

# **Evolving Paradigms in Management of Sarcomas**



**Dr. Supriya Mallick**

Assistant Professor

National Cancer Institute, Jhajjar

AIIMS, New Delhi

# Broad management of STS

## LG STS

- Treatment: Surgery
- LR: <15%
- Indication of RT
  - R1 resection
  - Difficult location
  - Recurrent lesion

## HG STS

- Treatment: LSS+RT
- LR:<15%
- Indication of RT
  - >5 cm size
  - Higher grade
  - Deep seated tumour

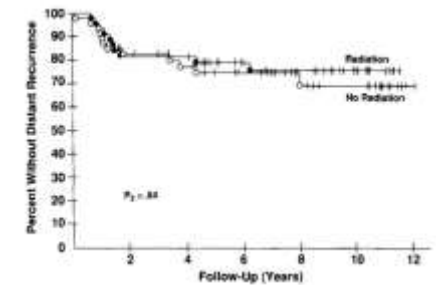
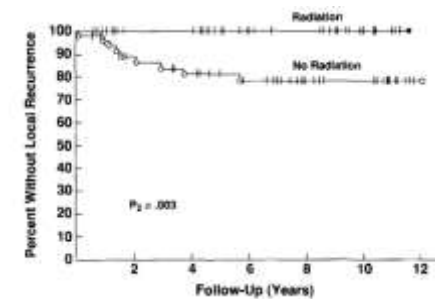
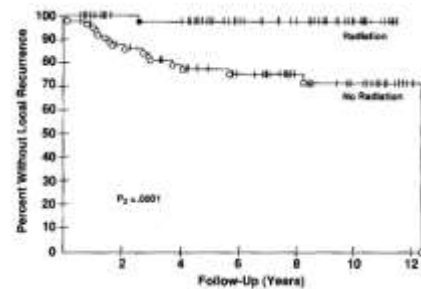
# Amputation vs Limb Salvage

Local recurrence:

- 90% after simple excision
- 39% after wide excision
- 25% after soft-part excision
- 7-18% after amputation

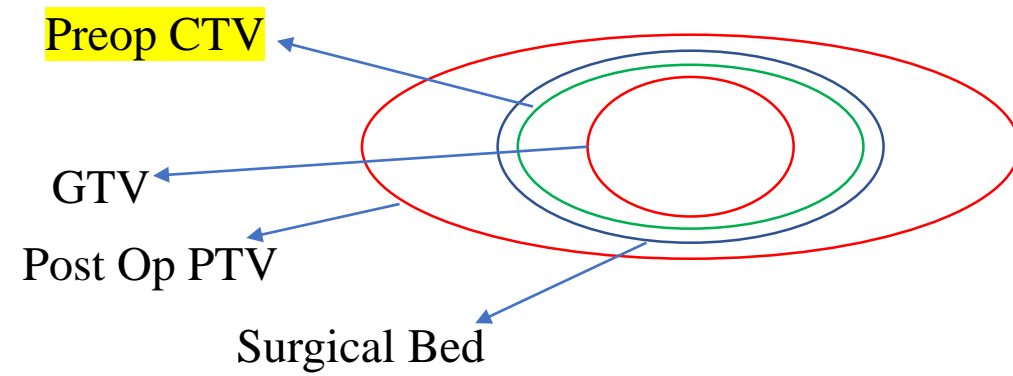
# Evolution of Radiotherapy Use in STS

- Limb-sparing surgery + Radiation offers similar outcomes to amputation
- 5-year DFS 71% vs 78% (NS); 5-year OS 83% vs 88% (NS)
- Limb-sparing surgery + Radiation offers better outcomes than limb-sparing surgery alone
- LSS+ Adjuvant CT vs LSS+ Adjuvant +Adjuvant RT
- 10 yr local control: 100% vs 81%
- Worse QoL noted with RT



Rosenberg et al., *Ann Surg.*, 1992  
Yang et al., *JCO*, 1998

# Adjuvant vs Neo-Adjuvant



# Evolution of radiation in STS

Trial	Prox-Dist Extent	Radial Extent	Rx
NCIC SR2 O'Sullivan et al., Lancet, 2002	5 cm	Not well defined	50 Gy in 25 fx
RTOG 0630 Wang et al., JCO, 2015	2-3 cm	1-1.5 cm	50 Gy in 25 fx
Candian IMRT O'Sullivan et al., Cancer, 2013	4 cm	1.5 cm	50 Gy in 25 fx

- Local recurrence rates only 7-11%
- Late grade 2+ toxicity rates only 10-14%
- Persistent wound healing toxicity rates of 30-37% in the pre-operative setting

# Adjuvant vs Neoadjuvant RT

	Adjuvant RT	Neoadjuvant RT
Level of evidence	I	I
Dose	60-66 Gy (LC: 66% vs 85%)	50 Gy
CTV	Operative area+4 cm	MR T1 post Gd + 4*cm ( newer trials: 1.5-2 cm)
LC rate	93%	92%
Toxicity	<p>Long term ROM, fibrosis 48 vs 32%; edema 15% v 23% joint stiffness and 18% v 23%</p> <p>Grade 2+ radiation dermatitis Pre vs post: 36% vs 68%</p> <p><small>Vortex Trial: A Randomized Controlled Multicenter Phase 3 Trial of Volume of Postoperative Radiation Therapy Given to Adult Patients With Extremity Soft Tissue Sarcoma (STS) M.H. Robinson,<sup>1</sup> P. Gaunt,<sup>2</sup> R. Grimer,<sup>3</sup> B. Seddon,<sup>4</sup> J. Wylie,<sup>5</sup> A. Davis,<sup>6</sup> D. Hughes,<sup>7</sup> D. Peake,<sup>8</sup> A. Cassoni,<sup>4</sup> D. Spooner,<sup>8</sup> A. Miah,<sup>9</sup> A. Hughes,<sup>2</sup> C.M.L. West,<sup>10</sup> K. Venables,<sup>11</sup> and L. Billingham<sup>2</sup>; <sup>1</sup>University of Sheffield, Sheffield, South Yorkshire, United Kingdom, <sup>2</sup>University of Birmingham, Birmingham, United Kingdom, <sup>3</sup>The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, United Kingdom, <sup>4</sup>University College Hospital, London, United Kingdom, <sup>5</sup>The Christie</small></p>	<p>Acute wound complication high (35 vs 17%, SS)</p> <p>[Predictor: LE (HR 10.4); DM (HR 5.6), Size (HR 6.2); Flap (HR 60.4)]</p>

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

## A Systematic Review and Meta-Analysis of Oncologic Outcomes of Pre- Versus Postoperative Radiation in Localized Resectable Soft-Tissue Sarcoma

Emad Al-Absi, MD<sup>1</sup>, Forough Farrokhyar, PhD<sup>1</sup>, Rajrishi Sharma, MD<sup>1</sup>, Kaitlyn Whelan<sup>1</sup>, Tom Corbett, MD<sup>2</sup>, Malti Patel, MD<sup>2</sup>, and Michelle Ghert, MD, FRCSC<sup>2</sup>

Study	Total no. of patients	Patients provided with preoperative	Patients provided with postoperative	Mets before surgery	Mets after surgery	Local recurrence preoperative	Local recurrence postoperative	Survival rate with preoperative	Survival rate with postoperative
Chang	7/48	6/63	0.384			1.660	0.517	5.272	
Kuklo	3/59	7/58	0.177			0.390	0.096	1.590	
SUT	6/60	13/110	0.719			0.829	0.298	2.306	
Zagers	36/271	56/246	0.006			0.520	0.328	0.824	
Random combined (4)	52/438	82/478	0.146			0.671	0.392	1.148	

Citation	Effect Name	Pre-Op	Post-Op	P Value	Pre-Op	Post-Op	Effect	Lower	Upper
Chang	Local recurrence	7/48	6/63	0.384			1.660	0.517	5.272
Kuklo	Local recurrence	3/59	7/58	0.177			0.390	0.096	1.590
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Risk for local recurrence lower in preoperative group: Odds ratio 0.61

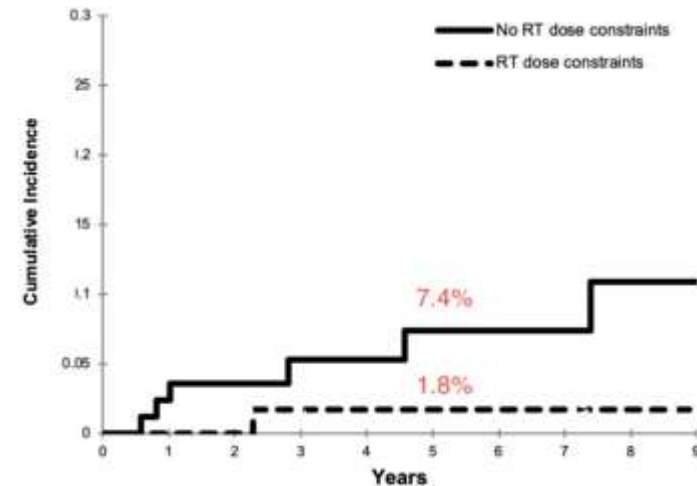


# 2D vs 3DCRT vs IMRT

## Planning Objective:

- Reduction of dose to OAR
- Prevent long term toxicity
- Improve dose delivery and outcome

- ❖ Mean radiation dose to the femur <37 Gy or Dmax <59 Gy
- ❖ V40 less than 64% of the bone reduces the risk of fracture
- ❖ Whole femur <50 Gy



# 3DCRT vs IMRT/VMAT

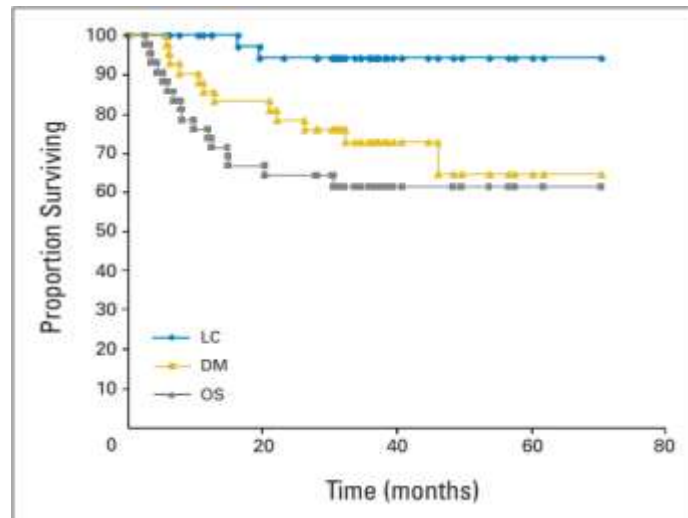
VOLUME 26 • NUMBER 20 • JULY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Khaled M. Alekhtiar, Murray F. Brennan, John H. Healey, and Samuel Singer



5-year LC 94% (regardless of margin status), 5-year DM-free 61%, 5-year OS 64%  
 Toxicity: Dermatitis Grade III- 10%. Fractures 6%. Joint stiffness Grade II- 19%. Edema Grade II- 13%  
 Femur V100 decreased by 57% (SS), femur D5 reduced 67% (SS).  
 Ipsilateral soft tissues V100 decreased by 78% (SS), D5 decreased 13%

Ann Surg Oncol  
 https://doi.org/10.1245/s10434-019-07182-5

Annals of  
**SURGICAL ONCOLOGY**  
 OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

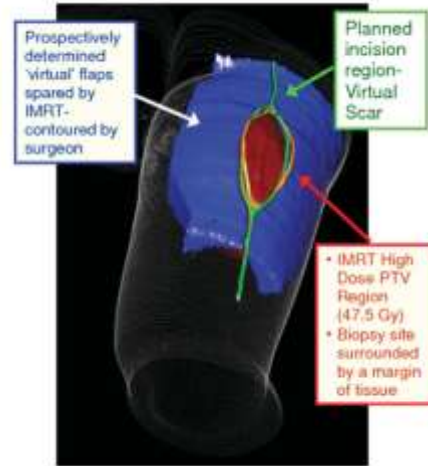


ORIGINAL ARTICLE - SARCOMA

## Femoral Fracture in Primary Soft-Tissue Sarcoma of the Thigh and Groin Treated with Intensity-Modulated Radiation Therapy: Observed versus Expected Risk

Michael R. Folkert, MD<sup>1</sup>, Dana L. Casey, MD<sup>2</sup>, Sean L. Berry, PhD<sup>3</sup>, Aimee Crago, MD<sup>4</sup>, Nicola Fabbri, MD<sup>4</sup>, Samuel Singer, MD<sup>4</sup>, and Kaled M. Alekhtiar, MD<sup>1</sup>

- Observed crude risk of fractures was 6.5% vs 25 expected risk from the nomogram
- Median time to fracture was 23 months (range 6-98-6)
- > 60 year



VOLUME 33 • NUMBER 20 • JULY 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial

Dian Wang, Rush University Medical Center, Chicago, IL; Qiang Zhang, NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Burton L. Eisenberg, Hoag/University of Southern California Norris Cancer Center, Los

Dian Wang, Qiang Zhang, Burton L. Eisenberg, John M. Kane, X. Allen Li, David Lucas, Ivy A. Petersen, Thomas F. DeLaney, Carolyn R. Freeman, Steven E. Finkelstein, Ying J. Hitchcock, Manpreet Bedi, Anurag K. Singh, George Dondos, and David G. Kirsch

	High risk	Low risk
CTV	GTV+ 3 cm cc and 1.5 cm radial (include oedema seen on T2)	GTV+ 2 cm cc and 1 cm radial (include oedema seen on T2)



**1956**



**2021**



# **Hypo-fractionated RT**

# Hypofractionation in STS

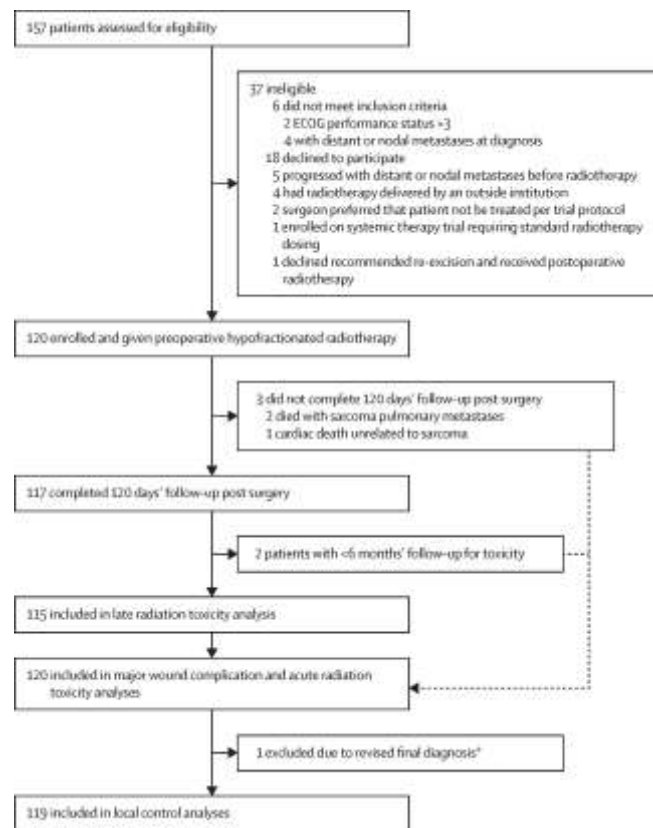
First author [ref no.]	Year published	No. patients	Dose	RT Modality	Time to surgery	Preoperative or concurrent ChT	LC	FU	Wound complications
Eilber et al. [11]	2001	496	17.5 Gy/5 fx 28 Gy/8 fx 35 Gy/10 fx	NR	4 weeks	Yes	89%	5 years	NR
Aguiar Junior et al. [25]	2009	49	30 Gy/12 fx	2D	4–6 weeks	Yes	81.5%	32.1 months	41.8%
MacDermed et al. [12]	2010	34	28 Gy/8 fx	3D	4–8 weeks	Yes	89%	5 years	17.2%*
Kosela-Paterczyk et al. [26]	2014	272	25 Gy/5 fx	3D	3–7 days	Yes, selected patients	81%	3 years	32.4%
Lu et al. [27]	2018	76	28 Gy/8 fx	3D	2–3 weeks	Yes	87.2%	4.3 years	32%
Pennington et al. [28]	2018	116	28 Gy/8 fx	3D	1–2 weeks	Yes	83%	5.9 years	NR
Kalbasi et al. [29]	2020	52	30 Gy/5 fx	Electrons 3D IMRT (76%)	2–6 weeks	No	94.3%	29 months	32%
Parsai et al. [30]	2020	16	30 Gy/5 fx	IMRT/ VMAT	7 days	Metastatic patients only	100%	10.7 months	31%
Current Series	2021	18	25 Gy/5 fx	3D/IMRT	4–8 weeks	Yes	95%	29 months	33%



# Hypofractionated, 3-week, preoperative radiotherapy for patients with soft tissue sarcomas (HYPORT-STs): a single-centre, open-label, single-arm, phase 2 trial

Prof B Ashleigh Guadagnolo, MD   • Roland L Bassett, MS • Devarati Mitra, MD • Ahsan Farooqi, MD • Caroline Hempel, PA • Courtney Dorber, PA • et al. [Show all authors](#)

Published: November 04, 2022 • DOI: [https://doi.org/10.1016/S1470-2045\(22\)00638-6](https://doi.org/10.1016/S1470-2045(22)00638-6) •



- ❖ Dose: 42.75 Gy in 15 fractions of 2.85 Gy/day for 3 weeks
- ❖ Primary endpoint: Major wound complication within 120 days of surgery
- ❖ Major wound complications:
  - Requiring a secondary operation, under general or regional anaesthesia
  - Readmission to the hospital
  - Invasive procedures for wound care
  - Deep wound packing of at least 2 cm in length
  - Prolonged dressing changes
  - Repeat surgery for revision of a split thickness skin graft
  - Wet dressings for longer than 4 weeks
- ❖ Median postoperative follow-up 24 months
- ❖ 37 (31%, 95% CI 24–40) developed a major wound complication at a median time of 37 days
- ❖ No patient had acute radiation toxicity

# **RT with Concurrent CT**

# Neoadjuvant CTRT in STS

VOLUME 24 • NUMBER 4 • FEBRUARY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Neoadjuvant Chemotherapy and Radiation Therapy in the Management of High-Risk, High-Grade, Soft Tissue Sarcomas of the Extremities and Body Wall: Radiation Therapy Oncology Group Trial 9514

William G. Kraybill, Jonathon Harris, Ira J. Spiro,† David S. Ettinger, Thomas F. DeLaney, Ronald H. Blum, David R. Lucas, David C. Harmon, G. Douglas Letson, and Burton Eisenberg

Clinical Investigation

Combined Preoperative Hypofractionated Radiotherapy With Doxorubicin-Ifosfamide Chemotherapy in Marginally Resectable Soft Tissue Sarcoma: Results of a Phase 2 Clinical Trial

Mateusz J. Spony, MD, PhD,\* Hanna Kosela-Paterczyk, MD, PhD,\* Aneta Borkowska, MD, PhD,† Michał Wągrodzki, MD, PhD,† Anna Szumera-Ciećkiewska, MD, PhD,†,‡ Anna M. Czarnecka, MD, PhD,†,§ Barbara Kłoda-Wysocka, MD,|| Iwona Kalinowska, MD,\* Piotr Cieszanowski, MSc, PhD,¶,|| Edyta Dąbrowska-Szewczyk, MSc,\*\*,†† and Piotr Rutkowski, MD, PhD\*



3-year rate for LRF 17.6% if amputation is considered a failure and 10.1% if not.

3-year rates for disease-free, distant relapse-free, and OS are 56.6%, 64.5%, and 75.1%

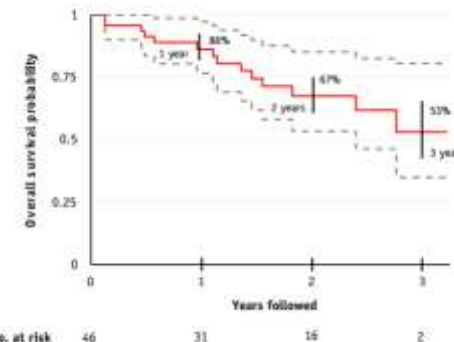
en bloc R0 resections was 71.7%

Wound complications that fulfill definitions described by O'Sullivan et al 34%



Original Article

Neoadjuvant hypofractionated radiotherapy and chemotherapy for extremity soft tissue sarcomas: Safety, feasibility, and early oncologic outcomes of a phase 2 trial





# **SBRT in Sarcoma**

# SBRT for recurrent or metastatic lesion



International Journal of Radiation  
Oncology\*Biology\*Physics  
Volume 114, Issue 4, 15 November 2022, Pages 771-779



CLINICAL INVESTIGATION

## Local Control Outcomes Using Stereotactic Body Radiation Therapy or Surgical Resection for Metastatic Sarcoma

Two-year cumulative incidences of LR for surgery and SBRT were 14.8% and 1.7% ;( $P = .003$ ).

Original Article

## A Multi-Institutional Phase 2 Trial of Stereotactic Body Radiotherapy in the Treatment of Bone Metastases in Pediatric and Young Adult Patients With Sarcoma

Christen R. Eilledge, MD<sup>1</sup>; Matthew J. Krasin, MD<sup>2</sup>; Matthew M. Ladra, MD, MPH<sup>1</sup>; Sara R. Alcorn, MD, MPH, PhD<sup>1</sup>; Peijin Han, MBBS, MHS<sup>1</sup>; Iris C. Gibbs, MD<sup>3</sup>; Susan M. Hiniker, MD<sup>3</sup>; Nadia N. Laack, MD, MS<sup>4</sup>; and Stephanie A. Terezakis, MD<sup>1,5</sup>

- Dose: 40 Gy in 5 daily fractions
- PTV: GTV was isometrically expanded by 2 mm
- PFS (median, 9.3 months vs 3.7 months; log-rank  $P = .03$ ) and OS (median not reached vs 12.7 months; log-rank  $P = .02$ )
- **All known sites of metastatic disease were consolidated with SBRT compared with partial consolidation**

# Definitive RT in unresectable sarcoma

- Most local failures 66–100% occur within 3 years
- Long-term disease control can be achieved in a fraction of patients
- 5-year PFS and OS: 0–39% and 24.7–63%
- Dose higher or equal 64Gy seem to improve the prognosis
  - 5 year LC 60% versus 20%

# Summary

- Small, High-grade Sarcomas: For stage II (T1G2-3) tumors, surgery + radiation is generally recommended
- Select patients **may** receive surgery alone based on prospective data
  - De novo T1 G2-3 STS resected with a **minimum 1 cm margin\*\***
  - 5 year and 10 year local recurrence rates of 7.9% and 10.6%
  - 10-year **local recurrence rate for high grade STS is 16.7%**
- Resectable, High-risk (T2-4 G2-3) Sarcomas: Treated with surgery with pre- or post-operative radiotherapy
  - **Toxicity profile differed considerably**
- **IMRT/IGRT considered standard of care**
- **Hypo-fractionated RT +/- Conc CT is being investigated and initial results are promising**



**Thank You**