treatment of brain metastases (BMs) with minimal toxicity and less systemic therapy interruption. Here we assessed clinical outcomes in BC patients who received upfront stereotactic radiosurgery (SRS). METHODS: We identified 236 patients who received upfront SRS with/without surgery for BMs from metastatic BC from 06/2007 to 05/2018. Twenty-four patients who received SRS for surgical cavity were excluded for analysis. Overall survival (OS) and salvage radiation-free survival (SRFS) were estimated using Kaplan-Meier analysis. Cox proportional hazard regression was used to identify prognostic factors. RESULTS: At a median follow-up time of 15.4 months (range, 0.8–119.6), the estimated median OS was 18.5 mo (95% CI, 14.9–21). Factors associated with OS on multivariate analysis (MVA) were molecular subtypes (12.2 months for triple-negative [n=68], 13.3 months for HR+/HER2- [n=66], 36.4 months for HR+/HER2+ [n=46], and 28.1 months for HER2+ [n=32], p=0.002), KPS >80 (p<0.0001), receipt of chemotherapy (p=0.016) or anti-HER2 therapy (p=0.029) after diagnosis of BM, and type of salvage radiation (p<0.0001). OS was comparable in patients who received upfront SRS to less or more than 4 lesions (19.3 months for <4 [n=162] vs. 17.8 months for >/= 4 [n=50], p=0.36). The 12-month salvage RT rate was 25% for WBRT and 26.4% for SRS. The median SRFS was 7.4 months (95% CI, 6.5–8.3). Factors associated with SRFS on MVA were subtypes (p=0.002), KPS (p=0.011), and receipt of hormone therapy after diagnosis of BM (p=0.031). CONCLUSIONS: The median OS for BC patients who developed BM is over 15 months. Molecular subtypes (HER2+ and HR+/HER2+), good KPS, and anti-HER2 or hormone therapy predicted better OS and SRFS. Prospective studies are needed to verify these results and refine the best treatment strategies for these patients.

RADI-19. THE INCIDENCE OF NEW BRAIN METASTASES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER FOLLOWING DISCONTINUATION OF SYSTEMIC THERAPY

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PURPOSE: Patients with non-small cell lung cancer (NSCLC) metastatic to the brain increasingly are living longer due to improvements in systemic therapy and local modalities. The risk of new brain metastases when these patients stop systemic therapy is unknown. Recognizing patterns of new tumor occurrence is necessary to determine the frequency of follow-up and the need for further treatment. METHODS: We included patients in a prospective registry who had non-small cell lung cancer (NSCLC) brain metastases, discontinued systemic therapy for at least 90 days, and underwent active surveillance. 63 patients with 73 off-periods were studied. The risk factors for the development of new tumors were determined using Cox regression and multi-state Markov modeling. RESULTS: The median time to new brain metastases off systemic therapy was 16.0 months. The probability of developing an additional new tumor at 6, 12, and 18 months was 26%, 40%, and 53%, respectively. There were no additional new tumors 22 months after stopping therapy. Patients who discontinued therapy due to intolerance or progression of the disease and those with mutations in RAS or receptor tyrosine kinase pathways (e.g. KRAS, EGFR) were more likely to develop new tumors (HR: 2.21, 95% CI: 1.25–3.91, p=6.3 x 10^{-3}; HR: 2.03, 95% CI: 1.09–3.77, p=0.026, respectively). CONCLUSION: The rate of new brain metastases from NSCLC in patients off systemic therapy decreases over time and is uncommon 2 years after cessation of cancer therapy. Patients who stop therapy due to toxicity or who have RAS or receptor tyrosine kinase pathway mutations have a higher rate of new metastases and should be followed more closely.

RADI-20. BRAIN METASTASIS TREATMENT WITH HIGH ENERGY RADIOTHERAPY AND CHERENKOV RADIATION-ACTIVATED PHOTOTHERAPY

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Radiation therapy is a mainstay in the treatment of brain metastasis, yet some tumors are resistant, and elsewhere brain recurrence outside the radiation field is common. Phototherapy using UV light-activated compounds can both kill cancer cells directly and trigger an immune response to extend tumor control. Poor penetration depth of ultraviolet light, however, has limited this treatment to superficial tumors. High-energy photon beams create high energy electrons within the patient which in turn produce Cherenkov radiation in the UV spectrum while traveling through tissue. Given that this Cherenkov radiation is generated deep within the patient and has the ability to activate photosensitive compounds, we therefore developed a platform to test this phenomenon to enhance radiation therapy for brain metastasis. We first tested UV-activated psoralen derivatives in combination with UV light *in vitro* for activity against murine 4T1 breast cancer cells, and then irradiated an *ex vivo* organotypic brain slice platform using a high energy linear accelerator to generate Cherenkov radiation. We tested the survival of 4T1 cells expressing fluorescent and bioluminescent reports in the presence and absence of these psoralen compounds in this *ex vivo* brain metastasis model. 8-methoxypsoralen (8-MOP) and 4'-Aminomethyltrioxsalen hydrochloride (AMT) both showed 365nm UVA light-specific cell killing *in vitro*. We optimized AMT cell loading (1 hour) and concentrations [1μM] AMT to maximize cytotoxicity. Testing of AMT using the organotypic brain slice platform and high-energy irradiation to generate Cherenkov-UV light demonstrated similar enhanced cell death of 4T1 cells despite high baseline levels of radiation-induced tumor cell kill. Cherenkov radiation-induced photo-activation of AMT improved cell killing in an *ex vivo* model of breast cancer brain metastasis. This application holds promise for the re-treatment of refractory tumors with high-energy, low dose radiation, and enhanced elsewhere brain metastasis control through activation of the immune system.

RADI-21. FEASIBILITY OF GAMMA KNIFE SURGERY FOR PATIENTS WITH 20 OR MORE BRAIN METASTASES

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BACKGROUND: The current standard-of-care treatment for brain metastases (BM)≥20 is Whole Brain Radiotherapy (WBRT), which can cause neurocognitive decline detrimental to patients' quality of life, especially if their functional status is good on presentation. The benefits of Gamma Knife Surgery (GKS) have been shown for BM≤10, but there is no consensus on the upper limit where GKS is no longer beneficial. We hypothesize that selected patients with ≥20 BM may benefit by replacing WBRT with GKS to preserve neurocognition without compromising intracerebral tumor control and overall survival, with additional treatments as needed. Methodology: This is retrospective analysis of 31 patients with ≥20 BM who underwent single-session GKS between 2016–2021. Twenty-two patients had ECOG of 0 at the time of GKS. Median number of BM at GKS was 30 (20–79) with median total tumour volume 4cm^3 (2–28 cm^3). Median marginal dose was 20Gy (10-25Gy). RESULTS: Median overall survival following GKS was 14-months (95%CI 4-24months), justifying GKS in this population. 11/12 patients that died succumbed due to extracranial disease, while 1 patient, who was treated with WBRT before GKS, succumbed to intracranial tumor progression. Local tumor control achieved was achieved for 63% of patients at 2-years and distal tumor control in 24% of patients at 1.5-years without additional radiation treatment. Salvage GKS was given in seven patients and salvage WBRT in three. One local recurrence was surgically resected. Systemic treatment given to most patients probably contributed to intracranial tumor control. No patients developed significant neurocognitive deficits attributable to GKS during the follow-up period of median 7-months (Q1-Q3: 3-12months). CONCLUSION: Most patients treated with GKS for ≥20 BM have sufficient survival time to benefit from the treatment. Local and distal recurrences can be managed with systemic treatment, salvage GKS, or WBRT, resulting in intracerebral tumor control in vast majority of cases.

RADI-22. TOXICITY AND LOCAL CONTROL OUTCOMES FOR BRAIN METASTASES MANAGED WITH RESECTION AND AGGRESSIVE REIRRADIATION AFTER INITIAL RADIOSURGERY FAILURE

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OBJECTIVES: To describe toxicity and tumor outcome after resection and aggressive re-irradiation (stereotactic radiosurgery(SRS) or brachytherapy) of brain metastasis that have pathologically confirmed recurrence after prior radiosurgery. METHODS: A retrospective chart review identified 40 lesions in 35 patients that were initially treated with SRS, then demonstrated evidence of recurrence with pathologic confirmation and underwent re-irradiation either with radiosurgery (n=28, 70%) or intracavitary brachytherapy with Cesium-131 seeds (n=12, 30%). Toxicity was measured by: steroids initiated or increased within 3 months, imaging evidence of treatment effect vs disease progression at any time point, further intervention for local recurrence or necrosis, and any grade 3/4 neurologic events. Local control (with failure defined by sustained progression on imaging or pathologic confirmation of tumor) was measured from time of retreatment. RESULTS: Median follow-up from time of re-irradiation was 11.8 months

(range 1 – 89.7 months). Dose for repeat radiosurgery was 18–25 Gy in 1–5 fractions, and brachytherapy dose was 55–65 Gy at 5 mm depth. Twelve lesions subsequently had imaging evidence of radionecrosis vs. progression. Of these, eight underwent repeat resection with pathology demonstrating radiation necrosis in five patients (n=4 with SRS, n=1 with brachy) and tumor recurrence in 3 (n=2 with brachy, and n=1 with SRS). Toxicities included: Steroids, 14(35%); imaging progression/necrosis 12(30%); grade 3/4 event, 3(20%); and surgically confirmed radionecrosis 5(12.5%). Local control of retreated lesions at 6 months is 85.5%, and at 12 months is 79.3%, OS at 1 year is 52.5% and at 2 years 46.6%. Local control at one year for repeat stereotactic treatment was 82.9% and for Cs131 brachytherapy was 80.8% CONCLUSIONS: Aggressive re-irradiation after resection for pathologic confirmation appears to be appropriately safe and effective for the majority of patients after local failure of initial radiosurgery.

RADI-23. EXPLORING THE OPTIMAL TIMING OF ROUTINE INITIAL SURVEILLANCE MRI FOLLOWING TREATMENT OF BRAIN METASTASES WITH STEREOTACTIC RADIOSURGERY: A COMPARISON OF TWO APPROACHES

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PURPOSE: To measure the value of early initial surveillance MRI scans in patients with brain metastases undergoing stereotactic radiosurgery (SRS), as MRI scans are a significant cost and patient stressor. METHODS: We identified a retrospective cohort of patients with brain metastases treated with SRS and followed at a single institution with scheduled 6-week or 12-week initial surveillance MRI. Imaging interval was based on policy of different providers. Outcome measures included new/progressive lesions, salvage treatment, detection of new lesions before symptoms, and use of surgical resection. RESULTS: Two hundred patients were included: 100 consecutive patients scanned with 6-week and 12-week imaging. Eighty-seven and 74 patients in each group had available follow-up imaging and were analyzed. Median time to MRI was 6.7 weeks and 13.5 (p<.001). No difference in primary site, prior SRS, number of treated brain metastases, or use of targeted therapy/immune checkpoint inhibitors was detected. A lower percentage of patients with 6-week MRI had controlled extracranial disease at initial treatment (30% vs 47%,p=.003). Twenty-eight percent with 6-week MRI had findings concerning for new/progressive disease, compared to 47% with 3-month MRI (p=0.01). Fifteen percent (10/87) with 6-week MRI underwent intervention (i.e. SRS, whole brain radiotherapy, or surgery) compared to 34% (20/74) with 12-week MRI (p=0.004). Of patients receiving SRS, a higher percentage had new/worsening neurologic symptoms (45% vs 30%) at follow-up although a lower percentage had new lesions >1cm (20% vs 50%) when discovered. One patient in each group underwent surgical salvage. CONCLUSION: While shorter 6-week interval MRI surveillance post-SRS may detect new/progressive disease less frequently than 12-week MRI surveillance intervals, short interval MRI may be more likely to detect new/progressive lesions before symptoms develop. Surgical salvage was uncommon with either schedule. Further study may identify a high-risk subgroup who would benefit from early surveillance.

SURGERY

SURG-01. MANAGEMENT OF SOLITARY BRAIN METASTASIS LESS THAN 4 CM IN DIAMETER. SURGICAL RESECTION VERSUS STEREOTACTIC RADIOTHERAPY: A META-ANALYSIS.

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INTRODUCTION: To treat a solitary metastasis in the brain, surgical resection and/or radiotherapy are the standard treatments of care. However, the clinical scenarios in which to use these techniques alone or in combination are controversial. While a course of stereotactic radiotherapy is often administered to a patient who presents with multiple metastases, surgical resection is often directed against a larger solitary brain metastasis before irradiating the resection bed. The management of a smaller solitary tumor (diameter less than 4 cm) is less clear. Accordingly, our meta-analysis assembled studies that focused on patients with a solitary tumor less than 4 cm in diameter. METHODS: Following PRISMA guidelines (PROSPERO ID: CRD42021242434), we searched PubMed, Web of Knowledge, and Cochrane Library databases for randomized controlled trials (RCT) and observational studies comparing surgery to radiotherapy for solitary metastatic brain tumors less than 4 cm in diameter. From 498 total records, we included 9 studies for meta-analysis. Analysis was performed on R. RESULTS: 2 RCTs and 7 observational studies were identified. 431 patients underwent surgical intervention, and 349 patients exclusively underwent radiotherapy. The surgical treatment cohort did not exhibit a difference in 1-year (OR [95% CI] = 0.866 [0.609–1.289]), 2-year (1.7 [0.843–3.428]), or overall survival (1.18 [0.598–2.327]). However, the surgical treatment group demonstrated greater local tumor recurrence after 1-year (3.975 [1.979–7.987]) and overall local recurrence (3.045 [1.276 - 7.268]). There was no difference between the overall rates of distant recurrence (0.565 [0.218 - 1.466]). CONCLUSIONS: Our analysis opens more discussion about the management of solitary brain metastasis. Patient selection is paramount in achieving better local control. Stereotactic radiotherapy should be considered for treatment of solitary brain metastasis less than 4 cm in diameter in selected patients. Future randomized control trials for small solitary masses are recommended.

SURG-02. STEREOTACTIC LASER ABLATION (SLA) FOLLOWED BY CONSOLIDATION STEREOTACTIC RADIOSURGERY (SRS) AS A TREATMENT STRATEGY FOR BRAIN METASTASIS THAT RECURRED LOCALLY AFTER INITIAL RADIOSURGERY (BMRS): A COLLABORATIVE INSTITUTIONAL EXPERIENCE

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INTRODUCTION: In independent clinical trials, ~30% of brain metastases recur locally after radiosurgery (BMRS). For these lesions, treatment with stereotactic laser ablation (SLA, also known as laser interstitial thermal therapy (LITT)) alone achieves a 12-month local control (LC^{12}) of 54–85% while repeat SRS achieved LC^{12} of 54–79%. Here, we report favorable outcomes for BMRS treated with SLA followed by consolidation radiosurgery (SLA/cSRS). METHODS: Clinical outcome of 18 patients with 19 histologically confirmed BMRS treated with SLA followed by consolidation SRS and >3 months follow-up were collected retrospectively across three institutions. Local control was defined as stability or decrease in contrast-enhancing (CE) and FLAIR volume. RESULTS: SLA achieved ablation of 73–100% of the BMRS CE volumes. Consolidation hypofractionated radiosurgery (5 Gy x 5 or 6 Gy x 5) was carried out 16–40 days post-SLA (median of 26 days). With a median follow-up of 185 days (range: 93–1367 days) and median overall survival (OS) of 185 days (range: 99–1367 days), 100% LC^{12} was achieved. 13/18 (72%) patients that required steroid therapy prior to SLA/cSRS were successfully weaned off steroid by three months post-SLA/cSRS. Post-SLA, KPS declined for 3/19 (16%) patients and improved for 1/19 (5%) patients. No KPS changes occurred subsequent to consolidation SRS. There were no 30-day mortalities or wound complications. Two patients required re-admission within 30 days of SRS (severe headache that resolved with steroid therapy (n=1) and new-onset seizure (n=1)). Except for two patients who suffered histologically confirmed, local failure at 649 and 899 days, all other patients are either alive (n=5) or died from systemic disease progression (n=11). None of the treated patients developed symptomatic radiation necrosis. CONCLUSIONS: This collaborative institutional experience support efficacy and safety of SLA followed by consolidation SRS as a treatment for BMRS. The treatment strategy warrants further investigations.

SURG-03. THE EFFECT OF SURGERY ON RADIATION NECROSIS IN IRRADIATED BRAIN METASTASES: EXTENT OF RESECTION AND LONG-TERM CLINICAL AND RADIOGRAPHIC OUTCOMES

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OBJECTIVE: Radiation therapy is a cornerstone of brain metastasis (BrM) management but carries the risk of radiation necrosis (RN), which can require resection for palliation or diagnosis. We sought to determine the relationship between extent of resection (EOR) of pathologically-confirmed RN and postoperative radiographic and symptomatic outcomes.