Poster #1

Application of Phage Mediated Immuno-PCR for Extracellular Vesicles as Biomarkers for Glioblastoma

Fultz M, Graner M, Zhou W, Yu X

Abstract.
Glioblastoma multiforme (GBM) is the most common yet most lethal type of malignant brain tumor. Studies of malignant tumor tissue identified the excessive release of extracellular vesicles (EVs), responsible for cellular communication in the tumor microenvironment. We previously identified 21 high-affinity phage peptides (12-mer & 7-mer) specific to GBM EVs by screening phage-displayed random peptide libraries. We showed these peptides inhibit GBM EV-induced neuronal cytotoxicity (Zhou et al., 2022). We aimed to develop a phage-mediated real-time immuno-PCR to detect GBM plasma EVs as novel biomarkers for early diagnosis of GBM. Phage IPCR takes advantage of the unique feature of physical association between phenotype (the displayed peptide) and genotype (the encoding DNA). Preliminary data showed that by phage PCR, over 12 times higher binding of GBM primary tumor cell line EVs (F3-8) with phage peptide B4 compared to control. This highly sensitive and specific technique may provide novel tools for identifying early GBM EV biomarkers for effective treatment strategies.

Poster #2

Abstract

Kennan Kushner

The prevalence of active epilepsy is 6.38 per 1,000 persons with 30% of epileptic patients becoming resistant to treatment with AEDs and therefore, may undergo resective surgery. Despite the prevalence of drug-resistant epilepsies, the underlying mechanisms of epileptogenesis remain obscured. Here, we used 4- aminopyridine (4-AP), a voltage-gated potassium channel blocker that is commonly used to induce seizure-like activity in *ex vivo* brain slices, to determine the underlying mechanism of the oscillations they induce. To do this, we wash on 4-AP while performing whole-cell patch clamp electrophysiology on L2/3 pyramidal neurons (PNs) from epileptic and tumor control brain tissue. We are the first to report 4-AP induced synchronized neuronal bursting and synchronized, slow hyperpolarizing oscillations (HypOs) by recording pairs of epileptic L2/3 PNs. We also determined that 4-AP induced HypOs are potassium currents and these were not mediated by $GABA_{A}/_{B}$ receptors, NMDA receptors or AMPA receptors, or NKCC1 and KCC2 channels. Instead, HypOs were dependent on network activity (blocked by TTX, Cd^{2+} and Ni^{2+}) and partially mediated by gap junctions (niflumic acid, meclofenamic acid and carbenoxolone). Interestingly, HypOs could also be eliminated by activation, but not inactivation, of Kv7.2- Kv7.5 (KCNQ) channels and were reduced via internal calcium chelation with BAPTA salt suggesting a role for calcium in KCNQ channel activation. Our results suggest 4-AP induced HypOs are due to GABAergic interneuron synchronization that leads to potassium fluctuation without the need for GABA neurotransmission and that KCNQ channel activation can help stabilize potassium fluctuations resulting in cessation of ictal and interictal events dictated by GABAergic interneurons.

Poster #3

Title: Intrathecal Baclofen Test Dose followed by Observational Gait Video Analysis for Determining Selective Dorsal Rhizotomy versus Baclofen Pump in Borderline Ambulatory Patients with Spasticity

Authors: Megan V Ryan, Kim Sawyer, James Carrolo, Julia Pazniokas, Rasha Elbadry, Joyce Oleszek, Corbett Wilkinson

Introduction:

Treatment for intractable lower extremity spasticity often involves selective dorsal rhizotomy (SDR) or baclofen pump implantation. A crucial difference is that while the pump rate can be adjusted if ambulation is affected post-implantation, loss of ambulation due to hypotonia after SDR may be irreversible. This study explores the utility of intrathecal baclofen (ITB) test dose combined with video gait analysis in patients with borderline walking ability to discern candidacy for SDR or ITB therapy.

Materials and Methods:

We reviewed the records of all patients aged 2-to-18 years who completed an ITB test dose and subsequent video gait analysis from 2008 through 2022. We documented the age of the patient, diagnosis, whether testing was helpful in deciding between surgeries, the type of surgery (SDR versus pump) and any complications of testing or surgery.

Results:

The average age at testing was 9.7 years (median age was 10 years). Nine patients had cerebral palsy. Testing was helpful in twelve cases and not helpful in one. Five patients underwent SDR, three underwent baclofen pump implantation, and five so far have undergone neither surgery. Tone was improved in all eight patients who underwent surgery. One patient (8%) had a temporary post-testing spinal headache and one patient (20%) who underwent SDR developed worsened ability to ambulate.

Conclusion:

ITB test dose followed by observational video gait analysis can be helpful in determining whether borderline ambulatory patients are candidates for SDR versus ITB therapy.

Poster #4

EFFECT OF COVID-19 ON LOCUS COERULEUS PATHOLOGY IN INDIVIDUALS WITH DOWN SYNDROME

AUTHORS: Campbell Pontin[1], Elizabeth Head[2], Eric Hamlett[3], Elisabet Englund[4], Elliott Mufson[5], Sylvia Perez[5] and Ann-Charlotte Granholm[1]

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INTRODUCTION. Individuals with Down Syndrome (DS), caused by a triplication of chromosome 21, have a ten times higher risk of death from COVID-19 compared to the general population. People with DS are at higher risk for Alzheimer's Disease (AD), yet research into the result of COVID-19 infection on AD-related neuropathology is limited. Here, we examined the effect that the SARS-COV-2 virus has upon the noradrenergic neurons of the locus coeruleus (LC) that display early Tau pathology in AD.

METHODS. Post-mortem LC tissue from people with DS who died from COVID, DS controls, DS-AD, AD only, AD-COVID, COVID only, and controls with neither AD nor COVID was obtained from the DSBC brain bank consortium. LC sections were stained using antibodies directed against tyrosine hydroxylase (TH), the rate-limiting enzyme for norepinephrine production, to examine neuropathological differences between groups.

RESULTS. Overall, reduced TH immunoreactivity was noted in the LC of DS-COVID compared to DS controls. Although TH positive neurites were observed in DS controls, similar profiles were not seen in DS-COVID cases. Less TH staining was found in both DS groups compared to AD-COVID, COVID and normal controls.

CONCLUSIONS. Preliminary data suggest that DS-COVID cases display greater damage to the LC compared to other groups, which may exacerbate AD-related symptoms. Further studies are planned to differentiate the effect of infection on tau pathology in the LC, between DS and AD cases.

FUNDING SUPPORT. *This work was supported by NIH grants R01AG070153, RO1AG061566, RFAG081286 and a BrightFocus Foundation grant CA2018010*.

Eric Bayman **Poster #5**

Subthalamic nucleus synchronization between beta band local field potential and single-unit activity in Parkinson's disease

Local Field Potential (LFP) oscillations in the beta band (13-30 Hz) in the subthalamic nucleus (STN) of Parkinson's disease patients have been implicated in disease severity and treatment response. The relationship between single-neuron activity in the STN and regional beta power changes remains unclear. We used a spike-triggered average (STA) to assess beta synchronization in STN. Beta power and STA magnitude at the beta frequency range were compared in three conditions: STN versus other subcortical structures, dorsal versus ventral STN, and high versus low beta power STN recordings. Magnitude of STA-LFP was greater within the STN compared to extra-STN structures along the trajectory path, despite no difference in percentage of the total power. Within the STN, there was a higher percent beta power in dorsal compared to ventral STN but no difference in STA-LFP magnitude. Further refining the comparison to high versus low beta peak power recordings inside the STN to evaluate if single-unit activity synchronized more strongly with beta band activity in areas of high beta power resulted in a significantly higher STA magnitude for areas of high beta power. Overall, these results suggest that STN single units strongly synchronize to beta activity, particularly units in areas of high beta power.

Poster #6

The Bigger Picture, Elucidating the Mechanisms of Down Syndrome related Alzheimer's Disease with Spatial Transcriptomics

Jeremiah Phares[1*], Ken Jones[2,3], Elizabeth Head[4], Eric Hamlett[5], Elliot Mufson[6], Ann-Charlotte Granholm[1], and Samuel J. Guzman[7]

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Introduction: Spatial transcriptomics (ST) is an emerging technology which provides a bigger picture of complex biological systems. Traditional methods, such as bulk RNA seq, have enabled us to examine transcription level changes of a cell (or multiple cells), but these methods lack systemic context. ST provides a novel way of viewing the distribution of mRNA transcripts with a detailed spatial resolution. Although this methodology provides insight into complex brain disorders such as Alzheimer's disease (AD), its application to individuals with Down's syndrome (DS), of which 40-80% develop AD-like pathology in their 30s-50s and then dementia.

Methods: We applied ST to postmortem paraffin embedded brain tissue. We used RNA extraction to determine the quality of RNA. 5-micron sections were then processed using the 10X Genomics Visium Spatial Gene Expression platform and sequenced using Illumina NovaSeq 6000. Following data acquisition, AI-driven meta-analysis was performed by the Bioinformatics Core at CU. We have currently sequenced and generated ST profiles from individuals with epilepsy, AD, DS and DS related AD.

Results/Conclusions: Our findings revealed novel pathways and cell populations within brain regions that provide a foundation for potential drug targets and other therapeutic alternatives. These data will be mined to create an expression driven database with translation to the clinic. Data can be validated using immunohistochemistry, single cell RNAseq and proteomic analysis. Pathways related to traditional AD-related protein aggregation and inflammation were altered in the DS and DS-AD brain, compared to findings previously obtained from AD cases.

Funding: *This work was supported by NIH grants R01AG070153, R01AG061566 and RF1AG081286 and a BrightFocus Foundation grant CA2018010.*

Poster #7

Glenn Kindt Research Symposium Abstract
Principal Investigator: Allyson Alexander
Presenter: Paige Hoffman

Assessing the Cause of Epileptogenesis in FCD and Similar MCDs by Tracking Neuronal Migration, Density, and Projections

Paige Hoffman B.S., Allyson Alexander M.D., Ph.D.

Malformations of Cortical Development (MCD) are neurodevelopmental disorders where the lamination in the cortex is altered during the formation of the brain. While the exact causes of MCD are unknown, it is suspected that during the first two months in-utero certain neurons fail to migrate properly, are incorrectly sequenced, or present with abnormal features. In addition to this, MCD causes irregular electrical activity and as a result causes epileptic seizures.

Epilepsy is typically more prominent in children, which can increase chances of premature mortality by 14-fold. In the Alexander lab, we focus on understanding whether epileptogenesis could be coming from a decrease in inhibitory cortical interneurons or an increase in excitatory cortical cells by investigating the connection between interneuron pathology and morphogenesis and the generation of severe seizures. In my most recent research, I have found that (1) the deficit in migration occurs between E18 and P2 in mice (roughly third trimester in humans), (2) migration in adjacent cells and interneurons is normal at all ages and through all layers, (3) dyslaminated cells express markers for the layer they were destined for, (4) epilepsy stemming from dyslamination, which is brought on by MCDs, is responsible for a decrease in cortical interneurons, and (5) mice with FCD have increased axonal proliferation. This suggests a dramatic loss of interneurons in the cortex of mice with FCD that doesn't stem from the MCD or neurodevelopmental disorder itself. Rather, the disorder with upregulated Rheb caused cortical dyslamination, which caused epileptogenesis, and the epilepsy was responsible for interneuron loss. However, in this case, the structures immediately surrounding the areas of cell loss remained unaffected and the increased axonal proliferation from dyslaminated cells may be aiding in the spreading and severity of seizures.

Poster #8

The APOE4 allele is involved in extracellular vesicle-dependent neurodegeneration in Alzheimer's disease and Down syndrome

Anne Vielle[1,3], Breanna Dooling[2,3], Daphne Quang[2,3], Noah R. Johnson[2,3], Aurélie Ledreux[1,3]

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People with Down syndrome (DS) develop Alzheimer's disease (AD) decades earlier than the general population. Among genetic factors known to increase the risk for AD, carriers of the apolipoprotein E ε4 allele(s) (APOE4) are up to 12-fold more susceptible of developing cognitive impairment. The ApoE4 protein impacts the endosomal-lysosomal pathway leading to a downregulation of extracellular vesicle (EV) biogenesis and release by the cells. In typical AD and DS-associated AD, EVs are implicated in neurodegeneration by spreading toxic amyloid-beta and phosphorylated tau proteins from cell to cell. While it is known that the APOE4 allele accelerates the development of AD in individuals with DS, it is unclear how APOE4 exacerbates the AD pathology in the brain.

To understand how different ApoE alleles impact EV biogenesis and function, we propose to analyze EVs released by ApoE3 and ApoE4 isogenic cerebral organoids (CO) derived from euploid and trisomic pluripotent stem cell lines. Our preliminary results indicate that trisomic COs produce and release EVs and that ApoE4 COs release EVs in smaller numbers and that these EVs exhibit a unique composition of surface markers when compared to ApoE3 EVs. Finally, we assessed AD biomarkers in our ApoE CO models and identify changes in misfolded protein content.

Overall, our results suggest that ApoE is an important modifier of EV release and trafficking in the brain. In the context of DS, our data point to a significant role of EVs in the spread of AD neuropathology.

Poster #9

Title: Biomarkers in CNS-derived extracellular vesicles to assess repeated subconcussive impacts in college athletes

Authors: Anah Gilmore[1], Anne Vielle[1], Camille Trautman[2], Ann-Charlotte Granholm[1], Kim Gorgens[3], Susan Minglis[4], and Aurélie Ledreux[1]

Affiliations: [1]Department of Neurosurgery, University of Colorado Anschutz Medical Campus, Aurora, CO, [2]Department of Neuroscience and Behavioral Biology, Emory University, Atlanta, GA, [3]Graduate School of Professional Psychology, University of Denver, Denver, CO, [4]Department of Mechanical and Materials Engineering, University of Denver, Denver, CO

Repeated concussions or mild traumatic brain injuries (mTBIs) in athletes may increase risk for neurodegenerative conditions, such as chronic traumatic encephalopathy (CTE) and Alzheimer's Disease (AD). While recent research has focused on sport-related repeated mTBIs, less research has been done on the consequences of sport-related repeated subconcusssive head impacts (RSHIs) on long-term brain health. In this study, a cohort of collegiate athletes had blood samples taken during their pre-season enrollment exams. Demographic information for enrolled athletes was also collected, including age, sex, and previous history of mTBI. Athletes who participated in sports where RSHIs are more common, such as soccer and lacrosse, were compared to control athletes, those who participated in sports such as basketball and tennis, where RSHIs are less common. A third cohort of athletes, those that had recently suffered an acute mTBI, were also used in this study. Neuron-derived small extracellular vesicles (NDEVs) were isolated from serum samples, and biomarkers previously explored in repeated mTBI cohorts were examined, including neurofilament light (NFL), glial fibrillary action protein (GFAP), ubiquitin C-terminal hydrolase L1 (UCH-L1), total tau, and phosphorylated tau (T231). The goal of this study is to explore biomarker trends in athletes in sports that are prone to RSHIs and to compare if any trends seen are similar to biomarker levels seen in athletes with a history of repeated mTBIs and acute mTBIs.

Poster #10

Title: The Potential Use of Senolytics in the Treatment of Adamantinomatous Craniopharyngioma

Authors: Stephen L Medlin MS, Todd C Hankinson MD
Institution: University of Colorado – Anschutz Medical Campus; Children's Hospital of Colorado

Abstract:

Objective:
Adamantinomatous Craniopharyngioma (ACP) is a neurologically devastating pediatric brain tumor that is associated with the lowest quality of life scores of any pediatric brain tumor. Standard therapy for ACP includes maximal safe surgical resection +/- adjuvant radiation and has not changed significantly in 50 years. The goal of the project was to determine if the addition of the senolytic navitoclax, could be an effective treatment in combination with binimetnib.
Material and Methods:
Using ACP tumor tissue obtained at surgery, we isolated and cultured ACP fibroblast and epithelial cells. Epithelial cell immortalization was achieved using SV40 lentiviral transfection and puromycin selection. Using patient derived epithelial cells, we first treated cells with single drug doses of navitoclax and binimetinib. We then treated the same cell line with varying combinations of both drugs. Cell proliferation was measured using the CCK8 cell proliferation assay by Abcam. Western blots will be used to confirm inhibition of MEK through binimetinib, and the inhibition of BCL-2/BCL-XL through navitoclax.
Results:
We observed ACP cells had a relevant sensitivity to navitoclax as a single drug. In contrary, we observed a resistance to binimetinib as a single drug dose. In combination, these drugs had a positive synergy score at low doses.
Conclusions:
A significant proliferation response was observed when navitoclax and binimetinib were used in combination. We believe that these drugs could be beneficial to use in combination clinically.

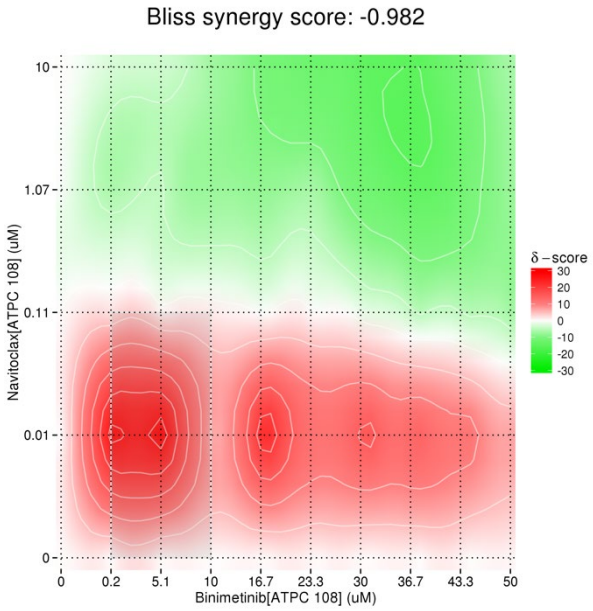

Figure 1. Bliss synergy score for navitoclax and binimetinib combination treatments on ATPC 108 epithelial ACP cells.

Poster #11

Lisa Hirt

Title: Quantifying loss aversion electrophysiology in the amygdala

Loss aversion, overweighting negative outcomes over positive ones when the options have equal weights, contributes to maladaptive thinking and has links to mental health disorders, but is employed in everyday life. The majority of loss aversion research has been conducted via fMRI and indicates that the amygdala may be driving loss aversion behavior. Intracranial recordings from human amygdala, which offer greater spatial and temporal resolution, may elucidate the amygdala's role in the magnitude of expression and timing of loss averse behavior.

Participants (N = 2) undergoing stereotactic EEG completed a validated gambling task that measures loss aversion behavior. A highly conservative co-registration process was utilized to localize electrodes within the amygdala. Amygdala voltages were band passed filtered, artifact rejected, bipolar refrenced, and analyzed to investigate if there was a difference in amplitude when the participant was shown if they won or lost a gamble.

A one-way ANOVA indicated no significant difference in amygdala activity during the outcome between wins or loses across participants (p = 0.5). When money values were incorporated into a Spearman's correlation, this indicated a significant correlation between money value lost and amygdala amplitude when participants saw they lost the gamble (p = 0.01). T-Tests between participants showed a significant difference between the two participant's overall amplitudes (p = 0.003), which may be related to their loss aversion scores.

Amygdala local field potential (LFP) modulation corresponds to periods of loss-averse related decision-making. Further research is needed to clarify how loss aversion behavior and amygdala electrophysiology are related.

Johnathan Platt **Poster #12**

Subthalamic Nucleus Response in Parkinson's Disease Between Movement Initiation and Cue After Holding During a Center-Out-Task

Introduction

Continuous deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) improves motor symptoms. Recent advances in sensing of brain signals could be used to provide adaptive stimulation during movement events, however few studies have explored the relationship between naturalistic movements and STN local field potentials (LFP).

Objectives

We quantified changes in LFP 3-150 Hz during DBS placement while subjects engaged in a center out task which elicited naturalistic reaches to radial targets.

Methods

The subject's index finger was tracked post-hoc using markerless deep learning tools. We used STN-LFP power to characterize shifts between movement initiation and when a cue is given after holding.

Results

In n = 5 PD subjects undergoing DBS, we collected LFP when a cue is shown during holding (N=91) and during movement initiation (N=95). Beta power showed a significant decrease when movement started compared to holding before a cue ($p = 1.7\ e^{-8}$). Gamma power, however, was not shown to significantly increase ($p = 0.236$). When looking at the narrow band of low gamma 31-60 Hz a significant increase in power was observed ($p = 0.0026$). Suggesting that each stage when moving has a unique frequency band which can lead to targeted therapy when a specific event occurs.

Conclusions

Having a narrow band outside of beta that contributes to the initiation of movement provides a marker that can aid in providing adaptive DBS and optimizing STN target location outside of the frequencies affected by standard therapy to mitigate PD symptoms.

Poster #13

Two-Photon GRIN Microendoscope for Stereotactic Neurosurgery

Skylar Suarez

During Deep Brain Stimulation (DBS) surgery for Parkinson's Disease (PD), it is critically important to accurately place the electrodes within specific deep brain targets, such as the subthalamic nucleus (STN). Current methods of evaluating electrode position in the operating room include: 1) micro-electrode recordings, which increase the risk of intracranial hemorrhage and often require the patient to be awake during invasive brain surgery, and 2) intraoperative imaging, which has a limited resolution. **We propose using two-photon micro-endoscopy to perform high resolution, real-time imaging along the surgical trajectory** through a narrow stereotactic cannula to assist with neuronavigation and detect blood vessels using Second Harmonic Generation (SHG). Here we show that conventional, two-photon microscopy and several rudimentary image classifiers can be used to distinguish the human STN from the surrounding tissue due to the spatial distribution of autofluorescence. **We also develop a 186 mm long and 1.2 mm diameter microendoscope composed of a series of Gradient Refractive Index (GRIN) lenses.** This device has a magnification of ~2.8X, a field of view of ~180 microns, and a resolution of 0.86 microns and 9.6 microns in the lateral and axial directions, respectively. The prototype was used to image endogenous autofluorescence and blood vessels in ex-vivo human brain tissue. **We also report on our progress towards a next generation prototype.**

Poster #14

Position of the Superior Sagittal Sinus in Pediatric Unilateral Sphenofrontal Craniosynostosis

Blasco, Sophia, Wilkinson, Charles Corbett

Department of Neurosurgery, University of Colorado Anschutz Medical Campus

Previous reports have shown that the superior sagittal sinus (SSS) may not directly underly the sagittal suture (SS) in unicoronal craniosynostosis. No equivalent literature relates the relative positions of the SSS and SS in unilateral lambdoid or sphenofrontal synostosis. Knowledge of this relationship is invaluable for surgical planning. We conducted a retrospective review of cases with sphenofrontal synostosis to quantify this relationship. We reviewed all cases of unilateral sphenofrontal synostosis treated at the craniofacial center at Children's Hospital Colorado between December 2008 and January 2023. All cases included preoperative CT scans. On each CT, I measured the distance between the SSS and SS at the bregma (immediately behind the anterior fontanelle), the lambda (the SSS terminus), and every 2 cm between the bregma and the lambda. I analyzed four male patients with unilateral sphenofrontal synostosis and two age-matched male controls for each patient. In controls, the sagittal suture is a good approximation for the location of the middle SSS. In unilateral sphenofrontal craniosynostosis cases, the mid-sinus distances from the SS were greater than those of the controls on average. However, this deviation is not clinically significant. Identifying any SSS deviation is essential to prevent injury of the SSS when planning craniofacial surgery in children with unilateral sphenofrontal craniosynostosis. This study suggests there is no significant deviation from the suture to the SSS in sphenofrontal craniosynostosis.

Poster #15

Authors

Andrew Mecum BA
Lindsey Freeman MD MA
Peter Lennarson MD

Abstract/Poster Title:

Sensitivity of the modified Brain Injury Guidelines (mBIG): a 3.5-year Retrospective Review at a Level I Trauma Center

Introduction: The modified brain injury guidelines (mBIG) have been determined safe, but statistical analysis has been limited to lower severity mBIG 1 and 2 populations.

Objective: To determine the sensitivity of mBIG criteria in need for neurosurgical intervention, and to evaluate associations between individual mBIG 3 radiographic criteria and need for intervention.

Methods: All head trauma patients presenting to a Level I Trauma Center from May 2020 to December 2023. Patients without intracranial hemorrhage on first CT Head and those who underwent intervention at an outside hospital were excluded. Patients were sorted based on previously published mBIG criteria.

Results: 1,128 patients with mean age 54.9 (± 21.2) years and 67.7% male were included. Most patients were mBIG 3 (69.7%). 97 patients (8.6%), all mBIG 3, received intervention after initial CT. An additional 113 patients (10.0%) underwent intervention after some period of observation and at least one repeat CT, of which 112 were mBIG 3, and one was mBIG 2 (0.6% of mBIG 2 patients, 0.5% of those requiring intervention, and 0.09% of entire study population). mBIG 3 criteria are 99.5% sensitive for need for neurosurgical intervention. mBIG 2+3 criteria are 100.0% sensitive. In post hoc multivariate analysis of mBIG 3 patients with GCS scores 13-15, significant associations were found between each specific mBIG 3 radiographic criterion and intervention, except for intraparenchymal hemorrhage (IPH) ($p = 0.205$) and subarachnoid hemorrhage (SAH) ($p = 0.274$).

Conclusions: mBIG 3 criteria are 99.5% sensitive for need for neurosurgical intervention. Criteria requiring hospital admission (mBIG 2-3) have a sensitivity of 100.0%. Radiographic mBIG 3 criteria for IPH and SAH alone are poor predictors for need for neurosurgical intervention in patients with favorable neurological status.

Tables

Table. Demographics and repeat neuroimaging data total in cohort and by mBIG

	mBIG 1 N = 166	mBIG 2 N = 176	mBIG 3 N = 786	P-value	Total N = 1128
Mean age (years)	55.0 ± 20.4	54.1 ± 20.0	55.0 ± 21.6	0.867	54.9 ± 21.2
Male	59.0% (98)	64.2% (113)	70.4% (553)	**0.01**	67.7% (764)
Mean GCS	14.7 ± 0.5	14.7 ± 0.6	11.9 ± 4.3	**< 0.001**	12.8 ± 3.8
NSG consult	98.2% (163)	100.0% (176)	99.9% (785)	**0.02**	99.6% (1124)
ETOH history	5.4% (9)	28.4% (50)	20.6% (162)	**< 0.001**	19.6% (221)
Intoxication	12.6% (21)	42.6% (75)	34.0% (267)	**< 0.001**	32.3% (364)
Anticoagulation	N/A	N/A	20.0% (157)	N/A	13.9% (157)
Repeat scan	95.2% (158)	98.3% (173)	83.3% (655)	**< 0.001**	87.4% (986)
Progression	17.1% (27)	20.8% (36)	39.7% (260)	**< 0.001**	32.8% (323)

Table. Univariate analysis of variables and associated multivariate-adjusted odds ratios and 95% confidence intervals of need for intervention

	Univariate analysis			Multivariate analysis		
Parameter	No intervention	Intervention	P-Value	OR	95% CI	P-value
Mean age (years)	56.3 ± 21.2	48.8 ± 20.0	**< 0.001**	0.996	0.987-1.005	0.361
GCS	13.5 ± 3.1	9.6 ± 4.8	**< 0.001**	0.807	0.778-0.839	**< 0.001**
Sex male	35.1% (N)	20.0% (N)	**0.008**	1.715	1.148-2.561	**0.008**
EtOH history	18.2% (167)	25.7% (54)	**0.01**	1.818	1.185-2.788	**0.006**
Intoxication	30.9% (N)	38.1% (N)	**0.04**	1.519	1.014-2.275	**0.04**
Anticoagulation	34.4% (N)	10.0% (N)	0.069	0.879	0.501-1.541	0.651

Table. Primary and secondary outcomes in cohort and by mBIG

	mBIG 1 N = 166	mBIG 2 N = 176	mBIG 3 N = 786	P-value	Total N = 1128
Intervention	0.0% (0)	0.6% (1)	26.6% (209)	**< 0.001**	18.6% (210)
Mean LOS (days)	5.7 ± 10.4	4.9 ± 7.0	14.4 ± 21.6	**< 0.001**	11.6 ± 19.1
Mortality	2.4% (4)	0.6% (1)	13.5% (106)	**< 0.001**	9.8% (111)

IDH-Mutant Astrocytoma in Persons Age 55 year and older: Survival differences vs younger age group

Poster #16

Ahmed Gilani, Samuel Guzman, Angus Toland, B.K. Kleinschmidt-DeMasters

Department of Pathology, University of Colorado Health Sciences Center, Aurora, CO

BACKGROUND

Mutations in the isocitrate dehydrogenase (*IDH1/2*) genes are common genetic alterations predictive of a better outcome compared to IDH-wildtype diffuse astrocytomas. Although the peak incidence occurs in young and middle aged adults, *IDH1/2* mutations can occasionally present in persons age 55 years and older. Few studies have reported the clinical, histologic, and prognostic differences in IDH mutant tumors in those >age 55 years.We now extend our original studies on this topic (Robinson 2017).

METHODS

Search of databases for IDH-mutant astrocytoma, 2014 - 2024, inclusive, with medical record search for follow up survival, date of death, or recurrence at last follow-up. Comparison cohorts were stratified into adults <55 yrs versus >/=55 years. We have used a standard screening panel for all diffuse gliomas regardless of patient age, hence IDH1 R132H status was available in a vast majority of gliomas. Patient survival was measured using Kaplan-Meyer analysis on SAS software.

RESULTS

Of the 78 identified patients, 51 were <55 years and 27 >/=55 years at diagnosis. The latter cohort consisted of 10 WHO grade 2, 6 WHO grade 3, and 11 WHO grade 4 tumors (Figure 1). The younger age group (<55) had comparably less grade 2 tumors (11% vs 37%). When equal grades were compared by Kaplan Meyer survival analysis, those >/=55 years showed worse prognosis (Figure 2). Chart review indicates similar treatment regimens for both cohorts with standard external beam radiotherapy and Temozolomide (Stupp 2005), thus treatment differences were not apparent. Given the high incidence of *MGMT* methylation in IDH-mutant tumors, few were assessed for that parameter at time of initial diagnosis.

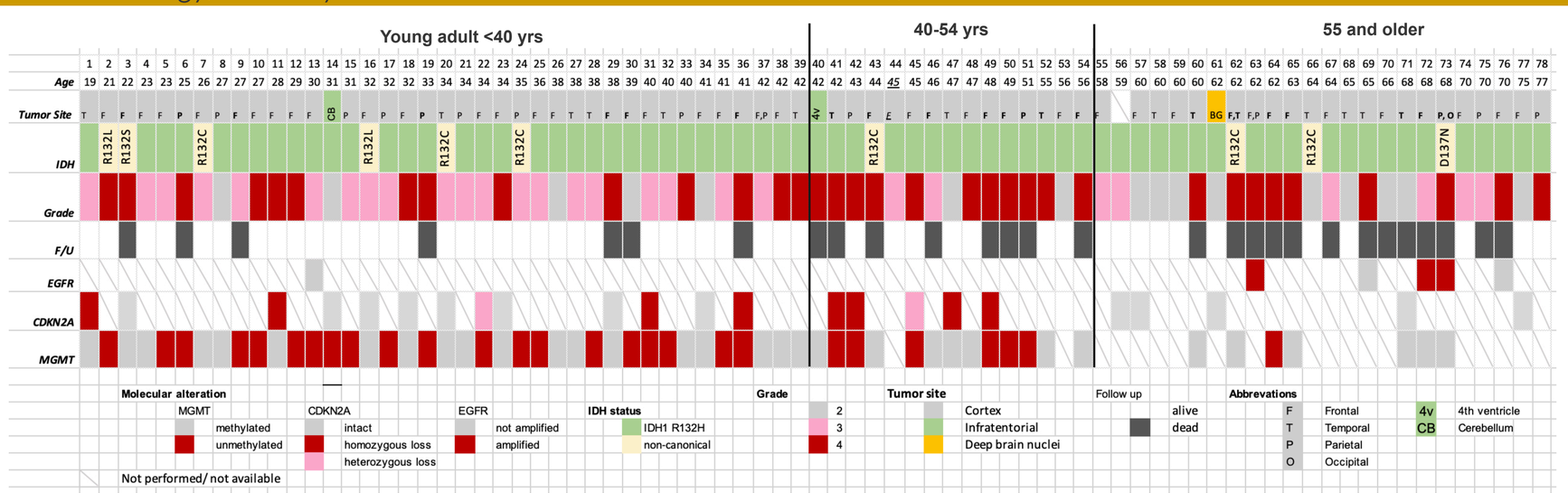

Figure 1: Summary of clinical data and molecular characteristics of the cohort n=78.

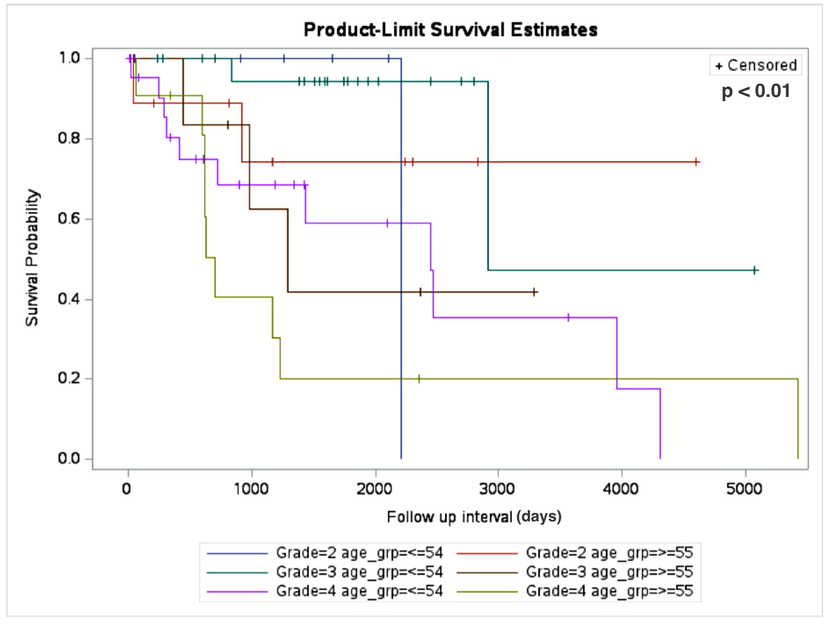

Figure 2: Kaplan Meyer plot showing overall survival by age (<55 yrs; >=55 yrs) and WHO grade.

Nevertheless, 1/8 (12%) cases tested for *MGMT* promoter methylation were unmethylated, while 26/50 (52%) cases in the younger age group were unmethylated with a correlation between *MGMT* unmethylated status, higher grade, and patient demise. For those patients in either cohort with at least 5 years follow-up, 5-year survival was 38% in those >/=55 years and 66% in those <55 years.

CONCLUSION

CNS WHO 2021 notes “adverse prognosis in patients >/=55 years”; while that is true in our cohort, survival of 5 years or more was seen in over 1/3rd (38%) of our patients >/=55 years indicating that long-term survival is possible in older patients with IDH-mutant astrocytoma. A likely explanation is due to administration of adjuvant chemo radiation in this group at par with younger patients in our hospital. Factors associated with adverse prognosis in older patients (biological differences in tumor vs comorbids) require further study.

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Abstract/Poster # 17

Kleinschmidt-DeMasters, B.K. Mixed pituitary adenoma-gangliocytomas: immunohistochemistry insights. American Association of Neuropathologists, 100th annual meeting, Lake Tahoe, CA, June 2024

Abstract/Poster # 18

Kleinschmidt-DeMasters, B.K., C. Turin. Re-assessment of Plurihormonal Pituitary Adenomas. American Association of Neuropathologists, 100th annual meeting, Lake Tahoe, CA, June 2024

Abstract/Poster # 19

Kleinschmidt-DeMasters, B.K., C. Turin. Plasmacytoma: Yet Another Rare Sellar Region Mass. American Association of Neuropathologists, 100th annual meeting, Lake Tahoe, CA, June 2024

Abstract/Poster # 20

Guzman, S, Kleinschmidt-DeMasters, B.K. Rheumatoid meningitis: 4 cases with possible links to Alzheimer disease. American Association of Neuropathologists, 100th annual meeting, Lake Tahoe, CA, June 2024

Abstract/Poster # 21

Guzman S, Gilani, A, Toland A, Kleinschmidt-DeMasters, B.K. Central neurocytoma: 20- year retrospective with clinical followup. American Association of Neuropathologists, 100th annual meeting, Lake Tahoe, CA, June 2024

(#20 and #21 will be on the same board/easel)