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A Phase II Study of Hypofractionated Pre-Operative Radiation Therapy for Localized, Resectable Soft Tissue Sarcoma of the Extremity or Superficial Trunk

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Protocol Resources

Questions:	Contact Name:
Patient eligibility, test schedule, treatment delays/interruptions/ adjustments, dose modifications, forms completion/ submission, & adverse events	Radiation Oncology Study Team Contacts listed on the consent form
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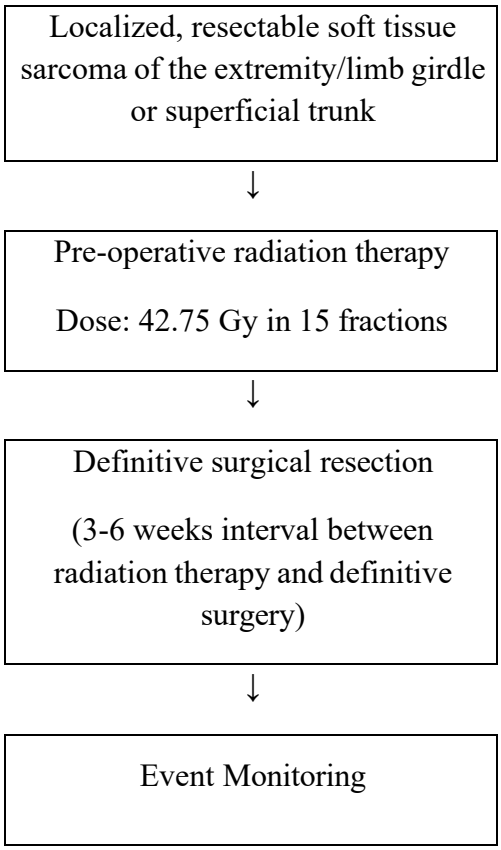
Study Schema



List of Abbreviations

AE	Adverse Event/Adverse Experience
BID	Twice daily
cGy	centiGray
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DSMB	Data and Safety Monitoring Board
DVH	Dose Volume Histogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ER / ES	Electronic Record and Electronic Signature
Gy	Gray
GTV	Gross Tumor Volume
ICRU	International Commission on Radiation Units and Measurements
IMPT	Intensity Modulated Proton Therapy
IMRT	Intensity Modulated Radiotherapy
IND / IDE	Investigational Drugs and Devices
IRB	Institutional Review Board
ITV	Internal Target Volume
LFR5	Local Failure Rate at 5 years
MCCC	Mayo Clinic Cancer Center
MRI	Magnetic Resonance Imaging
PROMISE	Patient-Reported Outcomes Measurement Information System
PS	Performance Status
PTV	Planning Target Volume
RBE	Relative Biological Effectiveness
RT	Radiation Therapy
SOC	System Organ Class
TESS	Toronto Extremity Salvage Score
UPIRTSO	Unanticipated Problems Involving Risks To Subjects or Others
VMAT	Volumetric Modulated Arc Therapy
3DCRT	3D Conformal Radiation Therapy

1.0 Background and Rationale

Approximately 12,000 patients are diagnosed with soft tissue sarcomas annually in the United States, accounting for 1% of all adult malignancies.[1] Given the rarity, diversity (> 60 different histologies), and treatment complexity associated with soft tissue sarcomas, patients routinely undergo treatment at specialty centers. Historically, extremity soft tissue sarcomas were treated with amputation. Advances in radiation therapy and surgical techniques, however, have made radiation therapy plus limb-salvage surgery the standard treatment for most localized, extremity soft tissue sarcomas.[2-5] Superficial trunk soft tissue sarcomas are treated in a similar fashion. With this multi-modal treatment approach, the 5 year local recurrence rate for extremity and superficial trunk soft tissue sarcomas is ≤10%.[6]

Radiation therapy can be administered preoperatively, intraoperatively, postoperatively, or as a combination of the aforementioned.[2,3,7] Preoperative radiation therapy is associated with a higher acute wound complication rate compared to postoperative radiation therapy.[6] O'Sullivan et. al. reported a 35% acute wound complication rate with preoperative radiation therapy compared to a 17% rate with postoperative radiation.[6] Acute wound complication was defined as a major wound issue requiring an invasive intervention (i.e., second surgery or hospitalization for wound care) within 3 months of surgery.[6] Several other reports document similar acute wound complication rates.[8-12]

Many centers in the Unites States and abroad favor pre-operative radiation therapy due to the lower total radiation dose administered (50 Gray (Gy) versus 60-66 Gy) and smaller treatment volume compared to postoperative radiation therapy. These aspects are thought to contribute to the lower irreversible, long-term toxicity rates seen with preoperative radiation therapy.[13,14] Davis et. al. reported more frequent rates of fibrosis (48.2% versus 31.5%), edema (23.2% versus 15.1%), and joint stiffness (23.2% versus 17.8%) with postoperative radiation therapy compared to preoperative radiation therapy.[14] Higher rates of irreversible, long-term toxicities adversely affect patient function.[13,14] Lastly, preoperative radiation therapy optimizes the chances of obtaining a margin-negative resection and may decrease the potential for metastatic cell spread at time of surgery.[6,8,15]

The radiation therapy course for soft tissue sarcomas is certainly long, with total number of fractions ranging from 25 fractions (preoperative treatment) to 33 fractions (postoperative treatment). Given the financial and time commitments associated with the radiation treatment length, there are potential benefits for patients by reducing the number of daily fractions administered. Shorter treatment duration can translate to reduced costs and improved patient experiences due to reduced travel times, decreased time off work and away from family, and lessened financial demands associated with pursuing treatment at a specialty center. Additionally, a shorter radiation course may lead to higher limb preservation rates and improved survival in minority groups as outcomes are known to be inferior in African American and Latino populations compared to the Caucasian population.[16,17]

One method to shorten radiation treatment length is to administer a hypofractionated treatment course. Hypofractionated radiation therapy administers the total radiation dose

as larger daily doses compared to conventionally fractionated therapy. This effectively reduces the overall treatment duration by weeks. Hypofractionated radiation therapy is proven to be a more convenient and lower cost option for early stage breast and prostate cancers, without compromising oncologic outcomes or increasing the likelihood of treatment-related side effects.[18-20] For example, Whelan et. al. demonstrated the efficacy of a hypofractionated postoperative treatment course (42.56 Gy in 16 fractions) for early stage breast cancer compared to conventionally fractionated treatment (50 Gy in 25 fractions).[20] At 10 years, the local recurrence rate was 6.7% for conventionally fractionated radiation therapy versus 6.7% for hypofractionated radiation therapy.[20] Additionally, there was no difference in overall survival or cosmetic outcomes between the two treatment arms.[20]

Hypofractionated radiation therapy has been studied to a more limited degree in soft tissue sarcomas. In Poland, a study of hypofractionated preoperative radiation therapy (25 Gy in 5 fractions) was conducted in 272 patients from 2006 to 2011.[21] This study yielded a higher local failure rate: 19%, with a median follow up of 35 months.[21] Of note, the biologic effective dose is 34.27 Gy_{10} with this regimen compared to 43.83 Gy_{10} with conventional fractionation, suggesting a higher biologic effective dose is needed with hypofractionation to achieve optimal outcomes. Another preoperative hypofractionated study from University of California Los Angeles studied 28 Gy in 8 fractions (biologic effective dose of 32.63 Gy_{10}).[22] The local failure rate at 3 years was 11%.[22] Again, these results suggest a higher total radiation dose is needed for efficacy when utilizing a hypofractionated radiation treatment course in soft tissue sarcomas.

We propose conducting a single arm, prospective study to evaluate the efficacy and safety of a preoperative hypofractionated course, 42.75 Gy in 15 fractions, for localized, extremity and superficial trunk soft tissue sarcomas. The biologic equivalent dose of this regimen is 45.20 Gy_{10}, similar to 43.83 Gy_{10} associated with conventionally fractionated 50 Gy in 25 fractions. The primary aim of the study is to determine acute wound complications rates, as defined by O'Sullivan et. al.[6] Secondary aims will analyze local failure rate, disease-free survival, overall survival, patterns of relapse, late toxicities, and quality of life/patient-reported outcomes. We hypothesize a 15 fraction hypofractionated radiation therapy course will be associated with equivalent short-term toxicity rates and oncologic outcomes as compared to historical standards.

2.0 Goals

2.1 Primary Objective

2.1.1 To report the major acute wound complication rate associated with hypofractionated preoperative radiation therapy, 42.75 Gy in 15 fractions. See section 11.1 for definition of major acute wound complications.

2.2 Secondary Objectives

2.2.1 To report the 5-year local failure rate associated with hypofractionated preoperative radiation therapy, 42.75 Gy in 15 fractions.

2.2.2 To report the 5-year disease-free survival rate associated with hypofractionated preoperative radiation therapy, 42.75 Gy in 15 fractions.

2.2.3 To report the 5-year overall survival rate associated with hypofractionated preoperative radiation therapy, 42.75 Gy in 15 fractions.

2.2.4 To report long-term toxicity rates associated with hypofractionated preoperative radiation therapy, 42.75 Gy in 15 fractions.

2.2.5 To describe patterns of relapse associated with hypofractionated preoperative radiation therapy, 42.75 Gy in 15 fractions.

2.2.6 To describe patient reported outcomes/quality-of-life outcomes with hypofractionated preoperative radiation therapy, 42.75 Gy in 15 fractions.

3.0 Patient Eligibility

The patient must meet all selection criteria as specified in Section 3.1 and be agreeable to adhere to the follow-up evaluations and schedule. Written informed consent must be obtained from the patient prior to enrollment and prior to any trial-specific evaluations.

3.1 Inclusion Criteria

3.1.1 Males and females age ≥ 18 years.

3.1.2 Newly diagnosed, histological confirmation of soft tissue sarcoma of the extremities (including limb girdle) or superficial trunk that present as either –

- Deemed a candidate for complete macroscopic resection of the primary sarcoma.

OR

- Having had non-oncologic excisional procedure with positive or uncertain resection margins and still be eligible if the evaluating sarcoma surgeon recommends oncologic re-resection of the surgical bed to obtain negative margins after a course of preoperative radiation therapy.

3.1.3 No evidence of nodal or distant metastases as determined by clinical examination on any form of imaging.

3.1.4 Eastern Cooperative oncology Group (ECOG) Performance Status (PS) ≤ 3 (Appendix I).

3.1.5 Life expectancy greater than 6 months.

3.1.6 Patients capable of childbearing must agree to use adequate contraception.

3.1.7 Ability to complete questionnaire(s) by themselves or with assistance.

3.1.8 Ability to provide written informed consent.

3.1.9 Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.2 Exclusion Criteria

3.2.1 Previous radiation therapy to the site of the sarcoma or area surrounding it such that it would be encompassed by the radiation field needed to treat the current sarcoma. In other words, treatment on this trial would require re-irradiation of tissues.

3.2.2 Patients with nodal or distant metastases.

3.2.3 Rhabdomyosarcoma, soft tissue osteosarcoma, soft tissue Ewing sarcoma, and benign histologies.

3.2.4 Any of the following:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

4.0 Test Schedule

	Pre-treatment/ Baseline *≤30 days prior to registration*	Hypo-fractionated RT *42.75 Gy in 15 fractions*	Post-RT Assessment *(+/- 5 days)*	Pre-Operative Assessment *Within 2 weeks of surgery*[9]	Post-Operative Assessment *4-8 weeks Post-*[Surgery6,9]	Years 1 & 2 Post-Surgery Assessment *Every 6Months Post-Surgery*[7,8,9] *(+/- 8 weeks)*	Years 3-5 Post-Surgery Assessment *Annually Post-Surgery*[7,8,9] *(+/- 8 weeks)*
History, physical exam[7], ECOG status	X		X	X		X	X
Pathology review [1]	X				X		
Primary site MRI [2, 5]	X			X		X	X
PET/CT or CT Chest[5,]	X			X		X	X
Pregnancy test [3]	X						
AE Acute Assessment (See section 10.0)	X		X	X			
Hypofractionated RT		X					
CTCAE v5.0 Solicited Late Toxicity Assessment (See section 10.0)	X				X	X	X
Wound Complication Assessment (Appendix VI/Section 11.0)					X	X	
Regional Alopecia Assessment (Appendix V)	X		X	X			
Joint Stiffness Assessment (Appendix IV)	X		X	X		X	X
PROMISE-10[a]	X			X		X[4]	
TESS[b]	X			X		X[4]	

1. Pathology review includes histopathologic diagnosis of soft tissue sarcoma and grade, where applicable.
2. CT is acceptable if MRI is not advisable.
3. For women of childbearing potential only. Must be done ≤7 days prior to beginning radiation treatment. Tubal ligation and IUD in place are exceptions.
4. Obtained at 12, 18, and 24 months.
5. Within 60 days of enrollment
6. Follow Up timepoints may be evaluated outside the anticipated window as deemed appropriate by Stand of Care Radiation Oncology and Orthopedic Surgery follow up schedule
   a. Patient-Reported Outcomes Measurement Information System
   b. Toronto Extremity Salvage Score
7. Assessments may be completed by NP/PA in person or by virtual and/or phone visit if patient is unable to return to study site.
8. Per physician discretion
9. If patient develops any type of disease progression or is unwilling to return to the institution, patients will move to yearly survival follow up. No additional assessments will need to be done.

5.0 Grouping Factors

5.1 Anatomical Sites of Tumor: Proximal lower extremity (includes knee) versus rest.

Note: As of July 19, 2023, there are no restrictions on number of patients enrolled per anatomical sites of tumor.

6.0 Registration Procedures

Patients will be registered by completing the registration through PTrax, and eligibility case report forms (CRFs) stored in MedidataRave.

6.1 Prior to patient enrollment, the investigator should ensure that all of the following requirements are met:

6.1.1 The patient meets all inclusion criteria and exclusion criteria apply.

6.1.2 The patient and investigator have signed and dated all applicable consent forms.

6.1.3 All baseline assessments and examinations have been performed.

6.1.4 All registration CRFs have been completed, signed, and dated.

6.1.5 Protocol treatment must begin within 2 weeks of registration.

7.0 Protocol Treatment

7.1 Radiation Therapy

All patients enrolled on this trial will receive radiation therapy as detailed below.

7.1.1 Simulation

7.1.1.1 Patient Positioning and Immobilization
The patient may be treated in any appropriate, stable position. No specific immobilization is mandated. However, reproducible setup is critical and the use of standard immobilization devices for the extremity and/or truck is strongly encouraged.

Bolus should not be used unless:
a. The tumor involves cutaneous structures,
b. The tumor is very superficial such that adequate target dose (<90% prescription dose to the planning target volume (PTV)) cannot be delivered without it,
c. Or, the surgeon indicates the biopsy scar and/or skin will not be resected.

7.1.1.2 Image Acquisition
Computed tomography (CT) imaging obtained during simulation will be the primary imaging modality for target delineation and

treatment planning. CT simulation imaging will be obtained per institutional policies and procedures.

Diagnostic or treatment position Magnetic Resonance Imaging (MRI) may be used to aid with target delineation and treatment planning at the discretion of the treating radiation oncologist. Similarly, use of intravenous contrast, breath hold techniques, and acquisition of 4D imaging sets are at the discretion of the treating radiation oncologist.

7.1.2 Target Volume Definitions

Treatment planning will be based on the following definitions.

7.1.2.1 GTV

Gross tumor volume (GTV) is the volume of all known disease based on CT simulation imaging and physical exam. If MRI is used for target delineation, GTV is best delineated on T1 contrast sequences.

If there has been prior surgical violation of the sarcoma (for example, a non-oncologic partial or positive-margin excision), the GTV may be extended to include the initial region of gross tumor as well as any disturbed tissues. In most cases, an open biopsy scar should not be included in the GTV as standard of care is for the incision to be resected. In the unusual situation where an open biopsy scar will not be resected, this should be confirmed with the surgeon and included in the GTV.

7.1.2.2 CTV

Clinical target volume (CTV) includes the GTV and sites of potential occult tumor involvement. A 2.0-4.0 cm longitudinal and 1.0-1.5 cm radial expansion from GTV will be used to generate the CTV. The expansions should follow natural planes of spread for sarcomas, while respecting intact bone and compartment boundaries. If MRI is used for target delineation, the CTV should also include physician-determined suspicious peri-tumoral edema seen on T2 sequence images. In patients who received neoadjuvant chemotherapy and experienced a reduction in tumor volume with chemotherapy, the pre-chemotherapy extent of the tumor in soft tissues should be included in the CTV.

7.1.2.3 PTV

A geometric margin of 5-10 mm will be used to create PTV. Daily image guidance is required.

7.1.2.4 Proton Therapy

7.1.2.4.1 GTV is the same for protons and photons

7.1.2.4.2 CTV is the same for protons and photons

7.1.2.4.3 PTV is not the same as photons due to differences in beam penetration with movement and set up uncertainty. PTV varies with each individual field and requires additional adjustments based on set up error for the involved body site. In general, adjustment margins are usually 2-7 mm and will follow institutional policies and procedures.

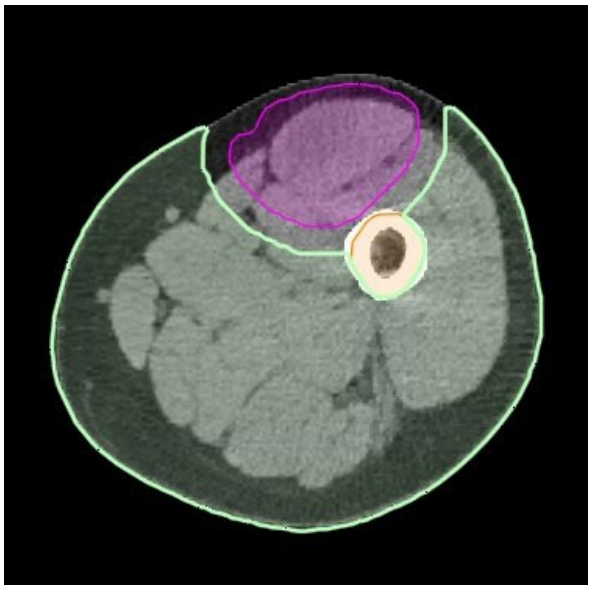
7.1.3 Organs at Risk Contouring Definitions

Only organs at risk relevant to the treatment field within 2 cm superior and inferior to the PTV edge should be contoured.

7.1.3.1 Bone avoid (only applicable for extremity tumors)
The bone immediately adjacent to the gross tumor is contoured as bone avoid. The bone avoid structure will extend 2 cm superior and inferior to the PTV edge.

7.1.3.2 Soft tissue avoid (only applicable for extremity tumors)
The soft tissue surrounding the PTV and extending 2 cm superior and inferior to the PTV edge is defined as soft tissue avoid. To create the soft tissue avoid structure, an intermediate structure is first created defined as PTV + a 2.0 cm geometric expansion. Then, the body only contour is subtracted from the PTV+2.0 cm intermediate structure and limited to 2 cm superior and inferior to the PTV edge. This final soft tissue avoid structure is cropped out of bone avoid and volumes $<1 cm^3$ are erased (Figure 1).

Figure 1. Example of the soft tissue avoid structure in axial plane. PTV is in magenta, soft tissue avoid is in light green, and bone avoid is in orange.



7.1.4 Radiation Therapy Planning

7.1.4.1 Dose definition

Photon dose will be specified in centigray (cGy). For proton therapy, the absorbed dose is specified in centigray equivalents (CGE), which is the same as ICRU 78 D_{RBE} using a standard RBE of 1.10 with respect to water.

7.1.4.2 Target Dose

The radiation dose prescribed to the PTV will be 4275 cGy in 15 daily fractions over 3 weeks. Treatment will be delivered once daily, except on weekends and holidays. Twice daily (BID) treatments are not allowed.

7.1.4.3 Treatment Planning

The treatment technique and modality are at the discretion of the treating radiation oncologist. The patient may be treated using conventional 3D radiotherapy (3DCRT); Intensity Modulated Radiotherapy (IMRT), rotational IMRT techniques such as Volumetric Arc Radiation Therapy (VMAT), or proton therapy (3D or Intensity Modulated Proton Therapy (IMPT)).

The dose will be prescribed to the treatment isocenter, which serves as the ICRU reference point. Appropriate beam modality and energy should be selected for the size and depth of the tumor, tissue, and site to be treated. Every attempt should be made to use techniques (i.e., 3DRT, IMRT, VMAT, etc.) and modalities (i.e.,

electrons, photons, protons) which avoid unnecessary irradiation of critical normal tissues.

7.1.4.4 Target Dose Requirements and Uniformity
Table 1.0 lists dose volume histogram (DVH) requirements for CTV and PTV. If DVH requirements cannot be met, an explanation must be submitted to the study co-chairs (S. K. Ahmed, M.D. or I.A. Petersen, M.D.).

Table 1.0 – DVH requirements for CTV and PTV

Structure	DVH Endpoint	Requirement	Priority	DVH Endpoint	Requirement	Priority
CTV_4275	D95%[%]	≥ 100%	2	D95%[%]	≥ 95%	1
				CV95%[cc]	<0.5cc	1
	V110%		Report			
PTV_4275	D95%[%]	≥ 99%	2	D95%[%]	≥ 95%	1
				CV95%[cc]	<0.5 cc	1
	V110%		Report			

7.1.4.4.1 Minor Deviation Definition

a) PTV_4275 D95% <95% but ≥ 90%

AND / OR

b) >20% but ≤ 25% of PTV_4275 receives ≥110% of prescription dose

7.1.4.4.2 Major Deviation Definition

a) PTV_4275 D95% <90%

AND / OR

b) >25% of PTV_4275 receives ≥110% of prescription dose

AND / OR

c) Dose to the priority 1 organs at risk is more than the recommended limit (Table 2.0)

7.1.4.5 Organs at Risk Dose Constraints

Normal tissue dose constraints are listed in Table 2.0. Every effort should be made to avoid treating the full circumference of any extremity. There is no special requirement for skin dose limit. However, full prescription dose to skin over areas commonly traumatized (e.g., elbow, knee, shin) should be avoided unless in the PTV.

While every effort should be made to deliver prescription doses to the PTV as specified while adhering to normal tissue constraints, it is recognized that certain anatomical factors may prevent this. As such, if normal tissue constraints are unachievable, the patient will be taken off the trial and treated with standard pre-operative RT to 50 Gy in 25 fractions meeting standardly accepted constraints for that fractionation schedule.

Table 2.0 –Organs at Risk Dose Constraints

Organ at Risk	Dose Constraints	Priority
Bone avoid	Mean < 32 Gy V35Gy < 64% V35Gy < 40%	1 1 2
Soft tissue avoid	Mean < 26 Gy V18Gy <50%	2 1
Joint (only major joints: hip/knee/shoulder)	V42.56Gy <50%	2
Anus	Max V42.75Gy (%) V40.6Gy (%)	Report Report Report
Genitalia	Max Mean <26 Gy	Report 1

Testis (if fertility preservation desired)	V1Gy ≤ 60% V1Gy ≤ 50%	1 2
Ovaries (if fertility preservation desired)	V4.8Gy ≤ 60% V1Gy ≤ 50%	1 2
Lungs	V18Gy≤ 20%	1
Brachial plexus	Max < 48 Gy	1
Heart	Mean < 10 Gy	1
Esophagus	Mean <26 Gy	1
Liver	Mean <26 Gy	1
Stomach	Max ≤38 Gy	1
Small Bowel	Max ≤ 45 Gy; if in PTV V42.75Gy <20 cc V26.5Gy <100 cc V39Gy <60 cc	21 2 1
Large Bowel	Max < 45 Gy; if in PTV V42.75Gy (%) V40.6Gy (%) V42.75Gy (cc) <50 cc	2Report Report 2
Kidney	V11.8 Gy < 10% for total kidney volume V11.8Gy <33% for each kidney V5Gy for each kidney	1 2 Report
Spinal Cord	Max	Report

	V39Gy <0.1%	2
Bladder	Max V42.75Gy <50% V30Gy <60%	Report 2 2

7.1.5 Radiation Therapy Delivery
Radiation therapy will be delivered using a linear accelerator or proton gantry. Patients will be set up according to the instructions from CT simulation and treatment planning. Image guidance procedures will be determined at the discretion of the treating radiation oncologist.

7.1.6 Treatment Delays
There will be no planned rests or breaks from treatment. Once radiation therapy has been initiated, treatment will not be interrupted except for severe illness or unplanned emergencies. The reason for any interruptions greater than three days should be recorded and submitted to the study Chair (S.K. Ahmed, M.D.). When treatment interruptions or delays occur, the total number of fractions or cumulative dose should not be modified.

7.1.7 Special Considerations

7.1.7.1 Tumor motion
Acquisition of 4D imaging sets, use of breath hold techniques, or treatment delivery via phase gating for tumors with internal motion are at the discretion of the treating radiation oncologist. In these cases, an internal target volume (ITV) will be delineated per standard institutional policies and procedures.

7.1.7.2 Nodal Radiation
For tumors with no evidence of nodal involvement, the draining regional lymph nodes should not be irradiated. Tumors with nodal involvement are excluded on this trial.

7.1.8 Quality Assurance
All target volumes and final treatment plans must be submitted for review and approval by a study co-chair (S. K. Ahmed, M.D. or I.A. Petersen, M.D.).

7.1.9 Intraoperative and Postoperative Radiation Therapy
Use of intraoperative and postoperative radiation therapy is discouraged. If intraoperative or postoperative radiation therapy is deemed to be of benefit for a high-risk case, contact a study co-chair (S. K. Ahmed, M.D. or I.A. Petersen, M.D.).

7.2 Surgery

Patients will undergo oncologic resection ideally 3-4 weeks after completion of preoperative radiation therapy per institutional standards. If surgery is not feasible during this ideal period, it must be performed within 6 weeks (± 1 week) of completing preoperative radiation therapy. Acute wound complications will be recorded as detailed in section 11.1.

7.3 Chemotherapy

The use of chemotherapy will be at the discretion of the multidisciplinary team and medical oncology consultant involved in the case. Chemotherapy will not be used concurrently with radiation therapy on this study. In cases where chemotherapy is used either neo-adjuvantly or adjuvantly, the agents used and number of cycles/doses of chemotherapy will be documented.

7.4 Patient reported questionnaires

All patients will complete Patient-Reported Outcomes Measurement Information System (PROMIS) and Toronto Extremity Salvage Score (TESS) questionnaires at baseline, post-radiotherapy, and post-surgery time-points as detailed in section 4.0.

8.0 Dosage Modifications Based on Adverse Events

N/A

9.0 Ancillary Treatment/Supportive Care

9.1 Permitted Supportive Therapy

All supportive therapies for optimal medical care are allowed during the study period at the discretion of the provider within the parameters of the protocol. Examples include skin care, physical therapy and rehabilitation, occupational therapy, anti-emetics, anti-diarrheals, prophylaxis for constipation, anti-inflammatories, anti-pyretics, intravenous fluids, and appetite enhancers.

9.2 Non-permitted Supportive Therapy

No investigational agents are permitted.

10.0 Adverse Event (AE) Monitoring and Reporting

10.1 Definitions

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event – Any grade 4 or 5 adverse event as defined by CTCAE v5.0. Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include in general:

- Death
- Life threatening adverse experience where emergent lifesaving treatment is necessary.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)- Any unanticipated problem or adverse event that meets the following three criteria:

Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data,

AND

Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected,

AND

Related: A problem or event is "related" if it is possibly related to the research procedures.

Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events

(CTCAE) version 5.0 will be utilized for AE reporting unless as otherwise stated in the table below.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.2.1 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 5.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.3).

10.2.2 Assessment of Attribution
Only G4 or G5 adverse events will require an attribution. Any change in the grade of an adverse event within the list of monitored AEs will be recorded and considered to be related to treatment. Any new adverse not listed occurring within the radiated area or in close proximity will be graded and attribution defined by the study PI.
Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the treatment and the adverse event.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

a. Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.3.1 Investigator Reporting: Notifying the Mayo IRB

The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

10.3.1.1 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon

as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.3.1.2 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs.

Consider the following information to collect when developing any forms for documentation of adverse events.

Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.4 Solicited toxicities to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated based on the schedule of events using the CTCAE v5.0 grading unless otherwise stated in the table below. This regimen has established safety, based on this article https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00638-6/fulltext so the focus is on solicited toxicities and not any adverse event after radiation therapy is completed.

ACUTE TOXICITIES – Upper Proximal Extremity			
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Baseline**	**During RT & Preoperative Assessment**

General disorders and administration site conditions	Fatigue	X	X
Skin and subcutaneous tissue disorders	Dermatitis Radiation	X	X
	Hyperpigmentation	X	X
Neoplasm benign, malignant and unspecified	Tumor pain	X	X

LATE TOXICITIES – Upper Proximal Extremity		
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Post-Surgery & Follow Up**
Skin and subcutaneous tissue disorders	Hyperpigmentation[1]	X
Vascular	Lymphedema[2]	X
General disorders and administration site conditions	Localized edema[1]	X
Musculoskeletal and connective tissue disorders	Fibrosis deep connective tissue[1]	X
	Joint range of motion decreased[2]	X
	Osteonecrosis[1]	X

Neoplasm benign, malignant and unspecified	Tumor pain[1]	X
Injury, poisoning and procedural complications	Fracture[1]	X
Gastrointestinal Disorders [1]	Esophageal fistula	X
Respiratory, thoracic and mediastinal disorders	Pneumonitis[1]	X

[1] Specific to radiation / surgery treatment area
[2] Specific to ipsilateral extremity / region

ACUTE TOXICITIES – Upper Distal Extremity (includes elbow)			
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Baseline**	**During RT & Preoperative Assessment**
General disorders and administration site conditions	Fatigue	X	X
Skin and subcutaneous tissue disorders	Dermatitis Radiation	X	X
	Hyperpigmentation	X	X
Neoplasm benign, malignant and unspecified	Tumor pain	X	X

LATE TOXICITIES – Upper Distal Extremity (includes elbow)		
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Post-Surgery & Follow Up**
Skin and subcutaneous tissue disorders	Hyperpigmentation[1]	X
Vascular	Lymphedema[2]	X
General disorders and administration site conditions	Localized edema[1]	X
Musculoskeletal and connective tissue disorders	Fibrosis deep connective tissue[1]	X
	Joint range of motion decreased[2]	X
	Osteonecrosis[1]	X
Neoplasm benign, malignant and unspecified	Tumor pain[1]	X
Injury, poisoning and procedural complications	Fracture[1]	X

[1] Specific to radiation / surgery treatment area
[2] Specific to ipsilateral extremity / region

ACUTE TOXICITIES – Lower Proximal Extremity (includes knee)			
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Baseline**	**During RT & Preoperative Assessment**
General disorders and administration site conditions	Fatigue	X	X

Skin and subcutaneous tissue disorders	Dermatitis Radiation	X	X
	Hyperpigmentation	X	X
Gastrointestinal disorders	Diarrhea	X	X
	Nausea	X	X
	Vomiting	X	X
Renal and urinary disorders	Dysuria	X	X
Neoplasm benign, malignant and unspecified	Tumor pain	X	X

LATE TOXICITIES – Lower Proximal Extremity (includes knee)		
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Post-Surgery & Follow Up**
Skin and subcutaneous tissue disorders	Hyperpigmentation[1]	X
Vascular	Lymphedema[2]	X
General disorders and administration site conditions	Localized edema[1]	X
	Fibrosis deep connective tissue[1]	X

Musculoskeletal and connective tissue disorders	Joint range of motion decreased[2]	X
	Osteonecrosis[1]	X
Neoplasm benign, malignant and unspecified	Tumor pain[1]	X
Injury, poisoning and procedural complications	Fracture[1]	X
Gastrointestinal Disorders [1]	Anal fistula	X
	Colonic fistula	X
	Duodenal fistula	X
	Ileal fistula	X
	Jejunal fistula	X
	Rectal fistula	X
	Anal ulcer	X
	Colonic ulcer	X
	Duodenal ulcer	X
	Ileal ulcer	X
	Jejunal ulcer	X
	Rectal ulcer	X
	Small intestine ulcer	X
	Anal stenosis	X
	Colonic stenosis	X
	Duodenal stenosis	X

	Ileal stenosis	X
	Jejunal stenosis	X
	Rectal stenosis	X
	Small intestine stenosis	X
	Rectal perforation	X
	Small intestine perforation	X
	Colonic perforation	X
	Duodenal perforation	X
	Ileal perforation	X
	Jejunal perforation	X
	Enterovesical fistula	X
Renal and urinary disorders[1]	Urinary fistula	X
	Bladder perforation	X

[1] Specific to radiation / surgery treatment area
[2] Specific to ipsilateral extremity / region

ACUTE TOXICITIES – Lower Distal Extremity			
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Baseline**	**During RT & Preoperative Assessment**

General disorders and administration site conditions	Fatigue	X	X
Skin and subcutaneous tissue disorders	Dermatitis Radiation	X	X
	Hyperpigmentation	X	X
Neoplasm benign, malignant and unspecified	Tumor pain	X	X

[1] Per study definition

LATE TOXICITIES – Lower Distal Extremity		
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Post-Surgery & Follow Up**
Skin and subcutaneous tissue disorders	Hyperpigmentation[1]	X
Vascular	Lymphedema[2]	X
General disorders and administration site conditions	Localized edema[1]	X
Musculoskeletal and connective tissue disorders	Fibrosis deep connective tissue[1]	X
	Joint range of motion decreased[2]	X
	Osteonecrosis[1]	X

Neoplasm benign, malignant and unspecified	Tumor pain[1]	X
Injury, poisoning and procedural complications	Fracture[1]	X

[1] Specific to radiation / surgery treatment area
[2] Specific to ipsilateral extremity / region

ACUTE TOXICITIES – Superficial Trunk			
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Baseline**	**During RT & Preoperative Assessment**
General disorders and administration site conditions	Fatigue	X	X
Skin and subcutaneous tissue disorders	Dermatitis Radiation	X	X
	Hyperpigmentation	X	X
Gastrointestinal disorders	Diarrhea	X	X
	Nausea	X	X
	Vomiting	X	X
Renal and urinary disorders	Dysuria	X	X
Neoplasm benign, malignant and unspecified	Tumor pain	X	X

LATE TOXICITIES		
CTCAE System/Organ/Class (SOC)	**Adverse Event / Symptoms**	**Post-Surgery & Follow Up**
Skin and subcutaneous tissue disorders	Hyperpigmentation[1]	X
General disorders and administration site conditions	Localized edema[1]	X
	Lymphedema	X
Musculoskeletal and connective tissue disorders	Fibrosis deep connective tissue[1]	X
	Joint range of motion decreased[2]	X
	Osteonecrosis[1]	X
Neoplasm benign, malignant and unspecified	Tumor pain[1]	X
Injury, poisoning and procedural complications	Fracture[1]	X
Gastrointestinal Disorders [1]	Anal fistula	X
	Colonic fistula	X
	Duodenal fistula	X
	Esophageal fistula	X
	Gastric fistula	X
	Ileal fistula	X
	Jejunal fistula	X

	Rectal fistula	X
	Anal ulcer	X
	Colonic ulcer	X
	Duodenal ulcer	X
	Gastric ulcer	X
	Ileal ulcer	X
	Jejunal ulcer	X
	Rectal ulcer	X
	Small intestine ulcer	X
	Anal stenosis	X
	Colonic stenosis	X
	Duodenal stenosis	X
	Gastric stenosis	X
	Ileal stenosis	X
	Jejunal stenosis	X
	Rectal stenosis	X
	Small intestine stenosis	X
	Rectal perforation	X
	Small intestine perforation	X
	Colonic perforation	X
	Duodenal perforation	X
	Gastric perforation	X
	Ileal perforation	X

	Jejunal perforation	X
	Enterovesical fistula	X
Renal and urinary disorders[1]	Urinary fistula	X
	Bladder perforation	X
Respiratory, thoracic and mediastinal disorders	Pneumonitis[1]	X

[1] Specific to radiation / surgery treatment area
[2] Specific to ipsilateral extremity / region

10.5 Submit via appropriate *reporting mechanisms* the following AEs experienced by a patient through the course of Radiation Therapy and not specified in Section 10.4:

10.5.1 Grade 3, 4, and 5 AEs regardless of attribution to the study treatment or procedure.

10.5.2 Grade 5 AEs (Death)

10.5.2.1 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.522 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.6 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

10.6.1 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10.5 "Monitoring and Auditing"). Medical monitoring will include a regular assessment of the number and type of serious adverse events. Any serious adverse events will be followed up by the sentinel event reporting procedure.

10.6.2 Internal Data and Safety Monitoring Board

The trial will be reviewed by the Cancer Center Auditing area on a bi-annual or yearly basis dependent on random study selection to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments.

11.0 Treatment Evaluation/Measurement of Effect

11.1 Development of a surgical wound complication: Secondary unplanned operation under general or regional anesthesia for wound repair (e.g., debridement, operative drainage, or secondary wound closure including rotationplasty, free flaps or skin grafts); or wound management without secondary operation including invasive procedures (e.g., aspiration of seroma or readmission for wound care such as intravenous antibiotics or persistent deep packing for 120 days or longer).

11.2 Local recurrence free survival: Any radiographic or pathologic evidence of recurrent disease inside the CTV and/or beyond the CTV to within a 3 cm distance from the edge of the CTV. Ideally assessed by radiographic imaging in comparison to the treatment fields in order to determine site of recurrence.

12.0 Descriptive Factors

12.1 ECOG Performance Status: 0 versus 1 versus 2 versus 3.

12.2 Sex: Male versus female.

12.3 Age: 18-30 versus 31-50 versus 51-70 versus ≥70.

12.4 Tumor Size: <5 cm versus 5-10 cm versus 11-15 cm versus >15 cm.

12.5 Anatomic location: Proximal upper extremity versus distal upper extremity (including elbow) versus proximal lower extremity (including knee) versus distal lower extremity versus superficial trunk.

12.6 Lesion presentation: de novo (biopsy only) versus status post inadvertent excision.

12.7 Histology: Undifferentiated pleomorphic sarcoma versus liposarcoma versus leiomyosarcoma versus myxofibrosarcoma versus other histology.

12.8 Tumor depth: Superficial and deep to fascia versus deep to fascia versus superficial to fascia.

12.9 Radiation Treatment Modality: 3D conformal versus IMRT versus proton therapy.

12.10 Neoadjuvant chemotherapy: Yes versus no.

12.11 Margin status: R0 vs R1 vs R2.

12.12 Surgical closure: Primary closure versus skin graft versus flap.

13.0 Treatment / Follow-up Decision at Evaluation of Patient

As per standard of care, throughout the study, investigators can prescribe any medications/treatments that have been deemed necessary for the well-being and over all treatment of the patient.

13.1 A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go off study.

- If the patient received MR for radiotherapy planning, all data up until the point of confirmation of ineligibility must be submitted.
- If the patient never received radiation therapy, on-study material must be submitted. No additional follow up is necessary.

13.2 Those patients who will not receive any radiation treatment or who will receive radiation treatment elsewhere will go off study.

13.3 Inevaluable Patients
If a patient fails to complete radiation therapy for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

13.4 Patients with a Major Deviation
A patient is deemed a major violation if:

a) PTV_4275 D95% <90%

AND / OR

b) >25% of PTV_4275 receives ≥110% of prescription dose
AND / OR

c) Dose to the organs at risk is more than the recommended limit (Table 2.0)

These patients will be flagged but included in the primary endpoint analysis. Separate sensitivity analysis will also be performed between the patients with major violation vs no major violation on major wound complication rate.

14.0 Body Fluid Biospecimens

N/A

15.0 Drug Information

N/A

16.0 Statistical Considerations and Methodology

16.1 Overview

This phase II single arm study will utilize a non-inferiority design approach to assess the rate of major wound complications associated with hypofractionated preoperative radiation therapy of 42.75 Gy in 15 fractions for localized, resectable soft tissue sarcoma of the extremity and superficial trunk compared to conventional fractionation of 50 Gy in 25 fractions.

16.1.1 Primary Endpoint

The primary endpoint of this trial is the proportion of patients who experience major wound complications within 120 days of surgical resection of soft tissue sarcoma of the extremity and superficial trunk following preoperative radiation therapy of 42.75 Gy in 15 fractions. Major wound complication is defined as secondary unplanned operation under general or regional anesthesia for wound repair (e.g.,debridement, operative drainage, or secondary wound closure including rotationplasty, free flaps or skin grafts); or wound management without secondary operation including invasive procedures (e.g., aspiration of seroma or readmission for wound care such as intravenous antibiotics or persistent deep packing for 120 days or longer). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for the primary endpoint.

16.2 Statistical Design

The non-inferiority one-sample test was utilized from PASS software for this design (Non-Inferiority of One Proportion using the Z-Test with S(P0) in PASS 16.0.4). A sample size of 108 evaluable patients achieves 80% power (1-sided significance level of 10%) to detect a non-inferiority margin of 10%, assuming that any major wound complication rate of 45% or above is inferior as compared to the current standard of care complication rate of 35%.[6] We hypothesize that the proposed hypofractionated preoperative radiation therapy of 42.75 Gy in 15 fractions is not inferior to the conventional fractionation of 50 Gy in 25 fractions

by showing the complication rate is < 45% for the proposed treatment (non-inferiority margin of 10%).

16.2.1 Decision Rule

After the first 108 eligible patients have completed 120 days post-treatment, we'll do the final analysis of the data, and if the Z-test is significant at the 10% significance level, we'll conclude that hypofractionated preoperative radiation therapy of 42.75 Gy in 15 fractions is not inferior to conventional fractionation of 50 Gy in 25 fractions and can be tested further in larger studies.

16.2.2 Sample Size

This study is expected to need to accrue 108 evaluable patients unless the study is closed early for excessive toxicity. We anticipate approximately 10% lost to follow-up due to 120 day endpoint, therefore we anticipate accruing an additional 12 patients to account for ineligibility, cancellation, or other reasons, making the overall sample size of 120 patients.

16.2.3 Accrual Rate and Study Duration

The expected accrual rate is about 4 patients per month. With this accrual rate, we expect to finish accrual within about 30 months of study activation, assuming we accrue 120 total patients. The final analysis can begin as soon as the last patient has been observed for 4 months post treatment, or at approximately 3 years after the study opens to accrual.

16.2.4 Power and Significance Level

Assuming that the number of major wound complications is binomially distributed, the significance level is 0.1 i.e. there is 10% chance of finding hypofractionated preoperative radiation therapy to be effective when it truly is not. The probability of declaring that the proposed radiation therapy warrants further studies (i.e., statistical power) is 80.01%, if the true acute wound complication is <45%.

16.2.5 Other Considerations

Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2.3) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., disease free survival, overall survival), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

Note: Both primary and secondary outcomes will be compared between anatomical sites (proximal lower limb (includes knee) vs rest). The comparison between groups will be exploratory in nature.

16.3.1 Primary Outcome Analysis

16.3.1.1 Definition: The primary endpoint of this trial is the proportion of patients who experience major wound complications within 120 days of surgical resection of soft tissue sarcoma following preoperative radiation therapy. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for the major wound complication rate.

16.3.1.2 Estimation: The proportion of major wound complications will be estimated by the number of patients who experience the major wound complications within 120 days following surgery divided by the total number of evaluable patients. 95% confidence intervals using normal approximation to binomial wound complication proportion will be calculated.

16.3.1.3 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process; however, they will be included in final endpoint estimates and confidence intervals.

16.3.2 Secondary Outcome Analysis

16.3.2.1 Local failure is defined any radiographic or pathologic evidence of recurrent disease inside the CTV and/ or to within 3 cm from the edge of the CTV. In the absence of censored patients prior to 5 years, local failure rate at 5 years (LFR5) will be equal to the binomial proportion. LFR5 will be evaluated by the number of patients free of local failure/recurrence at 5 year divided by the total number of evaluable patients. Exact binomial 95%

confidence interval for the point estimate will be provided. In the case of censoring prior to 5 years, LFR5 will be estimated using the Kaplan-Meier method.

16.3.2.2 Disease-Free Survival is defined as the time from registration date to the earliest date of documentation of either, local recurrence, regional recurrence, distant recurrence, or death due to any cause, censoring patients who are alive and local recurrence free at the date of last know clinical assessment. The distribution of disease-free survival will be estimated using method of Kaplan-Meier.

16.3.2.3 Overall Survival is defined as the time from registration date to death due to any cause, censoring patients alive at the date of last contact. The distribution of overall survival will be estimated using method of Kaplan-Meier.

16.3.2.4 Late toxicity is defined as toxicity occurs any time between 3 months and 24 months after completion of hypofractionated preoperative radiation therapy. The rate of ≥ grade 2 late toxicities will be estimated by the number of patients with a ≥ grade 2 late toxicity divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true rate of ≥ grade 2 toxicity events will be calculated.

16.3.2.5 Pattern of relapse will be evaluated by number of patients with patterns of tumor recurrence such as local recurrence, marginal recurrence, regional recurrence, distant metastasis, and second primary tumor divided by the total number of evaluable patients. Exact binomial 95% confidence interval for the point estimate will be provided.

16.3.2.5.1 Local tumor recurrence is defined as any tumor recurrence inside the CTV.

16.3.2.5.2 Marginal tumor recurrence is defined as any tumor recurrence beyond the CTV to within a 3 cm distance from the edge of the CTV.

16.3.2.5.3 Distant tumor recurrence is defined as any tumor that develops distantly from the primary site of sarcoma.

16.3.2.5.4 Second primary tumor is defined as any different histology of sarcoma or any other type of malignancy inside or outside the radiation field.

16.3.2.6 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. Late toxicities (as defined in sections 16.3.2.4) will be summarized separately.

16.3.2.7 Quality of Life Measurements – PROMIS-10: Results from the ten-item PROMIS questionnaire will be used to evaluate physical health and mental health, separately. Changes in raw score from baseline to 24-months post-surgery will be assessed, in each of the physical and mental health domains. The Wilcoxon signed-rank test will be utilized to assess changes in raw PROMIS scores. Mean change, along with standard deviation will be reported.

A scoring table to compare this patient population to global means may be utilized for various timepoints. However, because this scoring table is prepared for a fixed set of items, it can only be used when an examinee responds to all of the items in the set. This, along with all other analyses, including graphical representations and comparisons between other timepoints or subgroups of patients may be performed, but will be considered exploratory.

16.3.2.8 Quality of Life Measurements – TESS: Results from the Toronto Extremity Salvage Score (TESS) questionnaire will be used to evaluate functional outcomes. The TESS specifically measures performance of activities of daily living, and is separated into upper and lower extremity versions (29 and 30 questions, respectively).

Patients will fill out the appropriate version, and point totals will be summed. Mean change from baseline to 24 months post-surgery, along with standard deviation will be reported by version. The Wilcoxon signed-rank test will be used to assess changes in TESS scores within questionnaires. All other analyses, including graphical representations, GEE model creation, and comparisons between different timepoints or subgroups of patients may be performed, but will be considered exploratory.

16.4 Data Safety and Monitoring

16.4.1 Safety Review**:** The principal investigator(s) and the study statistician will review the study monthly to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least biannually, based on reports provided by the MCCC Statistical Office.

16.4.2 Adverse Event Stopping Rules: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual may be temporarily suspended to this study if at any time we observe events considered at least possibly related to Radiation Therapy (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy one of the following:

- If 8 or more of the first 20 patients (or 40% or more of all patients after 10 are accrued) experience a Grade 3+ AE.
- If 4 or more experience a Grade 5 AE at any time.

After consideration by the study team (Study Chair, statistician, etc.), a decision will be made as to whether accrual can be resumed. In addition, we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Subset Analyses for Minorities

16.5.1 Study Availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.5.2 Statistical Analysis by Subset

There is no information currently available regarding differential effects of this radiation treatment in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.5.3 Regional Population

The geographical region served by MCCC has a population which includes approximately 10% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	3	3	6
Not Hispanic or Latino	57	57	114
Ethnic Category: Total of all subjects*	**60**	**60**	**120**
Racial Category			
American Indian or Alaskan Native	2	1	3
Asian	1	2	3
Black or African American	2	2	4
Native Hawaiian or other Pacific Islander	1	1	2
White	54	54	108
Racial Category: Total of all subjects*	**60**	**60**	**120**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

N/A

18.0 Records and Data Collection Procedures

18.1 Data Collection and Processing
All data will be entered into electronic case report forms (eCRF's) through the Medidata Rave system. Case report forms will be automatically rolled out based on a predetermined, and visit based schedule to improve study staff workflow and data quality. Data will be exported nightly to a secure FTP for analysis and reporting.

18.2 Data Security and Confidentiality
The Medidata Rave database access model is role based and fully auditable at the study, form, and field levels. Data will be de-identified whenever possible and the ability to update will be limited to necessary staff. Access will be managed by the Mayo CTMS Service and Solution Center, under a controlled and monitored access request system. Medidata's platform specifically supports Electronic Record and Electronic Signature (ER/ES) requirements, including US 21 CFR part 11.

18.3 Data Quality Assurance
Each eCRF will contain edit checks and custom functions to ensure the highest possible data quality. Only necessary eCRF's will be available for data entry to reduce the possibility of erroneous entry.

The edit checks and custom functions on the eCRF's will trigger queries requesting the attention of appropriate study staff. The fields will be marked in pink to allow study staff to quickly identify the data fields that require attention or actions. Additionally, secure email notifications will be sent for adverse event tracking and monitoring.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: None

20.0 References

1. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305-15.
2. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996;14:859-68.
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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II – PROMIS-10

Mayo Patient Survey

Survey Date: _____ mm/dd/yyyy

Please respond to each item by choosing one number per row.

	Excellent	Very Good	Good	Fair	Poor
In general, would you say your **health** is:	5	4	3	2	1
In general, would you say your **quality of life** is:	5	4	3	2	1
In general, how would you rate your **physical health**?	5	4	3	2	1
In general, how would you rate your mental health, including your **mood and your ability to think**?	5	4	3	2	1
In general, how would you rate your satisfaction with your **social activities and relationships**?	5	4	3	2	1
In general, please rate how well you carry out your usual **social activities and roles**. (Includes activities at home, work, community, parenting, marriage, friends.)	5	4	3	2	1

	Completely	Mostly	Moderately	A little	Not at all
To what extent are you able to carry out your **everyday physical activities such as walking,climbing stairs carrying groceries, or moving a chair**?	5	4	3	2	1

In the past 7 days ...

	Never	Rarely	Sometimes	Often	Always
How often have you been bothered by **emotional problems such as feeling anxious, depressed or irritable**?	1	2	3	4	5

	None	Mild	Moderate	Severe	Very Severe
How would you rate your **fatigue** on average?	1	2	3	4	5

	No pain										Worst imaginable
How would you rate your **pain** on average?	0	1	2	3	4	5	6	7	8	9	10

Appendix III- TESS

SS Radiation Therapy Oncology Group
Phase II Soft Tissue Sarcoma
Toronto Extremity Salvage Score (TESS)

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

AMENDED DATA ☐ YES

INSTRUCTIONS: This sheet is the cover page used for submission of the (TESS) questionnaire. This page must be completed by the medical staff (nurse, data manager, physician, etc.) See detailed instructions for TESS questionnaire.

1 ☐ TIME POINT(1)

1 Baseline
2 12 months from start of treatment
3 18 months from start of treatment
4 24 months from start of treatment

2 ☐ WAS PATIENT QUESTIONNAIRE COMPLETED?(2)

1 No (Skip to question 3)
2 Yes

2A DATE PATIENT QUESTIONNAIRE COMPLETED

_____-_____-_____(3)

3 ☐ REASON QUESTIONNAIRE WAS NOT COMPLETED(4)

0 Not applicable, questionnaire was completed
1 Patient refused due to illness
2 Patient refused for other reason, specify _____(5)
3 Patient unable to be contacted
4 Institutional error
5 Tool not available in patient's language
6 Other reason, specify _____(6)
9 Unknown

4 ☐ SPECIFY METHOD OF COMPLETION(7)

0 Not applicable (not completed)
1 At appointment
2 By mail
3 By telephone
9 Unknown

5 ☐ DID THE PATIENT REQUIRE ANY ASSISTANCE IN COMPLETING THE QUESTIONNAIRE?(8)

0 Not applicable (not completed)
1 No
2 Yes
9 Unknown if assistance was given

6 ☐ SPECIFY THE PERSON WHO ASSISTED THE PATIENT(9)

0 Not applicable (not completed, no assistance)
1 Staff member
2 Family
3 Other, specify _____(10)
9 Unknown

7 ☐ EXTENT OF ASSISTANCE GIVEN(11)

0 Not applicable (not completed, no assistance)
1 Read items to patient
2 Interpreted items for patient
3 Marked items per patient's response
4 Combination of above, specify _____(12)
5 Other, specify _____(13)
9 Unknown

_____
Signature of person completing this form(14)

_____-_____-_____
Date form completed(15)

SS Radiation Therapy Oncology Group
Phase II Soft Tissue Sarcoma
Toronto Extremity Salvage Score (TESS)

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

Toronto Extremity Salvage Score (TESS)
Administration of the Questionnaire

General Guidelines

This questionnaire is designed as a measure of physical disability for patients undergoing limb salvage surgery for musculoskeletal tumours. It is a self-administered questionnaire.

There is an upper extremity and lower extremity version of the questionnaire. It is recommended that study personel complete the general information and review the instructions and sample questions with the subjects. The subjects can independently answer the remaining questions. Total completion time of the questionnaire averages 10 minutes.

Scoring

Each question is a measure of the difficulty that the individual has performing the task. The total potential score for an item is a perfect performance score (ie. 5).

The scale has been designed to allow individuals to respond to a non-applicable category on an item if it is not something they perform in their everyday life. Consequently, a total questionnaire score, if desired, would be a standardized score ranging from 0 to 100 calculated by:

$$\frac{\text{sum of the item scores - \# items}}{\text{possible score range}} \times 100\%,$$

where, sum of the item scores = sum of difficulty responses
items = items completed excluding the NA repsonse items
possible score range = (5 x #items) - (1 x #items)

Mail Administration

The TESS questionnaires have been administered by mail and, although formal testing of measurement properties has not been undertaken, patients are able and willing to complete the forms and the scores fall within anticipated ranges.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

Toronto Extremity Salvage Score
(Davis, 1996)

Upper Extremity Questionnaire
Lower Extremity Questionnaire

Completed by patient at baseline, 12, 18, and 24 months from the start of treatment.

Note: only the upper or lower extremity form is completed, not both

TESS - UPPER EXTREMITY

Patient Study ID#: _____ Patient Initials: _____
(first/middle/last)

Date of birth: _____ Form Completion Date: _____
(day/month/year) (day/month/year)

Months from start of treatment
- Baseline
- 12 months
- 18 months
- 24 months

Site: 1____ Bone
2____ Soft Tissue

Side of Lesion: 1_____Right
2_____Left

Are you: 1_____right handed
2_____left handed

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the **past week.** Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

EXAMPLE

Peeling vegetables is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

688____This task is not applicable for me.

You should choose the response "Impossible to do...." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "888" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

The following questions ask about your ability to perform activities that are common to everyday life. Considering the amount of difficulty you have performing the activity due to the current problem you are having with your arm, please answer the questions by choosing the answer that best describes your ability to do the activity **over the past week.**

1) Putting on a pair of pants is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.
688____This task is not applicable for me.

2) Tying shoe laces is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

688____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

3) Putting on socks or stockings is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

4) Showering is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

5) Dressing my arms and upper body is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

6) Buttoning a shirt is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

7) Tying a tie or a bow at the neck of a blouse is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

8) Putting on make-up or shaving is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

9) Brushing your teeth is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

10) Brushing your hair is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

11) Doing light household chores is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

12) Gardening or yard work is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

13) Preparing and serving meals is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

14) Cutting food while eating is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

15) Drinking from a glass is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

16) Performing heavy household chores is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

17) Going shopping is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

18) Giving or receiving change (ie. coins or bills) is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

19) Carrying a shopping bag or briefcase is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

20) Lifting a box to an overhead shelf is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

21) Turning a key in a lock is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

22) Pushing or pulling open a door is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

23) Writing is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

24) Picking up small items is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

25) Completing my usual duties at work is: (Work includes a job outside the home or as a homemaker.)

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

26) Working my usual number of hours is: (Working includes both a job outside the home and as a homemaker.)

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

27) Participating in my usual leisure activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

28) Socializing with friends and family is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

29) Participating in my usual sporting activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

1) Considering all the activities in which I participate in daily life, I would rate my ability to perform these activities during the past week as:

1_____impossible to do.
2_____extremely difficult.
3_____moderately difficult.
4_____a little bit difficult.
5_____not at all difficult.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

2) I would rate myself as being :

1_____completely disabled
2_____severely disabled.
3_____moderately disabled.
4_____mildly disabled.
5_____not at all disabled.

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your arm that you feel are important and have not been asked about in this questionnaire.

_____

_____

_____

_____

Please check to make sure that you have not missed any questions.

Thank you for taking the time to answer these questions.

SS Radiation Therapy Oncology Group
Phase II Soft Tissue Sarcoma
Toronto Extremity Salvage Score (TESS)

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.
Participant's Initials Participant's I.D. No.

TESS - LOWER EXTREMITY

Patient Study ID#: _____ Patient Initials: _____
(first/middle/last)

Date of birth: _____ Form Completion Date: _____
(day/month/year) (day/month/year)

Months from start of treatment
- Baseline
- 12 months
- 18 months
- 24 months

Site: 1____ Bone
2____ Soft Tissue

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the **past week.** Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE

Riding a bicycle is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

You should choose the response "impossible to do...." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "888" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

The following questions ask about your ability to perform activities that are common to every day life. Considering the amount of difficulty you have performing the activity due to the current problem you are having with your leg, please answer the questions by choosing the answer that best describes your ability to do the activity **over the past week.**

1) Putting on a pair of pants is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

2) Putting on shoes is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

3) Putting on socks or stockings is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

4) Showering is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.
888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

5) Light household chores such as tidying and dusting are:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

6) Gardening and yard work are:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

7) Preparing and serving meals is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

8) Going shopping is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

9) Heavy household chores such as vacuuming and moving furniture is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

10) Getting in and out of the bath tub is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

11) Getting out of bed is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

12) Rising from a chair is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

13) Kneeling is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

14) Bending to pick something up off the floor is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

15) Walking upstairs is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

16) Walking downstairs is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

17) Driving is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

18) Walking within the house is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

9) Walking outdoors is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

20) Sitting is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

21) Walking up or down hills or a ramp is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

22) Standing upright is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

23) Getting up from kneeling is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

24) Getting in and out of a car is:

1____Impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

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25) Participating in sexual activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

26) Completing my usual duties at work is: (Work includes both a job outside the home and as a homemaker.)

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

27) Working my usual number of hours is: (Working includes both a job outside the home and as a homemaker.)

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

29) Participating in my usual leisure activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

SS

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29) Socializing with friends and family is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

30) Participating in my usual sporting activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

1) Considering all the activities in which I participate in daily life, I would rate the ability to perform these activities during the past week as:

1_____impossible to do.
2_____extremely difficult.
3_____moderately difficult.
4_____a little bit difficult.
5_____not at all difficult.

2) I would rate myself as being :

1_____completely disabled
2_____severely disabled.
3_____moderately disabled.
4_____mildly disabled.
5_____not at all disabled.

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your leg that you feel are important and have not been asked about in this questionnaire.

_____
_____
_____

Please check to make sure that you have answered all the questions.
Thank you for taking the time to answer these questions.

Appendix IV

Joint Stiffness Assessment
(Specific to ipsilateral extremity/region)

MC: _____

Patient Name: _____

Date of Assessment: _____

Name of Assessor: _____

Was Joint Stiffness Present: Yes/No (circle one)

If yes, Joint Affected:
- ☐ Upper proximal extremity
- ☐ Upper distal extremity (includes elbow)
- ☐ Lower proximal extremity (includes knee)
- ☐ Lower distal extremity
- ☐ Superficial trunk

Grade:
- ☐ 1- Mild stiffness; slight ROM loss
- ☐ 2 - Moderate stiffness; pain, ROM loss
- ☐ 3 - Severe stiffness, pain, ROM loss
- ☐ 4 - Necrosis; complete fixation

Attribution to RT:
- ☐ Definite
- ☐ Possible
- ☐ Probable
- ☐ Unlikely
- ☐ Unrelated

Attribution to Surgery:
- ☐ Definite
- ☐ Possible
- ☐ Probable
- ☐ Unlikely
- ☐ Unrelated

Appendix V

Regional Alopecia Assessment

MC: _____

Patient Name: _____

Date of Assessment: _____

Name of Assessor: _____

Was Regional Alopecia Present: Yes/No

If yes, Region Affected:
- ☐ Upper proximal extremity
- ☐ Upper distal extremity (includes elbow)
- ☐ Lower proximal extremity (includes knee)
- ☐ Lower distal extremity
- ☐ Superficial trunk

Grade:
- ☐ 1 - Hair loss of <50% of normal for that individual that is not obvious on close inspection
- ☐ 2 - Hair loss of >50% normal for that individual that is readily apparent to others

Attribution to RT:
- ☐ Definite
- ☐ Possible
- ☐ Probable
- ☐ Unlikely
- ☐ Unrelated

Appendix VI

Surgical Wound Complication Assessment

MC: _____

Patient Name: _____

Name of Assessor: _____

Surgical wound complication: Yes/No

If yes,

Surgical wound start date: _____
Surgical wound end date: _____
Date notified of surgical wound complication: _____

Surgical wound complication classification:
☐ Wound management via secondary unplanned operation under anesthesia
☐ Wound management via invasive procedures other than operation

Surgical wound complication procedure performed: _____