

Phase 2 Trial of Hypofractionated Radiotherapy for Soft Tissue Sarcomas

5/5/2021

NCT03972930

Phase 2 Trial of Hypofractionated Radiotherapy for Soft Tissue Sarcomas

Protocol Number: UW18149

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TITLE	Phase 2 Trial of Hypofractionated Radiotherapy for Soft Tissue Sarcomas
PHASE	2
OBJECTIVES	<p><u>Primary Objective:</u></p> <ul style="list-style-type: none"> Assess 2-year local control of soft tissue sarcomas following hypofractionated radiation therapy and compare the rates to historical series of fractionated radiation treatments <p><u>Secondary Objective:</u></p> <ul style="list-style-type: none"> Assess short-term toxicity in patients with soft tissue sarcomas who are treated with hypofractionated radiotherapy Assess long-term toxicity in patients with soft tissue sarcomas who are treated with hypofractionated radiotherapy and compare these rates to historical fractionated series Assess rates of complete response of soft tissue sarcomas following hypofractionated radiotherapy Assess 5-year local control of soft tissue sarcomas following hypofractionated radiotherapy Evaluate progression-free and overall survival in patients with soft tissue sarcoma following hypofractionated radiotherapy
STUDY DESIGN	Single arm, interventional study
TOTAL NUMBER OF SUBJECTS	48
KEY INCLUSION CRITERIA	<ol style="list-style-type: none"> Biopsy proven soft tissue sarcoma, localized or metastatic Age ≥ 18 years Karnofsky performance status ≥ 60 Able to understand and sign an informed consent
TREATMENT PLAN	All patients will be treated with 3-8 fractions, with the maximum prescribed dose to the PTV volume being 60 Gy (a common hypofractionated dose for definitive treatment). Treatment with hypofractionated radiotherapy will be delivered over a period of at most 8 weeks. Subjects will be seen in the Radiation Oncology clinic per standard of care. This will include a clinical visit one month after treatment as well as three, six, nine, and twelve months after treatment with follow-up imaging and lab testing per the standard of care and the discretion of the treating physician. Long-term toxicity will be assessed at these follow-up visits.
STATISTICAL CONSIDERATIONS	Using a local control rate based on historical controls, we assume that the local control rate under the null hypothesis is 45%. A sample size of 44 patients achieves approximately 85% power to detect an improvement of 20% in the 2-year local control rate using a one-sided exact test with a significance level of 0.05. To account for the possibility of up to 10% dropout, we will enroll 48 patients. We estimate that approximately 15-20 eligible patients are seen at UWCCC each year. With an estimated 50% rate of enrollment, it will take 2-4 years for patient accrual and treatment.

ESTIMATED ENROLLMENT PERIOD	<u>24-48</u> months
ESTIMATED STUDY DURATION	<u>60</u> months

STUDY SYNOPSIS

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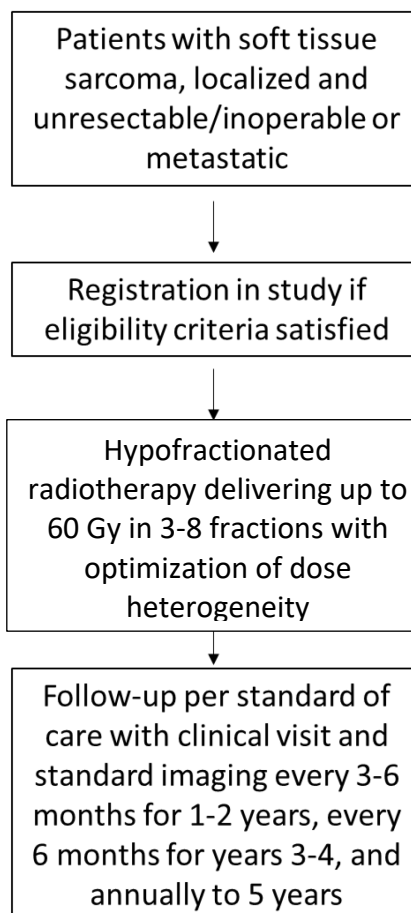
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SCHEMA

N = 48

Primary Objective:

Evaluate two year local control rate



ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ANC	Absolute neutrophil count
CT	Computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTV	Clinical tumor volume
DSMC	Data Safety Monitoring Committee
DSMS	Data and Safety Monitoring System
eCRF	Electronic case report form
EQD2	Equivalent dose in 2 Gy fractions
FDA	Food and Drug Administration
GTV	Gross tumor volume
Gy	Gray
HIPAA	Health Insurance Portability and Accountability Act
hr	Hour
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
min	Minute
MRI	Magnetic resonance imaging
OS	Overall survival
PFS	Progression-free survival
PSR	Protocol Summary Report
PTV	Planning tumor volume
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SBRT	Stereotactic Body Radiotherapy
SOC	Standard of care
SOP	Standard Operating Procedure
US	United States
wt	Weight

1. BACKGROUND AND RATIONALE

1.1 Soft Tissue Sarcoma and Radiation

Soft tissue sarcomas make up approximately 1% of all adult malignancies. Surgical resection of tumor with the goal of negative margins is the standard of care for soft tissue sarcomas¹. A case-control, propensity score-matched analysis of a nationwide clinical oncology database demonstrated that both preoperative and postoperative radiation were associated with increased overall survival as compared to surgery alone². Currently, there is one prospective randomized clinical trial comparing surgery and adjuvant radiation to surgery alone (NCT 0134401). For limb sarcoma, radiation in combination with surgery has been shown to improve local control as compared to surgery. When a sarcoma is in the retroperitoneum, patients often do not present until the tumor has grown quite large. Analysis of the Surveillance Epidemiology and End Results database found the median retroperitoneal sarcoma size to be 15.5 centimeters, with a range of 0.5 – 99.5 centimeters³. This large size can limit resection options. For patients with unresectable retroperitoneal sarcoma radiation is often the only local therapy available. Conventionally fractionated radiation alone has been shown to provide ~45 % and 33% local control at 2 and 5 years, respectively, with higher doses having better overall survival and local control⁴. This suggests that for patients with soft tissue sarcoma who cannot or will not have surgery, escalating the effective dose of radiation may improve local disease control.

1.2 Hypofractionated Radiotherapy for Soft Tissue Sarcoma

Hypofractionated radiotherapy is radiation delivered using highly conformal technique, allowing for a high dose of radiation to be delivered precisely over a smaller number of fractions as compared to standard 5-7 week courses of 2 Gy fractions. Sarcomas are generally considered to be relatively radioresistant when treated with conventionally fractionated radiation. Some recent small studies have suggested that hypofractionated radiation therapy is feasible and may provide excellent local control of soft tissue sarcomas⁵⁻⁷. Loi et al. discussed their single institution experience of 16 oligometastatic sarcoma patients, treated with a median total dose converted to equivalent dose in 2 Gy fractions (EQD2) dose of 115 Gy (ranging from 60 -150 Gy)⁸. They found 2 and 4 year local control rates of 84% and 78% respectively, providing durable local control, comparable to metastectomy⁸. Importantly, no acute or chronic grade 3 or greater toxicities were reported⁸. Paik et al. analyzed 23 patients with 36 unresectable soft tissue tumors in the trunk with a median EQD2 of 144 Gy (ranging from 72-240 Gy) and found a local control rate of 52% at five years⁹. There were no acute grade 3 or greater toxicities, however in a patient who had previous surgeries and radiation there was one late skin toxicity of Grade 3⁹. A retrospective review of SBRT for sarcomas, with 29% of treatment sites in the extremity, found excellent local control at 96% with a median follow-up of 6 months with no grade 3 or greater toxicities¹⁰. This small but growing body of evidence suggests that hypofractionated radiotherapy is safe and well-tolerated for both trunk and extremity sarcomas; however given the diversity of sarcoma histologies and locations more data is needed.

1.3 Approaches to Image-Guided Treatment

Certain tumors and certain areas of the body may be better visualized with CT versus magnetic resonance imaging (MRI). However, this can vary from patient to patient (i.e. some lung cancer is treated with SBRT guided by MRI and some is treated with SBRT guided by CT imaging). MRI provides improved soft tissue delineation in many locations of the body. For certain patients, MRI guided-therapy may allow for better visualization of the sarcoma and exact alignment to the tumor volume while avoiding bowel and other surrounding structures and adjusting for motion of the lungs and other structures. The treating physician will use all available imaging and clinical data to determine which imaging modality will provide the best delineation and radiation plan for each patient. All patients will be treated on linear accelerators with image guidance. The radiation delivered will be the exact same, with the same risks and benefits, regardless of if CT-guided therapy or MRI-guided therapy was given.

1.4 Rationale

One of the main challenges in treating sarcomas with radiation is the toxicity to normal structures around the sarcoma. Early reports suggest hypofractionated radiotherapy will be safe and effective for treatment of soft tissue sarcomas. However, given the rarity of this disease, the diversity of histological sub-types, and the variety of locations where these can occur (anywhere in the body), more data is needed to provide understanding of the safety and efficacy of hypofractionated radiotherapy for treatment of this disease. Our hypothesis is that by using hypofractionated radiotherapy we can deliver highly conformal high dose radiation to soft tissue sarcomas, while respecting established normal tissue constraints – we will have local control rates that are greater than historical rates reported with conventional fractionation⁴. Tepper et al. provides a landmark study on the dose response for soft tissue sarcomas with radiation alone, and one of the largest studies looking at local control in patients not undergoing surgery⁴.

2. OBJECTIVES

2.1 Primary Objective

- Assess 2-year local control of soft tissue sarcomas following hypofractionated radiotherapy and compare the rates to historical series of fractionated radiation treatments

2.2 Secondary Objectives

- Assess short- term toxicity in patients with soft tissue sarcomas who are treated with hypofractionated radiation therapy
- Assess long-term toxicity in patients with soft tissue sarcomas who are treated with hypofractionated radiotherapy and compare these rates to historical fractionated series
- Assess rates of complete response of soft tissue sarcomas following hypofractionated radiotherapy
- Assess 5-year local control of soft tissue sarcomas following hypofractionated radiotherapy

- Evaluate progression-free and overall survival in patients with soft tissue sarcoma following hypofractionated radiotherapy

3. ELIGIBILITY CRITERIA

This study will be offered to all patients according to the eligibility criteria below. Patients will be identified by the medical, surgical, and radiation oncologists and research staff at the UWHC.

3.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Biopsy proven soft tissue sarcoma, either localized and inoperable/unresectable or metastatic, that is deemed by the treating physician to be targetable with hypofractionated radiotherapy.
2. Patient refuses surgery or is aware that surgery is not recommended for them.
3. Age ≥ 18 years
4. Karnofsky performance status ≥ 60
5. Able to understand and sign an informed consent form

3.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant
2. Chemotherapy or systemic anti-cancer treatment within the preceding two weeks
3. Unable to undergo imaging or positioning necessary for radiotherapy planning
4. Prior radiation therapy in the field that, at the discretion of the treating physician, prevents safe delivery of hypofractionated radiotherapy

3.3 Additional optional specimen collection study

1. All patients enrolled in this trial are all also eligible for a specimen collection study (HS IRB approved study 2017-0394) where blood samples and archived tissue if available are collected at the completion of this trial.
2. Should patients opt to enroll specimen collection study their blood would be accessible to study various biomarkers under protocol 2017-0394

4. REGISTRATION PROCEDURES

Patients may not begin protocol treatment prior to registration. All patients must meet eligibility criteria listed in Section 3 and provide written informed consent. The study coordinator will verify eligibility, assign a case number, and register the patient in the UWCCC OnCore database prior to study treatment. The following information will be recorded:

- Protocol number
- Patient's name and initials

- Patient's medical record number
- Patient demographic data
- Signed patient consent form
- HIPAA authorization form

5. TREATMENT PLAN

5.1 Experimental Design

We will pursue a prospective interventional trial for patients with soft tissue sarcoma that is localized and inoperable/unresectable or metastatic. The standard of care for these patients would be a more fractionated and/or lower equivalent dose of definitive or palliative radiation therapy. Here, these patients will be treated with hypofractionated radiotherapy to evaluate the safety, feasibility, and efficacy of this method. Patients may already have received or may go on to receive systemic chemotherapy per standard of care.

5.2 Study Overview

Subjects will be referred to the study by the Medical Oncologist, Surgical Oncologist, or other providers as appropriate. Patients will be treated on study with a course of hypofractionated radiotherapy by a radiation oncologist. Patients will be followed for a minimum of two years with standard-of-care clinical visits, laboratory studies, and imaging. More typically this follow-up will extend to 5 years. Patients will be seen or contacted by phone for clinical follow-up at 1 month after treatment. They will then be seen 3 months after treatment completion with standard of care imaging, generally including CT or MRI of the treatment site and CT scan of the chest. Patients would then be typically seen every 3-6 months for 1-2 years, every 6 months for years 3-4, and annually to 5 years after treatment, at which point further follow-up will be at the discretion of the treating physician. See [SCHEMA](#).

Required Assessments	Screening ^A	Hypofractionated radiation therapy treatment	Month 1 post hypofractionated radiation therapy treatment ^G	Follow up 2-3 months (+/- 2 weeks) post radiation therapy ^{G, H}	Standard of care follow-up ^{D, G, H}
H&P	X			X	X
Documentation of bx proven soft tissue sarcoma	X				

SOC imaging ^B	X			X	X
Consent	X				
Urine pregnancy test for WOCBP	X				
Adverse Event (AE) assessment	X	X	X ^F	X	X
Simulation	X				
Hypofractionated radiotherapy		X ^E			

^AScreening: H&P, consent, pregnancy testing AE assessment within 28 days of registration. Imaging within 6 weeks of registration.

^BImaging modality utilized is at discretion of treating physician based on the tumor location. Recommended that followup imaging utilizes the same modality

^CAdverse events will be recorded for 12 months post hypofractionated radiation therapy

^DFollowup to be every 3-6 months years 1 and 2, then every 6 months years 3 and 4, and annually out to 5 years post treatment, at the discretion of the treating radiation oncologist. For patients subsequently receiving other treatments (e.g. chemotherapy) or those who would need to travel considerable distance to UWCCC, in-person follow-up may be with another provider (e.g. medical oncologist or local provider) and the treating radiation oncologist may follow-up by telephone.

^E Hypofractionated radiotherapy: 3-8 fractions within 8 weeks. Adaptive planning permitted.

^F Phone or clinic visit

^G For patients enrolled in hospice, an attempt to acquire long-term AEs and survival information will be made but no further imaging required

^H For patients that have transferred care to an outside facility, an attempt to acquire long-term AEs, imaging and survival information will be made

5.3 Radiotherapy Details

5.3.1 Pretreatment Work-up

Pretreatment work-up will consist of standard staging imaging and consultation of the treating radiation oncologist.

5.3.2 Simulation

Simulation scans will be performed under the direction of the treating physician with the patient in a highly reproducible position that will limit targeted tumor motion. CT and MRI imaging may be utilized as may any imaging fusion scans for target delineation. Re-planning and adaptive planning are permitted for any circumstance in which these are deemed necessary by the treating physician.

5.3.3 Target Delineation

Gross tumor volume (GTV) will be contoured with the help of co-registered pretreatment imaging. A clinical tumor volume (CTV) will be added per the RTOG sarcoma consensus guidelines, with CTV volumes reduced or expanded at the discretion of the treating physician to respect anatomic boundaries such as facial planes and bones. No CTV is required in the setting of metastatic disease. A planning tumor volume (PTV) will be customized for each patient at the time of treatment planning per the treating physician, to account for the estimated variation in daily setup.

5.3.4 Radiation dose

The PTV will be treated to a peripheral dose of 60 Gy in 3-8 fractions (20-10 Gy per fraction), optimizing dose heterogeneity within the GTV. This dose of 60 Gy can be decreased at the discretion of the treating physician in order to meet normal tissue constraints. A shorter course of fractionation may be prescribed at the discretion of the treating physician. Lower doses may be prescribed at the discretion of the treating physician.

5.3.5 Radiation Fractionation

Radiation treatments will be completed within 8 weeks of the first delivered radiotherapy fraction. The goal of therapy will be to treat either daily or every other day. However, in settings where normal tissue constraints are felt by the treating physician to limit the ability to deliver an adequate radiation dose, the treating physician may elect to prolong the treatment course or provide a break after some initial treatments with the intention of monitoring treatment response and performing adaptive treatment planning to allow for a definitive course within 8 weeks.

5.3.6 Hypofractionated Radiation Therapy Planning Process

Standard treatment planning procedures will be implemented under the direction of the treating physician.

5.3.7 Image Guidance

MRI-guided or CT-guided radiation therapy, given on image-guided linear accelerators, is to be used for all patients. The specific machine and type of image guidance will be at the discretion of the treating physician.

5.3.8 Normal Tissue Constraints

No volume outside of the PTV should receive more than 105% of the prescription dose. Planning dose-volume constraints (Table 1) are indicated below and are based on prior reported treatment constraints for hypofractionated regimens and institutional guidelines¹¹. If dose constraints are unable to be met for a given patient at the planned dose level, the dose per fraction may be decreased until acceptable constraints are met. Decision about compromising target coverage or exceeding normal tissue constraints will be made by the treating physician taking into account the circumstances and goals of treatment in each case.

Table 1. Hypofractionated Radiotherapy Dose Constraint Table

Structure	Dose Constraint
Spinal Cord	Dmax < 25 Gy
Stomach	D0.1cc < 32 Gy
Bowel	D0.1cc < 32 Gy
Liver	D700cc < 15 Gy
Kidney	V15 < 2/3 of one kidney, Mean < 10 Gy
Trachea/Larynx	Dmax < 24 Gy
Lung	V20 ≤ 10%, V12.5 ≤ 15%
Esophagus	D0.1cc < 30 Gy, V30 < 0.5 cc
Heart	V32 < 15 cc
Rectum/Colon	V42 < 0.03 cc
Bladder	Dmax < 42 Gy
Large Blood Vessels	V47 < 10cc
Brain	Dmax < 30 Gy
Brainstem	Dmax < 23 Gy
Skin	Goal Dmax < 40 Gy
Bones	Goal V30 < 70 cc (goal < 30 cc)
Carina/Trachea/Bronchial Tree	V18 < 4 cc
Brachial/sacral plexus, nerve root	Dmax < 24 Gy

5.4 Supportive Care

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on source documents as concomitant medication. No patients will receive chemotherapy or other systemic cancer treatments during the time of hypofractionated radiotherapy or for at least 2 weeks before or after hypofractionated radiotherapy.

5.5 Duration of Follow-up

Subjects will be seen in the Radiation Oncology clinic or by another physician's office on the care team, such as the Medical Oncologist, per standard of care. This will include a clinical visit one month after treatment as well as a visit 2-3 months after treatment and then every 3-6 months years 1 and 2, every 6 months years 3 and 4, and annually out to 5 years post treatment. Standard of care imaging typically ordered includes CT or MRI imaging of the treatment site and CT scan of the chest. This will be ordered by a physician on the care team as clinically appropriate, following standard guidelines. Lab testing will be per the standard of care and the discretion of the treating physician. Long-term toxicity will be assessed at each follow-up visits. Follow-up visits will be conducted by a physician who will document physical exam, laboratory, and imaging findings as well as evaluate for toxicity. Any other evaluations prompted by symptoms, laboratory evaluation, or at the treating physicians' discretion may be performed as per standard of care. If a patient opts to enroll on hospice, efforts will be made to get long term toxicity and survival information. However no further imaging will be ordered and no follow up

will be scheduled. For patients subsequently receiving other treatments (e.g. chemotherapy) or those who would need to travel considerable distance to UWCCC, in-person follow-up may be with another provider (e.g. medical oncologist or local provider) and the treating radiation oncologist may follow-up by telephone. If a patient decides to withdraw consent from the study for nontreatment related reasons, no additional study-specific information will be obtained from the patient's future follow-up visit.

Criteria for Removal from Treatment

A patient's ongoing treatment on protocol will be temporarily or permanently withheld if any of the events below occur:

- Illness that prevents further administration of treatment
- Unacceptable adverse events
- Patient decision to withdraw from study
- General or specific changes in patient's condition render the patient unacceptable for further treatment in the judgment of the treating physician or the study investigators. The reason for treatment stop/study removal and the date will be documented in a Case Report Form.

6. MEASUREMENT OF TREATMENT

6.1 Local Control

Imaging response will be measured whenever possible on standard of care follow-up imaging as per the RECIST criteria¹².

Complete Response (CR): Disappearance of entire target lesion.

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

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

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

Local control will be defined as all patients who have CR or PR or SD.

6.2 Definitions for Response Evaluation - RECIST 1.1

6.2.1 Progression-Free Survival

Progression free survival (PFS) defined with follow-up radiological assessment with PFS calculated from the point of start of hypofractionated radiotherapy to the point of recurrence or death.

6.2.2 Overall Survival

Overall survival (OS) defined from the point of start of hypofractionated radiotherapy to the time of death or last follow-up if alive.

7. STATISTICAL CONSIDERATIONS

7.1 Number of Patients

Using a local control rate based on historical controls, we assume that the local control rate under the null hypothesis is 45%. A sample size of 44 patients achieves approximately 85% power to detect an improvement of 20% in the 2-year local control rate using a one-sided exact test with a significance level of 0.05. To account for the possibility of up to 10% dropout, we will enroll 48 patients. We estimate that approximately 15-20 eligible patients are seen at UWCCC each year. With a non-randomized study design and an estimated 50% rate of enrollment, we estimate it will take 2-4 years for patient accrual and treatment. We will then have a 2-year follow-up for determination of the primary endpoint of 2-year local control.

7.2 Statistical Analysis

7.2.1 Primary Endpoint

The primary endpoint is 2-year local control, defined as the proportion of patients whose best response as determined per RECIST criteria using imaging is CR, PR, or SD out of all patients who have received at least one fraction. Local control will be reported with an exact 95% confidence interval (CI). For patients with multiple lesions treated, local control will be evaluated for each lesion.

7.2.2 Secondary Endpoints

2-year and 5-year local control rates will also be reported separately for primary sites vs. metastatic sites with exact 95% CI. The complete response (CR) rate will be reported with an exact 95% CI. PFS and OS will be estimated using the Kaplan-Meier method. For PFS, patients without documented progression who are alive at last follow-up will be censored at the date of the last radiologic assessment. For OS, patients who are alive at last follow-up will be censored. Exploratory associations of patient and treatment covariates such as dose of RT, primary vs secondary, tumor location (extremity, trunk, retroperitoneum, head neck, other), tumor size (by 5 cm intervals to >20cm), tumor grade (1-3), prior surgery at site, and age, with PFS and OS will be evaluated using Cox proportional hazards models.

Acute and long-term toxicities will be tabulated by type and grade. Exploratory associations of patient and treatment covariates with the occurrence of acute toxicity, the occurrence of late

toxicity, and time to late toxicity (estimated using the Kaplan-Meier method) will also be evaluated.

7.3 Analysis Population

The population of patients that will be analyzed for any endpoint will include all patients who have received at least one fraction. For patients with multiple lesions treated, local control will be evaluated for each lesion. Once a patient is enrolled on study, they may receive additional courses of hypofractionated radiation per protocol to additional tumor sites that arise during follow-up. The patient will be evaluated for local control with respect to each lesion treated and adverse events will be recorded for each completed treatment course.

8. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

8.1 Adverse Event List for Hypofractionated Radiation Therapy.

Note: Toxicities to be defined as detailed in CTCAE, v5.0 toxicity grading.

Likely acute toxicities

- Fatigue
- Mild to moderate radiation dermatitis/mucositis
- Musculo-skeletal aches/ pain flare at the treatment site

Less likely acute toxicities

- Severe dermatitis
- Skin ulceration, wound healing complications
- Hematuria, dysuria
- Bone fracture
- Nausea and vomiting
- Diarrhea
- Loss of appetite and weight loss
- Xerostomia
- Severe mucositis, esophagitis, or gastritis

Rare but serious late effects

- Bowel obstruction/adhesions
- Urinary obstruction
- Bleeding (Hemoptysis, hematochezia, hematuria, other)
- Gastric, duodenal or small-bowel ulceration or perforation
- Large blood vessel perforation
- Pneumonitis

- Hepatotoxicity
- Chronic Kidney Injury
- Pancreatitis
- Bone fracture
- Transient myelopathy or nerve injury
- Lymphedema
- Decrease in blood counts resulting in increased risk of infection, weakness, and/ or in bleeding and bruising easily
- Radionecrosis
- Severe damage to any normal tissues
- Second malignancy

8.2 Definitions

Adverse event (AE)

An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Include the type and duration of the follow-up of subjects after adverse events.

Serious adverse event (SAE)

A serious adverse event is defined as any adverse event that meets one of the following criteria:

- Results in death; OR
- Is life-threatening; OR
- Requires hospitalization or prolongs existing hospitalization; OR
- Results in significant or persistent disability or incapacity; OR
- Results in a congenital anomaly/birth defect
- Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Expected events

Expected events are those that have been previously identified as resulting from treatment of sarcomas with radiation therapy. These are defined above for acute and late toxicities (Section 8.1). For purposes of this study, reporting requirements are determined by the assessment of the following adverse event characteristics: the type or nature of the event; the severity (grade); the relationship to the study therapy (unrelated, not likely, possibly, likely, or definitely related), and whether the event is expected or unexpected.

8.3 Severity Assessment

Adverse events should be documented and recorded at each visit using NCI CTCAE version 5.0 (each event searchable using the Safety Profiler website)

(<https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx>). Definitions of the grading categories to assess severity of adverse events are as follows:

- **Mild (grade 1)** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate (grade 2)** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe (grade 3)** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
- **Life threatening (grade 4)** - The patient was at risk of death at the time of the event.
- **Fatal (grade 5)** - The event caused death.

8.4 Causality Assessment

The PI will determine the relationship of adverse events to the research intervention using the following scale:

- Definite = AE is definitely related to the study procedures
- Probable = AE is likely related to the study procedures
- Possible = AE is possibly related to the study procedures
- Unlikely = AE is doubtfully related to the study procedures
- Unrelated = AE is definitely not related to the study procedures

8.5 Procedures for Recording and Reporting Adverse Events

- AEs will be recorded in study database.
- AEs will be recorded from time of informed consent until 12 months after completion of hypofractionated radiation therapy or until the initiation of a new therapy.
- AEs will be recorded regardless of whether or not they are considered related to the study intervention.
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the study database.
- All AEs considered related to study drug(s) will be followed until resolution to \leq Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

8.6 Reporting of Pregnancy

- Pregnancy will be reported from time of first treatment until 6 months after completion of hypofractionated radiotherapy.
- Pregnancy will be within 1 business day of discovery of the event.

To ensure subject safety, each pregnancy in a subject on study treatment will be reported to UW within 1 business day of learning of its occurrence. The pregnancy will be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

8.7 Procedures for Recording and Reporting Serious Adverse Events

- All SAEs will be recorded in study database. SAEs will be reported to the thoracic DOT, UWCCC and UW HS-IRB per policy. All SAEs will be reported from the beginning of hypofractionated radiation until 30 days after completion of hypofractionated radiotherapy. More than 30 days post completion of hypofractionated radiotherapy only SAE's thought to be at least possibly related to the hypofractionated radiotherapy will be reported. Reporting criteria are summarized in Table 2.
- SAEs will be reported on the SAE Submission Form and entered in SAE tab in OnCore within 1 business day of discovery of the event.
- SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the study database.
- All SAEs will be followed until resolution to \leq Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

9. TRIAL SAFETY MONITORING

9.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at WONIX sites for which the UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.

- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

9.2 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCCC monitoring requirements for trials without an acceptable external DSMB are as follows:

9.2.1 Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

9.3 Review and Oversight Requirements

9.3.1 Serious Adverse Event – Reported within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

See Section 8.7 and 9.3 for detailed instructions on SAE reporting.

9.3.2 Serious Adverse Event – Reported within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate. The DSMC Chair will review

the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, and provides documentation of these notifications to the DSMC.

See Section 8.7 and 9.3 for detailed instructions on SAE reporting.

9.3.3 Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of noncompliance protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

9.4 Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 2 below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table.

Table 2. FDA Reporting Requirements.

FDA Reporting Requirements for Serious Adverse Events (21 CFR Part 312)
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NOTE: Investigators MUST immediately report to the PI; UWCCC DSMC; external sponsor] and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An adverse event is considered serious if it results in ANY of the following outcomes:

- 1) Death.
- 2) A life-threatening adverse event.
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹ Serious adverse events that occur more than 30 days after the last hypofractionated radiotherapy treatment and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

9.4.1 SAE Requiring [24] Hour Reporting Occurs at UWCCC

Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (<http://kb.wisc.edu/uwccc>) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial [24] hour report.** For this protocol, the following UWCCC entities are required to be notified:

- a. saenotify@uwcarbone.wisc.edu
- b. UWCCC PI: Zachary Morris, MD, PhD
- c. UWCCC Radiotherapy PM, Diana Trask
- d. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

Report to the IRB

Consult the UW HS-IRB website for reporting guidelines.

9.4.2 SAE Requiring [10] Day Reporting Occurs at UWCCC

Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website (<http://kb.wisc.edu/uwccc>) for specific instructions on how and what to report to the UWCCC for [10] day reports.

For this protocol, the following entities are required to be notified:

- a. saenotify@uwcarbone.wisc.edu
- b. Any appropriate parties listed on SAE Routing form

Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

10. DATA COLLECTION, STORAGE, RETENTION, AND CONFIDENTIALITY

10.1 Data Collection

Clinical trial coordinators in the Department of Human Oncology will do baseline data collection for each patient accrued into the protocol. The PIs, with the support of co-investigators would collect specific disease, treatment and outcome related data, which will include the following:

- Medical history including basic patient demographics as collected during registration
- Comorbidities/ habits and disease related variables including KPS score
- Histological differentiation and grade
- Tumor location and delineation as primary or metastatic site
- Maximal tumor dimension as measured on diagnostic CT imaging
- Presence or absence of regional LN on diagnostic imaging, presence of metastatic disease at diagnosis

- Other pertinent findings on diagnostic imaging
- Stage
- Weight loss at presentation
- Baseline pain assessment
- Baseline laboratory parameters, treatment details
- Toxicity outcomes
- Treatment outcomes (clinical, radiological)
- Follow-up course

10.2 Data Storage

The information collected for this study will be protected by limiting access to the data sheet to the study researchers. To ensure patient confidentiality information collected in this study will be kept on a secure computer within the Department of Radiation Oncology network, which is protected by a firewall that ensures the privacy of the network. Access to the information is limited to those listed in the protocol, all of whom have completed the requisite human subjects/HIPAA training and been given valid clinical access to this information.

10.3 Record Retention

To enable evaluations and/or audits from Health Authorities, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until UWCCC confirms destruction is permitted.

10.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Each subject will be assigned a research subject number, which is a code that can link the medical record number to the study data in the subject log. The subject log will be maintained on a secure password-protected computer in the Department of Human Oncology. In addition to the Principal Investigator, the co-investigators will have access to the subject log.

11. ETHICS

11.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by the UW SMPH HS-IRB.

The investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

11.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

11.3 Informed Consent Process

The Principal Investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

12. REFERENCES

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