Lezione Sof tissue tumors

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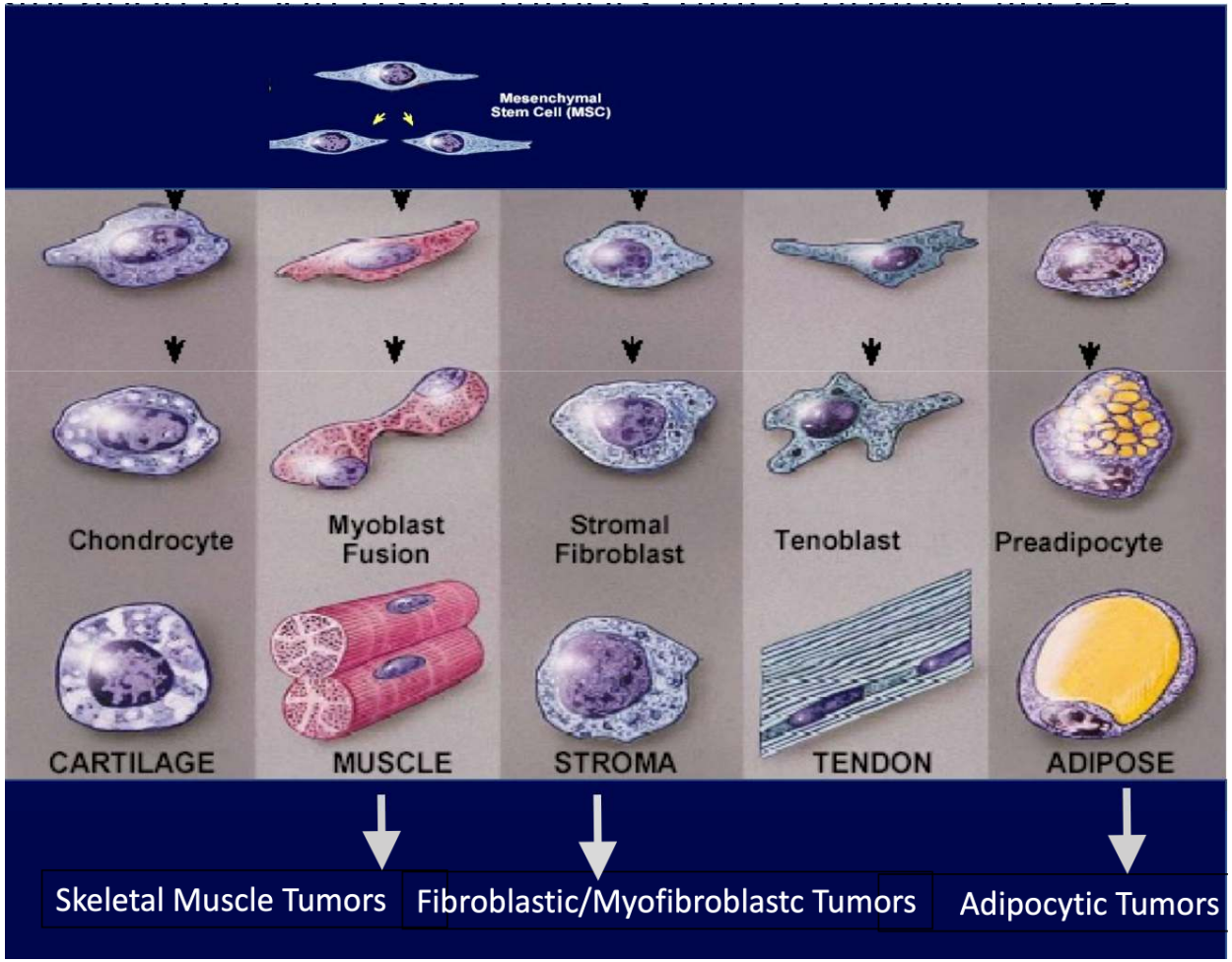
Roma

Soft tissue Tumors

Extra-skeletal mesechymal neoplasm, include also neoplasms of peripheral nerves



Soft tissue tumors: Epidemiology

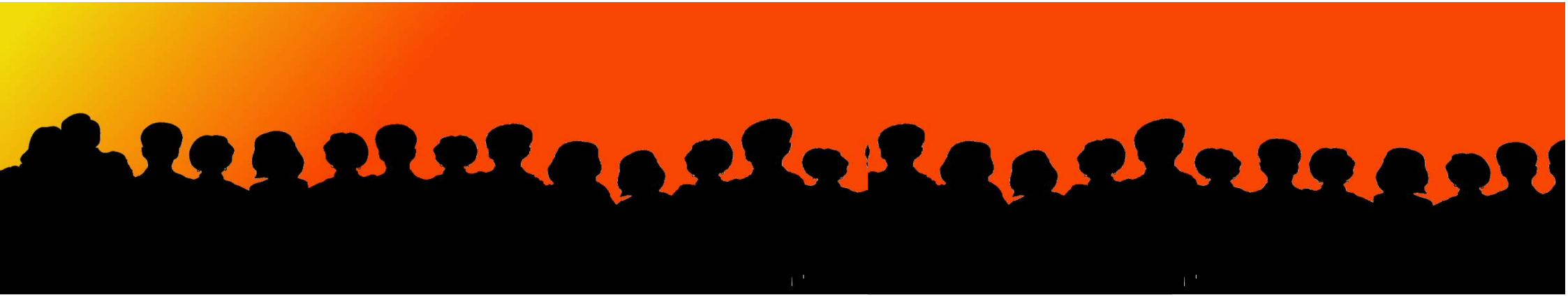
Soft tissue tumors: majority benign (e.g. lipoma)

Benign/malignant ratio about 200:1

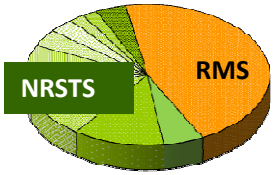
Malignant forms (Sarcomas) are rare (about 5/100.000)

Age: 50% from second decade, most frequently in the fourth

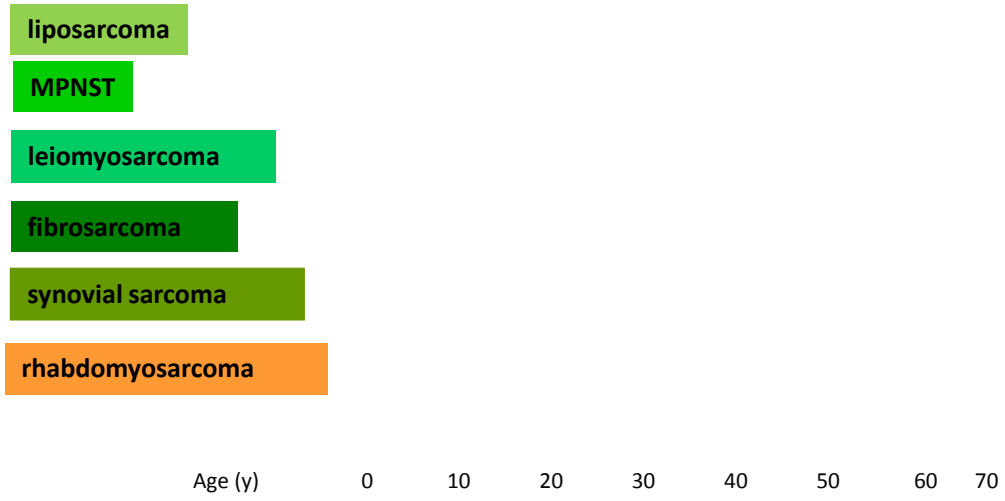
Different tumor types acc



Soft tissue tumors: Epidemiology

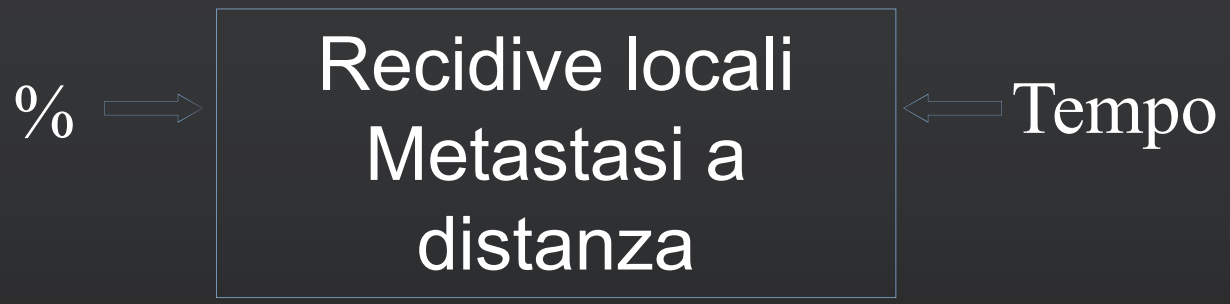


Pediatric STS
More than 50 histotypes and subtypes, with different biology and clinical behavior…
and their spectrum varies according to age



STM: generalità

- Spettro di aggressività biologica



TTM benigni

TTM a malignità intermedia (localmente aggressivi)

TTM a malignità intermedia (raramente metastatizzanti)

TTM maligni

STM: generalità

- Uno stesso istotipo di tumore presenta spesso una aggressività variabile in funzione di differenti parametri

Dimensioni

Sede

Topografici

Istopatologici

Età

Ploidia

Fattori cinetici

Alt. citogenetiche

Alt. molecolari

Distribuzione anatomica dei sarcomi dei tessuti molli

• *arto inferiore*	*37,8 %*
• *arto superiore*	*13,5 %*
• *testa - collo*	*11,8 %*
• *tronco*	*13,4 %*
• *retroperitoneo e mesentere*	*16,7 %*
• *mediastino*	*1,0 %*
• *Tratto urogenitale*	*2,9 %*
• *Cordone spermatico*	*1,3 %*
• *Altre sedi*	*1,6 %*

Soft tissue Tumors: Etiology

Unknown

Association with trauma not demonstrated

Foreign material

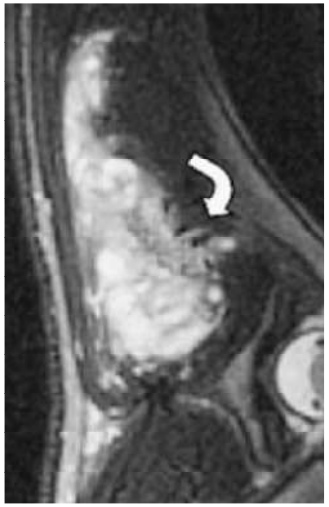
Radiation therapy (1% of sarcomas)

Chemical agents (e.g. angiosarcoma of liver and vynil polyclorure)

Virus (Kaposi Sarcoma, EBV)

Genetic predisposition (Li Fraumeni syndrome, Retinoblatoma, Neurofibromatosis type 1, Tuberous Sclerosis, FAP

La diagnosi di Neoplasia delle parti molli è difficile



Esame Clinico

Sintomi

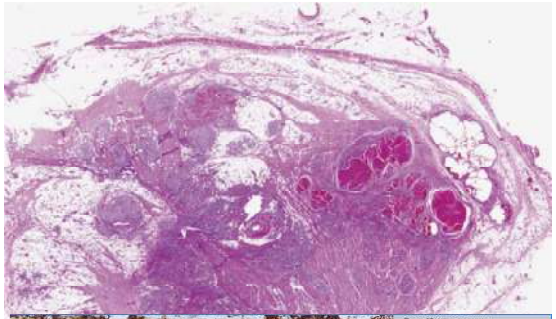
Caratteristiche cliniche della lesione:: età, sede, dimensioni, velocità di crescita

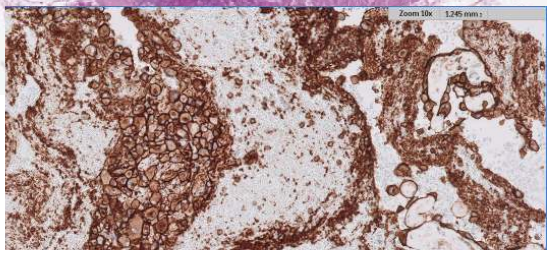
Esami di laboratorio

Esami ematochimici routinary; Markers tumorali

Imaging

- Rx standard
- Ecografia
- TAC
- RMN





Approccio alla lesione:

(Eventuale Agoaspirato)

Biopsia (tru-cut, chirurgica)

Exeresi

Valutazione Istologica

Utilizzo di tecniche ancillary:

Immunoistochimica

Analiisi citogenetiche/molecolari

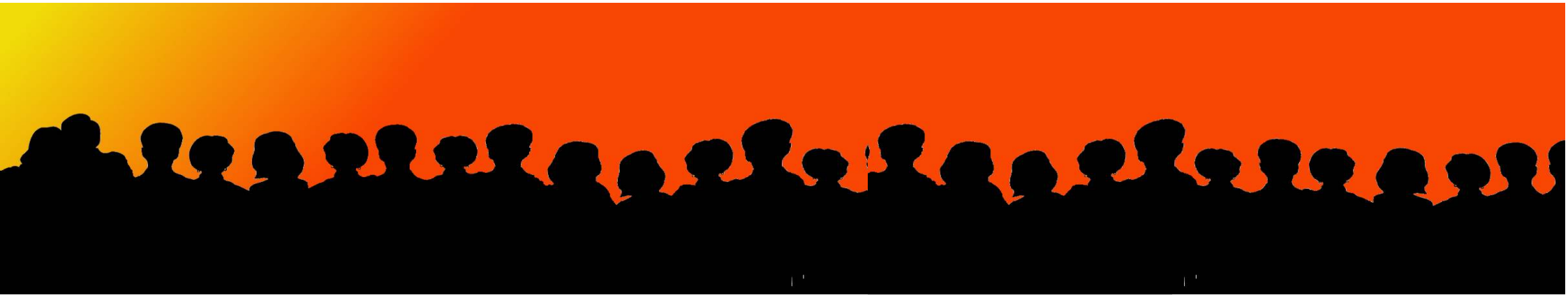
Soft tissue Tumors: Classification

Classification based on

- Differentiative lineage, i.e. histologic resemblance to normal tissue (e.g. lipoma resembles mature adipocytes)
- Presence of mature or immature components characteristic of sarcomas (e.g. liposarcoma is composed of immature adipocytes)
- *Exceptions:* lipoblastoma-a pediatric adipocytic tumor with immature adipocytes, not malignant

What about tumors with no evident differentiation lineage?

Category of Soft Tissue tumors with uncertain differentiation based on cytologic and/or molecular features



Soft tissue Tumors: Molecular Pathogenesis

STT with “simple” genome
1-Tumors with chimeric transcription factors and transcriptional deregulation into oncogenic gene fusions 2-Activating and inactivating point mutations 3-Gene amplifications
STT with complex genome
4-Tumors with highly complex karyotypes

Sarcoma Subtype	Translocation	Genes	Oncogenic Mechanism
Ewing sarcoma	t (11; 22) (q24; q12) t (21; 22) (q22; q12) t (16; 21) (p11; q22)	*EWSR1, FLI1* *EWSR1, ERG* *FUS, ERG*	Transcription factor
DSRCT	t (11; 22) (p13; q12)	*EWSR1, WT1*	Transcription factor
Alveolar rhabdomyosarcoma	t (2;13) (q35; q14) t (1; 13) (p36; q14)	*PAX3, FOXO1* *PAX7, FOXO1*	Transcription factor
Clear cell sarcoma	t (12; 22) (q13; q12)	*EWSR1, ATF1*	Transcription factor
Extraskeletal myxoid chondrosarcoma	t (9; 22) (q22–31; q11–12)	*EWSR1, NR4A3*	Transcription factor
Myxoid liposarcoma	t (12; 22) (q13; q12) t (12; 16) (q13; p11)	*EWSR1, CHOP* *FUS, CHOP*	Transcription factor
Alveolar soft part sarcoma	t (X; 17) (p11.2; q25)	*ASPL, TFE3*	Transcription factor
PEComa	Xp11 rearrangement	*, *TFE3*	Transcription factor
Low grade fibromyxoid sarcoma	t (7; 16) (q33; p11)	*FUS, CREB3L2*	Transcription factor
Sclerosing epithelioid fibrosarcoma	t (11; 22) (p11; q12)	*EWSR1, CREB3L1*	Transcription factor
Low grade endometrial stromal tumor	t (7; 17) (p15; q21)	*JAZF1, JJAZ1*	Transcription factor
Synovial sarcoma	t (X; 18) (p11; q11)	*SYT, SSX1, SSX2, SSX4*	Chromatin remodeling
Congenital fibrosarcoma	t (12; 15) (p13; q25)	*ETV6, NTRK3*	Tyrosine Kinase
Inflammatory myofibroblastic tumor	t (2; 19) (p23; p13.1) t (1; 2) (q22–23; p23)	*TPM4, ALK* *TPM3, ALK*	Tyrosine Kinase
Dermatofibrosarcoma protuberans	t (17; 22) (q22; q13)	*COL1A1, PDGFβ*	Growth Factor
PVNS/TGCT	t (1; 2) (p13; q37)	*COL6A3, CSF1*	Growth Factor

Abbreviations: DSRCT: desmoplastic small round cell tumor, PVNS/TGCT: pigmented villonodular synovitis/tenosynovial giant cell tumor. * Multiple gene partners.

Soft Tissue and Bone Tumours (5th ed.)

Adipocytic tumours
- Lipoma
- Lipomatosis
- Lipomatosis of nerve
- Lipoblastoma and lipoblastomatosis
- Angiolipoma
- Myolipoma of soft tissue
- Chondroid lipoma
- Spindle cell lipoma and pleomorphic lipoma
- Hibernoma
- Atypical spindle cell / pleomorphic lipomatous tumour
- Atypical lipomatous tumour / well-differentiated liposarcoma
- Dedifferentiated liposarcoma
- Myxoid liposarcoma
- Pleomorphic liposarcoma
- Myxoid pleomorphic liposarcoma

Fibroblastic and myofibroblastic tumours
- Myositis ossificans and fibro-osseous pseudotumour of digits
- Ischaemic fasciitis
- Elastofibroma
- Fibrous hamartoma of infancy
- Fibromatosis colli
- Juvenile hyaline fibromatosis
- Inclusion body fibromatosis
- Fibroma of tendon sheath
- Desmoplastic fibroblastoma
- Myofibroblastoma
- Calcifying aponeurotic fibroma
- EWSR1-SMAD3-positive fibroblastic tumour (emerging)
- Angiomyofibroblastoma
- Cellular angiofibroma
- Angiofibroma of soft tissue
- Nuchal-type fibroma
- Acral fibromyxoma
- Gardner fibroma
- Palmar fibromatosis and plantar fibromatosis
- Desmoid fibromatosis
- Lipofibromatosis
- Giant cell fibroblastoma
- Dermatofibrosarcoma protuberans
- Solitary fibrous tumour
- Inflammatory myofibroblastic tumour
- Low-grade myofibroblastic sarcoma
- Superficial CD34-positive fibroblastic tumour
- Myxoinflammatory fibroblastic sarcoma
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-called fibrohistiocytic tumours
- Tenosynovial giant cell tumour
- Deep fibrous histiocytoma
- Plexiform fibrohistiocytic tumour
- Giant cell tumour of soft tissue

Vascular tumours
- *Haemangiomas*
  - Synovial haemangioma
  - Intramuscular angioma
  - Arteriovenous malformation/haemangioma
  - Venous haemangioma
- Anastomosing haemangioma
- Epithelioid haemangioma
- Lymphangioma and lymphangiomatosis
- Tufted angioma and kaposiform haemangioendothelioma
- Retiform haemangioendothelioma
- Papillary intralymphatic angioendothelioma
- Composite haemangioendothelioma
- Kaposi sarcoma
- Pseudomyogenic haemangioendothelioma
- Epithelioid haemangioendothelioma
- Angiosarcoma

Pericytic (perivascular) tumours
- Glomus tumour
- Myopericytoma, including myofibroma
- Angioleiomyoma

Smooth muscle tumours
- Leiomyoma
- EBV-associated smooth muscle tumour
- Inflammatory leiomyosarcoma
- Leiomyosarcoma

Skeletal muscle tumours
- Rhabdomyoma
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma
- Spindle cell / sclerosing rhabdomyosarcoma
- Ectomesenchymoma

Gastrointestinal stromal tumour
- Gastrointestinal stromal tumour

Chondro-osseous tumours
- Soft tissue chondroma
- Extraskeletal osteosarcoma

Peripheral nerve sheath tumours
- Schwannoma
- Neurofibroma
- Perineurioma
- Granular cell tumour
- Dermal nerve sheath myxoma
- Solitary circumscribed neuroma
- Ectopic meningioma and meningothelial hamartoma
- Benign triton tumour / neuromuscular choristoma
- Hybrid nerve sheath tumour
- Malignant peripheral nerve sheath tumour
- Malignant melanotic nerve sheath tumour

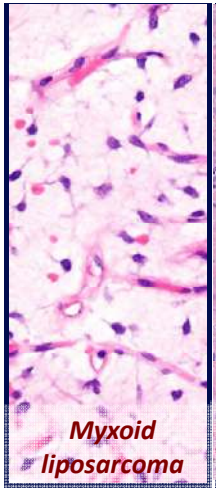
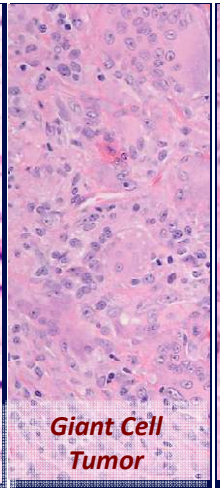
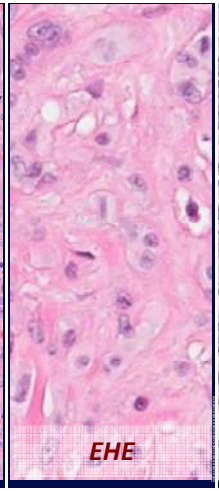
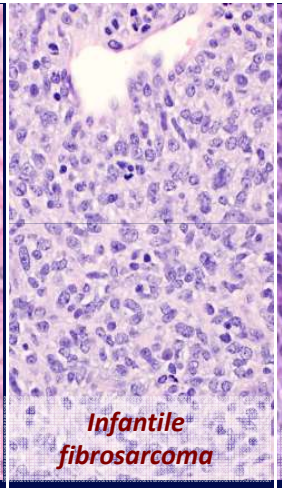
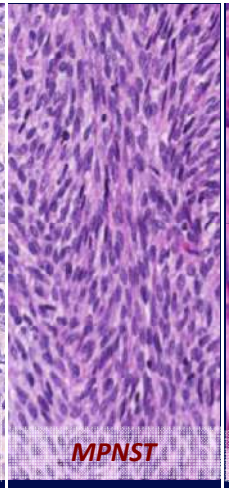
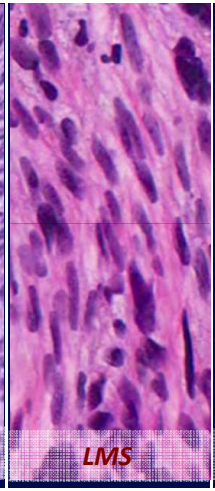
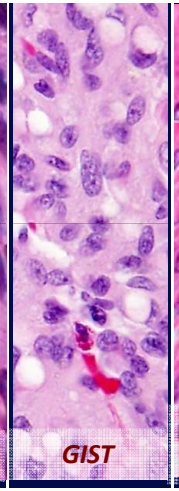
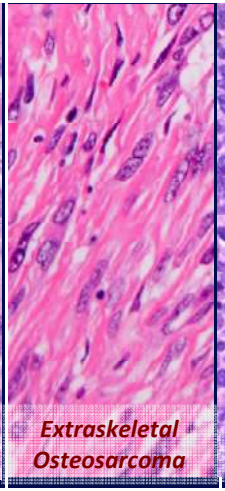
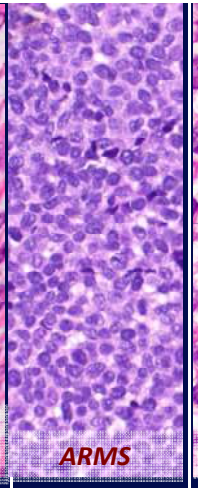
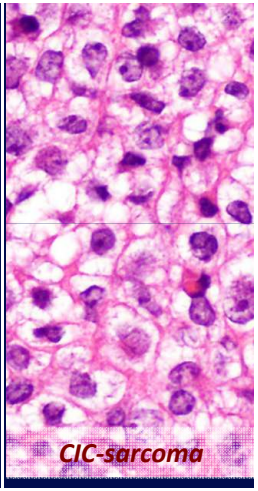
Tumours of uncertain differentiation
- Intramuscular myxoma
- Juxta-articular myxoma
- Deep (aggressive) angiomyxoma
- Atypical fibroxanthoma
- Angiomatoid fibrous histiocytoma
- Ossifying fibromyxoid tumour
- Myoepithelioma, myoepithelial carcinoma, and mixed tumour
- Pleomorphic hyalinizing angiectatic tumour of soft parts
- Haemosiderotic fibrolipomatous tumour
- Phosphaturic mesenchymal tumour
- NTRK-rearranged spindle cell neoplasm (emerging)
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Desmoplastic small round cell tumour
- Extrarenal rhabdoid tumour
- PEComa
- Intimal sarcoma
- Undifferentiated sarcoma

3. Undifferentiated small round cell sarcomas of bone and soft tissue

- Ewing sarcoma
- Round cell sarcoma with EWSR1-non-ETS fusions
- CIC-rearranged sarcoma
- Sarcoma with BCOR genetic alterations

Soft Tissue Sarcomas

World Health Organization

Adipocytic	Fibro Histiocytic	Vascular	Fibroblastic & myofibroblastic	Peripheral nerve sheath	Smooth muscle	GI Stromal	Chondro osseous	Skeletal muscle	Uncertain differentiation
									
Myxoid liposarcoma	*Giant Cell Tumor*	*EHE*	*Infantile fibrosarcoma*	*MPNST*	*LMS*	*GIST*	*Extraskeletal Osteosarcoma*	*ARMS*	*CIC-sarcoma*

WHO Subcategories based on **morphology**:

- **Round cell**
- Spindle cell
- Pleomorphic
- Epithelioid cell
- **N**ot **O**therwise **S**pecified (NOS)

Courtesy dr T. Santiago

Sarcoma Grading: FNCLCC system

Combination of tumor differentiation / histology, mitotic count and tumor necrosis

- Tumor differentiation
  - 1, 2 or 3 points based on resemblance to normal tissue
- Mitotic count: 10 successive high power fields (HPFs) in the most mitotically active area
  - 1 point: 0 - 9 mitoses
  - 2 points: 10 - 19 mitoses
  - 3 points: 20 or more mitoses
- Tumor necrosis
  - 0 points: no necrosis
  - 1 point: < 50% necrosis
  - 2 points: ≥ 50% necrosis

Tumor Grade: sum total of tumor differentiation, mitotic count and tumor necrosis scores

- Grade 1: 2 - 3 points
- Grade 2: 4 - 5 points
- Grade 3: 6 - 8 points

Histologic type	Score
Atypical lipomatous tumor / well differentiated liposarcoma	1
Well differentiated leiomyosarcoma	1
Malignant neurofibroma	1
Well differentiated fibrosarcoma	1
Myxoid liposarcoma	2
Conventional leiomyosarcoma	2
Conventional fibrosarcoma	2
Myxofibrosarcoma	2* (see **above**)
High grade myxoid liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Pleomorphic rhabdomyosarcoma	3
Poorly differentiated / pleomorphic leiomyosarcoma	3
Synovial sarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Extraskeletal Ewing sarcoma	3
Malignant rhabdoid tumor	3
Undifferentiated pleomorphic sarcoma	3
Undifferentiated sarcoma, NOS	3

Adipocytic tumours

World Health Organization

Adipocytic tumours

- Lipoma
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- Lipoblastoma and lipoblastomatosis
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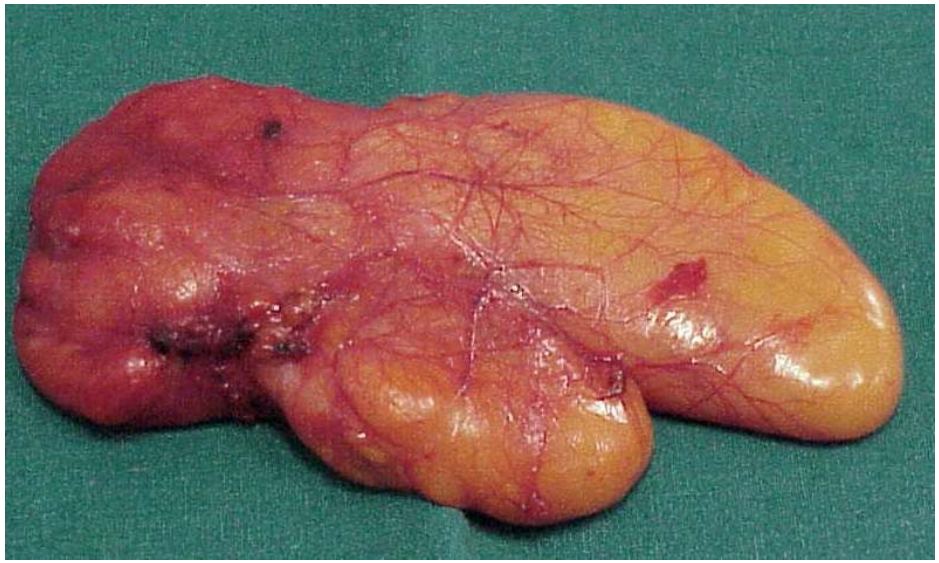
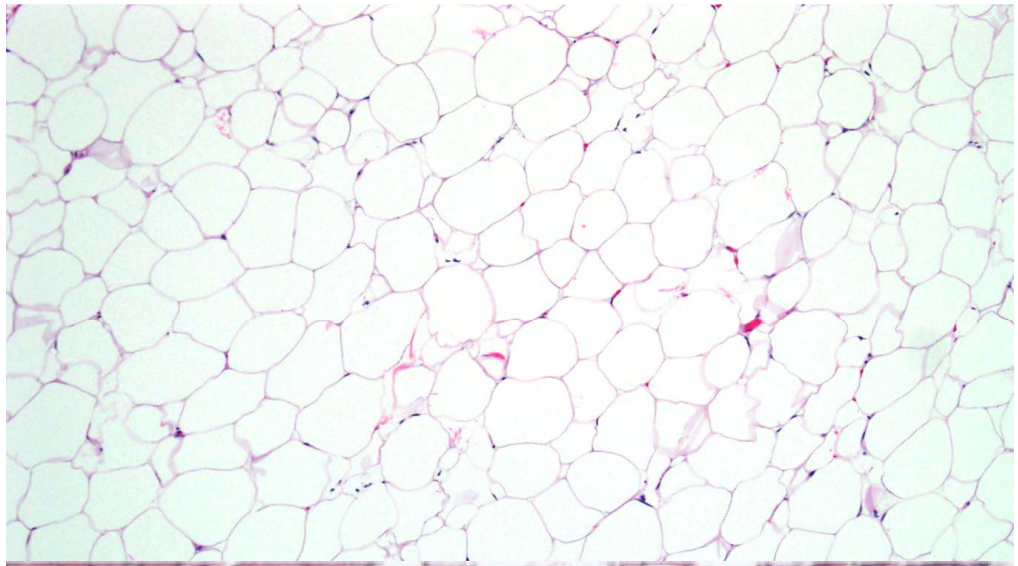
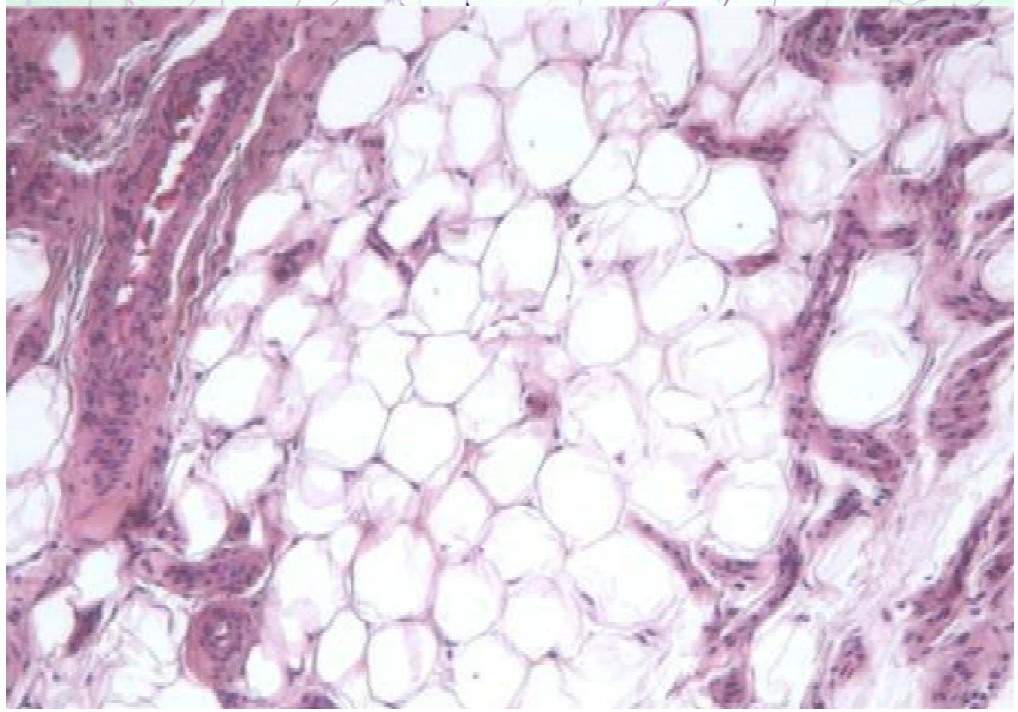


Lipoma





Lipoma

Epidemiology

- most common mesenchymal neoplasm in adults, more common in males, tends to be associated with obesity
- Age: fifth to seventh decades, rare in the paediatric population.

Clinical features

painless mass; larger tumours may compress peripheral nerves and result in pain or tenderness.

Site: upper back, proximal extremity, and abdominal region, mostly superficial (subcutaneous) soft tissue mass, less frequently deep-seated

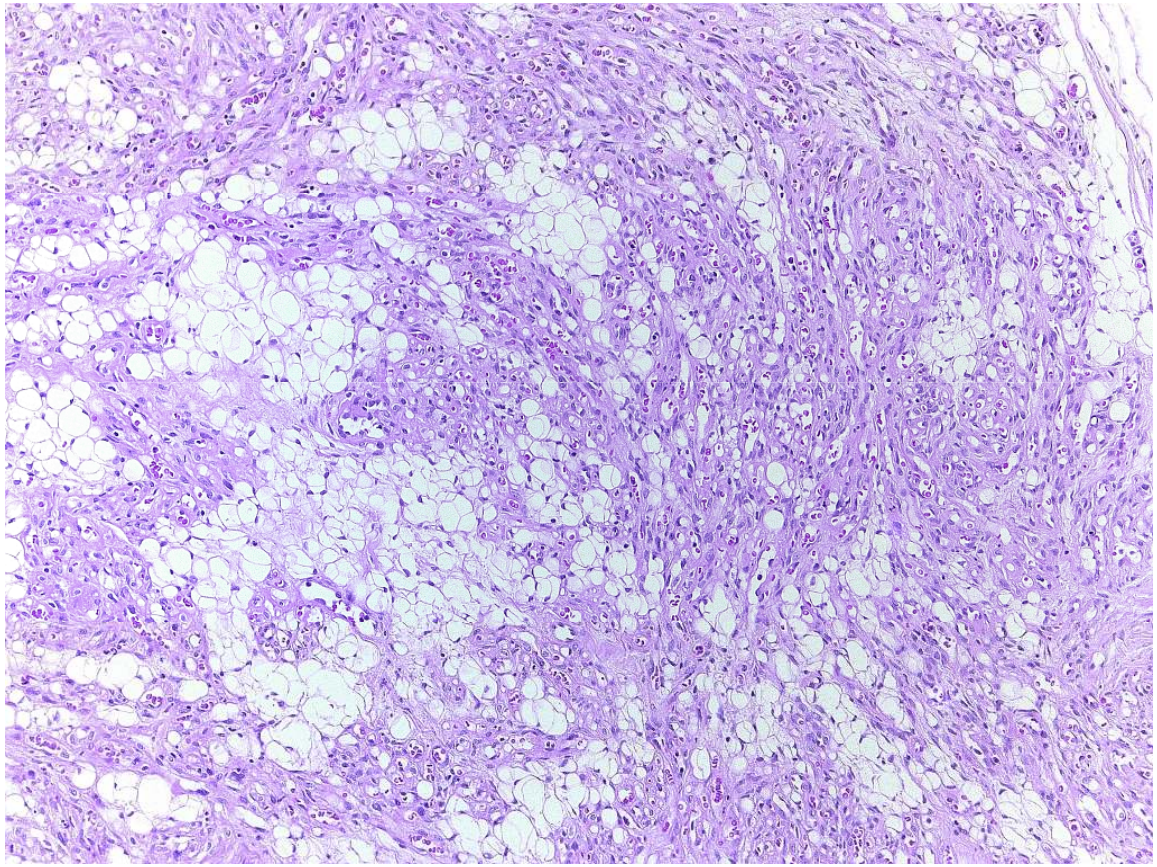
Prognosis

Benign, recurrence rate < 5%.

Angiolipoma

Multiple subcutaneous small nodules, tender to painful.

Mature fat cells intermingled with small and thin-walled vessels, a number of which contain fibrin thrombi.



Ibernoma

Clinical Features:

< 2% of benign adipocytic tumours.

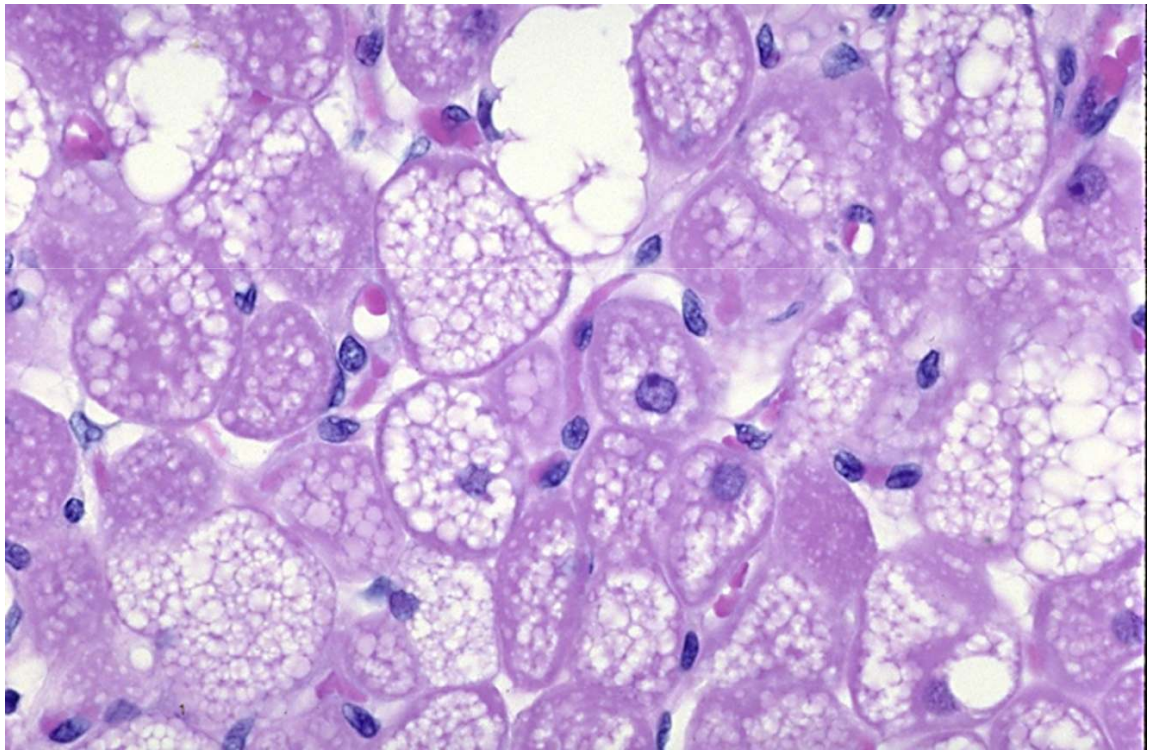
young adults (mean age: 38 years; range: 2–75 y)

small, slow-growing, painless, subcutaneous masses in thigh, trunk, chest, upper extremity, and head and neck.

10% intra-abdominal, retroperitoneal, or thoracic

Histology:

Composed of eosinophilic and pale, polygonal, multivacuolated, granular, brown fat cells



Lipoblastoma

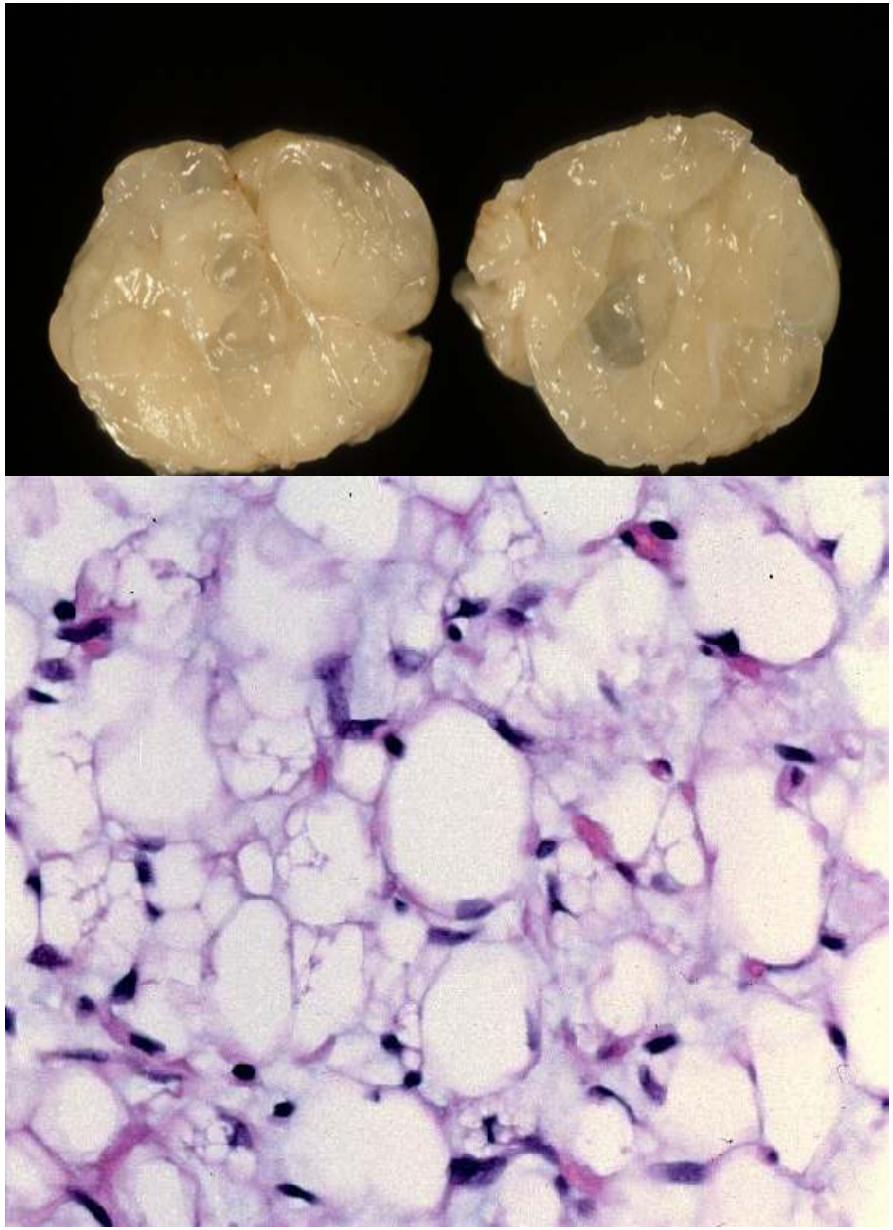
Benign neoplasm of embryonal white fat with a tendency for local recurrence if incompletely excised.

Age: 90% before 3 years, 40% 1st year of life

Site: trunk, extremities, less frequent in retroperitoneum, pelvis, abdomen, head/neck, organs (lung, heart)

Lobulated architecture with fibrovascular septa

Lipoblasts in various stages of differentiation to mature fat with orientation from periphery to the center:



Adipocytic tumours

World Health Organization

Atypical spindle cell / pleomorphic lipomatous tumour

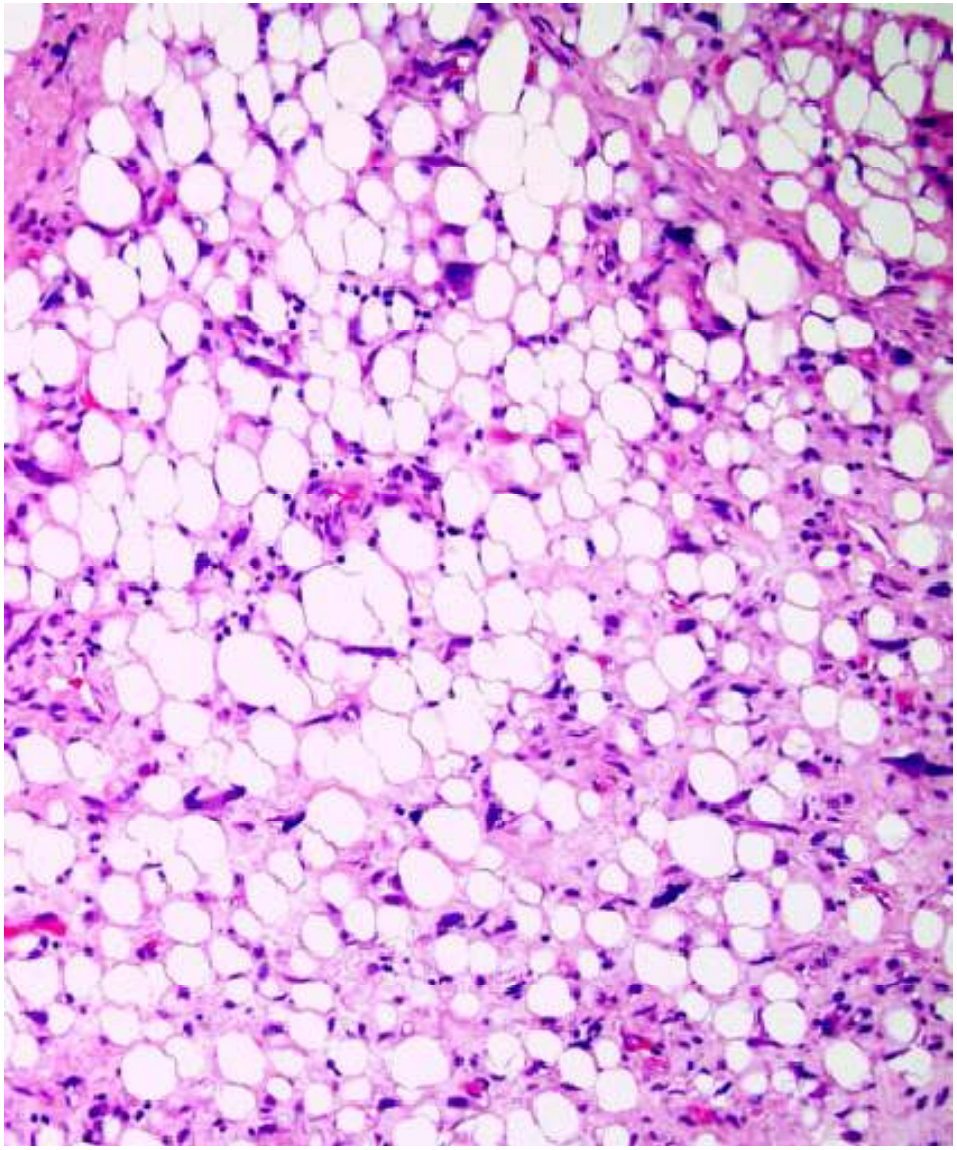
Atypical lipomatous tumour / well-differentiated liposarcoma

Dedifferentiated liposarcoma

Myxoid liposarcoma

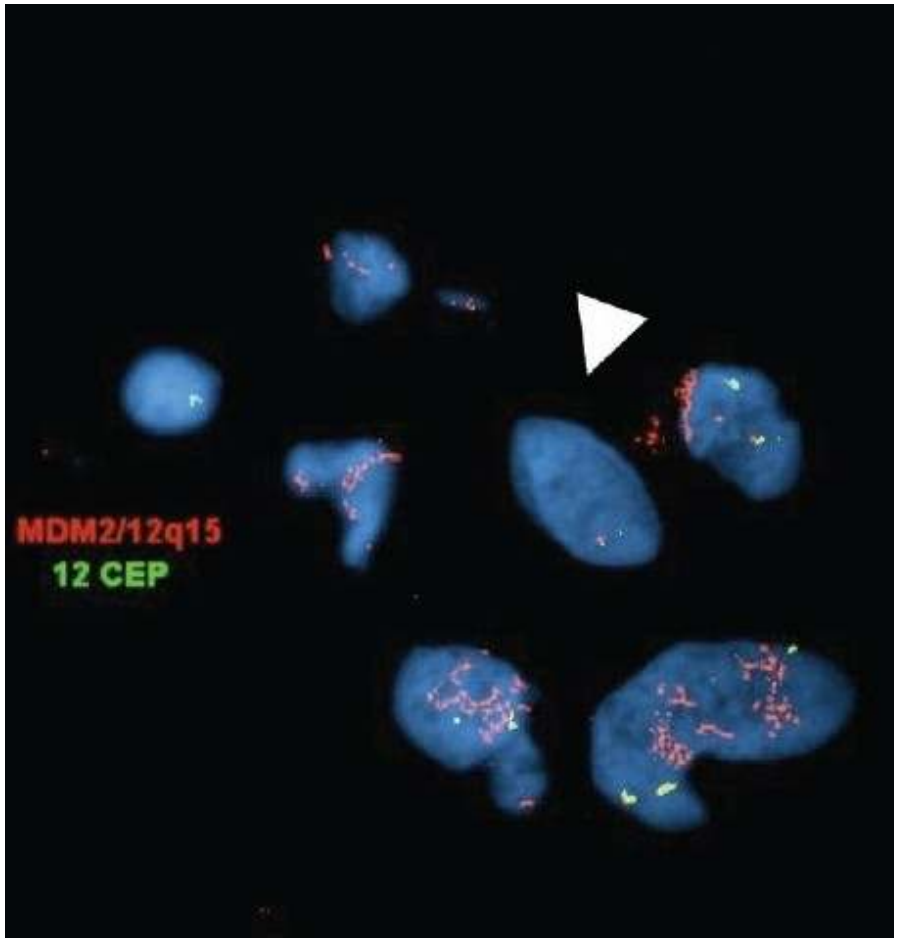
Pleomorphic liposarcoma

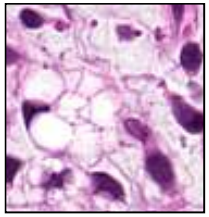
Myxoid pleomorphic liposarcoma



WD Liposarcoma

- MDM2 (12q14-15) ampl
- IHC (protein)
- FISH (gene amplification)





Histology: Adipose

Molecular Features:
MDM2 or CDK4 ampl+highly complex karyotype

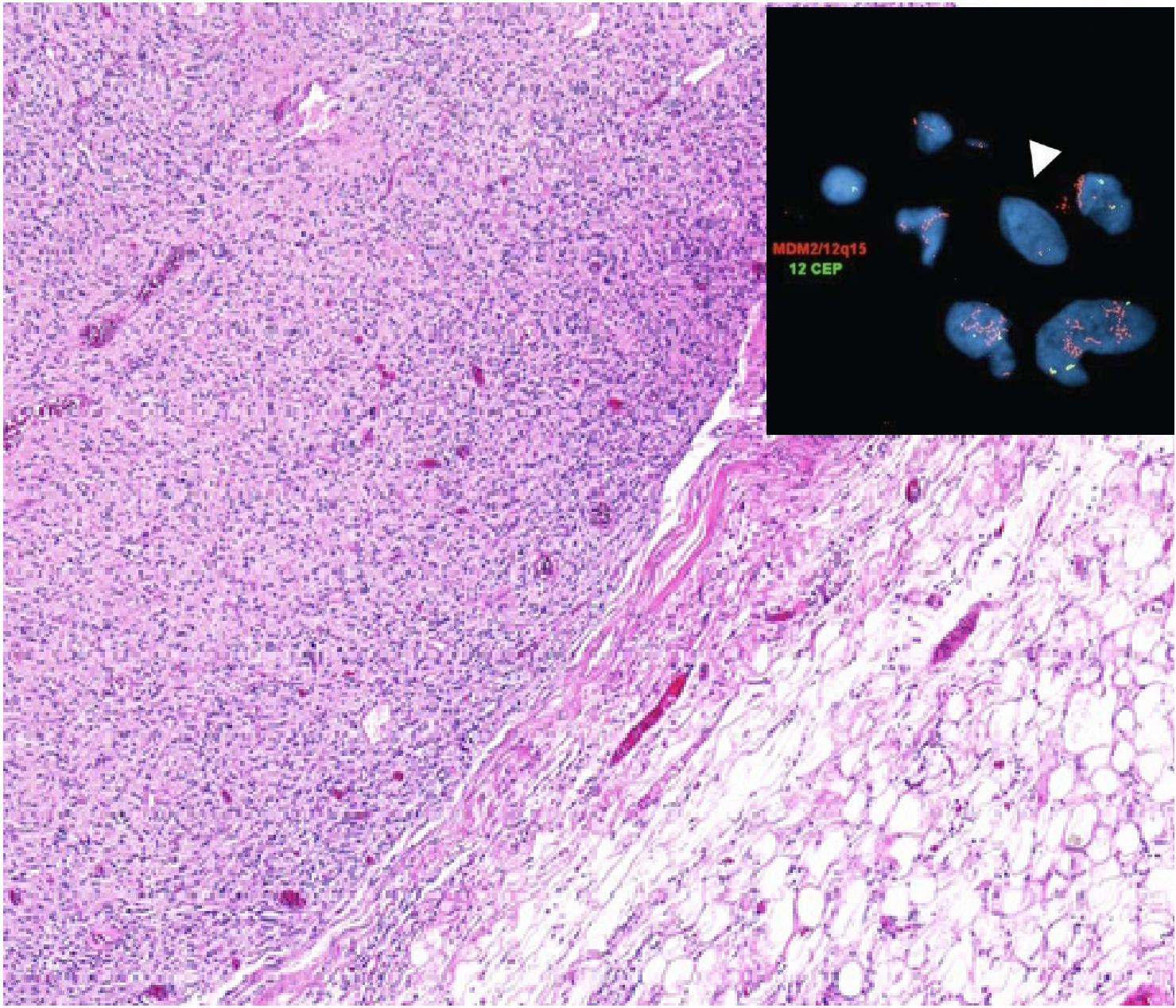
Diagnosis:

Dedifferentiated Liposarcoma (high grade)

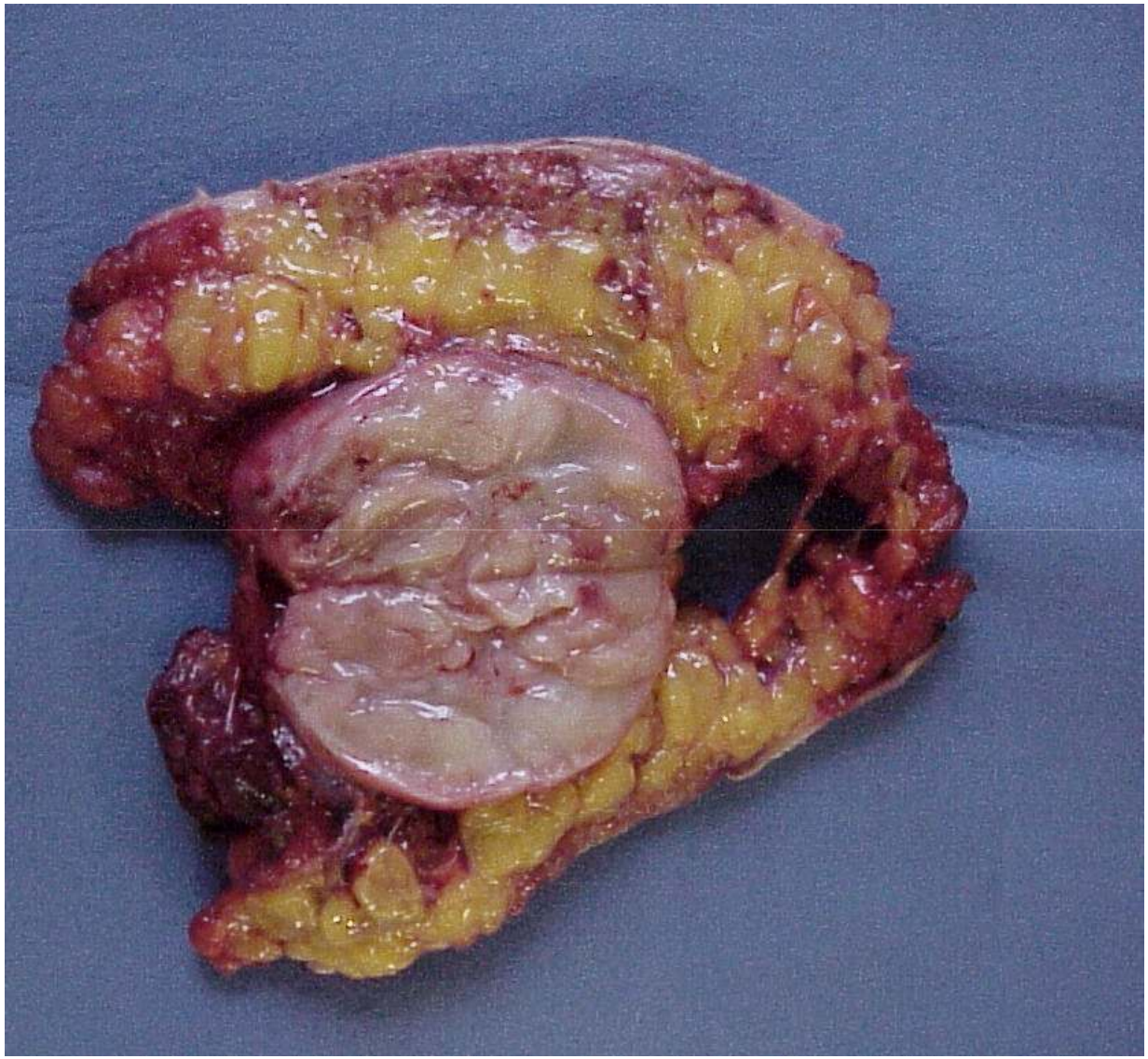
Distant metastases 15–20%, overall mortality rate:28–30% at 5-year follow-up

Prognostic significance of grade

Courtesy Silvia Vallese (OPBG, Rome)



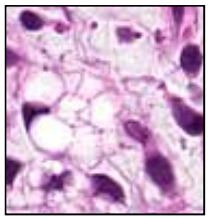
Adipocytic tumours



Clinical History

50 yr old, M

Mass in the upper leg



Histology: Adipocytic lineage

Lipoblasts

Myxoid Background

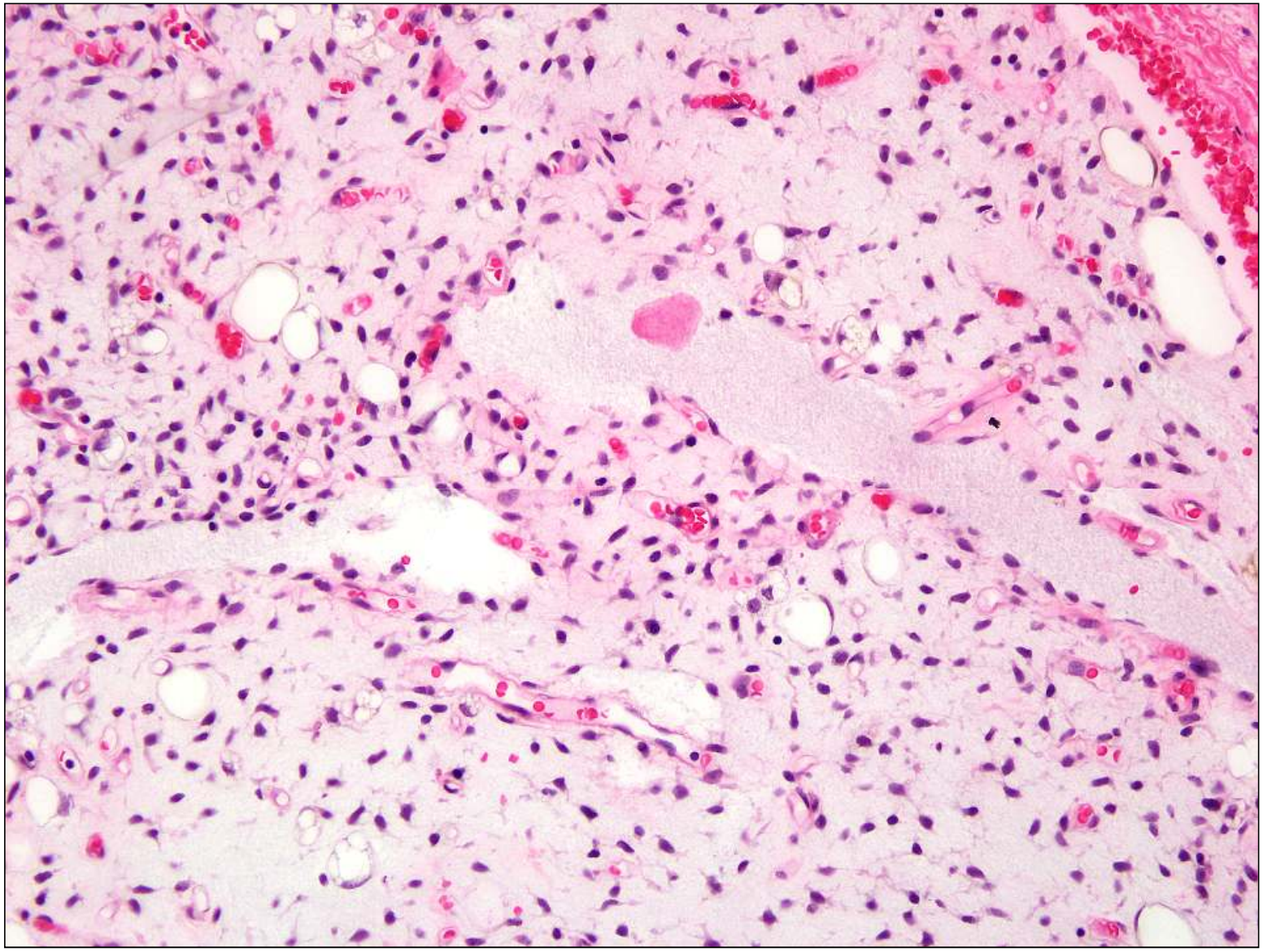
Prominent capillary vasculature

Molecular Features:
FUS::DDIT3

Diagnosis:

Myxoid Liposarcoma

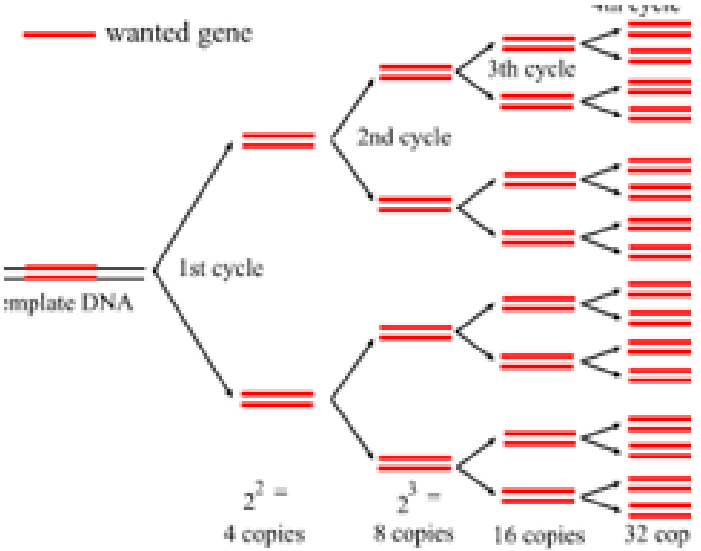
20–30% of liposarcomas
,5% of adult soft tissue sarcomas

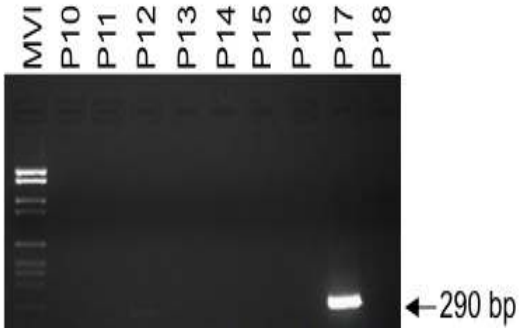


Molecular/Cytogenetic Testing

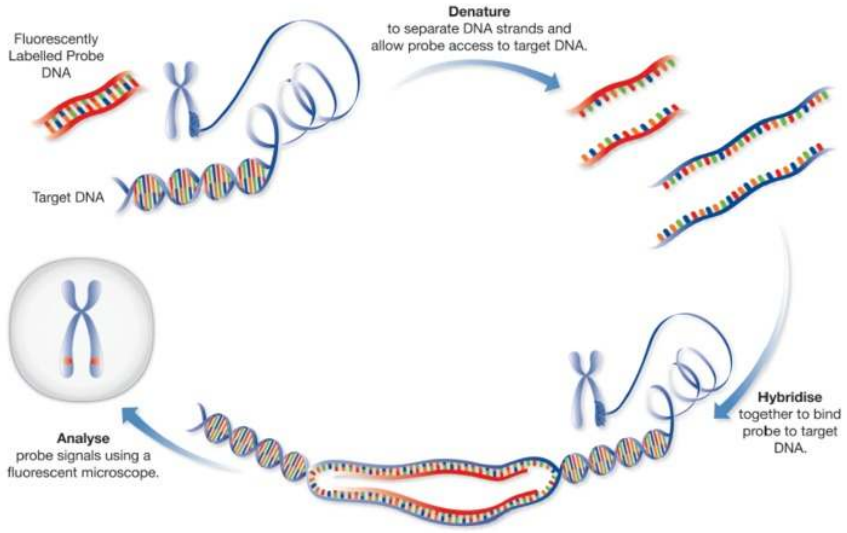
Reverse transcription polymerase chain reaction (RT-PCR)

A RNA template is converted into a complementary DNA (cDNA) using a reverse transcriptase. The cDNA is then used as a template for exponential amplification using PCR. RT-PCR is a sensitive method of detection of specific fusion transcripts in RNA (eg *FUS::DDIT3)*





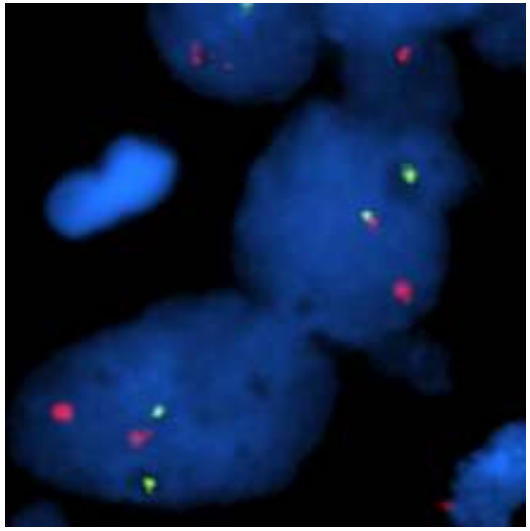
Molecular/Cytogenetic Testing



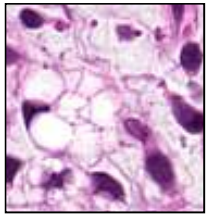
Fluorescence in situ hybridization (FISH)

Detects and localizes specific DNA sequences using fluorescently labelled complementary DNA probes

(eg a gene rearrangement)



Disadvantage: partner gene not known: eg *EWSR* rearrangement



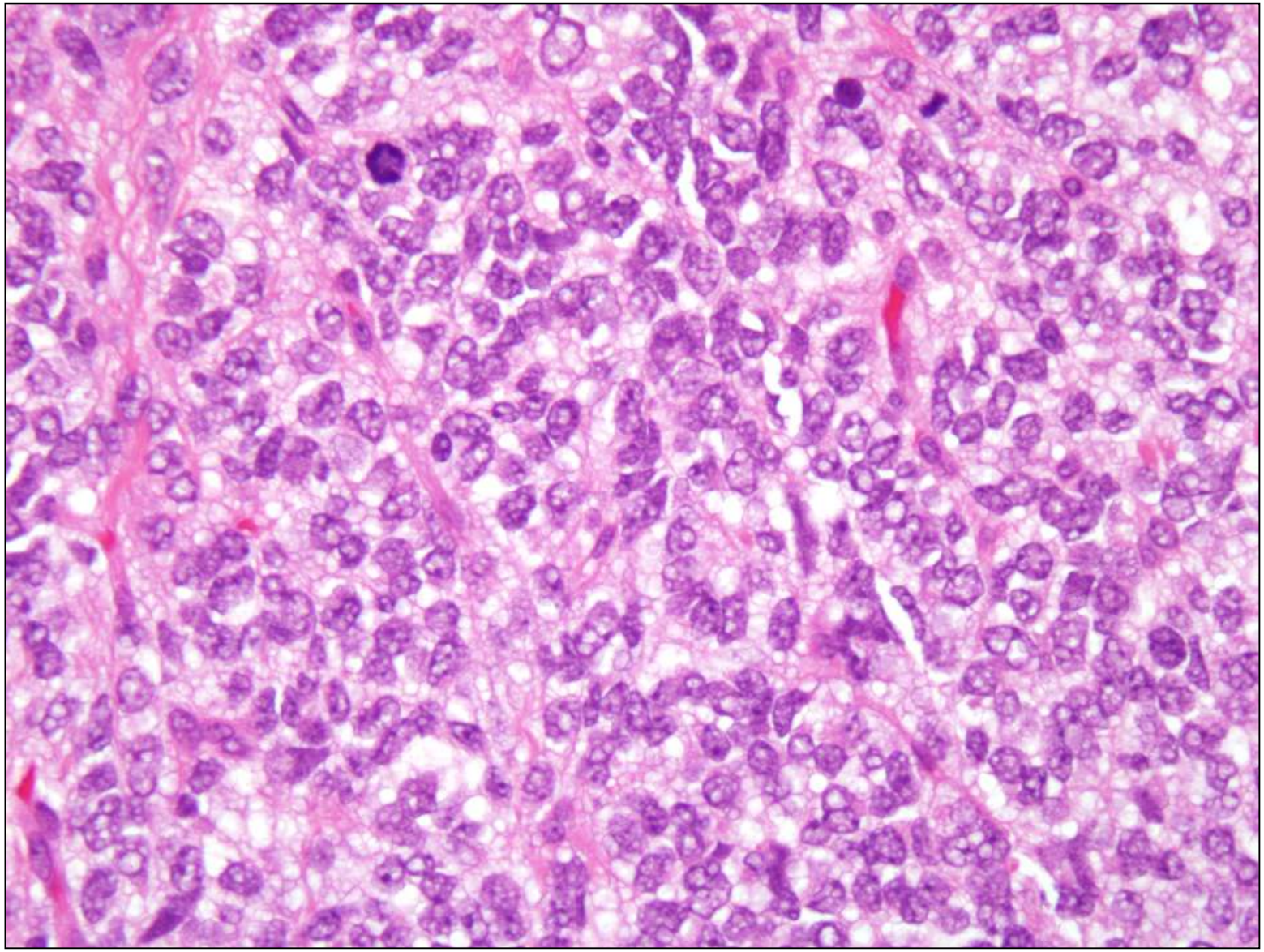
Histology: ? Lineage

Molecular Features:
FUS::DDIT3

Diagnosis:

High grade Myxoid Liposarcoma

- 5% of the tumour with cellular overlap, diminished myxoid matrix, less-apparent capillary vasculature, elevated nuclear grade, and increased mitotic activity.
- Significantly poorer prognosis

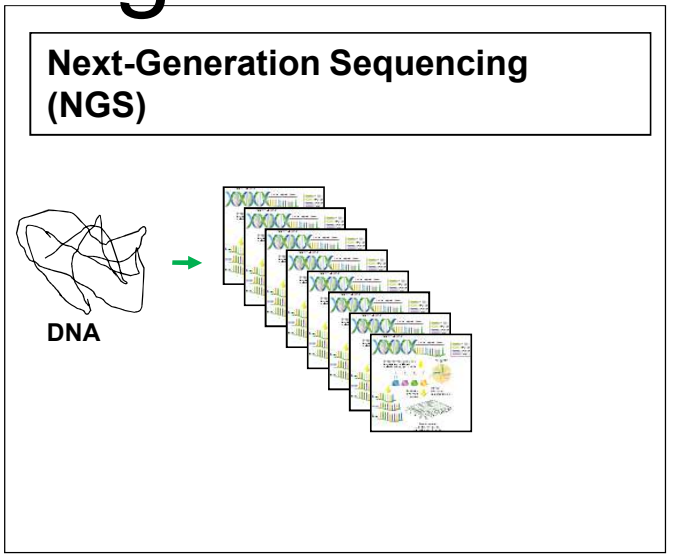


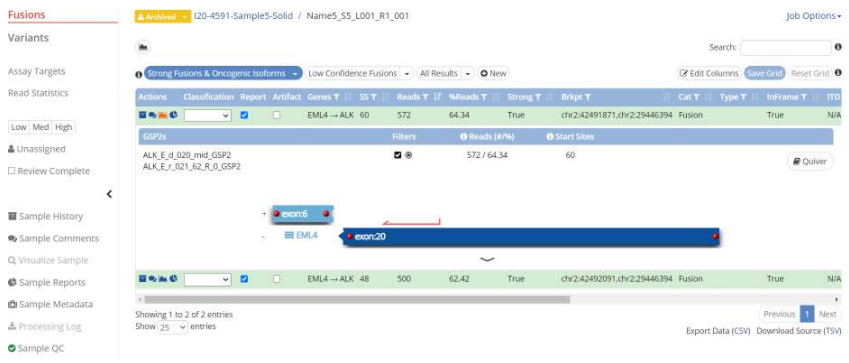
Molecular/Cytogenetic Testing

Next-generation sequencing (NGS)

Detects known and novel fusions with arbitrary breakpoints in DNA or RNA

Disadvantage: time consuming, costs

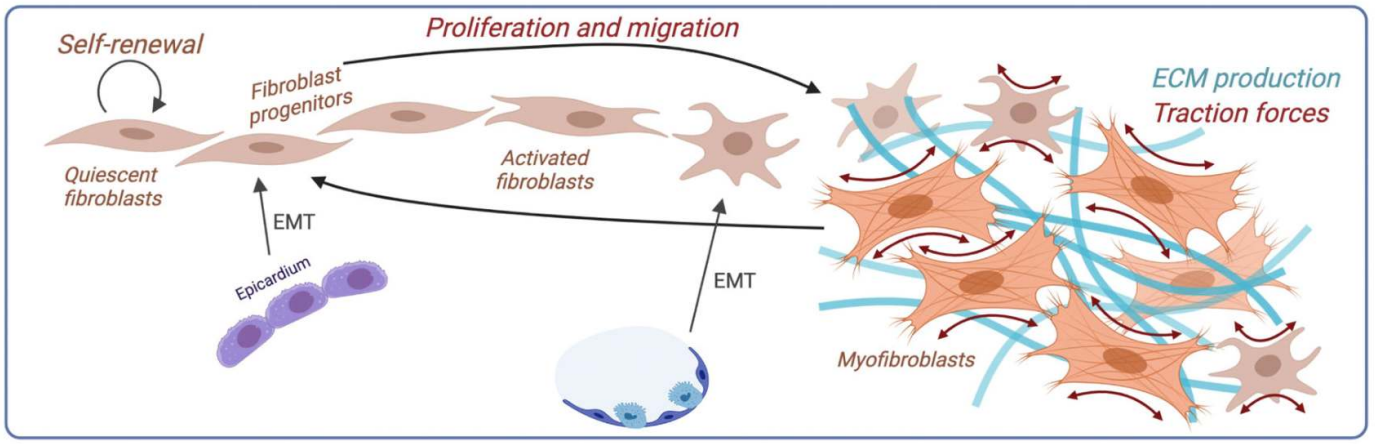


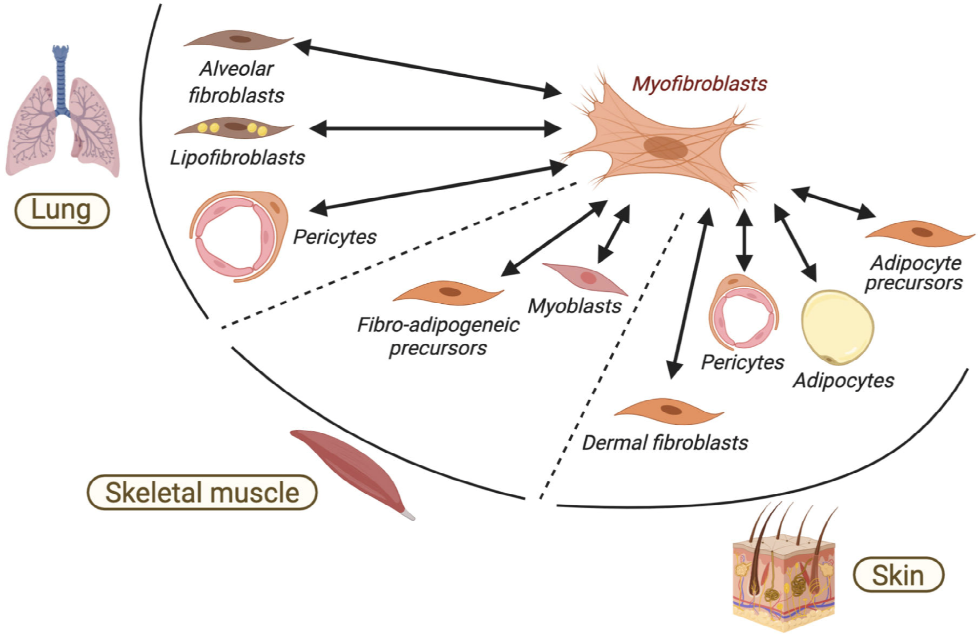


Myofibroblastic Tumors

World Health Organization

- Myositis ossificans and fibro-osseous pseudotumour of digits
- Ischaemic fasciitis
- Elastofibroma
- Fibrous hamartoma of infancy
- Fibromatosis colli
- Juvenile hyaline fibromatosis
- Inclusion body fibromatosis
- Fibroma of tendon sheath
- Desmoplastic fibroblastoma
- Myofibroblastoma
- Calcifying aponeurotic fibroma
- EWSR1-SMAD3-positive fibroblastic tumour (emerging)
- Angiomyofibroblastoma
- Cellular angiofibroma
- Angiofibroma of soft tissue
- Nuchal-type fibroma
- Acral fibromyxoma
- Gardner fibroma
- Palmar fibromatosis and plantar fibromatosis
- Desmoid fibromatosis
- Lipofibromatosis
- Giant cell fibroblastoma
- Dermatofibrosarcoma protuberans
- Solitary fibrous tumour
- Inflammatory myofibroblastic tumour
- Low-grade myofibroblastic sarcoma
- Superficial CD34-positive fibroblastic tumour
- Myxoinflammatory fibroblastic sarcoma
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma



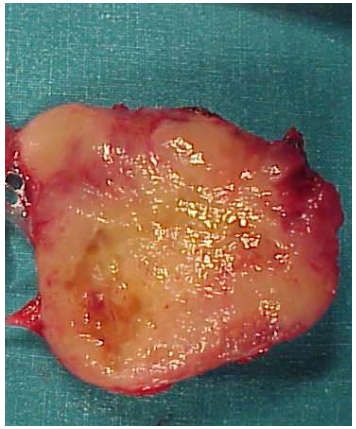


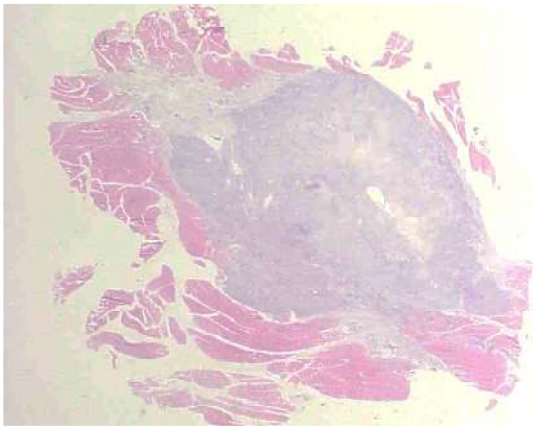
Nodular Fasciitis

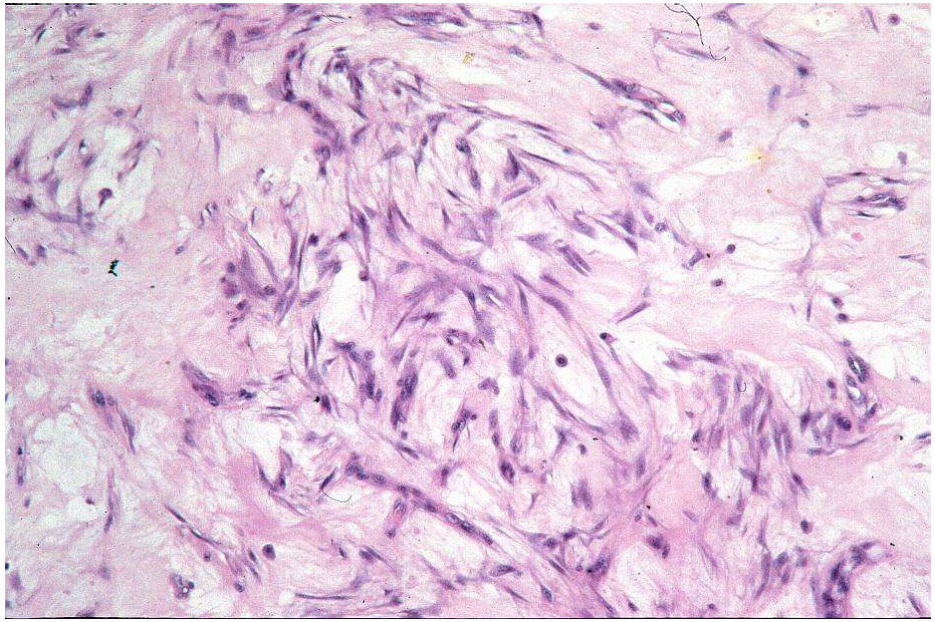
Self-limiting mesenchymal neoplasm that usually occurs in subcutaneous tissue.

It is composed of plump, uniform fibroblastic/myofibroblastic cells displaying a tissue culture–like architectural pattern,

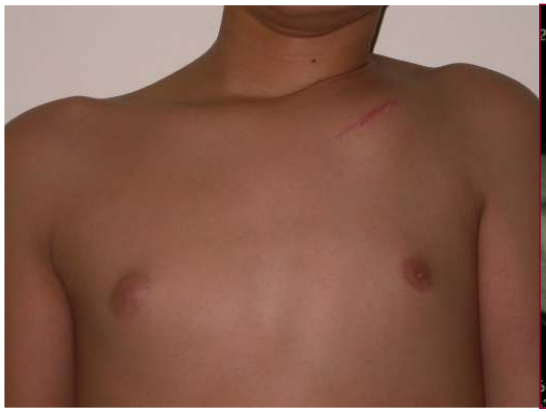
Usually harbours *USP6* gene rearrangement

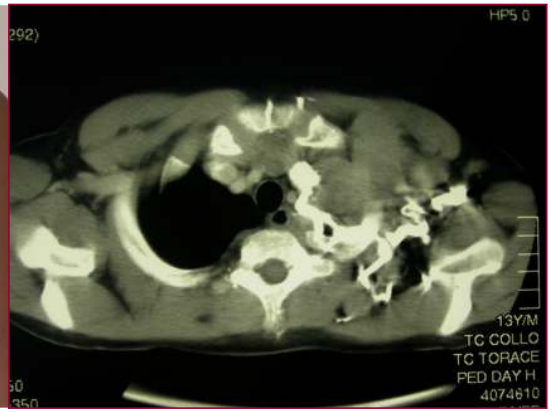






Desmoid Fibromatosis



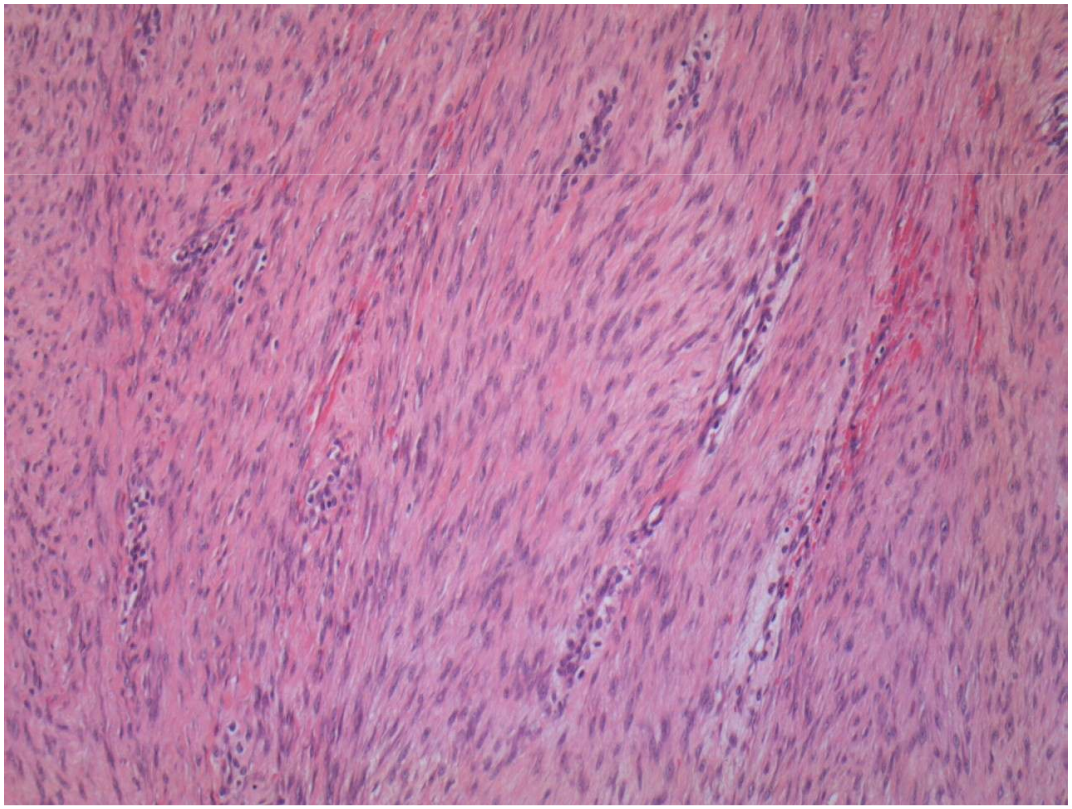


Locally aggressive but non-metastasizing deep-seated (myo)fibroblastic neoplasm with infiltrative growth and **propensity for local recurrence (especially after incomplete resection.**

Site: extremities (30–40%). retroperitoneum or abdominal cavity (15%), abdominal wall (20%), chest wall (10–15%). Other sites:head and neck, paraspinal region, flank

Molecular findings:

- Sporadic: 90–95% point mutations in the gene that encodes β-catenin (CTNNB1)
- Gardner syndrome: germline mutations in the APC tumour suppressor gene



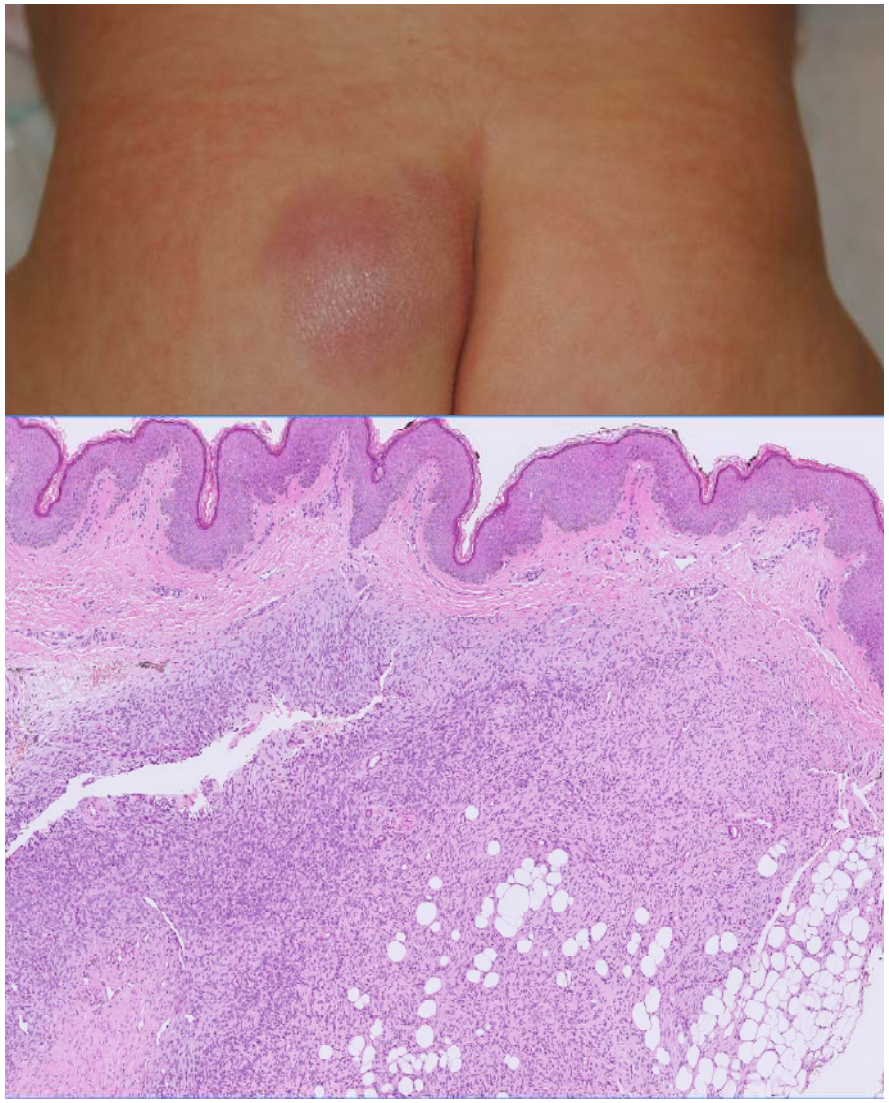
Dermatofibrosarcoma protuberans

1/100.000, rare in children (6% of all DFSP)
Pts are young/adults; more frequently male

Slow growing, firm, nodular dermal/subcutaneous mass, often present years before diagnosis in the trunk , extremities, less frequently head and neck

Histology: Infiltration of dermis and subcutis. cytologically uniform spindled tumour in storiform, whorled, or cartwheel growth patterns. Cytological atypia is minimal and mitotic activity is low.

Recurrence rate 1-9% (20-50% in adults) , Rare mets



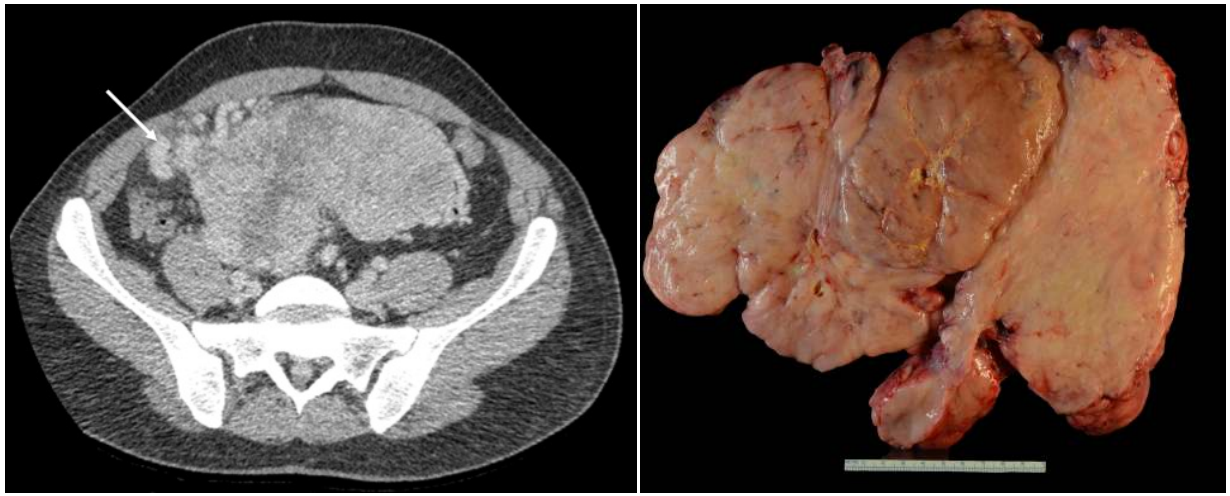
Solitary Fibrous Tumor

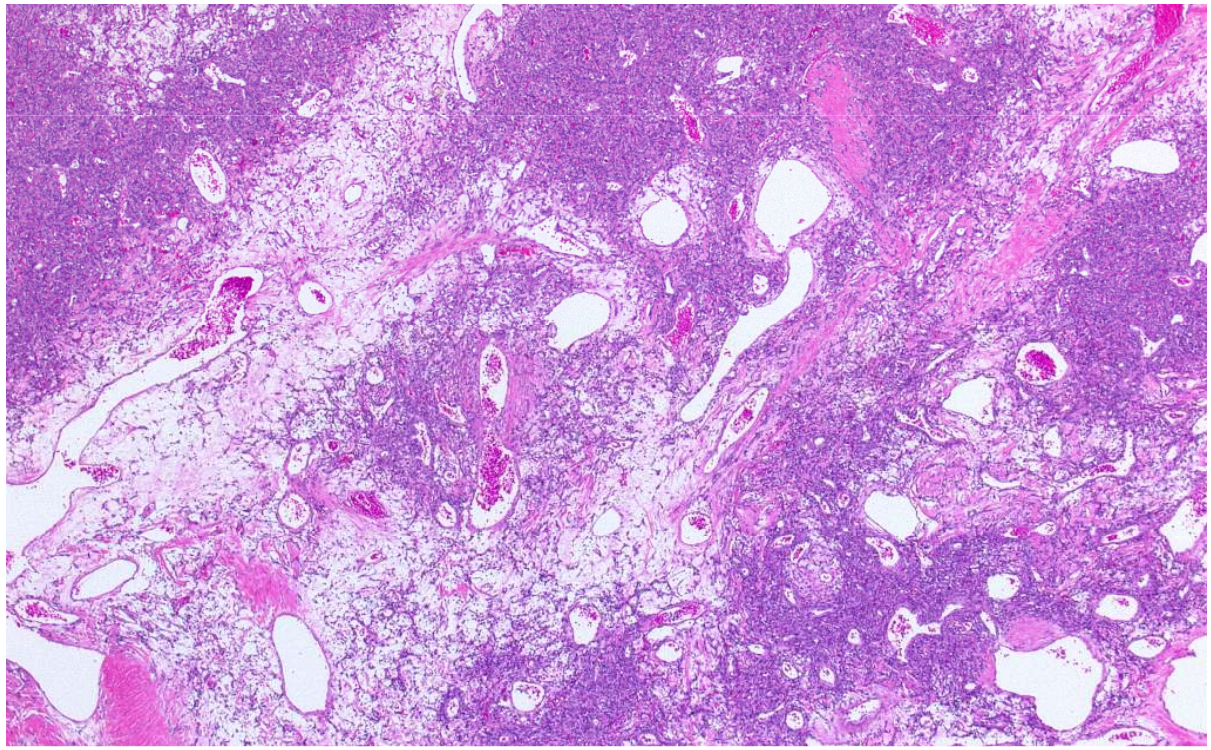
Adults

Localization:any anatomical site, including superficial and deep soft tissues (80-90%) and visceral organs

Slow-growing, painless masses. Paraneoplastic syndromes: Doege–Potter syndrome, severe hypoglycaemia or (more rarely) acromegaloid changes due to tumour production of IGF2

prominent, branching, thin-walled, dilated (staghorn) vasculature and NAB2-STAT6 gene rearrangement.





Soft Tissue Sarcomas

Smooth muscle tumours

- Leiomyoma
- EBV-associated smooth muscle tumour
- Inflammatory leiomyosarcoma
- Leiomyosarcoma

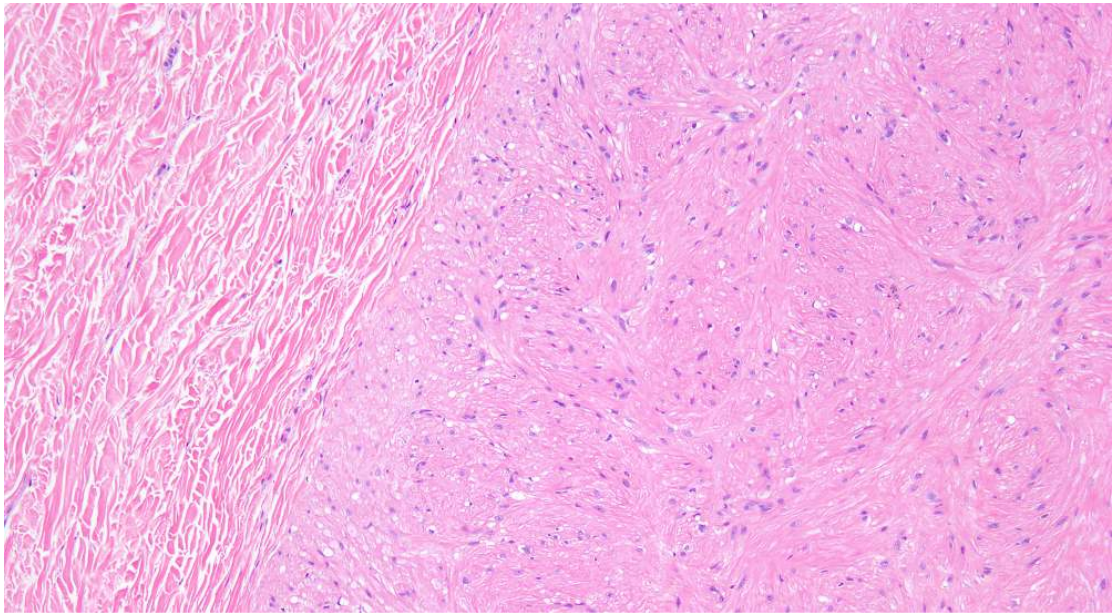
Leiomyoma

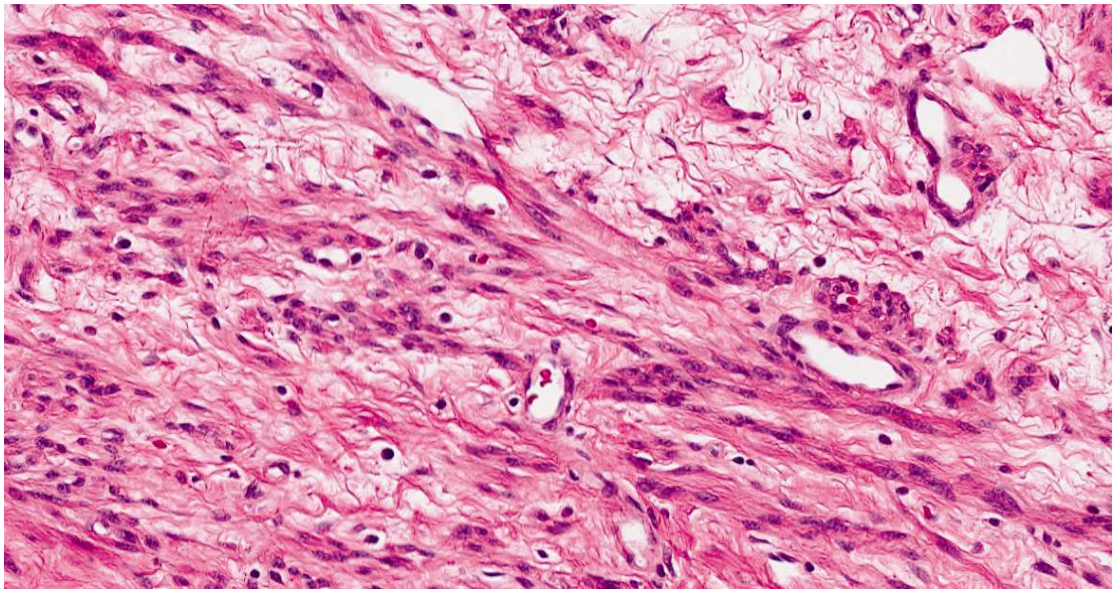
Benign smooth muscle tumour of somatic soft tissue
Middle-aged adults,

Cutaneous (from wall of blood vessels (vascular leyomyoma) or erector hair follicle muscle (pilar leyomyoma)

Deep soft tissue: retroperitoneal
with no sex difference
omentum, mesentery, and peritoneal surface, inguinal region
Although usually solitary, retroperitoneal tumours may be multiple

Histology:
Cells that closely resemble normal smooth muscle cells with eosinophilic cytoplasm and uniform blunt-ended, cigar-shaped nuclei. arranged in intersecting fascicles.





Leiomyosarcoma (LMS)

Definition: A malignant neoplasm composed of cells showing smooth muscle differentiation.

Site: Soft tissue (extremities, retroperitoneum, abdomen/pelvis, and trunk, large blood vessels (inferior vena cava, the large veins of the lower extremity)

Epidemiology: 7th decade, 11% of all soft tissue sarcomas

Women constitute the majority of patients with retroperitoneal and inferior vena cava LMSs

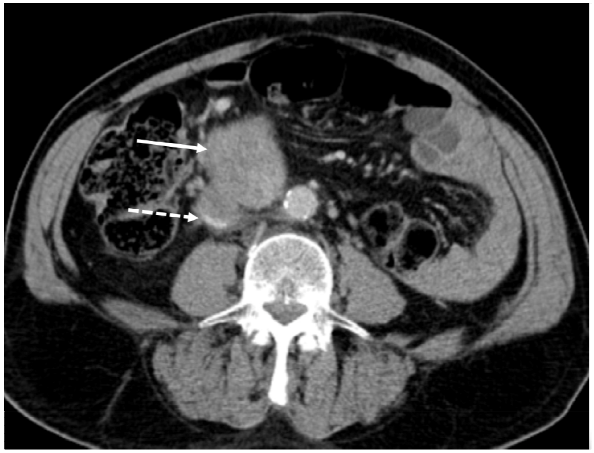
Progosis: aggressive neoplasms with local recurrences and distant metastases.

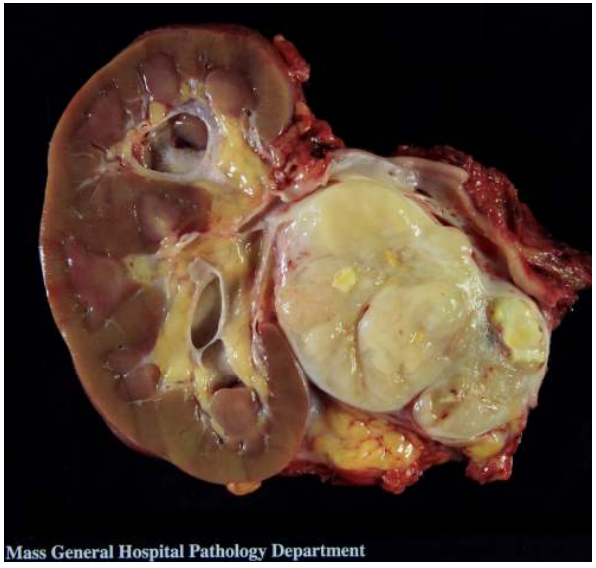
Prognostic factors: histological grade, tumour location and size

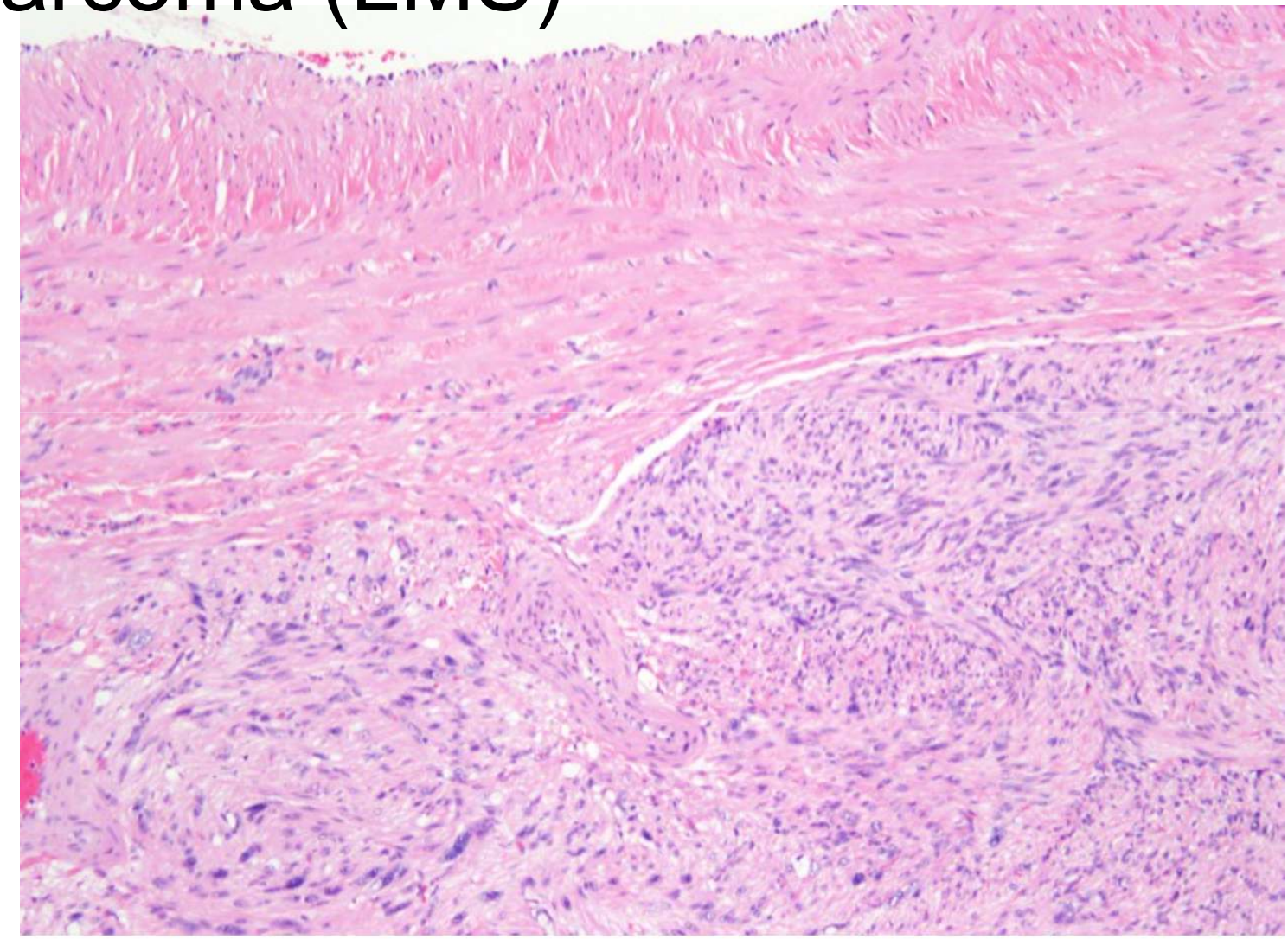
Retroperitoneal LMSs often fatal; typically large (> 10 cm), difficult or impossible to excise with clear margins

Non-retroperitoneal LMSs are generally smaller, more amenable to local control, and better prognosis. intramuscular rather than subcutaneous related to increased metastasis and poorer survival. Metastases in lung, liver, and soft tissue, and more rarely in bone

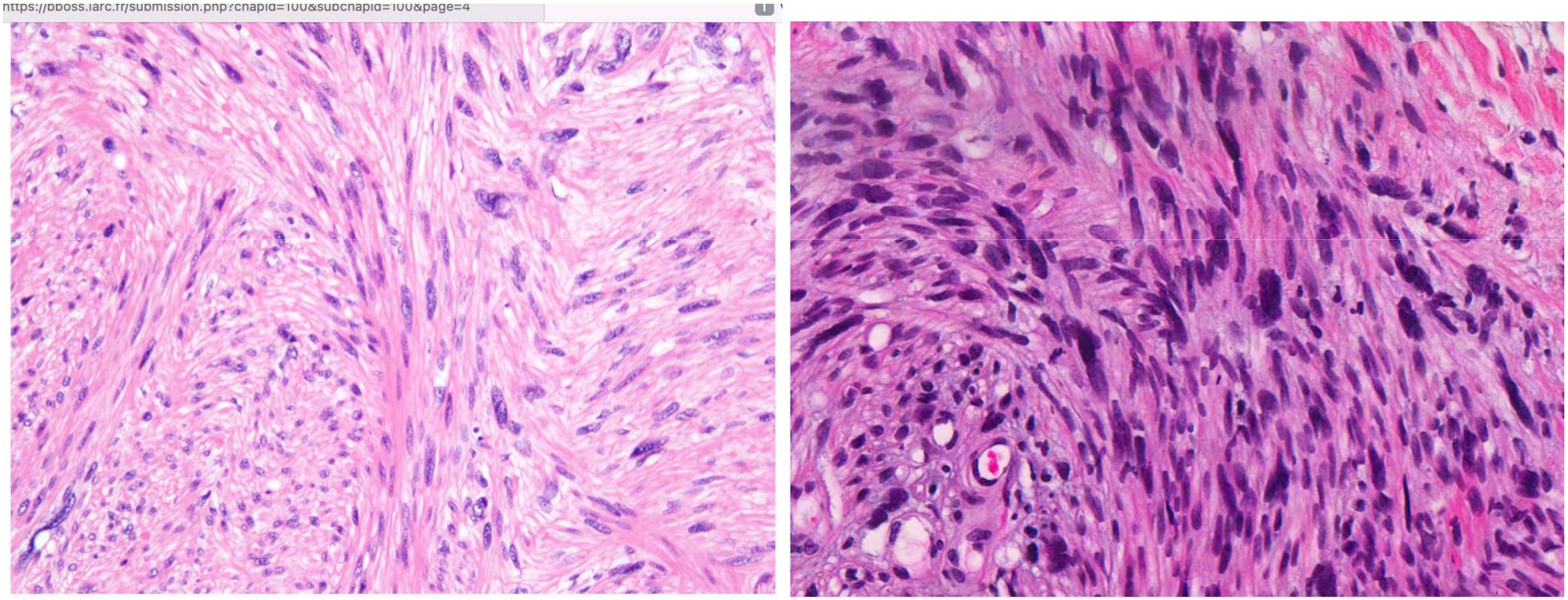
Leiomyosarcoma (LMS)







Leiomyosarcoma (LMS)



Soft Tissue Sarcomas

Skeletal muscle tumours

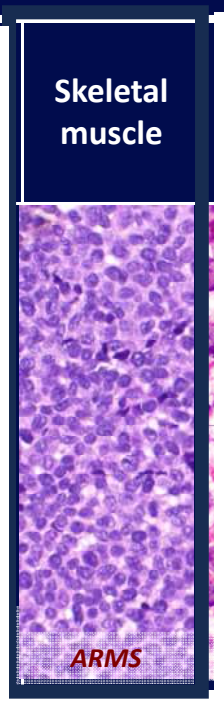
- Rhabdomyoma
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma
- Spindle cell / sclerosing rhabdomyosarcoma
- Ectomesenchymoma

Gastrointestinal stromal tumour

- Gastrointestinal stromal tumour

Chondro-osseous tumours

- Soft tissue chondroma
- Extraskeletal osteosarcoma



Rhabdomyosarcoma

Most frequent pediatric sarcoma

Malignant mesenchymal tumor with morphologic and/or immunophenotype of embryonal skeletal muscle

Prognosis related to:

Histology/Molecular features underlying RMS

Site

- Favorable (GU,non VP; Orbit; Head/neck non PM)
- Unfavorable (GU-VP, Extremities, Head/neck PM)

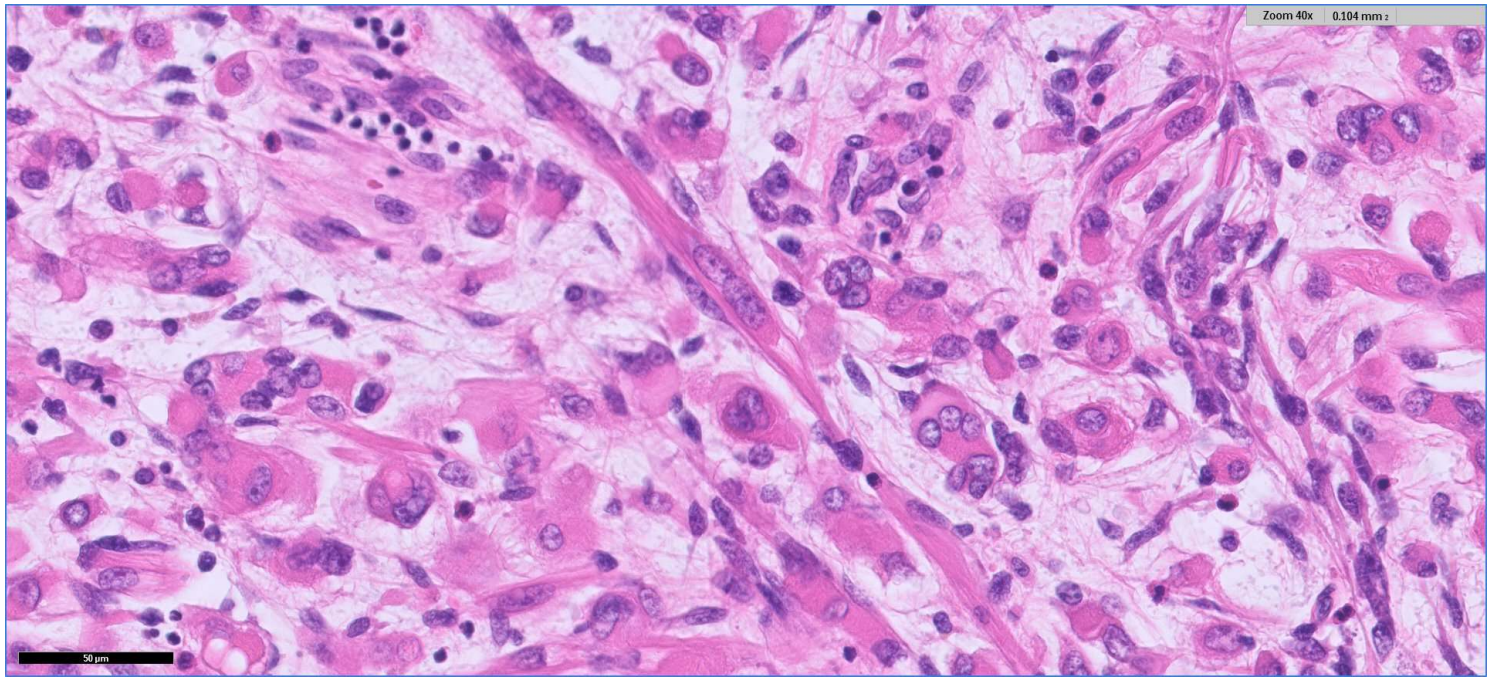
Age

Size

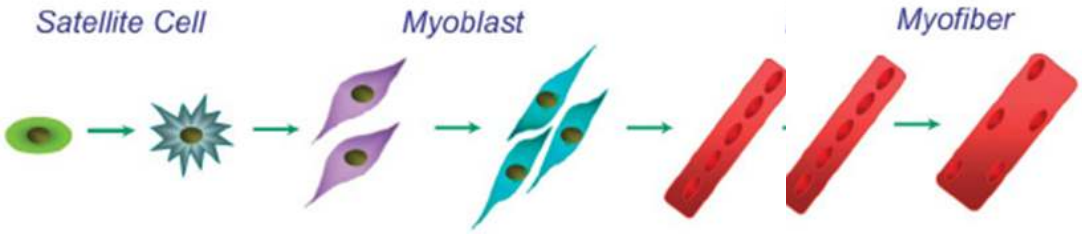
Stage (IRS)

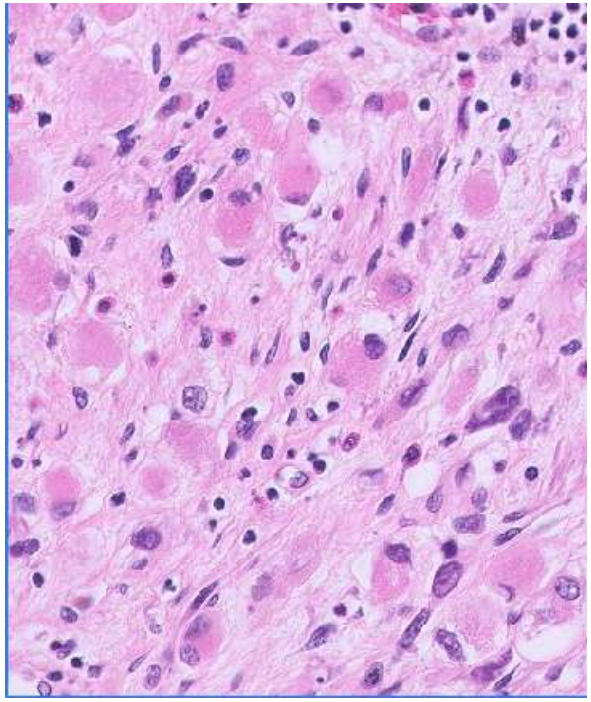
Rhabdomyosarcoma: Definition

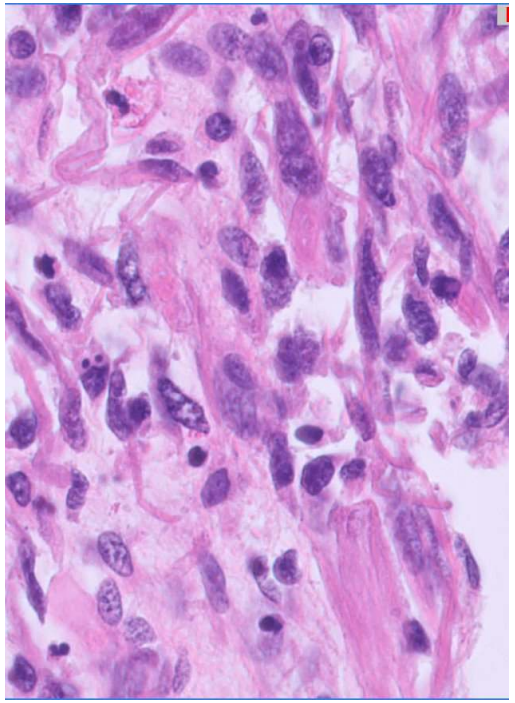
Malignant mesenchymal tumor with morphologic and/or immunophenotypic features of embryonal skeletal muscle

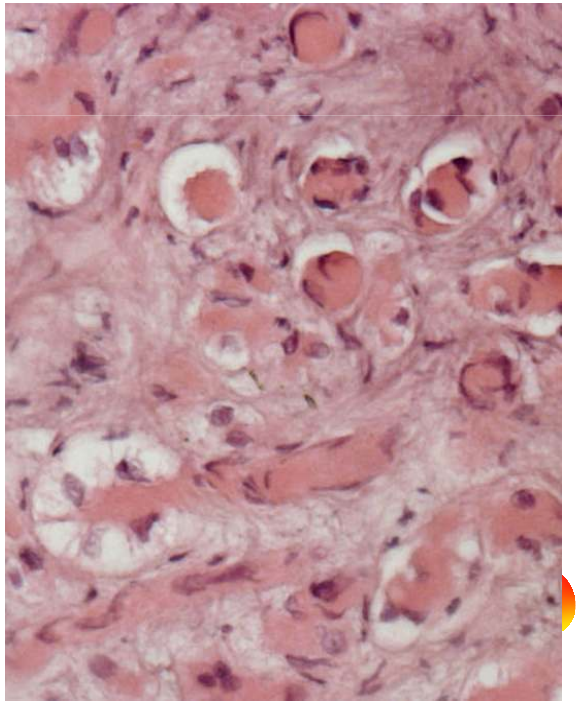


Rhabdomyosarcoma reproduces skeletal muscle development



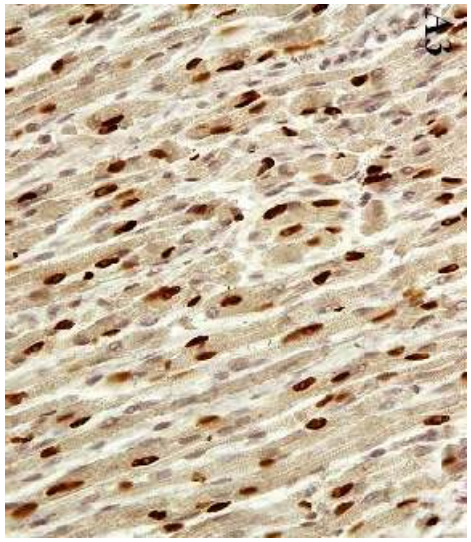




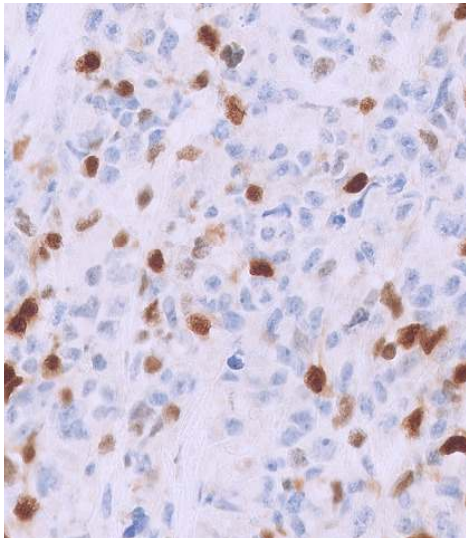


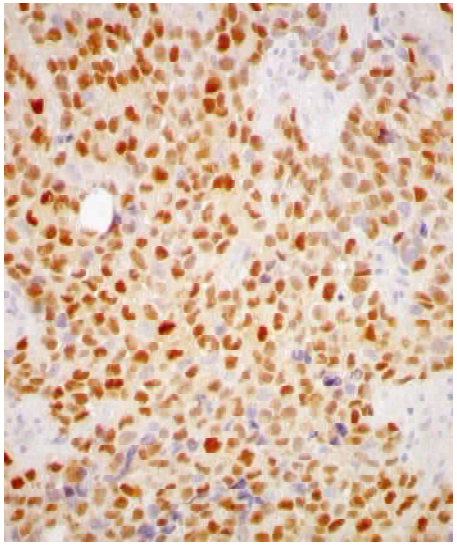
Rhabdomyosarcoma: Immunophenotype

Transcription Factors



Normal skeletal Muscle





Rhabdomyosarcoma

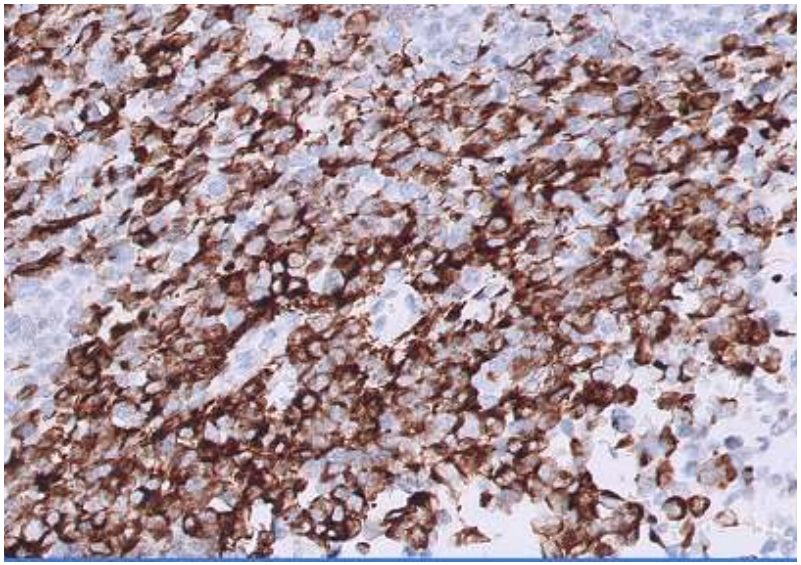
Pax7

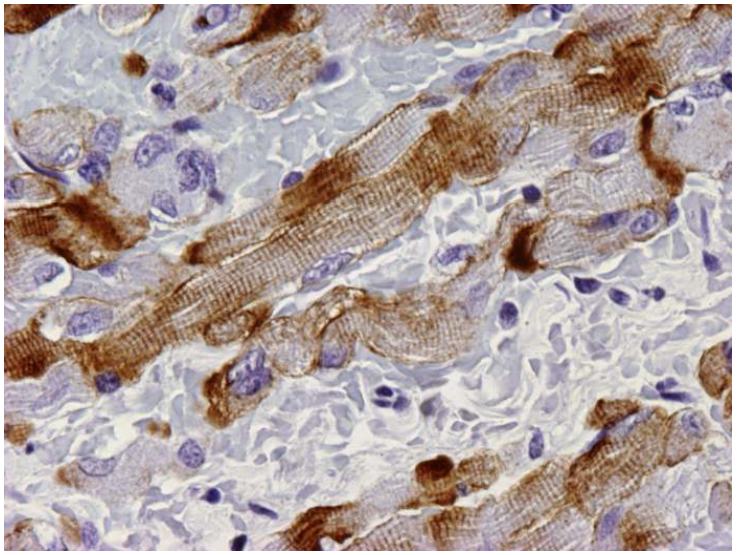
MyoD

Myogenin

Rhabdomyosarcoma: Immunophenotype

Intermediate Filaments: Desmin





Desmina

Rhabdomyosarcoma: WHO Classification 5th Edition

General Features

Classification

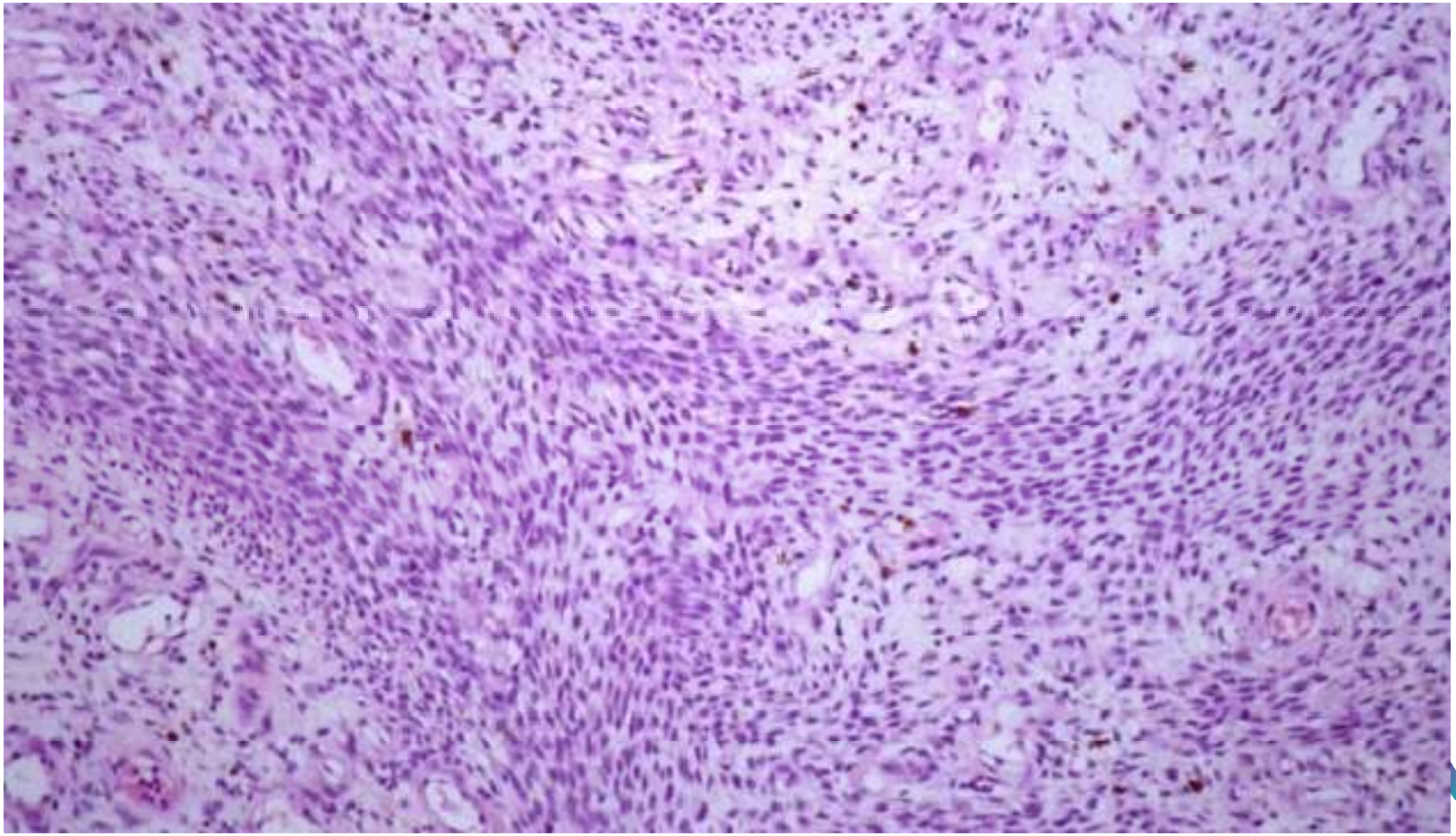
Histotypes

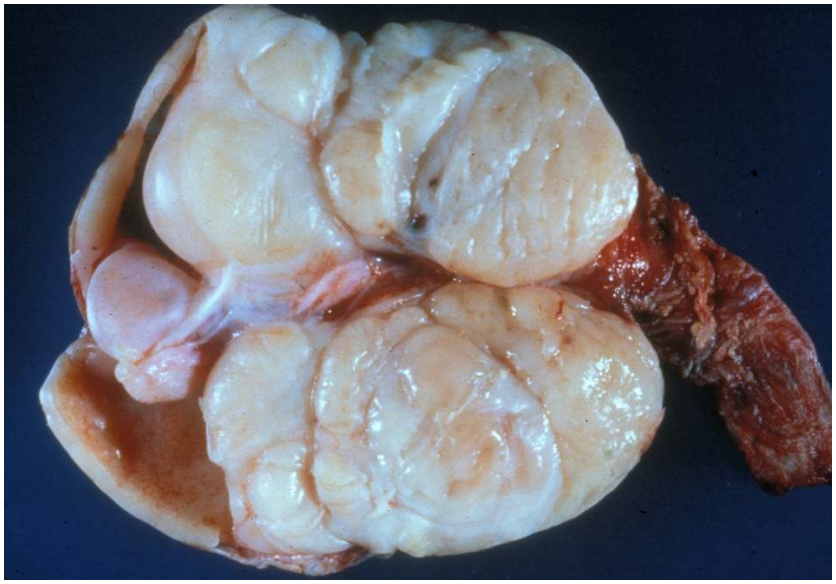
RMS in Tumor predisposition syndromes

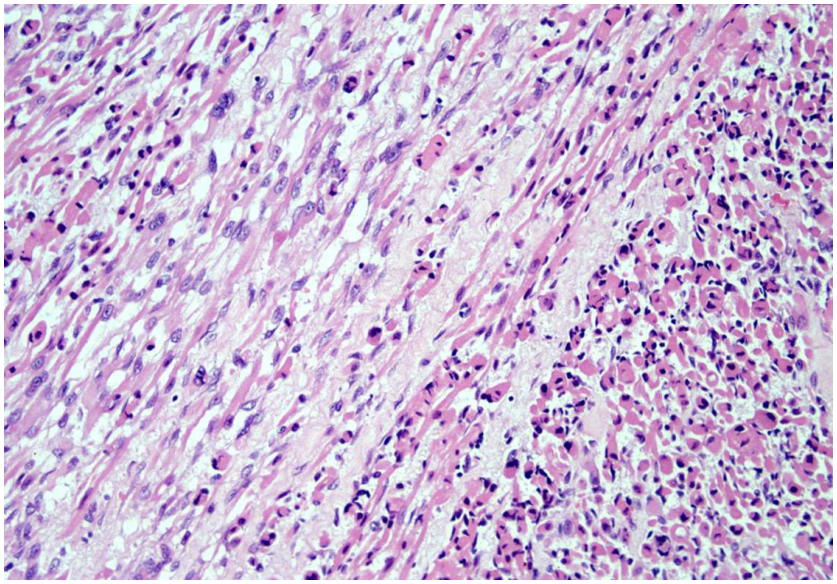
HISTOLOGY*	Age (yr)	Site
ERMS	0-5 (18% >10)	Head/neck GU-tract. orbit, bile ducts, retroperitoneum
SPINDLE/SCLEROSING RMS	Infantile	back
	Older children, adults	head and neck, trunk and extremities
	Older children, adults	Bone, facial bones
ARMS	6.8-9	extremities, paraspinal, perineal, breast

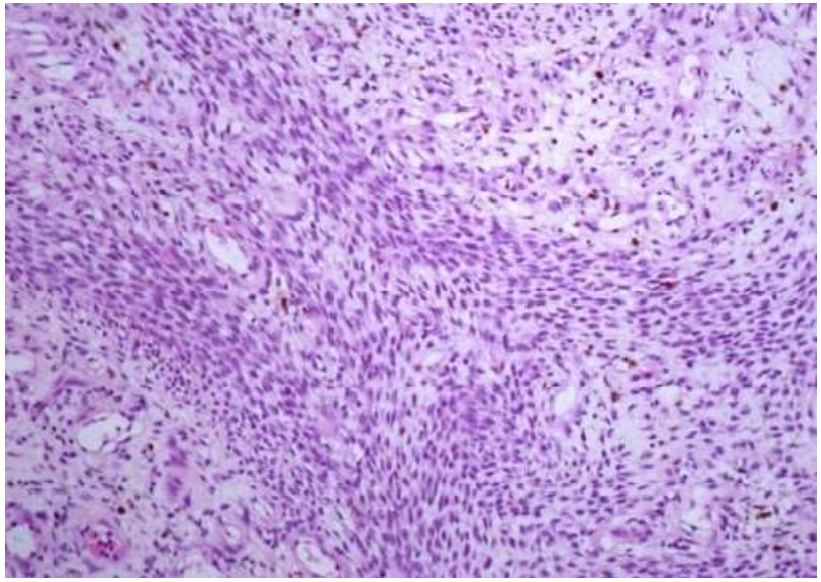
* Pleomorphic RMS are extremely rare in children

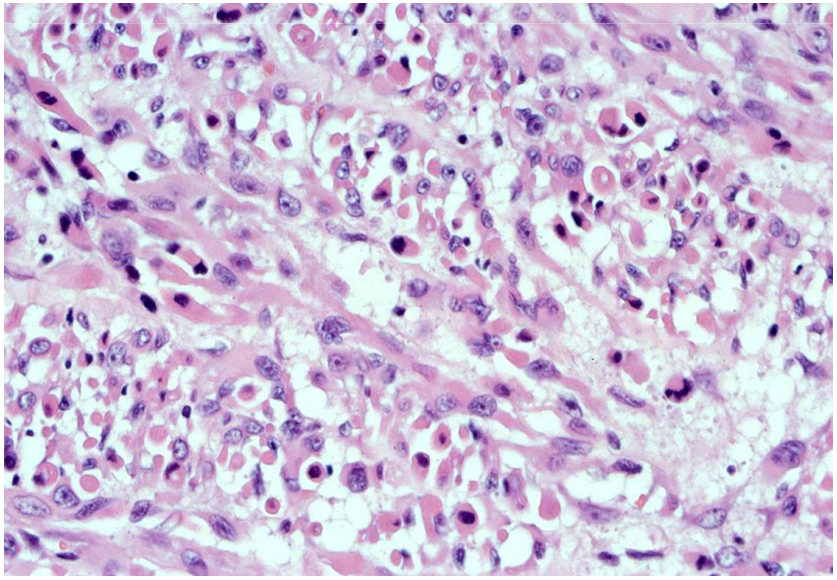
Embryonal Rhabdomyosarcoma: histological Features



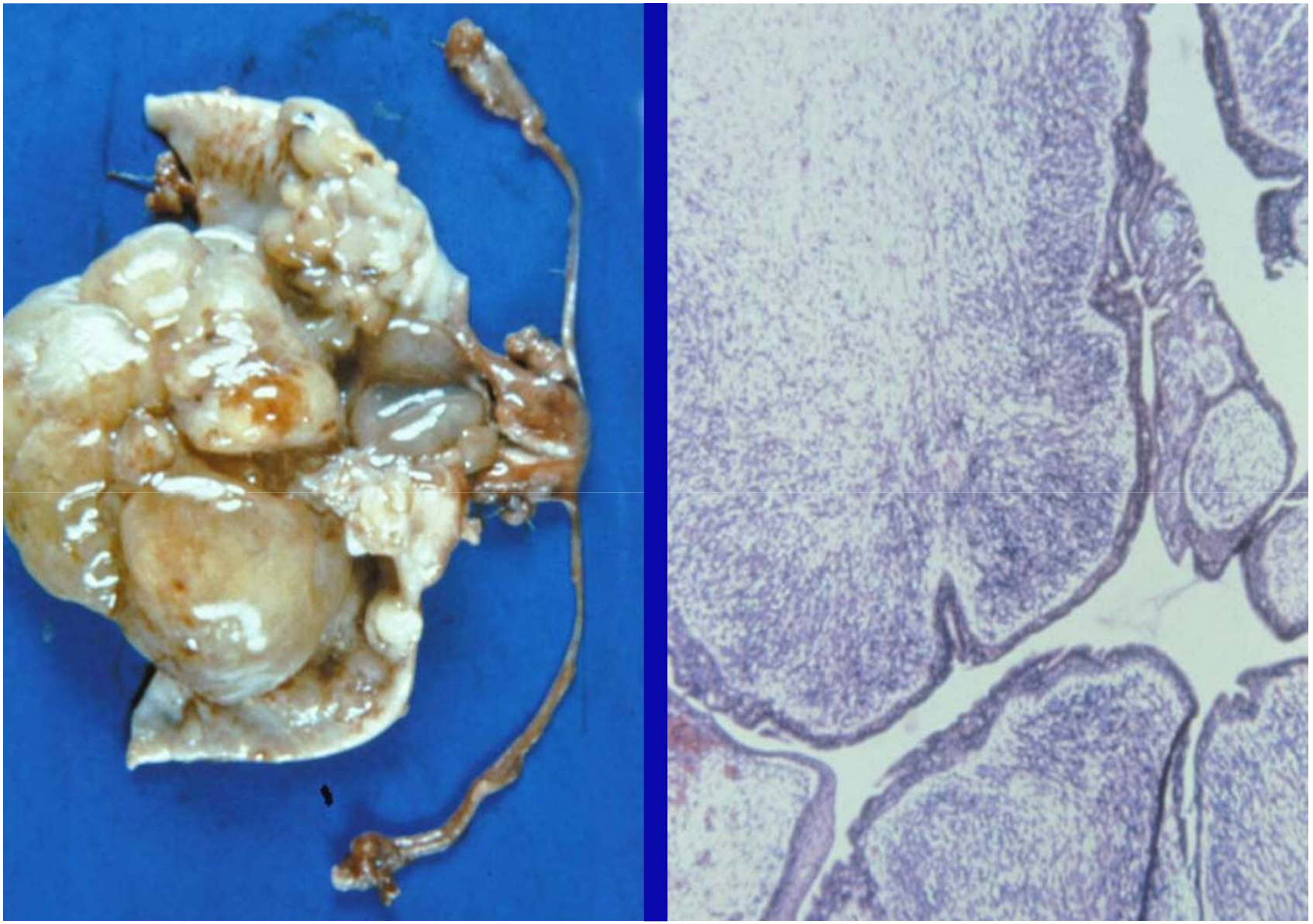


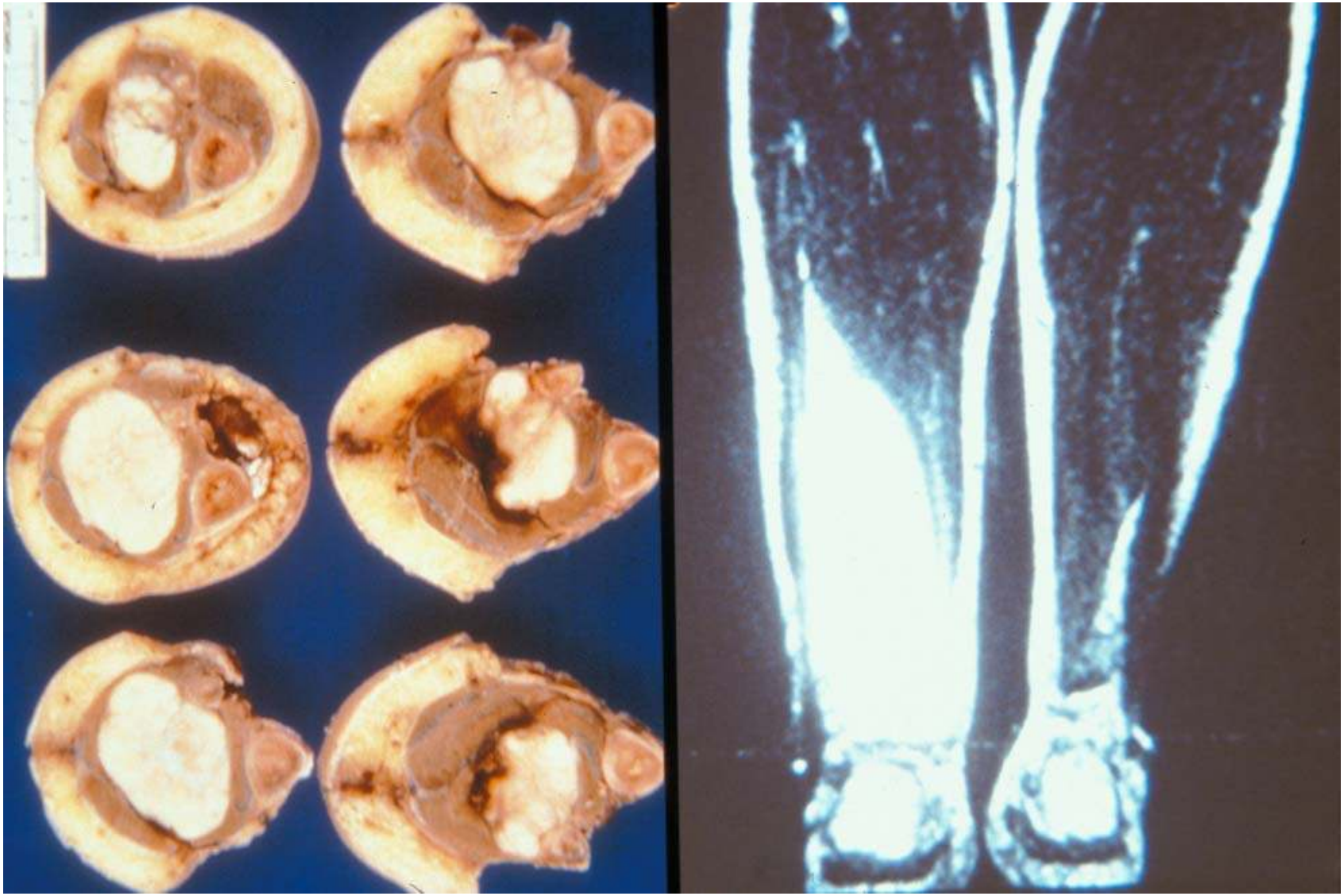






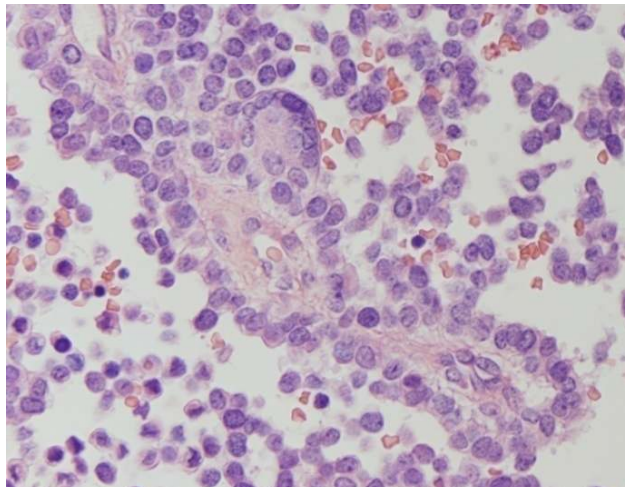
ERMS

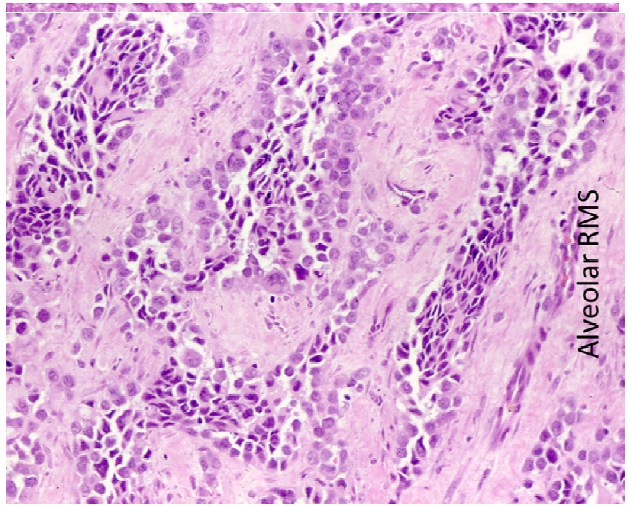


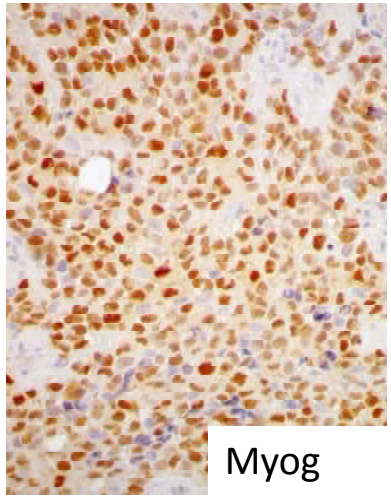


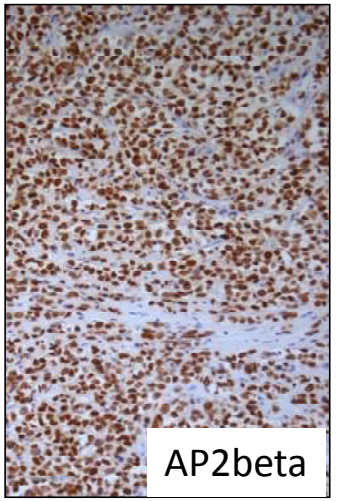
Alveolar Rhabdomyosarcoma

HISTOLOGY	Age (yr)	Site	Prognosis	FUSIONS
ARMS	6.8-9	extremities, paraspinal, perineal, breast	Unfavorable	PAX3/7-FOXO1

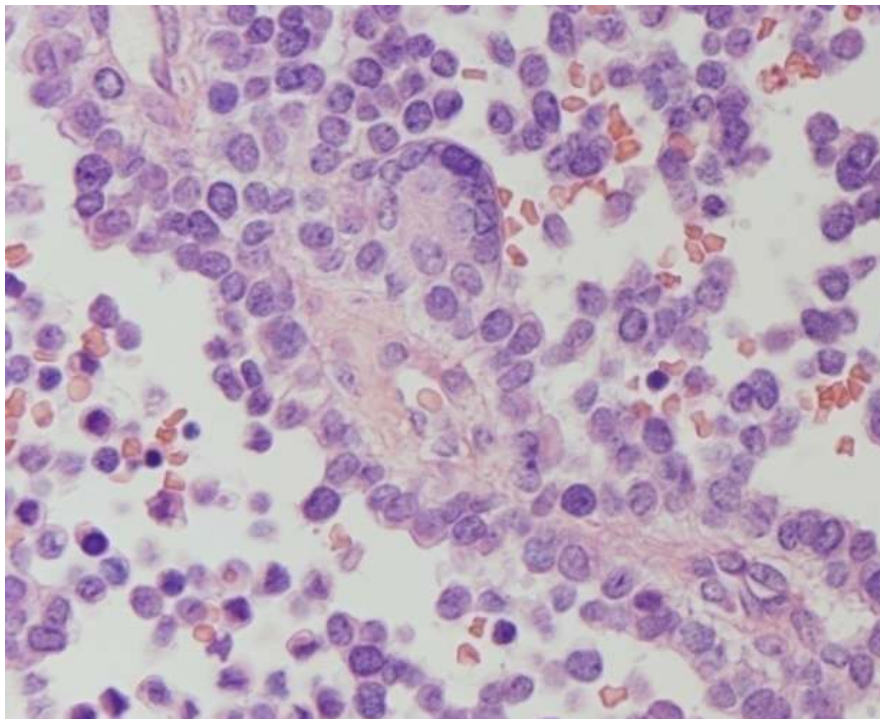


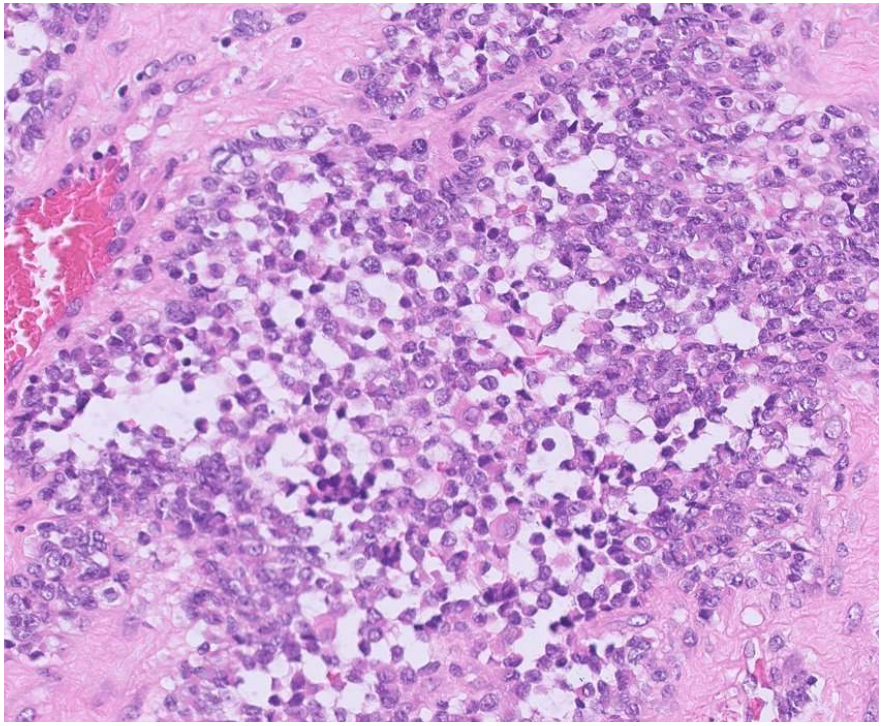






Alveolar Rhabdomyosarcoma: histological Features





Spindle/Sclerosing RMS: Histology

General Features

Classification

Histotypes

RMS in Tumor predisposition syndromes

Age (yr)	Site	Prognosis	FUSIONS
Infantile (1)	back	Favorable	NCOA2,VGLL2 fusions
Older children, adults (2,3)	head and neck, trunk and extremities	poor	MyoD1 mut ((L122R) *
Older children, adults	Bone, facial bones	poor	*FUS/EWSR1::TFCP 2*

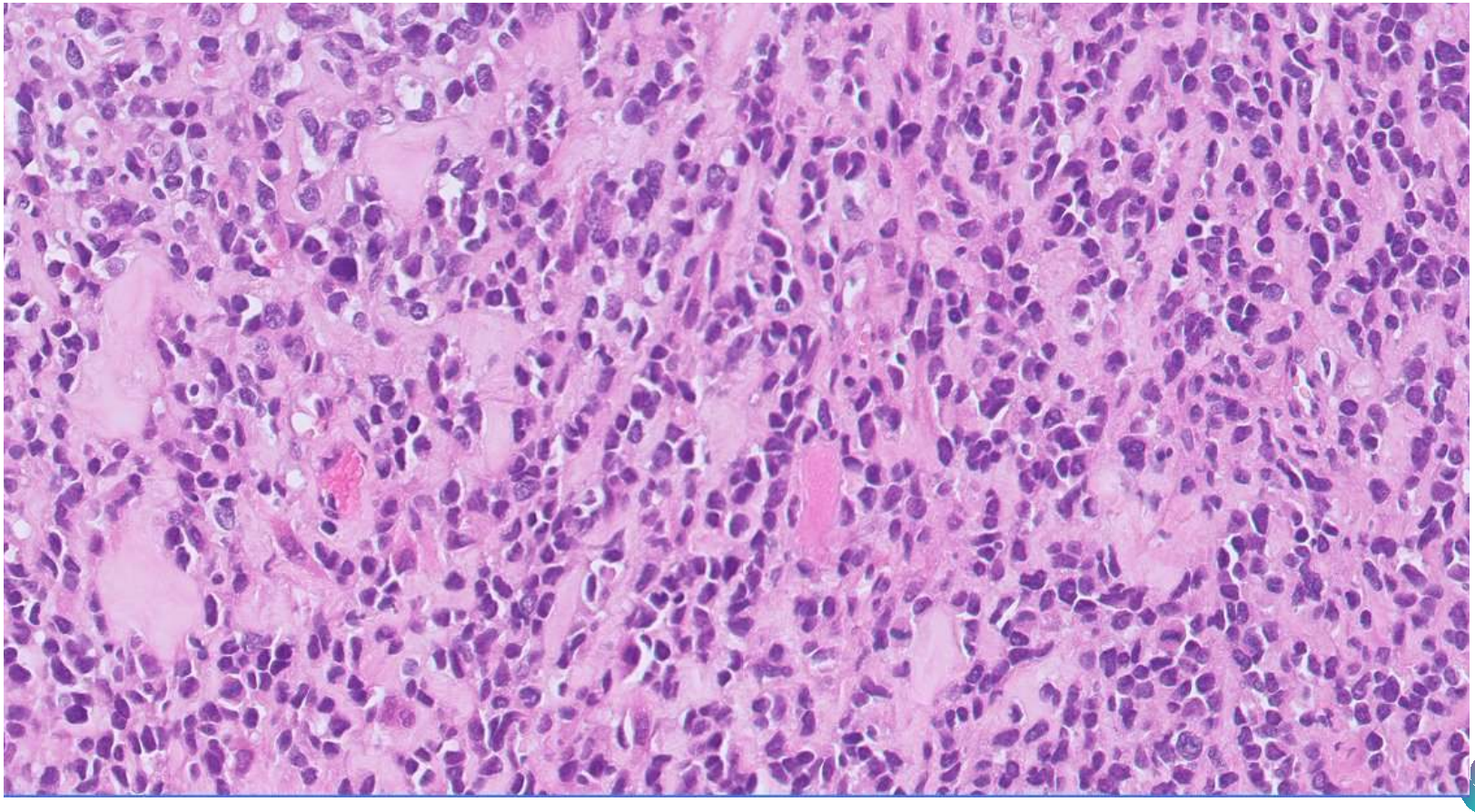
*Associated alterations of PIK3CA (53%); deep deletions in CDKN2A (24%).

Genomic Classification and Clinical Outcome in Rhabdomyosarcoma: A Report From an International Consortium

Jack F. Shern, MD[1,2]; Joanna Selfe, PhD[2]; Elisa Izquierdo, MD[1]; Rajesh Patidar, MS[1]; Hsien-Chao Chou, PhD[1]; Young K. Song, PhD[1]; Marielle E. Yohe, MD, PhD[2]; Sivasish Sindiri, MS[1]; Jun Wei, PhD[1]; Xinyu Wen, MS[1]; Erin R. Rudzinski, MD[3]; Donald A. Barkauskas, PhD[2,4]; Tammy Lo, MPH[2]; David Hall, MS[2]; Corinne M. Linardic, MD, PhD[5]; Debbie Hughes, PhD[5]; Sabri Jamal, MSc[4]; Meriel Jenney, MD[15]; Julia Chisholm, MD[11]; Rebecca Brown, MD[2,12]; Kristine Jones, PhD[13]; Belynda Hicks, PhD[13]; Paola Angelini, MD[11]; Sally George, MD[2,11]; Louis Chesler, MD[2]; Michael Hubank, MD[4]; Anna Kelsey, MD[14]; Susanne A. Gatz, MD[2,16]; Stephen X. Skapek, MD[16]; Douglas S. Hawkins, MD[17]; Janet M. Shipley, PhD[2]; and Javed Khan, MD[1]

J Clin Oncol 39:2859-2871

Spindle/Sclerosing RMS: Histology



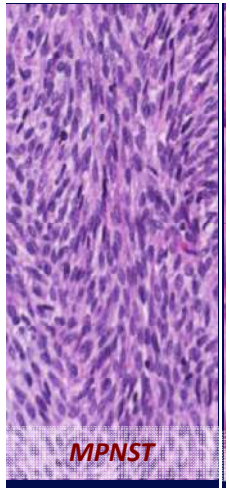
F, Abdominal Mass 14 yr: Sclerosing RMS with MyoD1 mut

Soft Tissue Sarcomas

Peripheral nerve sheath tumours

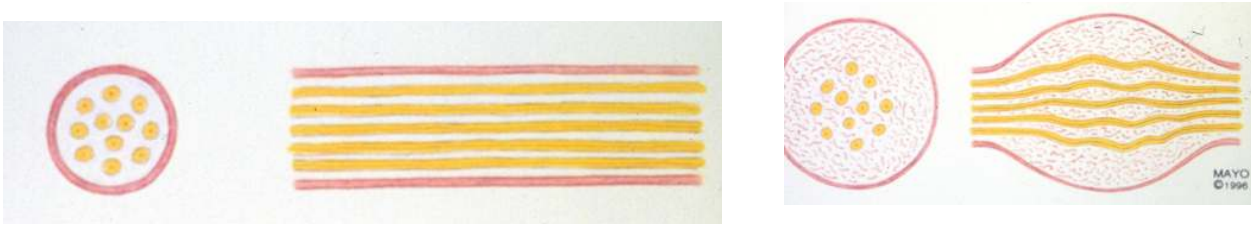
- Schwannoma
- Neurofibroma
- Perineurioma
- Granular cell tumour
- Dermal nerve sheath myxoma
- Solitary circumscribed neuroma
- Ectopic meningioma and meningothelial hamartoma
- Benign triton tumour / neuromuscular choristoma
- Hybrid nerve sheath tumour
- Malignant peripheral nerve sheath tumour
- Malignant melanotic nerve sheath tumour

Peripheral nerve sheath



NEUROFIBROMA

Benign peripheral nerve sheath tumor consisting of differentiated Schwann cells, perineurial-like cells, fibroblasts, mast-cells, residual myelinated and unmyelinated axons embedded in the extracellular matrix



Growth pattern: well-demarcated intraneural
or diffuse infiltration of soft tissue at extraneural sites

NEUROFIBROMA

Solitary NF

Adulthood, broad anatomic location, non NF1 (deep lesions associated with NF1 and malignant change)

Multiple NF

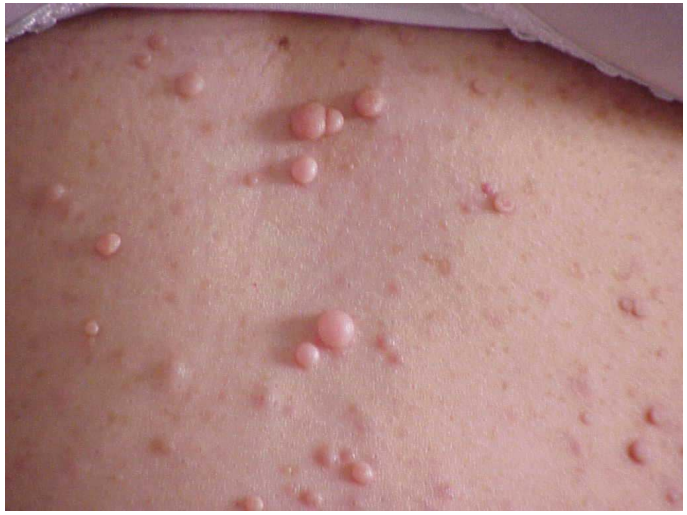
If associated with skin spots: NF1

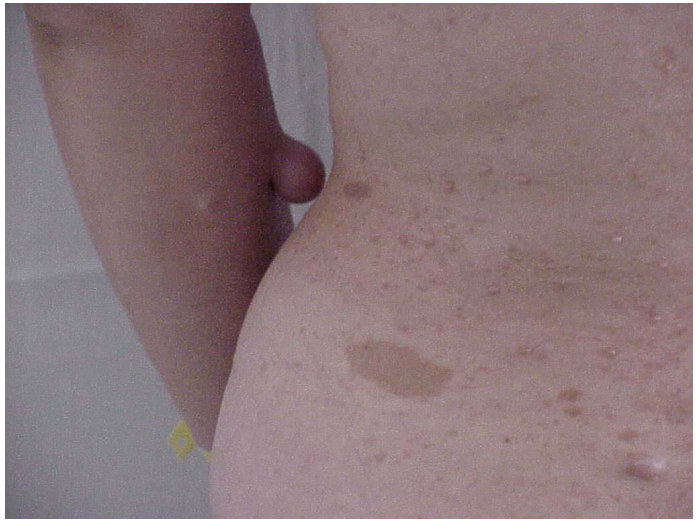
Diffuse NF (NF1)

1st – 3rd decades, trunk and head & neck, 10%, no malignant change

Plexiform NF (NF1)

Children and young adults, head and neck, malignant change





Neurofibromatosis

- NF1: 1/3500 newborn infants.
- Manifestations of NF1 highly variable, even in the same family:

Cafè-au-laits spots

Pigmented iris hamartoma (Lish nodules)

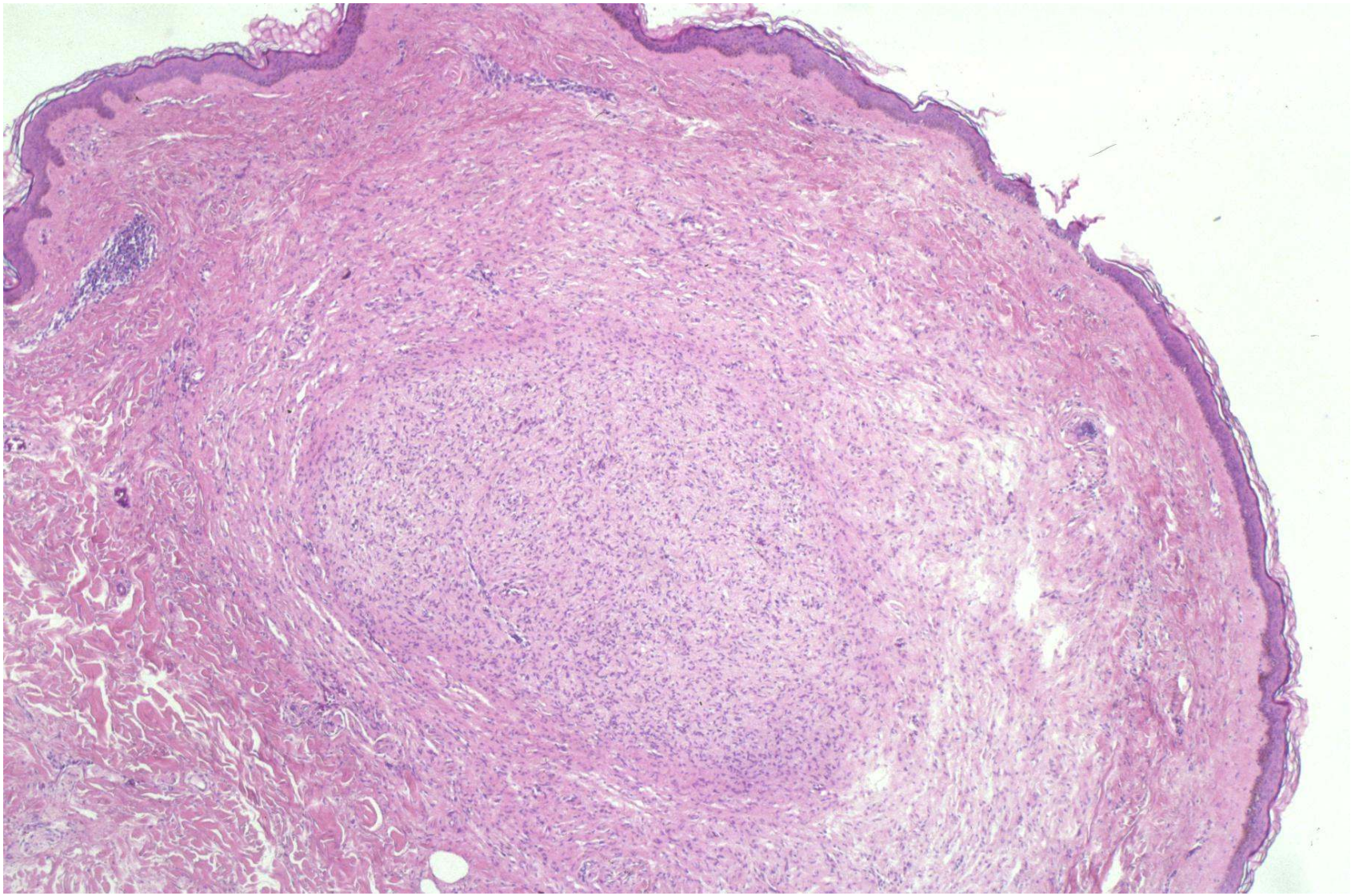
Neurofibromas (plexiform)

Gliomas

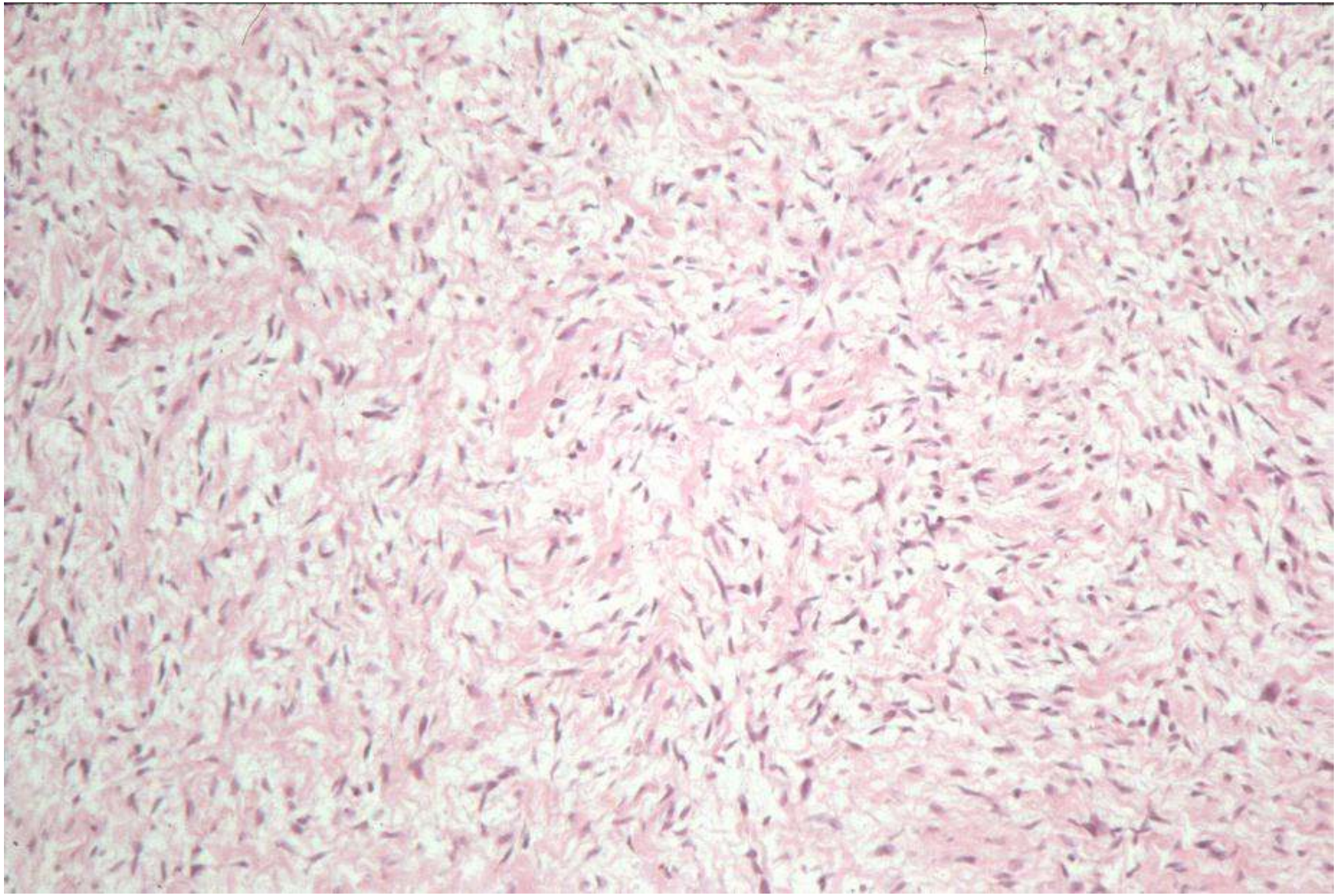
Molecular Features

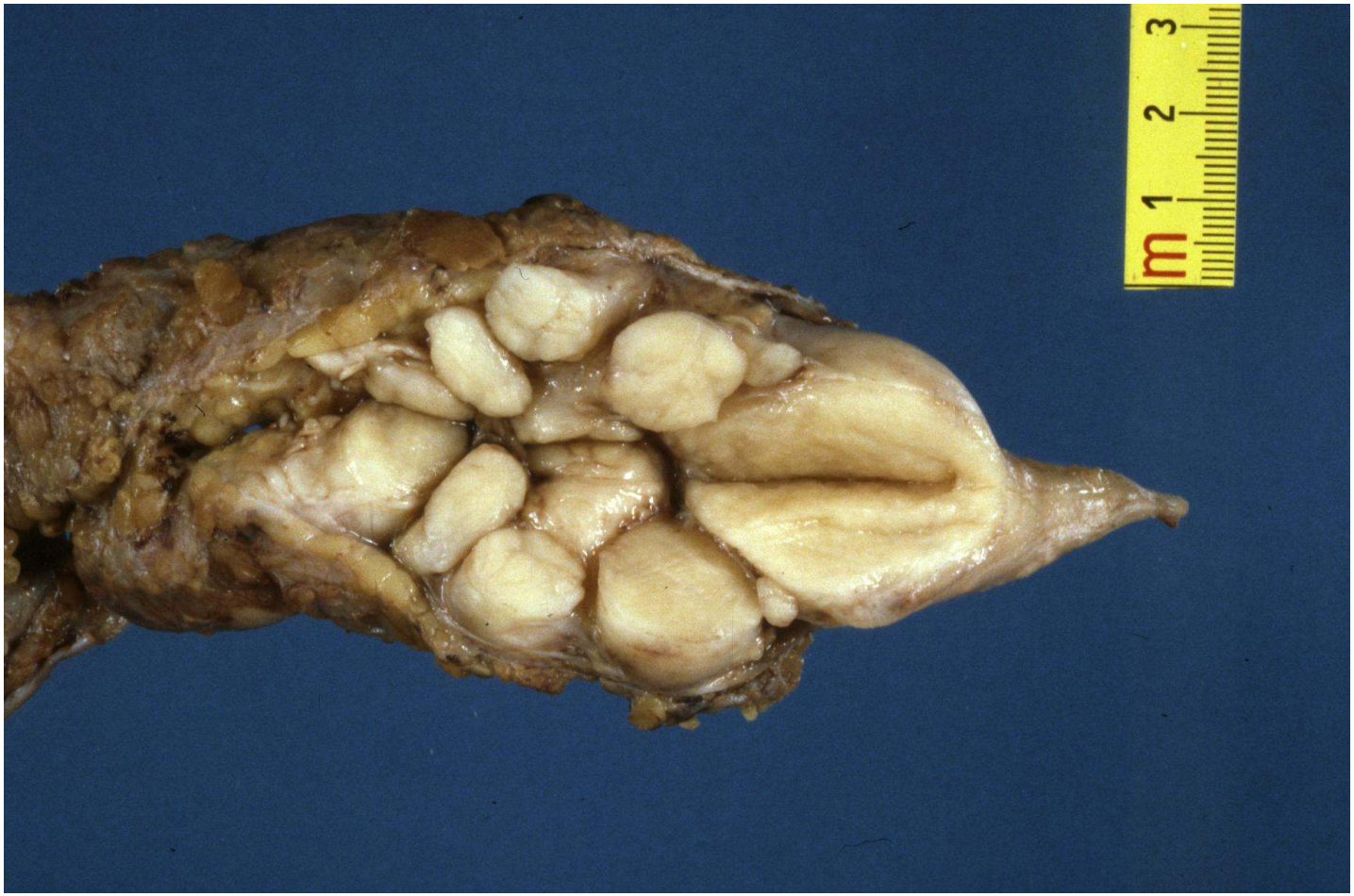
- Inactivation of one allele of neurofibromin 1 (NF1), a tumor suppressor gene (nonsense, missense or frameshift mutations, or mutations affecting RNA splicing)
- Complete deletion rare (5% of NF1)

•

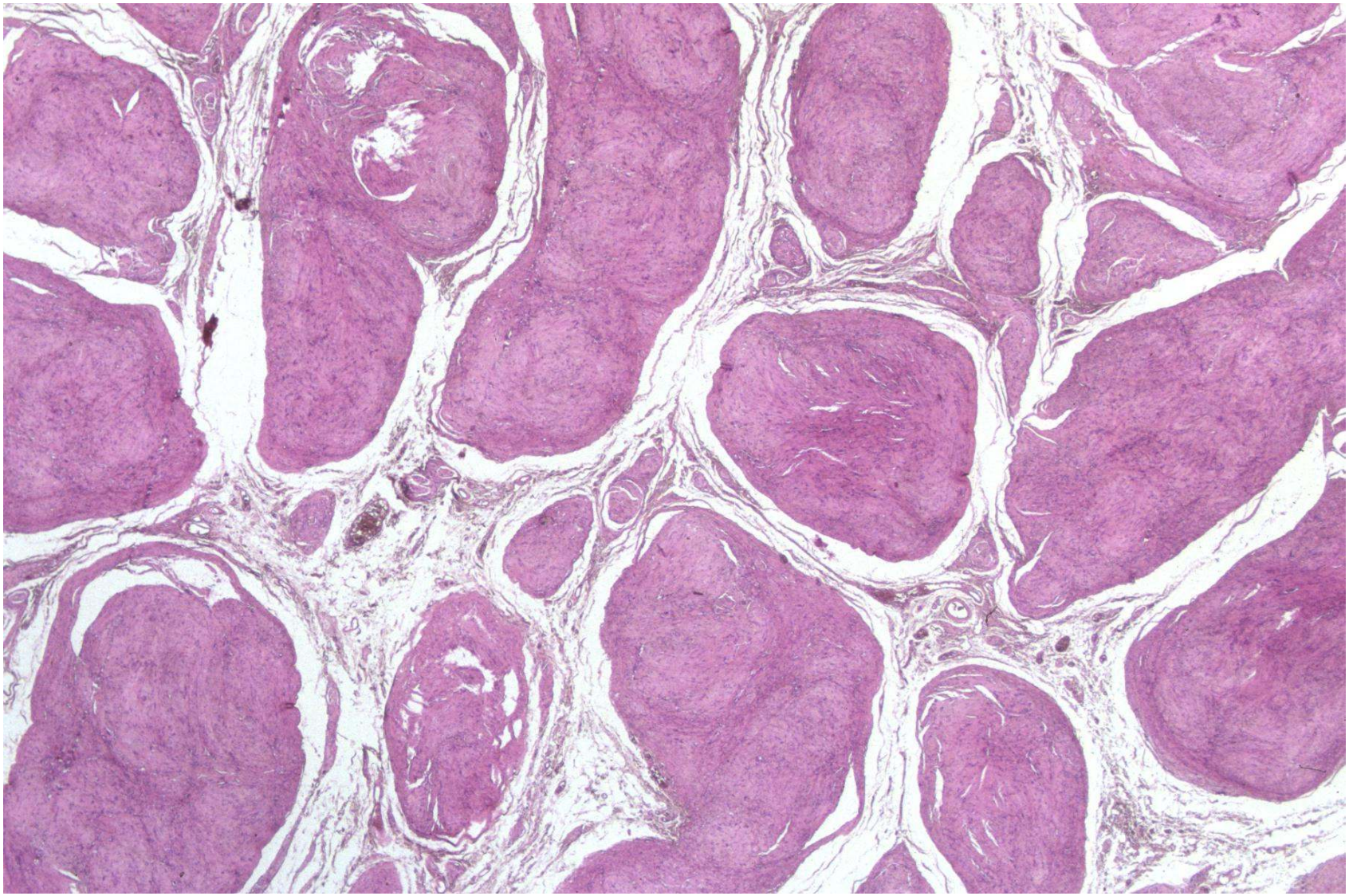


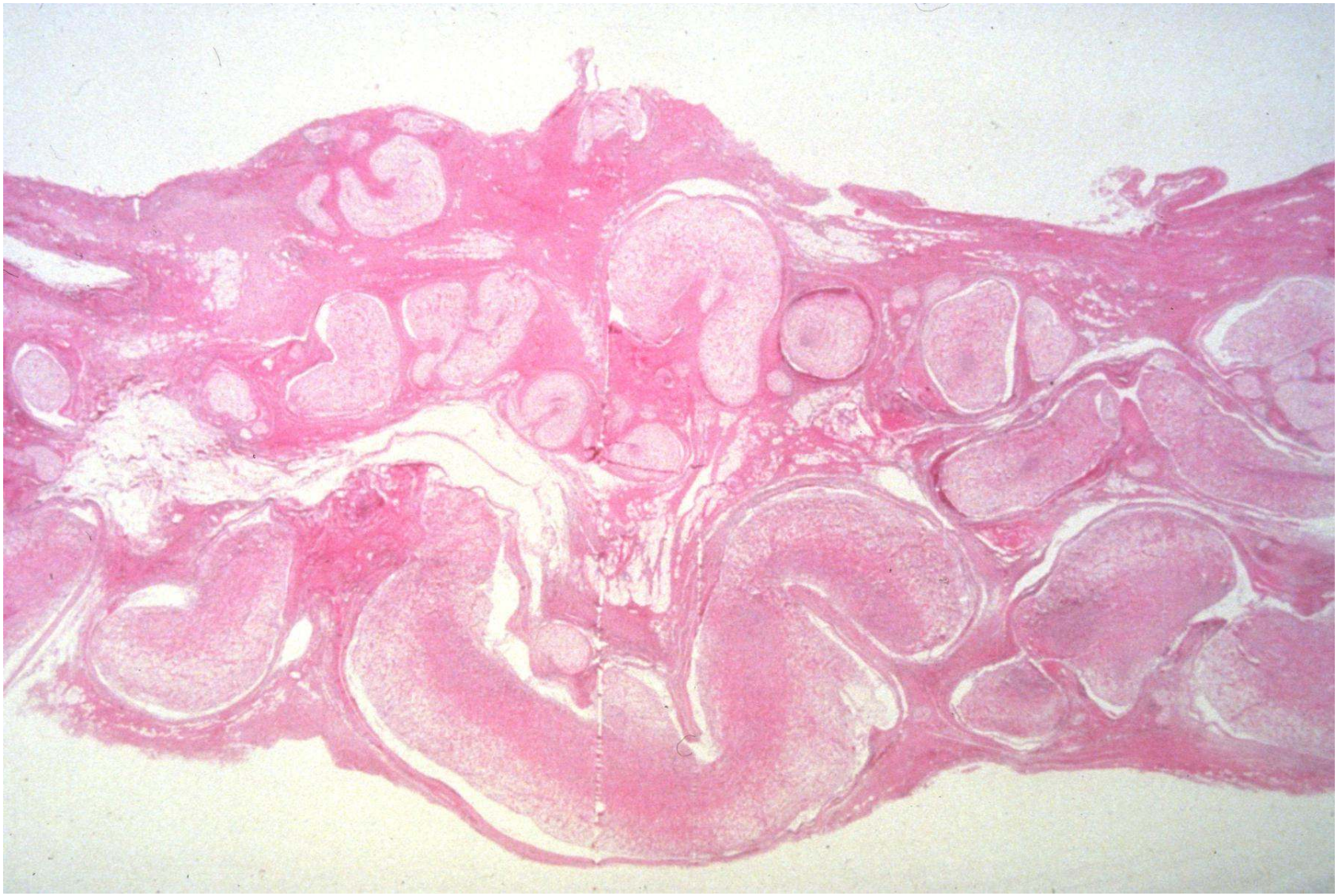
At superficial cutaneous sites,localized, pedunculated growths.





Plexiform neurofibroma in a major nerve trunk almost always associated with NF1.
Generally involvement of numerous adjacent nerve fascicles or
multiple components of a nerve plexus.



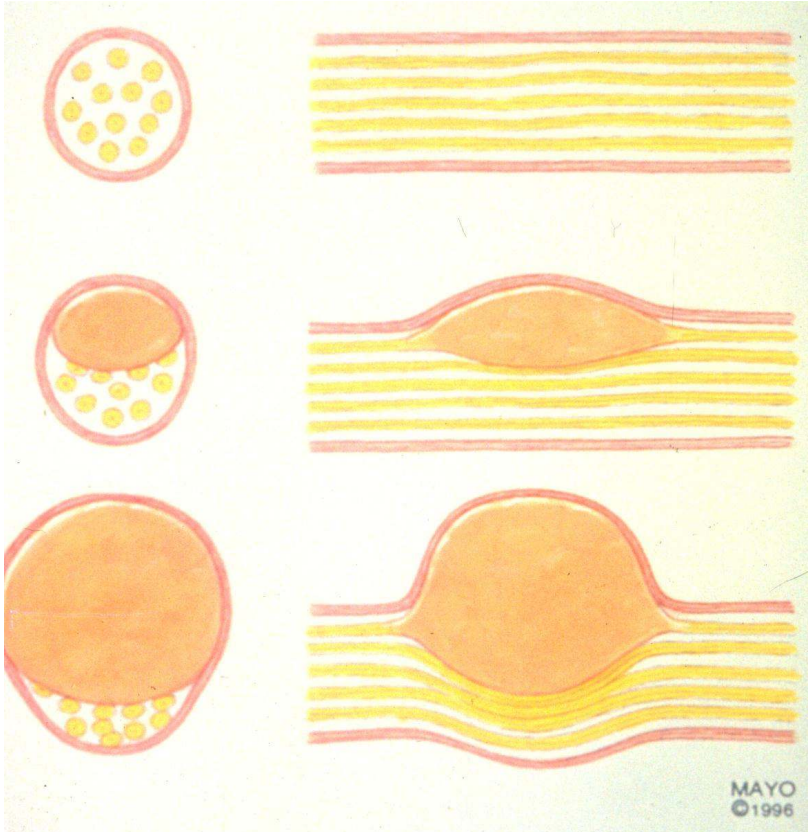


Admixture of areas resembling localized and diffuse-type
neurofibromas. Plexiform neurofibroma has a potential for malignant degeneration, and

Schwannoma

- Adulthood
- M = F
- Wide anatomic distribution
- Bilateral schwannomas of acoustic nerve = NF2 syndrome
- Malignant change exceptional

Schwannoma

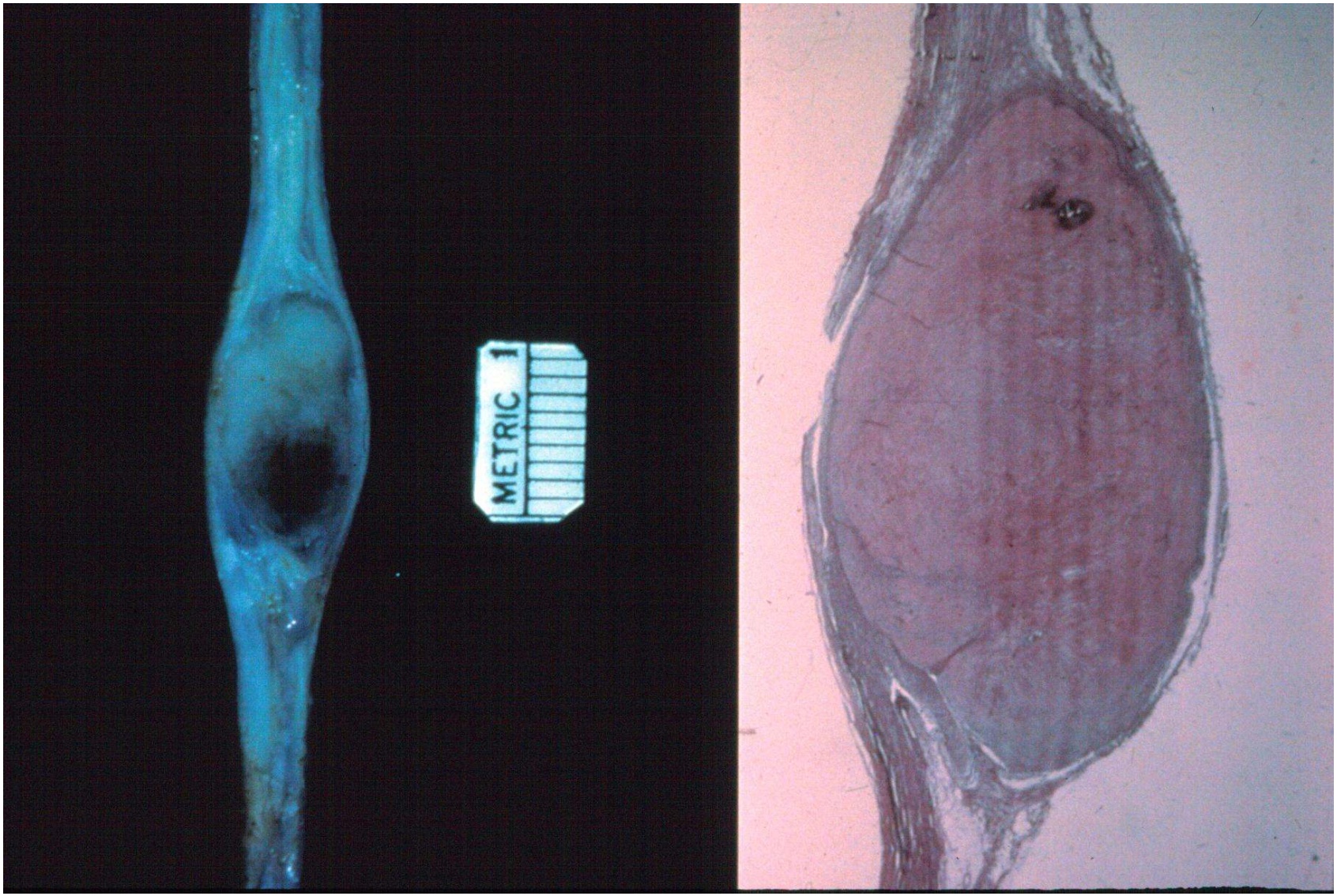


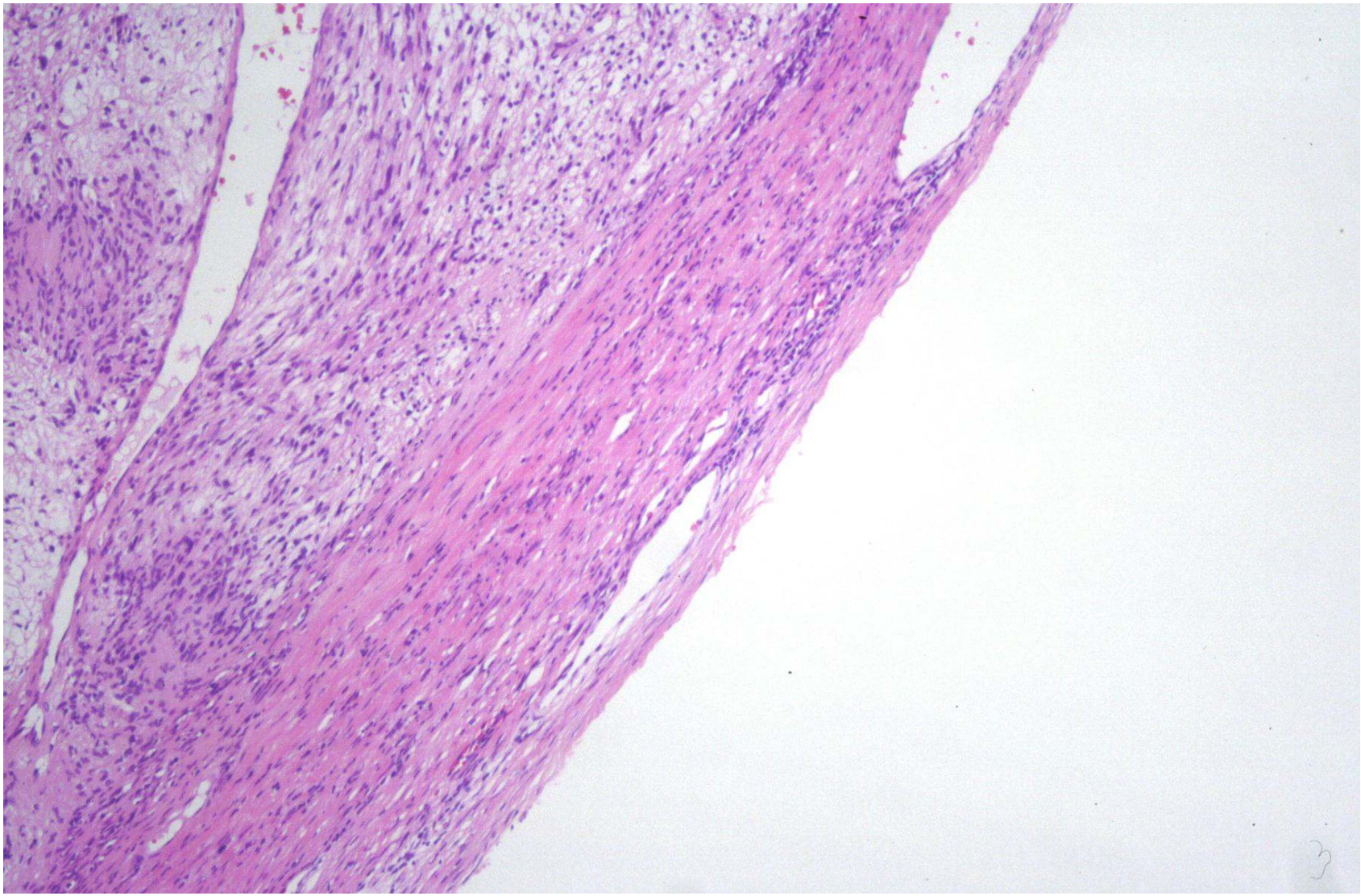
Encapsulated nerve sheath tumor, composed of well differentiated Schwann cells

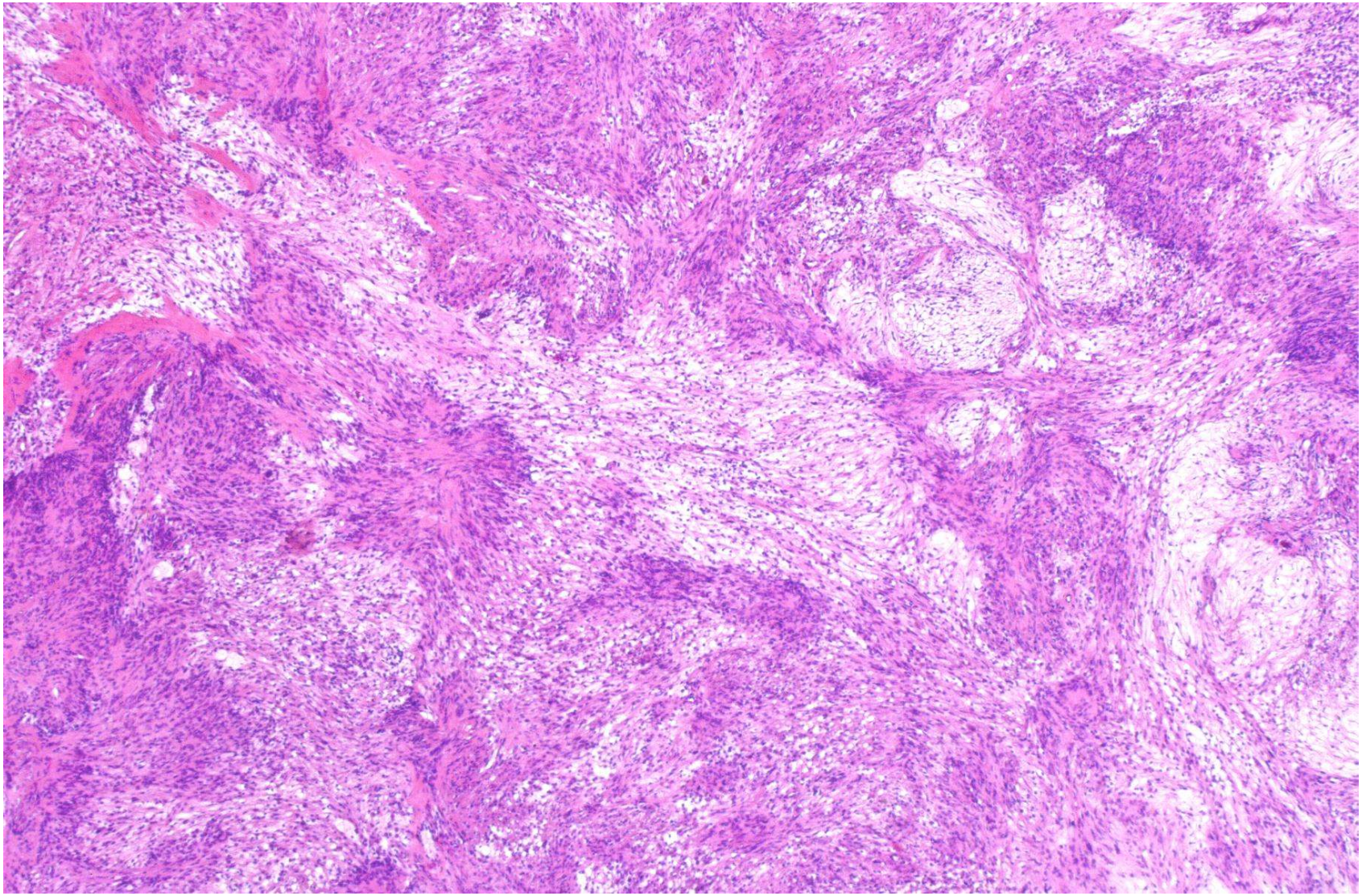
Biphasic with:

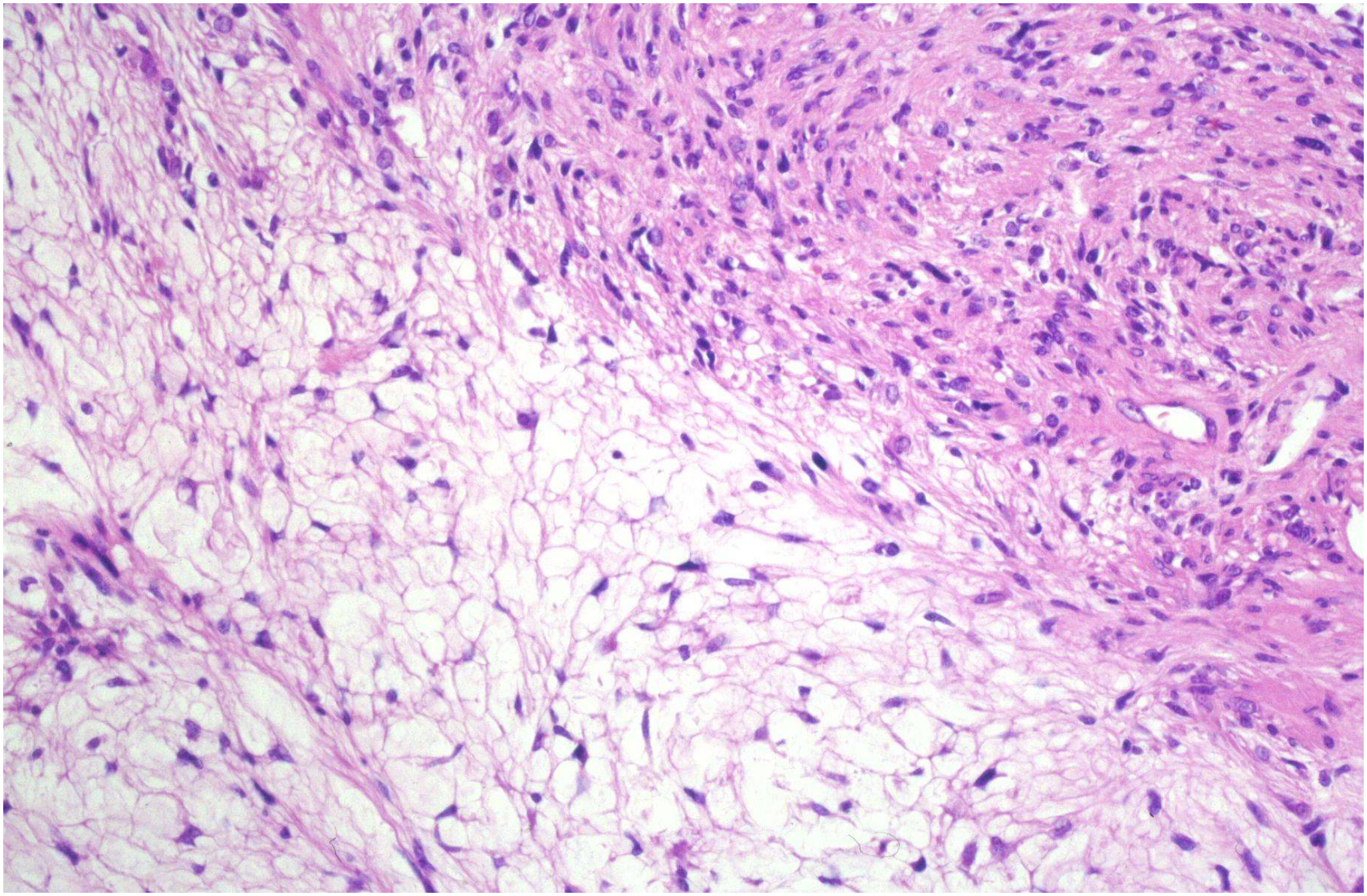
1-Compact cellular areas (Antoni A), occasional palisades (Verocay Bodies). Cytoplasmic nuclear inclusions

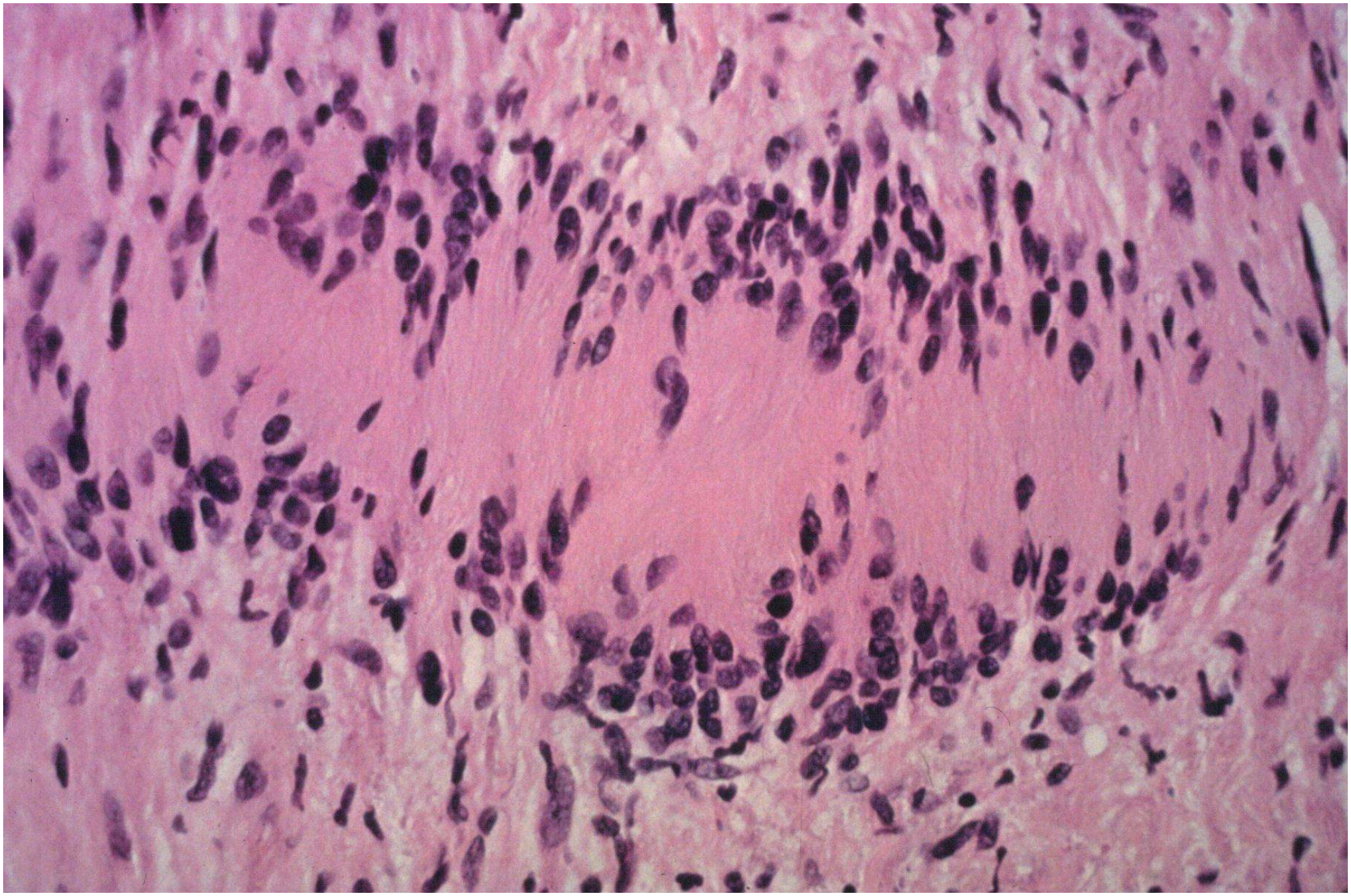
2-Hypocellular (Antoni B) areas

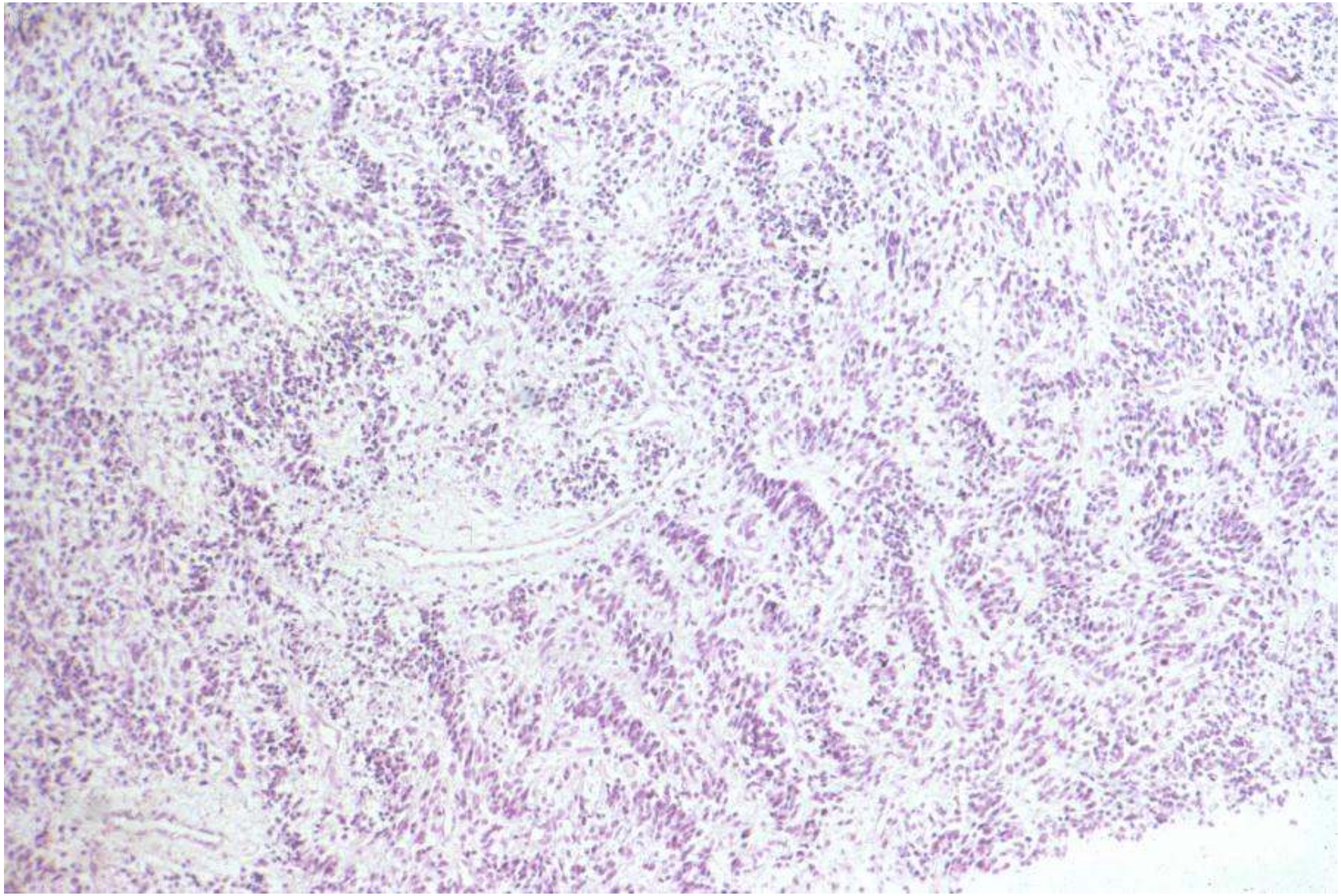

METRIC 1





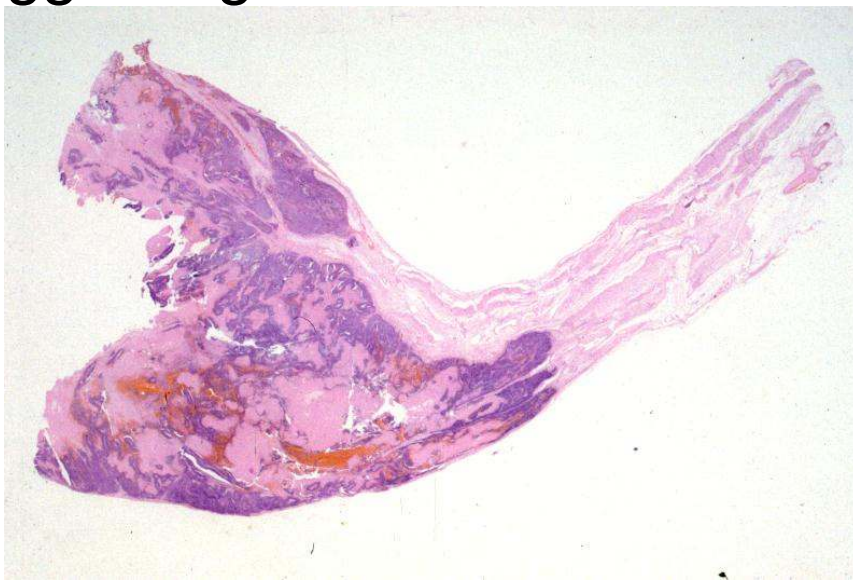






MPNST: Definition (WHO 2022)

Malignant peripheral nerve sheath tumour (MPNST) is a spindle cell sarcoma arising from a peripheral nerve, or from a pre-existing benign nerve sheath tumour or in patients with neurofibromatosis type-1 (NF1). Outside these settings, the diagnosis is based on morphological, immunophenotypical, or molecular features suggesting Schwannian differentiation.



MPNST: WHY A CHALLENGING DIAGNOSIS?

- The diagnosis of MPNST is not based on reproducible criteria
- NO specific morphologic features (e.g. rhabdomyoblasts or lipoblasts)
- NO highly specific and sensitive immunohistochemical markers
- NO recurrent genetic aberrations

MPNST: Clinical Features

3% to 10% of all soft tissue sarcomas

50% in patients with neurofibromatosis type 1

10% radiation induced

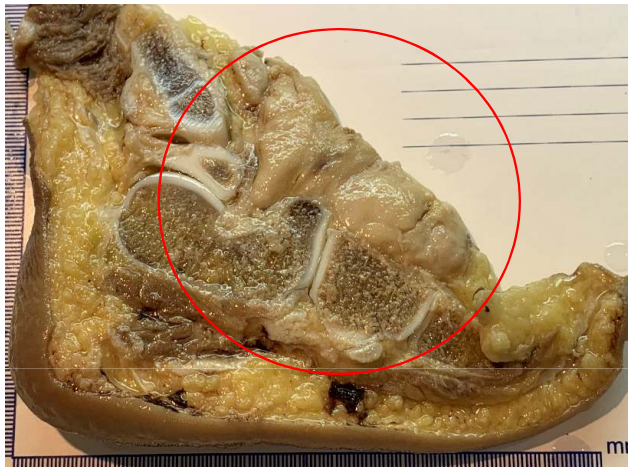
Remainders “sporadic” forms

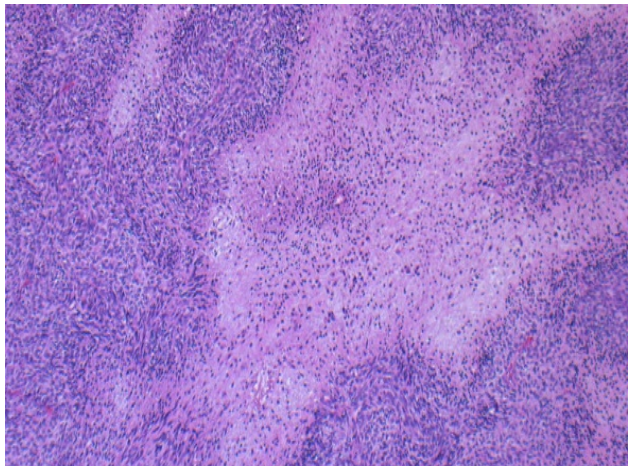
Mean age: 30

Male/Female ratio: 1.2:1

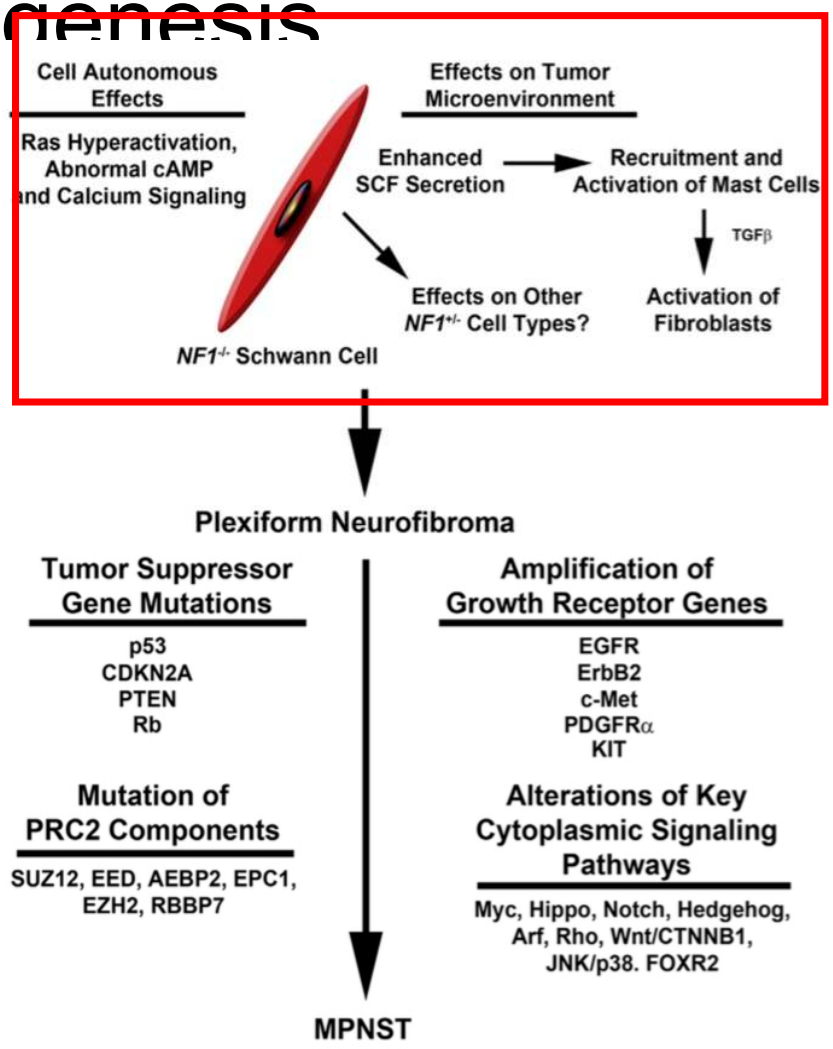
Site: trunk and extremities; less commonly MPNST affect the head and neck region

Overall survival 5 yrs< 50%



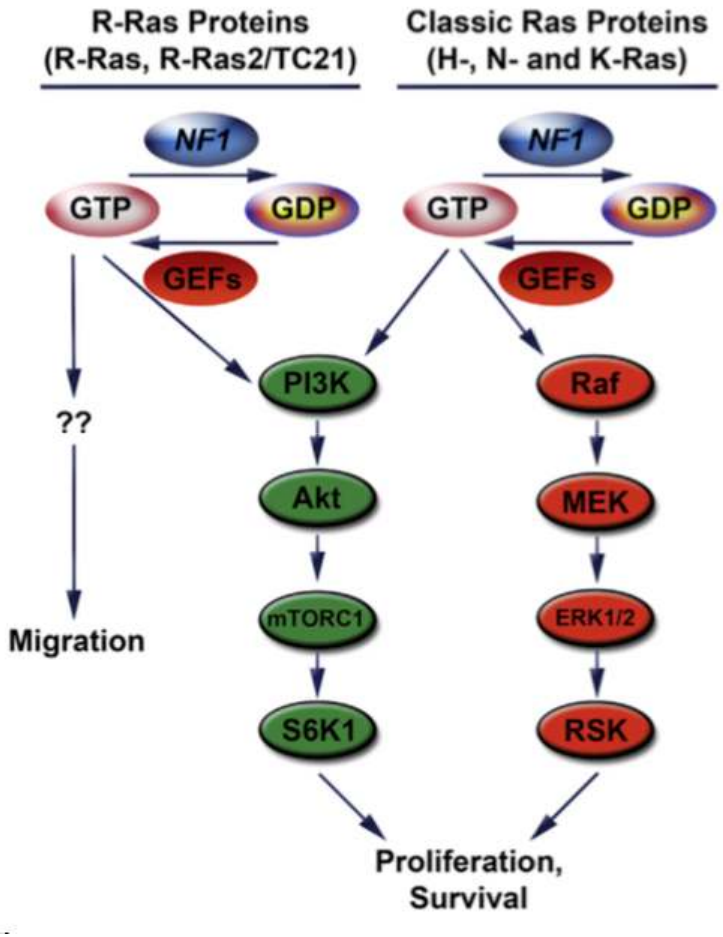


Molecular Mechanisms in MPNST genesis



NF1 loss: effect on Schwann cell:
Neurofibromin inactivates members of the Ras family both classic Ras (H-, N-, and K-Ras) and R-Ras (R-Ras, R-Ras2/TC21, and M-Ras) subfamilies.

Pathogenesis of Neurofibromas and MPNSTs

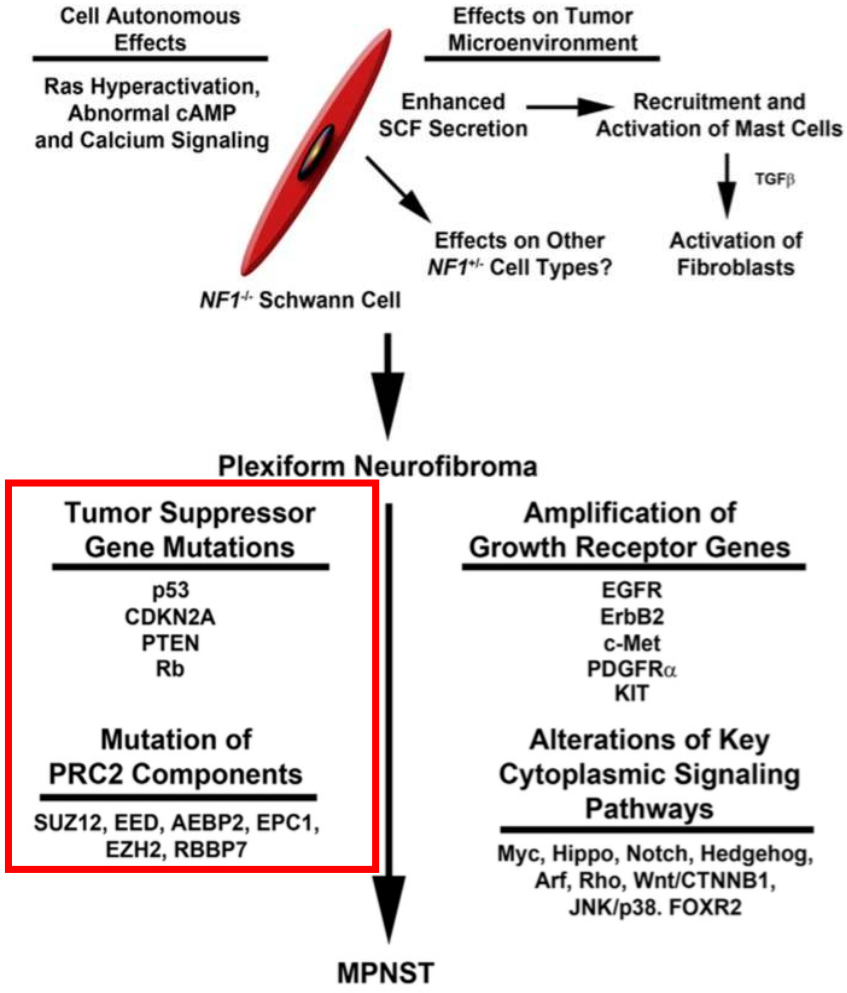


Multiple members of Classic Ras and R-Ras are simultaneously expressed and activated in MPNST.

Classic Ras and R-Ras proteins contribute to MPNST proliferation
Only classic Ras proteins promote the survival of MPNST, whereas R-Ras proteins drive their migration

.

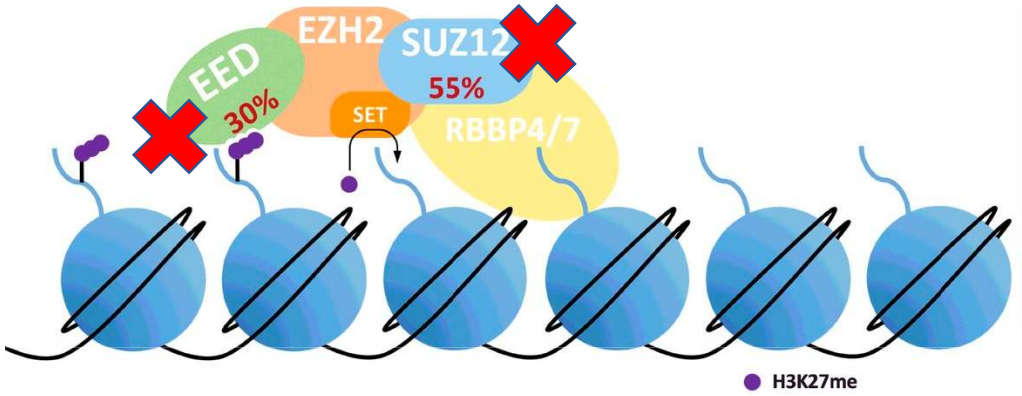
Molecular Mechanisms in MPNST genesis



Other genetic alterations:

- CDKN2A mutations in up to 50% of MPNSTs. It encodes p16INK4A (which inhibits CDK4 and CDK6) and p19ARF, (that inhibits Mdm2, which tags p53 for proteasomal degradation).
- Deletions and other loss of function mutations of TP53 occur in up to 75% of MPNSTs.
- Inactivating mutations of SUZ12, a gene encoding a chromatin-modifying protein that forms part of polycomb repressive complex 2 (PRC2).

Pathogenetic Mechanisms in MPNST



Polycomp Repressive Complex 2" (PRC2) *Korfhage J and Lombard DB, MCR, 2019*

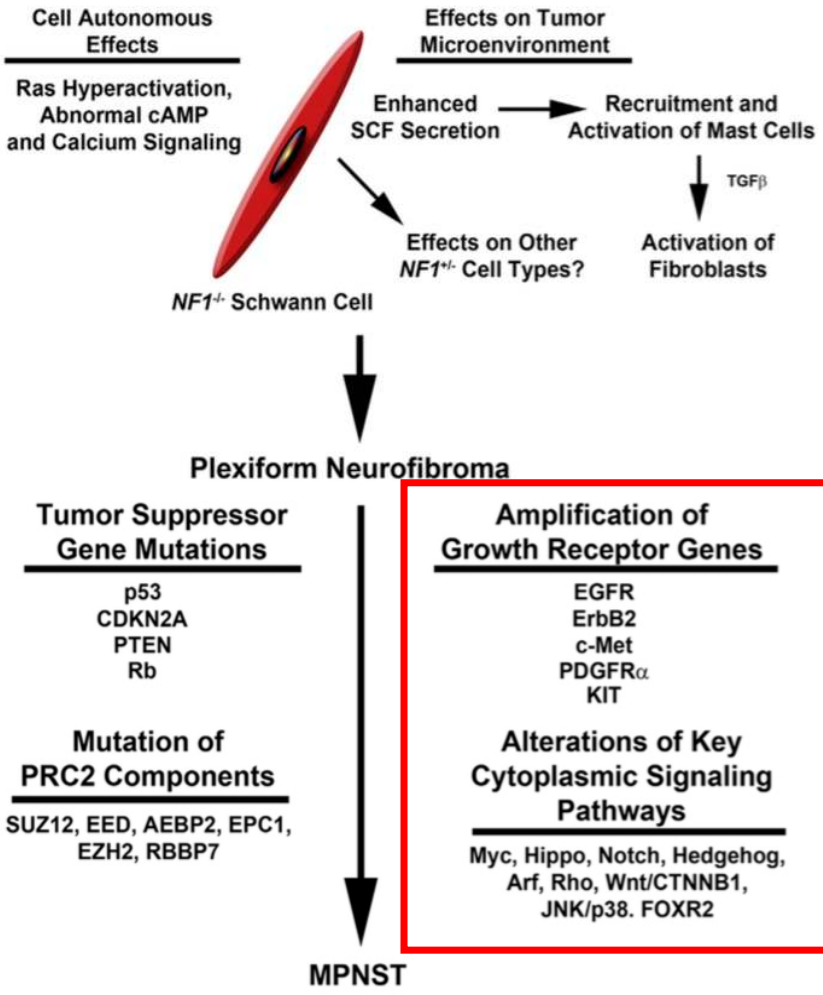
PRC2
inactivation

H3K27me3
Loss of metylation

Aberrant activation of target genes

MPNST

Mutually exclusive mutations in MPNSTs NF1-associated (70%), sporadic (92%) radiation- induced (90%)MPNSTs
SUZ12 mutations absent in neurofibromas

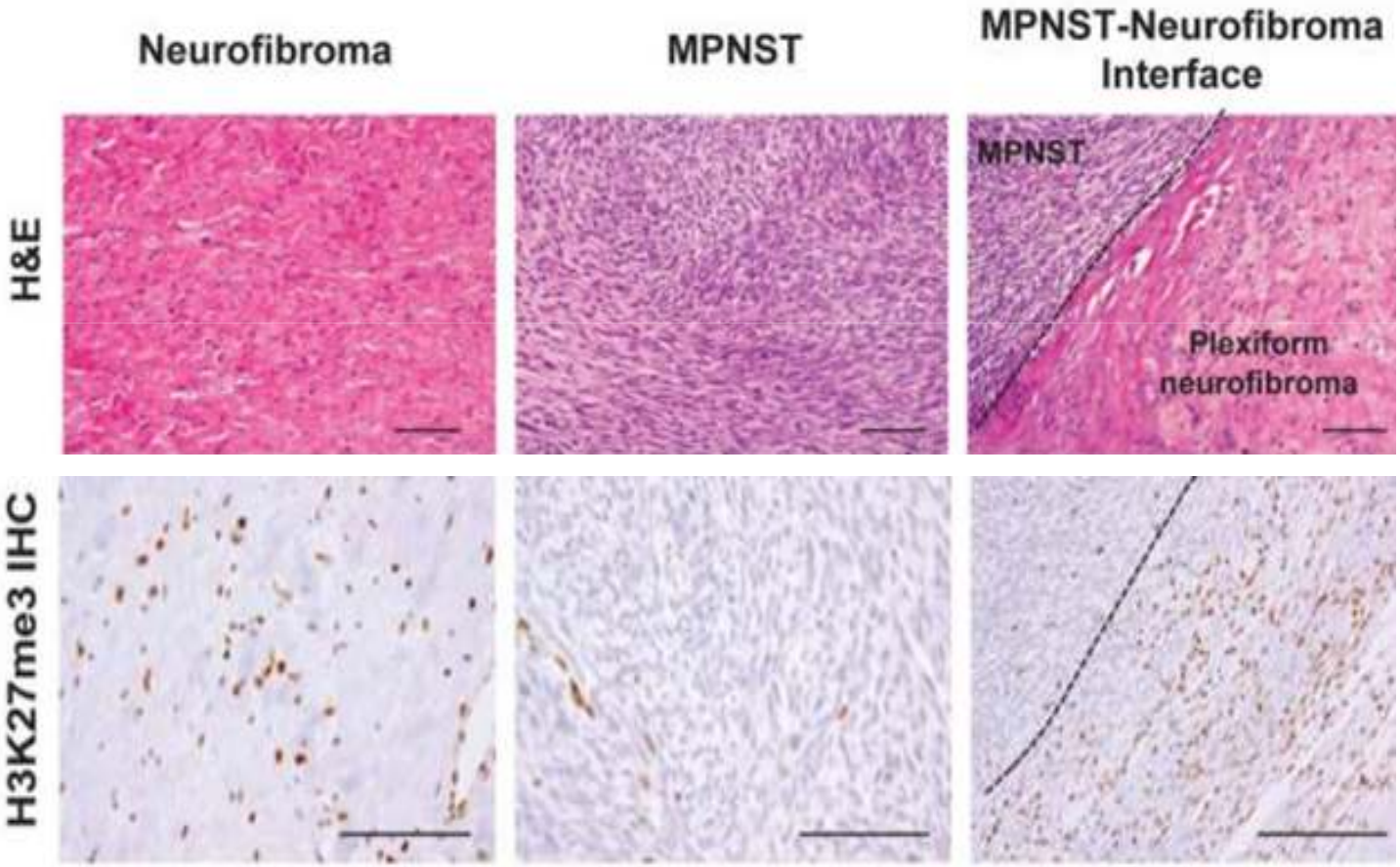


Growth factors/growth factor receptors contributing to MPNST/NF pathogenesis:

- EGFR, Neuuregulin-1 (NRG1), PDGF, Hepatocyte growth factor, and its c-Met receptor,

the Insulin-like growth factor 1 Receptor, Transforming growth factor-b1, Lysophosphatidic acid, Kit ligand and its c-Kit receptor, CXCR4 and its CXCL12 ligand, BFGF,VEGF

MPNST: loss of H3K27me3: an important marker

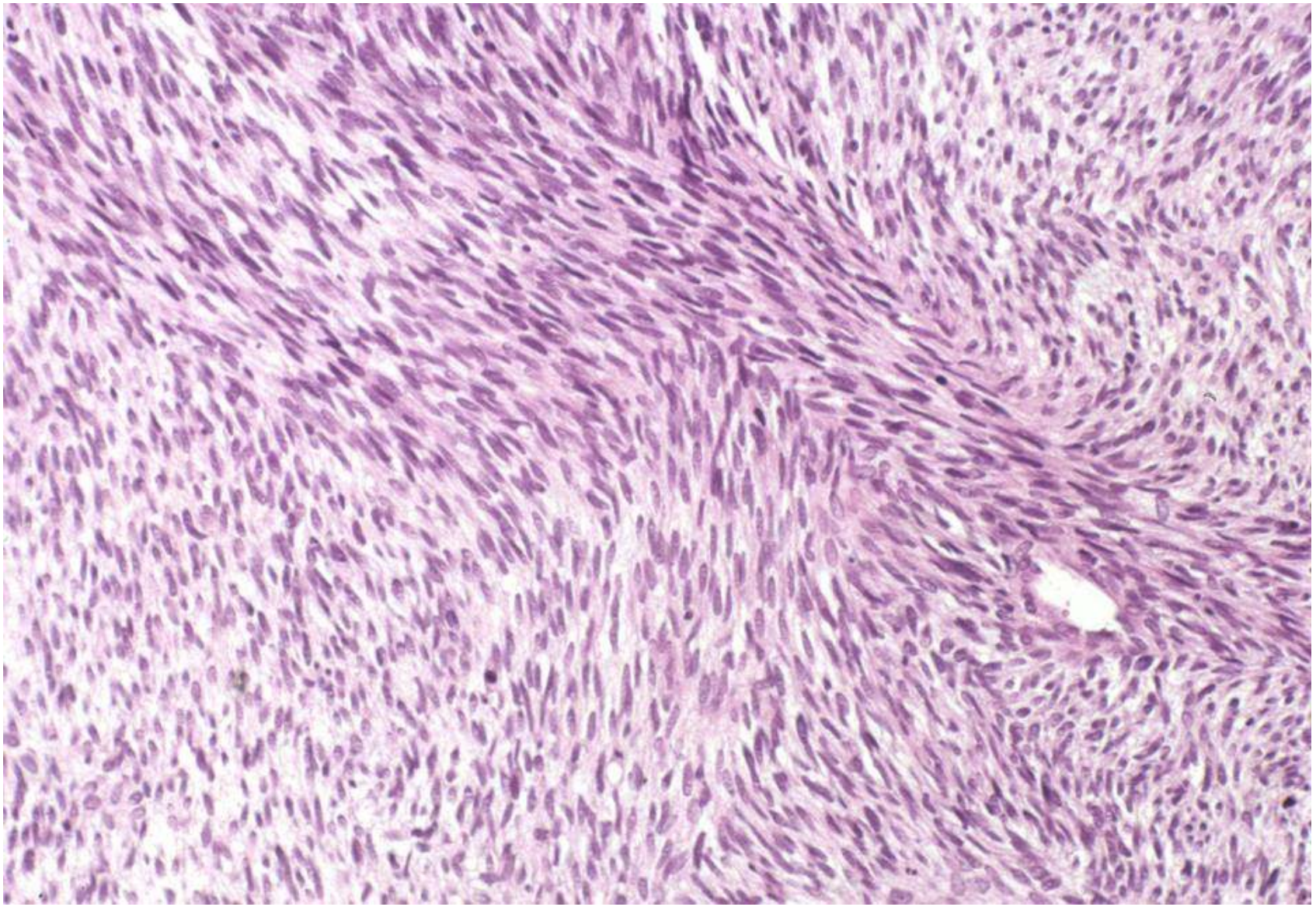


Lee W et al. Nat Genet. 2014

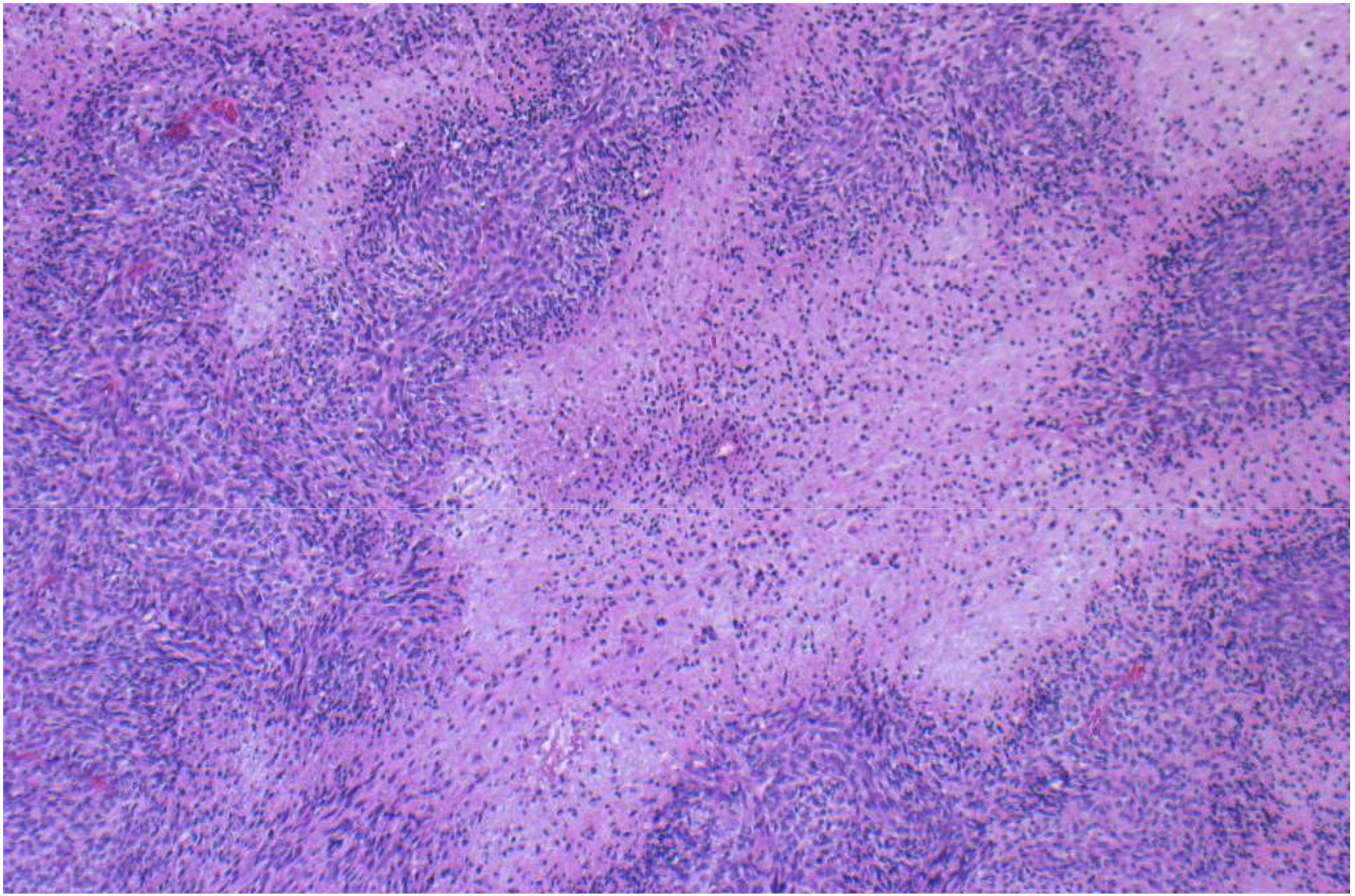
H3K27me3 lost in 34-84%

Schaefer IM et al. Mod Pathol 2016

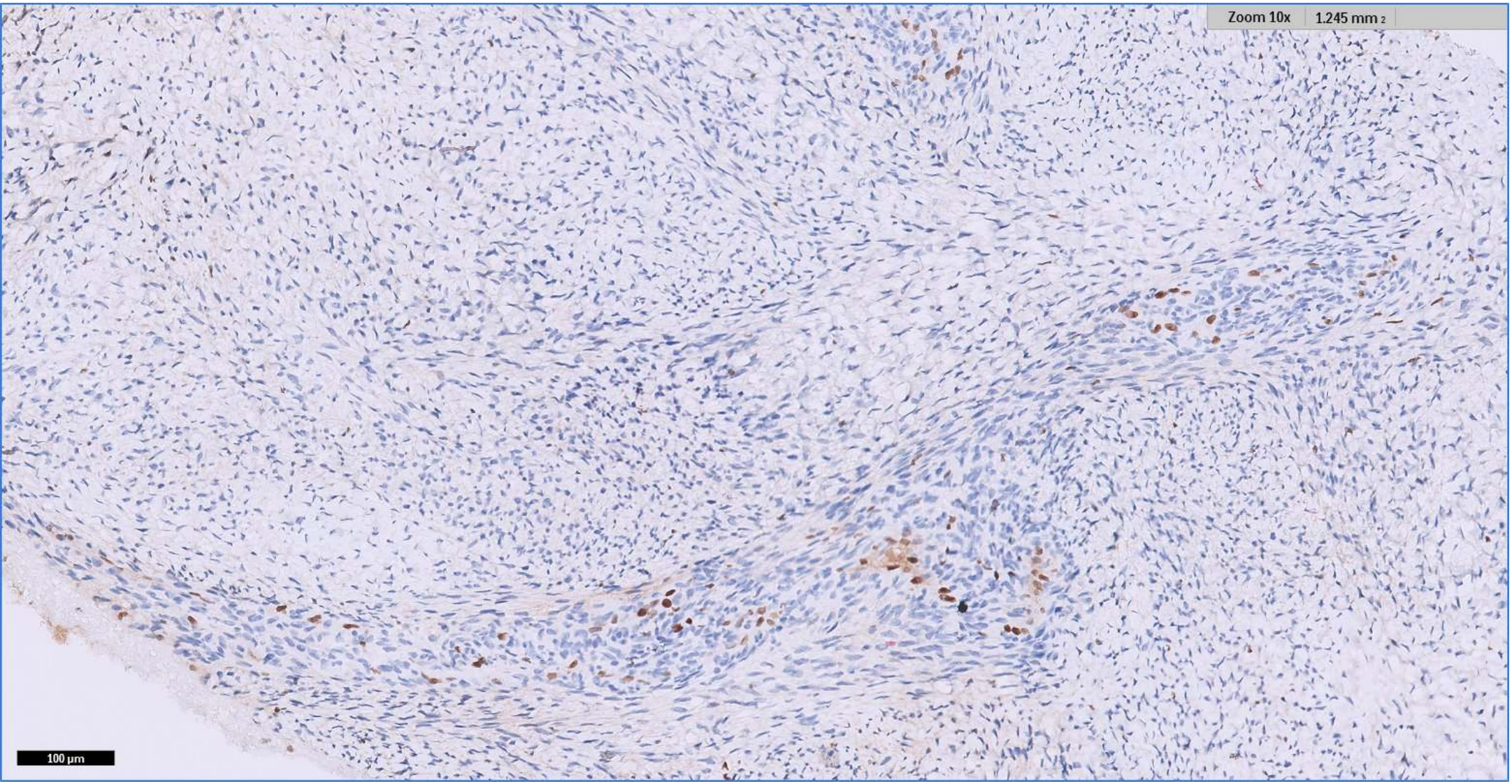
Lyskjær IJ et al. J Pathol 2020



Uniform spindle cells with hypercromic, weavy, serpentine-like nuclei



Alternance of hyper/hypo cellular areas
Palisade arrangement (around necrotic areas)



H3K27me loss (SOX10 and S100 –ve)

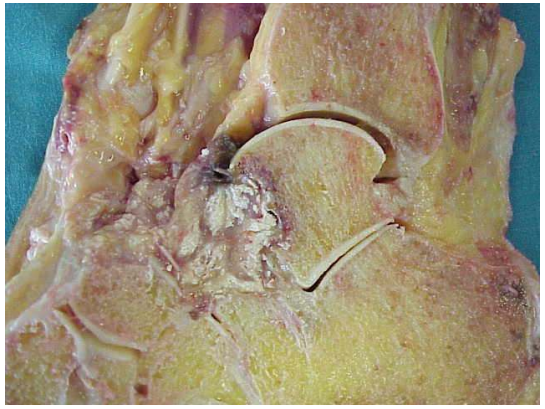
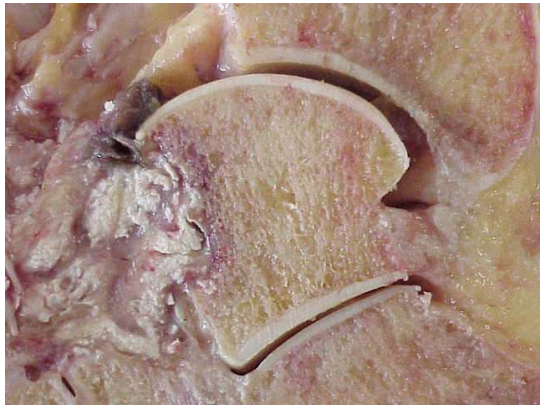
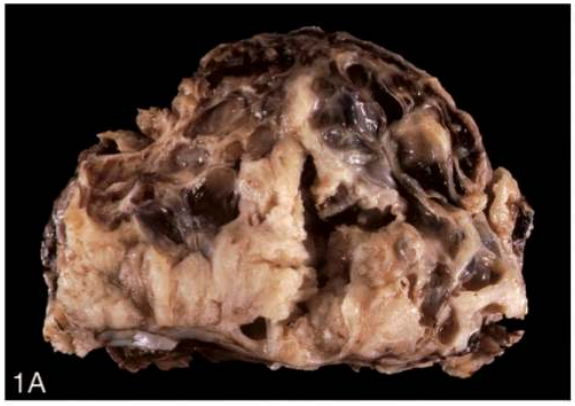
Soft Tissue and Bone Tumours (5th ed.)

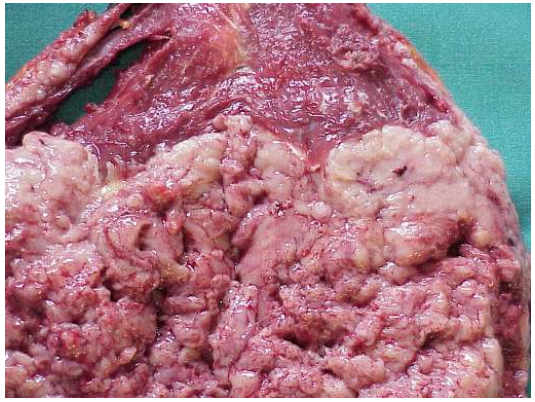
Tumours of uncertain differentiation
- Intramuscular myxoma
- Juxta-articular myxoma
- Deep (aggressive) angiomyxoma
- Atypical fibroxanthoma
- Angiomatoid fibrous histiocytoma
- Ossifying fibromyxoid tumour
- Myoepithelioma, myoepithelial carcinoma, and mixed tumour
- Pleomorphic hyalinizing angiectatic tumour of soft parts

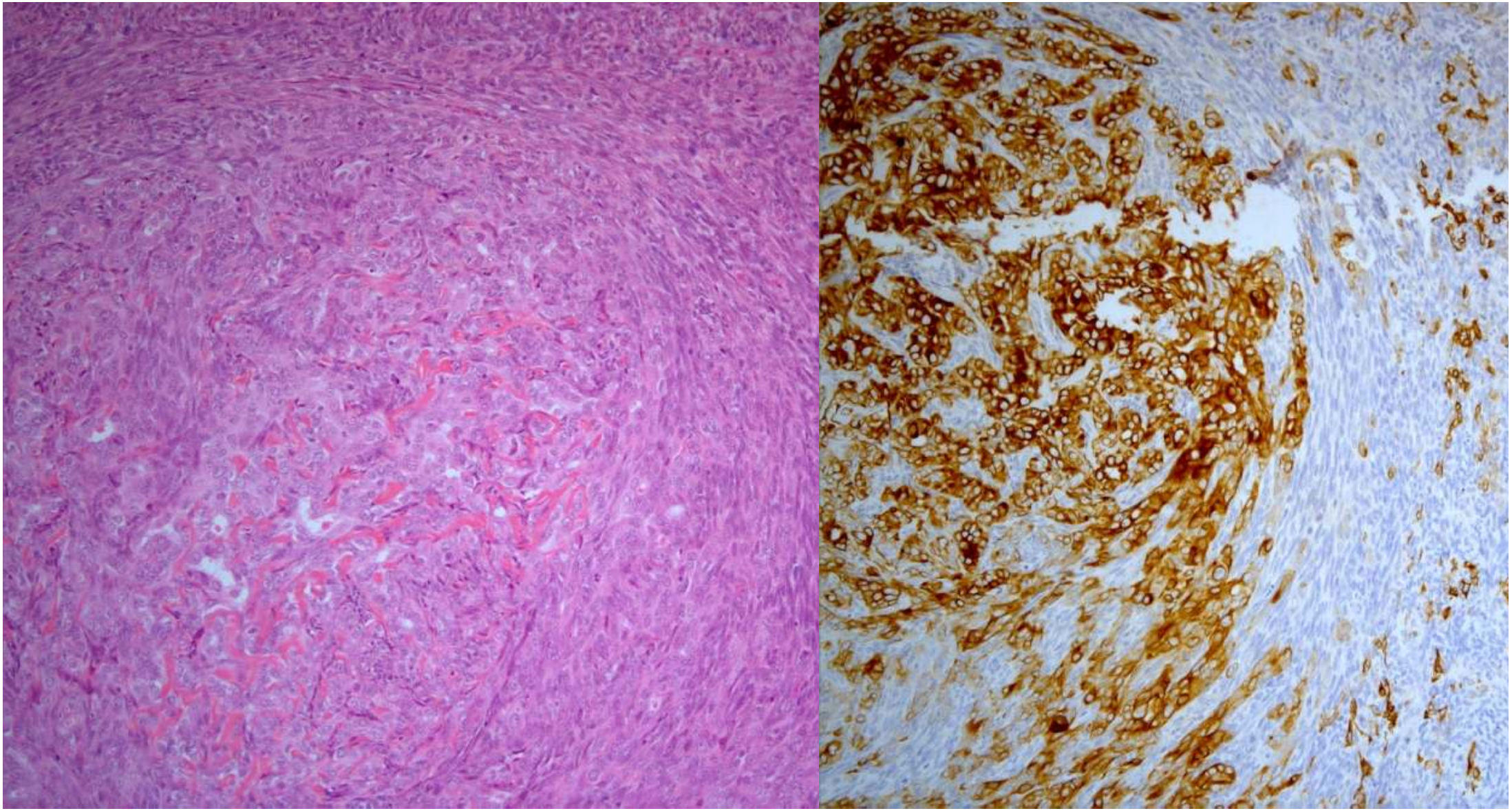
- Ossifying fibromyxoid tumour
- Myoepithelioma, myoepithelial carcinoma, and mixed tumour
- Pleomorphic hyalinizing angiectatic tumour of soft parts
- Haemosiderotic fibrolipomatous tumour
- Phosphaturic mesenchymal tumour
- NTRK-rearranged spindle cell neoplasm (emerging)
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Desmoplastic small round cell tumour
- Extrarenal rhabdoid tumour
- PEComa
- Intimal sarcoma
- Undifferentiated sarcoma

Synovial sarcoma

- Mass with infiltrative borders
- The cut surface is firm; pink or gray;
- focal mucoid, necrotic, hemorrhagic, or cystic changes
- Calcification may be extensive
- Size from 1 cm to very large.
- Lymph node metastases possible





Biphasic SS: spindle and epithelial-like cells, with areas recapitulating gland formation anastomosing network of epithelial strands

Synovial Sarcoma: immunohistochemical profile/Molecular Features

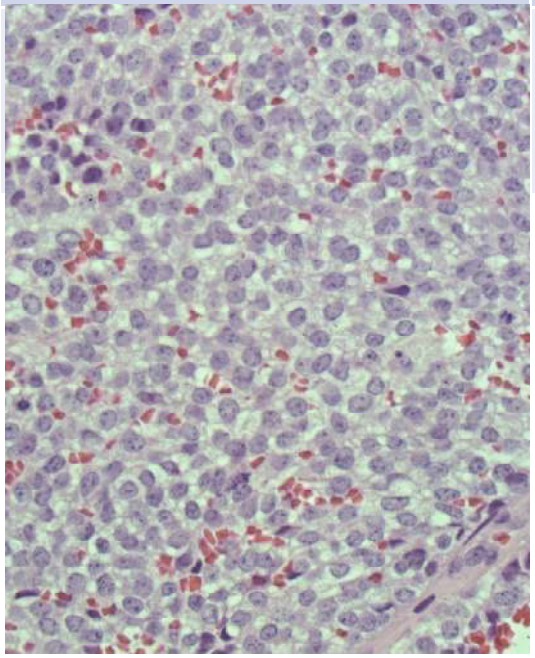
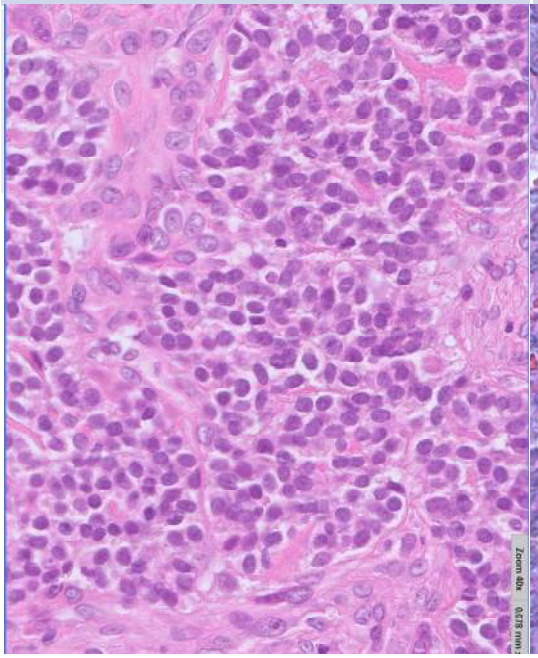
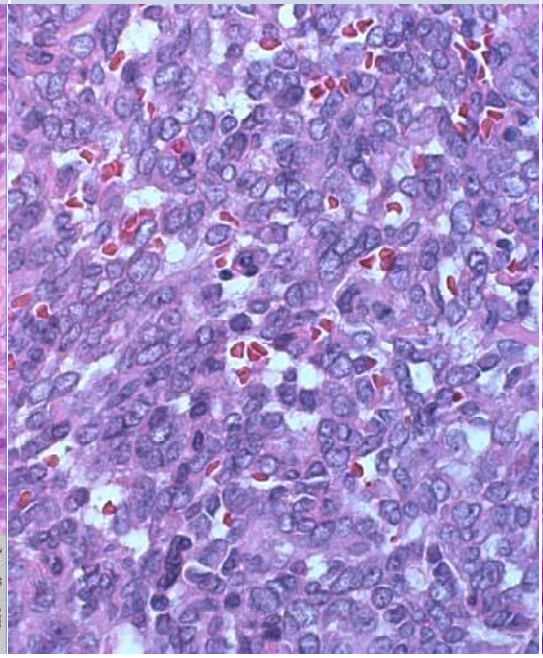
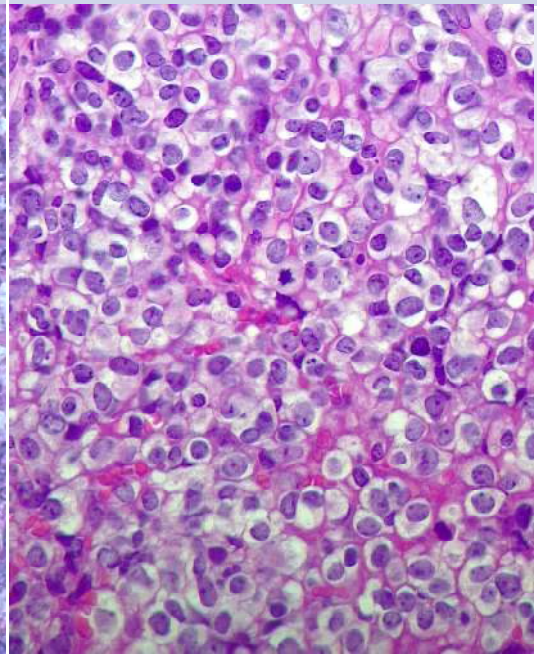
- **Cytokeratins +** patchy in spindle cells, diffuse in epithelial component
- Broad-spectrum cytokeratins AE1/AE3 and CAM5.2, keratins 7, 13, and 19
- **EMA+**
- TLE1+diffuse nuclear

Molecular Features

- Chromosomal t(X;18) translocation with transcripts: *SS18::SSX1, SS18::SSX2, SS18::SSX4*
- 5% alternative gene fusions (such as SS18L1/SSX1) or cryptic rearrangements.

3.Undifferentiated Sarcomas

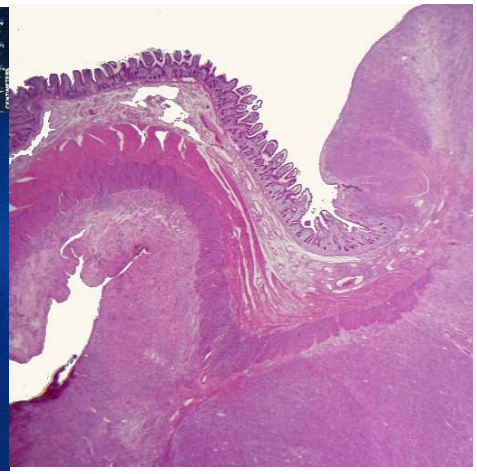
Undifferentiated Small Round Cell Sarcomas of Bone and Soft tissue

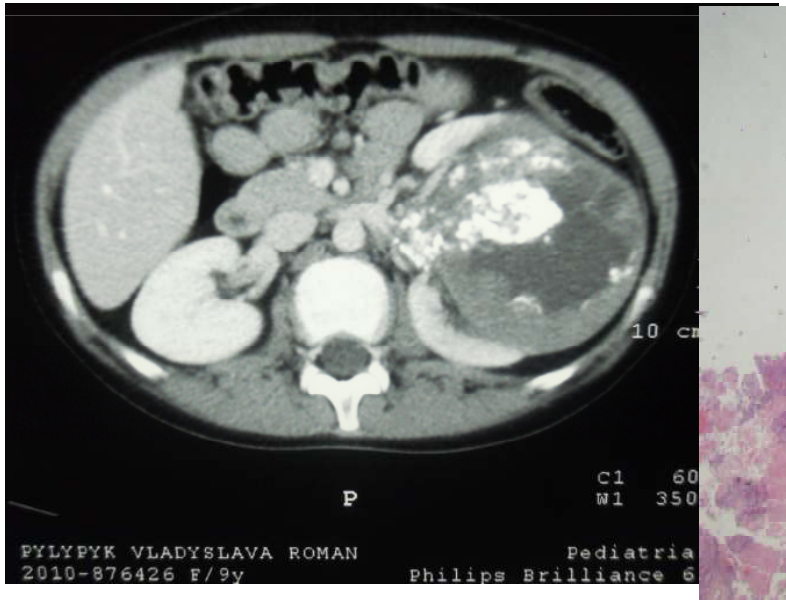
Ewing Sarcoma	USRCS with EWSR1–non-ETS fusions	USRCS with ***BCOR alterations***	USRCS with C***IC fusions***
			

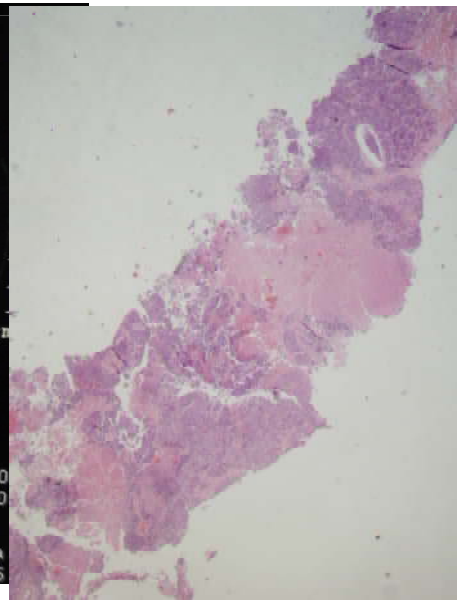
WHO Classification 2020, 5th edition

Ewing Sarcoma

Second most frequent bone malignancy
Young adults (80% < 20 yr old)
Site::
Bone (88%): lower extremities (41 %), Pelvis (26 %), chest wall (16 %), upper extremities (9 %), spine (6 %), foot, hand (3 %), skull (2 %)
Extra-osseousl(12%): Soft tissues, Skin, Visceral
Clinical features:
Pain, nerve trunk compression, fractures, fever
Diagnosis:
CT, MRI,
25 % metastatic at diagnosis

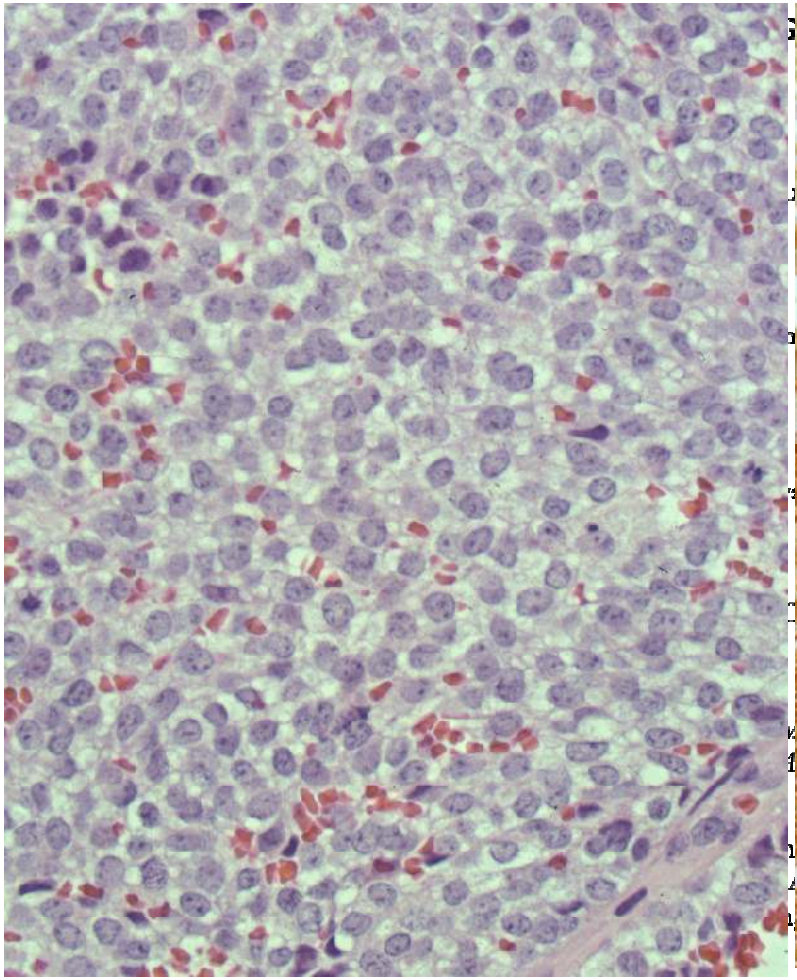


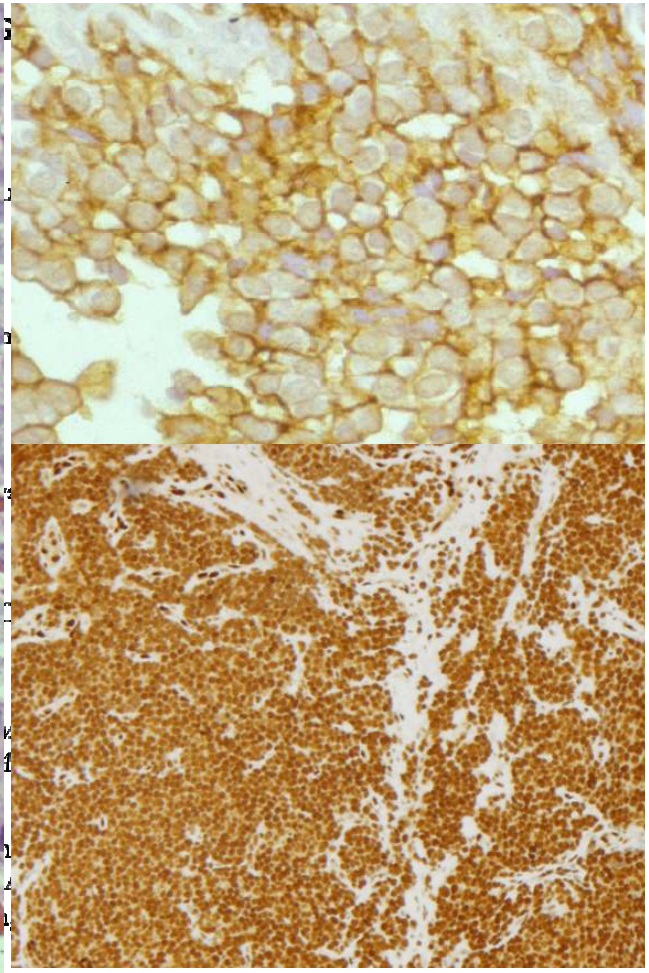




Undifferentiated Small Round Cell Sarcomas

	Ewing Sarcoma
Peak incidence	20y
Site	88% bone 14% soft tissue parenchymal
Cytology/Nuclear features	Monotonous round cells, fine chromatin
Pattern **Stroma**	Solid, alveolar
IHC	CD99, NKX2-2 , FLI1, ERG (in ERG fusion+)
Molecular Features	*EWSR1-FLI1, EWSR1-ERG, FUS-ERG*
Molecular Detection Method(s) [if necessary]	RT-PCR

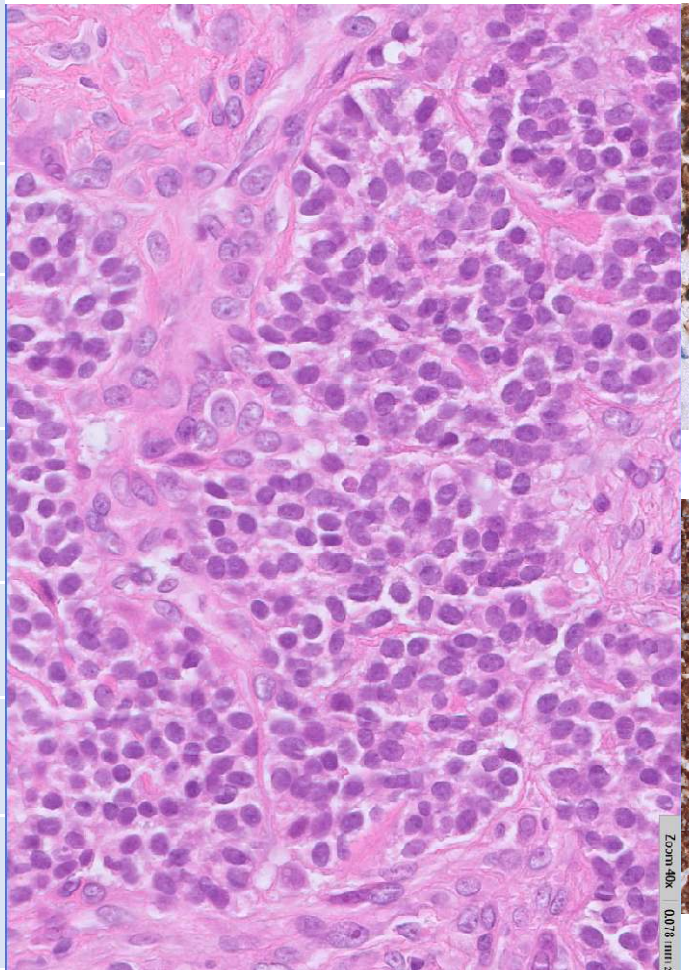


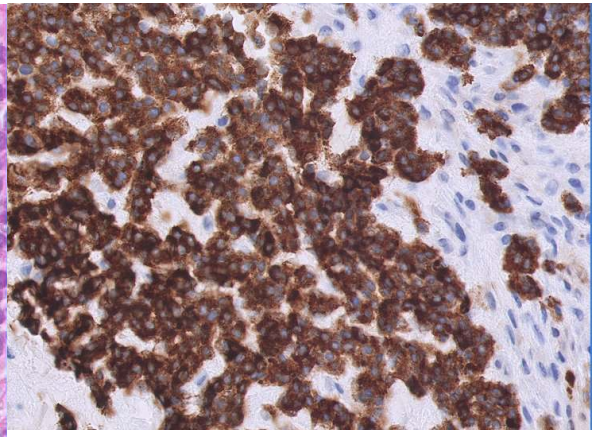


**Additional alterations STAG2. mut (17%); CDKN2A (12%);TP53 (7%, w STAG2 and TP53, Loss of 16q, y 9p ,gain 8, 1q, 2,*

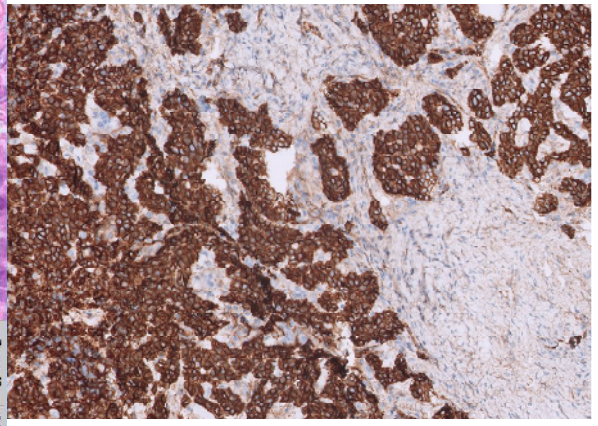
Undifferentiated Small Round Cell Sarcomas

	Round cell sarcomas with *EWSR1*–non-ETS fusions
Peak incidence	young
Site	long bones (metaphisis/diaphysis Soft tissue (head/neck, chest wall).
Cytology/Nuclear features	monotonous round cells Variations: pleomorphic cells, hyperchromatic/vesicular nuclei, small/prominent nucleoli
Pattern **Stroma**	Cords/nests/trabeculae Fibro (myxo)-hyaline stroma
IHC	CD99 (diffuse in 50%), PAX7, NKX2-2, CK AE1/AE3, CD138 (f), AGGRECAN.
Molecular Features	*EWSR1 (FUS)-NFATC2, EWSR1-PATZ1*
Molecular Detection Method(s) [if necessary]	RNA sequencing panel (e.g. Archer)





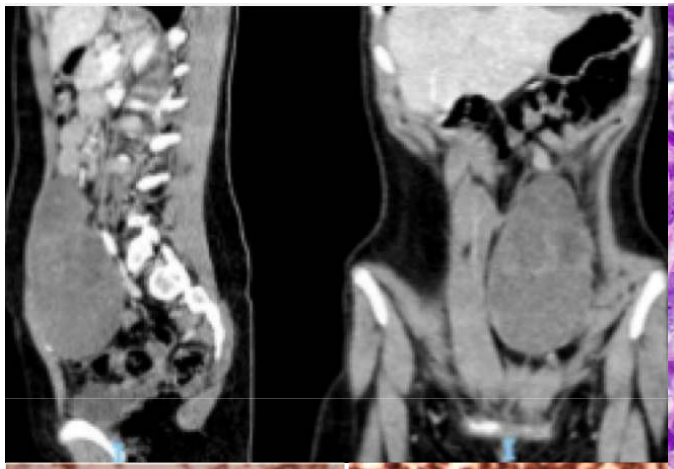
EMA

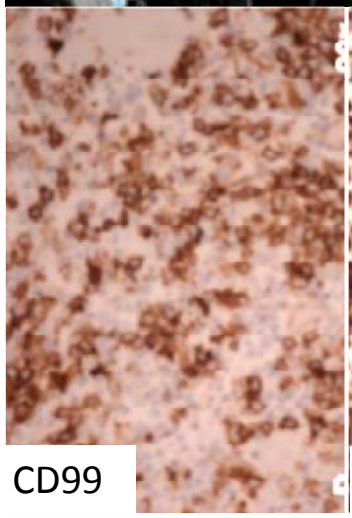


CD99

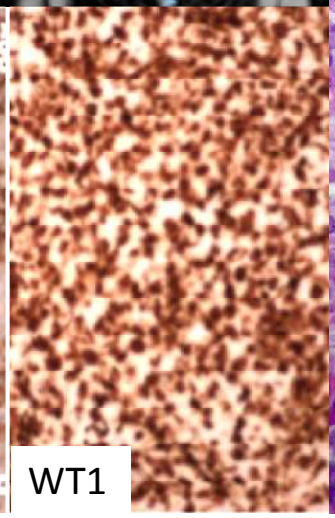
Undifferentiated Small Round Cell Sarcomas

	***CIC*-Rearranged Sarcoma**
Peak incidence	30-40 y
Site	Soft tissue (trunk, pelvis, extremities)
Cytology/Nuclear features	Round cells ,eosinophilic cytoplasm. Vescicular, pleomorphic, nucleoli
Pattern Stroma	Solid, Myxoid, hyaline
IHC	CD99 (p), ETV4, WT1, (ERG, FLI1)
Molecular Features	*CIC-DUX4, (*rare 3' partners: *FOXO4*, *LEUTX*, *NUTM1*, *NUT M2A)*
Molecular Detection Method(s) [if necessary]	FISH or RNA sequencing panel (e.g. Archer)

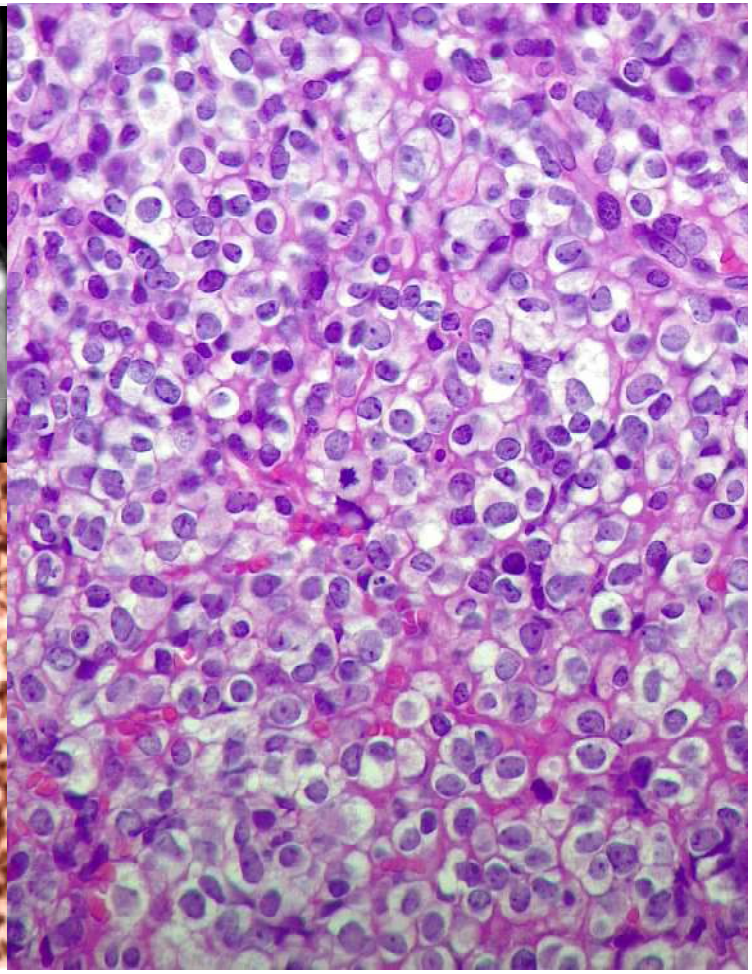




CD99



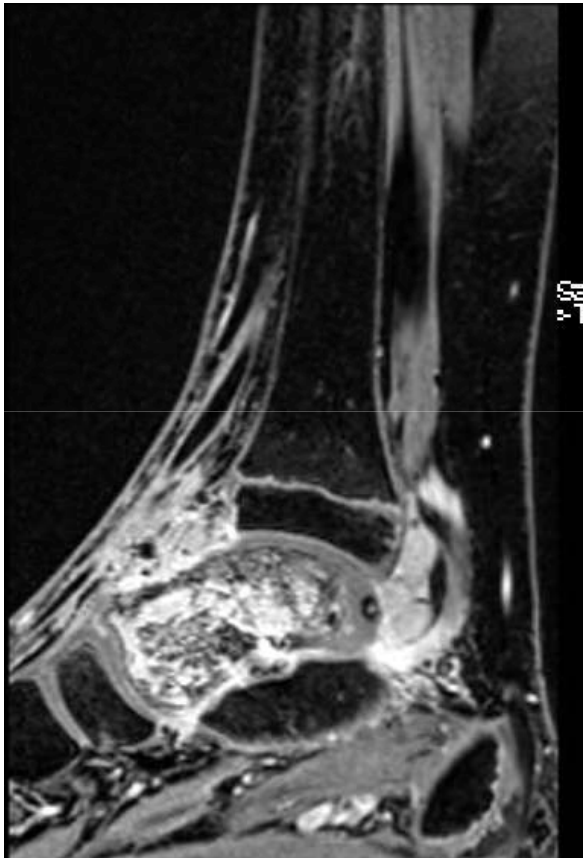
WT1



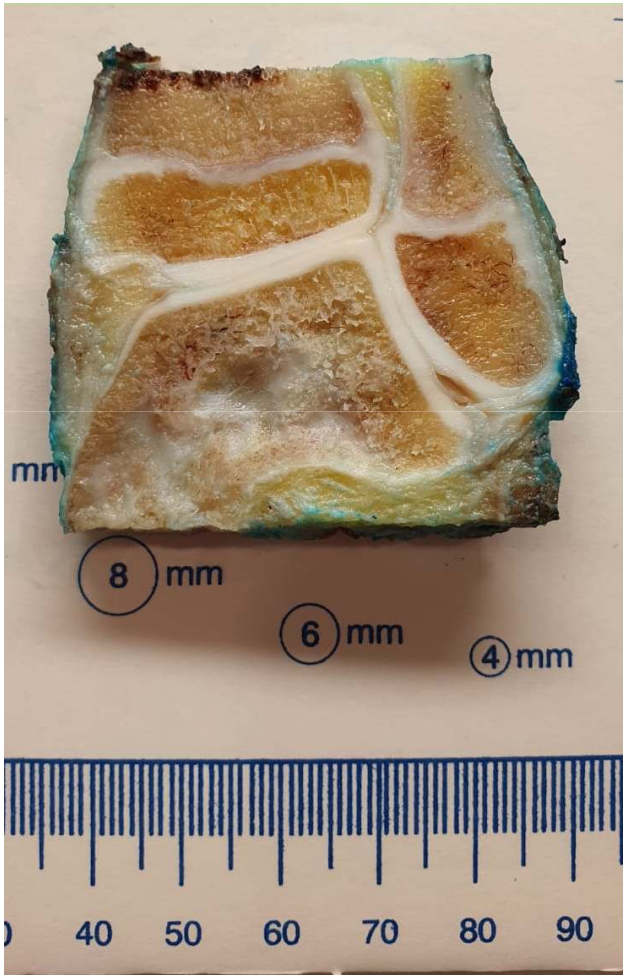
3. Undifferentiated small round cell sarcomas of bone and soft tissue

World Health Organization

	Sarcoma with *BCOR* Genetic alteration
Peak incidence	90% <20y
Site	Pelvis, metadiaphysis long bones (lower extr)
Cytology/Nuclear features	Round-spindle cells Pale nuclei, fine chromatin, no nucleoli
Pattern **Stroma**	Solid, nested Scant or myxoid plexiform vascular pattern
IHC	CD99 (p), TLE1, BCOR, CCNB3
Molecular Features	*BCOR-CCNB3, BCOR-MAML3, ZC3H7B-BCOR , BCOR* ITD*, YWHAE*-rearranged
Molecular Detection Method(s) [if necessary]	FISH detects fusions only, may be cryptic RNA sequencing panel (e.g. Archer) ITD detectable by sequencing or PCR based assay

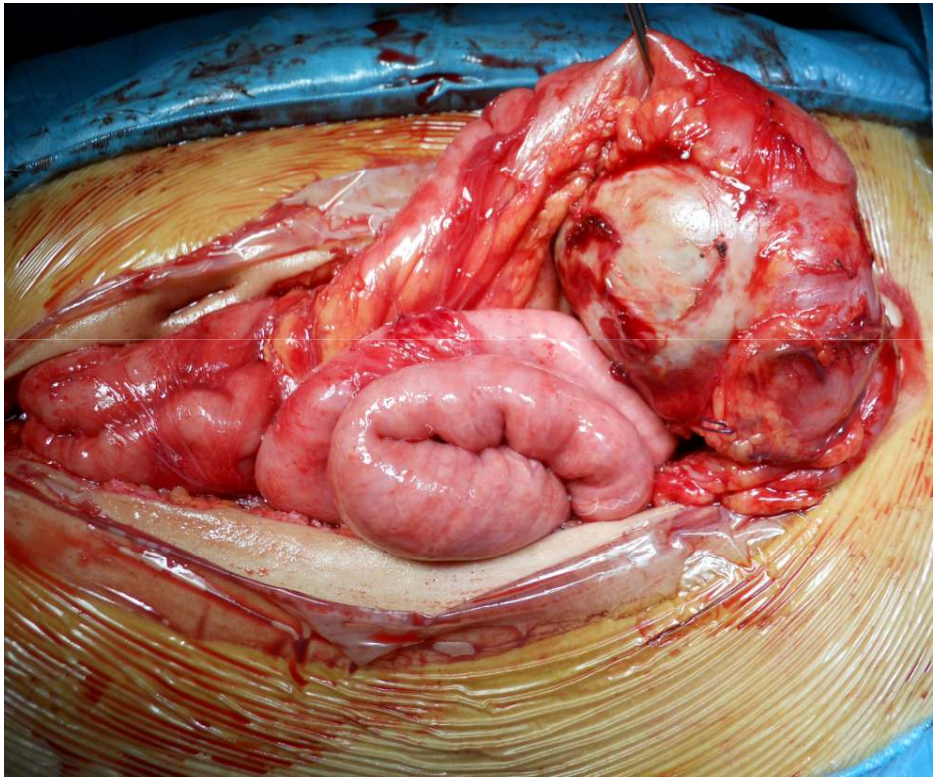


- Male, 7yr
- Mass of the left foot (astragalus bone), with extension to soft tissue (Surgical specimen after CT)

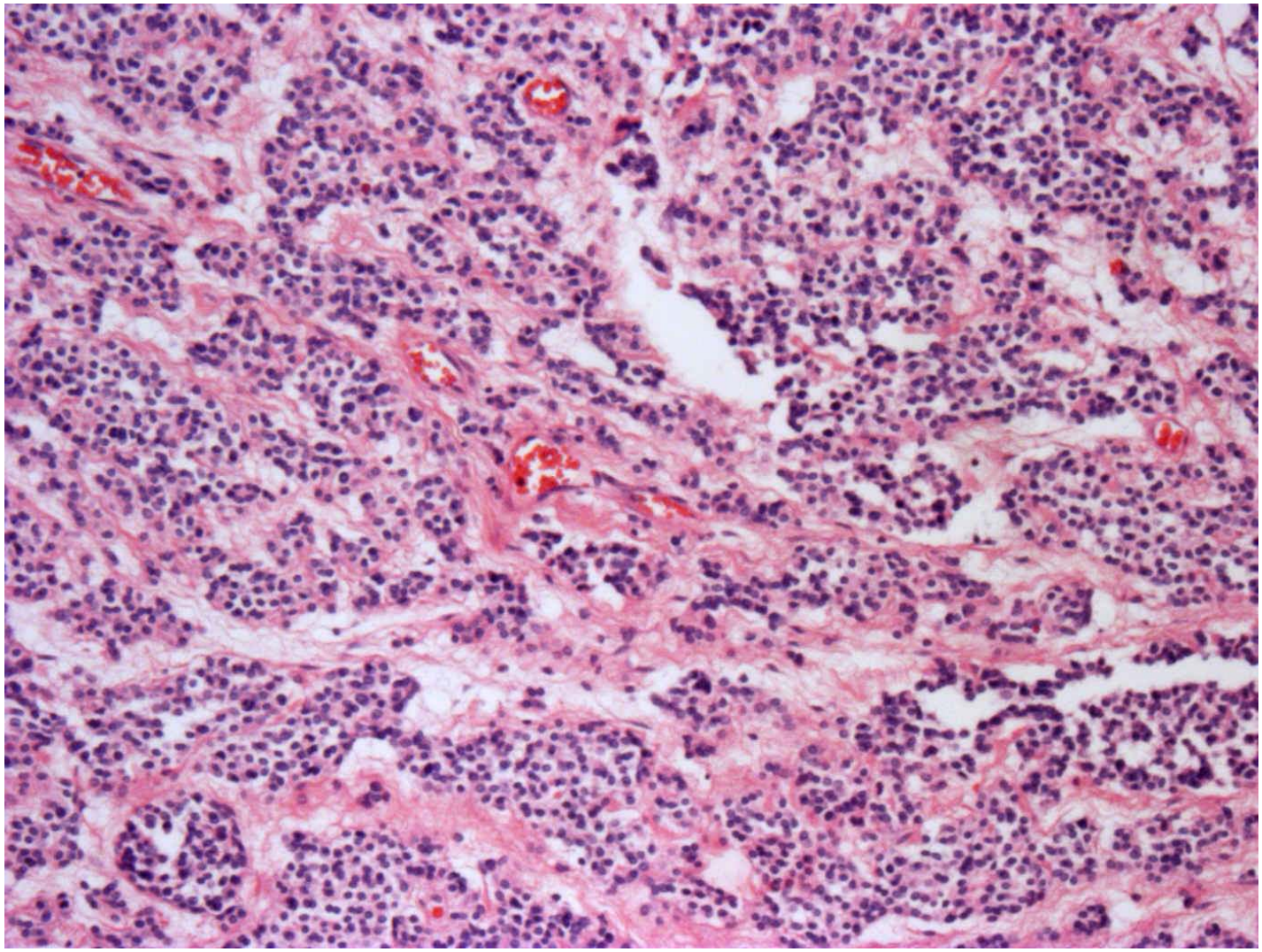


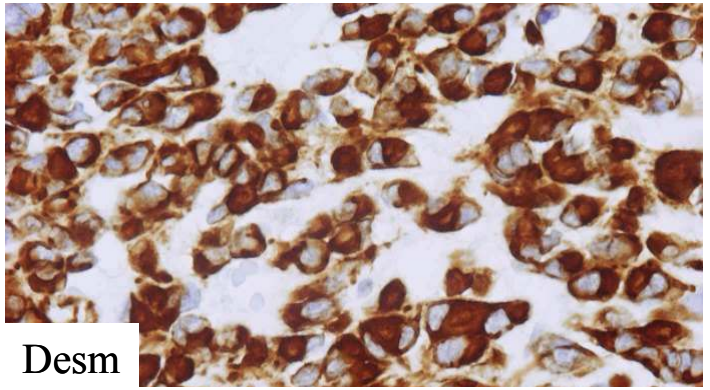
Desmoplastic Small Round Cell Tumor

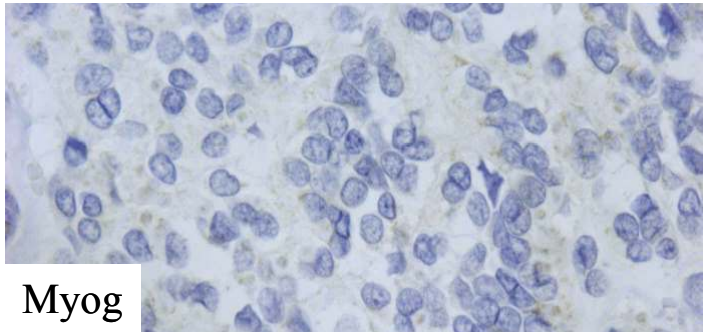
- Young adults
- Serosal surface of the abdominal cavity (90% of patients)
- At diagnosis usually intra-abdominal spread with lymph node involvement (50–80% of patients) and/or distant metastases (25%)

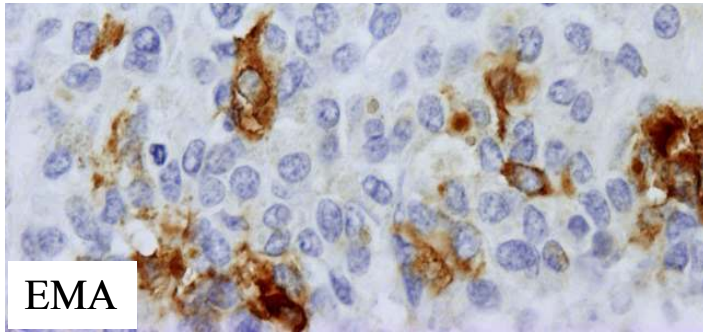


Desmoplastic Small round cell tumor









Fusion *EWSR::WT1*

Small Round Blue Cell Tumors (SRBCT)?

Definition

Descripitive term, not a histologic category

Small Roud Blue Cell Sarcomas

Undifferentiated Small Round Cell Sarcomas of Bone and Soft tissue

Rhabdomyosarcoma

DSRCT

Malignant Tumors non Sarcomatous

Neuroblastoma

Lymphomas

Retinoblastoma

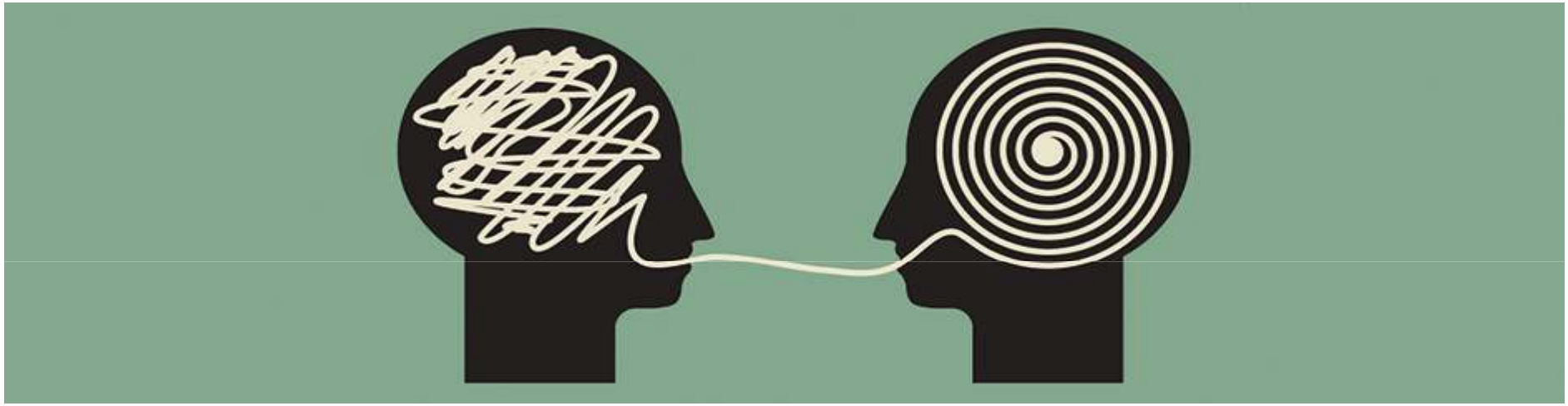
Conclusions

The evolution of surgical pathology
From “Histologic diagnosis” to “Integrated Diagnosis”

	Morphology	Immunoistochemistry	Molecular testing/genetic
Description	*Microscopic analysis*	*AB conjugated to an enzyme, that can catalyse a colour-producing reaction once they bind to specific proteins*	*Molecular testing/genetic*
Focus	Cytology (cell differentiation) Pattern Vascular network Stromal components	Intermediate filaments Transcription factors Mutated proteins (or loss of expression for mutation) Fusions Overexpression of proteins	**Comparatively cheaper & faster** FISH (fusions, amplifications) RT-PCR (fusions, Mutations) **High cost, long lead time** NGS (Fusions, Mutations, Amplifications)
Cost & Lead Time	Low cost, Short lead time		High cost, Longer lead time

A multidisciplinary approach and a common language are essential is for a correct diagnosis and an appropriate treatment

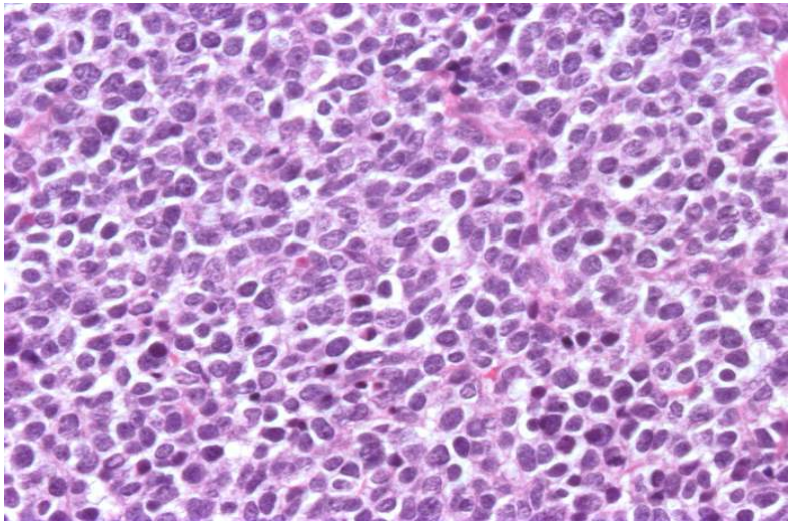
A shared language means…

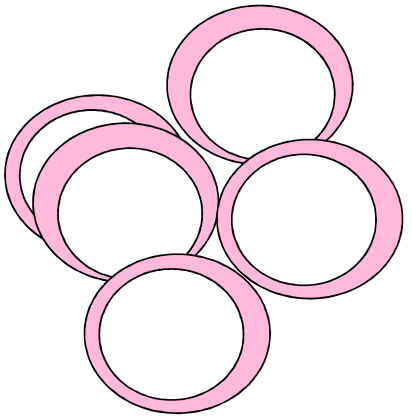


- Give the necessary information and know the steps deriving from it
- Avoid unnecessary information
- In case of a difficult diagnostic decision share doubts and certainties

Caratteristiche citologiche

Caratteristiche citologiche





Tumori a Piccole Cellule Rotonde dell'età pediatrica

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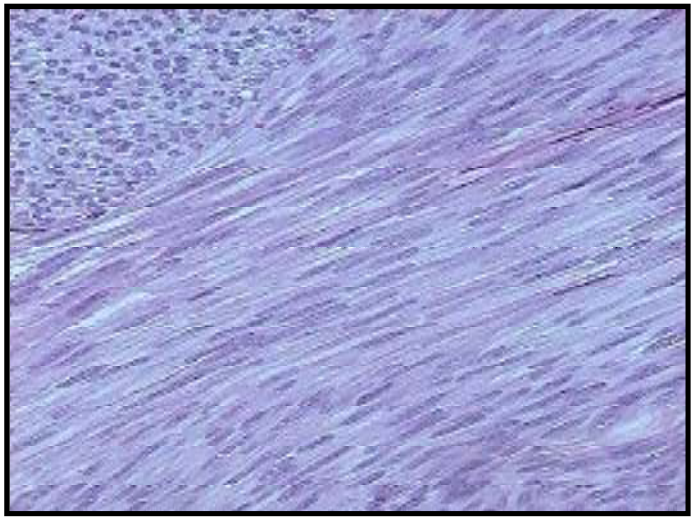

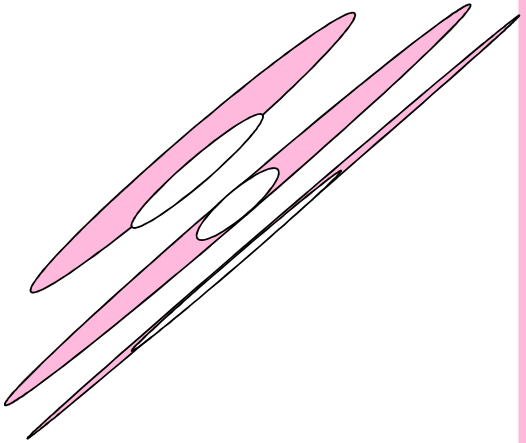

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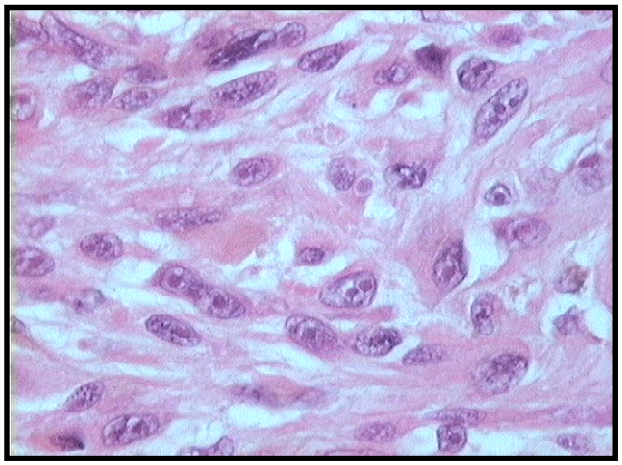

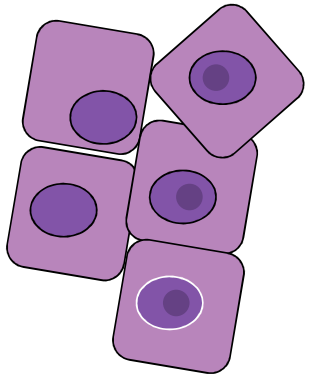

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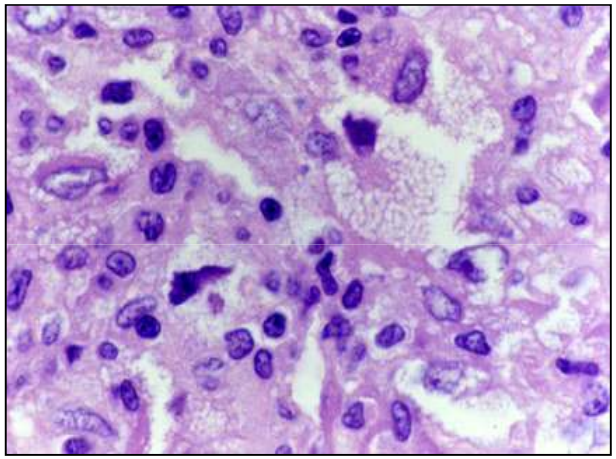
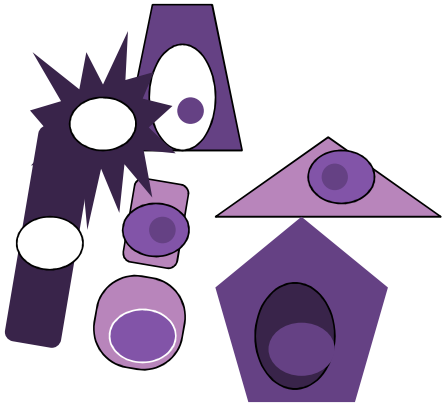
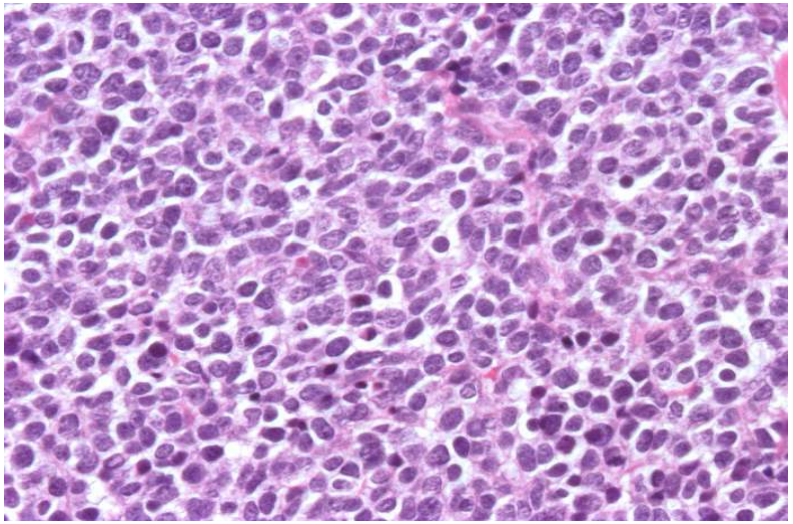
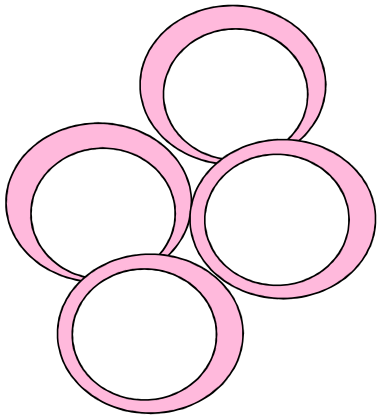




Pattern di aggregazione cellulare

Pattern di aggregazione cellulare





Tumori a Piccole Cellule Rotonde dell'età pediatrica

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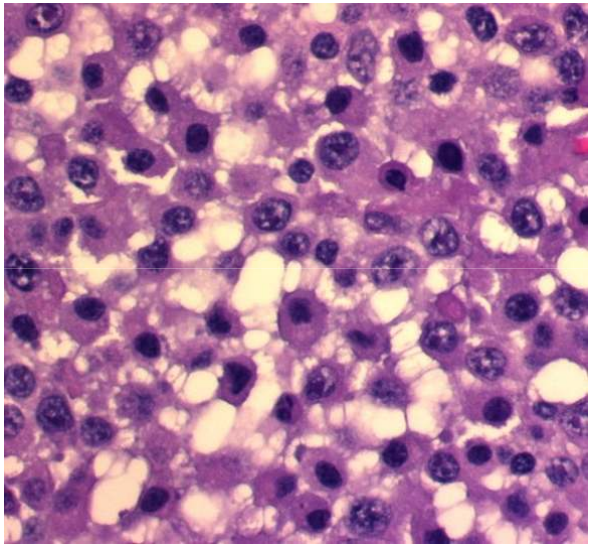

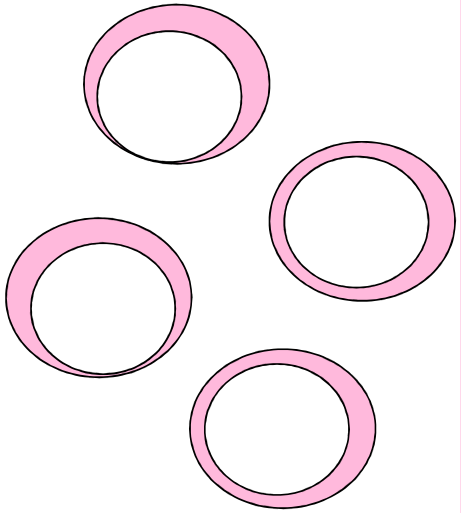

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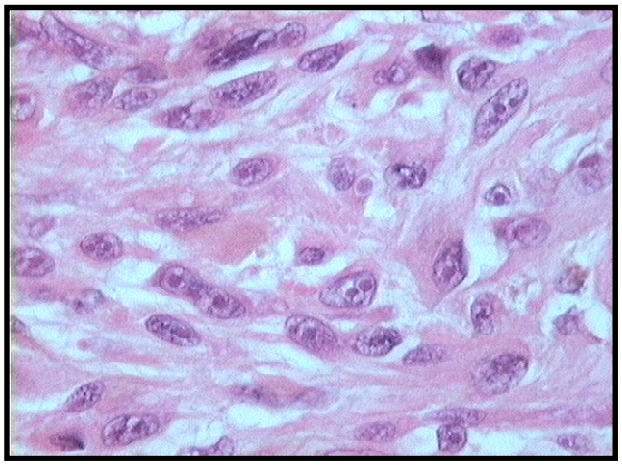

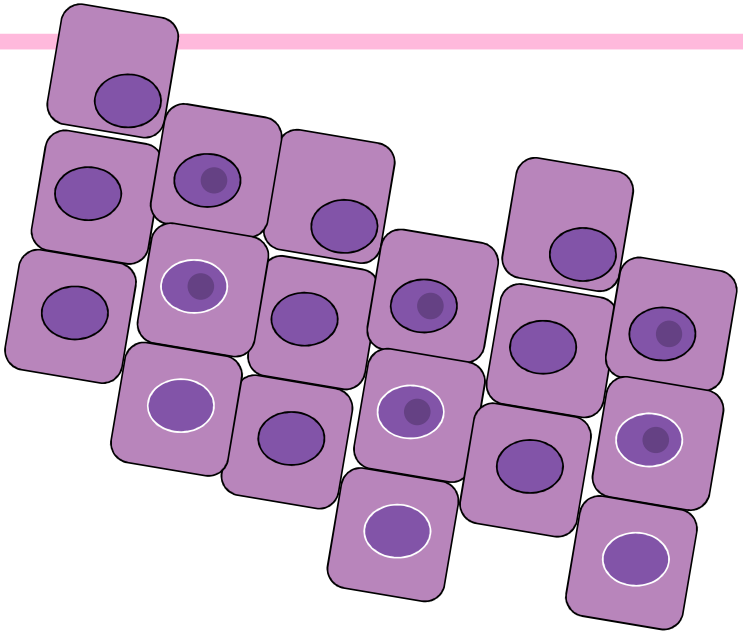

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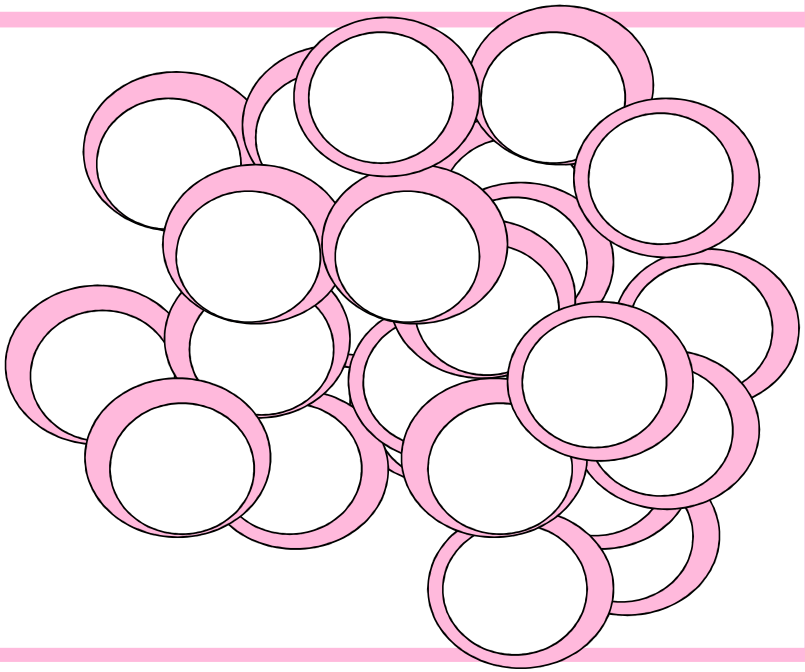

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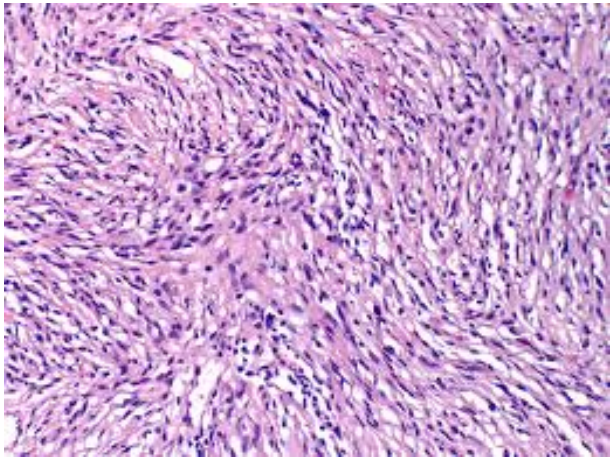

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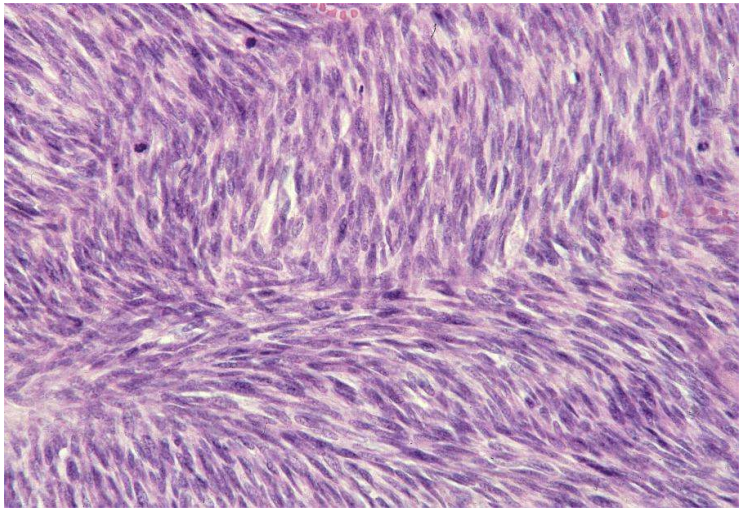
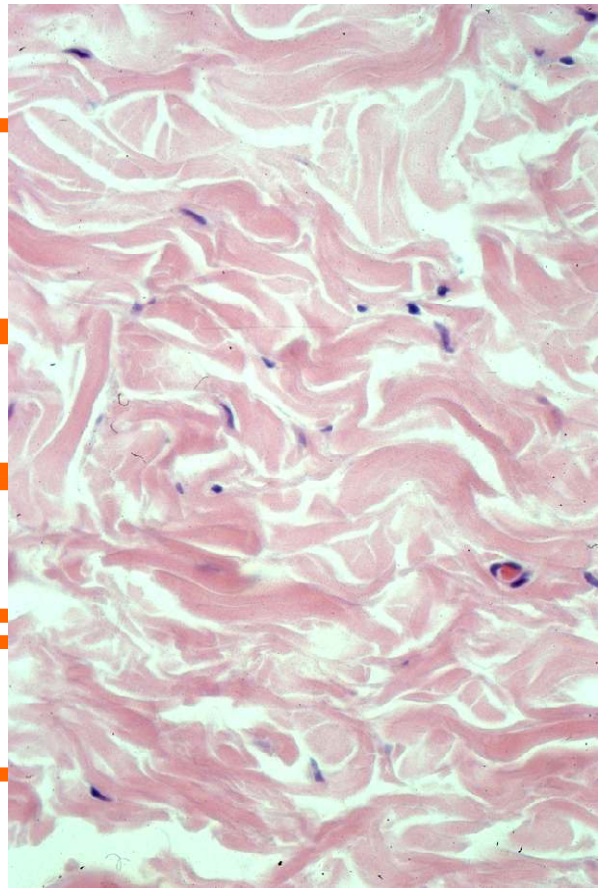


Stroma intercellulare



Stroma intercellulare