**DF/HCC Protocol #:** 16-207

**TITLE:** Phase II Protocol Evaluating Hypofractionated-Stereotactic Body Radiation Therapy for Oligometastatic Disease of the Bone.


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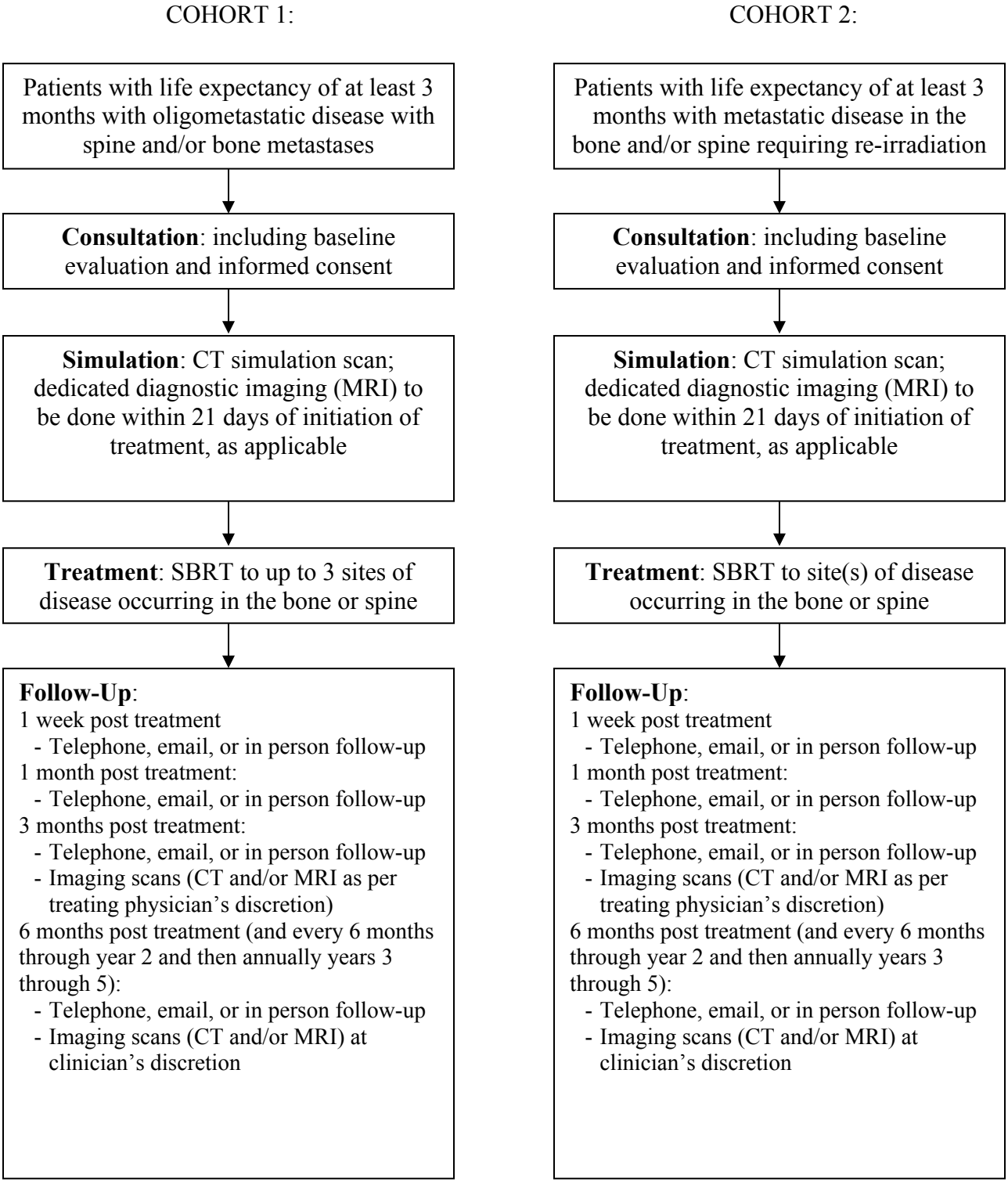
**IND Sponsor: N/A**

**Protocol Type / Version # / Version Date: Revised Protocol, V8.0, October 10, 2018**

# INDEX



**SCHEMA**


COHORT 1:
Patients with life expectancy of at least 3 months with oligometastatic disease with spine and/or bone metastases
**Consultation**: including baseline evaluation and informed consent
**Simulation**: CT simulation scan; dedicated diagnostic imaging (MRI) to be done within 21 days of initiation of treatment, as applicable
**Treatment**: SBRT to up to 3 sites of disease occurring in the bone or spine
**Follow-Up**:
1 week post treatment
- Telephone, email, or in person follow-up
1 month post treatment:
- Telephone, email, or in person follow-up
3 months post treatment:
- Telephone, email, or in person follow-up
- Imaging scans (CT and/or MRI as per treating physician's discretion)
6 months post treatment (and every 6 months through year 2 and then annually years 3 through 5):
- Telephone, email, or in person follow-up
- Imaging scans (CT and/or MRI) at clinician's discretion
COHORT 2:
Patients with life expectancy of at least 3 months with metastatic disease in the bone and/or spine requiring re-irradiation
**Consultation**: including baseline evaluation and informed consent
**Simulation**: CT simulation scan; dedicated diagnostic imaging (MRI) to be done within 21 days of initiation of treatment, as applicable
**Treatment**: SBRT to site(s) of disease occurring in the bone or spine
**Follow-Up**:
1 week post treatment
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- Imaging scans (CT and/or MRI as per treating physician's discretion)
6 months post treatment (and every 6 months through year 2 and then annually years 3 through 5):
- Telephone, email, or in person follow-up
- Imaging scans (CT and/or MRI) at clinician's discretion

# 1. INTRODUCTION

## 1.1 Study Disease

### 1.1.1 Bone Metastases

Bone is one of the most common sites of metastatic disease, affecting up to 70% of patients with advanced breast or prostate cancer and 15-30% of patients with carcinoma of other sites.[1] Bone metastases can be a significant source of morbidity, with symptoms including pain, fracture, hypercalcemia, and spinal cord or nerve root compression. Treatment for bone metastases is often a collaborative effort between multiple practitioners including surgeons, radiation oncologists, medical oncologists, pain medicine specialists and palliative medicine clinicians. External beam radiation (EBRT) is often used for management of bone metastases and has been shown in multiple trials to offer symptom relief and local control.[2,3] However, with standard palliative fractionation, either single fraction or multiple fractions, for metastatic disease there are moderate rates of toxicity, particularly fatigue and nausea/vomiting.[3–5]

### 1.1.2 Oligometastatic disease with long anticipated life expectancy

An oligometastatic state is considered a transitional state between localized and widespread systemic disease,[6] and though variably construed, is typically defined as patients with <4 metastatic lesions. Although some investigators hypothesize that these patients may still be curable, at the very least data support that these patients have life expectancies that are long, typically median survivals greater than 1-2 years.[7,8] With standard EBRT dosing among patients with longer life expectancies, there is a very real risk of local recurrence that can cause significant morbidity. In studies evaluating all patients with bone metastases, the median survival is approximately 9 months.[3] In patients with oligometastatic disease whose life expectancy surpasses this, local recurrence can be a source of significant morbidity. In a subgroup analysis of the Dutch Bone Metastasis Study specifically looking at patients who survived for longer than a year, around half of patients treated with EBRT for symptomatic bone metastases had progressive pain at a mean duration of 17-18 weeks from radiation.[9] As these patients are living longer, local control of metastatic disease that could cause morbidity becomes even more important.

In patients with long anticipated life expectancies as indicated by (1) oligometastatic disease and/or (2) a prognostic algorithm estimating a median life expectancy greater than 12 months, hypofractionated radiation therapy / stereotactic body radiation therapy (SBRT), a technique that conforms very closely to the target, thereby enabling high target doses and minimizing dose to normal surrounding tissue, can be a useful tool. Multiple publications looking at SBRT in oligometastatic disease have shown promising outcomes. These studies have treated oligometastatic sites throughout the body including lung, liver, lymph node and bone metastases. Among these patients with long overall survival (median survival of approximately 24 months), good local control (approximately 75% at 2 years) and low rates of toxicity (<10% risk of grade 3 toxicity) have been reported.[7,8]

### 1.1.3 Re-irradiation

Many anatomic structures have maximum cumulative tolerable doses; higher doses can cause severe toxicity. Re-irradiation, particularly in the spine, presents technical challenges due to safety concerns in re-irradiating normal tissues. The spinal cord has a tolerance that, if exceeded, can lead to cord myelopathy and/or spinal nerve radiculopathy[10] causing significant morbidity. SBRT allows high doses to be given in a highly conformal nature, minimizing dose to the spinal cord while still allowing the tumor to receive a high dose of radiation. A publication from Beth Israel Hospital reported their use of SBRT for re-irradiation of epidural spinal metastases. In patients with a local recurrence who were previously treated with EBRT (3 Gy x 10), SBRT was given (either 8 Gy x 3 if the tumor did not touch spinal cord or 5-6 Gy x 5 when tumor abutted the cord). They reported very low toxicity (40% grade 1 fatigue and 20% grade 2 nausea), adequate pain relief (65%), and good local control (93% of the patients had stable or improved disease).[11]

## 1.2 Rationale

We hypothesize that SBRT as used in this trial will allow high doses in only a few fractions to very conformal fields with acceptable toxicity. There are small, preliminary, published series of SBRT showing good local control and minimal toxicity using SBRT for metastasis in the spine and non-spine bone. A series from MD Anderson Cancer Center which treated 63 patients with spinal metastasis with fractionated SBRT (either 6 Gy x 5 or 9 Gy x 3) showed no grade 3 or higher neurologic toxicity, low rates of overall toxicity (4 patients with grade 3 toxicity), and a 1-year freedom from tumor progression of 84%.[12] A series from Memorial Sloan-Kettering Cancer Center that treated 93 patients with spinal metastasis using single-fraction SBRT (18-24 Gy) showed a local failure rate of 7.5% at two years.[13] The Mayo Clinic published their series of SBRT for non-spine oligometastatic disease showing excellent local control (92% at 1 year and 86% at 2 years) and no grade 3 or higher toxicities. Of the toxicity they observed, fatigue and pain flare were the most common.[14] Given the good local control and low rates of toxicity, there are two clinical situations where SBRT can be a useful tool in patients with metastatic disease: (1) patients with excellent life expectancies heralded either an oligometastatic state or (2) those who need adequate re-irradiation dose delivery to a previously treated bony site. These clinical applications are based on the goals of providing adequate dose to (a) control the lesion for the patient's long life expectancy and (b) ensure normal tissue sparing to minimize treatment risks, particularly in the re-irradiation setting.

The rationale behind the current study is the premise that in patients with metastatic disease who have a good life expectancy, the use of SBRT may increase local control and decrease morbidity, both from side effects of treatment as well as from disease progression.

Given the aforementioned data showing good local control and minimal toxicity using SBRT in oligometastatic disease as well as metastatic disease in the bone and spine, we propose a Phase II protocol to further evaluate the local control, patient quality of life outcomes, and toxicities of SBRT in the management of bony metastatic disease in its two major clinical applications: (a) patients with an oligometastatic state and a prognostic estimate of greater than 3 months and (b) re-irradiation of previously irradiated bony metastatic lesions.

## 2. OBJECTIVES

### 2.1 Study Design

This Phase II protocol will enroll patients on two cohorts. The first will comprise patients with oligometastatic disease and a life expectancy of at least 3 months. Oligometastatic state is defined by ≤3 active sites of disease, including the primary site. Life expectancy will be determined by agreement of both the Chow et al.[15] and TEACHH[16] models, indicating a median life expectancy of >3 months. The second cohort will be comprised of patients with life expectancy >3 months (as indicated by the Chow et al.[15] and TEACHH[16] models) who require re-irradiation of spinal disease. All patients will be treated with SBRT and followed and assessed for local control, local progression-free survival, progression free survival, overall survival, treatment toxicity and quality of life. The two cohorts will be evaluated separately.

### 2.2 Primary Objectives

To determine the 6-month local control rates of patients in both cohorts, evaluated separately.

### 2.3 Secondary Objectives

1. To assess patient reported quality of life, symptom control, and satisfaction with treatment using a modified version of the MD Anderson Symptom Inventory (MDASI)

2. To assess the rate of acute and chronic toxicity (e.g., fracture, myelopathy, radiculopathy)

3. To determine the median time to local failure, 1-year local progression-free survival, 1 year progression-free survival and 1-year overall survival in both cohorts.

4. To determine the 6-month local control rates, median time to local failure, 1-year local progression-free survival, and 1-year overall survival of patients in both cohorts, evaluated together.

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

Both cohorts:

- ≥18 years of age
- ECOG performance status ≤2
- Pathologically proven metastatic solid tumor (non-hematologic malignancy) of the bone (spine or non-spine bone)
- Bony metastatic lesions must be ≤8 cm in maximum dimension and evaluable on either a CT or MRI scan; metastatic lesions in the spine must involve ≤3 contiguous vertebral

bodies
- No other active malignancy within the past 2 years, except for non-melanoma skin cancers or carcinoma *in situ* of the cervix
- Ability to understand and the willingness to sign a written informed consent document
- Surgery to the lesion in question is allowed if size criteria outlined above are met
- Not currently pregnant or breast feeding

Cohort 1: Oligometastatic state
- Oligometastatic state is defined by ≤ 3 active sites of disease, including the primary site
- Agreement of both the Chow et al.[15] and TEACHH[16] models, indicating a median life expectancy of >3 months
- Among patients with multiple sites of metastatic disease, the other sites that will not be treated on this protocol have either been previously treated or are planned for local treatment

Cohort 2: Re-irradiation
- Previous radiation in the current area of disease requiring radiation
- Life expectancy of >3 months as defined by agreement of both the Chow et al.[15] and TEACHH[16] models

### 3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

- SBRT target size >8 cm in maximum diameter (or >100 cc in volume)
- Hematologic malignancies (including lymphoma, multiple myeloma)
- Prior RT of greater dose intensity than 100 $Gy_2$ based on a biological effective dose (BED) calculation [BED (Gy2) = nd x $(1+d/_{\alpha/\beta}$; where n=number of fractions, d=dose per fraction, α/ß=2)]
- Epidural tumor <2 mm from spinal cord
- Requirement of active receipt of systemic therapies concurrent with SBRT (concurrent hormonal therapies are allowed)
- Inability to lie flat and still for treatment delivery despite anti-anxiety and/or pain medications
- Non-English speakers are excluded from this study due to use of questionnaires which have not been validated in other languages.
- Patients lacking the capacity to describe their symptoms are excluded as that precludes them (or anyone on their behalf) from filling out the validated questionnaires about symptoms/toxicity.
- Pregnant women are excluded from this study because radiotherapy has the potential for teratogenic or abortifacient effects.
- Individuals with a history of a different malignancy are ineligible **except** for the following circumstances: if they have been disease-free for at least 2 years and are deemed by the investigator to be at low risk for recurrence of that malignancy; or if diagnosed and treated within the past 2 years for cervical cancer *in situ* or basal cell or

squamous cell carcinoma of the skin.

### 3.3 Inclusion of Women and Minorities

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

## 4. PRETREATMENT EVALUATIONS/MANAGEMENT

### 4.1 Table of acceptable time intervals of pretreatment assessments

| Assessment | Acceptable time interval prior to initiation of SBRT (days) |
|---|---|
| History & physical exam | 28 |
| Performance status | 28 |
| Adverse event evaluation | 28 |
| Pregnancy test* | 21 |
| Radiologic evaluation | 21 |
| QOL questionnaire | 28 |

* *For pre-menopausal women for whom pregnancy is a possibility (i.e., have not undergone a hysterectomy)*

### 4.2 Information regarding washout from prior therapies

For non-hormonal therapies, the study requires a wash out period of 3 half lives of the systemic agent. However it is also acceptable to begin sooner if there is agreement between the treating radiation oncologist and the medical oncologist based on discussion of data regarding particular biologic properties of the systemic agent, data regarding its safety when given with radiation therapy, and/or the needs of the patient.

## 5. REGISTRATION PROCEDURES

### 5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause

treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

## 5.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

## 5.3 General Guidelines for Other Investigative Sites

N/A

## 5.4 Registration Process for Other Investigative Sites

N/A

### 5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue as detailed in section 6.1 or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the treatment regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

The research team updates the relevant Off Treatment/Off Study information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Tracy Balboni, MD at pager # 39896.

### 5.6 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in REDCap.

The research team updates the relevant Off Treatment/Off Study information in OnCore.

## 6. RADIATION THERAPY

Protocol treatment must begin within 4 weeks after enrollment on the study.

### 6.1 Dose Specifications: SBRT

6.1.1 Prescription Dose: To be determined by the treating physician from the following previously employed regimens according to the clinical circumstances of each case (e.g. meeting normal-tissue constraints)

- Spine: 18 Gy x 1, 9 Gy x 3, or 6 Gy x 5
- Non-Spine Bone: 18Gy x 1, 9 Gy x 3 or 6 Gy x 5

6.1.2 Dose will be normalized such that at least 95% of the Planning Target Volume (PTV) receives the prescription dose and will be scored as per protocol. The minimum allowable dose within the PTV is >80% of the prescribed dose to a volume that is at least 1 cc.

6.1.3 Participants will be treated entirely via SBRT and shall receive prescription doses to the PTV (with the above constraints). All attempts should be made to deliver the PTV dose with the above heterogeneity constraints with adherence to the critical structure parameters listed below in Table 1.

See Section 6.5 below for specifics regarding when to implement a dose reduction.

6.1.4 In the retreatment of the spinal cord and/or cauda equina, BED calculations will be employed to ensure retreatment dose does not exceed BED=140 Gy2 (alpha/beta = 2). In retreatment to other normal tissues, the prior dose received to the organ(s) at risk will be taken into account together with dose constraints given in Table 1 to formulate final dose constraints tailored to each patient scenario.

### 6.2 Technical Factors

6.2.1 RT will be delivered with megavoltage equipment at energies ≥6 MV.

6.2.2 All treatments will be delivered on a dedicated stereotactic linear accelerator that includes dedicated imaging and a robotic couch top. Imaging can include either live imaging with orthogonal kV beams as part of a CyberKnife Treatment Delivery System or onboard conebeam CT imaging and orthogonal 2D/3D matching.

## 6.3 EBRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. The use of intravenous or intrathecal contrast at the time of simulation is allowed at the discretion of the treating physician, but is generally not required. Participants will be positioned on a flat tabletop with a customized immobilization for stabilization and setup reproducibility. CT images should be acquired at a slice thickness of 1-1.25 mm. For rib lesions which may move with respiratory motion, a 4D CT or inspiration/expiration breath hold, will be utilized for target delineation. Target volumes (Section 6.4.1) and normal critical structures (Section 6. 5) will be defined in the slices in which they are visualized. The treating radiation oncologist will review the fusion of the diagnostic MRI scan to the CT simulation scan, if applicable.

## 6.4 Treatment Planning/Target Volumes

6.4.1 The definition of volumes will be in accordance with the International Commission on Radiation Units and Measurements (ICRU) Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.4.1.1 The gross tumor volume (GTV) is defined by the physician as all known disease as defined by the planning CT and any other diagnostic imaging obtained.

6.4.1.2 The clinical target volume (CTV) is the GTV plus areas considered to contain microscopic disease, delineated by the treating physician. This is optional at the treating radiation oncologist's discretion. This is in accordance with the International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery.[17]

6.4.1.3 The planning target volume (PTV) will provide a 0-2 mm margin around the CTV to compensate for the variability of treatment setup and internal organ motion. This is in accordance with the International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery.[17]

6.4.1.4 For conventional linac based SBRT, the ICRU reference points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

6.4.1.5 Normal critical structures are to be defined on the treatment planning CT by the physician and/or treatment planner and will be based on the site being treated. Max doses are based on a point volume of 0.035 cc.

For example, for a thoracic spine metastasis around the level of the carina, the organs at risk would include:

- Heart
- Right lung, left lung, total lung
- Esophagus
- Bronchial structures
- Great vessels
- Spinal cord
- Skin

6.4.1.6 Volumetric modulated arc therapy (VMAT) or CyberKnife will be used to deliver conformal therapy to the entire PTV while limiting dose to critical structures as defined above.

## 6.5 Critical Structures

Critical structure dose constraints shall remain consistent with Table 1 above. While every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is recognized that certain anatomical factors may prevent this.

Excluding spinal cord and cauda equina, for purposes of compliance, up to a 5% absolute increase in the volume of a critical structure receiving greater than the specified dose will be considered “variation acceptable,” without a protocol deviation. Any increase in critical structure volume greater than 5% receiving more than the specified dose will be considered a “deviation unacceptable”. For spinal cord and cauda equina, any dose higher than stated in Table 1 will be considered “deviation unacceptable”. It is at this point that a dose reduction should be considered.

**Table 1. Critical Structure Dose Constraints** (from Benedict et al.[18])

| Serial tissue | Max critical volume above threshold | One fraction | | Three fractions | | Five fractions | | End point (≥Grade3) |
|---|---|---|---|---|---|---|---|---|
| | | Threshold dose (Gy) | Max point dose (Gy)[a] | Threshold dose (Gy) | Max point dose (Gy)[a] | Threshold dose (Gy) | Max point dose (Gy)[a] | |
| Optic pathway | <0.2 cc | 8 | 10 | 15.3 (5.1 Gy/fx) | 17.4 (5.8 Gy/fx) | 23 (4.6 Gy/fx) | 25 (5 Gy/fx) | Neuritis |
| Cochlea | | | 9 | | 17.1 (5.7 Gy/fx) | | 25 (5 Gy/fx) | Hearing loss |
| Brainstem (not medulla) | <0.5 cc | 10 | 15 | 18 (6 Gy/fx) | 23.1 (7.7 Gy/fx) | 23 (4.6 Gy/fx) | 31 (6.2 Gy/fx) | Cranial neuropathy |
| Spinal cord and medulla | <0.35 cc | 10 | 14 | 18 (6 Gy/fx) | 21.9 (7.3 Gy/fx) | 23 (4.6 Gy/fx) | 30 (6 Gy/fx) | Myelitis |
| Spinal cord subvolume (5–6 mm above and below level treated per Ryu) | <1.2 cc | 7 | | 12.3 (4.1 Gy/fx) | | 14.5 (2.9 Gy/fx) | | |
| | <10% of subvolume | 10 | 14 | 18 (6 Gy/fx) | 21.9 (7.3 Gy/fx) | 23 (4.6 Gy/fx) | 30 (6 Gy/fx) | Myelitis |
| Cauda equina | <5 cc | 14 | 16 | 21.9 (7.3 Gy/fx) | 24 (8 Gy/fx) | 30 (6 Gy/fx) | 32 (6.4 Gy/fx) | Neuritis |
| Sacral plexus | <5 cc | 14.4 | 16 | 22.5 (7.5 Gy/fx) | 24 (8 Gy/fx) | 30 (6 Gy/fx) | 32 (6.4 Gy/fx) | Neuropathy |
| Esophagus[b] | <5 cc | 11.9 | 15.4 | 17.7 (5.9 Gy/fx) | 25.2 (8.4 Gy/fx) | 19.5 (3.9 Gy/fx) | 35 (7 Gy/fx) | Stenosis/fistula |
| Brachial plexus | <3 cc | 14 | 17.5 | 20.4 (6.8 Gy/fx) | 24 (8 Gy/fx) | 27 (5.4 Gy/fx) | 30.5 (6.1 Gy/fx) | Neuropathy |
| Heart/pericardium | <15 cc | 16 | 22 | 24 (8 Gy/fx) | 30 (10 Gy/fx) | 32 (6.4 Gy/fx) | 38 (7.6 Gy/fx) | Pericarditis |
| Great vessels | <10 cc | 31 | 37 | 39 (13 Gy/fx) | 45 (15 Gy/fx) | 47 (9.4 Gy/fx) | 53 (10.6 Gy/fx) | Aneurysm |
| Trachea and large bronchus[b] | <4 cc | 10.5 | 20.2 | 15 (5 Gy/fx) | 30 (10 Gy/fx) | 16.5 (3.3 Gy/fx) | 40 (8 Gy/fx) | Stenosis/fistula |
| Bronchus-smaller airways | <0.5 cc | 12.4 | 13.3 | 18.9 (6.3 Gy/fx) | 23.1 (7.7 Gy/fx) | 21 (4.2 Gy/fx) | 33 (6.6 Gy/fx) | Stenosis with atelectasis |
| Rib | <1 cc | 22 | 30 | 28.8 (9.6 Gy/fx) | 36.9 (12.3 Gy/fx) | 35 (7 Gy/fx) | 43 (8.6 Gy/fx) | Pain or fracture |
| | <30 cc | | | 30.0 (10.0 Gy/fx) | | | | |
| Skin | <10 cc | 23 | 26 | 30 (10 Gy/fx) | 33 (11 Gy/fx) | 36.5 (7.3 Gy/fx) | 39.5 (7.9 Gy/fx) | Ulceration |
| Stomach | <10 cc | 11.2 | 12.4 | 16.5 (5.5 Gy/fx) | 22.2 (7.4 Gy/fx) | 18 (3.6 Gy/fx) | 32 (6.4 Gy/fx) | Ulceration/fistula |
| Duodenum[b] | <5 cc | 11.2 | 12.4 | 16.5 (5.5 Gy/fx) | 22.2 (7.4 Gy/fx) | 18 (3.6 Gy/fx) | 32 (6.4 Gy/fx) | Ulceration |
| | <10 cc | 9 | | 11.4 (3.8 Gy/fx) | | 12.5 (2.5 Gy/fx) | | |
| Jejunum/ileum[b] | <5 cc | 11.9 | 15.4 | 17.7 (5.9 Gy/fx) | 25.2 (8.4 Gy/fx) | 19.5 (3.9 Gy/fx) | 35 (7 Gy/fx) | Enteritis/ obstruction |
| Colon[b] | <20 cc | 14.3 | 18.4 | 24 (8 Gy/fx) | 28.2 (9.4 Gy/fx) | 25 (5 Gy/fx) | 38 (7.6 Gy/fx) | Colitis/fistula |
| Rectum[b] | <20 cc | 14.3 | 18.4 | 24 (8 Gy/fx) | 28.2 (9.4 Gy/fx) | 25 (5 Gy/fx) | 38 (7.6 Gy/fx) | Proctitis/fistula |
| Bladder wall | <15 cc | 11.4 | 18.4 | 16.8 (5.6 Gy/fx) | 28.2 (9.4 Gy/fx) | 18.3 (3.65 Gy/fx) | 38 (7.6 Gy/fx) | Cystitis/fistula |
| Penile bulb | <3 cc | 14 | 34 | 21.9 (7.3 Gy/fx) | 42 (14 Gy/fx) | 30 (6 Gy/fx) | 50 (10 Gy/fx) | Impotence |
| Femoral heads (right and left) | <10 cc | 14 | | 21.9 (7.3 Gy/fx) | | 30 (6 Gy/fx) | | Necrosis |
| Renal hilum/vascular trunk | <2/3 volume | 10.6 | 18.6 (6.2 Gy/fx) | | | 23 (4.6 Gy/fx) | | Malignant hypertension |

| Parallel tissue | Minimum critical volume below threshold | One fraction | | Three fractions | | Five fractions | | End point (≥Grade 3) |
|---|---|---|---|---|---|---|---|---|
| | | Threshold dose (Gy) | Max point dose(Gy)[a] | Threshold dose(Gy) | Max point dose(Gy)[a] | Threshold dose(Gy) | Max point dose(Gy)[a] | |
| Lung (right and left) | 1500 cc | 7 | NA-Parallel tissue | 11.6 (2.9 Gy/fx) | NA-Parallel tissue | 12.5 (2.5 Gy/fx) | NA-Parallel tissue | Basic lung function |
| Lung (right and left) | 1000 cc | 7.4 | NA-Parallel tissue | 12.4 (3.1 Gy/fx) | NA-Parallel tissue | 13.5 (2.7 Gy/fx) | NA-Parallel tissue | Pneumonitis |
| Liver | 700 cc | 9.1 | NA-Parallel tissue | 19.2 (4.8 Gy/fx) | NA-Parallel tissue | 21 (4.2 Gy/fx) | NA-Parallel tissue | Basic liver function |
| Renal cortex (right and left) | 200 cc | 8.4 | NA-Parallel tissue | 16 (4 Gy/fx) | NA-Parallel tissue | 17.5 (3.5 Gy/fx) | NA-Parallel tissue | Basic renal function |

[a]"Point" defined as 0.035 cc or less.
[b]Avoid circumferential irradiation.

## 6.6 Treatment Verification

6.6.1 A radiation oncologist will be present for set-up verification and treatment delivery of every fraction.

6.6.2 Orthogonal isocenter verification films (or images) must be obtained prior to each treatment. For VMAT the intensity profiles of each beam must be independently verified and compared to the planned field intensity. These images are to be archived by the institution for later review if requested by the study chair.

Set-up on the treatment machine will be verified using kV-kV imaging and cone-beam CT with robotic couch to match anatomy in all translational and rotational discrepancies. Exactrac imaging, kV-kV 2D/3D matching, or repeat cone-beam CT will be used between each rotational arc of radiation treatment to ensure stability of set-up and make ongoing set-up adjustments.

The CyberKnife Treatment Delivery System uses kV orthogonal X-ray imaging for live motion tracking to ensure stability of set-up and for motion correction throughout treatment.

6.6.3 Management of Radiation Dose to the Patient from Daily Localization

According to the literature, the estimates of patient dose per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy for BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from CyberKnife kV X-ray imaging is estimated to be in the range of 0.025-0.2 cGy. The doses from helical MV CT scans on a tomotherapy unit are estimated to be in the range of 1 to 3 cGy, similar to doses reported for kV cone beam CT on the Elekta Synergy machine. The doses for MV cone beam CT vary from 1 cGy to 10 cGy depending on the field size. Thus, the doses for 3D imaging systems used one time each day are in the range of 0.1 to 10 cGy and can contribute from 0.06 to 6% to a daily dose of 1.8 Gy. As a technique of controlling participant dose, it is recommended that a QA procedure be established at each participating institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of participant position is carried out. Additionally, it is not recommended that an institution use a daily imaging technique that delivers greater than 3cGy/day to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 3 cGy per study are used.

## 6.7 Quality Assurance

6.7.1 Radiation Documentation Requirements

The institution will archive treatment prescription and verification images for later review by the study chair if requested. At least one port film or pretreatment alignment film per field along with the digitally reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical. For CyberKnife SBRT, a screenshot of the alignment of the day of treatment X-Ray (Camera Image) to the DRR (Synthetic Image) will be acquired and kept for evaluation if requested.

6.7.2 Compliance Criteria

**Cases which meet criteria as stated in Section 6.1.2 will be scored as per protocol.** The minimum allowable dose within the PTV is >80% of the prescribed dose to a volume that is at least 1 cc. Cases in which this small volume of at least 1 cc receives a minimum dose that is <80% but >75% will be scored as a "deviation acceptable". Cases in which 1 cc receives less than 75% of the prescribed dose will be scored as a "deviation unacceptable". However, if this is what is required to keep the spinal cord or cauda equina within the maximum dose constraint, as specified above, this variation is considered "deviation acceptable".

6.7.2.1 Acceptable dose heterogeneity will be as follows: The maximum dose volume of the PTV must not be shared by a normal critical structure. (Section 6.4.1.5). The maximum point dose to normal critical structures outside the PTV including the unspecified tissue should not exceed dose specified in Table 1. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

## 6.8 Radiation Quality Assurance Reviews

RT quality assurance reviews will be ongoing and performed by the co-investigators and will be reviewed by the PI.

## 6.9 Radiation Adverse Events

6.9.1 All participants will be seen weekly by their treating radiation oncologist while undergoing therapy. The specific symptoms/side effects to be assessed will depend on the area(s) of the body undergoing treatment. A comprehensive list is below (see section 6.9.2); however every patient will not be assessed for every symptom if it is not relevant to the site(s) being treated.

Every patient will be assessed for:

- Pain – at the site(s) being treated
- Pain – at other locations
- Tiredness
- Skin reddening or irritation

- Skin peeling
- Nausea/Vomiting
- Hair loss

6.9.2 Comprehensive list of possible toxicities. The anticipated toxicity for each individual patient is very dependent on the location and the anticipated toxicities will be discussed in detail with the patient. These are listed in both the standard consent form the patient will sign for radiation treatment and the protocol-specific consent form as well as below.

**Short Term Reactions** (Appearing during radiation therapy or within 1 month thereafter; temporary, generally resolving within 2-3 months):

Common (> 20%):

- Tiredness
- Skin reddening & irritation that is reversible
- Loss of hair in the area of treatment
- Loss of taste
- Mild sore throat and difficulty swallowing
- Decreased blood counts that are reversible
- Weight loss that is reversible
- Pain flare

Rare (≤ 5%):

- Nausea
- Diarrhea
- Bladder irritation
- Fever and chills (within the first few hours of radiation)
- Severe esophagitis

**Long Term Reactions** (Appearing months after radiation; permanent, does not resolve)

Uncommon (10-20%):

- Mild scarring of skin or muscle without changes in function
- Mild scarring of the lung not requiring treatment
- Bone fractures

Rare (≤ 5%):

- Loss of hair in the treatment area
- Damage to spinal cord or nerves resulting in pain or other sensory changes
- Damage to spinal cord or nerves resulting in loss of motor function

- Damage to the esophagus limiting function

Extremely Rare (≤ 1%):

- Tumors caused by radiation
- Damage to bone or muscle limiting function
- Sterility
- Damage to the heart

### 6.10 Radiation Adverse Event Reporting

All adverse event reporting requirements are found in Appendix C.

### 6.11 Toxicity Assessment and Management

Any observations with respect to symptoms or side effects that are possibly, probably, or definitely related to SBRT treatment will be followed for AE reporting.

## 7. DRUG THERAPY

N/A – No medications will be given as part of this study. Medications for pain relief or other reasons may be given at the discretion of the treating physician and are covered in Section 9 below.

## 8. SURGERY

Surgery to the metastatic site(s) is allowed, but is not required, prior to enrollment on this study. The study does not include any surgical procedures.

## 9. OTHER THERAPIES

The following may be given at the discretion of the treating radiation oncologist:

- Dexamethasone – to be taken pre-treatment to prevent pain flare
- Benzodiazepines – as needed for anxiety during the SBRT planning and/or treatment
- Pain medications – as needed to control pain and allow the patient to be comfortable while undergoing treatment

## 10. TISSUE/SPECIMEN SUBMISSION

N/A: No tissue or specimens will be collected as part of this study nor will any previously collected tissue or specimens be used in any way as part of this study.

# 11. PARTICIPANT ASSESSMENTS

## 11.1 Definitions

11.1.1 Target Lesion(s) – Spine or non-spine bone metastatic site(s) being treated with SBRT. Up to a total of 3 lesions, as per the inclusion criteria. These will be recorded and measured at baseline. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.

11.1.2 Non-Target Lesion(s) – Any other lesions, either sites of stable disease or sites that have been or will be treated with other modalities than SBRT. Presence or absence of these lesions will be determined at the discretion of the treating radiation oncologist in collaboration with other treating physicians.

## 11.2 Methods/Requirements for assessments

11.2.1 Target Lesion(s): Will be evaluated via CT and/or MRI at the discretion of the treating physician. The same diagnostic modality(ies) will be used for assessment at each of the specified time points. A diagnostic radiologist reading the scan will be asked to measure the lesion(s) in the largest dimensions.

11.2.2 Non-Target Lesion(s): Will be evaluated via CT, PET/CT, and/or MRI at the discretion of the treating physician.

11.2.3 Toxicity Assessment

Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.2.4 QOL Assessment

QOL Assessment will be done using a modified MD Anderson Symptom Inventory (see Appendices D, E, F, and G), which is a validated questionnaire. The modified version to be used includes MDASI core questions, a spinal symptom inventory, and additional items pertinent to radiation therapy for palliation of bone metastases and pain.

11.2.5 Timing of Assessments

Baseline assessments will be done for the target lesion, non-target lesion(s), pre-existing toxicity and QOL. Participants' first assessment post-treatment will occur at 1 week (± 3 days) to assess for QOL. Participants will then undergo another evaluation at 1 month (± 1

week) to assess for QOL. Participants will then be evaluated at 3 months (± 4 weeks) with imaging (CT or MRI as per treating physician) done at the time of follow-up (± 2 weeks). Participants will then be evaluated at 6 months (± 2 months) and every 6 months thereafter through year 2 (± 3 months) and annually years 3-5 (± 6 months), with imaging (CT or MRI as per treating physician) done at the time of follow-up (± 2 weeks). We will attempt to coordinate all visits and scans with the patient's other medical providers to avoid duplicate visits or scans and minimize inconvenience to the patient and protocol violations. Please see Appendix B for additional study parameters.

| | Pre-Study | Treatment | Week 1[b] | Month 1[c] | Month 3[d] | Month 6[e] | Every 6 months after month 6 through year 2[f] | Annually Years 3-5[g] |
|---|---|---|---|---|---|---|---|---|
| Target Lesion(s) | X | | | | X | X | X | X |
| Toxicity Assessment | X | X[h] | | | X | X | X | X |
| QOL Assessment | X | X[a] | X | X | X | X | X | X |

a: On mid-point and last day of radiation
b: ± 3 days
c: ± 1 week
d: ± 4 weeks
e: ± 2 months
f: ± 3 months
g: ± 6 months
h: During on treatment visit

Note: The baseline "pre-study" questionnaire can be given anytime between the initial consult appointment and the first radiation therapy treatment, as long as the patient has not yet received radiation
Note: Imaging will be done at clinicians' discretion.

Participants will be given the option on each survey to decline.

Administration of questionnaires will be determined, as follows, by the time of follow-up.

| Questionnaire Version | Timeline | Appendix Reference |
|---|---|---|
| Symptom and Pain Baseline Assessment | Prior to initial RT | Appendix D |
| Symptom and Pain Assessment in the Past 24 Hours | Mid-point and on last day of treatment | Appendix E |
| Symptom and Pain Assessment in the Past 7 Days | 1 week and 4 week follow-up | Appendix F |
| Symptom and Pain Assessment, Long-Term Follow-Up | 3 months, every 6 months for 2 years, and annually from years 3 to 5 | Appendix G |

### 11.3 Response Criteria

11.3.1 Evaluation of Target Lesion(s): Each target lesion will be evaluated independently given that this is a local treatment only. Please note that the following criteria are adopted from the RECIST criteria for solid tumors for use in bony tumors, with tumor-related bony changes plus any soft tissue component (where applicable) evaluated to assess the size of the lesion and to determine response as noted below.

- Complete Response (CR): Disappearance of the target lesion.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesion, taking as reference the baseline sum LD.
- Progressive Disease (PD): At least a 20% increase in the sum of the longest diameter (LD) of target lesion, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
- Unknown (UN): Assessment of target lesion cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

11.3.2 Local failure is defined as the presence of biopsy-proven recurrent cancer at the treated site or radiologic scans that demonstrate progression at that site. Local control is defined as the absence of local failure. Participants will be followed for 5 years after the completion of treatment or until death.

11.3.3 Local Progression-free survival (LPFS) is defined as the duration of time from registration to time of local failure or death. Participants will be followed for 5 years after the completion of treatment or until death.

11.3.4 Progression-free survival (PFS) is defined as the duration of time from registration to time of any progression or death. Participants will be followed for 5 years after the completion of treatment or until death.

11.3.5 Overall Survival is defined as the time between registration and death. Participants will be followed for 5 years after the completion of treatment or until death.

## 12. DATA COLLECTION

### 12.1 Demographic, Disease and Treatment Information

The following information will be recorded for each patient:

- Age
- Race/Ethnicity
- Marital Status
- Diagnosis (pathology)
- Site of original disease
- Date of original diagnosis

- Date of diagnosis of metastatic disease (if different from above)
- Stage at diagnosis
- Sites and number of metastases
- Status of disease at each site (complete response, stable, progressing)
- Previous chemotherapy treatment(s)
- Previous radiation treatment(s)
- Previous surgeries
- Recent hospitalizations
- Specialties of physicians involved in their cancer care (i.e. palliative medicine, pain medicine, etc).
- Date of initial consultation with palliative care (if applicable)
- Charleson Co-morbidity Score

## 12.2 Additional Data Collection

| | **Maximum Time to Data Collection** | | | | | |
|---|---|---|---|---|---|---|
| | **Prior to 1st treatment** | **Within 1 Week after completion of treatment** | **2 weeks after completion of treatment** | **5 Weeks after completion of Treatment** | **4 Months after completion of treatment** | **10 months after completion of treatment, every 6-9 months through year 2, then annually through year 5** |
| Informed Consent | X | | | | | |
| History | X | | | | | |
| Medication Review | X | X | | | X | X |
| Physical exam (Ht, Wt, VS) | X | | | | | |
| Performance Status | X | X | | | X | X |
| Pre-existing condition or Adverse event evaluation | X | X | | | X | X |
| Tumor measurements | X | | | | X | X |
| Radiologic evaluation | X | | | | X | X |
| B-HCG* | X | | | | | |
| QoL questionnaire | X | X | X | X | X | X |
| Other malignancy related treatments undergone since last visit | | | | | X | X |
| SBRT GTV, CTV, PTV (as applicable) Dose Volume Information | | X | | | | |
| Critical Normal Tissue Dose Volume Data | | X | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Treatment Delivery Information | | X | | | | |

**For pre-menopausal women for whom pregnancy is a possibility (i.e., have not undergone a hysterectomy)*

### 12.3 Data Storage

Data will be identified only by medical record number when it is entered into a REDCap (Research Electronic Data Capture) Database which will be only accessible to investigators and study staff on this protocol. REDCap is a secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. The database design will be customized to suit the needs of this study.

The system offers easy data manipulation with audit trails, reports for monitoring and querying participant records, and an automated export mechanism to common statistical packages. Additionally, REDCap will enable us to provide each study member with only the minimum necessary access to the database and PHI with ultimate control of this access at the PI's discretion. Data may also be entered into an Excel or Access database file that will be stored on a password-protected secure Partners folder that is only accessible to investigators and study staff on this protocol.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Primary Endpoint

The primary objective of this study is to evaluate the 6-month local control rate of SBRT. The 6-month local control rate is the proportion of patients free of local failure at 6 months. Local failure is defined as the presence of biopsy-proven recurrence or radiologic scans that demonstrate progression at the treated sites.

Two cohorts of patients will be enrolled. Cohort 1 is comprised of patients with oligometastatic disease defined as ≤3 active sites of disease, including the primary site. Cohort 2 comprises patients who require re-irradiation of spinal disease. The primary analysis includes eligible and treated patients from both cohorts evaluated separately.

### 13.2 Sample Size, Accrual Rate and Study Duration

We planned to enroll a total of 100 patients, 50 per cohort, into this study in the original design. As the accrual was rapid and about half of the patients were prostate cancer patients in cohort 1, the sample size for cohort 1 was increased from 50 to 100 to allow patients with other histologies to participate in this trial.

The primary endpoint is local control rate at 6 months. Assuming a cumulative incidence of local failure at 6 months is 10%, the 6-month local control rate is 90% with 90% exact binomial confidence intervals of [83.6%, 94.5%] and [80.1%, 96.0%] for cohorts 1 and 2, respectively. The confidence intervals are narrow enough to provide a precise estimate local control rate. With the sample size increase in cohort 1, we can also estimate the local control rates with better precision for the subsets of patients with either prostate cancer or other histologies To be conservative, unevaluable patients (patients without valid assessments demonstrating free of local failure at 6 months) will be considered as failures in the analysis although we do not

anticipate many unevaluable patients on this study.

Approximately 250 patients per year are treated with conventional external beam radiation therapy for bone metastases in our department, with approximately one third being spine metastases. We estimate that approximately 10% of those 250 would be eligible for this study, yielding about 2 patients per month. Additionally, we are currently treating an average of 4 patients per month with SBRT for spinal metastases (75% eligible for cohort 1 and 25% eligible for cohort 2). It is expected that 70% of these patients will participate. Hence, we anticipate to accrue 3 and 1-2 patients per month for cohorts 1 and 2, respectively, and the accrual will be completed, in total for both cohorts, over about 3 years.

### 13.3 Stratification Factors

N/A

### 13.4 Interim Monitoring Plan

N/A

### 13.5 Analysis of Primary Endpoints

Proportion of patients with local control at 6 months in each cohort will be calculated along with the 90% exact binomial confidence intervals. This point estimate will serve to inform future study design.

### 13.6 Analysis of Secondary Endpoints

Secondary endpoints include, in each cohort, local progression-free survival (LPFS), progression-free survival (PFS), overall survival (OS) and patient reported quality of life (QOL) using the modified MD Anderson Symptom Inventory (MDASI).

LPFS is defined as the time from registration to local disease progression or death, whichever occurs first. PFS is defined as the time from registration to disease progression or death, whichever occurs first. Patients alive without documented progression will be censored at the date of last disease assessment. OS is defined as the time from registration to death or the date last known alive. Kaplan-Meier estimates will be used to describe event-time distributions.

Patient reported QOL, symptoms and satisfaction will be assessed using the modified MDASI general questionnaire and spine inventory at baseline, during treatment and all follow-up visits. The distributions of mean core symptom severity and mean interference score over time will be reported. The mean symptom severity of spine tumor will also be reported for patients with a spine site being treated on this study. The primary analysis for the QOL study is to evaluate the change in QOL from baseline to 3 months in this patient population using Wilcoxon signed rank test. Assuming 80% of patients complete the baseline and 3-month QOL assessments and a two-sided test with alpha=0.05, the study will have about 89% power to detect a difference of 0.3 standard deviation among all patients. All patients who receive at least one fraction of SBRT will

be monitored for toxicity, and the percent of patients with various toxicities will be tabulated for each cohort. The acute and chronic toxicity rates will also be reported. The probability of observing one or more toxicities with a true rate of 5% is 99.4% and 92.3% for cohort 1 and cohort 2, respectively.

## 14. REGULATORY CONSIDERATIONS

### 14.1 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; dose-limiting toxicity information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; any response information; audit results, and a summary provided by the study team. Other information (e.g., scans, laboratory values) will be provided upon request.

### 14.2 Multicenter Guidelines

N/A

### 14.3 COLLABORATIVE AGREEMENTS LANGUAGE

N/A

## 15. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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**APPENDIX A PERFORMANCE STATUS CRITERIA**

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## APPENDIX B STUDY PARAMETERS

| Assessments | Pre-Study | Simulation | Radiation Treatment | Follow-Up (1) |
|---|---|---|---|---|
| Informed Consent and Registration | X | | | |
| History/physical/vital signs | X | | | X |
| Performance Status | X | | | X |
| Pregnancy Test (B-HCG) | X | | | |
| Diagnostic CT or MRI (at discretion of treating physician) | | X(2) | | |
| Imaging study (CT or MRI to be determined by treating physician) | | | | X(3) |
| Toxicity Assessment | X | | X(6) | X |
| QOL questionnaire | X | | X(4) | X(5) |

(1) Follow up schedule: initial evaluation at 1 week after completion of radiation therapy (via telephone, in person or email), then at 1 month after completion (via telephone, in person or email), 3 months, 6 months and every 6 months thereafter through year 2 (in person, telephone or email), then annually through year 5. Visits can be scheduled within a pre-specified time window around the anticipated date.

(2) Baseline imaging is to be done within 21 days of start of first fraction of radiation

(3) Follow up imaging is to be done within 2 weeks before or after scheduled follow up visit.

(4) On mid-point and last day of radiation

(5) QOL questionnaire to be completed within 2 weeks of follow up visit.

(6) During on treatment visit

## APPENDIX C ADVERSE EVENT REPORTING REQUIREMENTS

**DEFINITIONS**:

Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

Expectedness: Adverse events can be 'Expected' or 'Unexpected.'

- Expected adverse event
    - Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list or is included in the informed consent document as a potential risk.
    - Refer to Section 6.9 for a listing of expected adverse events associated with the study agent.

- Unexpected adverse event
    - For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list or when it is not included in the informed consent document as a potential risk.

Attribution

- Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:
    - Definite – The AE is clearly related to the study treatment.
    - Probable – The AE is likely related to the study treatment.
    - Possible – The AE may be related to the study treatment.
    - Unlikely - The AE is doubtfully related to the study treatment.
    - Unrelated - The AE is clearly NOT related to the study treatment.

## PROCEDURES FOR AE AND SAE RECORDING AND REPORTING

Investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

## ADVERSE EVENT REPORTING REQUIREMENTS

Serious Adverse Event Reporting
All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Serious Adverse Event (as above), as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Tracy Balboni, MD MPH
617-525-6687 or 617-632-4621
TBALBONI@LROC.HARVARD.EDU

Within the following 24-48 business hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Non-Serious Adverse Event Reporting
Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the study sponsor: **N/A**

Reporting to the Institutional Review Board (IRB)
Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Reporting to the Food and Drug Administration (FDA): **N/A**

Reporting to the NIH Office of Biotechnology Activities (OBA): **N/A**

Reporting to the Institutional Biosafety Committee (IBC): **N/A**

Reporting to Hospital Risk Management
Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

## MONITORING OF ADVERSE EVENTS AND PERIOD OF OBSERVATION

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention through the study intervention period and up to 30 days after the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

# APPENDIX D: SYMPTOM AND PAIN BASELINE ASSESSMENT

*Confidential*



## Dual Enrolled Sbrt Mdasigi Pain Assessment Baseline (version AB)

Name (Last, First) _____

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fatigue (tiredness) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling drowsy (sleepy) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Disturbed sleep at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Problem with remembering things at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling sad at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feelings of being distressed (upset) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shortness of breath at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Having a dry mouth at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Nausea at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Vomiting at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Problem with lack of appetite at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|

*Confidential*



| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Difficulty swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Pain with swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Acid, indigestion, or heartburn at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Diarrhea or loose stools at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Change in bowel pattern (diarrhea/constipation) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Loss of control of bowel and/or bladder at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
| Numbness or tingling at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Radiating spine pain (starting in one place and going to another) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Weakness in the arms and/or legs at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Sexual function at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

*Confidential*



**How have your symptoms interfered with your life? Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 7 days from 0 (did not interfere) to 10 (interfered completely):**

| | 0 (did not interfere) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (interfered completely) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| General Activity in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Mood in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Work (including work around the house) in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Relations with other people in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Walking in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Enjoyment for life in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Pain Assessment**

Please rate your pain at its WORST in the last 24 hours on a scale of 0-10 with 0 being no pain at all, 10 being worst pain imaginable
(Includes pain related and unrelated to cancer)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of maximum pain _____

Location of first site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this treatment site (site 1, specified above) where you will be receiving radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of second site receiving radiation (to be filled in by study staff) _____



*Confidential*



Please rate your maximum pain in the past 24 hours at this treatment site (site 2, specified above) where you will be receiving radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of third site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this treatment site (site 3, specified above) where you will be receiving radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

## Medication Review

Have you taken any medications for pain in the last 7 days?
- ○ Yes
- ○ No

What kinds of pain medications are you taking? Check all that apply. If you are unsure, please ask your provider before answering this question.
- ☐ Narcotic pain medications (ex. morphine, oxycodone, dilaudid, or similar medications)
- ☐ Non-narcotic pain medications (ex. tylenol, ibuprofen, etc)

Have you taken any medications for HEARTBURN or REFLUX in the last 7 days?
- ○ Yes
- ○ No

(Examples include (but not limited to): zofran or ondansetron, compazine or prochlorperazine, reglan or metoclopramide, ativan)

Have you taken any medications for NAUSEA in the last 7 days?
- ○ Yes
- ○ No

(Examples include (but not limited to): Prilosec or omeprazole, Protonix or pantoprazole, Nexium or esomeprazole, Zantac or ranitidine)

Have you taken any medications for DIARRHEA in the last 7 days?
- ○ Yes
- ○ No

(Examples include (but not limited to): immodium, lomotil)

## APPENDIX E: SYMPTOM AND PAIN ASSESSMENT IN THE PAST 24 HOURS

*Confidential*



# Dual Enrolled Sbrt Mdasigi Pain Assessment Followup (version D)

Name (Last, First) _____

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fatigue (tiredness) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling drowsy (sleepy) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Disturbed sleep at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Problem with remembering things at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling sad at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feelings of being distressed (upset) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shortness of breath at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Having a dry mouth at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Nausea at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Vomiting at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Problem with lack of appetite at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|



*Confidential*



| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Difficulty swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Pain with swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Acid, indigestion, or heartburn at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Diarrhea or loose stools at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Change in bowel pattern (diarrhea/constipation) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Loss of control of bowel and/or bladder at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
| Numbness or tingling at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Weakness in the arms and/or legs at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Radiating spine pain (starting in one place and going to another) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Sexual function at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

*Confidential*



**How have your symptoms interfered with your life? Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 HOURS from 0 (did not interfere) to 10 (interfered completely):**

| | 0 (did not interfere) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (interfered completely) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| General Activity in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Mood in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Work (including work around the house) in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Relations with other people in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Walking in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Enjoyment for life in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Pain Assessment**

Please rate your pain at its WORST in the last 24 hours on a scale of 0-10 with 0 being no pain at all, 10 being worst pain imaginable
(Includes pain related and unrelated to cancer)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of maximum pain _____

Location of first site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this treatment site (site 1, specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10



*Confidential*



Please estimate the percent improvement in pain you have experienced at this treatment site (site 1, specified above) since starting radiation therapy.

0% (no change in pain or pain has worsened) to 100% (pain completely resolved)

◯ 0% ◯ 10% ◯ 20% ◯ 30% ◯ 40% ◯ 50% ◯ 60% ◯ 70% ◯ 80% ◯ 90% ◯ 100%

Location of second site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this treatment site (site 2, specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10

Please estimate the percent improvement in pain you have experienced at this treatment site (site 2, specified above) since starting radiation therapy.

0% (no change in pain or pain has worsened) to 100% (pain completely resolved)

◯ 0% ◯ 10% ◯ 20% ◯ 30% ◯ 40% ◯ 50% ◯ 60% ◯ 70% ◯ 80% ◯ 90% ◯ 100%

Location of third site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this treatment site (site 3, specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10

Please estimate the percent improvement in pain you have experienced at this treatment site (site 3, specified above) since starting radiation therapy.

0% (no change in pain or pain has worsened) to 100% (pain completely resolved)

◯ 0% ◯ 10% ◯ 20% ◯ 30% ◯ 40% ◯ 50% ◯ 60% ◯ 70% ◯ 80% ◯ 90% ◯ 100%

## Medication review

Have you started or increased your dose of any medications since last follow-up (or since starting radiation if this is your first follow-up) because you have experienced DIARRHEA?

◯ Yes
◯ No
(Examples include (but not limited to): imodium, lomotil)

Have you started or increased your dose of any medications since last follow-up (or since starting radiation if this is your first follow-up) because you have experienced NAUSEA?

◯ Yes
◯ No
(Examples include (but not limited to): zofran or ondansetron, compazine or prochlorperazine, reglan or metoclopramide, ativan)

*Confidential*



| | |
|---|---|
| Have you started or increased your dose of any medications since last follow-up (or since starting radiation if this is your first follow-up) because you have experienced HEARTBURN? | ○ Yes<br>○ No<br>(Examples include (but not limited to): Prilosec or omeprazole, Protonix or pantoprazole, Nexium or esomeprazole, Zantac or ranitidine) |
| Have you started or increased your dose of any medications since last follow-up (or since starting radiation if this is your first follow-up) because you have experienced SORE THROAT? | ○ Yes<br>○ No |
| Which medications have you started or increased in dose? Check all that apply: | ☐ magic mouth wash<br>☐ narcotic pain medications (i.e. morphine, oxycodone, dilaudid, or similar)<br>☐ non-narcotic pain medications<br>☐ other |
| If other, please describe | _____ |

**APPENDIX F: PAIN AND SYMPTOM ASSESSMENT IN THE PAST 7 DAYS (FOLLOW-UP)**

*Confidential*



# Dual Enrolled Sbrt Mdasigi Pain Assessment 1wk 4wk (version CE)

Name (Last, First) _____

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fatigue (tiredness) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling drowsy (sleepy) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Disturbed sleep at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Problem with remembering things at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling sad at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feelings of being distressed (upset) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |



*Confidential*



| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shortness of breath at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Dry mouth at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nausea at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Vomiting at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Lack of appetite at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Difficulty swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Pain with swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Acid, indigestion, or heartburn at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

*Confidential*



| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Diarrhea or loose stools at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Change in bowel pattern (diarrhea/constipation) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Loss of control of bowel and/or bladder at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |



| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|



| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Numbness or tingling at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Weakness in the arms and/or legs at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

*Confidential*



| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Radiating spine pain (starting in one place and going to another) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Your sexual function at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Part II. How have your symptoms interfered with your life?**

**Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 HOURS and LAST 7 DAYS from 0 (did not interfere) to 10 (interfered completely):**

| | 0 (did not interfere) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (interfered completely) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| General Activity in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Mood in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Work (including work around the house) in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

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| | 0 (did not interfere) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (interfered completely) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Relations with other people in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Walking in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Enjoyment for life in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...in the last 7 days? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## Part III. Pain Assessment

Please rate your pain at its WORST in the last 24 hours.

0 (no pain), 10 (as bad as you can imagine)
(Includes pain related and unrelated to cancer)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of maximum pain _____

Location of first site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this first treatment site (specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Please estimate the percent improvement in pain you have experienced at this first treatment site (specified above) since starting radiation therapy.

0% (no change in pain or pain has worsened) to 100% (pain completely resolved)

○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100%

Location of second site receiving radiation (to be filled in by study staff) _____

*Confidential*



Please rate your maximum pain in the past 24 hours at this second treatment site (specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Please estimate the percent improvement in pain you have experienced at this second treatment site (specified above) since starting radiation therapy.

0% (no change in pain or pain has worsened) to 100% (pain completely resolved)

○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100%

Location of third site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this third treatment site (specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Please estimate the percent improvement in pain you have experienced at this third treatment site (specified above) since starting radiation therapy.

0% (no change in pain or pain has worsened) to 100% (pain completely resolved)

○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100%

## Part IV. Medication review

Have you started or increased your dose of any medications since last follow-up because you have experienced DIARRHEA?
○ Yes
○ No

Have you started or increased your dose of any medications since last follow-up because you have experienced NAUSEA?
○ Yes
○ No

Have you started or increased your dose of any medications since last follow-up because you have experienced HEARTBURN?
○ Yes
○ No

Have you started or increased your dose of any medications since last follow-up because you have experienced SORE THROAT?
○ Yes
○ No

Which medications have you started or increased in dose? Check all that apply:
☐ magic mouth wash
☐ narcotic pain medications (i.e. morphine, oxycodone, dilaudid, or similar)
☐ non-narcotic pain medications
☐ other

If other, please describe _____



**APPENDIX G: SYMPTOM AND PAIN ASSESSMENT IN THE PAST 24 HOURS (LONG-TERM FOLLOW-UP)**

*Confidential*



## Dual Enrolled Sbrt Mdasigi Pain Assessment (version F)

Name (Last, First) _____

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fatigue (tiredness) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling drowsy (sleepy) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Disturbed sleep at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Problem with remembering things at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feeling sad at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Feelings of being distressed (upset) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shortness of breath at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Having a dry mouth at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Nausea at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Vomiting at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Problem with lack of appetite at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
|---|---|---|---|---|---|---|---|---|---|---|---|



*Confidential*



| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Difficulty swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Pain with swallowing at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Acid, indigestion, or heartburn at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Diarrhea or loose stools at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Change in bowel pattern (diarrhea/constipation) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Loss of control of bowel and/or bladder at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| | 0 (not present) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (as bad as you can imagine) |
| Numbness or tingling at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Weakness in the arms and/or legs at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Radiating spine pain (starting in one place and going to another) at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Sexual function at its WORST in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

*Confidential*



**Part II. How have your symptoms interfered with your life?**

**Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 HOURS from 0 (did not interfere) to 10 (interfered completely):**

| | 0 (did not interfere) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (interfered completely) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| General Activity in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Mood in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Work (including work around the house) in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Relations with other people in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Walking in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Enjoyment for life in the last 24 hours? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Part III. Pain Assessment**

Please rate your pain at its WORST in the last 24 hours on a scale of 0-10 with 0 being no pain at all, 10 being worst pain imaginable
(Includes pain related and unrelated to cancer)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of maximum pain _____

Location of first site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this treatment site (site 1, specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of second site receiving radiation (to be filled in by study staff) _____



*Confidential*



Please rate your maximum pain in the past 24 hours at this treatment site (site 2, specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Location of third site receiving radiation (to be filled in by study staff) _____

Please rate your maximum pain in the past 24 hours at this treatment site (site 3, specified above) where you have received radiation therapy.

0 (no pain), 10 (as bad as you can imagine)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10