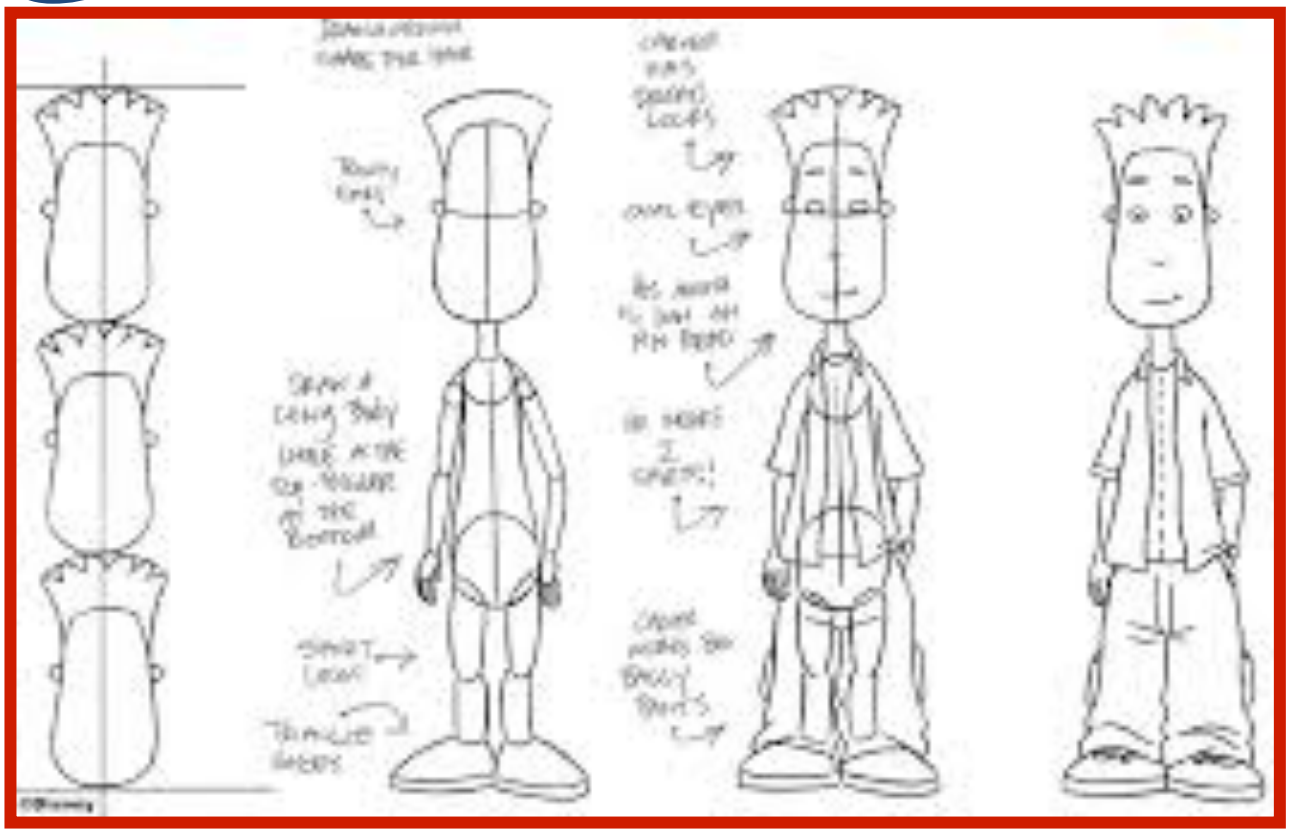
STS



LAB CONTOURING

SOFT TISSUE SARCOMA

Sarcoma of Soft Tissues constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin, including fat, muscle, nerve and sheath nerve, blood vassels, and other connective tissues.

More than 50 different histological subtypes of soft tissue sarcoma have been identified.

The anatomical site of primary disease represents an important variable that influences treatment and outcome.

OCCURRENCE OF SOFT TISSUE SARCOMA BY SITE,
BASED ON AMERICAN COLLEGE OF SURGEONS PATTERNS OF CARE SUMMERY
Donegan LW et al. Ann Surg 1987; 205:349-359

No. pts	H&N (%)	Trunk (%)	Upper Extremity (%)	**Lower Extremity (%)**	Retro-Peritoneum (%)	Mediastinum (%)
4,550	8.9	17.9	13.1	**46.4**	12.5	1.3

Why Radiotherapy in STS?

Amputation vs. Surgery and Radiotherapy

- Rosenberg et al. Ann.Surg. 1982

Surgery alone vs. Surgery and Radiotherapy

- Pisters et al. (MSKCC) BRT JCO 1996
- Yang et al. (NCI) EBRT JCO 1998

NCI TRIAL
AMPUTATION VS WLE+ RT

43 pts High Risk Soft Tissue Sarcoma

27 pts
WLE + RT

16 pts
Amputation

Rosemberg Ann Surg. 1982

NCI TRIAL
AMPUTATION VS WLE+RT

LOCAL CONTROL:

- Amputation: 1/16 failed
- WLE + RT: 5/27 failed

p=0.2

OVERALL SURVIVAL:

- Amputation: 11/16 failed
- WLE + RT: 13/27 failed

p=0.6

Rosemberg Ann Surg. 1982

NCI TRIAL
WLE VS WLE+EBRT

91 pts High Risk Soft Tissue Sarcoma

44 pts
WLE

47 pts
WLE+EBRT

Local failure: WLE+EBRT: 0% vs WLE: 22% p=.0001

Yang et al.JCO 1998

MSKCC TRIAL
Surgery Alone VS Surgery + BRT

164 pts High Risk Soft Tissue Sarcoma

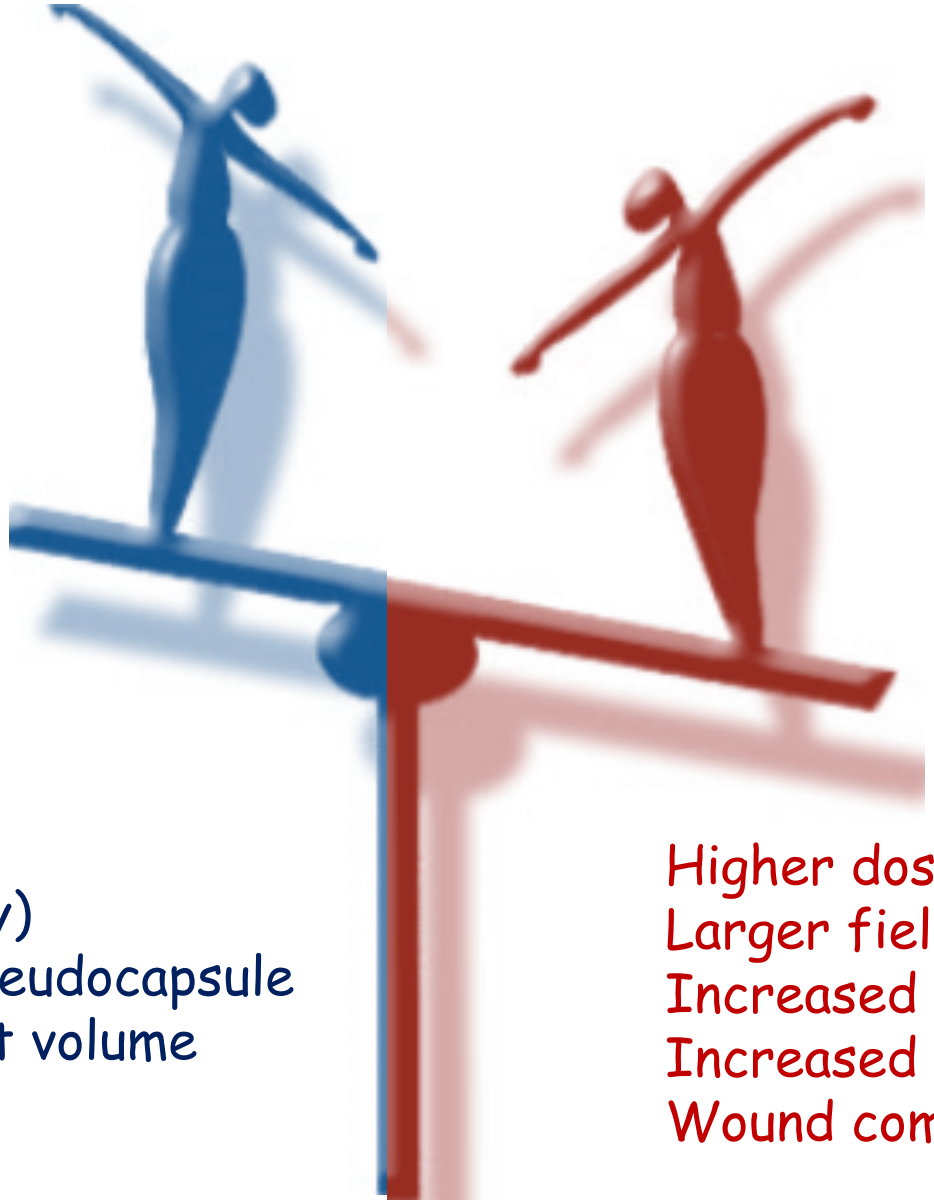
86 pts
WLE

78 pts
WLE+BRT

Freedom from relapse @60 mos:
WLE: 69% vs WLE+BRT: 82% p=.04

Pisters PW et al. JCO 1996

PRE-OPERATIVE VS POST-OPERATIVE

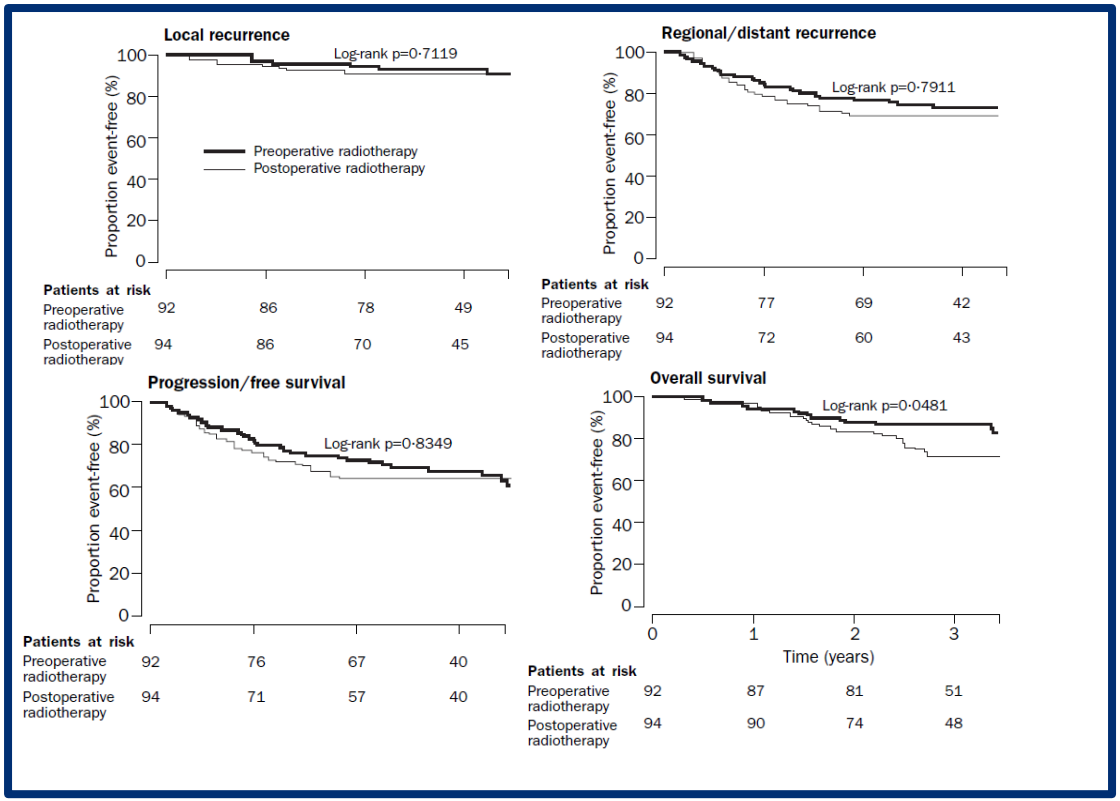


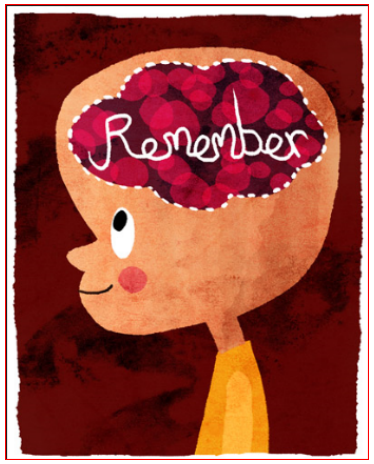
Lower dose (50 Gy)
Downsizing and pseudocapsule
Smaller treatment volume
Reduced fibrosis
Reduced edema
Increased wound complications

Higher dose (60-66 Gy)
Larger field size
Increased fibrosis
Increased edema
Wound complications risk

Davis AM et al. J Clin Oncol. 2002 ;20:4472-7.
O'Sullivan et al. Lancet 2002; 359: 2235-41

PRE-OPERATIVE VS POST-OPERATIVE





BUT

Higher acute wound healing complication rate (35% vs 17%; 43% in lower extremity tumors) in pre-operative RT

Fibrosis worse in postoperative RT with Higher RT doses and larger filelds

Davis AM et al. J Clin Oncol. 2002 ;20:4472-7.
O'Sullivan et al. Lancet 2002; 359: 2235-41

PRE-OPERATIVE VS POST-OPERATIVE

- ✓ Comparative efficacy of pre- versus postoperative radiation in oncologic outcomes such as LC and OS has not been established.

- ✓ One randomized controlled trial (O'Sullivan et al. Lancet 2002) showed wound complications rate 35% in the preoperative RT group vs 17% in the postoperative RT group; benefit in OS was observed in patients who had preoperative RT (p=0.0481) not confirmed at 5 years follow up (O'Sullivan et al JCO 2004)

- ✓ Data from a recent multicentric retrospective study on 821 patients suggest that preoperative RT is associated with a reduced cancer-specific mortality compared to postoperative RT in STS (Sampath et al. IJROBP 2011)

Is Delineation of Target Volume Relevant ?

768 pts treated with surgery + RT pre/post based on CT + diagnostic CT and MRI

LR preoperative RT alone (50 Gy) vs postoperative RT (60-66 Gy)
= 6.9% and 6.4%, respectively

Table 2. Radiotherapy scheduling and surgical margin status relative to local recurrence location

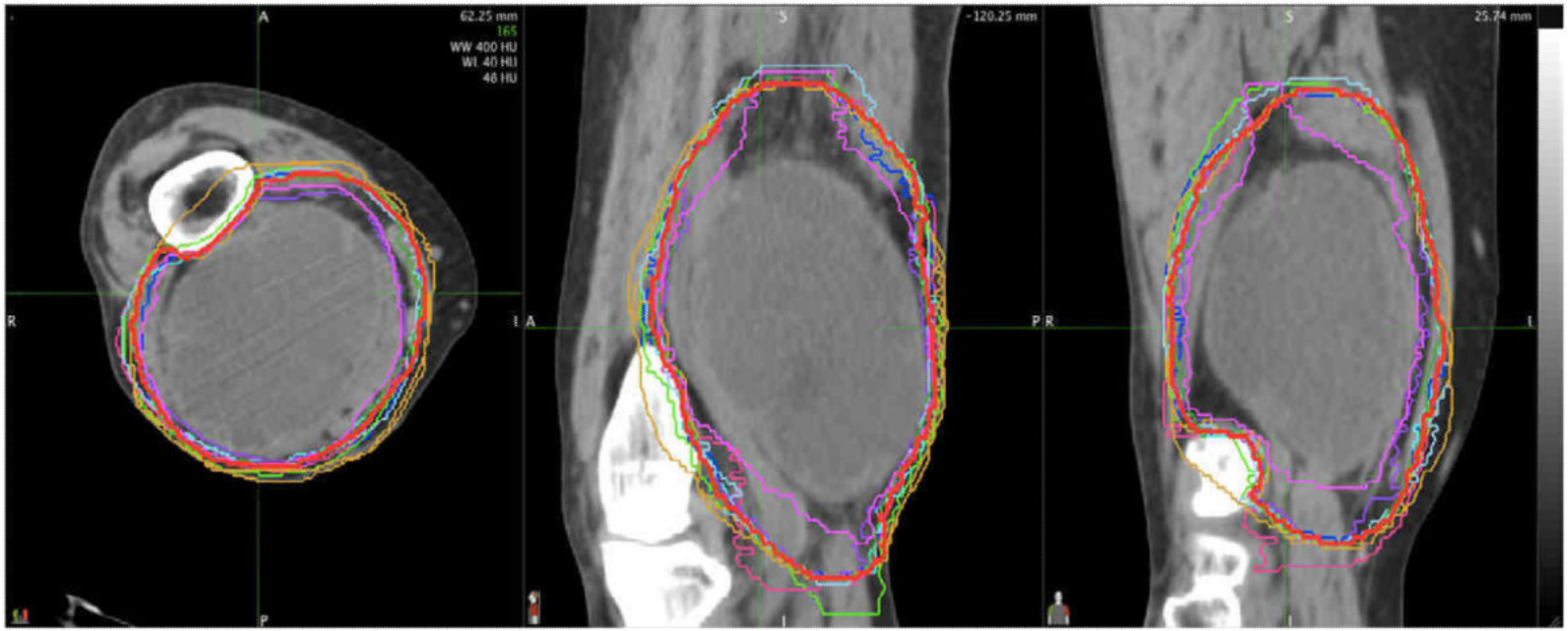
	Surgical margin status		RT scheduling		
LR location	Negative Sx margins: R0 (column %)	Positive Sx margins: R1 + R2 (column %)	Preop (column %)	Postop (column %)	Preop + Boost (column %)
In field	26 (4.3)	23 (14.0)	27 (5.8)	12 (4.8)	10 (18.5)
Out of field	6 (1.0)	3 (1.8)	4 (0.9)	4 (1.6)	1 (1.8)
Marginal	0 (0)	2 (1.2)	1 (0.2)	0 (0)	1 (1.8)
Total LR	32 (5.3)	28 (17.0)	32 (6.9)	16 (6.4)	12 (22.1)
Total study population	604 (100)	164 (100)	463 (100)	251 (100)	54 (100)

Abbreviations: LR = local recurrence; Postop = postoperative RT scheduling; Preop = preoperative RT scheduling; Preop + Boost = preoperative RT plus a postoperative boost with reduced RT volumes; R0 = negative resection margin; R1 = microscopic positive resection margin; R2 = gross positive resection margin; RT = radiotherapy; Sx = surgical resection.

Conclusions: The majority of STS tumors recur in field, indicating that the incidence of LR may be affected more by differences in biologic and molecular characteristics rather than aberrations in RT dose or target volume coverage. In contrast, only two patients relapsed at the IRV boundary, suggesting that the risk of a marginal relapse is low when the TV is appropriately defined. These data support the accurate delivery of optimal RT volumes in the most precise way using advanced technology and image guidance.

Dickie CI, Int J Radiat Oncol Biol Phys. 2012;82:1528-34

GTVdefined by **MRI T1 plus contrast** images
→**MRI** with contrast is required
→**Fusion of MRI and CT** is recommended.
→**Intravenous contrast** is recommended, particularly for upper extremity lesions, where there is a greater rotational mobility, and positioning fidelity between the diagnostic MRI and the planning CT may be more difficult to achieve.



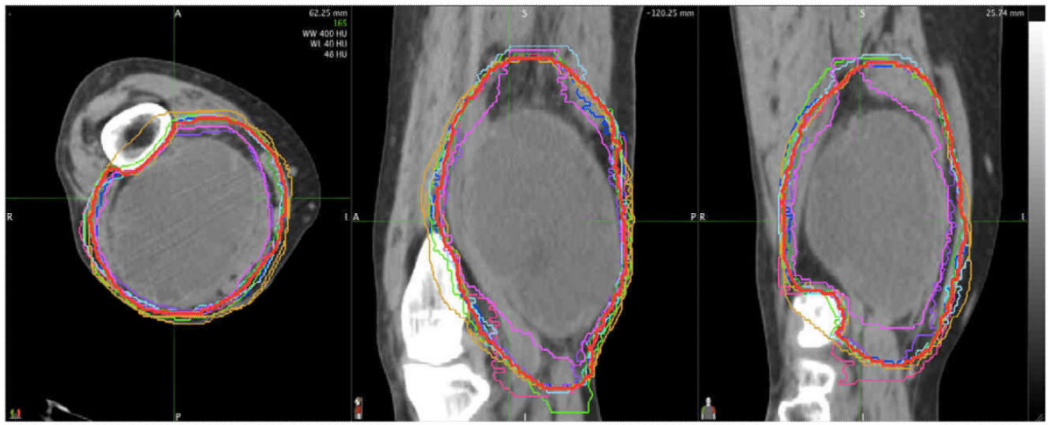
Wang D, Int J Radiat Oncol Biol Phys. 2011 81:775-80

CTV for intermediate-to-high grade sarcoma ≥ 5 cm
= **GTV plus 3** cm margins in the longitudinal (proximal and distal) directions.

The **radial margin** from the lesion should be **1.5 cm** including any portion of the tumor not confined by an intact fascial barrier, bone or skin surface.

The **suspicious edema defined on MRI T2** images is often included within the above margins.

However, clinical judgment **is required** to make sure if the above margins need to be extended to cover the T2 edema defined on MRI T2 images.



For example, the extensive T2 edema may be excluded if clinical judgment suggests that the risk of the edema harboring sarcoma many cm beyond the GTV is low or if extending the radiation field to include all of the edema would cause **excessive toxicity**.

RTOG
RADIATION THERAPY ONCOLOGY GROUP

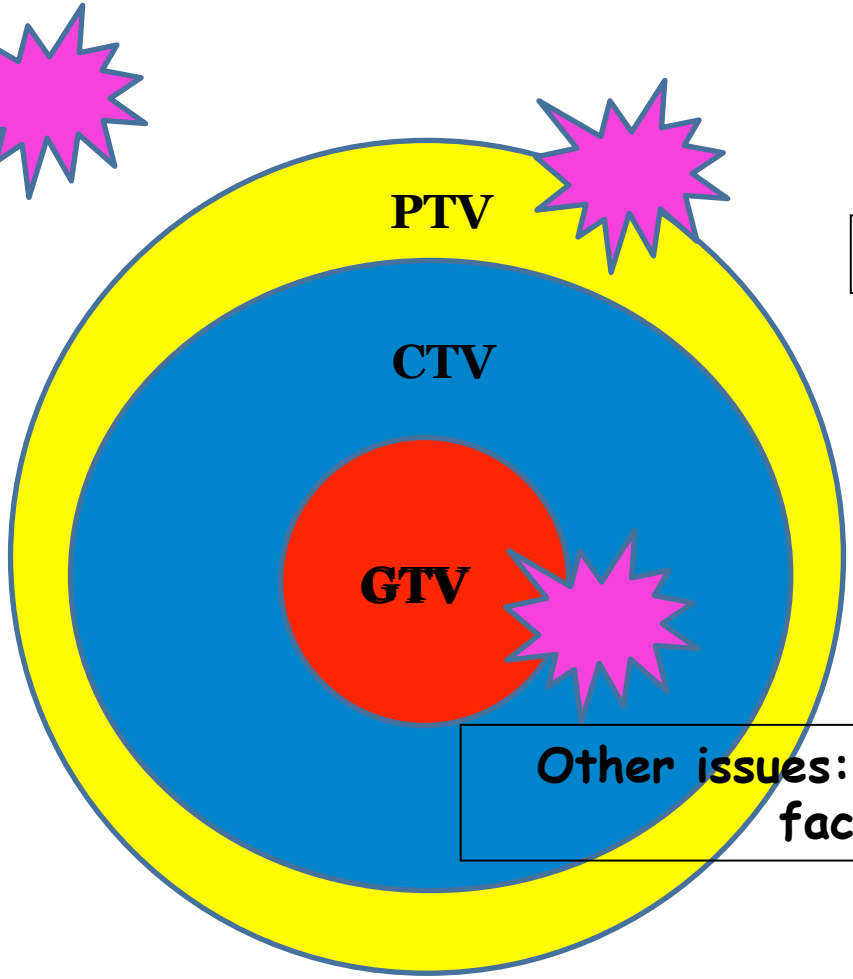
Wang D, Int J Radiat Oncol Biol Phys. 2011 81:775-80

GTV seems to be the easiest volume to define

BUT

GTV is not always completely obvious,
if it has been excised!

Radiotherapy Volume and LR



Inadequate CTV

Inadequate PTV

Other issues: Rt dose, biological factors, surgery

Dickie et al. IJROBP 2012

Postoperative RT Volume

Postoperative RT Volume

Radiation Morbidity related to treatment Volume

1. Fibrosis (p=0.002)

2. Edema (p=0.06)

3. Joint Stiffness (p=0.006)

Davis et al. Radiother Oncol 2005

Postoperative RT Volume

Background:

"Reactive Zone":tumor cells may be located in the surrounding soft tissue between tumor pseudocapsule and normal tissue

Enneking et al. Cancer 1981

Postoperative RT Volume: "historical changes"

Compartmental treatment volume:

The anatomical space where the tumor is contained, bounded on all sides by bone and/or deep fascial envelope

Rosemberg Ann Surg. 1982
Yang et al. (NCI) EBRT JCO 1998

Postoperative RT Volume

50 pts treated w/ WLE and RT

Treatment volume:

- "**Compartmental**": entire muscular compartment
- "**Subcompartmental**": at least 5 cm proximal and distant margin
- "**Limited**": <5 cm longitudinal margin or incomplete coverage of the transverse diameter of the compartment

Pao et al. IJROBP 1990

Postoperative RT Volume

Results: 10 local recurrence

- 1/10 **subcompartmental volume**
- 4/9 **limited volume**

"A minimal margin of at least 5 cm is necessary provided that the entire transverse diameter of the compartment is included…

No benefit in local control w/ the use of "*compartmental*" vs "*subcompartmental*"

Pao et al. IJROBP 1990

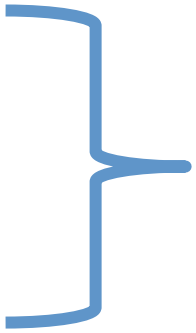
Postoperative RT Volume

64 pts treated w/WLE and adjuvant RT

Results: 11(17.5%) pts failed locally.

Difference between local control rates in pts treated w/ initial field margin:

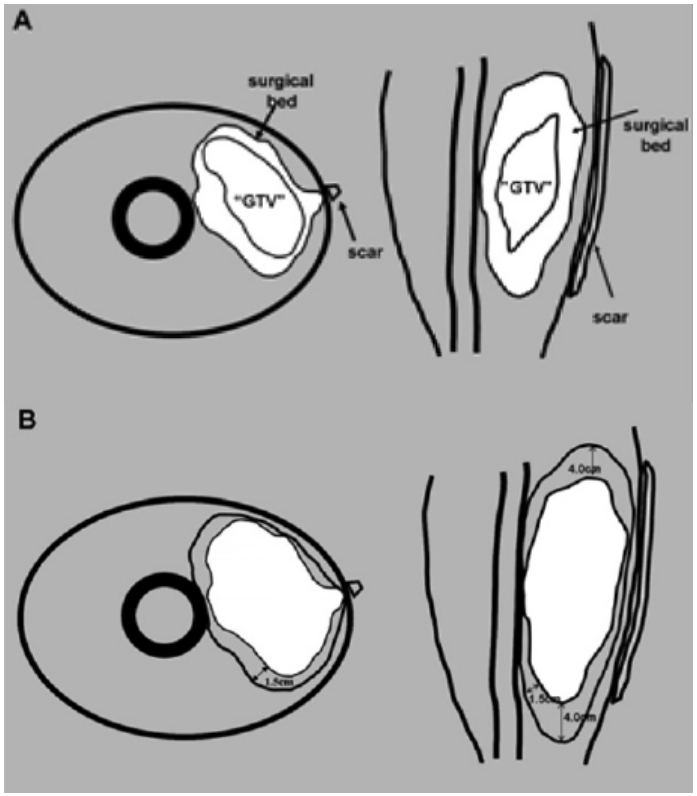
< 5cm(30.4%)
5-9.9 cm
10 cm (100%)



p=0.007

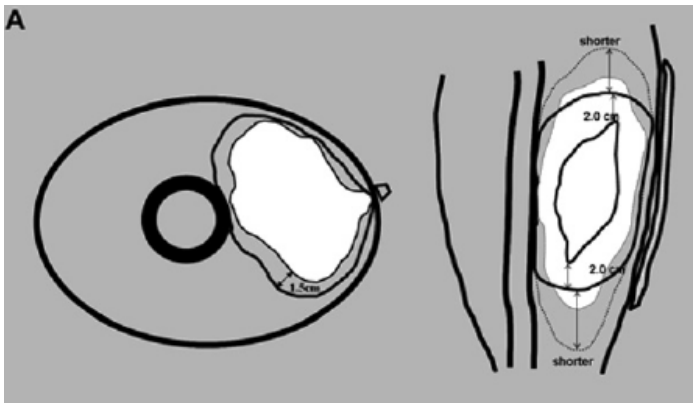
Mundt et al. IJROBP 1995

Target for post-operative RT



Imaging: CT and MRI, T2

CTV: surgical volume + 1.5 cm radially and 4 cm longitudinally
(no bone, fasciae and joints)



Boost: same as CTV except in the longitdinal direction where 2 cm margin are considered

Haas RL et al; Int J Radiat Oncol Biol Phys. 2012;84:572-80

Caso clinico post-operative RT

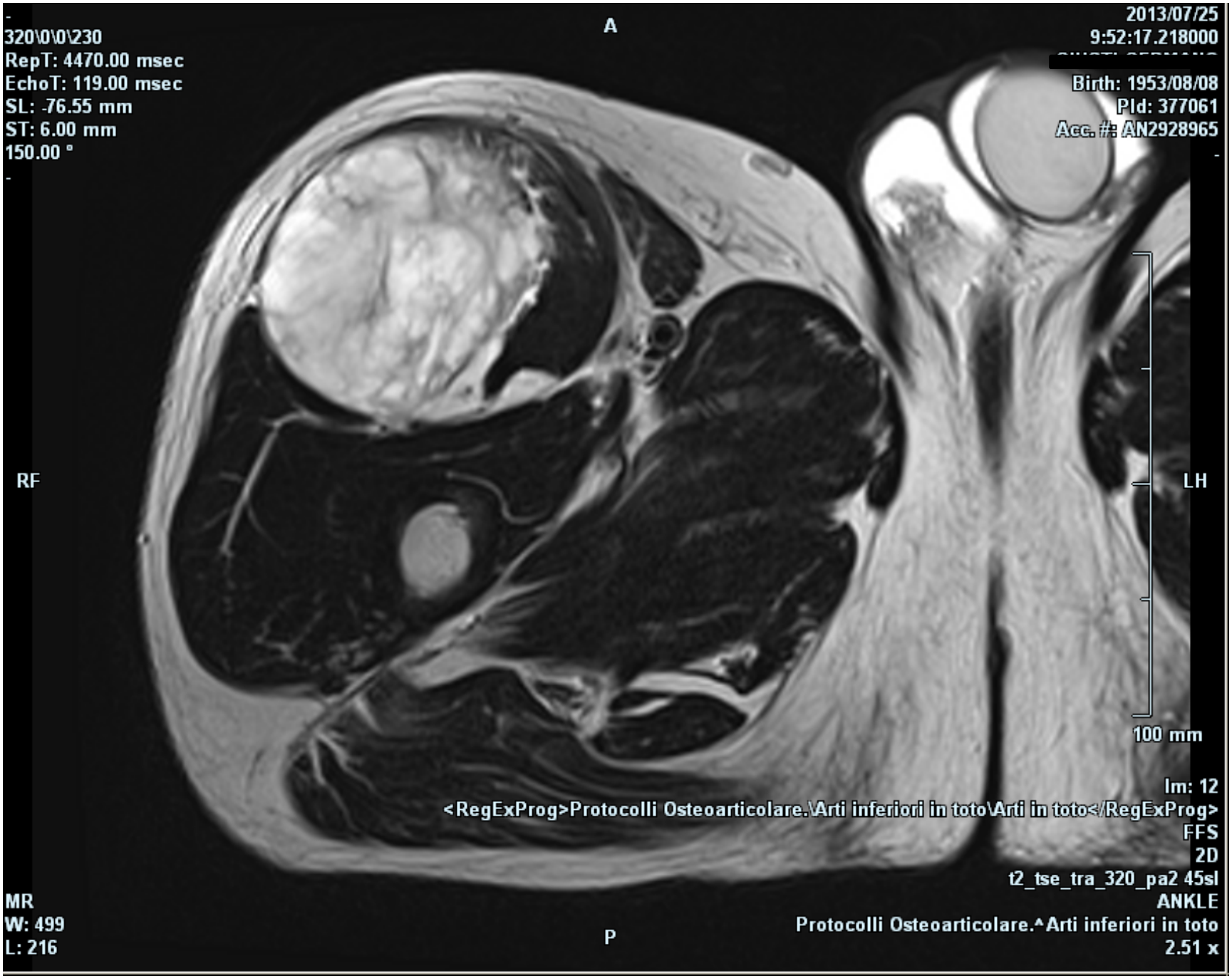
G.G. Male, 60 yo

- Familiar clinical history positive for cancer
- Clinical history: tonsillectomy, @33 yo acute pancreatitis for calculi.

On June 2013 for a swelling localized to the upper third of the right thigh he performed :

Caso clinico post-operative RT

- US (16/06/2013): a solid inhomogenous lesion of 6.9x2.9 cm
- MRI w/ contrast (20/08/2013): @the upper third of the right thigh, within the quadriceps femoris, between the rectus femoris and the lateral vasti, a lesion of 22 cm (longitudinal) x7.5 cm (trasversal)x6 cm (A-P). Inhomogenous enhancement after contrast. Hyperintense in T2 and Isointense in T1.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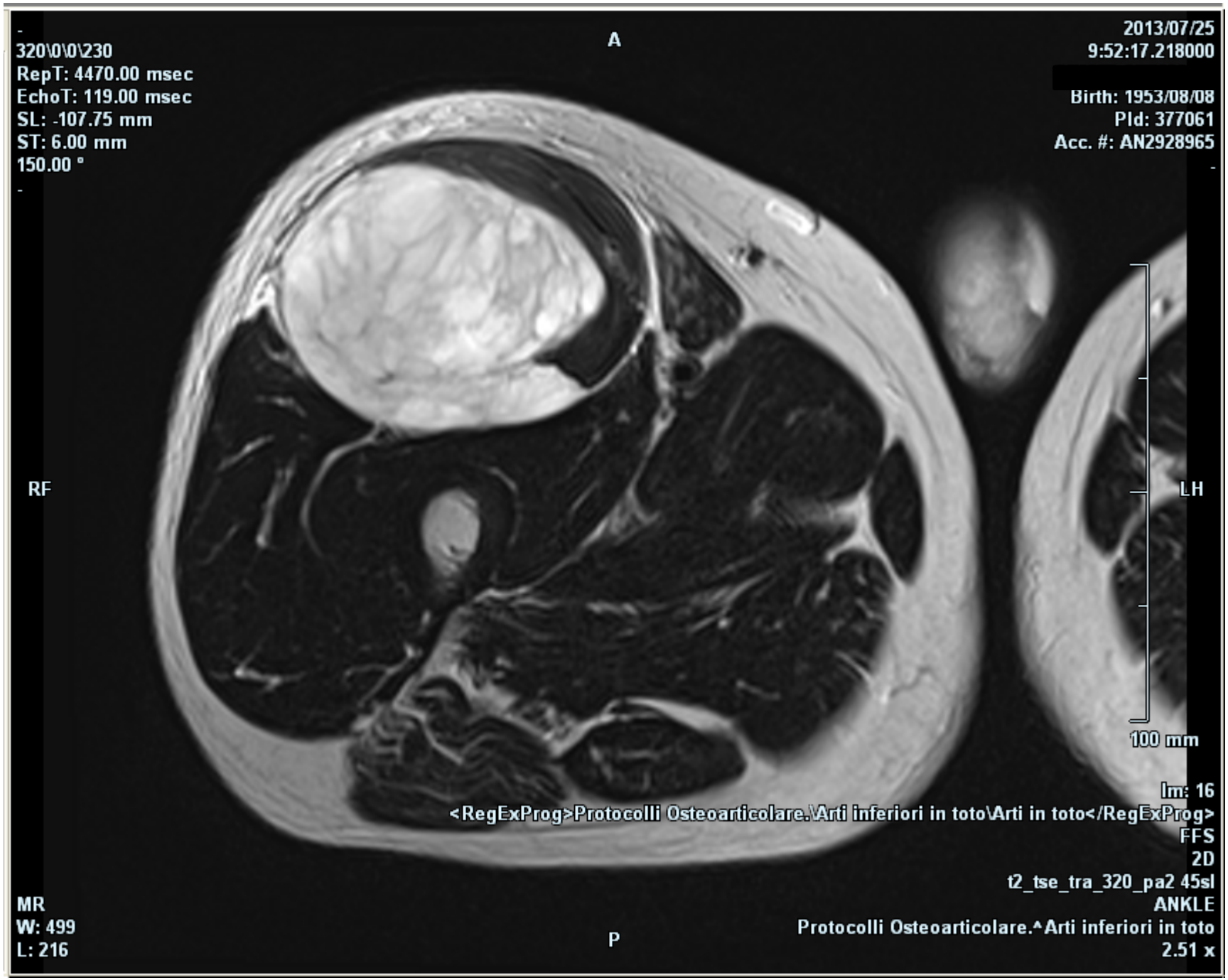
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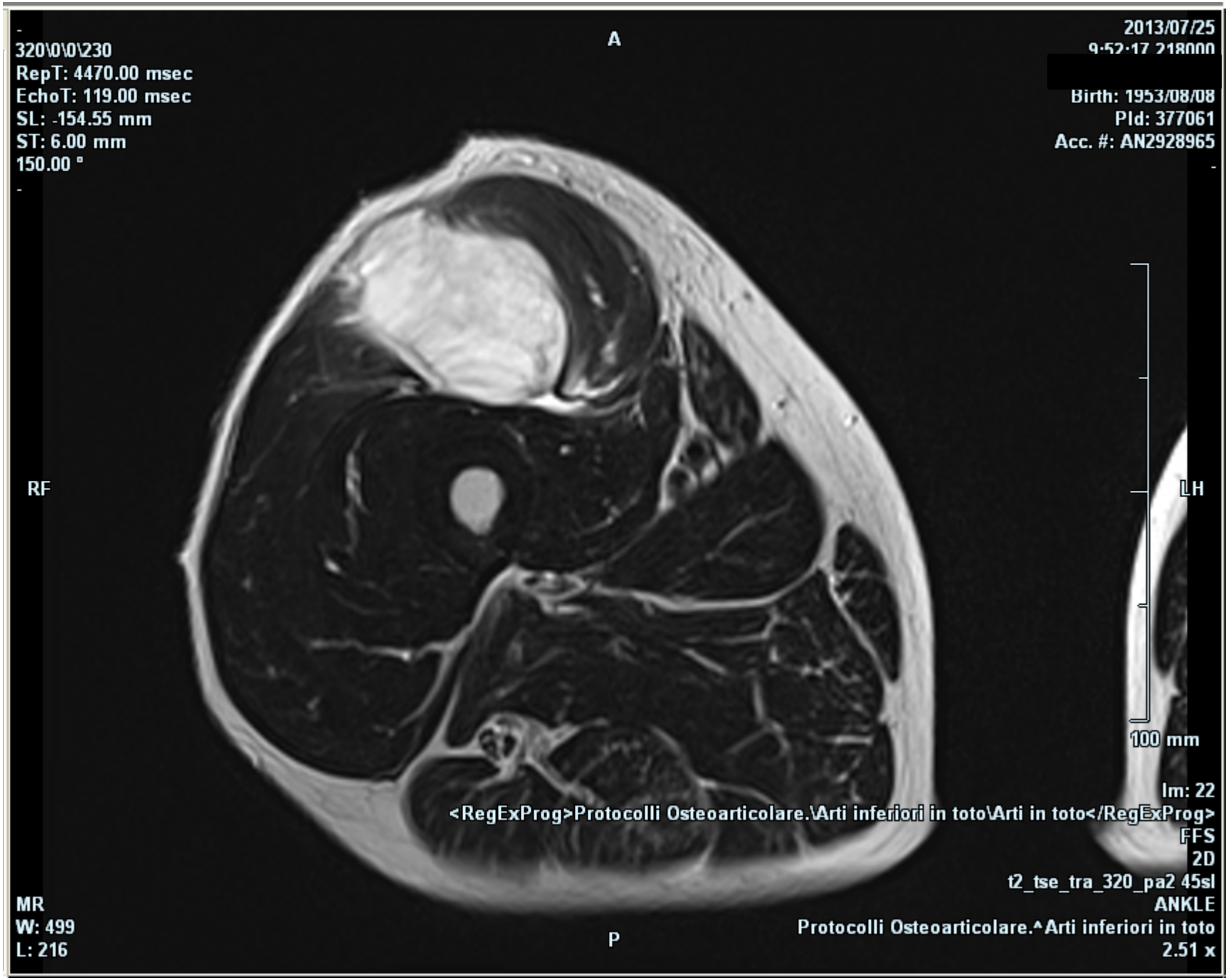
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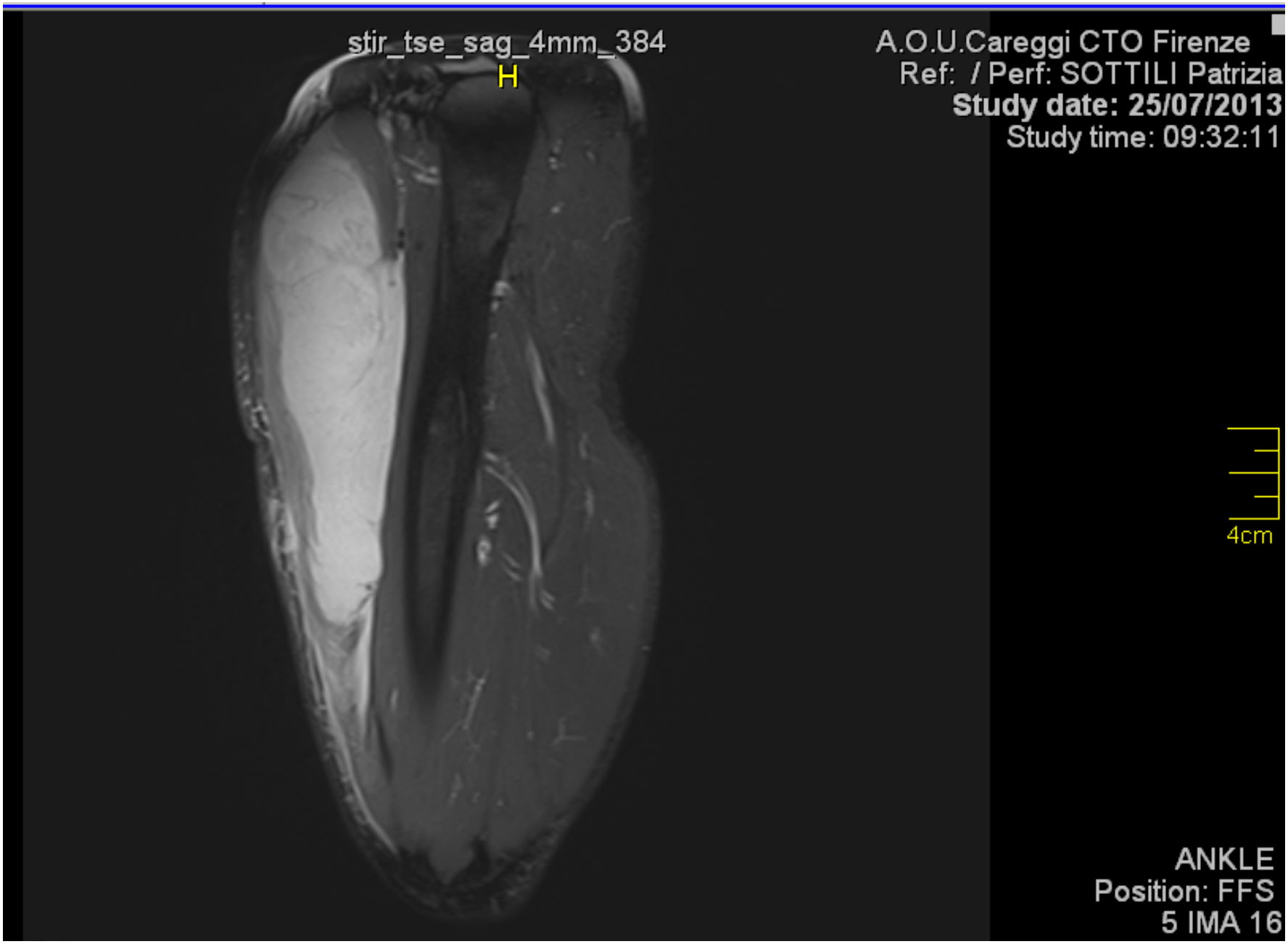
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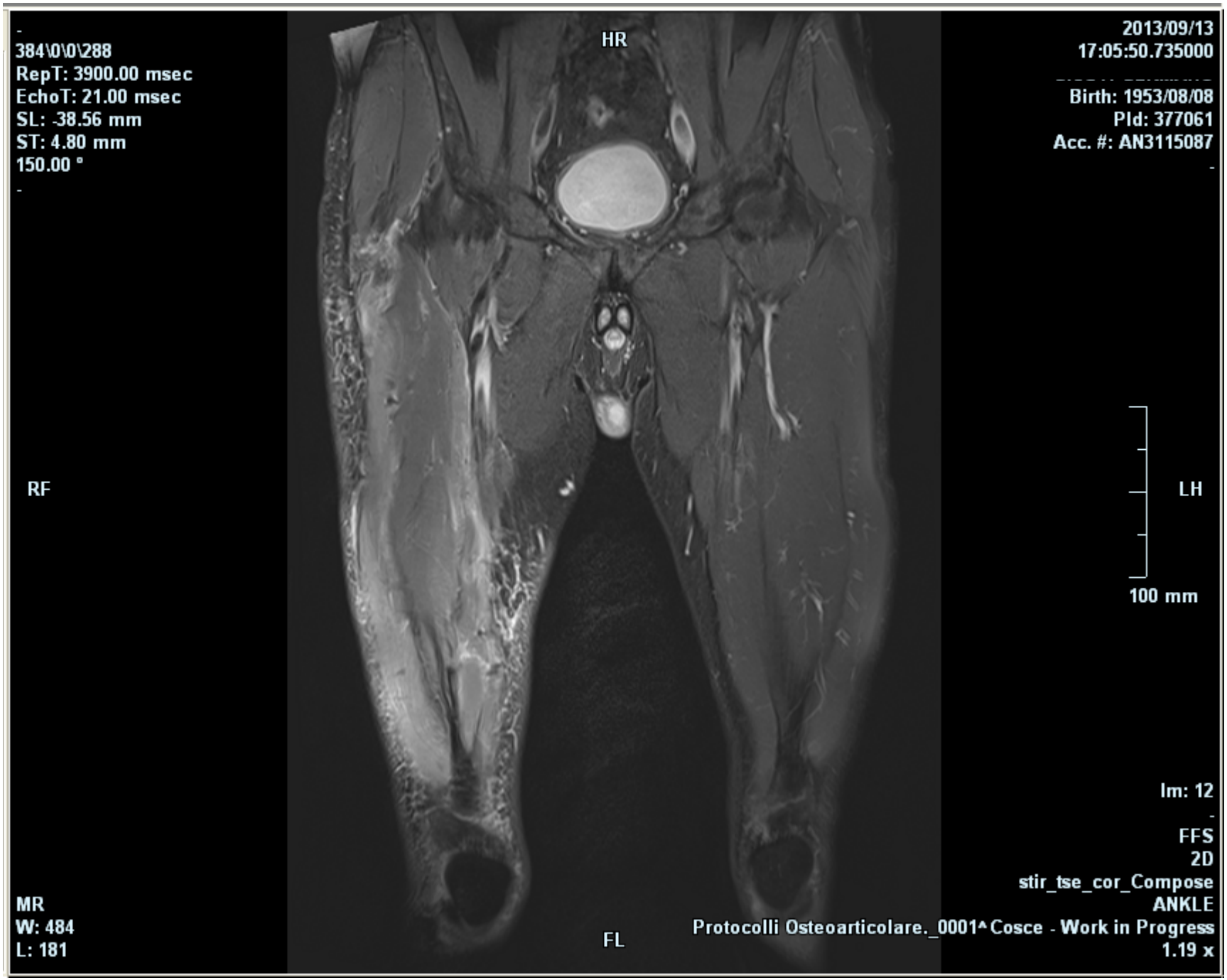
Study date: 25/07/2013
Study time: 09:32:11
4cm
ANKLE
Position: FFS
5 IMA 16

Caso clinico post-operative RT

- TB CT w/contrast (24/08/2013): negative
- Wide Excision (06/08/2013): Within the muscular tissue lesion of 19x7 cm.

  Negative Margins (R0)
- HE: High grade myxoid sarcoma .
- MRI w/contrast (13/09/2013): negative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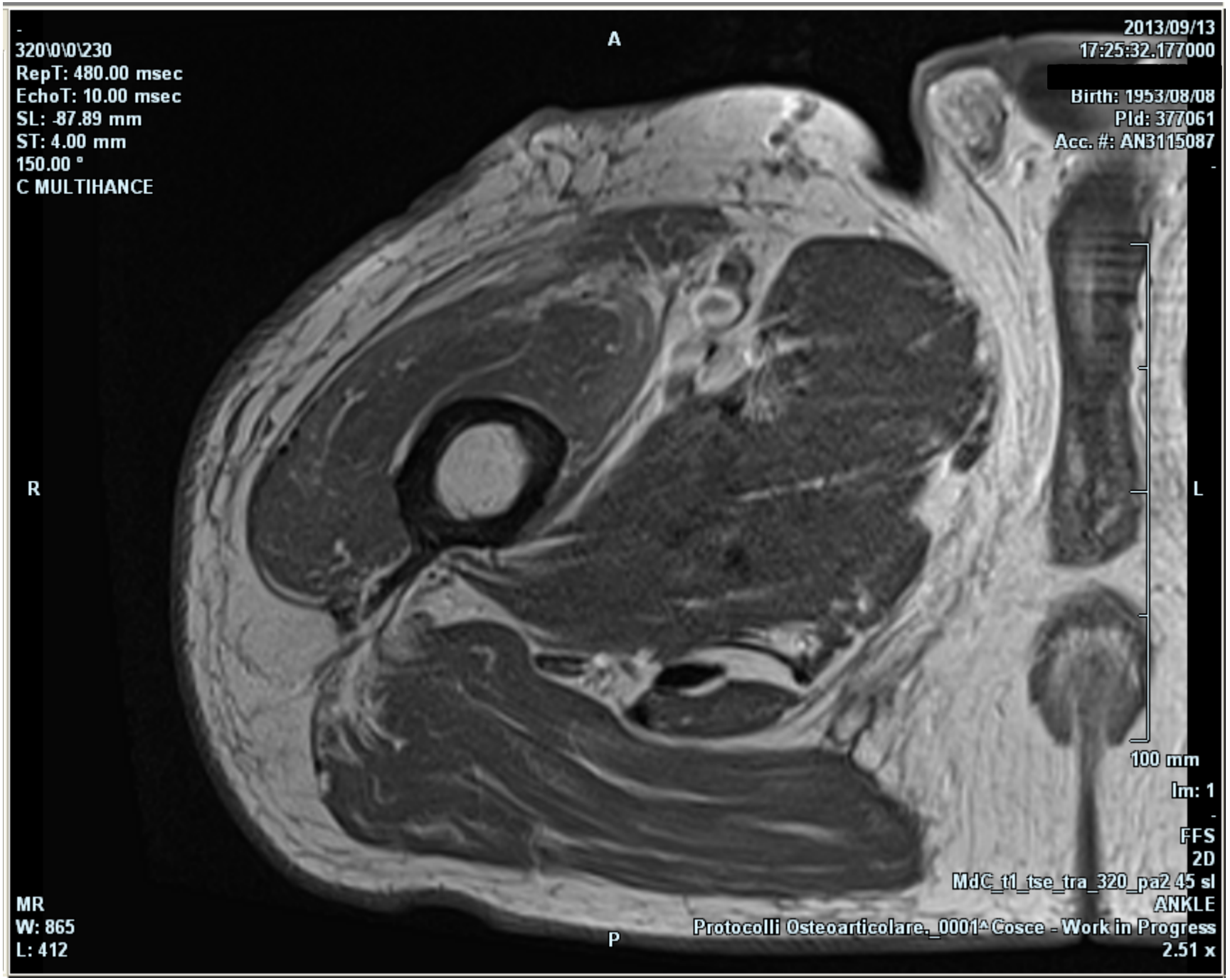
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Caso clinico post-operative RT

Postoperative EBRT

Elective PTV: 50 Gy and PTV boost :66 Gy w/ a conventional fractionation (2Gyx1x5)

BUON LAVORO

CRITICAL ISSUES

RT for SOFT TISSUE SARCOMA

- ✓Complex RT
- ✓Demands good anatomical knowledge
- ✓Highly individualised
- ✓Quality affects outcomes:
  - -Local control
  - -Normal tissue complications

Stinson et al. IJROBP 1991;21:1493-9
Davis AM et al. Radiot Oncol 2005; 75:48-53

RT for SOFT TISSUE SARCOMA

International Journal of Radiation Oncology biology • physics

www.redjournal.org

members of:
Connective Tissue Oncology Society,
RTOG,
European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group
Radiation Oncology Group
NCIC Clinical Trials Group have collaborated to produce consensus recommendations for the delineation of target volumes for preoperative and postoperative RT for ESTS.

CME ASTRO

Critical Review

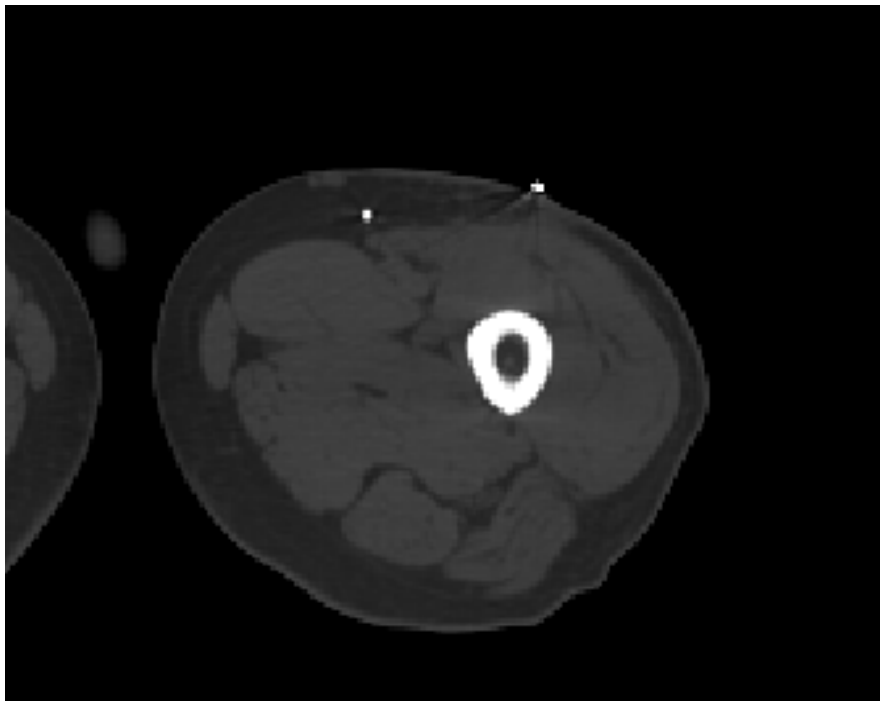
Radiotherapy for Management of Extremity Soft Tissue Sarcomas: Why, When, and Where?

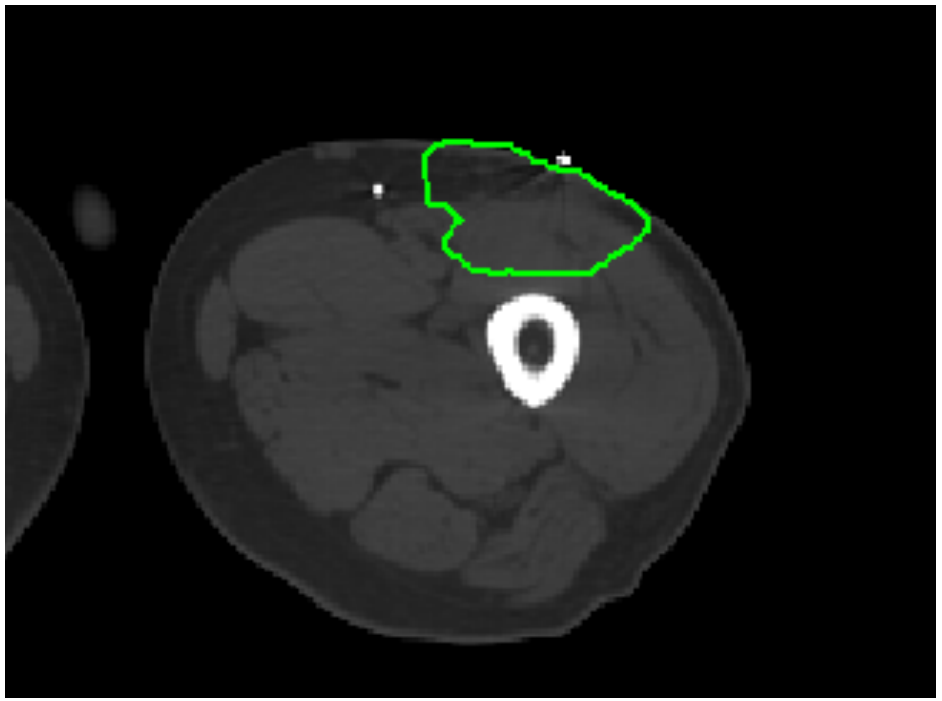
Rick L.M. Haas, MD, PhD,* Thomas F. DeLaney, MD, PhD,† Brian O'Sullivan, MD, PhD,‡ Ronald B. Keus, MD,§ Cécile Le Pechoux, MD, PhD,|| Patricia Olmi, MD, PhD,¶ Jan-Peter Poulsen, MD, PhD,# Beatrice Seddon, MD, PhD,** and Dian Wang, MD, PhD††

*From the *Department of Radiotherapy, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; †Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; ‡Department of Radiation Oncology, Princess Margaret Hospital, Toronto, ON, Canada; §Department of Radiotherapy, Arnhems Radiotherapeutisch Instituut, Arnhem, The Netherlands; ||Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France; ¶Department of Radiotherapy, Istituto Nazionale per lo Studio e la cura dei Tumori, Milan, Italy; #Department of Radiotherapy, Norwegian Radium Hospital—Oslo University Hospital, Oslo, Norway; **Department of Radiotherapy, University College London Hospitals, London, UK; and ††Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*

CTV DEFINITION

Surgical note
Phatology report

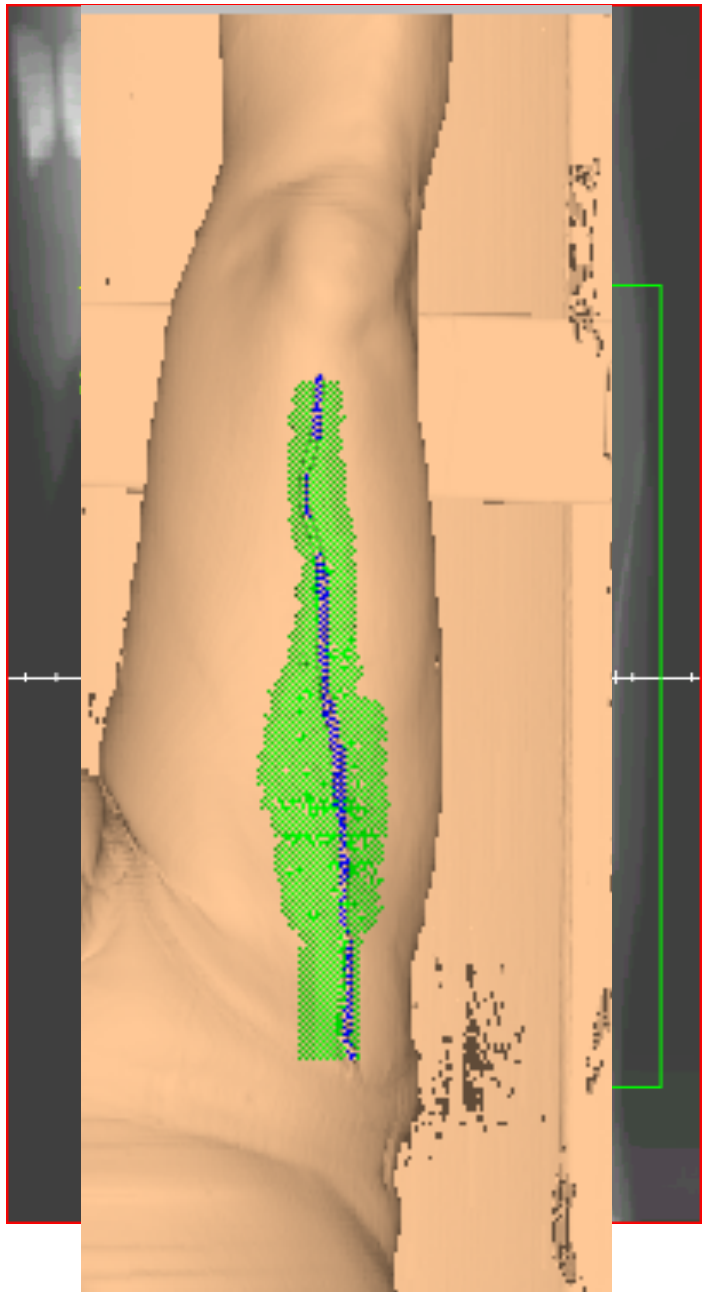




CTV DEFINITION

Scars
(wire for planning CT)

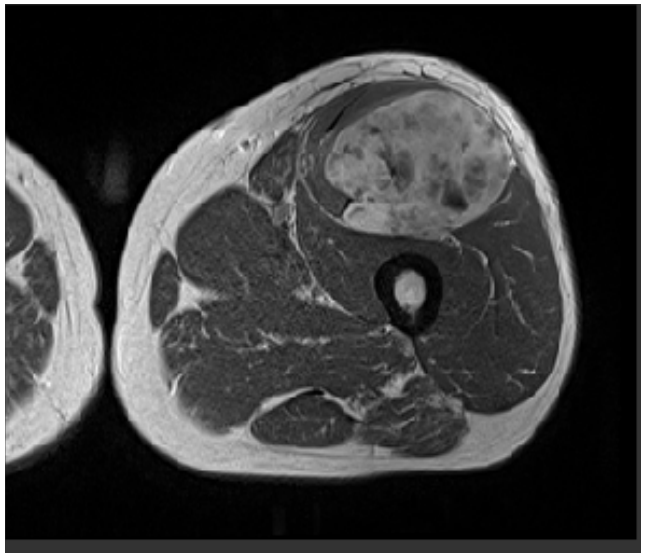
BUT
Do NOT use BOLUS as a routine;
After good surgery, the scar should NOT be at risk

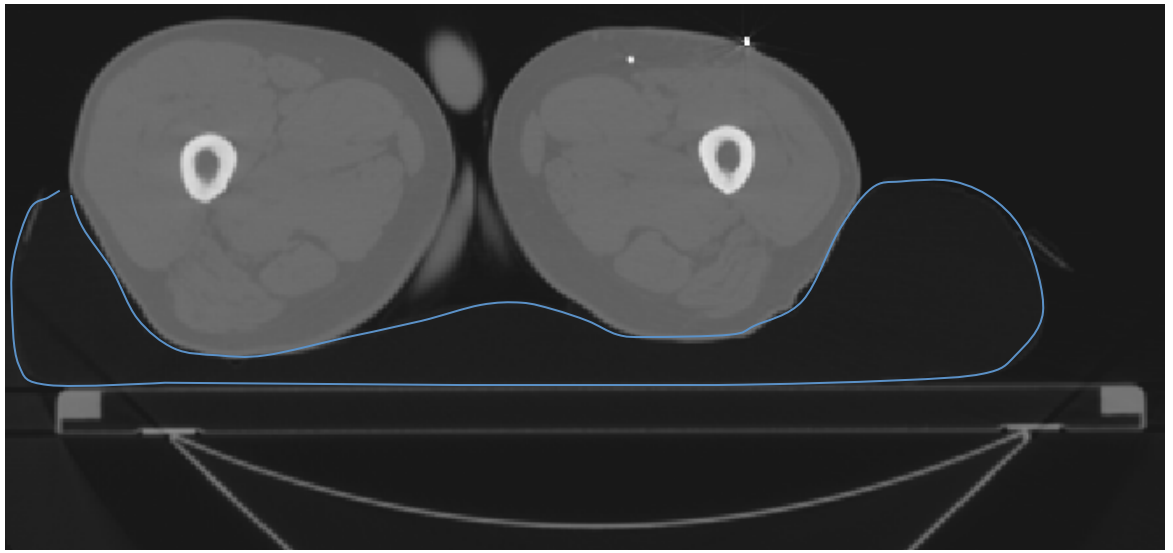


CTV DEFINITION

- Contour changes after surgery
- Pre-op MRI with post-op contour not a good match
- Need to correlate pre- and post- op imaging

MR co-registration (???)

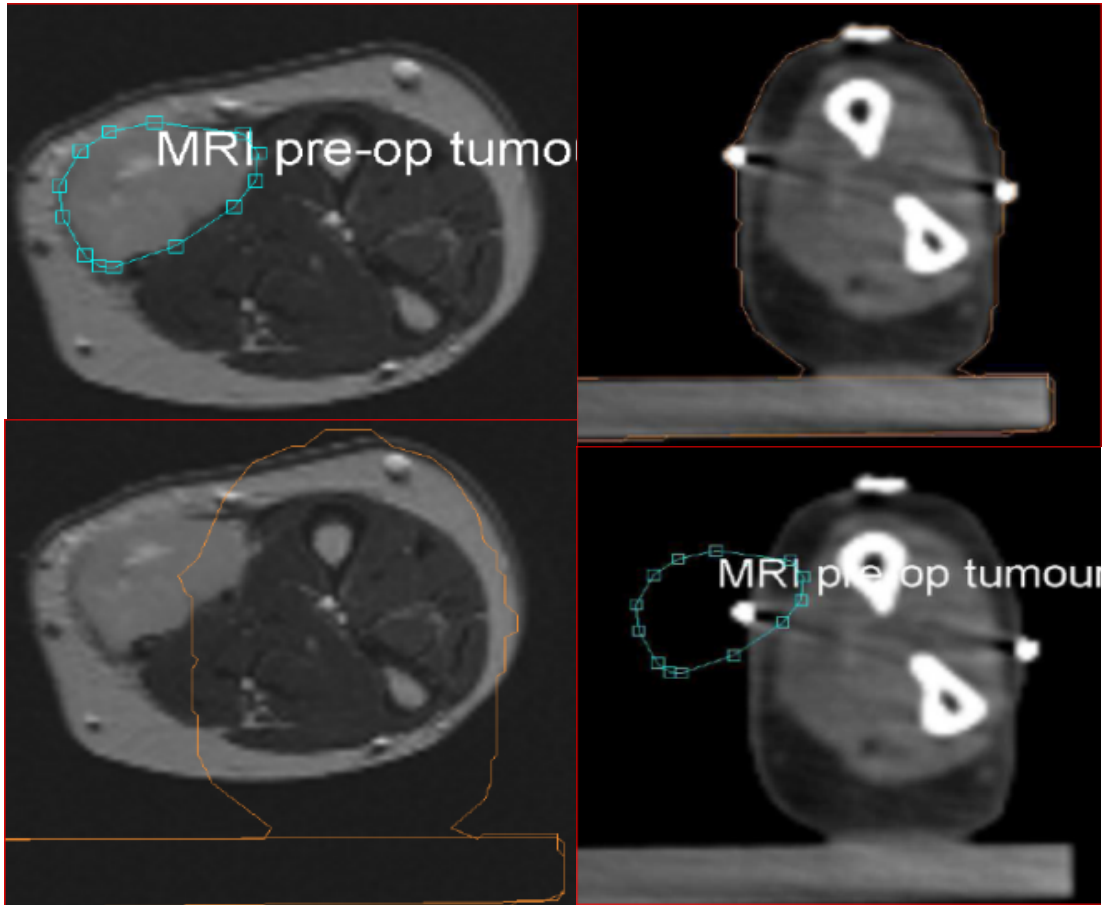




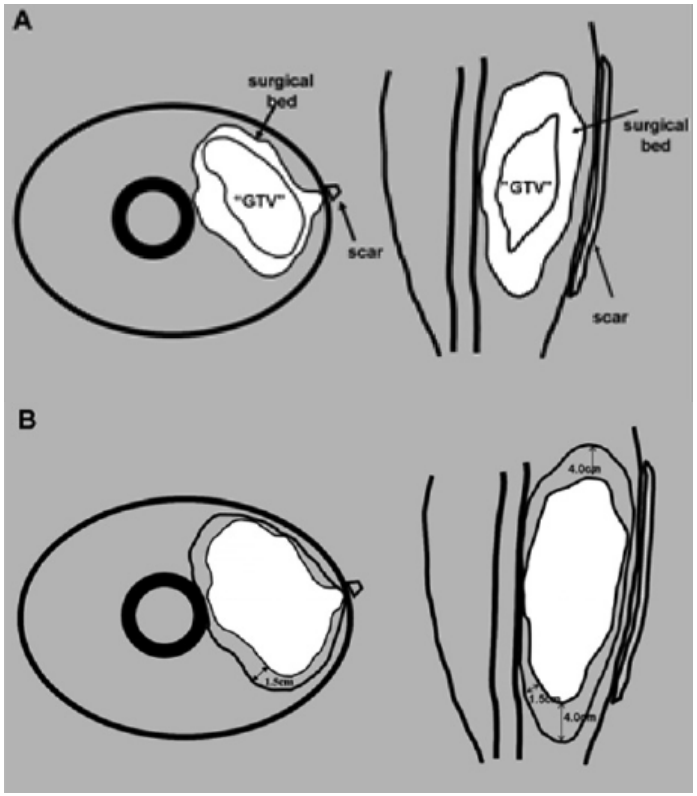
MR co-registration (???)

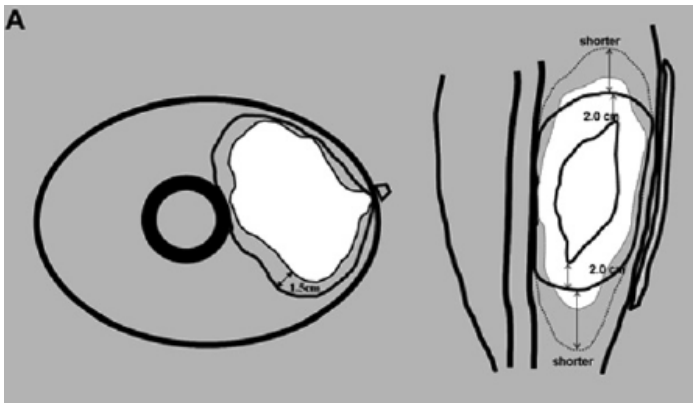
Co-registration works better for:

- Lower leg
- Knee- provided joint in same position
- NOT for mid thigh
- NOT for forearm



Target for post-operative RT





Imaging: CT and MRI, T2

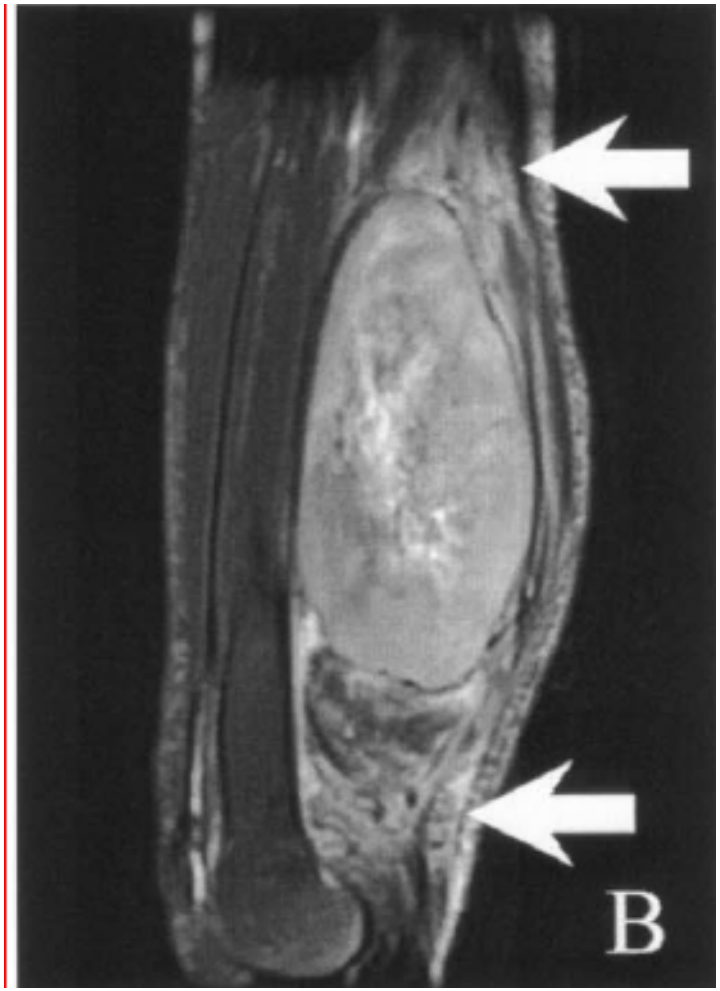
CTV: surgical volume + 1.5 cm radially and 4 cm longitudinally,
(no bone, fasciae and joints)

Boost: same as CTV except in the longitudinal direction where 2 cm margin are considered

Haas RL et al; Int J Radiat Oncol Biol Phys. 2012;84:572-80.

How far does tumour extended beyond surgical bed?

Recommended 4 cm margin



Assessed MRI and pathology in 15 STS patients undergoing surgery.

Surgical resection sought to maintain a minimal **1–2-cm layer of normal tissue around the sarcoma in all planes** unless a thick fascial barrier was present.

Tumor cells beyond main mass in 10/15:
- 6 pts < 1cm
- 4 pts 1-4 cm
- 9/10, in area of T2 edema, which was usuall proximal/distal to tumor

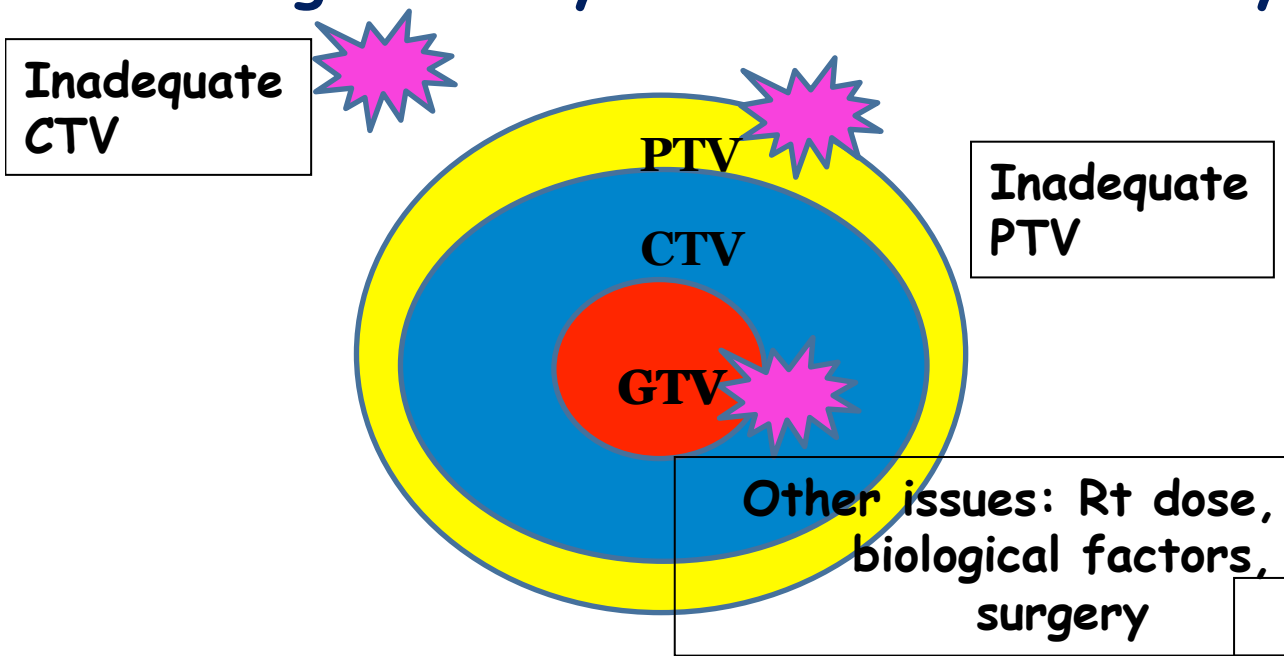
White LM et al. IJOBP; 2005, 61: 1439–1445

How far does tumour extended beyond surgical bed?

5@ local control rate of 88.5% applying a 3.5 cm proximal and distal margin and 1-1.5 cm radial margin beyond the T1-weighted postgadolinium-defined GTV.

Kim et al. IJROBP 2010

The GTV to CTV expansion:
4 cm longitudinally and 1-1.5 cm axially



7.8% LR:

- 6.4% in field
- 1.1% out of field
- 0.3% marginal

Dickie et al. IJROBP 2012

Are all sarcomas alike in their potential to microscopically invade surrounding tissues?

- **Growth Pattern "pushing borders"**
  (well differentiated liposarcoma) → rare microscopic foci at distance

- **Growth Pattern with aggressiveness**
  (high mitotic index, genetic mutations, lympho-vascular infiltration) → frequent microscopic foci at distance (dermatofibrosarcoma protuberans, aggressive fibromatosis, subcutaneous myxofibrosarcoma)

Haas RL et al; Int J Radiat Oncol Biol Phys. 2012;84:572-80.

Is 4 cm longitudinal expansion of surgically manipulated tissues always necessary for postoperative elective CTV?

- It is not known whether it is safe to reduce the expansion of the elective **CTV to <4 cm** if the surgical resection margins are negative (ie, an R0 resection), because of the possibility of tumor cells at distance from the dominant tumor mass

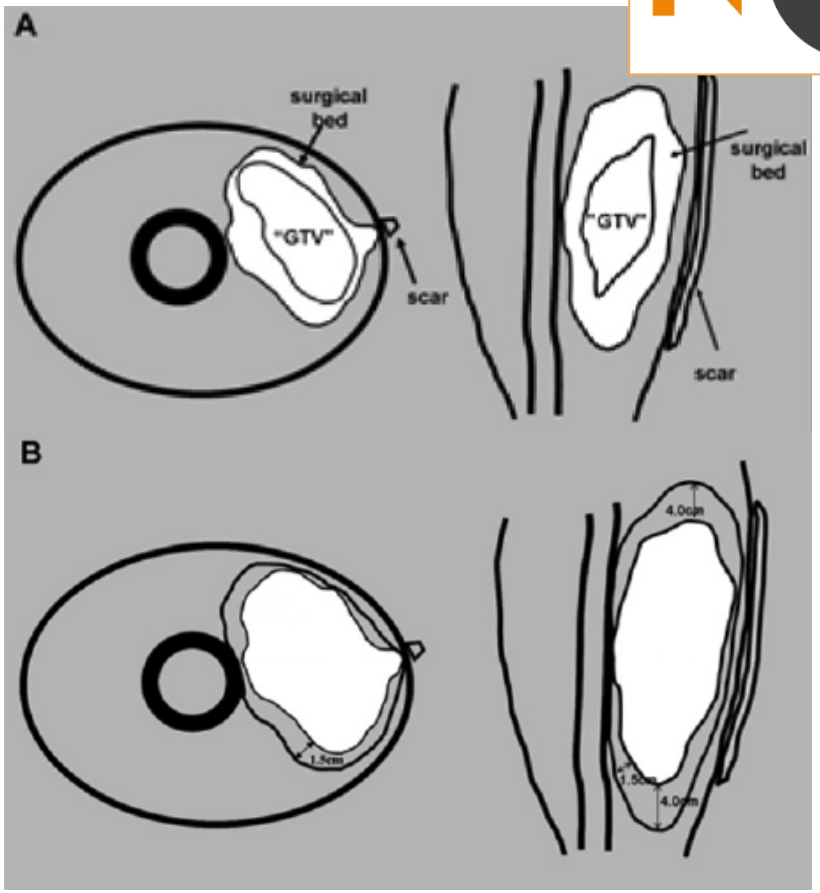
White LM et al. IJOBP; 2005, 61: 1439–1445

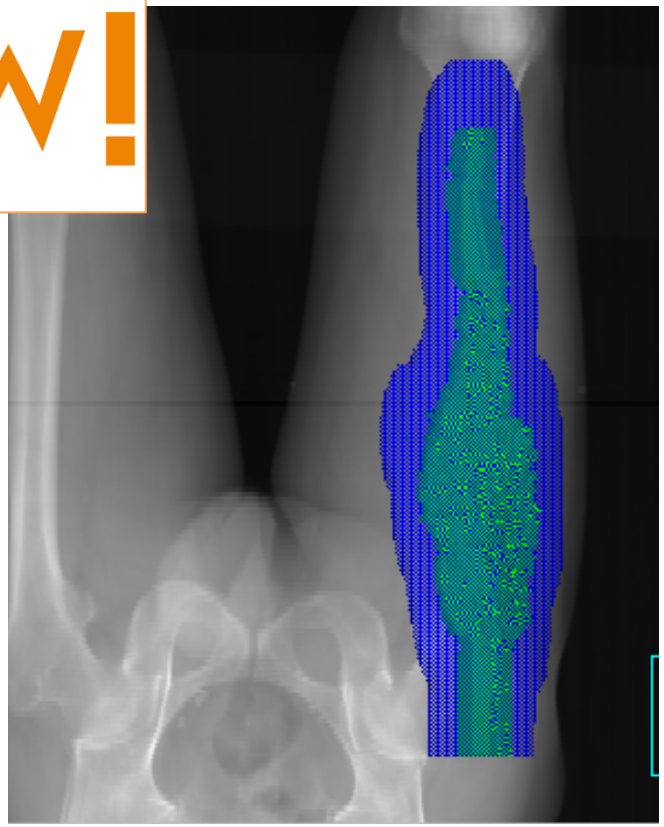
- If the surgical resection margins are positive (ie, R1 resection), re-excision should be performed whenever possible to achieve an R0 resection.

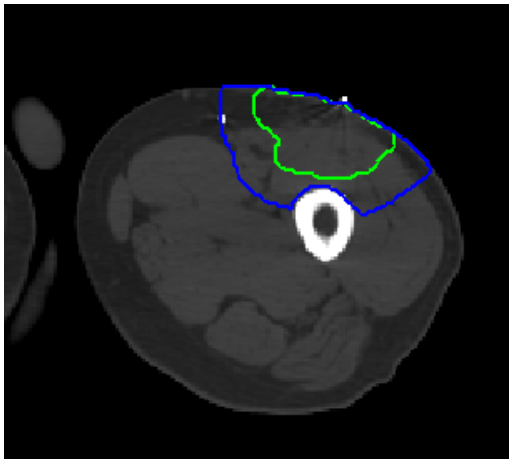
small (longitudinal CTV expansion of 2 cm)
vs large (longitudinal CTV expansion of 5 cm)
postoperative RTvolumes in the limb-sparing management of ESTS patients

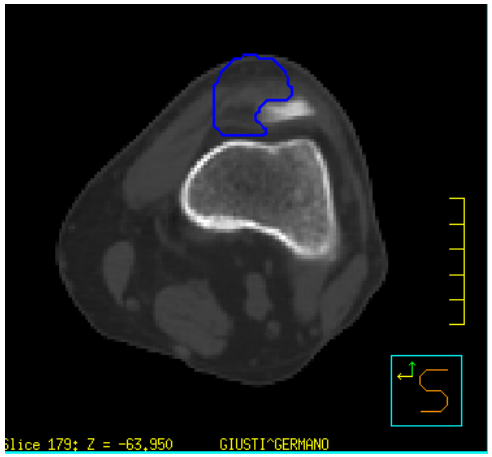
VorteX

Randomised trial of Volume of post-operative radiotherapy given to adult patients with eXtremity soft tissue sarcoma









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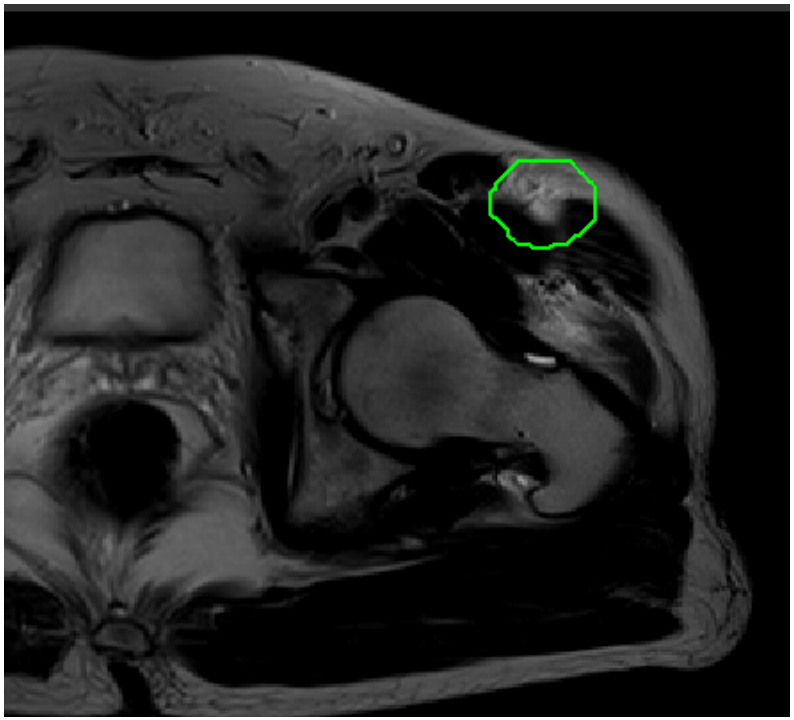

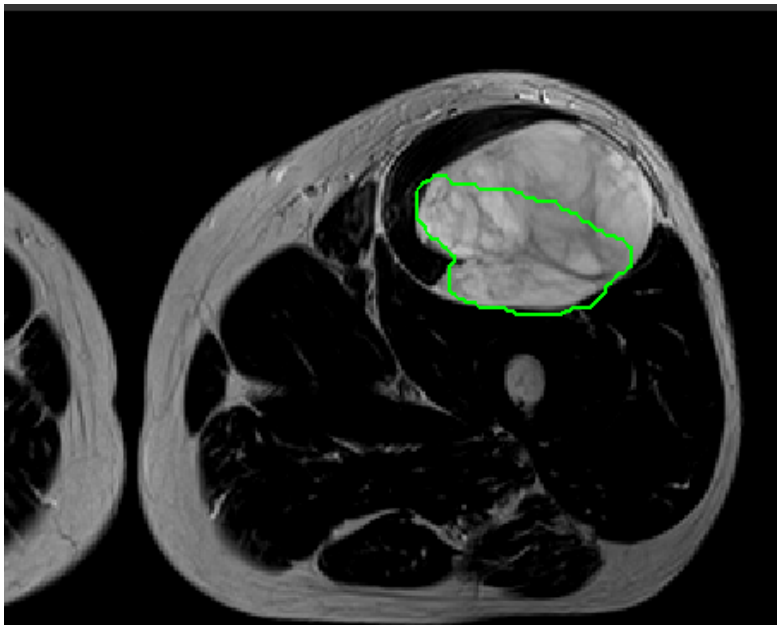
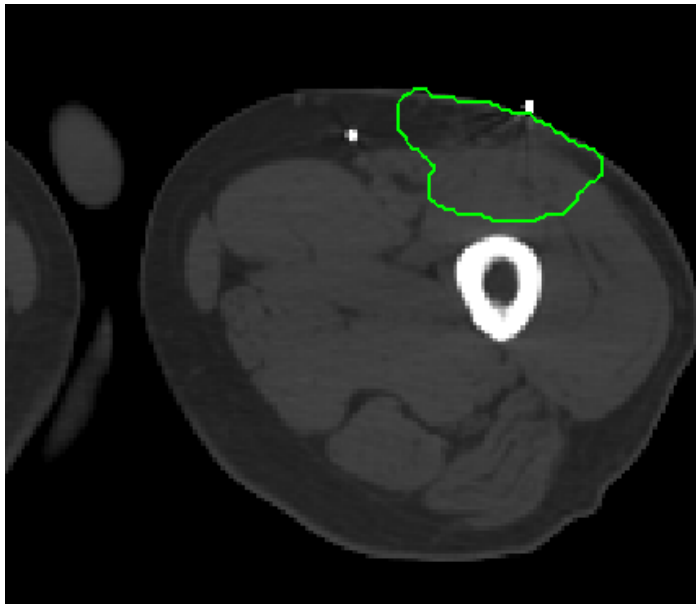

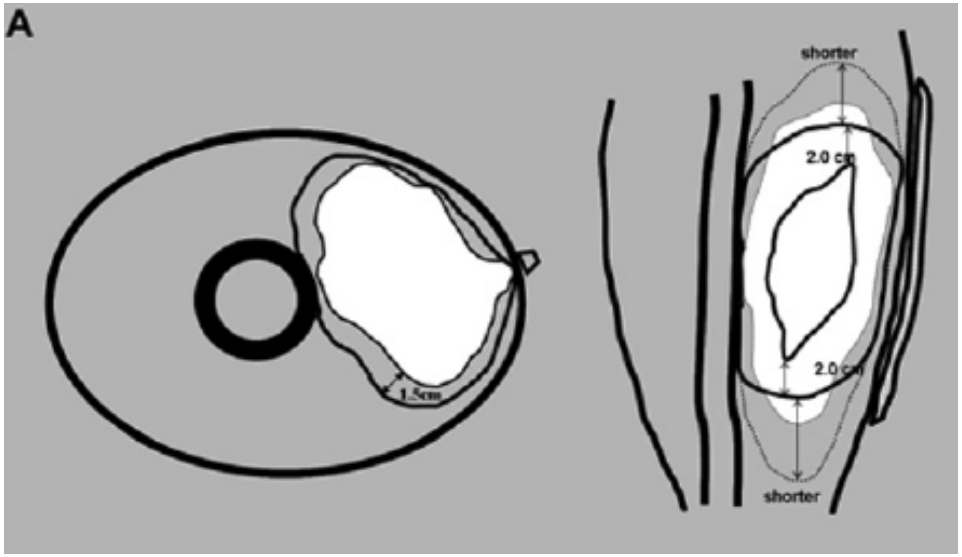

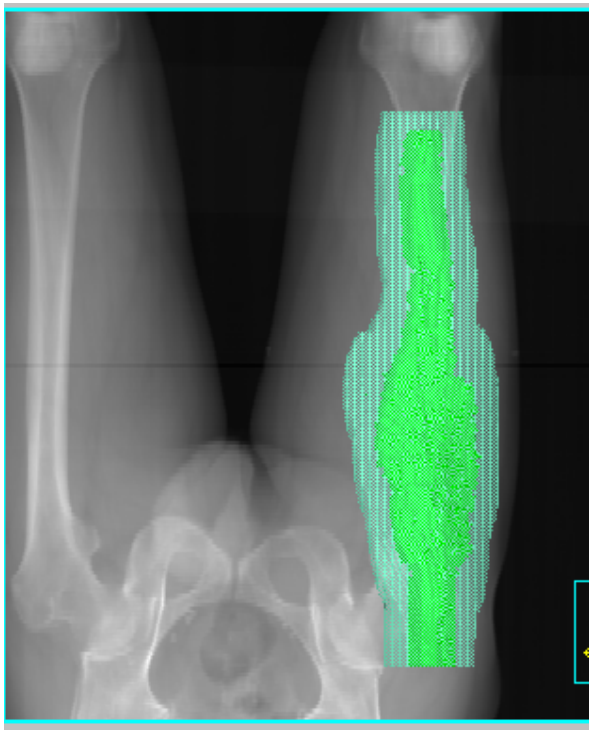

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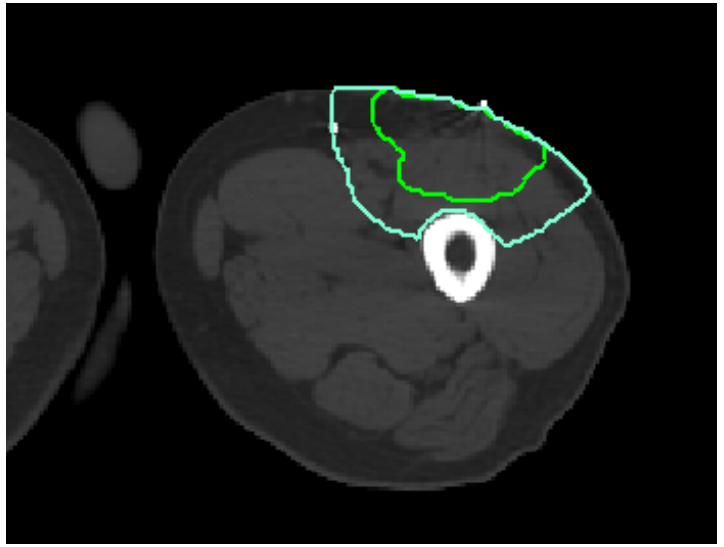
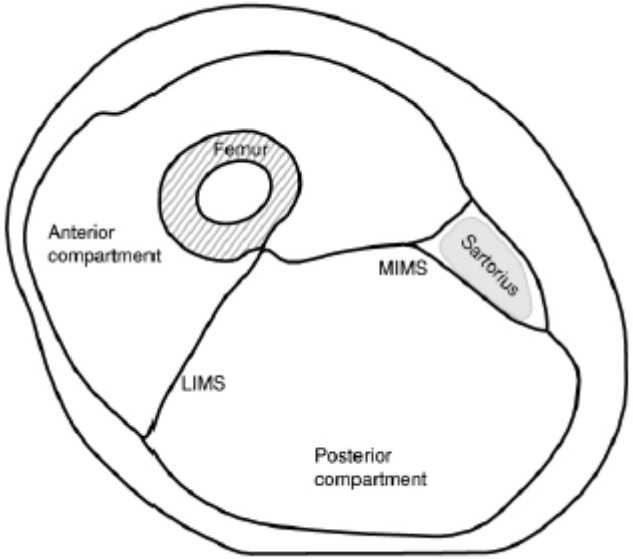


Haas RL et al; Int J Radiat Oncol Biol Phys. 2012;84:572-80.

- Sarcomas do not (normally) penetrate deep fascia
- Compartment barriers therefore limit spread
- Anatomical knowledge can aid planning

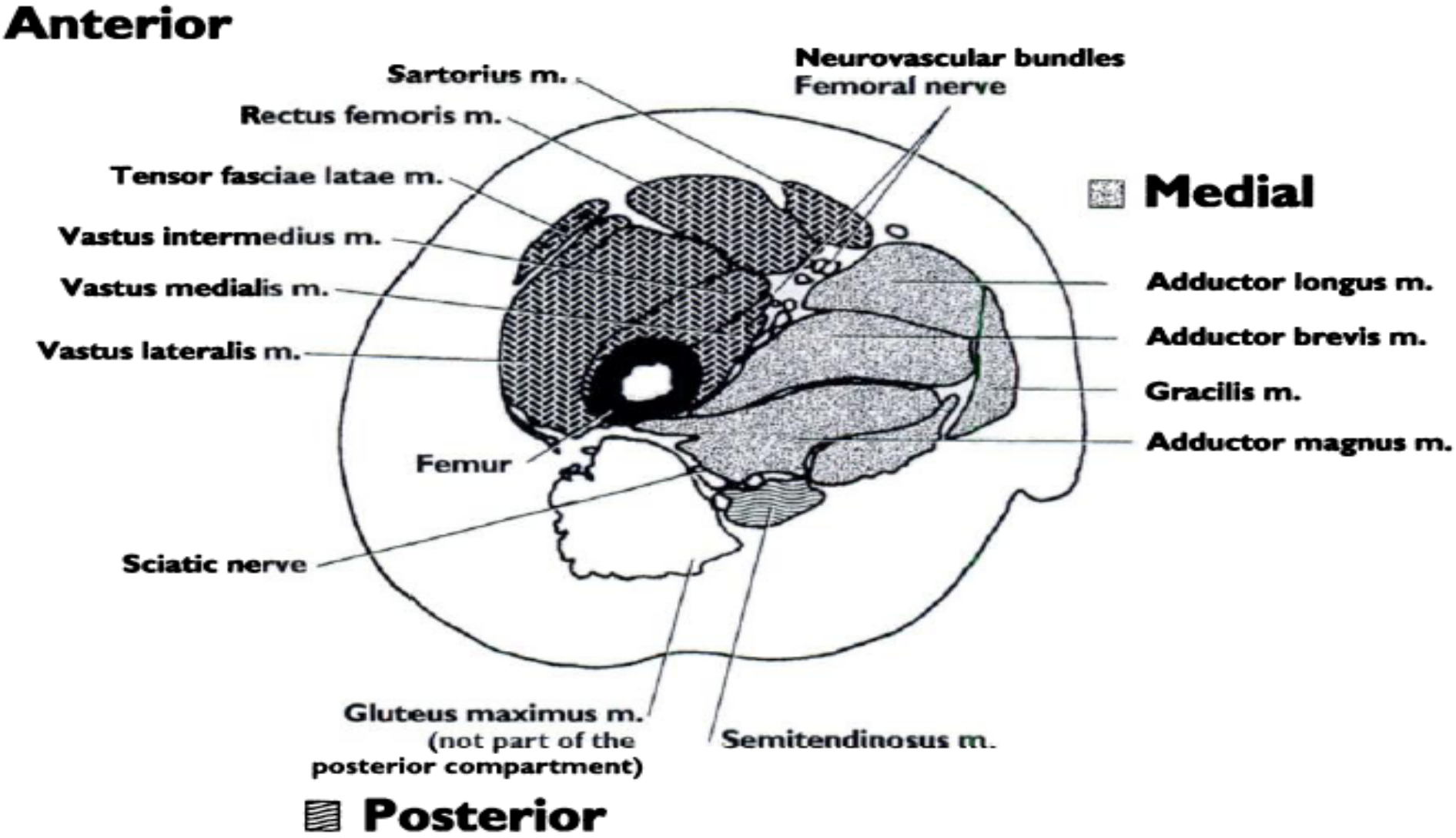
Anatomical Compartment:
a region enclosed by fascial boundaries



Muscles are contained by investing fascia that divides anatomical compartments

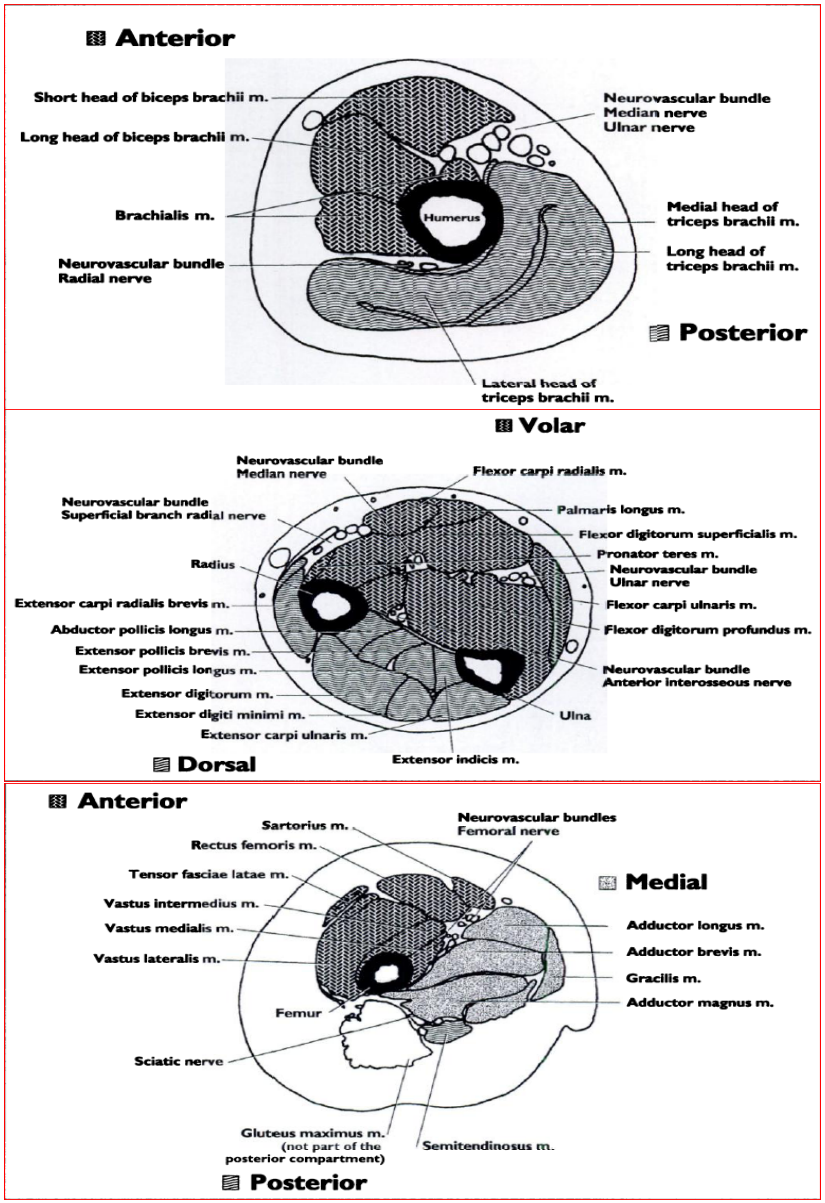
Burnet NG et al; Sarcoma. 2004;8:7-12.

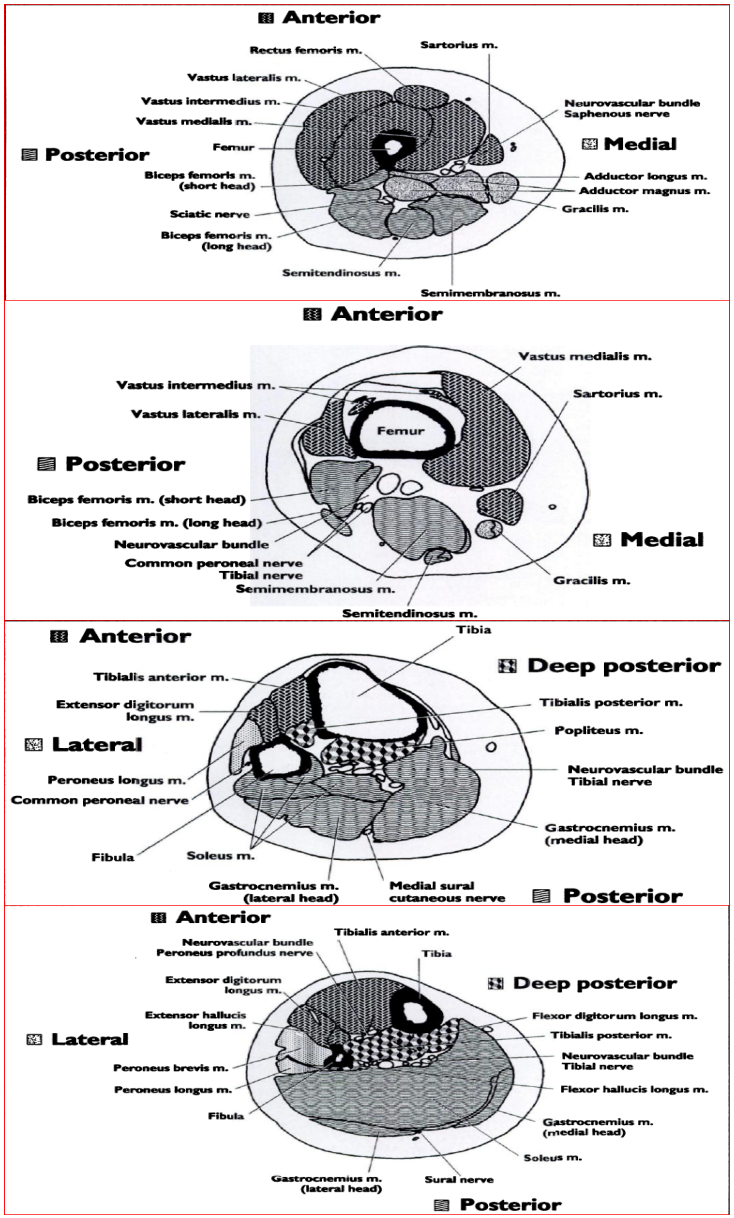
Compartmental Anatomy



Anderson MW et al, AJR AM J Roentgenol 1999;173:1663-1671

Compartmental Anatomy





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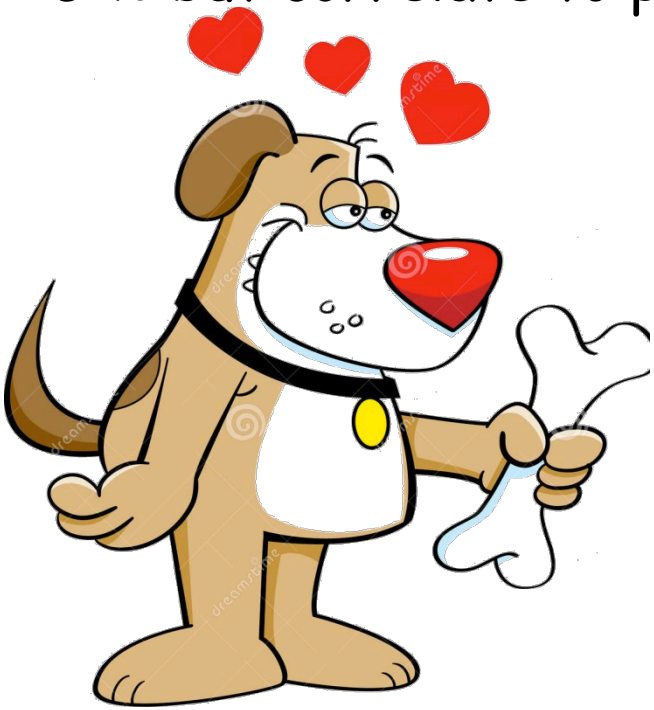
ORGANS @

Bones

Incidence of Radiation-induced bone fractures is less than 5 % but correlate to poor prognosis



Risk factors :

- ✓ Female sex after 50 yo
- ✓ Doses > 60Gy
- ✓ Dose per fraction
- ✓ Lenght of irradiated bone

(Sargos et al. CancerRad.2010)

Reccomandations

- ✓ Mean femoral neck dose below 40 Gy *(Lin et al. Cancer 1998; Zuckerman et al N Engl J Med 1996)*
- ✓ *V50: 50 %*
- ✓ *V60: 5% (www.rtog.org)*

Nerves

"Recommendations" on dose tolerance:

- The plexus and peripheral nerves are treated as organs at risk in series
- The maximum dose should not exceed 60 Gy
- The dose per fraction increase the nerve toxicity

Henriques de Figueiredo et al. Cancer Rad 2010

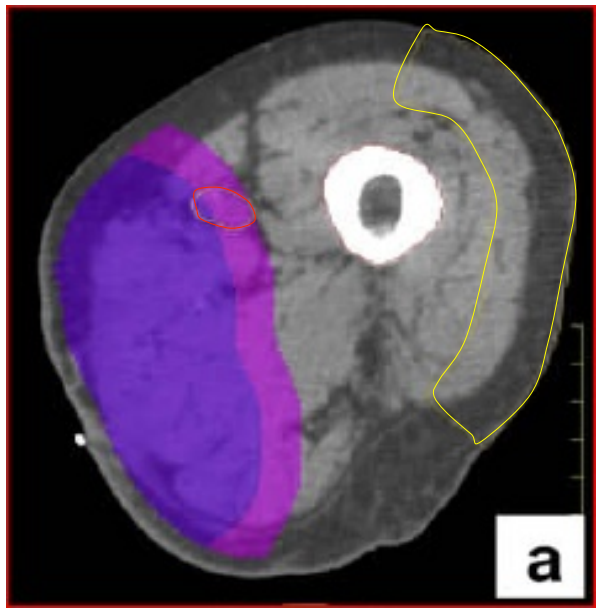
Joints

- Avoid joint if possible, or minimise dose
- Inclusion of >50% of Joint in the field can give Joint contracture
- Active physiotherapy

Stinson SF et al. Int J Radiat Oncol Biol Phys. 1991;21:1493-9

Skin Corridor

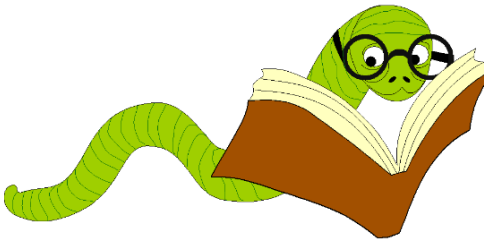
- Spare one third of the circumference of the limb
- Spare skin and fat
- If possible spare underlying muscle



Minimum skin corridor 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 over the length of PTV

Stewart AJ, Lee YK, Saran FH. Radiother Oncol. 2009;93:125-30.
Swedish Council on Technology Assessment in Health Care. Acta Oncologica 1996; 35:117-122

✓O'Sullivan et al. Lancet 2002
✓O'Sullivan et al JCO 2004
✓Wang D, et al. IJROBP 2011
✓Haas RL et al. IJROBP 2012
✓Anderson MW et al, AJR AM J Roentgenol 1999



Grazie