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