Abstracts

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PURPOSE: RTOG 0933 demonstrated benefits to memory following HA-WBRT, supporting the hypothesis of hippocampal radiosensitivity and associated treatment contralateral hippocampal toxicity. However, recent studies demonstrating negative 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 post-recall. 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 4-month post-treatment HVLT testing and post-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=.61, p=.08). Patients with higher pre-treatment disease burden experienced a greater magnitude of stability/positive shift in HVLT-recall and –delayed recall following HA-WBRT. (r=.36 and r=.36, p<.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. Additional brain metastases, degree of hippocampal stem cell radiosensitivity, hippocampal WMI, and 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 fractionated doses with brain metastases and evaluate outcomes. MATERIALS/METHODS: From June 2017 to November 2018, 29 patients with 43 separate intracranial lesions were treated with fractionated stereotactic radiosurgery 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 were 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 radiosurgery 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/BM, the radiosurgical dose-fractionation that optimizes the therapeutic window is unknown. MATERIALS/METHODS: A retrospective review of brain metastases (BM) with/without BM 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 equivalent radiosurgery (SFRS) BM volume were calculated using α/β=6. Characteristics were compared between patients with/without BMset and between BM/HS-SRS cohorts using Wilcoxon rank sum, chi-square, or Fisher’s exact tests. Radiographic progression (RP) was assessed in patients with BM and correlated with patients treated regardless of etiology (progression, radionecrosis, indeterminate). Kaplan-Meier estimates were compared between cohorts using log-rank test. RESULTS: 634 SRS/HF-SRS cohorts were identified, of which 59 (9.3%) treated 21 BM within 55 patients. BM were treated more commonly such as ≤4 BM (31% vs 10%, p<0.001) and intracranial relapse (39% vs 20%, p=0.003). BMs were treated in 1 (22/59), 37%, 2 (1/59), 2%, or 5 (36/59, 61%) fractions. Age, KPS, and primary tumor site were similar between BM-SRS/HF-SRS cohorts. The BM-SRS cohort had significantly larger BM (PTVmean 1.39cc vs 0.21cc, p=0.003) and smaller, 3.1 Gy (range 1.5Gy, 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 vs 6.55Gy, p=0.019). The BM 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 volumal difference (p=0.36). CONCLUSIONS: HF-SRS was associated with decreased RP and decreased likelihood of restarting steroids despite treating larger BMs.

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

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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 (GKS) for brain metastases after prior WBRT or PCI. METHODS: Retrospective analyses were conducted on 26 SCLC patients treated with GKS at one institution between May 2010 and June 2018. Factors predictive of OS were analyzed using Cox proportional hazards regression and Wilcoxon signed-rank testing. RESULTS: Median follow-up and median OS following GKS was 6.6 mos (range 0.7–24.2 mos). Median OS was from initial diagnosis (range 7.3–49.3 mos). Presence of extracranial metastases at the time of GKS was not significantly associated with median OS after GKS (5.8 mos for patients with extracranial metastases vs 7.2 mos for patients without extracranial metastases), and a greater number of lesions was 2.7 (range 1–19) on diagnostic brain MRIs and 4.1 (range 1–12) on GKS planning MRIs. Eleven patients (42%) had the same number of lesions between diagnostic MRI and GKS MRI, and 15 patients (58%) had additional lesions on GKS. Median number of lesions was 4 (range 1–12) on diagnostic brain MRIs and 4.1 (range 1–12) on GKS planning MRIs. Patients who had additional lesions on GKS 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 GKS (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 GKS planning MRIs is associated with decreased OS in SCLC patients treated with salvage GKS. Presence of extracranial metastases at the time of GKS 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 (BM) is stereotactic radiosurgery (SRS), whereas whole brain radiation remains the standard treatment for extensive BM, 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 BM. We conducted a survey to ascertain current neuro-oncology center practices for the treatment of BM from NSCLC and melanoma. OBJECTIVES: Our study aimed to assess practice patterns of oncologists who treat BM from NSCLC or melanoma. We also investi-
gated the extent to which various clinical factors influence decision making.

METHODOLOGY: We created 2 sets of surveys: one for Medical-/Clini-
cal-/Neuro-oncologists and another for Radiation oncologists/Neurosur-
gons. Surveys were conducted online or on-line. Following administration,
data was tabulated and analyzed. Statistical analyses were performed using
Fisher’s exact test. RESULTS: Of 361 respondents, 250 were Radiation on-
cologists/Neurosurgeons, and 111 were Medical-/Clinical-/Neuro-onco-
gists. Patients with 1–3 brain lesions, all < 2 cm, 34% of respondents
recommended systemic therapy alone as first-line treatment. In contrast,
only 15% recommend systemic therapy alone for >9 lesions, at least one >
2 cm. Medical-/Clinical-/Neuro-oncologists were more likely to recommend
systemic therapy alone compared to Radiation oncologists/Neurosurgeons
for 1–3 lesions, all < 2 cm (53% vs. 28%, p<0.0001). For patients with >
9 Brm, one >2 cm diameter, Medical-/Clinical-/Neuro-oncologists were not
significantly more likely to recommend systemic therapy alone (20% vs
13%, p=0.11). DISCUSSION: Our results reveal that significant numbers of
physicians advocate for systemic therapy alone as first-line therapy and
that management decisions correlate with a physician’s type of practice.
These findings underscore the need for prospective clinical trials to direct
appropriate Brm management.

RADI-09. DEFINING PROGRESSION IN PATIENTS TREATED WITH TEN OR MORE BRAIN METASTASES FOLLOWING STEREOTACTIC RADIOSURGERY
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BACKGROUND: An increasing trend has been to elect for Stereotactic
Radiosurgery (SRS) for the treatment of brain metastases. Progression follow-
treatment is typically defined as a ≥20% increase in the initial lesion
volume. However, the varying cut-offs in defining progression can arise as
the reported incidence of pseudoprogression or radiation necrosis following treatment ranges from 5%-30%. The purpose of this study was to assess patterns of failure in patients treated with 10 or more brain metastases. METHODS: From March 2014 to April 2018, fifty-five patients with 10 or more total brain metastases were retrospectively reviewed following frame-based radiosurgery to a dose of 12–20 Gy. Post-treatment MRI scans were used to assess tumor response in 3 month intervals. Tumor control was defined as tumor volume ≤ 1.2 times the baseline tumor volume at each measured interval. RESULTS: Fifty-five patients received 75 total radiosurgery treat-
ments to 692 tumors. Forty patients received synchronous treatment, while
15 received metachronous treatment. 20 patients (36%) and 72 tumors (10%)
experienced progression following treatment. 46 tumors were larger after
first MRI in 15 patients (28%). Of these 15 patients, eight had com-
plete resolution in 15 tumors on subsequent scan. Of the eight patients who
had resolution, six patients received immunotherapy during and after treat-
ment and all but one patient saw an initial increase >100% of their initial
tumor volume in the overall survival. Kaplan–Meier analysis revealed an association between larger brain volumes irradiated with 12 Gy and decreased overall survival (p<0.05). CONCLUSION: It is important to
consider tumor growth velocity and concurrent therapy when assessing true
progression after SRS treatment of brain metastases.

RADI-10. THERAPEUTIC EFFECTS OF ISRS IN 44 CASES OF BRAIN METASTASES OF NSCLC WITH A MAXIMUM DIAMETER ≥ 4CM
AND ANALYSIS OF ITS PROGNOSTIC FACTORS
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OBJECTIVE: To analyze the therapeutic effects of ISRS on brain metas-
tases of NSCLC with a maximum diameter ≥ 4 cm, and explore the pro-
gnostic factors. METHODS: A retrospective analysis was conducted on the clinical data of 44 cases of brain metastases of NSCLC with a maximum
diameter ≥ 4 cm in Guangdong Sanju Brain Hospital from January 2006
to December 2016. RANO criteria were adopted for imaging evaluation at
3 months after completion of radiotherapy. One- and 2-year survival rates
were calculated and the differences in survival rates between groups were
analyzed with Log-rank test. Kaplan-Meier method was used in univariate
analysis to investigate the effects of KPS, RPA classification, number of
metastases, total lesion volume, systemic treatment and surgery on pro-
gnosis; and Cox regression model in multivariate analysis. RESULTS: The
postoperative imaging evaluation showed that there were 3 cases of CR,
20 of PR, 12 of SD and 7 of PD. The median PFS, OS, 1- and 2-year sur-
vival rates were 6 months, 16 months, 65.9% and 20.5%, respectively. KPS,
RPA classification, number of metastases and surgery had no significant cor-
relations with prognosis. However, systemic treatment and the maximum
lesion volume <28.3cc were considered as favorable factors related to prog-
nosis (P=0.046, 0.027). Moreover, the maximum lesion volume <28.3cc was
found to be the independent prognostic factor for the survival (P=0.035).
CONCLUSION: Treatment of brain metastases of NSCLC with a maximal diameter ≥ 4 cm with ISRS is proved to be feasible. The maximum lesion
volume <28.3cc (compared with chemotherapy, TKI treatment, etc.) may improve prognosis, but more cases are needed to inves-
tigate the prognostic significance.

RADI-11. NRG ONCOLOGY CC001: A PHASE III TRIAL OF HIPPOCAMPAL AVOIDANCE IN ADDITION TO WHOLE-BRAIN RADIOTHERAPY (WBRT) PLUS MEMANTINE TO PRESERVE NEUROCOGNITIVE FUNCTION IN PATIENTS WITH BRAIN METASTASES (BM)
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INTRODUCTION: Postoperative stereotactic radiosurgery (postop SRS)
is potentially complicated by difficulty defining the target volume and the
risk of leptomeningeal seeding at the time of surgery. It is hypothesized that
preop SRS may render cells less viable to disseminate in the leptomeninge-
al space. This retrospective study compares the leptomeningeal dissemina-
tion (LMD) rate for preop versus postop radiosurgery METHODS: We
identified 140 patients with brain metastases who underwent resection and
radiosurgery at the University of Alabama at Birmingham including
91 postop patients (2005–2015) and 49 preop patients (2011–2018). The
postop group included 19 patients enrolled in a phase I trial of preoperative
Brain metastases better preserves NCF and patient-reported symptoms. Supported by
U1CA189867 (NCORP) and DCP from the NCI.

RADI-12. LEPTOMENINGEAL FAILURE AFTER PREOPERATIVE VERSUS POSTOPERATIVE RADIOSURGERY
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INTRODUCTION: Postoperative stereotactic radiosurgery (postop SRS)
is potentially complicated by difficulty defining the target volume and the
risk of leptomeningeal seeding at the time of surgery. It is hypothesized that
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91 postop patients (2005–2015) and 49 preop patients (2011–2018). The
postop group included 19 patients enrolled in a phase I trial of preoperative
neurocognitive function in patients with brain metastases.

NRG CC001, a phase III trial of WBRT+memantine (WBRT+m) with or without Hippocampal Avoidance (HA), sought to assess the neuro-protective effects of lowering the radiation dose received by the hippocampus. METHODS: Patients (pts) with brain metastases were stratified by RPA class and prior radiosurgery/surgery and randomized to either WBRT+m or HA-WBRT+m (30Gy/10 fractions). Standardized neurocognitive function (NCF) tests were performed at baseline, 2, 4, 6, and 12 months (mos.). The primary endpoint was NCF failure, defined as decline using the reliable change index on Hopkins Verbal Learning Test-Revised, Trail Making Test, or Controlled Oral Word Association. Cumulative in-
cidence estimated NCF failure (death without NCF failure was competing risk); between-arms differences tested using Gray’s test. Deterioration at each collection time point was tested using a chi-square test. Patient-reported symptoms were assessed using the MD Anderson Symptom Inventory with Brain Tumor module and analyzed using mixed effects models and t-tests.

RESULTS: From 7/2016 to 3/2018, 518 patients were randomized. Median follow-up was 7.9 mos. HA-WBRT+m was associated with lower NCF failure risk (adjusted HR=0.74, p=0.02) due to lower risk of deterioration in executive function at 4 mos. (p=0.011) and encoding (p=0.049) and con-
solidation (p=0.02) at 6 mos. Age61 predicted for lower NCF failure risk (HR=0.60, p=0.0002); non-significant test for interaction indicated inde-
pendent effects of HA and age. Patient-reported fatigue (p=0.031) and difficulty speaking (p=0.049); and problems remembering things (p=0.013) at 6 mos. favored the HA-WBRT+m arm. Imputation models accounting for missing data also favored the HA-WBRT+m arm for patient-reported cognition (p=0.011) and symptom interference (p=0.008) at 6 mos. Treatment did not significantly differ in toxicity; intracranial progression or overall survival. CONCLUSIONS: While achieving similar intracranial control and survival; Hippocampal Avoidance during WBRT+m for brain metas-
tases better preserves NCF and patient-reported symptoms. Supported by
U1CA189867 (NCORP) and DCP from the NCI.