A Radiation Therapy Study

Outcome in patients with 4 or more Brain Metastases Treated with Single-Isocenter, Multi-Target (SIMT) Stereotactic Radiosurgery: A prospective single-arm study in adults with brain metastases

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Principal Investigator
Grace J Kim, MD, PhD
Department of Radiation Oncology
Duke University Medical Center

Co-Principal Investigator
John Kirkpatrick, MD, PhD
Department of Radiation Oncology
Duke University Medical Center

Co-Investigator(s)
Justus Adamson, PhD
Peter E. Fecci, MD, PhD
Scott R. Floyd, MD, PhD
John H. Sampson, MD, PhD
Zhiheng Wang, PhD

Statistician
James E. Herndon, II, PhD

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2 LIST OF ABBREVIATIONS

3D	3 Dimensional
AE	Adverse events
BED	Biologically Equivalent Dose
CBCT	Cone Beam Computed Tomography
CPC	Cancer Protocol Committee
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Tumor Volume
DCI	Duke Cancer Institute
DLT	Dose Limiting Toxicity
Dmax	Maximum dose to any voxel within a volume
DUHS	Duke University Health System
G3 or G4	Grade 3 or Grade 4 toxicity
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
GY	Gray
HDR	High Dose Rate
HVLT	Hopkins Verbal Learning Test
ICRU	International Commission on Radiation Units and Measurement
ID	Identification
IMRT	Intensity Modulated Radiation Therapy (including Volumetric Modulated Arc Therapy)
IRB	Institutional Review Board
KPS	Karnofsky Performance Scale
LINAC	Linear Accelerator
LRC	Loco-regional control
MMSE	Mini-Mental Status Examination
MRI	Magnetic Resonance Imaging.
MTD	Maximum Tolerated Dose
MV	Megavoltage
NCI	National Cancer Institute
OS	Overall Survival
PET	Positron Emission Tomography
PI	Primary Investigator
PTV	Planning Target Volume
RTOG	Radiation Therapy Oncology Group
SIMT	Single Isocenter Multi-Target
SOC	Safety Oversight Committee
SRS	Stereotactic Radiosurgery
TD5/5	Toxic dose of 5% at 5 years
V_{12}	Volume of normal brain receiving 12 Gy
VMAT	Volumetric modulated arc therapy
WBRT	Whole Brain Radiation Therapy

3 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1 Purpose

To examine the effectiveness and efficiency of Single Isocenter Multi-Target Stereotactic Radiosurgery (SIMT SRS) in patients with four or more brain metastases.

Primary Objective

1. Assess the impact of using linear-accelerator-based, single-isocenter, image-guided stereotactic radiosurgery on the survival of patients with four or more brain metastases.

Secondary Objectives

1. Describe the time to local brain recurrence
2. Describe the time to distant brain recurrence
3. Describe the time to death due to neurologic causes
4. Describe the prevalence of significant adverse events

Exploratory Objectives

1. Describe changes over time in neurocognition
2. Describe changes over time in quality of life
3. Quantify treatment set-up and dosimetric data for this treatment technique
4. Describe the rate of salvage therapy
5. Describe prevalence of radionecrosis at the SRS site
6. Describe length and intensity of steroid usage post-SRS

Hypotheses

1. This protocol will test the hypothesis that SIMT SRS in patients with four or more brain metastases is efficacious and can be delivered efficiently with minimal toxicity and no significant effect on quality of life and neurocognition.

3.2 Background and Significance

Brain metastases (BM) occur in 10 - 40% of cancer patients[1,2] with variable incidences according to the primary disease. Despite advances in diagnosis and treatment, the development of brain metastases is typically associated with short life expectancy. For patients with a limited number of BM, surgery and whole brain radiotherapy (WBRT) may improve local control and survival.[3,4] However, WBRT is associated with neurocognitive deficits without offering a survival advantage over a more focal radiotherapy approach such as stereotactic radiosurgery (SRS).[5-8] The use of SRS alone provides a very high response rate and local control.[6,9,10]

SRS treatment is usually recommended for a limited number of BMs, mostly for 1-3 lesions.[8,11] However, with evolving radiotherapy technology and brain imaging and recognition of the WBRT long-term side effects, there is a growing interest in using SRS treatments for patients with more than a limited number of BM. A prospective trial looking into SRS, without WBRT, for patients with up to 10 brain metastases found no survival or local recurrence difference between patients treated for 2-4 BMs and those with 5-10 BMs.[12] In fact, cumulative tumor volume and largest treated tumor size were more significant predictors of outcome than the number of treated lesions.

Another obstacle in using SRS for the treatment of a larger number of BMs is the lengthy treatment time required when each lesion was treated with a separate stereotactic radiotherapy plan. SIMT volumetric modulated arc therapy (VMAT) for SRS planning and delivery enables the treatment of many lesions simultaneously. This technique was shown to substantially reduce treatment time with the potential for small improvements in conformity indexes and normal brain dose compared with multiple isocenter plans.[13,14] Data on clinical outcomes with the use of this technique is sparse with one study showing high local control and a survival rate of 60% after 6 months.[15]

The 2016 NCCN guidelines for treating patients with >3 brain metastases recommends WBRT or SRS based on the treating physicians' clinical assessment and judgment. Choosing the most appropriate patients with multiple BMs for SRS treatment rather than WBRT remains an unresolved issue. The goal of this study is to evaluate the efficacy and safety of SIMT SRS as well as the impact of this technology on neurocognition and quality of life.

3.3 Design and Procedure

Forty patients with four or more brain metastases will be enrolled prior to radiosurgery. A planning MRI brain scan will be performed with GD-DPTA within one week prior to radiosurgery, per the standard of care. Patients who have completed a diagnostic MRI with contrast within 14 days of radiosurgery do not need to have a planning MRI. At that time, Neurocognitive (Mini-Mental Status Examination (MMSE), Trail-making test A&B, Hopkins Learning Verbal (HVLT)) and functional assessment of cancer therapy-brain (FACT– Br) will also be obtained. Dose will be prescribed to the maximum isodose line encompassing the resulting PTV using the dose guidelines as described below.

The primary endpoint will be the proportion of patients who live longer than predicted based on the diagnosis-specific GPA score. The Kaplan-Meier estimator will be used to describe the survival of all patients treated with SIMT SRS. Secondary endpoints will be the rate of recurrence at the treated metastases sites, the rate of new brain metastases at a site different from the SRS-treated metastases sites, the rate of death due to neurological causes, and the prevalence of significant adverse events. Exploratory endpoints include change over time in neurocognition and quality of life, quantification of dosimetric measures, the rate of salvage therapy, the rate of radionecrosis at the SRS treatment sites, and the rate and intensity of steroid-usage post-SRS. Dosimetric endpoints to be collected include: maximum and minimum dose to GTV, and conformity index. These endpoints will be compared to historical data calculated by Sperduto et al. from the literature on radiosurgery alone, radiosurgery plus WBRT or WBRT alone, where appropriate.[16] All patients will be evaluated for neurocognitive function via MMSE, HVLT, and Trail-making tests A & B, quality of life via FACT-Br, and for local recurrence via MRI every 3 months over the course of the study. These evaluations will be done at regular follow-up evaluations or when local recurrence is suspected on the basis of symptoms. Distant recurrence is defined as the appearance of new brain metastases at a site different from that of the original metastases. Recurrence will further be defined as a new area of enhancement that measures greater than 5 millimeters in the axial plane on MRI. The length of time to recurrence of the original brain metastases will be calculated from the date of the brain metastases radiosurgery to the date that a recurrence was detected by MRI. Patients with suspected recurrent tumor and/or who are symptomatic may undergo a stereotactic biopsy to evaluate for radionecrosis versus recurrent brain metastases, as is standard of care.

There may or may not be a direct medical benefit to participants. The hope is that but the information gained from this study will help in treating patients with brain metastases in the future.

3.4 Selection of Subjects

Inclusion criteria:

1. A contrast-enhanced MRI scan showing ≥ 4 treatable brain metastases.
2. Age ≥18 years of age.
3. KPS ≥ 70
4. Patient must have a GPA score 0.5 or greater (See Appendix A)
5. Life expectancy of at least 3 months
6. Postoperative patients with resected brain metastases are eligible.
7. Largest lesion ≤ 4cm diameter
8. Must be a candidate for MRI imaging
9. Previous cranial SRS/WBRT is allowed if > 3 months prior to SIMT
10. Must be capable of providing informed consent.
11. Women of childbearing age must have a negative serum pregnancy test to meet eligibility per Duke Policy. Adequate birth control must be used if childbearing potential as outlined in the protocol.

Exclusion

1. Primary lesion with the following histologies: small cell carcinoma, germ-cell tumors, lymphoma, leukemia, and multiple myeloma.
2. Metastases within 2 mm of the optic apparatus
3. Patients unable to obtain MRI.
4. Evidence of leptomeningeal disease
5. Greater than 10 brain metastases; excluding previously treated and stable brain metastases.
6. Pregnant women are excluded.

3.5 Duration of study

The study will last three years. We aim to accrue 40 patients. Overall survival, local control, distant failure, neurocognition, and quality of life will be collected on the 3, 6, 9, and 12-month time points.

3.6 Data Analysis and Statistical Considerations

Though local control is of primary interest in this study, there is concern about the ability to differentiate between swelling due to radiation and disease progression without conducting a biopsy. The use of a biopsy to determine recurrence is not feasible given the number of brain metastases. Hence we focus on the survival of patients newly diagnosed with brain metastases who are treated with SIMT SRS. The goal of the study is to confirm that use of SIMT SRS does not reduce the prognosis of patients.

The population of patients newly diagnosed with brain metastases is a heterogeneous population with expected survival ranging between 3 and 25 months. We will use the expected survival defined by the diagnosis-specific GPA (Graded Prognostic Assessment) index to assess the efficacy of SIMT SRS.[16] Specifically, for each patient we will determine whether the patient lives longer than expected based upon the GPA index. If the survival of patients treated with SIMT SRS is truly comparable to the survival of patients treated with currently available treatment regimens, then we would expect that approximately half of the patients would live longer than expected. A test of non-inferiority will be conducted to assess whether the survival of patients treated with SIMT SRS is similar or better than that seen among Sperduto's cohort.[16] Factors such as the technical feasibility of administering SIMT

SRS and clinical factors such as neurologic control and local control will be considered in determining whether further usage of SIMT SRS is reasonable.

Additionally, the Kaplan-Meier estimator will be used to describe the survival of all patients treated with SIMT SRS. The survival of patients within diagnosis-specific subgroups will also be similarly described. Within the context of the Kaplan-Meier estimator, median survival, 6-month survival, and 12-month survival will be estimated. Survival is defined as the time between initiation of SIMT SRS and death, and will be censored at last follow-up if the patient remains alive.

4 INTRODUCTION

4.1 Study Disease

While systemic therapy has improved for many cancers including melanoma, breast, NSCLC, GI, and renal cell carcinoma, the blood brain barrier prevents many of these agents from being effective in the brain. Thus as systemic therapies have increased survival, brain metastases have become more prevalent. The consequences of brain disease are devastating with complications ranging from headache and seizures to paralysis, so maximizing control while minimizing side effects is crucial. The historical standard of care has been whole brain radiation therapy, which can be effective in controlling some tumors but patients will inevitably experience neurocognitive decline as a side effect of this therapy.

4.2 Radiation Therapy

Stereotactic radiosurgery (SRS) has emerged as standard of care treatment for those patients with 1-3 brain metastases. This treatment has surpassed whole brain radiation therapy with regard to superior local control of brain metastases as well as preservation of neurocognition and quality of life.[8] Now that new systemic therapies are increasing life expectancy, in patients who have brain metastases it is imperative to preserve neurocognition while managing local control.

With advances in radiosurgery technology, it has become possible to stereotactically treat multiple targets at once in an efficient and accurate manner rather than treating each metastasis with SRS individually which would be time consuming and difficult for the immobilized patient. There have been at least three single institutional studies that examine the feasibility of SIMT SRS but do not report clinical outcome.[13,14,17] There has been one small study of 26 patients with a range of 2-13 metastases which reported clinical outcome but did not study quality of life and cognitive endpoints. One year local control was reported to be 83%, but median follow up for all patients was only 3.3 months.[15]

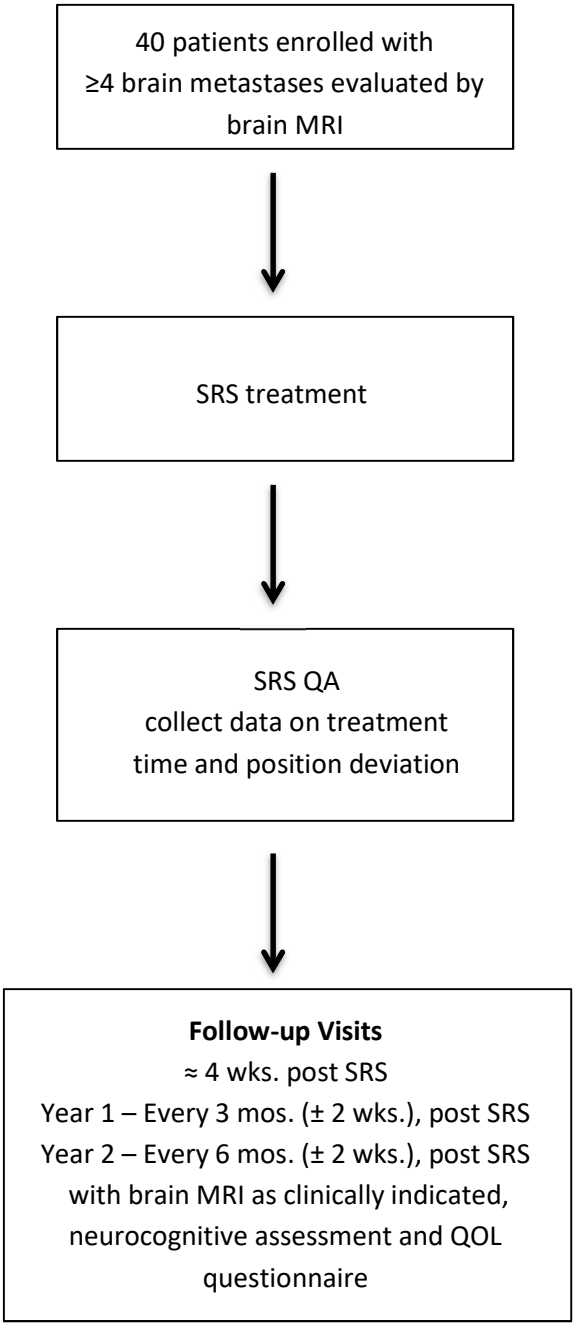
4.3 Study Purpose/Rationale

There has not been a prospective trial investigating efficacy, survival and quality of life endpoints. The purpose of this study is to demonstrate the efficacy and efficiency of SIMT technology for the simultaneous treatment of multiple brain metastases, as well as to evaluate quality of life and cognition endpoints. We are already using SIMT technology in our clinic as our current departmental standard of care for patients with multiple ($\geq$4) brain metastases and have seen excellent results in terms of local control and quality of life. We are currently working on publishing our retrospective results and there is a need for a prospective trial demonstrating the efficacy of this technology.

5 OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary	Assess the impact of using SIMT SRS for the treatment of brain metastases on survival	Proportion of patients who live longer than predicted according to the Graded Prognostic Assessment (GPA) score	See Section 13.4
Key Secondary	Describe the time to local brain recurrence	Proportion of patients that experience local brain recurrence within 1 year of SIMT SRS treatment.	See Section 13.5.1
Other Secondary	Describe the time to distant brain recurrence	Proportion of patients that experience a new brain metastasis at a site different from the original brain metastasis site 1 year after SIMT SRS treatment	See Section 13.5.2
Other Secondary	Describe the time to death due to neurological causes	Proportion of patients who are dead within 1 year of SIMT SRS treatment due to neurologic reasons	See Section 13.5.2
Other Secondary	Describe the prevalence of significant adverse events	Proportion of patients who experience grade 3, 4, or 5 neurologic adverse events attributable to SIMT SRS	See Section 13.5.2
Key Exploratory	Describe changes over time in neurocognition	Mean changes from baseline in subscales of the Trailmaking instruments and the HLVT	See Section 13.6.1
Key Exploratory	Describe changes over time in quality of life	Mean changes from baseline in subscales of the FACT-Brain instrument	See Section 13.6.1
Other Exploratory	Quantify treatment set up and dosimetric data for this treatment technique	Mean length of time to set-up and treat patient, Volume of brain exposed to 12Gy, Mean PTV dose, Total volume of all brain metastases, conformity index, maximum dose	See Section 13.6.2
Other Exploratory	Describe the rate of salvage therapy	The proportion of patients who receive salvage treatment after failing SIMT SRS	See Section 13.6.2
Other Exploratory	Describe prevalence of radionecrosis at the SRS site	Proportion of patients with radionecrosis at the SRS site; the proportion of lesions showing radionecrosis	See Section 13.6.2
Other Exploratory	Describe length and intensity of steroid usage post-SRS	Descriptive statistics	See Section 13.6.2

6 STUDY SCHEMA



7 SUBJECT ELIGIBILITY

All patients seeking treatment for cancer metastatic to the brain from an extracranial primary site with a contrast-enhanced MRI scan showing 4 or more brain metastases at the Duke Comprehensive Cancer Center will be considered.

7.1 Inclusion Criteria

1. A contrast-enhanced MRI scan showing ≥ 4 treatable brain metastases.
2. Age ≥18 years of age.
3. KPS ≥ 70
4. Patient must be GPA score 0.5 or greater (See Appendix A)
5. Life expectancy of at least 3 months
6. Postoperative patients with resected brain metastases are eligible.
7. Largest lesion ≤ 4cm diameter
8. Must be a candidate for MRI imaging
9. Previous cranial SRS/WBRT is allowed if > 3 months prior to SIMT
10. Must be capable of providing informed consent.
11. Women of childbearing age must have a negative serum pregnancy test to meet eligibility per Duke policy.

7.2 Exclusion Criteria

1. Primary lesions with the following histologies: small cell carcinoma, germ-cell tumors, lymphoma, leukemia, and multiple myeloma.
2. Metastases within 2 mm of the optic apparatus
3. Patients who are unable to obtain MRI
4. Evidence of leptomeningeal disease.
5. Greater than 10 brain metastases; excluding previously treated and stable brain metastases.
6. Pregnant women are excluded.

8 INVESTIGATIONAL PLAN

8.1 Study Design

This prospective study of 40 patients will assess the efficacy of SIMT SRS for multiple brain metastases. Dosimetric data, treatment delivery endpoints, clinical outcomes including local control, distant failure and quality of life will be assessed through this trial.

8.1.1 Dose Modification

Radiation doses will be adjusted as described below in Section 9

8.1.2 Safety Considerations

Patients will be evaluated throughout the study for toxicity. Patients will be assessed for all adverse events during treatment and post completion of SRS. Adverse events will be considered to be any grade 3, 4, or 5 event that is deemed by the PI to be probably, possibly, or definitely related to the SRS treatment. Acute adverse events will be collected at the first post-SRS visit. This visit will occur approximately 4 weeks after the last fraction of SRS is

delivered. These will be collected and reported. In our experience, SRS treatment side effects are rare and are solely neurologic.

In light of previous observations, it may be that increasing the treatment volume may also come with a potential cost of increased morbidity.

8.1.3 Treatment Interruptions during RT

There will be no need for treatment interruptions as most treatments will be a single treatment. Some patients will require five treatments on business days (refer to section 9.3) and in our experience, patients are able to complete all five treatments without interruption. Patients can start their treatment any day of the week and weekend breaks are permitted as long as patients have their treatments on consecutive business days. They will be evaluated daily by radiation therapists and if a treatment interruption occurs, as long as medically stable as deemed by the treating physician, patients will continue treatment until completion. If a treatment interruption occurs but the patient completes all five treatments within 10 business days, then this would not be considered a protocol deviation.

8.1.4 Concomitant Medications/Therapies

Symptomatic patients should be placed on dexamethasone at the time of brain metastasis diagnosis at the discretion of the treating radiation oncologist. The drug may be administered orally or intravenously and the dose adjusted throughout the course of treatment. In patients who cannot tolerate taper and/or cessation of steroids, the steroid dose will be maintained at the lowest dose consistent with good medical practice.

8.1.5 Randomization

There will be no randomization.

8.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

Doses for radiosurgery are derived from the RTOG 90-05 study, which calculated the maximum tolerated dose for brain metastases as a function of size.[18] We also found that for large lesions in our study of SRS for GBM that this fractionation was well tolerated[19] as it would certainly reduce the biologically effective dose likely leading to RN.

8.3 Rationale for Correlative Studies

Not applicable.

8.4 Definition of Evaluable Subjects, On Study, and End of Study

All patients who receive SIMT SRS will be included in analyses.

8.5 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.7, which describes procedures and process for prematurely withdrawn patients.

9 RADIATION THERAPY

9.1 Type, Classification, Location, and Short Description

SRS will be performed in the Department of Radiation Oncology, Duke University Medical Center. The gross tumor volume will be delineated by Grace Kim MD PhD, John P. Kirkpatrick, MD PhD, or Scott Floyd, MD PhD, and radiosurgery planning will be assisted by board-certified Physicists. Patients will be treated following the RTOG Stereotactic Radiotherapy Guidelines (Appendix B), available at http://dx.doi.org/10.1016/j.prro.2011.06.014

9.2 Equipment

SRS doses will be delivered as described below with a linear accelerator-based Novalis Tx and TrueBeam STX system, following established procedures for image guided stereotactic radiosurgery. Both systems are high-energy linear accelerators from Varian Medical Systems utilizing the same model of a high-definition collimator (2.5mm leaf thickness at isocenter) to precisely shape the radiation beam. Both units use kilovoltage orthogonal x-ray imaging systems and cone-beam CT to ensure the patient is set-up in the exact, correct position with each and every treatment. While the system names are different, the Novalis Tx and TrueBeam STx yield equivalent dose distributions.[20]

9.3 Dose Specifications

The total dose is dependent on the maximum diameter of the PTV and total lesion volume as described below:

Maximum PTV Diameter	*Assigned Dose*
< 2.0 cm	20 Gy x 1
2.0-3.0 cm	18 Gy x 1
≥ 3cm	5 Gy x 5

The total prescribed dose is determined by tumor size. These assigned doses may be decreased based on clinical judgment. V12 will be recorded for each case. V12 is defined as the volume of normal brain receiving 12 Gy. Normal brain is defined as volume of normal brain parenchyma (not including normal tissue outside of meninges), minus total PTV volume.

If V_{12Gy} (Volume receiving 12 Gy) for normal brain parenchyma (i.e., excluding the PTV's) exceeds 20 mL, then the dose to all lesions will be 5 x 5 Gy where one treatment will be delivered each day for five consecutive business days (i.e. the first treatment may start mid-week and be completed in the following week). If there is a lesion in the brainstem, all lesions will be treated with 5 Gy x 5 because the brainstem is particularly sensitive to high doses of radiation given in a single fraction.

The SRS dose has been selected in order to provide a high rate of local control with minimum risk of radionecrosis. These doses are already being used in our clinic as our departmental standard of care derived from the RTOG 9005 SRS dose escalation study.[18]

The dose will be prescribed to the absolute isodose surface, which encompasses the margin of the metastasis, as defined by the contrast-enhanced MRI. The maximum dose, minimum dose to the GTV and PTV, and percent volume coverage of the GTV and PTV will be recorded for each patient. The

prescription dose shall be delivered to the absolute isodose surface. The minimum dose shall be established by the SRS treatment planning software and/or by the target dose-volume histogram.

Each lesion will be prescribed an SRS dose according to the maximum diameter of the PTV as well as the total volume. If any two lesions are within 1 cm of one another, the prescription dose to these groups of lesions will be based on the maximum diameter across these two lesions. At the discretion of the PI, the dose to lesions in eloquent areas of the brain (e.g., the motor strip or the speech center) may be reduced from 20 to 18 Gy for PTV $\leq$ 2cm in diameter and from 18 to 16 Gy for PTV 2-3cm diameter.

To summarize, lesions will be treated in one fraction unless a lesion is greater than 3cm, located in the brainstem, or the V12 of the normal brain exceeds 20 cc.

In the setting of multiple metastases, a lesion(s) may need to be resected because of large size or mass effect that causes serious neurologic deficits. The resulting resection cavity/cavities can be treated along with the other unresected metastases with the SIMT technique. This has not occurred commonly in our practice but surgery does not preclude the use of this technology.

Isodose distributions must be calculated, and the prescription isodose line clearly designated, for each target lesion in the transverse, coronal, and sagittal planes. The isodose distributions on the required three planes for each target lesion will include isodose lines (in % dose) that represent 20% dose increments. Cumulative dose-volume histograms must be calculated for all target lesions, as well as the brainstem, optic chiasm, optic nerves, eyes and normal brain parenchyma.

Each lesion will be consistently labeled according to institutional protocol and separately followed and documented. With every MRI, any changes in each lesion will be recorded. MRI image registration using department radiation planning software (iPlan) will aid in detecting differences in lesion size and number.

9.4 Localization, Simulation, and Immobilization

An FDA-approved stereotactic radiosurgery system will be used for all localization and treatment planning. All patients must undergo a pretreatment contrast-enhanced planning MRI within one week prior to radiosurgery. Patients who have completed a diagnostic MRI with contrast within 14 days of radiosurgery do not need to have a planning MRI. All patients will be treated on the Varian/BrainLAB linear accelerator-based radiosurgery system (Novalis Tx & TrueBeam STX) following established QA procedures for treatment delivery.

Per the standard of care, target volume and isocenter determination will be based on a contrast-enhanced axial MRI scan. A CT scan will be performed with the patient's head immobilized in a custom thermoplastic mask, and the CT and contrast-enhanced axial 3D MR images fused. The MRI study used to plan the radiosurgical treatment must be the same as used to determine the size of the metastatic lesions. The MRI slice thickness may not exceed 1 mm. The target volume will include the enhancing portion of the metastatic lesion. Surrounding areas of edema will not be considered part of the target volume.

9.5 Imaging

Orthogonal KV and CBCT imaging of patient in the immobilization mask will be done before each radiation delivery.

9.6 Treatment Planning/Target Volumes

Target Volume Definitions

The volumes shall be defined by contrast-enhanced MRI with the patient in the treatment position. ICRU-50 nomenclature target volumes are defined as follows: GTV: Defined as contrast-enhancing tumor seen on pretreatment MRI. PTV: For the purpose of this study, the PTV is defined as the GTV uniformly expanded by 1 mm in all dimensions. The PTV must be $\leq$ 4.0 cm.

Target Dose

Prescription Specification: The dose should be prescribed to the highest isodose line encompassing the PTV.

Dose Definition

Dose is specified in Gray (Gy).

9.7 Dose Limitations for Normal Tissue

The treatment parameters should be modified to optimize the conformity of the prescription volume to the target volume while minimizing dose to critical structures. In patients receiving single fraction treatments, the maximum point dose to the optic chiasm and optic nerves should not exceed 10 Gy and maximum dose to the brainstem should be less than 12.5 Gy. In patients receiving 5 Gy per fraction for five fractions, the maximum point dose to the optic chiasm and optic nerves should not exceed 20 Gy and the maximum dose to 99% of the brainstem should not exceed 26 Gy.

9.8 Treatment Verification

Patients will be monitored by the treating physician (Dr. Grace Kim, Dr. John Kirkpatrick, or Dr. Scott Floyd), and the therapists and physicists during the procedure. The departmental policy has been standard of care time out prior to delivery of each fraction of radiation therapy and this will be meticulously adhered to.

9.9 Quality Assurance of Dose Distribution

Lesion Identification

Lesions must be uniquely identified by anatomical location, e.g., medial left frontal lobe, inferior/ superior right cerebellum, etc, so that these lesions can be readily followed on serial MRI's.

Isodose QA

Four isodose lines should be reviewed: The prescription isodose line, 90% of the prescription isodose line (not 90% of total dose), 80% of the prescription isodose line, and 50% of the prescription isodose line.

Target Coverage QA

Per protocol: The submitted 100% isodose line (100% of the prescription dose, not maximum dose) covers >99% of the target volume.
Acceptable variation: 100% isodose line covers >95% of the target.
Unacceptable deviation: 100% isodose line covers >90% of the target.

Dose QA

Per protocol: If the maximum dimension of the tumor is:

< 2.0 cm: 20 Gy
≥ 2.0 cm and < 3.0 cm: 18 Gy
≥3.0 cm: 5 Gy x 5 all lesions, regardless of diameter
In addition, if any lesion is located in the brainstem or the total V_{12Gy} calculated for single-fraction treatment exceeds 20 ml, all lesions will be treated with 5Gy x 5, regardless of diameter. For metastases that are close to critical structures, doses will be reduced as stated above in Section 9.3.
Unacceptable deviation: Anything else

Dose Conformity QA
The ratio of prescription isodose volume (for maximum planned prescription dose per plan) to the total target volume *(Conformity Index)* is:
Per protocol if between 1.0 and 2.0
Acceptable variation if ≥ 0.9 but < 1.0 or >2.0 but ≤ 3.5.
Unacceptable deviation if > 3.5.

10 PATIENT ASSESSMENTS

A clinical research nurse will contact each patient by telephone within 2 weeks after the SRS procedure to inquire as to the patient's health status if the patient does not have an appointment with an oncologist at DUMC within that time.

At follow-up visits patients will be evaluated as described in the Table below. Patients will be seen in clinic and undergo repeat MRI imaging as standard of care every 3 months for the first 12 months following completion of SRS and every 6 months for the following 12 months. During the follow up visits, the patient will be examined for new or recurrent neurologic signs/symptoms. On MRI, local recurrence is defined as the reappearance of a metastasis in the SRS treated field (within the 50% isodose line). Each treated lesion will be documented separately. Distant recurrence is defined as the appearance of a new brain metastasis outside the SRS field (completely outside the 50% isodose line). To be deemed a recurrence or new lesion, the lesion must measure at least 5 mm in the axial plane on MRI.

Patients with a recurrent or new lesion, who are symptomatic, may undergo a biopsy to determine if the lesion is secondary to radionecrosis or metastasis. Appropriate salvage therapy will be performed at the discretion of the treating radiation oncologist.

If on evaluation the treating physician decides not to pursue an MRI because of clinical decline, this will not be a protocol violation. The most current brain MRI will be used in the determination of local control. Conversely, if a brain MRI needs to be done at an earlier time point due to medical necessity, an MRI at that time point will also not be a protocol deviation and can be included in the data collection. Brain MRI's may be done at 3 month intervals with a one month before or after allowance.

In addition, included in the category of updated medical history is pertinent interim oncologic and medication history. A medical oncologist overseeing patient's standard of care will have been responsible for chemotherapy management as well as systemic staging scans. We will record the type and duration of systemic therapies with each visit as well as the latest information on staging scans (stable or regression vs. progression of disease).

Study Calendar

	Pre-study	During SRS	First visit post SRS (≈ 4 wks.)	Follow-up Yr.1: every 3-mos. Yr. 2: every 6-mos. (±2 wks.)
Informed Consent	X			
PE including Neurological exam, updated Med History.	X[1]		X	X
Neurocognitive Assessments	X		X[4]	X[4]
Performance Status	X		X	X
FACT-Br	X		X	X
Adverse Event Assessment	X	X	X[3]	X[2]
MRI	X			X[2]
Tumor Measurements	X			X[2]

1. No more than 15 days prior to SRS.
2. As clinically indicated
3. Acute toxicity will be collected at this visit which will occur approximately 4 weeks' after the last fraction of SRS. If patients are unable to attend follow up due to clinical decline this would not be considered a protocol deviation.
4. It will not be considered a protocol deviation if a patient declines to complete neurocognitive testing at any follow up visit.

10.1 Pretreatment Evaluations/Management

- Complete history and physical examination with a detailed neurological examination within 15 days of study registration.
- Quality of Life form FACT-Br completion (see Appendix F)
- Neurocognitive assessment: HVLT, TMT, MMSE (see Appendices D and E)

10.2 Screening Examination

Patients will be registered only after eligibility criteria are met. Once research staff and PI have verified that the patient is eligible per Departmental policy and that the study ongoing regulatory requirements have been met, a patient-specific case number will be assigned. An informed consent must be signed by the patient before any screening procedure takes place. If, however,

standard of care evaluation procedures have been obtained and are within the screening evaluation time points, the SOC procedures do not need to be repeated and may be included in the screening examination. All of the eligibility inclusion and exclusion criteria should be satisfied during each screening process.

10.3 Treatment Period

Treatment will range from 1 to 5 consecutive business days and those patients that get multiple treatments will be observed every day by radiation therapists.

Those patients that will be treated in 5 days are the following:
1) at least 1 metastasis > 3cm
2) V12 > 20 cc for normal brain parenchyma, all lesions will receive 5 Gy x 5
3) If there is a brainstem lesion

If a treatment interruption occurs but the patient completes all five treatments within 10 business days, then this would not be considered a protocol deviation.

Sexually active, subjects must agree to use appropriate contraceptive measures for the duration of the study treatment (i.e. from SRS CT simulation to the completion of SRS treatment, which is approximately 1-2 weeks).

10.4 End of Treatment

They will be seen by either an NP or MD to be given discharge instructions. Any acute side effects of treatment will be assessed via CTCAE v.4 and documented.

10.5 Follow-up Period

Follow-up period will be two years. The first visit is approximately 4 weeks post SRS, every 3 months in the 1st year post SRS, and then every 6 months in the 2nd year within ± 2-weeks. Each visit will include an updated medical history and physical exam, neurological exam, performance status, adverse events and toxicity assessment, quality of life, and neurocognitive testing. During the follow up period a standard of care contrasted MRI and/or tumor measurements will be performed as clinically indicated by the treating investigator.

10.6 End of Study

End of study will be completion of data analysis.

10.7 Early Withdrawal of Subject(s)

10.7.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Protocol deviation
- Administrative issues
- Local or distant recurrence evident on Brain MRI imaging

Patients who demonstrate local or distant progression in the brain after study treatment will be followed for overall survival only but will not have neurocognitive testing performed.

10.7.2 Follow-up Requirements for Early Withdrawal

Patients will continue to be assessed every three months with an MRI and history and physical exam which is our standard of care.

10.7.3 Replacement of Early Withdrawal(s)

We will accrue 40 patients and will not replace patients once the accrual process is through. We treat over 300 SRS patients a year and we estimate that we should be able to accrue to the study readily.

10.8 Study Assessments

10.8.1 Medical History

A thorough medical history and review of systems will be obtained by the NP/MD. Oncologic information will be updated each visit, such as: type and duration of systemic therapies and performance status. The HVLT, MMSE, and FACT-BR will also be administered with each visit.

10.8.2 Physical Exam

Standard Physical exam including extensive neurology exam will be performed with each follow up visit.

10.8.3 Correlative Assessment

Not applicable

11 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of radiation therapy, whether or not related to use of the radiation therapy. Abnormal laboratory findings with or without clinical significance will be attributed to systemic therapy and should not be recorded as AEs.

From the time the subject signs the informed consent form through the End of Study visit (as defined in Section 10.4), all AEs judged by the treating physician or study investigators to be possibly, probably, or definitely related to the SIMT treatment must be recorded in the subject medical record and adverse events case report form. AEs related to systemic therapies will be managed by the treating MD or study investigators and will not be collected.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

11.1.1 AEs of Special Interest

Patients will be evaluated throughout the study for toxicity. Patients will be assessed for all adverse events during treatment and post completion of RT. Adverse Events (AEs) that are deemed by the PI to be related to the SIMT SRS treatment will be collected and reported. Acute adverse events will be collected at the first post-SRS visit. This visit will occur approximately 4 weeks after the last fraction of SRS is delivered. While not all-inclusive, the list below indicates side effects that may be related to the treatment. In the largest trial examining SRS treatment to 5-10 multiple targets (n = 1194), grade I & 2 toxicity was seen in 5% and Grades 3-4 were seen in 3%, and grade 5 toxicity <1%. [12]

SRS Possible Side Effects

<u>Likely:</u>

Mild erythema in the treatment field
Nausea / vomiting
Headaches
Fatigue

<u>Less likely:</u>

Hair loss in the treatment field
Decreased mental abilities
Extremity weakness
Parathesias
Speech difficulties
Hydrocephalus
Radionecrosis
Seizures
Vision loss
Death

11.1.2 Reporting of AEs

For all adverse events deemed by the PI to be related to the SIMT SRS treatment, the information should be recorded in the patient's medical record and the Case Report Form or AE database for that patient. This should include a description of the event, its severity or toxicity grade, the relationship to the study treatment, and the intervention, outcome and sequelae of the event.

11.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions

Any serious or unexpected event, which occurs to any patient in the course of their treatment on this study or within 30 days following cessation of treatment, is reported immediately to the Study Coordinator by telephone 668-3726, within 24 hours of the clinician learning of its occurrence.

11.3 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews include but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 12.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements. The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

11.4 External Data and Safety Monitoring Board (DSMB)

We do not have a potential conflict of interest.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

12.2 Audits

The Duke School of Medicine Office of Audit, Risk and Compliance (OARC) may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

12.3 Data Management and Processing

12.3.1 Case Report Forms (CRFs)

The REDCap Database CRF (electronic) will be the primary data collection document for the study. The CRF will be updated in a timely manner following acquisition of new source data. Only approved study staff are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the REDCap electronic CRF management system. Designated personnel will complete user training, as required or appropriate per regulations.

12.3.2 Data Management Procedures and Data Verification

Clinical research nurses, all investigators, and statisticians involved in the project will have access to REDCAP based on their specific roles in the protocol. The designated data manager will be managing the REDCAP database.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

12.3.3 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories.

13 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

13.1 Analysis Sets

All patients who undergo SIMT SRS treatment will be included in both safety and efficacy analyses.

13.2 Patient Demographics and Other Baseline Characteristics

Socio-demographic and clinical characteristics of patients enrolled and treated on this study will be summarized. For categorical variables, frequencies and percentages will be provided. Means with standard deviations and medians/percentiles will summarize non-categorical variables. Included among the clinical variables that will be summarized will be diagnosis (i.e. site of primary disease), and size and location of brain metastases.

13.3 Treatments

A frequency distribution for the number and volume of brain metastases, as well as the total brain volume receiving 12 Gy or more (V_{12Gy}), will be generated. Details about concomitant treatment of the primary disease will also be summarized.

13.4 Primary Objective

The primary objective of this study is to assess the impact of using SIMT SRS for the treatment of patients with ≥4 brain metastases.

13.4.1 Variable

Though local control is of primary interest in this study, there is concern about the ability to differentiate between swelling due to radiation and disease progression without conducting a biopsy. The use of a biopsy to determine recurrence is not feasible given the number of brain metastases. Hence we focus on the survival of patients with brain metastases who are treated with SIMT SRS. The goal of the study is to confirm that use of SIMT SRS does not reduce the prognosis of patients.

The population of patients with brain metastases is a heterogeneous population with expected survival ranging between 3 and 25 months. We will use the expected survival defined by the diagnosis-specific GPA (Graded Prognostic Assessment) index to assess the efficacy of SIMT SRS.[16] Specifically, for each patient we will determine whether the patient lives longer than expected based upon the GPA index. If the survival of patients treated with SIMT SRS is truly comparable to the survival of patients treated with currently available treatment regimens, then we would expect that approximately half of the patients would live longer than expected.

Hence, the primary endpoint of the study will be the proportion of patients who live longer than expected according to the diagnosis-specific GPA index.

13.4.2 Statistical Hypothesis, Model, and Method of Analysis

The goal of the study is to confirm that the use of SIMT SRS does not significantly reduce or compromise the prognosis of patients. Within each of 5 diagnosis groups (non-small cell lung cancer, melanoma, breast cancer, renal cell carcinoma, and GI cancer), various prognostic groups have been defined by Sperduto.[16] Within each of these diagnosis-prognosis groups, an expected survival has been determined. It is hoped that the survival of patients treated with SIMT SRS is similar to or better than that seen among Sperduto's cohort. In other words, it is hoped that the survival with SIMT SRS is not inferior to that reported in the Sperduto paper.

With the expected proportion of patients living longer than expected to be 50%, a test of non-inferiority will be conducted. Details are provided in the section concerning sample size justification.

Additionally, the Kaplan-Meier estimator will be used to describe the survival of all patients treated with SIMT SRS. The survival of patients within diagnosis-specific subgroups will also be similarly described. Within the context of the Kaplan-Meier estimator, median survival, 6-month survival, and 12-month survival will be estimated. Survival is defined as the time between initiation of SIMT SRS and death, and will be censored at last follow-up if the patient remains alive.

13.4.3 Inferences

This study has been designed with the best historical data currently available to assess the efficacy of SIMT SRS in a single-arm study. However, this benchmark is imperfect, and does not reflect the possible impact of rapidly emerging novel therapeutics, including immunotherapies, that target the primary disease of these patients. In addition, this benchmark does not reflect the few

patients we may have with recurrent brain metastases as the GPA scoring was developed from a database that included patients who completed brain treatment within 2 months of the diagnosis of brain metastases. If a better benchmark data becomes available during the conduct of this study, the design of this single-arm study may be modified.

Though a decision-rule is provided in section 13.8 to test the non-inferiority of SIMT SRS treatment relative to the Sperduto GPA-based benchmark, other factors will be considered in determining whether further usage of SIMT SRS is reasonable. Two important issues that will factor into this decision-making include: technical feasibility of administering SIMT SRS, and clinical factors such as neurologic control and local control.

13.5 Secondary Objectives

The key secondary objective is to describe the time to local recurrence. Other secondary objectives focus on the time to distant recurrence, time to neurologic death, and the prevalence of significant adverse events.

13.5.1 Key Secondary Objective

The time until local brain recurrence will be calculated as the time between initiation of SIMT SRS and local recurrence of brain metastases. The time to local brain recurrence will be censored at the time of last follow-up if the patient remains alive without local recurrence, or will be censored at death if the patient dies without local recurrence of brain metastases. A Kaplan-Meier estimator will be used to describe the time until local recurrence. Within the context of Kaplan-Meier curve, an estimate of the proportion of patients without local brain recurrence one year after SIMT SRS treatment will be generated. The time until local brain recurrence will also be described within diagnosis-specific subgroups.

13.5.2 Other Secondary Objectives

The time until distant brain recurrence will be calculated as the time between initiation of SIMT SRS and distant recurrence of brain metastases. The time to distant brain recurrence will be censored at the time of last follow-up if the patient remains alive without distant recurrence, or will be censored at death if the patient dies without distant recurrence of brain metastases. A Kaplan-Meier estimator will be used to describe the time until distant recurrence. An estimate of the proportion of patients without distance recurrence one year after SIMT SRS treatment will be generated. The time until distant brain recurrence will also be described within diagnosis-specific subgroups.

Time to neurologic death is defined as the time between initiation of SIMT SRS and death due to neurologic causes. If a patient remains alive or dies for reasons unrelated to neurologic disease, the time to neurologic death will be censored at the time of last follow-up or death not due to neurologic causes. Analyses similar to other “time to an event” outcomes will be conducted including the generation of Kaplan-Meier curves.

The proportion of patients who experience grade 3 or worse neurologic toxicity attributable to SIMT SRS will be summarized. In addition, adverse events experienced by protocol subjects will also be summarized in several other forms to satisfy scientific and monitoring needs, as well as various regulatory reporting needs (e.g. DCI SOC, and ClinicalTrials.gov). The frequency of adverse events that are possibly, probably, or definitely related to protocol treatment will be tabulated by the maximum grade for each type of adverse event.

13.6 Exploratory Objectives

This protocol includes several exploratory objectives: (1) To describe changes in neurocognition over time, (2) To describe changes in quality of life over time, (3) To quantify treatment set-up and dosimetric data for the SIMT SRS treatment technique, (4) To describe the rate of salvage therapy, (5) To describe the prevalence of radionecrosis at the SRS site, and (6) To describe the length and intensity of steroid usage post-SRS.

13.6.1 Key Exploratory Objectives

The mean changes from baseline in neurocognition as measured by Trailmaking A and B, the MMSE and the HVLT will be summarized. Similarly, the mean changes from baseline in quality of life as measured by the FACT-Brain, will be summarized.

13.6.2 Other Exploratory Objectives

Descriptive statistics (e.g. mean, median, quantiles) will be used to describe the treatment set-up and dosimetric data associated with the SIMT SRS treatment technique. Specifically, the mean and median time to set-up of the patient's SIMT treatment will be generated. Means and medians will also describe the mean volume of brain exposed to 12Gy, the PTV dose, and the total volume of all brain metastases.

The proportion of patients who receive salvage treatment after failing SIMT SRS will be estimated, and the type of treatment received will be summarized.

Data concerning radionecrosis will be summarized at the level of a lesion, as well as the patient level. The proportion of lesions who exhibit radionecrosis after SIMT SRS treatment will be summarized. With each patient having multiple lesions, the percentage of lesions within a patient that show radionecrosis will also be summarized with medians and quantiles.

The length and dose of steroid usage post-SRS will be summarized using descriptive statistics.

13.7 Interim Analysis

Adverse events experienced by patients will be reviewed in an aggregate manner at least annually.

13.8 Sample Size Calculation

Forty (40) patients will be accrued to this study and treated with SIMT SRS. If 17 or more of these patients live longer than expected according to the GPA score, then SIMT SRS will be considered non-inferior to historical data pertaining to survival of patients with brain metastases. With this decision rule and 40 patients, there is 90% power to detect a non-inferiority difference of -0.2 using a one-sided exact test with a target significance level of 0.10 (PASS 14, 2015). The actual significant level achieved is 0.0633.

14 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

14.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

A REDCap case report form (CRF) will be the primary data collection document for the study. The CRFs will be updated within two weeks of acquisition of new source data. Only investigators and research nurse staff are permitted to make entries, changes, or corrections in the CRF. For paper CRFs, errors will be crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The investigators or authorized key personnel will maintain a record of the changes and corrections. For electronic CRFs, an audit trail will be maintained by the REDCap CRF management system.

14.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctors and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database (REDCap), which is housed in an encrypted and password-protected drive. Access to electronic databases will be limited to the research study team in the Department of Radiation oncology.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.6 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 11 (Sections 11.3 and 11.4 in particular) along with section 12.

14.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

14.8 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least six years after study completion

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16 Appendix A: GPA Criteria for NSCLC, Melanoma, Breast, Renal Cell & GI Cancers

GPA score: Graded prognostic assessment (GPA), is a prognostic index for patients with brain metastases based on histology. Sperduto et al [16], reported that the diagnosis-specific GPA is the least subjective, most quantitative and easiest tool to use based on a multi-institutional database of 3,900 patients with brain metastases.

Non–small-cell and small-cell lung cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	GPA Scoring Criteria 0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

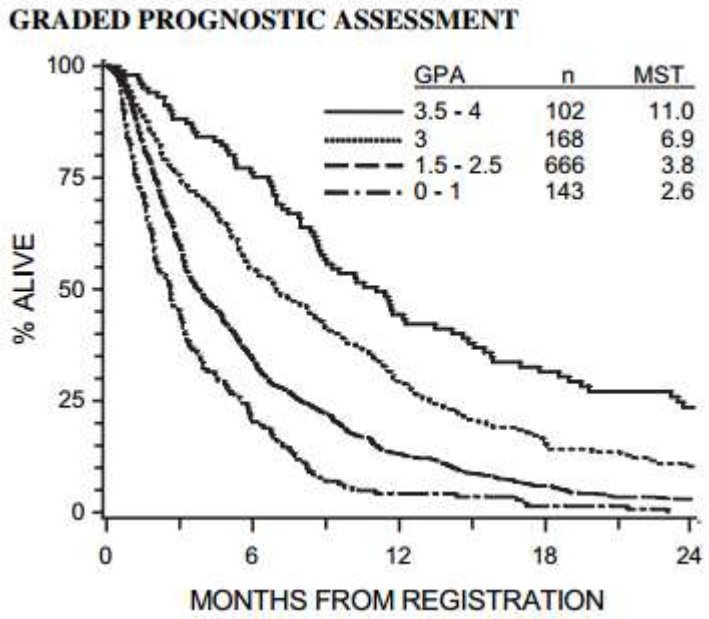
Abbreviations: Breast Subtype: Basal= Triple Negative (ER/PR/HER2-), LumA: (ER/PR positive, HER2 negative); LumB = (triple positive); HER2= (ER/PR negative, HER2 positive); brain metastases (BM), extracranial metastases (ECM); ER = estrogen receptor; HER = human epidermal growth factor receptor 2; KPS = Karnofsky performance score; LumA = luminal A; LumB =luminal B; PR = progesterone receptor. [16].

17 Appendix B: GPA Criteria for Other Cancer Histology

For histologies that are not listed above and are not excluded , GPA will be calculated using the following generalized formula from Sperduto et al [Sperduto PW1, Berkey B, Gaspar LE, Mehta M, Curran W.A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):510-4.]

	Score		
	0	0.5	1.0
Age	>60	50–59	<50
KPS	<70	70–80	90–100
No. of CNS metastases	>3	2–3	1
Extracranial metastases	Present	—	None

Abbreviations: KPS = Karnofsky Performance Status; CNS = central nervous system.



18 Appendix C: Stereotactic Radiotherapy QA Guidelines

Below is the direct link to the RTOG Stereotactic Radiotherapy Quality Assurance Guidelines:

http://dx.doi.org/10.1016/j.prro.2011.06.014

19 Appendix D: Performance Status

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out 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 any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

20 Appendix E: The Mini-Mental State Exam Instructions and Exam

Instructions for Administration of

Mini-Mental State Examination (MMSE)

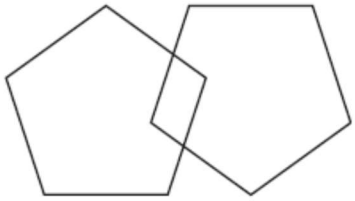
Orientation	1. Ask for the Date. Then ask specifically for parts omitted, eg, "Can you also tell me what season it is?" Score one point for each correct answer. 2. Ask in turn, "Can you tell me the name of this hospital?" (town, county, etc.) Score one point for each correct answer.
Registration	Ask the patient if you may test his/her memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each. After you have said all 3, ask the patient to repeat them. This first repetition determines his/her score (0-3) but keep saying them until he/she can repeat all 3, up to 6 trials. If all 3 are not eventually learned, recall cannot be meaningfully tested.
Attention and Calculation	Ask the patient to spell the word "world" backwards. The score is the numbers of letters in correct order (e.g, DLROW=5; DLRW=4; DLORW, DLW=3; OW=2; DRLWO=1).
Recall	Ask the patient if he/she can recall the 3 words you previously asked him/her to remember. Score 0 – 3.
Language	***Naming:*** Show the patient a wristwatch and ask him/her what it is. Repeat for pencil. Score 0 – 2.

	Repetition: Ask the patient to repeat the sentence after you. Allow only one trial. Score 0 – 1.
	3-stage command: Give the patient a piece of plain blank paper and repeat the command. Score 1 point for each part correctly executed.
	Reading*:* On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask him/her to read it and do what it says. Score 1 point only if he actually closes his eyes.
	Writing: Give the patient a blank piece of paper and ask him/her to write a sentence for you. Do not Dictate a sentence; it is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary.
	Copying: On a clean piece of paper, draw intersecting pentagons, each side about 1 in., and ask him/her to copy it exactly as it is. All 10 angles must be present and 2 must intersect to score 1 point. Tremor and rotation are ignored.

MINI MENTAL STATUS EXAMINATION

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 Common objects (eg, “apple,” “table,” “penny”). Take 1 second to say each. Then ask the patient to repeat all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7’s. 1 point for each correct answer. Stop after 5 answers. Alternatively, spell “world” backwards. The score is the number of letters in correct order (D__L__R__O__W__).
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer. [Note: recall cannot be tested if all 3 objects were not remembered during registration]
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following “No ifs, ands, or buts”
3	( )	Follow a 3-stage command: “Take a paper in your hand, fold it in half, and put it on the floor.”
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____

Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975.

21 Appendix F TRAIL MAKING TEST

PART A

Sample Instructions: "On this page (point) are some numbers. Begin at number 1 (point to '1') and draw a line from 1 to 2 (point to '2'), 2 to 3 (point to '3'), 3 to 4 (point to '4'), and so on, in order, until you reach the end (point to circle marked END). Draw the lines as fast as you can. Ready, begin. (If the patient makes a mistake, point out the error and explain it. If the patient completes Sample A correctly, say "Good! Let's try the next one." Proceed with the test and repeat instructions above. Start timing as soon as the instruction is given to "begin." Watch closely in order to catch any errors as soon as they are made. If the patient makes an error during the test, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred. DO NOT STOP TIMING. The patient must complete the test in 3 minutes or less.)"

Test Instructions: "On this page are numbers from 1 to 25. Do this the same way. Begin at number one (point to '1') and draw a line from one to two (point to '2'), two to three (point to '3'), three to four (point to '4'), and so on, in order until you reach the end (point to circle marked 'End'). Remember, work as fast as you can. Ready! Begin!"

I. Trail Making Test Part A:

1. Did the patient do Sample A before attempting Part A? Yes No

2. Total amount of time the patient was tested: __ :_ __ (min:sec)

3. Did the patient reach the "END" of the test?

Yes

No, tested for 3 minutes OR No, tested for <3 minutes

If No, specify the last number reached on the test: __ __

Comments: _____

PART B

Sample Instructions: "On this page (point) are some numbers and letters. Begin at number 1 (point to '1') and draw a line from 1 to A (point to 'A'), A to 2 (point to '2'), 2 to B (point to 'B'), B to 3 (point to '3'), 3 to C (point to 'C') and so on, in order, until you reach the end (point to circle marked 'End'). Remember, you first have a number (point to '1'), then a letter (point to 'A'), then a number (point to '2'), then a letter (point to 'B'), and so on. Draw the lines as fast as you can. Ready, begin. (If the patient makes a mistake, point out the error and explain it. If the patient completes Sample B correctly, say "Good! Let's try the next one." Proceed with the test and repeat instructions above. Start timing as soon as the instruction is given to "begin." Watch closely in order to catch any errors as soon as they are made. If the patient makes an error during the test, call it to his/her attention immediately and have

him/her proceed from the point the mistake occurred. DO NOT STOP TIMING. The patient must complete the test in 5 minutes or less.)"

Test Instructions: "On this page are both numbers and letters. Do this the same way. Begin at number one (point to '1') and draw a line from one to A (point to 'A'), A to two (point to '2'), two to B (point to 'B'), B to three (point to '3'), three to C (point to 'C'), and so on, in order, until the end (point to circle marked 'END'). Remember, first you have a number (point to '1'), then a letter (point to 'A'), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready! Begin!"

II. Trail Making Test Part B:

1. Did the patient do Sample B before attempting Part B? Yes No

2. Total amount of time the patient was tested: _ :_ _ (min:sec)

3. Did the patient reach the "END" of the test?

Yes

No, tested for 5 minutes OR No, tested for <5 minutes

If No, specify the last number/letter reached on the test: __ __

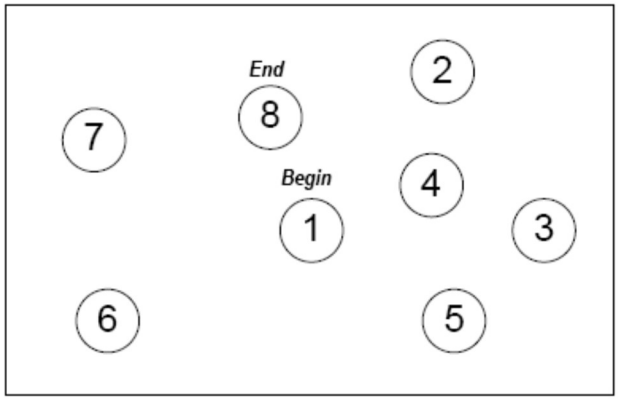
Comments:_____

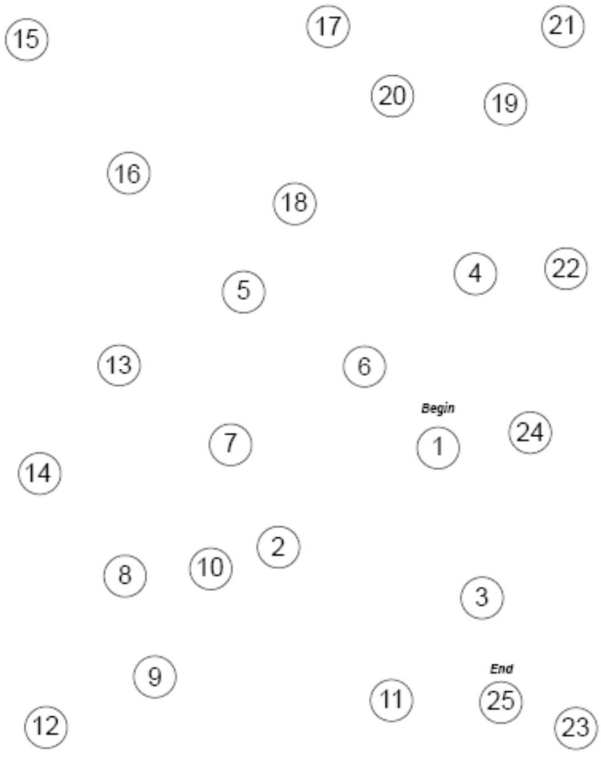
Trail Making (continued)

TRAIL MAKING

Part A

Sample

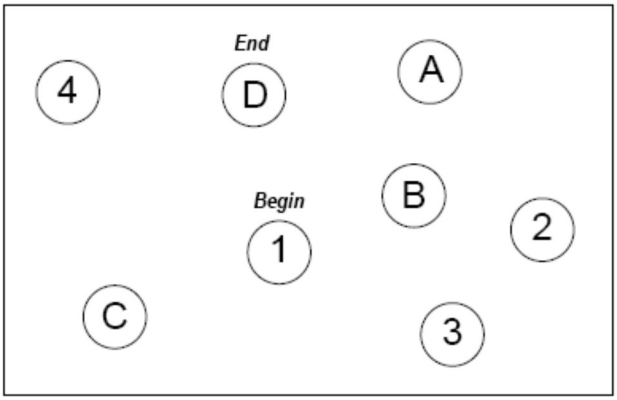


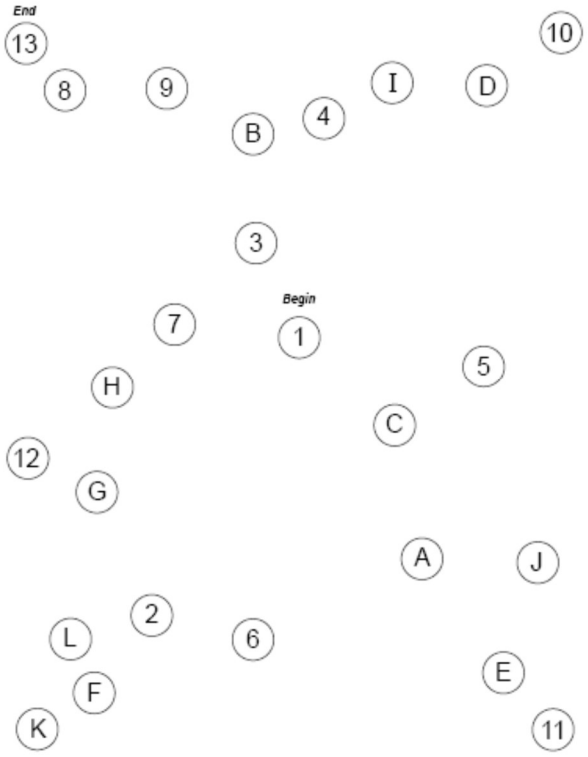


TRAIL MAKING

Part B

Sample





22 Appendix G: FACT-Br

FACT-Br (Version 4)

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

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

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

3/10/03
Page 1 of 3

FACT-Br (Version 4)

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

	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

FACT-Br (Version 4)

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

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

23 Appendix H: Hopkins Verbal Learning Test

HOPKINS VERBAL LEARNING TEST
Form 1: four-legged animals, precious stones, human dwellings

Part A: Free Recall

	Trial 1	Trial 2	Trial 3
EMERALD			
HORSE			
TENT			
SAPPHIRE			
HOTEL			
CAVE			
OPAL			
TIGER			
PEARL			
COW			
HUT			
# CORRECT			

HORSE	ruby*	CAVE	balloon	coffee	LION
house*	OPAL	TIGER	boat	scarf	PEARL
HUT	EMERALD	SAPPHIRE	dog*	apartment*	penny
TENT	mountain	cat*	HOTEL	COW	diamond*

Part B: Recognition:

 # True-Positives:_____/12

 # False-Positive Errors: Related:_____/6 Unrelated:_____/6

Discrimination Index: (# True-Positives) – (# False-Positives) = _____

HOPKINS VERBAL LEARNING TEST
Form 2: kitchen utensils, alcoholic beverages, weapons

Part A: Free Recall

	Trial 1	Trial 2	Trial 3
FORK			
RUM			
PAN			
PISTOL			
SWORD			
SPATULA			
BOURBON			
VODKA			
POT			
COW			
HUT			
WINE			
# CORRECT			

Part B: Recognition:

spoon*	PISTOL	doll	whiskey*	FORK	POT
harmonica	can opener*	SWORD	pencil	gun*	VODKA
knife*	RUM	trout	BOMB	PAN	gold
WINE	lemon	SPATULA	BOURBON	beer*	RIFLE

 # True-Positives:_____/12

 # False-Positive Errors: Related:_____/6 Unrelated:_____/6

Discrimination Index: (# True-Positives) – (# False-Positives) = _____

HOPKINS VERBAL LEARNING TEST
Form 3: musical instruments, fuels, food flavorings

Part A: Free Recall

	Trial 1	Trial 2	Trial 3
SUGAR			
TRUMPET			
VIOLIN			
COAL			
GARLIC			
KEROSINE			
VANILLA			
WOOD			
CLARINET			
FLUTE			
CINNAMON			
GASOLINE			
# CORRECT			

Part B: Recognition:

pepper*	GARLIC	WOOD	drum*	oil*	SUGAR
Harmonica	salt*	priest	chair	COAL	CLARINET
TRUMPET	basement	CINNAMON	FLUTE	electricity*	Moon
KEROSINE	VANILLA	GASOLINE	sand	piano*	VIOLIN

True-Positives:_____/12

False-Positive Errors: Related:_____/6 Unrelated:_____/6

Discrimination Index: (# True-Positives) – (# False-Positives) = _____

HOPKINS VERBAL LEARNING TEST
Form 4: birds, articles of clothing, carpenter's tools

Part A: Free Recall

	Trial 1	Trial 2	Trial 3
CANARY			
SHOES			
EAGLE			
BLOUSE			
NAILS			
CROW			
BLUEBIRD			
SCREWDRIVER			
PANTS			
CHISEL			
SKIRT			
WRENCH			
# CORRECT			

Part B: Recognition:

BLUEBIRD	shirt*	CHISEL	EAGLE	chocolate	robin*
chapel	SCREWDRIVER	CROW	sparrow*	WRENCH	PANTS
NAILS	socks*	child	SHOES	hair	hammer*
CANARY	apple	SKIRT	saw*	silver	BLOUSE

True-Positives:_____/12

False-Positive Errors: Related:_____/6 Unrelated:_____/6

Discrimination Index: (# True-Positives) – (# False-Positives) = _____

HOPKINS VERBAL LEARNING TEST
Form 5: occupations/professions, sports, vegetables

Part A: Free Recall

	Trial 1	Trial 2	Trial 3
TEACHER	_____	_____	_____
BASKETBALL	_____	_____	_____
LETTUCE	_____	_____	_____
DENTIST	_____	_____	_____
TENNIS	_____	_____	_____
BEAN	_____	_____	_____
ENGINEER	_____	_____	_____
POTATO	_____	_____	_____
PROFESSOR	_____	_____	_____
GOLF	_____	_____	_____
CORN	_____	_____	_____
SOCCER	_____	_____	_____
# CORRECT	_____	_____	_____

Part B: Recognition:

 # True-Positives:_____/12

TENNIS	football*	PROFESSOR	spinach*	lawyer*	submarine
GOLF	DENTIST	LETTUCE	spider	water	BEAN
BASKETBALL	doctor*	CORN	baseball*	TEACHER	snake
carrot*	ENGINEER	glove	SOCCER	POTATO	tulip

 # False-Positive Errors: Related:_____/6 Unrelated:_____/6

Discrimination Index: (# True-Positives) – (# False-Positives) = _____

HOPKINS VERBAL LEARNING TEST
Form 6: fish, parts of a building, phenomens

Part A: Free Recall

	Trial 1	Trial 2	Trial 3
SHARK			
WALL			
HERRING			
RAIN			
FLOOR			
HAIL			
CATFISH			
ROOF			
SALMON			
STORM			
CEILING			
SNOW			
# CORRECT			

Part B: Recognition:

 # True-Positives:_____/12

HAIL	bass*	SNOW	bank	FLOOR	mustard
window*	CEILING	canyon	RAIN	ladder	STORM
HERRING	SALMON	tornado*	trout*	melon	ROOF
SHARK	hurricane*	elbow	CATFISH	WALL	door*

 # False-Positive Errors: Related:_____/6 Unrelated:_____/6

Discrimination Index: (# True-Positives) – (# False-Positives) = _____