A PHASE I/II STUDY OF FRACTIONATED STEREOTACTIC RADIOSURGERY TO TREAT LARGE BRAIN METASTASES

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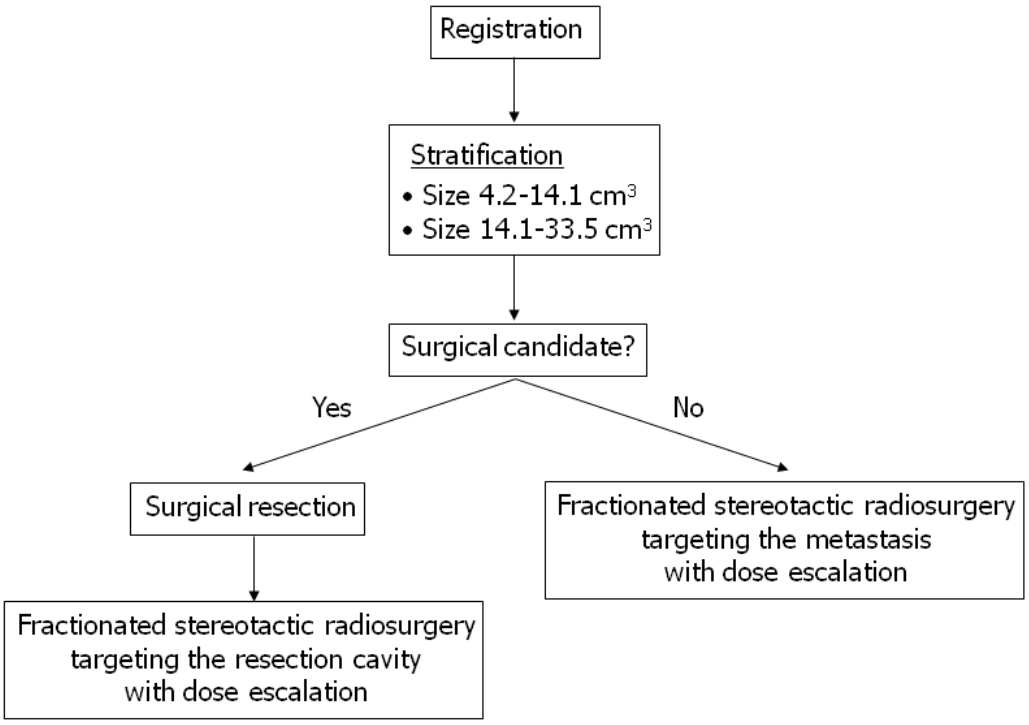
PROTOCOL SYNOPSIS

TITLE	**A PHASE I/II STUDY OF FRACTIONATED STEREOTACTIC RADIOSURGERY TO TREAT LARGE BRAIN METASTASES**
STUDY PHASE	I/II
INDICATION	Histologically or pathologically proven solid tumor malignancy and 1 to 4 total brain metastases, one of which is 4.2-33.5 cm^3, with no previous whole brain irradiation.
PRIMARY OBJECTVES	Determine the maximum tolerated dose (MTD) of SRS given in 3 fractions for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.
SECONDARY OBJECTIVES	1. Determine the local control rate as assessed on MRI and clinical exam. 2. Determine short- and long-term adverse effects. 3. Determine the distant intra-cranial control rate. 4. Determine the overall survival rate. 5. Assess the patient's health related quality of life.
HYPOTHESES	Fractionated SRS treatment of large brain metastases will improve local control and toxicity profile compared to single fraction SRS.
STUDY DESIGN	The MTD of SRS given in 3 fractions for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3 will be determined using the 6+6 study design.
PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS	**Primary Endpoint:** Determine the maximum tolerated dose (MTD) of SRS given in 3 fractions for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3. **Secondary Endpoints:** • To determine the local control rate of fractionated SRS for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.

	• To determine the distant brain control rate. • To determine the overall survival rate. • To determine the short- and long-term adverse effects of fractionated SRS for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3. • Patient health related quality of life will be assessed.
SAMPLE SIZE BY TREATMENT GROUP	If all four dose levels are reached, the maximum number of evaluable subjects in each arm is 30; therefore, the maximum number of subjects for the entire study is 60.
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	**Inclusion Criteria** • All patients age 18 years and older with pathologically proven solid tumor malignancy and 1 to 4 brain metastases, one of which is 4.2 – 33.5 cm^3. • Systemic therapy: Prior cytoxic systemic therapy must be completed ≥ 5 days prior to radiosurgery. No concurrent cytoxic systemic therapy along with SRS. Cytoxic systemic therapy to start ≥ 5 days after the completion of SRS. • Prior surgery or SRS is allowed as long as the target metastatic lesion in this study has not previously been treated with SRS. • Patient must exhibit the ability to understand and the willingness to sign a written informed consent. • Life expectancy of at least 12 weeks. **Exclusion Criteria** • Patients who have previously been treated with whole brain irradiation. • Patients whose metastatic lesion in question had previously been treated with SRS. • The patient has greater than 4 total brain metastases at the time of initial evaluation.

	• Pediatric patients (age <18), pregnant women, and patients who are unable to give informed consent will be excluded.
INVESTIGATIONAL PRODUCTS DOSAGE AND ADMINISTRATION	N/A
CONTROL GROUP	N/A
PROCEDURES	N/A
STATISTICAL CONSIDERATIONS	6+6 design for dose escalation

SCHEMA



Arm	Metastasis Size (cm^3)	Surgical Candidate?	Treatment
1	4.2 - 14.1	Yes	Surgery → SRS
2	14.2 - 33.5	Yes	Surgery → SRS

Dose Level	Dose Per Fraction	Total Dose
1	8 Gy	24 Gy
2	9 Gy	27 Gy
3	10 Gy	30 Gy
4	11 Gy	33 Gy

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
CNS	Central nervous system
CR	Complete response
CRF	Case report/Record form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
IRB	Institutional Review Board
IV	Intravenous
KPS	Karnofsky Performance Scale
MR	Minor response
OS	Overall survival
P	Progression (disease)
PD	Protocol Director
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SD	Stable disease
SRS	Stereotactic Radiosurgery
WBRT	Whole Brain Radiation

1. OBJECTIVES

1.1. Primary Objectives

Determine the maximum tolerated dose (MTD) of SRS given in 3 fractions for resection cavities from brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.

1.2. Secondary Objectives

1.2.1. Determine the local control rate as assessed on MRI and clinical exam.
1.2.2. Determine short- and long-term adverse effects.
1.2.3. Determine the distant intra-cranial control rate.
1.2.4. Determine the overall survival rate.
1.2.5. Assess the patient's health related quality of life.

2. BACKGROUND

2.1. Brain Metastases

Brain metastases are the most common intracranial tumors and occur in approximately 25% of patients with cancer[1]. In the U.S., approximately 170,000 cancer patients a year are diagnosed with brain metastases[2]. Likely as a result of improvements in systemic treatments, the incidence of intracranial metastases has increased over the past decade[3]. The most common malignancies to spread to the brain are lung, breast, kidney, colon/rectum, and melanoma. Clinically, patients with brain metastases can present with headache, neurologic deficits, cognitive dysfunction, seizures, or stroke. Diagnosis is made with neuro-imaging.

The prognosis of patients with brain metastases is variable and depends on several factors, including performance status, age, control of the primary tumor, and extent of extracranial disease[4]. Historically, patients with brain metastases who receive supportive care only have median survival of 1 to 2 months. However, a subgroup of patients with favorable prognosis who undergo treatment can enjoy an extended life expectancy with median survival of 10 to 16 months[5, 6]. Treatment options for brain metastases include medical management, surgery, and radiation. Surgery and radiation will be discussed further.

2.2. Surgery

Surgery has an important role in management of brain metastases. In patients with a large tumor causing mass effect, surgical resection can provide rapid relief of symptoms. Moreover, surgery followed by conventional whole brain radiation (WBRT) decreases local recurrence and improves median survival compared to WBRT alone[7]. In our study, patients deemed suitable for surgery will undergo upfront surgical resection followed by

radiosurgery to the resection cavity.

2.3. Neurocognitive Effects of Whole Brain Radiotherapy

Radiation therapy can be delivered using 1) conventional fractionated radiation to treat the whole brain (WBRT), 2) stereotactic radiosurgery (SRS) to treat individual metastases, or 3) both.

WBRT is associated with a short-term decline in quality of life and long-term deficits in neurocognitive function[8, 9]. In conventionally fractionated WBRT, radiation to the whole cranium is delivered in 10 to 20 daily treatments. Late toxicity of WBRT, such as memory impairment and dementia, is usually irreversible and is likely due to demyelination, vascular damage, and necrosis. Following WBRT, the actuarial rate of neurocognitive toxicity at 2 years can be up to 49%[10]. Meyers reported that 59% of the patients after WBRT demonstrated a greater than 2 standard deviation decline in their performance at 6 months[11]. Results from a recently presented phase III randomized trial reported WBRT to be linked to a marked decline in learning and memory function at 4 months compared to SRS alone (49% vs. 23%, respectively).

2.4. Stereotactic Radiosurgery

Unlike WBRT, stereotactic radiosurgery has the advantage of sparing normal brain. In SRS, high energy radiation is precisely directed at the target lesion. Due to the steep fall–off of the radiation dose away from the target, relative sparing of the normal brain is possible. To minimize the potential late effects of WBRT, investigators have explored the use of SRS alone, deferring the use of WBRT for salvage treatment if needed. Both retrospective analyses[12-15] and a prospective randomized trial[16] reported no apparent survival benefit to combining WBRT with SRS compared to SRS alone.

We have recently published a retrospective review of patients with brain metastases treated with surgical resection followed by adjuvant SRS to the resection cavity while deferring WBRT for salvage. Actuarial local control rates at 6 and 12 months were 88% and 79%, respectively. This value compares favorably with historic results with observation alone (54%) and postoperative WBI (80-90%)[17]. Given its negative neurocognitive effects in the absence of survival benefit, it is our current practice to omit WBRT in favor of SRS in patients with limited number of brain metastases.

2.5. Large Brain Metastases

Neither WBRT nor SRS has been shown to adequately control large brain metastases. WBRT has been shown to have less than 5% complete response rate with brain metastases larger than 2 cm[18]. Radiation Therapy Oncology Group (RTOG) 90-05 study determined maximum tolerated dose (MTD) and subsequent dose selection guidelines for *single* fraction radiosurgery in patients with recurrent brain metastases who had received prior partial or whole brain irradiation[19]. The MTD for metastases < 2cm, 2-3 cm and

3-4 cm were not reached, 24, and 18 Gy, respectively. Based on these results, the recommended *single* fraction radiosurgery dose for brain metastases of <2 cm, 2-3 cm, and 3-4 cm are 24 Gy, 18 Gy, and 15 Gy, respectively. However, subsequent reports on the usage of these dosing guidelines show a local control of only 49% and 45% for metastases 2-3 cm and 3-4 cm in diameter, respectively[20]. Similarly, a series from Pittsburgh showed only a 49% local control rate for tumors >4 cc (approximately >2 cm diameter)[21]. The importance of controlling brain metastases is demonstrated by the significant decline in neurocognitive function in those patients with disease progression compared to those with controlled disease[11]. Given the negative impact of recurrent intracranial disease on the quality of life and neurocognitive ability of patients, a great need exists for the improvement of local control in patients with large brain metastases.

2.6. Fractionated Radiosurgery

One technique which may improve local control and toxicity profile is fractionation of SRS treatments. Fractionation has been demonstrated to increase tumor kill by allowing inter-fraction re-oxygenation and cell reassortment to minimize radioresistance due to hypoxia and cell cycle[22]. In addition, fractionation reduces the late effects of radiotherapy.

Despite the widespread use of fractionated radiosurgery, no prospective data exist to 1) provide dose guidelines, 2) determine whether fractionation of SRS improves local control, and 3) examine the effects of fractionation on acute and late side effects.
The protocol outline here proposes SRS to be delivered in 3 fractions with initial dose of 24 Gy in 3 fractions (i.e., 8 Gy x 3 fractions) for brain metastases 4.2 - 14.1 cm^3 (2 – 3 cm diameter) and for metastases 14.2 - 33.5 cm^3 (3 - 4 cm diameter). This dose is radiobiologically equivalent to 16 Gy in a single fraction. This conservative dose of 24 Gy in 3 fractions is below or similar to the MTD for *single* fraction SRS determined in the RTOG 90-05 in patients who had already received previous brain irradiation.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix B.

3.1 Inclusion Criteria

3.1.1. All patients age 18 years and older with pathologically proven solid tumor malignancy and 1 to 4 brain metastases, one of which is 4.2 – 33.5 cm^3.

3.1.2. Systemic therapy: Prior cytoxic systemic therapy must be completed ≥ 5 days prior to radiosurgery. No concurrent cytoxic systemic therapy along with SRS. Cytoxic systemic therapy to start ≥ 5 days after the completion of SRS.

3.1.3. Prior surgery or SRS is allowed as long as the target metastatic lesion in this study has not previously been treated with SRS.

3.1.4. Patient must exhibit the ability to understand and the willingness to sign a written informed consent.

3.1.5. Life expectancy of at least 12 weeks.

3.2 **Exclusion Criteria**

3.2.1. Patients who have previously been treated with whole brain irradiation.

3.2.2. Patients whose metastatic lesion in question had previously been treated with SRS.

3.2.3. The patient has greater than 4 total brain metastases at the time of initial evaluation.

3.2.4. Pediatric patients (age <18), pregnant women, and patients who are unable to give informed consent will be excluded.

3.3 **Informed Consent Process**

3.3.1 Informed consent may be obtained by the PI or a designee who is a member of the research team.

3.3.2 The PI is ultimately responsible for determining whether a subject has the capacity to consent, although informed consent may be obtained by either the PI or designee. If the subject is lacking such capacity, whether due to cognitive impairment, the subject's age, or other causes, the PI/designee may obtain consent from a legally authorized representative.

3.3.3 As part of the consent process, the subject's or his/her representative's questions must be answered prior to consent being given and throughout the study. The subject or his/her representative should be asked if there are any questions prior to consent being obtained and at all subsequent visits or contacts. These elements of the informed consent process must be documented in the patient's medical record.

3.3.4 When giving the consent, the subject or a duly authorized legal representative needs to read each page and sign and date the last page of the form along with the investigator or designee obtaining consent.

3.3.5 The signed Informed Consent Form should be filed in the following location.

3.3.5.1 The signed consent will be filed in the patient's research study record.

3.3.5.2 One copy of the signed consent will be sent to Stanford Medical Records where it will be scanned into the patient's electronic medical record.

3.3.5.3 An additional copy of the consent form will be filed in the study Regulatory Binder.

3.4 **Randomization Procedures**

This is not a randomized trial. There will be no randomization.

4. TREATMENT PLAN

4.1 Investigational Agent or Device Administration

4.1.1. PRETREATMENT EVALUATIONS

Patients will be evaluated by a multi-disciplinary team composed of radiation oncologists and neurosurgeons to assess for their eligibility. Patient's oncologic history, presenting symptoms, physical examination, pathology, and imaging studies will be reviewed. Patients will be evaluated for surgical candidacy and resectability.

4.1.2. SURGICAL TREATMENT

Patients who are good surgical candidates, as determined by neurosurgical evaluation, will undergo a surgical resection prior to radiotherapy. All others will receive primary SRS.

4.1.3. RADIATION THERAPY

4.1.3.1. Dose specifications/escalation

SRS will be delivered in 3 fractions. Provided that the MTD has not been reached, the total dose will be increased in 3 Gy increments:

Dose Level	Dose Per Fraction	Total Dose
1	8 Gy	24 Gy
2	9 Gy	27 Gy
3	10 Gy	30 Gy
4	11 Gy	33 Gy

A minimum of six patients will be enrolled per arm:

Arm	
1	4.2 - 14.1 cm^3 brain metastasis following surgical resection
2	14.2 - 33.5 cm^3 brain metastasis following surgical resection

Similar to RTOG 90-05, the dose limiting toxicity (DLT) is defined as grade 3, 4, or 5 RTOG central nervous system (CNS) acute radiation morbidity scoring criteria (Appendix C) observed within 30 days of radiosurgery. The MTD is defined as one dose level below the highest toxic dose (i.e., the DLT dose).

The occurrence of late toxicities will be continuously monitored. If a late DLT occurs in 3 or more out of 6 (or 4 or more out of 12) patients at a certain dose level after the radiation dose had already been escalated to the next level, the MTD will be backtracked to the level

below the one at which the DLTs occurred.

Does escalation will proceed as follows, with minimum waiting period of 30 days before proceeding with the next higher dose level:

Number of Patients at a Given Dose Level with a DLT	**Escalation Decision Rule**
0-1 out of 6	Enter 6 patients at the next higher dose level
2 out of 6	Enter at least 6 more patients at the current dose level. • If 0-1 of these 6 experience a DLT (i.e., 2-3 out of 12), then proceed to next dose level. • If 2 or more of these 6 experience a DLT (4 or more out of 12), then dose escalation will be stopped. Six additional patients will be entered at the next lower dose level if only 6 patients were previously entered.
3 or more out of 6	Dose escalation will be stopped. Six additional patients will be entered at the next lower dose level if only 6 patients were previously entered.

Should a patient not be evaluable at 30 days (due to death or loss to follow-up or discontinuation of the protocol follow-up per patient preference), then additional patients may be enrolled on each arm such that at least 5 of 6 are evaluable and experience no DLT. For example, should one patient be lost to follow up, but the remaining 5 patients have no DLT, then dose escalation may proceed.

4.1.3.2.Technical factors

Treatment shall be delivered using the Trilogy™ Linear Accelerator (Varian Medical Systems, Palo Alto, CA) or the CyberKnife™ Robotic Radiosurgery System (Accuray, Sunnyvale, CA).

4.1.3.3.Localization, simulation, and immobilization

The patient shall be treated in the supine position. An aquaplast head mask will be used to ensure adequate immobilization during therapy. The target volume shall be either the resection cavity or the unresectable lesion. When the resection cavity is targeted, a uniform isotropic 2 mm expansion of the cavity will be the target volume[17].

4.1.3.4.Critical structures

Critical normal structures (e.g., optic apparatus, brain stem) will be contoured and their doses minimized. The patient will be excluded from the protocol if the tumor's proximity to critical structures is such that a dosimetrically acceptable plan is not achievable to conform to these constraints.

4.2 General Concomitant Medication and Supportive Care Guidelines

Supportive treatment may include anti-emetics, anti-diarrheal medications, anti-pyretics, anti-histamines, analgesics, antibiotics, and others, such as blood products. Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician.

Steroids may be given after each SRS treatment to decrease the risk of CNS symptoms due to cerebral edema. In addition, steroids may be used as required to control CNS symptoms due to tumor-associated or RT-associated cerebral edema, but wherever possible, should be tapered and stopped.

Nausea/vomiting: Nausea and vomiting should be treated aggressively. In particular, the use of antiemetics including 5HT3 antagonists and/or dexamethasone is encouraged. Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy.

4.3 Duration of Therapy

SRS will be given in 3 fractions, each approximately 24 hours apart.

4.4 Duration of Follow Up

Follow-up schedule is summarized in section 9. Study Calendar.

Patients will be seen in follow-up at 1^{st}, 3^{rd}, 6^{th}, 9^{th}, and 12^{th} months following radiation. The following will be obtained at pre-treatment evaluation and at each follow-up time point: Neurologic history and physical examination, KPS, steroid use assessment, and toxicity evaluation. MRI with gadolinium will be obtained at pre-treatment and at 3, 6, 9, and 12 months following treatment until progression is documented and continuing every 3 months for those without evidence of intracranial progression.

After the first 12 months, patients will be followed every 3-6 months at the discretion of the patient's physician. At each visit, interval history, physical exam, KPS, toxicity evaluation, and brain MRI scans will be obtained.

For those subjects who are unable to come for clinic visits, clinical follow-up information will be obtained via 1) a phone call to the patient and/or 2) clinic source document from his/her local physician. For subjects unable to appear in person for clinic visits, HRQOL questionnaires will be completed via a telephone interview or mail.

For patients unable to return for imaging studies, source documents from outside institutions will be used to document imaging follow-up.

4.5 Criteria for Removal from Study

- Disease progression or death
- Intercurrent illness that prevents further administration of treatment: a condition, injury, or disease unrelated to cancer, that renders continuing of radiation treatment unsafe or regular study visits impossible.
- Unacceptable adverse event(s) (see adverse events)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient ineligible for the study
- Non-compliance with protocol-required evaluations and study visits
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- Patients who inadvertently become pregnant
- At the discretion of the treating investigators

Subjects who are discontinued from the study will still be followed for disease progression and survival.

Subjects who discontinue should, if possible, be seen and assessed by an investigator(s). The reason for withdrawal and the date of withdrawal must be documented.

If the reason for withdrawal from the trial is the death of the subject, the two options for categorizing withdrawal are either progressive disease or an adverse event (AE; more than one AE may be documented as a reason for withdrawal). Only one event will be captured as the cause of death. Note that death is an outcome and not an AE.

All trial treatment-related toxicities and serious adverse events (SAEs) must be followed up until resolution.

At withdrawal, all on-going study-related toxicities and SAEs must be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons, or adverse events after registration but prior to receiving study therapy) may be replaced as required for the study to meet its objectives. The decision

to remove a subject/patient and to replace dropouts will be made by the treating investigator. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced.

4.6 Alternatives

Alternative treatments include conventional fractionated whole brain radiotherapy, stereotactic radiosurgery alone, systemic therapy, or no therapy.

4.7 Compensation

Subjects will not be paid for their participation in the study.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

N/A

5.2 Availability

N/A

5.3 Agent Ordering

N/A

5.4 Agent Accountability

N/A

6. DOSING DELAYS/DOSE MODIFICATIONS

N/A

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

7.1.1. Early, < 30 days from treatment: Expected adverse events include fatigue, headache, neck pain, nausea and vomiting, and lethargy.

7.1.2. Late, > 30 days from treatment: Possible adverse events include focal neurologic deficits, memory difficulties, dementia, radiation necrosis, and radiation induced neoplasm.

7.2 Adverse Event Reporting

In the event of an adverse event the first concern will be for the safety of the subject. Appropriate medical, psychological and/or supportive intervention should be initiated as soon as possible. All subjects/patients with serious adverse experiences must be followed up for outcome.

7.2.1. Definition:

7.2.1.1. **Definition of adverse event:** 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).

7.2.1.2. **Definition of serious adverse event:** any adverse experience that results in any of the following outcome: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2.1.3. **Definition of unanticipated problems involving risks to participants or others (UPs):** events (including internal or external events, death, life-threatening experiences, injuries, breaches of confidentiality, or other problems) that occur any time during or after the research study, which in the opinion of the PD are:

7.2.1.4. Unexpected - not in the consent form, protocol, package insert, or label; or unexpected in its frequency, severity, or specificity, AND

7.2.1.5. Related to the research procedures – caused by, or probably caused by research activity, or, if a device is involved, probably caused by , or associated with the device, AND

7.2.1.6. Harmful – caused harm to participants or others, or placed them at increased risk of harm (including physical, psychological, economic, or social harm.

7.2.1.7. **Definition of reportable information:** New information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency.

7.2.1.7.1. Protocol deviation or violation, only if:

7.2.1.7.1.1. Intended to eliminate apparent immediate hazard to a research participant, or

7.2.1.7.1.2. Harmful (caused harm to participants or to others, or placed them at increased risk of harm – including physical, psychological, economic, or social harm), or

7.2.1.7.1.3. Possible serious or continued noncompliance

7.2.1.7.2. Complaint that is unresolved by the research team, or that indicates increased or unexpected risks.

7.2.1.7.3. Incarceration when in the opinion of the PD it is in the best interest of the participant to remain on the study.

7.2.1.8. **Unanticipated adverse device effect.** New information about the effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare or subjects.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

If disease progression is noted during a protocol-specified reevaluation of the status of a patient's cancer, and the progression is manifested solely by results of tumor markers and/or radiologic imaging, that occurrence of progressive disease will NOT be recorded as an adverse experience.

7.2.2. Adverse Event Reporting

7.2.2.1. PIs or designees should report AEs, whether considered treatment related or not, to the CCTO Safety Coordinator per protocol and regulatory timeframes.

Events should be reported within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted in death).

7.2.2.2. Unanticipated adverse device effects should be reported to FDA, CCTO and participating investigators within 10 working days of becoming aware of the event (5 days if the event is life threatening or resulted in death).

7.2.2.3. RTOG central nervous system (CNS) acute radiation morbidity scoring criteria (Appendix C) will be used to grade acute CNS toxicity.

7.2.2.4. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for grading of adverse events (Appendix E).

8. CORRELATIVE/SPECIAL STUDIES

8.1. Dose heterogeneity and conformality within the target volume will be calculated for each lesion to investigate whether these factors have any correlation to local control or toxicity.

8.2. To identify potential predictors of response, the following pre-treatment tumor characteristics will be collected:

8.2.1. Lesion size

8.2.2. Histology

8.2.3. Pattern of enhancement on MRI scan

8.2.4. Presence or absence of extensive edema

9. STUDY CALENDAR

Parameters	Pre-Entry	1 month [a]	3 month [b]	6 month [b]	9 month [b]	12 month [b]
History/ Physical Exam	X	X	X	X	X	X
KPS	X	X	X	X	X	X
MRI	X		X	X	X	X
Steroid use Assessment	X	X	X	X	X	X
Toxicity Evaluation		X	X	X	X	X
QOL Evaluation	X	X	X	X	X	X

[a] time point ± 7 days

[b] time point ± 14 days

10. MEASUREMENT OF EFFECT

10.1 Anti-tumor Effect

Subjects will be seen in follow-up at 1, 3, 6, 9, and 12 months following SRS.At each follow-up, neurologic history and examination will be done. MRI with gadolinium will be obtained at 3, 6, 9, and 12 months.

10.1.1 Definitions

Early radiation toxicity is defined as those observed within 30 days of SRS. Late radiation toxicity is defined as those observed after 30 days following SRS. Tumor response will be measured using MRI with gadolinium obtained at 3, 6, 9 and 12 months following SRS.

10.1.2 Disease Parameters

Target lesion is defined as those treated with radiosurgery. The size and volume of the target lesion will be measured using the treatment planning software.

10.1.3 Methods for Evaluation of Measurable Disease

MRI with gadolinium will be obtained at 3, 6, 9, and 12 months following SRS.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

Radiographic response using MRI with gadolinium will be used. Follow-up MRI scans will be obtained at 3, 6, 9, and 12 months following SRS. Size of the treated lesion will be measured and compared to its pre-treatment size**.** Local tumor progression is defined as the radiographic appearance of a new or increasing enhancing lesion within the radiosurgical target volume. Local control is defined as lack of progression (P – below). Metabolic imaging may be necessary at times to distinguish tumor progression from treatment related radiation necrosis.

4.1.3.4.1. Complete response (CR): The tumor is no longer seen on the follow-up MRI scan.

4.1.3.4.2. Partial response (PR): Decrease of >50% in the product of two diameters on the follow-up MRI scan.

4.1.3.4.3. Minor response (MR): Decrease of <50% in the product of two diameters on the follow-up MRI scan.

4.1.3.4.4. Stable disease (SD): The scan shows no change.

4.1.3.4.5. Progression (P): A >25% increase in tumor area (product of two diameters).

10.1.4.2 **Evaluation of Non-Target Lesions**

The distant control rate will be determined. Distant brain failure is defined as the radiographic appearance of a new or enhancing lesion more than 5 mm from the radiosurgical target volume[19]. Elsewhere brain failure rate will be determined using MRI scanning with gadolinium obtained at 3, 6, 9, and 12 months following SRS.

10.1.4.3 **Evaluation of Best Overall Response**

N/A

10.1.5 **Duration of Response**

N/A

10.1.6 **Progression-Free Survival (or other parameters)**

Time to progression will be measured from the time of SRS. Overall survival will be measured from 1) the time of diagnosis, and 2) time of SRS.

10.1.7 **Response Review**

N/A

10.2 **Other Response Parameters**

The primary endpoint of this study is to determine the MTD of tri-fraction SRS. The MTD is defined as one dose level below the highest toxic dose (i.e., the DLT dose). Similar to RTOG 90-05, the dose limiting toxicity (DLT) is defined as grade 3, 4, or 5 RTOG central nervous system (CNS) acute radiation morbidity scoring criteria (Appendix C) observed within 30 days of radiosurgery.
The occurrence of late toxicities will be continuously monitored. If a late DLT occurs in 3 or more out of 6 (or 4 or more out of 12) patients at a certain dose level after the radiation dose had already been escalated to the next level, the MTD will be backtracked to the level

below the one at which the DLTs occurred.

11. DATA REPORTING / REGULATORY CONSIDERATIONS

11.1 Monitoring plan

Stanford Cancer Center (SCC) Data and Safety Monitoring Committee (DSMC) will be responsible for monitoring the research yearly and will operate independently from the clinical investigators. The primary responsibility of the DSMC is to review the reported study data to confirm it is accurate, complete, and verifiable from source documents. The DSMC will also confirm that the conduct of the trial maintains the safety and well being of human subjects, and is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements. Study safety data will be reviewed by the DSMC in the form of summary reports or data listings on a regular basis.

11.2 Stopping rules (for the individual patient and for the study as a whole)

The dose limiting toxicity (DLT) is defined as grade 3, 4, or 5 RTOG central nervous system (CNS) acute radiation morbidity scoring criteria (Appendix C) observed within 30 days of radiosurgery.

The occurrence of late toxicities will be continuously monitored. If a late DLT occurs in 3 or more out of 6 (or 4 or more out of 12) patients at a certain dose level after the radiation dose had already been escalated to the next level, the MTD will be backtracked to the level below the one at which the DLTs occurred.

Does escalation will proceed as follows:

Number of Patients at a Given Dose Level with a DLT	**Escalation Decision Rule**
0-1 out of 6	Enter 6 patients at the next higher dose level
2 out of 6	Enter at least 6 more patients at the current dose level. • If 0-1 of these 6 experience a DLT (i.e., 2-3 out of 12), then proceed to next dose level. • If 2 or more of these 6 experience a DLT (4 or more out of 12), then dose escalation will be stopped. Six additional patients will be entered at the next lower dose level if only 6 patients were previously entered.

3 or more out of 6	Dose escalation will be stopped. Six additional patients will be entered at the next lower dose level if only 6 patients were previously entered.

Should a patient not be evaluable at 30 days (due to death or loss to follow-up or discontinuation of the protocol follow-up per patient preference), then additional patients may be enrolled on each arm such that at least 5 of 6 are evaluable and experience no DLT. For example, should one patient be lost to follow up, but the remaining 5 patients have no DLT, then dose escalation may proceed.

11.3 **Data management**

All data files (contains patients' names, medical record numbers, treatment, and follow-up information) for this study will be kept in a secure office in the department of Neurosurgery and Radiation Oncology. The electronic data file for this study, which contains patients' names, medical record numbers, treatment, and follow-up information, is kept under password protection.

11.4 **Confidentiality**

All signed informed consents and data files (contains patients' names, medical record numbers, treatment, and follow-up information) for this study will be kept in a secure office in the department of Neurosurgery and Radiation Oncology. The electronic data file for this study, which contains patients' names, medical record numbers, treatment, and follow-up information, is kept under password protection.

12. STATISTICAL CONSIDERATIONS

12.1 **Endpoints**

12.1.1 **Primary endpoint**

Determine the maximum tolerated dose (MTD) of SRS given in 3 fractions for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.

12.1.2 **Secondary endpoints**

12.1.2.1. To determine the local control rate of fractionated SRS for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.

12.1.2.2. To determine the distant brain control rate of fractionated SRS for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.

12.1.2.3. To determine the overall survival rate of fractionated SRS for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.

12.1.2.4. To determine the short- and long-term adverse effects of fractionated SRS for brain metastases 4.2 - 14.1 cm^3 and 14.2 - 33.5 cm^3.

12.1.2.5. Patient health related quality of life will be assessed using the EORTC QLQ-C30 and EORTC Brain Cancer Module QLQ-BN20.

12.2 Analysis Populations

Each of the four arms will be analyzed separately to determine the MTD for each arm.

Arm	
1	4.2 - 14.1 cm^3 brain metastasis following surgical resection
2	14.2 - 33.5 cm^3 brain metastasis following surgical resection

There will be no subset analysis.

12.3 Sample Size

12.3.1 Accrual estimates

Six subjects per group will be enrolled at the starting dose for each of the four arms. Should a patient not be evaluable at 30 days (due to death or loss to follow-up or discontinuation of the protocol follow-up per patient preference), then additional patients may be enrolled on each arm such that at least 5 of 6 experience no DLT. The maximum number of subjects per arm will depend on the number of dose levels reached. If all four dose levels are reached, the maximum number of evaluable subjects in each arm is 30. If all four dose levels are reached for the all two arms of the study, the maximum number of subjects for the entire study is 60.

12.3.2 Sample size justification

The sample size will be determined by the number of dose levels reached.

12.3.3 Criteria for future studies

N/A

12.4 Interim analyses

N/A

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APPENDICIES

A. Informed Consent Form

Attach a copy of the protocol Informed Consent Form. A Stanford specific template can be found at http://humansubjects.stanford.edu/. The final IRB-approved Informed Consent Form and HIPAA Authorization document for each site must be provided to Stanford for approval by the Stanford PI and inclusion in the Regulatory Binder.

B. Participant Eligibility Checklist

II. Protocol Information:

Protocol Title:	**A Phase I/II Study of Fractionated Stereotactic Radiosurgery to Treat Large Brain Metastases**
Protocol Number:	**15107**
Principal Investigator:	**Scott Soltys, MD**

III. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**C. Supporting Documentation***
1. Is patient age 18 or older? (Yes)	☐	☐	
2. Does the patient have a pathologically proven solid tumor malignancy? (Yes)	☐	☐	
3. Does the patient have 1 to 4 brain metastases? (Yes)			
4. Does one of the tumors mentioned in (3) have a volume of 4.2 – 33.5 cm^3? (Yes)	☐	☐	
5. Has the patient completed cytotoxic systemic therapy ≥ 5 days prior to radiosurgery? (Yes)	☐	☐	
6. Will cytotoxic systemic therapy be administered concurrent with SRS? (No)	☐	☐	
7. Will the patient receive cytotoxic systemic therapy ≤5 days after the completion of SRS? (No)	☐	☐	
8. Has the target metastatic lesion undergone previous SRS? (No)	☐	☐	

9. Patient signed informed consent? (Yes)	☐	☐	
10. Life expectancy of at least 12 weeks? (Yes)	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Has the patient previously been treated with whole brain irradiation? (No)	☐	☐	
2. Has the metastatic lesion in question previously been treated with SRS? (No)	☐	☐	
3. Does the patient have greater than 4 total brain metastases at the time of initial evaluation? (No)	☐	☐	
4. Is the patient a pediatric patient (age <18), pregnant woman, or unable to give informed consent? (No)	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	
Secondary Reviewer Signature:	Date:
Printed Name:	
Study Coordinator Signature:	Date:
Printed Name:	

a.

C. RTOG CNS ACUTE RADIATION MORBIDITY SCORING CRITERIA

0. No Change

1. Fully functional status (i.e., able to work) with minor neurologic findings. No medication needed.

2. Neurologic findings present sufficient to require home case; nursing assistance may be required; medications including steroids and anti-seizure agents may be required.

3. Neurologic findings requiring hospitalization for initial management.

4. Serious neurologic impairment which includes paralysis, coma, or seizures > 3 per week despite medication. Hospitalization required.

5. Death

D. RTOG CNS LATE RADIATION MORBIDITY SCORING CRITERIA

0. None

1. Mild headache; slight lethargy

2. Moderate headache; great lethargy

3. Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)

4. Seizures or paralysis; Coma

5. Death

E. **NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0**

See Nervous System Disorders at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Grade1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade4 Life-threatening consequences; urgent intervention indicated.

Grade5 Death related to AE.

Activities of Daily Living (ADL):

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

F. EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at all	A Little	Quite a Bit	Very Much
31. Did you feel uncertain about the future?	1	2	3	4
32. Did you feel you had setbacks in your condition?	1	2	3	4
33. Were you concerned about disruption of family life?	1	2	3	4
34. Did you have headaches?	1	2	3	4
35. Did your outlook on the future worsen?	1	2	3	4
36. Did you have double vision?	1	2	3	4
37. Was your vision blurred?	1	2	3	4
38. Did you have difficulty reading because of your vision?	1	2	3	4
39. Did you have seizures?	1	2	3	4
40. Did you have weakness on one side of your body?	1	2	3	4
41. Did you have trouble finding the right words to express yourself?	1	2	3	4
42. Did you have difficulty speaking?	1	2	3	4
43. Did you have trouble communicating your thoughts?	1	2	3	4
44. Did you feel drowsy during the daytime?	1	2	3	4
45. Did you have trouble with your coordination?	1	2	3	4
46. Did hair loss bother you?	1	2	3	4
47. Did itching of your skin bother you?	1	2	3	4
48. Did you have weakness of both legs?	1	2	3	4
49. Did you feel unsteady on your feet?	1	2	3	4

50. Did you have trouble controlling your bladder?	1	2	3	4

G. EORTC QLQ – C30 follows on next page:

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent