Limb Preservation Treatment of Soft Tissue Sarcomas

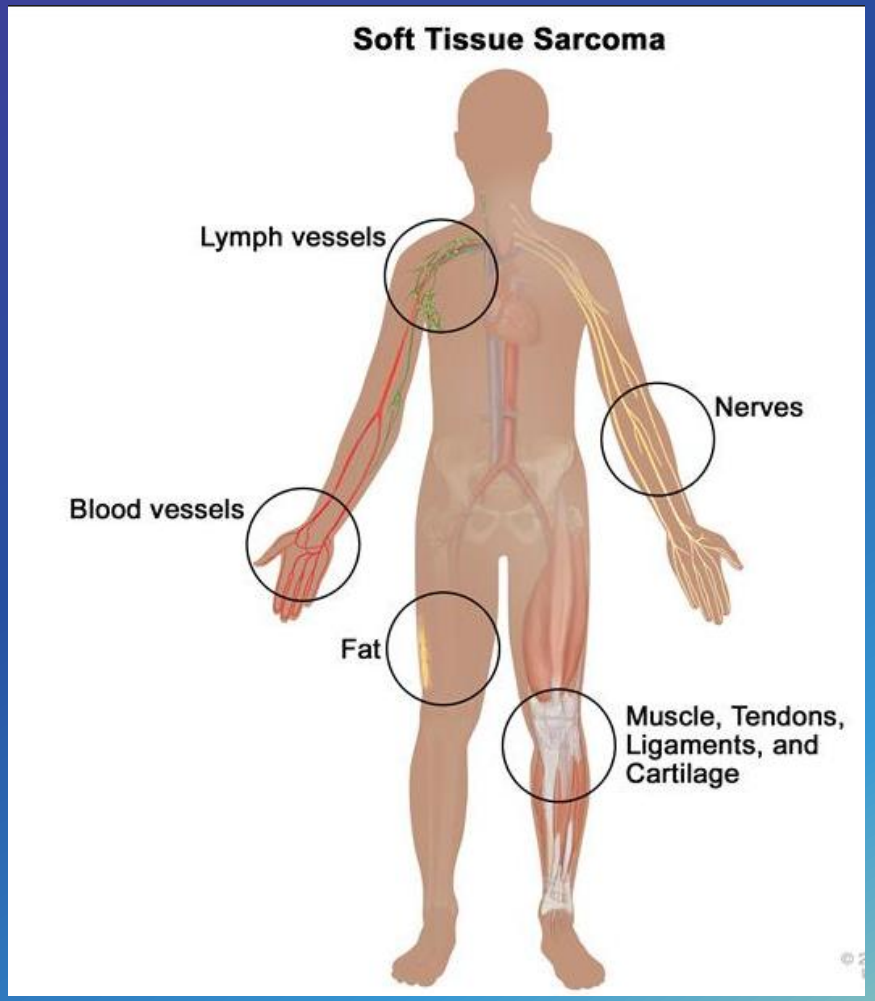
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Limb Preservation for Extremity Soft Tissue Sarcomas

- In the 1970's, over 50% of extremity soft tissue sarcomas were treated by amputation
- Evidence of remarkable progress in oncologic care is that ~95% are currently treated with limb preservation
  - Sarcoma teams are committed to limb preservation as long as treatment results in a functional limb
    - Non-functional limb is worse than an amputated limb
  - Our tumor board discussions are now focused on how to optimize oncologic and functional outcomes

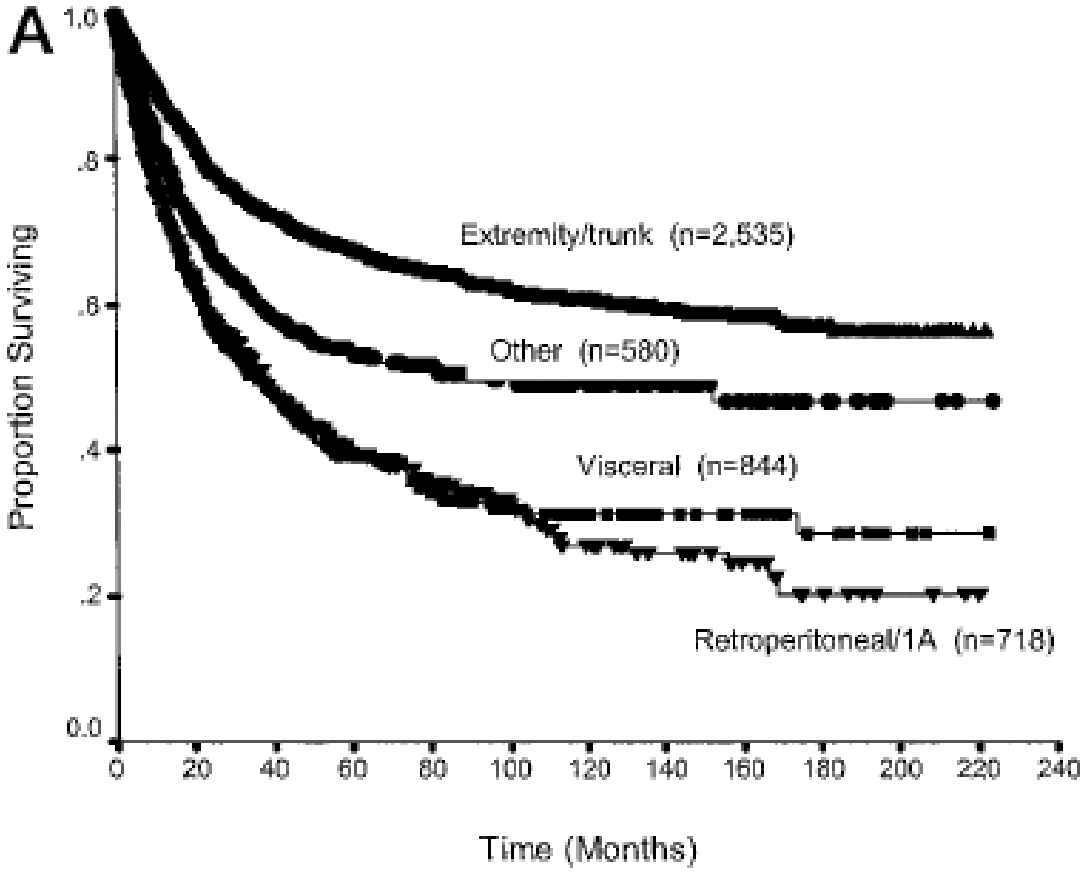
Overview

- **~19,000 new sarcoma cases in the US**
  - <1% all adult cancers
  - 7% all pediatric cancers
- **Arise from mesenchymal tissue at any site**
  - ~80% from soft tissue
    - >75 histologic subtypes
      - Pathology review is critical
    - Many have unique translocations
    - Extremity most common tumor site
      - 45% lower and 15% upper extremity
  - ~20% from bone
- Ideally managed by experienced, multidisciplinary team



STS Survival by Anatomic Site

- Within anatomic sites, grade and size are major drivers of OS
- May also influence Rx decisions re: local therapy since small, low-grade lesions unlikely to metastasize



Slide courtesy of Edwin Choy, M.D., Ph.D.

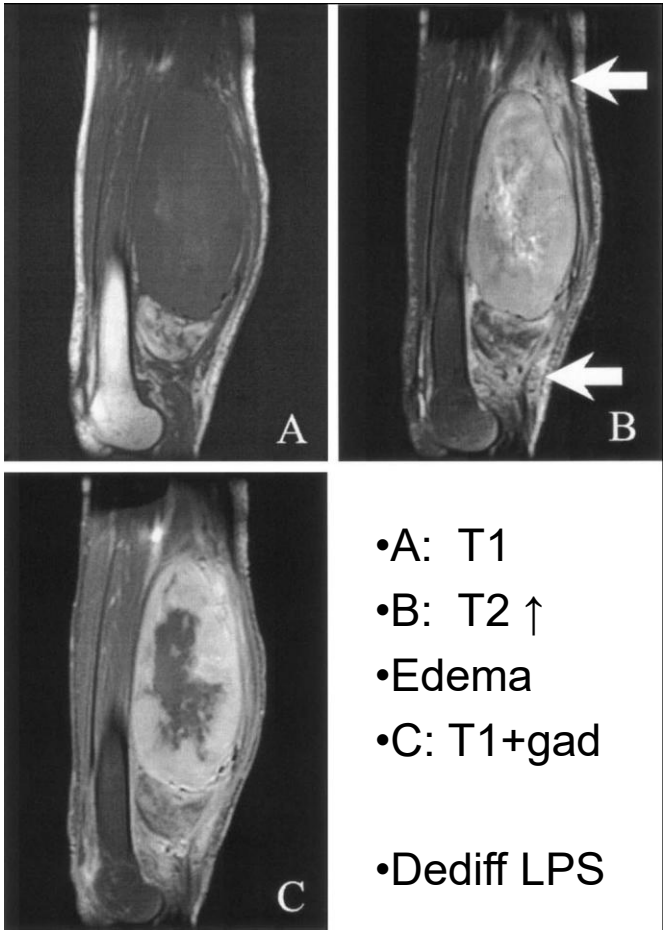
Borden et al, Clin Cancer Res 2003

MRI Assessment of Extent of Tumor

White et al (Princess Margaret)

- Correlated MRI and pathology findings in 15 STS pts undergoing surgery alone
- Tumor cells beyond main mass in 10/15
  - 6 pts < 1cm
  - 4 pts 1-4 cm
- In 9/10, cells were found in areas of T2 edema, which were usually proximal/ distal to tumor

- IJROBP 61:1439, 2005



- A: T1
- B: T2 ↑
- Edema
- C: T1+gad

- Dediff LPS

LR According to Type of Surgery

Marginal

- 40-90% local recurrence rate

Wide local excision

- Local recurrence
  - 25-30% Surgery alone
  - <10% Surgery + XRT→ Preferred for most pts
    - LR: 5-10% (-) margins vs. 20-40% (+) margins → Re-excise if possible

Amputations/Radical Resections

- Amputation is done one level above the affected portion of the limb
  - i.e. Above knee amputation for leg sarcoma
  - **Very significant functional loss**

Extremity STS Management : Surgery and RT

- Randomized trial at the US National Cancer Institute (NCI) showed wide resection (limb sparing) + adjuvant RT has local control of 85-90% and equivalent OS to amputation (Rosenberg S et al, Ann Surg 1982)

- Second randomized trial at NCI showed limb-preservation surgery + RT has higher local control than limb preservation surgery alone for both high- and low-grade extremity sarcomas (Yang J et al, JCO 1988)
  - High grade: LR : 0% S+ RT vs. 19% S
  - Low grade: LR: 4% S + RT vs. 33% S

Impact of Local Recurrence

- **Pisters et al (Memorial Sloan Kettering)**
  - Presentation with LR was adverse factor for DM and disease-specific survival (»J Clin Oncol 1996; 14:1679)
- **Eilber et al (UCLA)**
  - Pts with high grade STS with LR are ~ 3 x ↑ risk of sarcoma death vs. pts with local control
  - 38% required amputation
    - Ann Surg 2003;237:218.
- **Trovik et al (Stockholm)**
  - LR a risk factor for late DM in pts otherwise at low risk of DM.
    - (»Acta Orthoped Scand 1994;65;553)

Extremity STS Therapy : Function

Stinson S et al, National Cancer Institute

- 145 patients: Surgery and postoperative RT +/- chemoRx
- 84% of patients were ambulating free of assistive devices with no or only mild pain
  - **Non-functional limb worse than no limb**
- >50% joint inclusion in RT field associated with contracture
- Chronic ulcer or infection more common if >75% of the limb diameter were irradiated
- Doses >63 Gy at 1.8 Gy per fraction →more pain, edema, telangiectasias and worse muscle strength and ROM
- RT fields > 35 cm associated with edema, induration

Stinson S et al, IJROBP 1991

Extremity STS Therapy: Function

- **Reijers SJM et al, Holland (2022): 28 amp vs 69 LSS**
  - Compared 28 amputees with 69 limb-spared patients
  - **Limb-spared pts had improved physical and role function**
- **Sugarbaker P et al, NCI, 1982: 8 amputees vs 15 LSS**
  - No definite differences seen in QoL impact of Rx (pain, mobility, Rx trauma, and sexual function).
    - Sexual function worse in S + RT pts (gonadal scatter from RT)
- **Better physical function with LSS but mental health and psychological outcomes appear similar→ patients are remarkably resilient and often manage to adapt to loss of limb, which may be important in decision making if patient has a local recurrence that is recommended to be managed with amputation.**

NCIC/O'Sullivan Study

1994-1997

Previously untreated STS of the extremity (N= 190)

Arm I

Pre-operative RT
50Gy w/16Gy post-op if R1+
(N= 88)

Arm II

Post-operative RT
50Gy + 16Gy boost for all
(N= 94)

- RT margin: 5 cm to 50 Gy, then 2 cm for 16 Gy boost
- Primary endpoint: major wound complication within 4 months post-op
  - Repeat surgery/intervention
  - Re-admission for wound care
  - Packing present >120 days

Lancet. 2002;359:2235-2241
J Clin Oncol. 2004; 22:14S

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NCIC/O'Sullivan Study

- **Predictors of wound complication:**
- Pre-op RT (OR 3.1)
- Lower extremity site (OR 10.4)
  - No significant difference for upper extremity tumors
- Tumor size > 10 cm (OR 1.1).

	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

Lancet. 2002;359:2235-2241
J Clin Oncol. 2004; 22:14S

NCIC/O'Sullivan Study

Conclusions:

- Pre- & post-op RT have similar oncologic outcomes in terms of disease control
- Pre-op RT causes more major acute wound complications (generally reversible)
- Post-op RT treats larger fields to higher dose which increases late fibrosis, joint stiffness & edema (which are generally irreversible and relate to long-term physical disability)

Lancet. 2002;359:2235-2241
J Clin Oncol. 2004; 22:14S
Radiother Oncol 2005; 75:48-53

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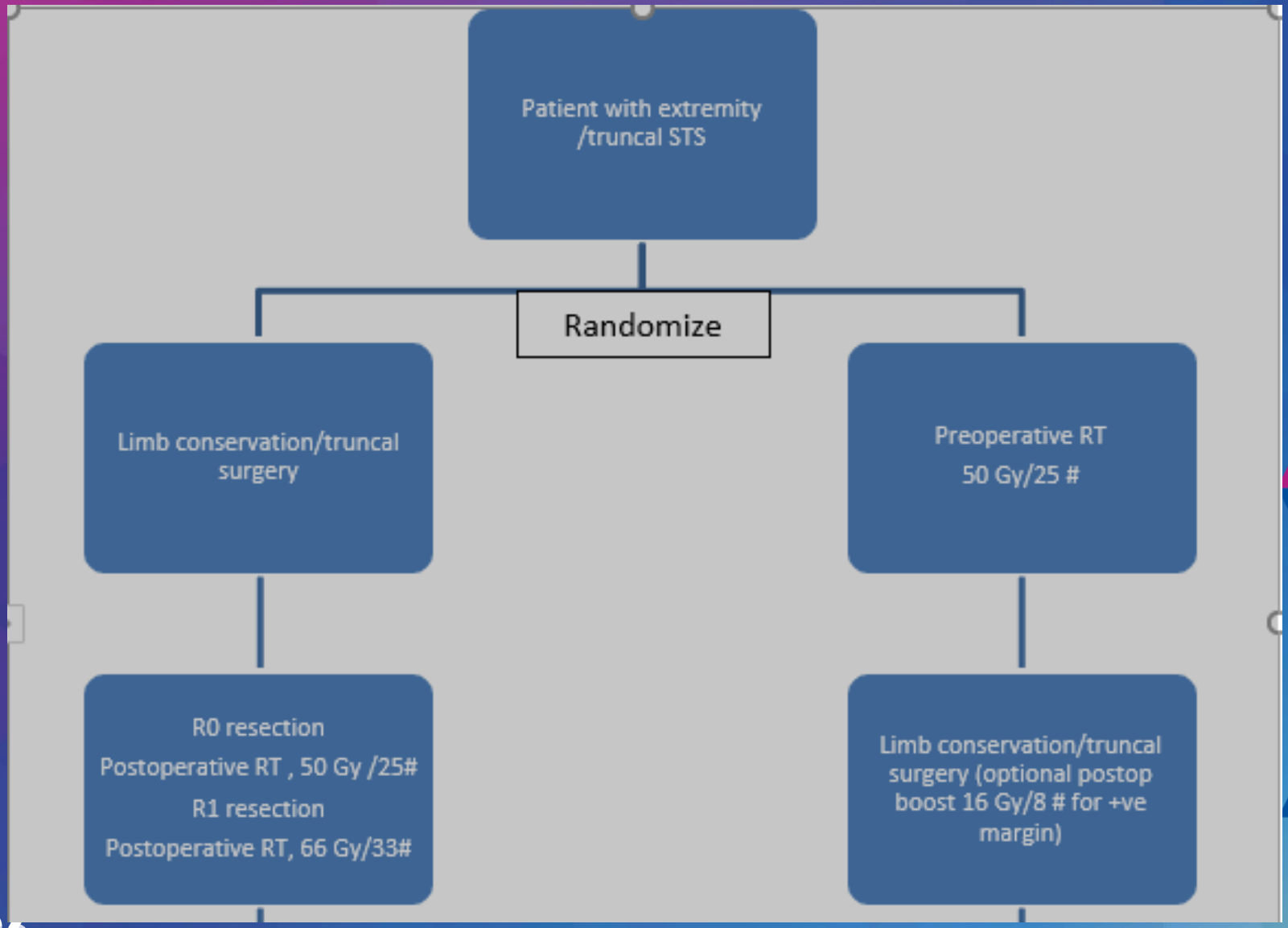
Practice Guideline

Radiation Therapy for Treatment of Soft Tissue Sarcoma in Adults: Executive Summary of an ASTRO Clinical Practice Guideline

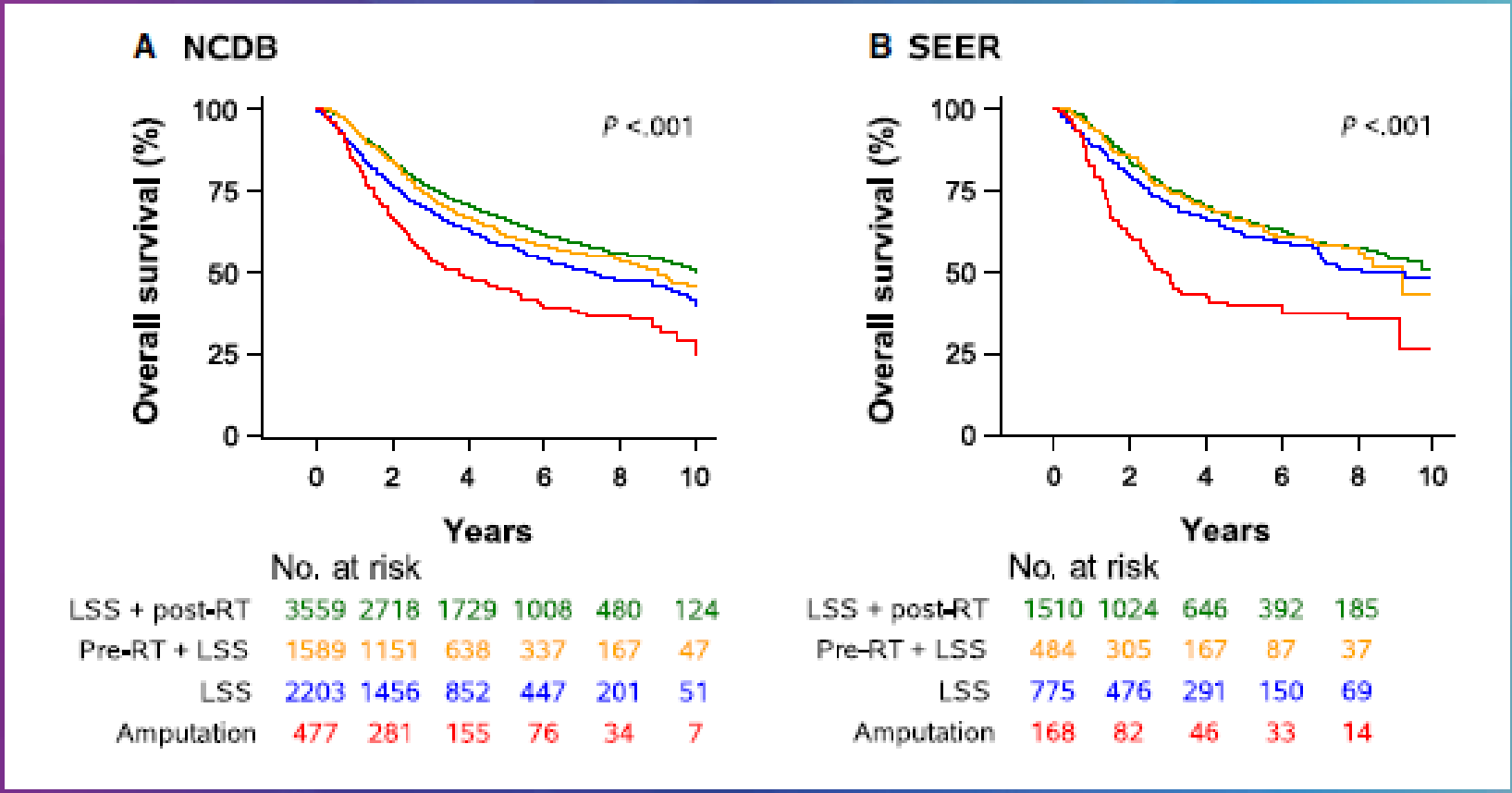
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Preoperative radiation is preferred for most deep soft tissue sarcomas involving/abutting critical structures.

Toronto Preop/Postop 50 Gy Study



Survival According to Therapy



OS after LSS+ RT > LSS alone > amputation

Ramey SJ, et al, Cancer Med 2018

Re-Irradiation for LR or RT-associated STS

- Some series show benefits and others no benefit
  - Consider on case by case basis, based on anticipated surgical margins

- Krcek et al., 2025 (Princess Margaret)
  - 93 recurrent and 13 radiation-associated
  - ReRT: 1.1 Gy b.i.d. to 44 Gy most common fractionation
    - 80% preop; 11% postop; 9% periop brachyRx
  - 5-y **LC**: 82.8% S+RT vs. 67.9% S, p = 0.336
  - 5-y **limb salvage 80.8% vs. 40.2%, p < 0.001, favors reRT**
    - More complications with reRT: 30% vs 6%, p = 0.002
  - 5-y OS was similar between groups (~55–57%)

- For ReRT, NCCN suggests protons (Guttman *et al.*, *U Penn*), brachytherapy (Pearlstone et al, *MDACC*), or IMRT to reduce morbidity

Surgery Alone for Soft Tissue Sarcoma

- **Baldini E et al (Brigham, DFCI), J Clin Oncol 1999**
  - 74/242 (30.6%) pts underwent function sparing surgery without RT; median size 4 cm; 54% G1
    - 10-year actuarial local control was 93%
      - Margin ≥ 1 cm: LC 100%; Margin < 1 cm: LC 87%
      - Narrow fascial barrier may be excellent margin; i.e. width alone doesn't capture quality of margin.

- **Pisters P et al (MDACC), Ann Surg 2007**
  - 88 pts with T1 STS, 51 G2,3, 60 superficial
    - 74 pts (-) margins→ no RT
      - 5-yr cumulative LR: 8%, 10-yr LR:11%
    - 14 pts (+) margins →RT → 5-yr cumulative LR: 43%

Hypofractionation

- **Guadagnolo A et al (MDACC), Lancet Oncol 2022**
  - Phase II Preop RT: 42.75 Gy/15 fx of 2.85 Gy/ 3 weeks
  - LC and morbidity similar to 50 Gy/25 fx
- **Kalbasi A et al (UCLA), Clin Cancer Res 2020**
  - Phase II Preop RT: 30 Gy/5 fx of 6 Gy/ 1 week
  - LC and morbidity similar to 50 Gy/25 fx
- **Haas R et al: SCOPES I: Randomized Phase II**
  - 50 Gy/25 fx vs 42 Gy/14 fx
- **Haas R et al: SCOPES II: Randomized Ph II:**
  - 42 Gy/14 fx vs 30 Gy/5 fx
- **SWOG S2505 study: Randomized Phase III**
  - 50 Gy/25 fx vs 30 Gy/5 fx

Unresected Soft Tissue Sarcomas: Tumor Size and RT Dose

112 patients with unresected sarcomas 1971-2001

	LOCAL CONTROL	
	< 63 Gy	>63 Gy
≤ 5 cm	22%	**72%**
>5 cm ≤ 10 cm	49%	42%
>10 cm	0%	25%
	p=0.08	p< 0.05

- Suggested radiation doses ~70-74 Gy

Kepka et al, IJROBP 2005

STS: A Collection of Related but Biologically Distinct Diseases

- **Many have unique molecular signature**
  - e.g. Myxoid liposarcoma: t(12;16)(q13;p11) translocation, which produces the FUS::DDIT3 (also known as TLS/FUS-CHOP) fusion oncogene.
  - Uniquely RT-responsive and sensitive (JAMA Oncol 2020)
    - DOREMY study: 36 Gy/18 fx preop→ 2 yr LC 100%→?5y
  - Chen M…Kirsch DG: FUS-CHOP drives sarcoma-genesis but also mediates RT sensitivity by RT-induced disruption of phase-separation properties of FUS-CHOP that diminishes protein-protein interactions required for tumor maintenance (Cancer Res 2021)

Summary

- Limb preservation is preferred approach for pts with extremity STS if Rx results in functional limb
- Treatment in experienced center preferred
- Most pts will undergo surgery and RT
  - Preoperative RT is preferred for most deep STS involving/abutting critical structures
  - Selected pts with T1 STS can undergo surgery alone
    - Selected others, generally those with superficial, low grade, widely resected tumors may also be Rx'ed with surgery alone
- Function can be optimized with rehabilitation