Radiotherapy for Soft Tissue Sarcoma

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Objectives

- Rationale for radiotherapy
- Implications on pathology and radiosensitivity/radioresistence
- Techniques
- Novel treatment approaches
- Will not discuss retroperitoneal sarcomas, metastatic/oligometastatic

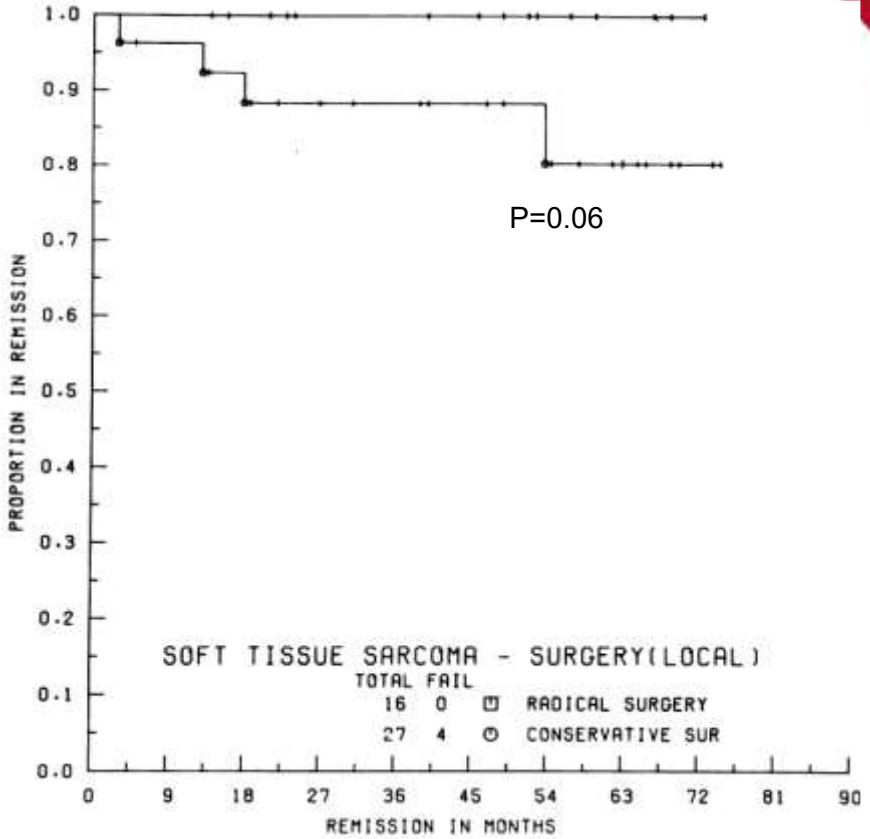
Rationale for radiotherapy

Local Recurrence-Historical Perspective

	Year	Amput/Rad Res	Wide Loc Exc	Marginal Resect
Cantin	1968	18%	30%	42%
Gerner	1975	8%	60%	93%
Abbass	1981	8%	36%	65%
Leibel	1982	13%	28%	70%
Enneking	1981	4%	25%	50%
Markhede	1982	0%	--	76%
		0-18%	**25-60%**	**42-93%**

NCI Trial - Rosenberg

- N=43, high grade STS extremity
- Randomized: Amputation vs wide excision + RT
- 5000 cGy + 1000-2000 cGy boost
- DFS 71% vs 78%, p=.75
- OS 83% vs 88%, p=.99
- Margin status associated with LR, (p<.0001)



Rosenberg, Ann Surg 1982

NCI Trial - Yang

- N=131, randomized controlled trial
  - High grade STS (n=91): CT vs CT+RT
  - Low grade STS (n=50): RT vs observation
- 4500 cGy to large field, 1800 cGy to tumor bed (clips)
- High grade received concurrent chemotherapy

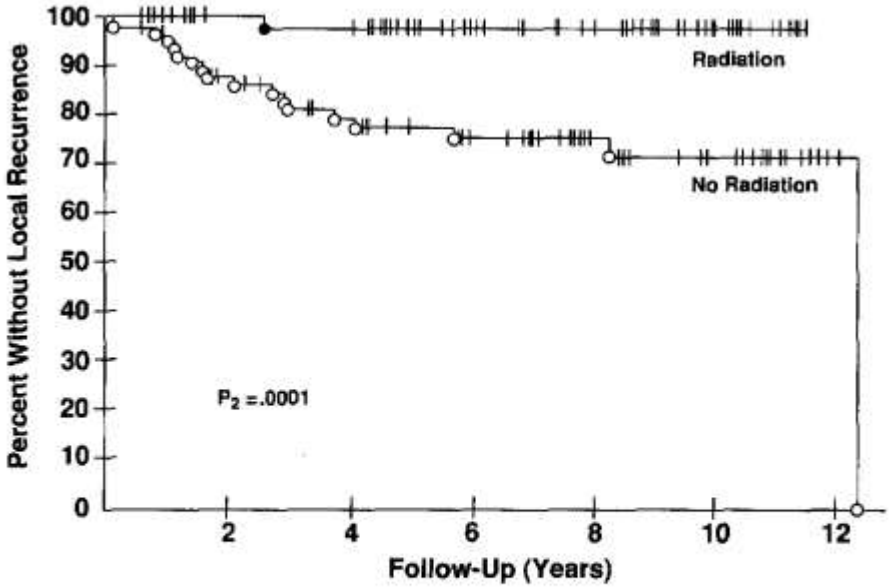


Fig 1. Local recurrence-free survival for all patients with soft tissue tumors of the extremity randomized to receive or not receive adjuvant postoperative external-beam XRT. Patients who develop metastatic disease are censored for LR.

Yang, JCO 1998

NCI Trial Low Grade - Yang

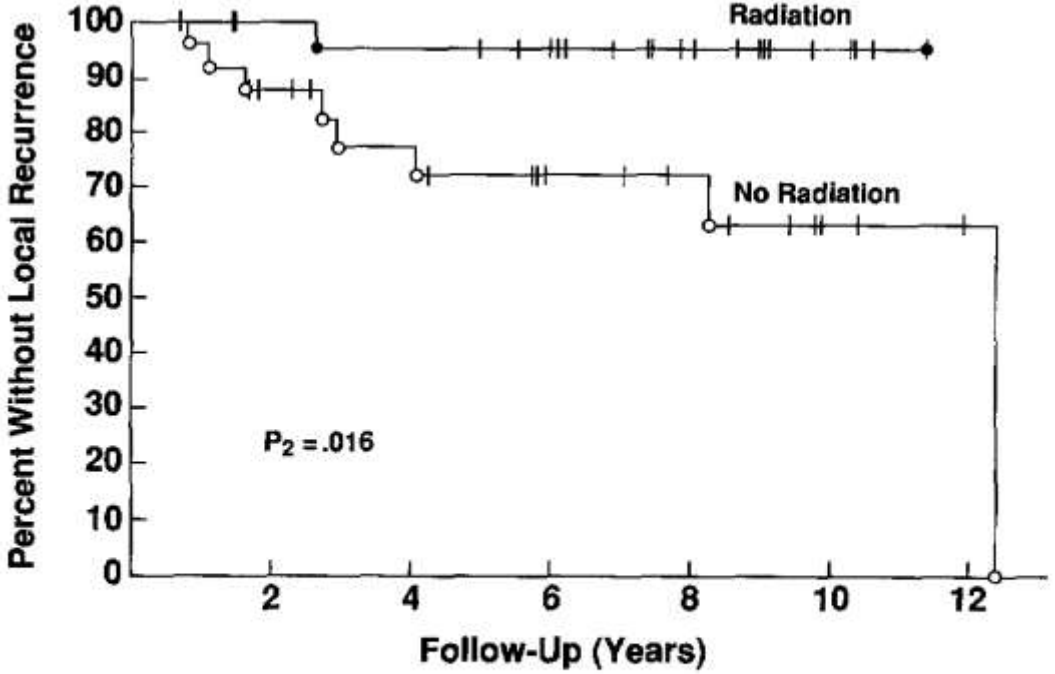


Fig 5. Local recurrence-free survival of patients with low-grade extremity tumors treated with surgery alone, or surgery and postoperative adjuvant XRT.

Yang, JCO 1998

NCI Trial High Grade - Yang

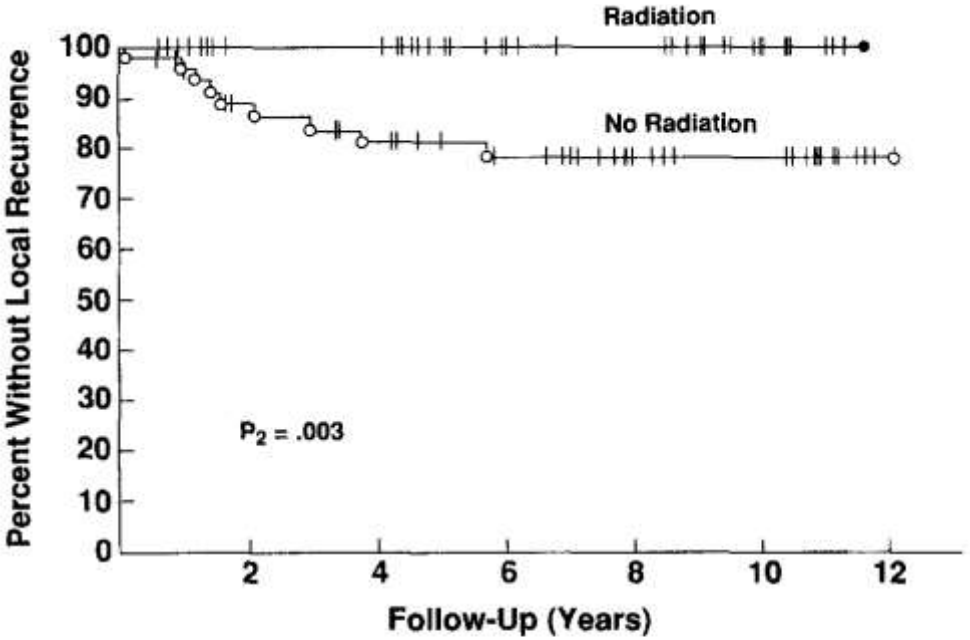


Fig 2. Local recurrence-free survival in patients with high-grade, locally resectable extremity soft tissue sarcomas randomized to treatment with surgery and adjuvant chemotherapy versus surgery, adjuvant chemotherapy, and postoperative XRT. LR occurred only in the absence of XRT.

Yang, JCO 1998

NCI Trial 20 yar follow up - Yang

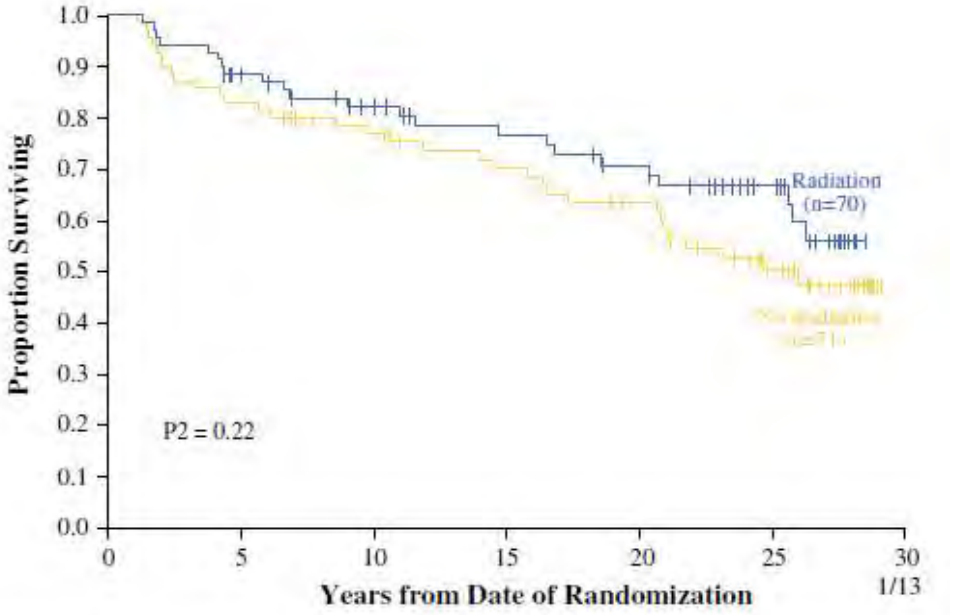


FIG. 1 Overall survival of all patients with extremity sarcoma randomized to treatment with surgery and adjuvant chemotherapy versus surgery, chemotherapy, and EBRT

Beane, JCO 2014

MSKCC RCT - Brachytherapy

- N=164
- Surgery +/- Brachytherapy
- 2 cm margins
- 4500 cGy

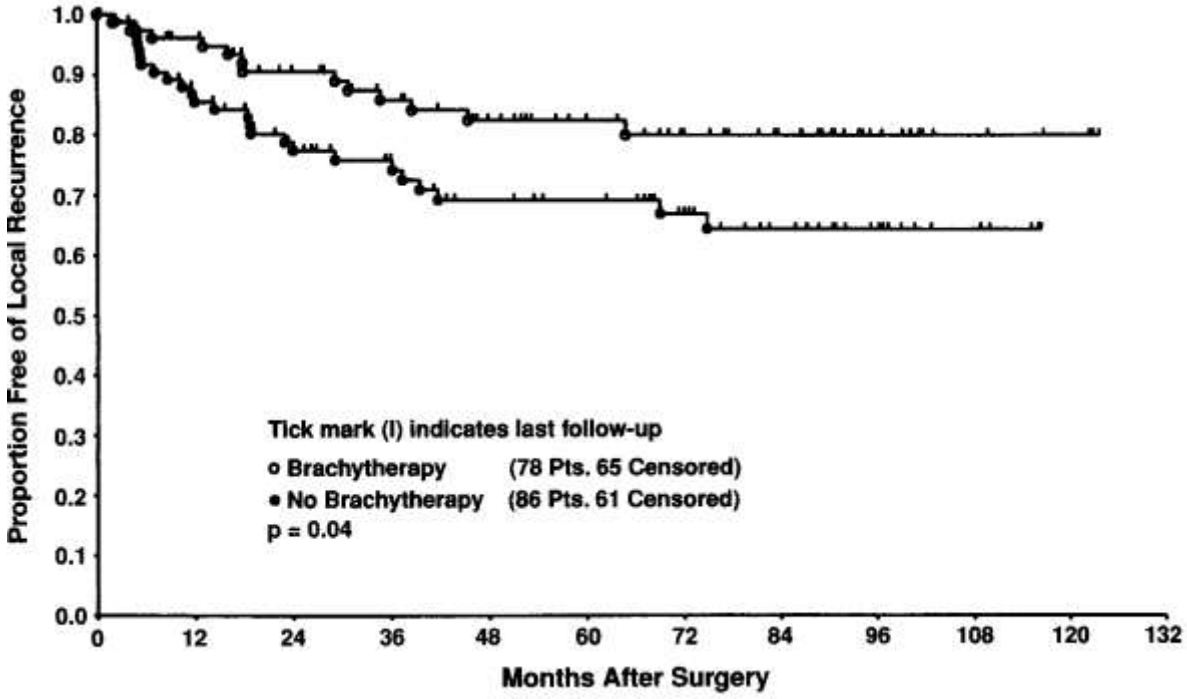
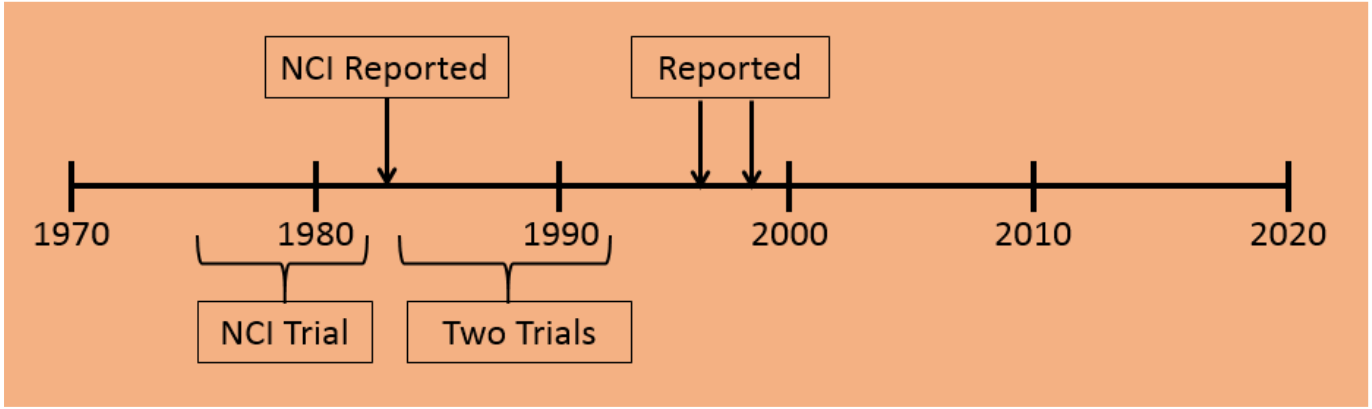


Table 2. Absolute Recurrence and Mortality Results

	No. of Patients		
	BRT (n = 78)	No BRT (n = 86)	P*
Any local recurrence	13	25	.040
Local recurrence only	12	21	.055
Distant recurrence	15	21	.600
Disease-specific mortality	12	16	.650

Pisters, JCO 1996

Combined Modality Therapy



- These 3 RCT established benefit of combined modality treatment
  - Limb-sparing surgery is standard of care
  - Addition of RT + LSS reduces local recurrence over WLE alone

Surgery Alone

- No prospective RCT of subsets of patients who may not need RT have been conducted
  - Trials to demonstrate equivalence of local control are not feasible
- Yet, RT has not been proven to improve OS and RT increases toxicity
- Single institution, retrospective studies exist
  - Selection bias
- Who may consider omission of RT
  - Low grade, small, superficial, wide margins (1-2 cm)

Surgery Alone

Study	Institution	N	Criteria	LR (%)	DR(%)
Geer	MSKCC	174	T1	10	5
Rydholm	Sweden	56	G/M margin neg	7	NR
Karakousis	RPCI	116	2 cm, margin neg	10	NR
Respondek	MDACC	57	Size, margin neg	2	3
Baldini	Harvard	74	Not spec	7	12
Fabrizio	Mayo	34	Not spec	15	12

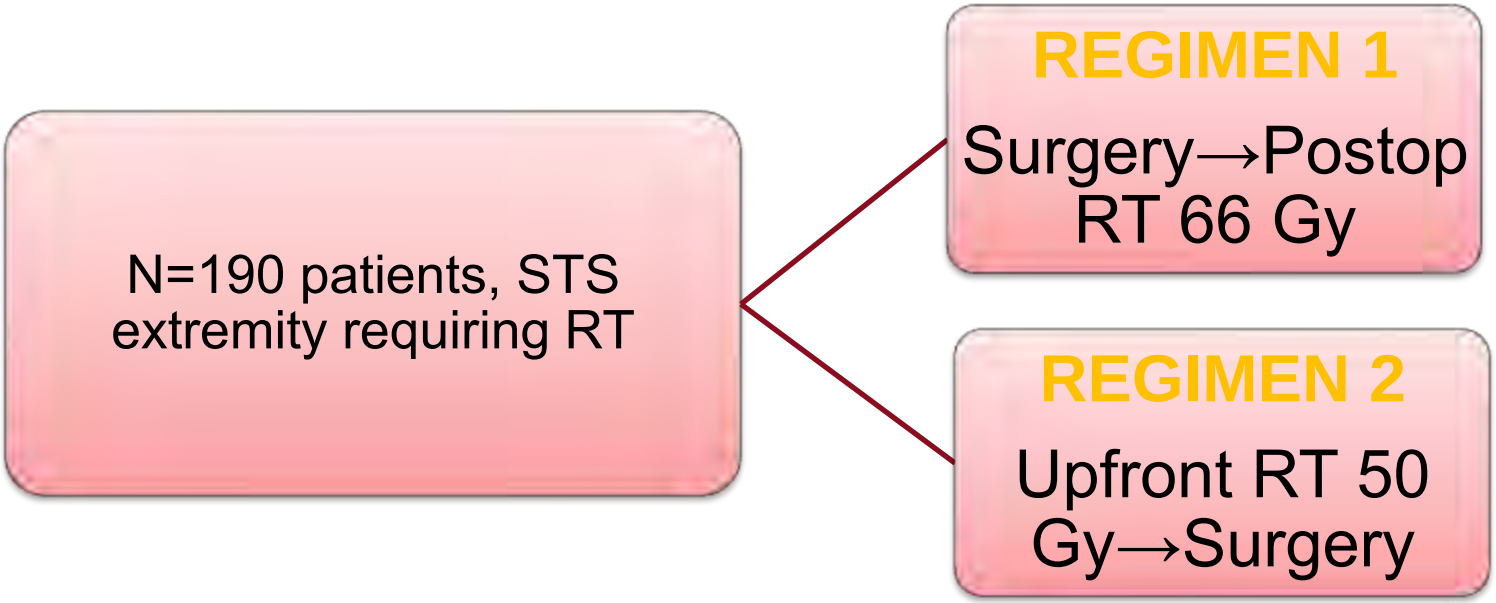
Pisters, JCO 2007

Treatment Approach: Neoadjuvant versus Adjuvant

Background

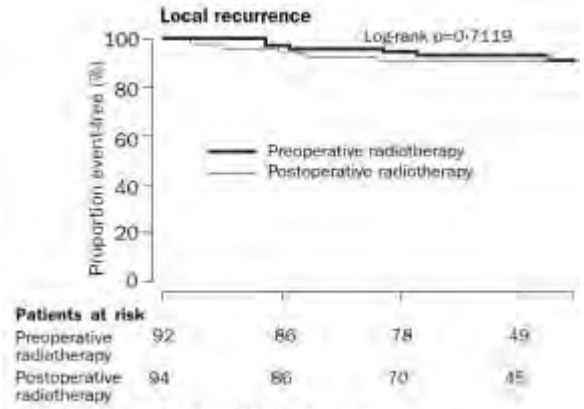
- Pre-operative radiotherapy has several theoretical advantages:
  - Surgery disrupts normal vasculature, leading to areas around the tumor bed that are hypoxic, leading to radioresistence
    - Post-operative RT dose is higher than preop RT
    - Potential improved local control
  - Post-operative RT fields are larger
  - Target identification easier in pre-operative setting

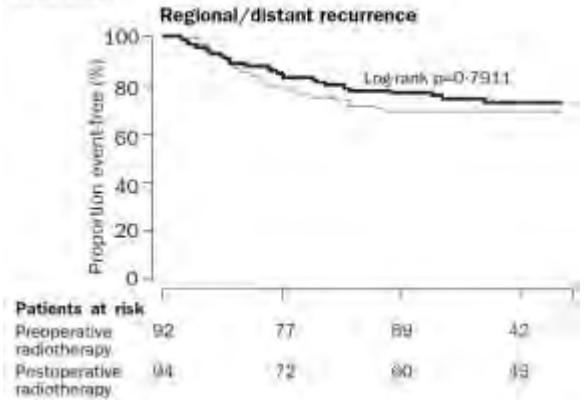
NCIC Trial: Pre-operative vs Post-operative Radiotherapy

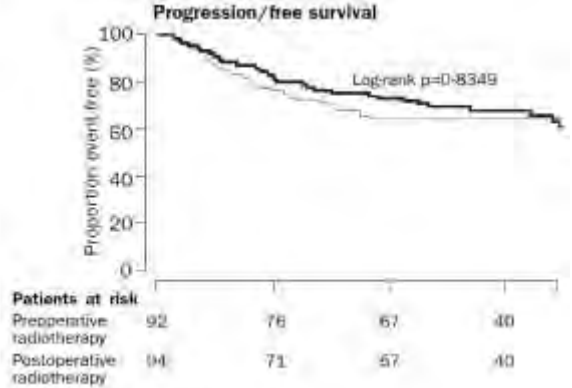


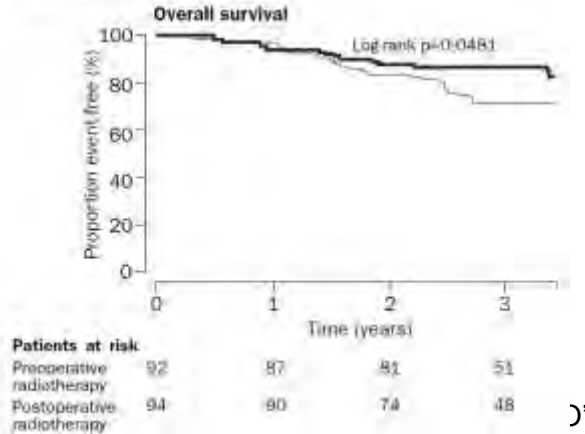
O'Sullivan, Radio Onc 2005

NCIC Trial: Pre-operative vs Post-operative Radiotherapy









O'Sullivan, Lancet 2002

NCIC Trial: Pre-operative vs Post-operative Radiotherapy

Wound complications

	Preoperative (n=88)	Postoperative (n=94)
Wound complications*		
Yes	31 (35%)	16 (17%)
Secondary operation for wound repair	14 (45%)	5 (31%)
Invasive procedure for wound management†	5 (16%)	4 (25%)
Deep wound packing deep to dermis in area of wound at least 2 cm with or without prolonged dressings >6 weeks from wound breakdown‡	11 (35%)	7 (44%)
Readmission for wound care§	1 (3%)	0
No complications	57 (65%)	78 (83%)

*p=0·01 for yes *vs* no. †Without secondary operation. ‡Without secondary operation or invasive procedure. §Without secondary operation, invasive procedure, deep wound packing, or prolonged dressing.

	Preoperative (n=88)	Postoperative (n=94)
Type of wound closure		
Primary	58 (66%)	72 (77%)
Vascularised tissue	25 (28%)	19 (20%)
Split skin graft	5 (6%)	3 (3%)
Wound complication by anatomical site		
Upper arm		
No	9 (90%)	11 (100%)
Yes	1 (10%)	0
Lower arm		
No	8 (100%)	8 (100%)
Yes	0	0
Upper leg		
No	24 (55%)	39 (72%)
Yes	20 (45%)	15 (28%)
Lower leg		
No	16 (62%)	20 (95%)
Yes	10 (38%)	1 (5%)
Wound complication by type of wound reconstruction		
Primary closure		
No	38 (66%)	58 (81%)
Yes	20 (34%)	14 (19%)
Non-primary closure		
No	19 (63%)	20 (91%)
Yes	11 (37%)	2 (9%)

O'Sullivan, Radio Onc 2005

NCIC Trial: Pre-operative vs Post-operative Radiotherapy

MSTS & TESS Functional Scores

- Lower with grade ≥ 2 fibrosis p<0.002
- Lower with grade ≥ 2 joint stiffness p=0.001
- Lower with grade ≥ 2 edema p<0.01

Field size with postoperative RT risk factor for

- Increased fibrosis p=0.002
- Joint stiffness p=0.006

Davis, Radio Onc 2005

Risk Factors for Wound Complications

- Wound complication rate at Cleveland Clinic
  - Overall rate: Acute 22.1% and Chronic 3.3%
  - Extremities: Acute 32.2% and Chronic 5.3%
  - Trunk/Other: Acute 9.2% and Chronic 0.8%

	OR	95% CI	p-value
Tumor Site (Extr vs Other)	2.95	1.26-7.40	**0.02**
RT (y/n) for Extremity	1.92	0.95-3.92	**0.07**
RT (y/n) for Other	0.29	0.04-1.50	0.17
Reconstruction	2.04	0.90-4.51	**0.08**
Tumor Size	1.03	0.99-1.07	0.17

Preop RT

Low Dose (50 Gy)

Smaller field size

Reduced fibrosis

Reduced edema

↑ Wound complications 35%

Postop RT

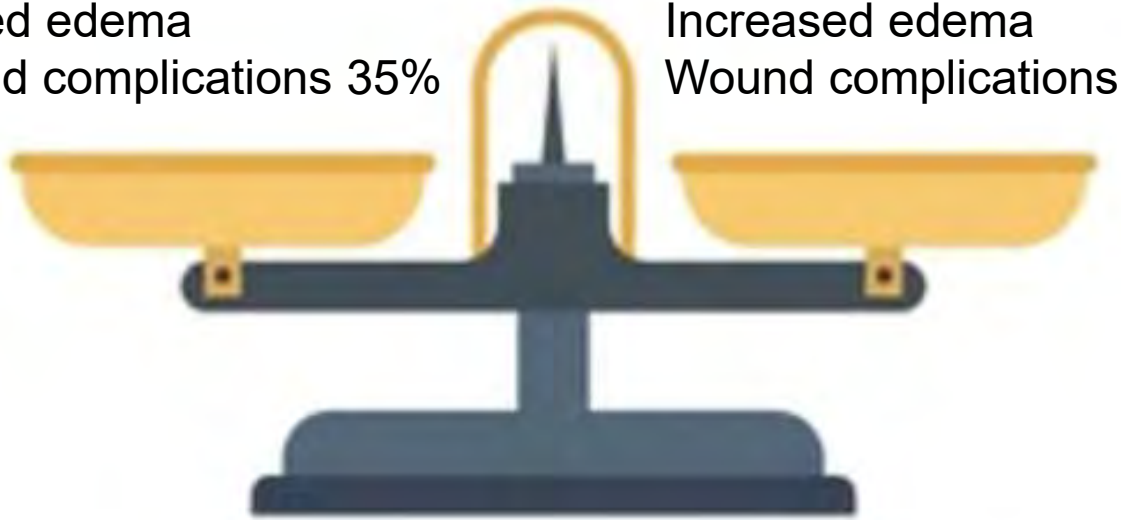
Higher Dose (60-66 Gy)

Large field size

Increased fibrosis

Increased edema

Wound complications 17%



Treatment Approach: Pathology Implications

Pathology: Radiotherapy Implications

- Myxoid liposarcoma: Workup CT C/A/P with bone scan or PET/CT
- Have a dramatic response to RT
- McGill retrospective review of 50 patients
  - Median decrease in tumor volume was seen:
    - <1% for high grade sarcomas
    - 13.8% for non-myoid low grade sarcomas
    - 82.1% for myxoid liposarcoma
- Consider dose reduction for neoadjuvant RT 36 Gy/18 fxn

Lansu, JAMA Oncol 2020 Roberge, Radio Oncol 2010

Pathology: Radiotherapy Implications

- Aggressive Fibromatosis (desmoid): benign tumor
- Associated with pregnancy, trauma and FAP
- Treatment approach at UNMC: medical therapy or surgery until inoperable
  - If a recurrence would lead to a morbid surgery then utilize RT
- RT dose is low to moderate: 54-56 Gy. EORTC trial
  - Complete response in13.6%, partial response in 36.4%, stable disease in 40.9%, progressive disease in 6.8%

Keus, Ann Oncol 2013

Pathology: Radiotherapy Implications

Aggressive Fibromatosis

TABLE 2. Local Control and Survival After Surgery and/or Radiotherapy

Series	No. of Patients	Local Control (Interval)	Cause-Specific Survival (Interval)	Survival (Interval)
Ballo et al.[2]	189	67% (10 y)	100% (median, 9.4 y)	92% (10 y)
Gronchi et al.[8]	203	70% (10 y)	—	94% (10 y)
Zlotecki et al.[3]	65	83% (5 y)	—	100% (5 y)
Park et al.[30]	24	89% (10 y)	—	100% (10 y)
Leibel et al.[21]	19	72% (5 y)	89% (median, 8 y)	88% (5 y)
Schulz-Ertner et al.[31]	28	73% (5 y)	—	—
Dalen et al.[1]	30	53% (mean, 26 y)	100% (range, 20–54 y)	—

Mendenhall, AJCO 2005

Pathology: Radiotherapy Implications

Aggressive Fibromatosis

TABLE 1. Local Control After Surgery and/or Radiotherapy

Series	Surgery		Surgery + Radiotherapy		Radiotherapy Alone	
	No. of Patients	Control (Interval)	No. of Patients	Control (Interval)	No. of Patients	Control (Interval)
Spear et al.[4]	51*	69% (5 y)	41*	72% (5 y)	15*	93% (5 y)
Ballo et al.[2]	122	62% (10 y)	46	75% (10 y)	21	76% (10 y)

*One hundred seven tumors in 105 patients.

Mendenhall, AJCO 2005

Pathology: Radiotherapy Implications

Myxofibrosarcoma

- Infiltrative beyond visible mass, can invade barriers, high rate + margin and LR
- MSKCC review of 114 patients
  - No difference in LR or DM; higher rate of positive margin
- Harvard review of 36 patients
  - High LR; multifocal LR
- French review of 425 patients (Contica)
  - 5-yr local control 67%
  - R0 resection and RT led to best outcomes

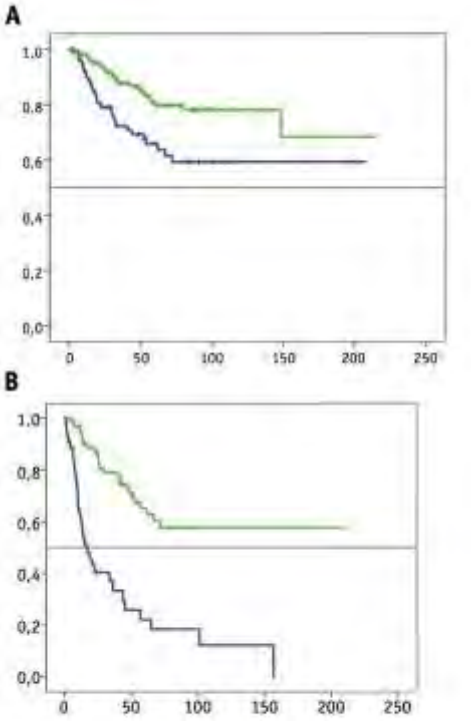


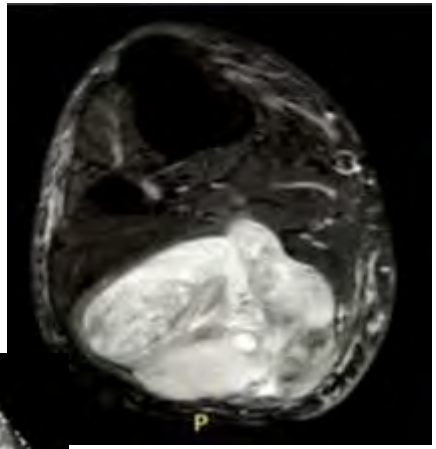
Fig. 1. Local relapse-free survival with adjuvant radiation therapy (green curve) or without radiation therapy (blue curve) after R0 resection (1A) and after R1 resection (1B)

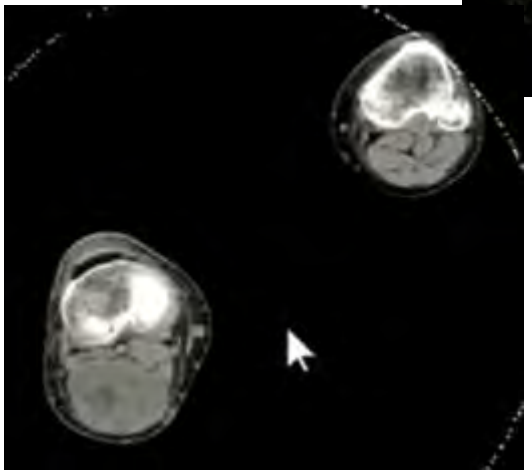
Haglund, Red J 2012
Mutter, Cancer 2012
Boughazala, Red J 2018

Radiotherapy Technique

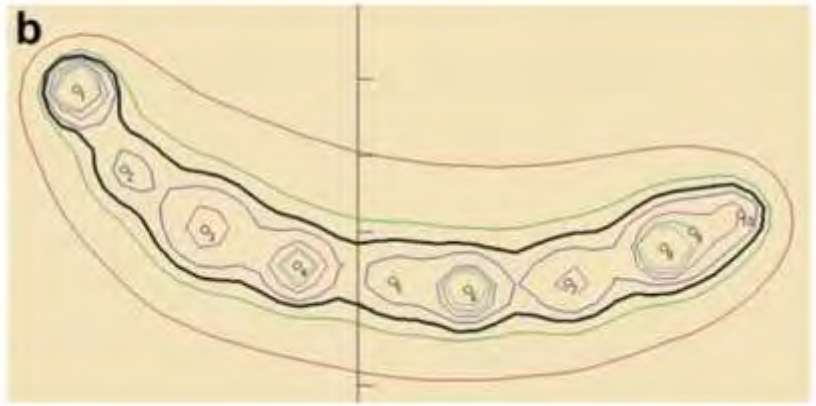
Radiotherapy Simulation

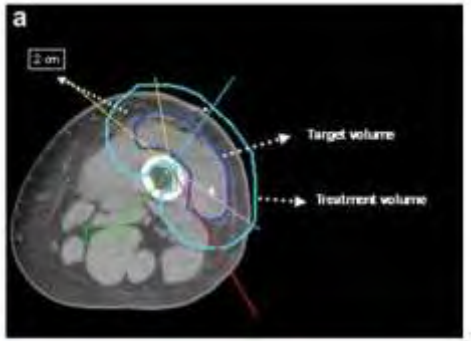
Extremity

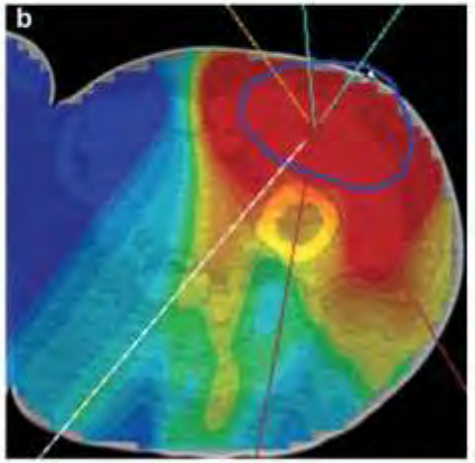




IMRT versus Brachytherapy







Alektiar, Cancer 2011

MSKCC IMRT versus Brachytherapy

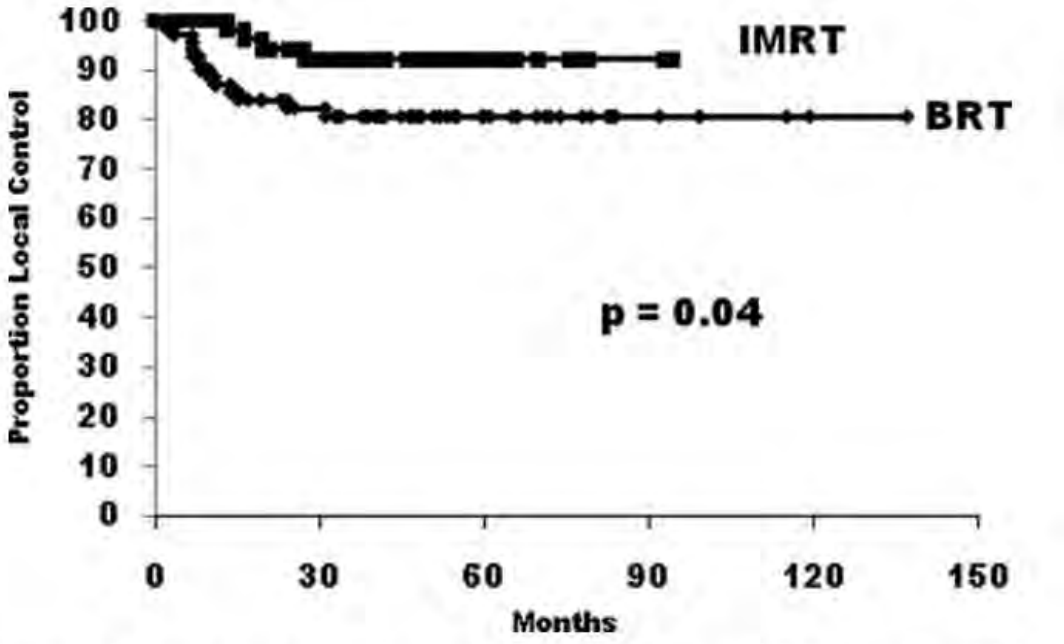
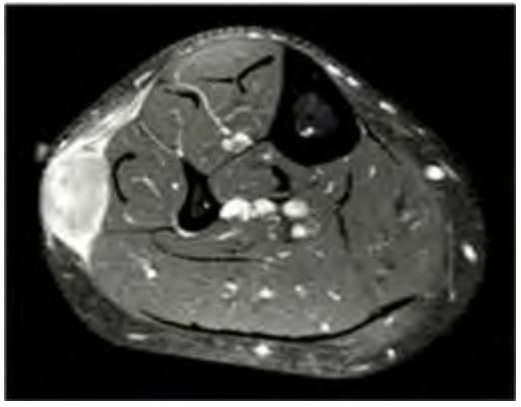


Figure 3. Local control and radiotherapy (RT) type. IMRT indicates intensity-modulated RT; BRT, brachytherapy.

Alektiar, Cancer 2011

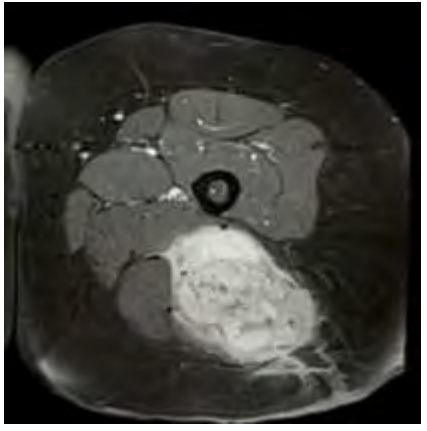
Patterns of Spread

- Extremity
  - Along the longitudinal tissue planes – within compartment
  - If vessels/nerves involved, can track along structure
  - Compresses/distorts adjacent soft tissue
  - Tumor can extend beyond radiographic mass



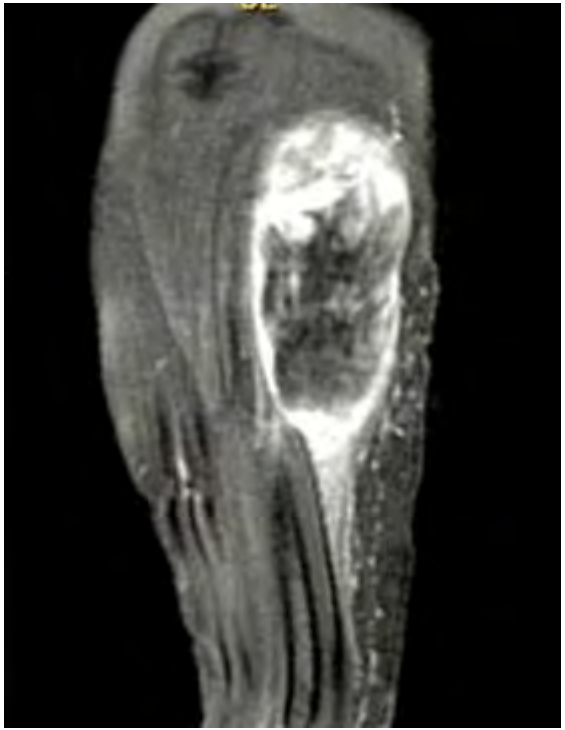
←Superficial UPS

Deep MPNST→



Patterns of Spread - Extremity

- 1980's: 10 cm margins used on high grade STS
- 1990's: NCIC trial used 5 cm margins
  - MRI signal changes in T2 0-7.1 cm from mass, mean 2.5 cm
  - Tumor cells present in 10/15 cases beyond mass, within 1 cm in most cases, up to 4 cm



White, Red J 2005
Tepper, Red J 1982

RT Dose/Margins

- CTV Margins
  - 3.5-4.0 cm along muscle fibers (Sup/Inf)
  - 1.5 cm radial margins, respect facia/bone
  - If superficial, 3.5-4.0 cm circumferential
- Pre-operative RT: 50 Gy/25 fractions (5 weeks)
- Postoperative RT: 66 Gy/33 fractions (6.5 weeks)

- *Positive margin after pre-operative RT???*
  - Sometimes at 16-20 Gy postoperatively
  - Evidence suggests little benefit though

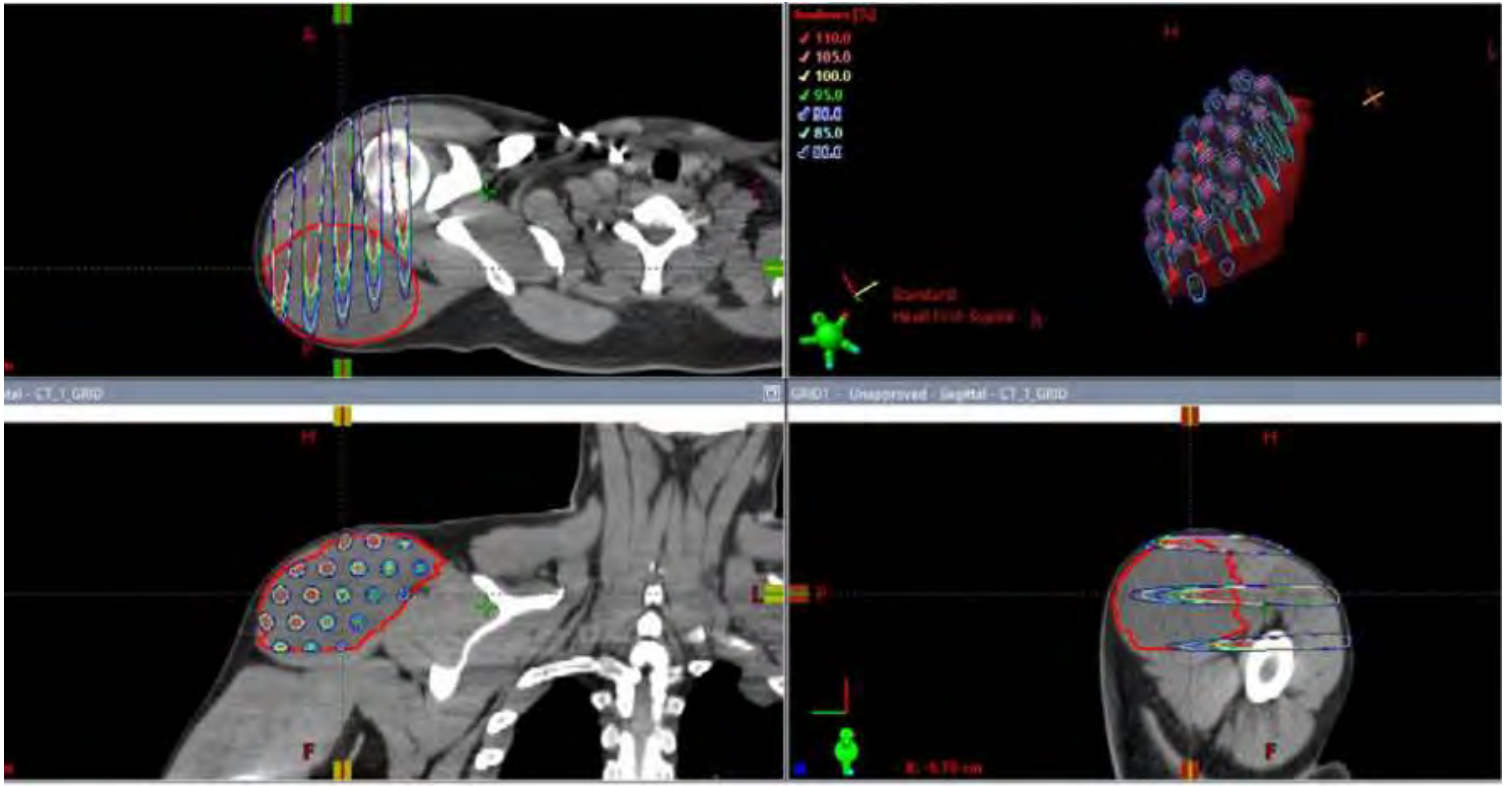
Yami, Red J 2014
Pan, J Surg Onc 2014

Novel Approaches

GRID and Lattice Spatially Fractionated Radiotherapy

- GRID RT: deliver non-uniform (highly heterogeneous) dose pattern to target with a grid-like dose layout
  - Advances in planning, imaging, linear accelerators have renewed interest in GRID RT
  - Stimulate biologic repsonses within tumor microenvironment. High dose regions kill tumor cells, low dose regions suppress re-growth
  - Might be beneficial for bulky or radioresistant tumors
  - Lattice RT: evolution of GRID using modern imaging and linear accelerators
    - Creates a 3-D lattice pattern of hot/cold spots

GRID and Lattice Spatially Fractionated Radiotherapy



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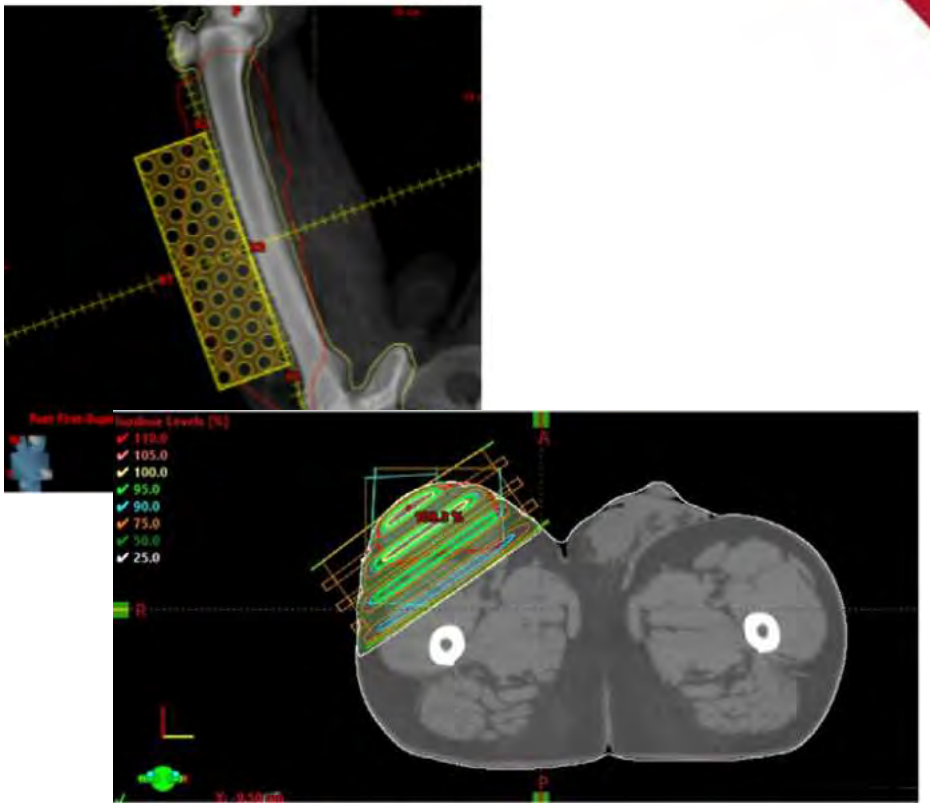
GRID and Lattice Spatially Fractionated Radiotherapy

- Deliver 15-20 Gy in single fraction
- Followed by 5000 cGy in 25 fractions
- Future directions include adding immunotherapy and/or chemotherapy following GRID



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