lactic and established leptomeningeal disease to investigate the efficacy of engineered tumor-homing neural stem cells (NSCs) therapy for breast cancer leptomeningeal carcinomatosis. METHODS: Personalized NSC carriers were created using Sox2 overexpression to transdifferentiate human fibroblasts into induced NSCs (iNSCs) that home to cancer cells and carry therapeutic agents to induce tumor kill. Leptomeningeal models were created by engineering MDA-MB231-Br human breast cancer cells with fluorescent and bioluminescent reporters, then using intracisternal injection to inoculate Nude mice with the tumor cells. iNSC therapy was evaluated by infusing iNSCs releasing the pro-apoptotic agent TRAIL into the lateral ventricle of mice either 1 week prior to or 3 days after tumor inoculation for prophylactic or established tumor treatment respectively. Tumor progression in the brain and spinal cord was monitored by serial bioluminescence imaging (BLI). RESULTS: Serial BLI showed that intracerebroventricular (ICV) iNSC-TRAIL therapy reduced the volume of metastatic tumor burden 99.49% in the brain and 99.80% in the spine within 2 weeks post-infusion and extended survival from 24 to 42 days. Additionally, prophylactic iNSC-TRAIL therapy delivered ICV markedly delayed tumor development, with tumors in the brain remaining >1000-fold smaller than control through 1-month post-treatment, below the limit of detection in the spinal cord through 1 month, and eliminating mortality through 50 days post-therapy. CONCLUSION: These data suggest that iNSC therapy could be a promising treatment option for breast cancer patients with leptomeningeal carcinomatosis.

57. CIRCULATING TUMOR CELLS (CTC) IN CEREBROSPINAL FLUID (CSF) AS A PREDICTOR OF SURVIVAL IN CNS METASTASES

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BACKGROUND: CSF-CTC testing using the CellSearch® platform is a validated diagnostic tool for leptomeningeal metastases (LM) from solid tumors. CSF-CTCs can also be detected in patients with brain metastases (BM), but their significance is unclear. Our objective was to evaluate the utility of CSF-CTC measurement in predicting outcomes in CNS metastases. METHODS: We conducted a retrospective single-institution review of patients who underwent CSF-CTC testing from 2016–2019. Information on neuroaxis imaging, CSF results, systemic cancer status, tumor molecular profile and survival was collected. LM was diagnosed by unequivocal MRI findings and/or positive or suspicious CSF cytology. Survival analyses were performed using Cox proportional hazards modeling, and CSF-CTC splits associated with survival were identified through recursive partitioning analysis. RESULTS: A total of 407 patients (38% lung primary, 34% breast, 28% other tumor types) were included; of these, 144 had LM and 233 had BM diagnosed before or around the time of CSF analysis (97 had both). We identified a subgroup of newly diagnosed CNS metastases, comprising 144 patients with LM, BM, or both diagnosed within 30 days of CSF sampling: 70 patients with LM, 43 with BM, and 31 with both. For 101 patients with newly diagnosed LM, mean and median CSF-CTCs were 127.3 and 200, respectively, compared to 44.6 and 0 in the overall cohort; 73/101 had positive (66) or suspicious (7) cytology. CSF-CTCs predicted survival in patients with newly diagnosed LM, with optimal cutoff identified at 61 CSF-CTCs, above which the risk of death doubled (HR=2.09, 95% CI: 1.13–3.87, p=0.02). For this group, positive/suspicious cytology was also associated with higher risk of death, but this result was not statistically significant (HR=1.79, 95% CI: 0.95–3.35, p=0.07). CONCLUSION: In newly diagnosed LM, quantification of CSF-CTCs predicts survival. CSF-CTC measurement can be used as a prognostic tool in patients with CNS metastases.

58. CLINICAL PRESENTATION AND IMAGING CHARACTERISTICS OF LEPTOMENINGEAL CARCINOMATOSIS (LC) IN PATIENTS WITH EGFR MUTATED NON-SMALL CELL LUNG CANCER (NSCLC)

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BACKGROUND: LC is a late and often fatal manifestation of advanced EGFR mutated NSCLC with up to 9% of patients developing LC. Given the higher incidence of LC in EGFR mutated tumors, we hypothesized it may have unique imaging and clinical characteristics. METHODS: We identified 23 patients with EGFR mutated NSCLC and LC treated at a large academic institution between 2016 and 2019. Clinical and treatment characteristics were obtained from the electronic medical record. Radiographic subtype of LC and presence of ventriculomegaly were determined by independent review of available brain and spine MRI imaging. RESULTS: Among 23 eligible patients, mean age was 57 years, 96% had advanced NSCLC at diagnosis and 61% had EGFR exon 19 deletion. Median time from NSCLC diagnosis to LC

development was 23 months (95% CI:13–33), with only 17% of patients presenting with LC in the absence of parenchymal brain metastases. Of the 91% of patients with radiographic evidence of LC, equal numbers had nodular or linear LC (22% each) and 39% had a mixed presentation. Additionally, 30% of patients had evidence of spinal LC. Ventriculomegaly was present in 52% of patients, with 48% developing clinical symptoms of hydrocephalus and 13% receiving shunt placement. Median overall survival (OS) from time of LC diagnosis was 3.9 months (95% CI:2.7–10.0), which is lower than in prior published studies. Patients with nodular LC and absence of ventriculomegaly fared better with a median OS of 6.5 months and 5.7 months respectively. CONCLUSIONS: OS is poor in patients with LC associated with EGFR mutated NSCLC, although appears better in patients with nodular LC. The high incidence of hydrocephalus emphasizes the need for its early recognition and treatment. Further studies are needed to identify promising treatment strategies and to determine factors associated with improved OS in this population.

59. A RADIOMICS-BASED MACHINE LEARNING MODEL FOR DISTINGUISHING RADIATION NECROSIS FROM PROGRESSION OF BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOSURGERY (SRS)

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PURPOSE: This study aims to test whether MRI radiomic signatures can distinguish radiation necrosis (RN) from tumor progression (TP) in a multi-institution dataset using machine learning. METHODS: Brain metastases treated with SRS were followed by serial MRI, and those showing evidence of RN or TP underwent pathologic confirmation. Radiomic features were extracted from T1 post-contrast (T1c) and T2 fluid attenuated inversion recovery (T2 FLAIR) MRI. High dimensional radiomic feature space was visualized in a two-dimensional space using t-distributed stochastic neighbor embedding (t-SNE). Cases from 2 institutions were combined and randomly assigned to training (2/3) and testing (1/3) cohorts. Backward elimination was used for feature selection, followed by random forest algorithm for predictive modeling. RESULTS: A total of 135 individual lesions (37 RN and 98 TP) were included. The majority (72.6%) received single-fraction SRS to a median dose of 18Gy. Clear clustering of cases around the institutional origin was observed on t-SNE analysis. 21 T1c and 4 FLAIR features were excluded from subsequent modeling due to significant correlation with the institutional origin. Backward elimination yielded 6 T1c and 6 FLAIR features used for model construction. A random forest model based on the 6 FLAIR features (cluster shade, neighborhood gray tone difference matrix (NGTDM) coarseness, NGTDM texture strength, run length nonuniformity, run percentage, and short run high gray-level emphasis) achieved sensitivity of 76% and specificity of 70% on the training cohort (AUC 0.74, 95% CI 0.60–0.88), and sensitivity of 67% and specificity of 83% on the testing cohort (AUC 0.75, 95% CI 0.59–0.93). Addition of the T1c features resulted in overfitting of the training cohort (AUC 1.00), but did not improve model performance on the testing cohort (AUC 0.69, 95% CI 0.51–0.87). CONCLUSION: MRI radiomics based machine learning can distinguish RN from TP after brain SRS in a heterogeneous image dataset.

60. IDEAL TREATMENT REGIMEN FOR PATIENTS WITH ≥1 BRAIN METASTASIS FROM PRIMARY NON-SMALL-CELL LUNG CANCER – A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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BACKGROUND: Brain metastases (BM) are common in non-small cell lung cancer (NSCLC). The aim of this study was to assess the comparative effectiveness of treatments for BM from NSCLC. METHODS: We searched MEDLINE, EMBASE, Web of Science, ClinicalTrials.gov, CENTRAL and references of key studies for randomized controlled trials (RCTs) published

until October 2018. We also searched the Chinese databases Wanfang Data, Wanfang Med Online, China National Knowledge Infrastructure, and Chongqing VIP Information for RCTs published until September 2019. Trials including > 10 patients were selected. The primary outcomes were overall survival (OS) and intracranial progression-free survival (PFS). We used a frequentist random-effects model for network meta-analysis and assessed the certainty of evidence using the GRADE approach. RESULTS: Among 8798 abstracts, 106 RCTs (9452 patients) met inclusion criteria. Median sample size was 67 (range 25–554). All trials included adult patients with histologically proven NSCLC and >1 BM proven on CT/MRI. Of trials that reported performance status (e.g. ECOG or KPS, n=67), 63/67 excluded patients with non-favorable performance status. Interventions assessed included surgery, WBRT, SRS, targeted therapies (i.e. EGFR/ALK inhibitors), and chemotherapy. Compared to WBRT alone, several interventions demonstrated a statistically significant increase in median OS, including non-targeted chemotherapy + surgery (MD: 415.3 days, 95% CI: 31.3–799.4), WBRT + EGFRi (MD: 200.2 days, 95% CI:146.3–254.1), and EGFRi alone (MD: 169.7 days, 95% CI: 49.7–289.7). Among all interventions, only WBRT + EGFRi showed a significant improvement in median PFS (MD: 108.0 days, 95%CI: 48.5–167.5). CONCLUSIONS: Our preliminary analyses indicate an OS and PFS benefit on the addition of EGFR inhibitors to WBRT for the treatment of BMs from NSCLC. Further analyses of hazard ratios for OS/PFS are underway, and subgroup analyses are planned. These data support the growing role of targeted therapies in the treatment of BMs, particularly in susceptible mutant tumours.

61. EXPRESSION OF ANDROGEN RECEPTOR IN BREAST CANCER BRAIN METASTASIS

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INTRODUCTION: Treatment options for women with breast cancer brain metastases (BrM) are generally limited to surgery and/or radiotherapy because most systemic therapies do not cross the blood-brain barrier. Androgen receptors (ARs) are frequently expressed in breast cancer and anti-androgenic therapies have been shown to penetrate the central nervous system. In this study, we analyzed the expression of AR in breast cancer BrM to identify patients who may benefit from anti-androgenic therapies. METHODS: Consecutive BrM resected in our institution (July 1999-June 2013) were identified from the Anatomic Pathology departmental database. Cases that were signed out as breast origin given the available immunohistochemical profile and clinical history were included. A tissue microarray was constructed using 1 mm cores in triplicates and studied by immunohistochemistry for AR, ER, PR and HER2 (SP107, SP1, IE2, 4B5; Ventana Medical Systems, Tucson AZ, USA). HER2 gene amplification was determined by INFORM HER2 DNA and Chromosome 17 (both by Ventana Medical Systems, Tucson AZ, USA). Immunohistochemistry was used as a surrogate to determine intrinsic subtypes. RESULTS: Among 61 breast cancer BrM with available tissue blocks, AR was expressed in 38 (62%) cases. Among BrMs of luminal A subtype (ER+, PR+/-, HER2-, Ki67<16%), 50% expressed AR (n=1/2). Within the luminal B subtype (ER+, PR+/-), all 15 HER2+ BrM expressed AR (100%), while only 50% of HER2- BrM expressed AR (n=8/16). Among 14 BrM of HER2+ subtype (ER-, PR-), 71% expressed AR (n=10/14). Only 30% of triple negative BrM (ER-, PR-, HER2-) were AR+ (n=4/14). CONCLUSION: Almost two-thirds of breast cancer BrM expressed AR. HER2+ luminal B and HER2+ subtypes were most likely to be AR+, while only 30% of triple negative BrM were AR+. Our data suggests that certain subtypes of breast cancer BrM are more likely to be AR+ and could serve as a potential therapeutic target.

62. PRESENCE OF EXTRACRANIAL TUMORS INFLUENCES RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN A PRE-CLINICAL MODEL OF MELANOMA BRAIN METASTASIS

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Up to 75% of patients with melanoma develop brain metastases. While immune checkpoint inhibitors (ICI) targeting PD-1 and CTLA4 have revolutionized the treatment of metastatic melanoma, responses within the immune-specialized microenvironment of the brain are not well understood and there is a paucity of animal models to investigate the effect of ICI intracranially. We characterized responses to checkpoint inhibitors in a syngeneic mouse model of melanoma brain metastasis with concurrent intracranial and subcutaneous melanoma. D3UV3 cells (obtained from David Fisher's laboratory) were derived using UVB irradiation from D4M.3A melanoma cell line and implanted into the striatum using stereotactic injection or subcutaneously injected into the flank of C57BL/6 mice. Mice were then treated with anti-PD-1 antibody, anti-CTLA4 antibody, a combination of

anti-PD-1 and anti-CTLA4, or isotype controls. While mice with intracranial melanoma alone had no response to monotherapy with anti-PD-1 or anti-CTLA4 antibody (p=1 and 0.1, respectively), and only a slight response to combination therapy (p=0.049), mice with concurrent subcutaneous tumors had significantly improved responses to anti-PD-1, anti-CTLA4 and combination treatment (p=0.002, 0.01 and 0.01 respectively compared to mice with intracranial tumors alone with equivalent treatment). These results demonstrate that the presence of an extracranial tumor influences response to ICI in pre-clinical mouse models of melanoma brain metastasis. We have therefore established a pre-clinical model with concurrent intracranial and extracranial tumors to better recapitulate the clinically observed context of melanoma brain metastases and lead to a better understanding of the setting in which ICI are effective for patients with this devastating complication.

64. AN ENT2-DEPENDENT, CELL-PENETRATING, AND DNA-DAMAGING LUPUS AUTOANTIBODY CROSSES THE BLOOD-BRAIN BARRIER TO TARGET BRAIN TUMORS

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The blood-brain barrier (BBB) limits conventional antibody-based approaches to brain tumors. ENT2, an equilibrative nucleoside transporter, facilitates penetration of autoantibodies into live cells and is expressed in the BBB. PAT-DX1 (also known as Deoxymab-1 or DX1) is an ENT2-dependent, cell-penetrating, and DNA-damaging lupus autoantibody that is synthetically lethal to cancer cells with defects in the DNA damage response. PTEN loss renders sensitivity to DX1 and is common in primary and metastatic brain tumors. We show that DX1 is toxic to spheroids derived from primary PTEN-deficient glioblastoma (GBM), and crosses the BBB to suppress the growth of orthotopic GBM and breast cancer brain metastases. Mechanistically, we find the ENT2 inhibitor dipyridamole blocks DX1 penetration into brain endothelial cells and transport across the BBB *in vitro* and *in vivo*, consistent with ENT2-mediated uptake of DX1 into brain tumors. Autoantibodies that hijack nucleoside transporters to cross cell membranes may open new frontiers in brain tumor therapy.

65. INVASIVE HISTOPATHOLOGY DRIVES POOR OUTCOMES IN SURGICALLY RESECTED BRAIN METASTASES

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BACKGROUND: Brain metastasis (BrM) patients treated with surgery and radiotherapy frequently experience local recurrence (LR), leptomeningeal metastasis (LM), and poor overall survival (OS). We sought to correlate the presence of invasive or circumscribed histopathological growth pattern, observed in the BrM lesion and surrounding brain, with these outcomes, and to study molecular mediators of parenchymal invasion. METHODS: We assessed the HGP of H&E-stained slides from 164 surgically resected BrM from 147 patients. HGP was correlated with incidence of LR, LM and OS. Single-cell RNA sequencing (scRNAseq) was performed on three invasive HGP patients, sampling the metastasis center (MC) and surrounding brain (SB) outside of the contrast-enhancing region. Orthotopic patient-derived xenograft models (OPDX) were established from N=30 brain metastasis via intracranial propagation. RESULTS: 56/164 BrM specimens (34%) showed a circumscribed growth pattern between the tumor and adjacent brain (cHGP) while 108/164 (66%) showed significant invasion of tumor lobules or single cells into the brain parenchyma (iHGP). iHGP was associated with LR, LM and shortened OS in BrM patients. OPDX models of BrM retain features of patient BrM, including HGP. scRNAseq identified abundant cancer cells in SB that overexpressed a number of genes involved in cell survival, invasion and metastasis compared to matched cancer cells in MC. Validation of these targets with immunohistochemistry in patient and OPDX tissues revealed cold-inducible RNA binding protein (CIRBP) overexpression in iHGP patient and OPDX BrM. Modulation of CIRBP expression in OPDX and cell line models of iHGP BrM delayed BrM progression and extended OS. CONCLUSION: iHGP is a poor prognostic indicator in patients with surgically resected BrM, establishing HGP as an