Protocol Title: Pilot Study Evaluating Stereotactic Body Radiation Therapy (SBRT) and Adaptive Radiation Therapy (ART) for Pulmonary Metastases from Soft Tissue Sarcomas

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TITLE

Pilot Study Evaluating Stereotactic Body Radiation Therapy (SBRT) and Adaptive Radiation Therapy (ART) for Pulmonary Metastases from Soft Tissue Sarcomas

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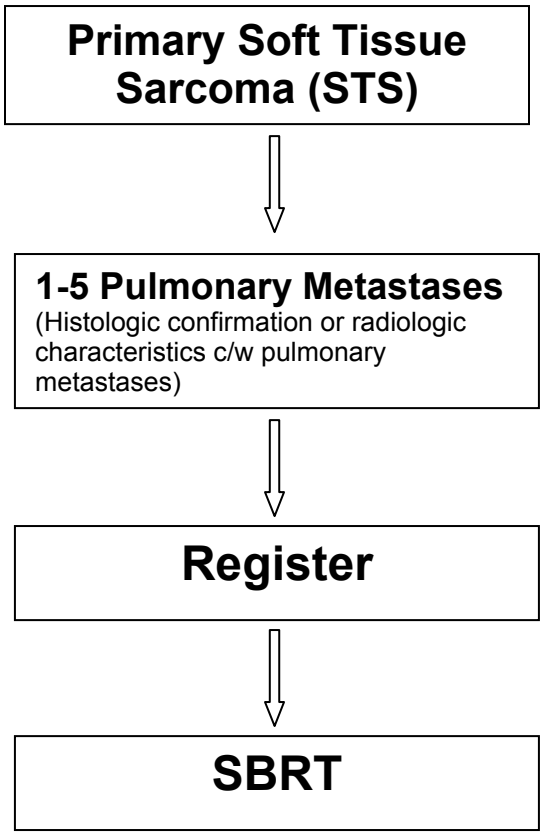
TITLE
Pilot Study Evaluating Stereotactic Body Radiation Therapy (SBRT) and Adaptive Radiation Therapy (ART) for Pulmonary Metastases from Soft Tissue Sarcomas
SCHEMA



Patient Population:

Accrual goal is 20 patients with pulmonary metastatic disease from soft tissue sarcoma primaries. A reasonable estimate for accrual at the Medical College of Wisconsin is 5 patients per year and 5 patients per year at Kraemer Cancer Center, West Bend with a conservative estimate of 40 tumors. The estimated duration of the study is 2 years.

Required Sample Size: 20

ELIGIBILITY CHECKLIST

_____ (Y) 1. Does the patient have a pathologically (histologically or cytologically) proven diagnosis of a soft tissue sarcoma?

_____ (Y) 2. Has the patient had a history and physical within 4 weeks of registration?

_____ (Y) 3. Was the patient deemed inoperable by cardiothoracic surgery, declined surgery, or surgery not recommended by the multidisciplinary tumor board?

_____ (Y) 4. Was pre-treatment imaging done within 6-8 weeks prior to registration?

_____ (Y) 5. Is the patient at least 18 years of age?

_____ (Y) 6. Was the Zubrod performance scale 0-2 4 weeks prior to registration?

_____ (Y) 7. Did the patient sign a study-approved informed consent?

_____ (N) 8. Does the patient have >5 pulmonary metastases disease?

_____ (N) 9. Does the patient have disease progression outside of the lungs within 3 months of enrollment?

1.0 INTRODUCTION

Management for patients with distant metastatic disease from solid tumors is usually conducted with palliative intent. Pulmonary tissue is a common site for metastatic seeding, in particular for sarcomatoid tumors (1). Historically, metastatic disease to the lungs from a primary sarcoma has traditionally been by surgical means in conjunction with the use of chemotherapy (2-6).

Recently, however, a multimodality approach to treatment for pulmonary metastatic lesions from various malignancies, including sarcoma, has been employed at this institution. NCCN guidelines for single organ and limited tumor bulk metastases recommend an approach of metastectomy +/- post-operative chemotherapy +/-post-operative RT, interventional techniques such as RFA or cryoablation, or SBRT/RT methods.

Patients with metastatic soft tissue sarcoma to any site often undergo chemotherapy. However, it is often difficult to determine whether the chemotherapy alone is effective treating widespread disease (7, 8).
In a study done by Canter, et al, those that were administered perioperative chemotherapy had a median post-metastasis disease-specific survival of 24 months vs. 33 months in those those that underwent both surgery and chemotherapy. (9). Thus, the need for local therapy in conjunction with chemotherapy may be warranted. Recently, less invasive techniques, such as SBRT and RFA have been employed in treating oligometastatic disease.

Radiation has typically been reserved for palliation. Hypofractionated sterotactic body radiation therapy (SBRT) is an emerging method of treatment for oligometastatic disease in the lungs. SBRT has become standard of care for stage I lung cancer in medically inoperable patients with local control rates exceeding 90% with minimal toxicity (10).

SBRT is increasingly being used to treat pulmonary metastases (11-17). This is particularly appealing as the toxicity is low, control rates are high and in many cases invasive procedures can be avoided. Large hypofractionated doses are used to treat metastatic lesions. SBRT can be safely administered because the volume of each lesion is small with tight margins. Moreover, many beams are utilized, so that a small fraction of the total dose is administered through each beam, thereby effectively minimizing toxicity through the trajectory of the beam. However, all beams coalesce at the target and result in a larger, summed, dose (11, 20-21). Many studies have evaluated outcomes and toxicity in patients who have undergone SBRT for pulmonary oligometastasis from various tumor primaries (12). Lesions are usually central or peripherally located and a small proportion is comprised of sarcoma primaries. Nonetheless, crude local control rates when utilizing this method of treatment are between 67-100% and 2-year survival ranging between 32-87% (11, 13-19). Toxicity was acceptable with very few developing grade 3 or 4 complications.

Although local control of pulmonary metastases with SBRT is high, there is no prospective data evaluating control with SBRT for pulmonary metastases from soft tissue sarcomas. This is a prospective study to document the local control rates with SBRT specifically for pulmonary metastases from soft tissue sarcoma. This study will prospectively document acute and late toxicity, quality of life (QoL), tumor control, and survival.

Siva, et al reported a literature review to critically review the effects of SBRT for treatment of pulmonary metastases. Data from 334 patients combined from 13 publications reported a 2 year weighted local control of 77.9% (12). Rusthoven et al conducted a multi-institutional Phase I/II trial of SBRT for patients with 1-3 lung metastases up to 7cm. Two year local control was 96% (19).

The University of Rochester retrospectively reviewed control rates of 74 sarcoma pulmonary metastases in 52 patients from 1990-2006 (22). Sixteen patients had surgical procedures for management. Fifteen patients were treated to 74 lesions with SBRT. The preferred dose was 50 Gy in 5 fractions. Two-year local control was 88% for all patients treated with radiation although with exclusion of one patient's lesion treated with 30 GY in 10 fractions, local control was 97%. There was no ≥ grade 3 pulmonary toxicity.

Daily treatment uncertainties include set-up error, internal organ motion, tumor size, patient position, and patient external contour (23-25). The precision of radiation depends on the consistency of these planning variables. Changes in these variables may change the dose to the tumor and organs at risk. In order to ensure coverage of the target during organ movement, conventionally margins have been added to the clinical target volume (CTV) to form a planning target volume (PTV). However, increasing the margin size leads to increased radiation dose to adjacent organs at risk. As such, adaptive radiation therapy (ART) has been done to decrease the effects of treatment deviation for each patient. This allows a re-optimization of the treatment plans in regards to dose distribution and delivery of radiation with each fraction (23-25).

In the lung, delineation of the target (tumor) for planning is critical (26). This is especially important when delivering radiation in a stereotactic manner, where margins are smaller compared to conventional 3D conformal radiation therapy. In the lung, target delineation may be confounded by respiratory motion and breathing patterns and changes in the position and shape of the target lesion. Respiratory cycle issues can be taken into consideration with a 4D CT scan, however, changes in breathing patterns of the patient and tumor changes need image guidance as well (26). Ramsey et *al*, showed that image-guided and ART in patients with lung cancer lead to a decrease of 21% of lung volume being treated receiving ≥ 20 Gy (27).

The primary goal of this study is to assess the local management with SBRT for patients with pulmonary oligometastatic disease from a sarcoma primary using ART. Toxicity, quality of life, progression and survival rates will be obtained for each method. The goal is to improve the care of metastatic sarcoma patients by employing techniques that are standard of care to treat oligometastatic disease. This study, however, will assess patients who have metastatic disease from a primary sarcoma, which has not yet been prospectively studied.

Studies and Publications Supporting SBRT for Pulmonary Metastatses Including Sarcoma:

1. Wulf, et al. Dose-response in stereotactic irradiation of lung tumors. Radiother Oncol. 2005 Oct;77(1):83-7.
    a. Conclusions: When normalization to a biologically effective dose (BED) is used a dose of 94 Gy at the isocenter and 50 Gy at the PTV margin are demonstrated to give 50% probability of tumor control (TCD50). Multivariate analysis revealed the dose at the PTV-margin as the only significant factor for local control.

2. Le QT, et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. J of Thorac Oncol, 2006 Oct;1(8):802-9.
    a. Conclusions: Single-fraction stereotactic RT is feasible for selected patients with lung tumors. For those with prior thoracic RT, 25 Gy may be too toxic. Higher dose was associated with improved local control. Longer follow-up is necessary to determine the treatment efficacy and toxicity.

3. Uematsu, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer 1998; 15;82(6):1062-70.
    a. Conclusions: With this unit and procedure, focal radiation therapy similar to stereotactic radiation therapy is possible for extracranial sites. The preliminary experience appeared safe and promising, and further exploration of this approach is warranted.

4. Nagata Y, et al. Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2001;51:352–353.
    a. Conclusions: 3D conformal hypofractionated single high-dose radiotherapy of 48 Gy in 4 fractions using a stereotactic body frame was useful for the treatment of lung tumors.

5. Song DY, Benedict SH, Cardinale RM, et al. Stereotactic body radiation therapy of lung tumors: preliminary experience using normal tissue complication probability-based dose limits. Am J Clin Oncol 2005;28: 591–596.

a. Conclusions: SBRT prescribed within the confines of NTCP-restricted dosing on this protocol resulted in no radiation pneumonitis. Tissues other than lung parenchyma which are unaccounted for by NTCP may be dose-limiting when performing hypofractionated SBRT in the lung.

6. Norihisa Y, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. Int J Radiat Oncol Biol Phys 2008; 72:398–403.
    a. Conclusions: The clinical result of SBRT for oligometastatic lung tumors in our institute was comparable to that after surgical metastasectomy; thus, SBRT could be an effective treatment of pulmonary oligometastases

7. Brown W, Wu X, Fowler J, et al. Lung metastases treated by CyberKnife image-guided robotic stereotactic radiosurgery at 41 months. South Med J 2008;101:376–382
    a. Conclusions: The delivery of precisely targeted radiation doses to lung tumors in a hypofractionated fashion is feasible and safe. Image-guided robotic stereotactic radiosurgery of pulmonary metastases with the CyberKnife achieves good rates of local disease control with limited toxicity to surrounding tissues and in many cases may be beneficial for patients for whom surgery is not an option.

8. Rusthoven KE, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009; 27:1579 –1584.
    a. Conclusions: This multi-institutional phase I/II trial demonstrates that high-dose SBRT is safe and effective for the treatment of patients with one to three lung metastases.

Studies and Publications Supporting Adaptive Radiation Therapy:

1. Wu, et al. Online Re-optimization of Prostate IMRT Plans for Adaptive Radiation Therapy. Phys. Med. Biol. 2008; 53: 673–691
    a. Conclusions: The feasibility of this technique is demonstrated with a clinical case with large deformation. Such on-line ART process can be highly valuable with hypo-fractionated prostate IMRT treatment.

2. Ahn, et al. Adaptive Planning in Intensity-Modulated Radiation Therapy in Head and Neck Cancers: Single Institution Experience and Clinical Implications. Int. J. Radiation Oncology Biol. Phys. 2011; 80: 677–685.
    a. Conclusions: Variations in patient positioning and anatomy changes during IMRT for head and neck cancer can
    affect dosimetric parameters and have wide-ranging clinical implications. The interplay between random positional
    variability and gradual anatomic changes requires careful clinical monitoring and frequent use of CT-based image-guided radiation therapy, which should determine variations necessitating new plans.

3. Yan, et al. The Us e of Adaptive Radiation Therapy to Reduce Set-Up Error: A Prospective Clinical Study. Int. J. Radiation Oncology Biol. Phys 1998; 41: 715–720.
    a. Conclusions: The prospective study demonstrates that the ART process can be effectively implemented in routine
    clinical practice to improve treatment accuracy. This process is also ready to be further extended to reoptimize the treatment plan by incorporating the predicted patient specific setup variation.

4. Ramsey et al. A Technique for Adaptive Image-Guided Helical Tomotherapy For Lung Cancer. Int. J. Radiation Oncology Biol. Phys.2006; 64: 1237–1244.
    a. Conclusions: Megavoltage CT-based image guidance can be used to position lung cancer patients daily. This has the potential to decrease margins associated with daily setup error. Furthermore, the adaptive therapy technique described in this article can decrease the volume of healthy lung tissue receiving above 20 Gy. However, further study is needed to determine whether adaptive therapy could result in the underdosing of microscopic extension.

2.0 OBJECTIVES

2.1 **Hypothesis and Specific Aims:** The primary objective of the study is to assess acute toxicity of SBRT and adaptive planning for up to 5 pulmonary metastases from STS. We hypothesize that SBRT for pulmonary metastases will result in local control similar to resection with less toxicity.

2.1.1 **Primary Objective**: Assess the acute toxicity of SBRT for ≤ 5 pulmonary metastases from soft tissue sarcoma.

2.1.2 **Secondary Objectives:**

2.1.2.1.1 Local control
2.1.2.1.2 QoL using FACT-L
2.1.2.1.3 Late toxicity
2.1.2.1.4 Overall Survival

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 ≥18 years of age
3.1.2 Pathologic confirmation of primary soft tissue sarcoma with pathologic or radiographic evidence of pulmonary metastatic disease
3.1.3 No evidence of extra pulmonary progression of disease for 3 months prior to enrollment on study.
3.1.4 1-5 pulmonary lesions all ≤5 cm in size.
3.1.5 Medically inoperable or declines surgery
3.1.6 Patients may have had previous treatment for pulmonary metastases

3.2 Conditions for Patient Ineligibility

3.2.1 Patients who have uncontrolled extra-pulmonary disease
3.2.2 Pregnant women
3.2.3 Patients who have greater than 5 pulmonary lesions at the time of study enrollment
3.2.4 Patients who have disease progression outside the lungs within 3 months of enrollment on the study.
3.2.5 Disease pathology other than sarcoma subtypes
3.2.6 Patients with a history of metastatic disease from a primary other than sarcoma

4.0 RECOMMENDED PRETREATMENT EVALUATIONS

4.1 CT of the chest within 6-8 weeks of study entry
4.2 Documentation of extra-thoracic disease control within 6 weeks of study entry
4.3 PFTs are recommended, but not required within 3 months study entry

5.0 REGISTRATION PROCEDURES: Eligible patients will be registered per the CTO standard procedure.

6.0 RADIATION THERAPY

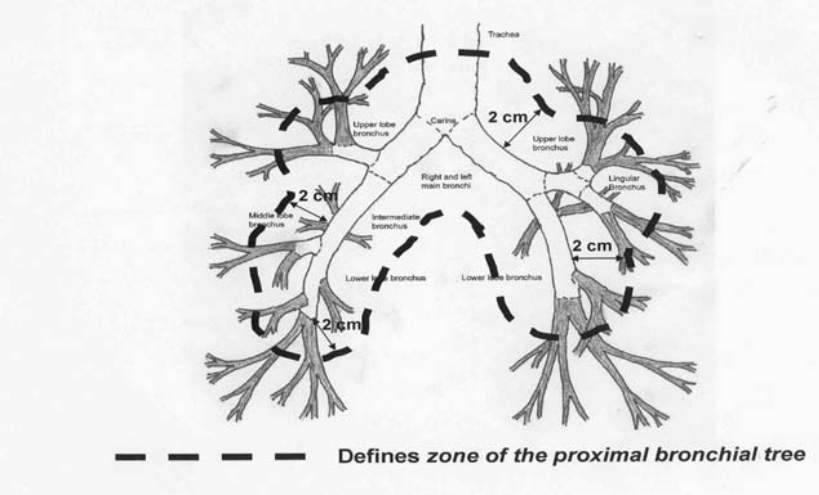
6.1 Dose Specifications

The treatment goal for each lesion peripherally located lesion is 54 Gy in 3 fractions at 18 Gy per fraction and for centrally located lesions 50 Gy in 5 fractions at 10 Gy per fraction. Peripherally located lesions are those that are >2cm beyond the proximal bronchial tree. Centrally located lesions are ≤2 cm from the proximal bronchial tree. Total dose and fractionation modifications may be required to meet normal tissue dose constraints. This will be at the treating physician's discretion based on tumor size, location, organs at risk, patient comorbidities and prior treatment. (Table 1).

Tumor Location	Dose per Fraction	Total Dose
> 2cm from proximal bronchial tree	18 Gy	54 Gy

≤2 cm from proximal bronchial tree	10 Gy	50 Gy

Table 1: Dose and Fractionation based on Tumor Location



6.2 **Treatment Schedule:** Treatments delivered with > 10 Gy per fraction will have a minimum of 48 hour interfraction interval. For treatments with≤10 Gy per fraction will have a minimum 24 hour interfraction interval. Treatments will be ideally completed over 14 days for 3 fraction treatments and over 21 days for > 5fraction treatment schedules.

6.3 **Technical Factors**

Photon (x-ray) beams with photon energies of 6 MV will be used for most beams. Photon beam energies >10 MV will be allowed for beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter. A minimum field dimension of 3.5 cm is required for any field used for treatment delivery.

6.4 **Simulation, Immobilization, Localization for Treatment Delivery**

6.4.1 Patient Positioning: All extra-cranial SBRT patients should be set-up with an alpha cradle or vacuum lock immobilization device. Multiple immobilization devices as well as abdominal compression and/or stereotactic body frames may be used upon physician request.

6.4.2 Image Acquisition: Unless otherwise instructed by the physician, 4D CT and 3D CT s will be acquired. The planning CT scans with IV contrast are recommended. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans in the region of the tumor.

6.4.3 Localization for Treatment Delivery: Image Guided Radiation Therapy (IGRT) will be used for each fraction with cone-beam CT or CT on rails. The physician will check and approve the IGRT alignment along with table shifts prior to each fraction. When multiple lesions are being treated at the same time with more than one isocenter, one isocenter will be chosen as the “primary” isocenter for purposes of positioning the patient. IGRT images will be acquired and table shifts made for the “primary” isocenter and the corresponding lesion will be treated. Shifts to the second isocenter will be made and orthogonal films acquired and compared to corresponding DRRs. If shifts are indicated they will be made films repeated and reviewed and approved by the MD prior treatment.

6.4.4 This will be repeated for each isocenter

6.4 **Treatment Planning/Target Volumes**

6.4.1 Target volumes: Each target lesion will be outlined uniquely designated GTVx (x=1, 2, 3, 4, or 5 depending on the number of lesions being treated). GTVs will include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical). The GTVs will be defined either on MIP (Maximum Intensity Projection) images or using GTVs at 3 phases (inspiration, expiration and midphase) of the respiratory cycle to create an ITV. An additional 0.5 cm in the axial plane and 0.5 to

1.0 cm in the longitudinal plane (craniocaudal) will be added to the each GTVx (ITVx) to create the PTVx

6.4.2 Treatment Planning: Three-dimensional coplanar or non-coplanar beam arrangements will be used. Non-opposing, non-coplanar beams are preferable. A minimum of 7 beams will be used although typically, ≥ 10 beams of radiation will be used. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view. An exception will be when observing the minimum field dimension of 3.5 cm when treating small lesions. Prescription lines covering the PTV will typically be the 60-90%. Higher isodoses (hotspots) must be within the target and not in adjacent normal tissue. The prescription dose will be delivered to the margin of the PTV and fulfill the requirements below.

6.4.3 Dose Calculations: Heterogeneity correction will be used for dose calculations.

6.4.4 Treatment planning criteria:

- Normalization: The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COMPTV). This point will typically also correspond to the isocenter of the treatment beams.
- Prescription Isodose Surface Coverage: 95% of the PTV is covered by the prescription isodose surface and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose.
- Target Dose Heterogeneity: The prescription isodose surface selected (above) must be ≥ 60% of the dose at the center of mass of the PTV (COMPTV) and ≤ 90% of the dose at the center of mass of the PTV (COMPTV).

6.4.5 High Dose Spillage:

- Location: 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 be no more than 15% of the PTV volume.
- Conformality The ratio of the prescription isodose volume to the PTV volume is ideally < 1.2.

6.4.6 Low Dose Spillage:

- Location: The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction should be no greater than 50% of the prescription dose.
- Volume: The ratio 50% of prescription isodose volume to the PTV volume should be, < 6.

6.5 **Critical Structures:** Critical Organ Dose-Limits: See Table 3 for dose limits to the point or volume. No part of any OAR will receive more than 105% of the prescribed. In addition, the volume of the OAR in question will be minimized, both in length and in the width, with efforts made to reduce the dose to the contralateral wall of the organ. Maximum point dose limits should be respected. The total dose will be adjusted when necessary to meet normal tissue dose constraints. (Table 3).

OAR	3 Fractions		5 Fractions	
	Max Dose	Volume Constraint	Max Dose	Volume Constraint
Spinal Cord	18 Gy (6 Gy/fx)	12. 3 Gy to < 1.2 cc	30 Gy (6 Gy/fx)	≤ 22.5 Gy to < 0.25 cc
Esophagus	30 Gy (10 Gy/fx)	17.7 Gy to < 5 cc	52.5 Gy (10.5 Gy/fx)	27.5 Gy to < 5cc (non-adj wall)
Brachial Plexus	21 Gy (7 Gy/fx)	20.4 Gy to < 3 cc	30 Gy (6 Gy/fx)	30 Gy to < 3 cc
Heart/ Pericardium	30 Gy (10 Gy/fx)	24 Gy to < 15 cc	52.5 Gy (10.5 Gy/fx)	32 Gy to < 15 cc
Great Vessels	45 Gy (15 Gy/fx)	39 Gy to < 10 cc	52.5 Gy (10.5 Gy/fx)	47 Gy to < 10cc
Trachea &	30 Gy	15 Gy to < 4 cc	52.5 Gy	18 Gy to < 4 cc

Proximal Bronchial Tree	(10 Gy/fx)		(10.5 Gy/fx)	(non-adj wall)
Rib*	36.9 Gy (12.3 Gy/fx)	28.8 to < 1 cc	52.5 Gy (10.5 Gy/fx)	30 Gy to < 3 cc
Skin	33 Gy (11 Gy/fx)	30 Gy to < 10 cc	40 Gy (8 Gy/fx)	30 Gy to < 10cc
Stomach	27 Gy (9 Gy/fx)	16.5 Gy to < 10 cc	35 Gy (7 Gy/fx)	
Lung	N/A	10.5 Gy to < 1500 cc 11.4 Gy to < 1000 cc	N/A	12.5 Gy to 1500 cc 13.5 Gy to < 1000 cc

*Rib constraints are not absolute. The max dose for lesions adjacent should be ≤ 105% prescribed dose if at all possible.

Table 3: Volume and Point Dose Maximum for Serial Tissues (28)

6.5.1 Spinal Cord: The spinal cord will be contoured based on the bony limits of the spinal canal on the entire planning scan.

6.5.2 Esophagus: The esophagus will be contoured from the cricoid cartilage to the GE junction

6.5.3 Brachial Plexus: The brachial plexus will be contoured using the RTOG thoracic contouring atlas guidelines

6.5.4 Heart: The heart will be contoured along with the pericardial sac. The superior aspect for purposes of contouring will begin at the level of the inferior aspect of the aortic arch and extend inferiorly to the apex of the heart.

6.5.5 Trachea: The trachea will be contoured to 2cm above the carina.

6.5.6 Proximal Bronchial Tree: This will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in Figure 1 using RTOG atlas standard

6.5.7 Lung: Both the right and left lungs should be contoured as one structure on pulmonary windows

6.5.8 Skin: The skin will be defined as the outer 0.5 cm of the body surface.

6.5.9 Great Vessels: The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT.

6.5.10 Non-adjacent Wall of a Structure: For the esophagus, trachea and proximal bronchial tree, and great vessels, the nonadjacent wall corresponds to the half circumference of the tubular structure not immediately touching the GTV or PTV, These contours would start and stop superiorly and inferiorly just as with the named structure. The half lumen of the structure should be included in this contour. (This anatomic association may occur for centrally located tumors. By definition if the GTV or PTIV is touching a central structure it is a centrally located tumor and fractionation for centrally located disease will be used)

6.5.11 Rib: Ribs within 5 cm of the PTV should be individually contoured.

6.6 Adaptive Planning

6.6.1 Patients will be placed a linear accelerator equipped with an EPID, MLCs and adaptive planning capabilities. All patients will treated using the SABR, which is planned as explained above in sections 6.1-6.5. Each treatment field will be shaped by the MLCs using an in-house MLC preparation system (3) and transferred through the computer network to the linear accelerator. The daily portal image of each treatment field was aligned off-line to a reference image using a treatment verification tool (6). The reference image will be obtained from the simulation film, which will include the planned treatment isocenter and delineations of each treatment field. Throughout the study, daily setup errors for each treatment field will be delineated separately using the department's adaptive planning software.

6.7 Documentation Requirements

6.7.1 Treatment interruptions should be avoided when possible by preventative medical measures and nutritional and psychological counseling. Treatment breaks and reasons need to be clearly documented.

6.8 Compliance Criteria

6.8.1 Section 6 describes appropriate conduct for treatment planning dosimetry. Criteria for both major and minor deviations are provided in Section 6.4. In addition to the criteria in Section 6.4, table 3 in Section 6.5 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor protocol violation. Exceeding these limits by more than 5% constitutes a major protocol violation.

6.9 Radiation Toxicity: All acute and late toxicity related to SBRT will be reported. Study accrual will be suspended for and Grade 4 or 5 events possibly related to study treatment.

6.8.1 Toxicities related to Stereotactic Body Radiation Therapy (24):
Cough, pneumonitis, atelectasis, bronchial obstruction, bronchial stricture, bronchopleural fistula, chest wall pain, fracture, changes in pulmonary function tests (see below), pulmonary fibrosis, radiation skin changes, including dermatitis from radiation, alopecia, dyspnea, fever, fatigue, pericarditis, pericardial effusion, chest pain – cardiac, palpitations, heart failure, myocardial infarction, paresthesias. All of these toxicities will be graded based on CTCAE 4.0 (Appendix III)

6.8.2 Lung Injury: Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis before completing therapy, therapy will be put on hold until symptoms resolve. All patients who have pneumonitis will be graded and documented

6.8.3 Bronchial Injury (e.g., bronchial obstruction; bronchial stricture; bronchopleural fistula): Focal collapse of lung secondary to bronchial injury may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking.

6.8.4 Chest Wall Pain and/or Fracture (Rib): Some patients will experience chest wall pain either as a result of intercostal neuropathy or rib fracture. Focal radiation induced osteoporosis can result in both occult and obvious rib fractures generally propagated by severe coughing/sneezing episodes or chest wall trauma/ The pain typically occurs several months after treatment and may last several more months.

6.8.5 Changes in Pulmonary Function Tests: Patients enrolled to this study may have some degree of impaired pulmonary function as measured by pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), and Diffusing Capacity for Carbon Monoxide (DLCO). In order to monitor changes in lung function from baseline, a protocol-specific toxicity classification for PFTs has been developed for use with this study. PFTs will be coded for all patients in both treatment groups using this scale. The RTOG Pulmonary Function Test Toxicity Scale is below. PFT acquisition, however, is suggested and not required for this study.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
FEV1 Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
FVC Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death

DLCO Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death

Table 4: RTOG Pulmonary Toxicity Scale (24)

7.0 DRUG THERAPY

NOT APPLICABLE TO THIS STUDY

8.0 SURGERY

NOT APPLICABLE TO THIS STUDY

9.0 OTHER THERAPY

9.1 Supportive Therapy

9.1.1 All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s).

10.0 TISSUE/SPECIMEN SUBMISSION

NOT APPLICABLE TO THIS STUDY

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Assessments	Pre-Study Entry	During Therapy (each fraction)	At 4-6 Weeks (+/- 1 month) after SBRT	Every -6 months (+/- 1 month) after RT for 12years
History/physical,	X		X	X
Zubrod PS	X	X	X	X
Toxicity Evaluation		X	X	X
QoL (FACT-L)	X			X
CT of the Chest	X*			X
PET/CT	X**			If Needed***
PFTs	X (not required)			X** (not required)

PFTs are not required for this protocol. PFTs may be done pre-treatment and 3 months after therapy and as clinically indicated.
*CT scan- within 6-8 weeks of study entry
** PET/CT -may be omitted if not covered by insurance although is recommended to assist in treatment planning and to assess the appropriateness of study therapy.
***PET/CT-to be done at discretion of physician

11.2 PATIENT ASSESSMENTS

11.2.1 Patients will be seen 4 to 6 weeks after the last fraction of radiation therapy, every 6 months for 2 years.

11.2.2 Prior to each visit, a CT of the chest with contrast will be obtained for disease assessment. If there is deemed to be progressive disease, a PET scan will be obtained per discretion of the physician. Biopsy is recommended although will be at the discretion of treating physician. Treatment after failure will be at the treating teams discretion and documented.

11.2.3 QOL assessments will be made using the FACT-L questionnaire. Questionnaires will be given every 6 months for 2 years.

11.3 *Measurement of Response*

11.3.1 Baseline Documentation of Target lesions

All treated tumors (GTV1-5) should be identified as the target lesions and recorded and measured at baseline and with each follow-up imaging evaluation. The longest diameter (LD) for the target lesion will be calculated from the treatment planning CT scan using pulmonary windowing and reported as the baseline LD. For follow-up assessment, diagnostic CT scans pulmonary windows are preferred as the method of evaluation for response. Cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor

11.3.2 Evaluation of Target and Involved Lobe Lesions

Complete Response(CR)	Disappearance of the target lesion; ideally, this determination will be made based on CT image evaluation.
Partial Response(PR)	At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT image evaluation.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started
Local Enlargement(LE)	At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started; Ideally, this determination will be made based on CT image evaluation.
Primary Tumor Failure (PTF)	Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2) The measurable tumor with criteria meeting LE should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. For outcome analysis, Marginal Failures (MF; see below) will also be counted as PTF; however, they should be distinguished specifically as MF, not PTF, on all report forms. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs. inflammation.46
Marginal Failure (MF)	Refers to the appearance after protocol therapy of a measurable tumor appearing since treatment within 1.0 cm of the treated PTV (see Section 6.4) and meeting the following two criteria: 1) Enlarging tumor dimensions corresponding to a 20% increase in the longest diameter compared to initial appearance on imaging evaluation. Ideally, this determination will be made based on CT image evaluation; 2) The measurable tumor within 1.0 cm of the treated PTV should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pre-treatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma.
Primary Tumor Control	The absence of Primary Tumor Failure.

(PTC)	
Involved Lobe Failure	Refers to the appearance of lung cancer after protocol therapy within the anatomical boundaries of the lobe in which the primary tumor arose (involved lobe). The measurable tumor apart from the primary tumor but within the involved lobe should meet criteria for LE, should be avid on Positron Emission Tomography (PET) imaging with uptake highly suspicious for cancer (e.g., SUV>3-5), OR the measurable tumor should be biopsied confirming viable carcinoma. Failure outside of the involved lobe (uninvolved lobes) will be considered metastatic disseminated (distant) failures. Local Failure Refers to either primary tumor failure or involved lobe failure or both.
Local Control (LC)	The absence of Local Failure

12. DATA COLLECTION

12.1. Study Design:

This is a non-randomized Phase II pilot protocol to determine the feasibility, toxicity, and disease control (overall and progression-free survival) using SBRT in patients with pulmonary oligometastatic disease from soft tissue sarcoma primaries.

12.2. Primary Endpoint:

The primary aim of this study is to assess toxicity and quality of life from SBRT. All patients will be followed for the primary endpoint for a minimum of 3 years. Based on historical data, we expect there will be minimal toxicity, both acute and long term. Adverse event rates will be compared at specific time points (3, 6 and 12 months after completion of SBRT). Quality of life will be measured with the FACT-L questionnaire (Appendix IV).

12.3. Secondary Endpoint:

The secondary objective of this study is to assess local and regional control, progression-free survival and overall survival. Local and regional recurrence will be defined for each lesion per criteria in section 11.3.2 Disease-free survival is defined as the time from randomization until documented disease-recurrence or death, whichever occurs first. Patients who are disease-free and alive at the time of analysis will be censored at the time of their last follow-up. Patients will be followed for disease-free survival for a minimum of 3 years.

12.4. Endpoint Analysis:

Crude rates of locoregional recurrences will be documented as well as the time to development of recurrence or relapse. Time of last follow-up or death will also be noted. This will allow us to calculate progression free and overall survival rates.

13.0 Statistical Considerations

13.1 **PRIMARY ENDPOINTS:** Assess the acute and late toxicity of SBRT for < 5 pulmonary metastases from soft tissue sarcoma.

13.1.1 Toxicity for various sub-sites are based on the CTC v 4.0 scale (see Appendix III)

13.2 **SECONDARY ENDPOINTS:** Local and regional control, QoL, and overall survival (see Section 12 and Appendix IV)

REFERENCES

1. Pastorino U. History of the surgical management of pulmonary metastases and development of the International Registry. *Semin Thorac Cardiovasc Surg* 2002;14:18-28.
2. Casson AG, Putnam JB, Natarajan G*, et al.* Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. *Cancer* 1992;69:662-668.
3. Putnam JB, Jr., Roth JA, Wesley MN*, et al.* Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas. *J Thorac Cardiovasc Surg* 1984;87:260-268.
4. Jablons D, Steinberg SM, Roth J*, et al.* Metastasectomy for soft tissue sarcoma. Further evidence for efficacy and prognostic indicators. *J Thorac Cardiovasc Surg* 1989;97:695-705.
5. Billingsley KG, Burt ME, Jara E*, et al.* Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. *Ann Surg* 1999;229:602-610; discussion 610-602.
6. van Geel AN, Pastorino U, Jauch KW*, et al.* Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. *Cancer* 1996;77:675-682.
7. Lanza LA, Putnam JB, Jr., Benjamin RS*, et al.* Response to chemotherapy does not predict survival after resection of sarcomatous pulmonary metastases. *Ann Thorac Surg* 1991;51:219-224.
8. Casper ES, Gaynor JJ, Harrison LB*, et al.* Preoperative and postoperative adjuvant combination chemotherapy for adults with high grade soft tissue sarcoma. *Cancer* 1994;73:1644-1651.
9. Canter RJ, Qin LX, Downey RJ*, et al.* Perioperative chemotherapy in patients undergoing pulmonary resection for metastatic soft-tissue sarcoma of the extremity : a retrospective analysis. *Cancer* 2007;110:2050-2060.
10. Timmerman R, Paulus R, Galvin J. Stereotactic body radiation therapy for inoperable early stage lung cancer. *Jama* 2010; 303 (11): 1070-6
11. Le QT, Loo BW, Ho A*, et al.* Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. *J Thorac Oncol* 2006;1:802-809.
12. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol* 2010;5:1091-1099.
13. Wulf J, Baier K, Mueller G*, et al.* Dose-response in stereotactic irradiation of lung tumors. *Radiother Oncol* 2005;77:83-87.
14. Nagata Y, Negoro Y, Aoki T*, et al.* Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002;52:1041-1046.
15. Uematsu M, Shioda A, Tahara K*, et al.* Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. *Cancer* 1998;82:1062-1070.

16. Song DY, Benedict SH, Cardinale RM*, et al.* Stereotactic body radiation therapy of lung tumors: preliminary experience using normal tissue complication probability-based dose limits. *Am J Clin Oncol* 2005;28:591-596.
17. Norihisa Y, Nagata Y, Takayama K*, et al.* Stereotactic body radiotherapy for oligometastatic lung tumors. *Int J Radiat Oncol Biol Phys* 2008;72:398-403.
18. Brown WT, Wu X, Fowler JF*, et al.* Lung metastases treated by CyberKnife image-guided robotic stereotactic radiosurgery at 41 months. *South Med J* 2008;101:376-382.
19. Rusthoven KE, Kavanagh BD, Cardenes H*, et al.* Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009;27:1572-1578.
20. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand* 1951;102:316 319.
21. Lax I, Blomgren H, Naslund I*, et al.* Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994;33: 677- 683.
22. Dhakal S, Corbin KS, Milano MT, et *al*. Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: excellent local lesion control and improved patient survival. *Int J Radiat Oncol Biol Phys* 2012;82:940-5.
23. Wu QJ, Thongphiew D, Wang Z, et *al*. Online Re-optimization of Prostate IMRT Plans for Adaptive Radiation Therapy. *Phys. Med. Biol.* 2008; 53: 673–691
24. Ahn PH, Chen CC, Ahn AI, et *al*. Adaptive Planning in Intensity-Modulated Radiation Therapy in Head and Neck Cancers: Single Institution Experience and Clinical Implications. *Int. J. Radiation Oncology Biol.* Phys. 2011; 80: 677–685.
25. Yan D, Ziaja E, Jaffray D, et *al*. The Us e of Adaptive Radiation Therapy to Reduce Set-Up Error: A Prospective Clinical Study. *Int. J. Radiation Oncology Biol. Phys* 1998; 41: 715–720.
26. Hasbeek CJ, Langerwaard FJ, Cuijpers JP, et al. Is Adaptive Treatment Planning Required For Steotactic Radiation Therapy in Stage I Non-Small Cell Lung Cancer? Int. J. Radiation Oncology Biol. Phys 2007; 67: 1370–1374.
27. Ramsey CR, Langen KM, Kupelian PA, et *al*. A Technique for Adaptive Image-Guided Helical Tomotherapy For Lung Cancer. *Int. J. Radiation Oncology Biol. Phys*.2006; 64: 1237–1244.
28. Radiation Therapy Oncology Group 0618, 0813, 0915, & 1015.
29. Americal College of Surgeons/Radiation Therapy Oncology Group: ACOSOG Z4099/ACOSOG 1021: Study Chair: Hiran Fernando

APPENDIX I

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

APPENDIX II

STAGING SYSTEM

AJCC 7th Edition (2009)
Primary Tumor:

- T1 - less than or equal to 5cm
    - T1a - superficial
    - T1b - deep
- T2 - greater than 5cm
    - T2a - superficial
    - T2b - deep

Regional Lymph Nodes:

- N0 - no
- N1 - yes

Distant Metastases:

- M0 - none
- M1 - yes

Stage Grouping:

- IA - T1a/b N0 G1 - low grade (grade 1), small
- IB - T2a/b N0 G1 - low grade (grade 1), large
- IIA - T1a/b N0 G2-3 - mod/high grade (grade 2-3), small
- IIB - T2a/b N0 G2 - mod grade (grade 2), large
- III - T2a/b G3, or N1 - high grade (grade 3), large; or node positive
- IV - M1 - metastatic

APPENDIX III

CTCAE 4.0 Toxicity Grading

Cough

Grade	Description
1	Mild symptoms; nonprescription intervention indicated
2	Moderate symptoms, medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL

Pneumonitis

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; oxygen indicated
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
5	Death

Pneumonitis

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; oxygen indicated
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
5	Death
Grade	**Description**
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; oxygen indicated
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
5	Death

Atelectasis

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning
3	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)
4	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
5	Death

Bronchial Obstruction

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)
3	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)
4	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
5	Death

Bronchial Fistula

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)
4	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated
5	Death

Bronchial Stricture

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)
3	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)
4	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
5	Death

Chest-wall Pain

Grade	Description
1	Mild
2	Moderate pain; limiting instrumental ADL
3	Severe pain; limiting self care ADL

Fracture

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic but non-displaced; immobilization indicated
3	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

Pulmonary Fibrosis

Grade	Description
1	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume
2	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 – 50%
3	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis

	>50 - 75%
4	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing
5	Death

Radiation Dermatitis

Grade	Description
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
5	Death

Dyspnea

Grade	Description
1	Shortness of breath with moderate exertion
2	Shortness of breath with minimal exertion; limiting instrumental ADL
3	Shortness of breath at rest; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

Fever

Grade	Description
1	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)
2	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)
3	>40.0 degrees C (>104.0 degrees F) for < =24 hrs
4	40.0 degrees C (>104.0 degrees F) for >24 hrs
5	Death

Fatigue

Grade	Description
1	Fatigue relieved by rest
2	Fatigue not relieved by rest; limiting instrumental ADL
3	Fatigue not relieved by rest, limiting self care ADL

Pericarditis

Grade	Description
1	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis
2	Symptomatic pericarditis
3	Pericarditis with physiologic consequences (e.g., pericardial constriction)
4	Life-threatening consequences; urgent intervention indicated
5	Death

Pericardial Effusion

Grade	Description
2	Asymptomatic effusion size small to moderate
3	Effusion with physiologic consequences
4	Life-threatening consequences; urgent intervention indicated
5	Death

Chest Pain

Grade	Description
1	Mild pain
2	Moderate pain; limiting instrumental ADL
3	Pain at rest; limiting self care ADL

Palpitations

Grade	Description

1	Mild symptoms; intervention not indicated
2	Intervention indicated

Heart Failure

Grade	Description
1	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities
2	Symptoms with mild to moderate activity or exertion
3	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
4	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
5	Death

Myocardial Infarction

Grade	Description
2	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes
3	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction
4	Life-threatening consequences; hemodynamically unstable
5	Death

APPENDIX IV

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

PHYSICAL WELL-BEING

		Not at all	A little bit	Some -what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some -what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness ...	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath.....	0	1	2	3	4
C2	I am losing weight.....	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me.....	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking.....	0	1	2	3	4