Innovation & Collaboration: Keys to the Treatment of Adult Soft Tissue Sarcomas

Meena Bedi, MD

ASTRO Refresher

Froedtert & Medical College of Wisconsin

Medical College of Wisconsin
Radiation Oncology

Disclosures

- I have nothing to disclose

Objectives

- Appreciate the importance of new and existing data in the management of adult sarcomas
- Discuss the unique nuances in the management of soft tissue sarcomas that impact treatment recommendations
- Implement the knowledge gained to facilitate multidisciplinary collaboration to effectively manage soft tissue sarcomas

Outline

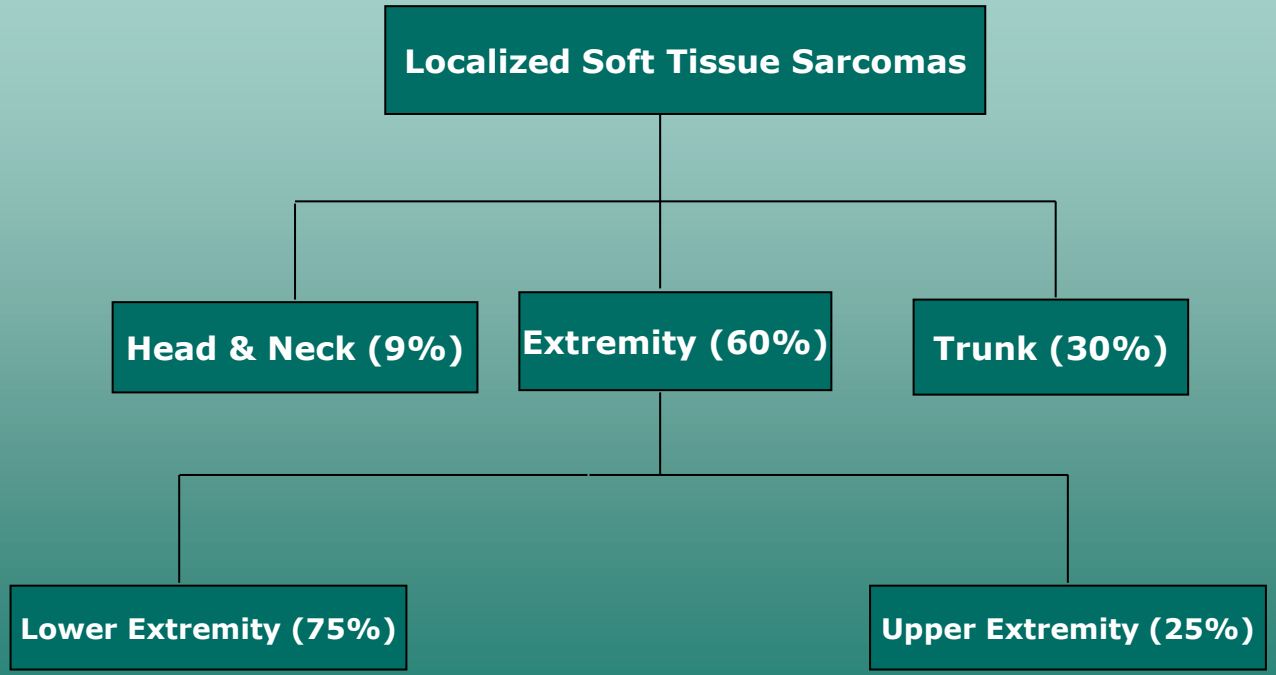
- Overview
- Evolution of Treatment
  - Extremity Sarcomas
  - Abdominal/Retroperitoneal
  - Special Scenarios
- Resources

Overview

Overview

- Rare
  - 1% of all adult malignancies
  - ~15-20% of pediatric malignancies
- Heterogenous
  - >50 subtypes
- Mesenchyme of mesoderm
  - Smooth Muscle → Leiomyosarcoma
  - Skeletal Muscle → Rhabdomyosarcoma
  - Fat → Liposarcoma
  - Connective Tissue → Fibrosarcoma
  - Blood Vessels → Angiosarcoma
  - Supporting cells of peripheral nervous system → MPNST
  - Bone → Osteosarcoma
  - Cartilage → Chondrosarcoma

Distribution



Risk Factors

- Sporadic (most common)
- Genetic Alteration
  - Familial polyposis
  - Retinoblastoma
  - NF-1
  - Li-Fraumeni Syndrome
- Radiation
  - RT-associated sarcoma
- Environmental
  - Vinyl chloride
  - Phenoxyacetic acid
  - Arsenic - hepatic angiosarcomas
- Chronic Edema
  - Stewart-Treves Syndrome
- Burns, foreign implants, scars (rare)

Pathologic Signature

- Translocations
  - Alveolar Rhabdomyosarcoma t(2;13) or t(1;13)
  - Ewing sarcoma t(11;22)
  - Myxoid liposarcoma t(12;16)
  - Synovial sarcoma t(X;18)

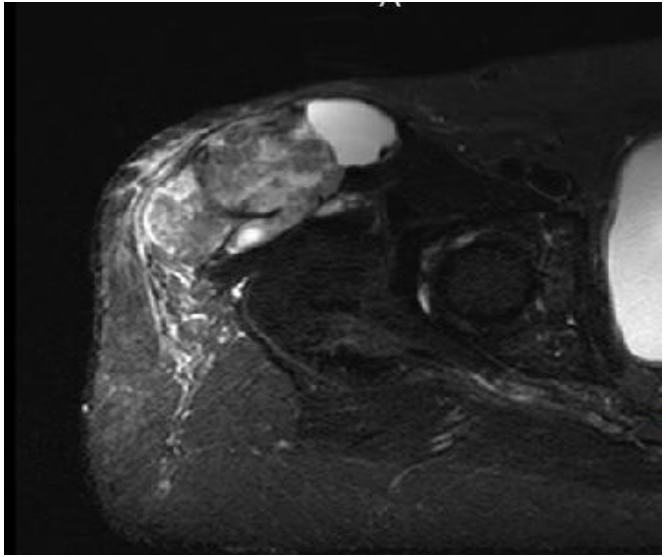
- Immunostains
  - **Desmoplastic small round cell tumor**: WT1, perinuclear dot-like desmin
  - **Rhabdomyosarcoma**: myogenin, myo-D1, myoglobin
  - **Leiomyosarcoma**: Desmin, h-caldesmon, smooth muscle or muscle specific actin
  - **Pleomorphic liposarcoma**: S-100
  - **Angiosarcoma**: CD31, CD34, ERG
  - **Follicular dendritic cell sarcoma**: CD21, CD35
  - **GIST**: CD117 (c-kit), DOG1 (discovered on GIST 1)

Clinical Presentation

- Extremity
  - Painless mass
    - Fullness
    - Muscle strain or hematoma
- Abdominal/Retroperitoneal
  - Bloating
  - Early satiety
  - Alteration in bowel or bladder habits
  - Inability to lose weight
  - Obstructive symptoms
    - More rare
  - Pain
    - Back

Workup

- Image of primary tumor
  - PRIOR TO BIOPSY!
  - Extremity: MRI with contrast, x-rays
  - Abdomen/Pelvis: CT +/- MRI with contrast
- Biopsy
  - Carefully planned
  - Core needle (preferred) or incisional biopsy
    - Core needle: fewer complications, diagnostic accuracy
  - Biopsy placement
- Additional imaging
  - After pathologic conformation
  - CT chest +/- abdomen, pelvis
  - PET/CT
  - MRI spine
    - Myxoid liposarcomas



Birgin E, et al., Cancer, 2020

AJCC Staging

AJCC 8th edition[b]	
T1	Tumor ≤5 cm in greatest dimension
T2	Tumor >5 cm and ≤10 cm in greatest dimension
T3	Tumor >10 cm and ≤15 cm in greatest dimension
T4	Tumor >15 cm in greatest dimension
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
Stage groups	
Stage IA	T1; N0; M0; G1
Stage IB	T2, T3, T4; N0; M0; G1
Stage II	T1; N0; M0; G2/3
Stage IIIA	T2; N0; M0; G2/3
Stage IIIB	T3, T4; N0; M0; G2/3
Stage IV	Any T; N1; M0; any G
	Any T; any N; M1; any G

Grade	Description
G1	Low
G2	Intermediate
G3	High

Cates JM, JNCCN, 2018

Management of Extremity Sarcomas

A Tale of 2 Sarcomas…

- 55-year-old male presents with a left thigh 9 cm heterogenous mass. Biopsy reveals a **high grade leiomyosarcoma**. Systemic imaging is negative

- 55-year-old male presents with a left thigh 9 cm heterogenous mass. Biopsy reveals a **myxoid liposarcoma** with a round cell component. Systemic imaging is negative

- Is there a difference in management of these patients?

Multi-D is the Key!

- Multidisciplinary Discussion
  - Tumor board
  - Surgical/Orthopaedic oncology
  - Radiation Oncology
  - Medical Oncology
  - Radiology
  - Pathology

ESSENTIAL:

- **Prior to the initiation of therapy, it is highly recommended that all patients be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma[a]**

2020 NCCN, Soft Tissue Sarcomas

Our Team!

Improved survival for extremity soft tissue sarcoma treated in high-volume facilities

Tyler Abarca BS[1] | Yubo Gao PhD[2] | Varun Monga MD[3] | Munir R. Tanas MD[4] | Mohammed M. Milhem MBBS[3] | Benjamin J. Miller MD, MS[5]

High-Volume Centers

- NCDB Analysis
  - >7000 localized soft tissue sarcomas
  - High Volume: ≥ 10 cases/year
  - Low Volume: <10 cases/year

- Outcomes
  - Improved 2-, 5- and 10-year survival at high volume centers

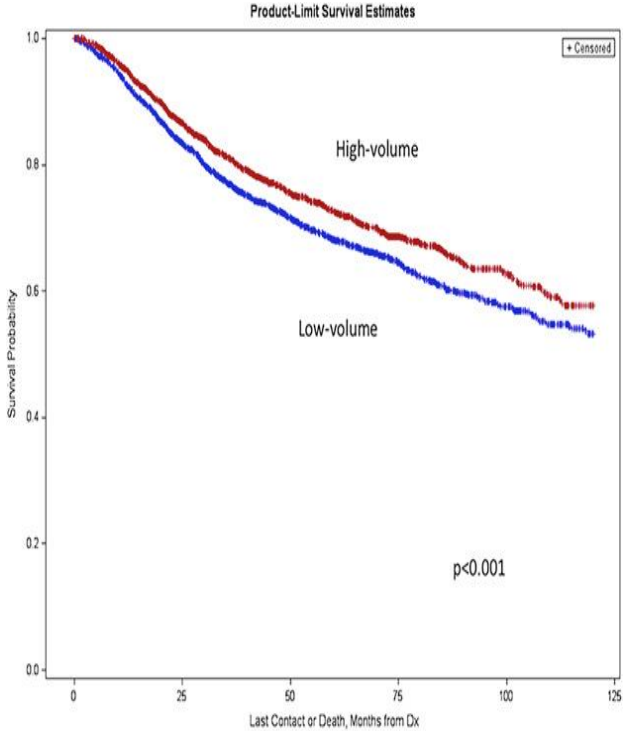
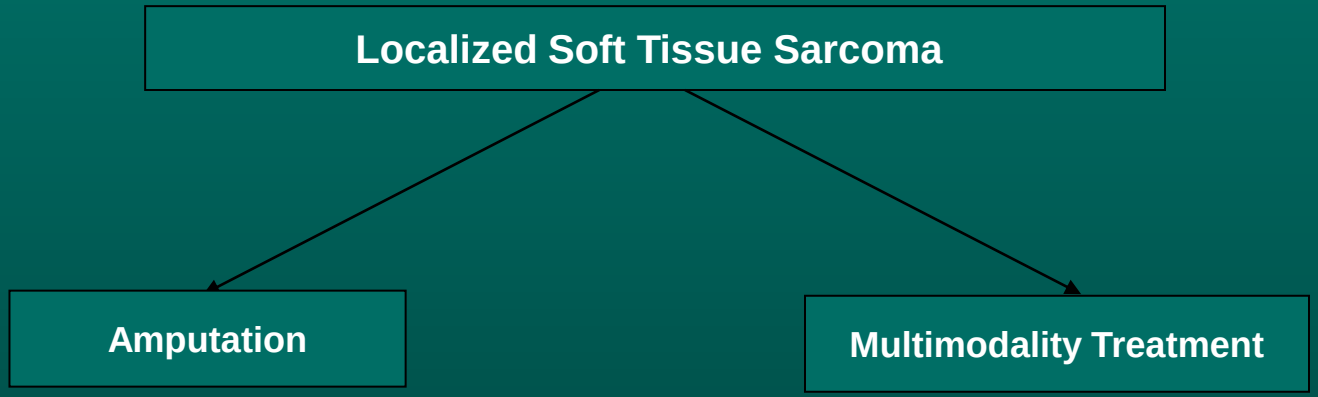


TABLE 3 Univariate comparison of 2-, 5-, and 10-year survival between low and high volume centers

	2-year (95%CI)	5-year (95%CI)	10-year (95%CI)
Low-volume	84.0 (82.5-85.5)	68.1 (66.0-70.2)	53.3 (50.0-56.6)
High-volume	87.0 (85.6-88.4)	72.7 (70.6-74.7)	57.6 (54.1-61.1)
P-value	0.003	0.001	0.001

Abarca T, et al., *J Surg Oncol*, 2018

Evolution of Surgical Management



Surgical Management

- **Surgery**
  - Historically treated with “monobloc” excision or amputation for extremity sarcomas
  - Increased morbidity

- **National Cancer Institute**
  - 43 pts
  - High grade soft tissue sarcomas (STS) of extremity
  - Amputation (17 patients) vs. WLE +margin + post-operative RT (27 patients)
    - 45-50 Gy→ boost to 60-70 Gy
  - Post-operative concurrent adriamycin + cytoxan (AC)→ high-dose MTX
  - Results
    - No difference in local failure, DFS and OS

Rosenberg et al., *Ann Surg*, 1982

Surgical Management

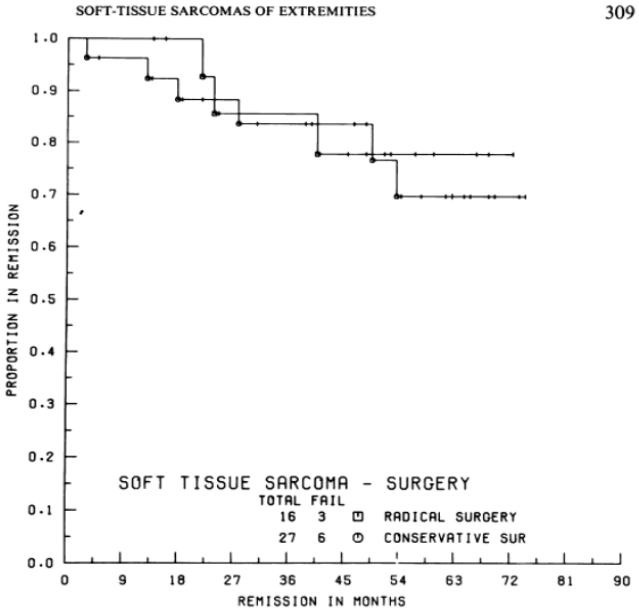


FIG. 1. Prospective randomized evaluation of continuous disease-free survival in patients receiving either amputation or limb-sparing surgery plus radiation therapy.

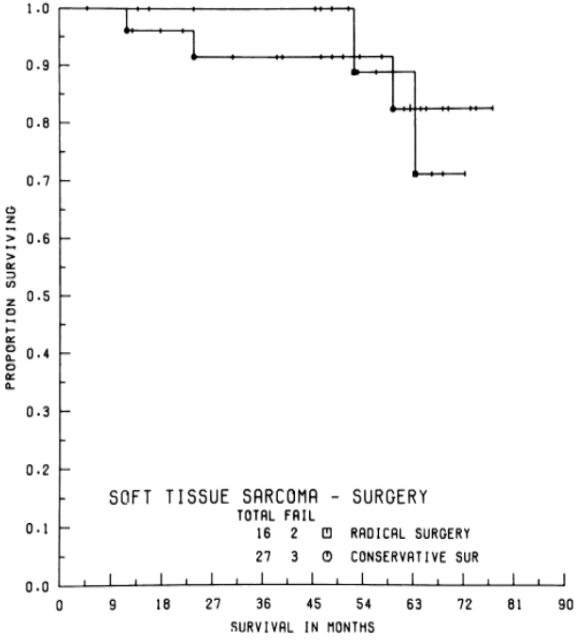
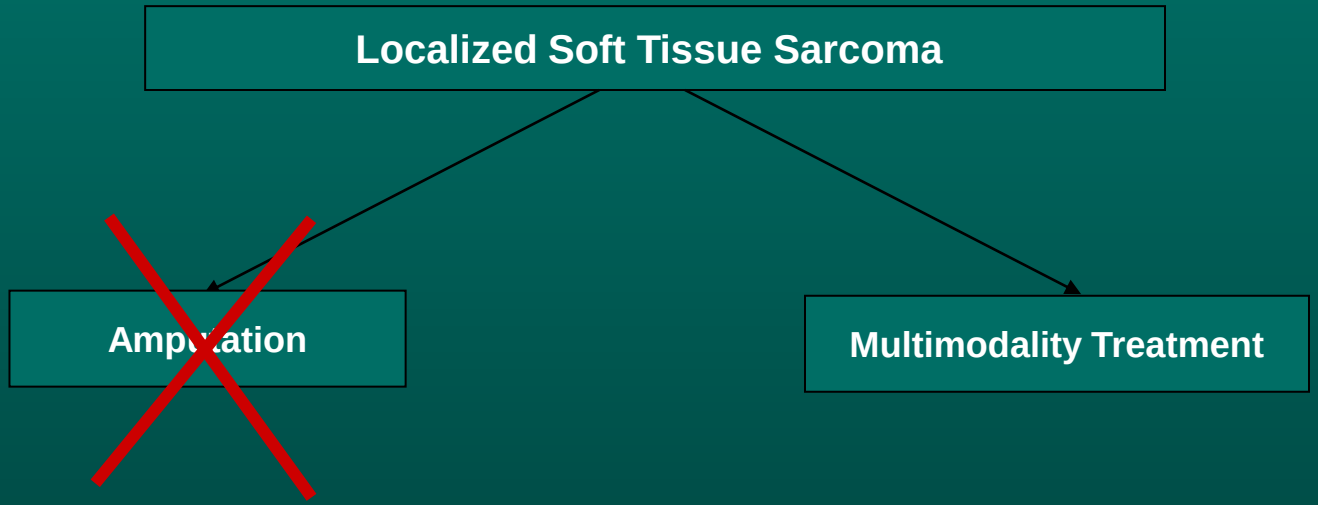


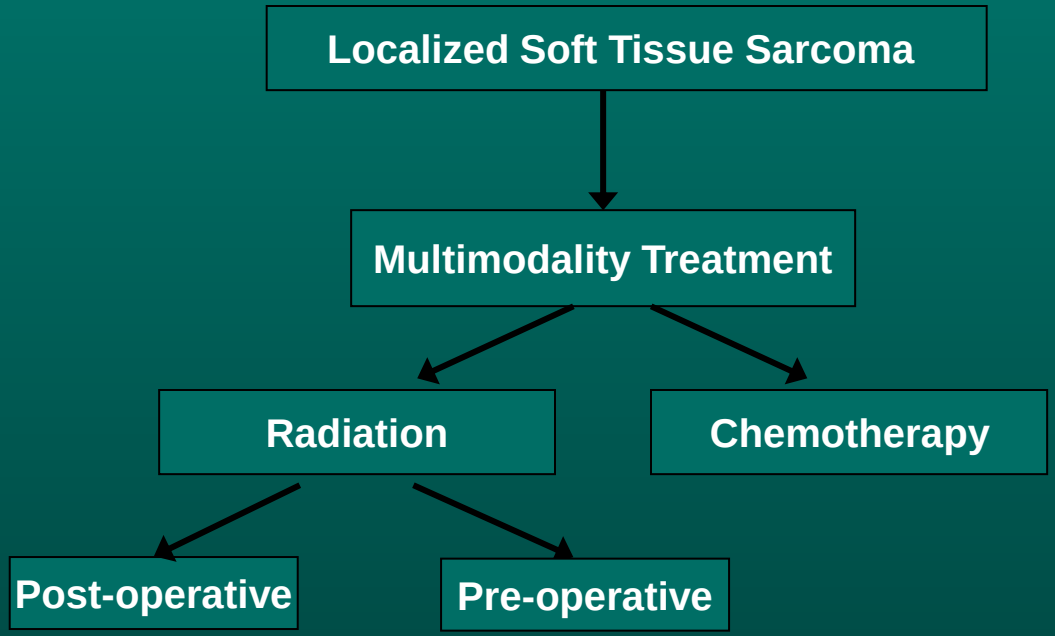
FIG. 2. Prospective randomized evaluation of overall survival in patients receiving either amputation or limb-sparing surgery plus radiation therapy.

Rosenberg et al., *Ann Surg*, 1982

Evolution of Surgical Management



Evolution of Treatment



Adjuvant Radiation

- **National Cancer Institute**
  - 141 pts with STS of extremity
    - High and low grade
  - Limb-sparing surgery
    - High-grade: Post-operative RT (63 Gy) + concurrent chemotherapy (AC) vs Chemotherapy alone
    - Low-grade: Post-operative RT (63 Gy) alone vs observation

Yang JC, et al., *J Clin Oncol.*,1998

Adjuvant Radiation

- **Results**
  - High grade: Increased LR with chemotherapy alone (0 vs 19%, p=0.0028)
    - No difference in 10-year DSS or OS
  - Low grade: Increased LR with observation (4% vs 33%, p=0.016)
    - No difference in 10-year OS

- Updated Results

	Limb-sparing surgery	Limb-sparing surgery + RT +/- chemo
Local Recurrence	4%	0%
10-year OS	75%	82%
20-year OS	64%	71%

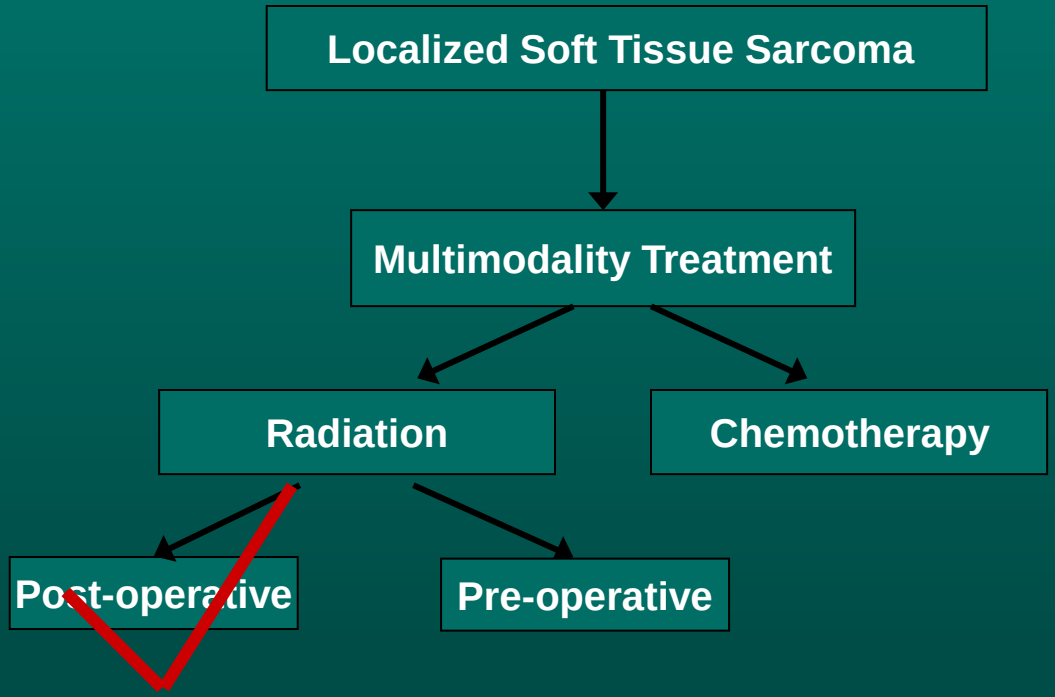
Yang JC, et al., *J Clin Oncol.*,1998
Beane JD, et al., *Ann of Surg Oncol.*,2014

Adjuvant Radiation

- **Memorial Sloan Kettering**
  - 164 pts with STS of extremity and trunk
  - Limb-sparing surgery
    - Adjuvant brachytherapy (Ir-192 implant to 42-45 Gy over 4-6 days) vs. observation
  - Results
    - 5-year LC 82% (brachytherapy) vs 69% (observation)
      - No difference low-grade
    - Improved LC with brachytherapy with negative margins
      - No difference in LC with positive margins
    - No Difference in DM or 5-yr DSS

Pisters PW, et al., *J Clin Oncol*, 1994

Evolution of Treatment



Benefits of Pre-operative RT

- Lower RT dose
- Smaller Treatment Volumes
- Facilitate Surgical Resection
  - Margin Status
- Improved Oxygenation of Tumor Cells
- Less Long-Term Toxicity
  - Fibrosis and Joint Stiffness

Pre-operative vs. Post-operative RT

- **NCI Canada**
  - 190 (out of 266 planned) pts with STS of extremity
  - RT
    - Pre-operative: 50 Gy
      - Positive margins: Boost of 16-20 Gy
    - Post-operative: 66-70 Gy
  - Results
    - Wound Complications: Pre-operative RT 35% vs. post-operative RT 17% (SS)
      - Highest rate of complications in thigh (45% vs. 28%)
    - No difference in LR, LRR, DM
    - OS better after >2.5 years for pre-operative group
      - Study not designed for survival

O'Sullivan B et al., *Lancet*, 2002

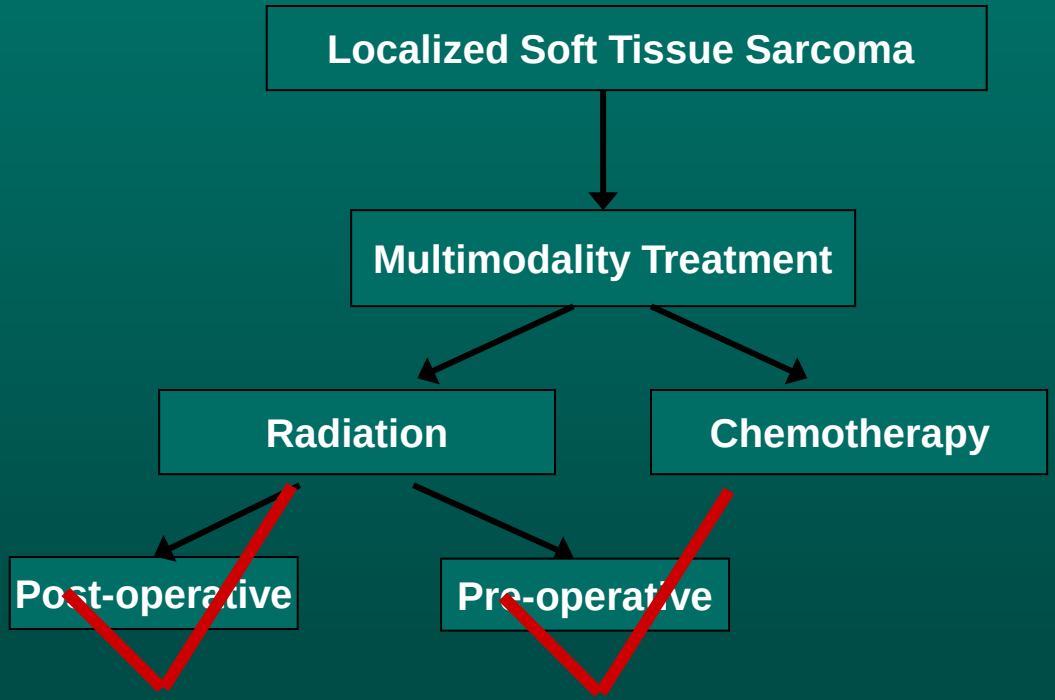
Historical Data: Pre-operative RT

Study	Institution	# of Preop Patients and Follow-up	Chemo?	Median RT Dose (Gy)	Local Control	5 yr Survival
Brant, et al.	U of Florida	58 4.35 y (mean)	No	50.4	91%	~45%
Barkley, et al.	MDACC	114 2 y (min)	No	50	90.3%	NR
O'Sullivan, et al.	NCI	93 3.3 y	No	50	93%	73%
Wang, et al.	Multi-institutional	86 3.6 y	No (Chemo cohort not included)	50	94%	NR
Sampath, et al.	Utah	293 5.25 y	Yes	50.4	93%	53%
Zagars, et al.	MDACC	271 6 y	Yes	50	87%	63%
Bedi, et al.	MCW	112 3.1 y	Yes	50.4	97%	74.2%

Range: 87-97%

Range: 45-74%

Evolution of Treatment



Adjuvant Chemotherapy

- **Sarcoma Meta-Analysis**
  - 1568 pts from 14 trials with resectable STS
  - Surgery +/- radiation→ Doxorubicin
    - RT in approximately 50%
    - Additional chemotherapy in 54%
    - ~2/3 had high grade disease
  - Results
    - Improved recurrence-free survival & trend toward OS in favor of adjuvant chemotherapy
    - OS improved in extremity soft tissue sarcomas

Tierney DF et al., *Lancet*, 1995

Adjuvant Chemotherapy

- **Another Sarcoma Meta-Analysis!**
  - 1953 patients from 18 trials with resectable STS
  - Surgery +/- radiation→ Doxorubicin +/- Ifosfamide
  - Results
    - Improved recurrence-free survival & OS in favor of adjuvant doxorubicin and ifosfamide
    - Local recurrence improved, but not SS (p=0.12)

Pervaiz N et al., *Cancer*, 2008

Neo-adjuvant Chemotherapy

- **Tailored Neoadjuvant Chemotherapy**
  - Histology-dependent
    - 287 patients
    - Randomized
  - Treatment
    - Arm 1: Epirubicin + Ifosfamide x 3
    - Arm 2: Histology-tailored therapy x 3
      - Myxoid LPS: trabectedin
      - Synovial Sarcoma: ifosfamide-high dose
      - LMS: gemcitabine + dacarbazine
      - Pleomorphic: gemcitabine + docetaxel
      - MPNST: ifosfamide + etoposide
  - Results
    - DFS in favor of standard arm (62% vs 38%, p=0.004)
    - Improvement of OS of ~20% at 3 years in favor of standard chemotherapy

Gronchi A, et. al. *Lancet Oncol*, 2017

Neoadjuvant Chemotherapy

Study	Type of Study	No of Pts	Tx Regimen	RT?	Outcomes	Toxicity
EORTC STBSG 62871	Phase II Randomized	134	Surgery vs Doxarubicin-Ifosfamide→Surgery	Yes	No difference in DFS or OS	Leukopenia: 32% G4 toxicity: 8%
Delaney, et al.	Retrospective	48	Interdigitated MAID sequential CRT→ surgery→ MAID x 3	Yes	Improvement in DFS and OS (vs historical control)	Wound Comp: 29% Tx- related deaths: 2%
RTOG 9514	Phase II	64	Interdigitated MAID sequential CRT→ surgery→ MAID x 3	Yes	LC: 89.9% OS: 75.1%	≤ G3 toxicity: 97%
Bedi, et al.	Retrospective	112	Sequential (AIM x 3→RT→surgery)	Yes	LC: 97% 3 yr OS: 86%	NR

Opinion

VIEWPOINT

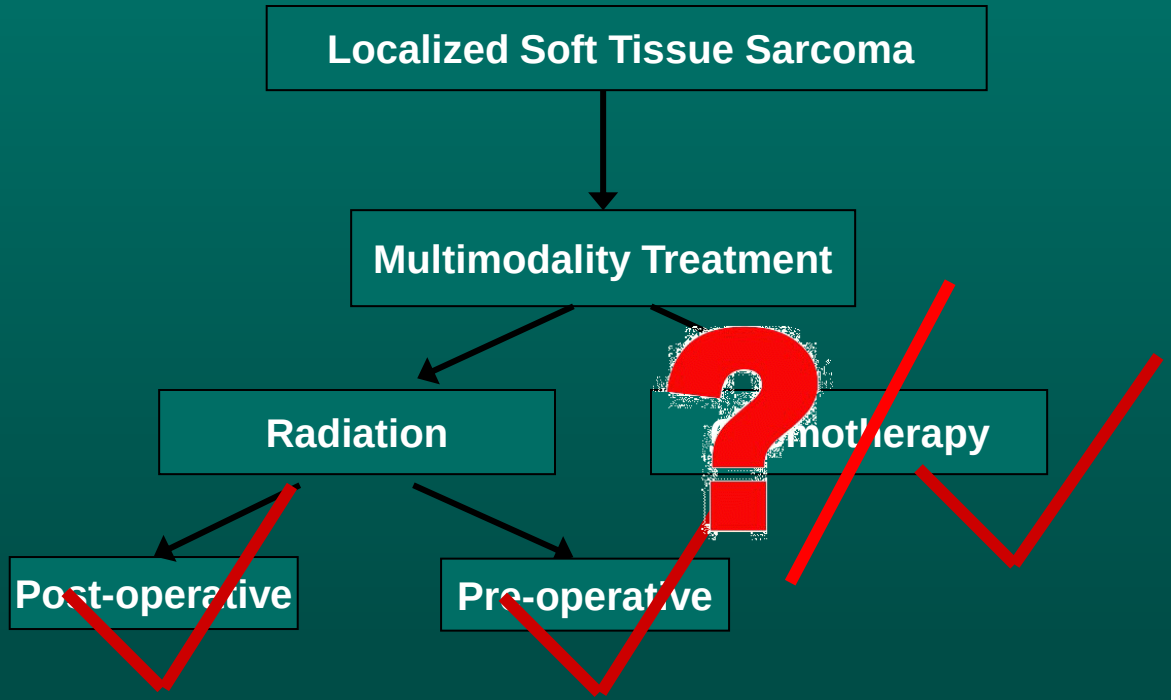
Low Levels of Evidence for Neoadjuvant Chemotherapy to Treat Soft-Tissue Sarcoma

Should neoadjuvant chemotherapy be used to treat localized high-risk soft-tissue sarcoma?

- No
  - Neoadjuvant and adjuvant chemotherapy trials in STS have been performed for the last 3 decades.
  - Relative benefit vs risks of adding chemotherapy to local control measures remains an ongoing topic of discussion without consensus
  - No RCT designed to determine whether chemotherapy in addition has definitively demonstrated a clinically significant and durable improvement in OS

George S, et al., *JAMA Oncol*, 2018

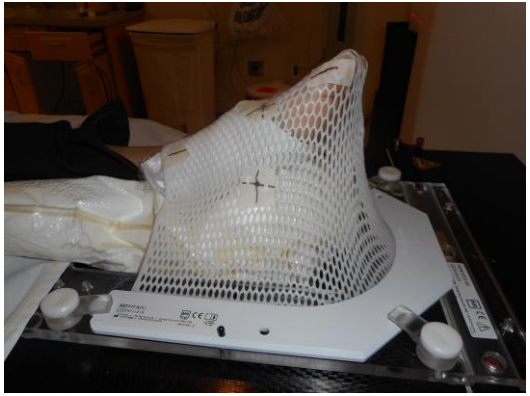
Evolution of Treatment



Radiation Planning

CT Simulation

- CT and **MR sim** if possible
  - MR fusion
- Immobilization
  - Vac-fix
  - Aquaplast
- Patient position
  - Supine or Prone
    - Tumor location
  - Frog-leg



Foot

Medial Thigh

Pre-operative Radiation Target

- Extremity or Trunk
- Gross Tumor Volume (GTV)
  - Tumor defined by T1 + gadolinium and/or T2 sequences on MRI
  - Fusion of MRI/CT recommended
- Clinical Target Volume (CTV)
  - Radial: GTV+1.5 cm
  - Longitudinal: GTV+3-4 cm
    - Encompass tumor-related edema, biopsy tract
    - Constrain anatomic boundaries (compartment fascia, bone, etc)
- Planning Target Volume (PTV)
  - 0.5 cm margin with daily IGRT
  - Consider ≥1 cm without daily IGRT
  - PTV may be trimmed 3-5 mm from skin

Wang D et al, *Int J Radiat Oncol Biol Phys*, 2011
Haas R, et al., *Int J Radiat Oncol Biol Phys*, 2012

Post-operative Radiation Targets

- Extremity or Trunk

- CTV1
  - Tumor bed
    - Clips, preoperative MRI
  - Radial: 1.5 cm
  - Longitudinal: 3-4 cm
    - Ensure to encompass operative bed, scar, drains
  - Constrain anatomic boundaries (compartment fascia, bone, etc)

- CTV2
  - Tumor bed
  - Radial: 1.5 cm
  - Longitudinal: 2 cm
    - Encompass tumor-related edema, biopsy tract
    - Constrain anatomic boundaries

- PTV
  - 0.5 cm margin with daily IGRT
  - ≥1 cm without daily IGRT

Wang D et al., *J Clin Oncol*, 2015

Dose/Fractionation

- Pre-operative RT
  - 50 Gy @ 2 Gy/fraction
- Post-operative
  - PTV1: 50-50.4 Gy @ 1.8-2 Gy/fraction
  - PTV2: 10-16 Gy at 1.8-2 Gy/fraction
    - Consider margins
- 3D vs IMRT?
  - IMRT to spare organs at risk
  - 3D may be preferred in certain clinical cases

Alektiar K, et al., *Int J. Radiation Biol Phys.*, 2007

Pre-operative Dose Reduction?

JAMA Oncology | Original Investigation

Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma A Nonrandomized Controlled Trial

Jules Lansu, MD; Judith V. M. G. Bovée, MD, PhD; Petra Braam, MD, PhD; Hester van Boven, MD, PhD; Uta Flucke, MD, PhD; Johannes J. Bonenkamp, MD, PhD; Aisha B. Miah, MD, PhD; Shane H. Zaidi, MD; Khin Thway, MD; Øyvind S. Bruland, MD, PhD; Elizabeth H. Baldini, MD, PhD; Nina L. Jebsen, MD, PhD; Astrid N. Scholten, MD, PhD; Piet L. A. van den Ende, MD; Augustinus D. G. Krol, MD, PhD; Jan F. Ubbels, MD, PhD; Jos A. van der Hage, MD, PhD; Erik van Werkhoven, MSc; Houke M. Klomp, MD, PhD; Winette T. A. van der Graaf, MD, PhD; Frits van Coevorden, MD, PhD; Yvonne Schrage, MD; Winan J. van Houdt, MD, PhD; Rick L. Haas, MD, PhD

DOREMY

- Phase II non-randomized trial of localized myxoid liposarcomas of the extremity or trunk
- RT Prescription: 36 Gy at 2 Gy/fraction
- Endpoints
  - Treatment response in surgical specimen (primary)
    - <50% viable tumor cells
  - Local control (secondary)
  - Wound complication (secondary)
  - Late toxicity (secondary)
  - Disease-specific survival (secondary)
  - Overall survival (secondary)

Lansu J, et al., *JAMA Oncol*, 2020

DOREMY Results

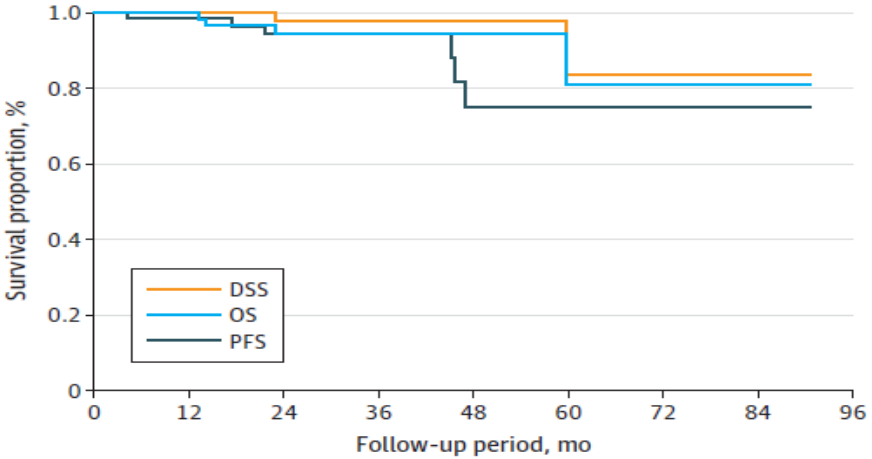
- 79 patients
- Median follow-up: 25 months

Endpoint	Outcome
Treatment Response	91% with ≥ 50% treatment response
Local control	100%
Wound complication	22%
1-year disease-specific survival	99%
1-year progression-free survival	97%
1-year Overall survival	99%
Late toxicity (≥grade 2)	11%

Lansu J, et al., *JAMA Oncol*, 2020

DOREMY Results

Figure 2. Kaplan-Meier Survival Analysis of the Intention-to-Treat Population



DSS indicates disease-specific survival; OS, overall survival; PFS, progression-free survival.

Conclusions:

-36 Gy at 2 Gy/fraction is safe, effective and **should be considered**

-Less morbidity than historical data

Lansu J, et al., *JAMA Oncol*, 2020

Back to our tale…

- 55-year-old male presents with a left thigh 9 cm heterogenous mass. Biopsy reveals a **high grade leiomyosarcoma**. Systemic imaging is negative

- 55-year-old male presents with a left thigh 9 cm heterogenous mass. Biopsy reveals a **myxoid liposarcoma** with a round cell component. Systemic imaging is negative

Abdominal/Retroperitoneal Sarcomas

A Tale of 3 Sarcomas…

- 55-year-old male presents with a 17 cm retroperitoneal high grade leiomyosarcoma Systemic imaging is negative…and it's the year 2015
- 55-year-old male presents with a 17 cm retroperitoneal high grade leiomyosarcoma Systemic imaging is negative…and it's the year 2021
- 55-year-old male presents with a 17 cm well differentiated liposarcoma. Systemic imaging is negative.

Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial

Sylvie Bonvalot, Alessandro Gronchi, Cécile Le Péchoux, Carol J Swallow, Dirk Strauss, Pierre Meeus, Frits van Coevorden, Stephan Stoldt, Eberhard Stoeckle, Piotr Rutkowski, Marco Rastrelli, Chandrajit P Raut, Daphne Hompes, Antonino De Paoli, Claudia Sangalli, Charles Honoré, Peter Chung, Aisha Miah, Jean Yves Blay, Marco Fiore, Jean-Jacques Stelmes, Angelo P Dei Tos, Elizabeth H Baldini, Saskia Litière, Sandrine Marreaud, Hans Gelderblom, Rick L Haas

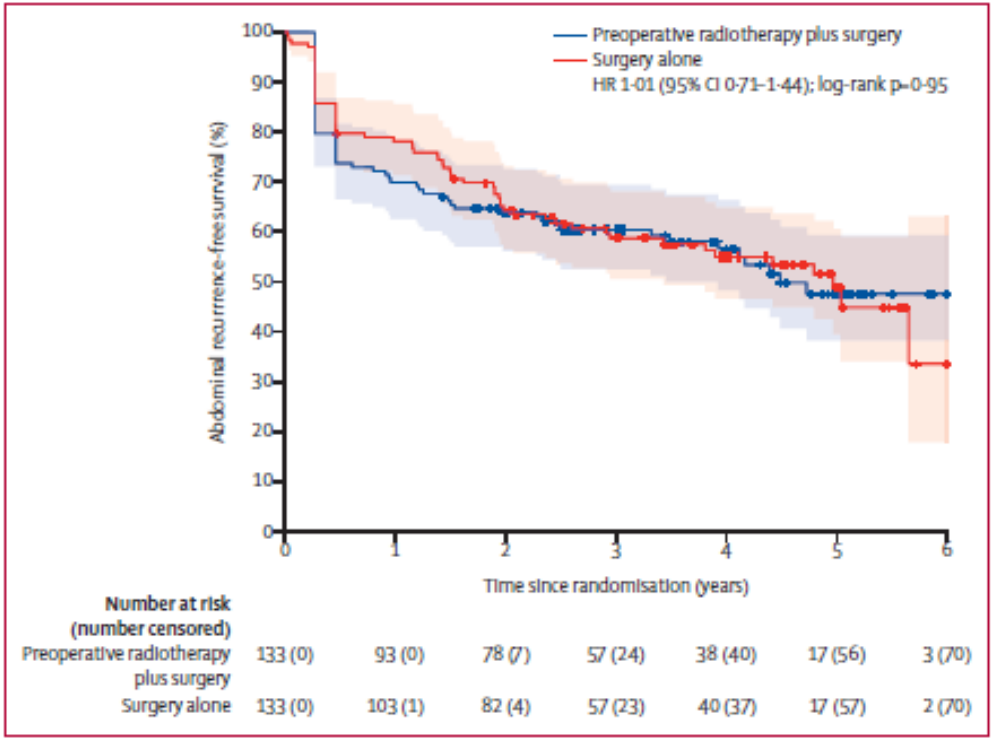
STRASS Trial

- Phase III randomized trial
- 266 pts
  - 133 received pre-operative RT (median dose 50.4 Gy)
  - 133 received surgery alone
  - 198 pts had liposarcomas (74%)
- Primary Endpoint
  - Abdominal Recurrence-Free Survival (ARFS)

Abdominal Recurrence-Free Survival

- ARFS
  - Progressive disease
  - Patient reaches score of 3 American Society of Anesthesiologists scale
  - Macroscopically incomplete resection
  - Sarcomatosis
  - Local relapse

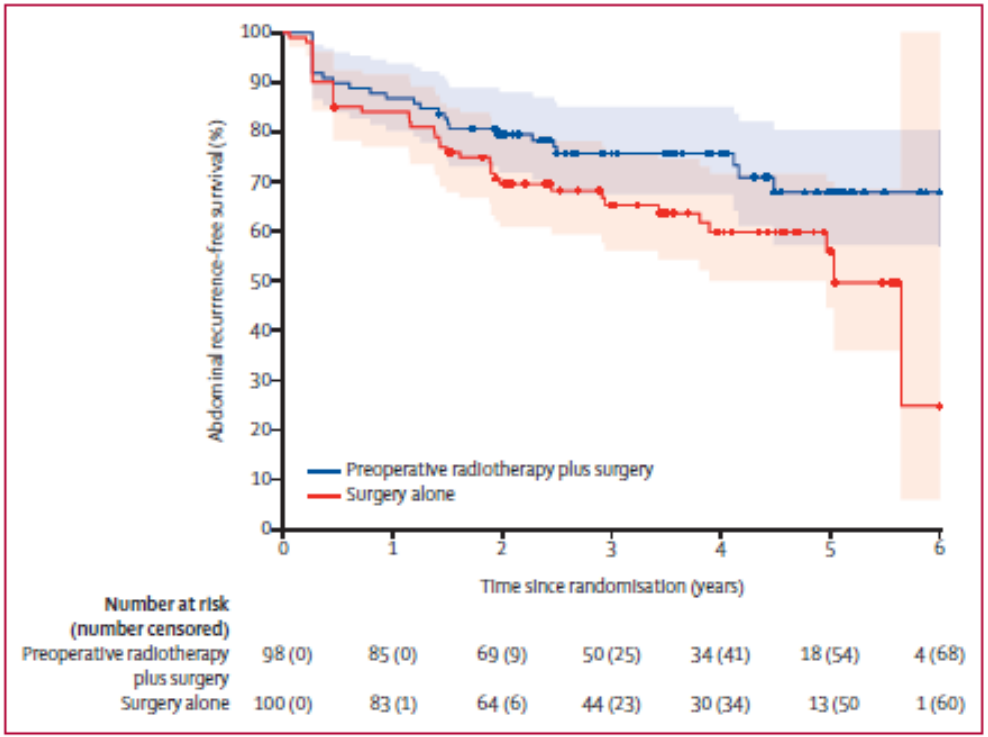
ARFS
All Patients



Number at risk (number censored)							
Preoperative radiotherapy plus surgery	133 (0)	93 (0)	78 (7)	57 (24)	38 (40)	17 (56)	3 (70)
Surgery alone	133 (0)	103 (1)	82 (4)	57 (23)	40 (37)	17 (57)	2 (70)

Figure 2: **Abdominal recurrence-free survival in all patients**
Shaded areas around the lines represent the 95% CI. HR=hazard ratio.

ARFS
Liposarcomas



Number at risk (number censored)							
Preoperative radiotherapy plus surgery	98 (0)	85 (0)	69 (9)	50 (25)	34 (41)	18 (54)	4 (68)
Surgery alone	100 (0)	83 (1)	64 (6)	44 (23)	30 (34)	13 (50	1 (60)

Figure 3: **Second sensitivity analysis of abdominal recurrence-free survival in the liposarcoma subgroup**
Shaded areas around the lines represent the 95% CI. HR=hazard ratio.

Outcomes

- 5-year OS
  - 79.4% surgery vs 76.7% in RT
- Toxicity

Grade 3-4 Toxicity	Pre-operative RT	Surgery Alone
Lymphopenia	77%	1%
Anemia	12%	8%
Hypoalbuminemia	12%	4%

*Serious adverse events: 24% RT group vs 10% surgery alone group

Conclusions

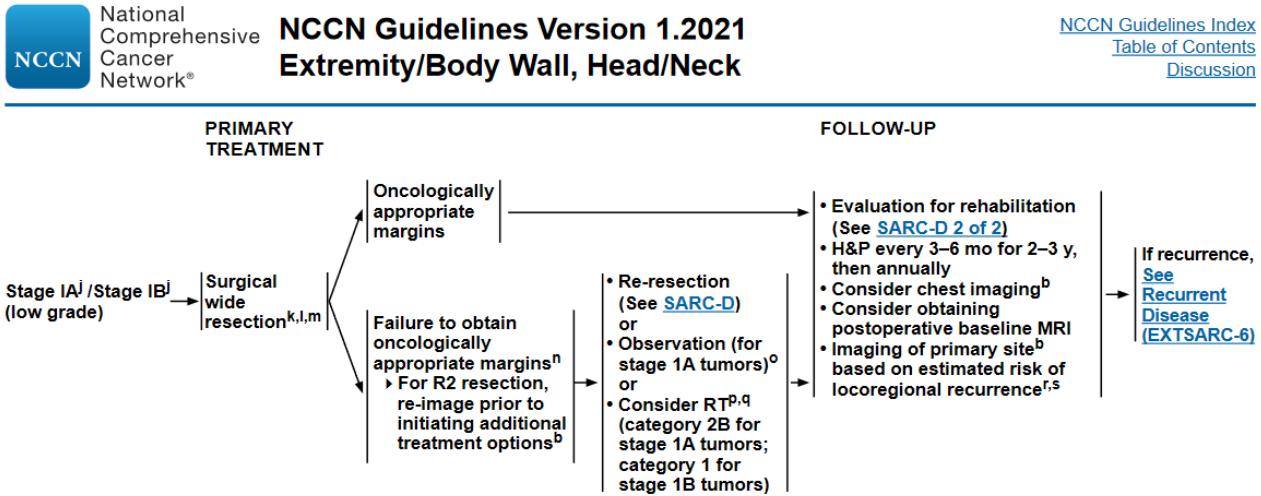
"Preoperative radiotherapy should not be considered as standard of care treatment for retroperitoneal sarcomas"

STRASS 2

- Histology Stratification
  - High-grade de-differentiated liposarcoma & leiomyosarcoma
  - Primary objective
    - Assess whether three cycles of pre-operative chemotherapy improves DFS vs. surgery alone
  - Chemo
    - Liposarcomas: Dox/ifosfamide
    - Leiomyosarcomas: Dox/Dacarbazine

Special Scenarios

No Radiation?



No Radiation?

- Stage IA
  - Superficial T1 (≤ 5 cm) and G1: Surgery alone
  - Deep tumor, abutment to neurovascular bundle, critical structures: Consider RT?
    - Multi-disciplinary discussion
    - Ability to achieve negative margins?

Hypofractionation

- α/β ratio
  - Sarcomas tend to have lower α/β ratios
    - α/β ratio ~ 4-5 (literature range: 0.5-5)

- Increasing number of protocols/studies investigating hypofractionation

Hypofractionation

Institution	Year	Study size (n)	Dose/ Fractionation	Median Follow-Up	Major Wound Complications	Grade 2+ Late Tox	Local Control
Kosela-Paterczyk	2014	272	5 Gy x 5	35 mo	~28.3%	~14.7%	80.5%
Kalbasi et al.	2020	52	6 Gy x 5	29 mo	32%	16%	94%
Paraso et al.	2020	16	6 Gy x 5	10.7 mo	19% (31% total)	N/A	N/A
Medical College of Wisconsin	Completed accrual	32	7.Gy x 5				
MDACC	Accruing	120	2.85 Gy x 15				
University of Wisconsin	Accruing	48	Up to 60 Gy x 3-8 fractions				

Immunotherapy

Reference	Agent	Phase	Pts (*n*)	Indication	Response rate	Survival
Checkpoint inhibitors						
Maki *et al.*, 2013[19]	Ipilimumab	I	6	Advanced SyS	0 of 6	mOS: 8.75 months
Tawbi *et al.*, 2017[16]	Pembrolizumab	II		Selected STSs and bone sarcomas	18% in STS, 40% in UPS, 20% in LPS, 10% in SyS	mPFS: 18 weeks; OS: 49 weeks
D'Angelo *et al.*, 2018[21]	Nivolumab with or without ipilimumab	II	96	Metastatic STS	Nivolumab: 5%; Ipilimumab–nivolumab: 16%	mPFS: 4.1 months; OS: 14.3 months
Toulmonde *et al.*, 2018[26]	Pembrolizumab, cyclophosphamide	II	57	Advanced STS	Solitary fibrous tumour in 1 patient	NA
Wilky *et al.*, 2019[22]	Axitinib, pembrolizumab	II		ASPS and other STSs	25%, all STS patients; 50.4%, ASPS patients	3-Month PFS: 66%; in ASPS patients: 73%
Adoptive cell therapy						
Robbins *et al.*, 2011[27]	Adoptively transferred autologous T cells transduced with a T cell receptor directed against NY-ESO-1	I	6	Metastatic SyS expressing NY-ESO-1	4 of 6	NA

Ayodele O, et al., *Current Oncol.*, 2020

Ongoing Immunotherapy Trials

ClinicalTrials.gov ID	Details
NCT03463408	*Study title:* Immunotherapy + radiation in resectable soft tissue sarcoma *Phase:* I *Status:* Recruiting *Location:* U.S.A. *Interventions:* Ipilimumab, nivolumab, and radiation
NCT03116529	*Study title:* Neoadjuvant durvalumab and tremelimumab plus radiation for high risk soft-tissue sarcoma (NEXIS) *Phase:* I/II *Status:* Recruiting *Location:* U.S.A. *Interventions:* Durvalumab, tremelimumab, and radiation
NCT02815995	*Study title:* Multi-arm study to test the efficacy of immunotherapeutic agents in multiple sarcoma subtypes *Phase:* II *Status:* Active, not recruiting *Location:* U.S.A. *Interventions:* Durvalumab and tremelimumab
NCT03138161	*Study title:* SAINT: trabectedin, ipilimumab and nivolumab as first line treatment for advanced soft tissue sarcoma *Phase:* I/II *Status:* Recruiting *Location:* U.S.A. *Interventions:* Trabectedin, ipilimumab, and nivolumab
NCT02609984	*Study title:* Trial of CMB305 and atezolizumab in patients with sarcoma (IMDZ-C232) *Phase:* II *Status:* Active, not recruiting *Location:* U.S.A. *Interventions:* Atezolizumab and CMB305
NCT03851614	*Study title:* Basket combination study of inhibitors of DNA damage response, angiogenesis and programmed death ligand 1 in patients with advanced solid tumors (DAPPER) *Phase:* II *Status:* Recruiting *Location:* Canada *Interventions:* Durvalumab and olaparib–cediranib
NCT02879162	*Study title:* Durvalumab and tremelimumab in patients with advanced rare tumours *Phase:* II *Status:* Recruiting *Location:* Canada *Interventions:* Durvalumab and tremelimumab

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Ongoing Immunotherapy Trials

NCT03141684	*Study title:* Atezolizumab in treating patients with newly diagnosed and metastatic alveolar soft part sarcoma that cannot be removed by surgery		
	Phase: II	*Status:* Recruiting	*Location:* U.S.A.
	Interventions: Atezolizumab		
NCT03450122	*Study title:* Modified T cells, chemotherapy, and aldesleukin with or without LV305 and CMB305 in treating participants with advanced or recurrent sarcoma		
	Phase: I	*Status:* Active, not recruiting	*Location:* U.S.A.
	Interventions: Modified T cells; LV305 or CMB305		
NCT00902044	*Study title:* HER2 chimeric antigen receptor expressing T cells in advanced sarcoma		
	Phase: I	*Status:* Recruiting	*Location:* U.S.A.
	Interventions: Autologous HER2-specific T cells; fludarabine, cyclophosphamide		
NCT02423863	*Study title:* *In situ,* autologous therapeutic vaccination against solid cancers with intratumoral Hiltonol (poly-ICLC)		
	Phase: II	*Status:* Recruiting	*Location:* U.S.A.
	Interventions: Hiltonol		

Ayodele O, et al., *Current Oncol.*, 2020

Surgery Conclusions

- Surgeon involvement from Day 1!

- Extremity
  - Limb-sparing surgery!
  - Surgical or orthopaedic oncology

- Retroperitoneal
  - Resection
  - Multi-disciplinary discussion
  - Surgical oncology

Radiation Conclusions

- Extremity
  - May avoid RT in small, superficial, low grade tumors
  - Preferable pre-operative RT for large, high grade tumors
  - Post-operative RT acceptable
  - Pre-operative Hypofractionation
    - Stay tuned!

- Retroperitoneal
  - Multi-disciplinary discussion
  - Benefit to surgery/surgeon?

Chemotherapy Conclusions

- Extremity
  - Mixed data
  - Marginal benefit
  - Multi-disciplinary discussion (common theme!!)
  - Risk/benefit
  - Consider in large, high grade tumors, certain histologies

- Retroperitoneal
  - STRASS 2
    - Stay tuned!

Sarcoma Resources

- NCCN Guidelines
  - https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
- New Sarcoma Consensus Guidelines
  - 2021
- Refresher courses
- Contour atlas/publications

Sarcoma Resources

Treatment Guidelines for Preoperative Radiation Therapy for Retroperitoneal Sarcoma: Preliminary Consensus of an International Expert Panel

Elizabeth H. Baldini, MD, MPH,* Dian Wang, MD, PhD,†
Rick L.M. Haas, MD, PhD,‡ Charles N. Catton, MD,§
Daniel J. Indelicato, MD,‖ David G. Kirsch, MD, PhD,¶
David Roberge, MD,# Kilian Salerno, MD,** Curtiland Deville, MD,††
B. Ashleigh Guadagnolo, MD, MPH,‡‡ Brian O'Sullivan, MD,§
Ivy A. Petersen, MD,§§ Cecile Le Pechoux, MD, PhD,‖‖
Ross A. Abrams, MD,† and Thomas F. DeLaney, MD, PhD¶¶

Radiotherapy for Management of Extremity Soft Tissue Sarcomas: Why, When, and Where?

Rick L.M. Haas, MD, PhD,* Thomas F. DeLaney, MD, PhD,† Brian O'Sullivan, MD, PhD,‡
Ronald B. Keus, MD,§ Cécile Le Pechoux, MD, PhD,‖ Patricia Olmi, MD, PhD,¶
Jan-Peter Poulsen, MD, PhD,# Beatrice Seddon, MD, PhD,** and Dian Wang, MD, PhD††

*From the *Department of Radiotherapy, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; †Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; ‡Department of Radiation Oncology, Princess Margaret Hospital, Toronto, ON, Canada; §Department of Radiotherapy, Arnhems Radiotherapeutisch Instituut, Arnhem, The Netherlands; ‖Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France; ¶Department of Radiotherapy, Istituto Nazionale per lo Studio e la cura dei Tumori, Milan, Italy; #Department of Radiotherapy, Norwegian Radium Hospital—Oslo University Hospital, Oslo, Norway; **Department of Radiotherapy, University College London Hospitals, London, UK; and ††Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*

Thank you!