PTCH1, BCOR, CLIC6, TLL2, COL1A1, PTPRK). Notably, mutations in *BCOR* and *PTCH1* have been previously implicated in both systemic neuroendocrine tumors as well as primary tumors of the pituitary gland, while *MYO18A, FGF4, and PTPRK* mutations had not been reported in systemic neuroendocrine tumors but have been implicated in tumor migration and pituitary adenoma progression. In summary, these data demonstrated an expected mutational pattern indicating a systemic lung neuroendocrine origin but also revealed new mutations previously implicated in primary pituitary pathologies that may have evolutionarily drove divergence from the primary tumor. Further genome studies of these rare lesions may yield further insight into the genetic alterations underlying metastasis to the sellar region.

29. ROLE OF AGE AND CNS MYELOID CELLS ON BREAST CANCER BRAIN METASTASIS

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Women diagnosed with breast cancer at a younger age (typically defined as < 40 years old) often have a poorer prognosis and an increased risk of brain metastasis compared to their older counterparts. Multivariate analyses accounting for differences in tumor characteristics have shown that age is an independent predictor of worse outcome. We therefore hypothesized that rather than intrinsic tumor properties, extrinsic microenvironmental factors contribute to age-related differences in aggressiveness. The effect of age was examined by injecting brain-selected breast cancer cells into young (2 – 6 months) and older (>12 months) mice. In four brain metastasis models examined, young mice developed 2- to 16-fold ($p < 0.05$) more brain metastases compared to older mice. The effect of age was not observed in mouse breast cancer models that metastasize to liver and lungs, suggesting that this is an organ-specific phenomenon. Flow cytometry-based immune-profiling of mouse brains showed that T-cells (CD4+, CD8+, and FOXP3+CD25+ regulatory T-cells), monocytes and neutrophils were elevated in brains with metastases, but the abundance of these populations did not vary dramatically with age. Furthermore, antibody-based depletion of T-cells, monocytes and neutrophils did not significantly alter brain metastasis development. Microglia, which are resident CNS myeloid cells, were 1.5-fold more abundant in young brains compared to older brains. Depletion of CNS myeloid cells using the colony stimulating factor-1-receptor inhibitor PLX3397 reduced brain metastatic tumor burden in young mice by 2.1-fold ($p < 0.001$). Importantly, loss of CNS myeloid cells/microglia, which are normally more activated in aged mice and thus may protect the older brain against metastasis, did not augment brain metastasis formation in older mice. These results suggest that the younger brain is more permissive for breast cancer metastasis and that targeting resident CNS myeloid cells may be an effective strategy to prevent brain metastasis development in younger patients.

30. RADIOSURGERY FOLLOWED BY TUMOR TREATING FIELDS FOR BRAIN METASTASES (1–10) FROM NSCLC IN THE PHASE 3 METIS TRIAL

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BACKGROUND: Tumor Treating Fields (TTFields) are non-invasive, loco-regional, anti-mitotic treatment modality comprising alternating electric fields. TTFields have demonstrated efficacy in preclinical non-small cell lung cancer (NSCLC) models. TTFields treatment to the brain was safe and extended overall survival in newly-diagnosed glioblastoma. The objective of the METIS study [NCT02831959] is evaluation of the efficacy and safety of TTFields in NSCLC patients with brain metastases. METHODS: NSCLC patients (N=270) with 1–10 brain metastases were randomized 1:1 to stereotactic radio surgery (SRS) followed by continuous TTFields ((150 kHz, > 18 hours/day) within 7 days of SRS or supportive care. The portable device delivered TTFields to the brain using 4 transducer arrays, while patients received the best standard-of-care for systemic disease. Patients were followed every two months until second intracranial progression. Key inclusion criteria: KPS ≥70, new diagnosis of 1 inoperable or 2–10 supra- and/or infratentorial brain metastases from NSCLC amenable to SRS; and optimal therapy for extracranial disease. Prior WBRT, surgical resection of metastases, or recurrent brain metastases were exclusionary. Primary endpoint was time to 1st intracranial progression. Secondary endpoints included time to neurocognitive failure (HVLT, COWAT and TMT), overall survival, radiological response rate (RANO-BM and RECIST V1.1); quality-of-life; adverse events; time to first/second intracranial progression for patients with 1–4 and 5–10 brain metastases; bi-monthly intracranial progression rate from 2–12 months; and time to second intracranial and distant progression. The sample size (N=270) was calculated using a log-rank test (Lakatos 1988 and 2002) with 80% power at two sided alpha of 0.05 to detect a hazard ratio of 0.57. On September, 2019, an independent Data Monitoring Committee (DMC) reviewed METIS trial data collected to that point. The DMC concluded that no unexpected safety issues had emerged and recommended continuation of the METIS study as planned.

31. RADIATION NECROSIS IN STEREOTACTIC RADIOSURGERY AND CHECKPOINTS INHIBITORS FOR BRAIN METASTASES FROM LUNG ADENOCARCINOMA

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PURPOSE: Treatment with stereotactic radiosurgery (SRS) and immune checkpoint inhibitors (ICI) is increasingly common for brain metastases (BM) from lung adenocarcinoma. Rates of radiation necrosis (RN) with SRS in the setting of ICIs is an ongoing area of research. We investigated rates of RN in patients with BM from lung adenocarcinoma treated with SRS with or without concurrent ICIs. METHODS: We identified 39 patients at a single institution who underwent SRS treatment for BM from lung adenocarcinoma. Of these, 19 (49%) received SRS without ICIs and 20 (51%) patients received ICIs within a month of SRS. The rate of RN, defined by MRI features and histology when available, was compared between each group using multivariate analysis. Kaplan Meier survival estimates were calculated based on overall survival and compared to median survival predicted by the graded prognostic assessment. RESULTS: Overall survival for all patients from diagnosis of brain metastases was 16.6 months (range 3.6–45.9) and median survival predicted by the graded prognostic assessment was 13.7 months (range 6.9–26.5). In total 11 (28%) patients developed MRI and/or histologic evidence for RN during the follow-up period; 5 of 20 (25%) from the SRS with ICI group and 6 of 19 (31%) from the SRS without ICI group. In multivariate analysis, ICI treatment had no significant impact on rates of RN between groups (OR 0.72 [95% CI: 0.17–2.93]; p=0.65) while bevacizumab treatment was associated with a decreased RN risk (OR 0.88 [95% CI: 0.43–0.99]; p=0.02). CONCLUSION: Retrospective analysis of patients with BM from lung adenocarcinoma treated with SRS suggested that administration of ICIs does not increase risk for development of RN. Further, concomitant treatment with bevacizumab may decrease risk of RN. These findings suggest that patients with BM from lung adenocarcinoma can be treated with combination therapy without increased risk of neurologic toxicity.

32. TREATMENT MONITORING OF IMMUNOTHERAPY AND TARGETED THERAPY USING AMINO ACID PET IN PATIENTS WITH BRAIN METASTASES

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PURPOSE: Recently, the RANO group has analyzed the additional diagnostic value of amino acid PET in patients with primary and secondary brain tumors and recommended the use of this imaging technique in addition to conventional MRI. Here, we investigated the value of PET using the radiolabled amino acid O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) for treatment monitoring of immune checkpoint inhibition (ICI) or targeted therapy (TT) alone or in combination with radiotherapy in patients with brain metastases (BM) since contrast-enhanced MRI often remains inconclusive. METHODS: We retrospectively identified 40 patients with 107 BM secondary to melanoma (n=29 with 75 BM) or non-small cell lung cancer (n=11 with 32 BM) treated with ICI or TT who had FET PET (n=60 scans) for treatment monitoring from 2015–2019. The majority of patients (n=37; 92.5%) had radiotherapy during the course of disease. In 27 patients, FET PET was used for the differentiation of treatment-related changes from BM relapse following ICI or TT. In 13 patients, FET PET was performed for response assessment to ICI or TT using baseline and follow-up scans (median time between scans, 4.2 months). In all lesions, static and dynamic FET PET

parameters were obtained (i.e., mean tumour-to-brain ratios (TBR), time-to-peak values). Diagnostic accuracies of PET parameters were evaluated by receiver-operating-characteristic analyses using the clinical follow-up or neuropathological findings as reference. RESULTS: A TBR threshold of 1.95 differentiated BM relapse from treatment-related changes with an accuracy of 85% (P=0.003). Metabolic Responders to ICI or TT on FET PET had a significantly longer stable follow-up (threshold of TBR reduction relative to baseline, ≥10%; accuracy, 82%; P=0.004). Furthermore, at follow-up, time-to-peak values in metabolic responders increased significantly (P=0.019). CONCLUSIONS: FET PET may add valuable information for treatment monitoring in BM patients treated with ICI or TT.

33. SYSTEMATIC REVIEW AND META-ANALYSIS OF BREAST CANCER BRAIN METASTASIS AND PRIMARY TUMOR RECEPTOR EXPRESSION DISCORDANCE

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BACKGROUND: Discordance in hormone receptor (estrogen [ER] and progesterone [PR]) and human epidermal growth factor receptor2 (HER2) status between the primary tumor and brain metastases and its effect on tumor classification subtype switching has been described but remains understudied. METHODS: Using the PRISMA guidelines, a systematic review was performed of series published prior to April 2020 of biopsied or resected breast cancer brain metastasis (BCBM) from the Medline database using the keywords "breast cancer" and "brain metastasis" combined with "estrogen receptor/ER," "progesterone receptor/PR," "HER2/neu," and "receptor conversion/dis- or concordance." Weighted random effects models were used to calculate pooled estimates. RESULTS: Fifteen full-text articles met inclusion criteria and cumulatively reported on 1373 patients who underwent biopsy or resection of at least one BCBM to compare to their primary tumor. At initial diagnosis, receptor expression profiles were 45.0% ER+, 41.0% ER-, 31.0% PR+, 51.0% PR-, 35% HER2+, and 47.0% HER2-. Corresponding receptor expression profiles from the BCBM were 19.0% ER+, 31.0% ER-, 13.0% PR+, 40.0% PR-, 21.0% HER2+, and 26.0% HER2-. Intra-patient receptor discordance comparisons revealed that 540 patients (42.6%) exhibited discordance in any receptor with 17.0% (95% CI: 13.0%-23.0%) discordance for ER status, 23.0% (95% CI: 18.0%-30.0%) for PR status, and 12.0% (95% CI: 8.0%-16.0%) for HER2 status. The most common receptor discordance events found in BCBM compared to primary tumors were ER loss 11.0% (95% CI: 8.0%-16.0%), PR loss 15.0% (95% CI: 11.0%-21.0%), and HER2 gain 9.0% (95% CI: 7.0%-11.0%). CONCLUSIONS: BCBM commonly exhibit receptor expression changes on comparison to primary tumors including a 10% HER2 gain rate, a potential actionable target. Classification patterns need to be updated to reflect changes in overall tumor subtype grouping and which factors predict for BCBM/primary tumor discordance. Overall, tumor subtype switching and its effect on clinical management remains underappreciated.

34. TARGETED THERAPY FOR HER2-POSITIVE BREAST CANCER BRAIN METASTASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRO: One in three women with HER2-positive breast cancer will develop brain metastases, or intracranial metastatic disease (IMD). Historically, treatment of IMD has been confined to surgery and radiotherapy, with a limited role for chemotherapy. However, recent interest has burgeoned in a role for targeted therapy for treatment of IMD. The lack of high-level evidence, such as meta-analyses, regarding the role of targeted therapy in the management of IMD has prevented its inclusion in guidelines directing treatment. We performed a systematic review and meta-analysis to clarify the role of targeted therapy for IMD in women with HER2-positive breast cancer. METHODS: Following PRISMA guidelines, a search of MEDLINE, CENTRAL, EMBASE, Google Scholar, and grey literature sources was conducted by two independent reviewers. Controlled trials and cohort studies that reported survival, safety, or response outcomes for patients receiving HER2-targeted therapy following IMD diagnosis were included. Meta-analyses using a random-effects model were conducted for OS and PFS. RESULTS: 111 studies reporting on 8226 patients were included. Primary analysis of only RCTs found that HER2-targeted therapy was associated with improved OS (HR 0.63; 95% CI, 0.46–0.86; n = 392) but not PFS (HR 0.75; 95% CI, 0.30–1.85; n = 392) following IMD diagnosis. Secondary analysis combining RCTs and comparative observational studies found that HER2-targeted therapy was associated with improved OS (HR 0.42; 95% CI, 0.35–0.51; n = 2756) but not PFS (HR 0.58; 95% CI, 0.27–1.21; n = 460) following IMD diagnosis. Full analysis will be conducted for all 111 studies for pre-specified outcomes including intracranial PFS. CONCLUSION: These findings support a potential role for HER2-targeted therapy in the management of IMD from HER2-positive breast cancer. Final analysis will synthesize current evidence for outcomes of intracranial response, survival, and safety.

35. EVALUATING CSF CIRCULATING TUMOR DNA IN INTRAPARENCHYMAL BRAIN METASTASIS

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INTRODUCTION: Discordant response between brain and systemic metastases occur in patients receiving targeted therapies and repeat tumor profiling of the progressing site could guide further therapy. We propose that circulating tumor DNA (ctDNA) might be detectable in the cerebrospinal fluid (CSF) and reflective of the genetic profile of intraparenchymal brain metastases. METHODS: Patients with brain metastases undergoing a craniotomy or lumbar puncture were enrolled between July 2018 to April 2019 under an IRB-approved protocol. CSF and blood were collected simultaneously. Cell-free DNA (cfDNA) were extracted and ctDNA were identified and quantified using an Error-Suppressed Deep Sequencing method previously published by our group. Forty-three mutation-prone regions of 24 cancer-associated genes were assayed, and the allelic fractions were calculated against wild-type sequence counts. RESULTS: Sixteen patients were enrolled in this study - 12 patients with intraparenchymal brain metastases, two patients with CSF cytology-positive leptomeningeal disease (LMD) and 2 patients with normal pressure hydrocephalus (NPH) as controls. Primary cancer types were lung (n=10), melanoma (n=2), renal cell (n=1) and colorectal (n=1) cancers. cfDNA was found in all sixteen samples of CSF. CSF ctDNA were found in eight patients (67%) and plasma ctDNA were only found in five patients (42%) with intraparenchymal tumors. In six patients with additional time-matched brain metastasis tissue, four were found to have congruent mutations in the CSF, while only one harbored such mutation in the plasma. DISCUSSION: Analysis of CSF can be a viable alternative to obtaining brain metastasis tissue for DNA profiling in the detection of novel and resistance mutations. The presence CSF ctDNA is not restricted to LMD and were isolated from two-thirds of patients with intraparenchymal disease in our cohort. Furthermore, CSF remains a better source than plasma for the detection of ctDNA across multiple brain metastases tumor subtypes.

36. A PROSPECTIVE TRIAL OF RESECTION PLUS SURGICALLY TARGETED RADIATION THERAPY FOR BRAIN METASTASIS

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INTRODUCTION: Achieving durable local control for larger brain metastases remains problematic. Resection (R) alone is typically insufficient. Even with the addition of stereotactic radiation the 12-month recurrence rate for larger lesions (i.e., >2.5–3 cm) is 20% or more in many series. To improve outcomes we designed and prospectively evaluated a permanently implanted radiation device consisting of Cs-131 seeds positioned within a collagen tile (GammaTile, GT Medical Technologies, Tempe AZ). We combined maximum safe resection and collagen tile brachytherapy (CTBT) with the hypothesis that immediate radiation initiation and/or dose intensification could improve outcomes. MATERIALS/METHODS: From 2013–2018 patients undergoing resection with either previously untreated or recurrent brain metastasis were enrolled on a single arm, multi-histology study (ClinicalTrials.gov, NCT#03088579). At resection completion the tumor bed was lined with collagen tiles imbedded with Cs-131, delivering 60–80 Gy at 5 mm depth. The device was designed to prevent direct source-to-brain contact and to maintain inter-source spacing after closure. No additional local therapy was given unless progression occurred. RESULTS: 16 metastases (12 recurrent/4 previously untreated) in 11 patients were treated. Median diameter 3.1 cm, range 1.9–5.1. Histology was 7 breast, 6 lung, and 3 sarcoma. Median age 60 years; 7 females/4 males. Average time for implantation was 5 minutes. At median radiographic follow-up of 9.5 months (range 0.1–25.2) treatment site progression occurred 1/16 (6%) at 10.9 months. Median treatment site time-to-progression (TTP) has not been reached (95% CI, >10.9 months). Median overall survival (OS) 9.3 months. No surgical adverse events occurred. One patient (6.2%) experienced radiation brain changes and was treated medically. CONCLUSION: R+CTBT demonstrated excellent safety and local control outcomes in this single-arm pre-commercial study. The device recently received FDA clearance for use in newly diagnosed and recurrent brain metastasis. Randomized clinical trials vs standard of care treatments are expected to open in 2020.