Protocol Title: Pilot Study Evaluating Hypofractionated Pre-operative Radiation Therapy for Soft Tissue Sarcomas of the Extremity and Chest-wall

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Pilot Study Evaluating Hypofractionated Pre-operative Radiation Therapy for Soft Tissue Sarcomas of the Extremity and Chest-wall

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TITLE

Pilot Study Evaluating Hypofractionated Preoperative Radiation Therapy for Soft Tissue Sarcomas of the Extremity and Chest-wall

I. SCHEMA

	Preoperative Image Guided Radiation Therapy (3D CRT or IMRT)	**Surgery**
Register	**All patients:**	**All patients**
	Patients with stage I to III STS of the extremity or chest wall who receive neoadjuvant, adjuvant, or no chemotherapy	**Limb sparing surgery 4 to 8 weeks after completion of radiation therapy**
	Radiation Dose: 35 Gy in 5 fractions (7 Gy per fraction)	

Patient Population:

Patients with localized, stage I-III histologically confirmed soft tissue sarcomas of the extremity and chest-wall primaries will be eligible for this study. Patients must be medically operable and have not had prior radiation therapy to the primary sarcoma site.

II. INTRODUCTION

There has been an evolution in management for patients with soft tissue sarcomas (STS) of the extremity since the 1970's. Historically, amputation was the mainstay of treatment. However, multimodality therapy with limb-sparing surgery and radiation with or without chemotherapy has been shown to yield equivalent control and survival for patients who underwent non-limb salvage techniques (1, 2). Thus, more conservative therapies have been employed.

The sequence of radiation therapy (RT) has also been examined in the treatment of STS of the extremity. Post-operative radiation is typically administered within 4 to 6 weeks after limb-salvage surgery; however, this may be technically challenging due to the lack of a known mass, large radiation fields, and higher radiation doses in the post-operative setting. The advantages of pre-operative radiation include, but are not limited to, lower radiation dose and field size, facilitation of surgical resection, improved tumor oxygenation and less long term toxicity. Thus, the use of pre-operative radiation therapy has been investigated and been shown to be feasible, and it can lead to excellent rates of local control and survival.

DeLaney, et *al*. examined the use of neoadjuvant interdigitated chemotherapy and radiation in 48 patients with ≥8 cm STS of the extremity. Patients received mesna, Adriamycin, Ifosfamide and Dacarbazine (MAID) followed by radiation therapy to 22 Gy at 2 Gy per fraction. This sequence was repeated once followed by limb-salvage surgery and 3 additional cycles of MAID. In this study, 5-year local control was 92% and 5-year disease-free and

overall survival were 75% and 44%, respectively. Both disease-free and overall survival was significantly improved compared to historical controls (3). This study led to the development of a national study that used a similar interdigitated method of treatment (4).

RTOG 95-14 was a phase II study that enrolled 64 patients with large (≥8 cm) grade 2 to 3 STS of the extremity or torso. Patients received a similar sandwich course of therapy, which included chemotherapy with MAID followed by radiation therapy to 22 Gy at 2 Gy per fraction. As in the Delaney et *al*. protocol, this sequence was repeated once followed by limb-salvage surgery and 3 additional cycles of MAID. The 3-year local-regional recurrence rate was 10% (when amputation was not considered a failure). The 3-year disease free and distant-disease free and overall survival was 57%, 64%, and 75%, respectively. However, toxicity was the limiting factor in this study, with 5% treatment-related deaths (mostly secondary AML) and an 84% rate of grade 4 toxicity. Thus the toxicity precluded further use of this regimen in future studies (4). One caveat of this study was that higher chemotherapy doses were used and thus thought to contribute to the added morbidity in patients enrolled on this study.

Although there are several advantages to pre-operative radiation therapy, it had remained unclear if pre-operative radiation led to poorer control or survival to the counterpart patients who received post-operative radiation until completion of the NCI Canadian Trial.

O'Sullivan, et *al.* randomized 190 patients (out of 266 planned) with localized STS of the limb to pre-operative RT to 50 Gy in 25 fractions versus post-operative RT to 66 to 70 Gy. Patients with positive margins in the pre-operative RT arm received a 16 to 20 Gy boost. At 5 years, the local control between the pre-operative and post-operative RT cohorts was 93% and 92%, respectively. There was no difference in relapse-free (58% versus 59%, p=NS) and overall survival (73% versus 67%, p=NS). The authors concluded that pre- and post-operative RT were equally effective in terms of disease control and survival (5).

Other studies have emulated the benefit of pre-operative radiation therapy. A Meta-Analysis reviewed 5 studies in which 1098 patients with localized and resectable STS were treated with either pre- or post-operative radiation therapy. In this study, local control and survival was improved in the pre-operative RT group (HR 0.6, SS) and 76% versus 67%. These results have also been shown in other studies (6).

Although pre-operative RT has been shown to compare favorably with post-operative RT, there are certain disadvantages. Acute wound complication rates are higher when radiation is administered in a pre-operative manner. In the NCI Canadian randomized control trial, the major acute wound complication rate was 35% versus 17% in patients who received post-operative radiation therapy. Moreover, a higher percentage of patients in the pre-operative cohort required non-primary wound closure and had poorer 6-week post-operative function. Increasing wound complications when RT is administered pre-operatively has been consistently seen in other studies and ranges from 25-35% (5). However, long term functioning and toxicity is improved with pre-operative radiation therapy (7).

As an extrapolation of the NCI protocol, late radiation morbidity was evaluated in patients who participated in this trial. In this study, post-operative RT was associated with worse fibrosis and joint stiffness compared to preoperative RT. In the post-operative treatment arm, 48% of patients developed grade 2 or higher fibrosis compared to 31% in the pre-operative arm (p=0.07). Moreover, edema was also higher in the post-operative radiation arm (7).

Because of the above studies, there has been a transition of treatment with pre-operative radiation therapy. This consists of daily radiation (Monday through Friday) over a course of 5 weeks (25 treatments). Pre-operative radiation is followed by surgical resection 4-8 weeks later.

While the approach of radiation, surgery, and chemotherapy has good outcomes in terms of toxicity and local control, there is always room to improve these treatments. The NCI of Canada SR2 trial had a wound complication rate of 43% and studies with more modern radiation techniques such as intensity modulated radiation therapy (IMRT) continue to have wound complication rates of 30.5% (8). One possible source for improving outcome for resectable STS is to use hypofractionated radiotherapy instead of conventional radiation. Hypofractionated radiation uses a small number of radiation treatments with a high dose per fraction. Due to improved imaging and immobilization techniques the treatment is more conformal with less normal tissue receiving radiation.

Hypofractionated radiation has been used successfully in other disease sites (9-14). Perhaps the most cited literature is in early stage breast cancer. Whelan, et *al*. randomized 1234 patients with T1-2N0 invasive breast cancer to a standard course of radiation for 25 treatments over 5 weeks versus a shortened course over 3 weeks for 16 treatments. In this study, there were no differences between the control and hypofractionated groups in overall survival (84.4% versus 84.5%, respectively) or local-recurrence (6.7 versus 6.2%, respectively). Moreover, there was no difference in cosmetic outcomes and toxicity, where 71.3% of subjects in the standard radiation group compared with 69.8% of the subjects in the hypofractionated-radiation group had good or excellent cosmesis (9).

Hypofractionated radiation therapy has also been investigated in prostate cancer patients. Arcangeli, et *al*. prospectively examined 168 patients with high risk prostate cancer and randomized this subset to conventional radiation to a total dose of 80 Gy at 2 Gy per fraction versus 62 Gy at 3.1 Gy per fraction. In this study, there was a higher 3-year freedom from biochemical failure in the hypofractionated group (87%) compared to the conventional fractionated group (79%), p=0.03. Moreover, there was no difference in late GU (14% versus 11%, respectively) or GI (17% versus 16%, respectively) toxicity between both groups (10).

Hypofractionation has also been used in STS study and has been shown to have favorable outcomes (11). Kosela-Paterczyk, et *al*. prospectively studied 272 patients with stage I-III STS of the extremity or trunk wall to 5 Gy x 5 fractions (25 Gy total) daily. 3-year overall survival was 72% and local control was 80%. Factors that impacted survival were STS > 10 cm and grade 3 disease. Forty-two percent of patients had some form of toxicity in this study, with the majority being the expected acute erythema and desquamation observed with RT. Seven percent of patients needed surgery to address these toxicities, which included procedures for wound healing (debridement) and wound closure. Late toxicities occurred in 15% of patients and were mainly associated with limb edema and fibrosis. Another prospective study, Kubciek, et *al*., assessed 12 STS of the extremity that were treated to 35 Gy in 5 fractions using stereotactic body radiation techniques. Median tumor size was 7.6 cm. In this study, the local control rate was 100% and the distant metastasis rate was 42%. Most patients had some form of erythema, dry or moist desquamation which resolved within 4 weeks after the completion of radiation. There were no wound complications or late toxicity (12).

Although there are studies demonstrating the feasibility of hypofractionated radiation therapy in STS, these studies do not correlate clinical outcomes with pathologic or radiologic changes seen after radiation has completed. Association of radiologic and pathologic impact from the treatment for STS is integral as it correlates to disease control in this setting. Thus, investigating these alterations on imaging and final pathology will provide a more complete understanding of the effects of hypofractionated radiation therapy in STS.

Hypofractionation has several potential advantages over conventional radiation. First, the biological equivalent dose to the tumor is higher with hypofractionation than it is with conventional radiation. In between radiation treatments there is repair of the radiation damaged cancer cells (on a cell survival curve this region of repair is referred to as the "shoulder" of the curve). Some cell lines are better at repair than others. Sarcoma is often referred to as a "radioresistant" tumor, which means that sarcoma cell lines have a larger capacity for radiation repair than do other cell lines. A treatment that can deliver a high dose in fewer fractions can potentially overcome some of this repair. There is a concept in radiation known as "biologically equivalent dose" (BED) which states that a higher dose per fraction results in more tumor kill than a lower dose per fraction. For example, radiation delivered to a total of 60 Gy in three 20 Gy fractions is the equivalent of 150 Gy in 2 Gy fractions.

The above is based on the biological equivalent dose calculation (Figure 1). Because of the higher dose per fraction delivered with SBRT there is a higher biologically equivalent dose which can translate into a higher rate of tumor cell death.

Figure 1: BED Equation

Biological equivalent dose (2 Gy fractions) = (Total Dose) x (Dose per fraction /(α/β))

A second advantage of hypofractionation is that there are fewer treatments, which makes it more convenient for patients in terms of travel to the hospital for radiation. Hypofractionation also leads to less time to completion of pre-operative radiation and surgical resection. This may lead to overall better outcomes. Treatment time has been shown to be an important metric in several cancer types (9-11).

To determine what dose to use for this study compared to the conventional 50 Gy in 2 Gy daily fractions, it is important to estimate the alpha/beta ratios for sarcomas. The range in the literature varies, but is usually less than for other malignancies for acute toxicity, where it is estimated to be 10. With conventional fractionation using the radiobiologic equation below, the biologic equivalent dose (BED) of 50 Gy in 2 fractions is 60 Gy. Thus, we chose a dose that would have a similar biologic equivalent dose for acute toxicity, which would be 7 Gy in 5 fractions (35 Gy total). The alpha beta range for long term toxicity in STS is between 0.5 to 5, although 5 is commonly used (13, 14). Using 50 Gy in 25 fractions daily, the BED_5 is 70 Gy. The BED_5 for 7 Gy x 5 fractions is 84 Gy, which we felt would be acceptable as we would treat patients every other day (as opposed to daily) to allow for tissue recovery and because all of the tissue radiated would be removed from surgery, so the propensity for long term toxicity would be low due to removal of radiated tissue.

Table 1 lists the possible alpha/beta ratios for sarcoma and what the 2 Gy equivalent doses would be based on the radiobiologic equation in Figure 1.

Table 1: BED calculation for 7 Gy x 5 fractions Alpha/Beta Ratio	2 Gy Equivalent Dose
0.5	490.0 Gy
1	280.0 Gy
3	116.67 Gy
5	84.0 Gy
10	59.50 y

While radiation therapy is often utilized to treat localized STS, chemotherapy is not as common due to more variable outcomes. Increasingly, targeted therapies are being utilized instead. . Thus, biomarkers, cytokines and genetic sequencing are becoming more important to determine which targeted agents combat this disease process. In STS, ERCC1, XPS, and BRCA1 are known to be predictive to the response to trabectin (19-21). TOP2A has also been shown to predictive of response to doxorubicin (19-21) and SPARC has been in radiation (21). Thus, expression of these markers may predicts for which patients have improved outcomes and would be assessed in this study.

The risks to the subjects enrolled on this study include the general risks of undergoing the standard procedures such as MRI, radiation and surgery, which will be discussed prior to the therapies and images each patient undergoes. There is also a risk of loss of confidentiality, but the data will be de-identified once acquired. Thus, this risk is minimal.

Table 2 Studies and Publications Supporting Hypofractionation, DCE and DWI, and Biomarker Analysis for Solid Tumors Including Sarcoma	**Study**	**Title**	**Conclusions**
Supporting Hypofractionation	Whelan, et *al.* 2002 (9)	Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer	No difference in 5-year locoregional, disease-free and overall. Shorter course of radiation therapy is acceptable.
	Arcangeli, et *al*. 2010 (10)	A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer	Hypofractionated schedule superior for biochemical control, comparable for late toxicity
	Norkus, et *al*. 2009 (15)	Three-dimensional external-beam radiotherapy for localized prostate adenocarcinoma: a report on acute toxicity	Hypofractionated schedule feasible, lower acute toxicity
	Kosela-Paterczyk, et *al.* 2014 (11)	Preoperative hypofractionated radiotherapy in the treatment of localized soft tissue sarcomas	In this non-selected group of locally advanced STS use of hypofractionated pre-operative radiotherapy was associated with similar local control (81%) when compared to previously published studies. The early toxicity is tolerable, with small rate of late complications.
	Kubiecek, et *al.* 2010 (12)	Preoperative stereotactic radiosurgery for soft tissue	They found this to be well tolerated, convenient for patients, allowing for surgery and subsequent chemotherapy to be administered quicker. Local control was 100% (though distant

			relapse remained an issue) and there were no long-term toxicities or wound complications. Will continue accrual on phase II study.
Supporting DCE and DWI	Dudek*, et al*. 2008 16)	Diffusion-weighted magnetic resonance imaging allows monitoring of anticancer treatment effects in patients with soft-tissue sarcomas	DWI can be used as a supplement to morphologic imaging for the evaluation of tumor response to anticancer therapy in patients with soft-tissue sarcomas. DWI performed at an early stage of fractionated therapy may provide unique prognostic information of its effectiveness.
	van Rijswijk*,* et *al*. 2003 17)	Dynamic contrast-enhanced MR imaging in monitoring response to isolated limb perfusion in high-grade soft tissue sarcoma: initial results	Results show that dynamic contrast-enhanced MR imaging offers potential for non-invasive monitoring of response to isolated limb perfusion in soft tissue sarcomas due to identification of residual areas of viable tumor and subsequently may provide clinically useful information with regards to timing and planning of additional surgery.
	Uhl, et *al*. 2006 (18)	Evaluation of tumour necrosis during chemotherapy with diffusion-weighted MR imaging: preliminary results in osteosarcomas	During chemotherapy of osteosarcomas, tumour ADC changes are related to the degree of tumour necrosis.
Supporting Biomarker Analysis	Ludwig, et *al*. 2008 (19)	Personalized therapy of sarcomas: integration of biomarkers for improved diagnosis, prognosis, and therapy selection	Improvement in aid of selection of therapy for patients with sarcoma.
	van Maldegem, et *al*. 2012 (20)	The clinical use of biomarkers as prognostic factors in Ewing sarcoma	We should continue to divide patients according to stage of disease and use phenotypic biomarkers metastasis, size of tumor and histologic response.
	Beck, et *al.* 2010 (21)	Gene expression profiling for the investigation of soft tissue sarcoma pathogenesis and the identification of diagnostic, prognostic, and predictive biomarkers	Discussion of strategies to further optimize the translation of gene expression data into a greater understanding of sarcoma pathogenesis and improved clinical outcomes for sarcoma patients
Supporting RNA Sequencing	Serrano, et *al*. 2015 (22)	RAS/MAPK pathway hyperactivation determines poor prognosis in undifferentiated pleomorphic sarcomas	The RAS/MAPK and PI3K/mTOR pathways are activated in the majority of cases of UPS. The RAS/MAPK pathway distinguishes a subgroup of patients with localized UPS with a worse outcome

	Beck et *al,* 2010 (23).	Discovery of molecular subtypes in leiomyosarcoma through integrative molecular profiling.	In this analysis that combined gene expression profiling, aCGH and IHC, we characterized distinct molecular LMS subtypes, provided insight into their pathogenesis, and identified prognostic biomarkers.
Supporting Cytokine Analysis	Rutkowski, et *al*. 2002 (24)	Cytokine serum levels in soft tissue sarcoma patients: correlations with clinco-pathologic features and prognosis	Serum levels of some proinflammatory, hematopoietic and angiogenic cytokines and cytokine receptors are elevated, frequently in parallel, in a large percentage of soft tissue sarcoma patients. Significant correlations of serum cytokine levels with tumor size and grade suggest that some of these cytokines may be directly or indirectly involved in the progression of soft tissue sarcomas. Serum assays of IL-6, IL-8 and TNF RII before or after the treatment may be useful in establishing soft tissue sarcoma patients prognosis.

III. OBJECTIVES

A. Hypothesis: We hypothesize that pre-operative hypofractionated radiation therapy for localized STS will result in local control and toxicity similar to conventional fractionation with less cost, more patient convenience and decreased overall treatment time.

B. Objectives:

i. The primary objective of the study is to assess the local control, which will be assessed via physical exam and MRI.

ii. The secondary objectives are as follows:

1. Assess toxicity, QOL using FACT-L
2. Assess disease-free and overall survival using the product limit estimator and presented as Kaplan-Meier plots.
3. Assess the acute and long term toxicity of hypofractionationed pre-operative radiation for localized, stage I-III STS will be assessed via the CTCAE version 4.0 (Appendix III) and the Musculoskeletal Tumor Rating Scale (Appendix III).
4. Assess radiologic changes due to hypofractionated radiation through the standard and advanced sequences of MRI
5. Assess pathologic changes due to hypofractionated radiation through the expression of tumor biomarkers, percent necrosis, fibrosis and viable cells.

IV. ELIGIBILITY CRITERIA

A. Inclusion Criteria

- **i.** ≥ 18 years of age
- **ii.** Biopsy obtained within 16 weeks prior to registration
- **iii.** Pathologic confirmation of primary soft tissue sarcoma of the upper or lower extremity or chest-wall. As per protocol per the STS tumor group, if biopsy was done at an outside hospital, then it will be reviewed by the pathologists at Froedtert and the Medical College of Wisconsin.
- **iv.** Stage I-III Soft Tissue Sarcoma of the extremity or chest wall without evidence of metastatic disease (Appendix II)
- **v.** Medically operable
- **vi.** (History and Physical within 16 weeks of registration
- **vii.** No prior radiotherapy to primary site or adjacent site that results in overlapping radiation fields.
- **viii.** If patient received neoadjuvant chemotherapy, it must be completed ≥ 21 days prior to start of radiation therapy
- **ix.** MRI obtained of the affected extremity or chest-wall within 16 weeks of registration
- **x.** CT chest or PET/CT acquired to assess distant disease within 16 weeks of registration
- **xi.** KPS 60 or above within 16weeks of registration
- **xii.** Informed consent obtained prior to registration
- **xiii.** Women of childbearing potential and male participants must practice adequate contraception.
- **xiv.** Documentation of no metastatic disease within 16 weeks of registration
- **xv.** Documentation of sarcoma pathology in electronic medical record
- **xvi.** CBC with differential within 16 weeks of registration with adequate bone marrow functioning as follows
    1. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
    2. Platelets ≥ 100,000 cells/mm^3
    3. Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other interventions to achieve a hemoglobin of ≥ 8.0 g/dl is acceptable)
- **xvii.** If a female of childbearing age and potential, serum pregnancy test is required within 72 hours prior to simulation.

B. Exclusion Criteria

- **i.** Patients who have metastatic disease
- **ii.** Pregnant women
- **iii.** Disease pathology other than sarcoma subtypes
- **iv.** Patients with a history of metastatic disease from a primary other than sarcoma
- **v.** Patients who cannot undergo MRI as part of pre-treatment or treatment planning process
- **vi.** STS of other than the extremity or chest wall
- **vii.** Tumor size ≥ 30 cm maximal dimension; proximal medial thigh tumors (>=20 cm)
- **viii.** Prior excision or resection of tumor

V. REGISTRATION PROCEDURES

A. Patients who are screened and eligible will have a discussion with the treating physician. There is no randomization of patients on the study

B. If the patient is amenable to the study, then the CTO will be called for the consent process. The research coordinator for the study will consent the patient, fill out eligibility forms, and assess the registration of each patient.

C. Currently the PI's are the contacts for registration procedures and their information is below:

- **I.** Meena Bedi: 9200 W Wisconsin Avenue. Milwaukee, WI 53223

II. Candice Johnstone: 3200 Pleasant Valley Road, West Bend, WI 53095

Once a research coordinator is assigned, the registration information will be registered in ONCORE, which is a secure software that is password protected that is used by the CTO.

D. Eligible patients will be registered per the CTO standard procedure.

VI. Treatment Plan

A. Radiation therapy

i. IGRT IS MANDATORY FOR THIS STUDY.

B. Dose Specifications

i. Pre-operative IGRT (3D-CRT or IMRT)

1. Either 3D conformal radiotherapy or intensity modulated radiation therapy (IMRT) may be utilized as long as the dose volume histogram (DVH) constraints for critical normal structures meet the criteria defined in Section 6.4.
2. A prescription dose of 35 Gy in 5 fractions given every other day with at least 48 hours in between each fraction will be prescribed to cover 95% of the PTV.

C. Treatment Schedule:

i. Treatments will have a minimum of a 48 hour inter-fraction interval. Treatments will be completed over 20 days maximum.

ii. Patients will be treated at Froedtert Hospital or at St. Joseph's Hospital.

D. Technical Factors:

i. Megavoltage photon beams produced by linear accelerators, betatrons or microtrons with energies of ≥ 4 MV are permitted. Preoperative IGRT (3D-CRT or IMRT)

Image Guidance Devices

Image guidance may be achieved using any one or more of the following techniques:

1. Linear-accelerator mounted kV and MV conebeam CT images
2. Linear-accelerator mounted MV CT images (e.g., Tomotherapy)

Image Guidance Procedures

The institution's procedure to register treatment day imaging dataset with the reference dataset should comply with the following recommendations:

1. Imaging must be done each day.
2. Region-of-Interest (ROI) or "clip box" for image registration should be set to encompass the high dose PTV and adjacent bony anatomy
3. Both manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the image registration must be visually checked for the alignment of the bony anatomy.

Management of Radiation Dose from IGRT

According to the literature, the estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scan on a Tomotherapy unit were estimated to be in range from 1 to 3 cGy, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT vary from 1 cGy to 10 cGy

depending on the field size. As a technique of controlling patient dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of patient position is carried out.

E. Simulation, Immobilization, Localization for Treatment Delivery

Patients should be immobilized in stable and comfortable positions to allow accurate repositioning from treatment to treatment and to prevent movement during treatments. A variety of immobilization devises may be utilized, including Alpha Cradle and thermoplastic casts.

Radiotherapy treatment plans will be generated after limb immobilization and computerized tomography (CT) simulation.

Adjustments of patient position should be made accordingly, if needed prior to treatment.

F. Treatment Planning and Target Volumes:

Target Definition

Gross Tumor Volume (GTV): Gross tumor defined by MRI T1 plus contrast images (MRI with contrast is required). Fusion of MRI and CT is recommended to delineate the GTV for radiotherapy planning, but this is optional.

Clinical Target Volume (CTV) for Intermediate-to-High Grade Tumors ≥ 8 cm: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 3 cm margins in the longitudinal (proximal and distal) directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1.5 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

CTV For All Other Tumors: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 2 cm margins in the longitudinal (proximal and distal) directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of compartment. The radial margin from the lesion should be 1 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

Planning Target Volume (PTV): Include CTV and error of setup and organ motion. Typically PTV includes CTV plus 5 mm.

Skin surfaces should not be contoured in CTV or PTV unless these are involved by gross tumor. If the incisional biopsy scar is small and will be resected at the time of surgery, it may not be contoured as CTV at the discretion of the treating radiation oncologist. Use of bolus on the skin surfaces is not encouraged when IMRT is used.

Critical Structures

Radiation dose to normal tissues should be kept within the accepted normal tissue tolerances. Every effort should be made to avoid treating the full circumference of an extremity, avoid treating anus, vulva and scrotum, avoid treating the lung, and avoid treating full dose, skin over areas commonly traumatized (e.g. the elbow, knee), and femoral head/neck. Less than 50% of any joints (including shoulder, elbow and knee) should receive 25 Gy. For any other normal tissue structures, no radiation dose more than he established TD5/5 limit should be given. The above criteria must be met in the CT based plan. No more than 50% of a longitudinal stripe of skin and subcutaneous tissue of an extremity should receive 10 Gy. This stripe of normal tissue is contoured at the discretion of treating radiation oncologist. Full prescription dose to skin over areas commonly traumatized (e.g., the elbow, knee, shin) should be avoided. No more than 50% of normal weight-bearing bone within the radiation field should receive 25 Gy except when the tumor invades the bone or when there is circumferential involvement of the surgical resection after radiation. There is no special requirement for skin dose limit. However, for IMRT of sarcoma, we recommend that skin surface (5-mm thickness) including scar from incision biopsy is not included in CTV or PTV and is not bolused for IMRT, unless the biopsy scar is not subsequently resected after radiotherapy.

G. Compliance Criteria

i. Treatment interruptions should be minimized. More than a 2-week interruption (holidays and weekend are not included) will be considered a major violation.

ii. Long term adverse effects will be measured 4 months after radiation for years 1 and 2

Table 3: Compliance Criteria

Per Protocol	90% of the PTV is covered with that prescription dose. No more than 10% of the PTV receives a dose that is >110% of the prescribed dose.
Minor Deviation	Greater than 10%, but no more than 20% of PTV receives ≥ 110% prescription dose. Exceeding normal tissue tolerances by >2.5%
Major Deviation	The minimum dose to any volume falls below 90% of the prescribed dose. Or, more than 20% of PTV receives ≥ 110% prescription dose. Dose to the normal tissue structure(s) is > 5%

H. Adverse Events

i. PLACEMENT OF FLAP: Flap reconstruction and/or placement at the time of resection or soon after resection within 1 month does not constitute as a graded toxicity, as these surgeries are done to close the primary wound. Flaps are often needed as STS are large and the tissue defect caused by surgery is not able to be primarily closed. In this setting, this does not constitute as a wound complication as the flap is used for closure. Should a flap need to be placed because of a wound complication after primary resection and final closure (either primarily or with a flap), then this would constitute as a CTC AE v 4.0 Grade 4 toxicity.

ii. Acute: Wound complications are expected to develop in about 30-40% of patients. Other common radiation adverse events include if applicable to site of lesion: fatigue, regional alopecia, diarrhea, skin erythema and desquamation within the treatment fields, and reduction in blood counts.

iii. Long-term: Common long-term treatment adverse events include: lymphedema of the extremity receiving radiation and surgery, subcutaneous fibrosis, and joint stiffness. Much less common radiation adverse events include osteoradionecrosis and bony fracture in the radiation field. There also is a risk of cancer occurring in a previously irradiated field.

iv. All AE's grade 3, 4 or 5 will be collected. AE's that are grade 1 or 2 will not be collected. AE's will be captured for up to 2 years post treatment, death, or initiation of a new therapy, whichever occurs first. Planned flaps are not considered an adverse event.

v. Table 5: Criteria for Early Closure or Dose Modification.

	Grade 4 Toxicity (per CTCAEv4.0)
Number of Events Prior to termination of accrual and evaluation of dose	>2
Evaluation	Assessment of treating physician, daily follow-ups with members of the radiation oncology department with toxicity specific management, documentation of care and progress.
Time to re-initiate Radiation	Once a grade 4 toxicity has resolved and at the discretion of treating radiation oncologist, the patient will be taken off study and treated to a lower dose per fraction. The physician will then close the study.
Action	Closure of trial

vi. The treating radiation oncologist will hold any radiation treatments as they feel is necessary due to the acute grade 3 or higher toxicity and the timing of re-initiation will be determined by the treating radiation oncologist, but will generally be when the grade 3 or higher toxicity resolves.

vii. Post-operative wound complications (not acute during radiation, as defined on Appendix III (Radiation dermatitis) are listed.

viii. If there are any grade 5 post-operative wound complications (Appendix III), then accrual will be halted and the protocol will be reviewed.

I. Documentation Requirements

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

J. Compliance Criteria

i. Section 6 describes appropriate conduct for treatment planning dosimetry. Criteria for both major and minor deviations are provided in Section 6.7.

K. Drug Therapy

i. Chemotherapy will be delivered prior to radiation at the discretion of the medical oncologists. Prior to radiation, patients will have a repeat MRI scan. Chemotherapeutic regimens will be determined at the discretion of the medical oncologist.

ii. There are no concomitant medications excluded for this patient population, with exception to chemotherapy. No chemotherapy will be delivered during this course of radiation therapy.

L. Surgery

i. Patients will have surgical resection 4 to 8 weeks after completion of radiation therapy. Prior to surgery patients will have repeat MRI scan with DCE and DWI sequences. (this is standard practice at our institution and would be done for patients not on protocol).

ii. Surgery type will be at discretion of surgeon. Pathology will evaluate the resected specimen and calculate the percent of necrotic (non-viable) tumor in the specimen. This is standard practice at most institutions is done for patients not on protocol. Pathology slides will be sent to the Wisconsin Diagnostic Laboratories (9200 West Wisconsin Avenue, Milwaukee, WI 53226). The designated pathologist reading the slides will be Dr. Saul Suster

iii. The patient's tissue will be stored at the MCW tissue bank. The patients will be consented for this prior to storing tissue.

M. Other Therapy

i. Supportive Therapy

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

VII. Post-Radiation and Surgery Follow-ups and Patient Assessments (Table 4)

A. Surgery will be scheduled 4-8 weeks after completion of hypofractionation radiation therapy.After surgery, patients will be seen by the radiation oncologists or surgeons every 4 months (+/- 2 month) for years 1 and 2 from the end of surgery. The exact assessments for these follow-up appointments are listed in Table 3. A 2-year follow-up is standard in STS and then endpoints assessed are overall and disease-free survival, as well as local control, toxicity and QOL in sarcoma studies.

B. Patients will be evaluated by a surgeon within 2 weeks (± 2 weeks) after surgery for evaluation of wound healing (this is standard practice).

C. Patients will be seen 4 months (+/- 2 month) after surgery (with physical exam) and at this time repeat imaging with a CT chest and MRI of the extremity will be obtained (this is standard practice for patients not on protocol). Treatment after failure will be at the treating team's discretion and documented.

D. Patient will be seen subsequently 4 months (+/- 2 months) afterwards with repeat imaging with a CT chest and MRI of the extremity for years 1 and 2. Anchor time points are from the end of surgery

E. Quality of life forms (see Appendix IV) will be filled out pre-treatment and at each follow-up visit beginning at the 4 months (+/- 2 month) from surgery visit with imaging.

F. Toxicity at all-time points will be assessed using the CTCAE version 4.0. This is the standard toxicity scoring system used in many protocols. QOL assessments will be made using the FACT-L questionnaire (Appendix IV).

Schedule of Events

Assessments	Within 16 weeks of Registration	Prior to start of RT	During RT	Prior to Surgery (within 4 weeks of surgery)	Surgery	Surgery Follow-up (Within4 weeks after surgery)	At 4 months (+/- 2 months) after Surgery and every 4 months (+/- 2 months) years 1 and 2
History/physical	**X**						**X**

Karnofsky PS	X			X			X
CBC with differential	X						
MRI - tumor site	X			X			X
CT Chest or PET CT	X			X			X
Pregnancy Test (if applicable)	X*						
Toxicity Evaluation		X	X	X		X	X
MSTS, FACT-L	X			X			X
Tissue Collection for Analysis	X				X		
Blood specimen for analysis	X						

Table 4: Study Parameters

***If applicable within 72 hours prior to CT simulation.**

VIII. Tissue/Specimen Submission

A. We will collect pretreatment diagnostic tissue and surgical specimens (1 formalin fixed paraffin embedded (FFPE) block) from patients who undergo biopsies to determine diagnosis for this research project, which is standard of care. Biopsy tissue will be sent for outside testing for RNA sequencing. The tissue will be stored on campus. The parameters to be reviewed are histologic, cell kinetic/proliferation, angiogenesis, and molecular markers have been and are under investigation. A number of biomarkers are under investigation by the Sarcoma group. These include SPARC, TYMS, RRM1, ENT1, ERCC1, TOP1, and TOP2A. These biomarkers will be assessed on biopsy and resection specimens for patients enrolled on the study. This assessment will be done in an ancillary study.

B. Blood specimen (10 ml EDTA) will be collected at the time of lab draw (within 16 weeks of registration) for biomarker testing. Specimens will be stored on campus and sent out for cytokine analysis.

i. Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
3. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 8) labeled with and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
5. Store frozen plasma until ready for testing.

IX. <u>Assessment of Safety, Dose Modifications and Dose Delays</u>

A. This study will be reviewed by the Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee (MCW CC DSMC). A summary of the MCW CC DSMC activities are as follows:

i. Review the clinical trial for data integrity and safety.

ii. Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.) Review all DSM reports.

iii. Sequential boundaries will be used to monitor the post-operative wound-complication rate. The accrual will be halted if excessive numbers of grade 3 or 4 (page 32) complications are seen, that is, if the number of complications is equal to or exceeds X out of N patients (X/N) with full follow-up (see below). This is a Pocock-type stopping boundary (Ivanova, et al. 2013) that yields the probability of crossing the boundary at most 5% when the complications rate is equal to 50% (O'Sullivan, eta l.2002).

iv. Accrual will halt for protocol review if 6/6 (6 patients out of the first 6), then 7/7, 8/8, 9/10, 10/11, 11/13, 12/14, 13/16, 14/18, 15/19, 16/21, 17/22, 18/24, 19/26, 20/27, 21/29, 22/31, 23/32, 24/34, and 25/35 grade 3-4 treatment related AE's.

v. Submit a summary of any recommendations related to study conduct.

vi. Terminate the study if deemed unsafe for patients.

B. A copy of the MCW Cancer Center Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes.

C. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

X. Subject Withdrawal Criteria

A. This Protocol is designed for 35 patients. Accrual will terminate early based on toxicity analysis. Patients may also withdraw at any point if they wish to not be on study.

B. Criteria for early Closure

i. Greater than 2 patients who have any grade 4 or higher toxicity during radiation. If a patient has a grade 4 or higher toxicity, then they will be taken off the study, administered a lower dose per fraction per the treating physician, and the study will be closed. We do expect grade 3 skin toxicity (moist desquamation in areas other than skin folds), as many patients have tumors that extend to the surface of the skin and thus will need to be bloused to get the appropriate dose to these areas. Thus, moist desquamation often occurs.

ii. ≥60% of patients with post-operative wound complications.

iii. As mentioned above, patients may also withdraw at any point if they wish to not be on study.

C. The research coordinator and PI will be notified of the withdrawal of a patient and the appropriate documentation will be made.

i. The IRB will be notified at the time of withdrawal.

D. Subjects will not be replaced.

E. Follow up and data collection for withdrawn subjects will terminate at the time of withdrawal.

F. Dose Modification

i. If any grade 4 toxicity occurs, the dose will be modified based on the BED calculator above and the study will be closed.

XI. Endpoint Assessment

A. Study Design:

i. This is a non-randomized Phase II pilot protocol to determine the feasibility, toxicity, and disease control (local control, overall and progression-free survival) using hypofractionated pre-operative radiation therapy in patients with primary localized STS.

B. Primary Endpoint:

i. The primary aim of this study is to assess local control. We expect local recurrence rates of <7%. Local and regional recurrence will be defined for each lesion per the treating physician(s). Local recurrence will be defined if the patient has evidence of disease on imaging (MRI or CT or PET CT) or physical exam.

C. Secondary Endpoint:

i. The secondary objective of this study is to assess quality of life, toxicity (see iii), disease-free survival and overall survival. Disease-free survival is defined as the time from enrollment until documented disease-recurrence or death, whichever occurs first. Patients who are disease-free and alive at the time of analysis will be censored at the time of their last follow-up. Patients will be followed for disease-free survival for a minimum of 2 years.

ii. Quality of life will be assessed via the FACT-L forms and given at the specified time points above.

iii. Toxicity from pre-operative hypofractionated radiation therapy for STS. Based on historical data, we expect there will be minimal toxicity, both acute and long-term. Adverse event rates will be compared at specific times using the CTCAE v 4.0.

iv. Changes in imaging with MRI (T2, T1 post contrast, DCE and DWI) as well as pathologic correlation (percent necrosis, fibrosis, viable cells and tumor biomarker expression will also be ascertained in this study.

v. Measure cytokine and tumor gene expression and immune response to radiation therapy and correlate with pathologic and clinical response.

D. Endpoint Analysis:

i. Crude rates of locoregional recurrences will be documented as well as the time to development of recurrence or relapse. Time of last follow-up or death will also be noted. This will allow us to calculate disease-free and overall survival rates. We will compare these results to an IRB approved database that exists on pre-operative radiation therapy using standard dose and fractionation at 2 Gy per fraction to 50 Gy.

1. This IRB approved database is a retrospective database in which patients with Stage I-III STS of the extremity and superficial trunk were treated with pre-operative radiation therapy using conventional fractionation. Crude rates of locoregional control, disease-free and overall survival will be assessed in this dataset.

2. The data in this database is acquired from all patients who were treated with preoperative RT for localized STS from 2000-2012. This is a retrospective database of the patients treated at Froedtert and the Medical College of Wisconsin

3. The variables included in this database include age, KPS, gender, cardiovascular history, smoking history, disease histology, location of disease, grade, MRI measurements, RT dose and dates, dates of surgery, pathologic findings including size, %necrosis, fibrosis and viable cells, margin status, wound complications, local recurrence, distant recurrence, survival, date of consult and last follow-up, and disease status.

XII. Statistical Considerations

A. The PRIMARY ENDPOINT of this study is to assess local control

B. The SECONDAY ENDPOINTS are to assess toxicity, quality of life, disease-free survival and overall survival. Also, changes in imaging (MRI) and pathologic outcomes (biomarkers, percent necrosis, fibrosis and viable cells) will also be assessed.

XIII. Power Considerations for Local Recurrence (Primary Endpoints)

A. The primary aim of a 2-year local recurrence rate of less than 3% will be evaluated by a one-sided equivalence test with an equivalence limit of 5% and a type I error rate of 10%. The study will conclude equivalence if the 2-year cumulative incidence of recurrence is less than 12% at the 0.10 type I error level. Power calculations are based on exact binomial probability calculations with an equivalence determined by no more than 12% local recurrence rate (within 5% of 7%), assuming a true 2-year local recurrence rate of 2.5%.
B. If the true local recurrence rate is 12%, then with 35 patients the probability of observing a recurrence rate of 3.1% or less (≤ 1 of 35) is 8.97% (one-sided type I error = 0.0897).
C. If the true local recurrence rate is 2.5%, then with 35 patients the probability of observing recurrence of 3.1% or less (≤ 1 out of 35) is 81.0% (Power).
D. This is as close as we can get to a one-sided equivalence test with 10% type I error and 80% power with exact binomial calculations. The probability of falsely rejecting the null hypothesis (*hypofractionation treatment is worse than standard*) with only 0 or 1 recurrence out of 35 patients is less than 10% if the actual recurrence rate is 12% or more. There will be at least 80% power to reject this hypothesis if the true recurrence is 2.5% or less.

XIV. Considerations for Toxicity, QOL, Disease-Free Survival and Overall Survival (Secondary Endpoints)

A. Overall survival and disease-free survival will be estimated using the product limit estimator and presented as Kaplan-Meier plots. Cumulative incidence rates will be calculated for local recurrence and adverse events. Quality of life data will be summarized for each time point, and compared using non-parametric statistical methods.
B. Toxicity will be measured via the CTCAE v. 4.0 and the MSTS score. We will compare toxicity to the standard historical control for preoperative radiation therapy in STS (NCIC, O'Sullivan et. *al*) (5)
C. Quality of Life will be measured with the FACT-L validated questionnaire.

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APPENDIX I

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX II

STAGING SYSTEM

AJCC 7th Edition (2009)
Primary Tumor:

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

Regional Lymph Nodes:

- N0 - no
- N1 - yes

Distant Metastases:

- M0 - none
- M1 - yes

Stage Grouping:

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

APPENDIX III

CTCAE 4.0 Toxicity Grading

Edema

Grade	Toxicity
1	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection
2	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL
3	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL
4	-
5	-

Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.

Radiation Dermatitis

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

Fibrosis

Grade	Toxicity
1	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)
2	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL
3	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL
4	Generalized; associated with signs or symptoms of impaired breathing or feeding
5	Death

Post-operative Wound Complications

Grade	Toxicity
1	Incisional separation of <=25% of wound, no deeper than superficial fascia
2	Incisional separation >25% of wound; local care indicated
3	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated
4	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated
5	Death

Musculoskeletal Tumor Rating Scale-Upper Extremity

PAIN		FUNCTION	EMOTIONAL	HAND POSITIONING	MANULA DEXTERITY	LIFTING ABILITY
5	No pain	No restriction	Enthused	Unlimited	Unlimited	Normal load
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
3	Modest/Non-disabling	Recreational restriction	Satisfied	Not above shoulder or no/Prosupination	Loss of fine movements	Limited
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
1	Moderate/Disabling	Partial restriction	Accepts	Not above waist	Cannot pinch	Helping only
0	Severe disabling	Total restriction	Dislikes	None	Cannot grasp	Cannot help

Musculoskeletal Tumor Rating Scale-Lower Extremity

SCORE	PAIN	FUNCTION	EMOTIONAL	SUPPORTS	WALKING	GAIT	Final Patient Score of FUNCTIONAL EVALUATION
5	No pain	No restriction	Enthused	None	Unlimited	Normal	
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	
3	Modest/Non-disabling	Recreational restriction	Satisfied	Brace	Limited	Minor cosmetic	
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	
1	Moderate/Disabling	Partial restriction	Accepts	One cane or crutch	Inside only	Major cosmetic	
0	Severe disabling	Total restriction	Dislikes	Two canes or crutches	Not independent	Major handicap	
Patient score							

Appendix IV-Fact-L (Version 4) Quality of Life

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

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

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

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

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

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

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

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

English (Universal) 16Nov2007

Abbreviations (Alphabetical Order)

3D-CRT: 3D Conformal Radiation Therapy

ANC: Absolute Neutrophil Count

BED: Biologic Equivalent Dose

cGy: Centigray

CTCAE: Common Terminology Criteria for Adverse Events

CTO: Clinical Trials Office

CTV: Clinical Target Volume

DCE: Dynamic Contrast Enhancement

DWI: Diffusion Weighted Imaging

DSMC: Disease Site Monitoring Committee

FACT-L: Functional Assessment Cancer Therapy-General

GTV: Gross Tumor Volume

Gy: Gray

HR: Hazard Ratio

IGRT: Image Guided Radiation Therapy

IMRT: Intensity Modulated Radiation Therapy

IRB: Institutional Review Board

KPS: Karnofsky Performance Status

MAID: Mesna, Adriamycin, Ifosfamide and Dacarbazine

MV: Megavoltage

NCI: National Cancer Institute

NS: Non-specific

QOL: Quality of Life

PTV: Planning Target Volume

PI: Principal Investigator

PNET: Peripheral neuroectodermal tumor

RT: Radiation Therapy

ROI: Region of Interest

RTOG: Radiation Therapy Oncology Group

STS: Soft Tissue Sarcomas