**Phase I Dose Escalation Trial of Hypofractionated Radiosurgery for Large Brain Metastases**

Principal Investigator
Bree Eaton
Co-investigators
Ian Crocker
Nelson Chen, PhD
Hui-Kuo Shu, MD, PhD
Walter Curran, MD
Kristen Higgins, MD
Pretesh Patel, MD
Shannon Kahn, MD
Ben Fischer-Valuck, MD
Elizabeth Butker, MS
Department of Radiation Oncology
Winship Cancer Institute of Emory University

Precis
Hypofractionated Radiosurgery (HR) is a treatment option for delivering focal brain radiation therapy to patients with brain metastases, who would otherwise not be candidates for single fraction stereotactic radiosurgery (SRS) based on size criteria. The optimal dose and fractionation schedule for HR is undefined. We propose a phase I dose escalation trial of HR delivered in 5 fractions, with a minimum of 2 and a maximum of 3 fractions being delivered per week, to patients with brain metastases or resection cavity greater than 3cm and less than 6cm. Dose escalation will proceed according to the Escalation with Overdose Control (EWOC) method with a planned total enrollment of 24 patients, in 8 patient cohorts with 3 patients per cohort. A 4 month observation period will occur for each completed cohort prior to dose escalation, with a goal timeline for trial completion of 4 years from first patient enrollment

## 1.0 INTRODUCTION/BACKGROUND

Brain metastases are the most common adult intracranial tumor, occurring in up to 40% of adult cancer patients, and represent an important cause of morbidity and mortality in this population[1]. The treatment of brain metastases may involve surgery followed by radiotherapy or radiotherapy alone [2-3]. There are multiple options for radiotherapy; including whole brain radiation (WBRT), whole brain radiation combined with stereotactic radiosurgery (SRS), or focal brain radiation with SRS alone. Level I and level II evidence, supports the use of SRS in multiple settings. Randomized controlled trials have shown the addition of SRS to WBRT leads to a significant increase in median survival and time to recurrence compared with WBRT alone for patients with solid single brain metastasis and a KPS >70 [3-5] . Stereotactic radiosurgery combined with WBRT is also supported as an alternative to resection plus WBRT for metastatic lesions < 3cm, as multiple retrospective cohort studies have shown relatively equivalent survival rates [6-8]. Focal brain radiation by SRS alone is commonly used as salvage therapy for patients who recur with brain metastasis after WBRT, and is also increasingly used as a primary treatment modality in attempts to prevent or delay the known neurocognitive toxicities of WBRT[9]. One randomized controlled trial and multiple retrospective cohorts report equivalent survival results with SRS alone when compared to SRS plus WBRT or WBRT alone [2, 10-12]. The data supporting SRS for intact brain metastasis is commonly extrapolated to support the use of SRS to resection cavities for improved local control following surgical resection of intracranial metastasis. Multiple published series have reported on the use of SRS in this setting and have demonstrates local control rates of 70 - 94% with additional benefits over WBRT including short treatment course and improved patient compliance[13]. Clearly, SRS is an effective and important tool for the treatment of brain metastasis in multiple clinical settings.

Stereotactic Radiosurgery, as defined by the American Society for Therapeutic Radiology and Oncology (ASTRO), the American Association of Neurological Surgeons (AANS), and the Congress of Neurological Surgeons (CNS), includes single dose SRS and well as HR delivered in 2-5 fractions over multiple days [14-15]. The majority of data supporting the use of SRS for the treatment of brain metastases has evaluated only single dose SRS and it is unclear whether the same results can be attributed to HR in 2-5 fractions. Brain metastasis amenable to single fraction SRS are typically defined as those measuring less than 3cm and producing less than 1cm of midline shift [3]. For brain metastasis not amenable to SRS, but for which focal brain radiation is indicated for boost or as salvage after WBRT or for avoidance of neurocognitive decline, HR provides an alternative treatment option. Current data describing the use and results of HR for the treatment of brain metastasis is limited to few retrospective series. Pater and colleagues from University of Cincinnati have demonstrated HR delivered to a dose of 30 Gy in 5 fractions to be effective and tolerable in a series of 34 patients, with a 6% (n=2) incidence of asymptomatic radiation necrosis and a 6 month actuarial local control rate of 68%[16]. A second series of 43 patients with metastatic breast cancer treated at Staten Island University Hospital utilized HR to a dose of 24 Gy delivered in 4 fractions, with a median survival from treatment of 7.5 months[17]. Recently, Wang et al. have reported on the use of HR is the setting of resected brain metastasis with resection cavities > 3cm and have demonstrated a local control rate of 80% at 6 months with the use of 24 Gy in 3 daily fraction[18]. With only a few series reported, the optimal dose and fractionation schedule is unknown.

In our own experience at Emory[19] with 47 patients receiving HR for both solid intact metastasis (22) and resection cavities (25), we have demonstrated 6 month and 1 year LC rates of 69% (CI 0.62-0.77) and 59% (CI 0.67 – 0.50), with 3 (6.4%) patients experiencing symptomatic radiation necrosis. On multivariate Cox-regression analysis, improved local control was associated with smaller planned target volume (PTV) volume (SS, p=0.02) and higher dose per fraction (NS, p=0.06). No significant association was found between LC and previous RT received, resection cavity vs. solid tumor, total dose, biological equivalent dose (BED) or single fraction equivalent dose (SFED). These results show HR is well tolerated in both new and recurrent, previously irradiated large intact or resected brain metastases. Significantly higher rates of local failure are observed with larger PTV volumes suggesting a need for dose escalation when using HR for large intracranial lesions.

We propose a prospective phase I trial for patients with sold brain metastasis greater than 3cm and less than 6 cm, who have either had no treatment or who are status post surgical resection. The purpose of this trial will be to determine the maximum tolerated dose for fractionated radiosurgery delivered in 5 fractions with a minimum of 2 and a maximum of 3 fractions being delivered per week. Results from this trial may form the basis of future trials evaluating the efficacy of fractionated radiosurgery regimens for local and distant control of brain metastasis and for directly comparing WBRT with FRS, for patients not amenable to single fraction SRS. Such a phase III study would answer the question about as to whether local irradiation is adequate treatment for patients with large brain metastasis.

## 2 .0 OBJECTIVES

To demonstrate the safety and feasibility of treating brain metastases or resection cavities greater than 3cm with hypofractionated radiosurgery and to determine the maximum-tolerated radiation dose for HR delivered in 5 fractions, 2-3 fractions per week.

### 2.1 Primary Endpoints:

2.1.1 Maximum tolerated dose (MTD)

2.1.2 Dose limiting toxicity (DLT): any acute or late CNS toxicity with grade greater than or equal to 3 with attribution score greater than or equal to 3.

### 2.2 Secondary Endpoints:

2.2.1 Local control: lack of progression of disease in resection cavity

2.2.2 Distant control: lack of progression of disease in surrounding brain

2.2.3 Overall survival: death from any cause

2.2.4 Long-term neurocognitive outcomes: using the Hopkins Verbal Learning Test–Revised (HVLT-R), Mini Mental Status Exam (MMSE) and Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS).

2.2.5 Quality of life (QOL) outcomes: using the quality of life questionnaire for the Functional Assessment of Cancer Therapy-Brain (FACT-Br).

## 3.0 STUDY DESIGN AND METHODS

### 3.1 Registration

Patients with a metastatic brain tumor or resection cavity greater than 3cm and less than 6cm who are referred for radiation therapy to the brain, who meet the inclusion criteria listed below, and who have signed formal consent for participation in this clinical trial

will be enrolled into the radiation therapy dose group according to the escalation with overdose control design described below.

**3.2 Enrollment/Randomization**

This study will include 8 patient cohorts with 3 patients per cohort. The patients will be enrolled and treated following a Bayesian method permitting precise determination of the therapeutic working-dose while directly controlling the likelihood of an overdose. The method, known as Escalation with Overdose Control (EWOC), has been used to design phase I clinical trials at several cancer centers including the Fox Chase Cancer Center (PA), the Sylvester Comprehensive Cancer Center (FL), and the Winship Cancer Institute (GA) and pharmaceutical companies. EWOC was the first dose-finding procedure to directly incorporate the ethical constraint of minimizing the chance of treating patients at unacceptably high doses. Its defining property is that the expected proportion of patients treated at doses above the MTD is equal to a specified value $\alpha$, the feasibility bound. This value is selected by the clinician and reflects his/her level of concern about overdosing.
The dose levels for the trial are summarized in Table 1. The dose for the first cohort of 3 patients in the trial will be the dose level 0, previous results indicating this to be a safe dose. The patient accrual will be suspended until the 4 month toxicity evaluation is completed for all previously enrolled patients. The dose for each subsequent cohort of 3 patients will be determined so that, on the basis of all available data and the target highest acceptable toxicity level of 25% DLT, the probability that it exceeds the MTD is equal to a pre-specified value $\alpha$. In this trial, we set $\alpha = 0.25$ and increase $\alpha$ in small increments until $\alpha = 0.5$, this value being a compromise between the therapeutic aspect of the agent and its toxic side effects. The dose selected for every patient in the trial will be between the minimum dose of 27.5 **Gy** and the maximum allowable dose of 40 **Gy**. The trial will be terminated if 3 DLTs are observed in any cohort of 3 patients treated with the lowest dose level. The trial will stop after 24 patients have been enrolled and MTD will be estimated from one of the 6 specified dose levels listed in the Table 1. If no MTD is found because even the highest dose level is still considered under toxic, then the highest dose group will be considered the MTD and expanded to 12 patients.

The enrollment will be done sequentially. If a grade 5 toxicity develops in the initial evaluation period (4 months), then the study will be halted and all patient data will be reviewed by the data safety monitoring committee to determine the likelihood that the treatment given was responsible and whether the study can resume. If a patient is not able to complete follow up to the toxicity assessment point of 4 months due to a toxicity judged not to be at least possibly related to therapy, then that patient will be replaced at the same dose level by the next patient enrolled into that cohort. After all patients in a designated dose group have completed the 4 month toxicity assessment, the documented DLTs, having previously been reviewed by the PI, co-investigators and data safety monitoring committee, will be again reviewed by the PI and co-investigators at the time the decision is made to escalate or de-escalate to the next dose level accordingly.

<u>Example of sequential enrollment</u>

Patients identified meeting eligibility criteria will be offered enrollment in this study. As with any other protocol, the risks, benefits, and alternatives of protocol enrollment will be

thoroughly discussed and patient consent form will be provided for further information. Once the patient agrees to be enrolled, they will be allocated to a specific dose level based on sequential enrollment. The first three patients assigned will be enrolled into dose level 1. Once this group has reached the accrual goal of three patients, then that cohort will be closed until the 4 month toxicity evaluation is completed for all 3 patients. The next three consecutive patients within that cohort will be enrolled to dose level 2 unless a grade 3 or 4 toxicity was documented (as detailed above). If there was such a toxicity, then the three next patients will be enrolled into the same dose level as an expansion.

### 3.3 Therapeutic and Diagnostic Procedures

All simulation and treatment procedures represent current institutional practice and will be the same for all study participants in each dose level

**3.3.1** Radiation Therapy will consist of partial brain irradiation delivered to the metastatic brain tumor or resection cavity, delivered in 5 treatments with 2-3 treatments delivered per week.

**3.3.2** CT Simulation will be performed for radiation therapy treatment planning purposes several days prior to the initiation of radiation therapy. This procedure consists of a CT scan performed in the treatment position. It is not for diagnostic purposes and is not itself therapeutic, but the CT image is required for radiation planning and delivery. This procedure is standard of care prior to therapeutic radiation.

**3.3.3** Pre-treatment and post-treatment MRI of the brain. The patient will be required to undergo diagnostic MRI before and after radiation treatment as well as a treatment planning MRI. MRI will be ordered with and without gadolinium. This diagnostic procedure is standard of care for follow-up of intracranial metastases.

### 3.4 Radiation Therapy

#### 3.4.1 Required Criteria

1. A high resolution MRI for treatment planning is recommended within 2 weeks of treatment delivery. If using a planning scan, methods for automatically registering the planning scan to the Simulation CT scan must be in place.
2. Utilize frameless stereotactic head immobilization with 6 degrees of freedom (DOF)[20] for simulation and treatment delivery.
3. Perform target localization utilizing stereotactic CT scan or MRI
4. Use treatment planning system capable of generating isodose distributions for a given treatment in 3 dimensions
5. Treatment shall be delivered with megavoltage machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy (ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue.
6. Treatment may be delivered with intensity modulated radiation therapy (IMRT) or dynamic conformal arcs (DCA), or via Gamma Knife.
7. Patients must be positioned for each treatment using 3 dimensional imaging ie Cone Beam CT, or comparable patient positioning verification system.

7. Treatment should be initiated within 6 weeks of surgical resection if applicable. It is anticipated that most patients will start within 3 to 4 weeks of surgery
8. Quality analysis of the treatment criteria described in this section (3.4) will be performed by study investigators prior to the patient completing the study treatment.

### 3.4.2 Target Volume Determination

1. Target volume and isocenter determination will be based on a simulation CT and/or treatment planning MRI (with and without contrast)
2. Stereotactic CT scan slice thickness may not exceed 1 mm
3. Treatment planning MRI slice thickness may not exceed 2 mm
4. The gross target volume (GTV) will include the entirety of the MRI defined T1 post contrast enhancing brain metastasis or the resection cavity including any residual enhancing disease. Surrounding areas of edema will not be considered part of the target volume.
5. A margin of 0.5 mm in all directions will be applied to the GTV to create the clinical target volume (CTV)
6. An additional margin of 1 mm will be added to the CTV to create the PTV.
7. Target volumes (in cc) will be determined for the GTV, CTV and PTV using the treatment planning software

### 3.4.3 Total dose determination

1. Total dose determination will depend on the currently accruing dose level
2. Starting dose level is based on current institution standards and retrospective reports from other institutions[15,19].

Table 1. Summary of dose levels to be tested.

| Dose level | Total Dose (Gy) | Dose per Fraction (Gy) | Fraction Number | $BED_{10}$ (Early Effects) | $BED_3$ (Late Effects) |
|---|---|---|---|---|---|
| -1 | 27.5 | 5.5 | 5 | 44 | 78 |
| 0 | 30 | 6 | 5 | 49 | 90 |
| 1 | 32.5 | 6.5 | 5 | 55 | 103 |
| 2 | 35 | 7 | 5 | 60 | 117 |
| 3 | 37.5 | 7.5 | 5 | 66 | 131 |
| 4 | 40 | 8 | 5 | 69 | 147 |
| SRS* | 18-21 Gy | 18-21 Gy | 1 | 53-68 | 126-168 |

*for comparison only, single fraction SRS will not be used in this protocol

### 3.4.4 Dose prescription and dosimetry requirements

1. Dose will be prescribed to the isodose line that encompasses the entirety of the PTV.
    1. If intensity modulated radiosurgery (IMRS) is utilized, standard prescription isodose is to 98% (range 95-100%)
    2. If dynamic conformal arcs (DCA) are utilized, standard prescription isodose is to 80% (range 70-90%).
    3. If gamma knife is utilized, standard prescription isodose is to 50%

2. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose.
3. Inhomogeneity within the PTV should be kept within ± 10% of the prescribed dose, and the minimum dose PTV should be kept within 10% of the dose at the isocenter.
4. The marginal dose and the 100% dose (isocenter dose) will be recorded for each patient.
5. For quality control, representative isodose lines (eg. 20%, 40%, 60%, 80%, 90%) must be generated for each patient.
Quality of PTV coverage will be categorized according to selected isodose line:

1. Total – selected isodose line completely encompasses the PTV
2. Marginal – selected isodose line incompletely encompasses the PTV, but not by more than 10% of the PTV volume.
3. Subtotal - selected isodose line incompletely encompasses the PTV, but by more than 10% of the PTV volume. This will not be accepted.

6. Conformality index requirements (ratio of prescription isodose volume to the target volume *(PI/TV)*)

1. Per protocol if between 1.0 and 2.0
2. Acceptable variation if ≥ 0.9 but < 1.0 or >2.0 but ≤ 3.5.
3. Unacceptable deviation if > 3.5.

### 3.4.5 Patient localization and immobilization

1. The CT or MR simulation will occur with the patient supine position in a frameless thermoplastic head mask.
2. The treatment planning software will be used to generate the isocenter position information
3. Accurate positioning is achieved by matching an in-room cone-beam CT (CBCT) to the planning CT (PCT) using a 6 DOF rigid registration method customized to use mutual information metric in Mattes's formulation. In addition to couch shifts, the 6 DOF-registration calculates the spin, tilt, and couch angles required for precise target positioning. The spin and tilt are applied using a customized couch mount while couch translations and rotation are applied using the treatment console. A second CBCT is acquired to verify positioning with the clinical system before treatment delivery[20].

### 3.4.6 Dose Limitation to Critical Structures

1. In addition to the above defined GTVs, CTVs and PTVs, both eyes, the lenses of both eyes, the optic nerves, the optic chiasm, the brainstem and the spinal cord and the whole brain and normal brain parenchyma will be contoured. Normal brain is defined as the whole brain minus the GTV. Dose-volume histograms will be generated and whole organ dose and maximum point dose will be recorded for each critical structure.
2. If the patient has received no prior cranial irradiation, the maximal point doses permissible to the structures from the current radiation therapy plan are listed below* (Table 2).

3. If the patient has received previous WBRT, the previous dose received to critical structures should be obtained or a representative dose distribution file should be simulated. This dose should then be converted to BED (assuming an alpha-beta ratio of 3 for late effects) and added to the BED to the critical structures from the current treatment plan. This sum BED must meet the cumulative dose constraint below¶ (Table 2). No adjustments for time between previous radiation treatment will be made for the purpose of this protocol.
4. If a patient is recommended to receive whole brain radiation after completion of the study treatment, the constraints listed in Table 3 should be met during the whole brain radiation treatment. It is recommended that the 90% isodose volume from the hypofractionated radiosurgery treatment be created into an avoidance structure and constrained such that the maximum dose to this structure or the normal brain has a cumulative $BED_3$ of ≤150 (equivalent to max dose 15-18 Gy when delivered in 3-3.5 Gy per fraction).

**Table 2. Normal Tissue Constraints for Hypofractionated Radiosurgery Treatment**

| Cumulative $BED_3$ | Volume | No Previous RT* | Previous RT¶ |
|---|---|---|---|
| | | Maximum Dose | Maximum Cumulative $BED_3$ |
| Brainstem | Max, ≤ 0.03cc | 26 Gy | 90 |
| Spinal Cord | Max, ≤ 0.03cc | 22 Gy | 75 |
| Eye (Globe), each | Max, ≤ 0.03cc | 20 Gy | 66 |
| Lens, each | Max, ≤ 0.03cc | 2.5 | 12 |
| Optic Nerve, each | Max, ≤ 0.03cc | 26 Gy | 90 |
| Optic Chiasm | Max, ≤ 0.03cc | 26 Gy | 90 |
| Normal Brain | Modal | 20 Gy | 15 Gy |
| Normal Brain | ≤ 23 cc | 4 Gy/fraction | 4Gy/fraction |

Table 3: Constriants for Whole Brain Radiation following hypofractionated radiosurgery

| Cumulative $BED_3$ | Volume | WBRT after study treatment |
|---|---|---|
| | | Maximum Cumulative $BED_3$ |
| Brainstem | Max, ≤ 0.03cc | 90 |
| Spinal Cord | Max, ≤ 0.03cc | 75 |
| Eye (Globe), each | Max, ≤ 0.03cc | 66 |
| Lens, each | Max, ≤ 0.03cc | 12 |
| Optic Nerve, each | Max, ≤ 0.03cc | 90 |
| Optic Chiasm | Max, ≤ 0.03cc | 90 |
| Dose within 90% isodose line from study treatment or within normal brain | Max, ≤ 0.03cc | 150 |

### 3.5 Drug Therapy
No medications will be administered as part of the protocol. Patients may receive systemic chemotherapy or other drugs at the discretion of the treating physician.

### 3.6 Surgery
Patients may be status post resection of solitary brain metastases as per neurosurgery before trial registration. No surgical procedures will be performed as part of this protocol.

### 3.7 Other Therapies
Not applicable to this protocol.

### 3.8 Patient Assessments
See appendix A for assessment timeline

#### 3.8.1 Neurologic Toxicity Assessment
1. Neurologic/CNS Toxicity will be graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03 **(Appendix B).**
2. Toxicity assessment will be made during treatment at weekly MD visits and at each follow up (1 month and 4 months after completion of radiation therapy, and every 3 months thereafter). A plus or minus 3 week window will be allowed for follow-up assessments.
3. Toxicity will be classified as immediate (within 24 hours of treatment), acute (within 4 months), or chronic (more than 4 months) based on timing after SRS.
4. Toxicities of any grade should be recorded by the radiation oncology staff on the study specific case report form at the prespecified assessment time points. All ≥ grade 3 nervous system toxicity will be reported to the study principle investigator (PI).
5. Toxicities attributed to chemotherapy recorded by medical oncology staff will not be captured as study related AEs.
6. Attribution will initially be scored by the study investigators on the case report form and/or the physician seeing the patient in follow-up visit on a five point scale: 5=definitely caused by radiation treatment, 4= probably caused by radiation treatment, 3=possibly caused by radiation treatment, 2= probably not caused by radiation treatment, 1= not due to radiation treatment. Attribution will be reviewed by the PI and co-investigators. Any ≥ grade 3 CNS toxicity with attribution ≥ 3 will be considered at DLT and will be reported to the DSMC. If a grade 3 CNS toxicity occurs after the patients is considered off study this will not be considered a DLT.
7. Any grade 5 toxicity will halt the study for review by the DSMC and IRB.
8. Maximal Tolerated Dose (MTD)

The MTD will be defined as the highest dose level where a grade 3 or greater with an attribution score of ≥ 3 develops in ≤2 of 6 patients in a dose group within 4 months of the treatment.

9. Laboratory values are not required for this protocol and will not be collected.

### 3.8.2 Imaging, Treatment Response and Tumor Control Assessment

Patients will undergo brain MRI prior to study entry and at 1 month, 4 months and every 3 months thereafter or when otherwise indicated (eg. at onset of clinical deterioration). A plus or minus 3 week window will be allowed for follow-up imaging and tumor response assessments.

1. Brain metastasis evaluation

The appearance (yes/no) of any new brain metastases will be recorded on all follow-up forms. Any new lesions on follow-up imaging will be defined as progression. Progression will be categorized as described below.

2. Primary Tumor or Resection Cavity response evaluation.

For intact solid tumors, the treated lesion will be evaluated on each follow-up MRI for evidence of progression and response according to the Response Evaluation Criteria for Solid Tumors (RECIST)(**Appendix C**). For resection cavities, residual disease or any new/progressive disease will also be measured. If there is no residual disease or progressive disease, the cavity will be considered stable and no measurements will be taken. New appearance of, or increase in, contrast enhancement of the cavity or surrounding vasogenic edema will be recorded.

3. Any situation where it is unclear whether the imaging changes are due to tumor relapse/progression versus radiation necrosis will require further work-up. This may include MR spectroscopy, MR perfusion, brain PET scan, or a combination of several modalities. In cases in which the patient is symptomatic and an unequivocal diagnosis cannot be made may require surgical intervention

### 3.8.3 Neurocognitive/Quality of Life Outcome Assessments

All tests will be given at baseline (if the patient consents to completing them) and at every follow-up for the first 7 months, then every 6 months thereafter (at 1, 4, 7, 13, 19, and 25 months).

1. Tests to be administered:

| **Cognitive Domain** | **Assessment** |
|---|---|
| Memory | Hopkins Verbal Learning Test-Revised |
| Global Function | Mini-Mental Status Examination |
| Cognitive Function (self-report) | Medical Outcomes Cognitive Scale |
| Quality of Life | Functional Assessment of Cancer Therapy-Brain (FACT-Br) |

2. Hopkins Verbal Learning Test- Revised (HVLT-R)

The patient learns 12 words read to them 3 times; free recall is tested after each learning trial. Delayed recall is evaluated after 20 minutes. Following the delayed recall trial, the patient completes a delayed recognition test to determine if an impairment of delayed recall is due to a retrieval deficit or to a consolidation deficit. Entire test requires about 5 minutes to complete, excluding waiting period before delayed recall.

3. Mini-Mental Status Examination (MMSE)

This is a brief, standardized tool to grade patients' global cognitive function. The MMSE begins with an assessment of orientation to place and time. Next is a test of memory (immediate recall) by having the subject immediately repeat the names of 3 objects presented orally. Following this, the patient subtracts sevens serially from 100. The subject is then asked to recall the three items previously repeated (delayed recall). The final section evaluates aphasia and apraxia by testing naming, repetition, compliance with a 3-step command, comprehension of written words, writing, and copying a drawing. The maximum score that can be obtained for the entire MMSE is 30 points.

4. Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS) (Self-report)

This 6-item, self-report measure is designed to measure day-to-day cognitive functioning of which the patient would be aware, including difficulty with problem-solving, slowed reaction times, forgetfulness, and concentration. Reliability and validity have been reported for patients with cancer. Scale is based on multiple choice questions asking about cognitive function where the item is present 1= all of the time to 6=none of the time. Scored in five steps (data cleaning, changing out of range values to missing, item re-calibration and skip pattern recording, reverse scoring of items so that the highest score reflects the best health state, transforming scores linearly to a common metric with a range of 0-100, averaging across items in the same scale). Completion time is estimated to be less than 5 minutes.

5. Functional Assessment of Cancer Therapy-Brain (FACT-Br)

This assessment is a commonly used instrument measuring general quality of life (QOL) reflecting symptoms or problems associated with brain malignancies across 5 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and concerns relevant to patients with brain tumors (23 items). Patients rate all items using a five-point rating scale ranging from "not at all" to "very much." The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale.

### 3.8.4 Data Collection

1. Data Fields

The following data will be collected on each patient: name, date of birth, medical record number, laboratory data, tumor characteristics by pathology of surgical specimen, surgical variables, previous radiation variables, radiologic results, performance status, radiation and chemotherapy treatment parameters, clinical outcome including local and distant brain control, recurrence patterns, overall survival, treatment complications, neurocognitive assessments, and QOL assessments.

2. Criteria for patient to be considered a local/marginal failure

2.1 Patient requires secondary treatment including surgery or repeat radiation therapy

2.2 Unequivocal imaging (contrast MRI) evidence of local recurrence as defined by RECIST criteria. At least a 20% increase in the sum of diameter of the treated lesion or the residual enhancement within the resection cavity, demonstrating at least an absolute increase of 5mm

3. Categorization of Recurrence Pattern

3.1 Local failure is defined as evidence of recurrence where >80% of tumor is within prescription isodose line)

3.2 Marginal Failure-is defined as evidence of recurrence where any part of the tumor is within prescription isodose line, but < 80%

3.3 Distant failure is defined as evidence of recurrence within the brain but none of the tumor volume lies within the prescription isodose line.

4. Data storage

Each patient will be assigned a study number to be used in data collection and storage so as to protect each patient's PHI. All patients will sign a HIPPA consent for release of PHI. PHI will be destroyed at completion of the study. Study database will be stored on a secure, password protected server in the department of radiation oncology.

## 4.0 PATIENT SELECTION

### 4.1 Inclusion Criteria

4.1.1 Pathologic proven diagnosis of solid tumor malignancy.

4.1.2 Age ≥ 18.

4.1.3 One brain metastasis or brain metastasis resection cavity with maximal diameter ≥ 3cm (or ≥ 14 cc.) and ≤ 6 cm ( or ≤113 cc.).

4.1.4 RPA class I-II/ Karnofksy Performance Status ≥ 70% (See **Appendix D for definitions**)

### 4.2 Exclusion Criteria

4.2.1 Prior SRS to adjacent lesion such that planning target volume would have received more than 12 Gy

4.2.2 RPA class III (KPS < 70%, see **Appendix D definitions**).

4.2.3 Brain metastasis or resection cavity volume < 3 cm or 14 cc. or > 6cm or 113 cc.

4.2.4 Radiosensitive or non-solid (eg. small cell lung carcinomas, germ cell tumors, leukemias, or lymphomas) or unknown tumor histologies.

4.2.5 Concurrent chemotherapy (no chemotherapy starting 14 days before start of radiation).

4.2.6 Evidence of leptomeningeal disease by MRI and/or CSF cytology.

4.2.7 Current pregnancy

4.2.8 More than 8 weeks between resection and radiosurgical procedure

4.2.9 Metastases to brain stem, midbrain, pons, or medulla or within 5 mm of the optic apparatus *(optic nerves and chiasm)*.

4.2.10 Inability to undergo MRI evaluation for treatment planning and follow-up

**4.3 Pre-treatment Evaluation/Screening**

4.3.1 MRI scan with and without contrast (at least 5mm resolution on T1 post-contrast imaging).
4.3.2 History and physical including a detailed neurologic exam.
4.3.3 Steroid and anti-convulsant doses must be documented.
4.3.4 Baseline MMSE.
4.3.5 Baseline neurocognitive function using the HVLT-R (memory).
4.3.6 Baseline neurocognitive function using MOS (self-report).
4.3.7 Baseline QOL assessment using FACT-Br.
4.3.8 Documentation of extent of systemic disease.
4.3.9 Pregnancy test in women of child bearing potential

**4.4 Recruitment Plan**

Patients with brain metastases who are referred to Emory Radiation Oncology for brain radiotherapy either in the setting of intact solid metastatic tumor(s) or after resection of the metastatic tumor(s) will be considered for this study. All Emory radiation oncology physicians will be made aware of the trial, including main objectives and patient eligibility. Once the trial is open to accrual it will be up to the primary radiation oncologist to screen patients for eligibility**,** explain the risk and benefits of trial participation, and inform patients of the alternative treatment options off of study. Copies of this study protocol and eligibility checklist (**Appendix E**), study consents (**Appendix F and G**) and initial assessment form (**Appendix H**) will be made available to all physicians in the radiation oncology department at Emory University Hospital and Emory University Hospital Midtown.

**4.5 Informed Consent**

Eligible patients will be informed of all options for brain radiotherapy, which may include whole brain radiation therapy, partial brain radiation therapy to the tumor/resection cavity only delivered with fractionated radiosurgery either on or off the this study, or a combination of the two. Risks and benefits of each option will be discussed and patients who elect to receive partial brain radiation therapy only will be offered participation in the trial and given a copy of the informed consent (**Appendix G**). Informed consent will be signed and witnessed after all patient questions have been

**4.6 Criteria for patient to be considered off study**

4.6.1 Patient death.
4.6.2 Patient undergoes whole brain radiation therapy. However, we will continue to follow the patient after whole brain radiation therapy to document whether there are any enhanced toxicities with the combination of the study treatment and whole brain radiotherapy.
4.6.3 Patient request to come off study.

## 5.0 STATISTICAL ANALYSIS

**5.1 Study endpoints**

5.1.1 Primary endpoints

1. MTD
2. Neurologic toxicity due to treatment

5.1.2 Secondary Endpoints

1. Local Control
2. Margin Conrol
3. Distant brain control
4. Freedom From Failure/Progression Free Survival
5. Overall Survival
6. Neurocognitive effects
7. QOL outcomes

**5.2 Sample size**

Dose escalation on this study will be using EWOC design. There will be 3 patients per dose escalation and enrollment will be done sequentially. A **fixed sample size of 24 will be used.**

If a patient is not able to complete follow up to the toxicity assessment point of 4 months due to a toxicity judged not to be at least possibly related to therapy, then that patient will be replaced at the same dose level by the next patient enrolled into that cohort.

**5.3 Statistical Analysis**

5.3.1 Primary Analysis: The rate of toxicities at 4 months will be calculated with 95% confidence interval (CI).

5.3.2 Secondary Analysis:

5.3.2.1 The median time to local/distant brain progression will be calculated by Kaplan-Meier method with 95% CI. For a given time point, say 4 month, the rate of local/distant progression will be calculated with 95%CI.

5.3.2.2 The median of OS time with 95% CI will be calculated by Kaplan-Meier method.

5.3.2.3 Neurocognitive effect and QOL outcomes will be regressed over time using GEE model. The population change over time (slope) will be estimated with 95%CI.

5.3.3 Patient Stratification: All enrolled patients will proceed through dose escalation as a single cohort, however patients will be analyzed as separate strata, should enrollment allow it, based on the following criteria.

5.3.3.1 Intact brain metastasis versus resection cavity.

5.3.3.2 No previous cranial irradiation versus previous WBRT or other cranial irradiation.

## 6.0 ADVERSE EVENT REPORTING

6.1 Adverse Events (AEs) is defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). These events will be

recorded for each patient at the specified assessment time points and are subject to review by the investigators and data safety monitoring committee (DSMC).

6.2 Serious Adverse Events (SAEs)

Any adverse event that results with any of the following outcomes:

- Death;
- A life-threatening experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect; or
- Other medically important events.

6.3 All adverse events will be reported to the PI and co-investigators.

6.4 Any SAE will be reported to the DSMC in a scheduled summary of toxicities and SAEs at 4 months after completed enrollment of the ongoing dose level/before dose escalation.

6.5 Any death thought to be at least possibly related to treatment will halt the study and will be reported to the DSMC within 24 hours of the investigators knowledge of the event.

6.6 The study may also be halted should the PI feel for any reason there is undo risk to patients with continued dose escalation.

## 7.0 DATA SAFETY MONITORING PLAN

### 7.1 Data Safety Monitoring Committee (DSMC)

The Winship Cancer Institute Phase I trial unit data safety monitoring committee will monitor this trial. As per WCI policy, the DSMC monitors all investigator initiated studies and cooperative group studies at Winship. Each qualifying study is reviewed at least once a year. Two of the first 5 patients enrolled to investigator-initiated studies and 10% of total accrual is reviewed. Once a chart is monitored, the PI and the study coordinator are presented with the findings. They have a 2 week period to respond to the findings. A summary report is submitted to the DSMC for committee review. Any serious unanticipated problem is reported to the IRB with due notice to the PI.

Included in the DSMC review:

- Regulatory documents
- Patient eligibility
- Informed consent process
- Accuracy and timeliness of data
- Verification of source documents
- Toxicity assessment process

### 7.2 Scheduled Monitoring

7.2.1 The study PI and co-investigators will meet every month to review enrollment, patient treatments, toxicities and attribution (originally graded by treatment physician), outcomes and categorization of any failures.

7.2.3 Radiation therapy quality assurance

Radiation specifics including simulation, treatment delivery and dose prescription specifications will be approved by treating physician. All treatment plans are routinely reviewed the week of treatment initiation by board certified radiation oncologists from the Emory Department of Radiation Oncology who are not co-investigators on the study. Any protocol violations will be reported to the PI and co-investigators.

7.2.4 Every 4 months from the date of first enrollment and/or prior to each dose escalation, a summary of all toxicities ≥ 3 and their graded attributions will be submitted to the DSMC.

## 8.0 REFERENCES


1. American Cancer Society (2008) Cancer facts and figures 2008. http://www.cancer.org/docroot/stt/content/stt_1x_cancer_facts_and_figures_2008.asp
2. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998 Nov 4;280(17):1485-9.
3. Linskey ME et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guidline. J neurooncol. 2010. 96:45-68.
4. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ Jr. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004 May 22;363(9422):1665-72.
5. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys. 1999 Sep 1;45(2):427-34.
6. Garell PC, Hitchon PW, Wen BC, Mellenberg DE, Torner J. Stereotactic radiosurgery versus microsurgical resection for the initial treatment of metastatic cancer to the brain. J Radiosurg. 1999. 2(1):1-5
7. O'Neill BP, Iturria NJ, Link MJ, Pollock BE, Ballman KV, O'Fallon JR. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastasis. Int J Radiat Oncol Biol Phys. 2003. 55(5):1169-1176
8. Schöggl A, Kitz K, Reddy M, Wolfsberger S, Schneider B, Dieckmann K, Ungersböck K. Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. Acta Neurochir (Wien). 2000;142(6):621-6.
9. Chang EL, Wefel JS, hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyes CA. (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole brain radiation: a randomized control trial.
10. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery

alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006 Jun 7;295(21):2483-91.
11. Li B, Yu J, Suntharalingam M, Kennedy AS, Amin PP, Chen Z, Yin R, Guo S, Han T, Wang Y, Yu N, Song G, Wang L. Comparison of three treatment options for single brain metastasis from lung cancer. Int J Cancer. 2000 Feb 20;90(1):37-45.
12. Rades D, Pluemer A, Veninga T, Hanssens P, Dunst J, Schild SE. Whole-brain radiotherapy versus stereotactic radiosurgery for patients in recursive partitioning analysis classes 1 and 2 with 1 to 3 brain metastases. Cancer. 2007 Nov 15;110(10):2285-92.
13. Rwigema, JM., Wegner, RE, Mintz, AH., Stereotactic Radiosurgery to the Resection Cavity of Brain Metastasis: A Retrospective Analysis of Literature Review. *Stereotact Funct Neurosurg.* 2011; 89:329-337.
14. Barnett GH, Linskey ME, Adler JR, Cozzens JW, Friedman WA, Heilbrun MP, Lunsford LD, Schulder M, Sloan AE; American Association of Neurological Surgeons; Congress of Neurolofical Surgeons Washington Committee Stereotactic Radiosurgery Task Force. Stereotactic radiosurgery--an organized neurosurgery-sanctioned definition. J Neurosurg. 2007 Jan;106(1):1-5.
15. American Society for Radiation Oncology Stereotactic Radiosurgery definition. In: ASTRO News. Int J Radiat Oncol Biol Phys. 2007. 67(4):1280.
16. Pater, L.E., McPherson C.M.,Guamaschelli, J., et al. Fractionated Stereotactic Radiosurgery for "High-Risk" Brain Metastases: Local Control and Risk of Necrosis. Congress of Neurological Surgeons Annual Meeting. 2010. [Poster Abstract]
17. Lederman G., Wronski M., Fine M. Fractionated Radiosurgery for Brain Metastases in 43 Patients with Breast Carcinoma. Breast cancer Res Treat. 2001. 65(2); 145-54.
18. Wang, CC., Floydm SR., Change, CH., et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an 800cGy x 3 daily fractions regimen. *J Neurooncol.* 2012. 106 (3): 601-10.
19. Eaton, BR., Gebhardt, B., Prabhu, S. Shu, HK., Curran W., Crocker, I. Hypofractionated Radiosurgery for Large Intact or Resected Brain Metastases. [ Abstract submitted to ASTRO 2012, Jan 5th 2012]
20. Dhabaan, A., Schreibmann, E., Siddiqi, A., et al. Six Degrees of Freedom (6 DOF) CBCT-Based Positioning for Intracranial Targets Treated with Frameless Stereotactic Radiosurgery (SRS). *Int J Radiat Oncol Biol Phys* 2010;78:S793-S794.

**APPENDIX B**

**CTCAE (Common Terminology Criteria for Adverse Events), version 4.03**
The exact full criteria for toxicity assessment can be obtained at the NCI CTEP website at the following link:
*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*

## APPENDIX C

**RECIST Guideline Version 1.1**
Eisenhauer, E.A., Therasse, P., Bogaerts, J., et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1). Europ J Cancer. 2009. 45; 228-247.
http://imaging.cancer.gov/clinicaltrials/imaging

## APPENDIX D

**RTOG RPA Classification System**

*RPA Class I* All of the following criteria:
KPS ≥ 70%
Age < 65 years
Absence of extracranial metastases
Controlled primary cancer

*RPA Class II* KPS ≥ 70% **and**
One or more of the following criteria:
Age > 65 years
Presence of extracranial metastases
Uncontrolled primary cancer

*RPA Class III* KPS < 70%

**KARNOFSKY PERFORMANCE SCALE**

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

**APPENDIX A – Patient Assessment Timeline**

| | Baseline | Weekly on RT | 1 month | 4 months | 7 months | 10 months | 13 months | 16 months | 19 months | 22 months | 25 months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H&P | X | | X | X | X | X | X | X | X | X | X |
| Toxicity Assessment | | X | X | X | X | X | X | X | X | X | X |
| MRI | X | | X | X | X | X | X | X | X | X | X |
| HVLT-R | X | | X | X | X | | X | | X | | X |
| MMSE | X | | X | X | X | | X | | X | | X |
| MOS | X | | X | X | X | | X | | X | | X |
| FACT-Br | X | | X | X | X | | X | | X | | X |
| Imaging Response Evaluation | | | X | X | X | X | X | X | X | X | X |

*Assessments may occur within a +/- 3 week window the specified time.

**APPENDIX E**

**Eligibility Checklist**

1. _____ Pathological proven diagnosis of solid tumor malignancy, not a radiosensitive or non-solid (eg. small cell lung carcinomas, germ cell tumors, leukemia, or lymphoma) or unknown tumor histology.
2. _____ Age ≥ 18.
3. _____ One brain metastasis or brain metastasis resection cavity with maximal diameter greater ≥ 3cm (or ≥ 14 cc.) and ≤ 6cm.
4. _____ RPA class I-II/ Karnofksy Performance Status ≥ 70% (See **Appendix D for definitions**)
5. _____ No Prior SRS to adjacent lesion such that planning target volume would have received more than 5 Gy
7. _____ No concurrent chemotherapy (no chemotherapy starting 14 days before start of radiation).
8. _____ No evidence of leptomeningeal disease by MRI and/or CSF cytology.
9. _____ Negative serum or urine pregnancy test within 4 weeks of enrollment
10. _____Less than or equal to 8 weeks between resection and enrollment
11. _____No metastases to brain stem, midbrain, pons, or medulla or within 5 mm of the optic apparatus *(optic nerves and chiasm)*.
12. _____Pateint is able to undergo MRI evaluation for treatment planning and follow-up