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-

tases (BrM) or surgical cavities larger than >4 cc: 127 and 237 treated with surgery plus stereotactic radiosurgery (S+SRS) and SRS alone, respectively. We compared the 2 treatment arms using propensity score-matched (PSMA) and multivariate analyses (MVA). P values <0.05 were considered statistically significant. RESULTS: Median target volume was 6.6cc (4-36.9cc) for intact BrM and 15cc (4-54) for cavities. Median OS was 19 and 12 months for the S+SRS and SRS groups, respectively [HR 1.73 (1.35-2.22) (P<0.001)]. On UVA, number of BrM [HR 1.13 (1.06-1.22) (P<0.001)], ECOG 3-4 [HR 2.78 (1.73-4.46) (P<0.001)], and extracranial disease (ECD) at BrM treatment [HR 1.82 (1.37,2.40) (P<0.001)], correlated inversely with OS. GPA [HR 0.61 (0.52,0.70) (P<0.001)] and receipt of systemic therapy after BrM treatment[HR 0.58 (0.45-0.75) (*P*<0.001)] correlated to improved OS. On MVA, S+SRS [HR 1.81 (1.19,2.74) (P<0.0054)], reduced target volume [HR 1.03 (1.01,1.06) (P<0.0042)], and receipt of immune/targeted therapy [HR 0.68 (0.50,0.93) (P<0.015)] correlated with OS. PSMA comparing the treatment arms matched by ECD, number of BrM, ECOG, and SRS target volume, demonstrated that treatment arm remained correlated to OS [HR 1.62 (1.20-2.19) (P=0.0015)]. The cumulative incidence (CI) of LF requiring surgical resection at 12 months was 3% versus 7% for S+SRS and SRS groups, respectively [(HR 2.04 (0.89-4.69) (P =0.091)]. CI of PMD at 12 months was 16% versus 0% for S+SRS and SRS groups, respectively. CONCLUSION: Reduced SRS target volume, treatment with systemic therapy following BrM treatment, and surgical resection prior to SRS correlate with survival in patients with large BrM. PMSA supports the hypothesis that surgery prior to SRS improves survival in patients with large BrM.

MMAP-10

ADVERSE RADIATION EFFECT AFTER STEREOTACTIC RADIOSURGERY AND IMMUNOTHERAPY/TARGETED THERAPY FOR MELANOMA BRAIN METASTASES

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BACKGROUND: Safety of immunotherapy (IO) and targeted therapy (TT) with stereotactic radiosurgery (SRS) in melanoma brain metastases (MBM) treatment remains incompletely understood. We aim to identify whether timing of IO/TT in relation to SRS impacts rates of adverse radiation effect (ARE) in MBM. METHODS: Retrospective review of patients with MBM treated with SRS and IO/TT within three months prior and one year after SRS, from 2011-2021 at a single institution with at least two months MRI follow-up, identified 108 patients with 939 unique MBM meeting criteria. ARE was confirmed on independent imaging review. Concurrent IO/TT was defined as receiving IO/TT within 4 weeks before or after SRS. Data analysis was performed with the univariate cox proportional hazard model and Kaplan-Meier method. RESULTS: Median radiographic follow-up from time of SRS was 16months. IO/TT was initiated prior to SRS for 681 (72.5%) metastases and after SRS for 258 (27.5%) metastases. 837 (89.1%) metastases received concurrent IO/TT. Most common IO agents were ipilimumab (n=416), nivolumab (n=448), and pembrolizumab (n=203). Most common TT agents were dabrafenib (n=548), trametinib (n=540), and vemurafenib (n=81). 2-year local progression-free survival (PFS), distant intracranial PFS, and overall survival were 94.1%, 33.3%, and 55.2%, respectively. 55 (5.9%) metastases in 33 (30.6%) patients experienced ARE. Median time to ARE was 5mo (IQR 4-9mo). Of those who experienced ARE, 22 (66.7%) patients were symptomatic and treated with steroids; 12 (36.4%) patients underwent surgical intervention. ARE rates were not impacted by concurrent vs nonconcurrent IO/TT (5.5% vs 4.9%, p=0.34) nor IO/TT initiation pre vs post SRS (6.0% vs 5.4%, p=0.61). CONCLUSION: IO/TT in conjunction with SRS resulted in low ARE rates as compared to historical controls in the pre-IO/TT era. Timing of IO/TT in relation to SRS may not significantly impact ARE rates in MBM treatment.

MMAP-11

VOLUMETRIC STUDY OF BRAIN METASTASES IN EGFR-POSITIVE NSCLC TREATED WITH OSIMERTINIB WITH OR WITHOUT CNS-DIRECTED RADIATION THERAPY

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BACKGROUND: In patients with brain metastases (BM) from EGFR-positive non-small cell lung cancer (NSCLC), recent data indicated that treating with CNS-penetrant tyrosine kinase inhibitors such as osimertinib may enable deferring radiotherapy (RT) in select patients. The purpose of this study was to describe the radiographic response of newly diagnosed BM to osimertinib with or without stereotactic radiosurgery or whole brain radiotherapy, to identify parameters that may guide early versus delayed salvage RT. METHODS: In this single-institution retrospective study, 35 patients with 186 newly diagnosed BM started on osimertinib between 2014 and 2020 were reviewed. BM with tumor volume ≥ 0.1 cm^3 were included in the volumetric analyses (N=106 BM). Survival was estimated with the Kaplan-Meier method, and univariable analysis was performed using log-rank tests. Cox proportional hazards was used for multivariable analyses for local control (LC), distant brain failure (DBF), and overall survival (OS). RESULTS: Of the 35 patients, 8 (23%) received osimertinib alone. Median follow-up was 29 months. The 1- and 2-year LC rates were 94% and 86%. The 1- and 2-year OS rates were 89% and 66%. Median time to DBF was 24 months. Patients treated with osimertinib and RT were more likely to have a significant radiographic volumetric response at early follow-up (4-12 weeks after treatment initiation) compared to osimertinib alone (median volumetric response of –80% vs. –41%, p=0.05). On per lesion analysis, early volumetric response of ≥ 80% was associated with improved LC (3-year LC 98% vs 72%, p=0.04). CONCLUSIONS: The combination of osimertinib and CNS RT is associated with greater early volumetric response in patients with BM from EGFR-positive NSCLC compared to osimertinib alone. BM with significant initial radiographic response remain well-controlled in the long term. Patients whose BM demonstrate limited initial volumetric response may benefit from targeted RT to provide long term control.

FINAL CATEGORY: NEUROIMAGING

NEIM-01

INCIDENCE AND DIAGNOSTIC TECHNIQUES FOR LEPTOMENINGEAL DISEASE IN PATIENTS WITH BRAIN METASTASIS

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BACKGROUND: Leptomeningeal disease (LMD) is malignant infiltration of the pia mater and cerebrospinal fluid (CSF) space. LMD carries a poor prognosis with median survival of a few months. Annually, 110,000 patients in the United States are diagnosed with LMD. The incidence is rising because of improvements in control of primary cancers and recognizing that LMD is a late sequelae of some malignancies. Definitive diagnosis of LMD is made by CSF cytology and/or spine MRI, although neither tool shows robust sensitivity. The diagnostic challenges for LMD have led to a lack of uniformity in the diagnostic approach. METHODS: A systematic chart review of brain metastasis patients was conducted at Froedtert Hospital between 2019-2021. Information on primary cancer, LMD suspicion, work up, confirmation, treatment, and survival were collected and analyzed. RESULTS: Among 151 patients with brain metastasis, 86 were suspected and 29 were confirmed to have LMD. Of the confirmed patients, the most common primary cancers were lung (n=8, 27.6%) and breast (n=8, 27.6%). Most patients (n=24, 82.8%) underwent both LP and MRI. LMD was confirmed by positive cytology in a minority of cases (n=9, 31%), with most patients being confirmed by positive MRI or clinical findings alone (n=20, 69%). All LPs had over 10 mL of CSF sent to analysis. A median of 2 LPs were required before a positive cytology confirmed the diagnosis. Due to small sample size, no statistical analysis was made to correlate positive LP with primary cancer sites. CONCLUSION: Less than one third of cancer patients with confirmed LMD have positive cytology, despite the majority (>80%) of them undergoing LP. The dissonance between diagnostic strategies and confirmatory results is expected considering the low sensitivity of LPs; however, it highlights the need for more precise diagnostic tools, and development of a data-based strategy for LMD confirmation.

NEIM-02

DEVELOPMENT OF A DEEP LEARNING MODEL FOR DISCRIMINATING TRUE PROGRESSION FROM PSEUDOPROGRESSION IN GLIOBLASTOMA PATIENTS

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INTRODUCTION: Glioblastomas (GBMs) are highly aggressive tumors. Despite multimodal treatment, its median overall survival ranges between 16 and 20 months. The standard treatment regimen consists of surgical resection followed by concurrent chemoradiotherapy and adjuvant temozolomide. Despite temozolomide's effectiveness, it may cause the clinical challenge of