Pilot Study of Same-session MR-only Simulation and Treatment with Stereotactic MRI-guided Adaptive Radiotherapy (SMART) for Oligometastases of the Spine

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Protocol #: 201903023
Version Date: 02/27/2023

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Study Device: MRIdian Linac System from ViewRay (0.35T MRI combined with a linear accelerator (MR-linac))
NCT #: NCT03878485
Funded by: Departmental of Radiation Oncology (seed grant)

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Protocol Revision History

Initial Approval Version	**03/04/2019**
Amendment #1 Version	**11/04/2019**
Amendment #2 Version	**11/02/2020**
Amendment #3 Version	**05/16/2022**
Amendment #4 Version	**09/20/2022**
Amendment #5 Version	**11/23/2022**
Amendment #6 Version	**02/27/2023**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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PROTOCOL SUMMARY

Synopsis

Title:	Pilot Study of Same-session MR-only Simulation and Treatment with Stereotactic MRI-guided Adaptive Radiotherapy (SMART) for Oligometastases of the Spine
Study Description:	This is a pilot study evaluating the ability to treat patients with metastatic disease to the spine with same-session MRI-only simulation and treatment with MRI-guided radiotherapy.
Objectives:	Demonstrate that same-session MRI-only simulation and treatment with stereotactic MRI-guided radiotherapy (SMART) for spinal oligometastases is feasible.
Endpoints:	Primary Endpoint(s): Feasibility will be defined as delivery of the first fraction of same-session MRI-only simulation and treatment with SMART in the first on-table attempt for at least 70% of patients. Secondary Endpoints: None
Study Population:	Patients with at least one disease site deemed to be suitable for treatment with spine SBRT as per radiation oncology evaluation.
Phase:	Not applicable.
Description of Sites/Facilities Enrolling:	This is a single center study enrolling at Siteman Cancer Center at Washington University School of Medicine.
Description of Study Intervention:	Consenting and eligible patients will receive MRI-only simulation and stereotactic MRI-guided radiotherapy (2 or 5 fractions).
Study Duration:	48 months for accrual + 4 months of participant duration (screening, treatment, and follow-up) + 12 months for data analysis = 64 months
Participant Duration:	Maximum of 4 months per patient (screening, 2 or 5 fractions of radiotherapy, 3-month follow-up).

1 BACKGROUND

1.1 Spinal Metastases

Despite advances in cancer therapy, metastatic disease is an eventual reality for innumerable oncology patients. With advances in systemic therapies, the life expectancy of cancer patients increases, concomitantly increasing the global burden of metastatic disease (1). As patients live longer with metastases, the role of local therapy to ablate individually symptomatic and threatening tumor foci is increasingly important. Spinal metastases, in particular, are considered critical disease foci for local treatment due to the substantial morbidity and mortality of disease progression in sites proximal to the spinal cord and nerve roots (2).

1.2 Stereotactic Body Radiation Therapy for Metastatic Disease

Within radiation oncology, stereotactic body radiation therapy (SBRT) is a favored modality for local ablation of metastatic disease. SBRT, defined as delivery of high-dose radiation in five or fewer fractions, offers sharp dose gradients that allow physicians to ablate such disease while sparing immediately adjacent critical structures. In-field control rates of metastases treated with SBRT are roughly 80% up to four years after therapy, even in series examining heterogeneous histologies, sites, and dose (3-5). SBRT is particularly favored for oligometastatic disease, a phase in oncogenic progression where malignant clones have not yet achieved widespread malignant potential, often defined as three or fewer progressive sites of disease. Ablation of metastases, particularly oligometastases, may improve not only patient functional status through local control but has also recently been shown to improve overall survival in solid tumor histologies (6-8). Although a majority of patients who undergo SBRT for oligometastatic disease will experience relapse with distant metastases, approximately 20% of patients with in-field control remain disease-free at 2-4 years of follow-up (3, 4, 6). In a randomized prospective study by Palma et al., delivery of SBRT for oligometastases of broad histologic types (five or fewer sites) improved median overall survival from 28 to 41 months compared to palliative standard of care treatments such as chemotherapy (7). Of patients treated with SBRT or other metastectomy who experience recurrence, as many as 60% have very limited metastatic progression that could be amenable to further intervention such as repeated SBRT (8). Epidemiologic data suggests that patients undergoing such repetitive metastectomy have a survival benefit that is comparable to those undergoing their first procedure (9).

Regarding spine metastases in particular, spine SBRT is a proven treatment modality and is often preferred over conventionally fractionated radiation for patients who have good performance status, potentially long projected life spans, and/or radioresistant tumors (10). However, given the proximity of the spinal cord, the clinical standard of care requires magnetic resonance imaging (MRI) or computed tomography (CT) myelography imaging in the process of radiation planning, in order to visualize the spinal cord itself as an organ-at-risk (OAR).

Typically, the spine SBRT treatment-planning paradigm is initiated through a simulation (planning) CT and a simulation MRI (or fusion of previously obtained diagnostic MR

image sets). Simulation typically takes place within several business days of the clinical consult appointment, and an additional 1-2 weeks are needed from the time of simulation before a treatment plan is prepared and verified for delivery. Therefore, a patient may not start treatment until two weeks after their consult appointment. This workflow prolongs patient discomfort from painful osseous and nerve pain and increases the opportunity for further threatening of neurologic functions like ambulation and continence as tumors progress. Ideally, this workflow could be substantially compressed through advances in technology and treatment planning processes.

1.3 Magnetic Resonance Image-guided Radiotherapy

One such advance within radiation oncology is the emergence of magnetic resonance image-guided radiotherapy (MRgRT) over the past five years. MRgRT, which involves RT delivery using an integrated MRI, radiotherapy device, and dedicated treatment planning system, has become a staple at our institution since we became the first to clinically implement it in 2014 (11). Currently, two MRgRT devices are widely used: the original 0.35 Tesla imaging unit integrated with a tri-Cobalt-60 radiotherapy device and the newer device comprising a 0.35T MRI combined with a linear accelerator (MR-linac) (11, 12). Although analyses have demonstrated that complex radiation plans created for the tri-Cobalt-60 source are acceptable (13), plans for small target volumes such as for SBRT are less conformal using a tri-Co-60 device compared to a traditional linear accelerator (14). Until now, this has limited some uses of MRgRT for SBRT, such as for the spine where rapid dose fall-off and conformality adjacent to the spinal cord is critical. However, we have recently completed commissioning of the newer MR-linac device and our institutional analyses indicate that plan quality with the MR-linac is equivalent to CT-based linac plans, like those widely used for spine SBRT (unpublished internal data).

Importantly, these MRgRT devices offer both daily imaging that is sufficient for treatment planning and plan modification “online” (while the patient lies on the treatment table) (15, 16). These daily plans, typically created in response to changes in daily anatomy, are termed “adaptive radiotherapy” (ART). Stereotactic, MRI-guided ART (SMART) has become common at our institution and we have delivered 1060 adaptive treatment fractions in 190 unique treatment courses since 2014 (17, 18). Our primary use of SMART is for abdominal malignancies, for which daily planning while the patient lies on the treatment machine is a useful way to respond to inter-fraction bowel motion (17). However, the SMART treatment planning process could theoretically also be used to generate the original plan, rather than to simply adapt existing plans. For sites like the spine, where treatment is urgent and the anatomy is more predictable, the SMART paradigm might allow creation of spine SBRT plans on the day of treatment, bypassing the need for simulation. Indeed, the SMART treatment planning process already comprises nearly all components of traditional treatment planning, including volumetric imaging, target volume and organ-at-risk delineation by the physician, treatment plan generation, and quality assurance with an independent, Monte Carlo-based dose verification (15, 18).

1.4 Same-Day Radiotherapy Treatment Planning

However, the current treatment planning workflow for SMART has two key characteristics that have precluded same-day original plan generation until this point. One is that SMART is still based on the use of a pre-treatment simulation session, allowing time (1-2 weeks) for careful selection of optimal beam angles and robust planning to target a particular disease site (18, 19). Additionally, the simulation process also includes a CT image that is used to provide geometric information and tissue relative electron densities (and therefore dose) information (13). Ideally, to expedite treatment for spine SBRT, treatment planning could rely on same-day MR imaging alone to create a same-session MR-only simulation and treatment SMART plan-of-the-day.

The first of these obstacles can be sufficiently overcome for same-session MR-only simulation and treatment spine SBRT through simple pre-planning. Spinal anatomy and target volumes are fairly predictable in comparison to other disease sites and follow a pre-determined set of consensus volumes (20). Use of physics pre-planning based upon typical spinal anatomy to create a standard initial set of beam angles could mitigate some of the same-session simulation and on-table planning time requirements. Additionally, spine tumor patients almost uniformly have volumetric diagnostic spine imaging prior to radiation consult, typically with MRI. These image sets can be used in the time between treatment consult and the first treatment day to adjust the standard set of beam angles to individually optimize the tentative pre-plan before the patient is on the treatment table for clinical treatment planning. This use of pre-planning will improve the feasibility of creating the clinical plan in a time frame that is acceptable and tolerable for the patient to be on the treatment table.

Regarding CT-free treatment planning for MRgRT, some progress has been made towards this goal at other institutions, but in a limited setting of very simple radiation treatments that lack the complexity of SBRT. Investigators at the University of Wisconsin have used their MRgRT device for same-session simulation and treatment planning and delivery of the first fraction of 2D and 3D-conformal palliative spine radiation treatments (21). However, following the first treatment fraction, patients then underwent traditional CT simulation and treatment planning; ART was used only to expedite the first fraction. In their treatment planning, bulk density overrides were used to assign electron densities based on typical values for basic tissue types (bone, fat, lung, soft tissue) (21). Bulk density overrides are the only current FDA-approved mechanism for dose extrapolation in MRgRT radiation planning, and can overcome the absence of CT density information (22). Such overrides carry an anticipated dose uncertainty of <3%, which is considered acceptable (23). For reference, the International Commission of Radiation Units and Measurements (ICRU) mandates that dosimetry systems be capable of delivering dose to an accuracy of 5% (24). Other techniques using MR image processing to infer more precise (voxel by voxel) density information are emerging within the field and may be useful in the future for improving the precision of dosimetry in MRI-only planning. However, these techniques are not yet FDA-approved (25). Prospective evaluation of such techniques would be useful to inform further MRI-only treatment planning.

1.4.1 Preliminary Studies

Given that bulk-density override planning is the only FDA-approved method available to use for this study, it is important to preliminarily establish the dosimetric safety of bulk density override MR-only planning for spine SBRT. To this end, we recently completed an *in silico* evaluation of dosimetric accuracy of this method specifically for spine SBRT. Five patients previously treated with MRgRT were identified and their 0.35-T MRI and CT datasets were used to create spine SBRT plans on the MR-linac treatment planning system (TPS). Patients were selected on the basis of availability of spinal imaging and with intent to represent anatomy of both sexes and varying body habitus. Patient demographics and characteristics are listed in Table 1 below. Six clinical target volume (CTV) and planning target volume (PTV) contours were created on each patient's MRI dataset, to represent the six possible contour target volumes endorsed by the International Spine Radiosurgery Consortium guidelines, described in the next section. Three sets of unique treatment plans were then created for each of the six target volumes on all five patients and were subjected to the planning constraints identified for use in this protocol.

Table 1. Planning analysis patient demographics

Patient #	Gender	Age	Habitus
1	Male	62	Normal
2	Male	67	Obese
3	Female	66	Underweight
4	Female	60	Obese
5	Female	70	Overweight

The first set of treatment plans (6 plans per each of 5 patients, 30 total plans) were made using bulk density override MR-only planning. Specifically, the bony anatomy, as contoured by study physicians (vertebral body and adjacent ribs), as well as adjacent soft tissues and lung, were assigned standard bulk relative electron density values by tissue type: bone (1.12 g/cc), soft tissue (1.01 g/cc), lung (0.25 g/cc).

After creating the bulk-density override plans, a second set of 30 corresponding plans were created by reassigning the relative electron density values based on the co-registered CT dataset, and a comparison of plan dosimetric characteristics was made, detailed in Supplementary Table 1. For comparison of PTV coverage, two metrics were used: coverage by 100% of the prescribed dose (35 Gy) and coverage by 95% of the prescribed dose (33.25 Gy). As the dose fall-off for PTV can be steep, these two metrics were used to adequately describe the differences when a small difference in coverage appears as a large difference in dose. The maximum dose to the spinal cord, as well as doses to circumferential volumes expanded 1, 3, 5, 7, and 10 mm outward from the cord, were compared to ensure the geometric robustness of plans calculated with bulk density overrides. Last, when appropriate, the dose received by a small portion of the esophagus (when it was adjacent to the

vertebral body) was compared, as well. The dosimetric differences observed between the plans with bulk density overrides and those recalculated using CT-based relative electron densities, as delineated in Table 1 in the Supplementary Data Section below, are clinically acceptable and were on average within the 5% dose uncertainty recommended by the ICRU.

More specifically, bulk density override MR-only planning is also projected to be safe in terms of dose to the spinal cord, which is the key safety consideration for spine SBRT. The average dose discrepancy for the maximum point was well within the 5% threshold recommended by the ICRU, ranging between 0.2 and 1.8% (Suppl. Table 1). Importantly, these dose discrepancies did not result in spinal cord constraint dose violation in any of the 30 plan comparisons. The projected dose discrepancy identified also met more stringent national guidelines set by the American Association of Physicists in Medicine (AAPM). Per AAPM Task Group (TG) 71, monitor unit (dose) calculations for external photon beam radiation should display 2-3% agreement between an initial calculation method and a second redundant check (26). Similarly, per AAPM TG-142's specific recommendations for stereotactic radiation delivery, the prescribed versus delivered monitor units (dose) discrepancy should be within a 2% threshold (27). Therefore, bulk density override MR-only planning results in a dose projection that not only meets ICRU requirements but also meets more stringent national consensus guidelines in terms of projected dose to the spinal cord. **This indicates that bulk density override MR-only planning is safe for spine SBRT.**

Use of MRI-simulation alone has also been limited by concern over geometric distortions of MR and the complexities of determining of electron density information without CT. These historical obstacles have been all but eliminated by modern advancements. Nyholm et al. found that after standard corrections, uncertainty from MR geometric distortions translated to a maximum error of only 1mm. In fact, by eliminating the need for CT and MRI registration, treatment planning directly on MR images actually reduced spatial uncertainty when compared to CT-based radiotherapy (28). Indeed, based upon our preliminary *in silico* planning analysis above, the any geometric uncertainties present did not meaningfully impact dose projected to serial volumetric expansions of the spinal cord, which is the principle planning concern for safety in SBRT.

1.5 Rationale

In light of our increasing experience with MRgRT and adaptive planning and advances in MR-only planning, we propose here to evaluate the feasibility and safety of same-session MR-only simulation and treatment with SMART for spinal metastases. Although spine SBRT is a standard-of-care treatment modality, this expedited same-session MR-only simulation and treatment with SMART workflow is novel. Previously, delivery of spine SBRT has typically required several days from time of consultation to simulation and then 1-2 weeks from simulation to the initiation of treatment. On this proposed study, patients will not undergo CT simulation and will instead have same-session MR-only simulation

and treatment planning, on-table, using SMART. In this manner, patients would initiate treatment within just several days from the consult. Feasibility of the workflow will be defined as successful delivery of the first fraction of same-session MRI-only simulation and treatment with SMART on the first on-table attempt for at least 70% of patients. Patients will be treated in either a two or five fraction course over 1-2 weeks. Although our long-term goal will be to achieve a significantly shortened time from consult to treatment as compared to traditional SBRT using simulation, the present study will be driven by short-term goals of workflow feasibility and safety.

2 OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
Demonstrate that same-session MRI-only simulation and treatment with stereotactic MRI-guided radiotherapy (SMART) for spinal oligometastases is feasible by confirming that the first fraction of same-session MRI-only simulation and treatment with SMART can be delivered on the first on-table attempt for at least 70% of patients.	Delivery of the first fraction of same-session MRI-only simulation and treatment with SMART within the first on-table attempt for at least 70% of patients.	Clinically relevant
Exploratory		
1. Determine the average time (days) from patient consult appointment to successful delivery of the first treatment fraction.	Average time (days) from patient consult appointment to successful delivery of the first treatment fraction.	Clinically relevant
2. Determine the local, in-field tumor response and control rates at three months.	Local control rate Local in-field tumor response	Clinically relevant
3. Demonstrate that same-session MR-only simulation and treatment with SMART for treatment of spinal metastases will lead to comparable toxicities compared with historically reported rates using standard, CT-based SBRT assessed prospectively at three months post-treatment and retrospectively for later time-points.	CTCAE version 5, treatment related Grade 3 or higher toxicities	Clinically relevant
4. Determine the projected dosimetric differences between the study method of MRI-only planning using standard	Dosimetric differences between MRI-only planning using standard bulk density	Generation of preliminary data for

bulk density override dose calculations (which will be clinically used for all patients) and an exploratory alternative method of a novel voxel-by-voxel MRI-based dose calculation using an institutionally developed machine learning algorithm (which will be simulated for comparison but not used in clinical treatment planning).	override dose calculations and voxel-by-voxel MRI-based dose calculation using MLA	future radiation planning techniques.
5. Determine the on-table time required for same-session MR-only simulation and treatment with plan generation for the initial treatment fraction and for subsequent treatment fractions.	On-table time required for initial treatment fraction and subsequent treatment fractions	Clinically relevant

3 STUDY POPULATION

3.1 Inclusion Criteria

1. At least one disease sit e deemed to be suitable for treatment with spine SBRT as per radiation oncology evaluation.
2. Karnofsky Performance Status (KPS) ≥ 60.
3. Deemed medically fit for SBRT by treating physician
4. Diagnostic CT with images through the projected treatment area within six months prior to enrollment.
5. At least 18 years of age.
6. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Past history of radiotherapy within the projected treatment field to be treated by MRI-guided SBRT
2. Medical contraindication to undergoing MR imaging.
3. Spine metastasis resulting in symptomatic spinal cord compression.
4. Any other condition that, in the opinion of the treating radiation oncologist, renders the patient unfit for SBRT.
5. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test within 14 days of study entry.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Strategies for Recruitment and Retention

Patients will be accrued on basis of presentation to the radiation oncology clinic with spinal metastasis amenable to SBRT. Potential participants will be identified in the inpatient and outpatient radiation oncology clinic setting, as well as from the multidisciplinary spine tumor board. Patients will be approached regarding participation at or around the time of

their radiation oncology consultation visit. Patients will be treated at a single facility, at the Siteman Cancer Center's Center for Advanced Medicine clinic, as the technology required for this study is confined to this center. We anticipate an accrual rate of approximately 15 patients per year, or an estimated study accrual period of 8-12 months. There will be no compensation or incentives offered for study participation.

5 TREATMENT PLAN

5.1 Study Intervention Description and Administration

Radiotherapy will consist of stereotactic body therapy to the spine, to be given over two or five fractions, delivered once daily or once every other day for a period of one to two weeks, for a total of two or five treatments.

5.1.1 Dose, Fractionation

Radiotherapy will consist of stereotactic body therapy, to be given over either a two or five fraction course, delivered once daily or once every other day for a period of one to two weeks, for a total of two or five treatments (depending on whether a 2 or 5 fraction course is selected). Patients will be planned for an initial prescription dose at the discretion of the treating physician, delivered in two or five total fractions to the PTV, with dose adaptation based on safety constraints that are already approved of to prevent OAR injury. Suggested dose prescriptions are 24 Gy in 2 fractions or 35 Gy in 5 fractions.

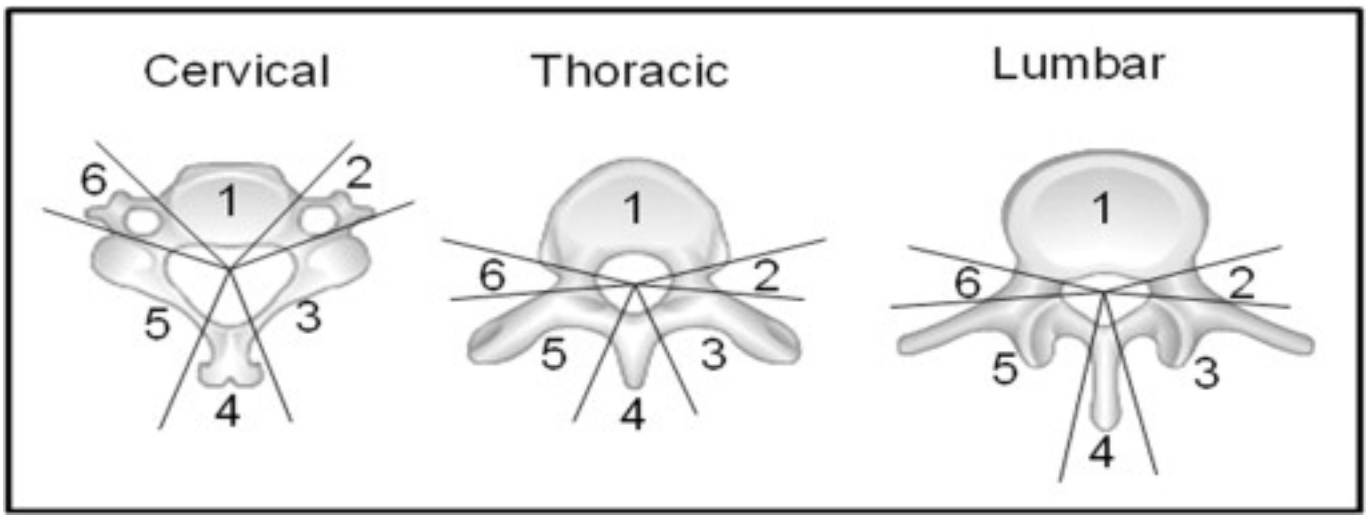
5.1.2 Patient Positioning

All patients will undergo volumetric MR imaging on treatment days in positioning appropriate for the specific treatment site.

5.1.3 Clinical Target Volume (CTV) and Planning Target Volume (PTV) Definitions

The treatment target will be defined based on the clinical target volume (CTV) only, based on International Spine Radiosurgery Consortium (ISRC) consensus guidelines. The PTV will be generated at the discretion of the treating physician but will generally range between 3 mm and 7 mm.

Vertebral bodies are divided into 6 sectors as illustrated below from the ISRC consensus guidelines:



CTV definitions are listed below and use the previously defined sectors to delineate volumes:

Tumor involvement	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	Include the entire vertebral body
Lateralized within the vertebral body	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
Tumor involves vertebral body and unilateral pedicle	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
Tumor involves vertebral body and bilateral pedicles/transverse processes	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
Tumor involves unilateral pedicle	2, 3 ± 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body

Tumor involves unilateral lamina	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
Tumor involves spinous process	3, 4, 5	Include entire spinous process and bilateral laminae

5.1.4 Same-session MR-only Simulation and Fraction 1 Adaptive Treatment Planning

All patients will be planned for a two or five fraction treatment course. Prescription dose will be at the discretion of the treating physician but will be subject to hard constraints based on the treatment site. Dose volume histogram (DVH) information for the target volumes and surrounding critical structures is mandatory. This is to assist in interpreting outcome, including morbidity. Coverage goal will be for 95% of the volume to be covered by 95% of the dose, although in situation where a critical structure is violated, reduction of dose will be allowed in areas of overlap. For specific hard constraints and optimization parameters, see Section 5.1.5.

Prior to day of first fraction and creation of the clinical plan, each patient will be tentatively pre-planned based on their diagnostic MRI volumetric image set obtained prior to study enrollment. A bulk density override method will be used to manually assign relative electron density values to the diagnostic dataset for the purpose of dose calculation and setting up initial plan parameters. For example, voxels representing the patient's bones will be assigned an average bone density, voxels representing fat will have a different density assignment, etc. This "pre-plan" will allow for efficient same-session simulation and clinical planning on the day of treatment. On treatment day one, another volumetric MRI image will be obtained on the treatment machine itself, and the plan will be adjusted based on anatomy and patient habitus of the day. Previously assigned density values will be reviewed and adjusted if needed, after which the final clinical treatment plan will be created.

In tandem with the clinical planning process above, a novel exploratory non-clinical density override method will be used for comparative dosimetry. In this method, the density values are assigned on a voxel-by-voxel basis automatically, rather than as a manual bulk override as clinically used, via a machine-learning algorithm. This will not be used for clinical decision making or affect treatment planning. The data gathered will be used to improve the MRI-only planning process in the future.

5.1.5 SMART Dose Constraints

These shall function as hard constraints in treatment planning, and coverage will be sacrificed to meet these constraints. All listed constraints are for 2 fraction treatment (Table A) or 5 fraction treatment (Table B), which are both acceptable

course fractionations for this study. Adaptive plans will be evaluated under the assumption that the delivered adaptive plan would meet all hard constraints for 2 or 5 fractions with stable anatomy. For example, on a given day, in a 5-fraction course, the maximum cord dose (to 0.5 cc) will be 5 Gy (extrapolate to maximum dose 25 Gy over 5 fractions).

Table A

Organ-at-Risk	Volume	Constraint (Gy)	Other
PRV spinal cord subvolume (thecal sac or 2mm)	<0.03cc	17	-
PRV Cauda Equina	<0.03cc	17	-
Sacral Nerve S1-5	<0.03cc	26	-
Esophagus	<0.03cc	20	-
Pharynx/Larynx	<0.03cc	20	Mean < 9Gy
Brachial Plexus	<0.03cc	21.5	-
Parotid	-	-	Mean < 7Gy
Rectum	<0.03cc	20	-
Trachea	<0.03cc	20	-
Rib	<5cc	45	57
Skin	<10cc	20	-
Stomach	<0.03cc	20	-
Duodenum	<0.03cc	20	-
Small Bowel	<0.03cc	20	-
Large Bowel	<0.03cc	20	-
Kidneys	<0.03cc	26	Mean < 6Gy
Lungs (combined)	- -	- -	V10Gy <10% V5Gy < 35%
Liver	-	-	Mean < 8Gy

Table B

Organ-at-Risk	Volume	Max Dose to Volume (Gy)	Max Point Dose* (Gy)
Brainstem (not medulla)	<0.5cc	23	31
Spinal Cord and medulla	<0.35cc <1.2cc	22 15.6	28 -
Spinal Cord Sub-volume (5-6mm above and below level treated)	<10% of sub-volume	22	28
Cauda Equina	<5cc	30	31.5
Sacral Plexus	<5cc	30	32
Esophagus	<5cc	19.5	35
Brachial Plexus	<3cc	27	32.5
Heart/Pericardium	<15cc	32	38

Great Vessels	<10cc	47	53
Trachea and Large Bronchi	<5cc	32	40
Rib	<5cc	45	57
Skin	<10cc	36.5	38.5
Stomach	<5cc	26.5	35
Duodenum	<5cc	18.5	26
Small Bowel	<30cc	20	32
Large Bowel	<20cc	28.5	40
Rectum	<35.cc <20cc	50 32.5	55 -
Ureter	-	-	45
Bladder Wall	<15cc	20	38
Penile Bulb	<3cc	30	-
Femoral Heads	<10cc	30	-
Kidneys	mean	18	-
Lungs (combined)	1500cc 1000cc	12.5 13.5	- -
Liver	700cc	21	-

*Max point dose defined as dose to ≤ 0.035 cc.

5.1.6 Adaptive Treatment Planning at Subsequent Fractions

After delivery of the first treatment fraction using a same-session MR-only simulation and treatment with SMART, the treating physician will evaluate the patient's individual anatomy at subsequent treatment fractions to determine if further daily adaptive planning is indicated. Treatment plan re-optimization will be performed for dose adaptation if it is determined that the patient's anatomy necessitates dose adaptation with the goal of sparing of normal structures (i.e., not violating the predetermined hard constraints based on safety constraints that are already approved of for routine, clinical use).

5.1.7 Quality Assurance of the Adaptive Plan

Patient specific QA will be performed at each fraction prior to delivery of the adaptive treatment plan. Given that dose measurements will not be possible with the patient on the table, this will be achieved by performing our standard process of an independent Monte Carlo dose calculation on the image of the day, using the exported beam parameters, and mapped electron density. The independently calculated dose distribution will be compared to the dose distribution exported from the MRIgRT system, looking at dose volume histograms and 3D gamma analysis of all voxels within the patient. In addition, in-house plan integrity verification software will be utilized to evaluate plan quality and integrity via plan parameters including contours, beam angles, segments, and monitor units. After completion of the automated checks, a final review by physics will be required prior to proceeding to treatment delivery.

5.2 Collection of AEs

For all patients, neurologic toxicities of concern include (but are not limited to) treatment-related spinal injury resulting in sensory alteration, muscle weakness, or neuropathic pain limiting self-care in activities of daily living. For patients receiving treatment to lower thoracic and lumbar spine sites, toxicities of concern also include (but are not limited to) gastrointestinal toxicities such as: severe pain, severe nausea or diarrhea, severe constipation, and/or gastrointestinal hemorrhage, stenosis, ulceration, fistula, perforation, etc. Patients undergoing treatment for thoracic metastases will additionally be assessed using the CTCAE v5.0 criteria for lung, esophageal (eg esophagitis), and cardiovascular toxicity. Regardless of treatment site, skin toxicity will be tabulated according to the CTCAE v5.0 criteria.

5.3 Definitions of Evaluability

Endpoint	**In order to be evaluable for this endpoint, a patient must have…**
Primary: Feasibility	Received simulation
Exploratory: Time from consult to delivery of first fraction	Had a consult and received at least 1 fraction of RT
Exploratory: Local, in-field tumor response rates at 3 mos	Received any study treatment and undergone volumetric imaging at 3 mos
Exploratory: Local, in-field tumor control rate at 3 mos	
Exploratory: Grade 3 or higher toxicity	Received any study treatment
Exploratory: Dosimetric differences between MRI-only planning using standard bulk density override dose calculations and voxel-by-voxel MRI-based dose calculation using MLA	Received MRI and dose calculated using bulk density vs voxel-by-voxel
Exploratory: On-table time required for initial treatment fraction and subsequent treatment fractions	Received at least 1 fraction of RT

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the first fraction of SBRT.

Female patients are required to use two forms of acceptable contraception, including one barrier method, during the course of study treatment.

If a patient is suspected to be pregnant, SBRT should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient becomes pregnant during therapy, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for a total of 2 or 5 fractions of SBRT or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will have a single follow-up visit at 3 months post-end of treatment.

5.7 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for the scheduled three-month follow up visit and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 3 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6 DOSE DELAYS / DOSE MODIFICATIONS

There will be no dose delays or modifications permitted.

7 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatmenthrough the 3-month post-treatment follow-up visit. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Grade 1-2 AEs regardless of relatedness
- Grade 3-4 AEs that predate SBRT
- Grade 3-4 AEs that are not at least probably attributable to treatment

Refer to the data submission schedule in Section 9 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 WU PI Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 1.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8 STUDY CALENDAR

	Screening	Pre-Treatment	D1	D2	D3	D4	D5	3 mos post-SBRT[1]
Informed consent	X							
Medical history	X							
Volumetric imaging	X[5]							X
Pregnancy test[2]	X							
Adaptive SBRT			X	X	X[3]	X[3]	X[3]	
Adverse events assessment		X	X ----------X					

1. Window is 10-14 weeks post-completion of SBRT
2. Women of childbearing potential only; within 14 days of start of treatment
3. Treatment days 3,4,5 are for a 5-fraction course of treatment only. If a 2-fraction course is selected, then there would be only two treatment days.
5. Collection of a standard of care diagnostic CT scan completed in the past 6 months

9 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Treatment Summary Form	End of treatment
Toxicity Form	During treatment and at 3-mo f/u
Follow Up Form	3-mo f/u

9.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

10 MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response at the 3-month follow-up visit.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the

study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both

approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.4 Response Criteria

10.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the

progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

10.4.4 Duration of Response

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

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

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

11 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason

- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

12 STATISTICAL CONSIDERATIONS

12.1 Stopping Criteria

If at any point in trial enrollment, >2 out of the first 5 patients, or >4 out of the first 10 patients experience symptoms of G3 or greater toxicity that is probably or definitely attributable to and did not pre-date SBRT, the trial will be suspended. Symptoms that pre-dated SBRT will not be count towards stopping criteria (example: thoracic spine patients requiring oxygen prior to and after SBRT will not be scored as G3 toxicity, however a new O2 requirement after RT would count towards stopping criteria). If at any time a grade 5 toxicity (death) is observed that is probably or definitely attributable to treatment, accrual will be suspended and the event will be reviewed by the principal investigator. Since patients accruing to the trial have metastatic disease, it is anticipated that deaths unrelated to the trial may be observed. Death that is felt either due to disease progression or patient comorbidity will not be scored as grade 5 toxicity and will not result in trial suspension.

12.2 Sample Size Calculation

As a pilot study, the sample size is determined based on clinical considerations rather than statistical power. For our primary objective, our goal will be to report the description of same-session MR-only simulation and treatment with SMART treatment workflows, adaptation, and the time to delivery of first treatment fraction. Goal accrual will be 10 evaluable patients. For the secondary objectives, sample size is also based on clinical considerations rather than statistical power.

12.3 Statistical Analysis Plan

Regarding toxicity, we will report descriptive statistics for acute toxicity at a three-month time point. Toxicity rates are anticipated to be identical to those of other linear accelerator based SBRT treatments. Because spine SBRT is a standard-of-care treatment that is not in and of itself investigational, further prospective toxicity assessments are not indicated. Given that no prior data exists for same-session MR-only simulation and treatment with SMART for spinal metastases, we will report descriptive statistics. As a pilot study we will establish these baseline parameters.

The primary objective is to demonstrate that same-session MRI-only simulation and treatment with stereotactic MRI-guided radiotherapy (SMART) for spinal oligometastases is feasible by confirming that the first fraction of same-session MRI-only simulation and treatment with SMART can be delivered on the first on-table attempt for at least 70% of patients.

Our principle objectives in this trial will be to determine the feasibility and safety of for same-session MR-only simulation and treatment with stereotactic MR-guided online-adaptive radiotherapy (SMART) for treatment of spinal oligometastatic disease. If we can successfully deliver the first treatment fraction at time of the first on-table treatment attempt in 70% of patients, while maintaining the safety and efficacy profile of standard spine SBRT, we will consider this study as having provided sufficient pilot data to support more widespread study of same-session SMART paradigm. The long-term goals will be to improve patient outcomes and care by reducing time to treatment, through an expedited radiotherapy delivery workflow for spinal SBRT.

All exploratory aims will be analyzed at the end of the study.

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APPENDIX A: Supplementary Data

Table 1. Difference in projected dosimetry for MR-only bulk density override planning versus CT-based plans (Calculated as bulk density - CT-based).

PTV1: Vertebral Body						
Metric	**Unit**	**Average**	**Median**	**Max**	**Ave. difference (% of original projected by bulk density plan)**	**Max difference (% of original projected by bulk density plan)**
Difference in PTV coverage by 100% Rx	*%*	-0.63	-0.64	1.01	-0.7%	1.1%
Difference in PTV coverage by 95% Rx	*%*	-0.18	-0.21	0.25	-0.2%	0.3%
Difference in spinal cord maximum dose	*Gy*	0.08	0.11	0.44	0.6%	2.8%
Difference in volume of cord+3mm receiving 28 Gy	*cc*	0.00	0	0.01		
Difference in volume of cord+5mm receiving 28 Gy	*cc*	0.00	0	0.05		
Difference in volume of cord+7mm receiving 28 Gy	*cc*	-0.03	-0.05	0.1		
Difference in volume of cord+10mm receiving 28 Gy	*cc*	-0.05	-0.05	0.14		
Difference in percent conformity index	*%*	-2%	-2%	6%		
Difference in percent gradient index	*%*	-3%	-1%	6%		
Difference in volume of esophagus receiving 19.5 Gy	*cc*	-0.03	-0.05	0.1		

PTV2: Vertebral Body and Unilateral Pedicle						
Metric	**Unit**	**Average**	**Median**	**Max**	**Ave. difference (% of original projected by bulk density plan)**	**Max difference (% of original projected by bulk density plan)**
Difference in PTV coverage by 100% Rx	*%*	-1.18	-0.91	3.33	-1.3%	3.7%
Difference in PTV coverage by 95% Rx	*%*	-0.21	-0.14	0.53	-0.2%	0.5%
Difference in spinal cord maximum dose	*Gy*	0.15	0.06	0.43	0.7%	1.9%
Difference in volume of cord+3mm receiving 28 Gy	*cc*	0.00	0	0.03		
Difference in volume of cord+5mm receiving 28 Gy	*cc*	-0.04	-0.03	0.09		
Difference in volume of cord+7mm receiving 28 Gy	*cc*	-0.08	-0.06	0.16		
Difference in volume of cord+10mm receiving 28 Gy	*cc*	-0.10	-0.11	0.15		
Difference in percent conformity index	*%*	-4%	-2%	11%		
Difference in percent gradient index	*%*	-3%	-4%	6%		
Difference in volume of esophagus receiving 19.5 Gy	*cc*	-0.14	-0.03	0.38		

PTV3: Vertebral Body and Bilateral Pedicles						
Metric	**Unit**	**Average**	**Median**	**Max**	**Ave. difference (% of original projected by bulk density plan)**	**Max difference (% of original projected by bulk density plan)**
Difference in PTV coverage by 100% Rx	*%*	-0.63	-0.48	1.49	-0.7%	1.6%
Difference in PTV coverage by 95% Rx	*%*	-0.24	-0.18	0.48	-0.3%	0.5%
Difference in spinal cord maximum dose	*Gy*	-0.05	-0.08	0.26	-0.2%	1.7%
Difference in volume of cord+3mm receiving 28 Gy	*cc*	0.00	0	0.01		
Difference in volume of cord+5mm receiving 28 Gy	*cc*	-0.02	-0.02	0.08		
Difference in volume of cord+7mm receiving 28 Gy	*cc*	-0.06	-0.05	0.17		
Difference in volume of cord+10mm receiving 28 Gy	*cc*	-0.09	-0.09	0.27		
Difference in percent conformity index	*%*	-3%	-2%	9%		
Difference in percent gradient index	*%*	-2%	-1%	4%		
Difference in volume of esophagus receiving 19.5 Gy	*cc*	0.00	0	0.23		

PTV4: Vertebral Body and Unilateral Pedicle and Lamina						
Metric	**Unit**	**Average**	**Median**	**Max**	**Ave. difference (% of original projected by bulk density plan)**	**Max difference (% of original projected by bulk density plan)**
Difference in PTV coverage by 100% Rx	*%*	-1.44	-0.54	3.35	-1.7%	3.9%
Difference in PTV coverage by 95% Rx	*%*	-0.37	-0.2	1.14	-0.4%	1.2%
Difference in spinal cord maximum dose	*Gy*	-0.36	-0.37	0.83	-1.8%	3.9%
Difference in volume of cord+3mm receiving 28 Gy	*cc*	-0.01	-0.01	0.05		
Difference in volume of cord+5mm receiving 28 Gy	*cc*	-0.05	-0.02	0.22		
Difference in volume of cord+7mm receiving 28 Gy	*cc*	-0.08	-0.03	0.37		
Difference in volume of cord+10mm receiving 28 Gy	*cc*	-0.14	-0.02	0.64		
Difference in percent conformity index	*%*	-6%	-4%	18%		
Difference in percent gradient index	*%*	-1%	-1%	5%		
Difference in volume of esophagus receiving 19.5 Gy	*cc*	-0.18	-0.175	0.34		

PTV5: Unilateral Pedicle and Lamina, and Spinous Process						
Metric	**Unit**	**Average**	**Median**	**Max**	**Ave. difference (% of original projected by bulk density plan)**	**Max difference (% of original projected by bulk density plan)**
Difference in PTV coverage by 100% Rx	*%*	-2.08	-2.22	3.54	-2.6%	5.0%
Differnce PTV coverage by 95% Rx	*%*	-0.50	-0.26	1.22	-0.5%	1.3%
Difference in spinal cord maximum dose	*Gy*	0.00	0.03	0.3	0.1%	1.9%
Difference in volume of cord+3mm receiving 28 Gy	*cc*	0.00	0	0.01		
Difference in volume of cord+5mm receiving 28 Gy	*cc*	-0.01	-0.01	0.05		
Difference in volume of cord+7mm receiving 28 Gy	*cc*	-0.07	-0.06	0.12		
Difference in volume of cord+10mm receiving 28 Gy	*cc*	-0.09	-0.08	0.14		
Difference in percent conformity index	*%*	-4%	-2%	10%		
Difference in percent gradient index	*%*	-2%	0%	13%		
Difference in volume of esophagus receiving 19.5 Gy	*cc*	-0.29	-0.29	0.29		

PTV6: Spinous Process and Bilateral Lamina						
Metric	**Unit**	**Average**	**Median**	**Max**	**Ave. difference (% of original projected by bulk density plan)**	**Max difference (% of original projected by bulk density plan)**
Difference in PTV coverage by 100% Rx	*%*	-3.00	-1.54	6.52	-4.1%	9.0%
Difference in PTV coverage by 95% Rx	*%*	-0.65	-0.32	1.63	-0.7%	1.8%
Difference in spinal cord maximum dose	*Gy*	0.25	0.26	1.04	1.3%	5.6%
Difference in volume of cord+3mm receiving 28 Gy	*cc*	0.00	0	0.02		
Difference in volume of cord+5mm receiving 28 Gy	*cc*	-0.02	-0.03	0.06		
Difference in volume of cord+7mm receiving 28 Gy	*cc*	-0.07	-0.04	0.22		
Difference in volume of cord +10mm receiving 28 Gy	*cc*	-0.10	-0.08	0.39		
Difference in percent conformity index	*%*	-8%	-8%	14%		
Difference in percent gradient index	*%*	1%	-1%	9%		

APPENDIX B: Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	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 signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX C: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:
Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

A. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

B. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

C. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

D. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX D: Reporting Timelines

Event	HRPO	QASMC
Serious AND unexpected suspected adverse reaction		
Unexpected fatal or life-threatening suspected adverse reaction		
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days.	

Event	HRPO	QASMC
	If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Event	HRPO	QASMC
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

APPENDIX E: Study-Specific DSM Tables

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
Demonstrate that same-session MRI-only simulation and treatment with stereotactic MRI-guided radiotherapy (SMART) for spinal oligometastases is feasible by confirming that the first fraction of same-session MRI-only simulation and treatment with SMART can be delivered on the first on-table attempt for at least 70% of patients.	
Exploratory	
Determine the average time (days) from patient consult appointment to successful delivery of the first treatment fraction.	
Determine the local, in-field tumor response and control rates at three months.	Local in-field tumor response = Local in-field control rate =
Demonstrate that same-session MR-only simulation and treatment with SMART for treatment of spinal metastases will lead to comparable toxicities compared with historically reported rates using standard, CT-based SBRT assessed prospectively at three months post-treatment and retrospectively for later time-points.	
Determine the projected dosimetric differences between the study method of MRI-only planning using standard bulk density override dose calculations (which will be clinically used for all patients) and an exploratory alternative method of a novel voxel-by-voxel MRI-based dose calculation using an institutionally developed machine learning algorithm (which will be simulated for comparison but not used in clinical treatment planning).	
Determine the on-table time required for same-session MR-only simulation and treatment with plan generation for the initial treatment fraction and for subsequent treatment fractions.	

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? No
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? No

Response				
UPN	**On tx date**	**1st fx delivered at 1st on table attempt? (Y/N)**	**Response at 3 mos**	**Pt replaced? (Y/N)**

Treatment Discontinuation and Survival				
UPN	**Date off tx**	**Reason off tx**	**Vital status**	**If dead, cause**