Soft Tissue Sarcoma

Principles of Radiotherapy & Toxicity

Dr SAJAL KAKKAR

MD, FUICC (USA), FAROI (Fr)

Director, Radiation Oncology

Max Super Speciality Hospital, Mohali

The Sarcomas

- Osteosarcoma
- Ewing's family of tumors
    - Ewing's sarcoma of bone and soft tissue
    - Peripheral Primitive neuroectodermal tumor
- Soft tissue sarcomas
    - Non-rhabdomyosarcoma STS
    - Rhabdomyosarcoma
        - Embryonal rhabdomyosarcoma
        - Alveolar rhabdomyosarcoma
        - Other variants

Natural History

- 50% in extremities, 30% intraabdominal
- Intra compartmental extension
- Centrifugal growth
- Pseudocapsule formation
- Hematogenous metastases (Lung, bone, liver)
- Lymphatic Spread
  (14%-20% risk in Synovial, Epithelioid, Angiosarcoma, ERMS)

Treatment

- Surgical Oncologist
- Radiation Oncologist
- Medical Oncologist
- Rehabilitation

Surgery

Organ Preservation

Negative margins

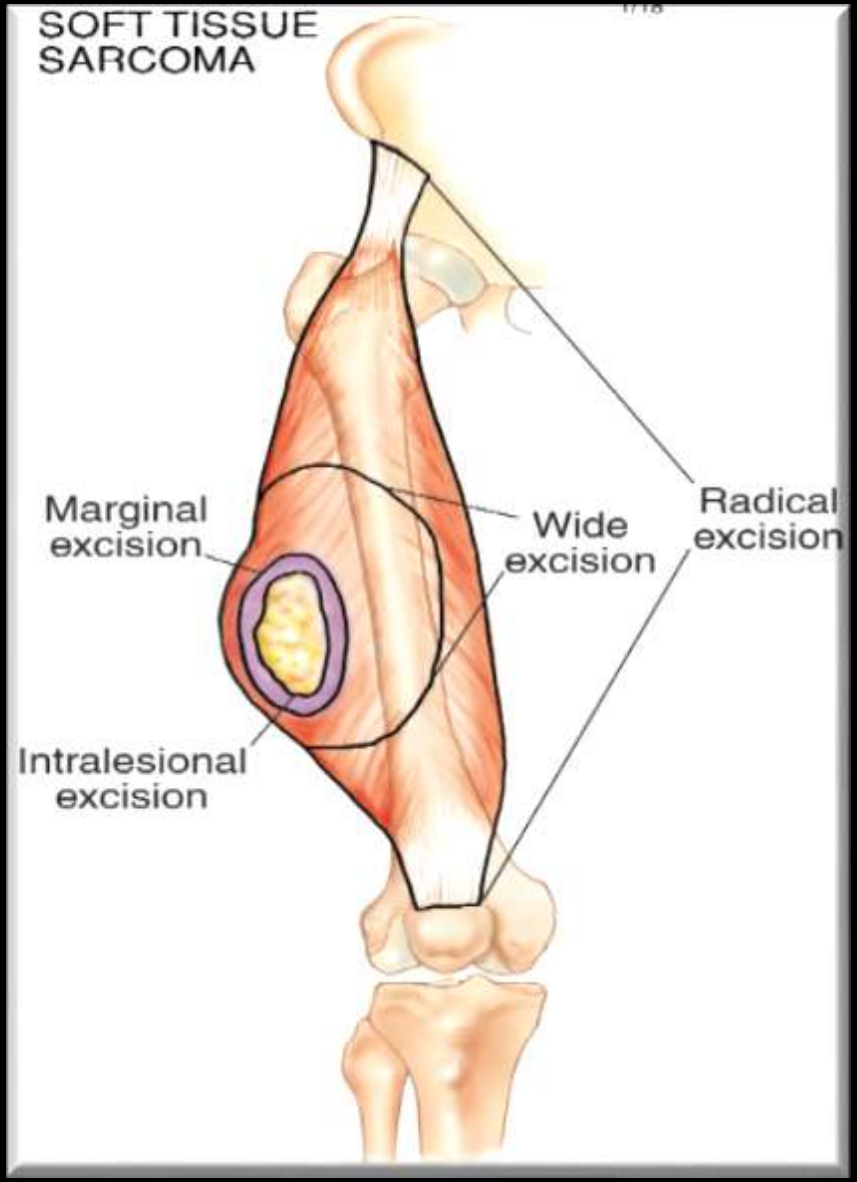
Surgery

Intralesional

Marginal

Wide Excision

Radical Excision



Radiation Therapy

- Indications
- Pre-op vs Post-op
- RT Planning/Dose
- Toxicity

Randomized Prospective Study of the Benefit of Adjuvant Radiation Therapy in the Treatment of Soft Tissue Sarcomas of the Extremity

JCO 1998

By James C. Yang, Alfred E. Chang, Alan R. Baker, William F. Sindelar, David N. Danforth, Suzanne L. Topalian, Thomas DeLaney, Eli Glatstein, Seth M. Steinberg, Maria J. Merino, and Steven A. Rosenberg

No local rec in pts with negative margins

91 pts, high grade lesions
- **RT – 47 pts**
- **No RT – 44 pts**

Median f/u 9.6 yrs

- **Significant decrease in local rec, p=0.028**
- **No OS difference**

50 pts, low grade lesions
- **RT – 26 pts**
- **No RT – 24 pts**

Median f/u 9.6 yrs

probability of local rec

RT improves local control rates in high/low grade sarcoma

RT may lead to lower QOL in short term

RT may not be beneficial in some scenarios

...ve QOL assessment

- **Significantly lower functional parameters in RT arm (ms edema, strength, joint motion)**

Long-Term Results of a Prospective Randomized Trial of Adjuvant Brachytherapy in Soft Tissue Sarcoma

By Peter W.T. Pisters, Louis B. Harrison, Denis H.Y. Leung, James M. Woodruff, Ephraim S. Casper, and Murray F. Brennan

JCO 1996

- 164 pts, extremity or superficial trunk sarcoma
- Localised, completely resected
- No major bone or neurovascular resection
- No violation of tumor during surgery

Adjuvant Brachytherapy OR no treatment

Technique

- 2cm isotropic margin
- Afterloading catheters
- 42Gy-45Gy, 4-6 days

Median f/u 6yrs:

- Significant local control in BRT arm, $p=0.04$
- Significant local control in high grade lesions, $p=0.0025$
- No difference in low grade lesions
- No OS difference

Local control benefit in high grade lesions
Simple, convenient, short course treatment

RT Indications

RT improves local control without affecting OS

- High Grade
- Stage II/III tumors
- Margins close (<1cm)
- Histology (Myxofibrosarcomas, Myxoid LPS)

When NOT to give?

- Low grade, T size< 5cm, superficial tumor with wide margins
- Unplanned excisions or non-oncologic resections

C Le Pechoux et al, Cancer Radiother 2022

What is adequate margin?

- Lack of consensus
- Variability of site, feasibility of wide negative margins
- Close margin at periosteum, fascia vs muscle, adipose tissue, skin

- R1/R2 resection – always discuss with the surgeon for re-resection and negative margins
- Close or positive margins near critical structure (major nerve, vessel, bone) warrants RT

RT Timing

Preoperative

Advantages:

- Decreased risk of i/o seeding
- Smaller target volume
- Reduced risk of late tox
- Tumor shrinkage

Disadvantages:

- Delay of Sx
- Major wound complications

Post operative

Advantages:

- Accurate HPE
- Immediate surgery
- No wound healing complications

Disadvantages:

- Large treatment volumes
- Irreversible S/E – lymphedema, fibrosis, decreased range of motion, fracture

Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial

Lancet 2002

Brian O'Sullivan, Aileen M Davis, Robert Turcotte, Robert Bell, Charles Catton, Pierre Chabot, Jay Wunder, Rita Kandel, Karen Goddard, Anna Sadura, Joseph Pater, Benny Zee

- **190 pts, b/w 1994-97**
- **Non-metastatic extremity sarcoma**
- **Primary end point – Major wound complication**
- **Sx & RT 3-6 weeks apart**
- **RT – 50Gy+/- 16-20Gy**
- **Median f/u 3.3yrs**

	Preoperative (n=88)	Postoperative (n=94)
Wound complications*		
Yes	31 (35%)	16 (17%)
Secondary operation for wound repair	14 (45%)	5 (31%)
Invasive procedure for wound management†	5 (16%)	4 (25%)
Deep wound packing deep to dermis in area of wound at least 2 cm with or without prolonged dressings >6 weeks from wound breakdown‡	11 (35%)	7 (44%)
Readmission for wound care§	1 (3%)	0
No complications	57 (65%)	78 (83%)

- **More w... in pre-op group, p=0.01**
- **Most complications in thigh pts**
- **No difference in local rec or PFS rates**

Higher risk of wound complications in preoperative RT
Similar local control rates

Radiotherapy and Oncology 75 (2005) 48-53
www.elsevier.com/locate/radonline

Phase III randomised trial

Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma

Aileen M. Davis[a,j,*], Brian O'Sullivan[b,j], Robert Turcotte[c], Robert Bell[b,d,j],

- 129 pts evaluated for late toxicities
- Jt. Stiffness, edema, fibrosis at 2 yrs
- EORTC/RTOG Criteria
- Musculoskeletal Tumor Rating Scale (MSTS)
- Toronto Extremity Salvage Score (TESS)

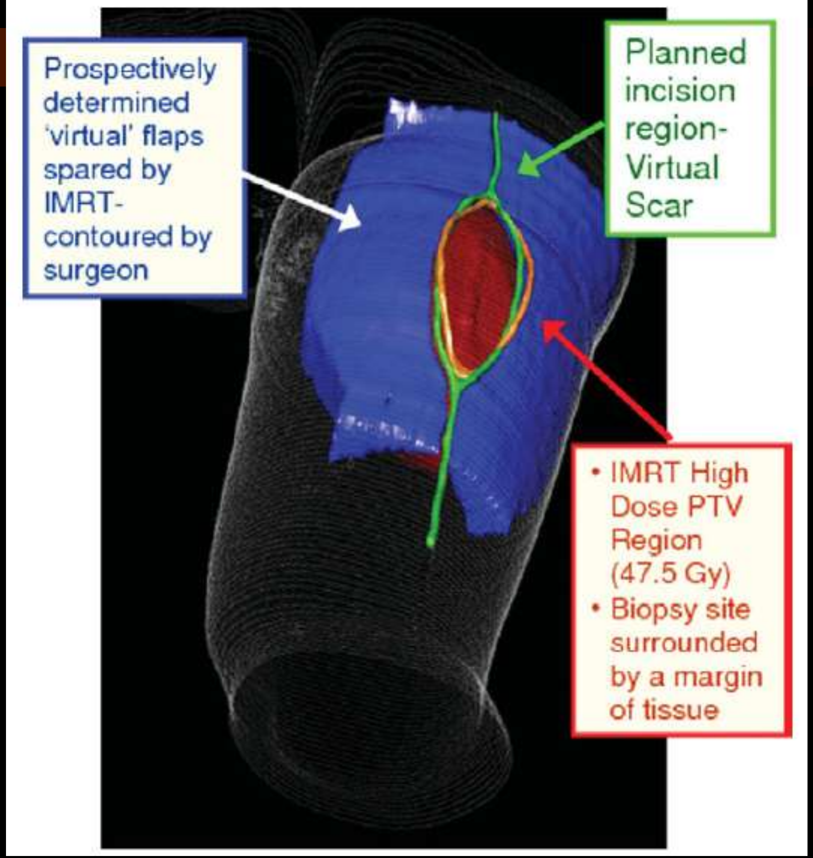
≥ Grade 2 Toxicity	Joint Stiffness	Edema	Subcut. Fibrosis
Pre-op RT	17.8%	15.1%	31.5%
Post-op RT	23.2%	23.1%	48.2%, p=0.07

- Significantly lower function scores on MSTS/TESS in > Grade 2 toxicities
- Field size sig. predictor for fibrosis and joint stiffness

Phase 2 Study of Preoperative Image-Guided Intensity-Modulated Radiation Therapy to Reduce Wound and Combined Modality Morbidities in Lower Extremity Soft Tissue Sarcoma

Cancer 2013

Brian O'Sullivan, MD[1,2]; Anthony M. Griffin, MSc[3]; Colleen I. Dickie, MSc[1]; Michael B. Sharpe, PhD[1,2]; Peter W. M. Chung,



- Phase II prospective study, 2005-09
- 70 pts, lower extremity STS
- Pre-op IG-IMRT
- Pri. End Point – Acute wound complication (WC)

✓Dose: 50Gy/25 frs

✓RT Avoidance – skin & s/c tissue required to close future resection site (virtual skin flap)

Results –

- 30.5% developed WCs vs 42% in Canada SR2 trial
- 93% primary closure vs 71%
- 33% secondary Sx for WC vs 43%

IG-IMRT reduces the risk & severity of WCs

VOLUME 33 · NUMBER 20 · JULY 10 2015

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial

Dian Wang, Qiang Zhang, Burton L. Eisenberg, John M. Kane, X. Allen Li, David Lucas, Ivy A. Petersen,

Dian Wang, Rush University Medical Center, Chicago, IL; Qiang Zhang, NRG Oncology Statistics and Data Manage-

- **Phase II prospective study**
- **79 pts, extremity STS**
- **Pre-op IG-IMRT**
- **Pri. End Point – RT morbidity at 2yrs (s/c fibrosis, edema, joint stiffness)**
- **Margins:**
  - **Int/High Grade Tm or T≥ 8cm: Longitudinal – GTV+3cm, radial – 1.5 cm**
  - **Low Grade or T < 8cm - GTV+2cm, radial – 1 cm**
- **Median fu 3.6 yrs**

Reduction in late toxicities & safety with reduced volumes

Results –

- **5 local failures, all in-field**
- **10.5% at least one ≥ Grade 2 toxicity vs 37% in Canada SR2 trial**
- **26/71 (36%) pts at least one major WC, all in lower extremity and common in proximal**

Preoperative vs Postoperative RT

- Localised extremity/truncal STS, pre-op RT is recommended over post-op RT

- Unresectable or difficult to resect, foreseeable risk of narrow margins - pre-op RT
- In conservative surgery requiring placement of vascular stent, flap or vasculo-nervous graft - pre-op RT
- Following an unplanned excision, pre-op RT recommended before oncologic resection, where RT indicated
- Radiosensitive histological subtype, like myxoid liposarcoma - pre-op RT
- Need to deliver limited dose, like upper limb, proximity to a nerve structure (brachial plexus)- pre-op RT
- Initial surgery in special situations like uncontrolled pain, bleeding, fungation followed by post-op RT

ASTRO Clinical Practice Guidelines, Pract Radiat Oncol 2021;
C Le Pechoux et al, Cancer Radiother 2022

When to start post-operative RT

- Between 3 to 8 weeks post Sx, without exceeding 12 weeks
- Assess the state of healing

RT Techniques

Key points

- Compartmental Anatomy
- Extent of tumor and Scar
- Tumor behavior
- Centrifugal spread, pathway of least resistance
- Delineate scar, drain sites
- Clip Placement
- Study CT/MRI closely, involve the surgeon/radiologist, intra-op findings

Perspective

Compartmental Anatomy: Relevance to Staging and Biopsy of Musculoskeletal Tumors

AJR 1999: 173; 1663-71

Mark W. Anderson[1,2], H. Thomas Temple[2,3], Robert G. Dussault[1,2], Phoebe A. Kaplan[1,2]

Cont..

Natural Barriers –
Synovium, articular cartilage, periosteum, tendinous origin & insertion of muscles

Poor Barriers – Fat, muscles

Positioning

Comfortable, Reproducible

Assess multiple limb positions

Rotate the extremity to minimise dose to surrounding tissue

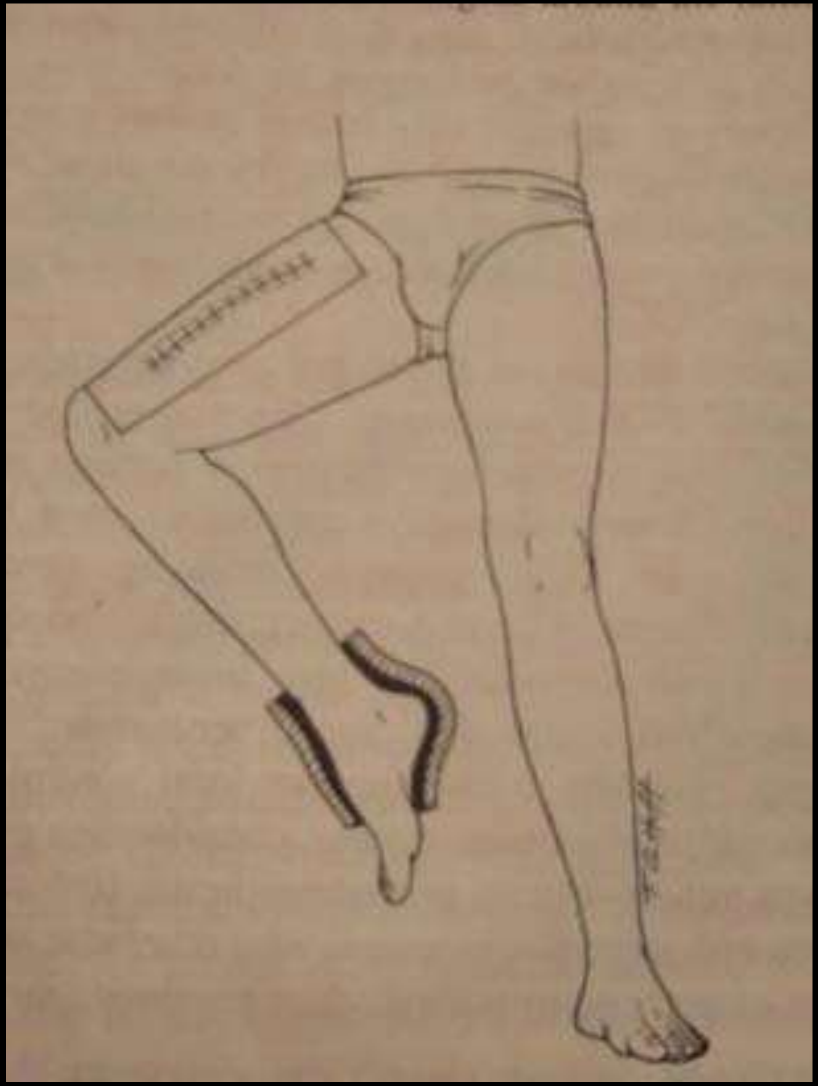
Contralateral leg away from anticipated beam angle range

Mind the diameter of CT SIM bore

FROG-LEG position

Separates ant. thigh from post. & medial compartments

Anterior compartment tumors treated in antero-lateral position

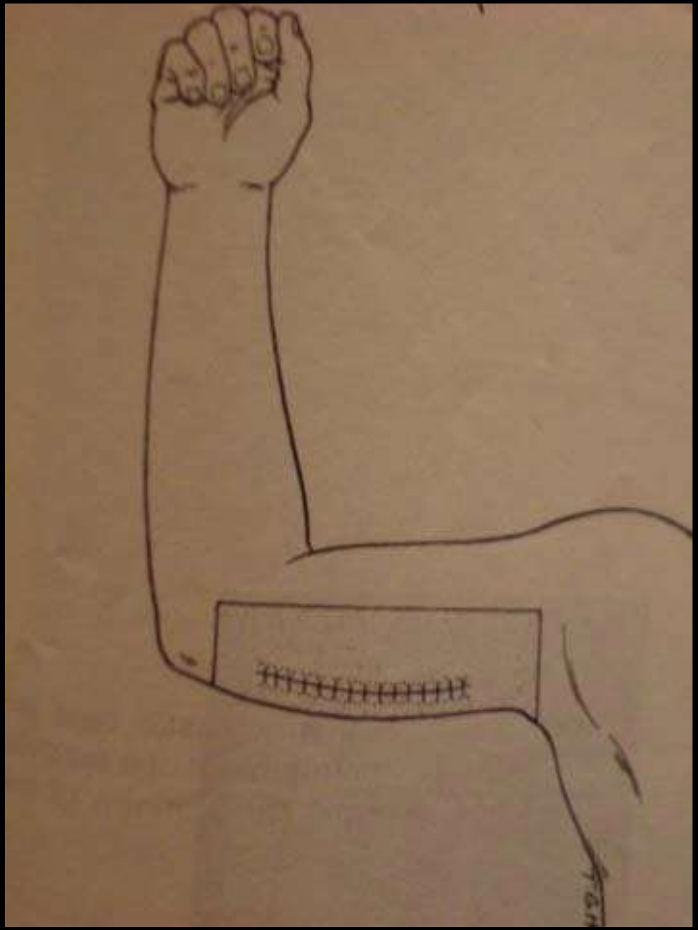


ARM

‘THROWING’ position

Shoulder 90· abduction & max ext rotation

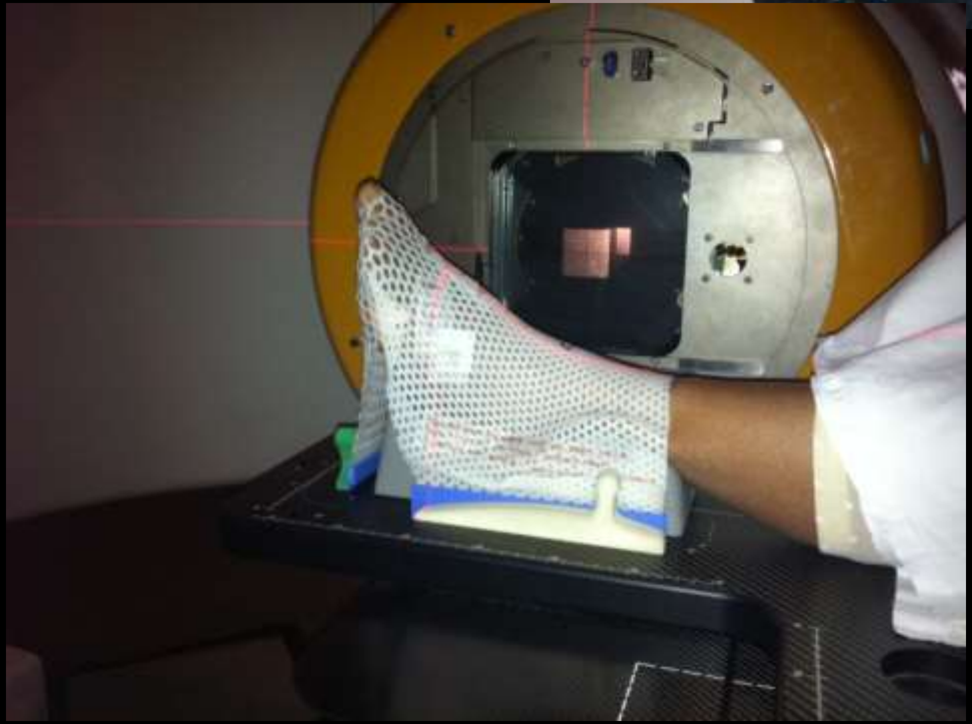
Adequately separates Biceps compartment from Triceps



Arm akimbo position

POST-MEDIAL Compartment

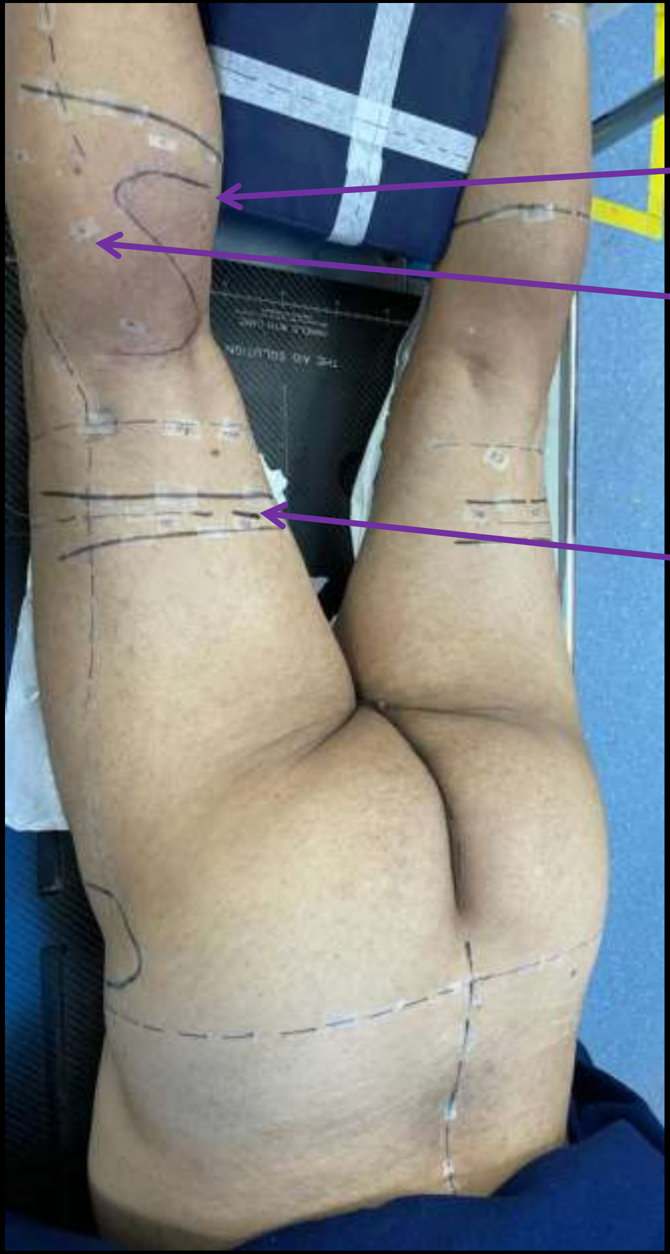
2D Simulator Planning



Patient Mold Fabrication

Scar Marking

Cont..



Scar

Skin Marks for Rotational error

Mould Edge

CT Acquisition

Planning CT

- Slice thickness 3 to 5mm
- Contrast use highly desirable in pre-op RT
- Entire limb segment with the joints above and below to be acquired

MRI in Target Delineation

- T1, T2w, contrast, fat suppression
- In planning position wherever possible for better fusion

- Perilesional edema – hyperintense on T2, non nodular, subcutaneous
- Soft tissue/Bony extensions - better in T2
- Intramedullary invasion – T1 seq
- Extracompartmental , vascular, nervous or cutaneous extension – T1 contrast
- Scars – hyperintense on T1/T2, sometimes nodular
- Collections – heterogenous hyposignal in T1/T2 with non-nodular peripheral enhancement

Field Placements

- ✓Keep uninvolved compartment out of radiation portal
- ✓Spare at least 1.5 - 2.0cm of limb circumference
- ✓Avoid joints as far as possible
- ✓Spare half circumference of uninvolved bone
- ✓Margins not extend beyond natural barriers (bone, fascial planes)
- ✓Cover surgical scar & drain sites
- ✓Bolus (not to be used in routine), in case of recurrence along the scar or unresectable disease

Pergamon

Int. J. Radiation Oncology Biol. Phys., Vol. 32, No. 4, pp. 977–985, 1995

0360-3016/95 $9.50 + .00

0360-3016(95)00111-5

● *Clinical Original Contribution*

CONSERVATIVE SURGERY AND ADJUVANT RADIATION THERAPY IN THE MANAGEMENT OF ADULT SOFT TISSUE SARCOMA OF THE EXTREMITIES: CLINICAL AND RADIOBIOLOGICAL RESULTS

ARNO J. MUNDT, M.D.,* AZHAR AWAN, M.D.,* GREGORY S. SIBLEY, M.D.,* MICHAEL SIMON, M.D.,[†] STEVEN J. RUBIN, M.D.,* BRIAN SAMUELS, M.D.,[‡] WILLIAM WONG, M.D.,* MICHAEL BECKETT, B.S.,* S. VIJAYAKUMAR, M.B., B.S., D.M.R.T.* AND RALPH R. WEICHSELBAUM, M.D.*

*Department of Radiation and Cellular Oncology, University of Chicago/Michael Reese Hospitals,

Methods and Materials: Sixty-four consecutive adult patients with soft tissue sarcoma of the extremities (40 lower, 24 upper) who underwent conservative surgery and adjuvant irradiation (7 preoperative, 50 postoperative, 7 perioperative) between 1978 and 1991 were reviewed. The initial radiation field margin surrounding the tumor bed/scar was retrospectively analyzed in all postoperative patients. Initial field margins were < 5 cm in 12 patients, 5–9.9 cm in 32 and ≥ 10 cm in 6. Patients with negative pathological margins were initially treated with traditional postoperative doses (64–66 Gy); however, in later years the postoperative dose was reduced
radiobiological parameters (mul

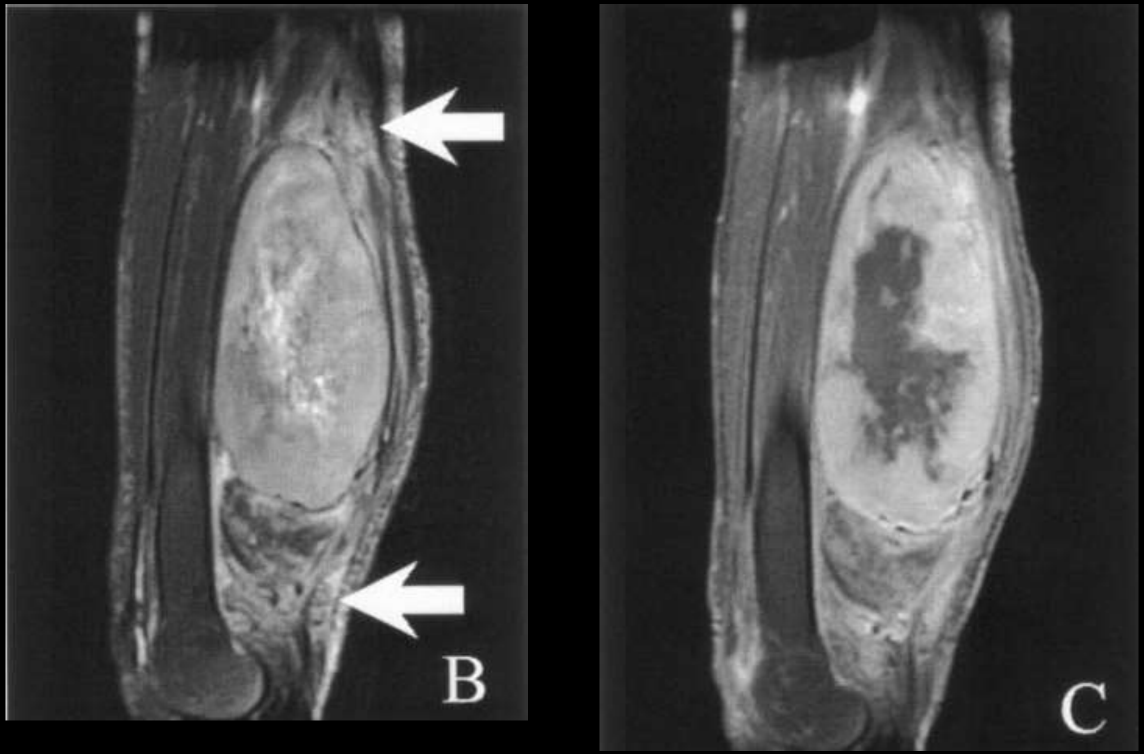
Results: Postoperative patients treated with an initial field margin of < 5 cm had a 5-year local control of 30.4% vs. 93.2% in patients treated with an initial margin of ≥ 5 cm ($p = 0.0003$). Five-year local control rates were similar in patients treated with initial field margins of 5–9.9 cm (91.6%) compared with those treated with ≥ 10 cm margins (100%) ($p = 0.49$). While postoperative patients receiving < 60 Gy had a

Defining The Target...

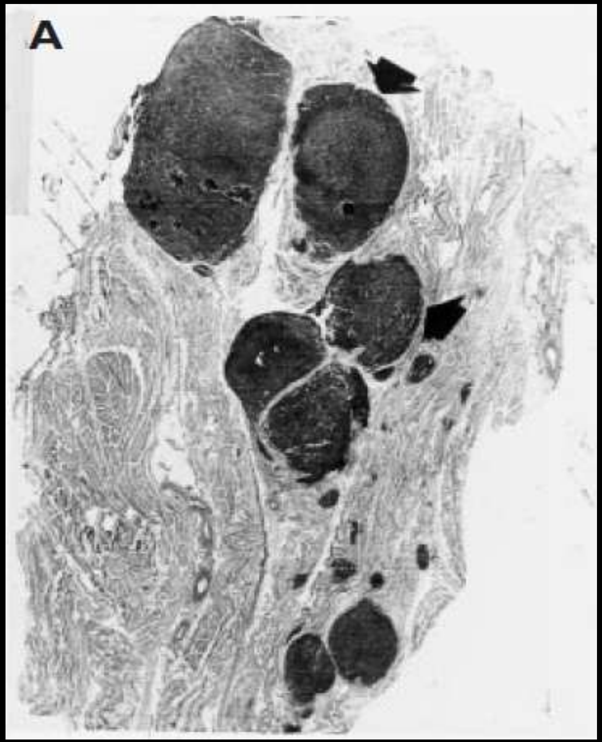
10-20% local recurrences after wide excision

'Reactive Zone' or 'Risk Zone'

- region surrounding the lesion, situated between the tumor margin/pseudocapsule and more remote normal tissues
- Radiologically, T2 weighted changes -> peritumoral edema



T2 w & T1 contrast MR scans



Section of high grade sarcoma with skip mets and intervening normal tissue

Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 5, pp. 1439–1445, 2005

0360-3016/05/$–see front matter

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doi:10.1016/j.ijrobp.2004.08.036

CLINICAL INVESTIGATION — **Sarcoma**

HISTOLOGIC ASSESSMENT OF PERITUMORAL EDEMA IN SOFT TISSUE SARCOMA

Lawrence M. White, M.D.,[*] Jay S. Wunder, M.D.,[†] Robert S. Bell, M.D.,[†] Brian O'Sullivan, M.D.,[‡] Charles Catton, M.D.,[‡] Peter Ferguson, M.D.,[†] Martin Blackstein, M.D., Ph.D.,[§] and Rita A. Kandel, M.D.[||]

Explains the reason for local relapse after Sx alone
Influences surgical/radiation margins
Cautious use of high precision techniques

- **Prospective study**
- **15 pts, extremity/truncal STS, post Sx**
- **Pre-op MRI: maximal extent of peritumoral edema measured**
- **Soft tissue beyond the tumor sampled for path. assessment**

Results:

- **Peritumoral edema/Reactive changes seen in MRI of all pts**
- **Extent: 0-7cm (mean 2.5 cm), mostly in sup-inf plane**
- **10/15 pts tumor cells beyond margin/pseudocapsule with intervening normal tissue in between**
- **6/10 such pts, tumor cells < 1cm from tumor margin and 4/10 pts > 1cm (max 4 cm)**

Satellite tumor cells seen in the region of edema as per MRI

cancers

MDPI

Article

Analysis of the Peritumoral Tissue Unveils Cellular Changes Associated with a High Risk of Recurrence

Cancers 2023

Audrey Michot [1,2,3,*], Pauline Lagarde [2,3], Tom Lesluyes [2], Elodie Darbo [1,3], Agnès Neuville [2], Jessica Baud [1],

- **Molecular profiling of pseudocapsule**
- **To identify biomarkers to predict recurrence post surgery**
- **Prospective study, 20 pts of STS**

Findings:

Peritumoral tissue infiltrated with M2 macrophages & low in healthy tissue expression -> greater risk of relapse

Volume Delineation

Postop CTV

- Must include tumor bed, scar and the drainage orifices

✓ Longitudinal is craniocaudal margin (3 to 4 cm)

✓ Reduce manually if bone, fascia, joints etc.

✓ Include hematomas, fluid collections

✓ Radial margin is anteroposterior and lateral, i.e. 1.5 cm

Boost volume –

- 2cm longitudinal and 1.5 cm radial around the tumor bed

C Le Pechoux et al, Cancer Radiother 2022

Target Volumes

Table 6 Target delineation guidelines for extremity and superficial truncal STS target volumes[65,75,83,94]

Target	Delineation Guidance
Preop RT extremity or truncal CTV	CTV = GTV + 1.5 cm radial and 3-4 cm longitudinal anatomically constrained expansion with inclusion of peritumoral edema and biopsy tract (when feasible)
Preop RT subcutaneous tumor CTV (for tumor not involving fascia)	CTV = GTV + 3-4 cm circumferential margins with expansion of 0.5-1 cm into underlying non-involved muscle with inclusion of peritumoral edema and biopsy tract (when feasible)
Postop RT extremity or truncal CTV1	CTV1 = tumor bed (defined by clips/preop MRI) + 1.5 cm radial and 3-4 cm longitudinal anatomically constrained expansion + the operative field, surgical scar, and drain sites (when feasible)
Postop RT extremity or truncal CTV2	CTV2 = tumor bed (defined by clips/preop MRI) + 1.5 cm radial and 2 cm longitudinal expansion
Postop subcutaneous tumor CTV1	CTV1 = tumor bed (defined by clips/preop MRI) + 3-4 cm circumferential margins with expansion of 0.5-1 cm into uninvolved muscle + the operative field, scar, and drain sites (when feasible)
Postop subcutaneous tumor CTV2	CTV2 = tumor bed (defined by clips/preop MRI) + 1.5-2 cm circumferential margins and 0.5 cm into uninvolved muscle
Extremity or truncal PTV expansion	PTV expansion of 0.5 cm may be used with daily image guidance however >1.0 cm may be needed without daily image guidance. For preop RT, dose coverage to the PTV can be trimmed 3-5 mm from skin to reduce wound healing complications if achievable without unacceptable compromise of CTV coverage and if surgeon plans to resect overlying skin and subcutaneous tissue[73]

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; MRI = magnetic resonance imaging; preop = preoperative; postop = postoperative; PTV = planning target volume; RT = radiation therapy; STS = soft tissue sarcoma.

Defining the PTV

- 5mm to 10mm concentric margin
- Adaptive planning if volume changes in preoperative RT

Elective Nodal Radiation?

NO

Targets and OARs		
3. For patients with primary, localized extremity and truncal STS receiving preoperative RT, an anatomically constrained CTV is recommended. (Table 6)	Strong	Moderate [17,65,73,75]
4. For patients with primary, localized extremity and truncal STS receiving postoperative RT, an initial dose to an anatomically constrained CTV1 and additional dose to a reduced volume CTV2 is recommended. (Table 6)	Strong	Moderate [17,88,94,95]
5. For patients receiving either preoperative or postoperative RT for primary, localized extremity and truncal STS, volumetric contouring of the OARs and use of appropriate dose constraints are recommended.	Strong	Moderate [65,66,73,75,94,96,97]
6. For patients with primary, localized extremity and truncal STS, elective nodal RT is **not** recommended.	Strong	Moderate [17,65,73,75,88,94,95]

ASTRO Clinical Practice Guidelines, Pract Radiat Oncol 2021

Dose Fractionation

Preoperative RT

Table 5 Dose-fractionation schedules and target volumes for EBRT in extremity and superficial truncal adult STS

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
Radiation Dose and Fractionation		
1. For patients with primary, localized extremity and truncal STS receiving preoperative RT, 5000 cGy in 25 once daily fractions is recommended.	Strong	Moderate 16,17,65,73,75

ASTRO Clinical Practice Guidelines, Pract Radiat Oncol 2021

National Comprehensive Cancer Network® NCCN **NCCN Guidelines Version 2.2023 Soft Tissue Sarcoma**

NCCN Guidelines Index
Table of Contents
Discussion

50-50.4 Gy

R1 resection –

- ✓ **No definite evidence of improved local control with boost dose**
- ✓ **Decision to be individualized, consider potential toxicities**
- ✓ **If needed, 14-20 Gy boost**

Unresectable Disease

50 Gy + Boost till 63 Gy (higher doses 70-80 Gy can be considered)

Postoperative RT

R0 resection

2. For patients with primary, localized extremity and truncal STS receiving postoperative RT, 5000 cGy in 25 once daily fractions or 5040 cGy in 28 once daily fractions to CTV1 and additional dose to a reduced volume CTV2 is recommended. *(see Table 6 for target volume definitions)* Implementation remark: Additional dose to CTV2 of 1000 to 1600 cGy is used for negative margins and 1600 cGy for microscopic positive margins.	Strong	Moderate 11,17,50,88-93

ASTRO Clinical Practice Guidelines, Pract Radiat Oncol 2021

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Soft Tissue Sarcoma

NCCN Guidelines Index
Table of Contents
Discussion

- **Phase 1 : 50-50.4 Gy**
- **Phase 2 : Tumor bed 10-20Gy (depending upon surgical margins)**

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Disponible en ligne sur ScienceDirect www.sciencedirect.com
Elsevier Masson France EM|consulte www.em-consulte.com
Clinical practice guidelines

Conformal radiotherapy in management of soft tissue sarcoma in adults

Radiothérapie conformationnelle dans la prise en charge des sarcomes des tissus mous de l'adulte

C. Le Péchoux, C. Llacer, P. Sargos, L. Moureau-Zabotto, A. Ducassou,

Boost –
10 Gy to a reduced volume, if higher risk of local rec, like recurrence, unfavorable histology like myxofibrosarcoma

Postoperative RT

R1 Resection –

- **50 Gy -> 10-16Gy to reduced volume**

R2 Resection –

- **50 Gy -> 10-20 Gy boost to reduced volume**

C Le Pechoux et al, Cancer Radiother 2022

RT Complications

- Fibrosis
- Atrophy
- Fracture
- Decreased range of movements
- Peripheral nerve injury
- Dependent edema

Defining OAR

- Avoid circumferential irradiation of limb
- Spare bone and joint, whenever possible
- Higher risk of fracture after periosteal stripping
- Avoid gonads/external genitilia in pelvic region

OAR Constraints

Radiotherapy for sarcomas of the limbs and of the trunk: dose constraints.

Organs at risk	Dose constraints
Bone	Dmax < 60 Gy Dmean < 40 Gy V40 < 60%
Joint	Spare at least 50% of the joint
Genitourinary organs[a]	Uterus < 25–30 Gy Ovaries < 6 Gy Testis < 4 Gy
Healthy tissue of treated limb	Dmax < 30–50 Gy
Skin	The least possible
Contralateral limb	Dmean < 2 Gy
Peripheral nerves	Dmax < 50 Gy
Medullary canal	Dmax < 38 Gy
Medullary canal + 7 mm	Dmax < 45 Gy
Medullary canal + 10 mm	Dmax < 50 Gy
Kidney	Dmax < prescribed dose Dmean < 10 Gy
Liver	Dmax < 50.4 Gy V20 < 20%
Digestive tract	Dmax < prescribed dose D200 cm^3 < 40 Gy D450 cm^3 < 30 Gy

Dmean: mean dose; Dmax: maximal dose; Vx: recipient volume *x* Gy; Dxcm^3: dose in *x* cm^3. [a] Young patients should be offered to go to Cécos (Centre d'étude et de

C Le Pechoux et al, Cancer Radiother 2022

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Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 4, pp. 1119–1124, 2009

0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.12.006

CLINICAL INVESTIGATION **Sarcoma**

BONE FRACTURES FOLLOWING EXTERNAL BEAM RADIOTHERAPY AND LIMB-PRESERVATION SURGERY FOR LOWER EXTREMITY SOFT TISSUE SARCOMA: RELATIONSHIP TO IRRADIATED BONE LENGTH, VOLUME, TUMOR LOCATION AND DOSE

Colleen I. Dickie, B.Sc., MRT(T)(MR),* Amy L. Parent, B.Sc., MRT(T),*

Methods and Materials: Of 691 LE-STS patients treated from 1989 to 2005, 31 patients developed radiation-induced fractures. Analysis was limited to 21 fracture patients (24 fractures) who were matched based on tumor size and location, age, beam arrangement, and mean total cumulative RT dose to a random sample of 53 nonfracture patients and compared for fracture risk factors. Mean dose to bone, RT field size (FS), maximum dose to a 2-cc volume of bone, and volume of bone irradiated to ≥40 Gy (V40) were compared. Fracture site dose was determined by comparing radiographic images and surgical reports to fracture location on the dose distribution.

Results: For fracture patients, mean dose to bone was 45 ± 8 Gy (mean dose at fracture site 59 ± 7 Gy), mean FS was 37 ± 8 cm, maximum dose was 64 ± 7 Gy, and V40 was 76 ± 17%, compared with 37 ± 11 Gy, 32 ± 9 cm, 59 ± 8 Gy, and 64 ± 22% for nonfracture patients. Differences in mean, maximum dose, and V40 were statistically significant (p = 0.01, p = 0.02, p = 0.01). Leg fractures were more common above the knee joint.

Fracture risk reduced –

- **Dmean < 37Gy**
- **V40Gy < 64%**
- **Dmax < 59Gy**

RT Technique

3DCRT:

- lateral beams, AP-PA
- Well lateralised lesions

IMRT, Rotational techniques:

- Cover large volume with uniform dose
- Limit excess dose to skin
- Concave isodoses at interface with bone
- Reduction in late toxicities

Radiotherapy and Oncology 93 (2009) 125–130

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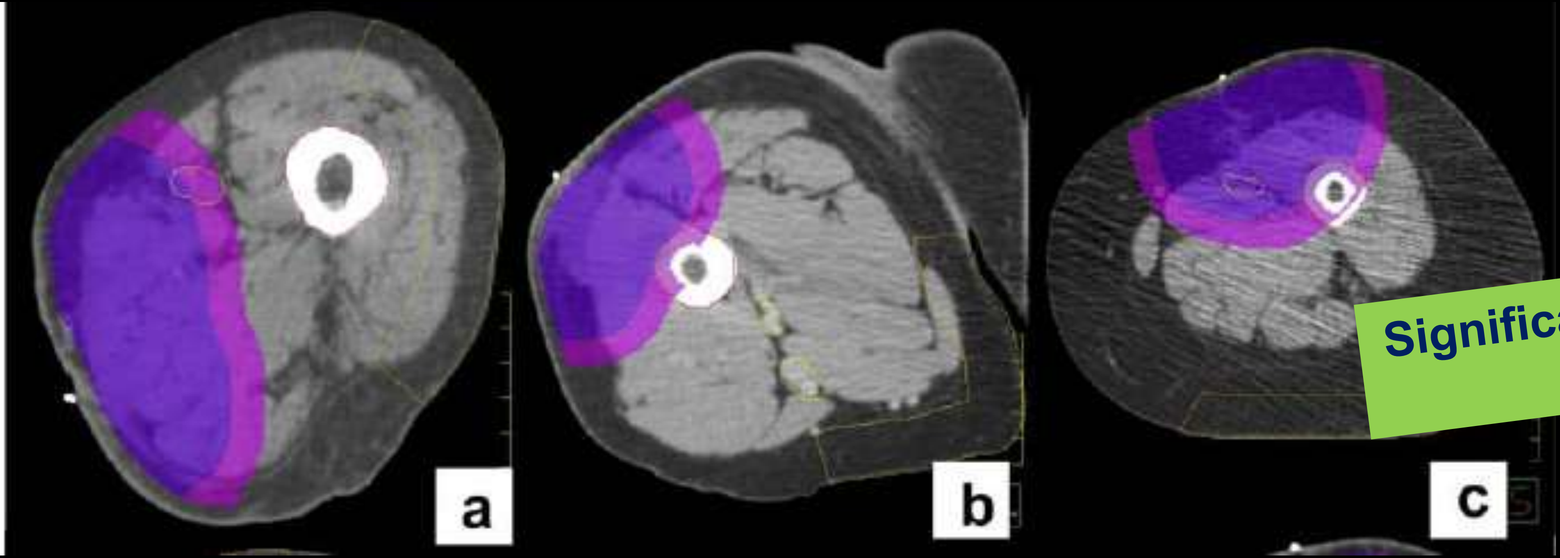
RT of soft tissue sarcoma

Comparison of conventional radiotherapy and intensity-modulated radiotherapy for post-operative radiotherapy for primary extremity soft tissue sarcoma

Alexandra J. Stewart[a,*], Young K. Lee[b], Frank H. Saran[c]

The neurovascular bundle was contoured manually from pelvic brim to mid knee joint. The whole femur was contoured using an auto contour setting and then checked and modified manually if necessary. The minimum skin corridor was defined as volume of a 2 cm thick band that covered 30% of the limb circumference at 180 degrees from the centre of the PTV_1 over the length of PTV_1, see Fig. 1 to demonstrate skin corridor (defined by yellow line) in each patient. A circumference of 30% was chosen since clinical experience has shown that a skin corridor of 20–30% is likely to give a minimal risk of lymphoedema in the future. Normal tissue was defined as the volume of ipsilateral limb lying outside PTV_1



Target	Volume (%)	Primary dose constraint
PTV_2	99%	90% (56.2 Gy)
	95%	95% (59.4 Gy)
	50%	100% (62.5 Gy)
	5%	105% (65.6 Gy)
	1%	110% (68.8 Gy)
PTV_1	99%	90% (45.0 Gy)
	95%	95% (47.5 Gy)
	50%	100% (50.0 Gy)
Organs-at-risk		
Femur	0–50% [illegible]	[illegible]
	[illegible]	[illegible] 2 Gy per fraction or equivalent
	[illegible] bone circumference within PTV	Aim to spare 1/3 of bone circumference if it is at least 1 cm from the PTV
	100% bone circumference within PTV	Aim for central sparing of cortex/bone marrow
Joint	<50% of any joint within the field	
Contralateral leg	No beams entering or exiting through contralateral leg if possible	
Genitalia	Exclude where possible	Max. dose to testes 6 Gy Max. dose to ovaries 8 Gy
Skin corridor	Aim for 0 Gy	
Soft tissue outside PTV	Less than 55 Gy in 2 Gy per fraction	
Neurovascular bundle	56 Gy in 2 Gy per fraction	

Significantly lower V45 femur, V55 normal tissue & better target coverage

Minimum Skin Corridor:

- 30% of skin circumference at 180· from PTV

Adjuvant volumetric modulated arc therapy compared to 3D conformal radiation therapy for newly diagnosed soft tissue sarcoma of the extremities: outcome and toxicity evaluation

BJR 2019

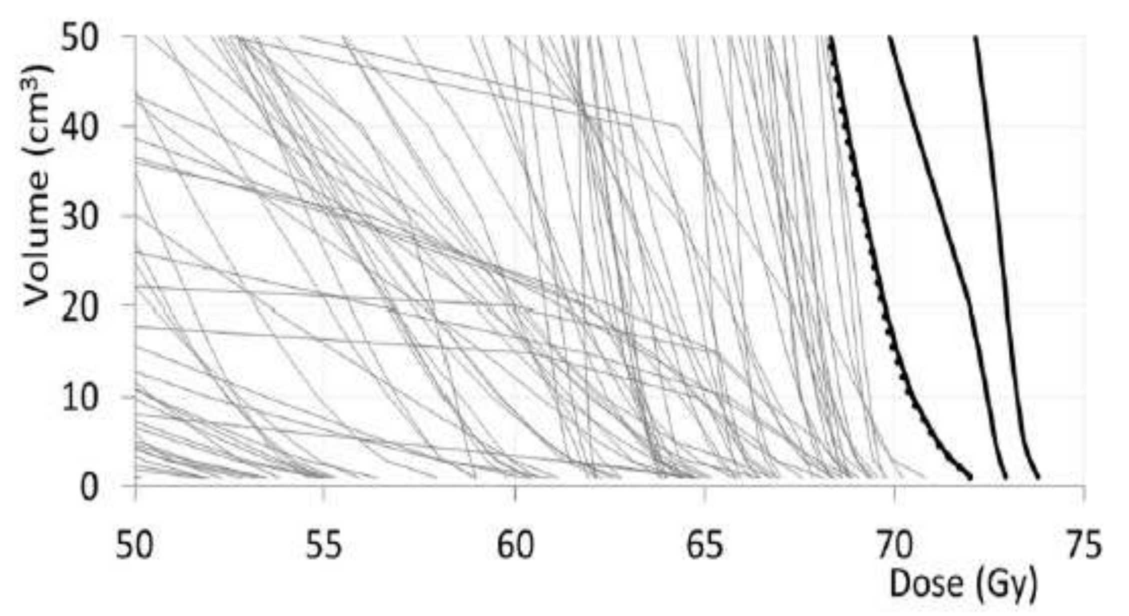
[1]LUCIA DI BRINA, [1]ANTONELLA FOGLIATA, [1]PIERINA NAVARRIA, [1]GIUSEPPE D'AGOSTINO, [1]CIRO FRANZESE,

Table 2. Dosimetric analysis summary, as mean values ± standard error of the mean, and range in brackets

Structure	Parameter	All patients	3DCRT	VMAT	p
Bone	D_{1ccm} (Gy)	60.6 ± 0.9	66.9 ± 0.5	57.3 ± 1.2	<0.001
	D_{5ccm} (Gy)	58.8 ± 1.0	66.1 ± 0.6	55.0 ± 1.3	<0.001
	D_{10ccm} (Gy)	57.5 ± 1.1	65.4 ± 0.8	53.3 ± 1.4	<0.001
	D_{max} (Gy)b	63.5 ± 0.8	67.7 ± 0.5	61.3 ± 1.2	<0.001

- **3 pts developed ORN, all treated with 3DCRT**
- **Better conformity and maximal sparing of**
- **normal tissues with VMAT**

DVH for bone for all pts



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Systematic Review

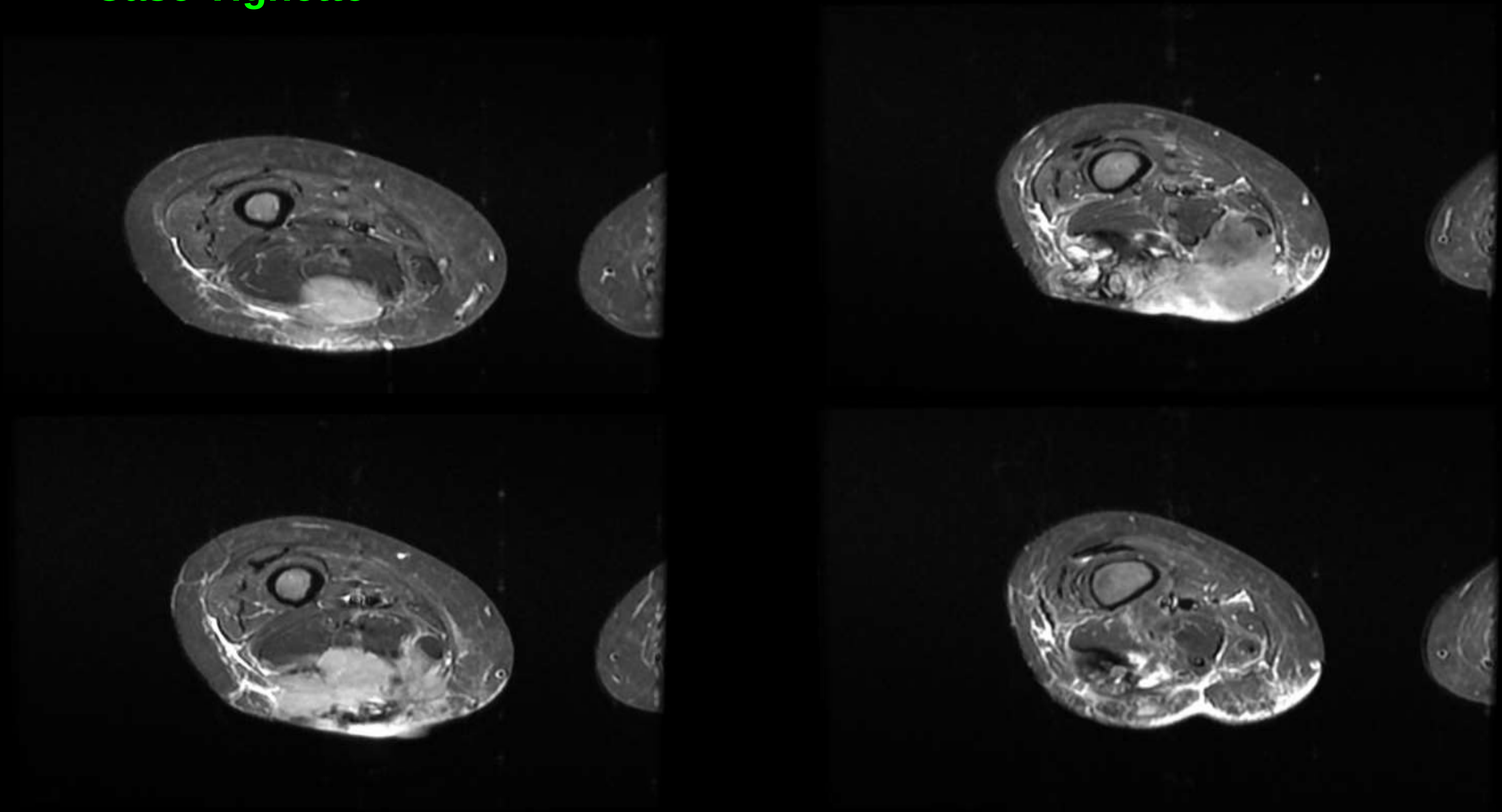
Toxicity, normal tissue and dose-volume planning parameters for radiotherapy in soft tissue sarcoma of the extremities: A systematic review of the literature

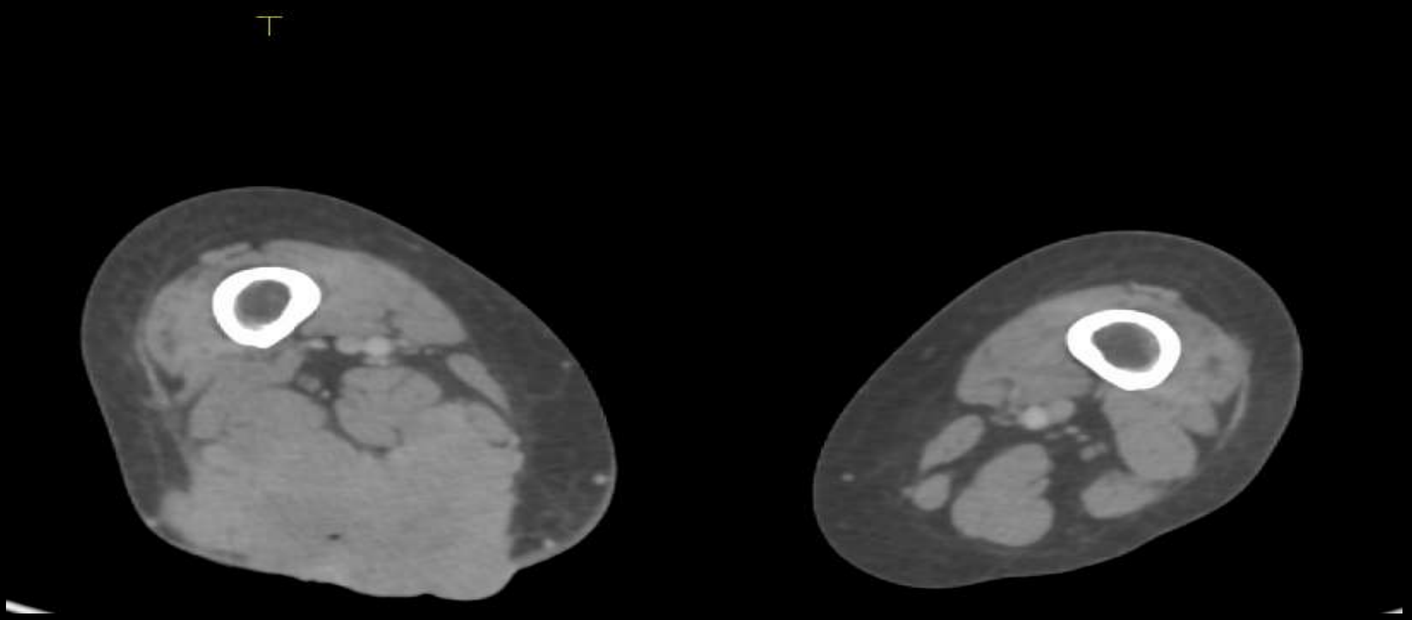
Rita Simões [a,b,c,d,*], Yolanda Augustin [b], Sarah Gulliford [d,e], Hakim-Moulay Dehbi [e], Peter Hoskin

Lack of evidence based guidelines on normal tissues and dose volume parameters

Author	Technique	Planning outcomes and/or dose volume constraints reported
Di Brina, L. et al[22]	Rotational IMRT & 3DCRT	Planning outcomes reported in the study comparing 3DCRT and IMRT (VMAT). Bone doses reported achieved: D1cm (Gy) - all patients 60.6 ± 0.9; 3DCRT 66.9 ± 0.5 vs VMAT 57.3 ± 1.2 (p < 0.001); D5ccm (Gy) - all patients 58.8 ± 1.0; 3DCRT 66.1 ± 0.6 vs VMAT 55.0 ± 1.3 (p < 0.001); D10ccm (Gy) - all patients 57.5 ± 1.1; 3DCRT 65.4 ± 0.8 vs VMAT 53.3 ± 1.4 (p < 0.001); Dmax (point dose) (Gy) - all patients 63.5 ± 0.8; 3DCRT 67.7 ± 0.5 vs VMAT 61.3 ± 1.2 (p < 0.001)
Devisetty, K. et al.[25]	not specified	Maximum doses reported from patients who developed severe toxicities
Stewart A. et al.[27]	IMRT & 3DCRT	Planning recommendations; Femur: 1) if 0–50% bone circumference within PTV aim to a) 100% bone cortex under 52 Gy or b) 50% of cortex of bone must not receive over 45 Gy in 2 Gy per fraction or equivalent; 2) if 50–99% bone circumference within PTV aim to spare 1/3 of bone circumference if it is at least 1 cm from the PTV; 3) if 100% bone circumference within PTV aim for central sparing of cortex/bone marrow; Joint: <50% of any joint within the field; Contralateral leg: No beams entering or exiting through contralateral leg if possible; Genitalia: Exclude where possible; Max. dose to testes 6 Gy; Max. dose to ovaries 8 Gy; Skin corridor: Aim for 0 Gy; Soft tissue outside PTV: Less than 55 Gy in 2 Gy per fraction; Neurovascular bundle: 56 Gy in 2 Gy per fraction
Kalbasi A. et al.[29]	IMRT	Planning recommendations as part of clinical trial protocol; Skin V12Gy ≤ 50%;2cm longitudinal strip of skin V12Gy ≤ 10%; Long bones (femur, humerus) V30Gy ≤ 50% Femoral or humeral head V30Gy ≤ 5 cc, Dmax ≤ 33 Gy
O'Sullivan, B.[31]	IMRT	Planning recommendations as part of clinical trial protocol; Bone mean dose < 37 Gy; Maximum bone dose < 59 Gy; The percentage of bone receiving ≥ 40 Gy < 64%; musculature/ tissue dose < 20 Gy Maximum 21 Gy
Pak D. et al.[33]	3DCRT & 2DRT	A dosimetric comparison was done in as much as a single subtrochanteric fracture case. Mean dose of 62.0 Gy, a V30 = 42.8 cc, V45 = 42.8 cc, and V60 = 42.8 cc at the subtrochanteric region for the fracture patient were substantially outside the upper limits of the 95% confidence intervals calculated for the nonfracture patients All fracture sites had mean doses greater than 40 Gy
Dickie, C. et al.[16]	3DCRT	Bone fractures modelled; The risk of radiation-induced fracture is reduced if femur V40 < 64%. Fracture incidence was lower when the mean dose to bone was < 37 Gy or maximum dose anywhere along the length of bone was < 59 Gy.
Lawless, A. et al.[45]	IMRT	A dosimetric study applying previously dose-volume constraints for femur: mean < 37 Gy and max dose < 59 Gy
Casey, D et al.[46]	IMRT	A dosimetric study testing the application of previous dose-volume constraints for femur: Dmean < 37 Gy, V40Gy < 64%, and Dmax < 59 Gy

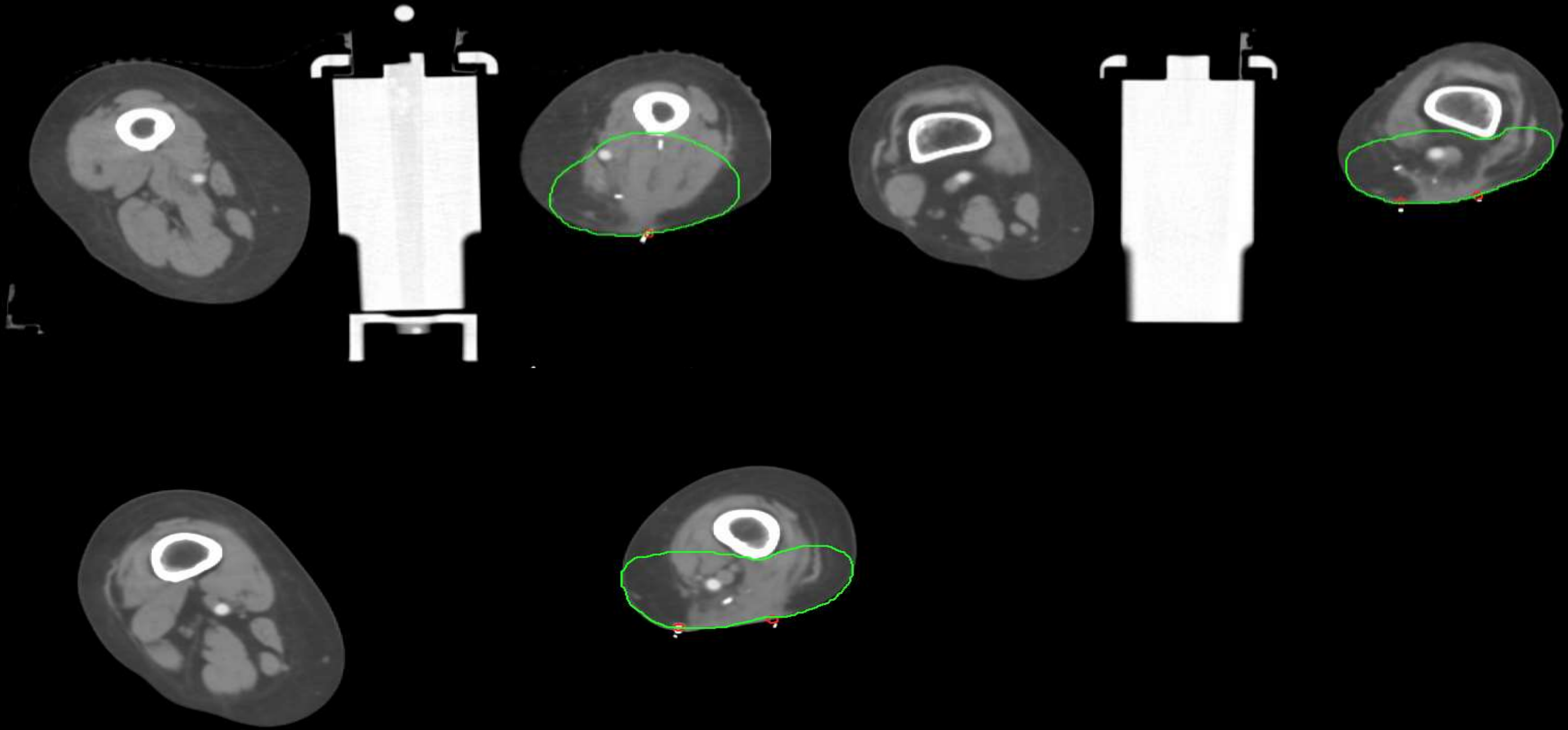
Case Vignette

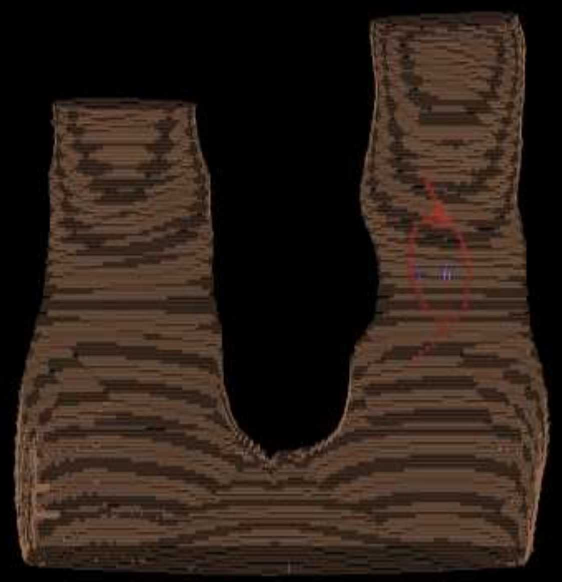


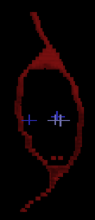


Pre-op CT scan

Volume Delineation

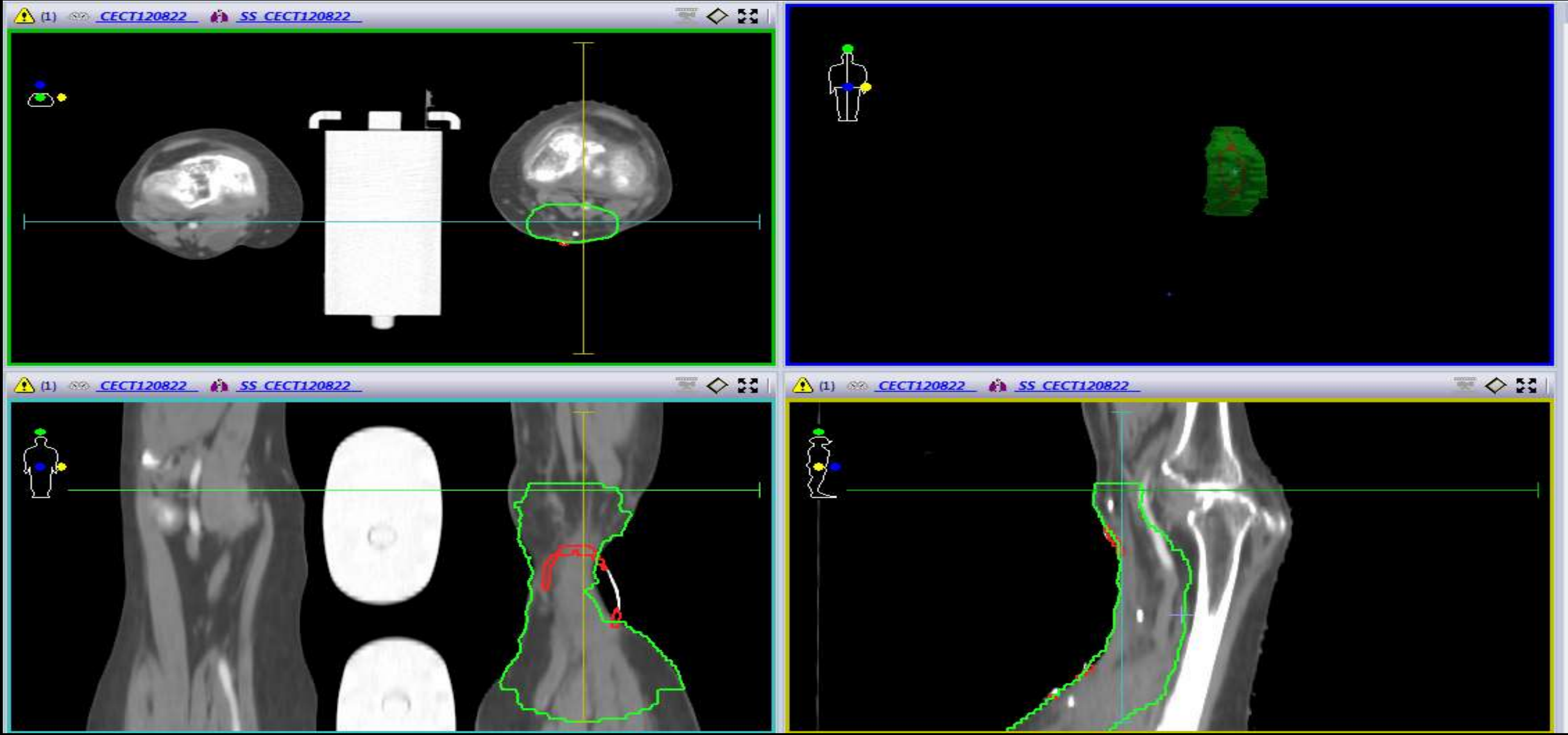




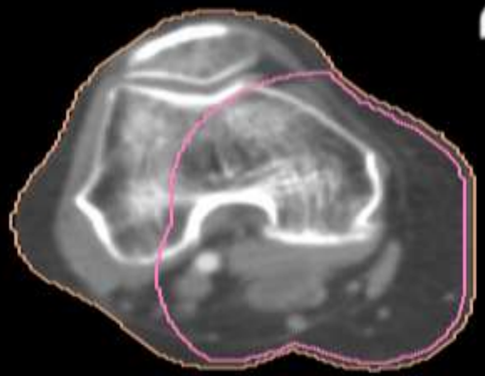


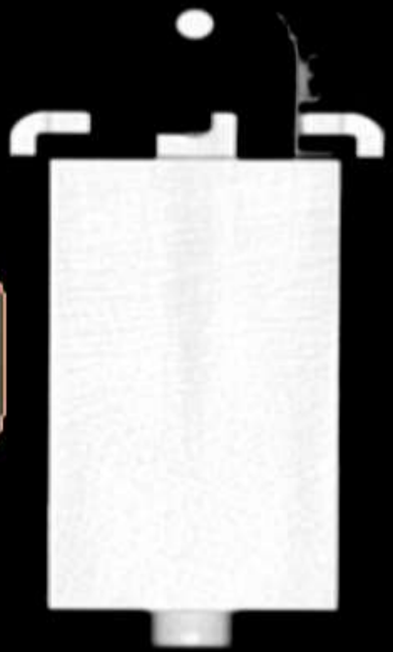
Scar Delineation

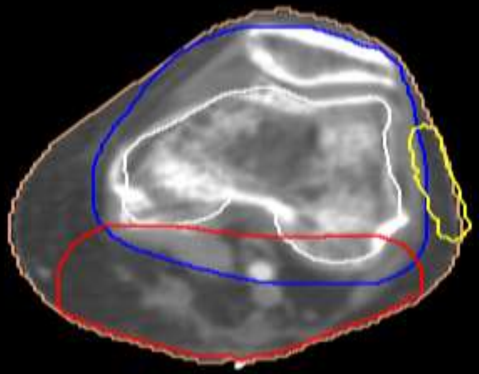
CTV in Proximity of Knee Joint

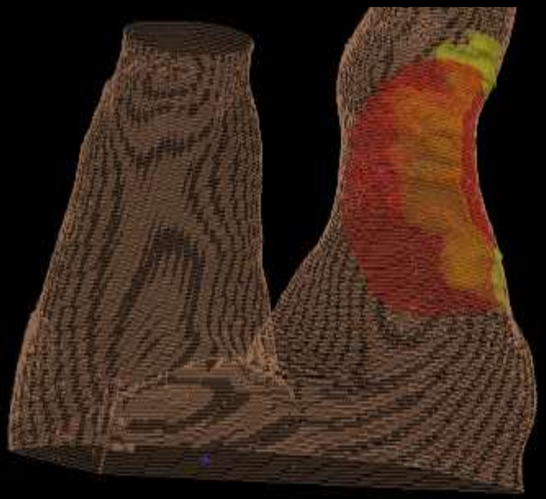


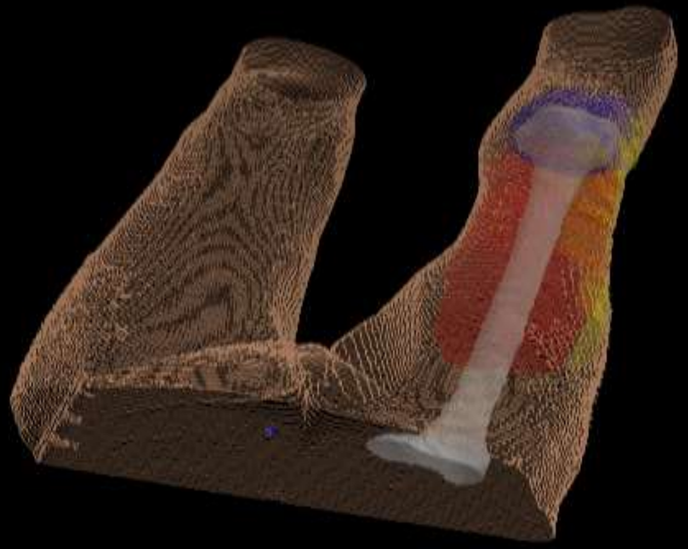
OAR Delineation

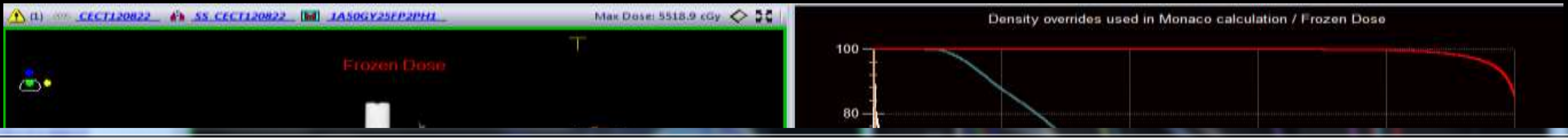






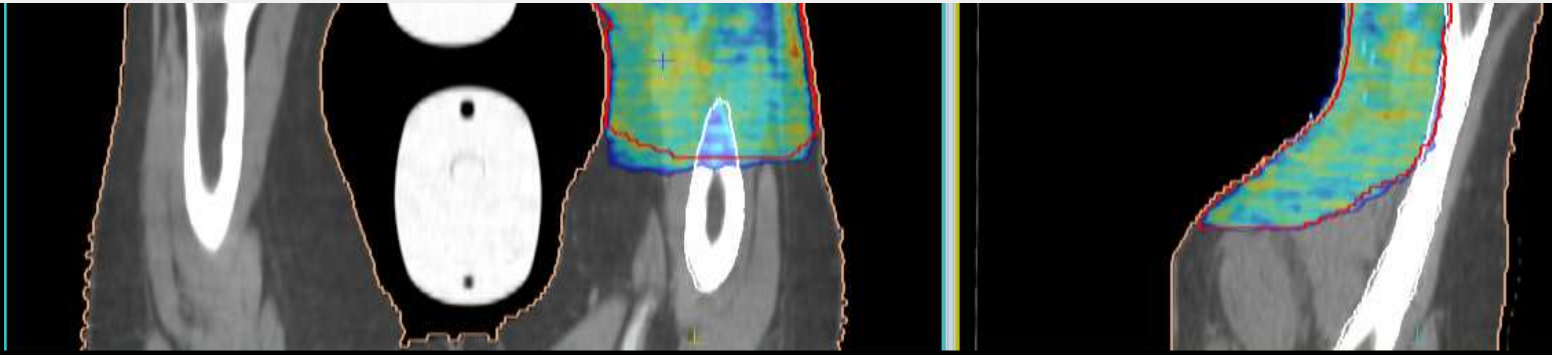




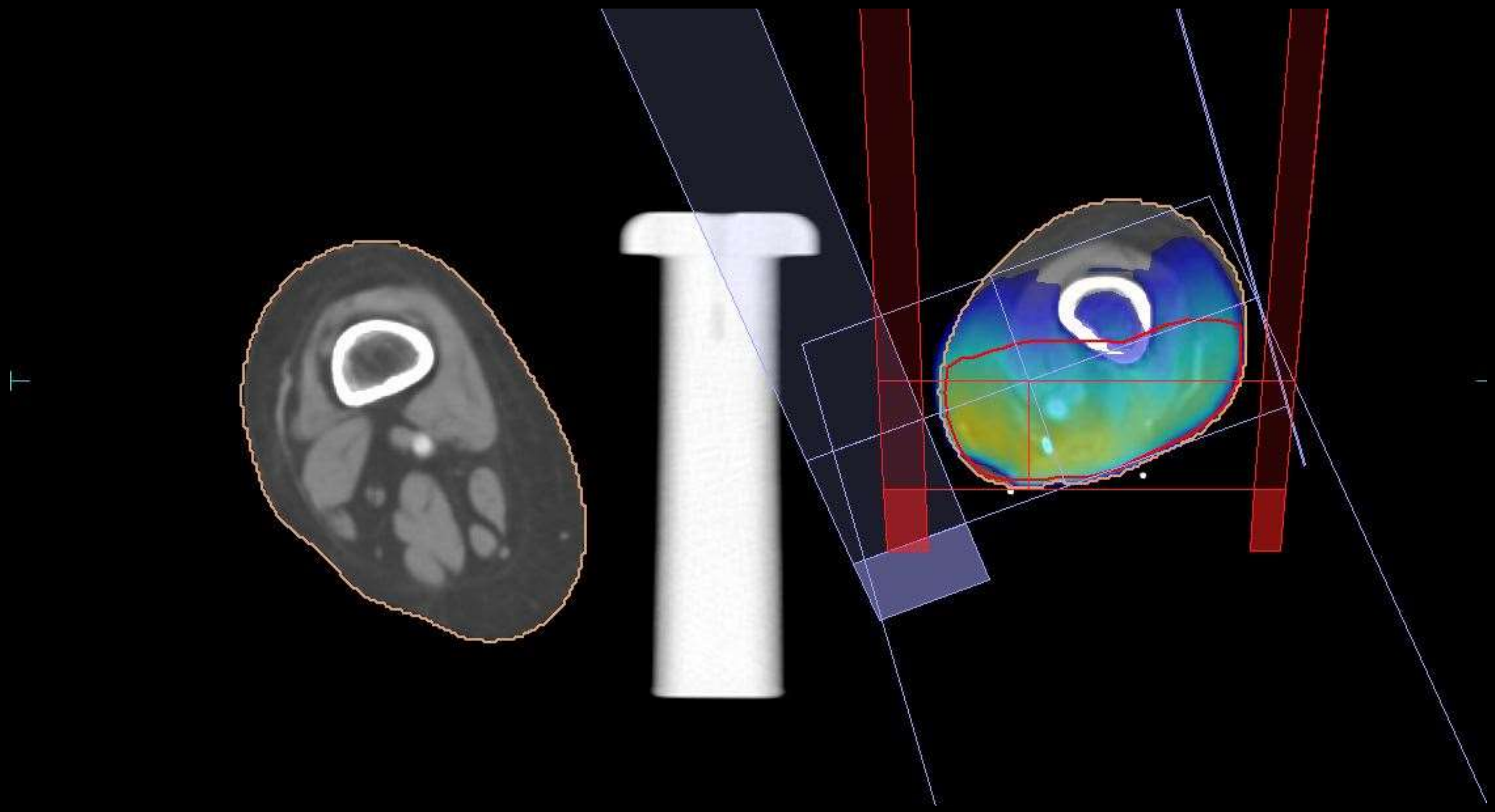


Statistics | Display

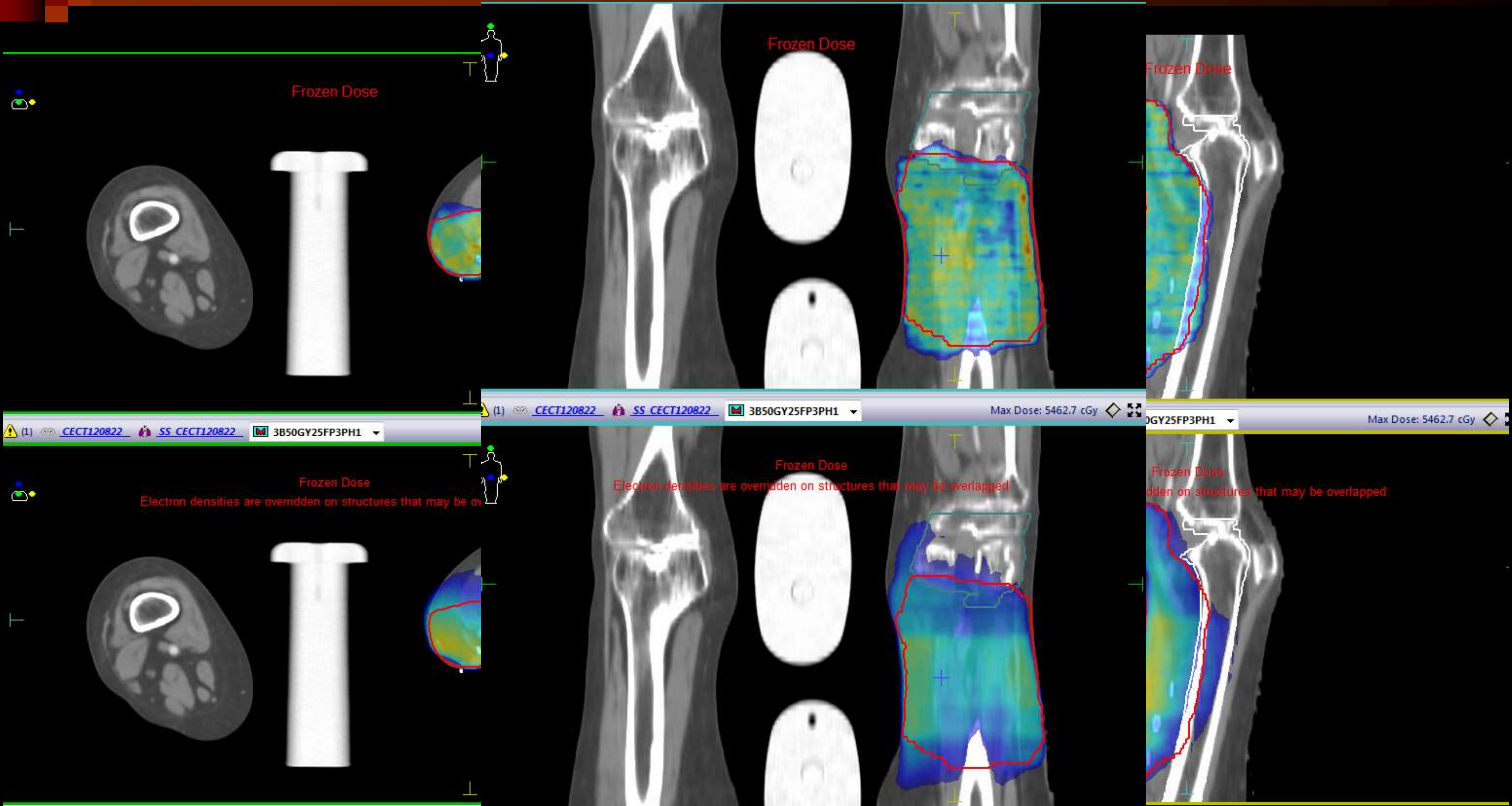
Structure	Volume (cm³)	Min. Dose (cGy)	Max. Dose (cGy)	Mean Dose (cGy)	Cold Ref. (cGy)	Volume < (cm³)	Volume < (%)	Hot Ref. (cGy)	Volume > (cm³)	Volume > (%)	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
PTV Tu Bed	876.536	1000.4	5518.9	5089.1				4828.7	**832.709**	**95.00**	100.00	yes	1.09	0.71
Femur Rt	345.427	5.3	5348.0	2032.3				**4000.0**	68.296	19.77	100.00	yes	490.57	0.00
Skin Strip	104.672	162.7	5192.4	2100.1							100.00	yes	10.50	0.00
Knee Jt Rt	319.719	284.6	5366.3	2506.1							100.00	yes	6.61	0.01
Lt Leg Avoidance	1403.506	62.5	299.5	142.5				139.2	**701.753**	**50.00**	100.00	yes	2.28	
patient	13778.598	0.0	5510.5	693.3							99.47	no	670.96	0.00
CTV Tu Bed	653.628	0.0	5518.9	5077.1				4744.6	**620.947**	**95.00**	100.00	yes	1.11	

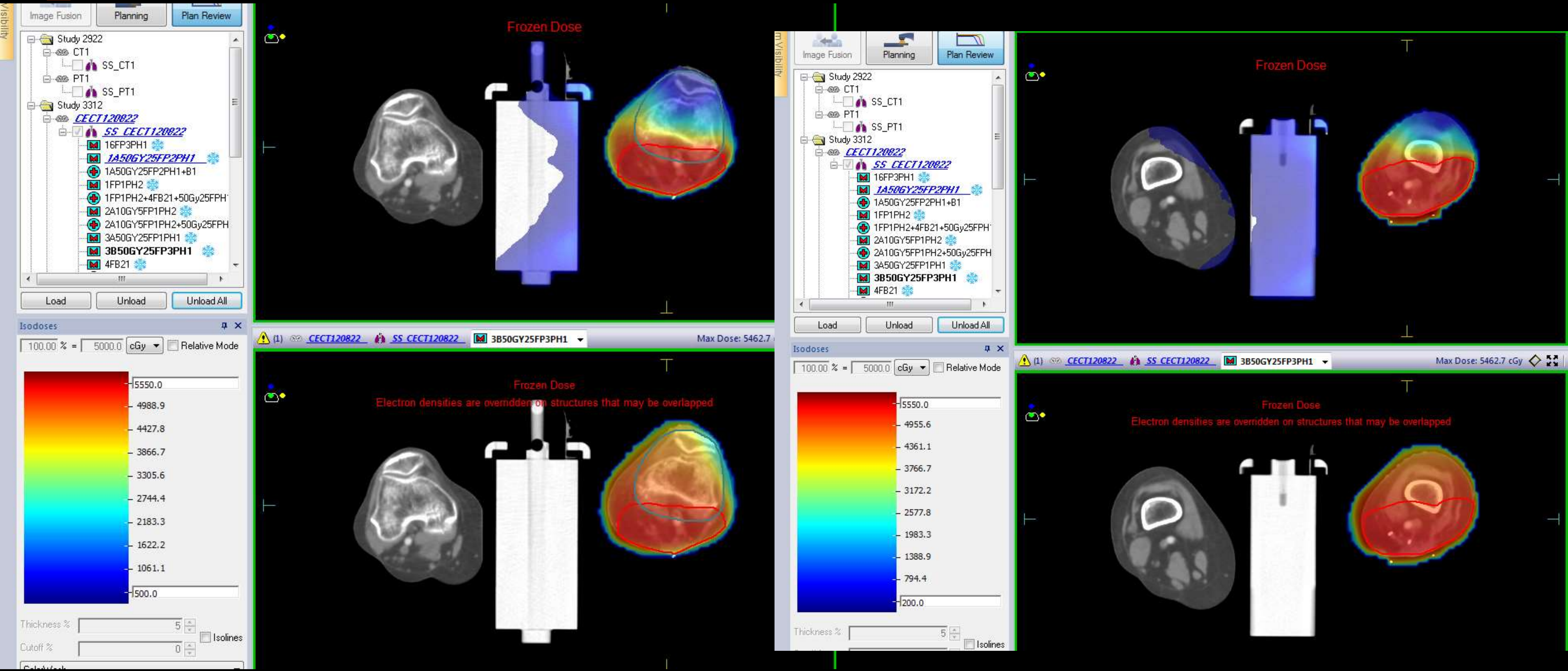


VMAT Plan 95% Isodose

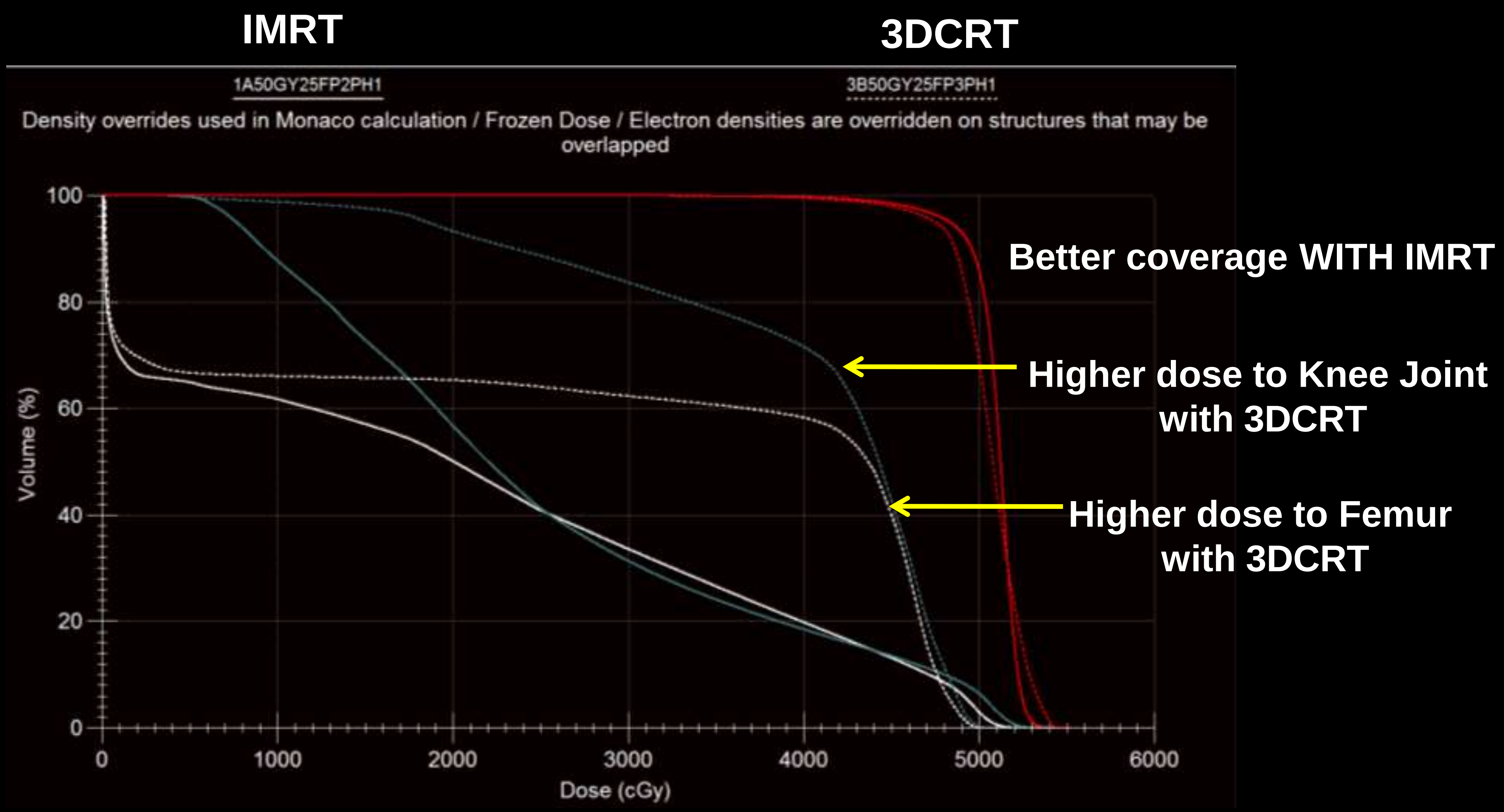


3DCRT Plan


Frozen Dose
(1) CECT120822 SS_CECT120822 3B50GY25FP3PH1
Frozen Dose
Electron densities are overridden on structures that may be ov
Frozen Dose
(1) CECT120822 SS_CECT120822 3B50GY25FP3PH1 Max Dose: 5462.7 cGy
Frozen Dose
Electron densities are overridden on structures that may be overlapped
Frozen Dose
0GY25FP3PH1 Max Dose: 5462.7 cGy
Frozen Dose
dden on structures that may be overlapped



Lower Isodose Region


IMRT
3DCRT
1A50GY25FP2PH1
3B50GY25FP3PH1
Density overrides used in Monaco calculation / Frozen Dose / Electron densities are overridden on structures that may be overlapped
100
80
60
40
20
0
Volume (%)
0
1000
2000
3000
4000
5000
6000
Dose (cGy)
Better coverage WITH IMRT
Higher dose to Knee Joint with 3DCRT
Higher dose to Femur with 3DCRT

DVH

Retroperitoneal Sarcoma

- 10-15% of adult STS
- WD Liposarcoma or Atypical Lipomatous Tumor, Dedifferentiated LPS, Leiomyosarcoma
- ‘Monobloc’ surgery is the standard treatment
- Large size, anatomic constraints, proximity to critical structures/vasculature
- RT – Preop/Intraop/Postoperative

Pre-op RT advantages:

- GTV defined accurately
- Lower OAR doses, as organs displaced by mass
- Lower RT doses

Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial

Lancet Oncol 2020

Sylvie Bonvalot, Alessandro Gronchi, Cécile Le Péchoux, Carol J Swallow, Dirk Strauss, Pierre Meeus, Frits van Coevorden, Stephan Stoldt,

Critical impact of radiotherapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: Results from the EORTC 62092-22092 STRASS trial

Cancer 2022

Rick Haas, MD, PhD [1,2]; Jean-Jacques Stelmes, MD [3]; Facundo Zaffaroni, PhD[4]; Nicolas Sauvé, PhD[4];

Multinational phase III RCT
Operable, localised RPS
Pri End Point – Abdominal RFS
266 pts, median fu 43 mths

R A N D O M I Z E

Surgery alone

Preop RT (50.4 Gy) -> Surgery
95% IMRT

- **28.8% pts non RT compliant group**
- **Sig. 3yr ARFS benefit with preop RT in RT compliant group**

Ann Surg. 2023 Jul 1;278(1):127-134. doi: 10.1097/SLA.0000000000005492. Epub 2022 Jul 14.

Preoperative Radiotherapy in Patients With Primary Retroperitoneal Sarcoma: EORTC-62092 Trial (STRASS) Versus Off-trial (STREXIT) Results

Dario Callegaro [1], Chandrajit P Raut [2], Taiwo Ajayi [3], Dirk Strauss [4], Sylvie Bonvalot [5],

Results –

- **No diff in ARFS or OS**
- **Local rec higher in Sx alone 37% vs 19% in preop RT arm**
- **Unplanned analysis – LPS pts, 10% abs benefit with RT**

- **266 STRASS pts, 871 STREXIT pts**
- **1:1 PS matching**
- **Better ARFS in LPS, esp Grade 1 or 2**
- **No benefit in LMS or G3DDLPS**

Preoperative RT not routinely recommended in RPS

RPS cont..

- Postoperative RT not recommended in RPS
- IORT with PreopRT is being evaluated, better local control, but with toxicities

- PreopRT NOT recommended in routine, in addition to oncologic resection
- can be considered in lower grade RPS, LPS histology
- IMRT is preferable

Treatment Guidelines for Preoperative Radiation Therapy for Retroperitoneal Sarcoma: Preliminary Consensus of an International Expert Panel

IJROBP 2015

Elizabeth H. Baldini, MD, MPH,* Dian Wang, MD, PhD,†

Myxoid LPS

- Unique subtype of Liposarcomas
- Presence of fusion gene, FUS-DDIT3
- Younger age, thigh region, metastasize to bone, soft tissue
- Higher RT responsiveness

JAMA Oncol. 2021 Jan; 7(1): e205865. PMCID: PMC76
Published online 2020 Nov 12. doi: 10.1001/jamaoncol.2020.5865: PMID: 331
10.1001/jamaoncol.2020.5865

Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma

A Nonrandomized Controlled Trial

Jules Lansu, MD,[1] Judith V. M. G. Bovée, MD, PhD,[2] Pètra Braam, MD, PhD,[3] Hester van Boven, MD, PhD,[4]

- Phase II single arm study
- 79 myxoid LPS pts extremity/trunk
- 36Gy/18 # preop RT ->Sx
- 100% local control at median fu 25 mths

Dose reduction to 36 Gy in PreopRT to be considered

Take Home Message

- Soft Tissue Sarcomas can be challenging to treat
- Multidisciplinary discussion essential
- Radiation Therapy, if indicated, maximizes local control
- Treatment Planning individualized

Thank You