tral nervous system (CNS) progression in a cohort of patients undergoing surgical resection of melanoma brain metastases. METHODS: This retrospective, single-center study included patients undergoing first-time surgical resection of melanoma brain metastases. A multivariate Cox proportional model was used to estimate the association of patient and treatment factors with OS and CNS progression. RESULTS: 85 patients underwent first-time resection of 97 melanoma brain metastases with a median follow-up of 9.5 months. Checkpoint inhibitors (Pembrolizumab, Ipilimumab, and/or Nivolumab) were used in 55.1% of cases (19 pre-op; 47 post-op; median 9 cycles). Patients treated with checkpoint inhibitors had similar peri-op systemic disease status and KPS but had been treated with more systemic agents and had more instances of CNS progression prior to surgery. Median OS and time to CNS progression for the cohort were 1 year and 237 days, respectively. In a multivariate Cox regression model, age (HR 1.03 by decade; p=0.02), treatment with a checkpoint inhibitor (HR 0.27; p<0.0001), prior radiotherapy (HR 2.44; p=0.007), and number of brain metastases at the time of surgery (HR 1.05 per metastasis; p=0.04) were significant predictors of OS. Checkpoint inhibitor treatment was associated with longer OS from surgery (median 3 vs 0.5 yrs, log-rank p=0.004). However, patients who underwent craniotomy after prior checkpoint inhibitor treatment had poor OS (median 0.56 yrs). Prior radiotherapy was also associated with poor OS (median 0.53 yrs). CONCLUSIONS: While checkpoint inhibitor treatment was associated with improved survival in this surgical cohort of melanoma brain metastases, patients who require surgical resection after checkpoint inhibitor treatment or radiotherapy are poor surgical candidates.

13. MANAGEMENT OF BRAIN METASTASES FROM SMALL CELL LUNG CANCER USING SRS

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PURPOSE/OBJECTIVE(S): The management of brain metastases in patients with SCLC has become controversial in the MRI era. We examine our institutional experience treating patients with SCLC with stereotactic radiosurgery. We hypothesize that an SRS strategy in well-selected patients with close MRI surveillance will result in acceptable tumor control, and without disproportionate future neurological symptoms associated with intracranial disease. MATERIALS/METHODS: Patients with a diagnosis of high grade neuroendocrine lung cancer who had undergone SRS between 2013 and 2019 were identified and divided into two groups: SRS-primary and SRS-salvage. SRS-primary was defined as patients who, at time of SRS, had not received previous PCI or WBRT. SRS-salvage was defined as patients who had received previous PCI or WBRT. Primary outcome was intracranial progression free survival. Secondary outcomes included overall survival and neurologic symptom free survival (N-SFS), defined as time to development of neurologic symptoms attributed disease. RESULTS: Twenty patients were identified with median follow-up of 14.1 months. 11 patients were identified as SRS-primary, 9 as SRS-salvage. Among SRS-primary, median PFS and OS were 6.1 months (range 0.9 – 14.5 months) and 15.6 months (4.1–43.5) respectively. N-SFS was 11.2 months (range 3.6–40.0). 3 of 11 patients developed neurological symptoms attributable to disease. 3 underwent salvage SRS and 2 salvage WBRT. None died from intracranial disease. Among SRS-salvage, median PFS following PCI/WBRT was 9.8 months (range 1.8 – 23.6 months) and OS following salvage SRS 5.5 months (range 1.1 – 27.8 months). 3 of 9 patients developed further brain metastases post-SRS. 1 patient died from intracranial disease. CONCLUSION: Among well-selected patients followed with MRI surveillance, our data suggest SRS as primary management of brain metastases from SCLC may be reasonable. Symptomatic intracranial disease was uncommon after SRS, and no patients undergoing upfront SRS died from intracranial disease. Prospective data are required to validate these results.

14. DELAYED MRI RESPONSE TO LITT IN PATIENTS UNDERGOING IMMUNOTHERAPY

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Laser interstitial thermal therapy (LITT) is an effective treatment for regrowing lesions after previous radiosurgery to brain metastases, typically resulting in decreased perilesional edema within weeks followed by delayed reduction in lesion size. We have anecdotally observed that patients on immunotherapy (IT) at time of LITT may exhibit a delayed edema resolution response to laser ablation. Post-operative imaging for cases of LITT, performed by the senior author from June 2012-July 2019, for regrowing lesions after prior radiosurgery for brain metastases were retrospectively reviewed. The IT group was defined as any patient receiving IT treatment within 3 months of LITT. Post-operative MRIs obtained at serial time points after surgery (2 weeks, 6 weeks, 3 months, 6 months, and 12 months) were reviewed for treatment response to LITT, defined as change in surrounding edema on T2 FLAIR and change of lesion size on T1-weighted post-contrast images. Out of 60 ablated lesions, 22 were in the IT and 38 were in the non-IT groups. There were no differences in distribution of original cancer pathology (IT: 9 melanoma, 8 lung, 5 other, non-IT: 6 melanoma, 20 lung, 12 other; p>0.05). Time to lesion size response on T1-weighted post-contrast MRI neared but did not reach statistical significance between the IT and non-IT groups: median 3.0 versus 2.25 months (HR 1.5, 0.8–2.5, 95% CI, p=0.08), respectively. However, time to reduction of perilesional edema on T2-weighted MRI was significantly longer in the IT group, compared to the non-IT group: median 2.25 versus 1.5 months (HR 1.5, 0.9–2.5, 95% CI, p=0.04), respectively. These data suggest that IT around the time of LITT may lead to delayed edema reduction on MRI after LITT. We hypothesize IT may enhance normal immune-mediated mechanisms thus increasing perilesional inflammation after LITT. Further studies are needed to corroborate our observations and explore the underlying pathophysiology.

16. GAMMA KNIFE CLINICAL DOSE PROFILE FOR EXTENSIVE BRAIN METASTASES

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BACKGROUND: The use of Gamma Knife stereotactic radiosurgery (GKSRS) for the treatment of extensive intracranial metastases has been expanding due to its superior dosimetry and efficacy. However, there remains a dearth of data regarding the dose parameters in actual clinical scenarios. We endeavored to calculate the radiation dose to the brain when treating >15 brain metastases with GKSRS. METHODS: This retrospective analysis reviewed dosage characteristics for patients requiring single session GKSRS for the treatment of ^{3}15 brain metastases. Forty-two patients met the inclusion criteria between 2008 and 2017. The median number of tumors at the initial GKSRS procedure was 20 (15–39) which accounted for 865 tumors in this study. The median aggregate tumor volume was 3.1cm^3(0.13–13.26) and the median marginal dose was 16Gy (14-19Gy). RESULTS: The median of the mean brain dose was 2.58Gy (range 0.95–3.67Gy) and 79% of patients had a dose <3Gy. The 12Gy dose volume was a median of 12.45cm^3, which was equivalent to 0.9% of the brain volume. The median percentage of brain receiving 5Gy and 3Gy was 6.7% and 20.4%, respectively. There was no correlation between the number of metastases and the mean dose to the brain (p=0.8). A higher tumor volume was significantly associated with an increased mean brain dose (p<0.001). The median of the mean dose to the bilateral hippocampi was 2.3Gy. Sixteen patients had supplementary GKSRS, resulting in an additional mean dose of 1.4Gy (0.2–3.8Gy) to the brain. CONCLUSION: GKSRS is a viable means of managing extensive brain metastases. This procedure provides a relatively low dose of radiation to the brain, especially when compared to traditional whole brain radiation protocols.

17. MELANOMA BRAIN METASTASIS: PRESENTATION, TREATMENT AND OUTCOMES IN THE AGE OF TARGETED- AND IMMUNO-THERAPIES

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BACKGROUND: Melanoma brain metastasis (MBM) prognosis has historically been dismal. However, breakthroughs in targeted and immunotherapies have improved long-term survival in advanced melanoma. As such, MBM presentation, prognosis and multimodality CNS-directed treatment use were reassessed in this contemporary age of treatment. METHODS: This retrospective study evaluated patients treated at Memorial Sloan Kettering Cancer Center between 2010–2019 with a diagnosis of melanoma brain metastases (MBM). Kaplan-Meier methodology was used to describe overall survival (OS). Recursive partitioning analysis (RPA) and time-dependent multivariable Cox modeling were used to assess prognostic variables and associate CNS-directed treatments with OS. RESULTS: Four hundred and twenty-five patients with 2,488 MBM were included. Median OS from MBM diagnosis was 8.9 months (95%CI: 7.9–11.3). RPA demonstrated significantly longer survival in patients diagnosed with MBM between 2015–2019 versus 2010–2014 (13.0 months [95%CI: 10.47–17.06]

versus 7.0 months [95%CI: 6.1–8.3]; p=0.0003) and patients with <5 BM versus ≥5 BM (12.49 months [95%CI: 10.52–16.03] versus 5.48 months [95%CI: 4.2–6.8]; p<0.0001). Prognostic multivariable modeling significantly associated shortened OS independently with leptomeningeal dissemination (p<0.0001), >5 BM at diagnosis (p<0.0001), MBM diagnosis year 2010–2014 (p=0.0007), immunotherapy treatment prior to BM diagnosis (p=0.02), and extracranial disease presence (p=0.03). CNS-directed treatment modalities associated with BM number, dominant BM size, presenting symptoms, diagnosis year, and extracranial disease presence. Multivariable analysis demonstrated improved survival for patients that underwent craniotomy (p=0.01). CONCLUSIONS: MBM prognosis has improved in the period following targeted and immunotherapy introduction, and even within the last 5 years of this study. Improving survival reflects and may influence the willingness to use aggressive multimodality treatment for MBM.

19. PLEKHA5 REGULATES TUMOR GROWTH IN METASTATIC MELANOMA

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Understanding the mechanisms behind melanoma brain metastasis, a disease that continues to portend a poor prognosis, will lead to the identification and development of novel drug targets. We previously identified PLEKHA5, a gene involved in brain development, as a novel molecule implicated in melanoma brain metastasis. Our aim was to further characterize the function of this protein in brain-tropic melanoma. We established stable loss- and gain-of-function cell lines to explore the underlying mechanisms of PLEKHA5-mediated tumor growth. The effect of PLEKHA5 expression silencing on proliferation and tumor growth was assessed using both in vitro systems and xenograft models of brain-tropic melanomas, respectively. The clinical relevance of PLEKHA5 dysregulation in brain metastasis was also investigated in two unique cohorts of melanoma patients with cerebrotropic disease and included analysis of matched cranial and extra-cranial specimens. Knock-down of PLEKHA5 in brain-tropic melanoma cells negatively regulated cell proliferation by inhibiting G1 to S cell cycle transition. This coincided with up-regulation of PDCD4, p21, and p27, as well as the downregulation of pRb protein, involved in the regulation of cell cycle. Conversely, the ectopic re-expression of PLEKHA5 had an inverse effect. Subcutaneous and direct cranial injections of PLEKHA5 knock-down cells in nude mice significantly inhibited tumor growth, while its overexpression upregulated the growth of tumors. This reduction in tumor growth in vivo might be attributed to decreased phosphorylation of Akt (S473) and mTOR (S2448), key mediators for tumor growth and survival. Our results demonstrate the role of PLEKHA5 as a mediator of melanoma brain metastasis. Our findings highlight the significance of PLEKHA5 as a possible regulator of cell cycle transition via crosstalk with the ubiquitin-proteasome and PI3K/AKT/mTOR signaling pathways, driving the proliferation and growth of brain-tropic melanomas. Our studies suggest that PLEKHA5 targeting should be further investigated for melanoma brain metastasis patient population.

20. MELANOMA CELL INTRINSIC GABAA RECEPTOR ENHANCEMENT POTENTIATES RADIATION AND IMMUNE CHECKPOINT INHIBITOR RESPONSE BY PROMOTING DIRECT AND T CELL-MEDIATED ANTI-TUMOR ACTIVITY

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Most metastatic melanoma patients exhibit poor and variable response to radiotherapy and targeted therapies, including immune checkpoint inhibitors. There is a need for therapeutics that can potentiate existing treatments to positively impact clinical outcomes of metastatic melanoma patients. We reanalyzed melanoma TCGA transcriptomes and identified, as linked to previously defined molecular subgroups, enhanced expression of genes coding for subunits of the Type A GABA receptor ($GABA_AR$), a chloride ion channel and major inhibitory neurotransmitter receptor. Using whole-cell patch clamp electrophysiology, we find that melanoma cells possess $GABA_ARs$ that control membrane permeability to anions. Select benzodiazepines, by enhancing $GABA_AR$ mediated anion transport, depolarize melanoma cell mitochondrial membrane potential and impair cell viability *in vitro*. Using a syngeneic melanoma mouse model, we find that a benzodiazepine promotes reduction in tumor volume when administered alone and potentiated radiation or immune checkpoint inhibitor α-PD-L1. When a benzodiazepine is combined with concurrent α-PD-L1 and a sub-lethal radiation dose, there is near complete loss of tumor, beyond what is observed for benzodiazepine with radiation or α-PD-L1. Mechanistically, benzodiazepine with radiation or α-PD-L1 results in ipsilateral and an abscopal tumor volume reduction commensurate with enhanced infiltration into the tumor milieu of polyfunctional CD8 T-cells. There is also an increased expression of genes with roles in the cytokine-cytokine receptor and p53 signaling pathways. This study provides evidence for melanoma cell $GABA_ARs$ as a therapeutic vulnerability with benzodiazepines promoting both direct and immune-mediated anti-tumor activity.

21. A PHASE II TRIAL OF COMPREHENSIVE TREATMENT BASED ON RADIOTHERAPY IN LEPTOMENINGEAL METASTASIS

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OBJECTIVES: To investigate the efficacy and security prospectively for patients with leptomeningeal metastases (LM) of comprehensive treatment based on radiotherapy. METHODS: From 2014 to 2017, 93 patients diagnosed with LM admitted to our hospital who underwent whole brain radiotherapy (WBRT) or craniospinal irradiation (CSI) with or without simultaneously boost were enrolled. The dynamic changes of enhanced magnetic resonance imaging, clinical signs and symptoms, cerebrospinal fluid cytology and liquid biopsy detection were recorded. The primary endpoint was overall survival (OS), the secondary endpoints were local control (LC), intracranial progress-free survival (IPFS), brain metastasis specific survival (BMSS) and toxicity. RESULTS: The major primary diagnosis was non-small cell lung cancer. Subjects received WBRT with boost (40 Gy in 20 fractions (f) for WBRT and 60Gy in 20 f for boost), focal radiation to LM, WBRT and CSI (40 Gy in 20 f or 50Gy in 25 f for WBRT and 36 Gy in 20 f for CSI). 20 patients were found tumor cells and were administrated intrathecal chemotherapy. 63 patients used target therapy. The median follow-up time was 33.8 months. OS/LC/IPFS at 1 year were 62.4%/77.2% and 52.6%, respectively. The median survival time was 15.9 months, and the median brain metastasis-specific survival was 42.2 months. Treatment-related grade 3–4 adverse events were rare and included eight grade 3 hematological toxicity. CONCLUSION: Reasonable comprehensive treatment including precise radiotherapy, intrathecal chemotherapy and targeted agents were well tolerated and could extend the survival time of LM patients compared with historical controls.

KEY WORDS: Leptomeningeal Metastasis; Tomotherapy; Comprehensive treatment

22. COMPARATIVE EFFICACY OF ALK-INHIBITORS IN ALK INHIBITOR-NAIVE ALK+ LUNG CANCER BRAIN METASTASES: A NETWORK META-ANALYSIS

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BACKGROUND: Lung cancer has been the leading cause of cancer death for both men and women worldwide. Non-small-cell lung cancer (NSCLC) displays an array of molecular abnormalities most commonly involving ALK and EGFR pathways. NSCLC with ALK rearrangements comprises around 5% of cases. Over the years, several ALK inhibitors (ALKI) have been approved with notable activity in brain metastases. However, there have been limited comparative studies exploring their relative efficacies. This analysis was conducted to compare the relative efficacy of ALKIs against ALKI-naïve ALK+ lung cancer brain metastases. METHODOLOGY: A review of the medical literature was conducted using online databases. Inclusion criteria consisted of English language; diagnosis of ALKI-naïve ALK+ lung cancer trials with brain metastases; treatment with Crizotinib (CRZ), Alectinib (ALC), Brigatinib (BRG), and Ceritinib (CER); and comparative studies reporting brain metastases specific responses/events. A Bayesian and a frequentists network meta-analysis were conducted using netmeta package and the random-effects model. RESULTS: Eight studies