"Indicazioni, Dosi e Volumi nell'irradiazione dei Sarcomi delle Parti Molli: stato dell'arte"

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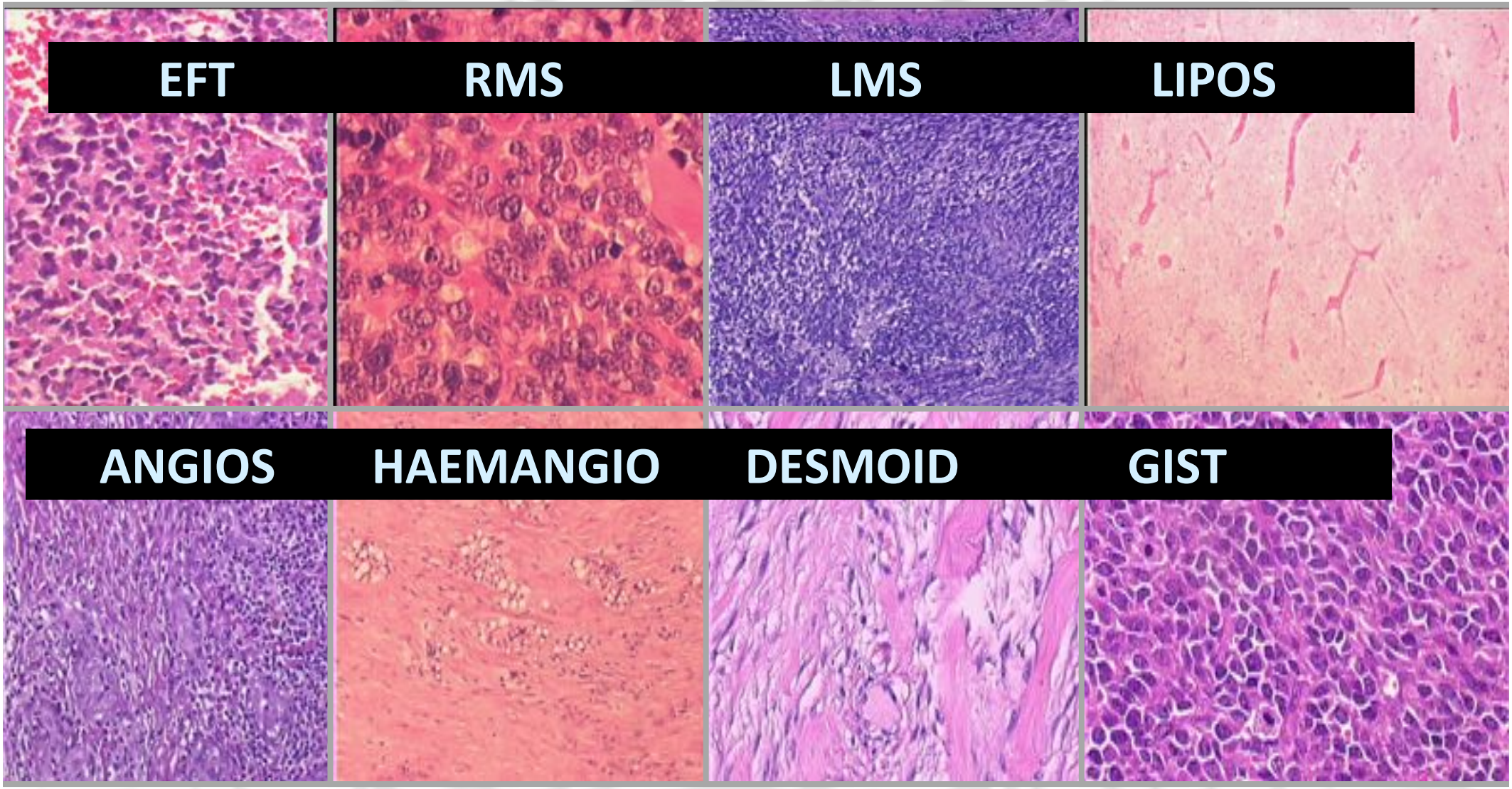
Radioterapia Oncologica
Università degli Studi di Firenze

Azienda Ospedaliero Universitaria Careggi

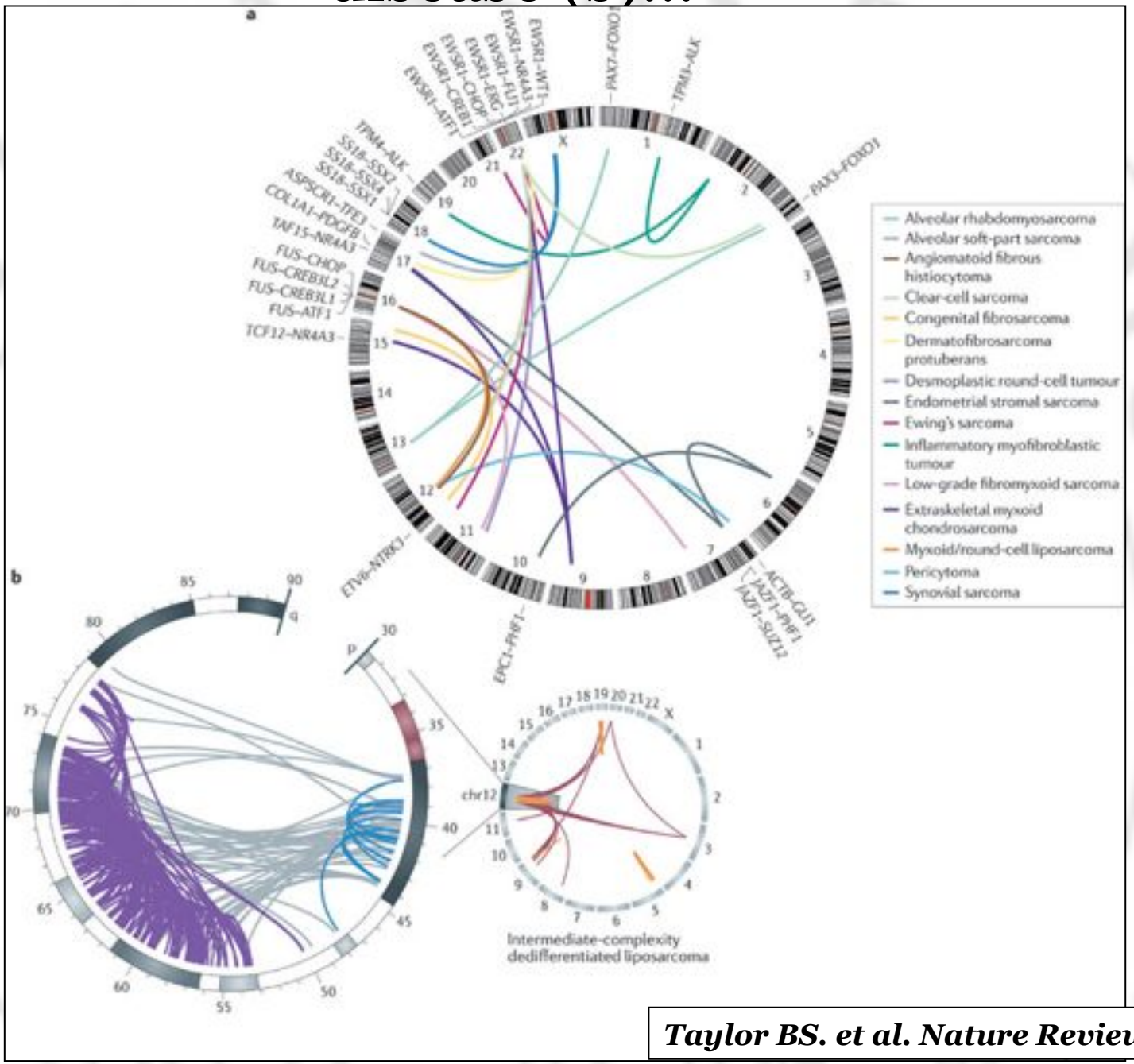
SARCOMA

SARCOMAS:



...a palette of histologies...

….a complex taxonomy for a very heterogeneous disease (s)…



Taylor BS. et al. Nature Reviews 2011

OVERVIEW

- ✓ Surgery is the cornerstone of treatment

- ✓ Local recurrence rates of 30-50% when local excision is utilized as sole treatment

Cantin J. et al, Ann Surg 1968; 168:47-53

- ✓ Radical compartmental excisions or amputations has reduced local recurrence rates to 5 to 20%

Shiu MH et al., Ann Surg 1975; 182:597
Simon MA, et al. J Bone Joint Surg 1976; 58-A:317

January 9 th 2007

AP / Paul Sakuma

...September 1982

The Treatment of Soft-tissue Sarcomas of the Extremities

Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjuvant Chemotherapy

STEVEN A. ROSENBERG, M.D., PH.D.,* JOEL TEPPER, M.D.,† ELI GLATSTEIN, M.D.,† JOSE COSTA, M.D.,‡
ALAN BAKER, M.D.,* MURRAY BRENNAN, M.D.,* ERNEST V. DEMOSS, M.D.,* CLAUDIA SEIPP, R.N.,*
WILLIAM F. SINDELAR, M.D., PH.D.,* PAUL SUGARBAKER, M.D.,* ROBERT WESLEY, PH.D.§

Ann. Surg. • September 1982

From the National Cancer Institute, Bethesda, Maryland

Postoperative RT: INDICATIONS

43 High Risk STS pts randomized

27 Limb Sparing Resection + RT vs. 16 Amputation

@ 5 years no differences in:

- ✓ disease free survival rates (71% vs 78%; p= 0.75)
- ✓ overall survival rates (83% vs 88%; p= 0.99)

KEEP in MIND…

The only correlate of local recurrence was the *final margin of resection* (p< 0.0001) even when postoperative radiotherapy was used

Postoperative Chemotherapy resulted in a gain of 3 years DFS (92% vs. 60%; p = 0.0008) and OS (95% vs. 74%; p= 0.04).

Rosemberg SA et al, Ann Surg 1982

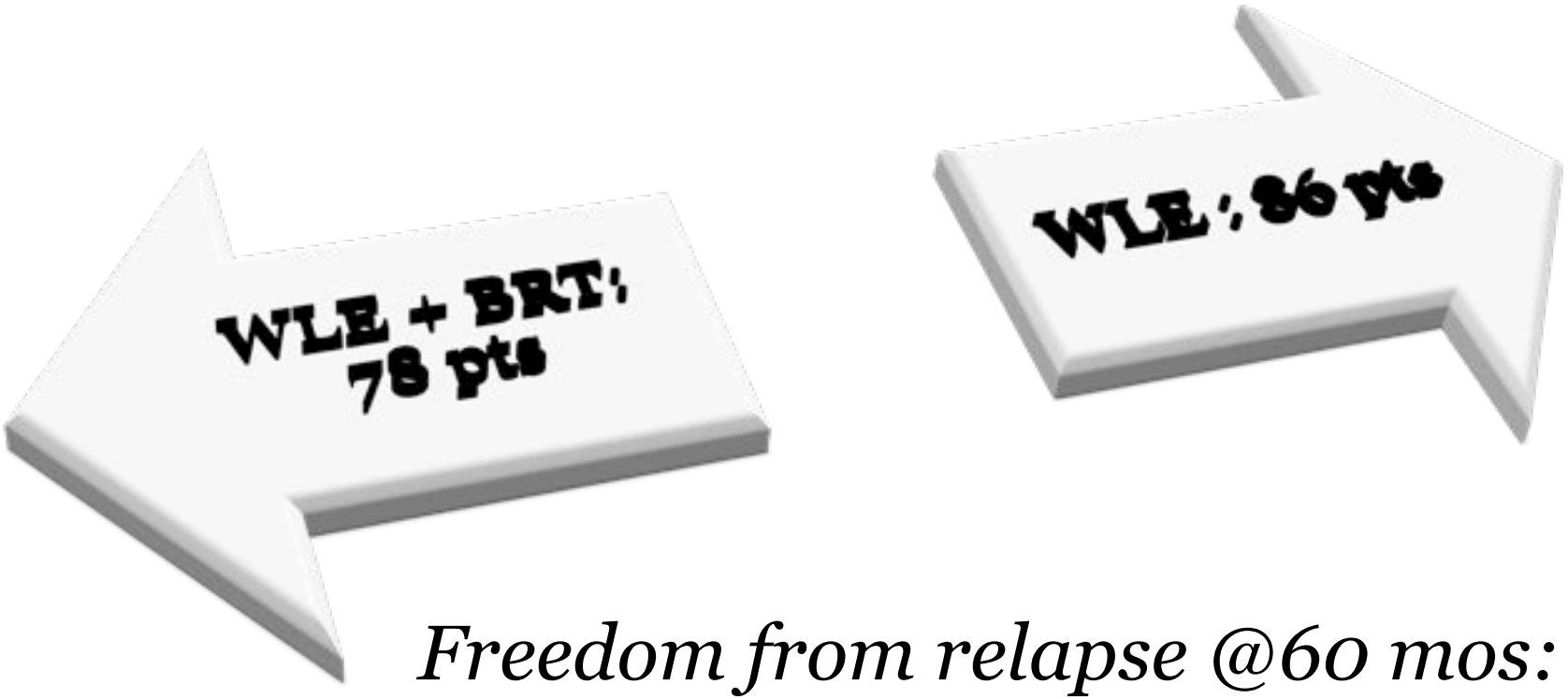
Postoperative RT: INDICATIONS

Amputation vs Limb sparing Surgery + RT

Limb sparing Surgery Alone

MSKCC TRIAL

164 pts High Risk Soft Tissue Sarcoma



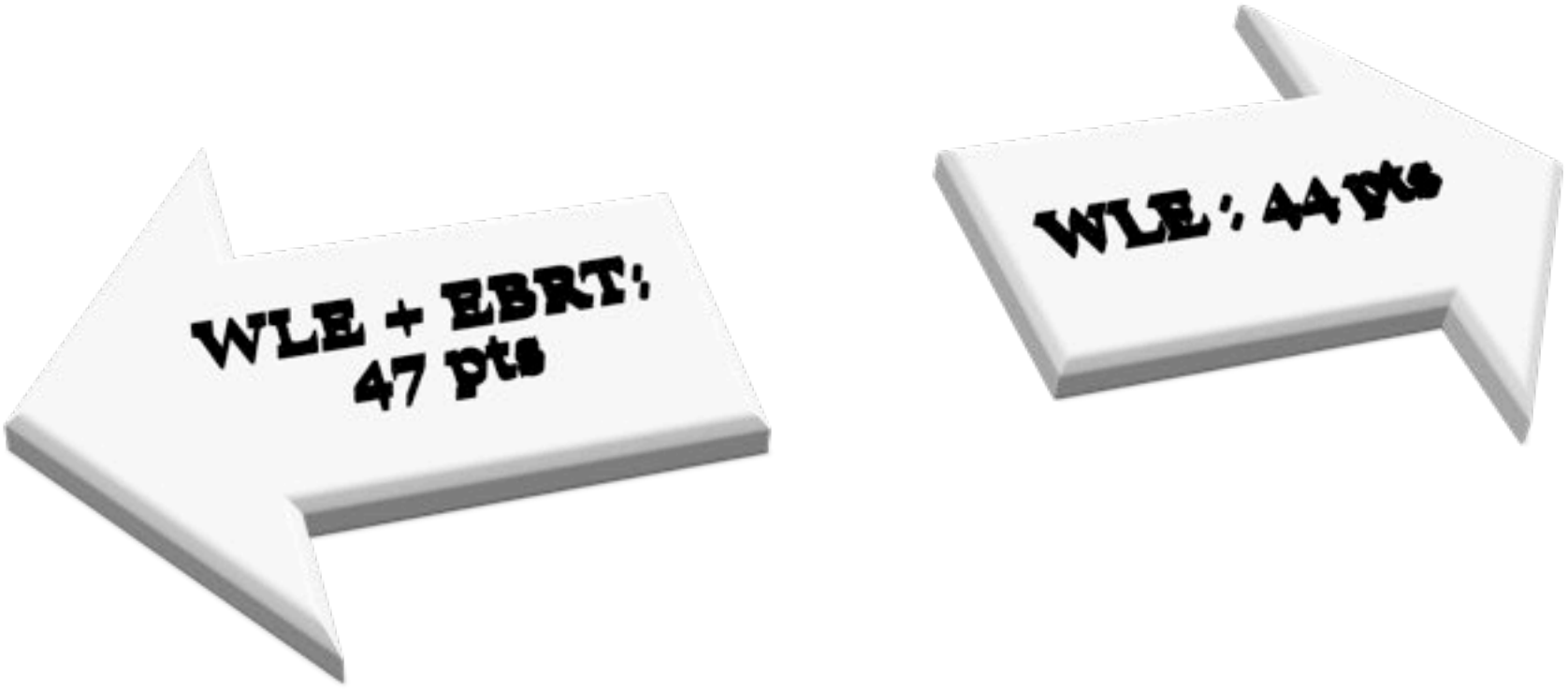
Freedom from relapse @60 mos:
82% vs 69% p=.04

Pisters et al. J Clin Oncol 1996

NCI TRIAL

Surgery alone vs Surgery + EBRT

91 High Risk Soft Tissue Sarcoma



Local Failure: 0% vs 22%, p=.0001

Yang JC et al. J Clin Oncol 1998; 16: 197–203

Ann Surg Oncol (2014) 21:2484–2489
DOI 10.1245/s10434-014-3732-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Efficacy of Adjuvant Radiation Therapy in the Treatment of Soft Tissue Sarcoma of the Extremity: 20-year Follow-Up of a Randomized Prospective Trial

Joal D. Beane, MD[1], James C. Yang, MD[1], Donald White, MS[1], Seth M. Steinberg, PhD[2], Steven A. Rosenberg, MD, PhD[1], and Udo Rudloff, MD, PhD[1]

[1]Surgery Branch, National Cancer Institute, Bethesda, MD; [2]Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, Bethesda, MD

141 EBRT + WLE vs 71 WLE , median follow up: 17.9 years

Conclusions: Adjuvant EBRT following surgery for STS of the extremity provides excellent local control with acceptable treatment-related morbidity and no statistically significant improvement in overall survival.

Postoperative RT: INDICATIONS

RT as complement of surgery is effective on LC (20-25% LRs reduction), NOT on OS!

... Yang et al from the NCI randomized trial concluded:
"...***although postoperative radiation therapy is highly effective in preventing LRs, selected patients with extremity soft tissue sarcoma may not require adjuvant RT after limb-sparing surgery***"

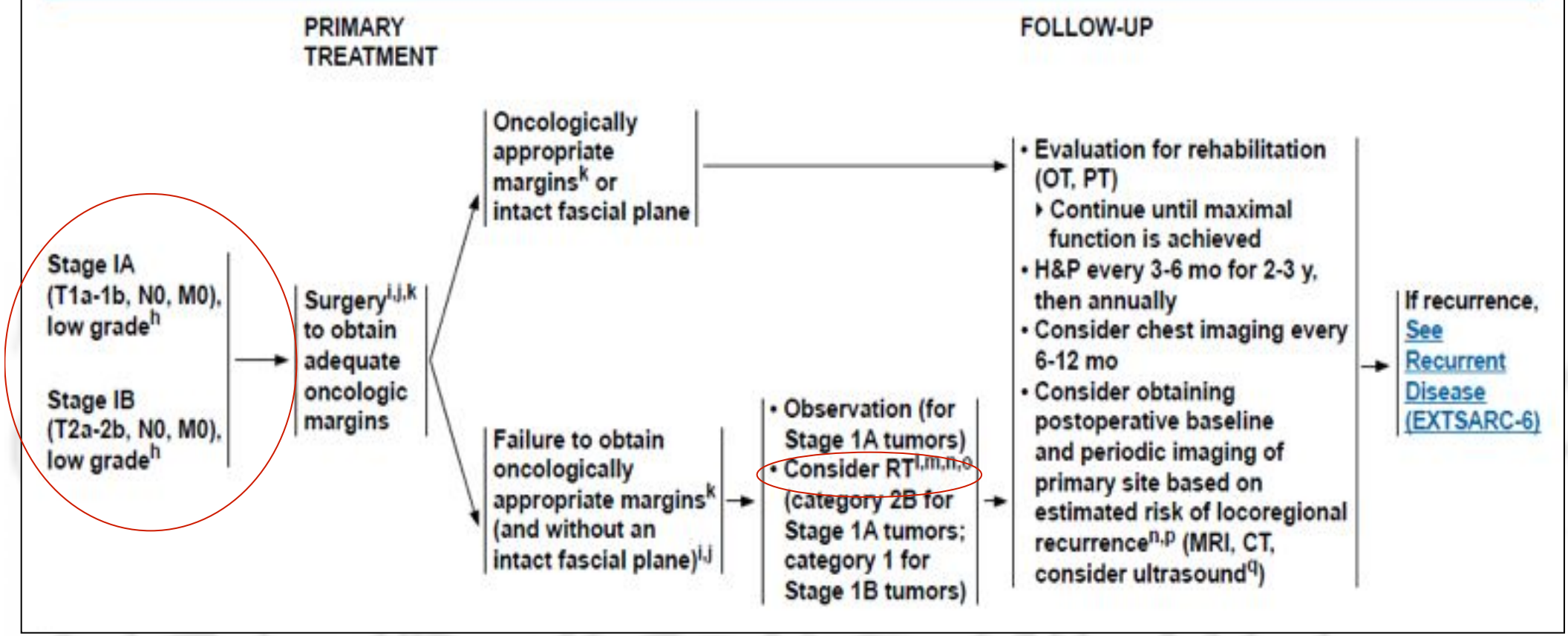
Yang JC et al. J Clin Oncol 1998; 16: 197–203.

INDICATIONS:summarizing

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Extremity/Superficial Trunk, Head/Neck

NCCN Guidelines Index
Soft Tissue Sarcoma, Table of Contents
Discussion



INDICATIONS: summarizing

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Extremity/Superficial Trunk, Head/Neck

NCCN Guidelines Index
Soft Tissue Sarcoma, Table of Contents
Discussion

Stage II, III[r] Resectable with acceptable functional outcomes

PRIMARY TREATMENT[s]

Stage IIA

- Surgery[i,t] to obtain oncologically appropriate margins
- or
- Surgery[i] to obtain oncologically appropriate margins → RT[l] (category 1)[w,x]
- or
- Preoperative RT[l] → Surgery[i,u] to obtain oncologically appropriate margins

Stage IIB, III

- Surgery[i,j] to obtain oncologically appropriate margins → RT[l] (category 1)[x] or RT[l] + adjuvant chemotherapy[v,y] (category 2B)
- or
- Preoperative RT[l] or Preoperative chemoradiation[l,v] (category 2B) → Surgery[i,u] to obtain oncologically appropriate margins → Consider RT boost[l,z] ± adjuvant chemotherapy[v,y] (category 2B)
- or
- Preoperative chemotherapy[v] (category 2B) → Surgery[i,u] to obtain oncologically appropriate margins → RT[l,x] or RT[l] + adjuvant chemotherapy[v,y] (category 2B)

FOLLOW-UP

- Evaluation for rehabilitation (OT, PT)
  - Continue until maximal function is achieved
- H&P and chest imaging (plain radiograph or chest CT) every 3-6 mo for 2-3 y, then every 6 mo for next 2 y, then annually
- Consider obtaining postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence[n,p] (MRI, CT, consider ultrasound[q])

→ If recurrence, See Recurrent Disease (EXTSARC-6)

INDICATIONS: summarizing

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

INDICATIONS: summarizing

✓Radiation therapy is not given in the case of a truly compartmental resection of a tumour entirely contained within the compartment [IV, A].

✓A wide excision is followed by radiation therapy as the standard treatment of high-grade (G2–3), deep, >5 cm lesions [II, B]

Yang JC, J Clin Oncol 1998; 16: 197–203
Beane JD et al. Ann Surg Oncol 2014; 21: 2484–2489
Pisters et al. J Clin Oncol 1996

INDICATIONS: summarizing

✓High-grade, deep, <5 cm lesions are treated with surgery, followed by radiation therapy [IV, A]

✓Radiation therapy is added in selected cases in the case of low- or high-grade, superficial, >5 cm and low-grade, deep,<5 cm STSs [II, B]

✓In the case of low-grade, deep, >5 cm STSs, radiation therapy should be discussed in a multidisciplinary fashion, considering the anatomical site and the related expected sequelae versus the histological agressiveness.

Postoperative RT: INDICATIONS

… Yang et al from the NCI randomized trial concluded:
"…***although postoperative radiation therapy is highly effective in preventing LRs, <u>selected patients</u> with extremity soft tissue sarcoma <u>may not require</u> adjuvant RT after limb-sparing surgery***"

Annals of Surgery • Volume 255, Number 2, February 2012

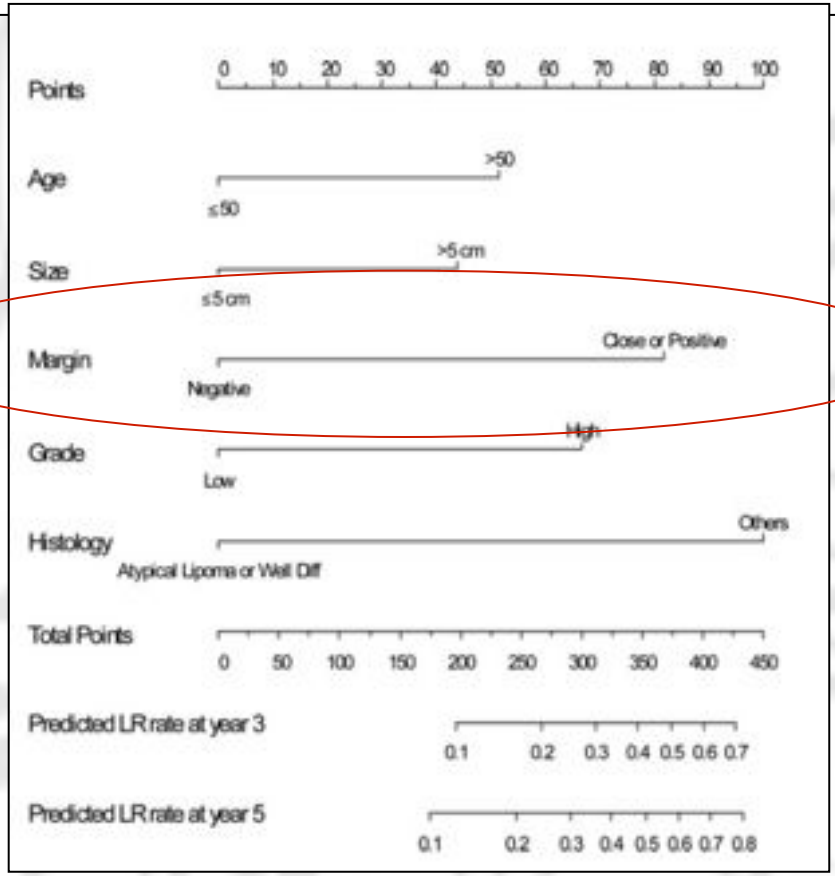
ORIGINAL ARTICLE

A Postoperative Nomogram for Local Recurrence Risk in Extremity Soft Tissue Sarcomas After Limb-Sparing Surgery Without Adjuvant Radiation

Oren Cahlon, MD, Murray F. Brennan, MD,† Xiaoyu Jia, MS,‡ Li-Xuan Qin, PhD,‡ Samuel Singer, MD,† and Kaled M. Alektiar, MD**

Results: With a median follow-up of 58 months for censored patients (73 months for all patients), the overall 3- and 5-year actuarial local recurrence rates were 11% and 13%, respectively. Factors included in the nomogram were age (≤50 vs. >50), size (≤5 vs. >5 cm), margin status (negative vs. positive), grade (low vs. high), and histology (atypical lipomatous tumor/well differentiated liposarcoma vs. other). The STS nomogram predicted the local recurrence rate with a C-index of 0.73.

Conclusions: A nomogram for extremity STS that includes age, size, margin status, grade of tumor, and histology predicts the 3- and 5-year risk of local recurrence after limb-sparing surgery in the absence of adjuvant RT.



INDICATIONS: Margins' Caveat

...the margin status was identified as a factor associated with local recurrence

Rosember SA et al, *Ann Surg 1982*

... a nearly 2-fold increase in LR for patients with a simple local excision versus a more extensive resection.

Coindre JM, et al *J Clin Oncol 1996*

Moreover, the subsequent use of radiation therapy in this scenario would not compensate for an unplanned positive microscopic margin (R1 resection)

Clark MA et al. *N Engl J Med 2005*

In the scenario of a planned radical resection near a critical neurovascular structure,where a positive margin was obtained,planned preoperative or postoperative radiation therapy targeted to this area would decrease the rate of a local recurrence to approximately 4%.

Gerrand CH et al. J Bone Joint Surg Br 2001

INDICATIONS

- No RT: compartmental resection of STS encompassed in compartment
- RT in selected case: G1 deep STS <5cm or superficial tumors
- RT should be performed in R0 G2-G3 deep STS >5cm or in R1-R2 that cannot be surgically rescued

Le Pechoux, Can Rad 2006

POSTOPERATIVE VOLUMES

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.JCO 1998

POSTOPERATIVE VOLUMES

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 VOLUMES

Current data do not allow to differentiate treatment volumes according to growth pattern
"pushing borders" tumors (i.e. LS) may behave differently from "locally infiltrating" (MFS)

Pao, IJROBP 1990

POSTOPERATIVE VOLUMES

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 VOLUMES

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 VOLUMES

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, Center for Radiation Therapy; †Department of Surgery, Section of Orthopedic Surgery and ‡Section of Hematology/Oncology, University of Chicago Hospitals, Chicago, IL 60637

POSTOPERATIVE VOLUMES

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 (91.6%)

10 cm (100%)

p=0.007

Mundt AJ et al. IJROBP 1995

POSTOPERATIVE VOLUMES

CME ASTRO

International Journal of Radiation Oncology biology • physics

www.redjournal.org

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††

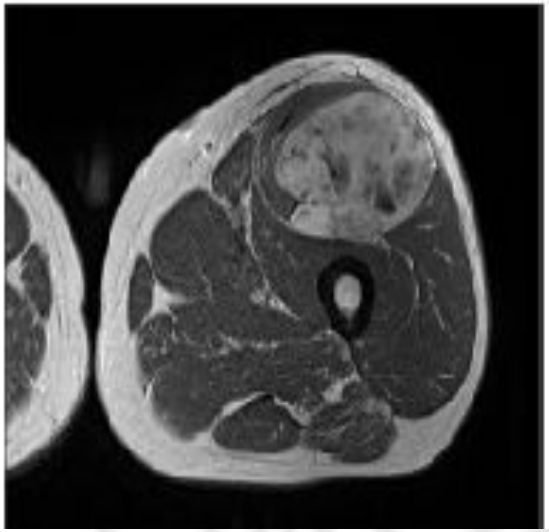
*From the *Department of Radiotherapy, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; †Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; ‡Department of Radiation Oncology, Princess Margaret Hospital, Toronto, ON, Canada; §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*

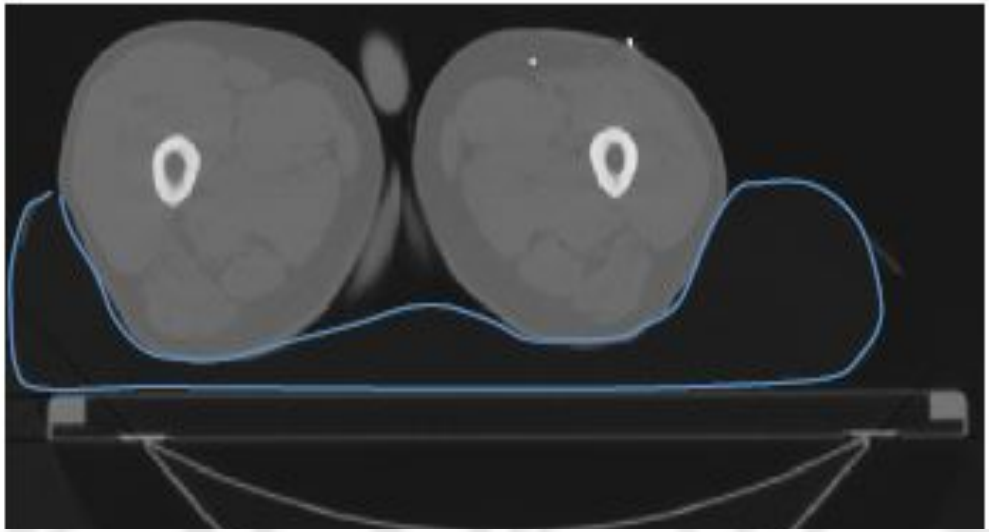
Received Sep 28, 2011, and in revised form Jan 9, 2012. Accepted for publication Jan 20, 2012

POSTOPERATIVE VOLUMES

✓Original GTV should be recreated in the planning CT set → fusion with preoperative imaging

✓GTV is encompassed in surgical volume

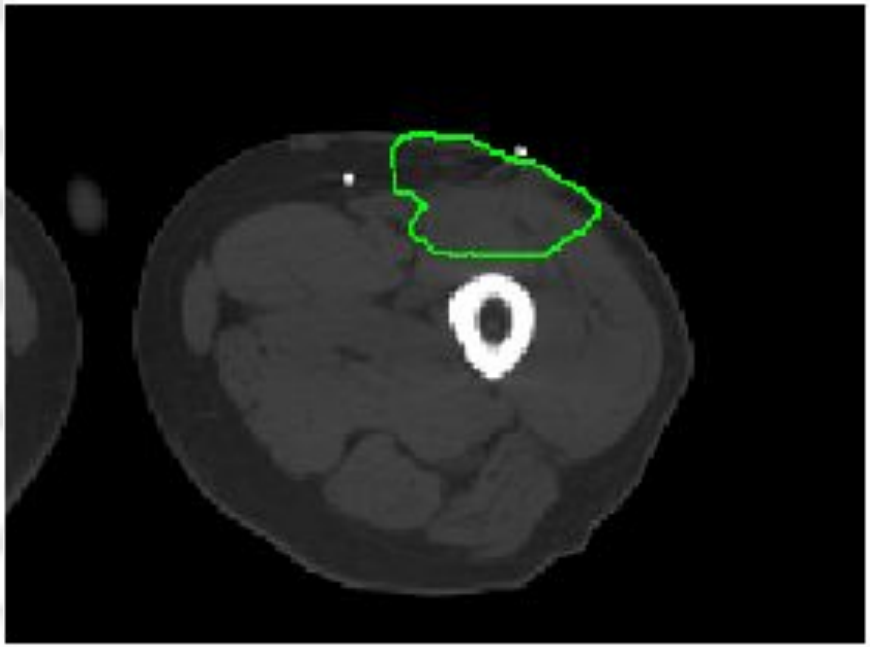


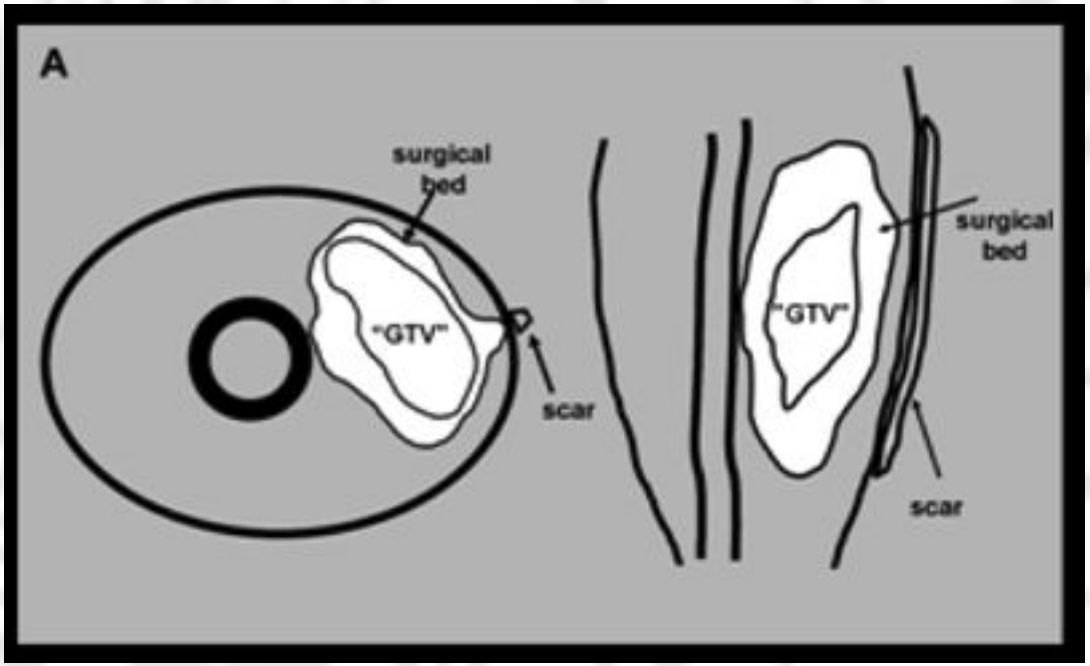


POSTOPERATIVE VOLUMES

✓ Surgical volume should be delineated according to postoperative imaging

✓DO NOT OMIT surgical scar (wire+++ on planning CT)





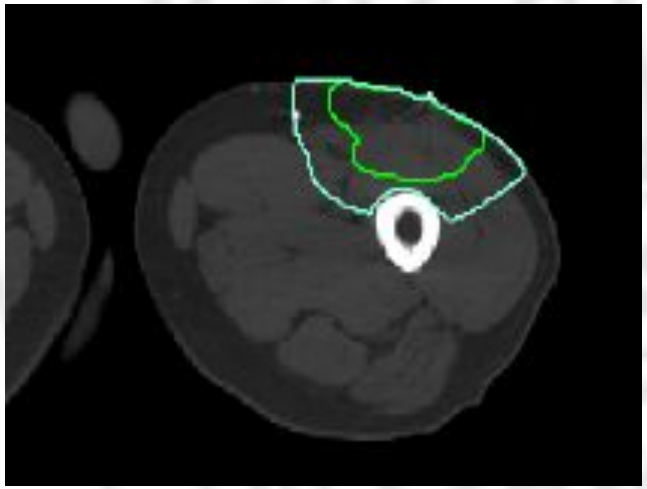
Haas , IJROBP 2012

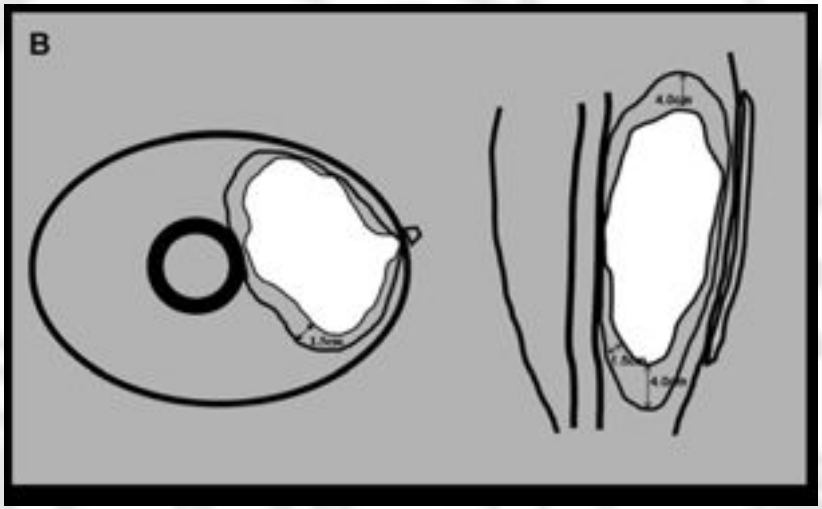
POSTOPERATIVE VOLUMES

✓ Elective CTV is built by expanding surgical volume:

→ +1.5 cm radially,constrained at uninvolved bones and fascia, inside the skin

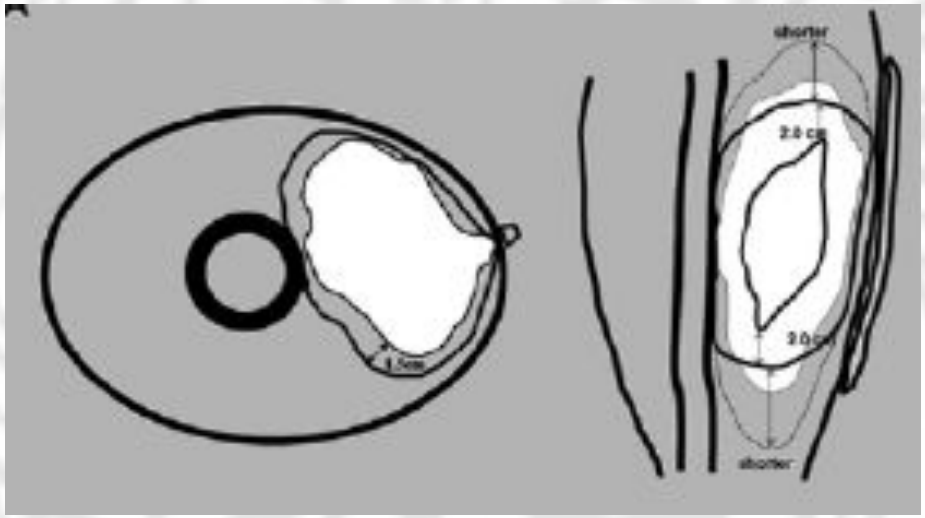
→ +4 cm longitudinally, encompassing the surgical scar





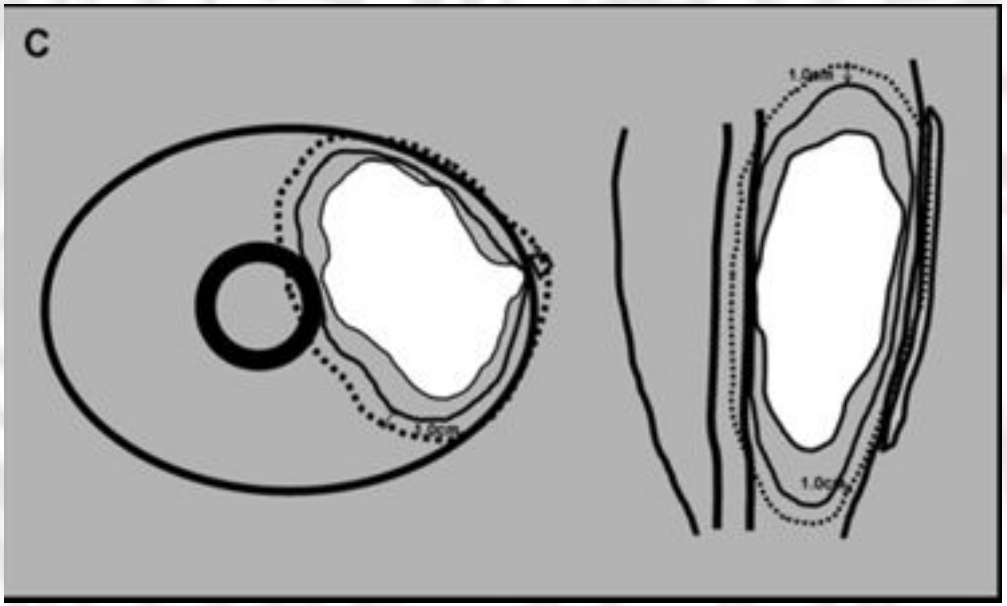
POSTOPERATIVE VOLUMES

✓ Boost CTV is defined :
→ same radial extension than elective CTV
→ longitudinal plane: 2 cm expansion of reconstructed CTV



POSTOPERATIVE VOLUMES

✓No agreement on PTV :dependent on immobilization, image guidance, and the reproducibility of the treatment setup
→ must be based on the local institutional protocol



POSTOPERATIVE VOLUMES

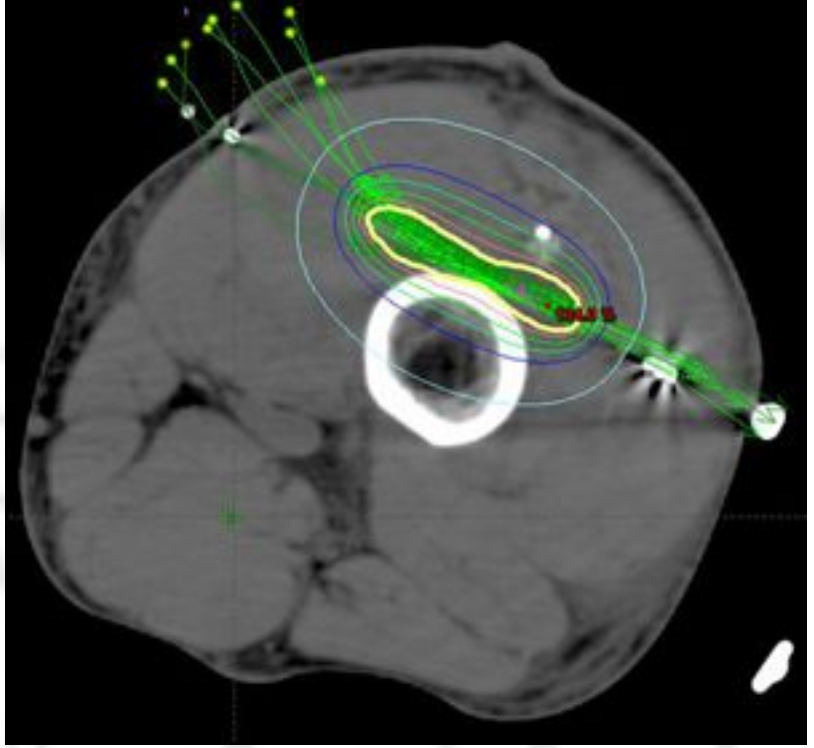
VORTEX trial is investigating small (longitudinal GTV to CTV expansion of 2 cm) vs large (longitudinal GTV to CTV expansion of 5 cm) postoperative RT volumes in the limb-sparing management of STS patients

Primary endpoints: Limb function and time to local recurrence

VorteX

INDICATIONS

Brachytherapy



✓Interstitial BRT has been demonstrated to be an effective method of delivering adjuvant RT, within a considerably shorter treatment time than EBRT, and with potentially smaller treatment volumes

Pisters P et al. J Clin Oncol 1996

✓However, it is a complex and labor-intensive technique, hence, its relatively limited use

✓A report by Alektiar et al. demonstrated a 5-year local control rate of 83%, which seemed lower than the rates achieved in EBRT series

Alektiar KM et al. Int J Radiat Oncol Biol Phys 2005

INDICATIONS

IMRT

✓Intensity-modulated RT (IMRT) offers the opportunity to reduce the normal tissue morbidity of EBRT while maintaining local tumor control

Hong L et al. Int J Radiat Oncol Biol Phys 2004

✓A local control rate of 94% at 5 years in STS patients treated with IMRT was recently reported, with potentially less morbidity than EBRT

Alektiar KM et al. J Clin Oncol 2008

VOLUME 32 · NUMBER 29 · OCTOBER 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Local Recurrence With Conventi… and Intensity-Modulated Radiation Thera… Soft-Tissue Sarcomas of the Extremi…

Michael R. Folkert, Samuel Singer, Murray F. Brennan… Wendy K. Kobayashi, Aimee M. Crago, and Kaled M. Alektiar

Memorial Sloan Kettering Cancer Center, New York, NY.

Published online ahead of print at www.jco.org on September 2, 2014.

This work was supported by the National Cancer Institute, National Institutes of Health SPORE in Soft Tissue Sarcoma (P50 CA140146, S.S. and L.Q.).

Terms in blue are d… sary, found at… and …

…ntal con… …author contribu… …d at the end of this …

Corresponding author: Kaled M. Alektiar, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: alektiak@mskcc.org.

0732-183X/14/3229w-3236w/$20.00

DOI: 10.1200/JCO.2013.53.9452

A C T

Purpose

The use of inte… …n therapy (IMRT) in the treatment of soft tissue sarcoma (STS) of … …sing, but no large-scale direct comparison has been reported bet… …rnal-beam radiation therapy (EBRT) and IMRT.

…nuary 1996 and December 2010, 319 consecutive adult patients with primary …astatic extremity STS were treated with limb-sparing surgery and adjuvant radiotherapy …T) at a single institution. Conventional EBRT was used in 154 patients and IMRT in 165 with similar dosing schedules. Median follow-up time for the cohort was 58 months.

Results

Treatment groups were comparable in terms of tumor location, histology, tumor size, depth, and use of chemotherapy. Patients treated with IMRT were older ($P = .08$), had more high-grade lesions ($P = .05$), close (< 1 mm) or positive margins ($P = .04$), preoperative radiation ($P < .001$), and nerve manipulation ($P = .04$). Median follow-up was 90 months for patients treated with conventional EBRT and 42 months for patients treated with IMRT. On multivariable analysis adjusting for patient age and tumor size, IMRT retained significance as an independent predictor of reduced LR (hazard ratio = 0.46; 95% CI, 0.24 to 0.89; $P = .02$).

Conclusion

Despite a preponderance of higher-risk features (especially close/positive margin) in the IMRT group, IMRT was associated with significantly reduced local recurrence compared with conventional EBRT for primary STS of the extremity.

J Clin Oncol 32:3236-3241. © 2014 by American Society of Clinical Oncology

IMRT reduced Local Recurrence p=.02

POSTOPERATIVE DOSES

Recommended total doses are 60 to 66 Gy (delivered in 1.8- or 2-Gy fractions) for the case of negative margins and 66 to 68 Gy for positive margins

The first course of treatment is typically treated to a dose of 45 to 50 Gy and the balance of the dose is either given in one reduced field or split about evenly between two reduced fields

Delaney TF et al. Int J Radiat Oncol Biol Phys 2007
Ballo MT et al. Int J Radiat Oncol Biol Phys 2004

The standard dose for low–dose-rate BRT is 45 Gy

Nag S et al. Int J Radiat Oncol Biol Phys 2001

PREOPERATIVE RADIOTHERAPY

…RATIONALE…

Surgical point of view

Potential advantages of preoperative radiotherapy include facilitating surgical resection through tumor shrinkage and reducing the risk of tumor cell seeding at the time of surgery

O'Sullivan B et al. Curr Oncol Rep 2003
Clarkson P et al. Curr Options Oncol 2004

...RATIONALE...
Radiooncological point of view

PREOPERATIVE RT	POSTOPERATIVE RT
Smaller volumes Lower doses Reduced edema Reduced joint fibrosis Reduced bone fracture Precise tumor targeting	Larger volumes Higher doses Increased edema Increased fibrosis Increased risk of fracture Mismatch RT field-tumor
Higher rate of wound complications	Lower risk of wound complications

PREOPERATIVE RADIOTHERAPY

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

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

Lancet 2002, **359:** 2235–41.

94 preoperative radiotherapy vs. 96 postoperative radiotherapy

Wound complications rate 35% in the preoperative RT group vs 17% in the postoperative RT group (p=0·01); benefit in OS was observed in patients who had preoperative RT (p=0.0481) not confirmed at 5 years follow up (**O'Sullivan Oral Presentation ASCO 2004**)

PREOPERATIVE RADIOTHERAPY

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 2, pp. 498–505, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2010.06.034

CLINICAL INVESTIGATION **Sarcoma**

PREOPERATIVE VERSUS POSTOPERATIVE RADIOTHERAPY IN SOFT-TISSUE SARCOMA: MULTI-INSTITUTIONAL ANALYSIS OF 821 PATIENTS

SAGUS SAMPATH, M.D.,* TIMOTHY E. SCHULTHEISS, PH.D.,† YING J. HITCHCOCK, M.D.,*
R. LOR RANDALL, M.D.,‡ DENNIS C. SHRIEVE, M.D., PH.D.,* AND JEFFREY Y. C. WONG, M.D.†

From the Departments of *Radiation Oncology and ‡Orthopaedic Surgery, Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT, and †Division of Radiation Oncology, City of Hope National Medical Center, Duarte, CA

Preop RT was associated with significantly improved OS and CSS compared with postop RT ($p < 0.01$)

PREOPERATIVE RADIOTHERAPY

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Extremity/Superficial Trunk, Head/Neck

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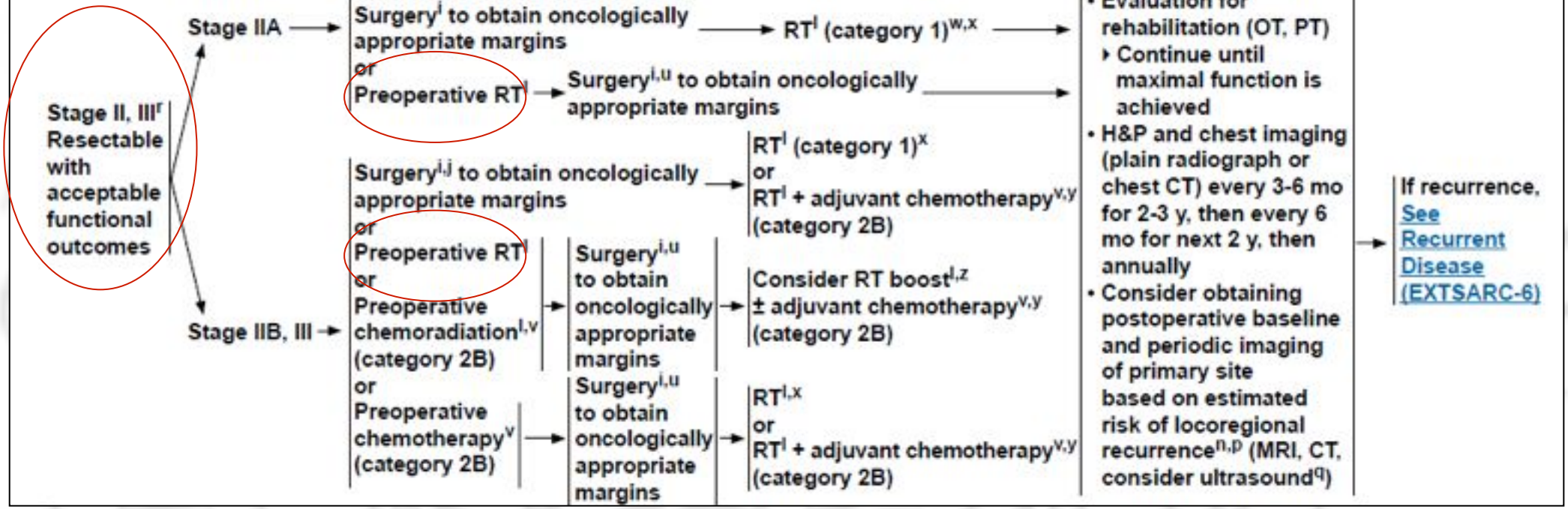

PREOPERATIVE RADIOTHERAPY

+ MODEL ARTICLE IN PRESS

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EJSO xx (2014)

EJSO the Journal of Cancer Surgery

www.ejso.com

Is preoperative radiotherap[y] [a]ll patients with primary soft ti[ssue] [o]f the limbs?

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Multidisciplinary Surgical and Oncology Team in a Specialist Sarcoma Center

Conclusi[on] [P]reoperative RT should be personalised according to histological subtype, tumour site and risks-benefit ratio of preoperative radiotherapy and is best managed by a multidisciplinary surgical and oncology team in a specialist sarcoma centre.

PREOPERATIVE VOLUMES

RTOG saves the day!!!

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

DIAN WANG, M.D., PH.D.,* WALTER BOSCH, PH.D.,† DAVID ROBERGE, M.D.,‡ STEVEN E. FINKELSTEIN, M.D.,¶ IVY PETERSEN, M.D,§ MICHAEL HADDOCK, M.D.,§ YEN-LIN E. CHEN, M.D.,** NAOYUKI G. SAITO, M.D., PH.D,** DAVID G. KIRSCH, M.D., PH.D.,†† YING J. HITCHCOCK, M.D.,‡‡ AARON H. WOLFSON, M.D.,¶¶ AND THOMAS F. DELANEY, M.D.‖

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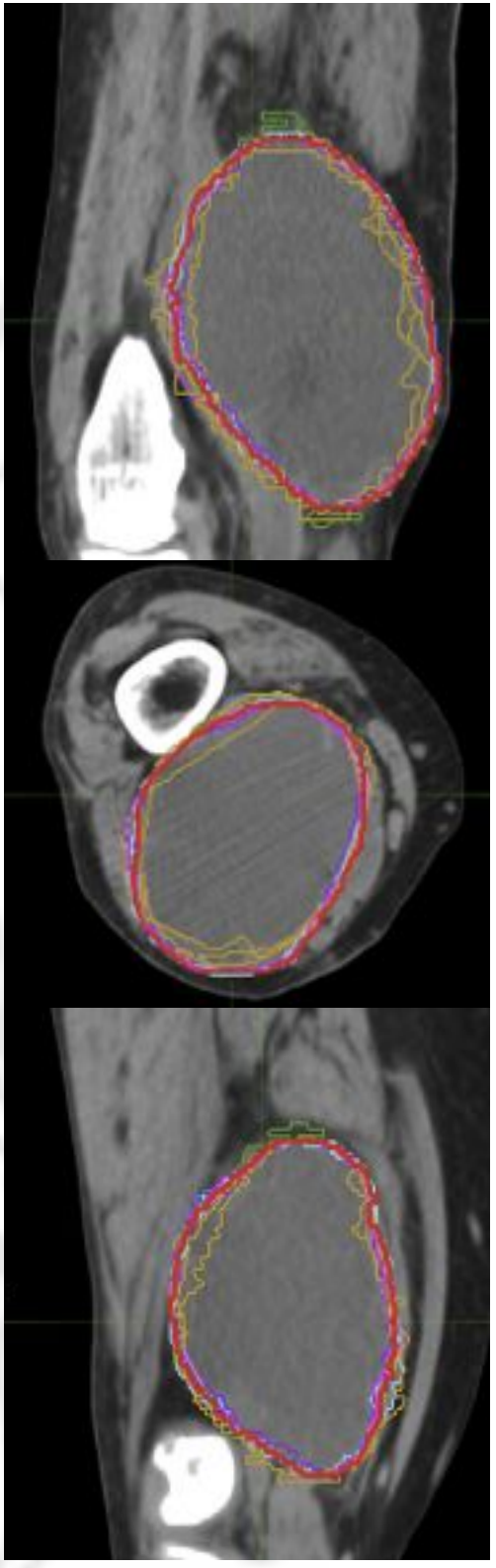
RTOG
RADIATION THERAPY ONCOLOGY GROUP

PREOPERATIVE VOLUMES

- ✓GTV is defined by MRI T1 plus contrast images
- ✓Fusion MRI-CT is recommended to delineate the GTV for radiotherapy
- ✓MRI should be performed in treatment position!!!
- ✓Contrast should be administred during simulation CT



Wang ,IJROBP 2011

PREOPERATIVE VOLUMES

ELSEVIER

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

0360-3016/05/$–see front matter

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.‖

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

The "*edema dilemma*" → peritumoral effusion (shown on T2-weighted MRI) might harbor proliferating cancer cells
Correlation MRI-specimen in 15 resected patients: in 4 cases, cells were found at a distance of 1-4 cm.

PREOPERATIVE VOLUMES

Int J Radiation Oncol Biol Phys, Vol. 86, No. 2, pp. 298–303, 2013

Clinical Investigation: Sarcoma

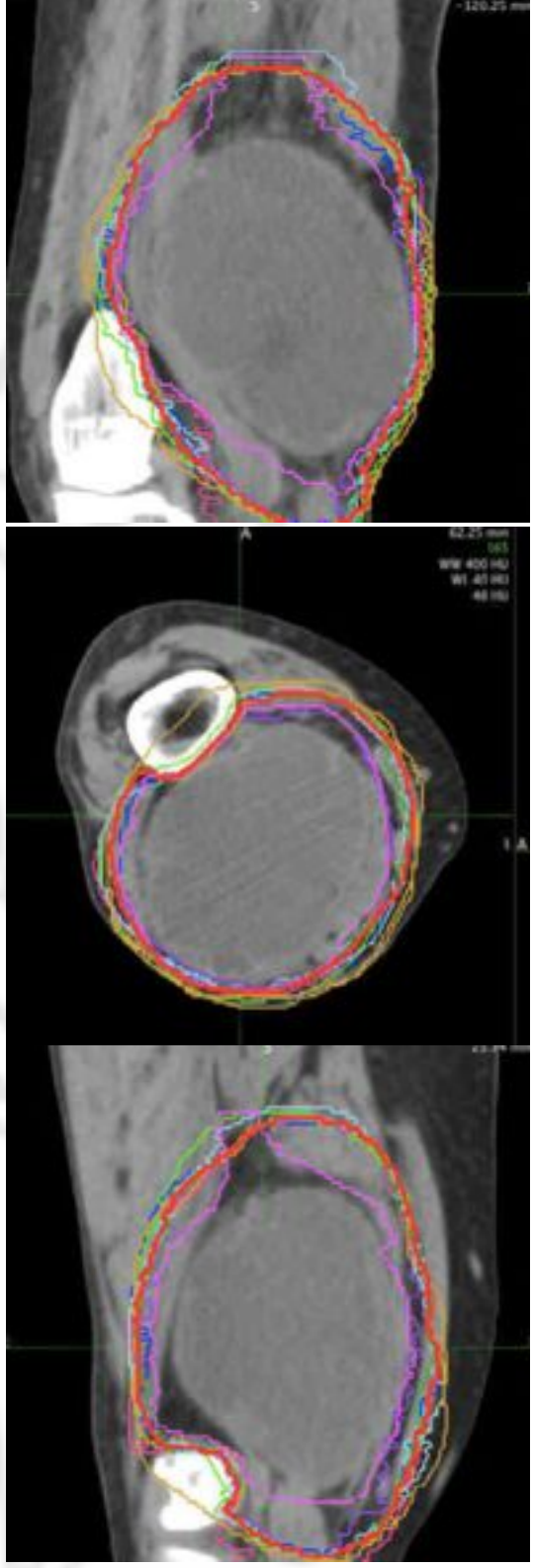
Agreement Among RTOG Sarcoma Radiation Oncologists in Contouring Suspicious Peritumoral Edema for Preoperative Radiation Therapy of Soft Tissue Sarcoma of the Extremity

Houda Bahig, MD,* David Roberge, MD,* Walter Bosch, PhD,† William Levin, MD,‡ Ivy Petersen, MD,§ Michael Haddock, MD,§ Carolyn Freeman, MBBS,|| Thomas F. DeLaney, MD,¶ Ross A. Abrams, MD,# Danny J. Indelicato, MD,** Elizabeth H. Baldini, MD, MPH,†† Ying Hitchcock, MD,‡‡ David G. Kirsch, MD, PhD,§§ Kevin R. Kozak, MD, PhD,|||| Aaron Wolfson, MD,¶¶ and Dian Wang, MD##

PREOPERATIVE VOLUMES

- ✓Building CTV: It's edema, again!
- ✓Edema detected on T2 weighted MRI will typically be included if 1.5 cm radial, 3 cm longitudinal are used
- ✓Balance between risk of geographical miss and radiation morbidity for larger volumes → clinical judgement in every case!

Bahing ,IJROBP 2013



PREOPERATIVE VOLUMES

Retrospective study on patients experiencing LR after preoperative RT:

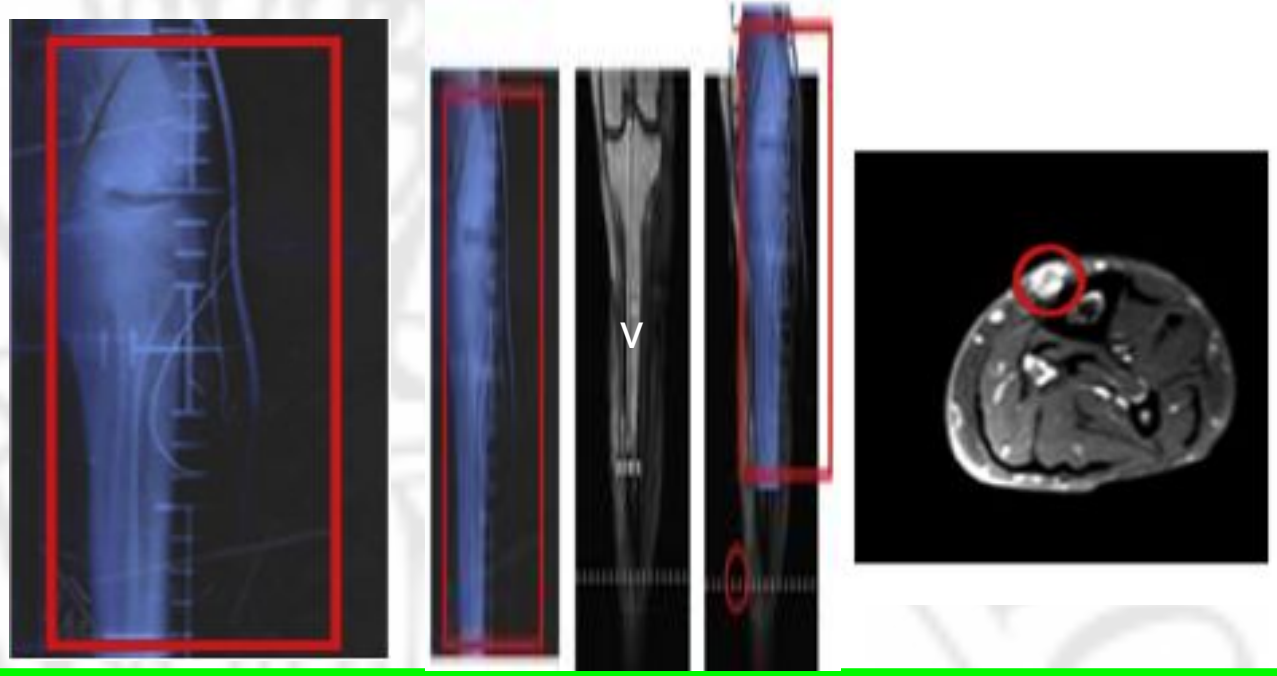
60/768 : 49 IFLR, 9 OFLR, 2 MLR

✓Occurence of out-of-field relapses and marginal relapses reflects the importance of accurate volume delineation

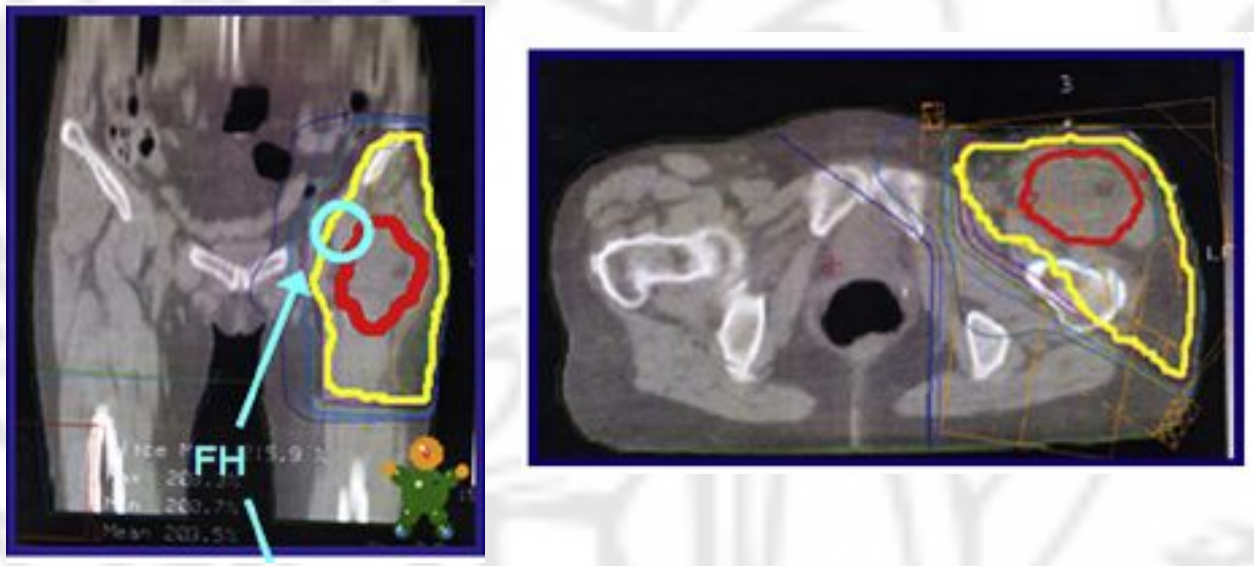
✓In-field LR occurence may mirror differences in tumor biology that must be taken into account in future trials

Dickie , IJROBP 2012

OUT
OF
FIELD LR



IN FIELD
LR



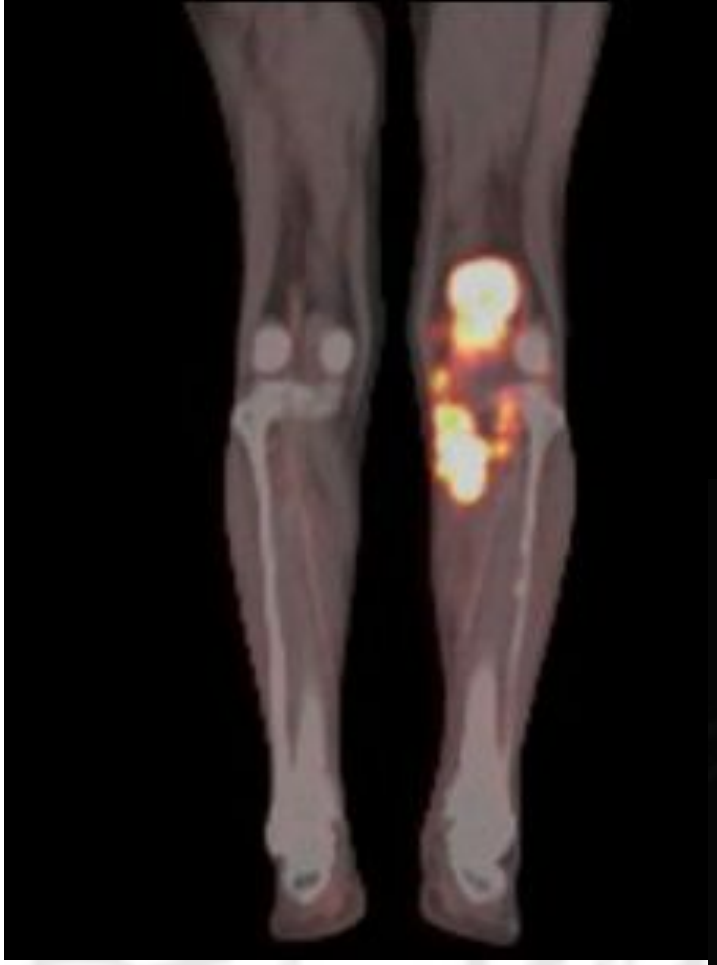
FUTURE DIRECTIONS

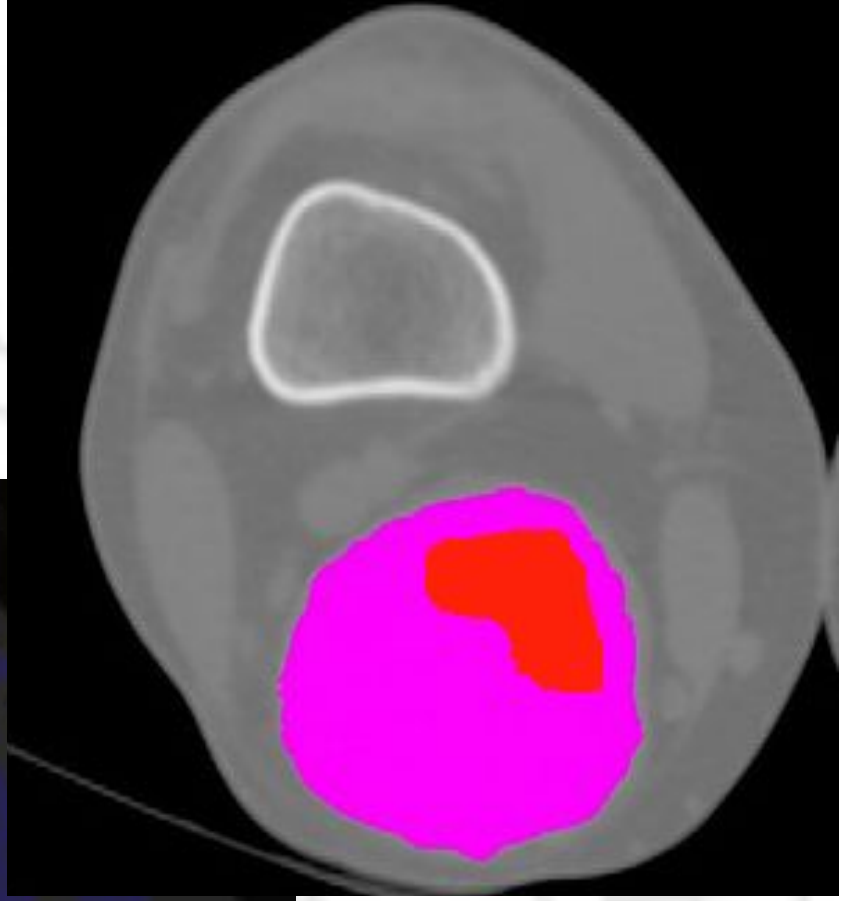
PET/CT: useful in staging/bone invasion, useless for delineation?

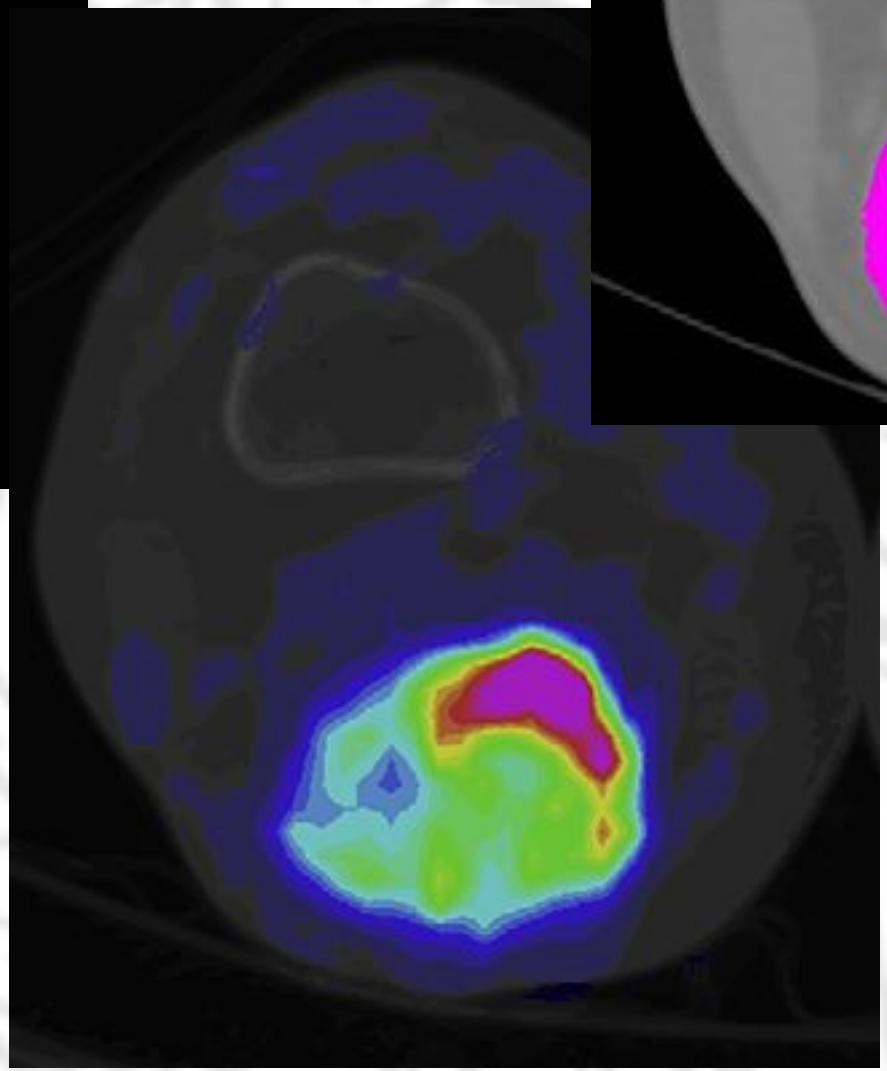
Concordance with MRI was deceiving
→ no contribution in target definition

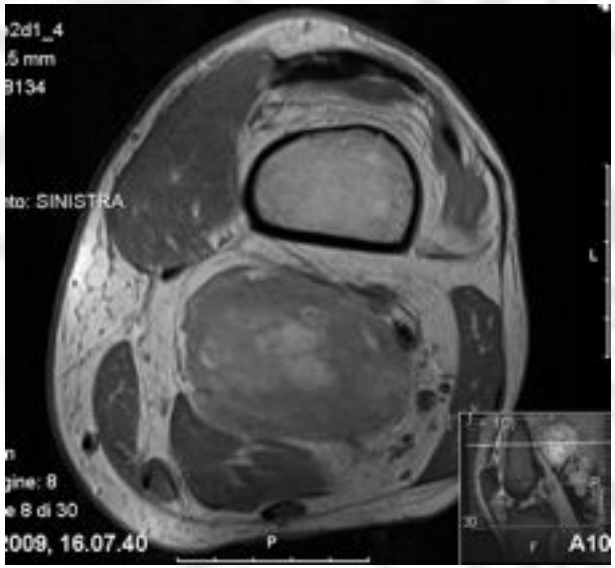
Data from PET/CT may be integrated in future dose-painting treatment delivery approaches (dose escalation in high SUV regions to avoid IFLR?)

Karam,IJROBP 2008





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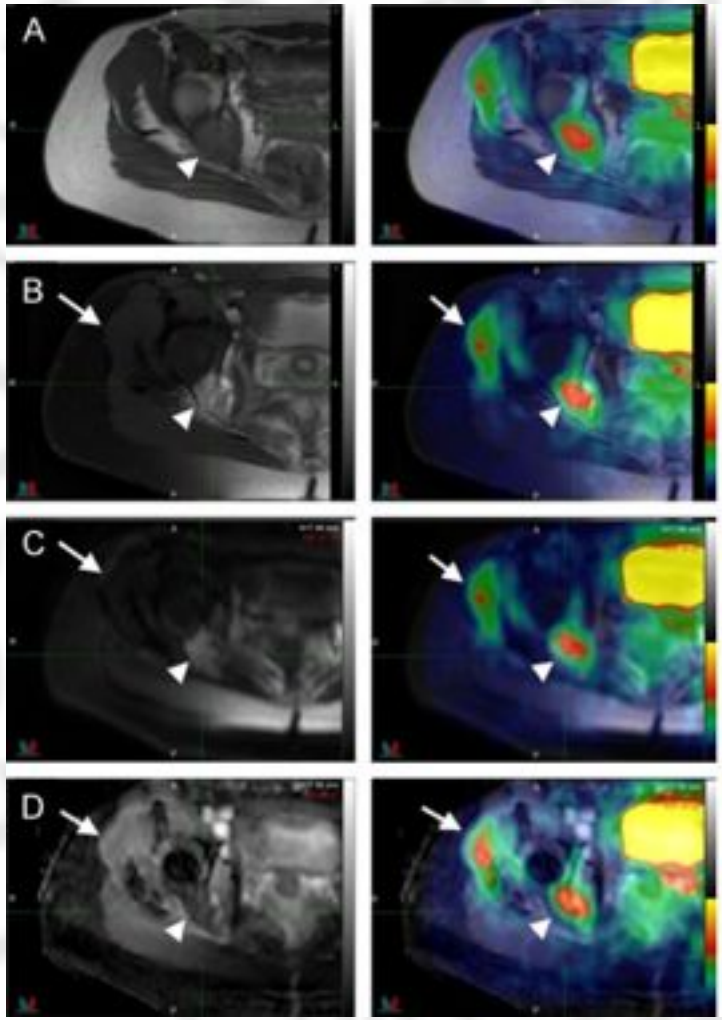
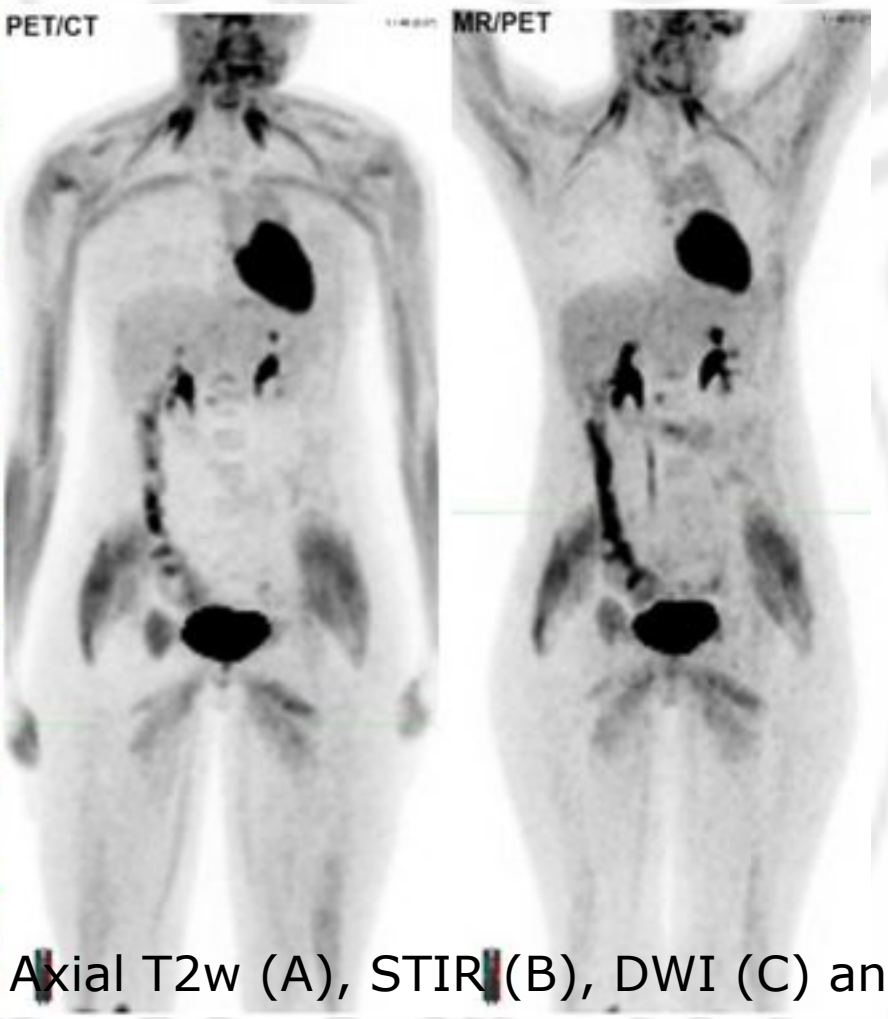
FUTURE DIRECTIONS

Hybrid PET/MRI may be valuable in this setting





Axial T2w (A), STIR (B), DWI (C) and ADC (D)

Partovi, Int J Clin Exp Med. 2014

IGRT

Effort to test impact of advanced RT technology on the reduction of radiation-related toxicities :

RTOG 0630 :

effect of reduced radiation volume through IGRT (3DCRT and IMRT) on late radiation morbidity (≥ grade 2 lymphedema, subcutaneous fibrosis, or joint stiffness)

Wang ,IJROBP 2013

IGRT

@ 2 years results compared to data from SR2:

✓Lower incidence of acute grade ≥2 toxicity (6/56 vs. 27/73; p = 0.0005)

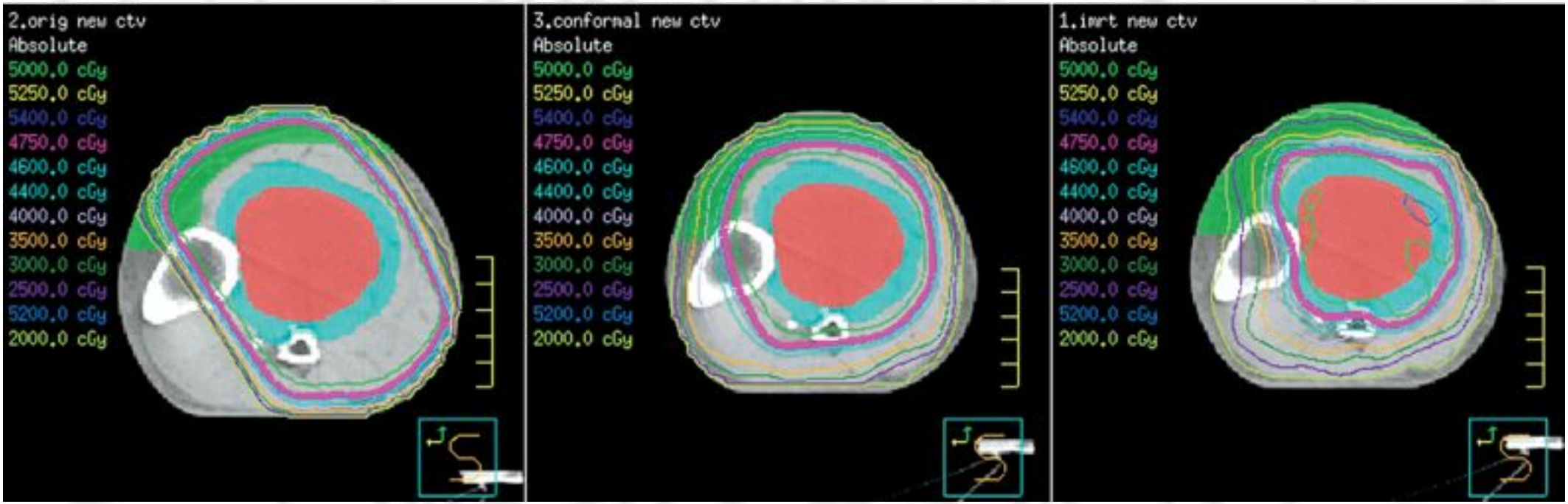
✓No impact on late toxicities

✓Rate of major acute wound complications: no differences with SR2 (36.6% vs 35%)

Wang ,IJROBP 2013

IMRT

In a retrospective review, preoperative IMRT substantially lowered the dose to the future surgical skin flaps, sparing a greater percentage of this structure's volume without compromising target coverage



Griffin , IJROBP 2007

IGRT

Original Article

Cancer May 15, 2013

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

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, MD[1,2]; Charles N. Catton, MD[1,2]; Peter C. Ferguson, MD[2,3]; Jay S. Wunder, MD[2,3]; Benjamin M. Deheshi, MD[2,3]; Lawrence M. White, MD[2,4]; Rita A. Kandel, MD[2,5]; David A. Jaffray, PhD[1,2]; and Robert S. Bell, MD[2,3]

CONCLUSIONS: The 30.5% incidence of WCs was numerically lower than the 43% risk derived from the NCI trial, but did not reach statistical significance.

Preoperative IG-IMRT significantly diminished the need for tissue transfer

RT chronic morbidities and the need for subsequent secondary operations for WCs were lowered, although not significantly, whereas good limb function was maintained.

PREOPERATIVE DOSES

The standard dose for preoperative external-beam RT is 50 Gy delivered in 2-Gy fractions.
In the situation of positive margins, a postoperative external-beam RT boost of 16 to 20 Gy (delivered in 1.8- to 2-Gy fractions) is sometimes delivered.

Zagars et al. Cancer 2003
Baldini EH et al. Ann Surg Oncol 2011

The efficacy of this boost dose has not been proven and, as it may be associated with increased toxicity, its use has been called into question

Al Yami et al. Int J Radiat Oncol Biol Phys 2010

CHEMOTHERAPY

✓Epirubicine-Ifosfamide chemotherapy+RT in G3 disease → local radiosensitization and theoretical action against micrometastases and CTCs

✓Efficacy elusive → metastatic relapse in 40-50% cases

Italiano, Ann Oncol 2010
Pervaiz, Cancer 2008

CHEMOTHERAPY

No tailored approach avalaible...

ITALIAN SARCOMA GROUP
GRUPO ESPAÑOL de INVESTIGACIÓN de SARCOMAS
GROUPE SARCOMES FRANÇAIS

Cooperative groups for clinical and translational research into sarcomas

LOCALIZED HIGH-RISK SOFT TISSUE SARCOMAS OF THE EXTREMITIES AND TRUNK WALL IN ADULTS: AN INTEGRATING APPROACH COMPRISING STANDARD VS HISTOTYPE-TAILORED NEOADJUVANT CHEMOTHERAPY (ISG-STS 10-01)

Prospective controlled randomized trial

October 2010

...an ongoing trial

CHEMOTHERAPY

Pilot study BV+ preoperative RT

(nearly as effective as EPI-IFO)

Yoong, IJROBP 2011

✓Pathological response :

35% → >95% necrosis;

15% → complete pathologic response

✓Toxicity G3 in <20% patients

✓High microvessel density and gene array profile correlated with high pathologic responders

CHEMOTHERAPY

Encouraging results of pazopanib in EPI-IFO refractory, non liposarcoma metastatic patients

Van der Graaf, Lancet 2012

Ongoing trial (PAZNTIS) :

→ Chemosensitive* patients: neoadjuvant radiochemotherapy +/- pazopanib

→ Chemoresistant* patients: preoperative radiotherapy +/- pazopanib

**** according to predictive criteria from ARST0332 and RTOG 9415 studies***

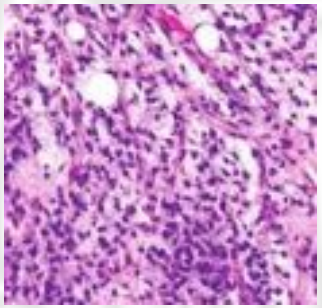
MOLECULAR BIOLOGY

1. Correct tumor classification

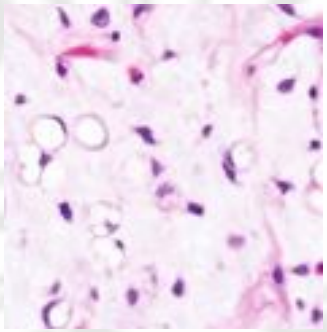
2. Definition of subsets

→ Predictors of outcome
→ Therapeutic targets

Liposarcoma, 1990



Round Cells
LPS



Myxoid Cells
LPS

MOLECULAR BIOLOGY

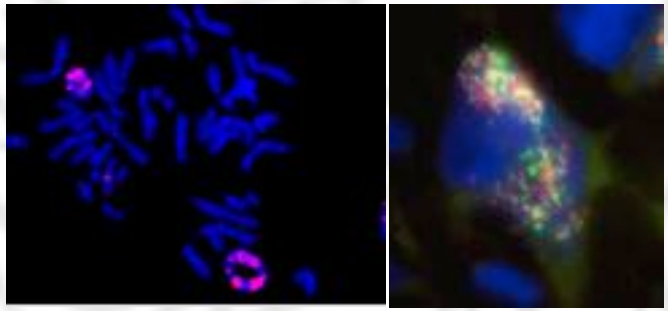
Liposarcoma, 2014

Myxoid Cells LPS

++Translocations
t(12;16)→ fusion gene FUS/DDIT3

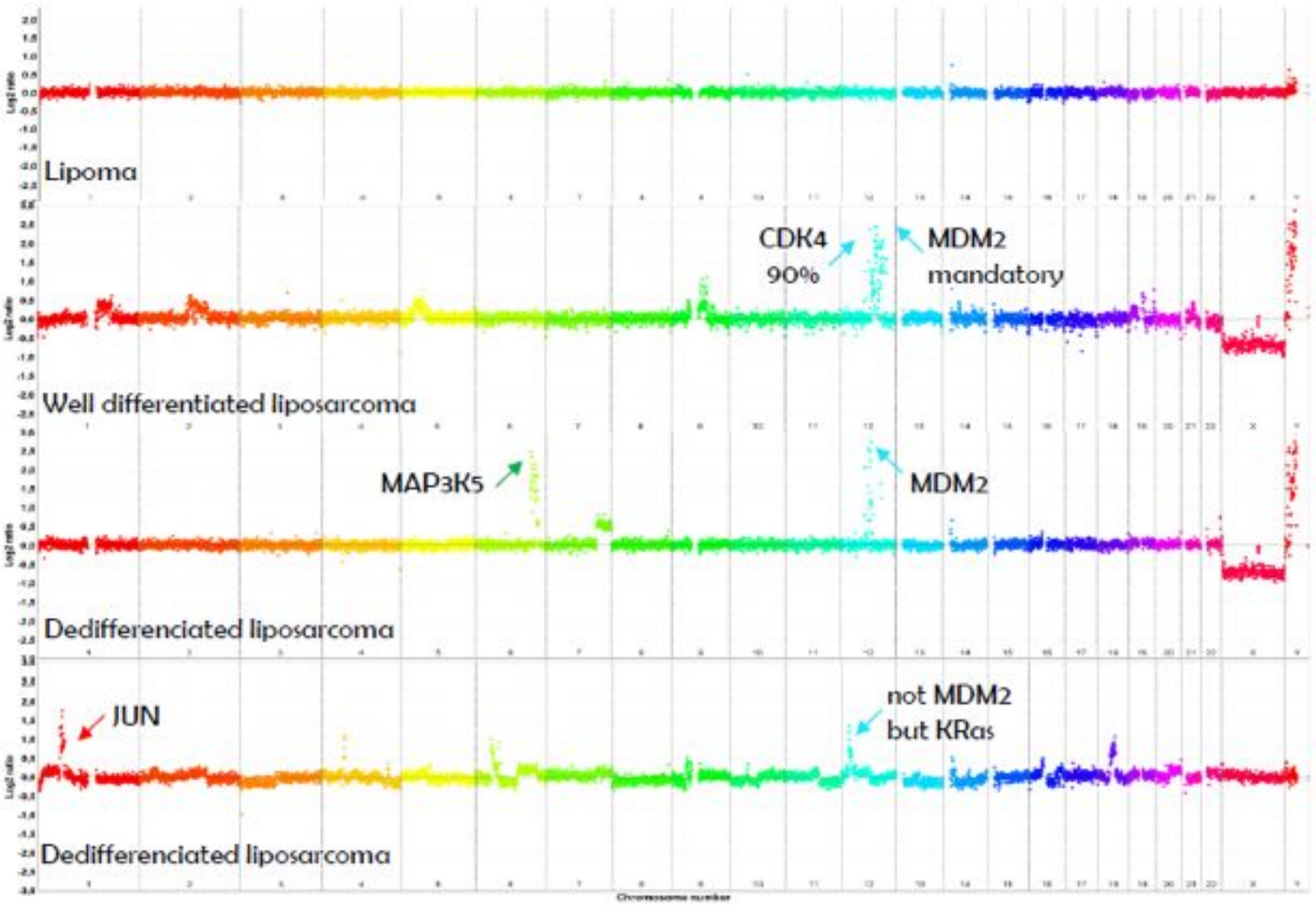
Well Differentiated LPS

++Amplifications
MDM2, CDK4…

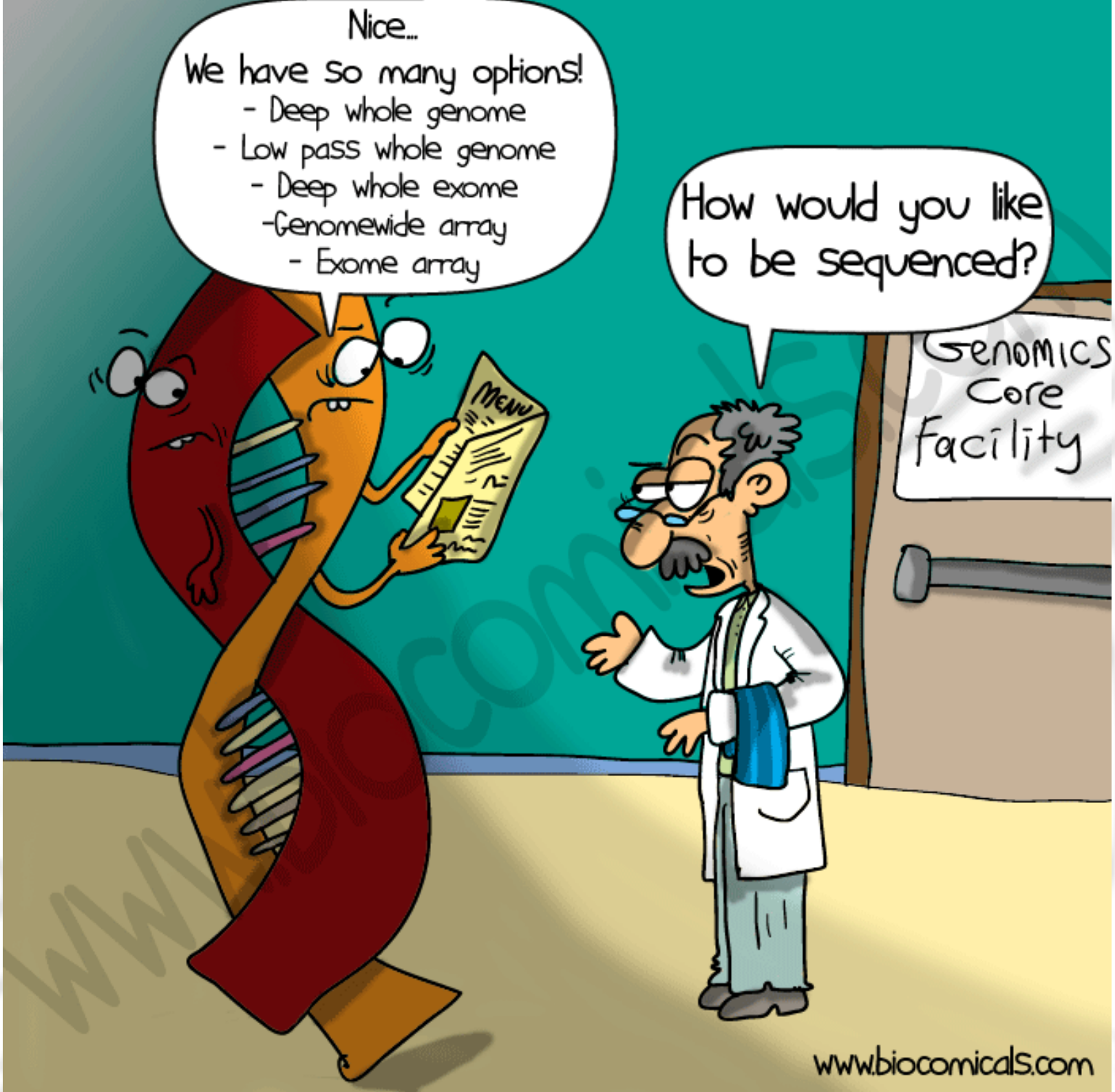


Pleomorphic LPS

++Complex Karyotypic Aberrations



Differences in gene amplification profile in Liposarcoma


Nice...
We have so many options!
- Deep whole genome
- Low pass whole genome
- Deep whole exome
-Genomewide array
- Exome array
How would you like to be sequenced?
MENU
Genomics Core Facility
www.biocomicals.com

CHEMOTHERAPY

Candidate strategies in association with RT:

- ✓Angiogenesis Inhibitors (sunitinib, bevacizumab, pazopanib)
- ✓Cell Cycle Regulators (MDM2 inhibitors, CDK4 inhibitors)
- ✓Inhibition of DNA Repair (PI3K-AKT pathway Host Immune Modulation

Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

Lancet Oncol 2012; 13: 1133–40

Crizotinib in *ALK*-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D'Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.

Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study

David Olmos, Sophie Postel-Vinay, L Rhoda Molife, Scott H Okuno, Scott M Schuetze, M Luisa Paccagnella, Gretchen N Batzel, Donghua Yin, Kathryn Pritchard-Jones, Ian Judson, Francis P Worden, Antonio Gualberto, Michelle Scurr, Johann S de Bono, Paul Haluska

Oncogene (2005) 24, 6201–6212

www.nature.com/onc

ORIGINAL PAPERS

Therapeutic potential of antibodies against FZD10, a cell-surface protein, for synovial sarcomas

Satoshi Nagayama[1,2,6], Chikako Fukukawa[1,6], Toyomasa Katagiri[1], Takeshi Okamoto[3,4], Tomoki Aoyama[3,4], Naoki Oyaizu[5], Masayuki Imamura[2], Junya Toguchida[3] and Yusuke Nakamura*[,1]