IRB# 5120263 A phase II study of preoperative proton therapy in soft tissue sarcomas of the extremities and body wall

NCT# 01819831

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Index

Schema

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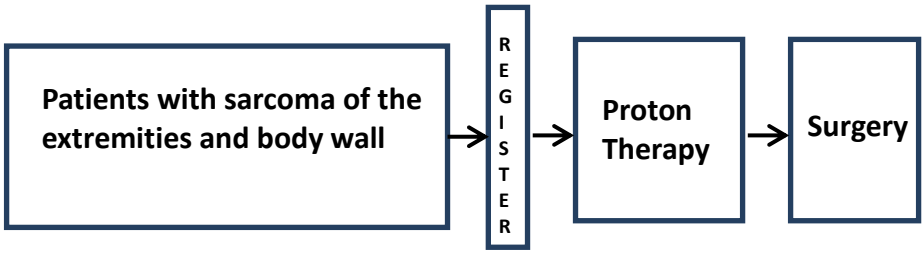

Registration → 50 Gy in 25 daily fractions with proton radiotherapy→ Surgery within 8 weeks after completion of radiation

Patient Population / disease: Histologically confirmed primary soft tissue sarcoma of the extremity and body wall; sarcomas of the retroperitoneum, hand, or foot are ineligible.

1.0 Introduction

1.1

Soft tissue sarcomas (STS) are relatively rare, heterogeneous malignancies that may arise almost anywhere in the body. However, the most common sites for STS are in the extremities and trunk. Kattan et al reported on 2136 patients treated at Memorial Sloan Kettering Cancer Center and observed these distributions: lower extremity (40.5%), upper extremity (16.6%) and thoracic or trunk (17.5%).[1] The mainstay of treatment for low-grade sarcomas is surgery with wide resection, which yields a high likelihood of local control; radical resection is required for high-grade lesions to achieve similar outcomes.[2-3] The goal of surgery is to obtain a tumor-free margin; if that is not possible due to adjacent structures, adjuvant radiation is often employed.

Although delivery of radiotherapy in large or high-grade extremity sarcoma is considered standard, there is controversy regarding the appropriate timing of radiation delivery in relation to surgery. Nonetheless, data support preoperative radiotherapy as one of the standard options in the management of extremity STS. The advantages of preoperative (as opposed to postoperative) radiotherapy are that, generally, a lower dose and smaller radiation volumes may be used with potential improvement of long-term side effects and extremity function.[4-6] Another potential advantage is assisting surgery through tumor shrinkage and reduction of tumor cell seeding.[7-8] A retrospective review of 317 patients treated at the University of Florida from 1980-2007 with preoperative radiotherapy as part of a limb-conservation strategy showed that marginal resection (no tumor at inked margin) after preoperative radiation does not compromise local control or amputation-free survival when compared to wide/radical margins.[9] This was felt to be related to radiosterilization of tumor cells within the reactive zone following preoperative radiation.

The disadvantage of preoperative radiation is the higher likelihood of postoperative wound complications.[6-12] A prospective randomized trial of preoperative versus postoperative radiotherapy by the NCIC CTG showed that the rate of wound complications increased from 17% to 35% with preoperative radiation therapy,[6] albeit these complications were generally temporary, without significant effect on long-term function. Additionally, the NCIC trial showed that more serious chronic side effects occurred in the cohort receiving postoperative radiotherapy because those patients were generally treated to higher doses with larger treatment volumes.[13]

Combined conservative surgery and radiotherapy has been shown to achieve excellent local control in sarcoma patients following margin-negative surgery, but late radiation morbidity and reduced quality of life may result from adjuvant radiation.[13-15] In the NCIC CTG trial, patients that received postoperative radiation had higher rates of grade 2 or greater fibrosis (48% versus 31.5%), increased edema (23% versus 15.1%) and joint stiffness (23% versus 17.8%).[13] Although patients in the preoperative group had a lower rate of late effects, these effects were still substantial, occurring in 64.4% in the preoperative arm at 2 years following treatment.Increased field size and higher radiation dose were predictive of increased late effects. A prospective trial of sarcoma patients at Memorial Sloan Kettering Cancer Center, which randomized patients to postoperative adjuvant brachytherapy versus observation, showed a significant improvement in local control for patients receiving brachytherapy.[7] The brachytherapy target region was determined by adding 2 cm margins in the superior and inferior dimensions of the tumor bed, with 1.5-2 cm

added in the medial and lateral directions. Among those patients with a local recurrence after adjuvant brachytherapy, the majority had “in-field” local recurrences. A retrospective review of patients treated in prospective trials at Princess Margaret Hospital, Toronto, Canada, for extremity soft tissue sarcoma with preoperative radiotherapy excised with a positive margin (including patients treated in the NCIC CTG trial) showed that including the postoperative radiation boost for patients treated with preoperative radiation and margin-positive excision did not provide an advantage in preventing local recurrence for patients treated with external-beam radiotherapy.[16] Given that higher radiation doses also place patients at higher risk for late radiation morbidity, patients on the proposed trial will not undergo an additional postoperative radiation boost after adequate preoperative proton radiation.

More recently the Radiation Therapy Oncology Group (RTOG) has completed a phase II trial to determine whether a reduced radiation volume preoperatively with image-guided, intensity-modulated radiation therapy (IMRT) can improve upon late effects of lymphedema, subcutaneous fibrosis, and joint stiffness. This study will provide important information about whether late radiation morbidity is further reduced without compromising tumor control using reduced-field-volume preoperative radiotherapy. Preliminary results presented in an abstract at the 53rd annual meeting of the American Society for Radiation Oncology in October 2011 showed that acute toxicity profiles in patients with extremity STS treated with preoperative image-guided radiation therapy followed by surgery were acceptable, with 37% of patients experiencing major acute wound complications.[16] Longer follow-up is required to show improvement in late toxicity and/or possible reduction in local control with smaller volumes irradiated.

The rationale for using proton beam radiotherapy is the superior dose distribution that can be achieved in comparison with photon-based techniques. Protons and other charged particles deposit little energy in tissue until near the end of the proton range; there, the residual energy is lost over a short distance, resulting in a steep rise in the absorbed dose known as the Bragg peak. Proton dose distributions are characterized by a lower-dose region in normal tissue proximal to tumor, a uniform high-dose region in the tumor, and zero dose beyond the tumor.[18-20] Also, IMRT treatment plans often include localized areas within the high-dose volumes where dose inhomogeneity can be as high as 15-20% above the target dose. Depending on the location of these “hot spots,” there can be unanticipated acute normal-tissue toxicity.[21] Whether there are late effects attributable to these focal hot spots is unclear. Proton dose distributions are generally more homogenous. The dosimetric advantage of proton radiotherapy may translate into improved acute and late effects due to improved normal-tissue sparing in the treatment of extremity and truncal soft tissue sarcoma. However, these potential advantages need to be validated in clinical trials.

We propose a phase II study to evaluate the effect of preoperative proton radiotherapy on the reduction of late radiation morbidity, patterns of failure, local failure rate, and impact of late radiation morbidity on general quality of life (QOL).

2.0 Objectives

2.1 Primary objective

2.1.1 – To determine the effect of reduced radiation volume with proton radiotherapy on combined late radiation toxicities (>grade 2 lymphedema, subcutaneous fibrosis, and joint stiffness) at 2 years from the start of radiation treatment

2.2 Secondary Objectives

2.2.1 – To estimate CTCAE, v4.0 grade 3-5 adverse events;

2.2.2 – To determine patterns of failure, including local failure (in-field, marginal, out-of-field), regional failure, distant failure, and death without disease progression;

2.2.3 – To estimate the rates of local failure, local-regional failure, distant failure, distant-disease-free survival, disease-free survival, overall survival, and second primary tumor;

2.2.4 – To estimate rates of wound complications

2.2.5 – To correlate degree of late radiation morbidity at 2 years with quality of life assessment (FACT-G)

2.2.6 – To estimate the tumor necrosis rate following preoperative proton therapy

3.0 Patient Selection

3.1 Conditions for Patient Eligibility

3.1.1 – Histologically proven primary soft tissue sarcoma of the upper extremity (including shoulder), lower extremity (including hip) or body trunk (excluding retroperitoneum). Sarcomas of the hand or foot are ineligible.

3.1.2 – A biopsy must be done within 16 weeks prior to registration.

3.1.3 – No distant metastatic disease based on history/physical, MRI or CT of the tumor with contrast, CT scan of chest, and CT scan of abdomen and pelvis for intermediate to high-grade lesions. These scans must be done within 16 weeks prior to registration.

3.1.4 – Evaluation by surgeon, with documentation that the tumor is resectable

3.1.5 – ECOG performance status 0-1

3.1.6 – Age >18

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3.1.6 – Age >18

3.1.7 – For females of childbearing potential, a serum pregnancy test within 4 weeks prior to registration

3.1.8 – Patient must practice adequate contraception

3.1.9 – Patient must provide study-specific informed consent prior to study entry

3.1.10 – CBC/differential obtained within 12 weeks prior to registration with adequate bone marrow function (ANC >1500 cells/mm^3, platelets >100,000, and Hemoglobin >8 g/dl.

3.2 Conditions for Patient Ineligibility

3.2.1 – Patients with sarcoma of the head, neck, intra-abdominal or retroperitoneal region, hand, or foot

3.2.2 – Histopathology demonstrating rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor (PNET), soft tissue Ewing's sarcoma, osteosarcoma, Kaposi's sarcoma, angiosarcoma, aggressive fibromatosis, dermatofibrosarcoma protuberans or chondrosarcoma

3.2.3 – Lymph node or distant metastases

3.2.4 – Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years

3.2.5 – Prior radiotherapy to the potential target anatomic region that would result in overlap of radiation fields for current sarcoma

3.2.6 – Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to used medically acceptable forms of contraception;

4.0 Drug Therapy – No Drugs used in this study

5.0 Surgery

5.1 Initial Biopsy

5.1.1 – An incisional biopsy or core needle biopsy is required. If needle biopsy is done, the site should be tattooed for future identification. Biopsy should be performed in such a way as to permit excision of the biopsy site at the time of formal resection

5.2 Surgery

5.2.1 –The surgeon and radiation oncologist must see the patient prior to preoperative therapy.

5.2.2 –Margin status. Sarcomas require resection of the entire tumor as well as a margin of normal tissue.[22] A positive margin or a negative margin of 2 mm or less has been shown to have a higher risk of local recurrence and decreased long-term survival.[23] The goal of radiation is to “sterilize” the periphery of the tumor to kill or disable tumor cells most at risk of remaining in the wound. In areas with ample soft tissue that can be removed without compromising future function or wound closure, wide margins is the goal of treatment; associated rates of local failure are low in such instances. Margins will be determined by the surgeon; the goal is to achieve at least a 2 mm negative margin resection. The surgeon should determine and document a high possibility of limb preservation approach after preoperative radiation to obtain local control.

However, smaller margins can be acceptable if it allows for limb-sparing surgery with conserved functional outcomes. A retrospective review of 132 patients treated at Massachusetts General Hospital from 1974-1998 for extremity STS with preoperative RT and limb-sparing surgery showed that 5-year local control was inferior in patients with positive margins (82%) compared to negative margins ≤ 1 mm (94%) and > 1 mm (97%).[24] A modern series from Massachusetts General Hospital of 56 similarly treated patients reported a 5-year local control rate of 93.2%, with all local failures observed occurring in patients with positive margins or <1 mm margins.[25] Similarly treated patients at MD Anderson Cancer Center showed decreased local control (62% vs 91%) for positive surgical margins compared to negative margins.[26] When radiation is used, margins that are 1 mm or less can be accepted, allowing for limb-sparing surgery and decreased morbidity.

Additionally, when the tumor grows close to a critical structure such as a major motor nerve or bone, the margins will be unavoidably close for function preservation. Careful dissection of these fixed structures, such as epineural dissection of a major nerve or periosteal resection along bone, is possible when combined with adjuvant radiation therapy.[27,28] These “planned positive” margins have similar local recurrence rates to those observed with negative margins.[29] After radiation, every effort should be made to have limb preservation surgery unless there is documented evidence of tumor progression during or after the course of radiation that would require amputation for an appropriate margin resection.

6.0 Radiation Therapy

6.1 Dose Specification

6.1.1 – Preoperative proton radiation therapy. The total dose will be 50 Gy in 25 fractions, with a minimum of 90% of PTV receiving 50 Gy.

6.2 Technical factors

6.2.1 -Treatment will be delivered with selection of appropriate proton energies to optimize the radiotherapy dose distribution within the target volume and minimize dose to non-target tissues

6.2.2 – PTV includes setup uncertainty and lateral uncertainties perpendicular to the beam direction. Each beam will be optimized to adjust for range uncertainties to guarantee adequate coverage of the PTV.

6.3 Localization, Simulation, and Immobilization

6.3.1 – Patient positioning will be based on clinical judgment to best achieve the ideal dose distribution using a variety of devices for limb/body immobilization

6.4 Treatment planning/Volume definitions

6.4.1 –CT-based 3D treatment planning will be used for all patients. Simulation will be done on a CT scan with limb/body immobilization

6.4.2 – Gross Tumor Volume (GTV): Gross tumor will be defined as MRI T1 plus contrast image (MRI with contrast is required). Fusion of MRI and CT will be used to delineate the GTV for radiotherapy planning.

6.4.3 – Clinical Target Volume (CTV): 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 directions. If this causes the radiation field to extend beyond the compartment, the field can be shortened to include the end of the 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.

6.4.4 – Planning Target Volume (PTV): Includes CTV and error of setup and organ motion. The PTV will include setup uncertainties, depending on immobilization method and daily image guidance.

6.4.5 – 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 or may not be contoured as CTV.

6.5 Critical Structures

6.5.1 – Radiation dose to normal tissues should be kept within accepted normal tissue tolerances when using standard 2 Gy fractionation schedules. Every effort will be made to avoid treating the full circumference of an extremity; avoid treating the anus, vulva, scrotum, or lung; and avoid treating the skin to the full dose over areas commonly traumatized (e.g. elbow, knee, etc.), and femoral head/neck.

6.5.2 – If tumor is close to the structures mentioned in 6.5.1, typically less than 50% volume of the anus and vulva should receive 30 Gy; less than 50% volume of the testis should receive 3 Gy, if fertility preservation is desired; 20% of lung should receive less than 20 Gy (V20); and less than 5% of the femoral head/neck should receive 60 Gy. Less than 50% of any joints (including shoulder, elbow, and knee) should receive 50 Gy. Less than 50% of kidney volumes should receive 14 Gy. For any other normal-tissue structures, no radiation dose more than established TD 5/5 limits should be given.

6.5.3 – No more than 50% of a longitudinal strip of skin and subcutaneous tissue of an extremity should receive 20 Gy. This strip of normal tissue will be contoured by the treating radiation oncologist. Full prescription dose to skin over areas commonly traumatized should be avoided.

6.5.4 – No more than 50% of weight-bearing bone within the radiation field should receive 50 Gy, except when the tumor invades the bone or when there is circumferential involvement of the tumor in more than a quarter of the bone, or when the bone will be resected in a subsequent surgical resection after radiation.

6.5.5 – There is no special requirement for skin dose limit. However, skin sparing is recommended if possible. Skin surface (5 mm thickness) including scar for incision biopsy is not included in CTV or PTV and is not bolused, unless the biopsy scar is not subsequently resected after preoperative radiotherapy.

6.6 Radiation adverse events

6.6.1 – Acute: Wound complications are expected in about a third of patients. Other common adverse events include: fatigue, regional alopecia, diarrhea, skin erythema, and desquamation in treatment fields.

6.6.2 – Long-term: Common long-term events include: lymphedema of the extremity receiving radiation and surgery, subcutaneous fibrosis, and joint stiffness. Less common events include bowel injury, osteoradionecrosis, and bony fracture in the radiation field. There is also a risk of secondary cancer in previously irradiated fields.

6.7 Radiation adverse event reporting

6.7.1 – This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for reporting of adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP web site.

http://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

7.0 Patient Assessments

7.1 – Study Parameters

	Pre-TX	Weekly during Proton treatment	Post Proton treatment prior to surgery	Q3 months in years 1-2 after surgery and/or postoperative proton therapy, then Q6 months in year 3-6
Pathologically confirmed dx	X			
History/Physical exam with weight	X	X	X	X
MRI and/or CT with contrast of tumor	X		X Can be either MRI or CT	Q6 months in years 1-2, then annually (either MRI or CT)
CT of chest	X			Q6 months in years 1-2, then annually
CT of abdomen & pelvis	X			
Performance status	X	X	X	X
CBC w/ diff & ANC	X			
Pregnancy test (if applicable)	X			
Thyroid function test	X If thyroid in RT field			
MSTS	X			At 12, 18, and 24 months from start of proton treatment
FACT-G	X			At 12, 18, and 24 months from start of proton treatment
Toxicity assessment		X	X	X

7.2 Pretreatment evaluation – see table above and section 3.0 for all pretreatment assessments

7.2.1 – The physician or designee will complete the Musculoskeletal Tumor Rating Scale (MSTS) prior to treatment (see Section 7.8)

7.2.2 – The patient will complete the Functional Assessment of Cancer Therapy –General (FACT-G) prior to protocol treatment

7.3 Evaluation during proton radiation treatment

7.3.1 – MRI or CT with contrast of primary site should be performed 3-5 weeks after preoperative radiation therapy for surgical evaluation (surgery is done within 8 weeks after RT).

7.3.2 – Physical examination should be done weekly during radiation therapy

7.4 Evaluation after Treatment

7.4.1 – Wound complications and late radiation morbidity are reported on appropriate scales. (see section 7.6)

7.4.2 – The patient will complete FACT-G quality of life assessment at 12, 18, and 24 months from the start of radiation treatment

7.5 Failure Pattern of Recurrence

7.5.1 – All tumor recurrences including local, regional, and distant recurrence, along with second primary tumors, shall be recorded.

7.5.2 – Local tumor recurrence – Any tumor recurrence inside the CTV is defined as “in-field recurrence”; any tumor recurrence beyond the CTV to within 2 cm distance to edge of CTV is defined as “marginal recurrence” and considered “geographic miss”; any other local recurrence is defined as “outside-field recurrence”.

7.5.3 – Local tumor progression: At least a 20% increase in the maximal dimension of the primary tumor, taking as reference the smallest maximal dimension recorded since treatment started

7.5.4 – Regional tumor recurrence – Any nodal metastasis adjacent to the primary soft tissue sarcoma

7.5.5 – Distant tumor recurrence – Any tumor recurrence that develops distantly from the primary site of sarcoma

7.5.6 – Second primary tumor – Any different histology of sarcoma or any other type of malignancy inside or outside the radiation field.

7.6 Wound Complications and Late Radiation Morbidity

7.6.1 – Wound complications – Major wound complications, such as secondary operations, re-admissions, and/or invasive procedures for wound complication (deep wound packing and/or prolonged dressing changes) will be reported

7.6.2 – Late radiation morbidity – Lymphedema, late subcutaneous fibrosis and joint stiffness arising directly from the radiation treatment, as well as limb function and physical disability, must be recorded

7.6.3 – Late subcutaneous fibrosis and joint stiffness are assessed using the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) late toxicity scoring criteria (see Table below)

Table 1. EORTC/RTOG Late Radiation Toxicity Criteria for late subcutaneous fibrosis and joint stiffness

Tissue	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Subcutaneous Tissue	None	Slight fibrosis; subcutaneous fat loss	Moderate fibrosis: slight field contracture	Severe fibrosis; field contracture >10%	Necrosis
Joint	None	Mild stiffness; slight range of motion loss	Moderate stiffness, pain, range of motion loss	Severe stiffness, pain, range of motion los	Necrosis; complete fixation

7.6.4 – Lymphedema is measured according to the criteria of Stern. (see Table below)

Table 2. Stern's Rating Scale for Edema

Score	Rating
0	None
1	Mild (but definite swelling)
2	Moderate
3	Severe (considerable swelling)
4	Very severe (skin shiny and tight +/- skin cracking)

7.6.5 – The scoring criteria provided in Tables 1-2 above are specific to subcutaneous fibrosis, joint stiffness, and edema. These scales were used in a randomized phase III trial in Canada and a recent phase II RTOG trial, to which our data will be compared.[13,16] For comparative purposes, subcutaneous fibrosis, joint stiffness, and edema should also be scored according to the CTCAE v.4.0. For grading of all other adverse events, we will use CTCAE v.4.0 only. Other late radiation morbidities, including bony fracture in the field of radiation, will be recorded.

7.7 Criteria for Discontinuation of Protocol Treatment

7.7.1 – Protocol treatment may be discontinued for any of the following reasons: disease progression; unacceptable adverse event; delay in protocol treatment >12 weeks.

7.7.2 – If protocol treatment is discontinued, follow up and data collection will continue as specified in protocol

7.8 Musculoskeletal Tumor Rating Scale (MSTS)

7.8.1 – The MSTS[30] is a measure of physical function across 7 items, completed by the physician (preferably by the orthopedic surgeon or Surgical Oncologist) or the physician's designated staff. The 7 items are: pain, range of motion, strength, joint stability, joint deformity, emotional acceptance, and overall function. Each item is scored from 0-5 with a maximum possible score of 35. The MSTS has been in use for over 20 years and is a widely recognized and utilized tool used to evaluate physical function. The MSTS can be completed in approximately 10 minutes by a clinician familiar with the rating. The MSTS rating will be performed at the following time points: prior to start offing on protocol (baseline), and at 12, 18, and 24 months after start of proton radiation therapy.

7.9 Quality of Life

7.9.1 – Patient quality of life will be assessed using the Functional Assessment of Cancer Therapy – General (FACT-G) assessment. The FACT-G[31] is a commonly used tool measuring general quality of life across 4 scales: physical, emotional, social/family and functional well-being. It has been written at a 4th grade reading level, and a patient can generally complete the survey in 5-10 minutes. The FACT has been translated into 26 languages, and translations are accessible at the FACIT web site, **http://www.facit.org/translation/licensure.aspx**.

8.0 Statistical considerations

8.1 Study endpoints

8.1.1 – Primary endpoint – To determine the effect of reduced radiation volume with proton radiotherapy on combined late radiation toxicities (>grade 2 lymphedema, subcutaneous fibrosis, and joint stiffness) at 2 years from the start of radiation treatment using EORTC/RTOG criteria. See section 7.6.3-7.6.4.

8.1.2 – Secondary endpoints

8.1.2.1 – To estimate the effect of reduced radiation volume with proton radiotherapy on late radiation morbidity at 2 years from start of radiation treatment using CTCAE, v.4.0 criteria.
8.1.2.2 – Other CTCAE, v.4.0 grade 3-5 events
8.1.2.3 – To determine pattern of first failure
8.1.2.4 – Time to local failure
8.1.2.5 – Time to regional failure
8.1.2.6 – Time to distant failure
8.1.2.7 – Distant-disease free survival (distant failure or death due to any cause).
8.1.2.8 – Disease free survival (local, regional or distant failure or death due to any cause)
8.1.2.9 – Overall survival (death due to any cause)
8.1.2.10 – Time to second primary tumor
8.1.2.11 – Estimate the rate of wound complications
8.1.2.12 – To assess the impact of late radiation morbidity at 2 years on clinical measure, MSTS
8.1.2.13 – To correlate late radiation morbidity at 2 years with quality of life assessment, FACT-G
8.1.2.14 – Estimate the rate of tumor necrosis

8.2 Overview and Sample size

8.2.1 – This prospective study is designed to assess late radiation toxicity. The primary endpoint is whether or not a patient experiences at least 1 of the 3 toxicities at a severity of grade 2 or greater at 2 years from start of radiation treatment. The NCIC study showed 31.5% grade 2 or greater fibrosis, 15.1% lymphedema and 17.8% joint stiffness in the preoperative arm at 2 years following treatment, and 37% of patients had at least one of these 3 toxicities at 2 years.

8.2.2 – We will test for a 20% absolute decrease in combined toxicity. A sample size of 41 patients is required to show a 20% decrease with a significance level of 0.05 and 90% power. Assuming that 5% of patients will be retrospectively ineligible and an additional 15% will not have a 2-year assessment for the primary endpoint due to death or loss to follow up, the total targeted sample size in this study is 51 patients.

8.3 Safety Monitoring and Data Reporting

8.3.1 – The overall safety data will be monitored regularly and incorporated into interim reports prepared at regular intervals during study enrollment and follow-up. Interim reports will be prepared every six months until the primary endpoint has been evaluated in all participants and made available to the institutional review board. Overall safety monitoring will occur weekly during treatment and at each follow-up visit. The principal investigator will be responsible for collection of data and preparation of interim reports. In general, these reports include:

8.3.1.1 – Institutional accrual, accrual rate with projected completion date

8.3.1.2 – Pretreatment characteristics

8.3.1.3 – Compliance rates of treatment delivery with respect to the protocol prescription

8.3.1.4 – Frequency and severity of reported adverse events

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