PLEOMORPHIC SARCOMAS

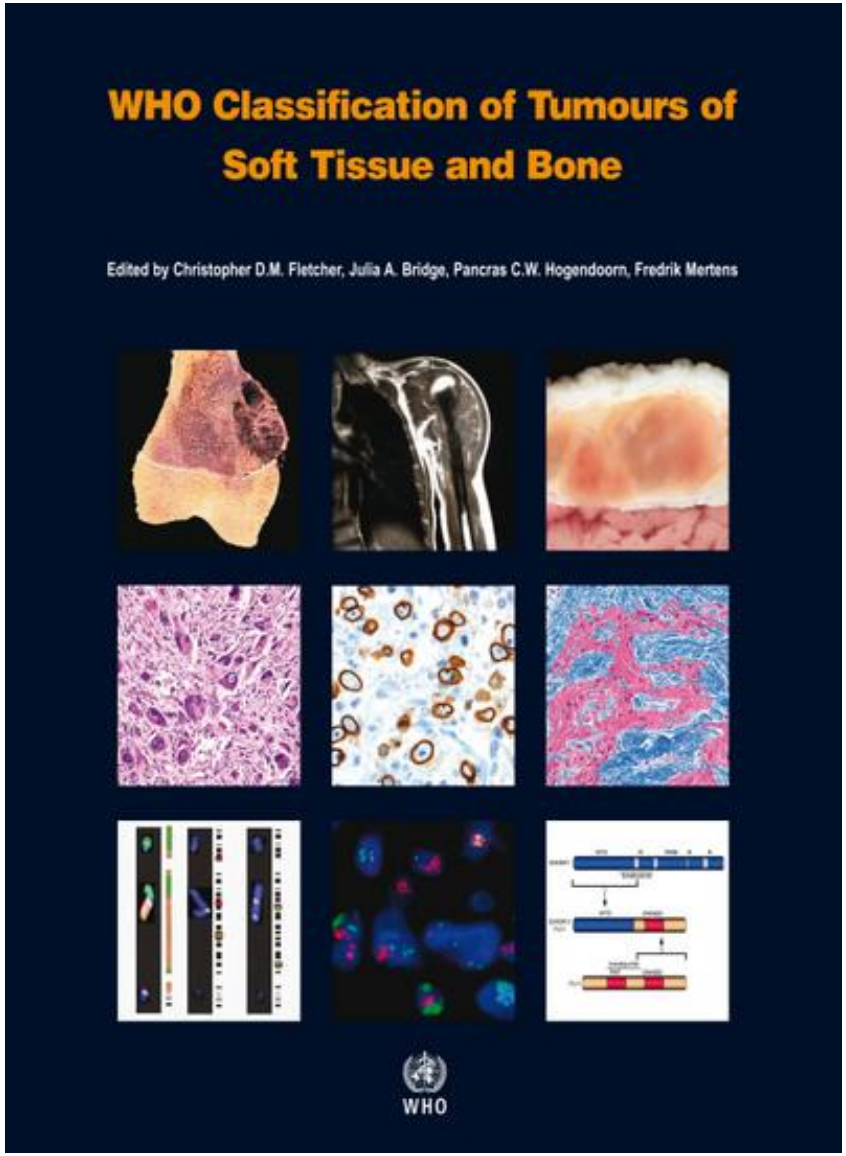
ANGELO PAOLO DEI TOS

DEPARTMENTS OF PATHOLOGY AND ONCOLOGY
TREVISO, ITALY

APDEITOS@ULSS.TV.IT

DISCLOSURE SLIDE

No conflicts to declare



- Adipocytic tumours
  - Well deifferentiated / dedifferentiated liposarcoma
  - Myxoid / round cell liposarcoma
  - Pleomorphic liposarcoma
- Fibroblastic / myofibroblastic tumours
  - Fibromatosis (desmoid)
  - DFSP
  - Solitary fibrous tumour / haemangiopericytoma
  - IMT
  - Low grade myofibroblastic sarcoma
  - Infantile fibrosarcoma
  - Adult fibrosarcoma
  - Mixofibrosarcoma
  - SEF
  - LGFMS
- Smooth muscle tumours
  - Leiomyosarcoma
- Skeletal muscle tumours
  - Embryonal rhabdomyosarcoma
  - Alveolar rhabdomyosarcoma
  - Pleomorphic rhabdomyosarcoma
- Vascular tumours
  - Epithelioid haemangioendothelioma
  - Angiosarcoma of soft tissue
- GIST
- Nerve sheath tumors
  - MPNST
  - Malignaant GCT
- Chondro-osseous tumours
  - Mesenchymal chondrosarcoma
  - Extraskeletal osteosarcoma
- Tumours of uncertain differentiation
  - Synovial sarcoma
  - Epithelioid sarcoma
  - Alveolar soft part sarcoma
  - Clear cell sarcoma of soft tissue
  - Extraskeletal myxoid chondrosarcoma
  - Extraskeletal Ewing sarcoma
  - Desmoplastic small round cell tumour
  - Extra-renal rhabdoid tumour
  - Malignant mesenchymoma
  - Malignant PEComa
  - Intimal sarcoma

How WHO classification was reshaped

- Pathologists and Cytogeneticists
- Integration of immunophenotype and genetics
- Broad authorships
- Discussion “word by word” of all contributions

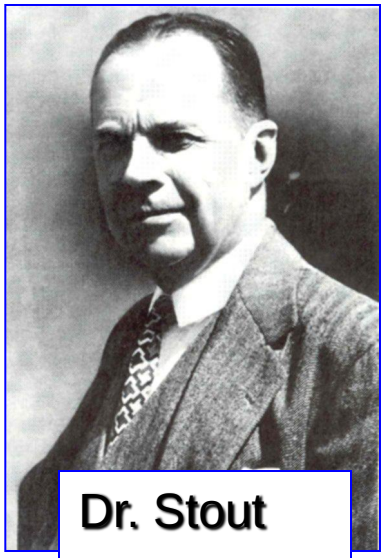
Major changes

- Definition of tumor category (both in bone and soft tissue)
- Genetics now part of tumor entity definition
- MFH and HPC formally abolished
- Undifferentiated sarcoma category
- New entities incorporated
  - i.e. pseudomyogenic hemangioendothelioma
- Few entities reshaped
  - GCA now part of SFT spectrum
- GIST, Neural neoplasms, AFX
- Atypical chondrogenic tumors
- Ewing sarcoma better described

MFH story

- 1963: Ozzello, Stout, Lattes, and Murray
- 1970-1980: Kempson, Enzinger and Weiss
- 1986: Brooks
- 1992: Fletcher
- 2002: WHO

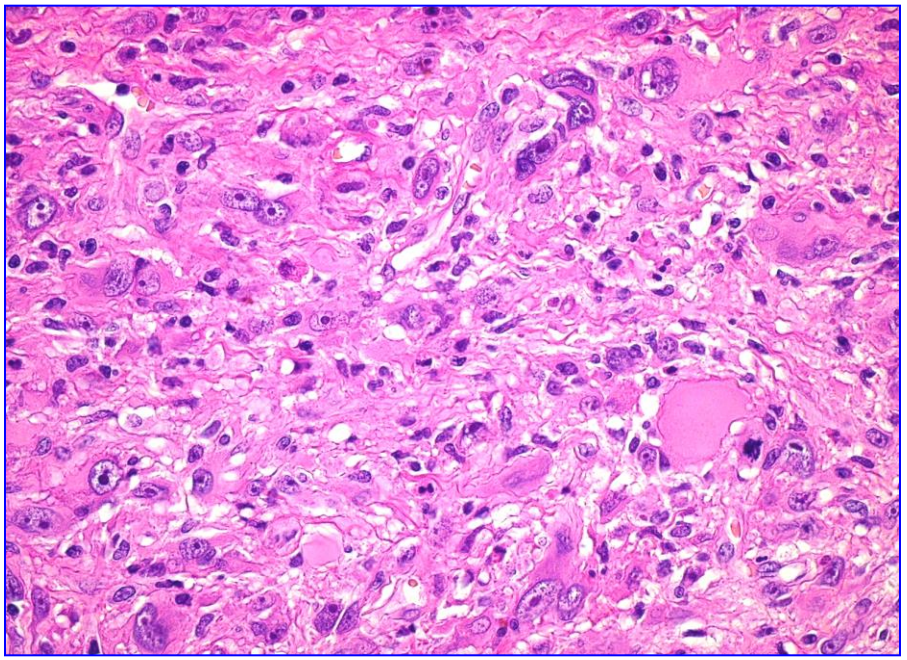
Dr. Murray



Dr. Stout

The MFH Legacy

- Pleomorpic and Storiform MFH
- Myxoid MFH
- Giant cell MFH
- Inflammatory MFH
- Angiomatoid MFH



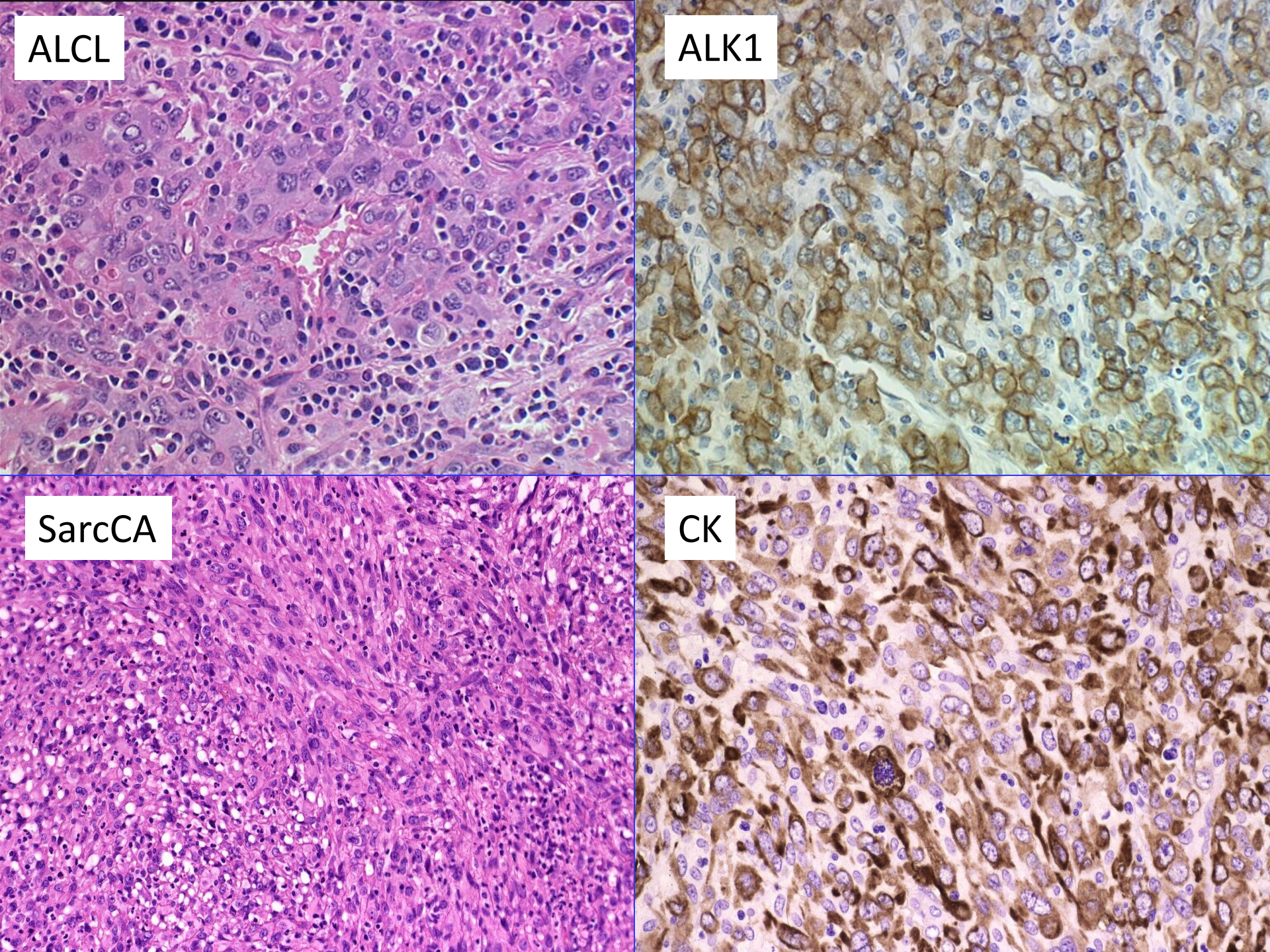
The American Journal of Surgical Pathology 16(3): 213–228, 1992

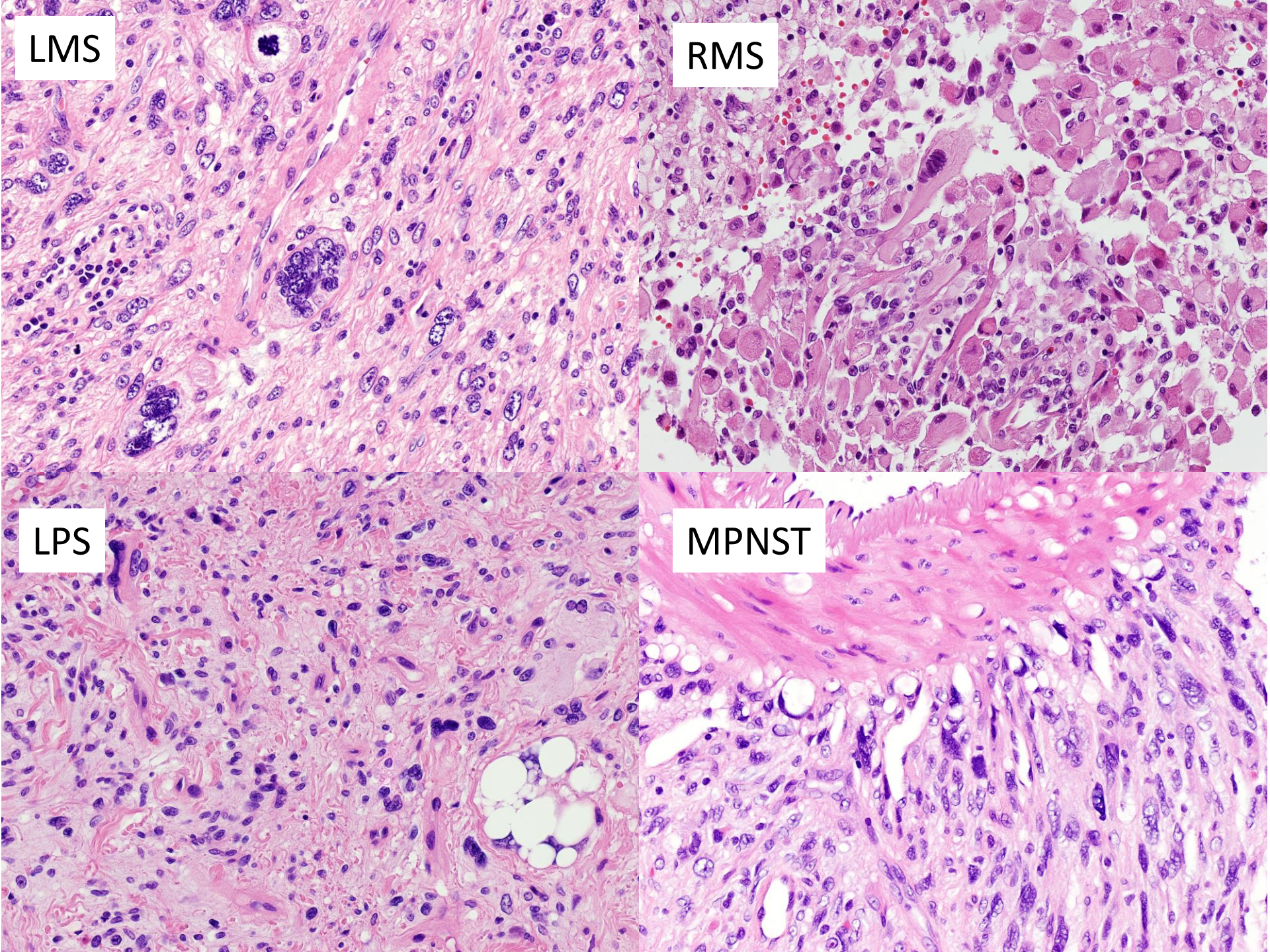
Pleomorphic Malignant Fibrous Histiocytoma: Fact or Fiction?

A Critical Reappraisal Based on 159 Tumors Diagnosed as Pleomorphic Sarcoma

Christopher D.M. Fletcher, M.D., M.R.C.Path.

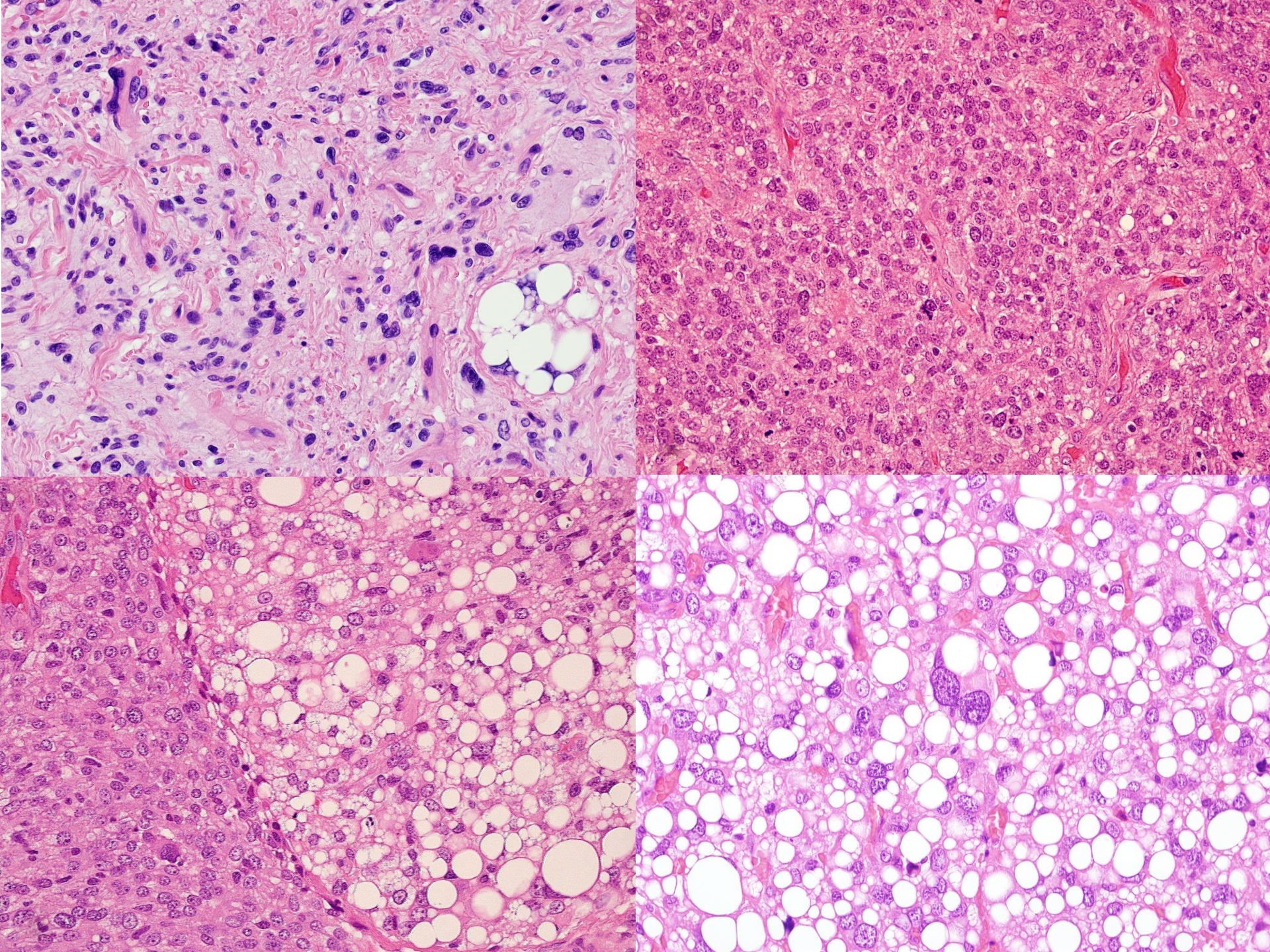
- Until 1992 MFH = most frequent soft tissue sarcoma
- Morphology + IHC reclassifies most MFH
  - Plep LPS, LMS; RMS, MPNST, DDLPS
- MFH = morphologic pattern
  - NHL
  - Metastatic Melanoma
  - Sarcomatoid Carcinoma


ALCL
ALK1
SarcCA
CK


LMS
RMS
LPS
MPNST

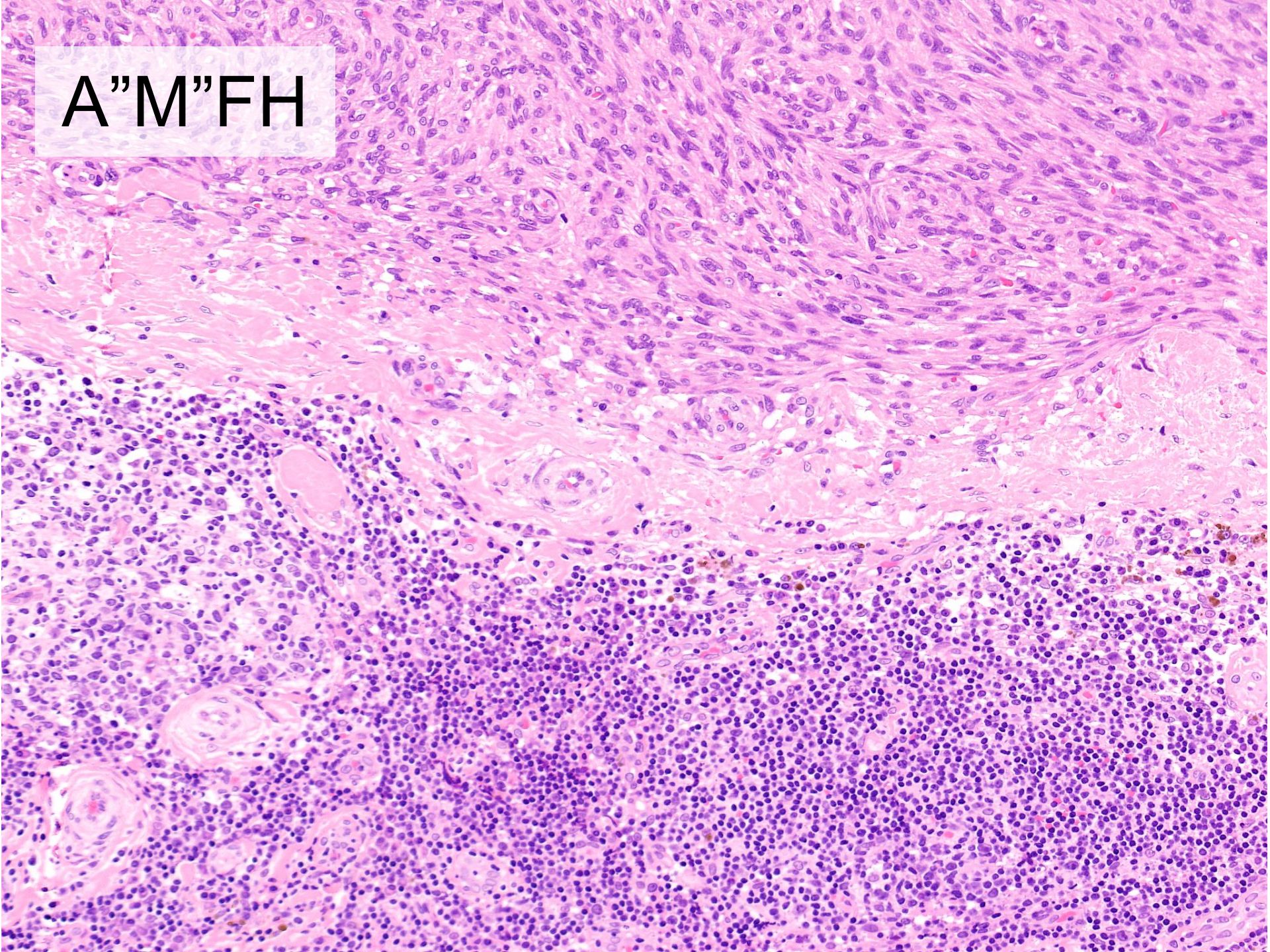
Pleomorphic liposarcoma

- 5% of all liposarcomas
- M > F, 6th decade
- Lower limbs, upper limbs, retroperitoneum
- Metastatic rate: 30-50%
- 5 yr survival rate = 57%
- Complex Karyotypic aberrations
- TP53 alterations in 50% of cases



MFH: What's Left?

- Myxoid MFH = myxofibrosarcoma
- Inflammatory MFH = dedifferentiated LPS
- Giant cell MFH = giant cell tumor of soft tissues, extraskeletal OS, other sarcomas (mostly leios) containing giant cells
- Angiomatoid (m)FH = moved to lesions of uncertain "histogenesis"
- Pleomorphic MFH = Undifferentiated Pleomorphic Sarcoma


A”M”FH

Angiomatoid Fibrous Histiocytoma

(rarely metastasizing lesion)

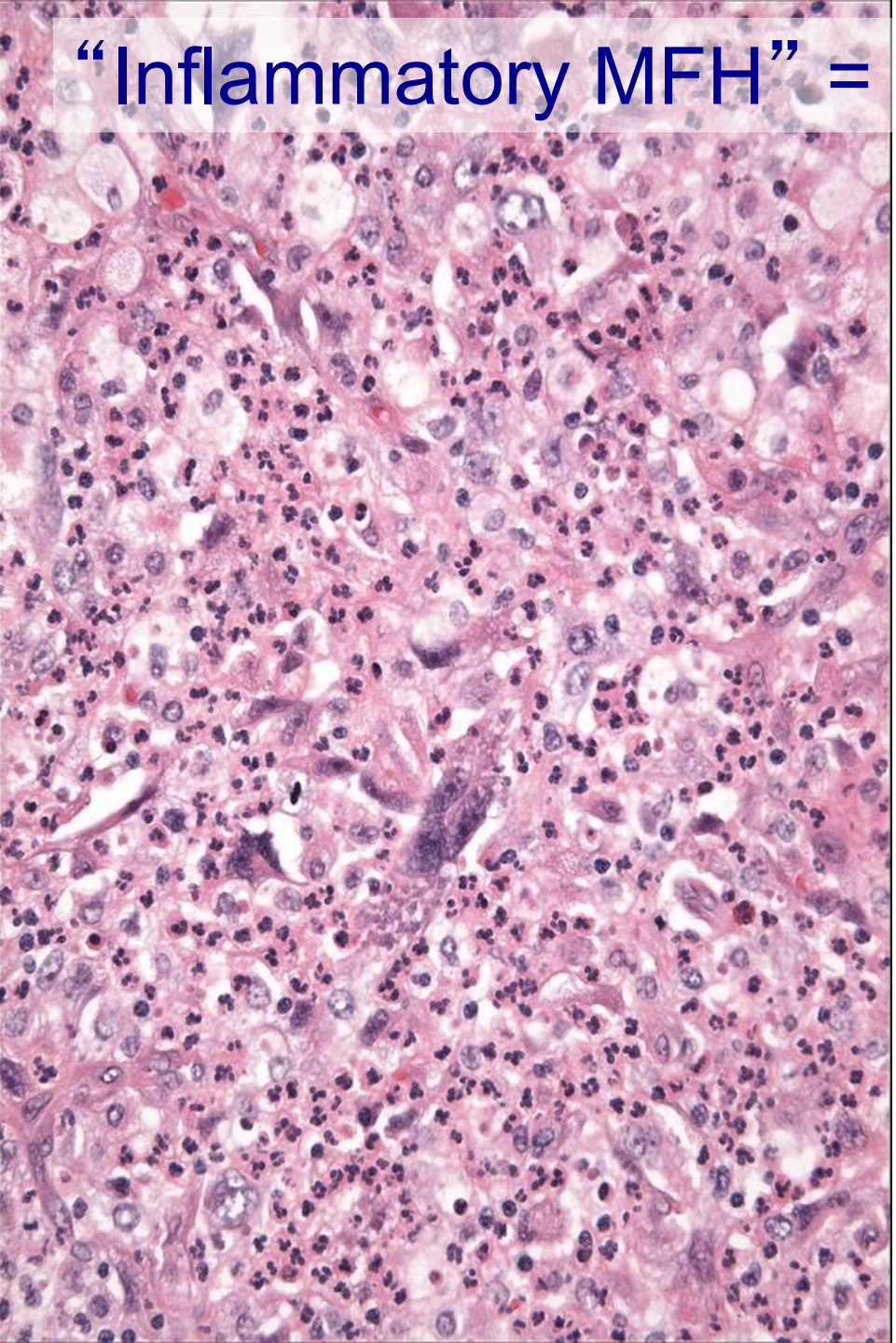
- t(12;22)(q13;q12)
  EWSR1-ATF1
  (in unusual site)
  Sommers et al 2005
- t(2;22)(q33;q12)
  EWSR1-CREB1
  (majority)
  Rossi et al 2007
- t(12;16)(q13;p11)
  FUS-ATF1
  Waters et al 2000

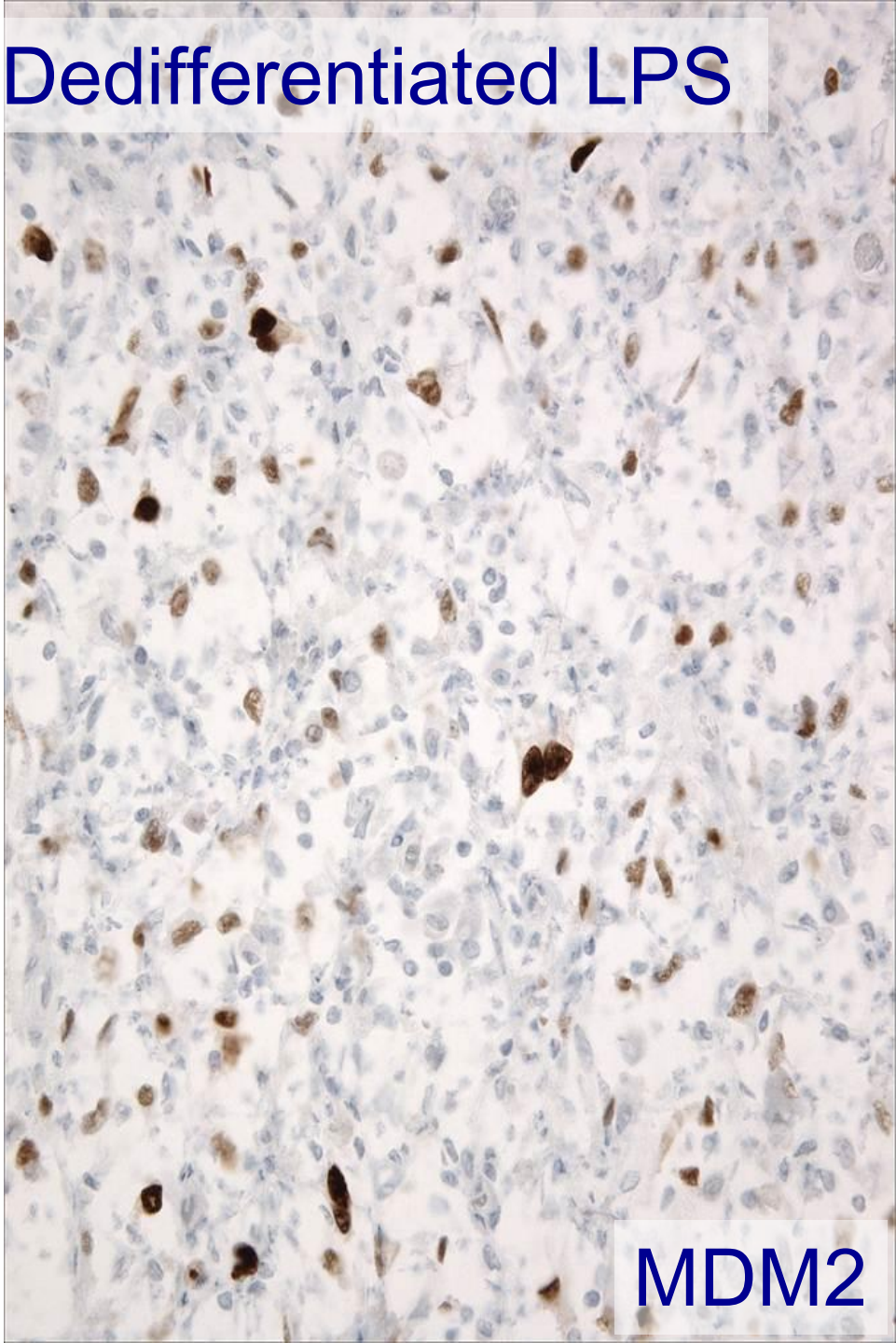
Clear cell sarcoma

(malignant lesion)

- t(12;22)(q13;q12)
  EWSR1-ATF1
  (most frequent in soft tissue)
  Zucman et al 1993
- t(2;22)(q33;q12)
  EWSR1-CREB1
  (mostly in GI tract)
  lack melanocytic markers
  Antonescu et al 2006

“Inflammatory MFH” = Dedifferentiated LPS





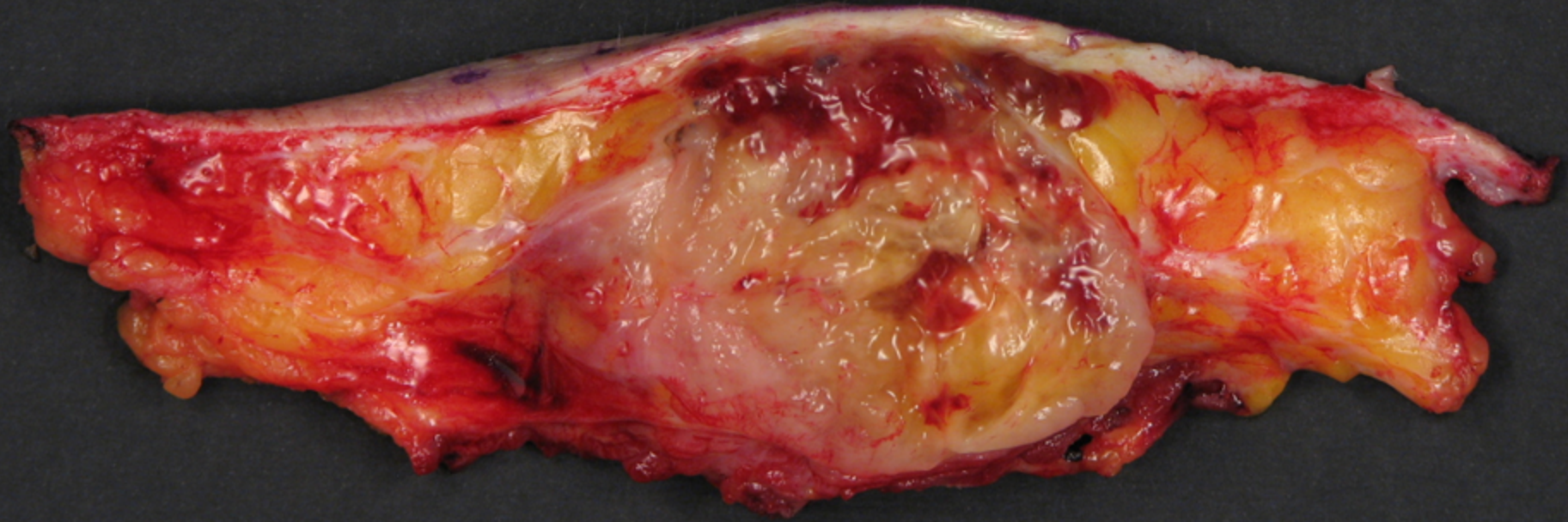
MDM2

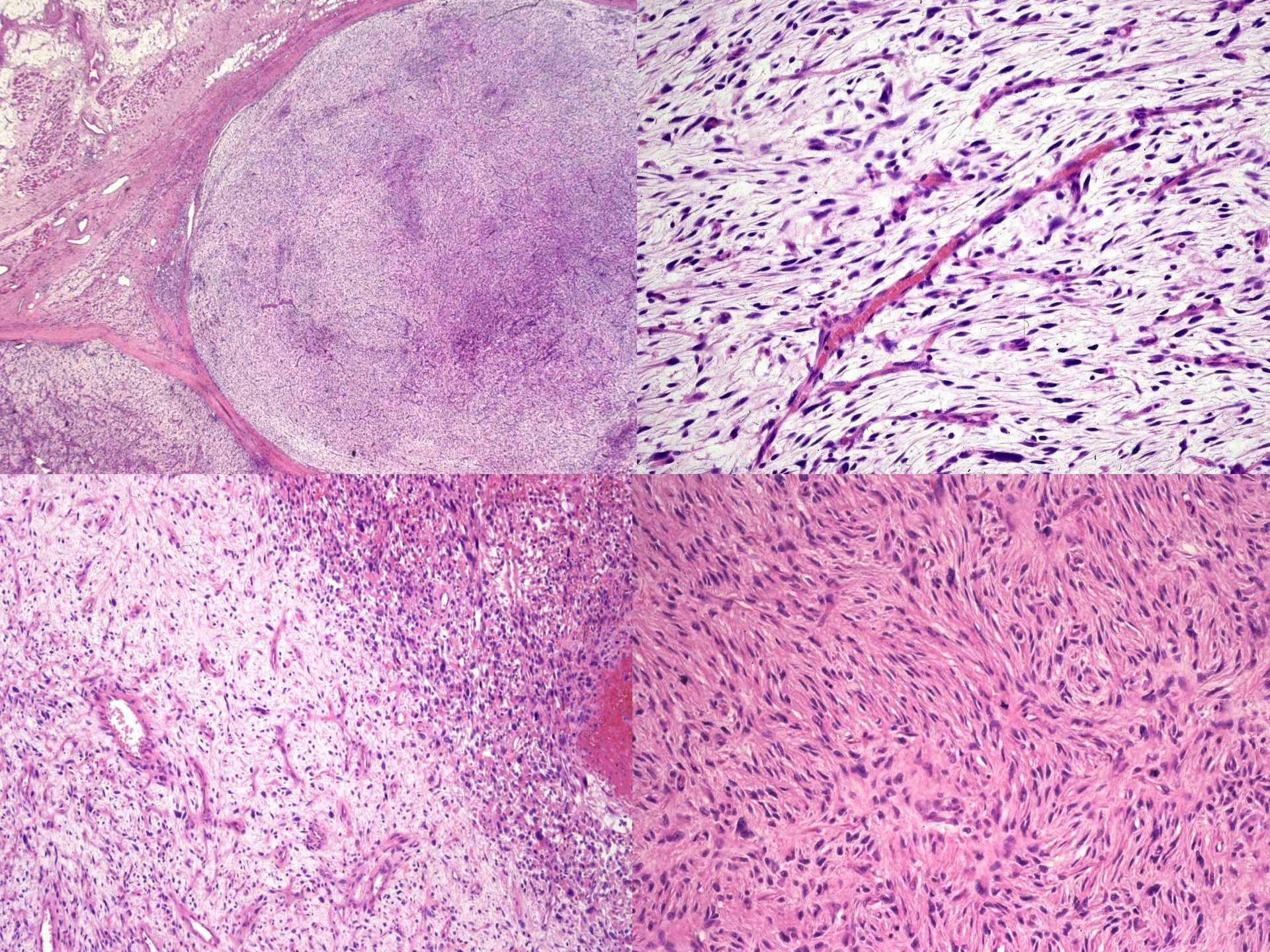
Myxofibrosarcoma

- Angervall, 1977
  - Myxoid MFH of Enzinger
- Spectrum of fibroblastic myxoid lesions
- High grade = myxoid “MFH”
- Histologic grade related to clinical outcome

Myxofibrosarcoma

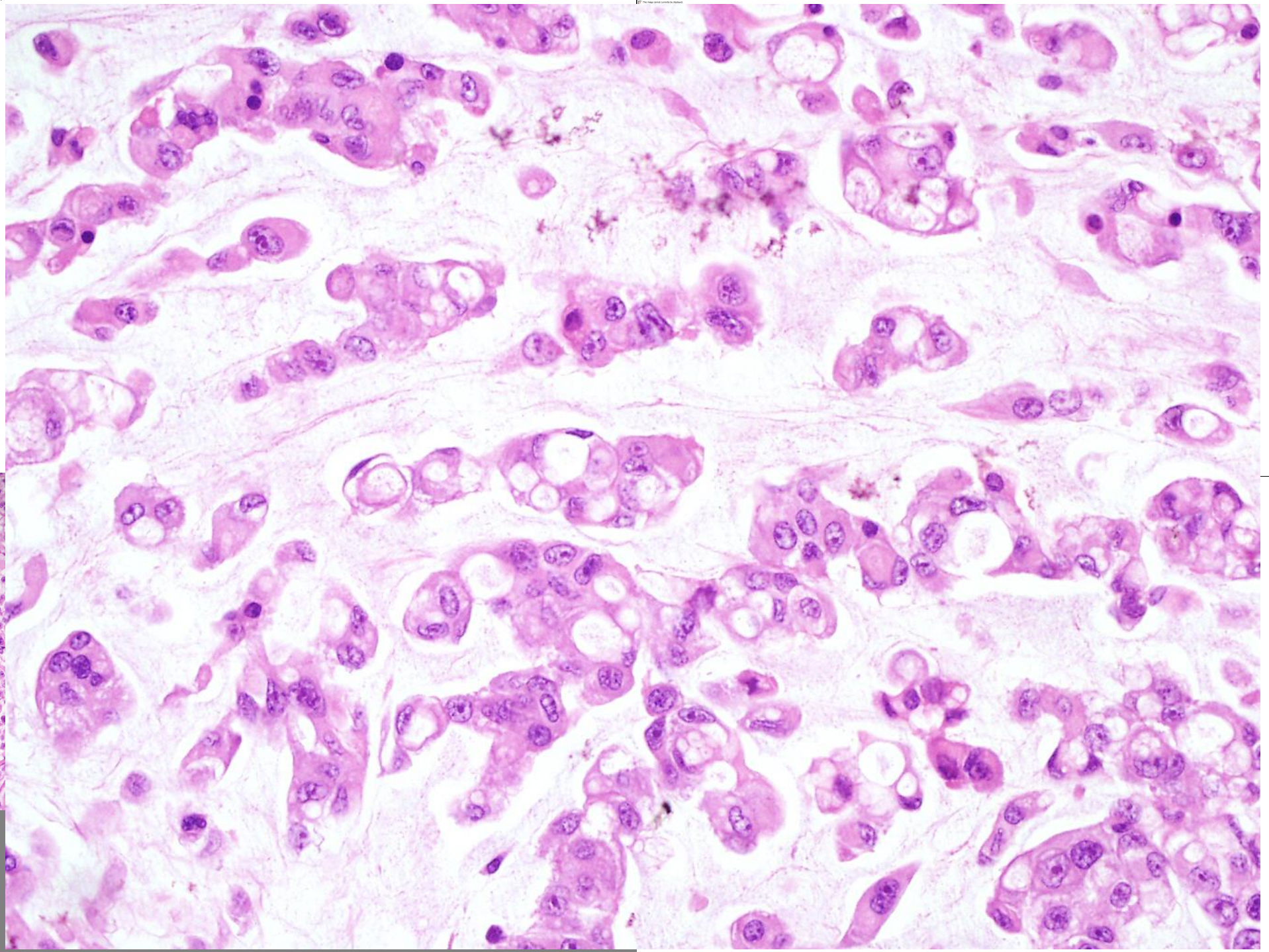
- Elderly patients
  - Very rare < 20 years
- Lower limbs >upper limbs > limb girdles
- Most cases in retroperitoneum = dedifferentiated LPS
- 2/3 subcutis, 1/3 deep seated
- IHC: MSA and SMA (focal)





Myxofibrosarcoma

- Low grade rarely metastazize
- Local recurrence: 50%
  - independent of grade
- Surgical resection is a challenge
  - Main Goal: wide margins
- High grade 30% metastatic rate
  - Lungs > bone > LN
- Overall SR @ 5 years = 60%

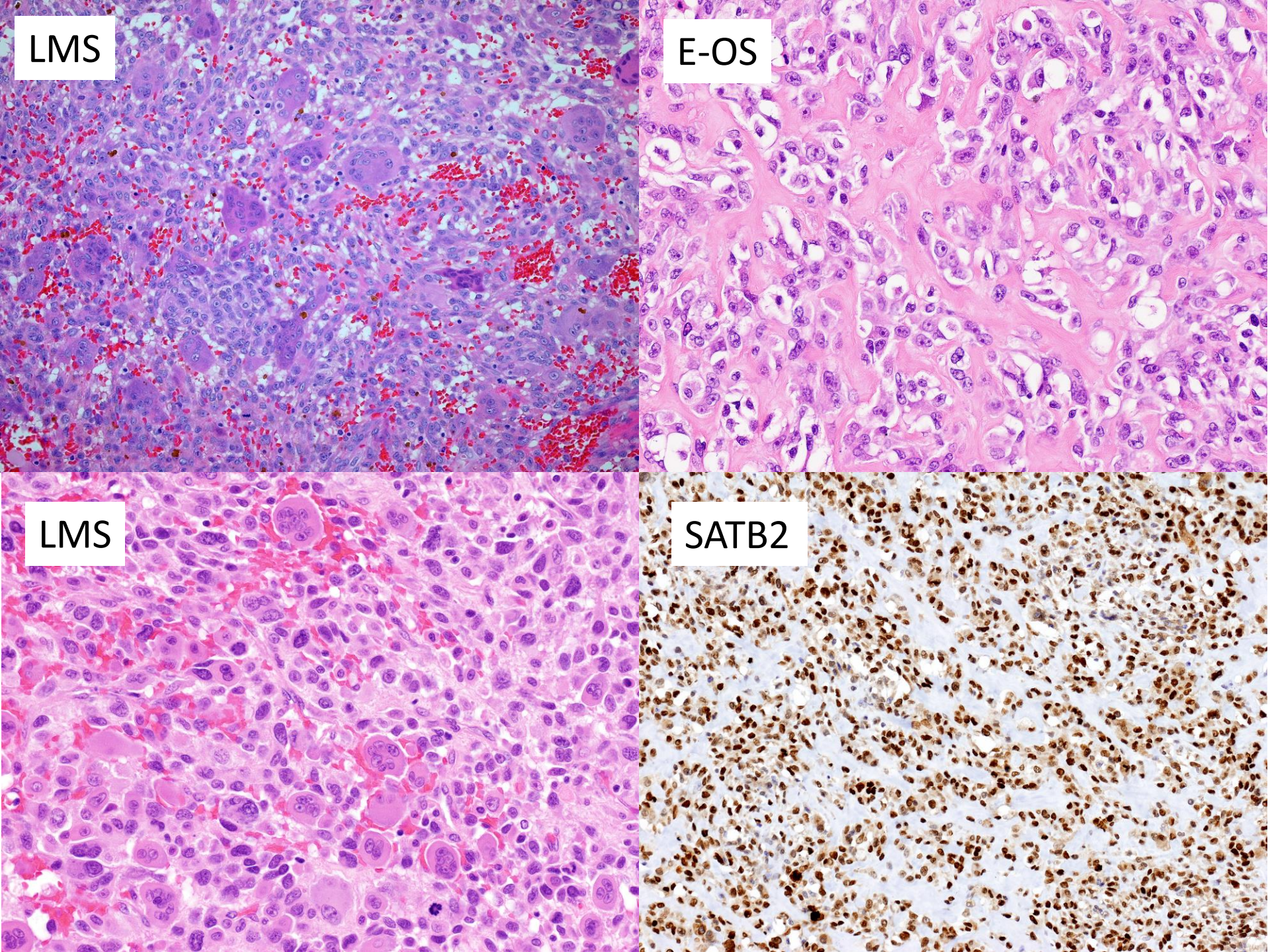


Epithelioid Myxofibrosarcoma

- Elderly patients
- Limbs
- 50% metastatic rate
  - Lungs > bone
- 73% recurrence rate
- Overall SR @ 5 years = 37%
- More aggressive then ordinary myxofibrosarcoma

Giant Cell MFH

- Histiocytic tumors
- GCT of soft tissues
  - Indolent clinical behavior
- Extraskeletal Osteosarcoma
  - Neoplastic osteoid
- Other high grade pleomorphic sarcomas with OC-like giant cells


LMS
E-OS
LMS
SATB2

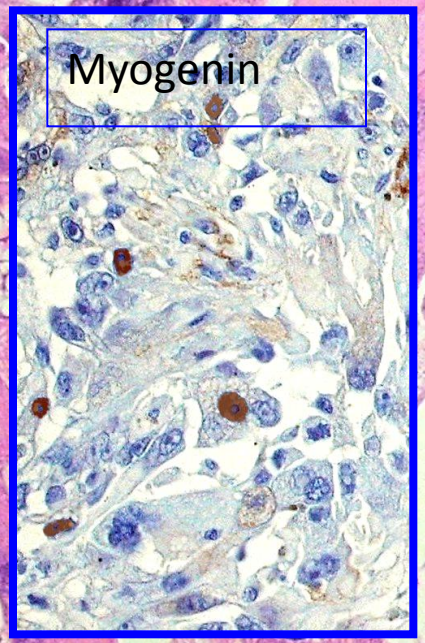
Pleomorphic Sarcomas: Is there a need for subtyping?

- Identification of non-mesenchymal neoplasms
- Myogenic differentiation related to worse prognosis
- Myxoid areas related to better prognosis
- Different treatment options for myogenic sarcomas

JCO 2001; 19:3045-3050.

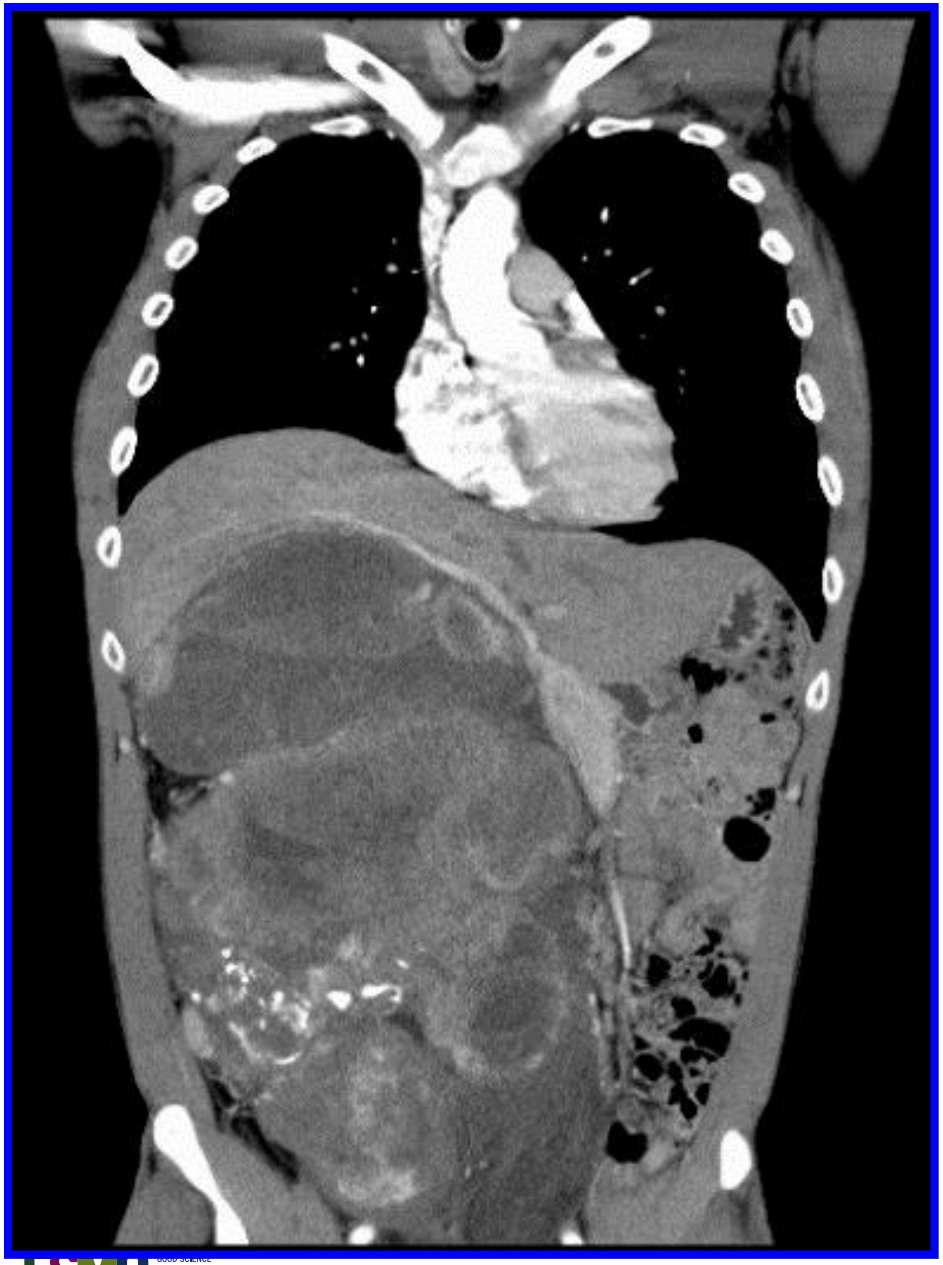
Clinicopathologic Re-Evaluation of 100 Malignant Fibrous Histiocytomas: Prognostic Relevance of Subclassification

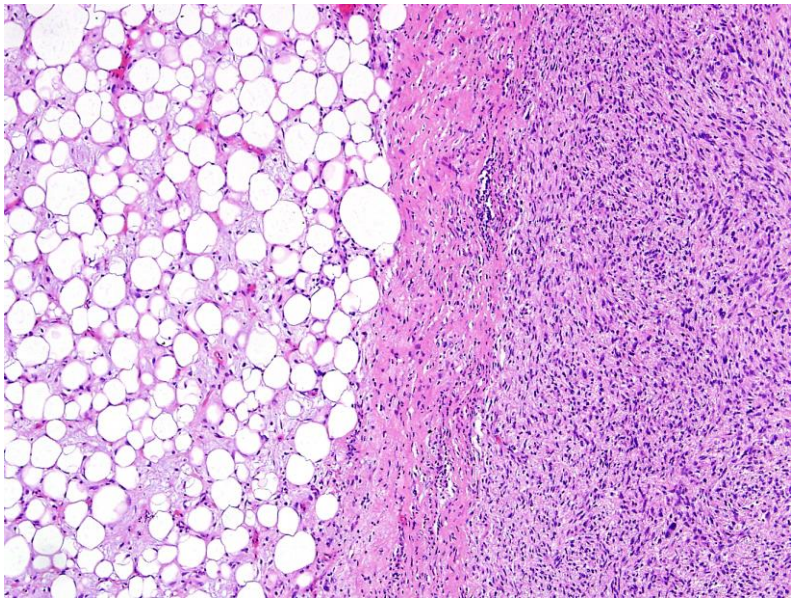
By Christopher D.M. Fletcher, Pelle Gustafson, Anders Rydholm, Helena Willén, Måns Åkerman

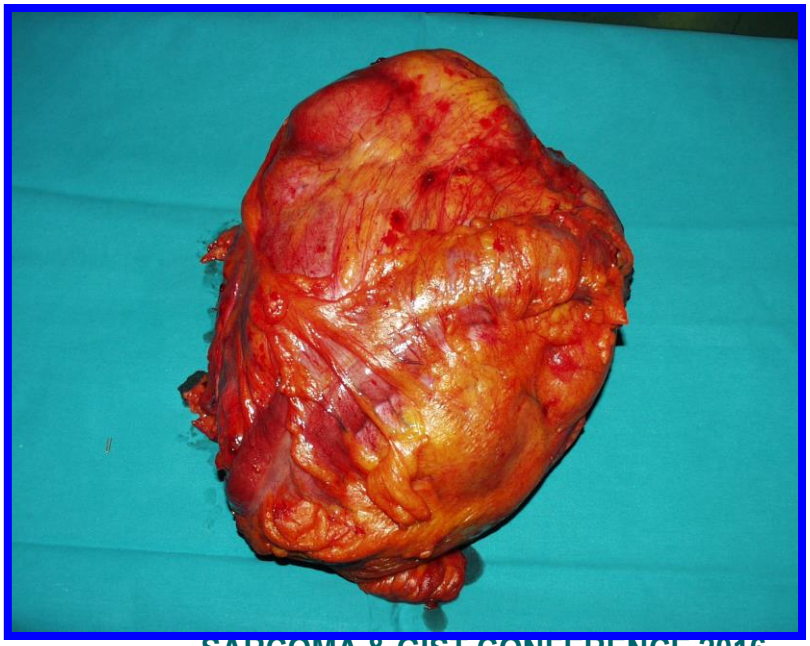


Dedifferentiated liposarcoma

- Evans, 1979
- Retroperitoneum of adults
- De novo (90%)
- Abrupt transition from WD liposarcoma to high grade non lipogenic sarcoma
- Rarely two components co-mingled
- Rarely non lipogenic component is low grade
- Rarely dedifferentiated component lipogenic
- MDM2/CDK4 overexpression/amplification







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

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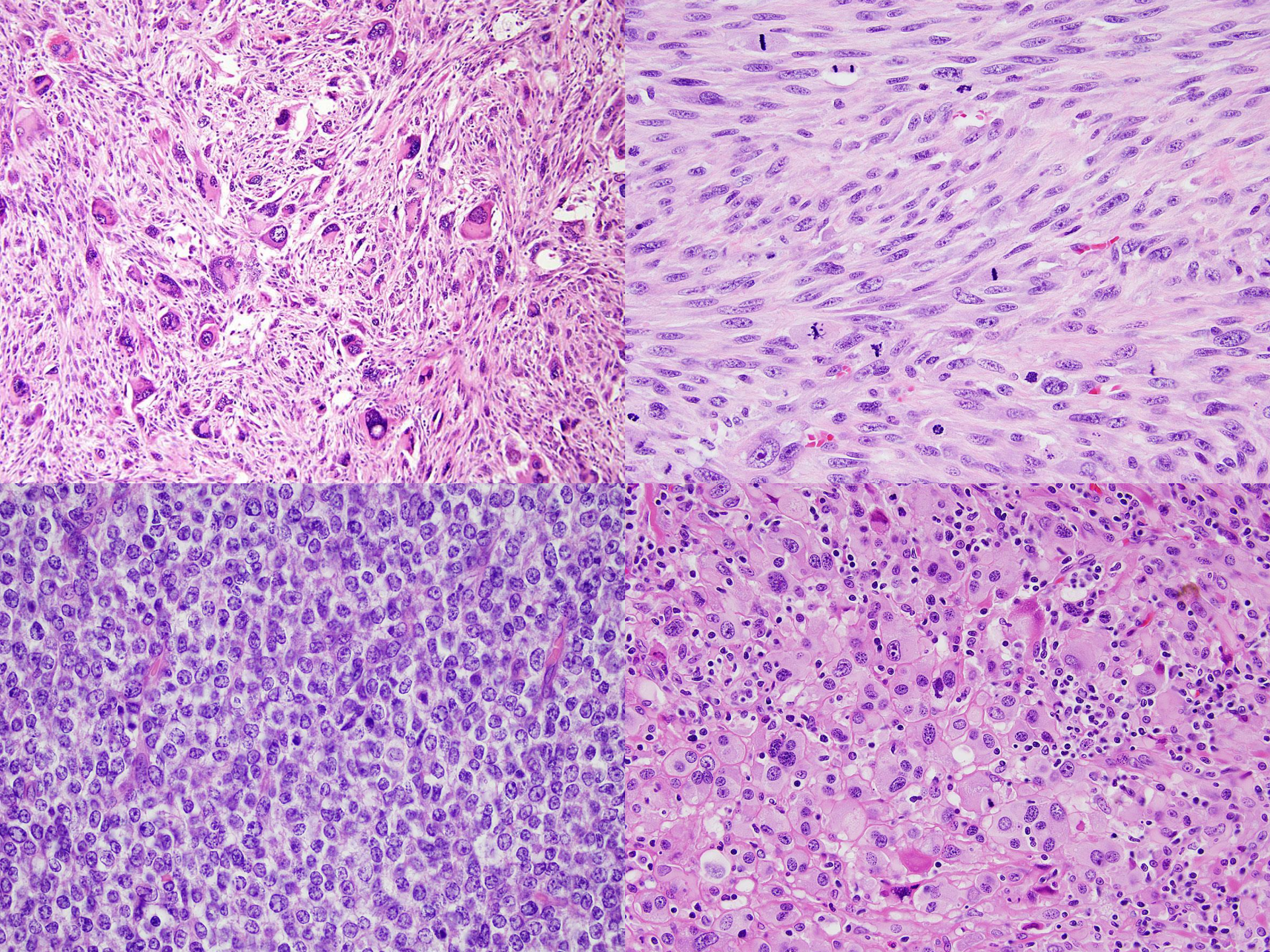
ORIGINAL REPORT

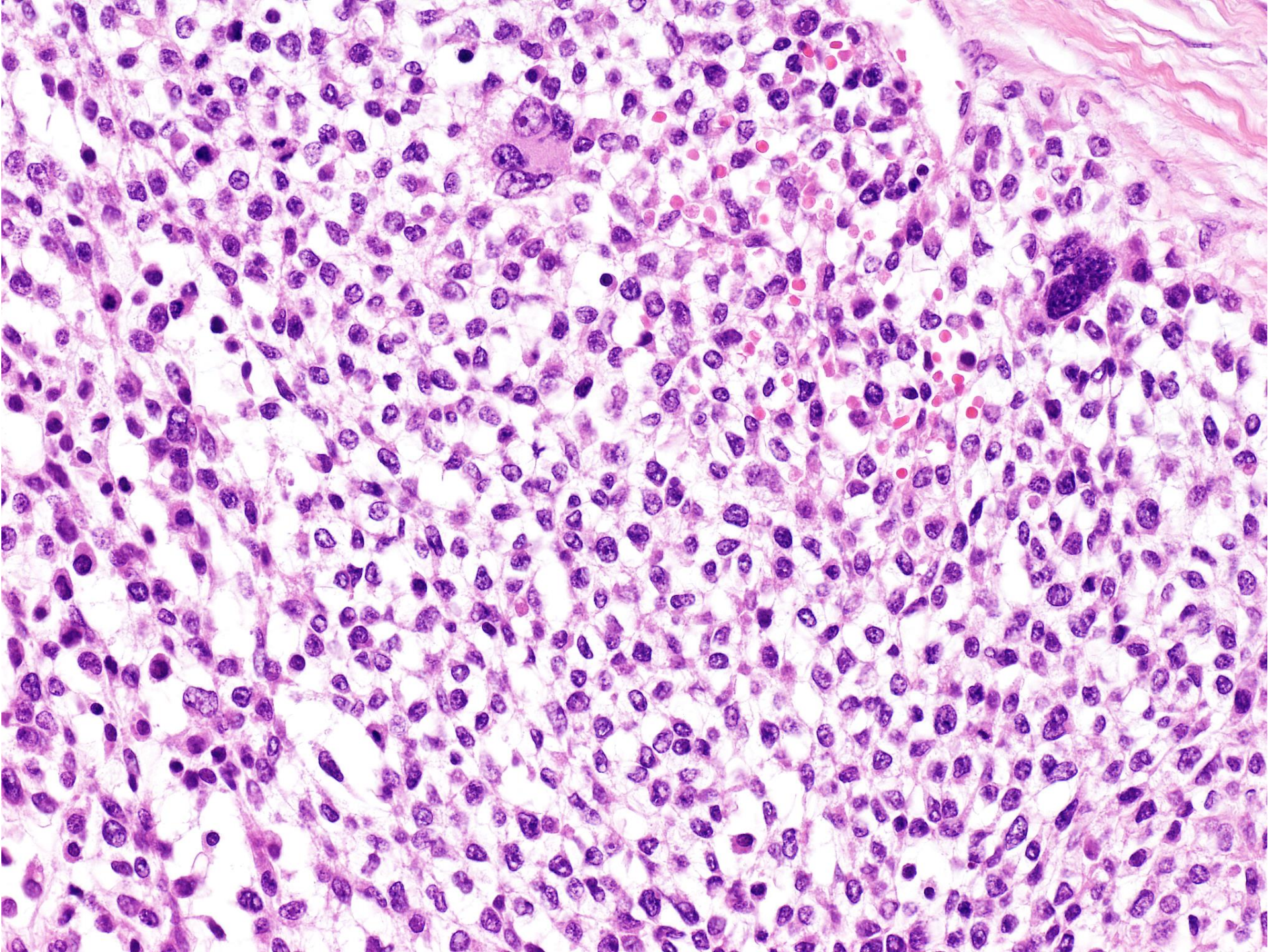
Primary Retroperitoneal Sarcomas: A Multivariate Analysis of Surgical Factors Associated With Local Control

Sylvie Bonvalot, Michel Rivoire, Marine Castaing, Eberhard Stoeckle, Axel Le Cesne, Jean Yves Blay, and Agnès Laplanche

Undifferentiated Pleomorphic Sarcomas

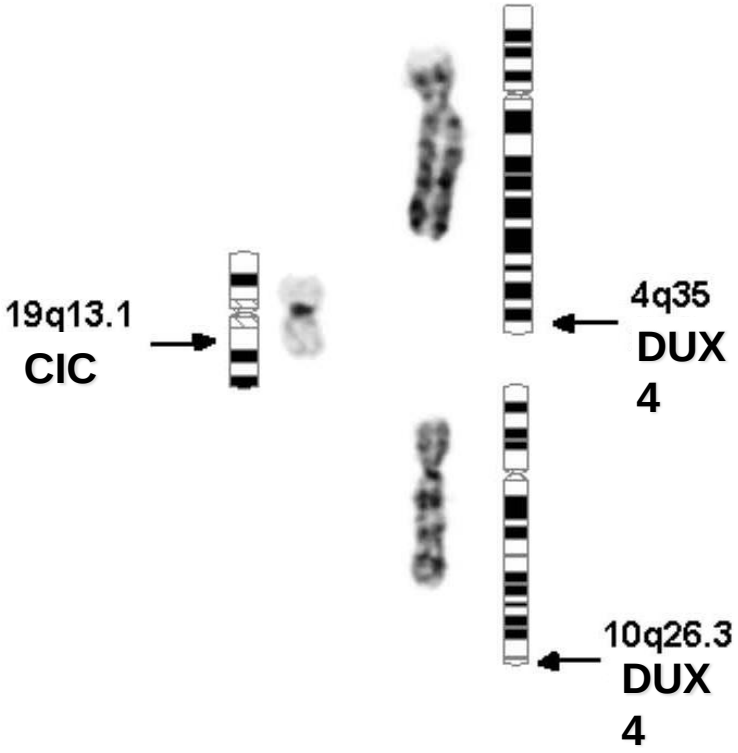
- Pleomorphic
- Epithelioid
- Round cell
  - Ewing like tumors with non canonical morphology as well as non ETS associated fusions (CIC-DUX4 etc.)
- Spindle cell





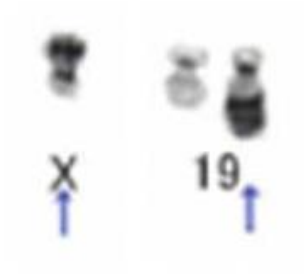
Undifferentiated small round sarcomas Ewing-sarcoma like

CIC-DUX4 fusions



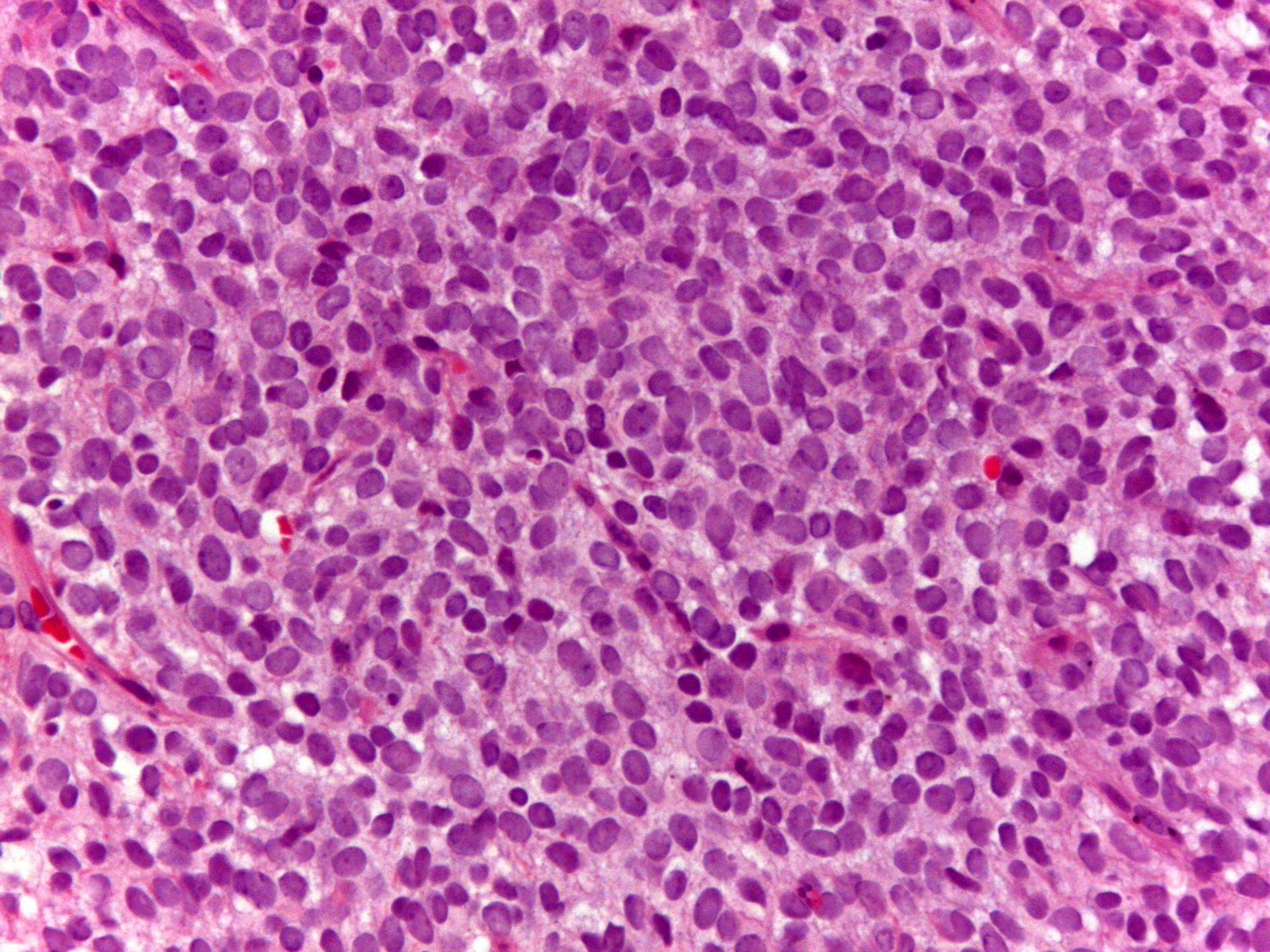
Italiano et al 2012

CIC (19q13.1) variant translocation



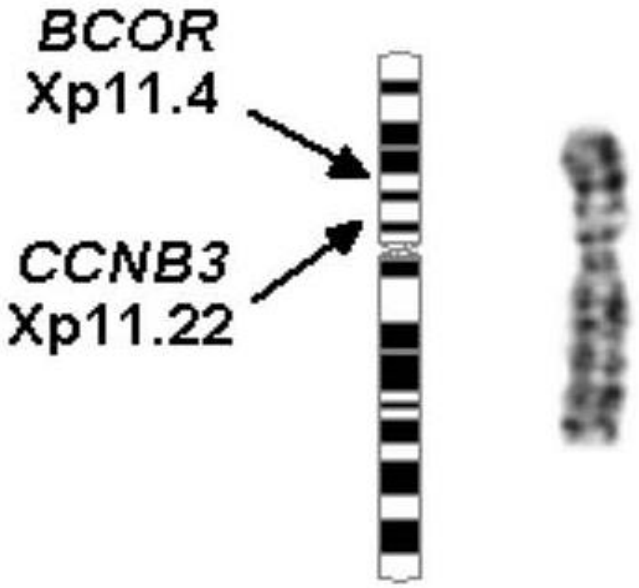
t(X;19)(q13;q13.1)/*CIC-FOXOA*

- *63-year-old man*
  Sugita et al 2014
- 13 year-old boy
  Solomon et al 2014
- ???
  Brohl et al. 2014*



Undifferentiated small round sarcomas Ewing-sarcoma like

BCOR-CCNB3 fusion



- RNA-Sequencing Cryptic rearrangement
- Gene expression profile no EWSR1-ETS signature
- SNP6.0 no gains of 8, 1q or loss 16q

inv(X)(p11.22p11.4)

Pierron et al 2012

Undifferentiated Sarcomas

- MFH label abandoned
- Pleomorphic RMS, LMS, LPS etc.
- Dedifferentiated liposarcoma
- UPS = diagnosis of exclusion base on morphology/IHC


THE
END