its generalizability has been called into question. Invasive ICPM is not considered the standard of care in the developing world and, when available, is often used at the discretion of the attending neurosurgeon. Our objective was to determine the impact of ICPM on mortality and 6-month functional outcomes following severe TBI.

Methods: During a 4-year period data was prospectively entered into a severe TBI registry at a referral trauma center. Patients 12 years and older meeting Brain Trauma Foundation (BTF) criteria for ICPM were included in the study. The registry was queried for validated predictors of outcome in addition to use of ICPM. Outcomes of interest were in-hospital mortality and poor 6-month functional outcome defined as Glasgow Outcome Scale (GOS) 3 or lower. A propensity score based analysis incorporating known predictors of outcome in TBI was utilized to examine the impact of ICPM on outcomes.

Results: Of 1345 patients meeting study criteria 497(37%) underwent ICPM. In-hospital mortality was 35%(471/1345). Of 454 patients for whom six-month outcome was available, 161(35%) suffered a poor functional outcome. Following propensity score based analysis ICPM use was associated with a 7.5% ($p=0.01$) decrease in mortality but no significant effect ($p=0.66$) on functional outcome.

Conclusions: The use of ICPM following severe TBI was associated with a decrease in mortality but no significant difference in 6-month functional outcome. Further clinical trials of ICPM are required.

845. Results of Delayed Follow-up Imaging in Traumatic Brain Injury

Adam Ross Befeler, MD; William Gordon, MD; Nicklaus Khan, MD; Julius Fernandez, MD; Michael Muhlbauer, MD; Jeffrey Sorenson, MD (Memphis, TN)

Introduction: There is a paucity of scientific evidence available about the benefits of outpatient follow-up imaging for traumatic brain injury patients. In this study we analyze one year of consecutive patients at our level 1 trauma center to determine if there is any benefit to routinely obtaining computerized tomography of the head at an outpatient follow-up visit.

Methods: A single-institution retrospective review was performed for all patients with a traumatic brain injury seen in 2013 at our level 1 trauma center. Demographic data, types of injuries, surgical interventions, radiographic imaging in the inpatient and outpatient settings, and outcomes were assessed through a review of our institution's trauma registry, patient charts and imaging.

Results: Five hundred twenty-five patients were seen for traumatic brain injury in 2013 at Regional One Healthcare in Memphis, Tennessee. One hundred eighty-five patients (35%) presented for outpatient follow-up – all with computerized tomography scans of the head. Seven of these patients (4%) showed worsening of their intracranial injuries on outpatient imaging studies, however surgical intervention was recommended in only three of these (2%). All patients requiring an intervention had neurological deterioration prior to their follow-up appointment.

Conclusions: Our experience suggests that outpatient follow-up imaging in traumatic brain injury should be done selectively, as it was not helpful in patients who did not exhibit worsening of neurological signs or symptoms. Furthermore, routine outpatient imaging results in unnecessary resource utilization and radiation exposure.

846. Prophylactic anticonvulsant therapy in chronic subdural hematoma

Souad Bakhti, MD; MOHAMED DJENNAS, MD, PhD (Algiers, Algeria)

Introduction: Prophylactic anticonvulsant therapy is used in some instances in patients with chronic subdural hematoma. Effectiveness of this treatment is still debated and there is no formal recommendations.

Methods: We report a prospective study of 189 patients with chronic subdural hematoma operated by burr hole and open drainage. These patients did not receive prophylactic anticonvulsant therapy. Results were compared to those of a retrospective study of 200 patients operated by same technique and anticonvulsants. Clinical and radiological data of patients with postoperative seizures were reviewed.

Results: We have observed 2 patients with postoperative seizures (1.05%) in the prospective study while there were 3 patients with postoperative seizures in retrospective study (1.5%). Paradoxically, rate of postoperative seizures was more important in patients with anticonvulsant therapy but difference was not statistically significant ($p=0.70$). Review of clinical and radiological data didn't give any information concerning etiology.

Conclusions: Results suggest that prophylactic anticonvulsant therapy is not necessary in chronic subdural hematoma. But no recommendation can be drawn because we have compared a prospective study with a retrospective one. Indeed there are no well randomized controlled studies in literature. There is an urgent need of guidelines in this field

847. Symptom Reporting in Acute Mild Traumatic Brain Injury (mTBI) and Persistent Post-Traumatic Symptom Patients

Michael D. Cusimano; Windsor Ting; Jane Topolovec-Vranic, PhD (Toronto, Canada)

Introduction: Validated tools for mTBI assessment are the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and the Symptom Scale Component of the Sport Concussion Assessment Tool, 3rd Edition (SCAT3). We hypothesized that in mTBI patients, longitudinal recovery profiles for symptom load after head injury should be mirrored between these two scales, and Persistent Traumatic Symptom (PTS) patients should report a greater symptom load than acute mTBI patients in the chronic stages.

Methods: Eleven mTBI patients recruited from St. Michael's Hospital completed the RPQ and SCAT3 within ten days ($n=11$),

14-21 days (n=8), and 3-7 months (n=3) post-injury. Thirteen PTS patients filled out the same scales once. Total scores of both questionnaires and their validated subscales were calculated and statistically analyzed using parametric and non-parametric tests.

Results: Acute mTBI patients significantly differed in SCAT3 total score (TS) across trials, $F(2, 7.74)=10.8$, $p=0.0058$ and SCAT3 symptom severity (SS) scores, $F(2, 9.38)=5.2$, $p=0.03$. The somatic subscore of the RPQ over the three trials was significantly different, $F=3.69$, $p=0.044$. Comparing the third visit of the acute mTBI patients with the PTS patients, the former reported smaller symptom load on the SCAT3 SS, $p=0.02$; SCAT3 TS, $p=0.02$; RPQ TS, $p=0.00024$; RPQ somatic subscore, $p=3.79e-06$ and emotional subscore, $p=0.02$, but not the RPQ cognitive subscore, $p=0.057$.

Conclusions: The SCAT3 is a better tool than the RPQ to track recovery of symptoms in acute mTBI patients over time since significant differences were observed over clinical course, while both questionnaires can be used to differentiate between different groups of mTBI patients.

848. Videonystagmography: an Objective Measure of Sport-Related Concussion

Matthew R. Quigley, MD, FAANS; Sam Akhavan, MD; Edward Snell, MD; Kevin Kelly, MD; Robin Ashmore, PhD; Alex Kiderman, PhD (Pittsburgh, PA)

Introduction: Athletic concussion is coming under increased scrutiny, both on medical and governmental fronts. The science remains handicapped by the absence of objective criteria on the playing field as well as later on for informing return to play decisions. Although paper and pencil tests have been the mainstay of diagnostic inquiry, with an ROC of .65-.70 their utility in any single individual is severely limited.

Methods: We performed videonystagmography (VNG) consisting of a battery of 76 tests on a proprietary device on 269 normal non-concussed high school athletes and 50 other athletes who had sustained a documented sports-related concussion.

Results: Athletes ranged from 13-18 years. VNG examinations were performed an average of 14.2+/- 13.4 days post-concussion. Logistic regression identified six testing parameters associated with concussion ($p<.0001$ for the model) relating to saccades, pursuit, reaction time and anti-saccades. The ROC for the model was .97 which remained unchanged with 100 three-fold validations. Using the default .5 likelihood cut-off, the model correctly predicted 37/50 concussed and 279/286 controls. By adjusting the threshold to where the sensitivity and specificity curves crossed (.2), we improved prediction to 46/50 concussed versus 268/286 controls. All 4 false negatives in the concussion group had symptom scores ≤ 7 .

Conclusions: VNG is a promising diagnostic test for concussion and exhibits a powerful ROC (.97) which is a marked improvement over paper and pencil testing. Adjusting the diagnostic cut-off improves sensitivity at the expense of modest specificity decline. The false negative concussed had minimal symptoms when tested which may explain why they were incorrectly assigned.

849. 3D-Printed Ventriculostomy Placement Simulator

Luis Savastano, MD; Bruce Tai, PhD; Deborah Rooney, PhD; Albert Shih, PhD; Oren Sagher, MD (Ann Arbor, MI)

Introduction: External ventricular drain (EVD) placement is one of the most common neurosurgical procedures. Residents must become proficient early in their training to decrease the risk profile of EVD placement, but to date realistic training tools are scarce and

mainly limited to virtual reality simulation systems. For low-cost, high-fidelity training tool for EVD placement skin-to-skin, we designed a physical simulator using 3D printing and traditional molding technologies and conducted a multi-institutional survey to prove the content validity.

Methods: Using 3D printing we directly built the model geometry from stealth head computed tomography scans, and manufactured a phantom brain mold based on 3D scans of a plastinated human brain. A cadaveric specimen was sent to the lab for haptic and biomechanical analysis of tissues and materials selection. Validity evidence was evaluated using a Rasch model and a performance rating was created to align all steps of EVD placement with a global rating matrix using the Objective Structured Assessment of Technical Skills tool.

Results: An anatomically accurate skull was created with a multi-layer replaceable insert for the operative area to simulate scalp incision, bicortical bone drilling, dura opening, skin closure, and catheter tunneling and anchoring. A brain phantom was made from gellan gum and held against a midline transparent plate, allowing for observation of catheter placement via windows in the left cranial vault. The ventricular system was filled with fluid pressurized by a 20 cm-high water reservoir to mimic pressure conditions and visualize fluid drainage. Validity survey indicated the simulator was valuable as a learning tool and able to distinguish novel from proficient practitioners.

Conclusions: This newly developed simulator based on 3D printing and molding technologies is a low-cost, high-fidelity training tool for EVD placement that could be incorporated in an international standardized curriculum to train residents.

850. Using FDA Approved Human Neural Stem Cells for Repair in a Penetrating TBI

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Introduction: Penetrating traumatic brain injuries (PTBI) are associated with the worst outcomes with both high mortality and severe disability. No treatment strategies are available, but stem cell transplantations have emerged as putative therapeutic approaches. In this rodent study, we evaluated the engraftment of FDA approved human fetal neural stem cells (hNSC; Neuralstem Inc.) in a rat model of PTBI.

Methods: 3 rat strains (Sprague-Dawley (SD), Fischer and Athymic SD) underwent a unilateral penetrating ballistic brain injury (PBBi). Immunosuppression was established before stereotactic injection of control or hNSCs into the PBBi penumbra. Animals were sacrificed at defined time points post-transplantation. Brains were sectioned and assessed for graft cell number, graft survival, maturation and potential tumor formation.

Results: 8 weeks after transplantation, grafted cells could be detected in 100% SD, 80% Athymic and 50% Fischer rats. Robust engraftment of 15% of cells was observed in all three strains. No overgrowth of undifferentiated cells/teratomas was observed. The transplanted cells stained predominantly for neuronal rather than astrocytic markers. Immature neurons with simple processes as well as mature neurons with complex dendritic arborizations were observed projecting towards the PBBi lesion. The graft volume in SD rats and athymic rats was comparable.

Conclusion: 1) Robust engraftment at 8 week post transplantation was observed; 2) No transplant derived tumors were seen; 3) Immunosuppressed SD rats had a preserved graft size, making them suitable for further studies. We conclude that PTBI may be

treated with NSC transplants. We are currently determining whether transplantation results in functional improvement.

851. Outcomes after Surgical Treatment of Meningioma-associated Proptosis

William T. Couldwell, MD, PhD, FAANS; Christian Bowers, MD (Salt Lake City, UT)

Introduction: Proptosis associated with sphenoorbital and other skull base meningiomas can be cosmetically and functionally problematic; however, the literature is limited regarding quantitative proptosis outcomes with no consensus regarding the optimal surgical technique. We evaluated proptosis outcomes to determine whether an aggressive surgical removal of the periorbital in addition to bone involvement yielded better improvement and whether this was associated with additional morbidity. No attempt was made to reconstruct the orbit.

Methods: The authors reviewed a retrospective cohort of surgeries for meningioma-associated proptosis by a single surgeon. The extent of proptosis resolution was measured by the exophthalmos index (EI) pre- and postoperatively and at final follow-up.

Results: Thirty-two patients (19 female; mean age 49 years) were treated for meningioma-associated proptosis. Twenty had additional visual symptoms, such as a loss of visual acuity, a field cut, or diplopia. None of the patients had worse vision after treatment: 15 had improved vision and 5 had stable vision (average follow-up 33.0 months). Diplopia was present postoperatively but resolved in all cases. No cases of enophthalmos were noted. The average preoperative EI was 1.33, and the average EI at most recent follow-up was 1.01, yielding an average EI improvement of 0.32. One case of delayed vasospasm was noted. One patient experienced recurrence of hyperostosis within the treatment zone, which was managed by repeat surgery and postoperative radiation therapy.

Conclusion: Experience from this series indicates that aggressive tumor removal involving the periorbital in cases of meningioma-associated proptosis achieves enhanced cosmetic outcome.

852. Surgical Resection and Interstitial 125-I Brachytherapy for High Grade Meningioma: A 25 year series.

Stephen T. Magill, MD, PhD; Darryl Lau, MD; Penny Sneed, MD; Michael McDermott, MD (San Francisco, CA)

Introduction: Atypical and anaplastic/malignant meningiomas (WHO Grades II-III) are aggressive tumors that recur despite resection and radiation, and do not respond well to chemotherapeutics. Thus, implantation of 125I brachytherapy seeds into the resection cavity has been used to augment surgical treatment. Here, we report the results of patients treated at our institution over a 25-year period.

Methods: Charts of patients treated at the University of California, San Francisco who underwent surgical resection and interstitial placement of 125I brachytherapy sources for atypical and malignant meningioma between 1988-2013 were reviewed to determine progression free survival, survival after brachytherapy and overall survival. Kaplan-Meier actuarial method was used to calculate progression free and overall survival. Log-rank comparisons between curves were performed.

Results: Forty-two patients with high grade meningioma underwent surgical resections with 125I brachytherapy. All patients had prior resections and 35 had prior radiation. At the time of brachytherapy, 13 patients had gross total resection, while 28 had subtotal resection. Median time to progression after resection with

125I brachytherapy was 8.9 months for atypical meningioma, 9.0 months for malignant meningioma ($p = 0.69$), and 8.95 months for the combined groups. Median survival after 125I brachytherapy was 3.5 years for subjects with atypical meningioma, 2.4 years for subjects with malignant meningioma ($p = 0.78$), and 3.3 years for all subjects. Median overall survival after diagnosis was 11.5 years for subjects with atypical meningioma, 8.0 years for subjects with malignant meningioma ($p = 0.27$), and 9.4 years for all subjects. Complications included radiation necrosis (8), wound breakdown (6), hydrocephalus (4), infection (3), and a meningocele (1).

Conclusions: These results are the largest case series of local brachytherapy with radioactive iodine sources as an adjuvant to resection for patients with high grade meningiomas. The favorable outcomes support the use of adjuvant brachytherapy in treating these aggressive tumors.

853. Novel Techniques of Real-time Blood Flow and Functional Mapping for Brain Surgery

Kyousuke Kamada; Hiroshi Ogawa, MD; Yukie Tamura, MD; Ryogo Anei, MD, PhD; Christoph Kapeller, PhD; Hideaki Hayashi, PhD; Robert Prueckl, PhD; Christoph Guger, PhD (Asahikawa, Japan)

Introduction: There are two trend applications for intraoperative monitoring in neurosurgery. One is fluorescent phenomena and the other is oscillatory neuronal activity. We developed novel techniques of real-time data processing to visualize blood flow conditions based on indocyanine green videography (ICG-VG) and electrocorticogram of high gamma activity (HGA).

Methods: We applied the real-time technique to 30 patients with moyamoya disease and 20 patients with brain tumors who underwent awake craniotomy. Real-time data processing of ICG-VG was based on perfusion imaging, which generated parameters such as arrival time (AT), mean transit time (MTT), and blood flow (BF) of brain surface vessels. During awake craniotomy, we analyzed the frequency components of brain oscillation and performed real-time HGA mapping to identify eloquent areas.

Results: After revascularization for moyamoya disease, AT and BF were significantly shortened and increased in 10 of 30 cases, suggesting hyperperfusion. All the cases suffered from transient seizure or neurological deficits and showed focal hyperperfusion on postoperative SPECT. Real-time HGA mapping during awake craniotomy rapidly indicated the eloquent areas of motor and language functions and significantly shortened the operation time compared to electrocortical mapping. Sensitivity and specificity of HGA mapping were 90.2% and 82.4%, respectively.

Conclusions: These novel techniques should improve reliability of intraoperative monitoring and enable the development of rational and objective surgical strategies.

854. Survival Patterns of Patients with Cerebral Metastases after Multiple Rounds of Stereotactic Radiosurgery (SRS).

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Introduction: With escalating focus on cost containment, there is increasing scrutiny on the practice of sequential SRS for patients suffering multiple rounds of brain metastases. A major concern is that such recurrence pattern may be a prognostic indicator of poor overall survival.

Methods: We retrospectively analyzed outcomes of 788

consecutively treated patients with 2838 cerebral metastases at the San Diego Gamma Knife Center (SDGKC), comparing survival patterns of patients who underwent a single-round (n=644) versus multiple-rounds (n=144) of SRS for subsequent brain metastases distant to the initial tumor. Multivariate analyses were performed to control for known prognostic variables, including RPA class, tumor histology, number of metastases, and cumulative tumor volume.

Results: Median survival of patients who underwent one round of SRS was 5 months from the time of SRS. For patients who underwent two or three rounds of SRS, the median survival from date of last SRS was 6 months and 5 months, respectively (p-value=0.11, log-rank test). Patients who underwent multiple-rounds of SRS tended to be younger, with systemic disease control, have melanoma histology, and harbor higher cumulative tumor volume (p-values 0.004, <0.001, and 0.009, respectively for Pearson chi-squared test). Median interval between treatments was 176 days (between first/second SRS) and 154 days (between second/third SRS).

Conclusions: For judiciously selected patients, no decrease in overall survival was observed in patients who underwent multiple rounds of SRS for new cerebral metastases. In light of the potential long-term toxicity of whole brain radiation therapy, serial SRS should be considered for select patient populations.

855. Microthrombus is the Most Powerful Histologic Predictor of IDH1/2 Mutation Status and Outcome in Gliomas

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Introduction: The purpose of this study is to evaluate the ability of microthrombi (MT) to predict isocitrate dehydrogenase 1 or 2 (IDH1/2) mutation status, and to act as a new histologic criterion for the diagnosis of glioblastoma.

Methods: All 171 grades II-IV gliomas tested for IDH1/2 mutation status since 2009 at the University of Kentucky were scored for key histologic markers: necrosis, microvascular proliferation (MVP) and MT. Data on tissue factor (TF) mRNA and promoter methylation was mined and analyzed from The Cancer Genome Atlas. A tissue microarray (TMA) of patient-derived gliomas was analyzed for TF expression via immunohistochemistry.

Results: Whereas 86% of WT-IDH1/2 gliomas had MT, only 1.9% of mut-IDH1/2 gliomas did (P less than 0.0001). MT was superior to age, necrosis and MVP in correlating with IDH1/2 status. On multivariate analysis, MT (P equals 0.0001) was also a more powerful prognostic marker for overall survival than either necrosis (P equals 0.38) or MVP (P equals 0.063). Of several genes known to be associated with MT, only TF procoagulant was consistently lower in IDH1/2 mutant gliomas in the TCGA (P equals 5.9×10^{-66}). Likewise, in the TMA cohort, TF protein expression was lower in IDH1 mutant gliomas (P less than 0.0001). Finally, 25% of patients with a wild-type glioma developed systemic hypercoagulation, in contrast to no patients with a mutant glioma (P less than 0.0001).

Conclusions: Microthrombi are the most powerful predictor of IDH1/2 mutation status and should be added to the histologic criteria for GBM, alongside necrosis and MVP.

856. Preoperative DTI, Intraoperative Visual Evoked Potentials, and Direct Cortical/Subcortical Stimulation for Visual Pathway Identification

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Anastasia Tasiou, MD, PhD; Haralampos Gatos, MD; Ioanna Kasselouri, PhD; Ioannis Fezoulidis, MD, PhD (Volos, Greece)

Introduction: Preservation of vision becomes of paramount importance during the resection of tumors located anywhere along the visual pathway. However, the actual location of the visual tract may be highly variable, and the possibility of its displacement is increased when intra-axial brain lesions are present. The purpose of our study was to preoperatively delineate, and intraoperatively identify the visual pathway in patients undergoing tumor resection.

Methods: In a prospective study, 18 consecutive patients, with tumors located along or close to the theoretical anatomical position of the post-chiasmatic visual pathway, were included. All patients were evaluated preoperatively with MR imaging including Diffusion Tensor Imaging (DTI) for delineating the visual pathway. They underwent surgery for tumor resection with frameless neuronavigation, intraoperative visual evoked potential recording, and bipolar cortical/subcortical stimulation. Pre- and post-operative visual acuity and visual field examinations were routinely obtained.

Results: Preoperative DTI identified the visual pathway in 13/18 (72.2%) cases. Visual evoked potential recording was feasible in all patients, while intraoperative stimulation confirmed the visual pathway in 12/18 (66.7%) cases. The topographic accuracy of DTI, compared to the stimulation studies, was ≤ 10 mm in 7/12 (58.3%) cases. Worsening of the preoperative visual examination was observed in 4/18 (22.2%) patients.

Conclusions: Our data support the concept of preoperative identification of the visual pathway by employing DTI. The accuracy of the DTI was approximately 58% in our cohort. However, in a significant number of cases (27.8%), our DTI methodology was not feasible. Further development of the method may well increase its clinical applicability and accuracy.

857. Quantitative Phosphoproteomics for Targeted Cancer Therapy

Teresa Purzner, MD; Jae Cho, MD; Matt Scott; Josh Elias (Stanford, CA)

Introduction: Most medulloblastomas (MB) originate from dysregulation of developmental pathways. To discover important drug targets within these pathways, we have undertaken the first quantitative mass spectrometry-based phosphoproteomic approach to identify important phosphorylation events, using the Hh signaling pathway as our model.

Methods: Quantitative phosphoproteomic analysis was performed using SILAC (Stable Isotope Labeling with Amino acids in Cell culture) combined with strong cation exchange fractionation and phosphopeptide enrichment by immobilized metal affinity chromatography (IMAC) followed by multiplexed quantitative mass spectrometry data.

Results: We have discovered changes in phosphorylation of 94 proteins only 25 minutes after Shh exposure. Motif analysis revealed a novel and critical role for the kinase, CK2, in mediating 45% of all early phosphorylation. Importantly, CK2 affects terminal Hh signaling components, circumventing challenges of emergence of resistance and a priori resistance commonly encountered with existing small molecule inhibitors targeting upstream at SMO. CK2 inhibitors demonstrated early and sustained inhibition of Hh signaling across several mammalian cell types, including MB cells. In vivo, mice harboring flank MB allografts derived from Ptc^{+/+};Tpr53^{-/-} and a point mutation in Smo rendering them resistant to Vismodegib, showed near-complete cessation of tumor growth in response to TBB, a highly potent and selective inhibitor of CK2.

Conclusions: Our quantitative phosphoproteomic approach to Hh signaling has provided a perspective that was unattainable with previous transcription and genome-based efforts. Our success using one pathway will set the foundation for others to apply a similar approach in different tumor initiating pathways.

858. Laser Thermo-Ablation for Metastases failing Radiosurgery – a Multicentered Retrospective Study

Veronica L. Chiang, MD, FAANS; E Leuthardt, MD; S Tatter, MD; A Mohammadi, MD; G Barnett, MD (New Haven, CT)

Introduction: Few options remain for treatment of brain metastases failing radiosurgery. Several case series have reported using laser thermo-ablation (LTA).

Methods: Cases of LTA performed for salvage treatment of brain metastases after radiosurgery at 4 Neurosurgical sites were reviewed retrospectively. Demographic, medical and surgical data was collected. Linear regression analyses were performed to determine factors associated with outcome after LTA.

Results: 30 patients were studied. Primary diagnoses included NSCLCa (53%), melanoma and renal (20%) and breast, colon and gynaecological cancers (27%). Median pre-op KPS was 80 (range 50-100). Median lesion volume treated was 7.6cm³ (range 0.6–38.9). Median changes in lesion volume at 1.5, 3 and 6 months were 3.4, 0.2 and -1.1% while median reduction in perilesional edema volume was 27.7%, 41.8% and 44.6% respectively. 41% of patients had resolution of their pre-op symptoms. Mean time to symptom resolution was 2 weeks and steroid cessation was 4.5 weeks. More perilesional edema reduction occurred following treatment of larger lesions ($p<0.001$), and was associated with improvement in KPS score ($p=0.006$) and ability to stop steroids ($p=0.035$). Survival rates after LTA were 61.8% at 6 months, 36.3% at 12 months, 30.2% at 18 months and 20.2% (6/30 patients) at 30 months. Pre-LTA KPS was the only factor significantly associated with survival ($p=0.028$).

Conclusions: Successful LTA treatment resulted, in this study, in symptom relief in 40% of patients and an almost 50% median reduction in perilesional edema which was significantly associated with improved KPS and cessation of steroid use. LTA should be considered when brain metastases fail radiosurgery.

859. Motor Evoked Potentials Predict Recovery in Spinal Cord Injury

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Introduction: Whilst the utilization of intraoperative neurophysiologic monitoring (IOM) with somatosensory (SSEP) and motor evoked potentials (MEP) has become widespread in spine surgery, scientific studies of its diagnostic and therapeutic benefit have been limited. This study aims to describe the IOM experience at a large level I trauma center and assess for prognostic capability of this technology.

Methods: The neurosurgery REDCAP database at San Francisco General Hospital (SFGH) was queried for patients with acute cervical spinal cord injury who underwent surgery with IOM between 2007 and 2011, yielding 32 patients. In addition to demographic data, we assessed preoperative and postoperative spinal cord injury severity (AIS grade), surgical data, use of steroids, and hemodynamic data.

Results: The mean age in this cohort of patients was approximately

56 (range 22-85 yrs) and AIS grades were A (n=10), B (n=5), C (n=6), D (n=11). All patients underwent surgical decompression and stabilization with intraoperative SSEPs and MEPs. In the group of severe SCI (AIS A, B, C) patients with elicitable MEPs, AIS improved by an average of 1.5 grades, as compared to the patients without elicitable MEP who improved by 0.7 grades ($p=0.005$).

Conclusions: In patients with severe SCI (AIS A, B, C) presence of MEPs was found to predict neurologic improvement. This significant finding warrants future prospective study MEP as a prognostic tool in SCI.

860. Outcome of Mechanical Thrombectomy in the Elderly for the Treatment of Acute Ischemic Stroke

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Introduction: Although there are debates about its efficacy, multiple studies support thrombectomy in select patient cohorts. However, elderly patients (age ≥ 80) are typically excluded from clinical trials. Besides a recently published retrospective cohort study from national patient database, there is virtually no literature addressing this area. We present our experience in a select cohort of patients ≥ 80 years.

Methods: We retrospectively reviewed all stroke-alert activations in our health system from January 2011 to June 2014 and identified 18 patients over age 80 whom received mechanical thrombectomy. Their clinical characteristics including physiologic imaging findings, whether they received intravenous thrombolytics prior to mechanical thrombectomy, baseline and post-op NIHSS, TICI score, discharge destination, and mRS at 3 months were analyzed.

Results: Mean NIHSS on presentation was 18.2 (6-31), and 13.3 (3-30) post thrombectomy. Three (16.6%) patients received IV r-TPA, 2 (11.1%) had symptomatic intracranial hemorrhage. 8 (44.4%) died, 8 (44.4%) were discharged to nursing home, and 2 (11.7%) were discharged to inpatient rehab and subsequently home. Favorable Outcome (mRS ≤ 2) was achieved in 2 (11.1%) patients. Fourteen (77.7%) patients had physiologic imaging prior to intervention. Three (75%) of four patients whom did not had physiologic imaging prior to thrombectomy died. Thirteen (66.6%) patients had TICI 3 recanalization.

Conclusions: Our study showed that although there remains a role of mechanical thrombectomy in the treatment of acute ischemic stroke in the elderly, it is associated with significant higher morbidity and mortality compared to younger patients.

Disclaimer: The Journal of Neurosurgery Publishing Group (JNSPG) acknowledges that the preceding abstracts and poster sessions are published as submitted and did not go through JNSPG's peer-review or editing process.