exomes between primary and metastatic sites including the brain. RESULTS: 281 extensive-stage patients and 40 limited-stage patients were included. 12% (30/281) of the extensive-stage patients and 25% (10/40) of limited-stage patients had isolated brain metastases. Patients with limited-stage disease who developed isolated brain metastases had significantly improved mOS as compared to those who developed other sites of metastasis (OS = 38.7 months vs. 20.2 months, p=0.033). Furthermore, mPFS for limited-stage patients with isolated brain metastases was improved compared to other patterns of metastases (PFS = 17.9 months vs. 10.1 months, p = 0.03). NGS demonstrated that NOTCH1 mutations were infrequent in biopsies from all metastatic sites but were common in primary lung tumors. CONCLUSION: In our single center review, patients with limited-stage SCLC who recurred only in the brain had improved survival as compared to those who had other patterns of metastases. Our initial work demonstrates differences in oncogenic gene mutations between the metastatic and primary tumors.

OTHR-16. MOLECULAR PROFILING USING THE 92-GENE ASSAY FOR TUMOR CLASSIFICATION OF BRAIN METASTASES

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BACKGROUND: Nearly 200,000 patients are diagnosed with brain metastases in the US annually. Advances in targeted therapies make definitive diagnosis of the primary tumor type important but can be challenging in many patients. The 92-gene assay is a validated gene expression classifier of 50 tumor types for patients with uncertain tissue of origin diagnoses. Results from a clinical series of brain biopsies and potential impact on treatment were evaluated. METHODS: An IRB approved, de-identified database of clinical and molecular information from biopsies (N = 24,486) submitted for testing with the 92-gene assay (CancerTYPE ID, Biotheranostics, Inc.) as part of routine care were reviewed. Descriptive analysis included patient demographics and molecular diagnoses. RESULTS: Analysis included 464 brain biopsies. A molecular diagnosis was provided in 433 (93.3%) tested (< 5% assay failure rate) with 24 different tumor types. Six primary tumor types made up the majority (67.4%) with almost one-third of the molecular predictions being Lung (31.2%), followed by Neuroendocrine (NET) (9.9%), Sarcoma (7.9%), Skin (6.4%), Gastroesophageal (6.2%), and Urinary bladder (5.8%). All of these 6 tumor types, for which activity in the CNS has been documented, have immune checkpoint inhibitors or other targeted therapies approved in selected cases by the US Federal Drug Administration (FDA). CONCLUSIONS: Molecular classification of brain metastases can identify distinct tumor types for which there are FDA approved targeted medications. Improving diagnostic precision with the 92-gene assay helps identify a subset of therapy-responsive metastatic brain tumors, thus improving therapy and possibly providing better outcomes and survival.

OTHR-17. PHYLOGENETIC RESOLUTION OF TISSUE-SPECIFIC METASTOGENIC CLONES IN RENAL CELL CARCINOMA

Nelson Moss, Samuel Berman, Salvatore Piscuoglio, Charlotte Ng, Pier Selenica, Rahul Kumar, Jorge Reis Filho and Cameron Brennan

Genomic factors predictive of organ-specific tropism have been established in several models of cancer. However, the evolutionary dynamics at work in metastatic carcinoma have yet to be characterized in detail. We identified a cohort of clear cell renal cell carcinoma (RCC) patients who also had multiple metastasectomies, and performed deep sequencing and statistical inference of subclonal populations to infer phylogeny and essential genetic features acquired prior to systemic dissemination and site-specific colonization. Exome capture and deep sequencing were performed on tissues from 3 patients with polymetastatic RCC (including 12 metastases, multiple regions of primary tumors, and paired germline tissue) to a mean depth of 250x. Somatic point mutations were called with Mutect, and insertions and deletions with Strelka and VarScan. Validation was performed with a custom NimbleGen panel hybridized to a custom sequence library and sequenced to a mean depth of >500x. Allele-specific copy number and clonal prevalence were established using ABSOLUTE, and analyzed with Pyclone across primary and metastatic lesions to determine clonal architecture. Phylogenetic reconstruction identified ancestral clones, with attendant driver mutations in RCC tumor suppressors (including VHL, SETD2, PBRM1, MTOR) and independent subclonal populations in the metastases of all 3 patients. In an index case with multiple metastases separated spatially and temporally, bone and soft tissue metastases demonstrate apparent independent ancestors. Convergent loss of known tumor suppressors was also noted in all cases, and in several cases found in conjunction with de novo mutations in known RCC driver genes acquired late in tumor development. In this demonstration of subclonal and evolutionary analysis of multiple paired multi-organ RCC metastases, we identified subclonal populations characterized by alteration of several tumor suppressors which subsequently exhibited organ-specific patterns of metastasis.

RADIATION

RADI-01. PROGNOSTIC FACTORS OF SHORT SURVIVAL FOR BRAIN METASTASES TREATED WITH SRS WITHOUT WBRT.

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Nowadays multiple brain metastases (up to 10–15 tumors) are treated with SRS alone. The most common diagnosis-specific Graded Prognostic Assessment and Score for Radiosurgery indices are based on data regarding limited brain metastases (1–4). Moreover, many of patients included in that analyses were treated with WBRT or combination of WBRT and SRS and some relevant data were not included due to a retrospective analysis of large datasets. SRS may increase intracranial control of disease, however, treatment of patients with a prognosis of fewer than 3 months survival after SRS may not be clinically reliable. Therefore we conducted an analysis of prospective registry to find the factors that correlate with very short survival after SRS. Materials and methods, A consecutive cohort of 84 patients treated with SRS only for brain metastases between 04.2018-03.2019. Data prospectively collected and introduced into a registry of patients treated with SRS in our department were analyzed. The analyzed factors are age, primary site, histopathology, previous surgery, molecular results, systemic therapy, duration of SRS planning, the extent of extracerebral metastatic disease, number of brain metastases, mass effect and neurological symptoms/ We performed a univariate analysis and multivariate Cox regression model to find a correlation between clinical and molecular data and survival in brain metastases patients treated with SRS only. Factors predicted early death and correlated with survival will be presented at the conference

RADI-02. SINGLE-SESSION VERSUS MULTISESSION GAMMA KNIFE RADIOSURGERY FOR LARGE BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER: RETROSPECTIVE ANALYSIS

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PURPOSE: To evaluate the efficacy of Gamma Knife radiosurgery (GKS) in patients with large brain metastases by comparing single-session radiosurgery (S-GKS) and multisession radiosurgery (M-GKS), the authors retrospectively analyzed the clinical outcomes of the patients who underwent GKS for brain metastases from non-small cell lung cancer (NSCLC). MATERIALS AND METHODS: Between January 2010 and December 2016, 66 patients with 74 lesions >=10 cm^3 from large brain metastases from only NSCLC were included. Fifty-five patients with 60 lesions were treated with S-GKS; 11 patients with 14 lesions were treated with M-GKS. Median doses were 16 Gy (range, 11–18 Gy) for the S-GKS group and 8 Gy (range, 7–10 Gy) in three fractions for the M-GKS group. RESULTS: With a mean follow-up period of 13.1 months (range, 1.3–76.4 months), the median survival duration was 21.1 months for all patients. Median tumor volume was 14.3 cm^3 (range, 10.0–58.3). The local control rate was 77.0% and the progression-free survival rate was 73.6% at the last follow-up. There were no significant between-group differences in terms of local control rate (p = 0.10). Compared with S-GKS, M-GKS did not differ significantly in radiation-induced complications (38.1% versus 45.4%, p = 0.83). While eight patients who underwent S-GKS experienced major complications of grade >=3, no toxicity was observed in patients treated with M-GKS. CONCLUSIONS: M-GKS may be an effective alternative for large brain metastases from NSCLC. Specifically, severe radiation-induced toxicity (≥ grade 3) did not occur in M-GKS for large-volume metastases. Although the long-term effects and results from larger samples remain unclear, M-GKS may be a suitable palliative treatment to preserve neurological function.

RADI-04. PRETREATMENT VOLUME OF MRI-DETERMINED WHITE MATTER INJURY (WMI) PREDICTS COGNITIVE DECLINE AFTER HIPPOCAMPAL AVOIDANT (HA) WBRT FOR BRAIN METASTASES: SECONDARY ANALYSIS OF NRG ONCOLOGY RTOG 0933

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PURPOSE: RTOG 0933 demonstrated benefits to memory following HA-WBRT, supporting the hypothesis of hippocampal radiosensitivity and associated memory specificity. However, some patients demonstrated cognitive decline, suggesting mechanisms outside hippocampal radiosensitivity playing a role. WMI has been implicated in RT-induced cognitive decline. This secondary analysis explored the relationship between pre-treatment WMI and memory following HA-WBRT. METHODS AND MATERIALS: 113 patients received HA-WBRT. Standardized cognitive assessments were performed at baseline, 2, 4, and 6 months. The primary endpoint was Hopkins Verbal Learning Test Delayed Recall (HVLT-DR) at 4 mos. Secondary endpoints included HVLT Total Recall (HVLT-TR) and Recognition (HVLT-Recog). Of 113 patients, 34 underwent pre-treatment and 4-month post-treatment HVLT testing and pre-treatment post-contrast volumetric T1 and axial T2/FLAIR MRI. Volumetric analysis of metastatic disease burden and disease-unrelated WMI was conducted on the pre-treatment MRI. Correlational analyses were performed examining the relationship between pre-treatment WMI and HVLT outcomes following HA-WBRT. RESULTS: Correlation was found between larger volumes of pre-treatment WMI and decline in HVLT-Recog (r=.54, p< .05) and a correlational trend was observed between larger volume of pre-treatment WMI and decline in HVLT-DR (r=.31, p=.08). Patients with higher pre-treatment disease burden experienced a greater magnitude of stability or positive shift in HVLT-recall and –delayed recall following HA-WBRT. (r=-.36 and r=-.36, p's < .05), compared to the magnitude of stability/positive shift in those with lesser disease burden. CONCLUSION: In patients receiving HA-WBRT, pre-treatment-WMI predicts memory decline, suggesting white matter integrity pre-treatment contributes to the pathogenesis of post-WBRT cognitive toxicity independent of hippocampal stem cell radiosensitivity. Less decline or improvement in HVLT following HA-WBRT for patients with higher pre-treatment intracranial metastatic burden supports the importance of WBRT-induced intracranial control on cognition. These imaging biomarkers for cognitive toxicity will be further explored on NRG CC001 and CC003, phase III trials of WBRT with or without HA.

RADI-05. FRACTIONATED TREATMENT OF BRAIN METASTASES WITH GAMMA KNIFE ICON

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PURPOSE/OBJECTIVE(S): Stereotactic radiosurgery with Gamma Knife is a common treatment modality for patients with brain metastasis. The Gamma Knife ICON allows for immobilization with an aquaplast mask, permitting fractionated treatments. We describe one of the first experiences utilizing this technique with brain metastasis and evaluate outcomes. MATERIALS/METHODS: From June 2017 to November 2018, 29 patients with 43 separate intracranial lesions were treated with fractionated stereotactic radiotherapy using the gamma knife ICON at a single institution. Patients received between 20–30 Gy in 3–5 fractions with no margin over the course of 5 to 23 days. Local control was physician assessed. Local failure over time was modeled using cumulative incidence; lesions were censored at last radiographic follow up. RESULTS: Median tumor volume and prescription isodose was 7.7 cm^3 (range 0.3–43.9) and 50% (range 40–65), respectively. Median radiographic follow-up was 7 months and median survival was 9 months. Radiation necrosis occurred in 3/3 patients treated with 27 Gy in 3 fractions, one requiring therapeutic resection. Incidence of local failure for all treated lesions was 9% at 1 year. Tumor volume >7 cm^3 was associated with local failure on univariate analysis (p=0.025). 100% (2/2) lesions treated with 20 Gy in 5 fractions developed local recurrence. CONCLUSION: Fractionated stereotactic radiotherapy with the Gamma Knife ICON provides excellent local control for small and large brain metastases with minimal toxicity. Tumors >7 cm^3 should receive at least 30 Gy in 5 fractions for optimal control. Treatment with 27 Gy in 3 fractions appears to have high rates of treatment related toxicity and should be avoided.

RADI-06. SINGLE- VERSUS MULTI-FRACTION STEREOTACTIC RADIOSURGERY FOR BRAINSTEM METASTASES

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BACKGROUND: For intracranial metastases with planning target volume (PTV) overlap of the brainstem (BSmet), the radiosurgical dose-fractionation that optimizes the therapeutic window is unknown. MATERIALS/METHODS: A retrospective review of brain metastases (BM) with/without BSmets treated with single-fraction stereotactic radiosurgery (SRS) or hypofractionated (2–5 fractions) radiosurgery (HF-SRS) between 2012–2016 was performed. Brainstem biologically effective doses (BED) and single-fraction equivalents of brainstem V10/V12 were calculated using $\alpha/\beta=3$. Characteristics were compared between patients with/without BSmet and between SRS/HF-SRS cohorts using Wilcoxon rank sum, chi-square, or Fisher's exact tests. Radiographic progression (RP) was assessed in patients with post-treatment contrasted MRI and defined as BSmet enlargement regardless of etiology (progression, radionecrosis, indeterminate). Kaplan-Meier estimates were compared between cohorts using log-rank test. RESULTS: 634 SRS/HF-SRS courses were identified, of which 59 (9.3%) treated ≥1 BSmet in 55 patients. BSmets occurred more commonly in patients with >4 BM (31% vs 10%, p< 0.001) and intracranial recurrence (39% vs 20%, p=0.003). BSmets were treated in 1 (22/59; 37%), 2 (1/59; 2%), or 5 (36/59; 61%) fractions. Age, KPS, and primary tumor site were balanced between SRS/HF-SRS cohorts. The HF-SRS cohort had significantly larger BSmet PTV (median 1.39cc vs 0.39cc, p=0.021), marginal dose (median 25Gy vs 15Gy, p< 0.001), brainstem V10 (median 1.60cc vs 0.47cc, p< 0.001), brainstem V12 (median 0.78cc vs 0.06cc, p< 0.001), and mean brainstem BED (median $9.27Gy_3$ vs $6.55Gy_3$, p=0.019). The SRS cohort was more likely to have prior whole brain radiotherapy (50% vs 14%, p=0.005) and restart steroids post-treatment (78% vs 41%, p=0.019). RP occurred in 6/17 vs 2/25 patients in the SRS vs HF-SRS cohorts, respectively (p=0.045). HF-SRS trended to higher freedom from RP (93% vs 74% @12mo; p=0.072). There was no overall survival difference (p=0.36). CONCLUSIONS: HF-SRS was associated with decreased RP and decreased likelihood of restarting steroids despite treating larger BSmets.

RADI-07. GAMMA KNIFE RADIOSURGERY FOR SMALL CELL LUNG CANCER: PROGNOSTIC FACTORS INCLUDING ADDITIONAL LESIONS IDENTIFIED ON THE DAY OF RADIOSURGERY

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OBJECTIVES: Prophylactic cranial irradiation (PCI) and whole brain radiation (WBRT) are standard of care for intracranial disease in small cell lung cancer (SCLC) patients. We sought to identify predictors of overall survival (OS) in SCLC patients treated with salvage Gamma Knife radiosurgery (GKRS) for brain metastases after prior WBRT or PCI. METHODS: Retrospective analyses were conducted on 26 SCLC patients treated with GKRS at one institution between May 2010 and June 2018. Factors predictive of OS were analyzed using Cox proportional hazards regression and Wilcoxon sum-rank testing. RESULTS: Median follow-up and median OS following GKRS was 6.6 mos (range 0.7–24.2 mos). Median OS was 21.4 mos from initial diagnosis (range 7.3–49.3 mos). Presence of extracranial metastases at the time of GKRS was not significantly associated with median OS after GKRS (5.8 mos for patients with extracranial metastases vs 7.2 mos for patients without, p=0.425). Mean number of lesions was 2.7 (range 1–10) on diagnostic brain MRIs and 4.1 (range 1–12) on GKRS planning MRIs. Eleven patients (42%) had the same number of lesions between diagnostic MRI and GKRS MRI, and 15 patients (58%) had additional lesions on the GKRS MRI. Number of lesions treated and total tumor volume were not associated with median OS. Patients who had additional lesions on GKRS MRI compared to diagnostic MRI had lower median OS from initial diagnosis of SCLC (29.9 mos vs 18.1 mos, p=0.0182) and a trend toward lower median OS from time of GKRS (7.3 mos vs 4.8 mos, p=0.0547) compared to patients who did not have additional lesions. CONCLUSIONS: Finding additional brain metastases on GKRS planning MRIs is associated with decreased OS in SCLC patients treated with salvage GKRS. Presence of extracranial metastases at the time of GKRS and number or total volume of brain metastases were not associated with OS.

RADI-08. A SURVEY BASED STUDY OF BRAIN METASTASES MANAGEMENT FOR PATIENTS WITH NON-SMALL CELL LUNG CANCERS OR MELANOMA

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INTRODUCTION: The standard of care for 1–4 brain metastases (BrM) is stereotactic radiosurgery (SRS), whereas whole brain radiation remains the standard treatment for extensive BrM, and surgical resection is appropriate in certain scenarios. Some newer systemic therapies such as tyrosine kinase inhibitors and immunotherapy have impressive CNS activity and are used by some practitioners either alone or in combination with other modalities as first-line treatment for BrM. We conducted a survey to ascertain current real-world practices for the treatment of BrM from NSCLC and melanoma. OBJECTIVES: Our study aimed to assess practice patterns of oncologists who treat BrM from NSCLC or melanoma. We also investi-