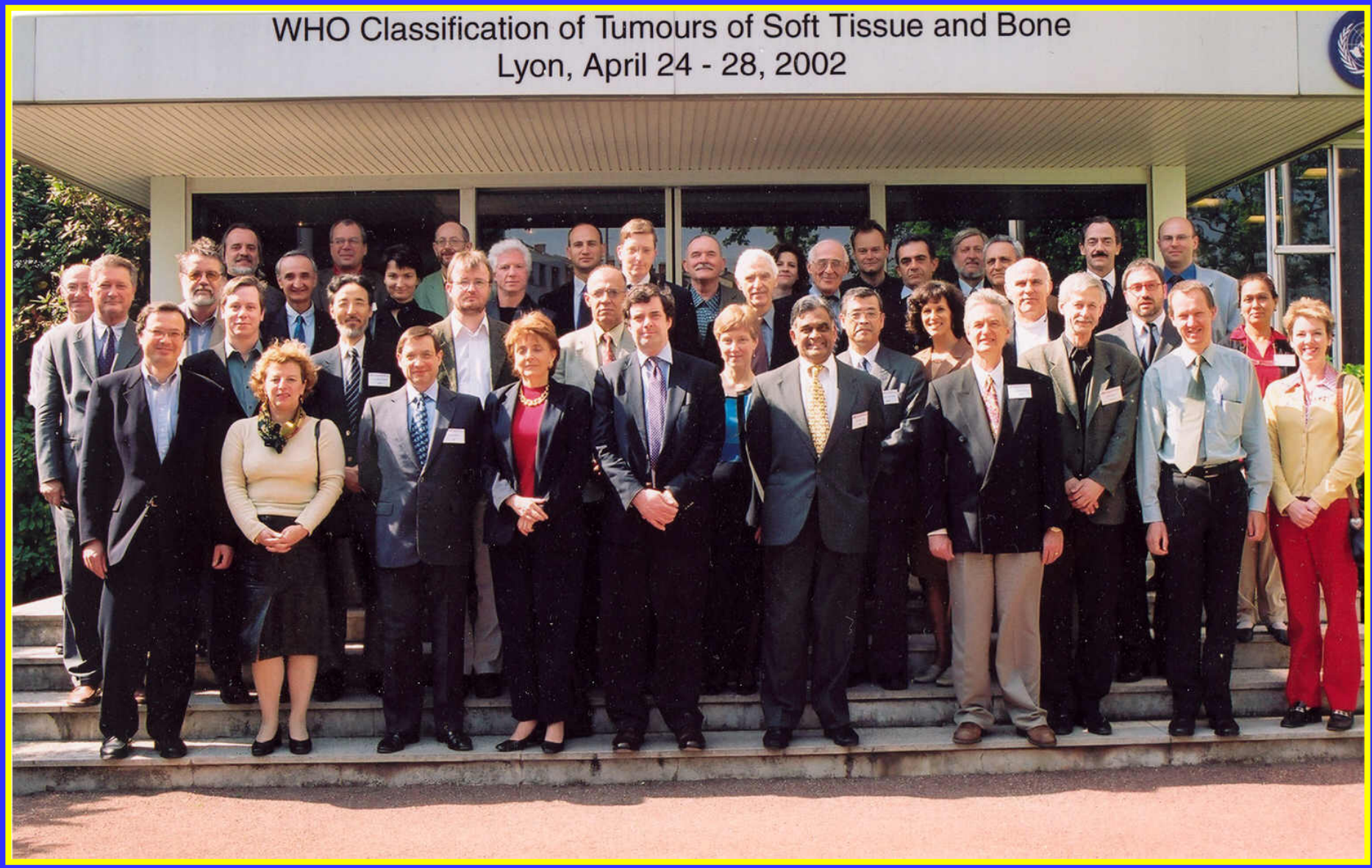
Conceptual Evolution of Soft Tissue Tumors Classification

Angelo P. Dei Tos M.D.
Departments of Pathology & Oncology
Treviso, Italy

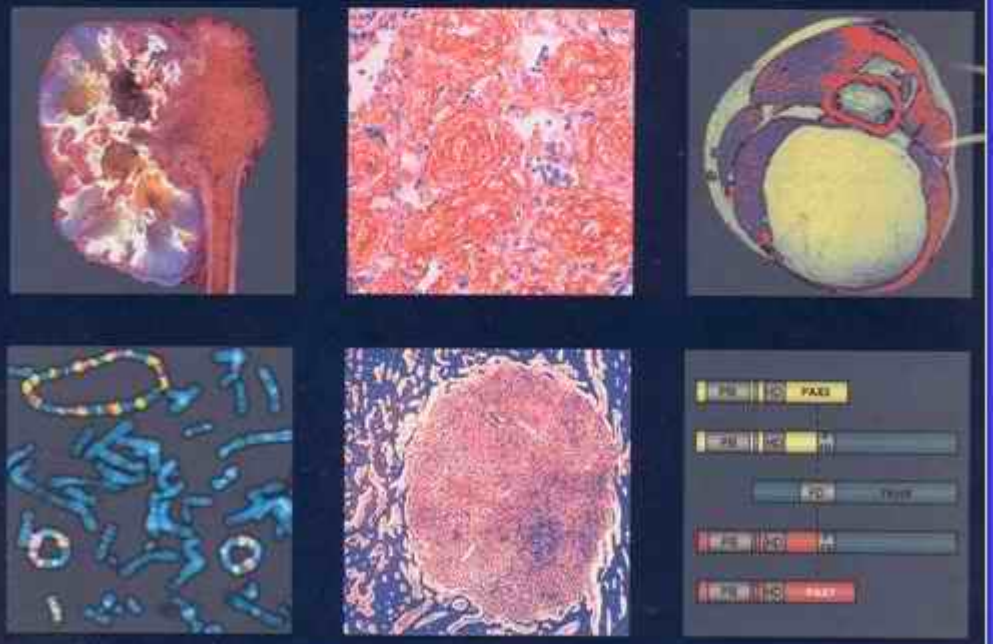

WHO Classification of Tumours of Soft Tissue and Bone
Lyon, April 24 - 28, 2002

World Health Organization Classification of Tumours

Pathology & Genetics

Tumours of Soft Tissue and Bone

Edited by Christopher D.M. Fletcher, K. Krishnan Unni, Fredrik Mertens



World Health Organization Classification of Tumours of Soft Tissue and Bone

Editors: C. D. Fletcher, K. Unni, F. Mertens

Tumours of Soft Tissue

Genetics

Only two plexiform fibrohistiocytic tumours with clonal chromosome aberrations have been reported, and no shared chromosome abnormalities were found (Redlich et al.,1999/100;Smith et al.,1999/99).

Postulated Cell of Origin

Myofibroblastic differentiation (Giard et al.,1991/354;Hollowood et al.,1991/355), histiocytic differentiation (Thomazy et al.,1994/357), and the participation of both cell lines (Angervall et al.,1982/351) are the leading theories for the histogenesis of PFT.

Prognostic Factors

PFT has been associated with a local recurrence rate ranging from 12.5% (Remstein et al.,1999/356) to 37.5% (Enzinger et al.,1988/353), a regional lymphatic metastatic rate of 6% (Enzinger et al.,1988/353;Remstein et al.,1999/356), a systemic (lungs only, to date) metastatic rate of 19% (Remstein et al.,1999/356), and a mortality rate of 6% (Remstein et al.,1999/356). No clinicopathologic or genetic factors seem to affect the prognosis of patients with PFT (Enzinger et al.,1988/353;Remstein et al.,1999/356).

Angiomatoid (malignant) fibrous histiocytoma

J.C. Fanburg-Smith

P. Dal Cin

Definition

Angiomatoid (malignant) fibrous histiocytoma (A(M)FH) is generally a tumour of children and young adults of the extremities, of fibrohistiocytic and myofibroblastic phenotype. It has rare metastatic potential, giving rise to the name "angiomatoid fibrous histiocytoma". The clinical location, gross and microscopic features, and myoid phenotype mimic an intranodal process, suggesting the possibility that A(M)FH may be related to fibroblastic reticulum cell sarcoma of lymph node, a tumour derived from myoid cells of lymphoid tissue (Andriko et al.,1998/333).

ICD-0 codes

A(M)FH

Synonyms

Angiomatoid fibrous histiocytoma

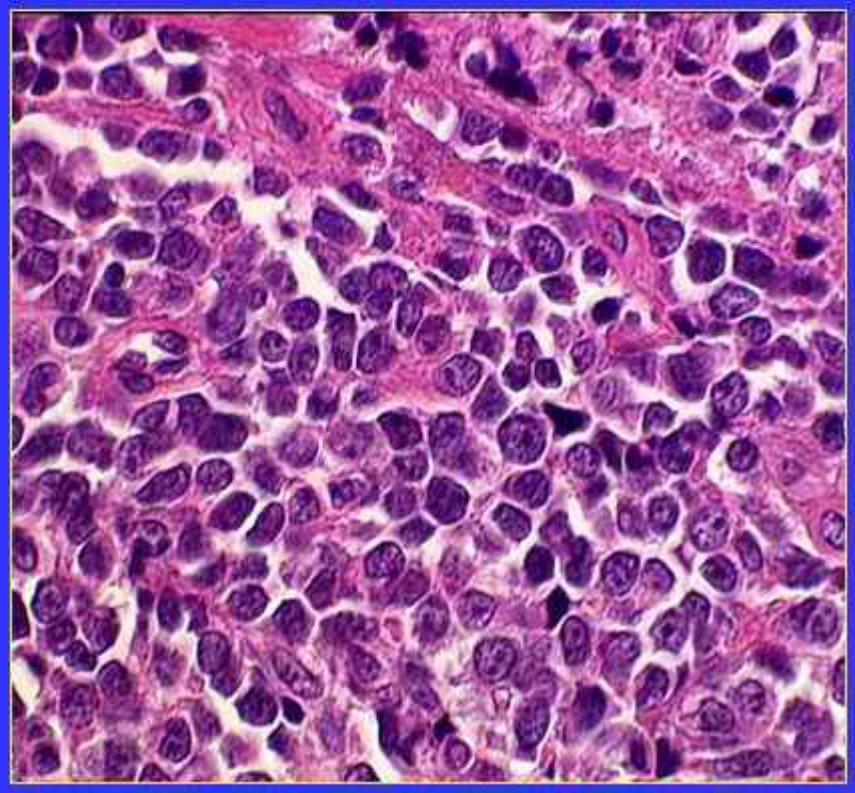
Epidemiology

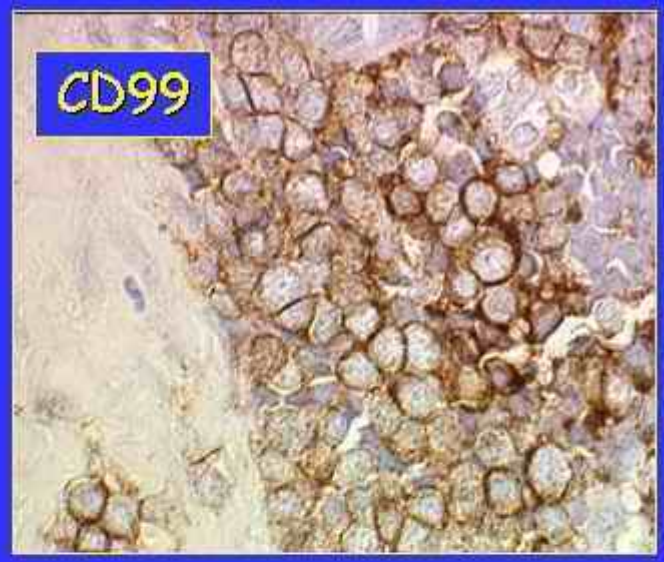
Originally described by Enzinger in 1979 (Enzinger,1979/340), A(M)FH comprises 5% of tumours designated as "malignant fibrous histiocytoma" and approximately 0.3% of all soft tissue tumours. Although A(M)FH has a wide age range from birth (Argenyi et al.,1988/334) to 71 years old (Fanburg-Smith et al.,1999/341), it is

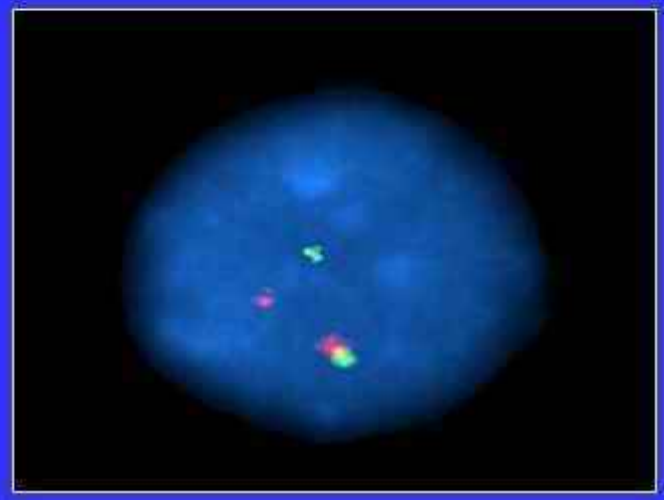
How WHO classification was reshaped

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

Integration between morphology, immunophenotype and genetics







Tumor type	Cytogenetic changes	Gene rearrang†
Ewing's sarcoma/PNET	t(11;22)(q24;q12)	*FLI-1-EWS*
	t(21;22)(q22;q12)	*ERG-EWS*
	t(7;22)(p22;q12)	*ETV1-EWS*
	t(17;22)(q12;q12)	*EIAF-EWS*
	t(2;22)(q33;q12)	*FEV-EWS*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FKHR*
	t(1;13)(p36;q14)	*PAX7-FKHR*
Myxoid/round cell liposarcoma	t(12:16)(q13;q11)	*CHOP-TLS*
	t(12;22)(q13;q11-12)	*CHOP-EWS*
DSRCT	t(11;22)(p13;q12)	*WT1-EWS*
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SSX1-SYT*
		SSX2-SYT
Clear cell sarcoma	t(12;22)(q13;q12)	*ATF-1-EWS*
Extraskeletal myxoid CHS	t(9;22)(q22;q12)	*TEC-EWS*
DFSP/*GCF*	t(17;22)(q22;q13)	*PDGFB-COL1A1*
Infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*ASPL-TFE3*
Low grade fibromyxoid sarcoma	t(7;16)(q33;p11)	*FUS-BBF2H7*

The Marriage between Pathology and Genetics

- Validation of morphology
- Classification
- Identification of prognostic/predictive factors
- Elucidation of oncogenetic mechanisms

Conceptual Advances

- Definition of tumor category
- Atypical lipomatous tumors
- "Malignant Fibrous Histiocytoma"
- "Hemangiopericytoma"
- New entities incorporated
- Many entities repositioned
- Many entities reshaped

World Health Organization
Classification of Tumours of Soft Tissue

BENIGN CATEGORY

Most benign soft tissue tumours do not recur locally. Those that do recur do so in a non-destructive fashion and are almost always readily cured by complete local excision. Exceedingly rarely (almost certainly <1/50,000 cases, and probably even less than that), a morphologically benign lesion may give rise to distant metastases. This is entirely unpredictable on the basis of conventional histological examination and, to date, has been best documented in cutaneous benign fibrous histiocytoma.

World Health Organization
Classification of Tumours of Soft Tissue

INTERMEDIATE CATEGORY
(Locally aggressive)

Soft tissue tumours in this category often recur locally and are associated with an infiltrative and locally destructive growth pattern. Lesions in this category do not have any evident potential to metastasise but typically require wide excision with a margin of normal tissue in order to ensure local control. The prototypical lesion in this category is desmoid fibromatosis.

World Health Organization Classification of Tumours of Soft Tissue

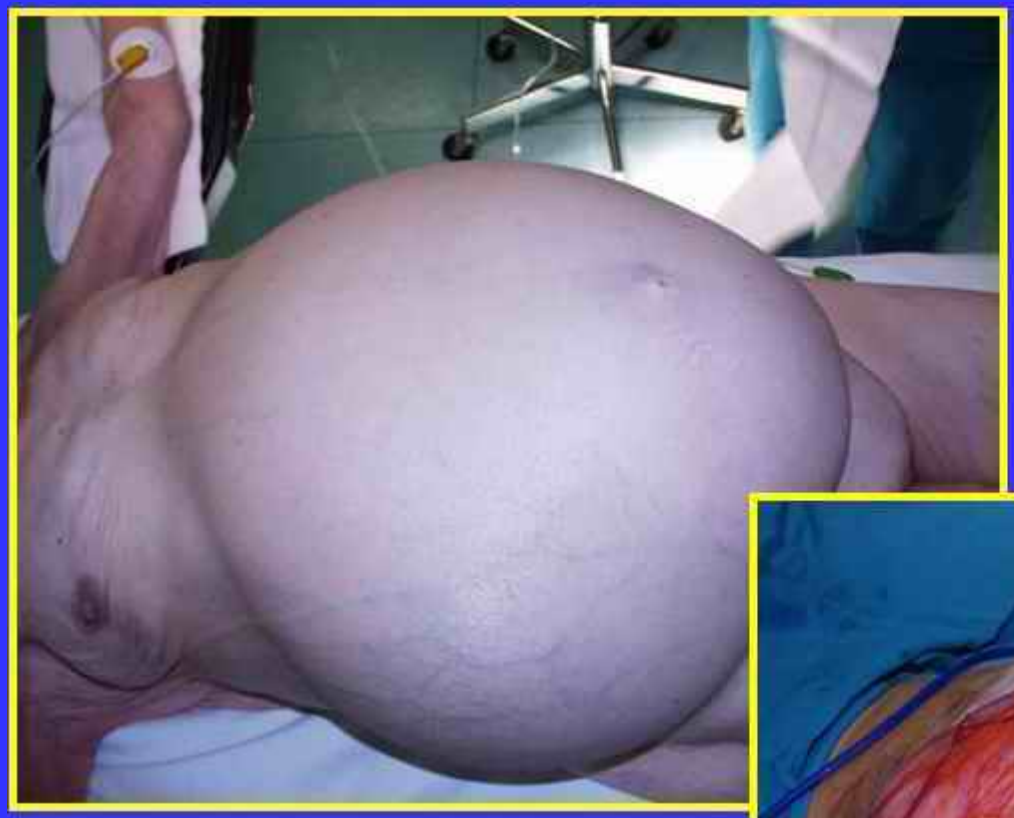
INTERMEDIATE CATEGORY (Rarely metastasising)

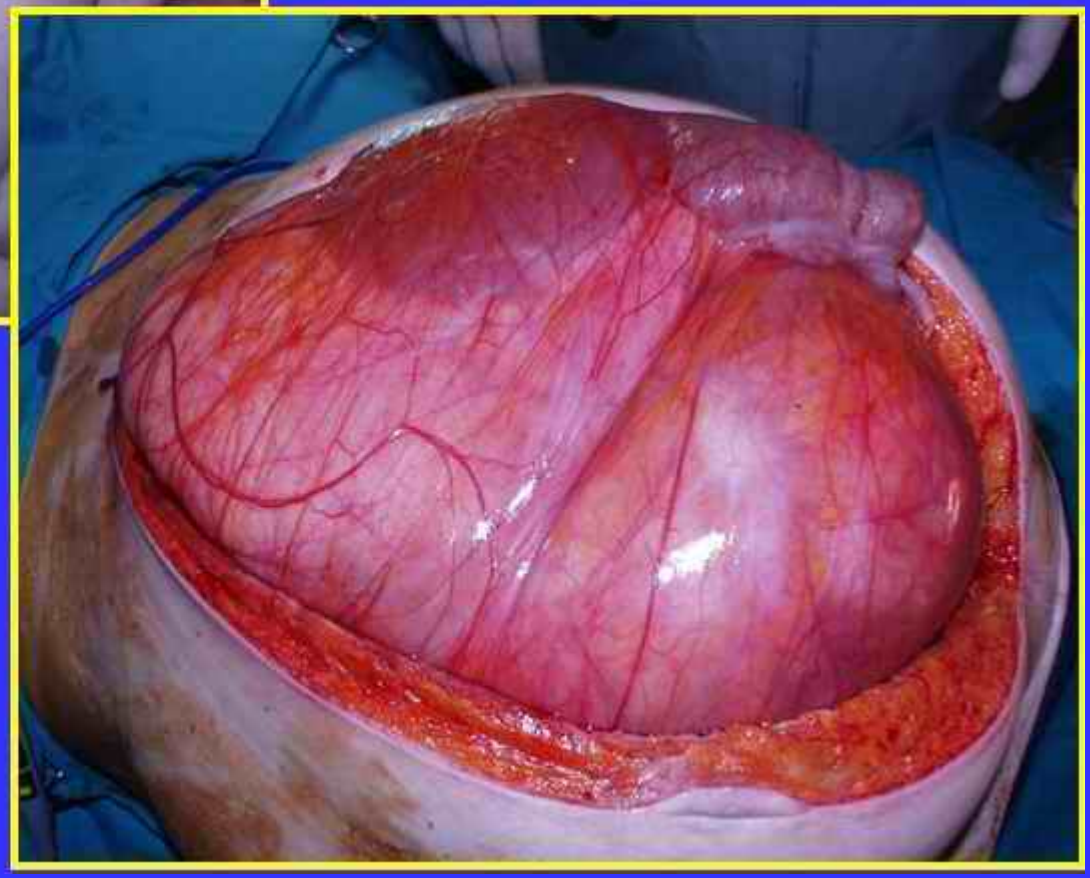
Soft tissue tumours in this category are often locally aggressive but, in addition, show the well documented ability to give rise to distant metastases in occasional cases. The risk of such metastases appears to be <2% and is not reliably predictable on the basis of histomorphology. Metastasis in such lesions is usually to lymph node or lung. Prototypical examples in this category include plexiform fibrohistiocytic tumour and so-called angiomatoid fibrous histiocytoma.

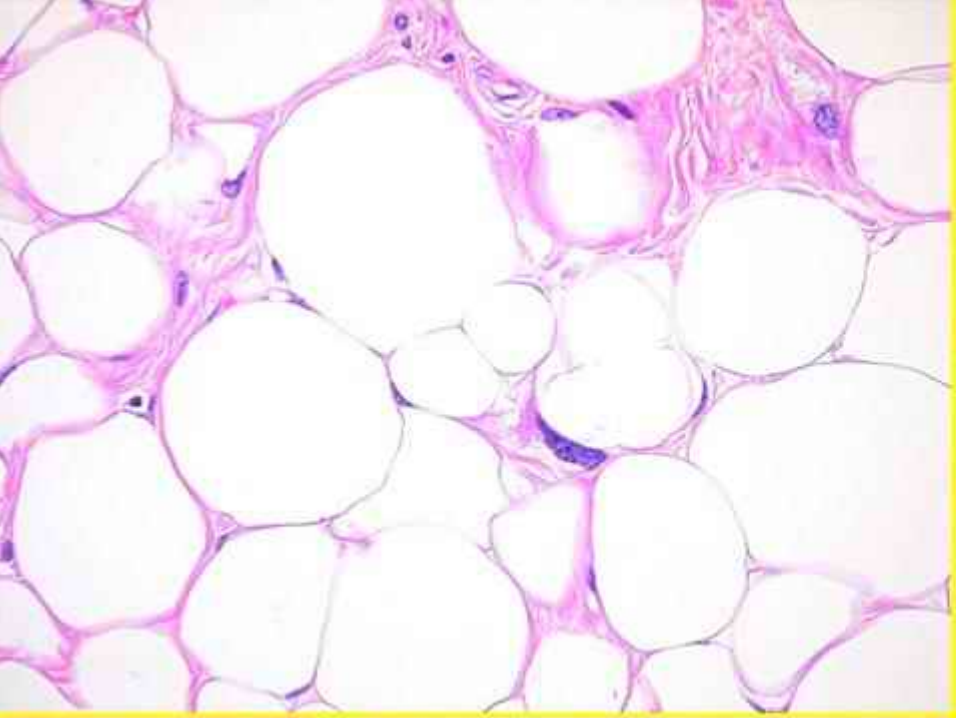
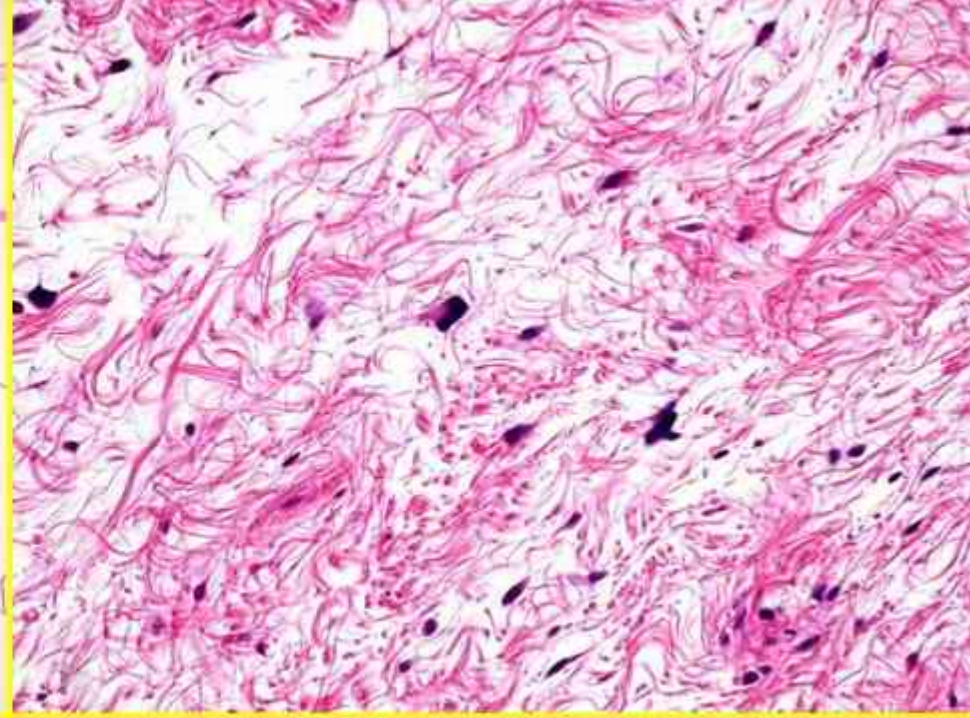
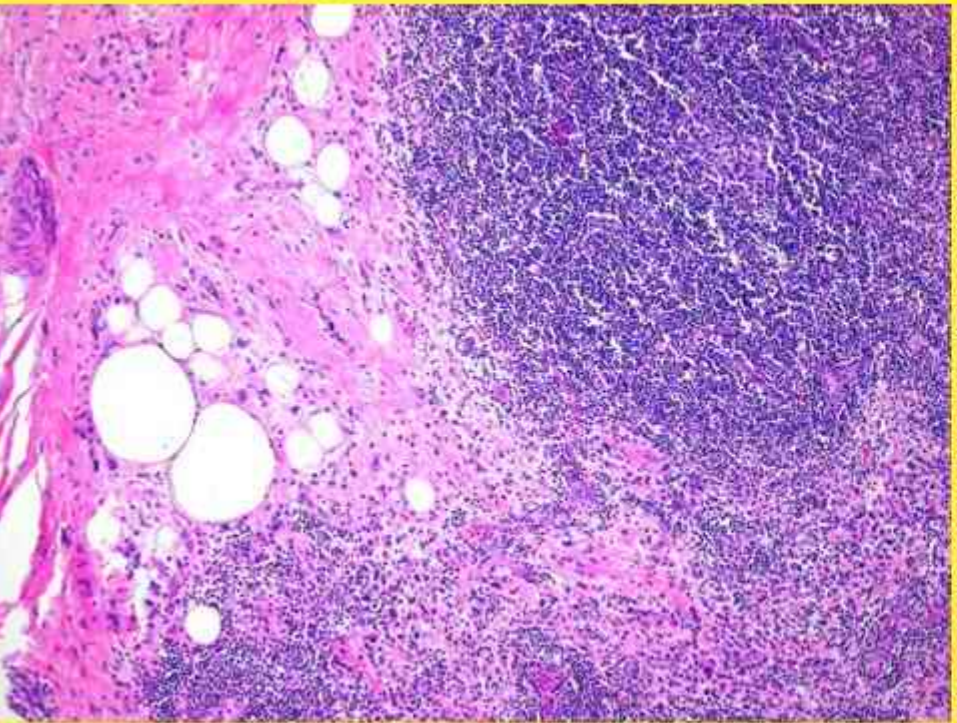
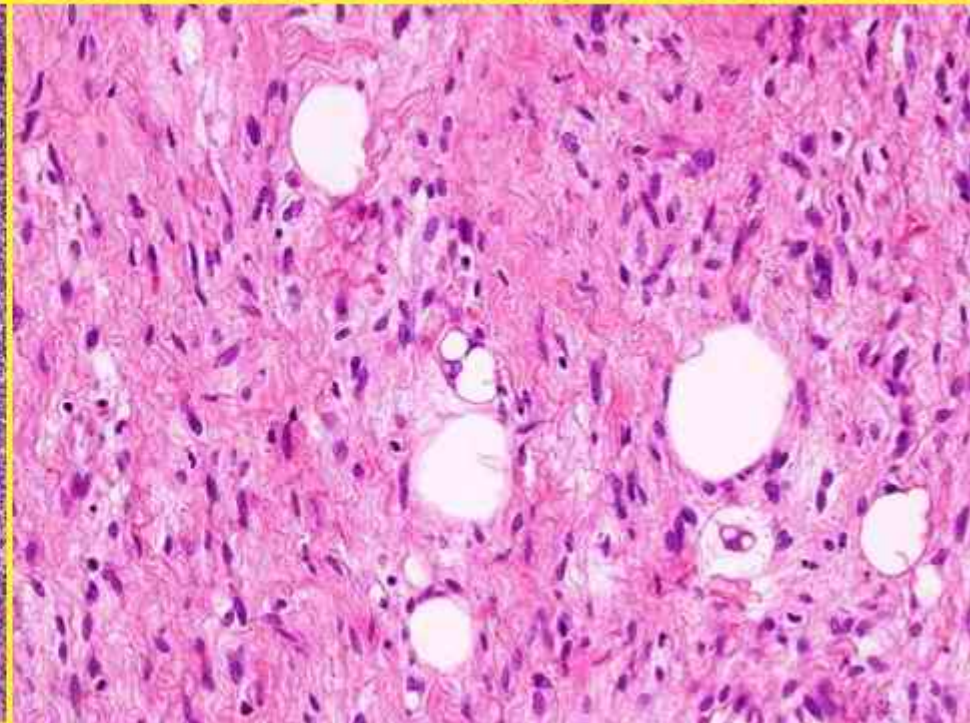
World Health Organization
Classification of Tumours of Soft Tissue

MALIGNANT CATEGORY

In addition to the potential for locally destructive growth and recurrence, malignant soft tissue tumours (known as soft tissue sarcomas) have significant risk of distant metastasis, ranging in most instances from 20% to almost 100%, depending upon histological type and grade. Some (but not all) histologically low grade sarcomas have a metastatic risk of only 2-10%, but such lesions may advance in grade in a local recurrence, and thereby acquire a higher risk of distant spread (e.g., myxofibrosarcoma and leiomyosarcoma).





WD Liposarcoma/ALT

- 1972, Evans
- Incoherent application
- Confusion among both clinicians and pathologists

Atypical lipoma

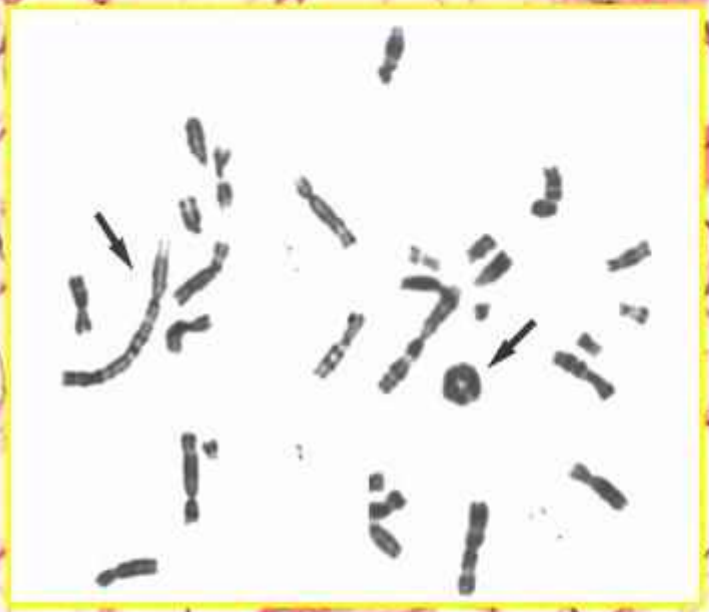
Background:
- WD liposarcoma never metastazizes
- Cured by wide surgical excision

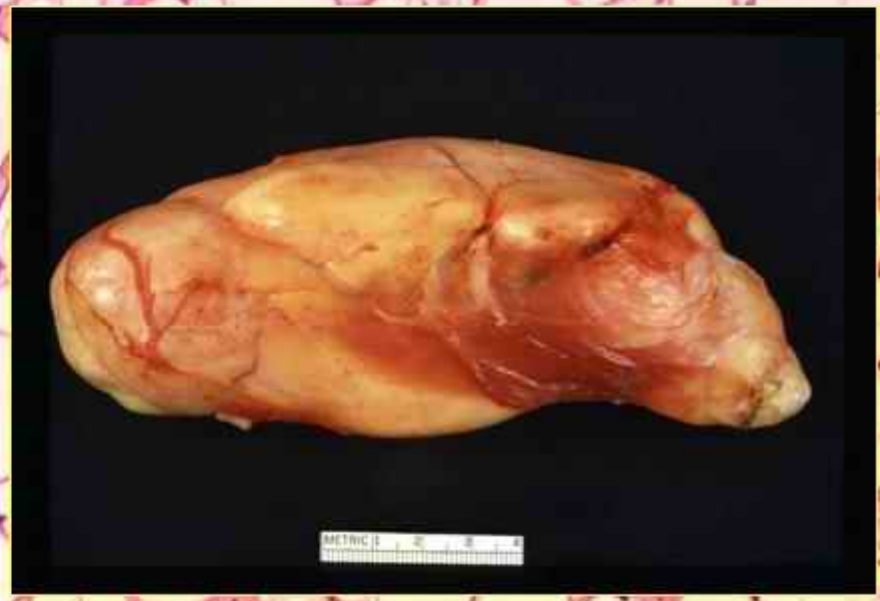
AL: subcutaneous, inter ed intra muscular WD liposarcoma (Evans, 1979)
Atypical lipomatous tumors: WD liposarcoma of the deep soft tissue without lipoblasts (Evans, 1988)

Atypical lipoma: Deep seated WD liposarcoma without lipoblasts (Kindblom, 1982)

AL: subcutaneous WD liposarcoma (Weiss, 1992)

Well differentiated LPS/ALT





- ALT and WD = synonyms
- WDLSP/ALT = intermediate category/locally aggressive

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

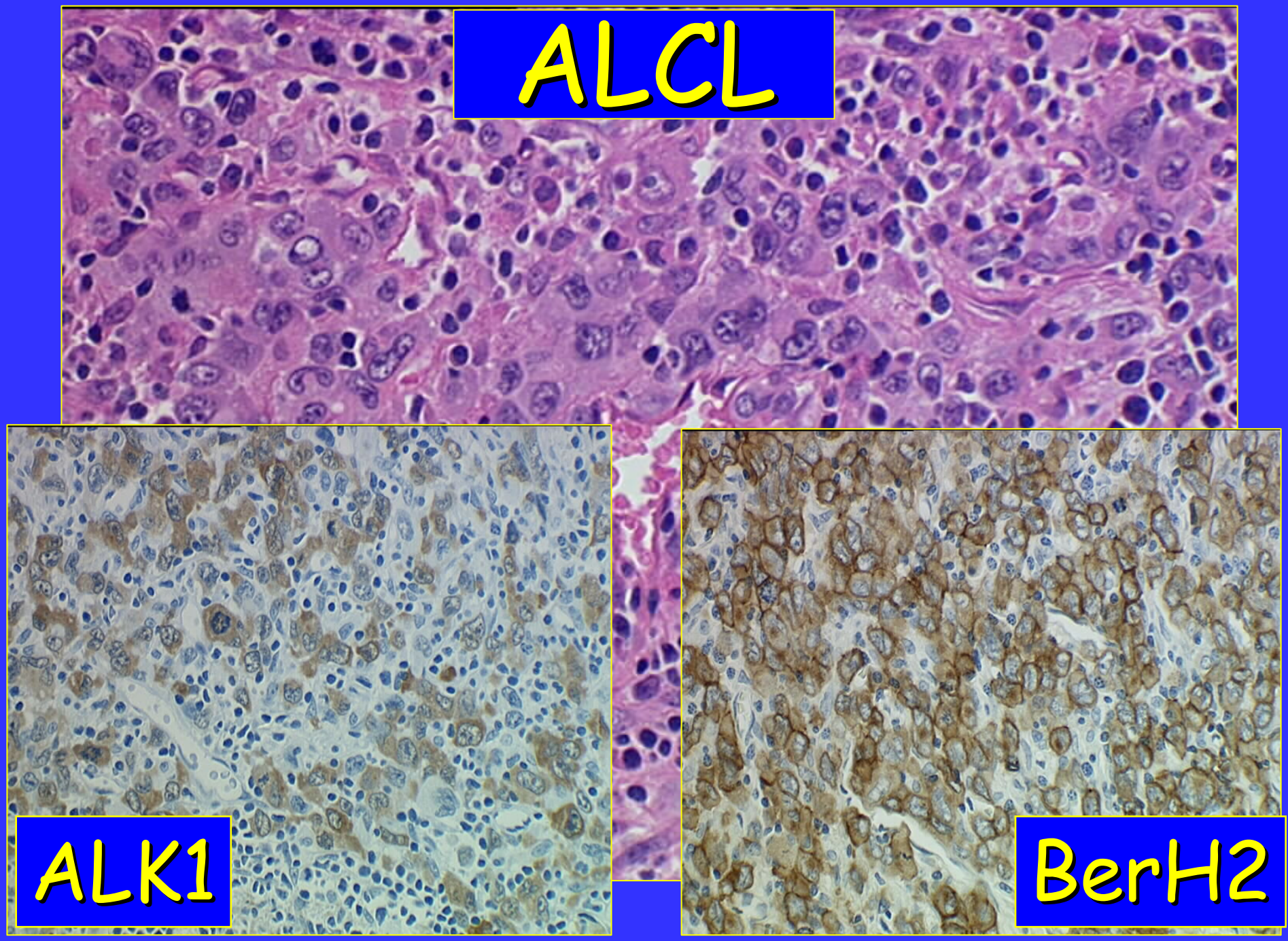
Pleomorphic Malignant Fibrous Histiocytoma: Fact or Fiction?

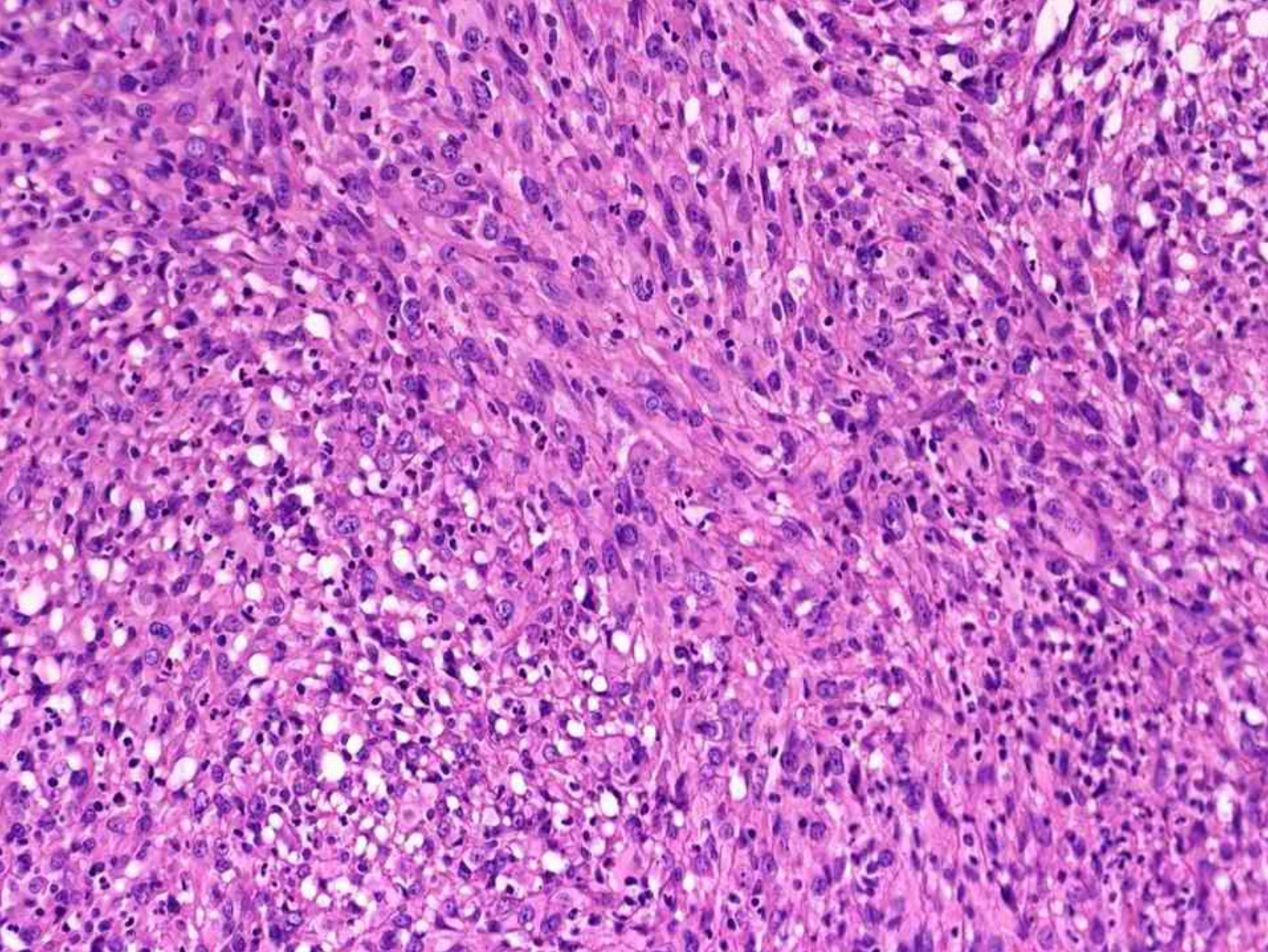
A Critical Reappraisal Based on 159 Tumors Diagnosed as Pleomorphic Sarcoma

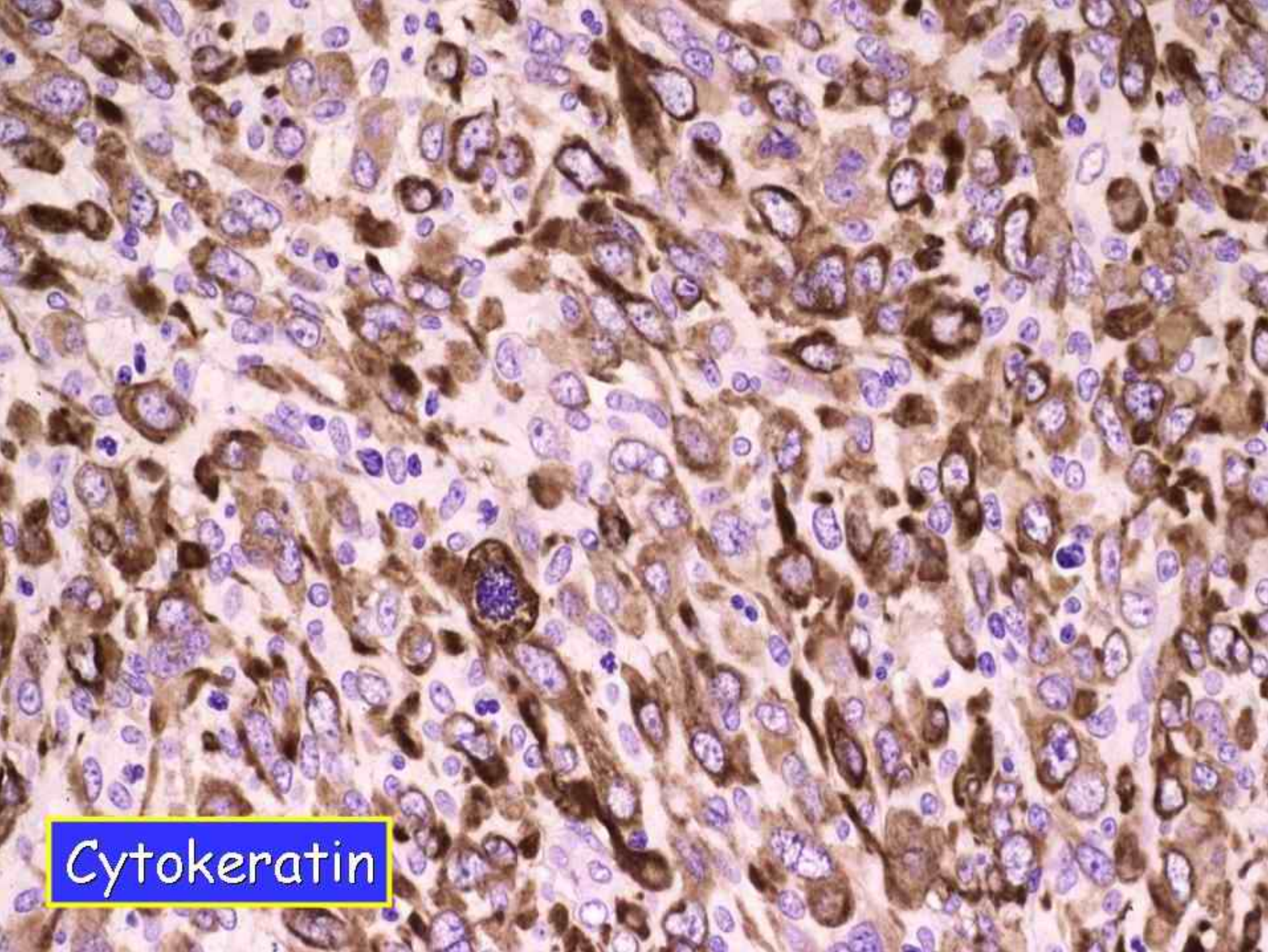
Christopher D.M. Fletcher, M.D., M.R.C.Path.

Until 1992 MFH = most frequent soft tissue sarcoma

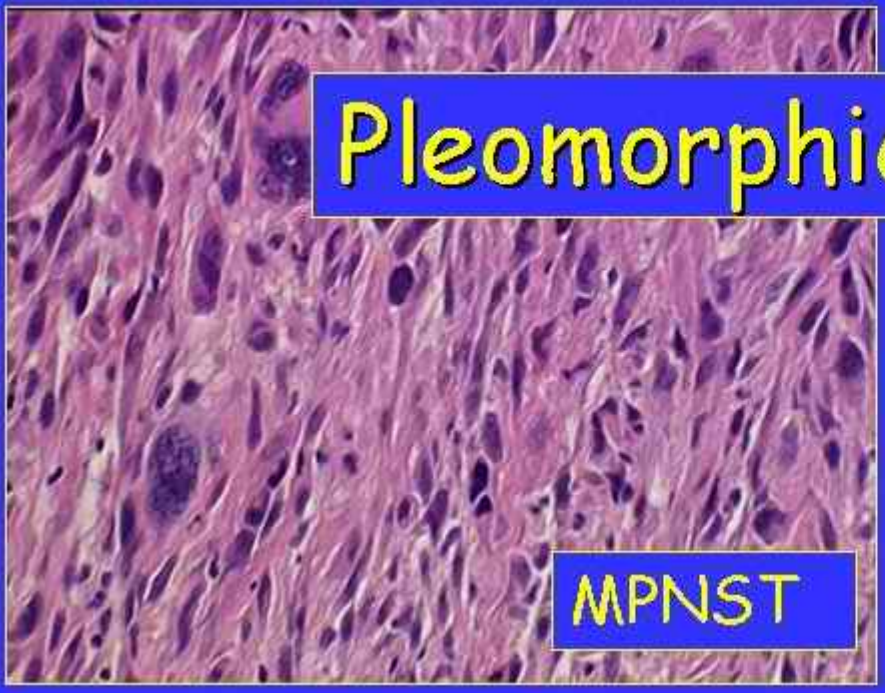
- MFH = morphologic pattern
  - NHL
  - Metastatic Melanoma
  - Sarcomatoid Carcinoma

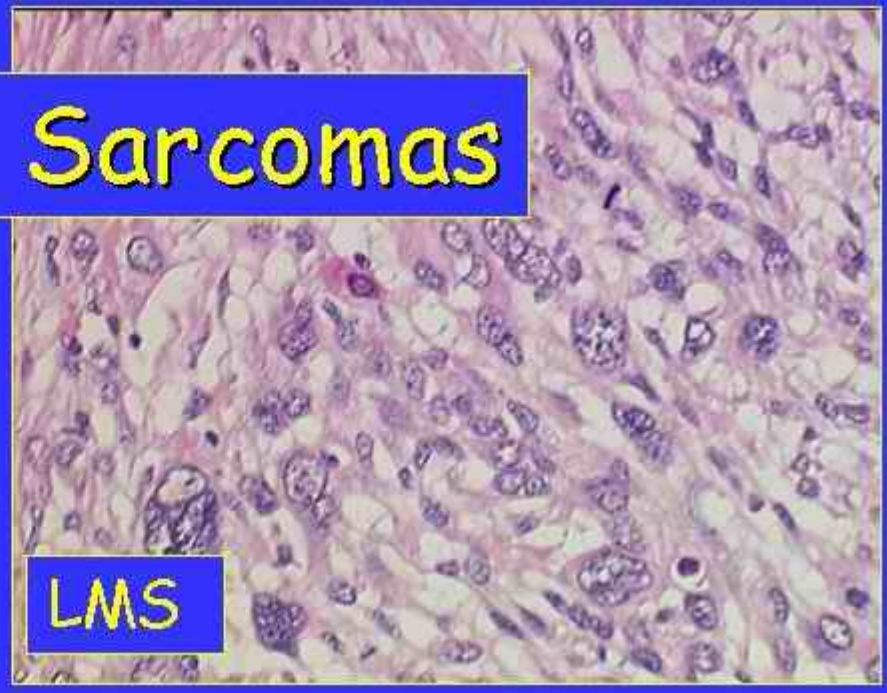

ALCL
ALK1
BerH2

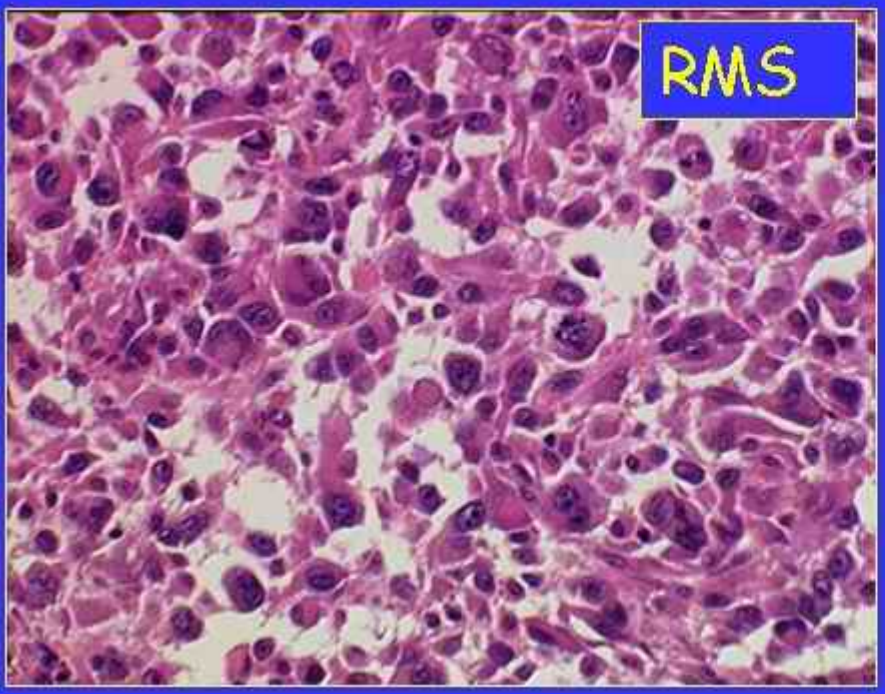


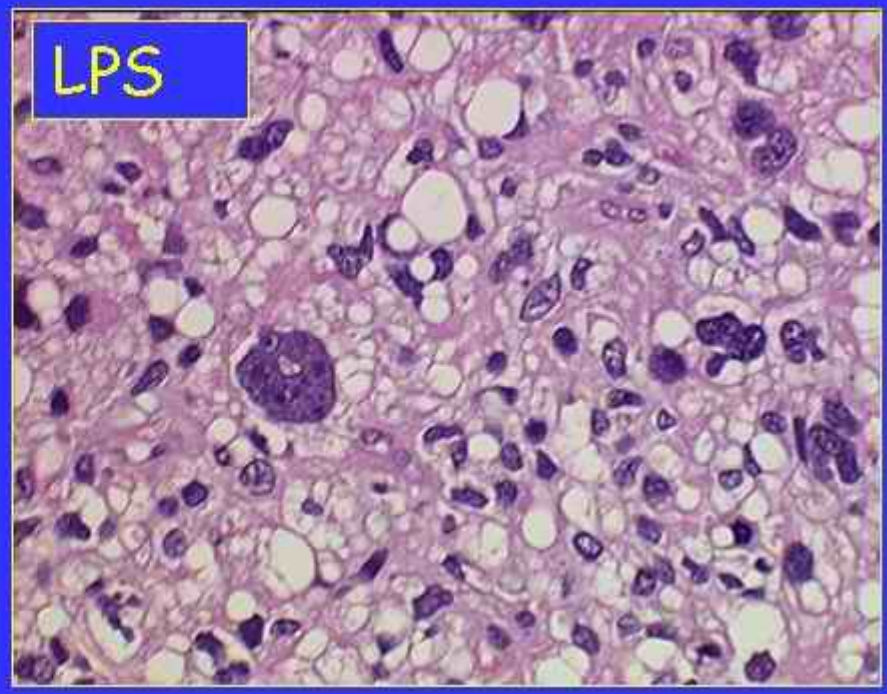

Cytokeratin

Pleomorphic Sarcomas









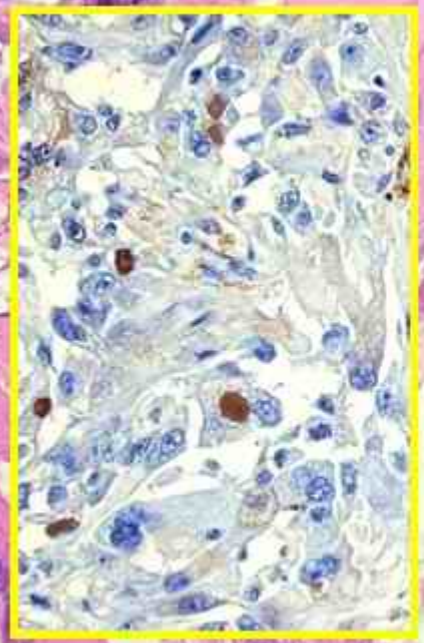
Pleomorphic Sarcomas: Is there a need for subtyping?

- Identification of non-mesenchymal neoplasms
- Myogenic differentiation related to worse prognosis
- Myxoid areas related to better prognosis

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



MFH story

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

MFH

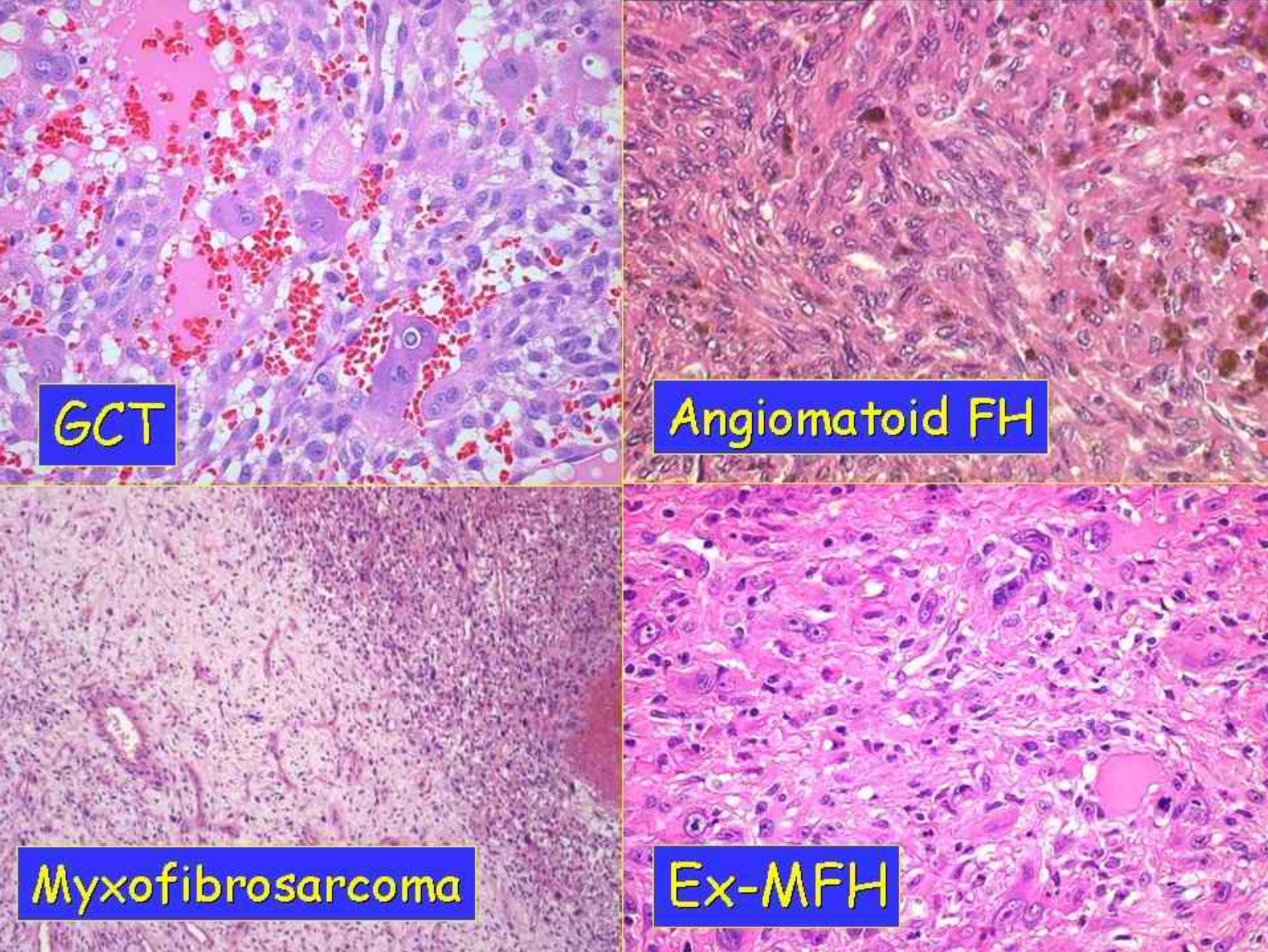
- Arthur Purdy Stout
  - Fibroblastic tumor
- Margareth Murray
  - Cell culture studies

Dr.Murray

Dr. Stout

MFH: What's Left?

- Myxoid MFH = myxofibrosarcoma
- Giant cell MFH = giant cell tumor of soft tissues, sarcomas with GC
- Angiomatoid (m)FH = moved to lesions of uncertain "histogenesis"
- Inflammatory MFH = mostly example of dedifferentiated LPS


GCT
Angiomatoid FH
Myxofibrosarcoma
Ex-MFH

MALIGNANT GIANT CELL TUMOR OF SOFT PARTS

An Analysis of 32 Cases

J. G. Guccion, MD, and F. M. Enzinger, MD

Cancer 1972; 29: 1518-1529

Giant Cell MFH

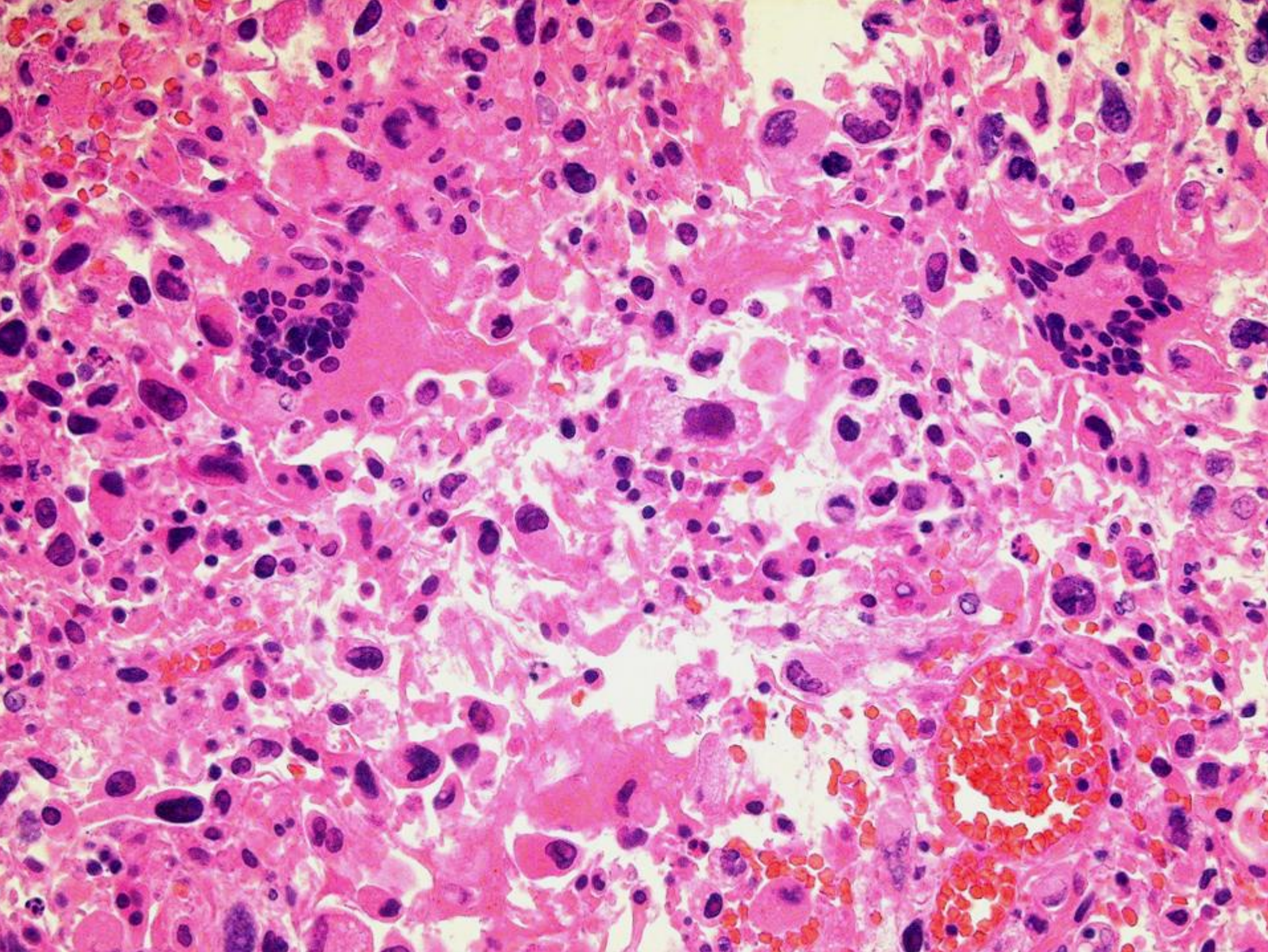
- Histiocytic tumors
- GCT of soft tissues
  - Indolent clinical behavior
- Extraskeletal Osteosarcoma
  - Neoplastic osteoid
- Other high grade pleomorphic sarcomas with OC-like giant cells

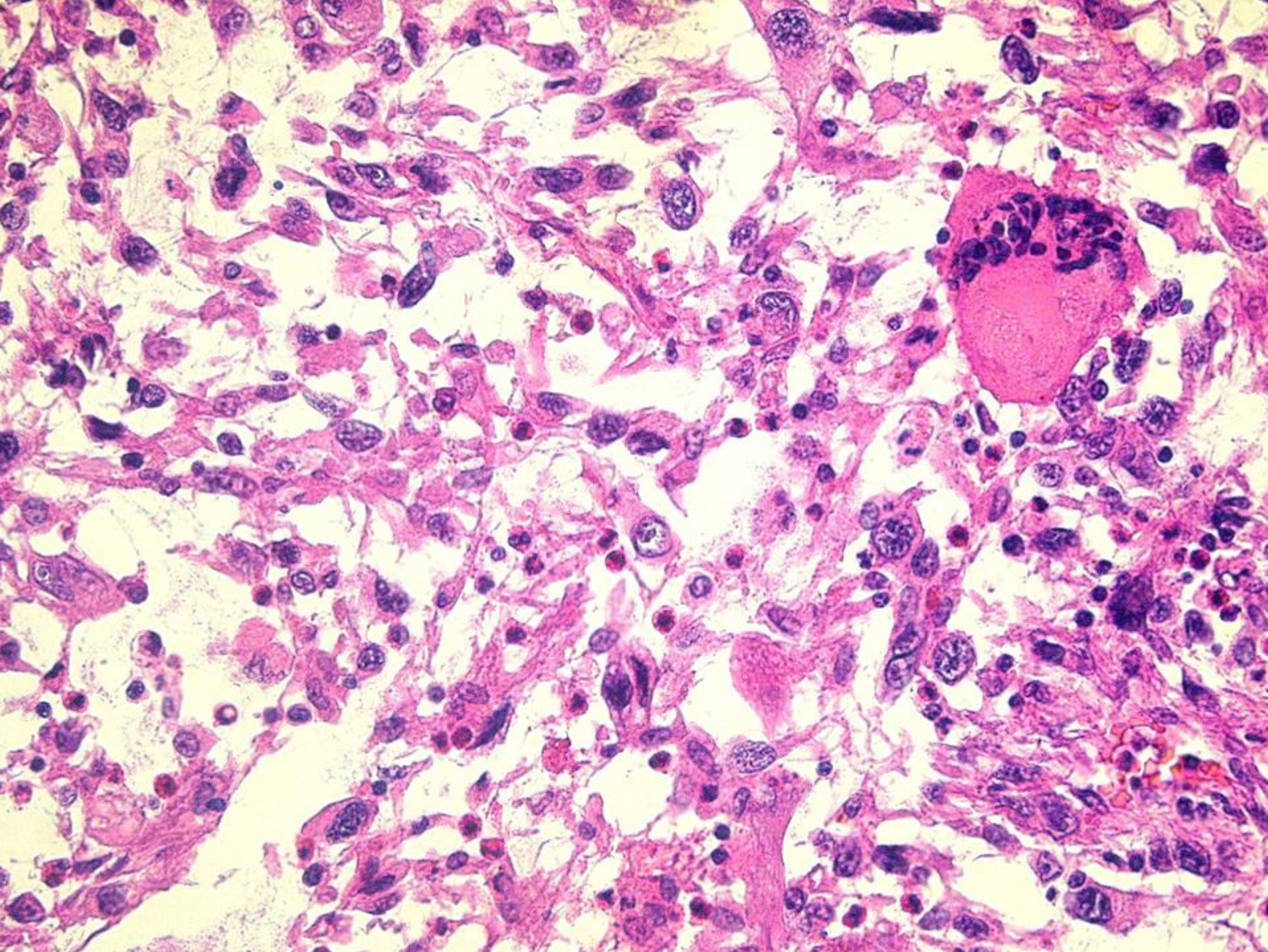
The American Journal of Surgical Pathology *18(3): 258–265, 1994*

Leiomyosarcoma with Prominent Osteoclast-like Giant Cells

Analysis of Eight Cases Closely Mimicking the So-called Giant Cell Variant of Malignant Fibrous Histiocytoma

Thomas Mentzel, M.D., Eduardo Calonje, M.D., and Christopher D.M. Fletcher, M.D., M.R.C.Path.





Soft Tissue Giant Cell Tumor of Low Malignant Potential: A Proposal for the Reclassification of Malignant Giant Cell Tumor of Soft Parts

A.L. Folpe, M.D., Robert J. Morris, M.D., Sharon W. Weiss, M.D.

Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia

The American Journal of Surgical Pathology *24(2): 248–256, 2000*

Primary Giant Cell Tumor of Soft Tissues

A Study of 22 Cases

Andre M. Oliveira, M.D., Angelo P. Dei Tos, M.D.,
Christopher D. M. Fletcher, M.D., and Antonio G. Nascimento, M.D.

Giant Cell Tumors of Soft Tissue

A Clinicopathologic Study of 18 Benign and Malignant Tumors

John X. O'Connell, M.B., F.R.C.P.C., Bret M. Wehrli, M.D.,
Gunnlaugur P. Nielsen, M.D., and Andrew E. Rosenberg, M.D.

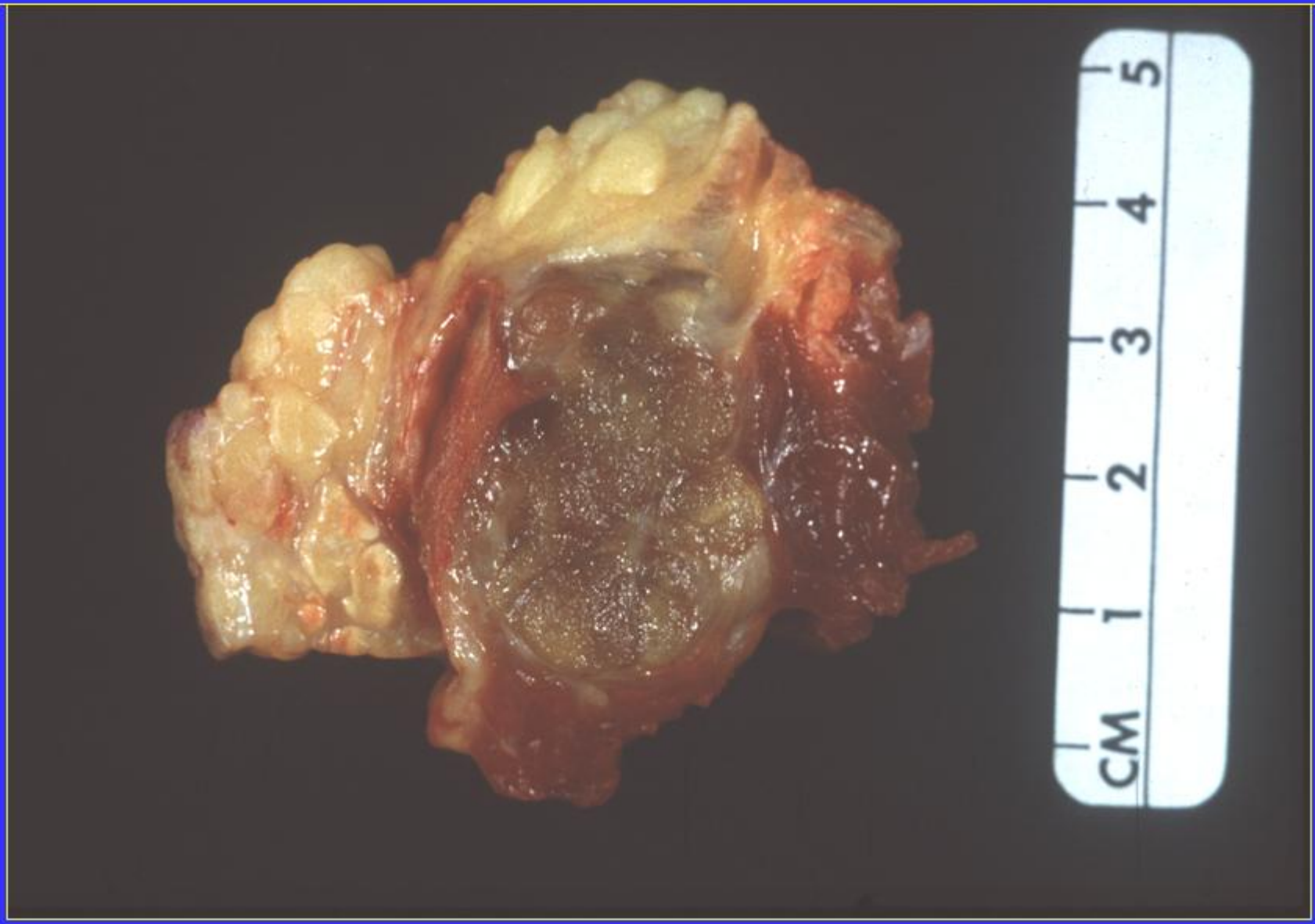
Giant Cell Tumor of Soft Tissue

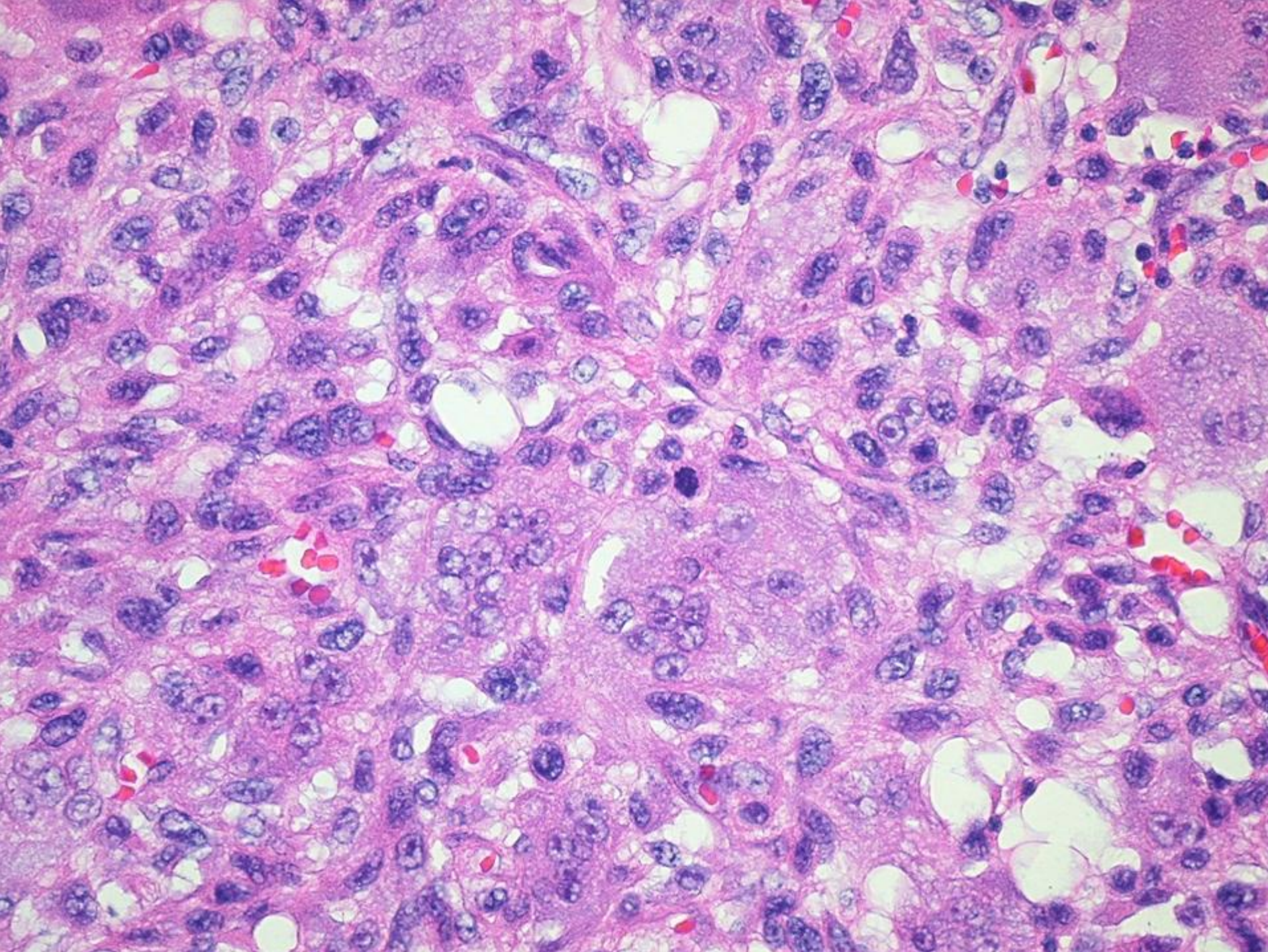
- Fifth decade
- Age range very broad (5-89 year)
- M = F
- Extremities (70%)/trunk/head & neck
- Subcutaneous soft tissue (70%) / deep seated (30%)

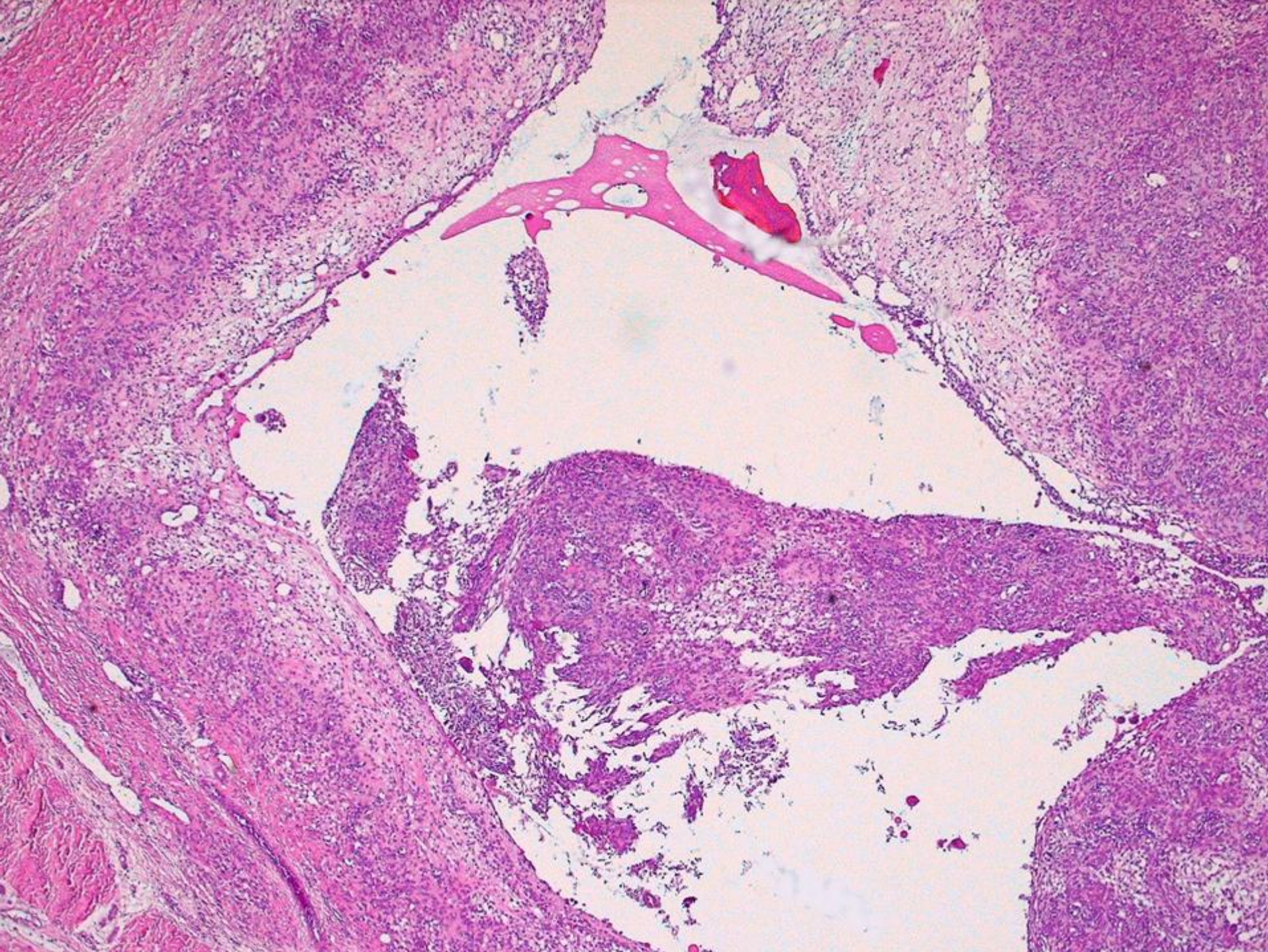
Giant Cell Tumor of Soft Tissue

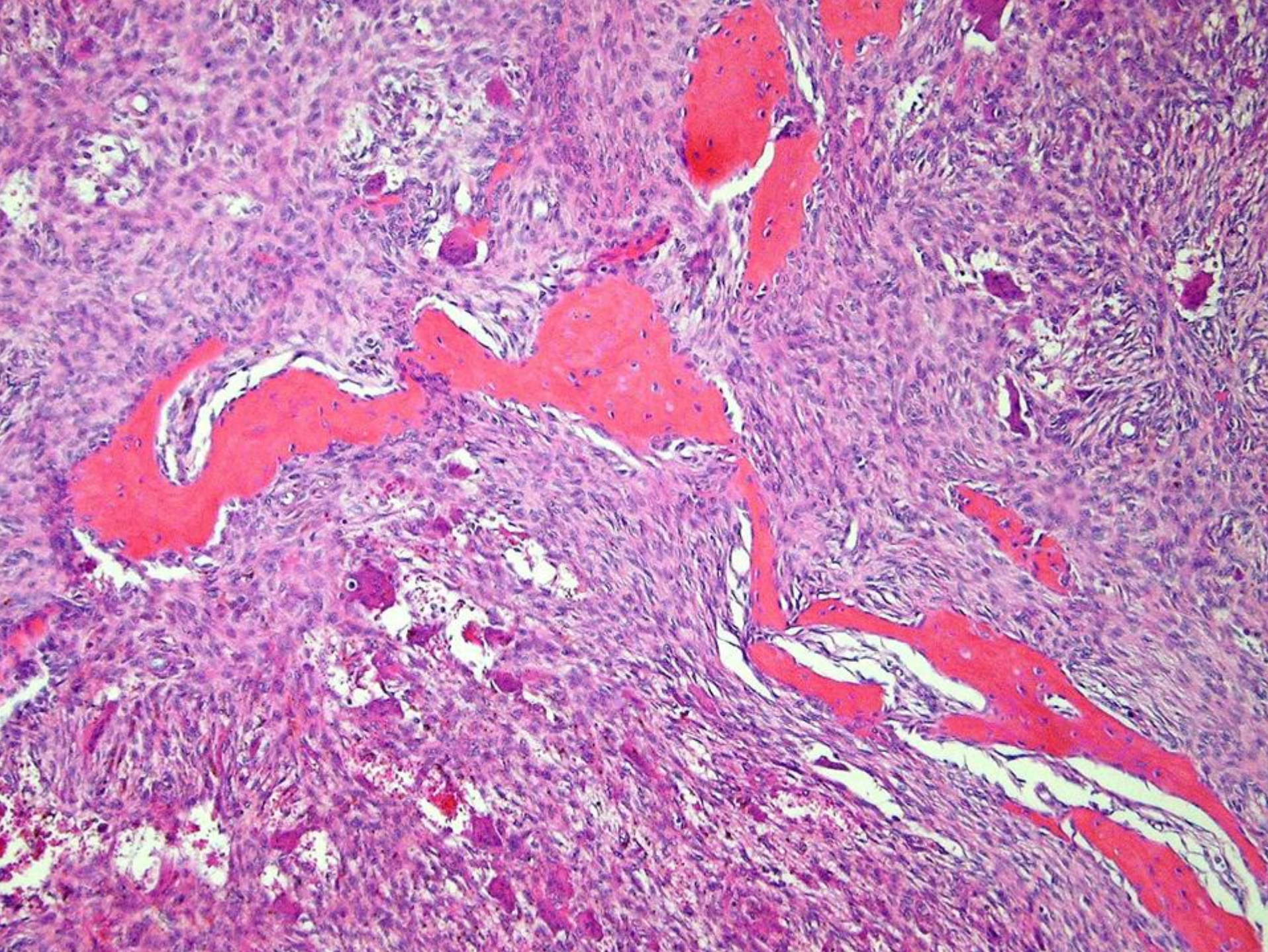
- Multinodular growth pattern
- Mononuclear round to oval cells intermingled with osteoclast-like multinucleated giant cells
- Brisk mitotic activity
- ABC-like change

Giant Cell Tumor of soft Tissue



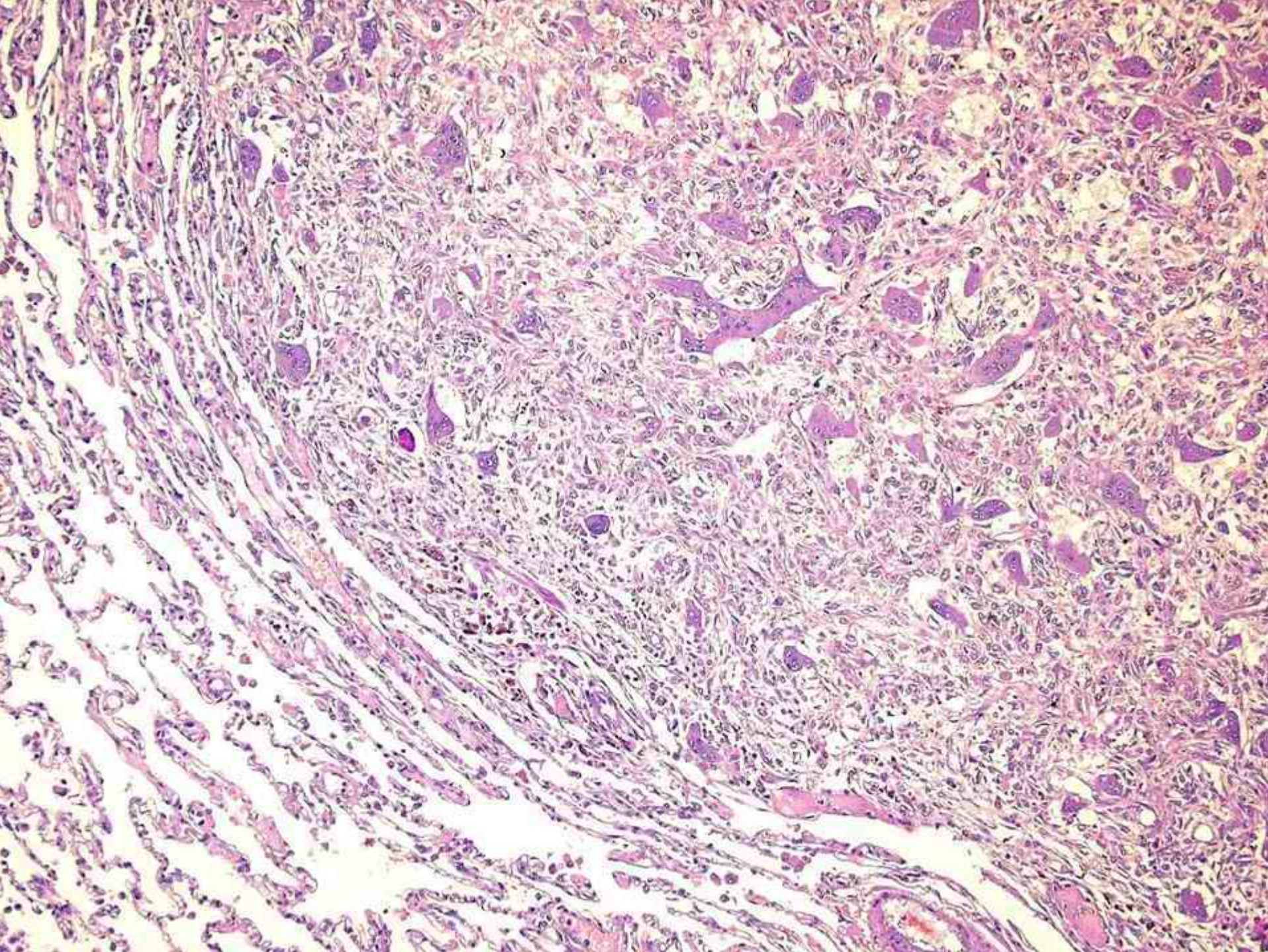


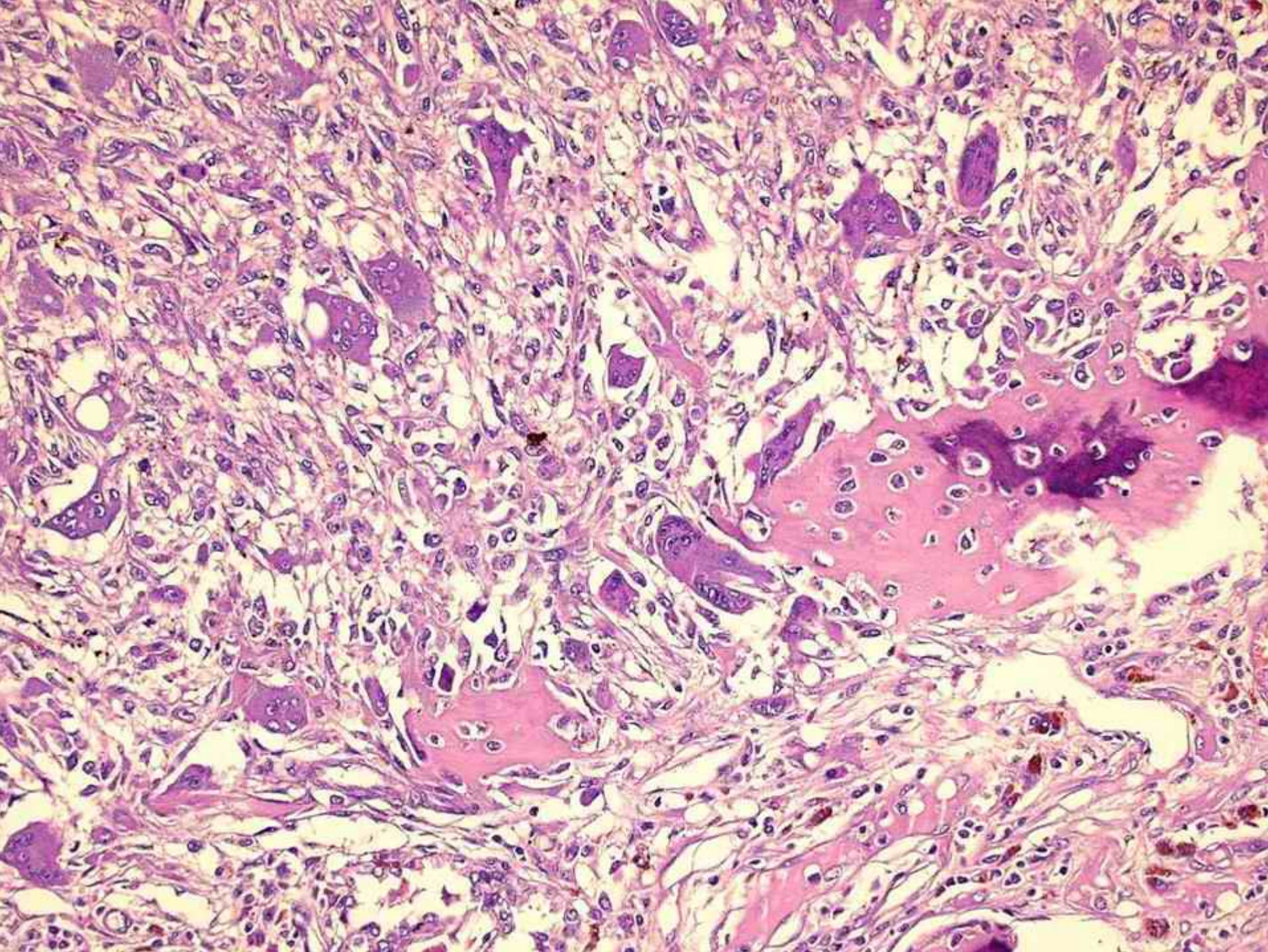




GCT of Soft Tissue

- Indolent clinical behavior
- Metastatic potential (?)
  - One patient (no histology)
- Similarity with GCT of bone





GIANT-CELL TUMOURS OF SOFT TISSUES

R. SALM AND H. A. SISSONS

Department of Histopathology, Royal Cornwall Hospital (Treliske), Truro, and Institute of Orthopaedics, Royal National Orthopaedic Hospital, London

J Pathol 1971; 107:27-39.

GCT of Soft Tissues

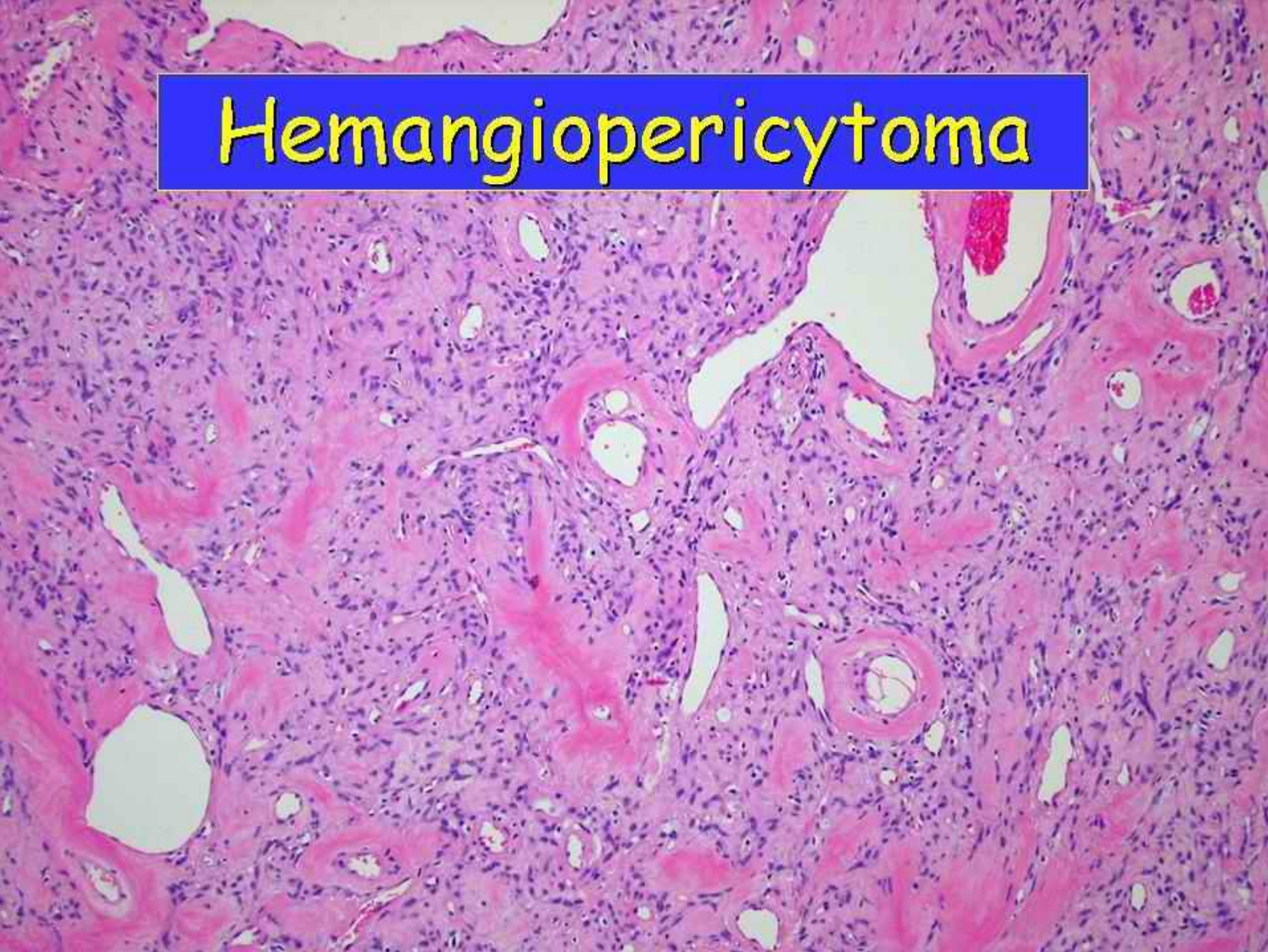
- Soft tissue tumors
  - Bone lesions extending in the soft tissues
- Morphologic overlap with GCT of bone
- Group 1 = GCT
- Group 2 = GCT with ABC-like features
- Group 3 = sarcomas with giant cells
- Group 4 = recurrent bone GCT

PLEOMORPHIC 'MFH'

KEY POINTS

- Synonymous with undifferentiated pleomorphic sarcoma
- Diagnosis of exclusion
- Accounts for no more than 5% of adult sarcomas
- Subclassification of pleomorphic sarcomas has clinical relevance
- MFH terminology will likely disappear

Hemangiopericytoma



Arthur Purdy Stout

Hemangiopericytoma

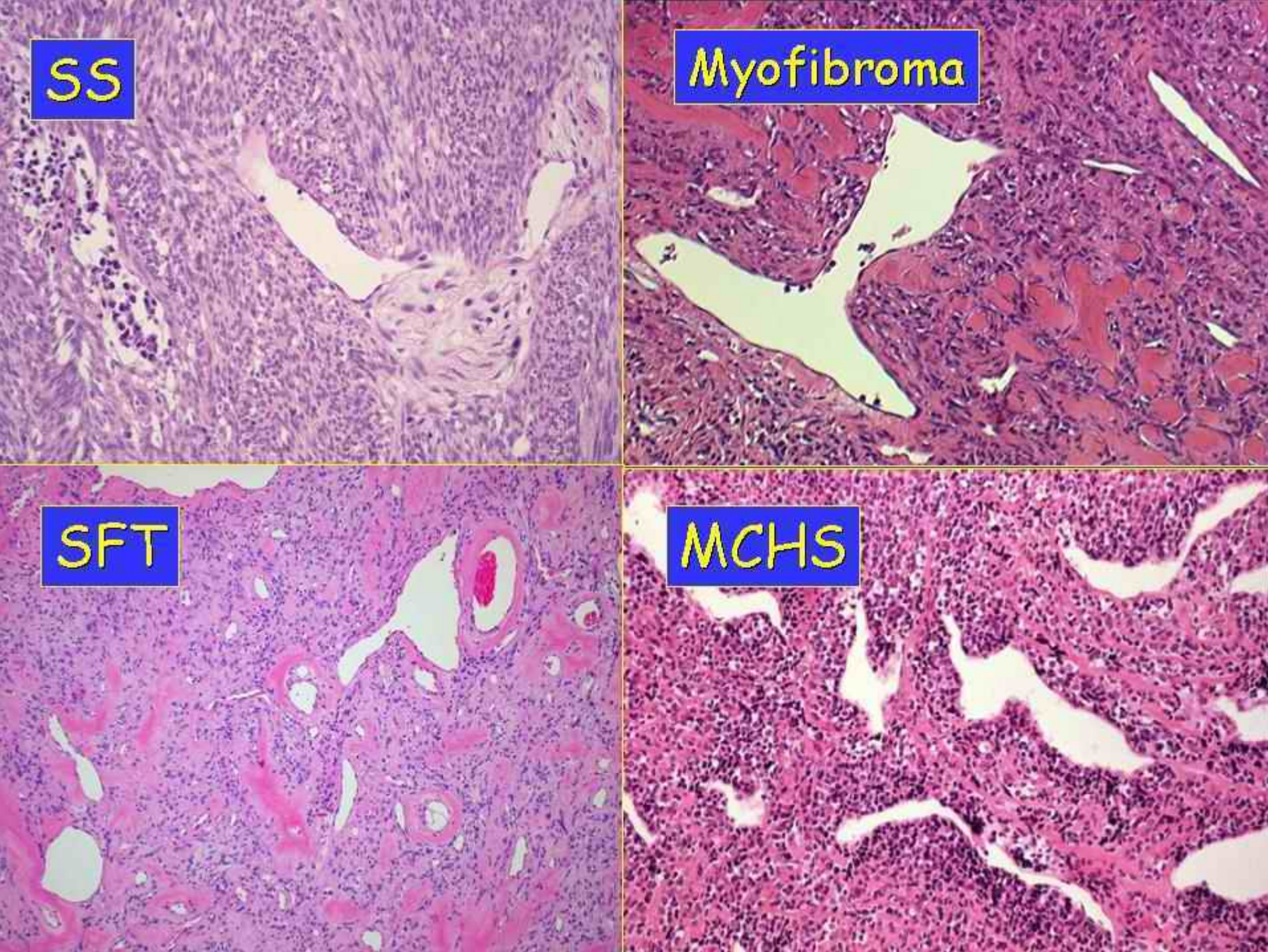
- An "entity" based on solid morphologic observations
- An "entity" inflated by addition of unrelated entities
- An "entity" erased by sequential drop-off of unrelated entities

Hemangiopericytoma

- 1942, Stout and Murray
- Concept of perivascular (pericytic) neoplasm
- Pericyte
  - Rouget (1873)
  - Zimmermann (1923)
- Subsequent integration of lesions with HPC-like vascular pattern

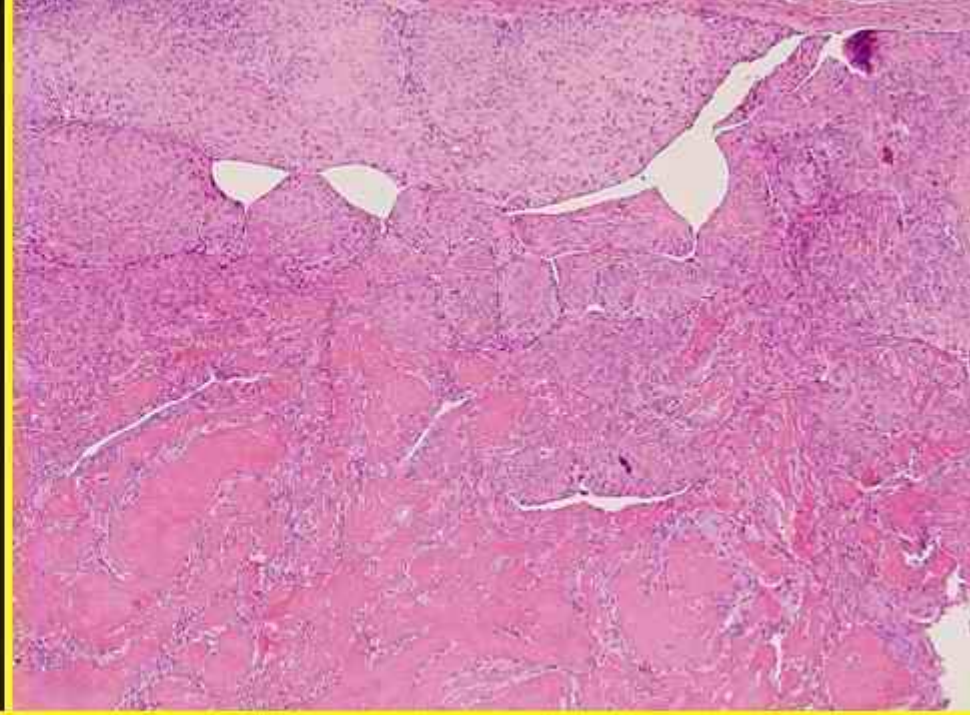
Hemangiopericytoma

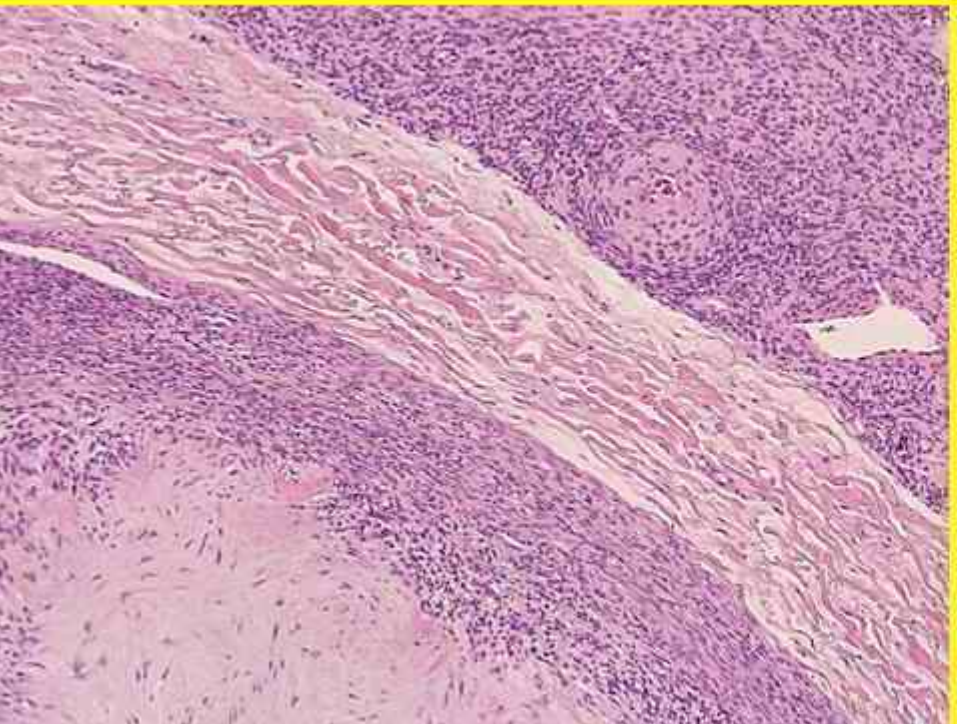
- Histologic Pattern
- Myofibroma/Myofibromatosis
- Solitary fibrous tumor and variants
- Synovial Sarcoma
- Mesenchymal Chondrosarcoma
- MPNST
- Myopericytoma


SS
Myofibroma
SFT
MCHS

Infantile Hemangiopericytoma

- Infantile HPC = infantile myofibroma/myofibromatosis

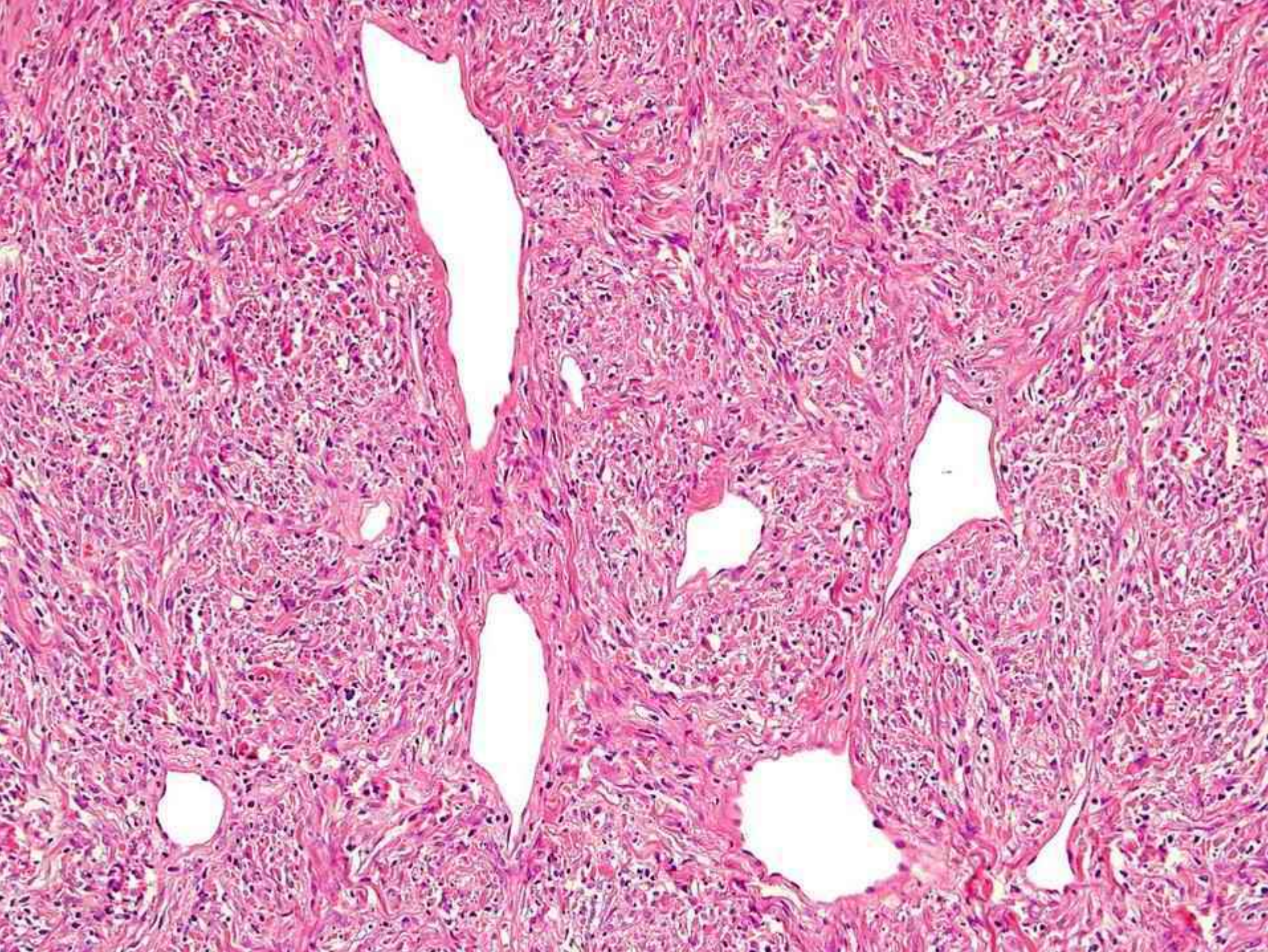





SMA

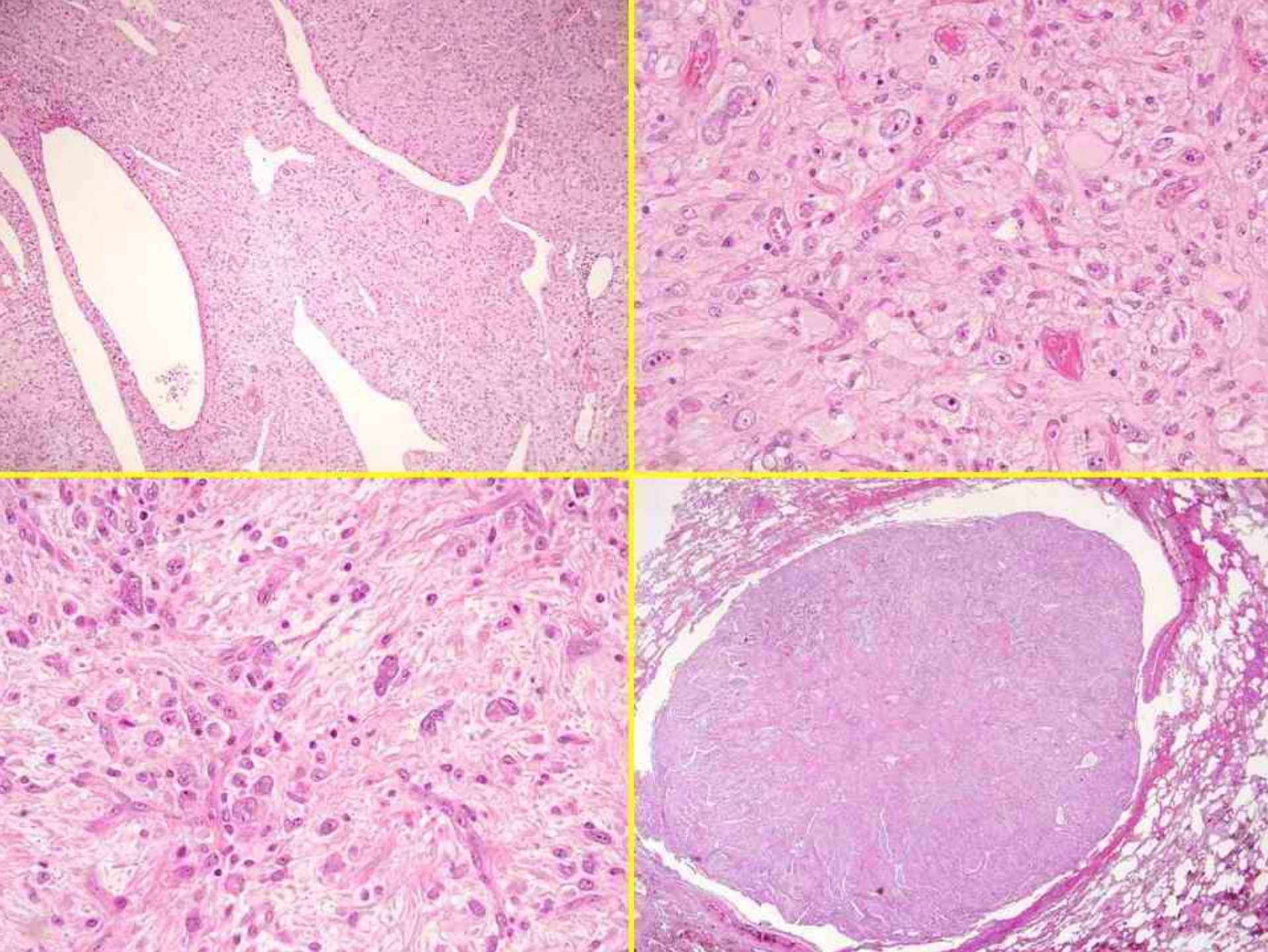
Solitary Fibrous Tumor

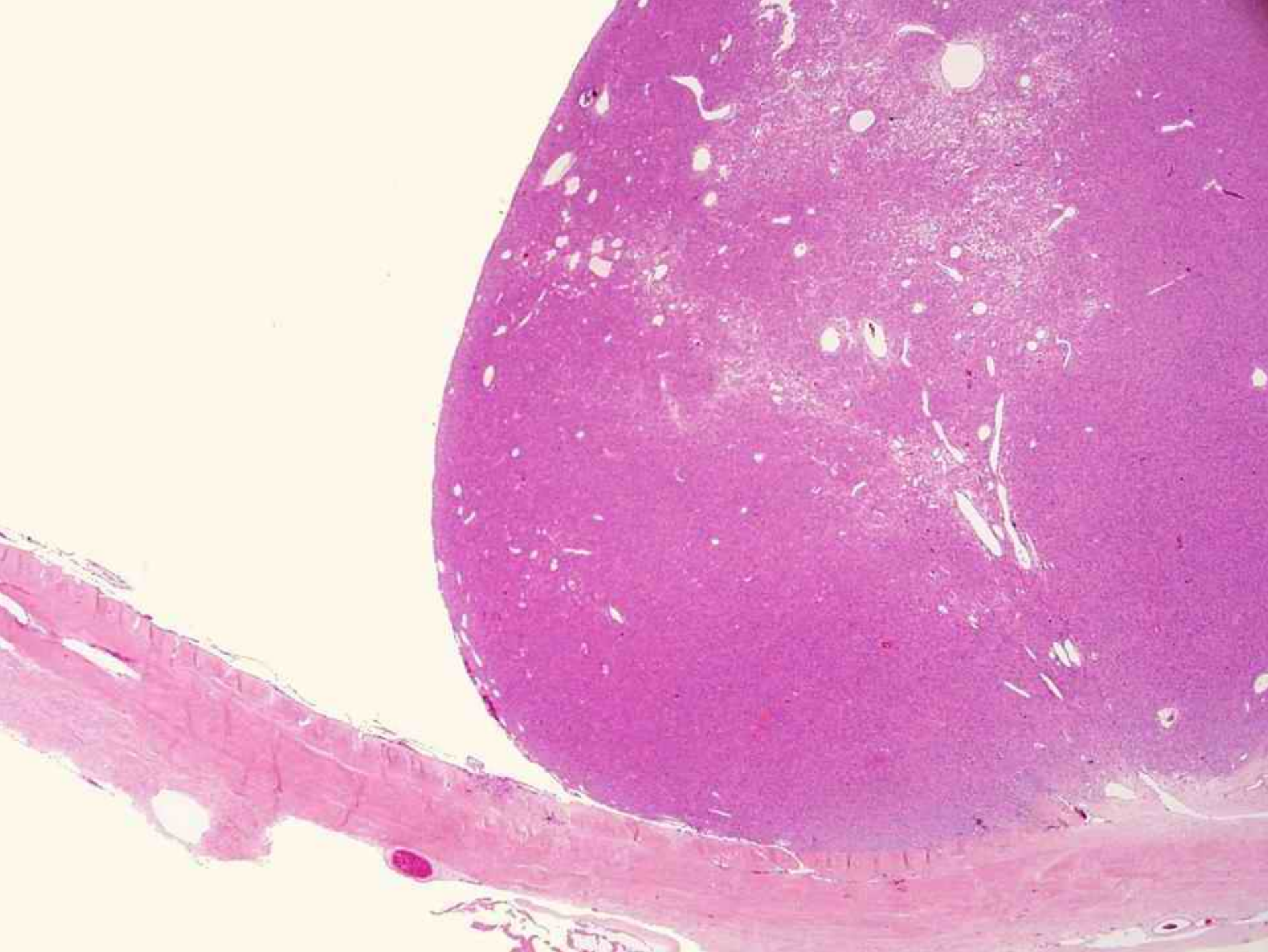
- Ubiquitous lesion
  - pleura, peritoneal surface, mediastinum, retroperitoneum, upper respiratory tract, orbit and urogenital tract
- Superficial soft tissue (40%)
- Deep soft tissue of extremities
- Broad age range (20-70) / M = F
- Systemic signs
  - hypoglycemia and digital hyppocratism
  - insulin-like growth factor

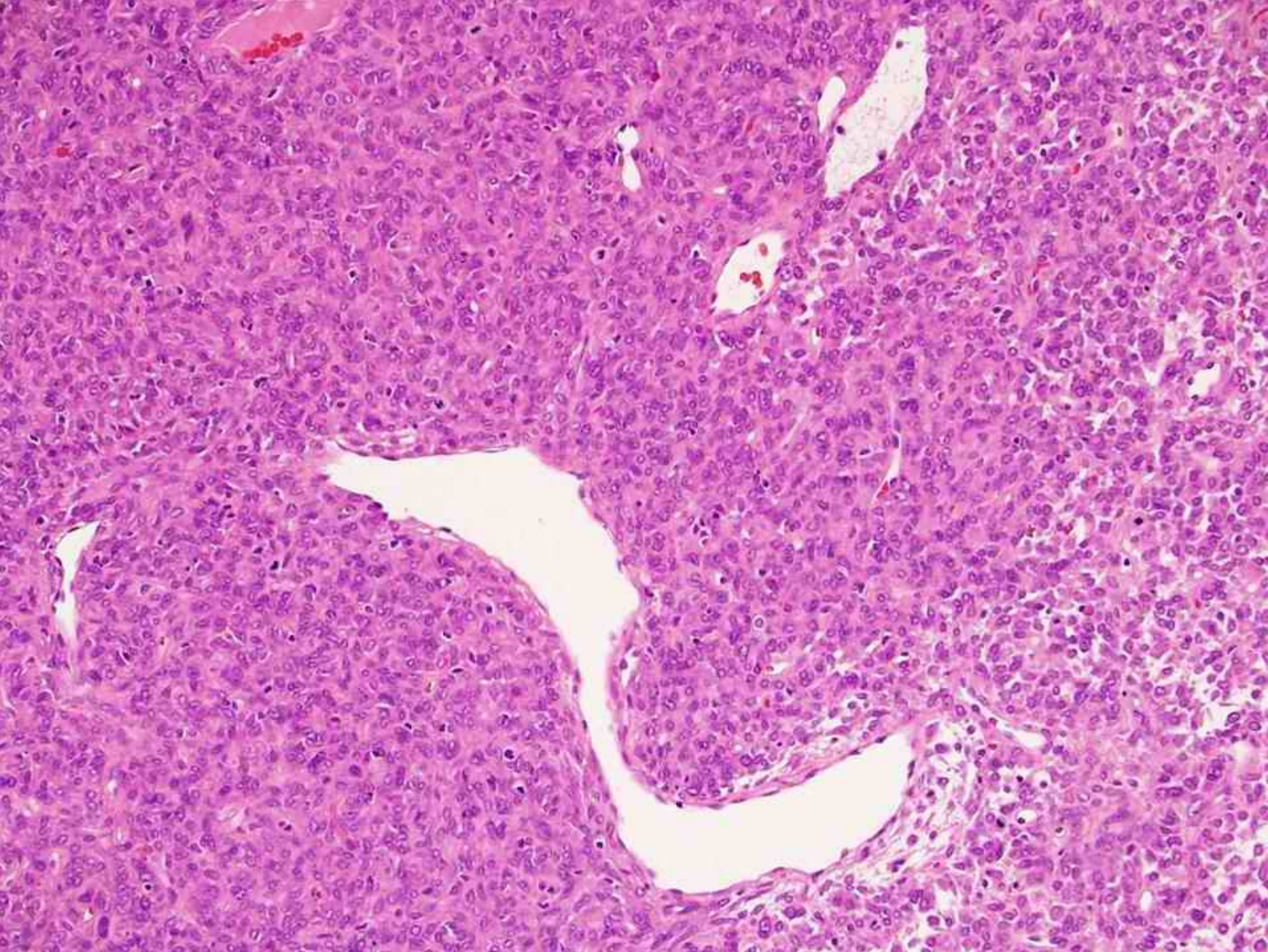


Solitary Fibrous Tumor

- Unpredictable behavior
- 10-15% behave aggressively
- No strict correlation between morphology and behavior
- Prognostic parameters
  - Cytologic atypia
  - tumor necrosis
  - > 4 mitoses/10HPF



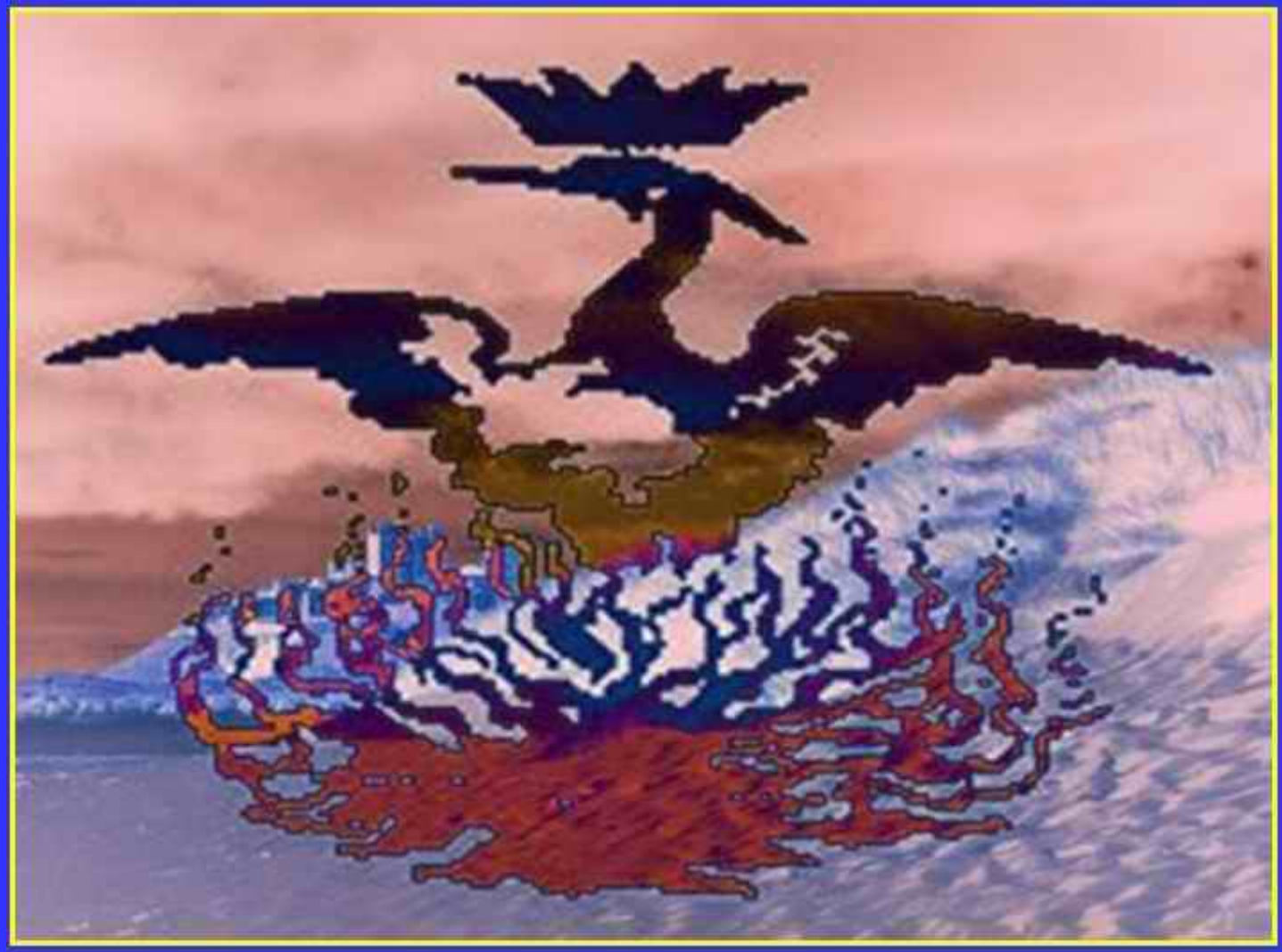


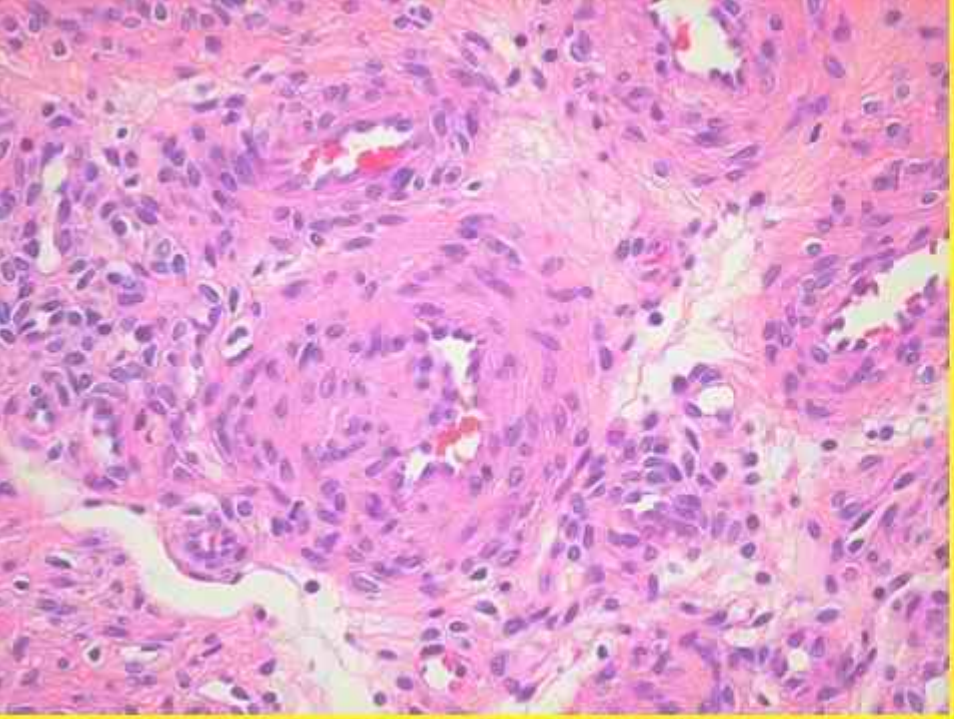


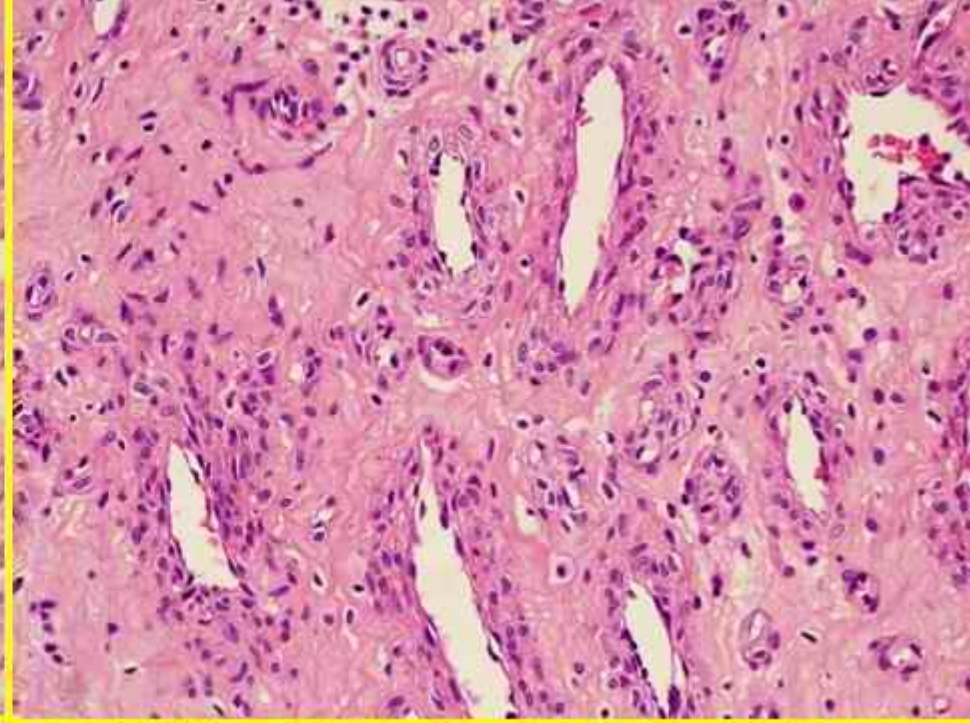
Meningeal HPC

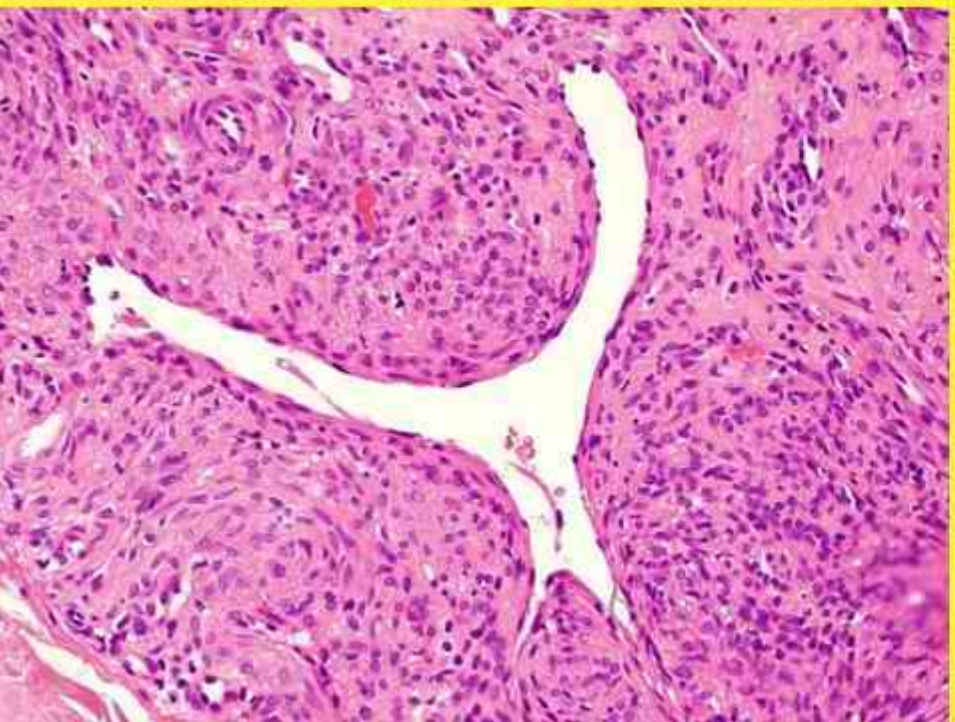
- Dural lesion
- "Histologically indistinguishable from HPC occurring in somatic soft tissue" (WHO)
- Formerly classified as angioblastic meningioma
- IHC: CD34+/EMA-
- Local rec > 90%
- Mets @ 15 yrs > 60%

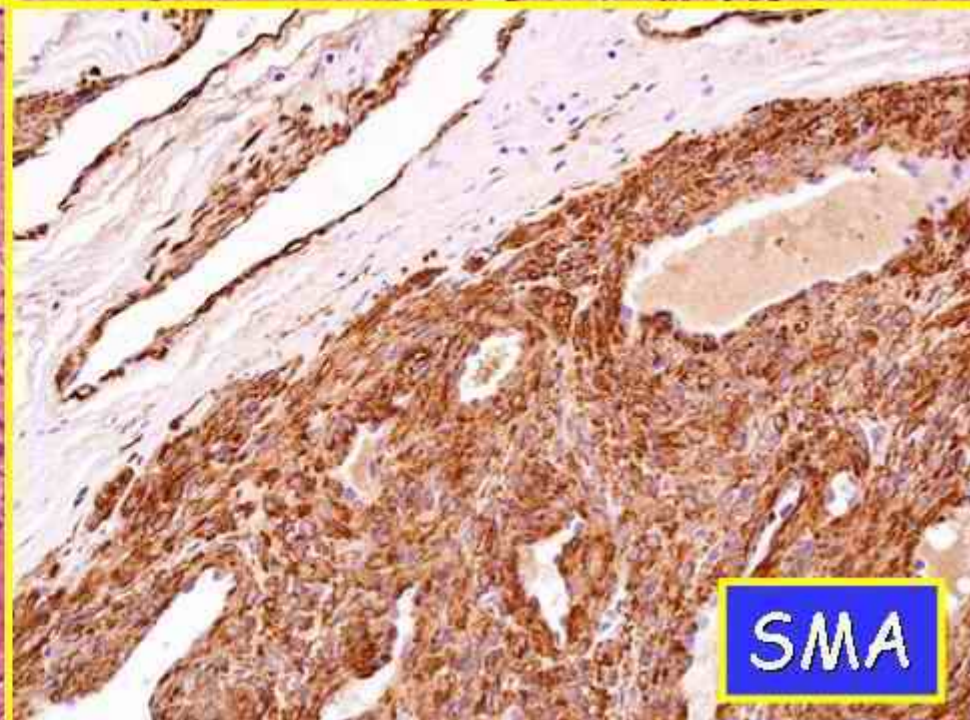
Is HPC estinct?










SMA

Myopericytoma

- Mid adulthood
- Subcutaneous
- Distal extremities > proximal extremities > neck
- Solitary nodules
- Most often painless

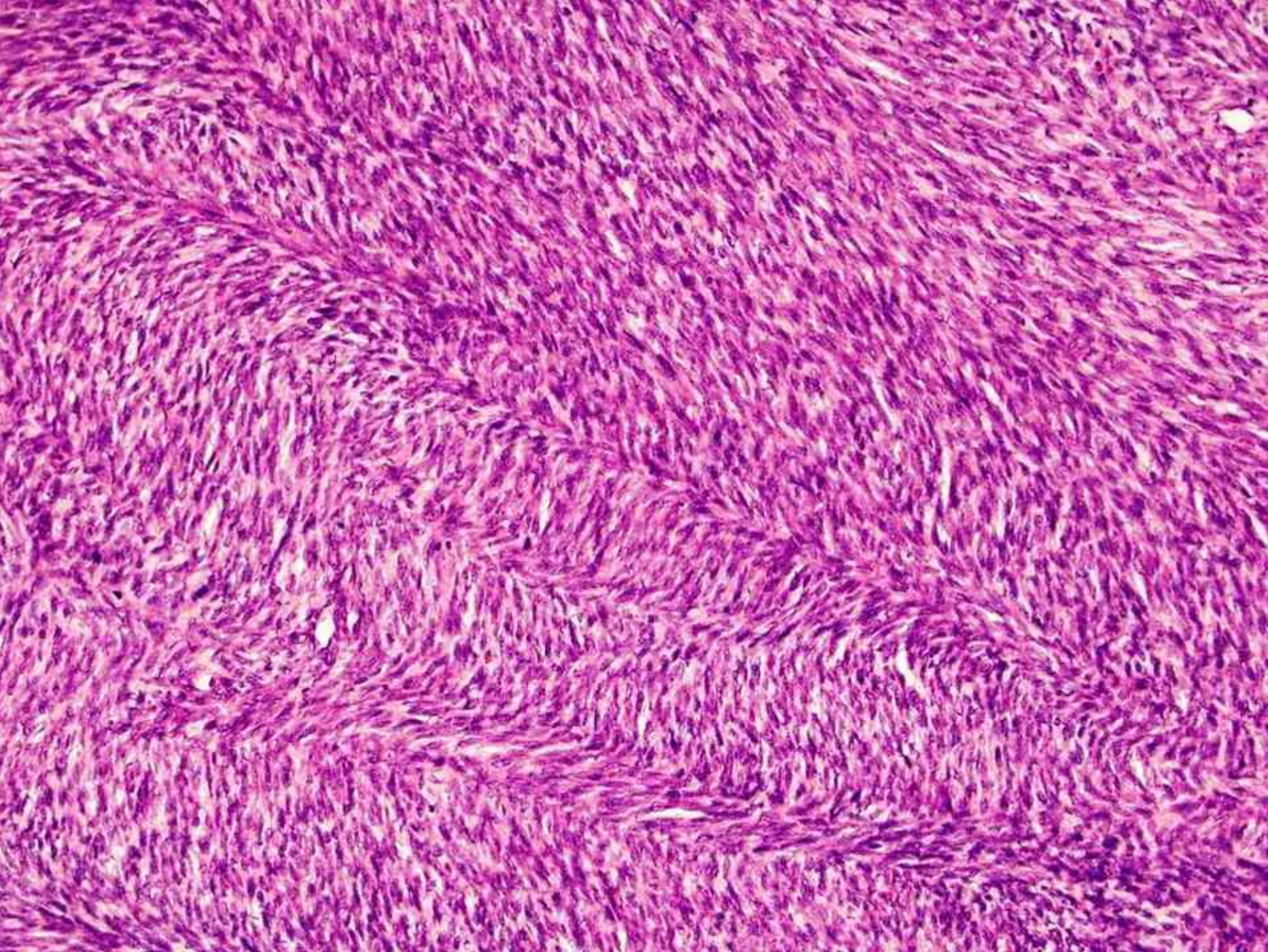
Hemangiopericytoma

=

Myopericytoma

SOLITARY FIBROUS TUMOUR / HAEMANGIOPERICYTOMA

- As currently used, haemangiopericytoma = meaningless term
- Solitary fibrous tumour (SFT) accounts for many of the lesions formerly described as HPC
- SFT is quite common in soft tissue
- Lipomatous HPC: variant of SFT
- Around 2-5% of SFT in soft tissue are malignant; not always predictable



Herringbone Pattern

Fibrosarcoma reshaped

- Most fibrosarcoma: FS-DFSP
- Myxofibrosarcoma
- Low grade fibromyxoid sarcoma
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Sclerosing epithelioid fibrosarcoma
- Inflammatory acral fibrosarcoma

Myxofibrosarcoma

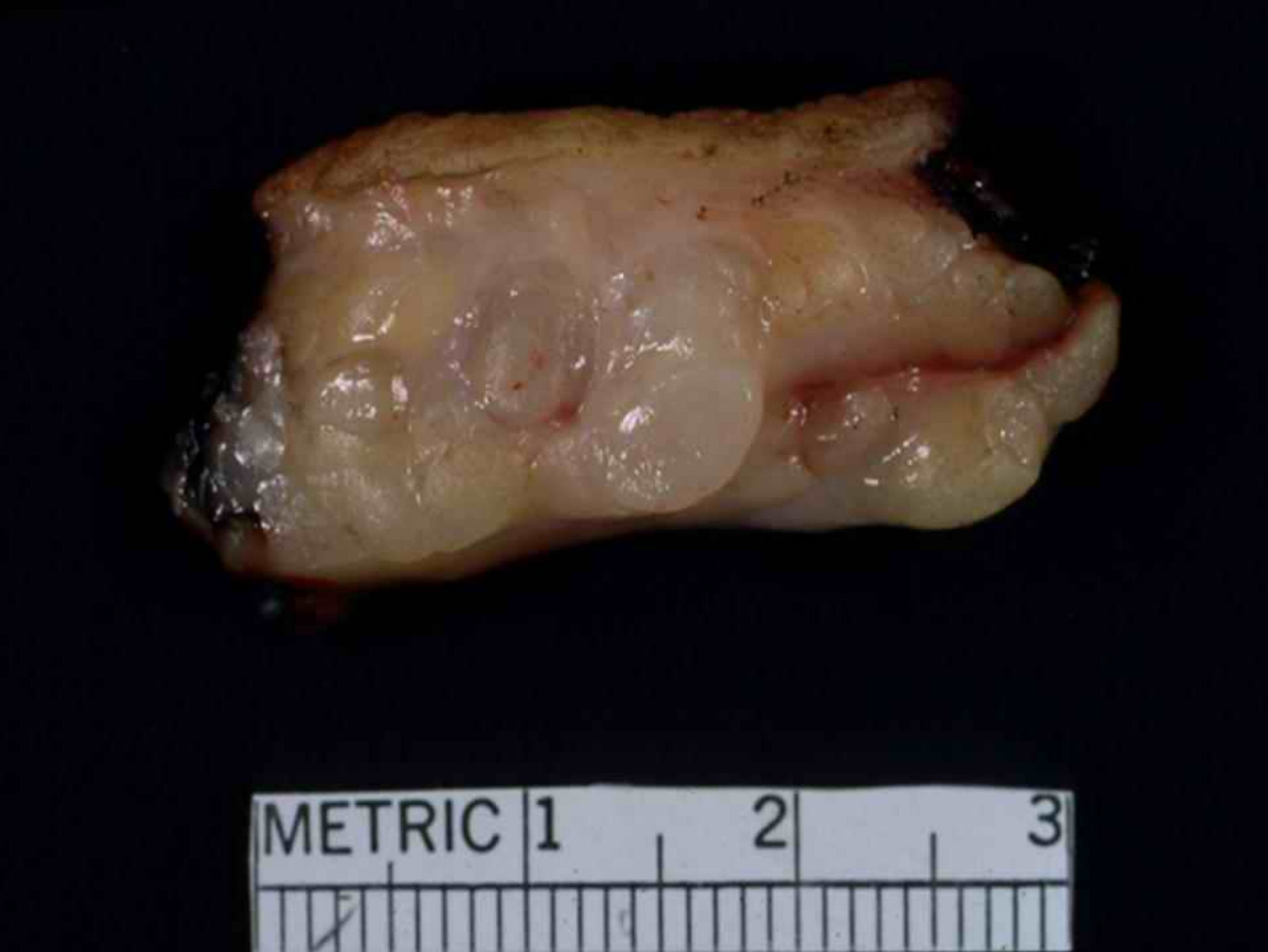
- Angervall, 1977
- Spectrum of myxoid lesions
- High grade = myxoid "MFH"
- Histologic grade related to clinical outcome

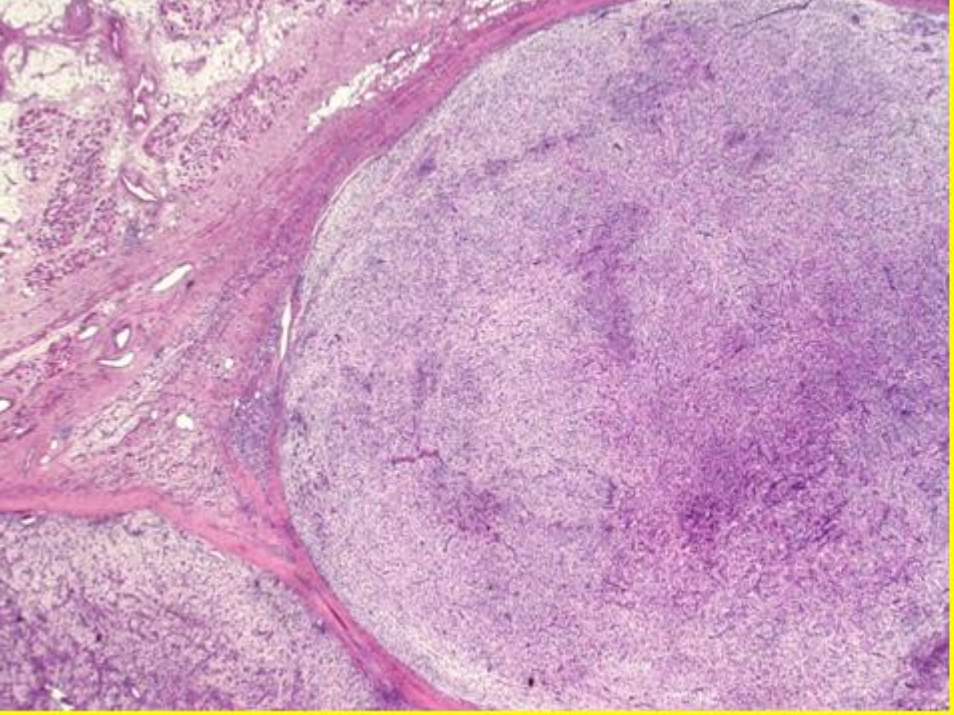
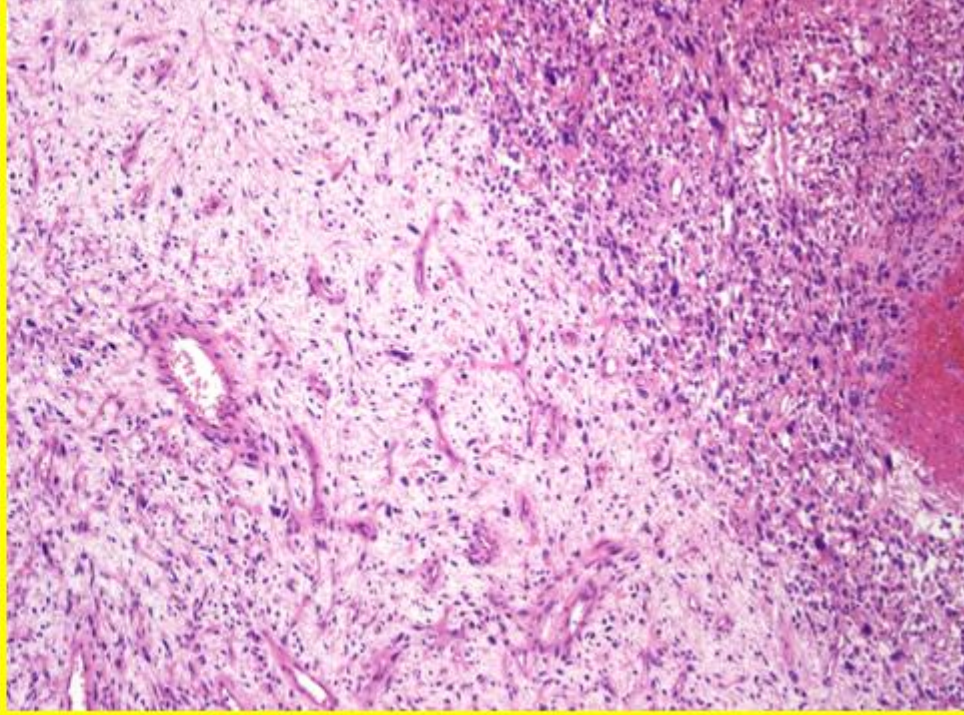
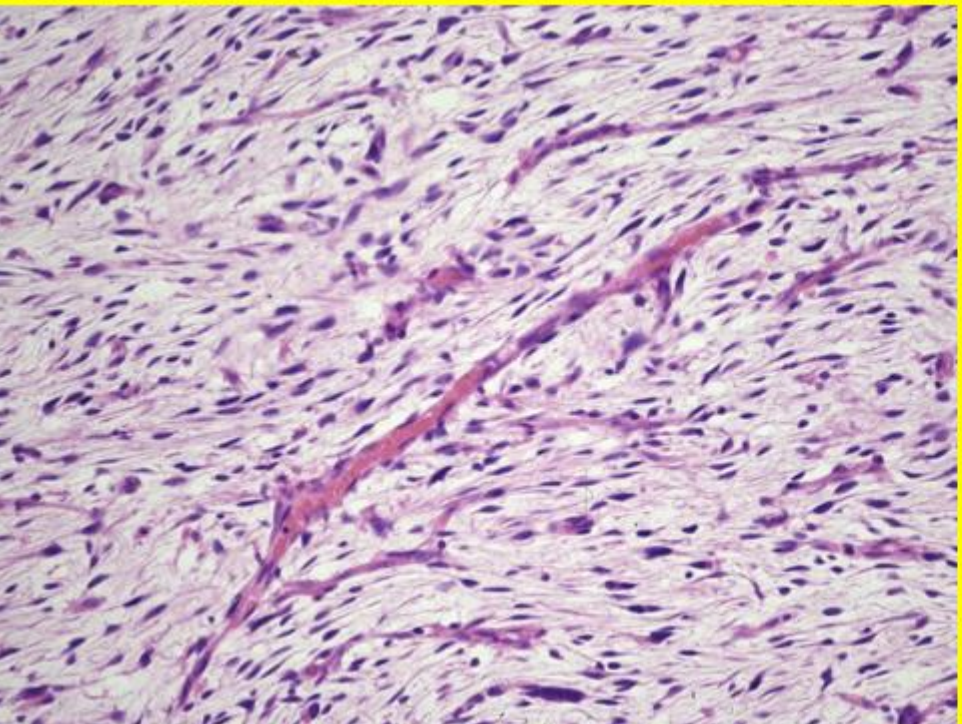
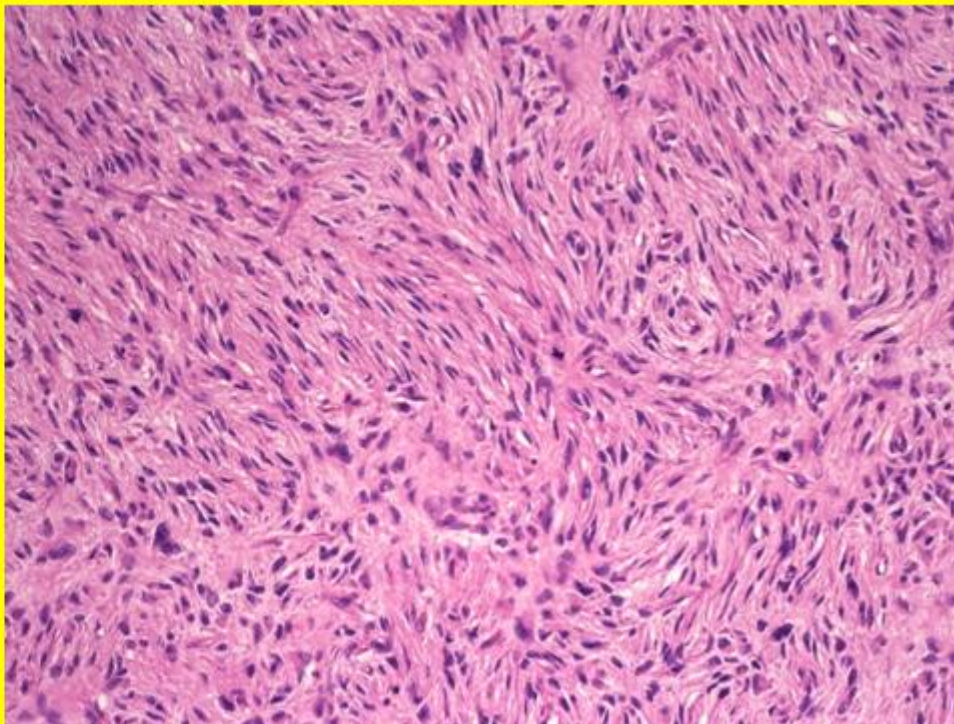
Myxofibrosarcoma

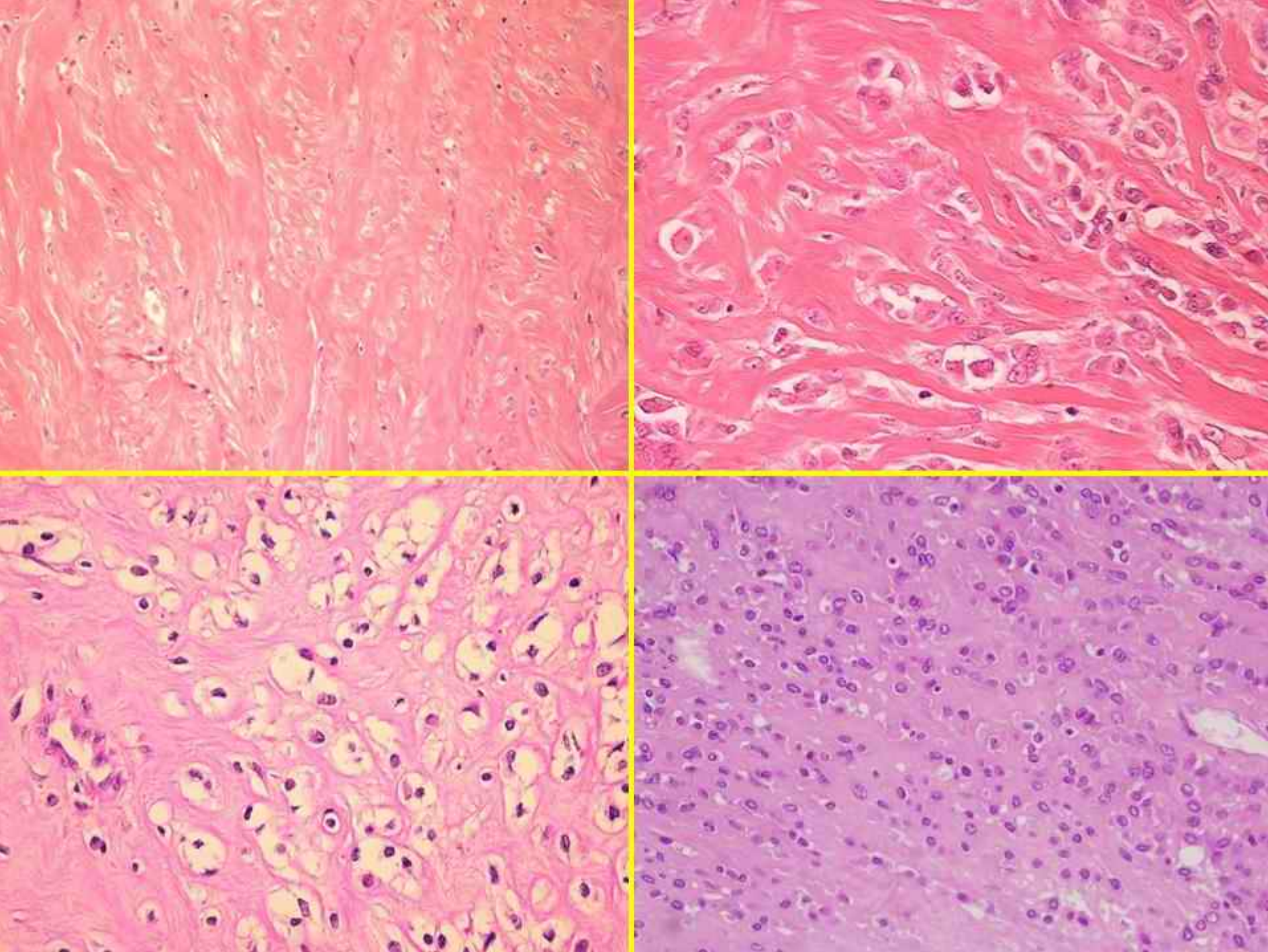
- Angervall, 1977
  - Myxoid MFH of Enzinger
- Spectrum of myxoid lesions
- High grade = myxoid "MFH"
- Histologic grade related to clinical outcome

Myxofibrosarcoma

- Elderly patients
- Lower limbs >upper limbs > limb girdles
- 2/3 subcutis, 1/3 deep seated
- IHC: vimentin, MSA and SMA (focal)
- Low grade no Mets
- High grade 30% metastatic rate
  - Lungs > bone > mets
- Overall SR @ 5 years = 60%


METRIC
1
2
3



Sclerosing epithelioid Fibrosarcoma

- Adults (4th decade)
- Lower extremities/limb girdles/trunk/head & neck
- Local recurrences: 50%
- Metastatic rate: 40%
  - Lungs, pleura and bone
- SR @ 10 years = 50%

The American Journal of Surgical Pathology 22(8): 911–924, 1998

Acral Myxoinflammatory Fibroblastic Sarcoma

A Low-Grade Tumor of the Hands and Feet

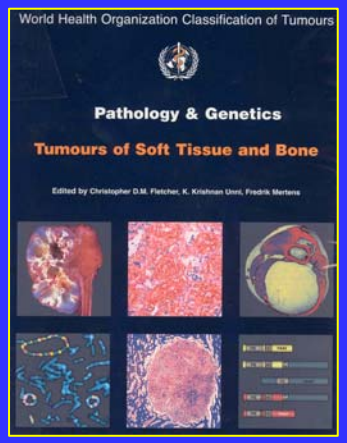
Jeanne M. Meis-Kindblom, M.D., and Lars-Gunnar Kindblom, M.D., Ph.D.

Inflammatory Myxohyaline Tumor of Distal Extremities with Virocyte or Reed-Sternberg–Like Cells: A Distinctive Lesion with Features Simulating Inflammatory Conditions, Hodgkin's Disease, and Various Sarcomas

Elizabeth A. Montgomery, M.D., Kenneth O. Devaney, M.D., Thomas J. Giordano, M.D., Sharon W. Weiss, M.D.

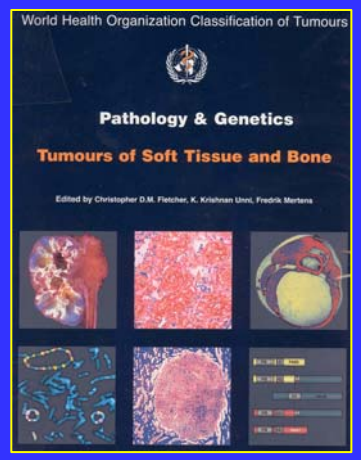
Departments of Pathology, Georgetown University, Washington, D.C. (EAM) and University of Michigan Medical Centers, Ann Arbor, Michigan (KOD, TJG, SWW)

Modern Pathology 1998; 11: 384-391

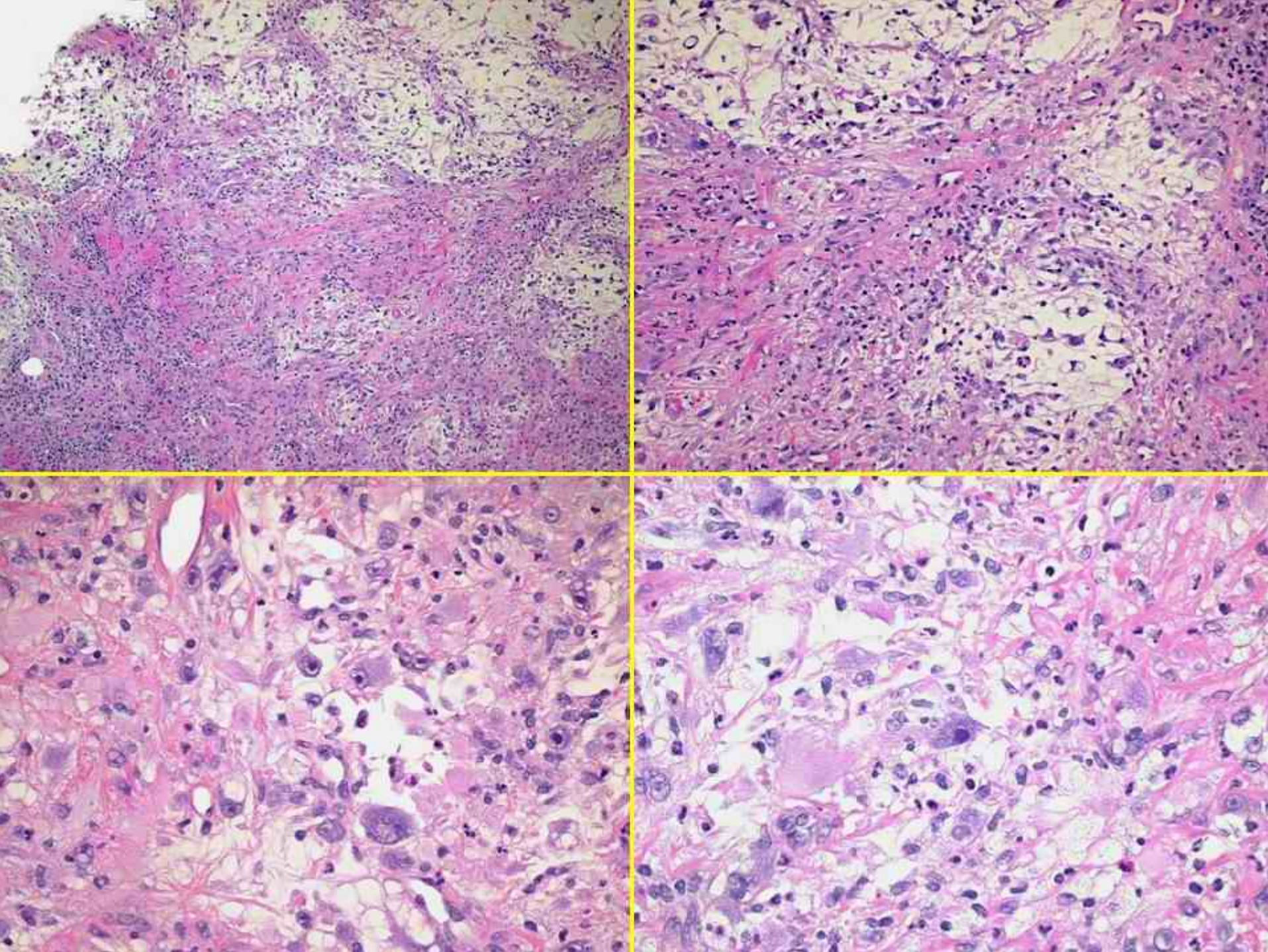


Myxoinflammatory fibroblastic sarcoma

WHO Definition



A unique low grade sarcoma with myxoid stroma, inflammatory infiltrate and virocyte-like cells that predominantly involves the hands and feet



Myxoinflammatory fibroblastic sarcoma

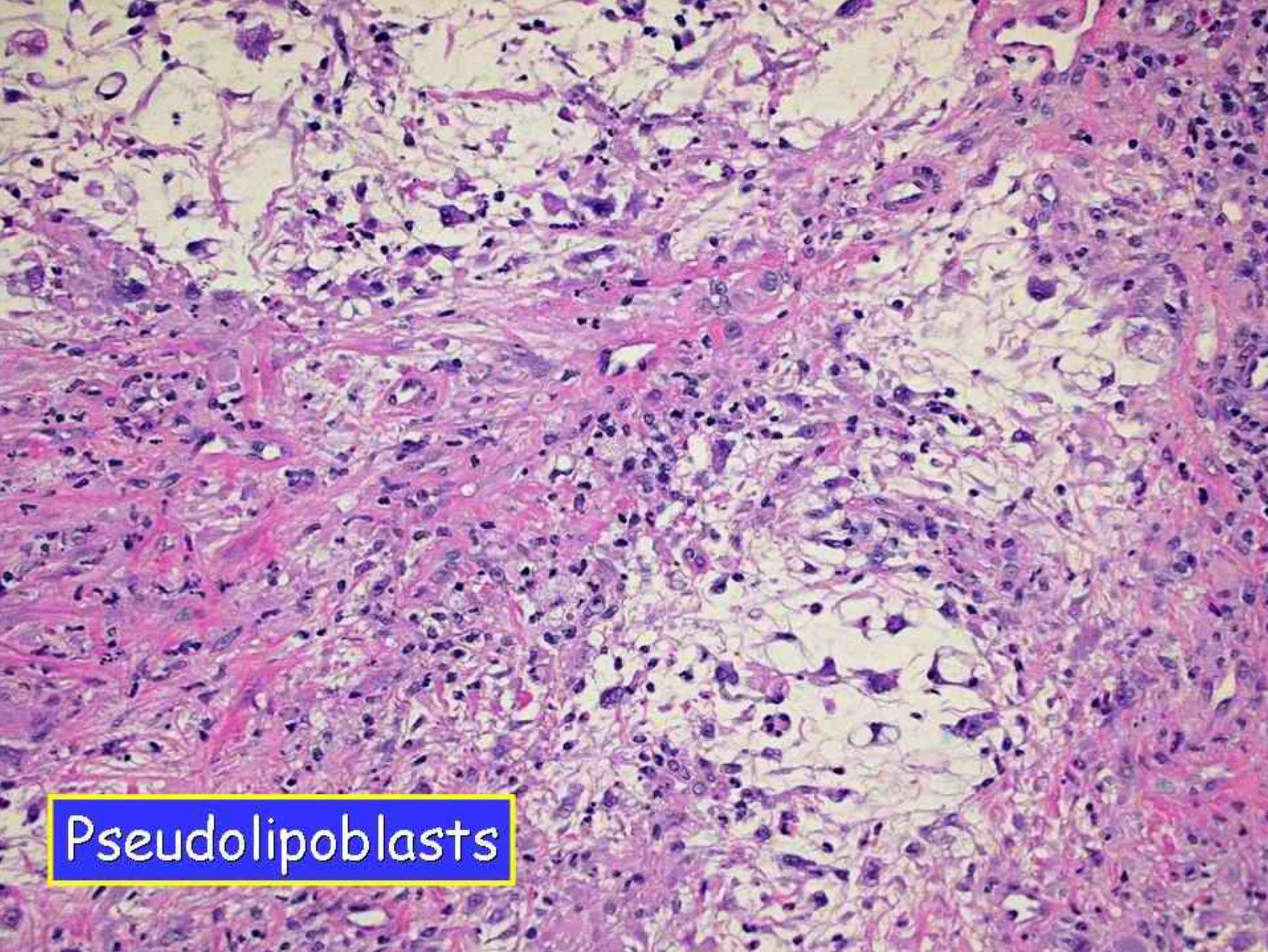
- Distal Extremities of adults (4th decade)
- 2/3 Hands and wrists
- 1/3 Ankle and feets
- Non acral sites
  - Forearm, arm, thigh

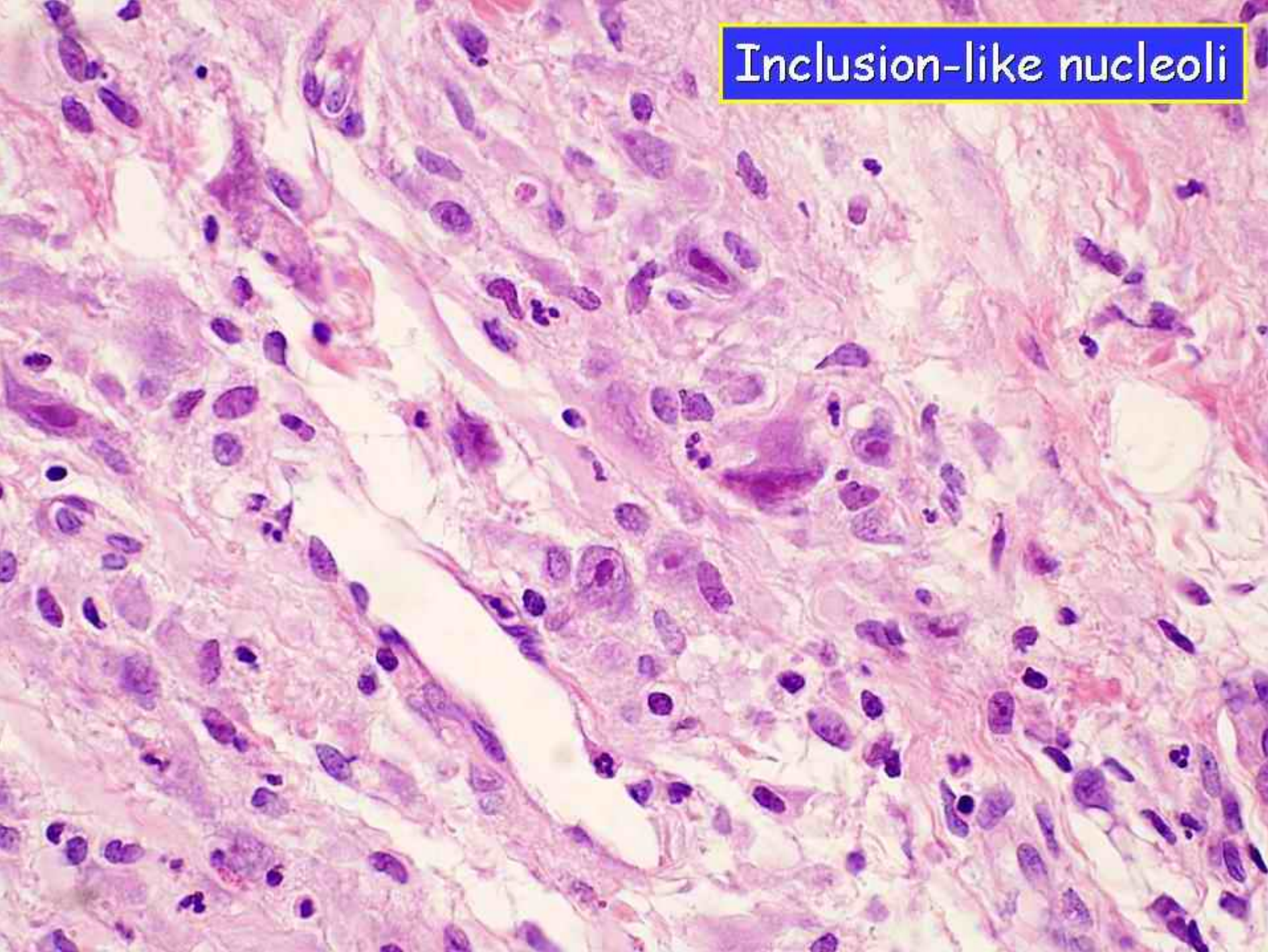
Myxoinflammatory fibroblastic sarcoma

- Poorly circumscribed
- Infiltrative growth pattern into joints, tendon and dermis
- Mixed inflammatory infiltrate
- Myxoid and collagenous stroma

Myxoinflammatory fibroblastic sarcoma

- Pseudolipoblasts
- Spindle cells
- Bizarre ganglion-like cells featuring inclusion-like nucleoli
- IHC: vimentin, CD34 and CD68


Pseudolipoblasts


Inclusion-like nucleoli

Myxoinflammatory fibroblastic sarcoma

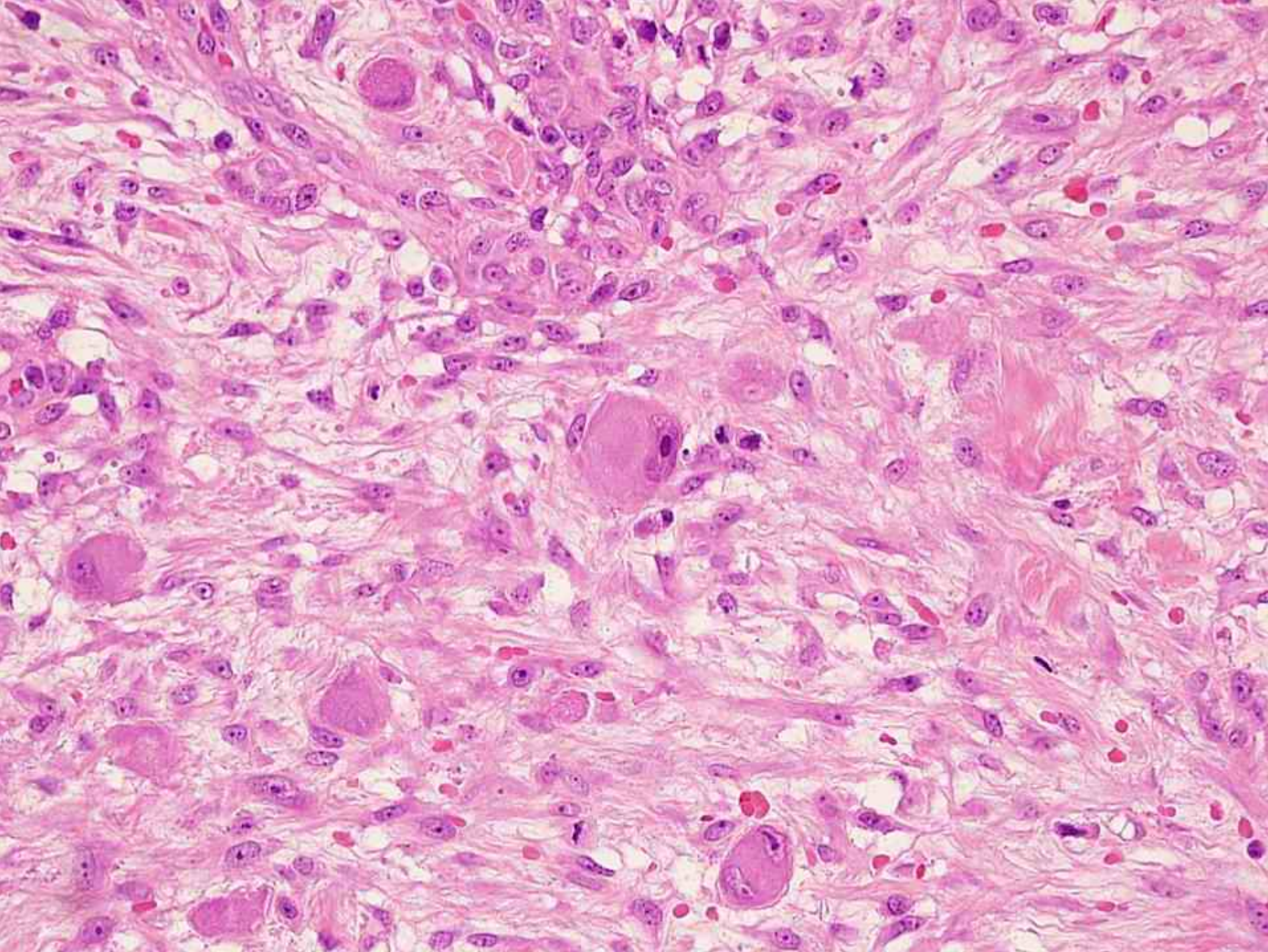
- Repeated local recurrences
  - 30-70%
- Surgical margins = key parameter
- Mets < 2%
  - Borderline category (WHO 2002)

Myxoinflammatory fibroblastic sarcoma - Genetics

- t(1;10)(p22;q24)
  - Breakpoints proximal to bcl10 (1p22) and proximal to GOT1 (10q24)
- Ring chromosome; der13
- ⇒ Neoplastic process
- ⇒ Distinct entity

What Myxoinflammatory fibroblastic sarcoma was?

- Proliferative fasciitis
- Pigmented villonodular tenosynovitis
- Reactive process NOS
- Neurothekeoma
- Hemangioma, lipoma, benign FH…
- Myxoid MFH
- Myxoid Liposarcoma
- Lymphomas



MFS
Differential Diagnosis

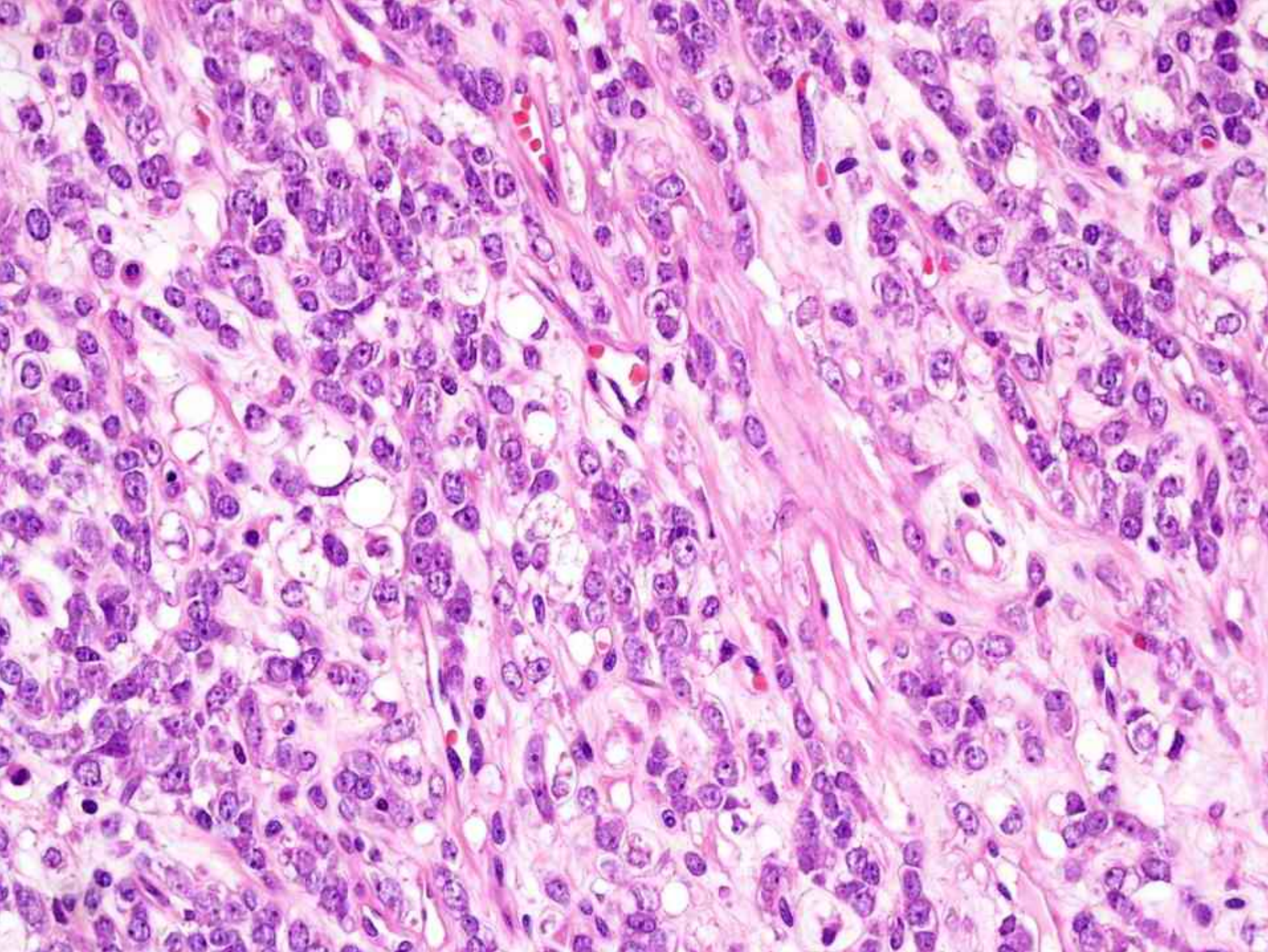
- Hematological malignancies
  - ALK -, CD30 -, B and T markers -
- Myxofibrosarcoma
- Inflammatory pleomorphic sarcomas
  - Low mitotic activity

WHO CLASSIFICATION OF SOFT TISSUE TUMOURS 2002
WEAKNESSES

- Arbitrary allocation of some lesions to other volumes
- Some 'newer' entities left out
- Continued nomenclatural anomalies
- Rigidity of ICD-O coding system
- Publication / editorial issues

Future Developments

- Treatment related entities
  - Synovial sarcoma and ifosfamide
  - GIST/DFSP/Chordoma and RKTs inhibitors
  - Angiosarcoma and taxanes
  - Leiomyosarcoma/myxoid liposarcoma and trabectidin (ET743)
  - Dedifferentiated LPS and antiMDM2 compounds
  - Anti mTOR trial about to start



Trabectedin in myxoid liposarcomas

Trabectedin

- Trabectedin (YondelisTM; Ecteinascidin-743; PharmaMar,
- Marine-derived alkaloid
  - covalently binds to the DNA minor groove, interfering with transcriptional factors in a promoter-dependent fashion.
- Active in a variety of malignancies, including sarcomas and ovarian carcinomas

Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study

Federica Grosso, Robin L Jones, George D Demetri, Ian R Judson, Jean-Yves Blay, Axel Le Cesne, Roberta Sanfilippo, Paola Casieri, Paola Collini, Palma Dileo, Carlo Spreafico, Silvia Stacchiotti, Elena Tamborini, Juan Carlos Tercero, José Jimeno, Maurizio D'Incalci, Alessandro Gronchi, Jonathan A Fletcher, Silvana Pilotti, Paolo G Casali

Summary

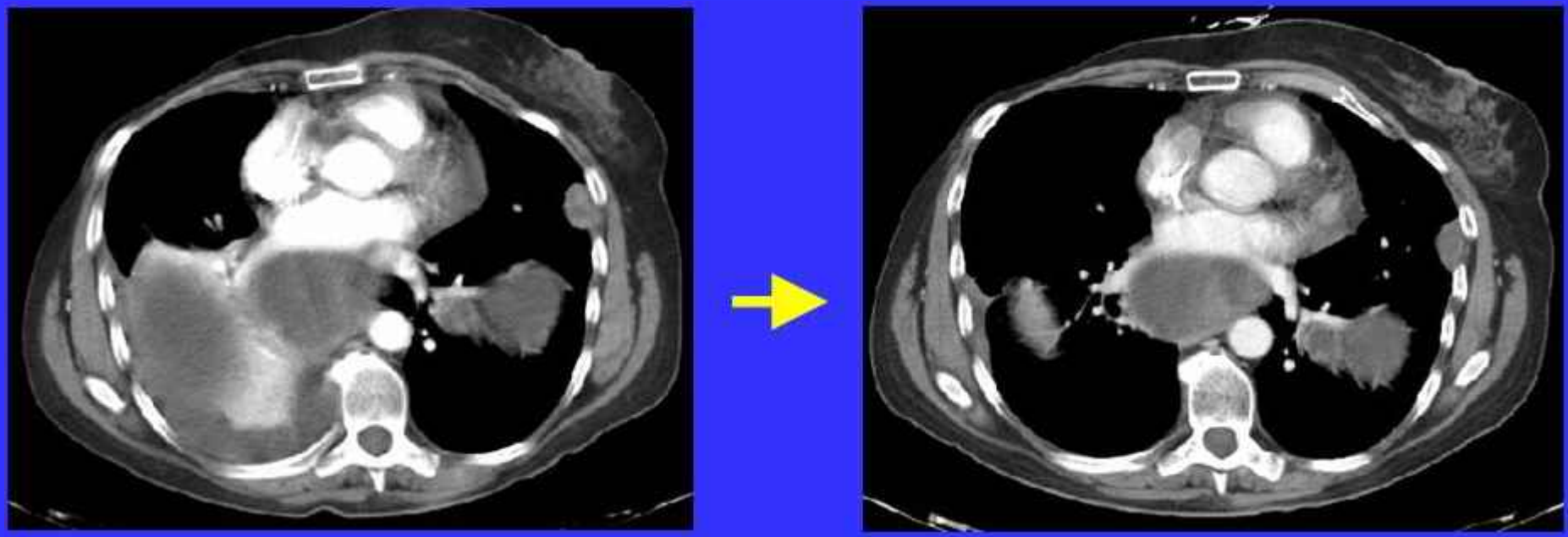
Background Previous studies have suggested that trabectedin (ecteinascidin-743) could have antitumour activity in soft-tissue sarcoma. We aimed to study the usefulness of trabectedin in the treatment of patients with myxoid liposarcomas, a subtype of liposarcoma that is associated with specific chromosomal translocations t(12;16)(q13;p11) or t(12;22)(q13;q12) that result in the formation of DDIT3-FUS or DDIT3-EWSR1 fusion proteins.

Methods 51 patients with advanced pretreated myxoid liposarcoma who started treatment with trabectedin between April 4, 2001, and Sept 18, 2006 at five institutions in a compassionate-use programme were analysed retrospectively. Centralised radiological and pathological reviews were done for most patients. Trabectedin was given either as a 24-h continuous infusion or as a 3-h infusion, every 21 days, at 1·1–1·5 mg/m². 558 courses of trabectedin were given in total, with a median of ten courses for each patient (range 1–23). The primary endpoints were response rate and progression-free survival, and the secondary endpoint was overall survival.

Findings According to Response Evaluation Criteria in Solid Tumors (RECIST), after a median follow-up of 14·0 months (IQR 8·7–20·0), two patients had complete responses (CR) and 24 patients had partial responses (PR); the overall response was 51% (95% CI 36–65). Five patients had early progressive disease. In 17 of the 23 patients who achieved PR or CR as defined by RECIST and who had centralised radiological review, tissue-density changes, consisting of a decrease in tumour density on CT scan or a decrease in contrast enhancement on MRI (or both), preceded tumour shrinkage. Median progression-free survival was 14·0 months (13·1–21·0), and progression-free survival at 6 months was 88% (79–95).

Interpretation Trabectedin was associated with antitumour activity in this series of patients with myxoid liposarcoma. The noted patterns of tumour response were such that tissue density changes occurred before tumour shrinkage in several patients. In some patients, tissue-density changes only were seen. Long-lasting tumour control was noted in responsive patients. The compassionate-use programme is still ongoing. This analysis has resulted in the initiation of two prospective studies to assess the role of trabectedin in the treatment of patients with myxoid liposarcoma in preoperative and metastatic settings. Furthermore, the selective mechanism of action for trabectedin in this translocation-related sarcoma is being studied.

F Grosso et al, Lancet Oncol 2007; 8: 595-602



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Thank
you!