

Image-Guided Cognitive-Sparing Radiosurgery for Brain Metastases: Avoidance of Eloquent White Matter and Hippocampal Regions

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1. Statement of Purpose

Brain metastases affect one third of all adult cancer patients¹. Stereotactic radiosurgery (SRS), a highly precise modality for focal ablative radiotherapy, is standard of care for patients with limited brain metastases¹⁻². However, many patients will experience decline in neurocognitive function after brain SRS^{3,4,5,6}, given the potential for high doses to eloquent brain tissue. Neurocognition has emerged as a critical endpoint along with survival and tumor control in brain tumor clinical trials^{7,5,8}. Radiation-induced cognitive impairment after SRS can manifest as a range of cognitive problems, particularly deficiencies in memory, language, attention and executive functioning, depending on tumor location and dose delivered to critical brain tissue.

Any focal intervention in the brain should occur with a detailed understanding of the brain's functional and anatomic relationships relative to the target⁹⁻¹⁰. With the aid of modern magnetic resonance imaging (MRI) techniques, eloquent brain regions can be well demarcated in imaging studies and projected into three-dimensional (3D) space. In particular, diffusion tensor imaging (DTI) tractography with automated white matter segmentation can be used to identify critical white-matter pathways (tracts) of the brain^{11,12,13}. 3-D volumetric MRI and automated brain parcellation software can be used to segment discrete areas of the brain including the hippocampus, a structure critical for memory^{14,15}. In radiation planning, particularly in brain SRS planning, these new technologies have **not yet** been prospectively tested for sparing healthy and sensitive parts of the brain from high doses of radiation.

These novel imaging techniques also allow us to directly and non-invasively measure microstructural changes after radiotherapy to critical brain structures *in vivo*. Using diffusion imaging biomarkers, we have shown that radiation therapy results in dose dependent damage to uninvolved white matter¹⁶ with greater susceptibility to injury among white matter tracts critical for neurocognition¹⁷. Our studies with 3-D volumetric MRI and automated parcellation of the hippocampus have shown dose-dependent hippocampal atrophy after fractionated brain radiotherapy^{15,18}. These imaging biomarkers hold promise to help elucidate the mechanisms behind radiation-induced cognitive decline.

In this study, we propose a novel approach to cognitive-sparing brain SRS. Specifically, we will incorporate eloquent white matter tracts and hippocampal volumes obtained from DTI and volumetric MRI, respectively, into brain SRS planning in a cohort of patients with brain metastases. We will use innovative, advanced image acquisition and robust, automated image processing techniques. Cognitive outcomes, specifically language, memory, attention, and executive functioning, along with imaging tests to measure microstructural changes in these eloquent areas will be prospectively assessed, along with tumor control.

The primary objectives of this study are: **1).** To evaluate whether the relative sparing of eloquent white matter tracts (those critical for memory, language, attention, and executive functioning) and hippocampal volumes from high doses during brain SRS results in improved 3-month post-SRS cognitive performance relative to historical controls among patients with 1 to 3 brain metastases and **2.)** To measure longitudinal trends in white matter damage (using diffusion imaging) and hippocampal atrophy (using volumetric change) among patients receiving cognitive-sparing brain SRS and correlate these imaging biomarkers with domain-specific cognitive outcomes.

2. Background and Significance

The incidence of brain metastases is rising, and they currently affect up to **one-third of all adult cancer patients**, most commonly among lung, melanoma, renal cell, and breast cancer primaries¹. As novel systemic therapies improve survival rates and systemic disease control in cancer patients, brain metastases become a greater burden: these therapeutic agents poorly cross the blood-brain-barrier, creating a sanctuary site in the brain to harbor metastatic disease. At the same time, targeted therapeutics have changed the prognoses associated with brain metastases patients from the historically dismal few months¹⁹ to several years for certain groups who receive targeted agents and radiotherapy²⁰. This has transformed the paradigm of management for brain metastases patients from rapid palliation to treatments with durable local control and few long-term side effects.

Radiotherapy (RT) is the mainstay of treatment for patients with brain metastases¹, with a shift over the past two decades from whole brain radiotherapy (WBRT), which treats the entire brain, to focal stereotactic radiosurgery (SRS) for patients with a limited number or volume of tumors^{2,21,22}. Randomized trials have shown that WBRT provides no survival benefit over SRS for these patients¹. SRS targets the metastases alone with high, ablative doses of radiotherapy, most commonly in a single treatment, with minimal interruptions to systemic therapy schedules.

The challenge of radiation-induced cognitive decline. While radiotherapy is indispensable for the management of intracranial tumors, it is associated with an inevitable decline in neurocognitive function in up to 90% of patients who survive more than 6 months after treatment²³. This manifests with changes in verbal and nonverbal memory, language and semantic processing, attention and processing speed, and/or executive functioning, and can be devastating for patients and their quality of life. Neurocognitive outcome is increasingly being recognized as a primary endpoint in brain tumor clinical trials, next to tumor control and patient survival^{7,24,25}. WBRT is notorious for significant post-treatment cognitive decline, and cognitive-sparing therapies that have been explored on WBRT trials include hippocampal-avoidance^{7,25-27} and the addition of medications like memantine (N-methyl-D-aspartate receptor blocker)²⁸ or donepezil²⁹.

A recent landmark phase III randomized controlled trial, Alliance study N0574, compared SRS alone vs. SRS + WBRT for patients with limited (1 to 3) brain metastases, with neurocognitive decline as the primary outcome⁵. The rate of cognitive deterioration at 3 months after treatment was significantly higher in the SRS + WBRT arm (91.7% vs. 63.5%), establishing SRS alone as the less toxic option and reflecting a general consensus in treatment strategy for limited brain disease^{1,2,22}. Yet the most striking result from this trial was the **high rate of cognitive deterioration (nearly 64% at 3 months) with SRS alone**. Another Alliance trial, N107C, which randomized patients with a resected brain metastasis to SRS vs. WBRT showed 52% cognitive deterioration at 6 months after SRS alone⁸. Clearly SRS is an improvement over WBRT for neurocognition, but the post-treatment cognitive outcomes are still dismal with standard SRS.

Mechanisms of radiation brain injury: the case for safer SRS. The pathogenesis of radiation-induced brain injury is complex^{4,30,31}. With higher, ablative single doses like those delivered in SRS, damage is driven by oligodendrocyte depletion and vascular injury with downstream white matter demyelination and necrosis³². Radiotherapy also causes inhibition of neurogenesis and depletion of neurogenic progenitor cells³³, which reside in the hippocampal dentate gyrus and subventricular zone, especially at higher doses. These effects, along with neuroinflammation, mediate radiation-induced cognitive impairment. Thus, efforts to avoid cognitive decline in SRS must be aimed at sparing critical brain regions from high doses of radiation, and **white matter tracts and the hippocampus are clear choices for avoidance**.

Imaging Tools for Cognitive Sparing. Within standard SRS planning, the division of the brain into eloquent structures to avoid remains crude; beyond the optic nerves, optic chiasm and brainstem, there is little attention paid to the anatomic and functional importance of eloquent regions. Diffusion tensor imaging (DTI) tractography can be used to non-invasively and accurately demarcate the brain's white matter pathways, and these imaging techniques have been implemented in modern neurosurgical navigation systems^{9,10}. In RT planning, such techniques have only sparsely been applied for white matter tract sparing. One previous study utilizing DTI of the corticospinal tract (white matter bundle critical for motor functioning) in RT planning showed reduced motor complications in a retrospective cohort³⁴, and another similar study found that relative sparing of the corticospinal tract was feasible using DTI³⁵. A retrospective DTI study correlated high RT doses to the arcuate fasciculus with symptomatic aphasia in 12 patients with brain lesions³⁶. Despite these initial studies, there are no prospective data on the use of DTI for increasing precision and white matter avoidance in SRS.

Hippocampal avoidance has been an area of great interest for cognitive sparing in the setting of WBRT^{25,26}, but has not yet been examined prospectively for cognitive sparing SRS. A recent retrospective planning study showed that sparing the hippocampi was feasible with SRS³⁷. We contend that **brain SRS should be safer and more precise**, and that by sparing eloquent white matter tracts and the hippocampi, this could help mitigate the cognitive effects of radiation injury.

Imaging as a biomarker of injury: Radiation-induced cognitive impairment can be observed before gross structural and histologic damage takes place, requiring highly sensitive means to detect these changes. Novel magnetic resonance imaging (MRI) techniques allow us to directly and non-invasively measure microstructural radiation-induced changes to brain tissue in vivo, and correlate with radiation dose effects and downstream cognitive outcomes. Diffusion tensor imaging (DTI), a highly sensitive technique to identify changes in white matter, measures the diffusion of water on a microscopic scale using directional gradients¹². Animal studies have shown that changes in diffusion imaging biomarkers correlate with pathologic white matter demyelination and axonal injury after radiation^{38,39}. In humans, DTI has been used to study dose-dependent white matter changes after RT^{16,40} and correlate these with cognitive functioning^{41,42}.

Measuring hippocampal volumetric changes with high-resolution 3D volumetric MR imaging has proven clinical utility in a variety of diseases, including Alzheimer's disease^{43,44}, temporal lobe epilepsy⁴⁵, and traumatic brain injury⁴⁶. In the setting of partial brain irradiation, there is evidence that higher RT dose to the hippocampus may be associated with worse memory impairment^{47,48}. Given the sensitivity of the hippocampal area to radiation

injury, our group has applied this quantitative biomarker to measure hippocampal volume changes in brain tumor patients receiving fractionated brain RT^{15,18,49}.

In this proposal, we introduce advanced diffusion and volumetric imaging techniques along with innovative, automated image parcellation methods to identify critical brain regions, incorporate into cognitive-sparing SRS, and analyze biomarkers of radiation response. This work will advance our understanding of neurocognitive changes after brain SRS and help create interventions that preserve cognitive-function in brain metastases patients.

3. Research Plan

We will prospectively enroll 60 adult patients with 1-3 brain metastases who are eligible for treatment with intracranial stereotactic radiosurgery (SRS) at UC San Diego(UCSD)/Moore's Cancer Center.

Inclusion criteria include: age ≥ 18 ; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (score of 0, no symptoms; 1, mild symptoms; 2, symptomatic, $< 50\%$ in bed during the day); pathologic confirmation of extra-cerebral tumor site (i.e. breast, lung, melanoma); ability to answer questions and follow commands via neurocognitive testing; estimated life expectancy > 6 months.

Exclusion criteria include: inability to undergo MRI with contrast, prior WBRT, ineligibility for brain SRS (i.e. leptomeningeal metastases; metastases from lung small cell carcinoma or primary CNS lymphoma), ineligibility for cognitive-sparing (tumor infiltrating hippocampus or critical white matter (WM) tracts). Concurrent chemotherapy with brain SRS is not allowed on study. These criteria closely follow the Alliance Trial N0574⁵, given that the cognitive deterioration rate from their standard SRS arm will be used as historical controls to power the current trial. Patient and tumor-specific variables including age, sex, race/ethnicity, educational status, occupation, primary tumor histology, systemic therapy, use of steroids and anti-epileptic drugs, tumor number, tumor size and tumor location, will be prospectively recorded.

The study protocol and timeline for each patient is shown in Figure 1 below. Patients will undergo MR imaging with DTI and 3D volumetric imaging at baseline (pre-SRS), and 1 month, 3 months, and 6 months afterwards. This regimen of post-SRS MR imaging is clinical standard of care². Segmentation of critical white matter and hippocampal volumes will be performed pre-SRS for use in brain SRS planning. Formal neurocognitive assessments will be performed at baseline and 3 months post-SRS⁵.

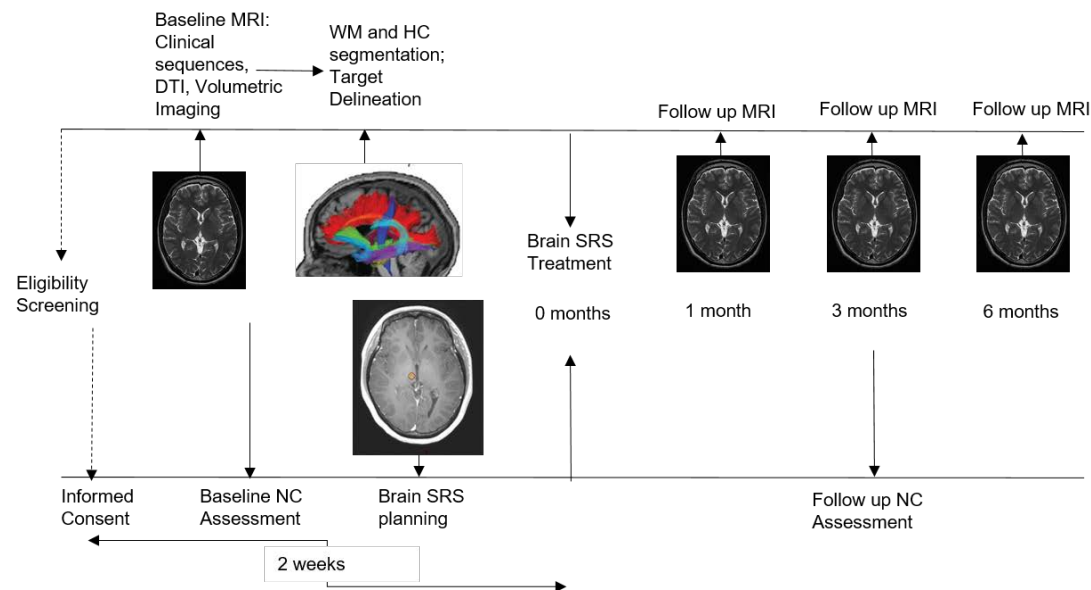


Figure 1. Timeline of consent, MRIs, Neurocognitive (NC) assessments, SRS planning and Delivery, and Follow-ups. WM=White matter; HC=Hippocampus.

Recruitment

Subjects will include those patients seen at UC San Diego/Moore's Cancer Center. A study coordinator will screen for eligible adult patients with brain metastases. They will review the patient's medical record and determine if they would be a candidate for the study. The principal investigator will be notified of subject eligibility and consult

with the treating radiation oncologist as to whether the patient is eligible. Study investigator(s) will approach the subject and offer participation in the trial. Subjects willing to participate will sign informed consent, approved by the UC San Diego Institutional Review Board. Approximately 150 patients are treated at UCSD yearly that meet our eligibility criteria.

Inclusion Criteria

1. Patients 18 years or older
2. One to three brain metastases targets, all smaller than 3 cm in diameter (intact or resected tumor bed)
3. Eastern cooperative Oncology Group (ECOG) performance status 0-2 (score of 0, no symptoms; 1, mild symptoms; 2, symptomatic, <50% in bed during the day)
4. Ability to answer questions and follow commands via neurocognitive testing
5. Estimated life expectancy greater than 6 months
6. Pathologic confirmation of extracerebral tumor site (eg, lung, breast, prostate) from either the primary site or a metastatic lesion
7. Willingness/Ability to undergo brain MRI scans
8. Able to give informed consent

Exclusion Criteria

1. Pregnant or nursing women
2. Women of childbearing potential unwilling to use adequate contraception
3. Inability to complete a magnetic resonance imaging scan with contrast
4. Tumor directly invading the critical area to be spared (for example a patient with tumor invading a critical white matter tract; ineligible for cognitive-sparing)
5. Planned chemotherapy during SRS (on the day of SRS)
6. Previous whole brain radiation therapy
7. Leptomeningeal metastases (ineligible for SRS)
8. Metastases from primary germ cell tumor, small cell carcinoma, or primary CNS lymphoma (ineligible for SRS)

Screening Evaluation

Evaluation includes standard studies for brain metastases which may include but are not limited to: appropriate blood work including CBC and a complete metabolic panel and brain MRI. Previous biopsy results and medical history are necessary to evaluate disease status. There are no study-related screening procedures other than the informed consent process.

Informed Consent

Subjects will be asked to provide written consent, using the IRB-approved consent form. The consent process will take place prior to performing any study related procedures and in a private location. The Investigator or study coordinator will describe the study, including detailed information about risks and benefits, to potential subjects. The investigator or study coordinator will provide potential subjects with an IRB-approved consent form. Subjects will be given ample time to read this consent form at the same visit or may take it with them to read at another time. Potential study subjects will be given the opportunity to ask and receive answers to all questions they may have about the study, its risks and benefits, or the consent form itself before signing the consent form. As this research is subject to HIPAA privacy rule provisions, participants will also be requested to sign a separate authorization for the use of protected health information (i.e., HIPAA form specific to the research study). The investigator or study coordinator will obtain informed consent in a language understood by the prospective using certified translations of study documents and qualified translators, where applicable.

Subjects who fulfill the eligibility criteria will be offered further participation in this study. Only subjects who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., subjects initials, study numbers, etc.) recorded on the Screening/Enrollment Log.

A copy of the signed informed consent and assent (when applicable) forms and HIPAA authorization will be placed in the research subject's medical record. The original consent form and HIPAA authorization will be retained in the master research file.

Standard of Care Treatment Procedures

Intracranial SRS will be performed identically to standard of care, except for implementing additional imaging techniques and software for additional regional avoidance for cognitive sparing, as outlined below. In cases where sparing of these structures cannot be performed without significantly sacrificing treatment of the tumor or another critical structure, this will be recorded and the default will be the standard clinical plan. While clinical benchmarks of SRS quality will not be sacrificed on this study, there is a possibility that changing the SRS plan to achieve cognitive sparing may change the dose distribution to other structures in the brain. It is unclear whether this would change any clinical outcomes since SRS plans must adhere to the same rigorous standards as the current standard of care.

Study Procedures

Neuroimaging:

MRI acquisition and pre-processing: All MR imaging will be performed on a 3T Signa Excite HDx scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with an 8-channel head coil, at the UCSD Center for Translational Imaging and Precision Medicine (CTIPM). The imaging protocol includes pre- and post-contrast 3D volumetric T1-weighted inversion recovery spoiled gradient-echo sequence, and a 3D T2-weighted FLAIR sequence. Diffusion-weighted data will be acquired using a single-shot pulsed field gradient spin-echo EPI sequence with diffusion weightings (b-values) of 0, 500, 1500, and 4000 s/mm², with 6, 6, and 15 unique gradient directions for each non-zero b-value, respectively. T1- and T2-weighted imaging data will be corrected for distortions attributed to gradient nonlinearities⁷⁴ and imaging non-uniformities arising from bias fields⁷⁵. Diffusion-weighted data will be corrected for spatial distortions arising from eddy currents⁷⁶, and B0 field inhomogeneities⁶⁴ using methods described in the literature and developed at our institution. Imaging series at each time point will be co-registered to each other using a rigid-body registration algorithm and mutual information-based cost function.

MRI study acquisition: The image acquisition parameters, including the echo time (TE), repetition time (TR), inversion time (TI), diffusion time (TD), and field-of-view for the T1-weighted, FLAIR, and diffusion-weighted sequences are included below:

	TE (ms)	TR (ms)	TI (ms)	TD (ms)	Field-of-View (mm)
T1	2.8	6.5	450	-	240 x 240 x 200
FLAIR	126	6000	1863	-	240 x 240 x 204
Diffusion	97	1700	-	90	240 x 240 x 120

RSI-modeling of DWI: As a summary, the diffusion-weighted signal in each voxel is modeled as a linear combination of the response functions of different diffusion components with pre-specified diffusion properties (primary and secondary apparent diffusion components) and geometries (spherical or cylindrical). The contribution of each component to the overall signal is then estimated using a Tikhonov-regularized linear regression. The signal contribution from any one or combination of these components can then be isolated and used for further analysis. In brain tumors, the RSI framework consists of four components: spherically-restricted, cylindrically-restricted, cylindrically-hindered and spherically-free. The signal contribution of the cylindrically restricted component can be thought to arise from pools of water whose motion is impeded (trapped) by the white matter axons, and can then therefore be used in its segmentation while minimizing the influences of other populations of water (such as edema) within the same voxel.

Estimation of tensor and RSI-derived biomarkers: Diffusion data acquired using b-values of 0, 500, and 1500 s/mm² will be fit to a single tensor using a linear least-squares optimization of the log-transformed signal at each voxel. The diffusion tensors will then be used to estimate 3D volumes of the mean, axial, and radial diffusivity as well as the FA. Second, the entire diffusion data set will be fit using the RSI framework described previously to generate signal contributions of the 4 diffusion components (spherically restricted, cylindrically-restricted,

cylindrically-hindered, and spherically free). The fraction of the total signal described by the cylindrically-restricted component will be estimated at each voxel location, and used as an RSI-derived feature of white matter structure.

White matter and hippocampal segmentation: Detailed descriptions of the RSI framework for modeling the diffusion-weighted signal as a function of the b-value and gradient direction has been previously published by our group⁵³. The cylindrically-restricted signal, assumed to arise from water trapped within white matter axons, is fit to a diffusion tensor, from which the per-voxel direction of the primary eigenvector (V0) and the fractional anisotropy (FA) are estimated. Population-based atlases of FA and V0 with ground-truth per-voxel white matter labels will then be non-linearly registered and resampled to the patient diffusion space⁶². This will be performed in AtlasTrack. The white matter atlas will be used to estimate the probability that a given patient voxel belongs to a particular white matter label. The voxel will be assigned the white matter label with the largest probability.

Pre-contrast high resolution volumetric T1-weighted images will be used as the input for the automated hippocampal segmentation software, FreeSurfer^{65,66} (<https://surfer.nmr.mgh.harvard.edu/>). Per-voxel segmentations of the hippocampi, with unique labels for each hemisphere, will then be extracted. White matter and hippocampal segmentations will be visually inspected for accuracy and manually corrected, if needed, by Dr. Hattangadi-Gluth (PI) and Dr. Farid (neuro-radiologist).

Critical Structures for Sparing: Brain structures to be included for cognitive-sparing (white matter tracts and hippocampi) are shown in Table 1. The rationale for hippocampal avoidance has been discussed previously⁷⁷. The cingulum, including the cingulate and parahippocampal portions, corpus callosum, and fornix were chosen based on their radiation sensitivity¹⁷ and critical importance to memory and attention/processing speed⁷⁸. The arcuate fasciculus is critical for language⁷⁹ and preliminary evidence has shown that selective avoidance during SRS may prevent radiation-induced language disorders³⁸. Microstructural changes to the inferior frontostriatal tracts results in poorer executive functioning⁸⁰, necessitating its inclusion. The uncinate fasciculus is implicated in both executive functioning and memory formation/retrieval, and the inferior longitudinal fasciculus in language and memory⁷⁸.

SRS Planning with Knowledge-based Planning (KBP): Radiation treatment plans are manually planned by medical dosimetrists and physicists using commercial treatment planning software. Brain SRS planning is especially complicated given the higher doses, small margins, and critical structures involved. This planning process is time-consuming and inefficient, requiring multiple iterations over several days, with a wide variation in plan quality^{66,67}. Automated knowledge-based SRS planning, which was developed by Dr. Moore and his team, is an innovative approach which eliminates the variability and inefficiency of standard planning, allows the addition of new critical structures and optimization objectives into complex treatment plans, and delivers high quality, deliverable brain SRS plans^{68,69}. This automated SRS planning system is ideal for use in this trial where new clinical objectives for critical structures (eloquent white matter tracts, hippocampus) will need to be optimized and accounted for in planning each brain SRS case, with targets in different areas around the brain. This system is already integrated into our clinical workflow with a fast planning turn-around time of 20-35 minutes.

Table 1: White Matter and Hippocampal Structures for Cognitive-Sparing

Eloquent Cognitive Structures
Cingulum
Uncinate Fasciculus
Inferior longitudinal fasciculus
Corpus Callosum
Arcuate fasciculus
Inferior frontostriatal tracts
Fornix
Hippocampus

*all bilateral except Corpus Callosum

Neuropsychological data: A well-established, well-validated, battery of neurocognitive tests will be performed prior to SRS and 3-months following SRS to evaluate different neurocognitive domains including verbal memory, executive functioning, attention/processing speed, and language. These are shown in Table 2. This cognitive battery takes 30 minutes to perform. This core battery is frequently employed in large-scale clinical trials, including Alliance Trial N0574⁵, because the tests are brief, repeatable, have good psychometric properties, and have been shown to be sensitive to cognitive decline in patients with metastatic brain tumors⁷⁰. Most tests have several alternate forms, making them ideal for repeat measurements. Health-related quality of life will also be assessed. Since depression may also influence test scores^{71,72}, we will administer the Beck Depression Inventory (BDI)⁷³ at each evaluation to screen for depression and include the BDI score as an additional covariate. All cognitive testing will be performed by a trained, certified neuropsychologist.

Table 2. Neurocognitive Domains and Tests

Cognitive Domain	Neuropsychological Test
Verbal Memory	<ul style="list-style-type: none"> Hopkins Verbal Learning Test–Revised (HVLTR); Immediate, Delayed Recall
Executive Functioning	<ul style="list-style-type: none"> Controlled Oral Word Association Test (COWA): letter fluency Trail Making Test Part B (TMT-B)
Attention/Processing Speed	<ul style="list-style-type: none"> Trail Making Test Part A (TMT-A)
Language	<ul style="list-style-type: none"> Boston Naming Test (BNT) Controlled Oral Word Association Test (COWA): category fluency
Mood	<ul style="list-style-type: none"> Beck Depression Inventory (BDI)
Quality of Life	<ul style="list-style-type: none"> Functional Assessment of Cancer Therapy-Brain (FACT-BR)

Radiation Planning Dose Constraints: As of yet, there are no evidence-based dose constraints for cognitive-sparing in brain SRS. Rational dose tolerances in clinical trials (a dose which predicts a particular likelihood of dysfunction) must be calculated based on normal tissue complication probability (NTCP) analyses⁷⁸. Hippocampal dose constraints used in WBRT trials²⁵ are not relevant to SRS (where high ablative doses are delivered) given that the prescription dose is so low in WBRT (30Gy in 10 fractions). In another IRB-approved longitudinal, prospective, observational study of primary brain tumor patients receiving definitive fractionated radiotherapy, we have been prospectively tracking domain-specific cognitive decline with all the standard cognitive measures in Table 1. Based on preliminary NTCP analyses from 28 patients, we found that maximum dose to the left hippocampus >28Gy (in 30 fractions) predicted for a >10% risk of significant decline (reliable change index <90% confidence interval) in HVLTR total and HVLTR delayed memory scores (p=0.01). Conversion of this maximum dose to a single fraction SRS dose constraint based on the linear quadratic formalism with $\alpha/\beta=2.5$ Gy for normal brain tissue yields a hippocampal maximum dose of 8.4Gy. This conversion was performed by solving for isoeffective dose by equating biologically effective doses from SRS single-fraction treatment, D_{SRS} , and reference fractionation, dose D_{ref} , delivered in N_{ref} fractions (set to 30):

$$D_{ref} \left(1 + \frac{D_{ref}}{\alpha/\beta} \right) = D_{SRS} \left(1 + \frac{D_{SRS}}{\alpha/\beta} \right)$$

For white matter tracts, within the left parahippocampal cingulum, V45Gy at 20.6% was predictive of significant decline on HVLTR total and HVLTR delayed memory scores (p=0.001). Conversion of this to a single fraction SRS dose constraint with $\alpha/\beta=2.5$ Gy for normal brain tissue (same method as above) yields a white matter maximum dose of 12Gy. Furthermore, a recently published analysis of SRS dose tolerances for the optic pathway (another critical white matter tract) established 12Gy in 1 fraction maximum dose as resulting in <1% risk of radiation-induced optic nerve neuropathy, supporting this white matter constraint. Dose constraints for single fraction SRS are summarized in Table 3. For lesions receiving 3 fractions, isoeffective dose constraints from Table 3 will be calculated based on $\alpha/\beta=2.5$ Gy.

Table 3: Dose Constraints

Eloquent Cognitive Structures	Max Dose (Gy)
Cingulum	12
Uncinate Fasciculus	12
Inferior longitudinal fasciculus	12
Corpus Callosum	12
Arcuate fasciculus	12
Inferior frontostriatal tracts	12
Fornix	12
Hippocampus	8.4

*all bilateral except Corpus Callosum

SRS planning, plan optimization, and treatment: Patients will undergo setup, immobilization and simulation for frameless linear accelerator-based intracranial SRS with non-coplanar volumetric modulated arc radiosurgery (VMAR) as previously described⁷⁹. White matter and hippocampal 3D segmentations will be imported into the Eclipse treatment planning software (Varian Medical Systems, Palo Alto, California) for each patient. High-resolution, distortion-corrected stereotactic-protocol contrast-enhanced T1-weighted images will be co-registered with CT. Target volumes (enhancing tumor + 1mm margin for planning target volume, PTV) and standard organs at risk (OARs), such as the brainstem, optic nerves, and optic chiasm, will be manually contoured by the treating radiation oncologist. Tolerance doses for SRS planning include the white matter and hippocampal doses above, and standard single fraction dose constraints for other OARs as previously published⁸⁰. Prescription doses to each target lesion will be based on volume: 24 Gy in a single fraction if the target is less than 1 cc, 22Gy for 1.1-4cc target, and 20Gy for those between 4.1-10cc. For larger lesions or tumor beds, fractionated SRS with 24Gy in 3 fractions will be used respecting the constraints above. These doses closely follow a large Japanese SRS study²² with modern target volume-based doses, and are also similar to the Alliance N0574 trial⁵.

Automated knowledge-based brain SRS plans will be generated as previously described⁶⁹, with dose optimized within standard clinical guidelines (98% of the PTV receiving 100% of the prescription dose^{34,36}) and tolerance OAR doses above. Dose volume histograms will be assessed and re-optimized if necessary, without compromising coverage of tumor or sparing of standard critical structures (i.e. brainstem, optic structures.). All plans will be reviewed by the PI and the UCSD CNS Radiosurgery team for approval. Treatment delivery will follow the UCSD standard frameless brain SRS protocol⁷⁹.

Patients will be seen by the treating physician on the day of SRS, and on subsequent follow-up visits. They will be followed closely with clinical and imaging exams for safety and tumor recurrence (i.e., 1 month, 3 months, 6 months post-SRS). All treatment-related toxic effects and adverse events will be recorded according to NCI Common Terminology Criteria for Adverse Events, version 4.0. Local tumor control rates for each treated lesion will be assessed according to the revised Response Assessment in Neuro-oncology (RANO) criteria^{81,82}.

Payment

Parking for study patients related to study visits will be complementary. Subjects will be compensated \$100 for participation in this study to help compensate for time and travel costs.

Statistical Considerations

Primary Objective Analysis:

Cognitive test results (pre- and post-SRS) will be scored based on standardized published norms^{72,87}. Cognitive deterioration will be defined as a decline of greater than 1 SD on at least 1 of the 7 cognitive tests (Table 2, not including BDI or FACT-BR). Fisher's exact 2-group binomial test will be used to compare the proportion of patients with 3-month post-SRS cognitive deterioration between the current cognitive-sparing SRS study and previously reported with standard SRS.⁵ Further analyses of pre- to post-SRS cognitive change for each test will

utilize a reliable change index (RCI)⁸⁷. This index is derived from the standard error of measurement of each test, and it represents the 90% confidence interval (CI) for the difference in raw scores from baseline to follow-up that is expected if no real change has occurred. RCI values below the 90% CI are indicative of significant decline. RCIs also account for practice effects, which is ideal for this study where evaluations are 3 months apart. One-sample t-tests ($H_0=0$) will be used to determine significant group decline in RCIs by test and cognitive domain. Pearson correlation coefficients will be used to assess associations between RCIs and depression scores. Bonferroni corrections will be applied to control for Type I errors due to multiple comparisons.

With RCI at 3-months post-SRS as the outcome variable, linear regression modeling will be used to analyze patient-specific (e.g. age, sex), tumor-specific (e.g. histology, number of lesions, imaging progression), and treatment-specific (e.g. previous chemotherapy, anti-epileptic drugs) predictors of neurocognitive change after cognitive-sparing SRS. Model selection will be based on Akaike Information Criterion (AIC)^{88,89}. Given the small sample size and multiple variables of interest, this will be an exploratory analysis. Given that cognitive-sparing on this study will not be performed at the sacrifice of tumor coverage, we expect the overall local control and survival rates in the cohort to be comparable to those in other studies of SRS alone for patients with 1-3 brain metastases^{1,5,6,22}. Treated tumor local control rates will be assessed at 3- and 6-months post-SRS. Local tumor control of each treated lesion will be assessed with modified RANO criteria⁸⁴ where tumor progression is defined as >25% increase in the size of a treated lesion. Tumor progression of treated metastases will be evaluated independently of the development of new lesions⁵. Local tumor control rate at 6 months and overall survival rate (death from any cause) at 12 months will be compared to historical values⁵ using a 1-sample t-test.

Secondary Objective Analyses

The imaging biomarker of each structure (mean white matter diffusivity metrics and hippocampal volume) will be modeled as a function of time using linear mixed effect models^{13,16}. These models are well-suited for longitudinal analysis since they account for within-subject correlation between repeated measures, and allow for incomplete outcome data. Individual structures will be classified based on whether they received greater or less than the median dose for that structure across all patients. The interaction of dose and time will be tested within the model to assess whether dose mediates longitudinal trends. In addition, potential fixed-effect covariates will be selected from a list of patient and tumor-specific variables, such as age, sex, tumor size and location. Model selection will be based on AIC. To account for correlated observations within subjects, patient-specific random intercepts and time-associated slopes will be tested.

Associations between average changes in imaging biomarkers at the 3-month time point and RCI of domain-specific neurocognitive tests will be estimated using linear models with model selection based on AIC. As an exploratory analysis, associations between early changes in imaging biomarkers, measured at the 1-month time point, with RCIs of domain-specific neurocognitive tests will also be estimated using the same methodology. This may help to identify those metrics that can serve as early indications of 3-month neurocognitive deterioration.

TractCrawler imaging software will be used to generate slices perpendicular to the medial axis for each white matter structure. We will then generate slice-averaged values of diffusion imaging metrics as a function of length along the medial axis of the tract, defined in a common coordinate system across patients at each time point. Sensitivity metrics will be generated per-patient and per-slice to quantify the degree to which changes in diffusion metrics in that slice differ from the mean change across the entire structure for each of the post-RT time points compared to baseline. T-tests can then be used to identify regions (slices or groups of slices) along the length of the white matter tract where changes are significantly greater or smaller than the rest of the tract.

Feasibility: Accrual of 60 patients over 3 years is feasible given that over 100 brain metastases patients are treated yearly at our institution that would meet eligibility criteria. Patients will be compensated \$100 for study participation to offset transportation costs and time. We will enroll approximately 3-4 patients per month, allowing full enrollment to be completed by around 15-20 months. This will allow all testing and analyses to be completed within the four-year grant period. The imaging methods, processing techniques and automated KBP capabilities are already integrated into our brain tumor imaging and brain SRS workflow, making the study execution highly feasible. The team of investigators and collaborators have already established a successful research and clinical collaboration for this and other research projects and grants.

Sample Size Determination: This study is powered based on the endpoint of cognitive deterioration at 3 months post-SRS, defined as decline of greater than 1 standard deviation (SD) from baseline on at least 1 of the neurocognitive tests. This was the primary endpoint of the Alliance N0574 study. With 60 accrued patients

and assuming a 20% drop-out rate, we will have sample size $n=48$. We have 85% power to detect a change in the cognitive deterioration rate from 64% in standard SRS to 42.5% in the current cognitive-sparing study with $n=48$ (Fisher's exact 2-group binomial test, 2-tailed $\alpha=0.05$).

4. Risks

The anticipated risk to patients in this study is minimal.

The MRI scans to be obtained at baseline would be added on to the same scan performed for routine SRS planning for patients. Follow up MRI would be standard of care imaging and would be obtained regardless of whether the patient is on or off study. These scans do not involve any radiation exposure. There are no additional risks associated with the research scans aside from discomfort due to the additional 8-10 minutes of scan time required. However, these scans are frequently performed as part of standard of care during presurgical planning without adverse effects. Some patients may experience claustrophobia in the MR scanner and may require the use of medications for this, as is prescribed routinely for brain MRIs when indicated.

Intracranial SRS would be performed identically to standard of care, except for adding additional regional avoidance for cognitive sparing. In cases where sparing of these structures cannot be performed without sacrificing treatment of the tumor or another critical structure, this will be recorded and the default will be the standard clinical plan. While clinical benchmarks of SRS quality will not be sacrificed on this study, there is a possibility that changing the SRS plan to achieve cognitive sparing may change the dose distribution to other structures in the brain. It is unclear whether this would change any clinical outcomes since SRS plans must adhere to the same rigorous standards as the current standard of care.

The directed neurocognitive evaluations are not standard of care unless a patient requires clinical referral to neuropsychology. Neuropsychological testing as described above is done verbally one-on-one with a licensed neuropsychologist. This is a 30 minute testing session that is frequently employed in clinical trials. One possible risk to neurocognitive testing is a possible increase in psychological strain in susceptible individuals (e.g., to the extent that thinking about their cognitive difficulties is stressful, patients might experience stress in being evaluated). However, these neurocognitive evaluations are designed to be non-stressful and to be used for patients who may have cognitive difficulties. Patients will be counseled that the testing is merely to assess particular functioning (short term memory, attention, etc) and that this would not affect their clinical care. These tests are not anticipated to be particularly stressful in any way and patients can stop the testing at any time. Patients may find it stressful to know whether they have deficiencies in their neurocognitive functioning. They can request to discuss this with the PI or neuropsychologist if they wish.

As mentioned, all imaging and neuropsychological data will be kept in a file that will not contain patient-identifying information. Thus, the risk for a breach of confidentiality is minimal. Moreover, the data will be stored in password-protected files only on the computers of investigators directly involved in the research.

5. Privacy and Confidentiality

Confidentiality of a subject's protected health information will be maintained by the following methods: study-specific records containing protected health information, and copies of study-related medical records, will be kept in locked filing cabinets at the Moores UCSD Cancer Center locked research administrative offices (Clinical Trials Office).

Computers containing access to protected health information will have password-access; and screen-savers will be utilized to prevent unauthorized viewers from inadvertently seeing information. Protected health information will be stored on secure servers. The servers supporting these studies are located inside a locked rack within the San Diego Supercomputer data center. The facility features restricted access by means of personal codes (PINs) and biometrics, and is monitored 24 hours a day 7 days a week. The electrical power is backed up by battery-powered uninterruptible power supplies, as well as by on-site generators. Both servers are behind firewalls configured to allow access only to credentialed personnel within the UCSD network. Velos, the clinical

trials management system, maintains an additional internal access control mechanism via user names and passwords. Data transactions executed over our intranet are encrypted via Secure Sockets Layer.

Access to a subject's protected health information will be limited to those study personnel who need to use it to accomplish the purpose of the research, and the minimum necessary information to accomplish the purpose of the research will be collected, stored, used, and reported. When protected health information is sent outside the University of California, San Diego, it will be disclosed only to those parties listed in the subject's authorization, and an audit trail log will be maintained of what information was sent and to whom it was sent.

Patients will be assigned a random study identification number for purposes of organizing the data and the data for the study will be kept in 2 main files: the "central" file and the "code" file. After the data is collected, it will be stored in the "central" file (that will contain no patient-identifying information such as name, date of birth, MRN, etc.). A separate, password-protected "code" file will contain the mappings of patient name with their random study identification number. This file will be password-protected, with the password known only to CITI-trained study personnel, and it will be stored exclusively on the computer of the principal investigator. These patient identifiers will be destroyed following the collection and aggregation of the dataset, and thus the patient data will be officially de-identified at this time.

Subject identifiers will be destroyed by the PI at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is required by law.

6. Data Safety and Monitoring

Personnel responsible for the safety review and its frequency

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. The principal investigator has the authority to stop or suspend the study or require modifications. This study has been approved by the UCSD Institutional Review Board.

Attribution of Adverse Events

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures by the principal investigator according to the following categories:

Definite: Adverse event is clearly related to investigational procedures

Probable: Adverse event is likely related to investigational procedures

Possible: Adverse event may be related to investigational procedures

Unlikely: Adverse event is likely not to be related to the investigational procedures
Unrelated: Adverse event is clearly not related to investigational procedures

Plan for Grading Adverse Events

Adverse events noted during the study will be graded using the NIH Common Toxicity Criteria for Adverse Events scale (CTC), version 4.0 (<http://evs.nci.nih.gov/ftp1/CTCAE/About.html>). Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is:

1 - Mild

2 - Moderate

3 - Severe

4 - Life threatening

5 - Death

Plan for Determining Seriousness of Adverse Events

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. Is life-threatening

2. Results in in-patient hospitalization or prolongation of existing hospitalization
3. Results in persistent or significant disability or incapacity
4. Results in a congenital anomaly or birth defect
5. Results in death
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
7. Adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the HIC or HSC is necessary.

Plan for reporting serious AND unanticipated AND related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others

The principal investigator will report the following types of adverse events to the HIC, and to any and all co-investigators:

- a) Serious AND unanticipated AND possibly, probably or definitely related events
- b) Anticipated adverse events occurring with a greater frequency than expected
- c) Other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the HIC within 48 hours of it becoming known to the investigator, using the appropriate forms found on the website.

The principal investigator will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

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