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Image Guided Radiotherapy for the Treatment of Musculoskeletal Tumors: A phase II Prospective Evaluation of Radiation-related Treatment Effects

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1.0 Objectives

Primary Objective

1.1 To estimate local control rates with image guided radiation therapy as defined in this study for patients with primary musculoskeletal tumors (MST).

1.1.1 Prospectively establish a baseline estimate of local control for patients with MST (Ewing's sarcoma family of tumors (ESFT), rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma soft tissue sarcoma (STS)) treated with image guided radiation therapy.

1.1.2 Demonstrate that the increased level of conformality afforded by image guided radiation therapy does not reduce its efficacy relative to previously utilized non-image guided radiation therapy techniques in patients with Ewing's sarcoma family of tumors, resected soft tissue sarcomas, and group III rhabdomyosarcomas.

1.1.3 Assess local and regional patterns of failure for patients with MST treated with image guided radiation therapy relative to their targeted volumes.

1.1.4 Provide a long term (>5 year) estimate of local disease control for patients with MST (Ewing's sarcoma family of tumors (ESFT), rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma soft tissue sarcoma (STS) treated with image guided radiation therapy.

Secondary Objectives

1.2 Establish a quantitative baseline estimate of radiation dose-related changes in normal tissues using novel objective measures of somatic change, musculoskeletal function, tissue biochemistry and physiology.

1.2.1 Investigate the dose and volume relationship for the developing physis and cortical bone using physical measures and imaging evaluations including:

1.2.1.1 Prospectively investigate whether an age based radiotherapeutic threshold of dose and volume that will induce premature physis closure and alter long bone length can be quantitatively identified.

1.2.1.2 Quantitatively explore the impact of radiation on cortical bone thinning and long bone curvature.

1.2.1.3 Relate radiation dose and volume to late (10+ year) alterations in bone integrity

1.2.2 Describe the severity and time course of radiation-induced changes in the soft tissues and adjacent organs, including muscle and subcutaneous tissues.

1.2.2.1 Delineate sequential changes in muscular volume, muscle function and organ function (delineated by imaging and measures of physical function) following image guided radiation for specific muscular groups.

1.2.2.2 Correlate the temporal changes in muscular volume and function with changes in vascularity and metabolism defined by imaging studies.

Exploratory Objectives

1.3 Correlate changes in quantitative scales assessing quality of life (QOL) and function with range of motion and dosimetric parameters.

2.0 Background

We will use the terminology musculoskeletal tumors (MST) to describe bone and soft tissue tumors that will be eligible for this protocol. MST includes Ewing's sarcoma family of tumors (ESFT), rhabdomyosarcoma (RMS), small round blue cell tumors that can only be classified as undifferentiated sarcoma, the soft-tissue tumors whose histiotypes are more commonly found in adults and classified as non-rhabdomyosarcoma soft-tissue sarcoma or soft-tissue sarcoma (STS), osteosarcoma (OS) and other localized tumors of the musculoskeletal tissues requiring focal therapy.

2.1 Issues in the Radiotherapeutic Management of Pediatric Sarcomas

The delivery of radiotherapy to pediatric patients with sarcomas is complicated, as one must balance the appropriate dose and volume of treatment needed for local control with radiotherapy's potential effects on developing tissues. These goals are often at odds with one another as critical structures are closely related geometrically to targets, and radiation tolerances of structures are not fully defined; as radiation techniques advance toward greater conformity of the high dose region to the target, lower heterogeneous doses are distributed more broadly in adjacent tissues (1,2).

The local control rates for Ewing's family sarcoma, rhabdomyosarcoma, and non-rhabdomyosarcoma soft tissue sarcoma are defined using conventional radiation therapy techniques prior to the conformal radiation therapy era (3-10). These techniques often deliver relatively high radiation doses to normal tissue not considered at risk for harboring microscopic or gross tumor. Image guided techniques may allow sparing of these normal tissues. Brachytherapy has also been utilized as a form of adjuvant radiotherapy in these tumor types, most commonly for non-rhabdomyosarcoma soft tissue sarcoma (11). Retrospective reviews of brachytherapy in pediatric patients appear to result in favorable local control rates but prospective data to confirm the benefit of this modality is needed (12). The addition of imaging with CT scans to assist in targeting and planning of brachytherapy cases should enhance the delivery of this local modality. We will test the hypothesis that treatment of pediatric sarcomas with image guided radiotherapy techniques will maintain at least the current levels of local tumor control achieved with conventional techniques, while studying the impact of 3-dimensional, image-guided radiation techniques to potentially decrease radiation-related normal tissue effects.

Patients treated on the RT-SARC protocol currently have local disease control outcomes at 2 years of 89% for patients with rhabdomyosarcoma (13), 94% for patients with soft-tissue sarcomas (14) and 95% for patients with Ewing's family tumors (unpublished data). These data begin to form the basis for local outcome measures with a well defined clinical cohort of patients receiving standardized, focal, limited-volume radiation therapy. Additional patient numbers and follow-up will help this cohort become the benchmark for future prospective focal radiation therapy studies measuring local disease control. Long term local control estimates obtained with 10+ year follow-up (or follow-up into adulthood 18 years of age}) will establish this as a reference dataset for future trials and comparisons.

Treatment related effects secondary to radiation therapy, both during and following treatment, have been a major area of concern relative to the use of therapeutic radiation in children and adolescents. The period of growth during the childhood and adolescent years is primarily responsible for the specific group of radiation related effects seen in children. These effects have often been ascribed to radiation by relating the site of the effect relative to the site of radiation treatment. Most historic information on treatment related effects of radiation is empiric and based on little data. Even in the adult radiation oncology community (where patient numbers are much greater than in pediatrics) definite normal tissue tolerances to radiation are not known (15). Data regarding treatment related effects of radiation on the pediatric patient are very limited and only correlate prescription doses of radiation with basic measurable endpoints (e.g. sitting and standing height or comparisons with normal populations) (16-20)). Prospective data in the pediatric population is noticeably absent. In the era of image guided radiation therapy, true analysis of the effects of radiation at a specific dose delivered to a specific volume may now be conducted. A prospective study in localized pediatric brain tumors conducted at St. Jude (RT-1) has made significant contributions to the understanding of these radiation dose and volume related effects (21,22). Within this study we propose to establish the needed baseline data to relate image guided radiotherapeutic parameters to functional and imaging measures of tissue function. This body of data will then allow meaningful comparisons with new treatment techniques and modalities.

Preliminary analyses from this clinical trial have yielded measures of normal tissue function (either structural, biochemical or functional) that appear to be well correlated with treatment dosimetry and clinical variables (23). As this dataset matures, additional patient cases accrued and more specific imaging implemented we anticipate to further refining the relationship of individual dosimetric features to quantifiable outcomes for normal tissue response. The additional numbers of cases and further specificity of imaging will add strength to our ability to correlate these outcomes.

Late effects of radiation continue to accumulate over time. Long term risks to bone integrity and strength result in fracture, altered bone growth or shape. Changes in soft tissue and organ function also continue to occur and evolve. Their cumulative effect on quality of life is frequently described relative to radiation therapy yet quality estimates do not exist in the context of well-defined dosimetry. Amendment 4.0 will focus on extending the long term follow-up of these patients as the protocol nears complete accrual. We will collect 5+ additional years of follow-up on the long-term survivors of this trial out to adulthood to better define and describe these effects. Imaging requirements will be reduced across the trial to transition this study towards a focus on long-term effect of therapy.

2.2 Image Guided Radiotherapy

Image guided radiotherapy defines a group of radiotherapy treatment techniques that deliver high doses (the prescription dose) of radiation to a specific volume, usually delineated by CT scan or MRI. Relatively lower doses may be incidentally delivered to surrounding normal tissues. Radiation therapy may be described as *image-guided* when four criteria are met: (1) three-dimensional imaging data (CT or MR) are acquired with the patient in the treatment position or brachytherapy catheters are in place, (2) imaging data are used to delineate and reconstruct a gross target volume, clinical target volume, planning target volume,

and normal or critical structures in 3-dimensions; (3) radiation beams can be freely oriented in 3-dimensions for both the planning and delivery process, and structures traversed by the beam can be visualized with the eye of the beam; for brachytherapy planning the activity of sources to be implanted can be freely manipulated to achieve the desired dose distribution; (4) the distribution of dose relative to the target volume or any structure is computable on a point by point basis in 3-dimensional space. Image guided radiotherapy for the purposes of this study include three different delivery systems outlined below. The general differences in each technique and the potential benefits and limitations are noted.

2.2.1 Conformal radiotherapy

The delivery of 3D-conformal radiotherapy (3D-CRT) allows specific targeting of tumor volumes based on imaging studies obtained in the treatment position. This method of external beam radiotherapy delivery utilizes multiple fields or portals delivered daily with shaping of each beam aperture to the tumor volume. Beam modifiers such as wedges are utilized to “conform” and homogenize dose to the tumor volume. Conformal radiotherapy excels when target volumes are convex and critical structures do not invaginate target volumes. Conformal radiotherapy has been aggressively studied in the adult radiation oncology setting in disease sites including head and neck cancer, lung cancer and prostate cancer. Available data demonstrate a decrease in toxicity despite escalating doses to the target volume (23-30). St. Jude has the largest pediatric experience using conformal radiotherapy to treat focal brain tumors in the RT-1 study (31). Current data in this group of patients demonstrates both its safety and efficacy in the CNS setting.

2.2.2 Intensity Modulated Radiotherapy

Intensity modulated radiotherapy or IMRT is another external beam radiotherapy delivery method that requires imaging in the treatment position and delineation of target volumes and critical structures. Dose is delivered to the target with multiple small fields that do not encompass the entire target volume, but summate to deliver the prescribed dose per fraction. IMRT differs from conformal radiotherapy in the following ways: 1) an increase in the complexity and time required for planning and delivery of treatment; 2) an increase in quality assurance work prior to treatment delivery; 3) an increase in dose heterogeneity within the target volume with inherent intralesional areas of relatively high dose; 4) the difference that both subclinical (microscopic) and clinical (gross) target volumes are treated concurrently (rather than sequentially, as in conventional or in 3-D CRT) resulting in daily fraction sizes that may be higher than 200 cGy in some cases; and 5) the ability to treat concave targets while sparing critical structures that invaginate the target volume. The last difference holds promise for increased normal tissue sparing and the potential for reduction in late toxicities. Data from adult series of patients treated with IMRT is becoming available demonstrating its potential for reduction in treatment toxicities when applied to brain tumors, head and neck cancer, lung cancer and prostate cancer (1,30,32,33).

2.2.3 Brachytherapy

Brachytherapy is a method of delivering irradiation to a tumor or tumor bed by placing radioactive sources within or adjacent to the target

volume. This is usually performed at the time of a surgical resection under direct vision. Planning of the dose to be delivered to the target volume is accomplished after surgery and may utilize CT or MRI imaging studies. In following the model of image-guided radiotherapy, target volumes and critical structures are outlined. The appropriate radioactive source strengths are determined by prospective planning of the dose to be delivered to the target volume and critical structures. Unlike the external beam modalities outlined above, brachytherapy (using low dose rate techniques) is delivered continuously over a period of two to five days, usually while the patient is admitted to the hospital. High dose rate brachytherapy (delivered in moderate 3-5 Gy fractions) will also be used as indicated. Benefits of the high dose rate technique are multiple and include: 1) the ability to better shape dose to the target and away from normal tissue, 2) reduced radiation exposure to family members and staff and 3) delivery of therapy as an outpatient reducing the hassle and cost associated with inpatient hospitalization. Experience with both modalities in patients with sarcomas is limited to smaller pediatric series and moderate sized adult trials. We have had experience with this modality in the pediatric setting as a single adjuvant modality and as a boost dose to external beam radiotherapy. Late toxicity data is not as well studied as compared to conformal radiotherapy or IMRT (34-36).

2.3 Tumor Control

Establishing long-term tumor control for pediatric musculoskeletal tumors necessitates a multi-disciplinary treatment approach. Treatment entails local and systemic therapy in specific sequences established through extensive clinical trials. Irradiation is frequently used to treat local or regional tumor. The sequencing of local control measures is typically derived from the tumor type, extent, and anatomic location; radiation therapy may be used post-operatively, pre-operatively, or as the sole local therapy. Similar factors determine whether irradiation is given following and/or concurrently with chemotherapy. Gross tumor or microscopic residual disease following surgery can often be effectively treated with local radiotherapy, as can disease that includes regional nodal involvement. Additionally, many sarcomas are infiltrative tumors with tissue beyond the resected volume at risk for harboring microscopic disease, even in the setting of apparently negative histologic margins. Clinical trials have established the benefits of local/regional radiotherapy including limb preservation, the avoidance of disfiguring surgery, increased local tumor control obviating a second surgery, and increased disease control that often relates to improvement in overall survival (3-7,9-12,34-36).

Local radiotherapy has several requirements to allow the highest chance of success. These are as follows: 1) adequate definition of the target volume including the gross tumor or tumor bed (gross tumor volume or GTV), and tissues at risk for microscopic disease (clinical target volume or CTV); 2) establishment of adequate immobilization of the target (external beam) with an appropriate planning target volume (PTV) to account for organ motion and daily set-up variability; 3) delivery of an adequate dose of radiation to the target volume through appropriate planning and treatment techniques. Deviation from adequate volume definition may risk local failure and overall survival. Tissue definitions and quantitative parameters defining radiation volume parameters have varied from 2-dimensionally derived margins of 2 cm to as much as 5 cm Volume recommendations have only recently included image-guided radiotherapy treatment planning techniques that include CT-based treatment planning with delineation of a three-dimensional target volume (40).

Modifications in quantitative margins have been interposed when natural barriers to tumor spread such as bone or joint-spaces, and sometimes fascial planes define tumor extent. If one utilizes image-guided radiotherapy for the treatment of sarcomas, the volume of tissue requiring high radiation doses usually decreases compared to traditional two-dimensional treatment techniques. Reduction in the high dose volume has potential implications for reduction of radiation-related toxicity, but a potential increased risk of local failure. A major prospective study of image-guided radiotherapy is needed to assess its benefits and ensure that the rates of local control for MST are at least maintained.

2.4 Radiation-Related Tissue Toxicities

Delivery of appropriate radiation dose to the target volume is the first priority in therapy for sarcoma patients. In addition, avoidance of surrounding critical structures is needed to minimize significant late toxicity. While doses required for tumor control are relatively well established, the tolerances of normal tissues in the pediatric population are only estimates. Treatment related side effects for patients with sarcomas treated with radiation therapy include decrease in bone growth, soft tissue fibrosis, muscle hypoplasia, and the “seminal” microvascular changes, which appear to underlie or enhance somatic effects. Radiation-related toxicities may be modified or enhanced by interaction with other treatment modalities, including surgery and chemotherapy. Radiation therapy’s contribution to late somatic changes is related to the dose and volume of radiation and the volume and anatomic location of intervening or adjacent normal tissues. Image guided radiotherapy is ideally suited for the measurement of radiation dose and volume effects on critical normal tissues. Prospective serial evaluations of specific musculoskeletal and vascular functions and their correlation with three-dimensional radiotherapy dosimetry and patient host factors can be uniquely studied in the context of the current clinical trial, allowing quantitative estimates of the relationships amongst radiation dose, volume and musculoskeletal toxicities.

2.5 Outline of Study

This trial is a therapeutic phase II study evaluating local disease control utilizing image guided radiotherapy (3D-CRT, IMRT and/or brachytherapy) to deliver local irradiation to the prospectively defined target volume. CT- and MRI- based treatment planning will be conducted for each patient to treat the GTV, CTV and PTV defined by imaging and/or surgical findings. Treatment plans for an individual patient will deliver the appropriate prescribed dose to the target volume while striving to minimize dose to specific critical structures. High gradients of dose fall-off outside the target volume and modest levels of heterogeneity across the target volume will help minimize unwanted high dose effects on adjacent normal tissues. With this amendment, we will continue to accrue new participants to the study until we reach 210 enrollments. In addition we will extend the follow-up for all patients that were enrolled on the trial out to 10+ years (10 years of follow-up or 18 years of age, whichever is greater) and focus on the long-term local control estimates and radiation dose toxicities. Patients currently in follow up will be offered participation in this amended trial. Participants who are currently off trial due to completing the study requirements are eligible to re-enroll on amendment 4.0. Due to the need for re-enrollment, we will accrue approximately 280 patients to this study. The increase in number will have no effect on statistical outcomes.

Follow-up for this study occurs over a planned 10+ years or until adulthood (18 years of age – whichever is longer) from the start of radiation therapy.

2.5.1 Primary Objectives

Patients with MST will have their target volumes (GTV, CTV and PTV) defined on planning imaging studies with anatomic and geometric margins defined in section 6.3. Target definitions are consistent with active national protocol guidelines when available. Radiation doses are prescribed relative to the PTV and are also consistent with available national protocol guidelines. Local tumor control will be evaluated by clinical exam and imaging studies as defined in section 10.1. Local control rates with image guided radiation therapy will be compared with expected rates of control using traditional techniques for patients with Ewing's sarcoma, resected soft tissue sarcoma and clinical group III rhabdomyosarcoma. Patients with rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma will have further reductions (by 5mm) in their clinical target volume (CTV) margins to remain consistent with national protocols. This group of patients will be monitored separately as well as together with the prior group of patients with RMS and STS for rates of local failure. This plan is outlined in statistical section 12.1. Local control and local/regional patterns of failure will be determined relative to the GTV, CTV, PTV, the volume irradiated to the prescription dose as noted in section 10.6 and primary site imaging parameters. The center or apparent origin of the recurrence will be considered when assigning a pattern of failure (appendix A).

2.5.2 Secondary Objectives

Radiation related toxicities as determined by clinical evaluation, laboratory studies, and imaging will be correlated with the radiation dose and volume delivered to defined normal tissues. Prospective assessment of normal tissue function will be done prior to, during and following radiation therapy.

2.5.2.1 Treatment Effects on Bone

Quantification of radiation effects on bone growth will be made by determining physical alterations in (1) overall standing and, where appropriate, sitting height, (2) specific bone length, (3) relative bone length for paired bones, (4) alterations in bone curvature and cortical bone thickness, and (5) reductions in bone density. Assessment of bone length will be correlated with (1) radiation dose and volume, (2) premature epiphysis closure or partial closure and (3) bone age. Bony effects will be assessed by physical examination, MRI and CT bone densitometry.

2.5.2.2 Treatment Effects on Muscle, End Organs and SoftTissue

Muscle, organ specific and soft tissue treatment effects will be measured by changes in function; alterations in both MR imaging-based signal via multi slice dynamic contrast enhanced MR (DCE MR), multi slice arterial-spin labeled MR (as appropriate), and PET 18F-Fluorodeoxyglucose uptake (by objective – standard uptake values or SUV's and subjective means) in muscle and soft tissue will be quantified. , Functional and quantitative scales, quantitative MRI data, and

PET imaging will be obtained during the study. Changes or assessments will be correlated with radiation dose and the volume subtended by the specific soft tissue or bone included.

2.5.2.3 Treatment Effects on the Vasculature

The changes in microvasculature caused by radiation are well recognized and will be measured by both DCE MR and arterial-spin labeled MR when feasible. Correlations between vascular measurements, the measurable endpoints of bone growth, muscle atrophy and soft tissue fibrosis and the three-dimensional radiation dosimetry will be evaluated in the context of this trial.

2.6 Image Guided Radiotherapy for Pediatric Sarcomas

The implementation of image-guided radiotherapy to treat pediatric sarcomas entails several distinct components. To utilize either 3D-CRT or IMRT, the region to be treated must be immobilized in a position to allow access of treatment beams while ensuring immobilization of the patient during each fraction of treatment and reproducibility of positioning each day of treatment. CT and MRI datasets are obtained in the immobilized position in the axial plane. Datasets are transferred to a treatment-planning computer and co-registered. Target volumes (GTV, CTV, PTV) as well as normal tissues are contoured on the computer based imaging datasets. These contoured structures are thus rendered in three-dimensions for planning purposes. Treatment beams are virtually positioned and shaped from any orientation attempting to avoid entering or exiting critical structures. The relative weights and shapes of beams are either “forward” planned based on experience (3D-CRT), or “inversely” planned using inverse planning algorithms (IMRT). The doses delivered to the target volumes and critical structures are calculated. Treatment plans are evaluated based on delivery of the prescribed dose to the target volume while limiting dose to critical structures. Treatment is then delivered on a daily basis in conventional fractions (1.8-2.0 Gy/fx) to the prescription dose.

Image guided brachytherapy follows a similar treatment planning process with inherent exceptions. Non-radioactive catheters or applicators for radioactive sources are placed under direct vision, typically in the operating suite at the time of tumor resection. CT imaging is obtained following catheter placement for volumetric treatment planning. Target volumes and critical structures are contoured on axial images following transfer of the dataset to a treatment-planning computer. Source type (usually seeds or ribbons of ^{125}I or ^{192}Ir), strengths, and positions along the catheters or applicators are varied to create a treatment plan with appropriate dosimetric coverage of the target volume.

2.6.1 Volume of Treatment for Pediatric Sarcomas

Definition of the appropriate treatment volume for pediatric sarcomas is critical to both maintain current levels of local tumor control yet avoid treating so much surrounding normal tissue to cause excessive late treatment toxicities. Volumes of treatment are specific for each histological type and will be addressed as such.

2.6.1.1 Treatment Volume and Dose in Ewing's family of Sarcomas

The appropriate radiotherapeutic volume of treatment for Ewing's sarcoma was originally felt to be the entire medullary cavity of the involved bone (9,41,42). This question was tested prospectively in POG study 8346 where whole bone radiation to 39.6 Gy followed by treatment field reductions and delivery of an additional 16.2 Gy was compared with treatment to the initial tumor with a 2 cm margin to a dose of 55.8 Gy. No difference in local control was seen between the techniques and the majority of local failures were in the irradiated volume (10). Patients treated on a St. Jude Ewing's sarcoma protocol received radiation to the pre-radiation therapy tumor volume with a 3 cm margin; in only one instance was local failure marginal to the targeted region. (8). Patients with extraosseous Ewing's sarcoma treated on the IRS I, II and III studies showed a local control rate of 89% when complete response to chemotherapy was followed by irradiation with margins of 2 cm beyond the primary tumor or tumor bed (4). Local treatment volumes to the initial bone and pre-radiation therapy soft tissue volume appear to be effective in controlling Ewing's sarcoma family of tumors locally. Limiting margins of normal adjacent tissue at risk for microscopic disease could reduce the risk of treatment related toxicities. Anatomically constrained margins of 1 cm (defined as the CTV) around MRI defined target volumes will be evaluated. The dose of radiation therapy delivery to the primary tumor site has varied by institution and clinical study. Dose reduction based on imaging or histologic response has met with limited success in achieving rates of local tumor control equivalent to surgical resection (8,64). Doses of radiation therapy in the range of 5040 cGy for patients with microscopic residual disease and 5580 cGy for patients with gross residual disease appear to achieve local tumor control rates in excess of 80% (64,65). Patients with gross residual disease and initial tumor volumes of 8cm or greater have local failure rates of 40% or greater. Delivery of an adequate dose of radiation therapy prior to the IGRT era has been limited by dose constraints of surrounding normal tissues. IGRT techniques including intensity modulated radiation therapy allow delivery of therapeutic doses of irradiation while protecting adjacent normal tissues. Patients with unresected or incompletely resected ESFT will receive 6480 cGy delivered to gross disease.

2.6.1.2 Treatment Volume and Dose in Rhabdomyosarcoma and Small Round Blue Cell Undifferentiated Sarcoma

Rhabdomyosarcoma has been approached with systematic radiotherapy in the vast majority of patients treated in the United States. Treatment has primarily been delivered according to guidelines within the serial Intergroup Rhabdomyosarcoma Studies. On these studies, local control rates have been well defined with a low incidence of marginal failure. Local control rates have ranged from 75% to 85% (6-7,35). Radiotherapeutic margins have included a treatment

volume of 2 cm around the gross tumor volume or tumor bed. Doses recommended have been protocol specific and varied by the degree of prior surgery. Experience from the IRS studies and other institutional series demonstrates that microscopic residual tumor in the tumor bed (margin negative or margin positive surgery) is almost systematically controlled with radiotherapy doses in the range of 3600 to 4140 cGy (7,35,43). Gross disease has been controlled in >80% of cases with doses of 5040 cGy (5,6).

2.6.1.3 Treatment Volume and Dose in Soft Tissue Sarcoma (excluding RMS and EOE)

Soft tissue sarcoma (STS) is frequently managed with radiation therapy (either brachytherapy or external beam radiotherapy) following surgical resection. Local control rates have been high with either modality alone or in combination. Traditional views on the appropriate margin of normal tissue to include when treating STS have ranged from a 2-5 cm margin to the entire muscle compartment. Larger field irradiation ($\geq$5 cm margin) is supported by older series with less precise imaging (44-45). A University of Chicago retrospective series utilizing external beam radiotherapy suggests a clinical margin below 5 cm may compromise local control (46). Conventional target volume definitions do not directly translate to conformally defined target volumes using the paradigm of GTV, CTV and PTV. Brachytherapy techniques, where tissues at risk are rigorously defined intra-operatively, document control rates for adult STS of 89% with margins of 2 cm beyond the surgically defined tumor bed (11-12). Benefits to minimizing treatment volume in STS are most critical as doses required for local tumor control are high and may be associated with significant late somatic effects. Experience from randomized studies of external beam radiotherapy and brachytherapy, as well as retrospective institutional series demonstrate that microscopic residual tumor in the tumor bed (margin negative or margin positive surgery) may be controlled with external beam radiotherapy doses in the range of 6300 – 6660 cGy or low dose rate brachytherapy doses of 4200-4500 cGy (3-4,11-12,45-48). Gross disease has been treated with doses of 7000 cGy or more with relatively poor long-term control (7).

2.7 Radiation Related Tissue Effects

Models and Mechanisms for Radiation Effects

Radiation-related normal tissue effects are the result of complex interactions involving somatic or visceral cell types and the surrounding cellular matrix. Tissues may have individual response profiles to radiation, but respond differently *in vivo* where they interact with other regionally affected and unaffected tissues. Adverse responses *in vivo* may be ameliorated where adjacent tissues provide the necessary environment for repair of acute and late

effects. Conversely, surrounding tissues may promote a cascade of events that further enhance regional tissue injuries. Direct effects of radiotherapy are seen on growing individual tissues that result in the depopulation of specific cells necessary for growth. Such a direct effect may be responsible for changes in the bony physes resulting in decreased or asymmetric long bone growth. The time of apparent “acute” or “late” effects of treatment relate to the rapidity of depopulation of the respective tissues, based most often on the timeframe of stem cell turnover. Indirect or regional tissue effects may occur in several theoretical ways. When multiple tissue-related injuries occur in a given region, the effect upon an individual tissue often reflects both tissue-specific stem cell depopulation and disruption of the regional support structure (microvascular injury, regional inflammation) further injuring normal tissues. Whether by direct or indirect effect, the complex normal tissue response to radiation is only beginning to be understood, and this complexity is greater in pediatric patients with developing normal tissues.

2.7.1 Bone Growth

Changes in growing bone are clinically evident following radiotherapy at doses below tumoricidal levels. The exact mechanism is not fully understood but likely involves depopulation of chondrocytes located in the epiphysis of long bones and below the periosteum in flat bones. The effects of radiation on the process of bone growth appear to have a dose and spatial or volume based component. Clinically evident effects are seen in children treated with conventional techniques to doses above 20 Gy, particularly in prepubertal patients (10,46-50). Kyphosis, lordosis and scoliosis are also seen following radiation to doses above 30-36 Gy. These curvatures may be secondary to inhomogeneous irradiation of the spine (i.e. non-uniform effects on the paired vertebral epiphyseal centers) and/or changes in the adjacent muscle secondarily affecting spinal growth. Full understanding of changes in bony growth are hampered by the retrospective nature of earlier studies, often relying on available plain films and measurements of sitting and standing height; these endpoints are correlated with retrospective estimates of dose delivered to the physis. Rarely is pretreatment bone age known for these patients. Assessments of bone densitometry are rarely obtained at the treated site using QCT. Understanding the direct biochemical alteration initiated by radiation therapy and its geometric relation to dosimetry for the first time may provide insight to a mechanism for injury. The patient will be used as their own control for this quantitative assessment. Adequate assessment of radiation bone growth effects requires prospective baseline and serial clinical and imaging evaluations correlated with clinical factors including other therapies (surgery and chemotherapy) and age of the patient at the time of treatment. When correlated with specific radiation dosimetric parameters, recognition of other impacting factors may lead to a greater understanding of the etiology of bony growth changes following radiation and potentially increase the likelihood of ameliorating such effects in the future.

2.7.2 Muscle, Adjacent Organs, and Soft Tissue

The pathophysiology of radiation-related changes in muscle, organs and soft tissue are poorly understood. The clinical manifestations of treatment to doses ranging from 50-60 Gy range from fibrosis to atrophy, and often result in diminished physical function (51). Anecdotal experiences in young children suggest doses at or below 20 Gy are

associated with readily discernible soft tissue alterations. Correlations have been evaluated in patients treated for breast cancer using breast conservation surgery followed by breast irradiation. Relationships have been established between radiation parameters (dose delivered to the intact breast and the volume receiving high dose radiation) and clinical cosmetic scores (52). Measurement of tissue compliance has also been used as an objective documentation of superficial fibrosis. Though not specific for a given tissue type, this technique appears to be a simple, method for determining changes in soft tissue compliance consistent with subjective grading of fibrosis (53). Evaluations of the available data suggest that the variability of site contains as much error as the ability to measure fibrosis. We will discontinue collecting tissue compliance with this amendment (amendment 5.0) and report the outcomes for the available data.

Muscle atrophy is a clinically evident phenomenon seen following radiotherapy to the soft tissues. (54). Treatment results in decreased development of major muscle groups in some patients. Correlations with radiotherapy dose and volume have been poorly defined, but this treatment effect appears to occur following large volume radiotherapy delivered to higher doses. The resultant functional effects of decreased strength and mobility are not documented. Incorporation of validated functional scales and assessments of quality of life related to function will provide needed data on the long term effects of specific dosimetric parameters. Relation of the outcome measures to radiation dosimetry through mathematical models will further our understanding of these effects and how they may be avoided in the future. Elucidation, through prospective evaluation, of possible factors affecting the formation of fibrosis, muscle atrophy and functional changes may allow improved treatment approaches with reduction of these effects in the future.

The study of basic functional changes, determined from standard imaging, clinical testing or functional scales, in individual irradiated organs is key to defining normal tissue tolerances as we move forward with increasingly conformal radiation modalities and techniques. We will continue to collect information about these toxicities and related them to dosimetry and clinical characteristics as patient numbers and organ exposure allow.

2.7.3 Vascular Changes

Tissue microvasculature and some macrovasculature are affected by radiation. Radiation induced endothelial cell proliferation and endothelial cell loss may result in thrombosis of capillaries and arterioles (17). Larger vessel injury has been reported in patients irradiated for parasellar central nervous system tumors (Moyamoya syndrome) (55), but has not been documented in the irradiation of other larger vessels. Radiation induced vascular changes may not be the primary pathophysiologic event responsible for late tissue effects, but in conjunction with direct visceral and somatic effects of radiation may further promote late treatment events.

Radiation related tissue effects on the musculoskeletal system among pediatric patients have been mostly anecdotal in nature. The available studies with specific musculoskeletal measurements evaluate a limited number of variables retrospectively and lack correlation with volumetric

dosimetry utilized in image-guided radiation therapy, required for accurately assessing radiation related treatment effects. Historic data reported in the literature lacks paired datasets with measurements of the contralateral untreated side, serial studies to adequately delineate the time course of treatment related effects and specifically designed imaging studies to assess effects on the musculoskeletal system. Within the context of this study these variables will be assessed in a prospective manner to establish a baseline for radiation related treatment effects with image-guided radiation therapy. From this protocol we hope to generate objective functions to describe the probability and/or severity of the above listed treatment effects based on radiotherapeutic dose, volume and pretreatment clinical factors. This paradigm has been established at St. Jude in the RT-1 protocol for localized pediatric brain tumors. Specific subjective and objective measurements are listed in table 2.7 below.

Table 2.7

	Measurement	
Evaluation	Objective	Subjective
Clinical		
Physical Examination	Sitting/standing height	Musculoskeletal/Radiation CTC
PT/OT		
Functional Evaluation	Measurements of tissue bulk Range of motion Bone length (when available)	Strength
Specific functional scales:		
DASH	Upper extremity function	
TESS	Lower extremity function	
U. of Wash. QOL	H&N function	
Diagnostic Imaging		
Standard of care imaging		
qCT Densitometry	Treated bone density Bone strength	

3.0 Drug Information – Drug therapy is given on concomitant chemotherapy protocols or a best clinical management plan.

4.0 Patient Eligibility

4.1 Age $\leq$ 25 years (new enrollments only). No age limit on participants who reconsent or reenroll.

4.2 Musculoskeletal tumor involving the primary site of origin requiring curative definitive, pre-operative or post-operative irradiation to that primary site.

4.3 No prior therapeutic irradiation at the primary site except for emergent radiation to the primary site lasting 1 week or less (5 treatment days) that can be dosimetrically accounted for in the analysis.

4.4 Negative serum or urine β-HCG for females of child bearing age (not applicable for reconsents and reenrolled females)

4.5 Patients will be stratified into 2 groups for evaluation of secondary objective endpoints based on the absence or presence of metastatic disease.

Patients may enter this study in specific clinical situations often defined by multimodality protocols that include the use of radiation therapy, including irradiation alone or combined with surgery (following surgical resection that may be macroscopically complete or incomplete, with positive or negative histologic margins) and/or chemotherapy (following neoadjuvant chemotherapy or combined with post-irradiation adjuvant chemotherapy). Patients requiring regional nodal irradiation and/or metastatic site irradiation are allowed as long as the primary site requires radiation. Patients with recurrent tumors or second malignant neoplasms are allowed on this study if the current primary tumor site requiring irradiation has not previously been irradiated. The treatment plan detailed in this study will allow most patients to be concurrently enrolled on institutional and COG studies.

Patients enrolled prior to amendment 4.0, who are still in active participation will be reconsented to the current version of the protocol (4.0). Patients off-study due to completion will be reenrolled on protocol version 4.0 to complete the 7/8 year, 10/11 year and adulthood (18 years of age) requirements. All patients will now follow the same follow-up schedule and procedures as outlined in Table 8.1.

5.0 Treatment Plan

5.1 Overview

Eligible patients will be accessioned at the time of irradiation and undergo a pre-radiotherapy evaluation, treatment planning, image-guided radiotherapy delivery and intra- and post-irradiation evaluations. Imaging studies obtained for other clinical protocols or routine clinical management may be accepted for use prior to, during or following radiation therapy on this study. Table B1 (appendix B) indicates which studies are considered “standard of care” and which are for research purposes only.

Table 5.1
Treatment Planning and Evaluation Schedule for All Patients

Evaluation Schedule	Pre-IGRT[1]	week 1	week 2	week 3	week 4	week 5	week 6	week 7
Clinical								
Physical Examination	X	X[2]	X	X	X	X	X	X
Physical / Occupational Therapy								
Functional Evaluation	X	X[1]	-	-	-	-	X[3]	-

[1] Pre-IGRT includes the interval of time 4 weeks prior to the initiation of treatment. Studies for determination of metastatic disease do not need to be repeated if done at diagnosis. Note for patients receiving brachytherapy only, functional evaluation, MRI and PET imaging will follow catheter removal during week 1 in place of Pre-IGRT imaging

[2] Sitting and standing height only need to be obtained prior to radiation therapy as tolerated by patient. No measurements of height are recorded during irradiation

[3] At or following the completion of radiation therapy

6.0 Radiation Therapy

6.1 Equipment for treatment delivery

External beam

6.1.1 Megavoltage linear accelerators utilizing 6MV to 21MV photon energies as well as 4 MeV through 21 MeV electron energies
6.1.2 Multileaf collimator or cerrobend block shaped fields
6.1.3 Immobilization devices for daily positioning for treatment

Brachytherapy

6.1.4 Interstitial catheters, custom molds or intracavitary applicators
6.1.5 Iodine-125 or Iridium-192 low dose rate or high dose rate sources

6.2 Techniques for radiation therapy treatment

External beam

6.2.1 Multiple static field conformal techniques with single or multiple field segments
6.2.2 Weekly portal imaging
6.2.3 All fields treated daily

Brachytherapy

6.2.4 Low dose rate or high dose rate source loadings with equal weight or variable weight sources
6.2.5 Transverse or longitudinal interstitial catheter placement
6.2.6 Low dose rate source loading for interstitial brachytherapy on the fifth post-operative day or later

6.3 Radiotherapy Volume and Dose

The gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) will be delineated for each patient on a treatment planning imaging study (CT with or without MRI) prior to planning treatment. The larger PTV (PTV-1) should be treated first followed by the smaller PTV (PTV-2). The appropriate margins for these volumes are outlined as follows:

6.3.1 Ewing's family of tumors

6.3.1.1 Definitive radiotherapy (no surgical resection)
GTV1 – Visible gross tumor consisting of bone initially involved with tumor and soft tissue contiguous with the initial tumor prior to radiotherapy (usually post-chemotherapy) defined by physical exam and imaging studies.

CTV1 – This target volume consists of GTV1 with a 1.0 cm anatomic margin of tissue, respecting anatomic barriers that limit tumor spread.

PTV1 – CTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.
PTV2 - GTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.

6.3.1.2 Post-operative radiotherapy (following surgical resection)

GTV1 – The surgical tumor bed consisting of the margin of bone initially involved with tumor and soft tissue contiguous with the tumor prior to surgical resection as defined by physical exam, imaging studies, operative notes, and pathology reports.

CTV1 – This target volume consists of GTV1 with a 1 cm anatomic margin of tissue, respecting anatomic barriers that limit tumor spread.

PTV1 – CTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.

6.3.1.3 Brachytherapy (limited to use in soft tissue Ewing's family of tumors)

GTV1b – The surgical tumor bed defined by intraoperative examination and preoperative imaging studies

CTV1b – This target volume consists of GTV1 with a 1 cm lateral margin and a 2 cm proximal and distal margin relative to the long axis of the tumor for interstitial approaches. For intracavitary and surface brachytherapy applications a margin appropriate for the tumor site and presentation, usually 1-2 cm is recommended.

No PTV exists for brachytherapy procedures.

6.3.2 Rhabdomyosarcoma and small round blue cell undifferentiated sarcoma

6.3.2.1 Definitive radiotherapy (no surgical resection)

GTV1 – Visible gross tumor including initially involved soft tissue prior to biopsy or therapy as defined by physical exam and imaging studies.

CTV1 – This target volume consists of GTV1 with a 1 cm anatomic margin of tissue, respecting anatomic barriers of

tumor spread, and regional areas of nodal involvement warranting irradiation.

PTV1 – This volume includes the CTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.

PTV2 – This volume includes the GTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.

6.3.2.2 Post-operative radiotherapy (following surgical resection)

GTV1 – The post-operative tumor bed consisting of the initially involved soft tissue contiguous with the initial tumor prior to any therapy as defined by physical exam and imaging studies.

CTV1 – This target volume consists of GTV1 with a 1 cm anatomic margin of tissue, respecting anatomic barriers of tumor spread, and regional areas of nodal involvement warranting irradiation.

PTV1 – This volume includes the CTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.

6.3.2.3 Brachytherapy

GTV1b – The surgical tumor be defined by intraoperative examination and preoperative imaging studies CTV1b – This target volume consists of GTV1 with a 1 cm lateral margin and a 1 cm proximal and distal margin relative to the long axis of the tumor for interstitial approaches. For intracavitary and surface brachytherapy applications a margin appropriate for the tumor site and presentation, usually 1-2 cm is recommended.

No PTV exists for brachytherapy procedures.

6.3.3 Non-rhabdomyosarcoma soft tissue sarcoma (STS)

6.3.3.1 Definitive radiotherapy (no surgical resection) or pre-operative radiotherapy*

GTV1 – Visible gross tumor including initially involved soft tissue prior to biopsy or therapy as defined by physical exam and imaging studies.

CTV1 – This target volume consists of GTV1 with a 1.5 cm anatomic margin of tissue, respecting anatomic barriers of tumor spread.

PTV1 – The CTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.

6.3.3.2 Post-operative radiotherapy (following surgical resection)

GTV1 – The post-operative tumor bed consisting of the initially involved soft tissue contiguous with the initial tumor prior to any therapy as defined by physical exam and imaging studies.

CTV1 – This target volume consists of GTV1 with a 1.5 cm anatomic margin of tissue, respecting anatomic barriers of tumor spread.

PTV1 – This volume includes the CTV1 with a treatment site and immobilization device specific margin for target motion and daily treatment set-up variation, usually 5 - 10mm.

6.3.3.3 Brachytherapy

GTV1b – The surgical tumor be defined by intraoperative examination and preoperative imaging studies

CTV1b – This target volume consists of GTV1 with a 1 cm lateral margin and a 1.5 cm proximal and distal margin relative to the long axis of the tumor for interstitial approaches. For intracavitary and surface brachytherapy applications a margin appropriate for the tumor site and presentation, usually 1-2 cm is recommended.

No PTV exists for brachytherapy procedures.

6.3.4 Other musculoskeletal tumors

6.3.4.1 Patients receiving radiotherapy for osteosarcoma will receive radiotherapy according to the volumetric and dosimetric guidelines given for Ewing's sarcoma given in section 6.3.1 and table 6.3.1. Patients receiving radiotherapy for other musculoskeletal tumors will receive radiotherapy according to the volumetric and dosimetric guidelines given for soft tissue sarcomas given in section 6.3.3 and table 6.3.3.

The radiation dose will be prescribed to the ICRU reference point, with the target volume minimum and maximum doses being recorded.

Total radiation doses recommended are disease specific and are designed to be consistent with current and proposed institutional and national protocols.

Table 6.3.1

Ewing's sarcoma family of tumors*

	Volume Dose	Cumulative Dose

Definitive radiotherapy		
Primary tumor <8cm		
PTV1 (GTV1 + CTV1)	4500 cGy	4500 cGy
PTV2 (GTV2)	1080 cGy	5580 cGy
Primary tumor ≥ 8cm		
PTV1 (GTV1 + CTV1)	4500 cGy	4500 cGy
PTV2 (GTV2)	1980 cGy	6480 cGy
Post-operative radiotherapy		
PTV1 (GTV1 + CTV1)	5040 cGy	5040 cGy
Post-operative brachytherapy and External beam radiotherapy		
CTV1b (brachytherapy)	1500 – 2500 cGy	1500 – 2000 cGy
PTV1 (GTV1 + CTV1 + CTV1b)	4500 cGy	6000 – 7000 cGy

Table 6.3.2

Rhabdomyosarcoma and undifferentiated sarcoma**

	Volume Dose	Cumulative Dose
Definitive radiotherapy		
PTV1 (GTV1 + CTV1)	3600 cGy	3600 cGy
PTV2 (GTV2)	900 – 1440 cGy	4500 – 5040 cGy
Post-operative radiotherapy		
PTV1 (GTV1 + CTV1)	3600 cGy	3600 cGy
Post-operative brachytherapy		
CTV1b (brachytherapy)	2100 cGy (7 fxn BID)	2100 cGy

Table 6.3.3

Soft tissue sarcoma*

	Volume Dose	Cumulative Dose
Definitive radiotherapy		
PTV1 (GTV1 + CTV1)	6600 – 7000 cGy	6600 – 7000 cGy
Pre-operative radiotherapy		
PTV1 (GTV1 + CTV1)	4500 - 5580 cGy	4500 - 5580 cGy
Post-operative radiotherapy		
PTV1 (GTV1 + CTV1)	5580 - 6300 cGy	5580 - 6300 cGy
Post-operative brachytherapy and external beam radiotherapy		
CTV1b (brachytherapy HDR)	1350 cGy (3 fxn BID)	1350 cGy
PTV1 (GTV1 + CTV1 + CTV1b)	4500 – 5040 cGy	5850 – 6390 cGy
Post-operative brachytherapy		
CTV1b (brachytherapy)	3400 cGy (10 fxn BID)	3400 cGy

* Patients receiving radiotherapy for osteosarcoma and other musculoskeletal tumors will receive radiotherapy according to the volumetric and dosimetric guidelines given for Ewing's sarcoma and soft tissue sarcomas respectively.

** RMS dose based on tumor group and stage at diagnosis and immediately prior to radiation defined in section 6.3.2

The daily radiation fraction size will be 1.8 Gy once daily, with the exception of cases treated with intensity modulation where the microscopic and gross tumor volumes are treated concurrently. In this situation the microscopic tumor daily dose shall be no less than 170 cGy per day.

Brachytherapy cases will be treated with high dose rate techniques where the prescription isosurface will cover the tumor bed (CTV1b) and be delivered at 300-340 cGy per fraction delivered BID.

6.4 Immobilization and Patient Positioning

Positioning of the patient for daily radiotherapy will be disease site and patient specific. Devices such as alpha-cradles, aquaplast and vac-lock treatment bags will be utilized to ensure daily reproducibility of set-up between 5-8 mm. Isocenter marks will be made on the patient and immobilization device; treatment table position and source to skin distance (SSD) will be noted for each patient and used daily for patient set-up.

6.5 Simulation and Treatment Planning

Simulation will consist of orthogonal simulation radiographs and CT scan in the treatment position or CT simulation on a CT simulator. These CT images and other imaging modalities (MRI) are transferred to a treatment-planning computer and undergo co-registration (image fusion) to define the treatment planning study set. Outlines of normal tissues and target volumes are created on axial, sagittal coronal, or any arbitrary plane within the study set. All targets and structures must define a three dimensional polygon and follow the target volume conventions previously (GTV, CTV and PTV) or describe a specific normal tissue structure. Normal tissues contoured may include (but are not limited to) the epiphysis, physis, metaphysis, cortical bone including long or flat bone, and individual muscle groups.

Treatment plans will be generated by a cooperative effort between medical physics and the responsible radiation oncologist. Brachytherapy catheter placement will follow the guidelines described by MSKCC (11). The most appropriate set of treatment beams, dose constraints or source activities will be evaluated for three-dimensional conformal, IMRT and brachytherapy treatment plans respectively. Plans will be evaluated subjectively by review of isodose distributions and objectively by review of dose-volume histograms. The most appropriate plan will be selected by weighing the benefits and complexities of target coverage, normal tissue sparing, dose heterogeneity and complexity of delivery. Guidelines for these parameters are as follows:

6.5.1 Target coverage – 95% of the PTV should be covered by 95% of the prescribed dose (note PTV excludes the contained CTV, i.e. PTV-CTV). In the case of brachytherapy treatment plans 100% of the CTV must receive 95% of the prescribed dose.

6.5.2 Normal tissue doses – Normal tissues should be treated to as low a dose as possible while maintaining adequate target coverage. Exceptions to mandating complete target coverage should be made in the case of critical structures such as spinal cord (limited to 4500-5000 cGy), large volumes of bowel (limited to 4500 cGy), excessive volume of lung, etc.

6.5.3 Dose heterogeneity – For 3-D conformal and IMRT treatment plans no more than 15% of the combined GTV, CTV and PTV volume may exceed 115% of the prescribed dose. For brachytherapy plans dose heterogeneity is anticipated and dose to 5% of the target volume (CTV) will be recorded.

6.5.4 Treatment plan complexity – As treatment plans allow more conformal delivery of radiation to complex target volumes, delivery times and delivery complexity will increase. No objective criteria exist for judging treatment plan complexity, but a less complex plan may be preferable if consistent and reliable delivery is better achieved.

6.6 Treatment Delivery

Following completion of treatment planning, the patient will return and undergo verification of position and individual treatment beams. After correct localization of the patient on the treatment couch, radiation therapy will commence. All fields are treated daily at the prescribed dose and fractionation scheme outlined in tables 6.3.1, 6.3.2, and 6.3.3. Localization images are obtained weekly or more often for accuracy of patient positioning. For brachytherapy treatments, following treatment planning, radioactive sources are ordered and catheter placement is again verified, either clinically or radiographically if indicated.

6.7 Treatment Related Effects of Radiation

6.7.1 Radiotherapy related treatment effects are both location- and time-dependent and clearly related to the dose delivered to specific organs or structures. Effects are divided into acute reactions, early delayed reactions and late reactions divided by arbitrary time periods indicated below.

6.7.2 Acute reactions (during radiotherapy): Hair loss, errythema of skin, desquamation, edema of soft tissues,

6.7.3 Subacute reactions (6 weeks to 3 months after irradiation): Soft tissue edema

6.7.4 Late reactions (more than 3 months after irradiation): Fibrosis of soft tissues including muscle, injury to muscle or bone, including changes in bone growth, and changes in tissue vascularity.

7.0 Pretreatment Evaluations

Pretreatment evaluations consist of examinations of physical function, and imaging studies. These studies will also be obtained during and following completion of delivery of radiation (table 5.1, 7.1). Imaging studies obtained pretreatment and during the follow-up period are designed to concur with national and institutional studies.

7.1 Evaluations of Physical Function

Analytic evaluations of physical function will be obtained in conjunction with the departments of physical and occupational therapy as well as consultation with orthopedic surgery. Evaluations will be made post surgery and prior to irradiation for patients undergoing external beam radiotherapy. For patients who will

receive brachytherapy with or without external beam irradiation an additional evaluation will be obtained prior to surgery. General information regarding height (sitting and standing), weight, and limb length or muscle bulk will be obtained, as relevant. All evaluations use quantitative subjective scales or absolute measurements and include the contralateral unirradiated side if relevant. Assessments are sequential in nature to develop data regarding the time course of specific treatment related effects. Specific instruments of physical function are included in appendix C. The scope of such evaluations will include information regarding range of motion, muscle tone and strength specific to the muscle groups and joints to be irradiated.

7.2 Diagnostic Imaging

7.2.1 Magnetic Resonance Imaging

Magnetic resonance imaging beyond the standard of care (RTSARC MRI) will no longer be used in the trial in new patients or those currently on study. The section below will be left in place as a reference for the patient data collected prior to this amendment.

Magnetic resonance imaging (MR) will be used for all patients enrolled on study unless implanted metallic objects preclude its use in which case a diagnostic CT study will be used. The specific MRI sequences required for this protocol are outlined in appendix D and are appended on to the site specific MR imaging protocol. Dynamic contrast enhanced MR (DCE-MR) has been applied to evaluate tumor response and necrosis in patients with osteosarcoma. This technique delineates rate of contrast leakage for specified regions of tissue, which provides imaging based objective measurements of microvascular changes in both adjacent normal tissue and intact tumor (if present). Arterial spin labeling also evaluated vascular flow and density in sites were it is applicable. Both DCE-MR and arterial spin labeling MR will be applied when feasible though certain anatomic sites such and chest wall may not be imaged with these techniques due to the effects of motion and technical limitations of the sequence

Anatomic measurements of the primary tumor, muscle volume, bone length, cortical thickness and physis closure will be made with multi-slice axial coronal and sagital imaging acquired with the typical clinical sequences (e.g T1 fat saturation VIBE, Flash,or MPR Rage techniques). Tumor measurements will be made using a unidimensional maximal diameter. All measurements, including those of bone length, volume, muscle volume and quantitative MR parameters will be obtained following post imaging processing of MR datasets at the time of analysis.

7.2.2 Positron Emission Tomography (PET)

PET imaging beyond the standard of care will no longer be used in this trial in new patients or those currently on study. The section below will be left in place as a reference for the patient data collected prior to this amendment.

PET scans will be obtained of the whole body following administration of 18F-Fluorodeoxyglucose (FDG) per standard imaging protocols. PET-FDG evaluates glucose uptake (and most often its metabolism) into tissues. This form of functional imaging is becoming more prevalent and

its application to pediatric oncology is promising. Currently, little data exist regarding the application of PET to pediatric patients with musculoskeletal tumors. Following surgical resection PET may better define the region at high risk for residual disease prior to radiation. In intact tumors PET obtained serially before and after radiation may define functional radiotherapeutic response and its clinical significance.

Normal tissue imaging with PET has usually occurred in the brain when functional neuro-imaging studies are desired. Extracranial assessment of normal (non-tumor) tissues is not well studied. PET-FDG may provide information about normal tissue metabolism following radiation.

A PET-FDG requires the administration of radioactive labeled glucose. The amount of radiation given for one PET scan is about one-third of the yearly limit for radiation workers (physicians, nurses, scientists) over the course of one year. Four PET scans are scheduled during this study. These imaging studies are encouraged but optional. The PET-FDG studies are optional; the patient or their guardian may decline any or all PET imaging studies.

7.2.3 QCT Bone Densitometry

Bone densitometry will be obtained using QCT at years 7 or 8, 10 or 11 of follow-up and at age 18 (if year 10 is earlier). This study may be performed at the same time as a QCT obtained to document / investigate bone loss due to systemic therapy. The entire treated bone or bone adjacent the treatment site will be identified and imaged in its entirety. This will allow assessment of bone density within and outside the high dose radiation regions (hypothesized to alter bone density). Correlations will be made between bone density and radiation dose. There may be limits of applying the QCT technique to whole bone imaging outside of long bones. Complex bony structures such as the face may have limited applicability of this technique, while adjacent bones such as vertebral bodies would be more appropriate. In these cases the P.I. will review the patient’s initial dosimetry from their radiation therapy treatment plan and consult with Dr. Kaste or her designee regarding the use of QCT.

The axial images of the entire bone will also be utilized to assess bone growth over the 10-year follow-up period and into adulthood (18 years of age) compared with the initial study MR and / or CT simulation study. Models of long-term bone growth will be generated based on this data.

QCT studies inherently deliver a small dose to the patient in order to obtain density information regarding the bone. Typical QCT studies would image one or more lumbar vertebral bodies or a portion of a long bone, but not the entire bone. For this study we are requiring the entire bone to be imaged to fully study the effects of radiation on these bones, including understanding its effect on growth, correlation with risk of fracture due to decreased bone density, as well as overall bone health. This could entail imaging the radius, a vertebral body, rib or tibia. All of the sites would have potentially different effective radiation exposures for the patient. Though there is some clinical benefit to this procedure, we obtained radiation phantom base dose estimates (in conjunction with Dr. Chia-ho Hua, Radiation Oncology Physics faculty and Dr. Sam Brady, Diagnostic Imaging Physics) for a number of possible scenarios in order to better assess the risk-benefit ratio to the patient. This information is

attached in appendix E. In brief, imaging of the upper arm, which would also likely expose a portion of the thorax, would result in the highest exposure to the patient. Our phantom measurements of a 10 year old and adult aged patient yielded exposures of 2.2 and 2.3 mSv respectively. This is significantly lower (by 67% and 72%) than our typical exposures from diagnostic quality scan protocols (yielding 7.5 and 9 mSv, respectively).

8.0 Evaluations During the Follow-up Period

These studies are identical to the pretreatment evaluations. The timing of these evaluations is outlined in table 8.1 for all patients. Imaging studies obtained pretreatment and during the follow-up period are designed to concur with national and institutional studies. Exceptions to the below schedule will be made at the discretion of the principal investigator. Table B2 (appendix B) indicates which studies are considered "standard of care" and which are for research purposes only.

Table 8.1

Evaluation following initiation of Radiation Therapy for All Patients

Evaluation	Months after Initiation of Radiation Therapy*											@18 years of age
	3	6	9	12	18	24	36	48	60	84/96		
Clinical												
Physical Examination	x	x	x	x	x	x	x	x	x	x		x
PT/OT												
Functional Evaluation	x	x	x	x	x	x	x	x	x	x	x	x
Site Specific Functional Scales	-	-	-	-	-	-	-	-	-	x	x	x
Diagnostic Imaging												
QCT	-	-	-	-	-	-	-	-	-	x	x	x

* Exceptions to the evaluation scheme will be made at the discretion of the principal investigator when clinical or logistical considerations preclude protocol-timely evaluation. Patients that are not seen at the 84 month time point will be evaluated at the following year's clinical visit (approximately 96 and 132 months).

9.0 Toxicity Monitoring

Toxicity will be monitored and graded at each visit for the musculoskeletal system and the bone, joint, skin and subcutaneous tissue sections of the late radiation morbidity scoring system according to the NCI Common Toxicity Criteria v2.0. Toxicity grades will be determined by the treating radiation oncologist at each follow-up evaluation utilizing the pertinent patient history, physical exam and imaging studies to assess grades.

9.1 Reporting Adverse Experiences and Deaths

Principal investigators are responsible for promptly reporting to the IRB any adverse events that are unanticipated, serious, and that may represent potential harm or increased risk to research participants. When an unanticipated death occurs, the PI should report it to the Director of the Office of Human Subjects' Protection immediately, [redacted]

A reportable event entry into TRACKS should follow within 48 hours. Serious, unanticipated, and related or possibly related events must be reported within 10 working days. At the same time, the investigator will notify the study sponsor (NIH or pharmaceutical company), cooperative group, and/or the FDA, as appropriate. To report adverse events in gene therapy trials, investigators should use specific RAC forms found at http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc .

The principal investigator is responsible for reviewing the aggregate toxicity reports and reporting to the IRB if the frequency or severity of serious toxicities exceed those expected as defined in the protocol or based on clinical experience or the published literature. Any proposed changes in the consent form or research procedures resulting from the report are to be prepared by the study team and submitted with the report to the IRB for approval.

The following definitions apply:

A serious event refers to any event in which the outcome is fatal or life-threatening, results in permanent disability, causes inpatient hospitalization or prolongs existing inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

An unanticipated adverse event refers to those not identified in their nature, severity, or frequency in the current risk documents (e.g., investigator's brochure), or consistent with the investigational plan.

The following are considered reportable: Any injuries, serious event or other unanticipated adverse events involving risk to participants or others which occur at a frequency above that considered acceptable by the investigators and the IRB. (FDA) As described in 4.3 above, the OHSP Director or designee performs the initial review of unanticipated problems or serious adverse event reports. Internal reports of events that are unanticipated, serious, and related or possibly related to study interventions or procedures are then forwarded to the IRB Chair or designee and if necessary, referred to the full IRB. Based on the frequency and seriousness of adverse events, the IRB Chair or Committee may deem it necessary to suspend or terminate a research study or studies.

10.0 Criteria for Response, Treatment Failure and Sites of Failure

Response to local therapy will be evaluated by history, physical exam and imaging studies as indicated in table 8.1. Additional evaluations will be at the discretion of the treating physicians as warranted by the clinical situation. Response will be determined serially prior to radiation therapy and at each follow-up evaluation. The designation of response is measured relative to initial imaging and physical examination for the current course of treatment (i.e. imaging at diagnosis or imaging at recurrence prompting treatment on this study).

10.1 Local Failure

Local Failure – Tumor recurrence or progressive disease by imaging or biopsy that falls within the original clinical target volume (CTV) is classified as a local failure counting as an event against tumor control. This can be accomplished by comparing the location of the recurrence by image fusion or direct measurement with the image guided radiotherapy target volumes. Patients that have a positive biopsy at the primary tumor site will be classified as a local failure only if the positive biopsy results in a change in therapy or change in patient status

(additional local or systemic therapy). Treatment failures are classified according to the location of the recurrent tumor relative to the targeted volumes (PTV, CTV and GTV) diagrammed in appendix A.

10.2 Complete Response – Disappearance of all primary and regional tumor as defined by physical examination and imaging. Patients undergoing complete resection prior to radiation or patients with no visible tumor on baseline imaging prior to radiation are considered a complete response at the time of irradiation.

10.3 Partial Response – More than 50% reduction in the unidimensional maximal diameter of the tumor compared with the baseline evaluation.

10.4 Stable Disease – Less than 50% reduction in the unidimensional maximal diameter of the tumor compared with the baseline evaluation.

10.5 Progressive Disease – More than 25 % increase in the unidimensional maximal diameter of the tumor compared with the baseline evaluation. In patients that have undergone complete resection prior to radiation, progressive disease is the appearance of any new local disease. Appearance of new regional or metastatic disease or a 25% increase in regional or metastatic disease will be classified as regional or metastatic progression. Any positive biopsy of a known metastatic disease site that results in a change in therapy or change in patient status (e.g. additional local or systemic therapy) will be classified as disease progression

11.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

11.1 Enrollment on Study

Confirm subject eligibility as defined in Section 4.0 Patient Eligibility. Complete and sign the 'Patient Eligibility Checklist.' Be sure that all required values and dates are filled in.

Fax the completed Checklist to the Central Protocol and Data Monitoring Office (CPDMO) at [redacted] Follow with a phone call to [redacted] to ensure that the fax has been received. Eligibility will be reviewed, a patient-specific consent form will be generated, and the consent, protocol, and protocol standard order set will be delivered to the area designated on the Checklist. The signed consent form must be faxed to the CPDMO in order to complete the enrollment.

The CPDMO is staffed 7:30 am-6:00 pm CST, Monday through Friday (excluding holidays) and 9:00 am to 1:00 pm on Saturday. The office is staffed 9:00 am to 3:00 pm CST all weekday holidays except Christmas. A staff member is available by pager Saturday afternoons, Sundays and on Christmas Day for SJCRH enrollments.

11.2 Data Collection

Case report forms (CRFs) will be completed and reviewed by the SJCRH data manager for accuracy and completeness. Data will then be entered into a secure CRIS database.

11.3 Study Monitoring

Source document verification of eligibility and informed consent for 100% of St. Jude participants will be performed by the Eligibility Coordinators within 10 working days of completion of enrollment.

The Clinical Research Monitor will perform monitoring of applicable essential regulatory documentation. Also, reviewing for the timeliness of serious adverse event reporting (type, grade, attribution, duration, timeliness and appropriateness) for selected study participants *semi-annually* and track accrual continuously. The monitor will verify those data points relating to the primary study objective for a certain number of study enrollees as specified in the Moderate Risk monitoring plan checklist for this study. Protocol compliance monitoring will include participant status, safety assessments, eligibility, the informed consent process, participant protocol status, off-study, and off-therapy criteria. The Monitor will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Monitoring may be conducted more frequently if deemed necessary by the CPDMO or the IMC.

Continuing reviews by the IRB and CT-SRC will occur at least annually. In addition, SAE reports in TRACKS (Total Research and Knowledge System) are reviewed in a timely manner by the IRB/ OHSP.

11.4 Confidentiality

Study numbers will be used in place of an identifier such as a medical record number. No research participant names will be recorded on the data collection forms. The list containing the study number and the medical record number will be maintained in a locked file and will be destroyed after all data have been analyzed.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, clinical research monitors, etc.

12.0 Statistical Considerations

12.1 To estimate the rates of local failure and tumor progression

The primary objective is to estimate the local control and patterns of failure for patients with primary musculoskeletal tumors including the Ewing's sarcoma family of tumors (ESFT), rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma soft tissue sarcoma (STS) treated with image guided three-dimensional conformal radiation therapy. Different tumor types are accessioned to this study and their local failure rates differ significantly. To account for these differences, three groups of patients will be selected for local failure analysis based on the expected accrual of these patients to this study (Appendix E). These groups are defined by histology, site and degree of surgical resection and are selected to allow meaningful comparison with targeted rates of local control. Target local control rates for these specific treatment groups are established and listed in appendix E based on selected literature (3, 5-6, 9-12, 64,65). A lower limit to the local control rate is given to define a threshold below which the paradigm for treatment described in this protocol is deemed unacceptable. Analysis of local control will be undertaken for a treatment group at each event

counted as a local failure, when each treatment group has completed accrual and has been followed for five years, and at intervals specified below. The accrual of patients in five years in the study for all tumor types is projected in Table 12.1.1 below. For the local control analysis, projections for accrual for the specific treatment groups are listed in Table 12.1.2 below. For nonsequential tests, if the actual final accruals are different from the projected accruals, then for Group III RMS or for the Resected or Small ESFT (target 85%), the lower limit to the local control rate is 60%, 70%, 72%, or 73.3%, respectively, for the final accrual of 15, 20, 25, or 30 patients. For the Resected STS (target rate 90%), the lower limit 73.3%, 75%, 76%, or 80%, respectively, for the final accrual of 15, 20, 25, or 30 patients. For the Large ESFT (target rate 55%), the lower limit 33.3%, 35%, 36%, or 40%, respectively, for the final accrual of 15, 20, 25, or 30 patients. A sequential safety-monitoring plan is given in Table 12.1.3 in terms of minimum number for the number of patients locally controlled corresponding to the number of patients accrued within a treatment group during the study, assuming the final accrual is 30 patients in each treatment group. The minimum number is calculated for each of the four treatment groups (Group III RMS, Resected STS, and Resected / Small ESFT, and Large ESFT), respectively. For each of the four treatment groups, when the number of patients accrued during the study reaches 5, 10, 15, 20, 25, or 30, the number of patients with local tumor control will be reviewed and must not be less than the corresponding minimum number (Table 12.1.3). If fewer patients than targeted are controlled locally, then the rate of local control is considered be too low for that treatment group and the study for that treatment group will be stopped for investigating the reasons. At any event counted as a local failure during study, the local control rate for that treatment group will be determined. If the local control rate is lower than targeted, then accrual to that treatment group will be halted and the reasons investigated. If the number of patients accrued is other than 5, 10, 20, 25, or 30, the assistance of the statistician (J.W..) may be requested by the PI (M.K.) to calculate the new minimum number of patients locally controlled according to the actual number of patients accrued. In the above monitoring scheme, the number of patients locally controlled is counted disregarding the timing (since initiation of radiation therapy) of events (local failures) as this calculation is based on a target rate of local control at 2 years that is identical at 5 years. These target rates are expected estimates of local control and not actual local control rates based directly on historic data. We will use the survival model with competing risk (e.g., patient death) (57) to estimate the rates of local failure and tumor progression (defined in 10.1-10.6) for each tumor group. One-hundred evaluable patients will be required based on the projected accruals in table 12.1.1 below. We expect to enroll a total of 110 patients based on our current accrual to generate 100 evaluable patients for analysis.

Table 12.1.1
Projected Accruals

	RMS	STS	ESFT
W/o Metastases	18	26	26
W & w/o Metastases	29	26	37

Table 12.1.2
Accrual in Groups for Local Control Analysis

	Group III RMS	Resected STS	Resected ESFT or Small (<8cm) ESFT	Large (≥8cm) ESFT
W/o Metastases	17	24	15	3
W & w/o Metastases	28	24	18	12

Table 12.1.3
Safety Monitoring Plan: Minimum number of patients locally controlled per patients enrolled in each treatment group*

	Minimum Expected Number of Patients with Local Tumor Control			
Number of Patients Enrolled in a Treatment Group	Group III RMS	Resected STS	Resected ESFT or Small (<8cm) ESFT	Large (≥8cm) ESFT
5	3	3	3	
10	7	7	7	1
15	10	11	10	3
20	13	15	13	4
25	16	19	16	7
30	19	22	19	11

*For each of the three treatment groups, when the number of patients accrued during the study reaches 5, 10, 15, 20, 25, or 30, if the number of patients locally controlled is equal to or less than the corresponding minimum number, then the rate of local control is considered be too low for that treatment group and the study for that group will be stopped for investigating reasons.

The Second Phase Accrual: The original plan of accrual of 110 patients has been completed (September 2007), and additional accrual of patients is planned for this study as the second phase of accrual. The numbers of patients anticipated for the four treatment groups for the second phase accrual are shown in Table 12.1.4. These numbers are estimated based on the accrual of an additional 100 patients with the same distribution of disease (histology, size and use of surgery) as the initial 110 patient cases. For the groups of ESFT-small/resected and ESFT-large, the treatments in the second phase are exactly the same as that in the first phase, so the patients in the second phase will be taking together with those in the first phase for safety monitoring according to the plan in Table 12.1.3. The treatments for the groups of Group III RMS and Resected STS will be changed such that the irradiation margin will be decreased from 2cm to 1.5cm for the Group III RMS, and be decreased from 1.5cm to 1.0cm for the Resected STS. Since the patients in the second phase in these two groups may be at higher risk for local failure than those in the first phase (due to clinical treatment margin reduction), these patients will be monitored separately from, as well as together with, the patients from the first phase. The monitoring plans for these two groups are given in Table 12.1.5. For each group, the accrual of patients will be held if the stopping rule is activated by any one of the two monitoring plans for the group.

Table 12.1.4
The Second Phase Accrual in Groups for Local Control Analysis

	Group III RMS	Resected STS	Resected ESFT or Small (<8cm) ESFT	Large (≥8cm) ESFT
W & w/o Metastases	35	35	13	12

For Group III RMS or for the Resected or Small ESFT (target 85%), the 5% lower limit for non-sequential tests for the local control rate is 26 (74.3%) or 50 (76.9%), respectively, for the final accrual of 35 or 65 patients. For the Resected STS (target rate 90%), the 5% lower limit is 28 (80.0%) or 54 (83.1%), respectively, for the final accrual of 35 or 65 patients. From the sample sizes of the fixed sample test design, we derived the sequential boundaries in Table 12.1.5 for monitoring the local control rates.

Table 12.1.5
The Second Phase Safety Monitoring Plan: Minimum number of patients locally controlled per patients enrolled in each treatment group*

	Minimum Expected Number of Patients with Local Tumor Control			
Number of Patients Enrolled in a Treatment Group	Group III RMS		Resected STS	
	2nd Phase Only	Two Phases Together	2nd Phase Only	Two Phases Together
5	2		2	
10	5		6	
15	9		10	
20	12		14	
25	16		18	
30	20		22	
35	25		27	
40		28		31
45		32		35
50		36		39
55		40		44
60		44		48
65		49		53

*For the second phase accrual for each of the two treatment groups, the local controls will be monitored simultaneously in two ways: 1) alone: when the number of patients accrued from the second phase accrual reaches 5, 10, 15, 20, 25, or 35, if the number of patients locally controlled is equal to or less than the corresponding minimum number, then the rate of local control is considered be too low for that treatment group and the study for that group will be stopped for investigating reasons; 2) together with patients accrued in the first phase: during the second phase accrual, if the number of all patients accrued so far from the two phases reaches 40, 45, 50, 55, 60, or 65 and if the number of patients locally controlled is equal to or less than the corresponding minimum number, then the rate of local control is considered be too low for that treatment group and the study for that group will be stopped for investigating reasons.

12.2 Assessment of Treatment Related Effects

12.2.1 Assessment of Changes in Bone

Changes in bone assessed by physical evaluation, quality of life measures, QCT and MRI (or CT) will be correlated with radiotherapeutic parameters including dose, and volume. Changes over time will be assessed by serial evaluations of patient height, bone length and imaging evaluations of physis closure when feasible. Assessment will be made relative to the untreated contralateral side or another normal site within the patient when available.

12.2.2 Assessment of Changes in Muscle

Assessment of muscular development by physical functional scales, assessments of function and QOL, and volumetric changes determined by MRI (or CT) will be correlated with radiotherapeutic parameters and vascular changes assessed by DCE-MR and arterial spin labeling MR. Assessment will be made relative to the untreated contralateral side when available. PET-FDG imaging will be used to evaluate the level of glucose metabolism in treated muscle groups both compared to the untreated contralateral side and serially over time. Functional scales (DASH, TESS, and U. of Wash. QOL) will be obtained at 2 time points (84 and 120 months). These assessments will be analyzed relative to normative population scores.

12.2.3 Assessment of Changes in Soft Tissue

The surrounding connective tissue (soft tissue) will be serially evaluated by the treating radiation oncologist and physical therapist using a site-specific physical evaluation. MRI of the primary site will be conducted serially for imaging related correlates of late soft tissue effects. We will investigate both acute and late changes noted in soft tissue relative to radiotherapeutic parameters including dose, and volume.

12.2.4 Assessment of Changes in Microvasculature

Microvasculature within and outside the treated volume will be assessed sequentially during and following radiation therapy utilizing DCE-MR and arterial spin labeling MR. The relationships between measured parameters and radiotherapeutic parameters will be assessed.

12.3 Data Management

All clinical, functional, and imaging datasets will be maintained under the control of the protocol PI (M.K.) in a relational database. Full imaging datasets in electronic form will be maintained in a database that is readily accessible for determination of completeness and for analysis. Portions of this study may be analyzed and reported prior to the completion of the study with the permission of the P.I. Data may be collected or processed in “batches” (i.e. not in real time to facilitate efficiency and consistency). We anticipate reporting primary outcomes for patients prior to accrual of the total of 210 patients.

12.4 Dose Effects Model for Radiation Therapy

The major difference between the IGRT and conventional RT is the difference of their dose distributions, i.e., the IGRT irradiates a smaller volume to with high doses and a larger volume to with low doses compared to the conventional RT. In this study we will use a statistical model, the dose effects model, to investigate the correlation between dose distribution and the acute and late treatment effects in 11.2. The dose effects model was first proposed in St. Jude protocol RT-1, and has been successfully used for assessing RT dose effects on neuropsychological deficits for brain tumor patients. In this model, the integral effect of radiation is a sum of effects of lower dose to higher dose weighted by the volumes of brain receiving those doses. Mathematically, the dose effects model is

$$E_{integral} = R \sum_{i=1}^{I} V_i \; E_{dose-i} \quad ,$$

where R is the total amount of radiation on the tumor, V_i is the volume that receiving ith dose (i.e., dosage at the ith interval) and E_{dose-i} is a parameter representing the effect of the ith dose. R and V_i are known and depend on the patient; E_{dose-i} s are unknown parameters of the population and are to be estimated. For example, if we divide the range of dose into 5 intervals: (0%, 20%), (20%, 40%), (40%, 60%), (60%, 80%), (80%, 100%) and for a specific patient, *R=60.0 Gy* is the total dose received, then V_1*=42%,* V_2*=27%,* V_3*=18%,* V_4*=8%,* V_5*=5%* are volumes receiving dose from those intervals. It follows that $V_1+V_2+V_3+V_4+V_5$*=100%.* The parameters E_{dose-i}*=1,.., 5* are, respectively, the effects of dose in those five intervals. If each patient receives a same total dosage, i.e., R is the same for each patient, we will use another dose effects model which is more direct,

$$E_{integral} = \sum_{i=1}^{I} R_i \; E^*_{dose-i}$$

For example, if each patient receives 60 Gy, we can assume the range of dosage is divided into, e.g., 3 intervals: (0Gy, 20Gy), (20Gy, 40Gy), (40Gy, 60Gy). R_1*=5.1Gy,* R_2*=8.6Gy,* R_3*=10.5Gy,* where R_i is the total of dosage received from the ith dose interval. E^*_{dose-i} is the effect of the ith dose interval and a parameter to be estimated. The dose effect model will be imbedded as part of covariates into regression models for analyses. As the *time since RT exposure* is the most important covariate variable in the regression models, $E_{integral}$ will be used as a coefficient of the *time since RT exposure* to estimate the slope of longitudinal change of a response variable (e.g., muscular development by physical functional scales and volumetric changes determined by MRI). Additional clinical pretreatment and treatment related variables will be evaluated in analysis of radiation related treatment effects. These variables will include bone age, patient age and other pretreatment clinical variables that may be collected and analyzed for their additional effects. Radiosensitizing chemotherapy administered as adjuvant therapy for musculoskeletal tumors (including, but not limited to, Adriamycin, Actinomycin-D, topotecan and irinotecan) will also be evaluated as a treatment related variable for regional tissue effects. It is anticipated that the cumulative chemotherapeutic dose prior to radiation, the schedule of drug delivery and the temporal relation of drug delivery to the initiation of radiation may be a clinical factor in treatment related effects.

13.0 Off Study Criteria

13.1 Criteria for Removal from Protocol Therapy or Protocol Evaluations

Patients may be taken off protocol for any of the following reasons:

13.1.1 Parent or patient request
13.1.2 Physician's discretion based on patient's ability to comply with protocol therapy or follow-up
13.1.3 Patient meets off study criteria (section 13.3)
13.1.4 Completion of study requirements
13.1.5 Recurrence or progression of local or metastatic disease following radiotherapy

13.2 Criteria for Removal from Follow-up

13.2.1 Parent or patient request
13.2.2 Patient meets off study criteria (section 13.3)

13.3 Off Study Criteria

13.3.1 Death
13.3.2 Recurrence or progression of local or metastatic disease following radiotherapy
13.3.3 Entry into another study not compatible with this protocol

14.0 Data Safety Monitoring Committee

RT-SARC will not be referred to the DSMB at St. Jude Children's Research Hospital because it does not fit any category for DSMB review. The safety in terms of efficacy of local control for this protocol will be monitored by the protocol PI (M.K.) according to the plan listed in Table 12.1.2.

15.0 Obtaining Informed Consent and Informed Assent

The process of obtaining informed consent will follow institutional guidelines. Informed consent will be obtained by the attending physician or his designee in the presence of at least one witness. Verbal assent will be obtained from patients 7 to less than 14 years old and written assent from patients 14 to less than18 years old.

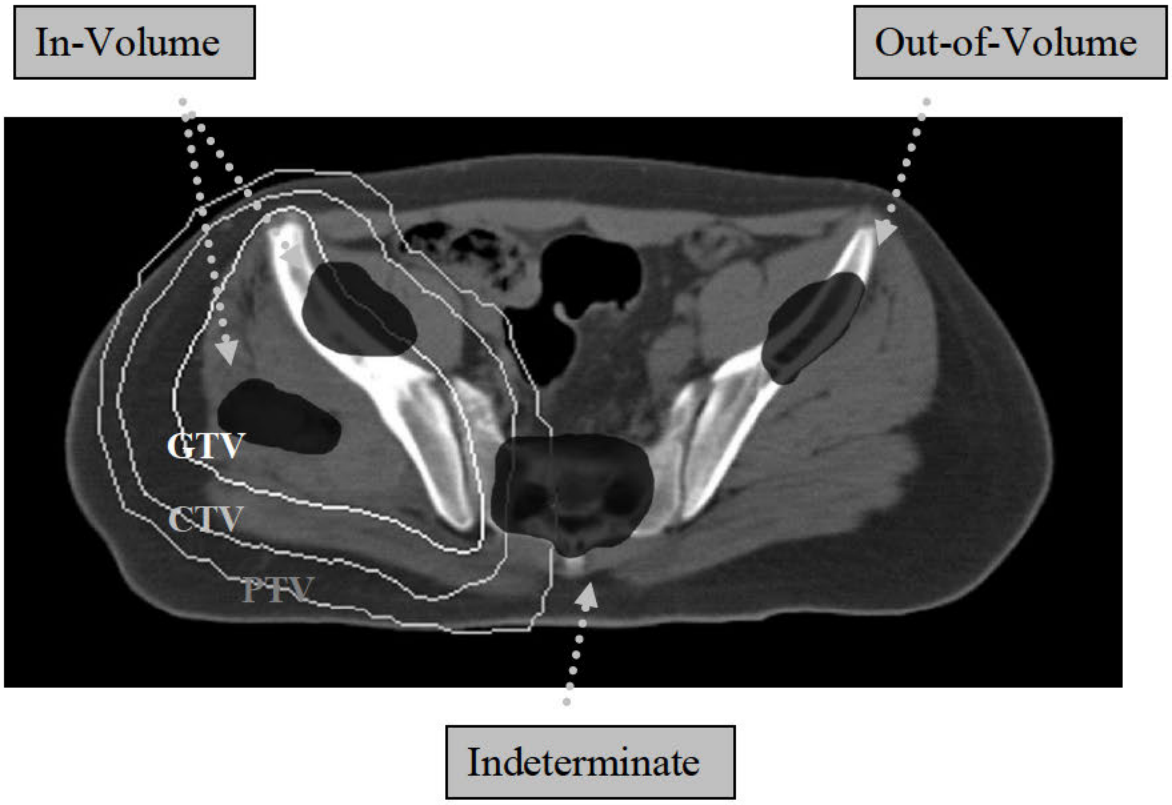
15.1 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Research participants must be consented at the next clinic visit after their 18th birthday.

Appendix A.

Classification of tumor recurrence based on imaging may be classified into one of three categories: 1) in-volume, 2) out-of-volume or 3) indeterminate. Tumor recurrences classified as out-of-volume must clearly fall outside the planning target volume (PTV). Those failures that fall fully within the gross tumor or clinical target volumes (GTV and CTV) are classified as in-volume failures. All other failures are marginal in nature and will be analyzed based on their geometric center of origin and percent volume within the target volumes. A failure that intersects the GTV or CTV is classified as a local failure and counts as an event against local control.

The image below provides a graphical representation of potential patterns of failure.



Appendix B

Comparison of “standard of care” vs. “research only” tests

A study that is utilized in the standard care of managing a patient (even if it is also used for research purposes) it is indicated with an “S”. Those studies with are for research purposes only are indicated with an “R”

Table B1

Treatment Planning and Evaluation Schedule

Evaluation Schedule	Pre-IGRT	week 1	week 2	week 3	week 4	week 5	week 6	week 7
Clinical								
Physical Examination	S	S	S	S	S	S	S	S
Physical / Occupational Therapy								
Functional Evaluation	S	S	-	-	-	-	S/R	-
Diagnostic Imaging								
Standard of care imaging								

Table B2

Evaluation following initiation of Radiation Therapy

Evaluation	Months after Initiation of Radiation Therapy*											
	3	6	9	12	18	24	36	48	60	84/96	120/132	18 yrs.
Clinical												
Physical Examination	S	S	S	S	S	S	S	S	S	S	S	S
PT/OT												
Functional Evaluation	S/R	S/R	S/R	S/R	S/R	S/R	S/R	S/R	S/R	S/R	S/R	
Functional Scales	-	-	-	-	-	-	-	-	-	S/R	S/R	S/R
Diagnostic Imaging												
Standard of care imaging												
Bone Densitometry	-	-	-	-	-	-	-	-	-	R	R or	R

Appendix C.

Functional assessment instruments are electronic documents entered directly into the participants electronic medical record by the treating physical therapist.

Appendix D

Local control will be estimated for the patient groups indicated below.

Tumor groups are defined as follows:

Rhabdomyosarcoma (RMS)

Group III patients (biopsy or partial resection) followed by definitive radiation

Soft Tissue Sarcoma (STS)

Surgery consisting of a wide local excision (negative or positive margins) followed by radiation

Small or Resected Ewing's Sarcoma Family of Tumors (ESFT)

Surgery consisting of a wide local excision (negative or positive margins) followed by radiation for any primary site of disease

or

Definitive radiation therapy for any small primary site of disease (<8cm in greatest dimension at diagnosis)

Large Ewing's Sarcoma Family of Tumors (ESFT)

Definitive radiation therapy for any large primary site of disease (≥8cm in greatest dimension at diagnosis)

Defined 5 Year Local Control Rates for Evaluable Patient Groups
Amend 2.0

	Group III RMS	Resected STS	Resected ESFT or Small ESFT	Large ESFT
Target Local Control Rate	85%	90%	85%	55%
Lower Limit LC Rate	71.4%	75%	66.7%	35%
Projected accrual (n)	28	24	18	12

Appendix E.

qCT exposure estimates obtained for relative risk analysis.

qCT Dosage report

Prepared by Sam Brady, PhD

Co-authors: Matthew Krasin, MD; Chia-ho Hua, PhD; & Sue Kaste, MD

Initially prepared on 6-16-10
Modified on 7-9-10 by SB,CH

Age (y.o.)				
0	1	5	10	Adult

Bone Density5.8cm scan length**

16 cm Phantom Diameter ED Calculations (mSv)				
3.0	1.8	1.2	N/A	
32 cm Phantom Diameter ED Calculations (mSv)				
N/A			0.5	0.5

Tibia25cm scan length**

16 cm Phantom Diameter ED Calculations (mSv)				
1.1	0.7	0.5	0.3	0.3
10 cm Phantom Diameter ED Calculations (mSv)				
1.4	0.9	0.6	0.5	0.4

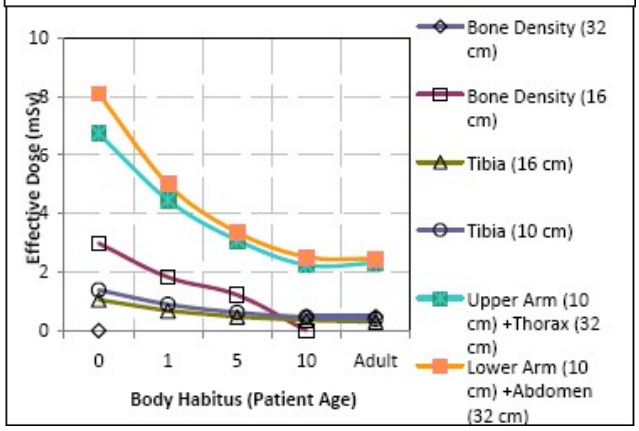
UpperArm + Thorax25 cm scan length**

10 cm Phan Dia for arm + 32 cm Phan for body (mSv)				
6.7	4.5	3.1	2.2	2.3

Lower Arm +Abdomen25 cm scan length**

10 cm Phan Dia for arm + 32 cm Phan for body (mSv)				
8.1	5.0	3.4	2.5	2.4

Comments: As previously mentioned in the 6-16-10 version of this report, the qCT protocol used auto mA with 200 mA as its max allowable output. The data in this report was measured using 200 mA and therefore represents a conservative estimate for dose to patient from qCT scan. The following is a summary of the changes to the results in this version of the qCT dose report. (1) The DLP_x values used to calculate effective dose (ED) for the extremeties (arm/leg) were changed to reflect a 25 cm scan length. The scan length for "Bone Density", or the Lumbar scan, was left at the prescribed 5.8 cm. (2) Additional ED calcualtions for arm scans provide a more accurate patient radiation risk assesment by accounting for the dose to the body along with the arm(s) in the scan FOV. **CONCLUSION:** The calculated ED to the trunk body region from a qCT scan protocol for a 10 year old and adult (~2.5 mSv) patient body habitus were (67 & 72)% lower than our traditional diagnositc quality scan protocols (7.5 & 9 mSv), respectively.



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