Leiomyosarcoma: the disease

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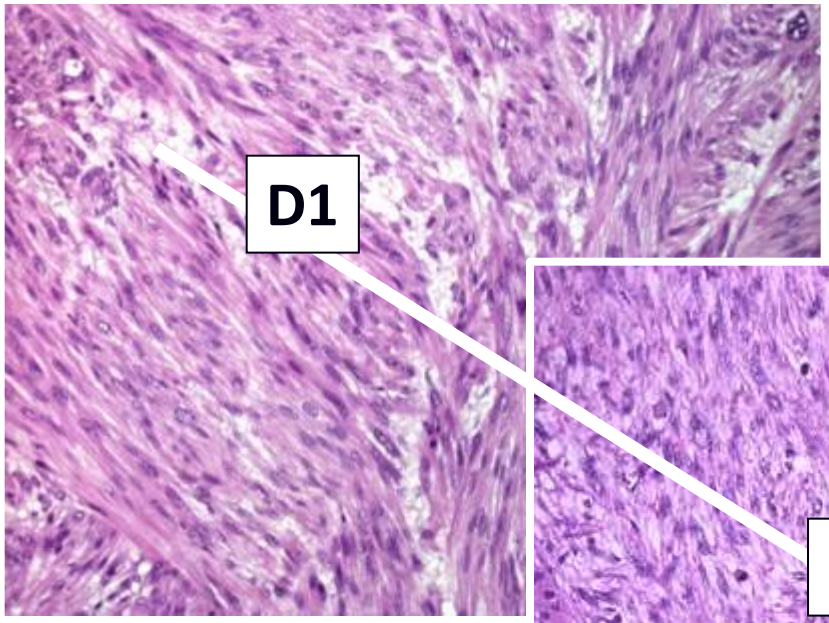
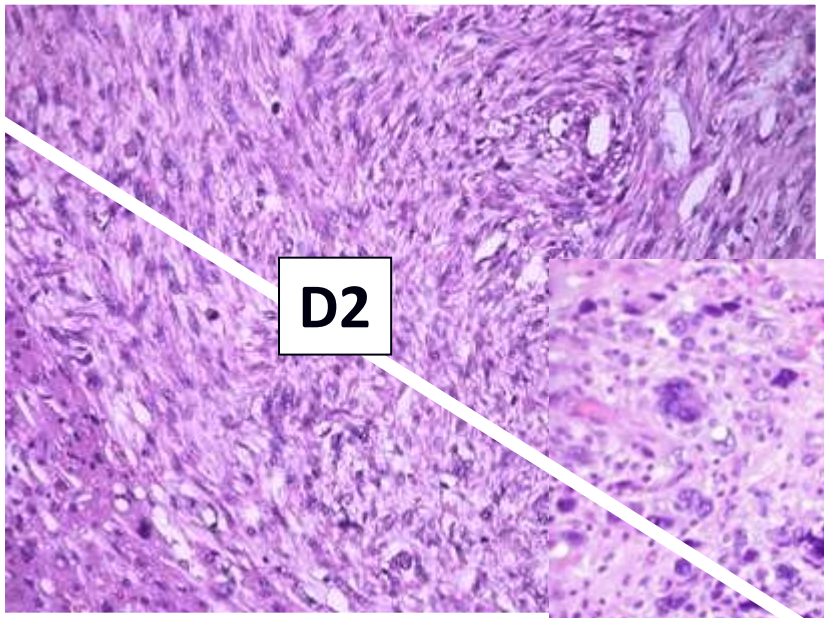
Definition

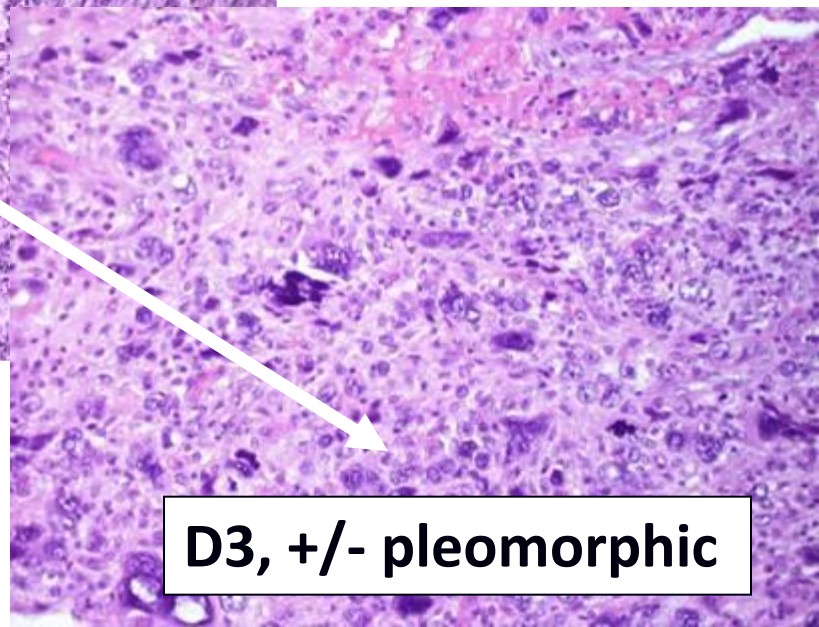
- Spindle cell and/or pleomorphic neoplasm featuring eosinophilic fibrillary cytoplasm, blunt ended nuclei, and variable expression of 2 or more smooth muscle markers (SMA, h-caldesmon and desmin)

LEIOMYOSARCOMA



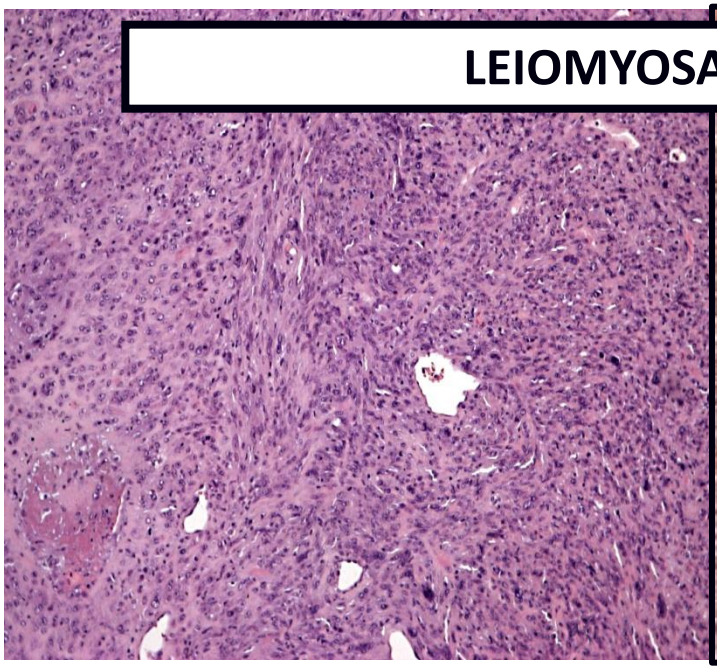
The most differentiated form

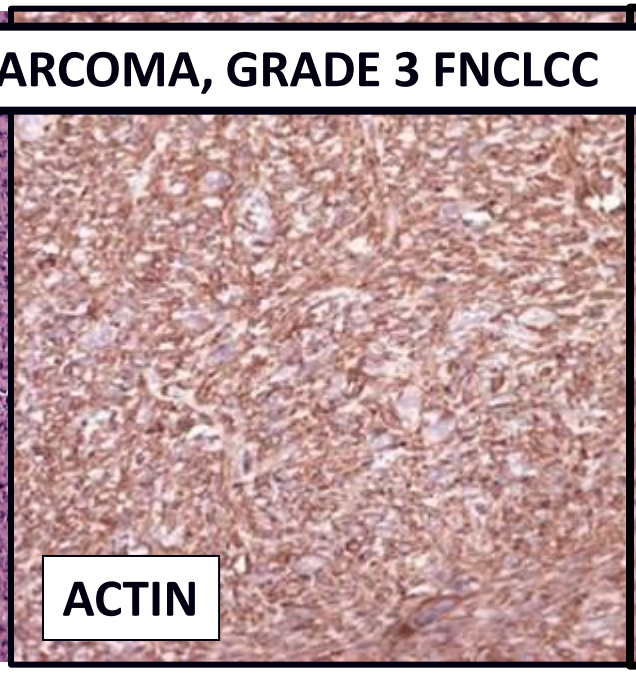


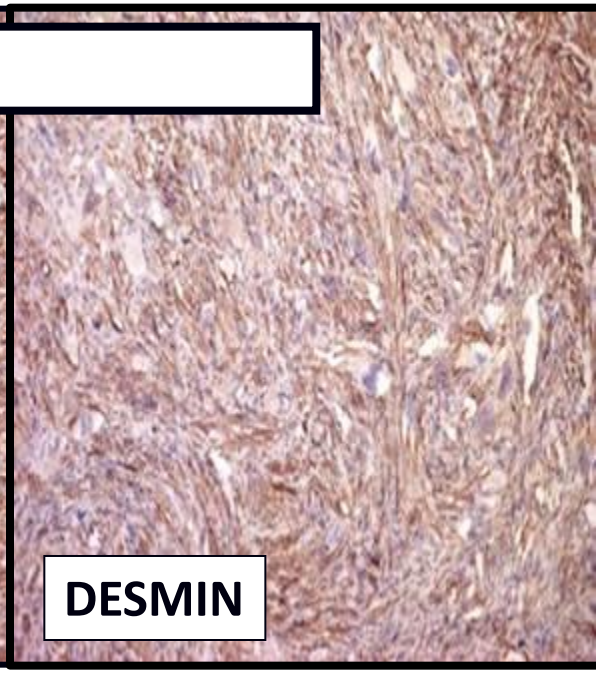


The least differentiated form

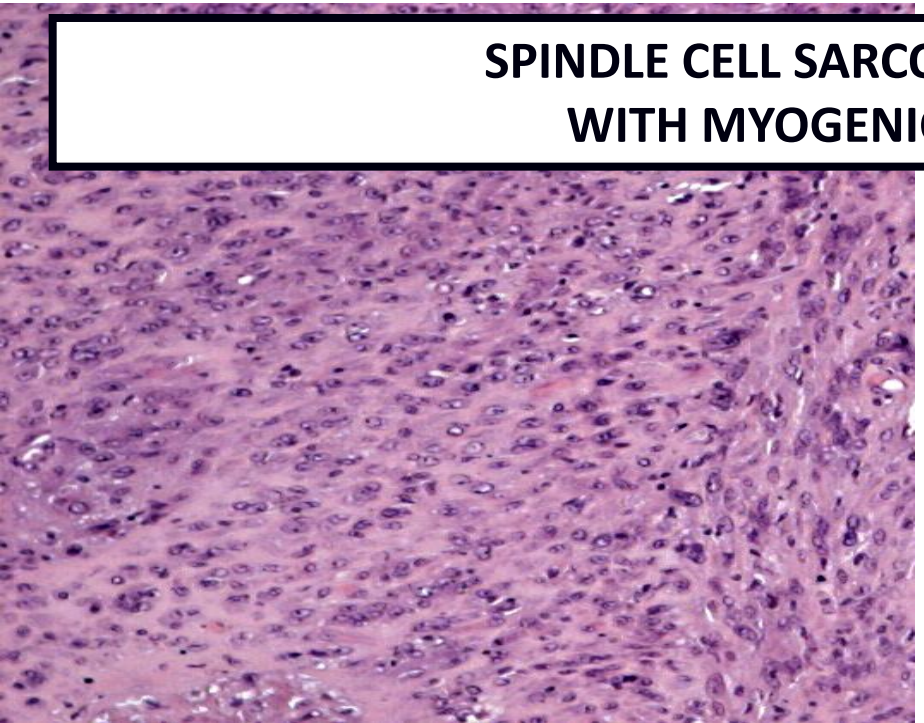
LEIOMYOSARCOMA, GRADE 3 FNCLCC

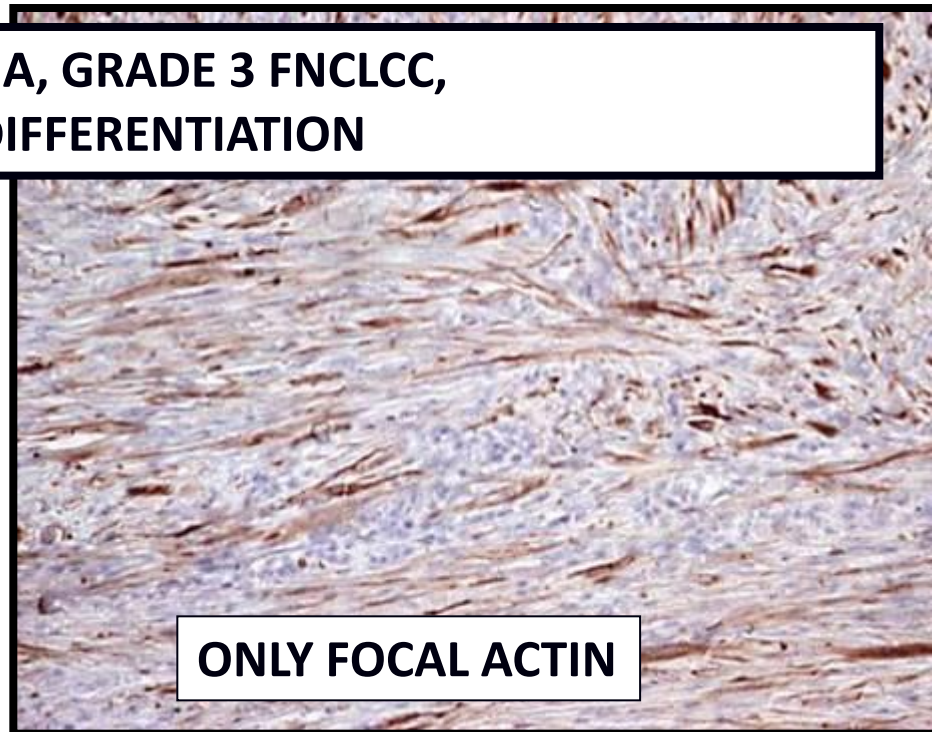


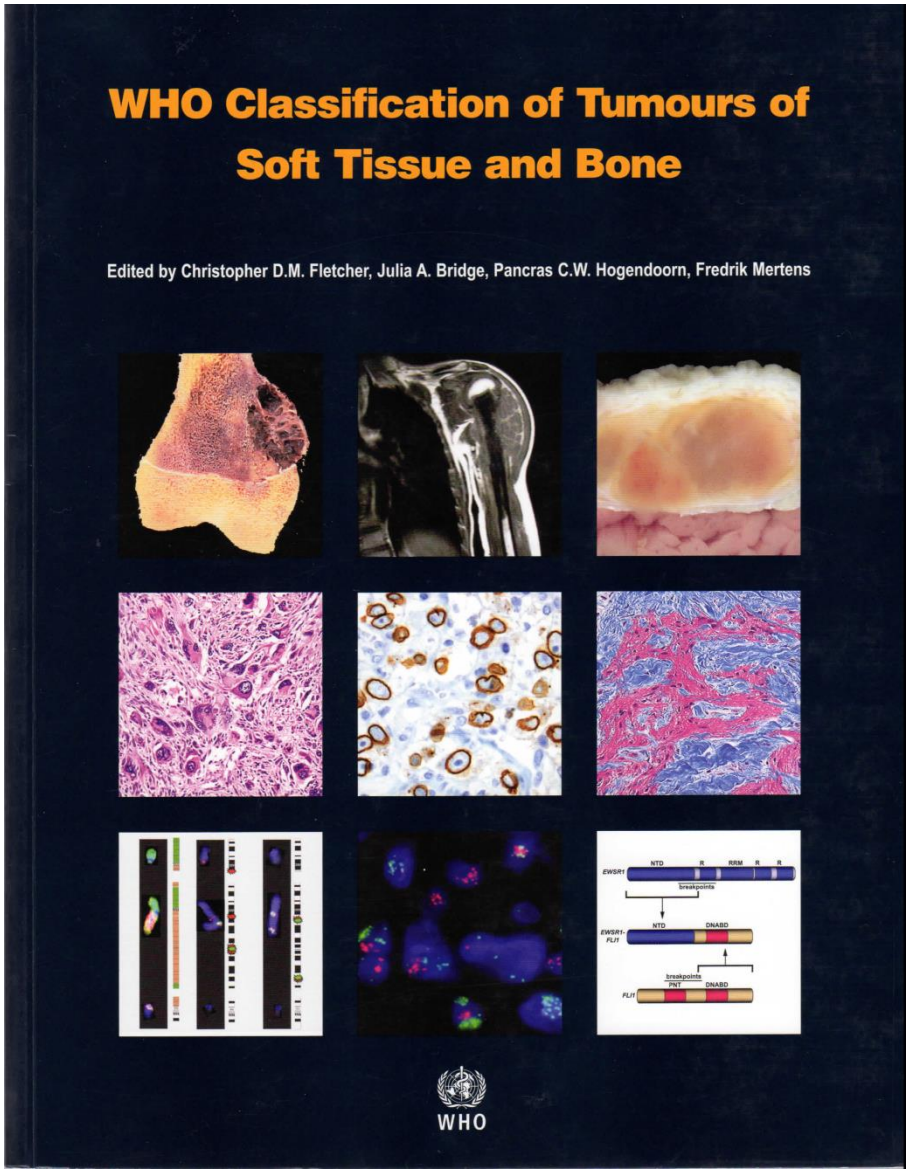




SPINDLE CELL SARCOMA, GRADE 3 FNCLCC, WITH MYOGENIC DIFFERENTIATION







Leiomyosarcoma

A. Lazar
H.L. Evans
J. Shipley

Definition
Leiomyosarcoma is a malignant neoplasm showing pure smooth-muscle differentiation.

ICD-O code 8890/3

Epidemiology
Soft tissue leiomyosarcoma usually occurs in middle-aged or older persons, although it may develop in young adults and even in children {605}. Leiomyosarcoma forms a significant percentage of retroperitoneal (including pelvic) sarcomas {1129,2289,2547,2964} and is the predominant sarcoma arising from larger blood vessels {194,1404,1549,1596,2856}. Aside from these locations, it is less common, accounting for 10–15% of limb sarcomas {1752}.
Women constitute the clear majority of patients with retroperitoneal and inferior vena cava leiomyosarcomas, but not among patients with tumours at other sites.

Sites of involvement
The most common location of soft tissue leiomyosarcoma is the retroperitoneum, including the pelvis. Another distinctive subgroup arises in large blood vessels, most commonly the inferior vena cava, its major tributaries, and the large veins of the lower extremity. Leiomyosarcomas involving nonretroperitoneal soft tissue sites constitute a third group {541,761,817, 1127,2663}. These are found most frequently in the lower extremity, but may develop elsewhere. Tumours occur at intramuscular and subcutaneous localizations in approximately equal proportions, and some originate from a small to medium-sized vein.

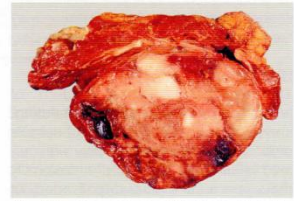


Fig. 5.03 Leiomyosarcoma. This high-grade lesion (19 cm) from the quadriceps muscle shows extensive necrosis and haemorrhage.

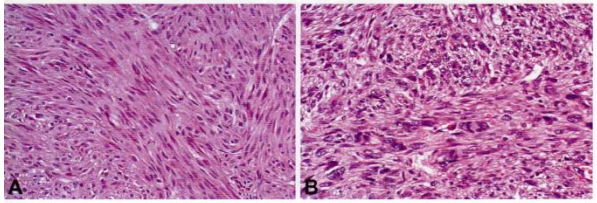


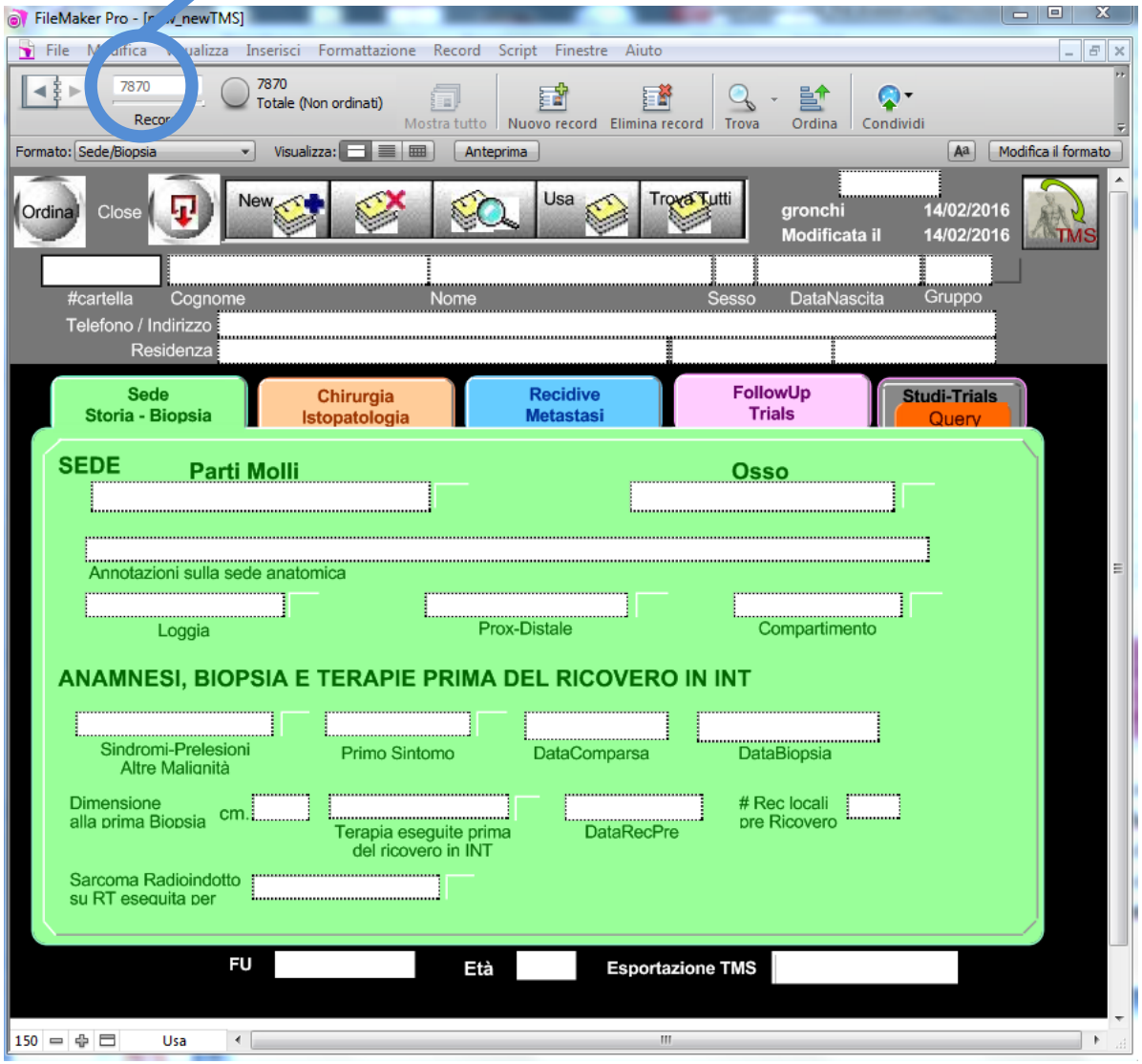
Fig. 5.04 Leiomyosarcoma. **A** This lesion shows distinctively well-differentiated histology. **B** Moderately differentiated features can be seen in this example.

Clinical features
Leiomyosarcoma of the soft tissue generally presents as a mass lesion. Retroperitoneal tumours may be painful. The symptoms produced by leiomyosarcoma of the inferior vena cava depend on the portion involved. In the upper portion, it obstructs the hepatic veins and can evince Budd-Chiari syndrome, with hepatomegaly, jaundice, and ascites. Location in the middle portion may result in blockage of the renal veins and consequent renal dysfunction, while involvement of the lower portion may cause leg oedema. Imaging studies of leiomyosarcoma are nonspecific, but helpful in delineating the relationship to adjacent structures, particularly in the retroperitoneum.

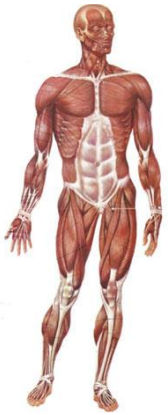
Macroscopy
Leiomyosarcoma of soft tissue typically

Most common location is the **retroperitoneum/pelvis**, followed by **large blood vessels** (IVC and large vein of the lower extremities) and non retroperitoneal soft tissues (mainly **extremties**)

7870 pts



- 2788 pts affected by primary STS since 2000
- 252 primary LMS



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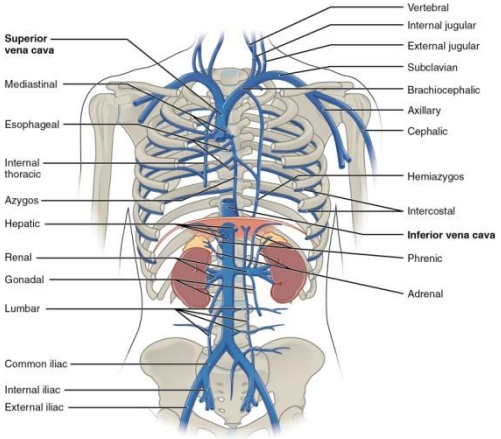
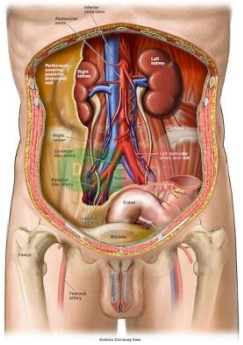
8%



22%



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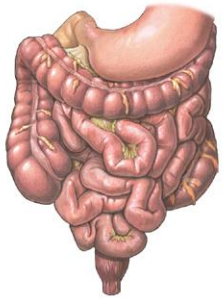

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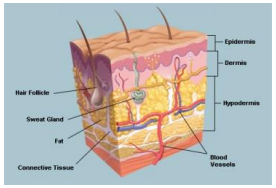

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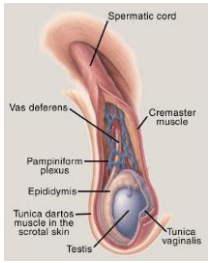
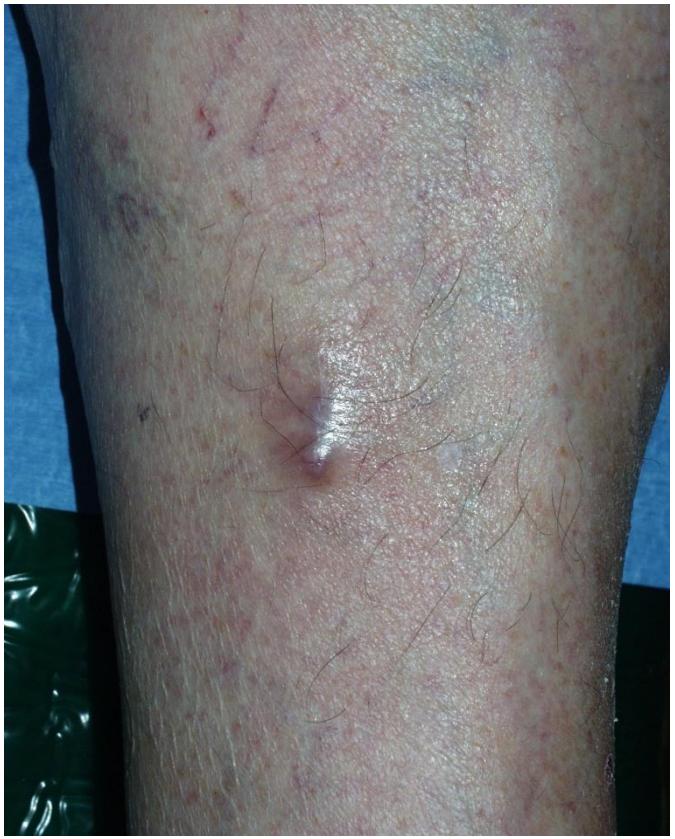
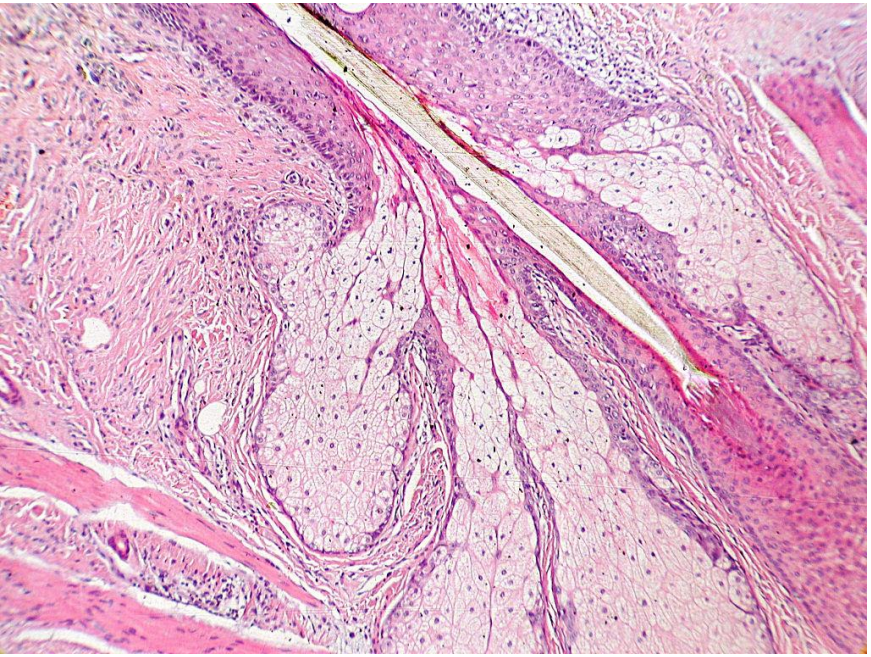
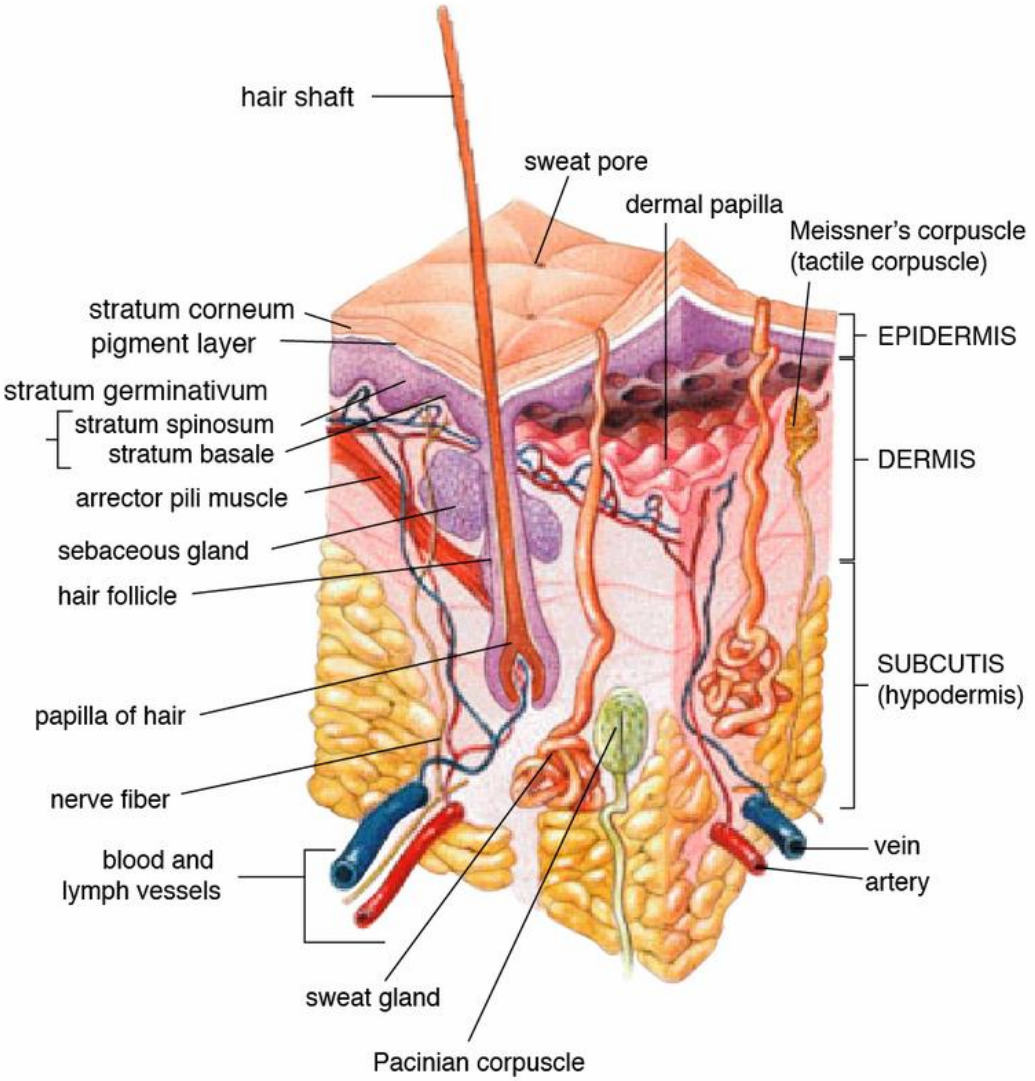


3%

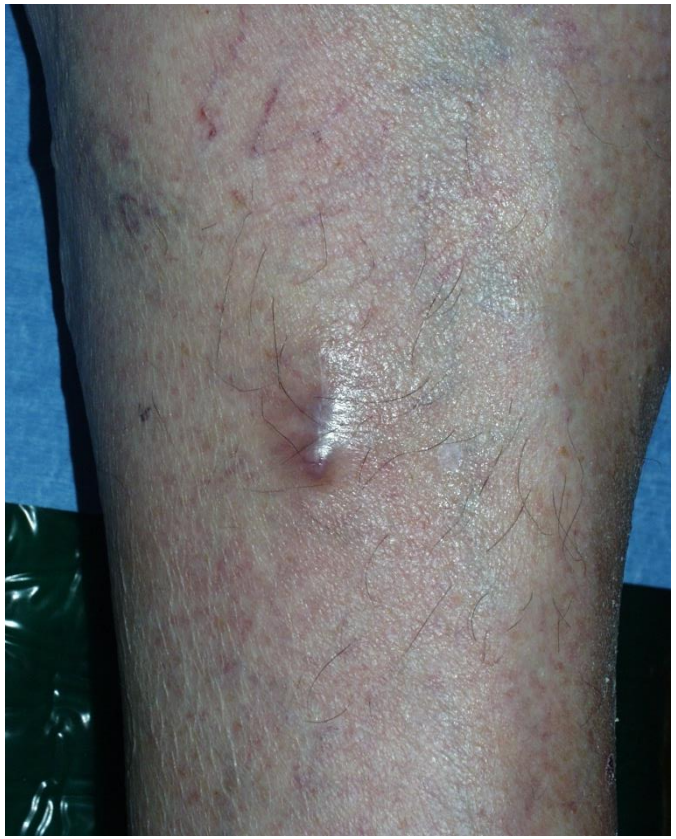
Skin LMS (10%)





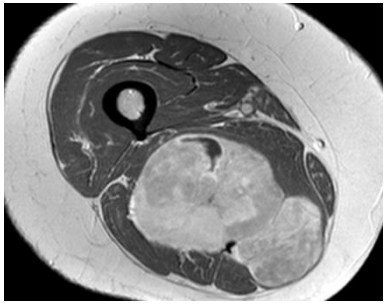

hair shaft
sweat pore
dermal papilla
Meissner's corpuscle
(tactile corpuscle)
stratum corneum
pigment layer
stratum germinativum
stratum spinosum
stratum basale
arrector pili muscle
sebaceous gland
hair follicle
papilla of hair
nerve fiber
blood and
lymph vessels
sweat gland
Pacinian corpuscle
EPIDERMIS
DERMIS
SUBCUTIS
(hypodermis)
vein
artery

Skin LMS (10%)

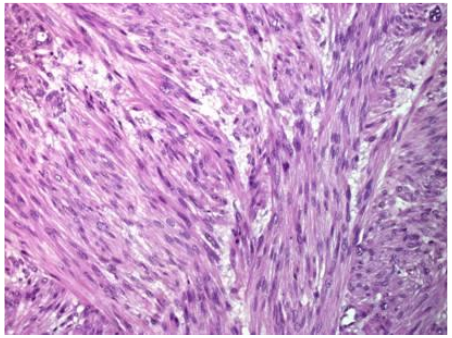


- Predominantly
  - Grade 1
  - < 5 cm (median 2)
- High cure rate

Extremity/Trunk LMS (52%)



33%



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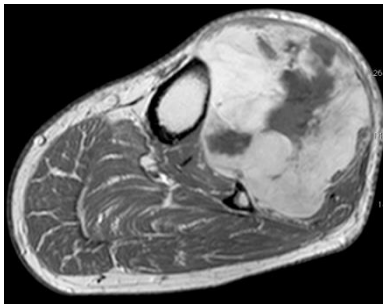

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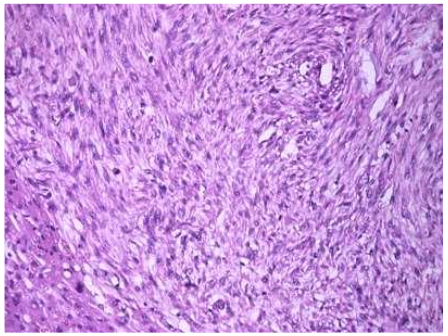

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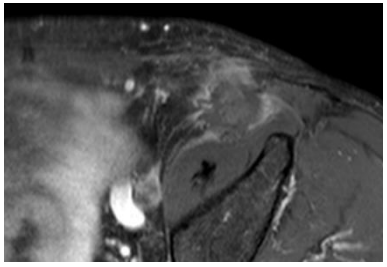

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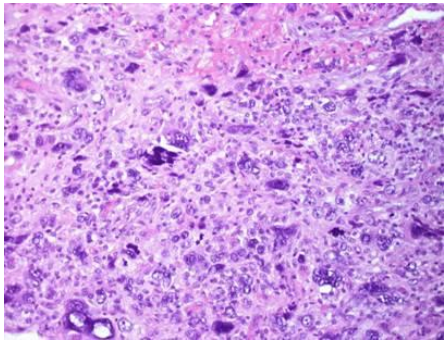


57%

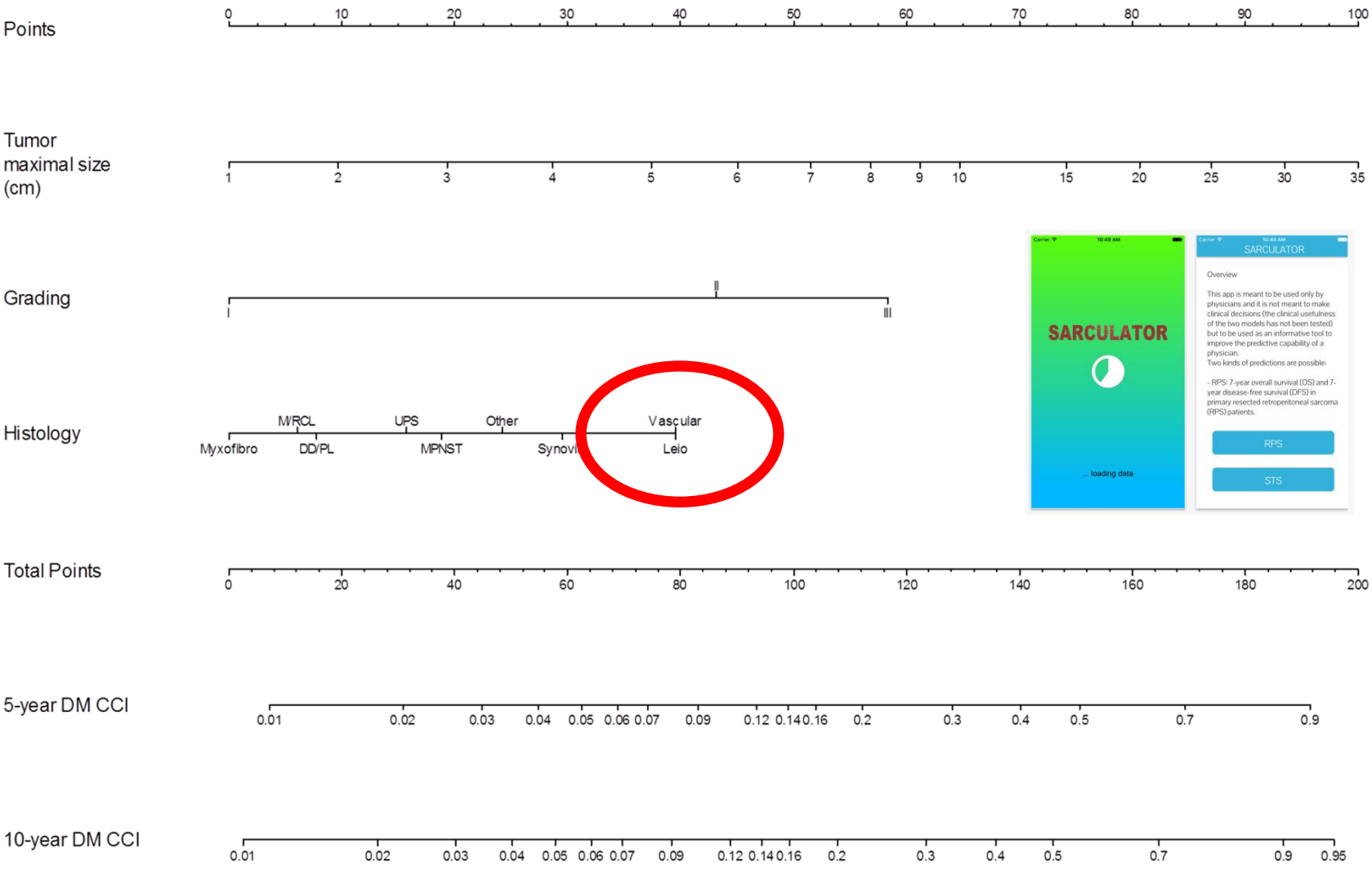
Clinical Cancer Research

Genetic Profiling Identifies Two Classes of Soft-Tissue Leiomyosarcomas with Distinct Clinical Characteristics

Antoine Italiano[1], Pauline Lagarde[3], Céline Brulard[3], Philippe Terrier[4], Marick Laë[7], Bernard Marques[9], Dominique Ranchere-Vince[11], Jean-Jacques Michels[13], Martine Trassard[15], Angela Cioffi[5], Sophie Piperno-Neumann[8], Christine Chevreau[10], Jean-Yves Blay[12], Corinne Delcambre[14], Nicolas Isambert[16], Nicolas Penel[17], Jacques-Olivier Bay[18], Sylvie Bonvalot[6], Axel Le Cesne[5], Jean-Michel Coindre[2,3], and Frédéric Chibon[2,3]

	MFS		OS	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y				
<60	— (—)	NS	1.0 (—)	<0.0001
≥60			1.7 (1.3–2.3)	
Tumor site				
Limb	1.0 (—)	0.01	— (—)	NS
Trunk wall	0.6 (0.3–1)			
Head and neck	1.0 (0.4–2.4)			
Internal trunk	1.4 (1.1–2)			
Tumor size, cm				
<5	1.0 (—)	0.04	1.0 (—)	0.007
≥5	1.4 (1.1–2)		1.7 (1.1–2.5)	
Tumor location				
Superficial	1.0 (—)	0.001	1.0 (—)	0.02
Deep	2.6 (1.5–4.7)		2.0 (1.1–3.5)	
FNCLCC grade				
I	1.0 (—)	0.001	1.0 (—)	0.001
II	2.5 (1.2–5.2)		4.2 (1.3–13.5)	
III	3.5 (1.7–7.4)		6.2 (1.9–19.8)	

ESTS (and TRUNK) DM Nomogram



Clinical Cancer Research

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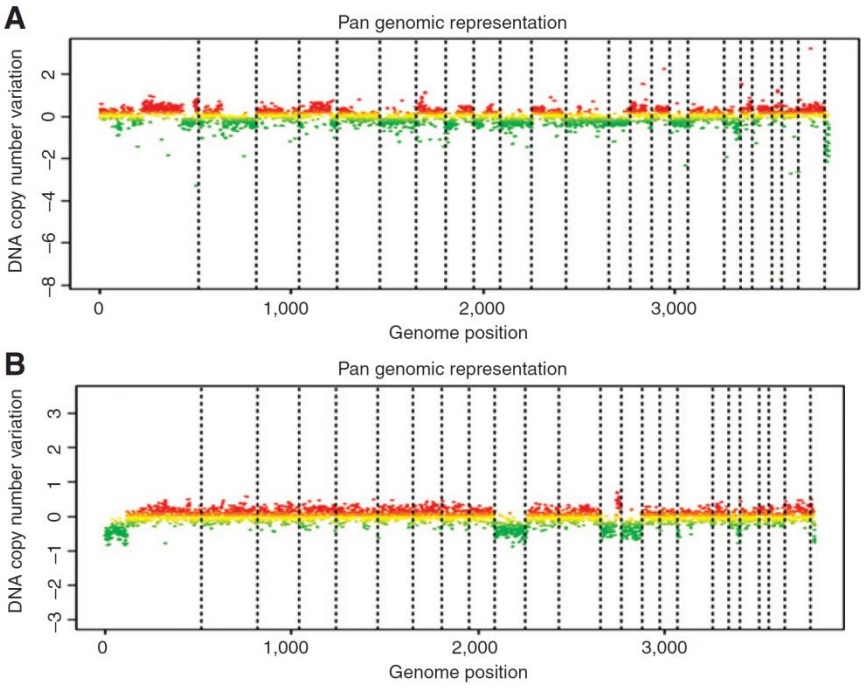
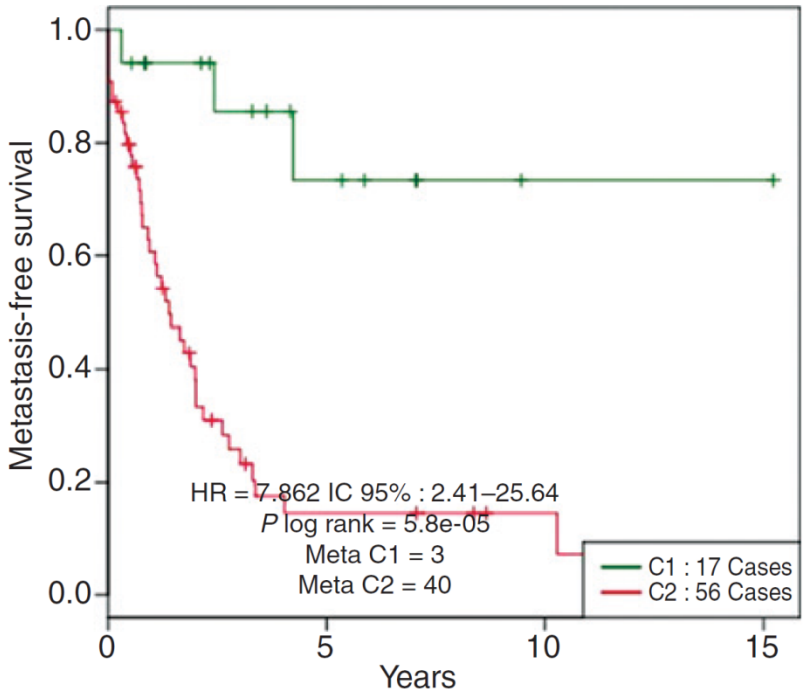
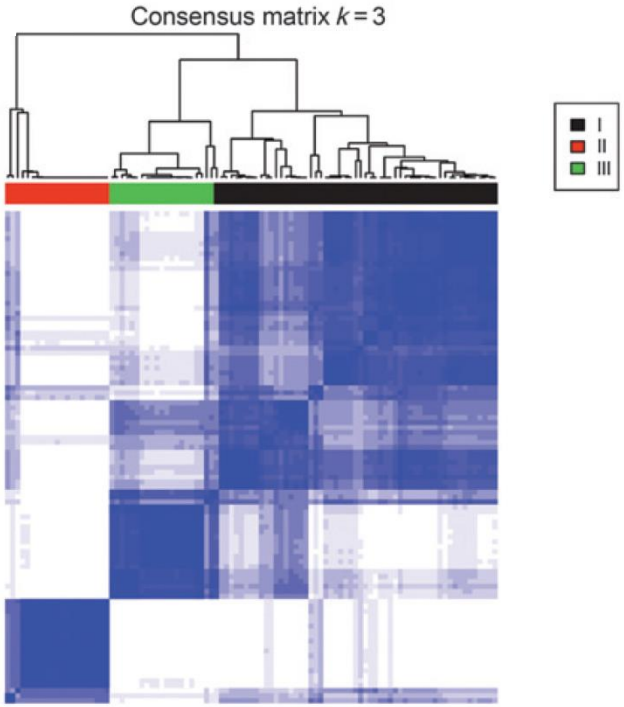


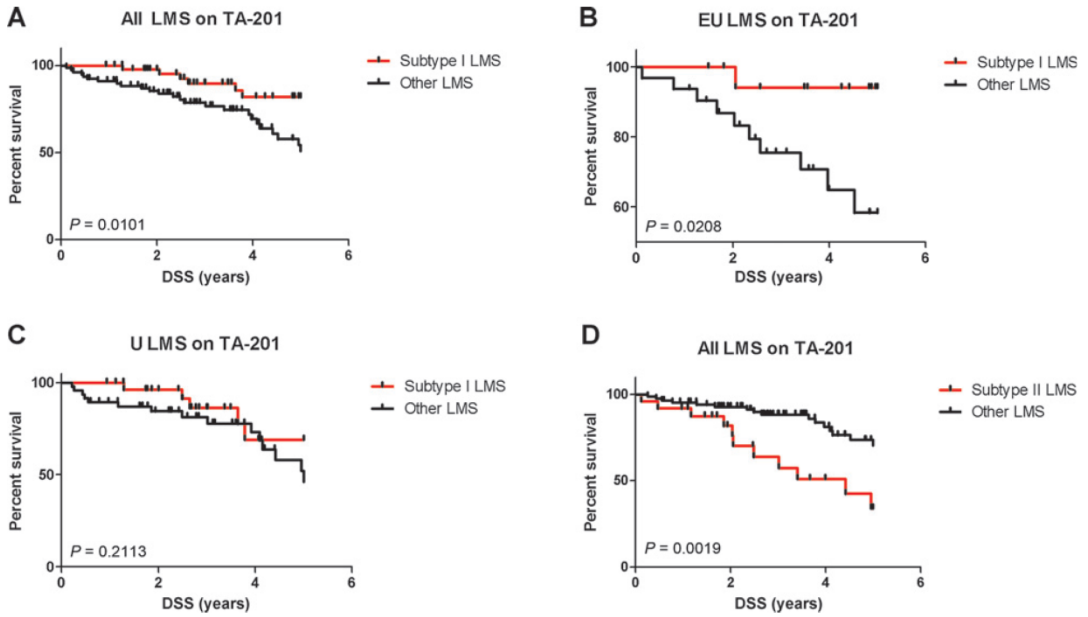


Clinical Cancer Research

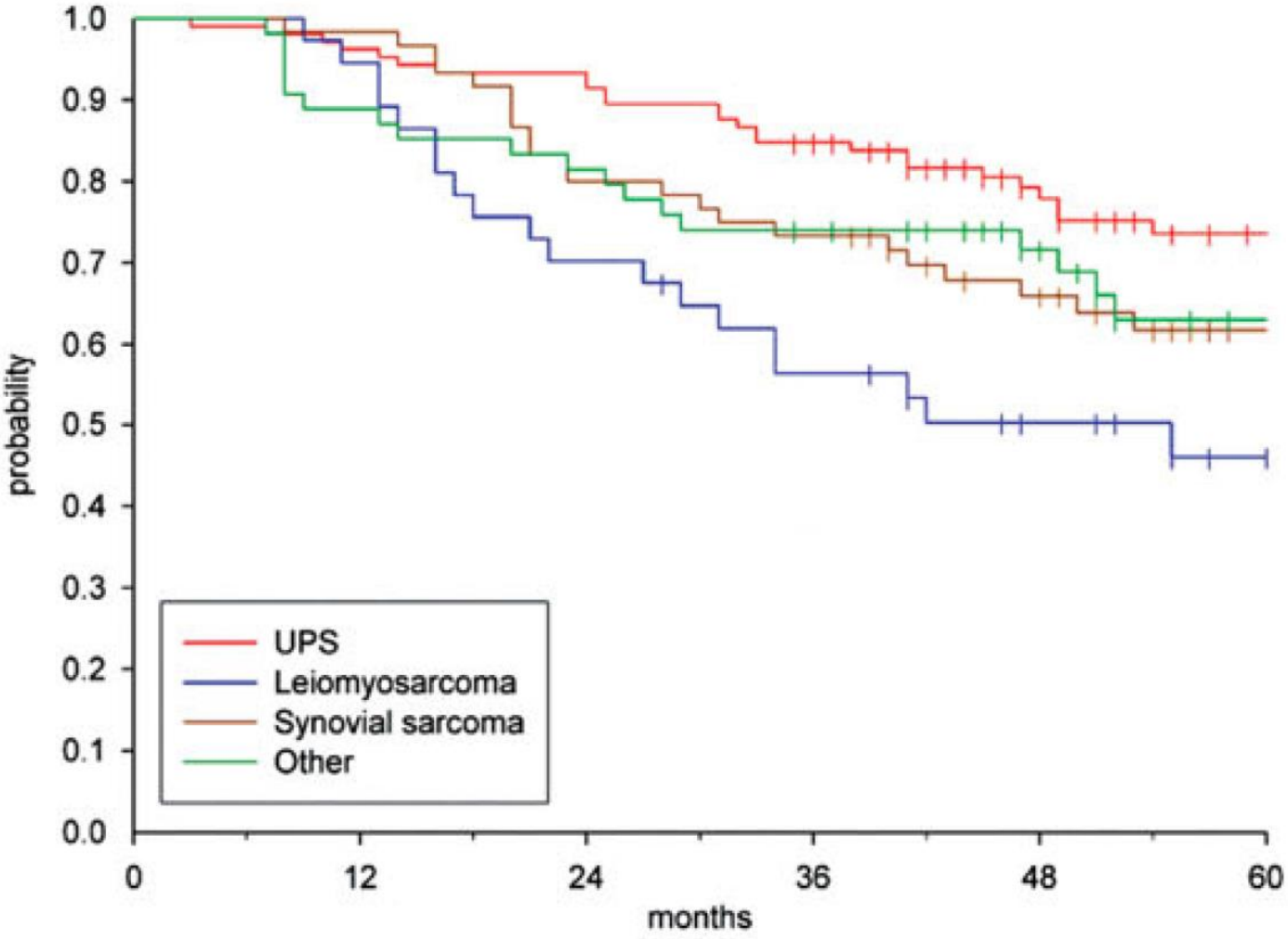
Clinically Relevant Molecular Subtypes in Leiomyosarcoma

Xiangqian Guo[1], Vickie Y. Jo[2], Anne M. Mills[3], Shirley X. Zhu[1], Cheng-Han Lee[4], Inigo Espinosa[5], Marisa R. Nucci[2], Sushama Varma[1], Erna Forgó[1], Trevor Hastie[6], Sharon Anderson[1], Kristen Ganjoo[7], Andrew H. Beck[8], Robert B. West[1], Christopher D. Fletcher[2], and Matt van de Rijn[1]

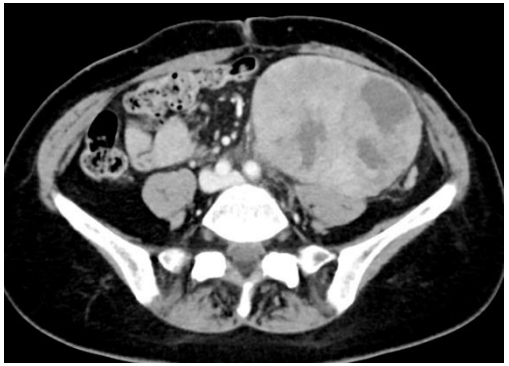




Clin Cancer Res; 21(15); 3501–11.


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
probability
UPS
Leiomyosarcoma
Synovial sarcoma
Other
0
12
24
36
48
60
months

Retroperitoneal/Pelvic LMS (30%)



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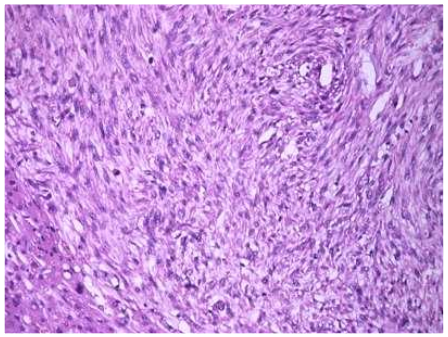

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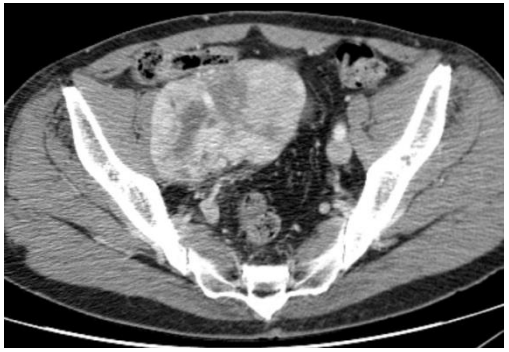

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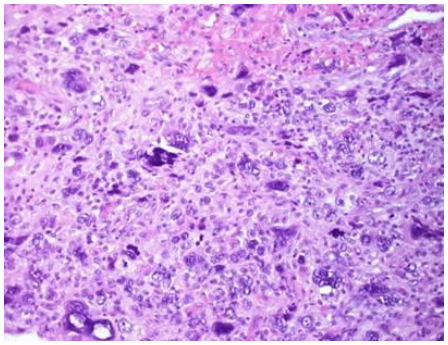
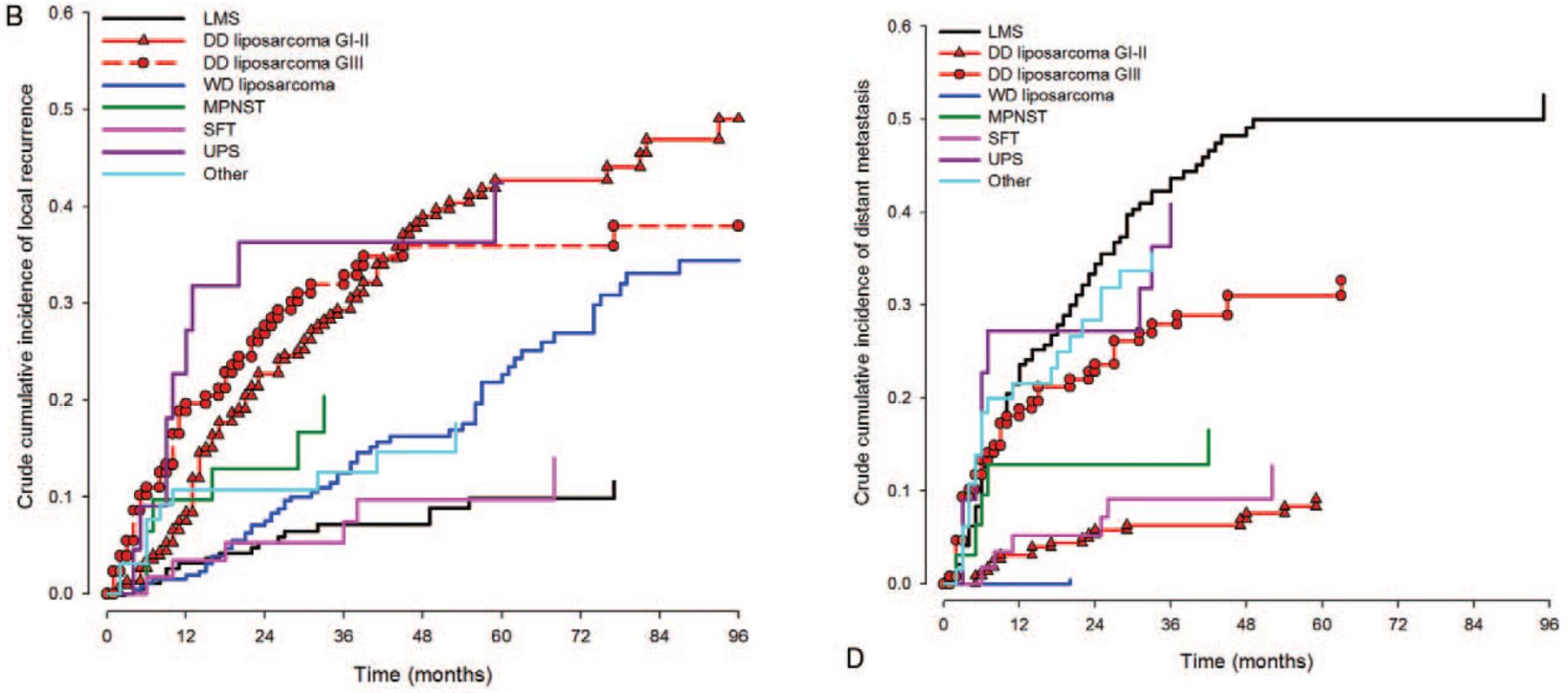


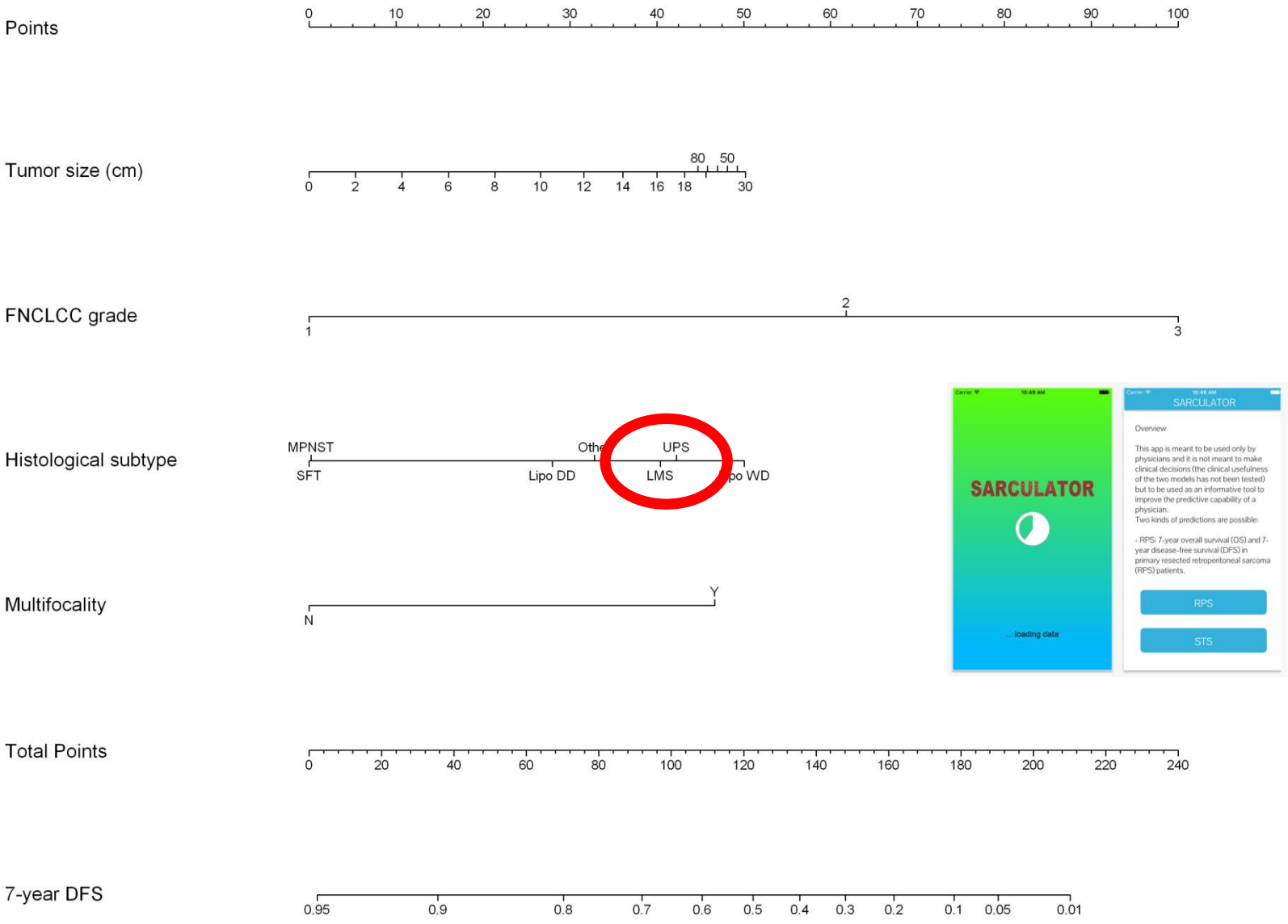
53%

Variability in Patterns of Recurrence After Resection of Primary Retroperitoneal Sarcoma (RPS)

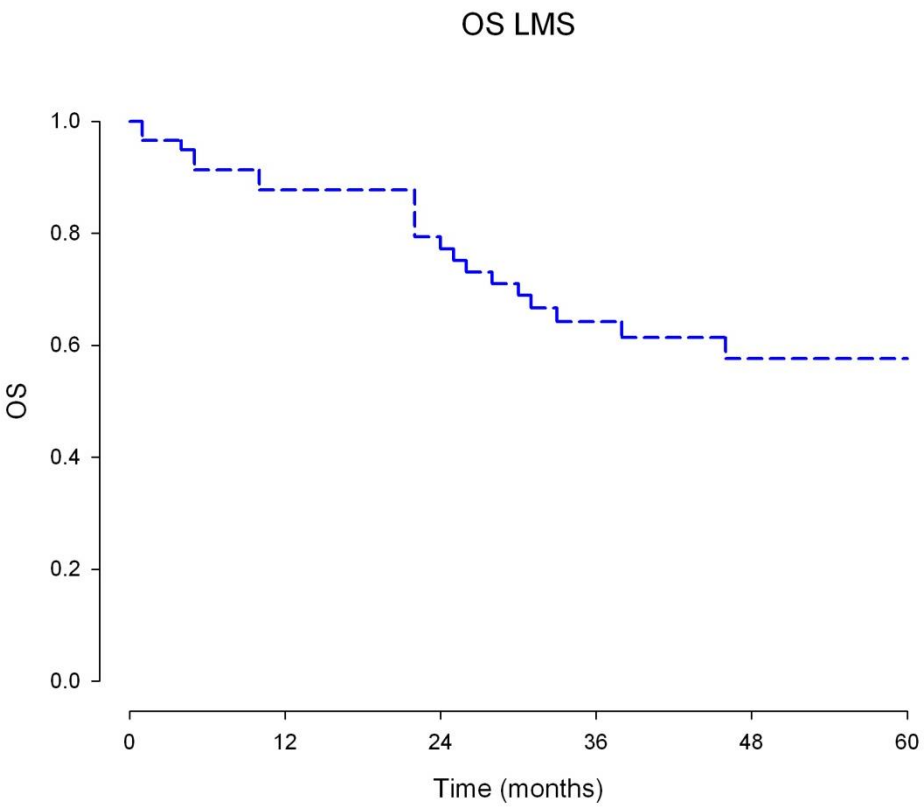
A Report on 1007 Patients From the Multi-institutional Collaborative RPS Working Group

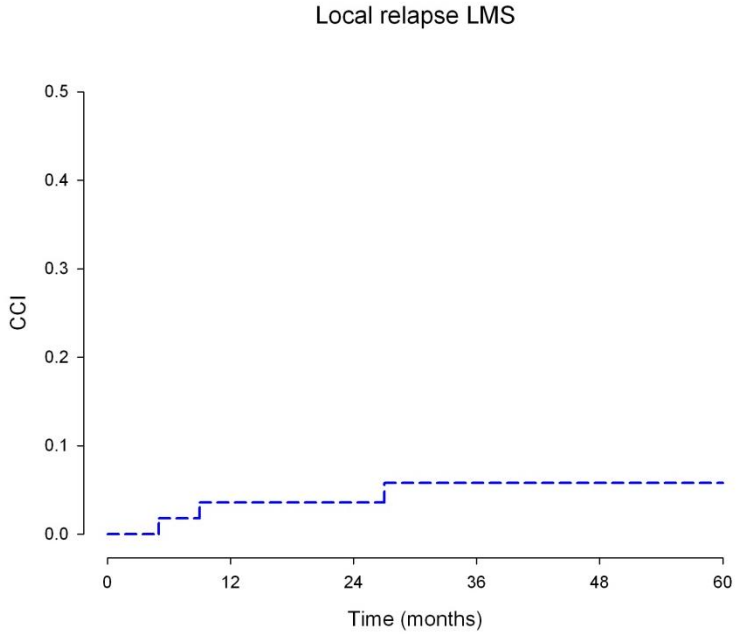
Alessandro Gronchi, MD, Dirk C. Strauss, MD,† Rosalba Miceli, MD, PhD,‡ Sylvie Bonvalot, MD, PhD,§ Carol J. Swallow, MD,¶ Peter Hohenberger, MD,|| Frits Van Coevorden, MD,** Piotr Rutkowsky, MD,†† Dario Callegaro, MD,* Andrew J. Hayes, MD, PhD,† Charles Honoré, MD,§ Mark Fairweather, MD,‡‡ Amanda Cannell, MD,¶ Jens Jakob, MD,|| Rick L. Haas, MD,§§ Milena Szacht, MD,†† Marco Fiore, MD,* Paolo G. Casali, MD,¶¶ Raphael E. Pollock, MD, PhD,|||| and Chandrajit P. Raut, MD‡‡*

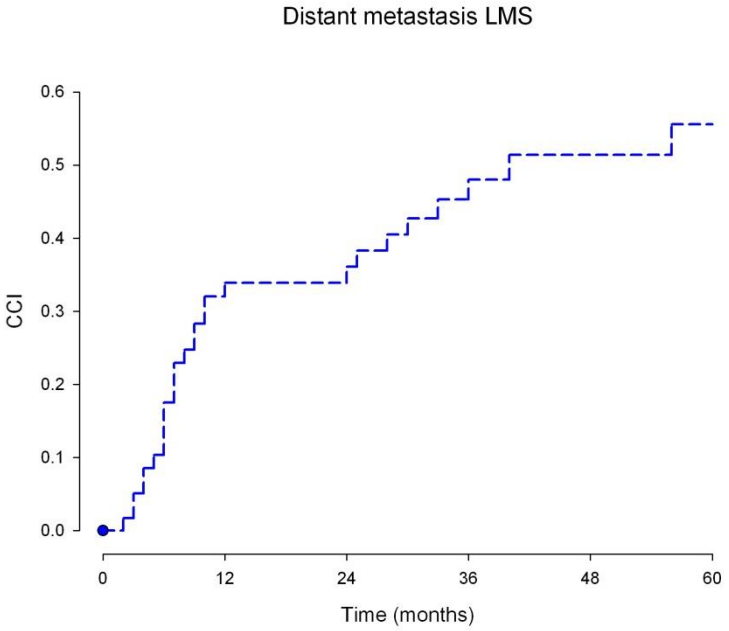




J Clin Oncol 2013; 31:1649


OS LMS
OS
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
Time (months)

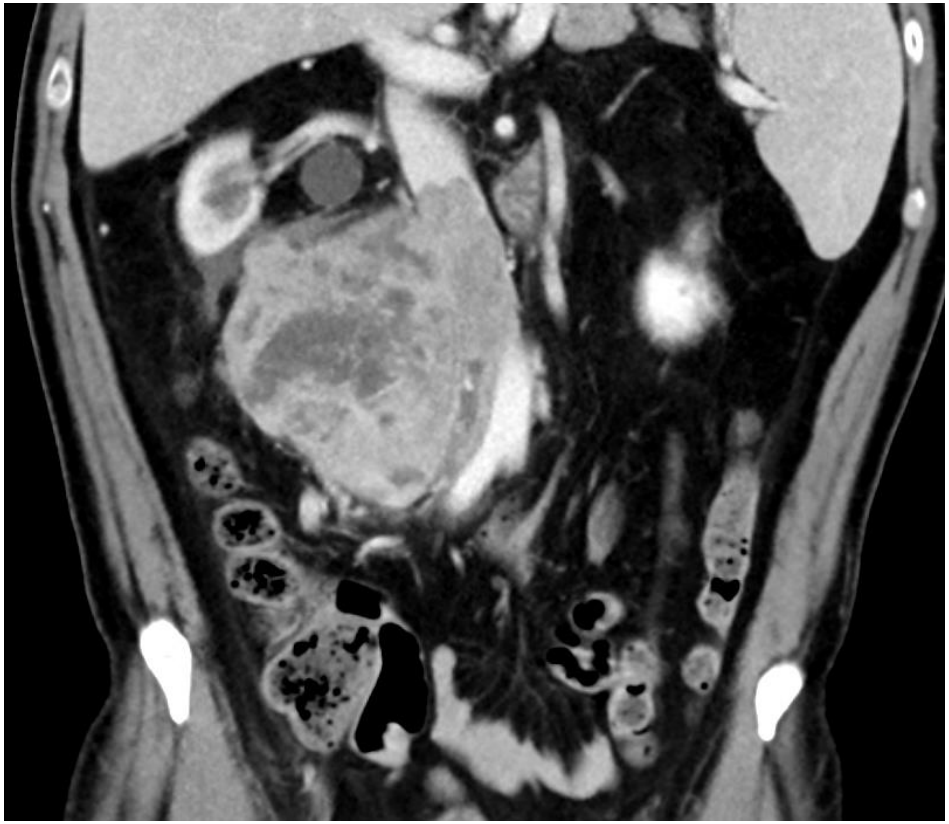

Local relapse LMS
CCI
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Time (months)

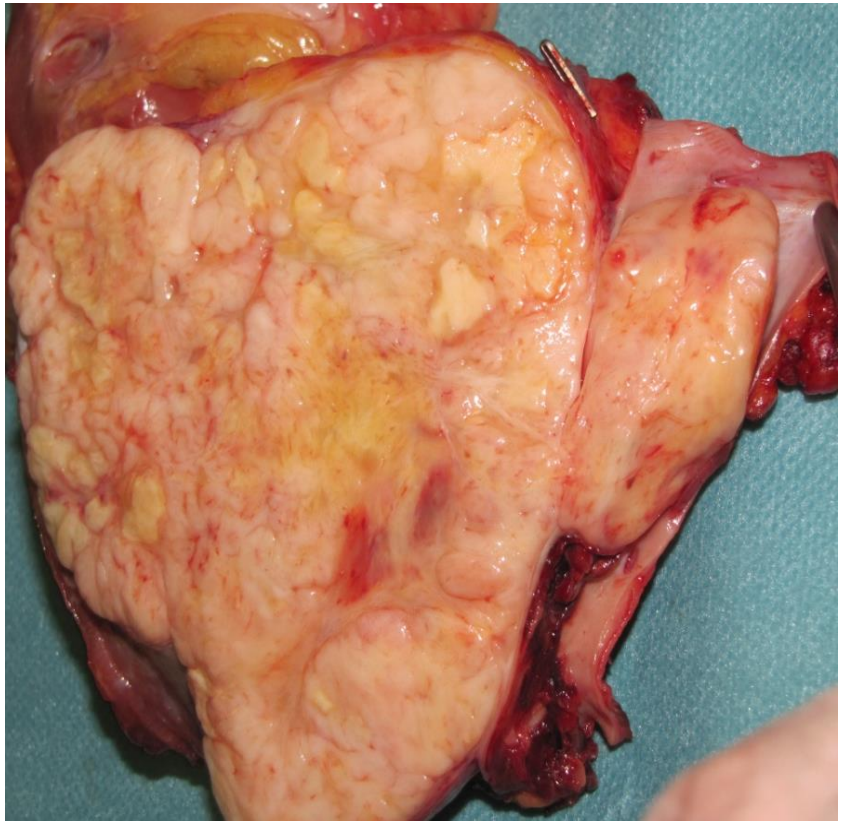

Distant metastasis LMS
CCI
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Time (months)

Vascular LMS

- 30% of all LMS
- 5 times more frequent in veins than in arteries
- 50% of the vein LMS occur in the inferior vena cava

IVC Leiomyosarcoma
(40% of all retroperitoneal LMS)

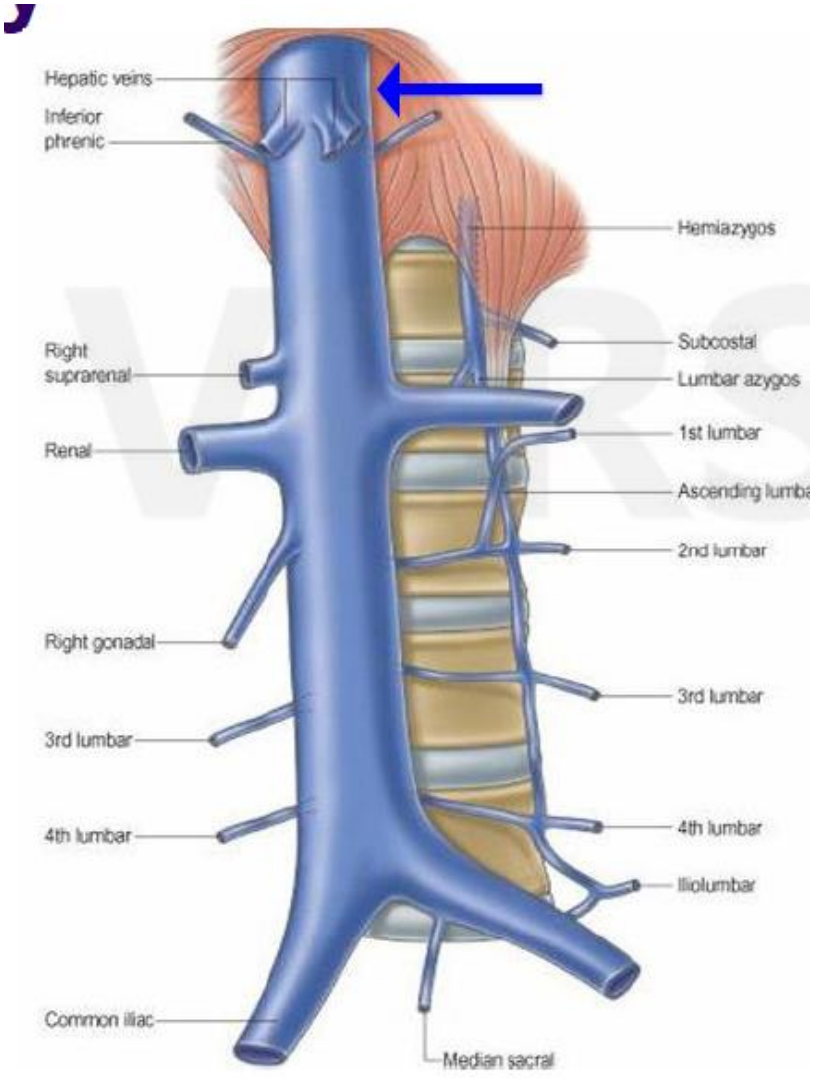




IVC LMS

- Female predominance (3:1)
- Median age: 60
- Median size at diagnosis: 9 cm
- Often asymptomatic (vague back pain)
- Surgery is the treatment mainstay, but may be technically challenging
- 2 distinct prognostic groups based on histology grade

IVC Segments



Segment 3 (10%)

Segment 2 (50%)

Segment 1 (40%)

Original Investigation

Clinical Observations and Molecular Variables of Primary Vascular Leiomyosarcoma

Christina L. Roland, MD; Genevieve M. Boland, MD, PhD; Elizabeth G. Demicco, MD; Kristelle Lusby, MD; Davis Ingram, BS; Caitlin D. May, PhD; Christine M. Kivlin, BS; Kelsey Watson, BS; Ghadah A. Al Sannaa, MD; Wei-Lien Wang, MD; Vinod Ravi, MD; Raphael E. Pollock, MD, PhD; Dina Lev, MD; Janice N. Cormier, MD; Kelly K. Hunt, MD; Barry W. Feig, MD; Alexander J. Lazar, MD, PhD; Keila E. Torres, MD, PhD

IMPORTANCE Vascular leiomyosarcomas are a rare subtype of leiomyosarcomas that most commonly affect the inferior vena cava and account for 5% of all leiomyosarcomas. These tumors are aggressive malignant tumors for which adjuvant modalities have not shown increased efficacy compared with surgery.

OBJECTIVES To evaluate the outcomes of patients with vascular leiomyosarcoma and the association between vascular leiomyosarcomas and immunohistochemical molecular markers, to determine their potential prognostic and therapeutic utility.

DESIGN, SETTING, AND PARTICIPANTS Retrospective medical record review of a cohort of 77 patients who presented to the University of Texas MD Anderson Cancer Center in Houston during the period from January 1993 to April 2012. Data were analyzed during the period from November 2012 to May 2015. All of the patients received a confirmed diagnosis of vascular leiomyosarcoma. Immunohistochemical studies for biomarkers were performed on a tissue microarray that included 26 primary specimens of vascular leiomyosarcoma.

MAIN OUTCOMES AND MEASURES Demographic and clinical factors were evaluated to assess clinical course, patterns of recurrence, and survival outcomes for patients with primary vascular leiomyosarcoma. A univariate Cox proportional hazards model was used to correlate disease-specific survival and time to recurrence with potential prognostic indicators.

RESULTS Sixty-three patients with localized disease who underwent surgical resection formed the study population, and their data were used for subsequent outcomes analysis. The median age at diagnosis was 58 years (range, 22-78 years). The majority of patients were female (41 patients [65%]) and white (51 patients [81%]). The 5-year disease-specific survival rate after tumor resection was 65%. The median time to local recurrence was 43 months, the median time to distant recurrence was 25 months, and the median time to concurrent local and distant recurrences was 15 months ($P = .04$). Strong expressions of cytoplasmic β-catenin (hazard ratio, 5.33 [95% CI, 0.97-29.30]; $P = .06$) and insulinlike growth factor 1 receptor (hazard ratio, 2.74 [95% CI, 1.14-6.56]; $P = .02$) were associated with inferior disease-specific survival.

CONCLUSIONS AND RELEVANCE Vascular leiomyosarcomas are aggressive malignant tumors, with high recurrence rates. Expressions of β-catenin and insulinlike growth factor 1 receptor were associated with poor disease-specific survival. Prospective studies should evaluate the clinical and therapeutic utility of these molecular markers.

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Invited Commentary

Supplemental content at jamasurgery.com

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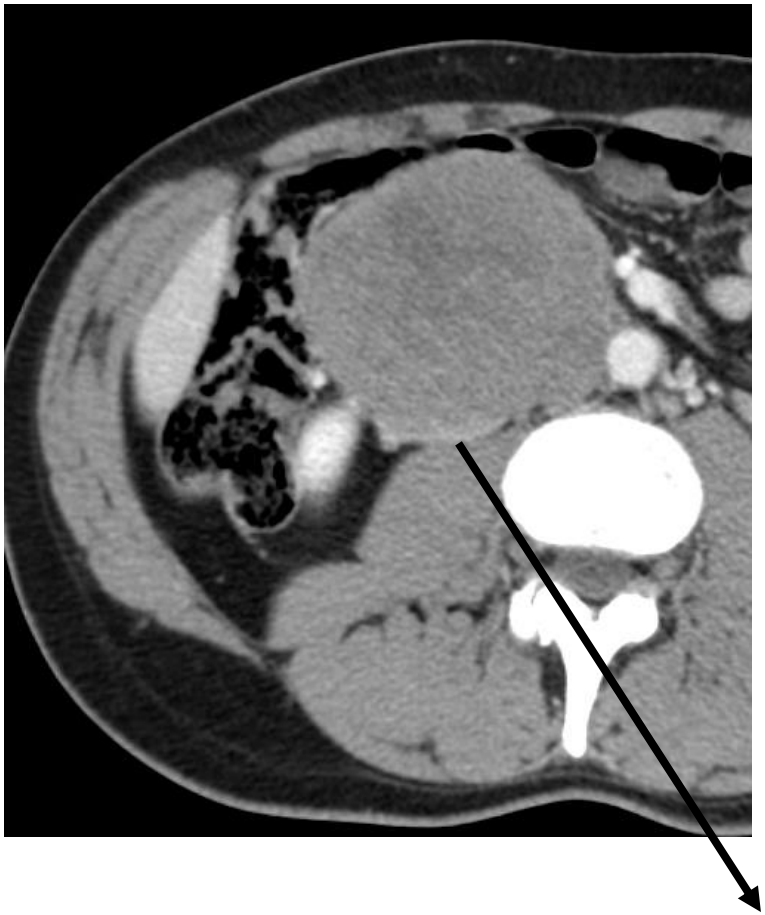
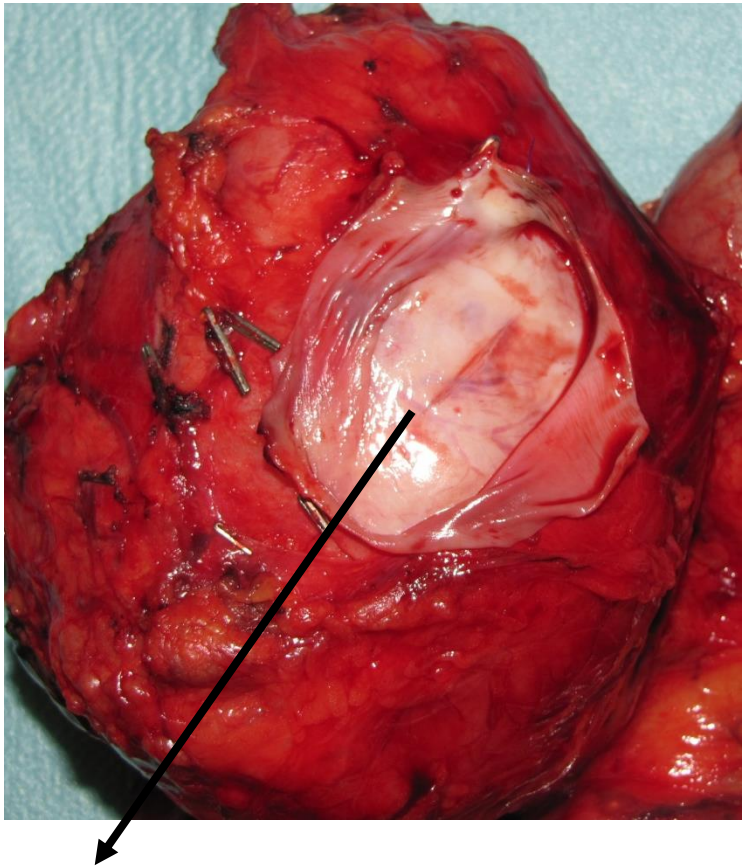
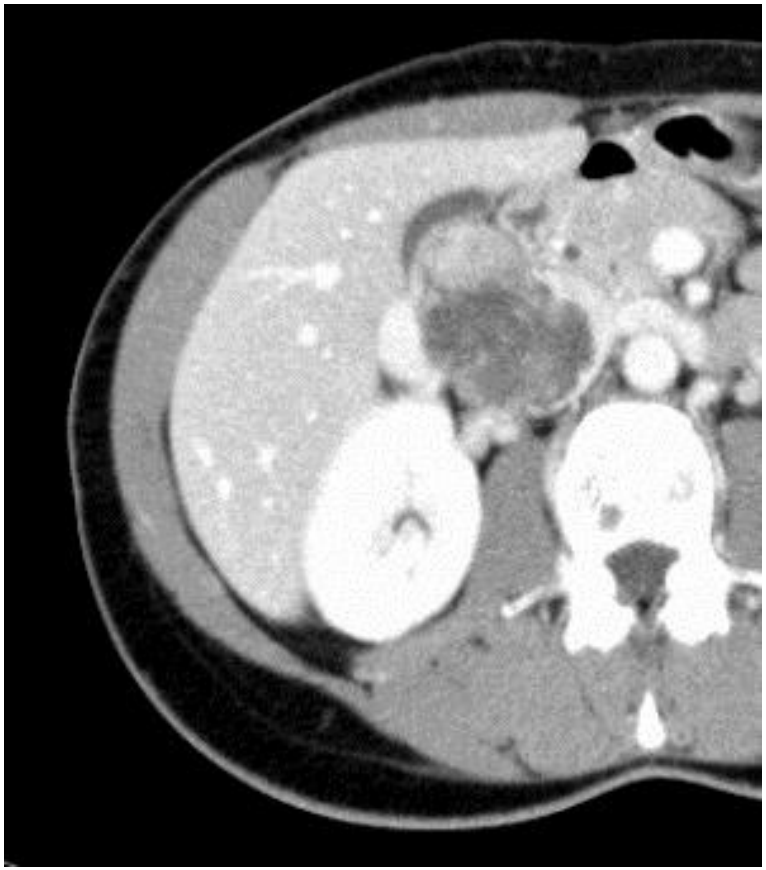
IVC LMS – primarily exofitic (60%)

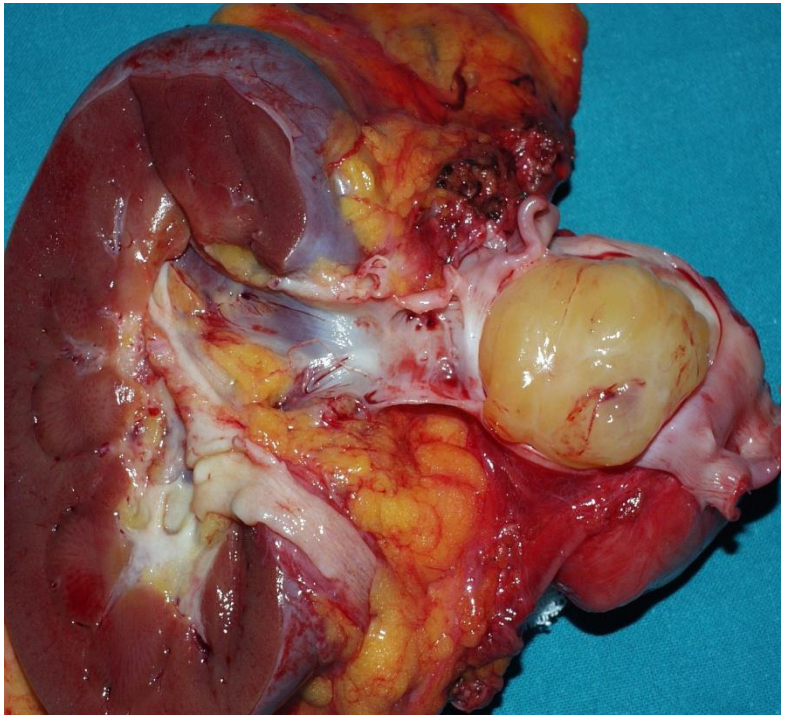




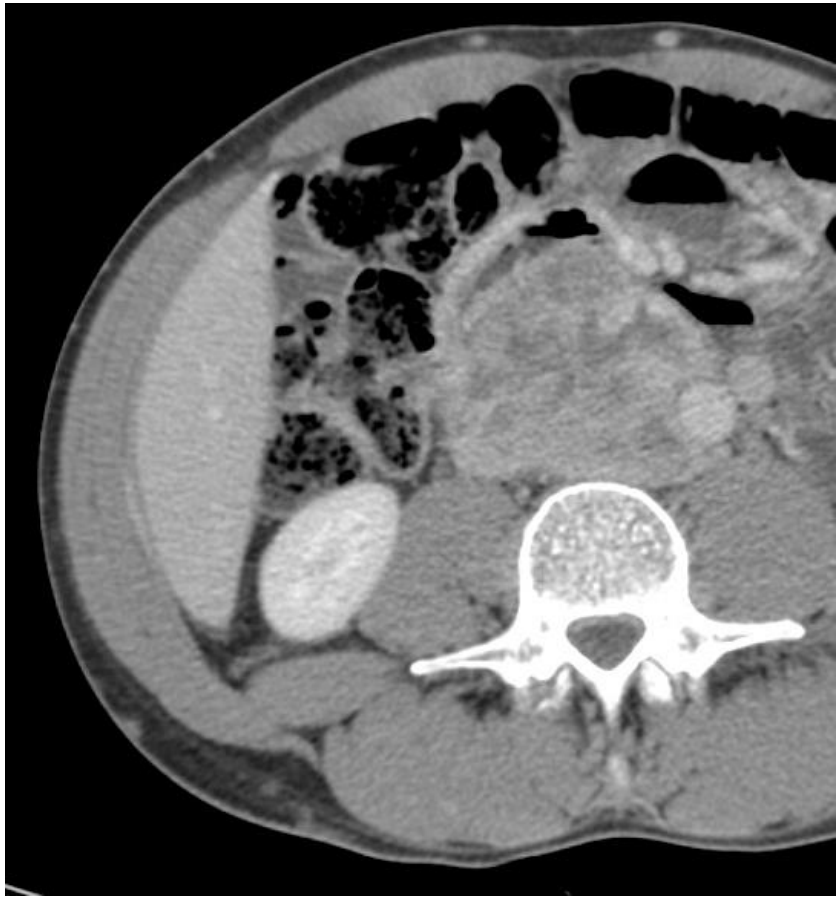
Inferior Vena Cava

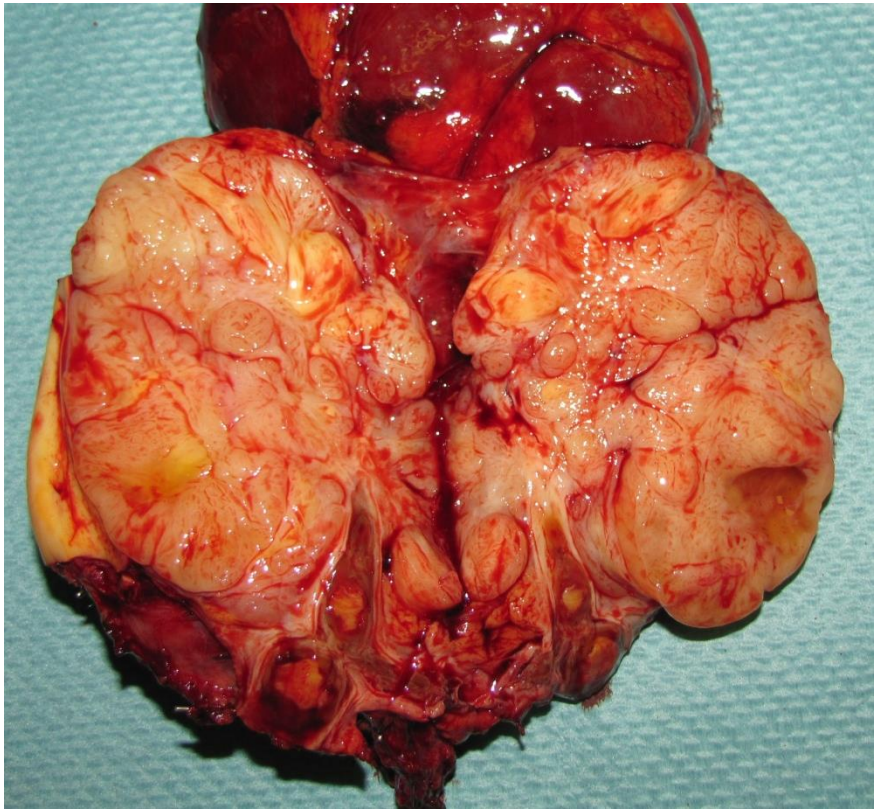
IVC LMS – primarily endoluminal (5%)



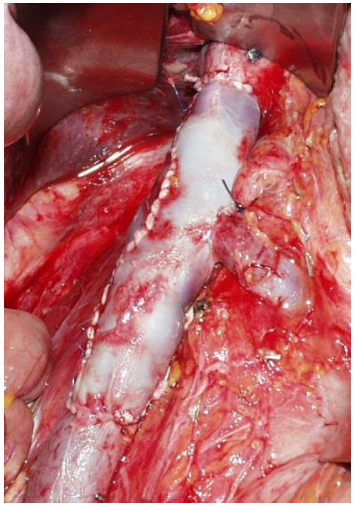
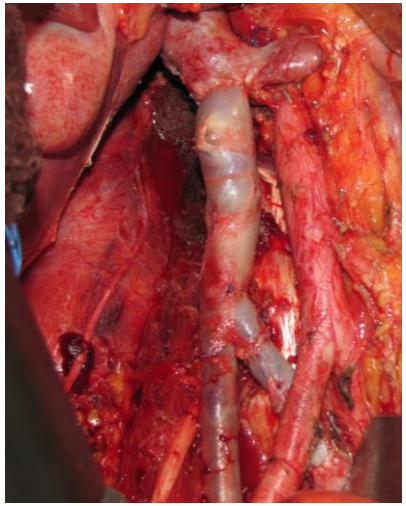
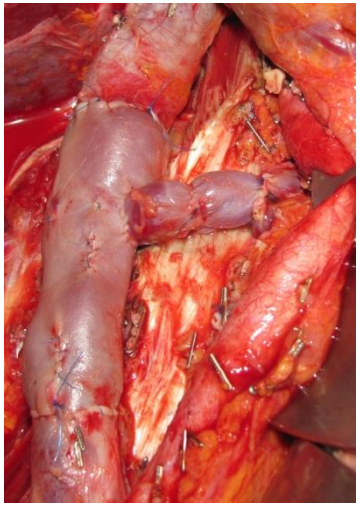
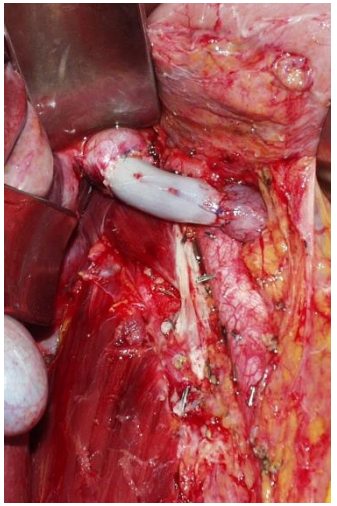
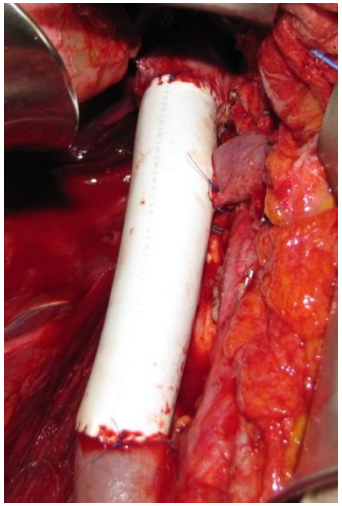
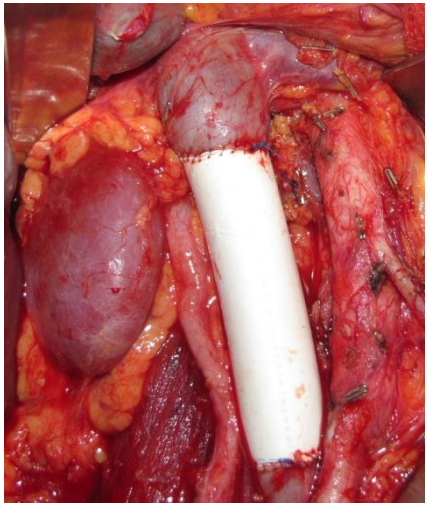
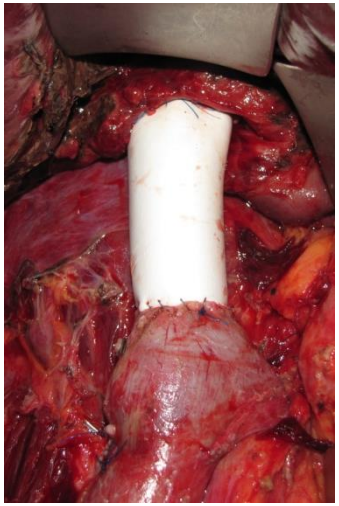
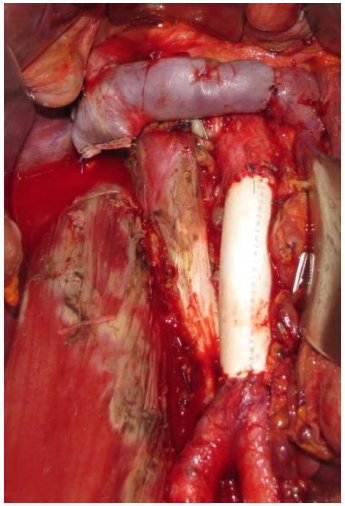


IVC LMS – combined (35%)





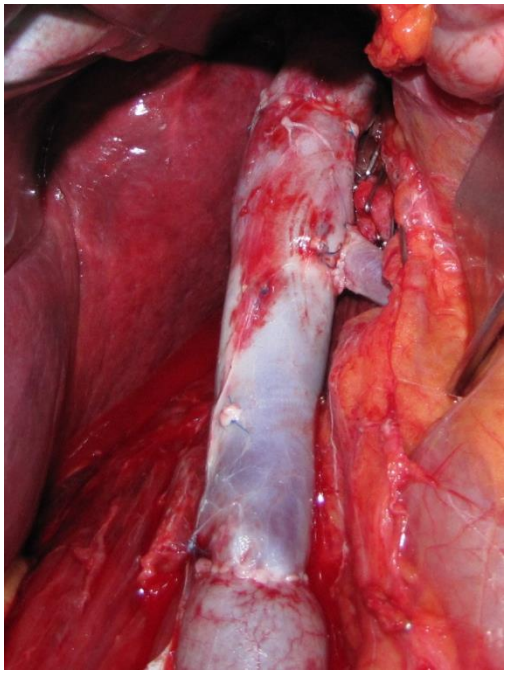
IVC Reconstructions

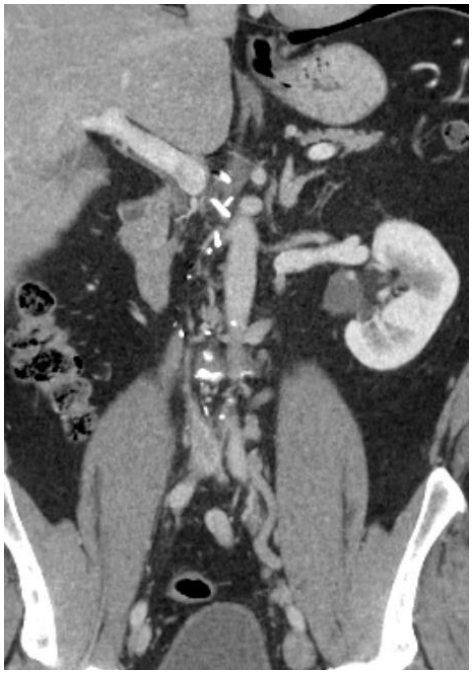









Patency rate

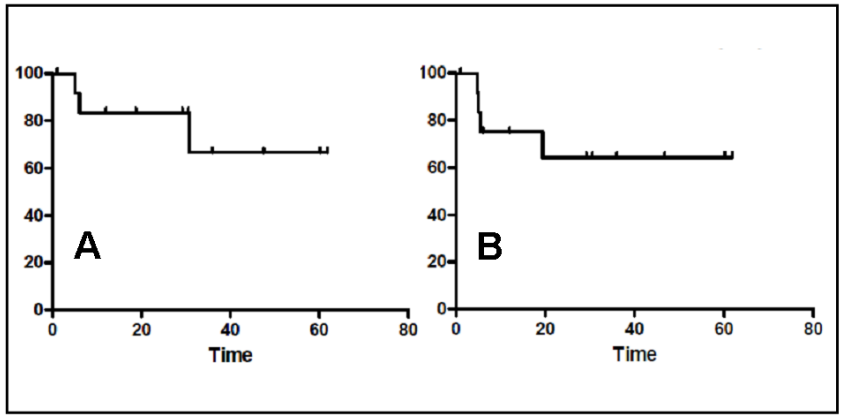
- PTFE 85%

- Cadaveric grafts 50%





IVC Leiomyosarcoma 2000-2015



- 50% are cured by surgical resection
- Prognosis largely depends on grade

Vascular LMS

- Iliac and femoral veins
- Renal/gonadal veins
- Superior Vena cava
- Subclavian-axillary-brachial veins
- Superficial veins (ie greater saphena)

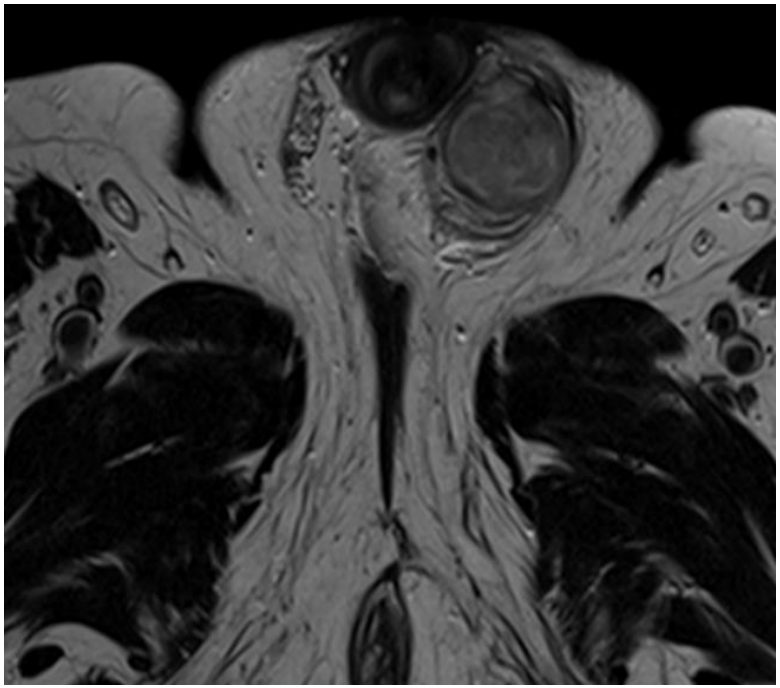
70% of all RPS LMS have a vascular origin

16% of all Extremity LMS have a vascular origin

Of note Vascular LMS have a distinct metastatic pattern

- Intra-abdominal
- Soft tissue
- Skin
- …

Spermatic Cord LMS (3%)



- 2° commonest histotype at this site
- Predominantly G2

Ann Surg Oncol (2014) 21:3557–3563
DOI 10.1245/s10434-014-3751-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

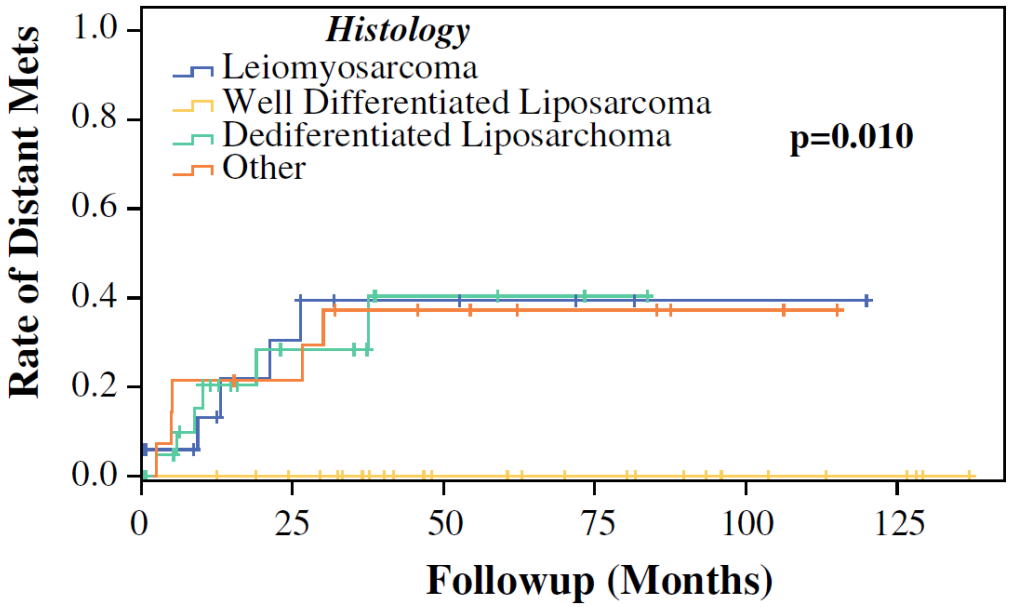
Prognostic Factors and Outcome of Spermatic Cord Sarcoma

Stefano Radaelli, MD[1], Anant Desai, MD, FRCS[2], James Hodson, BSc[3], Chiara Colombo, MD[1], Keith Roberts, MD, PhD[2], David Gourevitch, MD, FRCS[2], and Alessandro Gronchi, MD[1]

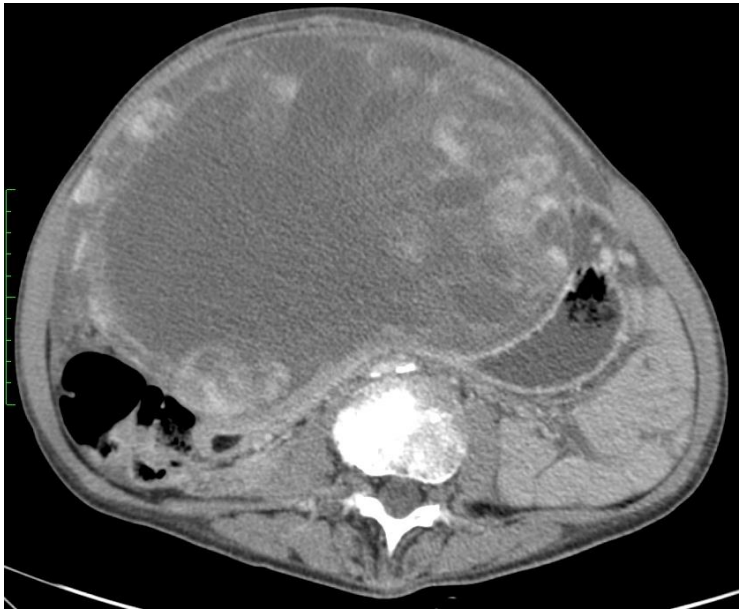
TABLE 1 Patient and tumor characteristics

Characteristic	Value
Patients	82
Age (year)	69 (60–77)
Tumor size, cm	5 (4–8)
Presentation	
Primary	61 (74 %)
Recurrent	21 (26 %)
Site	
Spermatic cord	71 (87 %)
Intrascrotal	11 (13 %)
Histotypes	
Well-differentiated liposarcoma	27 (33 %)
Dedifferentiated liposarcoma	24 (29 %)
Leiomyosarcoma	17 (21 %)
Other (rhabdomyosarcoma, solitary fibrous tumor, synovial sarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma)	14 (17 %)
FNCLCC (grading)	
I	29 (35 %)
II	23 (28 %)
III	30 (37 %)
Surgical procedure	
Orchifunicolectomy	49 (60 %)
Mesh repair of inguinal canal	41 (50 %)
Bone resections	7 (9 %)
Vascular resections	3(4 %)
Visceral resections	3(4 %)
Lymphadenectomy	3(4 %)
Testicular prosthesis	3(4 %)
Flap/skin graft	1(1 %)
Margins	
R0	58 (71 %)
R1	24 (29 %)
Radiotherapy	
Yes	17 (21 %)
No	65 (79 %)
Chemotherapy	
Yes	12 (15 %)
No	70 (85 %)

FNCLCC Fédération française des centers de lutte contre le cancer

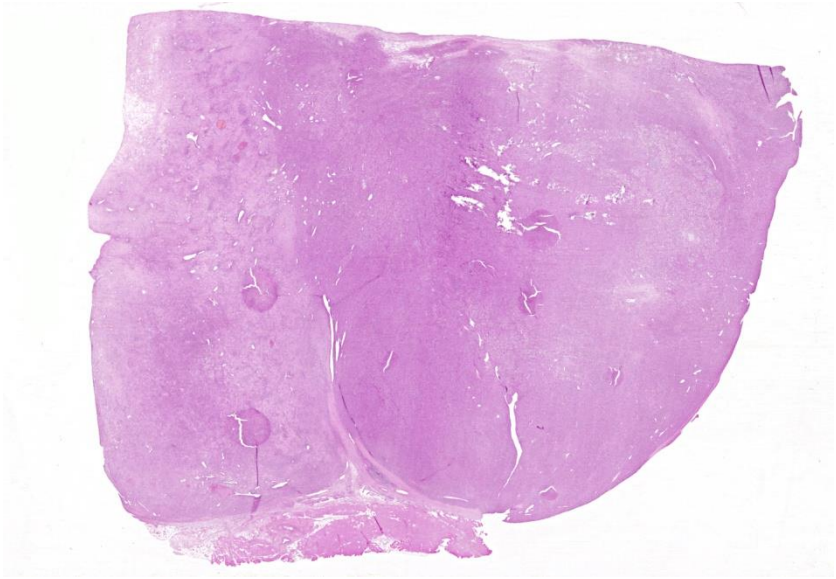


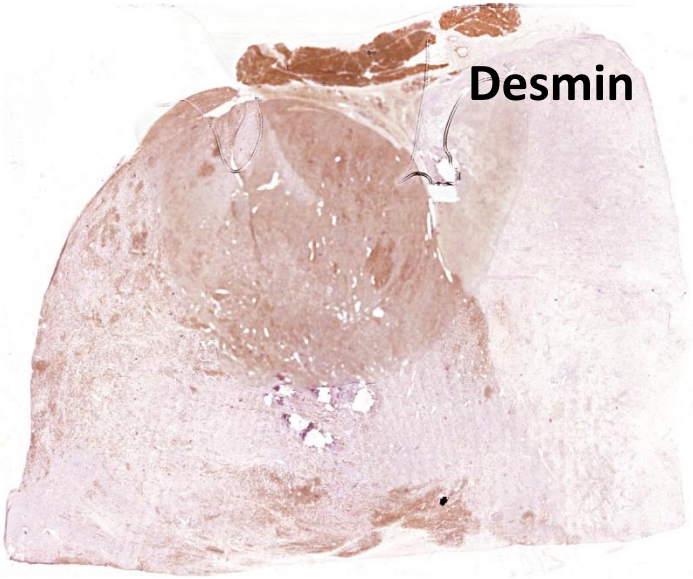
GI LMS (1%)

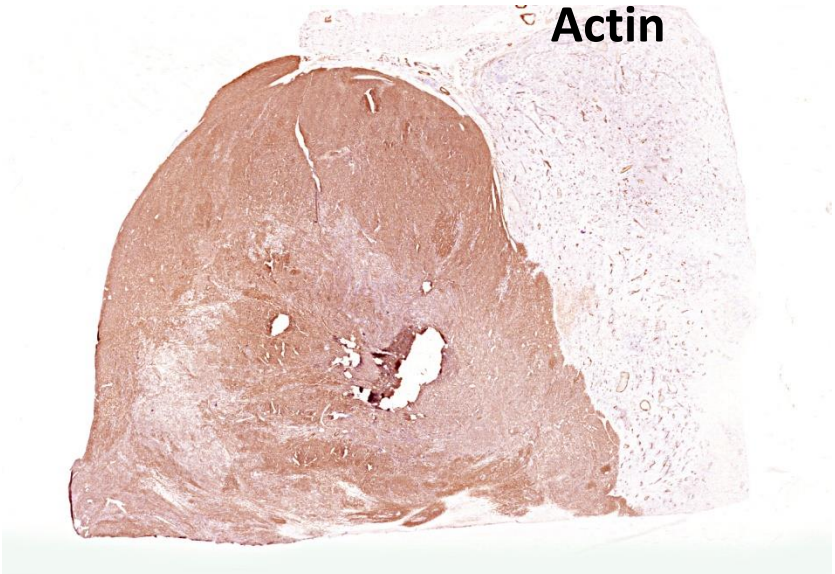


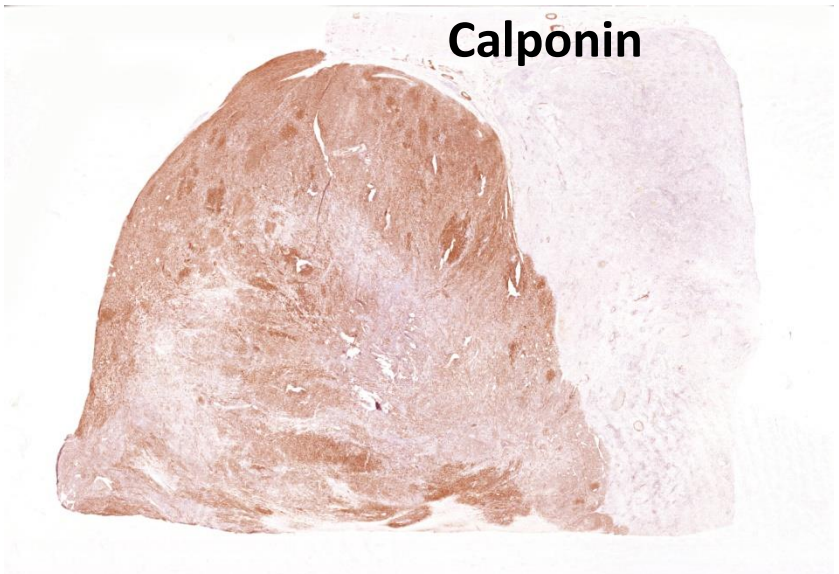
- Very rare
- Predominantly G3
- Very high metastatic risk

LMS and UPS with miogenic differentiation…









Original Article

Leiomyosarcoma and Sarcoma With Myogenic Differentiation

Two Different Entities or 2 Faces of the Same Disease?

Chiara Colombo, MD[1]; Rosalba Miceli, PhD[2]; Paola Collini, MD[3]; Stefano Radaelli, MD[1]; Elena Palassini, MD[4]; Silvia Stacchiotti, MD[4]; Marco Fiore, MD[1]; Luigi Mariani, PhD[2]; Paolo G. Casali, MD[4]; and Alessandro Gronchi, MD[1]

BACKGROUND: The objective of this study was to evaluate whether the distinction between leiomyosarcomas (LMS) and sarcomas with myogenic differentiation (SMD), based on the expression of muscular markers, has any clinical implications. **METHODS:** Patients with localized LMS (excluding any gynecologic subtype) or SMD who underwent surgery at the authors' institution from 1994 to 2010 were analyzed. Overall survival (OS) and the crude cumulative incidence of local recurrence and distant metastasis (DM) were calculated, and multivariable analyses for DM and OS were carried out. **RESULTS:** In total, 327 patients were studied (71% LMS, 29% SMD). The median follow-up was 58 months (interquartile range, 31-97 months). The 5-year overall survival rate was 72.9% (95% confidence interval, 66.3%-80.2%) for the patients with LMS and 64.4% (95% confidence interval, 53.7%-77.1%) for the patients with SMD. The 5-year crude cumulative incidence of distant metastasis was 36.2% (95% confidence interval, 30.1%-43.5%) in the LMS group and 32.6% (95% confidence interval, 24%-44.2%) in the SMD group. Although tumor grade in LMS identified 3 distinct classes of risk, patients with grade 2 and grade 3 SMD had a similar course. The median postmetastasis survival was longer in patients with grade 3 LMS compared versus patients with grade 3 SMD (31 months vs 15 months, respectively). In patients who had grade 3 lesions, adjuvant chemotherapy yielded a better outcome in the SMD group compared with the LMS group (hazard ratio, 0.38). Patients who had superficial LMS had better outcomes compared with patients who had superficial SMD. **CONCLUSIONS:** The current results indicated that LMS and SMD do not share the same natural history. A limited prognostic impact of grade was observed in patients with SMD. Differences in response to chemotherapy should be taken into account in planning the therapeutic approach for patients with these tumors. The current clinical observations may correspond to the biology of a different disease and deserve further study. ***Cancer* 2012;118:5349-57.** © *2012 American Cancer Society.*

KEYWORDS: sarcoma, leiomyosarcoma, myogenic differentiation, survival, metastasis, prognostic factors.

INTRODUCTION

Leiomyosarcoma (LMS) of soft tissues is a relatively uncommon malignant tumor.[1] It may occur anywhere in the body, including the uterus and gynecologic sites.[2] Cutaneous LMS typically originates in the dermis from the arrectores pilorum muscles of the hair follicles and from the smooth muscle surrounding sweat glands. A significant number of soft tissue LMS have been reported arising from vessels.[3] Smooth muscle cells have a distinctive morphology that is spindle-shaped with blunt-ended, cigar-shaped nuclei and eosinophilic cytoplasm. These cells express smooth muscle immunocytochemical markers, such as smooth muscle actin, calponin, caldesmon, and desmin, in the absence of myogenin, In tumors, the intensity and percentage of expression of these differentiation markers are correlated with the degree of differentiation.[4] Myogenic markers also are expressed by other cell types, such as myofibroblasts.[5] The distinction between smooth muscle cells and other cell types with muscle differentiation can be based on ultrastructural findings, such as the presence/absence of fibronexus.[6,7] A good concordance between immunohistochemistry and electron microscopy in recognizing myogenic differentiation in soft tissue pleomorphic sarcomas has been reported.[6] Routinely, because electron microscopy is not available in most pathology departments, this distinction is based on morphology and immunophenotype.[8,9] The problem can arise when dealing with poorly differentiated sarcomas in which morphology is nondistinctive, a true leiomyosarcomatous morphology is no more evident, and myogenic differentiation is very scanty. This group encompasses poorly differentiated, high-grade LMS together with other high-grade sarcomas that have myogenic differentiation, such as myosarcomas and undifferentiated pleomorphic sarcomas. Myofibroblasts were defined first on electron microscopy features. Morphology plus immunohistochemistry can discriminate well/moderately differentiated sarcomas and a part of poorly differentiated sarcomas but are not applicable with certainty to all poorly differentiated lesions. This is the reason why all

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[1]Department of Surgery-Sarcoma Service, Scientific Institutes for Recovery and Cure (IRCCS) Foundation, National Cancer Institute, Milan, Italy; [2]Unit of Clinical Epidemiology and Trial Organization, IRCCS Foundation, National Cancer Institute, Milan, Italy; [3]Department of Pathology, IRCCS Foundation, National Cancer Institute, Milan, Italy; [4]Department of Cancer Medicine, IRCCS Foundation, National Cancer Institute, Milan, Italy.

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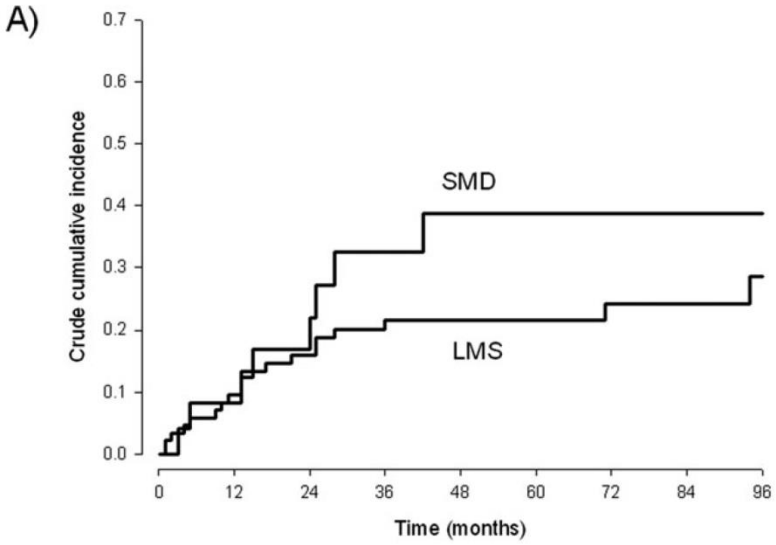
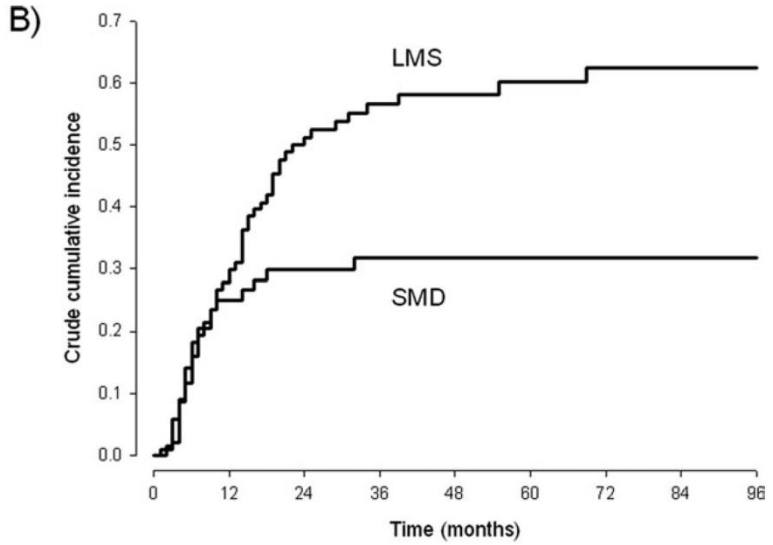
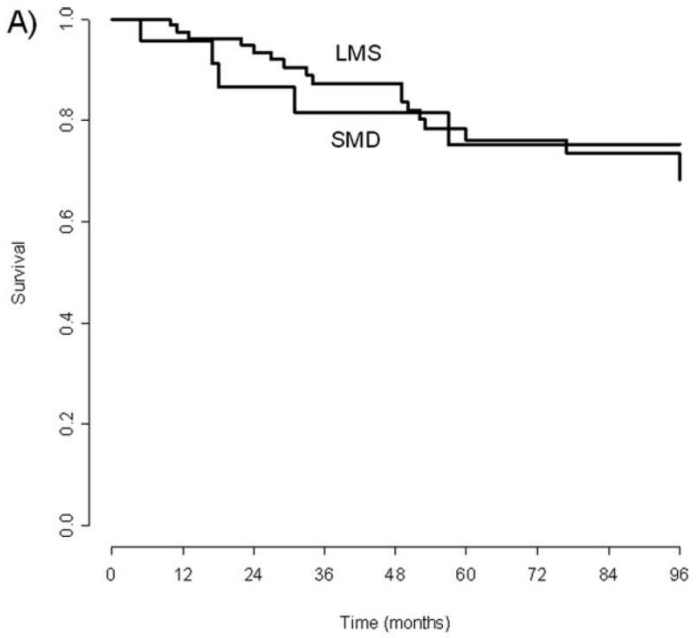
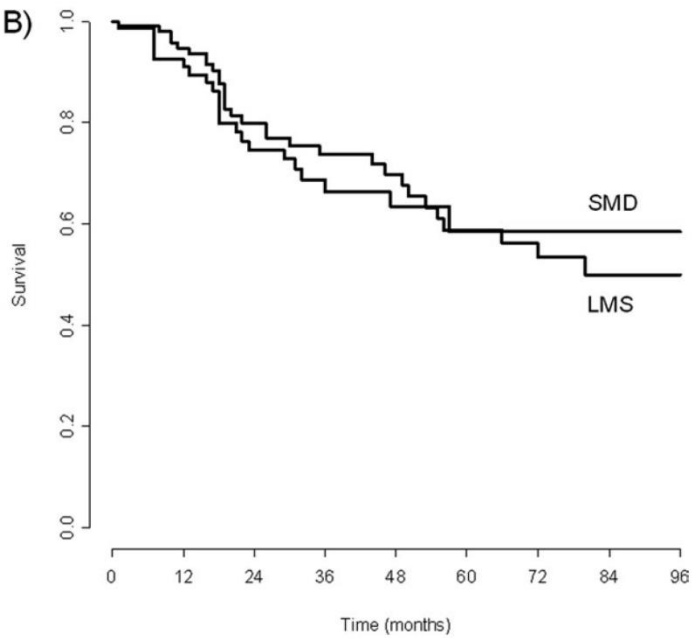
- 231 LMS
- 96 UPS with MD
- 1994-2010
- Median FU 5-yr


A)
Crude cumulative incidence
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
SMD
LMS
0
12
24
36
48
60
72
84
96
Time (months)


B)
Crude cumulative incidence
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
LMS
SMD
0
12
24
36
48
60
72
84
96
Time (months)


A)
Survival
0.0
0.2
0.4
0.6
0.8
1.0
LMS
SMD
0
12
24
36
48
60
72
84
96
Time (months)


B)
Survival
0.0
0.2
0.4
0.6
0.8
1.0
SMD
LMS
0
12
24
36
48
60
72
84
96
Time (months)

DM by subtype and Ad CT

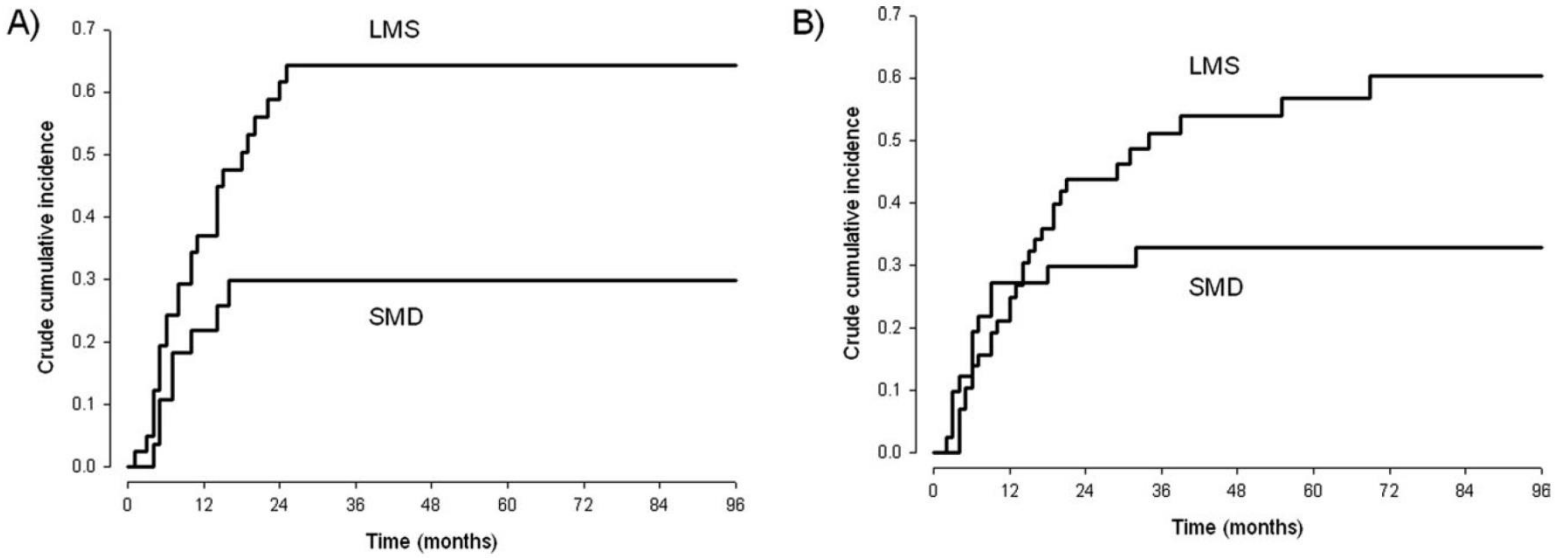
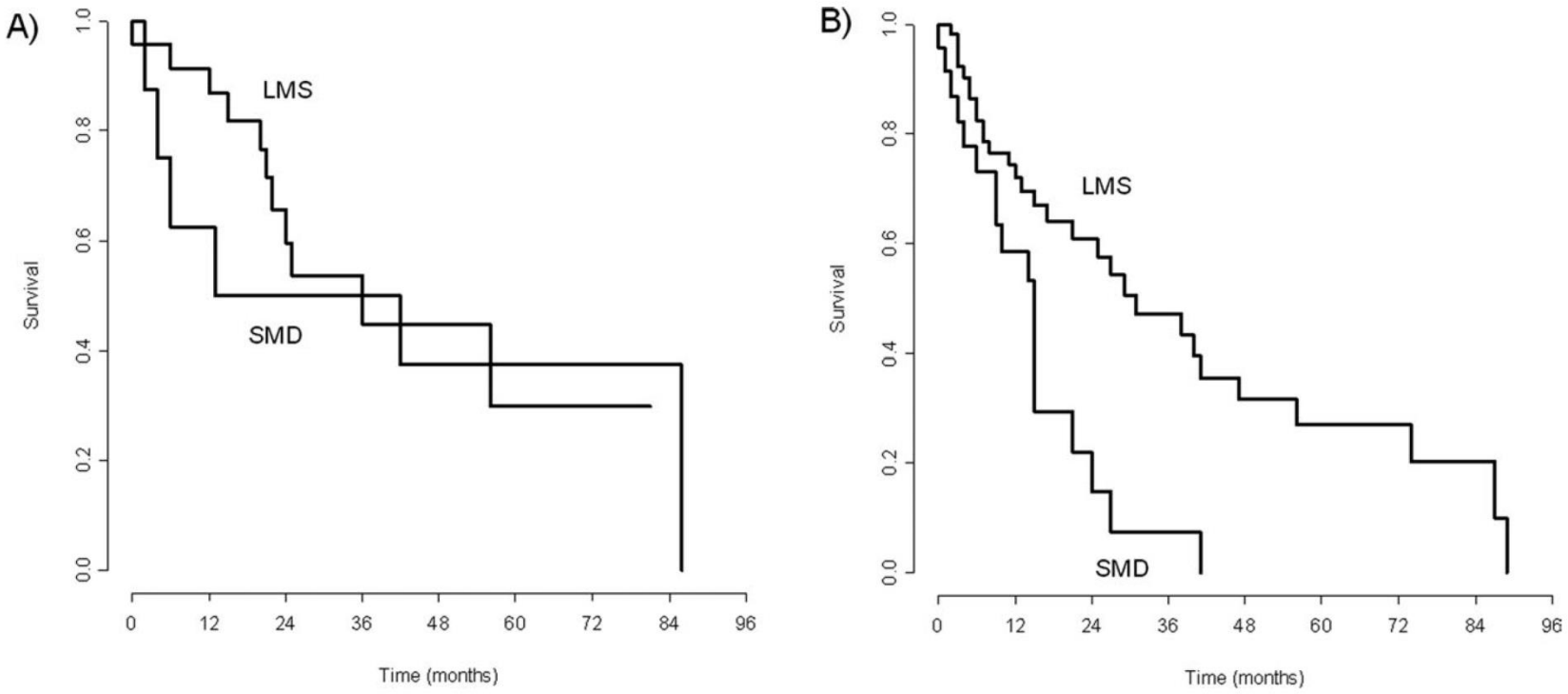


Figure 2. The crude cumulative incidence of distant metastasis is illustrated according to histologic subgroup for patients with grade 3 lesions who (A) did receive and (B) did not receive adjuvant chemotherapy. SMD indicates sarcoma with myogenic differentiation; LMS, leiomyosarcoma.

Post mets OS


A)
LMS
SMD
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
84
96
Time (months)
B)
LMS
SMD
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
84
96
Time (months)

in brief

- Metastatic risk largely depend on grade, location and size, one of the highest among STS

- Vascular LMS represent a distinct subgroup, with a peculiar natural history

- LMS and UPS with MD: the spectrum of a single disease?

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