Finding effective treatment options for patients with brain metastases remains an unmet need. Given the limitations imposed by the blood-brain barrier and systemic approaches, radiotherapy offers a superior ability to access the brain. While clinical practice recently adapted the use of stereotactic radiosurgery (SRS), Whole-Brain-Radiotherapy (WBRT) continues to be an important treatment option, since many patients present with multiple lesions and poor performance scores, rendering them ineligible for SRS. Unfortunately, overall survival of patients remains unaffected by radiotherapy. Despite this clinical data, the molecular mechanisms that allow metastatic cells to resist radiotherapy in the brain is unknown. We have applied WBRT to experimental brain metastasis from lung and breast adenocarcinoma and validated their resistance in vivo. An unbiased search to identify potential mediators of resistance identified the S100A9 RAGE-NFκB JUNB pathway. Targeting this pathway effectively reverses the resistance to radiotherapy and increases therapeutic benefits in vivo. In two independent cohorts of brain metastasis from lung and breast adenocarcinoma patients, levels of S100A9 correlate with the response to radiotherapy, offering a novel approach to stratify patients according to their expected benefit. In order to make this biomarker also available for brain metastasis patients receiving radiotherapy surgery, we compared a specimen-based approach with the less invasive detection of S100A9 from liquid biopsies. Here, serum S100A9 also correlated with a worse response to WBRT in brain metastasis patients. Furthermore, we have validated the use of a blood RAGE barrier permeable RAGE inhibitor to restore radiosensitivity in experimental brain metastasis models in vivo and in patient-derived organotypic cultures of radio-resistant brain metastasis ex vivo. In conclusion, we identified S100A9 as a major mediator of radio-resistance in brain metastasis and offer the molecular framework to personalize radiotherapy by exploiting it as a biomarker and as a therapeutic target, thus maximizing the benefits for the patient.
resresents an alternative to surgery in poor surgical candidates. We aimed to investigate the clinical efficacy and safety of 2-SSRS in patients with LBM.

METHODS: LBM of patients treated with 2-SSRS between 2014 and 2020 were evaluated. Demographic, clinical, and radiologic information was obtained. Volumetric measurements at first SSRS, second SSRS, and follow-up imaging studies were obtained. RESULTS: Twenty-six patients with 28 LBM were included in the study. Fifteen patients (58%) were male. Median age at time of diagnosis was 70 years (range: 31-94). Mean marginal doses for first and second SSRS were 15 Gy (range: 12-18 Gy) and 15 Gy (range: 12-16 Gy), respectively. Median duration between sessions was 32 days. Two patients (8%) failed to receive their second SSRS due to local progression. Median treatment times for first SSRS, second SSRS, and SSRS 3-month follow-up were 8.7 cm² (range: 1.5–14.7 cm²), 3.3 cm³ (range: 0.8–26.1 cm³), 1.7 cm³ (range: 0.2–10.1 cm³), and 1.4 cm³ (range: 0.4–20.7 cm³), respectively. The median absolute and relative decrement between S-SSRS sessions was 3.7 cm² (range: 2.8–16.3 cm²) and 49.5% (range: 17.1–87.1%), respectively. Two patients (8%) demonstrated early local control following the first SSRS with 18 lesions (69%) demonstrating a decrease in volume of >30% and 3 lesions (12%) remaining stable. Six lesions (23%) showed disease progression. There were no grade 3 adverse events. CONCLUSIONS: Our study supports the effectiveness and safety of 2-SSRS as a treatment modality for patients with large, symptomatic brain metastases, especially in non-surgical candidates. The local failure rate and low occurrence of adverse effects are comparable to other staged radiosurgery series.

RADI-06. GAMMA KNIFE SURGERY FOR BRAIN STEM METASTASES
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INTRODUCTION: Gamma Knife Surgery (GKS) is widely used for treat- ment of brainstem metastases (BSMs) with or without whole brain radiation therapy (WBRT). We hypothesized that BSMs treated with GKS using lower doses and omitting WBRT result in acceptable tumor control rates and low complication rates. METHODS: A retrospective single center study was performed to investigate the outcome following GKS of BSMs. All 33 patients with follow-up information treated with GKS for 39 metastases located in the cerebral peduncle, midbrain, pons or medulla oblongata were included in the study. The median treatment dose delivered as the lowest dose to 95% of the tumor volume, was 18 Gy. The tumor control rate as well as the survival time were related to a number of patients, tumor and treat- ment parameters. RESULTS: The local tumor control rate was 100% at one year and 89% at five years, and the overall median survival was 17 months. A good performance status and a treatable extracranial disease were favor- ably related to survival time. Two complications were observed, one was hemorrhage at the day of the treatment and one transient complication three months following GKS, resulting in a 6% complication rate at five years. Follow-up of the 10 patients with symptomatic BSM improved clinically after GKS, while six remained unchanged. CONCLUSIONS: High local control and a low complication rates can be achieved using GKS for BSMs using lower doses as compared to brain metastases in other locations.

RADI-07. INDIVIDUALIZED NOMOGRAM FOR PREDICTING SURVIVAL OF PATIENTS WITH BRAIN METASTASES AFTER STEREOTACTIC RADIOSURGERY
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BACKGROUND: Given the increasing use of stereotactic radiosurgery (SRS) for brain metastases (BM), there is an emerging need for more precise assessment of survival outcomes after SRS in the modern targeted therapy era. METHODS: Patients with BM and treated by SRS were eligible. Cox models were used to identify independent prognostic factors. Survival predictive nomo- gram was constructed and evaluated by Concordance index (C-index) 0.780, under the curve (AUC) and calibration curve. RESULTS: From January 2016 to December 2019, a total of 356 BM patients were eligible. Median OS was 17.7 months (95%CI 15.5–19.9) and actual OS at 1- and 2-year meas- ured 63.2% and 37.6%, respectively. Nomogram for OS was developed by incorporating four independent prognostic factors: Karnofsky Performance Score, cumulative tumor volume, driver gene mutation status and serum lactate dehydrogenase. The nomogram was validated in a separate cohort dem- onstrating a well calibration and good discriminating ability (C-index 0.780, AUC 0.784). The prognostic accuracy of the nomogram (0.792) was consi- derably enhanced compared with classical prognostic indices, i.e., GPA (0.708), RPA (0.587) and SIR (0.546). Kaplan-Meier curves showed significa- nt difference among stratified low- and high-risk groups (hazard ratio and high-risk group < .001). CONCLUSION: In conclusion, we developed and validated an in- dividualized prognostic nomogram by integrating physiological, volumetric, clinical chemistry and molecular biological surrogates. This nomogram, should be validated by independent external study, has a potential to facilitate more precise risk-stratifications to guide personalized treatment for BM.

RADI-08. ELUCIDATING THE ELECTROPHYSIOLOGY OF INTRAOPERATIVE RADIOTHERAPY – EXPERIENCE FROM TWO CASES
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Brain metastases require multimodal treatment, often combining surgical resection, radiation therapy, and individualized systemic chemotherapy based on oncogenic drivers. Intraoperative radiation therapy (IORT) is an emerging treatment option where radiation is delivered directly to the resec- tion cavity at the time of surgery. We present two patients who underwent electrocorticography (ECog) during IORT, providing information regarding electrophysiological safety and tolerability of the technique. In the first case, a 65-year-old woman underwent resection of a hemorrhagic right occipital metas- tasis from non-small cell lung cancer. IORT was administered over sixteen minutes for a surface dose of 30 Gy. In the second case, a 73-year-old man with a right parietal metastasis from non-small cell lung cancer. IORT was delivered over eleven minutes for a surface dose of 30 Gy. In both cases, a 1x6 contact array of subdural electrodes was placed adjacent to the planned field of radiation. Electrocorticography (ECoG) at 70 Hz, TC 0.3 sec, sensitivity 150uV/mm) was obtained from the array two minutes prior to initiation of therapy, during therapy, and two minutes after completion of therapy in both cases. We found that IORT did not induce electrophysiological change in the tissue surrounding it in both cases with no epileptiform or ictal discharges during 20 minutes of ECoG recording around the time radiation therapy, nor did the patients have episodes suggestive of epileptic seizures in the acute post-operative period. One of the patients (case 1) experienced a single epileptic seizure 4 months after IORT, but this was temporally related to a new intraparenchymal hemorrhage and unlikely due to radiation therapy. These two cases illustrate the relative safety of IORT with respect to induction of imme- diate epileptiform changes within the brain parenchyma.

RADI-09. CLINICAL FACTORS ASSOCIATED WITH DEATH AFTER RADIOTHERAPY FOR BRAIN METASTASES
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INTRODUCTION: It can be challenging to accurately identify patients with brain metastases who have very poor prognoses and are unlikely to benefit from radiation therapy (RT). We characterized factors of patients who died within 30 days of receiving RT for brain metastases. METHODS: All patients who received whole brain RT (WBRT) or stereotactic radiosurgery (SRS) for brain metastases between 1/1/2017-9/30/2020 at a single institution were identified. Patient, tumor, treatment, and death variables were collected. Characteristics between those who did and did not die within 30 days were compared using the Wilcoxon Rank-Sum or Chi-Square test. Survival was esti- mated with Kaplan-Meier method. RESULTS: 636 patients received WBRT (n=117) or SRS (n=519). Median age was 61. Median survival was 6 months (95%CI 0.7–7 months). 75 (12%) died within 30 days of RT. Patients who died within 30 days had worse Karnofsky performance score (KPS) (<60 vs 70, p<0.001), higher burden of intracranial/extra- cranial leptomeningeal disease at baseline (16% vs 3%, p<0.001), and leptomeningeal disease (16% vs 5%, p<0.001). Patients who did not die within 30 days had median KPS (50 vs 80, p<0.001). A higher proportion who did die within 30 days had innumerable intracranial metastases (45% vs 11%, p<0.001), leptomeningeal disease (16% vs 5%, p<0.001), and higher burden of neurologic symptoms at presentation (seizures (12% vs 4%, p<0.003), cranial neuropathies (32% vs 9%, p<0.001), motor/sensory deficits (51% vs 29%, p<0.001), altered mental status (60% vs 26%, p<0.001), head- aches (48% vs 30%, p<0.001); steroid use (68% vs 48%, p<0.001). Patients who died within 30 days had progressive extracranial disease (intrathoracic: 87% vs 50%; spinal: 57% vs 18%; liver/adenal: 60% vs 24%), p<0.001. More patients who died within 30 days received inpatient RT (39% vs 4%, <0.001) and did not complete RT (24% vs 1%, p<0.001). CONCLUSION: Patients who died within 30 days of RT had higher burden of intracranial/ex- tracranial disease, and neurologic symptoms. Future analyses will assess whether these factors can inform a prognostic model to identify patients with poor prognosis who may be appropriate for supportive care alone.

RADI-10. IS THERE ANY BENEFIT FOR POST-OPTERATIVE RADIATION IN BRAIN METASTASES? A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS
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PURPOSE: The benefits of adding upfront post-operative radiotherapy (either whole-brain or cavity radiation) have been debated, particularly due to the pos-