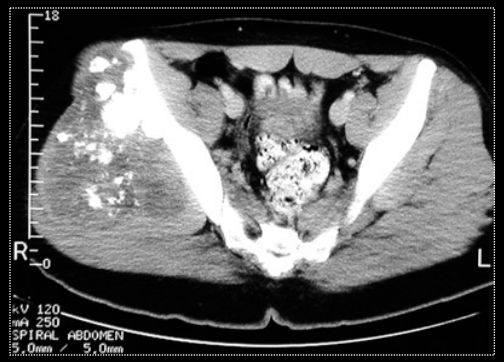
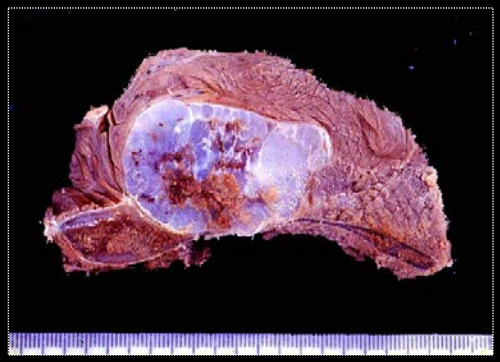
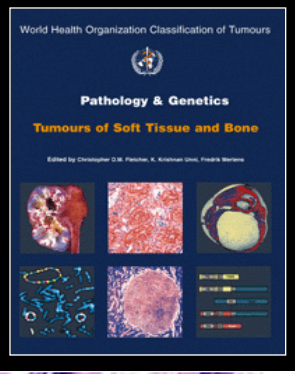
RETROPERITONEAL SARCOMA
Pathology and molecular analysis

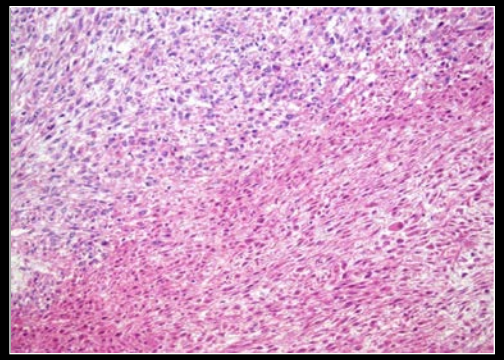
ENRIQUE DE ALAVA

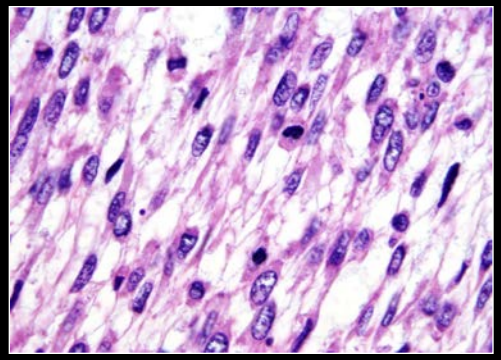
Sarcoma diagnosis is an integrative activity

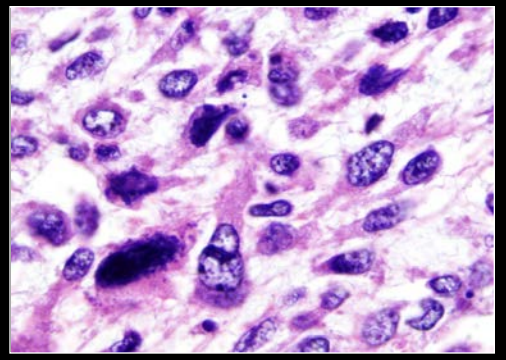


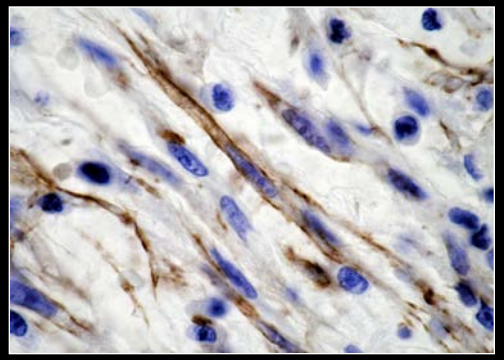


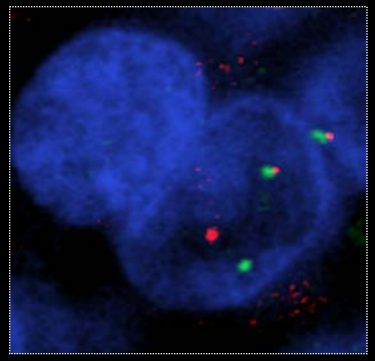


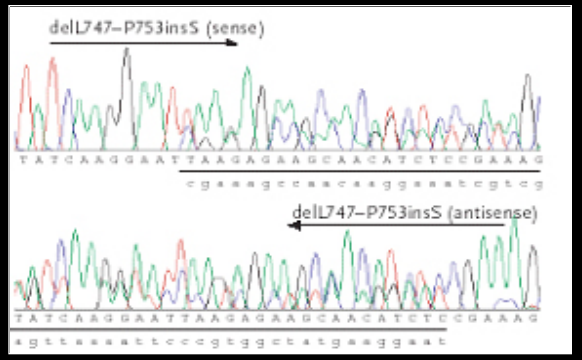


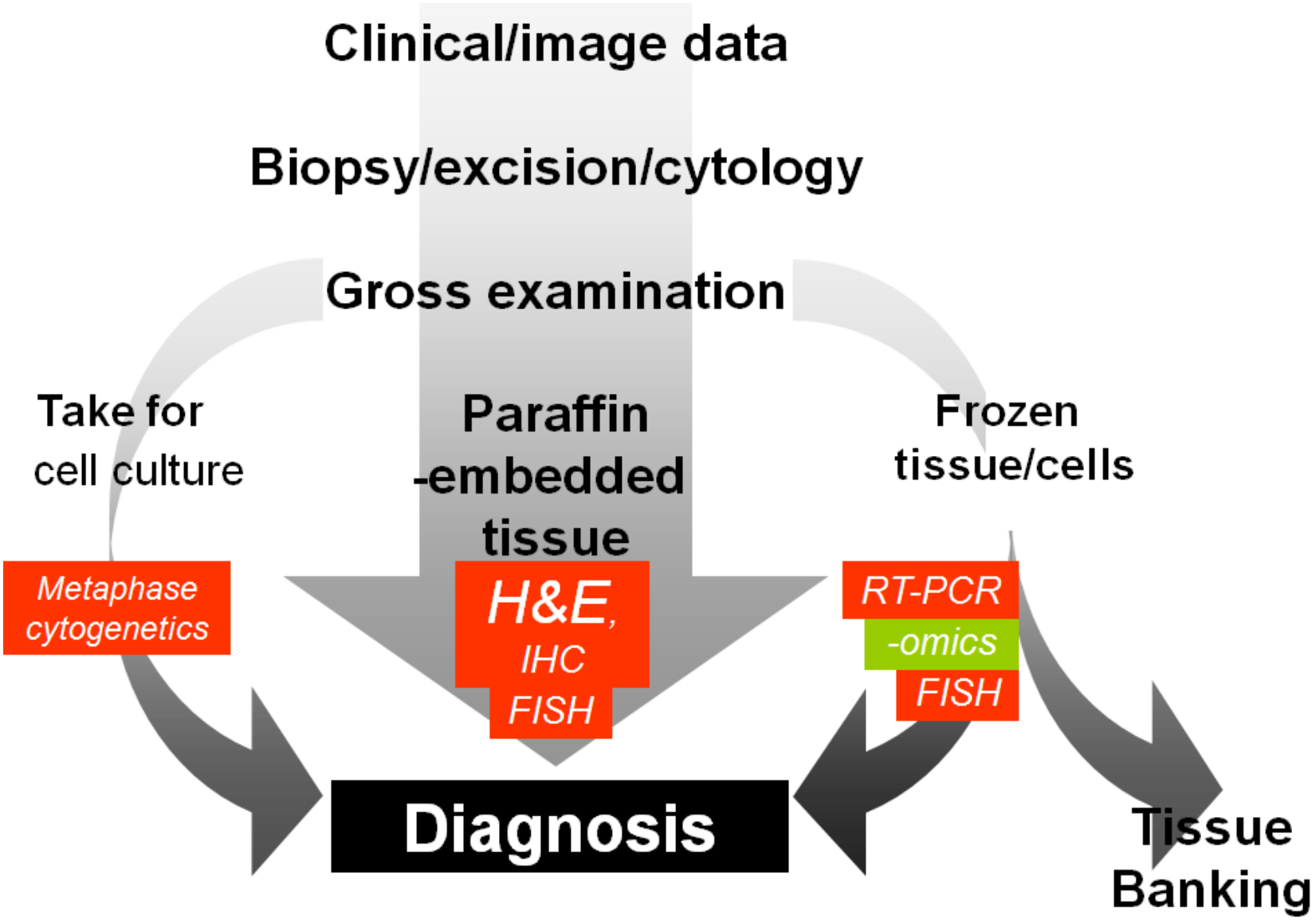








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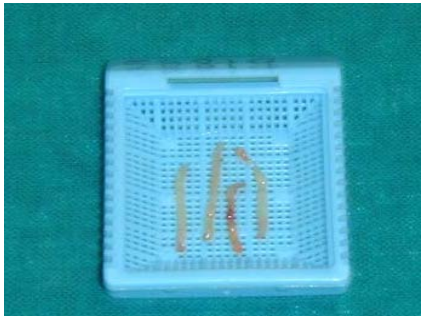
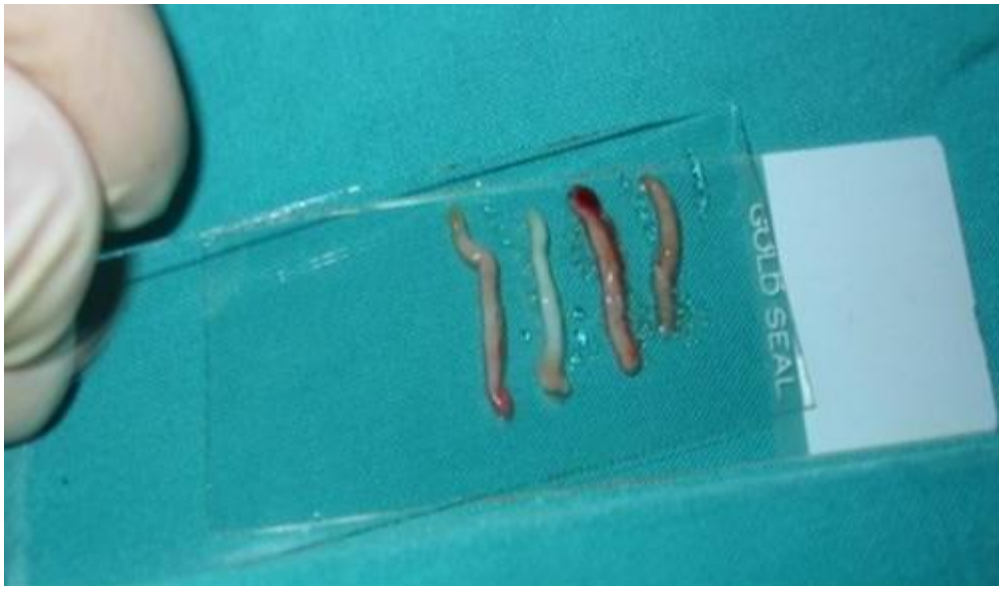
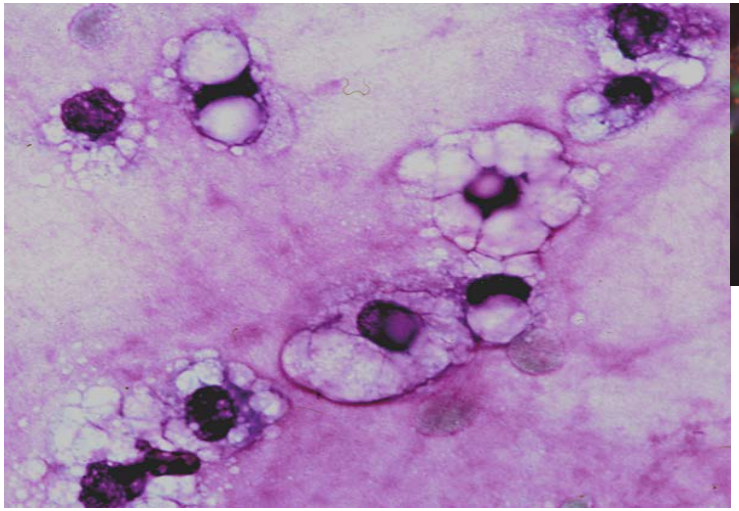
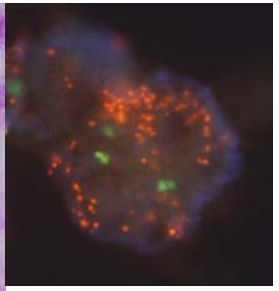


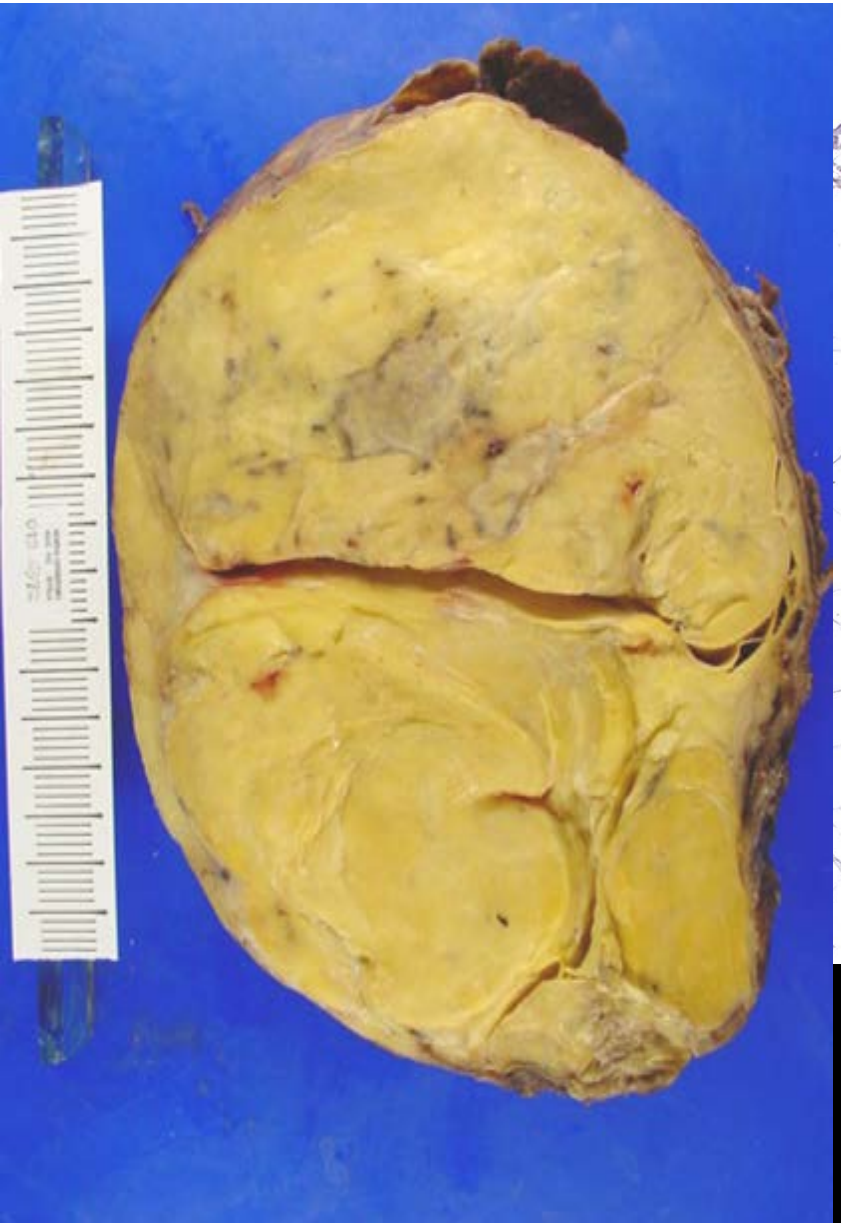

GOLD SEAL

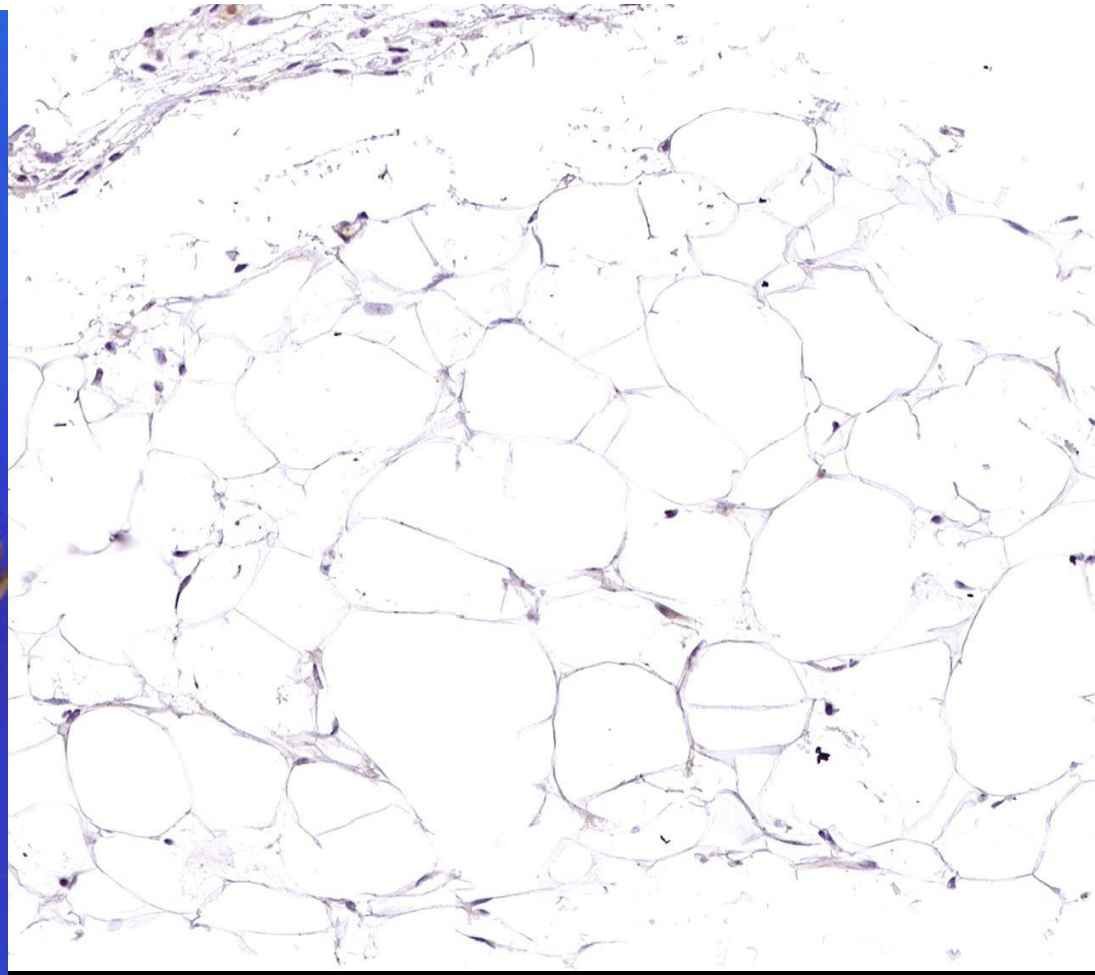




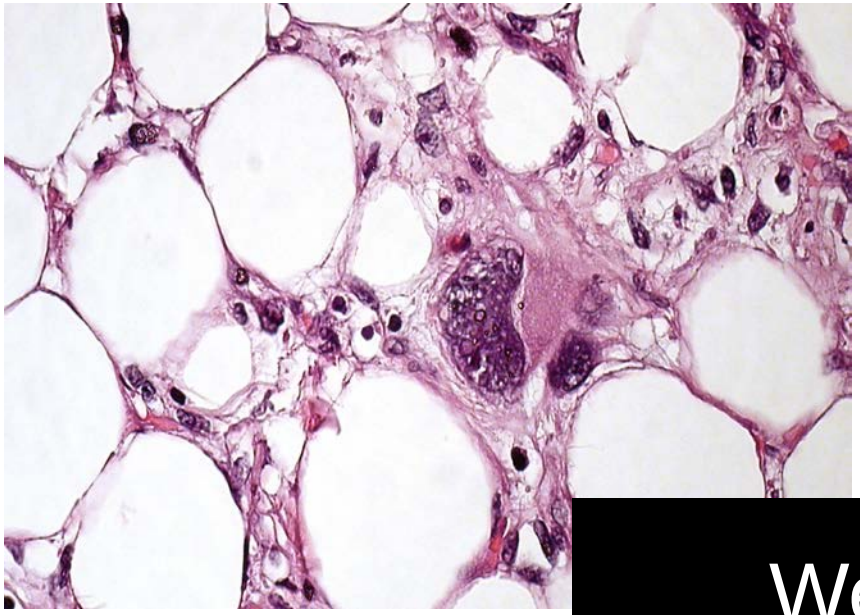
Diagnostic possibilities

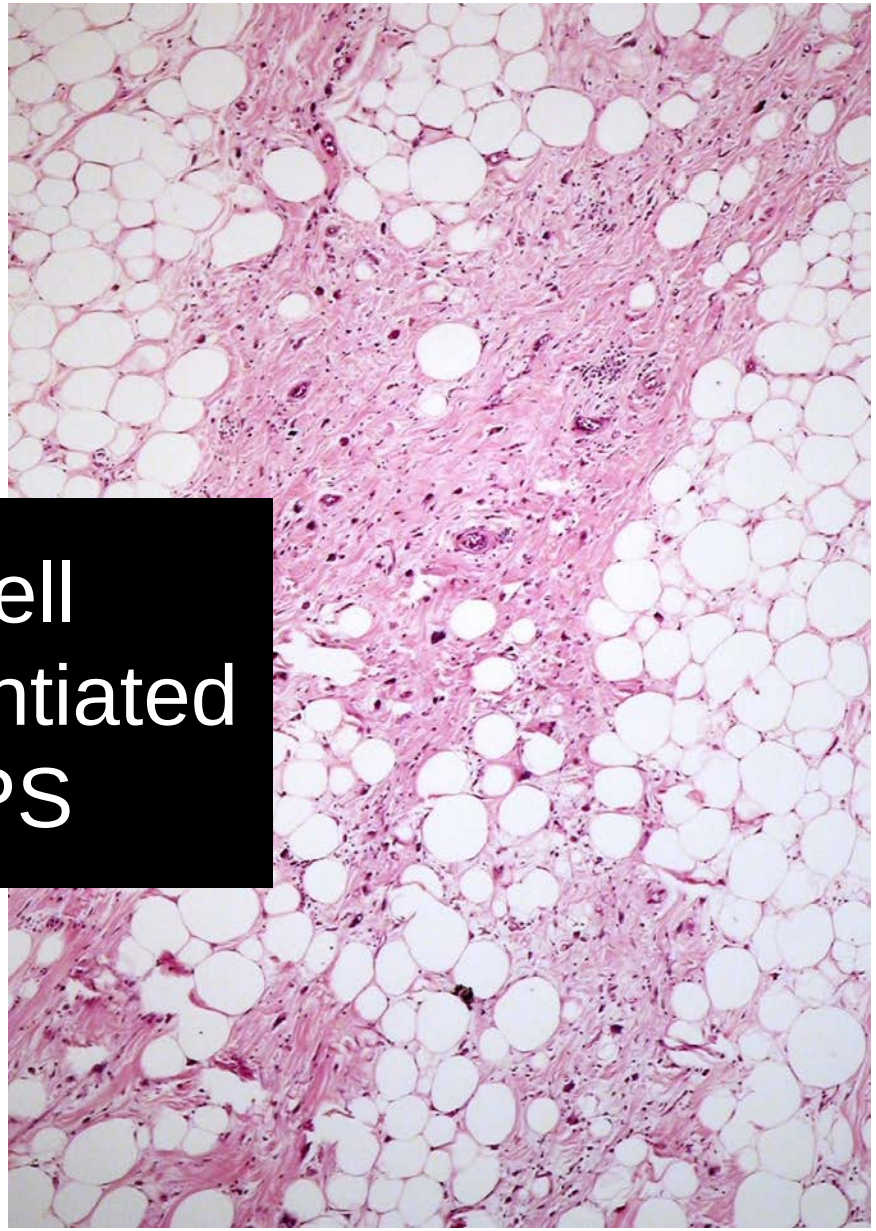
- Liposarcoma (*almost 2/3*)
  - Well differentiated /dedifferentiated
  - ~~Myxoid/round cell~~
  - Pleomorphic
- Leiomyosarcoma (*almost 1/3*)
- The other ones

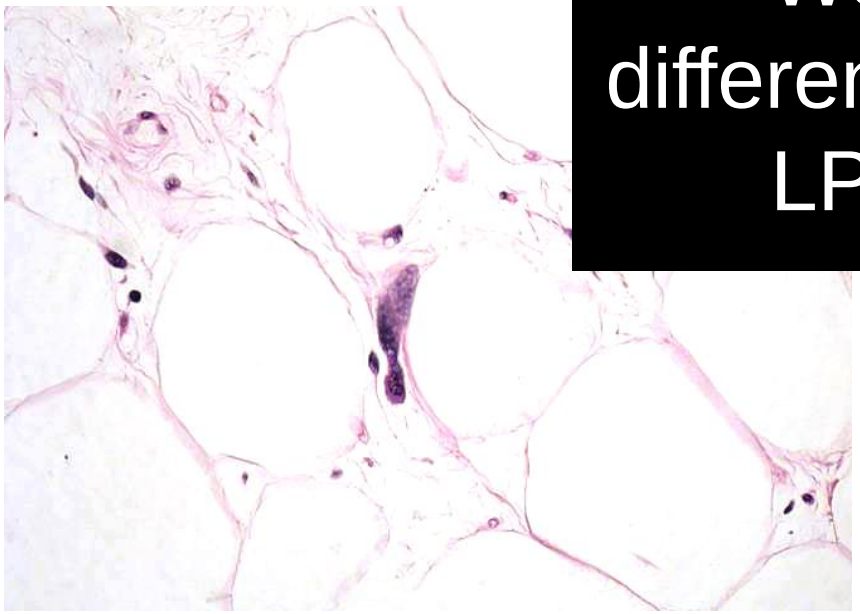




Well differentiated LPS

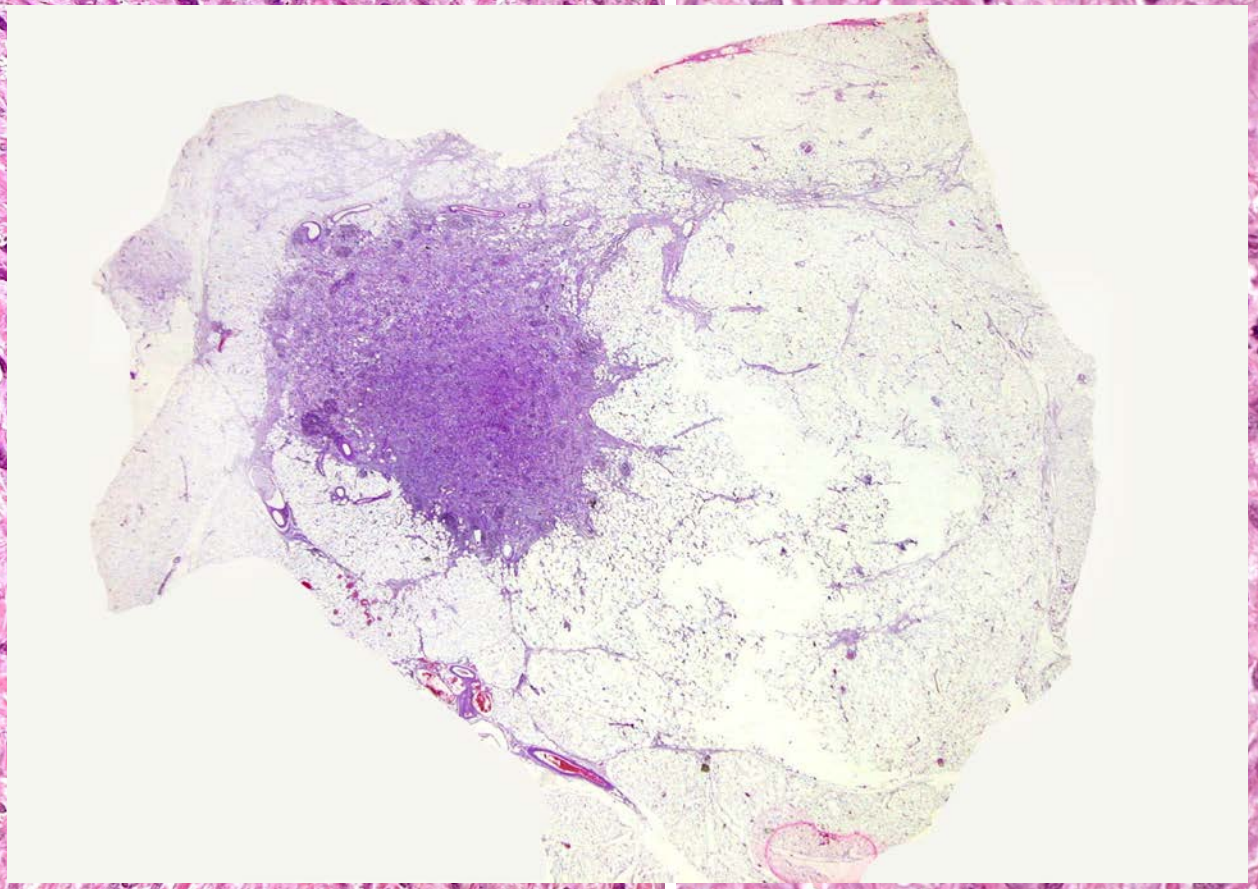




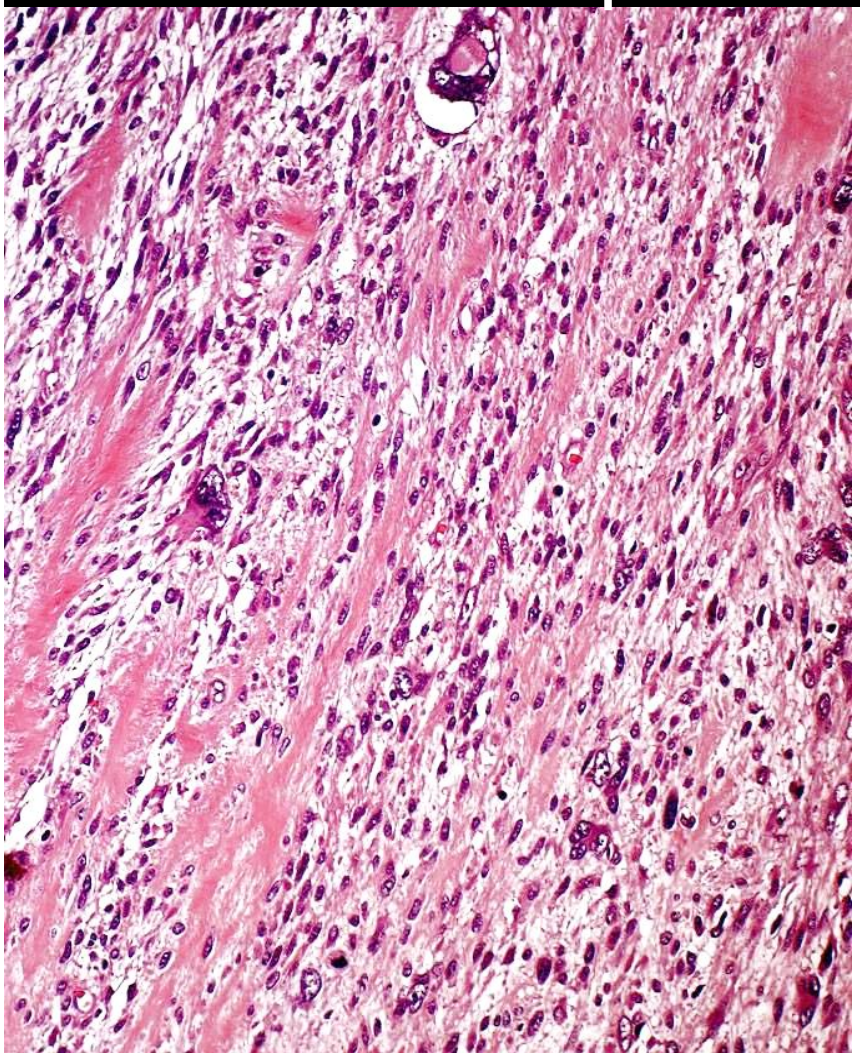


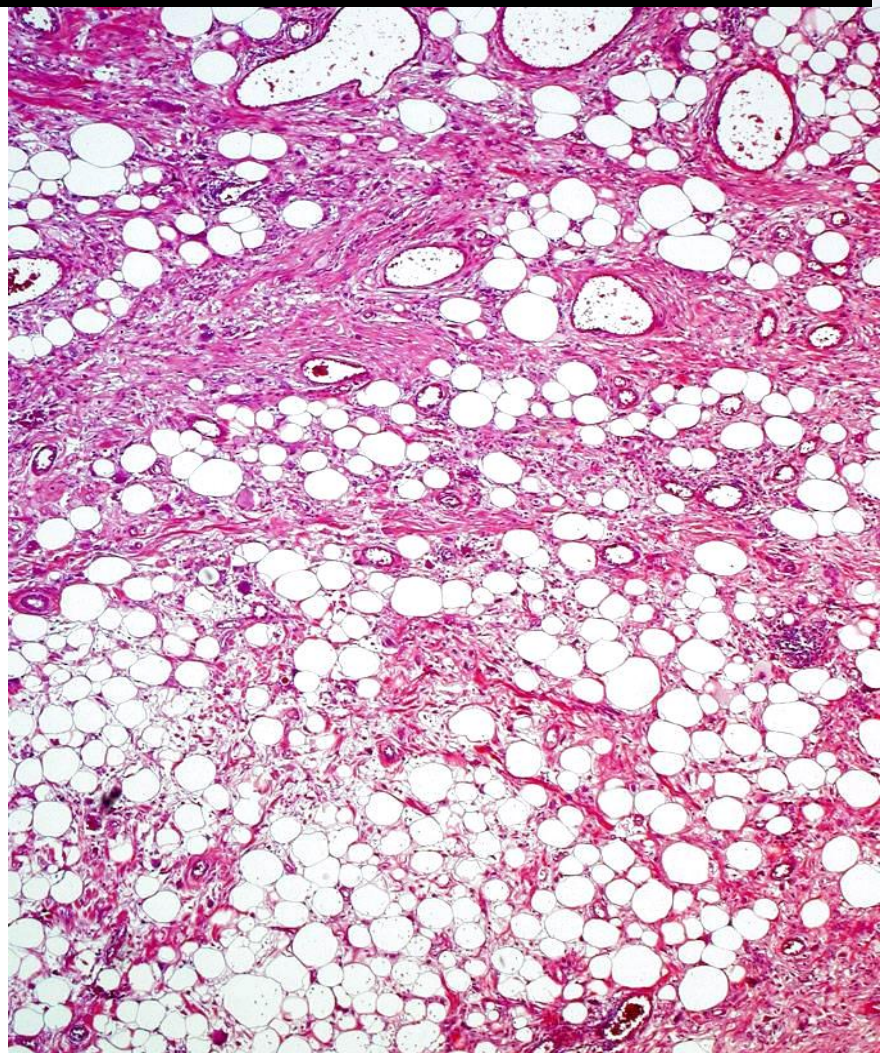
Well differentiated LPS

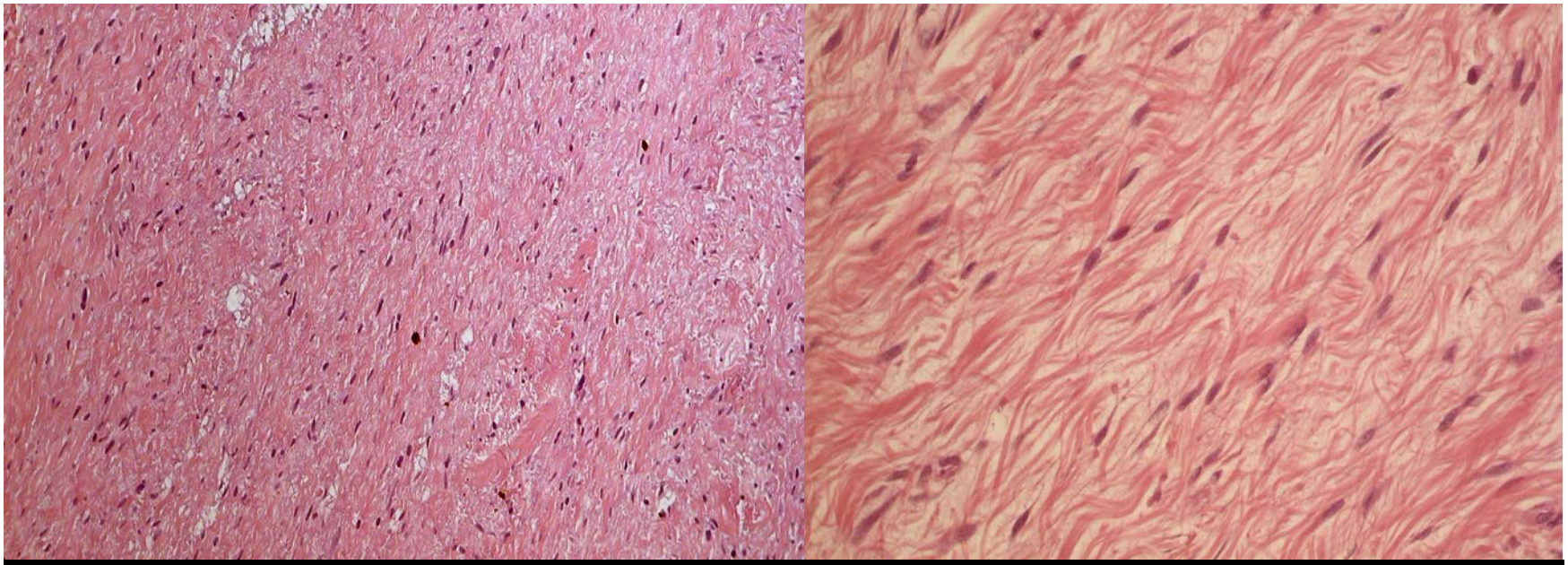
dedifferentiated LPS



Dedifferentiated LPS
Look for lipomatous differentiation

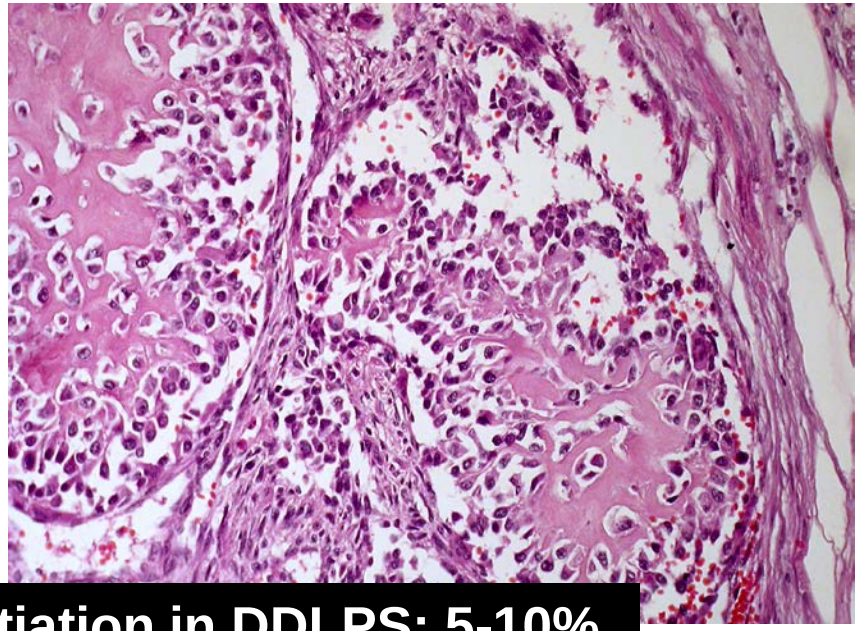




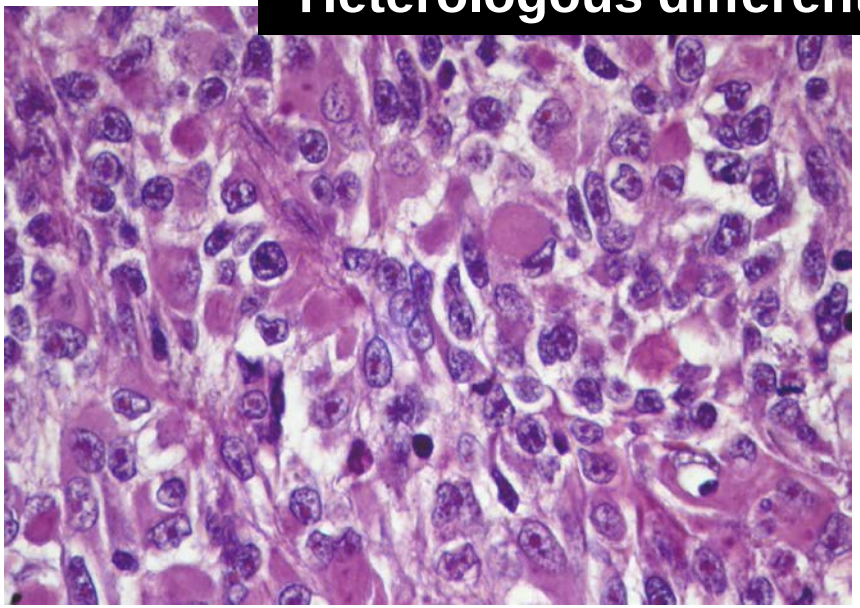
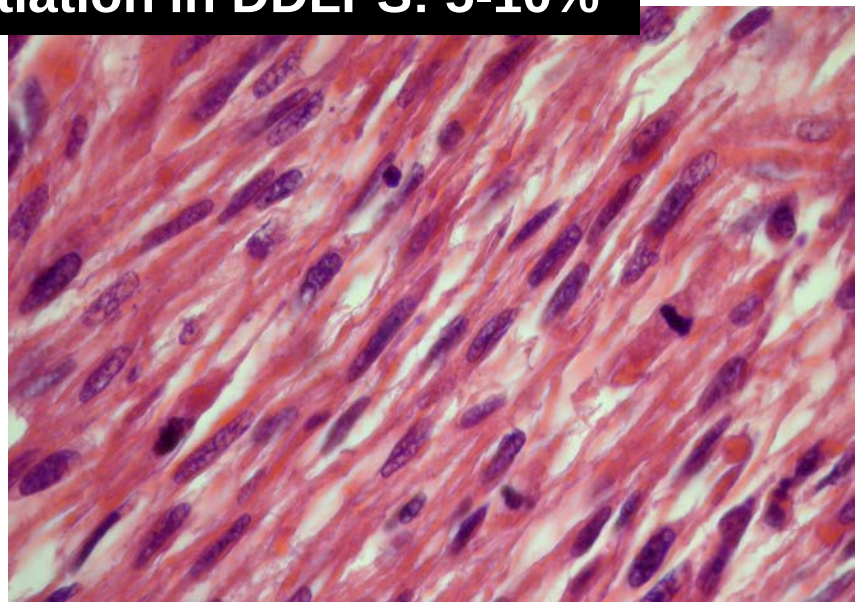


Dedifferentiated LPS, low grade

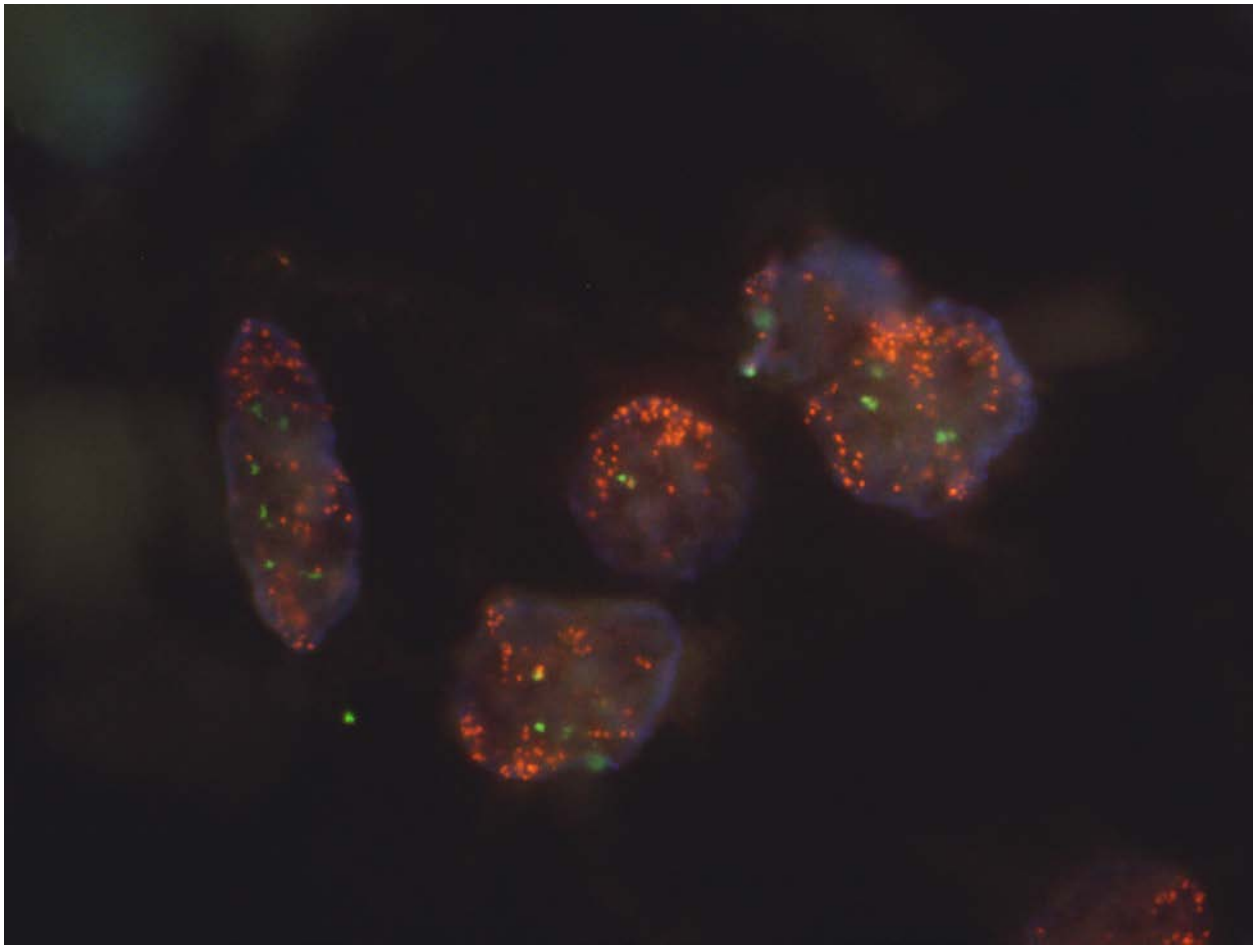
Am J Surg Pathol 1997; 21: 271-281

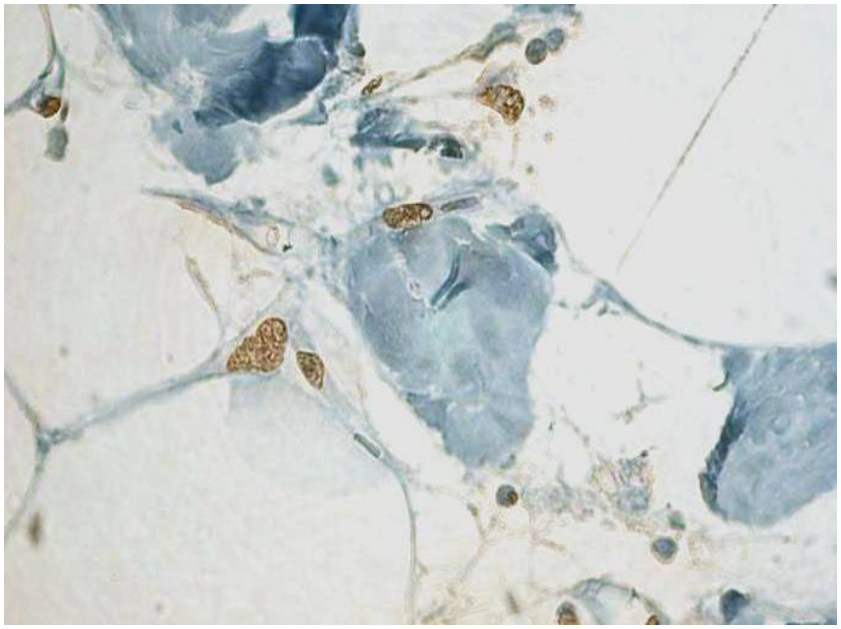



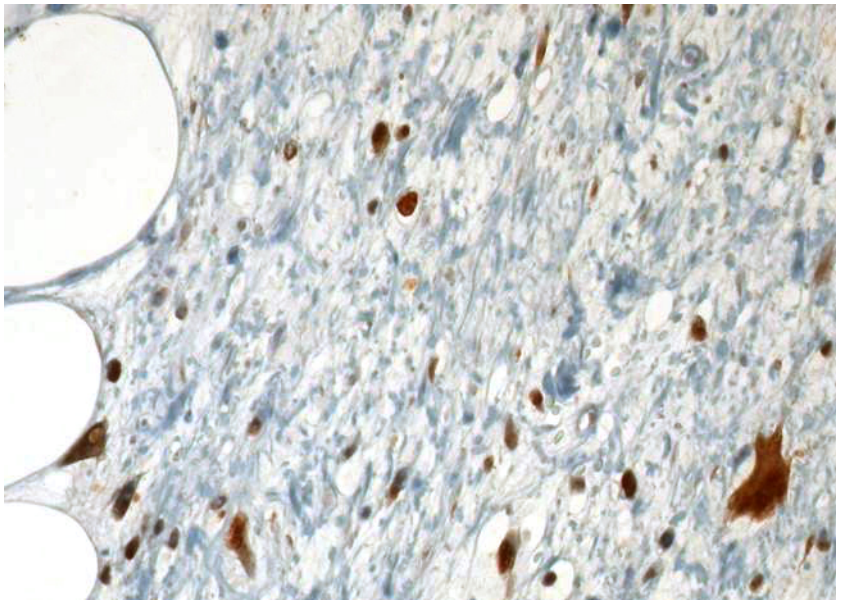
Heterologous differentiation in DDLPS: 5-10%

Well differentiated /dedifferentiated LPS show MDM2/CDK4 amplification







MDM2 and CDK4 Immunostainings Are Useful Adjuncts in Diagnosing Well-Differentiated and Dedifferentiated Liposarcoma Subtypes

A Comparative Analysis of 559 Soft Tissue Neoplasms

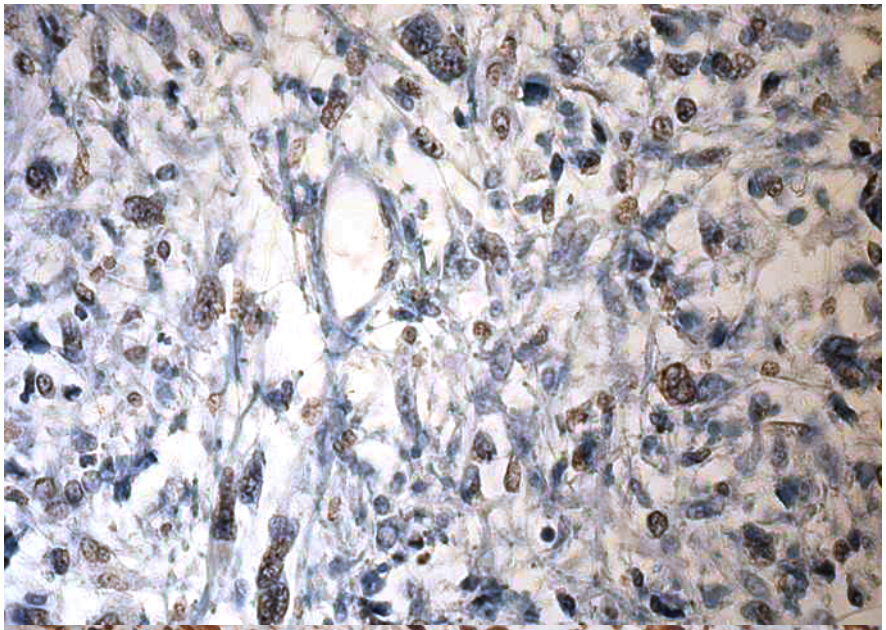
(*Am J Surg Pathol* 2005;29:1340–1347)

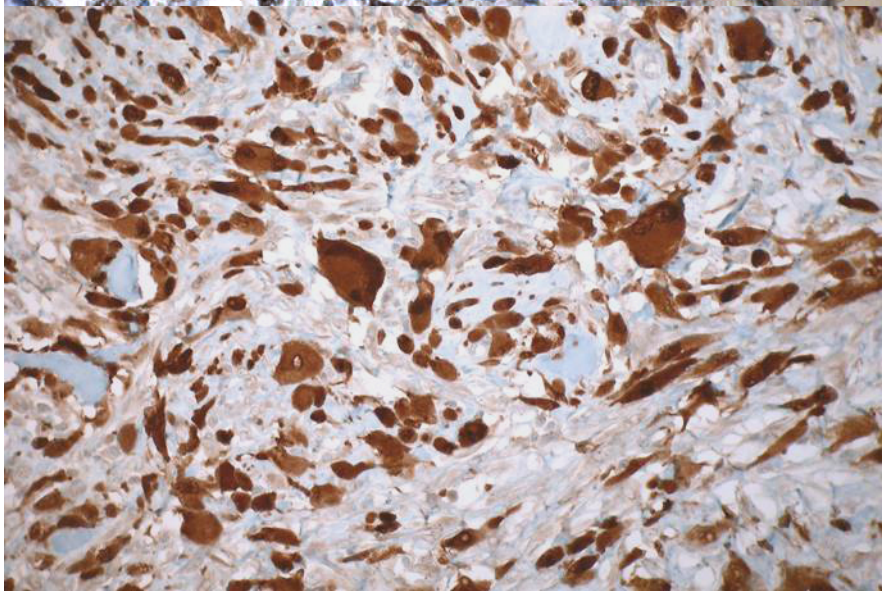
*Mattnieu Dui Nguyen Binn,† Xavier Sastre-Garau,‡ Louis Guillou,† Gonzague de Pinieux,‡ Philippe Terrier,§ Réal Lagacé,‖ Alain Aurias,** Isabelle Hostein,¶ and Jean Michel Coindre, MD¶#*

TABLE 3. Immunohistochemistry Results in Well-Differentiated Adipocytic Tumors

Type of Tumor	MDM2 [n/T (%)]	CDK4 [n/T (%)]	MDM2 and CDK4 [n (%)]
ALT-WDLPS	44/44 (100)	40/44 (90.9)	40 (90.9)
Superficial lipoma	0/15 (0)	0/15 (0)	0 (0)
Deep lipoma	0/12 (0)	0/12 (0)	0 (0)
SC and P lipoma	2/16 (12.5)	1/16 (6.2)	1 (6.2)
Angiomyolipoma	0/4 (0)	0/4 (0)	0 (0)
Hibernoma	0/2 (0)	0/2 (0)	0 (0)

ALT-WDLPS, atypical lipomatous tumor/well-differentiated liposarcoma; SC and P lipoma, spindle cell and pleomorphic lipomas.





MDM2 and CDK4 Immunostainings Are Useful Adjuncts in Diagnosing Well-Differentiated and Dedifferentiated Liposarcoma Subtypes

A Comparative Analysis of 559 Soft Tissue Neoplasms With Genetic Data

Matthieu Bui Nguyen Binh, Xavier Sastre-Garau,* Louis Guillou,† Gonzague de Pinieux,‡ Philippe Terrier,§ Réal Lagacé,‖ Alain Aurias,** Isabelle Hostein,¶ and Jean Michel Coindre, MD¶#*

TABLE 2. Immunohistochemistry Results in Dedifferentiated Liposarcomas, Potential Simulators, and Other Sarcomas

Type of Sarcoma	MDM2 [n/T (%)]	CDK4 [n/T (%)]	MDM2 and CDK4 [n (%)]
DDLPS	58/61 (95.1)	56/61 (91.80)	55 (90.2)
Simulators	55/309 (17.8)	21/308 (6.8)	14 (4.5)
MPNST	21/33 (63.6)	4/34 (11.8)	3 (8.8)
Myxofibrosarcoma	10/24 (41.7)	4/23 (17.4)	2 (8.3)
Emb RMS	12/41 (29.3)	9/40 (22.5)	5 (12.2)
MFH	7/63 (11.1)	2/64 (3.1)	1 (1.6)
LMS	4/72 (5.6)	1/71 (1.4)	1 (1.4)
Myxoid/RC LPS	1/24 (4.2)	1/24 (4.2)	1 (4.2)
Pleo LPS	0/5 (0)	0/5 (0)	0 (0)
GIST	0/15 (0)	0/15 (0)	0 (0)
Osteosarcoma	0/6 (0)	0/6 (0)	0 (0)
Alv RMS	0/20 (0)	0/20 (0)	0 (0)
Pleo RMS	0/5 (0)	0/5 (0)	0 (0)
MSFT	0/1 (0)	0/1 (0)	0 (0)
Others	21/94 (22.3)	1/92 (1.1)	1 (1.1)
SS	6/39 (15.4)	0/38 (0)	0 (0)
Angiosarcoma	4/11 (36.4)	0/11 (0)	0 (0)
DFSP	3/12 (25)	1/11 (9.1)	1 (8.3)
CCS	3/7 (42.9)	0/7 (0)	0 (0)
Kaposi's sarcoma	2/3 (66.7)	0/3 (0)	0 (0)
Epith S	2/2 (100)	0/2 (0)	0 (0)
DSRCT	1/3 (33.3)	0/3 (0)	0 (0)
PNET	0/9 (0)	0/9 (0)	0 (0)
SPAS	0/4 (0)	0/4 (0)	0 (0)
Myxoid chondrosarcoma	0/4 (0)	0/4 (0)	0 (0)

MPNST, malignant peripheral nerve sheath tumor; Emb RMS, embryonal rhabdomyosarcoma; MFH, malignant fibrous histiocytoma; LMS, leiomyosarcoma; Myxoid/RC LPS, myxoid or round cell liposarcoma; pleo LPS, pleomorphic liposarcoma; GIST, gastrointestinal stromal tumor; Alv RMS, alveolar rhabdomyosarcoma; Pleo RMS, pleomorphic rhabdomyosarcoma; MSFT, malignant solitary fibrous tumor; SS, synovial sarcoma; DFSP, dermatofibrosarcoma protuberans; CCS, clear cell sarcoma; Epith S, epithelioid sarcoma; DSRCT, desmoplastic small round cell tumor; PNET, primitive neuroectodermal tumor; SPAS, soft part alveolar sarcoma.

DDLPS vs pleomorphic sarcoma

- Look for WD LPS areas
- Do IHC and/or FISH for MDM2/CDK4

Impact of molecular assays on reclassification of retroperitoneal sarcomas
Two examples

Most Malignant Fibrous Histiocytomas Developed in the Retroperitoneum Are Dedifferentiated Liposarcomas: A Review of 25 Cases Initially Diagnosed as Malignant Fibrous Histiocytoma

Jean-Michel Coindre, M.D., Odette Mariani, M.Sc., Frédéric Chibon, Ph.D., Aline Mairal, M.Sc., Nicolas de Saint Aubain Somerhausen, M.D., Elizabeth Favre-Guillevin, M.D., Nguyen Binh Bui, M.D., Eberhard Stoeckle, M.D., Isabelle Hostein, Ph.D., Alain Aurias, M.D.

Department of Pathology (JMC, IH), Medical Oncology (EFG, NBB) and Surgery (ES), Institut Bergonié, Bordeaux, France; Laboratoire de Pathologie Moléculaire des Cancers, INSERM U 509 (OM, FC, AM, AA), Institut Curie, Paris, France; and Department of Pathology (NSAS), Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Modern Pathology (2009) 22, 223–231

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Primary retroperitoneal myxoid/round cell liposarcoma is a nonexisting disease: an immunohistochemical and molecular biological analysis

Ronald SA de Vreeze[1], Daphne de Jong[2], Ivon HG Tielen[2], Henrique J Ruijter[2], Petra M Nederlof[2], Rick L Haas[3] and Frits van Coevorden[1]

[1]*Department of Surgical Oncology, Antoni van Leeuwenhoek Hospital, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [2]*Department of Pathology, Antoni van Leeuwenhoek Hospital, The Netherlands Cancer Institute, Amsterdam, The Netherlands and* [3]*Department of Radiation Oncology, Antoni van Leeuwenhoek Hospital, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

Almost all primary retroperitoneal liposarcomas can be classified as well-/dedifferentiated liposarcoma. Rarely, however, primary retroperitoneal liposarcoma is classified as myxoid/round cell liposarcoma, based on the presence of myxoid areas and vascular crow's feet pattern, which has resulted in a debate on the classification of liposarcoma in the retroperitoneum. Genetically, myxoid/round cell liposarcoma and well-/dedifferentiated liposarcoma are different diseases. Myxoid/round cell liposarcoma is characterized by a translocation causing *FUS-CHOP* or *EWSR1-CHOP* fusion, whereas well-/dedifferentiated liposarcoma is characterized by an amplification of the 12q13-15 region, including *MDM2* and *CDK4* genes. As myxoid/round cell liposarcoma is highly radio- and chemosensitive, differentiation between subtypes is important to optimize treatment. We studied whether primary retroperitoneal liposarcomas diagnosed as myxoid/round cell liposarcoma represent molecularly true myxoid/round cell liposarcoma or are histopathological mimics and represent well-/dedifferentiated liposarcoma. Primary retroperitoneal myxoid/round cell liposarcoma ($n=16$) were compared to primary extremity myxoid/round cell liposarcoma ($n=20$). Histopathological and immunohistochemical features were studied. Amplification status of the 12q13-15 region was studied using a multiplex ligation-dependent probe amplification analysis, and *FUS-CHOP* or *EWS-CHOP* translocations were studied using RT-PCR. In primary retroperitoneal myxoid/round cell liposarcoma, *MDM2* and *CDK4* staining was both positive in 12 of 15 cases. In primary extremity myxoid/round cell liposarcoma, *MDM2* was negative in 18/20 and *CDK4* was negative in all cases. Multiplex ligation-dependent probe amplification showed the amplification of 12q13-15 region in 16/16 primary retroperitoneal myxoid/round cell liposarcomas and in 1/20 primary extremity myxoid/round cell liposarcomas. Translocation was present in all (18/18) primary extremity myxoid/round cell liposarcomas, but absent in all primary retroperitoneal myxoid/round cell liposarcomas. On the basis of immunohistochemical and molecular characteristics, apparent primary retroperitoneal myxoid/round cell liposarcoma can be recognized as well-/dedifferentiated liposarcoma with morphological features mimicking myxoid/round cell liposarcoma. In these cases, treatment should probably be specifically designed as for well-/dedifferentiated liposarcoma. Moreover, finding of myxoid/round cell liposarcoma translocations in a retroperitoneal localization is highly suggestive of metastasis and should prompt search for a primary localization outside the retroperitoneum.
Modern Pathology (2009) **22,** 223–231; doi:10.1038/modpathol.2008.164; published online 26 September 2008

Keywords: liposarcoma; retroperitoneal; myxoid/round cell; well-/dedifferentiated; RT-PCR; multiplex ligation-dependant probe amplification

Forty-four samples from 25 cases of retroperitoneal sarcoma initially diagnosed as malignant fibrous histiocytoma were histologically reviewed. Immunohistochemistry for mdm2 and cdk4 was performed on 20 cases. Comparative genomic hybridization was performed on 18 samples from 13 patients. Seventeen cases were reclassified as dedifferentiated liposarcoma. Twenty-one of 32 samples from these patients showed areas of well-differentiated liposarcoma, allowing the diagnosis of dedifferentiated liposarcoma. Immunohistochemistry performed in 15 of these cases showed positivity for mdm2 and cdk4. Comparative genomic hybridization analysis performed on 15 samples from 11 of these patients showed an amplification of the 12q13–15 region. Eight cases were reclassified as poorly differentiated sarcoma. Twelve samples from these patients showed no area of well-differentiated liposarcoma. Immunohistochemistry showed positivity for mdm2 and cdk4 in one of six of these patients and showed positivity for CD34 in another one. Comparative genomic hybridization analysis performed on three samples from two of these patients showed no amplification of the 12q13–15 region but showed complex profiles. This study shows that most so-called malignant fibrous histiocytomas developed in the retroperitoneum are dedifferentiated liposarcoma and that a poorly differentiated sarcoma in this area should prompt extensive sampling to demonstrate a well-differentiated liposarcoma component, immunohistochemistry for mdm2 and cdk4, and if possible, a cytogenetic or a molecular biology analysis.

KEY WORDS: Cdk4, Comparative genomic hybridization, Dedifferentiated liposarcoma, Immunohistochemistry, Malignant fibrous histiocytoma, Mdm2, Retroperitoneum.

Mod Pathol 2003;16(3):256–262

Malignant fibrous histiocytoma (MFH) was first described as a distinct histologic type of soft tissue sarcomas in 1964 (1), and thereafter, large series of cases were reported (2–4). For several years, MFH has been considered the most common soft tissue sarcoma of adult patients (5–7). A few years ago, Fletcher (8) doubted whether MFH was a diagnostic entity, and he emphasized that in most cases initially diagnosed as so-called MFH, a specific line of differentiation can be demonstrated, so only a few cases may be classified as undifferentiated pleomorphic sarcoma.

Retroperitoneal sarcomas represent between 10 and 15% of all soft tissue sarcomas in adults (9, 10). The most frequent type encountered in this location is liposarcoma, well-differentiated or dedifferentiated types, followed by leiomyosarcoma and MFH. Dedifferentiated liposarcomas mainly occur in the retroperitoneal space, and the most common pattern of dedifferentiated areas consists of high-grade pleomorphic MFH or storiform fibroblastic MFH (11, 12). Nowadays, many pathologists recognize that most so-called MFH located in the retro-

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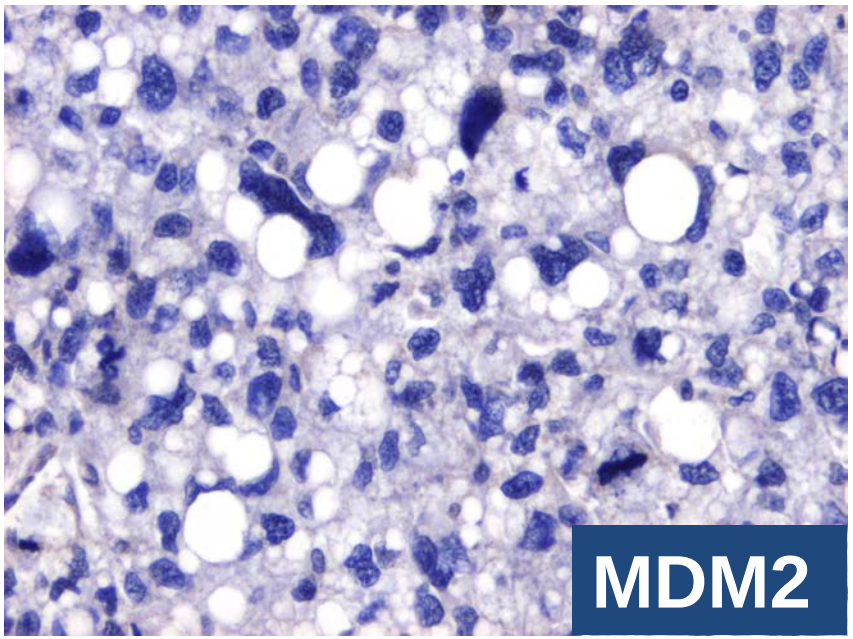
DOI: 10.1097/01.MP.0000056983.78547.77

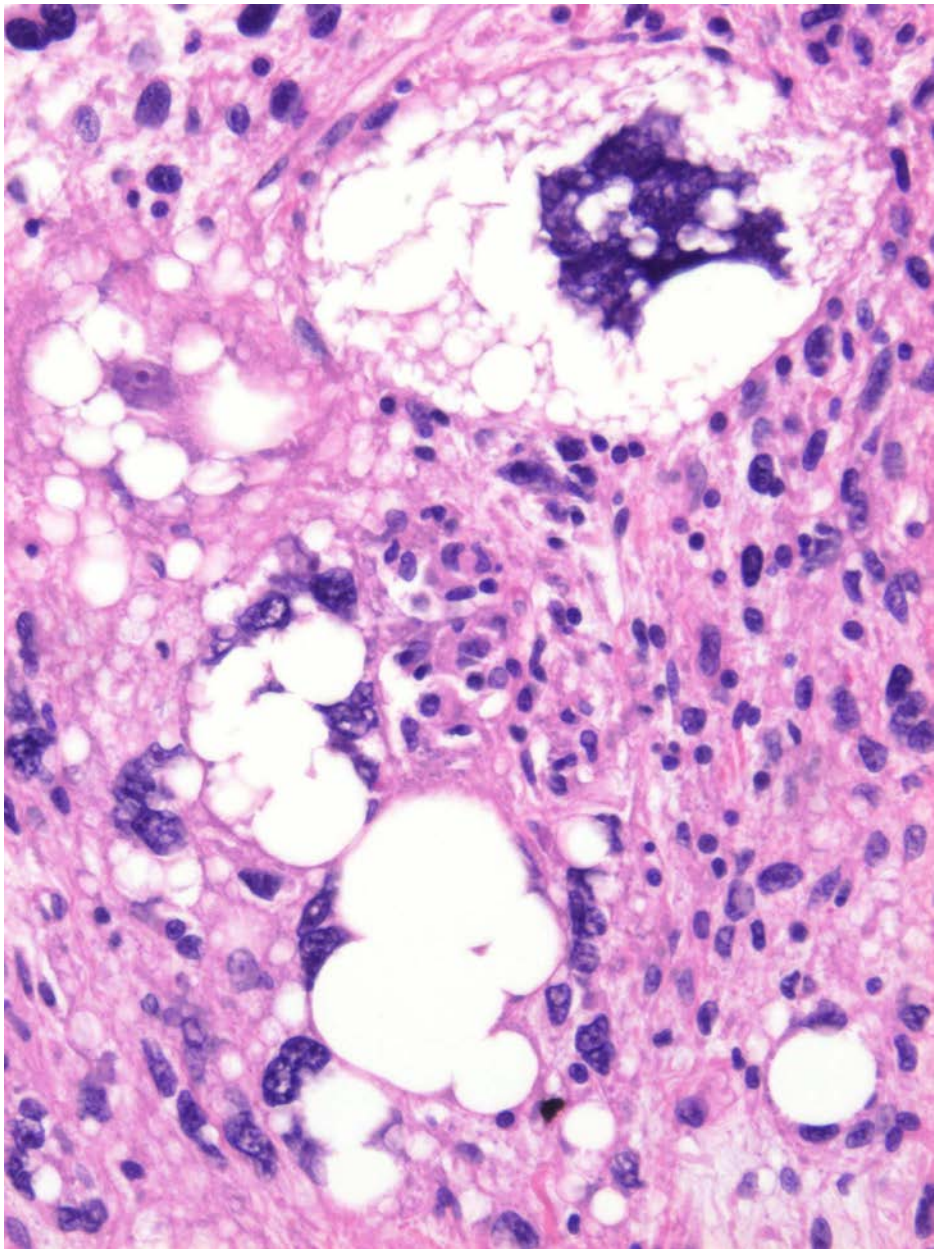
Diagnostic possibilities

- Liposarcoma (*almost 2/3*)
  - Well differentiated /dedifferentiated: MDM2
  - ~~Myxoid/round cell~~
  - Pleomorphic
- Leiomyosarcoma (*almost 1/3*)
- The other ones

Pleomorphic liposarcoma

- 5% of liposarcomas
- Extremities>retroperitoneum
- High metastasis rate
- No MDM2 amplification



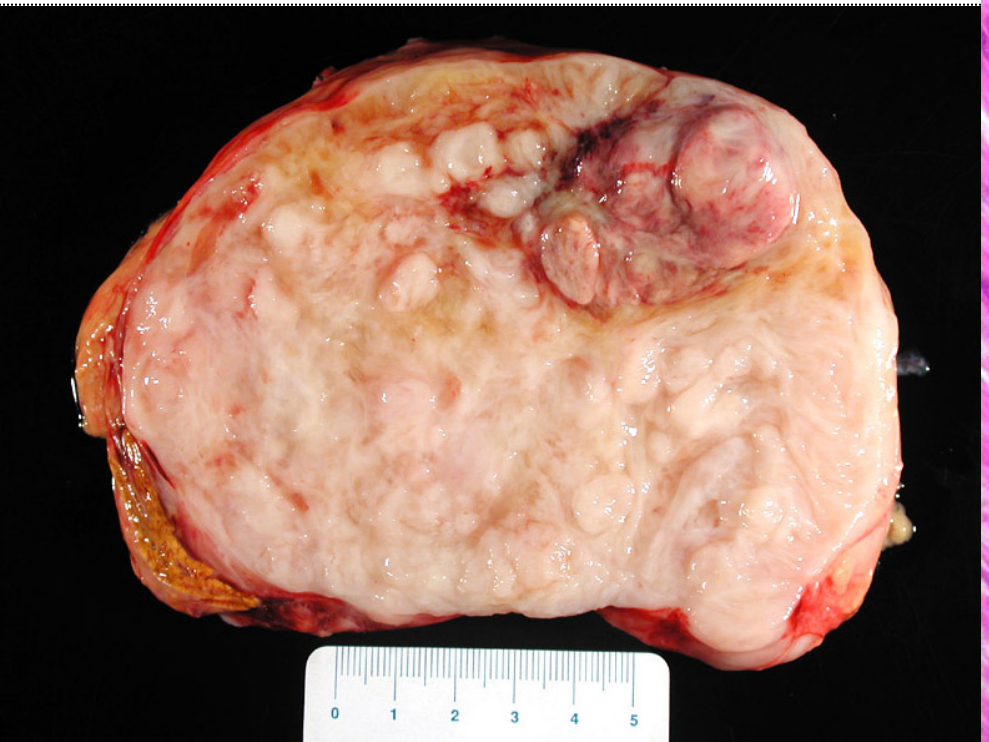


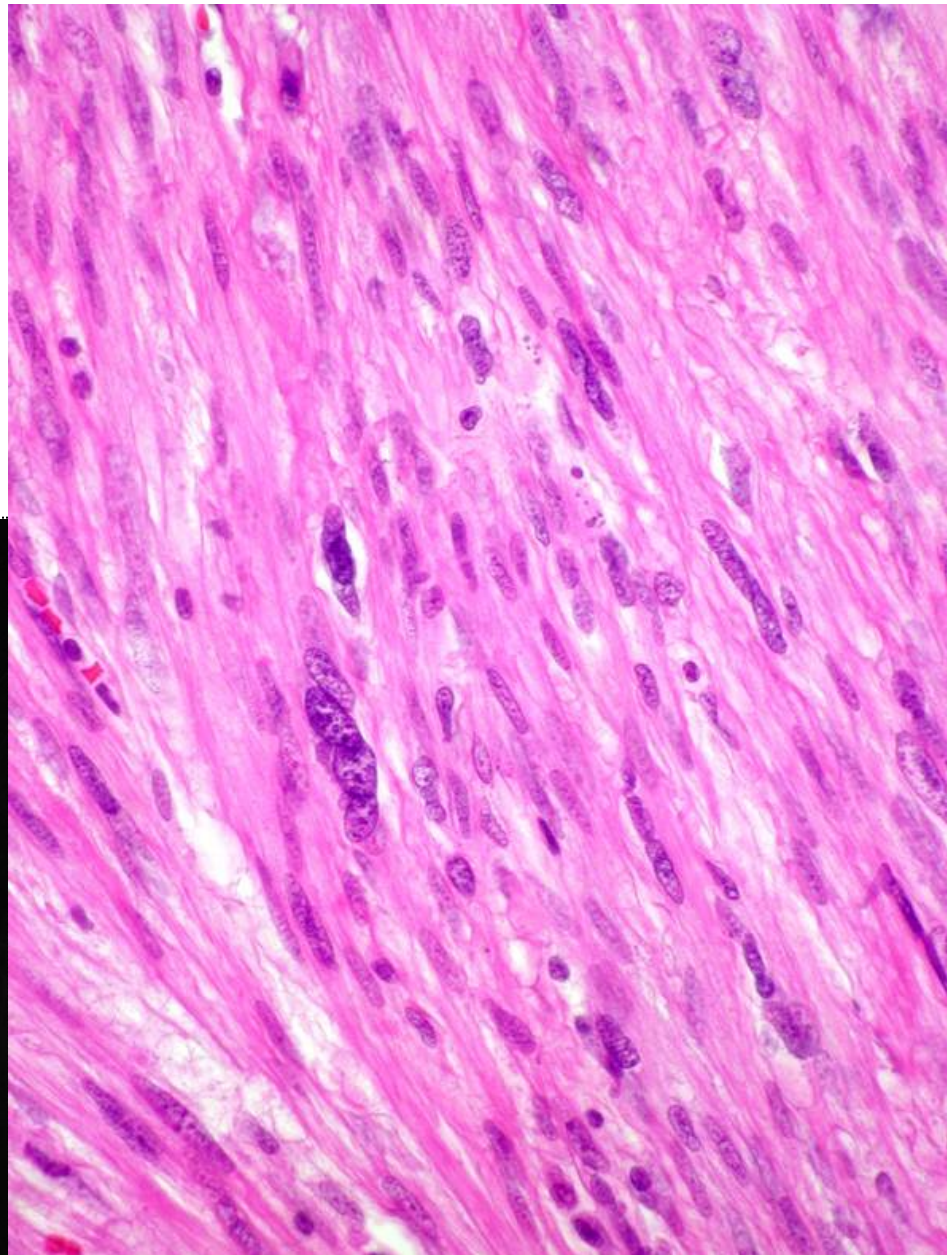
Diagnostic possibilities

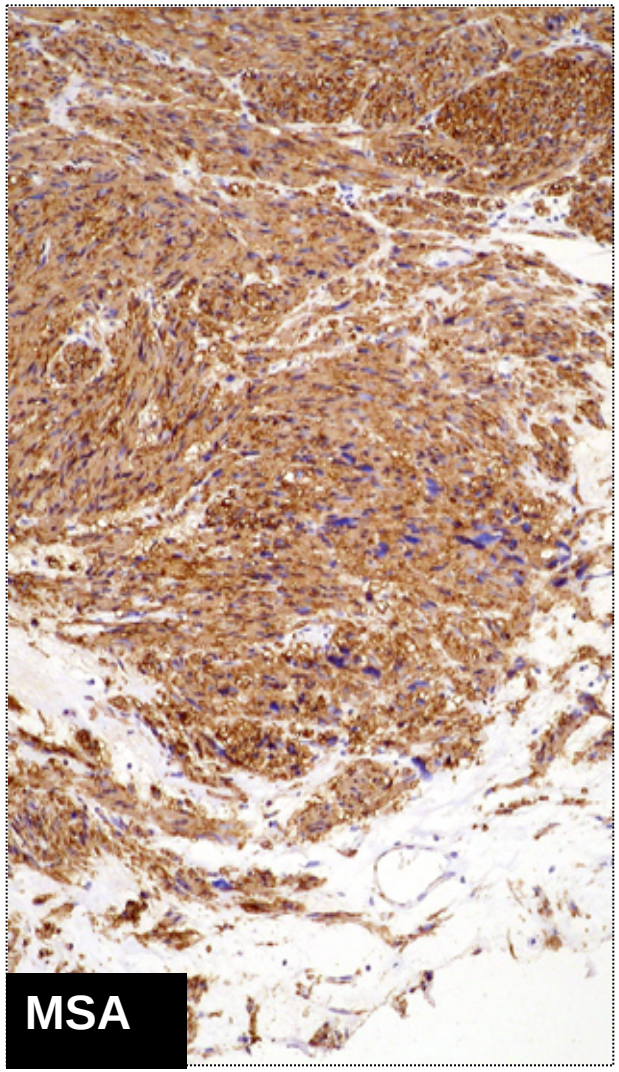
- Liposarcoma (*almost 2/3*)
  - Well differentiated /dedifferentiated: MDM2
  - ~~Myxoid/round cell~~
  - Pleomorphic: unusual, characteristic morphology
- Leiomyosarcoma (*almost 1/3*)
- The other ones

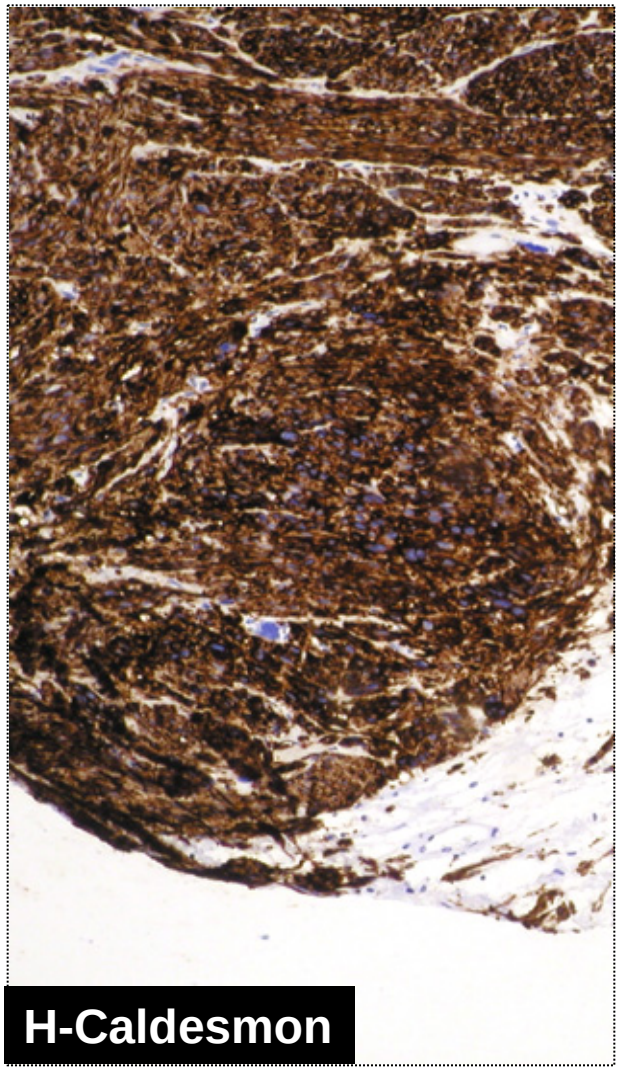
Leiomyosarcoma

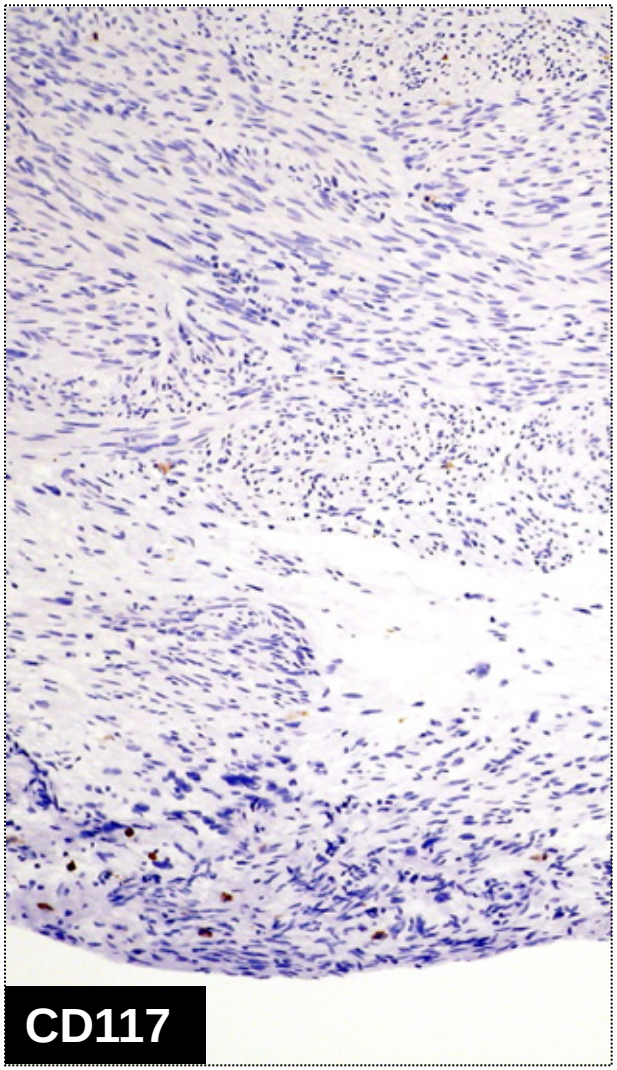
- Women
- 6-7th decades
- Vascular, GI tract, visceral
- High metastasis rate











Leiomyosarcoma

Metastatic rate of retroperitoneal sarcomas

- Well differentiated LPS: 5%
- Dedifferentiated LPS: 20%
- Pleomorphic LPS: 50%
- Leiomyosarcoma: 50%

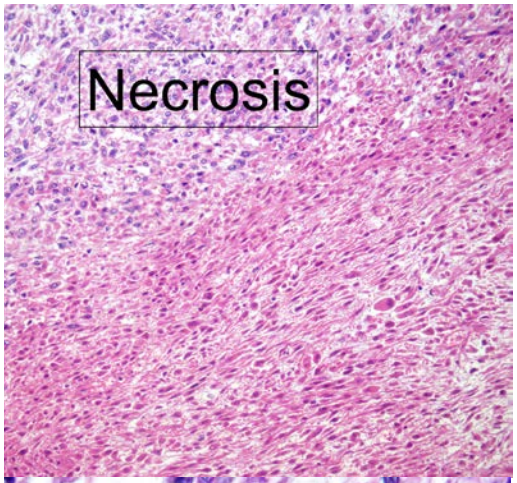
The other ones

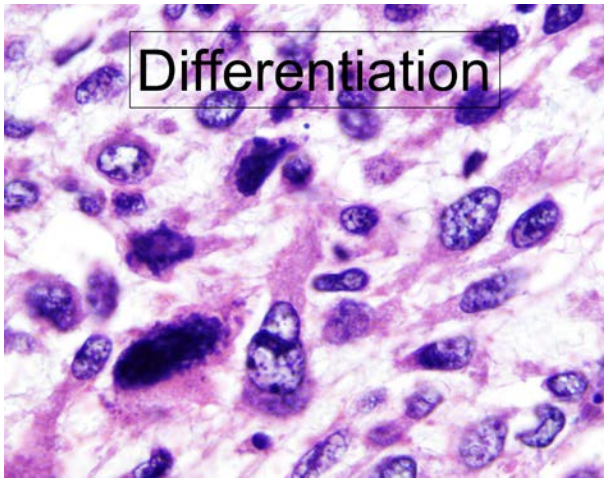
- e-GIST (CD117/DOG1)
- Desmoid-type fibromatosis (*CTNNB1*)
- PEComa (Muscle+melanocytic markers)
- Solitary fibrous tumor (CD34)
- Inflammatory myofibroblastic tumor (ALK)
- MPNST
- …

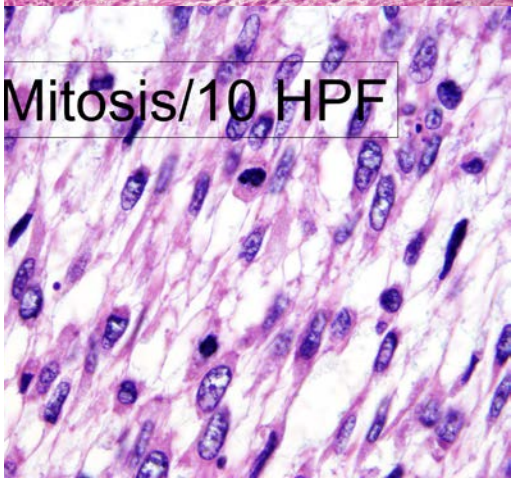
Comparison of the NCI and FNCLCC systems for the histological grading of soft tissue tumours

Histological type	NCI grading system	FNCLCC grading system
Well differentiated liposarcoma	1+(*)	1
Myxoid liposarcoma	1+	2
High grade myxoid liposarcoma (round cell liposarcoma)	2-(**) 3	3
Pleomorphic liposarcoma	2 3	3
Dedifferentiated liposarcoma		3
Fibrosarcoma		
Well differentiated	1+	1
Conventional	2	2
Poorly differentiated	3	3
Pleomorphic sarcoma (MFH, pleomorphic type)		
With storiform pattern	2	2
Patternless pleomorphic sarcoma	3	3
With giant cells		3
With prominent inflammation		3
Myxofibrosarcoma (MFH, myxoid-type)	1+ 2 3	2
Leiomyosarcoma		
Well differentiated	1+	1
Conventional	2	2
Poorly differentiated / pleomorphic / epithelioid	3	3
Pleomorphic rhabdomyosarcoma	2 3	3
Embryonal / alveolar rhabdomyosarcomas	3	3
Myxoid chondrosarcoma	1 2 3	
Mesenchymal chondrosarcoma	3	3
Osteosarcoma	3	3
Ewing sarcoma / PNET	3	3
Synovial sarcoma	2 3	3
Epithelioid sarcoma	2 3	
Clear cell sarcoma	2 3	
Angiosarcoma	2 3	

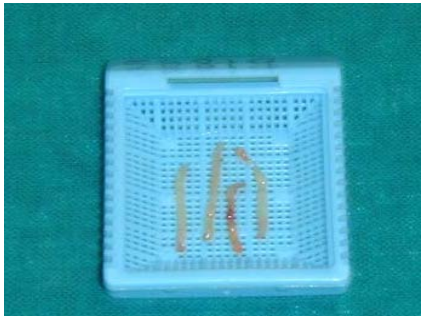
Modified from Costa et al (401), Costa (402) and Guillou (851). The original diagnostic terms are shown in parentheses.
MFH: malignant fibrous histiocytoma; PNET: primitive neuroectodermal tumour.
(*) + grade is attributed by a combination of histological type, cellularity, pleomorphism and mitotic rate.
(**) - grade is attributed according to the extent of tumour necrosis (< or > 15%).



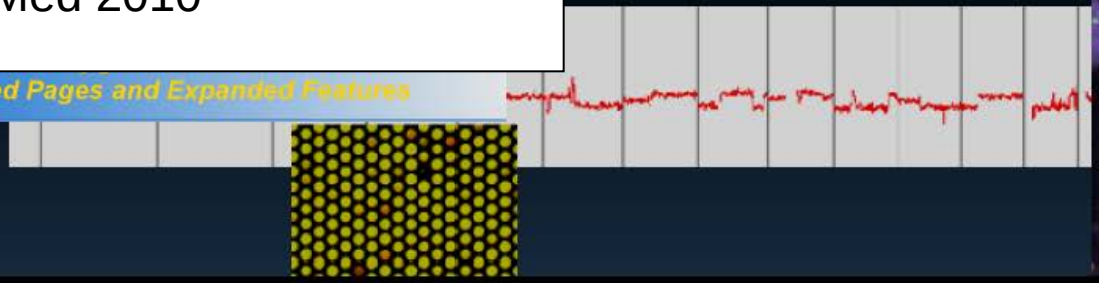


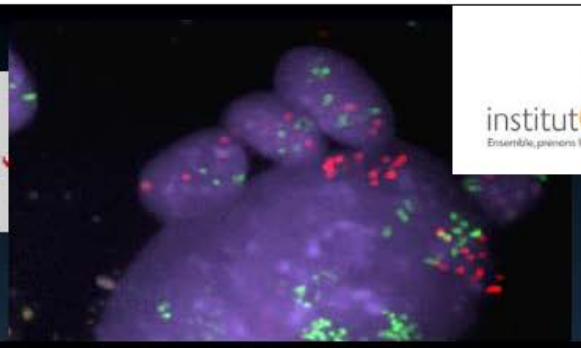


Scores: 2+2+2=6
FNCLCC Grade 3



Chibon et al.
Nat Med 2010



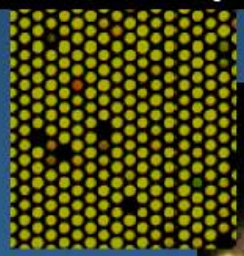


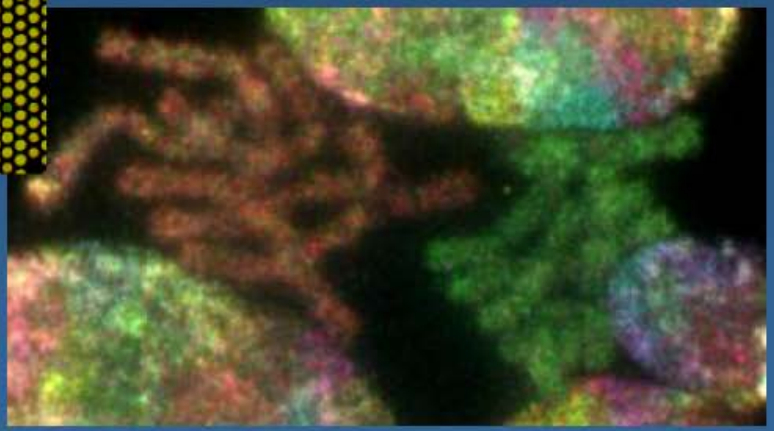
institutCurie
Ensemble, prenons le cancer de vitesse.

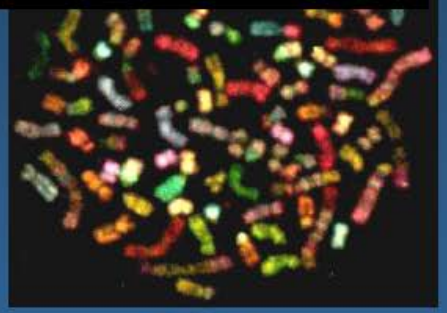
CINSARC

PREDICTION OF CLINICAL OUTCOME IN SARCOMAS BASED ON A GENE-EXPRESSION SIGNATURE RELATED TO GENOME COMPLEXITY

(Compexity INdex of SARComas)







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In conclusion

- Retroperitoneal sarcoma diagnosis is integrative.
- The domain of the sample: diagnosis and research.
- Lipos and leios (mostly)
- Molecular techniques: Present and future.

Gracias!

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