delay to SRS and LR, local recurrence-free survival (LRFS), and overall survival, as well as the predictors of and reason for delays. RESULTS: In our cohort of 159 patients, median age was 64.0 years, 56.5% patients were female, median tumor diameter was 2.9 cm, and gross total resection was achieved in 83.0%. On intention-to-treat analysis, LR was 22.6%. Delays to SRS correlated with LR: 2.3% with SRS ≤4 weeks postoperatively, 14.5% with SRS at >4–8 weeks (p=0.03), 48.5% with SRS at >8 weeks (p<0.001). No LR difference was observed with SRS delayed by >8 weeks, vs. never completed, 48.5% vs. 50.0% (p=0.91). 53 (33.3%) patients comprised these latter two categories. A similar relationship emerged between delay to SRS and LRFS (p<0.01). Non-small cell lung cancer pathology (p=0.04) and earlier year of treatment (p<0.01) were predictive of delays. Common reasons for delays included logistics, management of systemic disease, complications, or comorbidities. CONCLUSION: A significant number of patients referred for SRS never receive it, or are treated with a delay >8 weeks, conferring equivalent LR risk. Accordingly, the actual efficacy of adjuvant SRS may need reassessment. Reasons for delays and mechanisms for reducing them are discussed. For patients likely to experience significant delays, other techniques, such as preoperative SRS or intraoperative brachytherapy, may be considered.

46. PAN-CANCER ANALYSIS OF ORTHOTOPIC PATIENT DERIVED XENOGRAFTS FROM BRAIN METASTASES

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Brain metastases (BM) are a leading cause of cancer death and prognosis remains poor despite treatment advances at other sites. Models are central to therapeutic development, but few orthotopic patient-derived xenograft (PDX) models of BM exist. To represent diversity across BM types, we established a program to create orthotopic PDX at scale from all BM patients. To date BM were received from 100 patients and PDX attempted by direct brain injection (PDX, n=89) or injection of low passage patient-derived cell lines (PDCLX, n=11). We created 65 successful BM PDX from 13 cancers: 17 lung (55% take), 15 breast (68%), 6 melanoma (75%), 5 CNS lymphoma (83%), 3 gastrointestinal (75%), 2 esophageal (40%), 2 ovarian (67%), 1 sarcoma (100%), 1 laryngeal (100%), 1 prostate (100%), 1 pancreatic (100%), 1 uterine adenosarcoma (100%), and 1 yolk sac tumor (100%). Take rate was similar for models derived from patients with prior chemotherapy-only versus immune/targeted therapy-only (63 vs 58%). Fifteen patients had live tumor and matching PBMCs archived for modeling in vitro immunotherapy responses. Mean time to moribund among different cancer types ranged from 27 days (yolk sac tumor) to 177.5 days (ovarian). BM PDX had a favorable timeline for preclinical study (90% moribund at 180 days). All PDX matched the patient driver SNVs and copy aberrations, even at >P4. No significant differences noted by immunodeficient strain (SCID versus NSG) or injection site (orthotopic versus heterotopic). Explants from BM PDX were able to generate long-term cell lines (60%) or short-term cultures with qualitative concordance of model-to-patient responses to targeted therapy (Osimertinib, EGFRi) and immunotherapy (Pembrolizumab, PD1i). Genomic and clinical data were used to create the DFCI BM PDX cBioPortal for public release and models distribution will be available through the DFCI Center for Patient Derived Models.

47. UNCOVERING A NOVEL ROLE FOR HLA-G IN BRAIN METASTASES

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Brain metastases (BM) are the most common brain tumour in adults and are ten times more likely to develop than primary brain tumours. More than 20% of patients with cancer will develop BM with the three most common sources being primary cancers of the lung, breast, and melanoma. Unfortunately, current treatment options for BM do not effectively eradicate BM, with a mere median overall survival time of 12 months in treated patients. This indicates the need for better and more effective therapies against BM. Using patient-derived cell lines established from surgically removed brain metastatic tumours of lung-, breast- and melanoma-BM patients, we generated patient-derived orthotopic murine xenograft (PDX) models of lung-, breast-, and melanoma-BM. From these PDX models, we isolated a rare population of stem-like brain metastasis initiating cells (BMICs) we termed "pre-metastatic", that had traveled from their primary/orthotopic tumours and lodged in the brain but had not yet developed into mature BM. Transcriptomic analyses performed on pre-metastatic and non-pre-metastatic BMICs from lung, breast and melanoma PDX models of BM, identified a set of deregulated genes exclusive only to pre-metastatic BMICs. Further analysis revealed *HLA-G* as being commonly up-regulated only during the pre-metastatic stage of the lung-, breast-, and melanoma-BM cascade. *In vitro* and *in vivo* analyses demonstrated that HLA-G knock-down reduced the proliferation and survival of BMICs from all BM cohorts, and attenuated the establishment of mature brain metastatic tumours, implying a crucial role for HLA-G in the formation of BM. Developing a therapeutic strategy that targets HLA-G in BM may prove effective at completely eliminating brain metastatic cells at an early stage of the BM cascade, thereby turning a fatal disease into an eminently more treatable one.

48. DEVELOPING TUMOR-HOMING CYTOTOXIC HUMAN INDUCED NEURAL STEM CELLS AS AN ADJUVANT TREATMENT FOR RADIATION THERAPY OF BRAIN METASTASES

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INTRODUCTION: Non-small cell lung cancer (NSCLC) is the most common primary cancer to metastasize to the brain. Radiation is first-line for multifocal brain metastases, but recurrence is observed in 40% of patients. An adjuvant treatment to radiation is needed to effectively treat post-radiation tumor. Genetically engineered neural stem cells (NSCs) have the unique ability to seek out tumors and deliver therapeutic payloads that significantly reduce tumor burden. Here we have transdifferentiated human fibroblasts into induced neural stem cells (hiNSC) and explored the efficacy of hiNSCs therapy for NSCLC brain metastases. METHODS: hiNSCs were infused intracerebroventricularly (ICV) into mice with bilateral intracranial H460 NSCLC tumors. Bioluminescent imaging (BLI) was used to determine hiNSCs persistence while fluorescent analysis of brain sections characterized tumor-homing migration. *In vitro* co-culture assays and isobologram analysis were used to determine the synergistic effect of the cytotoxic protein TRAIL and radiation therapy on NSCLC tumor cells. To determine efficacy *in vivo*, H460 cells were implanted in the brains of mice and treated with either hiNSC-TRAIL alone or in combination with 2 Gy radiation. Tumor volumes were then tracked via BLI. RESULTS/CONCLUSION: hiNSCs persisted in the brain >1 week after ICV injection, and hiNSCs were found to co-localize with both bilateral tumor foci. Isobologram analysis showed a combination index of 0.64, suggesting radiation and TRAIL have a synergistic cytotoxic effect on NSCLC tumors. *In vivo*, radiation and hiNSC-TRAIL therapy reduced tumor volumes 90% compared to control-treated animals, while each therapy alone only reduced tumors 21% and 52%, respectively. While neither monotherapy significantly impacted survival, combination therapy demonstrated a 40% extension in survival, with treated mice surviving a median of 28 days while controls animals only survived 20 days. Together, these results demonstrate the therapeutic potential of hiNSC-TRAIL as an adjuvant to radiation for treatment of NSCLC brain metastases.

49. CORRELATES AND PREDICTORS OF HEALTH-RELATED QUALITY OF LIFE IN METASTATIC BRAIN CANCER

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PURPOSE: Neurocognitive functioning (NCF), mood disturbances, physical functioning, and social support all share a relationship with health-related quality of life (HRQOL). However, a characterization of these

relationships in persons with brain metastases (BM) has yet to be identified. METHODS: Ninety-three newly diagnosed persons with BM were administered a cognitive battery to assess neurocognitive functioning, mood disturbances, physical functioning, and social support. The Functional Assessment of Cancer Treatment (FACT) scale was used to measure HRQOL. RESULTS: Mood and physical function correlated with lower HRQOL in every measured domain. Verbal learning and memory correlated with every FACT subscale except emotional quality of life. Social support also correlated with several HRQOL domains. Stepwise linear regressions revealed that mood was the predominate predictor of HRQOL. Social support, physical functioning, verbal learning, and memory also contribute to HRQOL, but to a lesser extent. CONCLUSION: HRQOL is a complex construct affected by mood, physical functioning, and learning and memory. Mood is a domain-independent predictor of HRQOL, while non-mood variables predict HRQOL in domain-specific ways. Thus, multifactorial baseline assessments of persons with BM are encouraged to help mitigate the impact that BM has on HRQOL.

50. RISK OF TRACT RECURRENCE WITH STEREOTACTIC BIOPSY OF BRAIN METASTASES: AN 18-YEAR CANCER CENTER EXPERIENCE

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BACKGROUND: Stereotactic biopsy is increasingly performed on brain metastases (BrM) as improving cancer outcomes drive aggressive multimodality treatment, however the risk of tract recurrence for such biopsies, in both the upfront and recurrent settings, are poorly defined in an era defined by focused-irradiation paradigms. As such, the rate of tract recurrence was evaluated. METHODS: A retrospective review was performed to identify stereotactic biopsies performed for BrM at Memorial Sloan Kettering Cancer Center from 2002–2020. Data including surgical indications, tumor type, radiographic characteristics, stereotactic planning, pre- and post-operative CNS-directed and systemic treatments, and clinical courses were collected. Recurrence was evaluated using RANO-BM criteria. RESULTS: Four-hundred-and-seventy-nine patients underwent stereotactic intracranial biopsy for any diagnosis (>80% were gliomas or CNS lymphoma). Twenty-two (4.5%) were for pathologically-confirmed viable BrM and 91% (20/22) of these underwent postoperative irradiation with either stereotactic radiotherapy (14/20, 70%; SBRT) in plans that did not specifically target the biopsy tract, or whole-brain irradiation (6/20, 30%; WBRT). Eleven patients (50%) had >/=3 months radiographic follow-up (median 11.9; 4.5–30.6), of which 6 (55%) developed discontinuous enhancement along the tract at a median 6.4 months (2.3–17.1) post-biopsy. Of these, 2 had previously been treated with SBRT and were sampled in the setting of diagnostic ambiguity (one additionally with WBRT for small cell carcinoma) and underwent intraoperative laser interstitial thermal therapy (LITT) immediately following biopsy. The remainder were treated with SBRT +/- LITT (n=3 and 4, respectively) following biopsy. Tract recurrences were treated with resection (n=2, both with pathologic confirmation), re-irradiation (n=1) or observation/systemic therapy. CONCLUSIONS: In this largest reported series of biopsied BrM, we identify a nontrivial rate, higher than previously described, of recurrence along stereotactic biopsy tracts. As BrM are most commonly treated with focused radiotherapy centered on enhancing tumor margins, consideration should be made to include biopsy tracts where feasible.

51. BRAIN METASTASES FROM ENDOMETRIAL CARCINOMA: TUMOR GENETIC ALTERATIONS IN A CASE SERIES AND META-ANALYSIS

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INTRODUCTION: Endometrial carcinoma (EC) is the most common gynecologic malignancy in the world. While most patients (80%) can be cured with a hysterectomy, the remaining 20% patients who are diagnosed with advanced or recurrent disease have worse survival rates and limited adjuvant treatment options. Discovery of novel target(s)/pathway(s) is needed for better understanding of the pathogenesis and treatment development for this disease. The aim of this study is to review clinical characteristics and genetic signatures of histologically proven EC brain metastasis (BM). METHODS: For the period 2000–2019 the medical records of patients with histological diagnosis of EC BM at our Institution were reviewed. Data were collected and analyzed for age, time interval between EC and EC BM diagnoses, tumor molecular and genetic signatures, and outcome. Immunohistochemistry and sequencing performed as published. A meta-analysis was also performed for the same time period. Data presented as mean+SD and analyzed by t-test and Chi square. RESULTS: There were 6 BM from 5 patients meeting our cohort entry criteria and a total 123 cases reported in the literature. The mean age was 57.6 + 11.7 (range 39–69) consistent with reported data. The time interval between EC and EC BM diagnoses was 145.7 + 119.7 (range 33.1–275.7), significantly longer than reported (19.4 + 27.8; range 0–156; $p<0.05$). All BM in our cohort were metachronous, while only 59% were in the literature. Whereas all FIGO grades are reported in the literature (I=20%; II=6%; III=42%; IV=32%), only I and III were found in our cohort (I=60%, III=40%). Tumor microsatellite instability genes MSH2 and MSH6 were intact, whereas MLH1 and PMS2 showed mutations. PD-L1 expression was low. EC BM genomic reports were not found in the literature. CONCLUSIONS: Our study provides insight into the genomic alteration burden on EC BM. Information-driven genomic testing will continue to lead patient-centered therapeutic approaches.

52. BRMPANEL: A PUBLIC RESOURCE OF ORGANOTROPIC CELL LINES

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Central nervous system (CNS), notably brain, metastases are most prevalent in lung cancer (20–56% of patients), breast cancer (5–20%) and melanoma (7–16%). Lesions occur in both the brain parenchyma and the meninges. To mechanistically understand CNS metastasis formation and develop preventive and therapeutic strategies, it is essential to use model systems that, as much as possible, faithfully recapitulate the clinical disease process. Furthermore, the complexities of brain metastases dictate that studies should utilize multiple model systems in various stages of brain metastases progression. To facilitate brain metastasis research, 19 laboratories around the world have compiled comprehensive information on their brain metastasis mouse models. Each lab has provided details on the cell lines that they have generated or characterized as being capable of forming metastatic colonies in the brain, as well as principle methodologies of brain metastasis research. This Brain Metastasis Cell Lines Panel (BrMPanel, https://apps.