Medical education programme in soft-tissue sarcoma (STS)

The role of radiotherapy

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Challenges

- Timing
- Dose
- Tools
- Combinations with chemotherapy
- Exclusive irradiation
- Radiation-associated sarcomas (RAS)

Timing

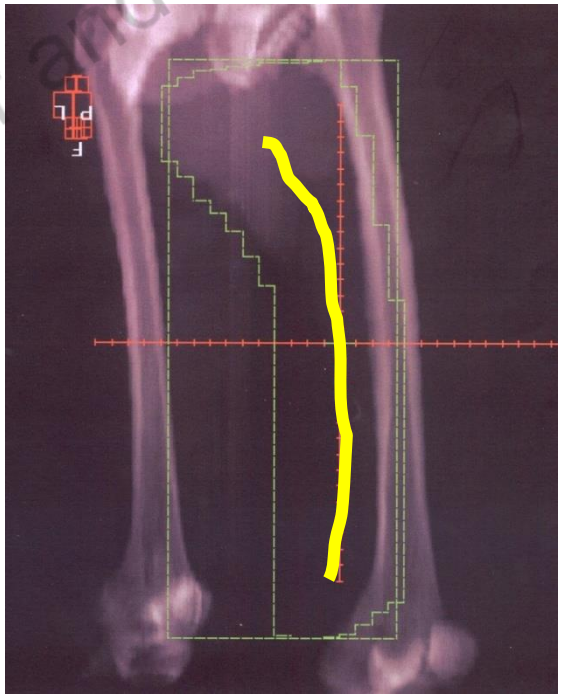
- Most centres apply RT after surgery
- Reasons
  - Full pathology report on a heterogeneous sarcoma mass
  - Unaffected by prior RT
  - Fewer wound complications
- In other words: rationale for surgery is based on surgical endpoints first
- But what about late quality of life?

RT, radiotherapy

Timing

- Surgery followed by external-beam RT
  - Large fields
  - More joints in field
  - → Late functional toxicity

- These fields are so large because of the length of the surgical scar

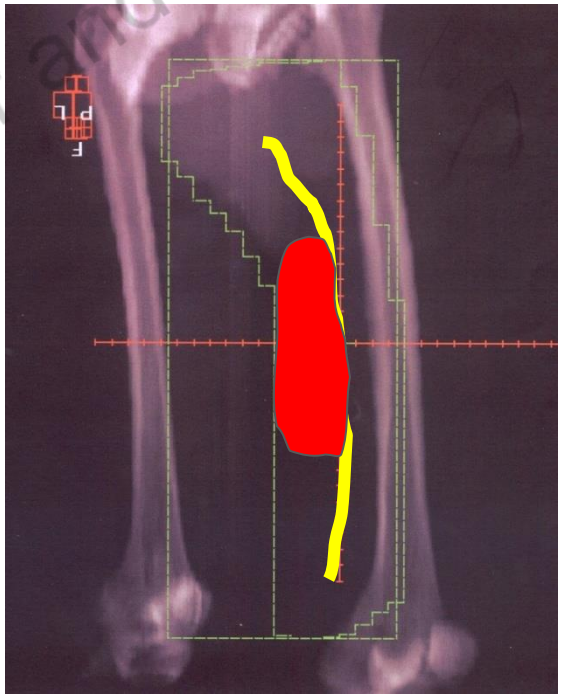


Standard simulation film

Timing

- Surgery followed by external-beam RT
  - Large fields
  - More joints in field
  - → Late functional toxicity

- Whereas the sarcoma was much smaller than the necessary scar



Sarcoma size with respect to the surgical scar

Timing

- Canadian SR-2 trial: 50 Gy pre-op RT vs. 66 Gy post-op RT.
  Study prematurely closed due to more post-op morbidity in the pre-op arm

	Lancet 2002		
	Post-op		**Pre-op**
Median FU	3.3 years		
Alive			
Local control	94%		96%
(+) Margins			
(-) Margins			
Early toxicity	17%	*p*=0.01	35%
Late toxicity	26%		20%

FU, follow-up

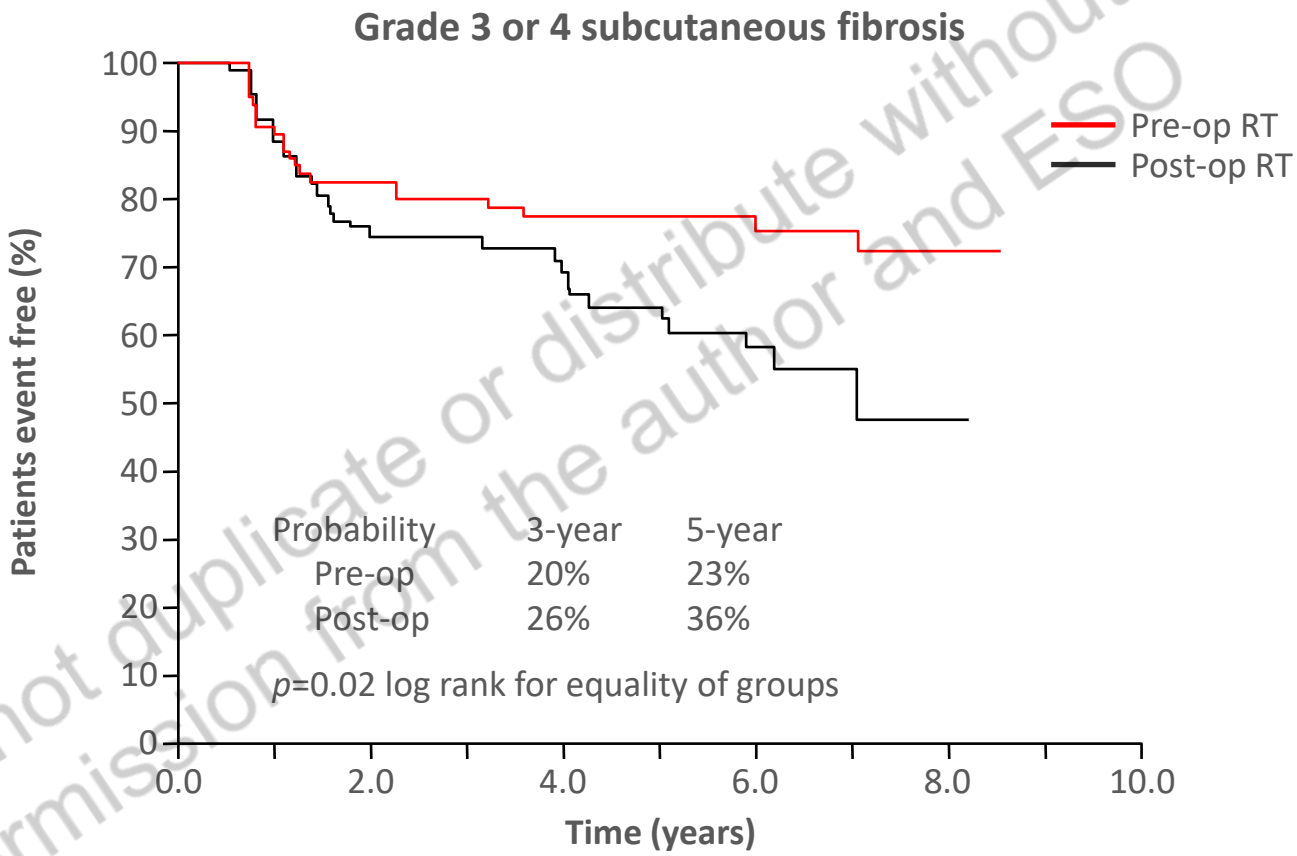
Timing

- Canadian SR-2 trial: 50 Gy pre-op RT vs. 66 Gy post-op RT.
  Study prematurely closed due to more post-op morbidity in the pre-op arm

	Lancet 2002			CTOS/ASCO 2004		
	Post-op		Pre-op	Post-op		Pre-op
Median FU	3.3 years			6.9 years		
Alive				70%		
Local control	94%		96%	93%		92%
(+) Margins				77%		73%
(-) Margins				96%		95%
Early toxicity	17%	*p*=0.01	35%			
Late toxicity	26%		20%	36%	*p*=0.02	23%

O'Sullivan *et al*. *Lancet* 2002;359:2235–41

Timing



Evaluable patients only

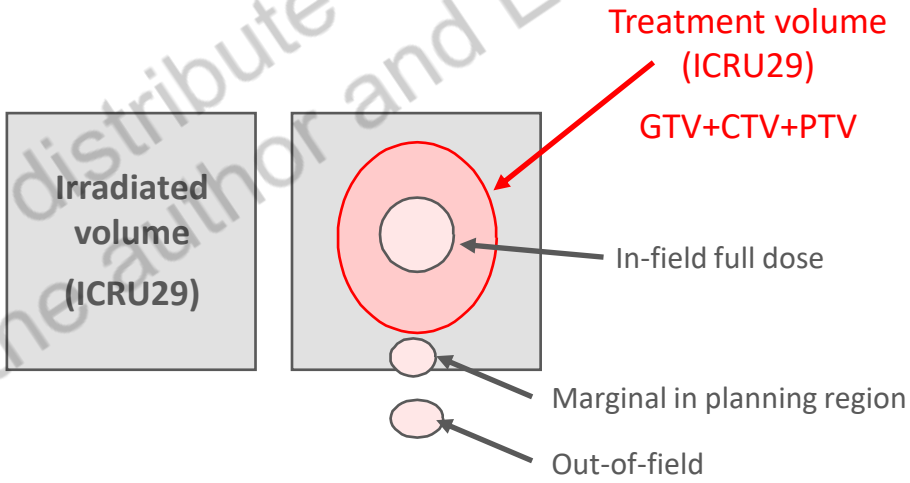
Number at risk (pre-op RT)	92	67	55	40	12	0
Number at risk (post-op RT)	89	53	41	24	2	0

Local failures with respect to field size

- In the subgroup of patients with local failures; where do these failures occur ?

The Princess Margaret Hospital Toronto data

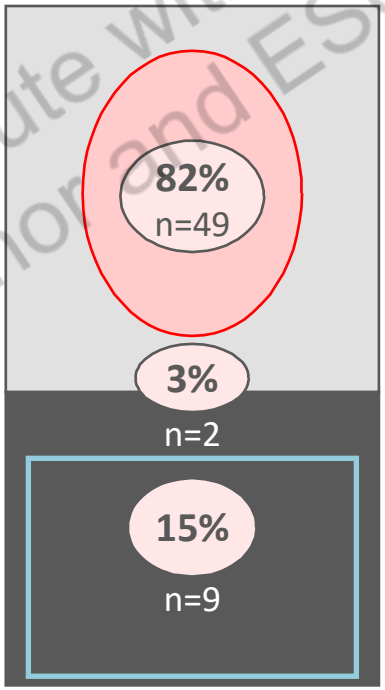
- 60 / 780 LR = 7.7% (1990-2006)
  - Two- or 3-field RT approach
- MRI/CT scans overlaid on planning RT films



LR, local relapse; MRI, magnetic resonance imaging; CT, computed tomography; GTV, gross tumour volume; CTV, clinical target volume; PTV, planning target volume

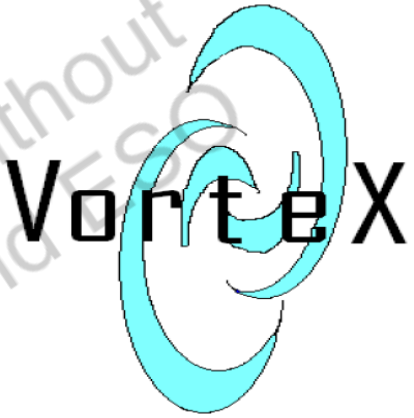
The Princess Margaret Hospital Toronto data

- Results
  - 82% of LRs developed in the RT field (n=49)
  - 18% of LRs occurred out of the prescribed dose region (n=11)
    - 15% were out of the RT field (n=9)
    - 3% were marginal (n=2)



The VORTEX trial

- Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

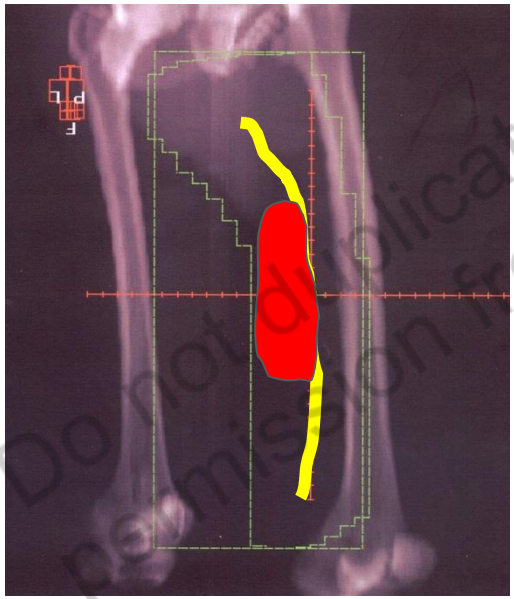


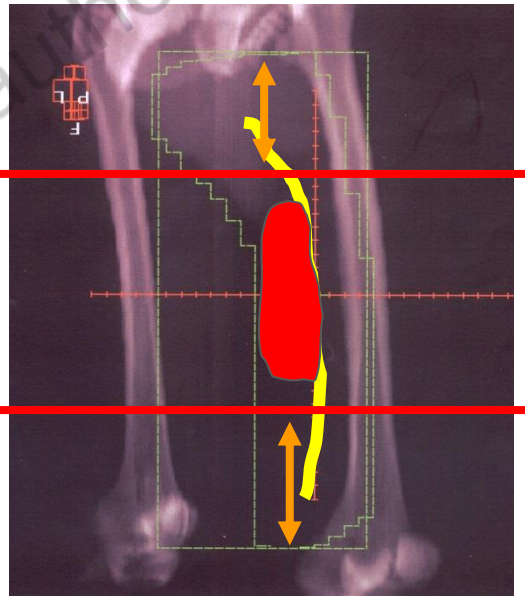
The VORTEX trial

Large- vs. small-volume external-beam RT

VorteX

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





Field size reduction

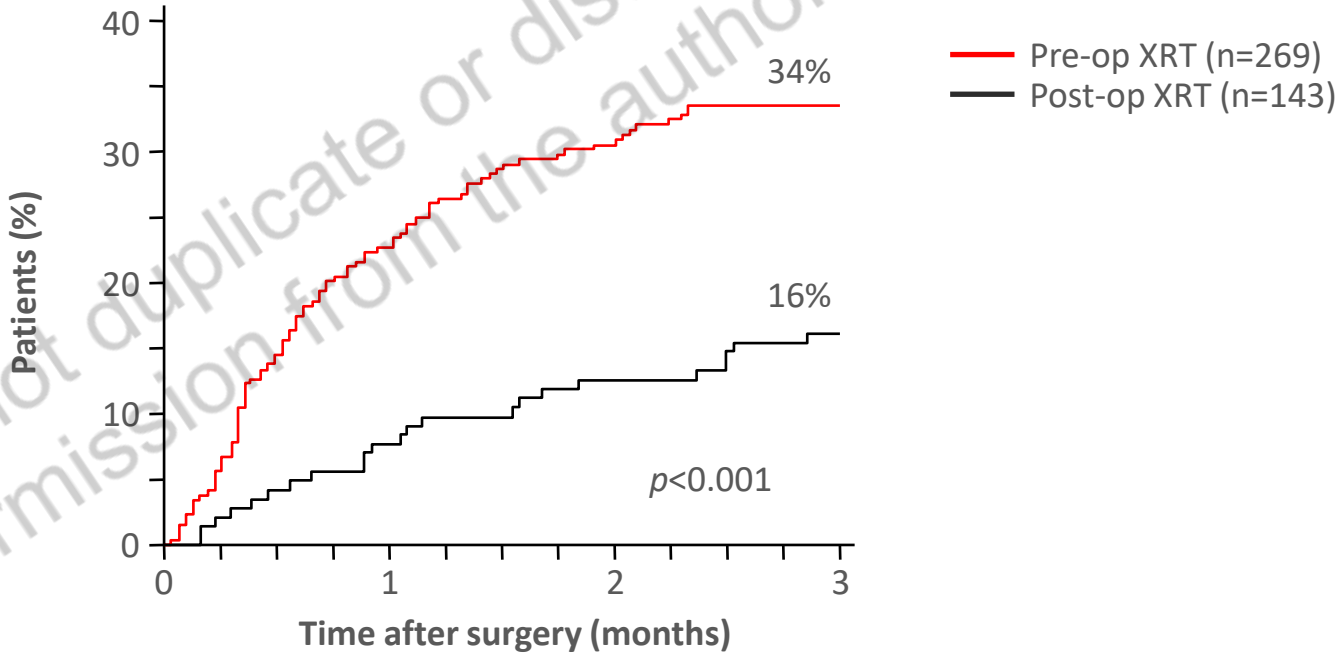
Timing: conclusions SR-2 trial

- At longer follow-up, pre-op RT is as "good" as post-op RT
  - Efficacy as endpoint

- At longer follow-up, pre-op RT is "better" than post-op RT
  - Toxicity as endpoint

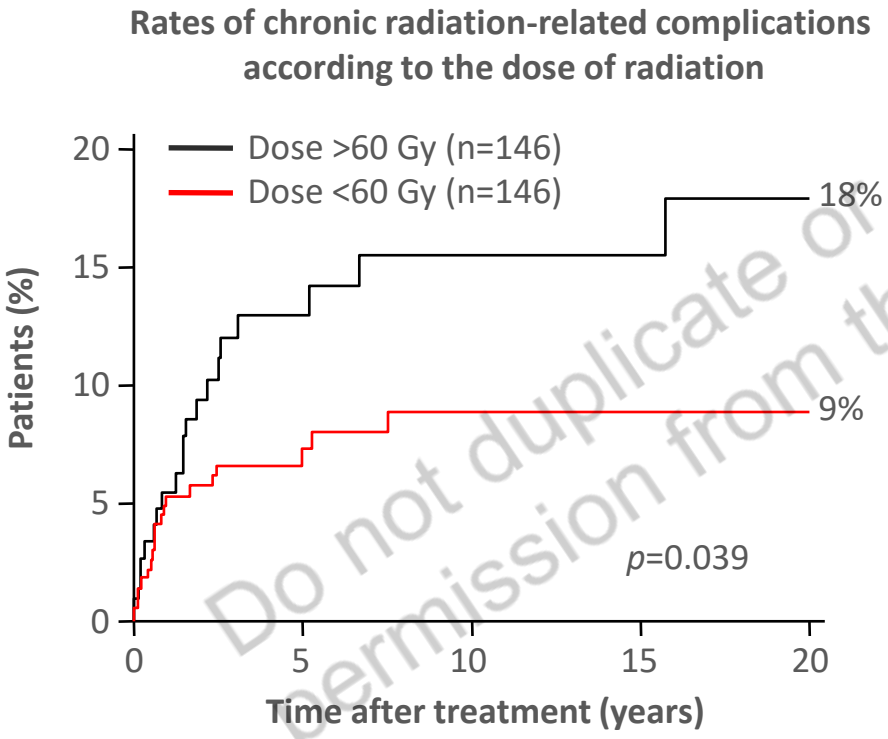
Timing: MDACC Houston

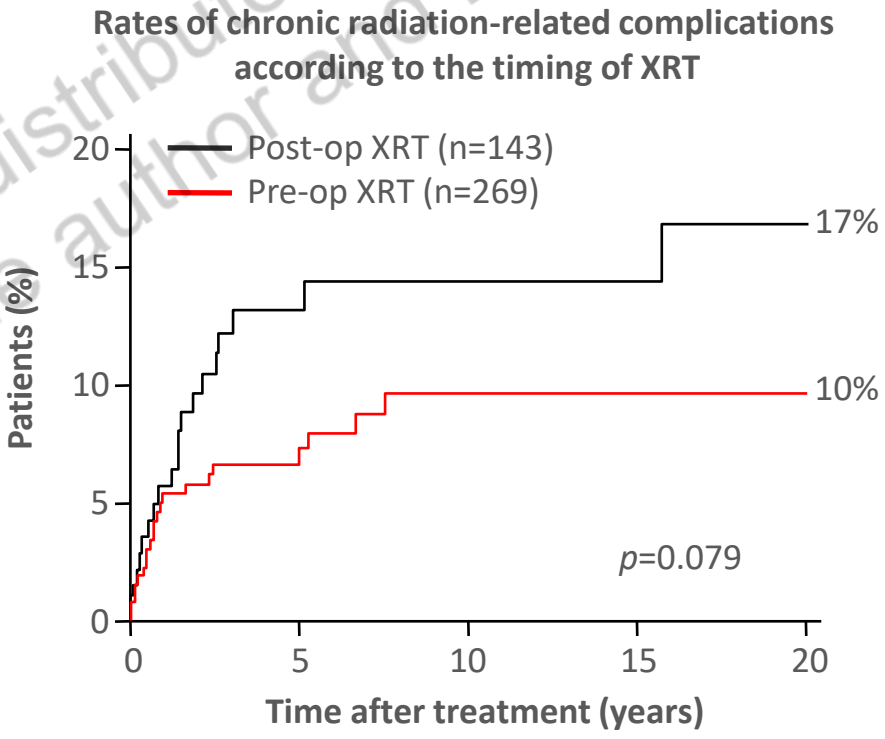
- Acute wound complications according to the timing of radiation therapy (XRT): data similar to SR-2 trial



Timing: MDACC Houston

- Late complications: data similar to SR-2 trial





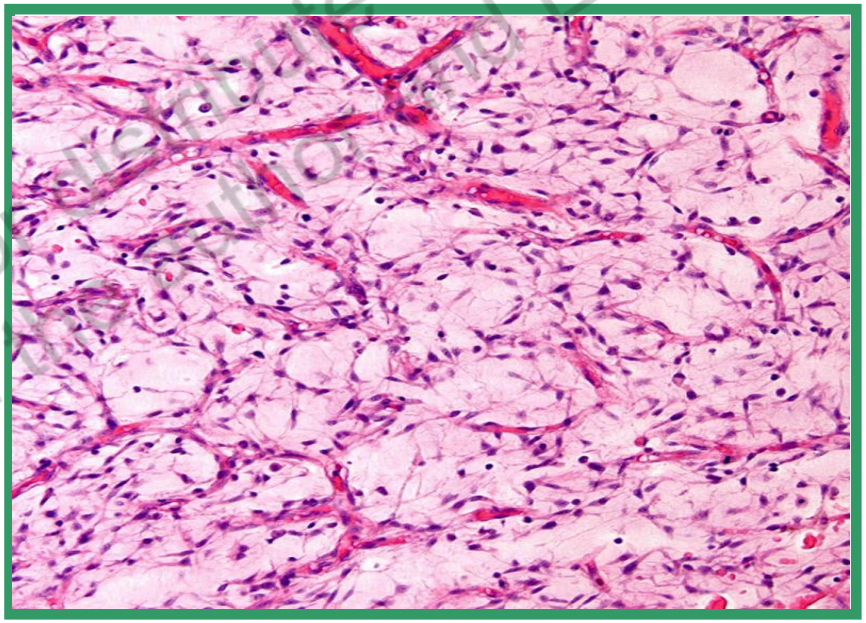
Dose

- Conventional RT in nonhematological cancers
  - 46–50 Gy for microscopic disease
  - 66–70 Gy boost for macroscopic disease

- The evidence for sarcomas?

Dose in myxoid liposarcomas (MLS)

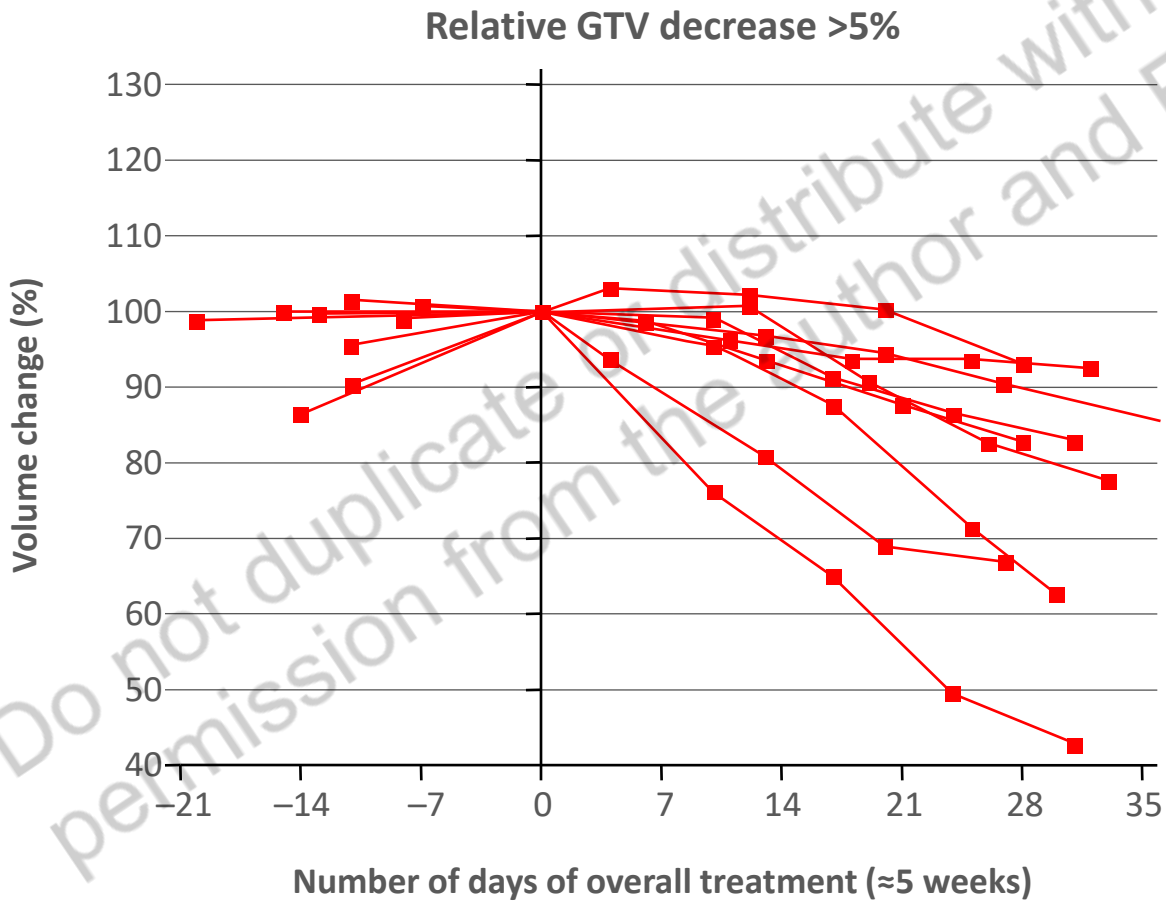
- Several studies of MLS show volume reduction after pre-op RT
  - Pitson 2004[1]
  - Engström 2007[2]
  - de Vreeze 2008[3]
  - Betgen 2013[4]



- Vasculature?

1. Pitson *et al. Int J Radiat Oncol Biol Phys* 2004;60:522–6; 2. Engström *et al. Acta Oncol* 2007;46:838–45;
3. de Vreeze *et al. Int J Radiat Oncol Biol Phys* 2008;72:1480–7; 4. Betgen *et al. J Radiat Oncol* 2013;2:55–62

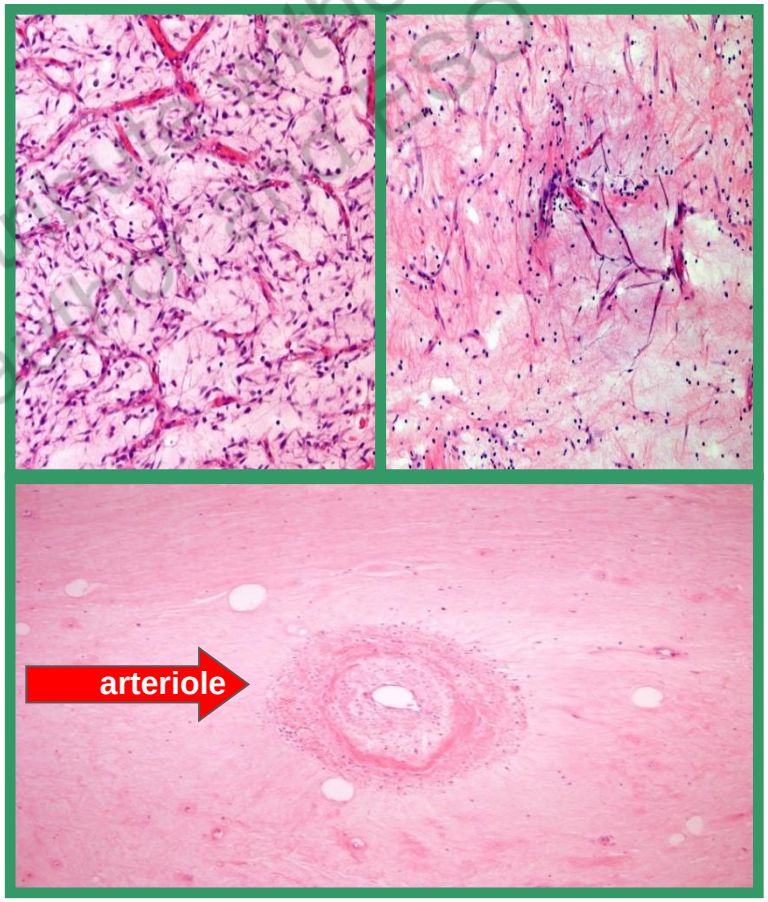
Dose in MLS



Dose in MLS

- Vasculature as target
  - Hypoxia
  - Deprivation of nutrients

- Dose reduction feasible? = Phase II study; 18 × 2 Gy*



* NCT 02106312

Dose in MLS

- DOREMY
- N = 79
- 18 x 2 Gy preoperative RT
- Median FU 25 months
- Local control @ 2 yrs 100%
- Wound complications 17%

JAMA Oncology | Original Investigation

Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma

A Nonrandomized Controlled Trial

JAMA Oncol. doi:10.1001/jamaoncol.2020.5865
Published online November 12, 2020.

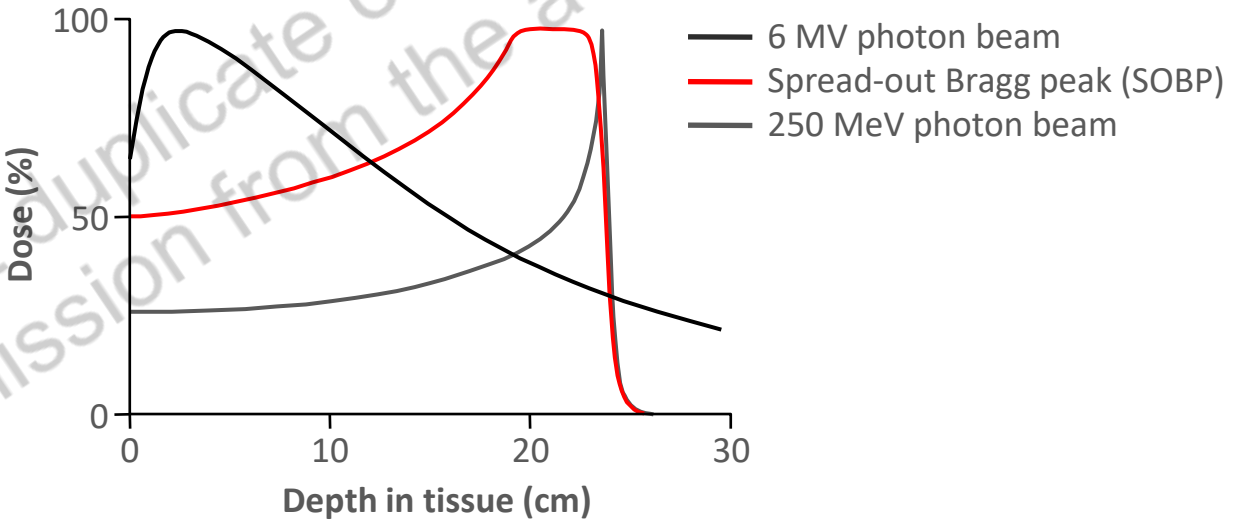
Dose in MLS

- DOREMY
- International Registry
  - Surgery alone
  - 25 Gy preopRT
  - 36 Gy preopRT
  - 50 Gy preopRT
  - 60-66 Gy postop RT

* NCT 02106312

New tools for RT

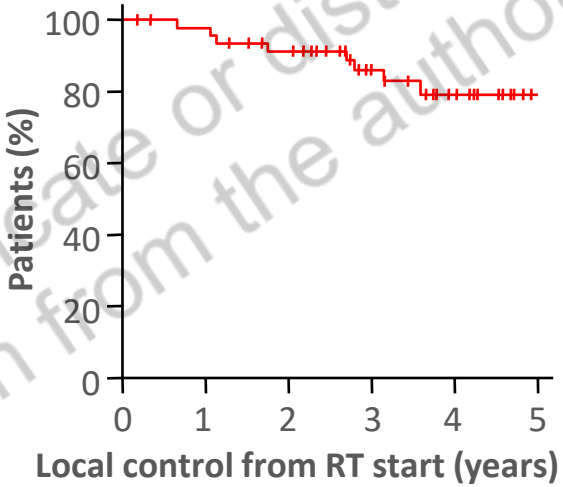
- Does all external beam irradiation need to be performed by linear accelerators?
- What is the role of proton beam generators?

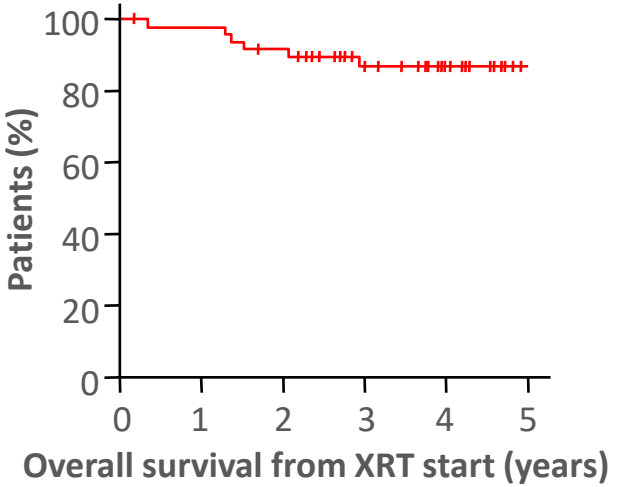


New tools for RT: sarcomas of the spine

- Predominantly chordomas and chondrosarcomas

Characteristic	*n*
Number of patients	50
Follow-up (months) (42 patients alive)	
Median	48
Range	37–124
Histology	
Chordoma	29 (58%)
Chondrosarcoma	14 (28%)
Osteosarcoma	1
Ewing's sarcoma	1
Giant cell tumour of bone	1
Angiosarcoma	1
Spindle and round cell	1





DeLaney *et al. Int J Radiat Oncol Biol Phys* 2009;74:732–9

New tools for RT: sarcomas of the spine

- Predominantly chordomas and chondrosarcomas

Skull base chordoma						
Beam	No. of patients	Dose Gy (RBE)	Dose/Fx Gy (RBE)	BED Gy α/β = 2	Local control at years	Late ≥GIII injury
^{1}H	115	69	1.8	66	59% at 5	Not given
^{1}H	100	67	1.9	65	54% at 4	GI–IV: 42%
	90					≥GII: 6%
^{1}H	33	72 [67–79]	1.8	68	59% at 5	GIII–IV in 4 [7%]
^{1}H	42	74	1.9	72	81% at 5	GIII in 4 in 64 patients [6%]
^{12}C	10	52.8	3.3	70	60% at 5	GIII none
	19	60.8	3.8	88	91% at 5	
^{12}C	84	60	3.0[a]	75	63% at 5	GIII in 5 [5%]
	12	70	3.5	96	100% at 5	
X	37	67	1.8	64	50% at 5	Serious in 1 [3%]
X	18	16 at margin 33 at max	1 Fx		53% at 5	None

Skull base chondrosarcoma [low–intermediate grade]					
Beam	No. of patients	Dose Gy (RBE)	Dose/Fx Gy (RBE)	BED Gy α/β = 2	Local control at years
^{1}H	200	72	1.9 [1.8–2]	70	99% at 5
^{1}H	25	69	1.8	66	75% at 5
^{1}H [PBS]	22	68	1.9 [1.8–2]	66	94% at 5
^{12}C	54	60	3.0	75	90% at 4
X	10	16; 33	16		80% at 5

Combinations with chemotherapy

- Conventional chemotherapy
  - Cisplatin → NSCLC, cervical
  - Taxanes → oesophageal
  - 5-FU → colorectal
  - Temolozomide → glioblastoma
- Targeted therapy
  - Monoclonal antibodies
  - Tyrosine kinase inhibitors
    - Erlotinib → NSCLC, pancreas
    - Sunitinib → renal cell

NSCLC, non-small-cell lung carcinoma; 5-FU, fluorouracil

Combinations with chemotherapy

- Interdigitating regimens like “MAID”[1]
- Concurrent regimens
  - Sunitinib
  - Sorafenib
  - Pazopanib
  - Bevacizumab
  - Sirolimus
  - Cabozantinib

MAID, mesna, adriamycin, ifosfamide, dacarbazine

1. Mullen *et al. Cancer* 2012;118:3758–65

Exclusive irradiation: for whom?

- With curative intent
  - Desmoid/aggressive fibromatosis
  - DFSP
- With palliative intent
  - Relative short course irradiation (e.g. 10–13 × 3Gy) for
    - Palliation of pain
    - Neurological complaints by compression on nerves
    - Dyspnoea by atelectasis due to lung metastases
    - Bleeding, etc.

DFSP, dermatofibrosarcoma protuberans

Exclusive irradiation: desmoids

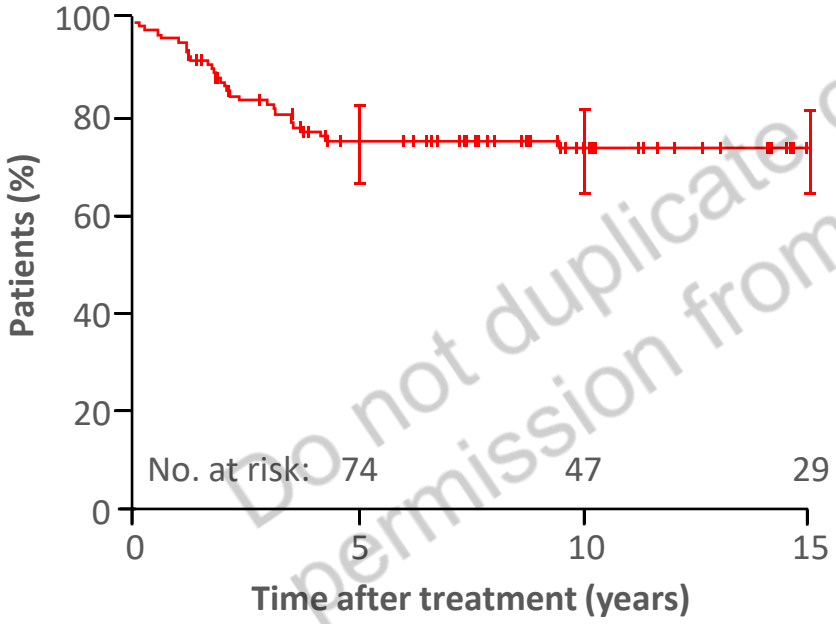
- MDACC series 1965–2005, n=115; median follow-up 10.1 years
  - 41 patients received RT alone for gross disease
  - 74 patients had surgery + RT (CMT)
  - Equal LC (RT vs. CMT); 75% at 10 years

CMT, combined modality therapy; LC, local control

Exclusive irradiation: desmoids

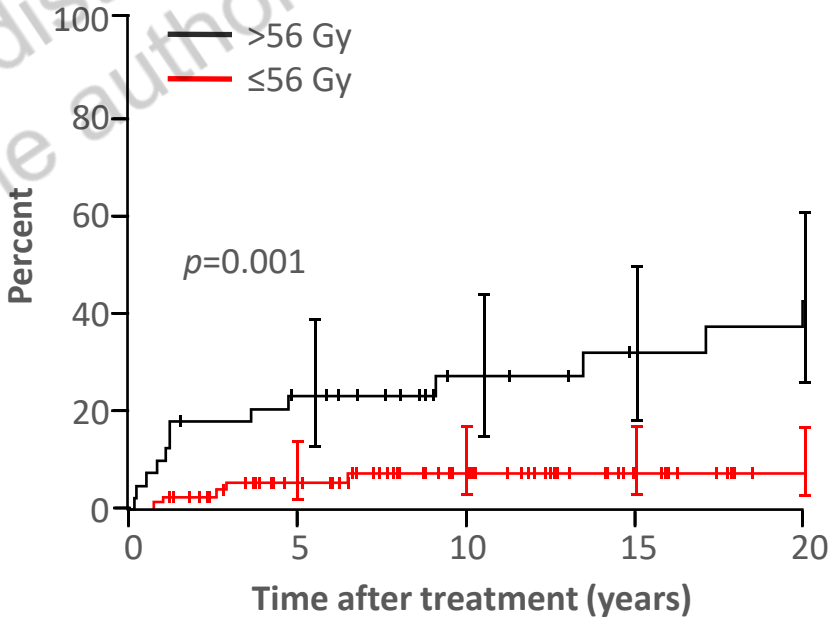
Actuarial LC for all 115 patients

Tick marks represent censored observations
95% confidence intervals also shown



Actuarial incidence of radiation-related complications according to radiation dose

Tick marks represent censored observations
95% confidence intervals also shown



Exclusive irradiation: desmoids

LC results based on univariate analysis for all 115 patients			
Characteristic	**n (%)**	**Actuarial 10-year LC (%)**	***p* value**
Entire cohort	115	74	
Age, y			
≤30	60 (52)	66	
>30	55 (48)	83	0.02
Tumour size, cm			
≤5	35 (30)	90	
5–10	52 (45)	69	
>10	27 (23)	62	0.01
Prior treatment			
No	46 (40)	72	0.77
Yes	69 (60)	76	
Surgery + RT	74 (64)	78	0.12
RT	41 (36)	65	
RT dose, Gy			
<56	76 (66)	73	0.81
>56	39 (34)	76	

Univariate analysis of LC for 41 patients treated with XRT alone for gross disease			
Characteristic	**n (%)**	**Actuarial 10-year LC (%)**	***p* value**
Age, y			
≤30	17 (41)	50	
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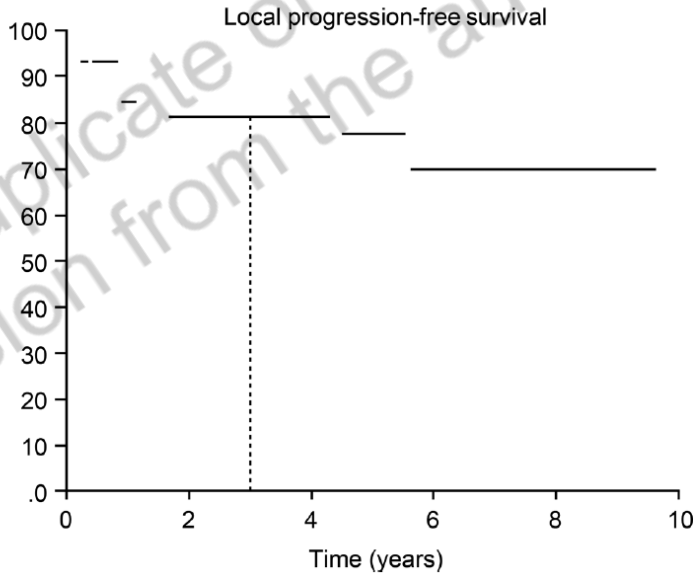
Exclusive irradiation: desmoids EORTC 62991–22998

- N = 44
- Median follow up 4.8 years
- The 3-year local control rate 81.5%.
- Best overall response during the first 3 years
  - CR 6 (13.6%)
  - PR 16 (36.4%)
  - SD 18 (40.9%)



Exclusive irradiation: DFSP[1]

- 3 patients RT alone; 67–75 Gy
- LC in all 3 after 85, 106, and 108 months
- Good cosmetic outcome

- Note: there is definitely a role for imatinib in the modern management of inoperable cases[2]
- Nirogacestat (a γ-secretase inhibitor) is currently under investigation[3]

Radiation-associated sarcomas (RAS)

- RAS incidence, 0.03%–0.2%
- Median latency time, 15 years
- 5-year overall survival, rarely >30%
- Histology
  - High-grade UPS
  - Angiosarcoma

UPS, undifferentiated pleomorphic sarcoma

RAS

- Management: surgery if feasible
- There is probably a role for hyperthermia and re-irradiation
  - 32–36 Gy in 3–4 Gy fractions
  - 4–6 times hyperthermia therapy (HT), 1 hour at 41–43°C

A: Chest wall RAS after mastectomy and post-op RT (prior to HT and RT)

B: Local CR 11 months after HT and RT

Concluding remarks: timing

- In case of large, deep seated, Grade II–III sarcomas
  - Preferably RT prior to surgery
- In case of small and/or Grade I and/or superficial
  - Preferably surgery only for first-line management

Concluding remarks: dose

- In case of post-op RT
  - 45–50 Gy surgical area
  - 15–20 Gy boost on primary site
- In case of pre-op RT
  - 50 Gy on sarcoma mass only
- In case of MLS
  - consider a lower dose (participate in DOREMY Registry)

Concluding remarks: tools

- Linac-based RT
- Proton beam generators
- Carbon ion irradiation

Concluding remarks: combinations with chemo

- Conventional chemotherapy
- Studies
  - Targeted therapy
  - Monoclonal antibodies

Concluding remarks: exclusive irradiation

- Role of RT in palliation
- Role of RT in desmoids

Concluding remarks: RAS

- Rare
- Usually aggressive
- Preferably managed by surgery
  - Role for RT and HT

European School of Oncology
learning to care

Thank you

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