NCI National Clinical Trials Network

S2505
Protocol Summary Sheet

Phase III Randomized Study Testing Non-Inferiority of Short-Course Ultra Hypofractionated Radiation (UHRT-5) Versus Standard Fractionation (RT-25) For Stage II-IIIB, Extremity, Resectable Soft Tissue Sarcoma

Target Accrual: 296

Study Chair:
Jeremy Harris, MD, MPhil

Study Co-Chair:
Lara Davis, MD

ECOG-ACRIN Study Champion:
Sibo Tian, MD

Inclusion / Exclusion Criteria

See Section 5 of the Protocol for Complete Eligibility Criteria

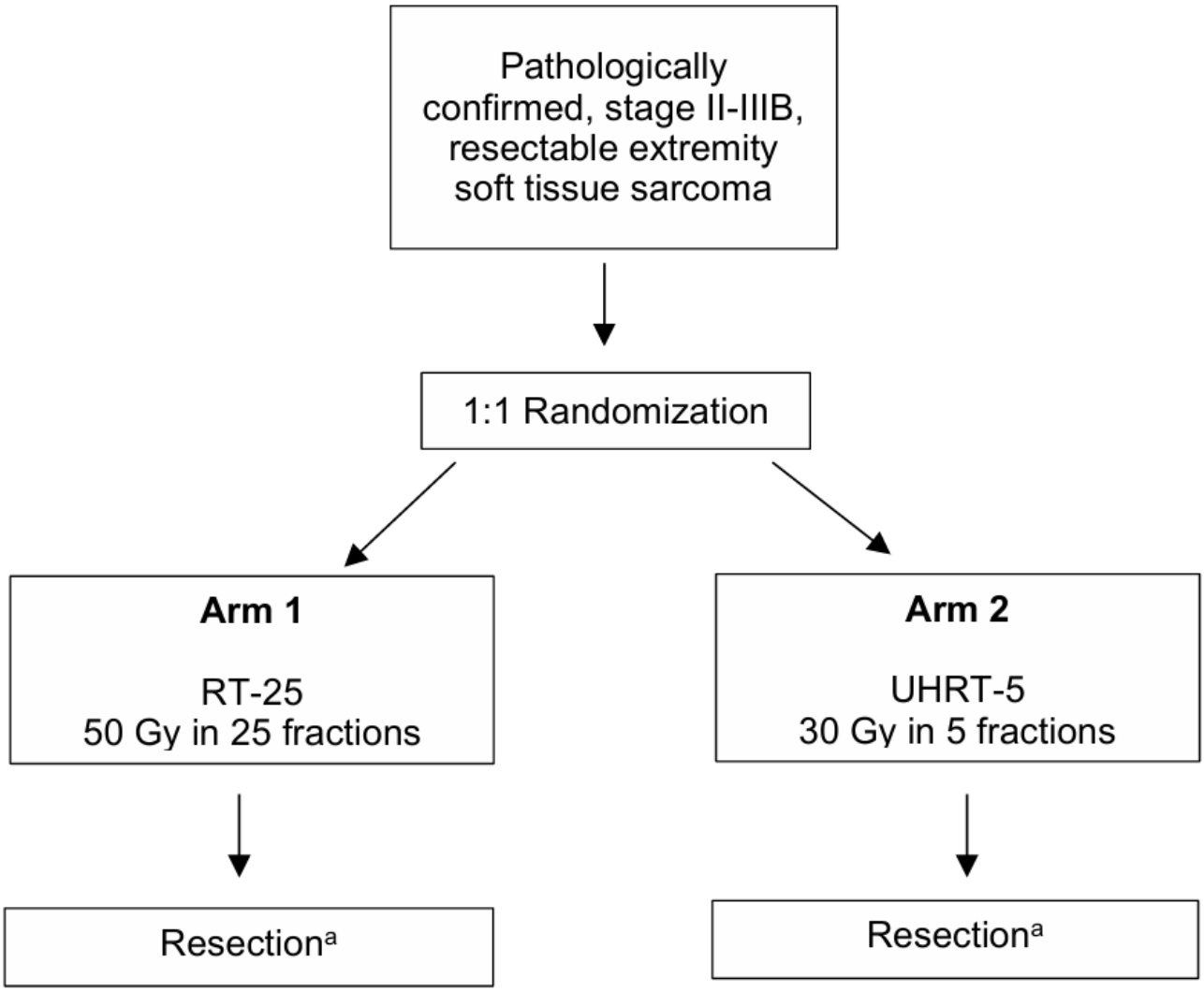
- Must have histological evidence of a soft tissue sarcoma from core or incisional biopsy. Participants must have a primary or locally recurrent tumor. Stage II-IIIB (by AJCC 8th edition) soft tissue sarcoma is required. See 5.1a.
- Must have a primary site of disease in the extremity, including the shoulder girdle and hip girdle but excluding the hands and feet. See 5.1b.
- Must have an MRI of the primary site within 90 days prior to randomization. The MRI field of view must contain the entirety of the tumor. See 5.1c.
- Must have no evidence of metastatic disease by CT imaging of the chest (or PET CT), within 28 days before randomization. See 5.1d.
- Must not have fungating tumor. (i.e., tumor breakthrough of skin).
- Must not have myxoid liposarcoma, embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, gastrointestinal stromal tumor, osteosarcoma, NTRK-rearranged spindle cell neoplasm, desmoplastic small round cell tumor, Ewing sarcoma, or sarcoma arising from bone.
- Must not have known brain metastases.
- Must have been evaluated by a surgeon, and it must have been determined that they are a good candidate for a limb salvage resection with an expectation of negative margins, within 35 days prior to randomization. Anticipated positive margins on fixed critical structures are allowed.
- Must not have had prior treatment for the current tumor (systemic therapy, radiation, or complete surgical resection).
- Must not have had prior radiation to the anatomical site.
- Must be ≥ 18 years old at the time of randomization and have Zubrod PS of 0-2.
- Must not have a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) has the potential to interfere with the safety or efficacy assessment of the investigational regimen.
- Participants with a history HIV-infection must be on effective anti-retroviral therapy at registration and have undetectable viral load test on the most recent test results obtained within 6 months prior to registration.
- Must not have uncontrolled intercurrent illnesses.

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S2505

Schema

See Section 7 of the Protocol for Treatment Details



[a]Surgery will take place 22-56 days following radiation completion.

SWOG CANCER RESEARCH NETWORK

CTSU Cancer Trials Support Unit
A SERVICE OF THE NATIONAL CANCER INSTITUTE
Linking practice to progress

THIS PROTOCOL SUMMARY SHEET IS INTENDED TO BE USED AS A REFERENCE TOOL *ONLY* AND SHOULD NOT BE USED IN PLACE OF THE PROTOCOL.

Clinical trial summary (S2505)

Testing Short-Course Radiation Versus Standard-Course Radiation for Soft-Tissue Sarcomas That Need Surgery and Radiation

What is the purpose of this clinical trial?

This trial asks whether using radiation therapy for a shorter time period before surgery works as well as using radiation for the usual period in people with **high-risk soft-tissue** sarcoma in the arm or leg.

Soft-tissue sarcoma is a rare cancer that starts in muscle, fat, blood vessels, or other types of soft tissue in the body. In this study, "high risk" means the cancer is likely to come back if people have surgery without getting radiation.



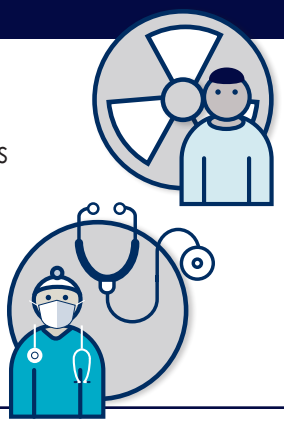
This trial is set up to find out:

- If radiation for a shorter period (short-course radiation) works as well as radiation for the usual period (standard-course radiation) at keeping the cancer from coming back
- What complications short-course radiation and standard-course radiation can cause

Why is this trial important?

The standard treatment for high-risk soft-tissue sarcoma in the arm or leg is radiation therapy followed by surgery to remove the cancer. Researchers think that lowering the number of radiation treatments could work as well as standard-course radiation at keeping the cancer from coming back after surgery. This short-course radiation could also cost patients less money and allow them to have surgery to remove the cancer sooner.

This is the first study to directly compare these 2 treatment approaches to find out which may be the better option for patients.



Who can be in this trial?

This trial is for adults, age 18 or older, with high-risk soft-tissue sarcoma.

This trial is for people who:

- Have sarcoma in the arm or leg (but not the hand or foot)
- Are able to have surgery to remove the sarcoma

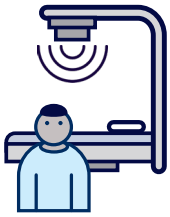
This trial is not for people who:

- Have sarcoma anywhere besides the arm or leg
- Were already treated for sarcoma, unless it has come back in the same location
- Are pregnant or breastfeeding

What treatments will I get?

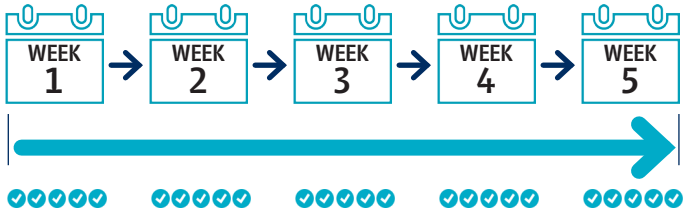
Everyone in the study will get radiation therapy followed by surgery to remove the cancer. Radiation therapy uses X-rays to kill cancer cells. It's targeted specifically at the part of the body with cancer rather than traveling through the whole body.

A computer will randomly assign you to one of 2 study groups.



Group 1: Usual Treatment

- First you'll get **standard-course radiation therapy**: 25 radiation treatments over 5 weeks.
- Then you'll have surgery to remove the cancer.



Group 2: Study Treatment

- First you'll get **short-course radiation therapy**: 5 radiation treatments over 1 week.
- Then you'll have surgery to remove the cancer.



Your doctor won't have control over which group you're assigned to. This helps make sure the study results are fair and reliable.

How long will I be in the trial?

You'll be in the study for 10 years.

During the treatment part of the study, you'll have visits with the study team so they can check for side effects. After surgery, you'll have visits so they can watch to see if the cancer comes back.

For the first 5 years, you'll have a visit at least once every 6 months. After that, you'll have a visit once a year.

Are there costs? Will I get paid?

Ask your health care provider and insurance provider about what costs will and won't be covered in this study.

You will not be paid for joining the study.

Where can I find more information about this trial?

- Talk with your health care provider
- Call the National Cancer Institute at **1-800-4-CANCER**
- Go to www.ClinicalTrials.gov and search the national clinical trial number: **NCT07615049**
- For a list of trial locations, visit **swog.org/NCI-S2505**

Key information

Protocol number: S2505
NCT number: NCT07615049
Trial sponsor: SWOG Cancer Research Network
Publishing date: June 16, 2026

Full trial title: Phase III Randomized Study Testing Non-Inferiority of Short-Course Ultra-Hypofractionated Radiation (UHRT-5) Versus Standard Fractionation (RT-25) for Stage II-IIIB Extremity, Resectable Soft Tissue Sarcoma

Thank you!

When you join a clinical trial,
you're moving cancer medicine and patient care forward.

Welcome to the S2505 Kick Off Meeting

We are looking forward to your active participation and feedback.

- **There will be time at the end of the meeting for open forum discussion and Q&A.**

Hybrid Meeting Logistics:

- When asking questions or contributing to the discussion:
  - **In-person participants**: **Please use the in-room microphones (and ensure that the microphone is turned on), so that your question/contribution can be heard by all in-person and online participants.**
  - **Online participants**:
    - During the presentation: Please place any questions in the **chat box**.
    - During open forum discussion: Please "**raise your hand**" and then un-mute yourself when called upon to contribute to the discussion. **If you are not speaking, please mute your line.**
- **This meeting is being recorded.**
  - The meeting slide set and recording will be posted via the SWOG.org website and CTSU CLASS learning management system (as a resource link under the current S2505 Optional Site Initiation Training course).
- Meeting attendance is optional. We will not be providing certificates of attendance.



The meeting will begin at 2:00 PM CT.

S2505

Phase III Randomized Study Testing Non-Inferiority of Short-Course Ultra-Hypofractionated Radiation (UHRT-5) Versus Standard Fractionation (RT-25) for Stage II-IIIB Extremity, Resectable Soft Tissue Sarcoma

NCT # 07615049

Study Chair:
Jeremy Harris, MD, MPhil (Radiation Oncology)

Medical Oncology Chair:
Lara Davis, MD

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David Konieczkowski, MD, PhD

Orthopedic Surgery Chair:
Thomas Scharschmidt, MD, FAOA, FACS, MBOE

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Champions

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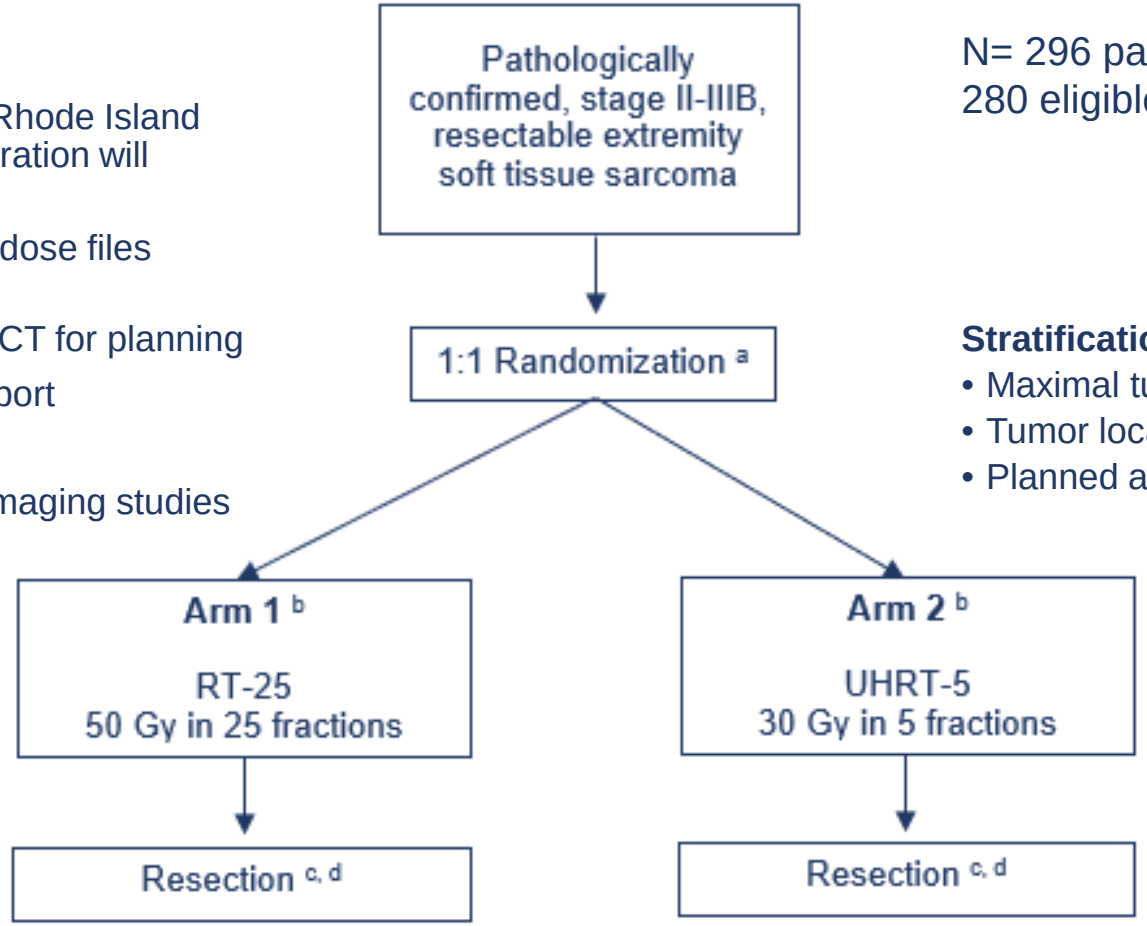
Schema

Submission of treatment plans to IROC Rhode Island via TRIAD within 14 calendar days of registration will include:

- Planning CT scan; structures; plan; and dose files (as DICOM RT)
- MRI (or any other images) registered to CT for planning
- Treatment planning system summary report
- RT-1 Dosimetry Summary Form
- Copies (DICOM format) and reports of imaging studies used to define target volume

Required if Participant Consents:

- **Biospecimen Banking**
  - FFPE tissue and 10 ml whole blood (in EDTA tubes) at timepoints indicated in Protocol Section 15.2.



N= 296 participants to achieve
280 eligible participants (140/arm)

Stratification based on:

- Maximal tumor dimension (≥ 10 cm versus < 10 cm)
- Tumor location (upper extremity versus lower extremity)
- Planned adjuvant systemic therapy (yes versus no)

[a] Site submits the simulation plan via TRIAD no more than 14 calendar days after randomization to allow time for central QA review (up to 3 business days for initial review) and subsequent plan revisions (allow another 3 business days for review of plan revisions) prior to start of radiation treatment.

[b] Radiation treatment should start no more than 21 calendar days after randomization.

[c] Surgery will take place 22-56 days following radiation completion. The latest allowable time from randomization to completion of surgery:
Arm 1 = 126 days
Arm 2 = 91 days

[d] After completion of S2505 treatment (radiation and surgery), adjuvant therapy is allowed at the discretion of the treating physician. See Protocol Section 7.6.

Background

- In the phase II study RTOG 0630, a preoperative dose of 50 Gy in 25 fractions resulted in a 2-year local failure of 11% [1].
- Radiation courses are typically lengthened to achieve higher total doses while allowing DNA repair to occur within healthy, non-malignant cells.
- For tumors with smaller alpha/beta ratios, larger doses per fraction may result in improved cell kill without the need for lengthy courses. In soft-tissue sarcoma, it has been established that the alpha/beta ratio is 3-5 Gy [2-4].
- Using an alpha/beta of 4 Gy, the standard preoperative dose is comparable to 30 Gy in 5 fractions. Many recent single-arm studies employed hypofractionation [5-10].

1. Wang 2015, PMID 25667281
2. Thames 1986, PMID 3700173
3. Haas 2016, PMID 26718153
4. Haas 2021, PMID 33914890
5. Kalbasi 2020, PMID 32054730
6. Nikitas. 2025, PMID: 41405883
7. Bedi 2022, PMID 35647402
8. Kubicek 2021, PMID 35387414
9. Guadagnolo 2022, PMID 36343656
10. Ahmed 2025, PMID 40389098

Rationale

- There has not been a randomized, head-to-head study comparing standard to hypofractionated radiation.
- Such a randomized trial is necessary to evaluate the hypothesis that the hypofractionation doses chosen from radiobiologic modeling do not result in higher rates of local failure.

Study Objectives (1)

Primary Objective

- To evaluate whether the incidence of local tumor recurrence at 2-years with short-course radiation is non-inferior to standard-course radiation

Secondary Objectives

- Acute wound complications.
- Late-term complications at 2-years post surgery.
- Physician-assessed functional outcome from pre-randomization to 12 and 24 months post surgery using the Musculoskeletal Tumor Society Scoring system.
- Overall survival, progression-free survival, and distant-metastasis-free survival

Study Objectives (2)

Exploratory Objectives:

- Local tumor recurrence at 2 years using a per-protocol analysis.
- Delayed wound healing.
- Type of surgical resection by treatment arm, including limb-salvage versus amputation and margin status (R0, R1, or R2).
- Supportive therapy medications
- Adjuvant therapy

Banking Objective

- To bank tissue specimens for future correlative studies.

Statistical Considerations

- The primary endpoint is time to local tumor recurrence measured from randomization, with death analyzed as a competing event.
- 296 participants will be enrolled (corresponding to 280 participants [140/arm] allowing for 5% eligibility inflation) with an expected rate of approximately 9 pts/month.
- There is 85% power to detect non-inferiority of the experimental arm assuming a 2-year failure rate of 11% in both arms, a non-inferiority margin of 10%, and a 1-sided alpha of 5%.
- The final analysis will be completed after the minimum follow-up on participants without local tumor recurrence event or death is 2 years.

Statistical Considerations – Interim Analyses (1)

- 2 Safety Analyses – 1st at 60 patients (30 per arm) and 2nd at 120 patients (60 per arm)
  - For both: The rate of acute wound toxicities within 4-months after resection
  - For both: If the difference is significant ($p < 0.05$), then early termination of accrual will be considered
- 1 interim harm and 1 interim futility analysis:
  - For both: Estimates of 1-year local tumor recurrence rates by arm
  - Interim Harm Analysis – 1 year after randomization of the 70th eligible participant (25% accrual).
    - Potential harm: >10% difference between arms (non-inferiority margin)
  - Futility Analysis – Among the first 100 participants
    - Futility: >10% higher local recurrence in experimental arm (evidence that the experimental arm is not non-inferior)

Statistical Considerations – Interim Analyses (2)

- Non-compliance – monitored routinely after first 40 patients (20 per arm). For trial to remain feasible, it will require:
  - a maximum non-compliance rate of 15%
  - a maximum non-compliance of adjuvant therapy based on pre-randomization declaration of 20%

Key Eligibility – Disease Criteria (1)

- Histological evidence of Stage II-IIIB (by AJCC 8th edition) soft tissue sarcoma from core or incisional biopsy and a primary or locally recurrent tumor.
  - Participants who have prior partial excision or partial excisional biopsy of the tumor, even if there is evidence of gross residual disease, or who have undergone any prior surgical procedure or biopsy resulting in complete removal of the tumor with no gross residual disease remaining are not eligible.
- Primary site of disease in the extremity, including the shoulder girdle and hip girdle but excluding the hands and feet.
  - Extension of the primary tumor into adjacent regions (e.g. torso, hands, feet) is allowed.
  - Primary sites of trunk, head, neck, or intra-abdominal, intra pelvic, or retroperitoneal region are not eligible.
- MRI of the primary site within 90 days prior to randomization.
  - The MRI field of view must contain the entirety of the tumor (may be accomplished with multiple MRI scans).
  - MRI must contain axial acquired T1 weighted with fat suppression, T1 weighted sequence with gadolinium contrast with fat suppression, and T2 weighted fat suppression sequence.

Key Eligibility – Disease Criteria (2)

- No evidence of metastatic disease by CT imaging of the chest (or PET CT), within 28 days before randomization.
- No fungating tumor (i.e., tumor breakthrough of skin).
- No myxoid liposarcoma, embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, gastrointestinal stromal tumor, osteosarcoma, NTRK-rearranged spindle cell neoplasm, desmoplastic small round cell tumor, Ewing sarcoma, or sarcoma arising from bone.
- No known brain metastases.
  - Brain imaging studies are not required.
  - If brain imaging studies are performed, they must be negative for disease.

Key Eligibility – Prior/Concurrent Therapy Criteria

- Participants must have been evaluated by a surgeon, and it must have been determined that they are a good candidate for a limb salvage resection with an expectation of negative margins, within 35 days prior to randomization.
    - Anticipated positive margins on fixed critical structures are allowed.
- No prior treatment for the current tumor (systemic therapy, radiation, or complete surgical resection).
- No prior radiation to the anatomical site.

Key Eligibility – Clinical Laboratory Criteria

- ≥ 18 years old at the time of randomization.
- Zubrod Performance Status of 0-2.
- Medical history and physical exam within 28 days prior to randomization.
- No prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen.
- Not pregnant or nursing.
- No uncontrolled intercurrent illnesses or any other significant condition(s) that would make this protocol unreasonably hazardous.
- Participants with a history of human immunodeficiency virus (HIV)-infection must be on effective anti-retroviral therapy and have undetectable viral load test.

Treatment Administration: Allowable Concomitant Medication and Supportive Care

- Neoadjuvant or concurrent chemotherapy or immunotherapy is not allowed.

Treatment Administration: Radiation Therapy

- Arm 1 – RT-25: RT-25 is given daily for 25 fractions. The shortest duration this may be given is 32 calendar days. To allow for holidays, unexpected machine down-time, and toxicity related delays, the maximum time allowed is 49 days. Treatment more than once per day is not allowed.
  - The prescribed dose to the primary tumor will be 5000 cGy delivered in 25 fractions (200 cGy per fraction) at no more than 5 fractions per week.
- Arm 2 – UHRT-5: UHRT-5 is given daily for 5 fractions. The shortest duration this may be given is 5 calendar days. To allow for holidays, unexpected machine down-time, and toxicity related delays, the maximum time allowed is 14 days. Treatment more than once per day is not allowed.
  - The prescribed dose to the primary tumor will be 3000 cGy delivered in 5 fractions (600 cGy per fraction).

Treatment Administration: Radiation Therapy

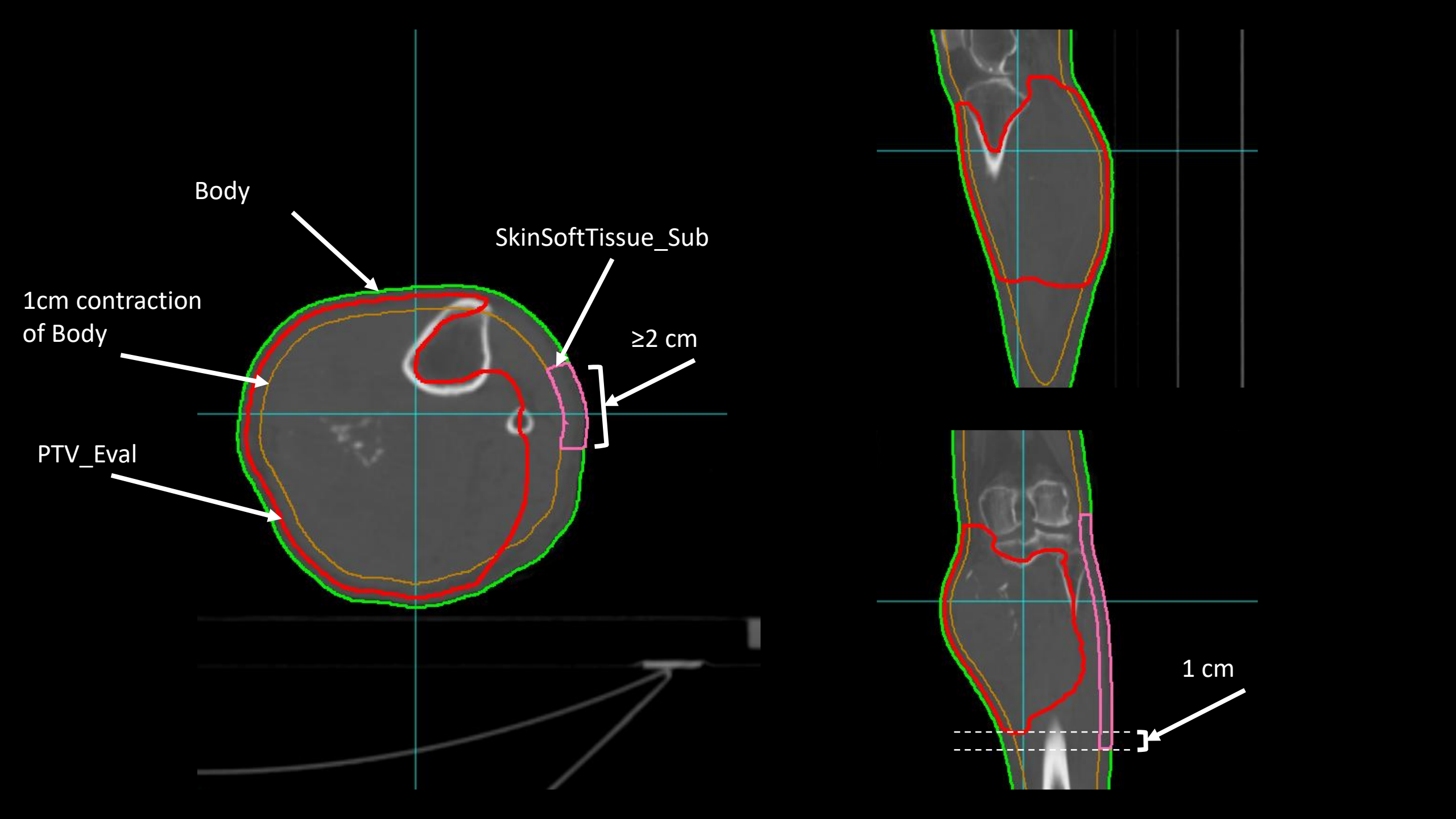
- No radiation dose reduction is allowed.
- Allowable radiation treatment techniques are 3D-conformal (3D CRT) or intensity modulated radiation therapy (IMRT), both with image guidance. IMRT is strongly recommended unless specific factors indicate the use of 3D CRT in an individual case.
- Proton therapy and electron therapy are not allowed.
- Use of bolus is not allowed.
- Adaptive Radiotherapy (ART) is allowed (offline, online, and library-based).
- Tumors >5 cm maximal dimension. A 3 cm longitudinal and 1.5 cm radial margin will be used to define the clinical target volume (CTV). For tumors in the subcutaneous fat space, a 3 cm circumferential margin will be used, limited to 0.5-1 cm into uninvolved muscle.
- Tumors ≤ 5 cm maximal dimension. A 2 cm longitudinal and 1 cm radial margin will be used to define the clinical target volume (CTV). For tumors in the subcutaneous fat space, a 2 cm circumferential margin will be used, limited to 0.5-1 cm into uninvolved muscle.

Extremity Tumor and Anatomy Contouring

- Practice variation exists in tumor and Organ at Risk (OAR) contouring and naming.
- S2505 has built-in real-time quality assurance through central plan review, which will include review of imaging, contouring, dosimetry, and the radiation plan.
- The training for S2505 covers naming and contouring for:
  - Gross tumor volume (GTV),
  - Clinical target volume (CTV),
  - Planning target volume (PTV),
  - Sciatic nerve (Sciatic_Nrv_L, Sciatic_Nrv_R),
  - Skin strip (SkinSoftTissue_Sub)
  - Knee joint (Knee_L, Knee_R),
  - Hip joint (Femur_Joint_L, Femur_Joint_R),
  - Shoulder joint (Joint_Glenohum_L, Joint_Glenohum_R), and
  - Elbow joint (Joint_Elbow_L, Joint_Elbow_R)

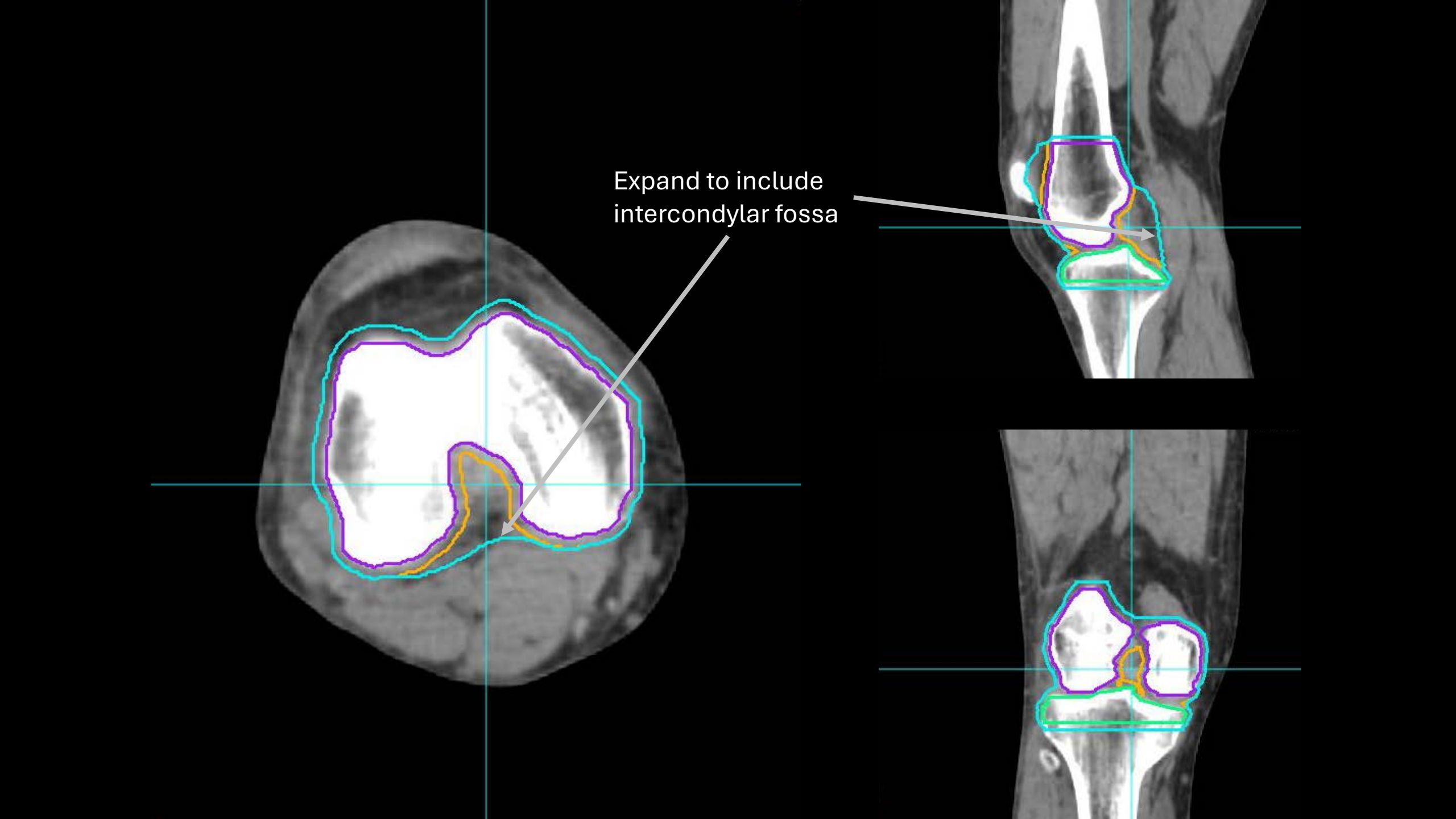
SkinSoftTissue_Sub

- The skin strip should be contoured as follows:
  - Begin with a 1 cm thick outer wall of the body.
  - The width should be at least 2 cm.
  - The longitudinal length should be 1 cm beyond the most proximal axial slice to 1 cm beyond the most distal axial slice of the PTV.
  - Bone should be excluded from the skin strip (i.e. soft tissue only).


Body
SkinSoftTissue_Sub
1cm contraction of Body
≥2 cm
PTV_Eval
1 cm

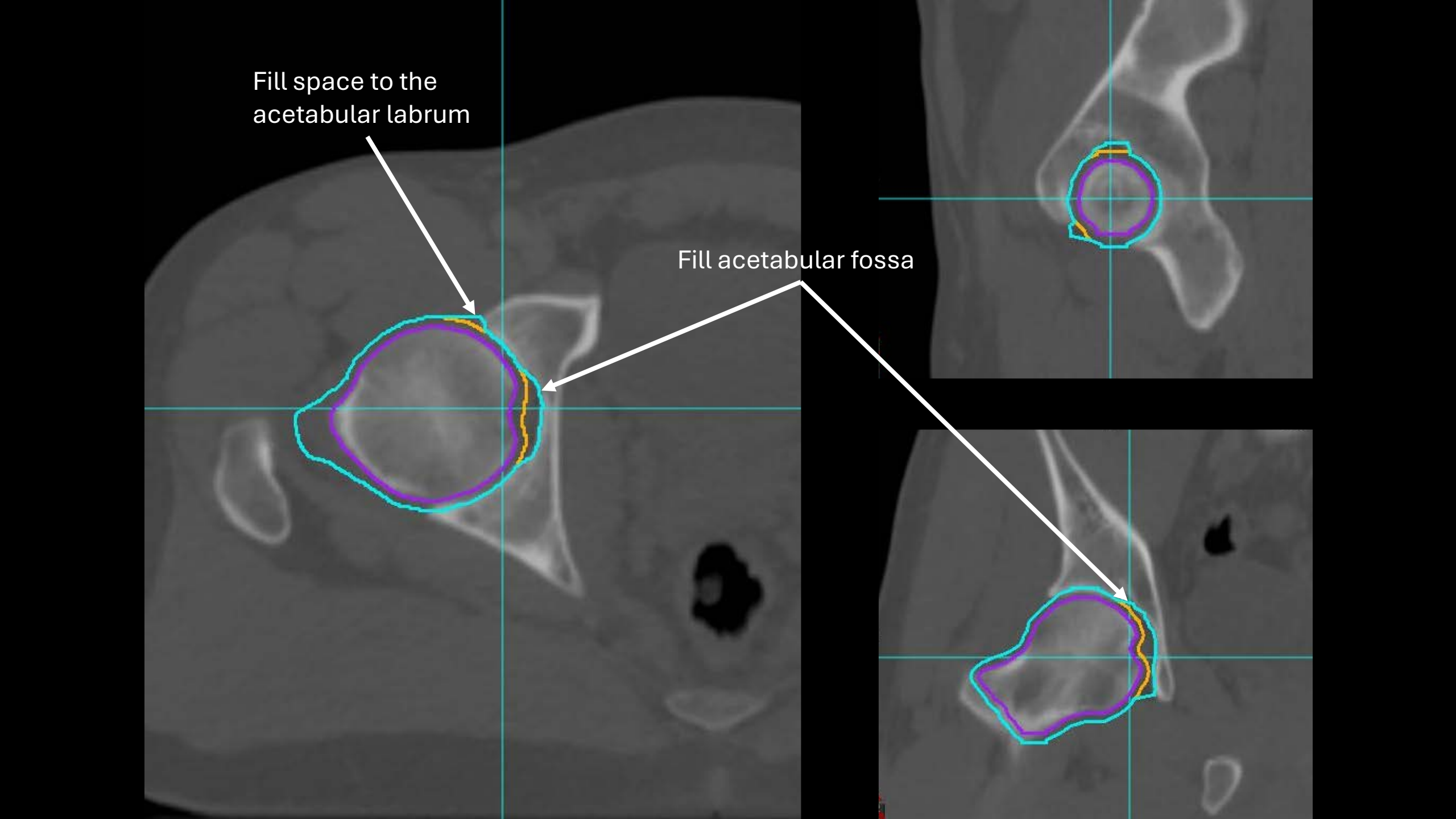
Knee_L & Knee_R - Contouring

- Contour the femur and tibia (most easily appreciated with a bone window, e.g. window 2000 HU, level 400 HU). Limit the proximal border to the proximal most portion of the femoral condyles and the superior portion of the patella. Limit the distal border to the widest portion of the tibial plateau.
- Expand the femur and tibia 3 mm.
- Expand to encompass the fibrous soft tissue (appreciated with a soft tissue window, e.g. window 400 HU, level 40 HU). Take care to expand to the posterior border of the patella, the patellar retinaculum, and the intercondylar fossa (up to the gastrocnemius).


Expand to include
intercondylar fossa

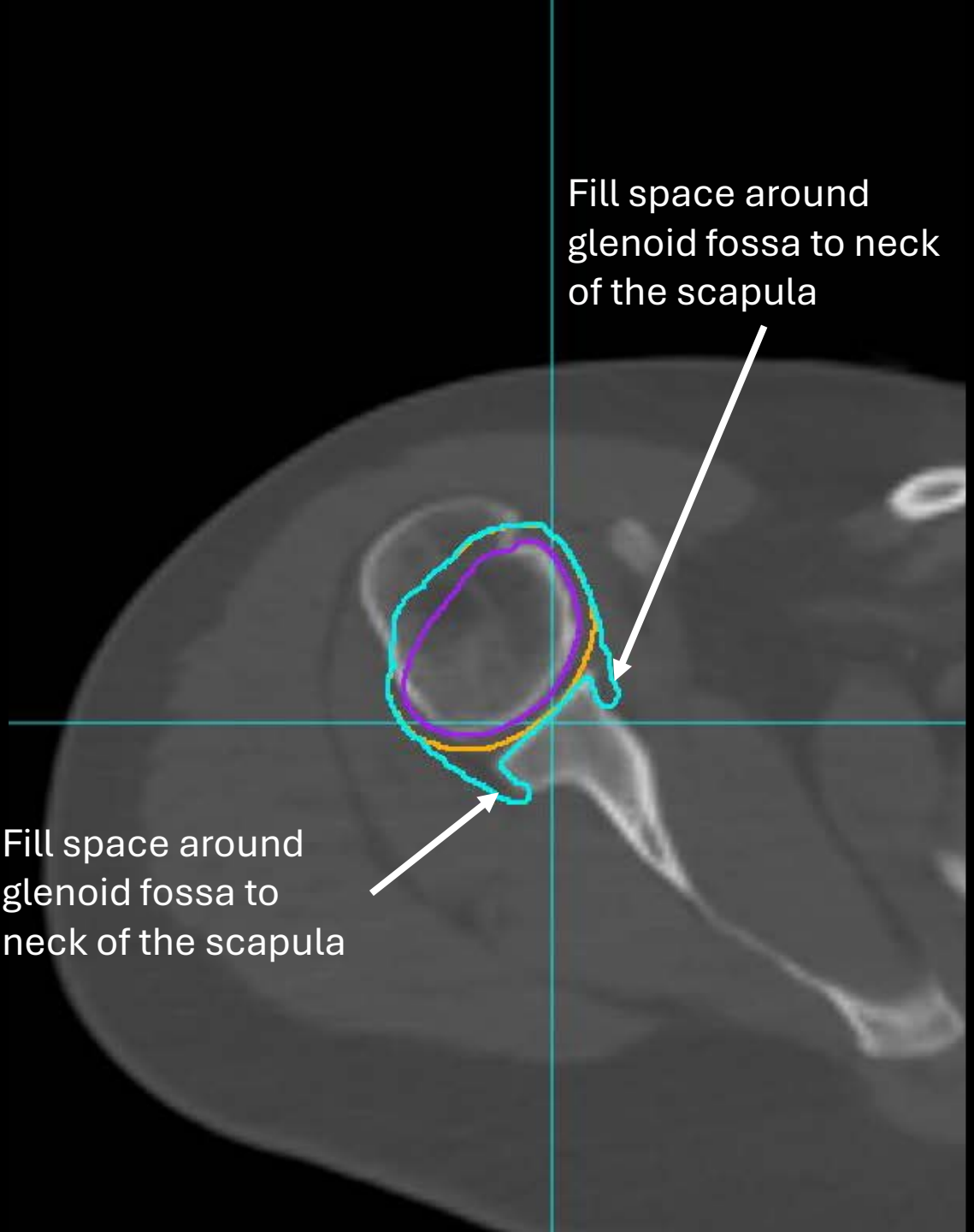
Femur_Joint_L & Femur_Joint_R - Contouring

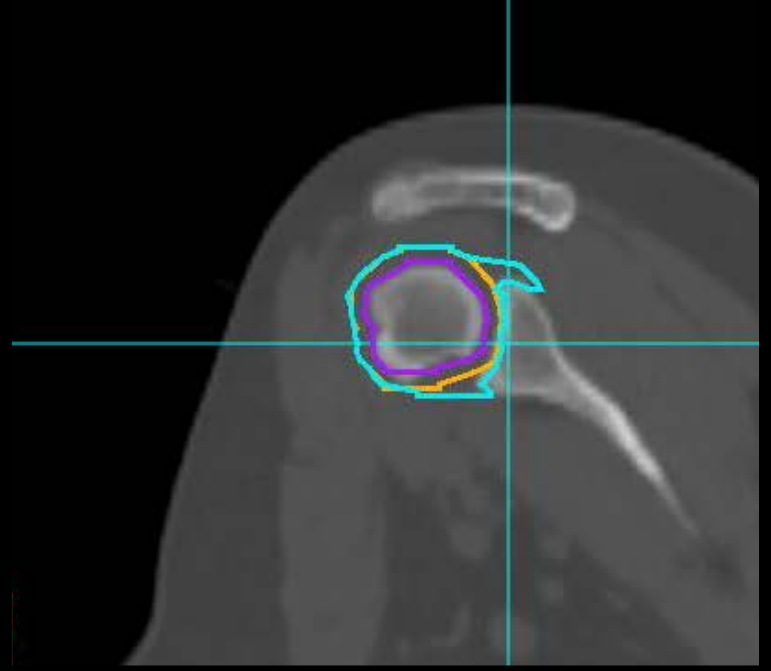
- Contour the femoral head above the intertrochanteric line (most easily appreciated with a bone window, e.g. window 2000 HU, level 400 HU).
- Expand the femoral head 3 mm.
- Expand to fill the acetabular fossa and space to the acetabular labrum.

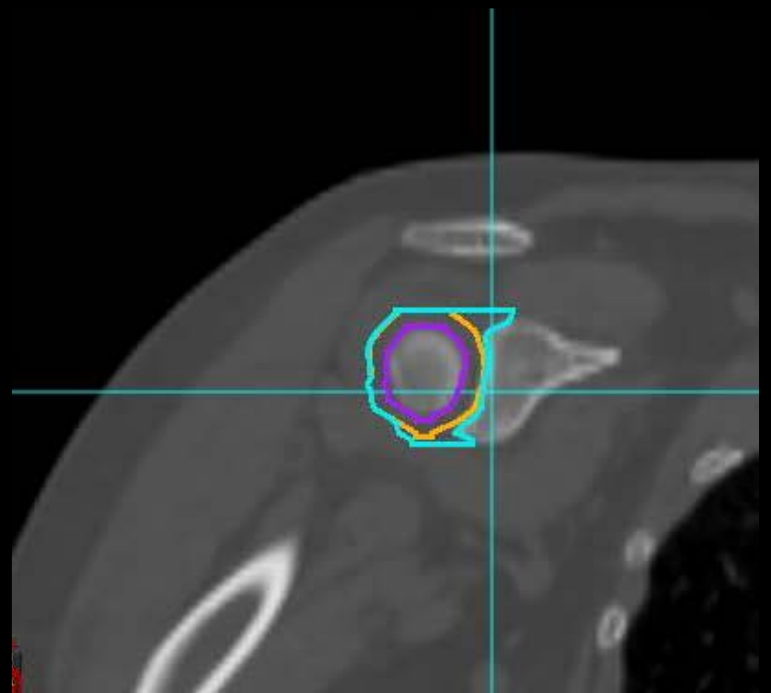

Fill space to the acetabular labrum
Fill acetabular fossa

Joint_Glenohum_L and Joint_Glenohum_R - Contouring

- Contour the humeral head (coronal projection is helpful and most easily appreciated with a bone window, e.g. window 2000 HU, level 400 HU).
- Expand the humeral head 3 mm.
- Expand to encompass the glenoid fossa; space around the glenoid fossa to the anatomic neck of the scapula; and space lateral to the subscapularis.

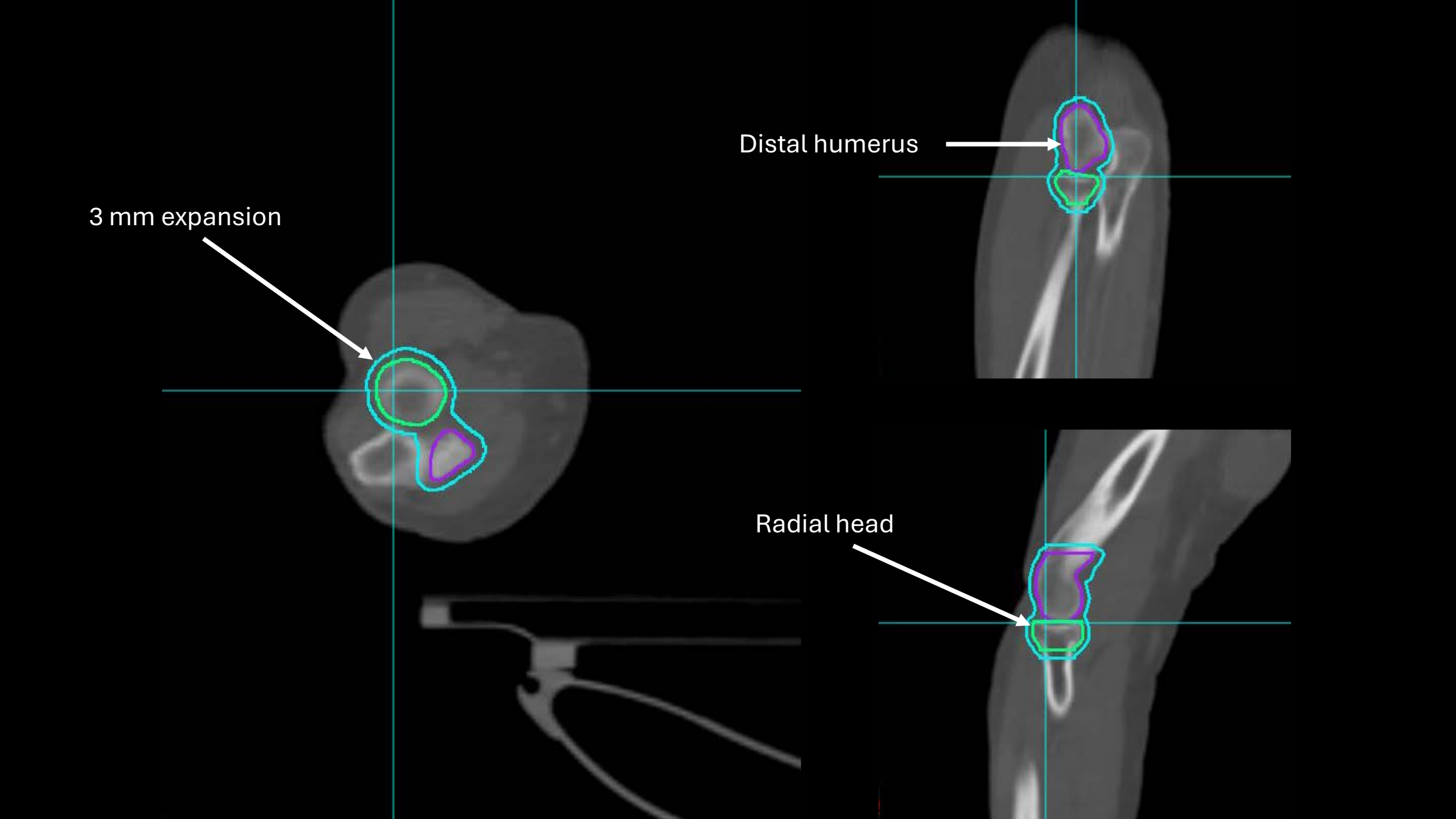

Fill space around glenoid fossa to neck of the scapula
Fill space around glenoid fossa to neck of the scapula





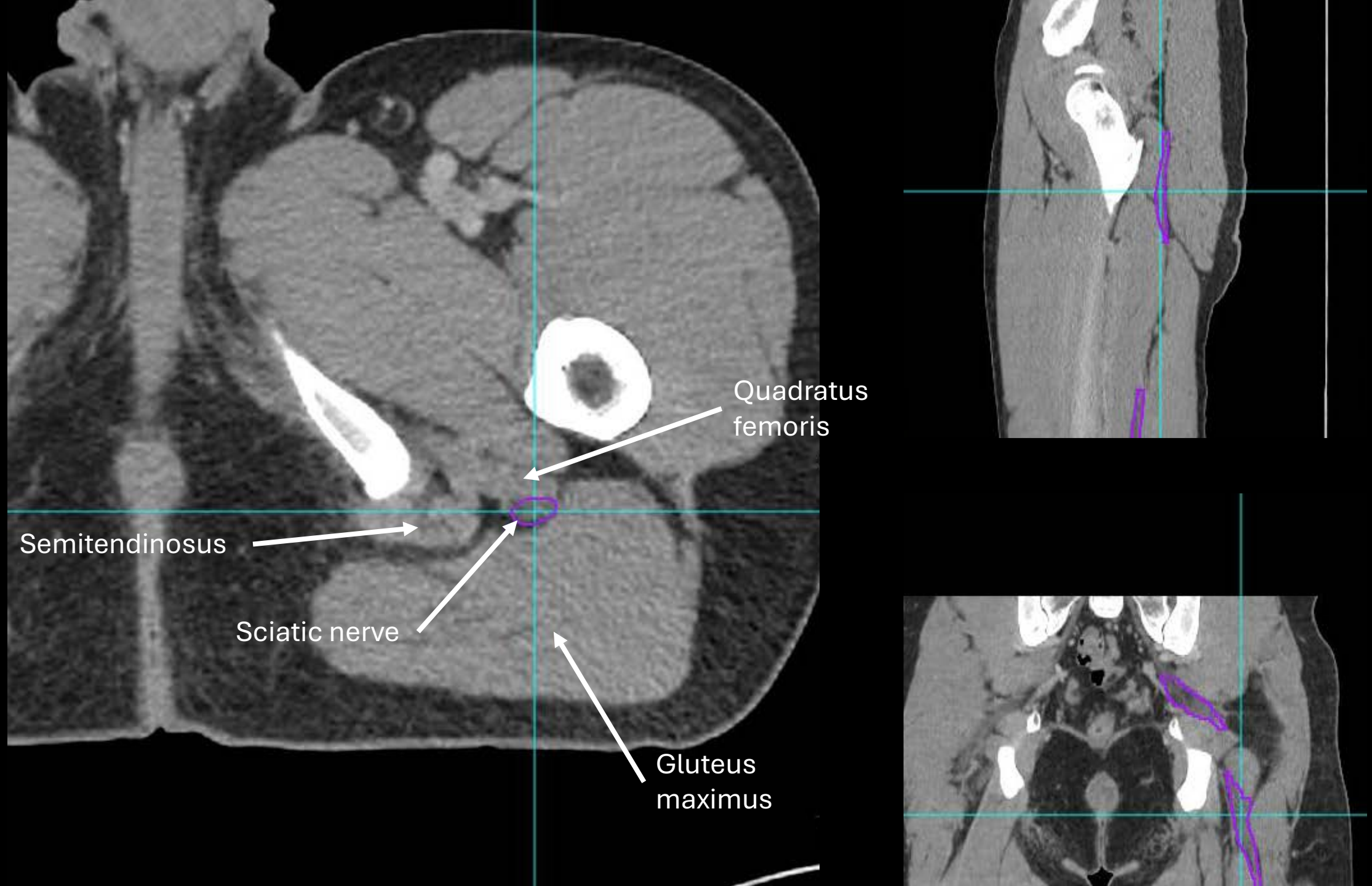
Joint_Elbow_L & Joint_Elbow_R - Contouring

- Contour the radial head (up to the radial neck; proximal to radial tuberosity) and distal humerus inclusive of epicondyles (most easily appreciated with a bone window, e.g. window 2000 HU, level 400 HU).
- Expand the humerus and radial head 3 mm.
- Crop any expansion outside of the body.


3 mm expansion
Distal humerus
Radial head

SciaticNrv_L & SciaticNrv_R- Contouring

- Use a 4 mm brush to contour the sciatic nerve from at least 1 cm above to at least 1 cm below the PTV. The nerve can be seen on CT (best with a soft tissue window, e.g. window 400 HU, level 40 HU) and can be up to ~2 cm thick. When the nerve exceeds 4 mm in diameter, expand to encompass the entire cross-sectional thickness. The origin is the in pelvis from the lumbosacral plexus to upper popliteal fossa where it splits into the tibial and common peroneal nerves.


Quadratus femoris
Semitendinosus
Sciatic nerve
Gluteus maximus

Radiation Therapy: Arm 1 Key Constraints

Organ	DVH Metric	Per Protocol	Variation Acceptable
Humerus_L, Humerus_R, Radius_L, Radius_R, Femur_L, Femur_R, Tibia_L, Tibia R	D0.03cc [Gy]	<57.5 Gy	≤57.5 Gy
	V40Gy [%]		≤64%
	V50Gy [%]	<50%	
	Mean	<37 Gy	
	Dmin [Gy] (Every axial slice)		≤50 Gy
Joint_Glenohum_L, Joint_Glenohum_R, Joint_Elbow_L, Joint_Elbow_R, Femur_Joint_L, Femur_Joint_R, Knee_L, Knee_R	V50Gy [%]	<50%	≤60%
SkinSoftTissue_Sub	V20Gy[%]	0%	<50%

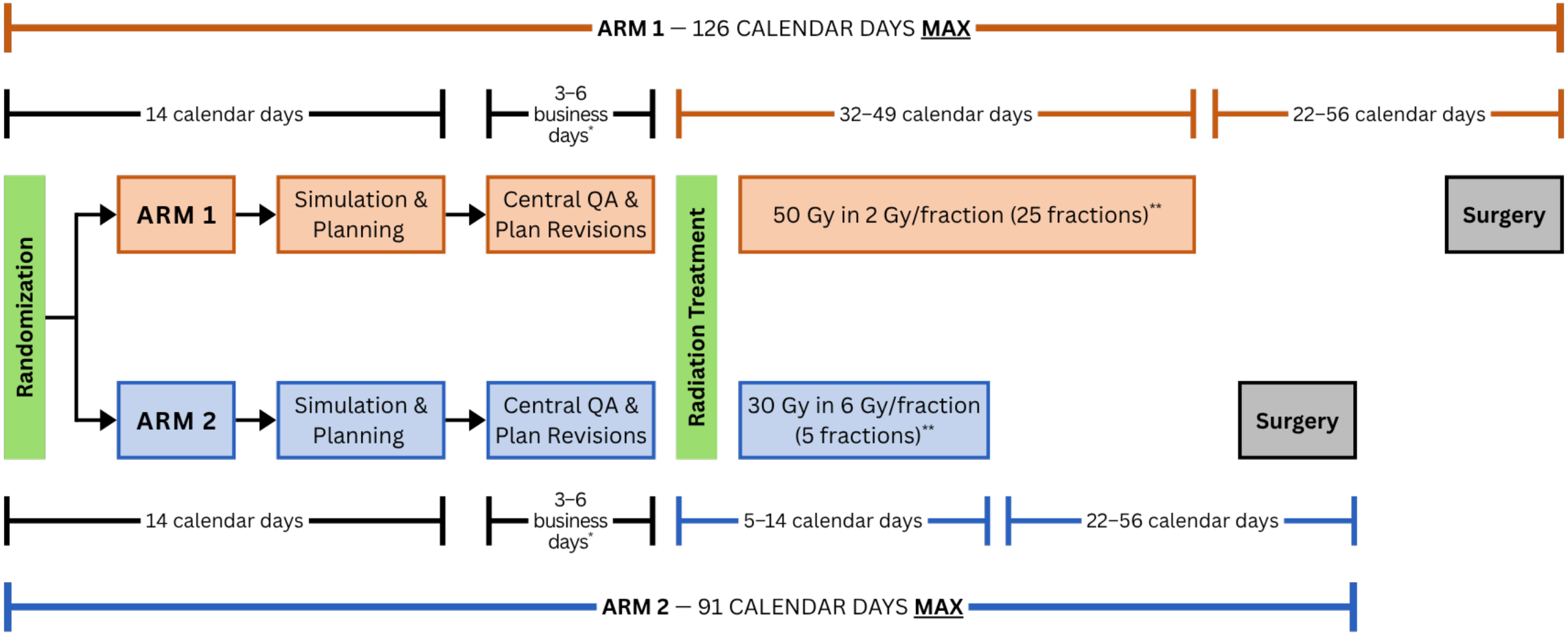
Radiation Therapy: Arm 2 Key Constraints

Organ	DVH Metric	Per Protocol	Variation Acceptable
Humerus_L, Humerus_R, Radius_L, Radius_R, Femur_L, Femur_R, Tibia_L, Tibia R	D0.03cc [Gy]	<31.5 Gy	≤32.4 Gy
	V25Gy [%]	<50%	≤64%
	D50cc [Gy]	<25 Gy	
	Mean	<22.5 Gy	
	Dmin [Gy] (Every axial slice)		≤30 Gy
Joint_Glenohum_L, Joint_Glenohum_R, Joint_Elbow_L, Joint_Elbow_R, Femur_Joint_L, Femur_Joint_R, Knee_L, Knee_R	V30Gy [%]	<50%	≤60%
SkinSoftTissue_Sub	D0.03cc [Gy]	32.4 Gy	34.5 Gy
	D5cc [Gy]	<28 Gy	<31.5 Gy
	D150cc [Gy]	<12 Gy	

Treatment Administration: Surgery

- Surgery will take place 22-56 days (29-56 days is encouraged) following radiation completion.
  - Latest time from randomization to completion of surgery:
    - ARM 1: 126 days
    - ARM 2: 91 days
- Every effort should be made for limb preservation surgery unless there is documented progression that requires amputation.
- Updated imaging (MRI is preferred but CT is an alternative) after radiation treatment and prior to surgery is recommended but optional.

Study Flow Diagram



*Central QA takes up to 3 business days. In the case of revision recommendations, an additional 1–3 business days are needed for revision and central QA.

**RT delivered daily, at ≤ 5 fractions/week. RT more than once per day is not allowed.

Treatment Administration: Adjuvant Therapy

- Radiation boost
  - Radiation boost is not recommended for an unplanned R1 resection but is allowed. A dose of 16 Gy in 2 Gy/fraction is suggested.
  - Adjuvant radiation boost is not recommended for planned positive microscopic margin along fixed critical structures (such as neurovascular bundles).
  - Radiation boost is recommended for any R2 resection. A dose of 20 Gy in 2 Gy/fraction is recommended.
  - Post-operative boosts, when delivered, will be recommended in conventional fractionation in both treatment arms.
  - Intraoperative radiation therapy and intraoperative catheter placement for adjuvant brachytherapy are not allowed.
- Systemic therapy
  - Adjuvant chemotherapy or immunotherapy is allowed at the treating medical oncologists' discretion.
  - Compliance with the upfront declaration for adjuvant systemic therapy will be monitored.

Disease Assessment

- During treatment
  - Pre-Surgical Local Imaging Scan (recommended but optional): MRI of the primary site (CT is allowed as an alternative) is done for operative planning ≥2 weeks following completion of radiation.
  - Pre-surgical: Optional Chest CT recommended every 3-6 mo
- Post-treatment assessments are recommended and include MRI (preferred, or CT if MRI not done) of the primary site and CT chest for distant site evaluation. Recommended schedule:
  - Years 1-3: Every 3-6 months.
  - Years 4-5: Every 6 months.
- In the case of distant recurrence, primary site imaging according to the above schedule is recommended to evaluate local recurrence.

Toxicity Monitoring and Radiation Dose Interruptions – General Considerations

- Radiation dose reductions are not allowed.
  - Twice daily radiation is not allowed.
- Radiation interruptions are allowed to manage toxicity.
- Major interruptions in radiation therapy are strongly discouraged.
- Any interruptions in treatment beyond those listed below will mandate participant removal from protocol treatment.
  - RT-25: The maximum time to complete radiation is 49 days from the start of radiation treatment
  - UHRT-5: The maximum time to complete radiation is 14 days from the start of radiation treatment.

Adverse Event Reporting

- S2505 utilizes the NCTN Streamlined Data Collection Standard Practices; therefore, only adverse events of Grade 3 or higher need to be collected unless otherwise specified in S2505 Protocol Section 8.3.

Adverse Event Reporting – Collection of Grade 1-5 Acute and Late Adverse Events Related to Early and Later Radiation Side Effects and Wound Complications

- Acute Wound Complication Form (Grade 2 or higher 4 months post surgery).
  - CTCAE graded wound complication
  - Wound complications as used in prior NCIC clinical trials
- Delayed Wound Healing Form (Grade 2 or higher at 6 months post surgery).
  - Delayed Wound Healing: CTCAE graded wound complication, wound dehiscence, wound infection, postoperative hemorrhage, seroma, and soft tissue necrosis (upper or lower limb).
- Late Term Radiation Complications Form (Grade 2 or higher 24 months post surgery)
  - CTCAE peripheral edema, superficial soft tissue fibrosis, joint range of motion decreased, osteonecrosis, and fracture
  - Complications as described by the RTOG – edema, fibrosis, joint stiffness.

Anticipated Adverse Events: CTCAE Wound Toxicities (1)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Wound complication	Observation only; topical intervention indicated	**Bedside local care indicated**	Operative intervention indicated	Life-threatening consequences
Wound dehiscence	Incisional separation, intervention not indicated	Incisional separation, **local care (e.g., suturing) or medical intervention indicated (e.g., analgesic)**	Fascial disruption or dehiscence without evisceration; revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated
Wound infection	Localized, local intervention indicated	**Oral intervention indicated** (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated

Anticipated Adverse Events: CTCAE Wound Toxicities (2)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Postoperative hemorrhage	Mild symptoms; intervention not indicated	**Moderate bleeding requiring transfusion** <2 units of RBCs	Transfusion indicated of ≥2 units pRBCs; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	**Symptomatic; simple aspiration indicated**	Symptomatic, elective invasive intervention indicated	-
Soft tissue necrosis (upper or lower limb)	-	**Local wound care; medical intervention indicated** (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated

Anticipated Adverse Events: NCIC Wound Toxicities

Toxicity	Definition
Operation	Secondary operations required for wound treatment (debridement, secondary closure procedures such as rotation flaps, free flaps, or skin grafts [including repeat surgery for revision of a split thickness skin graft]).
Admission	Hospital admissions for wound care
Procedure	Invasive procedures required for wound care (drainage of hematoma, seroma or infected wound collection, use of vacuum-assisted closure therapy)
Deep Packing	Deep wound packing required at any time (deep packing defined as packing deep to dermis in an area of dehisced wound) to an area of the wound measuring at least 2 cm in length
Prolonged Dressing Changes	Prolonged dressing changes, including packing of the wound for greater than 6 weeks from wound breakdown
Wet Dressing	Requirement for wet dressings for longer than 4 weeks. (It is permissible for a participant to protect a totally epithelialized skin graft with a dry dressing without declaring a major wound complication)

Anticipated Adverse Events: CTCAE Late-Radiation Associated Toxicities (1)

Toxicity	Grade 1	Grade 2	Grade 3
Peripheral Edema	Swelling or obscuration of anatomic architecture on close inspection	**Readily apparent obscuration of anatomic architecture; obliteration of skin folds;** readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self-care ADL
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, **able to slide skin, unable to pinch skin**; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL
Joint range of motion decreased	≤25% loss of ROM (range of motion); decreased ROM limiting athletic activity	**>25-50% decrease in ROM;** limiting instrumental ADL	>50% decrease in ROM; limiting self-care ADL

Anticipated Adverse Events: CTCAE Late-Radiation Associated Toxicities (2)

Toxicity	Grade 1	Grade 2	Grade 3
Osteonecrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	**Symptomatic; medical intervention indicated** (e.g., analgesics or bisphosphonates); limiting instrumental ADL	Severe symptoms; limiting self-care ADL; elective operative intervention indicated
Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	**Symptomatic but non-displaced; immobilization indicated**	Severe symptoms; displaced or open wound with bone exposure; operative intervention indicated; limiting self-care ADL

Anticipated Adverse Events: RTOG Late Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Edema	Mild (but definite swelling)	**Moderate**	Severe (considerable swelling)	Very severe (skin shiny and tight or skin cracking)
Fibrosis	Slight induration (fibrosis) and loss of subcutaneous fat	**Moderate fibrosis** but asymptomatic; slight field contracture; ≤10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear	Necrosis
Joint stiffness	Mild joint stiffness; slight limitation of movement	**Moderate stiffness;** intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/ Complete fixation

Specimen Submission: Plasma and Buffy Coat

Specimen Type	Amount	4 Collection Timepoints	Additional Instructions	Shipping Instructions

*Whole Blood processed to plasma and buffy coat***
 	
(Required with Participant Consent*)
 	
** For detailed **NEW** processing instructions: See S2505 memo distributed 10/1/26 (accessible via the protocol abstract page on the CTSU website).
	Collect 10 mL Whole Blood in EDTA tube
	
	Process to plasma and buffy coat.
	
	Submit:
	• One 2 mL cryovial buffy coat
	• 1mL plasma in one 2 mL cryovial
		• Pre-registration (± 10 days)
		• 4 months post-surgery (± 14 days)
		• 12 months post-surgery (± 21 days)
		• Progression* (± 14 days)
		
		* Blood is only collected at progression if the 4- or 12-months post-surgery specimens were not collected.
			• Immediately after blood is drawn, gently invert the tube 5-10 times to mix the blood with the anticoagulant.
			• Process whole blood in EDTA within 2 hrs after venipuncture to plasma and buffy coat:
			  • Pre-label cryovials.
			  • Centrifuge vacutainer at 1500g for 10 mins.
			  • Remove plasma and transfer to fresh 15mL tube.
			  • Remove buffy coat and place in one pre-labeled 2 mL cryovial.
			  • Centrifuge 15mL tube plasma at 3000g for 10 mins. Then transfer supernatant to a fresh 15 mL tube. Gently mix plasma then aliquot 1 mL plasma into a pre-labeled 2 mL cryovial.
			  • Immediately freeze both cryovials (bury in dry ice or store in -70 to -80°C freezer)
				Ship to: Lab #201, SWOG Biospecimen Bank Solid Tissue, Myeloma & Lymphoma Division
				Phone: 614-722-2865;
				Email: bpcbank@nationwidechildrens.org
				• Should be shipped **frozen** the same day as collected, when possible or by the next business day.
				• Batch shipping is not allowed.
				• Include the Specimen Tracking System Packing List with each submission.

*Note: Non-United States Institutions follow SWOG Membership of Non-United States Institutions Policy #40 guidance.

Specimen Submission: FFPE Tissue

Specimen Type and Amount	3 Submission Timepoints	Additional Instructions	Shipping Instructions

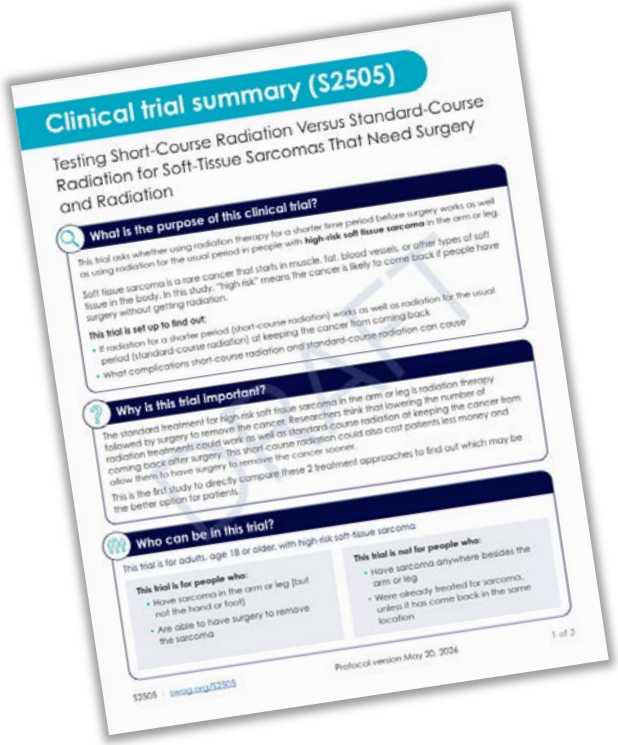
Tissue:
(Required with Participant consent*)
• 1-2 FFPE tissue block(s) (preferred)
AND
• 2 H&E slides from each representative block (2-4 total)
 	
OR
• 10-20 consecutive FFPE sections in air-dried, uncharged slides, 4-5 micron (20 slides strongly recommended)
AND
• 2 H&E slides from the same block as the unstained slides
	• Diagnostic Biopsy (Pre-registration)
	  • Submit archival tissue (diagnostic biopsy baseline sample) within 15 days after registration.
	
	• Surgery
	  • Submit surgical tissue within 60 days after surgery.
	
	• Progression (if available)
	  • Submit tissue specimen within 30 days after progression if on protocol treatment at time of progression or within 60 days after progression if off protocol at time of progression.
		Store FFPE blocks and slides at room temperature until shipment.	Ship to: Lab #201, SWOG Biospecimen Bank Solid Tissue, Myeloma & Lymphoma Division
			Phone: 614-722-2865; Email: bpcbank@nationwidechildrens.org
			
			• Batch shipping is not allowed.
			• With each submission, include:
			  • The Specimen Tracking System Packing List
			  AND
			  • Corresponding partially redacted diagnostic pathology report

*Note: Non-United States Institutions follow SWOG Membership of Non-United States Institutions Policy #40 guidance.

Resources and Materials — Patient-Friendly Clinical Trial Summary

The Patient-Friendly Summary is an educational tool to share key information about the trial

- Easy to understand, written in plain language
- Explains why the study is important, study treatments, who is eligible, length of trial involvement, costs, and how to learn more
- May include graphics to illustrate study design or treatments
- Translated into Spanish


Clinical trial summary (S2505)

Testing Short-Course Radiation Versus Standard-Course Radiation for Soft-Tissue Sarcomas That Need Surgery and Radiation

What is the purpose of this clinical trial?

This trial asks whether using radiation therapy for a shorter time period before surgery works as well as using radiation for the usual period in people with high-risk soft tissue sarcoma in the arm or leg.

Soft tissue sarcoma is a rare cancer that starts in muscle, fat, blood vessels, or other types of soft tissue in the body. In this study, "high risk" means the cancer is likely to come back if people have surgery without getting radiation.

This trial is set up to find out:

- If radiation for a shorter period (short-course radiation) works as well as radiation for the usual period (standard-course radiation) at keeping the cancer from coming back
- What complications short-course radiation and standard-course radiation can cause

Why is this trial important?

The standard treatment for high-risk soft tissue sarcoma in the arm or leg is radiation therapy followed by surgery to remove the cancer. Researchers think that lowering the number of radiation treatments could work as well as standard-course radiation at keeping the cancer from coming back after surgery. This short-course radiation could also cost patients less money and allow them to have surgery to remove the cancer sooner.

This is the first study to directly compare these 2 treatment approaches to find out which may be the better option for patients.

Who can be in this trial?

This trial is for adults, age 18 or older, with high-risk soft tissue sarcoma

This trial is for people who:

- Have sarcoma in the arm or leg (but not the hand or foot)
- Are able to have surgery to remove the sarcoma

This trial is not for people who:

- Have sarcoma anywhere besides the arm or leg
- Were already treated for sarcoma, unless it has come back in the same location

1 of 3

S2505 | swog.org/S2505

Protocol version May 20, 2024

We recommend a study team member review the summary with the patient as an introduction to the trial, or alongside the consent

- Also available as a PDF to be printed or shared electronically

The summary is accessible from:

- **swog.org/S2505** (publicly accessible link, with printable PDF)
- Also via the S2505 protocol abstract page on the CTSU website under Documents >> CIRB Approved Documents tab >> Support Documents filter, listed as “Clinical Trial Summary” (login required)

Additional Resources and Materials

- S2505 Social Media Toolkit (text and graphics) is available:
  - via the S2505 protocol abstract page on the CTSU website under Documents>>CIRB Approved Documents tab>> Support Documents filter
  - **or** via swog.org/clinical-trials/S2505 under “Other Study Materials” (no login)
- Resources available via the S2505 protocol abstract page on the CTSU website under Documents>>Protocol Related Documents>>Education and Promotion:
  - S2505 Protocol Summary Sheet (now available)
  - S2505 Required Training for Conduct of Extremity Tumor and Anatomy Contouring (also accessible via direct link or CTSU CLASS catalog search)
  - S2505 Optional Site Initiation Training (also accessible via direct link or CTSU CLASS catalog search)

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  - Sibo Tian
- ALLIANCE
  - Meng Welliver
- Patient and Community Advocates
  - Marcia Horn
  - Bill Minh Thach

Contact Information

Eligibility, RAVE, Data Submission:	SWOG Statistics and Data Management Center E-mail: raretumors@crab.org or Phone: 206/652-2267
Regulatory, Protocol, Informed Consent:	SWOG Network Operations Center E-mail: protocols@swog.org or Phone: 210/614-8808
Medical Queries (treatment or toxicity related questions):	S2505@swog.org Direct Spanish medical queries to Natalia Jara, MD
MSTS questions	Email: S2505@swog.org Direct MSTS form questions to Michael Hoyt, PhD
Radiation Therapy Requirements	See Protocol Section 12 Email: S2505RT@swog.org / Phone: 401/753-7600
Specimen collection/submission questions	Jeremy Harris, MD, MPhil Email: S2505@swog.org
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) (e.g., new account requests, reset password)	https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL), Oncology Patient Enrollment Network (OPEN) questions	See Protocol Sections 14.3 or 13.5 or contact the CTSU Help Desk at: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Serious Adverse Event Reporting questions:	See Protocol Section 8.6 or Email: adr@swog.org

Required Credentialing Clarification

- IGRT is required for radiation treatment on S2505;
  - Separate IGRT credentialing is **not** required. (See S2505 Clarifications memorandum distributed on 10/1/2026; accessible via the protocol abstract page on the CTSU website under Protocol-Related Documents>>Supplemental Documents)
- Per S2505 Protocol Section 12.2, sites must continue to meet applicable RT credentialing requirements for the treatment modality used (3DCRT or IMRT)

  and
- Per S2505 Protocol Section 13.3c, sites must complete and submit the IROC Credentialing Status Inquiry (CSI) Form.

Planned Post Activation Revisions

- Biospecimen Banking
  - Currently collecting whole blood (EDTA) at pre-registration, 4 months post surgery, and 12 months post surgery
  - Banking Objective: To bank tissue specimens for future correlative studies
  - Eligibility: Participants registered by sites located in the United States
  - In the revision, will ask sites to process locally for plasma and buffy coat (double spin) and ship frozen (batched is acceptable).
  - The timepoints will remain the same (pre-registration, 4 months post surgery, and 12 months post surgery)
- Imaging Substudy. Imaging Chair: James Tsui
  - Objective 1: To describe and compare the proportion of in-field local recurrences with ultra-hypofractionated (UHRT-5) and standard (RT-25) fractionation.
  - Objective 2: To describe and compare the prediction of distant metastasis for the two treatment regimens (UHRT-5 vs RT-25) based on quantitative features extracted from pre- and post-RT MRI scans with deep learning.
  - Eligibility: Participants with MRI performed during pre-registration with axial acquired T1 weighted with fat suppression, T1 weighted with gadolinium contrast with fat suppression, and T2 weighted with fat suppression sequences
  - The timepoints of MRI/CT collection are pre-registration, after radiation and before surgery (recommended at least 2 weeks from completion of radiation), and at time of local recurrence

Open Forum Discussion – Questions and Answers

Thank you

- Scan the QR code

  or follow the link below

  to download the

  S2505 Kick Off Meeting Handouts and Slide Set

  https://www.swog.org/S2505-F26handouts

The meeting recording will be posted in ~3-4 weeks via the SWOG Members' website and via the CTSU CLASS learning management system, as a resource link under the current S2505 Optional Site Initiation Training course (login required).