

NRG ONCOLOGY

RTOG 0630

A PHASE II TRIAL OF IMAGE GUIDED PREOPERATIVE RADIOTHERAPY FOR PRIMARY SOFT TISSUE SARCOMAS OF THE EXTREMITY

Study Chairs (4/3/14)

Principal Investigator/Radiation Oncology

Dian Wang, MD, PhD
Rush Univ. Medical Center
500 S. Paulina St., Atrium Bldg., Ground Flr.
Chicago, IL 60612
312-942-5751/FAX 313-942-2894
Dian_Wang@rush.edu

Radiation Oncology Co-Chair

David G. Kirsch, MD, PhD
Duke University Medical Center, 00568 Sub-basement,
Duke South, White Zone Box 3085 DUMC
Durham, NC 27710
919-668-7339/FAX 919-668-7345
david.kirsch@duke.edu

Medical Oncology Co-Chair

Scott H. Okuno, MD
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
507-284-4849/FAX 507-284-1803
okuno.scott@mayo.edu

Surgical Oncology Co-Chair

Burton L. Eisenberg, MD
Hoag Memorial Hospital Presbyterian
One Hoag Dr., P.O. Box 6100
Newport Beach, CA 92663
949-764-6124/FAX 949-764-8102
Burton.eisenberg@hoag.org

Surgical Oncology Co-Chair

John M. Kane III, MD
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263
716-845-3284/FAX 716-845-2320
John.Kane@roswellpark.org

Medical Physics Co-Chair

X. Allen Li, PhD
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53226
414-805-4362/FAX 414-805-4369
ali@radonc.mcw.edu

Pathology Co-Chair

David Lucas, MD
University of Michigan
2G332 UH
Ann Arbor, MI 48109
734-936-1888/FAX 734-763-0495
drlucas@med.umich.edu

Translational Research Co-Chair

William Kraybill, MD
The Ohio State University
410 W. 10th Avenue/N924 Doan Hall
Columbus, OH 43210
614-293-0968/FAX 614-293-3465
William.Kraybill@osumc.edu

Study Chairs continued on next page

Study Chairs (Continued)

Quality of Life Co-Chair

Margaret Chamberlain Wilmoth, MSS, RN, PhD
UNC Charlotte/College of Health & Human Services
9201 University City Blvd.
Charlotte, NC 29223
704-687-7949/FAX 704-687-6017
mcwilmot@uncc.edu

Senior Statistician

Qiang Zhang, PhD
Radiation Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19103
215-574-3197/FAX 215-928-0153
ezhang@acr-arrs.org

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RTOG Headquarters/Department of Statistics
215-574-3189
1-800-227-5463, ext. 4189

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INDEX (10/2/08)

Schema

Eligibility Checklist

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluations/Management
- 5.0 Registration Procedures
- 6.0 Radiation Therapy
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Other Therapy
- 10.0 Tissue/Specimen Submission
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent Form
- Appendix II - Study Parameters
- Appendix III - Performance Status Scoring
- Appendix IV - Staging System
- Appendix V - Fresh Frozen Tissue Kit and
RNA/ater™ Preserved Tissue Kit and Instructions
- Appendix VI - Specimen Plug Kit and Instructions
- Appendix VII - Blood Kit and Instructions
- Appendix VIII - Urine Kit and Instructions

NRG ONCOLOGY

RTOG 0630

A Phase II Trial of Image Guided Preoperative Radiotherapy
for Primary Soft Tissue Sarcomas of the Extremity

SCHEMA

	Preoperative IGRT (3D-CRT or IMRT)		Postoperative Radiotherapy Boost For patients with positive margins
		All patients:	External beam RT
R	Cohort A (Closed 1/8/10)		2 weeks post-surgery
E	Patients receiving neoadjuvant or adjuvant	Surgery	16 Gy in 8 daily fractions
G	chemotherapy or both = 50 Gy in 25 daily fractions	4-8 weeks	OR
I	OR	after	<u>Brachytherapy</u>
S	Patients receiving concurrent or interdigitated	completion of	5 days post-surgery
T	chemotherapy = 44 Gy in 22 daily fractions	preoperative	LDR = 16 Gy at ≤ 80 cGy per hour
E		RT (and chemo	OR
R	<u>Cohort B</u>	if given)	HDR = 3.4 Gy/fraction in 4 fractions
	Patients not receiving chemotherapy =		with at least 6 hours between fractions
	50 Gy in 25 daily fractions		OR
			<u>Intraoperative RT</u>
			10-12.5 Gy in a single fraction

Note: In order to be eligible to enroll patients onto this trial, the center must be certified for Sarcoma image-guided radiotherapy (IGRT) as well as one of the following: 3D-CRT and/or IMRT. See Section 5.0 for pre-registration requirements. It is mandatory that the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.

See Section 6.0 for details of Radiation Therapy.

Patient Population: (See Section 3.0 for Eligibility)

Histologically confirmed primary soft tissue sarcoma of the extremity; extraskeletal myxoid chondrosarcoma is eligible; sarcomas of the hand or foot are ineligible.

(1/8/10) Required Sample Size: 83 for Cohort B

RTOG Institution # _____

RTOG 0630

ELIGIBILITY CHECKLIST (3/25/08, 1/8/10)

Case # _____

(page 1 of 3)

- _____(Y) 1. Is the primary tumor histologically proven soft tissue sarcoma of the upper extremity (including shoulder) or lower extremity (including hip)?
- _____(N) 2. Is the primary tumor a sarcoma of the head, neck, intra-abdominal or retroperitoneal region or body wall, hand or feet, or a sarcoma \geq 32 cm in any direction?
- _____(Y/N) 3. Was an incisional biopsy done 8 weeks prior to registration?
- _____(Y) If no, were core biopsies done?
- _____(N) 4. Does the patient have distant metastases, based on the required diagnostic workup specified in Section 3.1?
- _____(Y) 5. Were the required history/physical and diagnostic imaging completed within 8 weeks prior to registration, as specified in Section 3.1?
- _____(Y/N) 6. Was the patient evaluated by a surgeon within 8 weeks prior to registration?
- _____(Y) If yes, did the patient meet the listed requirements in Section 3.1?
- _____(Y) 7. Is the Zubrod Performance Status 0-1?
- _____(Y) 8. Is the patient \geq 18 years of age?
- _____(Y/NA) 9. Was the required CBC/differential done within 2 weeks prior to registration on study ?
- _____(Y) If yes, were results within required protocol parameters specified in Section 3.1?
- _____(Y/NA) 10. For women of childbearing potential: Was a serum pregnancy test completed within 2 weeks of registration?
- _____(Y) If yes, was the serum pregnancy test negative?
- _____(Y/N/NA) 11. For women of childbearing potential: Will pelvic radiation be given?
- _____(Y) If yes, was the serum pregnancy test done within 48 hours prior to registration?
- _____(Y) If yes, was the serum pregnancy test negative?
- _____(Y/NA) 12. For male participants or women of child bearing potential: Did the patient agree to practice adequate contraception?
- _____(Y) 13. Did the patient sign a study specific informed consent prior to study entry, which includes mandatory submission of tissue for pathology central review?
- _____(N) 14. Does the histopathology demonstrate rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor (PNET) soft tissue Ewing's sarcoma, osteosarcoma, Kaposi's sarcoma, angiosarcoma, aggressive fibromatosis (desmoid tumor), or dermatofibrosarcoma protuberans or chondrosarcoma?

(Continued on next page)

RTOG Institution # _____

RTOG 0630

ELIGIBILITY CHECKLIST (3/25/08, 1/8/10)

Case # _____

(page 2 of 3)

- _____(N) 15. Is there a lymph node or distant metastases?
- _____(N) 16. Is there a recurrent tumor following previous potentially curative therapy?
- _____(N) 17. Did the patient undergo an excisional biopsy in which $\geq 50\%$ of the tumor was removed?
- _____(Y/N) 18. Did the patient have a prior invasive malignancy (with the exception of non-melanomatous skin cancer)?
- _____(Y) If yes, has the patient been disease free for at least 3 years?
- _____(N) 19. Did the patient have previous irradiation to the region of the study cancer that would result in overlap in radiation fields for the current sarcoma?

The following questions will be asked at Study Registration:

IGRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the patient provided study-specific consent prior to study entry
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)

(Continued on the next page)

RTOG Institution # _____

RTOG 0630

ELIGIBILITY CHECKLIST (10/13/09, 1/8/10)

Case # _____

(page 3 of 3)

- _____ 14. Method of Payment
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date
- _____ 17. Registration/randomization date: This date will be populated automatically.
- _____ 18. Medical Oncologist
- _____ (Y/N) 19. Tissue kept for cancer research?
- _____ (Y/N) 20. Blood kept for cancer research?
- _____ (Y/N) 21. Urine kept for cancer research?
- _____ (Y/N) 22. Tissue kept for medical research?
- _____ (Y/N) 23. Blood kept for medical research?
- _____ (Y/N) 24. Urine kept for medical research?
- _____ (Y/N) 25. Allow contact for future research?
- _____ (Y/N) 26. Will IMRT be used?
- _____ (Y/N) 27. Did the patient agree to participate in the quality of life component?

_____ If no, please specify the reason from the following:

1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify _____

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Limb conserving surgery with or without adjuvant radiation therapy has become the standard of care for the treatment of soft tissue sarcomas (STS).¹⁻⁵ Adequate surgical resection has remained a cornerstone to the successful treatment of sarcomas.⁶⁻⁷ The goal of surgery is to obtain a tumor free margin; when this is not possible because of important adjacent structures, either preoperative or postoperative radiotherapy is often employed.

Although debate continues regarding the sequencing of radiotherapy and surgery, recent data has supported preoperative radiotherapy as one of the standard options in the management of STS of the extremities. The advantages of preoperative radiation include the delivery of a smaller radiation dose to a smaller target volume when compared with postoperative radiotherapy, which translates into fewer long-term treatment complications and better function of the extremity,⁸⁻⁹ as demonstrated by the NCIC CTG prospective randomized trial of preoperative versus postoperative radiotherapy.¹⁰ The latest report was recently updated at the 2004 annual meeting of the American Society of Clinical Oncology and was based on an analysis by these investigators in December of 2003 (O'Sullivan, et al.; oral presentation).

Other potential advantages of preoperative radiotherapy include facilitating surgical resection through tumor shrinking and reducing the risk of tumor cell seeding at the time of surgery.¹¹ The main concern of preoperative radiotherapy has been centered on the risk of increasing the rate of delayed wound healing.⁸ In the above mentioned NCICCTG study, the rate of wound complications increased from 17% to 35% with preoperative radiation therapy; however, these wound complications were limited to the lower extremity and were generally temporary and without significant, long-term effect on function.¹⁰ Instead, the Canadian trial showed that the more serious chronic side effects occurred in the cohort that underwent postoperative radiotherapy.¹²

A combination of conservative surgery and radiotherapy already has been shown to achieve excellent local control in sarcoma patients following margin negative surgery; however, late radiation morbidity, physical disability, and reduced quality life may result from treatment morbidity.¹²⁻¹⁷ In the recent Canadian phase III study, patients that received postoperative radiation therapy had increased rates of grade 2 or greater fibrosis (48% vs. 31.5%), increased edema (23% vs. 15.1%), and joint stiffness (23% vs. 17.8%).¹² These late effects correlated with significantly lower physical function. Although late effects were lower in the preoperative cohort, they were still substantial with a total of 64.4% (31.5% fibrosis, 15.1% lymphedema, and 17.8% joint stiffness) in the preoperative arm at 2 years following treatment. Field size was predictive of higher rates of late effects. Therefore, a further decrease of the field volume may translate into reduced late radiation toxicities in sarcoma treatment. Indeed, investigators in the United Kingdom have conducted a randomized trial to evaluate the impact of changes in the field and volume of postoperative radiotherapy on late toxicity and limb function. The UK study will provide important information about whether late radiation morbidity is further reduced without compromising tumor control using reduced field volume postoperative radiotherapy.

Recently, image-guided radiotherapy (IGRT) technologies such as image-guided intensity modulated radiotherapy (IG-IMRT) have emerged.¹⁸⁻²² IMRT is able to deliver a highly conformal dose to the gross disease planning target volume and high risk subclinical disease regions, while dose to surrounding critical structures such as the adjacent normal tissue, bone, testis, spinal cord, kidney and ovary is minimized. Recent studies have demonstrated the dosimetrical and technical advantages of IG-IMRT in terms of dose conformity to tumor and normal tissue volume reduction, which in turn may result in improvement of clinical outcomes, reduction of side effects and improved quality of life. In addition, daily pretreatment image and position adjustment prior to radiation treatment may prove to be another key factor to successful tumor radiotherapy.^{20,23} Therefore, IGRT technologies may benefit sarcoma treatment in the following ways: 1) Since the sarcoma patient often is not in a rigid immobilization device during radiotherapy, setup error can be significant in irradiating sarcomas of certain sites and 2) A large field size often is required for conventional radiotherapy of sarcoma.²⁴ It is conceivable that improved techniques of delivering radiotherapy (i.e., IGRT) that decrease tumor conformity and decrease radiation dose to critical normal tissues may further reduce late radiation toxicity.

1.2 Chemotherapy for Soft Tissue Sarcomas of the Extremity

The utility of chemotherapy (neoadjuvant or adjuvant or chemotherapy given during the course of radiotherapy) in the treatment of localized soft tissue sarcoma (STS) of the extremity remains controversial. Theoretically, treatment with drugs active against advanced or metastatic sarcoma, such as doxorubicin or ifosfamide, may eradicate micro-metastases and thus, increase the cure rate of surgery plus radiation alone. Indeed, patients with large, high-grade sarcomas (Grade 2 or 3 in a three-tier grading system or Grade 3 or 4 in a 4-tier grading system) are at significant risk of treatment failure and ultimately, death from metastatic disease.²⁵ For patients with high-grade sarcoma, the risk for distant metastatic disease increases with the size of the primary sarcoma. For example, Spiro, et al. reported a 34% risk of developing distant metastases in patients with lesions 5.1-10 cm, and the risk increases to 43% and 58% for 10.1-15-cm and 15.1-20-cm lesions, respectively.²⁶ Systemic chemotherapy is theoretically justified for high-grade deep large STS of extremity if it is able to eliminate micro-metastasis and prolong patients' survival.

1.2.1 Adjuvant Chemotherapy

A relatively large published literature is available on adjuvant chemotherapy of soft tissue sarcoma, including several randomized clinical trials. A meta-analysis using updated data on 1568 patients treated on 14 trials using doxorubicin-based adjuvant therapy was previously published.²⁷ Statistically significant benefits for local (6% at 10 years from 75% to 81%, $p=0.016$) and recurrence free survival (10% at 10 years from 45% to 55%, $p=0.0001$) were demonstrated for chemotherapy. A trend towards absolute overall survival benefit of 4% at 10 years (from 50% to 54%, $p=0.12$) was not statistically significant but did reach statistical significance upon subgroup analysis of extremity sarcoma ($p=0.029$, the hazard ratio was 0.8, equivalent to a 7% absolute benefit at 10 years). However, this meta-analysis has been criticized because of the potential dilution of possible chemotherapy benefit by the inclusion of patients with low-grade (5%) or unknown grade (28%) sarcoma, patients with tumors at sites other than the extremities, incorporation of non-active chemotherapy drugs into the treatment regimens, and possible underdosing of doxorubicin. Since the publication of the meta-analysis, 2 additional randomized trials using more modern dosing schedules have explored the benefit of doxorubicin- or ifosfamide-based chemotherapy.²⁸⁻³⁰ These trials demonstrate that chemotherapy improves 5-year survival rates compared to no therapy.

1.2.2 Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy may provide the same theoretical benefits as adjuvant chemotherapy in reducing the risk of distant relapse and death. Additional theoretical advantages associated with neoadjuvant chemotherapy would be to facilitate limb salvage surgery by decreasing tumor burden, to control micrometastasis without extensive delay from surgery or postoperative recovery, and to assess the degree of tumor necrosis at the time of surgery, which would be used as a tumor response indicator and/or prognostic factor. Recently Grobmyer, et al. compared patients with high-grade STS tumors ≥ 5 cm treated with local therapy only versus those given neoadjuvant chemotherapy in addition to local therapy.³¹ In the subset of patients with tumors ≥ 10 cm in maximal diameter, the 3-year recurrence-free survival was 0.62 (95% CI, 0.53 to 0.71) for patients not receiving neoadjuvant chemotherapy. In patients with tumors between 5 and 10 cm in maximal diameter, there was no difference in clinical outcomes.

1.2.3 Neoadjuvant Chemoradiotherapy

In combination with preoperative radiotherapy, neoadjuvant chemotherapy may sensitize radiation to improve local control in addition to the theoretical advantages mentioned above. Indeed, high tumor response rates with combined chemoradiotherapy have been reported.³²⁻³³

RTOG recently published its experience to evaluate the efficacy and toxicity of a chemoradiotherapy for patients with large (≥ 8 cm), high-grade extremity STS.³⁴ This regimen was previously piloted by investigators at the Massachusetts General Hospital (MGH).^{33,35} Briefly, patients received 3 cycles of preoperative chemotherapy consisting of mesna, adriamycin, ifosfamide, and dacarbazine (MAID) interdigitated with split-course radiotherapy followed by resection and 3 cycles of adjuvant chemotherapy with or without radiotherapy. The preoperative radiation dose was 44 Gy in 22 fractions. For patients with positive margins, 16 Gy in 8 fractions was delivered postoperatively. Sixty-six patients were enrolled, of whom 64 were analyzed. The estimated 3-year rate for local-regional failure was 17.6%, if amputation is considered a failure and 10.1%, if not. Estimated 3-year rates for disease-free, distant disease-

free and overall survival were 56.6%, 64.5% and 75.1%, respectively. Significant acute toxicities also were reported in patients receiving this treatment regimen. The importance of long-term follow up in assessing the benefit from this treatment regimen was shown in a recent presentation at the 2006 ASTRO.³⁶

Another established neoadjuvant chemoradiotherapy regimen was reported by investigators at the Mayo Clinic.³⁷ Briefly, patients with large, high-grade extremity STS received 2 monthly cycles of neoadjuvant chemotherapy consisting of ifosfamide, mitomycin, doxorubicin, and cisplatin (IMAP) plus granulocyte macrophage-colony-stimulating factor (GM-CSF). This was followed by 3 cycles of MAP concurrent with daily preoperative irradiation (45 Gy in 25 fractions) and then surgery. For patients with close/positive margins, an additional radiation boost was given to the tumor bed. Thirty-nine patients were recruited into this study. Kaplan-Meier curves indicate an estimated 5-year survival of approximately 80% and approximately 85% freedom from metastasis at 2 years. Rates of high-grade acute toxicities appear to be less than those reported for the interdigitated chemotherapy.³⁴ To improve upon chemoradiotherapy, slight modification of the chemotherapy was made, and the addition of inhalation GM-CSF was studied. The treatment was well tolerated, but the addition of inhalation GM-CSF did not improve further the results of chemoradiotherapy alone.³⁸

Overall, chemotherapy (neoadjuvant or adjuvant or concurrent/interdigitated chemotherapy) may result in some benefit in STS of extremity. This benefit is likely to be of limited degree, confined to the highest risk patients and requires a fully active chemotherapy regimen. Available evidence suggests that anthracycline plus ifosfamide regimens have a somewhat higher antitumor activity in soft tissue sarcoma.³⁹⁻⁴⁰ Currently doxorubicin-ifosfamide regimens are recommended for the extremity STS in the treatment guidelines of the National Comprehensive Cancer Network (www.nccn.com).

In this proposed study, doxorubicin-ifosfamide regimens are allowed for patients with deep, large (≥ 8 cm), high-grade sarcomas. Radiation dose will be reduced from 50 Gy to 44 Gy (12% reduction) when chemotherapy (concurrent/interdigitated) is given during the course of radiotherapy, based on the above reported experience.^{34, 36-38} The late radiation morbidities (subcutaneous fibrosis, lymphedema, and joint stiffness) in patients who receive the concurrent/interdigitated chemotherapy are anticipated to be similar to those who receive a standard dose of radiation and chemotherapy (neoadjuvant or adjuvant) because of this radiation dose reduction.

1.3 Biomarkers and Methodology

In this study we plan to perform immunohistochemistry of potential biological/prognostic markers as discussed Section 10.0 in pretreatment biopsy and repeat biopsies of cutaneous/subcutaneous tissues within the radiation field in order to find a marker or markers or gene expression pattern that correlates with or predicts late radiation morbidity. Also, we plan to perform immunohistochemistry of potential biological/prognostic markers in pretreatment tumor biopsy and tumor specimen from surgery after radiotherapy in order to find a marker or markers that correlate with or predict pattern of failure including in-field recurrence or outside-field recurrence or distant metastasis. Immunohistochemistry will be done using standard method and automated analyzer. Imaging analysis will be used for quantification. The data will be distributed as continuous variable, and cut points will be determined to correlate with clinical outcomes. In addition, we plan to perform Enzyme-linked immunosorbent assay (ELISA) of several potential biomarkers in blood and urine for the above purpose.⁴¹ Finally, cDNA microarrays may be further performed⁴² to help find gene expression profiling signature(s) that predict(s) for late radiation morbidity, pattern of failure, and poor quality of life especially if the studies discussed above do not provide any definitive evidence for the purpose of this study.

Comparisons of gene expression profiles will include 1) patients that do or do not develop grade 2 or greater late radiation morbidity; 2) patients without local failure versus those patients with in-field recurrence; 3) patients that do not develop distant metastasis versus those that do develop metastasis without local failure; and 4) patients that do or do not develop poor quality of life (patient's function and physical disability). Gene expression analysis will be focused on cell proliferation, apoptosis, cell cycle progression, collagen synthesis, DNA damage-repair, and genes related to fibrosis. Expression changes of the above potential biological

markers/predictive markers and their associated pathways also will be assessed in comparison with the findings from immunohistochemistry.

1.3.1 Biomarkers of Interest for Late Radiation Morbidity

Transforming growth factor beta (TGFβ): TGFβ is a peptide that has a fundamental role in controlling proliferation of many cell types. Its main effect upon connective tissues *in vivo* is to stimulate growth. It can result in endothelial cell proliferation but tends to inhibit epithelial cell growth. Damage to the connective tissues and the vasculature are the principal findings in late radiation damage.⁴³ Expression of TGFβ was found in relation to the pathological changes of late radiation damage in the non-tumor-bearing tissues in previously irradiated patients.⁴⁴ This suggests that TGFβ activity may modulate late post-radiation changes.

PINP: Collagen is synthesized by fibroblasts. Collagen is the main structural protein in skin, accounting for 70-80% of its dry weight. Type I collagen comprises 80-85% of skin collagen, and type III collagen comprises 10-15%. Previously, it has been shown that type I and type III collagen synthesis is increased in radiotherapy-related human skin at the levels of protein and mRNA.⁴⁵⁻⁴⁶ However, a correlative study between expression of collagen type I/type III and radiation-induced fibrosis has not been performed in a large number of patients with sarcoma. Immunohistochemistry of procollagen amino-terminal propeptides (PINP) is important in reflecting levels of collagen synthesis of type I and type III.

Tryptase, chymase, kit receptor: Mast cells in the skin dermis are very important in promoting fibrosis. Several lines of evidence suggest that mast cells increase fibroblast proliferation and collagen synthesis. Increased activities of mast cells were demonstrated in irradiated skin in patients with breast cancer.⁴⁷ In addition, mast cells have been shown to be involved in the pathogenesis of scleroderma and in wound healing.⁴⁸⁻⁴⁹ Tryptase and chymase are serine proteinases and are the most abundant proteins in mast cells. Previous studies have suggested that tryptase and chymase stimulate the proliferation of fibroblasts, induce collagen synthesis *in vitro* and induce collagen fibril formation *in vitro*.⁵⁰⁻⁵¹ Kit receptor on mast cells and its interaction with the stem cell factor is essential for growth, survival, and activation of mast cells.⁵²⁻⁵³ Significant alterations in the Kit receptor expression have been found in wound healing and chronic wounds.⁵⁴⁻⁵⁶ Recently, increased expression of tryptase, chymase and kit receptors have been reported in irradiated skin of the breast.⁴⁷

ATM, XRCC1 and XRCC3: ATM protein functions as a protein kinase involved in cellular stress responses, cell-cycle checkpoint control and DNA repair. The primary function of XRCC1 protein is to coordinate the activities of the enzymes that perform base excision repair of radiation-induced damage. Cells lacking a functional XRCC1 protein have demonstrated a hypersensitivity to radiation. XRCC3 is involved in the repair of radiation-induced DNA double strand breaks. Previous studies have shown activities of ATM, XRCC1, and XRCC3 influence risk of subcutaneous fibrosis after radiotherapy.⁵⁷⁻⁵⁹ A significant association was found between homozygote carries of the transversion G→A transition at ATM nucleotide 5557 and radiation induced fibrosis in patients with breast cancer.⁵⁷⁻⁶⁰ The Thr/Thr genotype in XRCC3 codon 241 and Arg/Arg genotype in XRCC1 codon 399 are associated with increased risk of radiation-induced subcutaneous fibrosis in patients receiving post-mastectomy radiotherapy.⁵⁹ However, the above hypothesis has not been examined in a prospective, well-defined clinical setting or in sarcoma patients.

1.3.2 Biomarkers of Interest for Patterns of Failure

Vascular endothelial growth factor (VEGF) is the most abundant and potent of the known pro-angiogenic factors. Whether secreted by the primary tumor or associated inflammatory cells, VEGF acts through 2 receptors (VEGFR-1 (Flt-1) and VEGFR-2 (KDR)). Given the high rate of hematogenous metastases in STS, several studies have examined the relationship between circulating VEGF levels and clinical factors. There are significant increases in circulating VEGF in the setting of STS, which also appear to correlate with tumor volume and sometimes grade.⁶⁰⁻⁶¹ In regard to tumor tissue expression of VEGF, the rate appears to vary in STS from 25-75%. Although some studies have shown high STS VEGF expression is associated with poor survival (especially leiomyosarcoma), others have shown no correlation with survival (especially synovial sarcoma). Due to the development of both the anti-VEGF monoclonal antibody bevacizumab (Avastin) and a VEGF receptor 2 small molecule inhibitor (SU5416), the role of VEGF in STS biology clearly warrants further investigation.

Basic fibroblast growth factor (bFGF) is another factor associated with tumor angiogenesis. Alternatively, some preclinical data in mice suggests that low levels of bFGF may protect against radiation induced bone marrow and gut injury. Similar to VEGF, circulating bFGF levels are elevated in the setting of STS and may be related to tumor volume.⁶²⁻⁶³ Paradoxically, low preoperative serum bFGF levels were associated with a higher risk of recurrence in one study.

Epidermal growth factor receptor (EGFR) is a member of the HER family. EGFR overexpression and activation by ligand correlates with radioresistance. Preclinical studies have demonstrated enhanced radiation- and chemotherapy-induced tumor cytotoxicity when EGFR antagonists are administered. In addition, there is cross-talk between the EGFR and angiogenesis pathways.⁶² Currently available EGFR targeted therapies include the monoclonal antibody cetuximab (Erbix®) and the EGFR tyrosine kinase inhibitor gefitinib (Iressa®). Therefore, the potential interaction between EGFR expression and response to radiation combined with several clinically available anti-EGFR therapies make it an interesting biomarker to evaluate in STS.

p53 is a tumor suppressor gene in which high levels of expression lead to cell cycle arrest (through p21/cdk2) or apoptosis. Inactivation of p53 may occur through point mutation or association with viral proteins or MDM2 (murine double minute type 2). When MDM2 binds to functional p53, p53 is inactivated and targeted for destruction. In normal cells, there is a balance between active p53 and MDM2 bound inactive p53. Therefore, MDM2 overexpression by tumor cells is an alternative mechanism for overcoming wild-type p53 function. While some studies have shown that p53 overexpression in STS correlates with a poor prognosis,⁶³ others studies have failed to support these findings. MDM2 overexpression has also been associated with high grade STS and poor outcome.⁶⁴

Survivin is an intracellular protein that is a member of the inhibitor of apoptosis protein (IAP) family. Survivin appears to prevent apoptosis by associating with and inhibiting the activation/activity of caspases in the apoptotic pathway. Independent of its caspase interaction, it also regulates mitotic activities such as microtubule formation and cytokinesis. Survivin is expressed during development but usually disappears from terminally differentiated tissues. However, survivin overexpression has been consistently identified in most human cancers. For STS, overexpression of either survivin mRNA or protein is inversely correlated with survival.⁶⁵ In addition, inhibition of survivin in human sarcoma cell lines with small inhibitory RNA was found to reduce survival (by a p53 independent mechanism) and also radiosensitize cells (by a p53 dependent mechanism).

The Fas receptor and its ligand (FasL) are a very important pathway for inducing apoptosis in immune cells such as lymphocytes. The immune privileged status of many sites in the body may be due to the ability of Fas/FasL to destroy invading inflammatory cells. FasL production by tumor cells has also been postulated as a mechanism to avoid immune detection/destruction. Previous studies have shown that approximately two-thirds of STS express FasL.⁶⁶ Alternatively, *in vitro* stimulation of STS cells with a Fas agonist antibody increased tumor cell sensitivity to adriamycin and other chemotherapeutic agents. Therefore, the extent of FasL production by STS may help to predict response to treatment and overall outcome.

1.4 Quality of Life

1.4.1 Background

Quality of life (QOL) is a global concept with a variety of meanings attributed to it based on personal beliefs. Health-related quality of life (HRQOL) is one attempt to narrow the perspective of this construct to allow for measurement of the impact of pathology and treatments on QOL. Components commonly accepted as part of HRQOL are physical well-being, social/family well-being, emotional well-being and functional well-being.⁶⁷ Sugarbaker, et al. in their classic study of QOL in sarcoma patients could be considered the 'grandfathers' of outcomes measurement in clinical trials.⁶⁸ This research also was one of the first to include an assessment of sexuality in sarcoma patients. In the ensuing years, the answers to these quality of life related questions remain elusive.

Recently, Davis and colleagues evaluated impact of late radiation morbidity on HRQOL in 194 patients with extremity sarcoma randomized to either preoperative (94) or postoperative (96)

radiotherapy.⁶⁹ The focus of their HRQOL inquiry was patient function and physical disability using the musculoskeletal tumor rating scale (MSTS) and the Toronto Extremity Salvage Score (TESS). Of the 129 patients available for analysis of late radiation morbidity symptoms and scores in the HRQOL inquiry, 52 patients were less than age 50; neither mean age nor range was reported. They reported no statistically significant difference in the scores of TESS and MSTS between preoperative versus postoperative radiotherapy (preop mean 85.1 versus postop mean 81.3; $p=0.17$ for TESS, and preop mean 29.9 versus postop mean 28.0; $p=0.08$ for MSTS, respectively). However, patients who had \geq grade 2 fibrosis, joint stiffness, and edema reported significantly physical disability as measured by the TESS (fibrosis 77.1 versus 87.0, $p=0.001$; joint stiffness 69.4 versus 86.4, $p=0.001$; edema 71.9 versus 85.0, $p=0.001$) and significantly greater impairment as measured by MSTS (fibrosis 27.7 versus 30.5, $p=0.002$; joint stiffness 24.2 versus 30.8, $p=0.001$; edema 21.9 versus 30.4, $p < 0.001$). With the above background in mind, we hypothesize that image-guided reduction in volume and field size of radiotherapy may result in reduction of late radiation morbidity and may further improve the patients' physical function and quality of life.

Other research suggested similar degrees of QOL in both limb salvage surgical (LSS) patients and those with an amputation for lower extremity sarcoma.⁷⁰ The difference was in how QOL was expressed: LSS patients described having a higher QOL in terms of physical performance status, and patients with limb amputations associated their QOL with their social acceptability. Still other research suggested that the degree of alteration in QOL is independent of whether it is limb amputation or limb salvage that occurs but dependent upon the level of the insult, e.g., greater change in QOL if above-the-knee amputation or LSS occurs versus below-the-knee amputation.⁷¹

It is apparent that the data are variable regarding the impact on the functional aspect of QOL in patients with soft tissue sarcoma (STS) treated by radiotherapy and surgery. The reported research did not report function stratified by age or gender nor were other aspects of QOL reported; neither was a holistic, validated measure of HRQOL used as one of the outcome measures. In this proposed study, we hypothesize the degree of late radiation morbidities will correlate positively not only with the MSTS⁷² and TESS,⁶⁹ but also with the functional well-being component of the Functional Assessment of Cancer Therapy – General (FACT-G).⁶⁷ We will begin with a correlation between the late radiation morbidities (primary endpoint) and the MSTS, TESS and the FACT-G in patients with extremity sarcoma treated with image-guided radiotherapy followed by limb salvage surgery (Cohort B) at 2 years from the start of sarcoma treatment. In addition, we will examine if the addition of chemotherapy to the radiation and surgery (Cohort A patients) will result in poor functional well-being scores on the FACT-G when compared with radiation and surgery (Cohort B) for patients with extremity sarcoma. We will further correlate the late radiation morbidities with the MSTS, TESS and the FACT-G in the patients with extremity sarcoma with the combination of chemoradiotherapy and surgery (Cohort A).

Diagnosis of the various types of STS to be included in this study can occur anywhere between the ages of 10-75 years; however, those eligible for this study will be over age 18 with the anticipated mean age to be in the mid-40's. The years 18-50 are prime years for marriage and reproduction; further, it is well known that chemotherapy causes either temporary or permanent menopause in women who are in their late 30's to 40's. There is a great deal of literature on the impact of chemotherapy in women with breast cancer whose physical disfigurement can be easily hidden by clothes, and there has been a similar degree of work in men diagnosed with prostate cancer. However, there continues to be a paucity of work investigating the impact of treatment of STS on the social/family well-being and emotional well-being aspects of HRQOL. These aspects of HRQOL include sexuality. Recent literature on re-integration into previous life activities has highlighted the continued lack of data on social discomfort, body-image anxieties, and sexuality in those with limb amputation.⁷³⁻⁷⁴

One report on STS patients and HRQOL looked at patients' perceptions of their ability to reintegrate into their life roles following treatment.⁷⁵ Clinicians completed the MSTS evaluating each patient, and patients completed the TESS, the Reintegration to Normal Living Index (RNL) and the EQ-VAS, a one-item visual analogue scale asking subjects to rate their QOL on a 0 to 100 scale. The RNL measures patient perceptions about their ability to reintegrate into

their lives. The study sample of 100 was one year-post treatment; the majority of patients were male, with a mean age of 55 years. The stepwise regression model, after adjustment for demographic and clinical variables, found that only restrictions from resuming previous life activities had a significant impact on HRQOL, explaining 63% of the variation. This study notwithstanding, questions remain unanswered concerning issues surrounding sexuality and aspects of the social/family well-being and emotional well-being components of HRQOL. For example, do the radiation and surgery (Cohort B) result in a great change in sexuality of patients with extremity sarcoma? When over the course of follow up do changes in sexuality become apparent? In which gender? At what age? Does the addition of chemotherapy to the radiation and surgery result in a greater change than radiation and surgery for patients with extremity sarcoma? Does the Sexual Adjustment Questionnaire (SAQ)⁷⁶ and items related to sexuality on the TESS correlate with the Social/Family and Emotional Well-being components of the FACT-G?

Thus, there remains a gap in the literature on the intimacy and related QOL issues in patients with STS and the effects of radiation therapy +/- chemotherapy with surgery on QOL. Most research in this area is limited to the alterations in physical mobility. There also is little information on the impact of STS and STS treatment on sexuality. Due to this gap in knowledge, the measurement of sexual function is a secondary objective of this study. There is a dearth of research in this area and few validated, free instruments available. The SAQ was validated in males and females,⁷⁶ and the revised scale has been validated by the RTOG in males.⁷⁷ The revisions were made to decrease patient burden while maintaining scales hypothesized to be most affected by cancer therapy. The RTOG-validated SAQ for males (SAQ-M) will be used in this study, and a newly revised SAQ for females (SAQ-F) will be used. The SAQ-F retains the same subscales as the SAQ-M. Patients will complete a baseline version of the SAQ-M and SAQ-F prior to treatment and then will complete a follow-up version of the SAQ-M and SAQ-F at 12, 18, and 24 months from the start of radiation treatment. Results will be correlated with items on sexuality on the TESS and FACT-G. It is hypothesized that patients receiving radiotherapy and surgery (Cohort B) will experience fewer alterations in sexuality than those in Cohort A, who will receive the combination of chemoradiotherapy and surgery.

1.4.2 Quality of Life Assessments

Quality of life will be measured from 3 perspectives: global quality of life using the Functional Assessment of Cancer Therapy-General form (FACT-G), physical disability from the patient's perspective using the Toronto Extremity Salvage Score (TESS), and looking specifically at the impact on sexuality of loss/alteration in a limb using the Sexual Adjustment Questionnaire (for Males and Females; SAQ-M and SAQ-F). If the patient consents to participate in the QOL portion of the study, the patient will complete 3 assessments, the FACT-G, the TESS, and the SAQ, at 4 time points: Prior to start of protocol treatment (baseline), and at 12, 18, and 24 months from the start of radiation treatment. Use of 3 measures of quality of life will provide answers to some of the unanswered questions highlighted above. Each of these measures has established psychometric properties, and they are widely used in cancer research.

1.5 Summary

We propose a phase II study to evaluate the effect of preoperative image-guided radiotherapy (IGRT) on the reduction of late radiation morbidity, patterns of failure, impact of late radiation morbidity on limb function and physical ability, quality of life (QOL) and sexuality. Correlative biomarker studies, including gene expression profiling, will be included in the study to identify a molecular signature that predicts for late radiation morbidity, poor QOL, local failure, and distant failure. It is important to note that this single arm phase II study is not intended to resolve the debate discussed above regarding the sequence of radiotherapy and surgery.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the effect of reduced radiation volume through IGRT on \geq Grade 2 lymphedema, subcutaneous fibrosis, and joint stiffness at 2 years from the start of radiation treatment

2.2 Secondary Objectives

2.2.1 To estimate rates of other CTCAE, v.3.0 grade 3-5 adverse events;

2.2.2 To determine the pattern of failure including local failure (in-field, marginal, and outside-field failure), regional failure, distant failure, and death without disease progression;

- 2.2.3 To estimate the rates of local failure, local-regional failure, distant failure, distant-disease-free survival, disease-free survival, overall survival, and second primary tumor;
 - 2.2.4 To estimate the rate of wound complications;
 - 2.2.5 To correlate the degree of late radiation morbidity (defined as any \geq grade 2 lymphedema, subcutaneous fibrosis, or joint stiffness) at 2 years with scores on the clinical measure, MSTS.
- 2.3 Tertiary Objectives** (Exploratory)
- 2.3.1 To correlate degree of later radiation morbidity at 2 years with the 3 quality of life assessments (FACT-G, TESS, and SAQ);
 - 2.3.2 To compare the TESS and the MSTS scores at 2 years between cohort B patients and the preoperative RT patients from the NCIC CTG study;
 - 2.3.3 To compare the SAQ scores at 2 years for Cohort A patients with Cohort B patients;
 - 2.3.4 To describe the trend over time with respect to 4 variables: late radiation morbidity, FACT-G, TESS, and SAQ;
 - 2.3.5 To collect sarcoma tumor samples, adjacent normal tissue, cutaneous/subcutaneous tissue, serum, plasma, buffy coat, and urine for correlative biomarker studies.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (1/8/10)

- 3.1.1 Histologically proven primary soft tissue sarcoma of the upper extremity (including shoulder) or lower extremity (including hip); extraskeletal myxoid chondrosarcoma is eligible. Sarcomas of the hand or foot are ineligible.
- 3.1.2 A biopsy must be done within 8 weeks prior to registration. If the patient refuses an incisional biopsy, core biopsies are required for histological diagnosis (see Sections 8.1 and 10.1);
- 3.1.3 No distant metastases, based upon the following minimum diagnostic workup:
 - 3.1.3.1 History/physical examination including a detailed description of the location, size, and stage (see Appendix IV) of the sarcoma within 8 weeks prior to registration;
 - 3.1.3.2 MRI with contrast of the primary within 8 weeks prior to registration; the maximal dimension of the primary tumor will be measured in MRI images. See Section 6.6 for preferred MRI specifics (a pretreatment MRI with T1 weighting and gadolinium contrast and T2 weighting is mandatory);
 - 3.1.3.3 CT scan of the chest within 8 weeks prior to registration;
 - 3.1.3.4 For intermediate-to-high grade sarcomas (histology grade 3 or 4, AJCC, 6th ed., Appendix IV) of the upper thigh, a CT scan with contrast of the abdomen and pelvis to rule out metastases within 8 weeks prior to registration;
- 3.1.4 Evaluation by a surgeon who specializes in soft tissue sarcoma within 8 weeks prior to registration; the patient's tumor must be surgically resectable, and the surgeon must feel that limb preservation surgery alone would not provide adequate local control.
- 3.1.5 Zubrod Performance Status 0-1;
- 3.1.6 Age \geq 18;
- 3.1.7 For females of childbearing potential, a serum pregnancy test within 2 weeks prior to registration; **note:** if pelvic irradiation is to be given, the serum pregnancy test must be done within 48 hours prior to registration.
- 3.1.8 Women of childbearing potential and male participants must practice adequate contraception.
- 3.1.9 Patients must provide study-specific informed consent prior to study entry, which includes mandatory submission of tissue for pathology central review.
- 3.1.10 CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:
 - 3.1.10.1 Absolute neutrophil count (ANC) \geq 1,500 cells/mm³;
 - 3.1.10.2 Platelets \geq 100,000 cells/mm³;
 - 3.1.10.3 Hemoglobin \geq 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb \geq 8.0 g/dl is acceptable.)

3.2 Conditions for Patient Ineligibility (1/8/10)

- 3.2.1 Patients with sarcomas of the head, neck, intra-abdominal or retroperitoneal region or body wall, hand or feet or with a sarcoma \geq 32 cm in any direction are ineligible;
- 3.2.2 Histopathology demonstrating rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor (PNET) soft tissue Ewing's sarcoma, osteosarcoma, Kaposi's sarcoma, angiosarcoma, aggressive fibromatosis (desmoid tumor), or dermatofibrosarcoma protuberans or chondrosarcoma;

- 3.2.3 No lymph node or distant metastases; **note:** multiple pulmonary nodules < 8 mm without a histological diagnosis detected incidentally in a non-screening CT scan may not be a basis for study exclusion because of the sensitivity/specificity of the CT scans of chest/abdomen/pelvis. MacMahon's guidelines are referenced⁷⁸ for treating physicians' use in determining eligibility of patients with low-risk factors.
- 3.2.4 Recurrent tumor following previous potentially curative therapy;
- 3.2.5 Patients that undergo excisional biopsy in which the majority of the tumor (≥ 50%) is removed are not eligible.
- 3.2.6 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (e.g., carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible);
- 3.2.7 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields for current sarcoma;
- 3.2.8 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

- 4.1.1 (4/20/09) Representative histology slides for central review must be collected from both the pre-treatment diagnostic biopsy (see Section 3.1.2) and from the post-radiation surgery and submitted (see Sections 8.2 and 10.1);
- 4.1.2 A thyroid function test must be done prior to start of radiation if the thyroid gland is inside the radiation field.
- 4.1.3 The physician (an orthopedic surgeon or surgical oncologist is preferred) or the physician's designated staff must complete the Musculoskeletal Tumor Rating Scale (MSTS) prior to start of protocol treatment (see Section 12.1).
- 4.1.4 If the patient consents to participate in the quality of life component of the study, sites are required to administer baseline quality of life questionnaires prior to the start of protocol treatment: The Functional Assessment of Cancer Therapy-General (FACT-G); The Toronto Extremity Salvage Score (TESS); and The Sexual Adjustment Questionnaire (SAQ) (see Section 12.1).

5.0 REGISTRATION PROCEDURES

IGRT IS MANDATORY FOR THIS STUDY.

In order to be eligible to enroll patients onto this trial, the center must be credentialed both for 3D-CRT and/or IMRT and for Sarcoma image-guided radiotherapy (IGRT). **NOTE:** It is mandatory for the treating physician to determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.

5.1 Preregistration Requirements for Image-Guided Radiotherapy (IGRT) Treatment Approach

- 5.1.1 In order to utilize IGRT, the center must be credentialed for its use. This means the institution must have met technology requirements and have provided the baseline physics information (Part II of the Facility Questionnaire; see Section 5.1.2). This information is available on the Advanced Technology Consortium (ATC) web site, <http://atc.wustl.edu>. The ATC is in part comprised of RTOG RT Quality Assurance, the Image-Guided Therapy Center (ITC) at Washington University, and the Radiological Physics Center (RPC) at MD Anderson Cancer Center.

In order to become credentialed for IGRT, the institution must have already become credentialed for either 3D-CRT and/or IMRT. Institutions that have not been credentialed by the RTOG to perform 3D-CRT and/or IMRT MUST apply for 3D-CRT and/or IMRT credentialing as described below in Sections 5.2 and 5.3.

5.1.2 IGRT Credentialing Process (4/20/09)

- 5.1.2.1 This is the first Sarcoma daily IGRT study and thus, each institution will be required to undergo credentialing for Sarcoma IGRT (review of at least one case from each institution).

The first step is for the institution or investigator to complete a new Facility Questionnaire and/or set up an SFTP account for digital data submission. Both of these requirements can be completed using information on the ATC web site at <http://atc.wustl.edu>.

5.1.2.2 Next, the institution must submit a series of daily treatment images along with a spreadsheet of IGRT data from an anonymized patient with either extremity Sarcoma or other extremity disease. See the ATC web site, <http://atc.wustl.edu>, for the spreadsheet. This series must include a minimum of 5 daily pretreatment images and a minimum of 2 of the 5 must have post-shift images. Pretreatment images may include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (KV) x-ray or Orthogonal (MV or KV) 2D electronic images. These images and the spreadsheet will be reviewed by the Medical Physics Co-chair, Dr. Li prior to credentialing. Upon approval of the images and spreadsheet by Dr. Li, RTOG Headquarters will notify the institution that the institution is credentialed.

5.1.2.3 Tolerance Levels for IGRT

For those institutions that plan to use one of the above pretreatment 3D volumetric images for target localization and position adjustment if needed, a three-dimensional view of bony structures adjacent to gross tumor planning target volume (PTV) is recommended as a standard for position adjustment. Three-dimensional views of gross tumor and other adjacent normal tissue structures are recommended as reference at the discretion of the treating radiation oncologist. After shifts based on pretreatment images, an error of ≤ 3 mm is acceptable. After shifts based on pretreatment images, an error of > 3 mm but ≤ 5 mm is considered as minor variation, while an error of > 5 mm is considered a major variation (unacceptable).

For those institutions that plan to use orthogonal images for target localization and position adjustment if needed, placement of fiducial markers such as seeds (typically 3 or more) in or outside the gross tumor is strongly recommended (not required). Fiducial markers are often placed under the guidance of ultrasound or CT scan. An orthogonal view of fiducial markers and/or bony anatomy adjacent to the gross tumor planning target volume (PTV) is recommended as a standard for position adjustment. After shifts based on pretreatment images, an error of ≤ 3 mm is acceptable. After shifts based on pretreatment images, an error of > 3 mm but ≤ 5 mm is considered as minor variation, while an error of > 5 mm is considered a major variation (unacceptable).

5.2 Pre-Registration Requirements for Institutions Intending to Use the IMRT Treatment Approach for Some Patients (4/20/09)

In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit <http://rpc.mdanderson.org/rpc> and select "Credentialing" and "Credentialing Status Inquiry".

5.2.1 An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement. Instructions for requesting and irradiating the phantom are available on the RPC web site at <http://rpc.mdanderson.org/rpc/>; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.2.2 The institution or investigator must complete a new IMRT facility questionnaire and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at <http://atc.wustl.edu>. Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study using either 3DCRT or IMRT.

5.3 Pre-Registration Requirements for 3D-CRT Treatment Approach

5.3.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients to this study.

5.3.2 The new facility questionnaire (one per institution, available on the ATC web site at <http://atc.wustl.edu>) is sent to RTOG for review prior to entering any cases. Upon review and

successful completion of a “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3DCRT trials of this same disease site may enroll patients on this study without further credentialing.

5.4 Regulatory Pre-Registration Requirements (9/26/08, 4/20/09,10/13/09)

5.4.1 U.S. and Canadian institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution’s first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language version)
*Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

5.4.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

5.4.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.4.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.4.3.1 For institutions that do not have an approved LOI for this protocol:

International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.4.3.2 For institutions that have an approved LOI for this protocol:

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.5 Registration

5.5.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (<http://www.rtog.org>), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

(10/13/09) Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrs.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (1/8/10) **IGRT IS MANDATORY FOR THIS STUDY.**

Protocol treatment must begin within 7-10 calendar days from date of registration.

6.1 Dose Specifications (1/8/10)

6.1.1 Preoperative IGRT (3D-CRT or IMRT) [4/20/09]

Either 3D conformal radiotherapy or intensity modulated radiation therapy may be utilized as long as the dose volume histogram (DVH) constraints for critical normal structures meet the criteria defined in Section 6.4.

A prescription dose of 50 Gy in 25 daily fractions will be prescribed to cover 95% of the PTV. More than 99% of the PTV should receive > 97% of the prescribed dose. No more than 20% of the PTV will receive \geq 110% prescription dose.

6.1.2 Postoperative Radiotherapy Boost (External Beam or Brachytherapy or Intraoperative Radiotherapy)

Postoperative radiation will be given to the positive tumor margin (residual tumor) only plus a margin of 1 cm within 2 weeks following surgery or after adequate wound healing has occurred. The patient can receive postoperative external beam, brachytherapy (low-dose-rate or high-dose-rate), or intraoperative radiation therapy as a boost to the residual tumor bed (positive margin). Metallic clips or gold seeds are recommended to be placed during surgery to aid in defining the residual tumor bed for a positive margin. The target volume for postoperative radiotherapy will be the residual tumor bed as defined by the surgical and pathological findings.

6.1.2.1 External Beam Radiotherapy

Postoperative external beam boost dose is 16 Gy in 8 fractions (once a day). Postoperative external beam radiotherapy boost will begin 2 weeks following resection, if the healing of the surgical wound is satisfactory at the discretion of surgeon. Bolus should be avoided unless positive margins occur in cutaneous or subcutaneous tissues. Because preoperative radiation therapy has been delivered, it is not necessary to include the entire surgical bed, drain sites, and wound. Unless brachytherapy or intraoperative RT is to be used, postoperative RT should be consistent with the technique used for the patient's preoperative RT, i.e., if image-guided 3D-CRT was used for preoperative RT, it should be used for postoperative RT; if image-guided IMRT was used for preoperative RT, it should be used for postoperative RT. The boost can be started more than 2 weeks following surgery if wound healing requires. The reasons for a delay in boost treatment should be documented and reported.

6.1.2.2 Brachytherapy

Either low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy as a boost to the positive tumor margin is acceptable as an alternative to external beam radiotherapy. Brachytherapy should not start until day 5 after the surgery (day 0) and must be completed within 2 weeks following surgery. Typically, brachytherapy catheters are placed at an interval of 0.5 -1.0 cm on the residual tumor bed (positive margin) plus a margin of 1 cm during surgery. Skin surface dose should be kept below 50% of the prescription dose unless positive margins occur in cutaneous or subcutaneous tissues. It is not necessary to include the entire surgical bed, drain sites and wound. For LDR brachytherapy, the dose is 16 Gy at no more than 80 cGy per hour. For HDR brachytherapy, 4 fractions of 3.4 Gy are delivered in a b.i.d. fashion, with an interval of at least 6 hours between fractions.

6.1.2.3 Intraoperative Radiotherapy Boost

For those institutions that deliver intraoperative radiation therapy (electron therapy or high-dose-rate interstitial brachytherapy), the dose is 10 to 12.5 Gy in a single fraction to a margin that is microscopically positive at the time of resection. **Note:** A frozen section diagnosis of positive margin must be obtained prior to intraoperative radiotherapy. Typically the dose is prescribed to 1 cm depth or 90% isodose line. However, prescription depth or isodose line coverage should be decided at the discretion of the treating radiation oncologist based on the consideration of boost target volume, surgical/pathological findings, and adjacent normal tissue structure tolerance.

6.2 Technical Factors

6.2.1 Megavoltage photon beams produced by linear accelerators, betatrons, or microtrons with energies of ≥ 4 MV are permitted.

6.2.2 Image Guidance Devices

FOR ALL QUESTIONS REGARDING IGRT TECHNOLOGY CONTACT THE MEDICAL PHYSICS CO-CHAIR, DR. ALLEN LI.

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

- Orthogonal 2D kilovoltage (KV) and MV electronic images, e.g., ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);
- Other mechanism, after discussion with the Medical Physics Co-chair.

6.2.2.1 Image Guidance Procedures

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

- Imaging must be done each day.
- Region-of-Interest (ROI) or "clip box" for image registration should be set to encompass the high dose PTV and adjacent bony anatomy;
- If the image registration software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects (e.g., patient support system structure) seen on in-room X-rays should be excluded from the registration;
- Both manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the image registration must be visually checked for the alignment of the bony anatomy.
- Institutions are encouraged to include joints in the imaging process in order to increase the information used in the image registration process.

6.2.2.2 Management of Radiation Dose to the Patient from IGRT

According to the literature, the estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scan on a Tomotherapy unit were estimated to be in range from 1 to 3 cGy, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT vary from 1 cGy to 10 cGy depending on the field size. Thus, the doses for 3D imaging systems are in the range from 1 to 10 cGy for sarcoma imaging and can contribute from 0.5 to 5% to the daily dose of 2.0 Gy. The number of pretreatment images and total doses from these images will be tracked and recorded on a spreadsheet (the spreadsheet is available on the ATC web site, <http://atc.wustl.edu>). The daily pretreatment images for each case should be archived at each treating institution and should be available for central review by RTOG upon request. As a technique of controlling patient dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of patient position is carried out.

6.3 Localization, Simulation, and Immobilization

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

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

Adjustments of patient position should be made accordingly, if needed prior to treatment. Pretreatment images may include 2 or 3D imaging acquired using the techniques described in Section 6.2.2. The number of pretreatment images and the total doses from these images should be tracked and recorded on a spreadsheet (the spreadsheet is available on the ATC web site, <http://atc.wustl.edu>).

6.4 Treatment Planning/Target Volumes

6.4.1 Target Definition

The definition of volumes will be in accordance with the ICRU Report #62: Prescribing, recording and Reporting Photon Beam Therapy (supplement to ICRU Report #50).

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

6.4.1.2 (4/20/09) Clinical Target Volume (CTV) for Intermediate-to-High Grade Tumors \geq 8 cm: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 3 cm margins in the longitudinal (proximal and distal) directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1.5 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

6.4.1.3 (4/20/09) CTV For All Other Tumors: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 2 cm margins in the longitudinal (proximal and distal) directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of compartment. The radial margin from the lesion should be 1 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

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

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

6.5 Critical Structures (4/20/09)

Radiation dose to normal tissues should be kept within the accepted normal tissue tolerances when using standard 2 Gy fractionation schedules.

Every effort should be made to avoid treating the full circumference of an extremity, avoid treating anus, vulva and scrotum, avoid treating the lung, and avoid treating full dose, skin over areas commonly traumatized (e.g. the elbow, knee), and femoral head/neck.

If the tumor is close to the following structures, typically less than 50% volume of the anus and vulva should receive 3000 cGy; less than 50% volume of the testis should receive 300 cGy, if the patient prefers to reserve fertility; 20% of the lungs should receive less than 2000 cGy (V20); and less than 5% of the femoral head/neck should receive 60 Gy. Less than 50% of any joints (including shoulder, elbow and knee) should receive 50 Gy. Less than 50% of kidney volumes should receive 1400 cGy. For any other normal tissue structures, no radiation dose more than the established TD5/5 limit should be given. The above criteria must be met in the CT based plan.

No more than 50% of a longitudinal stripe of skin and subcutaneous tissue of an extremity should receive 2000 cGy. This stripe of normal tissue is contoured at the discretion of treating radiation oncologist. Full prescription dose to skin over areas commonly traumatized (e.g., the elbow, knee, shin) should be avoided.

No more than 50% of normal weight-bearing bone within the radiation field should receive 50 Gy except when the tumor invades the bone or when there is circumferential involvement of the

tumor more than a quarter of the bone or when the bone will be resected in a subsequent surgical resection after radiation.

There is no special requirement for skin dose limit. However, for IMRT of sarcoma, we recommend that skin surface (5-mm thickness) including scar from incision biopsy is not included in CTV or PTV and is not bolused for IMRT, unless the biopsy scar is not subsequently resected after radiotherapy.

6.6 Documentation Requirements (9/26/08)

Each radiation oncologist from the participating institution must understand and agree with the target definitions in this study (see Section 6.4). A copy of the pretreatment MRI (T1 weighting + gadolinium contrast and T2 weighting) and CT simulation of each case from each treating radiation oncologist should be submitted to the ITC along with contoured GTV, CTV, PTV, and adjacent normal tissue structures for central review within the first week of radiotherapy.

Volume and location of the GTV and CTV in the pretreatment MRI scans and CT based planning will be used for a subsequent comparison to the post-treatment MRI/CT images only when local failures occur. These post-treatment MRI/CT images are to be available upon request (see Section 11.2.1).

6.6.1 IGRT Documentation

- IGRT images obtained on the first day of treatment;
- One IGRT image data set per week of treatment **Note: Sites should retain all daily images. Any or all of the institution’s daily images may be subject to auditing.**
- Spreadsheet that includes data on daily variances based on analysis of daily IGRT. See the ATC web site, <http://atc.wustl.edu>, for the spreadsheet.

6.7 Compliance Criteria (4/20/09)

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

Per Protocol	The minimum dose to a point (defined as having a volume of 8.0 cubic mm) within the PTV is 97% of the prescription dose and 95% of the PTV is covered with that prescription dose. No more than 20% of the PTV receives a dose that is >110% of the prescribed dose.
Minor Variation	The minimum dose to a volume of 8 cubic mm within the PTV falls below 97% of the prescribed dose, but not below 95% of the prescribed dose. Greater than 20%, but no more than 25% of PTV receives \geq 110% prescription dose
Major Variation	The minimum dose to any volume of 8 cubic mm falls below 95% of the prescribed dose. Or, more than 25% of PTV receives \geq 110% prescription dose or dose to the normal tissue structure(s) is more than the recommended limit in Section 6.5

6.8 R.T. Quality Assurance Reviews (4/20/09)

The Principal Investigator/Radiation Oncologist, Dian Wang, MD, and the Radiation Oncology Co-Chair, David Kirsch, MD, PhD, will perform an RT Quality Assurance Review after complete data for the first 30 cases enrolled has been received at ITC. Drs. Wang and Kirsch will perform the next review after complete data for the next 30 cases enrolled have been received at ITC. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received, whichever occurs first. These reviews will be ongoing.

6.9 Radiation Therapy Adverse Events (4/20/09)

Acute: Wound complications are expected to develop in about one third of patients. Other common radiation adverse events include: fatigue, regional alopecia, diarrhea, skin erythema and desquamation within the treatment fields, and reduction in blood counts.

Long-term: Common long-term treatment adverse events include: lymphedema of the extremity receiving radiation and surgery, subcutaneous fibrosis, and joint stiffness. Much less common radiation adverse events include bowel injury, osteoradionecrosis, and bony fracture in the radiation field. There also is a risk of cancer occurring in a previously irradiated field. Also see Section 11.5, "Wound Complications and Late Radiation Morbidity".

6.10 Radiation Adverse Event Reporting (4/3/14)

6.10.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the CTEP Adverse Event Reporting System (CTEP-AERS) application as directed in this section.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via CTEP-AERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via CTEP-AERS.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

CTEP-AERS REPORTING REQUIREMENTS

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the CTEP-AERS RT-only pathway.

As of April 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, MedDRA version 12.0 for grading of all adverse events reported via CTEP-AERS. All RTOG case report forms will continue to use CTCAE, v. 3.0. A copy of the CTCAE v. 4 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE v. 4.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as

indicated in the following tables using the CTEP-AERS application. CTEP-AERS can be accessed via the CTEP web site (<https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613>). Use the patient's case number without any leading zeros as the patient ID when reporting via CTEP-AERS. In order to ensure consistent data capture, AEs and SAEs reported using CTEP-AERS **must also be reported to RTOG on the AE case report form (see Section 12.1)**. In addition, sites must submit CRFs in a timely manner after CTEP-AERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour CTEP-AERS Notification:

- **Phase II & III Studies:** All unexpected potentially related SAEs
- **Phase I Studies:** All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

Any event that meets the above outlined criteria for an SAE but is assessed by CTEP-AERS as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CRITERIA FOR CTEP-AERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpecte d	Expecte d
	With Hospitalizatio n	Without Hospitalizatio n	With Hospitalizatio n	Without Hospitalizatio n		
Unrelate d Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

CRITERIA FOR CTEP-AERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpecte d	Expecte d
	With Hospitalizatio n	Without Hospitalizatio n	With Hospitalizatio n	Without Hospitalizatio n		
Unrelate d Unlikely	Not required	Not required	Not required	Not Required	Not required	Not required
Possible Probable Definite	10 Calendar Days	Not required	Not required	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

- Expedited AE reporting timelines defined:
 - “24 hours; 5 calendar days” – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
 - “10 calendar days” - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- **(2/16/11)** Any medical event equivalent to CTCAE, v. 4 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following protocol treatment or procedure.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

RTOG REPORTING REQUIREMENTS (4/3/14)

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the CTEP-AERS RT-only pathway.

As of April 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, MedDRA version 12.0 for grading of all adverse events reported via CTEP-AERS. All RTOG case report forms will continue to use CTCAE, v. 3.0. A copy of the CTCAE v. 4 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE v. 4.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via CTEP-AERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. CTEP-AERS Reports are forwarded to RTOG electronically via CTEP-AERS. Use the patient's case number as the patient ID when reporting via CTEP-AERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via CTEP-AERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

6.11.2 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) [4/3/14]

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via CTEP-AERS **within 30 days of AML/MDS diagnosis**. If the site is reporting in CTCAE, v. 4, the event(s) maybe reported as 1) Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment-related secondary malignancy.

7.0 DRUG THERAPY (4/3/14)

Not applicable for this study. **Cohort A (patients receiving neoadjuvant, adjuvant chemotherapy, or both, or concurrent, or interdigitated chemotherapy) was closed on 1/18/10 (in amendment 4) due to slow accrual.**

Note: Patients accrued to Cohort A are being followed as patients accrued to Cohort B are followed: every 3 months from start of treatment in years 1-2, every 6 months in years 3-5, then annually for the patient's lifetime. Instructions for reporting adverse events and serious adverse events that Cohort A patients experience will be reported to CTEP-AERS per the instructions below:

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely,

possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. **Definition of an SAE:** Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via CTEP-AERS as a medically significant event.

CTEP-AERS REPORTING REQUIREMENTS

Per NCI guidelines, all serious adverse events occurring greater than 30 days after last dose of study agent attributed possibly, probably, or definitely related to the protocol treatment must be reported via CTEP-AERS.

As of April 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, MedDRA version 12.0 for grading of all adverse events reported via CTEP-AERS. All RTOG case report forms will continue to use CTCAE, v. 3.0. A copy of the CTCAE v. 4 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm All appropriate treatment areas should have access to a copy of the CTCAE v. 4.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following table using the CTEP-AERS application. CTEP-AERS can be accessed via the CTEP web site (<https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613>). Use the patient’s case number without any leading zeros as the patient ID when reporting via CTEP-AERS. In order to ensure consistent data capture, AEs and SAEs reported using CTEP-AERS **must also be reported to RTOG on the AE case report form (see Section 12.1).** In addition, sites must submit CRFs in a timely manner after CTEP-AERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour CTEP-AERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Any event that meets the above outlined criteria for an SAE but is assessed by CTEP-AERS as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CRITERIA FOR CTEP-AERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpecte d	Expecte d
	With Hospitalizatio n	Without Hospitalizatio n	With Hospitalizatio n	Without Hospitalizatio n		
Unrelate d Unlikely	Not required	Not required	Not required	Not Required	Not required	Not required

Possible Probable Definite	10 Calendar Days	Not required	Not required	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days
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- Expedited AE reporting timelines defined:
 - “24 hours; 5 calendar days” – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
 - “10 calendar days” - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE, v. 4 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following protocol treatment or procedure.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

RTOG REPORTING REQUIREMENTS

Per NCI guidelines, all serious adverse events occurring greater than 30 days after last dose of study agent attributed possibly, probably, or definitely related to the protocol treatment must be reported via CTEP-AERS.

As of April 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, MedDRA version 12.0 for grading of all adverse events reported via CTEP-AERS. All RTOG case report forms will continue to use CTCAE, v. 3.0. A copy of the CTCAE v. 4 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm All appropriate treatment areas should have access to a copy of the CTCAE v. 4.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via CTEP-AERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. CTEP-AERS Reports are forwarded to RTOG electronically via CTEP-AERS. Use the patient’s case number as the patient ID when reporting via CTEP-AERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via CTEP-AERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

7.1.1 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via CTEP-AERS **within 30 days of AML/MDS diagnosis**. If the site is reporting in CTCAE, v. 4, the event(s) maybe reported as 1) Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment-related secondary malignancy.

8.0 SURGERY

8.1 Initial Biopsy for Diagnosis and Tissue Submission

An incisional biopsy is preferred, even if the patient had a prior diagnostic core needle biopsy before being evaluated by the participating RTOG institution. The rationale for this preference is to obtain adequate tissue particularly from the tumor/stromal interface. Sufficient tumor must be obtained to determine the histologic subtype of the soft tissue sarcoma and the tumor grade. The biopsy should be done in such a way as to permit excision of the biopsy site at the time of formal

resection. If the patient had an initial needle biopsy before being evaluated by the participating RTOG institution, then the needle biopsy site should be tattooed for future identification during and following radiation. If extenuating circumstances would preclude a safe open incisional biopsy (e.g., a very deep tumor) or if patient refuses the open biopsy, multiple core biopsies would be acceptable (typically 2-3 core biopsies are required for histological diagnosis).

8.2 Surgery (1/8/10)

- 8.2.1** Both surgeon and radiation oncologist must see any eligible patient prior to instituting pre-operative therapy. The surgeon should determine and document a high possibility of a limb preservation approach after preoperative radiation to obtain local control. After radiation, every effort should be made to have limb preservation surgery unless there is documented evidence of tumor progression during or after the course of radiation that would require amputation for an appropriate negative margin resection. At the discretion of the treating physician(s), a plastic surgeon may be consulted.
- 8.2.2** Resection of the sarcoma will occur following combined preoperative radiation. The resection should be done with the goal of having negative pathologic margins. Quality assurance for surgical resection will be provided by both a review of the operative note and assessment of the specimen by surgical pathology (see Section 10.1). Microscopic absence of tumor on the inked margins will be accepted as a negative margin resection (see Section 10.2.4).
- 8.2.3** Definitions of operative procedures will be made after assessment of the operative note and pathologic evaluation of the resected specimen. The definitions include:
- 8.2.3.1** Amputation: Margin status will still be assessed and categorized if a limb preservation approach is not possible after the preoperative radiation.
- 8.2.3.2** Limb sparing surgery with the following margin status:
- R0: No residual tumor-microscopically negative margins;
 - R1: Microscopic residual tumor- microscopic positive margin(s) but no gross tumor;
 - R2: Macroscopic residual tumor-this margin status is not acceptable for the purposes of this protocol. The patient should be assessed for surgical re-excision.

8.3 Definitive Surgical Procedure

The surgical procedure necessary to resect the tumor with negative margins should be used. The definitions, as noted above, will be recorded in the surgical form. The goal of all surgery should also be limb preservation, if possible, within the realm of an appropriate oncologic resection.

8.4 Principles of Surgery (1/8/10)

- 8.4.1** All lesions of the extremities should be treated with wide excision after preoperative radiation. Any biopsy site should be excised *en bloc* with the definitive surgical specimen. Ideally, surgical resection should include a 2-3 cm margin of normal tissue surrounding the tumor, if possible, without compromising function. Dissection should always be done through grossly normal tissue planes and should be done beyond the fascial plane adjacent to the tumor. If the tumor is close to or displaces major vessels or nerves, these need not be removed if the adventitia or perineurium is removed and the underlying neurovascular structures are not involved with gross tumor. Radical excision or entire anatomic compartment resection is not recommended for patients on this study.

Frozen section at the time of surgery must be performed on the closest margin and should be confirmed as being free of tumor if feasible within the context of limb preservation surgery. If postoperative pathologic evaluation reveals positive soft tissue margins other than bone, nerve or large blood vessels, surgical re-resection to obtain negative margins should strongly be considered if it will not have a major impact upon the patient's functionality. If the margin on bone, major blood vessel or nerve is microscopically positive, additional radiation should be given as noted in the protocol.

In general, lymph node dissection is not recommended, but primary tumors overlying major lymph node stations may be treated with surgical resection to include the associated lymph nodes. Surgical clips (titanium) should be placed to mark the periphery of the surgical field of resection and other relevant structures to help guide the radiation oncologist if postoperative radiation boost is necessary. Closed suction drainage should be used in all anatomic regions (Hemovac, JP, etc.). The drains should exit the skin close to the edge of the surgical incision.

- 8.4.2** *Clearly state* in the operative note what type of surgical procedure was performed (R0, R1, or R2) and from where the frozen sections of the margins were taken. The final margin status (R status) should be based on the permanent pathology assessment (not frozen section) [see Section 10.2.4].

- 8.4.3** Because all patients will have had preoperative radiation, special attention must be given to the skin flaps. Use of muscle flaps, pedicled myocutaneous flaps, and even free flaps are encouraged to fill dead space and provide well-vascularized tissue. These flaps should be used if there is any concern regarding the viability of the skin flaps.
- 8.4.4** Because all patients will have preoperative radiation, if periosteum is resected for an extremity sarcoma, consideration should be given to internal fixation to prevent future fracture. Extent of periosteal stripping needs to be documented as none; minimal (< 10 cm); moderate (10-20 cm); or extensive (> 20 cm) in the operative report. Internal fixation, if used, should also be documented after periosteum resection.
- 8.4.5** In general, the following principles should be followed in postoperative management of these patients:
- Maintain staples or skin sutures per surgeon preference. Due to potential delays in wound healing following preoperative radiation, at least 3-4 weeks is strongly encouraged.
 - Leave drains in place until the drainage meets the surgeon's criteria for removal.
 - Begin rehabilitation slowly.
- 8.4.6** Resectability will depend upon the judgment of the operating surgeon. As stated in Section 8.3, the goal of all surgery for extremity tumors should be limb preservation, if possible within the realm of an appropriate oncologic resection. Every effort should be made to have limb preservation surgery. However, some extremity tumors may require amputation to obtain even grossly negative margins. Only amputation due to treatment complications or recurrence (not primary surgical therapy) will be considered a local failure.

8.5 Surgical Adverse Events

8.5.1 Wound Complications

Major wound complications, such as secondary operations, re-admissions, and/or invasive procedures for wound complications: deep wound packing and prolonged dressing changes will be reported on the appropriate case report form (see Section 12.1).

8.6 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chairs, Burton Eisenberg, MD, and John Kane, MD, will perform a Quality Assurance Review after complete data for the first 30 cases enrolled have been received at RTOG Headquarters. Drs. Eisenberg and Kane will perform the next review after complete data for the next 30 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

Surgical quality assurance review will include examination of the original baseline tumor imaging, imaging following radiation but prior to surgery (with emphasis on the proximity to associated major neurovascular or bony structures), the formal operative report for the surgical resection, the treating institution's final pathology report (including gross, frozen section, and microscopic pathologic descriptions), and the RTOG central pathology review. The reported resection (R) status from the operative note will be assessed and re-evaluated based upon the final pathology report and the RTOG central pathology review. The surgical quality assurance review will then assign an official protocol resection status based upon this information using the definitions in Section 8.2.3.2.

From a clinical treatment and protocol standpoint, an R0 or R1 resection (especially following an attempt to preserve a major neurovascular or bony structure) would be considered an adequate surgical resection. For the purposes of this protocol, an R2 resection would not be considered adequate surgical therapy, even in the context of limb preservation. The treating surgeon and RTOG institution will be contacted with a recommendation that the patient should undergo re-resection to remove all gross tumor, if technically feasible (and within the time constraints of the protocol).

Although every effort should be made to perform limb preservation surgery, some extremity tumors may require amputation to obtain negative margins if a limb preservation approach is not possible after preoperative radiation. In this scenario, amputation would still be considered adequate surgical therapy and margin status will be assessed or categorized based upon the R criteria for limb sparing surgery.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapies for optimal medical care are allowed during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. These therapies include, physical therapy and rehabilitation, occupational therapy, anti-emetics, anticonvulsants, prophylactic anticoagulants, antidiarrheals, hematopoietic growth factors including G-CSF (filgrastim/Neupogen® or pegfilgrastim/Neulasta®) and epoetin/Procrit®/Aranesp®, colace or senekot prophylactically for constipation, and appetite enhancers (e.g., Megace®).

9.2 Non-permitted Supportive Therapy (1/8/10)

9.2.1 No investigational agents are permitted.

9.2.2 Neoadjuvant, concurrent, or adjuvant chemotherapy is not permitted.

10.0 TISSUE/SPECIMEN SUBMISSION (4/20/09, 10/13/09)

In this study, it is required that tissue be submitted to the RTOG Biospecimen Resource for the purpose of central review of pathology (see Section 10.2). In addition, it is strongly recommended (but optional) that tissue, blood, and urine be submitted for banking and translational research

If the patient consents to participate in the optional tissue/specimen component of the study (see Section 10.3), the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission (10/13/09)

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each specimen is preserved through careful specimen storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. These studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects specimens when required for central review of pathology.

Note: The RTOG Biospecimen Resource will provide collection kits and instructions at no charge for the submission of specimens in this protocol (see Appendices VI-X).

10.2 Tissue Collection For Central Review: Required

Patients must consent to participate in submission of tissue for central review.

The purpose of central pathology review is to obtain uniform evaluation of pathology and histology grade of the soft tissue sarcoma entered into this study. These tumors often pose some of the greatest diagnostic challenges to anatomic pathologists. Their confounding morphology all too frequently results in seemingly incompatible diagnoses, versus high-grade sarcomas. In addition, soft tissue sarcomas are notorious for mimicking carcinomas, melanomas, and lymphomas. Finally, the percentage of post-treatment viable tumor needs to be uniformly analyzed to correlate with clinical outcome.

Tissue specimens for central review will be taken from both pre-treatment diagnostic biopsy and from surgical specimens, if post-radiotherapy surgery is performed. On the pre-treatment biopsy specimen, sarcoma type will be determined by the most recent WHO (2002) classification system.⁷⁹ Histologic grade will be assessed with the 3-grade French Federation of Cancer Centers Sarcoma Group System.⁸⁰ (If the AJCC 4-grade staging system in Appendix IV is used, intermediate-to-high grade sarcomas would be grade 3-4.) Other parameters that will be tabulated are: mitotic rate, percent necrosis, type of tumor matrix, vascular invasion, and host lymphocytic response.

On the post-treatment excision specimen, margin status assessed by pathology will be scored with a 3-tier system:

1. A positive margin is defined by tumor directly touching the inked margin of excision in any area. It also will be noted whether there are viable tumor cells (any cell with nuclear staining) touching the inked margin (a) versus acellular hyalinized or necrotic tumor touching ink (b).
2. A marginal excision is defined by tumor contained by a pseudocapsule in any area. A measurement to the closest margin will be tabulated.
3. A wide local excision is defined by a layer of normal tissue (e.g., skeletal muscle, fat, or fibroconnective tissue) surrounding the tumor at all areas. A measurement to the closest margin is to be included. Only direct contact with the inked surface will be regarded as a positive margin.

Regarding assessment of post-treatment response to therapy: microscopic slides from one entire cut surface of a cross-sectional slab of tumor are required be submitted, similar to what is done with osteosarcoma. The reason for this is that when pathologists sample soft tissue tumors, they often selectively take only what appears to be viable tumor. Thus, the histology slides tend to underestimate the amount of non-viable tumor. Post-treatment tumors show 4 major histologic changes: viable tumor (i.e., tumor cells with nuclear staining); fibrotic/hyalinized areas; necrotic tumor; and hemorrhage. By examining all histologic slides from an entire cut surface, one can estimate the percentages of these four histologic patterns to determine the percent of viable tumor. All 4 histologic patterns will be tabulated such that the sum of their individual percentages will equal 100%. Tumor border (pushing versus infiltrative), host lymphocytic response, and vascular invasion will also be tabulated.

The following material must be provided to the RTOG Biospecimen Resource for Central Review:

- 10.2.1 (4/20/09)** Representative slides, including one H & E stained slide and immunohistochemistry slides for morphology and grade in the pre-treatment biopsy specimen and for margin and percentage of viable tumor in the post-RT surgery specimen.
- 10.2.2 (4/20/09)** Additional slides, including H & E slide and immunostained slides for central review upon request to the institution by the Pathology Co-Chair, David Lucas, MD.
- 10.2.3** A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- 10.2.4 (7/3/12)** A Specimen Transmittal Form stating that the tissue is being submitted for Central Review. Sites can access the form (no password required) at <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0630&mode=html&pid=383>
- The form must include the RTOG protocol number and the patient's case number. If the patient also is enrolled on other RTOG trials, this should be indicated on the form.
- 10.2.5** Central Review will be performed by the Pathology Co-Chair, David Lucas, MD, after complete data for the first 30 cases enrolled have been received at RTOG Headquarters. Dr. Lucas will perform the next review after complete data for the next 30 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

The morphology and grade of pretreatment soft tissue sarcoma as well as surgical margin status and the percentage of post-treatment viable tumor of each case will be assessed during the central review. Microscopic absence of tumor on the inked margins will be accepted as a negative margin of excision. The final margin status (R status) of each case also will be assessed.

10.3 Specimen Collection for Banking and Translational Research: Strongly Recommended (But Optional)

The RTOG has been collecting pretreatment diagnostic tissue and/or surgical specimens from the soft tissue sarcoma protocols over the last decade. A number of histologic, cell kinetic/proliferation, angiogenesis, and molecular markers have been and are under investigation. A number of biomarkers are under investigation by the RTOG Sarcoma TRP group. The results of these ongoing studies will lead to the investigation of promising similar or new biomarkers with the goals of 1) identifying factors predictive of outcome such that patients may be better stratified

in future trials, and 2) developing novel treatment strategies which target the molecular abnormalities identified.

Unique to this study is the assessment of late radiation morbidity as the primary endpoint and to assess the impact of the radiation morbidity on a patient's function and physical disability (quality of life). A correlative biomarker study would be extremely important because this may lead to future mechanistic investigations or interventions to prevent late radiation morbidity and improve quality of life for patients receiving radiotherapy. The goal is to measure using the fresh and archived pathologic materials. In this study, we plan to perform immunohistochemical studies and other types of biomarker studies on the pretreatment biopsy specimen (tumor and matched normal tissue, as well as cutaneous/subcutaneous inside and outside the radiation field), surgical specimen (tumor and matched normal tumor tissue as well as cutaneous/subcutaneous tissue inside and outside the radiation field), and post-treatment punch skin biopsy.

10.3.1 Tissue Collection

10.3.1.1 Fresh Tumor Tissue (10/2/08)

Fresh tumor tissue and matched normal tissue may be obtained at both the time of each pretreatment biopsy and surgical resection, wrapped in foil, and placed immediately into dry ice or a liquid nitrogen bath. See Appendix V for instructions.

Alternatively, the tumor tissue and matched normal tissue can be preserved in RNAlater™ rather than freezing the samples. The institution should request a vial or vials of RNAlater™ from the RTOG Biospecimen Resource, and the Biospecimen Resource will mail RNAlater™ and instructions overnight to the institution. When samples are obtained, they are placed directly into the vials of RNAlater™. The vials should then be stored at 4° Celsius and shipped refrigerated via overnight mail to the Biospecimen Resource. See Appendix V for instructions

The specimens (frozen or preserved in RNAlater™) should be labeled with the study protocol and case numbers, the date and time of collection, and the time point which it was taken.

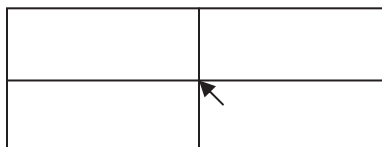
10.3.1.2 Fixed Tumor Tissue (9/26/08, 10/2/08, 4/20/09, 10/13/09)

If submission of fresh tissue is not possible, fixed tissue from the pretreatment biopsy and surgical specimens may be submitted. Either the FFPE block or a 2 mm diameter core of tissue (punched from the tissue block containing the tumor with a punch tool will be submitted in a plastic tube labeled with the surgical pathology number). **Note:** A kit with the punch tool, tube, and instructions can be obtained free of charge from the Biospecimen Resource (see Appendix VI). The core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.3.1.3 Fresh or Fixed Cutaneous/Subcutaneous Tissue (9/26/08, 10/2/08)

Cutaneous/subcutaneous tissues from inside and outside the radiation field (normal control) may be collected at the following time points: pre-radiotherapy, post-radiotherapy (during surgery if performed), and then annually up to 2 years after surgery. Cutaneous/subcutaneous tissue can be obtained by doing a skin punch biopsy of 2 mm in diameter.

- Cutaneous/subcutaneous tissues from **inside the radiation field** should be obtained from the skin over the center of radiation field as shown in the following figure. Please note that the skin biopsy site must be 2 cm away from the pretreatment biopsy scar for the purpose of diagnosis or from the reconstructed flap scar in the postoperative setting. The rectangle below is an assumed radiation field. An arrow points to the skin surface over the center of the radiation field.



- Normal cutaneous/subcutaneous tissue used as a control should be obtained from **outside the radiation field** (preferably in the opposite extremity or at least 5 cm from the radiation field border or from the reconstructed flap).

- Sample preparation for the cutaneous samples is identical to that for fresh pretreatment samples (see Section 10.3.1.1). See detailed instructions for tissue collection in Appendices V-VI.

10.3.2 Blood Collection (10/2/08)

Buffy coat will be collected prior to protocol treatment only. Serum and plasma will be collected prior to the protocol treatment, during surgery (if performed), and then annually from the start of treatment until the end of the 2-year follow up. **Note:** A blood collection kit and instructions can be obtained free of charge from the Biospecimen Resource (see Appendix VII)

10.3.2.1 Serum Collection

- Specimens are collected in red-top tubes (5-10 mL tubes).
- After allowing the serum to clot, keep serum tubes refrigerated (4-8° C) until processing (tubes may be on ice up to 2 hrs). Centrifuge specimens at approximately 2500 RPM in a standard clinical centrifuge at for 10 minutes.
- Using sterile techniques to avoid contamination, aliquot 0.5-1 mL serum into cryovials and freeze. Take great care to collect only serum, and avoid collecting any solid particulate matter before transferring serum into the cryovials.
- Label each aliquot with study protocol and case numbers, the date and time of collection, specimen type (i.e., serum) and the time point taken.

10.3.2.2 Plasma Collection

- Specimens are collected in tubes containing EDTA (purple/lavender-top tubes).
- After thoroughly mixing, centrifuge specimens at approximately 2500 RPM in a standard clinical centrifuge for 10 minutes.
- Using sterile techniques to avoid contamination, aliquot 0.5-1 mL plasma into cryovials and freeze. Take great care to collect only plasma and avoid collecting any solid particulate matter before transferring plasma into the cryovials.
- Label each aliquot with study protocol and case numbers, the date and time of collection, specimen type (i.e., plasma) and the time point taken.

10.3.2.3 Buffy Coat Collection

- Specimens are collected in tubes containing EDTA (purple/lavender-top tubes).
- Carefully remove plasma from the collection tubes (see instructions in Section 10.3.2.2).
- Using a pipette, remove the buffy coat layer, place into cryovials, and freeze.
- Label each aliquot with study protocol and case numbers, the date and time of collection, specimen type (i.e., buffy coat) and the time point taken.

10.3.2.4 Storage/Shipment of Blood Specimens (10/13/09)

Store all frozen biospecimens at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

A Specimen Transmittal Form documenting the date and time of collection of the specimen, the RTOG protocol number, the patient's case number, and method of storage, (e.g., stored at -80° C), must be included with the blood specimens. Sites can access the form (no password required) at <http://www.rtog.org/members/forms/list.html> (under "Pathology").

10.3.3 Urine Collection (10/2/08)

Urine will be collected prior to the protocol treatment, during surgery (if performed), and then annually from the start of treatment until the end of the 2-year follow up. A minimum of 10 mL urine should be collected in a sterile collection cup labeled with patient ID, date and time of collection, and placed into a freezer for storage. See specific instructions in Appendix VIII.

10.4 Documentation and Submission for Banking and Translational Research

The following material for banking and translational research must be provided in order for the case to be evaluable for the Biospecimen Resource:

- 10.4.1** A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- 10.4.2 (10/2/08)** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number. For blood and urine specimens, the following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the blood and/or urine; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included.
- 10.5 Specimen Collection Summary (10/2/08, 4/20/09, 10/13/09)**

Tissue for Central Review: Required		
Pretreatment and During Surgery (if post-radiotherapy surgery is performed)		
Specimens taken from patient:	Submitted as:	Shipped:
One H&E stained slide of the primary tumor from pretreatment biopsy, as well as any available immunohistochemistry stained slides	H&E stained slide and Pathology report	Slide shipped ambient
All H&E slides taken from 1 complete cut surface of a cross sectional slab of the primary tumor from surgery	H&E stained slides	Slide shipped ambient
All H&E slides taken from the resection margins of the treated primary tumor from surgery.	H&E stained slides and Pathology report	Slide shipped ambient
Specimens for Banking and Translational Research: Recommended		
Specimens taken from patient:	Submitted as:	Shipped:
Tissue Collection at Each Time Point		
Tumor tissue obtained by incision or core biopsy (the preradiation therapy tissue) and tumor tissue from surgery	A FFPE block or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool; see Appendix VI.	Shipped ambient
Cutaneous/subcutaneous tissue obtained using a sterile dermal skin punch biopsy of 2mm diameter or greater at each time point from inside and outside the radiation field (pre-RT, during surgery, if performed) and annually post-surgery for 2 years)	A 2 mm diameter core of tissue, punched from the tissue block with a skin punch; see Appendix VI.	Shipped ambient
Fresh tumor tissue and normal tissue obtained by incision or core biopsy and surgery (if surgery is performed)	Frozen or placed in RNA later^{TM} ; see Appendix V.	Frozen sample must be shipped frozen. RNA later^{TM} sample should be shipped at 4° C.
Cutaneous/subcutaneous tissue obtained with dermal skin punch biopsy of 2mm diameter or greater at each time point from inside and outside the radiation field (pre-RT, post-RT (during	Frozen or placed in RNA later^{TM} ; see Appendix V.	Frozen sample must be shipped frozen. RNA later^{TM} sample should be shipped at 4° C.

surgery, if performed), and annually post-surgery for 2 years)		
Buffy Coat: 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat; buffy coat will be collected prior to the protocol treatment only	Frozen buffy coat sample containing a minimum of 0.5 mL per aliquot in 1 mL cryovials; see Appendix VII.	Buffy coat sent frozen on dry ice via overnight carrier Monday-Wednesday. Do not ship on Friday.
Serum: 5-10 mL of whole blood in red-top tube and centrifuge for serum; serum will be collected prior to the protocol treatment, during surgery (if performed), then annually from the start of treatment until the end of the 2-year follow up	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials; see Appendix VII.	Serum sent frozen on dry ice via overnight carrier Monday-Wednesday. Do not ship on Friday.
Plasma: 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for plasma; plasma will be collected prior to the protocol treatment, during surgery (if performed), then annually from the start of treatment until the end of the 2-year follow up	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials; see Appendix VII.	Plasma sent frozen on dry ice via overnight carrier Monday-Wednesday. Do not ship on Friday.
Urine: 10-25 mL clean-catch (mid-stream); urine will be collected prior to the protocol treatment, during surgery (if performed), then annually from the start of treatment until the end of the 2-year follow up	A minimum of 5 mL unpreserved urine in 2 separate sterile collection containers; see Appendix VIII.	Urine sent frozen on dry ice via overnight carrier Monday-Wednesday. Do not ship on Friday.
NOTE: Sites should call or e-mail to alert the RTOG Biospecimen Resource (415-476-7864; RTOG@ucsf.edu) that a frozen specimen is being sent and to provide the tracking number of that shipment.		

10.6 (10/13/09) Submit materials for Central Review, Tissue Banking, and Translational Research as follows:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.7 Reimbursement

RTOG will reimburse submitting institutions \$200 per case for a block or core of material. Serum, plasma, and buffy coat cells are reimbursed at \$300 per specimen, and urine is reimbursed at

\$50 per specimen. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.8 Confidentiality/Storage (9/26/08)

(See the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/biospeciment/tissuefaq.html> for further details.)

- 10.8.1** Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.
- 10.8.2** Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the specimen is consumed/exhausted or study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS: See Appendix II for a Summary of Assessments and Time Frames

11.1 Pretreatment Evaluation See Sections 3.0, 4.0, and Appendix II for all pretreatment assessments.

- 11.1.1** The physician or physician's designee will complete the Musculoskeletal Tumor Rating Scale (MSTS) prior to protocol treatment (see Section 11.7).
- 11.1.2** If the patient agrees to participate in the quality of life component, the patient completed the following assessments prior to protocol treatment: The Functional Assessment of Cancer Therapy-General (FACT-G); Toronto Extremity Salvage Score (TESS); Sexual Adjustment Questionnaire (for Males and Females; SAQ-M and SAQ-F) [see Section 11.8].

11.2 Evaluation During RT (4/20/09,1/8/10)

- 11.2.1** The MRI or CT with contrast of the primary site should be performed 3-5 weeks after preoperative RT for surgical evaluation (surgery is performed in 4-8 weeks after RT).
- 11.2.2** The CT of the chest should be performed 3-5 weeks after preoperative RT for surgical evaluation.
- 11.2.3** A CBC/differential should be performed every other week to monitor effects of radiation on bone marrow.
- 11.2.4** A physical examination should be done weekly during radiation therapy; documentation of the patient's weight in these exams is not required.

11.3 Evaluation After Treatment

- 11.3.1** Wound complications and late radiation morbidity must be reported on the appropriate case report form (see Section 12.1). **Note the criteria in Section 11.5.**
- 11.3.2** If the patient consents to participate in the quality of life portion of the study, the patient will complete the QOL assessments (FACT-G, the TESS, and the SAQ) at 12, 18, and 24 months from the start of radiation treatment.

11.4 Failure Pattern of Recurrence (4/20/09, 1/8/10)

All tumor recurrences including local recurrence, regional recurrence, distant metastasis, and second primary tumor shall be recorded in this study. All tumor recurrences should be documented on cross-sectional imaging (CT or MRI with contrast). Pathological confirmation of recurrence is strongly recommended.

- Local tumor recurrence: Any tumor recurrence inside the clinical target volume (CTV) is defined as "in-field recurrence"; any tumor recurrence beyond the CTV to within 3 cm distance from the edge of the CTV is defined as "marginal recurrence"; this marginal recurrence is considered "geographic miss". Any other local recurrence is defined as "outside-field recurrence".
- Local tumor progression: At least a 20% increase in the maximal dimension of the primary tumor taking as reference the smallest maximal dimension recorded since treatment started;
- Regional tumor recurrence: Any nodal metastasis adjacent to the primary soft tissue sarcoma;

- Distant tumor metastasis: Any tumor that develops distantly from the primary site of sarcoma;
- Second primary tumor: Any different histology of sarcoma or any other type of malignancy inside or outside the radiation field.

11.5 Wound Complications and Late Radiation Morbidity

11.5.1 Wound Complications

Major wound complications, such as secondary operations, re-admissions, and/or invasive procedures for wound complications: deep wound packing and prolonged dressing changes will be reported on the appropriate case report form (see Section 12.1).

11.5.2 Late Radiation Morbidity

Lymphedema, late subcutaneous fibrosis, and joint stiffness arising directly from the radiation treatment as well as limb function and physical disability must be recorded on the appropriate case report form.

Late subcutaneous fibrosis and joint stiffness are assessed using the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) late toxicity scoring criteria. **Lymphedema** is measured according to the criteria of Stern.

(1/8/10) Note: The scoring criteria provided in Tables 1-2 below and specific to subcutaneous fibrosis, joint stiffness, and edema, was utilized in the recent Canadian phase III randomized Sarcoma trial¹² to which 0630 data will be compared. For comparative purposes, subcutaneous fibrosis, joint stiffness, and edema also should be scored according to the Common Terminology Criteria for Adverse Events (CTCAE), v.3.0. **For grading of all other adverse events, use CTCAE, v. 3.0 only** (see Sections 6.9 and 6.10).

Table 1: EORTC/RTOG Late Radiation Toxicity Criteria for late subcutaneous fibrosis and joint stiffness (9/26/08)

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

Table 2: Stern's Rating Scale for Edema

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

Other late radiation morbidities including bony fracture in the field of radiation shall be recorded.

11.6 Criteria for Discontinuation of Protocol Treatment (1/8/10)

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease;
- Unacceptable adverse events [at the discretion of the treating physician(s)];
- A delay in protocol treatment > 12 weeks.

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

11.7 Musculoskeletal Tumor Rating Scale (MSTS)

The MSTS⁷² is a measure of physical function across 7 items, completed by the physician (preferably by the Orthopedic Surgeon or Surgical Oncologist) or the physician's designated staff. The 7 items are: pain, range of motion, strength, joint stability, joint deformity, emotional acceptance, and overall function. Each item is scored from 0-5 with a maximum possible score of 35. The MSTS has been in use for over 20 years and is a widely recognized and utilized tool used to evaluate physical function; no psychometric data are available on the MSTS. A clinician familiar with the MSTS should be able to complete the rating in approximately 10 minutes and will complete the MSTS at the following time points: Prior to start of protocol treatment (baseline), and at 12, 18, and 24 months from the start of radiation treatment.

11.8 Quality of Life Assessments (4/20/09)

Patients must be offered the opportunity to participate in the correlative components of the study, such as the quality of life assessment. **Note:** Sites are not permitted to delete the quality of life component from the protocol or from the sample consent. If the patient consents to participate in the QOL portion of the study, the patient will complete 3 assessments, the FACT-G, the TESS, and the SAQ at 4 time points: Prior to start of protocol treatment (baseline), and at 12, 18, and 24 months from the start of radiation treatment.

11.8.1 The Functional Assessment of Cancer Therapy-General (FACT-G)

The FACT-G⁶⁷ is a commonly used tool measuring general quality of life across 4 scales: physical well being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well being (7 items). It has been written at the 4th grade reading level, and patients can complete the FACT-G in 5-10 minutes. The FACT has been translated into 26 languages, and translations are accessible at the FACIT web site, <http://www.facit.org/translation/licensure.aspx>.

11.8.2 Toronto Extremity Salvage Score (TESS)

The TESS⁶⁹ is a 30-item questionnaire completed by patients. It asks them to describe their ability to perform activities of daily living based on difficulty of performance. There are 2 versions of the TESS: one for individuals with an upper extremity tumor and the other for lower extremity tumors. Each item is scored from 1 to 5, with total score calculated as a percentage. Internal consistency for the TESS has been reported as 0.94 (LE version) and 0.92 (UE version). Construct validity was estimated by showing a moderate correlation with the MSTS. The TESS is available in English only (no translations available) and takes approximately 15 minutes to complete.

11.8.3 Sexual Adjustment Questionnaire (for Males and Females; SAQ-M and SAQ-F)

The SAQ⁷⁶ contains 16 items that measure 4 components of sexuality (dysfunction, desire, satisfaction, activity) using a Likert-type scale and one additional item on fatigue. Patients will complete a pretreatment (baseline) version of the questionnaire and then will complete a follow-up version of the questionnaire, at 12, 18, and 24 months from the start of radiation treatment. Psychometric data on the revised version is forthcoming. The tool takes approximately 10 minutes to complete. Currently, the SAQ is only available in English.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

Item	Due
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Demographic Form (A5) Initial Evaluation Form (I1) Pathology Report (P1) Slides/Blocks (P2) Musculoskeletal Tumor Rating Scale (MSTS) (QF) The Functional Assessment of Cancer Therapy-General (FACT-G) [FA] Toronto Extremity Salvage Score (TESS) [SS] Baseline Sexual Adjustment Questionnaire-Male (SAQ-M) [SA] Baseline Sexual Adjustment Questionnaire-Female (SAQ-f) [FL]	Within 2 weeks of study entry
Treatment Form (TF)	Within 2 weeks of completion of pre-op chemotherapy and within 3 months of protocol surgery
Surgery Form (S1)	Within 2 weeks of protocol surgery
Follow-up Form (F1)	Every 3 months from start of treatment in years 1-2, every 6 months in years 3-5, then annually; also at death
Wound Assessment Form (PO)	At 4 months after protocol surgery
Musculoskeletal Tumor Rating Scale (MSTS) (QF) The Functional Assessment of Cancer Therapy-General (FACT-G) [FA] Toronto Extremity Salvage Score (TESS) [SS] Follow-up Sexual Adjustment Questionnaire-Male (SAQ-M) [SB] Follow-up Sexual Adjustment Questionnaire-Female (SAQ-f) [FM]	At 12, 18, and 24 months from the start of radiation treatment.
Radiotherapy Summary Form (T1) [copy to ITC] Note: Two T1 forms will be submitted: First T1 at end of pre-op RT and second T1 within 2 months of end of boost RT or post-surgery if no RT boost given.	Within 1 week of end of pre-op RT and within 2 months of protocol surgery

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) [10/13/09]

Item

Preliminary Dosimetry Information (DD)

Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist.

- CT data, critical normal structures, all GTV, CTV, and PTV contours
- Digital beam geometry for initial and boost beam sets
- Doses for initial and boost sets of concurrently treated beams
- Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan **(DV)**
- Pretreatment MRI (T1 weighting and gadolinium contrast, and T2 weighting) **[MR]**; see Section 6.6

Due

Within 1 week of start of RT

Digital Data Submission Information Form (**DDSI**)
Submitted online (Form located on ATC web site,
<http://atc.wustl.edu/forms/DDSI/ddsi.html>)

Hard copy isodose distributions for total dose plan as described
in QA guidelines† (**T6**)

**NOTE: Sites must notify ITC via e-mail (itc@wustl.edu)
after digital data is submitted. The e-mail must include
study and case numbers or, if the data is phantom, “dry
run” or “benchmark”.**

Final Dosimetry Information

Radiotherapy Form (**T1**) [**copy to RTOG HQ**]

Note: Two T1 forms will be submitted: First T1 at end of pre-op
RT and second T1 within 2 months of end of boost RT or post-
surgery if no RT boost given.

Within 1 week of end of pre-op RT
and within 2 months of protocol
surgery

Daily Treatment Record (**T5**) [**copy to RTOG HQ**]

Note: A second T5 will be submitted if RT boost is given
Modified digital patient data as required through consultation
with Image Guided Therapy QA Center

Within 1 week of end of pre-op RT
and within 1 week of end of RT boost
if given

IGRT Submission (see Section 6.6.1 for details) [**4/20/09**]

IGRT images obtained on first day of treatment (**IG**)

Within 1 week of RT end

One IGRT image data set per week of treatment (**IG**)

IGRT Data Collection Spreadsheet on Daily Variances (Final)
[SG]

Within 1 week of RT end

Post-treatment MRI (**MR**) or CT (**C2**) images with contrast
(Section 11.2.1); will be compared to pre-treatment images
only when local failures occur (Section 6.6)

Submission upon request only

†Available on the ATC web site, <http://atc.wustl.edu/>

12.2.1 Digital Data Submission to ITC (10/13/09)

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC
shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should
be addressed to:

Image-Guided Therapy Center (ITC)

ATTN: Roxana Haynes

4511 Forest Park, Suite 200

St. Louis, MO 63108

314-747-5415

FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

All study endpoints will be evaluated separately by cohort, except as noted in Section 13.4.3.

13.1.1 Primary Endpoint

To estimate the effect of reduced radiation volume through image-guided radiation technology (IGRT) on late radiation morbidity (\geq Grade 2 lymphedema, subcutaneous fibrosis, or joint stiffness) at 2 years (window period of 21– 27 months) from the start of radiation treatment (using the EORTC/RTOG criteria; see Section 11.5.2)

13.1.2 Secondary Endpoints

- 13.1.2.1** To estimate the effect of reduced radiation volume through image-guided radiation technology (IGRT) on late radiation morbidity (\geq Grade 2 lymphedema, subcutaneous fibrosis, and joint stiffness) at 2 years (window period of 21 – 27 months) from the start of radiation treatment (using CTCAE, v3.0 criteria)
- 13.1.2.2** Other CTCAE, v.3.0 grade 3-5 adverse events;
- 13.1.2.3** To determine the pattern of first failure, including local failure (in-field, marginal, and outside-field failure), regional failure, distant failure, and death without disease progression;
- 13.1.2.4** Time to local failure (Local recurrence or progression as defined in Section 11.4 that occurs after surgery will be considered a local failure; local recurrence or progression prior to surgery will not be considered a local failure. Amputation for treatment complications or recurrence/progression will be considered a failure at the date of surgery; amputation due to any other reason will not be considered a local failure. Any patient that does not continue on to surgery will be considered to have local failure; failure time will be the minimum time to surgery as calculated from the patients that do continue on to surgery).
- 13.1.2.5** Time to regional failure (Failure: Regional recurrence as defined in Section 11.4);
- 13.1.2.6** Time to distant failure (Failure: Distant metastasis as defined in Section 11.4);
- 13.1.2.7** Distant-disease free survival (Failure: Distant failure or death due to any cause);
- 13.1.2.8** Disease-free survival (Failure: Local, regional, or distant failure, or death due to any cause);
- 13.1.2.9** Overall survival (Failure: Death due to any cause);
- 13.1.2.10** Time to second primary tumor (Failure: Second primary tumor as defined in Section 11.4.2.3);
- 13.1.2.11** Estimate the rate of wound complications;
- 13.1.2.12** To assess the impact of late radiation morbidity (\geq Grade 2 lymphedema, subcutaneous fibrosis, or joint stiffness) at 2 years on the clinical measure, MSTs;
- 13.1.3 Tertiary Endpoints** (Exploratory)
- 13.1.3.1** To correlate late radiation morbidity at 2 years with the 3 quality of life assessments (FACT-G, TESS, and SAQ);
- 13.1.3.2** To compare the TESS and the MSTs scores at 2 years between Cohort B patients and the preoperative RT patients in the NCIC CTG trial;
- 13.1.3.3** To compare the SAQ scores at 2 years for Cohort A patients with Cohort B patients;
- 13.1.3.4** To describe the trend over time with respect to 4 variables: late radiation morbidity, FACT-G, TESS, and SAQ;
- 13.1.3.5** To collect sarcoma tumor samples, adjacent normal tissue, serum, plasma, and urine for correlative biomarker studies.

13.2 Overview and Sample Size

This is a prospective study designed to assess late radiation toxicities, specifically lymphedema, subcutaneous fibrosis, and joint stiffness. The primary efficacy endpoint is whether or not a patient experiences at least 1 of the 3 toxicities at a severity grade 2 or greater at 2 years from the start of radiation treatment. Published results from the recent NCIC CTG phase III randomized trial showed 31.5% grade 2 or greater fibrosis, 15.1% lymphedema, and 17.8% joint stiffness in the preoperative arm at 2 years following treatment.¹² Since a patient can experience 2 or even 3 of these late effects at 2 years, NCIC CTG performed a special analysis using the same dataset from their publication. They found that 27 (37%) of 73 patients on the preoperative arms experienced at least one of these late radiation toxicities.

Therefore, in this study, we will test for a 20% absolute decrease in combined toxicity rate (from 37 to 17%). A sample size of 41 patients is required, with significance level of 0.05 and 90% power. Assuming approximately 5% will be retrospectively deemed ineligible and an additional 15% will not have a 2-year assessment for the primary endpoint due to death or loss to follow up, the total targeted sample size of cohort A and cohort B in this study is **102 patients (51 patients for each cohort)**.

(1/8/10) As of January 8, 2010, 11 patients were accrued to Cohort A, and 47 patients were accrued to Cohort B. Due to slow accrual for Cohort A, the decision was made to close this cohort and increase the sample size of Cohort B to test for a 15% absolute decrease in combined

toxicity rate (from 37 to 22%). A sample size of 66 patients is required, with a significance level of 0.05 and 85% power. Assuming approximately 5% of patients will be retrospectively deemed ineligible and an additional 15% will not have a 2-year assessment for the primary endpoint due to death or loss to follow up, **the total targeted sample size of cohort B is 83 patients**. Patients treated on cohort A will not be analyzed per the protocol endpoints but will be followed for adverse events to monitor safety.

Of note is that the sample sizes of Cohorts A and B are separately calculated, since patients in Cohort A receive chemotherapy while patients in Cohort B do not. Late radiation morbidity in Cohort A patients may be different from that in patients in Cohort B; therefore, a separate estimation of late radiation morbidity is adequate.

Since there is paucity of health-related quality of life (HRQOL) data available from sarcoma treatment trials, such data will be collected using 3 instruments (TESS, FACT-G, and SAQ) on this study. The results from this study will not provide definitive answers to any HRQOL related questions. Rather, the results from any analyses using these instruments will be considered exploratory to generate future hypotheses, for the following reasons: First, this study does not have a concurrent control arm. Secondly, the study is not statistically powered for any specific HRQOL question, and finally, patient participation in the HRQOL component is not mandatory for this study. Of these 3 instruments, only the TESS instrument was used in the NCIC CTG study. So the TESS results for Cohort B (preoperative arm RT only) from this study will be compared with TESS results for the preoperative RT arm of the previous NCIC CTG phase III study using individual patient data, if available. However, the statistical power to detect effect sizes of 0.33 and 0.50 based on the average TESS score and its standard deviation for the preoperative RT arm from the NCIC CTG study is inadequate at 0.30 and 0.57 given the sample sizes (projected 40 in this study and 60 observed in the NCIC CTG study). The effect sizes of 0.33 and 0.50 would translate into an increase in the average TESS score of 2.6 and 3.9 in this study.

13.3 Patient Accrual

RTOG 95-14 accrued approximately 1.9 patients with large (≥ 8 cm) and high grade sarcoma per month. A majority of patients with sarcoma of the extremity encountered in the clinic are anticipated to be eligible for this study. Therefore, we project an accrual of 3 patients with either low or intermediate-to-high grade sarcoma per month for this study. Allowing for approximately 6 months at the beginning of the study for institutional IRB approvals, patient accrual to this study should be completed in 40 months. Each cohort will be closed to accrual separately when it reaches the required 51 patients.

13.4 Analysis Plan

13.4.1 *Statistical Methods*

The rates of late radiation morbidity will be estimated using a binomial distribution. Only patients with a follow-up assessment between 21 and 27 months will be included. The rates of local, regional, and distant failure and second primary tumor will be estimated using the cumulative incidence method⁸¹ to account for the competing risk of death without failure. Overall, disease-free, and distant disease-free survival will be estimated using the Kaplan-Meier Method.⁸² Spearman's rank correlation coefficient will be used to assess the potential correlation between 2 factors. All estimates will be accompanied by their associated 95% confidence intervals.

The comparisons of the TESS and the MST5 scores at 2 years between Cohort B and the NCIC CTG preoperative RT arm will use the Wilcoxon rank sum test⁸³ because the data are expected not be normally distributed. These 2 comparisons initially will be done Wilcoxon rank sum test not for any other baseline variable because the NCIC CTG study showed on multivariate logistic analysis that field size was the only prognostic factor for late effects at 2 years. In 0630, treatment planning for IGRT uses the volume instead of field size, and it would not be possible to create field size as the patient was treated on the NCIC CTG study. The comparison between the SAQ scores for cohort A and the SAQ scores for cohort B will use the Wilcoxon rank sum test stratified by gender.

The mean and standard deviation will be reported for all HRQOL measures.

In addition to 2-year results, overall trends in the following 4 variables, late radiation morbidity, FACT-G, TESS, and SAQ, will be described with longitudinal data analysis. These assessments also will be collected at 12 and 18 months from the start of radiation. Specifically, the general linear mixed-effect model⁸⁴ will be used to describe the change trend of these scores over time between the treatment cohorts A and B in this study. The model allows for adjustments using other covariates of interest such as gender and age.

Since there will probably be missing observations at 2 years for late radiation morbidity, FACT-G, TESS, or SAQ, we will conduct a sensitivity analysis to determine the impact of their exclusion on the results if 20% or more patients have been excluded in a treatment cohort. The imputation of missing the 2-year observations for surviving patients will be performed with the Markov Chain Monte Carlo (MCMC) algorithm.⁸⁵ The following variables will be utilized in the imputations: treatment cohort, gender, age, KPS, primary site, race, MSTs, FACT-G, TESS, FACT-G, SAQ, and late morbidity.

13.4.2 Interim Analysis to Monitor Study Progress

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events. This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31. This study will be monitored by the Clinical Data Updated System (CDUS), version 3.0. Full reporting of cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.3 Interim Analysis to Monitor Local Failure Rate

After the first 30 eligible patients, regardless of cohort, have been followed for 18 months, an analysis to determine the local failure rate across cohorts in these 30 patients will be undertaken. Patients that do not meet the eligibility criteria (per Section 3.0) or do not start protocol treatment will be excluded. The IGRT quality assurance reviews (per Section 6.8) will have been completed for these patients by this time and will be available to the study chairs and statistician for comparison with local failure status. If the local failure rate is greater than 20%, then either the radiation therapy was not accurately delivered or the tailored fields/volumes for radiation defined in this study may not be adequate. If 50% of the local failures are marginal or outside-field recurrences (per Section 11.4), then no additional patients will be enrolled in this trial, and the local failure data will be reported.

13.4.4 Analysis for Reporting the Initial Treatment Results

The analysis reporting the initial treatment results will be performed after each patient has been potentially followed for 6 months. This analysis will focus on adverse events, including wound complications. No analysis of HRQOL measures will be reported at this time. All study endpoints will be evaluated separately by cohort. Patients that do not meet the eligibility criteria (per Section 3.0) or do not start protocol treatment will be excluded. All eligible patients that start protocol treatment, even if they receive a postoperative radiation boost, will be included. If patient accrual is finished much earlier (i.e., at least 1 year) for one cohort, the results for that cohort may be reported separately.

13.4.5 Analysis for Reporting the Final Treatment Results

The analysis reporting the final treatment results will be performed after each patient has been potentially followed for 2 years. This analysis will focus on 2-year late radiation morbidity, pattern of first failure, and 2-year HRQOL measures. The degree of late radiation morbidity (\geq grade 2 lymphedema, subcutaneous fibrosis, or joint stiffness) will be correlated with MSTs, FACT-G, TESS, and SAQ. The TESS scores will be correlated with the FACT-G scores. The SAQ scores for Cohort A will be compared to the SAQ scores for Cohort B. The pretreatment characteristics reported in the NCIC CTG study also will be reported for RTOG 0630. The TESS and the MSTs scores will be compared between Cohort B in RTOG 0630 and the NCIC CTG preoperative RT arm without any adjustment and also with adjustment for any pretreatment characteristic where there is a difference of $> 20\%$ in the distributions between the 2 patient groups. All study endpoints will be evaluated separately by cohort. Patients that do not meet the eligibility criteria (per Section 3.0) or do not start protocol treatment will be excluded. All eligible patients that start protocol treatment, even if they receive a postoperative

radiation boost, will be included. If the patient accrual is finished much earlier (i.e., at least one year), for one cohort, the results for that cohort may be reported separately.

13.5 Gender and Minorities

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, we also have considered the possible interaction between race and treatments. Based on the accrual statistics from RTOG 95-14, we project that 80% of patients enrolled to this study will be white, and 20% black. The following table lists the projected accrual for each group.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	0	0	0
Not Hispanic or Latino	44	58	102
Ethnic Category: Total of all subjects	44	58	102
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	4	16	20
Native Hawaiian or other Pacific Islander	0	0	0
White	40	42	82
Racial Category: Total of all subjects	44	58	102

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APPENDIX I

RTOG 0630

Informed Consent Template for Cancer Treatment Trials **(English Language)**

A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

(7/3/12) You are being asked to take part in this study because you have a soft tissue sarcoma of your arm, shoulder, leg, or hip. Your doctor has recommended that you receive radiation therapy and surgery to treat the sarcoma.

Why is this study being done?

When treated with surgery alone, many soft tissue sarcomas have a high chance of coming back. Radiation therapy is frequently used in addition to surgery to reduce the chances of the sarcoma coming back. However, radiation can have long-term side effects on the normal tissues surrounding the tumor, such as swelling, scarring, and joint stiffness.

Recently, there have been advances in the way that radiation therapy can be given, including the ability to precisely locate the tumor during radiation using image-guided radiation therapy (IGRT). With IGRT, it is possible to give radiation over a smaller area surrounding the tumor, with less radiation to the surrounding normal tissues.

The purpose of this study is to find out what effects, good and/or bad, IGRT has on you and your cancer. This study will find out whether IGRT decreases the long-term side effects of radiation on normal tissues. It also will find out if IGRT reduces the chances of the sarcoma coming back compared to the larger radiation fields that have been used in prior studies.

How many people will take part in the study? (1/8/10)

When this study began, it was planned that about 102 people would take part in this study, 51 in Group A and 51 in Group B.

As of January 8, 2010, Group A (patients receiving chemotherapy as well as radiation therapy) was closed because not enough patients had been enrolled to this group.

When Group A was closed, the study was redesigned, and about 83 people now will take part in Group B.

What will happen if I take part in this research study? (1/8/10)

Radiation Followed By Surgery

All patients will receive radiation as an outpatient, once a day, Monday through Friday. All patients will have surgery 4-8 weeks after radiation treatment is complete.

Required Submission of Tumor Tissue

Your study doctor will need to send some of the tumor tissue obtained at the time of your biopsy or surgery to a central office. There, a pathologist will confirm your type of tumor. This tissue submission for review is required for this study.

Group A (receiving chemotherapy) [Closed 1/8/10]

You will receive radiation as an outpatient, once a day, Monday through Friday, for about 22-25 days. Each radiation treatment takes up to 30 minutes. Your doctor will discuss the type, dose, and timing of chemotherapy (before or during radiation or after surgery) you receive.

Group B

You will receive radiation as an outpatient, once a day, Monday through Friday, for about 25 days. Each radiation treatment takes up to 30 minutes.

Radiation After Surgery

Patients with tumor cells at the edges of the tissue removed in surgery will receive radiation either during surgery (a large dose in 1 treatment) or will receive radiation after surgery (smaller doses, 1-2 treatments per day, for no more than 8 treatments). You and your doctor will talk about the type and dose of radiation that is best for you.

Before you begin the study (1/8/10)

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical examination
- Evaluation by a surgeon
- Evaluation of your ability to carry out daily activities
- MRI (Magnetic Resonance Imaging) with contrast of your tumor; MRI: Imaging using a strong magnetic field to look at one part of your body. Contrast: Dye injected into your vein to increase the differences between normal and abnormal tissue
- CT scan of your chest;
- For sarcomas of the upper thigh: A CT scan of the abdomen and pelvis
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- For women able to have children, a pregnancy test

During the study (1/8/10)

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

Before radiation treatment begins:

- A test of your thyroid gland function, if your gland is in area to be treated

During radiation:

- Weekly physical examinations to evaluate any side effects from treatment you may be having
- Evaluation of your ability to carry out daily activities
- Blood tests every other week (about 2 teaspoons of blood will be taken from your vein)

Prior to surgery:

- Physical examination
- Evaluation of any side effects from treatment you may be having
- Evaluation of your ability to carry out daily activities
- MRI or CT (Computed Tomography) scan with contrast of your tumor; A CT scan is a study using x-rays to look at one part of your body.
- CT scan of your chest

You will need these tests and procedures in follow-up visits: (1/8/10)

They are being done to see how you and your cancer was affected by the treatment you received.

Every 3 months in years 1-2 and every 6 months in years 3-5, then once a year:

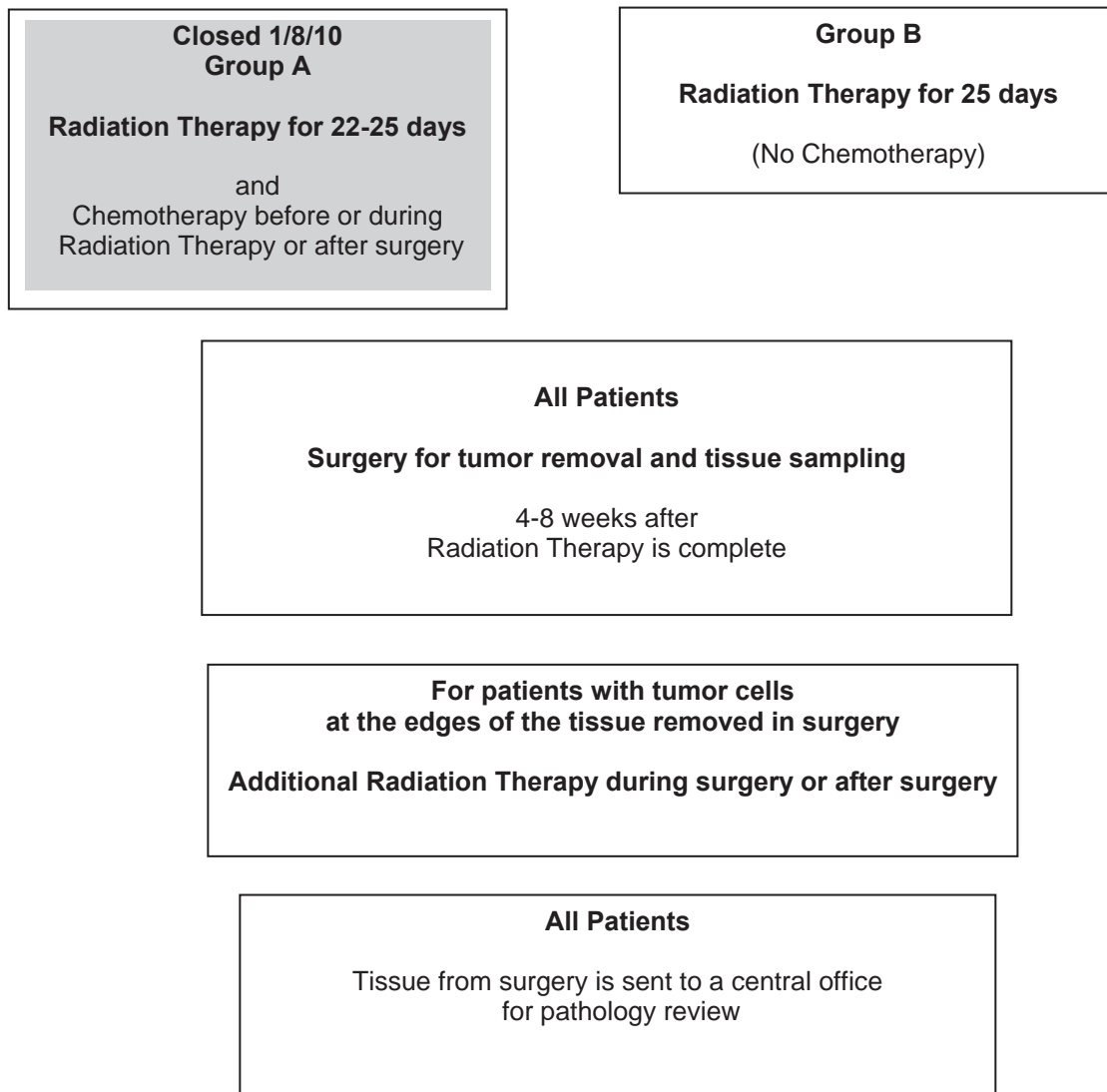
- Physical examination
- Evaluation of your ability to carry out daily activities
- Evaluation of any side effects from treatment you may be having

Every 6 months in years 1-2 and once a year in years 3-5, then once a year:

- MRI or CT scan with contrast of your tumor
- CT scan of your chest

Study Plan (1/8/10)

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study? (1/8/10)

All patients will receive radiation treatment for about 25 days, and all patients will have surgery 4-8 weeks after radiation treatment is completed.

Patients with tumor cells at the edges of the tissue removed in surgery will receive radiation either during surgery or after surgery. You can discuss the length of time of this radiation with your doctor.

Patients will be seen for follow-up visits at least every 3 months for years 1 and 2, although it may be more frequent, if your doctor recommends it. Then follow-up visits will take place every 6 months during years 3 through 5 and once a year after year 5 for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation treatment and/or surgery can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study? (1/8/10)

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop receiving radiation treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also a rare risk of death (less than 2 percent).

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to Radiation Therapy

Your doctor will use image-guided radiation therapy (IGRT) to deliver radiation to your tumor. A daily image (either CT scan or x-ray) will be taken prior to each radiation treatment to locate your tumor and check the accuracy of the planned radiation treatment. With IGRT, it is possible to give radiation over a smaller area surrounding the tumor, with less radiation to the surrounding normal tissues. This may reduce the long-term side effects on the normal tissues surrounding the tumor, such as swelling, scarring, and joint stiffness. However, there is a risk that your tumor could come back outside of this smaller radiation area.

In this study, you will receive radiation treatment before surgery, one of the standard treatments for your type of cancer. Receiving radiation therapy after surgery also is one of the standard treatments for your type of cancer. A Canadian study of radiation therapy after surgery showed that there were less complications of wound healing with radiation after surgery than with radiation before surgery. However, the complications of wound healing with radiation after surgery were generally more serious and long lasting than the complications with radiation before surgery.

You should discuss the possible benefits and risk of this treatment approach with your doctor.

The risks associated with radiation can be divided into early side effects (those happening during or shortly after radiation) and late side effects (those happening well after the completion of radiation). Sometimes after radiation,

the skin in the treated area may turn red, blister, and/or peel. In general, most radiation reactions (other than fatigue) are limited to the site being treated. For example, if your leg is being treated, you will not feel nauseated from radiation treatment. Your doctor will specifically identify those risks associated with the location of your tumor.

Early Side Effects

Likely

- Mild (slight redness) to severe (painful skin blistering) skin reactions
- Tiredness
- Reduction in blood counts, which may result in bleeding or infection
- Diarrhea (if the pelvis is treated)
- Wound healing delay after surgery

Late Side Effects

Likely

- Skin in the treated area may appear tanned and may stay this way for a number of years after radiation.
- Tissues in the treated area may feel hard and woody: If this occurs, it is likely to be permanent.
- Skin in the treated area, especially over the shin and elbow, may heal more slowly if injured or bruised.
- Pain in a treated limb, which may occur one to several years after completion of treatment and may last for many years.
- Swelling, which may occur in the first year after treatment; in many patients the swelling will go away. Some patients will have temporary swelling after they exercise. Some patients will have continual swelling and will need to use elastic stockings. If this swelling is severe, it may require the use of a pump that pushes swelling out of the arm or leg.
- Bones are more likely to break.

Less Likely

- Injury to the bowel (if abdominal wall is treated), such as a narrowing of the bowel or hole in the bowel and which may require surgery
- If the heart, lung, liver, or stomach is in the treatment area, these organs could be damaged, which may result in
 - Heart: dizziness, weakness, shortness of breath, chest pressure and/or pain, and/or irregular heart beat
 - Lung: Inflammation of the lungs, cough, shortness of breath
 - Liver and stomach: Tiredness, digestion problems, pain in the upper abdomen, bloating, constipation, nausea and/or vomiting

Rare but serious

- Injury to the spinal cord (if the back area is treated), which may result in weakness, muscle contraction, and/or loss of muscle function,
- Radiation can cause tumors in the tissues that were treated. This is rare (1 in 2,000) in adults but can occur many years after treatment.

Risks and side effects related to Surgery (1/8/10)

Complications may occur when tumors are removed from the legs or arms whether or not radiation is given. If you have other health problems such as heart disease, lung disease, or diabetes at the time of surgery, you may have an increased risk for having heart or lung problems during surgery. Rarely, these complications may result in death.

With surgery alone, some patients also will have problems with the healing of their wound after removal of the tumor. However, the addition of radiation may increase the risk of wound healing problems. However, most patients will heal satisfactorily.

Likely

- Decreased function of the arm or leg because of muscle, nerve, or skin damage

Less Likely

- Treatment of large tumors with radiation and surgery may result in infection or lack of healing, which could lead to a longer time in the hospital and rarely, to surgically removing the arm or leg.

Risks and side effects related to Blood Draws

Risks seen with taking blood from a vein in your arm include pain, bruising, lightheadedness, fainting, and, on rare occasions, infection.

Reproductive risks (1/8/10)

You should not become pregnant or father a baby while on this study because the radiation treatment in this study can affect an unborn baby. Women who can have children are required to have a pregnancy test before treatment on this study. Women should not breastfeed a baby while on this study. It is important you understand that you 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. Some methods might not be approved for use in this study. The radiation treatment may make you unable to have children in the future.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope that the addition of image-guided radiation therapy or IGRT to surgery will be more useful in reducing long-term side effects compared to larger radiation fields and surgery, there is no proof of this yet. We do know that the information from this study will help researchers learn more about IGRT as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting the following treatments or care for your cancer without being in a study
 - Large field radiation followed by surgery is one of the standard treatments of your type of cancer.
 - Surgery followed by radiotherapy is one of the standard treatments of your type of cancer.
 - Surgery alone
 - Large field radiation, surgery, and chemotherapy
- Taking part in another study
- Getting no treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number)*. *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to each of the following studies. Below, please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of Life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete 3 questionnaires at the following times: before starting protocol treatment and at 12, 18, and 24 months from the start of treatment. It takes about 10-15 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the three Quality of Life Questionnaires.

YES

NO

Consent Form for Use of Tissue, Blood, and Urine for Research

About Using Tissue, Blood, and Urine for Research (4/20/09)

You will have a biopsy to see if you have cancer, and you will have surgery to remove the tumor. Your doctor will remove body tissue during the biopsy and surgery to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: <http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>

We also would like to collect some of your skin tissue before radiation, and for patients who have surgery: during surgery and once a year after surgery for 2 years. If you agree, you will receive some type of numbing medicine (anesthetic) before your doctor removes a small round piece of skin (usually the size of a pencil eraser) using a sharp, hollow instrument. The risks associated with this skin biopsy include swelling, bleeding, and infection at the biopsy site.

In addition, we would like to keep about 4 teaspoons of your blood and 6-7 tablespoons of your urine for future research. Your blood and urine will be collected prior to radiation treatment, during surgery, and once a year during years 1 and 2.

Your tissue, blood, and urine may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue, blood, and urine will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue, blood, and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue, blood, and urine. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it and the blood and urine will be destroyed.

In the future, people who do research may need to know more about your health. While the (doctor/institution) may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new products in the future.

Benefits

The benefits of research using tissue, blood, and urine include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice (10/13/09)

Please read each sentence below and think about your choice. **After reading each sentence, circle "Yes" or "No"**. If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
 - Tissue Yes No
 - Blood Yes No
 - Urine Yes No
2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
 - Tissue Yes No
 - Blood Yes No
 - Urine Yes No

3. Someone may contact me in the future to ask me to take part in more research.
 Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II: STUDY PARAMETER TABLE
 (*See Sections 11.2 & 11.3 for details and exceptions) [4/20/09, 10/13/09, 1/8/10]

Assessments	Pretreatment			During Radiation Treatment	Prior to Surgery	Follow Up	
	Within 8 wks of registration	Within 2 wks of registration	Prior to the start of RT			Every 3 mos. in years 1-2	Every 6 mos. in years 3-6
Biopsy	X						
History/physical & weight	With height and location, size, stage of tumor			See Section 11.2.4	X	X	X
MRI or CT scan with contrast of tumor	MRI with contrast only; no CT scan pretreatment				X* Can be either MRI or CT scan	q 6 mos. Can be either MRI or CT scan	annually Can be either MRI or CT scan
CT of chest	X				X*	q 6 mos.	annually
CT of abdomen & pelvis	For sarcomas of the thigh						
Surgeon Eval							
Performance status				X	X	X	X
CBC w/ diff & ANC		X		X*			
Serum pregnancy test (if applicable)		X (see Section 3.1.7)					
Tissue for central review	X				In surgery		
Thyroid function test			If thyroid is in RT field				
MSTS			X			* See Section 11.7	
FACT-G, TESS, SAQ			X			*See Section 11.8	
Tissue, blood, urine for research		Recommended			Recommended		Recommended annually for 2 years

APPENDIX III (4/20/09)

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all pre-disease activities without restriction**
- 1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
- 4 Completely disabled. Cannot carry on self-care. Totally confined to bed or**
- 5 Death**

APPENDIX IV

Staging System for Soft Tissue Sarcomas (AJCC, 6th ed.)

Grade and TNM definitions

Tumor grade (G)

- GX: Grade cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor 5 cm or less in greatest dimension
 - T1a: Superficial tumor [*Note: Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia, or superficial and beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.]*]
 - T1b: Deep tumor
- T2: Tumor more than 5 cm in greatest dimension
 - T2a: Superficial tumor
 - T2b: Deep tumor

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

APPENDIX IV (Continued)

Stage I

- G1-2, T1a, N0, M0
- G1-2, T1b, N0, M0
- G1-2, T2a, N0, M0
- G1-2, T2b, N0, M0

Stage II

- G3-4, T1a, N0, M0
- G3-4, T1b, N0, M0
- G3-4, T2a, N0, M0

Stage III

- G3-4, T2b, N0, M0

Stage IV

- Any G, any T, N1, M0
- Any G, any T, any N, M1

APPENDIX V (10/2/08, 10/13/09)

Fresh Frozen Tissue and RNA^{later}™ Preserved Tissue Kit and Instructions

Sites can call or e-mail the RTOG Biospecimen Resource with questions (contact information below) or to request fresh tissue collection kits.

Instructions for processing Fresh Tissue for RTOG 0630:

- A. If you have access to liquid nitrogen (preferred method), please follow the **Fresh Frozen Tissue Kit Instructions** below.
- B. If you do not have access to liquid nitrogen, please follow the **Fresh Preserved Tissue in RNA^{later}™ Kit** instructions below.

A. Fresh Frozen Tissue Kit Instructions

This kit includes:

- Biohazard pads/wipes 4" x 4" (orange)
- Two (2) 5 ml cryovials
- Disposable scalpel
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label
- UN 3373 sticker
- UN 1845 Dry Ice sticker

Preparation of Fresh Frozen Tissue:

Process:

1. On clean cutting board, lay out the under pads. Alternatively, a sterile petri dish may be used to section tissue.
2. Keep biohazard wipes nearby to keep area clean throughout process.
3. Label cryovials with RTOG study number, RTOG case number and pathology accession number, collection date and time, time point of collection, and clearly mark as "Fresh Frozen Tissue".
4. Using provided disposable scalpel, obtain at least one 5 mm³ section of fresh tissue. (Note: If a frozen core was obtained, do not cut but send it whole).
5. Use sterile or disposable forceps to place each piece of tissue into individual 5 ml cryovials.
6. Snap freeze tissue samples in liquid nitrogen.
7. Once frozen, place all of the cryovials into biohazard bag.

Storage Conditions:

Store at -80° C (-70°C to -90°C) until ready to ship on dry ice. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

- **OR:**

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).

- **OR:**

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

B. Fresh Preserved Tissue in RNA^{later}™ Kit instructions: This kit is used when liquid nitrogen is not available to snap freeze the tissue as in instructions (A) above for frozen tissue processing.

This kit includes:

- Biohazard pads/wipes 4" x 4" (orange)
- Two (2) 5 mL cryovials containing RNA^{later}™
- Biohazard bags
- Absorbent shipping material

Continued on next page

APPENDIX V (Continued)

- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label
- UN 3373 Sticker

Preparation of Fresh Preserved Tissue in RNAlater™:

Process:

1. On clean cutting board, lay out the under pads. Alternatively, a sterile petri dish may be used to section tissue.
2. Keep biohazard wipes nearby to keep area clean throughout process.
3. Label cryovials with RTOG study number, RTOG case number and pathology accession number, collection date and time, time point of collection, and clearly mark as “Fresh Tissue- RNAlater”.
4. Using a sterile or disposable scalpel, cut at least one 3 mm³ section of fresh tissue (Note: If a tumor core was obtained, do not cut but send it whole).
5. Use sterile or disposable forceps to place each piece of tissue into individual 5 mL cryovials filled with RNAlater™.
6. Make sure that the RNAlater™ completely covers the specimen.
7. Place the cap on the cryovial and seal tightly.
8. Place labeled cryovial(s) in a biohazard bag.
9. Store refrigerated at 4° Celsius until ready to ship (Can be stored up to 30 days).
10. Ship at 2 - 8° Celsius using a cold (not frozen) gel pack.

Shipping/Mailing:

- ❑ Place all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap each cryovial in absorbent shipping material and then place into a separate biohazard bag. Wrap the biohazard bag with some additional padding (paper towels)
- ❑ **For Frozen Cryovials:**
 - **Wrap frozen specimens in absorbent shipping material and then place in a biohazard bag. Use extra padding (paper towels) around plastic bags to prevent the dry ice from crushing or breaking the vials during transport. Place specimen bag in a Styrofoam cooler and fill with dry ice (4-5 lbs/ 2-2.5 kg minimum of dry ice, more during hot weather). Place Styrofoam cooler into outer cardboard box, and attach shipping label, UN 1845 dry ice label and UN3373 Biological Substance Category B sticker to outer cardboard box.**
- ❑ **For RNAlater™ preserved Tissue:**
 - **Place specimens in Styrofoam cooler with a cold (not frozen) gel pack. Place Styrofoam cooler into outer cardboard box, and attach shipping label and UN3373 biological substance category B to outer cardboard box.**
- ❑ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
- ❑ Send samples by overnight mail **Monday through Wednesday (Monday or Tuesday from Canada)**. Saturday and holiday deliveries cannot be accepted. Send samples within one (1) week of collection.
- ❑ For Questions regarding collection, shipping or to request a frozen specimen kit RNAlater™ kit, please email RTOG@ucsf.edu or phone (415)476-7864.

Sites must submit the required documentation according to Section 10 of the protocol with specimens. All specimens will be shipped to:

FedEx/Courier address (all courier packages & frozen samples)
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115
415-476-7864

**APPENDIX VI (10/2/08, 10/13/09)
RTOG Specimen Plug Kit and Instructions***

The Specimen Plug Kit contains a shipping tube and a punch tool. Sites can call or e-mail the RTOG Biospecimen Resource with questions (contact information below) or to request additional specimen Plug Kits.



Step 1

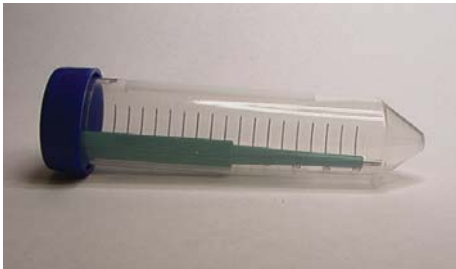
Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2

Label punch tool with proper specimen ID. DON'T try to remove specimen from the punch

Use a separate punch tool for every specimen. Please do not mix specimens. Call or email us if you have any questions or need additional specimen plug kits.



Step 3

Once punch tool is labeled, place in shipping tube and mail to address below.

At the Biospecimen Resource, the specimen will be removed from the punch, embedded in a cassette, and labeled with the specimen identification.

***NOTE:** If an institution is uncomfortable obtaining the plug but wants to retain the tissue block, the institution should send the entire tissue block to the RTOG Biospecimen Resource. The Biospecimen Resource will sample a plug from the tissue block and return the remaining block to the institution. Sites must document the request to perform the plug procedure and return the block on the Specimen Transmittal Form.

Ship: Specimen Plug Kit, specimen in punch tool, and all paper work as follows:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX VII (10/2/08, 10/13/09)
RTOG Blood Collection Kit and Instructions

Instructions for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:

- Twelve (12) 1 ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN 3373 Sticker
- UN 1895 Dry Ice Sticker

Serum (if requested):

- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
3. Aliquot 0.5-1 ml serum into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected, and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and store serum frozen until ready to ship. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (If requested):

- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
4. Carefully pipette and aliquot 0.5-1 ml plasma into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma".
5. Place cryovials into biohazard bag and store plasma frozen until ready to ship. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buffy coat (if requested):

For a visual explanation of Buffy coat, please refer to diagram below.

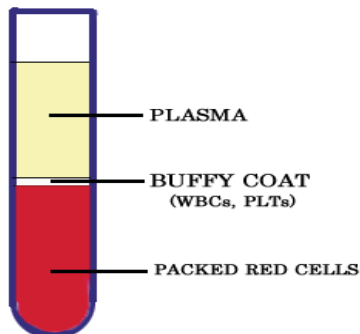
- Using one (1) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) "buffy coat".

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).

Blood Collection (Continued)

4. Remove the buffy coat cells carefully and place into cryovials labeled "buffy coat" (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date/time of collection and time point collected.
5. Place cryovials into biohazard bag and store buffy coat frozen until ready to ship. See below for storage conditions.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Storage:

- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
If a -80°C Freezer is not available,
 - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
 - OR:
 - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).
 - OR:
 - Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

*RTOG labels are obtained at the time of patient registration. **PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

Shipping/Mailing:

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Ship specimens overnight frozen on Dry Ice **Monday-Wednesday. (Monday-Tuesday for Canada)**
Avoid shipping on a weekend or around a holiday.
- ❑ Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is still plenty of space for 10 lbs of Dry Ice.*

Ship: Specimens and all paper work as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX VIII (10/2/08, 10/13/09)
RTOG Urine Collection Kit and Instructions

Sites can call or e-mail the RTOG Biospecimen Resource with questions (contact information below) or to request urine collection kits. This kit includes:

- One (1) Sterile Urine collection cup
- Biohazard bags

Instructions for use of urine collection kit:

Preparation for collecting **urine**:

- A clean catch urine specimen will be collected.

Process:

1. To collect the specimen, use the following instructions:
 - Males should wipe clean the head of the penis and females should wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
 - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
 - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
 - Finish voiding the bladder into the toilet bowl.
 - Place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
2. Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimen as "urine".
3. If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
4. Place urine cup into biohazard bag and seal the bag.
5. Immediately freeze urine sample at -20°C.
6. Store specimens frozen at -20°C until ready to ship.

Shipping/Mailing:

- ❑ Urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag).
- ❑ Urine specimens may be sent in batches, if within 30 days of collection, but *make sure each specimen is in a separate bag*. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs/2-2.5 mg minimum). Seal the box with plastic tape.
- ❑ All RTOG paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box.
- ❑ Note: Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box "biohazard".
- ❑ Ship specimens overnight express on **Monday – Wednesday (Monday or Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Samples received thawed will be refrozen and held. A notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date, if possible.

Sites must submit the required documentation with specimens. All specimens will be shipped as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115
Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu