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