Pre-operative Stereotactic Radiosurgery Followed by Resection for Brain Metastases

Phase II Study Determining the Efficacy of Pre-operative Stereotactic Radiosurgery Followed by Resection for Brain Metastases (HCC 14-150) (Version dated 04-07-2021)

NCT02514915

Principal Investigator: Christopher T. Wilke, MD, PhD
Mary Hillman Jennings Radiation Oncology Center
at UPMC Shadyside
5230 Centre Avenue
Pittsburgh, PA 15232
siddiquza@upmc.edu
Ph: (412) 623-7070

Version Date: 11/28/2022

TABLE OF CONTENTS

List of Abbreviations

3D CRT	3 Dimension Conformal External Beam Radiation Therapy
5-FU	5-fluorouracil
AE	Adverse Event
BSA	Body Surface Area
CAPEOX	Capecitabine plus Oxaliplatin
CMR	Complete Metabolic Response
CR	Complete Response
CS	Clinical Stage
CT Scan	Computed Tomography Scan
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Treatment Volume
CXR	Chest X-Ray
DSMC	Data Safety Monitoring Committee
DVH	Dose Volume Histogram
EB	External Beam
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
EGD	Esophagogastroduodenoscopy
EQD	Equivalent Dose
EUS	Endoscopic Ultrasound
FACT-G	Functional Assessment of Cancer Therapy - General
FDG-PET/CT	[18F]-flourodeoxyglucose Positron Emissions Tomography / Computed Tomography
FHSI	FACT-Hepatobiliary Symptom Index
FNA	Fine Needle Aspirate
Fx	Fraction
GEMCAP	Gemcitabine and Capecitabine
GEMOX	Gemcitabine and Oxaliplatin
GERCOR	European Groupe Cooperateur Multidisciplinaire en Oncologie
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GITSG	Gastrointestinal Tumor Study Group
GTVc	Gross Tumor Volume on CT
GTVp	Gross Tumor Volume on PET
GU	Genitourinary
Gy	Gray
HCC	Hepatocellular Carcinoma
HDR	High-Dose Rate
IMRT	Intensity Modulated Radiotherapy
INR	International Normalized Ratio
IORT	Intraoperative Radiation Therapy
IR	Intermediate Risk
IV	Intravenous
LDR	Low-Dose Rate

LFT	Liver Function Test
LINAC	Linear Accelerator
LPFS	Local Progression-Free Survival
MD	Maximum Dose
MLC	Multi-Leaf Collimation
MRI	Magnetic Resonance Imaging
MV	Mega Voltage
NCI	National Cancer Institute
NCR	Near Complete Response
OESM	Ordered Subset Expectation Maximization
OS	Overall Survival
PD	Prescription Dose
PD	Progressive Disease
PE	Physical Exam
PET/CT	Positron Emissions Tomography / Computed Tomography
PIV	Prescription Isodose Volume
PIV/TV	Prescription Isodose Volume/Tumor Volume
PMD	Progressive Metabolic Disease
PMR	Partial Metabolic Response
PO	By mouth
PR	Partial Response
PTV	Planning Target Volume
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RPM	Real-time Position Management
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SD	Stable Disease
SBRT	Stereotactic Body Radiotherapy
SMA	Superior Mesenteric Artery
SMD	Stable Metabolic Disease
SMS	Short Metal Stent
SMV/PV	Superior Mesenteric Vein / Portal Vein
SUV	Standard Uptake Value
TTP	Time to Progression
TV	Tumor Volume
WOOCBP	Women of Child-Bearing Potential

PROTOCOL SUMMARY

Title

Pre-operative Stereotactic Radiosurgery Followed by Resection for Brain Metastases Phase II Study Determining the Efficacy of Pre-operative Stereotactic Radiosurgery Followed by Resection for Brain Metastases

Objectives

The *primary* objective of this study is to determine the efficacy of giving pre-operative radiosurgery to patients pending resection of a brain metastasis.

The *secondary* objectives of this study are:

1. To evaluate overall survival (OS)
2. To evaluate distant intracranial failure associated with this therapy.
3. To evaluate the Health Related Quality of Life (HRQL) associated with this therapy.

The *exploratory* objectives of this study are:

1. To collect and store the resected body tissue(s) and blood samples for potential correlation to clinical outcome.

Patient population

In order to be eligible for this study, patients must have an extra-cranial primary tumor diagnosis and no more than 4 distinct lesions within the brain. Patients mut be at least 18 years of age and able to give informed consent. They must have a Karnofsky Performance Status ≥ 50 and a life expectancy of at least 12 weeks.

Number of patients

24

Study design and methodology

This is a prospective single-arm phase II study. The treatment schema detail is in Section 6.3.

Treatment administered

Patients will receive a single fraction pre-operative stereotactic radiosurgery radiation dose. The dose will be determined by the diameter of the tumor.

Efficacy data collected

The following evaluations will be performed to assess the efficacy of preoperative stereotactic radiation therapy:

- Objective local control rate measuring tumor volume
- Health Related Quality of Life assessment using the Functional Assessment of Cancer Therapy – Brain (FACT-Br) tool.

Safety data collected

The following evaluations will be conducted to assess the safety of radiosurgery:

- Recording of all toxicity data per NCI CTCAE version 4.0

1.0 BACKGROUND

1.1 Brain metastases and whole brain radiation therapy
Brain metastases are a frequent cause of morbidity and mortality representing the most common intracranial tumor in adults, affecting upwards of 30-40% of all cancer patients [1-3]. There exist multiple treatment options for patients with brain metastases including: whole brain radiation therapy (WBRT), surgical resection, and stereotactic radiosurgery (SRS) [4-9]. Without treatment the prognosis is often poor, with survival limited to only a few months [10].

The mainstay of treatment for brain metastases has been WBRT, which has been used for decades and is thus well studied. The use of WBRT for patients with brain metastases from various primary cancers has been shown to improve both existing neurologic symptoms and overall survival compared to corticosteroids and supportive care (median survival = 4-5 months) [11]. Unfortunately, the use of WBRT is associated with neurotoxicity and neurocognitive decline, especially in long-term survivors [12].

Surgical resection has been typically reserved for patients with good performance status, limited intracranial disease, isolated symptomatic lesions, and lesions resistant to WBRT [13, 14]. For patients with a solitary accessible lesion, surgical resection has been shown to be an effective primary treatment approach that is able to relieve mass effect and improve survival [14]. However, the limitation of surgical resection alone as a treatment modality is associated with high rates of local failure [8]. Interestingly, the benefit of WBRT as an adjuvant treatment post-surgical resection has been established. WBRT alone has been compared to surgery followed by WBRT and several studies have shown both improved local control (LC) and reduced neurological death with the latter approach [15-17].

1.2 Sterotatic radiation surgery (SRS)
In more recent years, SRS has been shown to be an effective alternative therapy for patients with brain metastases. It is especially useful in patients with progression of disease following WBRT, for whom treatment-related neurotoxicity is a major concern. SRS enables the delivery of a highly focused radiation dose to a small target with rapid fall-off, thereby limiting radiation to the surrounding normal brain tissue. This feature should potentially reduce the likelihood of developing late neurocognitive deficits, an issue that becomes an increasing concern in long-term survivors. SRS has even emerged as a treatment strategy to limit WBRT and has been studied in the setting of brain metastasis. SRS has been investigated in postoperative management of solitary brain metastases. At least a dozen retrospective reports have been published describing the results of adjuvant SRS. The reported 1-year local control rates is variable and has been found to be as low as 35% and as high as 100% [18, 19]. Review of UPMC's institutional experience showed 6-month and 1-year LC of 76% and 76% respectively, which is consistent with most other reports [20].

However, delivery of postoperative SRS is particularly challenging due to the nebulous appearance of the tumor bed after resection. This difficulty of delineating the margins of the resection cavity may be responsible for the rate of local failure (LF) despite the utilization of adjuvant therapy and lead to additional symptomatic brain necrosis. A commonly employed strategy to improve LC with adjuvant SRS is the addition of a margin to account for target uncertainty and microscopic extension of disease. The Stanford University group reported a significant improvement in (LF) rates with the addition of a 2-mm margin (1-year LF: 3% vs. 16%) without an associated increase in toxicity [21]. In contrast, a French group has reported an experience of delivering SRS with a 2-mm margin and reported no improvement in 1-year LC (69% vs. 72%) and an increased rate of severe parenchymal complications [22].

In addition to localizing the tumor bed, another potential negative consequence to the sequence of postoperative SRS is the time course between resection and radiation treatment. Typically SRS is performed several weeks after surgical removal of brain metastases. During this interval, the tumor bed is given additional time and may have a detrimental impact on LC.

For these reasons, once a patient has been deemed a candidate for surgical resection of a brain metastasis, it is generally accepted that radiation of some form must be given to facilitate local control. For patients with a symptomatic or sizable brain metastasis that requires surgical resection, one option is to perform radiosurgery up front, followed by surgical removal of the tumor.

1.3 Pre-operative SRS

For patients who require surgical removal of a brain metastasis, we hypothesize a more sensible strategy to improve LC may be the delivery of pre-operative SRS followed by immediate tumor resection. Pre-operative target delineation is likely to be more accurate and result in fewer marginal misses. Furthermore, this treatment package could be completed more expeditiously by eliminating the prolonged interval from surgery to SRS. In our experience, this interval was approximately 5 weeks. In addition, the same MRI scan could be used for SRS and surgical resection; resulting in cost savings for patients who otherwise would receive two separate MRI scans for treatment. Finally, pre-operative SRS may facilitate better resection margins by the delivery of dose in the radiation penumbra surrounding the tumor. An early study of pre-operative SRS on brain metastases by Stuart Burri et al., 2010 demonstrated actuarial LC of 97.7%, 84.6%, and 64.0% at six, twelve, and twenty four months, respectively [23]. More recently according to the interim analysis from a phase 1 study of pre-operative SRS for brain metastases by the University of Alabama, pre-operative SRS appears safe with low rates of wound complications or acute grade toxicity along with target volume reduction of 39% [24]. We therefore propose a phase II clinical trial to further investigate the efficacy of this novel approach.

2.0 OBJECTIVES

Primary

2.1 To determine the efficacy of giving pre-operative radiosurgery to patients pending resection of a brain metastasis. The primary outcome will be measured by local control rate; that is, the tumor volume as measured at a later date and compared to the tumor volume at the start of radiotherapy (time frame: up to 3 years).

Secondary

The *secondary* objectives of this study are:

2.2 To determine the overall survival (OS) as measured by the length of time after the beginning of treatment that diagnosed patient remains alive.

2.3 To evaluate distant intracranial failure associated with this therapy as measured by the presence of new brain metastatses identified via magnetic resonance image. The imaging will be conducted every 3 months for 12 months, then every 4 months for up to 3 years.

2.4 To measure Health Related Quality of Life (HRQL) in patients with primary brain tumors treated with stereotactic radiosurgery using the Functional Assessment of Cancer Therapy-Brain assessment tool for up to 3 years.

The *exploratory* objective of this study is:

To collect and store the resected body tissue(s) and blood samples for potential correlation to clinical outcome.

3.0 INVESTIGATIONAL PLAN

3.1 Overall design and plan of the study
Detailed visit-by-visit study procedures and a study flow chart are provided in Section 6.3. Prior to enrollment, all subjects will be evaluated with physical examination, histologic confirmation and baseline imaging to establish the size and location of the brain metastatic lesions. Patients will receive a single SRS radiation dose and then followed periodically for up until 3 years.

3.2 Screening procedures
- Complete physical evaluation with a performance status, vital signs, height, and weight, and a complete medical history.
- CT (computed tomography) Scan of the brain
- MRI (Magnetic Resonance Imaging) Scan of the brain
- For women of childbearing potential, i.e., females who are not at least 1 year postmenopausal or who have not undergone a surgical sterilization procedure, a urine pregnancy test will be done. If this comes back positive or questionable, a serum pregnancy test will be completed by taking a small sample (about 1 teaspoonful) of blood. Pregnant women, or women who are currently breast-feeding an infant, will not be allowed to take part in this study.

3.3 Personnel performing the procedures
All procedures will be performed by appropriate certified medical personnel, including but not limited to physicians, nurses, technologists and research staff. Potential candidates for the study will be identified by Dr. Amankulor based on his clinical judgment of a need for resection of a presumed brain metastasis. Potential research subjects will be sent to radiation oncology co-investigators for possible enrollment, and pre-operative SRS.

3.4 Location and duration of procedures
All study visits will take place on an outpatient basis in the UPMC Shadyside Radiation Oncology Department. However, it is possible that a subject may be an inpatient at the time of diagnosis. The duration of study visits will vary dependent on the procedures to be completed during that study time-point. We expect for visits to last between 1-4 hours.

3.5 Timeline of study procedures
Once eligible by screening, stereotactic radiosurgery will take place, 1-7 days later, there will be a surgical removal of the tumor. Monitoring will take place 10-14 days after surgery, every 3 months for the first year and every 4 months thereafter.

3.6 Research Activities

3.6.1 Pretreatment Evaluation
The following tests/procedures will be performed in order to ascertain subject eligibility within 28 days prior to registration unless otherwise specified.

- Complete physical evaluation with a performance status, vital signs, height, and weight, and a complete medical history.
- CT (computed tomography) scan of the brain

- MRI (Magnetic Resonance Imaging) Scan of the brain
- For women of child bearing potential, a urine pregnancy test will be done. If this come back positive or questionable, a serum pregnancy test will be completed by taking a smal sample (about 1 teaspoonful) of blood. Pregnant women, or women who are currently breast-feeding an infant, will not be allowed to take part in this study.
- Pretreatment blood sample for research bank if patient agrees.

In addition to the procedures listed above, the following Quality of Life questionnaire will be done for research purposes:

- FACT – BR (FACT – BRAIN) - This assessment will take approximately 5 (five) minutes to complete.

3.6.2 Evaluation during treatment
Administration of stereotactic radio surgery:

Patients will receive a single fraction pre-operative SRS radiation dose. The dose will be determined depending on diameter of the tumor as follows: 24 Gy, 18 Gy, and 15 Gy for tumors < 21 mm, 21-30 mm, and 31-40 mm in maximum diameter respectively.

Dose	Diameter
15 Gy	31-40 mm
18 Gy	21-30 mm
24 Gy	< 21mm

Tumor tissue collection only if participant agrees and there is leftover from clinical collection.

Blood sample collection pre and post SRS treatment (within 24 hours)

Complete physical evaluation with a performance status, vital signs, height, and weight, and a complete medical history

3.7 Surgical removal
One to seven days after the single SRS, patient will then be prepared for surgical removal of the tumor that was designated by surgeon as part of normal standard of care for dominant brain metastasis. Only the symptomatic tumor will be removed surgically. Surgery will be performed at Shadyside Hospital.

3.8 Follow-up procedures
Standard care procedures will be performed and assessed 10-14 days post-surgery. These include:

- Complete physical evaluation with a performance status (a measure of how well you carry on daily activities), vital signs (blood pressure, temperature, heart rate, respiration rate), height, and weight, and a complete medical history.
  MRI (magnetic resonance imaging).
- Scan of the brain will be performed every 3 months after your surgical procedure. If additional brain metastases are detected on one of your follow up scans, then they will be treated as per standard of care, likely using either additional SRS or whole brain radiation.

In addition, patient will be asked to complete a health-related quality of life assessment at each visit. The assessment is for research purposes and will take approximately 5 (five) minutes to complete.

2.5 SUBJECT SELECTION AND ELIGIBILITY

4.1 Selection of subjects
Enrollment is defined as the first day of protocol therapy.

Patients enrolled in this study must have a measurable brain metastasis which is defined as lesions that can be accurately measured in at least one dimension: [longest diameter to be recorded] on the MRI scan. Patients will have no more than 4 distinct lesions within the brain. The target lesion must measure at least 15mm in at least one dimension and no more than 40mm in any dimension.

4.2. Screening and sample size
50 patients will be screened with an expectation that 24 patients will proceed to study protocol. Patients will not be excluded based upon gender nor ethnicity. This study will be limited to adults, in whom stereotactic radiosurgery is a common treatment modality used in the management of brain metastases. Brain metastases are less frequent in children and when they do occur are often represented by histologies with an increased sensitivity to radiotherapy and would have drastic differences in clinical outcome. Research with children under the age of 18 is conducted at Children's Hospital of UPMC.

4.2.2 Justification of sample size/accrual rate
No more than 24 evaluable patients will be treated in the trial. This study of 24 patients will have 80% power to detect a difference in postulated local tumor control of 85% to a known inference local tumor control set at 60% to be excluded, using a 1-sided test with Type I error rate of 0.05 for 6, 12, and 24 months. The sample size was estimated using a non-inferior power analysis for inference of a single proportion compared to a known proportion. Also, an attrition rate of 20% was included into the estimated sample size. Based on previous efforts in recruiting patients at the University of Pittsburgh Cancer Institute, it is anticipated that at least 5 patients per year will be enrolled in the protocol and the accrual will be completed within 5 years. An evaluable patient is defined as one who completes a single fractions of preoperative SRS followed by surgical resection of appropriate brain metastases. Patients who are not evaluable will be replaced.

4.3 Identification and initiation of contact with study participants
Potential research subjects are first identified by their neurosurgeon (Dr. Amankulor). These patients will be deemed as candidates for surgical resection of their brain metastasis, either because of regional mass effect (i.e. pressure on other brain structures) or neurologic symptoms/signs related to the tumor (e.g. weakness, visual disturbance, gait dysfunction, seizures, speech disorder). Once a potential subject has been set up for surgical resection of a brain metastasis by Dr. Engh or Dr. Amankulor, they will then be referred to radiation oncology for discussion of the clinical trial and potential up front SRS. "Cold-calling" will not be used to recruit subjects. "Finder's fees" for referring a potential subject for participation in a research study are prohibited.

Physicians and other health care professionals in the area are aware of active studies at the Department of Radiation Oncology at UPMC by means of various publications including the

World Wide Web. Such publication and Web listings are not advertisements for specific studies. Rather, they are public listings of trials available.

Once a subject is identified as a potential participant in a research study as indicated above, he/she is screened for eligibility. No identifiable information (e.g. name, diagnosis, treatment, etc.) will be released until the subject has given written authorization. No research-related procedures (including review of the subject's medical records) will be performed until the subject has provided written informed consent. The consent process will be carried out as a joint effort among the subject's physicians, the study coordinators, and a physician who is listed as an investigator on the study.

4.4 Inclusion criteria

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

a. Male or female patients ≥ 18 years of age
b. A life expectancy of at least 12 weeks with a Karnofsky performance status of at least 50 (Appendix I)
c. Patient has no contraindications to MRI scanning with intravenous contrast.
d. MRI scan consistent with brain metastasis as per radiology report.
e. The target lesion must measure at least 15 mm in at least one dimension, and no more than 4 cm in any dimension.
f. Patients must have an extra-cranial primary tumor diagnosis.
g. Patients will have no more than 4 distinct lesions within the brain. At least 1 lesion has been recommended for surgical removal based on size, symptomology, or regional mass effect on the brain.
h. The additional lesions will each be treated with stereotactic radiosurgery.
i. Patients with a documented symptomatic lesion size smaller than 3cm requiring clinical surgical resection
j. Must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks and discomforts.
k. Signed consent

4.5.1 Exclusion criteria

Subjects meeting any one of the following exclusion criteria are not to be enrolled in the study:

a. Primary tumor histology of lymphoma, leukemia, multiple myeloma or germ cell tumor.
b. Moribund status or status epilepticus.
c. Supratentorial mass effect with greater than 5 mm of midline shift or hydrocephalus.
d. Infratentorial mass effect with fourth ventricle effacement or hydrocephalus.
e. More than four additional diagnosed brain metastases.
f. Contraindication to general anesthesia.
g. Adjacent tumor location to optic apparatus or brainstem, precluding achievement of meaningful dose with SRS.
h. Primary brain tumor.
i. Contraindication to MRI scans or intravenous contrast.

j. Pregnant and breast-feeding females.

4.5.2 Specific criteria to exclude pregnant females and feta/neonatal exposure
For all females who are not at least one year post-menopausal or who have not undergone a surgical sterilization procedure, a urine pregnancy test will be done. If this is positive or questionable a serum pregnancy test will be done. The results of the pregnancy test must be negative in order for the patient to participate in this study.

Women who are pregnant or breastfeeding are excluded from participation in this study. All females of childbearing potential must have a serum pregnancy test within 14 days of the radiation. The results of the pregnancy test must be negative for the patient to participate in this study.

Subjects will be informed by the study staff that is extremely important that they not become pregnant or father a baby while participating in this study, and that avoiding sexual activity is the only certain method of preventing pregnancy. However, if a subject chooses to be sexually active, he or she must agree to use an appropriate "double barrier" method of birth control starting from the subject's participation in the screening process and continuing until two weeks following the subject's participation in the study. Birth control methods can include intrauterine device (IUD), contraceptive sponge and spermicide, in addition to male use of a condom, or the female should be using prescribed birth control implant. Subjects will be instructed to notify the study doctor of their birth control method prior to the start of the study, and also if they plan to change their birth control method.

Subjects that choose to be sexually active must be made aware that even with the use of birth control measures, pregnancy could still result. Subjects will be informed that if they become pregnant or impregnate a woman while taking part in this study, they must immediately notify one of the doctors listed on the consent form.

The information listed above will be relayed to applicable subjects by the study staff. If will also be listed in the consent form, a copy of which will be provided to the patients for them to take home.

5.0 TREATMENT EVALUATION, ADMINISTRATION, AND MODIFICATION

5.1 Tissue constraints
Treatment shall be delivered via linear accelerator (LINAC) commissioned and equipped to deliver stereotactic radiosurgery. Normal tissues and sensitive critical structures (e.g. spinal cord, brainstem, optic nerves, optic chiasm, and pituitary) shall be contoured and the dose to these organs limited. Normal tissue constraints are outlined below.

Normal Tissue Constraints:
Organ Maximum Dose in 1 Fractions
Brain V12 <5-10 cc Dose/Volume
Spinal Cord <13 Gy
Brainstem <12.5 Gy
Optic Nerves <12 Gy
Optic Chiasm <12 Gy
Pituitary <20 Gy
Cochlea <14 Gy Dose/Volume

Normal Tissue Constraints	
Organ	Maximum Dose in 1 Fraction
Brain V12	<5-10 cc Dose / Volume
Spinal Cord	< 13 Gy
Brainstem	<12.5 Gy
Optic Nerves	<12 Gy
Optic Chiasm	<12 Gy
Pituitary	<20 Gy
Cochlea	<14 Gy Dose / Volume

5.2 Dose Specification, Homogeneity Considerations & Plan Evaluation
The treatment plan used shall be based on the assessment of the dose-volume histogram (DVH) with attention to coverage of the planning tumor volume (PTV) and critical normal structures.

The prescription dose is the isodose cloud that encompasses at least 80% of the PTV.
No more than 20% of any PTV shall receive doses >110% of its prescribed dose.
No more than 2% of any PTV shall receive <93% of its prescribed dose.
No more than 5% of any normal tissue shall receive doses in excess of 110% of the primary PTV dose.

5.3 Follow-up procedures

Patients will be seen in follow-up 10-14 days post treatment then every 3 months for 12 months, then every 4 months up until 3 years, with the following evaluations:

- Complete physical evaluation with a performance status, vital signs, height, and weight, and a complete medical history
- MRI scans at 3 months post-treatment and every 3 months for 12 months, then every 4 months up until 3 years for assessment of response to therapy and

6.0 STUDY EVALUATION

6.1 Pre-research screening
After signing consent form, participant will undergo the following screening tests and/or procedures (some may not have to be repeated if they were recently performed as part of standard of care):

- Complete physical evaluation with a performance status (a measure of how well you carry on daily activities), vital signs (blood pressure, temperature, heart rate, respiration rate), height, and weight, and a complete medical history.
- CT (computed tomography) Scan of the brain (an imaging test that takes many xrays from different angles to form images of the brain).
- MRI (Magnetic Resonance Imaging) Scan of the brain (an imaging test that uses no radiation, but rather a magnetic field to create high detailed images of the brain)
- For women of who are not at least one year post-menopausal or who have not undergone a surgical sterilization procedure, a urine pregnancy test will be done. If this comes back positive or questionable, a serum pregnancy test will be completed by taking a small sample (about 1 teaspoonful) of blood from a vein in the arm for a pregnancy test. Pregnant women, or women who are currently breast-feeding an infant, will not be allowed to take part in this study.
- A health-related quality of life assessment for research purposes. This assessment will take approximately 5 (five) minutes to complete.

6.2 Ending subject's participation in the study
A subject's participation in the study will be halted if any one of the following would occur:

- Pregnancy test proves to be positive.
- Disease status becomes worse.
- Develop side effects from treatment.
- Physician feels that this preoperative SRS is no longer in your best interest.
- Patient is not compliant with the study.

6.3 Treatment schema

Parameter	Pre-Study	SRS	Within 24 hrs post SRS	Surgical resection 1-7 days post SRS	10-14 days post surgery	Q3 months for 12 months, then q4 months to 3 years
History	X	X		X	X	X
Physical exam	X	X		X	X	X
Vital Signs	X	X			X	X
Performance Status	X	X			X	X
MRI	X					X
CT Scan for treatment planning	X					
Serum or Urine Pregnancy Test for WOCBP	X					
FACT - Brain assessment	X				X	X
Blood sample for research *		X	X			

6.4. Tumor response on CT (RECIST)

Measurable Disease Response: CTEP's RECIST guidelines will be followed. A quick reference to the RECIST guidelines can be downloaded at the following URL: http://ctep.info.nih.gov/Policies/WordDocs/RCSTF.PH2TEMPF.doc.

6.5 Post-surgery procedures

Patients will be seen in follow-up 10-14 days post treatment then every 3 months for 12 months, then every 4 months up until 3 years, with the following evaluations:

- Complete physical evaluation with a performance status, vital signs, height, and weight, and a complete medical history
- MRI scans at 3 months post-treatment and every 3 months for 12 months, then every 4 months up until 3 years for assessment of response to therapy and monitoring.
- Administration of Fact-Brain questionnaire at each follow-up visit/scan.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study objectives and design
The primary objective of this study is to determine the efficacy of giving pre-operative radiosurgery to patients pending resection of a brain metastasis.

The *secondary* objectives of this study include:
1. To evaluate overall survival (OS)
2. To evaluate distant intracranial failure associated with this therapy.
3. To evaluate the Health Related Quality of Life (HRQL) associated with this therapy.

This clinical trial is planned as a prospective single-arm phase II study.

7.2 Sample size and accrual rate
No more than 24 evaluable patients will be treated in the trial. This study of 24 patients will have 80% power to detect a difference in postulated local tumor control of 85% to a known inference local tumor control set at 60% to be excluded, using a 1-sided test with Type I error rate of 0.05 for 6, 12, and 24 months. The sample size was estimated using a non-inferior power analysis for inference of a single proportion compared to a known proportion. Also, an attrition rate of 20% was included into the estimated sample size. Based on previous efforts in recruiting patients at the University of Pittsburgh Cancer Institute, it is anticipated that at least 5 patients per year will be enrolled in the protocol and the accrual will be completed within 5 years. An evaluable patient is defined as one who completes a single fractions of preoperative SRS followed by surgical resection of appropriate brain metastases. Patients who are not evaluable will be replaced.

7.3 Data analysis
When possible, generalized linear models (subsuming, for example, logistic regression) will be used to combine data from different dose levels. Model assumptions will be checked graphically prior to analysis. If model assumptions are not met the analysis will be primarily descriptive. Baseline description statistics on all evaluable patients will be provided for demographic variables (age, sex, race/ethnicity), Karnofsky performance status, disease stage and status at the time of enrollment and treatment regimens previously used.

7.4.1 Analysis of the Primary Endpoints
Local control rates for 6 months, 12 months, and 24 months will be analyzed with Kaplan-Meier Survival Curves and the Log-Rank Test.

7.4.2Analysis of Secondary Endpoints
1. The patient's overall survival rates for 6 months, 12 months, and 24 months will be analyzed with Kaplan-Meier Survival Curves and the Log-Rank Test.
2. The probability of distant intracranial failure associated with this therapy will be analyzed with Kaplan-Meier Survival Curves and the Log-Rank Test.
3. The analysis of HRQL data will be descriptive. The data will be summarized by question at each time point with the frequency and percentage of each quality level. For each patient, the trajectory of the score will be plotted against time.

8.0 DATA SAFETY AND MONITORING

8.1 Data monitoring plan
All patient data will be collected by the Clinical Research Department of Radiation Oncology. All data will be secured in a password protected file with observance of all applicable HIPAA regulation. A data safety monitoring board will meet monthly to evaluate toxicity for this trial. Patients/adverse events will be discussed at these the Radiation Oncology Data Safety monthly meetings. Unexpected serious adverse events will be reported to the IRB and DSMC and minutes of the monthly disease center meetings will be reviewed at the DSMC meetings.

Reports will be submitted annually at the time of the yearly renewal.

All research-related procedures will be conducted by certified medical personnel. The study staff will monitor the subjects closely throughout the study for any adverse events, and subjects will be strongly encouraged to report all issues to the study staff. All supportive measures consistent with optimal patient care will be given throughout the study.

8.2 Stopping criteria
Research subjects will be withdrawn from the study if any one of the following occur:

1) Documented neurological worsening following SRS.
2) Inability to tolerate SRS prior to surgical resection.
3) Multiple seizures following SRS.
4) Progression of tumor or radiation/treatment effect at the target site sufficient to necessitate repeat surgical resection or repeat SRS.

8.3 Adverse events
Adverse Events will be graded for intensity according to the National Cancer Institute Common Toxicity Criteria, CTCAE Version 4.0. All appropriate treatment areas will have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

The dose limiting toxicity (DLT) will be defined as any adverse event that occurs within 60 days of treatment initiation of radiotherapy and meets any of the following criteria:

Grade 4 or worse or central nervous system necrosis, or cerebral edema, or encephalopathy, or intracranial hemorrhage, or myelitis, or seizure, or stroke, or,

Any other Grade 3 neurologic toxicity which does not improve to grade 2 within 60 days of treatment initiation of radiotherapy, or,

Any neurologic patient death within 60 days of treatment initiation of radiotherapy will be considered a DLT unless in the opinion of the study radiation oncologist and the neurosurgeon, the death is definitely unrelated to treatment or death is definitely related

to disease progression.

There is a theoretical risk that pre-operative SRS could increase the risk of wound healing complications, due to exposure of the scalp to radiation before surgical intervention. However, the dose of radiation to the scalp in these cases is generally less than 1 Gray, so this potential risk is not believed to be a real risk to these patients.

8.4 Assessment of adverse events
Any clinically significant or unexpected disease or condition that is found during the course of this study, will be immediately evaluated by the Principal Investigator and appropriate medical staff and then it will be determined how to proceed with the study/ study treatment.

The subject would likely be referred to the appropriate specialists for standard follow-up medical care.