Simposio AIRO-SIRM: Diagnostica per immagini morfologica e funzionale nella stadiazione, terapia e follow-up dei sarcomi delle parti molli

Ruolo dell'imaging nella pianificazione del trattamento

Marco Krengli

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University Hospital "Maggiore della Carità", Novara

Imaging in Soft Tissue Sarcoma

- **Different tumor sites**
  (extremities, retroperitoneum, thorax, H&N)

- **Different histologic types**
  with diffrent molecular changes and natural history

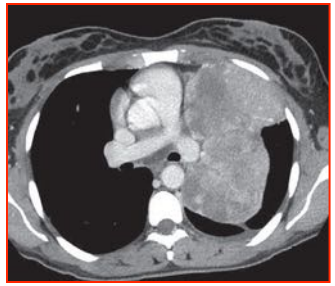
- **Different treatment approaches of RT**
  (preoperative/exclusive, postoperative, perioperative, intraoperative)

Morphological Imaging

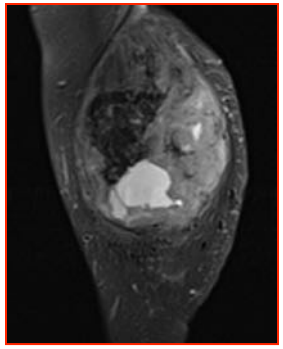
- **Rx**

- **US**

- **CT** (with contrast)



- **MRI** (T1 without and with contrast, T2)



Functional Imaging

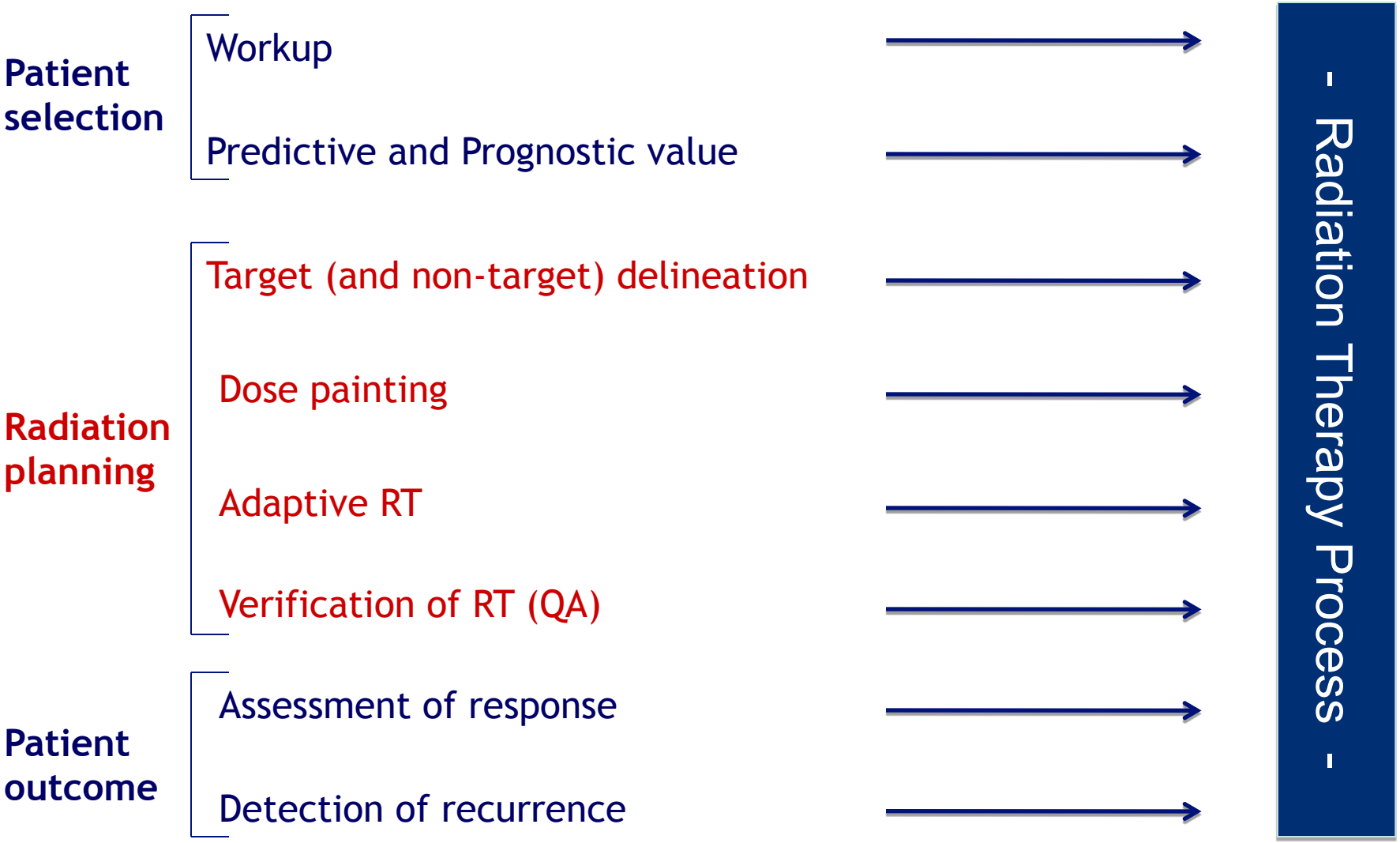
Available at present:

- Increased/decreased content of molecules
  - Active transport of metabolites → PET/SPECT
  - Passive diffusion of molecules → PET/SPECT
  - Different concentration of normal molecules → MRS
- Different distribution of H2O → DW-MRI
- Increased blood flux (angiogenesis) → PW-MRI, P-CT

Optimal:

- Specific marker of clonogenic cells → ???

Imaging in Radiation Oncology



Is Delineation of Target Volume Relevant ?

CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 4, pp. 1528–1534, 2012 Sarcoma

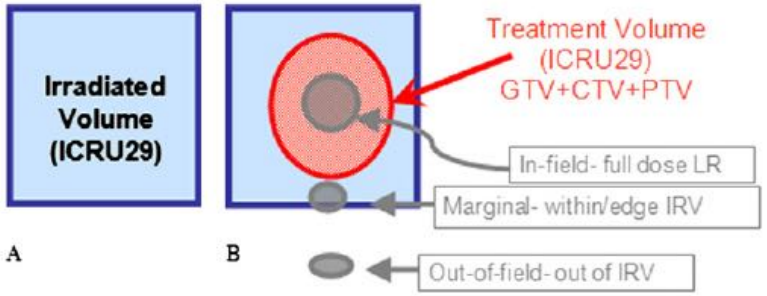
THE RELATIONSHIP BETWEEN LOCAL RECURRENCE AND RADIOTHERAPY TREATMENT VOLUME FOR SOFT TISSUE SARCOMAS TREATED WITH EXTERNAL BEAM RADIOTHERAPY AND FUNCTION PRESERVATION SURGERY

Colleen I. Dickie, M.Sc.,* Anthony M. Griffin, M.Sc.,†‡ Amy L. Parent, B.Sc.,*
Peter W. M. Chung, M.D., F.R.C.P.C.,*‡ Charles N. Catton, M.D., F.R.C.P.C.,*‡
Jon Svensson, M.A.,§ Peter C. Ferguson, M.D., F.R.C.S.C.,†‡ Jay S. Wunder, M.D., F.R.C.S.C.,†‡
Robert S. Bell, M.D., F.R.C.S.C.,†‡ Michael B. Sharpe, Ph.D.,*‡
and Brian O'Sullivan, M.D., F.R.C.P.C.*‡

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

7.8% developed local recurrence

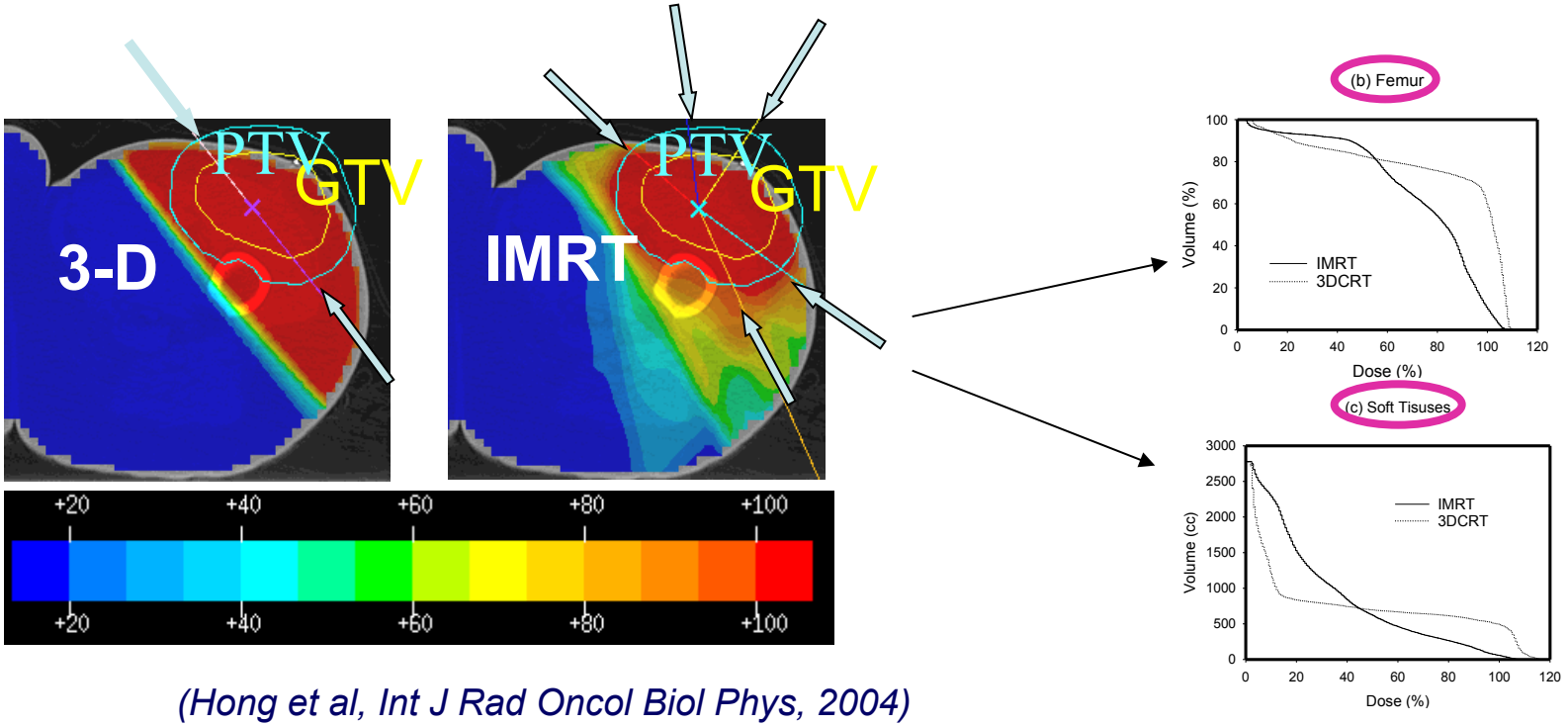
- 6.4% in field
- 1.1% out of field
- 0.3% marginal



The proportion of LR patients that received either preoperative RT alone (50 Gy), or postoperative RT (60-66 Gy) was nearly equivalent (6.9% and 6.4% respectively)

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.

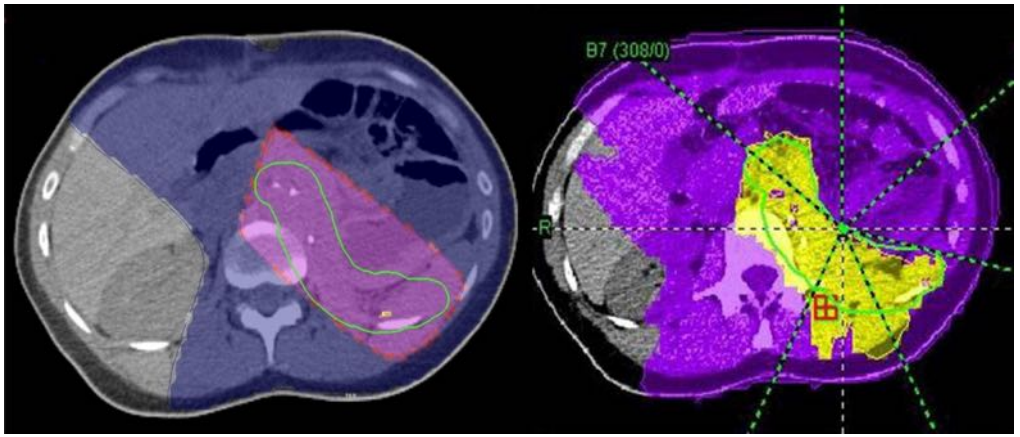
IMRT vs. 3D-CRT



(Hong et al, Int J Rad Oncol Biol Phys, 2004)

Significant sparing by IMRT:

- Intestinal cavity
- Stomach
- Contralateral kidney



(Paumier et al, Radiother Oncol, 2011)

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e525–e528, 2011

RTOG SARCOMA RADIATION ONCOLOGISTS REACH CONSENSUS ON GROSS TUMOR VOLUME AND CLINICAL TARGET VOLUME ON COMPUTED TOMOGRAPHIC IMAGES FOR PREOPERATIVE RADIOTHERAPY OF PRIMARY SOFT TISSUE SARCOMA OF EXTREMITY IN RADIATION THERAPY ONCOLOGY GROUP STUDIES

GTV

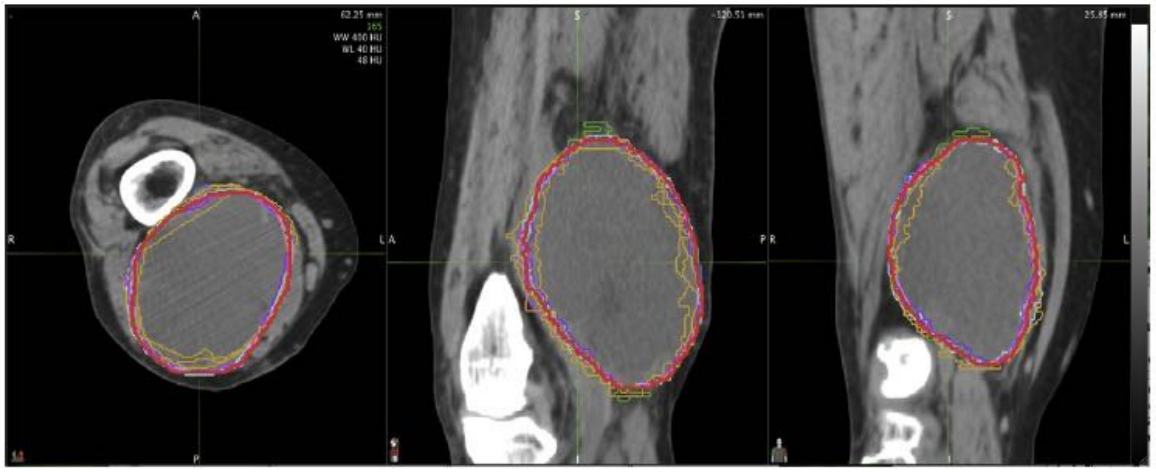


Fig. 1. Example of individual and consensus (red) contours of gross tumor volume on axial computed tomography for patient with large high-grade sarcoma of distal aspect of right thigh.

Gross tumor defined by **MRI T1 plus contrast** images (MRI with contrast is required). **Fusion of MRI and CT** is recommended to delineate the GTV for radiotherapy planning. 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.

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e525–e528, 2011

RTOG SARCOMA RADIATION ONCOLOGISTS REACH CONSENSUS ON GROSS TUMOR VOLUME AND CLINICAL TARGET VOLUME ON COMPUTED TOMOGRAPHIC IMAGES FOR PREOPERATIVE RADIOTHERAPY OF PRIMARY SOFT TISSUE SARCOMA OF EXTREMITY IN RADIATION THERAPY ONCOLOGY GROUP STUDIES

CTV

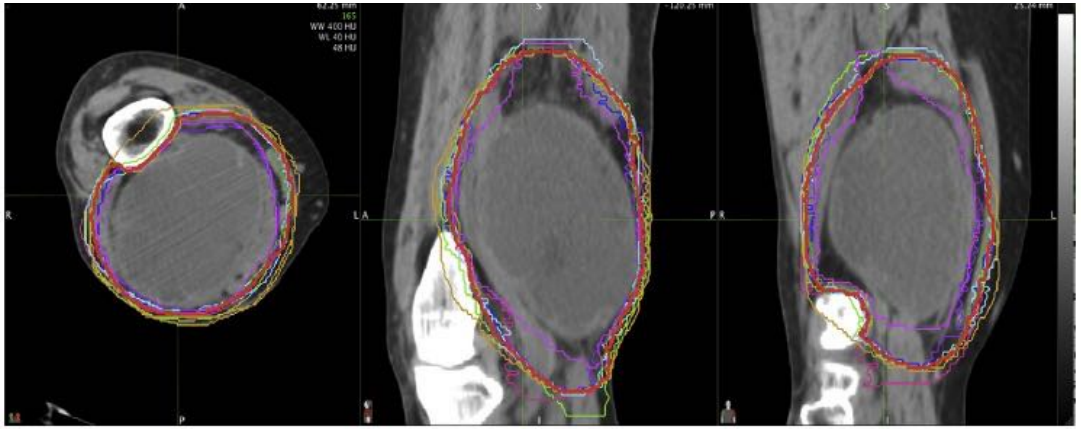


Fig. 2. Example of individual and consensus (red) contours of clinical target volume on axial computed tomography for patient with large high-grade sarcoma of distal aspect of right thigh.

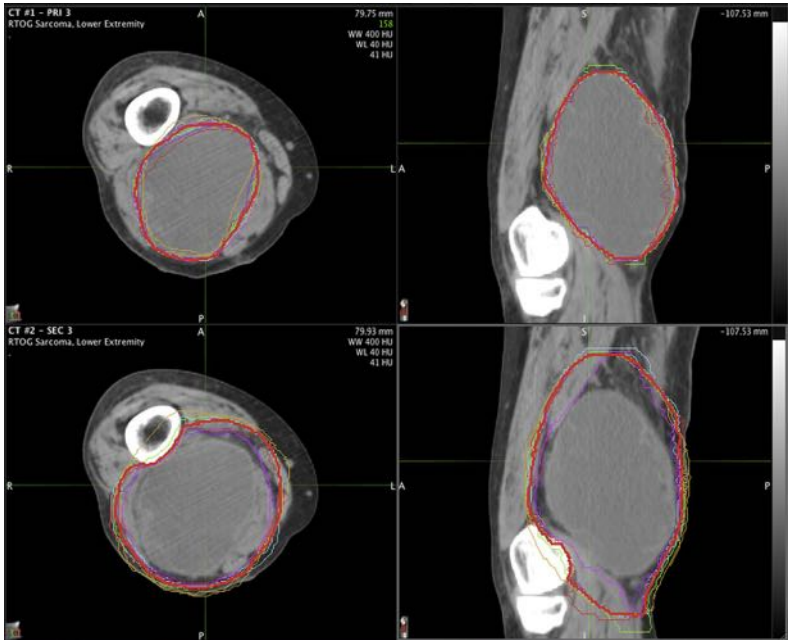
Include gross tumor and clinical microscopic margins (**CTV = GTV plus 3-cm margins**) in the **proximal and distal directions**. If this causes the field to extend beyond the compartment, the field can be shortened.

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 suspect edema (**MRI T2**) is often included. However, clinical judgment is required to make sure whether the above margins need to be extended to cover the T2 edema defined on MRI T2 images.

Variation in GTV and CTV for preoperative RT of primary large high-grade STS of the extremity among RTOG sarcoma radiation oncologists

Delineations of GTV and CTV
GTV: Gross tumor defined by MRI T1 plus contrast images (MRI with contrast is required). Fusion of MRI and CT is recommended to delineate the GTV for radiotherapy planning, but this is optional.
CTV for intermediate- to high-grade Tumors ≥8 cm: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 3-cm margins in the longitudinal (proximal and distal) direction. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1.5 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

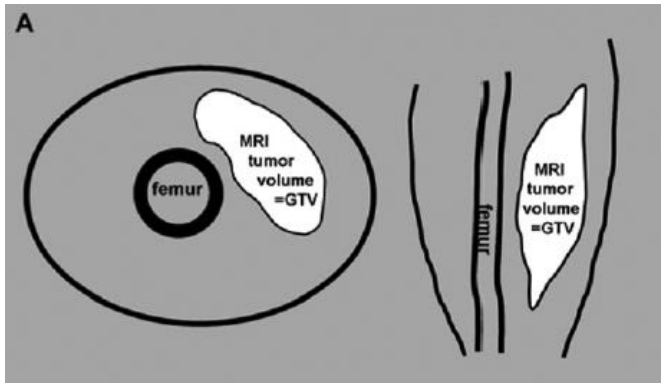


Conclusions: Almost perfect agreement existed in the GTV of these two representative cases. There was no significant disagreement in the CTVof the lower extremity, but variation in the CTVof upper extremity was seen, perhaps related to the positional differences between the planning CTand the diagnostic MRI.

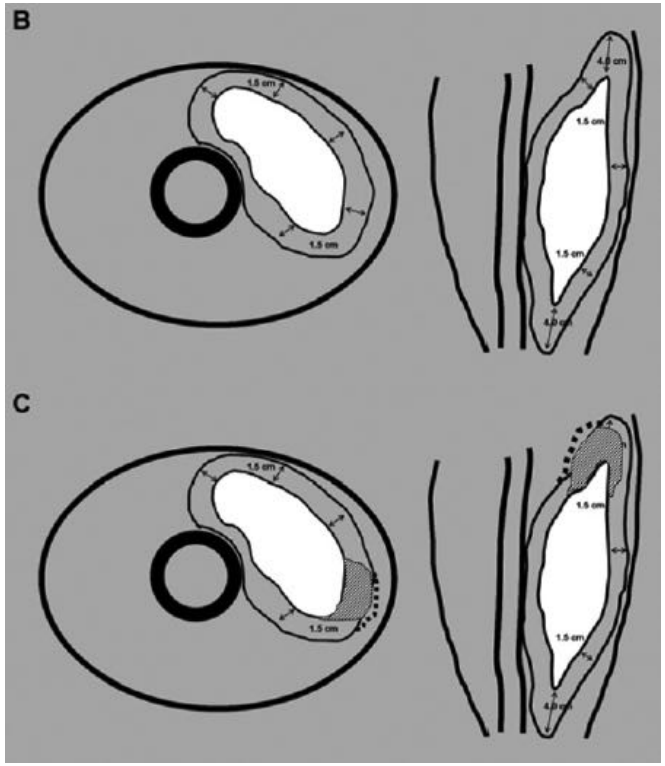
(Wang et al, Int J Radiat Oncol Biol Phys, 81:775-80, 2011)

Target for pre-operative RT

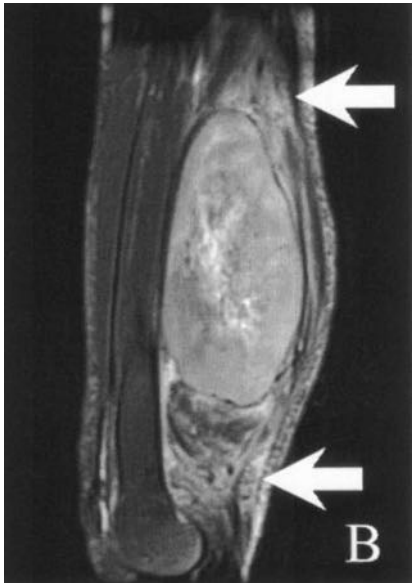
(Haas et al, 2012)



GTV:
T1(contrast)-MRI
+ CT



CTV: GTV + 1.5 cm radially and 4 cm longitudinally including edema



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

CLINICAL INVESTIGATION **Sarcoma**

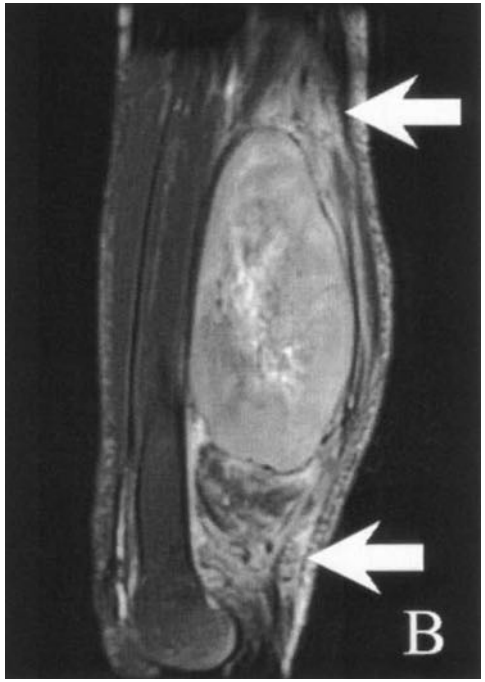
HISTOLOGIC ASSESSMENT OF PERITUMORAL EDEMA IN SOFT TISSUE SARCOMA

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.‖

Departments of *Medical Imaging, †Oncologic Orthopedics, ‡Radiotherapy, §Medical Oncology, and ‖Pathology and Laboratory Medicine, Mt. Sinai Hospital and Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

Assessed MRI and pathology in 15 STS patients undergoing surgery.

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



Recommended 4 cm margin

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

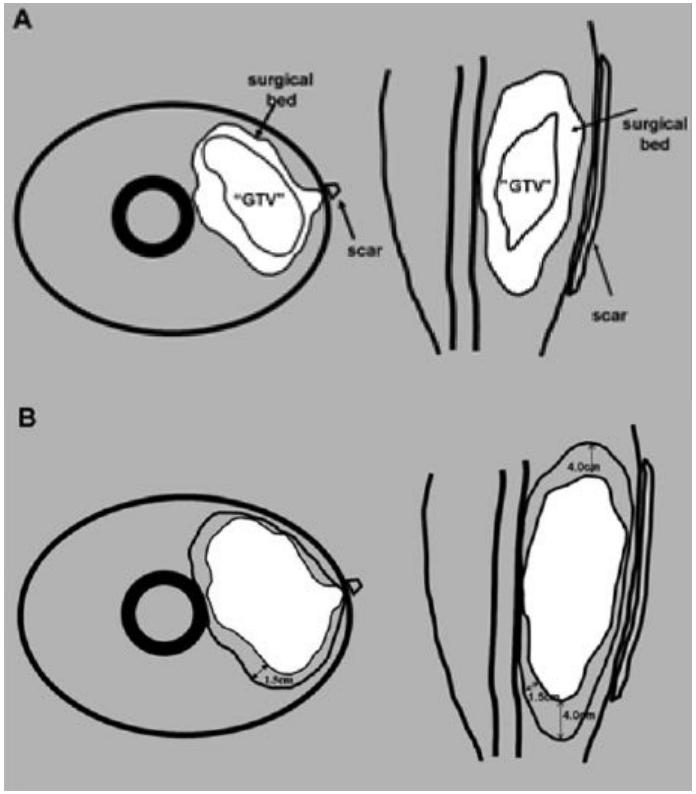
- **Growth Pattern "pushing borders"** (well differentiated liposarcoma ben differenziato) → rare microscopic foci at distance

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

(Haas et al, 2012)

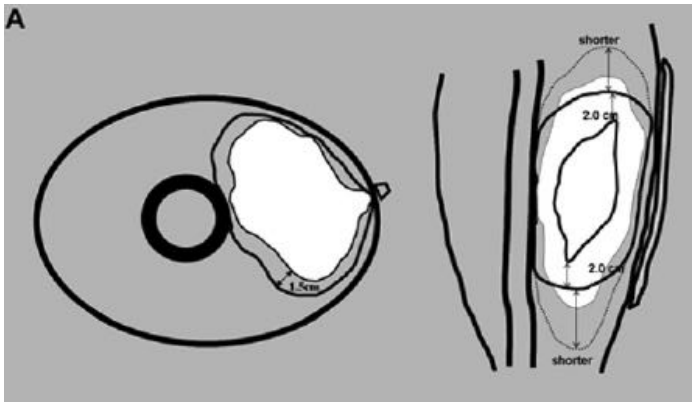
Target for post-operative RT

(Haas et al, 2012)



Imaging: CT and MRI, T2

CTV: surgical volume + 1.5 cm radially and 4 cm longitudinally, if R0 <4 cm (no bone, fasciae and joints)



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

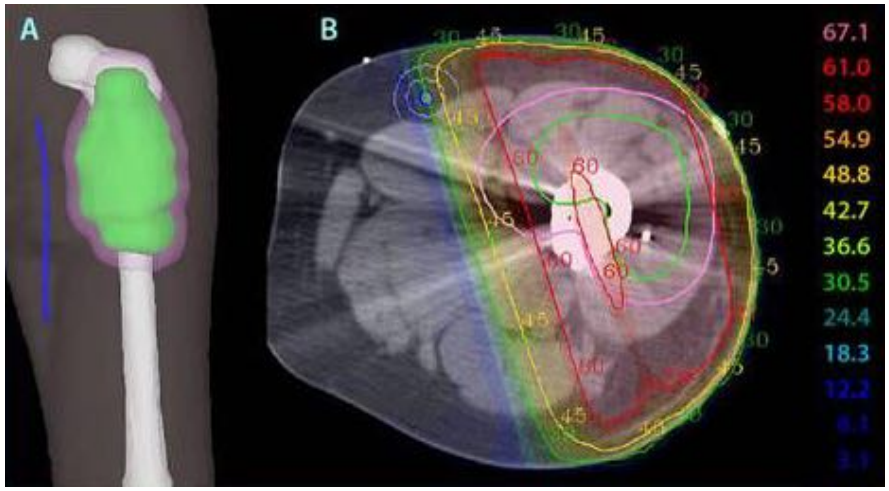
Non-target Structures: Saphenous Volume

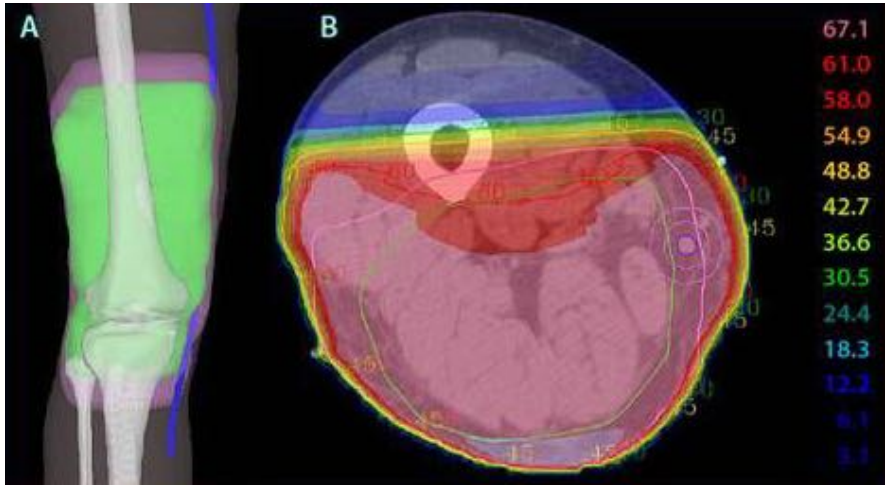
(Liss et al, ASTRO 2012)

131 pts

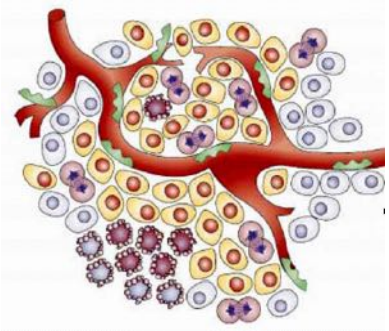
Pts with higher total volume of saphenous vein is associated with development of late edema in the lower extremity

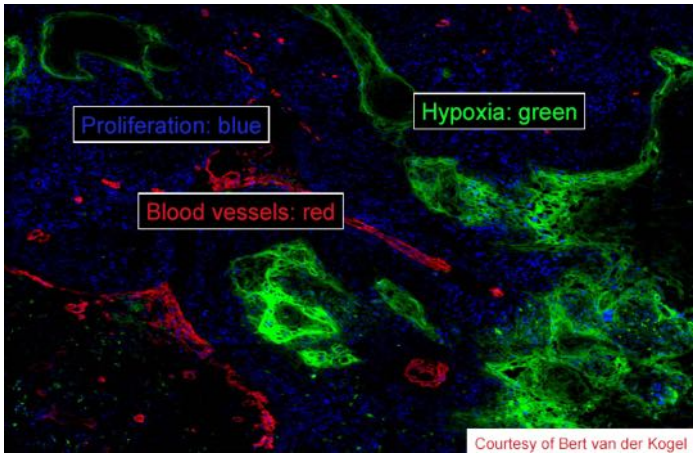
A trend of higher dose to the saphenous vein was also associated with this late effect





Dose Painting ?





FDG PET/CT

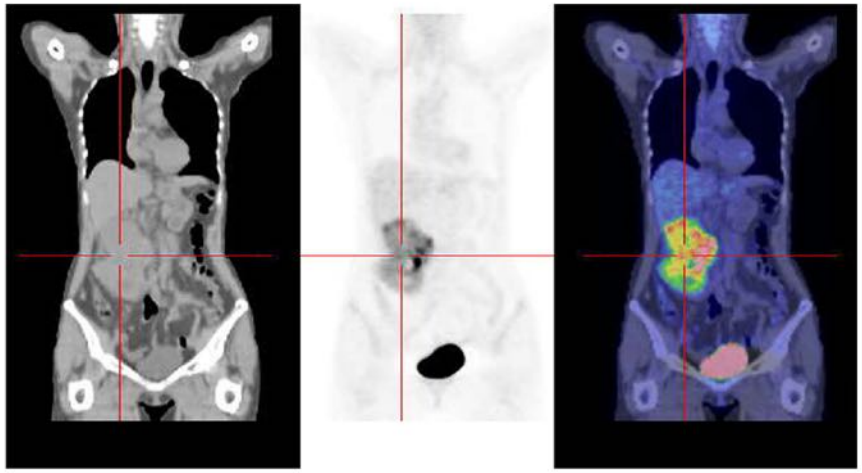


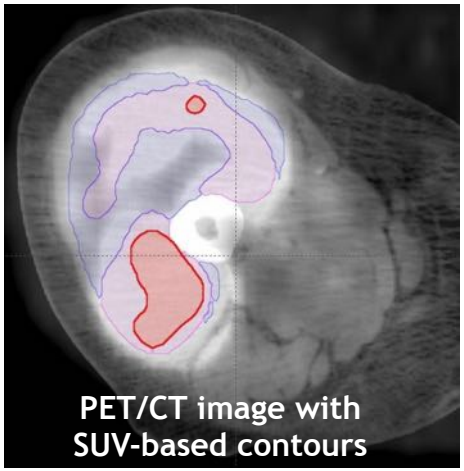
Figure 1. FDG-PET imaging of a patient with a large retroperitoneal sarcoma. The image demonstrates significant heterogeneity in tumour FDG uptake.

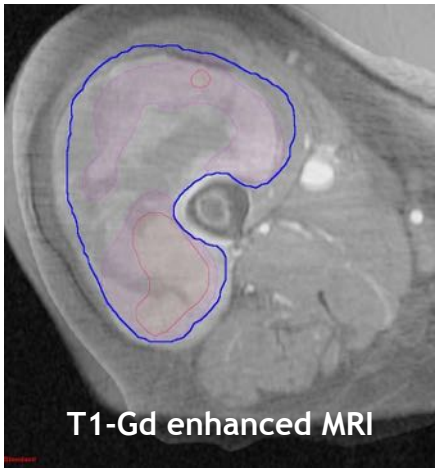
- Sensitivity 90-05%, specificity 85-90%
- May help determine high vs. low grade
- May predict pathologic response
- May be helpful in recurrences

Open issues:

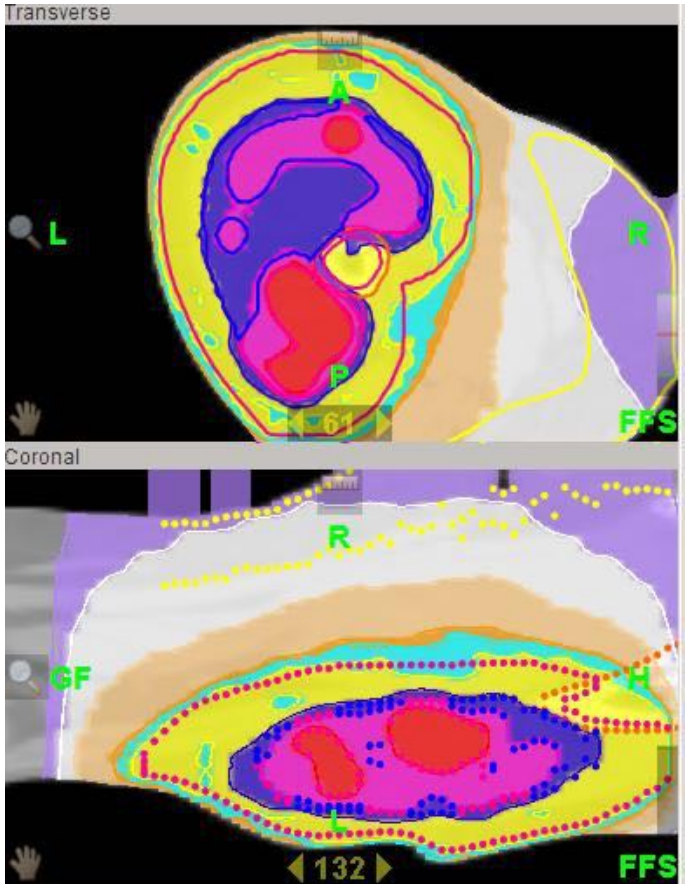
- **How to define positivity (SUV>2 ?)**
- **How to outline on PET images (visual method, SUV value, SUV%, SBR, specific algorithms)**

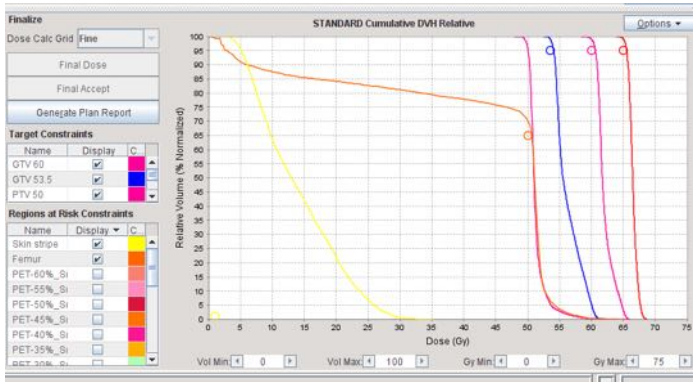
FDG-PET Dose Painting





	$D_{98\%}$ (Gy)	$D_{2\%}$ (Gy)	$D_{50\%}$ (Gy)	Mean Dose (Gy)	HI	CI
GTV_{65Gy}	65.2	67.9	66.4	66.4	1.03	0.85
GTV_{60Gy}	60.2	65.1	61.6	62.0	1.07	0.88
$GTV_{53.5Gy}$	53.6	60.3	55.5	56.3	1.11	0.90
PTV_{50Gy}	49.7	55.6	50.9	51.3	-	0.93
Skin	-	-	-	44.6	-	-
Femur	-	60 (D_{1cc})	-	43.7	-	-





Dose painting distributions and DVHs in FDG PET/CT defined sub-regions

(Serban et al, ASTRO 2012)

CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 3, pp. 817–821, 2009 **Sarcoma**

PET/CT FOR RADIOTHERAPY TREATMENT PLANNING IN PATIENTS WITH SOFT TISSUE SARCOMAS

FDG

IRENE KARAM, M.D.,* SLOBODAN DEVIC, PH.D.,† MARC HICKESON, M.D.,‡ DAVID ROBERGE, M.D., F.R.C.P.C.,* ROBERT E. TURCOTTE, M.D.,§ AND CAROLYN R. FREEMAN, M.B., B.S., F.R.C.P.C.*

Departments of *Radiation Oncology, †Medical Physics, ‡Nuclear Medicine, and §Orthopedic Surgery, McGill University Health Centre, Montreal, Quebec, Canada

in vivo 23: 105-110 (2009)

^{11}C-Methionine *vs.* ^{18}F-FDG PET in Soft Tissue Sarcoma Patients Treated with Neoadjuvant Therapy: Preliminary Results

GIULIA GHIGI[1], RENATO MICERA[1], ANNA MARGHERITA MAFFIONE[2], PAOLO CASTELLUCCI[2], SILVIA CAMMELLI[1], ILARIO AMMENDOLIA[1], CRISTINA NANNI[2], ENZA BARBIERI[1], GAIA GRASSETTO[3], STEFANO FANTI[2] and DOMENICO RUBELLO[3]

Departments of [1]Radiotherapy and [2]Nuclear Medicine, Policlinico "S. Orsola-Malpighi" Hospital, Bologna; [3]Department of Nuclear Medicine, "S. Maria della Misericordia" Hospital, Rovigo, Italy

EJSO 2003; 29: 908–915

Thallium-201 scintigraphy–a predictor of tumour necrosis in soft tissue sarcoma following preoperative radiotherapy?

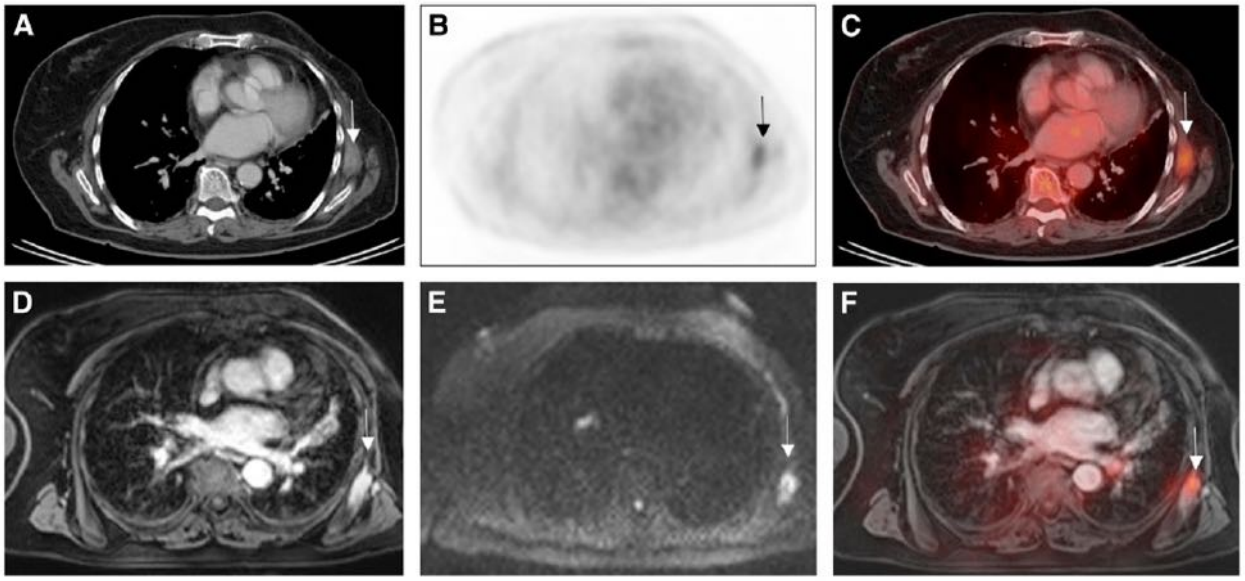
P. F. M. Choong*,¶, I. Nizam*, S. Y. K. Ngan, S. Schlict†, G. Powell*,¶, J. Slavin‡, P. Smith†, G. Toner†† and R. Hicks§**

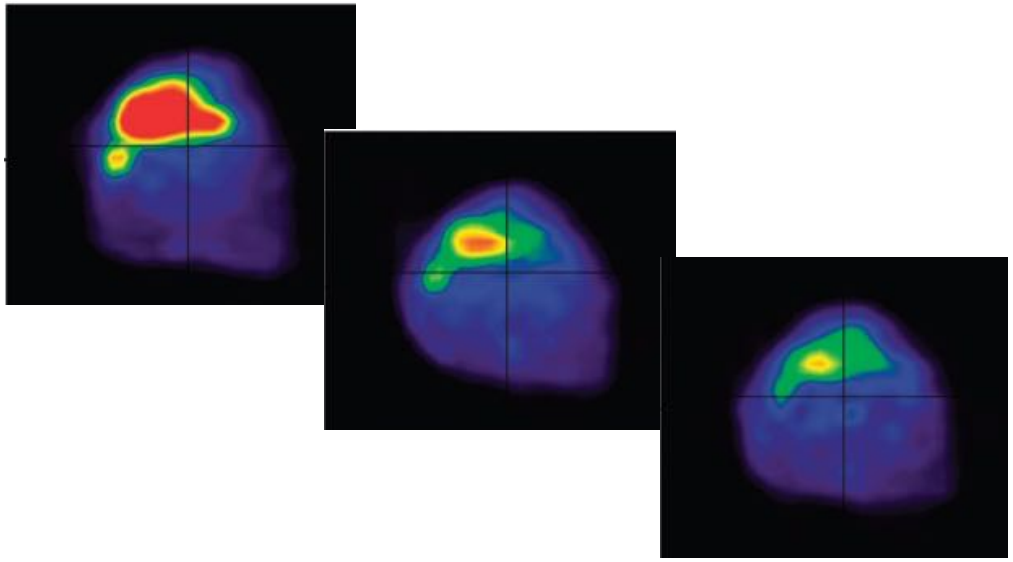
THE JOURNAL OF NUCLEAR MEDICINE • Vol. 53 • No. 8 • August 2012

Oncologic PET/MRI, Part 2: Bone Tumors, Soft-Tissue Tumors, Melanoma, and Lymphoma

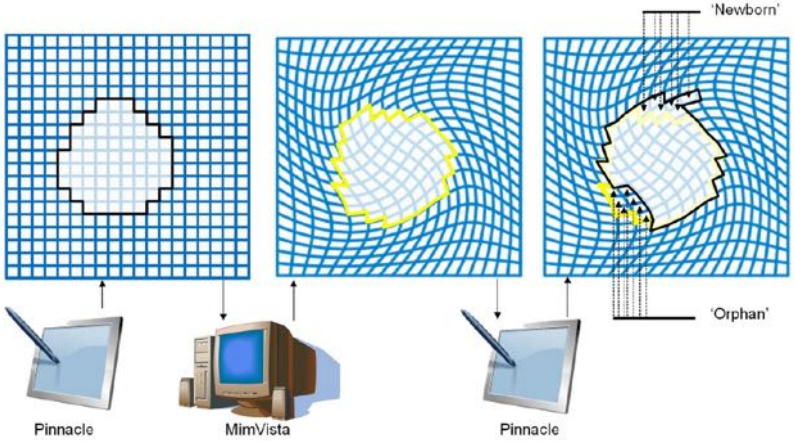
Christian Buchbender[1], Till A. Heusner[1], Thomas C. Lauenstein[2], Andreas Bockisch[3], and Gerald Antoch[1]

18F-FDG PET does not add information to MRI for T-staging in soft-tissue sarcomas. On the other hand, 18F-FDG PET provides additional prognostic information.
DW-MRI has been shown to provide a measure of tumor cellularity and could serve to identify areas for boost dose of radiation as **dose painting**.
DCE-MRI could map the areas of neoangiogenesis and serve for **dose painting**.
MR-spectroscopy could potentially contribute to differentiation between malignant and benign soft-tissue masses and help in **dose painting** showing hypoxic areas.





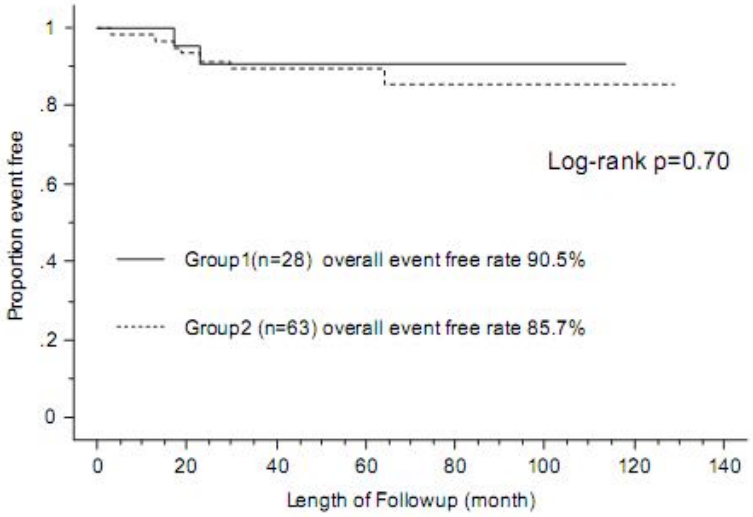
Adaptive Radiotherapy ?



EJSO 36 (2010) 678–683

The significance of size change of soft tissue sarcoma during preoperative radiotherapy

Y. Miki [a,1], S. Ngan [b], J.C.M. Clark [a], T. Akiyama [a], P.F.M. Choong [a,b,*]



Histology	Group 1 ($n = 28$)	Group 2 ($n = 63$)
Pleomorphic undifferentiated sarcoma (MFH)	21	25
Liposarcoma	4	17
Neurosarcoma	2	6
Synovial sarcoma	0	7
Leiomyosarcoma	1	5
Rhabdomyosarcoma	0	1
Clear cell sarcoma	0	1
Epithelioid sarcoma	0	1

Group 1: increase in tumor size

Group 2: no change or decrease in tumor size

Similar local control and survival in both groups

J Nucl Med 1992; 33:373–379

Radiation-Induced Inhibition of Tumor Growth as Monitored by PET Using L-[1-^{11}C]Tyrosine and Fluorine-18-Fluorodeoxyglucose

Bernard J. G. Daemen, Philip H. Elsinga, Anne M. J. Paans, Andre R. Wieringa, Antonius W. T. Konings, and Willem Vaalburg

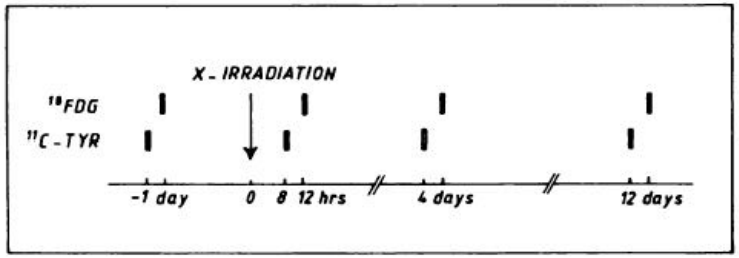
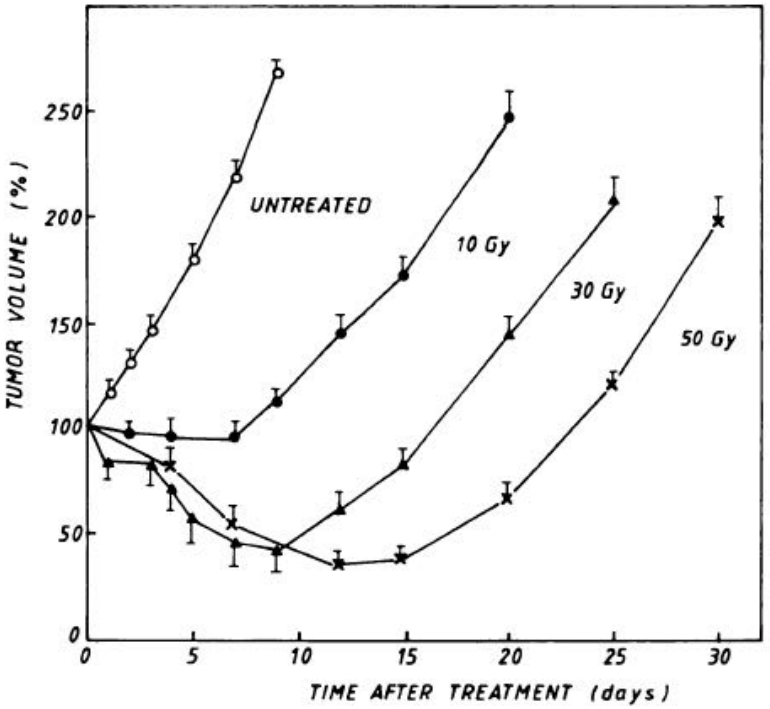


FIGURE 1. Time schedule of the experimental procedure for PET measurements. Carbon-11-tyr (□) and ^{18}FDG (■) data were acquired for 45 min. Time interval between ^{11}C-Tyr and ^{18}FDG studies is 4 hr.

TABLE 3
Effect of Radiotherapeutic and Hyperthermic Treatments on Tumor Growth of Rhabdomyosarcoma

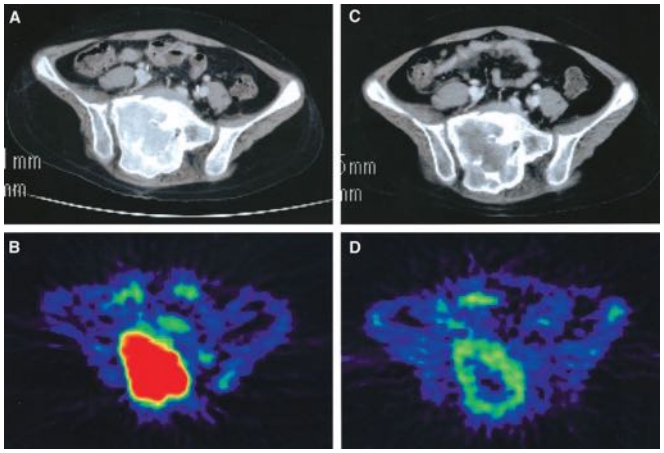
Treatment	Growth delay (GD)	P value	Number
10 Gy	1.98 ± 0.09	$p < 0.004$	n = 8
30 Gy	3.54 ± 0.32	$p < 0.016$	n = 6
50 Gy	4.47 ± 0.38	$p < 0.016$	n = 6
15 min at 45°C	0.17 ± 0.04	$p < 0.11$	n = 6
30 Gy + 15 min at 45°C	6.75 ± 0.04	$p < 0.07$	n = 4

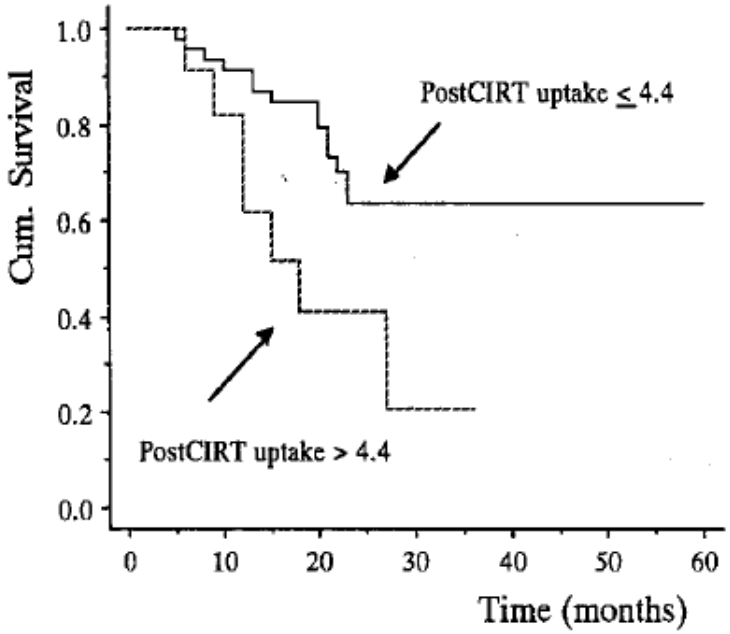
Values are mean ± s.e.m.
P values obtained with Fisher's distribution free sign test (*25*).



[11C]Methionine Positron Emission Tomography and Survival in Patients with Bone and Soft Tissue Sarcomas Treated by Carbon Ion Radiotherapy *(Zhang H et al, Clin Cancer Res, 2004)*

MET-PET uptake showed a mean T/N (Tumor/Non-Tumor) ratio of 4.58 2.57. After CIRT, the mean T/N ratio decreased to 3.11 2.04 significantly (*P* 0.00029).



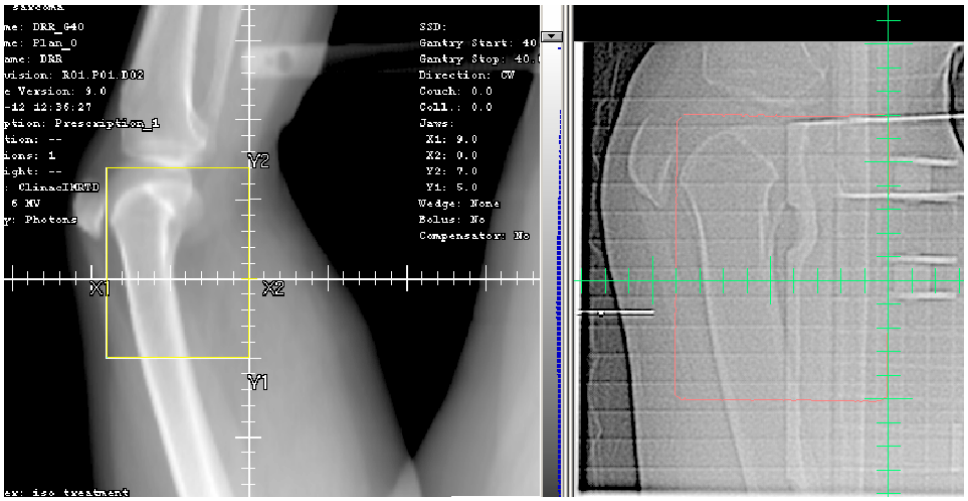


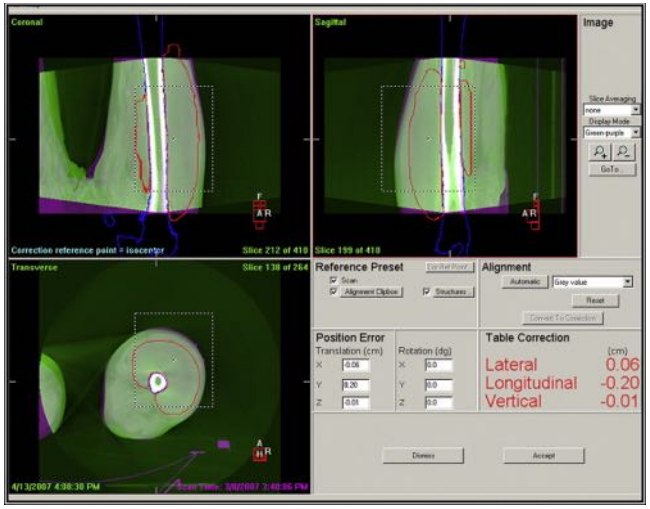
Advantage compared to FDG-PET:

- early changes
- better prognostic value

Also FLT-PET could be considered

Imaging for Verification of RT





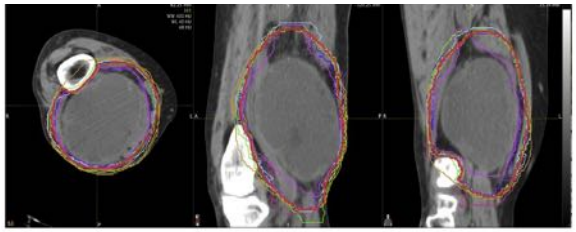


Fig. 2. Example of individual and consensus (red) contours of clinical target volume on axial computed tomography for patient with large high-grade sarcoma of distal aspect of right thigh.

Conclusions

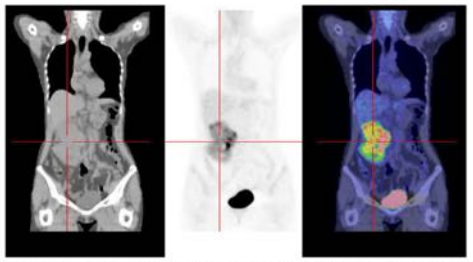


Figure 1. FDG-PET imaging of a patient with a large retroperitoneal sarcoma. The image demonstrates significant heterogeneity in tumour FDG uptake.

- CT and MRI (especially in the extremities) are the standard imaging modalities to identify and outline the target and non-target structures for radiotherapy planning.

- PET (not only with FDG), DW-MRI and PW-MRI are a very exciting research fields to implement dose painting and biologically adaptive radiotherapy.