as survival is prolonged. We sought to identify subsequent LMD in patients with EGFR-mutated NSCLC treated initially with SRS for BM and describe the associated features, treatment, and outcome. METHODS: Review of our prospective Gamma Knife registry identified 177 patients with EGFR-mutated NSCLC between 2005 and 2021 treated with SRS. The EMR was queried for development of LMD, and type of LMD was recorded (focal/nodular or diffuse). RESULTS: 38 (21%) of the 177 patients developed LMD at a median of 10 months (range 1-25 IQR) following SRS. 27 (71%) of these were on tyrosine kinase inhibitors (TKI) at time of LMD diagnosis. Median overall survival (OS) from initial SRS for the entire cohort was 21 months (18-27 95%CI). Median OS after LMD diagnosis was 5 months (2-32 95%CI). LMD was diagnosed radiographically in 35 patients (92%); 20 patients had diffuse, 15 had focal/nodular, and 3 had positive CSF cytology. 26 (68%) had systemic progression synchronously with LMD. 33 (87%) had treatment for LMD including 19 with whole brain radiation therapy, 16 with the addition of or increased dosing of TKI, 6 with SRS for nodular disease, and 9 with intraventricular chemotherapy. The one- and two-year survival rates following the diagnosis of LMD was 21% and 3%, respectively. CONCLUSION: LMD developed in a substantial subset of our patients, and despite the use of a variety of salvage therapies, survival was poor. Investigation to identify factors correlating with the development of LMD and those related to outcome are ongoing. The development of LMD on TKI in several of our patients supports efforts to pursue development of therapeutic agents with long-lasting CNS efficacy.

LOCL-12

OUTCOMES OF STEREOTACTIC RADIOSURGERY FOR BRAIN METASTASES OF BREAST CANCER IN RELATION TO MOLECULAR SUBTYPES

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PURPOSE: To determine intracranial outcomes following stereotactic radiosurgery (SRS) for brain metastases of breast cancer in relation to molecular subtypes of HER2 (human epidermal growth factor receptor) overexpression and estrogen receptor (ER) expression. METHOD: From a retrospective institutional database of SRS using VMAT (volumetric modulated arc therapy) carried out between 2012 and 2019, patients with a primary diagnosis of breast cancer were identified. Outcomes following first course of SRS were analyzed using radiotherapy plans and electronic patient records. Systemic anticancer treatments were not registered. Time to intracranial progression (TTP) was calculated using the Kaplan Meier method as the time between SRS and recurrence, whereas dates of death or last follow up without recurrence were censored. The study was approved by the Danish Patient Safety Authority (nr. 31-1521-125). RESULTS: The study included 159 patients. 132 patients (83%) underwent a brain MRI examination after SRS and, of these, 101 had recurrence, either local (41%), remote (43%) or both (16%). Tumors were HER2 positive in 50% of cases and 61% were ER positive and 15% were triple negative. The median intracranial TTP was for the whole study group 9.1 months. Median intracranial TTP for patients with the HER2+ / ER+ subtype was 15.4 mos. whereas patients with the triple negative subtype had a significantly shorter median intracranial TTP of 5.1 mos. (p=0.007). Patients with HER2+/ER- and HER2 normal/ER+ had similar median intracranial TTP times of 7.7 mos. and 8.4 mos., respectively (n.s.). CONCLUSION: This study found high rates of intracranial recurrence following SRS and poor intracranial TTP that was highly dependent on molecular subtypes, reflecting either biological differences or intracranial effect of systemic treatments or both. The study confirms the universally poor prognosis for breast cancer patients with brain metastases and the high frequency of HER2 overexpression in this patient group.

LOCL-13

SURGICAL RESECTION PLUS STEREOTACTIC RADIOSURGERY (SRS) VERSUS SRS ALONE FOR LARGE POSTERIOR FOSSA BRAIN METASTASES: OUTCOMES AND FACTORS GUIDING THE DECISION OF TREATMENT MODALITY

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INTRODUCTION: Approximately 20% of brain metastases (BM) occur in the posterior fossa (PF). However, the criteria to treat large PF BM with surgery (S) followed by stereotactic radiosurgery (SRS) or SRS alone are still unclear. We aim to identify parameters that can help in the decision of treating PF BM with S+SRS or SRS and to compare outcomes between the two groups. METHODOLOGY: We reviewed a prospective registry database (2009 to 2020) and identified all patients with PF BM (≥4cc in volume) treated with SRS or S+SRS. Clinical and radiological, parameters were analyzed. We examined two endpoints: Overall Survival (OS) and Local Failure (LF). RESULTS: 64 patients were identified; 30 were treated with S+ SRS and 34 with SRS. Gait imbalance and Intracranial pressure symptoms were significantly different between the groups; 97% and 80% for S+SRS vs 47% and 35% for SRS, respectively. Radiologically, there were significant differences in the mean volume of the lesions [6.7 cm3 in SRS vs 29.8cm3 in S+SRS cohort] (p<0.001), compression of the IV ventricle (47% in SRS vs 96% in S+SRS cohort, (p<0.001)) and hydrocephalus (0% in SRS vs 29% in S+SRS cohort, (p<0.001)). One surgical patient required salvage SRS and two SRS patients required salvage S. Patients with S+SRS (HR 0.35, p<0.001) and higher GPA scores (HR 0.62, p=0.007) correlated with better OS. There was no significant difference in rates of LF between the 2 groups. CONCLUSIONS: Patients treated with S+SRS were more likely to be symptomatic, have larger tumors, and have compression of the IV ventricle with hydrocephalus. Non-symptomatic patients with moderately sized lesions were safely managed with SRS. S+SRS treatment and higher GPA were associated with improved OS.

LOCL-14

FACTORS ASSOCIATED WITH TRACT SEEDING AFTER LASER INTERSTITIAL THERMAL THERAPY FOR INTRACRANIAL TUMORS

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Laser interstitial thermal therapy (LITT) is a growing minimally-invasive approach for treatment of intracranial tumors. Stereotactic placement of the laser catheter within the target lesion carries a theoretical risk of tract seeding, which could lead to disease progression. A retrospective analysis of patients treated with LITT for biopsy-confirmed tumor from 2016-2020 was conducted to characterize the risk of post-LITT tract seeding. Forty-two patients met inclusion criteria, of whom 23 (54.7%) had primary brain tumors and 19 (45.3%) metastases. Thirty-three (78.6%) lesions were recurrent disease at the time of LITT. On follow-up MRI, 3 patients (7.1%) were identified to have had tumor seeding along the LITT tract resulting in progressing disease. There were no significant differences in tumor histology, pre-operative maximum lesion diameter, number of LITT trajectories, rounds of lasing, or post-LITT radiotherapy or surgery between patients with and without tract seeding. All patients with tract seeding were treated for periventricular lesions (<1cm). Patients with tract seeding were also more likely to have received LITT ablations administered from the superficial to deepest elements of the lesion (p=0.05). The median time to progression post-LITT for patients with tract seeding was significantly shorter than those without (1.1 vs 5.9 months, p=0.02). Additional analyses revealed trends towards longer median tract length (4.0 vs. 2.2 cm, p=0.23) and shorter overall survival (5.4 vs. 14.2 months, p=0.17) in the tract seeding cohort. In summary, tract seeding is an infrequent complication associated with both LITT and traditional biopsy. In LITT, tract seeding progression occurs significantly faster than at the treated site, which may be associated with a worse overall prognosis. Prophylactic stereotactic radiosurgery to the LITT tract could be of benefit, however this may pose further risk to patients given the low overall frequency. More frequent monitoring may be necessary lesions in periventricular or difficult to ablate regions, or with longer LITT tracts.

LOCL-15

PERMANENT CARRIER-EMBEDDED CESIUM-131 BRACHYTHERAPY FOR THE SALVAGE TREATMENT OF PREVIOUSLY IRRADIATED, RECURRENT BRAIN METASTASES

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BACKGROUND: Salvage of recurrent of previously-irradiated brain metastases (rBrM) is a significant clinical challenge. High local failure rates are seen following salvage resection without adjuvant re-irradiation, while reirradiation is associated with high radionecrosis rates. Salvage surgery plus intraoperative Cs131 brachytherapy may offer dosimetric and biologic advantages including improved local control versus observation, with reduced integral brain dose versus re-irradiation. METHODS: A prospective registry of consecutively treated patients with rBrM after prior stereotactic radiosurgery (SRS) was analyzed. Following maximal-safe re-

section and intraoperative viable-disease confirmation, cavities were implanted with commercially-available, collagen-matrix embedded Cs131 seeds (GammaTile, GT Medical Technologies). Prescribed dose was 60Gy at 5mm from the cavity. RESULTS: Twenty patients underwent 24 operations with Cs131 implantation in 25 cavities. Previous SRS occurred a median of 358d preoperatively (range=56-1334). Median maximum preoperative diameter was 3.0cm (range=1.1-6.3) and enhancing volume was 9.5cm3 (range=0.6-69.7). Gross- or near-total resection was achieved in 60% of lesions. A median of 16 Cs131 seeds (range=6-30), with a median activity of 3.5U/seed were implanted. Maximal preoperative diameter and enhancing volume were weakly associated with the number of implanted seeds (correlation coefficients=0.50, 0.41, respectively). There was one postoperative wound dehiscence in a multiply resected and irradiated patient with hydrocephalus. With median follow-up of 12.5 months, 2 tumors recurred (one in-field, one marginal) resulting in a 1-year progression incidence of 9.8% (95%CI=0.0-23.2). Radiographic seed migration was identified in 7/25 cavities (28%) on surveillance scans ranging from 1.9-11.7 months post-implantation, without clinical sequelae. CONCLUSIONS: With >1 year of follow-up, intraoperative brachytherapy with commercially-available Cs131 implants was associated with a high rate of local control and a favorable toxicity profile. Modest correlation between preoperative tumor geometry and implanted tiles in the context of high associated cost suggests a need to optimize planning criteria. A randomized trial of salvage resection with or without Cs131 is ongoing (NCT04690348) to assess the incremental benefit of brachytherapy.

LOCL-16

IMPACT OF MGMT PROMOTER METHYLATION STATUS ON TUMOR DYNAMICS DURING WEEKLY ADAPTIVE RADIOTHERAPY FOR GLIOBLASTOMA

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PURPOSE: Adaptive MRI-guided radiotherapy (RT) on a 1.5T-MR-Linac using reduced clinical target volumes (CTV) of 5mm instead of the 15mm standard for glioblastoma (GBM) is currently being evaluated on the UNITED clinical trial (NCT04726397). We explored the morphological changes that occur during adaptive RT with concurrent temozolomide between tumors with MGMT promotor methylation (MGMT-m) vs. unmethylation (MGMT-um). METHODS: Thirty patients with IDH-wildtype GBMs were treated with 60Gy in 30 (n=12) or 40Gy in 15 fractions (n=18) (Fx). The CTV included a 5mm expansion on the gross tumor volume (GTV) +/- FLAIR hyperintense areas-at-risk and a 3mm planning target volume. Planning was performed on a pre-treatment reference MRI (FxRef) followed by weekly on-line adaptive re-planning at Fx1, Fx6, etc. acquired on the MR-Linac. Interim fractions were image-guided by pre-beam-on onboard MRI. The GTV/CTVs were quantified by their absolute volumes, volumes relative to the FxRef and the maximum linear distance from the edges of the reference contour to the weekly adapted contours (migration distance, d_{mig}). MGMT promoter methylation status was explored as a fixed effect in a linear mixed statistical model. RESULTS: Weekly median changes in GTV relative to FxRef in MGMT-um tumors (n=12) were 10.3%, 9.2%, 10.6%, 14.5%, 18.0% and 17.3%, respectively, while for MGMT-m (n=18) were 3.4%, 0.0%, -8.6%, -11.3%, -11.3% and -5.6% (p=0.021). Between FxRef and Fx1, the GTV increased by over 10% in 58% of MGMT-um tumors vs. 33% of MGMT-m tumors. Similar significant trends were observed with the CTVs. MGMT-um tumors had significantly larger d_{mig} compared to tumors with MGMT-m (median 9.6mm vs. 5.8mm, respectively (p=0.018)). CONCLUSIONS: MGMT-um GBM exhibited significant changes in morphology and migration distance between the time of treatment planning to the first treatment fraction, as well as throughout a course of RT. In this population, our results support a greater frequency of imaging and plan adaptation when applying personalized reduced CTV margins.

FINAL CATEGORY: MULTIMODALITY APPROACHES

MMAP-02

A POPULATION - BASED STUDY ON RADIATION THERAPY FOR BRAIN METASTASIS FROM MALIGNANT MELANOMA IN BRITISH COLUMBIA: EVALUATING THE IMPACT OF IMMUNOTHERAPY AND STEREOTACTIC TECHNIQUES.

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BACKGROUND: To evaluate population-based outcomes for patients with brain metastasis from malignant melanoma, treated using radiation therapy, and to assess the impact of immunotherapy (IMT) and stereotactic radiation techniques (SRT). METHODS: Data was obtained from the BC Cancer Registry for all patients diagnosed with Melanoma in British Columbia, between 1st Jan 2005 and 31st Dec 2018. A total of 5133 patients were identified. These patients had received 2244 courses of RT, of which 461 were directed to the Brain, in 419 unique individuals. The median age was 62 years and majority, 89.5% (n=375), had cutaneous melanomas while 44 had mucosal or choroidal primary sites of disease. A total of 106 (25.3%) patients received IMT, and pembrolizumab was most commonly used (n=48). Over 85% of patients (n=358) received Whole Brain Radiation Therapy (WBRT) alone, with 20 Gy/5 being the most common dose fractionation. Stereotactic Radio-Surgery (SRS) or SRT alone was used in 31 patients, while 30 patients received a combination of SRS/SRT and WBRT. The most used fractionation for SRS was 30Gy/1 (n=9), and for SRT was 35 Gy/5 (n=25). Overall Survival (OS) was calculated from the date of starting radiation therapy. RESULTS: After a median follow-up of 43 months (95% CI: 18.2 - 67.7), a total of 377 patients had died, with a Median Survival of 2 months (95% CI: 1.46 - 2.53 months) and a 2 year OS of 11.7%. On univariate analysis, age over 65, use of IMT, and SRS/SRT had a significant impact on 2-year OS (14.5% vs 7.4%, p<0.0001; 27.6% vs 6.7%, p<0.0001; and, 38.7% vs. 7.1% p <0.0001, respectively). These factors retained statistical significance on multi-variable analysis. The 2 year OS for patients who received IMT and SRS/SRT alone (n=22) was 54.7%. CONCLUSION: Selected patients treated aggressively with SRS/SRT and IMT have a median survival of >25 months and a 2-year OS > 50%.

MMAP-04

CYTOTOXIC, TUMOR-HOMING INDUCED NEURAL STEM CELLS AS AN ADJUVANT TO RADIATION IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER LEPTOMENINGEAL METASTASES

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INTRODUCTION: Non-small cell lung cancer (NSCLC) is the most common cancer to spread to the brain, and spread to the leptomeninges is particularly devastating, with a median survival of only months. While radiation may offer symptomatic relief, new adjuvant therapies are needed for more durable tumor kill. Spheroidal, human induced neural stem cells (hiNeuroS) transdifferentiated from fibroblasts are inherently tumoritropic. When engineered to secrete the cytotoxic protein TRAIL, they provide the potential for a personalized, targeted approach to NSCLC leptomeningeal metastases. METHODS: hiNeuroS-TRAIL *in vivo* efficacy was determined by tracking the progression and survival of mice with NSCLC leptomeningeal tumors treated with intracerebroventricular hiNeuroS, radiation, or both. To determine the impact of radiation on the tumor tropism of hiNeuroS, we performed 2-dimensional motion assays on hiNeuroS with and without the presence of NSCLC pre- and post-radiation. Migrational capacity *in vivo* was determined by infusing hiNeuroS into the lateral ventricles of mice with established NSCLC tumors and monitoring hiNeuroS accumulation using post-mortem fluorescent analysis. RESULTS/CONCLUSION: Mice treated with the combination of hiNeuroS-TRAIL and 2 Gy showed a significantly reduced mean tumor signal (2.7%) compared to controls (100%) or 2 Gy-only (54.9%). Mice treated with 2 Gy alone showed no significant survival difference compared to controls. Both combination and hiNeuroS-TRAIL-only-treated mice showed a significant improvement in median survival compared to controls (36.6% and 46.3% improvement, respectively). hiNeuroS showed enhanced directionality and displacement in the presence of NSCLC in 2-dimensional motion assays, indicating directional migration, and they maintained this ability following exposure to radiation. Co-localization of hiNeuroS with NSCLC was also observed *in vivo*. These results suggest the potential of hiNeuroS-TRAIL as a powerful adjuvant to radiation in the treatment of leptomeningeal NSCLC.

MMAP-05

PHASE I STUDY OF CONCURRENT PAXALISIB AND RADIATION THERAPY IN PATIENTS WITH SOLID TUMOR BRAIN METASTASES OR LEPTOMENINGEAL METASTASES HARBORING PI3K PATHWAY MUTATIONS: RESULTS FROM THE DOSE-ESCALATION COHORT

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INTRODUCTION: Radiation therapy (RT) is an effective treatment for patients with central nervous system metastases, but disease control is poor in patients with tumors that harbor PI3K pathway alterations. We hypothesized that combining RT with paxalisib, a CNS-penetrant small molecule PI3K/mTOR inhibitor, could abrogate this effect via downregulation of prosurvival pathways. METHODS: This is a single institution, open-