Optimizing Outcomes for Patients With Soft-Tissue Sarcoma Through the Multidisciplinary Medical Oncology/Radiation/Surgical Team Approach

Arash Naghavi, MD
Dave Johnson, PA-C
Leah Clark, ARNP
Sarcoma Program
Moffitt Cancer Center

2017 JADPRO Live in APSHO

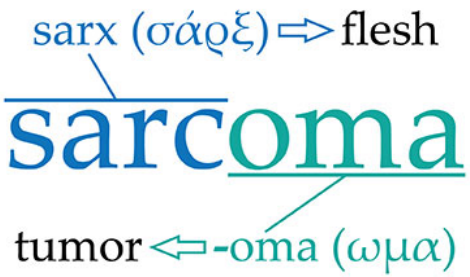
Learning Objectives

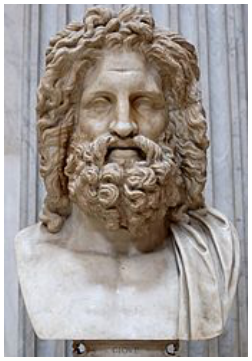
- Determine a personalized multidisciplinary approach to soft-tissue sarcoma (STS) patients
- Discuss the role of surgery and how it is being used in conjunction with other therapies
- Determine ideal candidates for various forms of adjuvant radiation delivery
- Identify both the utility of commonly used systemic agents in STS and opportunities for treatment resistant STS
- Recognition and management of various acute and chronic sequela from STS treatment

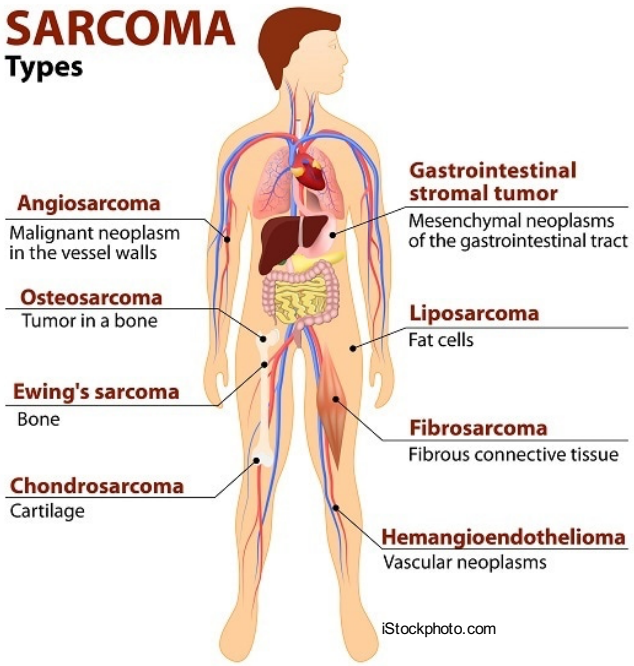
Financial Disclosure

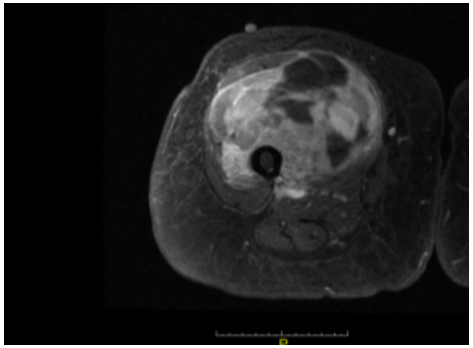
- Dr. Naghavi has nothing to disclose.
- Mr. Johnson has acted as a consultant and served on the speakers bureau for Amgen.
- Ms. Clark has served on the speakers bureau for Genentech.

Sarcoma









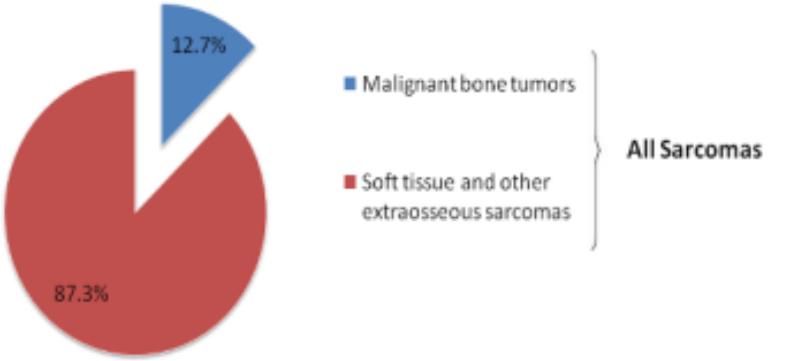
Photos courtesy of Dr. G. Douglas Letson Moffitt Cancer Center

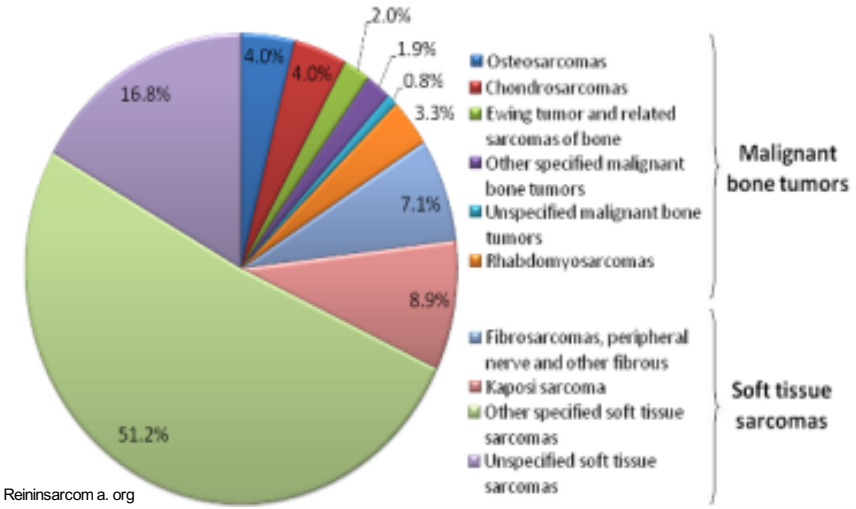
Transformed cells of mesenchymal origin

- i.e., bone, cartilage, fat, muscle, vascular

Soft-Tissue Sarcoma (STS)

- Neoplasms of connective tissue (mesoderm)
- Benign mesenchymal neoplasms 100x more common than soft-tissue sarcoma
- Named primarily based on apparent similarity to a normal cell of origin on H&E
  - Often misnomer
  - Many times cell of origin unknown





Reininsarcom a. org

Epidemiology

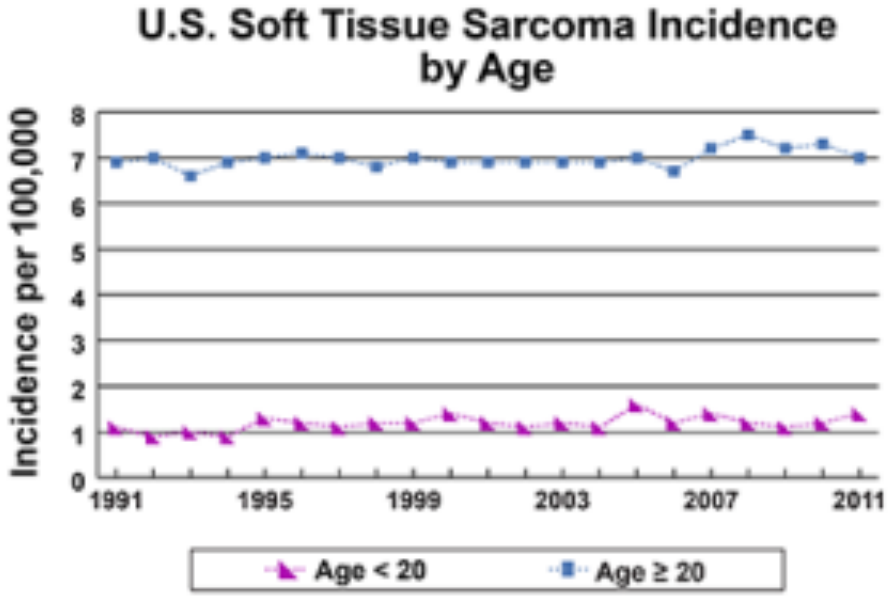
Soft-tissue sarcoma (2015)

- Incidence: ~11,930
  - 0.7% of all cancers
- Cancer deaths: ~4,870
  - 0.8% of all cancer deaths
- Sex: Males > females (1.2:1)

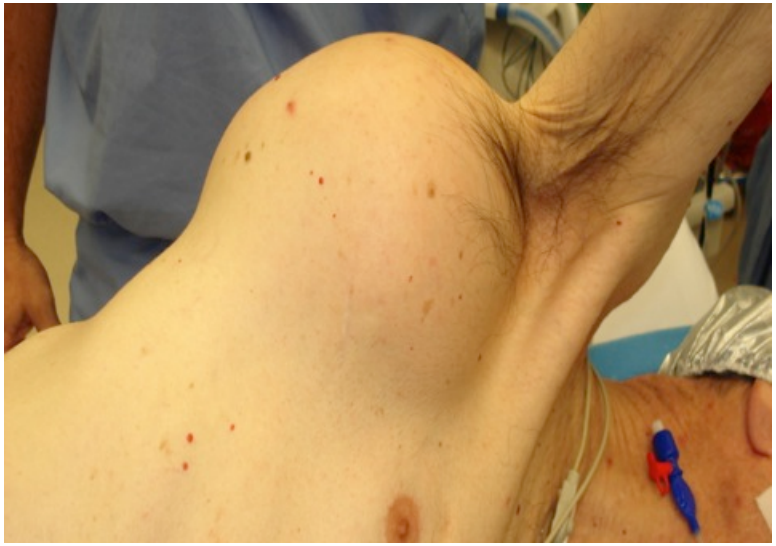
Siegel RL, et al. *CA Cancer J Clin*. 2015;65:5-29.

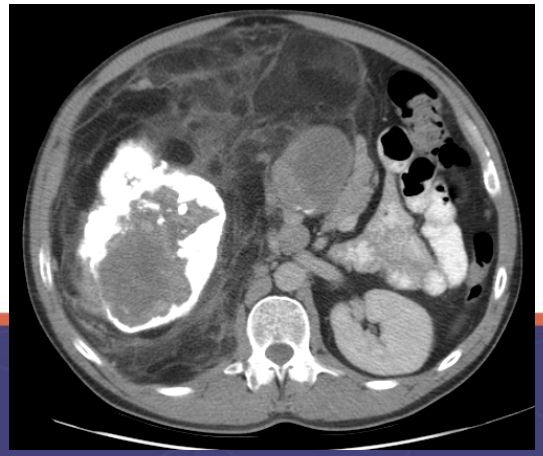
Soft-Tissue Sarcomas

- 1% of all cancers
  - 1.8 to 5 per 100,000 per year
- 12,310 new cases estimated in 2016
  - 4,990 expected to die of disease



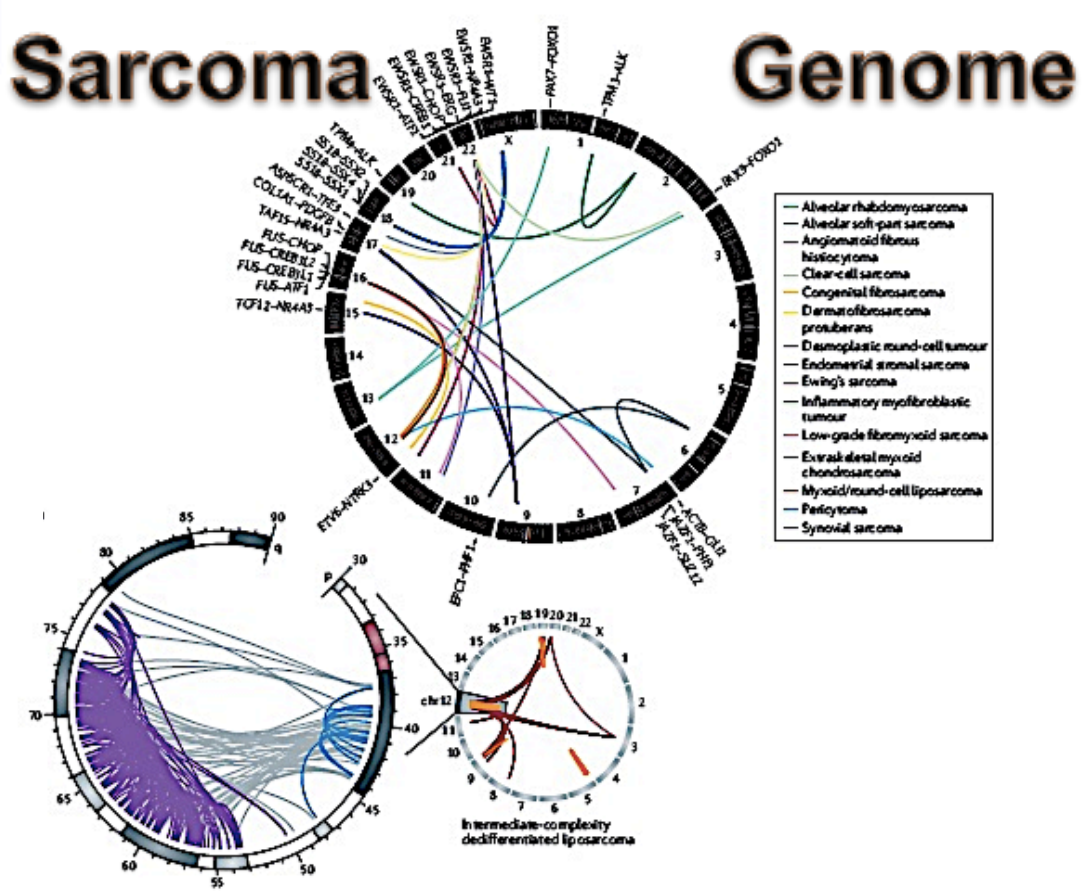
Siegel RL, et al. *CA Cancer J Clin*. 2016;66:7-30.





Images courtesy Dr. G. Douglas Letson Moffitt Cancer Center

Sarcoma Genome



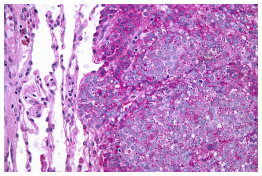
Workup

History and physical

- Limb function, performance Status, age, recurrent disease, wound issues

Biopsy

- Histology, grade



Imaging

- Staging (localized, depth, size)

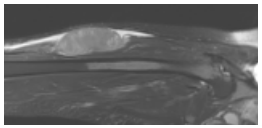


TABLE 63-4 TNM Classification of Soft Tissue Sarcomas

Primary Tumor (T)				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Tumor 5 cm or less in greatest dimension			
T1a	Superficial tumor[a]			
T1b	Deep tumor			
T2	Tumor more than 5 cm in greatest dimension			
T2a	Superficial tumor[a]			
T2b	Deep tumor			
Regional Lymph Nodes (N)				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1[b]	Regional lymph node metastasis			
Distant Metastasis (M)				
MX	Distant metastasis cannot be assessed			
M0	No distant metastasis			
M1	Distant metastasis			
Stage Grouping				
Stage IA	Grade 1	T1a, T1b	N0	M0
Stage IB	Grade 1	T2a, T2b	N0	M0
Stage IIA	Grade 2-3	T1a, T1b	N0	M0
Stage IIB	Grade 2	T2a, T2b	N0	M0
Stage III	Grade 3	T2a, T2b	N0	M0
Stage III	Any grade	Any T	N1	M0
Stage IV	Any grade	Any T	Any N	M1

Halperin EC, et al. *Perez and Brady's Principles and Practice of Radiation Oncology*, 6th ed. Wolters Kluwer, 2013.

Systematic Approach

- Clinical presentation
  - Age
  - Symptoms
  - Location
- Radiologic information
  - X-ray
  - MRI: T1, STIR, contrast
  - CT: for fatty tumors

Image courtesy of Dr. G. Douglas Letson
Moffitt Cancer Center

STIR = short tau inversion recovery.

Soft-Tissue Sarcoma

- Larger than 4 cm
- Increased signal on STIR and contrast, dark on T1
- Heterogeneous
- Necrosis
- Well circumscribed (pseudocapsule)
- Peritumoral edema

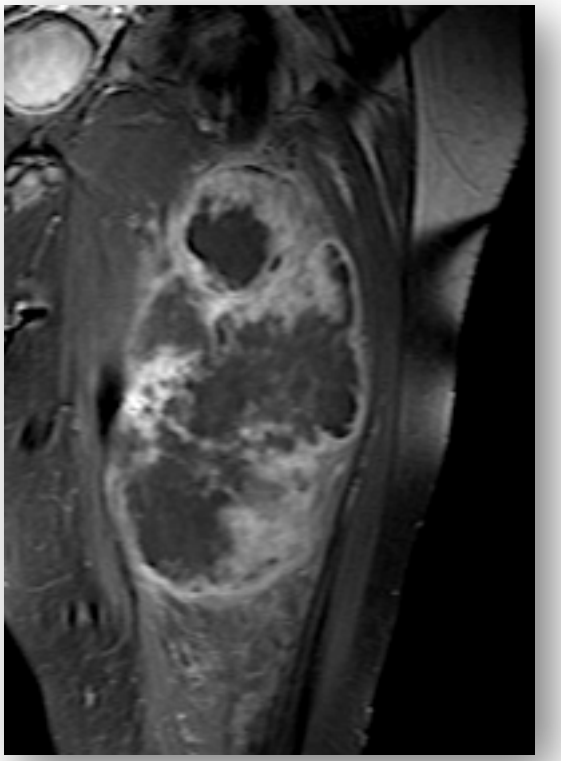
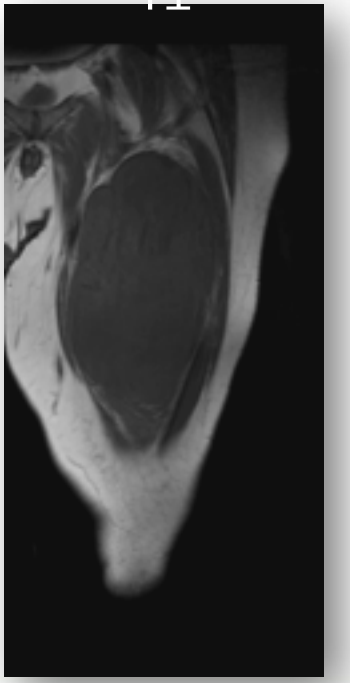
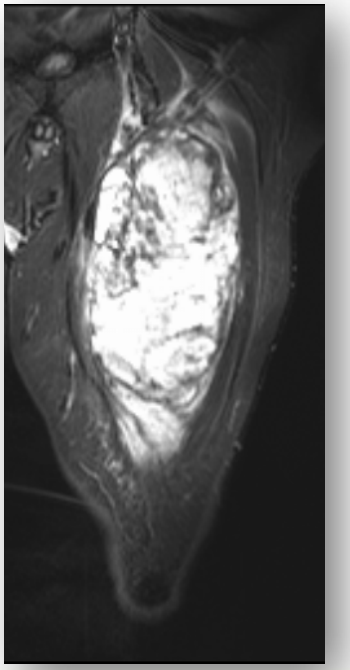


Image courtesy of Dr. G. Douglas Letson
Moffitt Cancer Center

High-Grade Undifferentiated Sarcoma



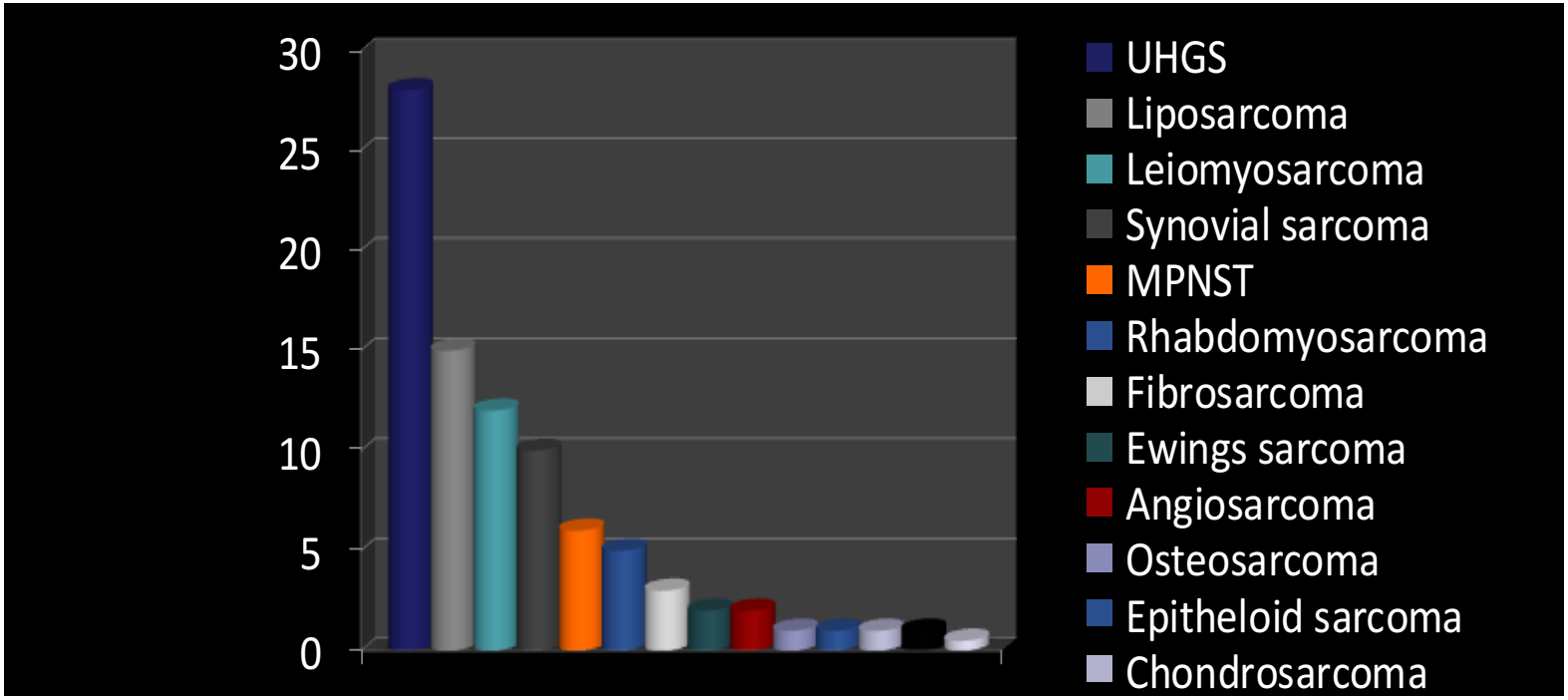


Images courtesy of the Moffitt Cancer Center

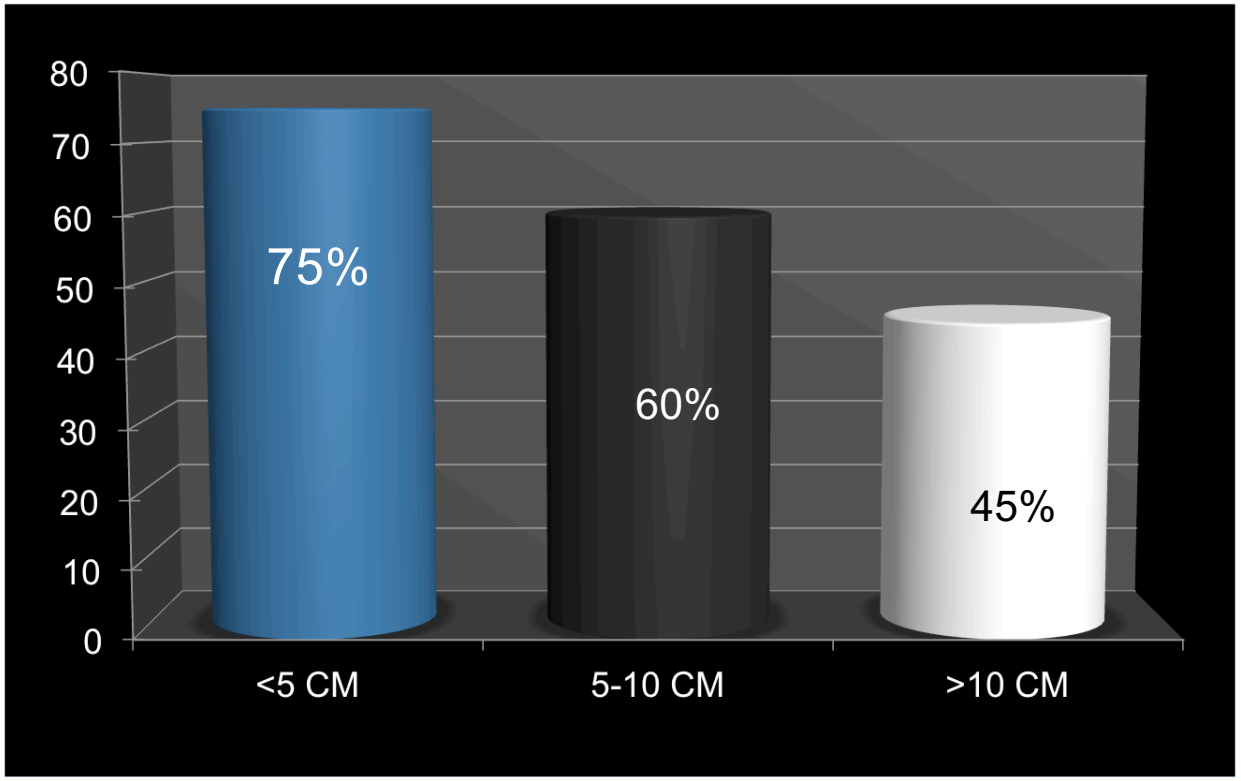
STS Outlook

- Prognosis depends on
  - Age/comorbidities
  - Subtype
  - Size
  - Histologic grade
  - Stage
- Poorer prognosis: >60 years old, high grade, >5 cm, positive margins

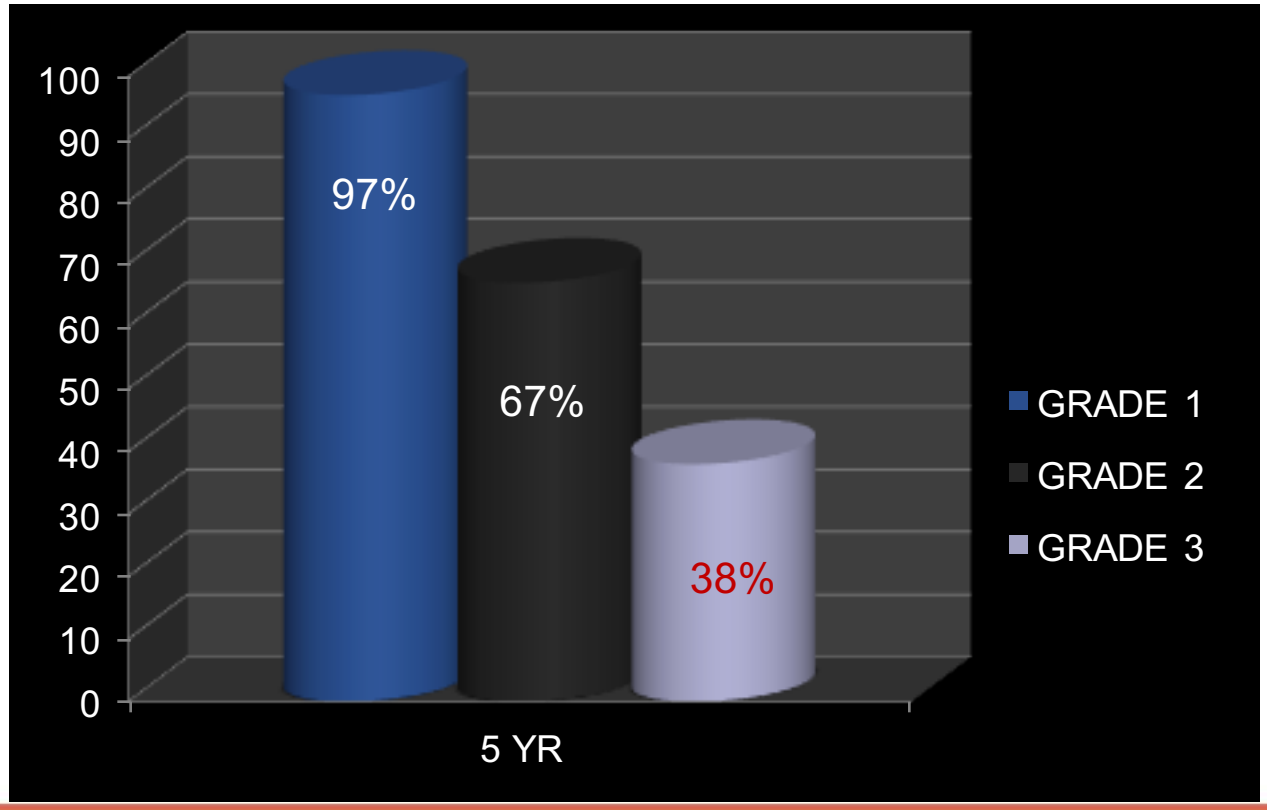
Subtypes


30
25
20
15
10
5
0
UHGS
Liposarcoma
Leiomyosarcoma
Synovial sarcoma
MPNST
Rhabdomyosarcoma
Fibrosarcoma
Ewings sarcoma
Angiosarcoma
Osteosarcoma
Epitheloid sarcoma
Chondrosarcoma

Size and 5-Year Survival



Grade and 5-Year Survival



Staging

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Staging
Soft Tissue Sarcoma

NCCN Guidelines Index
Soft Tissue Sarcoma, Table of Contents
Discussion

Table 1

American Joint Committee On Cancer (AJCC) Staging System For Soft Tissue Sarcoma

(7th ed, 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension*
T1a	Superficial tumor
T1b	Deep tumor*
T2	Tumor more than 5 cm in greatest dimension*
T2a	Superficial tumor
T2b	Deep tumor

*Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1†	Regional lymph node metastasis

†Presence of positive nodes (N1) in M0 tumors is considered Stage III.

Distant Metastases (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade

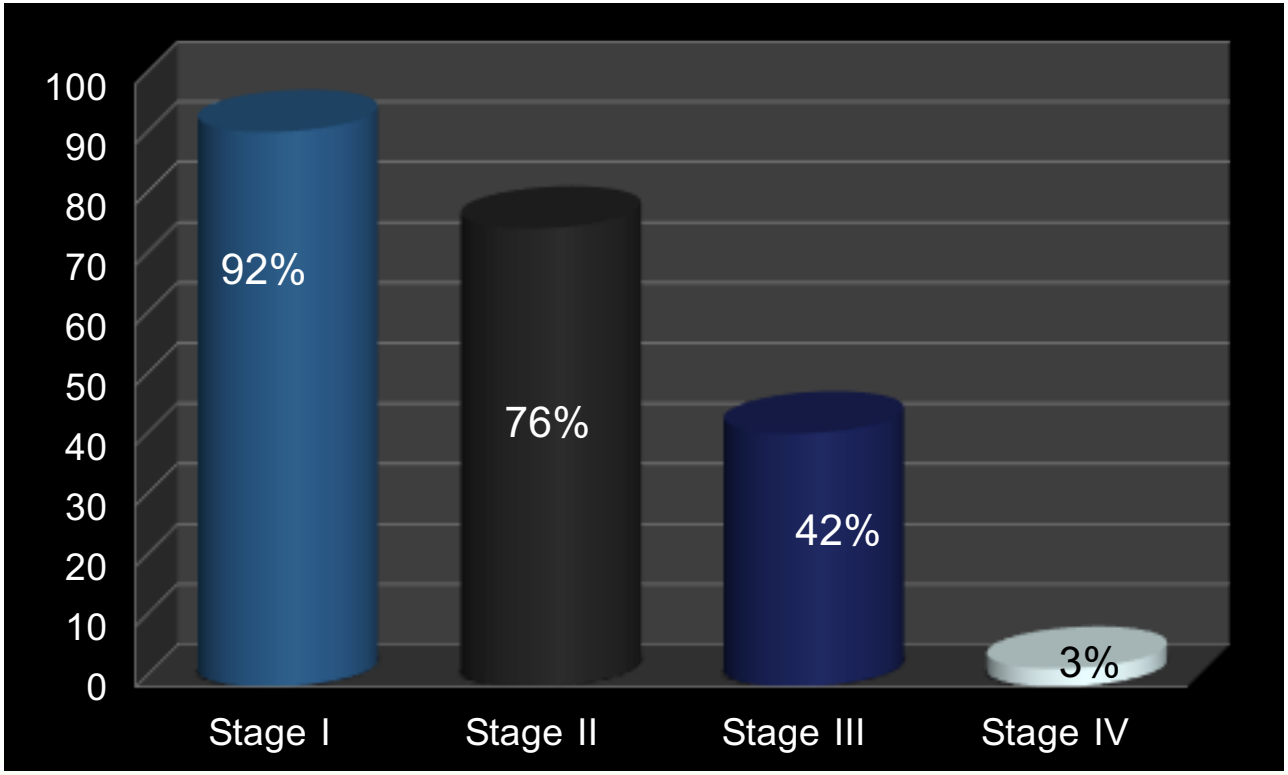
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

Anatomic Stage/Prognostic Groups

Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a,T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

Continued...

Survival and Stage



Metastatic Sarcoma

- Lung most common site
- Staging: CT chest
  - Add abdomen and pelvis
    - Myxoid liposarcoma
    - Synovial sarcoma
    - Rhabdomyosarcoma
    - Angiosarcoma
- Lymph node metastasis
- “RACES”: Rhabdomyosarcoma, alveolar/angiosarcoma, clear cell, epithelioid, synovial

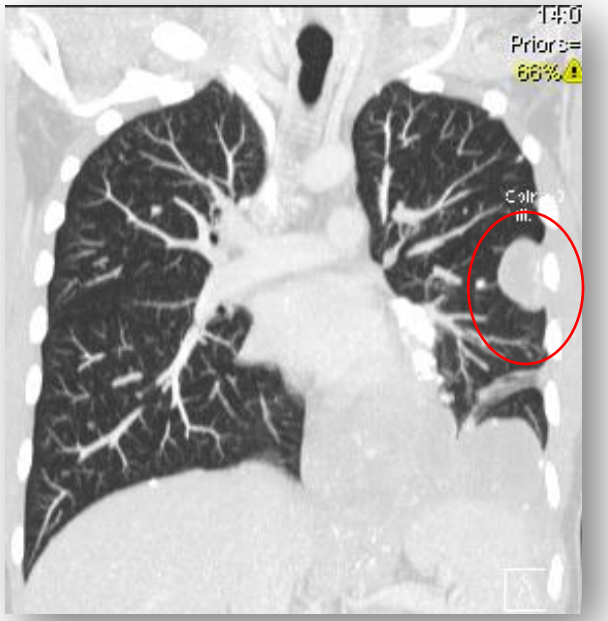


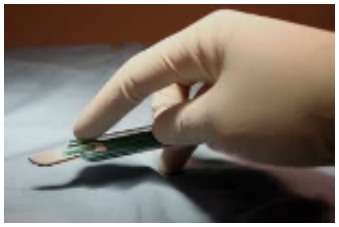
Image courtesy of Dr. G. Douglas Letson

Multimodal Treatment

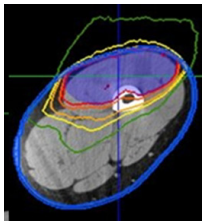
- Mainstay is surgical resection
- Radiation therapy
- Chemotherapy

Local Therapy Options

- Surgery alone
  - Increased extent = Increase local control
    - Increased toxicity
    - Decreased limb function



- Adjuvant radiation
  - Benefit: local control, limb preservation
  - Detriment: toxicity



- Definitive radiation
  - Benefit: limb preservation
  - Detriment: toxicity, local control

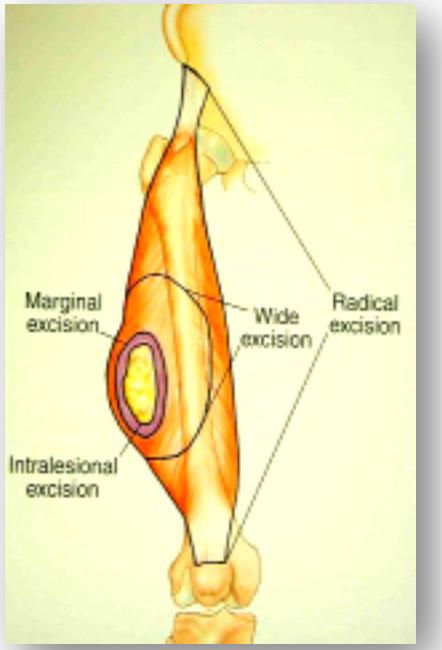
Low-Grade Sarcomas

Treatment

- Surgical resection only
- Consider adjuvant radiation
  - Large tumors (>10 cm)
  - Recurrence
  - Re-resection lead to loss of limb function
  - Positive margins

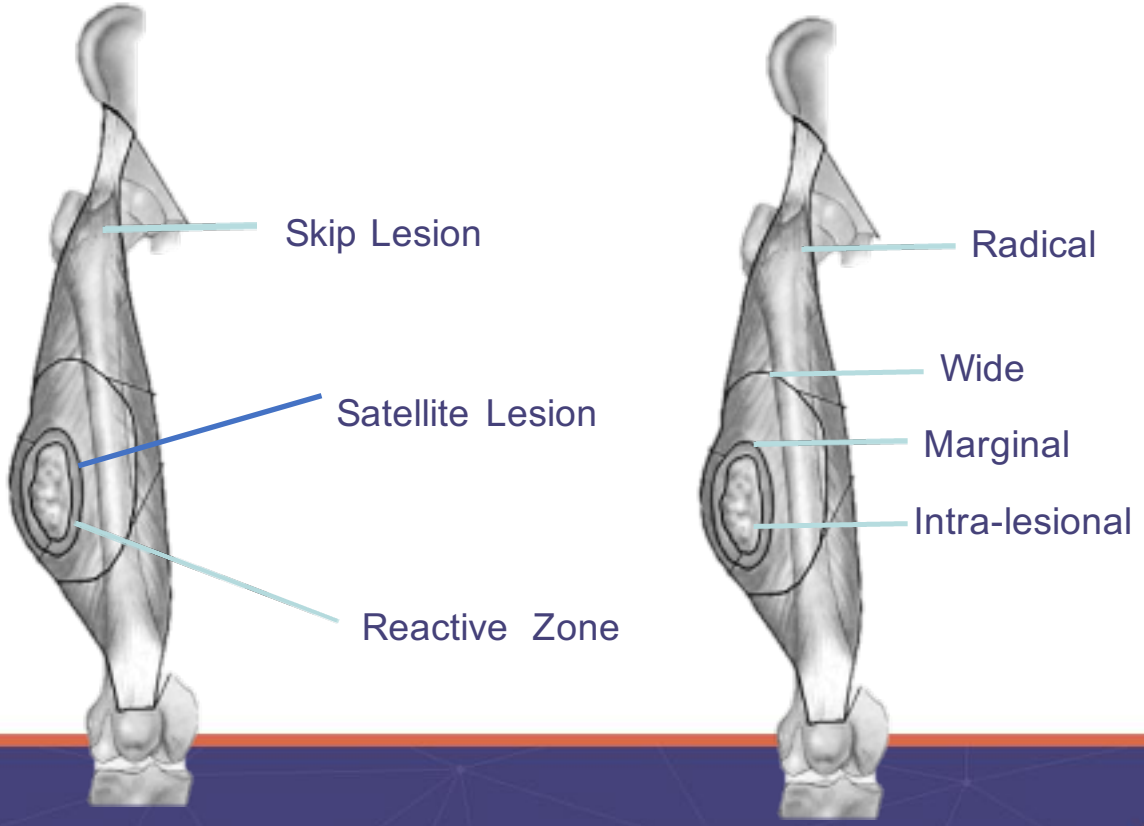
High-Grade STS

- Limb-sparing surgery
  - Resection + XRT no difference in overall survival compared to amputation (slight increase in LR)



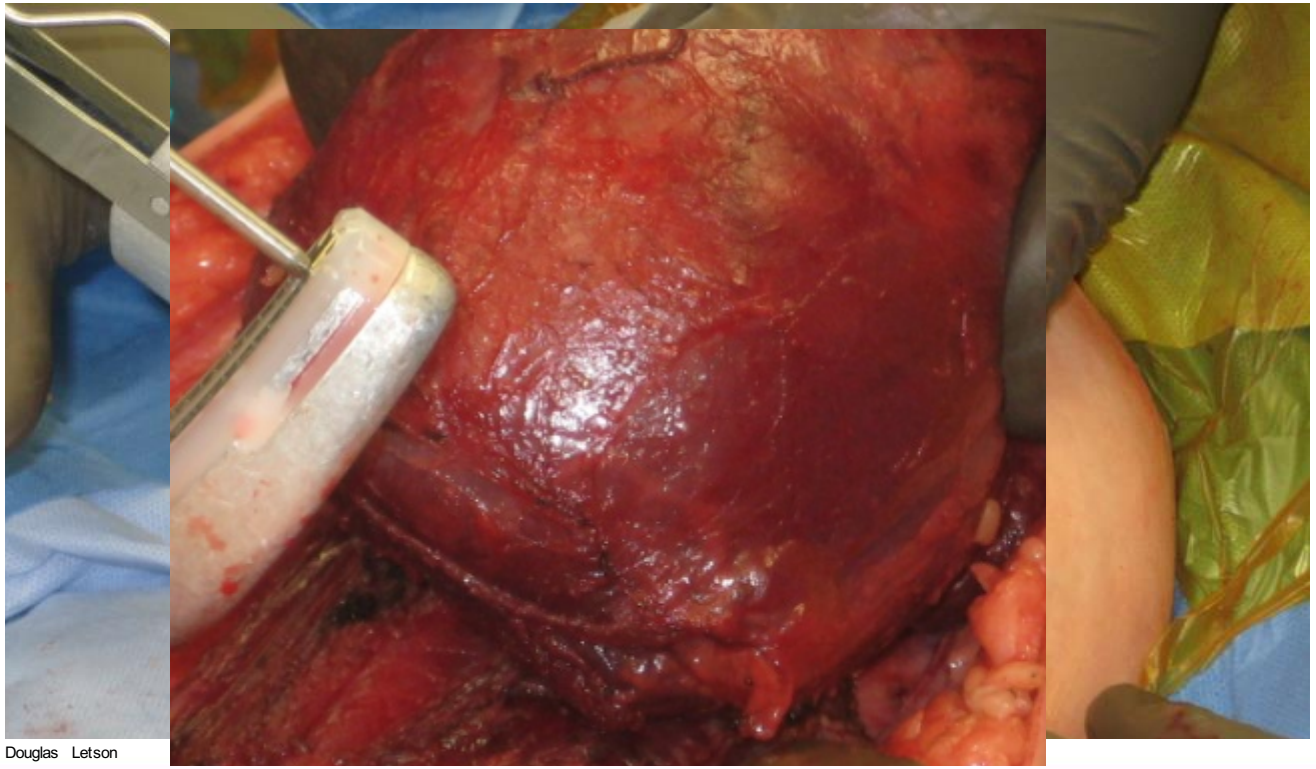
LR = local recurrence.

Surgical Margins



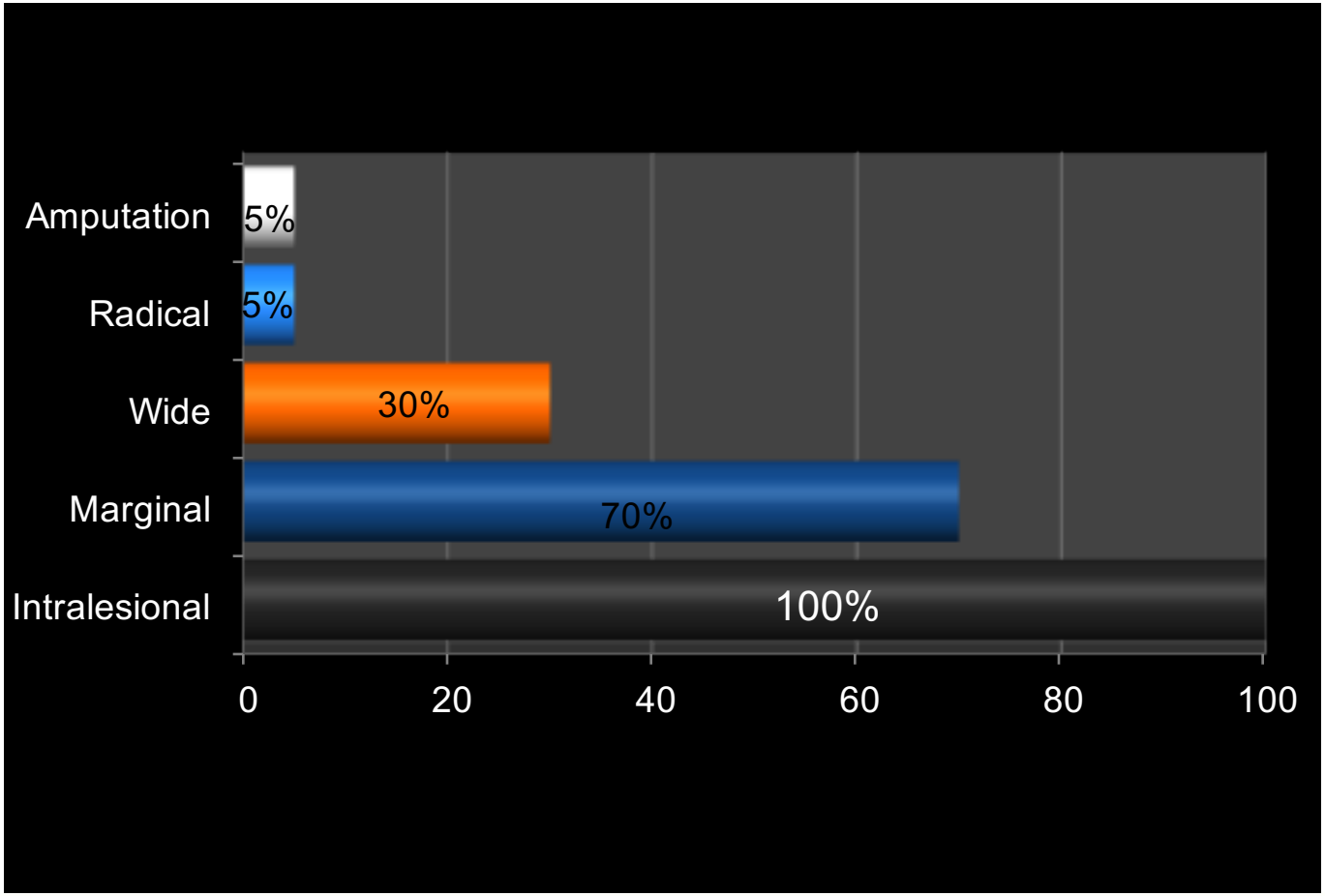
Animalcancersurgeon.com

High-Grade Undifferentiated Sarcoma



Images courtesy of Dr. G. Douglas Letson

Surgical Margins

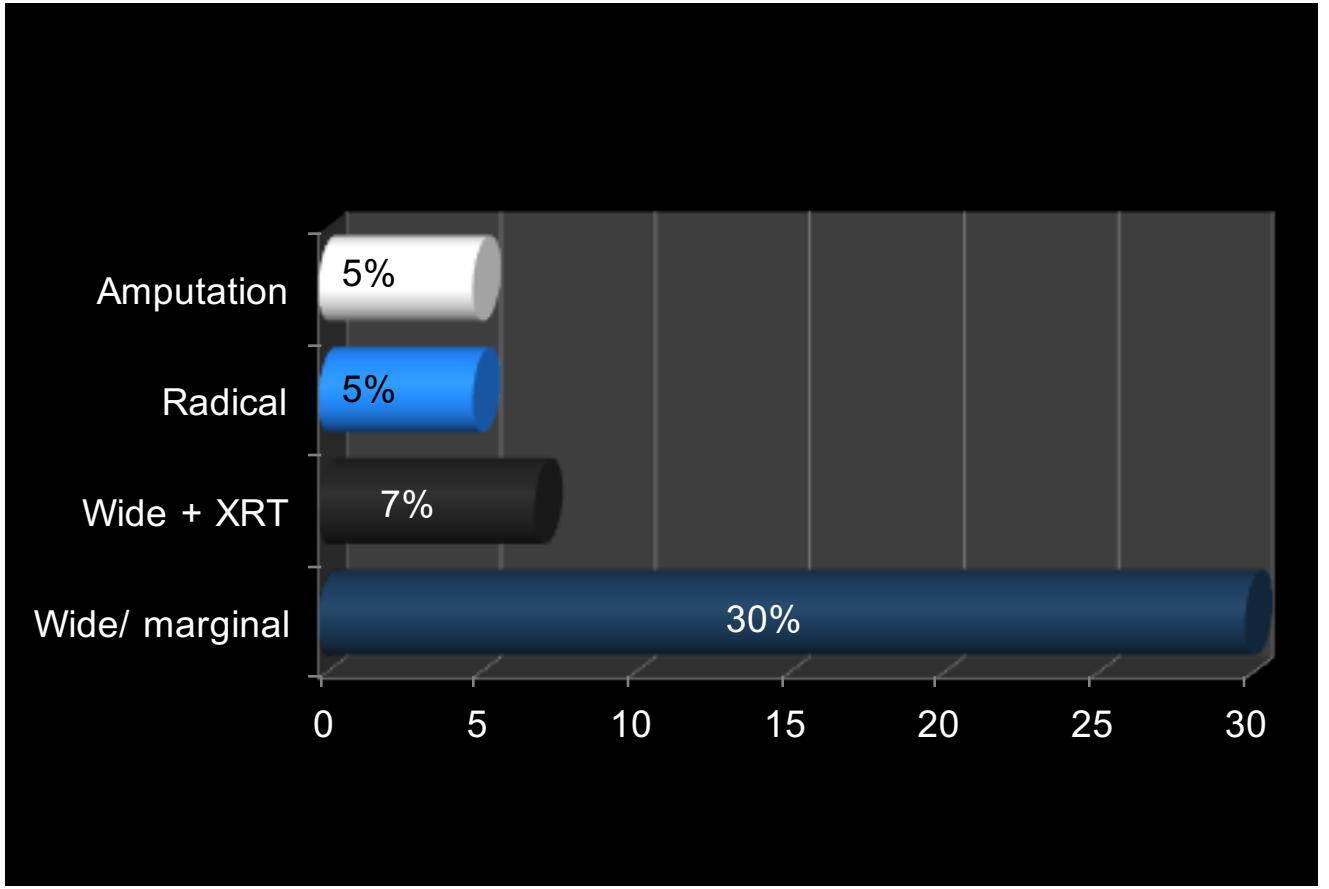


Local Therapy Options

Historical perspective of local recurrence with surgery alone

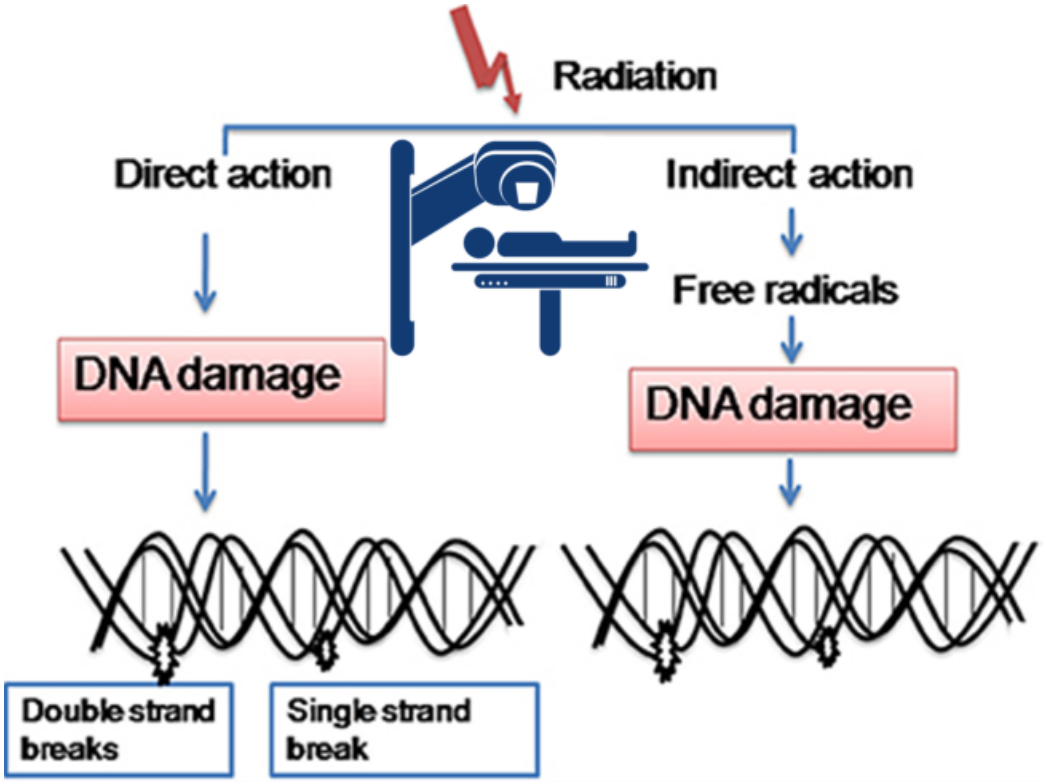
Report	Radical amputation or radical resection	Wide local excision	Marginal resection
Cantin, 1968	18%	30%	42%
Gerner, 1975	8%	60%	93%
Abbass, 1981	8%	36%	65%
Leibel, 1982	13%	28%	70%
Enneking, 1981	4%	25%	50%
Markhede, 1982	0%		76%
Rydholm, 1987		27%	
Shiu, 1975	18%		
Potter, 1986	0%		
Wiliard, 1992	6%		

Local Recurrence



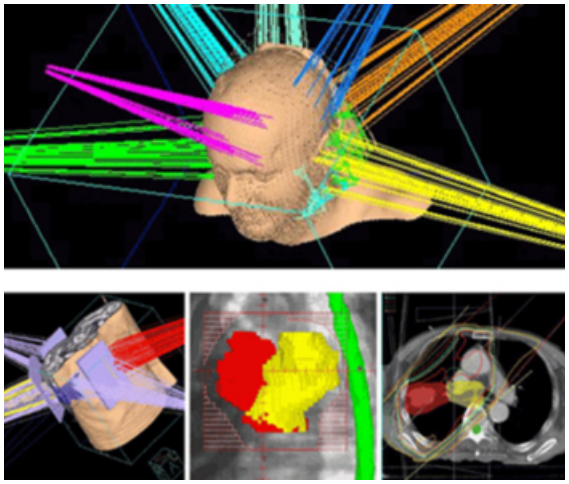
The Role of Radiation

How Does Radiation Work?

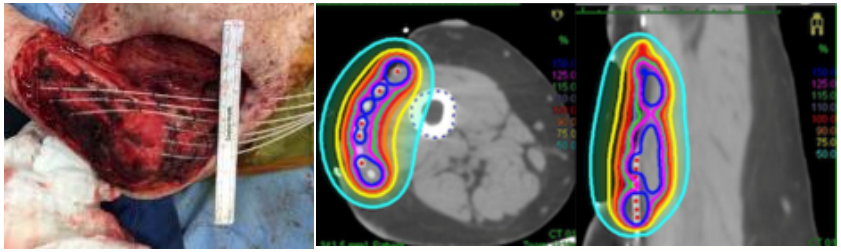


Adjuvant Radiation

I. External beam radiation
   I. Preoperative
   II. Postoperative



II. Brachytherapy
   I. Immediate reconstruction
   II. Staged reconstruction

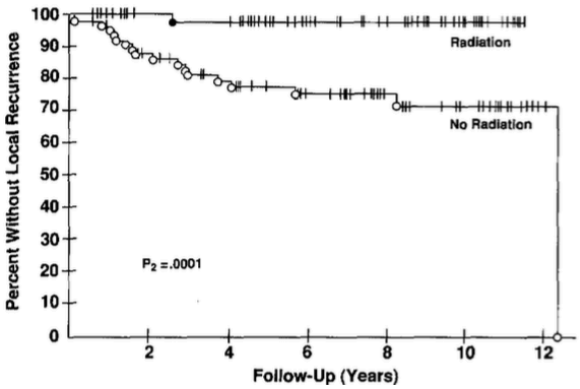


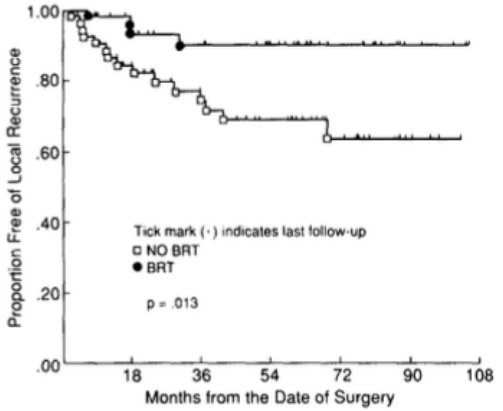
Adjuvant Radiation

LSS alone vs. LSS + adjuvant RT

- External beam radiation (EBRT)[1]
  - Improved local control
    - EBRT vs. no EBRT (98% vs. 72%, *p*=.001)

- Adjuvant brachytherapy (BRT)[2]
  - Improved 5-year LC (BRT vs. No BRT)
    - Overall (82% vs. 67%, p=.049)
    - High grade (90% vs. 65%, p=.013)
    - Low grade (NSS)





LC = local control.

1. Yang JC, et al. *J Clin Oncol.* 1998;16:197-203. 2. Harrison LB, et al. *Int J Radiat Oncol Biol Phys*. 1993;27:259-65.

Preop RT vs. Postop RT: Preop RT Benefit

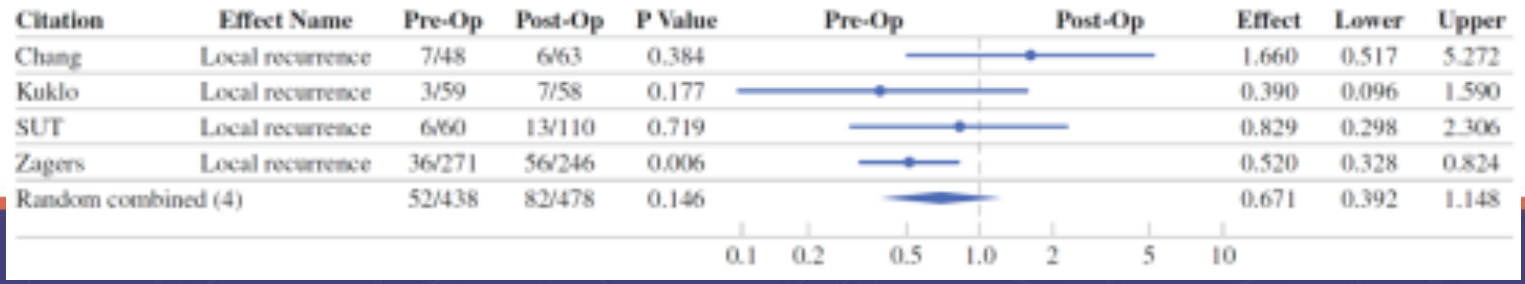
Preop RT benefits (vs. postop)

1. Require lower dose: 50Gy vs. 66Gy
   - Well oxygenated tumor = improved RT efficacy
   - Potential long-term toxicity benefit[1]
2. Fewer fractions
   - Decreased cost and improved patient convenience
3. Smaller RT volumes
   - Not include surgically manipulated tissues, drains, incision
   - Known long-term toxicity benefit
4. Tumor response/Shrink
   - Improve R0 resection[2]

5. Disease control benefit
   - LC benefit on meta-analysis[3]
   - LC, DM, OS[4]
   - OS benefit on trial[5]
   - Explanation:
     - Easier to define lesion
     - Prevent tumor seeding during surgery
     - Possible immuno-response
     - LC benefit→ decrease tumor seeding

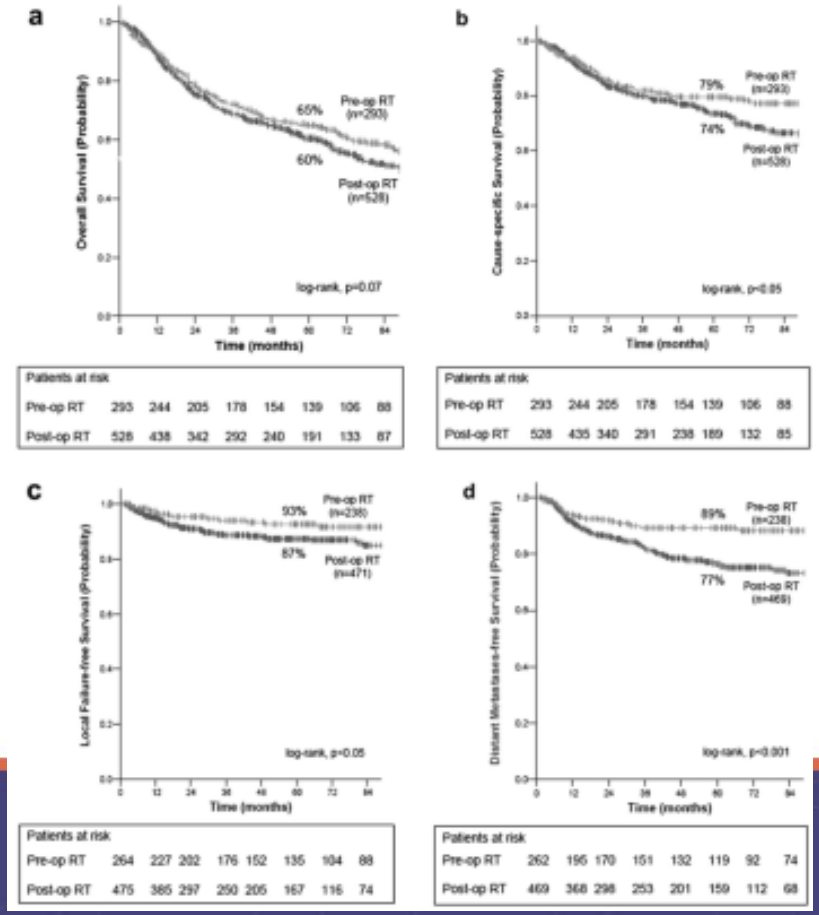
LC benefit (76 vs. 67%)[3]

DM = distant metastasis; OS = overall survival.



1. Zagars GK, et al. *Int J Radiat Oncol Biol Phys*. 2003;56:482-8. 2. Robinson MH, et al. *Clin Oncol (R Coll Radiol)*. 1992;4:36-43. 3. Al-Absi et al., *Ann Surg Oncol*. 2010;17:1367-74. 4. Sampath S, et al. *Int J Radiat Oncol Biol Phys*. 2011;81:498-505. 5. O'Sullivan B, et al. *Lancet*. 2002;359:2235-41.

Preop RT vs. Postop RT: Preop RT Detriment



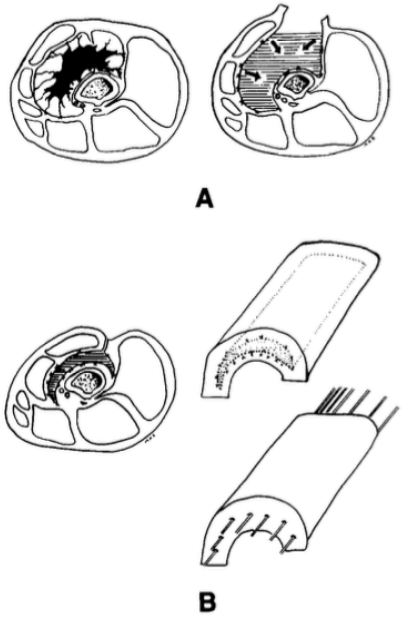
Preop RT detriment (vs. postop)

1. Doubles acute major wound complications (35% vs. 17%)
2. Possible tumor progression

Sampath S, et al. *Int J Radiat Oncol Biol Phys*. 2011;81:498-505.

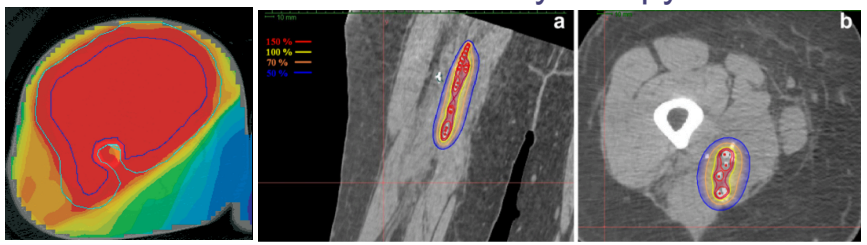
Brachytherapy

- en bloc WLE
- Single-plane of catheters
  - 1-cm intervals
  - parallel to the wound bed
  - LDR: 40–200 cGy/hr
  - HDR: >1200 cGy/hr
- Localized radiation dose
  - Decreased normal tissue re-irradiation



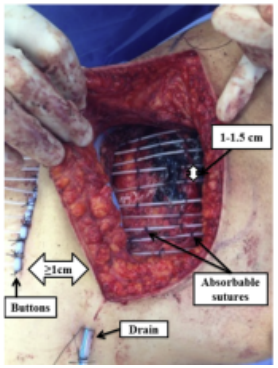
IMRT

Brachytherapy



HDR = high dose rate; LDR = low dose rate; WLE = wide local excision.

Shiu MH, et al. *Int J Radiat Oncol Biol Phys*. 1991;21:1485-92; Holloway CL, et al. *Brachytherapy*. 2013;12(3):179-90.

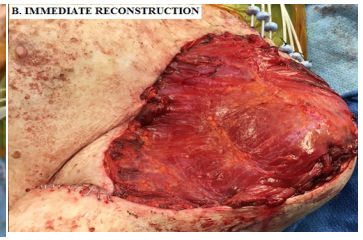


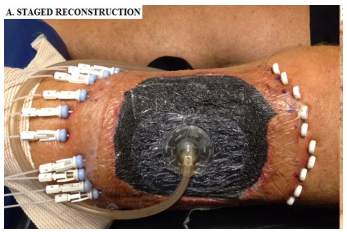
Catheter Placement

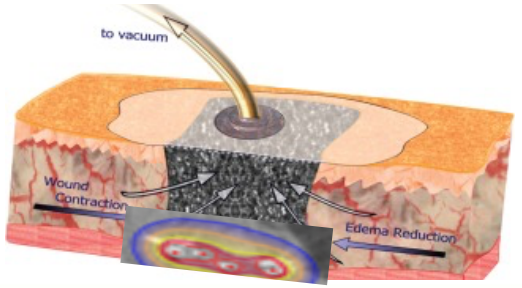
- Surgeon and radiation oncologist identify areas of highest risk of microscopic disease
- Direct visualization of treatment field with surgical clips aid in treatment planning
- Catheters positioned in tumor bed and sewn with absorbable sutures
- Buttons anchor catheters to skin surface

Closure

- **Immediate reconstruction (IR)**
  - "Traditional technique"
  - Immediate closure
  - Postoperative RT >5 days
- **Staged reconstruction (SR)**
  - Temporary closure
  - Wound VAC
  - RT day 1-4 postop
  - "Staged" closure

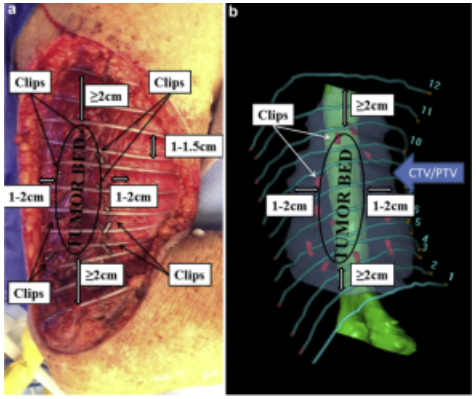






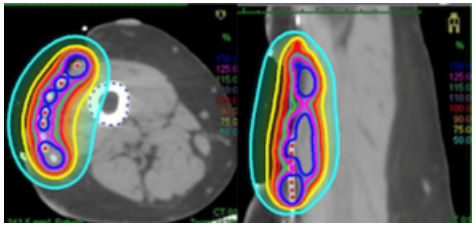
VAC = vacuum assisted closure.

Naghavi AO, et al. *Brachytherapy*. 2016;15:495-503; Heller L, et al. *Ann Plast Surg*. 2008;60:58-63.



Computed tomography (CT) simulation:

- CT scan used to digitize catheters
- Clips outline tumor bed and aids in planning



Radiation planning

- HDR brachytherapy: customizable radiation dose delivery
- High dose to area at risk
- Rapid drop off in dose to normal structures (e.g. bone, muscle, nerve, joints, etc.)

Treatment delivery (outpatient)

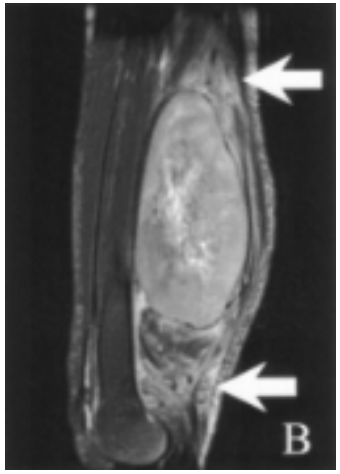
- Radioactive isotope in the afterloader (left)
- Wires feed isotope into each catheter
- Treatment delivered in <30 min, treated bid (>6 hours between treatments)
- After treatment completion catheters removed as outpatient

Naghavi AO, et al. *Brachytherapy*. 2017;16:466-89.

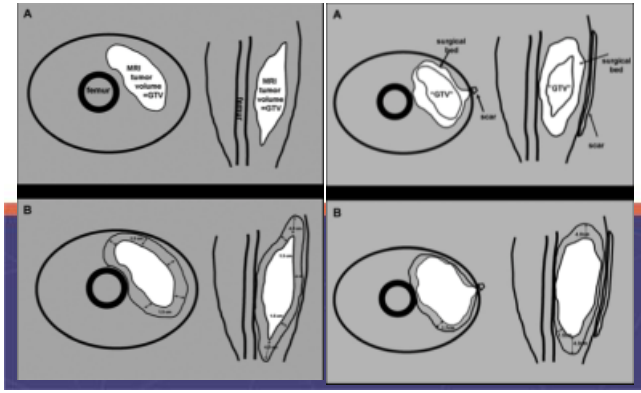
Toxicities

Background

- History of RT volumes used
- 1970s–1980s: 10-cm margins (5 cm for low grade)
- 1990s: NCIC study used 5 cm margins
  - Histologic data showed MRI signal 0-7.1 cm, mean 2.5
  - Tumor cells seen in 10/15 cases most within 1 cm but up to 4 cm from mass
    - Presence of tumor cells not correlate with edema/tumor size
    - 9/10 cases were within edema
- O'Sullivan phase II preop IG-IMRT 4 cm longitudinal



Preoperative vs. Postoperative



Tepper J, et al. *Int J Radiat Oncol Biol Phys.* 1982;8:263-73; White LM, et al . *Int J Radiat Oncol Biol Phys*. 2005;61:1439-45; O'Sullivan B, et al. *Cancer*. 2013;119:1878-84.

Radiation Sequelae

• Impaired wound healing	15–40%
• Edema	~20%
• Fibrosis, decreased ROM	~20%
• Bone fracture	2–10%
• Peripheral nerve injury	1–10%
• Secondary malignancy	<1%/year

ROM = range of motion.

Mitigating Toxicity

- Appropriate patient selection
  - e.g., wound complication risk (PVD, DM, etc.)
- Acute toxicity
  - Flap sparing[1]
  - RT to surgery ≤6 weeks[2]
  - Wound VAC
- Long-term sequelae
  - Larger field size correlates with:[3]
    - Fibrosis (p=.002)
    - Joint stiffness (p=.006)
    - Edema (p=.06)
  - Improve targeting
    - Image guidance (RTOG 0630)
    - Conformal treatment (IMRT)[4]
    - Concise treatment volumes (RTOG 0630)
  - Reduced dose
    - >63 Gy: pain, edema, decreased ROM[5]
    - >60 Gy: fracture[6]

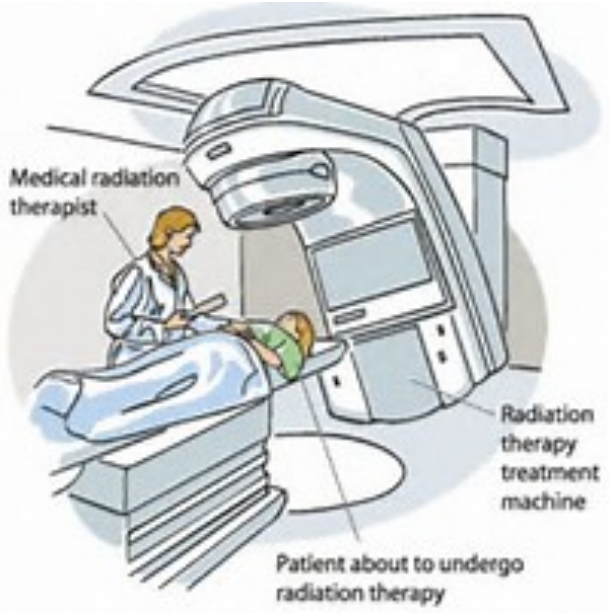
DM = diabetes mellitus; PVD = peripheral vascular disease.

1. O'Sullivan B, et al. *Cancer*. 2013;119:1878-84. 2. Griffin AM, et al. *Ann Surg Oncol*. 2015;22:2824-30. 3. Davis AM, et al. *Radiother Oncol*. 2005;75:48-53. 4. Folkert MR, et al. *Int J Radiat Oncol Biol Phys*. 2014;90:362-8. 5. Stinson SF, et al. *Int J Radiat Oncol Biol Phys*. 1991;21:1493-9. 6. Holt et al. 2005.

Systemic Therapy Options

Reynolds courtesy of Pinterest.com

Clipart-library.com

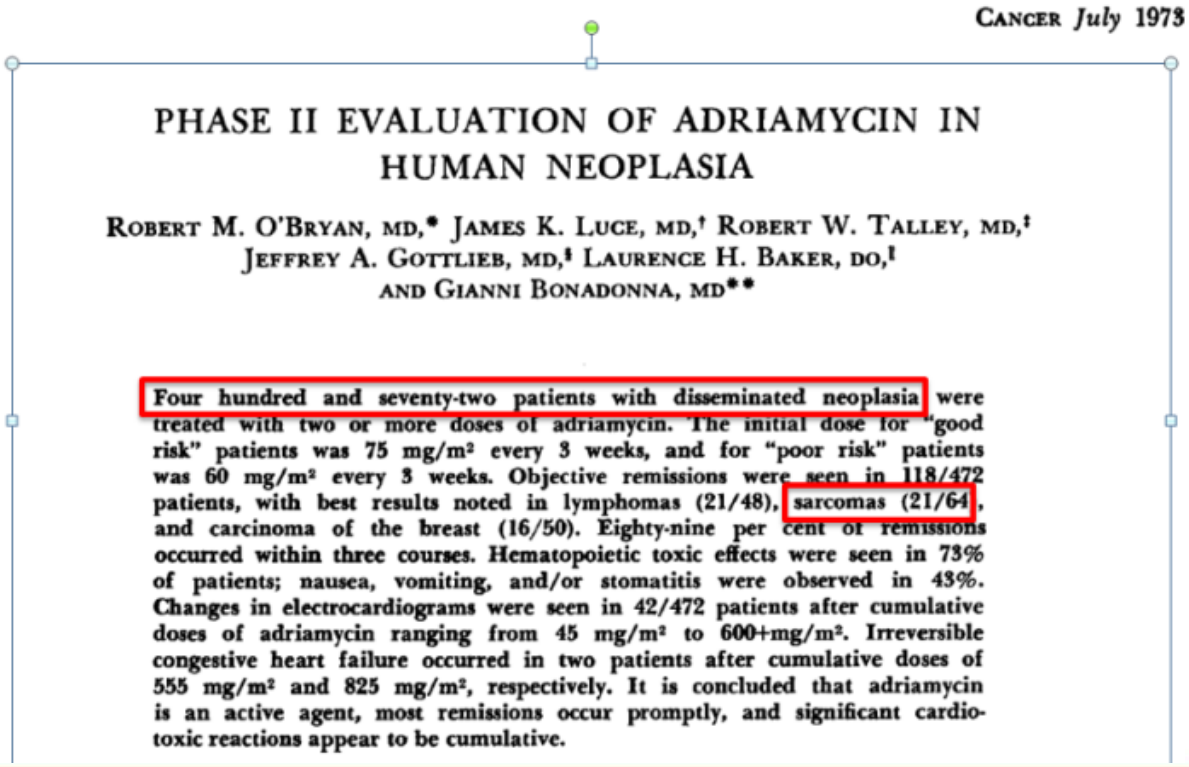


Weclipart.com

Systemic Therapy Options for Soft-Tissue Sarcoma

- Classic agents: Doxorubicin, ifosfamide
- Combos
  - Doxorubicin, olaratumab
  - Doxorubicin, ifosfamide
  - Doxorubicin, dacarbazine
  - Gemcitabine, docetaxel
- Additional agents: Liposomal doxorubicin, topotecan, irinotecan, etoposide, vinorelbine, temozolomide, epirubicin, trabectedin, eribulin, pazopanib

Doxorubicin Use in Sarcomas



CANCER *July* 1973

PHASE II EVALUATION OF ADRIAMYCIN IN HUMAN NEOPLASIA

ROBERT M. O'BRYAN, MD,* JAMES K. LUCE, MD,† ROBERT W. TALLEY, MD,‡
JEFFREY A. GOTTLIEB, MD,‡ LAURENCE H. BAKER, DO,‡
AND GIANNI BONADONNA, MD**

Four hundred and seventy-two patients with disseminated neoplasia were treated with two or more doses of adriamycin. The initial dose for "good risk" patients was 75 mg/m² every 3 weeks, and for "poor risk" patients was 60 mg/m² every 3 weeks. Objective remissions were seen in 118/472 patients, with best results noted in lymphomas (21/48), sarcomas (21/64), and carcinoma of the breast (16/50). Eighty-nine per cent of remissions occurred within three courses. Hematopoietic toxic effects were seen in 73% of patients; nausea, vomiting, and/or stomatitis were observed in 43%. Changes in electrocardiograms were seen in 42/472 patients after cumulative doses of adriamycin ranging from 45 mg/m² to 600+mg/m². Irreversible congestive heart failure occurred in two patients after cumulative doses of 555 mg/m² and 825 mg/m², respectively. It is concluded that adriamycin is an active agent, most remissions occur promptly, and significant cardiotoxic reactions appear to be cumulative.

O'Bryan RM, et al. *Cancer*. 1973;32(1):1-8.

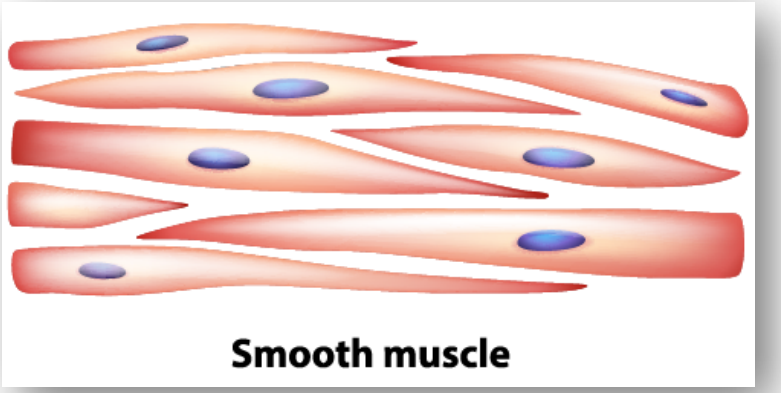
History of Drug Development for Treatment of STS

- 1970s: Doxorubicin – STS
- 1980s: Ifosfamide – STS

- 2002: Imatinib – GIST (Gastrointestinal Stromal Tumor)

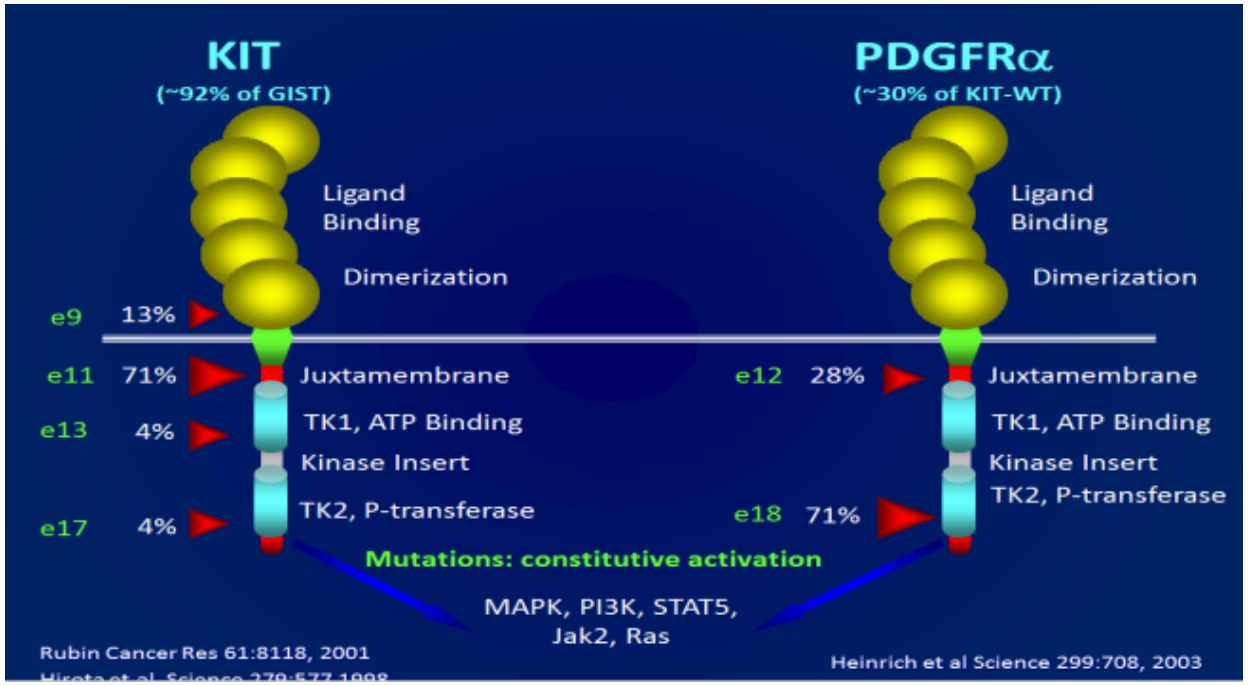
Gastrointestinal Stromal Tumors

- GISTs originally thought to derive from smooth muscle
- Some had ultrastructural evidence of autonomic neural differentiation (gastrointestinal autonomic nerve tumors [GANTs])



Gastrointestinal Stromal Tumors

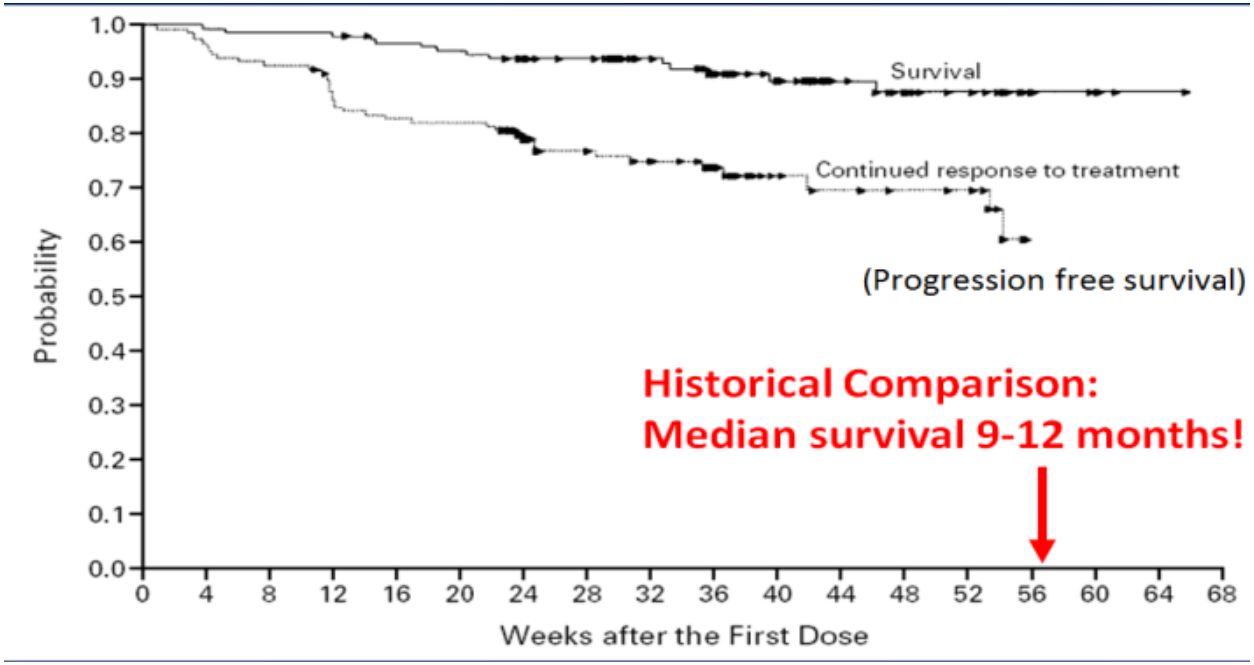
KIT tyrosine kinase is constitutively phosphorylated and mutated in GIST



Imatinib

- FDA approved for adjuvant therapy
- FDA approved for locally advanced, unresectable, and metastatic GIST

Efficacy and Safety of Imatinib Mesylate in Advanced GIST



Demetri GD, et al. *N Engl J Med*. 2002;347:472-80.

Imatinib: Toxicities

- Edema 11–86%
  - Peripheral edema 41%
  - Facial edema 17%
- Skin rash 9–50%
- Gastrointestinal
  - Nausea 41–73%
  - Diarrhea 25–59%
  - Vomiting 11–58%
  - Anorexia 36%
- Ophthalmic
  - Periorbital edema 15–74%
- Hepatic
  - Increased AST/ALT 34–38%
  - Increased bili 13%
- Renal
  - Increased serum creatinine 44%

ALT = alanine transaminase; AST = aspartate transaminase.

History of Drug Development for Treatment of STS

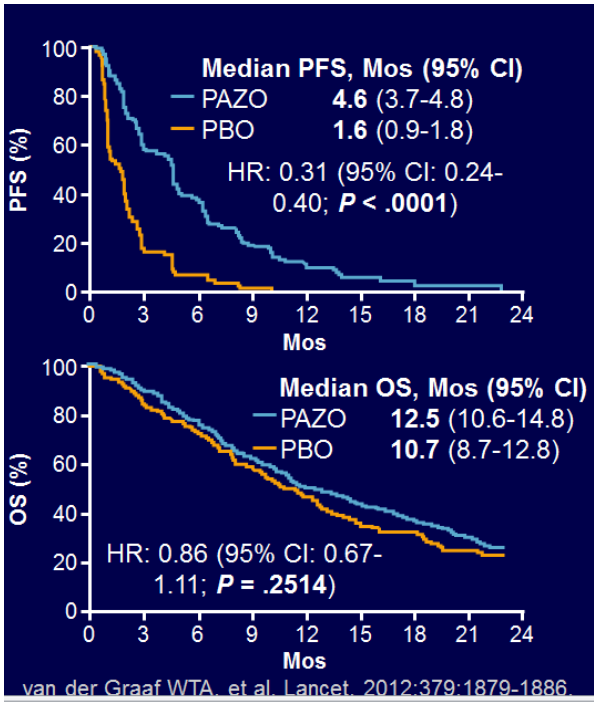
- Novel therapeutics
  - Pazopanib (PALETTE): 2012
    - STS (except LPS)
  - Trabectedin: 2015
  - Eribulin: 2016
  - Olaratumab (+ doxorubicin): 2016

LPS = liposarcoma.

Novel Therapy: Pazopanib

- Multi–tyrosine kinase inhibitor with antiangiogenic properties
  - Targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα, PDGFRβ, FGFR-1, FGFR-3, Kit, Itk, Lck, c-Fms
- FDA indications
  - Patients with advanced STS having previously received chemotherapy
    - Efficacy for adipocytic STS/GIST has not been demonstrated
  - Patients with advanced renal cell carcinoma

PALETTE: Efficacy



Toxicity	Pazopanib (n = 239)	Placebo (n = 123)
Any-grade AE,* %		
Fatigue	65	49
Diarrhea	58	16
Nausea	54	28
Weight loss	48	20
Hypertension	41	7
Anorexia	40	20
Hair hypopig	38	2
Vomiting	33	11
Increased liver enzymes, %		
ALT	10	3
AST	8	2
Total bilirubin	2	2

*Incidence > 30% in any group.

Van der Graaf WTA, et al. *Lancet*. 2012;379:1879-86.

Pazopanib: Toxicities

- Cardiovascular
  - HTN 40–42%
  - Cardiac Insufficiency 11–13%
- Endocrine
  - Weight loss 48%
  - hypothyroidism
- Gastrointestinal
  - Diarrhea 59%
  - Nausea 56%
  - Anorexia 22%
- Dermatologic
  - Hair discoloration 39%
  - Hand-foot syndrome 11%
- Hematologic
  - Leukopenia 44%
  - Thrombocytopenia 36%
- Hepatic
  - Increased AST/ALT 53%
  - Increased bili 36%

HTN = hypertension.

Information from Lexicomp.com

Novel Therapy: Trabectedin

- Alkylating agent that bends the DNA helix via minor groove guanine binding; affects DNA-binding proteins, perturbs cell cycle, induces cell death

- FDA Indications: Unresectable/mets liposarcoma or leiomyosarcoma, previously treated with anthracycline-containing regimen

Anticancer Drugs. 2002;13(supp 1):3-6.

Trabectedin vs Dacarbazine: Efficacy

Endpoint	Trabectedin (n = 345)	Dacarbazine (n = 173)	HR (95% CI)	*P* Value
Median OS, mos*	12.4	12.9	0.87	.37
Median PFS, mos	**4.2**	**1.5**	**0.55 (0.44-0.70)**	**< .001**
TTP, mos	4.2	1.5	0.52 (0.41-0.66)	< .001
ORR, n (%)	34 (10)	12 (7)	1.47 (0.72-3.2)	.33
DoR, mos	6.5	4.2	0.47 (0.17-1.32)	.14

*Interim analysis, 64% censored.

Demetri GD, et al. *J Clin Oncol*. 2016;34:786-93.

Trabectedin: Toxicities

- Cardiovascular
  - Peripheral edema 28%
  - Cardiomyopathy 6%
- Gastrointestinal
  - Nausea 75%
  - Vomiting 46%
  - Constipation 37%
  - Diarrhea 35%
- Neuromuscular
  - Increased CK 33%
  - Arthralgia/Myalgia 15/12%
- Hematologic
  - Anemia 96%
  - Neutropenia 66% with 43% grade 3 or 4
  - Thrombocytopenia 59%, 21% gr 3 or 4
- Hepatic
  - Increased ALT/AST 90%
  - Increased bili 13%
- Renal
  - Increased creatinine 46%

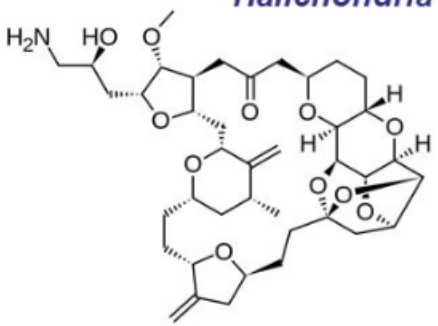
CK = creatine kinase.

Information from Lexicomp.com

Novel Therapy: Eribulin

- Synthetic analogue of halichondrin B; natural product from marine sponge *Halichondria okadai*

Halichondria okadai



Microtubule dynamics inhibitor that sequesters tubulin, disrupts mitotic spindles, and leads to apoptosis

FDA indication:
Unresectable or **metastatic liposarcoma previously treated with anthracycline-based regimen;** metastatic breast cancer previously treated with ≥ 2 chemotherapy regimens

Jordan MA, et al. *Mol Cancer Ther*. 2005;4:1086-95.

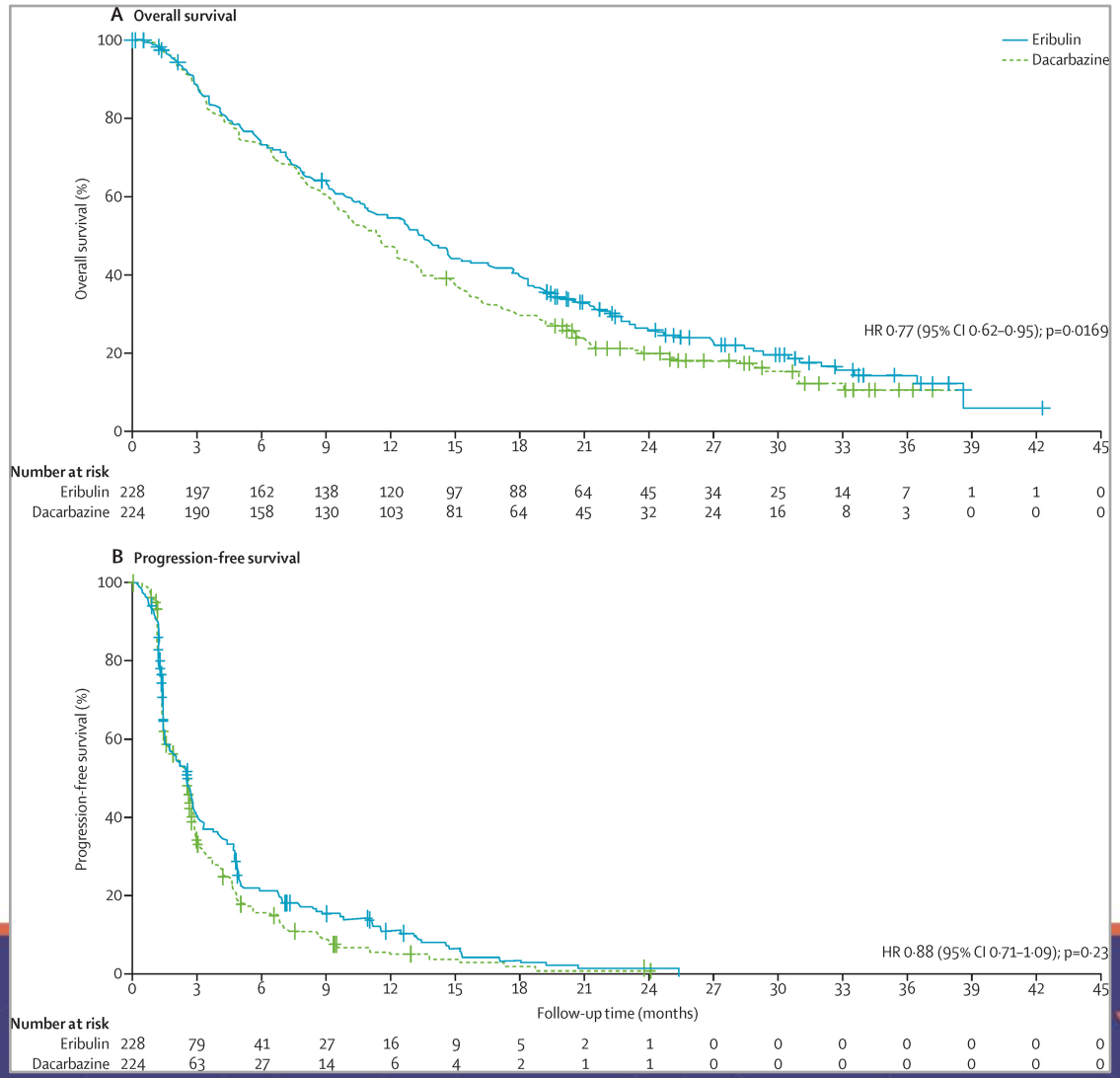
Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: A randomised, open-label, multicentre, phase 3 trial

Prof Patrick Schöffski, MD, Sant Chawla, MD, Prof Robert G Maki, MD, Antoine Italiano, MD, Prof Hans Gelderblom, MD, Edwin Choy, MD, Giovanni Grignani, MD, Veridiana Camargo, MD, Sebastian Bauer, MD, Sun Young Rha, MD, Prof Jean-Yves Blay, MD, Peter Hohenberger, MD, David D'Adamo, MD, Matthew Guo, PhD, Bartosz Chmielowski, MD, Axel Le Cesne, MD, Prof George D Demetri, MD, Prof Shreyaskumar R Patel, MD

The Lancet
Volume 387, Issue 10028, Pages 1629-1637 (April 2016)
DOI: 10.1016/S0140-6736(15)01283-0

The first randomized, phase 3 trial of a single-agent systemic therapy with an active control to show a significant improvement in overall survival as the primary endpoint in patients with previously treated advanced leiomyosarcoma and liposarcoma.

OS and PFS



Schoffski P, et al. *Lancet*. 2016;387:1629-37.

Eribulin vs Dacarbazine

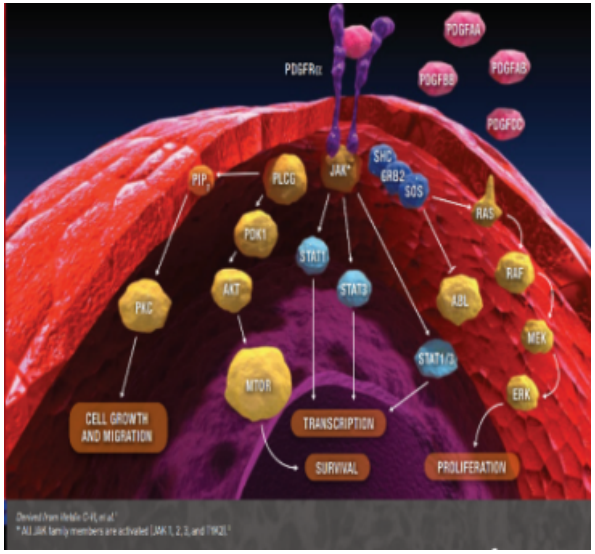
- Liposarcoma
  - Median OS in the eribulin group was 15.6 months vs 8.4 months in the dacarbazine group
- Leiomyosarcoma
  - Median overall survivial was 12.7 months eribulin group vs 13 months in the dacarbazine group

Schoffski P, et al. *Lancet.* 2016;387:1629-37.

Eribulin: Toxicities

- Cardiovascular
  - Peripheral edema 12%
- Gastrointestinal
  - Nausea 35–41%
  - Constipation 32%
  - Anorexia 20%
- Endocrine
  - Weight loss 21%
- Hematologic
  - Neutropenia 63–82%
  - Anemia 58–70%
- Miscellaneous
  - Fever 21–28%

Novel Therapy: Olaratumab

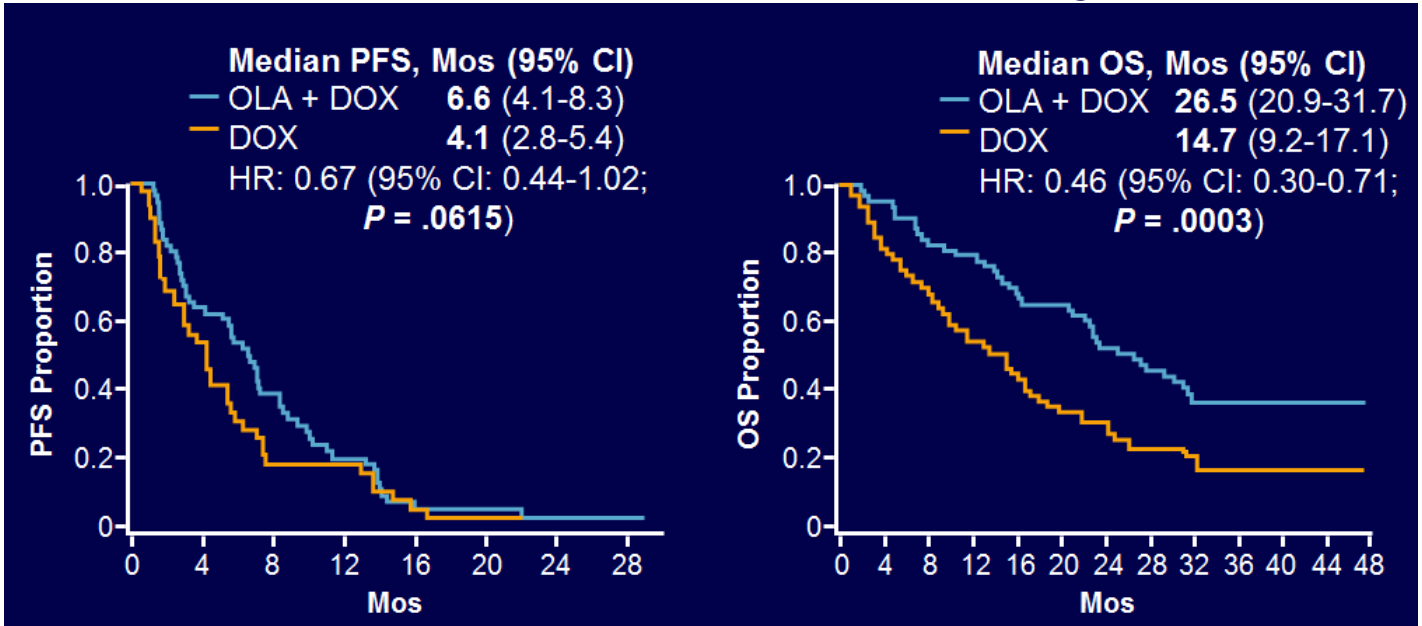


PDGFRα Antibody
Olaratumab, LY3012207, IMC-3G3

Monoclonal antibody that binds to PDGFRα
Inhibits PDGF ligand binding and cellular signaling that may lead to cell proliferation, angiogenesis, and recruitment of stromal-derived fibroblasts

FDA breakthrough therapy designation for soft-tissue sarcoma

Doxorubicin ± Olaratumab: Efficacy



- No statistical difference in ORR between groups
  - OLA + DOX: 18.2% (95% CI: 9.8% to 29.6%); DOX: 11.9% (95% CI: 5.3% to 22.2%)

Tap WD, et al. ASCO 2015, Abstract 10501.

Toxicities: Olaratumab

- Central nervous system
  - Fatigue 69%
  - Headache 20%
- Dermatologic
  - Alopecia 52%
- Endocrine
  - Hyperglycemia 52%
- Hematologic
  - Neutropenia 65%
  - Thrombocytoepnia 63%
- Neuromuscular
  - Musculoskeletal pain 64%

Information from Lexicomp.com

Linkedin.com

Surveillance: NCCN

- Low-grade tumors
  - Local imaging 3–6 mo for 2–3 yr, then annually
    - Consider postop baseline and periodic imaging of the primary site based on estimated risk of LR
  - Consider chest imaging every 6–12 mo
- High-grade tumors
  - Local imaging 3–4 mo for 2 years, 6 mo for 2 yr, then annually
    - Consider postop baseline and periodic imaging of the primary site based on estimated risk of LR
  - Chest imaging 3–6 mo for 2–3 yr, then 6 mo for 2 yr, then annually.

Multidisciplinary Care

Working With Surgery

- Toxicity/QOL
  - Concise treatment volumes
    - Tumor localization (e.g. discussion, surgical clips)
  - Closure
    - Flap, wound VAC
    - Determine proper wound healing before starting adjuvant treatment
  - Timing
    - Coordinate to ensure <6-8 weeks between preop-RT and surgery
- Improving disease control
  - Concise treatment volumes
    - Areas concerning for close/positive margins
    - Areas difficult to obtain R0 (retroperitoneal, abutting NVB)
    - Brachytherapy: direct interaction and visualized field

NVB = neurovascular bundle.

Multidisciplinary Care (cont.)

Working With Medical Oncology

- Toxicity/quality of life
  - Evaluating appropriate overlap in care
  - Managing hematologic issues

Multidisciplinary Care (cont.)

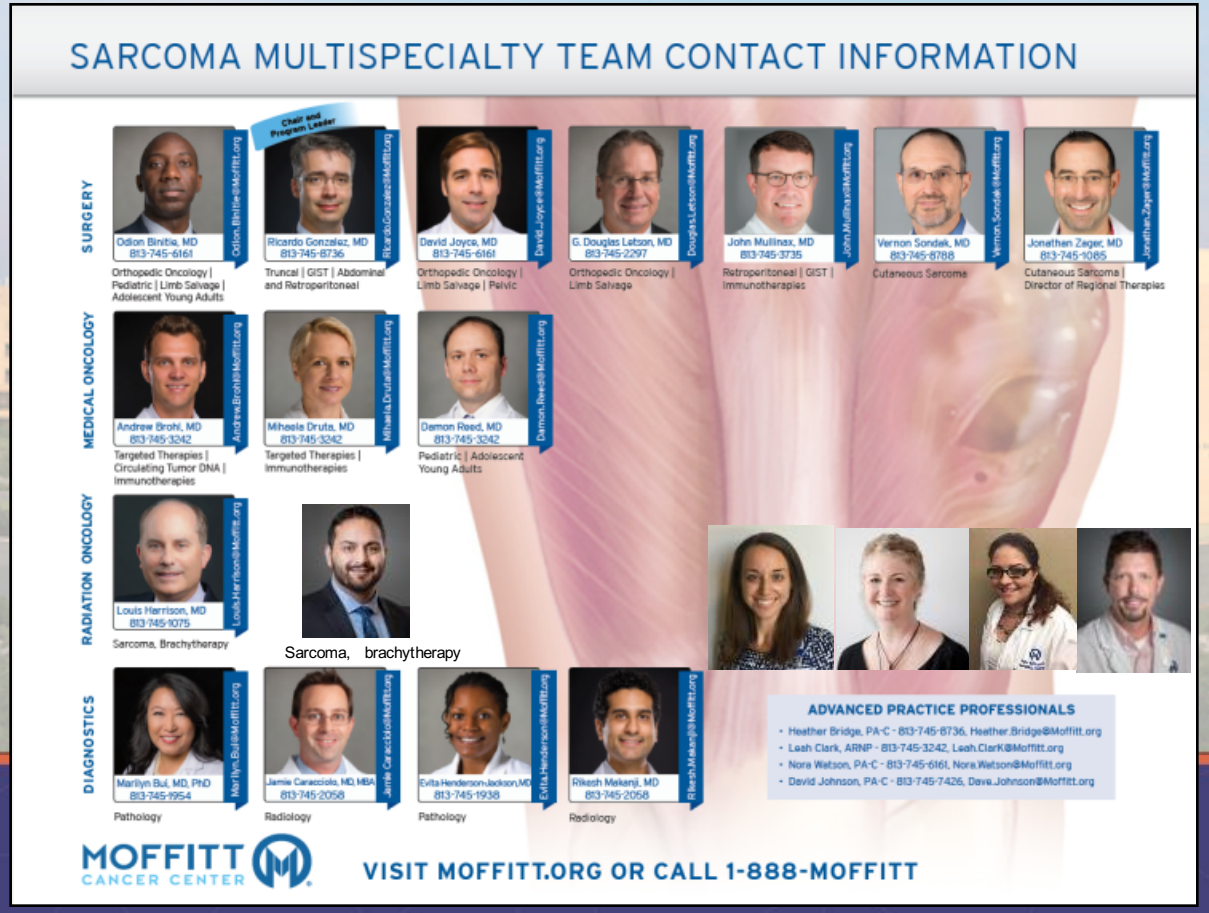
Patient-Centric Care

- Multidisciplinary tumor board
- Evaluate patient's personal goals
- Coordinate toxicity care and follow-up between specialties

Summary

- Varied group of tumors
- Large, deep, fixed, heterogenous with necrosis on MRI = high grade
- Treatment: Resection/chemotherapy/XRT for high grade sarcomas (multimodule approach)
- Surveillance

Sarcoma Team at Moffitt Cancer Center



2017 JADPRO Live in APSHO


SMARTIE
This has been a SMARTIE presentation.
SMARTIE participants, you can now go to smartie2017.com
or visit the SMARTIE booth to answer the post-session
questions for this presentation.
If you would like more information about this program, please ask
a conference staff member or visit the SMARTIE booth.