City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Tumor Board: Management of Sarcoma

Surgical Oncology: William Tseng, MD

Radiation Oncology: Boryana Eastman, MD, PhD

Medical Oncology: Mark Agulnik, MD

Panel & Disclosures

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- *No relevant financial relationships*

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- Consultant for Aadi, Bayer and Coherus.
- Speakers Bureau in Decipher.
- Grant/Research Support from Exelixis.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- *Recognition of potential cultural barriers to execution of proposed sarcoma treatment plan.*
- *Impact of insurance (bias) on sarcoma patient care.*
- *The needs of the AYAO group and the difference compared to patients > 39 years of age.*
- *Patient population with rare disease may experience socio-economic barriers in terms of access to high quality care, despite recommendations provided for best practices.*
- *Health literacy and lack of access to primary care may affect the time to proper diagnosis and delays patients care.*
- *Patients with more advance disease may experience disparity in care.*

Case Presentation

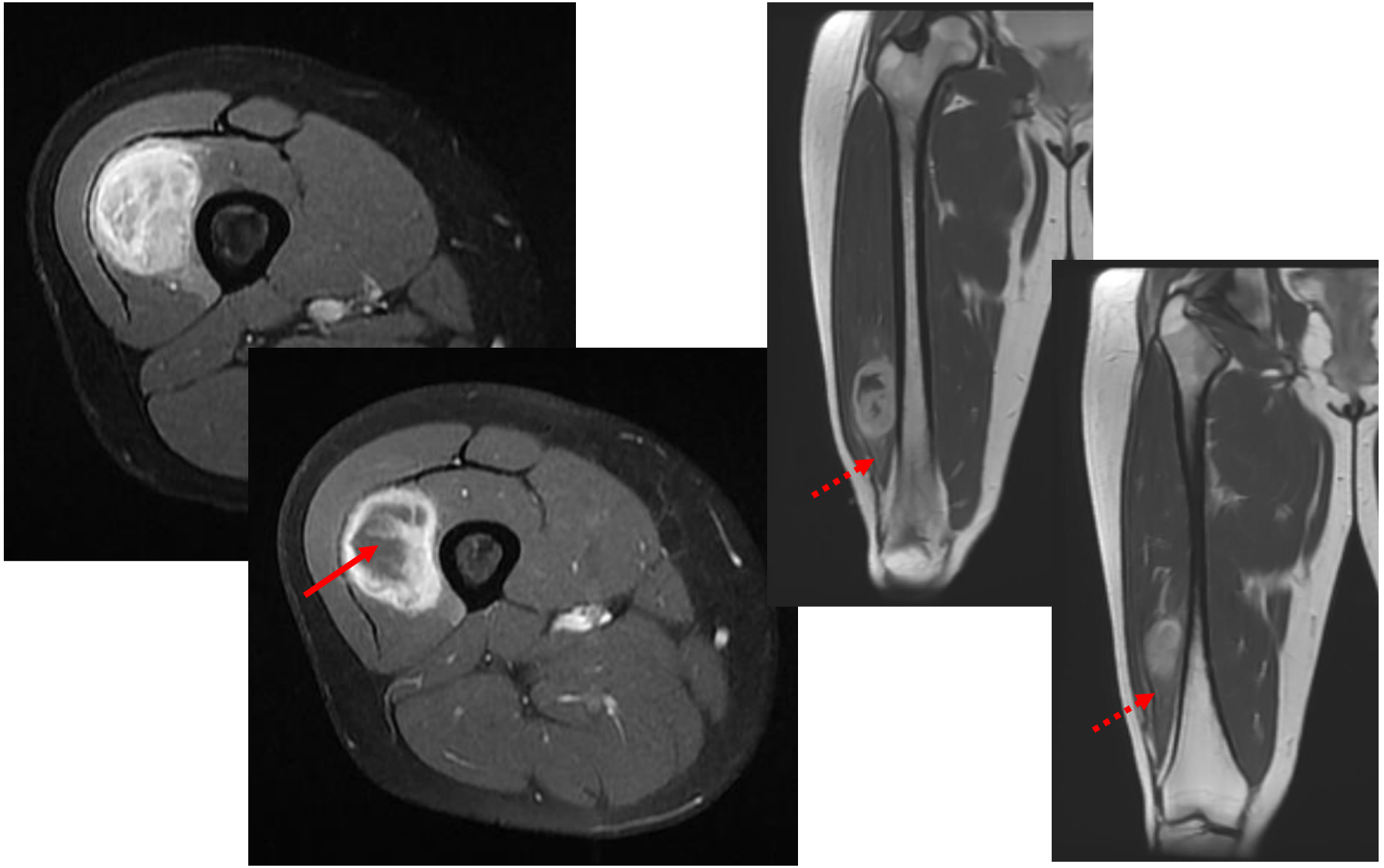
31F whose massage therapist appreciated an ill-defined "lump" in her right thigh

- No pain, but pt went to see PCP who rendered Dx of lipoma based on physical examination; **Plan: observe**

- 6 mo later – mass persisted, f/u with PCP; obtained ultrasound: not lipoma, recommend MRI

- MRI thigh w/contrast: 8 cm heterogeneous, enhancing soft tissue mass within vastus intermedius

Case Presentation



Case Presentation

- Needle biopsy performed: initial Dx unclear, likely malignant; tissue sent for 2nd opinion
- Pathology re-review: **undifferentiated pleomorphic sarcoma (UPS)**, high grade (FNCLCC 3/3)
- CT chest: negative for metastatic disease
- Remains asymptomatic (~10-11 mo since initial presentation…)

What next?

Surgical Management of Sarcoma

William Tseng, MD

Sarcoma Surgical Oncologist

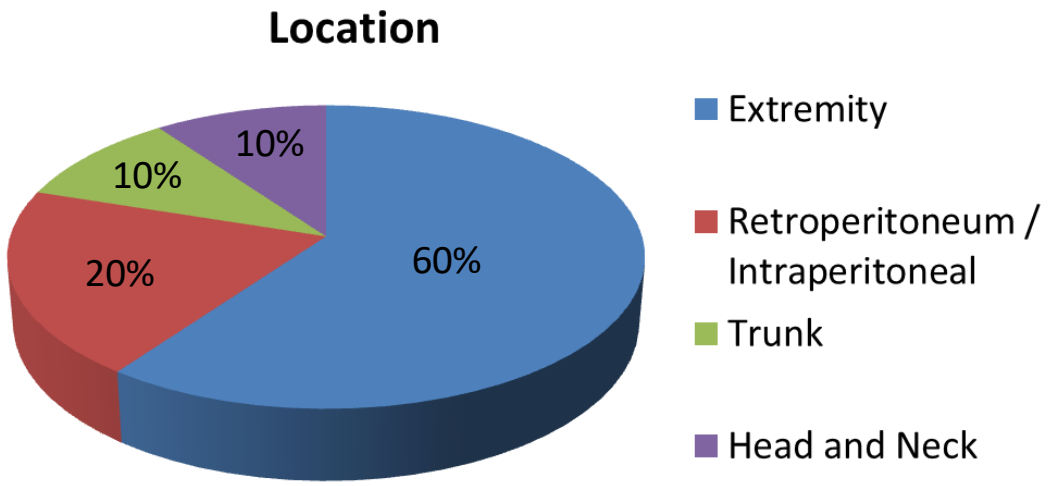
Associate Professor of Surgery

City of Hope National Medical Center, Duarte, CA

Soft Tissue Sarcoma (STS)

- **Rare: 1%** of all adult cancers
- Can develop **anywhere in the body**

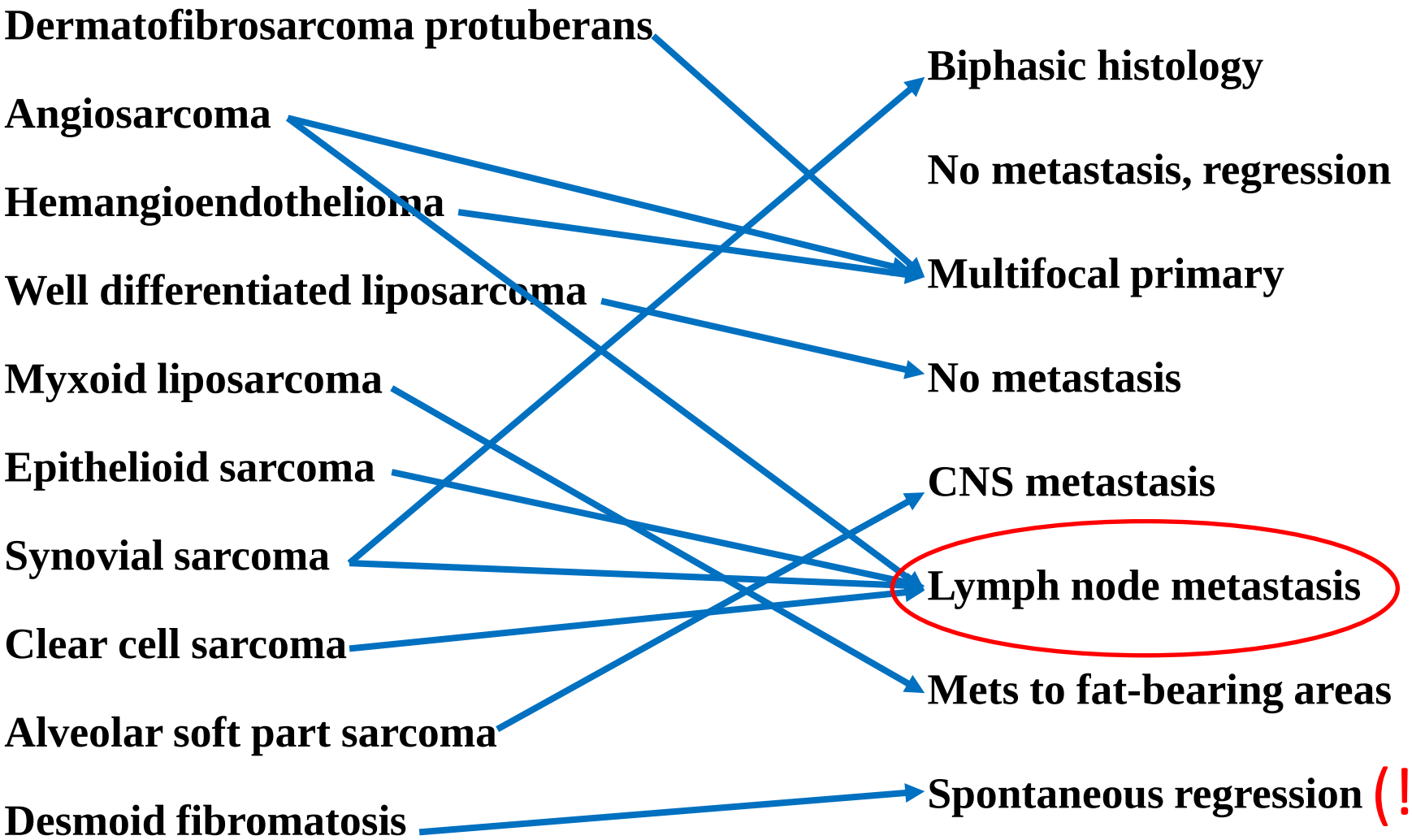
Histology is KEY!



- **Diverse: 50-70 different histologic types**

Tseng et al., *Ann Surg Oncol* 2016

Distinct Tumor Behavior



Adapted from R Pollock

Treatment of Sarcoma:

"A Team Effort"

Surgery | **Chemotherapy** | **Radiation therapy**

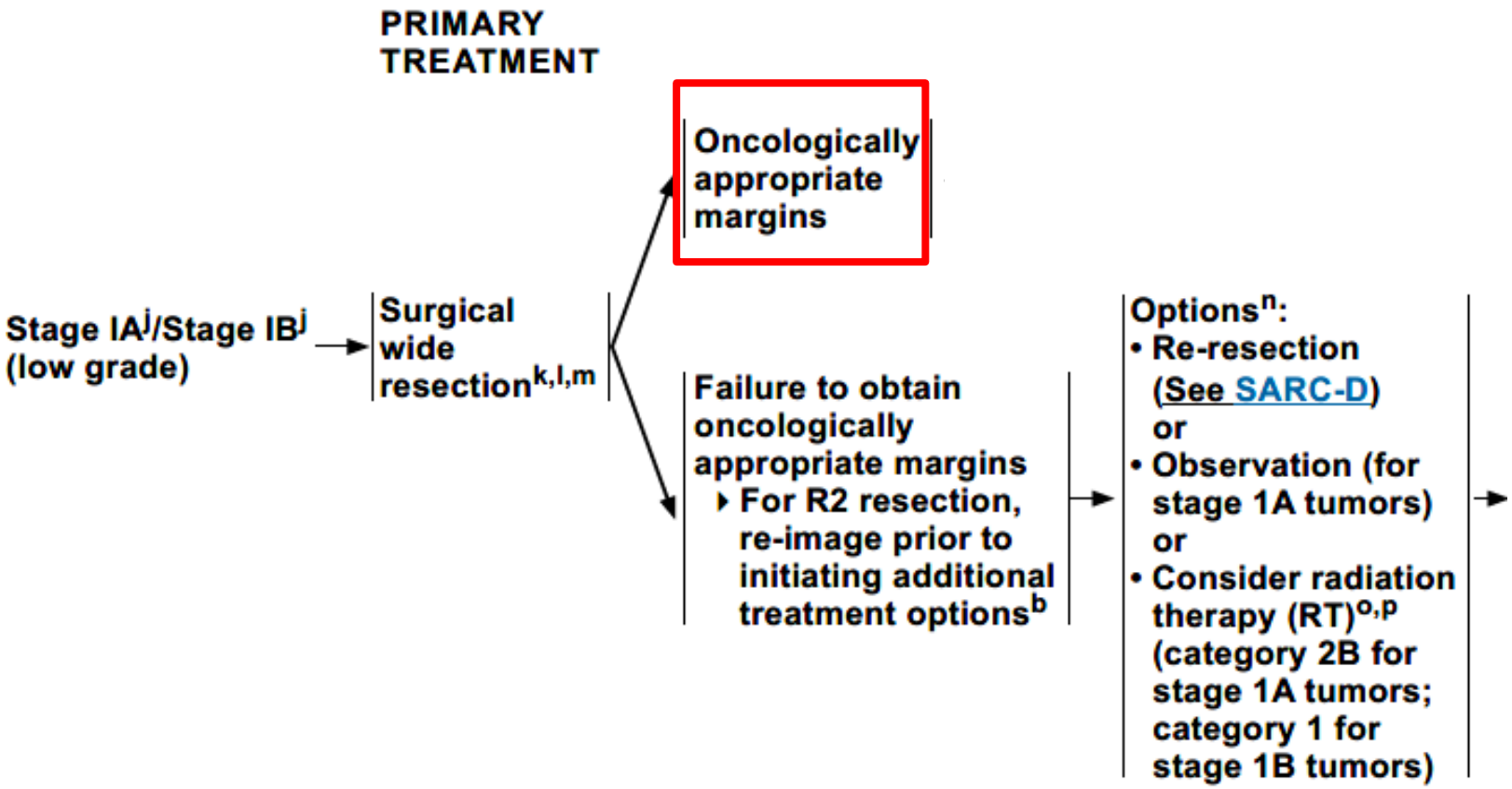
Multidisciplinary Tumor Board

Surgical,
Medical,
Radiation
Oncology

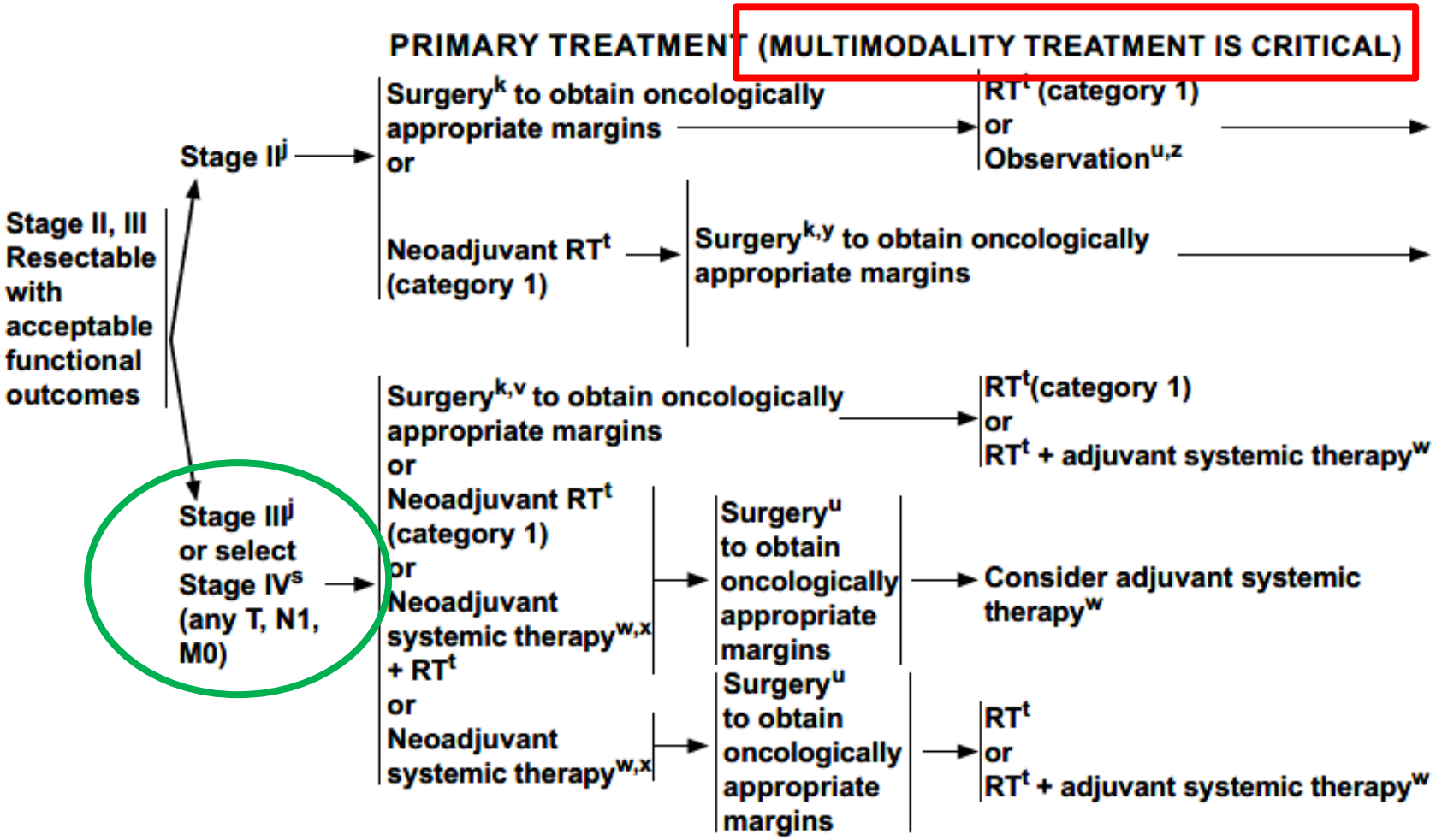
Radiology
Pathology

Ideally → ALL sarcoma specialists

NCCN Guidelines
Extremity STS: Stage 1



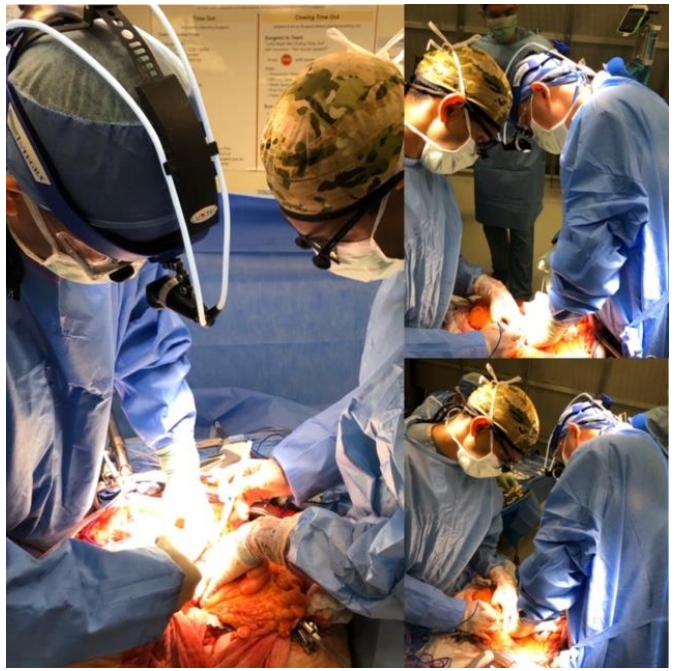
NCCN Guidelines
Extremity STS: Stage 2, 3

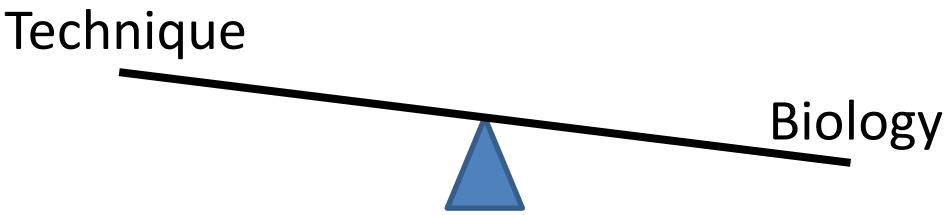


V1.2024

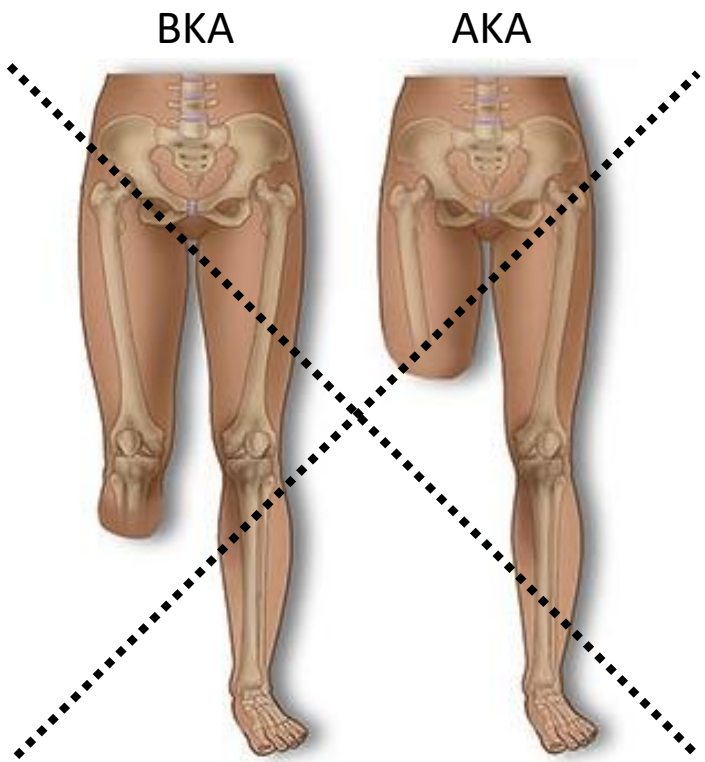
Sarcoma Surgery

- Main form of treatment for **localized** disease





Sarcoma Surgery
- Extremity



Limb salvage is standard of care

- Optimal cancer operation

+/- **Radiation therapy**

Rosenberg et al, *Ann Surg* 1982
Pisters et al, *J Clin Oncol* 1996
Yang et al, *J Clin Oncol* 1998

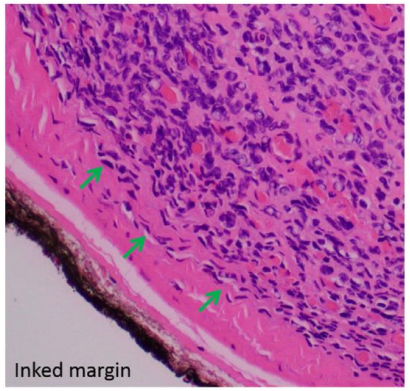
- **Function preservation**

Plastic Surgery

Sarcoma Surgery - Extremity

Negative margins? **YES**

- *Depends* on subtype, tissue barriers (e.g., fascia), adjacent critical structures (e.g., vessels, nerves)



Byerly, Tseng et al, *J Surg Oncol* 2015

~UPS

Myxofibrosarcoma

WD Liposarcoma

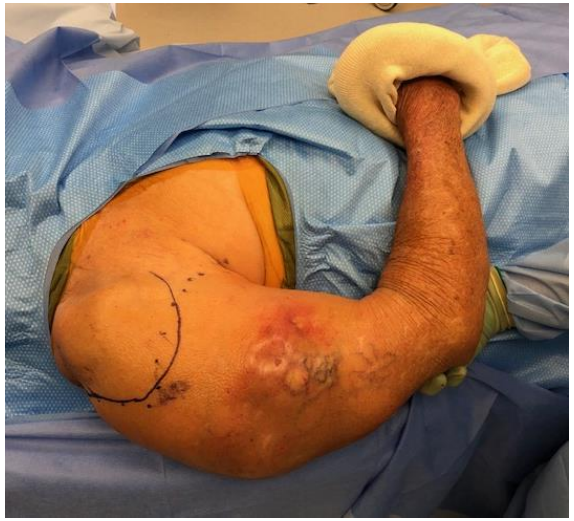
Myxoid Liposarcoma

Desmoid Tumor

Planned close or *positive* margins…

O'Donnell et al, *Cancer* 2014
Gundle et al, *J Clin Oncol* 2018

Sarcoma Surgery
- Extremity

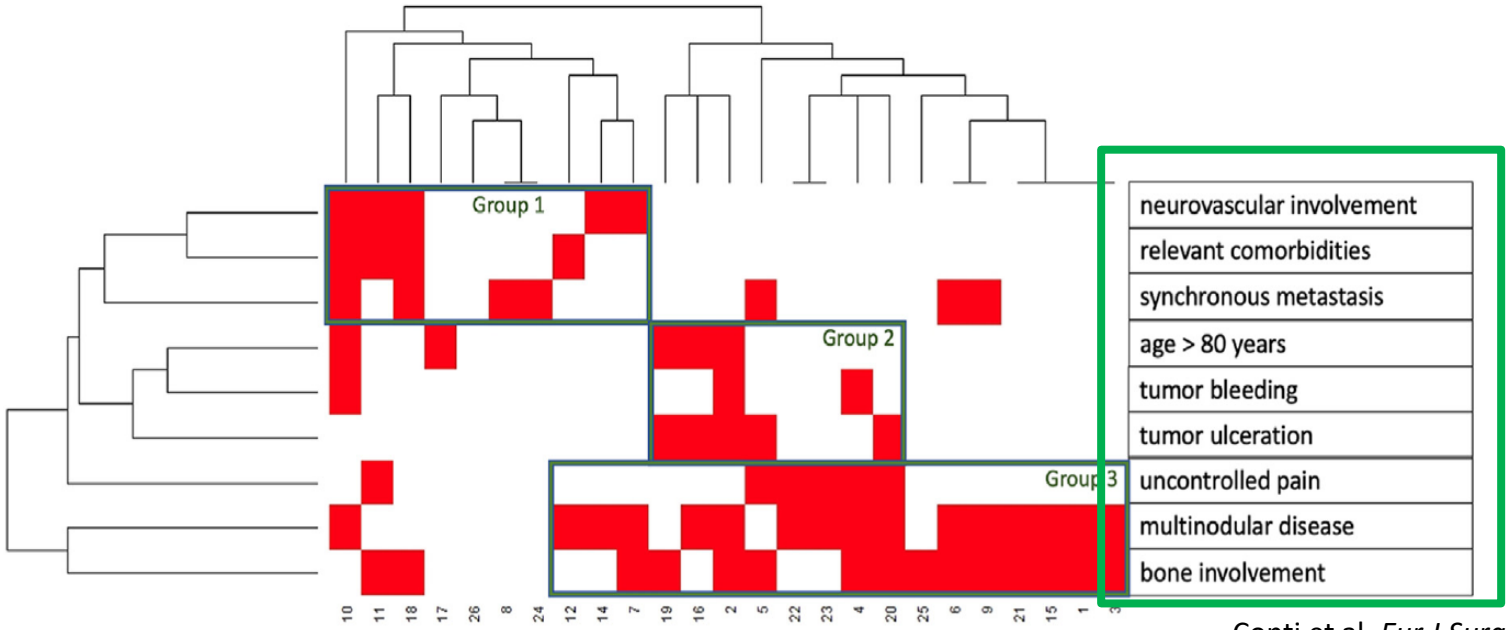


83M w/R arm UPS

…"Sometimes amputation is better"

Sarcoma Surgery
- Amputation

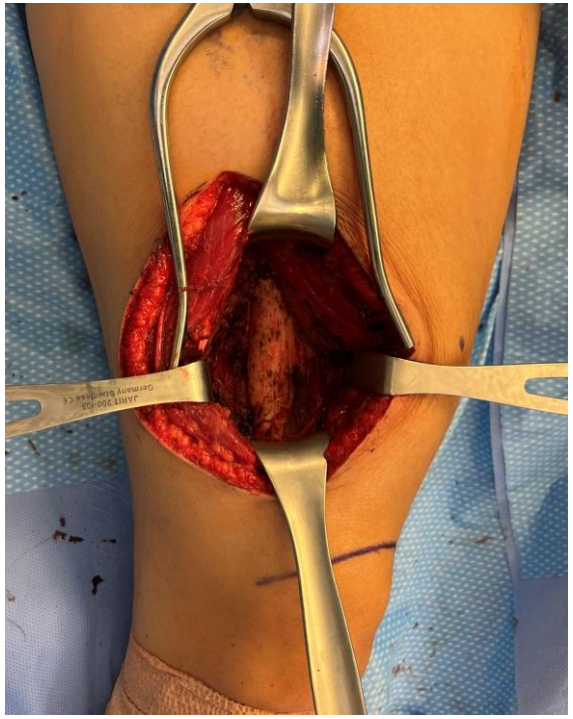
- 1.8% primary disease; 1.0% recurrent
- Majority: grade 3, median size 16 cm, received preop therapy
- Most common histologies: **UPS**, myxofibroarcoma

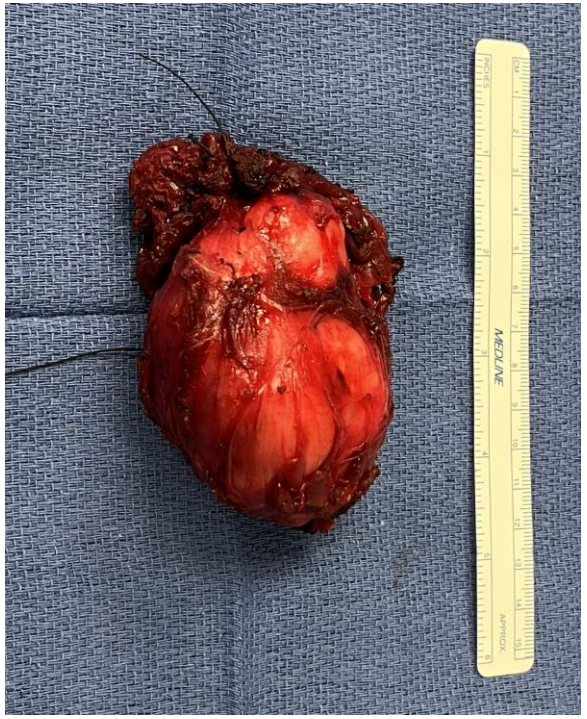


Conti et al, *Eur J Surg Onc* 2022

Case Presentation

- Surgery:

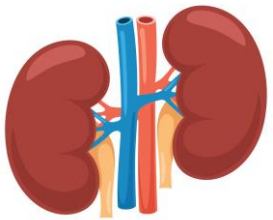


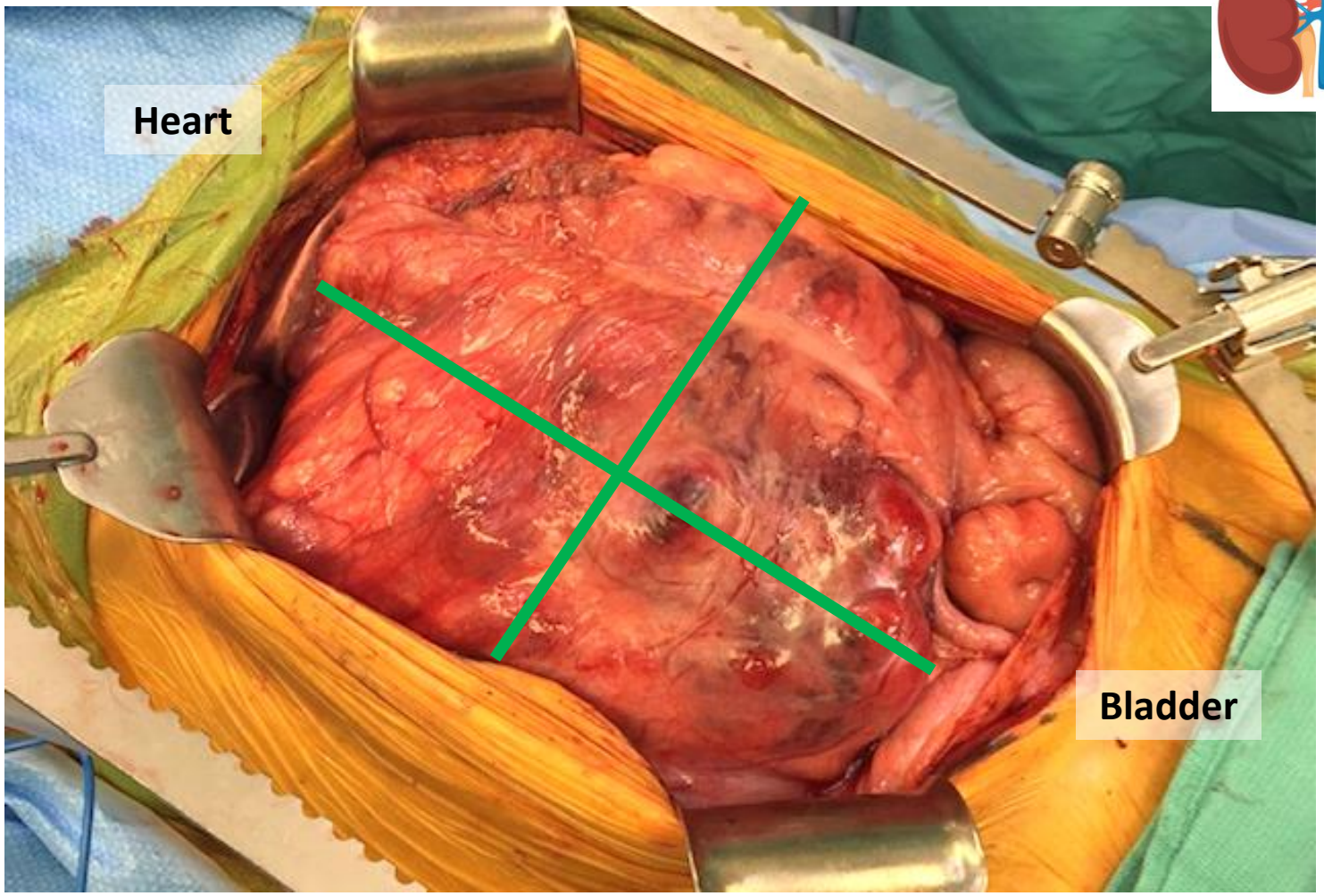


- Pathology: high grade sarcoma with rhabdomyogenic features, 7 cm, margins negative (close)

What next?

Retroperitoneal Sarcoma





STRASS 2

A Randomized Phase 3 Study of Neoadjuvant Chemotherapy followed by Surgery versus Surgery Alone for Patients with High Risk Retroperitoneal Sarcoma

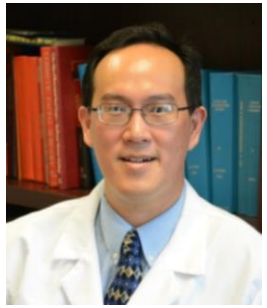
STRASS (1): Neoadjuvant Radiation Therapy
Bonvalot et al., *Lancet Oncol* 2020

Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG)

EORTC – Intergroup Study 1809-STBSG

ECOG-ACRIN – EA7211
activated 6/13/23

Thank you!



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Undifferentiated Pleomorphic Sarcoma:

Management Perspectives in both the Adjuvant and Metastatic Setting

Mark Agulnik, MD
Professor
Sarcoma Section Chief
Department of Medical Oncology & Therapeutics Research

Treatment of Soft Tissue Sarcomas: Adjuvant Chemotherapy

The role of chemotherapy in the adjuvant setting for standard adult soft tissue sarcoma remains controversial.

There are situations when adjuvant therapy clearly is not indicated.

- no benefit for soft tissue sarcomas that arise from visceral or abdominal sites, and surgery alone remains the standard of care.

Specific subtypes of adult soft tissue sarcomas may benefit from adjuvant chemotherapy:

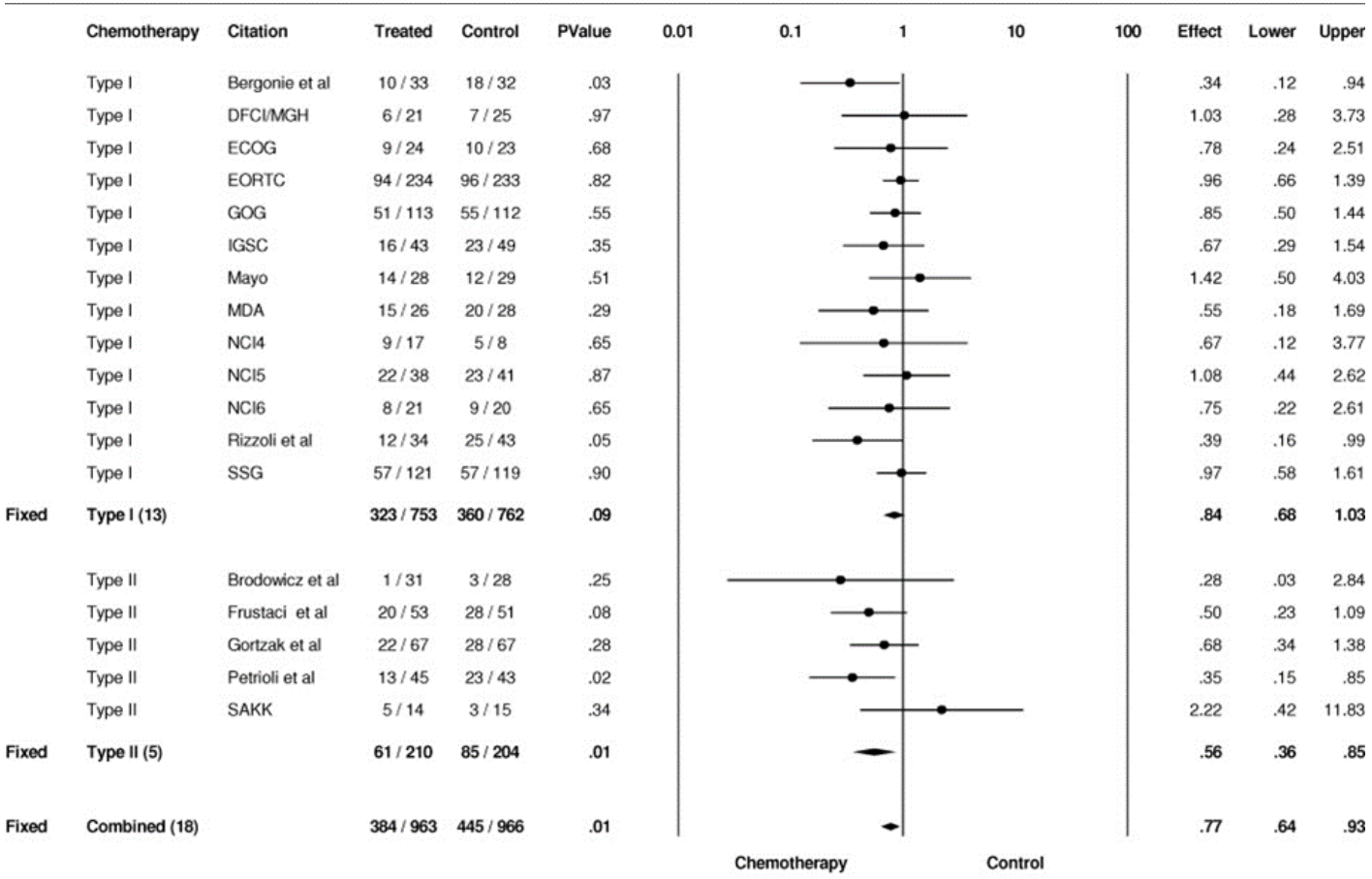
- synovial sarcoma
- MPNST
- high-grade myxoid/round cell liposarcoma
- LMS
- UPS

Treatment of Soft Tissue Sarcomas: Adjuvant Chemotherapy

- Overall, approximately 25% of patients with STS will develop distant metastatic disease, even after undergoing curative resection of the primary tumor.
- This incidence increases to 50% in high-risk tumors that measure >5 cm, are deep to the fascia, and are intermediate-grade or high-grade.
- In nearly 70% of the metastatic cases, disease occurs in the lungs, with other sites including the skin, bone, liver, and brain.
- The role of adjuvant chemotherapy in STS has been explored in 20 randomized trials and 2 meta-analyses.

Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997 Dec 6;350(9092):1647-54. PMID: 9400508.
Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008 Aug 1;113(3):573-81. doi: 10.1002/cncr.23592. PMID: 18521899.

A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma



	Chemotherapy	Citation	Treated	Control	PValue	Effect	Lower	Upper
	Type I	Bergonie et al	10 / 33	18 / 32	.03	.34	.12	.94
	Type I	DFCI/MGH	6 / 21	7 / 25	.97	1.03	.28	3.73
	Type I	ECOG	9 / 24	10 / 23	.68	.78	.24	2.51
	Type I	EORTC	94 / 234	96 / 233	.82	.96	.66	1.39
	Type I	GOG	51 / 113	55 / 112	.55	.85	.50	1.44
	Type I	IGSC	16 / 43	23 / 49	.35	.67	.29	1.54
	Type I	Mayo	14 / 28	12 / 29	.51	1.42	.50	4.03
	Type I	MDA	15 / 26	20 / 28	.29	.55	.18	1.69
	Type I	NCI4	9 / 17	5 / 8	.65	.67	.12	3.77
	Type I	NCI5	22 / 38	23 / 41	.87	1.08	.44	2.62
	Type I	NCI6	8 / 21	9 / 20	.65	.75	.22	2.61
	Type I	Rizzoli et al	12 / 34	25 / 43	.05	.39	.16	.99
	Type I	SSG	57 / 121	57 / 119	.90	.97	.58	1.61
Fixed	**Type I (13)**		**323 / 753**	**360 / 762**	**.09**	**.84**	**.68**	**1.03**
	Type II	Brodowicz et al	1 / 31	3 / 28	.25	.28	.03	2.84
	Type II	Frustaci et al	20 / 53	28 / 51	.08	.50	.23	1.09
	Type II	Gortzak et al	22 / 67	28 / 67	.28	.68	.34	1.38
	Type II	Petrioli et al	13 / 45	23 / 43	.02	.35	.15	.85
	Type II	SAKK	5 / 14	3 / 15	.34	2.22	.42	11.83
Fixed	**Type II (5)**		**61 / 210**	**85 / 204**	**.01**	**.56**	**.36**	**.85**
Fixed	**Combined (18)**		**384 / 963**	**445 / 966**	**.01**	**.77**	**.64**	**.93**

Cancer, Volume: 113, Issue: 3, Pages: 573-581, First published: 02 June 2008, DOI: (10.1002/cncr.23592)

Treatment of Soft Tissue Sarcomas: Adjuvant Chemotherapy- Survival

- This analysis was conducted on 18 trials including 1953 patients and 829 deaths.
- Data from all trials showed that adjuvant chemotherapy significantly reduced the risk of death with an HR of 0.77 (95% CI, 0.64-0.93; P = .01).
- Adjuvant doxorubicin-based treatment resulted in a reduction in mortality that was not significant, with an HR of 0.84 (95% CI, 0.68-1.03; P = .09).
- The studies involving doxorubicin combined with ifosfamide, however, showed significantly reduced mortality, with an HR of 0.56 (95% CI, 0.36-0.85; P = .01).
- Doxorubicin in combination with ifosfamide analyzed alone also had a significant ARR of 11% (95% CI, 3%-19%; P = .01), or a 30% versus 41% risk of death.
- Data from all trials showed an NNT of 17 to prevent 1 death.

Role of adjuvant chemotherapy in patients with localized, undifferentiated pleomorphic sarcoma of soft tissue

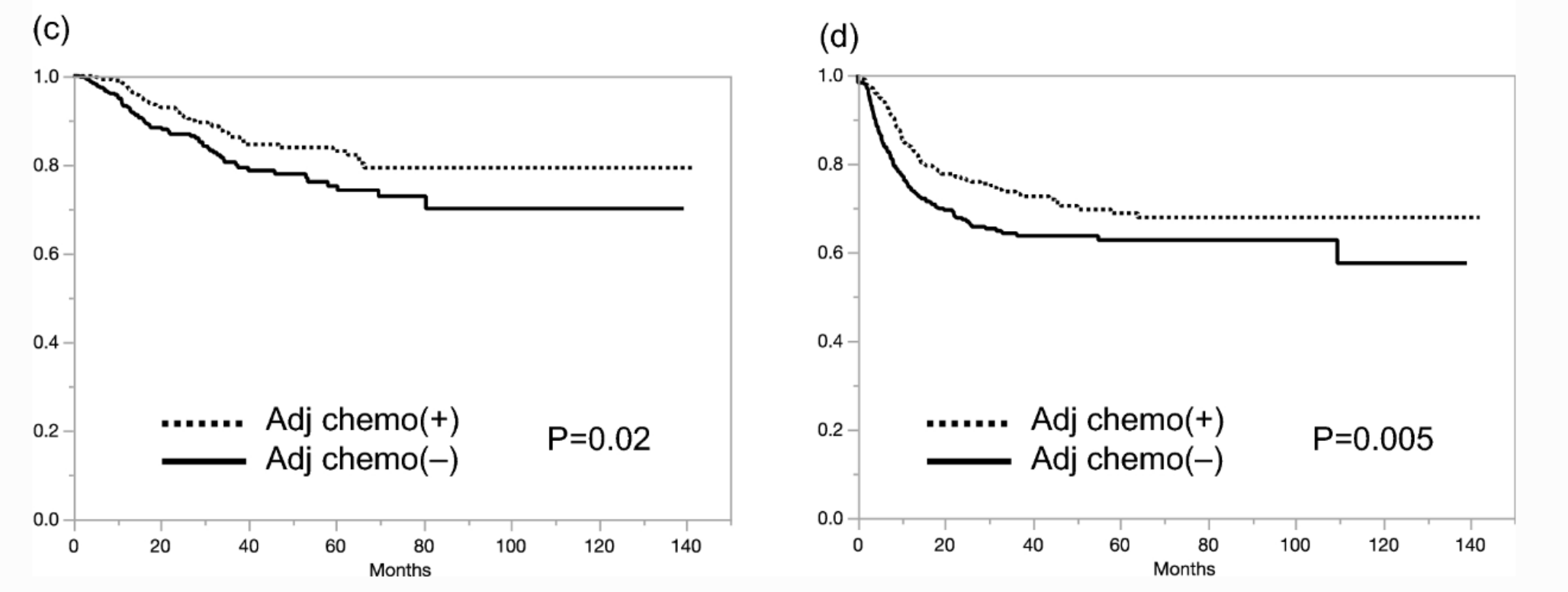
- Retrospective analysis included data of 2112 patients with localized UPS arising in the extremities and trunk.
- To analyze the efficacy of adjuvant chemotherapy, excluded cases with the following criteria:
  - (1) advanced cases (that is, metastatic at first presentation);
  - (2) low-grade cases;
  - (3) cases diagnosed as myxoid type malignant fibrous histiocytoma;
  - (4) cases treated without radical local therapy, resection, or amputation;
  - (5) cases with the primary anatomical location at the retroperitoneum, peritoneum, thoracic cavity, mediastinum, vertebra, head and neck, and pelvis; and
- In total, 4117 cases of undifferentiated pleomorphic sarcoma of the soft tissue were identified, and 2112 cases of localized, resectable, high-grade tumors were extracted based on the inclusion criteria.

Kobayashi H, Zhang L, Hirai T, Tsuda Y, Ikegami M, Tanaka S. Role of adjuvant chemotherapy in patients with localized, undifferentiated pleomorphic sarcoma of soft tissue: a population-based cohort study. Int J Clin Oncol. 2022 Apr;27(4):802-810. doi: 10.1007/s10147-021-02102-8. Epub 2022 Jan 22. PMID: 35064354.

What does the data look like for UPS?

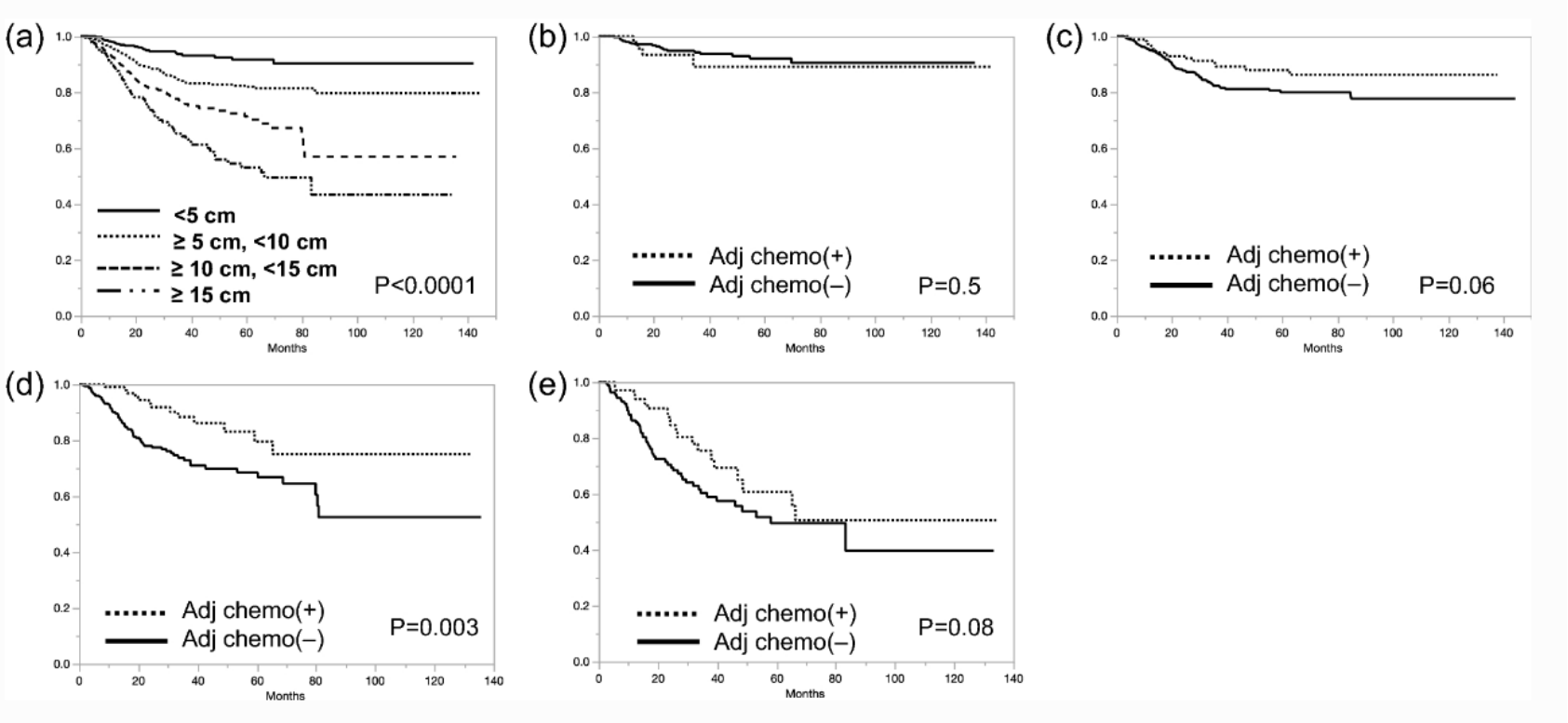
	Adjuvant chemotherapy			
	+ (*N* = 425)		− (*N* = 1687)	
	N	%	*N*	%
Sex				
Male	269	63.3	964	57.1
Female	156	36.7	723	42.9
Age (years) median				
< 40	37	8.7	38	2.3
40–64	242	56.9	375	22.2
≥ 65	146	34.4	1274	75.5
Primary location				
Upper extremity	58	13.7	261	15.5
Lower extremity	250	58.8	932	55.2
Trunk	117	27.5	494	29.3
Tumor size (cm)				
< 5	50	12.1	392	24.7
≥ 5, < 10	186	45	689	43.4
≥ 10, < 15	107	25.9	335	21.1
≥ 15	70	17	171	10.8
Surgical margin				
R1 or R2	46	10.8	212	12.6
R0	379	89.2	1470	87.4

Impact of adjuvant chemotherapy



Impact of adjuvant chemotherapy on **C** overall survival (OS) and **D** distant metastasis-free survival (DMFS) in patients with undifferentiated pleomorphic sarcoma of soft tissue.

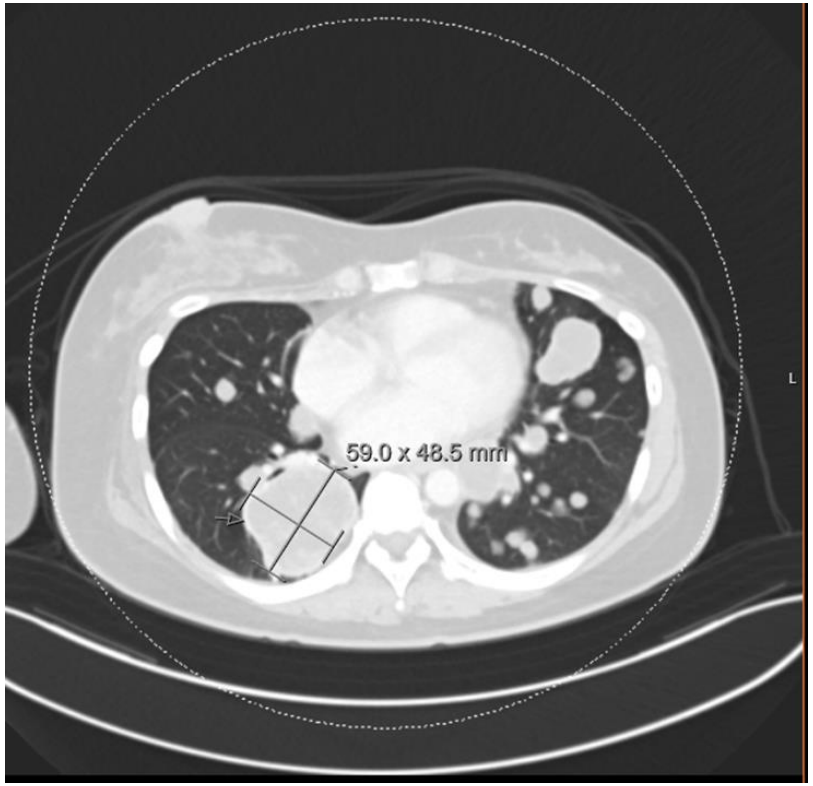
Impact of adjuvant chemotherapy



a Overall survival (OS) depending of the size of the tumor and effect of adjuvant chemotherapy in patients with UPS of soft tissue of size **b** < 5 cm ($N = 442$), **c** 5 cm to < 10 cm ($N = 875$), **d** 10 cm to < 15 cm ($N = 442$), and **e** ≥ 15 cm ($N = 241$).

Patient Case

- Patient proceeded with 5 cycles of adjuvant doxorubicin 75 mg/m2/cycle and Ifosfamide 9g/m2/cycle.
- Follow-up as per NCCN guidelines included CT Chest and MR extremity.
- 2 years after completion of all therapies- pt presents with a cough, mild dyspnea.
- CT chest completed the same day.



Therapeutic options for UPS- NCCN Guidelines

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES[a,b,c,d] AND AGGRESSIVE SOFT TISSUE NEOPLASMS

Regimens Appropriate for General Soft Tissue Sarcoma[e,f]; see other sections for histology-specific recommendations[g]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/ Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD (doxorubicin, dacarbazine)[1,2,10,11] for LMS, or if ifosfamide is not considered appropriate • Doxorubicin[1,2,6,7] • Gemcitabine and docetaxel[20,21]	• Ifosfamide[5,7,20-24] • Trabectedin (for myxoid liposarcoma)[30]
First-Line Therapy Advanced/Metastatic	• Anthracycline-based regimens: ▸ Doxorubicin[1,2,6,7] ▸ Epirubicin[8] ▸ Liposomal doxorubicin[9] ▸ AD (doxorubicin, dacarbazine)[1,2,10,11,12] ▸ AIM[1-4,6] ▸ Ifosfamide, epirubicin, mesna[5] • *NTRK* gene fusion-positive sarcomas only ▸ Larotrectinib[h,13] ▸ Entrectinib[i,14]	• Gemcitabine-based regimens: ▸ Gemcitabine ▸ Gemcitabine and docetaxel[20,21] ▸ Gemcitabine and vinorelbine[22] ▸ Gemcitabine and dacarbazine[23]	• Pazopanib[k,15] (patients ineligible for IV systemic therapy or patients who are not candidates for anthracycline-based regimens) • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,31,32] • Trabectedin and doxorubicin (for LMS)[33,34] • Selpercatinib (for *RET* gene fusion-positive tumors)[35]
Subsequent Lines of Therapy for Advanced/Metastatic Disease	• Pazopanib[j,k,15] • Eribulin[j,16] (category 1) recommendation for liposarcoma, category 2A for other subtypes • Trabectedin[j,17-19] (category 1 recommendation for liposarcoma and LMS, category 2A for other subtypes)	• Dacarbazine[23] • Ifosfamide[5,7,21,22,24,25] • Temozolomide[j,26] • Vinorelbine[j,27] • Regorafenib[k,28] • Gemcitabine-based regimens ▸ Gemcitabine ▸ Gemcitabine and docetaxel[20,21] ▸ Gemcitabine and vinorelbine[12] ▸ Gemcitabine and dacarbazine[23] ▸ Gemcitabine and pazopanib (category 2B)[29]	• Pembrolizumab[36,37] or Nivolumab ± ipilimumab[38-41] ▸ For myxofibrosarcoma, UPS,[f] dedifferentiated liposarcoma, cutaneous angiosarcoma, and undifferentiated sarcomas OR ▸ For TMB-H (≥10 mutations/megabase [mut/Mb])[l] regardless of soft tissue sarcoma sub-type • Pembrolizumab[42] ▸ For MSI-H or dMMR tumors[m] (regardless of soft tissue sarcoma sub-type)

How do you navigate metastatic STS?

- Histology
- Extent of disease
- Asymptomatic vs Symptomatic
- NGS results
- Prior therapies
- Co-morbidities

Classic Chemotherapy Drugs for Metastatic Sarcoma: Response Rates

Doxorubicin	20%
Ifosfamide	20%
Dacarbazine	10%
Pegylated doxorubicin	10%
Trabectedin	10%
Gemcitabine	8%
Eribulin	7%

Edmonson JH, et. al. J Clin Oncol 1993; 11:1269 – 1275.; Santoro A., et. al. J Clin Oncol. 1995; 13: 1537-1545.;Patel A, et. Al. J Clin Oncol. 1997; 15 – 2378.; van Oosterom et. al., Eur J Cancer. 2002; 2397 – 2406; Judson I, et. Al. Eur J Cancer. 2001; 37:870-77.;Demetri G, et. al. Hematol Oncol Clin North Am. 1995; 9 (4): 765-85.;Antman K, et. al. Semin Surg Oncol. 1988; 4: 53 – 58.;Skubitz KM, D'Adamo DR. Sarcoma. Mayo Clin Proc. 2007; 82:1409-1432, Demetri GD, et. al. PNAS 1999;96: 3951-56; Debrock G, et. Al. Br J Cancer. 2003; 89:1409-12;Schoffski P et. al. Lancet Oncol 2011: 12: Demetri GD et al. JCO 2015: 33: Abst 10503*; Schoffski P et al. JCO 2015: 33 Abstr LBA10502**

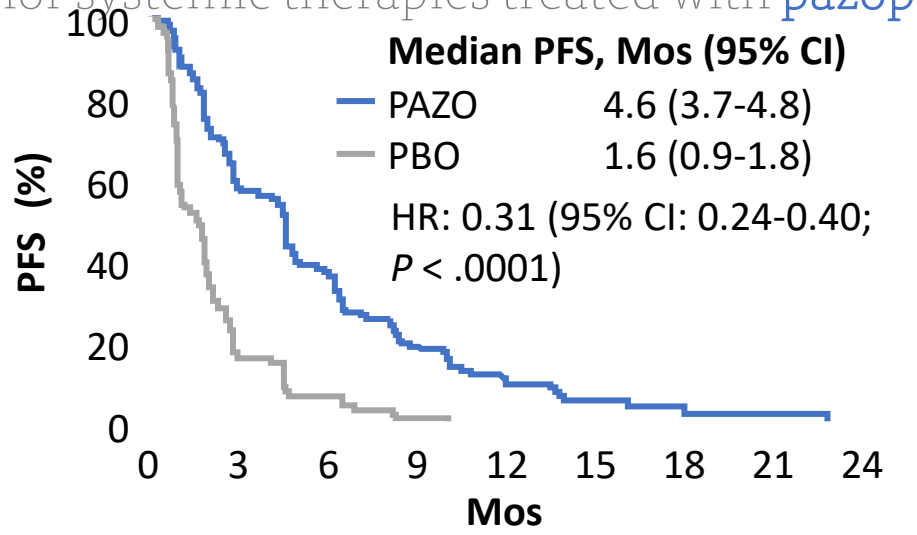
Combination Therapy

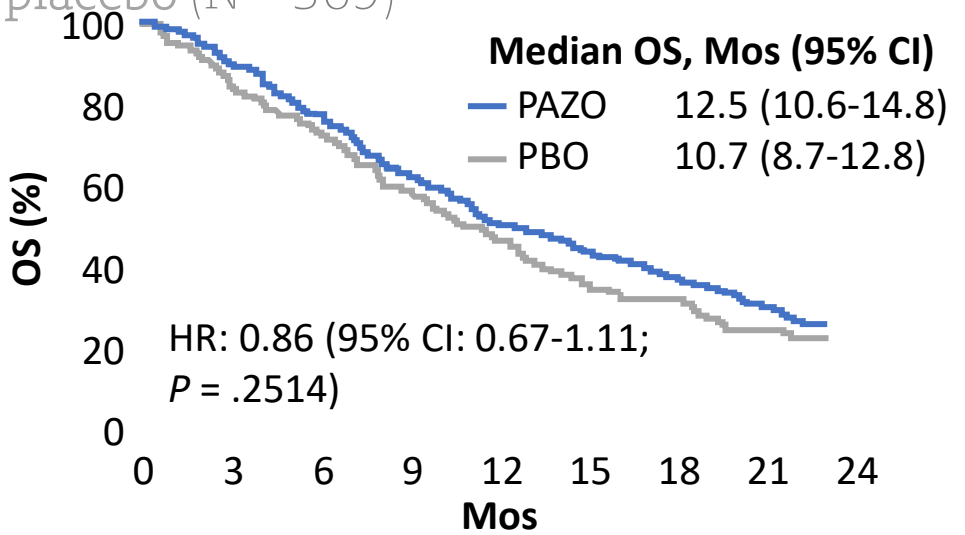
AIM	• ~40% RR
MAID	• ~40% RR
Gemcitabine/Docetaxel vs Gemcitabine	• RR in a phase II trial: ~18% vs 8%
Gemcitabine/DTIC vs DTIC	• RR in a phase II trial: ~12% ORR vs 4%

Elias A, et. al. J Clin Oncol. 1989; 7:1208 – 1216.; Antman K et. al. J Clin Oncol. 1993; 11: 1276 – 1285; Judson, et. al. Lancet Oncol 2014;
Maki RG et al. J Clin Oncol. 2007; 25:2755;
Hensley et. al. JCO 2002;
Garcia-del-Muro, X, et. al. JCO 2011, Tap, William D et al.The Lancet , Volume 388 , Issue 10043 , 488 - 497

PALETTE: Pazopanib for Treating Metastatic Soft Tissue Sarcoma

Randomized, double-blind phase III trial in which fit adult patients with metastatic STS* and PD despite ≤ 4 prior systemic therapies treated with pazopanib or placebo (N = 369)[1]





Pazopanib similarly improved survival (vs placebo) for LMS, synovial sarcoma, and other sarcomas
Pazopanib FDA approved for treating patients with advanced STS who have received prior chemotherapy (limitation of use: not assessed in adipocytic STS or GIST)[2]

Pazopanib: oral multi-tyrosine kinase inhibitor targeting VEGFR-1, -2, -3, PDGFRα, and others.
Median follow-up: 14.6 mos. *Excluded: adipocytic sarcoma, bone sarcomas, GIST, others. †Primary endpoint.

1. van der Graaf. Lancet. 2012;379:1879. 2. Pazopanib PI.

How is UPS different than other STS?

- Immune checkpoint inhibitors have demonstrated activity in multiple tumor types but their activity in soft tissue sarcomas remains limited.

- In the multicenter phase II study, SARC028, the anti-PD-1 antibody, Pembrolizumab demonstrated objective responses that were largely restricted to UPS and LPS subtypes.

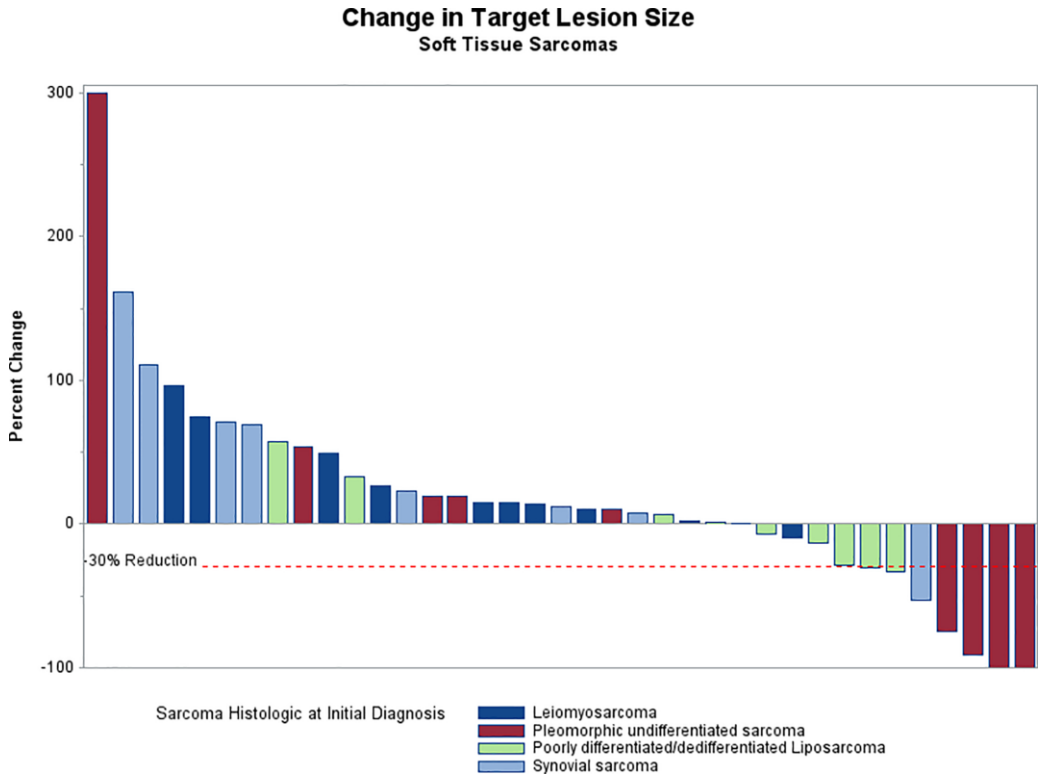
Best response in 80 evaluable patients by sarcoma histological subtype

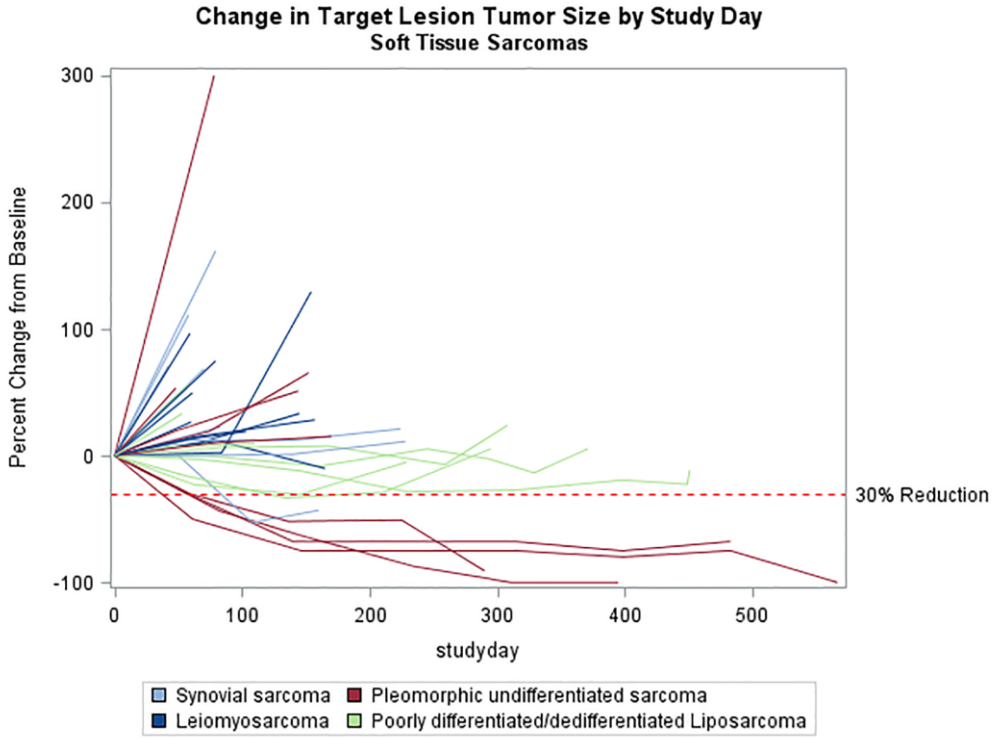
	Complete response	Partial response	Stable disease	Progressive disease
Soft-tissue sarcomas (n=40)	1 (3%)	6 (15%)	15 (38%)	18 (45%)
Leiomyosarcoma (n=10)	0 (0%)	0 (0%)	6 (60%)	4 (40%)
Undifferentiated pleomorphic sarcoma (n=10)	1 (10%)	3 (30%)	3 (30%)	3 (30%)
Liposarcoma (n=10)	0 (0%)	2 (20%)	4 (40%)	4 (40%)
Synovial sarcoma (n=10)	0 (0%)	1 (10%)	2 (20%)	7 (70%)
Bone sarcomas (n=40)	0 (0%)	2 (5%)	9 (23%)	29 (73%)
Chondrosarcoma (n=5)	0 (0%)	1 (20%)	1 (20%)	3 (60%)
Ewing's sarcoma (n=13)	0 (0%)	0 (0%)	2 (15%)	11 (85%)
Osteosarcoma (n=22)	0 (0%)	1 (5%)	6 (27%)	15 (68%)

Data are n (%).

Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, D'Angelo S, Attia S, Riedel RF, Priebat DA, Movva S, Davis LE, Okuno SH, Reed DR, Crowley J, Butterfield LH, Salazar R, Rodriguez-Canales J, Lazar AJ, Wistuba II, Baker LH, Maki RG, Reinke D, Patel S. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017 Nov;18(11):1493-1501. doi: 10.1016/S1470-2045(17)30624-1. Epub 2017 Oct 4. Erratum in: Lancet Oncol. 2017 Dec;18(12):e711. Erratum in: Lancet Oncol. 2018 Jan;19(1):e8. PMID: 28988646; PMCID: PMC7939029.

Results


Change in Target Lesion Size
Soft Tissue Sarcomas
Percent Change
300
200
100
0
-100
-30% Reduction
Sarcoma Histologic at Initial Diagnosis
Leiomyosarcoma
Pleomorphic undifferentiated sarcoma
Poorly differentiated/dedifferentiated Liposarcoma
Synovial sarcoma


Change in Target Lesion Tumor Size by Study Day
Soft Tissue Sarcomas
Percent Change from Baseline
300
200
100
0
-100
0
100
200
300
400
500
studyday
30% Reduction
Synovial sarcoma
Pleomorphic undifferentiated sarcoma
Leiomyosarcoma
Poorly differentiated/dedifferentiated Liposarcoma

NGS

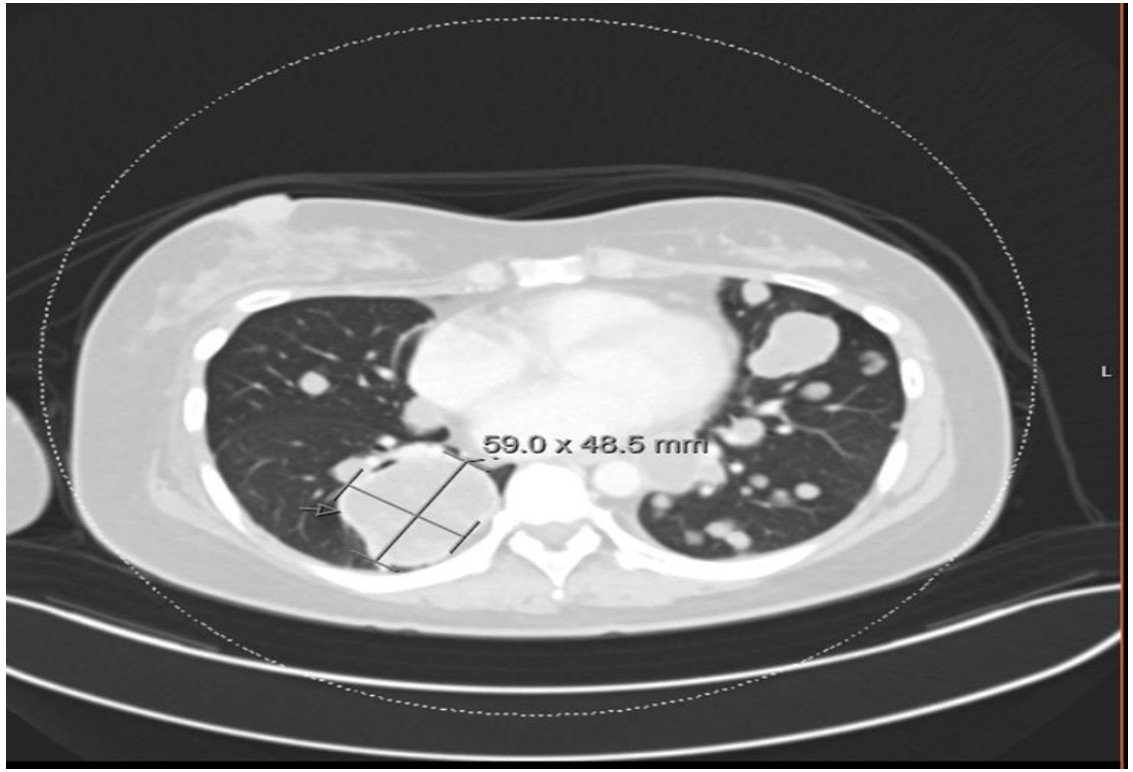
HopeSeq Solid Tumors Comprehensive

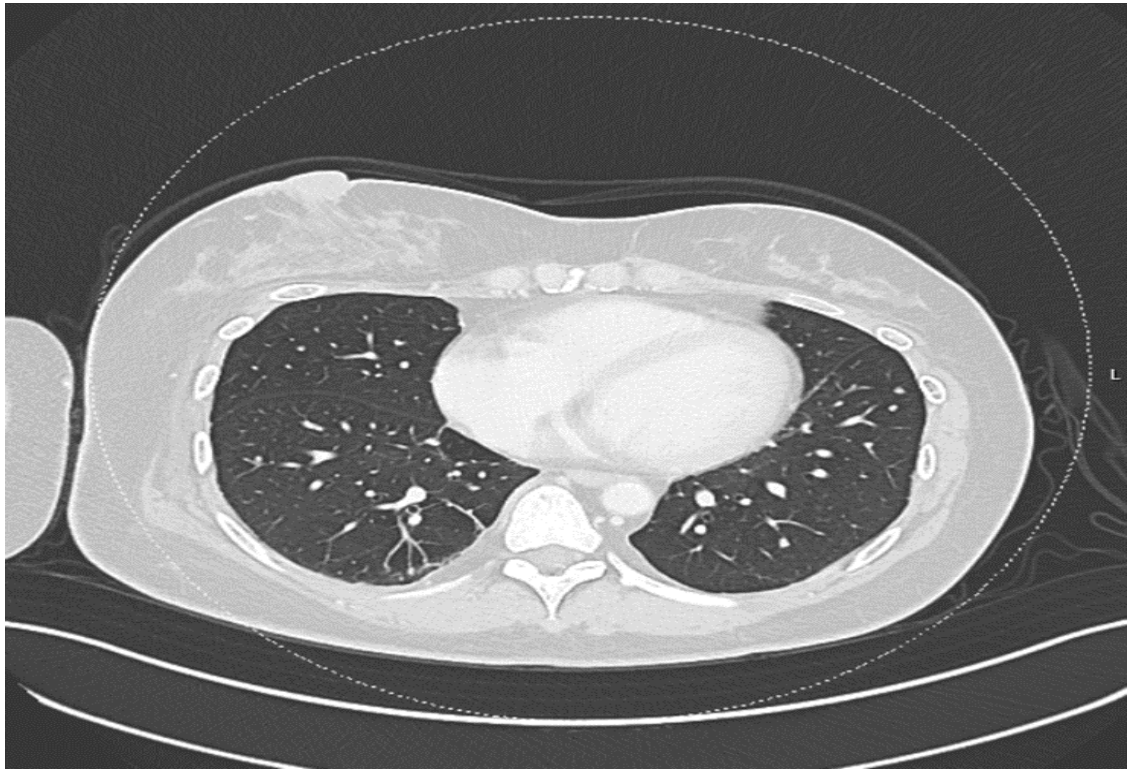
FORMALIN FIXED PARAFFIN EMBEDDED TISSUE- SOFT TISSUE, RIGHT SHOULDER/NECK TUMOR , RESECTION- (S22-00348 A2), COMPREHENSIVE GENOMIC ANALYSIS:

Genomic Alterations Detected	Allele Frequency	FDA-Approved Therapies in patient's tumor*	FDA-Approved Therapies in other tumor type*
IDH1 (c.394C>G; **p.R132G**)	**9%**	**None**	**Ivosidenib**
TP53 (c.332T>C; **p.L111P**)	**11%**	**None**	**None**

TUMOR MUTATIONAL BURDEN STATUS (TMB)
Low
MICROSATELLITE STATUS (MSI)
Stable

Patient Case: s/p C#24 pembrolizumab

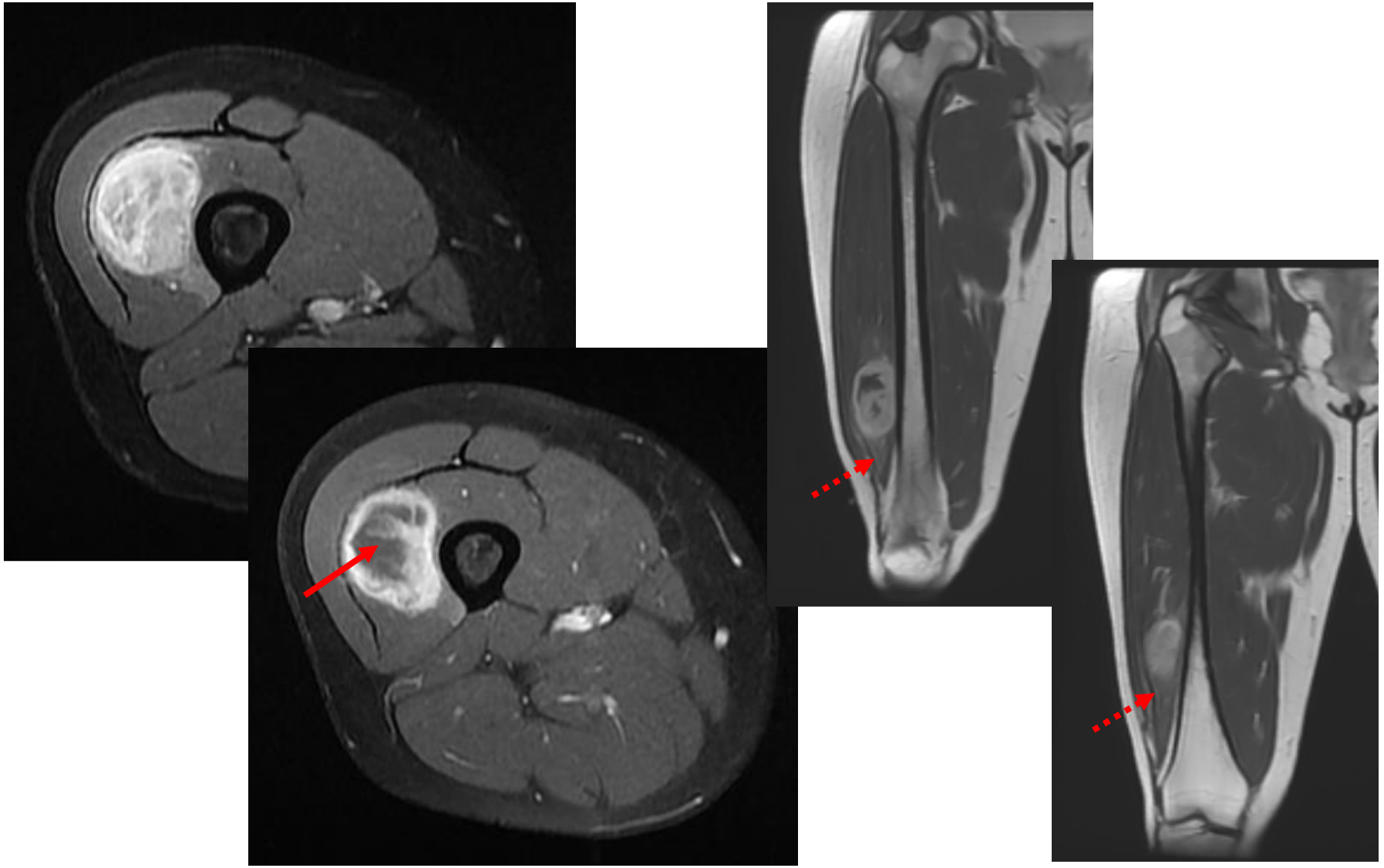




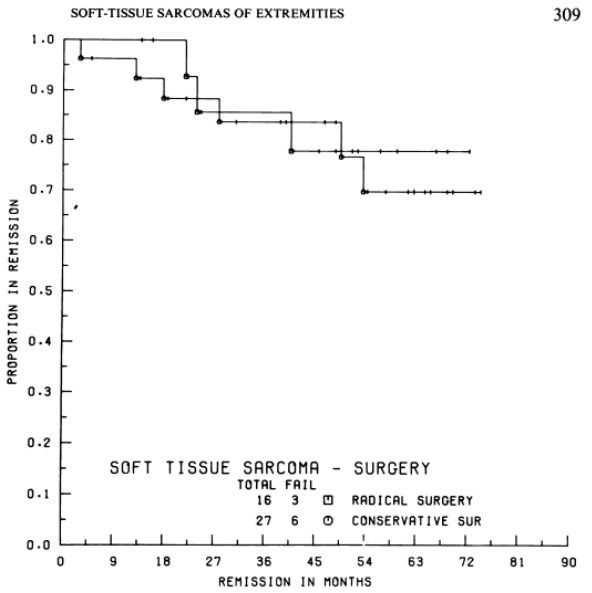
Take Away

- Histology is key
- NGS is standard of care
- Clinical Trials
- Second Opinions

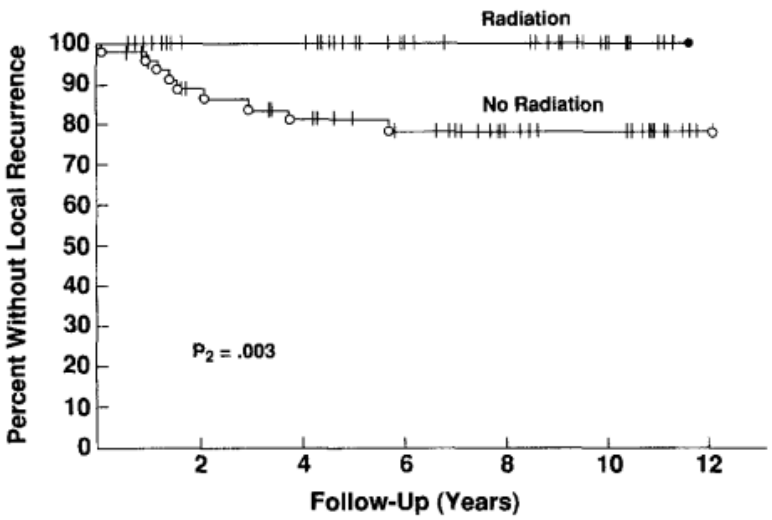
Case Presentation



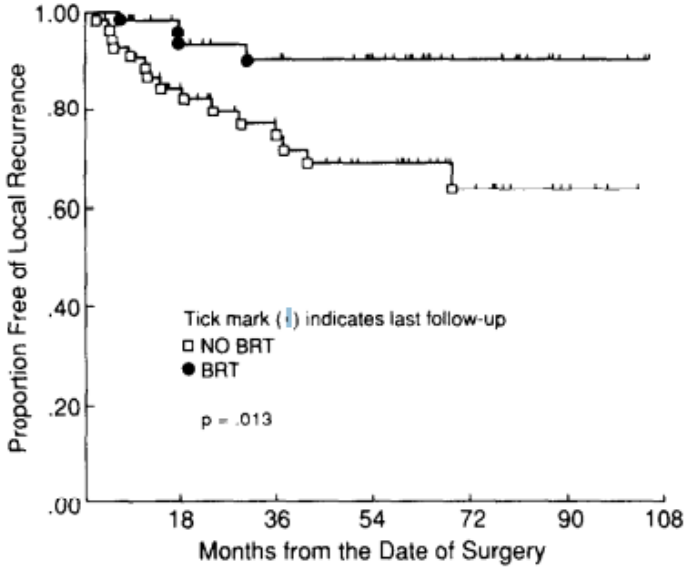
Limb Sparing Surgery (LSS) in Combination with Radiation Therapy Provides Similar Outcomes to Amputation



43 patients with high grade extremity STS
Randomized to amputation vs LSS + RT (60-70Gy)
Local recurrence: 14% (LSS) vs 0% (amputation)
No difference in 5y DFS (~75%) or OS (~85%)
Rosenburg, Ann Surg 1982



91 patients with high grade extremity STS
Randomized to LSS + chemotherapy +/- RT
Local recurrence: 19% (no RT) vs 0% (RT)
Adjuvant RT to 45Gy + 18Gy boost
No difference in 5y DFS (~75%) or OS (~80%)
Yang, JCO 1998



96 patients with high grade extremity STS
Randomized to LSS +/- Brachytherapy
Local recurrence – 5y: 35% (no BRT) vs 10% (BRT)
Adjuvant BRT to 42-45Gy over 4 days with I-192
No difference in 5y DFS (~70%) or DSS (~75%)
Harrison, IJROBP 1993

Post-Op vs Pre-Op Radiation Therapy?

Pre-Op Radiation Therapy	Post-Op Radiation Therapy
Lower dose (50Gy) – 5 weeks	Higher dose (66Gy)- 6.5 weeks
Smaller field size	Larger field size
Reduced fibrosis/joint stiffness (32%/18%)	Increased fibrosis (48%/23%)
Reduced edema (15%)	Increased edema (23%)
Increased rate of wound complications (35%) Upper Leg (45%) Lower Leg (38%)	Decreased rate of wound complications (17%) Upper Leg (28%) Lower Leg (5%)

O'Sullivan, Lancet 2002, Davis, Rad Onc 2005

How can we reduce toxicity?

O'Sullivan, Cancer 2013, Folkert, JCO 2014, Richard, IJROBP 2016)

How can we reduce toxicity?

Better dosimetry/planning

Reduced volume/margins

O'Sullivan, Cancer 2013, Folkert, JCO 2014, Richard, IJROBP 2016)

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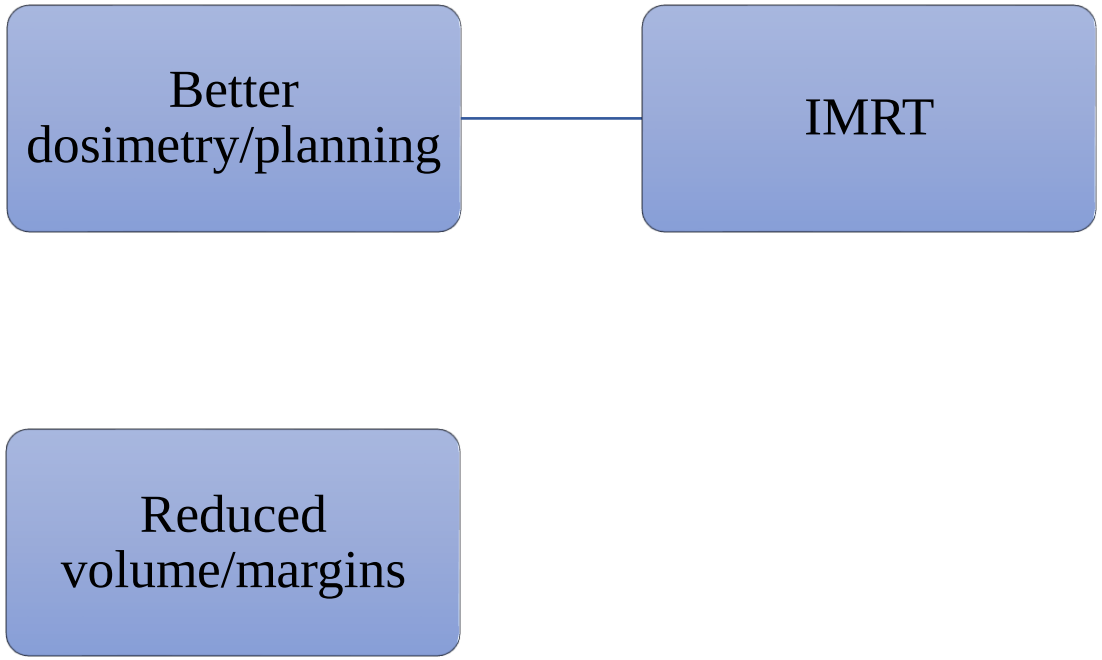

O'Sullivan, Cancer 2013, Folkert, JCO 2014, Richard, IJROBP 2016)

How can we reduce toxicity?

Better dosimetry/planning

IMRT

Reduced volume/margins

59 pts treated with IMRT in Canada 2005-2009
Mean tumor size 10.6cm
49% high grade tumors, 35% UPS
Wound complications in 31% vs 43% historic controls
Grade 2 fibrosis 9% vs 31% historic controls
Edema 11% vs 15% historic controls

O'Sullivan, Cancer 2013, Folkert, JCO 2014, Richard, IJROBP 2016)

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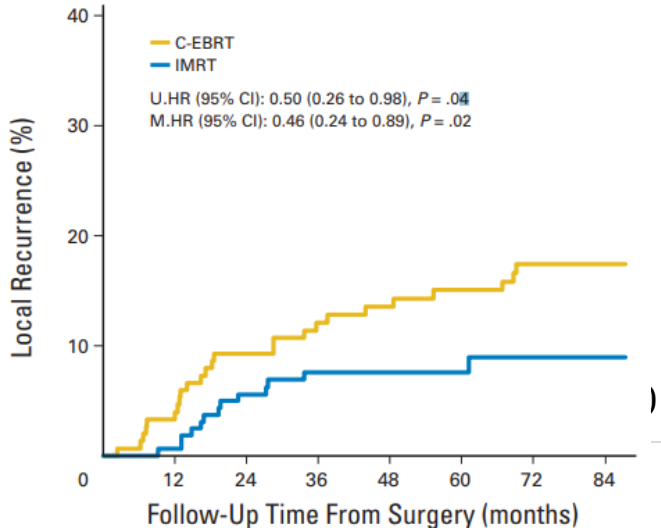
Decreased toxicity

319 patients treated with 3D-RT vs IMRT 1996-2010
45% with tumors >10cm, 46% with close/positive margins
82% high grade tumors, 37% UPS
Local recurrence 7.6% (IMRT) vs 15.1% (3D-RT)



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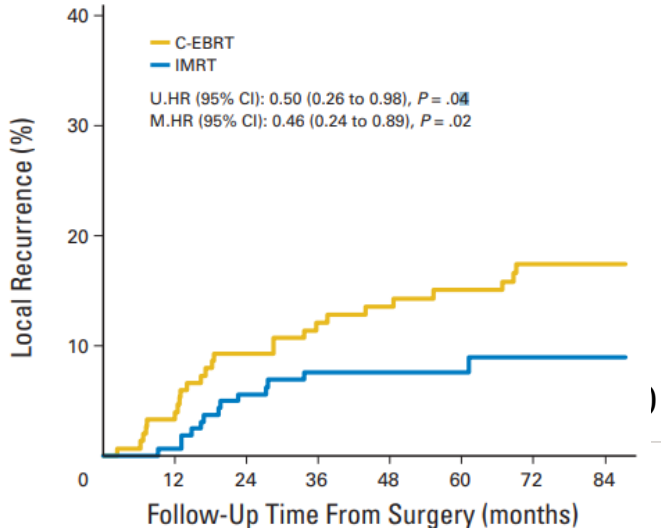
Better local control



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Cost comparison of 3D-RT vs IMRT in the pre-operative RT
IMRT reduces rates of severe toxicity & LR, improves QOL
Compensates for increased upfront cost

O'Sullivan, Cancer 2013, Folkert, JCO 2014, Richard, IJROBP 2016)

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IMRT reduc & LR, improves QOL
Compensate ased upfront cost

More cost effective

O'Sullivan, Cancer 2013, Folkert, JCO 2014, Richard, IJROBP 2016)

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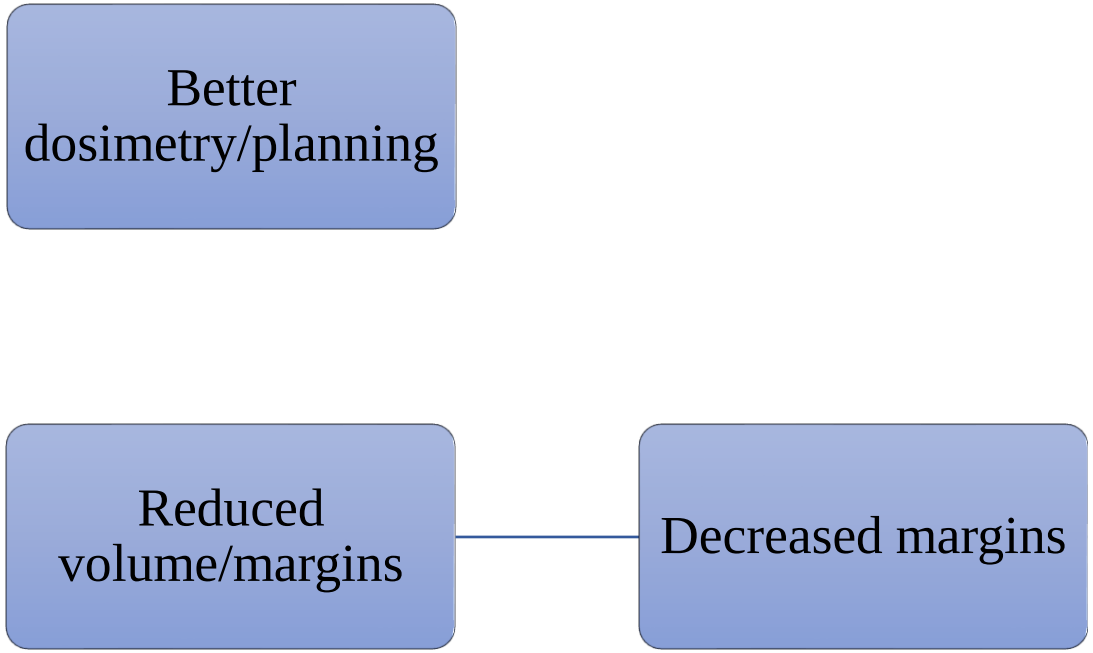

Wang JCO 2015, Hass, PRO 2019

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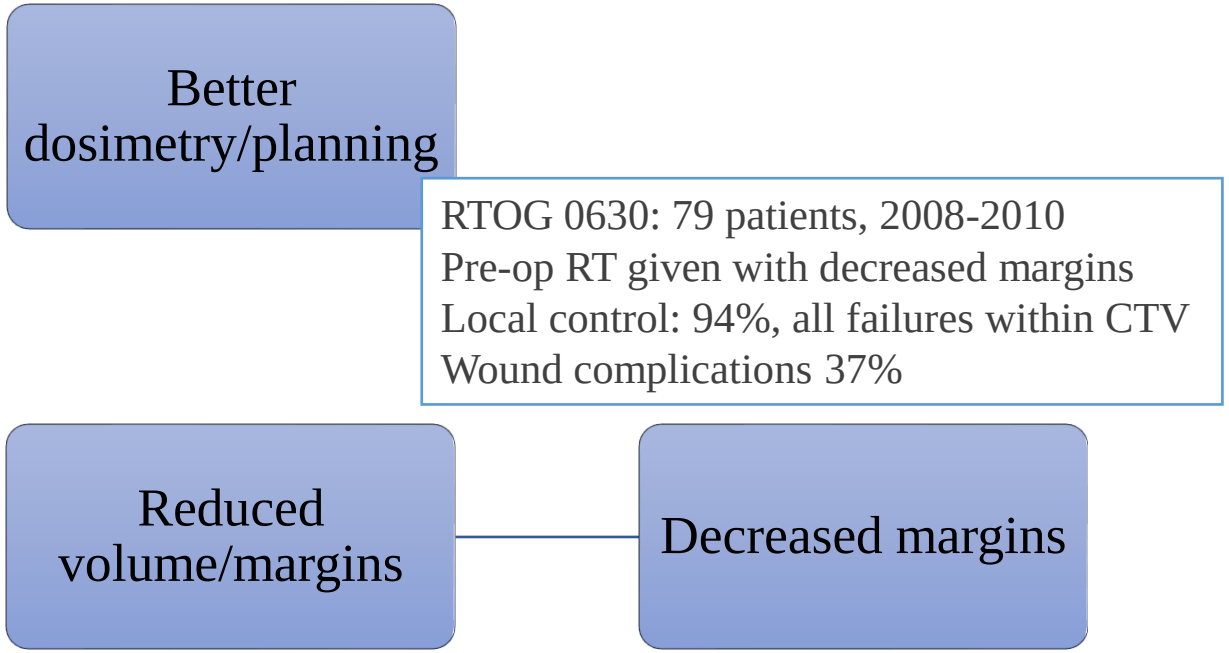

Wang JCO 2015, Hass, PRO 2019

How can we reduce toxicity?

Better dosimetry/planning

RTOG 0630: 79 patients, 2008-2010
Pre-op RT given with decreased margins
Local control: 94%, all failures within CTV
Wound complications 37%

Reduced volume/margins

Decreased margins

ASTRO Consensus Guidelines 2021

Target	Delineation Guidance
Preop RT extremity or truncal CTV	CTV = GTV + 1.5 cm radial and 3-4 cm longitudinal anatomically constrained expansion with inclusion of peritumoral edema and biopsy tract (when feasible)
Preop RT subcutaneous tumor CTV	CTV = GTV + 3-4 cm circumferential margins with expansion of 0.5-1 cm into underlying non-involved muscle with inclusion of peritumoral edema and biopsy tract (when feasible)
Postop RT extremity or truncal CTV1	CTV1 = tumor bed (defined by clips/preop MRI) + 1.5 cm radial and 3-4 cm longitudinal anatomically constrained expansion + the operative field, surgical scar, and drain sites (when feasible)
Postop RT extremity or truncal CTV2	CTV2 = tumor bed (defined by clips/preop MRI) + 1.5 cm radial and 2 cm longitudinal expansion
Postop subcutaneous tumor CTV1	CTV1 = tumor bed (defined by clips/preop MRI) + 3-4 cm circumferential margins with expansion of 0.5-1 cm into uninvolved muscle + the operative field, scar, and drain sites (when feasible)
Postop subcutaneous tumor CTV2	CTV2 = tumor bed (defined by clips/preop MRI) + 1.5-2 cm circumferential margins and 0.5 cm into uninvolved muscle
Extremity or truncal PTV expansion	PTV expansion of 0.5 cm may be used with daily image guidance, however, >1.0 cm may be needed without daily image guidance. For **preop** RT, dose coverage to the PTV can be trimmed 3-5 mm from skin to reduce wound healing complications if achievable without unacceptable compromise of CTV coverage and if surgeon plans to resect overlying skin and subcutaneous tissue

Wang JCO 2015, Hass, PRO 2019

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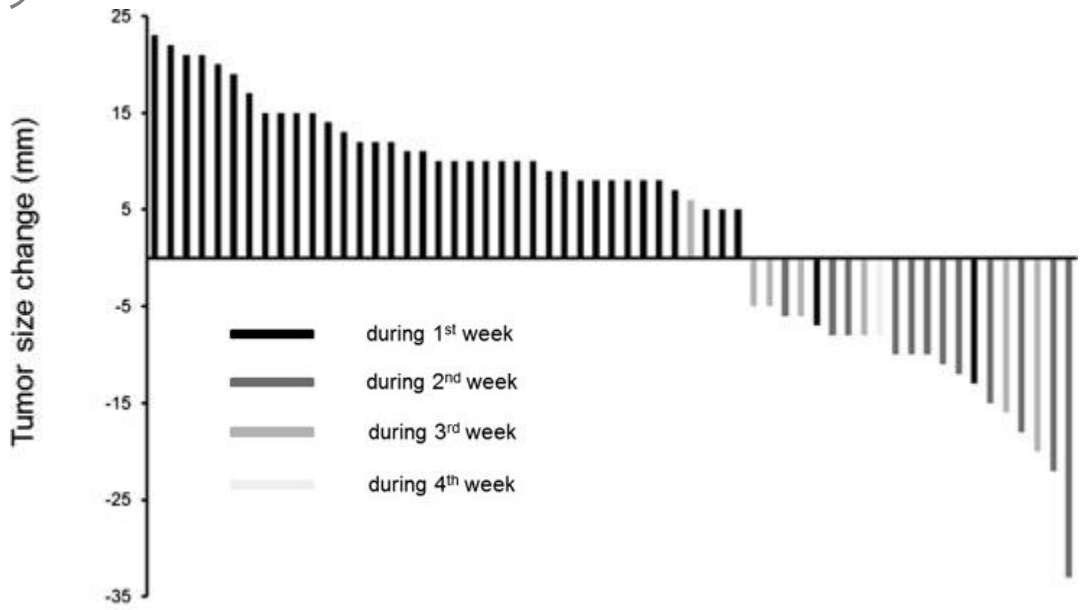
Better dosimetry/planning

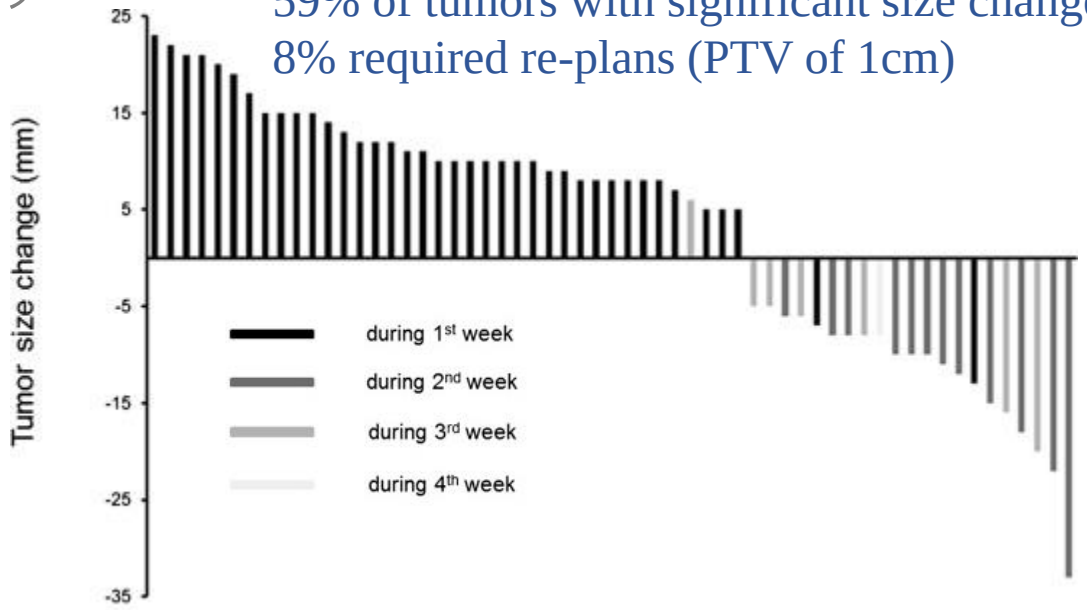


Reduced volume/margins → Decreased margins → When to replan?

Wang JCO 2015, Hass, PRO 2019

How can we reduce toxicity?

59% of tumors with significant size change
8% required re-plans (PTV of 1cm)



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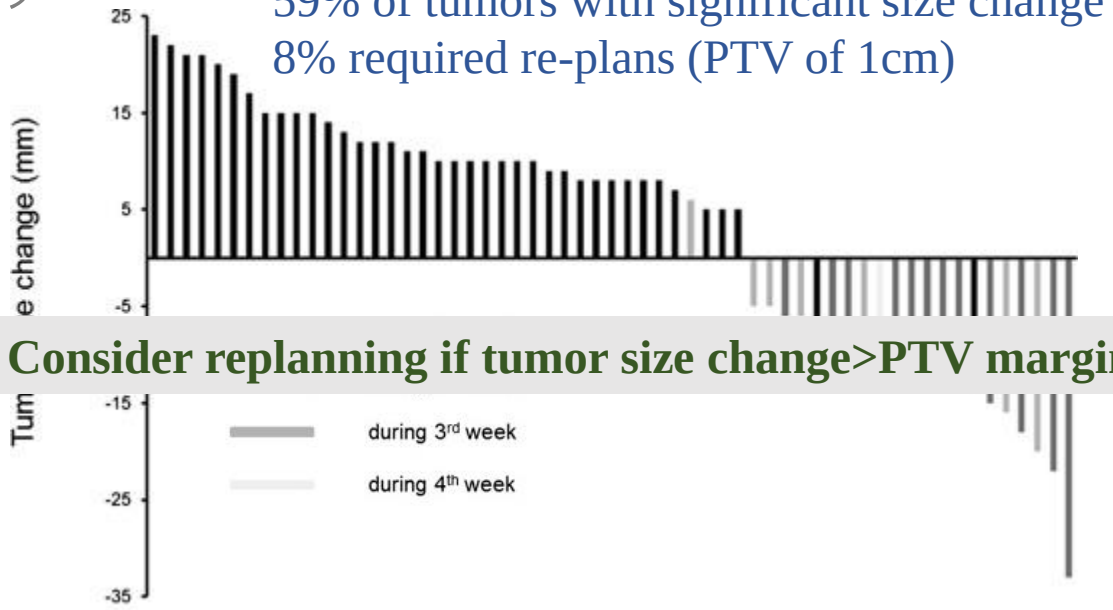

Consider replanning if tumor size change>PTV margin

Better dosimetry/planning

Reduced volume/margins → Decreased margins → When to replan?

Wang JCO 2015, Hass, PRO 2019

What About Margin Status?

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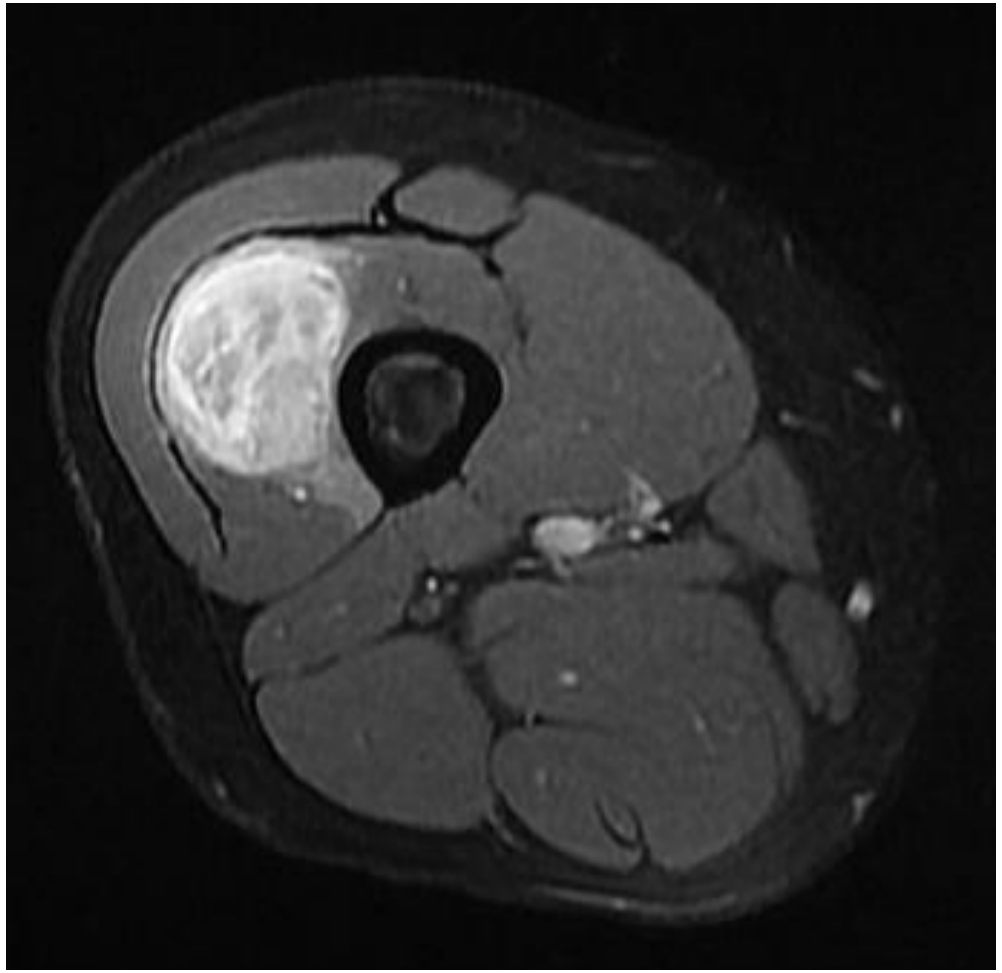

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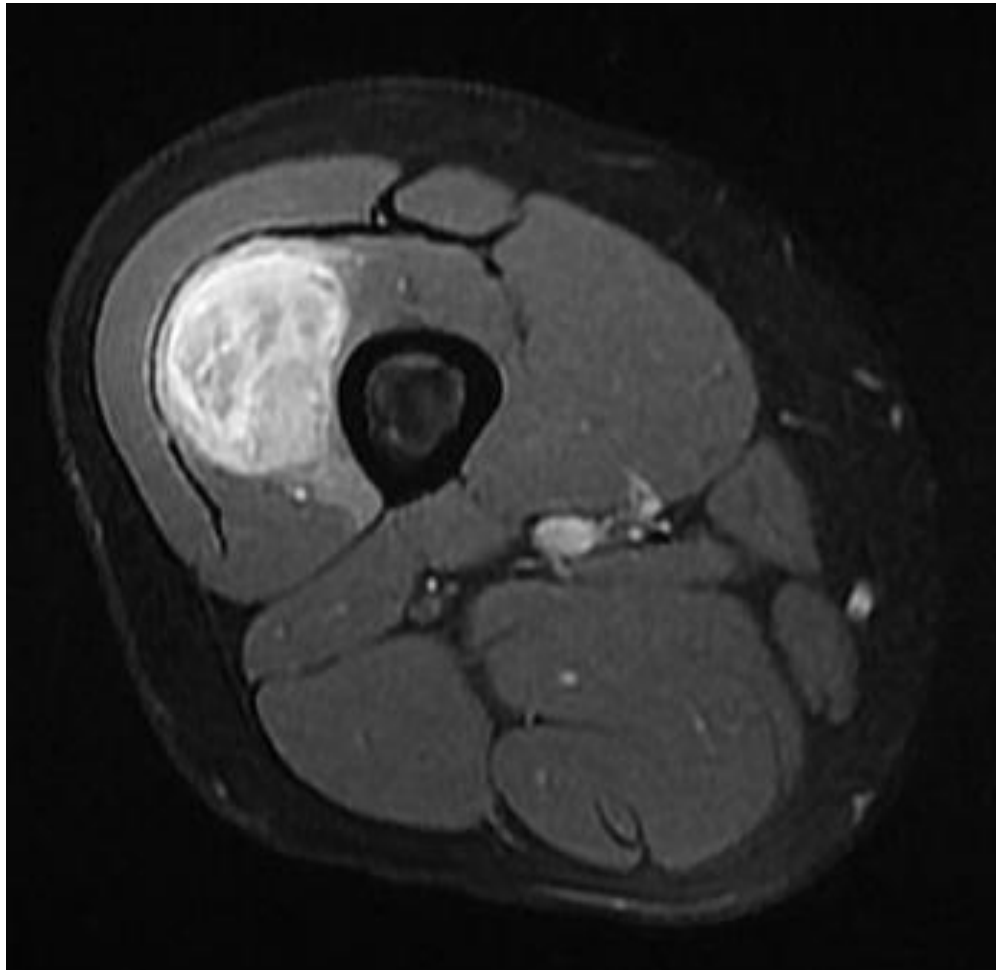
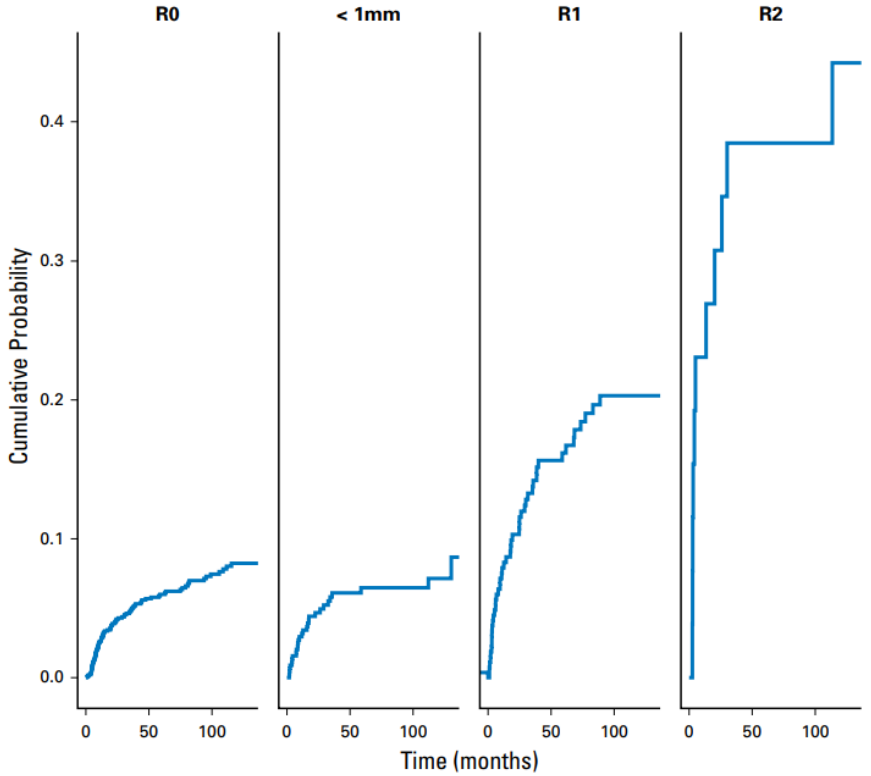
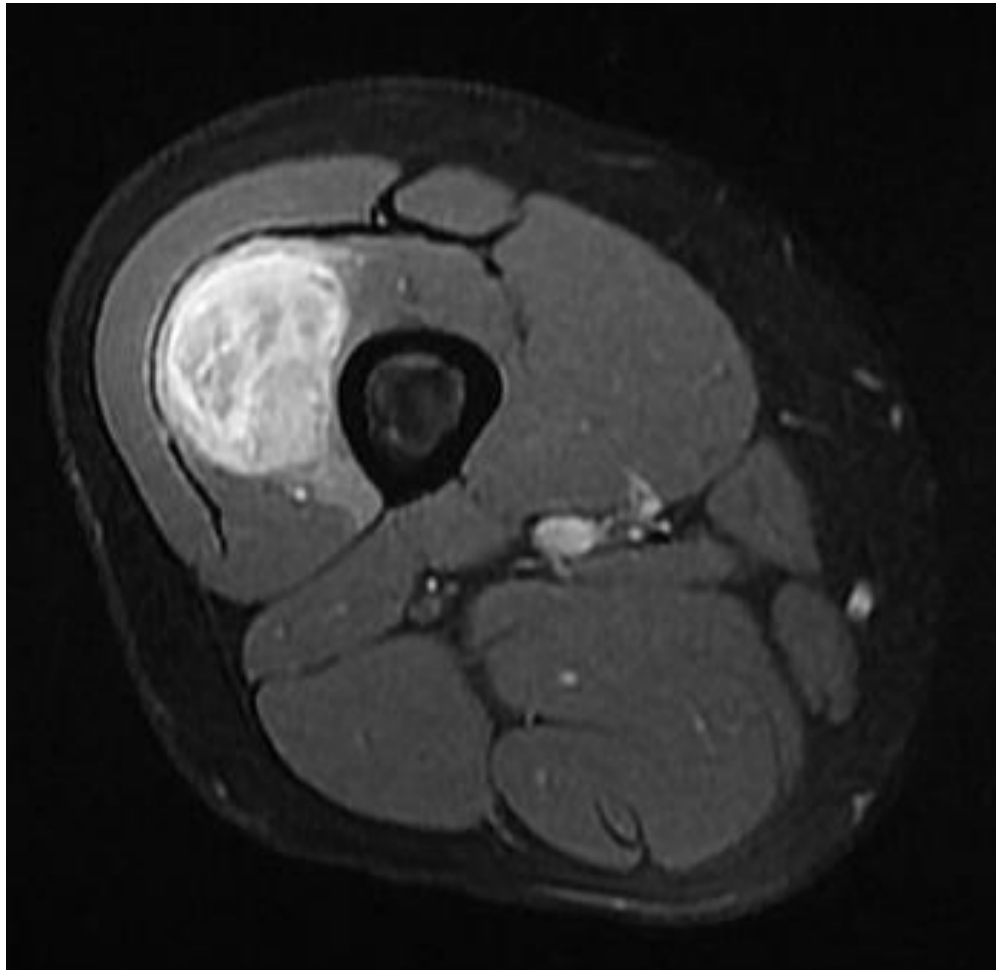


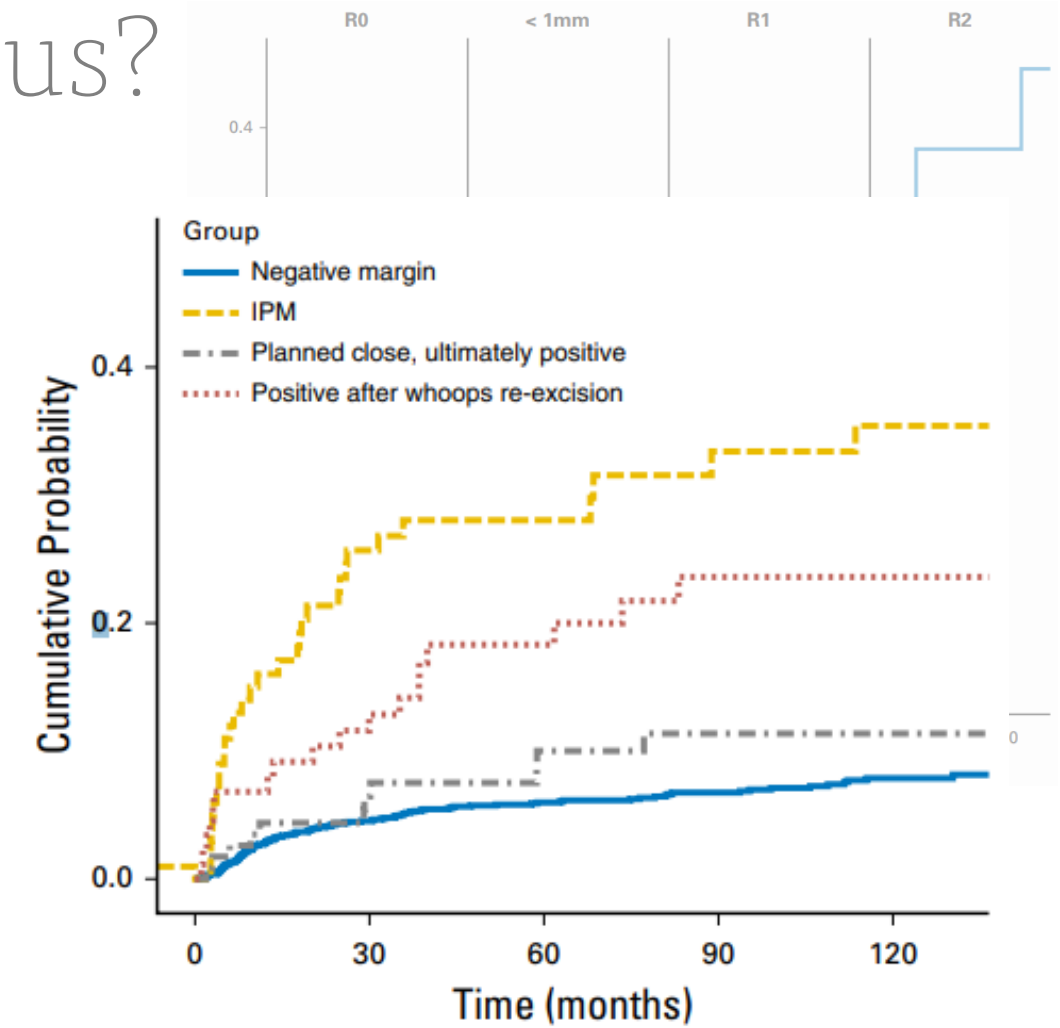


2217 patients with STS treated with surgical resection + RT
Retrospective review
Tumor within 1mm of resection margin does not predict higher risk of recurrence

Gundle JCO 2018

What About Margin Status?

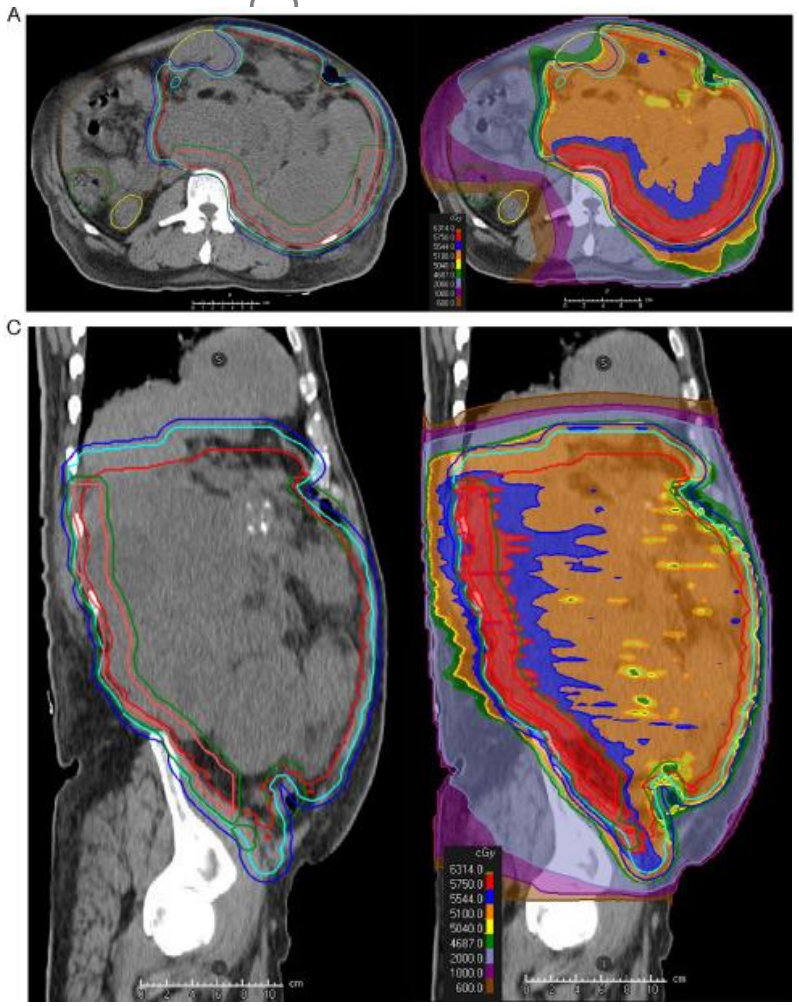




Gundle JCO 2018

Should We Boost “Problematic” Margins?

- Retrospective study from Moffit Cancer Center
- 103 patients with retroperitoneal sarcomas, receiving neoadjuvant RT
- Simultaneous integrated boost (SIB) to 57.5Gy-63Gy

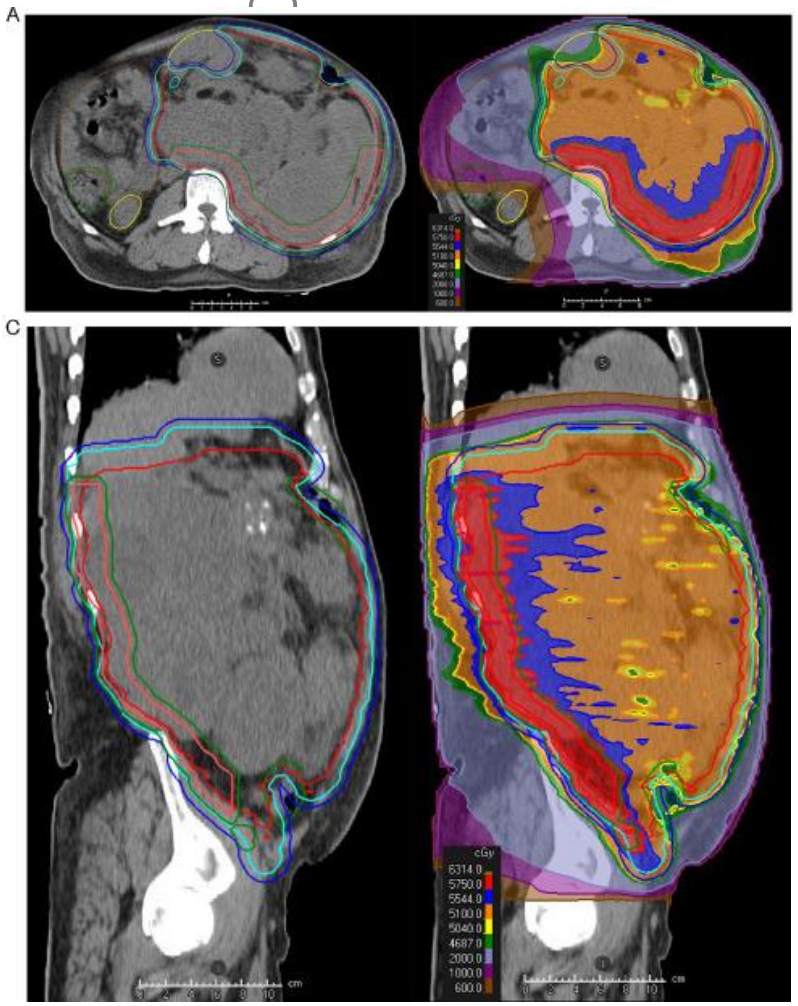


Liveringhouse, IJROBP 2023, DeLaney IJROBP 2021

Should We Boost "Problematic" Margins?

- Retrospective study from Moffit Cancer Center
- 103 patients with retroperitoneal sarcomas, receiving neoadjuvant RT
- Simultaneous integrated boost (SIB) to 57.5Gy-63Gy
- Similar rate of R0 resection, despite more advanced tumors (T4 57% vs 14%)
- Better abdominal control and RFS with SIB

- Another phase II trial with SIB utilizing IMPT is ongoing



Liveringhouse, IJROBP 2023, DeLaney IJROBP 2021

Should We Boost Positive Margins Post-op?

Yami, IJROBP 2010

Should We Boost Positive Margins Post-op?

- Princess Margaret Retrospective study
- 93 patients receiving pre-op RT (50Gy) had positive surgical margins
- 41 patients received 16Gy boost

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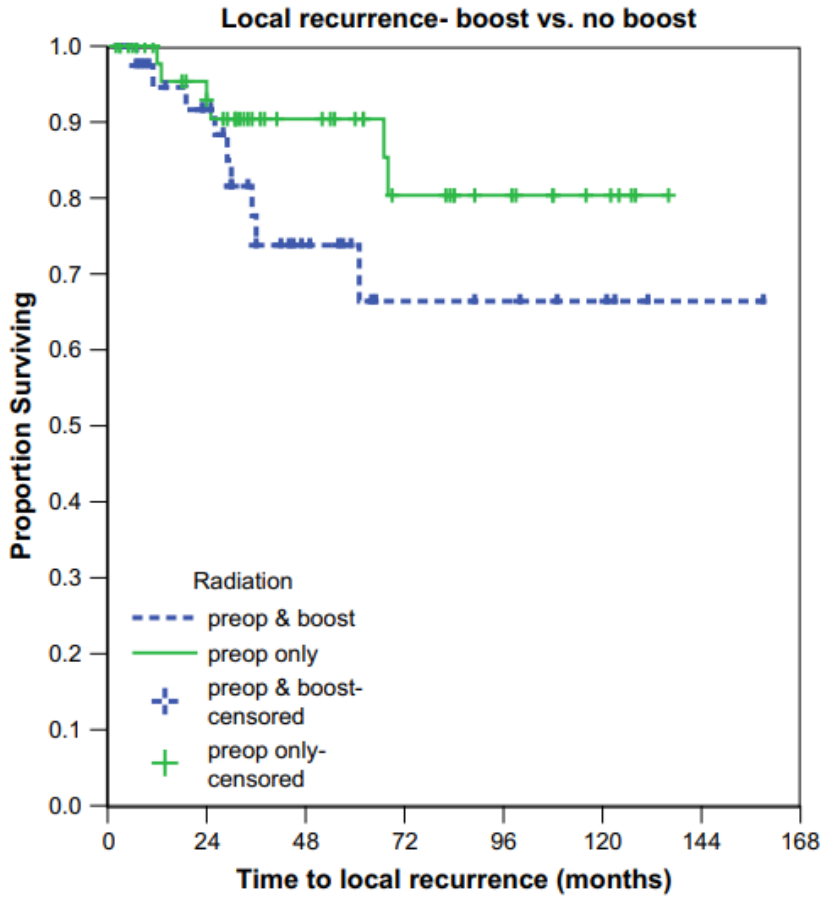
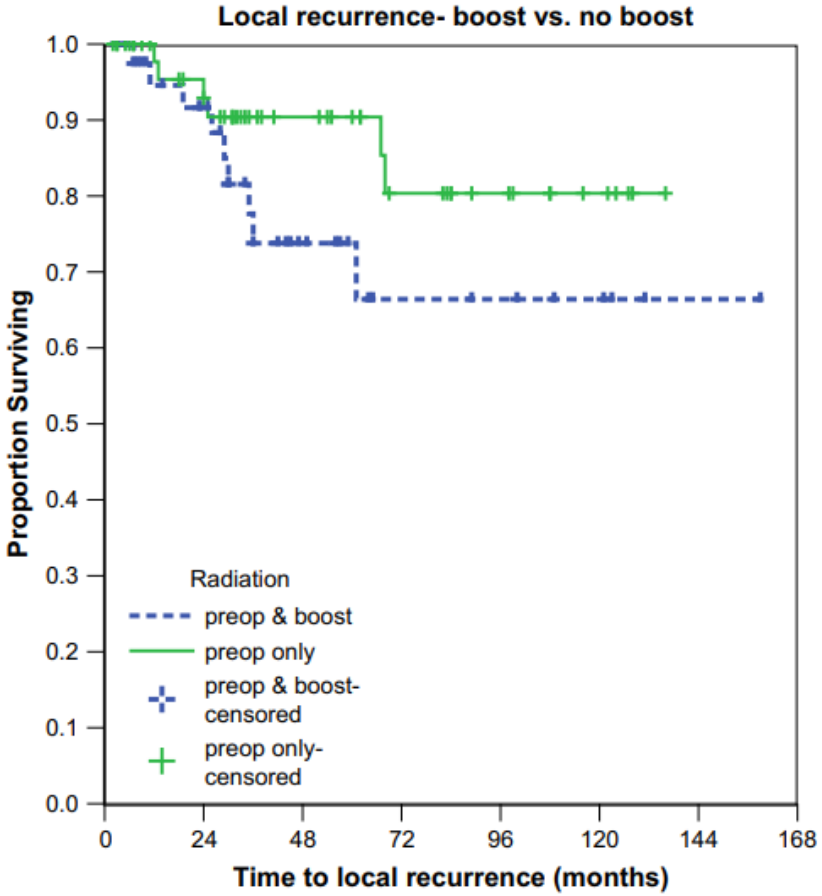


Yami, IJROBP 2010

Should We Boost Positive Margins Post-op?

- Princess Margaret Retrospective study
- 93 patients receiving pre-op RT (50Gy) had positive surgical margins
- 41 patients received 16Gy boost

- No local control benefit
- Worse toxicity with boost



Yami, IJROBP 2010

Planning Considerations

- Dose: 50 Gy in 25 fractions, IMRT or 3DCRT or Proton therapy
  - Consider 50.4Gy in 28 fractions if given concurrently with chemotherapy
- Target Coverage:
  - PTV 47.5 Gy (95%Rx) at least 95% vol
  - PTV Max 55 Gy (110%Rx)
  - PTV Min 46.5 Gy (93%Rx)
- OARs:
  - Bone (humerus, radius, ulna, ankle bones, tibia, fibula, or femur) to reduce path fracture and periosteal stripping
    - Dmax 59 Gy
    - Mean < 37 Gy
    - V40 Gy < 64% volume
    - Limit circumferential radiation of 50 Gy isodose line
- Joint 50 Gy < 50% to preserve synovial function
- Contralateral limb: Dmax < 10 Gy
- Normal tissue/skin strip (ipsilateral extremity minus PTV @ at least >=1 cm)
  - 20 Gy < 30% vol

Dickie IJROBP 2009, Bishop PRO 2016

Future Directions

Guadagnolo IJROBP 2022, Kalbasi Clin Can Res 2020

Future Directions

Hypofractionation

Guadagnolo IJROBP 2022, Kalbasi Clin Can Res 2020

Future Directions

Hypofractionation

42.75Gy/15Fx

HYPORT-STS
Phase 2, single arm
120 patients
Wound complications 31%
Late grade 3 toxicity: 3%

Phase II – Mayo Clinic

30-35Gy/5Fx

UCLA
Phase 2, single arm
52 patients
Wound complications 32%
Late grade 2 toxicity: 16%

Registry – Cleveland Clinic
Phase II – MCW
Phase I/II – McGill
Phase II – Poland
Phase II – Russia

Phase II – 14Gy x 3 – The Netherlands

28-36Gy/8-12Fx

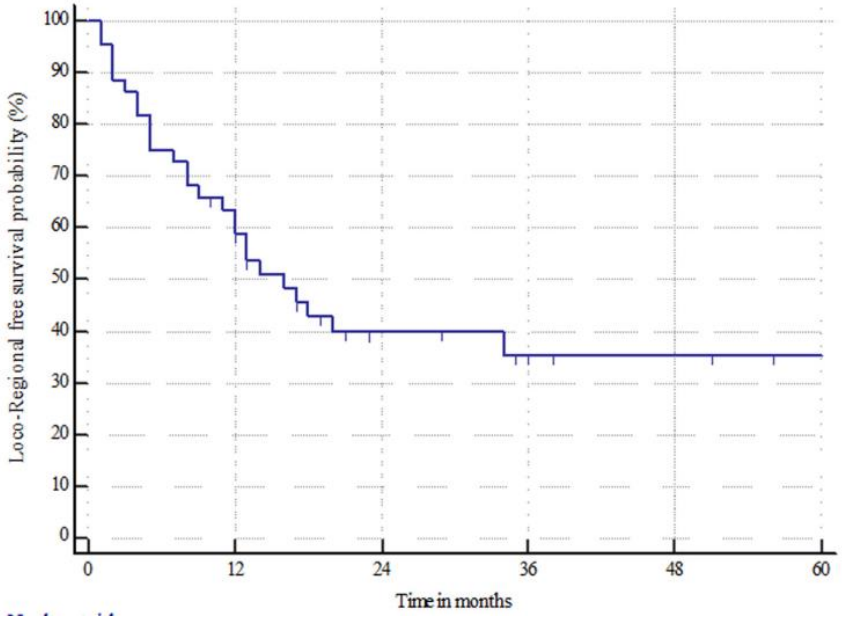
Phase I – OHSU
Phase II - Poland

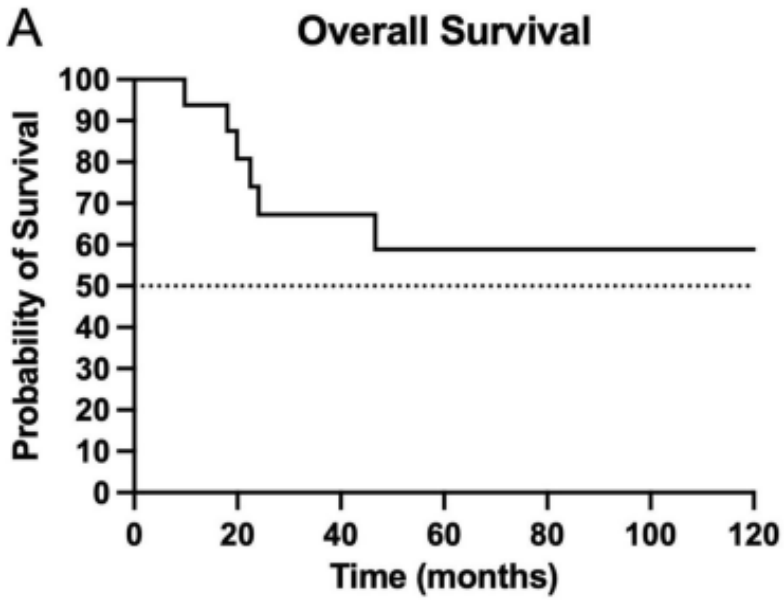
Guadagnolo IJROBP 2022, Kalbasi Clin Can Res 2020

Limited Metastatic Disease – can SBRT help?

Navaria IJROBP 2022, Gutkin Rad Onc 2023

Limited Metastatic Disease – can SBRT help?





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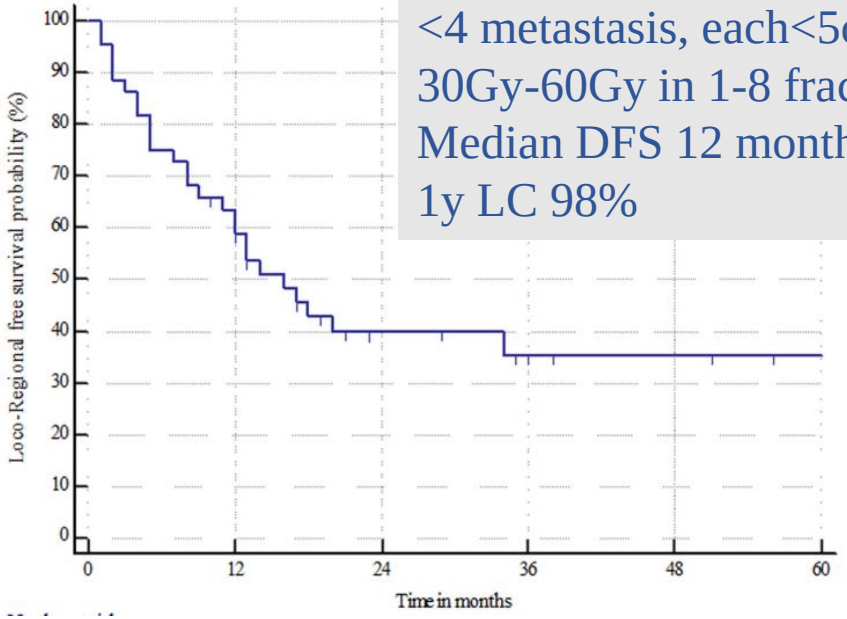
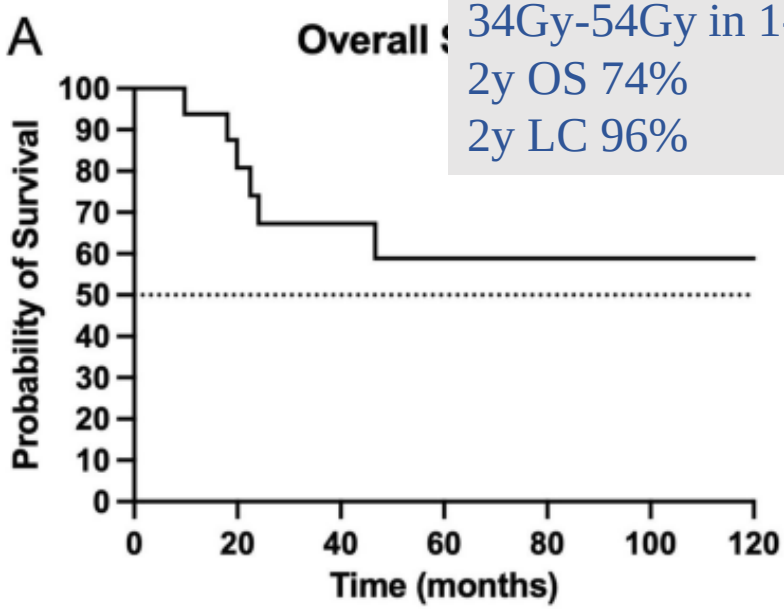
Limited Metastatic Disease – can SBRT help?

Prospective phase 2 study (Italy)
44 patients with 71 lung metastasis
<4 metastasis, each<5cm
30Gy-60Gy in 1-8 fractions
Median DFS 12 months
1y LC 98%



Prospective phase 2 study (MCW)
18 patients with 26 lung metastasis
34Gy-54Gy in 1-10 fractions
2y OS 74%
2y LC 96%



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