

Feasibility Trial of Preoperative 5-Day Hypofractionated Radiotherapy for Primary Soft Tissue Sarcoma

Protocol Number: CTO 103725

Principal Investigator: Jennifer L. Harper, MD

Funded by: Hollings Cancer Center Developmental Cancer Therapeutics Grant

Version Number: v.3

06 February 2025

Table of Contents

STATEMENT OF COMPLIANCE 1
1 PROTOCOL SUMMARY 1
1.1 Synopsis 1
1.2 Schema 5
1.3 Schedule of Activities (SoA) 6
2 INTRODUCTION 7
2.1 Study Rationale 7
2.2 Background 7
2.3 Risk/Benefit Assessment 10
2.3.1 Known Potential Risks 10
2.3.2 Known Potential Benefits 12
2.3.3 Assessment of Potential Risks and Benefits 12
3 OBJECTIVES AND ENDPOINTS 13
4 STUDY DESIGN 15
4.1 Overall Design 15
4.2 Scientific Rationale for Study Design 15
4.3 Justification for Dose 15
4.4 End of Study Definition 15
5 STUDY POPULATION 15
5.1 Inclusion Criteria 15
5.2 Exclusion Criteria 16
5.3 Screen Failures 16
5.4 Strategies for Recruitment and Retention 16
6 STUDY INTERVENTION 16
6.1 Study Intervention(s) Administration 16
6.1.1 Study Intervention Description 16
6.2 Study Intervention Compliance 18
6.3 Concomitant Therapy 18
6.4 Rescue Medicine 18
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 18
7.1 Discontinuation of Study Intervention 18
7.2 Participant Discontinuation/Withdrawal from the Study 18
7.3 Lost to Follow-Up 19
8 STUDY ASSESSMENTS AND PROCEDURES 19
8.1 Efficacy Assessments 19
8.2 Safety and Other Assessments 20
8.3 Adverse Events and Serious Adverse Events 22
8.3.1 Definition of Adverse Events (AE) 22
8.3.2 Definition of Serious Adverse Events (SAE) 22
8.3.3 Classification of an Adverse Event 22
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up 24
8.3.5 Adverse Event Reporting 24
8.3.6 Serious Adverse Event Reporting 24
8.3.7 Reporting Events to Participants 25
8.3.8 Reporting of Pregnancy 25

8.4 Unanticipated Problems 25
8.4.1 Definition of Unanticipated Problems (UP) 25
8.4.2 Unanticipated Problem Reporting 26
8.4.3 Reporting Unanticipated Problems to Participants 26
9 STATISTICAL CONSIDERATIONS 26
9.1 Statistical Hypotheses 26
9.2 Sample Size Determination 26
9.3 Populations for Analyses 27
9.4 Statistical Analyses 28
9.4.1 General Approach 28
9.4.2 Analysis of the Primary Efficacy Endpoint(s) 28
9.4.3 Analysis of the Secondary Endpoint(s) 28
9.4.4 Safety Analyses 28
9.4.5 Baseline Descriptive Statistics 29
9.4.6 Sub-Group Analyses 29
9.4.7 Tabulation of Individual participant Data 29
9.4.8 Exploratory Analyses 29
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 30
10.1 Regulatory, Ethical, and Study Oversight Considerations 30
10.1.1 Informed Consent Process 30
10.1.2 Study Discontinuation and Closure 31
10.1.3 Confidentiality and Privacy 31
10.1.4 Future Use of Stored Specimens and Data 32
10.1.5 Key Roles and Study Governance 32
10.1.6 Safety Oversight 33
10.1.7 Clinical Monitoring 33
10.1.8 Quality Assurance and Quality Control 33
10.1.9 Data Handling and Record Keeping 34
10.1.10 Protocol Deviations 34
10.1.11 Publication and Data Sharing Policy 35
10.1.12 Conflict of Interest Policy 35
10.2 Abbreviations 37
11 REFERENCES 39

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Feasibility Trial of Preoperative 5-Day Hypofractionated Radiotherapy for Extremity Soft Tissue Sarcoma
Study Description:	This study is investigating the feasibility of preoperative 5-day hypofractionated radiotherapy (HFRT) for extremity soft tissue sarcoma (STS). The primary objective is to assess the uptake of 5-day HFRT in patients with STS who are candidates for preoperative radiotherapy and limb preserving surgery. Secondary objectives include evaluation of the rates of favorable pathologic response, major wound complications, local control, acute toxicity, and 1-year late toxicity will be assessed. Exploratory objectives include evaluation of the impact of preoperative 5-day HFRT on access to care, the socio-demographic profile of the trial participants will be compared to that of extremity STS patients seen within Hollings Cancer Center (HCC) and recommended preoperative conventional fractionation radiotherapy (CFRT) in the 3 years prior to the study opening. The retention rate for radiotherapy at HCC in patients meeting trial criteria during the prior 3 years will be compared with the retention rate for radiotherapy during the study period. An exploratory analysis will measure serum SFRP2 pre- and post- radiotherapy to assess changes in response to preoperative 5-day HFRT. Changes in serum SFRP2 will be evaluated for association with a favorable pathologic response to determine the potential of serum SFRP2 as a predictive biomarker. Patient satisfaction with the decision to participate in a trial of preoperative 5-day HFRT will be assessed.
Objectives:	
	<u>Primary Objective</u>:

To determine the feasibility of preoperative 5-day HFRT for extremity STS within the HCC patient population

Secondary Objectives:
To evaluate the rates of favorable pathologic response, major wound complications, local control, acute toxicity, and 1-year late toxicity associated with preoperative 5-day HFRT

Exploratory Objectives:
To compare the socio-demographic profile of trial participants with those of extremity STS patients who would have meet trial criteria and were offered preoperative CFRT in the 3 years prior to the study opening at HCC

To compare the retention rate for radiotherapy at HCC in patients meeting trial criteria during the prior 3 years with the retention rate for radiotherapy during the study period

To compare serum levels of SFRP2 before and after preoperative 5-day HFRT

To evaluate changes in serum SFRP2 levels before and after preoperative 5-day HFRT for an association with favorable pathologic response

To evaluate patient satisfaction with the decision to participate in a trial of preoperative 5-day HFRT

To assess the importance of the shorter duration of radiotherapy in an individual patient's decision to participate in the study

Endpoints:

Primary Endpoint:
Feasibility: The preoperative 5-day HFRT uptake rate, defined as the proportion of eligible patients who elect to participate in the trial

Secondary Endpoint(s):
Rate of favorable pathologic response: proportion of patients with extent of tumor fibrosis/hyalinization > 12.5%

Rate of major wound complication: major wound complication defined according to CAN-NCIC-SR2 Multi-center trial within 6 months of surgery

Local Control: Local control defined as 1-year Local Recurrence Free Survival, calculated from the date of surgery to the date of 12-month follow up

Acute toxicity: Acute toxicity defined by CTCAE v 5.0 assessed during radiotherapy treatment and 2 weeks following completion of radiotherapy

1-year late toxicity: Defined by physician assessment using the RTOG/EORTC criteria and the Stern scale for edema

Exploratory Endpoint(s):
Comparison of socio-demographic profiles: age, race, gender, marital status, health insurance status, comorbidities, geocode defined rural vs urban residence, estimated distance traveled to HCC, census tract level American Community Survey variables to include Socioeconomic status, Household Composition and Disability, Minority Status and Language, Housing Type, and Transportation

Comparison of retention rate for radiotherapy at HCC: number of patients meeting trial eligibility criteria in prior 3 years that received radiotherapy at HCC compared with the number of patients that were trial eligible and received radiotherapy at HCC during the study period

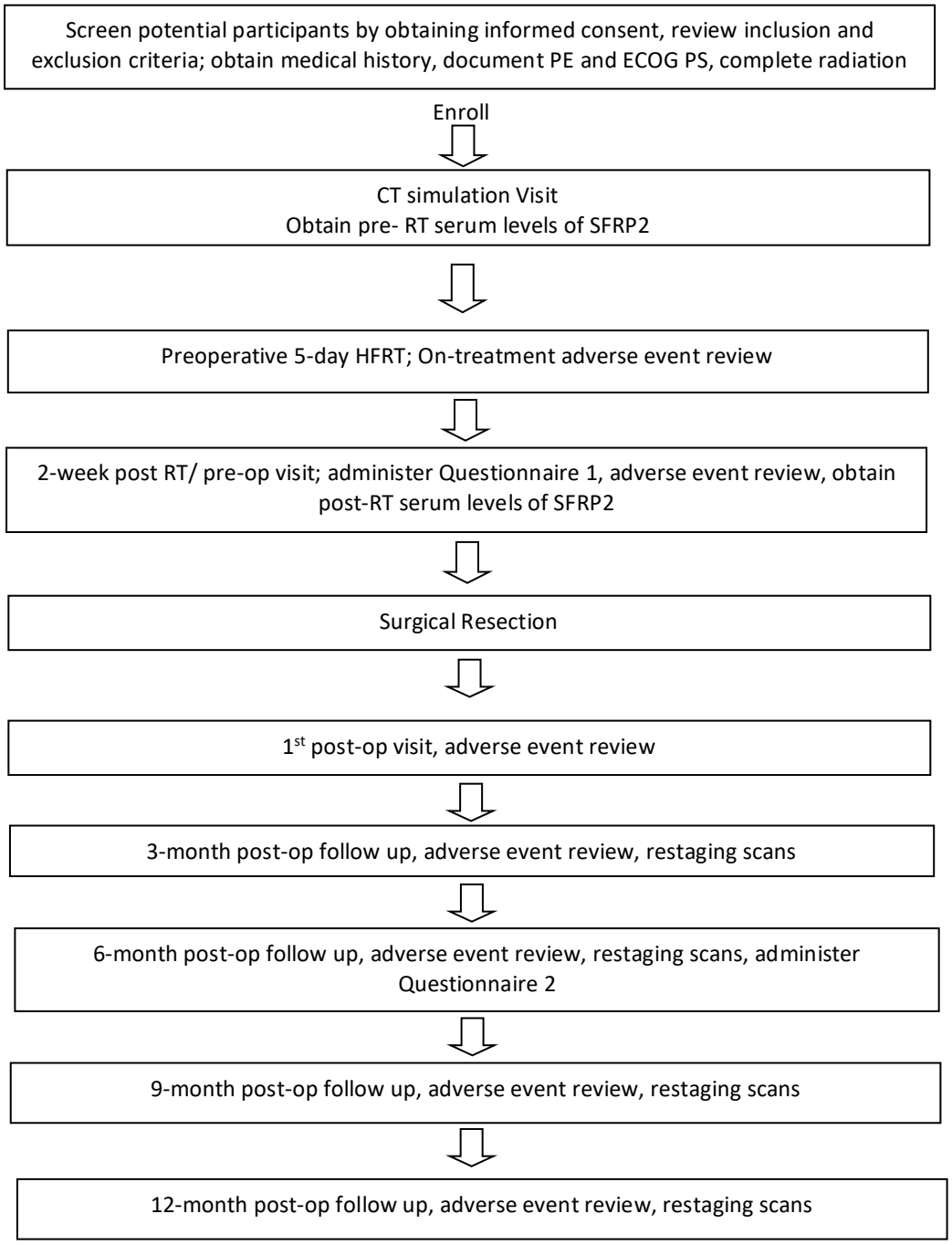
Comparison of serum SFRP2 levels before and after preoperative 5-Day HFRT: changes in serum SFRP2 levels before and after preoperative 5-day HFRT and the incidence of favorable pathologic response defined as extent of tumor fibrosis/hyalinization > 12.5%

Evaluating patient satisfaction with trial participation: Decision Regret Scale(1) at the 2-week post radiation visit and the 6-month postoperative visit.

Assessing patient rated importance of short course of radiotherapy in decision to participate in study: patient questionnaire administered at the 2-week post-radiation visit will assess how the patients prioritized the convenience of preoperative 5-day HFRT in making the decision to participate in the study.

Study Population:	Adults with non-metastatic STS of the extremity or trunk , eligible for wide local excision, presenting to Hollings Cancer Center sarcoma program. Sample size is 15 patients.
Phase:	Feasibility Study
Description of Sites/Facilities	Medical University of South Carolina, Hollings Cancer Center
Description of Study Intervention:	Preoperative 5-day HFRT
Study Duration:	48 months
Participant Duration:	15 months

1.2 SCHEMA


Screen potential participants by obtaining informed consent, review inclusion and exclusion criteria; obtain medical history, document PE and ECOG PS, complete radiation
Enroll
CT simulation Visit
Obtain pre- RT serum levels of SFRP2
Preoperative 5-day HFRT; On-treatment adverse event review
2-week post RT/ pre-op visit; administer Questionnaire 1, adverse event review, obtain post-RT serum levels of SFRP2
Surgical Resection
1st post-op visit, adverse event review
3-month post-op follow up, adverse event review, restaging scans
6-month post-op follow up, adverse event review, restaging scans, administer Questionnaire 2
9-month post-op follow up, adverse event review, restaging scans
12-month post-op follow up, adverse event review, restaging scans

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Calendar Parameters:

- Screening activities are considered standard of care and should be completed within 60 days of study registration.
- Follow-up post-operative visits at 3-,6-,9-,12-months will have a visit window of +/- 14 days.
- Additional visit window exceptions may be made for holidays, inclement weather, or other unforeseen circumstances.
- Procedures marked (R) are research specific, all others are considered clinical care.

Procedures	Screening and registration	CT simulation Visit	Radiation Treatment (RT)	2-week post RT/preop visit (+/-3days)	Surgical Resection	2-week post-op follow up visit	3-month post-op follow up visit	6-month post-op follow up visit	9-month post-op follow up visit	12-month post-op follow up visit
Surgical Consult	X									
Radiation Oncology Consult	X									
Review Clinical Biopsy Results	X									
Physical Examination	X		X[1]	X		X	X	X	X	X
ECOG or Karnofsky PS	X			X		X	X	X	X	X
Medical History	X									
Demographics	X									
Radiographic Staging	X[2]			X			X[2]	X	X	X
Informed Consent	X									
Questionnaire 1 (R)				X						
Questionnaire 2 (R)								X		
Radiation Dermatitis Assessment			X[1]	X						
Late Toxicity Assessment (fibrosis, joint stiffness, edema)						X	X	X	X	X
Wound Complication Assessment						X	X	X		
Adverse Event Review			X[1]	X		X	X	X	X	X
Serum Sample for SFRP2 (R)		X[3]		X[4]						
Preoperative 5-day HFRT			X							
Surgical Resection					X					

Footnotes:

1. During radiation treatment, patients will be evaluated at least once by the radiation oncologist with a physical examination and toxicity assessment during the 5-day treatment.
2. Staging imaging should include a CT Chest, MRI of the primary site, and imaging of any additional site as dictated by histology and per health care professional determination/discretion. The timing and type of radiographic staging performed after radiation therapy and prior to surgery will be per health care professionals determination/discretion. Radiographic surveillance imaging will be obtained post-operatively at 3-months, 6-months, 9-months and 12- months visits within standard of care. Extended visit windows are acceptable for surveillance imaging, especially if there are delays in scheduling. The same imaging modality should be used consistently throughout the study and RECIST 1.1 will be used. Radiographic staging intervals are conducted per standard of care.
3. Serum sample for SFRP2 will be coordinated with the timing of the CT simulation visit and utilize the venipuncture required for IV contrast administration.
4. Serum sample for SFRP2 will be coordinated with the timing of standard of care venipuncture for pre-operative laboratory test.

2 INTRODUCTION

2.1 STUDY RATIONALE

The current standard approach to the management of extremity STS is a combination of radiotherapy and limb preserving surgery. Currently guidelines recommend preoperative conventionally fractionated radiotherapy (CFRT) given at 1.8-2.0 Gy/fx, which involves 5-6 weeks of daily treatments.(2) Preoperative hypo-fractionated radiotherapy (HFRT) is an approach that can shorten the duration of treatment. Clinical outcomes with preoperative HFRT in STS have been reported from retrospective case series(3, 4), prospective institutional registries(5) and phase I-II trials. However, preoperative HFRT has not been compared in a prospective randomized trial to CFRT and due to the rarity of extremity soft tissue sarcoma, attempts to develop such a trial would face feasibility challenges. Therefore, single arm trials of preoperative HFRT will be critical to defining the feasibility, toxicity, efficacy, and potential improvement in access to care associated with this approach.

2.2 BACKGROUND

Radiation therapy combined with wide local excision in the preoperative or postoperative setting optimizes local control for extremity STS. Preoperative radiotherapy confers a higher rate of wound complications but a lower rate of irreversible sequela such as fibrosis and lymphedema compared with postoperative radiotherapy.(6) Resultantly, preoperative radiotherapy is the preferred approach in most cases.(2) Preoperative radiotherapy with CFRT given at 1.8-2.0 Gy/fx, involves 5-6 weeks of daily treatments. The burden of daily travel and time away from work or care giving can be a barrier to utilization of radiotherapy. A recent analysis of the National Cancer Database demonstrated that farther distance to treatment was a negative predictor for receipt of radiotherapy in extremity STS.(7) Sociodemographic factors such as female sex, older age ($\geq$70 years), Black race, and noncommercial insurance coverage were also negatively associated with receipt of radiotherapy. The authors summarized that radiotherapy is underutilized in the treatment of STS and that sociodemographic disparities exist in access to radiotherapy. Receipt of radiation therapy and surgery within a high volume (HV) sarcoma center has been associated with improved overall survival, while Black race and non-metropolitan residents were negative predictors for treatment within such centers. (8) To address disparities in access to radiation therapy, the American Society for Radiation Oncology Committee on Health Equity, Diversity, and Inclusion has proposed studying novel HFRT schedules.(9) As validation of this strategy, Kalbasi et al. increased retention of extremity STS patients within a HV sarcoma center by 3-fold with the utilization of preoperative HFRT.(10) Further, the decreased time and travel associated with HFRT, can address an established barrier to clinical trial participation, particularly for those living remote from clinical trial sites.(11) Clinical trial participation is particularly low in rural areas which results in these populations being underrepresented in the clinical research.(12, 13) A survey of South Carolina based medical researchers, identified rural residents as a group that are difficult to find and recruit to clinical trials.(14) In a survey of urban and rural South Carolina residents, there was no difference in reported willingness to participate in clinical trials, but rural residents were more likely to perceive limited access to clinical trial sites.(15) Investigating cancer treatment approaches that decreased the economic and logistical burdens incurred by patients, such as preoperative 5-day HFRT, may increase clinical trial participation by rural South Carolina residents and ultimately address disparities in representation of these populations in cancer research.

HFRT, using >2.2 Gy/fx, has resulted in equivalent oncologic outcomes to CFRT in other tumor sites such as breast(16), prostate(17) and rectum.(18, 19) For STS, HFRT may confer a radiobiologic advantage in that the linear-quadratic model predicts larger doses per fraction provide better tumor control for tumors with a lower α/β ratio.(20) For liposarcomas and rhabdomyosarcomas, their α/β ratio (~4 Gy) is similar to breast and prostate cancer, malignancies in which HFRT has been widely adopted.(21) While histologic variability certainly exists, most STSs have estimated α/β ratios lower than 10, suggesting increased sensitivity to larger fraction size. (21)

Clinical outcomes with preoperative HFRT in STS have been reported from retrospective case series(3, 4), prospective institutional registries(5) and phase I-II trials(10, 22-24). Comparing oncologic outcomes across these series is hindered by heterogeneous clinicopathological features, surgical techniques, samples sizes, and radiation fractionation schedules. However, the local control and rates of wound complications associated with HFRT and CFRT regimens appear similar as summarized Spalek and Rutkowski.(25)

Table 1: Summary of publications in preoperative HFRT in STS

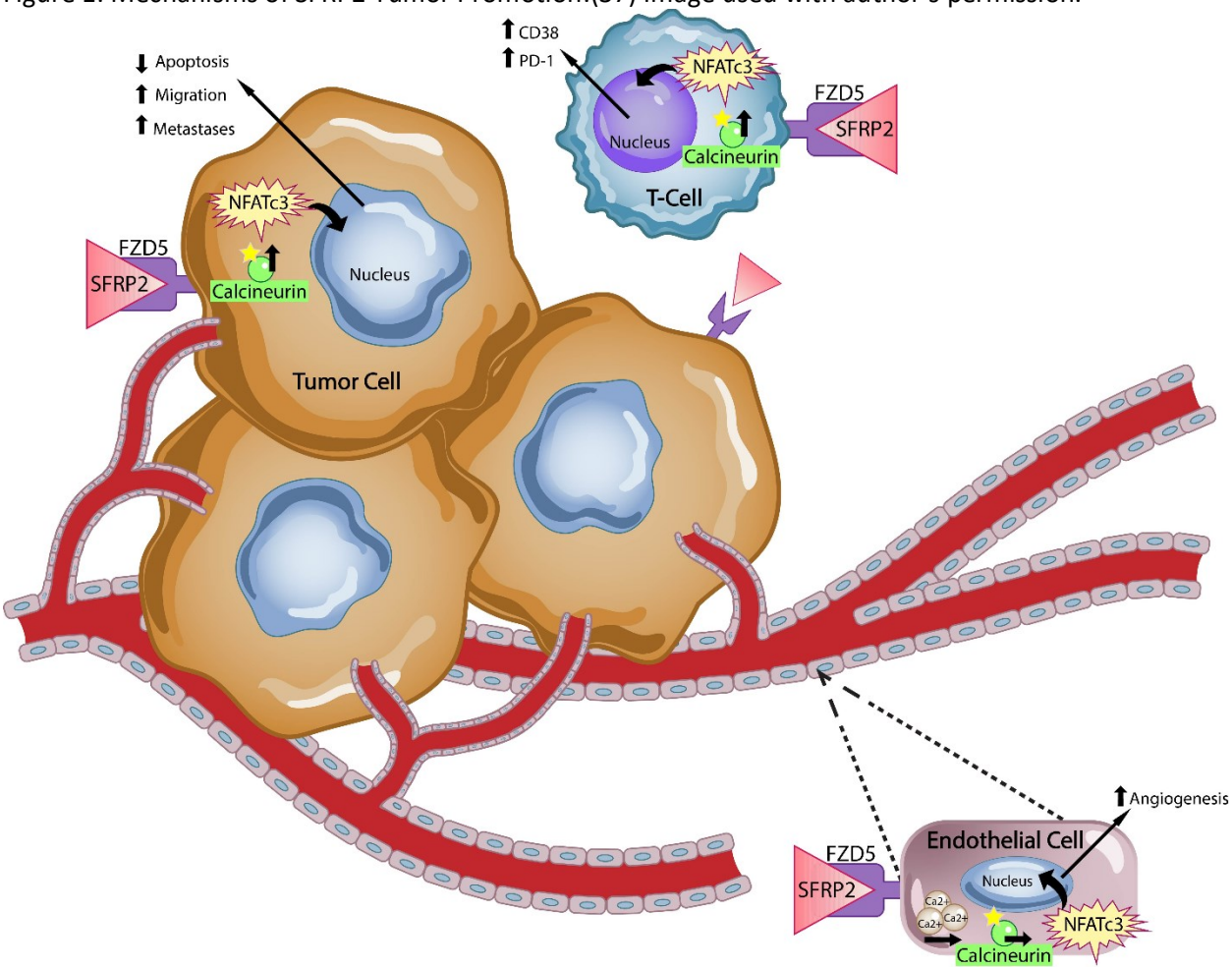
Author	N	Evidence	Dose/fx	Median Follow-up (mon)	Local Control @ y	Overall Survival @ y
Kosela-Paterczyk et al[23]	272	Prospective register	25/5	35	81% @ 3 y	72% @ 3 y
Kalbasi et al[10]	52	Phase II	30/5	29	94.3% @2 y	Not reported
Kubicek et al[26]	14	Phase II	35-40/5 SBRT	9.3	92.3% @ 1 y	Not reported
Temple et al[27]	42	Prospective register	30/10	72	97% @ 5y	79% @ 5y
Parasi et al[5]	16	Retrospective cohort	30/5	10.7	100% @ 1y	Not reported
MacDermed et al[3]	34	Retrospective cohort	28/8	33.5	89% @ 5y	42.3%@ 5 y
Meyer et al[28]	16	Phase I	28/8	26	100% @ 2y	86% @ 2 y
Ryan et al[4]	25	Retrospective cohort	28/8	24	88% @ 2y	84% @ 2 y
Pennington et al [29]	116	Retrospective cohort	28/8	71	89% @ 3 y	82% @3y
Bedi et al[24]	32	Phase II	35/5	36.4	100% @ 3 y	82.2% @ 3 y
Kosela-Paterczyk et al[30]	29	Phase II (MYXOID LIPOSARCOMA)	25/5	27	100% @ 2 y	Not Reported
Spalek et al[22]	46	Phase II (MARGINALLY RESECTABLE)	25/5	24.4	67% @ 2 Y	53% @ 3y

This study will utilize a 30Gy/5fx preoperative regimen as it has an estimated EQD_2 of 50 Gy (based on a α/β ratio=4) and therefore would be expected to closely parallel the biologic effect of CFRT. This preoperative 5-day HFRT regimen was studied in a phase II trial at UCLA and the 2-year rates of acute wound complications were favorable compared to historical controls.(3, 10, 27)

Exploratory Analysis of SFRP2 as a Predictive Biomarker:

Secreted Frizzled-Related Protein 2 (SFRP2) is a secretory protein involved in activation of the Wnt signaling pathway. Wnt signaling regulates normal embryonic development but aberrations in this pathway have been linked with tumor progression.(31) SFRP2 is a tumor promotor that which exerts effects on endothelial cells, tumor cells and T-cells (Figure 1). SFRP2 has been shown to stimulate angiogenesis in endothelial cells through activation of the non-canonical Wnt/Ca^2 pathway.(32) SFRP2 mediated activation of the Wnt/Ca^2 pathway results in downstream dephosphorylation of the nuclear factor of activated T-cells (NFAT). NFAT then can translocate from the cytoplasm to the nucleus where it mediates processes involving tumor cell growth, survival, invasion, and angiogenesis.(33) Inhibition of SFRP2 has been shown to inactivate NFAT in tumor cells and imped tumor cell migration. (34) NFAT also is involved in regulation of T-cell activity.(35) SFRP2 has been shown to promote NFATc3, CD38 and PD-1 expression in T-cells, which are mechanisms for immunotherapeutic resistance.(36) Monoclonal antibodies to SFPR2 in an osteosarcoma model lowered serum SFPR2 levels, lowered CD38 levels in tumor-infiltrating lymphocytes and T-cells and lowered PD-1 levels in T-cells. (37)

Figure 1: Mechanisms of SFRP2 Tumor Promotion:(37) Image used with author's permission.



SFRP2 has been identified as a tumor promotor in multiple histological subtypes of STS. (34, 38, 39) In mouse angiosarcoma models, a humanized monoclonal antibody to SFRP2 has been shown to lower serum levels of the protein and inhibit tumor proliferation. (40)

In humans with breast cancer, serum SFRP2 levels are elevated over healthy controls and correlate with increasing tumor size, presence of lymph node metastasis, increasing TMN stage and higher Ki67, a marker of proliferation.(41)

In humans with STS, the levels of serum SFRP2 expression and the response of serum SFRP2 levels to therapeutic interventions such as radiotherapy are unknown. This study will compare serum levels of SFRP2 before and after preoperative 5-day HFRT to define levels of expression in patients with STS and assess the effect of radiotherapy on SFRP2 expression. Further, we will evaluate the association of the change in serum SFRP2 levels with extent of tumor fibrosis/hyalinization, a histologic predictor of oncologic outcome, to determine the potential of SFRP2 as a predictive biomarker for favorable pathologic response. (42) If a preoperative predictive biomarker were established in STS, then it potentially could be utilized to intensify neoadjuvant therapies.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

RISK ASSOCIATED WITH HFRT: The preoperative 5-day HFRT regimen in this study uses 6 Gy per fraction. Radiobiologic theory dictates a larger dose per fraction increases the risk of late toxicity in normal tissue.(43) However, similar fraction sizes have been investigated in clinical trials for other tumor sites without increased late toxicities. (44, 45) Late toxicities such as pathologic fractures are associated with tumors in a periosteal location and dosimetric factors that include mean bone dose, maximum bone dose, and volume of bone receiving > 40Gy in 2Gy fractions.(46) The pathologic fracture risk can be lowered by treatment planning with consideration of bone dose constraints. The risks of late toxicities such as subcutaneous tissue fibrosis, joint stiffness, and lymphedema can be mitigated by using image guided radiotherapy (IGRT) and treating smaller volumes, as demonstrated in RTOG 0630. (47) Wound complications, the most morbid acute complication associated with preoperative radiotherapy, have occurred at rates like that of CFRT in two single arm phase II trials of HFRT. (10, 23) In an effort to ensure similar wound complication rates, the normal tissue dosimetric constraints used in the UCLA phase II trial will be adopted in this study. Patient related factors such as obesity, smoking, diabetes, and tumor location in the lower limbs impact the risk of wound complications but are not easily modified.(48) Radiation dermatitis is an expected acute toxicity. Radiation dermatitis rates were low in a recently reported Phase II study of preoperative HFRT (35Gy/5x) by Bedi et al.(24) Grade 2 radiation dermatitis occurred in 15.6% of patients and there were no grade 3 or higher reactions.

An inherent risk associated with participating in this trial and receiving a preoperative 5-day HFRT is that of receiving an oncologically inferior treatment regimen. Preoperative 5-day HFRT has not been compared in a prospective randomized trial to preoperative CFRT. While a phase III randomized trial represents the “gold standard” for determining equivalence in between two fractionation regimens, the rarity of extremity STS would challenge the feasibility of such a trial. The clinical outcome data for preoperative HFRT from retrospective case series, prospective institutional registries, and phase I-II trials were summarized by Spalek and Rutkowski, who asserted that the results seemed quite similar to that of CFRT. (25)

There is a risk of developing a secondary malignancy because of exposure to therapeutic ionizing radiation. This is not a risk unique to preoperative 5-day HFRT for soft tissue sarcoma. Based on a

prospective cohort study in the US SEER cancer registries, the absolute excess risk of developing a second solid malignancy by 15 years after diagnosis is estimated to be 0.5% for patients receiving radiation therapy as a component of their initial treatment. (49)

In summary, risks related to radiation therapy include the following:

Likely

- Temporary itchy rash, peeling, redness, or darkening of skin in treatment area (radiation dermatitis)
- Permanent hair loss in the treatment area
- Temporary fatigue
- Permanent swelling of the arm or leg (lymphedema)
- Permanent stiffness of the skin or soft tissue in the treatment area (soft tissue fibrosis)
- Permanent decreased flexibility of joints in the treatment area
- Increased risk of wound healing complications after the surgery to remove the tumor

Less likely

- Increased risk of fracture in bones that are in the treatment area
- Treatment may be less effective than the standard course of 5 weeks of daily radiation
- Possibility of delayed toxicities

Rare

- Risk of secondary malignancy

Reproductive risks
You should not become pregnant or father a baby nor donate sperm while on this study or during the first 6 months after completion of therapy because the radiation can affect an unborn baby. It is important you understand that you and/or your partner need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. The most common forms of acceptable birth control are the use of an oral contraceptive for women and a spermicidal condom for men.
Loss of confidentiality
There is a risk of loss of confidentiality since medical records will be reviewed during this study. MUSC and its study team members will take every effort to ensure that your information is kept confidential during this study.

Risks of blood draws
Blood samples for this trial will be taken when patients are having venipuncture for contrast administration and for routine preoperative labs. This protocol does not require venipuncture specifically for the trial. Patients may have bruising or temporary bleeding when having blood drawn. The blood draw site will be carefully bandaged after blood is collected. In rare cases, fainting may occur.

Unknown risks
All research studies may have unknown side effects. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

Preoperative 5-day HFRT for STS has been shown to increase access to a HV sarcoma center. (10) Receiving radiotherapy and surgery in HV sarcoma center has been associated with improved overall survival. (8) Thus, participation in a preoperative 5-day HFRT trial may address the time of travel/distance of travel barriers to care in a HV sarcoma center and thereby, improve a patient's oncologic outcome. Preoperative radiotherapy has a more favorable late toxicity profile than postoperative radiotherapy.(50) In a recent NCDB analysis of radiotherapy practice patterns in STS, treatment at an academic center was correlated with receipt of radiotherapy preoperatively. (7) Thus, participation in a preoperative 5-day HFRT trial within an academic center could increase patient access to a preoperative radiotherapy approach and decrease the risk of late toxicities. Preoperative image-guided intensity-modulated radiation therapy (IG-IMRT) has been investigated as a means of reducing treatment related morbidity, including wound complications, by minimizing dose to normal tissue.(51) O'Sullivan et al. demonstrated that preoperative IG-IMRT decreased the requirement for free tissue transfers and good limb function was preserved. The NCDB analysis demonstrated a greater rate of IMRT utilization at academic centers.(7) Thus, participation in a preoperative 5-day HFRT trial within an academic center could increase patient access to IG-IMRT with resultant lower morbidity. Finally, HFRT regiments such as that proposed in this study have been proven to be more cost effective than courses of CFRT in other malignancies.(52) Participation in a preoperative 5-day HFRT trial may result in less financial burden to the patient.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

While current national guidelines recommend preoperative CFRT for the treatment of STS, vulnerable populations including the elderly, racial minorities and those living in rural areas do not have the same access to radiotherapy or treatment within a HV sarcoma center. (2, 7, 53) By decreasing the duration of treatment and travel requirements, preoperative 5-day HFRT regimen can address known barriers to receiving radiotherapy as a component of treatment and receiving treatment within a HV sarcoma center.(10) Participating in preoperative 5-day HFRT trial may also increase the likelihood that a patient will receive radiotherapy in a preoperative approach and IG-IMRT both of which can decrease late toxicity.(6, 51) HFRT regimens have been shown to be more cost-effective than CFRT in other malignancies and participation in a preoperative 5-day HFRT can decrease the financial toxicity of treatment.(52) Clinical trials directly comparing the treatment related toxicities and oncologic outcomes of HFRT and CFRT have not been performed, but based on the available literature the incidences of acute complications and local recurrence appear comparable.(25)

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the feasibility of preoperative 5-day HFRT	*Preoperative 5-day HFRT uptake rate, defined as the proportion of* eligible and approached *patients who elect to participate in the trial.*	The historical incidence of STS patients meeting eligibility for this trial in HCC registry was ~10/year. Only the endpoint of feasibility could be assessed in this small sample size. The feasibility of preoperative 5-day HFRT in HCC patient population is unknown.
Secondary		
To evaluate incidence of favorable pathologic response, incidence of major wound complications, local control, acute and 1-year late toxicity of preoperative 5-day HFRT	• Favorable pathologic response defined as extent of tumor fibrosis/hyalinization >12.5% (yes/no) • Major wound complications defined according to CAN-NCIC-SR2 Multi-center trial within 6 months after limb-sparing surgery(6) • Local control defined as 1-year Local Recurrence Free Survival • Incidence of grade $\geq$ 2 radiation dermatitis CTCAE v 5.0, assessed during radiotherapy and 2 weeks post-RT using • *1-year late toxicity defined incidence of grade $\geq$2* subcutaneous fibrosis, joint stiffness (RTOG/EORTC Criteria) and edema (Stern scale)	To define the early efficacy and treatment related toxicities associated with preoperative 5-day HFRT
Tertiary/Exploratory		
To compare the socio-demographic profiles of trial participants with	Age, race, gender, marital status, health insurance status, comorbidities,	To inform the hypothesis that

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
those of STS patients who would have met trial eligibility criteria and were treated with CFRT at HCC in the 3 years prior to study opening	geocode defined rural vs urban residence, estimated distance traveled to HCC, census tract level American Community Survey variables to include Socioeconomic status, Household Composition and Disability, Minority Status and Language, Housing Type, and Transportation	preoperative 5-day HFRT increases access to radiotherapy at a HV sarcoma center for those that have potential barriers to care
To compare the retention rate for radiotherapy at HCC in patients meeting trial eligibility criteria during the prior 3 years with the retention rate for radiotherapy during the study period	Proportion of patients meeting trial eligibility criteria in prior 3 years who received radiotherapy at HCC compared with the proportion of patients who were trial eligible and received radiotherapy (CFRT or HFRT) at HCC during the study period. Both cohorts would be identified by the HCC cancer registry.	To inform the hypothesis that preoperative 5-day HFRT increases access to radiotherapy at a HV sarcoma center
To compare serum levels of SFRP2 before and after preoperative 5-day HFRT	Change in SFRP2 serum levels before and after preoperative 5-day HFRT	The response of serum SFRP2 levels to preoperative radiotherapy is unknown
To evaluate the association between changes in serum levels of SFPR2 and pathologic response to preoperative 5-day HFRT	Change in SFRP2 serum levels before and after preoperative 5-day HFRT Incidence of a favorable pathologic response defined as extent of tumor fibrosis/hyalinization >12.5% (yes/no)	Any correlation between change in serum SFRP2 levels in response to HFRT and a favorable pathologic response is unknown
To evaluate patient satisfaction with the decision to participate in a clinical trial of preoperative 5-day HFRT	Decision Regret Scale(1) at the 2-week post radiation visit and the 6-month postoperative visit	Patient satisfaction with the decision participate in a clinical trial of preoperative 5-day radiotherapy is unknown and would be an important factor when considering future studies of preoperative 5-day HFRT
To assess the importance of the shorter duration of radiotherapy in	Patient questionnaire administered at the 2-week post-radiation visit	To inform the hypothesis that

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
an individual patient's decision to participate in the study		preoperative 5-day HFRT increases access to radiotherapy at a HV sarcoma center

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis: It is hypothesized that a preoperative 5-day HFRT is a feasible regimen for the treatment of extremity STS.
Phase of trial: Feasibility study
Trial Design: This is a single site, single arm, feasibility study of preoperative 5-day HFRT for the treatment of extremity STS.
Interim analysis: Not planned
Study stratification: Not applicable

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a feasibility trial. This study design was selected as STS are rare tumors and the estimated trial eligible population based on historical institutional data is approximately 10 patients per year.

4.3 JUSTIFICATION FOR DOSE

There have been several dose and fractionation schedules utilized in the clinical outcome literature for preoperative HFRT (see table 1). The 30Gy/5fx regimen was selected for this study because it was utilized in the UCLA phase II trial, and it has been utilized rarely in our institution for rapidly progressing tumors where the opportunity for limb preservation could be jeopardized by a protracted preoperative CFRT.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:
1. Willingness and provision of informed consent via a signed and dated copy

2. AJCC 8th edition stage I-III histologically confirmed STS of the extremities or trunk
3. Male or female, aged ≥ 18 years old
4. ECOG Performance Status 0-3
5. Meets screening criteria for receipt of radiotherapy
6. Deemed eligible for wide local excision

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Distant metastatic disease
2. Prior radiation therapy in the proposed treatment area
3. Simultaneous treatment of another malignancy
4. Planned neoadjuvant or adjuvant chemotherapy
5. Women who are pregnant or planning to become pregnant during study participation

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not entered in the study due to not meeting enrollment criteria or otherwise do not initiate study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a <specify modifiable factor> may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients with non-metastatic STS of the extremity or trunk presenting to HCC HV sarcoma center will be reviewed at the multi-disciplinary tumor board and screened for trial eligibility. To minimize invasive interventions that could be barriers to trial participation, the pre- and post- radiation serum SFRP2 samples will be obtained at the time of venipuncture for IV contrast administration and routine preoperative laboratory studies. To compensate patients for their time required to complete patient satisfactory questionnaires, they will receive 50 dollars compensation.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Participants will receive preoperative 5-day HFRT (30Gy/5fx once daily over consecutive weekdays) followed by "standard of care" wide local excision 2-6 weeks later.

Radiation therapy treatment planning and target volume delineation:
Patients will undergo CT simulation with custom immobilization of the limb using standard treatment devices. CT images will be obtained with 3 mm slice thickness through the region of interest. The gross (GTV), clinical (CTV), and planning (PTV) target volumes will be defined in accordance with 2021 ASTRO Clinical Practice Summary for the Treatment of STS.(2): The GTV will be defined with the aid of T1 post-gadolinium and/or T2 weighted sequences. When feasible, the preoperative MRI will be fused with the treatment planning CT for target volume delineation. The CTV will be defined as the GTV + 1.5 cm radial margin and a 3-4 cm longitudinal margin. The CTV will be anatomically constrained (cropped out of uninvolved bone and nonadjacent muscle compartments) and include the peritumor edema and biopsy tract (when feasible). For subcutaneous tumors (tumors not involving the fascia), the CTV will be defined as the GTV + 3-4 cm circumferential margin and an expansion of 0.5 cm-1 cm into the underlying non-involved muscle with *inclusion* of peritumor edema and biopsy tract (when feasible). The PTV will be defined as the anatomically constrained CTV + 0.5 cm with daily image guidance. The PTV will be trimmed 3-5 mm from the skin to reduce wound healing complications if achievable without unacceptable compromise to the CTV coverage. Organs at risk (OAR) should be contoured but can vary based on tumor location. The dosimetric constrains to OAR are defined in Table 2. These OAR constrains have been adopted from prior Phase II trials of preoperative HFRT for extremity STS with 2-3 years of follow up for late toxicities.(10, 24)

Table 2. Dosimetric parameters for radiation treatment planning	
PTV[1]	V100(%) $\leq$ 110%, V100% $\geq$ 95%
Skin	V12Gy $\leq$ 50%
2 cm longitudinal strip of skin[2]	V12Gy $\leq$ 10%
Long bones (femur, humerus)[3]	V30Gy $\leq$ 50%
Femoral or humeral head	V30Gy $\leq$ 5cc, Dmax <30Gy
Spinal cord	Dmax < 30Gy
Chest wall	V30Gy $\leq$ 70cc
Bowel	V32Gy $\leq$ 5cc
Liver	V15Gy $\leq$ 700cc
Kidney	V10Gy $\leq$ 10%
Involved lymph nodes[4]	

Footnotes:

1. If treatment plan utilizes electrons, then the dosimetric parameters for the PTV may vary from the those provided in Table 2 in accordance with clinical judgement of the treating physician. In cases where the PTV coverage and the OAR constraints cannot be met, the clinical judgement of the treating physician will dictate which can be safely compromised. STS of the trunk are eligible for this study. Current available guidelines recommend CTV expansions that are the same as those for extremity site when feasible(2).
2. The strip of skin volume will be defined as a $\geq$1 cm strip of skin, 2 mm in depth, with a cranio-caudal extent that matches that of the PTV.
3. The long bone volume will be defined as the long bone 2 cm above and below the PTV with this is anatomically feasible.
4. Current available guidelines do not provide specific dosimetric parameters for the coverage of involved lymph nodes and thus this will be dictated by the clinical judgement of the treating physician(2).

Assessment of Serum SFRP2 before and after preoperative 5-day HFRT: Serum SFRP samples will be collected before and after preoperative 5-day HFRT. These serum samples will be collected and processed at the time of scheduled venipunctures required for standard of care by the MUSC tumor bank.

6.2 STUDY INTERVENTION COMPLIANCE

Patients will be assessed by a Radiation Oncologist during the preoperative 5-day HFRT. Compliance with prescribed course of radiotherapy will be documented in a Treatment Summary at the close of radiotherapy.

6.3 CONCOMITANT THERAPY

Not applicable as planned neoadjuvant chemotherapy is an exclusion criterion.

6.4 RESCUE MEDICINE

Patients will receive any supportive care necessary as part of their HFRT at the discretion of the treating investigator.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may withdraw voluntarily from the study, or the PI may discontinue a participant from the study. In addition, participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints. In addition, a dedicated Case Report Form (CRF) page will capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

Pregnancy

Significant study intervention non-compliance

If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

Disease progression which requires discontinuation of the study intervention

If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Participant unable to receive study treatment for an extended delay as deemed unacceptable by the investigator

The reason for participant discontinuation or withdrawal from the study will be recorded on the End of Treatment Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a determined number of scheduled visits by the investigator, and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

The site will attempt to contact the participant and reschedule the missed visit, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

<u>Evaluation of Serum SFRP2 pre- and post- preoperative 5-day HFRT</u>:
A pre- HFRT serum SFRP2 sample will be obtained on the day of CT simulation. The CT simulation requires venipuncture for IV contrast administration. Thus, the pre- HFRT serum SFRP2 sample will not require an additional venipuncture.

A post- HFRT serum sample will be obtained at the 2-week post HFRT. At this visit patients undergo standard preoperative laboratory assessments. Thus, the post-HFRT serum SFRP2 assessment will not require an additional venipuncture.

Administration of questionnaires or other instruments*:*
Questionnaires will be administered to evaluate decision regret and factors impacting medical decision making.

Questionnaire 1 will inquire about how a shorter course of radiation treatment impacted the patient's decision to participate in the study and assess decision regret. It will be administered at the 2-week post RT visit and include questions 1-12. Questionnaire 2 will reassess decision regret (questions 7-12) and be administered at the 6-month follow up visit. Patients will be compensated 50 dollars for completion of questionnaires.

Procedures that will be completed during the study as part of regular standard of clinical care*:*

Clinical Biopsy: *Pathologic confirmation of STS will be obtained through a biopsy as it is standard of care.*

Physical examination: *Physical examinations will be performed by physician, physician's assistant, or nurse practitioner at the time of consultation, on-treatment and follow up visits. Focused examination will describe the tumor/operative site and any associated functional disability if applicable.*

Performance Status: *ECOG or Karnofsky performance status will be documented at consultation and in follow up visits.*

Radiographic or other imaging assessments*: Staging and surveillance imaging will include an MRI of the primary site and Chest CT. MRI imaging of the primary site will be performed with and without contrast. Chest CT imaging will be non-contrasted unless otherwise clinically indicated. There are subtypes of STS that require staging and surveillance imaging of sites that are at higher risk for distant involvement. Current guidelines for imaging of these sites at presentation and in follow up should be considered(54).*

Routine Preoperative Labs: *Complete blood count (CBC)will be obtained preoperatively.*

CT simulation: *CT simulation with administration of IV contrast and construction of custom immobilization devices will be performed as a standard component of radiation therapy treatment planning.*

Surgical Resection: *Wide Local Excision of STS (limb sparing surgery) will be performed. The surgical technique and need for tissue coverage of operative defect will be determine by treating surgeon.*

8.2SAFETY AND OTHER ASSESSMENTS

Physical examination: *Physical examinations will be performed by physician, physician's assistant, or nurse practitioner at the time of consultation, on-treatment and follow up visits. Focused examination will describe the tumor/operative site and any associated functional disability if applicable.*

Performance Status: *ECOG performance status will be documented at consultation and in follow up visits.*

Radiographic or other imaging assessments. *Staging and surveillance imaging will include an MRI of the primary site and Chest CT. MRI imaging of the primary site will be performed with and without contrast. Chest CT imaging will be non-contrasted unless otherwise clinically indicated. There are subtypes of STS that require staging and surveillance imaging of sites that are at higher risk for distant involvement. Current guidelines for imaging of these sites at presentation and in follow up should be considered(54).*

Assessment of study intervention adherence *or see Study Intervention Compliance, section 6.2*

Administration of questionnaires: *see section 8, Study Assessments and Procedures*

Assessment of adverse events. *The incidence of major wound complications will be assessed at the time of postoperative follow up (2 weeks to 6 months). Major wound complications are define in accordance with the CAN-NCIC-SR2 Multi-center randomized trial(6). Major wound complications are defined as a secondary operation under general or regional anesthesia for wound repair (debridement, operative drainage, and secondary wound closure including rotationplasty, free flaps, or skin grafts) or wound management without secondary operation. Wound management requiring an invasive procedure without general or regional anesthesia (mainly aspiration of seroma), readmission for wound care such as requirement of IV antibiotics, or deep packing for 120 days or longer.*

Radiation dermatitis will be assessed during the on-treatment visit and at the 2-week post RT/preoperative visit by a Radiation Oncologist. The NCI CTACE v 5.0 radiation dermatitis scoring system will be utilized(55).

NCI CTCAE v5.0 radiation dermatitis

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

The radiation related late toxicities of subcutaneous fibrosis and joint stiffness will be assessed using the RTOG/EORTC criteria(47, 56). Limb edema will be assessed using the Stern scale(57).

Late Radiation Toxicity Grading					
Late Radiation Toxicity	*0*	*1*	*2*	*3*	*4*
RTOG/EORTC CRITERIA					
Subcutaneous tissue (subcutaneous fibrosis)	*None*	*Slight fibrosis; loss of subcutaneous fat*	*Moderate fibrosis; slight field contracture*	*Severe fibrosis; field contracture > 10%*	*Necrosis*
Joint (joint stiffness)	*None*	*Mild stiffness; slight range of motion loss*	*Moderate stiffness, pain, range of motion loss*	*Severe stiffness, pain range of motion loss*	*Necrosis; complete fixation*
Stern scale					
Edema	*None*	*Mild but definite swelling*	*Moderate*	*Severe swelling*	*Very severe (skin shiny and tight with or without skin cracking*

Retrospective Chart Abstraction: This study will conduct an exploratory analysis to compare sociodemographic data of the trial participants to a historical cohort of STS patients identified from the HCC Tumor Registry. Once STS patients are identified from the HCC Tumor Registry, we will obtain sociodemographic (e.g., race, age, gender) and other social determinants of health (SDOH) data (e.g., financial class, comorbidities, social vulnerability index) from the electronic medical record (EMR) to assess the social profiles of STS patients and carry out the aims of the project. We will obtain a waiver of consent to access and utilize this data for purposes of this study. Additionally, a waiver of written HIPAA Authorization will be obtained to retrieve personal health information (PHI) related to their MRN, address, and other clinical data (e.g., date of diagnosis). All PHI collected will be kept electronically in a secured, restricted-access database through MUSC's secure server. Access to the computerized datasets generated as part of this study will be restricted using passwords to study personnel identified by the principal investigators as requiring access. No personal identifiers will be reported from any study activity involving human subjects.

In order to define the socio-demographic profile of the trial cohort the following Protect Health Information will be obtained: Residential Street address, financial class, medical record number, marital status, health insurance, comorbidities.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Rechallenge information is not required to fulfill this definition.
Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

EXPECTEDNESS

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The clinical study team, with assistance of the investigator or designee, will record all reportable events with start dates occurring any time from time of study treatment initiation until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

<Insert text>

8.3.5 ADVERSE EVENT REPORTING

Adverse events will be reported utilizing the Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0, available at the following link:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Adverse events will be recorded in the Electronic Data Capture (EDC) system's electronic case report forms (eCRFs) utilizing the REDCap database.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the MUSC Hollings Cancer Center's Clinical Trials Office Sponsor-Investigator Support Unit (SISU), and to the MUSC IRB per their policies, any serious adverse event, including those listed in the protocol, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the SISU and IRB, at a minimum within 24 hours of knowledge of the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the SISU or Hollings Cancer Center Data Safety and Monitoring Committee (DSMC) and should be provided as soon as possible.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be notified immediately of any unexpected serious adverse events (SAEs) as they occur throughout the study. Participants on active study treatment must be re-consented to the most current version of the ICD and receive a signed copy for their records.

8.3.8 REPORTING OF PREGNANCY

Female participants that are women of childbearing potential (WOCBP) and their male partners, if appliable, will be advised by the study clinician that they must adhere to adequate contraception measures as defined by the study clinician during the timeframe that the participant is receiving study treatment and for any additional duration as deemed necessary after study treatment concludes, per institutional standard of care for patients receiving radiation therapy.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and

Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
A detailed description of the event, incident, experience, or outcome;
An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

UPs that are serious adverse events (SAEs) 10 working days of the investigator becoming aware of the event.
Any other UP will be reported to the SISU at the time of routine Data Safety and Monitoring Committee (DSMC) auditing and/or progress reporting.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unexpected, related serious adverse events (SAEs) will be communicated to participants via a revised informed consent form (ICF). Participants on active study treatment will be required to read and sign the ICD, and a signed copy will be provided for their records.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s): Preoperative 5-day HFRT uptake rate, defined as the proportion of eligible and approached patients who elect to participate in the trial.

We hypothesize that preoperative 5-day HFRT uptake rate among eligible STS patients will be at least 50%. If the data provide weak evidence in favor of this hypothesis, we will conclude 5-day HFRT is not feasible in this patient population.

9.2 SAMPLE SIZE DETERMINATION

Our target sample size is n = 15 patients in the full analysis set, as described in Section 9.3, and we anticipate enrollment in 2-3 years based on historical counts at our institution (~10/year). Enrollment will

terminate when we have reached our target sample size of n = 15 patients in the full analysis set, or the trial has been open for accrual for 3 years, whichever occurs first. If at the end of 3 years fewer than 15 trial participants have been enrolled who meet the conditions of the full analysis set, the study team will evaluate accrual rates and determine whether to halt accrual or amend the protocol to achieve the desired sample size.

Our primary objective is to demonstrate feasibility of pre-operative 5-day HFRT and our primary endpoint is the pre-operative 5-day HFRT uptake rate, defined as the proportion of eligible patients who elect to participate in the trial. We assume trial enrollment with intention to participate is a reasonable surrogate measure for 5-day HFRT uptake since our study introduces no additional interventions or blood sampling beyond standard of care. We will summarize the frequency and percentage of eligible and approached patients who enroll and construct exact binomial 90% confidence interval (CIs). We justify sample size based on precision, defined as the width of the corresponding CI (Table 1).

Table 1: Precision of observed participation rates.

Accrual time (yrs)	No. eligible	Observed proportion	Exact binomial 90% CI of true proportion	CI width = upper bound (UB) – lower bound (LB)
2	20	15/20 = 0.75	(0.54, 0.90)	0.35
2.5	25	15/25 = 0.6	(0.42, 0.76)	0.35
3	30	15/30 = 0.5	(0.34, 0.66)	0.32

Our target is a minimum participation rate of 50%. However, given the small sample size, the probability of observing a participation rate less than 50% is high even if the true 5-day HFRT uptake rate is 50%. For example, if the number of eligible patients is 20, there is a 25% probability that the observed uptake rate is at most 40% even if the true 5-day HFRT uptake rate equals 50%. If the number of eligible patients is 30, there is an 18% probability that the observed uptake rate is at most 40% even if the true 5-day HFRT uptake rate equals 50%. Given this limitation, we establish a feasibility threshold based on the posterior probability derived from a beta-binomial distribution. Specifically, 5-day HFRT will not be considered feasible in this patient population if there is weak evidence the true uptake rate exceeds 50%. We assume the true uptake rate follows a Beta(1,1) prior distribution and, conditional on this rate, the number of eligible patients who participate follows a binomial distribution. Five-day HFRT will not be considered feasible if Prob(true 5-day HFRT uptake rate > 50%|data) < 10% at the end of the trial. The threshold for declaring the intervention not feasible will depend on the total number of eligible patients approached. Feasibility boundaries are summarized in Table 2 for eligible patient numbers ranging from 20-30.

Table 2: Feasibility decision rule boundaries

No. eligible	5-day HFRT is not feasible if No. enrolled is ≤ _____	Observed participation rate
20 – 22	7	≤ 0.35
23 – 24	8	≤ 0.35
25 – 26	9	≤ 0.36
27 – 29	10	≤ 0.37
30	11	0.37

9.3 POPULATIONS FOR ANALYSES

- The **feasibility analysis set** comprises all patients who are eligible and approached for trial participation during the time of active patient enrollment. The primary feasibility endpoint will be evaluated using the feasibility analysis set.

- The **radiotherapy retention analysis set** comprises all patients who are eligible for trial participation during the time of active patient enrollment who received any form of pre-operative CFRT or HFRT at any location, and regardless of whether the patient is approached for participation. The radiotherapy retention analysis set will be used for the analysis of patient retention at HCC.

- The **safety analysis set (SAS)** comprises all patients enrolled who receive any administration of 5-day HFRT. The SAS will be used for all safety analyses, including the analysis of secondary safety endpoints (major wound complications, acute toxicity and 1-year late toxicity associated with preoperative 5-day HFRT).

- The **full analysis set (FAS)** is equivalent to the SAS and will be used for the analysis of all clinical secondary endpoints (favorable pathologic response, local control), and analysis of exploratory endpoints (except for biomarker endpoints).

- The **biomarker analysis set** comprises all trial participants with both a pre- and post-HFRT serum SFRP2 measurement. The biomarker analysis set will be used for all SFRP2 analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Frequencies and percentages will be used to summarize the distributions of categorical variables. Mean, median, range, inter-quartile range and standard deviation will be used to summarize distributions of continuous variables.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary analysis will be performed using the feasibility analysis set described in Section 9.3. The primary endpoint is the incidence of **preoperative 5-day HFRT uptake** in eligible and approached extremity STS patients. The frequency and percentage of uptake positive patients and corresponding exact binomial 90% CIs will be reported. “Patients in the feasibility analysis set who consent to 5-day HFRT but progress or die prior to treatment initiation will be considered uptake positive. Patients in the feasibility analysis set who consent to 5-day HFRT but fail to obtain any of the intervention will be considered uptake negative.” The trial will be considered negative and 5-day HFRT for extremity STS patients considered not feasible if there is weak evidence the true uptake rate exceeds 50% based on a Beta-binomial posterior probability as described in Section 9.3.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Favorable pathologic response and **local control** will be summarized using frequencies, percentages and 90% exact binomial confidence intervals. The analysis set is the FAS as described in Section 9.3.

Major wound complications, **acute toxicity** and **1-year late toxicity** will be summarized using frequencies, percentages and 90% exact binomial confidence intervals. The analysis set is the SAS as described in Section 9.3.

9.4.4 SAFETY ANALYSES

All patients in the safety analysis set will be evaluated for safety and toxicity. Adverse events, SAEs and TEAEs will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term within SOC. Safety analyses will include the following summaries:

- AEs, including severity and possible relationship to study intervention

- SAEs, including possible relationship to study intervention
- AEs leading to dose adjustments
- DLTs and DLT-E events
- Discontinuations from study treatment due to AEs or death
- Treatment-emergent abnormal changes in laboratory values
- Treatment-emergent abnormal changes in vital signs and ECGs

9.4.5 BASELINE DESCRIPTIVE STATISTICS

A summary of baseline patient and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported using descriptive statistics.

9.4.6 SUB-GROUP ANALYSES

This is small 15-patient feasibility study. There are no pre-planned sub-group analyses.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual trial participant data will be listed by measure and time point for safety data only.

9.4.8 EXPLORATORY ANALYSES

Comparative analysis of the socio-demographic profiles of preoperative 5-day HRFT protocol cohort vs institutional historical control cohort.

It is hypothesized that preoperative 5-day HFRT can increase access to radiotherapy treatment within a high-volume sarcoma center for patients with barriers to health care access. To investigate this hypothesis, a cohort of patients with STS receiving preoperative CFRT at HCC and meeting the eligibility criteria of this protocol during the period of 12/31/18-12/31/21 will be identified from the HCC cancer registry. Descriptive statistics will be used to summarize the following sociodemographic metrics from this institutional cohort and the protocol cohort: age, race, gender, marital status, health care insurance status, comorbidities, geocode defined as rural versus urban residence, estimated distance traveled to HCC, US census tract level American Community Survey (ACS) variables. ACS variables include socioeconomic status, household composition and disability, minority status and language, housing type and transportation. Defining the socio-demographic profiles of these two cohorts will require obtaining patient “identifiers” such as health insurance identification number, medical record number, as well as EMR data to include marital status, health care insurance status, and comorbidities. Comparisons between the historical and protocol cohort will be considered exploratory and conducted using Wilcoxon rank sum test or Fisher’s exact test, depending on variable (continuous or discrete). A two-sided type I error rate of $\alpha = 0.1$ will be used for all hypothesis tests. The trial protocol cohort data will be derived from patients in the full analysis set, as described in Section 9.3.

Compare the retention rate for radiotherapy at HCC during the study period vs institutional historical rates.

It is hypothesized that preoperative 5-day HFRT can increase access to radiotherapy treatment within a high-volume sarcoma center. To investigate this hypothesis, a cohort of patients with STS receiving

preoperative CFRT (at any location) and meeting the eligibility criteria of this protocol during the period of 12/31/18-12/31/21 will be identified from the HCC cancer registry (defined as denominator cohort). The proportion of patients in this historical control cohort who received radiotherapy at HCC will be compared to the proportion of patients who meet trial criteria during the trial period and received pre-operative CFRT or 5-day HFRT at HCC, independent of their trial participation (defined as the numerator cohort). The numerator cohort will be identified by the HCC cancer registry. Comparisons will be performed using Fisher's exact test. A two-sided type I error rate of $\alpha = 0.1$ will be used. The trial protocol cohort data will be derived from patients in the radiotherapy retention analysis set, as described in Section 9.3.

Exploratory Analysis of SFRP2

The **change in serum levels of SFRP2** pre- and post- HFRT will be reported with corresponding 90% confidence intervals. We will test the hypothesis that SFRP2 change differs significantly from 0 using Wilcoxon sign rank test with two-sided $\alpha = 0.1$.

The **association between change in serum levels of SFRP2 and pathologic response** (favorable versus not favorable) will be evaluated using Wilcoxon rank sum test with two-sided $\alpha = 0.1$.

All analyses of SFRP2 data will be conducted using the biomarker analysis set as described in Section 9.3.

Patient-reported outcomes

Scores for Decision Regret Scale (patient satisfaction) and other patient-reported outcomes will be summarized at each time point using descriptive statistics (mean, median, SD, IQR and range). Analyses of patient reported outcomes will be conducted using the FAS as described in Section 9.3 using a complete case analysis. Given the small sample size, there will be no attempt at multiple imputation for item non-response.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Informed consent will be obtained on all wiling participants in accordance with 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and ICH GCP. Participants will be fully informed about the study and given sufficient time to review the written informed consent form (ICF) and have all questions satisfactorily answered. Participants will receive a copy of the signed ICF for their records. No study-specific procedures will be conducted prior to participants signing the ICF. Standard of care (SOC) procedures performed prior to ICF signing are permissible, provided they are within the allocated screening timeframe for the study.

CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional

Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the sponsor-investigator and funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

Determination of unexpected, significant, or unacceptable risk to participants
Demonstration of efficacy that would warrant stopping
Insufficient compliance to protocol requirements
Data that are not sufficiently complete and/or evaluable
Determination that the primary endpoint has been met
Determination of futility
Accrual not within institutional goals

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor-investigator and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in a HIPAA-compliant setting.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each investigational site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the institutional REDCap database.. This will not include the participant's contact information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the investigational site's research staff will be secured and password protected. At the end of the study, all study databases will be locked and archived.

10.1.4 FUTURE USE OF STORED SPECIMENS (SFRP2 BLOOD SAMPLING) AND DATA

Data collected for this study will be analyzed and stored at the investigational site. After the study is completed, the de-identified, archived data will remain stored within the REDCap database.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the designated co-investigator's research laboratory These samples could be used to research the causes of the disease under study, its complications and other conditions for which individuals with this disease are at increased risk, and to improve treatment. The investigator lab will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to specimen storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the investigator lab.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**

Jennifer Harper, MD	*David Marshall, MD*
Medical University of South Carolina	*Medical University of South Carolina*
86 Jonathan Lucas St., Charleston SC 29425	*86 Jonathan Lucas St., Charleston SC 29425*
843-792-3271	*843-792-3271*
harperjl@musc.edu	*marshadt@musc.edu*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including the care of oncology patients. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the principal investigator, internal auditor and clinical trials office leadership.

10.1.7 CLINICAL MONITORING

Investigational site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the biostatistics core and an internal auditing agency within the clinical trials office.
Monitoring will occur within the biostatistics core monthly via interaction with the study principal investigator. A summary of data timeliness and quality will be provided and action items pertaining to any delinquent data or outstanding data queries will be addressed. Auditing will occur at least annually via a detailed review of the enrolled subjects' informed consent forms, review of eligibility for each subject, and up to 100% source data verification on all subject case report forms.
The study principal investigator will be provided copies of monitoring reports prior to monthly meetings, and copies of auditing reports within approximately 30 days of the audit.
Details of investigational site monitoring are documented in a Clinical Data and Monitoring Plan (CDMP). The CDMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The investigational site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the clinical study team for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors/auditors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring, auditing and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by license to the investigational site. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 6 years per MUSC institutional policy.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The

noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:
4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1 Quality Assurance and Quality Control, section 5.1.1
5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the Sponsor-Investigator Support Unit (SISU) Program Manager/Coordinators. Protocol deviations must be sent by the SISU to the reviewing Institutional Review Board (IRB) and Data Safety Monitoring Board (DSMB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details on protocol deviation reporting is included in a separate investigational site SOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the SISU Program Manager.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Medical University of South Carolina has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

UP	Unanticipated Problem
US	United States

11 REFERENCES

1. AM OC. User Manuel-Decision Regret Scale [doument on the Internet]1996 [modifed 2003; cited 2022 08 21]:[3 p.]. Available from: *http://decisionaid.ohri.ca/docs/develop/User_Manuels/UM_Regret_Scale.pdf*.

2. Salerno KE, Alektiar KM, Baldini EH, Bedi M, Bishop AJ, Bradfield L, et al. Radiation Therapy for Treatment of Soft Tissue Sarcoma in Adults: Executive Summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2021;11(5):339-51. Epub 20210726. doi: 10.1016/j.prro.2021.04.005. PubMed PMID: 34326023.

3. MacDermed DM, Miller LL, Peabody TD, Simon MA, Luu HH, Haydon RC, et al. Primary tumor necrosis predicts distant control in locally advanced soft-tissue sarcomas after preoperative concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2010;76(4):1147-53. Epub 20090704. doi: 10.1016/j.ijrobp.2009.03.015. PubMed PMID: 19577863; PubMed Central PMCID: PMC2931332.

4. Ryan CW, Montag AG, Hosenpud JR, Samuels B, Hayden JB, Hung AY, et al. Histologic response of dose-intense chemotherapy with preoperative hypofractionated radiotherapy for patients with high-risk soft tissue sarcomas. Cancer. 2008;112(11):2432-9. doi: 10.1002/cncr.23478. PubMed PMID: 18348295.

5. Parsai S, Lawrenz J, Kilpatrick S, Rubin B, Hymes C, Gray M, et al. Early Outcomes of Preoperative 5-Fraction Radiation Therapy for Soft Tissue Sarcoma Followed by Immediate Surgical Resection. Adv Radiat Oncol. 2020;5(6):1274-9. Epub 20200629. doi: 10.1016/j.adro.2020.06.024. PubMed PMID: 33305088; PubMed Central PMCID: PMC7718495.

6. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002;359(9325):2235-41. doi: 10.1016/s0140-6736(02)09292-9. PubMed PMID: 12103287.

7. Reddy VK, Jain V, Venigalla S, Levin WP, Wilson RJ, Weber KL, et al. Radiotherapy Remains Underused in the Treatment of Soft-Tissue Sarcomas: Disparities in Practice Patterns in the United States. J Natl Compr Canc Netw. 2021:1-12. Epub 20210208. doi: 10.6004/jnccn.2020.7625. PubMed PMID: 33556919.

8. Venigalla S, Nead KT, Sebro R, Guttmann DM, Sharma S, Simone CB, 2nd, et al. Association Between Treatment at High-Volume Facilities and Improved Overall Survival in Soft Tissue Sarcomas. Int J Radiat Oncol Biol Phys. 2018;100(4):1004-15. Epub 20171221. doi: 10.1016/j.ijrobp.2017.12.262. PubMed PMID: 29485042; PubMed Central PMCID: PMC5830163.

9. Mattes MD, Suneja G, Haffty BG, Takita C, Katz MS, Ohri N, et al. Overcoming Barriers to Radiation Oncology Access in Low-Resource Settings in the United States. Adv Radiat Oncol. 2021;6(6):100802. Epub 20210910. doi: 10.1016/j.adro.2021.100802. PubMed PMID: 34693080; PubMed Central PMCID: PMC8515237.

10. Kalbasi A, Kamrava M, Chu FI, Telesca D, Van Dams R, Yang Y, et al. A Phase II Trial of 5-Day Neoadjuvant Radiotherapy for Patients with High-Risk Primary Soft Tissue Sarcoma. Clin Cancer Res. 2020;26(8):1829-36. Epub 20200213. doi: 10.1158/1078-0432.CCR-19-3524. PubMed PMID: 32054730; PubMed Central PMCID: PMC7189949.

11. Comis RL, Miller JD, Aldige CR, Krebs L, Stoval E. Public attitudes toward participation in cancer clinical trials. J Clin Oncol. 2003;21(5):830-5. doi: 10.1200/JCO.2003.02.105. PubMed PMID: 12610181.

12. Cohen GI. Clinical research by community oncologists. CA Cancer J Clin. 2003;53(2):73-81. doi: 10.3322/canjclin.53.2.73. PubMed PMID: 12691265.

13. Maurer LH, Davis T, Hammond S, Smith E, West P, Doolittle M. Clinical trials in a rural population: professional education aspects. J Cancer Educ. 2001;16(2):89-92. doi: 10.1080/08858190109528739. PubMed PMID: 11440069.

14. Tanner A, Kim SH, Friedman DB, Foster C, Bergeron CD. Barriers to medical research participation as perceived by clinical trial investigators: communicating with rural and african american communities. J Health Commun. 2015;20(1):88-96. Epub 20140910. doi: 10.1080/10810730.2014.908985. PubMed PMID: 25204763.

15. Kim SH, Tanner A, Friedman DB, Foster C, Bergeron CD. Barriers to clinical trial participation: a comparison of rural and urban communities in South Carolina. J Community Health. 2014;39(3):562-71. doi: 10.1007/s10900-013-9798-2. PubMed PMID: 24310703.

16. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362(6):513-20. doi: 10.1056/NEJMoa0906260. PubMed PMID: 20147717.

17. Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. J Clin Oncol. 2016;34(20):2325-32. Epub 20160404. doi: 10.1200/JCO.2016.67.0448. PubMed PMID: 27044935; PubMed Central PMCID: PMC4981980.

18. Erlandsson J, Holm T, Pettersson D, Berglund A, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 2017;18(3):336-46. Epub 20170210. doi: 10.1016/S1470-2045(17)30086-4. PubMed PMID: 28190762.

19. Erlandsson J, Martling A. Short-course radiotherapy with delayed surgery for rectal cancer - Authors' reply. Lancet Oncol. 2017;18(6):e295. doi: 10.1016/S1470-2045(17)30323-6. PubMed PMID: 28593850.

20. Thames HD, Suit HD. Tumor radioresponsiveness versus fractionation sensitivity. Int J Radiat Oncol Biol Phys. 1986;12(4):687-91. doi: 10.1016/0360-3016(86)90081-7. PubMed PMID: 3700173.

21. van Leeuwen CM, Oei AL, Crezee J, Bel A, Franken NAP, Stalpers LJA, et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiat Oncol. 2018;13(1):96. Epub 20180516. doi: 10.1186/s13014-018-1040-z. PubMed PMID: 29769103; PubMed Central PMCID: PMC5956964.

22. Spalek MJ, Kosela-Paterczyk H, Borkowska A, Wagrodzki M, Szumera-Cieckiewicz A, Czarnecka AM, et al. Combined Preoperative Hypofractionated Radiotherapy With Doxorubicin-Ifosfamide Chemotherapy in Marginally Resectable Soft Tissue Sarcomas: Results of a Phase 2 Clinical Trial. Int J Radiat Oncol Biol Phys. 2021;110(4):1053-63. Epub 20210216. doi: 10.1016/j.ijrobp.2021.02.019. PubMed PMID: 33600887.

23. Kosela-Paterczyk H, Szacht M, Morysinski T, Lugowska I, Dziewirski W, Falkowski S, et al. Preoperative hypofractionated radiotherapy in the treatment of localized soft tissue sarcomas. Eur J Surg Oncol. 2014;40(12):1641-7. Epub 20140920. doi: 10.1016/j.ejso.2014.05.016. PubMed PMID: 25282099.

24. Bedi M, Singh R, Charlson JA, Kelly T, Johnstone C, Wooldridge A, et al. Is 5 the New 25? Long-Term Oncologic Outcomes From a Phase II, Prospective, 5-Fraction Preoperative Radiation Therapy Trial in Patients With Localized Soft Tissue Sarcoma. Adv Radiat Oncol. 2022;7(3):100850. Epub 20220125. doi: 10.1016/j.adro.2021.100850. PubMed PMID: 35647402; PubMed Central PMCID: PMC9133395.

25. Spalek MJ, Rutkowski P. Coronavirus Disease (COVID-19) Outbreak: Hypofractionated Radiotherapy in Soft Tissue Sarcomas as a Valuable Option in the Environment of Limited Medical Resources and Demands for Increased Protection of Patients. Front Oncol. 2020;10:993. Epub 20200605. doi: 10.3389/fonc.2020.00993. PubMed PMID: 32582558; PubMed Central PMCID: PMC7292147.

26. Kubicek GJ, LaCouture T, Kaden M, Kim TW, Lerman N, Khrizman P, et al. Preoperative Radiosurgery for Soft Tissue Sarcoma. Am J Clin Oncol. 2018;41(1):86-9. doi: 10.1097/COC.0000000000000236. PubMed PMID: 26535989.

27. Temple WJ, Temple CL, Arthur K, Schachar NS, Paterson AH, Crabtree TS. Prospective cohort study of neoadjuvant treatment in conservative surgery of soft tissue sarcomas. Ann Surg Oncol. 1997;4(7):586-90. doi: 10.1007/BF02305541. PubMed PMID: 9367026.

28. Meyer JM, Perlewitz KS, Hayden JB, Doung YC, Hung AY, Vetto JT, et al. Phase I trial of preoperative chemoradiation plus sorafenib for high-risk extremity soft tissue sarcomas with dynamic contrast-enhanced MRI correlates. Clin Cancer Res. 2013;19(24):6902-11. Epub 20131016. doi: 10.1158/1078-0432.CCR-13-1594. PubMed PMID: 24132922; PubMed Central PMCID: PMC3869565.

29. Pennington JD, Eilber FC, Eilber FR, Singh AS, Reed JP, Chmielowski B, et al. Long-term Outcomes With Ifosfamide-based Hypofractionated Preoperative Chemoradiotherapy for Extremity Soft Tissue Sarcomas. Am J Clin Oncol. 2018;41(12):1154-61. doi: 10.1097/coc.0000000000000443. PubMed PMID: 29664796.

30. Kosela-Paterczyk H, Spalek M, Borkowska A, Teterycz P, Wagrodzki M, Szumera-Cieckiewicz A, et al. Hypofractionated Radiotherapy in Locally Advanced Myxoid Liposarcomas of Extremities or Trunk Wall: Results of a Single-Arm Prospective Clinical Trial. J Clin Med. 2020;9(8). Epub 20200801. doi: 10.3390/jcm9082471. PubMed PMID: 32752185; PubMed Central PMCID: PMC7464815.

31. Yamamura S, Kawakami K, Hirata H, Ueno K, Saini S, Majid S, et al. Oncogenic functions of secreted Frizzled-related protein 2 in human renal cancer. Mol Cancer Ther. 2010;9(6):1680-7. Epub 20100525. doi: 10.1158/1535-7163.MCT-10-0012. PubMed PMID: 20501806.

32. Courtwright A, Siamakpour-Reihani S, Arbiser JL, Banet N, Hilliard E, Fried L, et al. Secreted frizzle-related protein 2 stimulates angiogenesis via a calcineurin/NFAT signaling pathway. Cancer Res. 2009;69(11):4621-8. Epub 20090519. doi: 10.1158/0008-5472.CAN-08-3402. PubMed PMID: 19458075; PubMed Central PMCID: PMC2699405.

33. Mancini M, Toker A. NFAT proteins: emerging roles in cancer progression. Nat Rev Cancer. 2009;9(11):810-20. doi: 10.1038/nrc2735. PubMed PMID: 19851316; PubMed Central PMCID: PMC2866640.

34. Singh S, Vinson C, Gurley CM, Nolen GT, Beggs ML, Nagarajan R, et al. Impaired Wnt signaling in embryonal rhabdomyosarcoma cells from p53/c-fos double mutant mice. Am J Pathol. 2010;177(4):2055-66. Epub 20100909. doi: 10.2353/ajpath.2010.091195. PubMed PMID: 20829439; PubMed Central PMCID: PMC2947299.

35. Macian F. NFAT proteins: key regulators of T-cell development and function. Nat Rev Immunol. 2005;5(6):472-84. doi: 10.1038/nri1632. PubMed PMID: 15928679.

36. Chen L, Diao L, Yang Y, Yi X, Rodriguez BL, Li Y, et al. CD38-Mediated Immunosuppression as a Mechanism of Tumor Cell Escape from PD-1/PD-L1 Blockade. Cancer Discov. 2018;8(9):1156-75. Epub 20180716. doi: 10.1158/2159-8290.CD-17-1033. PubMed PMID: 30012853; PubMed Central PMCID: PMC6205194.

37. Nasarre P, Garcia DI, Siegel JB, Bonilla IV, Mukherjee R, Hilliard E, et al. Overcoming PD-1 Inhibitor Resistance with a Monoclonal Antibody to Secreted Frizzled-Related Protein 2 in Metastatic Osteosarcoma. Cancers (Basel). 2021;13(11). Epub 20210530. doi: 10.3390/cancers13112696. PubMed PMID: 34070758; PubMed Central PMCID: PMC8199140.

38. Fontenot E, Rossi E, Mumper R, Snyder S, Siamakpour-Reihani S, Ma P, et al. A novel monoclonal antibody to secreted frizzled-related protein 2 inhibits tumor growth. Mol Cancer Ther. 2013;12(5):685-95. Epub 20130419. doi: 10.1158/1535-7163.MCT-12-1066. PubMed PMID: 23604067; PubMed Central PMCID: PMC3780986.

39. Tanaka M, Homme M, Yamazaki Y, Shimizu R, Takazawa Y, Nakamura T. Modeling Alveolar Soft Part Sarcoma Unveils Novel Mechanisms of Metastasis. Cancer Res. 2017;77(4):897-907. Epub 20161215. doi: 10.1158/0008-5472.CAN-16-2486. PubMed PMID: 27979841.

40. Garcia D, Nasarre P, Bonilla IV, Hilliard E, Peterson YK, Spruill L, et al. Development of a Novel Humanized Monoclonal Antibody to Secreted Frizzled-Related Protein-2 That Inhibits Triple-Negative Breast Cancer and Angiosarcoma Growth In Vivo. Ann Surg Oncol. 2019;26(13):4782-90. Epub 20190912. doi: 10.1245/s10434-019-07800-2. PubMed PMID: 31515721; PubMed Central PMCID: PMC8261905.

41. Huang C, Ye Z, Wan J, Liang J, Liu M, Xu X, et al. Secreted Frizzled-Related Protein 2 Is Associated with Disease Progression and Poor Prognosis in Breast Cancer. Dis Markers. 2019;2019:6149381. Epub 20190303. doi: 10.1155/2019/6149381. PubMed PMID: 30944668; PubMed Central PMCID: PMC6421737.

42. Rao SR, Lazarides AL, Leckey BL, Lane WO, Visgauss JD, Somarelli JA, et al. Extent of tumor fibrosis/hyalinization and infarction following neoadjuvant radiation therapy is associated with improved survival in patients with soft-tissue sarcoma. Cancer Med. 2022;11(1):194-206. Epub 20211127. doi: 10.1002/cam4.4428. PubMed PMID: 34837341; PubMed Central PMCID: PMC8704179.

43. Thames HD, Jr. Effect-independent measures of tissue responses to fractionated irradiation. Int J Radiat Biol Relat Stud Phys Chem Med. 1984;45(1):1-10. doi: 10.1080/09553008414550011. PubMed PMID: 6607228.

44. Meattini I, Marrazzo L, Saieva C, Desideri I, Scotti V, Simontacchi G, et al. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. J Clin Oncol. 2020;38(35):4175-83. Epub 20200824. doi: 10.1200/JCO.20.00650. PubMed PMID: 32840419.

45. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol. 2002;20(3):817-25. doi: 10.1200/JCO.2002.20.3.817. PubMed PMID: 11821466.

46. Dickie CI, Parent AL, Griffin AM, Fung S, Chung PW, Catton CN, et al. Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: relationship to irradiated bone length, volume, tumor location and dose. Int J Radiat Oncol Biol Phys. 2009;75(4):1119-24. Epub 20090411. doi: 10.1016/j.ijrobp.2008.12.006. PubMed PMID: 19362782.

47. Wang D, Zhang Q, Eisenberg BL, Kane JM, Li XA, Lucas D, et al. Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. J Clin Oncol. 2015;33(20):2231-8. Epub 20150209. doi: 10.1200/jco.2014.58.5828. PubMed PMID: 25667281; PubMed Central PMCID: PMC4486342.

48. Slump J, Bastiaannet E, Halka A, Hoekstra HJ, Ferguson PC, Wunder JS, et al. Risk factors for postoperative wound complications after extremity soft tissue sarcoma resection: A systematic review and meta-analyses. J Plast Reconstr Aesthet Surg. 2019;72(9):1449-64. Epub 20190523. doi: 10.1016/j.bjps.2019.05.041. PubMed PMID: 31302071.

49. Berrington de Gonzalez A, Curtis RE, Kry SF, Gilbert E, Lamart S, Berg CD, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol. 2011;12(4):353-60. doi: 10.1016/S1470-2045(11)70061-4. PubMed PMID: 21454129; PubMed Central PMCID: PMC3086738.

50. Davis AM, O'Sullivan B, Turcotte R, Bell R, Catton C, Chabot P, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol. 2005;75(1):48-53. doi: 10.1016/j.radonc.2004.12.020. PubMed PMID: 15948265.

51. O'Sullivan B, Griffin AM, Dickie CI, Sharpe MB, Chung PW, Catton CN, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. Cancer. 2013;119(10):1878-84. Epub 20130219. doi: 10.1002/cncr.27951. PubMed PMID: 23423841.

52. Shah C, Ward MC, Tendulkar RD, Cherian S, Vicini F, Singer ME. Cost and Cost-Effectiveness of Image Guided Partial Breast Irradiation in Comparison to Hypofractionated Whole Breast Irradiation. Int J Radiat Oncol Biol Phys. 2019;103(2):397-402. Epub 20180922. doi: 10.1016/j.ijrobp.2018.09.021. PubMed PMID: 30253236.

53. Venigalla S, Carmona R, VanderWalde N, Sebro R, Sharma S, Simone CB, 2nd, et al. Disparities in Perioperative Radiation Therapy Use in Elderly Patients With Soft-Tissue Sarcoma. Int J Radiat Oncol Biol Phys. 2018;102(1):155-65. Epub 20180514. doi: 10.1016/j.ijrobp.2018.05.019. PubMed PMID: 29958721.

54. Network NCC. Soft Tissue Sarcoma (Version: 2.2022) [August 24, 2022]. Available from: *https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf*.

55. U.S. Department of Health and Human Services NIoHaNCI. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 2017 [updated November 27, 2017]. Available from: *https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf*.

56. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6. doi: 10.1016/0360-3016(95)00060-C. PubMed PMID: 7713792.

57. Stern T. Clinical Examination: A Textbook for Physical Diagnosis Chicago, IL: Year Book Medical 1964.