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Harold C. Simmons Cancer Center

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SRS Dose-Escalation Study for Brain Metastasis
A Phase I Dose-Escalation Study of Stereotactic Radiosurgery for Brain Metastasis without Whole Brain Radiation

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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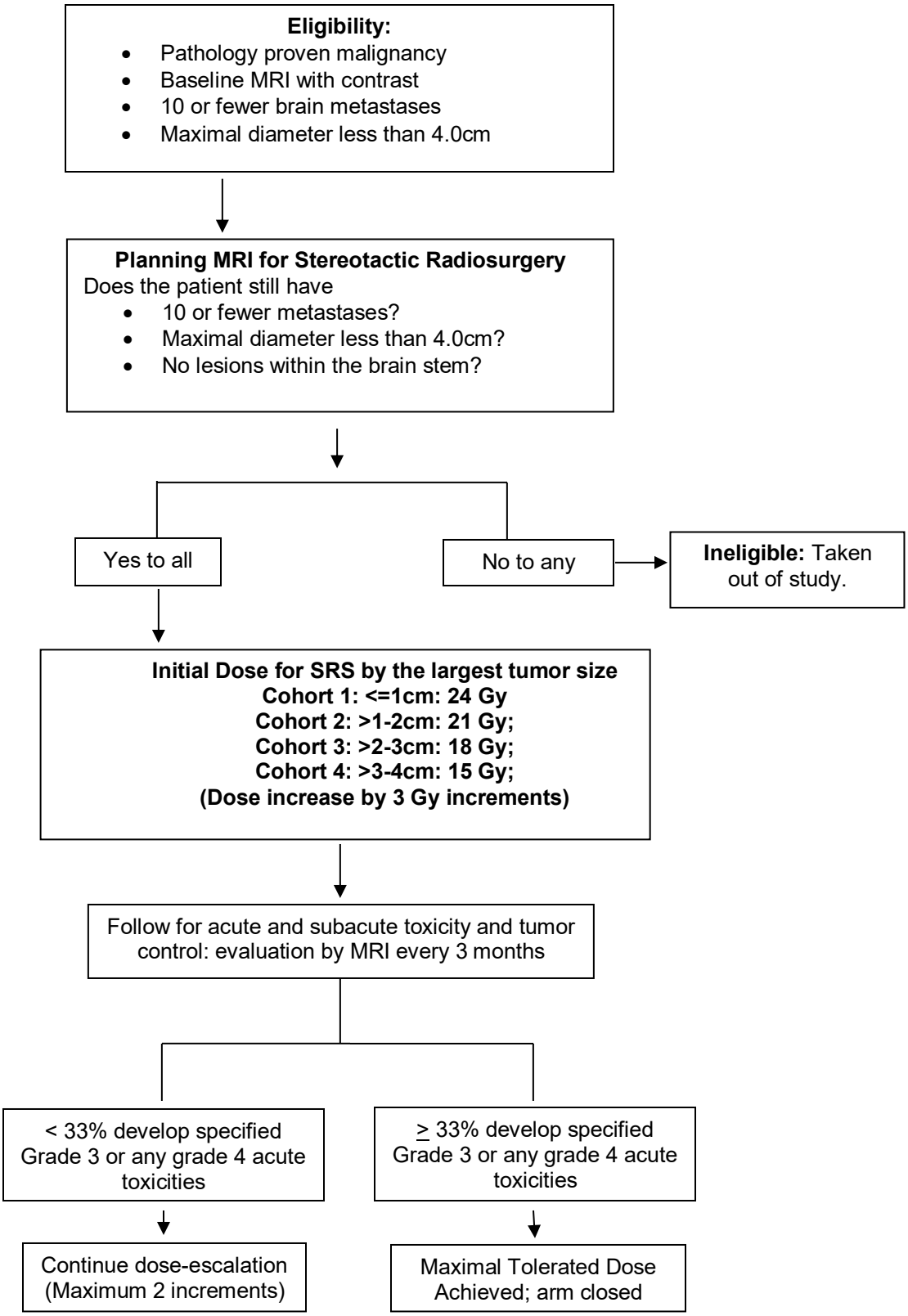
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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Conformality Index
CNS	Central Nervous System
Co-60	Cobalt 60
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol ™ health questionnaire
Gy	Gray
FACT-G	Functional Assessment of Cancer Therapy-P
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HRQOL	Health-Related Quality of Life
IHC	Immunohistochemistry
LINAC	Linear Accelerator
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NICE	National Institute for Clinical Excellence
ORR	Overall Response Rate
OS	Overall Survival
pCR	Pathologic Complete Response
PD	Progressive Disease
PE	Physical Exam
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	Per os/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
TTP	Time To Progression

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase I Dose-Escalation Study of Stereotactic Radiosurgery for Brain Metastasis without Whole Brain Radiation
Short Title	SRS Dose-Escalation Study for Brain Metastasis
Protocol Number	The standard protocol number used to identify this study
Phase	I
Methodology	Prospective dose-escalation study
Study Duration	3 years
Study Center(s)	Single-center
Objectives	Evaluate the acute and subacute CNS toxicity of single-fraction stereotactic radiosurgery in patients with brain metastases who have not undergone prior brain irradiation.
Number of Subjects	between 28-180 for phase I (depending on tolerance)
Diagnosis and Main Inclusion Criteria	Patients with 10 or fewer brain metastases that are less than 4cm in maximal diameter.
Study Product(s), Dose, Route, Regimen	Radiation, Stereotactic Radiosurgery Size <= 1cm: 24 Gy; + 3Gy incremental escalation up to 30 Gy >1-2cm: 21 Gy; + 3Gy incremental escalation up to 27 Gy >2-3cm: 18 Gy; + 3Gy incremental escalation up to 24 Gy >3-4cm: 15 Gy; + 3Gy incremental escalation up to 21 Gy
Duration of administration	One day procedure
Reference therapy	Radiation, Stereotactic Radiosurgery after previous brain radiation Lesion size <= 2cm: 24 Gy; >2-3cm: 18 Gy; >3-4cm: 15 Gy
Statistical Methodology	The maximal tolerated dose will be identified if more than 33% develop grade 3-4 toxicities. For each dose level cohort, a total of seven to fifteen patients will be enrolled.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Brain metastasis is the most common intracranial malignancy, outnumbering primary brain malignancies by almost a factor of ten. Autopsy series have shown up to 30 % incidence of brain metastases for all patients with a cancer diagnosis, amounting to an annual incidence of approximately 170,000 - 200,000 in the U.S [1, 2]. Despite the recent improvement in systemic therapy for cancer patients with metastases, the efficacy of chemotherapy inside the blood-brain-barrier (BBB) is limited and the incidence of brain metastasis is expected to rise. Historically, untreated patients with brain metastases have a survival time of only a few weeks [3, 4]. Surgical resection and brain irradiation are main treatment modalities for brain metastases, which can provide palliation and prolong survival in many cases.

The optimal treatment for brain metastases is an active area of investigation. In particular, the optimal stereotactic radiosurgery (SRS) dose for the treatment of brain metastases remains unclear. The current standard for a single fraction SRS is based on the Phase I dose-escalation study by the Radiation Therapy Oncology Group (RTOG 90-05; [5]). Patients in this study had either brain metastases or primary brain tumors, which were treated with SRS, and the maximal tolerated dose (MTD) was identified by dose escalation until significant acute toxicity (RTOG Grade 3 or greater) was observed in more than 30% of the patients. However, there are two important caveats to consider in this study. First, all of these patients had previous brain irradiation, and the true MTD may be higher in radiation-naïve patients. Secondly, more than a third of the patients in the trial had primary brain cancer, mostly gliomas. The tolerant doses may be significantly different in brain metastases. The optimal dose of SRS for brain metastases in radiation-naïve patients has not been investigated.

1.2 Radiation Therapy and Stereotactic Radiosurgery

Historically, therapy for brain metastases consisted of glucocorticoids and whole brain irradiation, which relieve various symptoms and in some cases restore neurological functions. Three prospective randomized trials involving more than 1,800 patients conducted by the RTOG in the 1970s evaluated 9 different whole brain radiation therapy (WBRT) doses and schedules [6]. In summary, all fractionation schemes with doses up to 50 Gray (Gy) were equivalent with respect to toxicity, neurological improvement and survival. The cause of death in 30-50% was persistence of intracranial lesions or recurrence following WBRT. In the study by Patchell et al., patients with a single metastasis were randomized to either WBRT alone or surgical resection followed by WBRT. The addition of surgical resection was shown to improve median survival time (MST) from 4 months to 10 months, functional independent survival from 2 months to 9.5 months and the intracranial recurrence rate from 52% to 20% [7]. This study and others [8] suggested the benefits of local treatment of metastasis in combination with whole brain radiation.

In addition to surgical resection, stereotactic radiosurgery (SRS) is another local treatment modality that is effective and minimally invasive. Particularly for elderly patients or those with comorbidities that make them poor surgical candidates, SRS may be a preferable treatment option over surgery for brain metastasis. In SRS, a potent dose of highly conformal radiation is delivered in a single fraction to a small target [9]. Brain metastases are ideal targets for SRS because the majority are small, most displace rather than infiltrate the surrounding normal brain, and most are spherical with distinct margins [10]. Retrospective reports of SRS from a number of institutions report local failure rates of 4 to 15% [11-14]. These results are comparable with the local failure rates of 10-20% [7, 8] observed for surgery. There is also recent evidence from prospective study that suggests that even for patients with up to 10 brain metastases, SRS may be considered, as the elsewhere intracranial recurrence risk was not any higher in these patients, compared to those with 4 or less metastases[15]. Moreover, retrospective analyses show that brain metastases from a large number of different types of malignancies, including those that are considered radio-resistant such

as colon cancer, renal cell carcinoma and melanoma, have responded favorably to SRS [15-18]. Furthermore, SRS can treat metastases located in areas of the brain not amenable to complete surgical resection [19, 20]. Finally, its ease of administration as a one-day noninvasive, outpatient treatment makes SRS an attractive treatment approach. Literature suggests that SRS offers good local control of the targeted lesions [21] and cost-effective [22-24].

1.3 Rationale for the Protocol

The RTOG dose-escalation study (RTOG 90-05) established the maximum tolerated dose (MTD) of SRS in patients with previously irradiated primary brain tumors and brain metastases. For lesions 2.1-3.0 cm and 3.1-4.0 cm in maximum diameter, the MTD were 18Gy and 15Gy, respectively [5]. For small lesions less than 2 cm, the MTD was not reached at 24Gy. There are two important patient characteristics to consider in this study. First, all of the enrolled patients had previous radiation to the brain. Since the radiation effect is cumulative, the MTD for SRS is likely higher in radiation-naïve patients. Second, 37% of the patients in this trial had primary brain malignancies, not brain metastases. The MTD identified in these patients may not be applicable to patients with brain metastasis.

Recently, several large randomized studies have shown that in patients with limited brain metastases, whole brain radiation can be safely deferred when treated with SRS and close surveillance. In light of this, most of such patients are now treated with SRS alone without WBRT. However, the SRS doses set by RTOG 90-05 continue to be applied to patients without previous cranial irradiation.

The potential insufficiency of current SRS dose for long-term tumor control is of pressing concern. The advances chemotherapy has led to an improvement in overall survival in many patients with metastatic cancer, including malignancies often associated with brain metastases, such as lung (40-50%; [25, 26]) and breast (15%; [27]). As these patients survive longer, more patients may develop brain metastases and the current dose of SRS may not be adequate to control the brain metastases for the duration of their survival. In fact, there is evidence that the control rate declines with time after SRS, and after 3 years, the local control rate may be only about 60% [28]. In the case of brain metastases from relatively radio-resistant melanoma, the reported 12-months local control rates for SRS range from 52% to 75% (reviewed in [29]). More potent SRS doses could lead to improved long-term control of brain metastases.

In summary, SRS dose escalation for brain metastases in radiation-naïve patients will establish true tolerable doses, which may exceed the current standard doses. This may lead to an improvement in local control, patient survival, and/or quality-of life.

1.4 Correlative Studies

In the United States, total national health expenditures (NHE) increased from $7.14 billion in 1990 to $2.23 trillion in 2007, which represents an average annual growth rate of 7.0%. In contrast, over the same period, U.S. gross domestic product (GDP) increased from $5.8 trillion in 1990 to $13.8 trillion, or average 5.2% annual growth rate. Given that national health expenditures have grown faster than GDP, the share of GDP devoted to health expenditures has increased from 12.3% in 1990 to 16.2% in 2007[30]. Moreover, national health expenditure growth is expected to continue to outpace income growth, with total NHE reaching $4.35 trillion by 2018, accounting for 20.3% of GDP[30]. There is growing concern that these trends in health expenditures are not sustainable. For the Medicare program, current estimates of the present value of total unfunded liabilities through the year 2083 (the present value of the difference between projected future Medicare expenditures and Medicare revenues over the next 75 years under current Medicare policy) total $89 trillion, with Medicare's Hospital Insurance ("Part A") trust fund projected to be depleted by 2017[31].

Prior studies have estimated that about half of the recent growth in health expenditures is attributable to advances in various forms of health technology, including new pharmaceutical products, surgical procedures, imaging modalities, and biomarkers [31]. While almost all of these new drugs and technologies offer some potential to improve clinical outcomes, they often add to health expenditures. Within the context of unsustainable trends in health care expenditures, a key policy question relates to whether the extent of improvement in outcomes associated with the use of a new technology is attained at a "reasonable" additional cost. Indeed, the value offered by new technologies is being subjected to increasing scrutiny by reimbursement authorities in many health systems worldwide. For example, in the United Kingdom, the National Health Service bases payment policy decisions for new technologies on recommendations from the National Institute for Health and Clinical Excellence (NICE), which in turn are substantially influenced by cost-effectiveness analysis yielding an estimated additional "cost per quality-adjusted life-year (QALY) gained" via use of the new technology. Currently, NICE usually considers technologies offering improved outcomes at a cost less than £20,000 to £30,000 per QALY gained (about $33,000 - $50,000) acceptable, though exceptions are common [32].

We will use a brief and validated instrument, FACT-G, that sums the functional well-being (FWB), physical well-being (PWB), the social/family well-being (S/FWB), and emotional well-being (EMB) to analyze the QOL of patient undergoing the proposed treatment. Weitzner et al. reported FACT-G served as a good psychometric instrument to provide a well-rounded view of the various aspects of QOL from the patient's perspective in 101 patients with primary brain tumors [33]. Additionally, the EuroQol 5D (EQ-5D) will be utilized as a standardized measure of health outcome. EQ-5D provides a simple descriptive profile and a single index value for health status applicable to a wide range of health conditions and treatments. For example, Jakola et al. analyzed the QOL of patient with intracranial glioma before and after surgery [34]. In this study, they measured pre-operative QOL by measuring EQ-5D and reported EQ-5D appeared to be a good outcome measure with a strong correlation to traditional variables while offering a more detailed description of health outcome. The US version of the EQ-5D will be used in this trial, to enable mapping of general HR-QoL scores from EQ-5D scores into health state utility scores (ranging from 0 to 1) for the US population.

Therefore, we propose to collect assess patients' health related quality of life, in order to evaluate the potential non-cancer benefits of SRS in treatment of brain metastases.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

To identify the maximal tolerated doses for single-fraction stereotactic radiosurgery, within 90 days from the date of procedure, in patients with brain metastases who have not undergone prior brain irradiation.

2.2 Secondary Objectives

2.2.1 To evaluate the overall survival (OS), which is defined as the time between date of SRS and the date of death due to any cause.

2.2.2 To evaluate time to progression (TTP), which is defined as the time between date of SRS and date of documented progression. Specific TTP will be determined for the target lesion, non-target lesions, and elsewhere in brain.

2.2.3 To evaluate the local progression rate of the target lesion. Local progression will be defined by MRI imaging according to the modified RECIST 1.1 criteria.

Suspected radiation necrosis and/or psuedoprogression will be similarly evaluated (See section 6.1.4.2).

2.2.4 To evaluate the response rate [35], consisting of complete response (CR) and partial response [36] according to the modified RECIST 1.1.

2.2.5 To measure the improvement in health-related quality of life (HRQoL).

2.2.6 To identify the chronic toxicity for single-fraction stereotactic radiosurgery, after 90 days up to 3 years from the date of procedure, in patients with brain metastases who have not undergone prior brain irradiation.

2.2.7 To perform subgroup analysis of the variables listed above. Subgroups may be defined by age, initial performance status (ECOG), number of metastases (e.g. single, 2-4 and 5-10 lesions), primary tumor histology, tumor volume, target volume receiving 12 Gy (V_{12Gy}[37]), and patients who are treated with whole brain radiotherapy after the protocol.

2.3 Endpoints

2.3.1 Response: Treatment response will be defined according to RECIST 1.1 criteria as > 30% decrease in the size of metastatic lesion.

2.3.2 Death: Death due to any cause, although in this patient population, a large portion is expected to be due to the malignancy [38].

2.3.3 Progression: CNS progression will be specified as 1) target lesion progression, 2) non-target lesion progression, and 3) elsewhere in brain progression. Please see section 6.1.2 for detail. Progression must be verified by another MRI at least 4 weeks apart.

2.3.4 Toxicity: All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria of Adverse Events (CTCAE) version 4.0. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

2.3.5 HRQoL: HRQoL will be measured using FACT-G and EQ-5D questionnaires prior to treatment and at three-month intervals after treatment.

3.0 PATIENT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Biopsy-proven non-hematopoietic malignancy, except for small cell lung cancer, germ cell cancer, or unknown primary tumor.

3.1.2 Radiographic evidence by MRI of brain metastasis. (If patient is unable to tolerate contrast, an MRI without contrast is acceptable)

3.1.3 All brain metastases must be outside the brain stem (midbrain, pons and medulla).

3.1.4 Patient must have 10 or less brain metastases.

3.1.5 The maximum diameter of any lesion must be less than 4.0 cm.

3.1.6 Previous treatment with surgery, radiation, chemotherapy, immunotherapy or any targeted agents are allowed provided that:
3.1.6.1 Systemic therapy was administered ≥ 7 days before SRS
3.1.6.2 Radiation was not to the brain.
3.1.6.3 Surgery to the brain was ≥ 7 days prior to SRS and there remains at least one additional brain metastasis that can be targeted with SRS

3.1.7 Age ≥ 18 years.

3.1.8 ECOG Performance Score of 2 or better.

3.1.9 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of protocol therapy.

3.1.10.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.10 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy, immunotherapy or any targeted therapy within 7 days prior to anticipated SRS treatment date or those planning for systemic therapy within 7 days following the protocol treatment.

3.2.2 Patients had craniotomy and surgery to the brain within 7 days from the date of SRS.

3.2.3 Patients with leptomeningeal metastasis.

3.2.4 Patients with a contraindication to MRI such as implanted metal devices or foreign bodies or severe claustrophobia.

3.2.5 Patients with life expectancy < 3 months.

3.2.6 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia.

3.2.7 Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Patients must not be pregnant at the time of SRS treatment.

4.0 TREATMENT PLAN

4.1 SRS Dose and Technique

4.1.1 SRS Dose

Dose Level	SRS Dose by lesion diameter (Gy)				Number of Patients
	<=1.0cm	>1.0 - 2.0 cm	>2.0 - 3.0 cm	>3.0 - 4.0 cm	
1 (starting)	24	21	18	15	7 to 15
2	27	24	21	18	7 to 15
3	30	27	24	21	7 to 15

Patients with up to 10 brain metastases may be enrolled, but only the largest lesion, labeled as target lesion, will be treated on protocol (see section 6.1.2).

All other lesions will be treated to a dose that is deemed tolerable by the current protocol, based on their sizes.

Example:
A patient with 3 metastases measuring 3.5, 2.5, and 1.5 cm is enrolled. The protocol is currently investigating the 3rd dose level for all cohorts (i.e. 6Gy higher than the starting dose).

Since the 3.5 cm is the largest lesion, the patient will be placed in the treatment cohort examining 3-4 cm lesions, and only the 3.5cm lesion will be treated on protocol (defined as Target lesion) to 21 Gy (the current dose level). The other two smaller lesions (defined as Non-target lesions, see section 6.1.2) will be treated based on their sizes with doses 3Gy less than the current dose level. The 2.5cm lesion will be treated to 21Gy and the 1.5cm lesion will be treated to 24 Gy.

4.1.2 SRS Technique, Pre-SRS Image acquisition and target planning with Conformality Index

Protocol SRS will be administered with a linear accelerator (LINAC), Vero ® (BrainLab, Feldkirchen, Germany), CyberKnife ® (Accuray, Sunnyvale, CA) or Gamma Knife® Perfexion (Elektra Instruments, Inc., Atlanta, GA). Fixed-frame stereotactic localization and planning will be used for SRS.

Pre-SRS Image Acquisition: MRI with gadolinium contrast is the recommended imaging method for stereotactic localization. In the case of LINAC, Vero or CyberKnife, MRI with contrast has to be obtained within 14 days of SRS with an acquisition of <= 1.5 mm slice thickness. The target is the contrast-enhancing tumor as defined on MRI with contrast.

In patients who cannot tolerate the contrast, other MR sequences may be utilized without the contrast, as long as the target lesion can be clearly demarcated for treatment and follow up.

Conformality Index (CI) is derived from dividing the volume encompassed by the prescription isodose line by the target volume.

CI = Rx Isodose Vol / (Target Vol)

The target lesion in the SRS planning MRI will be contoured, and its volume will be calculated. Planning should achieve a conformity index specified below.

Size of Target	Prescription Isodose	Rx Isodose	Conformality Index
<=1cm	≥95% coverage of target	35-100%	≤ 2
1-2cm			≤ 2
2-3cm			≤ 1.5
3-4cm			≤ 1.25

At least 95% of the target volume must receive the prescription dose; the plan should be adjusted to achieve such coverage by the isodose line between 35-100%. No part of the target should receive less than 90% of the prescription dose.

4.1.3 Normal Tissue Dose Constraints

The following table lists maximum dose limits, in one fraction, to a point or volume within several critical structures of the cranium. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation (see section 11.6.2).

Critical Structure and margin	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)***	**Endpoint (≥Grade 3)**
Optic Pathway	<0.2 cc	8 Gy	10 Gy	neuritis
Brainstem (not medulla)	<0.5 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35cc <1.2 cc	10 Gy 8 Gy	14 Gy	myelitis

* “point” defined as 0.035cc or less

Patients with lesions within or near the above structures and the dose constraints cannot be satisfied, will be deemed ineligible and treated off protocol, as described in the Eligibility (see section 3.1.3).

4.1.4 Radiation Therapy Quality Assurance

The principle investigator or his designee will perform an RT Quality Assurance Review after every 15 patients treated and at the end of accrual. A summary report will be generated after each review.

4.2 Pre-therapy Assessment

Pre-therapy assessments will be performed as follows:

- Perform careful history and physical examination.
- Verify the primary tumor histology is a biopsy-proven non-hematopoietic malignancy, except for small cell lung cancer, germ cell cancer, or unknown primary tumor.
- Verify the brain metastases meets the inclusion criteria outlined in section 3.1.2 thru 3.1.5.
- Verify no recent (≤7 days) use of chemotherapeutic or systemic biological agents.
- Verify no recent (≤ 7 days) surgery to the brain.

- Verify age ≥ 18 years.
- Verify ECOG Performance Score of 2 or better.
- Verify patient is not pregnant.
- Verify women of child-bearing potential and men agree to use adequate contraception
- Verify patient is able to understand and the willingness to sign a written informed consent.
- If any of the above criteria does not meet inclusion criteria, postpone SRS as appropriate.

4.3 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (5.3). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0.

The following acute (≤30 days) and subacute (>30 days - <90 days) toxicities attributable to the protocol treatment, as defined in CTCAE v4.0, will be dose limiting toxicities (DLT) of the study.

- Grade 3 or higher Ataxia
- Grade 3 or higher Central Nervous System Necrosis
- Grade 3 or higher Cerebral Edema
- Grade 3 or higher Intracranial Hemorrhage
- Grade 3 or higher Seizure
- Any Grade 4 or 5 toxicities probably or definitely attributable to the protocol treatment.

4.4 Concomitant Medications/Treatments

4.4.1 Benzodiazepine for agitated patients: Short-acting benzodiazepine such as midazolam (Versed) to avoid general discomfort from head frame placement is recommended, at the discretion of treating physicians and surgeons.

All other supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented as concomitant medication.

4.4.2 Anticonvulsants

4.4.3 Antiemetics

4.4.4 Anticoagulants

Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (tests of blood clotting time).

4.4.5 Antibiotics (for infection under control or prophylaxis, see Section 3.2.9)

4.5 Post therapy Assessment

Continue monitoring vital signs until patient is discharged.

4.6 Post therapy Intervention

- Analgesics such as morphine, acetaminophen, or ibuprofen may be administered for headaches at the discretion of treating Radiation Oncologists, experienced Nursing staff and/or Neurosurgeon.
- For patients experiencing severe headaches, unremitting to above pain medications, they should be closely monitored. Corticosteroids such as dexamethasone may be administered at the discretion of attending physicians.

4.7 Duration of Therapy

The SRS administration will typically be completed in one day. Multiple SRS sessions are allowed, as long as all lesions are treated within 14 days. The date of the protocol therapy is the date on which the Target lesion was treated. SRS administration will proceed unless:

- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the stereotactic team.

4.8 Duration of Follow Up

Subjects will be followed up to 1 year or death, whichever occurs first. The follow-up will be every 3 months (+/- I month) from the day of SRS administration with brain MRI and physical exam and toxicity evaluation. . See section 5.0 for details.

4.9 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.4 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

4.10 Subject Replacement

Subjects will be replaced should they be removed, as listed in 5.4, or expire from causes other than Nervous system dysfunction outlined in section 4.3 deemed definitively caused by SRS treated, within 90 days from the day of SRS (i.e. unevaluable patients, Section 5.4.6). Notify the Principal Investigator, and document the reason for study replacement and the date the subject was removed in the Case Report Form.

4.11 Dose Escalation Regimen

For each dose level cohort, a total of seven to fifteen patients will be enrolled. A heuristic dose-escalation scheme will be used in this "therapeutic" phase I trial. If zero or one out of the first seven, two or fewer out of the first nine, three or fewer out of the first twelve, or four or fewer out of the first fifteen of patients with 3-month follow-up experience a dose-limiting toxicity (DLT) as defined in section 4.3, then the dose will escalate to the next dose level. If three or more of the first nine patients, four or more of the first twelve, or five or more of the first fifteen patients experience a DLT, then the maximum tolerated dose (MTD) will be considered to have been exceeded. The phase I portion of this study will be completed when either of the following events occurs: 1) the MTD for a given cohort is reached or 2) when the highest protocol dose level is completed and tolerated. As mentioned above in sections 2.2 and 4.1, each cohort will have maximum of two increments of dose escalation, a 6 Gy increase from the starting dose.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 ***Informed Consent***

5.1.2 ***Medical history***

Complete medical and surgical history, history of infections

5.1.3 ***Demographics***

Age, gender, race, ethnicity

5.1.4 ***Review subject eligibility criteria***

5.1.5 ***Review previous and concomitant medications***

5.1.6 ***Physical exam***

Vital signs (temperature, pulse, respirations, blood pressure), height, weight, neurologic exam

5.1.7 ***Performance status***

Performance status evaluated prior to study entry according to ECOG scale.

5.1.8 ***Adverse event assessment***

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.1.9 ***Serum Creatinine***

5.1.10 ***Pregnancy test (for females of child bearing potential)***

See section 3.1.10.1 for definition.

5.1.11 **Procedures During Treatment**

Not applicable to this protocol.

5.2 Follow-up Procedures

Subject will be followed accordant to 5.3. The following procedures will be performed at each follow up:

- Physical exam, including complete neurological exam, vital signs
- QoL questionnaire
- Toxicity assessment
- MRI of the brain with contrast
- Should the patient experience a decline in his or her kidney function that precludes an MRI with contrast, MRI without contrast using fast field Echo (FFE) sequence will be an acceptable imaging substitute, as long as the size of the brain lesions can be measured accurately.
- Follow up check sheet (see appendix E)

5.3 Time and Events Table

	Pre-study	Treatment of Target Lesion	Month 1-12	

			up to 1 yr. (Every 3 M +/- 1 M up to 1 yr	
Assessment		X		
Informed Consent	X			
History and PE (Complete Neurologic Exam)	X		X	
Tumor Biopsy	X			
Performance Status	X		X	
AE Assessment	X		X	
Toxicity (include DLT) Evaluations		X	X	
Brain MRI *	X	X	X	
Serum Creatinine	X			
Pregnancy Test (if applicable)	X			
QoL Questionnaires	X		X**	
Follow-up Checklist (Appendix E)			X	

*MRI with contrast is preferred, if not possible, MRI without contrast will be accepted as long as the brain lesion can be measured accurately.

**If patients progress in the CNS during the year 1 follow- up, QoL forms may be deferred at physician's discretion.

5.4 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.4.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.4.2 Subject withdraws consent (termination of treatment and follow-up);

5.4.3 Subject is unable to comply with protocol requirements;

5.4.4 Treating physician judges continuation on the study would not be in the subject's best interest;

5.4.5 Lost to follow-up. *Example language: If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.*

5.4.6 Unevaluable.

6.0 Measurement of Effect

6.1 Antitumor Effect

Response and progression will be evaluated in this study based on the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1 [39] with modification, as RECIST criteria do not define lesions smaller than 1 cm in diameter (see section 6.1.4).

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their treatment with the study procedure. Acute (<=30days) and subacute (>30 - <=90days) toxicity will be recorded towards DLT and Chronic (>90days – <1 year) .
Evaluable for objective response. Only those subjects who have received SRS, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to SRS will also be considered evaluable as long as the eligibility criteria outlined in section 3.0. are still satisfied)

6.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those within the brain parenchyma that can be accurately measured of the longest diameter with MRI. All tumor measurements must be recorded in millimeters.

Target lesion. The largest lesion, up to a maximum diameter of 4 cm, is identified as the target lesion and the longest diameter is measured at baseline (i.e. MRI image used for SRS).

Non-target lesions. All other lesions in the brain will be identified as non-target lesions measured at baseline.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements will be done digitally. All baseline evaluations will be performed by the MRI used for the SRS procedure.

Follow up imaging will be MRI with and without contrast. These techniques should be performed with thickness of 5 mm or less. The same method of assessment and the same technique should be used to characterize the target lesion at baseline and during follow-up.

6.1.4 Response Criteria

Each treated lesion, both the target lesion(s) and non-target lesion(s), will be assessed.

6.1.4.1 Evaluation of Target Lesion

Complete Response (CR): Disappearance of the target lesion, determined by two separate MRI scans conducted more than 4 weeks apart. If confirmed, the date of CR is the date of the first imaging study which demonstrated CR.

Partial Response [36]: At least a 30% decrease in the maximum diameter of the target lesion, taking the baseline maximum diameter as the reference. Any PR must be confirmed by a separate imaging more than 4 weeks apart.

Progressive Disease (PD):

For lesions > 1cm in maximum diameter, progression will be defined according to RECIST 1.1 criteria of > 20% increase in the maximum diameter from the nadir, and verified by a second set of imaging more than 4 weeks apart.

For lesions ≤ 1cm in maximum diameter, a minimum increase of 5 mm in the maximum diameter will be necessary to score as progression. This specification is included to account for potential variability in measurement, which will be most susceptible to proportionate errors at smaller sizes.

Progressive disease will be specified as PD-Target Lesion. Any PD must be confirmed by a separate imaging more than 4 weeks apart.

In the case of radiological suspicion of pseudoprogression and/or radionecrosis, additional imaging study will be obtained at the discretion of the treating physician to distinguish treatment effect from PD. If confirmed, the date of pseudoprogression and//or radionecrosis is the date of the first imaging that demonstrated the finding.

Stable Disease (SD): Neither sufficient regression to qualify for PR nor sufficient increase to qualify for PD, taking as reference the nadir diameter since the treatment started.

6.1.4.2 **Evaluation of Non-target Lesions**

Same criteria applied for the Target lesion evaluation as discussed above. Progressive disease will be specified as PD-Non-Target Lesion.

The appearance of one or more new lesions will be classified as PD-elsewhere brain progression.

6.1.4.3 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference the nadir measurement since the treatment started). This evaluation takes into account not only the target lesion but all non-target lesions as well. The best response assignment will depend on the achievement of both measurement and confirmation criteria.

We know from experience that a certain portion of non-target lesions will develop progressive disease. Hence, the standard overall response nomenclature and classification by RECIST1.1 was modified to have an overall (OA) designation, in order to distinguish the response of the target lesion from that of overall intracranial response.

Target Lesion	Non-Target Lesions	New Lesions (elsewhere intracranial)	Overall Response	Best OA Response for this category also requires:
CR	CR	No	OA-CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	OA-PR	≥4 wks. confirmation
PR	Non-PD	No	OA-PR	
SD	Non-PD	No	OA-SD	documented at least once ≥4 wks from baseline
PD	Any	Yes or No	OA-PD	≥4 wks. confirmation
Any	PD	Yes or No	OA-PD	
Any	Any	Yes	OA-PD	

Note: Subjects with a global deterioration of health status without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression.

6.1.5 Response Rate:

Response rate [35] is defined by combining CR and PR of target lesions within the cohort.

6.1.6 Duration of Response

Duration of target lesion response: The duration of target lesion response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that PD is objectively documented (taking as reference for progressive disease the smallest measurements recorded since SRS was delivered).

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for OA-CR or OA-PR (whichever is first recorded) until the first date that PD is objectively documented (taking as reference for progressive disease the smallest measurements recorded since SRS was delivered).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the SRS treatment until the criteria for PD are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.7 Time to Progression

Time to progression (TTP) is defined as the time between the date of SRS and the first date of documented progression. Given the enrolled patients can have progression of non-target lesions or progression elsewhere in the brain, TTP will be measured for all three types of progression (i.e. TTP-Target lesion, TTP-non-target lesion, TTP-elsewhere progression).

6.2 Safety/tolerability

Analyses will be performed for all subjects having received the treatment under the protocol. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html).

6.3 Quality of Life (QoL)

6.3.1 Functional Assessment of Cancer Therapy-General (FACT-G)

Patient-reported functional status will be assessed with subscales of the Functional Assessment of Cancer Therapy-General (FACT-G) (See appendix for form). The FACT-G is a 28-item questionnaire that uses 5-point Likert-type response choices (0 = not at all; 1 = a little bit; 2 =somewhat; 3 = quite a bit; 4 = very much). It will take less than 10 minutes to complete the questionnaire. The Trial Outcome Indices (TOI) will also be utilized to measure the summed functional well-being, physical well-being [40, 41]. A 5-point deterioration in the FACT-G TOI between pre-treatment and at post treatment or at year 1 will be considered clinically significant [42].

Changes in QOL will be analyzed using all available data at baseline, 12, 24, 36 and 48 weeks with semiparametric generalized estimating equations (GEE).

6.3.2 EQ-5D

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete (See appendix for form). The first part consists of 5 items covering 5 dimensions that include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added.

The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score or the cost-utility equation can be used in the quality adjusted survival analysis depending on the health state(s) of interest.

Additionally the EQ 5D is utilized to establish health state utility which is used in cost-effectiveness analysis to calculate quality adjusted life years. This is the recommended health state utility form used in the United Kingdom and approved by the National Institute for Clinical Excellence (NICE) and has been used to establish health state utility. The EQ-5D will also be available in the Spanish language.

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7.0 ADVERSE EVENTS

7.1 Stereotactic Radiosurgery (SRS)

The contraindications and adverse events for SRS are mostly related to the treatment site and its radiation dose tolerance, as discussed in detail in section 4.1.

7.1.1 Contraindications: None.

7.1.2 Special Warnings and Precautions for Use: N/A

7.1.3 Interaction with other medications: None.

7.1.4 Adverse Reactions: Sites-specific. Please see section 4.1.

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to radiation, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study treatment for the changes observed; or
- death.

7.3 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study. Refer to the UTSW IRB website at http://www.utsouthwestern.net/intranet/research/research-administration/irb/study-management/adverse-events.html to determine when a serious adverse event requires reporting to the IRB.

Unanticipated Problems

The term “unanticipated problem” is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) ***AND***
- Definitely, probably, or possibly related to participation in the research ***AND***
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.4 Reporting Requirements for Serious Adverse Events

Local unanticipated problems require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required.

All local serious adverse events which occur on research subjects on protocols for which the SCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events within upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Radiation Oncology Clinical Research Manager at 214-648-1892. UTSW SCC Data Safety Monitoring Committee Coordinator (if fax report is not available) within 2 working days to 214-648-7097.
Written reports to: Lucien A. Nedzi, MD. 2280 Inwood Road Dallas, TX 75390- 9303 FAX: 214-645-8526

UTSW SCC Data Safety Monitoring Committee Coordinator
Email: SCCDSMC@utsouthwestern.edu
Fax: 214-648-7018 or deliver to NB 2.418

UTSW Institutional Review Board (IRB)
Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs

Local serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems

Local unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.

Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.5 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.6 Phase I Waiting Periods

Dose escalation on the phase I portion of this study should not occur until a sufficient waiting period has occurred after patients have been treated. A period of 90 days must pass in order to assess toxicity. If 90 days have transpired without DLT in each of the first seven (7) patients enrolled to a specific dose level, then dose escalation to the next level may proceed. Patients will continue to be enrolled to each dose level (up to a maximum of 15 patients) with ongoing assessment of those reaching 90 day follow-up so long as either criteria for defining the MTD or criteria for further dose escalation is not reached. If fifteen patients are enrolled to a given dose level yet criteria for adequate follow-up are not reached in a representative sample of patients, further enrollment to the protocol will be suspended until adequate follow-up is reached. Patients deemed non-evaluable for toxicity will be replaced by new patients in order to meet preceding criteria.

7.7 Stopping Rules

The phase I study is designed to end if the rate of DLTs within 90 days from the start of treatment is 33% or higher. For each dose level cohort, a total of seven to fifteen patients will be enrolled. If zero or one out of the first seven, two or fewer out of the first nine, three or fewer out of the first twelve, or four or fewer out of the first fifteen of patients, with 90 day follow-up experience a DLT as defined above, then the dose will escalate to the next level. If three or more of the first nine patients, four or more of the first twelve, or five or more of the first fifteen patients experience a DLT, then the MTD will be considered to have been exceeded. The MTD will be defined as the immediately previous lower dose level.

8.0 DRUG INFORMATION

Not applicable to this trial.

9.0 CORRELATIVES STUDIES- QUALITY OF LIFE

The study design is to prospectively analyze the Health related Quality of Life (HRQOL) among patients with brain metastases treated with SRS. While increased dose of SRS is hypothesized to yield greater tumor cell kill, it may also increase the normal tissue toxicity, in which case there may be a decrease in HRQOL. Prior studies have demonstrated that the most sensitive and clinically meaningful method for accurately capturing the normal tissue toxicities is via patients reported outcomes (PROs), such as HRQOL.

9.1 Health-Related Quality of Life (HRQOL) Analysis

In this non-randomized trial, we plan to assess the FACT-G at specific time points to minimize patient burden: baseline (pretreatment) and at subsequent follow ups (Please see section 6.4 and Appendix). In order to analyze the QOL, we plan to use a brief, validated instrument that is user friendly and has clinical relevance [33]. FACT-G is a measure that sums the functional well-being (FWB), physical well-being (PWB), the social/family well-being (S/FWB), and emotional well-being (EMB).

In addition, the EQ-5D will be utilized. EQ-5D is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The US version of the EQ-5D will be used, to enable mapping of general HR-QoL scores from EQ-5D scores into health state utility scores (ranging from 0 to 1) for the US population. These utility scores are needed for cost-utility analysis (estimates of costs per “quality adjusted” life-year gained) [43, 44]

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

The primary endpoint of the phase I portion is to either reach the maximum tolerated dose (MTD) or a dose of 30, 27, 24 or 21 Gy total for lesions measuring <=1cm, >1.0 - 2cm, >2.0 – 3.ocm, > 3.0 – 4.0 cm respectively, (whichever comes first) by escalating the dose of radiation beyond palliative doses toward tumoricidal doses. Patients will be treated in cohorts of seven to fifteen. The secondary end points include OS, RR and quality of life (Please see endpoint details in section 2; stopping rules in section 7.5.)

Toxicity will be graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v. 4.0. A dose-limiting toxicity (DLT) is a grade 3 or worse toxicity, listed in section 4.3, or any grade 4 or 5 toxicity deemed definitely attributable to the therapy. All reported DLTs will be verified by study chair, data monitoring committee, and, as appropriate, independent review before final determination that a DLT has in fact occurred. Doses will be escalated an additional 3 Gy per treatment for 1 SRS treatment (3 Gy per increment, maximum 6 Gy escalation per treatment cohort). The phase I portion of the study will be completed when either of the following events occurs: 1) the MTD for a cohort is reached or 2) when the highest protocol dose level is treated and tolerated (3 Gy per increment, maximum 6 Gy escalation per cohort).

10.2 A “Therapeutic” Phase I Trial

Most (not all) oncology-related drug discovery phase I trials are non-therapeutic. In fact, the drug being studied has often never been used in humans or for the stated indication. Therefore, the dose used may be wholly ineffective at providing efficacy to the patient. Second, the typical drug discovery phase I trial focuses primarily on toxicity dose response, with no formal plan to evaluate efficacy. In this context, it is assumed that the optimal dose will be the maximum tolerated dose. Neither assumption is true for the radiotherapy used in this phase I trial. Since radiotherapy is well known to provide efficacy, even the starting dose of this trial, this phase I trial is a therapeutic trial. What’s more, the maximum tolerated dose may or may not be the most ideal dose balancing benefit and toxicity with the widest therapeutic window. While the primary endpoint and statistical design focuses on toxicity, efficacy information regarding tumor response/control will be collected (see below).

10.3 Phase I Dose Escalation

The phase I study is designed to end if the rate of DLTs within 90 days from the start of treatment is greater than 33%. A heuristic dose-escalation scheme will be used in this “therapeutic” phase I trial. For each dose level cohort, a total of seven to fifteen patients will be enrolled. If zero or one out of the first seven, two or fewer out of the first nine, three or fewer out of the first twelve, or four or fewer out of the first fifteen, of patients with 90 day follow-up experience a DLT as defined above, then the dose will escalate to the next dose level. If four or more of the first nine patients, five or more of the first twelve, or six or more of the first fifteen patients experience a DLT, then the MTD will be considered to have been exceeded. The MTD will be defined as the immediately previous dose level tolerated.

The study aims to improve the toxicity determination as well as afford some evaluation of efficacy. 15 patients would distinguish a 1 standard error difference in means of two dose levels with 90% power at a one-sided 10% significance level[45].

The sample size of the phase I component of this study will not exceed 180 patients. An accrual rate of 4 patients per month is anticipated; the sample size of this study will not exceed 180 patients (4 tumor size cohorts x 3 dose levels x 7-15 patients per cohort). It is expected that it will take approximately three years to complete this study.

10.4 Data Analysis Plans

Interim Reports: Interim reports will be prepared every six months until the results of the study are published. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, and the frequencies and severity of toxicity.

The dose-limiting toxicity (DLT) and the maximum tolerable dosage (MTD) will be determined based on this Phase I design. The assessment of safety will be mainly based on the frequency of adverse events. The incidence of AEs together with the 95% confidence interval will be reported. The overall complete response rate and corresponding 95% confidence interval will be presented. Various survival rates will be described using Kaplan-Meier curves.
HR-QOL data will be used only for descriptive secondary analysis given the phase I nature of this protocol. No formal statistical test will be performed and hence no multiplicity adjustment will be applied. Descriptive statistics will be primarily used to summarize the scored scales. The 5-item index score from EQ-5D is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score or the cost-utility equation can be used in the quality adjusted survival analysis depending on the health state(s) of interest.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient’s participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

Not applicable for this protocol.

11.4 Registration Procedures

All subjects must be registered with the Clinical Research Office, Department of Radiation Oncology, UTSW, before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Clinical research office Study Coordinator. To register a subject, call 214-633-1753 Monday through Friday, 9:00AM-5:00PM.

11.5 Data Management and Monitoring/Auditing

The UTSW Simmons Cancer Center (SCC) Data and Safety Monitoring Committee (DSMC) is the DSMC of record and responsible for overall monitoring of data quality and patient safety. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The Quality Assurance activity of the SCC DSMC provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance based on risk.

Quality assurance audits of participating sites will be performed at a minimum of once a year by the Department of Radiation Oncology Clinical Research Office, UTSW. More frequent audits may be performed based on higher accrual or issues related to previous research conduct or data quality. These site audits may be performed electronically, by report evaluation, or even on-site.

The SCC-DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it is the DSMC of record. The Quality Assurance and Education Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the patient population to be studied; adequacy of the data management system; and procedures to ensure the safety of study subjects based on the associated risks of the study. The Department of Radiation Oncology Clinical Research Office, UTSW, meets monthly to review adverse events for this protocol observed within the institution as well as all participating sites with evaluations that include attribution. This information is forwarded to the SCC-DSMC as a resource for its determinations.

The Radiation Oncology Clinical Research Office (CRO) reports serious adverse events (SAEs) to Radiation Oncology Safety Assurance Committee (ROSAC) monthly. The principal investigator and study coordinator will review the SAEs on a real time basis via email or meeting. These SAEs are also reported to the University of Texas Southwestern Medical Center (UTSW) IRB per IRB guidelines and SCC DSMC.

All clinical trials are reviewed on monthly basis for enrollment. A summary of adverse events will also be reviewed at the time of SAEs review during the monthly ROSAC meeting. For investigator-initiated trials, all SAEs are monitored – both local and at affiliated institutions.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 **Emergency Modifications**

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

11.6.2 **Other Protocol Deviations/Violations**

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to principal investigator. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

13.1 Appendix A: ECOG Performance Status

ECOG/ZUBROD PERFORMANCE SCALE

0	*Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).*
1	*Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).*
2	*Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).*
3	*Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).*
4	*Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).*
5	*Death (Karnofsky 0).*

13.2 Appendix B: US EQ-5D-3L



Health Questionnaire

English version for the US

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

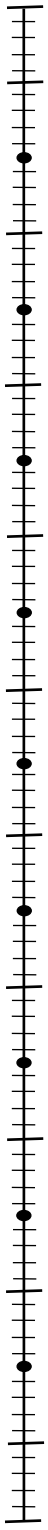
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Best imaginable health state



0

Worst imaginable health state

13.3 Appendix C: FACT-G

Below is a list of statements that other people with your illness have said are important. **Please circl or mark one number per line to indicate your response as it applies to 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 mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to 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

13.4 Appendix E: SRS Dose Escalation Study Follow Up Check Sheet

Patient Name: **MRN:**
Date of Evaluation:

Treatment:

Total number of lesions treated	
Size Cohort (e.g. 0-1, 1-2, 2-3, or 3-4cm)	
Maximum diameter of target lesion	
Dose cohort (Gy)	

Toxicity: Grade 1: Asymptomatic Grade 2: moderate, requires outpatient care (example: steroids) Grade 3: severe, requires medical intervention, Grade 4: life threatening, Grade 5: death

Is there a grade 3 or 4 toxicity?	Yes	No			
If yes, specify the symptom and severity					
Is this attributable to protocol therapy?	Definitely	Possibly	Plausible	Unlikely	Not related

Response:

Date of MRI: _____
Maximum diameter of the target lesion: _____

- Partial response (PR): > 30% reduction in the maximum diameter.

- Progressive Disease (PD): > 20% increase in the maximum diameter (for lesions that are smaller than 1cm: minimum of 5mm increase)

Target lesion response	CR	PR	SD	PD
Non-target lesions response	CR	PR	SD	PD
Overall Response	CR	PR	SD	PD

New elsewhere lesion(s)	Yes	No

If yes,

How many new lesions in addition to baseline?	n=	Too many to count	
Is there a plan for salvage therapy?	Yes	No	Unknown
Salvage modality? (planned or performed)	SRS	WBRT	Surgery