RAD 1705/UAB 1796: A Phase I Dose Escalation Trial of
Five Fraction Stereotactic Radiation Therapy for Brain Metastases

TABLE OF CONTENTS

APPENDICES

PRINCIPAL INVESTIGATOR:	**John Fiveash, MD**
CO-INVESTIGATORS:	**Samuel Marcrom, MD** **Andrew McDonald, MD** **Richard Popple, PhD** **James Markert, MD** **Barton Guthrie, MD** **Kristen Riley, MD** **Markus Bredel, MD, PhD** **Sharon Spencer, MD** **Christopher Willey, MD, PhD** **Drexell Hunter Boggs, MD** **Michael C. Dobelbower, MD, PhD**
Biostatistician:	**Sejong Bae, PhD**
Research Nurse Coordinator:	**Laronica Conway**
Data Coordinator:	**Laronica Conway**
Regulatory:	**Kristin Webb, CCRP** **Tiffany Williams**

Document History Table

	Version/Update Date
Amendment # 1	March 5, 2020
Activation	May 10, 2018
Original	January 4, 2018

Summary of Changes

Protocol Amendment #1

Protocol: RAD 1705/UAB 1796

Date: March 5, 2020

#	Section	Comments
1	Title Page	The current investigator list has been updated.
2	Title Page	The current regulatory staff has been updated.
3	Title Page	The UAB 1796 trial name has been added to the protocol title.
4	Footer	The protocol version and amendment number has been updated.
5	8.2	Table 8.1 updated to include 2 week post-treatment phone call.
6	11.5.1	Added paragraph highlighting the more conservative enrollment schema.

1.0 OBJECTIVES

1.1 **Primary**:

1.1.1 To determine the maximum tolerated dose of five fraction stereotactic radiotherapy for patients with either tumors 2.1-4.0 cm in diameter or 4.1-6.0 cm in diameter

1.2 Secondary:

1.2.1 To assess the acute toxicity of five fraction stereotactic radiotherapy for tumors 2.1-6.0 cm in diameter

1.2.2 To assess the late toxicity of five fraction stereotactic radiotherapy for tumors 2.1-6.0 cm in diameter

1.2.3 To determine the rate of local tumor control with five fraction stereotactic radiotherapy for tumors 2.1-6.0 cm in diameter

1.2.4 To obtain preliminary estimates of changes in QOL after five fraction stereotactic radiotherapy for tumors 2.1-6.0 cm in diameter (FACT-BR)

1.3 Exploratory:

1.3.1 To assess the feasibility of capturing patient reported outcomes (FACT-Br) electronically in the Radiation Oncology clinic

2.0 BACKGROUD AND RATIONALE

2.1 Brain Metastases Overview

Brain metastases are one of the most commonly encountered complications of cancer, and they represent the most common intracranial neoplasm in adults. Brain metastases are a well-established cause of morbidity and mortality, affecting approximately 20%-40% of patients with cancer.[1-3] Due to the significance of brain metastases, there has been a great deal of focus on the appropriate treatment for these lesions.

Treatment options for brain metastases are broadly divided into three categories of systemic therapy, surgical resection and radiation therapy. The selection of the appropriate management option involves a complex decision-making process that considers patient performance status, extent of intracranial and extracranial disease, degree of symptoms secondary to tumor mass effect, systemic therapy options, and

patient preferences. As treatment decisions are guided by several important nuances, additional prospective data is needed to better inform decision making.

2.2 Role of Radiation Therapy in Brain Metastases Treatment

The rationale for the management of brain metastases with radiation therapy is based on several factors regarding systemic therapy, surgery, and radiation. These include the presence of the blood-brain barrier that reduces the efficacy of many systemic therapies in the central nervous system and the invasiveness of surgical resection with a prohibitively high risk of permanent neurologic deficits associated with resections of tumors in certain locations. Additionally, radiation therapy is a relatively non-invasive treatment strategy that has the potential of targeting any location within the brain.

The use of whole brain radiation therapy (WBRT) to target brain metastases dates back to the mid-twentieth century.[4] In the 1970s, whole brain radiation to treat brain metastases was shown to improve survival compared to corticosteroids alone.[5] Several randomized trials have since evaluated the role of surgery, whole brain radiation, and stereotactic radiosurgery (SRS). WBRT alone renders a 6-12-month local tumor control rate of approximately 50%-70%, and the addition of surgery or SRS improves local control rates to 80%-90%. Although WBRT decreases the rate of distant brain failures, the addition of WBRT to either surgery or SRS has not been shown to improve survival.[6-9] Furthermore, WBRT has the potential to negatively impact cognitive function; therefore, appropriately selected patients may be treated with focal therapy while omitting WBRT.[10]

2.3 Increasing Role of Stereotactic Radiosurgery (SRS)

The management of patients with brain metastases is currently evolving. Focal techniques are gaining favor as the initial radiotherapy treatment for patients with an increased number of brain metastases, and whole brain radiotherapy (WBRT) is commonly being deferred citing toxicity concerns and lack of proven survival advantage.[9-11]

Studies that have compared SRS and WBRT have discovered that SRS alone offers a relatively high rate of local tumor control.[9,12] WBRT has the benefit of decreasing distant brain failure, but the feasibility of salvage SRS after an initial course of radiosurgery has been demonstrated.[12,13] Additionally, WBRT does not offer a survival advantage over SRS alone, and WBRT is more likely to induce cognitive decline in treated patients.[10,11]

Despite the advantages of treating patients with limited brain metastases with SRS, there are many patients that are likely best served with an alternative treatment strategy. In fact, increasing tumor size is associated with an increased risk of CNS toxicity with the use of single-fraction radiosurgery.[13] The desire to utilize an

alternative focal therapy that is both safe and effective has created interest in fractionated stereotactic radiation therapy (FSRT).

2.4 Rationale for Fractionated Stereotactic Radiation Therapy (FSRT)

As focal radiation techniques are utilized more frequently in the treatment of brain metastases, there is increasing need to accurately define the appropriate patient and tumor characteristics for focal therapy. Unfortunately, not all patients are good candidates for single fraction stereotactic radiosurgery (SRS) since large tumors and those in unfavorable locations have been associated with unacceptable rates of treatment-related toxicity. Given the limitations of WBRT, extending the paradigm of focal therapy to those patients who are not candidates for SRS represents an important clinical challenge.

A longstanding principle of radiation biology is that fractionating a course of radiotherapy may reduce normal tissue effects while maintaining tumor control. The use of multiple smaller fractions of radiation instead of a single large dose of radiation to minimize normal tissue toxicity is supported by both preclinical and clinical literature.[14] Fractionated stereotactic radiotherapy (FSRT) combines the steep dose gradients and small treatment margins of SRS with the radiobiologic advantages of fractionation.

Radiation dose schedules that utilize more radiation than 2 Gy per fraction are termed hypofractionated dose schedules. At dosages as high as those typically administered for FSRT, even slight increases in dose per fraction can have a significant impact on overall cell kill and calculated biological effective dose (BED). The BED is useful for isoeffective dose calculations as it is a measure of true biological dose experienced by a respective tissue. It is important to understand that normal tissues and tumor are impacted differently by a set dosing schedule. This is represented by the alpha/beta ratio (α/β). Alpha represents the component of cell death that occurs via non-repairable radiation damage, and beta represents the component of cell death occurring via potentially repairable damage. A low α/β tissue, as is found in normal tissues, experiences a high degree of cell death from potentially repairable damage; therefore, fractionating a course of radiation will have a greater relative effect on low α/β tissues than on high α/β tissues, such as tumor cells. This phenomenon explains the therapeutic advantage of utilizing multiple radiation fractions. This is illustrated in Figure 2.1.[15]

A commonly utilized technique for comparing various radiation fractionation schemes relies on calculation of the equivalent dose in 2 Gy per fraction (EQD2). Calculating an EQD2 allows comparison of a wide range of prescription doses to their equivalent total dose if 2 Gy fractions were used instead of the altered fractionation scheme. Standard

conventional fractionation uses 2 Gy per fraction; therefore, this is used as the reference standard when comparing various regimens.

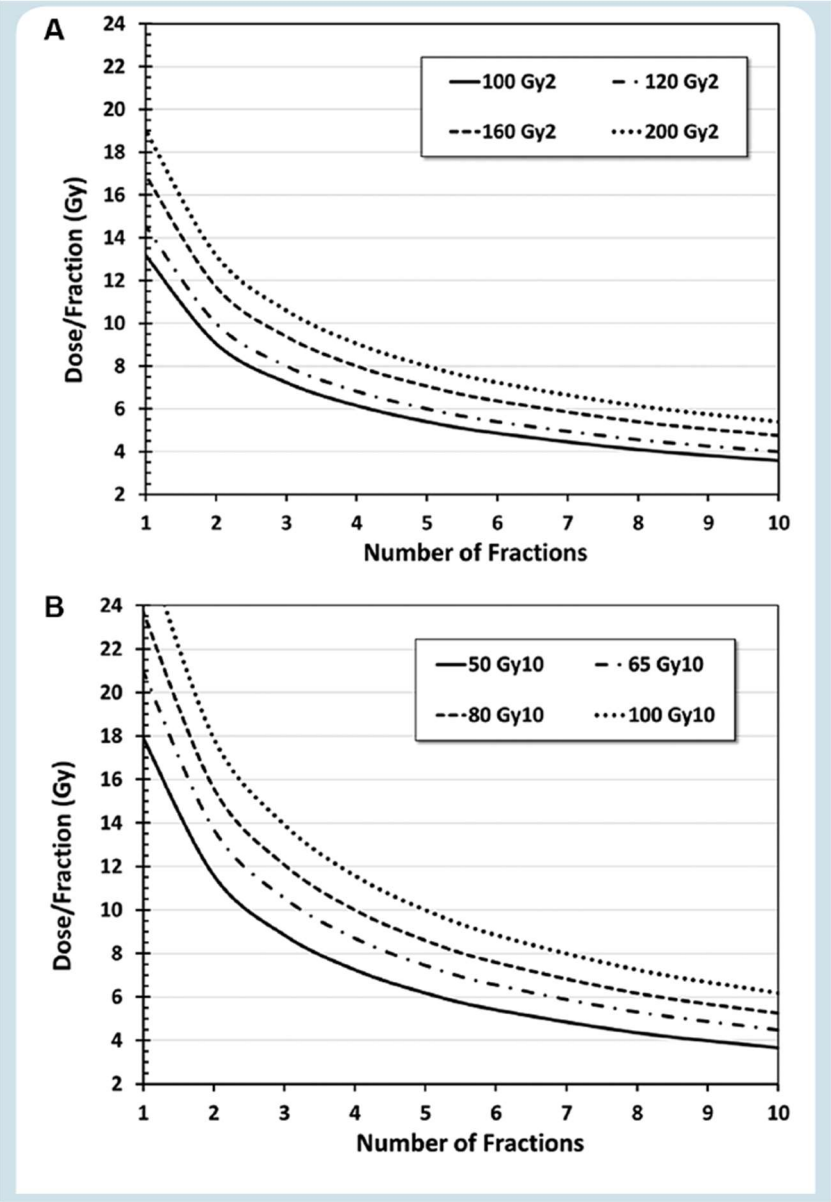


Figure 2.1 BED isoeffect plots for dose/fraction and number of fractions administered for (A) α/β = 2 Gy and (B) α/β = 10 Gy calculated using the linear-quadratic model.

The BED equation is displayed below:

$$\mathrm{BED} = \mathrm{D}\cdot\left(1+\frac{\mathrm{d}}{\alpha/\beta}\right)$$

Where BED = biologically effective dose, D = total dose, d = dose per fraction, and α/β = the dose at which cell killing by non-repairable damage is equal to that of repairable damage.

2.5 FSRT dose schedules are feasible

Several authors have reported on the feasibility of FSRT for brain metastases, and it appears to be both safe and effective. Previously reported 12-month local control estimates of FSRT have ranged from 52%-95%.[16-22] Furthermore, FSRT appears to have a favorable toxicity profile when compared to SRS for treatment among patients with similar tumor characteristics. A summary of previously published reports on FSRT is displayed below in Table 2.1.

Table 2.1 Summary of dose prescriptions, tumor size, and toxicity in prior FSRT studies

First Author	Sample Size	Tumor Size (cm)	FSRT Schedule	Presciption Point	Toxicity
Rejakesari	60 patients 70 lesions	Median diameter: 1.7 (0.4-6.4)	5 Gy x 5 fxns	90-95% IDL	Symptomatic RN = 4.3% (n=3) Seizures = 3% (n=2)
Minniti	135 patients 171 lesions	Not reported	9 Gy x 3 fxns (56%) 12 Gy x 3 fxns (44%)	80-90% IDL	Gr ≥3 toxicity = 4% (n=5)
Feuvert	12 patients 12 lesions	Median diameter: 4.4 (3.2-5.95)	7.7 Gy x 3 fxns	70% IDL	Gr 2 toxicity = 25% (n=3) No grade ≥3 toxicity
Aoyoma	87 patients 140 lesions	Not reported	8.75 Gy x 4 fxns	80-90% IDL	Gr ≥3 toxicity = 4.6% (n=4)
Kim	40 patients 49 lesions	Not reported	6 Gy x 6 fxns	91% IDL	Gr 1 = 5% (n=2) No Gr ≥2 toxicity
Aoki	44 patients 65 lesions	Not reported	18-30 Gy in 3-5 fxns	90% IDL	Gr 1 = 2% (n=1) No Gr ≥2 toxicity
Kwon	27 patients 52 lesions	Median diameter: 1.6 (0.17-3.12)	20-36 Gy in 4-6 fxns	85% IDL	Gr ≥3 toxicity = 3.7% (n=1)
Narayana	20 patients 20 lesions	Not reported	6 Gy x 5 fxns	100% IDL	Irreversible Gr ≥3 toxicity = 15% (n=3)
Saitoh	49 patients 78 lesions	Median diameter: 1.2 (0.4-3.8)	39-42 Gy in 3 fxns	90% IDL	Gr ≥3 toxicity = 12% (n=6)
Fokas	107 patients	Not reported	5 Gy x 7 fxns (50%) 4 Gy x 10 fxns (50%)	Not reported	Gr ≥3 toxicity = 3% (n=3)

2.5.1 **UAB Experience with FSRT**

The University of Alabama at Birmingham Department of Radiation Oncology began utilizing FSRT for the management of brain metastases in 2008. Since that time, the number of patients receiving this treatment as well as treating physician comfort with FSRT has steadily increased. We retrospectively evaluated our experience and identified 72 patients with 182 brain metastases that were treated with definitive FSRT. The Kaplan-Meier estimate of overall 12-month local control was 86%; however, local tumor control in larger tumors was significantly lower than smaller tumors. The 12-month local control estimate of tumors <2 cm in diameter was 100% compared to 74% for the tumors ≥2 cm in diameter. A dose response was observed with greater 12-month local tumor control observed in patients receiving 30 Gy in 5 fractions as compared to 25 Gy in 5 fractions (91% vs. 75%) ($p<0.001$). Serious toxicity occurred in only 4 patients (6%) in which subsequent surgical resection was required; however, we observed that increasing tumor diameter was associated with increased toxicity risk {HR 2.45 (1.04-5.742) ($p=0.04$)}.[23]

This experience highlights the problem that clinicians face. Overall, the rate of local tumor control as well as the toxicity profile of FSRT is quite favorable. However, increasing tumor diameter results in lower tumor control and higher toxicity rates. Additionally, dose escalation appears to improve local tumor control, but it could also lead to an increase in toxicity. The purpose of this study is meant to identify the appropriate radiation prescription to balance tumor control with adverse events.

2.6 **Rationale for Radiation Dose Escalation**

Multiple reports suggest that local tumor control with single-fraction SRS improves in a dose dependent fashion.[24,25] Among studies looking at FSRT there has been a suggestion of improved tumor control with dose escalation, particularly in tumors receiving an EQD2 >35 Gy (alpha/beta = 10) or BED12 >40 Gy (linear quadratic cubic model).[25-27] Furthermore, a recent review of available FSRT literature found a dose dependent local tumor control associated with increasing BED.[28] Unfortunately, none of these dose studies were prospective and did not systematically evaluate the relationship between prescription dose and tumor volume in determining the risk of toxicity.

2.7 Rationale for Dose Selection in Current Trial

As previously discussed, there are reports of improved tumor control with dose escalation. Additionally, multiple authors have found that increasing tumor size is associated with decreased local tumor control.[24,29] Furthermore, increasing tumor size is also associated with increased risk of CNS toxicity.[13] As tumor size increases, identifying the balance between dose escalation to improve tumor control and avoiding excessive risk of CNS toxicity remains an important clinical challenge.

Small tumors (i.e. ≤ 2 cm in diameter) appear to have excellent tumor control with SRS along with minimal CNS toxicity from the treatment. As per RTOG 9005, tumors 2.1-4 cm in diameter were 7.3-16 times more likely than tumors ≤ 2 cm in diameter to experience CNS toxicity from SRS.[13] The elevated toxicity risk in tumors > 2 cm in diameter has created interest in the utilization of FSRT in this patient population. The proposed dosing schedule (Table 2.2) stratifies patients by tumor size (2.1-4 cm vs. 4.1-6cm) to account for the increased risk of CNS toxicity in the larger tumor group.

As demonstrated in Table 2.1, institutions have utilized a variety of dosages, ranging from 5 Gy x 5 fractions to 14 Gy x 3 fractions in their retrospective studies with excellent safety. Also, the previously mentioned review article included patients treated with BEDs ranging from 29-100. The authors of this review found that at BEDs of 40, 50, and 60, the 1-year local tumor control was 73%, 78%, and 84% respectively.[28] The proposed doses fall well within the range of that previously reported. In this trial, we expect that larger diameter tumors will have a lower maximum tolerated dose (MTD); therefore, we are starting at a lower dose level in larger tumors. Table 2.3 displays the BED and equivalent 2 Gy per fraction dose schedules proposed in this study.

Table 2.2 Dose Escalation Schedule

Dose Level	2.1-4.0 cm diameter	4.1-6.0 cm diameter
1	7 Gy	6 Gy
2	8 Gy	7 Gy
3	9 Gy	8 Gy

Table 2.3 BED and EQD2 of FSRT Dose Schedules

FSRT Dose Schedule	Biologically Effective Dose (BED)	2 Gy per fraction dose equivalent (EQD2)
6 Gy x 5 fractions	48.0 Gy	40.0 Gy
7 Gy x 5 fractions	59.5 Gy	49.6 Gy
8 Gy x 5 fractions	72.0 Gy	60.0 Gy
9 Gy x 5 fractions	85.5 Gy	71.3 Gy

2.8 **Rationale for Inclusion of Patients with More Than One Tumor**

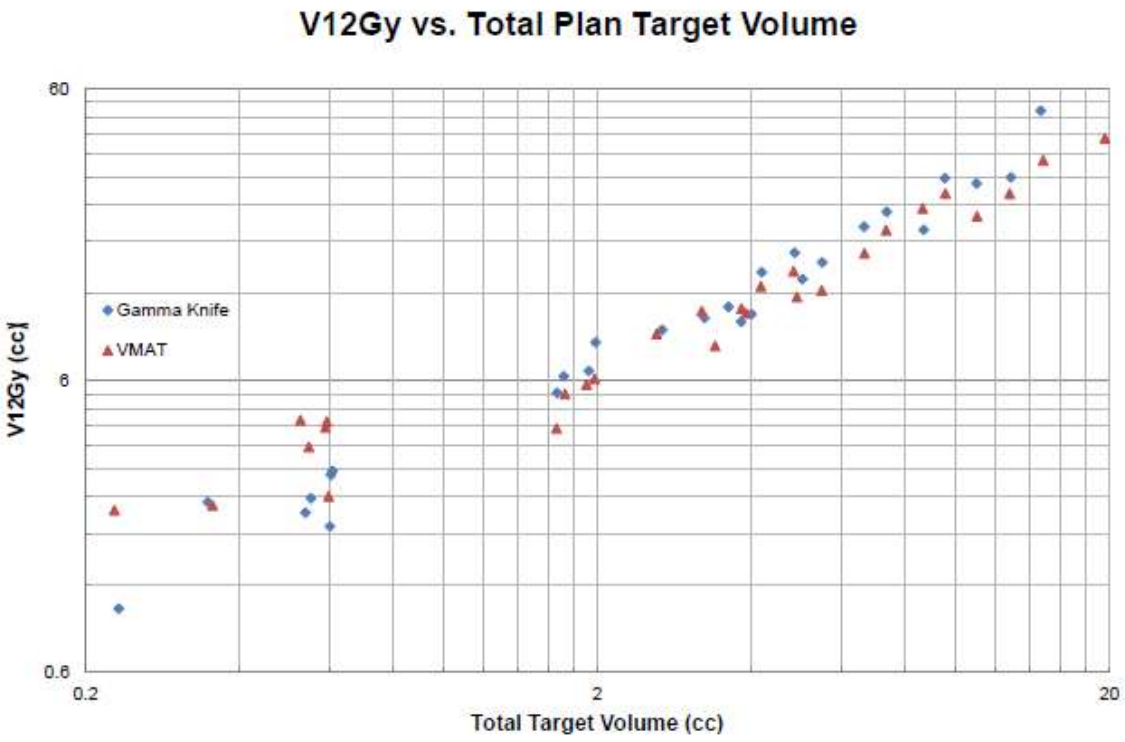
In this trial, dose escalation will only occur to the single largest tumor with other tumors receiving a standard of care dose of five fraction radiosurgery. The possibility exists that more than one tumor could be large and therefore patients with more than one tumor over 3 cm in diameter are excluded. Otherwise, up to 10 tumors total could be treated.

Although tumor volume is a well-recognized risk factor for radiosurgery toxicity, tumor number by itself is not. In a retrospective study of over 1800 patients with multiple tumors undergoing single fraction radiosurgery, the treatment of 2-9 tumors vs 10 or more tumors did not predict radiosurgery toxicity.[30] In the largest prospective trial of radiosurgery ever performed, Yamamoto et al treated 1194 brain metastases patients with radiosurgery alone for up to ten tumors. The number of tumors was not predictive of toxicity.[31]

For patients treated with single fraction radiosurgery to a single target, the total volume of brain receiving 12Gy (V12) is an established factor predictive of radiation toxicity. In an effort to understand predictors of the 12Gy volume treated with either Gamma Knife radiosurgery or single isocenter volumetric modulated arc therapy (VMAT) radiosurgery, investigators at UAB performed a regression analysis of patients treated with multiple metastases. V12 was independent of the number of tumors and is a simple function of tumor volume. This relationship is demonstrated in Figure 2.2.[32] Others have reported large volume computer simulations of radiosurgery for 1-25 tumors of varying tumor volume and can predict V12 as a linear function of tumor volume independent of tumor number.[33]

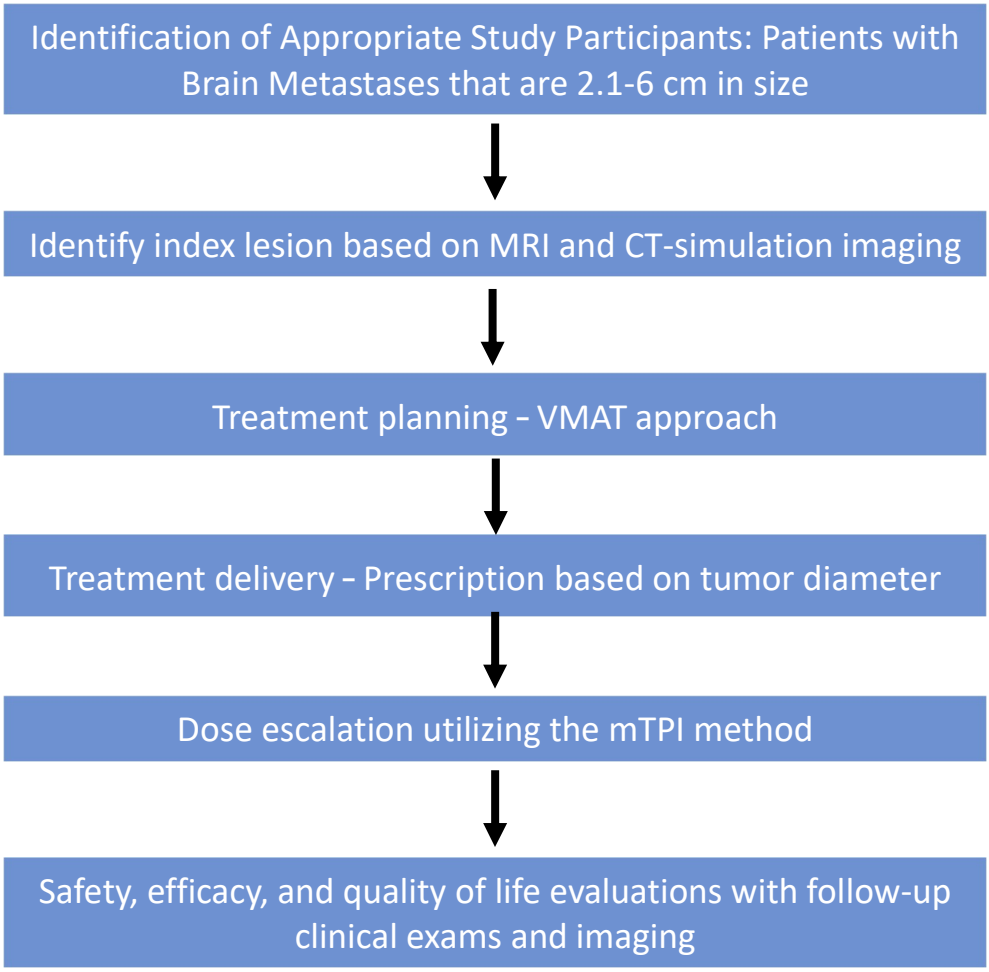
In the retrospective UAB experience of FSRT, increasing tumor diameter, evaluated as a continuous variable, was significantly associated with increased risk of CNS toxicity {HR 2.45 (1.04-5.742) (p=0.04)}. Additionally, 3 out of the 4 (75%) grade ≥3 grade 3 CNS toxicities occurred in patients with tumor diameter ≥3 cm.[23] By limiting the inclusion criteria to not having a second tumor over 3 cm, we will ensure that the main risk of toxicity to the patient is the index lesion undergoing dose escalation.

Figure 2.2 The Volume of Brain Receiving 12 Gy is Directly Related to Tumor Volume



Data from: Thomas, E., et al. "Comparison of Plan Quality and Delivery Time between Volumetric Arc Therapy (RapidArc) and Gamma Knife Radiosurgery for Multiple Cranial Metastases." *Neurosurgery* (2014).

3.0 SCHEMA



3.1 Patients will be enrolled if they have a pathologic diagnosis of cancer along with imaging consistent with one or more brain metastases. All patients must meet all enrollment criteria.

3.2 Only 1 target per patient, termed the index lesion, will be enrolled and receive the investigational dose prescription. The enrolled index lesion will be the largest brain metastasis by definition. Any additional treated non-index lesion will receive a standard of care dose prescription that has previously been demonstrated to be safe.

3.2.1 Therefore, each enrolled patient will be included in either the cohort of patients with an index lesion measuring 2.1-4 cm in maximum diameter or the cohort of patients with an index lesion measuring 4.1-6 cm in maximum diameter. An individual patient can only be included in 1 of the 2 cohorts as

determined by the index lesion diameter. The index lesion maximum diameter will determine the cohort and subsequent dose escalation schedule.

3.3 Enrolled patients will undergo appropriate MRI brain imaging that will be fused with the treatment planning CT-simulation scan for target identification.

3.4 Utilizing available clinical data (pathology, physical exam, MRI, and CT-simulation) physicians, medical dosimetrists, and physicists will create and approve a treatment plan if all dosimetric and quality assurance requirements are met.

3.5 FSRT will be delivered over 5-14 calendar days. The exact treatment schedule will be at the discretion of the treating physician.

3.6 Following completion of treatment, patients will be evaluated with clinical exams, imaging, and quality of life questionnaires at regular intervals.

4.0 PATIENT SELECTION CRITERIA

4.1 **Inclusion Criteria**

4.1.1 All patients must have histologically confirmed malignancy.

4.1.2 All patients must have imaging suggestive of one or more brain metastases.

4.1.3 Karnofsky performance status (KPS) ≥ 60

4.1.4 Age > 18 years

4.1.5 Patients must provide written informed consent to participate in the study.

4.1.6 Patients must have less than or equal to 10 brain metastases as identified on brain MRI.

4.2 **Exclusion Criteria**

4.2.1 History of surgical resection to the tumor of interest

4.2.2 History of radiation to the tumor of interest

4.2.3 History of previous whole brain irradiation

4.2.4 Receipt of systemic therapy within one week of planned radiation treatment except for hormonal agents

4.2.5 Patient is unable to have MRI or MRI contrast

4.2.6 Inability to meet the appropriate normal tissue dose constraints secondary to tumor location should result in exclusion of the patient / tumor

4.2.7 Patients with a non-index tumor (second tumor) greater than 3 cm in diameter will be excluded

4.2.8 Patient is currently pregnant

4.2.9 Patients with histologies that are considered exquisitely radiosensitive, including germ cell tumors, small cell carcinoma, and lymphomas

5.0 DRUG INFORMATION

5.1 No experimental medications are utilized in this study.

5.2 Oral or intravenous corticosteroids are considered standard of care and will be utilized at the discretion of the treating physician.

6.0 TREATMENT PLAN

6.1 **Treatment planning CT-simulation and contour/volume delineation**

6.1.1 Patients will undergo a pre-treatment CT-simulation scan in the supine position. The CT scan will be obtained with thin slices (1 mm) to improve target delineation. Intravenous contrast will be administered at the time of CT-simulation. A personalized thermoplastic facemask will be utilized for immobilization.

6.1.2 CT-simulation images will be electronically fused with MRI images within the treatment planning software. The fused images will be used for contours and treatment planning.

6.1.2.1 The treating physician will define the gross target volume (GTV) and adjacent organs at risk.

6.1.2.2 The GTV is defined as the enhancing tumor on post-contrast imaging as well as any additional component as determined by the treating physician.

6.1.2.3 Adjacent organs at risk to be contoured include the brain, brainstem, spinal cord, optic nerves, optic chiasm, cochlea and eyes.

6.2 FSRT Dose Specifications

6.2.1 The radiation prescription dose is normalized to cover 99-100% of the index target volume. If a patient has more than one tumor being treated, the largest tumor is considered the index lesion. Smaller tumors will receive a previously demonstrated safe dose prescription.

6.3 Critical Structures

6.3.1 All radiation plans will follow the standard of care normal tissue constraints as outlined by the UAB Department of Radiation Oncology treatment planning guidelines. The following table lists the 5 fraction constraints:

Table 6.1 Normal tissue constraints for CNS structures

Central Nervous System Constraints (5 Fraction Treatment)		
Organ	Constraint (Max Dose)	Priority
Brain-GTV	30 Gy	II
Brainstem	31 Gy, V26 Gy < 1 cc	I
Optic Nerve / Chiasm	25 Gy, V20 Gy < 0.2 cc	I
Cochlea	27.5 Gy	II
Lens	7 Gy	II
Retina	15 Gy	II
Spinal Cord	30 Gy, V22.5 < 0.25 cc	I

I = Do not violate. Achieving constraint is more important than target coverage.
II = Planning goal, but less important than target coverage.

6.4 Treatment plan physics quality assurance

6.4.1 All treatment plan dose distributions will be verified by UAB staff physicists and must meet the standard of care quality assurance procedures set forth by the Department of Radiation Oncology prior to radiation treatment administration.

6.4.2 Dose will be validated by either an ion chamber/film combination in a solid water phantom or a dose calibrated diode array. In either case, the phantom will be irradiated with the same plan as the patient including all couch angles and beam projections. A dose plane will be calculated and exported from the

treatment planning system and will be compared with the measured dose plane from the one of the above techniques.

6.5 Technical Factors

6.5.1 All treatment plans will be devised utilizing intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT).

6.5.2 Treatments will be delivered on an appropriately selected linear accelerator, equipped with image guided radiation therapy (IGRT) capability and a six degree of freedom couch.

6.6 Treatment Delivery

6.6.1 Image-guidance with kilovoltage orthogonal x-rays and cone-beam CT scans are to be utilized immediately prior to administration of each radiation fraction. At the treating physician's discretion, Optical Surface Monitoring System (OSMS) may be utilized during treatment to monitor intra-fraction motion. A physician is to approve appropriate patient positioning based upon set-up imaging for each radiotherapy fraction.

6.7 Treatment Delivery Schedule

6.7.1 Radiation treatments will be delivered in accordance with the standard radiation oncology clinic procedures. Treatment must be completed within the time frame of 5 to 14 calendar days, in which the first day of treatment will be considered day 1. The exact treatment schedule is left to the discretion of the treating physician.

6.7 Treatment Dose Schedule

Dose Level	2.1-4.0 cm diameter	4.1-6.0 cm diameter
1	7 Gy	6 Gy
2	8 Gy	7 Gy
3	9 Gy	8 Gy

7.0 THERAPY MODIFICATIONS

7.1 Dose Modifications

All prescription doses are determined in accordance with the previously described dosing schema. The index lesion will receive the current investigational dose, and all

other treated tumors will receive a previously demonstrated safe, standard of care dose prescription. No dose modifications are to be made outside of the selected dose prescriptions utilized in the study.

7.2 **Concomitant Medication**

7.2.1 All medications administered since protocol enrollment will be recorded in the medical record

7.2.2 No cytotoxic chemotherapies are to be administered during the administration of FSRT

7.2.3 Administration of pre-treatment or post-treatment corticosteroids (for example, dexamethasone 4-10 mg within 1 hour of radiation) is at the discretion of the treating physician.

7.3 **Adverse Events (AE's) and Serious Adverse Events (SAE's)**

7.3.1 Definition of Adverse Event (AE): Any untoward medical occurrence, which does not necessarily have a causal relationship with the study treatment. This includes any physical or clinical change experienced by the subject, whether or not considered related to the study treatment. An AE can therefore be any unfavorable or unintended sign, symptom, or disease temporally associated with the study treatment. Progression of the patient's cancer, including intracranial progression, is not considered to be an AE. AE's will be recorded in the medical record.

7.3.2 Definition of Serious Adverse Event (SAE): Any event occurring during the study evaluation period that results in any of the following outcomes:

- Death attributed to treatment
- Inpatient hospitalization
- Any irreversible grade ≥ 3 CNS toxicity per the Common Terminology Criteria for Adverse Events (CTCAE) CNS toxicity criteria

All SAE's must be recorded in the medical record. The onset and end dates, severity, duration, effect on study administration (discontinuation/cancellation, for example), relationship to study treatment, and administration of any drugs or therapies to treat the SAE's will be recorded in the medical record.

7.4 Guidelines for adverse event recording

7.4.1 The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) will be used for grading adverse events.

7.4.2 The investigator must assess the relationship of any AE or SAE to the use of the study treatment using the following guidelines outlined in the table below:

Table 7.1 Attribution of Adverse Events

Code	Descriptor	Definition
5	Definite	The adverse event is clearly related to the investigational treatment
4	Probable	The adverse event is likely related to the investigational treatment
3	Possible	The adverse event may be related to the investigational treatment
2	Unlikely	The adverse event is doubtfully related to the investigational treatment
1	Unrelated	The adverse event is clearly not related to the investigational treatment

7.5 Monitoring of adverse events

Subjects having AE's or SAE's will be monitored with relevant clinical assessments and laboratory tests as determined by the subject's treating physician. All adverse events must be followed to satisfactory resolution or stabilization of the event(s). Any actions taken and follow-up results must be recorded in the subject's medical record. For all AE's or SAE's which require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically indicated, until final resolution or stabilization of the event(s).

7.6 Adverse event reporting

7.6.1 Notification of all SAE's must be reported to the Principal Investigator or his designee. A written report should be submitted to the appropriate Institutional Review Board (IRB) and UAB Clinical Trials Monitoring Committee per institutional policy.

7.6.2 Adverse events will be reported to the Clinical Trials Monitoring Committee.

7.7 **Data and safety monitoring plan**

7.7.1 This protocol will follow the UAB Data and Safety Monitoring Plan maintained by the UAB Comprehensive Cancer Center.

7.7.2 Serious adverse events will be reviewed in the UAB radiation oncology treatment planning or new patient conference, and the SAE's will also be reviewed by the Department of Radiation Oncology Quality Assurance committees.

7.8 **Early Termination**

Patients may be discontinued from the study prior to completion of study requirements for any of the following reasons:

7.8.1 The patient has a clinically significant adverse event as determined by the principal investigator.

7.8.2 The patient requests to be withdrawn from the study.

7.8.3 The patient fails to comply with the requirement for study evaluation/visits.

7.8.4 Other conditions for which, in the investigator's opinion, it is in the patient's best interest to be withdrawn from the study.

7.8.5 The patient did not meet eligibility requirements.

8.0 STUDY PARAMETERS

8.1 For the purposes of this study, acute toxicity will be defined as event(s) that occur within 90 days of the completion of radiotherapy. Acute toxicity will be determined by both intra-treatment examinations and by scheduled follow-up evaluations after the treatment has completed. Late toxicity will be defined as any toxicity occurring > 90 days after the completion of treatment.

8.2 Baseline evaluations of enrolled patients must occur within four weeks of study enrollment.

Table 8.1 Required study evaluations

	Baseline	2 wk. post-FSRT	1 month	3 months	6 months	12 months
History and physical exam	x		x	x	x	x
Toxicity / AE evaluation		X[1]	x	x	x	x
Performance status (KPS)	x		x	x	x	x
MRI brain (Local & CNS control per protocol/RANO-BM)	x		x	x	x	x
FACT-Br (QOL evaluation)	x		x	x	x	x
[1] A 2 week post-treatment phone call will be made to the patient to see how they are feeling and evaluate if the patient is experiencing any toxicities.						

9.0 EVALUATION CRITERIA

9.1 **Pretreatment evaluations (baseline) will include the following:**

- Complete medical history
- Physical examination including neurologic examination
- Vital Signs including weight
- Karnofsky performance status
- MRI of the brain
- Completion of FACT-Br questionnaire

To be eligible for enrollment, the patient must meet all inclusion criteria. Results of all baseline or screening evaluations, which assure that all inclusion and exclusion criteria have been addressed, must be reviewed by the investigator prior to enrollment of each patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule, required evaluations, and all regulatory requirements for informed consent. Written informed consent must be obtained from the patient prior to enrollment.

9.2 **Treatment delivery**

9.2.1 All treatment plan dose distributions will be verified by UAB staff physicists and must meet the quality assurance standards set forth by the Department of Radiation Oncology prior to patient FSRT administration. Pre-treatment tissue phantom quality assurance checks will be completed. The phantom will be irradiated with the same plan as the patient including all couch angles and beam projections.

Once plans have met physics quality assurance parameters, treatment delivery will commence. Clinical treatment delivery feasibility will be determined by the ability of the patient to be set up accurately with confirmation of appropriate geometry on kilovoltage orthogonal imaging and cone beam CT imaging. Treatment delivery will be considered feasible if each set of pre-treatment set up images is approved by the treating physician(s) prior to administration of radiotherapy.

9.3 **Treatment phase**

9.3.1 The patient will be evaluated at least once by the treating physician during the time that he or she is undergoing radiation treatment.

9.4 **Follow-up**

Enrolled patients will participate in a follow-up schedule as outlined in Table 8.1. Two weeks post- FSRT, the study coordinator will call the patient to assess how they are feeling and/or experiencing any toxicities. This will include a history and physical examination, performance status evaluation, MRI of the brain, and completion of the FACT-Br questionnaire at 1 month, 3 months, 6 months, and 12 months after completion of radiation treatment.

10.0 PATIENT REGISTRATION

10.1 Patients can be registered by contacting the study coordinator, Laronica Conway, at 205-975-2879.

11.0 STUDY ENDPOINTS

11.1 The primary endpoint of this study is to clinically assess early toxicity, specifically, to evaluate for the presence of a dose-limiting toxicity within 90 days of the initial treatment. We are interested in a risk of 20% or less.

11.1.1 The definition of a dose-limiting toxicity event will be the same as that used in RTOG 9005. It will be defined as an irreversible grade 3, any grade 4, or any grade 5 neurologic toxicity related to treatment that occurs within 90 days of the start of treatment. Since a patient may have more than one tumor treated the toxicity should be assigned to the tumor and not the patient if at all possible. Only 1 target per patient will receive the investigational dose prescription, and this target will be considered the index lesion. Any additional treated non-index lesion will receive a standard of care dose prescription that has previously been demonstrated to be safe.

11.2 **Secondary endpoints include toxicity and efficacy assessments.**

11.2.1 Determine the frequency and severity of acute neurologic toxicity.

11.2.2 Determine the frequency and severity of late neurologic toxicity.

11.2.3 Determine the rate of local tumor control with FSRT.

11.2.3.1 The index lesion's treatment response will be assessed according to the RANO-BM criteria where a 20% increase in maximal diameter from nadir represents local tumor progression.[34] Additionally, the presence of more than scant tumor cells present at the time of salvage surgery will be considered a local tumor failure. An apparent increase in tumor diameter that is observed and found to subsequently decrease in size upon further imaging will be considered an effect of therapy rather than a local failure.

11.2.4 Determine the extent of central nervous system disease control in accordance with the Response Assessment in Neuro-Oncology (RANO) criteria for brain metastases.[34]

11.2.5 Determine quality of life over time as assessed by the FACT-Br questionnaire.

11.3 **Exploratory endpoint**

11.3.1 The feasibility of capturing patient reported outcomes (FACT-Br) electronically in the Radiation Oncology clinic will be assessed. Feasibility will be defined as 75% or greater compliance with electronic completion of the questionnaire at the specified time points.

11.4 **Toxicity evaluation**

11.4.1 Acute and late toxicity will be graded per the CTCAE version 4.0.

11.4.2 Definition of acute toxicity: any possible, probable, or definite treatment-related AE or SAE occurring within 90 days of the completion of radiotherapy.

11.4.3 Definition of late toxicity: any possible, probable, or definite treatment-related AE or SAE occurring later than 90 days from the completion of radiotherapy.

11.5 **Dose Escalation and statistical considerations**

11.5.1 The modified toxicity probability interval (mTPI) method with adjustment based on observed dose limiting toxicity (DLT) rate will be employed in decision making concerning dose escalation within each cohort investigated.[35] The assumptions to be applied in establishing the mTPI methodology are:

- Each specific tumor size cohort exploration may include up to 30 patients for a total enrollment of up to 60 patients.
- The MTD is defined to have 0.20 probability of toxicity.
- The acceptable variance around the MTD is ± 0.05 (i.e., the region of the MTD is 15% to 25% incidence of dose limiting toxicity).

The dose assignment recommendations for cumulative number of patients are presented in Table 11.1. The size of each patient cohort during the dose escalation phase of the study will be at least 3 patients. Once the initial three evaluable patients have cleared the DLT evaluation period then an mTPI design will be used to determine whether to escalate or de-escalate the dose. Up to 10 evaluable patients may be enrolled at a specific dose prior to making a final dose escalation/de-escalation decision. If the DLT rate of the current dose does not exceed the maximum permitted toxicity rate as defined by the mTPI, then we will evaluate the next dose level. Patients not evaluable for assessment of DLT may be replaced. For any subsequent cohort of patients, the recommended dose assignment action will be based on the total number of patients with DLTs in the current and prior cohorts treated at the same dose level. For example, if a cohort of 3 patients are treated at dose level 1 for the first time and one of them experiences a DLT, then the recommended action for the next cohort of patients will be to stay at the current dose level (S); if this recommendation is accepted, then the selected dose level for the next cohort of patients will be 1; if a total of 6 additional patients are treated at dose level 1 and there are no more DLTs observed, then the cumulative number of patients treated at dose level 1 is 9, and the cumulative number of patients with DLTs at dose level 1 is 1 out of 9, thus the recommendation would be to escalate the dose for the subsequent cohort (E).

The dose escalation plan will allow enrollment of a three-patient cohort prior to the mTPI rule taking effect at the beginning of each dose level. Up to three patients can be enrolled at the beginning of each dose escalation level. Those three patients must be followed throughout the dose evaluation period (90 days). If one of those three patients develop a DLT, then cohorts of up to three additional patients may be treated at that dose level and be within the 90-day evaluation period at any given time. For example, if 1 out of the 3 patients develops a DLT, then patients 4-6 may then be enrolled. Patient 7

may be enrolled after patient 4 has been followed without toxicity for 90 days.

Dose-finding for a cohort may be stopped when one of the following criteria is met:

- The lowest dose level appears too toxic after at least 3 patients are dosed at that dose level.
- The maximum sample size in dose finding of 30 evaluable patients per cohort has been reached.
- A minimum of 10 evaluable patients have been treated at the estimated MTD.

Analysis will be descriptive and exploratory. Data will be summarized and listed by dose level. Toxicity, local tumor control local, central nervous system disease control in accordance with the Response Assessment in Neuro-Oncology (RANO) criteria for brain metastases, and QOL, will be presented in the form of patient data listings that include, but are not limited to, age, gender, dose, and tumor response at each visit. If the data permits, local tumor control rate, central nervous system disease control rate and corresponding exact confidence interval will be calculated. Additional exploratory data analysis will be performed as data permits.

Interim review of enrolled patients demonstrated that the first three patients were not evaluable at the timepoint for the primary endpoint due to systemic disease progression and/or other medical illnesses that were deemed to be unrelated to their radiation treatment. This was presented to the clinical trials monitoring committee, and it was decided that study continuation was appropriate; however, it was agreed upon that there should be enrollment of 6 patients at dose level 1 in the cohort of patients with tumors 2.1–4 cm in diameter prior to consideration of dose escalation in order to ensure safety. After this, dosing decisions will return to the originally proposed chart as displayed below.

Table 11.1 Dose Escalation rule of the modified toxicity probability interval method

Number of toxicities	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E
4		DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
6				DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S	S	S	S	S
7					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S
8						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S
9							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S
10								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
13											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
14												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
19																	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
20																		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
21																			DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
22																				DU	DU	DU	DU	DU	DU	DU	DU	DU
23																					DU	DU	DU	DU	DU	DU	DU	DU
24																						DU	DU	DU	DU	DU	DU	DU
25																							DU	DU	DU	DU	DU	DU
26																								DU	DU	DU	DU	DU
27																									DU	DU	DU	DU
28																										DU	DU	DU
29																											DU	DU
30																												DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 20%

11.5 **Toxicity rates**

11.6.1 The primary endpoint of the study is to assess the rate of dose limiting toxicity experienced within 90 days of the completion of treatment. The maximum tolerated dose is defined to have a dose limiting toxicity rate of 20% or less. This will be assessed according to the mTPI method as described above.

11.6 **Sample size**

11.6.1 The total number of subjects enrolled in the study may vary as the study may terminate if the DLT rate exceeds the maximum permitted toxicity rate per the mTPI. Each specific tumor size cohort exploration may include up to 30 patients for a total enrollment of up to 60 patients.

12.0 REFERENCES

1. Patchell RA. The management of brain metastases. Cancer Treat Rev. 2003;29(6):533-40.

2. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. Neurosurg Clin N Am. 2011;22(1):1-6, v.

3. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer. 2002;94(10):2698-705.

4. Chao JH, Phillips R, Nickson JJ. Roentgen-ray therapy of cerebral metastases. Cancer. 1954;7(4):682-9.

5. Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. Am J Roentgenol Radium Ther Nucl Med. 1971;111(2):334-6.

6. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322(8):494-500.

7. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280(17):1485-9.

8. Andrews DW, Scott CB, Sperduto PW, et al. 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;363(9422):1665-72.

9. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol. 2011;29(2):134-41.

10. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10(11):1037-44.

11. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA. 2016;316(4):401-9.

12. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2015;91(4):710-7.

13. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000;47(2):291-8.

14. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. Lippincott Williams & Wilkins; 2012.

15. Kirkpatrick JP, Soltys SG, Lo SS, Beal K, Shrieve DC, Brown PD. The radiosurgery fractionation quandary: single fraction or hypofractionation?. Neuro-oncology. 2017;19(suppl_2):ii38-ii49.

16. Rajakesari S, Arvold N, Jimenez R, et al. Local Control after Fractionated Stereotactic Radiation Therapy for Brain Metastases. Journal of Neuro-Oncology. 2014; 120(2): 339-346.

17. Fokas E, Henzel M, Surber G, Kleinert G, Hamm K, Engenhart-Cabillic R. Stereotactic Radiosurgery and Fractionated Stereotactic Radiotherapy: Comparison of Efficacy and Toxicity in 260 Patients with Brain Metastases. Journal of Neuro-Oncology. 2012; 109(1):91-98.

18. Matsuyama T, Kogo K, Oya N. Clinical Outcomes of Biological Effective Dose-Based Fractionated Stereotactic Radiation Therapy for Metastatic Brain Tumors From Non-Small Cell Lung Cancer. International Journal of Radiation Oncology, Biology, Physics. 2013; 85(4): 984-990.

19. Fahrig A, Ganslandt O, Lambrecht U, et al. Hypofractionated Stereotactic Radiotherapy for Brain Metastases. Strahlentherapie Und Onkologie. 2007; 183(11): 625-630.

20. Minniti G, Angelillo R, Scaringi C, et al. Fractionated Stereotactic Radiosurgery for Patients with Brain Metastases. Journal of Neuro-Oncology. 2014; 117(2): 295-301.

21. Märtens B, Janssen S, Werner M, et al. Hypofractionated Stereotactic Radiotherapy of Limited Brain Metastases: A Single-centre Individualized Treatment Approach. BMC Cancer. 2012; 12(1): 497-505.

22. Eaton B, Gebhardt B, Prabhu R, Shu H, Curran W, Crocker I. Hypofractionated Radiosurgery for Intact or Resected Brain Metastases: Defining the Optimal Dose and Fractionation. Radiation Oncology. 2013; 8(1): 135-141.

23. Marcrom SR, McDonald AM, Thompson JW, Popple RA, Riley KO, Markert JM, et al. Fractionated stereotactic radiation therapy for intact brain metastases. Advances in Radiation Oncology. In press, accepted July 2017. http://dx.doi.org/10.1016/j.adro.2017.07.006.

24. Vogelbaum MA, Angelov L, Lee SY, Li L, Barnett GH, Suh JH. Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin. J Neurosurg. 2006;104(6):907-12.

25. Wiggenraad R, Verbeek-de kanter A, Kal HB, Taphoorn M, Vissers T, Struikmans H. Dose-effect relation in stereotactic radiotherapy for brain metastases. A systematic review. Radiother Oncol. 2011;98(3):292-7.

26. Aoyama H, Shirato H, Onimaru R, et al. Hypofractionated stereotactic radiotherapy alone without whole-brain irradiation for patients with solitary and oligo brain metastasis using noninvasive fixation of the skull. Int J Radiat Oncol Biol Phys. 2003;56(3):793-800.

27. Märtens B, Janssen S, Werner M, et al. Hypofractionated stereotactic radiotherapy of limited brain metastases: a single-centre individualized treatment approach. BMC Cancer. 2012;12:497.

28. Baliga S, Garg MK, Fox J, et al. Fractionated stereotactic radiation therapy for brain metastases: a systematic review with tumour control probability modelling. Br J Radiol. 2017;90(1070):20160666.

29. De azevedo santos TR, Tundisi CF, Ramos H, et al. Local control after radiosurgery for brain metastases: predictive factors and implications for clinical decision. Radiat Oncol. 2015;10:63.

30. Yamamoto M, Kawabe T, Sato Y, et al. Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 versus 10 or more tumors. J Neurosurg. 2014;121 Suppl:16-25.

31. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014;15(4):387-95.

32. Thomas EM, Popple RA, Wu X, et al. Comparison of plan quality and delivery time between volumetric arc therapy (RapidArc) and Gamma Knife radiosurgery for multiple cranial metastases. Neurosurgery. 2014;75(4):409-17.

33. Hatiboglu MA, Akdur K. Evaluating Critical Brain Radiation Doses in the Treatment of Multiple Brain Lesions with Gamma Knife Radiosurgery. Stereotact Funct Neurosurg. 2017;95(4):268-278.

34. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16(6):e270-8.

35. Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol. 2013;31(14):1785-91.

APPENDICES

Appendix A: Karnofsky Performance Status (KPS)

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 signs 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; hospital admission is indicated although death is not imminent
20	Very sick; hospital admission necessary, active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Appendix B: Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM)

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion(s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

*Progression occurs when this criterion is met. †A new lesion is one that not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression. ‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

FACT-BR (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An 10	I get headaches	0	1	2	3	4