Personalizing surgical margins to RPS

Alessandro Gronchi
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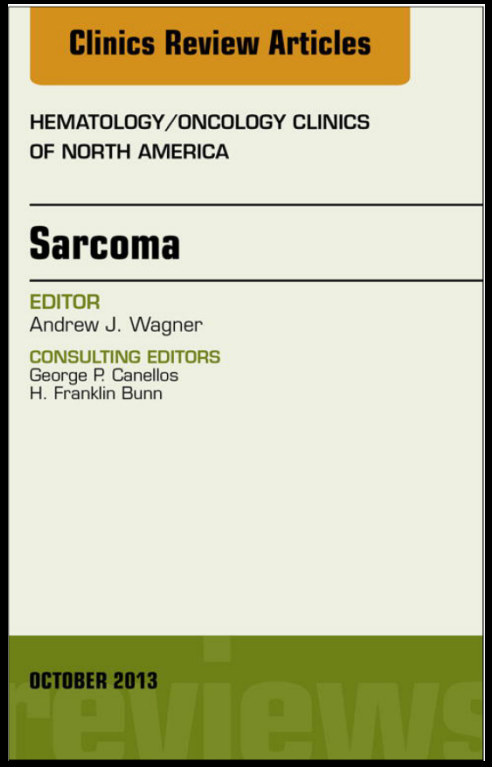
Disclosures slide

- No disclosures to make



Treatment of Localized Sarcomas

Alessandro Gronchi, MD[a], Chandrajit P. Raut, MD, MSc[b,*]

KEYWORDS

• Sarcoma • GIST • Surgery • Radiation therapy • Chemotherapy
• Tyrosine kinase inhibitors • Survival • Outcome

KEY POINTS

- Sarcomas may arise in a variety of body sites and within a variety of tissues. The management of soft tissue sarcomas (STSs) and gastrointestinal stromal tumors (GISTs) requires a thorough understanding of the biology of the different histologies and molecular subtypes as well as the constraints of specific anatomic site.
- Limb-sparing and function-sparing approaches should be used when feasible for STSs located in the extremities and girdles, but extent of surgery should not be compromised for ease of closure. Margins of resection and use of adjuvant/neadjuvant radiation therapy and chemotherapy are contingent on accurate histologic diagnosis. Adjuvant therapy after a marginal resection, however, is not an appropriate substitute for a margin negative operation.
- Extended resections, including adjacent viscera, which may be adherent but not invaded, should be the goal in retroperitoneal sarcoma (RPS), to minimize microscopic intralesional margins and maximize local tumor control and possibly improve survival. The use of neoadjuvant radiation therapy is under investigation. Adjuvant (postoperative) radiation therapy is of limited value. Chemotherapy is not routinely used, save for specific sensitive subtypes.
- Complete tumor resection avoiding tumor rupture should be the goal in GIST. Preoperative imatinib should be considered whenever the expected morbidity is not minimal or surgery is not expected to be microscopically complete.
- Treatment planning should include multidisciplinary consultation to determine optimal therapy, taking into consideration tumor histology, site, and extent of the disease; its natural history and sensitivity to available treatments; surgical challenges; and the wishes of patients.

INTRODUCTION

Surgery remains the standard and only potentially curative therapy in the management of localized STSs of the adult and GISTs. Although belonging to the same family of

Disclosures: The authors have nothing to disclose.

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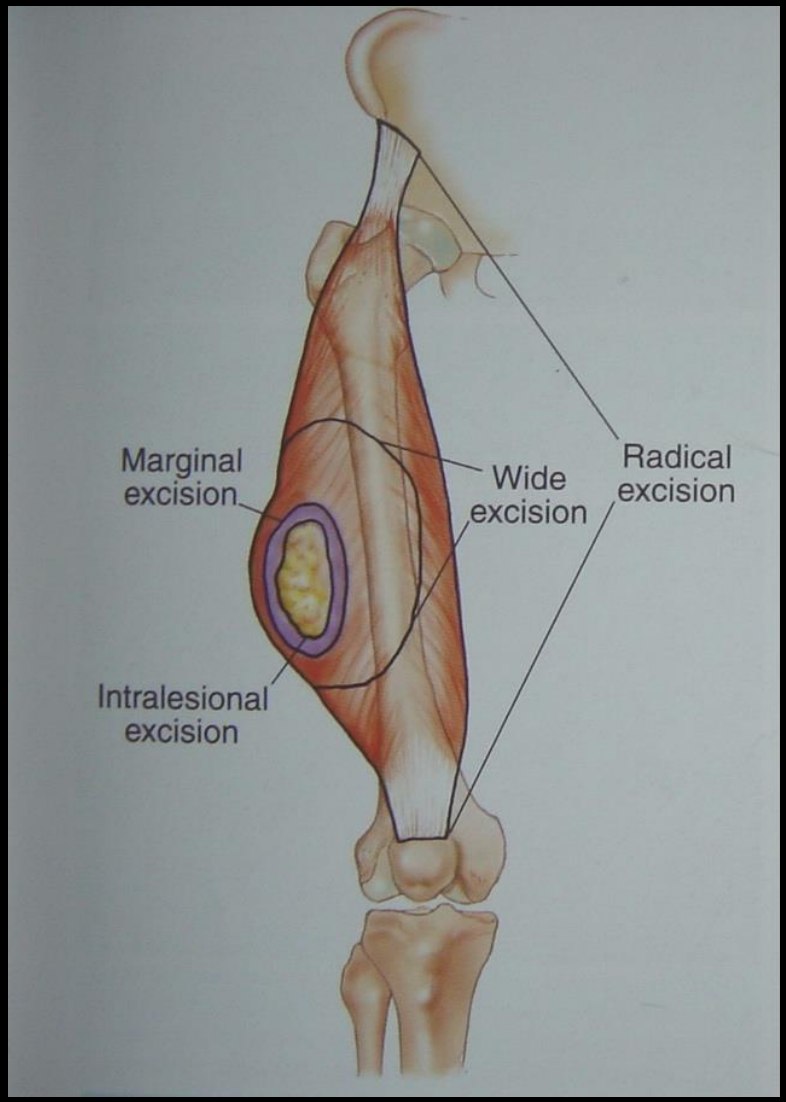
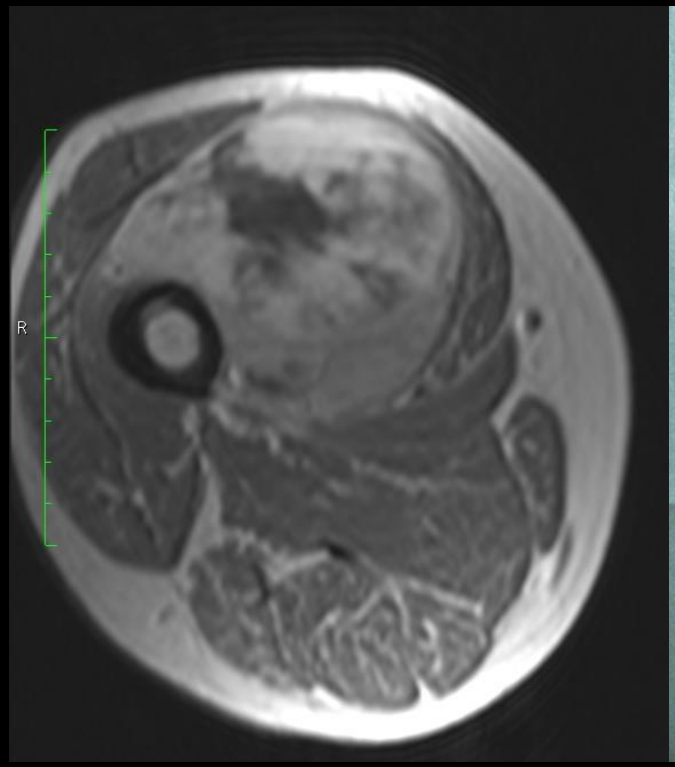
http://dx.doi.org/10.1016/j.hoc.2013.07.006 hemonc.theclinics.com
0889-8588/13/$ – see front matter

Surgery is the primary and only curative treatment of localized disease

Basic principles of surgery

- Remove the whole tumor
- Avoid tumor rupture in the surgical field
- Take the tumor out surrounded by a cuff of healthy tissue, in order to obtain negative microscopic surgical margins all around.


Marginal excision
Wide excision
Radical excision
Intralesional excision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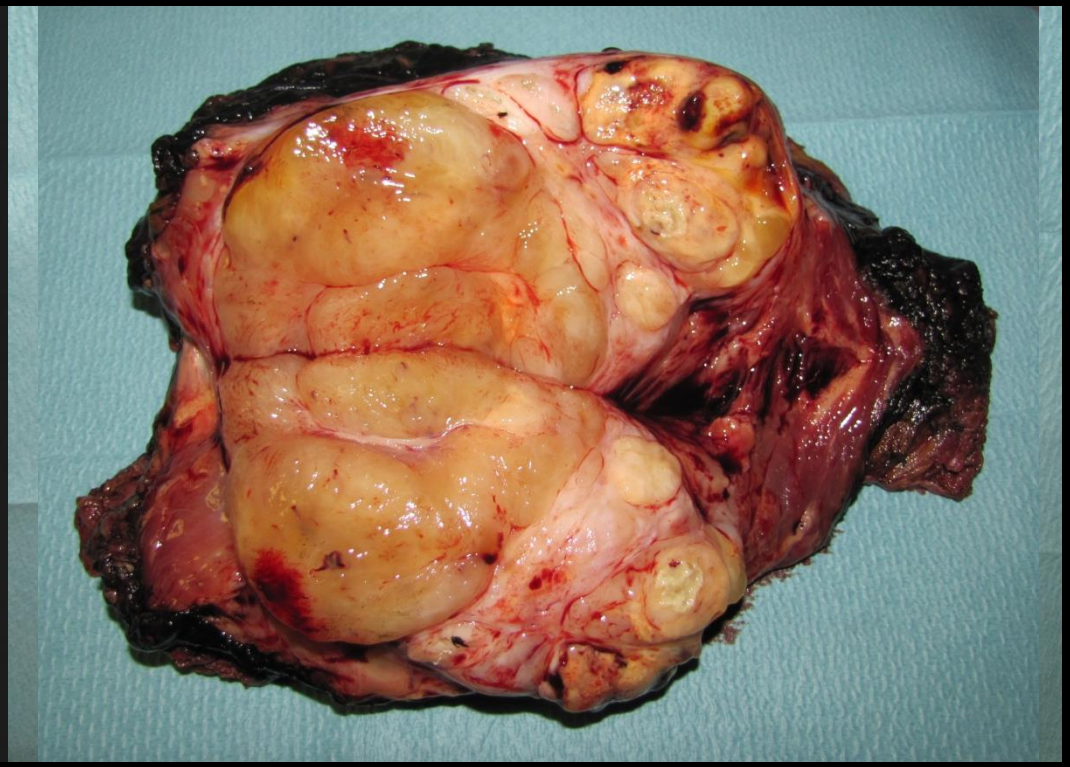
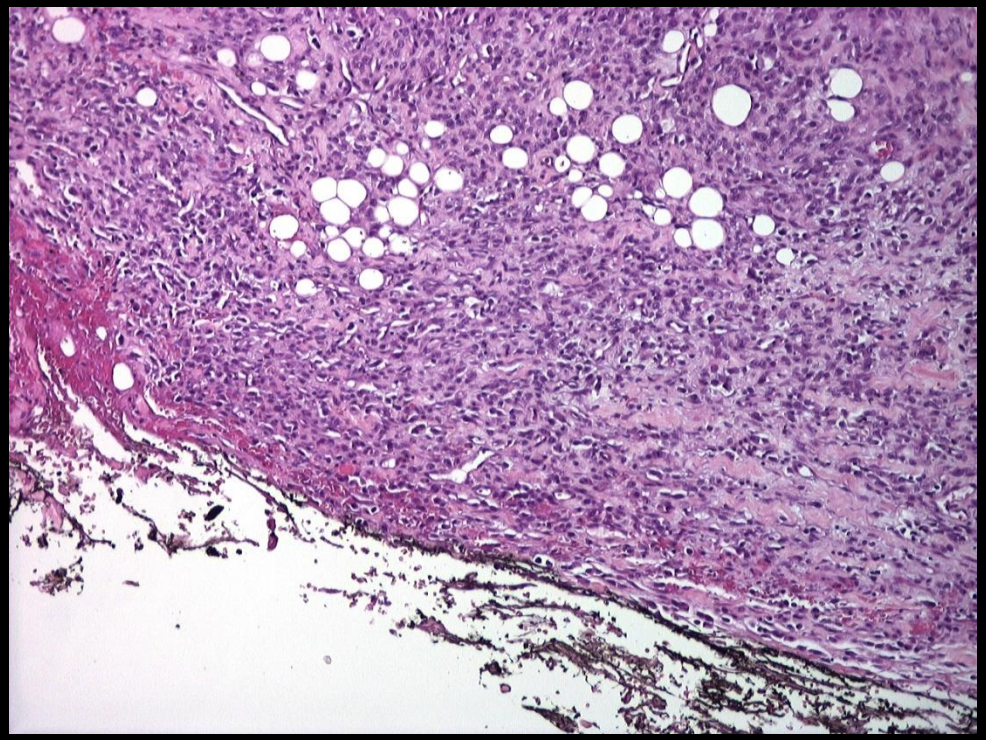


…every attempt should be made to avoid positive microscopic surgical margins

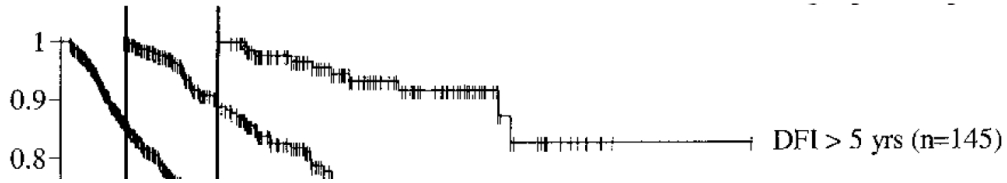
Tumor edge at the inked surface (within 1 mm)



Primary Adult Soft Tissue Sarcoma: Time-Dependent Influence of Prognostic Variables

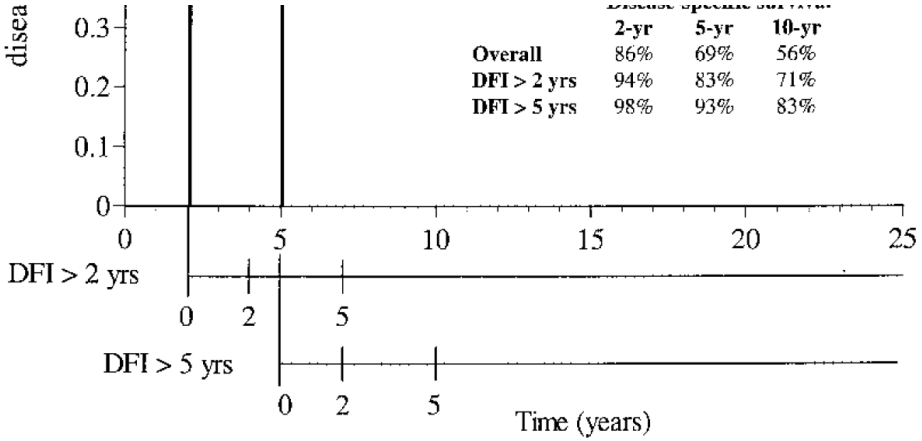
By Alexander Stojadinovic, Denis H.Y. Leung, Peter Allen, Jonathan J. Lewis, David P. Jaques, and Murray F. Brennan

J Clin Oncol 20:4344-4352. © 2002



- biology governs early tumor-related mortality

- microscopic resection margins influence late outcome.



VOLUME 23 · NUMBER 1 · JANUARY 1 2005

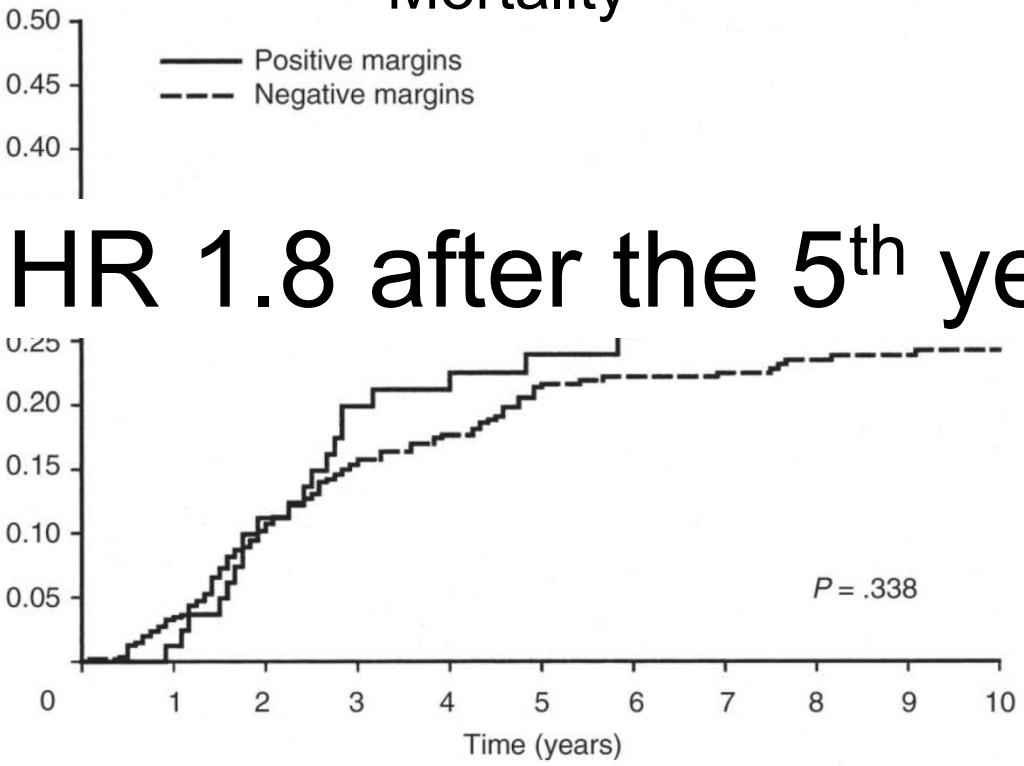
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Status of Surgical Margins and Prognosis in Adult Soft Tissue Sarcomas of the Extremities: A Series of Patients Treated at a Single Institution

A. Gronchi, P.G. Casali, L. Mariani, R. Miceli, M. Fiore, S. Lo Vullo, R. Bertulli, P. Collini, L. Lozza, P. Olmi, and J. Rosai

Mortality



HR 1.8 after the 5th year

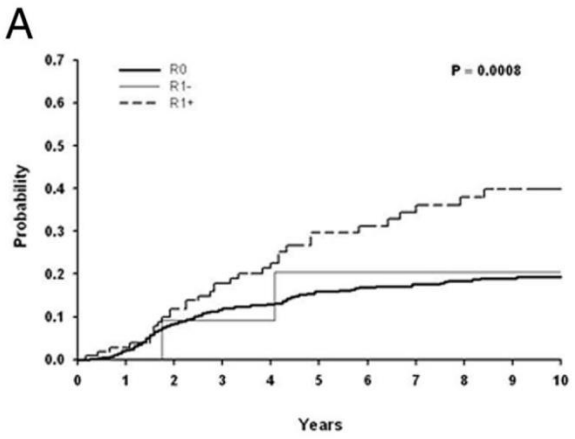
Extremity Soft Tissue Sarcoma in a Series of Patients Treated at a Single Institution

The Local Control Directly Impacts Survival

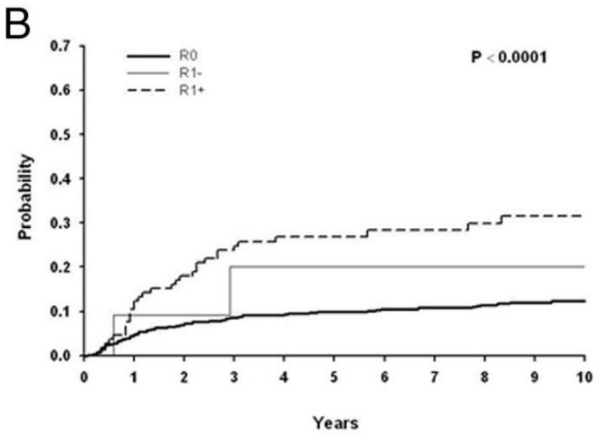
Alessandro Gronchi, MD, Salvatore Lo Vullo, BSc,† Chiara Colombo, MD,* Paola Collini, MD,‡ Silvia Stacchiotti, MD,§ Luigi Mariani, MD,† Marco Fiore, MD,* and Paolo Giovanni Casali, MD§*

(*Ann Surg* 2010;251: 512–517)

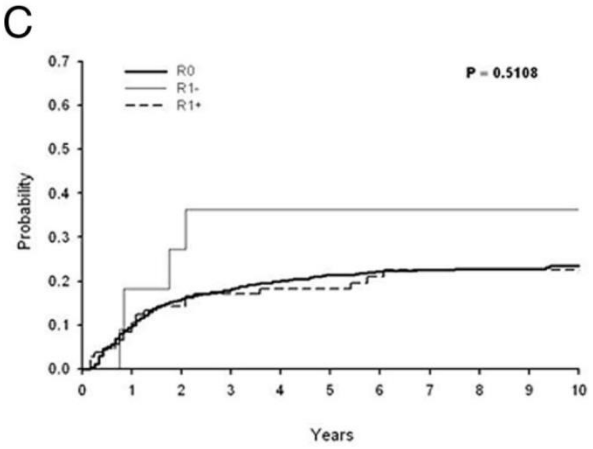
Disease-Specific Mortality, by Margins (R0 / R1- / R1+)



Local relapse, by Margins (R0 / R1- / R1+)

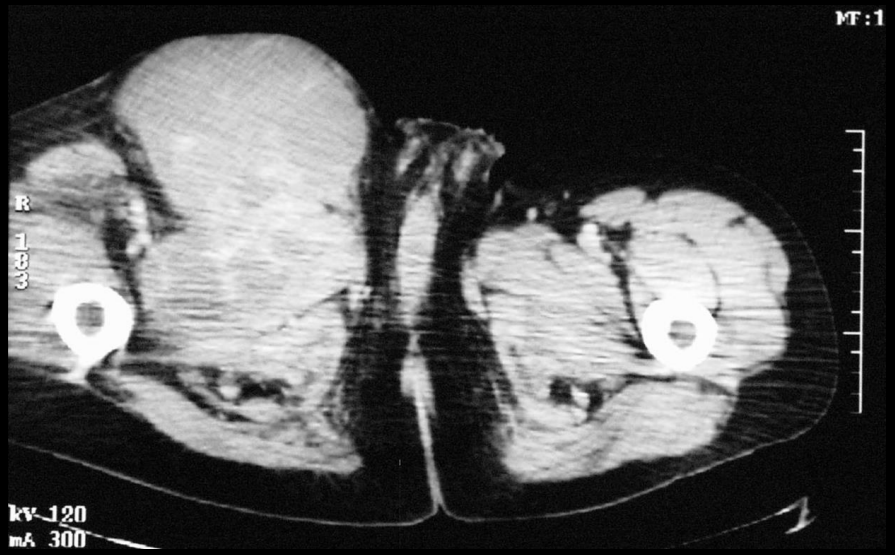


Distant metastases, by Margins (R0 / R1- / R1+)



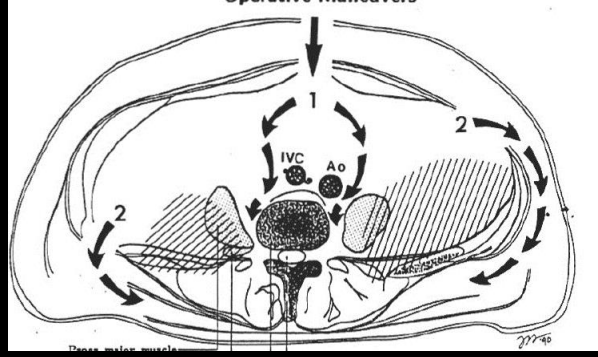
Locoregional failure at critical sites can lead to death

- 20% patients affected by ESTS, who had undergone R1 resection and died of disease, did so for loco-reginal recurrence without any distant disease.



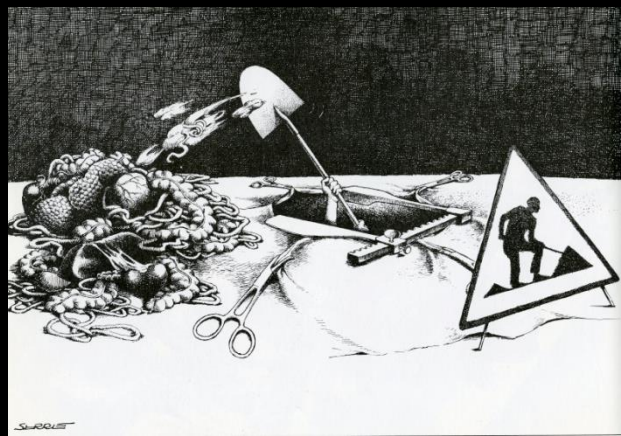
This is all the more true in RPS

“Extended surgical approach”

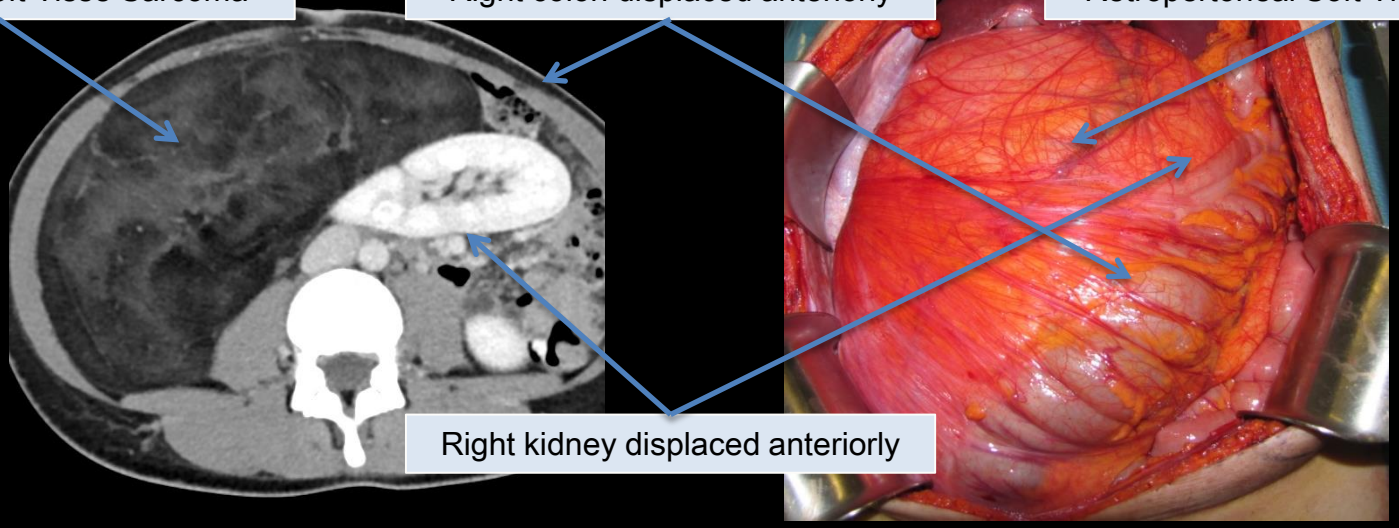


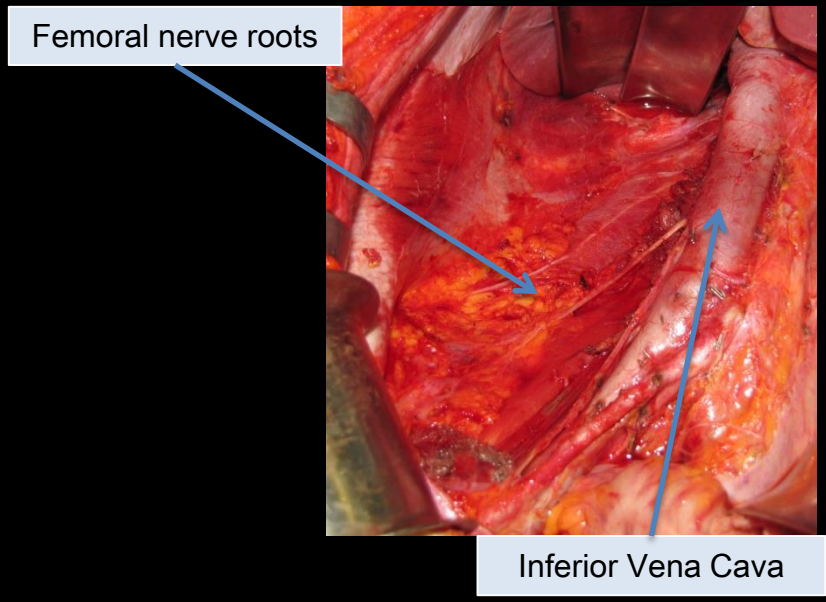
Storm, Mahvi – Ann Surg 1990

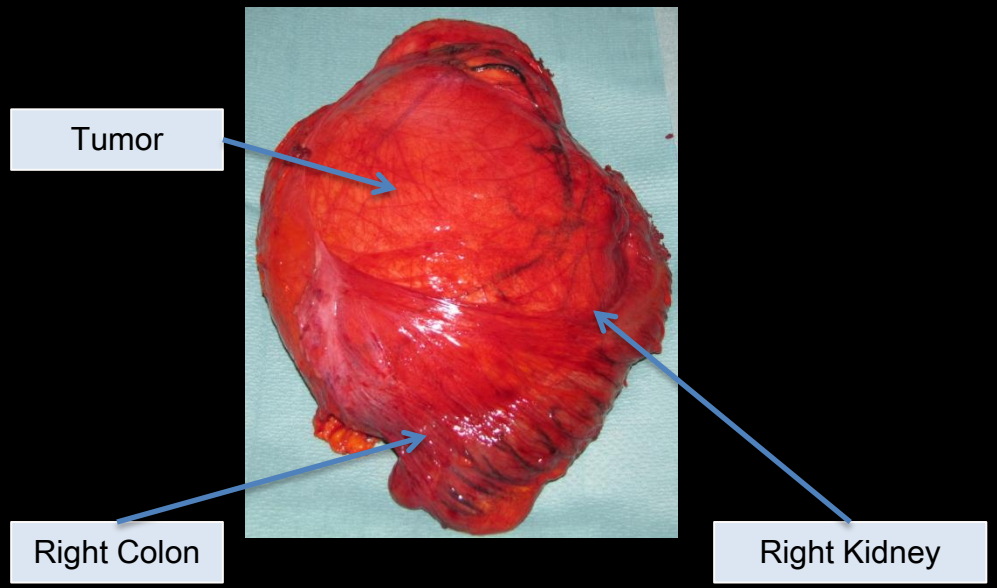
- Liberal en-bloc visceral resections:
  - Ipsilateral nephrectomy and colectomy
  - Splenectomy and left pancreatectomy for left sided tumors
  - Pancreato-duodenectomy and major hepatectomy only when infiltrated for right sided tumors
  - Sigmoid and rectal resection for pelvic lesions (bladder only if directly infiltrated)
- Loco-regional peritonectomy and miomectomy of the psoas:
  - To accomplish better en-bloc resection
- Vascular surgery and bone resection
  - Performed only if vessels/bone infiltrated



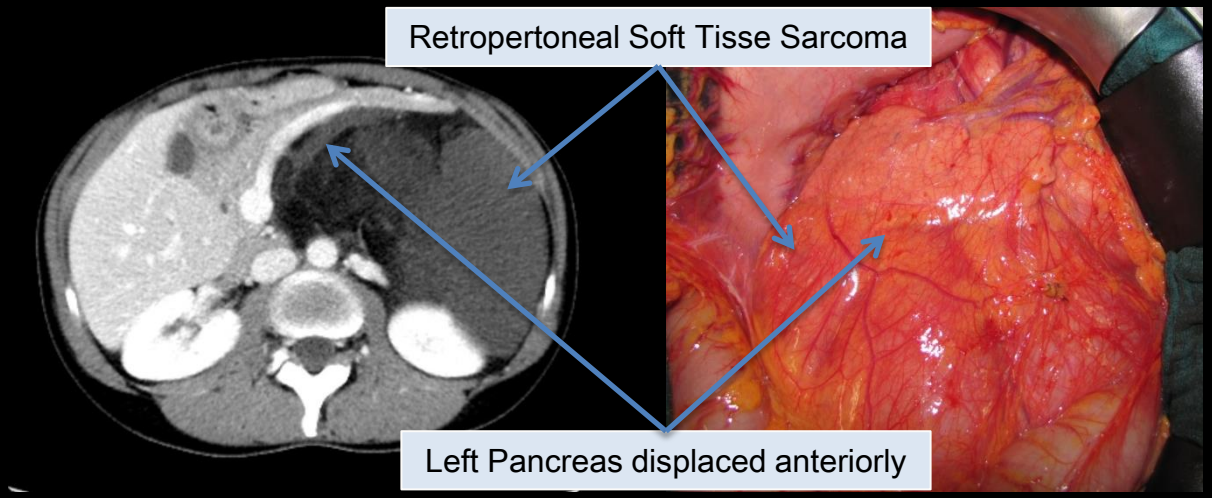
Ipsilateral nephrectomy and colectomy

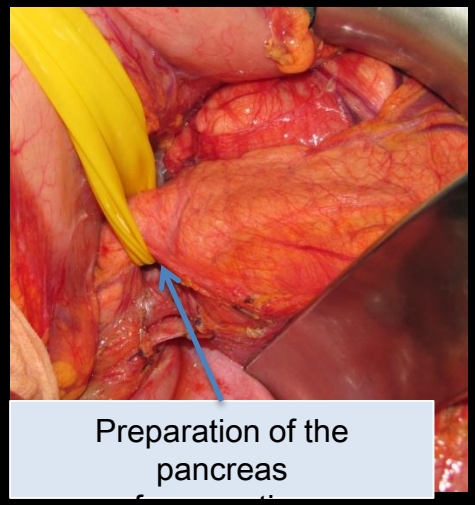


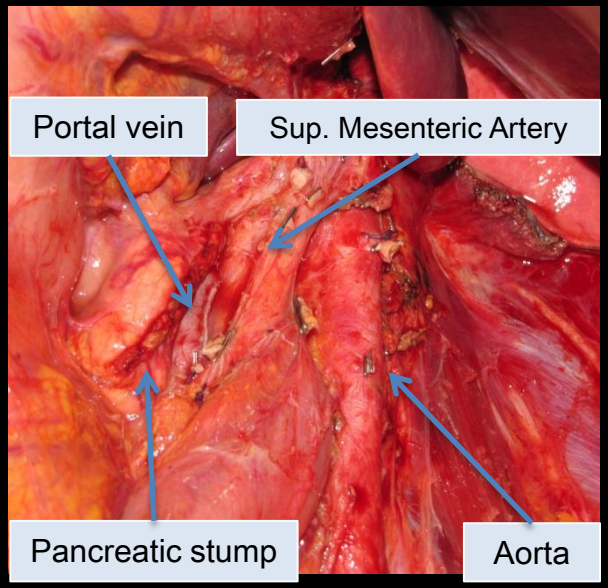


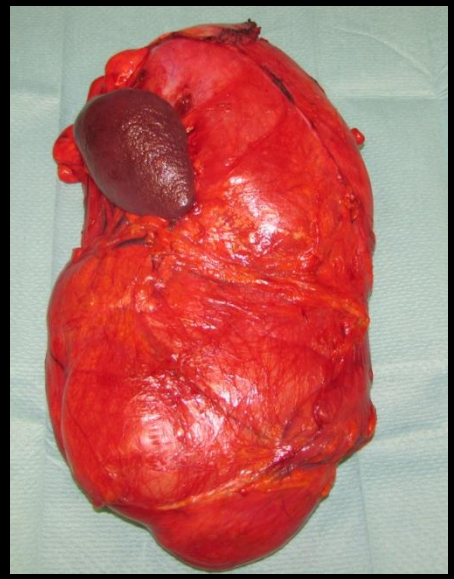


Splenectomy and left pancreatectomy



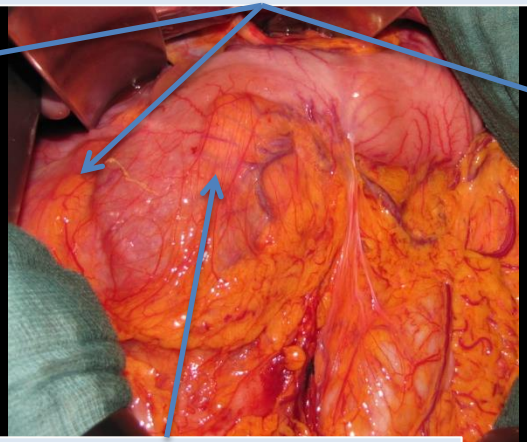






Vascular resection

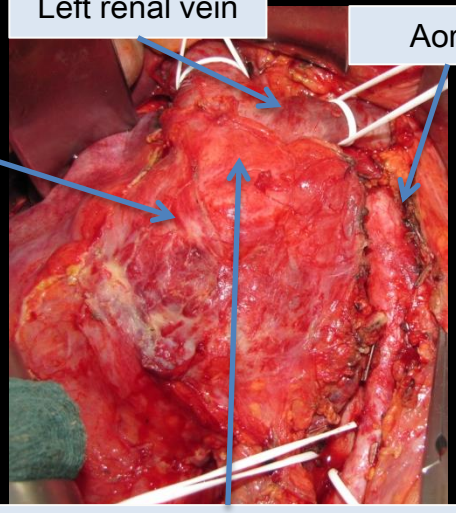
Retropertoneal Soft Tisse Sarcoma



Duodenum and head of the pancreas

Left renal vein

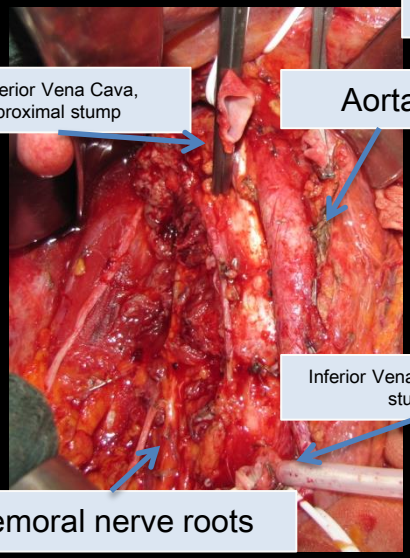
Aorta



Inferior Vena Cava encased by the tumor

Inferior Vena Cava, proximal stump

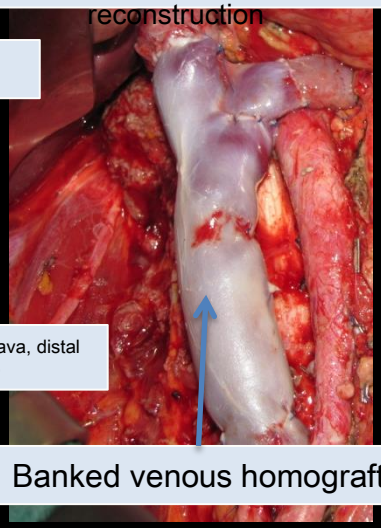
Aorta



Inferior Vena Cava, distal stump

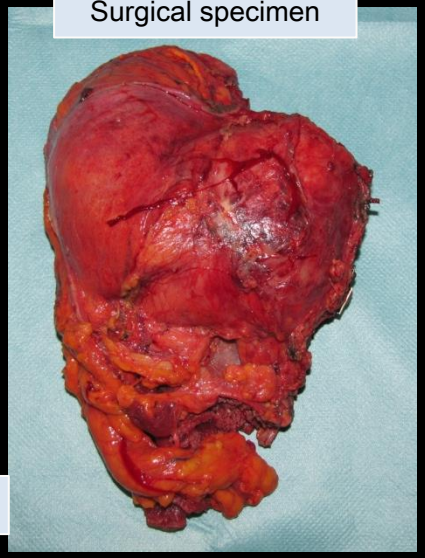
Femoral nerve roots

Inferior Vena Cava reconstruction



Banked venous homograft

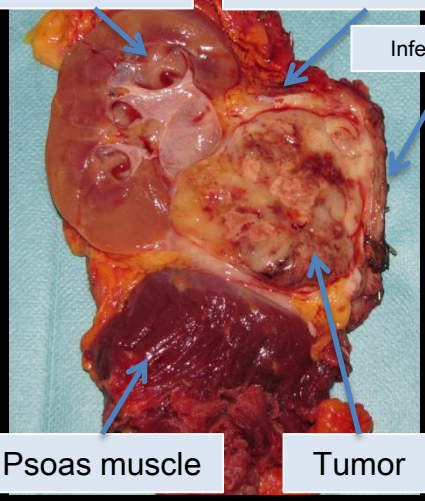
Surgical specimen



Kidney

Right renal vein

Inferior vena



Psoas muscle

Tumor

VOLUME 27 · NUMBER 1 · JANUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Aggressive Surgical Policies in a Retrospectively Reviewed Single-Institution Case Series of Retroperitoneal Soft Tissue Sarcoma Patients

Alessandro Gronchi, Salvatore Lo Vullo, Marco Fiore, Chiara Mussi, Silvia Stacchiotti, Paola Collini, Laura Lozza, Elisabetta Pennacchioli, Luigi Mariani, and Paolo Giovanni Casali

Early = ≤ 2001

Recent = > 2001

	Early		Recent	
	No.	%	No.	%
Total	136	47.2	152	52.8
Organs involved by surgery				
None	55	40.4	28	18.4
1	52	38.2	46	30.3
≥ 2	29	21.3	78	51.3

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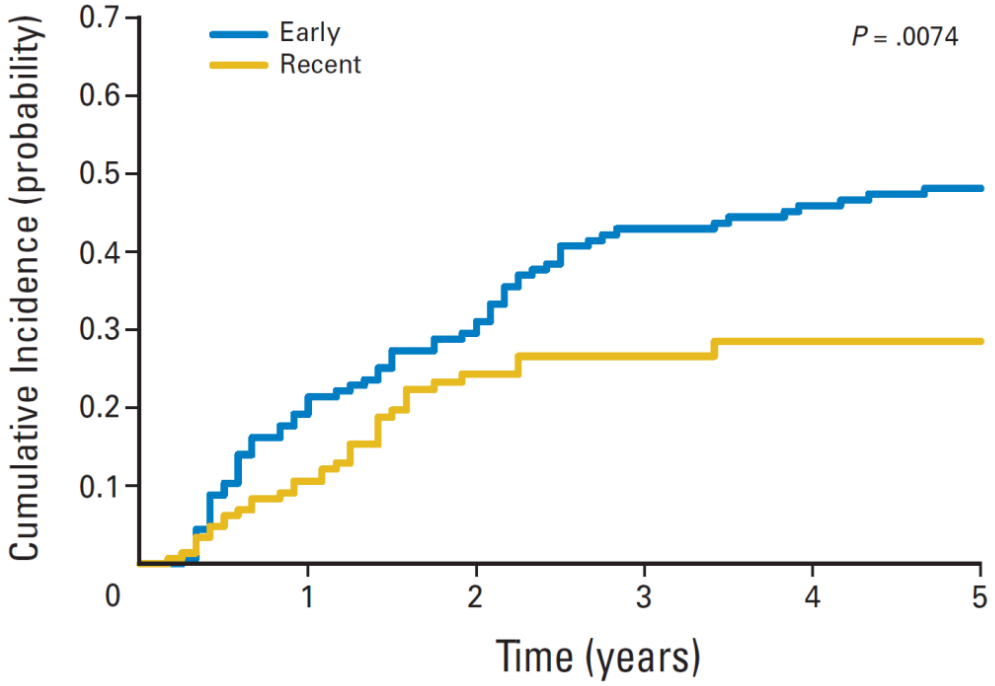
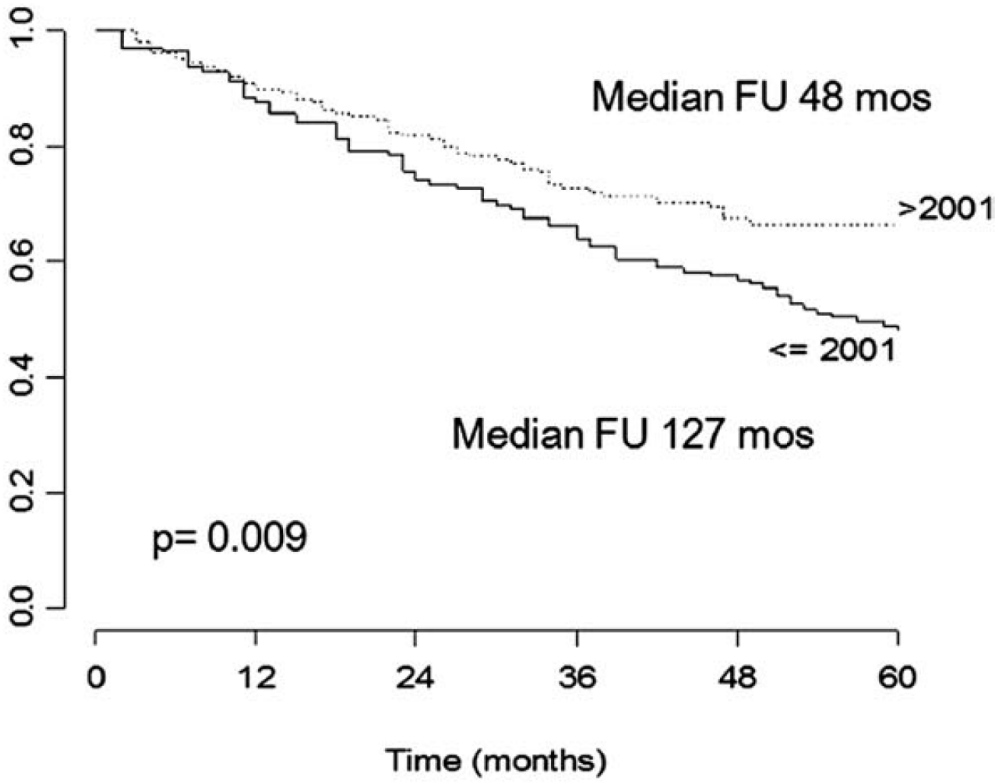


Annals of Oncology 23: 1067–1073, 2012
doi:10.1093/annonc/mdr323
Published online 16 July 2011

Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas

A. Gronchi[1]*, R. Miceli[2], C. Colombo[1], S. Stacchiotti[3], P. Collini[4], L. Mariani[2], C. Sangalli[5], S. Radaelli[1], R. Sanfilippo[3], M. Fiore[1] & P. G. Casali[3]



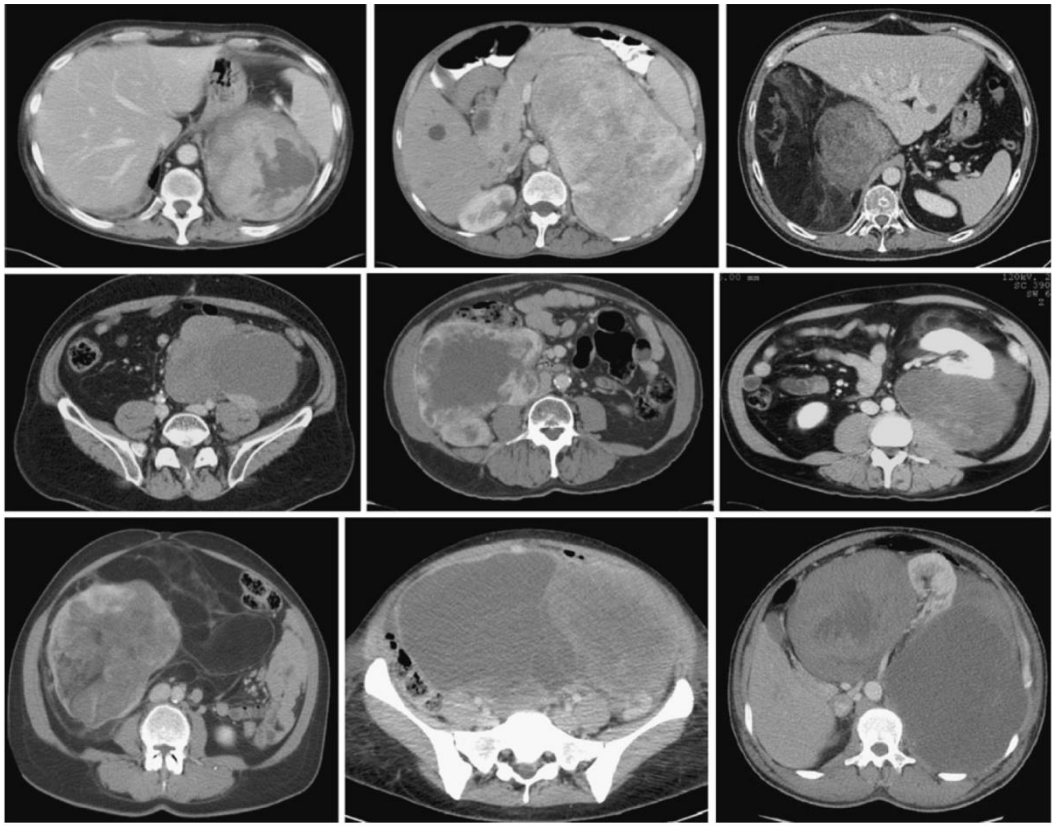
Ann Surg Oncol (2012) 19:2981–2991
DOI 10.1245/s10434-012-2342-2

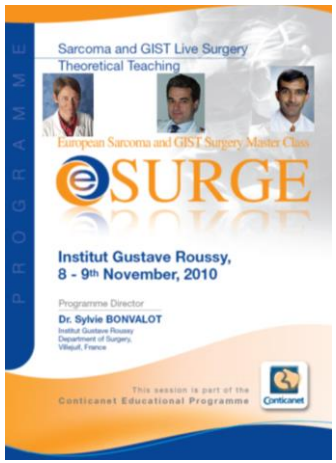
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

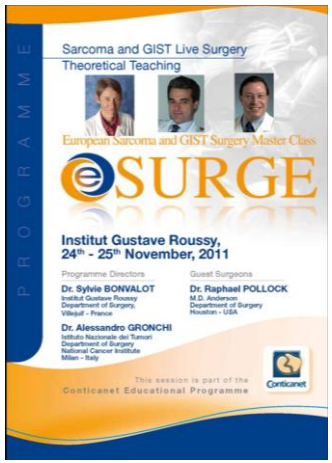
ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Technical Considerations in Surgery for Retroperitoneal Sarcomas: Position Paper from E-Surge, a Master Class in Sarcoma Surgery, and EORTC–STBSG

Sylvie Bonvalot, MD, PhD[1], Chandrajit P. Raut, MD, MSc[2], Raphael E. Pollock, MD, PhD[3], Piotr Rutkowski, MD[4], Dirk C. Strauss, MD[5], Andrew J. Hayes, MD[5], Frits Van Coevorden, MD[6], Marco Fiore, MD[7], Eberhard Stoeckle, MD[8], Peter Hohenberger, MD, PhD[9], and Alessandro Gronchi, MD[7]







EXPERT REVIEWS

Optimal management of primary retroperitoneal sarcoma: an update

Aisha B Miah[1,2], Jonathan Hannay[1,3], Charlotte Benson[1,4], Khin Thway[1,5], Christina Messiou[1,6], Andrew J Hayes[1,3] and Dirk C Strauss*[1,3]

Expert Rev. Anticancer Ther. Early online, 1–15 (2014)

Key issues

- Retroperitoneal sarcoma (RPS) is a rare cancer occurring in a complex space and encompass several different histological subtypes with influence the natural history, response to treatment and clinical outcomes.
- RPSs are best managed in specialist sarcoma referral centers in the context of an experienced multidisciplinary team.
- The diagnosis of retroperitoneal liposarcoma is often established with cross-sectional imaging usually in the form of CT scan.
- Unless … biopsy is manda…
- Macro… …nd often involve… …tivisceral en blo…
- Tumor grade and macroscopic complete resection are the two most important and consistent independent factors that dictate oncological outcome. Other factors that play a role in the long-term oncological outcome includes patient age, tumor subtype, microscopic resection margins, tumor size, primary or recurrent disease, multifocality, multimodality treatment and centralized multidisciplinary management in a specialist sarcoma center.
- Retroperitoneal liposarcoma is the most common histological subtype and locoregional recurrence following resection is the main reason for sarcoma-related deaths.
- Retroperitoneal leiomyosarcoma is the second commonest histological subtype and systemic metastasis is the main mode of postresection failure.
- The role of radiotherapy to improve local control is evolving, and the results of a multicenter randomized trial are eagerly awaited to establish the optimal roll to improve local control in RPSs.
- The choice of systemic treatment in RPSs, whether used for investigational studies, locally advanced or unresectable recurrent disease, should be histology driven.

Quality of primary surgery is the major determinant of outcome

EXPERT REVIEWS

Optimal management of primary retroperitoneal sarcoma: an update

Aisha B Miah[1,2], Jonathan Hannay[1,3], Charlotte Benson[1,4], Khin Thway[1,5], Christina Messiou[1,6], Andrew J Hayes[1,3] and Dirk C Strauss*[1,3]

Expert Rev. Anticancer Ther. Early online, 1–15 (2014)

Table 1. Demographics, histology subtypes, rate of complete resections and outcomes from major series reporting on retroperitoneal sarcomas.

	Gronchi *et al.* (2011) [8]	Strauss *et al.* (2010) [2]	Bonvalot *et al.* (2009) [3]	Gronchi *et al.* (2009) [4]	Lehnert *et al.* (2009) [5]	Van Dalen *et al.* (2007) [6]	Lewis *et al.* (1998) [7]
Period	2002–2008	1990–2009	1985–2005	1985–2001	1988–2002	1989–1994	1982–1997
Total cases	191	200	374	136	110	123	500
Primary (%)	71	100	100	62	65	100	56
Centre	Single	Single	Multicenter	Single	Single	Multicenter	Single
Age – median (years)	59	56	57	56	58	60	58
Tumor size – median (cm)	18	27	18	15	–	–	–
Tumor grade							
Low (%)							
High/intermediate							
Histology (%)							
Liposarcoma	45	76	59	57	54	38	41
Leiomyosarcoma	17	14	18	15	23	29	27
Other	38	10	23	28	23	33	32
R0/R1 resection	94	85	75	88	67	55	80
Median follow-up (months)	48	29	53	120	89	122	28
5-year overall survival (%)	67	64	57	51	51	39	54
5-year local recurrence-free survival (%)	72	55	51	52	59	39	59
Postoperative mortality (%)	3	3	3	–	6	4	4

LR rate 45-60% → 20%

Post-op RT should be banned

Pre-op RT is under investigation

Ann Surg Oncol
DOI 10.1245/s10434-013-2971-0

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

EDITORIAL – BONE AND SOFT TISSUE SARCOMAS

Quality of Local Treatment or Biology of the Tumor: Which are the Trump Cards for Loco-regional Control of Retroperitoneal Sarcoma?

Alessandro Gronchi, MD[1] and Raphael E. Pollock, MD, PhD[2]

we are to move a new set-point in RPS, in which specifically useful treatment options can be tailored to the individual patient.

QUALITY OF LOCAL THERAPY

Surgical Strategy

Some authors have advocated for the widest possible surgical resection at presentation, a strategy at variance with past recommendations advocating grossly complete extirpation in which the need or utility of resecting adjacent organs was limited to unequivocal direct tumor involvement.[3,4] These retrospective analyses have favored a more aggressive adjacent organ resection approach, reporting greater than 75 % local control at 5 years. The need to standardize these seemingly disparate surgical strategies has been addressed recently by a panel of European and North American experts who have described how these tumors might be optimally approached. In essence, this surgical strategy consists of liberal en bloc resection of surrounding adjacent organs, even if not directly infiltrated, tempered by survival. Manifestly, patients affected by any of these tumors are best treated by surgeons who are comfortable and familiar with the uncertainties of these biological issues and how such vagaries impact multidisciplinary approaches to these diseases.

Radiation Therapy

As correctly pointed out by McBride et al.,[7,8] given that RT has a demonstrated benefit in the treatment of soft tissue sarcoma of the extremity and trunk, there is strong reason to believe that it may similarly benefit those with RPS. Nevertheless, this has never been demonstrated in any prospective trial. Radiotherapy appears to improve local control as reported in several retrospective studies; [9,10] however, this potential advantage must be weighed against potential side effects. Most series favor the use of external beam RT in the preoperative setting, because it is well tolerated and can be administered at a total dose of 50.4 Gy. Postoperative RT usually is no longer considered given that effective doses (60 Gy or higher) cannot be delivered to the tumor bed, which is usually occupied or

BIOLOGY OF THE TUMOR

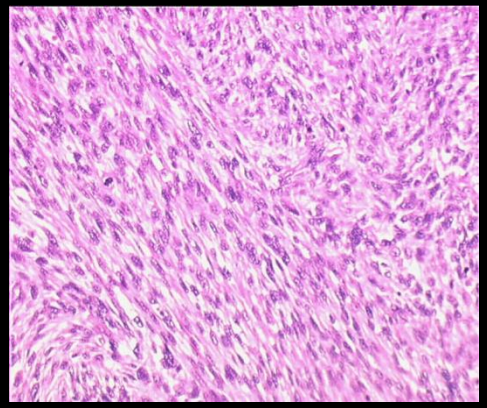
Histological Subtype

RPS is not a single disease entity. Even the commonest subtype, liposarcoma, cannot be considered as a single malignancy and is further subdivided into at least four distinctive tumor biologic categories: atypical lipomatous tumor, also referred to as well differentiated liposarcoma, dedifferentiated liposarcoma, myxoid/round cell liposarcoma, and pleomorphic liposarcoma.[12] Taken together, these liposarcoma subtypes account for 50 % of all RPS.

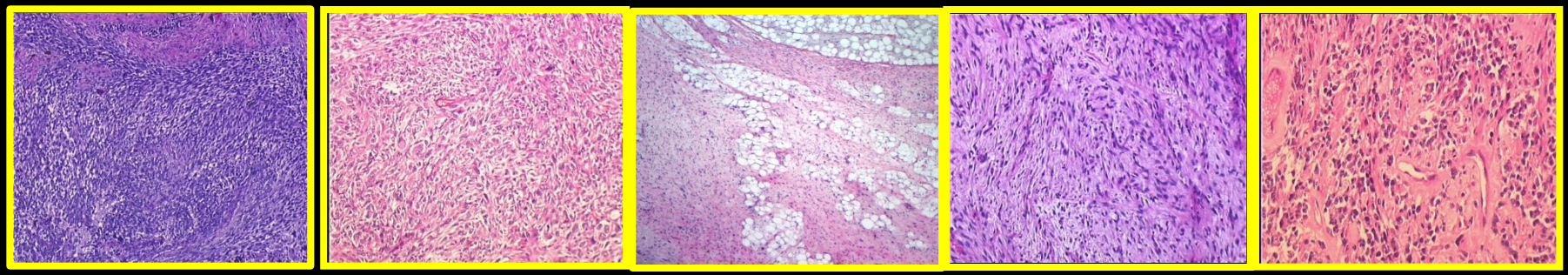
The approach to these different types of liposarcoma must be individualized, although this remains an area of unresolved controversy. Some authors advocate a more conservative approach when dealing with pure atypical lipomatous tumor given the very indolent biology of this [illegible] The trade-off between expected benefits versus morbidity must be carefully balanced when contemplating RT as a therapeutic adjunct in patients affected by high-grade RPS.

Multifocality/Multicentricity

Patterns of presentation, especially in retroperitoneal liposarcoma, may confer useful information about extent of



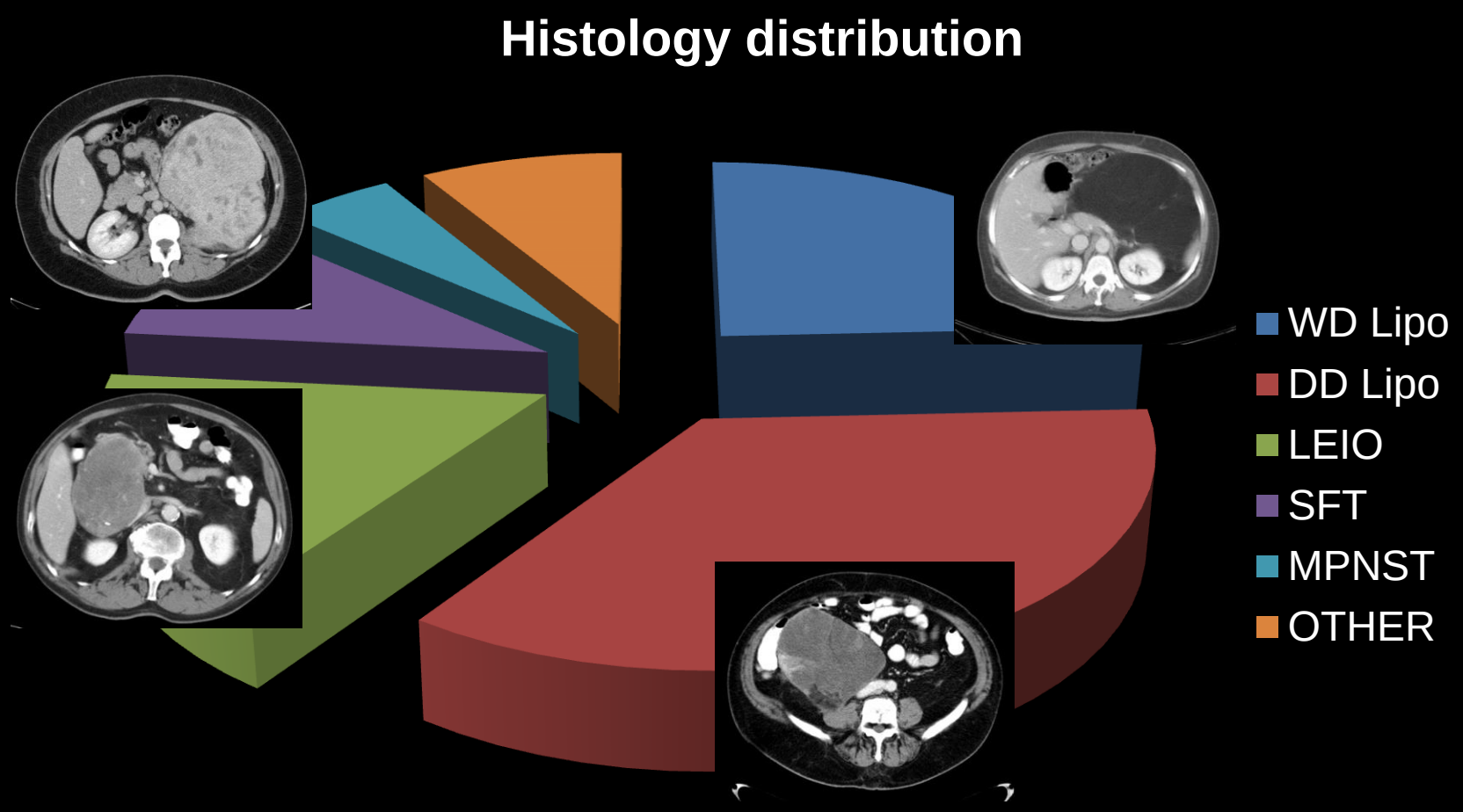
Adult type soft tissue sarcoma



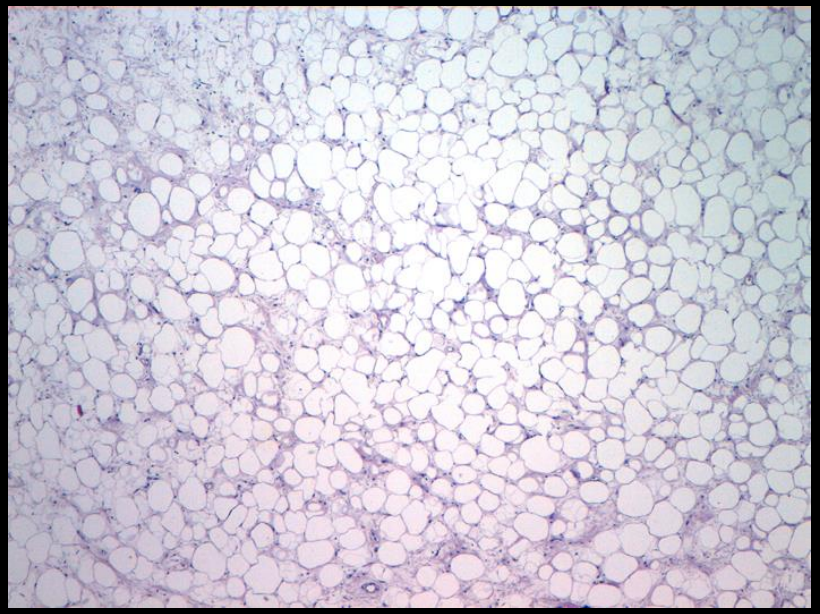
UPS SYNOVIALSA LIPOSA LEIOMIOSA MPNST

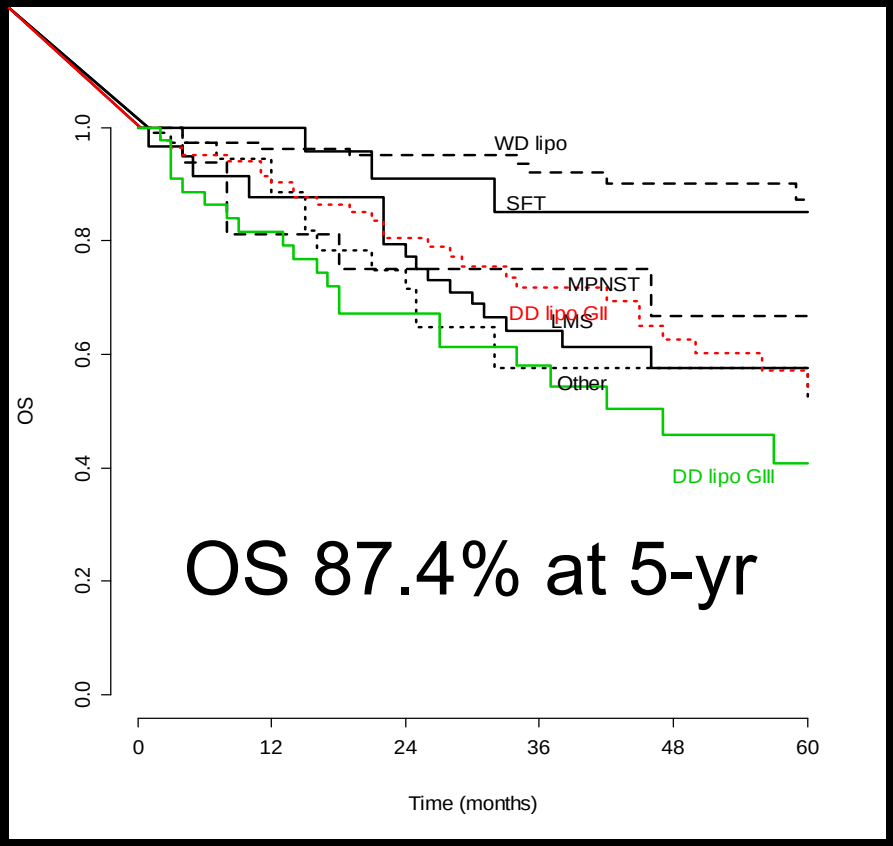
. . . . . .

377 primary RPS between 2002-2011 at INT-IGR

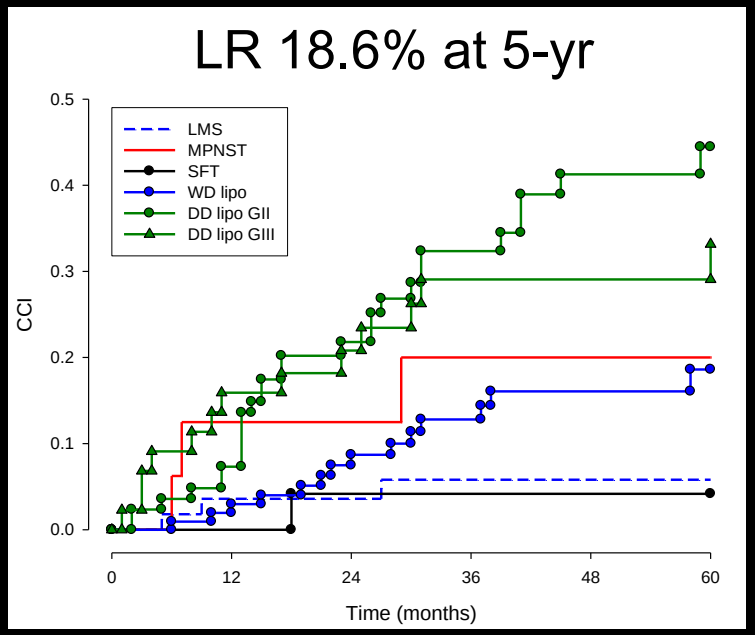


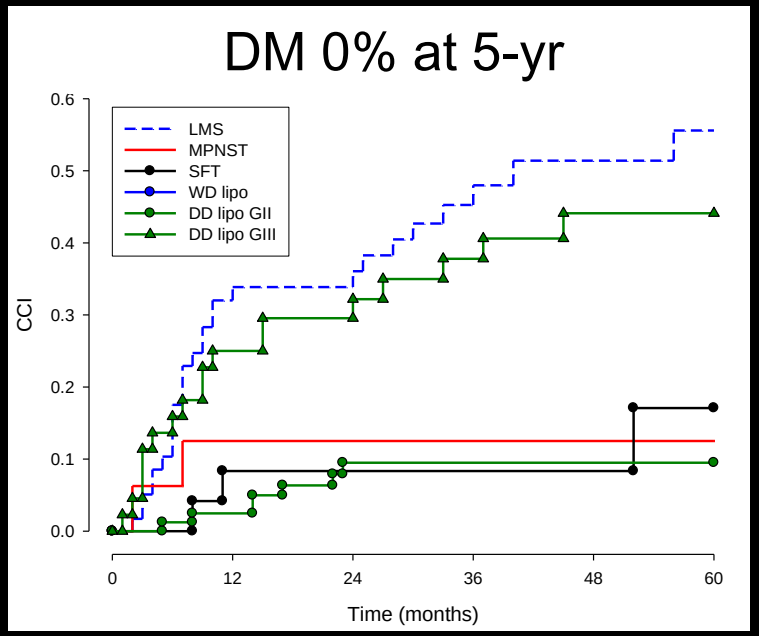
1. Well Differentiated Liposarcoma




OS
1.0
0.8
0.6
0.4
0.2
0.0
WD lipo
SFT
MPNST
DD lipo GII
LMS
Other
DD lipo GIII
0
12
24
36
48
60
Time (months)

OS 87.4% at 5-yr

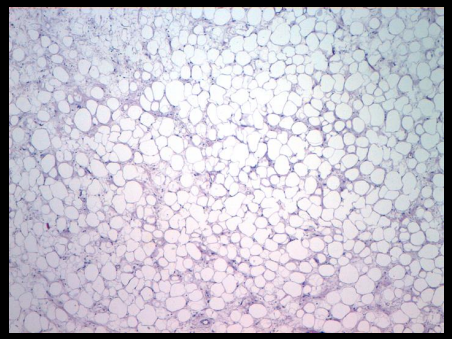

LR 18.6% at 5-yr
CCI
0.5
0.4
0.3
0.2
0.1
0.0
LMS
MPNST
SFT
WD lipo
DD lipo GII
DD lipo GIII
0
12
24
36
48
60
Time (months)

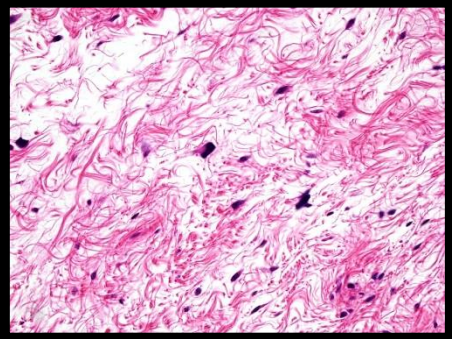

DM 0% at 5-yr
CCI
0.6
0.5
0.4
0.3
0.2
0.1
0.0
LMS
MPNST
SFT
WD lipo
DD lipo GII
DD lipo GIII
0
12
24
36
48
60
Time (months)

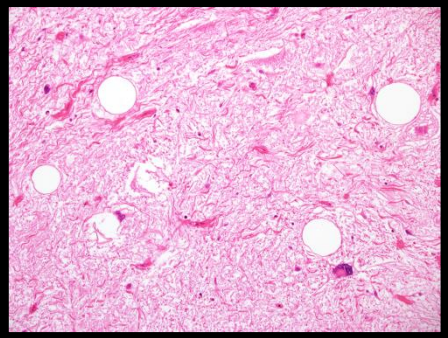
1. The spectrum of WD Lipo

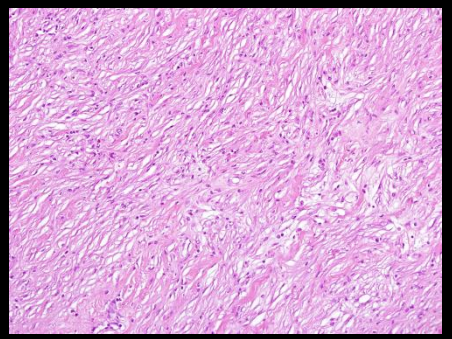
Pure ALT

Lipoma-like, sclerosing, inflammatory, myxoid like, cellular (GI DD)









Tailoring extent of surgery to histology

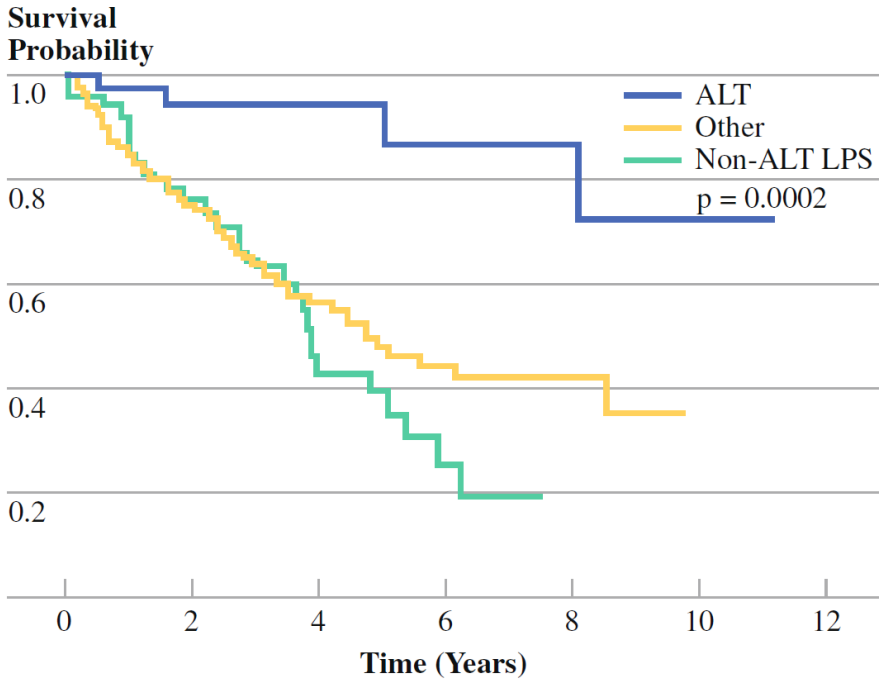
Ann Surg Oncol (2009) 16:667–675
DOI 10.1245/s10434-008-0250-2

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

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Establishing Prognosis in Retroperitoneal Sarcoma: A New Histology-Based Paradigm

Daniel A. Anaya, MD[1], Guy Lahat, MD[1], Xuemei Wang, MS[2], Lianchun Xiao, MS[2], Daniel Tuvin, MD[1], Peter W. Pisters, MD[1], Dina C. Lev, MD[3], and Raphael E. Pollock, MD, PhD[1]

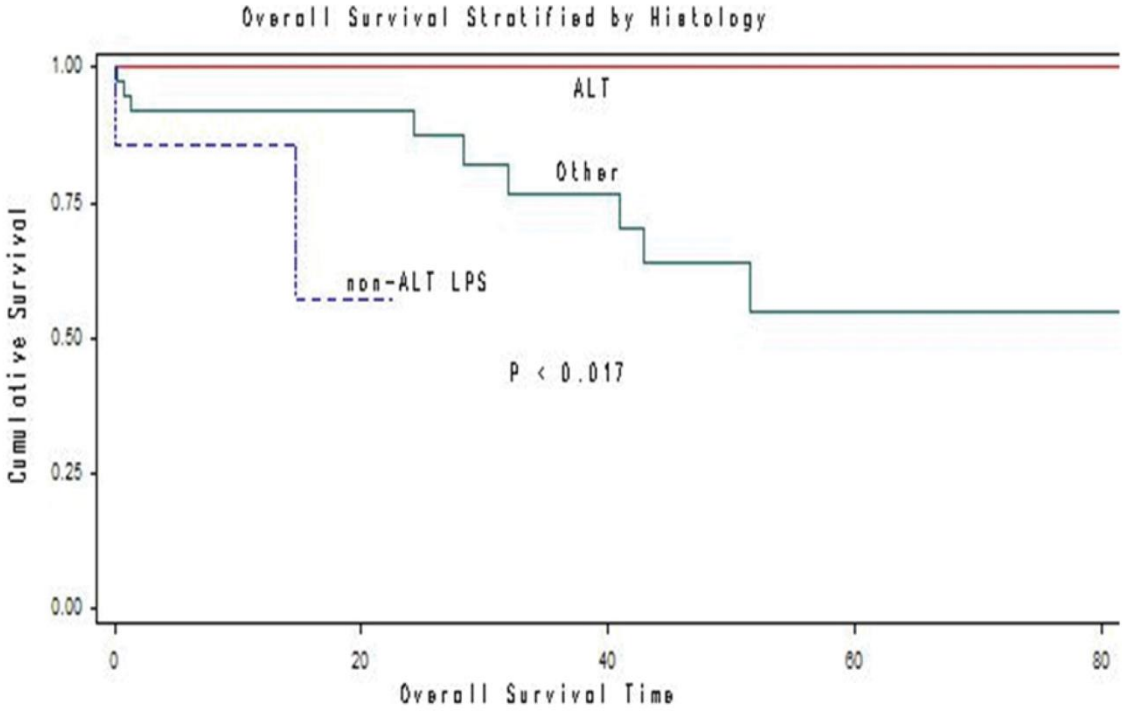


The American Journal of Surgery®

Impact of histology on survival in retroperitoneal sarcoma

Russell E. Brown, M.D., Charles R. St. Hill, M.D., Quincy J. Greene, M.D., Russell W. Farmer, M.D., Nathan P. Reuter, M.D., Glenda G. Callendar, M.D., Robert C.G. Martin, M.D., Ph.D., Kelly M. McMasters, M.D., Ph.D., Charles R. Scoggins, M.D., M.B.A.*

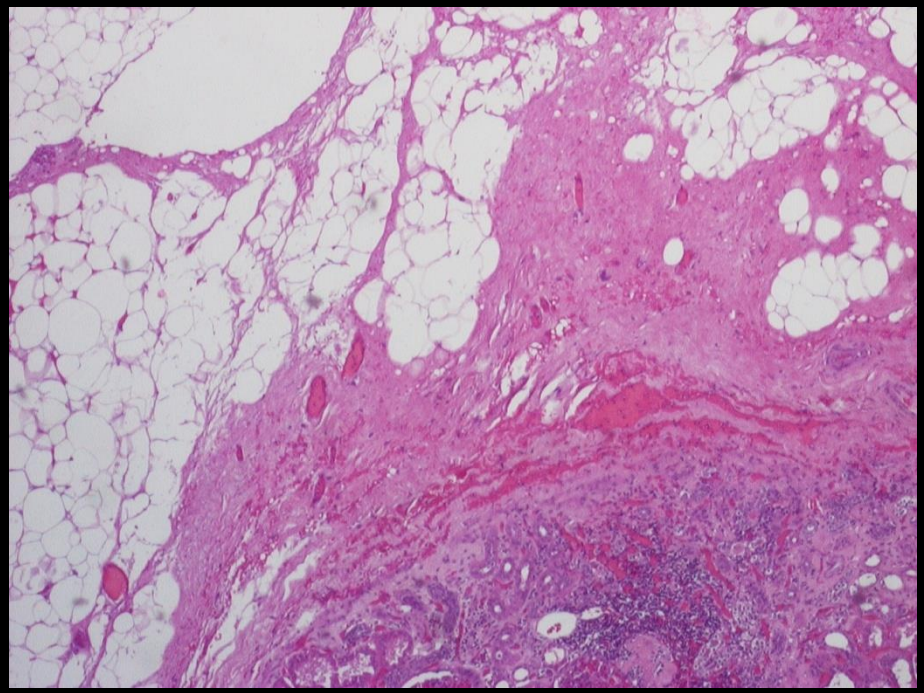
Am J Surg. 2011 202(6):748-52

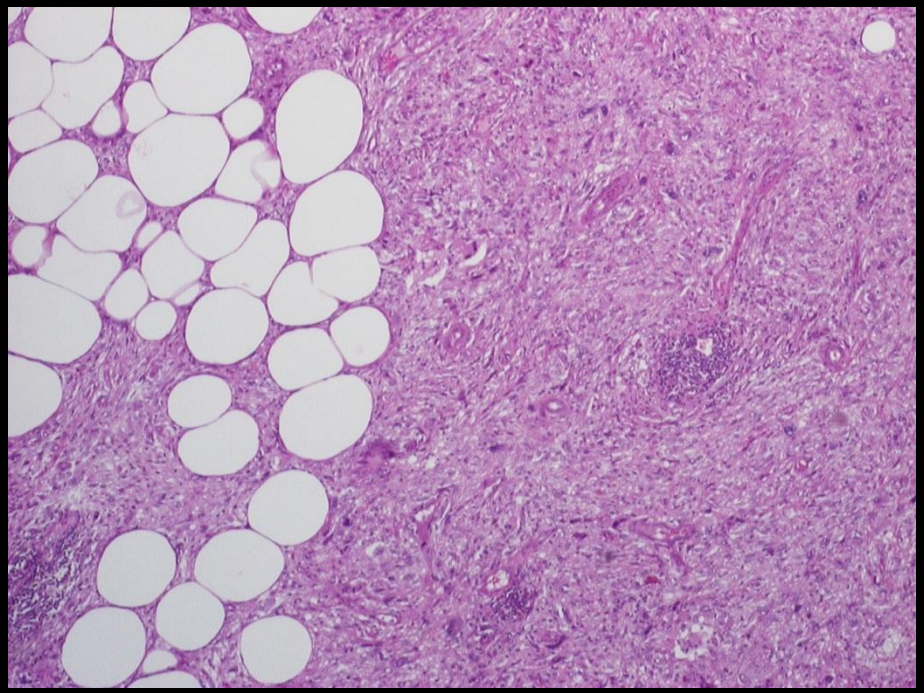


…but

…don’t miss the chance for cure !


L

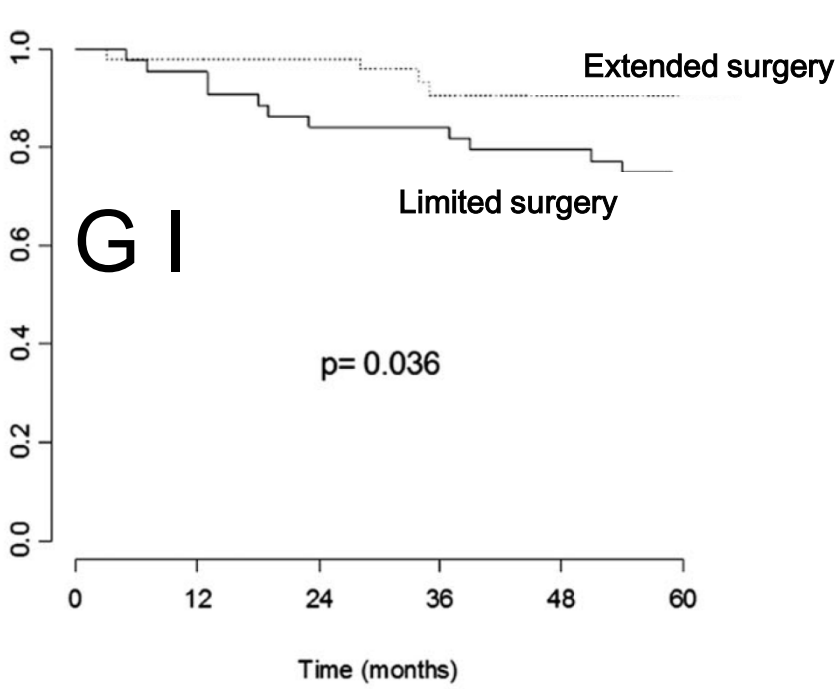


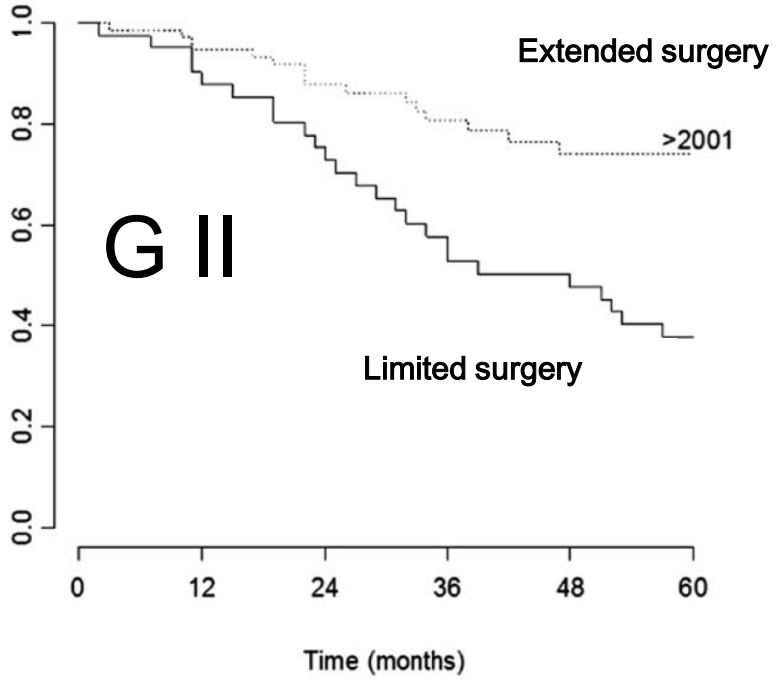


Annals of Oncology 23: 1067–1073, 2012
doi:10.1093/annonc/mdr323
Published online 16 July 2011

Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas

A. Gronchi[1]*, R. Miceli[2], C. Colombo[1], S. Stacchiotti[3], P. Collini[4], L. Mariani[2], C. Sangalli[5], S. Radaelli[1], R. Sanfilippo[3], M. Fiore[1] & P. G. Casali[3]

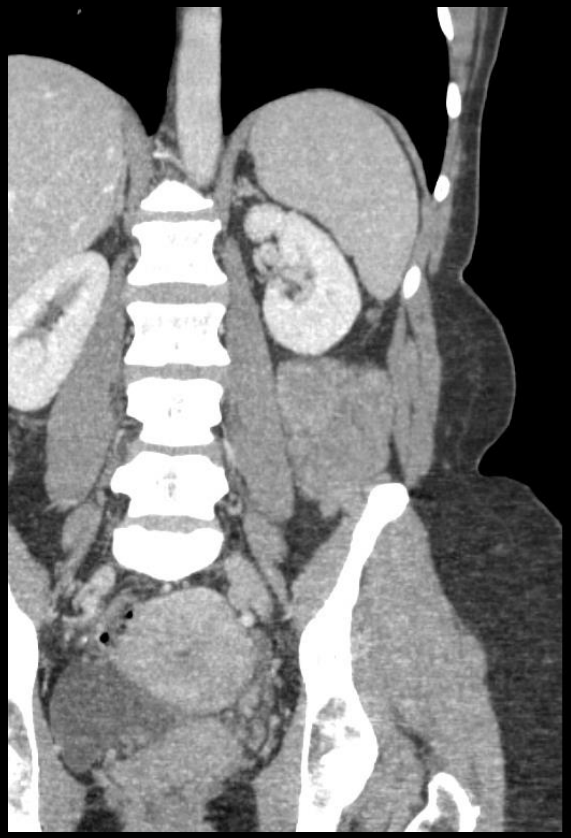


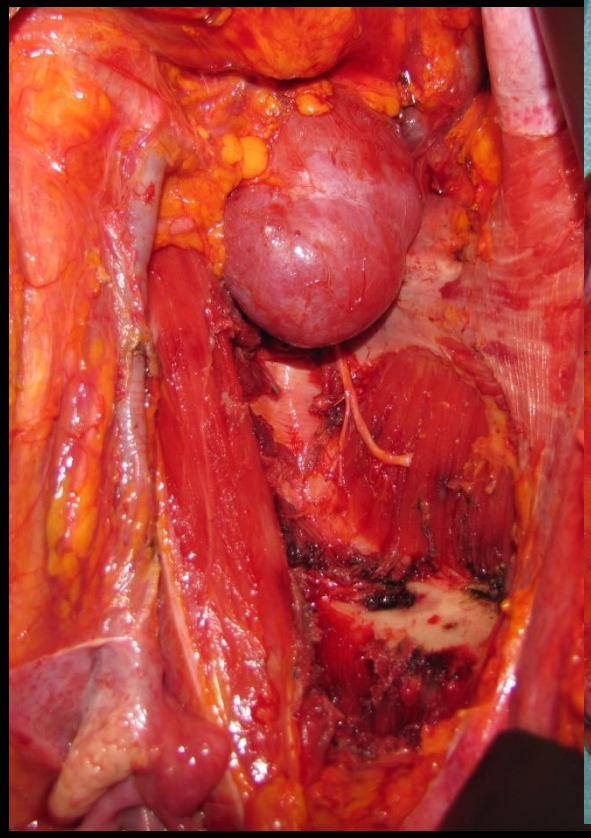


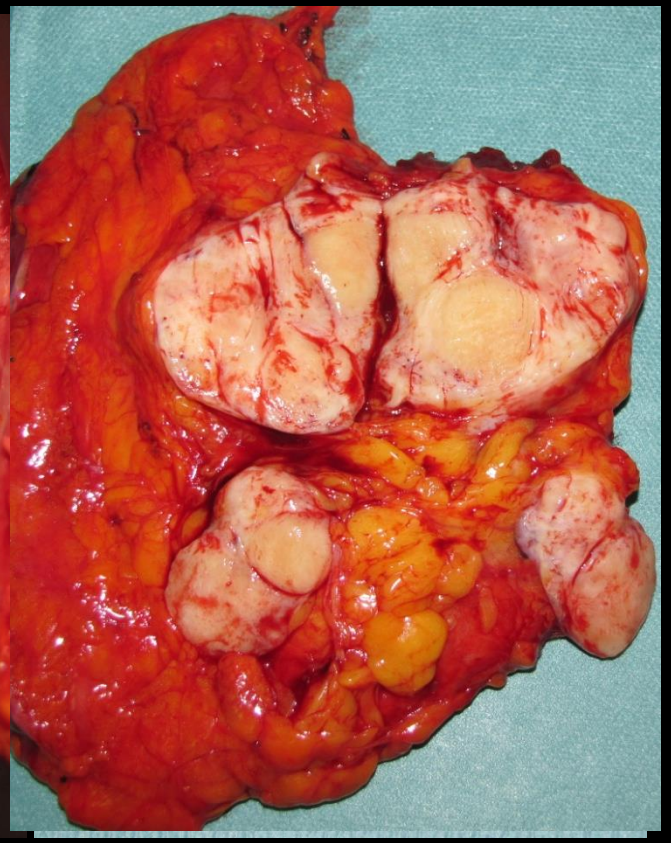
1. WD liposarcoma

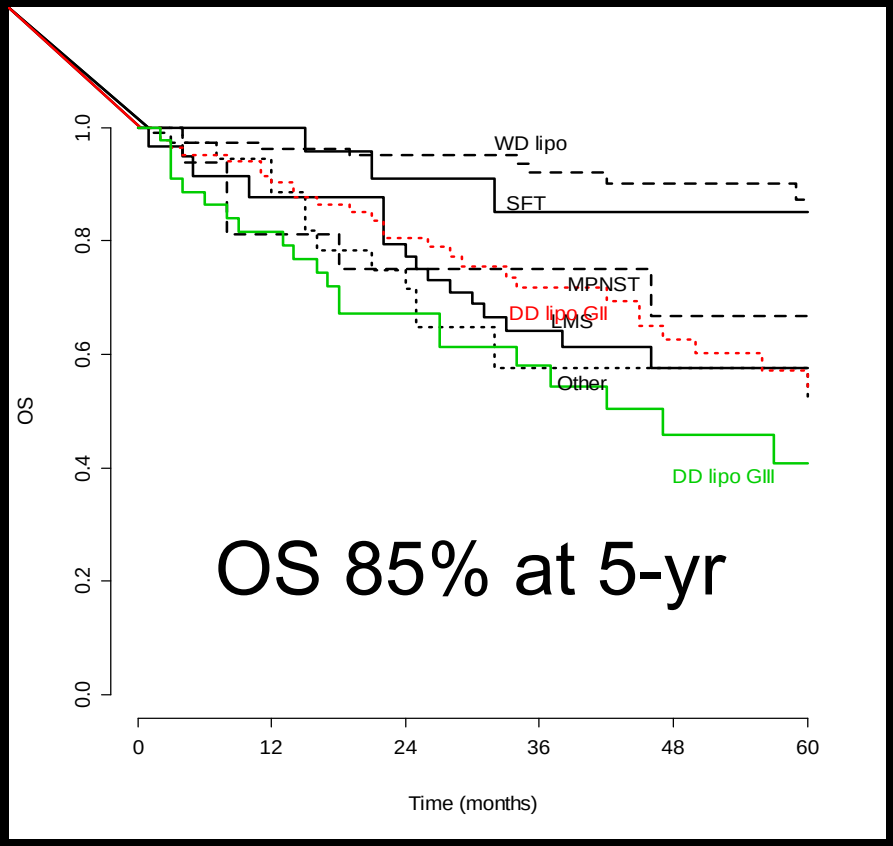
- Need to extend the resection to surrounding organs because:
  - It’s important to clear all the retroperitoneal “fat”, since it is macroscopically undistinguishable from tumor
  - It’s difficult to predict the absence of a DD component only on CT scan/MRI, and this approach benefit both WD and GII DD liposarcoma

2. Solitary Fibrous Tumor

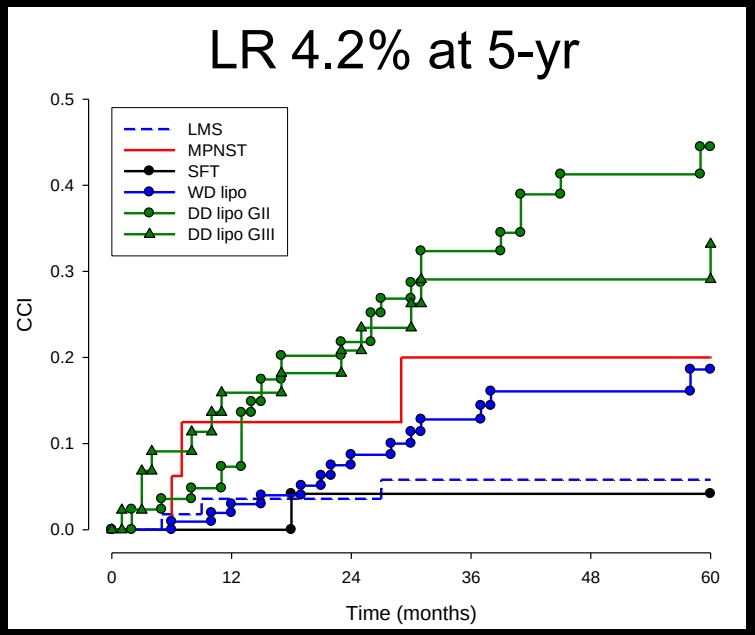







OS
1.0
0.8
0.6
0.4
0.2
0.0
WD lipo
SFT
MPNST
DD lipo GII
LMS
Other
DD lipo GIII
0
12
24
36
48
60
Time (months)

OS 85% at 5-yr


LR 4.2% at 5-yr
CCI
0.5
0.4
0.3
0.2
0.1
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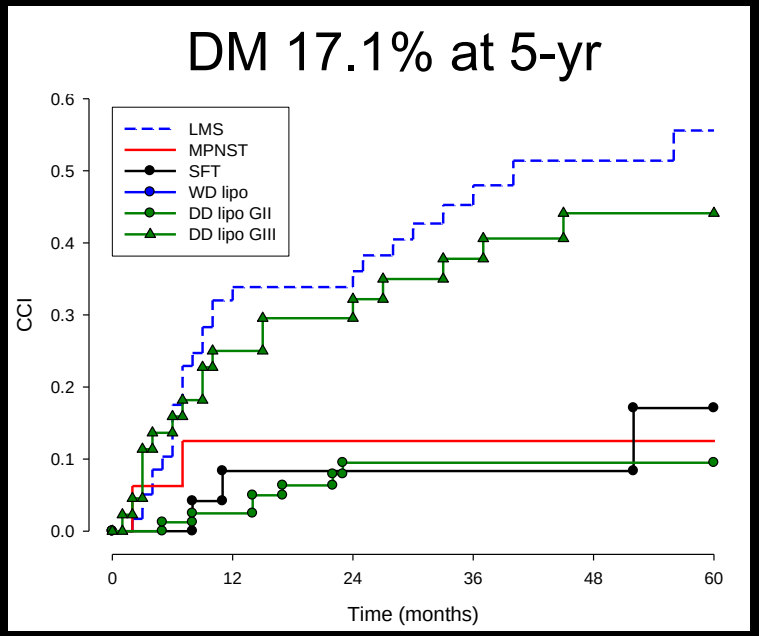
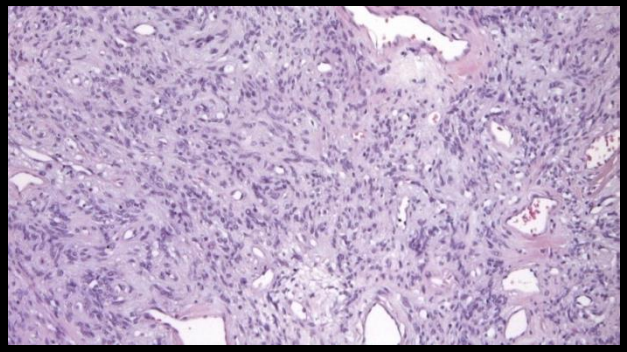
LMS
MPNST
SFT
WD lipo
DD lipo GII
DD lipo GIII
0
12
24
36
48
60
Time (months)

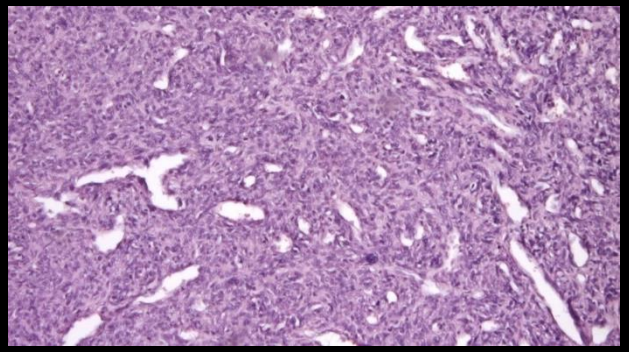

DM 17.1% at 5-yr
CCI
0.6
0.5
0.4
0.3
0.2
0.1
0.0
LMS
MPNST
SFT
WD lipo
DD lipo GII
DD lipo GIII
0
12
24
36
48
60
Time (months)

2. The spectrum of SFT

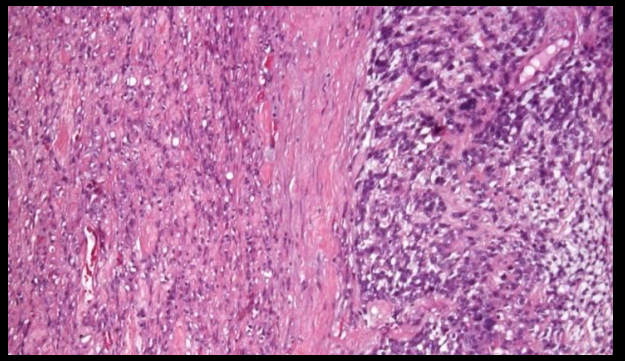
Classic SFT



Malignant SFT



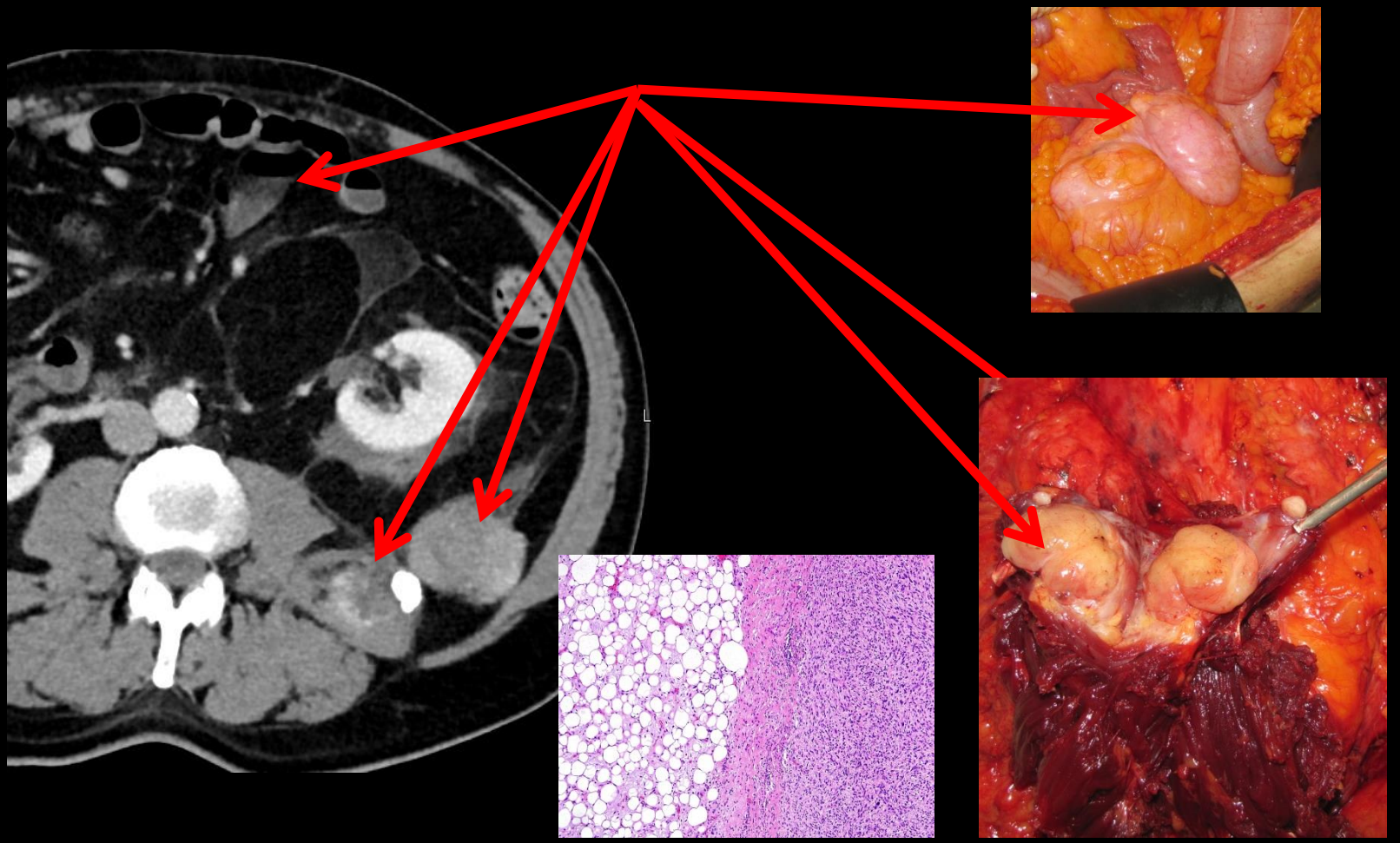
DD SFT

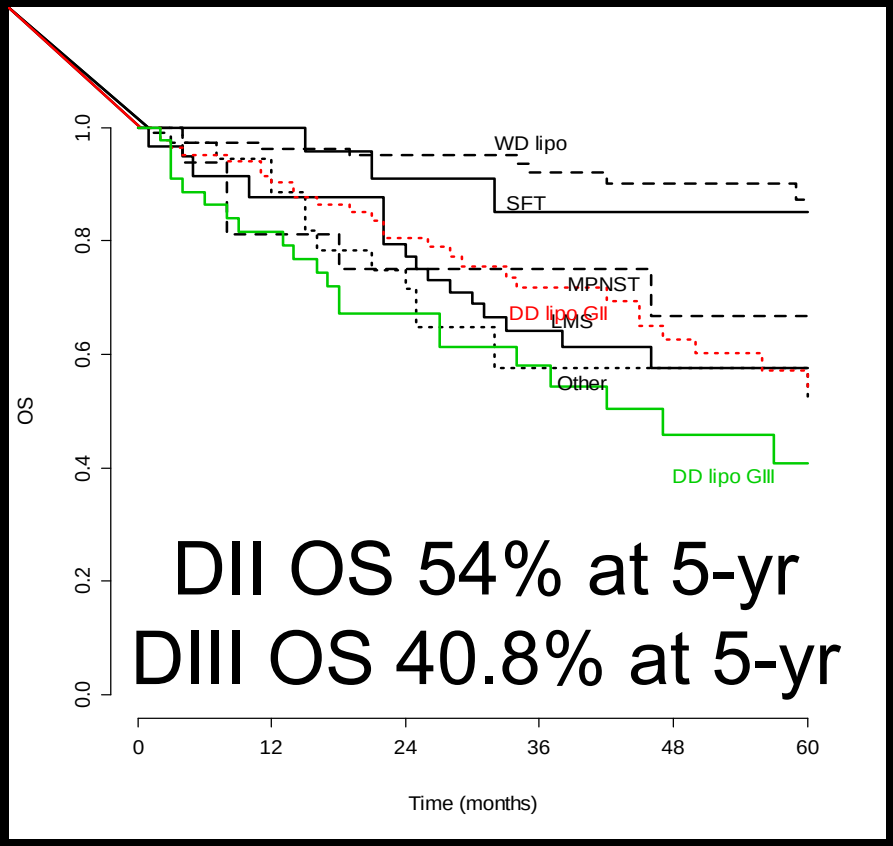


2. Solitary Fibrous Tumor

- The 2nd commonest low grade sarcoma at this site
- Easier to eradicate from the retroperitoneum
- Retroperitoneal organs may be sometimes spared, given the different pattern of growth and spread through the retroperitoneum
- Late recurrences in low grade SFT and distant recurrence in high grade variants are possible.

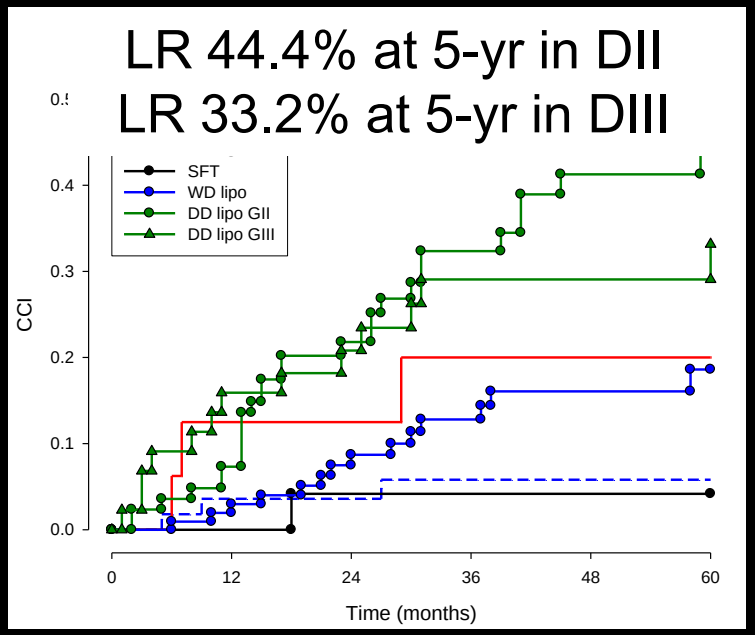
3. Dedifferentiated Liposarcoma

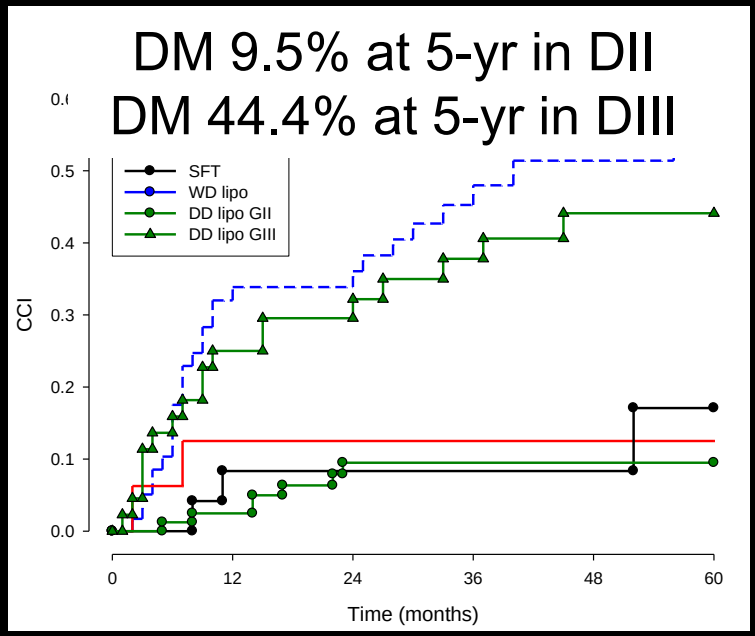




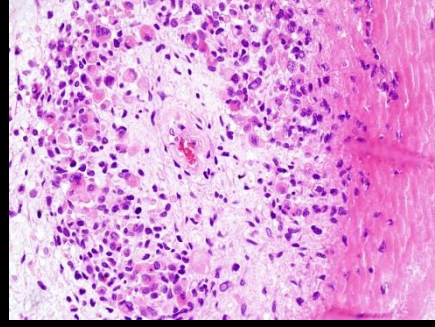
DII OS 54% at 5-yr

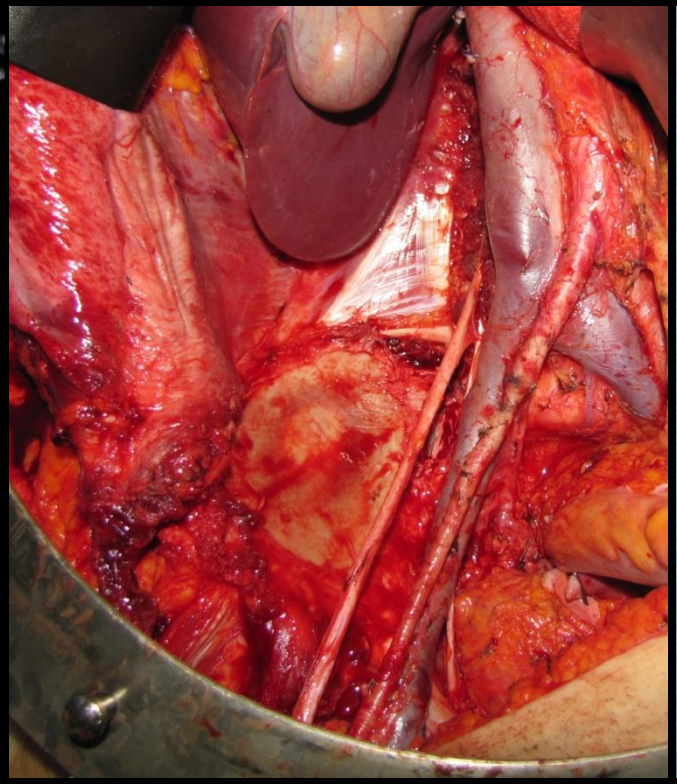
DIII OS 40.8% at 5-yr

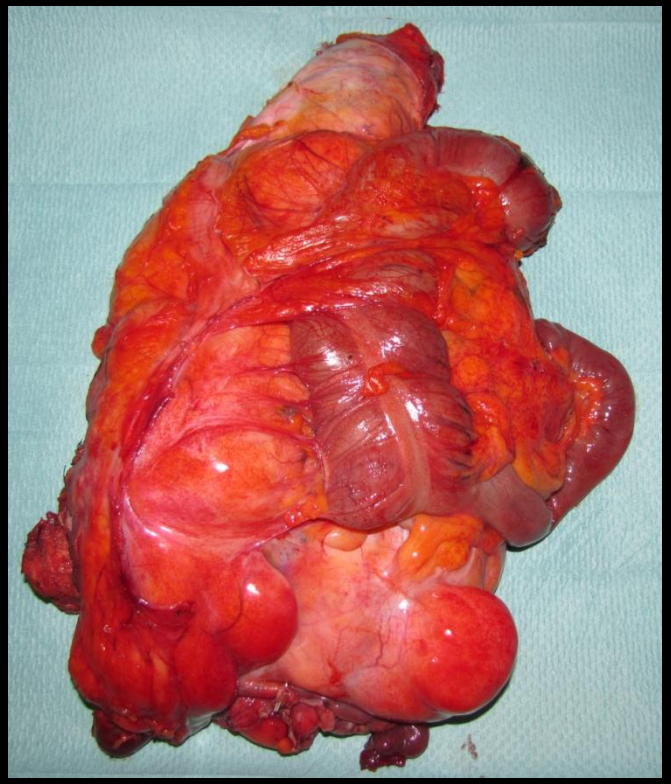




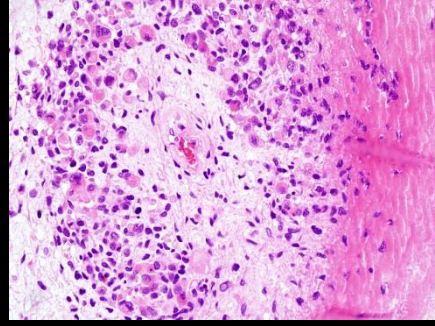
DD Lipo with rabdo component

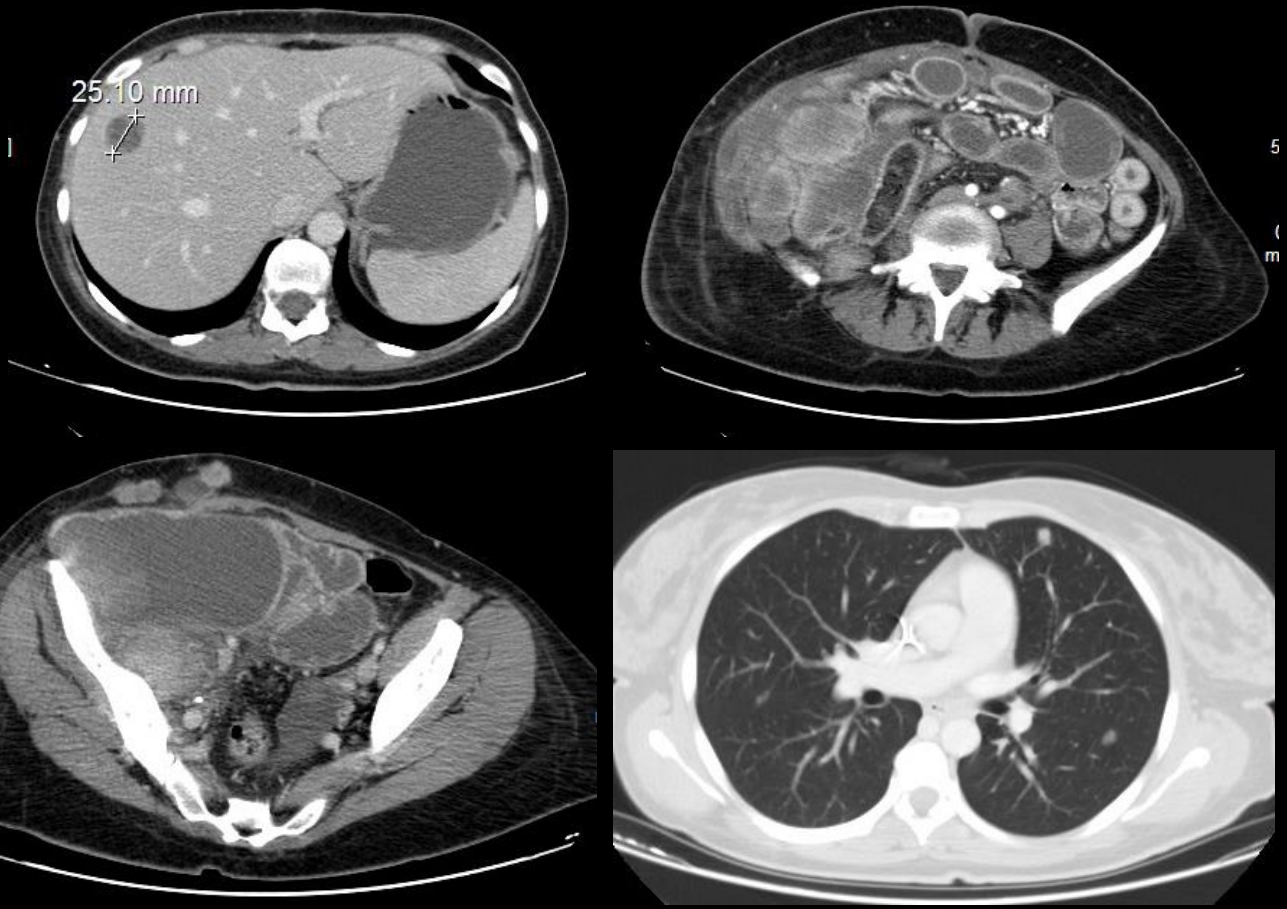






2 months later





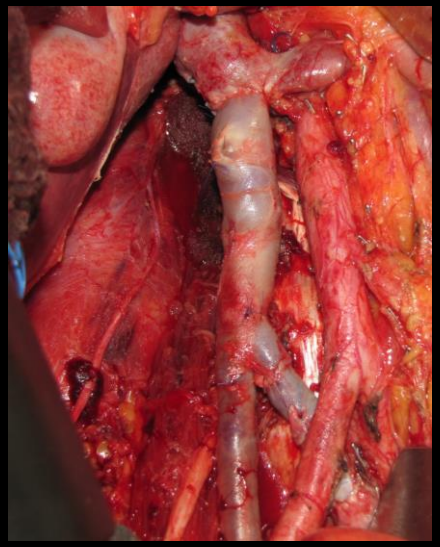
3. Dedifferentiated liposarcoma

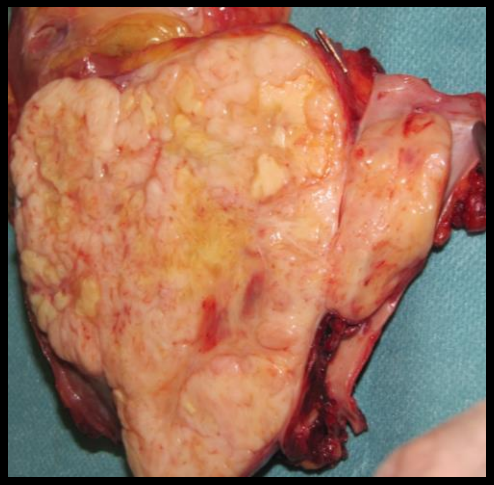
- More difficult to eradicate
  - Shorter clinical history
  - Higher risk of invasion of surrounding organs/muscles
  - Higher risk of peritoneal cavity involvement

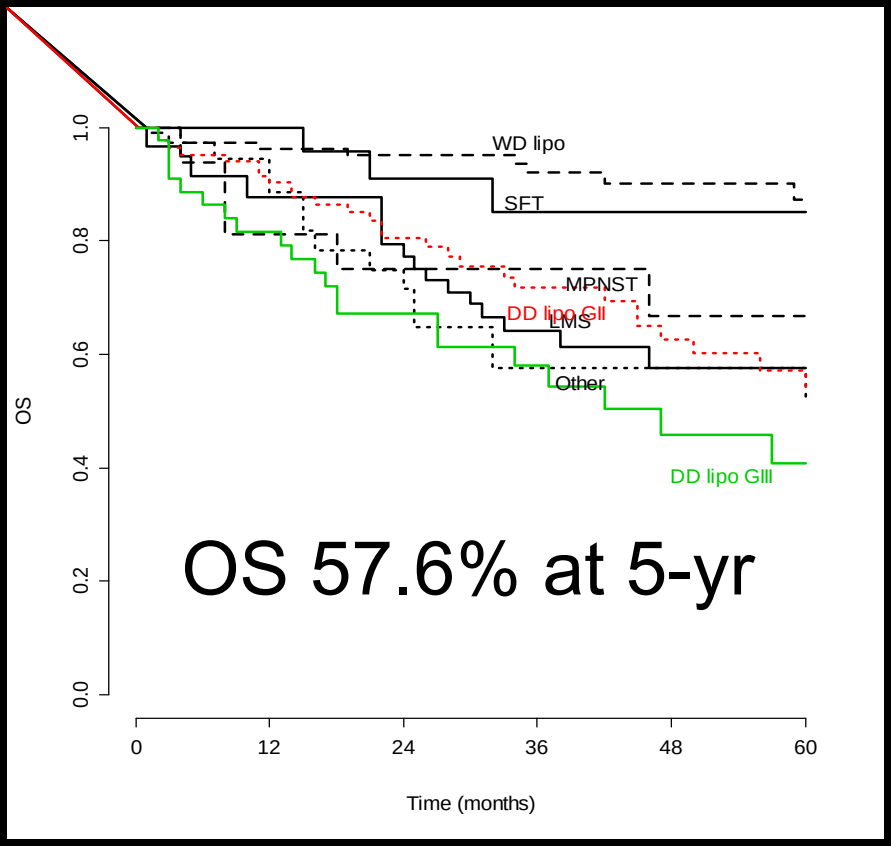
- Higher risk of loco-regional recurrences and of distant spread– especially for the high grade and miogenic differentiation group.

- Comlementary therapies are needed to address the systemic risk

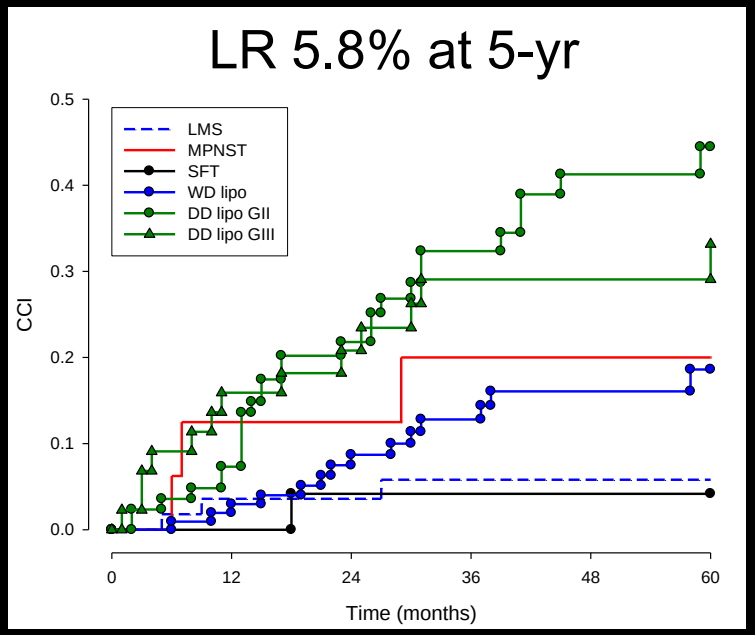
4. Leiomyosarcoma






OS
1.0
0.8
0.6
0.4
0.2
0.0
WD lipo
SFT
MPNST
DD lipo GII
LMS
Other
DD lipo GIII
0
12
24
36
48
60
Time (months)

OS 57.6% at 5-yr


LR 5.8% at 5-yr
CCI
0.5
0.4
0.3
0.2
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LMS
MPNST
SFT
WD lipo
DD lipo GII
DD lipo GIII
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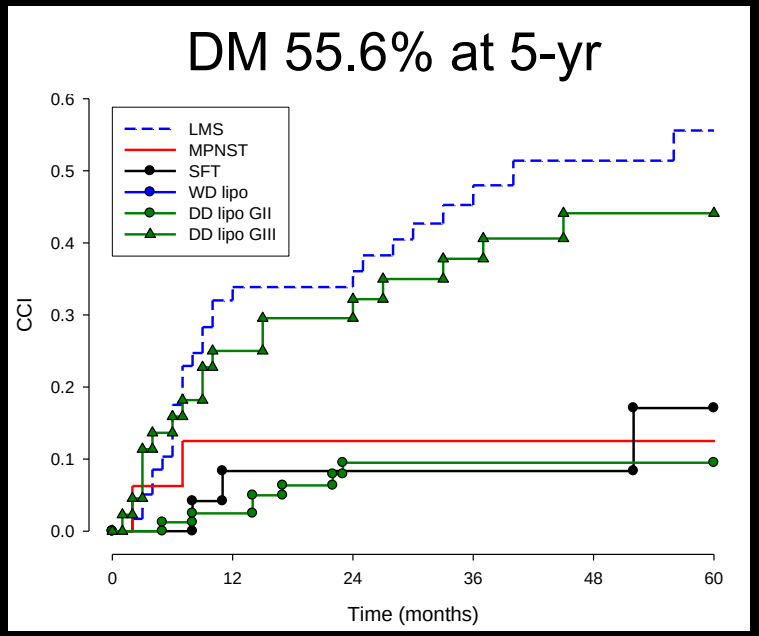
60
Time (months)


DM 55.6% at 5-yr
CCI
0.6
0.5
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0.3
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SFT
WD lipo
DD lipo GII
DD lipo GIII
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12
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60
Time (months)


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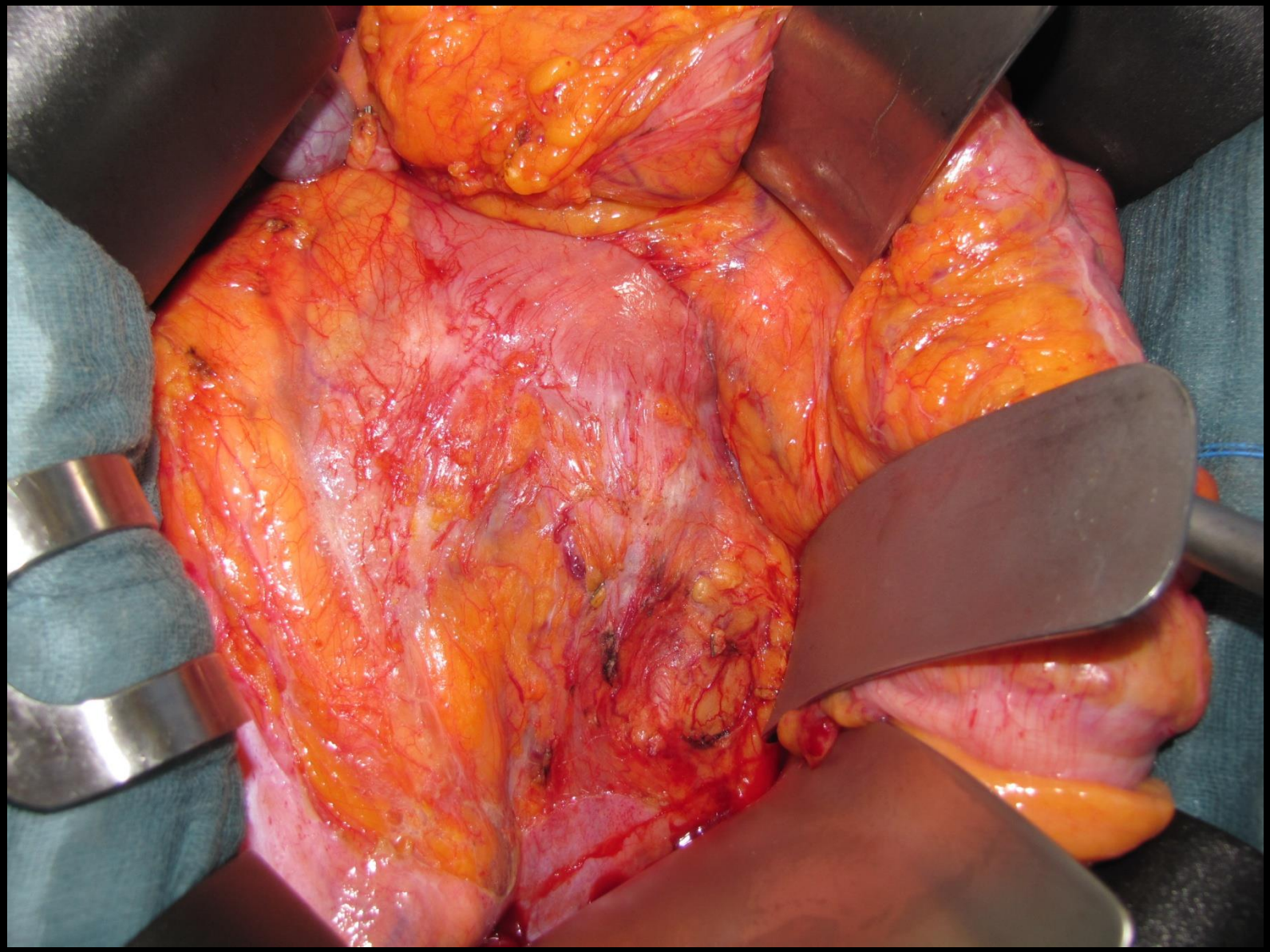
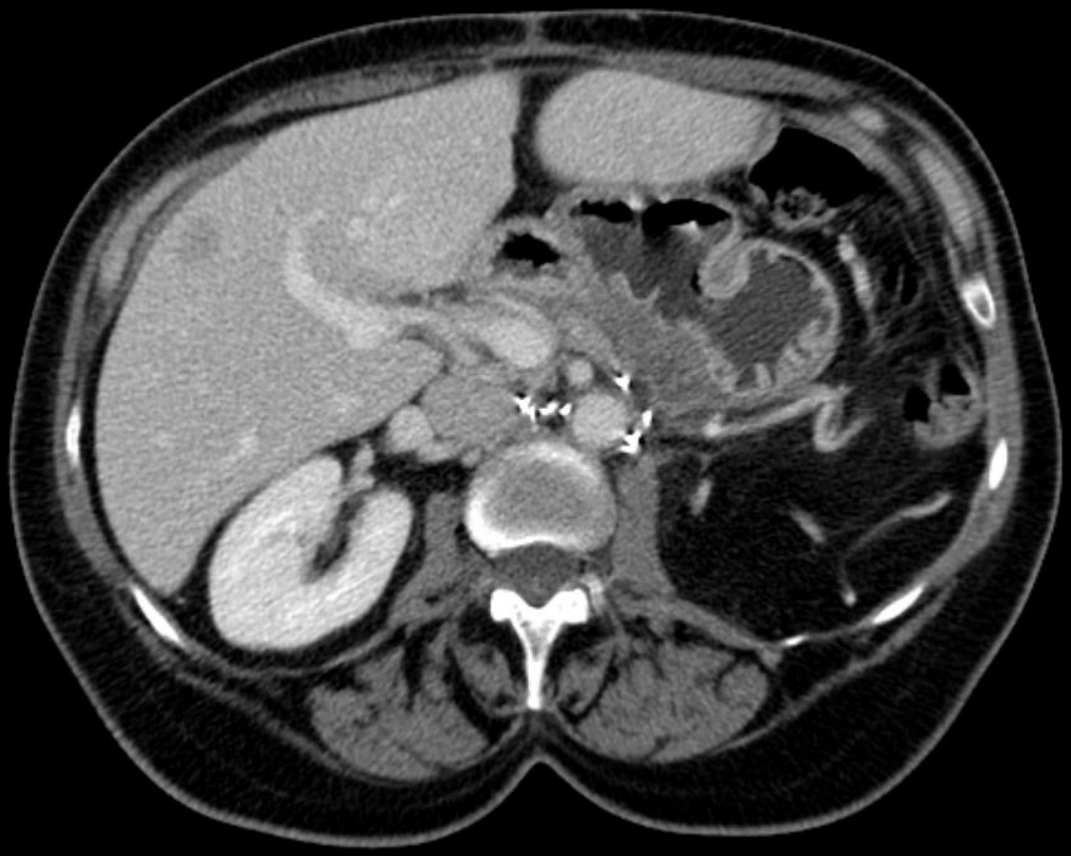


8 months later



4. Leiomyosarcoma

- No need to clear all the retroperitoneal fat
- Some adjacent organs may be spared
- Often arises/involves a major retroperitoneal vein (IVC, renal, gonadal veins)
- Optimal surgery obtains local control in the vast majority of patients.

- High risk of distant spread.

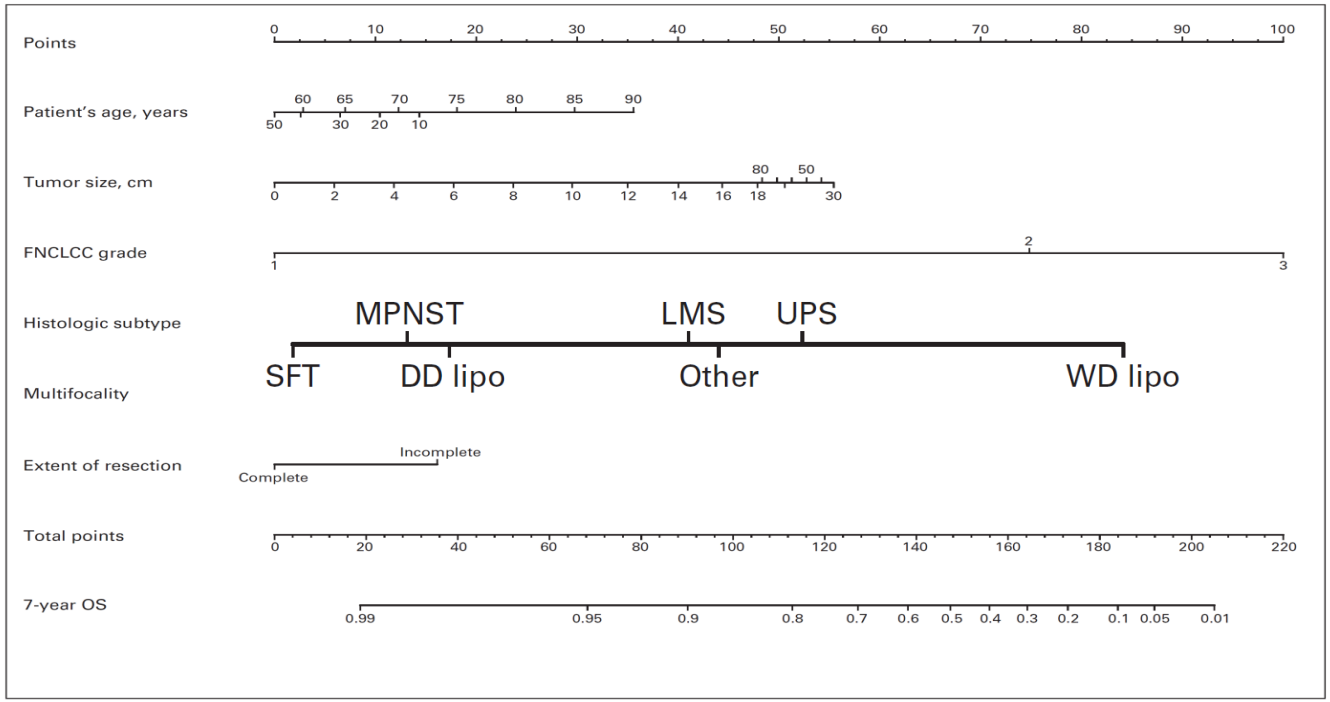
VOLUME 31 · NUMBER 13 · MAY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcome Prediction in Primary Resected Retroperitoneal Soft Tissue Sarcoma: Histology-Specific Overall Survival and Disease-Free Survival Nomograms Built on Major Sarcoma Center Data Sets

Alessandro Gronchi, Rosalba Miceli, Elizabeth Shurell, Fritz C. Eilber, Frederick R. Eilber, Daniel A. Anaya, Michael W. Kattan, Charles Honoré, Dina C. Lev, Chiara Colombo, Sylvie Bonvalot, Luigi Mariani, and Raphael E. Pollock



…in brief

- A frontline extended approach is associated with improved LR and OS.
- The primary approach is crucial: need to minimize marginal margins, often resecting adherent uninvolved visceral organs.
- Preservation of specific organs (ie kidney, duodenum-head of the pancreas, bladder, etc.) should be considered on an individualized basis and adapted to histological subtypes. It mandates a specific expertise in the disease to make the right decisions
- Use of preop RT is under investigation and will possibly benefit low-intermediate grade tumors.
- Medical treatments should be considered when the systemic risk is high (GIII DD Lipo and Leio)

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

…in December










… alessandro.gronchi@istitutotumori.mi.it

Ann Surg Oncol (2010) 17:1507–1514
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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Aggressive Surgery in Retroperitoneal Soft Tissue Sarcoma Carried Out at High-Volume Centers is Safe and is Associated With Improved Local Control

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