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-

label, phase I trial of concurrent paxalisib and RT (NCT04192981) for patients with brain metastases, leptomeningeal metastases, or both with PI3K pathway mutations. Part A comprised a standard 3 + 3 dose escalation of paxalisib at 45mg, 60mg, or 75mg daily for two weeks with concomitant RT. The primary objective was to establish the maximum tolerated dose (MTD) of paxalisib when combined with cranial RT. RESULTS: Between 3/2020-1/2022, 12 patients were enrolled to Part A, of which 9 were evaluable (3 did not complete protocol therapy). Median followup was 4.5 months (0.9-14.9 months). All patients received paxalisib with whole brain RT (30Gy in 10 fractions)- 10 patients for brain metastases, and 2 for leptomeningeal metastases. The most common histology was breast cancer (4 [33%]), and the most common PI3K pathway alterations were PIK3CA mutation (7 [58%]). No patient experienced dose-limiting toxicity (DLT) at 45mg paxalisib daily with concurrent RT, and 2 experienced DLT at 60mg paxalisib: 1 with grade 3 nausea and vomiting and 1 with grade 4 enterocolitis and neutropenia. When combined with cranial RT, the paxalisib MTD was established at 45mg/day. We also observed robust response with all evaluable patients experiencing partial or complete response per RANO-BM within 3 months of protocol therapy. CONCLUSION: A MTD of 45mg/day has been established for paxalisib with concurrent cranial RT in patients with solid tumor brain metastases and leptomeningeal metastases harboring PI3K pathway mutations. Additional patients are being recruited to an expansion cohort at this dose (Part B) to confirm safety and preliminary evidence of activity.

MMAP-06

INTEGRATED TEAM-BASED BRAIN METASTASIS CARE REDUCES PATIENT VISITS AND SHORTENS TIME TO ADJUVANT IRRADIATION

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PURPOSE: Timely surgical cavity stereotactic radiosurgery (SRS) is an important adjuvant to brain metastasis resection, with earlier treatment associated with less frequent recurrence. The logistical complexity of treatment organization, however, has resulted in suboptimal start times post-surgically. We implemented a team-based process improvement approach to reduce the time from surgery to adjuvant irradiation of resected brain metastases. METHODS: A multidisciplinary working group used process-mapping to identify opportunities to reduce visits and shorten treatment times. The care delivery process was modified to streamline perioperative SRS preparation with (1) early patient identification, (2) preoperative intra-team communication, and (3) consolidation of required steps. Plan-Do-Study-Act cycles were used for process improvement. The surgery-to-SRS initiation time interval was the primary outcome. Secondary outcomes included the number of associated patient encounters. RESULTS: Following implementation, the median (IQR) interval from surgery to SRS was reduced 48% from 27 (21,34) to 14 (13,17) days (p<0.001). The rate of surgical-cavity SRS within 30 days increased from 64% (n=63/98) to 97% (n=60/62; p<0.001). The median (IQR) number of CNS-associated encounters between resection and SRS decreased from 5 (4,6) to 4 (3,5; p<0.001). The proportion of patients who had >1 MRI/CT between surgery and SRS decreased from 45% (44/98) to 13% (8/62; p<0.001). The time from surgery to systemic therapy resumption/initiation among patients treated within 90 days post-operatively decreased from 35 (24,48) to 32 days (23,40; p=0.074). There were no wound complications in either group. CONCLUSION: Adjuvant SRS latency and treatment-associated encounters were significantly reduced after care-coordination implementation. This approach reduces patient and healthcare system burden and can be applied to other scenarios where early post-operative SRS administration is critical.

MMAP-07

IMPACT OF SINGLE AND DUAL IMMUNE CHECKPOINT BLOCKADE ON RISK OF RADIATION NECROSIS AMONG PATIENTS WITH BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOSURGERY

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PURPOSE: While stereotactic radiosurgery (SRS) is often an efficacious treatment for brain metastases, it carries a significant risk of radionecrosis (RN). Single and dual immune checkpoint inhibition (ICPI) have emerged as common treatment options for many patients, particularly those with melanoma and non-small cell lung cancer (NSCLC). While data suggest a cancer control benefit of combining SRS and ICPI, we hypothesized that concurrent receipt of dual ICPI with SRS increases the risk for RN. METHODS: We performed a retrospective review of serial patients with metastatic melanoma or NSCLC treated with SRS for intact brain metastases from 2014-2020 at our single institution. Patients were stratified by receipt of dual vs. single ICPI vs. SRS alone. RN was biopsy confirmed or determined radiographically, in combination with clinical assessment and steroid use. Kaplan-Meier estimates were used to compare rates of RN between cohorts. RESULTS: 673 brain lesions from 93 patients met inclusion criteria [median (Q1, Q3): 5.0 (2.0-10.0) lesions per patient]. Median follow-up of lesions was 8.1 months (95% CI: 7.3, 8.7). Most (82.8%) lesions were supratentorial and histologies included melanoma (53.5%), adenocarcinoma NSCLC (27.3%), squamous cell NSCLC (6.1%), and NSCLC NOS (6.1%). In the entire cohort, 88 lesions from 25 patients (27%) developed RN. 77 (87%) lesions were diagnosed clinico-radiographically and 11 (13%) were biopsy-proven. ICPI use was highly enriched among lesions that developed RN (85.2%) versus those that did not (19.8%). Freedom from RN at 6 months was 80% for dual ICPI, 82% for single ICPI, and 97% for SRS alone; 12 month rates were 78% in each of the ICPI cohorts and 95% with SRS alone (P=0.0002). CONCLUSIONS: In a large cohort of SRS-treated brain metastases, we observed an increased risk of RN among patients who received either dual or single ICPI concurrently with SRS.

MMAP-08

CHEMO-REIRRADIATION (NORMOFRACTIONATED VS. HYPOFRACTIONATED) WITH OR WITHOUT BEVACIZUMAB IN RECURRENT ADULT DIFFUSE HIGH-GRADE GLIOMA (COBRA): PHASE III RANDOMIZED CONTROLLED TRIAL WITH A 2 X 2 FACTORIAL DESIGN

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BACKGROUND: Adult diffuse high-grade gliomas (HGG) predominantly recur locally despite adequate treatment. At recurrence, salvage chemo-reirradiation (CTRT) provides durable local control with significant risk of symptomatic radionecrosis (RN). Reirradiation (reRT) is delivered using either conventional fractionation (CFRT) or hypofractionation based on institutional preferences. Studies have shown that the addition of bevacizumab, a monoclonal antibody inhibiting vascular endothelial growth factor to reRT reduces the risk of RN and potentially improves survival, providing strong scientific rationale for the combination. OBJECTIVE: Primary endpoint would be a composite endpoint of 1-year event-free survival (EFS) comprising recurrence, symptomatic RN or death as an event. Secondary endpoints include progression-free survival, cumulative incidence of symptomatic RN, and overall survival. Quality-of-life assessment and health-economics would be tertiary endpoints. METHODS: Target population includes adults with local recurrence (radiology and/or histology) of biopsy-proven diffuse HGG >2-years from primary RT. This is an open-label, phase III randomised control trial using a 2 x 2 factorial design comparing the addition of bevacizumab to chemo-reirradiation (test arm) versus chemo-reirradiation alone (control arm) using a superiority hypothesis. Patients in test arm will receive 6 months of bevacizumab (5mg/kg) 2 weekly, along with standard 6 cycles of temozolomide, starting 1 month following reRT completion. All patients will be further randomized to CFRT (50.4-55.8Gy/28-31/5.5-6 weeks) as control arm versus moderately HFRT (35Gy/10 fractions/2 weeks) as test arm in 1:1 ratio using a non-inferiority hypothesis. The desired sample size is 257 (two-sided alpha 0.05, power 80%, and 10% attrition rate) with a superiority hypothesis of 1-year EFS 45% (bevacizumab with CTRT) vs 30% (CTRT), and non-inferiority hypothesis of 25% (HFRT) vs 37% (CFRT),with delta of 12%. DISCUSSION: The study will answer critical questions regarding the role of bevacizumab in recurrent HGG along with reRT, along with the differences in outcomes using normofractionated or hypofractionated RT.

MMAP-09

CHARACTERISTICS CORRELATING WITH SURVIVAL IN PATIENTS TREATED FOR LARGE BRAIN METASTASES

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BACKGROUND: We aimed to identify factors predicting survival following treatment to large (>4cc) BrM. METHODS: From a prospective registry database, we identified 364 adult patients treated for brain metas-