NKI-AVL
Het Nederlands Kanker Instituut
Antoni van Leeuwenhoek Ziekenhuis

Innovative combination of targeted agents with radiotherapy in soft tissue sarcomas.

ESMO 2014

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Disclosure

Investigator Initiated Research Grant GSK, but GSK had no part in the design nor the conduct of my studies

Role of RT in STS ??

Role of RT “in general” in STS

Arguments for postoperative RT

Arguments for preoperative RT

What dose ?

When not to irradiate at all

Interaction with targeted therapy

Role of RT “in general” in STS

There are not so many prospective randomized clinical trials performed in the past !

Role of RT “in general” in STS

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1 Pisters PW et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996; 14: 859-868.

2 Yang J et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998; 16: 197-203.

3 O’Sullivan B et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomized trial. Lancet 2002; 359: 2235-2241.

4 Strander H et al. A systematic overview of radiation therapy effects in soft tissue sarcomas. Acta Oncol. 2003; 42: 516-31.

Now running: EORTC 62092 / 22092 for RPS

Role of RT "in general" in STS

Role of RT on LC and OS as reported by randomized trials					
Ref (# pts)	LC-RT (5yr)	LC+RT (5yr)		OS (5yr)	comments
Pisters 1996 n= 164	All: 69% High grade: 66%	All: 82% (p=0.04) High grade: 89% (p=0.0025)		81-84%	**Brachytherapy had no impact on local control in patients with low-grade lesions.**
Yang 1998 n= 141	High grade: 78% Low grade: 6/19 failures	High grade: 100% (p= 0.003) Low grade: 1/22 failures (p= 0.067)		75%	**High grade patients also received chemotherapy.**
O'Sullivan 2002 n= 190		Pre-op RT 92%	Post-op RT 93%	68% at 7yrs	**Due to wound complications prematurely closed**

Arguments for postoperative RT

Arguments for postoperative RT

Many centers apply RT after surgery.

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

Arguments for postoperative RT

Surgery followed by external beam RT.

=> large fields

=> more joints in field.

=> late functional toxicity

Because of the scar

Arguments for preoperative RT

NCIC SR-2 trial: 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		pre-op	postop		pre-op
med FU		3,3 yr			6,9 yr	
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)

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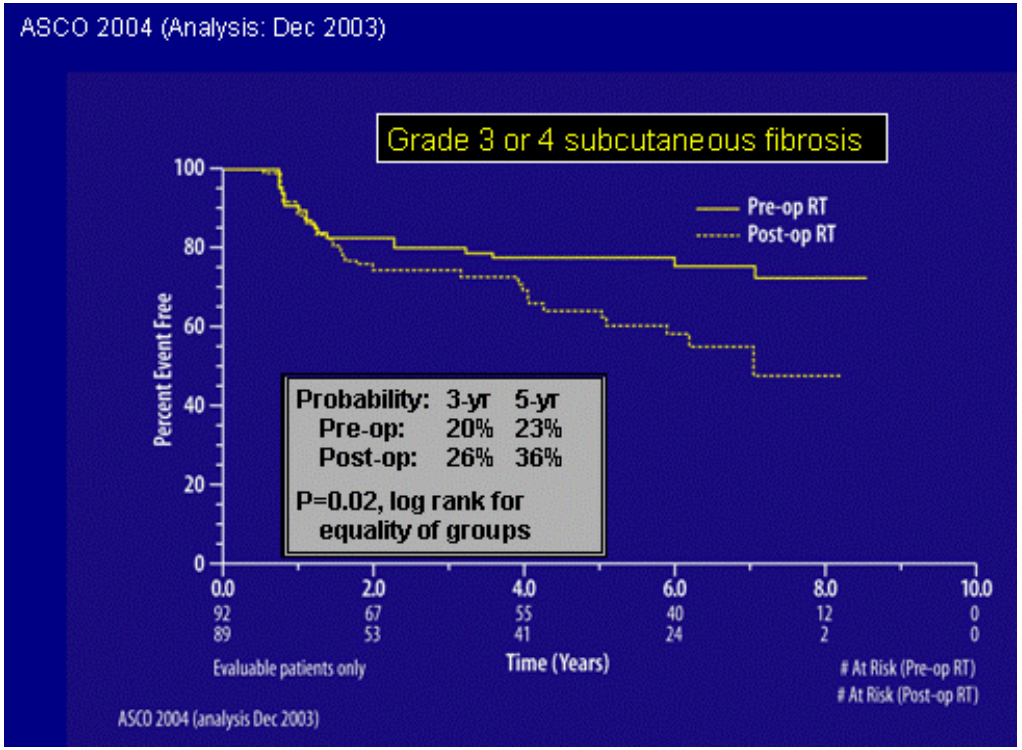

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36% 23%

p=0,02

Arguments for preoperative RT

NCIC SR-2 trial: 50Gy preoperative RT versus 66Gy postoperative RT.

Conclusion:

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

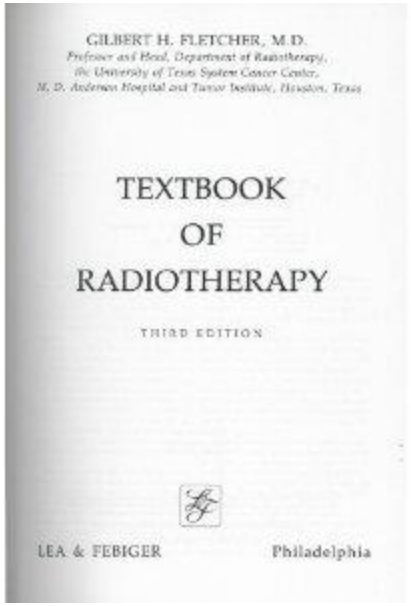
at longer FU preoperative RT “better” than postop (toxicity)

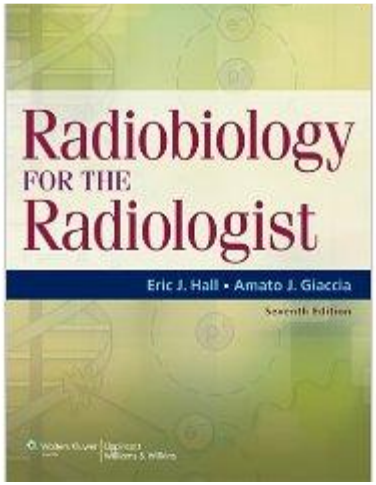
What dose ?

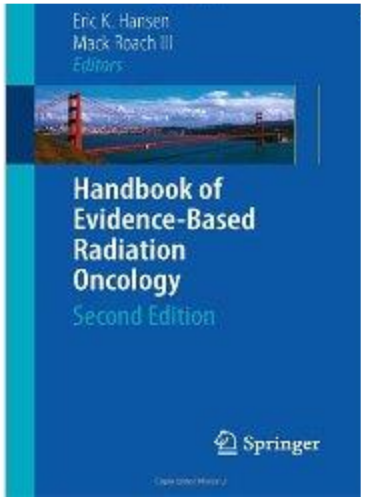
Conventional RT in non-hematological diseases

46-50Gy for microscopic disease

66-70Gy boost for macroscopic disease







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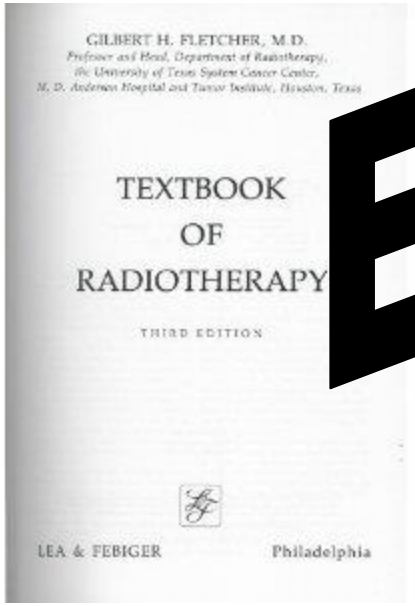
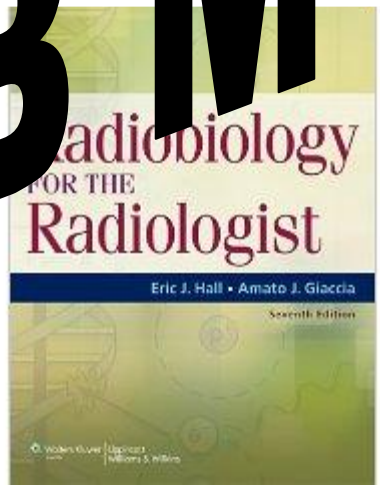
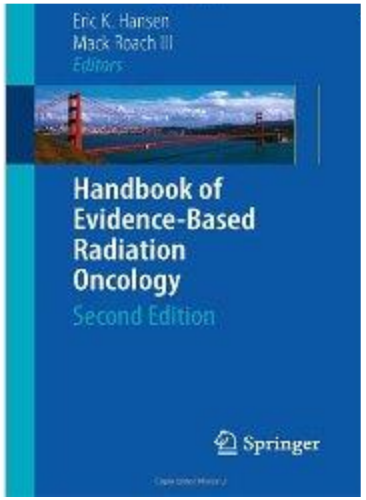






What dose ?

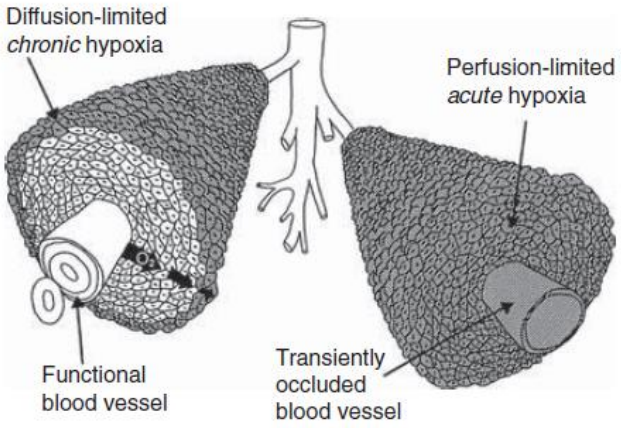
Also the Canadian NCIC SR-2 dose levels; 50Gy versus 66Gy

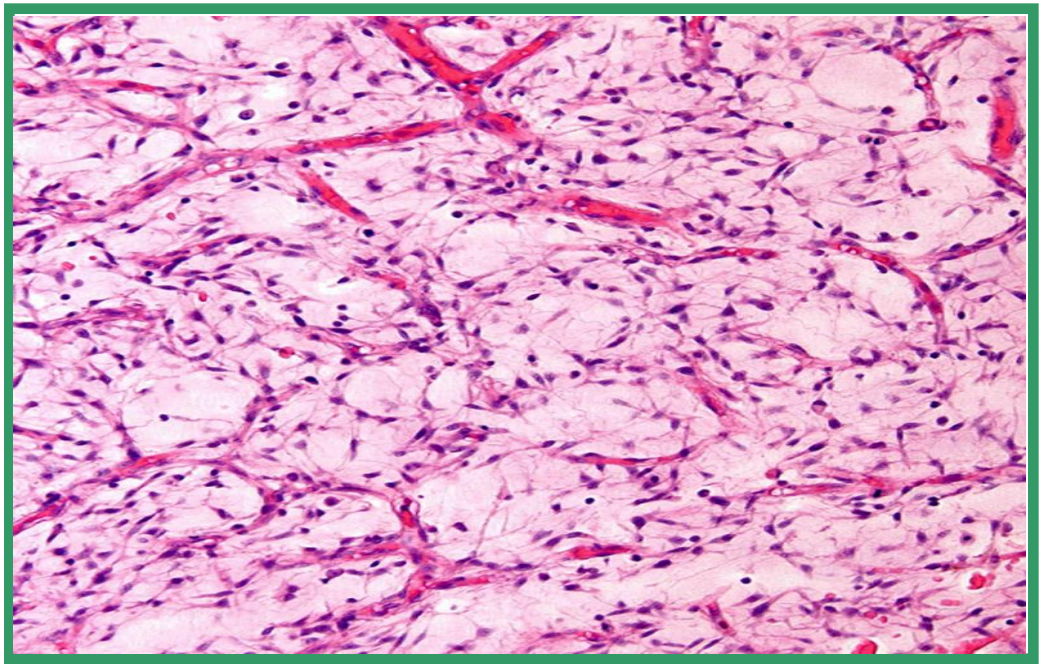
The dose in myxoid liposarcomas (MLS)

4 studies of MLS show volume reduction during preoperative RT

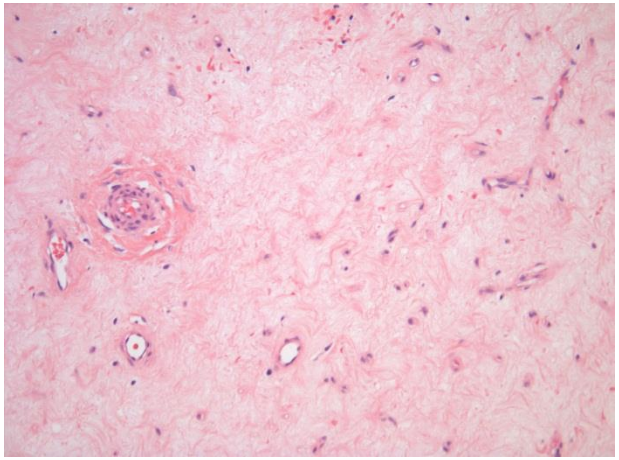
Pitson et al 2004
Engström et al 2007
de Vreeze et al 2008 (NKI-AVL)
Betgen et al 2013 (NKI-AVL)

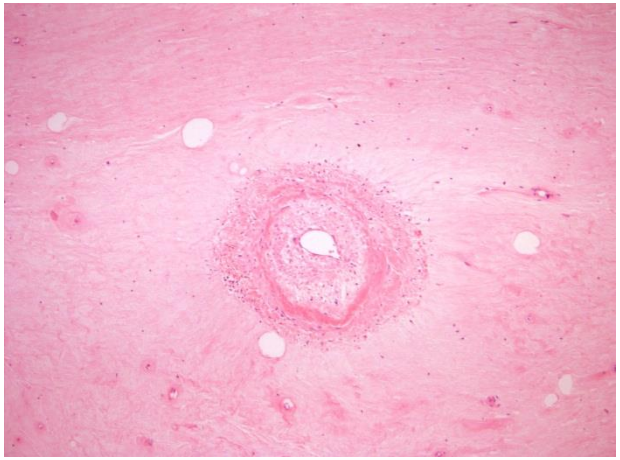
Vasculature ???





Radiation response in MLS after 25 x 2 Gy





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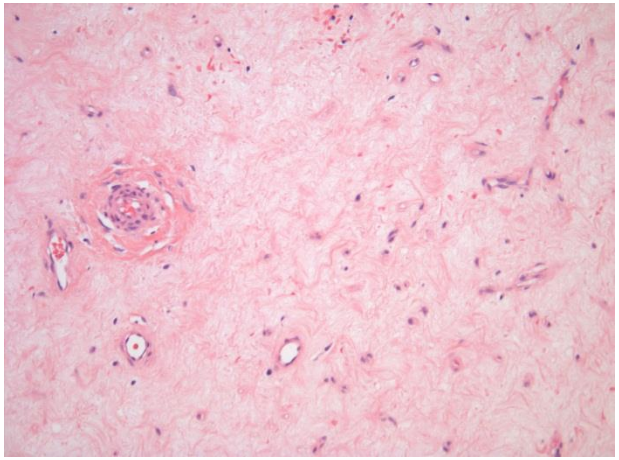
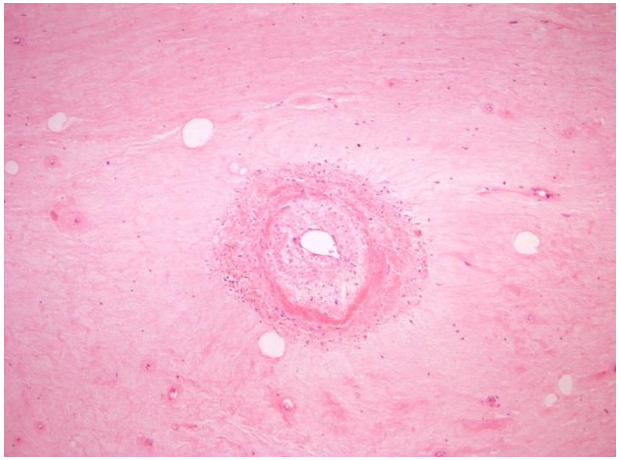
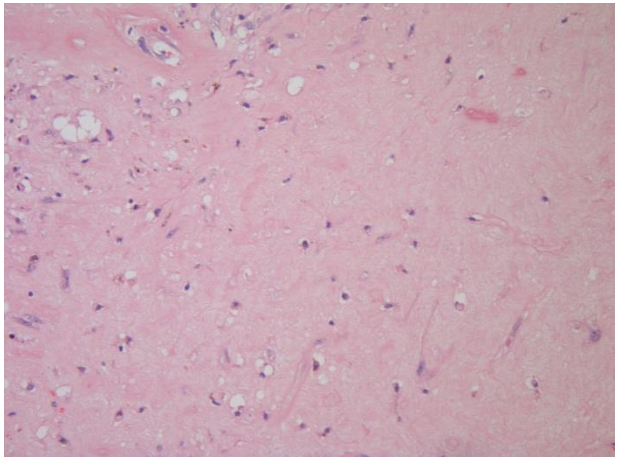
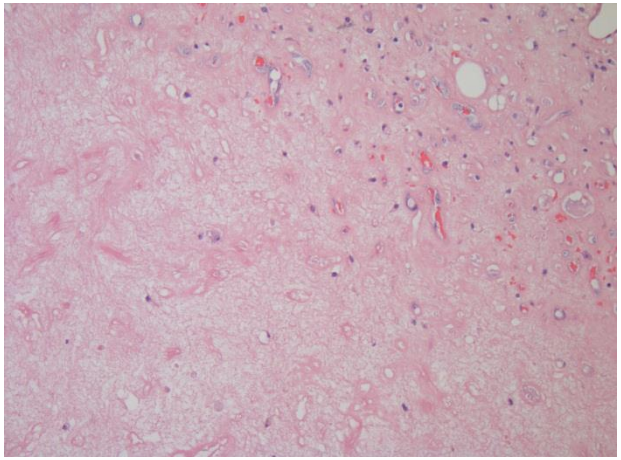




Radiation response in MLS after 18 x 2 Gy





Interaction with targeted therapy

Issues to address:

1. The total dose to deliver
2. The fraction size to deliver the total dose with
3. Interactions with sensitizers

Interaction with targeted therapy (1)

Is 50 Gy total dose the Holy Grail in STS management ?

Interaction with targeted therapy (2)

Why 2 Gy per fraction for all STS subtypes without systemic treatment ?

Interaction with targeted therapy (2)

Why 2 Gy per fraction for all STS subtypes without systemic treatment ?

In “carcinomas”; interaction with conventional chemotherapy
smart molecules

=> increased local control
=> sometimes increased OS
=> be it at the cost of increased acute / temporary toxicity

Interaction with targeted therapy (2)

Why 2 Gy per fraction for all STS subtypes without systemic treatment ?

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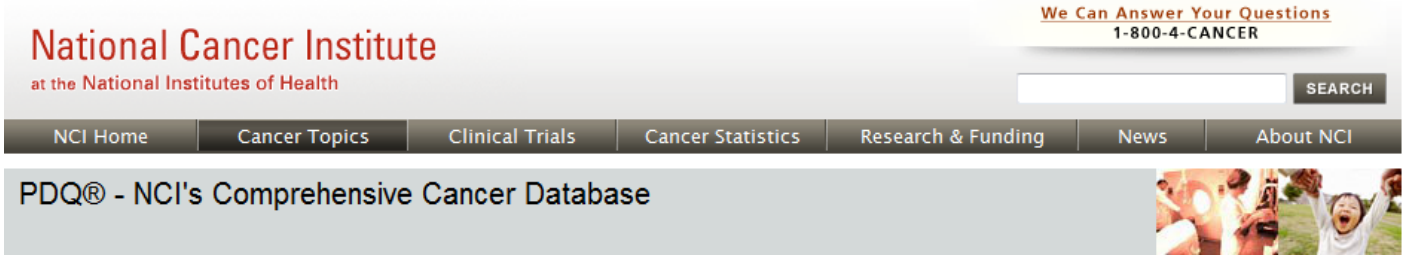
But what about STS?

Interaction with targeted therapy (3)

PDQ search:



Jean-Yves Blay, Lyon, France	Sunitinib
David Thomas, Australia	Sunitinib
Robert Canter, California, USA	Sorafenib
Yen-Lin Chen, Boston, USA	Bevacizumab
Rick Haas, Amsterdam NL	Pazopanib
Sylvie Bonvalot, Paris, France	nanoparticles

Interaction with targeted therapy versus RT alone

Necrosis induction by preoperative RT in ESTS						
Setting	**Author**	**Journal**	**regimen**	**n**	**% necrosis in % of patients**	**remarks**
RT only	Canter	Ann Surg Oncol 2010	RT	25	Median 30% ≥ 95% in 8% ≥ 80% in <20%	
	Shah	Anticancer Res 2012	RT	30	Median 35% ≥ 95% in 10%	In pCR patients DRFS improves (ns)
RT + conventional chemotherapy	Kraybill	JCO 2006	RT interdigitated in MAID	59	≥ 95% in 27%	
	Ryan	Cancer 2008	AI + RT	25	≥ 95% in 40%	
	MacDermed	Red J 2010	I + RT	34	> 90% in 50% ≥ 95% in 11.8%	In pCR patients DRFS improves (p =0.02)
"Biologicals"	Yoon	Red J 2011	Avastin + RT	20	≥ 80% in 45% > 95% in 20%	
	Canter	Ann Surg Oncol 2014	Sorafenib + RT	8	≥ 95% in 38%	
PASART-1	Haas	Red J …	Pazopanib + RT	8	≥ 50% in 87.5% ≥ 95% in 50%	
Nanoparticles	Bonvalot	ASCO / CTOS	NP + RT	20	>90% in 18% average pathological response 74%	At 10% injection => average tumor volume reduction 49%

Interaction with targeted therapy versus RT alone

Necrosis induction by preoperative RT in ESTS; ≥ 95 % necrosis

Setting	Author	Journal	regimen	n	≥ 95% necrosis	
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	Canter	Ann Surg Oncol 2014	Sorafenib + RT	8	38%	
PASART-1	Haas	Red J …	Pazopanib + RT	8	50%	
Nanoparticles	Bonvalot	ASCO / CTOS	NP + RT	20	18%	

Interaction with targeted therapy

A clinical meaningful necrosis induction (pCR; defined as ≥ 90% / ≥ 95% necrosis) may result in an increase in local control and DRFS

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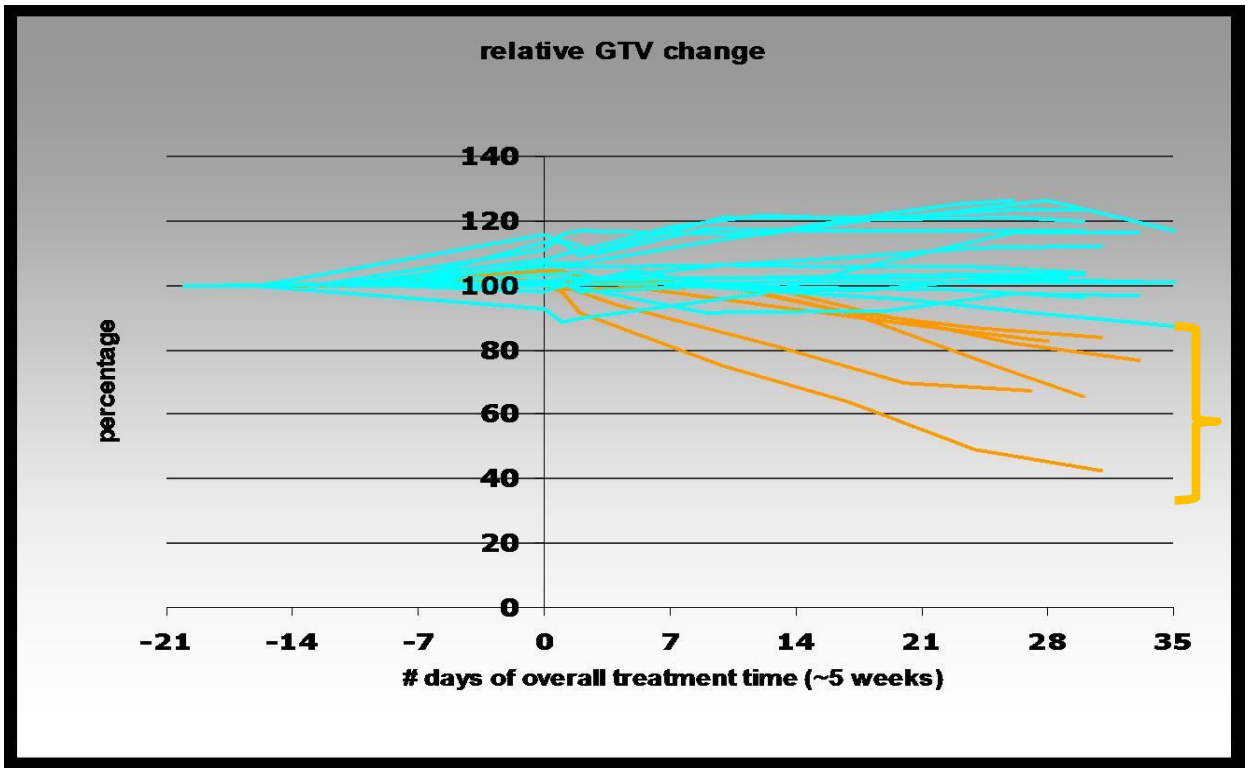

"Others"

Myxoid Liposarcoma → **~100%**

Betgen A, Haas RL, Sonke JJ. J Radiat Oncol. 2013; 2: 55-62

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1. take your gain and profit from the better outcome data
2. lower the radiation dose in order to decrease wound complications

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Thanks for the invitation

Aurora Borealis
March 2014, Lapland