Whole Lung IMRT in Children and Adults with Synovial Sarcom a and Lung Metastases

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PRO ¯OCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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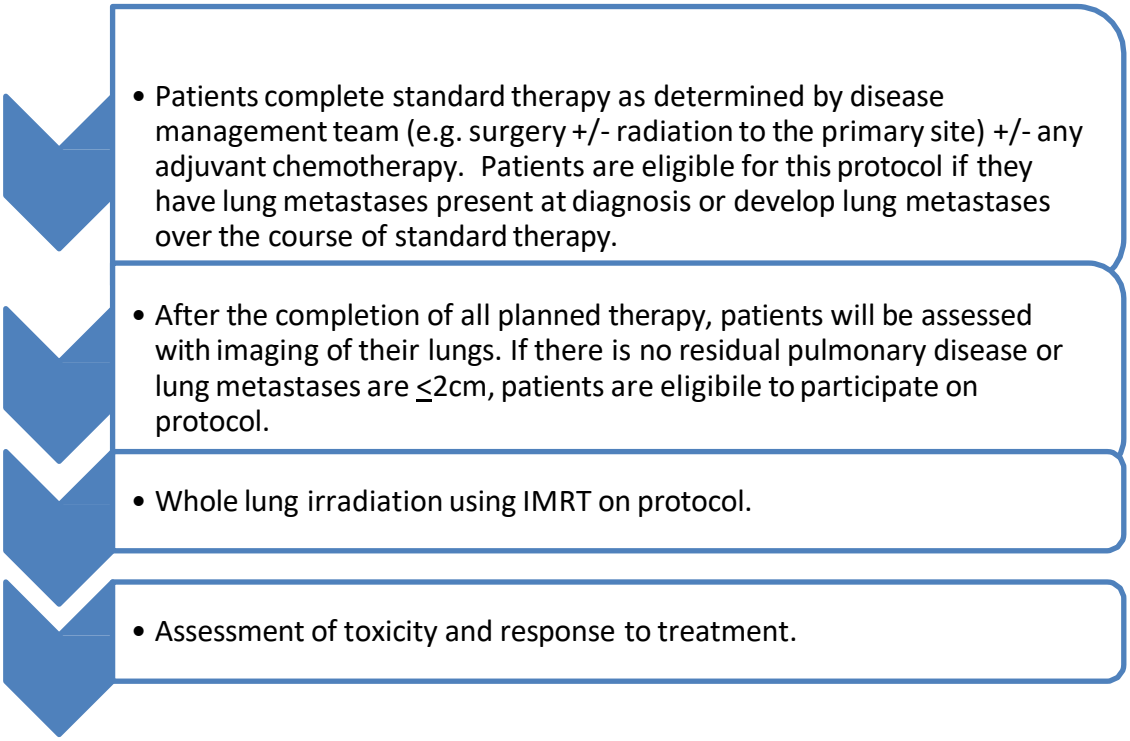
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a safety study to evaluate toxicity and other clinical outcomes of whole lung intensity-modulated radiation therapy (IMRT) following standard treatment in patients with synovial sarcoma and lung metastases. Patients who received standard therapy for synovial sarcoma will be assessed for residual disease in the lungs by post-therapy imaging. Patients with pulmonary metastases ≤2 cm will then be eligible to receive Whole Lung Irradiation (WLI). The treatment plan will involve 1500 cGy of radiation delivered using IMRT in 150 cGy fractions.

Following completion of treatment, patients will have CT chest, physical exams, and toxicity assessments at 3, 6, 12, 18, and 24 months (+/-3 weeks for 3 and 6 months and +/-6 weeks for 12, 18, and 24 months), an echocardiogram at 6, 12, and 24 months, and pulmonary function tests at 6 and 24 months.

Fifteen patients will be enrolled in 6 years. The duration of the study will be 6 years.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective

- To assess the overall toxicity rate at 1 year after whole lung IMRT in this patient population

Secondary objectives

- To determine rates of pulmonary failure-free survival after completion of whole lung IMRT.
- To determine rates of overall survival (OS) after completion of whole lung IMRT.

3.0 BACKGROUND AND RATIONALE

3.1 The usage of whole lung irradiation in the management of pulmonary metastases

Whole lung irradiation (WLI) is standard of care in the treatment of patients with pulmonary metastases from rhabdomyosarcoma (RMS), Ewing Sarcoma, and Wilms Tumor[1-3]. The dose of WLI in modern Children's Oncology Group (COG) protocols is 15Gy for RMS and Ewing Sarcoma and 12 Gy for Wilms tumor. WLI reduces the rates of lung recurrences in patients with RMS[1]. In the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS), WLI was associated with a trend to improved overall survival (OS),[4] reduced pulmonary relapses and improved event-free survival (EFS)[5]. Similarly, patients with Wilms tumor with lung metastases at diagnosis demonstrate reduced pulmonary relapse when treated with WLI as demonstrated in both the UK Children's Cancer Study Group (UKCCSG) [6] and the National Wilms Tumor Study Group (NWTSG)[3]. The UKCCSG also demonstrated an association between EFS with the use of WLI. Taken together, these studies demonstrate that WLI is an accepted and efficacious treatment in the management of pulmonary metastases from RMS, Ewing Sarcoma, and Wilms Tumor.

3.2 Rationale for using whole lung irradiation in synovial sarcoma

Synovial sarcoma comprises approximately 8% of all soft tissue sarcomas (STS) and is the third most common extremity STS[7]. Synovial sarcoma is frequently a disease of young adults with a mean age of 30-40 years[8]. About 6-18% of patients have distant metastases at presentation and the lungs are the most common site of metastases. In one series of patients <21 years of age with synovial sarcoma, rates of metastases at diagnosis are about 6% with the vast majority of metastases (86%) located in the lungs[9]. An adult series reported 18% of patients with metastatic disease at time of presentation with 78% of metastases located in the lungs[10]. In a Surveillance, Epidemiology and End Result (SEER) database study of 1,268 adult and pediatric patients with synovial sarcoma, the rate of distant disease at presentations was 13%[11].

In contrast to RMS, Ewing Sarcoma, and Wilms tumor, the use of WLI in patients with synovial sarcoma and lung metastases is not standard of care. In the recently closed COG phase III ARST0332 trial for non-rhabdomyosarcoma soft tissue sarcoma, which included synovial sarcomas, the use of WLI or focal radiation to the lungs was not allowed. However, like RMS and Ewing sarcoma, synovial sarcoma is a radiosensitive histology[8]. In the non-metastatic setting, the use of radiotherapy has been shown in large series to be associated with local control[12] and EFS in patients with localized disease[10].

Data indicate that local control of pulmonary metastases is associated with improved survival. In a study from this institution that included 41 pediatric patients <22 years old with synovial sarcoma, patients who underwent pulmonary metastasectomy had a 2-year OS of 65% compared to 0% among patients who did not undergo pulmonary metastasectomy[13]. In this series, 10 of 41 patients could not undergo pulmonary metastasectomy due to diffuse non-resectable disease. A larger series examining pulmonary metastasectomy in all patients at this institution with soft tissue sarcoma (STS) and pulmonary metastases showed a 3-year overall survival rate of 46% in those patients who underwent complete resection of pulmonary metastases compared to 17% in patients with no resection. Of note, of the 20

patients in this series with long term survival, 13 relapsed in the lungs requiring repeat resections leading the authors to conclude that "pulmonary metastases frequently represent diffuse involvement of the lung parenchyma. As such, it is difficult to eradicate all foci of metastatic disease with resection[14]." A series from Japan that included pediatric and adult patients with STS demonstrated a 2-year actuarial survival rate of 49.7% from time of first pulmonary resection with the use of aggressive pulmonary metastasectomy[15].

In addition to metastasectomy, local therapy to the lung in the form of radiation has been shown to provide excellent local control and improved OS. A series from the University of Rochester using stereotactic body radiotherapy (SBRT) for pulmonary metastases from STS showed an 82% rate of local control at three years and an improvement in OS from .6 years to 2.1 years with the use of SBRT[16]. Synovial sarcoma comprised 15% of the patient population in this study. A German study investigated the use of WLI to 12Gy with a boost of 50-60 Gy to the single metastases in eight patients. Complete remissions were achieved in 6 of 8 patients[17].

3.3 Delivering whole lung irradiation utilizing IMRT

3.3.1 Cardiac complications associated with thoracic radiation

Cardiac morbidity is well-recognized sequelae of radiation therapy. Irradiation of the heart can affect the coronary arteries, cardiac valves, pericardium, myocardium, and endocardium[18]. The complications can ensue while the patient is receiving radiation though many of the effects of radiation on the heart are not seen until years after the completion of radiation. With regard to late toxicity, the rates of radiation-induced cardiac disease are between 10-30% with the onset of symptoms ranging from 5-10 years post-treatment[19].

In an analysis of the Childhood Cancer Survivor Study cohort which included 14,358 five year survivors of cancer diagnosed under the age of 21, a dose-response relationship was seen with regard to rates of congestive heart failure (CHF), myocardial infarction, pericardial disease, and valvular disease with a significant increase in these late complications when cardiac radiation exposure exceeded 15Gy[20]. Another study of childhood cancer survivors showed that the risk of dying as a result of cardiac disease was significantly higher in patients who had received an average radiation dose greater than 5Gy to the heart (RR 12.5) and was further increased at doses exceeding 15 Gy (RR 25.1). There was a linear relationship between radiation dose and risk of cardiac mortality[21].

The NWTSG reported the rates of congestive heart failure in a cohort of patients treated on NWTS 1-4. The RR of CHF was increased in females, by cumulative doxorubicin dose, lung irradiation, and abdominal irradiation. The risk of CHF increased by a factor of 1.6 for every 10Gy of lung irradiation[22].

3.3.2 The use of IMRT to reduce the cardiotoxicity of WLI

A dosimetry study performed at Northwestern University, compared WLI plans for 22 patients using standard anteroposterior-posteroanterior (S-RT) technique and cardiac-sparing IMRT (CS-IMRT)[23]. Dosimetric parameters were calculated for the

whole heart, right atrium, left atrium, right ventricle, left ventricle, liver and thyroid gland. The volume of the heart receiving 6Gy, 8Gy, 10Gy and 11.4Gy was significantly lower in the CS-IMRT plans as compared to the S-RT plans. This was also true for the left ventricle, right ventricle and myocardium. The volume of left atrium and right atrium receiving 10Gy or above was significantly less in the IMRT plans. Similarly, the volume of coronary vessels receiving ≥11.4Gy was lower in the IMRT plans.

There is a recently completed multi-institutional protocol (IRB# 11-100), including this institution, investigating the feasibility of cardiac-sparing whole lung IMRT in children and young adults (<30 years old) with a diagnosis of Wilms tumor, Ewing Sarcoma or RMS and lung metastases.

3.3.3 Pulmonary toxicity following WLI

There is no data on pulmonary toxicity following WLI delivered with IMRT. However, there have been studies examining acute and late toxicity in patients who received WLI delivered with conventional fractionation. Lung irradiation at higher doses is correlated with adverse events including pneumonitis, pneumonia, chronic cough, dyspnea, chest wall deformity, interstitial lung disease, and supplemental oxygen requirement[24]. This study included patients who received up to 64.8 Gy of radiation. The mean lung irradiation dose was significant associated with adverse pulmonary outcome. In studies that examine patients treated with low-dose whole lung irradiation exclusively, there are often mild reductions in pulmonary function abnormalities with low rates of clinically symptomatic moderate or severe pulmonary symptoms on follow-up[4,25,26], In one study that examined patients with osteogenic sarcoma treated with 16Gy WLI, restrictive pulmonary function abnormalities present at 6 and 12 months post-irradiation resolved by 2 years and no patients reported any significant pulmonary symptoms or decrease in exercise tolerance[26]. A second study of patients with Ewing Sarcoma treated with WLI showed a rate of late lung toxicity of .6 (on a 0-3 scale with 0 indicating no toxicity) and no severe pulmonary function test abnormalities among patients treated with WLI and no thoracic surgery. An additional study showed reductions in FEV1 in 50% of patients, reductions in total lung capacity in 60% of patients, and reductions in diffusing capacity in 81% of patients, but all but one patient had none or mild self-reported respiratory symptoms in follow-up[25]. In one study of patients treated with WLI for Wilms Tumor, a failure of chest wall growth was thought to contribute to late effects on pulmonary function though the mean age of patients was young (3 years and 9 months) and the radiation dose delivered was 20Gy[27]. Taken together, these results indicate that while pulmonary function test abnormalities are often seen after whole lung irradiation, the incidence of clinically significant pulmonary toxicity is low, particularly at low-doses of 15Gy, which is the dose prescribed in this protocol.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single institution study involving patients with synovial sarcoma who have completed all standard therapy (e.g. surgery +/- radiation to the primary site) +/- any adjuvant chemotherapy. The sequence and types of therapy offered prior to WLI will likely vary based on primary tumor site, tumor resectability, extent of metastatic disease, performance status, and comorbidity. Each patient's therapy will be determined by the disease management team irrespective of participation on this protocol.

Patients are eligible for this protocol if their pulmonary metastases are present at diagnosis or develop over the course of treatment. After completion of all planned therapy, patients will be assessed with a CT scan of their lungs and a PET scan if the CT scan shows residual lung metastases. Assuming there is no residual pulmonary disease or that any remaining pulmonary metastases are $\leq$2 cm, patients will proceed to WLI. If there is gross disease in the lung >2 cm, patients will be evaluated for metastasectomy. If they undergo metastasectomy and subsequently have no residual pulmonary disease or have pulmonary metastases $\leq$2 cm, they are eligible to receive WLI on this protocol. Patients will also have an echocardiogram and pulmonary function tests (PFTs) prior to initiation of whole lung irradiation to assess baseline cardiac and pulmonary function. Patients will be simulated for external beam radiation with the use of a 4D CT to account for respiratory motion, as per standard practice. Patients will be treated with IMRT to 1500cGy in 150cGy fractions.

After completion of WLI, patients will be followed by members of the Radiation Oncology department for toxicity evaluations and will be evaluated by physical exams and chest CT scans at 3, 6, 12, 18, and 24 months (+/-3-6 weeks depending on timepoint). Patients will also have echocardiograms at 6 months (+/- 3 weeks) and 12, and 24 months (+/- 6 weeks). Patients will also undergo pulmonary function tests (PFTs) at 6 months (+/- 3 weeks) and 24 months (+/- 6 weeks). Any severe toxicity due to radiation will be carefully evaluated and further accrual will be terminated if the level of toxicity is greater than expected. The protocol may be terminated or modified as determined by the principal investigator. Please see section 11.0 regarding specific dose limiting toxicities and stopping rules for the protocol.

4.3 Intervention

External beam radiation therapy will be administered on an outpatient basis, once daily (except weekends and holidays) for approximately two weeks. Patients will undergo a simulation prior to initiation of radiation. Once an IMRT plan is generated which meets all dose constraints specified in section 9.3.3**,** patients will be treated with 6MV photons for 10 treatments. Any pediatric patients who are too young to lay still on a daily basis will receive general anesthesia per department practice.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

IMRT is a sophisticated technique that uses a computer controlled multileaf collimator to shape the intensity of each treatment beam to optimally deliver the dose to the tumor and protect normal tissue. IMRT is being used to deliver WLI in order to minimize the dose to the heart as explained in section 3.3.2.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Patients with synovial sarcoma confirmed by MSKCC pathological review
- Patients with single or multiple lung metastases at diagnosis or that develop over the course of treatment.
- After completion of all chemotherapy, lung metastases must be ≤2 cm.
- Age ≥12 months of age
- Karnofsky performance status (KPS) must be ≥ 70 for patients ≥ 16 years of age and Lansky performance status must be ≥ 70 for patients < 16 years of age.
- Normal cardiac function
    - No active coronary artery disease;
    - No New York Heart Association class II, III or IV disease;
    - No arrhythmia requiring treatment.
    - Baseline echocardiogram with a shortening fraction of ≥ 27% or an ejection fraction ≥ 50%.
- Female patients of childbearing potential must have a negative pregnancy test within 14 days of radiation start.
- Female patients who are lactating must agree to stop breast-feeding.
- Sexually active patients of childbearing potential must agree to use effective contraception.

6.3 Subject Exclusion Criteria

- Patients with a history of prior radiation therapy to the thorax.
- Patients requiring a field size >40 cm as IMRT cannot be performed at extended SSDs.
- Patients with any concurrent medical or psychiatric condition or disease which, in the investigator's judgment, would make them inappropriate candidates for entry into this study.

7.0 RECRUITMENT PLAN with recruitment plan addendum

All patients meeting the eligibility requirements will be considered for enrollment regardless of gender, race, or religion. Patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits that the patient may incur. Patients will be consented by the treating radiation oncologist at MSKCC. They will be required to agree to and sign an IRB-approved informed consent form prior to registration. There will be no financial compensation for patients enrolling in this protocol.

As a comprehensive cancer center, MSKCC is in a unique position to recruit patients for this protocol as we are hoping to recruit both pediatric and adult patients and MSKCC has high-volume adult and pediatric sarcoma services. This study mirrors the national trend of including both pediatric and adult patients on sarcoma protocols. The soon to open ARST 1321-RTOG 1313 is a joint protocol sponsored by the COG and RTOG to study non-rhabdomyosarcoma soft tissue sarcoma across the age spectrum.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reason, we seek a limited waiver of authorization for the purposes of (1) reviewing relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

Any time prior to treatment start:

- Confirmation of pathology at MSKCC

The following are to be completed within 45 days of registration:

- History and physical exam
- Echocardiogram
- Pulmonary function tests

The following are to be completed within 30 days of registration:

- Chest CT scan with or without contrast to evaluate pulmonary metastases after completion of systemic therapy and to serve as a baseline for follow-up scans. To be done within 30 days of treatment start.
- If lung metastases are present on Chest CT and are <2 cm, FDG-PET scan to assess avidity of pulmonary metastases after completion of systemic therapy

The following is to be completed within 14 days of treatment start

- Serum pregnancy test (for women of childbearing potential)

9.0 TREATMENT/INTERVENTION PLAN

9.1 Simulation

These simulation procedures represent our standard simulation procedures for comprehensive radiation therapy.

9.1.1 In order to develop a conformal treatment plan, all patients will undergo a CT simulation. IV contrast is not necessary for simulation.

9.1.2 All patients will undergo simulation in the treatment position with both upper extremities extended above their head using an Alpha Cradle (Alpha Cradle, Smithers Medical Products, North Canton, OH) or slant board immobilization.

9.1.3 Patients will be scanned with 3mm slices from the level of the mandible to the pelvic brim.

9.1.4 A 4D CT will be obtained to capture motion in all phases of the respiratory cycle. A free-breathing scan will also be obtained to be used as the planning CT scan.

9.2 Target Volume Definitions

These procedures generally represent our standard procedures.

9.2.1 Normal structure and treatment volume contours will be delineated on the planning CT scan.

9.2.2. The following normal structures will be contoured.

- Heart
- Liver
- Stomach
- Right kidney
- Left kidney
- Esophagus
- Thyroid
- Right and left breast (in female patients only)

9.2.3 The following target structures will be contoured

- Target volumes will be defined according to International Commission on Radiation Units and Measurements Report-50 and 62 definitions for gross tumor volume (GTV), clinical target volume (CTV), internal target volume (ITV), and planning target volume (PTV).
- The GTV will include all areas of pre-chemotherapy lung metastases.

- The CTV is the bilateral lung volume including all pleural recesses and bilateral hila.
- The ITV is defined as an expansion on the CTV to encompass the bilateral lungs on all phases of the respiratory cycle as defined by the 4DCT. Careful review of the sagittal and coronal views of the costo-diaphragmatic recesses should help determine the inferior extent of the pleural cavity and care must be taken to ensure that they are included in the ITV.
- The PTV is defined as a 1 cm expansion on the ITV in order to account for spatial uncertainties in patient positioning and treatment delivery. This 1cm expansion of the ITV should be made in all dimensions. Compared to the standard AP-PA technique using 2-D or 3-D planning, the final PTV for IMRT in this protocol will be more accurate because we are utilizing 4-D scanning and then giving a dosimetric margin of 1cm beyond the maximum lung expansion (ITV).

- **9.3 Radiation Dose, Fractionation, Energy, and Parameters**

9.3.1 The prescribed dose for all patients will be 1500cGy in 10 fractions. 6MV energy photons will be used. Multi-beam IMRT plans, utilizing dynamic multileaf collimation, will be created based on the target tissue coverage and normal tissue avoidance parameters described below. VMAT plans are also acceptable if all specified dose constraints are achieved.

9.3.2 Ninety-five percent of the PTV should receive at least 95% of the prescribed dose. The PTV used for the purposes of the DVH is the PTV as drawn by the physician minus 5mm from the skin (i.e. the buildup region) as is our departmental practice. No more than 5% of the PTV should receive more than 105% of the prescribed dose and no more than 1% of the PTV should receive more than 110% of the prescribed dose. For organs at risk (OARs): the maximum doses to the spinal cord, breast (in female patients), and liver should be <107%, <108%, and <110% respectively of the prescribed dose. For the heart:

1) The maximum dose should be <110%.

2) The planner should reduce the mean heart dose until the specified PTV coverage constraints are approached (i.e. until the planner gets close to the D95, D05, D01 PTV limits).

9.4 Treatment Plan Evaluation

The treatment plan will be evaluated by the treating physician prior to treatment to ensure that all treatment parameters have been met. Isodose curves and dose volume histograms (DVH) will be analyzed. Evaluation criteria will include.

1. Isodose curves:
    a. The 95% isodose line must generally conform to the PTV with visually acceptable target volume coverage and visually acceptable critical structure avoidance.
2. Dose-Volume Histogram (DVH):

a. The maximum allowed heterogeneity will be limited to less than 5% of the PTV receiving more than 105% of the prescribed dose.
b. The DVH must include all normal structures listed in section 9.2.2
c. PTV DVH must meet all prescription parameters.
d. Critical structure DVH should meet constraint parameters (described in 9.3.2).

9.5 Radiation Therapy Daily Treatments and Quality Assurance

Patients will receive external beam treatment once a day, 5 days a week (except weekends and holidays) for 10 treatments. Any missed radiation days will be recorded and made up. Set-up error will be minimized by weekly orthogonal pair films per departmental guidelines. These films will be checked by an attending physician weekly.

9.6 Treatment Interruptions

In the event that a patient must miss a scheduled treatment for non-toxicity related reasons (ie: weather, sickness, family emergencies, etc), the treatment visit will be made up at the end. If the patient misses more than 3 consecutive treatments, they will be removed from the protocol and considered inevaluable.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Pre-treatment	During WLI	3 mo post-WLI	6 mo post-WLI	12 mo post-WLI	18 mo post-WLI	24 mo post-WLI	Follow up years 2-5
History	x		x	x	x	x	x	
Physical	x	x (weekly)	x	x	x	x	x	
Feasible Plan Generated	x							
Weekly Setup Data		x						
CT chest	x		x	x	x	x	x	
PET scan	x (If CT chest shows mets $\leq$ 2 cm)							
Echocardiogram	x			x	x		x	
PFTs	X			X			x	
TSH					x		x	
Pregnancy test	x							

(if relevant)								
Toxicity assessment	x	x (weekly)	x	x	x	x	x	
Chart review for overall survival								x

10.1 Evaluations During Treatment

All patients will undergo a routine status check visit approximately weekly during treatment. The maximum RT related toxicities graded by CTCAE version 4.0 will be submitted to the Research Study Assistant at the completion of WLI.

10.2 Evaluations After Treatment

Patients will have follow-up visits with physical examinations at 3 and 6 months (+/- 3 weeks) and at 12, 18, and 24 months (+/-6 weeks) following the completion of radiation therapy. CT scans of the chest will be obtained at 3 and 6 months (+/- 3 weeks) and at 12, 18, and 24 months (+/- 6 weeks). Echocardiograms will be obtained at 6 months (+/- 3 weeks) and at 12, and 24 months (+/- 6 weeks). PFTs will be obtained at 6 months (+/- 3 weeks) and at 24 months (+/- 6 weeks). TSH levels will be obtained at 12 and 24 months (+/- 6 weeks).

In order to obtain data on overall survival, routine chart reviews will be conducted until 5 years following the completion of treatment.

10.3 Evaluations of Early and Late Toxicity

The CTCAE version 4.0 scale will be used. Early toxicities are those toxicities that occur within 3 months of the completion of treatment. Late toxicities are those that occur after 3 months following the completion of treatment.

11.0 TOXICITIES/SIDE EFFECTS

Adverse events from WLI

Likely

- Nausea
- Emesis
- Skin erythema
- Low blood counts
- Esophagitis

Less Likely

- Thyroid dysfunction
- Pericarditis

- Cardiac dysfunction

Rare but serious

- Pneumonitis
- Increased risk of secondary cancer
- Pulmonary fibrosis

Reproductive risks: Treatment on this study can affect an unborn child. Patients should not become pregnant or breastfeed a baby while being treated on this study. Sexually active patients who are at risk of getting pregnant or fathering a baby must use an effective method of contraception to avoid pregnancy while on treatment and for at least 3 months thereafter.

Definition of a Serious Adverse Events (SAE):

- A Serious Adverse Event is an adverse experience that:
  - Is fatal or life-threatening
  - Is disabling
  - Results in hospitalization or prolongation of hospitalization
  - Results in a congenital anomaly or occurrence of malignancy
  - Any adverse event that is possibly related to WLI that is grade 3 or higher will be considered an adverse event.

Evaluation of SAE:

Review of the patient record including the treatment dosimetry will be undertaken by the principal investigator and investigators of the study. The principal investigator in conjunction with the investigators of the study may decide to continue the protocol without modification, discontinue the study altogether, or to modify the protocol prior to enrolling more patients pending the results of the review.

Unacceptable Toxicity:

Enrollment on the protocol will be suspended for WLI related acute toxicities ≥ grade 4 radiation pneumonitis, esophagitis, pericarditis, cardiac dysfunction, and acute chest wall pain. If one of these events is observed in one patient, then the protocol will be closed to further accrual until review by the principal investigator in conjunction with the investigators of the study.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Assessment of Primary Objectives

12.1.1 Assessment of the overall toxicity rate will occur at the pre-specified follow-up time-points using the CTCAE version 4.0 grading system. The radiation oncologist will score toxicity at each visit. Any toxicity recorded within three months of completion of radiation will be considered acute. Any toxicity after three months from completion of radiation will be considered late toxicity.

12.2 Assessment of Secondary Objectives

12.2.1 Assessment of Pulmonary Failure-Free Survival

A CT scan of the chest will be obtained at 3 and 6 months (+/- 3 weeks) and at 12, 18, and 24 months (+/- 6 weeks) post-treatment. This study will use a modified Response Evaluation Criteria in Solid Tumor (RECIST) for assessment of tumor response. The baseline scan will be the pre-irradiation CT scan.

All patients will be assessed as failure or failure free as defined below. Pulmonary failure-free survival will be defined as survival with no progressive disease in the lungs. CR, PR, and SD will be considered failure-free.

For patients with measurable (≥5mm but <10mm) lung lesions at the time of study entry:

a. The investigator will identify up to 5 measurable lung lesions to be followed for response. The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.
b. Complete response (CR) is defined as the disappearance of all target lesions.
c. Partial response (PR) is defined as at least a 30% decrease in the disease measurement, taking as reference the pre-irradiation CT scan.
d. Progressive disease (PD) is defined as at least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since start of treatment, or the appearance of one or more new lung lesions.
e. Stable disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

For patients with no measurable disease present at baseline:

a. Stable disease (SD) is defined as no appearance of measurable lesions in the treated area

b. Progressive disease (PD) is defined as the appearance of measurable lesions on post-treatment scans and will be considered failure-free if no measurable lesions develop.

12.2.2 Assessment of overall survival will be performed for each patient using clinical data and information from the social security database.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient desires to quit participation in the study or if the treating physician determines study participation is no longer appropriate, the patient will be removed from the study.

Toxicity will be evaluated in all patients enrolled who receive any whole-lung irradiation. Pulmonary progression free survival will only be evaluated in patients who complete all radiation treatments and have at least 1 follow-up chest CT.

14.0 BIOSTATISTICS

The primary objective of this protocol is to assess the safety of whole lung IMRT following standard treatment in patients with synovial sarcoma and lung metastases. To this end we will enroll 15 eligible patients which will take about 6 years. Due to this long enrollment time the safety endpoint

will include both acute (<=3 months from the end of WLI) and late toxicities (>3 months from the end of WLI). Namely, we will evaluate the rate of any grade 3 toxicities (including pneumonitis, esophagitis, pericarditis and cardiac dysfunction) by using Kaplan-Meier estimation. If a patient withdraws from the protocol (expected to be 10% within 1 year), or dies without any grade 3 toxicities (expected to be 50% at 1 year) he/she will be regarded as a censoring at such time points. We will not use a competing risks analysis because it is expected that the withdrawal and death are independent from toxicities, and the actuarial estimate is believe to be more illustrative of the toxicity profile than the cumulative incidence rate by regarding death as a competing risk. For the decision rule we will look at the 1-year toxicity rate. If, the higher bound of the 85%, 1-sided confidence interval of the 1-year toxicity rate based on the (one minus) Kaplan-Meier estimate is lower than 0.25 than we will declare the whole lung IMRT procedure safe. This unusually high type 1 error rate, 15%, is used due to the rareness of such patients and the high progression/mortality rate without WLI. To roughly assess the power of the study with 15 patients, we simulated 10,000 datasets based on the above assumptions and examine the 1-year toxicity rate by Kaplan-Meier method. The following table shows probabilities of claiming whole lung IMRT safety under various values of the true 1-year toxicity rate.

True 1-year toxicity rate	0.05	0.10	0.15	0.20	0.25	0.30	0.35
Probability of claiming whole lung IMRT safe	0.894	0.712	0.536	0.364	0.243	0.154	0.094

As mentioned in Section 11.0, this study is also subject to early stopping if any radiation-related acute toxicities of grade 4 or higher are observed among the patients. If one of these events is observed in one patient, then the protocol will be closed to further accrual until reviewed by the principal investigator in conjunction with the investigators of the study.

Rates of pulmonary failure-free survival will be assessed by cumulative incidence functions. To this end pulmonary failure is the event of interest and other progressions and death are considered as the competing risks. Overall survival rates will be estimated by the Kaplan-Meier method.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

For patients enrolled, immediately after consent is obtained, the RSA at MSKCC will register participants in the Clinical Trial Management System (CTMS). Once the participant's eligibility is established, the registration will be finalized and the participants will be randomized using the Clinical Research Database (CRDB).

15.2 Randomization

This is not a randomized study.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected from this study will be entered into a secure Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

Data collection will principally assess:

- Adherence to informed consent procedures. The informed consent must contain a full explanation of the possible advantages, benefits, risks, alternative treatment options, and availability of treatment in the case of injury, in accordance with Federal Regulations as detailed in 21CFR50. The investigator is responsible for obtaining written informed consent from potential patients. A copy of the signed document will be given to the patient, and the original will be retained by the investigator with his/her copy of the record forms.

- Adherence to eligibility criteria. The study RSA will ensure that documentation exists for all eligibility criteria and that the checklist is complete and signed by the consenting professional, prior to initiation of treatment. All supporting source documentation must be maintained in the patient's research file.

- Safety Evaluation: Radiation related toxicities will be recorded as they occur, and graded according to the CTCAE Version 4.0. Toxicities that cannot be graded using the CTCAE will be graded as grade 1 (mildly symptomatic), grade 2 (moderately symptomatic but not interfering significantly with function), grade 3 (causing significant interference with function), or grade 4 (life-threatening). All SAEs will be recorded, whether or not related to study treatment.

- The occurrence of unacceptable toxicity indicating the need for cessation of treatment will require mandatory reporting to the IRB. In this circumstance, the IRB will be consulted before a patient is removed from therapy. If the physician feels it is in the best interests of the patient to stop treatment, the IRB will be consulted.

- We expect to enroll 15 patients in 6 years. Since we are assessing two-year follow-up, we estimate that it will take 6 years to complete the study.

16.1 Quality Assurance

Regular registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and extent and accuracy of evaluations and follow-up, will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data

quality and protocol compliance audits will be conducted by the study team at a minimum of twice per year, or more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. These plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials". This document is available at: *http://cancertrials.nci.nih.gov/researchers/dsm/index.html*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm* There are several different mechanisms by which clinical trials are monitored for data, safety and quality. Institutional processes are in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. Additionally, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The Data and Safety Monitoring Committee (DSMC) for phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for phase III clinical trials, report to the MSKCC Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and the degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed, and monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

17.2.1

This protocol is not an Industry or Cooperative group protocol.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Not applicable