



THE AMERICAN ACADEMY OF NEUROLOGICAL SURGERY

81ST ANNUAL SCIENTIFIC MEETING
WALDORF ASTORIA CAVALIERI ROME
SCIENTIFIC PROGRAM AT A GLANCE

WEDNESDAY, SEPTEMBER 18, 2019

ITALIAN NEUROSURGICAL SOCIETY & AMERICAN ACADEMY OF NEUROLOGICAL SURGERY - COMBINED SCIENTIFIC PROGRAM

1:00 – 1:20 Welcome and Introduction – Alex Olivi & Michael McDermott

Welcome Remarks from the SINch: *Roberto Delfini and Alberto Delitala*

Moderators: Michael McDermott & Francesco Tomasello

1:20 – 1:45 Neurotraumatology and Neurosurgery: A Worldwide Approach

Franco Servadei (*Italy*)

1:50 – 2:10 Trends & New Developments in Glioma Therapy

E. Antonio “Nino” Chiocca (*AAcNS*)

2:15 – 2:35 The Treatment of Pediatric AVMs

Marco Cenzato (*Italy*)

2:40 – 2:55 Trends & New Developments in Endovascular Therapy

Howard Riina (*AAcNS*)

2:55 – 3:15 - BREAK

Moderators: Antonio Raco & Alex Olivi

3:20 – 3:40 Endonasal Approaches to Craniopharyngiomas

Paolo Cappabianca (*Italy*)

3:45 – 4:05 Trends & New Developments in Spinal Surgery

Mark Hadley (*AAcNS*)

4:10 – 4:30 Changing Paradigms in Neurosurgical Education. The Case of Virtual Reality and Surgical Simulation

Francesco DiMeco (*Italy*)

4:35 – 4:55 Trends & New Developments in Functional - Epilepsy

G. Rees Cosgrove (*AAcNS*)

5:00 – 5:20 Intraoperative Neurophysiological Monitoring in Spinal Cord Tumor Surgery: How Much Evidence Do We Need?

Francesco Sala (*Italy*)

5:30 Adjourn

Evening Social Event:
Opening Reception ~ 6:30 pm – 9:00 pm
Terraza Aranci, Waldorf Astoria Cavalieri Hotel
Business Casual Attire recommended



THURSDAY, SEPTEMBER 19, 2019

7:30 – 7:35 WELCOMING REMARKS

Michael McDermott (Scientific Program Chair) & Alex Olivi (Local Arrangements Chair)

7:35 – 8:45 Peer Reviewed Abstract Session I: Functional Science

Moderators: Daniel Yoshor

7:35 – 7:45 Safety/Efficacy of Bone Marrow-Derived Mesenchymal Stem Cell (SB623) Implantation After Chronic Traumatic Brain Injury

Gary Steinberg

7:45-7:55 Extracellular microRNAs in Blood Differentiate Between Ischemic and Hemorrhagic Stroke

Yasar Kalani

7:55 – 8:05 Hemodynamic Predictors of Long-Term Patency in Cerebral Revascularization Surgery

Fady Charbel

8:05 – 8:15 Early Results of Clinical Testing of a Visual Cortical Prosthetic in Blind Subjects

Daniel Yoshor

8:15 – 8:25 Nerve transfers to improve upper extremity function and quality of life in tetraplegic patients

Wilson Ray

8:25 – 8:35 Mapping brain response patterns to Deep Brain Stimulation with fMRI

Andres Lozano

8:35 – 8:45 Trigeminal Nerve Stimulation as a Neuroprotectant

Raj Narayan

8:45-9:25 Peer Reviewed Abstract Session II: Spine Science

Moderators: Nicholas Theodore & Mark Shaffrey

8:45 - 8:55	12-Month Safety and Efficacy Results from the SCiStar Study – A Phase 1/2a Trial of Richard Fessler
8:55 - 9:05	Early Surgery and Recovery in Central Cord Syndrome: Analysis of 211 Patients from a Prospective, Multi-Center Dataset Michael Fehlings
9:05 - 9:15	Transpedicular vertebrectomy for thoracic spine metastasis Ehud Mendel
9:15 - 9:35 Break	
9:35-10:45	Peer Reviewed Abstract Session III: Tumor Science Moderators: Nino Chiocca & Mitchel Berger
9:35 - 9:45	Meningioma Genomic Subgroup and Predicting Post-operative Patient Outcomes: Implications for Treatment and Follow-up Jennifer Moliterno
9:45 - 9:55	Oncolytic G207 Produces immunologic Signature Predicting Response to Therapy James Markert
9:55 - 10:05	Evolution of Low Grade Gliomas During Malignant Transformation Mitchel Berger
10:05 - 10:15	Flies, worms and fish: What do these have to do with brain tumours? Jim Rutka
10:15 - 10:25	Neurosurgical management of sinonasal malignancies involving the skullbase. A 25-year experience. Franco DeMonte
10:25 - 10:35	Opening of blood brain barrier in the hippocampus and entorhinal cortex in Alzheimer's disease with focused ultrasound Ali Rezai
10:35 - 10:45	CAR T cell therapy for glioblastoma: Current observations and future directions Don O'Rourke
10:50-11:50	Peer Reviewed Abstract Session 4: Vascular Science Moderators: Elad Levy & Robert Spetzler

10:50 - 11:00 Functional Connectivity Deficits After Subarachnoid Hemorrhage

Greg Zipfel

11:00 - 11:10 Microbiome Signatures of Cavernous Angioma

Sean Polster

11:10 - 11:20 The New Generation Hydrogel Endovascular Aneurysm Treatment Trial (HEAT): Final Results

Bernard Bendok

11:20 - 11:30 The R2eD AVM score: a novel predictive tool for arteriovenous malformation presentation with hemorrhage

Judy Huang

11:30-11:40 Cerebral Aneurysm Formation and Rupture: Role of Nrf2 Signaling

Aaron Dumont

11:40 - 11:50 Early Gene Deletion Generates a High-Fidelity Transgenic Mouse Model of Familial Brain Arteriovenous Malformations

Michael Lawton

11:50 - 12:00 Break

12:00 - 12:50 **Special Lecture I**

Moderator: Alex Golby / James Rutka

The Rhetoric of Medicine: Lessons on Professionalism From Ancient Greece

Nate Selden/Nigel Nicholson

Evening Social Event:

Visit to the Musei Vaticani and Sistine Chapel

Dinner at the Paolo VI Residence and Terrace

Buses depart from hotel at 5:30 pm. Business casual attire recommended



FRIDAY, SEPTEMBER 20, 2019

7:30 - 7:35 WELCOME & REMARKS

Michael McDermott (Scientific Program Chair) & Alex Olivi (Local Arrangements Chair)

7:35-8:35	Peer Reviewed Abstract Session V: Vascular Moderators: Michael Lawton & E. Sander Connolly
7:35 - 7:45	Deletions in CWH43 Cause Sporadic Idiopathic Normal Pressure Hydrocephalus Mark Johnson
7:45-7:55	NEWTON-2: Randomized, Double-blind, Placebo-controlled study of EG 1962 in Aneurysmal Subarachnoid Hemorrhage R. Loch MacDonald
7:55-8:05	When Flow Diversion Fails: Predictive Factors of Incomplete Aneurysm Occlusion after Pipeline Embolization Chris Ogilvy
8:05-8:15	Transradial Cerebral Angiography: A Safer Alternative Felipe Albuquerque
8:15-8:25	Somatic mutations in cerebral aneurysms Rose Du
8:25-8:35	Intracranial Aneurysms: Does Size Really Matter? Phil Stieg
8:35-9:15	Peer Reviewed Abstract Session VI: Tumor Moderators: Henry Brem & Don O'Rourke
8:35-8:40	Long-Term Outcomes in the Treatment of Pediatric Skull Base Chordomas Paul Gardner
8:40-8:50	MRI Perfusion Radiomic Machine Learning Identifies Pseudoprogression in Glioblastoma - A Multicenter Study Pascal Zinn
8:50-9:00	The evolution of epilepsy surgery for children: lessons from tuberous sclerosis complex over 20 years Howard Weiner
9:00-9:10	Stimulated Raman Histology for Rapid Neurosurgical Intraoperative Histology: A Prospective Series Allan Levi
9:10-9:20	Role of Visual Cortex in Essential Tremor Jean Regis

9:20-9:30	Break
9:30-10:30	Peer Reviewed Abstract Session VII: Spine Moderators: Kevin Foley & Praveen Mummaneni
9:30-9:40	Early Results from the CSM-S RCT: Quality of Life, Cost, and Complications Zohar Ghogawala
9:40-9:50	Fusion for Spondylolisthesis Is Associated with Greater Improvements: A Multicenter Registry Study Kevin Foley
9:50-10:00	Frailty, Long-Term Outcomes and Management Implications for Type II Odontoid Fractures in the Elderly Michelle Clarke
10:00-10:10	The use of intraoperative sodium fluorescein for diagnostic biopsy of intramedullary spine cord lesions Timothy Ung
10:10-10:20	Robot-Assisted vs Freehand Instrumentation in Short-Segment Lumbar Fusion: Experience with Real-Time, Image-Guided Spinal Robot Nicholas Theodore
10:20-10:30	Maximal Safe Resection in Thalamic Gliomas is Superior to Biopsy: Personal Reflections on 40 Cases Mustafa Baskaya
10:30-11:30	Peer Reviewed Abstract Session VIII: Functional/Trauma/Vascular Moderators: Bernard Bendok / Sepi Amin-Hanjani
10:30-10:40	Dopamine, serotonin, and norepinephrine micro-fluctuations during conscious choice and subjective experience in humans Charles Branch
10:40-10:50	Intracranially delivered IL-12 secreting CAR T cells recruit host immunity to eradicate heterogeneous GBM John Sampson
10:50 - 11:00	A New Treatment for Acute TBI – a phase II multicenter trial using novel MRI derivatives as surrogate outcome measures Howard Eisenberg
11:00-11:10	Dynamic blood brain barrier regulation in mild traumatic brain injury Gerald Grant
11:10-11:20	Computer-Learning to Identify High Risk Unruptured Aneurysms and Guide Decision Making: Rupture Resemblance Score Elad Levy

11:20-11:30 Distribution and radiologic features of SEDAVFs in a modern single-center series of patients with spinal vascular shunts

Giuseppe Lanzino

11:30 -11:40 HDFT as a tool to enhance outcomes in the management of hypereloquent lesions

Robert Friedlander

11:40-11:50 Break

11:50-12:20

Special Lecture 2

Introduction of Academy Special Lecturer: Alex Olivi & Mike McDermott

Fast cars and fast trains: The Ferrari and Italo stories

Luca Cordero di Montezemolo

12:20 - 1:20

Presidential Address

12:20 - 12:30

Introduction of the Academy President : Mark Johnson

12:30 - 1:20

Quo Vadis, Academia?

Nino Chiocca, MD

Evening Social Event:
Academy Gala Dinner
Villa Miani
Attire: Black Tie Optional



7:30 – 8:25	<u>Special Lecture 3: The Oldfield Lectureship</u>
7:30 – 7:35	Introduction, Moderator: Nino Chiocca
7:35 - 8:05	Oldfield Lecture: Bench to bedside development of a novel STAT3 inhibitor for CNS malignancies - Amy Heimberger
8:05 - 8:15	NIH Funding Overview: Russell Lonser
8:15 - 8:20	NREF Funding Overview: Reg Haid
8:20 - 8:25	AAcNS/NREF Young Clinician Award Update - Brian JA Gill
8:25 - 8:30	AAcNS/NREF Research Fellowship Grant Update - Benjamin Grannan
8:30 - 8:40	American Academy Young Clinician Investigator Award – North America Single-cellular representations of semantic meaning during natural language perception Benjamin L. Grannan
8:40 - 8:50	American Academy Young Clinician Investigator Award – Italy Monitoring language networks in the asleep patient during surgery: an electrophysiological approach - Davide Giampiccolo
8:55 – 9:30	<u>Special Lecture 4:</u>
8:55-9:00	Introduction of Academy Special Lecturer: Alex Olivi
9:00-9:30	<i>Thirty generations of winemaking and still feeling young</i> Lamberto Frescobaldi, President Azienda Agricola “Marchesi Frescobaldi” Firenze
9:30 - 10:30	Peer Reviewed Abstract Session 9: Various topics Moderators: Jacques Morcos / Robert Harbaugh
9:30-9:40	Brain growth and developmental outcome after treatment of post-infectious hydrocephalus in infants in Uganda Abhaya Kulkarni
9:40-9:50	Impact on Facial Nerve Outcomes and Extent of Resection Using Subperineural Dissection Technique for Surgical Resection James Liu
9:50-10:00	Phase 0/1 Clinical Trial of Low-Dose Capecitabine in Recurrent GBM: Global Immune Fingerprinting of Tissue and Blood Michael Vogelbaum

10:00-10:10	Sexual Dysfunction: Prevalence, Prognosis, and Predictors of Outcomes in Patients Operated for Lumbar Spondylolisthesis
Praveen Mummaneni	
10:10-10:20	Cerebro-vascular remodeling following ischemic stroke: cellular and molecular mechanisms.
Robert Dempsey	
10:20-10:30	Glioblastoma organoids: A model system for patient-specific therapeutic testing
Ryan Salinas	
10:30-10:45 Break	
10:45-11:55	Peer Reviewed Abstract Session 10: Various topics Moderators: Michael McDermott / Aviva Abosch
10:45-10:55	Outcomes from Asleep and Awake Dominant Temporal Lobe Glioma Surgery: Risk, Extent of Resection, and Survival
Michael McDermott	
10:55-11:05	Real-time CED of Nanoliposomal CPT-11 for recurrent GBM: Interim results of a phase I clinical trial
Manish Aghi	
11:05-11:15	Leptomeningeal dissemination, a sinister pattern of medulloblastoma growth
Daniel Fults	
11:15-11:25	Characteristics of Clots Retrieved by Mechanical Thrombectomy Associated with Stroke Etiology and Device Performance
Adnan Siddiqui	
11:25-11:35	Integration of 5-ALA and CEUS in the Surgical Resection of High Grade Glioma
Alex Olivi	
11:35-11:45	Mesenchymal Stem Cell Delivery of Oncolytic Adenovirus Delta-24-RGD Following Surgical Resection of Glioblastoma
Fred Lang	
11:45-11:55	An Epigenetic Liquid Biopsy Machine Learning Algorithm to Predict Glioma and Glioma Subtypes
Steve Kalkanis	
12:00	Closing Remarks Meeting Adjourn 2020 Scientific Chair - Aviva Abosch

Immediately following Adjournment, Lamberto Frescobaldi will host a wine tasting entitled “*A Journey Through Tuscany*”

SCIENTIFIC PROGRAM

81ST ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGICAL SURGERY

ITALIAN NEUROSURGICAL SOCIETY & AMERICAN ACADEMY OF NEUROLOGICAL SURGERY - COMBINED SCIENTIFIC PROGRAM

1:00 – 1:20 Welcome and Introduction – Alex Olivi & Michael McDermott

Welcome Remarks from the SINch: *Roberto Delfini and Alberto Delitala*

Moderators: Michael McDermott & Francesco Tomasello

1:20 – 1:45 Neurotraumatology and Neurosurgery: A Worldwide Approach

Franco Servadei (*Italy*)

1:50 – 2:10 Trends & New Developments in Glioma Therapy

E. Antonio “Nino” Chiocca (*AAcNS*)

2:15 – 2:35 The Treatment of Pediatric AVMs

Marco Cenzato (*Italy*)

2:40 – 2:55 Trends & New Developments in Endovascular Therapy

Howard Riina (*AAcNS*)

2:55 – 3:15 - BREAK

Moderators: Antonio Raco & Alex Olivi

3:20 – 3:40 Endonasal Approaches to Craniopharyngiomas

Paolo Cappabianca (*Italy*)

3:45 – 4:05 Trends & New Developments in Spinal Surgery

Mark Hadley (*AAcNS*)

4:10 – 4:30 Changing Paradigms in Neurosurgical Education. The Case of Virtual Reality and Surgical Simulation

Francesco DiMeco (*Italy*)

4:35 – 4:55 Trends & New Developments in Functional - Epilepsy

G. Rees Cosgrove (*AAcNS*)

5:00 – 5:20 Intraoperative Neurophysiological Monitoring in Spinal Cord Tumor Surgery: How Much Evidence Do We Need?

Francesco Sala (*Italy*)

5:30 Adjourn

7:30 – 7:35 WELCOMING REMARKS

Michael McDermott (Scientific Program Chair) & Alex Olivi (Local Arrangements Chair)

7:35 – 8:45 Peer Reviewed Abstract Session I: Functional Science

Moderators: Robert Gross & Daniel Yoshor

7:35 – 7:45 Safety/Efficacy of Bone Marrow-Derived Mesenchymal Stem Cell (SB623) Implantation After Chronic Traumatic Brain Injury

Albert Lai, Achal Achrol, MD, Alan Weintraub, Susan Paadre, Hideaki Imai, Robert Gross, Gary Steinberg, Laroslav Zinkevych, MD, Mena Niakian, David Okonkwo, Takehiko Kaneko, Masahito Kawabori, MD, PhD, Damien Bates, Jefferson Chen, MD, PhD, Peter McAllister, MD, Daniel Lu, Ihor Semeniv, MD, Benjamin Frishberg, MD, Takao Yasuhara

Introduction

Traumatic brain injury (TBI) is a major cause of neurologic disability with no effective treatments.

Objective

This double-blind, randomized, sham-controlled, Phase 2 trial evaluated efficacy and safety of stereotactic intracerebral implantation of allogeneic modified bone marrow-derived mesenchymal stem cells (SB623) in patients with chronic motor deficits secondary to TBI.

Methods

Sixty-one subjects (mean age 34 years) from 18 sites (US, Japan and Ukraine) received 2.5x10⁶, 5.0x10⁶, or 10x10⁶ SB623 cells or sham procedure (1:1:1:1) ratio; n=46 SB623, 15 controls). Primary outcome was mean change from baseline in the Fugl-Meyer Motor Scale (FMMS) of pooled SB623 subjects c/w controls at 24 weeks. MR at 8 days post-implant was evaluated for new FLAIR signal changes.

Results

Mean (SE) change from baseline in FMMS (Week 24) was 8.3 (1.4) for SB623 versus 2.3 (2.5) in the control group (p=0.04). Eight (17.4%) serious adverse events (SAEs) in five (10.9%) SB623-treated subjects occurred versus three (20%) SAEs in three (20%) controls. No abnormal MR FLAIR signal changes were observed in any patients at post-implant Day 8.

Conclusion

The primary efficacy endpoint of improved motor function at 6 months was achieved. SB623 cell implantation was well tolerated. Unlike a prior Phase 1/2a study of patients with chronic ischemic stroke undergoing intracerebral implantation of SB623 cells, where a new transient premotor cortex MR FLAIR signal at 1 week post-implantation was highly correlated with neurologic recovery at 6, 12, and 24 months post-implantation, no new MR FLAIR signal was detected at 1 week post-implant in any of the patients.

7:45-7:55 Extracellular microRNAs in Blood Differentiate Between Ischemic and Hemorrhagic Stroke

Robert Spetzler, Yashar Kalani

Introduction

Rapid identification of patients suffering from cerebral ischemia, while excluding intracerebral hemorrhage, can assist with patient triage and expand patient access to chemical and mechanical revascularization.

Objectives

We sought to identify blood-based, extracellular microRNAs (ex-miRNAs) predictive of major stroke subtypes using clinical samples from subjects with intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), and ischemic stroke due to cerebral vessel occlusion.

Methods

We collected blood from patients presenting with IPH (n=19), SAH (n=17) and ischemic stroke (n=21). We isolated extracellular vesicles from plasma, extracted RNA cargo, sequenced the small RNAs, and performed bioinformatic analyses to identify ex-miRNA biomarkers predictive of the stroke subtypes.

Results

67 miRNAs were significantly variant across the stroke subtypes. A subset of ex-miRNAs differed between hemorrhagic and ischemic strokes, and LASSO analysis could distinguish SAH from the other subtypes with an accuracy of 0.97 p< 0.002. Further analyses predicted miRNA classifiers that stratify IPH from ischemic stroke with accuracy of 0.81 p< 0.004 and distinguish hemorrhagic from ischemic stroke with accuracy of 0.81 P< 0.003.

Conclusion

Blood-based, ex-miRNAs have predictive value, capable of distinguishing between major stroke subtypes. Such a biomarker may serve as point-of-care tests to rapidly and reliably differentiate between major stroke subtypes and aid with the triage of patients to expand the pool eligible for chemical and mechanical revascularization.

7:55 – 8:05 Hemodynamic Predictors of Long-Term Patency in Cerebral Revascularization Surgery

Christopher Stapleton, Ahmed Hussein, Sepideh Amin-Hanjani, Fady Charbel

Introduction

Cerebral revascularization remains an important part of neurovascular surgery, but large cohort analyses with robust hemodynamic data and long-term angiographic follow-up are lacking in the literature.

Objectives

We sought to evaluate hemodynamic factors that predict long-term patency in a large cohort of cerebral bypasses.

Methods

All intracranial bypass procedures performed between 2001 and 2018 were reviewed.

Results

A total of 308 consecutive bypasses were performed during the study period, of which 300 (aneurysm, n=112; atherosclerosis, n=94; moyamoya, n=92) had angiographic follow-up. At a mean follow-up of 2.3 ± 3.0 (range: 0-15.9) years, 225 (75.0%) bypasses were patent. While male sex was associated with long-term bypass patency (patent: 100 [44.4%]; non-patent: 18 [24.0%]; p=0.002), there were no significant differences in patient age (p=0.99), indication for bypass (p=0.81), bypass type (p=0.68), number of bypasses (p=0.21), or number of anastomoses (p=0.45). With respect to hemodynamic factors, there were no significant differences in intra-operative bypass flow (p=0.63), post-operative bypass flow (p=0.41), or ratio of post-operative bypass flow to intra-operative bypass flow (p=0.96). For all EC-IC bypasses (n=223), the cut flow index (CFI), or ratio of bypass flow to donor vessel cut flow, was significantly higher for patent (0.89 ± 0.50) than non-patent (0.71 ± 0.42) bypasses (p=0.008), especially when performed for flow augmentation (i.e., moyamoya or atherosclerosis) purposes (p=0.001).

Conclusion

In this cohort of 300 cerebral revascularization procedures, the CFI was most closely associated with long-term bypass patency, especially when performed for the purpose of flow augmentation.

8:05 – 8:15 Early Results of Clinical Testing of a Visual Cortical Prosthetic in Blind Subjects

William Bosking, **Daniel Yoshor**, Michael Beauchamp, Denise Oswalt

Introduction

It has long been recognized that a visual cortical prosthesis (VCP) has the potential to restore vision to patients with acquired blindness due to damage to the eyes or optic nerves.

Objectives

Here we report on initial findings in the first FDA-approved early feasibility trial of a VCP.

Methods

Two blind subjects at Baylor were implanted with an Orion VCP system, and visual function testing was conducted following implantation.

Results

Using the standard stimulation methods for Orion, subjects demonstrated the ability to locate a bright square on a computer touchscreen. Subject performance was much better using the Orion (3.5-4.5cm) than before implantation or with the system off (12-15cm). One subject also demonstrated the ability to identify the direction of motion of a high contrast bar moving across the touchscreen, with an average error of $\sim 22^\circ$, far better than the $\sim 94^\circ$ average error (chance level performance) with the device off. While the standard Orion settings have not succeeded in produced form vision, we have found that novel electrical stimulation protocols may be used to significantly enhance the functionality of Orion toward this goal . The use of dynamic sequences of stimulation can improve perception of visual forms, and current steering can be effectively used to activate the cortex at a location in between the location of the two physical electrodes.

Conclusion

Early testing of the Orion VCP demonstrate efficacy in performing several basic visual tasks. Novel stimulation paradigms, including the use of dynamic stimulation and current steering, offer the promise of enhanced functionality, including potential for the perception of visual forms.

8:15 – 8:25 Nerve transfers to improve upper extremity function and quality of life in tetraplegic patients

Christopher Dibble, Martin Boyer, **Wilson Ray**, Jawad Khalifeh

Introduction

Spinal cord injury (SCI) is a public health problem. Greater than 50% of SCI occur in the cervical spine resulting in some form of tetraplegia. Recently nerve transfers have been considered as a treatment option to restore upper extremity function in tetraplegic patients.

Objectives

Motor nerve transfers traditionally used to treat peripheral nerve injuries are increasingly used to treat patients with tetraplegia (Figure 1). We present our early results of a prospective clinical trial using nerve transfers to restore upper extremity function in tetraplegia.

Methods

Participants with American Spinal Injury Association (ASIA) A – B cervical SCI) were prospectively enrolled at a single institution and nerve transfer(s) were performed based on pre-operative function and level of injury. Functional recovery and strength were independently assessed and prospectively tracked.

Results

Seventeen participants with a median age of 28.4 years who underwent nerve transfers at a median 18.2 months after injury were included. Median follow-up was 24.9 months. Patients who underwent transfers to median nerve motor branches achieved finger flexion strength MRC 3/5 in 4/15 (26.7%) and wrist flexion strength MRC 3/5 in 5/15 (33.3%) treated upper limbs. Nerve transfers to the posterior interosseous nerve

restored MRC 3/5 strength in finger extension in 5/9 (55.6%) and 3/5 strength in thumb extension in 5/9 (55.6%) patients.

Conclusion

Nerve transfers are a promising treatment option to restore upper extremity function in chronic tetraplegia. Our early experience suggests, nerve transfers for the reinnervation of hand and finger flexors provide variable functional recovery. Transfers for the reinnervation of arm, hand, and finger extensors provide more consistent and meaningful return of function.

8:25 – 8:35 Mapping brain response patterns to Deep Brain Stimulation with fMRI

Suresh Joel, Vijayashankar Paramanandam, Mojgan Hodaie, Walter Kucharczyk, David Xu, Sreeram Prasad, Alexandre Boutet, Manish Ranjan, Ailish Coblenz, Jeffrey Ashe, Gavin Elias, Suneil Kalia, Radhika Madhavan, Robert Gramer, Eugen Hlasny, **Andres Lozano**, Alfonso Fasano

Introduction

Deep brain stimulation (DBS) modulates dysregulated brain circuits. Commonly used in Parkinson's disease (PD), this surgical treatment can produce striking clinical benefits when the stimulation is appropriately programmed. However, DBS programming often requires numerous clinic visits to test the large number of possible stimulation parameters.

Objectives

Here, we examined whether optimal DBS stimulation settings produce a characteristic functional magnetic resonance imaging (fMRI) pattern that could inform DBS programming.

Methods

We performed 3T fMRI in PD patients with either subthalamic nucleus or internal globus pallidus DBS (n=28), obtaining the brain activation patterns with each of the four DBS contacts activated. fMRI brain response patterns to stimulation at clinically determined optimal and non-optimal contacts were compared, and subsequently integrated into a machine learning (ML) framework for optimal contact identification.

Results

Optimal contact stimulation recruited motor areas such as primary motor cortex, thalamus, and anterior cerebellum. In contrast, stimulation through non-optimal contacts resulted in more variable brain circuit engagement accompanied by spillover to non-motor brain areas. The ML model predicted the optimal contact in both previously programmed (76%) and stimulation-naïve patients (75%).

Conclusion

There is a specific and reproducible fMRI brain response pattern in PD-DBS patients at settings associated with optimal clinical benefits. The pattern of fMRI brain responses to stimulation can help elucidate DBS's mechanism of action and perhaps serve as a step towards more effective programming and improved clinical outcomes.

8:35 – 8:45 Trigeminal Nerve Stimulation as a Neuroprotectant

Chunyan Li, **Raj Narayan**

Introduction

Pharmacological interventions to block cortical spreading depolarization (CSD) typically have significant side effects. Therefore, new strategies are needed to reduce CSDs in the injured brain. The trigeminal nerve is unique because of its intimate connection with cerebral and meningeal blood vessels, referred to as the trigemino-cerebrovascular system. It is also capable of activating the so called "diving reflex", whose primary role is to conserve oxygen for sensitive brain tissue.

Objectives

We aim to investigate the effect of trigeminal nerve stimulation (TNS) to minimize CSD-induced brain injuries.

Methods

Studies were performed on 32 rats. Animals were randomized following middle cerebral artery occlusion (MCAO): (1) control animals with MCAO; (2) MCAO animals with Pre-TNS; (3) MCAO with 3-hour post-TNS (open-loop); (4) MCAO with targeted TNS (closed-loop). The number of CSDs, CBF and oxygen tension were recorded. Brains were collected at 24h after MCAO to measure the lesion volume.

Results

MCAO resulted in a sequence of changes in CBF and DC potentials. Upon occlusion, CBF immediately fell by $68 \pm 11\%$. Spontaneous waves of depolarization appeared in the ischemic penumbra zone, averaging about eight events (8.1 ± 2.1 ; $n=8$) over the 3 h after occlusion. The first CSD episode appeared at 7.1 ± 3.6 min after occlusion. TNS significantly lengthened the latency until the appearance of the first CSD almost 7-fold, and decreased their number by 53% (3.8 ± 0.8 vs. 8.2 ± 2.1 ; $n=8$). Both open-loop and closed-loop post-TNS also significantly reduced infarction volumes by 47% and 39%, respectively.

Conclusion

Our study demonstrate that TNS can selectively reduce the deleterious consequences of CSDs in the injured brain.

8:45-9:15 **Peer Reviewed Abstract Session II: Spine Science**
Moderators: Nicholas Theodore & Mark Shaffrey

8:45 - 8:55 **12-Month Safety and Efficacy Results from the SCiStar Study – A Phase 1/2a Trial of AST-OPC1**

Ed Wirth, **Richard Fessler**, Charles Liu, Gary Steinberg, Shekar Kurpad

Introduction

Spinal cord injury (SCI) causes disruption of motor, sensory, and autonomic function. Cellular transplantation offers a new and promising method of reconstituting the architecture of the damaged cord by providing a permissive substrate, replacing lost cells, enhancing tissue preservation, supporting axonal regeneration, and modulating the inflammatory response.

Objective

The purpose of this study is to evaluate the 12 month outcome data for the 10 million cell AST-OPC1 cohort group in the SCI-Star study.

Methods

The SCiStar study is an open-label, single-arm trial evaluating three escalating doses of AST-OPC1 (2, 10 & 20 million cells) administered to five cohorts of subjects via direct intraparenchymal injection between 21 and 42 days post-SCI. A total of 27 subjects across the five cohorts have been dosed. All subjects in cohort 1 (N=3, 2 million cells) have completed 2 year follow up. All subjects in cohort 2 (N=6 10 million cells) have completed 1 year follow up.

Results

To date, there have been no intraoperative complications or safety issues associated with the cells. No patient demonstrated decreased neurological function or experienced a serious SAE. At 2 year follow up, subjects in cohort 1 gained 1 motor level relative to baseline. In cohort 2, 100 % of subjects gained at least 1 motor level and 67 % regained two motor levels on at least one side, compared to 26 % in the comparison group.

Conclusion

The results of the SCiStar study demonstrate a strong safety profile. The 2 year efficacy data indicate a dose-dependent increase in recovery of upper extremity motor function.

8:55 - 9:05 Early Surgery and Recovery in Central Cord Syndrome: Analysis of 211 Patients from a Prospective, Multi-Center Dataset

Michael Fehlings, Jefferson Wilson, Jetan Badhiwala

Introduction

There remains a paucity of data on the contemporary outcomes of central cord syndrome (CCS) and their predictors. Further, the efficacy of early surgical decompression for CCS remains unclear.

Objectives

We sought to: 1) develop a prediction model for neurological outcome; and 2) evaluate the effect of early surgery (<24 hrs) on neurological recovery.

Methods

Patients with CCS (AIS C or D; LEMS&UEMS≥5) were identified from two prospective multi-center datasets. A prediction model was developed by multiple linear regression; the outcome was change in ASIA motor score (AMS) at 1-year. Covariates were chosen a priori: 1) age; 2) AMS; 3) AIS; 4) time to surgery (early [<24 hrs] vs. late [>24 hrs]); and 5) time to surgery´AIS. Effect sizes were summarized by β coefficients. Internal validation was by bootstrapping.

Results

In total, 211 patients were eligible. β coefficients were significant for all variables in the model: age (-0.12, P=0.04); AMS (-0.71, P<0.01); AIS (9.69, P=0.01); time to surgery (12.67, P<0.01); time to surgery´AIS (-13.18, P<0.01). The mean R² value across bootstraps was 0.66. In patients with AIS C injury, early surgery resulted in significantly improved motor recovery (marginal mean: 12.7, 95%CI 5.8–19.6); there was no difference in recovery with early surgery in patients with AIS D injury.

Conclusion

To our knowledge, this is the largest study to date to examine central cord syndrome. We found motor recovery after CCS may be predicted by age, AMS, AIS grade, and time to surgery. Early surgery improves recovery, particularly in patients with more severe injury.

9:05 - 9:15 Transpedicular vertebrectomy for thoracic spine metastasis

Tarush Rustagi, Hazem Mashally, Asad Akhter, **Ehud Mendel**, Ranjit Ganguly

Introduction

To study the feasibility, outcomes and complications of Transpedicular vertebrectomy (TPV) and reconstruction for metastatic lesions to the thoracic spine.

Objectives

From 2008-16, consecutive cases (single-surgeon) undergoing TPV for thoracic spine metastasis (T2 -12) were included. Demographic, surgical and clinical data was collected through chart review. MRI, CT, PET images were used to identify extent of disease, epidural spinal cord compression (ESCC), and degree of vertebral body collapse. Hall-Wellner confidence band was used for the survival curve.

Methods

96 patients were studied with a median age 60 years. Most patients 56 (58%) presented with mechanical pain. 29% cases had Lung metastasis. Single level TPV was performed in 73 patients (76%). Anterior reconstruction included PMMA in 78 patients (81.25%), and titanium cage in 18 patients (18.25%).

Results

Frankel grade improvement was seen in 16 cases (P=0.013). ESCC improved by a median of 5.9 mm (P<0.001). Kyphosis reduced by median of 7.5° (P<0.001). VAS improved by median of 7 (P<0.001). Total 59 deaths were observed. The median survival time was estimated to be 6 months (95% CI [5, 10]). Surgical outcome and complication rates are similar between the two construct types. Correction of kyphosis was seen to be slightly better with the use of PMMA. Overall 29.16% cases developed complications (11.4% major). Two cases developed neurological deficit following epidural hematoma requiring surgery. One case had instrumentation failure from cement migration, needing revision.

Conclusion

The result of our study shows good clinical and radiological outcomes for TPV for thoracic metastatic lesions.

9:15 - 9:35 Break

9:35-10:45 Peer Reviewed Abstract Session III: Tumor Science
Moderators: Nino Chiocca & Mitchel Berger

9:35 - 9:45 Meningioma Genomic Subgroup and Predicting Post-operative Patient Outcomes:
Implications for Treatment and Follow-up

Daniel Duran, Amar Sheth, Koray Ozduman, Zeynep Erson-Omay, Chang Li, Julio Montejo, Evgeniya Tyrtova, Murat Gunel, Bulent Omay, Michel Kalamarides, Julien Boetto, Mark Youngblood, **Jennifer Moliterno**, Matthieu Peyre, Amy Zhao

Introduction

Previous studies have classified meningiomas into six molecular subgroups, including NF2, SMARCB1, KLF4, POLR2A, PI3K-activated and Hedgehog-activated. Each subgroup carries specific associations with clinical and molecular features, such as tumor location and histology.

Objectives

We sought to ascertain whether underlying genomic subgroup may provide prognostic value in meningioma management.

Methods

The genomic subgroup of over 500 meningiomas was determined based on targeted sequencing data and clinical annotations were retrospectively collected, including grade, recurrence, extent of resection (EOR), post-operative radiation, and follow-up. Statistical relationships were investigated between genomic subgroup and recurrence using Kaplan-Meier, Fisher's exact tests, and Cox proportional hazards modeling, including stratification based on the aforementioned variables.

Results

During the first five post-operative years, meningiomas in the PI3K subgroup exhibited higher rates of early recurrence. PI3K activating mutations were found to be an independent predictor of recurrence free survival and irrespective of grade, Ki-67, and other clinical features. Conversely, recurrence was rare in KLF4, POLR2A, and SMARCB1 mutant tumors, and these tumors were typically associated with use of post-operative radiation. The longest average recurrence free survival was observed in POLR2A mutant meningiomas.

Conclusion

These results indicate divergence in meningioma patient outcomes based on underlying driver mutation and suggest patients with PI3K activating events may require closer surveillance. These cases, which often occur along the sphenoid wing and can encase critical neurovascular structures, may benefit from consideration of

radiation and emerging targeted medications. By contrast, for other subgroups which rarely recur, caution may be entertained before use of potentially morbid adjuvant therapies.

9:45 - 9:55 Oncolytic G207 Produces immunologic Signature Predicting Response to Therapy

Elaine Mardis, Naomi Barker, Kathleen Schieffer, Dragan Maric, Anthony Miller, G. Yancey Gillespie, Justin Roth, Josh Bernstock, **James Markert**, Nripesh Prasad, Kristen Leraas, Jianmei Leavenworth, Jennifer Coleman, Kevin Cassady, Gary Cutter, Bernard Roizman, Richard Whitley, Katherine Miller

Introduction

Our Phase I trials of experimental virotherapy for recurrent glioblastoma (GBM) have shown that inoculation with a conditionally replication-competent early generation oncolytic herpes simplex virus (oHSV), G207, is safe. However, while 17 of 37 subjects experienced objective clinical responses, the highly attenuated oHSV did not uniformly improve survival.

Objectives

We sought to identify predictors that would identify mechanisms contributing to survival and improve future trial design, by studying accrued samples.

Methods

We analyzed pre-treatment biopsy and post-G207-treatment tumor samples (collected D2-5 post injection) banked from the patients enrolled in the phase IB G207 trial. RNAseq and Nanostring transcriptome analysis with deconvolution using Cibersort was used to determine differences in immune response between samples. Multiplex fluorescent immunohistochemistry using immunocompatible primary antibodies and highly cross-absorbed secondary antibodies conjugated to spectrally-compatible dyes was also performed.

Results

The key findings from these analyses suggest that productive G207 infection and G207-induced changes in gene expression were predictive of oHSV therapeutic success in the G207-treated patients. RNAseq-based transcriptome analysis of these samples revealed that both the intrinsic IFN mediated antiviral response and adaptive immune functional response in patients correlated significantly with improved survival following G207 inoculation. Further, GBM tissue stained using multiplex fluorescent immunohistochemistry supported differences in the tumor microenvironments that were identified from RNAseq data analysis.

Conclusion

Our data indicate that both viral gene expression and the resulting intrinsic anti-viral and recruited adaptive response were critical for survival after G207 inoculation and predict survival with this early generation oHSV in patients with recurrent malignant glioma.

9:55-10:05 Evolution of Low Grade Gliomas During Malignant Transformation.

Joseph Costello, **Mitchel Berger**

Introduction

Newly diagnosed IDH mutant LGG may remain indolent for a decade after initial surgery, or may undergo malignant transformation (MT) to high grade glioma (HGG).

Objectives

We sought to elucidate the mechanisms and cause of malignant transformation as a critical step towards preventing MT and positively impacting overall survival for patients whose original diagnosis is LGG. In some cases this occurs at the first progression but in others there are multiple surgeries or other treatments before the diagnosis is made. Herein we discuss three distinct but related genetic mechanisms leading to malignant transformation, and one potential cause of malignant transformation.

Methods

Next generation sequencing was applied to primary and recurrent tumor pairs, along with multiple intratumoral samples to discover mutations and gene expression patterns during malignant transformation. Tumor evolution was elucidated using phylogenetic analysis.

Results

Phylogenetic analyses show that heterozygous mutations in IDH1 or IDH2 are the earliest genetic alteration in LGG and appear to be fully clonal. However, data from spatiotemporal tumor samples and in vitro and in vivo model systems showed deletion of the locus containing the IDH mutation during malignant progression. We also discovered Temozolomide induced hypermutation in LGG was strongly associated with malignant transformation.

Conclusion

We will discuss translational implications of the dynamic molecular, cellular, metabolic and clinical features of initially IDH1-mutant LGG as they undergo MT. The data also shows that Temozolomide induced hypermutation drives the outgrowth of tumor clones with increasingly malignant genotypes, and is associated with malignant transformation

10:05-10:15 Flies, worms and fish: What do these have to do with brain tumours?
--

James Rutka

Introduction

Although mammalian models have been commonly used to study cancer, the advent of molecular genetic manipulations in lower species has led to the development of a variety of highly reproducible and informative cancer models.

Objectives

To establish novel brain tumor models in lower species organisms; and to use high-throughput drug screening, and RNAi screening to identify novel drugs that are effective against these brain tumour models.

Methods

We used a *let-60* (KRAS) and *daf-18* (PTEN) mutant model of GBM in *C. elegans* in which the worms develop a highly invasive phenotype. We also developed a *Drosophila* Gal4/UAS transgenic line which overexpresses the fly homologues of human phosphoinositide-3 kinase (PI3K) and epidermal growth factor receptor (EGFR) in *Drosophila*.

Results

In the *let-60* (KRAS) and *daf-18* (PTEN) mutant model of GBM in *C. elegans*, we demonstrate enhancement of a multi-vulvar phenotype, indicative of a highly invasive alteration in cellular function that resembles invasion in cancer cells. Our RNAi screen in *C. elegans* has uncovered several novel "hits" which are being explored. The developing pupae in the *Drosophila* model of GBM develop a highly proliferative and aggressive glial tumor resembling GBM. By treating these flies with anti-metabolic and novel chemotherapeutics, we show a reduction in tumor size and enhanced survival of the organism.

Conclusion

Just as science has advanced inordinately from taking advantage of the genetic manipulations in lower species, so it is hoped that these brain tumour models can be used to advance novel drug and therapeutics that would not be imaginable using conventional mammalian models to date.

10:15 - 10:25 Neurosurgical management of sinonasal malignancies involving the skullbase. A 25-year experience.
--

Franco DeMonte, Ehab Y Hanna, Gautam Mehta, Shaan M Raza

Introduction

Neurosurgical management of sinonasal malignancies extending to the skull base has a rich 6 decade long history. Early reports described high rates of morbidity and mortality. The most recently published large studies now date back over a decade.

Objectives

This longitudinal 25-year single institution study was undertaken to highlight how changes in patient demographics, practice patterns and outcomes have evolved. Over this time there has been a significant evolution in surgical instrumentation and techniques without a clear assessment of their impact on patient outcomes.

Methods

Patients with malignancies arising from the sinonasal cavities and extending to involve the skullbase who underwent surgical resection between 1993 and 2018 were included in this study. Only patients with at least a 6 month followup were included.

Results

191 patients met criteria for inclusion. Mean age was 51yrs and did not significantly change over time. Olfactory neuroblastoma was the most commonly encountered neoplasm. A trend of an increasing number of neuroendocrine tumors vs fewer SCCs and adenocarcinomas was seen. More extensive/higher stage disease was seen over time. Surgical approaches evolved from open transcranial/transfacial to transcranial/endoscopically-assisted and endoscopic-only approaches. Median OS was 10.1 years and did not change over time. Complications were significantly reduced in those patients not undergoing lumbar spinal CSF drainage.

Conclusion

There has been an evolution over the past 25 years in the management of patients with sinonasal malignancies extending to the skull base. Changes in surgical technique and management has lowered morbidity. Survival has remained unchanged despite treating patients with higher staged disease.

10:25-10:35 Opening of blood brain barrier in the hippocampus and entorhinal cortex in Alzheimer's disease with focused ultrasound
--

Jeff Carpenter, Marc Haut, **Ali Reza**i, Manish Ranjan, Rashi Mehta, Umer Najib

Introduction

There are no effective treatments for Alzheimer's disease (AD). Animal studies have demonstrated that MR-guided focused ultrasound (FUS) reversibly opens the blood brain barrier (BBB)-reducing amyloid plaques, improving memory and allowing targeted drug delivery. A phase I safety study demonstrated opening of BBB in frontal lobe in five patients with AD.

Objectives

We report the initial results of a phase II study in AD evaluating if FUS treatment can safely and reversibly open the hippocampal BBB, and reduce amyloid plaques and cognitive decline.

Methods

The study was FDA and IRB approved. Three patients with early AD and positive amyloid PET each underwent three treatment sessions at two-week intervals with FUS (220 kHz ExAblate, Insightec) to the hippocampus/entorhinal cortex. Outcome assessments included MRI evaluating BBB opening, fMRI, adverse events, behavior/cognition, and amyloid PET.

Results

Three female participants (61-73 years) completed all treatments successfully. Three FUS treatments of the hippocampus/entorhinal cortex was performed in 3 separate target regions (5X5X7 mm each) in the first, and four targets in the subsequent two subjects. There was no hemorrhage, edema, or treatment-related adverse effects. Immediate post FUS MRI with gadolinium revealed parenchymal contrast enhancement in

all target regions indicating BBB opening. Contrast enhancement was not present 24 hours after each treatment. Additional follow-up clinical, MRI, and PET outcomes will be available for presentation.

Conclusion

This is the first report demonstrating the safety, reversibility, reproducibility of multiple openings of BBB in the hippocampus/entorhinal cortex in AD with FUS. FUS provides a unique opportunity for targeted neurosurgical treatment approaches.

10:35 - 10:45 CAR T cell therapy for glioblastoma: Current observations and future directions

Donald O'Rourke

Introduction

Our work at the University of Pennsylvania involves the clinical application of chimeric antigen receptor T (CAR-T) cells for the treatment of glioblastoma (GBM). We identified antigen heterogeneity and adaptive immunosuppression in the tumor microenvironment (TME) as major challenges, based on our phase Ib study of a single peripheral infusion of CAR-T cells targeting EGFRvIII in recurrent GBM. We have defined strategies to overcome these challenges, representing the basis of a portfolio of new CAR-T clinical trials.

Objectives

First, we hypothesized that using a combination of CART-EGFRvIII cells and immune checkpoint blockade (ICB) would abrogate the TME response and improve clinical efficacy. Next, we have developed both cross-reactive scFvs in CAR constructs and multivalent CAR-T cells to address target heterogeneity and antigen escape.

Methods

Our single-arm, open-label, phase Ib trial is enrolling patients with newly diagnosed, MGMT-unmethylated, EGFRvIII+ GBM. Following maximal safe tumor resection, patients receive short course adjuvant radiation (40Gy), followed by three separate peripheral IV infusions of 2x10⁸ CART-EGFRvIII cells and 200mg pembrolizumab.

Results

Kinetics of engraftment of EGFRvIII CAR-T cells was comparable in newly diagnosed GBM and recurrent GBM and resulted in disease stability. Combination of CAR-T cells with the PD-1 inhibitor pembrolizumab has not resulted in significant adverse events. Multivalent CARs, in parallel or tandem, resulted in activation by GBM cells expressing multiple antigens.

Conclusion

Combination of CAR-T cells and ICB presents a viable route to address TME immunosuppression while multivalent CAR constructs enable broader tumor targeting. Multivalent CAR-T cells with ICBs will likely improve clinical efficacy in GBM.

10:50-11:50 Peer Reviewed Abstract Session 4: Vascular Science

Moderators: Elad Levy & Robert Spetzler

10:50 - 11:00 Functional Connectivity Deficits After Subarachnoid Hemorrhage

Deepti Diwan, Ananth Vellimana, Annie Bice, Lindsey Brier, Joseph Culver, **Gregory Zipfel**, Julian Clarke

Introduction

Previously, we showed that hypoxic conditioning is a novel therapy against two components of SAH-induced delayed cerebral ischemia (DCI), and that this protection is SIRT1-mediated. Functional connectivity (FC) refers to correlation analysis across cortical regions and is commonly used as a readout of coordinate neural activity. FC can be measured via Optical Intrinsic Signal (OIS) imaging, which measures correlations in

vascular reactivity via quantitation of fluctuations in oxy- and deoxy-hemoglobin. The impact of experimental SAH and conditioning on FC has yet to be examined.

Objectives

This study examined three questions: 1) Does experimental SAH induce FC deficits; 2) Does hypoxic conditioning provide protection against these FC deficits and is this protection SIRT1-mediated; and 3) does treatment with the SIRT1 activator, resveratrol, mimic the protective effect of hypoxic conditioning against these FC deficits?

Methods

Cranial windows were adhered on C57BL/6 mice. Mice underwent sham or SAH surgery. Mice were then treated with hypoxic conditioning (with or without EX527, a SIRT1-inhibitor) or resveratrol beginning 3hr after surgery. Mice were serially imaged post-surgery.

Results

We found that experimental SAH induces global and network-specific deficits in FC by day 3, corresponding with the time of DCI in mice; and that hypoxic conditioning provides SIRT1-mediated protection against these SAH-induced FC deficits (see Figure). We also found that the SIRT1 activator, resveratrol, mimics the protective effect of hypoxic conditioning on SAH-induced FC deficits.

Conclusion

OIS imaging is a useful technique for identifying FC deficits following experimental SAH. SIRT1 targeted therapies attenuate FC deficits observed post-SAH and may be an important step in treatment of DCI after SAH.

11:00 - 11:10 Microbiome Signatures of Cavernous Angioma

Le Shen, Amy Akers, **Sean Polster**, Issam Awad, Kimberly Yan, Julian Carrion-Penagos, Helen Kim, Agnieszka Stadnik, Jack Gilbert, Connie Lee, Anukriti Sharma, Ying Cao, Romuald Girard, Myranda Robinson, Leslie Morrison, Seán Lyne, Atif Zafar, Mark Kahn, Patricia Mericko, Alan Tang

Introduction

Cavernous angiomas (CA) can result in hemorrhage and/or seizure. The disease course is variable which may be affected by immune and inflammatory processes. Mouse studies have linked CA to the microbiome, but its clinical relevance has not been defined.

Objectives

Here we investigate the composition of the microbiome of CA patients and its relationship to clinical disease.

Methods

Fecal samples from 123 CA patients, across four centers, were assayed using metagenomic 16S rRNA and shotgun sequencing. Following taxonomic classification microbiome composition was compared with those of a non-CA population (n=263), or between subgroups of CA patients based on clinical characteristics. Univariate and random forest identified species were assembled to compare with plasma biomarkers of angiogenic and inflammatory cytokines.

Results

Analyses of microbiome composition identified groups and networks of bacterial species that identify CA from non-CA patients. Four species differentiate CA from non-CA by receiver operating characteristic classification [area under the curve (AUC)=0.875, specificity=0.890, sensitivity=0.815]. Within CA cohorts, a combination of microbiome and a plasma biomarker improved our ability to differentiate patients with unique CA characteristics; sporadic vs. familial (AUC=0.71), aggressive vs. non-aggressive (AUC=0.90) and those with a symptomatic hemorrhage (CASH) in the last year (AUC=0.86).

Conclusion

This data is the first to show that CA patients have a distinct microbiome that is strongly associated with CA disease and CA behavior. This study supports further investigation into the mechanistic link between CA

disease and the microbiome for a better understanding of the brain-gut axis and as a potential biomarker of disease behavior.

11:10 - 11:20 The New Generation Hydrogel Endovascular Aneurysm Treatment Trial (HEAT): Final Results

Bernard Bendok, Salah Aoun, Jason Kniss, Jennifer Ward, Karl Abi-Aad, Tarek El Ahmadih, Samer G. Zammar, Rudy Rahme, Najib El Tecla, Mary Kwasny, Rami James Aoun

Introduction

Aneurysm recurrence after coiling has been associated with (re)hemorrhage and a greater need for follow-up. The second-generation HydroCoil Embolic System (HES) consists of a platinum core with integrated hydrogel and was developed to reduce recurrence through enhancing packing density and healing within the aneurysm.

Objectives

To compare the imaging and clinical outcomes of the second-generation HES to bare platinum coils in a long-term study of 600 patients.

Methods

HEAT is a randomized, controlled clinical trial that enrolled subjects with ruptured or unruptured intracranial small-to-medium aneurysms amenable to endovascular coiling. Subjects were randomized in a 1:1 fashion at 46 participating sites. The primary endpoint was aneurysm recurrence using the Raymond-Roy scale at final follow-up. Secondary endpoints included minor and major recurrence, packing density, adverse events related to the procedure and/or device, mortality, initial complete occlusion, aneurysm retreatment, hemorrhage from target aneurysm during follow-up, aneurysm occlusion stability, and clinical outcome at final follow-up.

Results

A total of 600 patients were randomized including 28% with ruptured aneurysms. Recurrence occurred in 11 (4.4%) subjects in the HES arm and 44 (15.4%) subjects in the BPC arm ($p=0.002$). While the initial occlusion rate was higher with BPC, the packing density and both major and minor recurrence rates were in favor of HES. Secondary endpoints including adverse events, retreatment, hemorrhage, mortality and clinical outcome did not differ at follow-up.

Conclusion

Coiling of 3-14 mm ruptured and unruptured aneurysms with second-generation HES resulted in significantly less recurrence when compared to BPC, without increased harm.

11:20 - 11:30 The R2eD AVM score: a novel predictive tool for arteriovenous malformation presentation with hemorrhage

Wuyang Yang, Cameron McDougall, Jason Liew, Rafael Tamargo, Risheng Xu, Justin Caplan, **Judy Huang**, James Feghali

Introduction

The management of unruptured brain arteriovenous malformations(AVMs) remains unclear.

Objectives

We developed a predictive tool to determine risk factors predictive of AVM hemorrhage on presentation.

Methods

789 AVM patients presenting between 1990 and 2017 were analyzed. A hold-out method of model building and validation split the data randomly in half into training and validation datasets. Factors significant at the univariable level in the training dataset were utilized to construct a model based on multivariable logistic regression. Model performance was assessed using receiver operating curves(ROC) on the training, validation,

and complete datasets. The model predictors and the complete dataset were used to derive a formula for risk prediction and scoring system where every risk factor was worth 1 point except race, worth 2 points (total score varies from 0 to 6), comprising acronym R2eD AVM.

Results

Among 755 patients, 272(36%) presented with hemorrhage. From the training dataset, a model was derived containing the following: non-white race (odds ratio [OR]=1.8,P=0.02), small nidus size (OR=1.47,P=0.14), deep location (OR=2.3,P<0.01), single arterial feeder (OR=2.24,P<0.01), and exclusive deep venous drainage (OR=2.07,P=0.02). Area under the curve from ROC analysis was 0.702, 0.698, and 0.685 for training, validation, and complete datasets, respectively. In the study population, the predicted probability of hemorrhagic presentation increased in a stepwise manner from 16% for patients with no risk factors (score 0) to 78% for patients having all the risk factors (score 6).

Conclusion

A score ranging from 0-6, known by acronym R2eD AVM, can be used as predictive tool that supplements clinical judgement and assists in patient counselling.

11:30-11:40 Cerebral Aneurysm Formation and Rupture: Role of Nrf2 Signaling

Christopher Carr, Crissey Pascale, Peter Amenta, Alejandra Martinez, **Aaron Dumont**

Introduction

Oxidative stress and chronic inflammation have been implicated in cerebral aneurysm (CA) formation and rupture. Nrf2 is an endogenous anti-oxidant/anti-inflammatory mediator that normally promotes vascular homeostasis.

Objectives

The objective of this study is to evaluate the role of Nrf2 signaling in CA formation and rupture and to specifically examine the therapeutic potential of the Nrf2 activator, dimethyl fumarate (DMF), in preventing cerebral vascular smooth muscle cell (VSMC) damage and CA formation and rupture.

Methods

The therapeutic potential of DMF was evaluated in vitro and in vivo. Cultured cerebral VSMC were treated with TNF- α ; and/or DMF. Gene and protein expression for Nrf2, cytokines and VSMC markers were then evaluated using real-time RT-PCR and a Bio-Plex Immunoassay. Mitochondrial function was assessed using the Seahorse analyzer to evaluate oxygen consumption rate. Aneurysms were induced in C57BL/6 mice using the elastase model. The mice were then treated with either DMF at 100mg/kg/day or vehicle for two weeks. Subsequently, the circles of Willis were harvested for gene expression analysis and mass spectrometry.

Results

DMF treatment protected VSMCs from TNF- α ; induced inflammation as demonstrated by its downregulation of cytokines and upregulation of Nrf2 and smooth muscle cell markers. Furthermore, DMF appeared to mitigate TNF- α ; induced oxidative stress and preserved mitochondrial dysfunction. In mice, DMF treatment increased vascular Nrf2 expression and significantly decreased the incidence of CA formation and rupture through suppression of inflammation and oxidative stress while preserving mitochondrial function.

Conclusion

Nrf2 activation with DMF represents a novel medical therapy to prevent CA formation and rupture through suppression of inflammation/oxidative stress and preservation of mitochondrial function.

11:40 - 11:50 Early Gene Deletion Generates a High-Fidelity Transgenic Mouse Model of Familial Brain Arteriovenous Malformations

SP Oh, Michael Lawton

Introduction

The pathogenesis of BAVMs has been explored in animal models using genetic insights from patients with hereditary hemorrhagic telangiectasia (HHT) and the technique of regional conditional gene deletion. These experimental lesions lack the anatomical and hemodynamic hallmarks observed in human BAVMs, likely because they are induced in fully developed mice, long after fetal development when abnormal vasculogenesis is thought to trigger BAVM formation. Here, we present a mouse model for BAVM that, for the first time, replicates human BAVMs anatomically and hemodynamically by deleting HHT genes during embryonic gestation.

Methods

We used Tagln (SM22a)-Cre:Alk12f/2f and Tagln-Cre:Eng2f/2f mice that were previously shown to develop BAVMs. Magnetic resonance imaging with GEFC (gradient echo with flow compensation) was acquired serially from the mutant and control mice starting at 1-2 months of age up to 12 months using Bruker 7T MR spectrometer.

Results

The survival rate of Tagln-Cre:Alk12f/2f mice at 1 and 3 months of age was 90% and 70% respectively. In total, 41 mice were subjected to MR imaging: 5 control, 29 Alk1-mutants, and 6 Eng-mutants. Obvious lesions of varying sizes and locations in the brain were detected in 95% (33/35) of mutant brains but none of control brains. While MR angiography visualized only arteries in control brains, BAVMs including feeding arteries, draining veins, and varying sizes and shapes of nidus were detected in 54% of mutants (19 of 35). Repeated MRA images in 11 mutant mice in a course of 12 months revealed that most BAVMs detected in the first scan remained stable, but some changed dynamically.

Conclusion

This study demonstrates the formation of BAVMs in transgenic mice with the morphological, anatomical, and hemodynamic features of BAVMs seen clinically in humans, based on MR imaging, angiography, and histology. Timing of ALK1 and ENG deletion is critical in generating clinically relevant pathology. This model provides an experimental system for studying BAVM rupture and evaluating drugs that may induce regression of BAVMs.

11:50 - 12:00 Break

12:00 - 12:50 Special Lecture I

Moderator: Alex Golby / James Rutka

The Rhetoric of Medicine: Lessons on Professionalism From Ancient Greece

Nate Selden/Nigel Nicholson

7:30 – 7:35 WELCOME & REMARKS

Michael McDermott (Scientific Program Chair) & Alex Olivi (Local Arrangements Chair)

7:35-8:35 Peer Reviewed Abstract Session V: Vascular

Moderators: Michael Lawton & E. Sander Connolly

7:35 – 7:45 Deletions in CWH43 Cause Sporadic Idiopathic Normal Pressure Hydrocephalus

Mark Johnson

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a neurological disorder of aging that is characterized by enlarged cerebral ventricles, gait difficulty, incontinence and dementia. The cause and pathophysiology of sporadic iNPH are unknown.

Objectives

The goal of this study was to identify genetic abnormalities associated with sporadic iNPH.

Methods

We performed whole-exome sequencing of DNA obtained from 53 unrelated iNPH patients in 3 independent cohorts. Single nucleotide variations that were statistically overrepresented among iNPH patients, present in at least two of the three cohorts, and predicted to adversely affect protein function were identified. Deletions affecting the most frequently altered gene were studied further using genetically engineered mice and human cell lines.

Results

A heterozygous deletion in CWH43 was observed in four iNPH patients and was enriched 6.6 fold when compared to the general population ($P < 0.0002$, X2 Test). A second heterozygous CWH43 deletion was identified in four additional patients and was enriched 2.7 fold ($P < 0.0406$, X2 Test). We show that Cwh43 regulates the membrane localization of GPI-anchored proteins in mammalian cells, and both of the iNPH-associated CWH43 deletions disrupt this function. Cwh43 expression is high in choroid plexus and ependymal cells. Genetically-engineered mice harboring CWH43 deletions displayed enlarged ventricles, gait and balance abnormalities, decreased numbers of ependymal cilia and aberrant localization of GPI-anchored proteins in ventricular epithelial cells.

Conclusion

Approximately 15% of patients with sporadic iNPH harbor deletions in CWH43. Mice harboring CWH43 deletions develop an iNPH-like syndrome. Our findings provide new mechanistic insights into iNPH and demonstrate that it represents a distinct disease entity.

7:45-7:55 NEWTON-2: Randomized, Double-blind, Placebo-controlled study of EG 1962 in Aneurysmal Subarachnoid Hemorrhage

E. Francois Aldrich, Daniel Haenggi, Stephan Mayer, Michael Diringer, Newton Investigators, Nima Etminan, Andrew Carlson, George Wong, **R. Loch Macdonald**, Erich Schmutzhard

Introduction

EG-1962 is a sustained release nimodipine formulation administered via an external ventricular drain (EVD) to patients with aneurysmal subarachnoid hemorrhage (aSAH). A randomized, open-label, phase 1/2a, dose-escalation study found EG-1962 was safe and well-tolerated.

Objectives

To evaluate efficacy and safety of a single intraventricular 600 mg dose of EG-1962 in patients with aSAH, compared to standard of care nimodipine in a randomized, double-blind, placebo-controlled phase 3 study.

Methods

Subjects were WFNS grades 2-4, modified Fisher grades 2-4 and had an EVD. EG-1962 was administered within 48 hours of aSAH. The primary endpoint was favorable outcome at 90 days (extended Glasgow outcome scale [eGOS] 6-8).

Results

The study was halted after planned interim analysis (282 subjects randomized) found the study was unlikely to achieve its primary endpoint. After 90 day follow-up, the proportion with favorable outcome on the eGOS was 46% (64/138) for EG-1962 and 43% (62/144) for placebo group ($p=0.74$). Consistent with its mechanism of action, EG-1962 significantly reduced vasospasm (50% [69/138] EG-1962 versus 63% [91/144], $p=0.025$), rescue therapy (27% [37/138] versus 35% [50/144]) and hypotension (7% [9/138] versus 10% [14/144]). Mortality also was lower (7% [10/138] versus 10% [15/144]). Prespecified subgroup analysis suggested efficacy in WFNS 3-4 subjects (46% [32/69] EG-1962 versus 32% [24/75] placebo, $p=0.063$). No safety concerns or imbalance in adverse events were identified.

Conclusion

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

7:55-8:05	When Flow Diversion Fails: Predictive Factors of Incomplete Aneurysm Occlusion after Pipeline Embolization
------------------	---

Christopher Ogilvy, Peter Kan, Paul Foreman, Sricharan Gopakumar, Clemens Schirmer, Christoph Griessenauer, Santiago Gomez-Paz, Abhi Jain, Mohamed Salem, Georgios Maragos, Ajith Thomas, Luis Ascanio, Alejandro Enriquez-Marulanda

Introduction

Flow diversion with the Pipeline Embolization Device (PED) has become an alternative endovascular treatment for select intracranial aneurysms. To date, high rates of aneurysmal occlusion have been reported with no recanalizations after aneurysm obliteration.

Objective

To identify factors predictive of incomplete aneurysmal occlusion on last angiographic follow-up after PED treatment.

Methods

A multi-center retrospective cohort analysis was conducted on consecutive patients treated with PED at 3 academic institutions in the United States. Patients with angiographic follow-up assessing the degree of aneurysm occlusion were selected to identify the factors associated with incomplete occlusion.

Results

Among all 3 participating institutions we identified a total of 523 PED placement procedures. Three hundred and ninety-five of these (75.5%) had radiographic follow-up and were included in this analysis (age median 58 years; female-to-male ratio 4.4:1). Complete occlusion (Raymond-Roy class I) was noted in 68.6% of cases, while incomplete occlusion (Raymond-Roy class II or III) at last follow-up was identified in 31.4% after a median of 6 months. After accounting for factor collinearity and confounding, multivariate analysis identified older age (≥ 70 years; OR=3.07, 95% CI 1.77-5.32, $P<0.001$), higher maximal diameter (≥ 15 mm;

OR=3.33, CI 1.65-6.71, P=0.001) and fusiform morphology (OR=3.04, CI 1.56-7.42, P=0.002) to be independently associated with higher rates of incomplete occlusion on last follow-up.

Conclusion

In this study we demonstrate that age, aneurysm diameter and fusiform morphology are associated with incomplete aneurysm occlusion after PED placement. Such predictive factors can be utilized to guide individualized treatment selection and counseling in cerebrovascular neurosurgical patients. Furthermore, these results provide a clinical background for research on the biologic factors affecting endothelialization of the PED.

8:05-8:15 Transradial Cerebral Angiography: A Safer Alternative

Andrew Ducruet, **Felipe Albuquerque**, Vance Fredrickson, Joshua Catapano

Introduction

Neurointerventionalists have not widely embraced transradial access as a conduit for cerebrovascular angiography.

Objectives

We sought to analyze the Barrow Neurological Institute experience with the transradial approach specifically assessing complications occurring as a result of distal (anatomic snuffbox) and proximal (standard) radial artery catheterization.

Methods

We reviewed all cerebral angiograms performed at our institution from October 1, 2018 to June 1, 2019, when our service adopted transradial catheterization as an option to femoral artery sheath placement. We specifically assessed type of procedure (diagnostic versus neurointerventional), type of transradial approach (snuffbox versus standard), laterality of puncture, and complications.

Results

From a total of 1104 diagnostic and neurointerventional cerebral angiograms performed during this 8-month period, 140 were completed through a transradial approach. Of these, 83 were done through proximal catheterization and 57 via the snuffbox. Snuffbox catheterization was performed at greater frequency during the later weeks of the study after proficiency had been achieved with standard catheterization. Ninety-five of these procedures involved diagnostic angiography while the remaining 45 were neurointerventions. The majority of the procedures were performed via the right radial artery (133 or 95% of cases). Only 1 permanent complication (0.71%), a small thromboembolic cerebrovascular accident, and 3 minor complications (2.14%) occurred.

Conclusion

Transradial catheterization for both diagnostic and neurointerventional angiography is exceptionally safe. Understanding the specific clinical scenarios in which transradial access is contraindicated or likely to fail is essential to ensuring the safety of this procedure. Both the standard and snuffbox approaches had similar safety profiles.

8:15-8:25 Somatic mutations in cerebral aneurysms

Geoffrey Colby, Mike Niemela, Alan Boulos, Scott Weiss, Edison Valle-Giler, Wendy Huang, H. Hunt Batjer, Arthur Day, Lawrence Dickinson, Xiangen Shi, Anthony Wang, Spiros Blackburn, Bradley Gross, Daniel Barrow, Pui Man Rosalind Lai, **Rose Du**, Kai Frerichs, Nirav Patel, Edie Zusman, Sarajune Dagen, Edward Chang, Babu Welch, G. Rees Cosgrove, Steven Ojemann, Mohammad Ali Aziz-Sultan, P. Roc Chen, Carlos David

Introduction

Despite recent genome-wide association studies, the pathogenesis of cerebral aneurysms remains unclear.

Objectives

While somatic mutations have been well-studied in cancer, their roles in other complex traits are much less understood. Our goal is to identify somatic variants that may contribute to the formation of cerebral aneurysms.

Methods

We performed whole exome sequencing on aneurysm tissues and matched peripheral blood obtained from 30 patients. Differential expression analysis was additionally performed on aneurysm tissue and control intracerebral arteries.

Results

284 non-synonymous somatic mutations within exon regions of 263 genes (median 7 per aneurysm tissue, range 1-29) were found with the highest representation of single-nucleotide variants predicted as missense mutations. Somatic variants that involve supervillin (SVIL) and its regulation were found in 17% of aneurysm tissues. SVIL was differentially down-regulated in aneurysm tissues of patients with mutations in SVIL compared to normal controls. Pathway enrichment analysis demonstrated that mutations in the vascular endothelial growth factor (VEGF) signaling pathway (FDR=0.011), chromatin modifying enzymes (FDR=9.33x10⁻³), and integrin signaling pathway (FDR=0.025), were found in 60% (N=18) of patients.

Conclusion

We propose that these somatic changes in aneurysm tissue may explain the heterogeneity of genetic inheritance and environmental influences on the development of this disease.

8:25-8:35 Intracranial Aneurysms: Does Size Really Matter?

Philip Stieg, Kashif Majeed, Srikanth Boddu

Introduction

To stratify the risk of rupture from intracranial aneurysms, size remains the primary criteria as proposed by two ISUIA trials. Observation for ≤ 7 mm aneurysms which have low propensity to rupture has been proposed. Given the severe outcome after subarachnoid hemorrhage, the application of these recommendations has been contested.

Objectives

To retrospectively assess whether size correlates with aneurysmal rupture, and to analyze outcomes of endovascular and microsurgical procedures.

Methods

Aneurysm cases between 2016-2019 were reviewed. Age, gender, comorbidities, rupture and unruptured status, modes of treatment (clipping, coiling and observation) and their outcomes were noted. The descriptive statistics, and cross-tabulations were generated. Regression analysis was done to correlate size with aneurysmal rupture.

Results

Of the 633 aneurysms, 109 had ruptured. In the five size groups: 0-6mm, 7-12mm, 13-18mm, 18-24mm and giant, the proportion of ruptured aneurysms was 63.3%, 30.2%, 1.8%, 6.4 and 0.9% respectively.

Ruptured aneurysms were 0.0%, 16.5%, 50.4%, and 30.2% in age groups 0-18, 19-44, 45-64 and ≥ 65 , respectively.

The majority (400) were managed endovascularly. 87 (14%) underwent clipping, 26 of those were ruptured and 61, unruptured. The mean modified Rankin score for clipped aneurysms was zero. One inpatient death, and single brainstem stroke was noted in the coiled group. 142 were followed. The mean modified Raymond-

Roy classification for treated aneurysms was 1.1, with 264 completely occluded; 31 had a score of 2, and 33, of score 3.

Conclusion

Small aneurysms ruptured more frequently than reported previously. Surgical clipping was superior in outcome. Further studies to better understand unique aneurysmal characteristics to predict the risk of rupture are needed.

8:35-9:15 Peer Reviewed Abstract Session VI: Tumor Moderators: Henry Brem / Don O'Rourke

8:35-8:40 Long-Term Outcomes in the Treatment of Pediatric Skull Base Chordomas

Eric Wang, Michael McDowell, **Paul Gardner**, Carl Snyderman, Nathan Zwagerman, Elizabeth Tyler-Kabara

Introduction

Pediatric skull base chordoma is a rare entity that is traditionally considered to display aggressive behavior and a tendency to recur. However, there is an absence of literature examining outcomes using the endoscopic endonasal approach.

Objectives

Assess the outcomes of pediatric skull base chordoma patients undergoing endonasal resection.

Methods

We retrospectively reviewed all patients presenting up to age 18 with skull base chordomas to the University of Pittsburgh Medical Center from 2004 to 2018.

Results

Eighteen patients met criteria. The most common presenting complaints were diplopia (n = 7), headache (n = 5), and swallowing difficulty (n = 4). Three cases were incidentally discovered. Eleven patients underwent endoscopic endonasal approach (EEA) alone, five patients had combined EEA with open far lateral or extreme lateral approaches, and two patients had two-stage EEA procedures. Thirteen patients had gross total resection based on intraoperative impression and post-operative imaging and five patients had near total resection (>95%). Five patients developed cerebrospinal fluid leaks requiring re-operation, one patient developed a permanent abducens palsy, one patient suffered an internal carotid injury that required carotid sacrifice and resulted in a Horner's syndrome, one patient developed an epidural hematoma, and one patient developed a subdural empyema. Three (16.7%) patients developed tumor progression during follow-up. The mean radiographic follow up was 57 months.

Conclusion

Pediatric skull base chordoma, when managed aggressively at a specialized center with a goal of gross total resection, may have a better outcome than traditionally believed. Elevated Ki-67 rates may predict poor outcome.

8:40-8:50 MRI Perfusion Radiomic Machine Learning Identifies Pseudoprogression in Glioblastoma - A Multicenter Study

Samuel Bergamaschi, Nabil Elshafeey, Ahmed Hassan, Meng Law, **Pascal Zinn**, Aikaterini Kotrotsou, Nancy Elshafei, Jason Huse, Fanny Moron, Anand Agarwa, Gregory Fuller, Sara Ahmed, Rivka Colen, Kamel Salek, Srishti Abrol, Jay Acharya

Introduction

Multi-modal Glioblastoma therapy with radiation and Temozolomide, including immunotherapy and clinical trials is common. Advanced glioblastoma treatment may complicate MR image assessment for therapy response. Therapy related inflammatory changes typically stabilize or subside without further treatment, but they are often difficult to distinguish from progressive disease (PD). This PD-mimicking phenomenon is called pseudoprogression (PsP). Early discrimination of PsP from PD is a clinical challenge that currently requires biopsy for definite diagnosis.

Objectives

To address this gap in assessment tool availability our objective was to create a radiomic texture image analysis pipeline for perfusion MR images and to leverage machine learning algorithms to diagnose PsP with high accuracy.

Methods

A total of 98 patients from 3 institutions with histopathologically confirmed PsP and PD and available dynamic susceptibility contrast and dynamic contrast-enhanced perfusion MRI images were included. A classifier using radiomic features obtained from both Ktrans and rCBV maps coupled with support vector machines was derived and tested in the primary data set and in a separate prospective patient cohort.

Results

MRI perfusion radiomic texture analysis demonstrates an accuracy of 90.82% (area under the curve (AUC)=89.10%, sensitivity=91.36%, specificity=88.24%, p=0.017) in differentiating between PsP and PD. The diagnostic performances of the models built using radiomic features from Ktrans and rCBV separately were equally high (Ktrans: AUC=94%, p=0.012; rCBV: AUC=89.8%, p=0.004).

Conclusion

The MR perfusion based radiomic model demonstrates high accuracy, sensitivity and specificity in discriminating PsP from PD, thus providing a tool for noninvasive identification of PsP versus PD at the time of clinical question.

8:50-9:00	The evolution of epilepsy surgery for children: lessons from tuberous sclerosis complex over 20 years
-----------	--

Howard Weiner

Introduction

Pediatric epilepsy surgery has grown significantly over the last 20 years, due to both philosophical and technological advances. Because of the multiple epileptogenic brain lesions in Tuberous Sclerosis Complex (TSC), targeted epilepsy surgery was only considered in the small subset of children with focal epilepsy, with the remainder offered palliation. We previously treated 120 TSC patients with staged craniotomy and seizure focus resection.

Objectives

Given the natural history of TSC, and the evolving concept of palliative surgery, our objective was to develop a novel comprehensive treatment paradigm, which incorporates both traditional resective and minimally invasive strategies.

Methods

Over 36 months, we treated 37 TSC children with refractory epilepsy, who had VEEG, MRI, CT, MEG, PET, and were referred for either resective surgery or stereotactic laser ablation (SLA). Most patients underwent an initial phase of stereo EEG (SEEG) monitoring, some had subdural grid electrodes, and two had no intracranial EEG. Outcome was considered improved with at least a 50% reduction of the targeted seizure type.

Results

12 children had prior epilepsy surgery elsewhere. 21 had SLA, 14 resection, one SLA after failed resection, and one resection after failed SLA. 17 of the 22 SLA and 11 of 15 resection patients were improved. Complications included one abscess.

Conclusion

Advances over 20 years reveal that more TSC patients are candidates for targeted surgery, and have changed our notion of palliation. Children can improve after surgery, despite not being completely seizure free. A new, less invasive approach is possible for select children with TSC and has facilitated a new, iterative epilepsy surgery paradigm.

9:00-9:10	Stimulated Raman Histology for Rapid Neurosurgical Intraoperative Histology: A Prospective Series
------------------	--

Ricardo Komotar, Michael Ivan , Ashish Shah, Long Di, Alexa Semonche, **Allan Levi**, Daniel Eichberg, Sakir Gultekin, Christopher Sarkiss

Introduction

Within neurosurgical oncology, intraoperative frozen section diagnosis remains a mainstay of surgical practices, permitting accurate diagnosis and potentially influencing intraoperative decision making. However, delays in frozen section diagnosis can prolong surgical times and potentially adversely affect the extent of resection. Stimulated Raman Histology (SRH) allows for non-invasive, fast, high resolution acquisition of structural information through spectral image generation. Here we investigate the utility of a novel system, SRH, to prospectively identify pathological tissue by creating a simulated “frozen section”; potentially facilitating a rapid diagnosis.

Objectives

To assess frozen/permanent histopathology diagnostic time and accuracy to novel Raman Stimulated Histology

Methods

We prospectively conducted a single center cohort study comparing time from specimen collection to diagnosis for stimulated intraoperative pathology consult with SRH, with actual intraoperative frozen section diagnosis. Additionally, diagnostic accuracy was determined by concordance of SRH simulated intraoperative pathology consult with a blinded board-certified neuropathologist, with frozen section and permanent section results. Primary outcome was time from specimen collection to diagnosis for stimulated intraoperative pathology consult with SRH and for actual intraoperative frozen section diagnosis. Secondary outcome was Cohen’s Kappa coefficient (κ) for concordance between SRH simulated intraoperative pathology consult with a blinded board-certified neuropathologist, with actual frozen section and permanent section results.

Results

Of the 82 patients, average age was 60.2 years and 50% were female (n=40). Time to diagnosis was 10.14 minutes for SRH and 40.65 minutes for frozen section ($p < 0.0001$). Diagnostic correlation was 91.5% for SRH and permanent section and 91.5% for frozen and permanent section. Correlation between SRH and standard histopathological permanent section was greater than 95%.

Conclusion

SRH is a promising histological adjunct for rapid intraoperative pathologic consultation, and can be successfully implemented in the workflow of a neurosurgery operating room to shorten operative times.

9:10 – 9:20:	Role of Visual Cortex in Essential Tremor
---------------------	--

Jean Régis, Tatiana Witjas, Axelle Cretol, Eric Guedj and Constantin Tuleasca.

Introduction/Objective

In order to study predictors of outcome after Gamma Knife Radiosurgery (GKS) in essential tremor (ET), and to better understand the physiology of tremor, we studied clinical and imaging data pre and postoperatively.

Methods

Between January 2004 & November 2018, 626 patients had GKS at our center. In this prospective cohort the tremor was an essential tremor (ET) in 432 patients. GKS was performed on the left Vim in 81% of the patients. The mean age was 73 years (min 31- max 93). Tremor, neuropsychological exam, speech, gait and balance were all assessed before and 1 year after. We performed modern neuroimaging techniques for the study of the radiobiology of Vim GKS. We used both structural [e.g. T1 weighted (T1-w), voxel-based morphometry (VBM)] and functional resting-state functional MRI (rs-fMRI).

Results

The mean follow up is 18 months. The mean delay of action of radiosurgery was 4,5 months. The mean disability was before GKS of 30.2/75 and at the last FU of 8.9/75 for a mean improvement of 70.5%. The mean amplitude of the hand tremor on the treated side before GKS was 18.7 and at the last FU, 6.6 for a mean improvement of 65%. The mean functional impact before GKS was 7.7/28 and at the last FU, 2.5/28 for a mean improvement of 68%. An hyper-response to radiosurgery associated neurological side effects (proprioceptive ataxia, dysarthria, hemiparesis) was observed in 7% of the patients and led to rehabilitation. Despite a standard radiosurgical procedure, there is a variability in the clinical effect, with a similar efficacy rate as compared to standard deep-brain stimulation, the reference technique.

The most relevant and novel contribution was the presence of a visually-sensitive structural and functional network, involved in tremor generation and further arrest after Vim GKR. The patients with this network benefited more from GKS. We modified the term “cerebello-thalamo-cortical” into the “cerebello-thalamo-visuo-motor” network, as a step forward in the understanding of essential tremor’s pathophysiology. Two structures were proposed as main calibrators of this network: the cerebellum (as the most probable) versus the thalamus itself. Moreover, a more classical basal ganglia network, as well as a cerebellar, interconnected with the motor and visual one, were reported. Other longitudinal changes involved dorsal attention, insular or supplementary motor area circuitries, shedding new light on tremor arrest after surgery. Particular phenotypes of ET, including patients with head tremor, were analyzed.

Conclusion

We found a high safety to efficacy ratio of GKS in this population of aged and fragile patients. The ET network classically involves mainly the dentate nucleus, the ventrolateral thalamus and the primary motor cortex. However, our data from structural & functional connectivity, PET and VBM are showing the role of visual cortical areas as predictors of response to radiosurgery. These areas are demonstrated additionally to be modified by radiosurgery, in a way different in responders and non-responders. We provide a new network perspective to this disorder.

9:15-9:30

Break

9:30-10:30 Peer Reviewed Abstract Session VII: Spine
Moderators: Kevin Foley & Praveen Mummaneni

9:30-9:40 Early Results from the CSM-S RCT: Quality of Life, Cost, and Complications

Robert Heary, Todd Albert, Paul Arnold, Michael Fehlings, Jill Curran, **Zoher Ghogawala**, Adam Kanter, Erica Bisson, Edward Benzel, Robert Whitmore, John Heller, Frederick Barker, Praveen Mummaneni, Michael Steinmetz, Subu Magge, K Daniel Riew, Marjorie Wang

Introduction

The optimal surgical approach (ventral vs. dorsal) for treating CSM is not known.

Objectives

To compare the effectiveness of three major surgical treatments for CSM.

Methods

A prospective RCT was conducted on patients aged 45-80 years with multi-level CSM. Patients were randomized to ventral or dorsal surgery (2:3 randomization) from 15 sites from 2014-2018. Dorsal surgical approach (dorsal fusion or laminoplasty) was at the discretion of surgeon and patient. Outcome assessments (SF-36, NDI, mJOA, and EQ-5D) along with patient work status were obtained pre-operatively, 3 months, 6 months, and 1 year post-operatively. Complications were assessed by an independent study coordinator.

Results

Fifteen sites randomized 163 patients. 63 (38.7%) were randomized to ventral surgery and 100 (61.3%) to dorsal. Average age was 62.2 years (49% male). Baseline characteristics were comparable. Crossover rate was 3%. Follow-up was 95% (155 patients) at 1 year. Analysis was done as treated: 66 patients underwent ventral fusion (VF), 69 dorsal fusion (DF), and 28 dorsal laminoplasty (DL). All strategies demonstrated significant improvements. Return to work rate was similar among the three groups. DL had superior SF-36 PCS outcome when compared with VF (P=0.04) and DF (P=0.04). DL patients had fewer complications (42.4% VF vs. 27.5% DF vs. 10.7% DL; P=0.007) and lower hospital charges (VF \$90,687 vs. DF \$ 111,705 vs. DL \$ 55,332; P<0.05).

Conclusion

At 1 year, surgery improved overall quality of life with favorable return to work rates. Dorsal laminoplasty surgery for CSM is associated with greater improvements in health-related quality of life, fewer complications, and lower hospital costs.

9:40-9:50 Fusion for Spondylolisthesis Is Associated with Greater Improvements: A Multicenter Registry Study

Steven Glassman, **Kevin Foley**, Eric Potts, Mohamad Bydon, Michael Wang, Anthony Asher, Erica Bisson, John Knightly, Jonathan Slotkin, Paul Park, Mark Shaffrey, Kai-Ming Fu, Praveen Mummaneni

Introduction

Extensive investigation has not ascertained the ideal surgical management of grade 1 lumbar spondylolisthesis. Using the large, multicenter, prospectively collected Quality Outcomes Database (QOD), we compared 24-month outcomes for patients undergoing decompression alone versus decompression and fusion.

Objectives

Compare decompression and fusion for grade I spondylolisthesis.

Methods

Patients undergoing surgery from 7/1/2014 through 6/30/2016 were identified. The primary outcome measure, 24-month Oswestry Disability Index (ODI) change, was analyzed with univariate and multivariable linear regression. Pain, quality of life, and satisfaction were also analyzed.

Results

Of the 608 patients (85.5% with at least 24-month follow-up) who met the inclusion criteria, 140 (23.0%) underwent decompression alone and 468 (77.0%) underwent decompression and fusion. The 24-month change in ODI was significantly greater in the fusion group than the decompression-only group (-25.8 ± 20.0 vs. -15.2 ± 19.8 , $p < 0.001$). Fusion remained independently associated with 24-month ODI change in our multivariable model ($B = -7.05$, 95% CI -10.70 to -3.39 , $p < 0.001$). Patients in the fusion group were significantly more likely to reach minimal clinically important difference (MCID, 12.8 points) in ODI (73.3% vs. 56.0%, $p < 0.001$) and to experience significantly greater NRS back pain improvement (-3.8 ± 3.1 vs. -1.8 ± 3.9 , $p < 0.001$) at 24 months. Fusion was also independently associated with achieving MCID for ODI at 24 months in our logistic regression model (OR 1.767, 95% CI 1.058-2.944, $p = 0.029$).

Conclusion

The results of our study suggest that decompression plus fusion may offer superior outcomes to decompression alone in patients with grade 1 lumbar spondylolisthesis at 24 months. Longer-term follow-up is warranted to assess whether this effect is sustained.

9:50-10:00	Frailty, Long-Term Outcomes and Management Implications for Type II Odontoid Fractures in the Elderly
-------------------	--

Christopher Graffeo, **Michelle Clarke**, Avital Perry

Introduction

Type II odontoid fractures are common and highly morbid injuries in elderly patients. The modified 5-item frailty index (mFI-5) is a validated comorbidity-based tool for risk stratification which has been shown to predict adverse outcomes after various surgeries.

Objectives

Determine whether the mFI-5 predicts long-term outcome following Type II odontoid fractures in the elderly and determine if mFI-5 is useful in operative vs. non-operative treatment decisions.

Methods

A single-center prospective trauma registry was retrospectively reviewed to identify patients over age 79 with Type II odontoid fractures. Prospective outcomes included Abbreviated Injury Scale, Injury Severity Score, and calculated mFI-5. Statistical tests included a Cox proportional hazards model, with frailty score as the dichotomized predictor (frail defined as $mFI \geq 3$).

Results

Of 111 patients identified, 106 had complete frailty data and met inclusion criteria. The basic univariate frailty model resulted in a hazard ratio for death of $HR = 2.07$ (95%CI=1.25-3.34, $p = 0.005$), for frailty score 3-5 as compared to frailty score 0-2. Adjusting for management strategy (operative vs observation), the frailty score retains statistical significance, with the adjusted $HR = 2.08$ (95%CI=1.25-3.36)

Conclusion

Among elderly patients with type II C2 fractures and no neurologic injury, a frailty score of ≥ 3 is a significant predictor of mortality, which is independently associated with a 2-fold increase in risk of death, after adjusting for management strategy. Correspondingly, a low frailty index (≤ 2 , using the 5-point scale) may identify patients within this high risk cohort who would be reasonable candidates for operative management.

10:00-10:10 The use of intraoperative sodium fluorescein for diagnostic biopsy of intramedullary spine cord lesions

Jens-Peter Witt, Kevin Lillehei, **Timothy Ung**, Edin Nevzati, Leslie Robinson, Michael Finn

Introduction

Sodium fluorescein-guided microsurgery facilitates resection of intrinsic and metastatic lesions in the brain and may prove to be beneficial when used in the spinal cord. Spinal cord lesions present a unique challenge to neurosurgeons and often lesions are not amenable to resection. Diagnostic biopsy of spinal cord lesion is often challenging and the localization of such lesions intraoperatively is paramount. However, there has been limited research elucidating potential application of sodium fluorescein for such use.

Objectives

Demonstrate the utility of sodium fluorescein for Intramedullary Spinal Surgery.

Methods

Five patients with spinal cord lesions received fluorescein sodium (10%, 3 mg/kg) prior to surgical resection. Intraoperative visualization of fluorescence was performed using microscopes equipped with a Yellow560 filter and diagnostic tumor samples were obtained.

Results

Importantly, no adverse reactions were observed in our five patients. Administration of sodium fluorescein resulted in lesional fluorescent contrast extravasation and facilitated diagnostic tumor biopsy in all five patients. The addition of sodium fluorescein allowed for identification of pathology from normal spinal parenchyma. Pathology confirmed the diagnosis of anaplastic astrocytoma (2), glial tumor (1), EBV lymphoproliferative disease (1), and bacterial abscess (1).

Conclusion

Limited modalities exist facilitating the localization of intramedullary spinal lesions. Sodium fluorescein may be a sensitive and specific in guiding the location of intramedullary spinal lesions when diagnostic biopsy is the goal of surgery.

10:10-10:20 Robot-Assisted vs Freehand Instrumentation in Short-Segment Lumbar Fusion: Experience with Real-Time, Image-Guided Spinal Robot

Nicholas Theodore, A. Karim Ahmed , Ethan Cottrill, Erick Westbroek, Tej Azad, Zach Pennington, Corinna C. Zygourakis, Bowen Jiang, Alex Zhu

Introduction

Rising patient demand for minimally invasive surgery and increased payer emphasis on quality-based payment schema have created a need for technologies that provide consistent, high-quality outcomes for patients undergoing spine surgery. Robot assistance is one such technology.

Objectives

To report the early experience with a novel real-time, image-guided robot system for use in surgical procedures of the spine.

Methods

A consecutive series of patients undergoing robot-assisted one- or two-level TLIF were compared to matched controls who underwent free-hand surgery. Screw accuracy, intraoperative outcomes, and 30-day outcomes were compared.

Results

We identified 56 patients who underwent 1- or 2-level lumbar fusion during the study period: 28 who underwent robot-assisted procedures and 28 matched controls who underwent freehand instrumentation placement. No significant differences were found between the robot-assisted surgery cohort and the freehand

surgery cohorts with respect to matched variables. Patients who underwent robot-assisted surgery had less intraoperative blood loss (266.1±236.8 vs. 598.8±360.2mL; p < 0.001) and shorter hospitalizations (3.5±1.8 vs. 4.5±2.0d; p = 0.01). No differences in complication rates or 30-day outcomes or screw accuracy were noted. Profiling of our initial series reveal an average reduction in operation duration of 4.6 minutes with each additional case.

Conclusion

Patients undergoing robot-assisted fusion experienced less intraoperative blood loss and shorter hospitalizations. The results of this initial experience suggest that the ExcelsiusGPS™ system may provide similar short-term outcomes compared with freehand instrumentation placement.

10:20-10:30 Maximal Safe Resection in Thalamic Gliomas is Superior to Biopsy: Personal Reflections on 40 Cases
--

Mustafa Baskaya

Introduction

Thalamic gliomas (TGs) are difficult-to-access tumors which has historically high operative morbidity. TGs are commonly regarded as inoperable tumors. Although maximal safe resection (MSR) has become standard for lobar and insular gliomas, the location in the thalamus precludes the same treatment for TGs.

Objectives

Biopsy and adjuvant treatment has long been the mainstay management strategy for TG. We hypothesize that if MSR can be achieved with low morbidity and no mortality, then TG patients would have the chance to receive treatments similar to gliomas in other locations, thereby increasing overall survival.

Methods

A retrospective single-center review was performed for patients harboring TGs who underwent a MSR with at least 80% subtotal resection.

Results

A total of 40 patients were included. The extent of resection was gross-total in 35%, near-total (>95%) in 30% and subtotal (>80%) in 35%. Low-grade tumors comprised one-third of the study group whereas more than half of the patients (51%) had a glioblastoma. There was no operative mortality. Although temporary postoperative motor deficits were observed in 12 patients (30%), all improved during the early postoperative period except one patient who remained with mild hemiparesis. Mean overall survival was 116.8±12.4 months for low-grade, and 20.3±3.4 months for high-grade tumors. Multivariate analysis revealed that histological grade, age, and extent of resection, were independent prognostic factors.

Conclusion

Our results show that MSR yields significantly better outcomes, particularly in younger patients with low-grade tumors. Therefore, we advocate for MSR for most TGs using carefully selected surgical approaches, contemporary intraoperative adjuncts, and meticulous microsurgical techniques.

10:30-11:30 Peer Reviewed Abstract Session VIII: Functional/Trauma/Vascular
Moderators: Bernard Bendok & Sepi Amin-Hanjani

10:30-10:40 Dopamine, serotonin, and norepinephrine micro-fluctuations during conscious choice and subjective experience in humans

Kenneth Kishida, **Charles Branch**, Adrian Laxton

Introduction

The ascending neuromodulatory systems that release the neurotransmitters dopamine, serotonin, and norepinephrine are critical for healthy human brain function. Until recently, it was not possible to monitor the release of these neurotransmitters in the human brain with the temporal resolution necessary to investigate their role in encoding human behavior and conscious experience.

Objectives

We sought to develop an approach to directly monitor dopamine, serotonin, and norepinephrine with sub-second temporal resolution in the human brain.

Methods

We have developed a novel approach, which we call ‘elastic net electrochemistry’, that permits sub-second detection of dopamine, serotonin, and norepinephrine (as well as other neurochemicals of interest). These first-of-their-kind recordings require electrodes implanted in the brain, thus we have deployed our approach in humans undergoing deep brain stimulation electrode implantation surgery and, more recently, in patients undergoing stereo-EEG monitoring. We have paired these novel measurements with tasks designed to investigate the computational underpinnings of human choice behavior and associated moment-to-moment changes in subjective experience.

Results

Simultaneously recorded dopamine and serotonin micro-fluctuations in the striatum encode computational signals critical for learning and ongoing adaptations in behavior. These neurochemically encoded signals correlate with moment-to-moment changes in consciously reported subjective experience. Notably, these neurochemically encoded signals are disrupted in patients taking selective serotonin reuptake inhibitors for depression.

Conclusion

Direct, ultra-fast, intracranial monitoring of dopamine, serotonin and norepinephrine is now possible. Going forward, such work is likely to lead to novel insights into how these neuromodulatory systems contribute to the changes in behavior and subjective feeling associated with psychiatric and neurological dysfunction.

10:40 - 10:50 Intracranially delivered IL-12 secreting CAR T cells recruit host immunity to eradicate heterogeneous GBM

Andrew Barbour, Qi-Jing Li, Kendra Congdon, **John Sampson**, Luis Sanchez-Perez, Steven Shen, Adam Swartz, Carter Suryadevara, David Snyder

Introduction

Glioblastoma (GBM) remains uniformly lethal with an overall survival of <21 months despite surgery, radiation, chemotherapy, and tumor-treating fields. Chimeric antigen receptor (CAR) T cell immunotherapy has induced remarkable efficacy, including complete responses, in many hematologic cancers. However, CAR T cells recognizing a single tumor antigen, such as Epidermal Growth Factor Receptor variant III (EGFRvIII), have failed thus far to completely eradicate GBM. These failures can be partially attributed to the high

antigenic heterogeneity present within GBM tumors and the outgrowth of tumor cells lacking the targeted antigen.

Objectives

We hypothesize that intracranial delivery of CAR T cells secreting cytokines or chemokines aimed at inducing endogenous immunity against tumors antigens other than those targeted by the CAR will result in the eradication of heterogeneous GBM.

Methods

In order to evaluate our hypothesis we generated EGFRvIII-CAR T cells secreting one of four immunomodulatory molecules (IL-12, FLT-3L, CCL-3, and GM-CSF) known to increase T cell immunity. These EGFRvIII-CAR T cells were then delivered intracranially into immunocompetent mice with established orthotopic GBM possessing heterogeneous antigen expression (50%EGFRvIIIPositive: 50%EGFRvIIINegative). Survival was monitored overtime as the efficacy endpoint.

Results

Out of these four molecules, EGFRvIII-CAR T cells secreting IL-12 were the only therapy capable of mediating eradication of heterogeneous GBM in immunocompetent mice. Eradication of heterogeneous tumors required the presence of an intact endogenous immune system.

Conclusion

Therefore, our pre-clinical studies suggest that intracranial delivery of IL-12 secreting EGFRvIII-CAR T cells could eradicate tumors with antigenic heterogeneity and overcome a major limitation in the immunotherapy of solid tumors.

10:50 - 11:00 A New Treatment for Acute TBI – a phase II multicenter trial using novel MRI derivatives as surrogate outcome measures

Howard Eisenberg, J. Marc Simard

Introduction

SUR1-TRMP4, a membrane channel that is only expressed after injury. The open channel results in inward movement of water and causes oncotic cell death. When the receptor binds with glyburide the channel closes. Pre-clinical studies show that glyburide reduces edema in hemorrhagic progression of contusions.

Objectives

We tested whether glyburide was safe and effective in acute TBI. MRI indices of hemorrhage and edema, [free water (FW), mean diffusivity (MD), and tissue water (MDt)] were the outcome measures.

Methods

Baseline MRIs were made at or less than 10 hours from injury and then again at 72+/- 12 hours or if not safe, delayed up to 168 hours post impact. Blood was assessed using SWI. The dose was derived from animal data and a phase 1 study.

Results

28 patients were randomized. Both arms were balanced regarding initial GCS and other indices of injury, and time to second scan. 14 patients had contusions. Indicators of injury severity and time to second scan was also balanced here.

MRI measures of edema were greater in the delayed scan compared with baseline. Hemorrhage, however, increased in the placebo arm and decreased in the drug arm. The MRI indices for contusions when compared with unaffected white matter, showed the drug was associated with greater stability (less progression baseline to second scan) than placebo. The difference between the two arms for all indices were significant (Anova p<0.02 to 0.004). There were no differences in the AEs/SAEs between the two treatment arms.

Conclusion

In the context of this study, glyburide was safe and effective.

11:00-11:10 Dynamic blood brain barrier regulation in mild traumatic brain injury

Gerald Grant

Introduction

While the etiology of moderate and severe TBI is readily visible using MRI and CT, a far greater challenge is associated with the diagnosis of mild TBI (mTBI). We investigated the integrity of the blood-brain barrier (BBB) of professional mixed martial arts (MMA) fighters and adolescent rugby players and correlated the perceived BBB disruption observed with measurement of severity and number of impacts using instrumented mouthguard technology.

Objectives

The overall goal was to correlate the perceived BBB disruption observed with the measurement of severity and number of impacts.

Methods

MMA fighters were examined pre-fight and again within 120 hours post competitive fight, while rugby players were examined pre-season and again post-season or post-match. DCE-MRI, serological analysis of BBB biomarkers, and analysis of instrumented mouthguard data were examined.

Results

We provide pilot data that demonstrates disruption of the BBB occurs in both professional MMA and adolescent rugby, dependent on the level of exposure. We show evidence of a disrupted BBB in several players on DCE-MRI after a full season of competitive play as manifested by increased gadolinium extravasation in periventricular regions and at the depths of the cerebral sulci. Analysis of plasma samples also show increased levels of BDNF and MCP-1.

Conclusion

Our data suggest that biomechanical forces in professional MMA and adolescent rugby lead to BBB disruption. These pilot findings may lead the way to objectively predicting and quantifying neural damage in the context of exposure of the brain to repetitive sub-concussive forces and mild traumatic brain injury.

11:10-11:20 Computer-Learning to Identify High Risk Unruptured Aneurysms and Guide Decision Making: Rupture Resemblance Score

Stephan Munich, Muhammad Waqas, Kenneth Snyder, Hamidreza Rajzabadeh-Oghaz, L. Nelson (Nick) Hopkins, Adnan Siddiqui, Hui Meng, Elad Levy, Kunal Vakharia, Jason Davies

Introduction

Studies show ruptured intracranial aneurysms have unique morphology and hemodynamics, including higher size ratio, higher oscillatory shear index, and lower wall shear stress. Unruptured intracranial aneurysms (UIAs) that possess these characteristics may be at higher risk of rupturing compared to those without them. Rupture Resemblance Score (RRS) is a data-driven model which can objectively gauge the similarity of UIAs to past ruptured IAs.

Objectives

We explored the clinical application of RRS in management decision of UIAs. We hypothesized that RRS could identify UIAs that resembled ruptured IAs, that may be overlooked.

Methods

We retrospectively (September 2018 and January 2019) collected challenging UIAs discussed in neurovascular conference at our center. RRS scores were compared to unruptured intracranial aneurysm treatment score (UIATS) and the real-world decision.

Results

Twenty-seven (27) patients with 54 UIAs (87% UIAs size \leq 7mm) were included. Average RRS [range: 0.0-1.0] was 0.23 ± 0.31 . With a cut-off of RRS=0.3, 24% of the UIAs had high RRS, suggesting they

were at higher risk. UIATS and clinicians in our center endorsed treatment for 33% and 52% of UIAs, respectively. RRS was not significantly different between patients recommended for observation and treatment when UIATS was used. On the other hand, RRS was significantly higher in patients who were recommended to undergo treatment of UIA. Five UIAs had high RRS while UIATS suggested “conservative Management”, four of those received treatment in real-world.

Conclusion

RRS can be used to objectively quantify the similarity of UIAs to past ruptured IAs. We showed that UIATS may overlook the risk of these aneurysms which are treated in the real-world.

11:20-11:30	Distribution and radiologic features of SEDAVFs in a modern single-center series of patients with spinal vascular shunts
--------------------	---

Elisa Colombo, **Giuseppe Lanzino**

Introduction

Spinal epidural arteriovenous fistulas (SEDAVFs) are rare pathologic shunts. MRI characteristics are often indistinguishable from spinal dural arteriovenous fistulas (SDAVFs), causing diagnostic uncertainty. Early recognition reduces post-treatment recurrence and guarantees better outcomes. DSA represents the tool to recognize and differentiate SEDAVFs.

Objectives

Raise awareness on SEDAVFs as novel epidemiologic entity. Emphasize similar and distinguishing aspects from SDAVFs.

Methods

Among Mayo Clinic patients evaluated for a spinal arteriovenous shunt between 2000 and 2018, we isolated SEDAVFs, identified by an abnormal connection between extradural arteries and an epidural vein, creating a venous pouch.

Results

213 patients met the inclusion criteria. Relative frequency of SEDAVFs made them the second most common lesions after SDAVFs. Most SEDAVF patients were male, mean age at diagnosis was 63.5 +/- 14.8 years. Lower extremity weakness and mRs 1 were the major clinical characteristics at presentation. Abnormal T2 cord signal was the most represented MR feature at diagnosis; we observed preferential distribution of SEDAVFs in the lumbar spine. On DSA, all SEDAVFs showed an epidural venous pouch with variable drainage. Endovascular obliteration was the preferred treatment for SEDAVFs.

Conclusion

Understanding of SEDAVFs is incomplete, mainly because we lack large case series. This study represents the largest cohort of single-center spinal arteriovenous shunts and the most numerous series of SEDAVFs. In our cohort SEDAVFs are the second most common lesions after SDAVFs. SEDAVF patients’ analysis demonstrates demographics comparable to those reported for SDAVFs. This cohort emphasizes the epidural venous pouch as the fundamental distinguishing feature from SDAVFs.

11:30 -11:40	HDFT as a tool to enhance outcomes in the management of hypereloquent lesions
---------------------	--

Fang-Cheng Yeh, Jessica Barrios, David Fernandes, **Robert Friedlander**

Introduction

We measure surgical success if the management of lesions in extreme eloquent brain regions results in lack of neurological deterioration. Surgical management of complex lesions often exposes patients to significant risk of neurological decline. Decline or lack of recovery likely results from surgical interruption of functional white matter pathways. Having an accurate understanding of deep white matter pathways may improve surgical outcomes.

Objectives

To evaluate patients with lesions in hypereloquent areas using high definition fiber tractography (HDFT) with the goal of optimizing neurological outcomes.

Methods

Eleven patients with brainstem cavernous malformations were evaluated using HDFT. HDFT information was used to guide decision of operative timing and approach.

Results

Eleven patients with brainstem cavernous malformations were operated (5-potome, 1-pontomesencephalic, 1-thalamo-mesencephalic, 1-posterior midbrain, 2-floor 4thventricle). Surgical approaches were 8-subtemporal, 1-infratentorial/supracerebellar and 2-telovelar. Gross total resection was achieved in 9/11. Five (46%) patients had transient worsening of preoperative symptoms or new deficits. All new postoperative deficits improved (average time for improvement 1.8 months). None of the patients had a new permanent deficit. Preoperative symptoms recovered: partially in 7 (64%), and completely in 4 (36%) patients. With a mean follow-up of 37 months (3.1 yr.), there has been one asymptomatic bleed and no symptomatic bleeds (3.0% asymptomatic bleed/year, 0% symptomatic bleed/year). No approach related complications.

Conclusion

HDFT as a surgical adjunct optimizes likelihood of minimizing chances for neurological deterioration and increases chance for neurological improvement following resection of brainstem cavernous malformation. Knowing the status and location of perilesional functional white matter pathways is critical to optimize patient outcome.

11:40-11:50 Break

11:50-12:20 **Special Lecture 2**
Introduction of Academy Special Lecturer: Alex Olivi & Mike McDermott
Fast cars and fast trains: The Ferrari and Italo stories
Luca Cordero di Montezemolo

12:20 - 1:20 **Presidential Address**
12:20 - 12:30 Introduction of the Academy President: Mark Johnson
12:30 - 1:20 Presidential Address: *Academia: Quo Vadis?*
Nino Chiocca, MD

7:30 – 8:25 **Special Lecture 3: The Oldfield Lectureship**
 7:30 – 7:35 Introduction, Moderator: **Nino Chiocca**

7:35 – 8:05 **Oldfield Lecture Bench to bedside development of a novel STAT3 inhibitor for CNS malignancies**

Daniel Zamler, Ling-Yuan Kong, Jun Wei, Martina Ott, Karl-Heinz Tomaszowski, Anantha Marisetty, John de Groot, Gregory Fuller, **Amy Heimberger**, Waldemar Priebe, Erik Sulman, Cynthia Kassab

Introduction

The signal transducer and activator of transcription 3 (STAT3) pathway is a potent regulator of tumorigenesis and is a key molecular hub of tumor-mediated immune suppression.

Objectives

To target p-STAT3 in brain tumors, we used molecular modeling and medicinal chemistry approaches to create a unique small molecule that achieves high CNS concentrations.

Methods

To be able to administer this drug to human subjects, a unique oral formulation of WP1066 using nanoparticles was devised that markedly increased its in vivo half-life, thereby reducing the dosing frequency.

Results

WP1066 increased survival in a wide variety of preclinical tumor models. In addition to direct tumor cytotoxic effects, WP1066 can restore T cell dysfunction, inhibit Tregs, and block immune suppressive macrophages. In multiple preclinical models of intracerebral tumors, WP1066 used in combination with radiation enhanced median survival time and induced immunological memory that was protective against tumor rechallenge. The combination triggered immunological reprogramming in the CNS tumor microenvironment, specifically affecting antigen presentation and T cell-effector functions. In the first-in-man phase I clinical trial of WP1066 (NCT01904123) in patients with recurrent GBM, eligible patients were assigned to a dose based on an accelerated-titration design followed by a 3 + 3 design algorithm. To date, toxicities have been grade I and II, mostly associated with minor bone marrow suppression. Target inhibition of p-STAT3 was verified in the peripheral blood mononuclear cells in subjects receiving WP1066.

Conclusion

Targeting STAT3 in patients with brain tumors is a promising therapeutic strategy.

8:05 - 8:15 NIH Funding Overview: **Russell Lonser**
 8:15 - 8:20 NREF Funding Overview: **Regis Haid**
 8:20 - 8:25 AAcNS/NREF Young Clinician Award Update - **Brian JA Gill**

8:25 - 8:30 AAcNS/NREF Research Fellowship Grant Update - **Benjamin Grannan**

8:30 - 8:40 American Academy Young Clinician Investigator Award - North America
 Single-cellular representations of semantic meaning during natural language perception
Benjamin L. Grannan

8:40 - 8:50 American Academy Young Clinician Investigator Award – Italy
Monitoring language networks in the asleep patient during surgery: an electrophysiological approach - **Daive Giampiccolo**

8:55 – 9:30 **Special Lecture 4:**
8:55-9:00 Introduction of Academy Special Lecturer: Alex Olivi
9:00-9:30 *Thirty generations of winemaking and still feeling young*
Lamberto Frescobaldi, President
Azienda Agricola “Marchesi Frescobaldi” Firenze

9:30 - 10:30 **Peer Reviewed Abstract Session IX: Various topics**
Moderators: Jacques Morcos / Robert Harbaugh

9:30-9:40 **Brain growth and developmental outcome after treatment of post-infectious hydrocephalus in infants in Uganda**

Jody Levenbach, John Mugamba, **Abhaya Kulkarni**, Edith Mbabazi Kabachelor, Vishal Monga, Peter Ssenyonga, Mallory Peterson, Steven Schiff, Ruth Donnelly, Benjamin Warf, Venkateswararao Cherukuri

Introduction

In Uganda, post-infectious hydrocephalus (PIH) in infants is a major health burden. Our randomized trial showed a strong association between brain growth and cognitive outcome 1 year after treatment, with no significant difference between endoscopic versus shunt treatment.

Objective

To present 2 year brain growth and cognitive outcome results for this randomized trial.

Methods

One-hundred infants were enrolled. At 2 years after treatment, developmental outcome (Bayley Scales of Infant Development [BSID-3]) and brain volume (from CT scan) were assessed. The trial was funded by National Institutes of Health R21TW009612/R01HD085853.

Results

Eighty-nine infants were analyzed for 2 year outcome. Raw brain volumes increased between baseline and 24-months ($p < 0.001$), but almost all of this increase was seen exclusively in the first 1 year ($p < 0.001$). Only 3.4% had normal brain volume at 24 months, compared to 24.5% at 12 months. Most patients (70.8%) suffered substantial brain volume loss between 12 and 24 months, despite clinically-successful hydrocephalus treatment. Those suffering substantial brain volume loss had lower scores in all BSID-3 domains. There were significant positive correlations between brain volume and all BSID-3 scores and BSID-3 changes from baseline. None of the brain volume or BSID-3 outcomes were significantly different between treatment arms.

Conclusion

Despite seemingly clinically-successful treatment, the overall outcome for infants with PIH in Uganda is poor, with stagnation of brain growth after the first year. Our results raise questions about the impediments to delayed brain growth and how best to prioritize neurosurgical care and preventive health policy to maximize child health in under-resourced settings.

9:40-9:50 Impact on Facial Nerve Outcomes and Extent of Resection Using Subperineural Dissection Technique for Surgical Resection

Yu-Lan Ying, **James Liu**, Robert Jyung, Jorge Naranjo, Naveed Kamal, Gurkirat Kohli

Introduction

There has been recent interest in planned subtotal resection of acoustic neuromas (ANs) followed by radiosurgery to minimize facial nerve injury. However, the risk of recurrence is proportional to the volume of residual tumor. The authors report their experience with attempted maximal resection using a facial nerve-sparing strategy via a subperineural dissection technique.

Methods

A retrospective study was performed on 74 consecutive patients who underwent retrosigmoid (79.7%) or translabyrinthine (20.3%) resection of AN using a subperineural dissection technique. During extracapsular tumor removal, the perineurium of the vestibular nerves are identified and dissected away from the tumor capsule, leaving a thin layer of perineurium as an anatomic buffer overlying the facial nerve. Patients were evaluated for tumor size, extent of resection, facial nerve outcomes, and recurrence.

Results

The mean patient age at surgery was 52.3 years with a mean follow-up of 14.4 months. Majority of the tumors were Koos grade III-IV (64.9%) while 35.1% had Koos grade I-II tumors. Gross-total resection (GTR) and near-total resection (NTR, >95% resection) were achieved in 94.6% of patients. There was a decrease in GTR and increase in NTR, with increased Koos grade I to IV (GTR: 100%, 93.3%, 75%, 42.5%; NTR: 0%, 6.7%, 25%, 50%, respectively). Favorable facial nerve outcomes (House-Brackmann grade I-II) were achieved in 94.6%, overall (100% Koos I-II, 87.5% Koos III, 92.5% Koos IV). The extent of resection did not appear to affect final facial nerve outcome. There was one recurrence (1.4%) that was treated with radiosurgery.

Conclusion

The subperineural dissection technique appears to be useful for preserving facial nerve function when attempting maximal resection of ANs. The perineurium of the vestibular nerves provides an anatomic buffer to avoid direct dissection on the facial nerve. The technique will be demonstrated in the presentation via case examples.

9:50-10:00 Phase 0/1 Clinical Trial of Low-Dose Capecitabine in Recurrent GBM: Global Immune Fingerprinting of Tissue and Blood

Michael Vogelbaum

Introduction

Immunosuppressive myeloid derived suppressor cells (MDSCs) are elevated in GBM patient circulation and tumor tissue. Low-dose 5-FU selectively reduces circulating and tumor MDSC levels and promotes survival in mice with GBM.

Objectives

Determine the immune profile of patients with recurrent GBM after low-dose 5-FU treatment.

Methods

We conducted a phase 0/1 clinical trial in recurrent GBM with low dose capecitabine (5-FU oral prodrug) administered before and after surgery. Eleven patients were enrolled over three escalating dose cohorts ranging from 150 to 450 mg BID (typical clinical dose is 2500 mg BID).

Results

Circulating MDSCs were elevated after surgery in a control cohort as well as in the 150 mg dose cohort; they were lower in the 300 and 450 mg dose cohorts. We used our previously reported approach of mass cytometry (CyTOF) and found significant increases in CD4 central memory T cells, CD8+ effector memory cells,

classical monocytes, dendritic cells, macrophages, microglia, and NK cells in tumor tissue. Further, we used an artificial intelligence algorithm to predict, and then validate via manual gating of CyTOF data, a significant reduction in CTLA-4 expression in lymphocytes and number of CTLA-4+/PD-1+ macrophages. No serious adverse events were observed. OS has been 22.1 months (range: 11.9 – 36.6 months).

Conclusion

This tissue-based clinical-translational study revealed that a low dose chemotherapy approach could reduce circulating MDSCs and increase cytotoxic immune infiltration within the tumor microenvironment. We plan to explore the use of more selective inhibitors of GBM-induced MDSC expansion in combination with immune stimulating therapies to further drive an immune response to GBM.

10:00-10:10 Sexual Dysfunction: Prevalence, Prognosis, and Predictors of Outcomes in Patients Operated for Lumbar Spondylolisthesis

Steven Glassman, Andrew Chan, Kevin Foley, Eric Potts, Mohamad Bydon, Leslie Robinson, Mohammed Alvi, Michael Virk, Michael Wang, Anthony Asher, Erica Bisson, John Knightly, Christopher Shaffrey, Jonathan Slotkin, Regis Haid, Paul Park, Mark Shaffrey, Kai-Ming Fu, Domagoj Coric, **Praveen Mummaneni**, Panagiotis Kerezoudis, Jian Guan

Introduction

There is a paucity of investigation on the impact of spondylolisthesis surgery on back-pain related sexual inactivity.

Objectives

We utilized the prospective Quality Outcomes Database (QOD) registry to investigate predictors of improved sex life postoperatively.

Methods

218 patients who underwent surgery for grade 1 degenerative lumbar spondylolisthesis (DLS) were included who were sexually active. Sex life was assessed by Oswestry Disability Index Item #8 at baseline and 24-month follow-up.

Results

Mean age was 58.0±11.0 years and 108 (49.5%) patients were women. At baseline, 178 patients (81.7%) had sex life impairment. At 24 months, 130 patients (73.0% of the 178 impaired) had an improved sex life. Those with improved sex lives noted higher satisfaction with surgery (84.5% vs. 64.6% would undergo surgery again, $p=.002$). In multivariate analyses, lower BMI was associated with improved sex life (OR=1.14;95%CI[1.05-1.20]; $p<.001$). In the subgroup of younger patients (age<57 years), lower BMI remained the sole significant predictor of improvement (OR=1.12;95%CI[1.03-1.23]; $p=.01$). In the older patients (age≥57 years)—in addition to lower BMI (OR=1.12;95%CI[1.02-1.27]; $p=.02$)—lower ASA grades (1 or 2) (OR=3.7; 95%CI[1.2- 12.0]; $p=.02$) and ≥4 years of college education (OR=3.9;95%CI[1.2-15.1]; $p=.03$) were predictive of improvement.

Conclusion

Over 80% of patients who present for DLS surgery report a negative effect of the disease on sex life. However, most patients (73%) report improvement postoperatively. Sex life improvement was associated with greater satisfaction with surgery. Lower BMI was predictive of improved sex life. In older patients—in addition to lower BMI—lower ASA grade and higher education were predictive of improved sex life.

10:10-10:20 Cerebro-vascular remodeling following ischemic stroke: cellular and molecular mechanisms.

Katelin Cunningham, **Robert Dempsey**, Umadevi Wesley

Introduction

Focal brain ischemia causes destruction of vascular integrity and neuronal cell death leading to poor functional recovery. Thus, therapeutic strategies for ischemic stroke must emphasize both neuro and microvascular restoration. Molecular/cytokine signals regulate these processes and also endogenous and exogenous stem cells, and improve post-stroke outcome. However, the number and functional capacity of stem cells are impaired in an ischemic microenvironment, leading to inadequate tissue regeneration and repair.

Objectives

The overall objective is to modulate the ischemic brain microenvironment to enhance stem cell survival and function for improving post-stroke recovery and cognitive abilities of patients affected by cerebrovascular diseases.

Methods

Cellular, biochemical and molecular, proteomics, gene arrays, and in vitro oxygen glucose deprivation approaches were used. Pre-clinical animal models subjected to focal ischemia through middle cerebral artery occlusion were used to examine the therapeutic effects of selected molecules.

Results

Expression of cytokines including galectin-3 (Gal-3) and osteopontin were up-regulated in the ischemic brain following ischemia-reperfusion. Blocking of these cytokines decreased neuroblast and blood vessel numbers in vivo. Administration of Gal-3 increased CD31 positive blood vessels in the ischemic brain, and significantly decreased the infarct size and improved neurological functional recovery. Gal-3 increased in vitro mesenchymal stem and neuronal cell survival under ischemic conditions through activation of anti-apoptotic AKT, integrin-linked kinase (ILK), an angiogenic factor, and decreased levels of pro-apoptotic caspase-3.

Conclusion

Cytokines including Gal-3 promote stem cell survival, increase angiogenesis, and thus are potential therapeutic agents for enhancing restoration of the neuro-vascular unit to improve cognitive abilities and neurological functional recovery after ischemic stroke.

10:20-10:30 Glioblastoma organoids: A model system for patient-specific therapeutic testing

Fadi Jacob, Donald O'Rourke, **Ryan Salinas**, Phuong Nguyen, Hongjun Song, Saad Sheikh, Maclean Nasrallah, Steven Brem, Radhika Thokala, Guo-Li Ming, Daniel Zhang, Jay Dorsey, Stefan Prokop

Introduction

Glioblastoma remains invariably lethal due to its aggressive and invasive nature. It is increasingly appreciated that molecular heterogeneity between tumors and within tumors likely contributes to lack of treatment advances.

Objectives

To characterize and test glioblastoma organoids for patient-specific treatment responses.

Methods

To maintain the inherent heterogeneity of glioblastoma, we employed a novel method to rapidly culture glioblastoma organoids (GBOs) directly from neurosurgical resection. To minimize selection bias, cultures were generated from fresh glioblastoma tissue in media free of serum, exogenous EGF/FGF, and matrigel. Histologic and sequencing analyses assessed similarity to primary tumors. Leveraging clinical sequencing data, selected GBOs were treated with radiation/temozolamide, targeted inhibitors, and CAR-T immunotherapy.

Results

Rounded GBOs form within 2 weeks and maintain similarity to the primary tumor by histology and sequencing. Radiation/temozolamide treatment led to a decrease in the percentage of KI67+ cells in select tumors with some evidence of correlative radiographic response. GBO response to gefitinib treatment was specific to EGFR altered tumors. Two GBOs had downstream NF1 mutated that responded to MEK

inhibition. One GBO line was found to have a PI3K mutation and responded dramatically to mTOR inhibition. One tumor with EGFRviii expression was treated with CAR-T immunotherapy. Two weeks following initial CAR-T exposure, we observed antigen loss and decreased KI67+ cells, which was attenuated by dexamethasone.

Conclusion

This novel culturing method of GBOs maintains intertumoral and intratumoral heterogeneity for therapeutic testing. As clinical sequencing because increasingly prevalent, GBOs may become a valuable tool to functionally test mutation-specific treatment strategies in a rapid and patient-specific manner.

10:30-10:45 Break

10:45-11:55 Peer Reviewed Abstract Session X: Various topics
Moderators: Michael McDermott / Aviva Abosch

10:45 - 10:55 Outcomes from Asleep and Awake Dominant Temporal Lobe Glioma Surgery: Risk, Extent of Resection, and Survival

Jacob Young, Philip Theodosopoulos, Shawn Hervey-Jumper, **Michael McDermott**, Mitchel Berger, Edward Chang, Manish Aghi, Caleb Rutledge

Introduction

Awake speech language mapping is a recognized standard for safely removing dominant hemisphere gliomas, although it requires an experienced, multidisciplinary team. We sought to compare the outcomes for asleep versus awake dominant temporal lobe glioma surgery to determine if there are instances where asleep surgery yielded comparable outcomes to awake surgery.

Objectives

To evaluate risk and outcomes with 2 approaches to craniotomy in the dominant temporal lobe.

Methods

The electronic medical record of patients with pathologically proven newly diagnosed left temporal lobe glioblastomas who underwent resection at UCSF between 2005-2018 were retrospectively reviewed.

Results

117 patients with mean age of 57.4 years (range 15 – 79 years) were included. 63 patients underwent asleep craniotomy (63.5% had pre-operative language deficit) and 54 patients underwent awake craniotomy (83.3% had pre-operative language deficit). At 6 months, only 3.7% of patients who underwent awake craniotomy had a persistent language deficit compared to 15.9% of patients who underwent asleep craniotomy (p = 0.02). Patients with have awake operations are more likely to get discharged to home (96% vs 75%, p = 0.001), had a shorter length of stay (4.2 days vs 7.1 days, p < 0.001), and more commonly a gross total resection was achieved (53.7% vs. 30.2%, p = 0.01), and had longer overall survival (median 1.78 years vs 1.10 years, p = 0.03).

Conclusion

Awake craniotomy resulted in fewer persistent language deficits than patients who underwent asleep craniotomy. Patients who underwent awake craniotomy had higher rates of gross total resection, were more like to be discharged to home, and had longer overall survival.

10:55-11:05 Real-time CED of Nanoliposomal CPT-11 for recurrent GBM: Interim results of a phase I clinical trial

John Bringas, Jennifer Clarke, Krystof Bankiewicz, Jesus Eduardo Rodriguez Almaraz, Nicholas Butowski, Alastair Martin, Susan Chang, **Manish Aghi**, Nancy Ann Oberheim Bush, Karishma Kumar, Jennie Taylor

Introduction

Chemotherapy for high-grade gliomas (HGGs) is limited by the blood-brain-barrier and systemic toxicity. Convection enhanced delivery (CED) of chemotherapy addresses these challenges via continuous, low–positive-pressure intratumoral bulk flow.

Objectives

Based on encouraging preclinical data, we launched a phase I clinical trial (Clinicaltrials.gov NCT02022644) of real-time CED of liposomal-irinotecan (Onivyde) in recurrent HGG patients. An advance of this trial is real-time CED, in which MRI continuously visualizes CED in real-time by co-convecting gadolinium to monitor intratumoral delivery, enabling corrective catheter repositioning.

Methods

This 3x3 dose-escalation trial uses 20 and 40 mg/mL Onivyde. Onivyde and gadolinium were co-infused via the same catheters in one-time delivery at rates up to 50 µL/min. Infusate volume and dose were personalized to tumor volume, ranging from 20-680 mg Onivyde via up to four 14G catheters with 10-15 mm tips. Tumor diameters of 1–4 cm and infused volumes of 2–17 mL were allowed.

Results

Thirteen recurrent HGG patients with tumor volumes=0.8-9.3 cm³ (mean=3.9 cm³) have been treated to date, with 1-4 hour infusion times (mean=1.8 hours). Eight of 10 patients with sufficient post-treatment time lived over a year post-treatment, which is encouraging since median survival for recurrent HGG is 9 months. Utilizing imaging software, we correlated pre-infusion modeling of drug distribution with post-infusion imaging. CED ensured that the volume of distribution (V_d) to volume infused (V_i) ratio averaged 1.7 (range=0.3-3.5), while real-time imaging enabled 49% average tumor coverage (range=23.8%-91.1%).

Conclusion

Image-guided distribution allows for safe real-time CED of Onivyde into recurrent HGG. Real-time CED maximizes tumor coverage and warrants further studies with repeat dosing.

11:05-11:15 Leptomeningeal dissemination, a sinister pattern of medulloblastoma growth

Livia Garzia, Michael Taylor, **Daniel Fults**

Introduction

Leptomeningeal dissemination (LMD) is the defining pattern of metastasis for medulloblastoma. The fact that medulloblastomas rarely metastasize outside the central nervous system but rather almost exclusively to the spinal and intracranial leptomeninges has fostered the long-held belief that medulloblastoma cells spread directly through the cerebrospinal fluid (CSF). Recent experimental evidence reveals an alternative scheme in which medulloblastoma cells can enter the bloodstream and subsequently home to the leptomeninges.

Objectives

We sought to build a conceptual model to visualize the cellular events in dispersal of medulloblastoma cells through the CSF, analogous to the invasion-metastasis cascade of hematogenous metastasis of carcinomas.

Methods

We reviewed selected molecules for which current experimental evidence is strong enough to explain how the physiological effects of these molecules contribute mechanistically to LMD. We assigned the molecules to three stages of the LMD cascade: initiation, dispersal, and colonization.

Results

The LMD cascade is based on the molecular themes that (1) transcription factors launch cell programs that mediate cell motility and invasiveness and maintain tumor cells in a stem-like state, (2) disseminating medulloblastoma cells escape multiple death threats by subverting apoptosis, and (3) inflammatory cytokine signaling promotes LMD by creating an oncogenic microenvironment.

Conclusion

Although LMD is responsible for virtually 100% of medulloblastoma deaths, it remains the least understood part of medulloblastoma pathogenesis. The LMD cascade can serve as a framework for organizing our thinking about LMD as new molecular mediators of LMD are discovered in the future.

11:15-11:25 Characteristics of Clots Retrieved by Mechanical Thrombectomy Associated with Stroke Etiology and Device Performance

Vincent Tutino, Matthew McPheeters, Muhammad Waqas, John Tomaszewski, Kenneth Snyder, Shashiprakash Avinash, **Adnan Siddiqui**, Michael Tso, Hui Meng, Elad Levy, Kunal Vakharia, Pinaki Sarder

Introduction

The introduction of mechanical thrombectomy (MT) devices for the treatment of acute ischemic stroke enabled the extraction and analysis of human clots. Histological structure and molecular composition of the retrieved clot material may provide information about underlying stroke pathology, and could be biomarkers to diagnose cryptogenic strokes.

Objective

Our objective was to investigate associations between the histology and biology of retrieved clots, and stroke etiology, efficacy of MT, and recanalization outcomes.

Methods

Clot samples from 50 stroke patients with large-vessel occlusion were collected during MT recanalization into tubes of either 10% phosphate-buffered formalin (for histology) or RNALater (for gene expression analysis). H&E-stained specimens were quantitatively analyzed to determine relative fractions of red blood cells, white blood cells, and fibrin/platelet aggregates. Extracted clot RNA was subjected to next-generation RNA sequencing on the NovaSeq platform (Illumina). Clinical and interventional parameters, as well as stroke subtype by TOAST criteria were also collected.

Results

Cardioembolic thrombi had significantly higher proportions of fibrin/platelet aggregates, significantly less erythrocytes, and more leukocytes than large artery atherosclerosis thrombi. The number of passes to achieve recanalization was significantly higher in clot samples that were fibrin/platelet-rich. Clot composition was not correlated with change in (delta) NIHSS and reperfusion outcomes defined by the TICI score. RNA sequencing analysis for biological study of the clots is still underway.

Conclusion

Quantitative evaluation of clot composition may help to distinguish between different stroke subtypes. Clot composition may play a role in successful recanalization by MT devices.

11:25-11:35 Integration of 5-ALA and CEUS in the Surgical Resection of High Grade Glioma

Giuseppe M. Della Pepa, **Alessandro Olivi**

Introduction

Survival benefit in maximizing resection in high grade gliomas (HGG) has been demonstrated by numerous studies. The infiltrative nature of HGG has been an overwhelming obstacle and several technological advances (some of them quite expensive such as iMRI or iCT) have been introduced to identify residual neoplastic tissue.

Objectives

This study evaluates the role of the integration of the use of 5-aminolevulinic acid (5-ALA) with microbubbles contrast enhancement ultrasound (CEUS) in the identification of residual neoplastic disease and the related impact on the extent of resection (EOR), progression free survival (PFS) and overall survival (OS)

Methods

270 HGG procedures were retrospectively studied. Cases were stratified according to the surgical procedures into four groups: 5-ALA + CEUS guided surgeries, 5-ALA guided surgeries, CEUS guided surgeries and conventional microsurgical procedures.

Results

Patients undergoing conventional microsurgical procedures displayed worse EORs when compared to those operated with the assisted techniques (5-ALA and CEUS procedures). Both 5-ALA and CEUS techniques improved the EOR with respect to standard microsurgical procedures. However, it is their association which yielded the best results in terms of EOR. Median EOR percentage and the number of supramarginal resections were therefore superior in the 5-ALA+CEUS group compared with the others. This was found to have demonstrated positive repercussions on PFS and OS in our series.

Conclusion

In terms of EOR, best results can be achieved through a combination of both techniques (5-ALA + CEUS). Compared with other intraoperative imaging techniques, this approach is a real-time, reproduceable, relatively inexpensive technique which ultimately can improve the outcome of our patients.

11:35-11:45 Mesenchymal Stem Cell Delivery of Oncolytic Adenovirus Delta-24-RGD Following Surgical Resection of Glioblastoma
--

Sricharan Gopakumar, Shawn Hingtgen, **Frederick Lang**, Joy Gumin, Matthew Ewend

Introduction

The oncolytic virus Delta-24-RGD is a novel treatment of GBM. Prior studies have examined intratumoral injection of “naked” Delta-24-RGD into unresected recurrent GBM, and an ongoing clinical trial is examining the potential of using human Mesenchymal Stem Cells (hMSCs) to deliver Delta-24-RGD endovascularly. However, the ideal delivery strategy of Delta-24-RGD after surgical resection of newly diagnosed GBM is not defined.

Objectives

To address this clinical problem, we undertook a series of translational experiments to determine the efficacy of delivering hMSCs loaded with Delta-24-RGD (hMSC-D24) into the surgical resection cavity using a fibrin-scaffold.

Methods

For in vitro studies, MSCs-D24 were seeded in a fibrin scaffold or in PBS in the upper wells of transwell plates with U87 placed below, and U87 viability was determined after 7 days. For in vivo studies, mCherry-Luciferase-U87 was implanted into the brains of athymic mice (N=16). After fluorescence-guided surgical resection, hMSCs (control) or hMSCs-D24 were delivered into the resection cavity using a fibrin scaffold. Tumor recurrence was assayed by Bioluminescence Imaging.

Results

In transwell experiments, hMSCs-D24 in fibrin were as effective as hMSCs-D24 alone in killing U87 cells. In in vivo studies, treatment of the post-resection cavity with hMSCs-D24 suspended in fibrin resulted in sustained retention of hMSCs-D24 within the tumor bed, and in statistically significant improved survival compared with controls, with 50% of animals demonstrating complete tumor eradication ($p < 0.05$).

Conclusion

Delivering DNX-2401 into the post-resection surgical cavity using hMSCs seeded in a fibrin-scaffold is capable of eradicating residual GBM. These studies support the clinical translation of this approach to surgically resected newly-diagnosed GBM.

11:45-11:55 An Epigenetic Liquid Biopsy Machine Learning Algorithm to Predict Glioma and Glioma Subtypes

Steven Kalkanis

Introduction

In patients with newly diagnosed intracerebral lesions based on MRI, gliomas are often suspected, but other conditions are possible. Biopsy can be challenging due to eloquent and/or deep location. In this prospective, blinded study, analysis of plasma isolated cell-free DNA and exosome mRNA and miRNA from glioma patients and cancer-free volunteers was used to predict disease.

Objectives

Results were then used to develop a machine learning algorithm to predict glioma progression and response to therapy based on epigenetic biomarkers.

Methods

Plasma was drawn from 52 newly-diagnosed glioma patients (28 high grade, 10 low grade) and 14 healthy volunteers. DNA and RNA were sequenced using Next Generation Sequencing, and Digital Droplet PCR was used for detection of trace molecular artefacts. Multianalyte processing yielded data that was harmonized and interpreted through an Artificial Intelligence based algorithm to assess for glioma while assigning grade. EGFRvIII, TP53 and IDH1 mutations were also analyzed and compared to tumor specimen molecular testing.

Results

96% (27 of 28) of high grade glioma patients were deemed to have gliomas by plasma testing. 82% of low grade patients were correctly graded. Of 10 healthy controls, 8 were deemed cancer-free. Two patients were suspicious for malignancy. IDH1, TP53 and EGFRviii and mutation had concordance at 84 %, 82% and 75%, respectively.

Conclusion

Machine learning genetic analysis was highly sensitive for detecting glioma and grade. Further testing will follow, with the goal of using this modality to assess response to therapy and direct patients to appropriate clinical trials. Prognostic epigenetic liquid biopsies could also be used for monitoring during active treatment.

12:00 Closing Remarks Meeting Adjourn
2020 Scientific Chair - Aviva Abosch

Immediately following Adjournment, Lamberto Frescobaldi will host a wine tasting entitled “*A Journey Through Tuscany*”