A Phase II Study of Hypofractionated Stereotactic Radiotherapy in the Treatment of Metastatic Pediatric Sarcomas of Bony Sites

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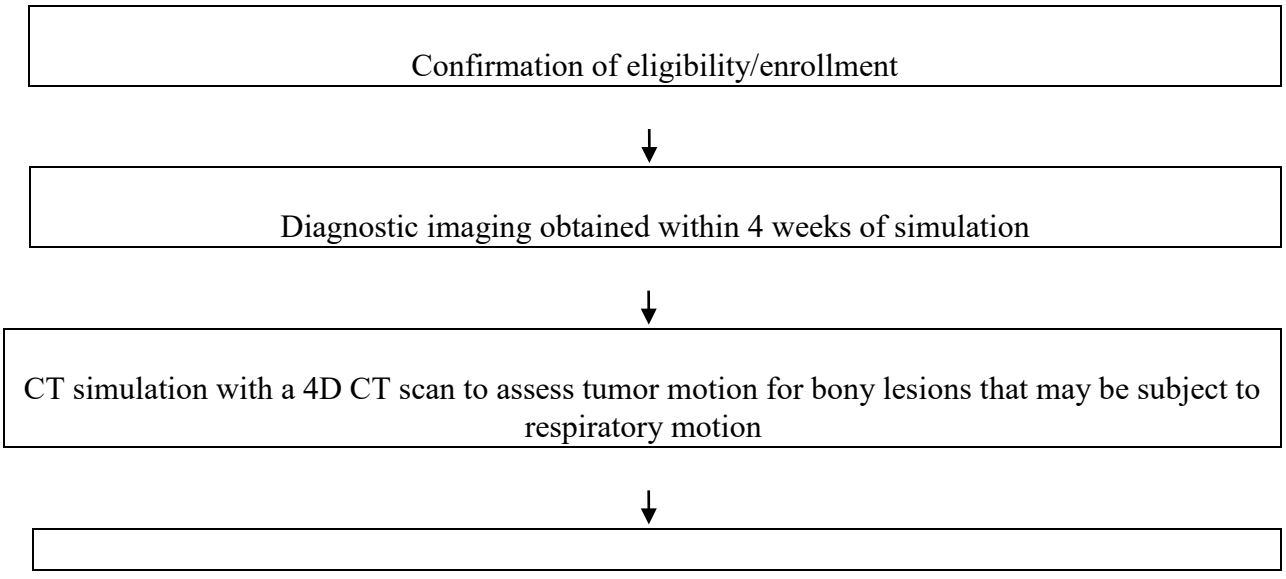
SUMMARY OF CHANGES

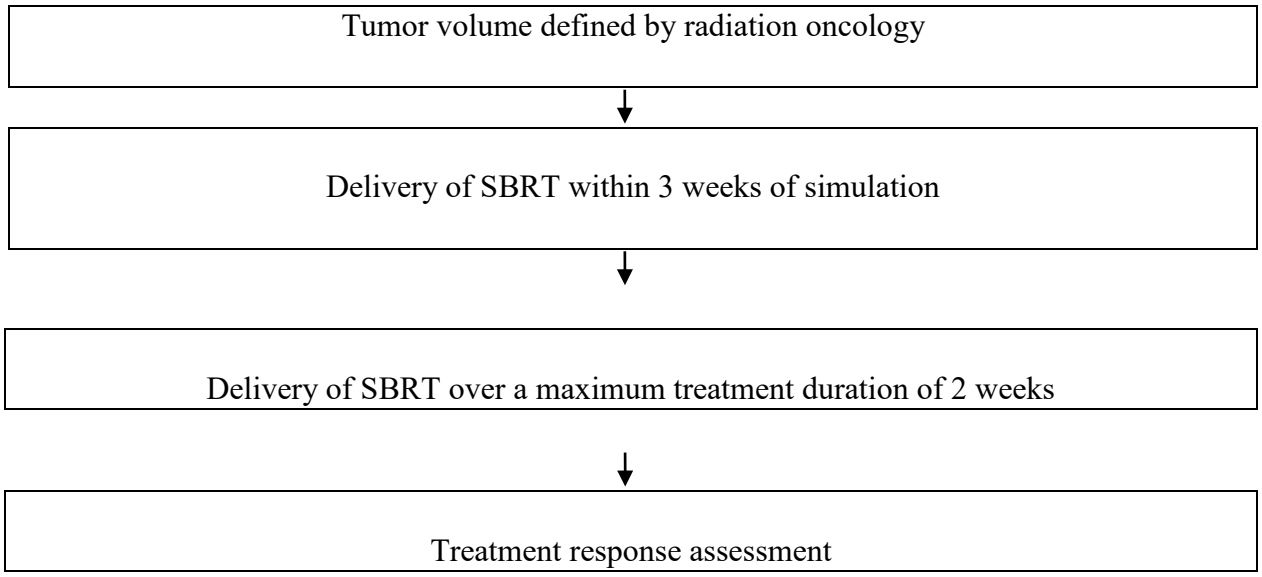
Protocol Revision Date	**Protocol Revision**	**Description of Change**
8/26/2014	**1.0**	**Transcription Error Reconciliation**
8/16/2016	**2.0**	**Adding Sibley Memorial Hospital**

PROTOCOL SUMMARY

Patient with pediatric sarcoma who have limited metastases are still potentially curable with aggressive local therapy. However, conventional moderate dose radiation is unlikely to provide durable local control. Given the recent technologic advances in radiation delivery, it is now possible to deliver tumoricidal doses, using stereotactic body radiotherapy (SBRT) over a short time course with highly focal techniques. Stereotactic radiation has proven efficacious in the intracranial setting and in multiple extracranial sites in adults. It has not yet been well studied in the pediatrics population where there is a particularly strong rationale due to the ablative doses that can be delivered to tumor while simultaneously reducing high dose to normal tissues. The proposed trial is a single arm phase II study to determine the efficacy of SBRT in pediatric sarcomas with surgically unresectable metastatic disease. Metastatic sites eligible for treatment in this study include bony sites of disease. SBRT will be delivered to each eligible site to a total dose of 4000 cGy delivered in 5 fractions of 800 cGy per fractions each day. Following completion of SBRT, patients will undergo treatment response assessment with the use of diagnostic imaging, clinical examination, and completion of the Brief Pain Inventory to assess quality of life. The primary objective of this study is to determine the efficacy of SBRT delivered to a dose of 4000 cGy in 5 fractions of 800 cGy each for patients greater than 3 years of age and $\leq$ 40 years of age with metastatic disease of bone secondary to pediatric sarcoma. The secondary objectives of this study include describing the toxicity of SBRT with this regimen; assessing clinical response rate of each target lesion; assessing long-term clinical outcomes; and assessing quality of life following completion of treatment. For patients with potentially curable oligometastatic disease, surgical resection in conjunction with systemic therapy remains the standard of care. Patients on this study will be able to receive chemotherapy 2 weeks after completion of SBRT. Issues that may limit participation include our inability to assess late effects that may not develop till at least 10 years after therapy. For this reason, we will limit the population in this study to patients who are surgically unresectable and would be otherwise incurable with current standard systemic therapies.

SCHEMA





1. OBJECTIVES

1.1 Primary Objectives

To determine the lesion-specific local control at 6 months of SBRT delivered to a dose of 4000 cGy in 5 fractions of 800 cGy each for patients greater than 3 years of age and ≤ 40 years of age with metastatic disease of bone secondary to pediatric non-rhabdomyosarcoma soft tissue or bone sarcoma.

1.2 Secondary Objectives

1.2.1 To describe the toxicity of SBRT delivered to a dose of 4000 cGy in 5 fractions of 800 cGy each for the population enrolled using grading with CTCAE v. 4.0

1.2.2 To assess clinical response rate of each treated site by serial CT assessment (FDG- PET/CT is optional for assessment)

1.2.3 To assess long-term clinical outcomes of this patient population after completion of SBRT by measuring relapse-free survival and overall survival

1.2.4 To assess quality of life following completion of SBRT using pre- and post-SBRT completion of the Brief Pain Inventory form and 10 point Visual Analog scale which will be filled out by the patient

2. BACKGROUND

2.1 Oligometastatic Disease

Cancer is the second leading cause of death in the United States, primarily due to an inability to control metastatic disease. The metastatic capacity of cancers behaves along a spectrum of disease progression, such that some tumors have spread widely before clinical detectability and others never metastasize. Contained within this spectrum, is an oligometastatic state where metastases are limited in number and location. The presence of an oligometastatic state was originally proposed by Hellman who suggested that these oligometastatic patients would benefit from effective local therapy in addition to systemic therapy (1). In agreement with this hypothesis, surgery and chemotherapy for isolated pulmonary metastases can result in long term disease-free periods (2). Additionally, some 25% of patients following resection and chemotherapy for colorectal cancer and isolated liver metastases can similarly have longterm disease free survival (3-5). Patients who may benefit most from curative therapy are most likely those patients with limited systemic disease when metastatic disease is generally confined to a lesion state of five metastatic sites or fewer.

2.2 Stereotactic Body Radiotherapy (SBRT)

The treatment of metastases depends on multiple factors including 1) the location of the primary tumor, 2) the presence or absence of other metastatic foci, 3) the size, number and location of metastases, 4) the effectiveness of various forms of therapy, and 5) the patient's functional status. Conventional moderate dose radiation for metastatic disease is given primarily for palliation. Recent advances in radiation delivery now make it possible to image and treat precisely within any anatomical region of the body. As a result, the capacity to deliver tumoricidal doses in a single or few (1-10) outpatient treatments is now possible. In addition, by minimizing the irradiation of surrounding healthy tissue, it should also be possible to decrease the rate of complications. Intracranial stereotactic radiation therapy has been shown to be a highly effective treatment for brain metastases in both the adult and pediatrics population (6,7). This suggests that selective small extracranial tumors may be effectively controlled by similar focal high-dose stereotactic body radiotherapy (SBRT). Local control in excess of 75% has been reported using extracranial SBRT for metastatic tumors of the spine, lung and liver, which is significantly higher than conventional moderate dose radiation (8-24). Toxicity has been minimal in these reports despite the use of very high biological equivalent doses (8-24).

2.3 Rationale

The SBRT literature focuses on clinical outcomes in the adult population. However, SBRT has a particularly strong rationale for application in pediatrics given that high biologically effective doses have been shown to increase control in histologies, such as sarcoma, which are common in the pediatrics population (11,25). With stereotactic radiation therapy techniques, a reduction in normal tissue dose surrounding the target lesion of interest may also be accomplished resulting in lower toxicity. Given that pediatric patients with sarcomas, presenting with limited metastases in lung and bone, are still considered to be a curable

population with aggressive local therapy, SBRT could have a significant impact on outcomes in oligometastatic patients who may be otherwise unresectable (25-28).

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed nonrhabdomyosarcoma of soft tissue or bone at any site

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan within 4 weeks of treatment start. See Section 9.1.3 for the evaluation of measurable disease.

3.1.3 Greatest tumor dimension of all sites must be $\leq$ 5.0 cm or <250 cm^3

3.1.4 There is at least 1 metastatic site at one or more of the following sites: spine or non-spine bone and at maximum 5 sites can be treated on protocol

3.1.5 Surgically unresectable site as determined by tumor board or surgeon or patients who decline surgery.

3.1.6 Patients must be greater than 3 years of age and $\leq$ 40 years of age.

3.1.7 Life expectancy of at least 9 months

3.1.8 Lansky performance status $\geq$ 50 (See Appendix E)

3.1.9 Ability to understand and the willingness to sign a written informed consent document and if a minor, have a guardian who meets the above criteria.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 2 weeks prior to starting radiation treatment

3.2.2 Patients who have had any prior radiotherapy to the treatment site(s).

3.2.4 A patient may not participate in a concurrent treatment protocol. All patients will be eligible to receive chemotherapy alone, systemic therapeutic agents, or conventional chemo-radiotherapy at the time of clinical or radiographic disease progression or at 2 weeks following completion of SBRT.

3.2.5 Pregnant women are excluded from this study because radiation treatment has known potential for teratogenic or abortifacient effects.

3.2.6 Refusal to take a pregnancy test prior to treatment if the patient is a woman with child bearing potential.

3.2.7 Patients with a rhabdomyosarcoma will be excluded due to the radiosensitive nature of their disease.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Institutions will register eligible participants with the Coordinating Center. Registration must occur prior to the initiation of therapy.

A member of the study team will confirm eligibility criteria and complete the protocolspecific eligibility checklist.

Participants should begin protocol treatment within 3 weeks from simulation. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the Study Coordinator should be notified as soon as possible.

4.2 Registration Process

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an IRB approved consent form. All patients must be registered centrally at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

To register a patient, the following documents should be completed and faxed or e-mailed to the Coordinating Center:

- Signed patient consent form
- HIPAA authorization form
- Completed and signed eligibility checklist
- De-identified copies of source documentation verifying eligibility

The Coordinating Center will review the documents to confirm eligibility. To complete the registration process, the Coordinating Center will:

- assign a patient study number
- register the patient on the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office
- fax or e-mail the patient study number to the participating site

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy concurrently.

5.1 Pre-Treatment Procedures

The following will be completed prior to radiation initiation:

- Medical history and clinical examination
- Pathologic confirmation of malignancy
- CBC, chemistry panel
- CT of treatment site (not required if MRI is obtained)
- MRI of treatment site, optional depending on site (required for spinal lesions)
- Positron Emission Tomography (FDG-PET) scan (optional)

5.2 Simulation

Stereotactic radiation requires meticulous definition of the target, normal tissue structures, and visualization for localization during treatment delivery. Prior to treatment, a simulation CT scan will be performed for tumor localization using rigid immobilization appropriate for stereotactic treatment. A separate FDG-PETCT or MRI is optional for diagnostic purposes and can be used for treatment planning with fusion -- this study would be done identically if the patient were having standard fractionated radiation. These studies can assist with delineation of the target and visualization for stereotactic treatment. While MRIs are optional for diagnostic evaluation and treatment planning of non-spine bony sites, they are required for patients who will be treated to the spine.

Patients will be positioned in a reproducible treatment position with an appropriate immobilization device custom-made for each patient and specific to treatment site. A variety of immobilization systems can be used on study such as stereotactic frames which surround the patient on three sides or large rigid pillows that reference to a stereotactic coordinate system.

CT simulation will be performed. The simulation study must include the target and all organs at risk for treatment planning. Simulation scan length should be 510 cm superior and inferior to the target. All organs at risk within the scan length should be contoured for dose-volume histogram analysis. For stereotactic treatment, tomographic slice thickness of 1-3 mm through the target is recommended.

Special consideration should be given to the analysis of internal organ motion if the target lesion is located in a site subject to motion such as the chest wall. Techniques to image moving targets such as active breath-hold techniques, accelerator gating with respiratory cycle, tumor tracking, 4D CT scan acquisition in conjunction with maximum intensity projection (MIP), will be considered acceptable maneuvers to account for organ motion. If the target cannot be visualized or localized on the planning imaging modality as a result of motion or metal artifact, stereotactic treatment should not be used.

The treating radiation oncologist will identify the location of the tumor. Gross tumor volume (GTV) delineation will be performed with a diagnostic radiologist on sequential axial computed tomography images. A radiosurgical treatment plan will be developed based on tumor geometry and location. Adjacent normal structures including but not limited to the heart, esophagus, aorta, spinal cord, kidneys, rectum, bowel, liver, and stomach within 5 cm of the GTV will be identified for the purpose of limiting incidental radiation to these structures (please see Appendix D for a list of normal tissue dose constraints to be used on protocol as well as constraints for high and low-dose spillage).

We plan to deliver 800 cGy at each fraction for five fractions every day for a total dose of 4000 cGy, over a treatment duration at a maximum of 2 weeks. For bony sites aside from spine, the GTV will be expanded uniformly to the PTV by 2 mm and treated to 4000 cGy to cover at least 90% of the defined target volume. For patients with spinal metastases undergoing treatment on protocol, the vertebral body will be contoured as a separate clinical target volume (CTV) encompassing the GTV. The CTV vertebral body will be expanded by 2 mm to create a PTV. The GTV will be treated to 4000 cGy and the PTV treated to 3000 cGy in 5 fractions..

The main criteria for dose prescription will be the achievement of the spinal cord dose constraint (see table below):

Normal Tissue	Volume	Volume Max (cGy)	Max Point Dose (cGy)	Endpoint (≥Grade 3)
Spinal Cord	<0.25 cc <1.2 cc	1550cGy 1000cGy	2000cGy (400cGy /fx)	Myelitis

The spinal cord will be contoured as the true cord with use of MRI for fusion. Spinal cord volume will be defined as 6 mm above and below the radiosurgery target volume. The spinal cord can move within the thecal sac. The thecal sac will be contoured based on T2 MRI or bony limit of spinal canal and will serve as a PRV (planning organ at risk volume) for the spinal cord. Thecal sac volume will be defined as 6 mm above and below the radiosurgery target volume. The skin will be defined as the outer 0.5 cm of the body surface. The skin is essentially a rind of 0.5 cm enveloping the entire body in axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations. Ribs within 5 cm of the PTV should be contoured by outlining bone and bone marrow. The intercostal spaces should not be included as part of the ribs. The minimum, mean, and maximum dose to the PTV will be reported. Only $\leq$ 1 cc or $\leq$ 1-5% of unspecified tissue outside of the PTV can receive $\geq$ 100-110% of the prescribed dose.

5.3 SBRT Treatment Delivery

All patients should receive 5 fractions of 800 cGy over a five-day period (See Section 6 for dose modification). Ideally all 5 fractions should be delivered Monday through Friday, however it may be delivered over two weeks.

Within three weeks of the initial treatment planning imaging study, SBRT will be administered using image-guidance. This protocol allows conventional linear accelerators and specialized linear accelerators with image guidance (e.g. Novalis, Trilogy, Synergy, Artiste) capable of conformal dose delivery and IMRT. Specialized accelerators (e.g. Cyberknife or Tomotherapy) are also allowed.

During treatment, real time cone beam CT images of the patient's body site of interest will be obtained. Cone beam CT scan will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the CT planning scan and the cone beam CT scan performed on the day of treatment, is within 2 mm.

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments. Anesthesia will be delivered by a dedicated pediatric anesthesiologist.

5.4 General Concomitant Medication and Supportive Care Guidelines

There are no known potential interactions between SBRT and concomitant medications.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 2 weeks or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient or parent/guardian (for minors) decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.6 Post-SBRT Follow-up

Subsequent to SBRT, patients will be monitored as follows: 5.6.1
4 Weeks Post-SBRT
5.6.2 At 3, 6, 9, 12, 18, 24, 30, and 36 months Post-SBRT

5.7 Duration of Follow-Up

It is anticipated the patients that remain on-study will be followed for 3 years. Patients will remain enrolled on this protocol until there is evidence that their disease has progressed either locally or distally, at which case they will be removed from the protocol and be followed for survival only. Patients removed from study for unacceptable adverse events will be followed per protocol until resolution or stabilization of the adverse event and then followed for survival only.

5.8 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSE MODIFICATIONS

In young children less than 10 years of age where the study dose is not considered safe to deliver as a result of the radiation dose that will be delivered to surrounding normal tissues, a dose of 3500 cGy delivered in 700 cGy fractions in 5 fractions every day to the GTV, will be allowed as a prescription dose. A dose modification may be made at the discretion of the treating physician but the Principal Investigator must be informed and approve this change.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Adverse Events and Potential Risks

Because patients are receiving standard treatments, which are not part of this study, their treating physician will be counseling them on the risk of their treatments, including the risk of surgery, radiation therapy, and/or chemotherapy, whichever is appropriate for the type and the stage of their cancer. Clinically significant toxicities in the study will include Grade 3, 4, and 5 non hematologic toxicities. The procedures related to the study are phlebotomy, CT imaging, MRI imaging, and SBRT. Recording and reporting requirements are discussed in Section 7.3.

Risks associated with blood draw:
Phlebotomy can cause pain, bleeding, and rare needle site infection. CT imaging results in low dose radiation exposure, which has an extremely small risk of causing a secondary cancer.

Risks associated with SBRT:
It is difficult at this time to predict with confidence the complication rate from the proposed SBRT. However, it is reasonable to extrapolate from the current experience with SBRT to the spine, lung and pancreas in adults.

Toxicities commonly associated with such treatment will depend on the location of the treated metastasis. These toxicities can include skin erythema and desquamation, pain, neuropathy, dysphagia, nausea, vomiting, anorexia, and weight loss. Some of these symptoms can also be due to tumor progression. One significant toxicity is radiation pneumonitis, which can be manifested as fever, increased excertional dypsnea, pleuritic chest pain, and peritumoral infiltrate on chest imaging. It generally occurs between 1 to 3 months of completion of radiotherapy. The risk of grade 2-4 radiation pneumonitis is aproximately 10-15% in patients treated with standard fractionated large field radiotherapy and higher in patients treated with combined chemoradiotherapy. It is highly dependent on the volume of the lung treated to high dose and the mean lung dose. At this point, the incidence of RT pneumonitis from stereotactic radiosurgery for small pulmonary tumors is unknown. However, if the treated tumor volume is kept $\leq$ 65 cc, the risk should be < 10-15% with the proposed dose level. Also, given that this protocol focuses on SBRT to bone and spine, rather than lung, the risk of pneumonitis is expected to be low. Fracture is also a potential risk of radiotherapy to bone and spine, although doses in this study will be lower than the radiosurgery doses thought to put patients at high risk for fracture as reported in the literature (29).

Growth delay or arrest is a potential late effect of radiotherapy to bone for children who have not completed puberty. For this reason, patients in this protocol are limited

to those who have surgically unresectable disease or to those patients whose families refuse surgery. Given the data that demonstrates the improvement in clinical outcomes associated with aggressive local therapy in properly selected metastatic patients, the potential benefit of delivering a therapeutic dose of radiation likely outweighs the risks. The alternative treatment in this scenario is the delivery of subtherapeutic doses of radiation with palliative rather than curative intent.

Clinical and radiographic assessments will be performed as indicated to identify all adverse effects, ascertain their etiology, and provide the most appropriate palliative measures. Complications other than radiation pneumonitis, if any, will be graded according to the CTCAE version 4.0

7.2 Definitions

7.2.1 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.

7.2.2 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

7.2.3 Expectedness

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

7.2.3.1 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 <u>expected</u> when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 7.1 for a listing of expected adverse events associated with the study agent(s).

7.2.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered <u>unexpected</u> when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

7.2.4 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.

7.3 Recording and Reporting of Adverse Events

Participating 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. Low grade toxicities are to be expected given the disease profile. Any toxicity below CTCAE v4.0 grade 3 will not be reported on the Master AE Log or Case Report Forms. However, this information will be monitored and retained in patient charts.

Hematologic toxicity will be assessed and monitored but not reported.

Hospitalization events occur within this patient population. Hospitalizations that occur greater than 30 days from completion of SBRT and that are not attributable to research intervention will be recorded on the Master AE Log and reported at the time of continuing review and SMC monitoring.

These parameters are drafted in accordance with CFR21, though provide realistic expectations based on the sickness of this patient population.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.3.1 Reporting Requirements

7.3.1.1 Adverse Events Reports

The Coordinating Center is the central location for the collection and maintenance of documentation of adverse events and is responsible for submitting adverse event reports to the Protocol Chair promptly. The Coordinating Center will maintain documentation of all adverse event reports for each participating site. Adverse event reports submitted to the Coordinating Center must be signed and dated by the participating site's Principal Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study treatment

7.3.1.2 Participating Sites

Participating sites are responsible for reporting adverse events to their IRB according to its specific requirements and to the Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events as defined above must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within **three (3) working days** of the participating site Principal Investigator's learning of the event.

Adverse Events which result in no change to protocol, informed consent, or risk to subjects must be reported to the Coordinating Center on a monthly basis.

Adverse event reports are to be faxed or e-mailed to the Coordinating Center Study Coordinator. Follow-up reports are faxed, mailed, or sent electronically to the Coordinating Center as necessary.

The investigator must also report follow-up information about SAEs within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within the same time frames described above.

All SAEs must be collected whether or not they are considered causally related to the investigational product. Investigators and other site personnel are responsible for reporting all casually related SAEs to their IRB and the Protocol Chair.

8. STUDY CALENDAR

Note that the study calendar is based on the ideal subject. The schedule should be followed as closely as realistically possible, but may be modified due to problems such as scheduling delays, conflicts such as clinic closure or poor weather conditions, or other unforeseeable events.

	Pre-Study[1]	SBRT[3,9]	Follow-up (in time Post-RT)									
			4 weeks (± 7 days)	3 mo[6]	6 mo[6]	9 mo[6]	12 mo[6]	18 mo[7]	24 mo[7]	30 mo[7]	36 mo[7]	
Informed Consent	X											
Demographics	X										Follow for survival	
Medical History	X											
Physical Exam	X		X	X	X	X	X	X	X	X	X	
Height	X											
Weight & Vitals	X	X	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X	X	X	X	X	X	X	X	X	
Biopsy-confirmed sarcoma	X											
Treatment planning scan	X											
CBC w/ diff, plts, CMP	X[4]		X	X	X	X	X	X	X	X	X	
CT of treatment site	X[8]			X	X	X	X	X	X	X	X	
MRI	X[5]			X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	
FDG-PET (optional)	X			X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	
Tumor measurements	X			X	X	X	X	X	X	X	X	
Pregnancy test[2]	X											
Pain Assessments[10]	X	X	X	X	X	X	X	X	X	X	X	
Toxicity Assessment		X	X	X	X	X	X	X	X	X	X	

[1]Pre-SBRT assessments should be performed within 4 weeks of radiation treatment

[2]Pregnancy test by urine or serum, for women who are not post-menopausal as defined in Appendix A

[3]Patients will receive SBRT over a five-day period. Ideally all 5 fractions should be delivered Monday through Friday, however it may be delivered over two weeks
[4]Within 1 week prior to radiotherapy
[5]Optional depending on treatment site
[6] Follow-up should occur +/- 14 days
[7] Follow-up should occur +/- 30 days
[8]CT scan must be performed within 4 weeks prior to the start of therapy, not required if MRI is obtained.
[9] Patients will be able to receive chemotherapy 2 weeks after the completion of SBRT.
[10] Brief Pain Inventory (Appendix C) and 10 point Visual Analog Scale (Appendix F); given the age population, the completion of these assessments may not be possible and therefore are optional for subjects under 18 years of age
[11]Follow-up PET/CT and MRI are at the discretion of the treating physician and are optional

9. MEASUREMENT OF EFFECT

9.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 4 weeks after the initial treatment, every 3 months for the first year, and every 6 months for the second and third year.

9.1.1 **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with SBRT.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have completed all fractions of SBRT, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of SBRT will also be considered evaluable.) Evaluable patients will also be those who received the protocol-specified dose.

9.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with diagnostic techniques (CT, FDG-PET/CT, or MRI). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm with diagnostic techniques), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. Target lesions in this study will be considered metastatic sites up to a maximum of 5 lesions per patient. They should be recorded and measured at baseline. Target lesions should be larger than 10 mm in the smallest crosssectional diameter on CT or MRI and/or any lesion that shows increase metabolic uptake on FDG-PET/CT scans.

Non-target lesions. N/A

9.1.3 **Methods for Evaluation of Measurable Disease**

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT, FDG-PET/CT, and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

9.1.4 **Response Criteria**

9.1.4.1 **Response Assessment of Bone Metastases**

Radiographic assessment of bone metastasis can be difficult as remodeling bone may lead to residual abnormalities on bone scan, CT scan, and MRI scan. This leads to inherent difficulties in using RECIST 1.1 criteria for response assessment. For the purposes of the current protocol, response at bone metastasis will be graded as follows:

Complete response (CR) = A negative FDG-PET at the irradiated lesion in patients who have a positive FDG-PET at the time of SBRT at the target lesion. FDG-PET is optional on study. Therefore, CR will be recorded but not required to constitute a response.

Progressive disease (PD) = Any of the following will constitute PD:

- Development of a new soft tissue mass $\geq$ 1 cm in maximum axial dimension at a previous site of bone metastasis without a soft tissue component or with a soft tissue component < 1 cm in maximum axial dimension on previous evaluations.

- For bone metastasis with a soft tissue component $\geq$ 1 cm in maximum axial dimension on previous evaluations, an increase in the longest axial diameter of the soft tissue component by > 20%.

- A previous bone metastasis that was positive on FDG-PET, became negative with protocol therapy, and then becomes positive again should prompt concern

for progression at that site. Confirmatory testing is required to document progression at a previous site of bone metastasis. Together with return of FDG-PET uptake, MRI scan with documentation of an enhancing bone lesion will constitute adequate evidence to support progression at that site. Biopsy is strongly encouraged, but not required to confirm progression at a previous site of bone metastasis.

- Biopsy evidence of viable sarcoma at a previously radiated bone metastasis.

Stable disease (SD) = Patients not meeting either CR or PD criteria.

9.1.4.2 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Best overall response will be based on the overall response of the target lesions.

9.1.5 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.1.6 **Clinical Response Parameters**

Progression-free survival (PFS) is defined is the time from starting treatment to the time of first documented tumor progression or death due to any cause, whichever occurs first. Death is considered as an event here. For subjects whose disease does not progress or who do not die, PFS will be censored at the time of the last visit.

Time to progression (TTP) is defined as the time from starting treatment to the time of first documented tumor progression. Subjects who do not progress will be censored at the time of the last contact. In addition, death from any cause will also be censored.

Overall survival (OS) is defined as the time from starting treatment until death due to any cause. For subjects who do not die, time to death will be censored at the time of last contact.

Local Control (LC) is defined as the time from starting treatment until local relapse is documented. The target lesion will be considered locally controlled if criteria for progression are not met, taking as reference the smallest measurements recorded since the treatment started.

10. DATA REPORTING

10.1 Data Collection and Submission

Data and/or completed Case Report Forms (CRFs) must be transmitted by fax or email to the Coordinating Center. Case report forms will be provided to the participating sites by the Coordinating Center.

The schedule for completion and submission of Case Report Forms to Johns Hopkins is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration
On-Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of treatment completion
Adverse Event Report Form	Within 14 days of visit date
Response Assessment Form	Within 14 days of visit date
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow-up/Survival Form	Within 14 days of the protocol defined follow up visit date

The composite volumetric radiation therapy treatment plan will be submitted in a DICOM format to the Radiation Oncology PI (as feasible) in a manner determined appropriate for each participating institution. This information will include:

- DICOM RT dataset (structures, targets, dose, CT simulation study)
- Copy of the total dose records (treatment chart)

11. DATA SAFETY MONITORING

11.1 Monitoring Plan

This is a Level I study under the SKCCC Data Safety Monitoring Plan. Data Monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally

at SKCCC by Matthew Ladra, MD and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee at SKCCC.

Authorized representatives of the Coordinating Center may visit participating sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

11.2 Stopping Rules

The study will enroll 20 patients and toxicity will be monitored continuously throughout. Any Grade 5 toxicity that is possibly related to radiation will suspend accrual until the study chair reviews the case. The criteria for severe adverse events to be considered clinically significant toxicities are presented in Section 7.1. We established a safety monitoring rule that will recommend stopping the study if there appears to be high probability that the adverse event (AE) rate is convincingly above 30%. Specifically, if the posterior probability of the AE rate exceeding 30% is 65% or greater, we will consider stopping the study for safety consultation. The prior distribution for the risk of AE is beta (0.5, 3.5), representing our prior guess at the AE rate is 12.5% on average and there is 90% certainty that it is between 0.05% and 45%. The stopping rules and corresponding operating characteristics based on 5000 simulations are shown in the tables below.

Suspend enrollment if	3 AEs	4 AEs	5 AEs	6 AEs	7 AEs	8 AEs
Out of N	3-5	6-8	9-11	12-14	15-17	18-20

True risk of AE	Probability declare treatment unsafe	Average sample size
0.20	13.7%	18.2
0.25	25.6%	16.8
0.30	41.2%	15.0
0.35	57.6%	13.2
0.40	73.7%	10.9
0.45	84.7%	9.3
0.50	92.2%	7.6

12. REGULATORY CONSIDERATIONS

12. 1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.
Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Coordinating Center will disseminate protocol amendment information to all participating institutions.
All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using an IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the research file.

12.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki ○ Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research

participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

12.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

12.6 Multi-center Guidelines

12.6.1 Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites.

12.6.2 Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.

- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

12.6.3 Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Definition of primary outcome/endpoint

The efficacy of SBRT delivered with a dose of 4000 cGy in 5 fractions on 800 cGy each to pediatric nonrhabdomyosarcoma soft tissue sarcoma or bone sarcoma patients who are greater than 3 years of age and $\leq$ 40 years of age with metastatic disease will be determined by measuring local control at 6 months.

13.1.2 Analysis plan for primary endpoint

The primary endpoint of this study will be local control at 6 months of the patient treated with SBRT. Given the inherent difficulties in defining response in bony lesions after radiotherapy by RECIST 1.1 criteria, local control at the radiated site will be defined as the absence of progression of disease as defined in Section 9.1.4.1. Thus, CR and SD will constitute local control. Local control assessment will start at one month following completion of protocol treatment and continuous assessment will be pursued during the follow-up period. The reference response probability for comparison will be 70%. This is based on the study by Kepka et al. (31)

13.2 Sample Size/Accrual Rate

The primary endpoint of this trial is to estimate the local control of SBRT at 6 months. We anticipate that the local control rate will be roughly 90% as opposed to a 70% historical response with conventional moderate dose radiation. With 20 subjects participated, we will be able to estimate the local control rate to within 20% (i.e., maximum width of the 90% confidence interval reached is when the observed rate is 50%). If we observe a 6-month local control rate of 90%, we will be 90% certain that the true rate is greater than 70%. The associated exact 90% confidence interval will be (0.72, 0.98).

Using a Simon optimal two-stage design with a type I error of 10% and a type II error of 20%, the first stage would consist of 6 patients. A responder is considered to have local disease control at 6 months. If 4 or fewer patients respond, the study would terminate after the first stage. Otherwise, accrual would continue to a total of 20 patients. If 17 or more patients respond at the end of the second stage, the regimen with SBRT is considered promising (i.e., local control at 6 months is greater than 70%). This design has a 58% chance of early stopping when the true probability of response is 70% (the null hypothesis) and 11% chance of early stopping when the true probability of response is 90%.

The goal of enrollment is 20 patients. Based on the current institutional referral base, we expect that 12 patients will be eligible each year. Of these patients, we expect that two thirds will enroll on protocol. With this projection, we plan to complete accrual to the study in 3 years.

The proportion of patients with local control at six months will be reported with an exact binomial 90% confidence interval.

13.3 Analysis of Secondary Endpoints

13.3.1 Definition of secondary outcomes/endpoints:

- To describe the toxicity of SBRT delivered to a dose of 4000 cGy in 5 fractions of 800 cGy each for the population enrolled using grading with CTCAE v. 4.0
- The clinical response rate of each lesion will be assessed by serial CT assessment (FDG-PET/CT is optional for assessment) and defined by criteria as defined above. The absence of progression will constitute a response. Therefore, lesionspecific CR or SD will be measured as a response.
- To assess long-term clinical outcomes of this patient population after completion of SBRT by measuring relapse-free survival and overall survival. Relapse-free survival will be measured from time of enrollment to date of disease progression or death. Patients who are lost to follow-up will be censored for determination of

progression-free survival on the date of their last evaluation. Overall survival is defined as time from enrollment to death due to any cause.

- To assess quality of life following completion of SBRT using pre- and post-SBRT completion of the Brief Pain Inventory form and 10 point Visual Analog Scale which will be filled out by the patient at the treatment response intervals outlined above.

13.3.2 Analysis plan for secondary endpoints:

- Toxicities will be graded and tabulated at the time of each follow-up assessment. The proportion of toxicities by type and grade will be reported with exact 95% confidence intervals.
- Each metastatic lesion will be considered a target lesion and independently evaluated for response. The proportion of these lesions that have a stable or better response and the intra-cluster correlation will be estimated with an intercept only generalized estimating equation (GEE) regression. This will be estimated directly with SAS Genmod by specifying binomial variation, the identity link function, and an exchangeable correlation structure.
- Hazard rate estimates and 95% confidence intervals as well as Kaplan-Meier (KM) estimates will be used to summarize survival (OS), progression free survival (PFS), time to progression (TTP) and locoregional control (LRC) functions over time. The median OS, PFS, TTP and LRC will be reported. Cox proportional hazards models will be used to evaluate the impact of key covariates on these endpoints as the sample size permits.
- Quality of life will be assessed using the Brief Pain Inventory form and 10 point Visual Analog Scale. An overall score will be calculated pre-treatment and at the time of the 2nd radiologic reassessment. The change in score will be evaluated with a Wilcoxon signed-rank test.

13.4 Reporting and Exclusions

13.4.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with SBRT.

13.4.2 **Evaluation of response.** All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) stable disease, 3) progressive disease, 4) early death from malignant disease (defined as death prior to first evaluation after completion of SBRT), 5) early death from toxicity, 6) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who were enrolled on the trial should be included in the main analysis of local control.

All conclusions should be based on all enrolled subjects. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The reason for performing subset analyses would be to generate hypotheses for future prospective clinical trials.

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Appendix A

Definition of Menopausal Status:

Menopausal status will be defined according to the following criteria:

Post-menopausal:

- Woman 60 years of age or older
- Woman aged 45-59 years with spontaneous cessation of menses for at least 12 months prior to registration
- Woman aged 45-59 years with cessation of menses for less than 12 months prior to registration AND an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)
- Woman aged 45-59 years on hormone replacement therapy who have discontinued hormone replacement therapy at diagnosis of breast carcinoma and have an FSH level in the postmenopausal range according to institutional/laboratory standards (or 34.4
  IU/L if the institutional range is not available)
- Prior bilateral oophorectomy
- Woman younger than 60 years of age who have had a prior hysterectomy (without bilateral oophorectomy) AND who have an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

Pre- or peri-menopausal: Not meeting definition for postmenopausal as outlined above.

APPENDIX B

Dose Fractionation Schedule				
Dose Level	**Dose/Fraction (cGy)**	**Fractions**	**Total Dose (cGy)**	**Biologic Equivalent Dose* (BED_4) cGy**
Standard Dose for Palliation	300	10	3000	5250
Standard Dose for Definitive RT	180	28-30	5040 5400	7308-7830
Study Dose	800	5	4000	12000

Biologically Equivalent Dose (BED) Calculation

APPENDIX C Brief Pain Inventory Form

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

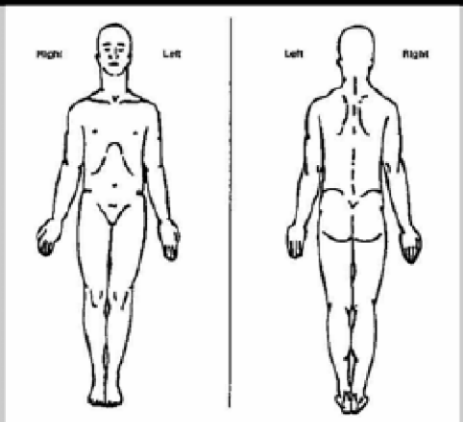
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

APPENDIX D DOSE CONSTRAINTS

Dose Constraints for Five Fractions – Based upon the AAPM Report TG 101[32] reduced by 10% based on the assumption that patients on protocol have received prior systemic chemotherapy.

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	18 Gy (3.6 Gy/fx)	22.5 Gy (4.5 Gy/fx)	neuritis
Cochlea			24.7 Gy (4.95 Gy/fx)	hearing loss
Brainstem	<1 cc	23.4 Gy (4.68 Gy/fx)	31 Gy (6.2 Gy/fx)	cranial neuropathy
Spinal Cord	<0.25 cc <1.2 cc	20.2 Gy (4.05 Gy/fx) 12.1 Gy (2.43 Gy/fx)	27 Gy (5.4 Gy/fx)	myelitis
Thecal Sac	<2.5 cc <5 cc	20.2 Gy (4.05 Gy/fx) 15 Gy (3 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Cauda Equina	<5 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuritis
Sacral Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Rib	<1 cc	31.5 Gy (6.3 Gy/fx)	38.7 Gy (7.74 Gy/fx)	Pain or fracture
Esophagus*	<5 cc	24.7 Gy (4.95 Gy/fx)	31.5 Gy (6.3 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	28.8 Gy (5.76 Gy/fx)	34.2 Gy (6.84 Gy/fx)	pericarditis
Great vessels	<10 cc	42.3 Gy (8.46 Gy/fx)	47.7 Gy (9.54 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	16.2 Gy (3.24 Gy/fx)	34.2 Gy (6.84 Gy/fx)	stenosis/fistula
Skin	<10 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Stomach	<10 cc	25.2 Gy (5.04 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	16.2 Gy (3.24 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	17.5 Gy (3.51 Gy/fx)	31.5 Gy (6.3 Gy/fx)	enteritis/obstruction
Colon*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	colitis/fistula
Rectum*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	proctitis/fistula
Bladder wall	<15 cc	16.4 Gy (3.28 Gy/fx)	34.2 Gy (6.84 Gy/fx)	cystitis/fistula
Penile Bulb	<3 cc	27 Gy (5.4 Gy/fx)	45 Gy (9 Gy/fx)	impotence
Femoral Heads (Right & Left)	<10 cc	27 Gy (5.4 Gy/fx)		necrosis
Renal hilum/vascular trunk	<2/3 volume	20.7 Gy (4.14 Gy/fx)		malignant hypertension
Parallel Tissue	Volume	**Critical Volume Dose**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	11.2 Gy (2.25 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	12.1 Gy (2.4 Gy/fx)		Pneumonitis
Liver	700 cc	18.9 Gy (3.78 Gy/fx)		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15.7 Gy (3.15 Gy/fx)		Basic renal function

***Avoid circumferential irradiation**

Guidelines for Spillage

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High Dose Spillage:

1. Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should not be more than 15% of the PTV volume.
2. Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2.

Low Dose Spillage

1. The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
   a. The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2cm where D2cm is given by the table below.
2. The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than R50% where R50% is given. See Table below.
3. Respect all critical organ dose-volume limits listed above

Table 1: Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, R50%		Maximum dose (in% of dose prescribed) @ 2 cm from PTV in Any Direction, D2cm (Gy)		Percent of Lung Receiving 20 Gy Total or More, V20 (%)	
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0	<10	<15

163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0	<10	<15

APPENDIX E Performance Status Criteria – Lansky Performance Scale

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.

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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 F - 10 point Visual Analog Scale