



# Principles of RT in STS

**6<sup>th</sup> ESMO CONFERENCE ON SARCOMA & GIST**

**Rick Haas**

**Department of Radiotherapy, The Netherlands Cancer Institute Amsterdam**



# Disclosure

Investigator Initiated Research Grant

GSK

Novartis

Nanobiotix Company

but none of them had part in the design nor the conduct of my studies

# What principles apply to RT in STS ??

timing ??

dose ??

machine ??

interaction ??

location / sarcoma site ??

patient characteristics ??



# Principles concerning timing

Many centers apply RT after surgery.

Reasons:                full pathology report on a heterogeneous sarcoma mass,  
                                 unaffected by prior RT  
                                 less wound complications

In other words:        Rationale for surgery first is based upon early mainly  
                                 surgical endpoint

# Principles concerning timing

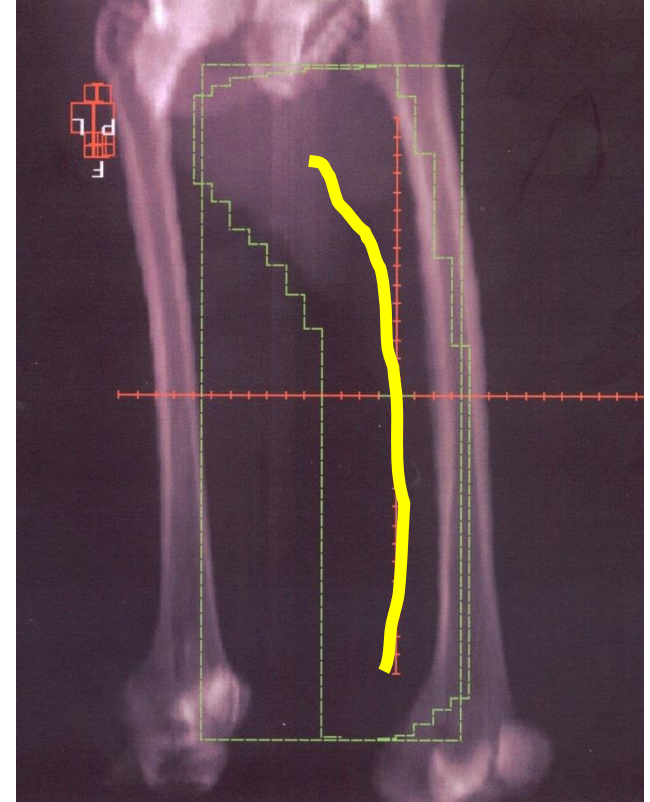
Surgery followed by external beam RT.

=> “huge” fields

=> more joints in field.

=> late functional toxicity

Because of the scar



# The “VORTEX trial”

Estimated Enrollment: 400  
Study Start Date: March 2006  
Study Completion Date: July 2011

Source: <http://clinicaltrials.gov/ct2/show/NCT00423618?term=vortex&rank=5>



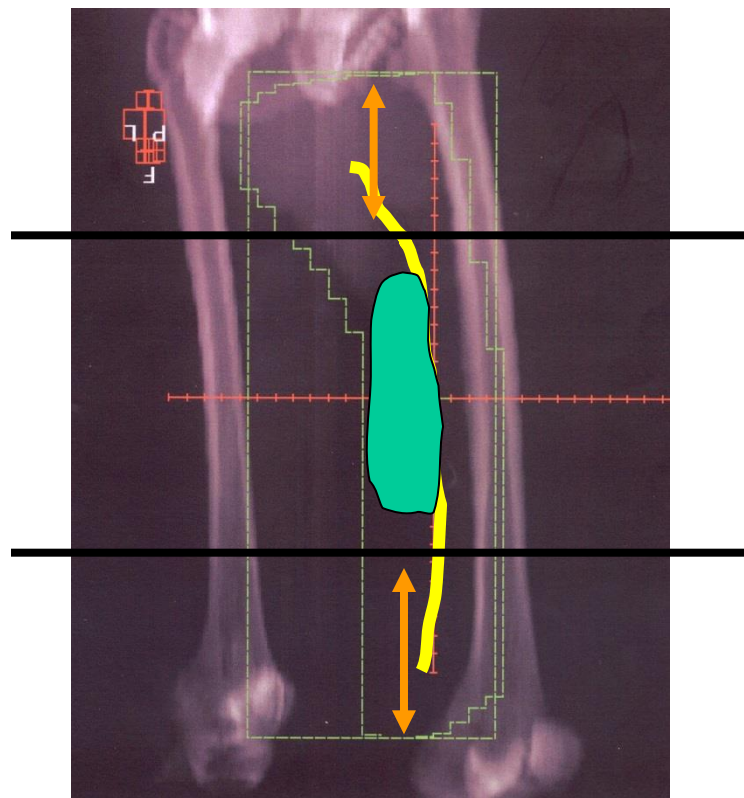
**Randomised trial of Volume of post-operative  
radiotherapy given to adult patients with eXtremity  
soft tissue sarcoma**

# The “VORTEX trial”



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

Large versus small volume external beam RT.



# Timing: Canadian SR-2 trial Brian O'Sullivan

50Gy preoperative RT versus 66Gy postoperative.

Study prematurely closed due to more postoperative morbidity in the pre-op arm.

	2002; Paper Lancet			2004 CTOS / ASCO		
	postop	3,3 yr	pre-op	postop	6,9 yr	pre-op
med FU alive					70%	
local control	94%		96%	93%		92%
(+) margins				77%		73%
(-) margins				96%		95%
early tox	17%	p=0,01	35%			
late tox	26%		20%	36%	p=0.02	23%

(grade III = fibrosis, Graad IV = necrosis)



## Timing: Canadian SR-2 trial Brian O'Sullivan

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		20%		
(grade III = fibrosis, Graad IV = necrosis)				
			p=0,02	

## **Timing: Canadian SR-2 trial Brian O'Sullivan**

50Gy preoperative RT versus 66Gy postoperative RT.

Conclusion:

**at longer FU preoperative RT as “good” as  
postoperative RT (efficacy)**

**at longer FU preoperative RT “better” than postop  
(toxicity)**

# Principles concerning timing

Clinical setting:

Male, 50 years old, high grade undifferentiated sarcoma, deep seated, 10 cm, medial thigh.....

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Comorbidity ??    Hypertension?, diabetes?, smoking habits?, habitus ?

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# Principles concerning timing

Clinical setting:

Male, 50 years old, high grade undifferentiated sarcoma, deep seated, 10 cm, medial thigh.....



surgery first !!



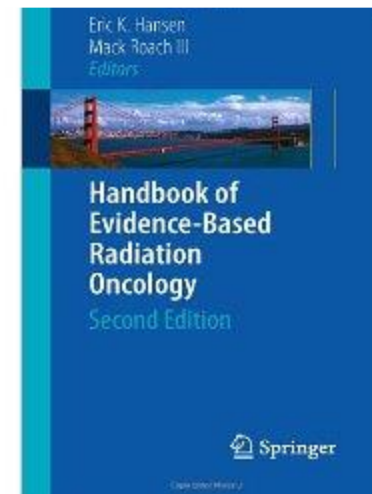
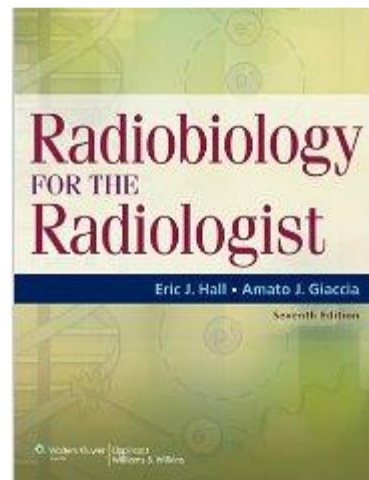
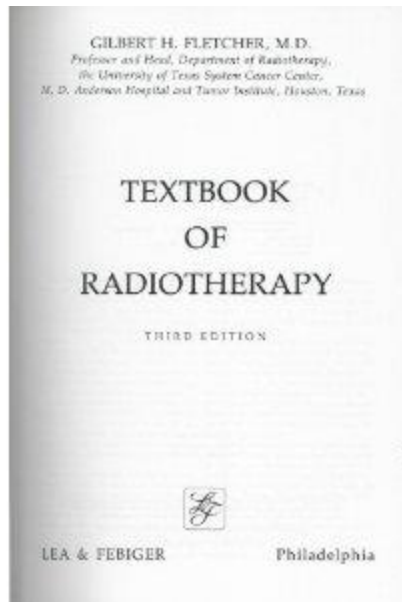
RT first ??

# Principles concerning dose

Conventional RT in non-hematological diseases

46-50Gy for microscopic disease

66-70Gy boost for macroscopic disease



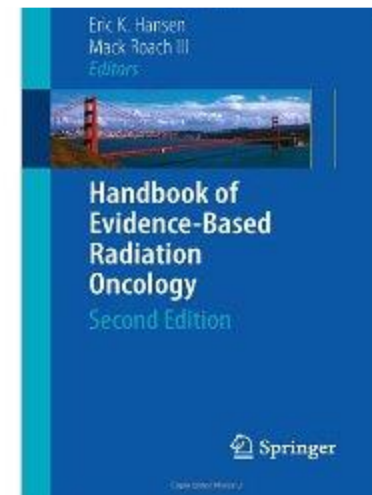
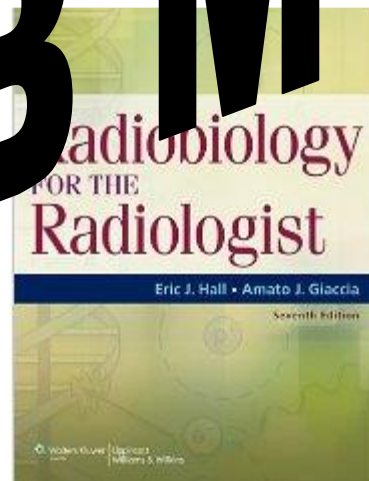
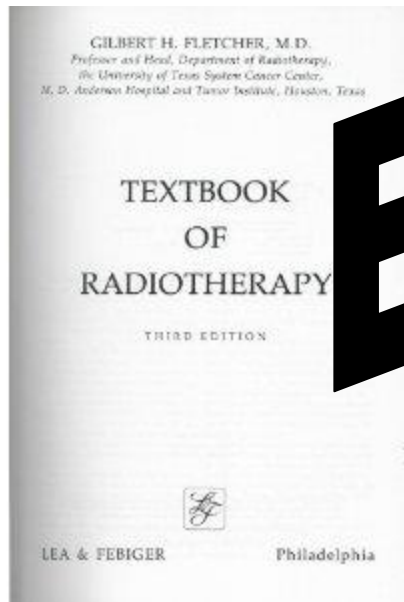
# Principles concerning dose

Conventional RT in non-hematological diseases

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**EBM??**





# Principles concerning dose

Also the Canadian SR-2 dose levels; 50Gy versus 66Gy

# The dose in myxoid liposarcomas (MLS)

4 studies of MLS show volume reduction during preoperative RT

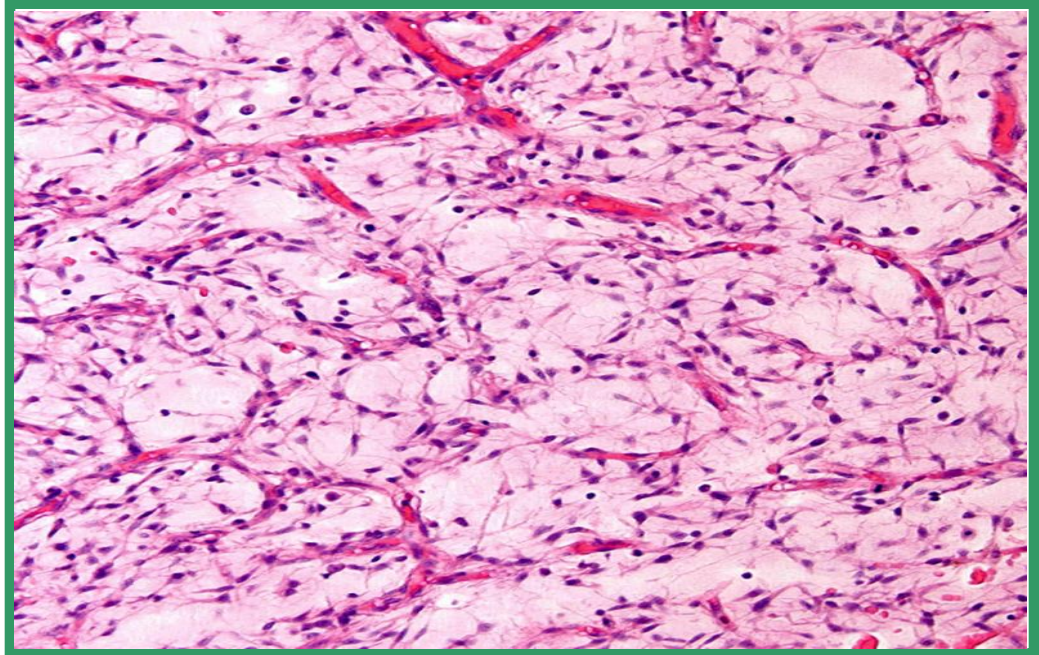
Pitson et al 2004

Engström et al 2007

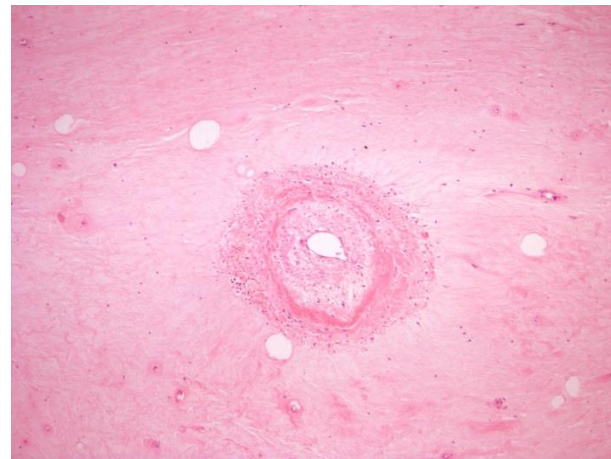
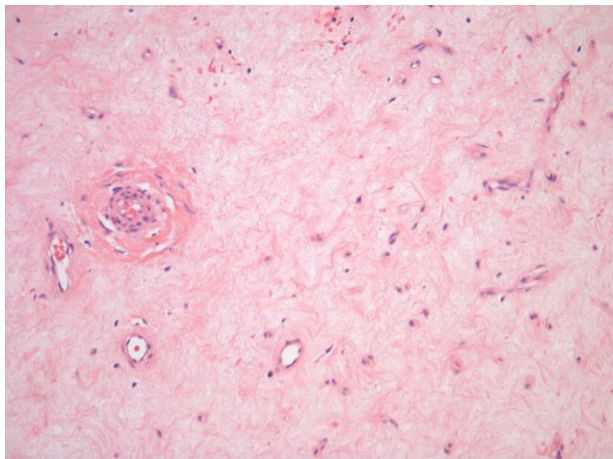
de Vreeze et al 2008 (NKI-AVL)

Betgen et al 2013 (NKI-AVL)

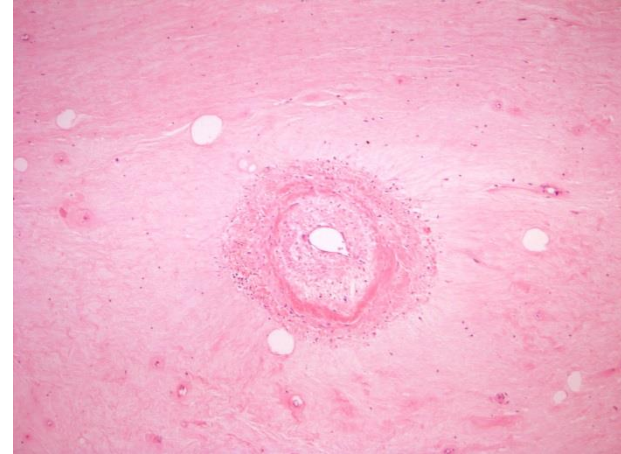
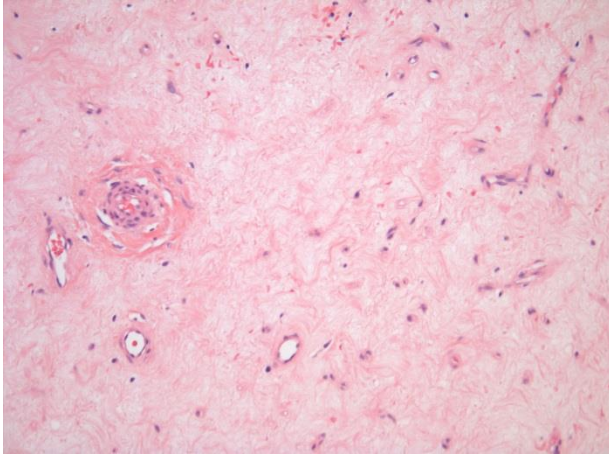
Vasculature ???



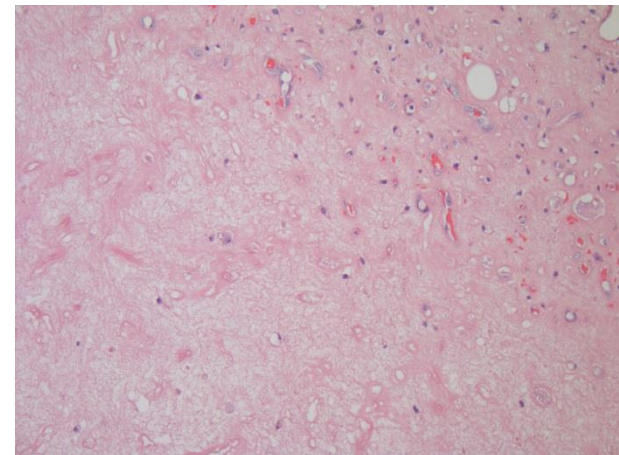
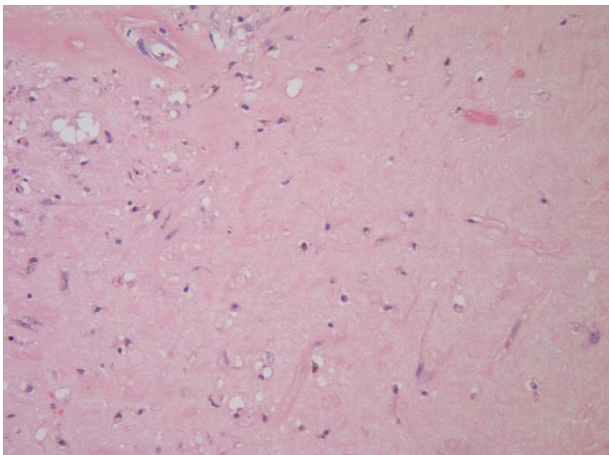
## Radiation response in MLS after 25 x 2 Gy



## **Radiation response in MLS after 25 x 2 Gy**



## **Radiation response in MLS after 18 x 2 Gy**





# Radiation response in MLS after 25 x 2 Gy



## Radiation

### Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcomas (DOREMY)

**This study is currently recruiting participants. (see [Contacts and Locations](#))**

*Verified November 2012 by The Netherlands Cancer Institute*

**Sponsor:**

The Netherlands Cancer Institute

**Information provided by (Responsible Party):**

The Netherlands Cancer Institute

ClinicalTrials.gov Identifier:  
NCT02106312

First received: March 6, 2014

Last updated: April 10, 2014

Last verified: November 2012

[History of Changes](#)



# The dose of 50Gy “fits all” ??

Probably not

=> Dose reduction => less wound complication => less fibrosis => better QoL

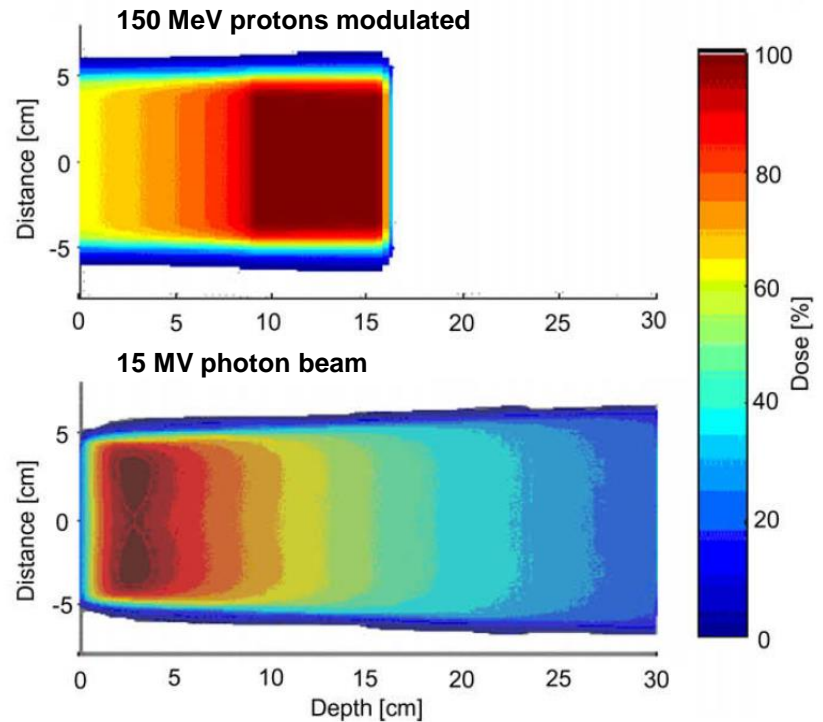
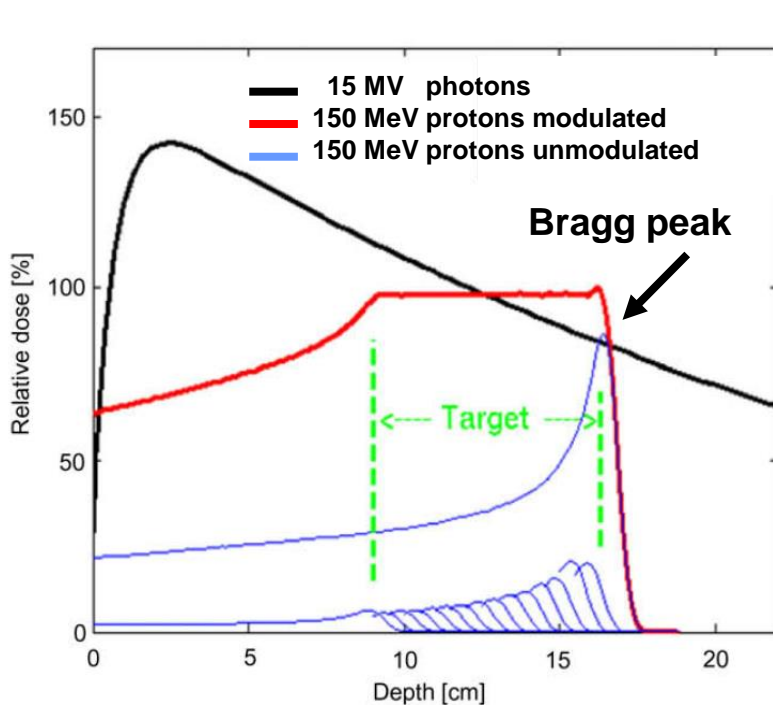


# Principles concerning the machine

Does all external beam RT in STS needs to be applied by Linacs ??



# Principles concerning the machine; protons ?





# Principles concerning the machine

A “must have read” – paper by Prof. Herman Suit

=> chordomas & chondrosarcomas



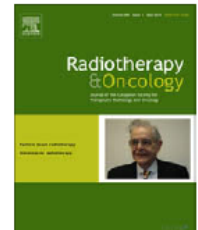
Radiotherapy and Oncology 95 (2010) 3–22



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)



Review

Proton vs carbon ion beams in the definitive radiation treatment of cancer patients

Herman Suit<sup>a,\*</sup>, Thomas DeLaney<sup>a</sup>, Saveli Goldberg<sup>a</sup>, Harald Paganetti<sup>a</sup>, Ben Clasie<sup>a</sup>, Leo Gerweck<sup>a</sup>, Andrzej Niemierko<sup>a</sup>, Eric Hall<sup>b</sup>, Jacob Flanz<sup>a</sup>, Josh Hallman<sup>a</sup>, Alexei Trofimov<sup>a</sup>

<sup>a</sup> Department of Radiation Oncology, Boston, MA, USA; <sup>b</sup> Center for Radiological Research, Columbia University, New York, NY, USA

# Principles concerning interaction with systemic agents

## Conventional chemotherapy

Cisplatin	=> NSCLC, cervical
Taxanes	=> esophageal
5-FU	=> colorectal
Temolozomide	=> glioblastoma

## Smart drugs

monoclonal Ab's => Bevacizumab => colorectal

tyrosine kinase inhibitors

=> Erlotinib	=> NSCLC, pancreas
=> Sunitinib	=> renal cell

Etc etc....many more

# Principles concerning interaction with systemic agents

## Conventional chemotherapy

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Etc etc....many more

# But, what about STS....

# **Principles concerning interaction with systemic agents**

Sunitinib

Sorafenib

Bevacizumab

Pazopanib

# **Principles by location**

## Principles by location

The opportunity to obtain negative margins in a tumor of this size is small



# Principles by location

The clinical characteristics

Local failure 52-60% at 5 years

Continuous risk of local recurrences after five years (low-grade)

# Principles by location

Most important for long-term tumor control:

- complete resection with gross negative margins

- aggressive en bloc resection of primary disease  
=> management in a reference center

- possibly radiotherapy (retrospective series!)  
=> need for a prospective randomized phase III trial



# Principles by location

Most important for long-term tumor control:

complete resection with gross negative margins

aggressive en bloc resection of primary disease

=> management in a r

possibly radiotherapy (retrospect

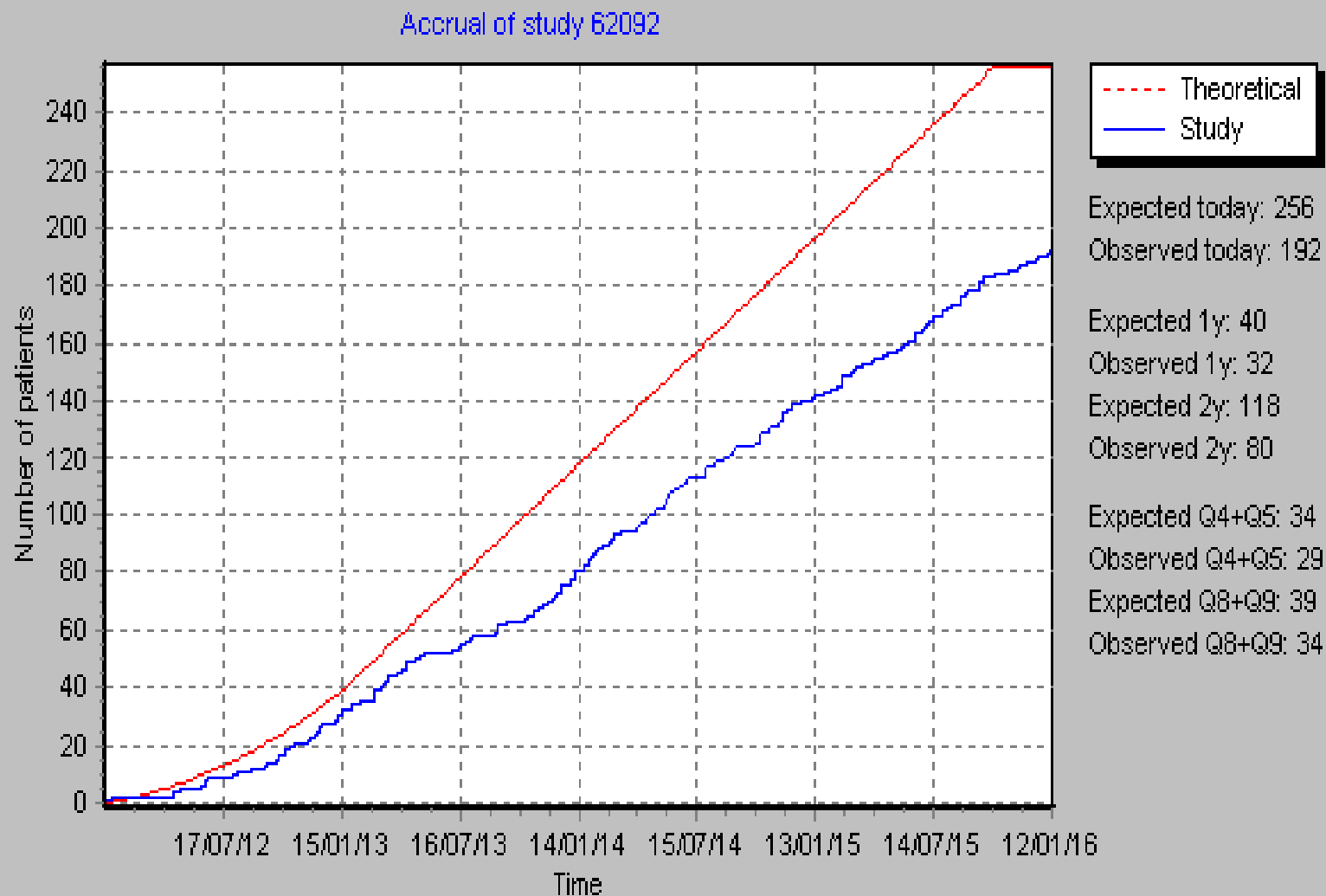
=> need for a prospec

**EORTC**  
European Organisation for Research  
and Treatment of Cancer  
ASBL International Non-Profit Association under Belgian law (VZW)

EORTC  
Avenue E. Mounierlaan 83 / 11  
Brussel 1200 Bruxelles  
Belgie - Belgique  
Tel : +32 2 774 16 11  
Fax : +32 2 772 35 45  
E-mail : [eortc@eortc.be](mailto:eortc@eortc.be)  
Web : <http://www.eortc.be>

**EORTC Soft Tissue and Bone Sarcoma Group**  
**EORTC Radiation Oncology Group**  
  
**A phase III randomized study of  
preoperative radiotherapy plus surgery  
versus surgery alone for patients with  
Retroperitoneal sarcoma (RPS)**  
  
**EORTC protocol 62092-22092**  
  
**STRASS**  
  
Study Coordinator: Sylvie Bonvalot  
Phone: +33 142114383  
Fax: +33 145115256  
E-mail: [bonvalot@igr.fr](mailto:bonvalot@igr.fr)  
  
Study Co-Coordinator: Rick Haas  
Phone: +31 20 5122124  
Fax: +31 20 6691101  
E-mail: [r.haas@nki.nl](mailto:r.haas@nki.nl)

# Principles by location



# **Principles based upon patient characteristics**

When to refrain from radiotherapy ?

# Principles based upon patient characteristics

When to refrain from radiotherapy ?

The MSKCC nomogram

684 patients with primary, nonmetastatic, extremity STS treated with **surgery alone**

between June 1982 and December 2006, median FU 58 months.

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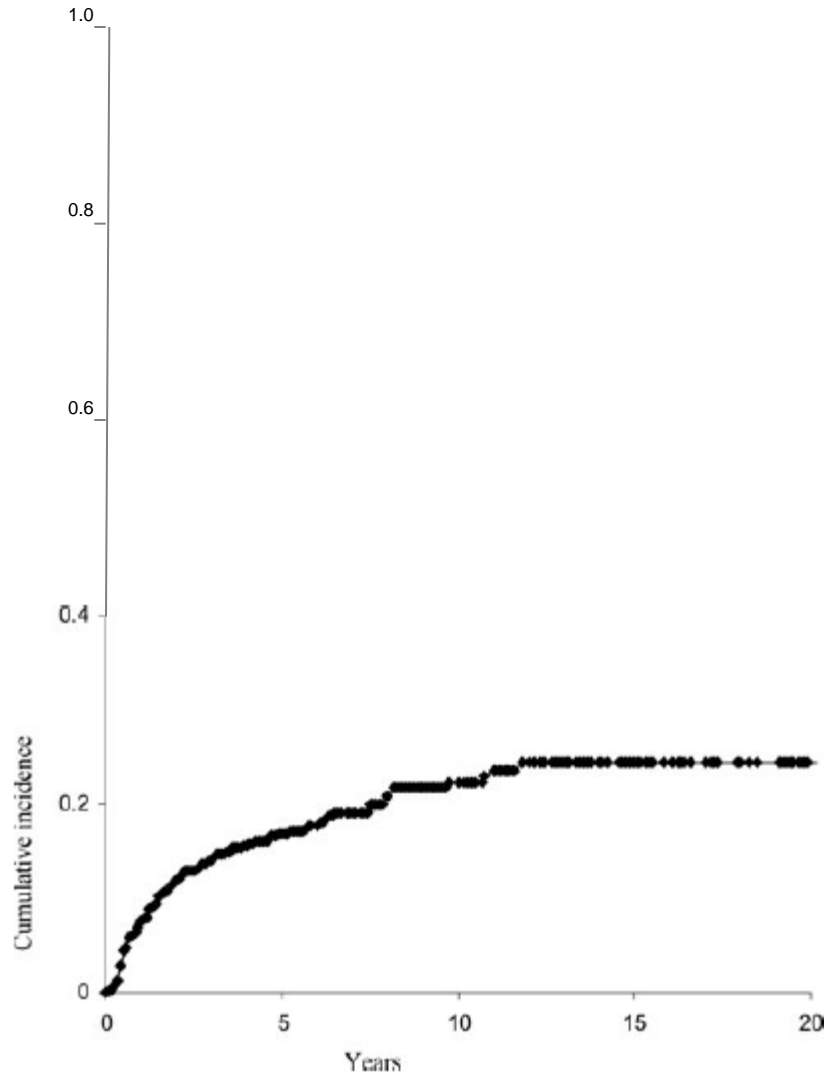
ORIGINAL ARTICLE

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## 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\**

# Principles based upon patient characteristics

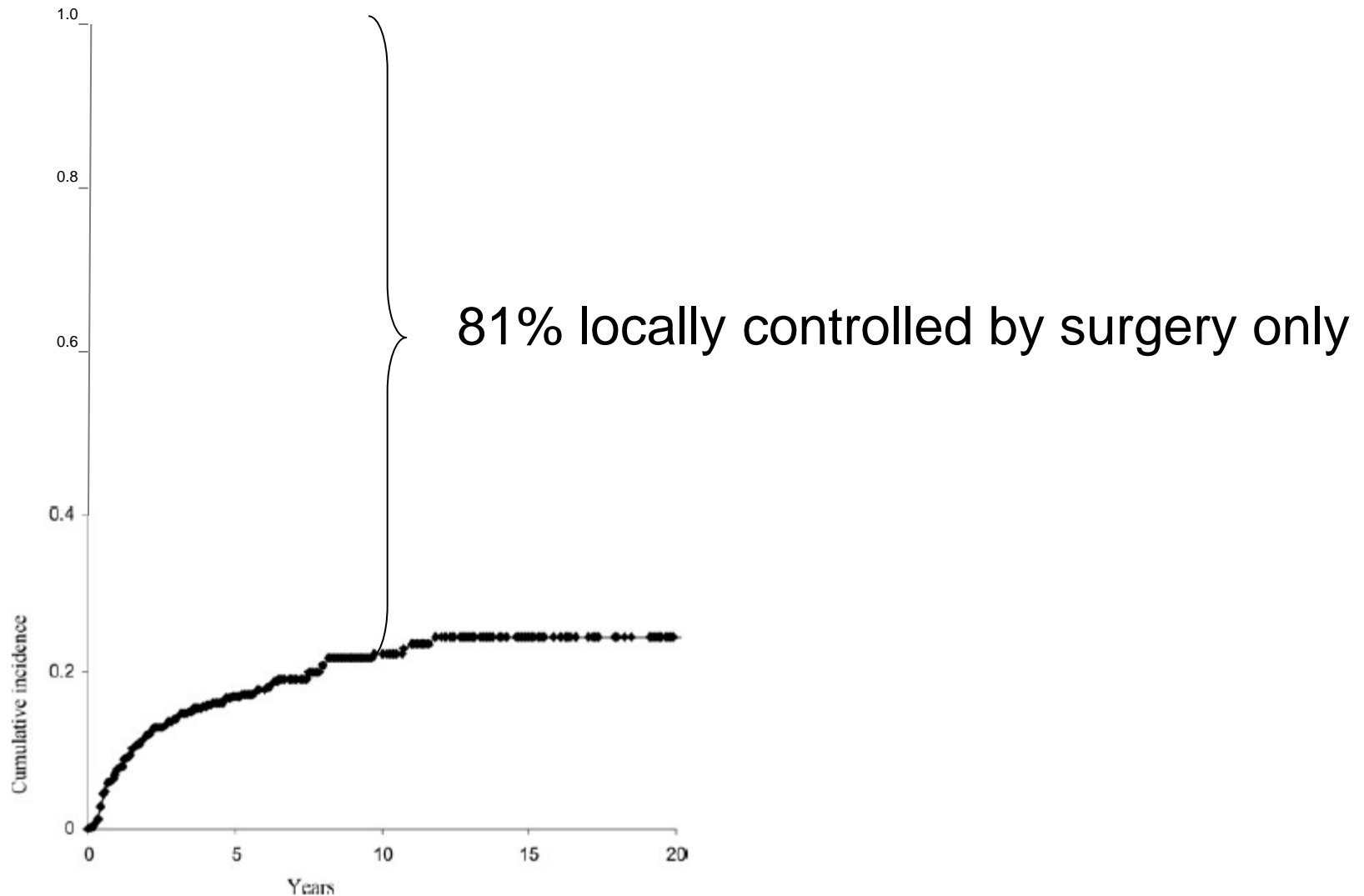


**FIGURE 1.** Cumulative incidence curve for local recurrence for the entire cohort.

actuarial risk of LR

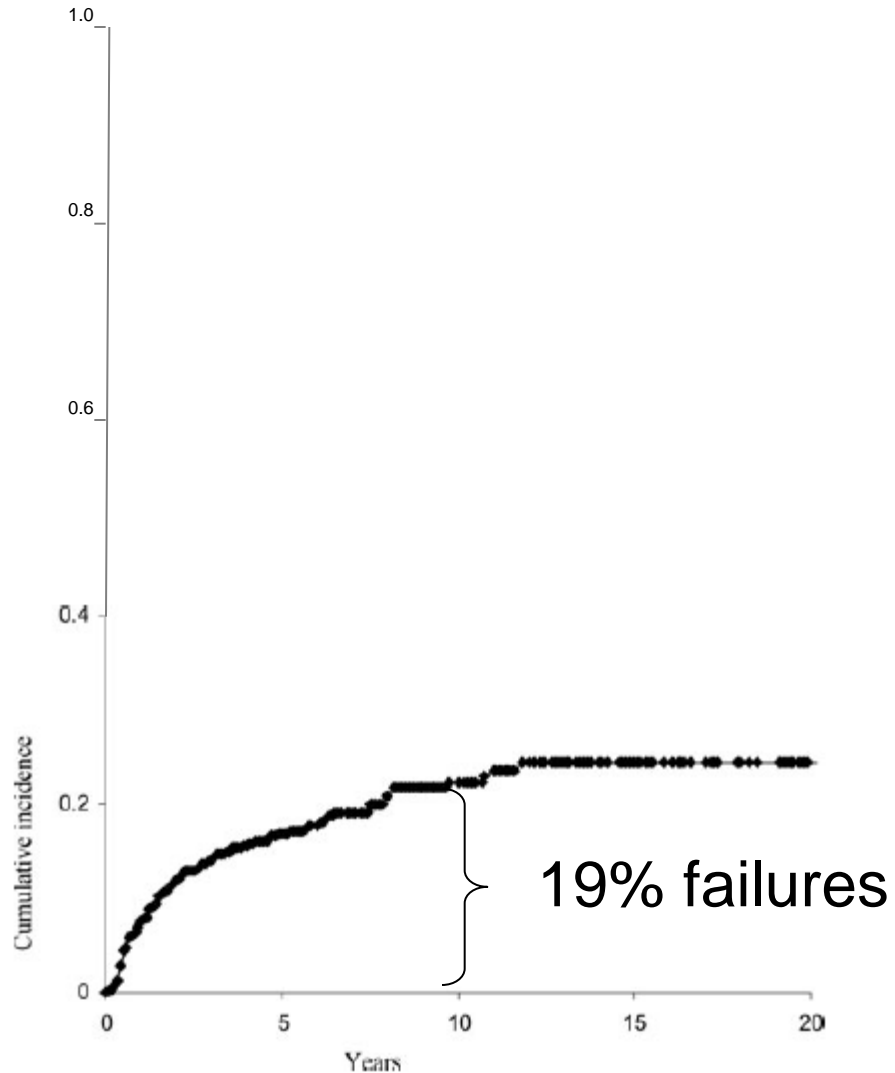
At 3 yrs	11%
At 5yrs	13%
At 10yrs	19%

# Principles based upon patient characteristics



**FIGURE 1.** Cumulative incidence curve for local recurrence for the entire cohort.

# Principles based upon patient characteristics



**FIGURE 1.** Cumulative incidence curve for local recurrence for the entire cohort.

# Principles based upon patient characteristics

When to refrain from radiotherapy ?

**TABLE 2.** Univariate Analysis for Predictors of Local Recurrence

Covariate	3-Year Cumulative Incidence of LR	5-Year Cumulative Incidence of LR	<i>P</i>
Age			
≤50	7	9	<0.001
>50	15	17	
Sex			
Male	11	12	0.61
Female	11	14	
Site			
Lower	11	13	0.65
Upper	8	13	
Size			
≤5 cm	8	10	0.017
>5 cm	13	16	
Depth			
Superficial	10	12	0.34
Deep	11	13	
Histology			
Others	13	15	0.003
WDL/ALT	2	6	
Grade			
Low	6	8	<0.001
High	16	19	
Margin			
Negative	8	10	<0.001
Positive/close	17	22	

**TABLE 3.** Multivariate Analysis for Predictors of Local Recurrence

Covariate	HR	95% CI	<i>P</i>
Margin (positive/close)	2.37	(1.49, 3.77)	<0.001
Grade (high)	2.02	(1.27, 3.22)	<0.001
Age (>50)	1.72	(1.09, 2.72)	0.02
Size (>5 cm)	1.59	(1.00, 2.52)	0.05
Histology (Other than WDL or ALT)	2.86	(1.28, 6.42)	0.001



# Principles based upon patient characteristics

When to refrain from radiotherapy ?

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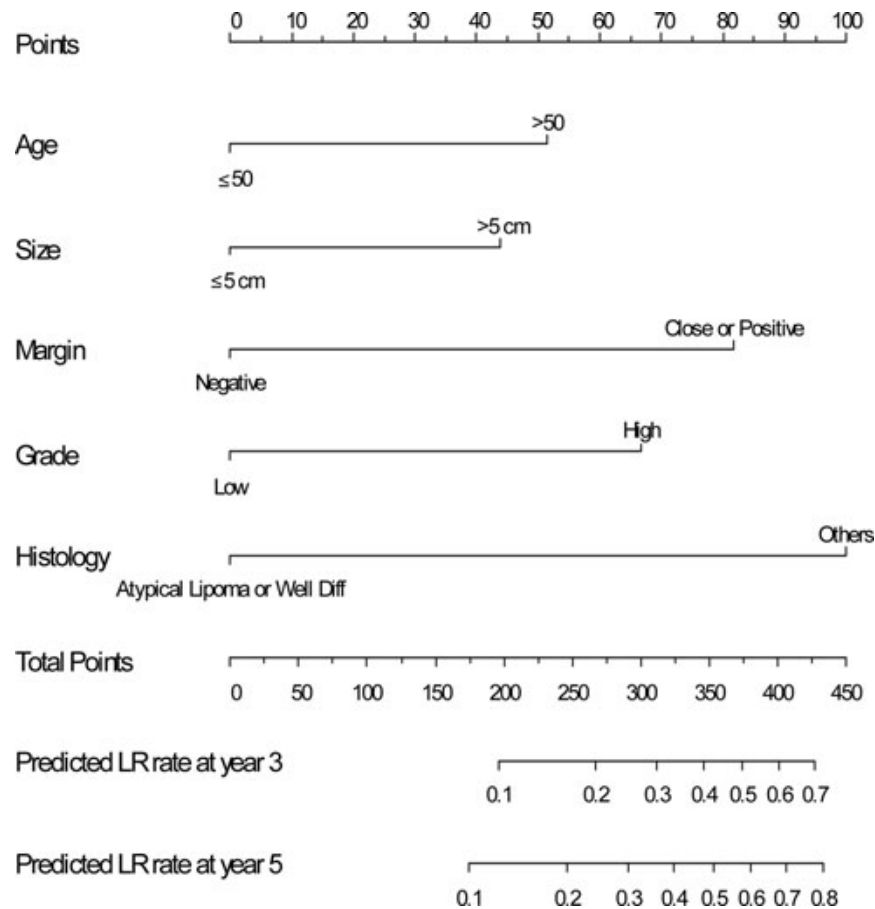
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# Principles based upon patient characteristics

When to refrain from radiotherapy ?



# The challenges.....

The timing           => pre- versus postoperative RT           => preop RT preferred

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The dose

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The machine

## The challenges.....

The timing => pre- versus postoperative RT => preop RT preferred

The dose => not much EBM for 50 Gy  
=> lower dose in MLS

- The machine
  - => Linac's
  - => proton beams
  - => heavy particles like Carbon ions



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The interaction

# The challenges.....

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The dose           => not much EBM for 50 Gy  
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The machine       => Linac's  
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The interaction   => conventional chemotherapeutic agents  
                     => smart molecules and TKI's

# The challenges.....

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The location

## The challenges.....

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- The machine
  - => Linac's
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The location => difficulties in RPS  
=> EORTC 62092 / 22092 “STRASS” study

# The challenges.....

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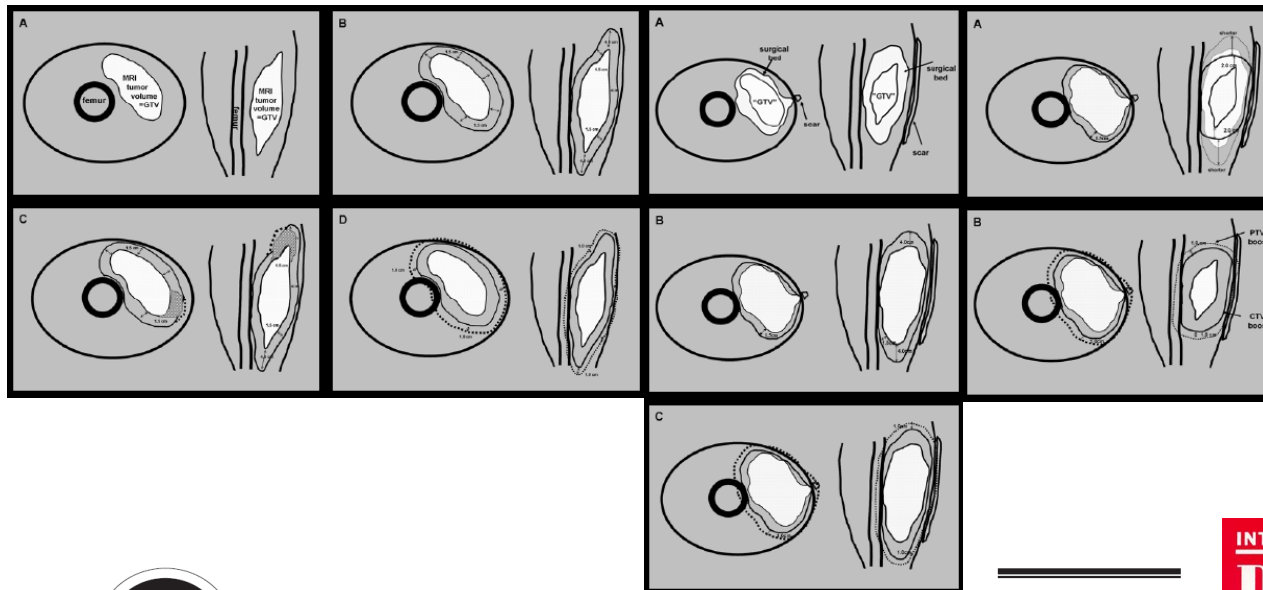
The location         => difficulties in RPS  
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The patient

# The challenges.....

The timing	=> pre- versus postoperative RT	=> preop RT preferred
The dose	=> not much EBM for 50 Gy => lower dose in MLS	
The machine	=> Linac's => proton beams => heavy particles like Carbon ions	
The interaction	=> conventional chemotherapeutic agents => smart molecules and TKI's	
The location	=> difficulties in RPS => EORTC 62092 / 22092 "STRASS" study	
The patient	=> when to refrain from RT (MSKCC nomogram)	

# Technical details



International Journal of  
Radiation Oncology  
biology • physics

[www.redjournal.org](http://www.redjournal.org)



Critical Review

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

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

Int J Radiat Oncol Biol Phys. 2012; 84: 572-80

# The challenges.....

The sky is the limit







**Thanks for the invitation  
and  
thanks for your attention**



European Society for Medical Oncology