CRP Breakout: Sarcoma

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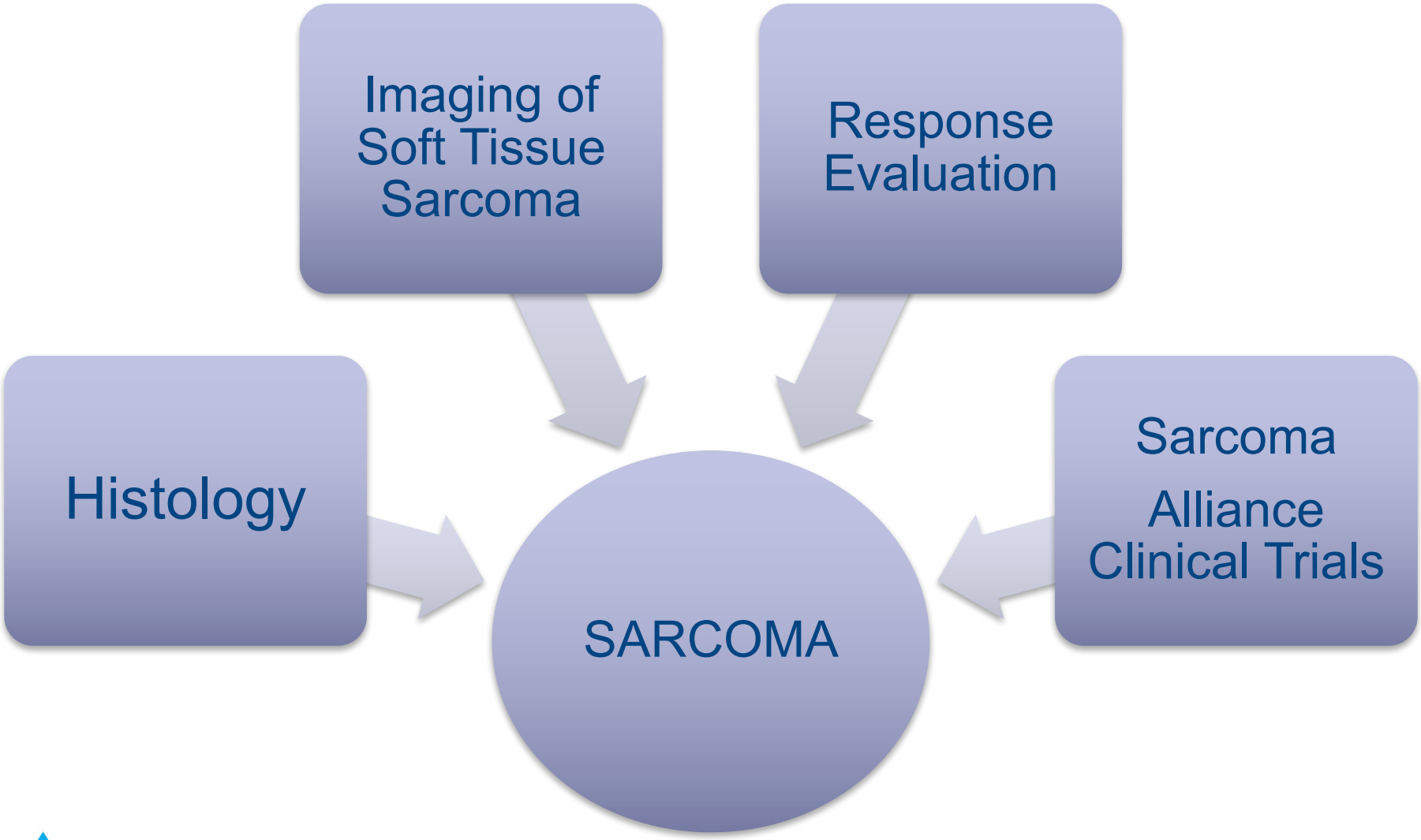
Mayo Clinic

May 11, 2017 Alliance Group Meeting



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Sarcomas: Not Just One

RMS
MFH
Desmoid
Myxoid Round Cell Liposarcoma
Chondroblastic OGS
Hemangioendothelioma
Undifferentiated Sarcoma
Liposarcoma
LMS
Epithelial Sarcoma
GCT
Osteoblastic OGS
OGS
Pleomorphic Sarcoma
GIST
Wild Type GIST
Fibroblastic OGS
Chondrosarcoma
Angiosarcoma
Leiomyosarcoma
ERMS
RAAS
Angiomatoid MFH
MPNST
ASPS
Clear Cell Sarcoma of Soft Parts
Extraskeletal OGS
ARMS
Malignant Solitary Fibrous Tumor
Ewings
Myofibroblastic Tumors
Hemangiopericytoma
Parosteal OGS
SFT
MFH Bone
Uterine LMS
Myxofibrosarcoma
Endometrial Stromal Sarcoma
Fibrosarcoma
Dedifferentiated
Synovial Sarcoma
Myxoid Liposarcoma
Liposarcoma
Chordoma
Dedifferentiated Chondrosarcoma
Mesenchymal Chondroarcoma
Kaposi

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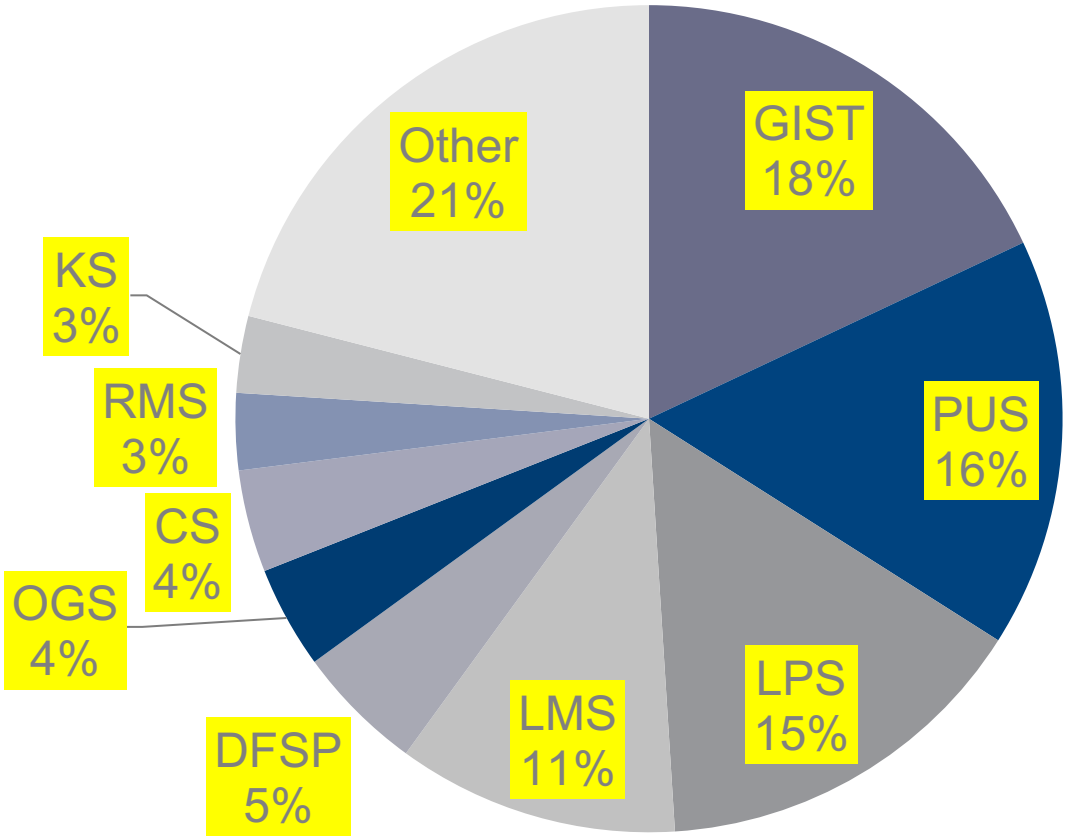
Histological types and subtypes	Number				Sex ratio	Age		CIR[1]
	Total	%	2005	2006	(M/F)	Median	Range	
GIST	135	(18)	70	65	0.8	65	(34–91)	1.12
Unclassified sarcoma[2]	117	(16)	57	60	1.4	66	(3–92)	0.97
Pleomorphic cell sarcoma	55	(7)	27	28	1.4	67	(18–91)	0.46
Spindle cell sarcoma	41	(5)	15	26	1.6	67	(27–92)	0.34
Round cell sarcoma	11	(1)	7	4	0.4	25	(3–83)	0.09
Sarcoma not otherwise specified	10	(1)	8	2	4.0	68	(49–84)	0.08
Liposarcoma	112	(15)	56	56	1.7	61	(26–88)	0.93
Well differentiated liposarcoma	71	(9)	36	35	1.8	60	(32–88)	0.59
Dedifferentiated liposarcoma	27	(4)	14	13	1.2	72	(47–84)	0.22
Myxoid-round cell liposarcoma	12	(2)	5	7	2.0	47	(26–81)	0.10
Pleomorphic liposarcoma	2	(<1)	1	1	1.0	78	(72–85)	0.02
Leiomyosarcoma	85	(11)	40	45	0.5	62	(28–87)	0.71
Non uterine leiomyosarcoma	62	(8)	28	34	0.9	62	(28–87)	0.51
Uterine leiomyosarcoma	23	(3)	12	11	-	53	(40–84)	0.20
Dermatofibrosarcoma protuberans	38	(5)	22	16	1.2	37	(8–91)	0.32
Osteosarcoma	31	(4)	19	12	2.1	36	(6–80)	0.26
Conventional osteosarcoma	26	(4)	17	9	3.3	32	(6–80)	0.22
Soft tissue osteosarcoma	4	(1)	1	3	0.5	60	(30–67)	0.02
Parosteal osteosarcoma	1	(<1)	1	0	-	25	(25)	0.01
Osteosarcoma grade 2	1	(<1)	0	1	-	49	(49)	0.01
Chondrosarcoma	29	(4)	11	18	1.2	59	(20–83)	0.24
Ewing sarcoma/PNET	27	(4)	13	14	0.9	23	(1–83)	0.22
Rhabdomyosarcoma	26	(3)	13	13	3.3	12	(1–83)	0.22
Embryonal rhabdomyosarcoma	12	(2)	5	7	3.0	11	(2–25)	0.10
Alveolar rhabdomyosarcoma	8	(1)	4	4	3.0	7	(1–34)	0.07
Pleomorphic rhabdomyosarcoma	4	(<1)	2	2	3.0	64	(38–82)	0.03
Spindle cell rhabdomyosarcoma	2	(<1)	2	0	-	76	(70–83)	0.02
Kaposi sarcoma	25	(3)	14	11	5.3	59	(30–90)	0.21
Angiosarcoma	25	(3)	13	12	0.5	75	(39–84)	0.21
Myxofibrosarcoma	17	(2)	9	8	0.9	63	(37–84)	0.14
Synovial sarcoma	16	(2)	8	8	0.6	35	(13–87)	0.13
Monophasic synovial sarcoma	13	(2)	7	6	0.4	32	(13–87)	0.11
Biphasic synovial sarcoma	3	(<1)	1	2	2.0	41	(26–43)	0.02
Endometrial stromal sarcoma	14	(2)	6	8	-	49	(23–71)	0.12
Malignant solitary fibrous tumor	8	(1)	3	5	1.7	71	(61–77)	0.07
Other	43	(6)	24	19	1.1	-	-	0.36
TOTAL	**748**	**(100)**	**378**	**370**	**1.1**	**60**	**(1–92)**	**6.21**

35 Listed histologies
43 Other histologies that make up 6%

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0020294

Histology



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http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0020294

Table 8. Sarcoma types by percentage of cases for age groups.

Age 0–14 Children (n = 44 ; 6%)		Age 15–29 Adolescents and young adults (n = 55 ; 7%)		Age 30–49 Adults (n = 133 ; 18%)		Age 50–69 Adults Middle-aged (n = 294 ; 39%)		Age 70+ Elderly (n = 222 ; 30%)	
Rhabdomyosarcoma	36	Osteosarcoma	20	DFSP	14	GIST	22	GIST	24
PNET/Ewing	20	PNET/Ewing	18	Liposarcoma	14	Liposarcoma	19	Unclass. sarcoma	21
Unclass. sarcoma	9	DFSP	11	GIST	13	Unclass. sarcoma	17	Liposarcoma	15
Osteosarcoma	7	Unclass. sarcoma	11	Unclass. sarcoma	8	Leiomyosarcoma	11	Leiomyosarcoma	10
Rhabdoid tumor	7	Synovial sarcoma	9	Kaposi sarcoma	7	Chondrosarcoma	4	Angiosarcoma	7
DFSP	5	Chondrosarcoma	5	Uterine LMS	6	DFSP	3	Chondrosarcoma	3
Synovial sarcoma	5	Rhabdomyosarcoma	5	Chondrosarcoma	5	Uterine LMS	3	Kaposi sarcoma	3
DSRCT	5	Leiomyosarcoma	4	Leiomyosarcoma	5	Osteosarcoma	3	Myxofibrosarcoma	3
Other	6	Liposarcoma	4	ES sarcoma	5	Kaposi sarcoma	3	Uterine LMS	3
		Epithelioid sarcoma	4	Myxofibrosarcoma	5	ES sarcoma	2	Mal. solit. fibr. tumor	2
		DSRCT	4	Angiosarcoma	3	Angiosarcoma	2	Osteosarcoma	2
		MIM Tumor	4	Osteosarcoma	3	PNET/Ewing	2	Rhabdomyosarcoma	2
		ES sarcoma	2	Synovial sarcoma	3	Synovial sarcoma	1	Other	5
				Other	9	Myxofibrosarcoma	1		
						Other	7		

PNET, primitive neuroectodermal tumor; Unclass. sarcoma, unclassified sarcoma; DFSP, dermatofibrosarcoma protuberans; DSRCT, desmoplastic small round cell tumor; Other, other sarcoma; MIM tumor, malignant inflammatory myofibroblastic tumor; ES sarcoma, endometrial stromal sarcoma; GIST, gastrointestinal stromal tumor; Uterine LMS, uterine leiomyosarcoma; Mal. solit. Fibr. tumor, malignant solitary fibrous tumor.

doi:10.1371/journal.pone.0020294.t008

Ducimetière F, Lurkin A, Ranchère-Vince D, Decouvelaere AV, Péoc'h M, et al. (2011) Incidence of Sarcoma Histotypes and Molecular Subtypes in a Prospective Epidemiological Study with Central Pathology Review and Molecular Testing. PLOS ONE 6(8): e20294. doi:10.1371/journal.pone.0020294
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0020294

Sarcoma Facts

- Rare
- Around 15,000 - 16,000 cases diagnosed per year
- Adults
  - 70% soft tissue
  - 30% bone
- 50% survival

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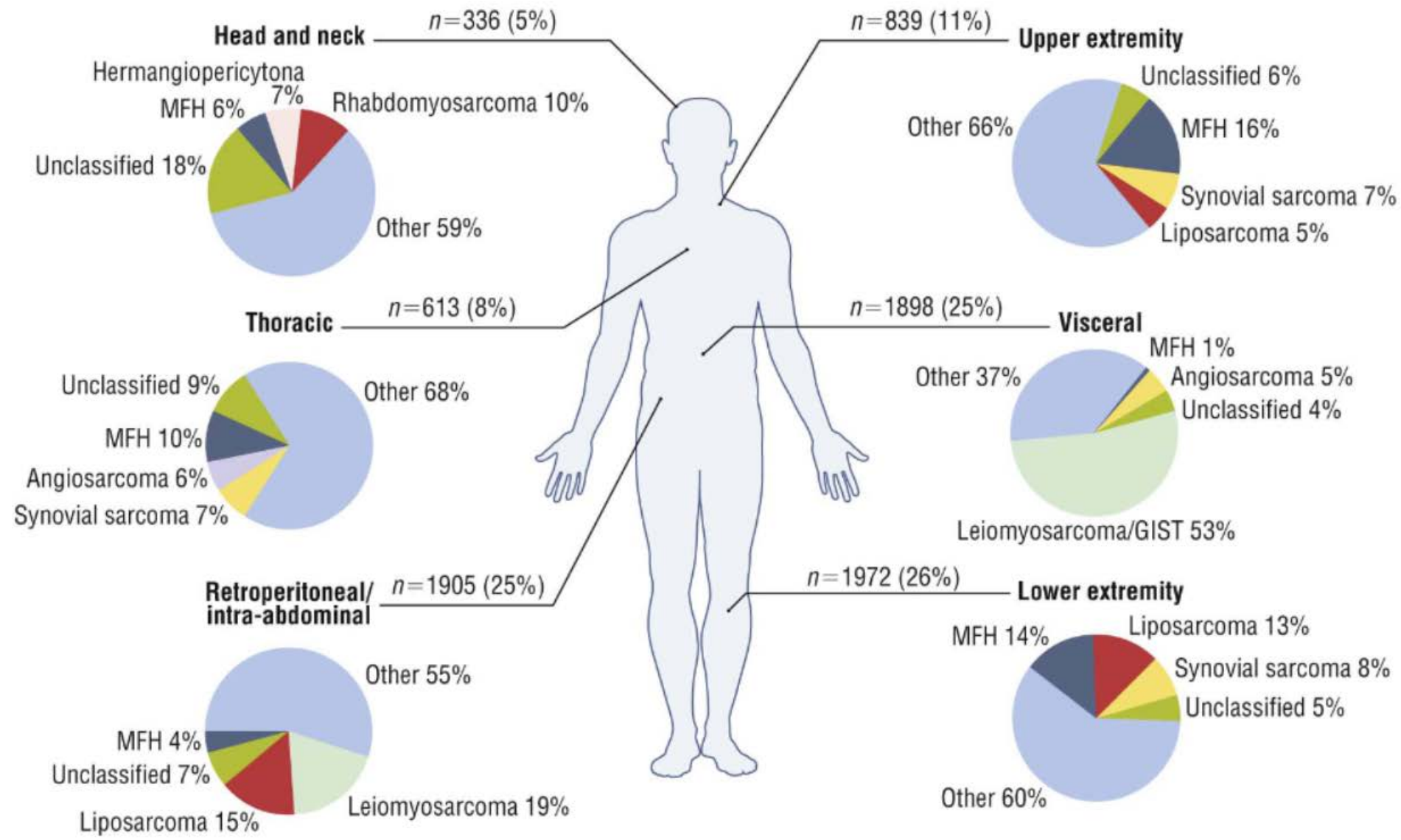
CA Cancer J Clin 2017;67:7–30

Location of Soft Tissue Sarcoma



Soft Tissue Tumors, 6th Ed. Enzinger & Weiss fig 2.1

Sarcoma

Pathology

- Size
- Grade
- Histology

Clinical

- Location
- Age
- Performance Score
- Organ function
  - CBC
  - Creatinine
  - Liver
  - Heart

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Histology Specific Treatments

- GIST
- Angiosarcoma
- PEComa
- Liposarcoma
- Leiomyosarcoma

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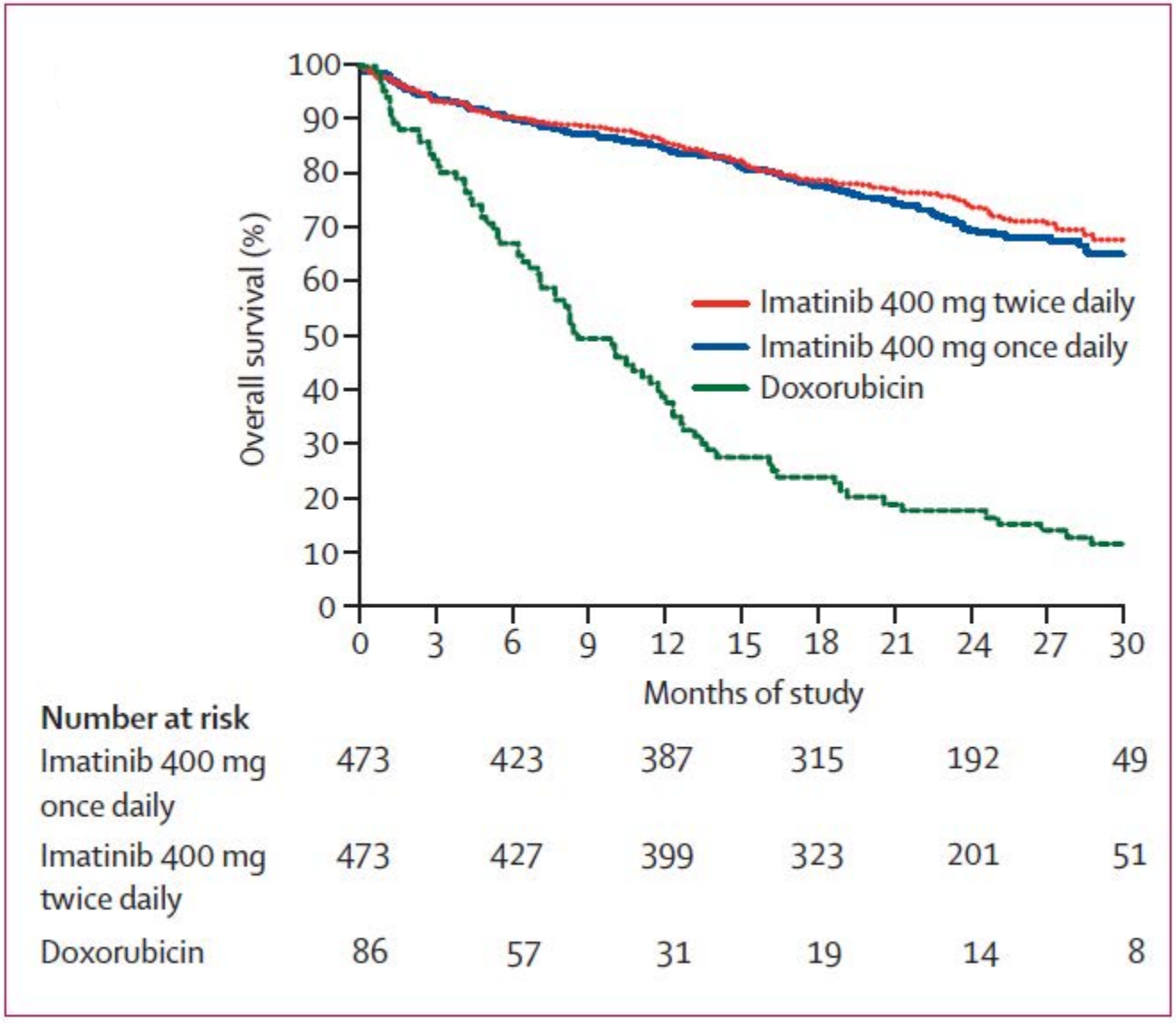
Imatinib for GIST



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Figure 6: Overall survival for total study population

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Lancet 2004; 364: 1127–134

Paclitaxel for Angiosarcoma

Table 3. Response Rates

Disease Status	No. of Patients		
	At 2 Months	At 4 Months	At 6 Months
Assessable patients	27*	22	21
Progressive disease	7	12	16
Complete response	0	1	3†
Partial response	5	3	1
Stable disease	15	6	1
Overall response rate			
%	18	18	19
95% CI	4 to 33	2 to 34	3 to 35
Nonprogression rate			
%	74	45	24
95% CI	57 to 90	25 to 66	6 to 42

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J Clin Oncol 26:5269-5274. 2008

Sirolimus for PEComa

Table II. *Results treatment duration and response*

Patient	Primary site	Performance status	Previous surgery/ chemotherapy	Duration of treatment (days)	Assessable for radiological response	Symptom improvement	Best RECIST 1.1 response
1	Gynaecological	0	No	94	Yes	Yes	Stable disease
2	Gynaecological	1	Total abdominal hysterectomy, RT	1366	Yes	Yes	Partial response
3	Gastrointestinal	0	Right hemicolectomy	637[a]	Yes	Yes	Partial response
4	Retroperitoneal	0	No	7	No	No	N/A
5	Retroperitoneal	1	Transverse colectomy	56	Yes	No	Disease progression
6	Bone	2	No	217	No	Yes	N/A
7*	Renal	1	Left nephrectomy, doxorubicin	158	Yes	Yes	Partial response
8	Gastrointestinal	1	Gastrectomy	16	No	No	N/A
9	Renal	1	Nephrectomy	311[a]	Yes	Yes	Partial response
10	Renal	0	Nephrectomy	98[a]	Yes	Yes	Partial response

*Patient received temsirolimus, [a]patients remain on treatment as of January 2013.

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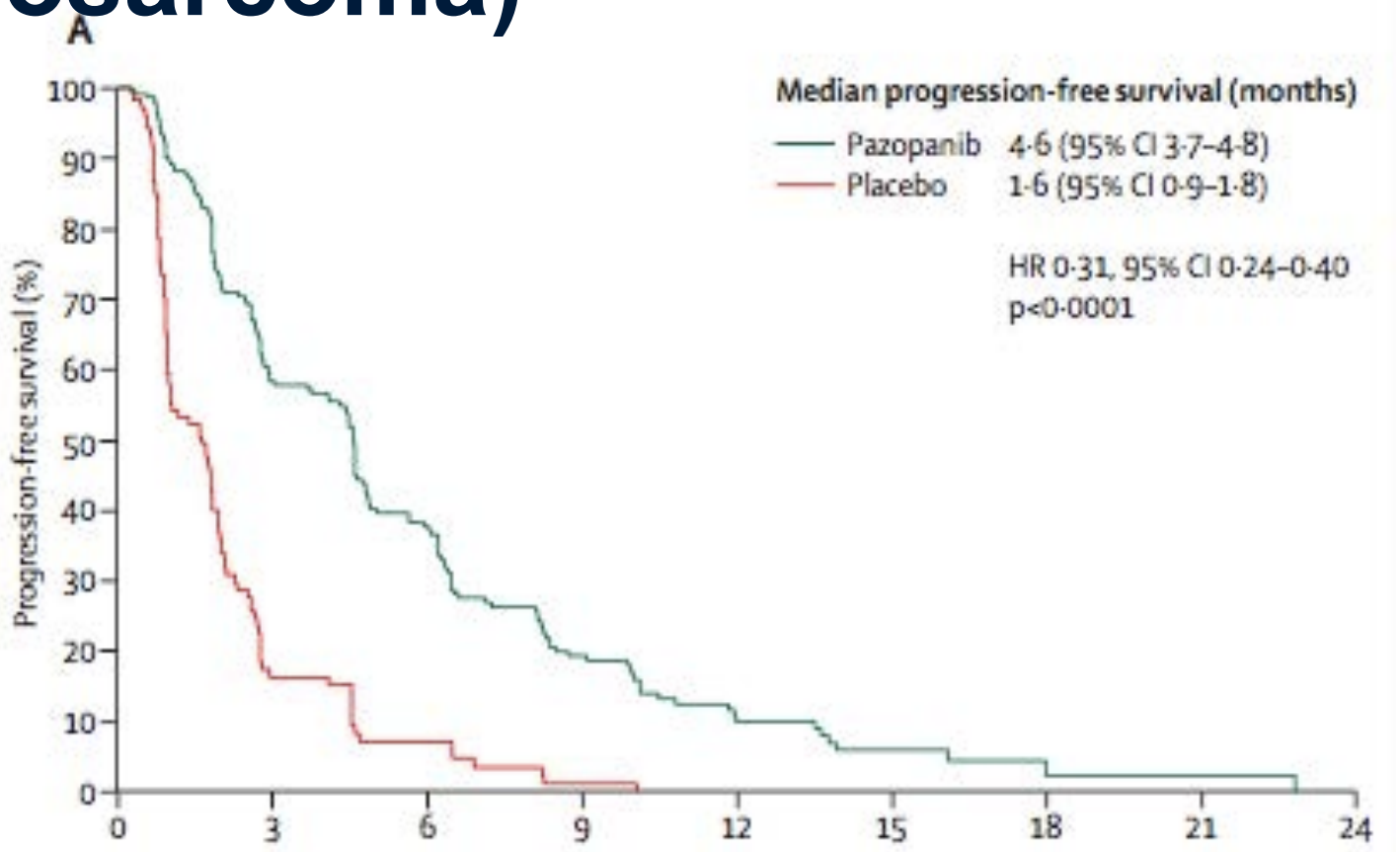
ANTICANCER RESEARCH *34*: 3663-3668 (2014)

PALETTE: Pazopanib for Soft Tissue Sarcoma (Except Liposarcoma)



Lancet 2012

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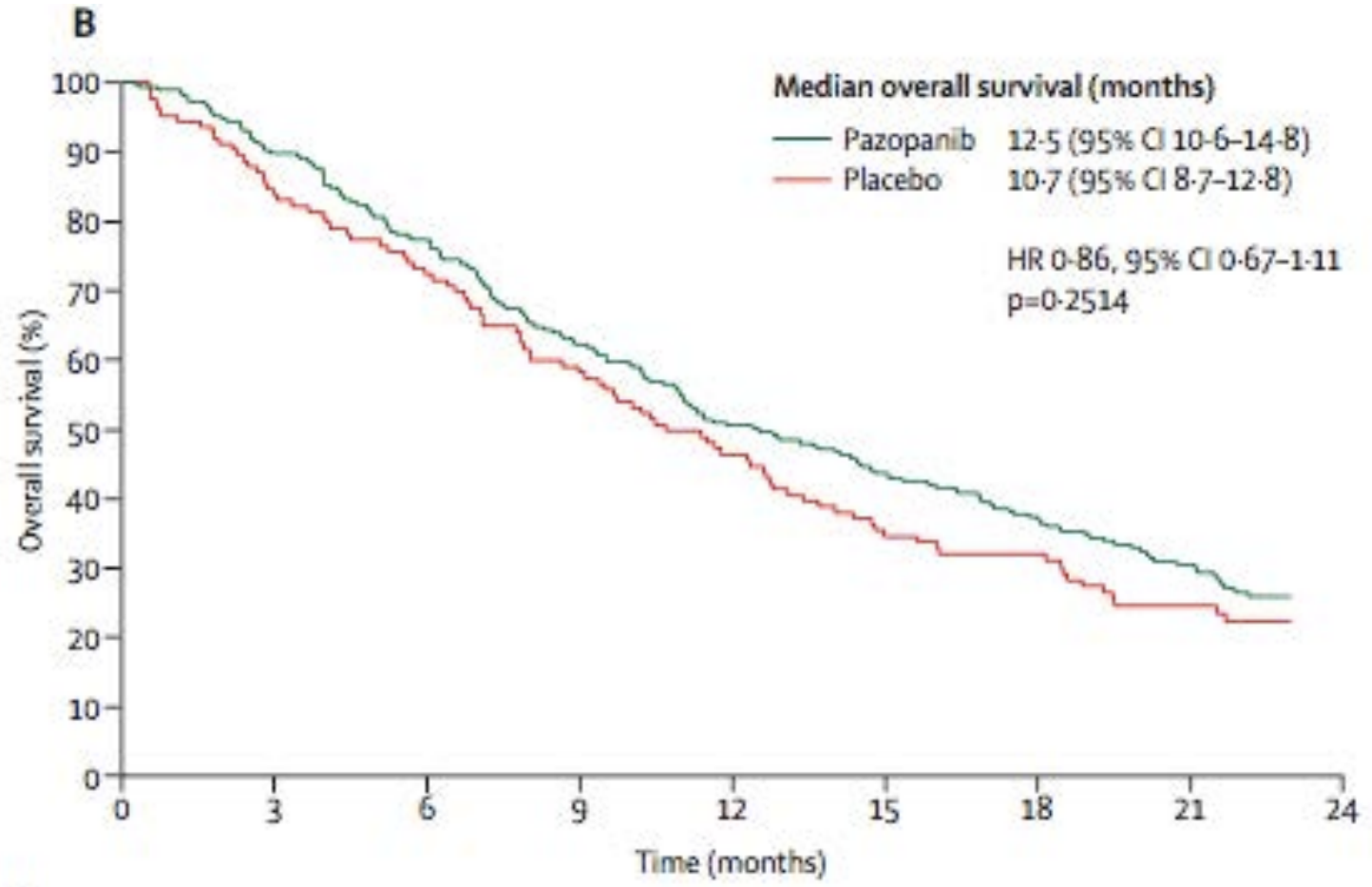
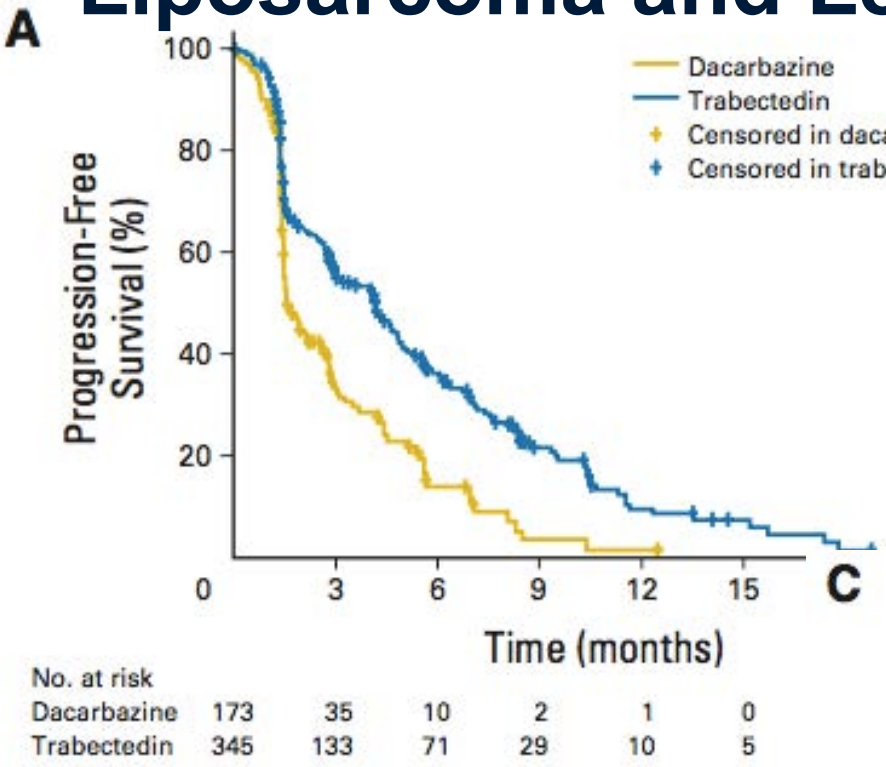
PALETTE: Pazopanib for Soft Tissue Sarcoma (except Liposarcoma)



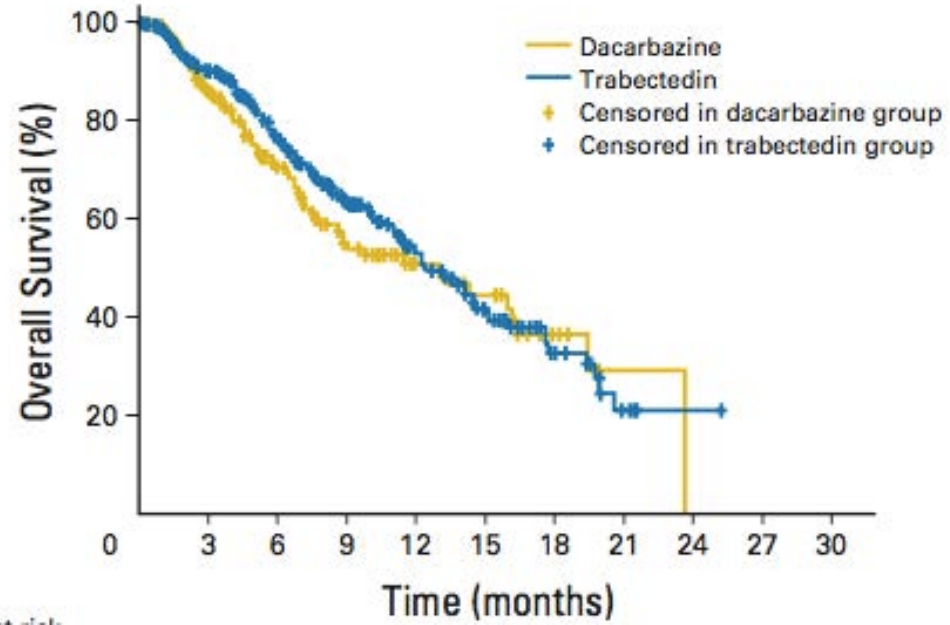
Lancet 2012

Trabectedin vs Dacarbazine
Liposarcoma and Leiomyosarcoma



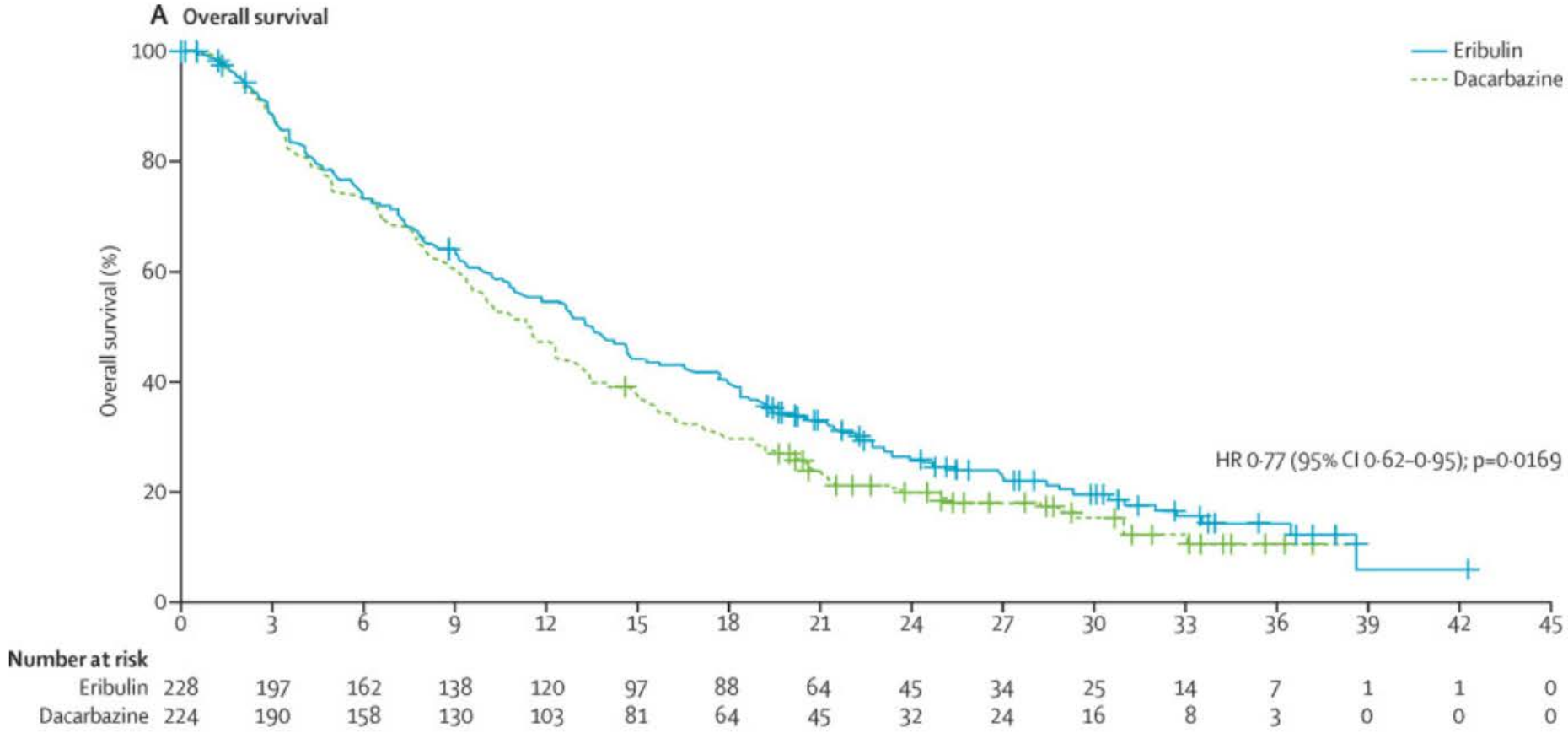
October 23, 2015

FDA Approves Trabectedin to Treat Two Types of Soft Tissue Sarcoma LMS and LPS



JCO 2015

Eribulin vs Dacarbazine For LMS and LPS



Lancet Oncology 2016

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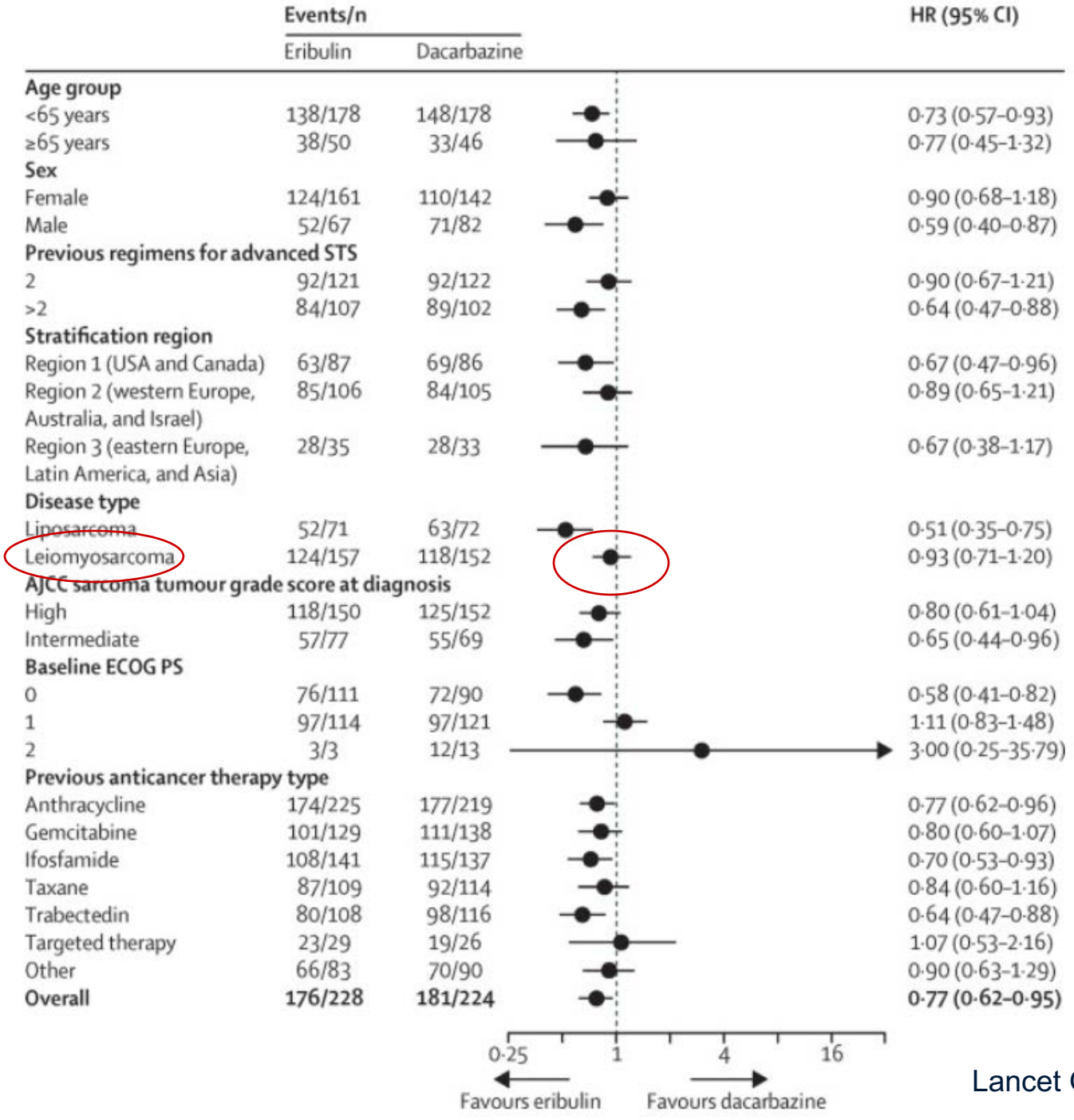

Lancet Oncology 2016

Imaging of Soft Tissue Sarcoma

- MRI of the lesion
- CT Chest
- +/- PET Scan or Bone Scan

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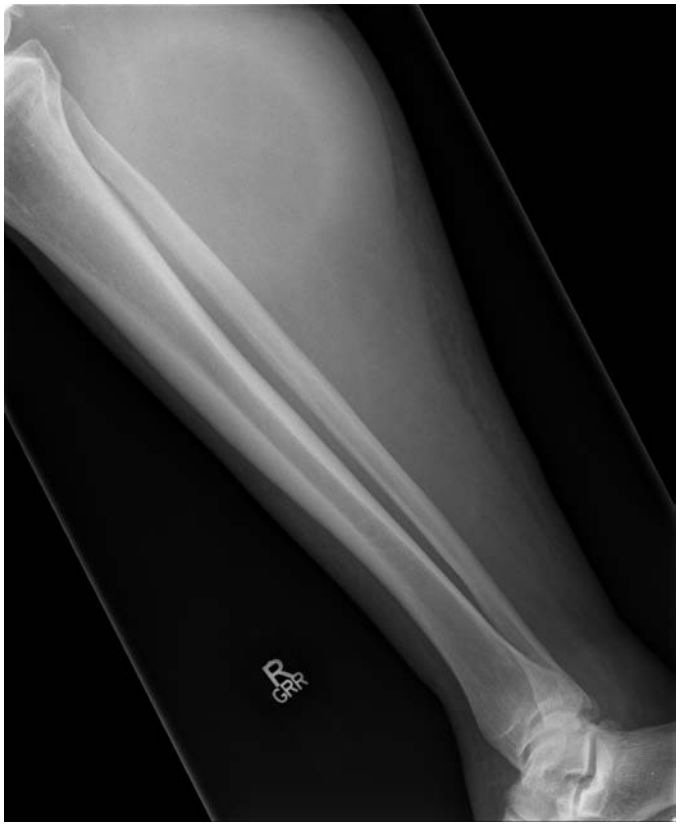
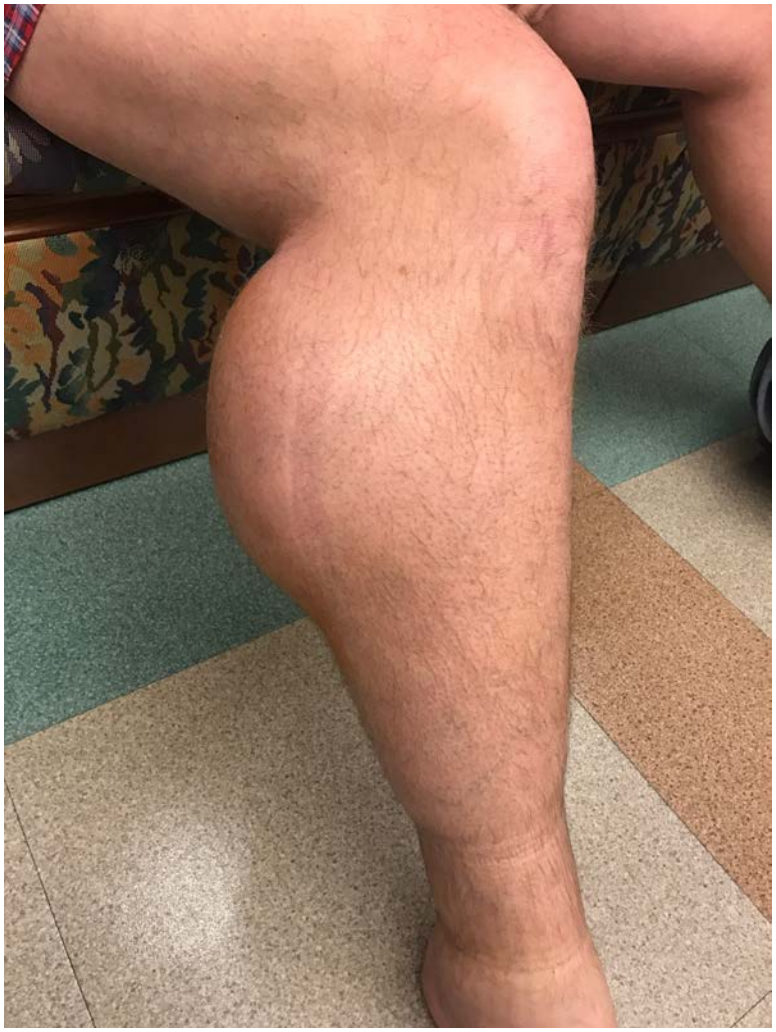
46 Year Old Male Slowly Enlarging Painless Lump





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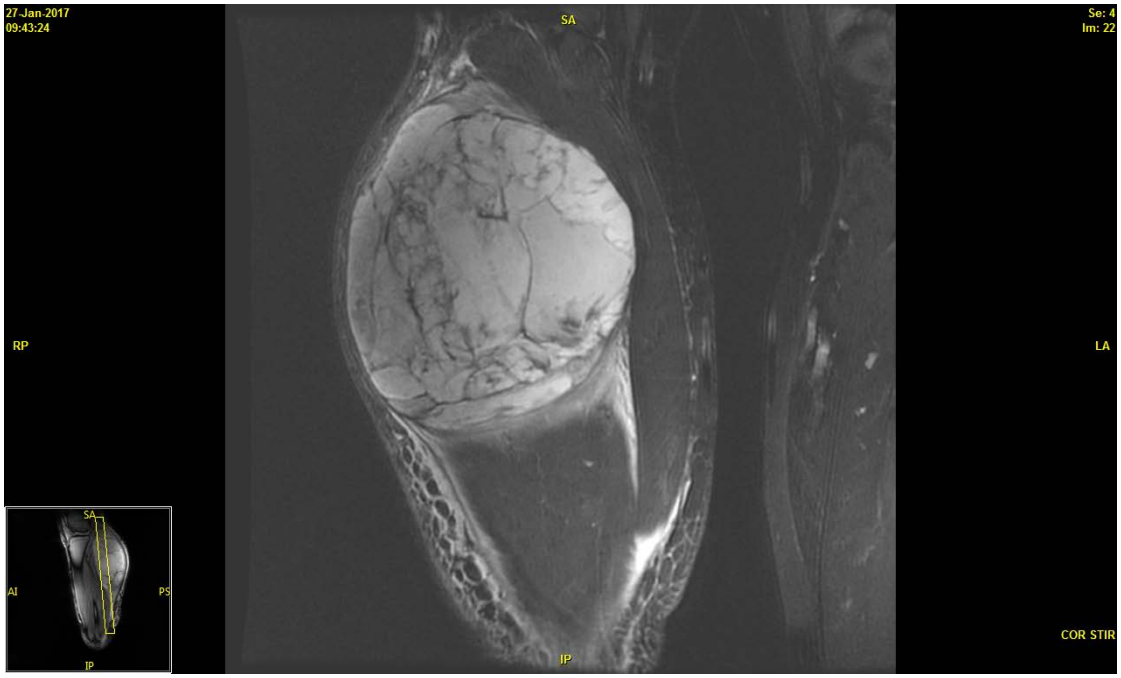

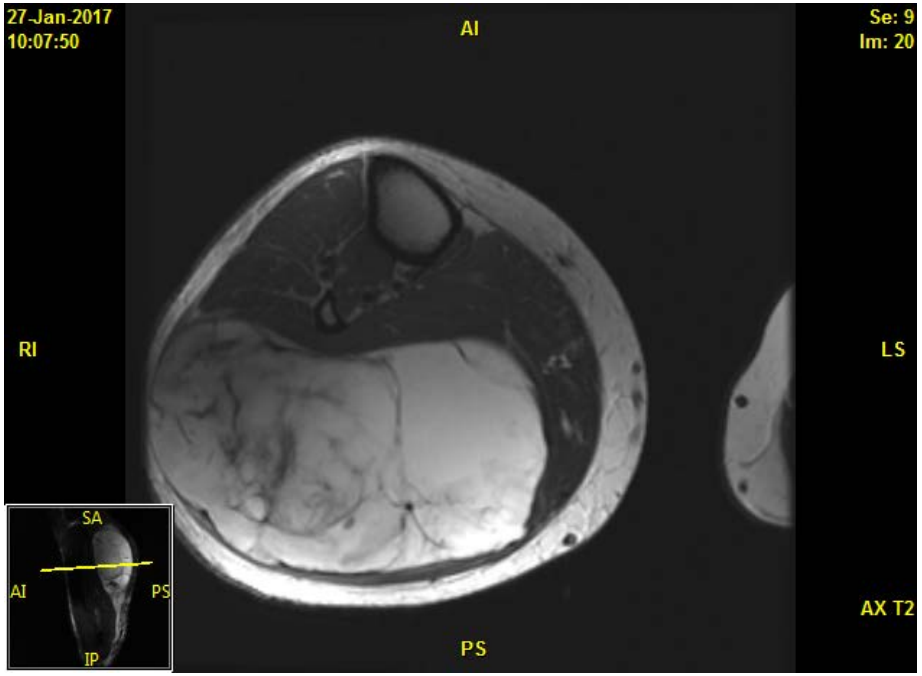

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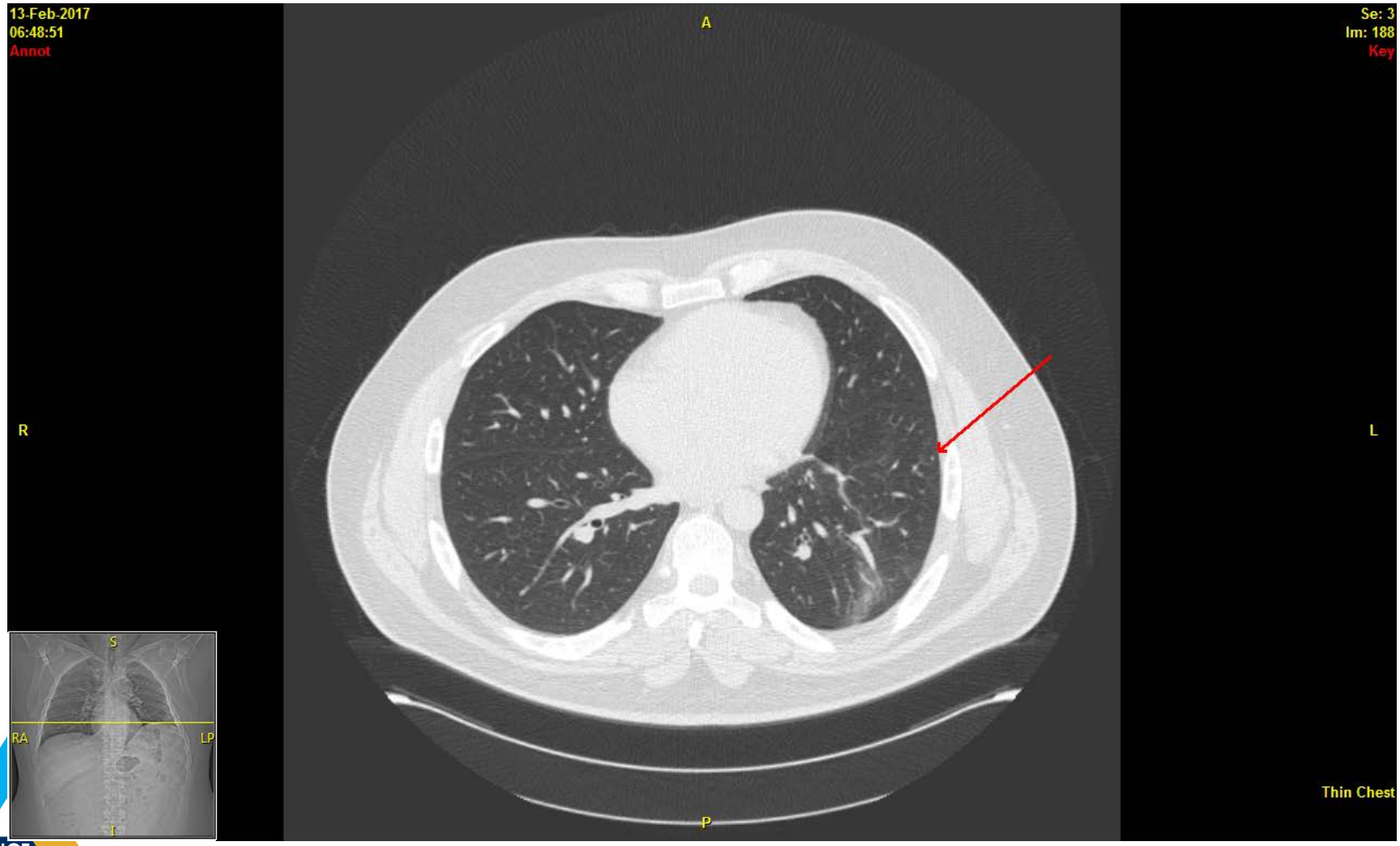
46 SM Bx of Right Calf
High Grade Pleomorphic Sarcoma



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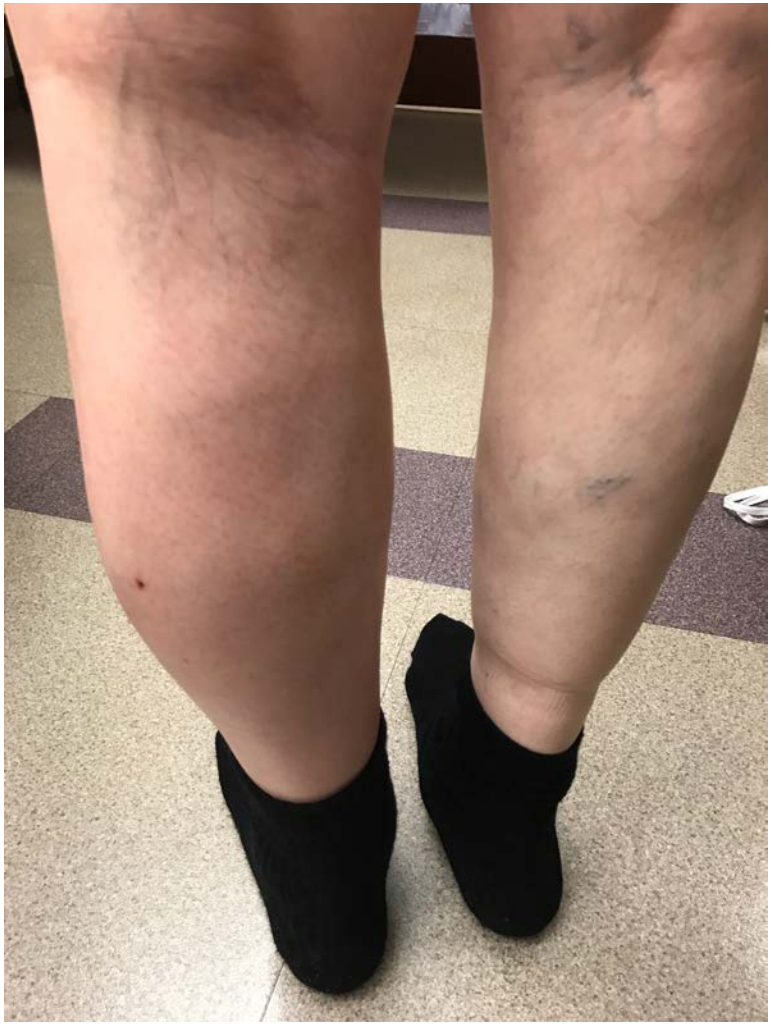
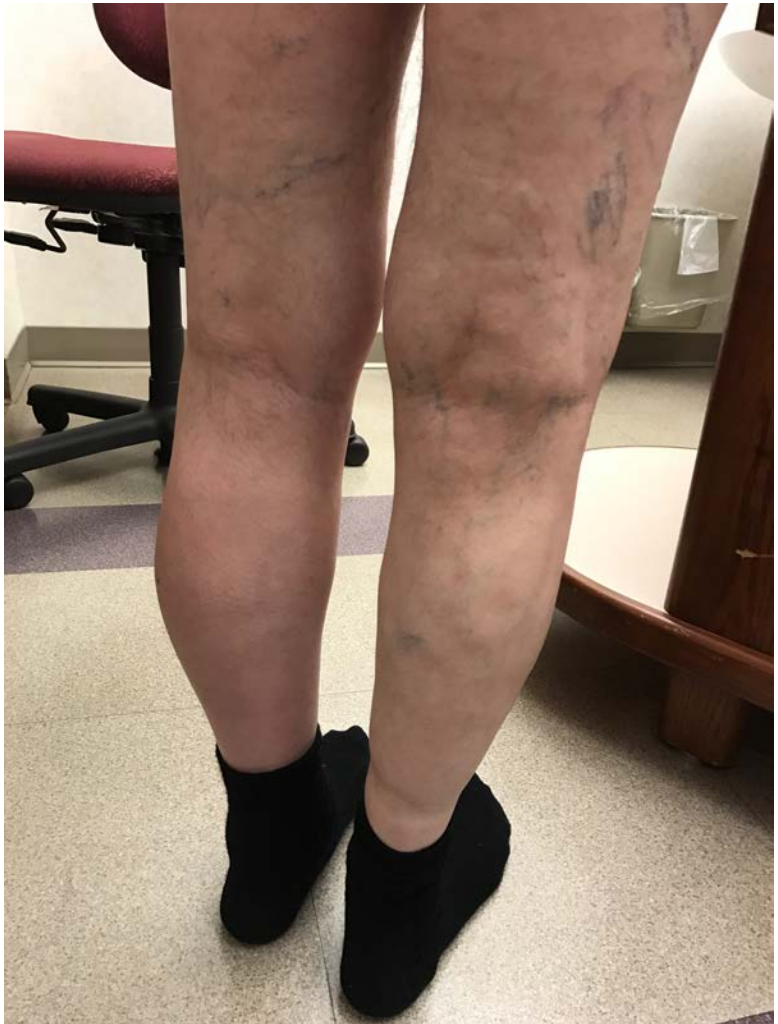
79 Year Old Female 1 Month History of Enlarging Calf Lesion





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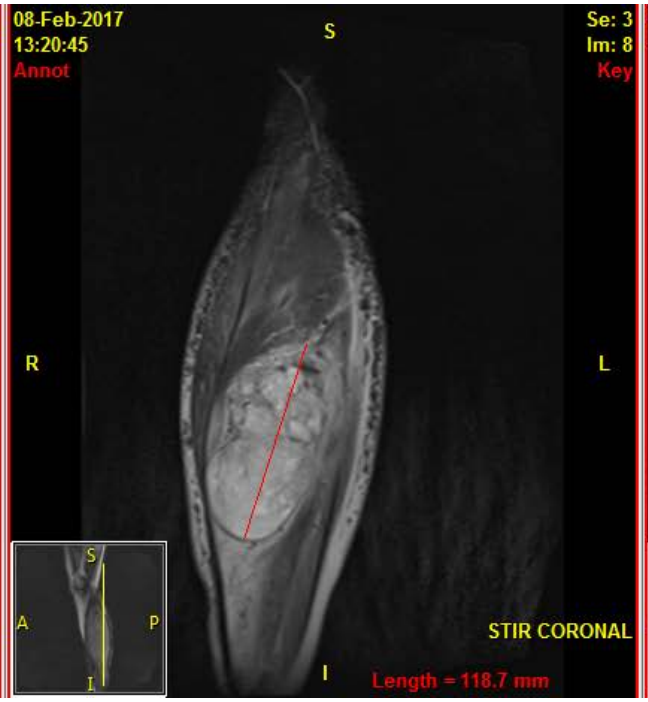

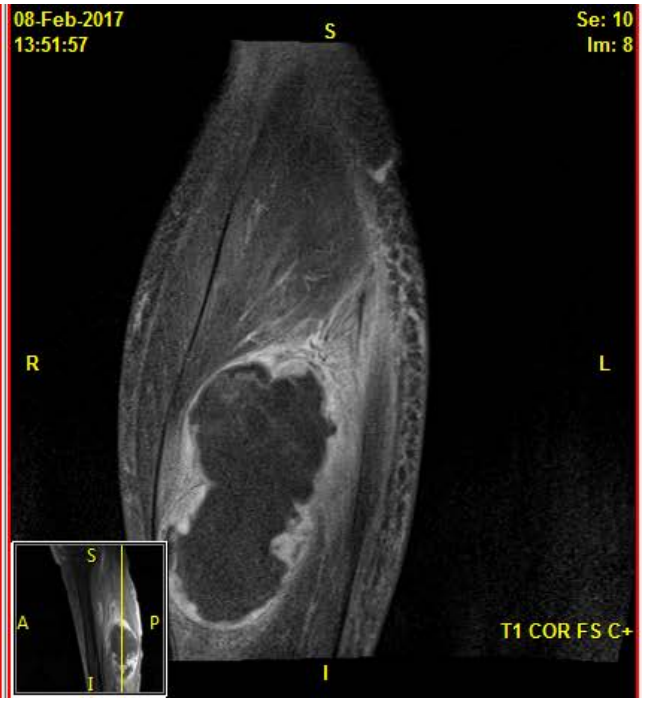

T1 T2 FS T1 GAD

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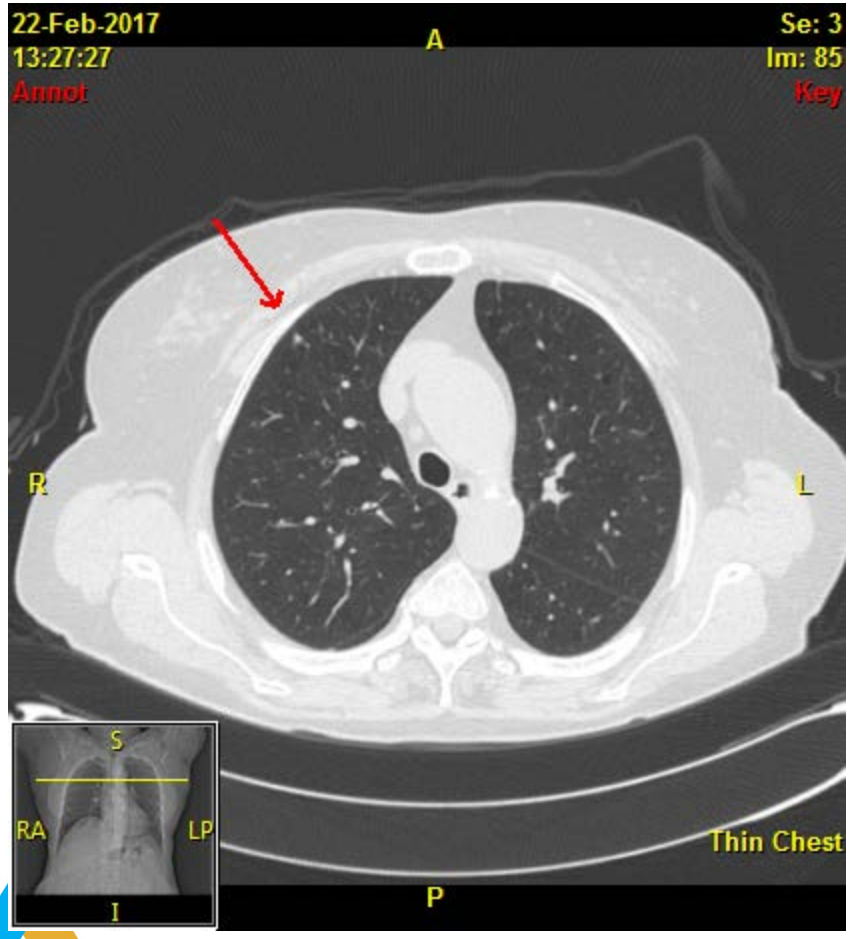
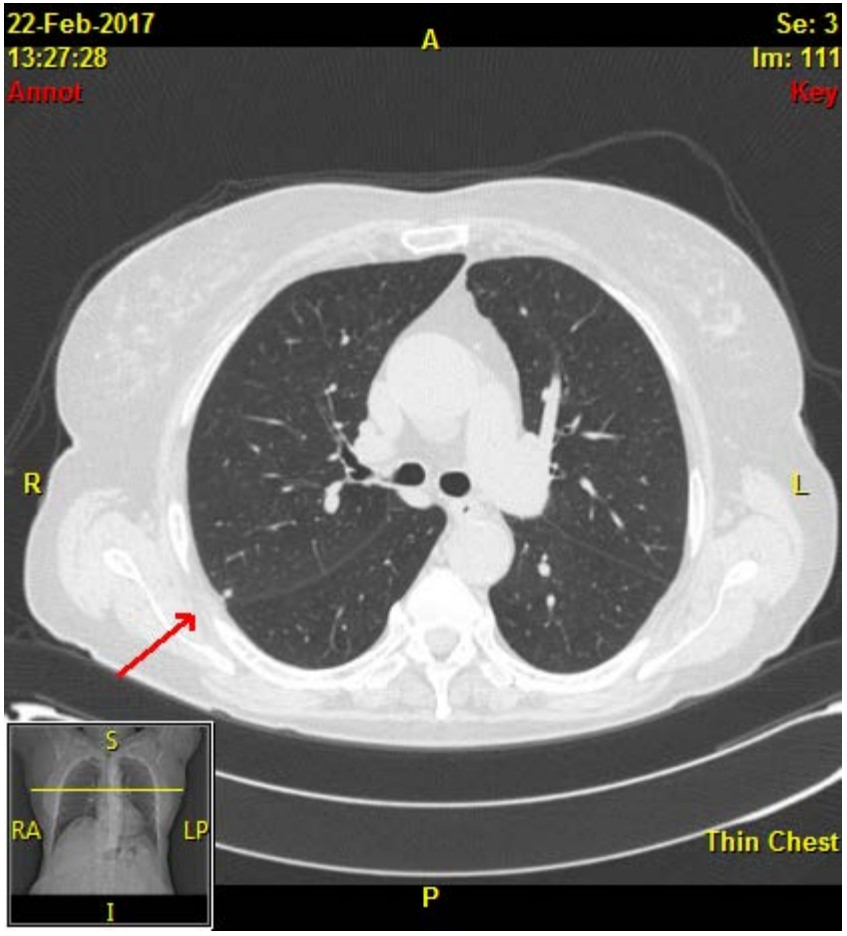
PB CT Chest Several Bilateral Indeterminate Pulmonary Nodules





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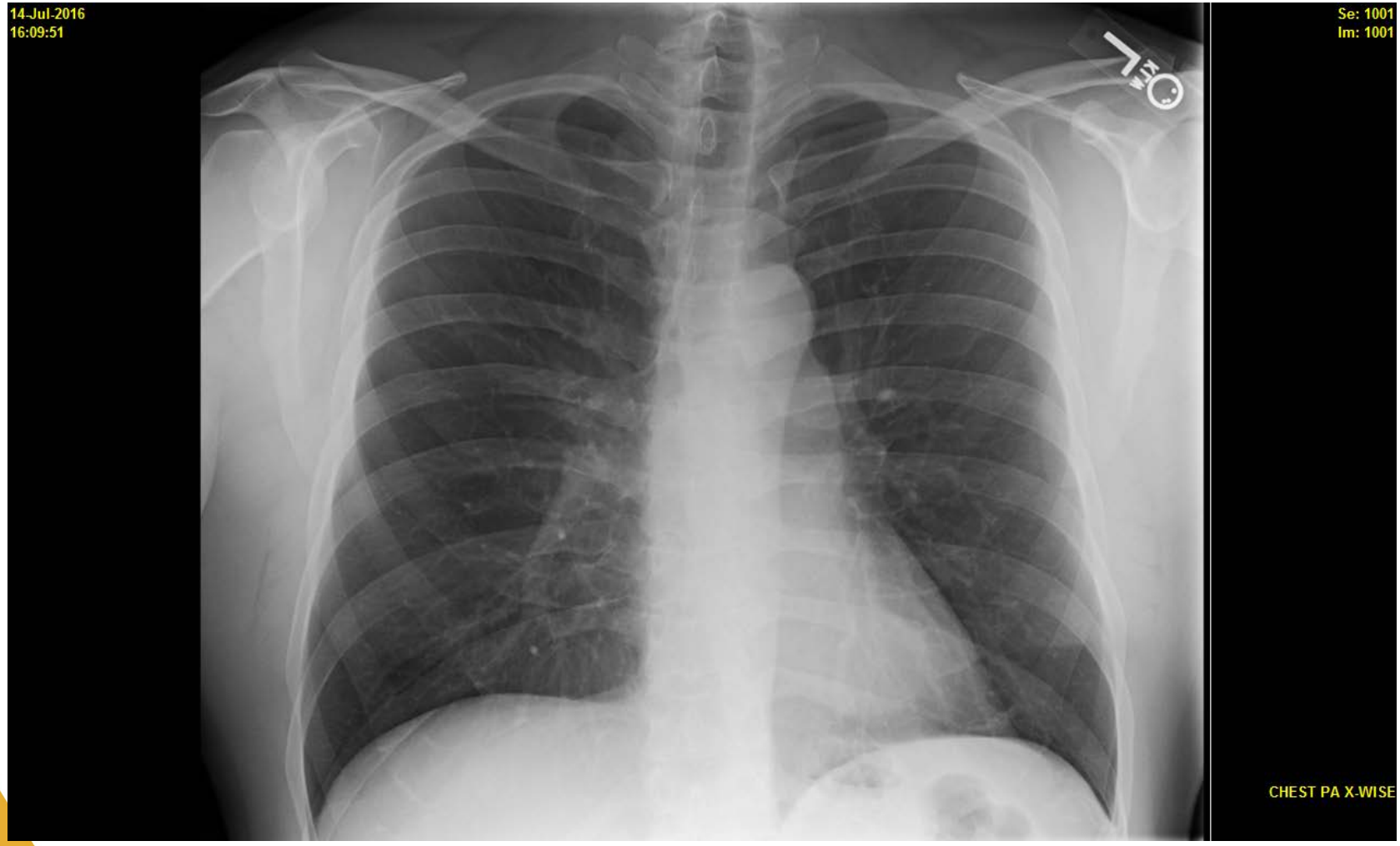
40 Year Old Male Lump in Right Chest Wall



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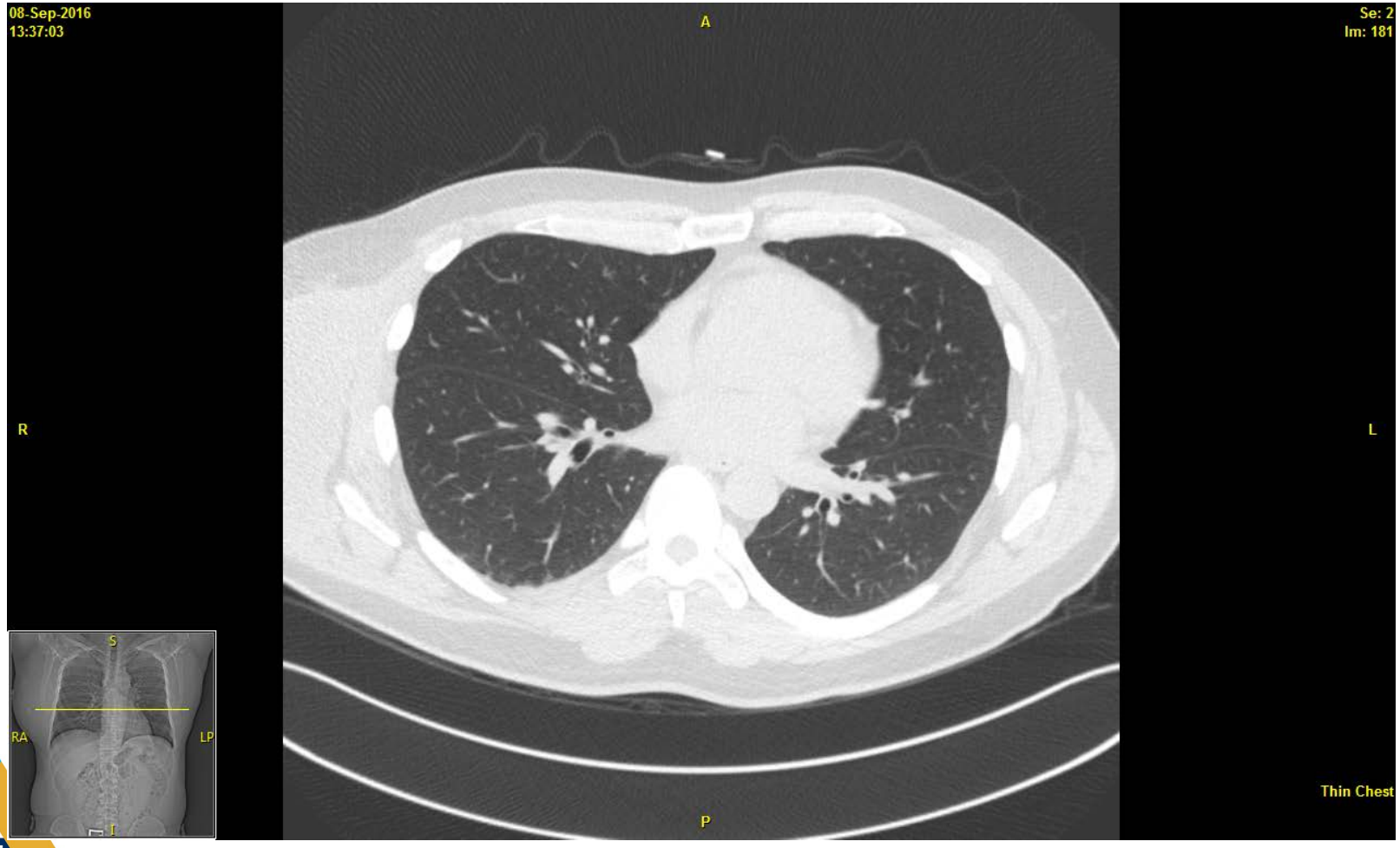
JG CT Chest With Lung Windows



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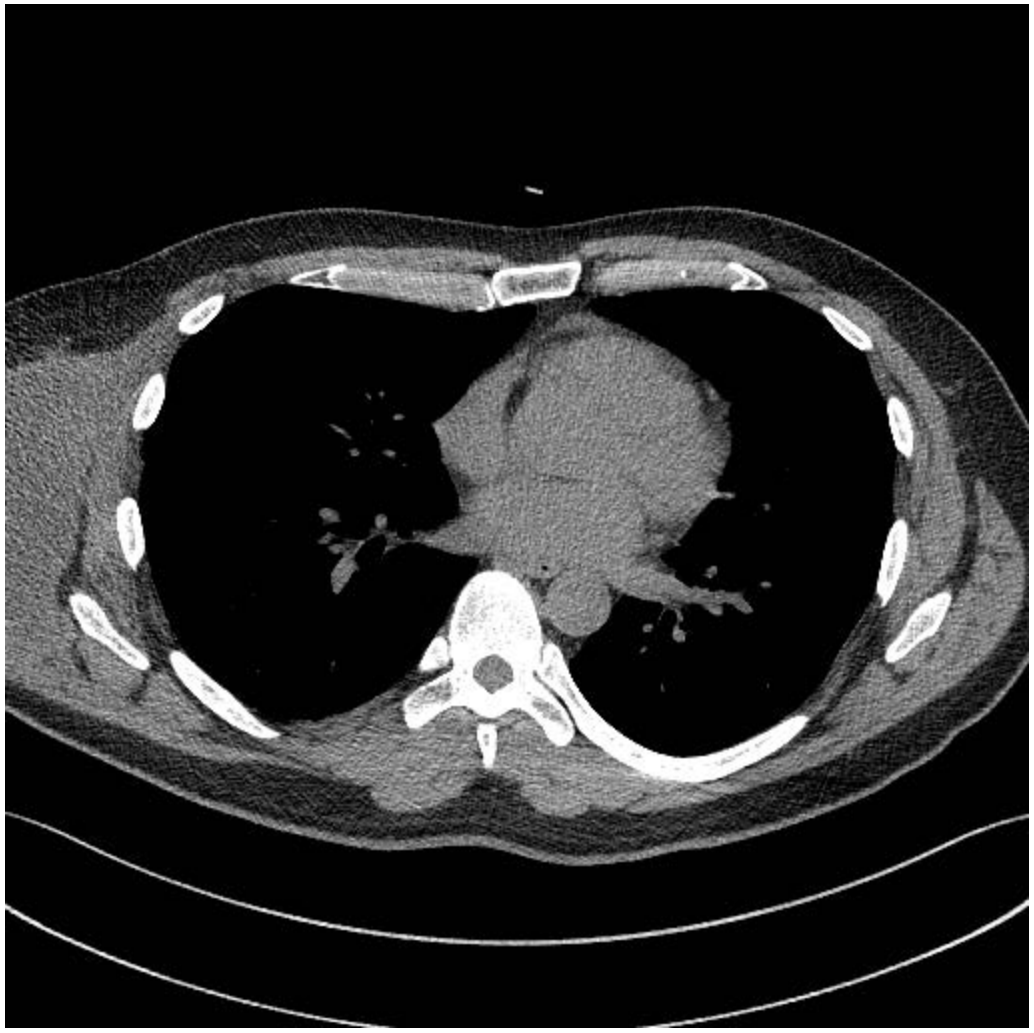
JG CT Chest Soft Tissue Window



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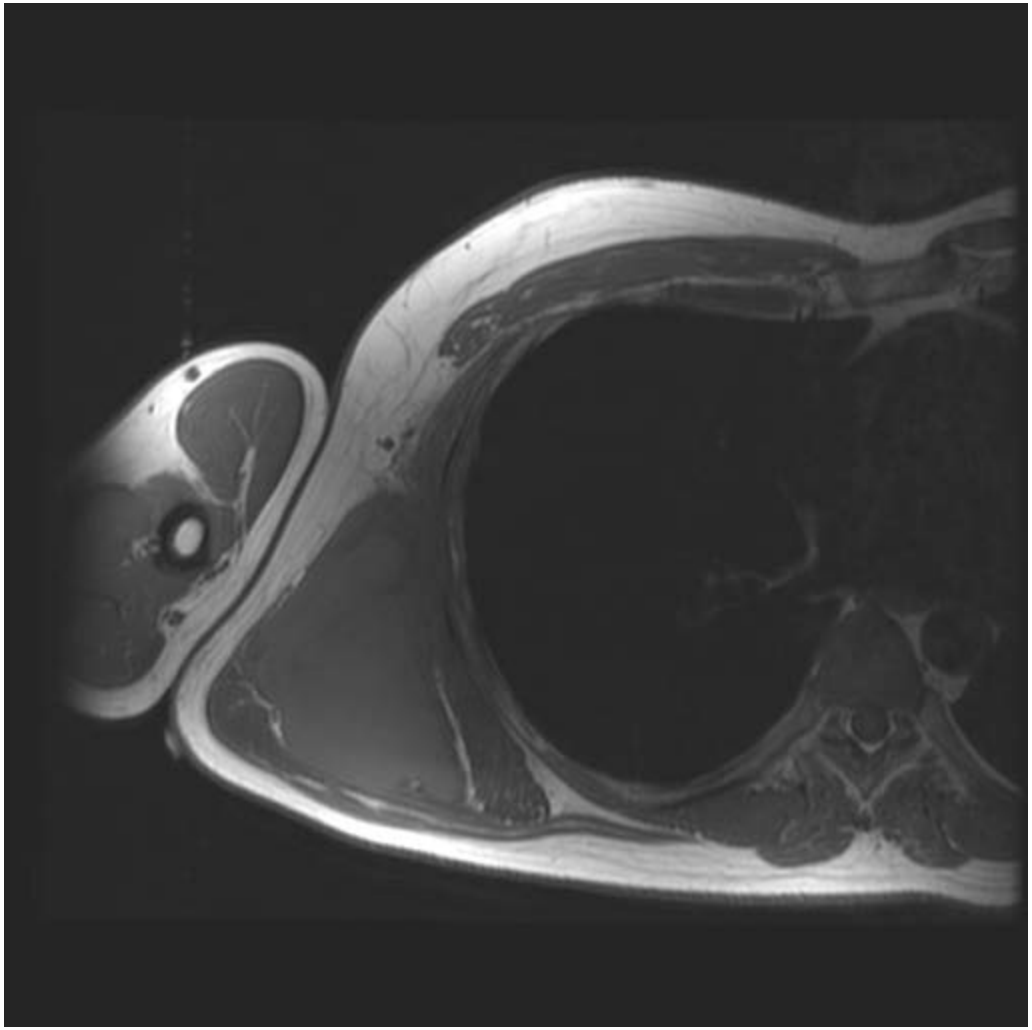
JG MRI TI



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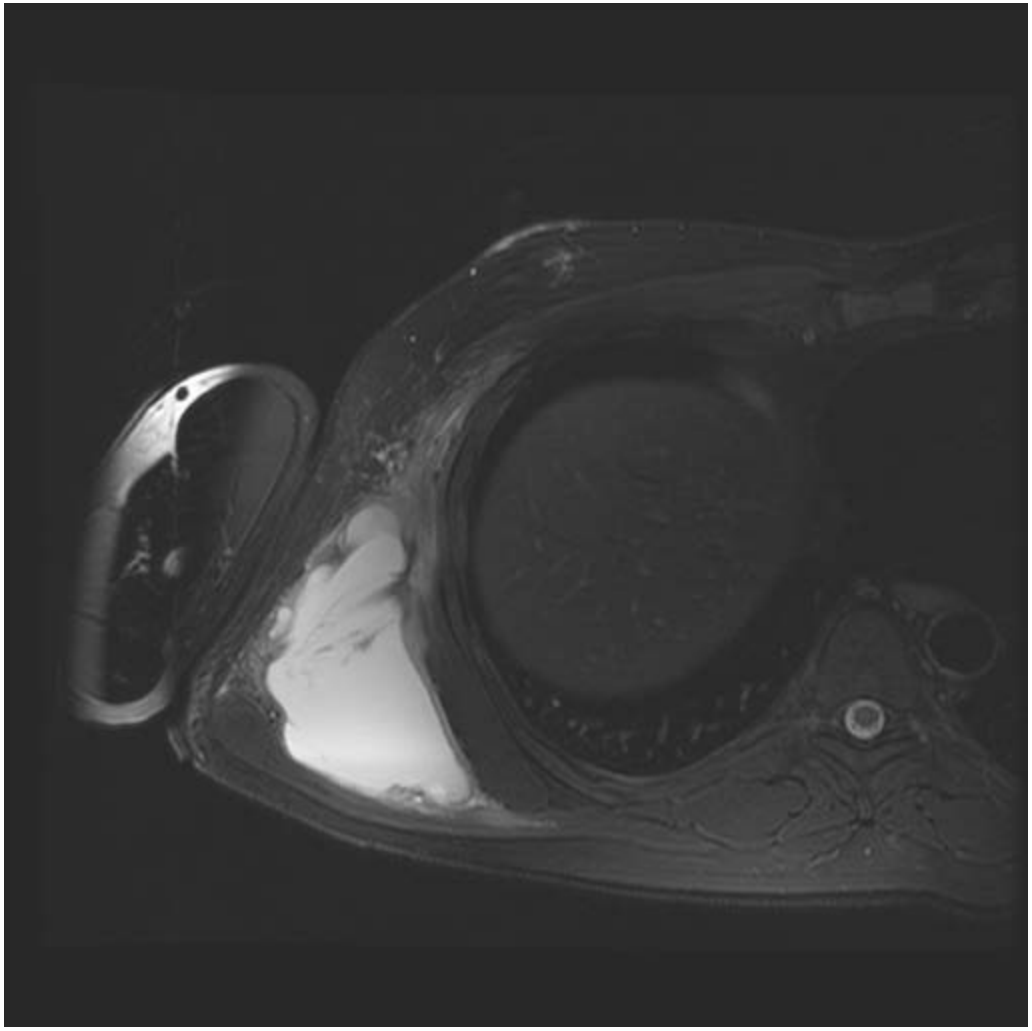
JG MRI T2 Fat Suppressed



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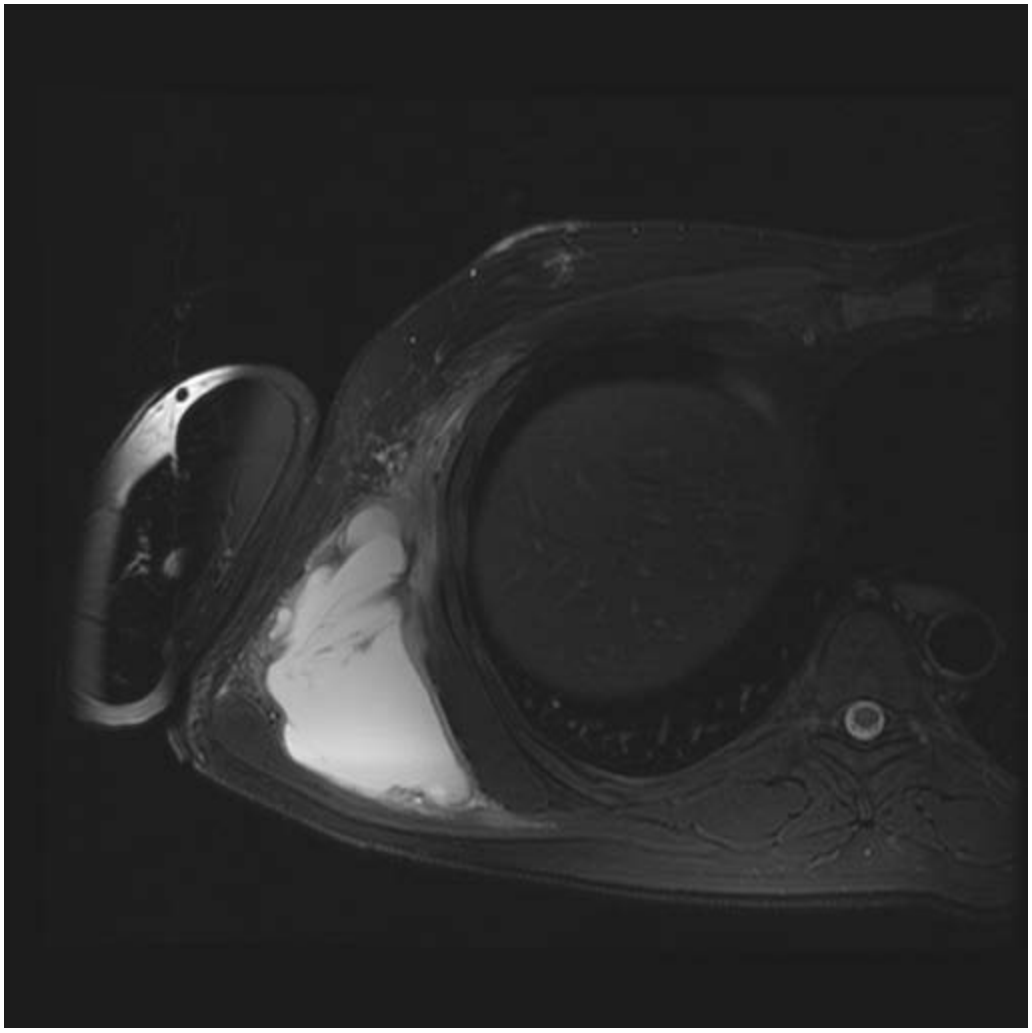
JG T1 FS with Gadolinium



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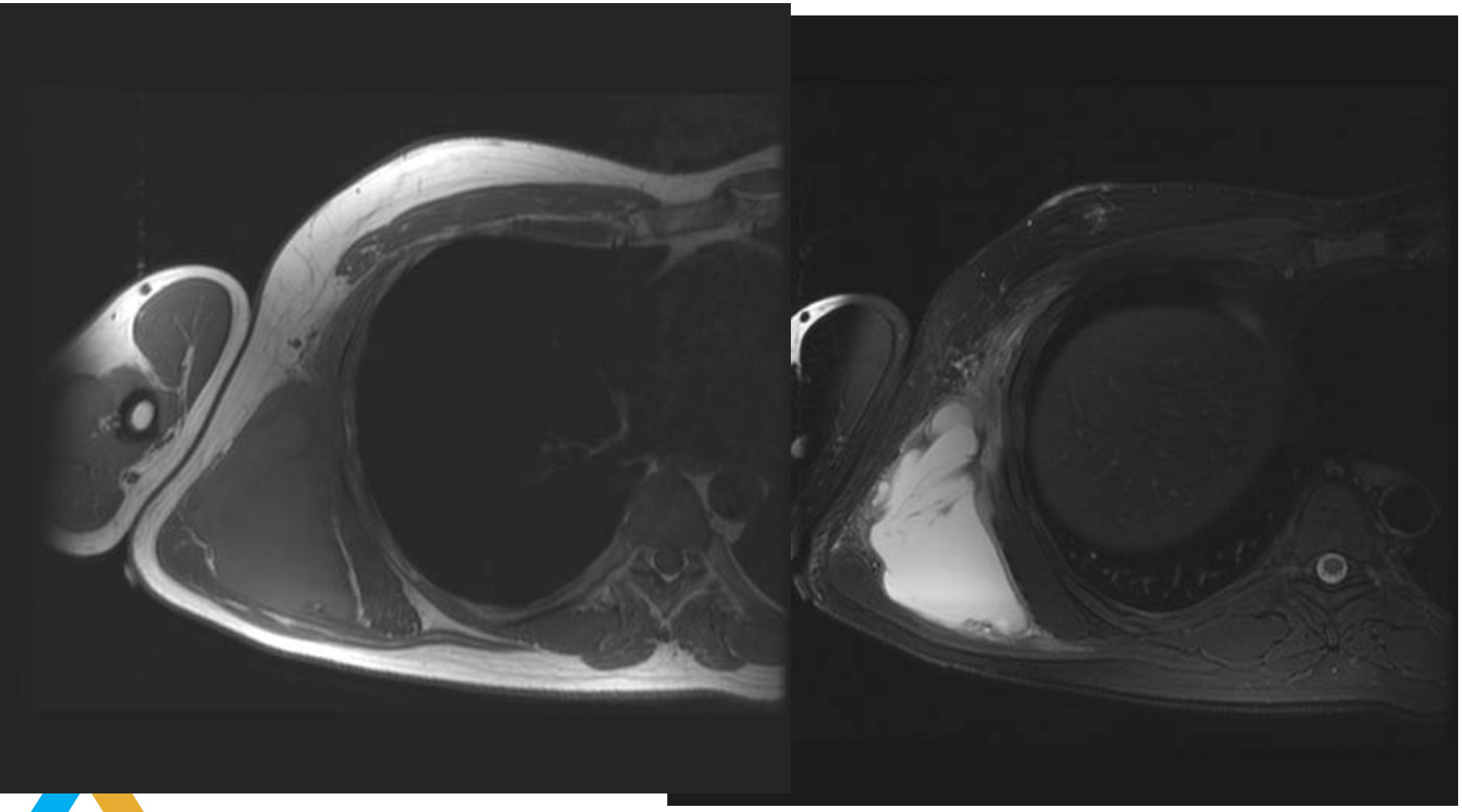
JG T1 with and without GAD



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JG Biopsy Right Chest Wall Pleomorphic Sarcoma

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Tumor Response Criteria for STS

- RECIST 1.1
- iRECIST
- WHO
- Choi

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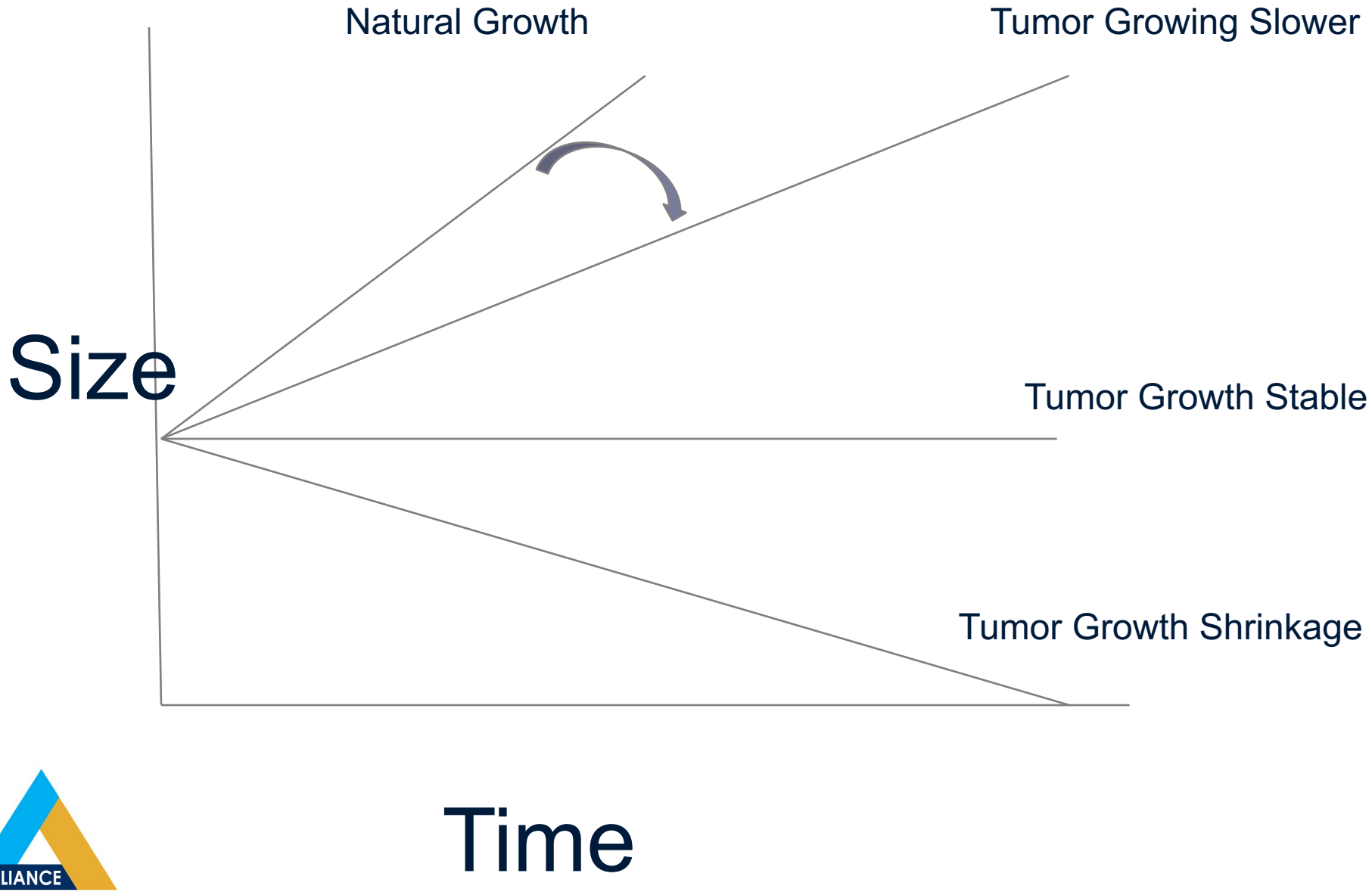
Chemotherapy



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Clinical Trials Response Criteria

- Measurement
  - RECIST 1.0 and 1.1
  - WHO
  - Immune RECIST
- Disease and Time
  - Progression Free Survival (PFS)
  - Progression Free Rate at X month
  - Disease Free Survival (DFS)
  - Overall Survival (OS)

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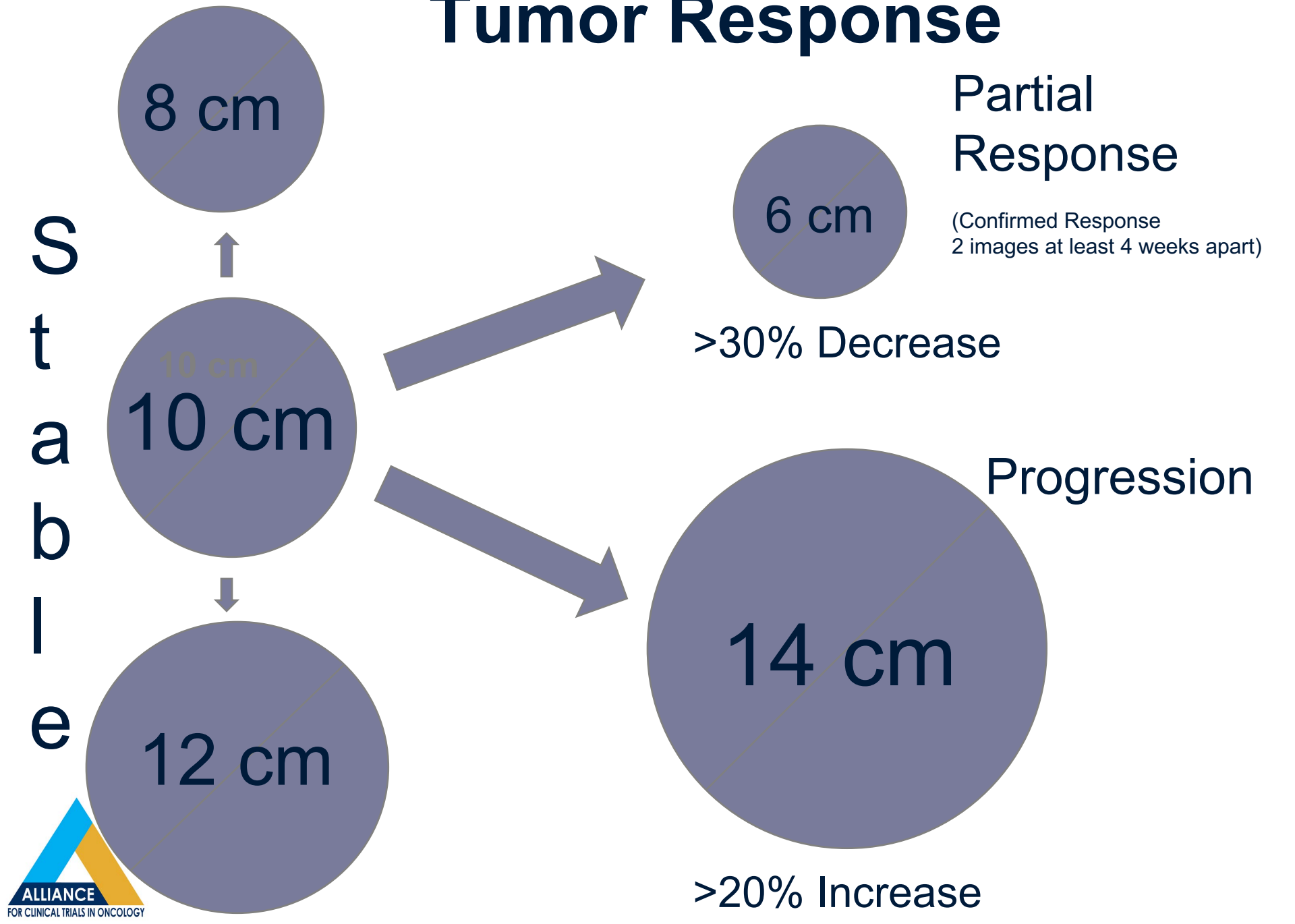
Tumor Response



Response Measures in Sarcoma

	Measurement	Response Decrease	Progression Increase	Duration of Response	# Lesions
RECIST	Size One Dimension	> 30%	> 20%	None	5 (2 per organ)
iRECIST	Size Bi-Dimension Tumor Burdon	≥ 50	≥ 25%	Lasting at least 4 weeks	5 per organ, 10 Visceral
WHO	Size Bi-Dimention	≥ 50%	≥ 25%	Lasting at least 4 weeks	All
Choi	CT Density and Size	≥ 10% Size and ≥15% HU	≥ 10% Size	None	Same as RECIST

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EUROPEAN JOURNAL OF CANCER 45 (2009) 228 – 247
Cancer 47207-214. 1981
Clin Cancer Res 2009;15(23):7412, 20
J Clin Oncol 25:1753-1759, 2007

WHO vs irRC

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

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Clin Cancer Res 2009;15(23) December 1, 2009

Choi Criteria for GIST

Table 3. Modified CT Response Evaluation Criteria

Response	Definition
CR	Disappearance of all lesions No new lesions
PR	A decrease in size* of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT No new lesions No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.

*The sum of longest diameters of target lesions as defined in RECIST.[10]

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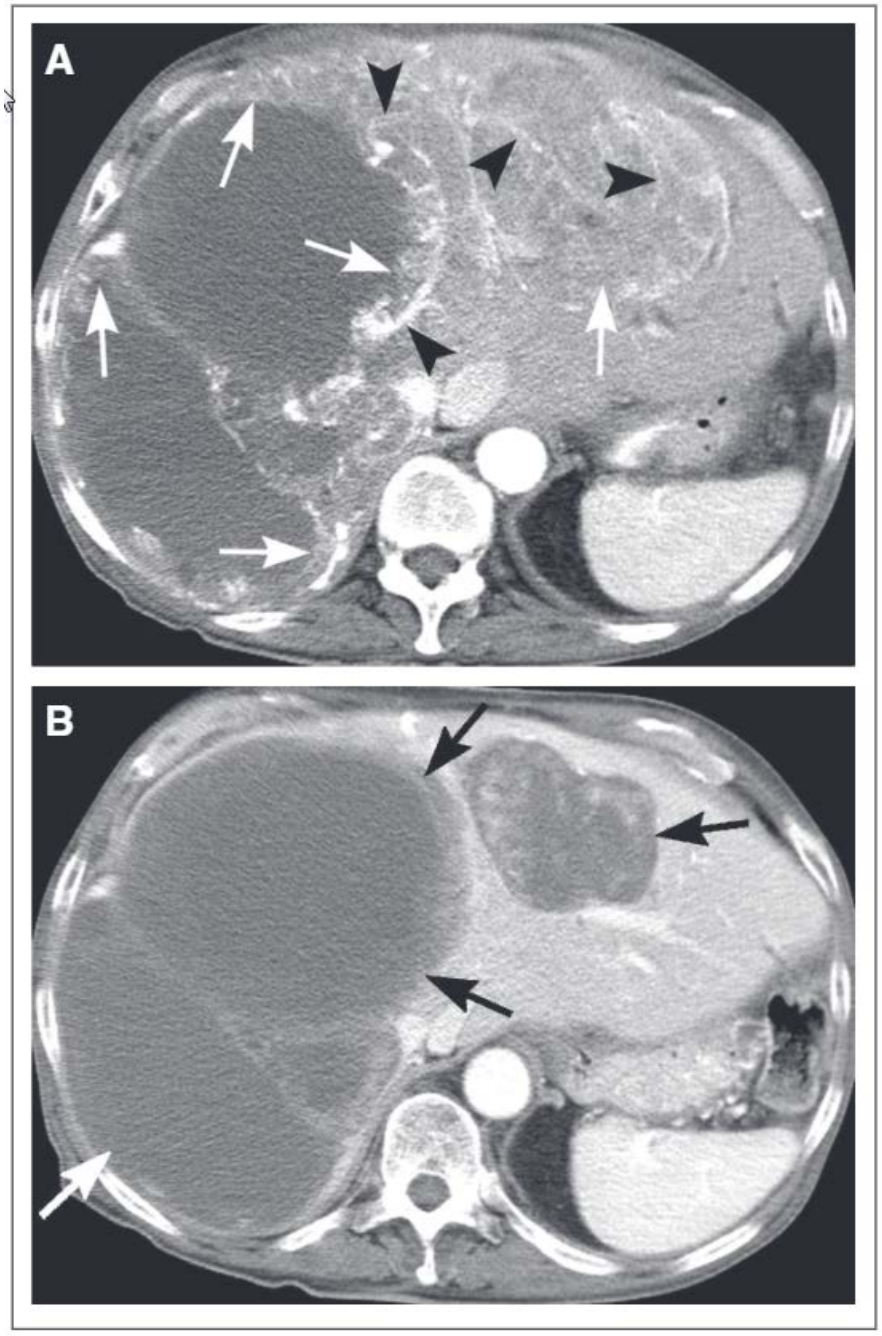
J Clin Oncol 25:1753-1759, 2007



J Clin Oncol 25:1753-1759, 2007

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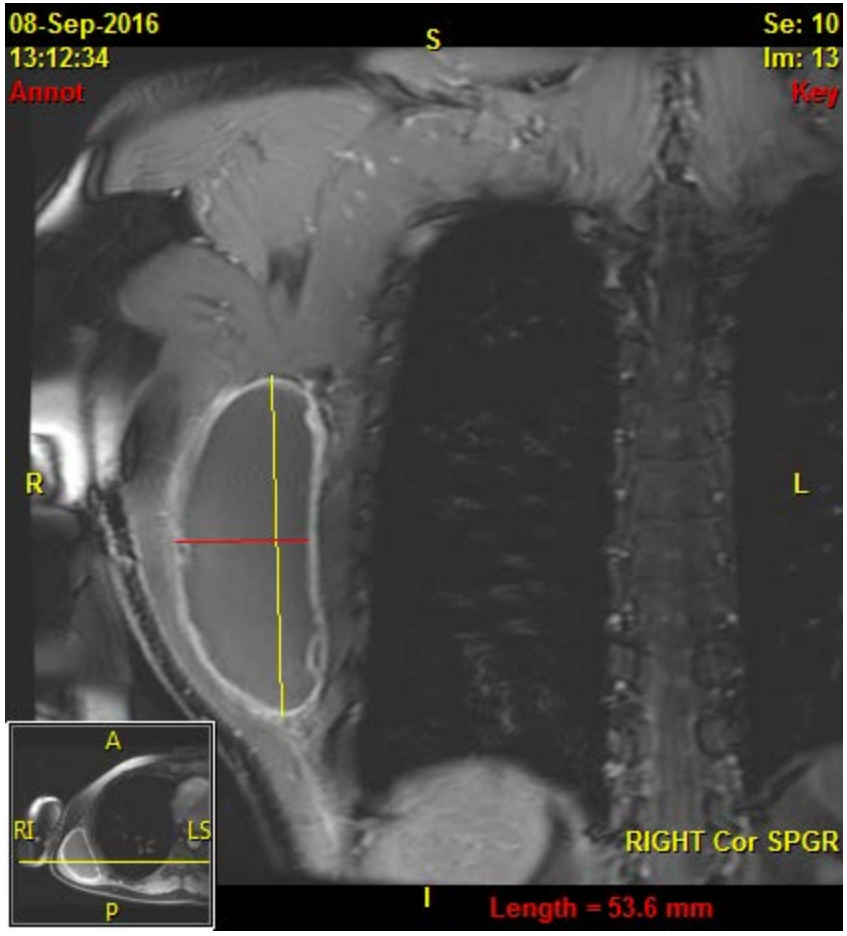
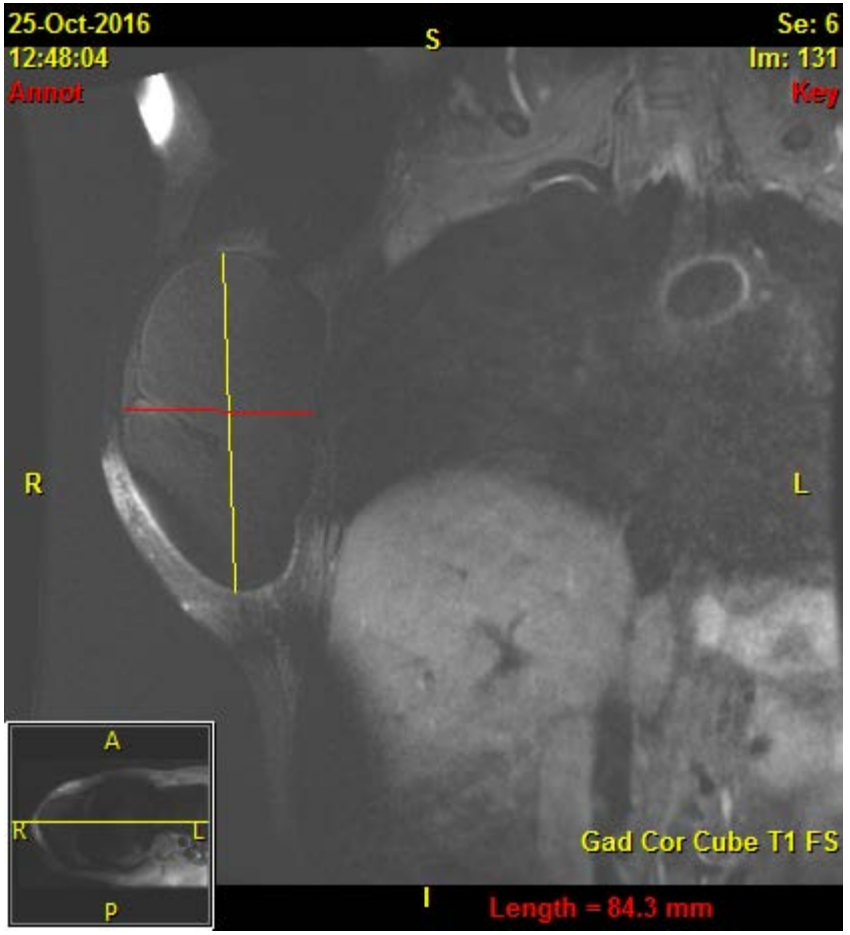
Is The Tumor Responding?





Sept 8, 2016
13.8 x 5.4 cm

Chemo
IA

Oct 25, 2016
15.3 x 8.4 cm

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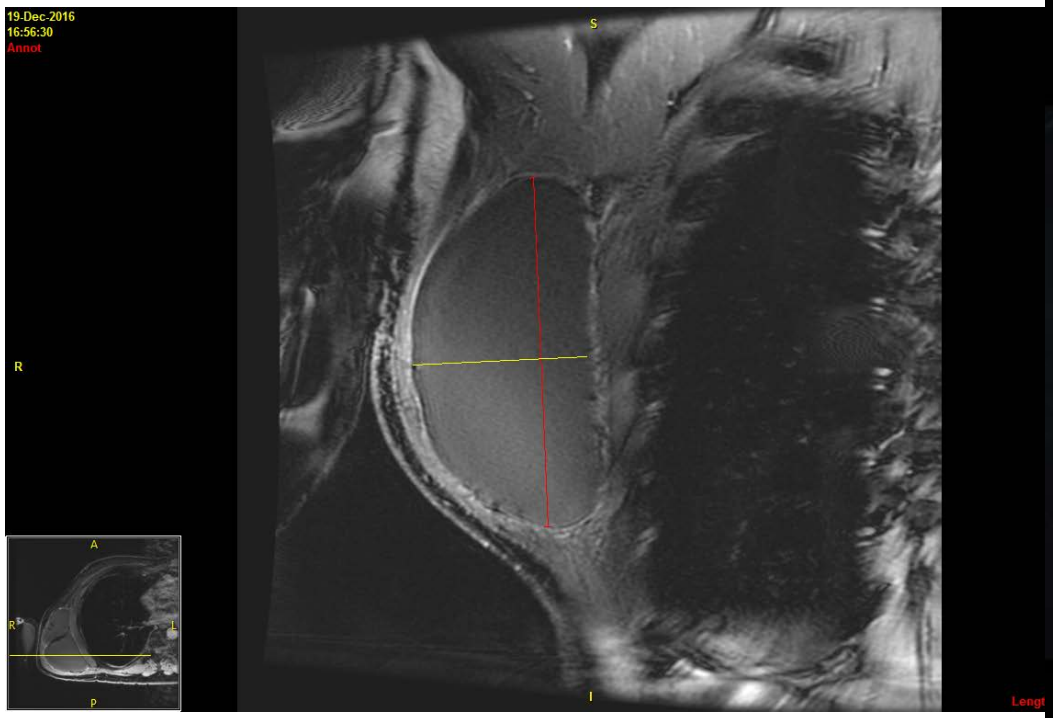
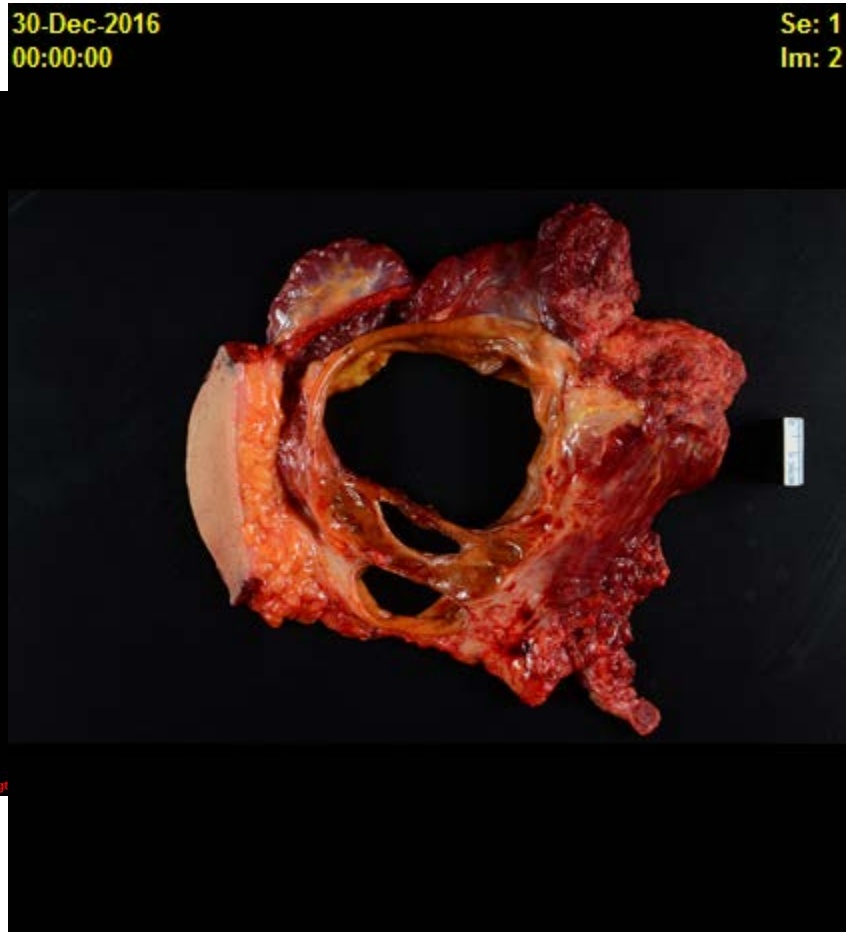
JG Progression?





Dec 19, 2016
13 x 6.4 cm after
XRT and Chemo

Dec 30, 2016
Rare Viable PUS

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DF 40 Year Old Female Lump in Right Arm: Summer 2016

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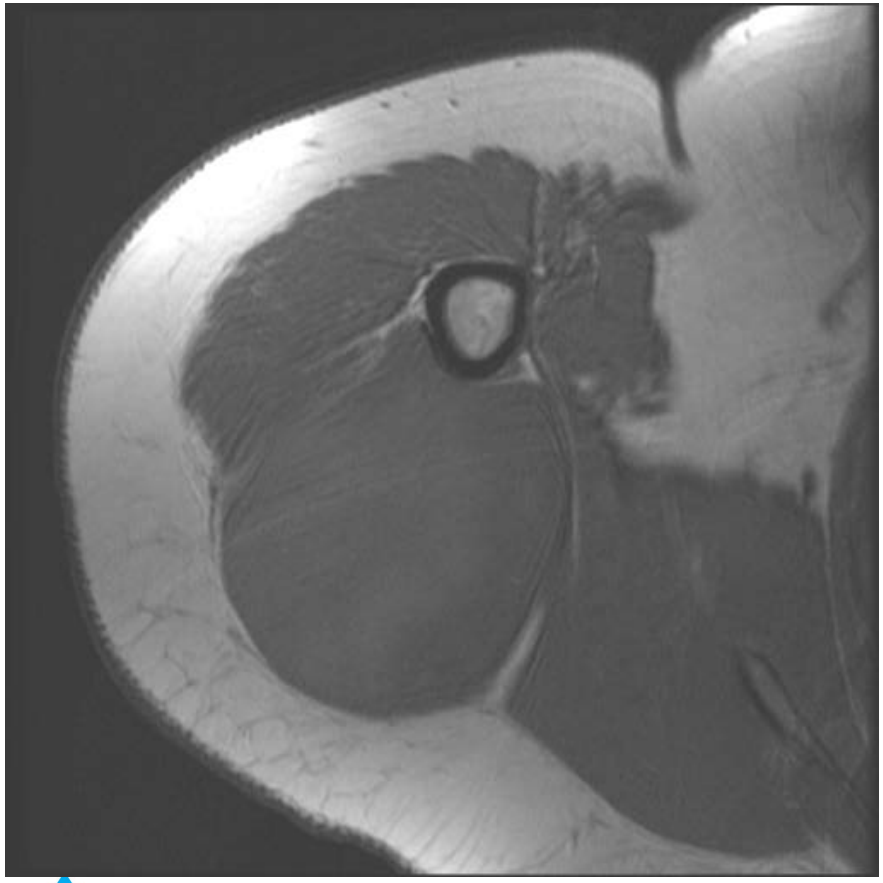
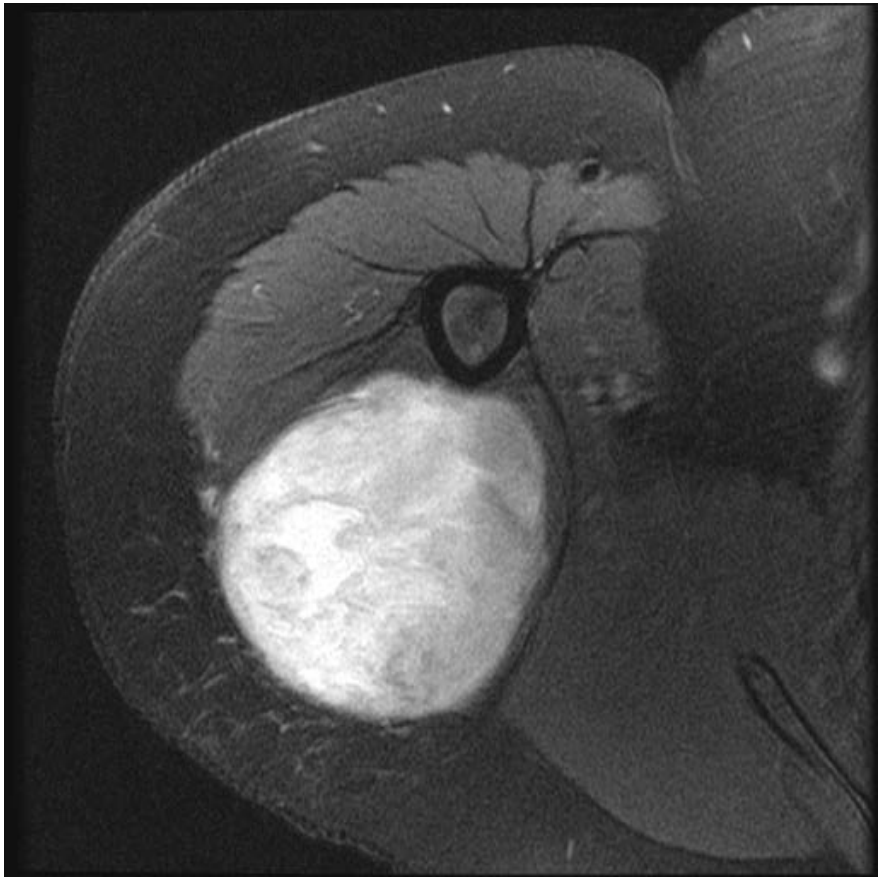
DF 40 Year Old Female 6.5 cm Lump in Right Arm: June 2016



T1



T2 FS

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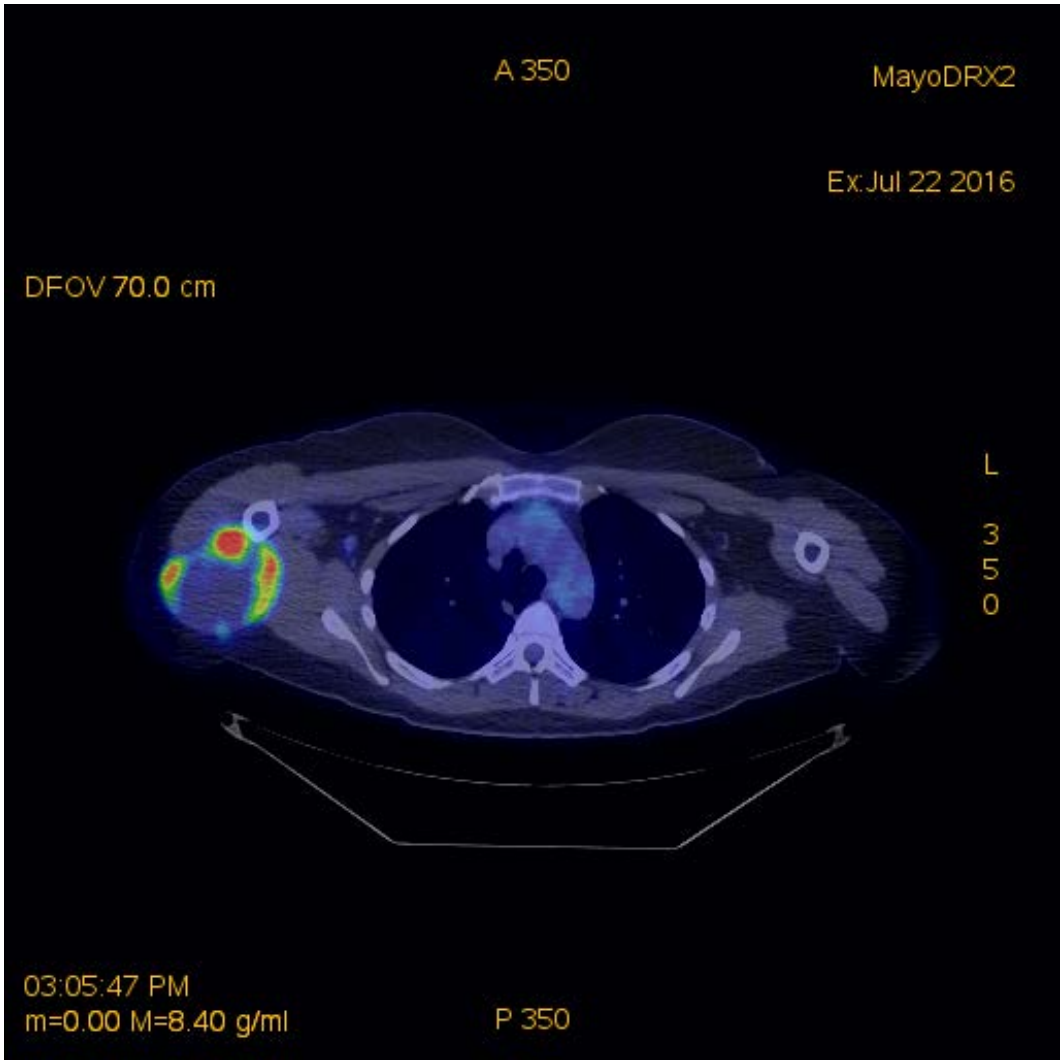
Extensively necrotic primitive round cell sarcoma, high grade FISH: EWSR1 and NR4A3 gene rearrangements are both negative



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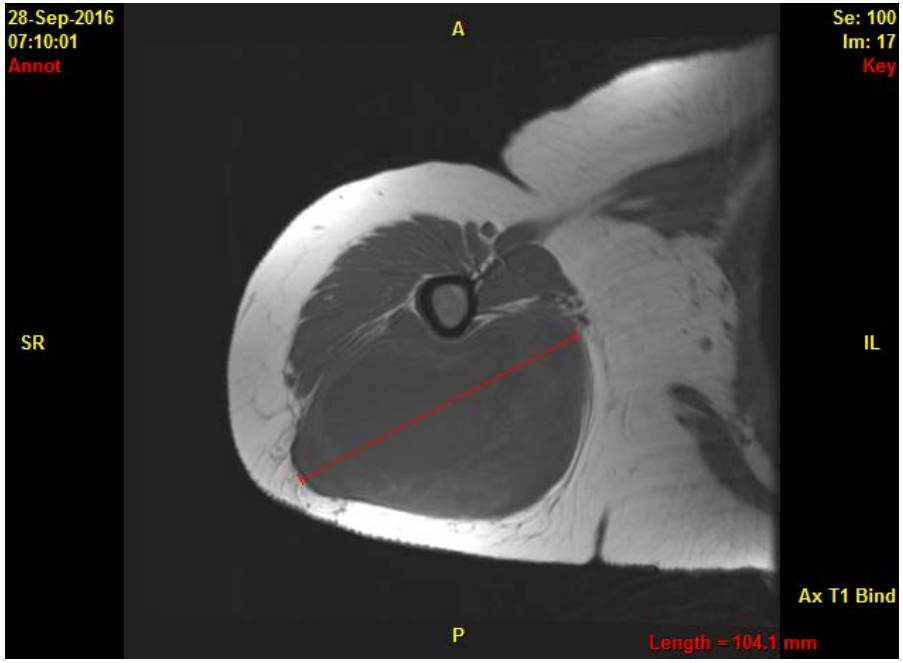
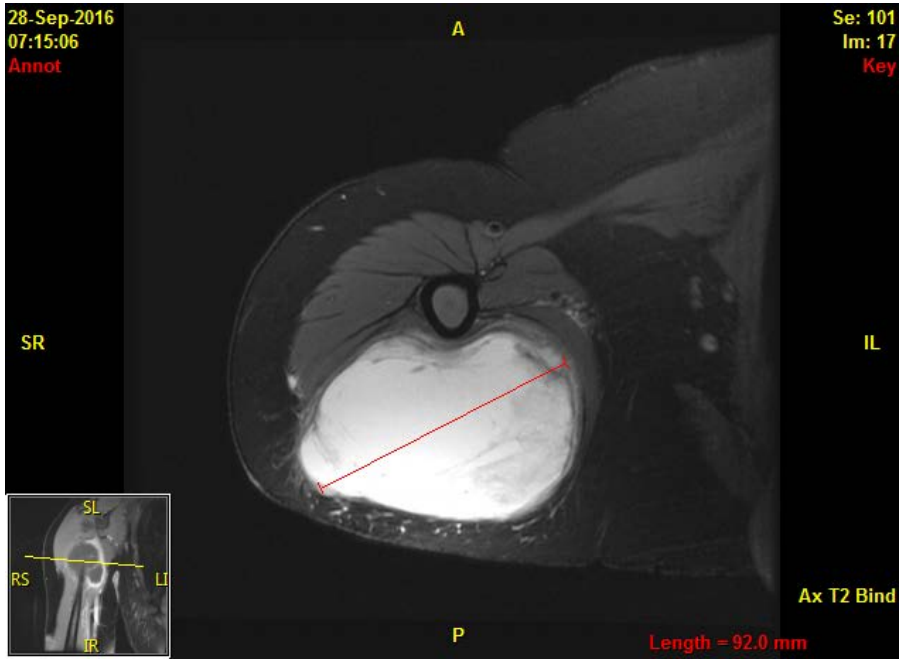
After 4 Cycles of CAV/IE Chemotherapy: Increasing Mass 10 cm. Is She Progressing?



T1



T2 with FS

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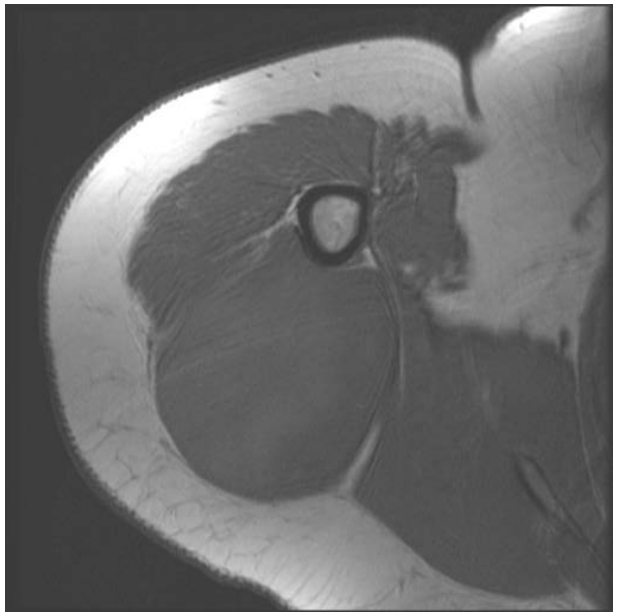
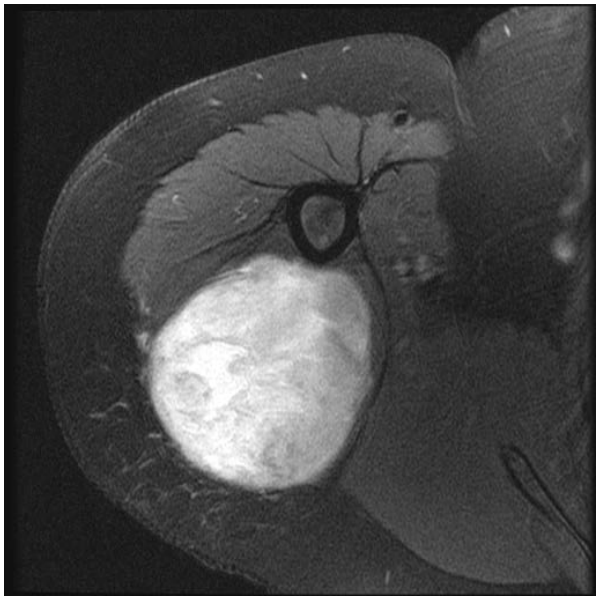
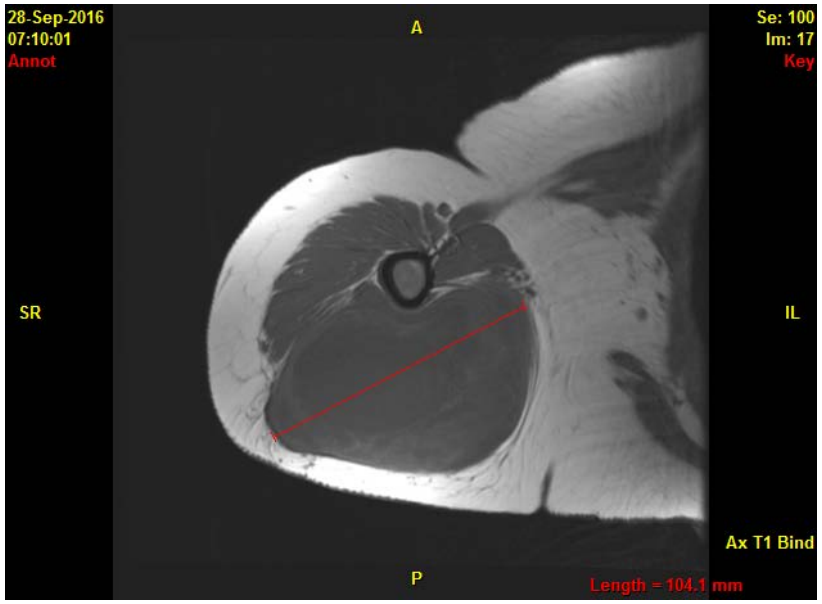
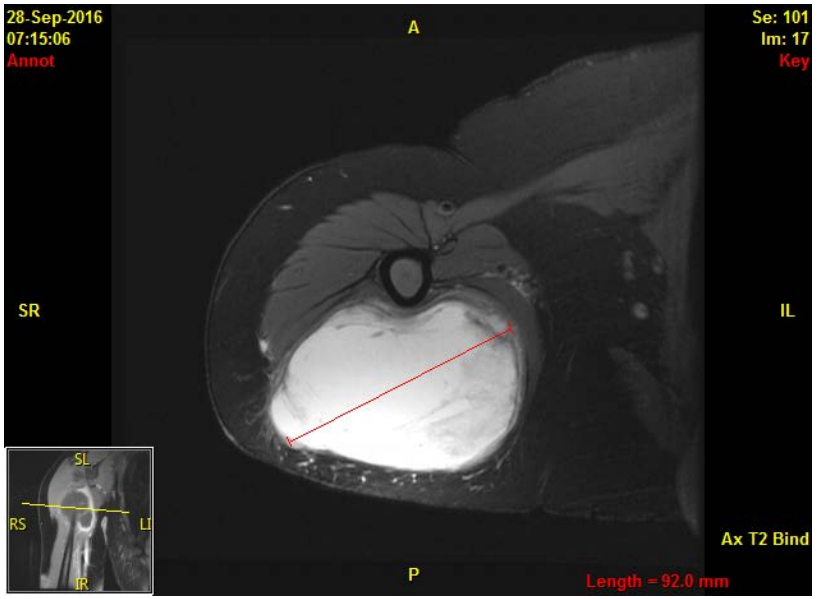


Pre Chemo

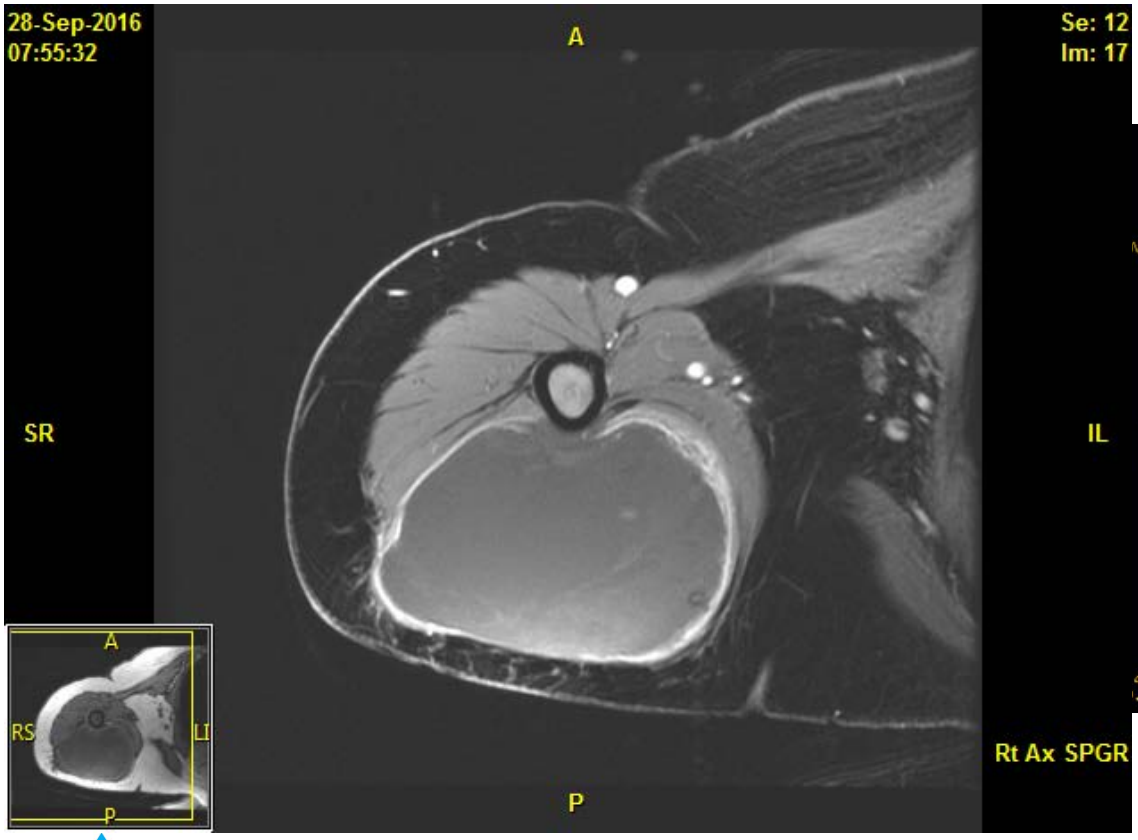


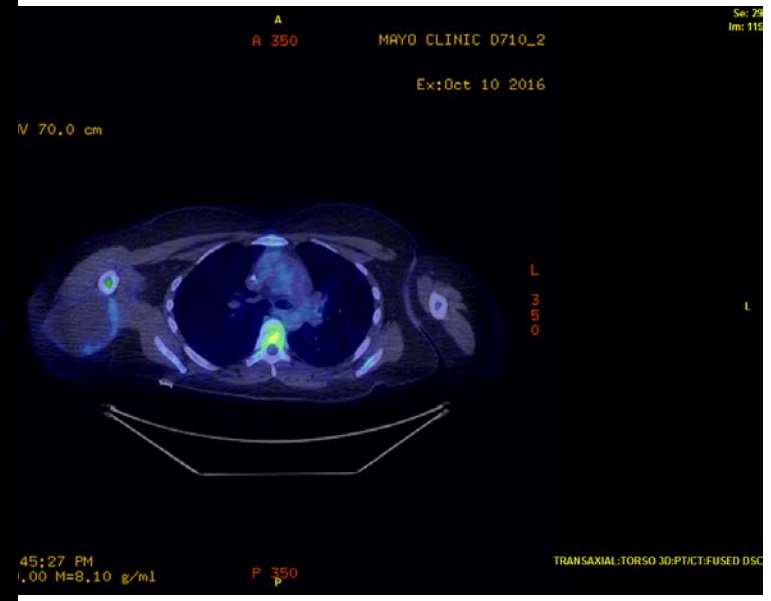


Post Chemo



After 4 Cycles of CAV/IE Chemotherapy





T1 FS with GAD

PET

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Open Alliance Sarcoma Trials

- A091304: A Phase II study of MLN0128 vs. pazopanib in patients with locally advanced/unresectable and/or metastatic sarcoma
  - MLN0128 is a selective and highly potent ATP competitor mTORC1 and mTORC2
  - PFS is primary endpoint
  - Histologies: UPS, MFH, MFS,HGNOS, LMS,SS,MPNST

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Open Alliance Sarcoma Trials

- A091202: A phase II study of the peroxisome proliferator-activated receptor gamma agonist, efatutazone in patients with previously treated, unresectable myxoid liposarcoma
  - Primary endpoint confirmed response rate

(Per RECIST 1.1: Confirmed response = 2 consecutive responses at least 4 weeks apart)

  - Histology: Myxoid liposarcoma

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Alliance Sarcoma Trials Closed to Accrual

- A091105: A phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors or aggressive fibromatosis (DT/DF)
  - Primary endpoint: Progression Free Survival Rate between Sorafenib vs placebo
  - Histology: Desmoid
  - Elig: Progression by radiographic imaging (10% increase in size by RECIST v1.1 within 6 months of registration)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Alliance Sarcoma Trials Closed to Accrual

- A09140: Randomized phase II study of nivolumab with or without ipilimumab in patient with metastatic or unresectable sarcoma
  - Primary endpoint is confirmed response
  - Can continue despite progression
  - At cross over, new baseline measurements
  - Histologies: Bone or Soft Tissue

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Conclusions

- Sarcoma is not just one type
- Imaging of sarcoma is mainly MRI and CT
- Response evaluation of sarcoma to treatment is challenging
- Alliance sarcoma trials open and closed to accrual the importance of imaging and histology

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Questions:

OKUNO.SCOTT@MAYO.EDU

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