Radiotherapy for Extremity Sarcomas –New Developments

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Historical perspectives

- **Surgery** is integral to management of Extremity Soft Tissue Sarcomas (**ESTS**)
  - Wider the excision, lower the probability of local failure

	Recurrence Rate
Simple Excision	60-90%
Wide Excision	20-30%
Compartmental resection	10-20%
Amputation	0-10%

- Then (1970s) – 50% of ESTS patients underwent **amputation**
- Movement towards **limb preservation** through use of **reconstructive techniques** and **adjuvant RT**

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

From the National Cancer Institute, Bethesda, Maryland

- 43 patients with **high grade** ESTS
- **2:1 randomization** between limb-sparing resection + post-operative radiotherapy (**PORT**) and **amputation**
- Results:

Local treatment modality	***LR (n)***	***5y DFS (%)***	***5y OS (%)***
Limb-sparing sx + PORT (27)	4	71	83
Amputation (16)	0	78	88
p value	*0.06*	*0.75*	*0.99*

- **Positive margins** was the only correlate of local recurrence on multivariate analysis

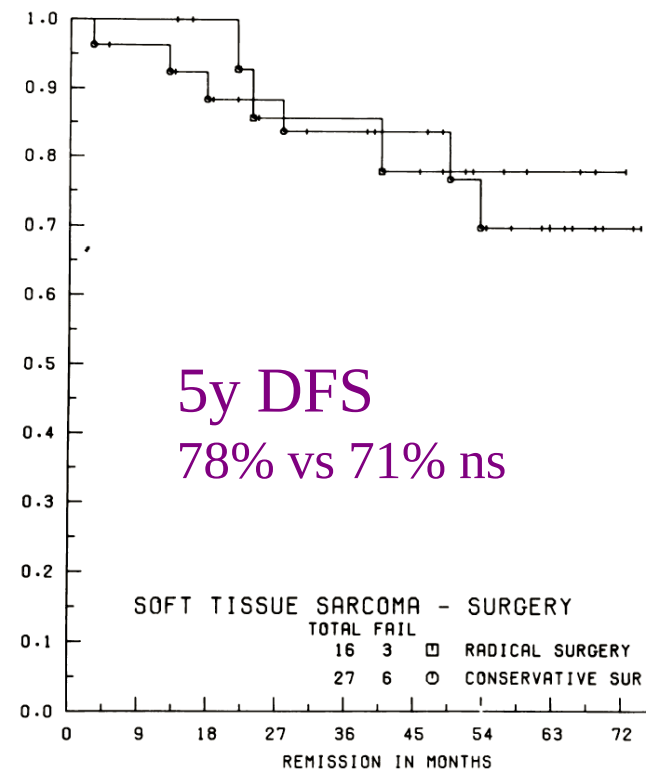
Rosenberg et al, Ann Surg Sep 1982 Vol 196 No.3

Limb preservation

Amputation

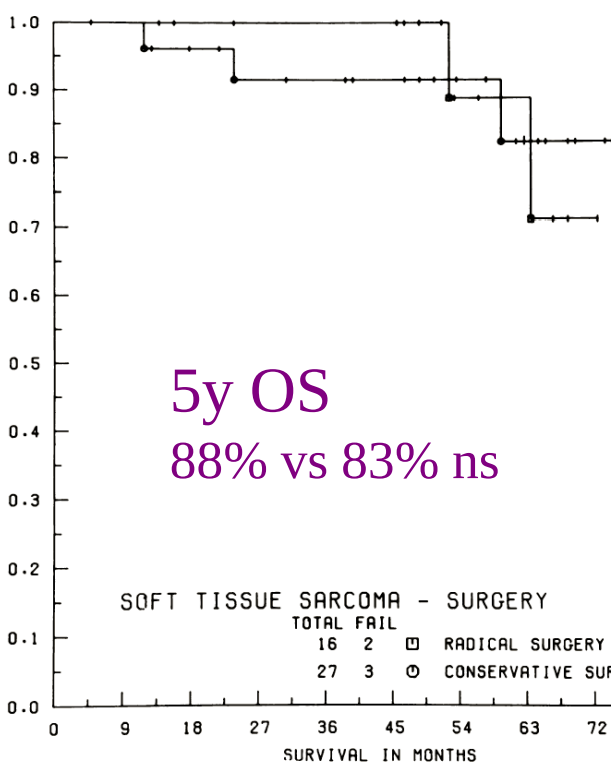
Vs

Wide Excision + 60Gy



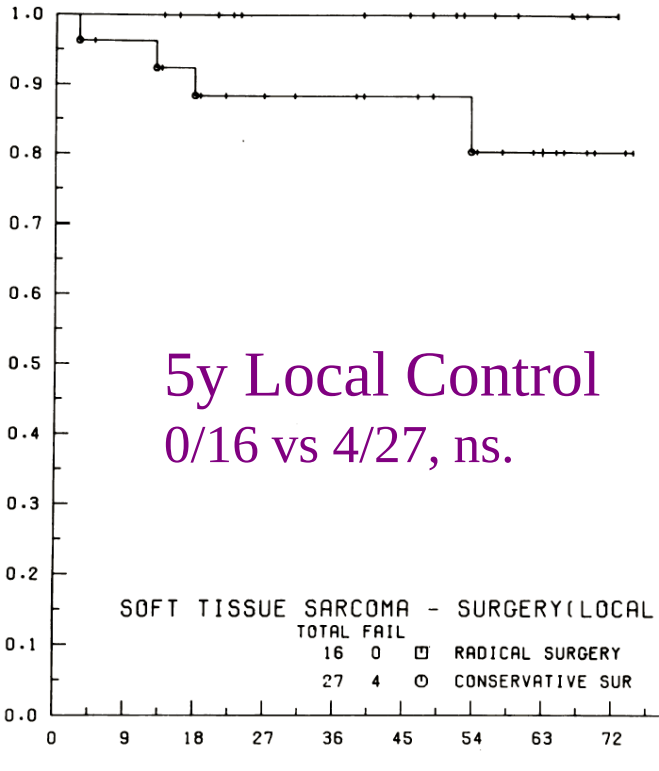
5y DFS

78% vs 71% ns



5y OS

88% vs 83% ns



5y Local Control

0/16 vs 4/27, ns.

Rosenberg et al, Ann Surg Sep 1982 Vol 196 No.3

Randomized Prospective Study of the Benefit of Adjuvant Radiation Therapy in the Treatment of Soft Tissue Sarcomas of the Extremity

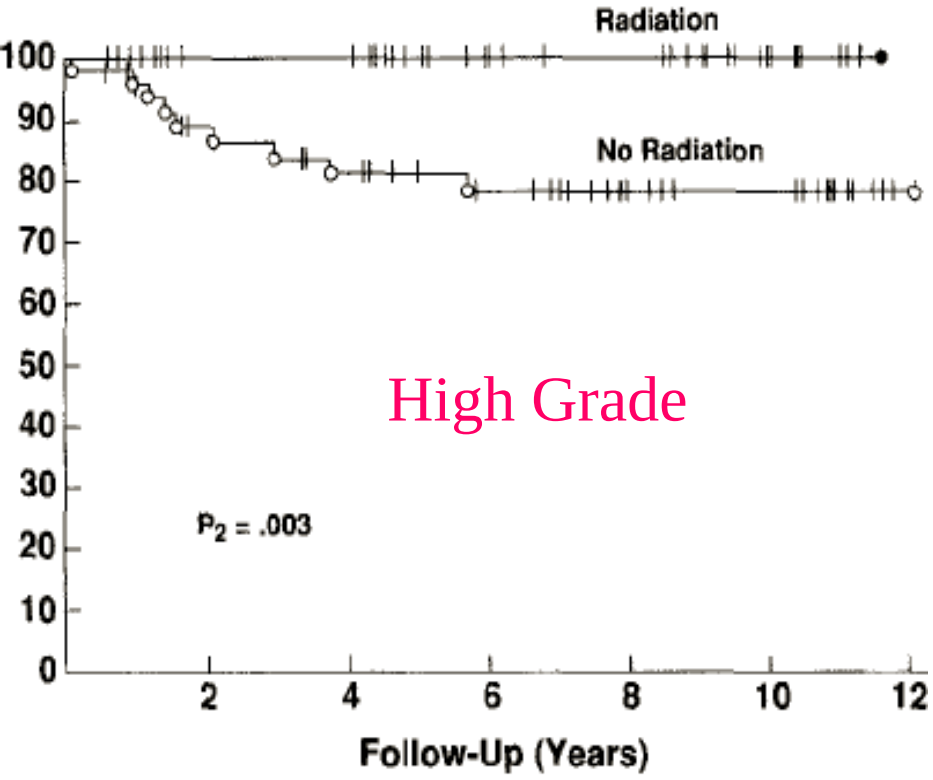
National Cancer Institute, Bethesda, MD.

- Yang et al, JCO 1998 Jan
  - 141 patients (91 high grade, 50 low grade)
  - Randomized to receive **external beam radiotherapy** (EBRT) or not
  - **High grade** received adjuvant chemotherapy
  - LF rate @ 10y
    - High grade 0% with RT, 22% without (p=0.0001)
    - Low grade also benefited (p=0.003)
  - No difference in **OS** regardless of grade

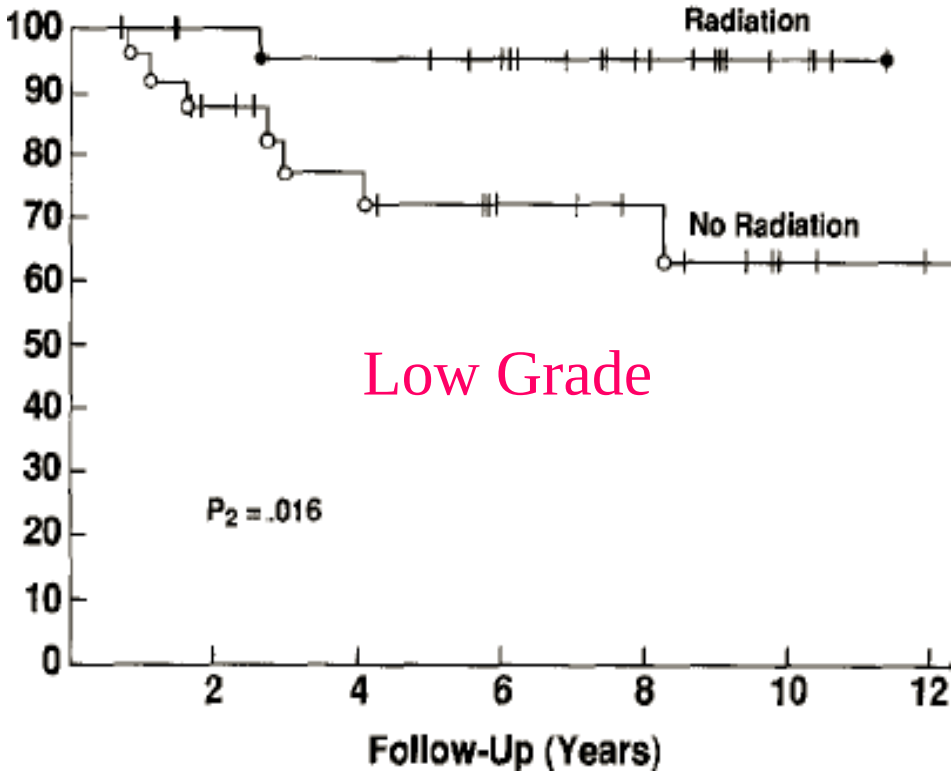
Wide Excision:

NCI, Ph III. Yang. JCO 1998.

Local Control



High Grade



Low Grade

No difference in overall survival

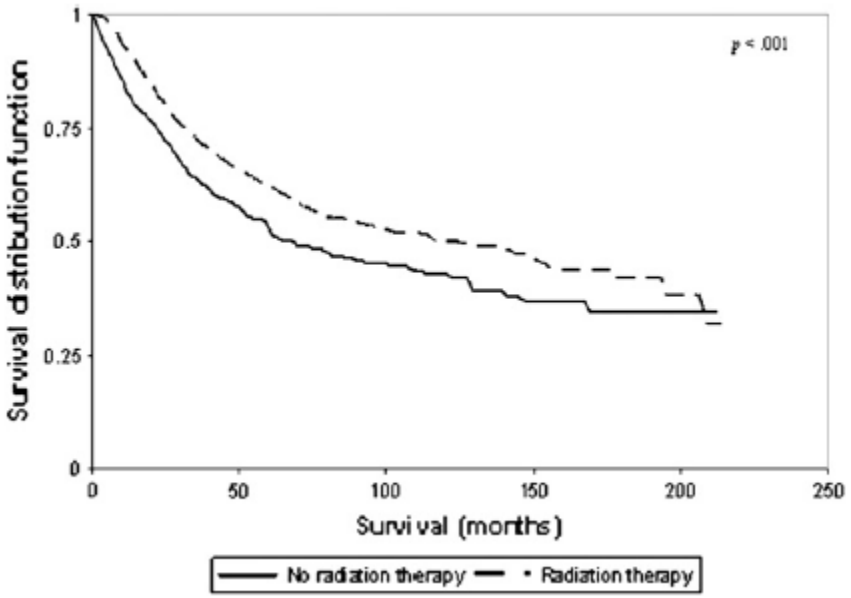
Taylor & Francis
healthsciences

A Systematic Overview of Radiation Therapy Effects in Soft Tissue Sarcomas

- Strander et al, Acta Oncologia 2003
  - **Systematic review** of 5 RCTs, 6 prospective studies, 25 retrospective studies, 3 other articles involving 4579 patients who had RT for STS
  - Local control rate with adj RT ~ 90%
  - **Conclusion**: 'Strong evidence that adjuvant radiotherapy improves the **local control** rate in combination with conservative surgery in the treatment of STS of extremities and trunk in patients with negative, marginal or minimal microscopic positive surgical margins.'

IMPROVED SURVIVAL WITH RADIATION THERAPY IN HIGH-GRADE SOFT TISSUE SARCOMAS OF THE EXTREMITIES: A SEER ANALYSIS

- Koshy et al, IJROBP May 2010
  - **SEER database analysis** of **6960** patients
  - OS @ 3y
    - High grade 73% w/ RT vs 63% no RT **(p<0.001)**
    - Low grade **no significant difference**



Chosing patients properly

- Factors to consider
  - Tumour **grade**
    - Low grade (G1)
    - Intermediate – High grade (G2-3)
  - Tumour **size**
    - ≤5cm (T1)
    - >5cm (T2)
  - Tumour **depth**
    - Superficial (a)
    - Deep (b)
  - **Margins** of resection
    - <1cm
    - ≥1cm
- Staging system reflects these prognostic factors

Primary tumor (T)[a]				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Tumor 5 cm or less in greatest dimension			
T1a	Superficial tumor			
T1b	Deep tumor			
T2	Tumor >5 cm in greatest dimension			
T2a	Superficial tumor			
T2b	Deep tumor			
Regional lymph nodes (N)[b]				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Regional lymph node metastasis			
Distant metastasis (M)				
M0	No distant metastasis			
M1	Distant metastasis			
Anatomic stage/prognostic groups				
Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a	N0	M0	G3
	T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

Indications

Stage I (G1)

- **Surgery**
- Margins
  - ≥ 1cm or intact fascial plane – observation*
  - <1cm without intact
- >5cm – pos

Stage II – III (G2-3)

- Surgery + **RT**
- Can omit RT in ≤ 5cm, superficial lesion excised with ≥ 1cm margin*

* Baldini EH, Goldberg J, Jenner C, et al. Long-term outcomes after functon-sparing surgery without radiotherapy for soft tissue sarcoma of the extemities and trunk. J Clin Oncol 1999;17:3252.

	10y local control (%)	
Margin <1cm	87±6	
Margin ≥1cm	100	p = 0.04

Aims of Sarcoma Treatment - Role of RT

1. Local Control ✓
2. Survival X

3. Limb salvage ✓
4. Retaining function ✓
5. Cosmesis ✓

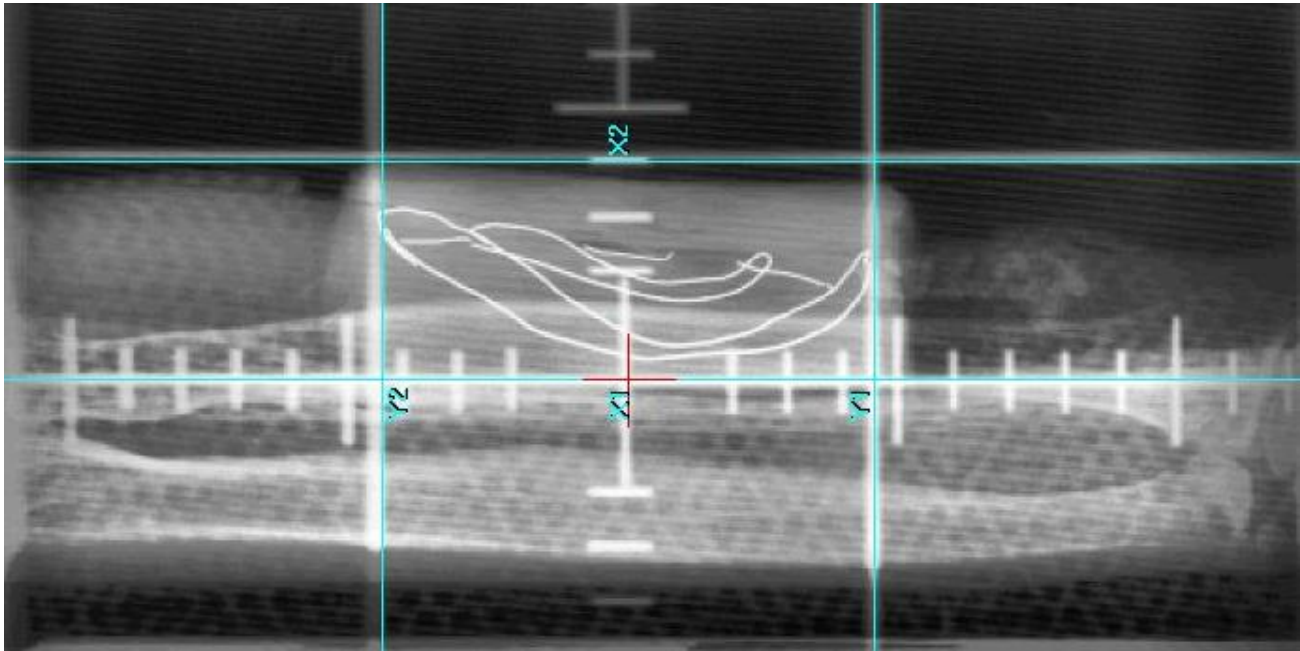
6. Unresectable disease ✓
7. Palliation ✓

How RT is done

Positioning Immobilisation

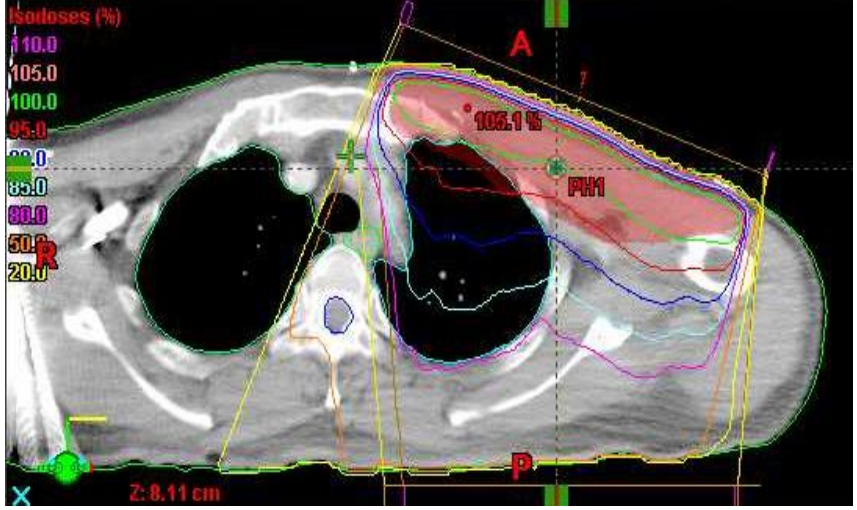
Get Creative

Simulation



CT Planning

PHASE 1



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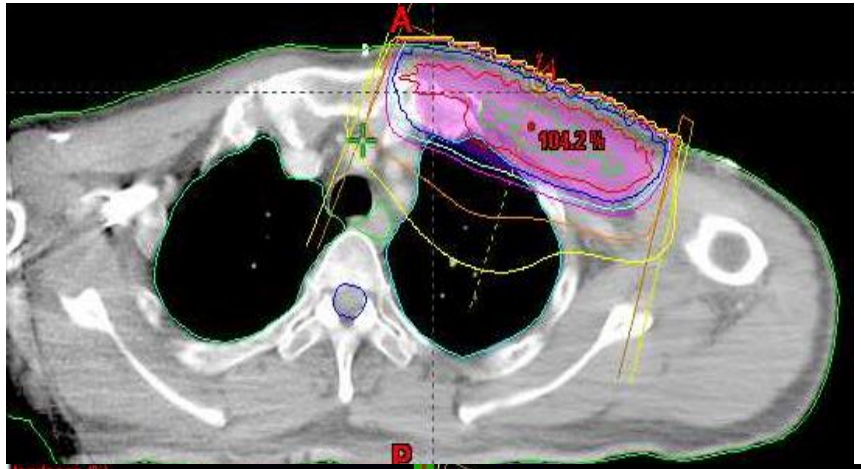

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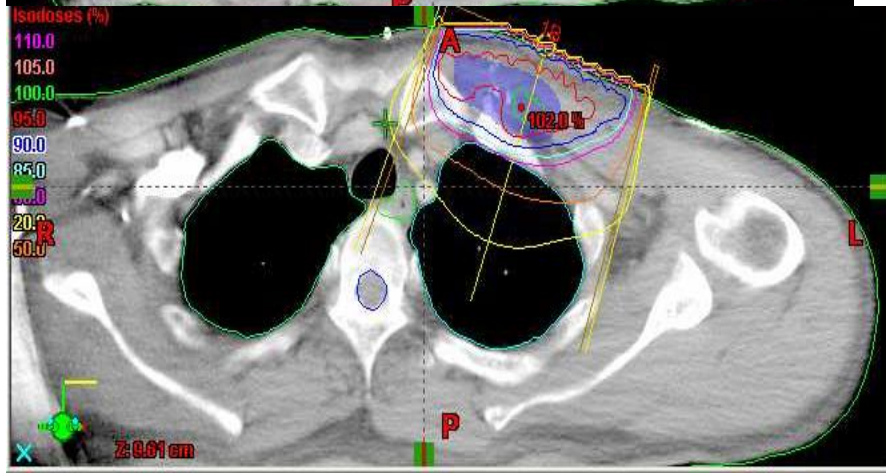
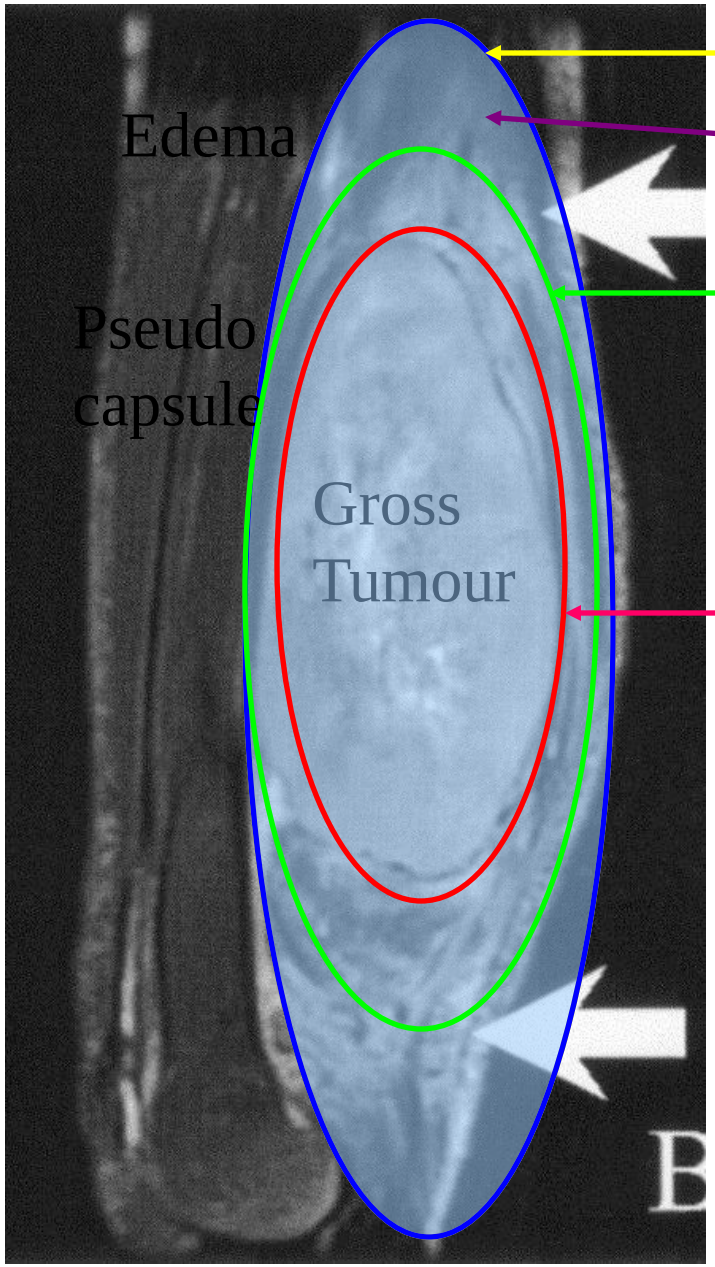


Microscopic Extention

Surgery



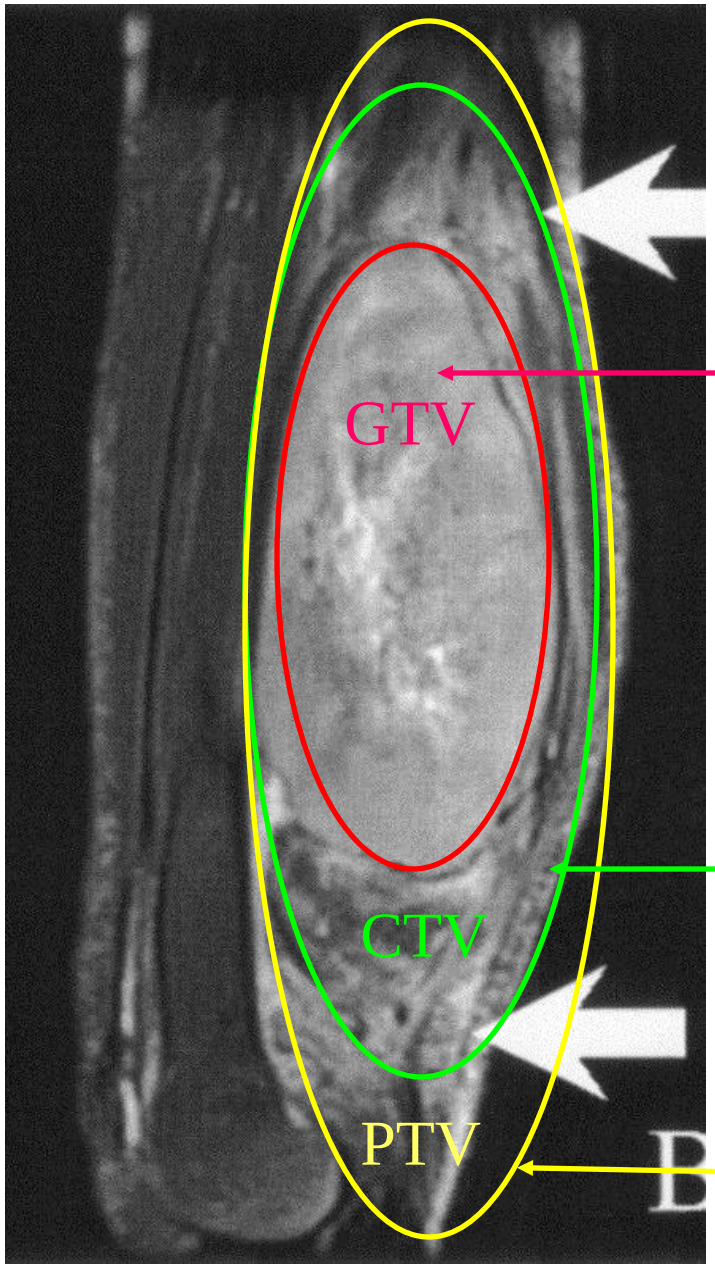
Radical Surgery

Adjuvant Radiation

Wide excision

Marginal excision

Target Volumes & Margins



Gross Tumour Volume
(no margin)

Clinical Target Volume
Margin 5cm ↕ 2cm ↔

Planning Target Volume
Another 0.5cm

Treatment Delivery

Daily, 5 fractions/week

Phase I: Wide Margins. 50Gy/25#,

Phase II: 2cm margins. 10Gy/5#,

Phase III: 1cm around margin+. 6-10 Gy

What’s new

1. Reducing Toxicity
2. Improving control

REDUCING TOXICITY

1. Preoperative RT
2. Reducing treated volume
3. IMRT/Tomo/Proton
4. Patient Selection

Timing for RT

- Traditional approach is to give RT **post-operatively**
  - Allows **histologic** examination especially of margins
  - This information directs RT **dose/delivery**
  - Given **4-6 weeks** after surgery ideally – allow for wound healing
- Pre-operative vs post-operative RT is still debated
- Rationale of pre-op RT
  - Reduce tumour burden before resection - more conservative surgery?
  - Smaller RT fields
  - Lower RT doses

Reducing Toxicity

1. PRE-OPERATIVE RT

- Smaller volumes radiated
- Lower doses applied

} Less radiation toxicity

- Less tissue hypoxia
- Potential downstaging

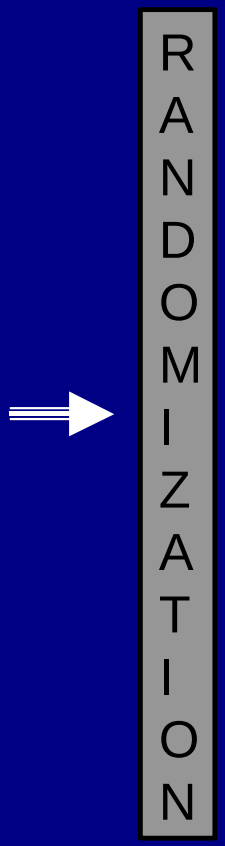
Preop RT:

NCIC PhIII. O'Sullivan et al, Lancet 2002.

CTOS 2004

SR-2 Trial (NCIC CTG / CSG)

- Extremity Soft tissue sarcoma (appropriate histology)
- No chemotherapy
- Any T,N0,M0
- Any grade
- Combined modality treatment needed:
  - ? Surgical and Radiation Oncology opinion
- Stratification at 10 cm cut-point



Pre-op RT
- 50 Gy in 25 fractions
- Phase 2 to 66 Gy, if margins positive

Phase 1: 5 cm longitudinal
2 cm axial

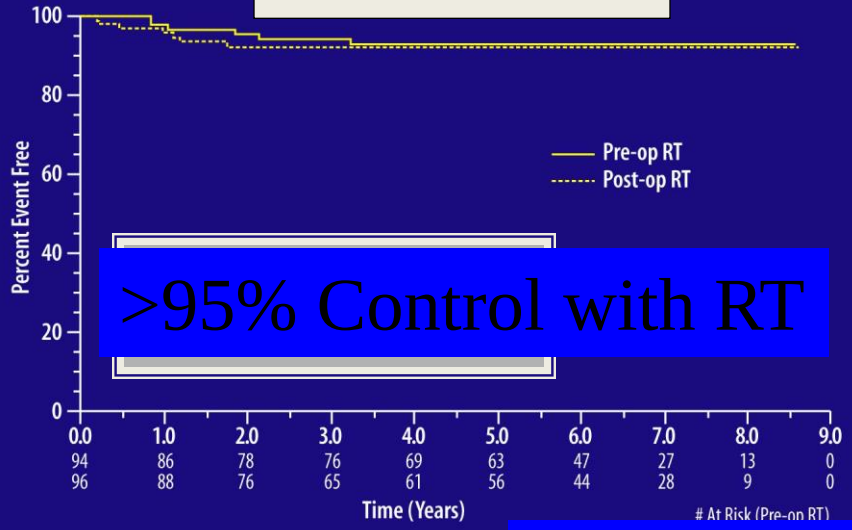
Phase 2: 2 cm coverage

Post-op RT
- 50 Gy in 25 fractions
- Phase 2 to 66 Gy, all cases

National Cancer Institute of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe des essais cliniques

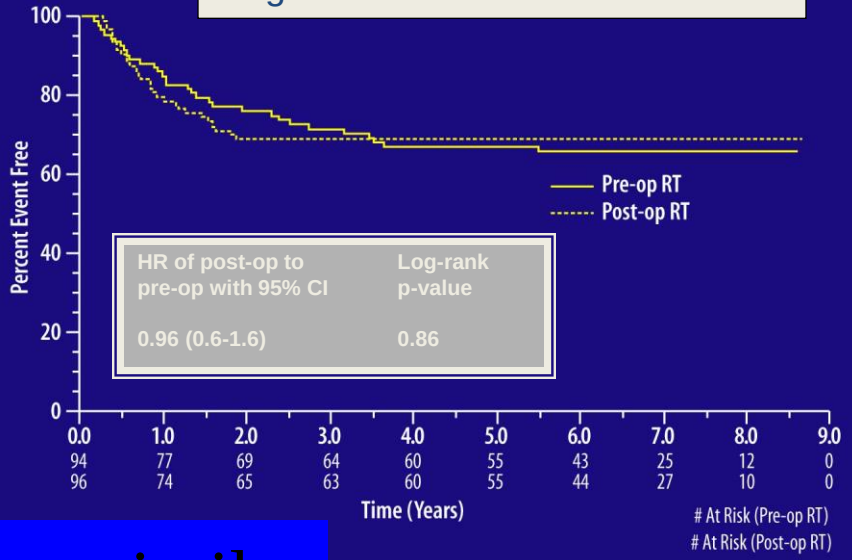
Princess Margaret Hospital

Local recurrence free



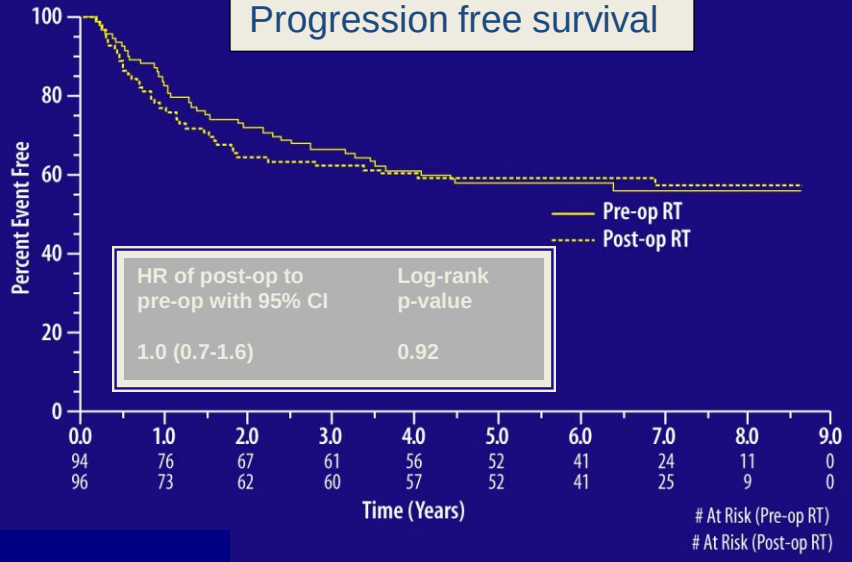
>95% Control with RT

Regional / distant recurrence free

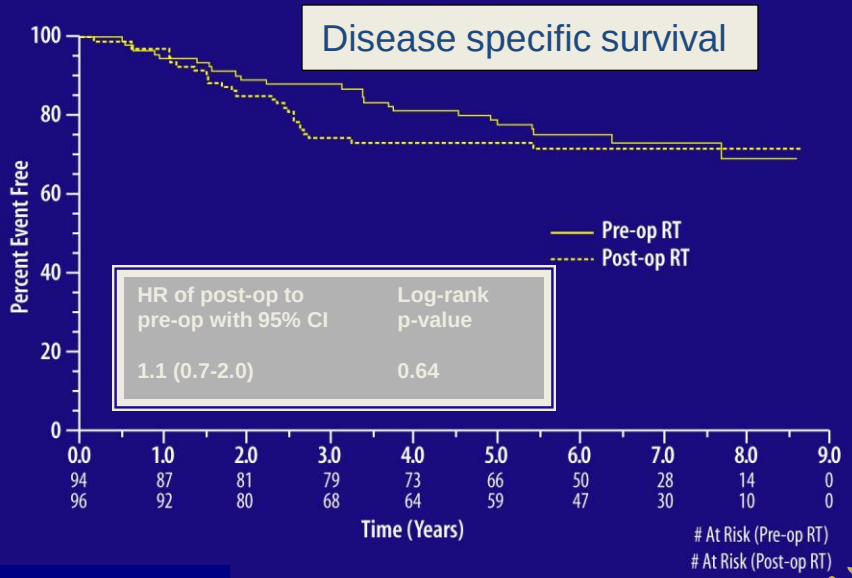


Cancer outcomes similar

Progression free survival



Disease specific survival



Toxicity	Preop	Postop	p
Acute wound complications	**35%**	17%	.01
Fibrosis	**32%**	48%	.07
Edema	**15%**	23%	NS
Stiffness	**18%**	23%	NS

Morbidity profiles of Preop RT:

- **More Acute** (*recoverable*) complications
- **Less Late** (*permanent*) tissue effects:

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

- O'Sullivan et al, Lancet 2002
  - 182 ESTS patients
  - Comparing **pre-op** (50Gy in 25f) vs **post-op** (66Gy in 33f) RT
  - Primary endpoint – major **wound** complications
- Wound complications
  - Pre-op 35% vs Post-op 17%
  - Difference predominantly in **lower limb**
- ASCO Update 2004: **No difference** in local control, progression-free survival, overall survival at **MFU 6.9y**
  - Not **powered** to formally evaluate these end-points

Pre-op vs Post-op Late Morbidity

- Update in *Radiotherapy and Oncology Apr 2005:* Late complications @ 2 years

>G2	Post-op (%)	Pre-op (%)	P-value
Fibrosis	48.2	31.5	0.07
Oedema	23.3	15.5	ns
Joint stiffness	23.2	17.8	ns

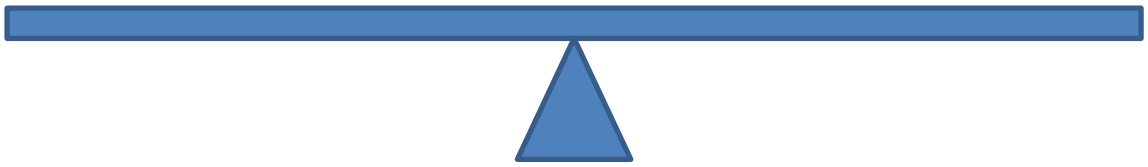
Davis AM et al

- **RT Field size** was predictive of greater rates of fibrosis and joint stiffness and marginally predictive of oedema
- Patient with significant fibrosis/oedema/joint stiffness had significantly lower **function** scores ($p<0.01$)

Pre-op vs Post-op - Summary

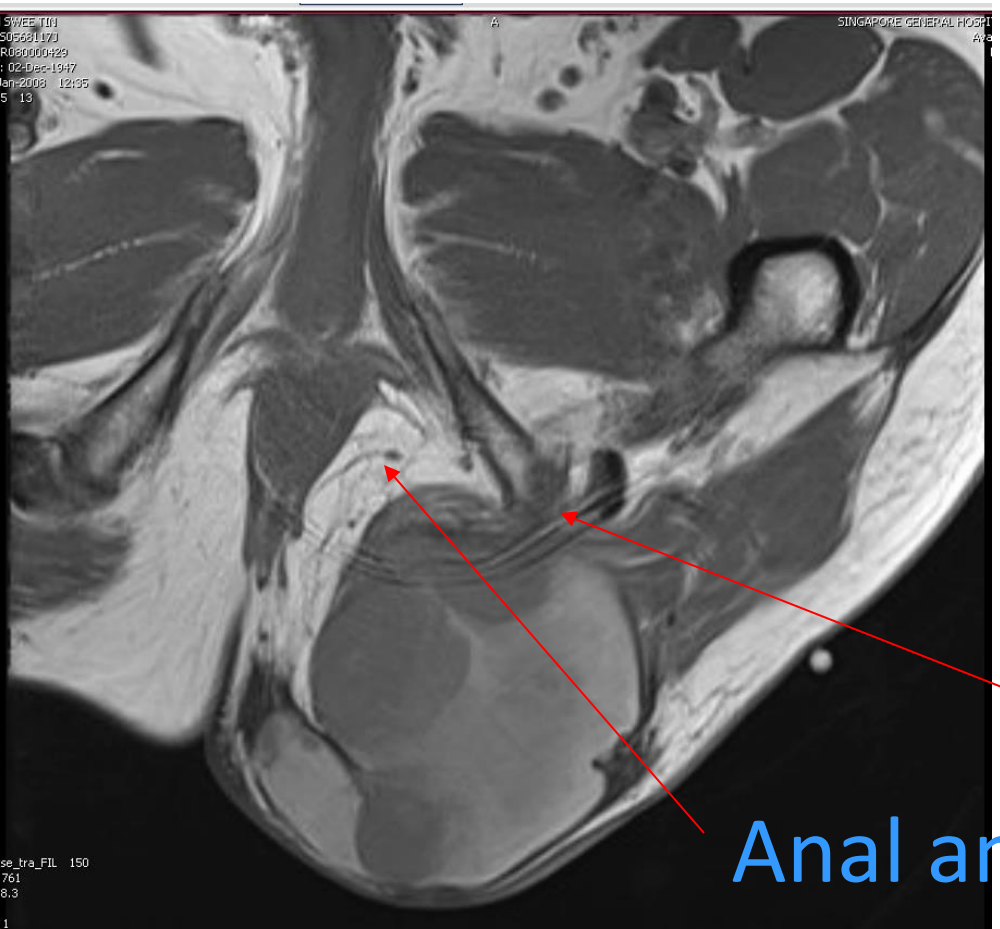
Preop RT
Lower dose (50Gy)
Smaller field size
Reduced fibrosis
Reduced oedema
Increased wound complications (35%)

Postop RT
Higher dose (60-66Gy)
Larger field size
Increased fibrosis
Increased oedema
Wound complication risk as high as 17%



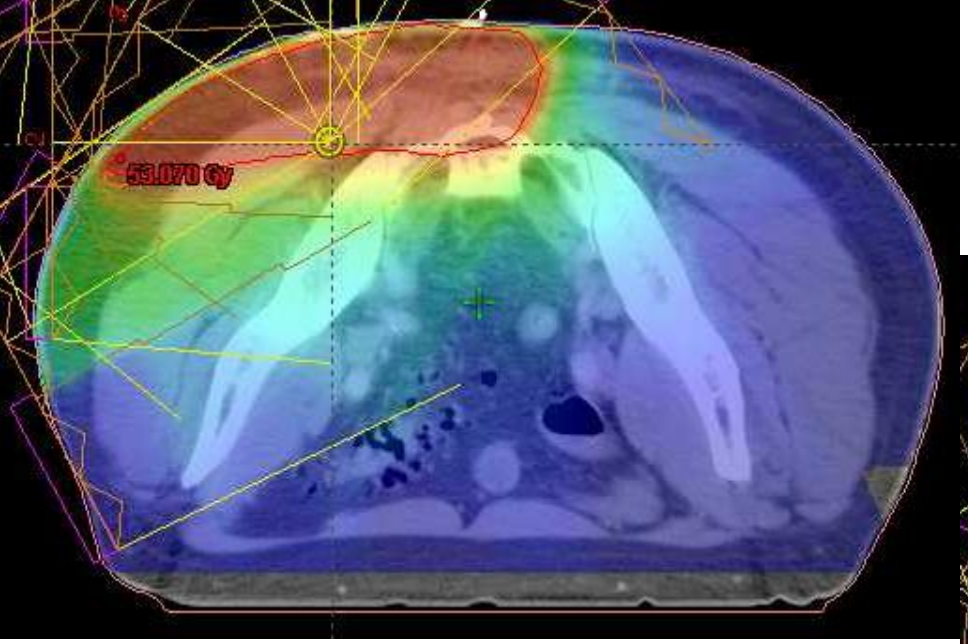
1.May require hindquater amputation
2. May have to sacrifice the anus.
3. Sciatic Neurovascular Bundle at Risk

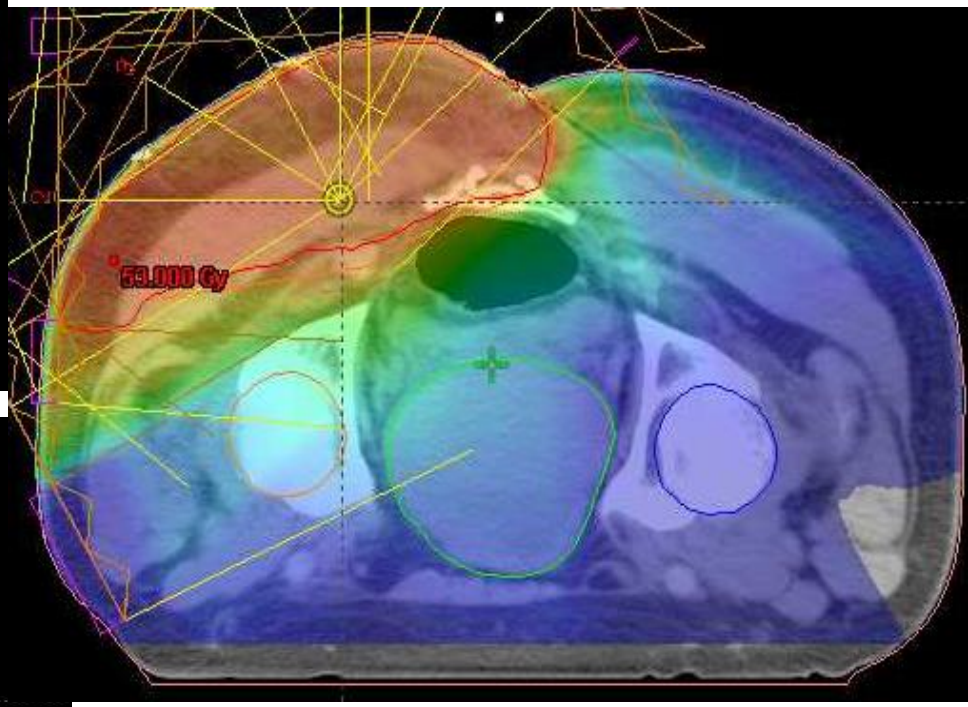
Offered Preop RT.

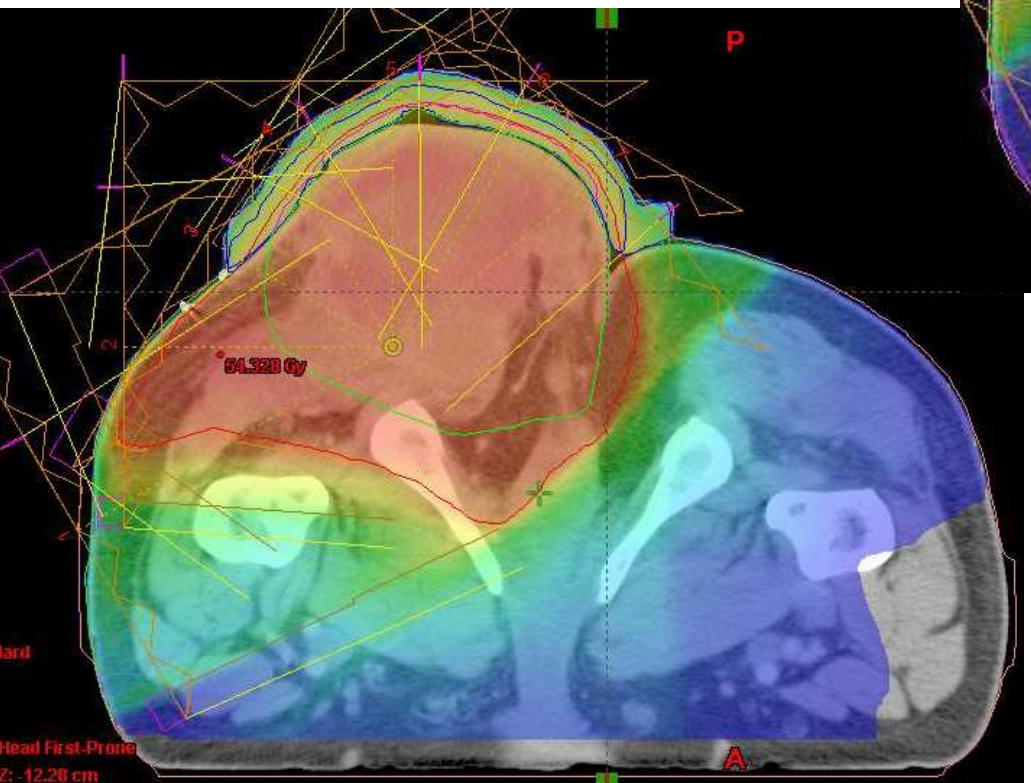


Anal and bony margins at risk

RT







Mass showed a partial response
Underwent limb sparing surgery
Margins(-)

2. Reducing treatment volume?

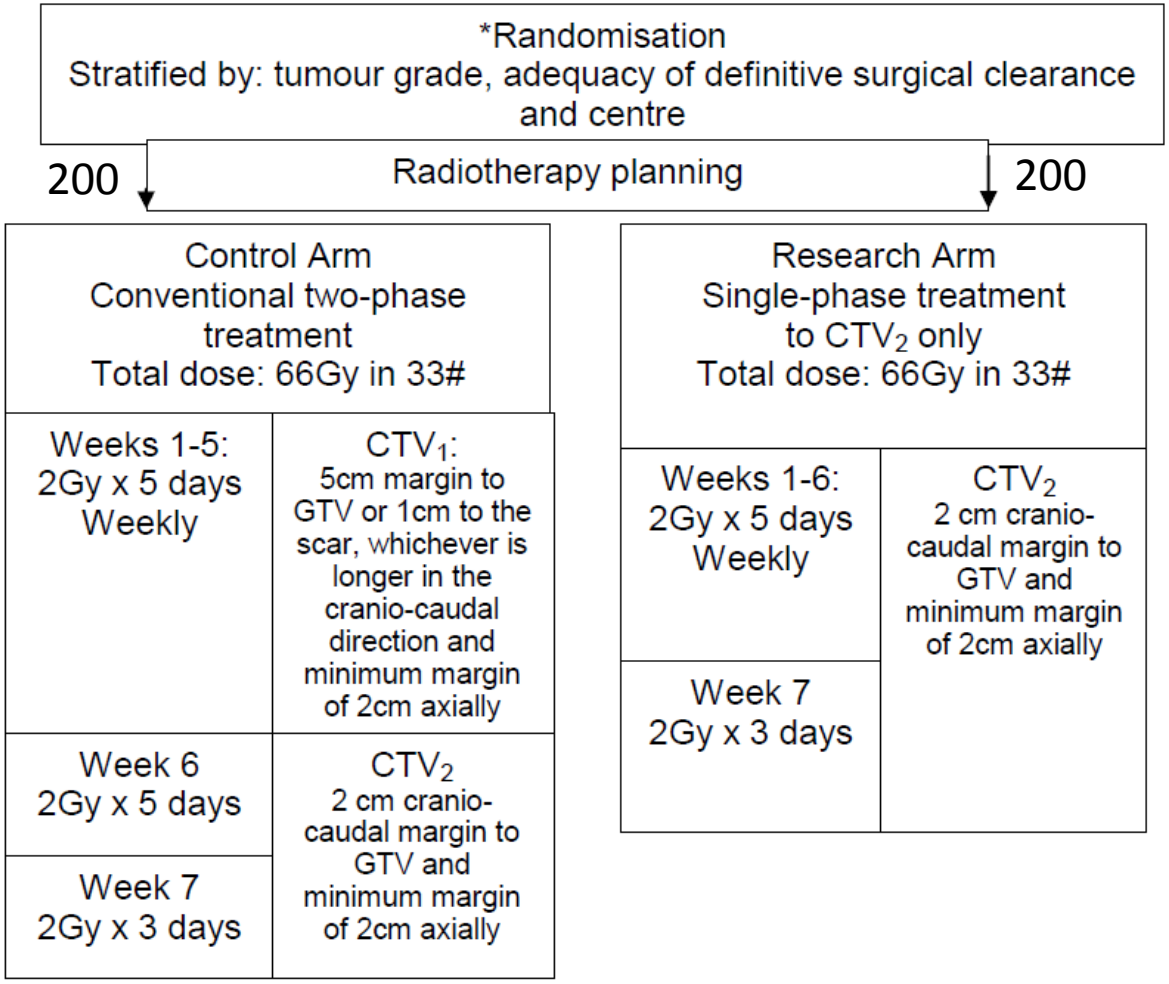
- 'Standard' margin
  - 5cm prox/distal, 2cm radial

- Vortex Trial (UK, Ph III, adj RT)
  - Proximal&Distal margin: *5cm vs 2cm*

- RTOG Phase II (preopRT)
  - Tumour + edema + 2cm margin

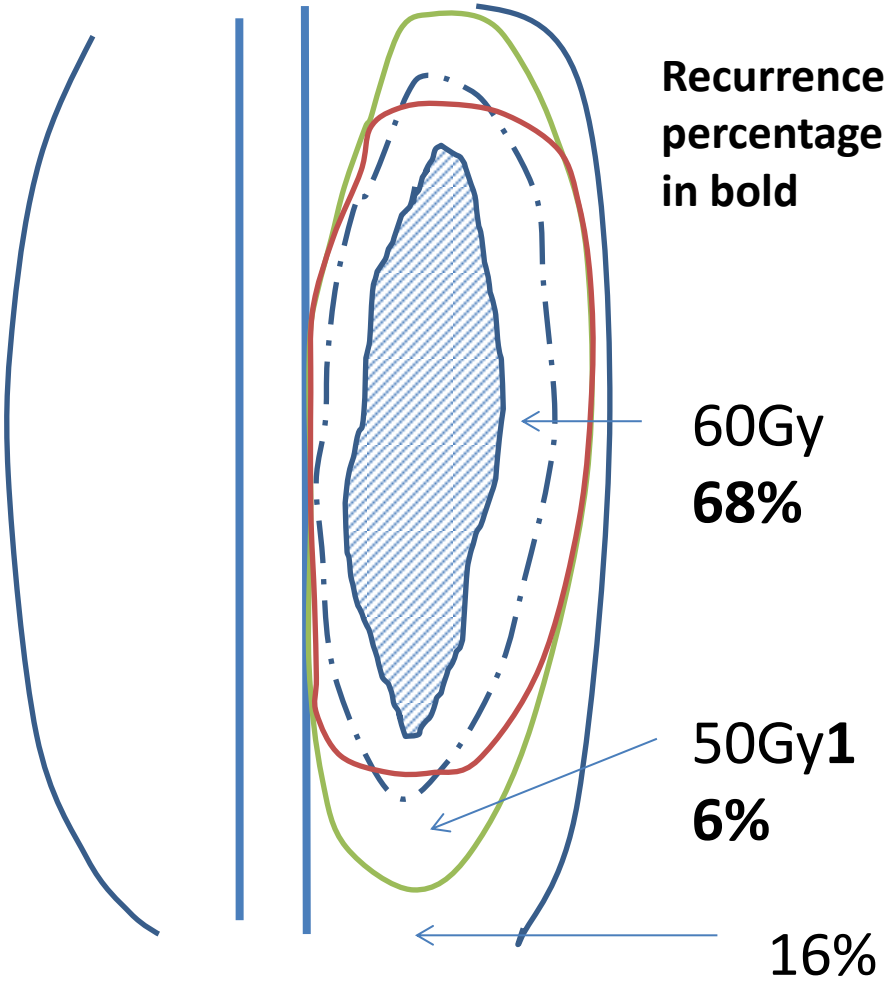
2. Reducing Volume - Vortex Trial

- Primary endpoints
  - Limb function (TESS)
  - Time to local recurrence
- TESS
  - Toronto Extremity Salvage Score
  - Patient completed measure of physical disability



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

- Rationale
  - RMH study suggested majority of recurrences in **high-dose region**[1]
  - **Brachytherapy** RCT showed good control rates even though treatment volume was only 2cm beyond tumour bed
  - Pre-op vs post-op trial showed late morbidity correlated with radiotherapy **field size**
  - 'Giving a high dose where you need it'
- Recruitment 2007 – 2013 (UK)

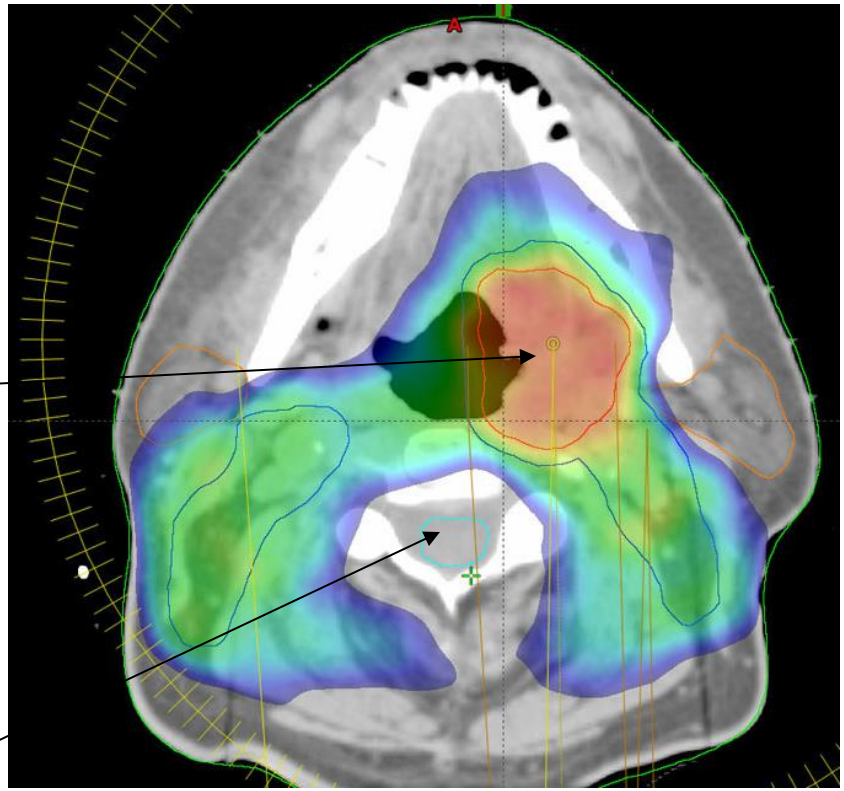


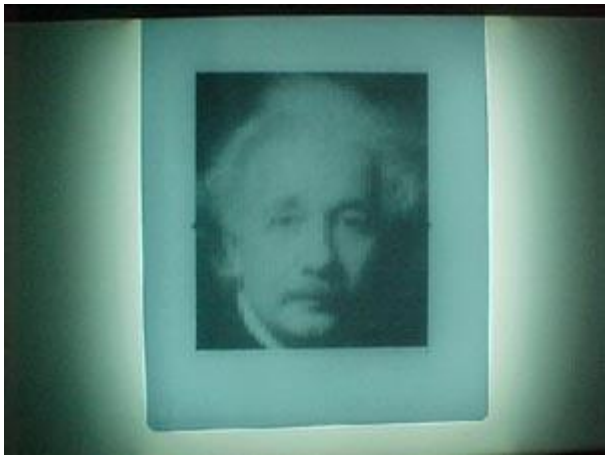
[1] *Cleator et al* Sarcoma 2001

Reducing Toxicity: volume conformity

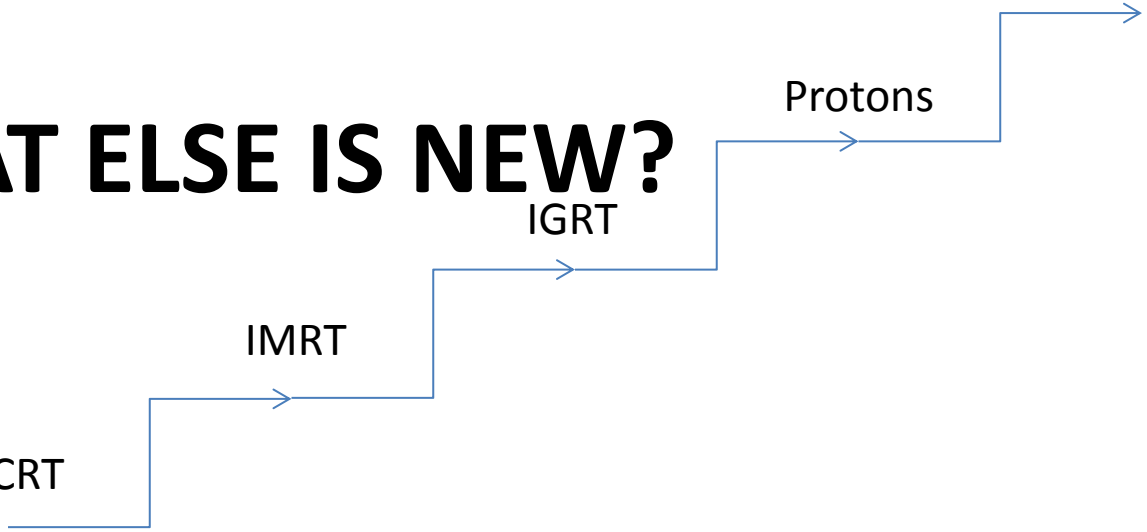
3. Intensity Modulated RT

- Multiple Beams, varying intensity
- Varying doses - boost high risk areas.
- ‘odd-shaped’ volumes, avoid critical organs



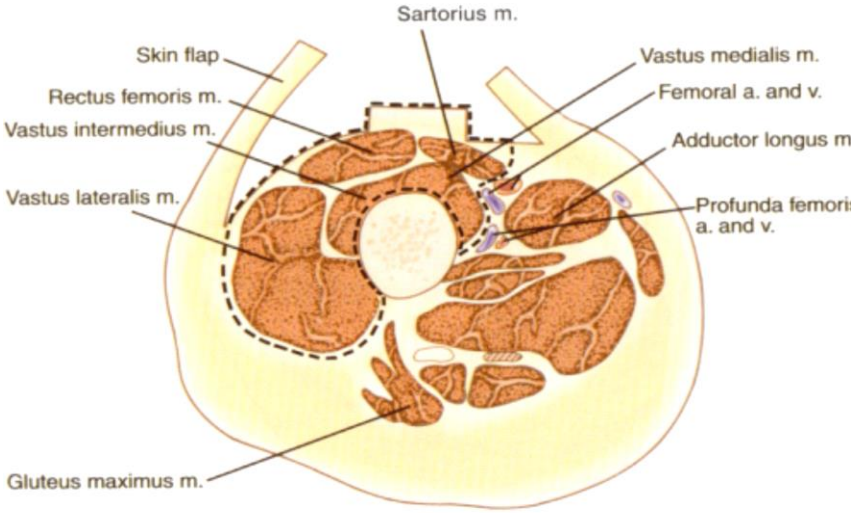


WHAT ELSE IS NEW?

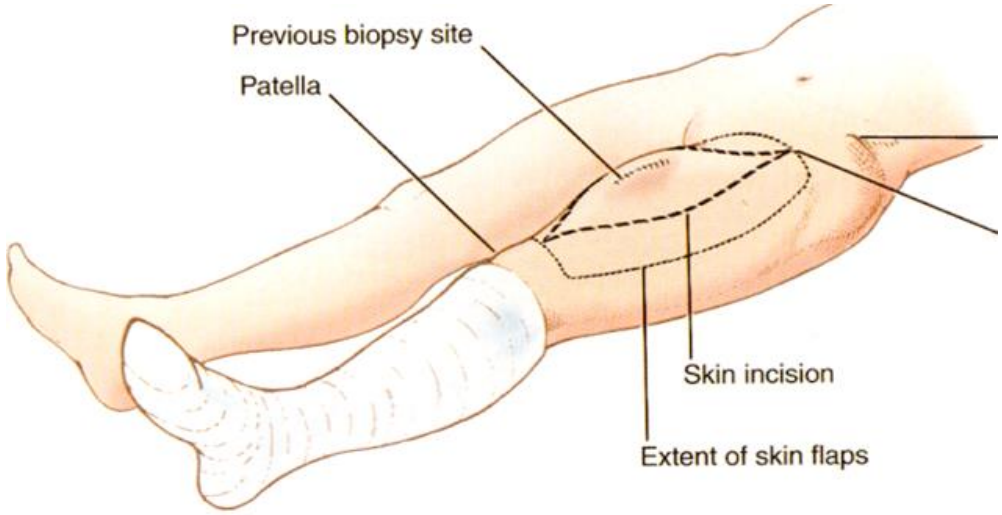


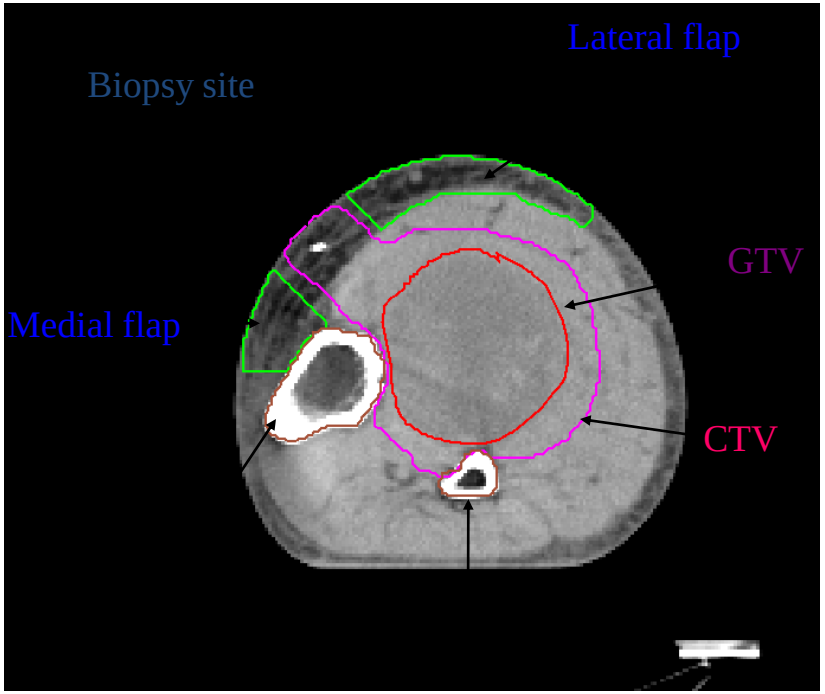
IMRT

- Spare Flap
  - (reduce wound complications for preop RT)



- Spare bone
  - Reduce fracture risk



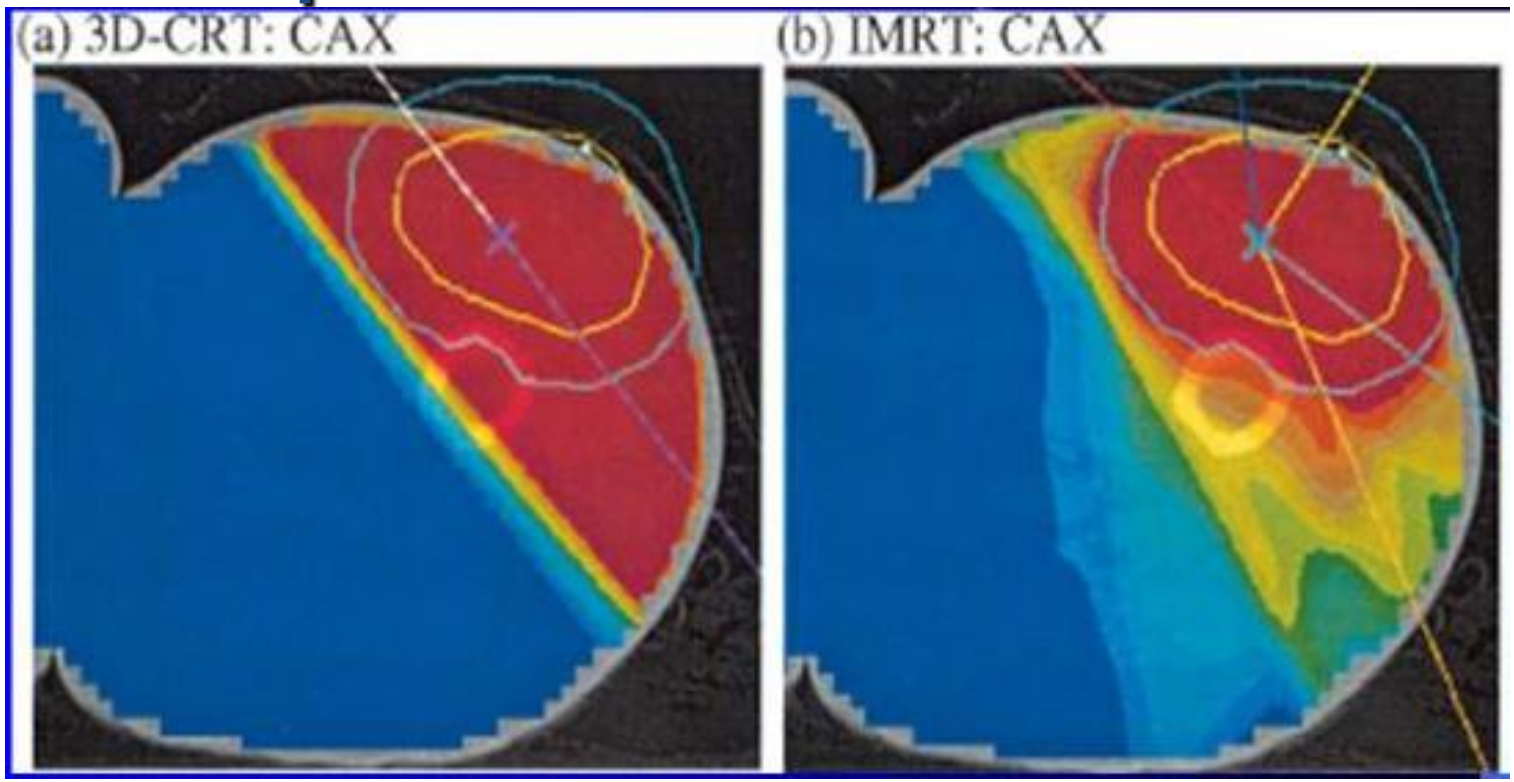


Intensity Modulated Radiotherapy (IMRT)

- Able to conform to the shape of intended treatment target
- Minimize dose of RT to surrounding normal structures
- Particular advantage in sparing bone which is a natural barrier to local spread

Hong et al, IJROBP 2004

Plan comparison:



24 patients	**Conformal Plans**	**IMRT Plans**
Mean dose to flap	40.1	**26.7**
Mean dose to bone	25.9	**21.9**
Mean dose to CTV	50.3	**50.1**

(O'sullivan)

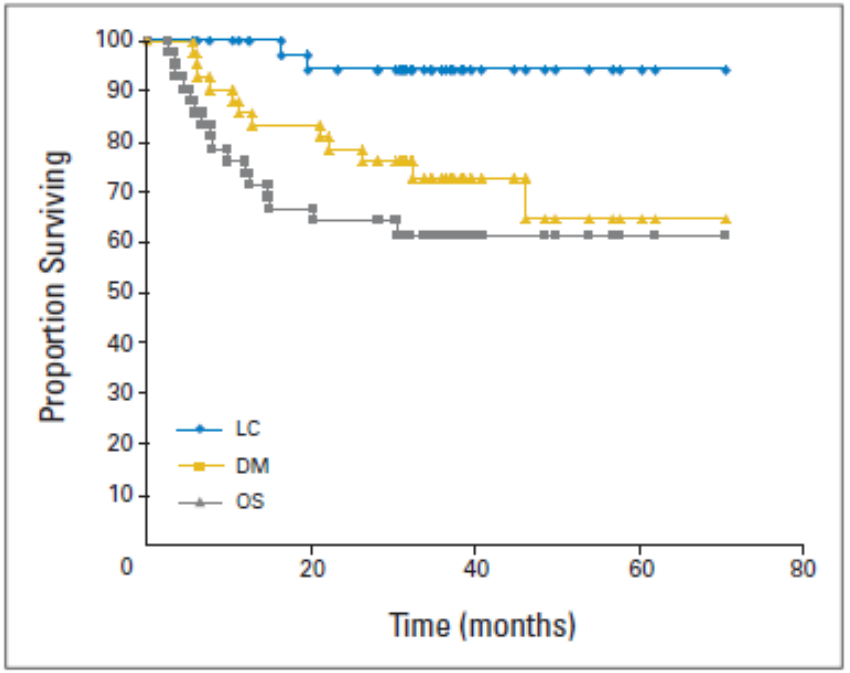
VOLUME 26 · NUMBER 20 · JULY 10 2008
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

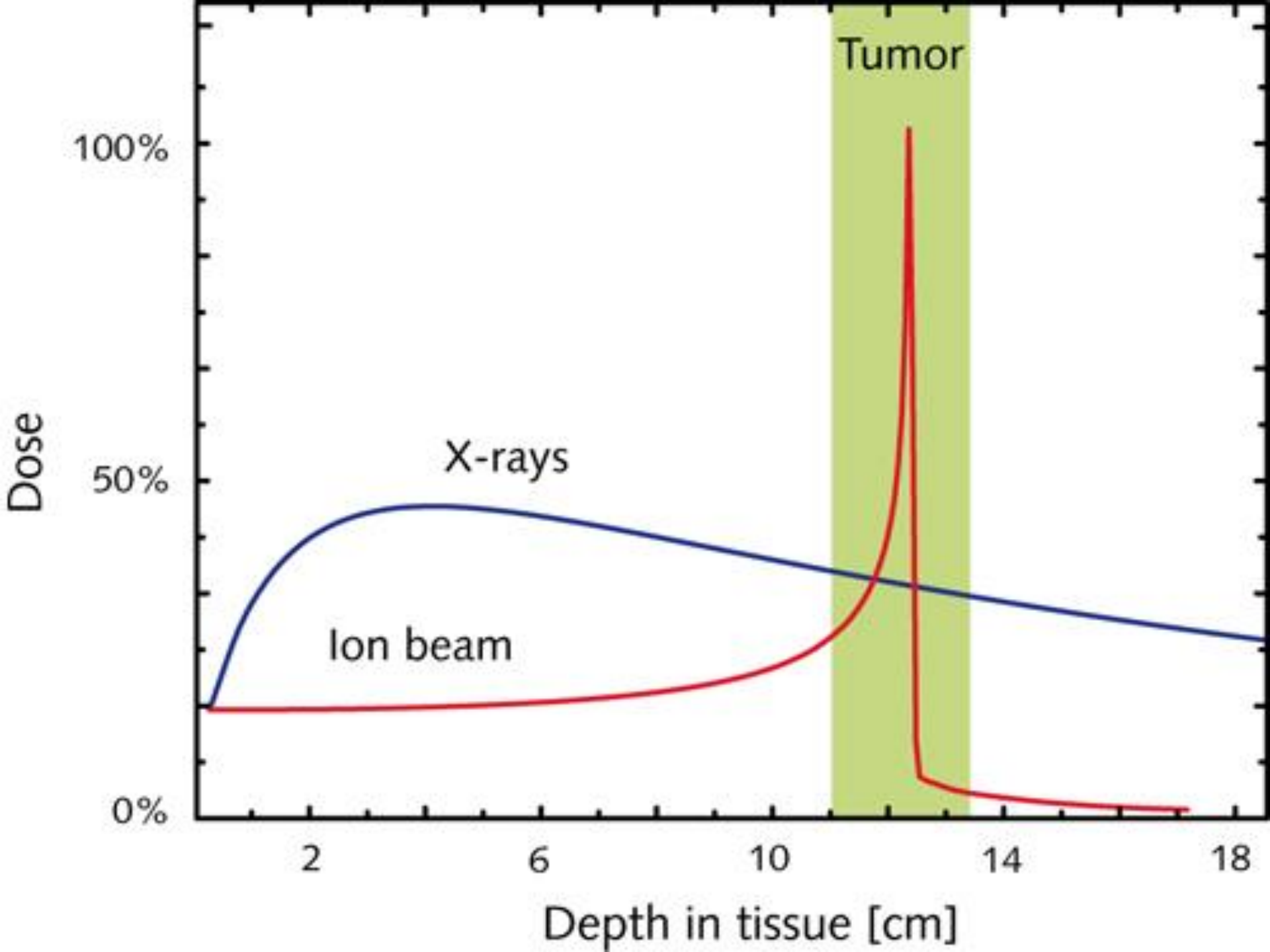
Impact of Intensity-Modulated Radiation Therapy on Local Control in Primary Soft-Tissue Sarcoma of the Extremity

Kaled M. Alektiar, Murray F. Brennan, John H. Healey, and Samuel Singer

- MSKCC r**etrospective** study
- 41 patients
  - 51% **positive/close** margins
  - 68% tumours **>10cm**
  - 83% **high grade**
- 50Gy Preop IMRT (7) or ~63Gy Postop IMRT (34)
- Complications
  - 2 (4.8%) fractures not req op
  - 32% edema (all <G3 – less than 30% discrepancy)

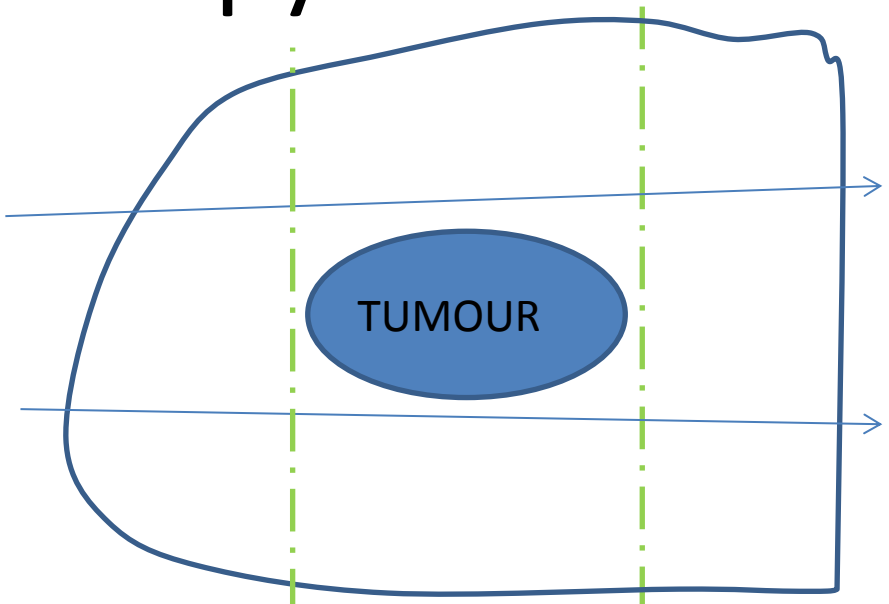
MFU 35m	5-year (%)	95% CI
LC	94	86-100
DMFS	61	45-76
OS	64	45-84

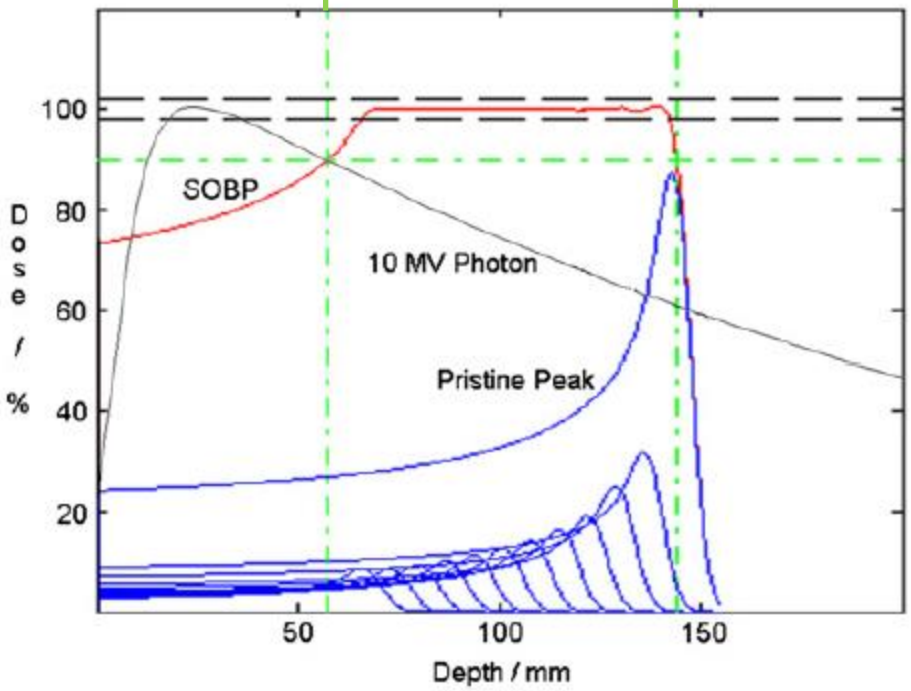


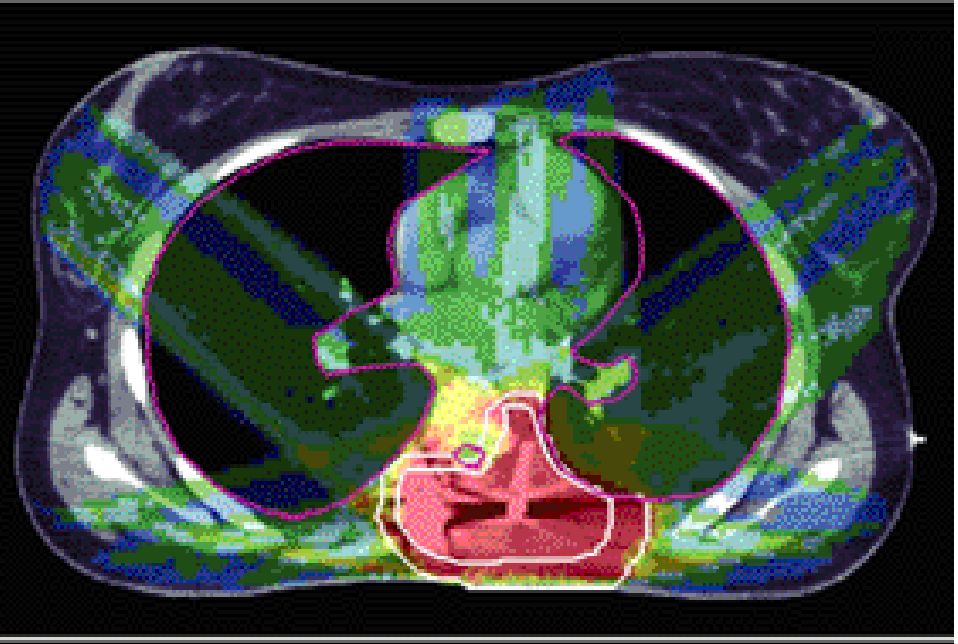

Tumor
100%
50%
0%
Dose
X-rays
Ion beam
2
6
10
14
18
Depth in tissue [cm]

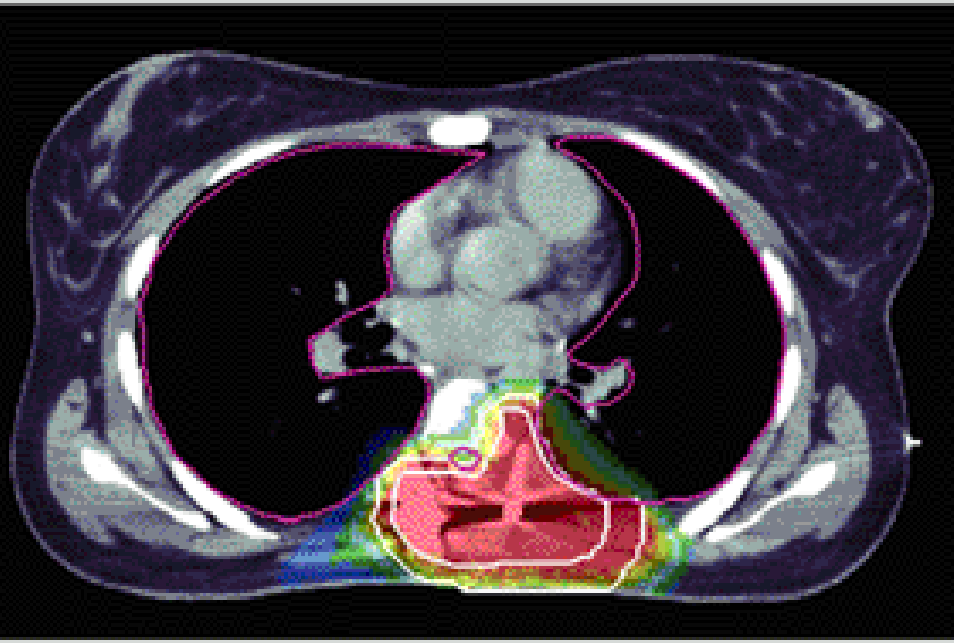
Proton Therapy

- Rationale
  - 60% reduction in radiation dose to normal tissue
    - Lower dose region **proximal** to tumour
    - Uniform dose **in region** of tumour
    - Close to **zero** dose **beyond** tumour
- Extensive use in **skull base/spinal sarcomas**
- Potential in ESTS
  - **Large, medial prox** thigh tumours
    - Spare femur, hip joint, genitalia, anorectal tissues
  - **Shoulder** lesions
    - Spare lung apex, shoulder joint









Paraspinal Epithelioid Sarcoma

IMRT

Protons

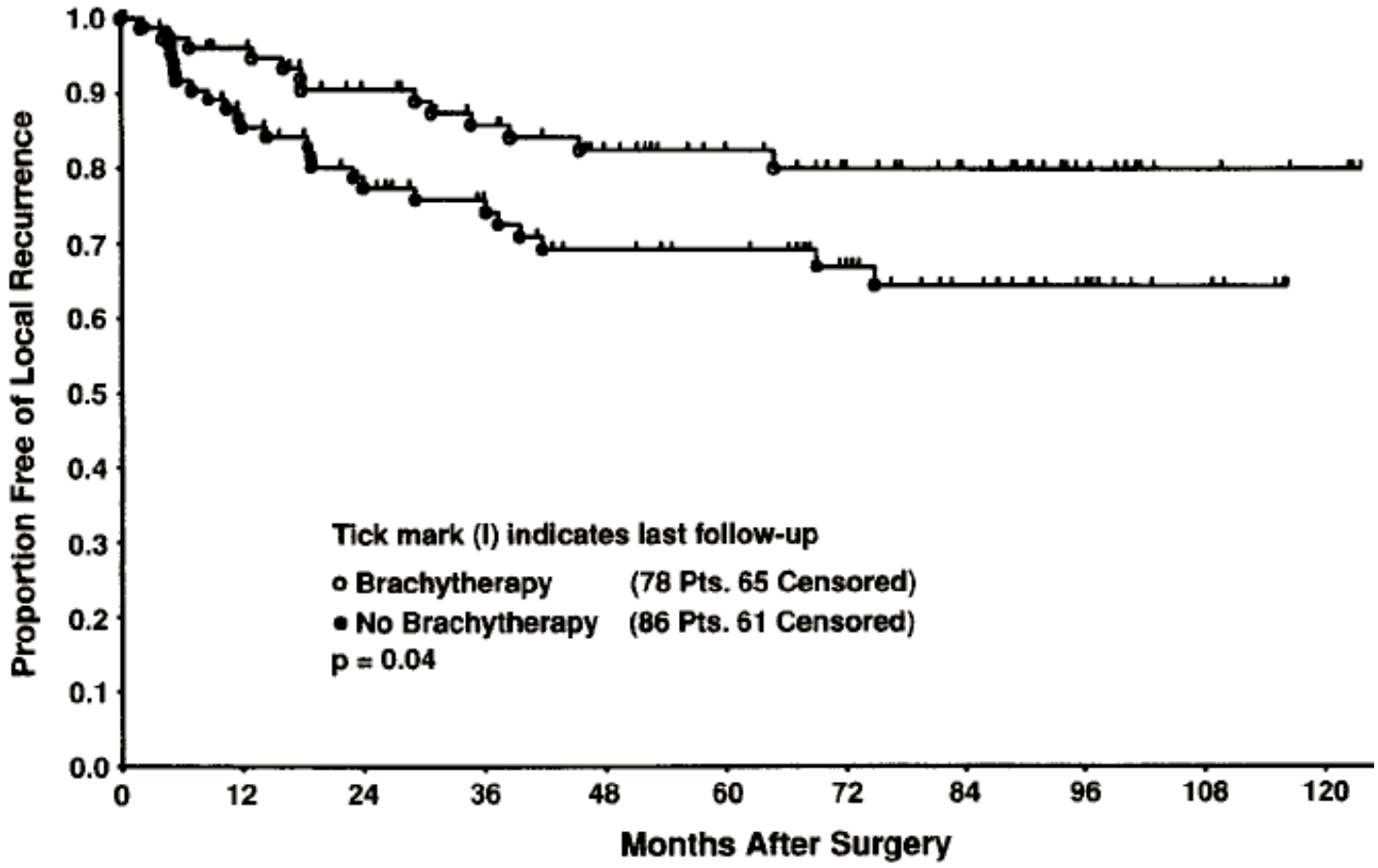
Lower integral dose

Long-Term Results of a Prospective Randomized Trial of Adjuvant Brachytherapy in Soft Tissue Sarcoma

- Pisters et al, JCO 1996 Mar
  - 164 patients
  - Randomized to post-operative **brachytherapy** (BRT) or not
  - Freedom from local recurrence @ 5y
    - High grade 89% with BRT, 66% without (p=0.0025)
    - Low grade no impact (p=0.6)
  - No significant impact on **distant metastasis** or **disease specific survival**

Brachytherapy:

MSKCC, Ph III. Harrison. JCO 1996.

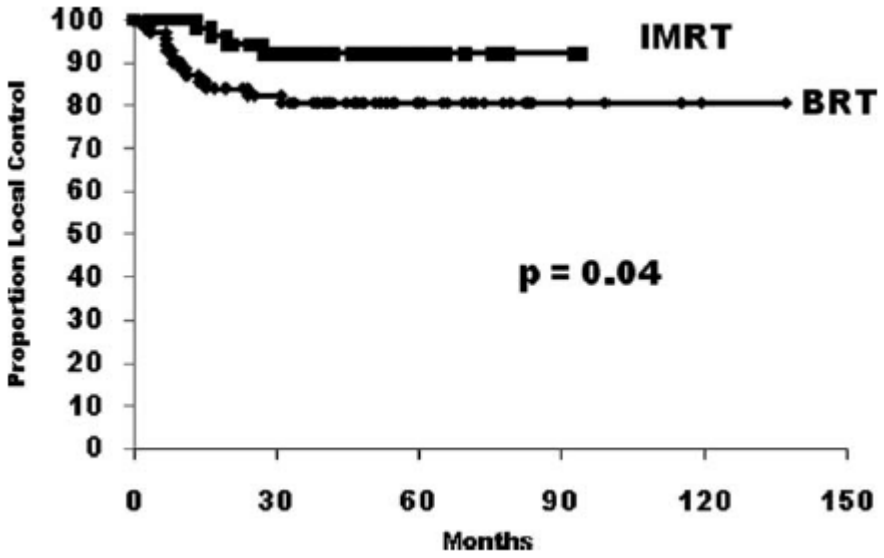


42-46Gy LDR, from 6th POD. (Benefit for High Grade only).

Local Control Comparison of Adjuvant Brachytherapy to Intensity-Modulated Radiotherapy in Primary High-Grade Sarcoma of the Extremity

Kaled M. Alektiar, MD[1]; Murray F. Brennan, MD[2]; and Samuel Singer, MD[2]

	IMRT	BRT	p
Size >10cm	48	30	.005
Margin +/close	49	20	.006
Periosteal/bone resection	30	13	.02
Nerve resection	54	14	.002
5y LC	92	81	.04



'On **multi-variate** analysis, IMRT was the **only** predictor of improved local control'

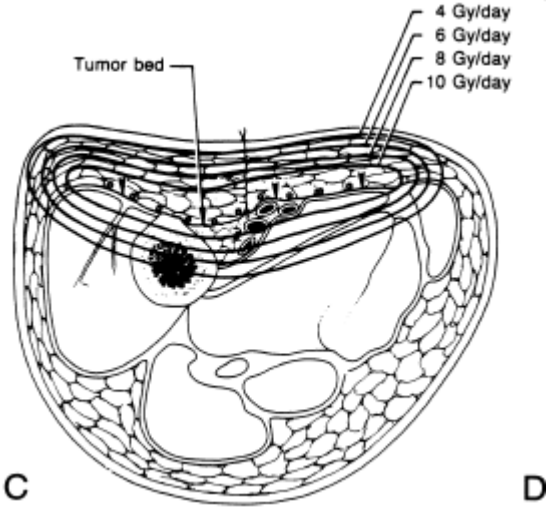
Cancer 2011;117:3229–34.

BRACHYTHERAPY

- Why brachytherapy

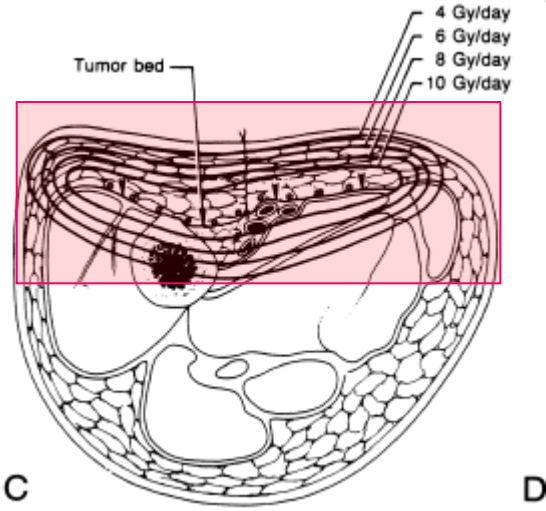
Advantage

- high doses to tumour bed
- Low overall dose to normal tissues



Role

- As *main* RT
- As *boost* in combination with EBRT



- Re-treatment, after previous EBRT

Interstitial Brachytherapy

Reducing Toxicity

4. Patient Selection

Can we avoid RT?

Series:

Rydholm JCO 1991. LRR 7%

Baldini JCO 1999. LRR 10%

Alektiar JCO 2002. LRR 20% (no RT), 16% (with RT)

Randomised:

NCI JCO 1998. LRR 28% (no RT), 2% (with RT)

Indications for Adjuvant RT

1. All High Grade STS.

2. Low-Int Grade STS with close or positive margins.

3. Tumour recurrence

SUMMARY:
Where we are

- Excellent local control (80-90%) with wide excision and adjuvant RT
- Most High grade STS should receive adjuvant RT
- Low Grade lesions with close/positive margins, or where local recurrence is morbid.
- Preoperative RT should be considered:
  - Reducing late toxicity
  - For downstaging (near critical structures)
  - Cancer outcome preserved

Summary – ESTS + RT

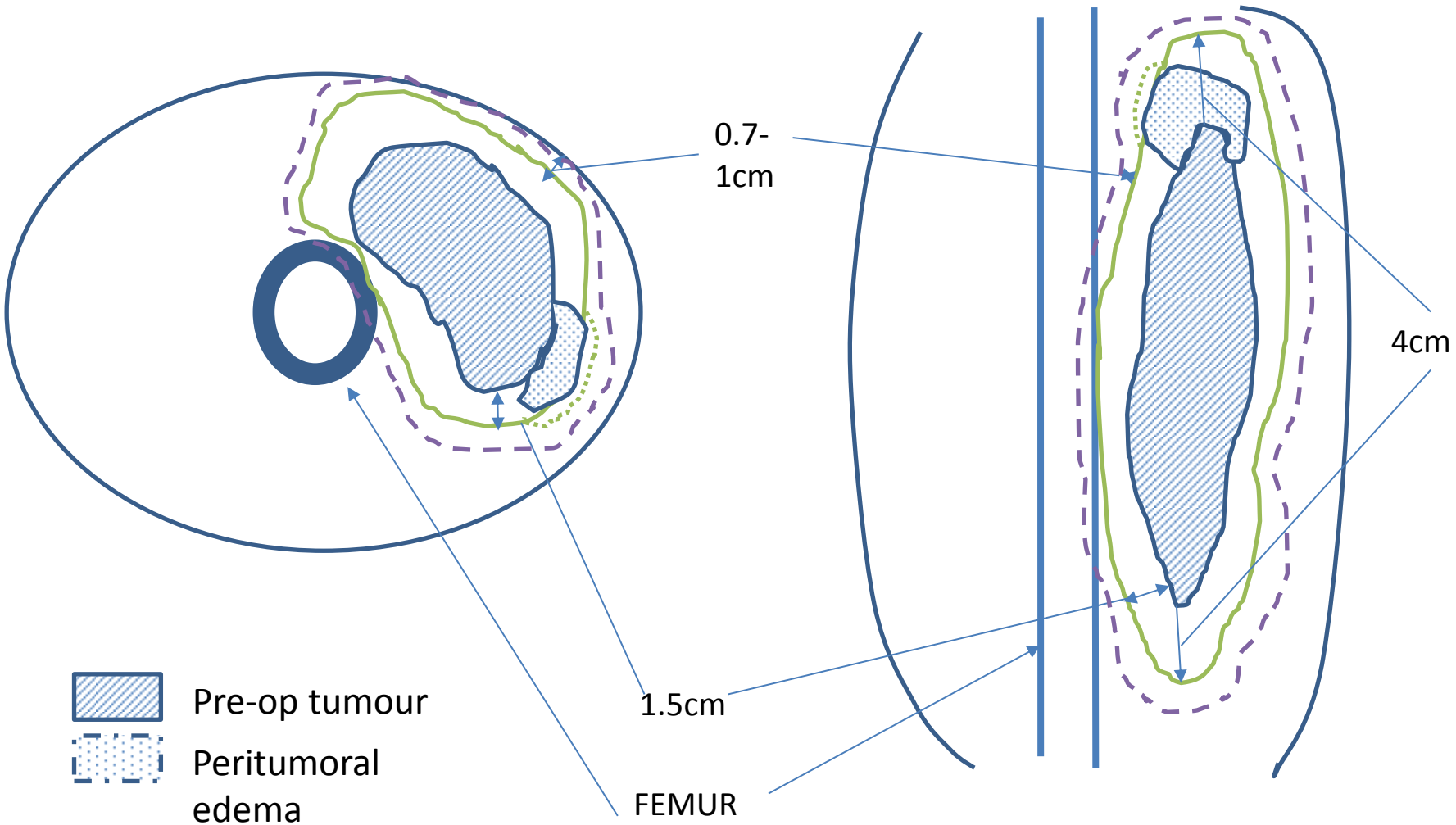
- Radiotherapy **reduces local recurrence rates** after limb sparing surgery, with **good functional result**
  - High grade – 10%
  - Low grade – 0-10%
- No RCT evidence that it improves **overall survival**
- Optimal radiotherapy **volume** is still under investigation
- **Pre-operative** radiotherapy may afford better functional sequelae without compromising local control
- Advances in RT (**IMRT, IGRT, protons**) can potentially reduce morbidity while maintaining local control rates

Thank You.

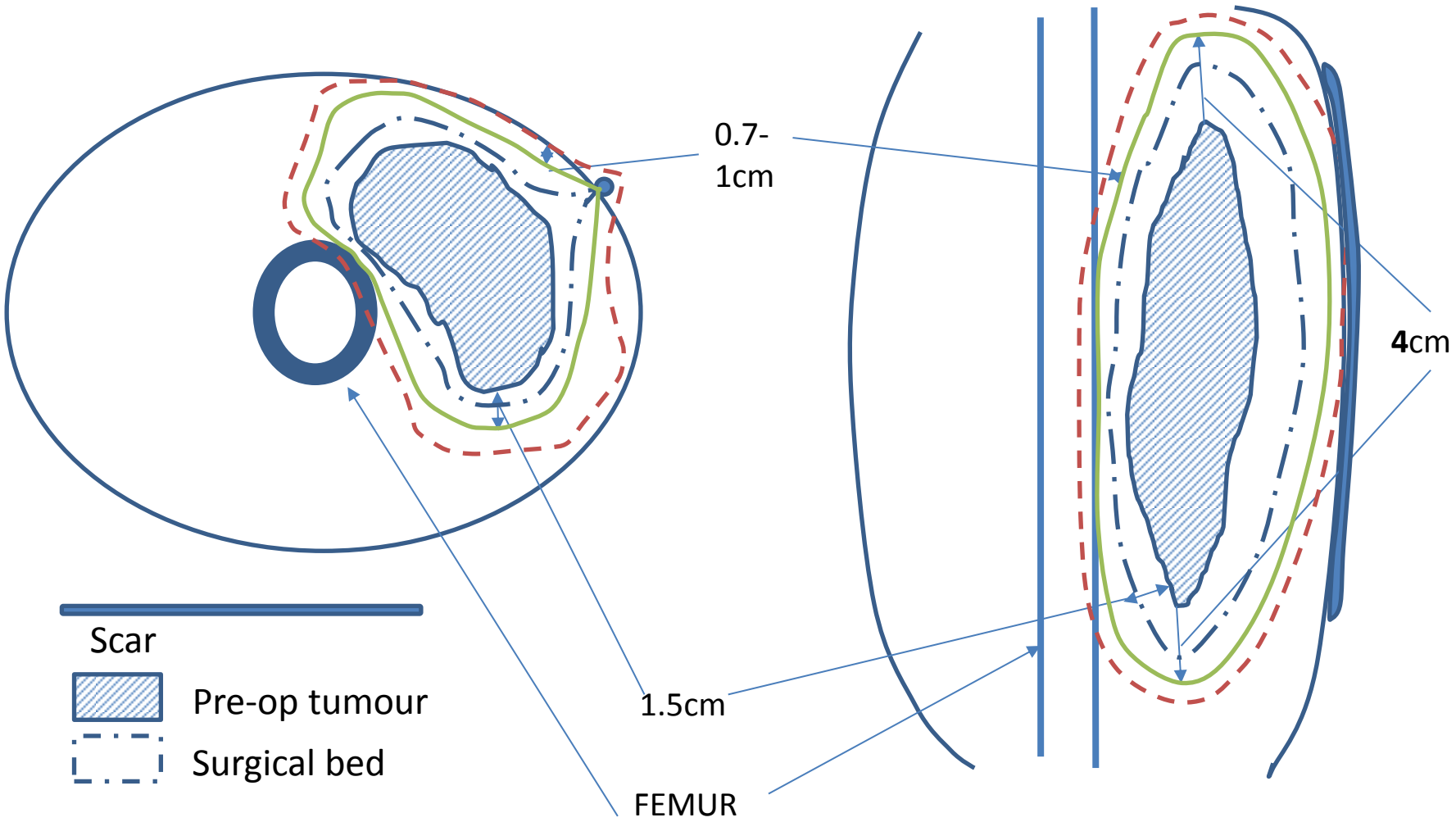
Appendix

- Pre-op RT
  - Single Phase Treatment to **50Gy**
- Post-op RT
  - 2 phases
    - Wide ‘elective’ phase to **50Gy**
      - **Scar** and **drain exit** included
    - Narrower ‘boost’ phase to **10Gy**, or **16Gy** in the case of **microscopic positive margins**

Pre-op RT – Single phase



Post-op RT – Elective phase



Post-op RT – Boost phase