Pattern base approach to soft tissue tumors

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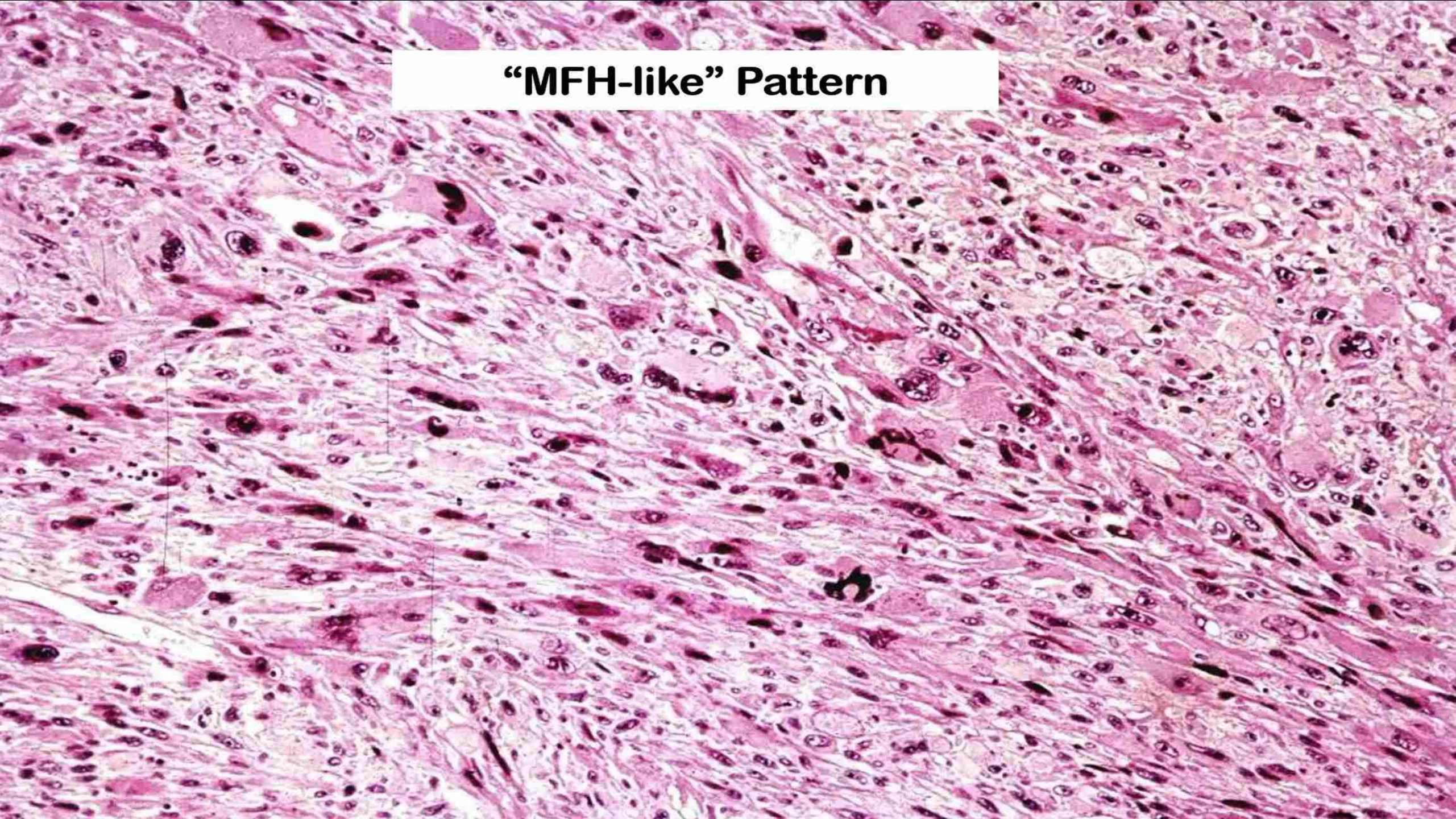
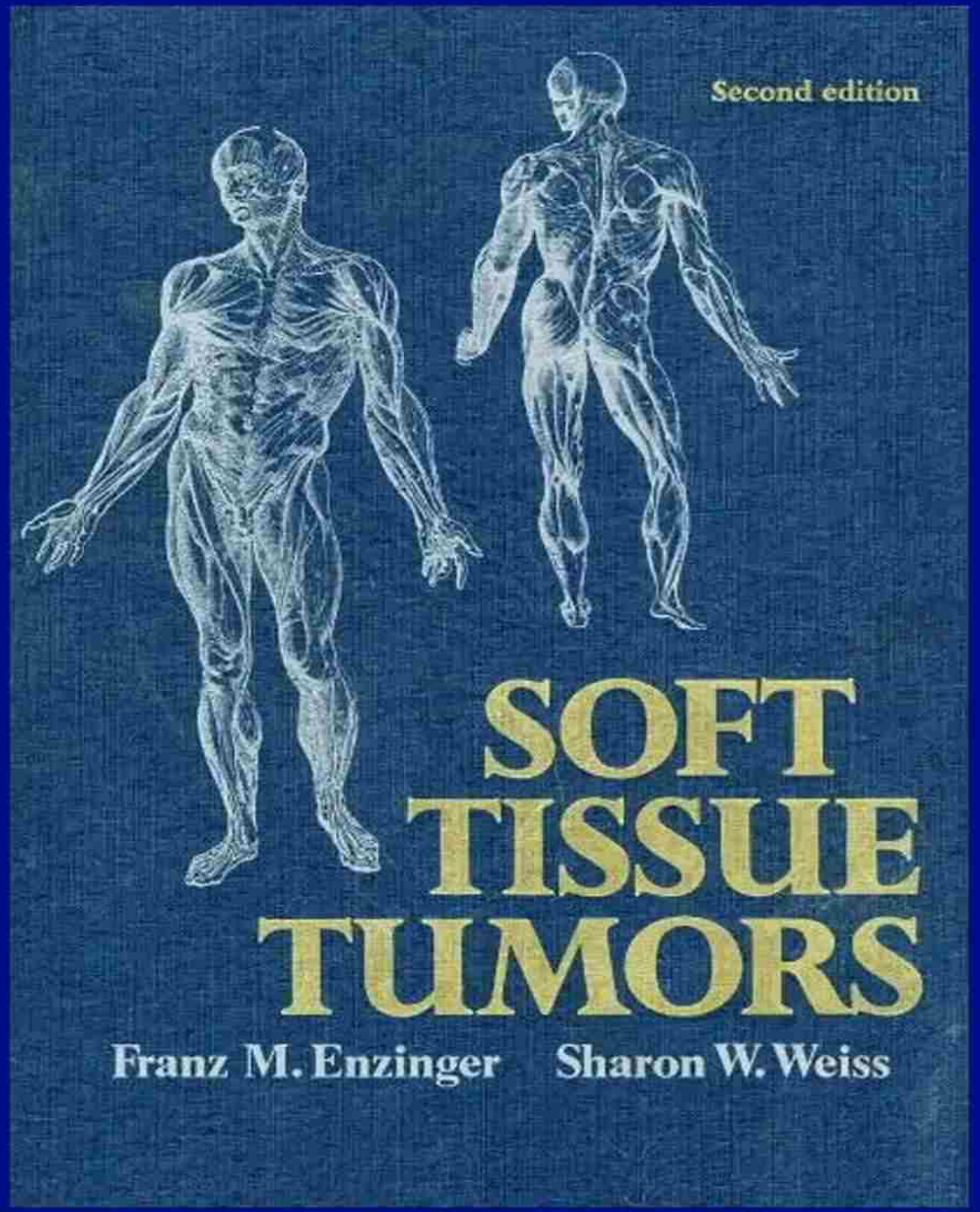
Tumor Patterns

- "MFH-like" pattern
- Highly cellular spindle cell pattern
- Myxoid soft tissue lesions
- Round cell pattern


“MFH-like” Pattern



Malignant Fibrous Histiocytoma

- Storiform-pleomorphic
- Myxoid
- Giant cell
- Inflammatory
- Angiomatoid

“MFH-like” Pattern

- Pleomorphic sarcoma with a specific line of differentiation
- Dedifferentiated sarcoma
- Pseudosarcoma with “MFH-like” pattern
- Undifferentiated pleomorphic sarcoma (so-called MFH)

Pleomorphic Sarcomas

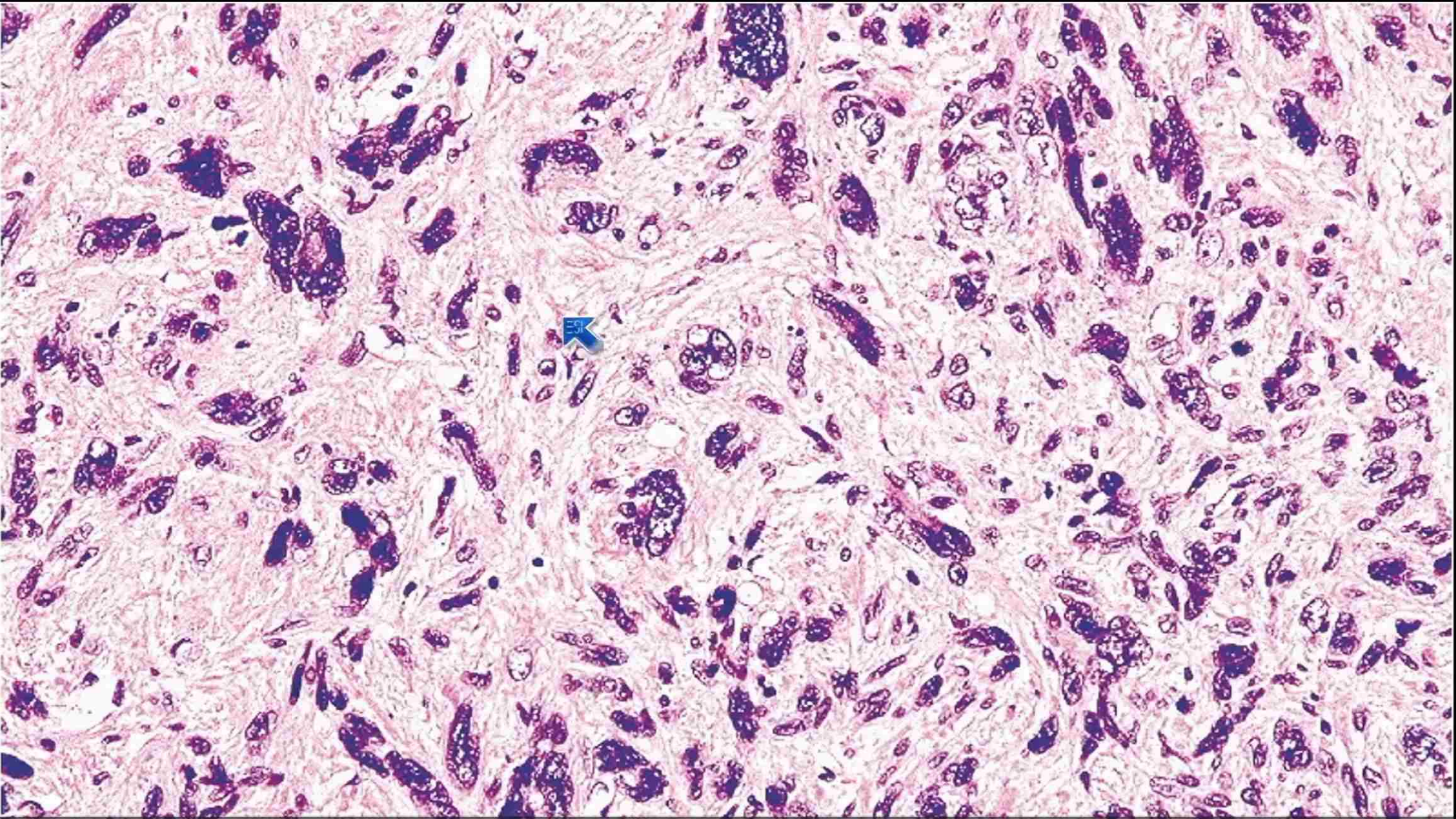
Tumor	Metastatic Risk
Pleomorphic leiomyosarcoma	70%
Pleomorphic liposarcoma	50%
Pleomorphic rhabdomyosarcoma	>90%
Extraskeletal osteosarcoma	60%
Undifferentiated pleomorphic sarcoma (UPS)	50%
Myxofibrosarcoma (high-grade)	25-30%
Dedifferentiated liposarcoma	15-20%

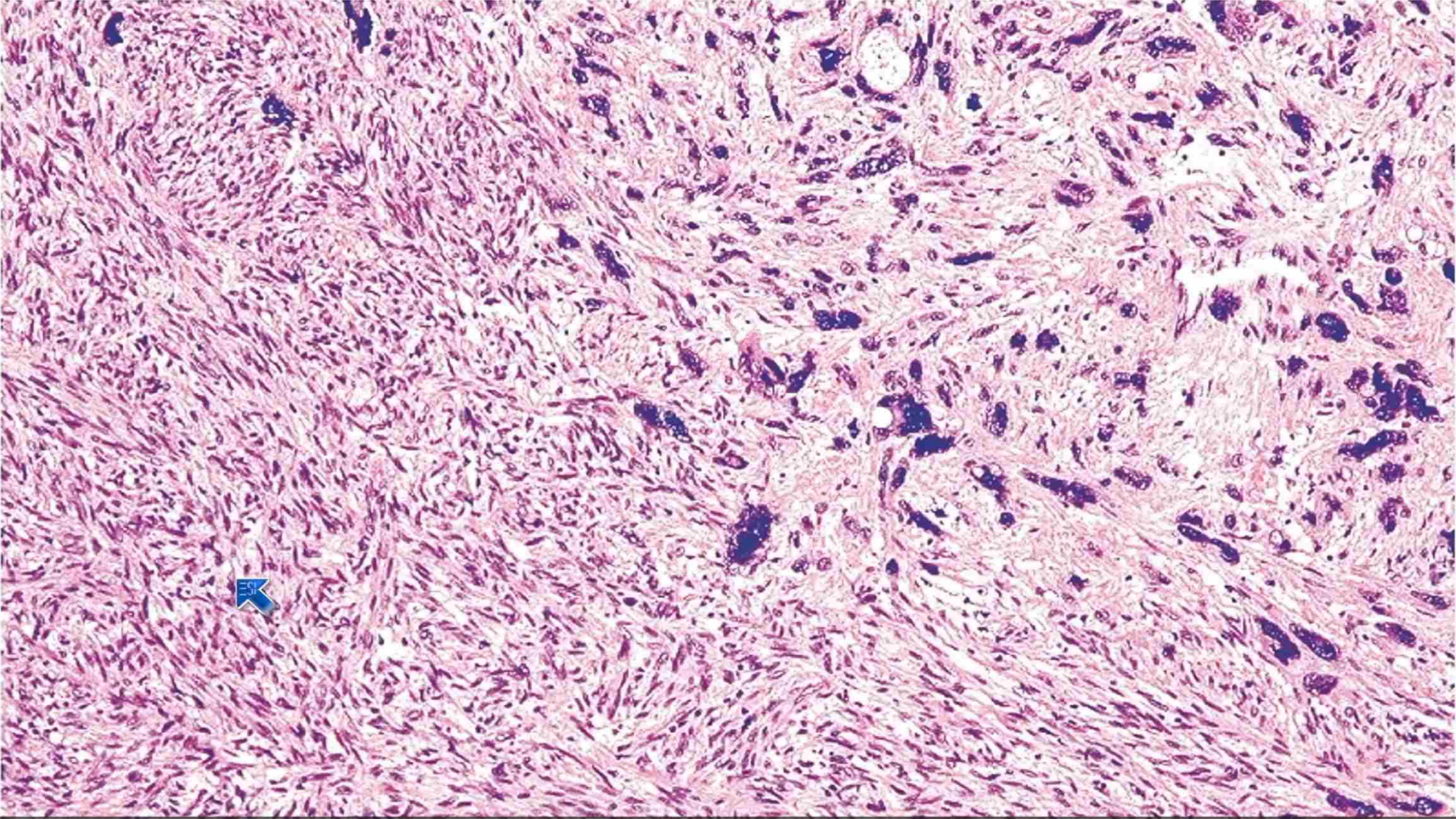
Pleomorphic Sarcomas: Considerations

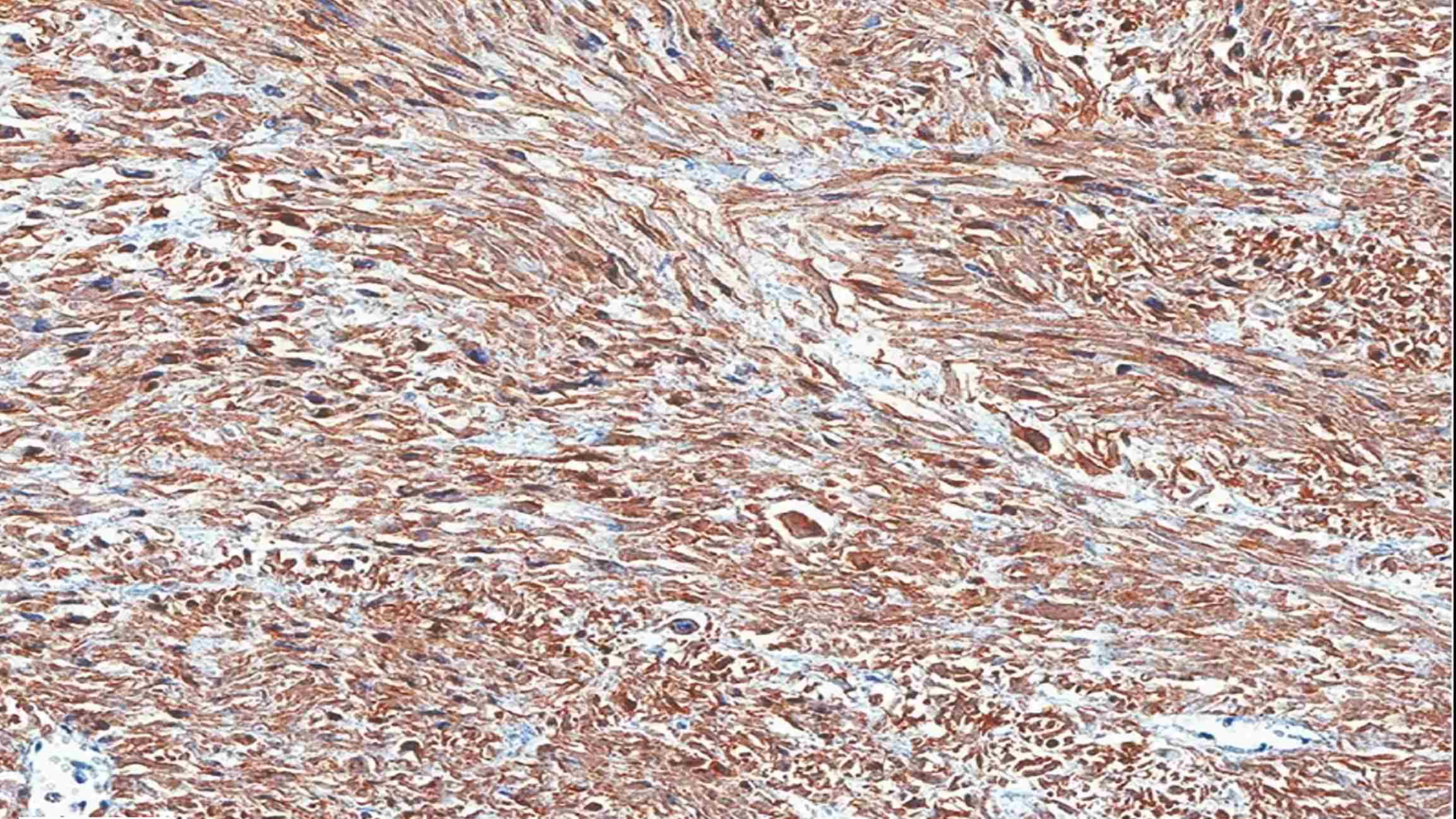
- Anatomic site
  - Extremities: myxofibrosarcoma (superficial), pleo LMS, UPS
  - Retroperitoneum: dediff liposarcoma, pleo LMS
- Sample extensively: diagnostic clues may be very focal (e.g. lipoblasts)
- IHC and molecular analysis (e.g. MDM2) can be helpful in select cases

Pleomorphic Leiomyosarcoma

- Middle-aged to elderly
- Extremities, retroperitoneum, great vessels
- High metastatic risk (70%)
- IHC: SMA, desmin, caldesmon

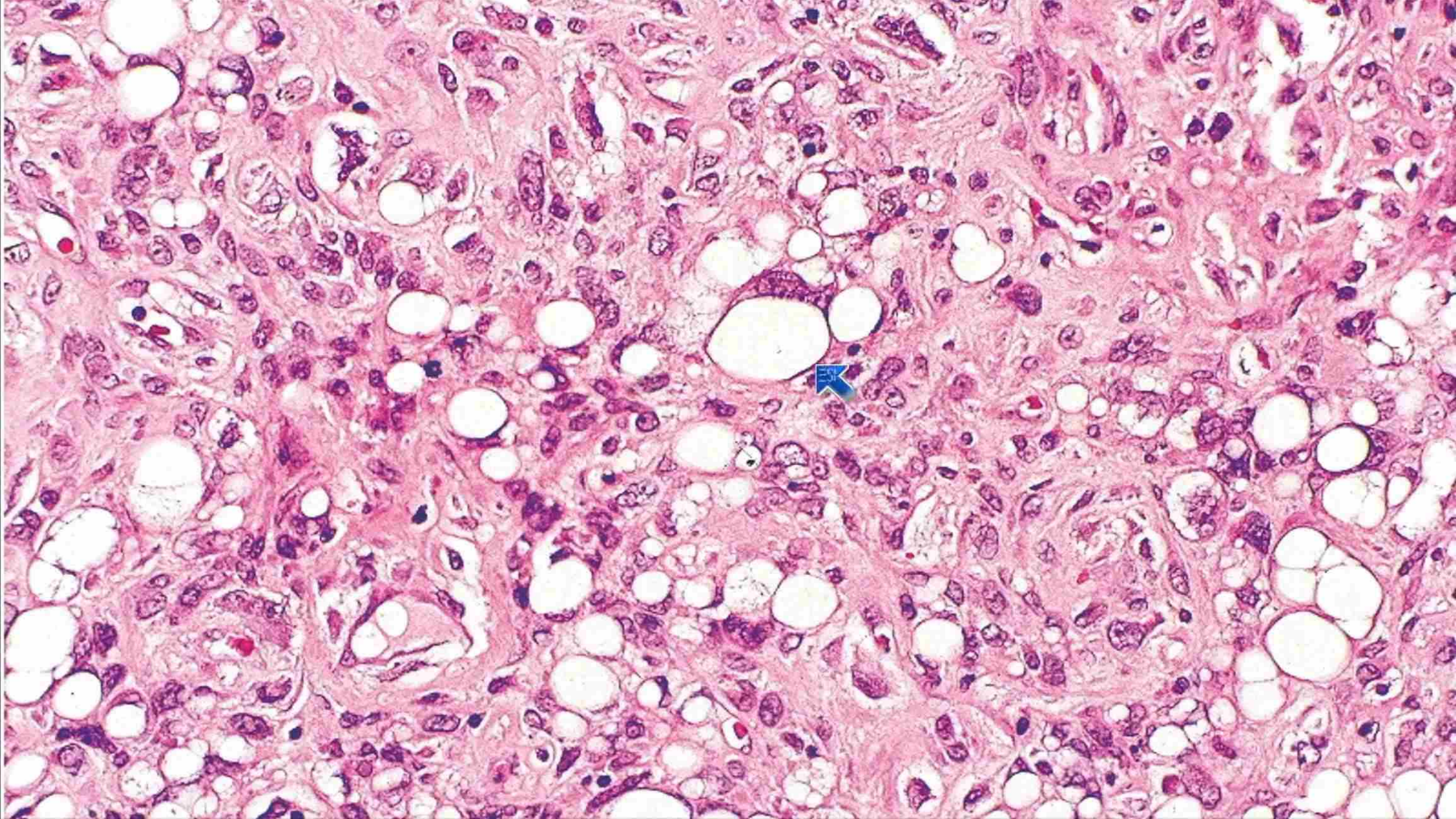


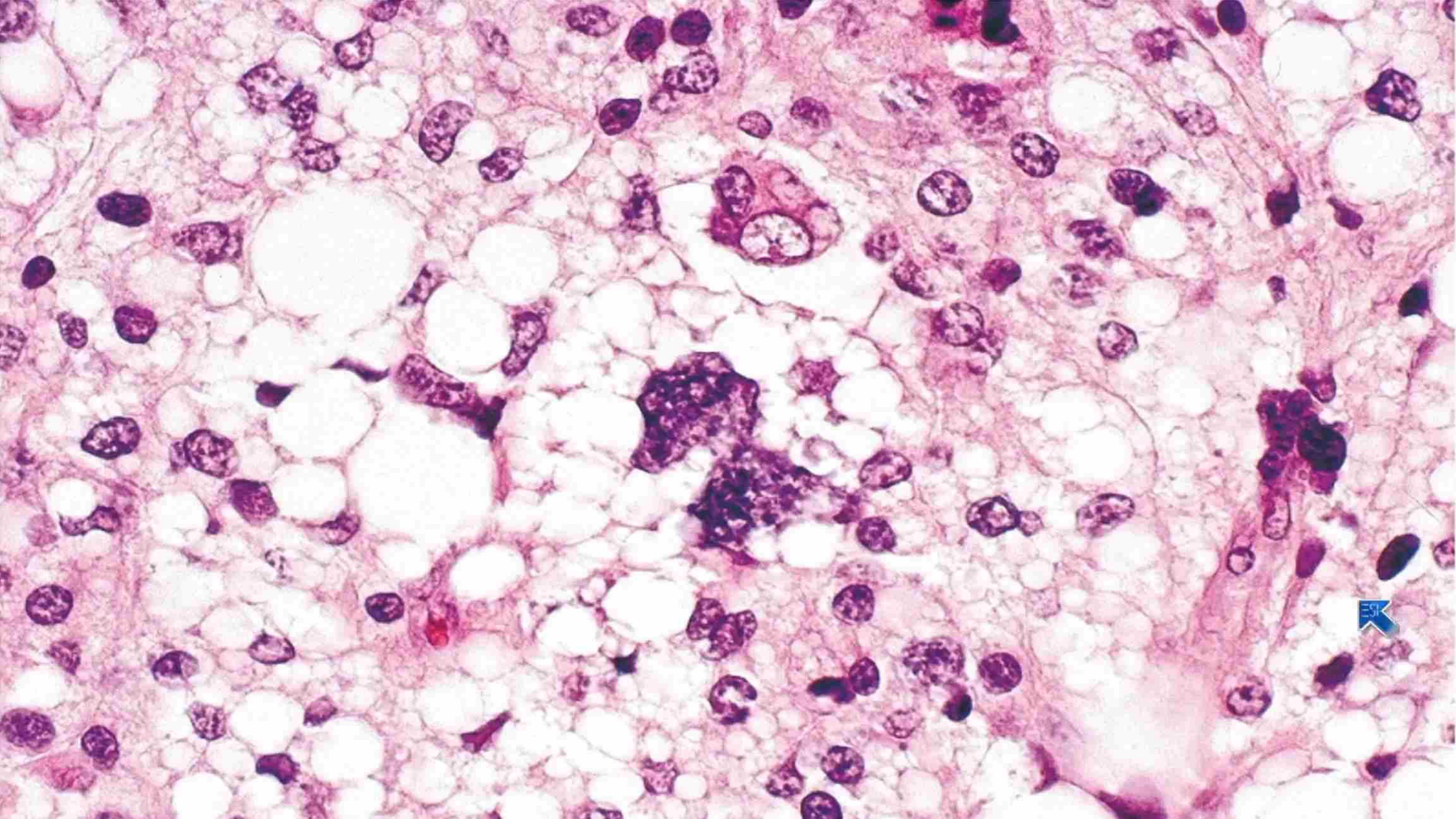


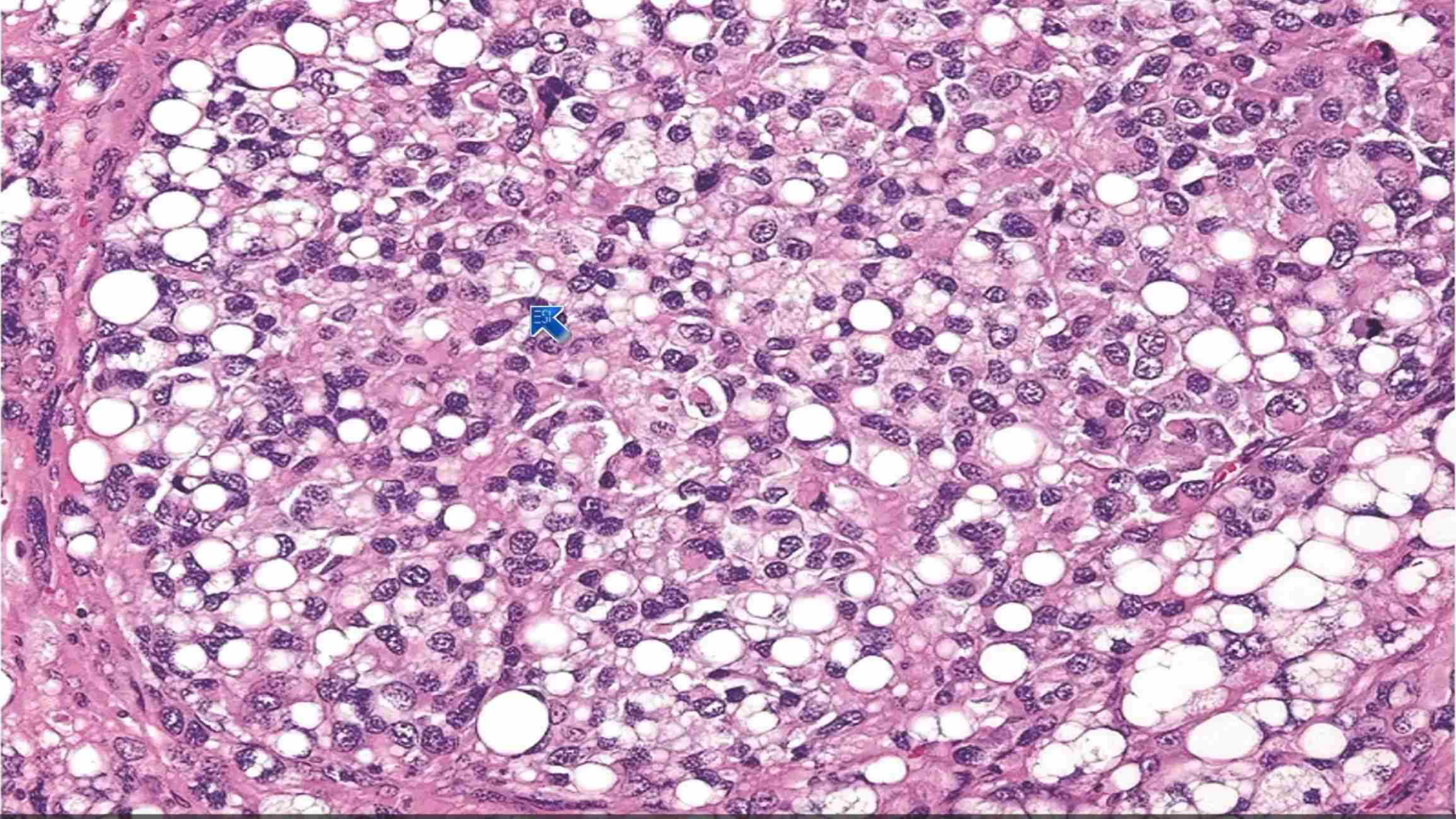


Pleomorphic Liposarcoma

- Middle-aged to elderly
- Extremities (rare in retroperitoneum)
- Deep>>superficial
- Metastatic rate 50%
- IHC: not useful ⟶ identify pleomorphic lipoblasts

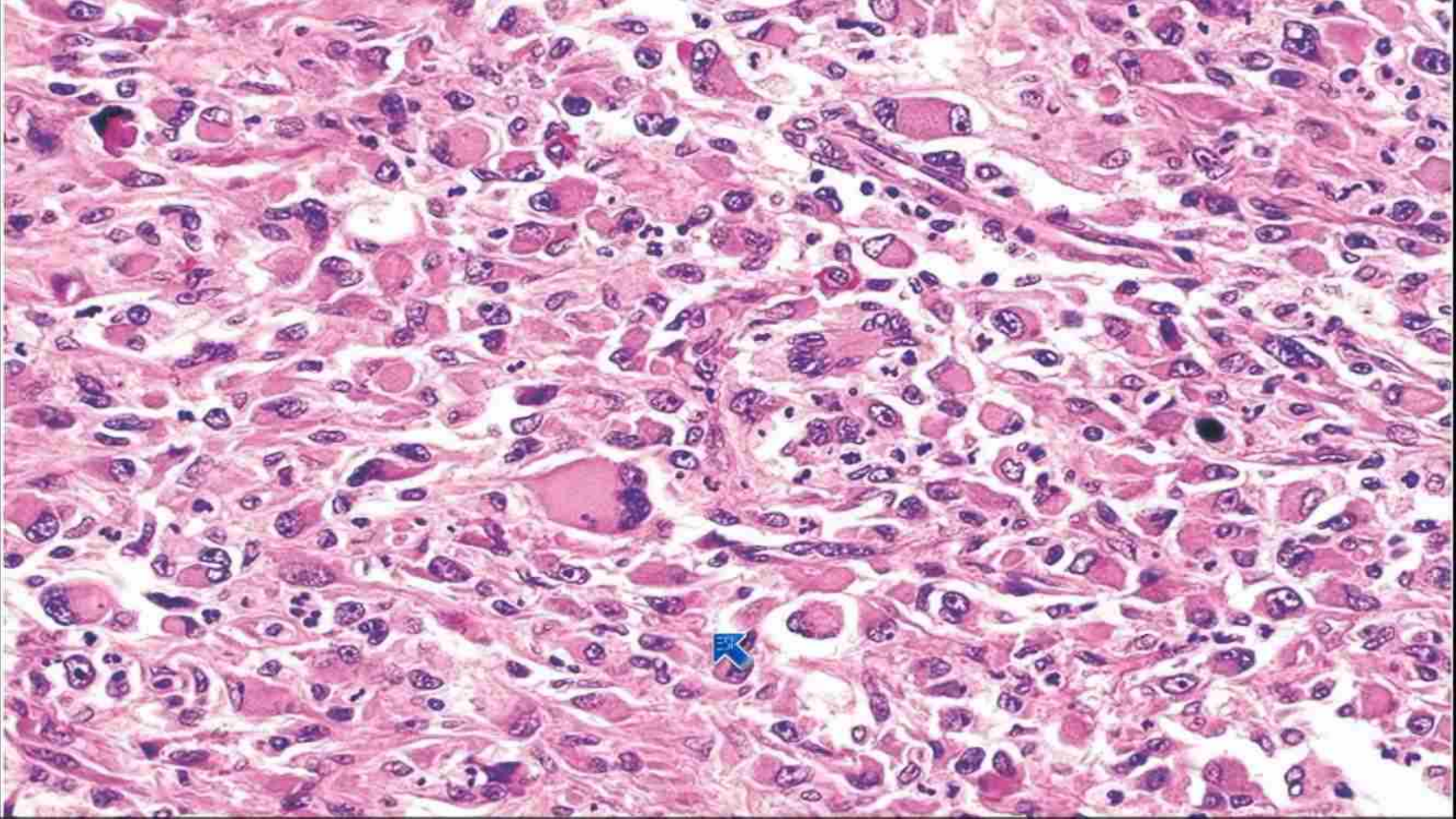


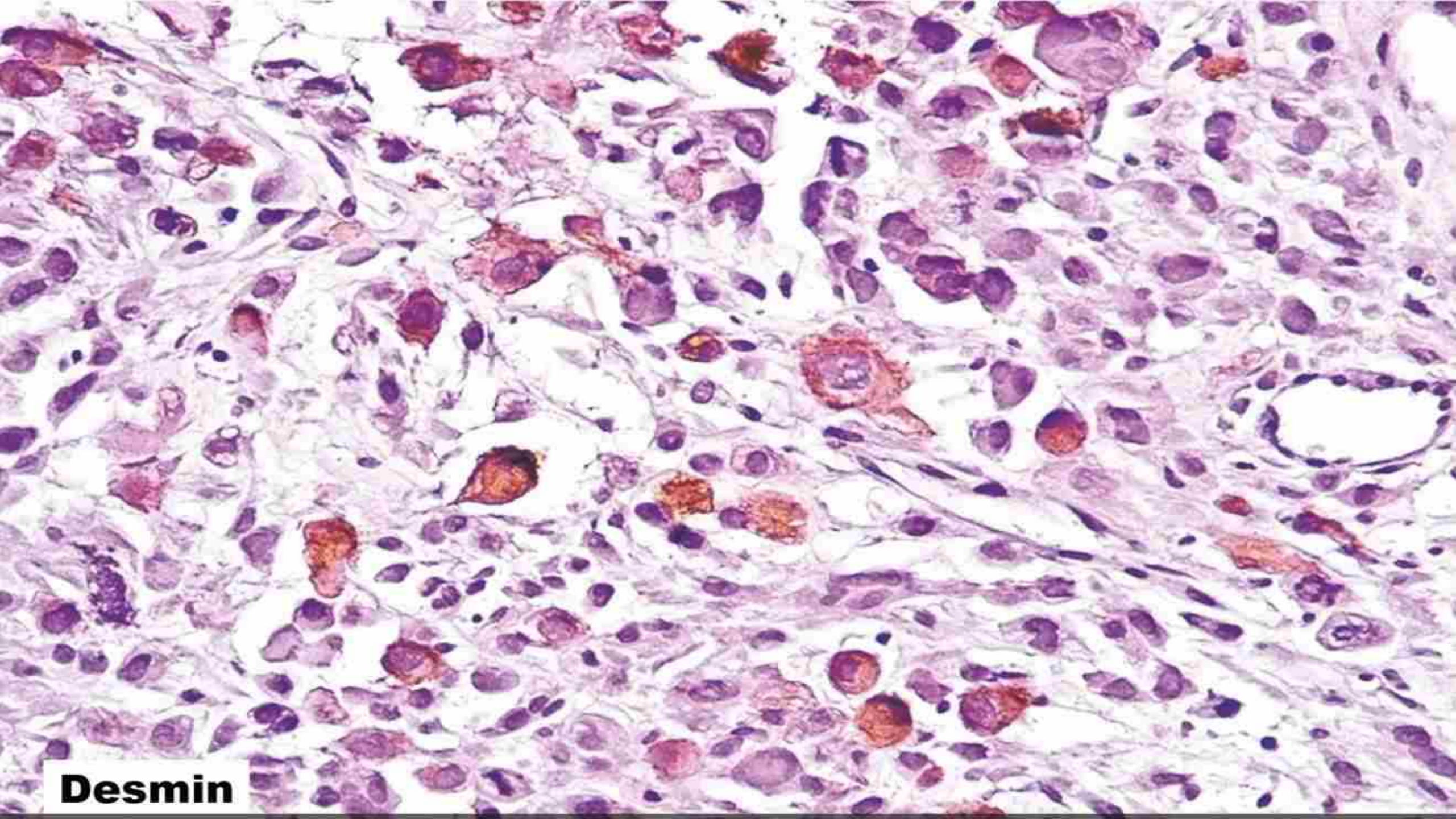




Pleomorphic Rhabdomyosarcoma

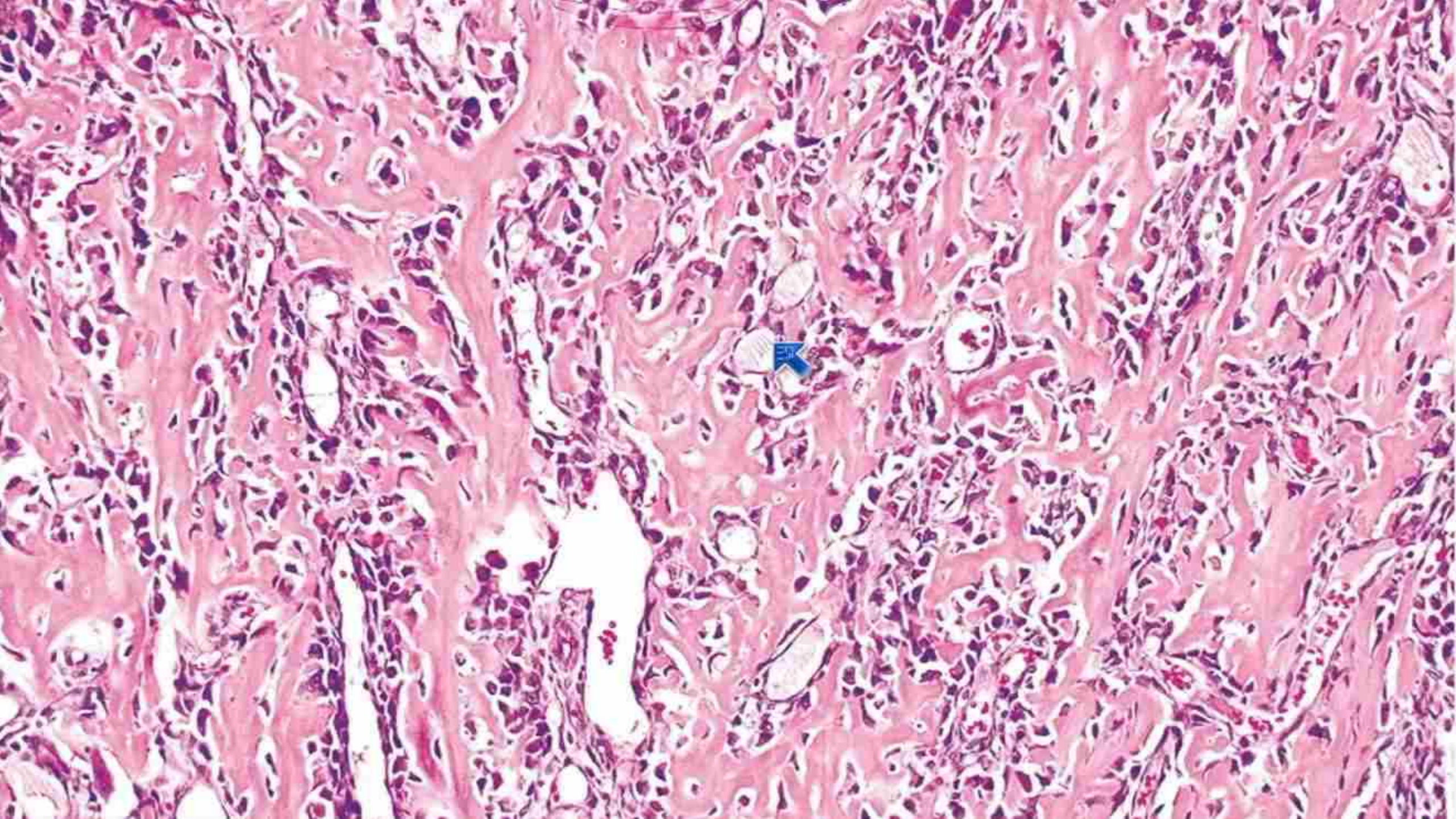
- Elderly patients
- Deep soft tissue of extremities (esp lower)
- Highest metastatic rate of all pleomorphic sarcoma (>90%)
- IHC: desmin, myogenin, MyoD1




Desmin

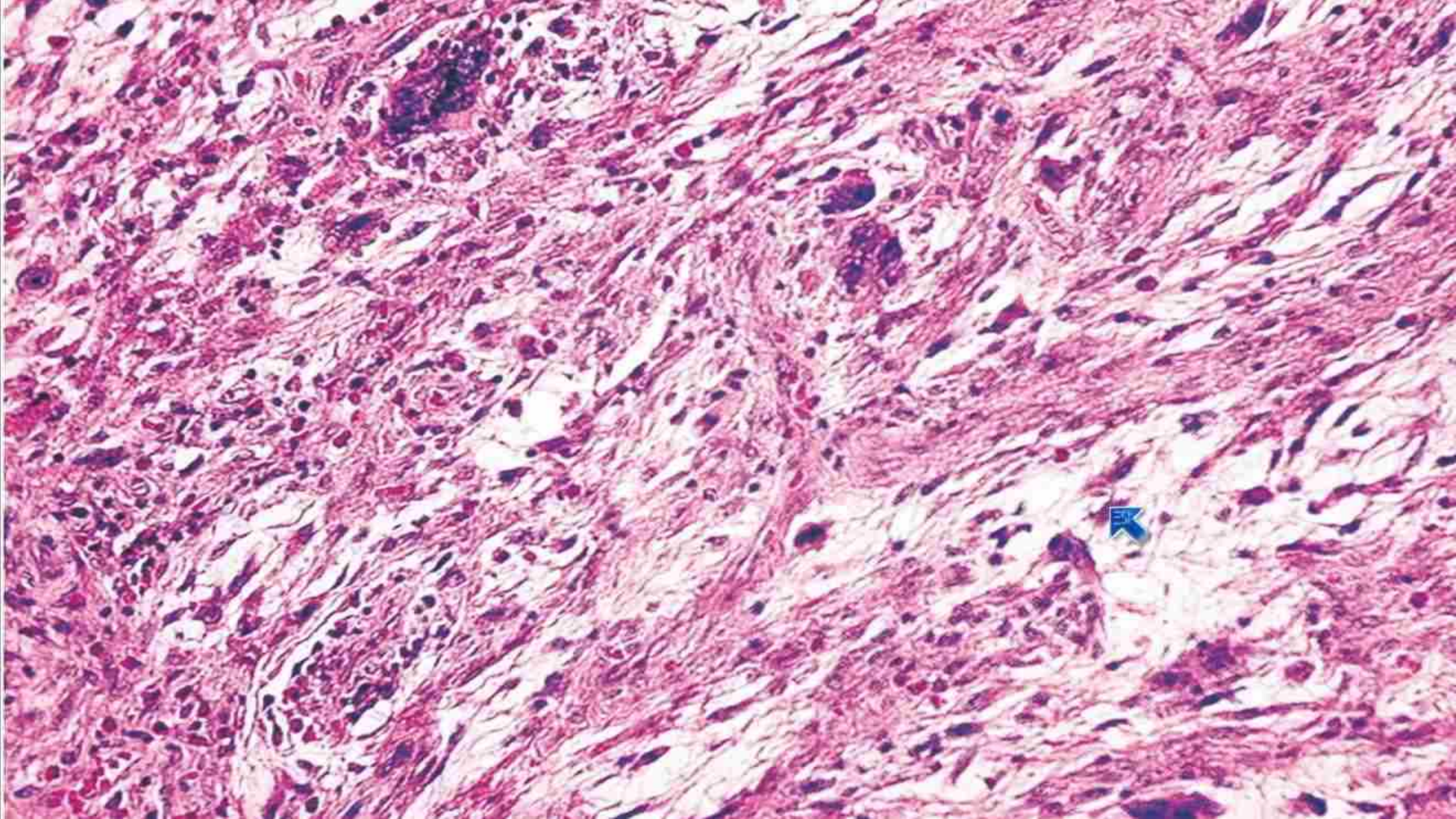
Extraskeletal Osteosarcoma

- Middle-aged to elderly patients (men>women)
- Deep soft tissue of extremities (esp proximal; thigh, shoulder)
- Frequent local recurrence and high metastatic rate (60%)
- IHC: SATB2



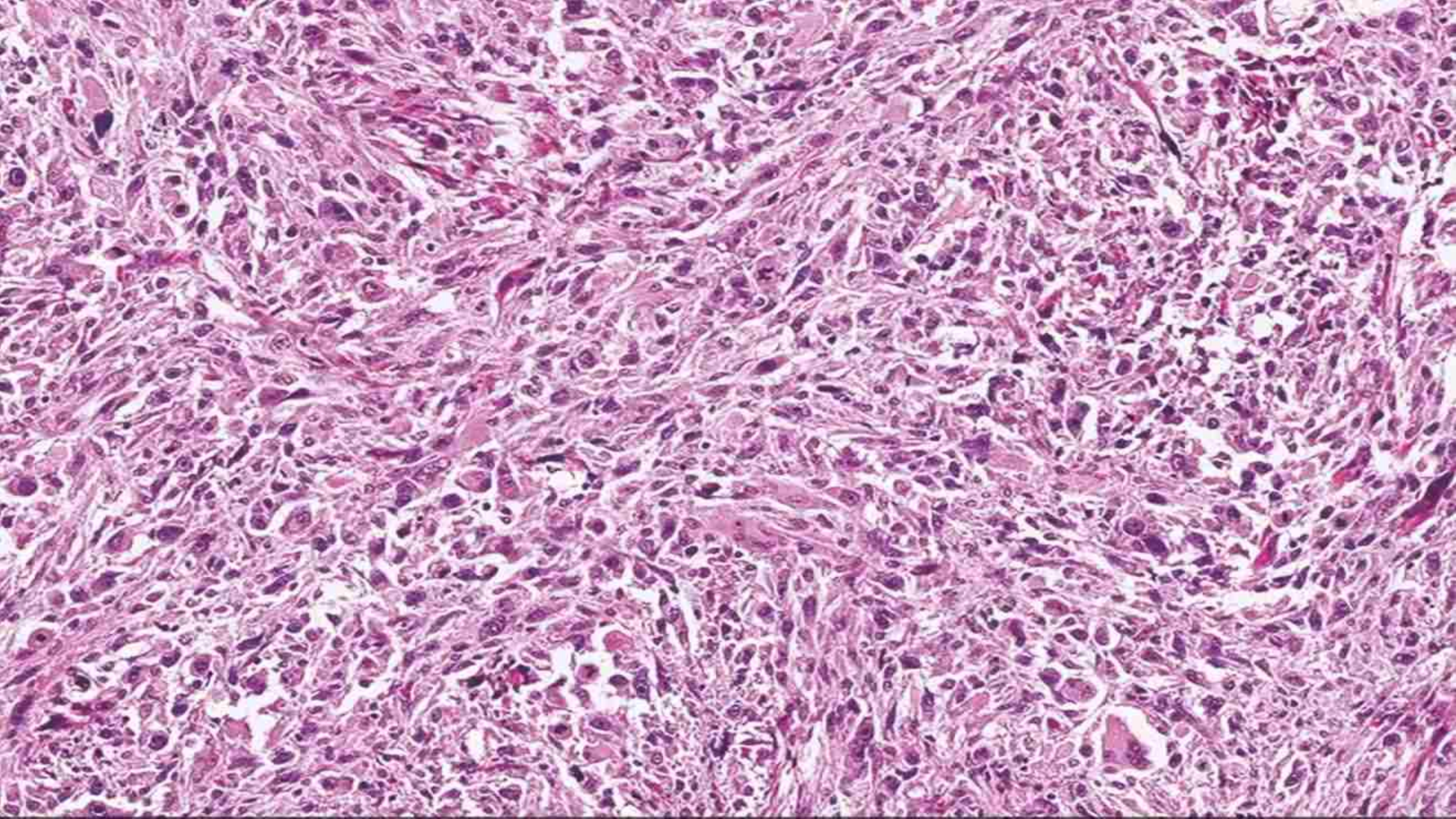
High-Grade Myxofibrosarcoma

- Middle-aged to elderly patients (most common sarcoma of elderly)
- Proximal extremities, trunk
- 70% superficial
- Frequent local recurrence
- Metastatic rate 25-30% (lower risk at lower grade)
- IHC: not particularly useful



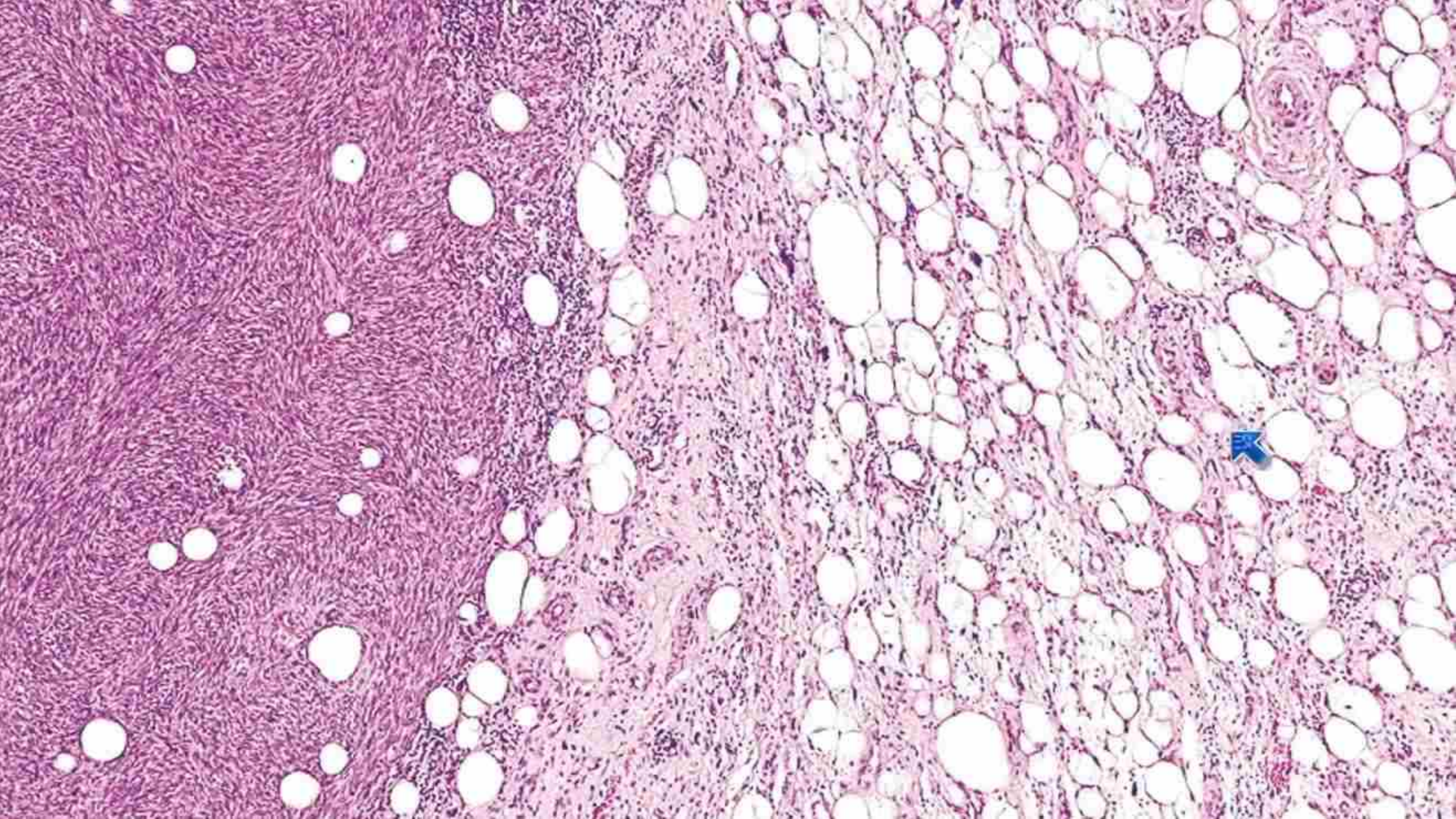
Undifferentiated Pleomorphic Sarcoma (UPS)

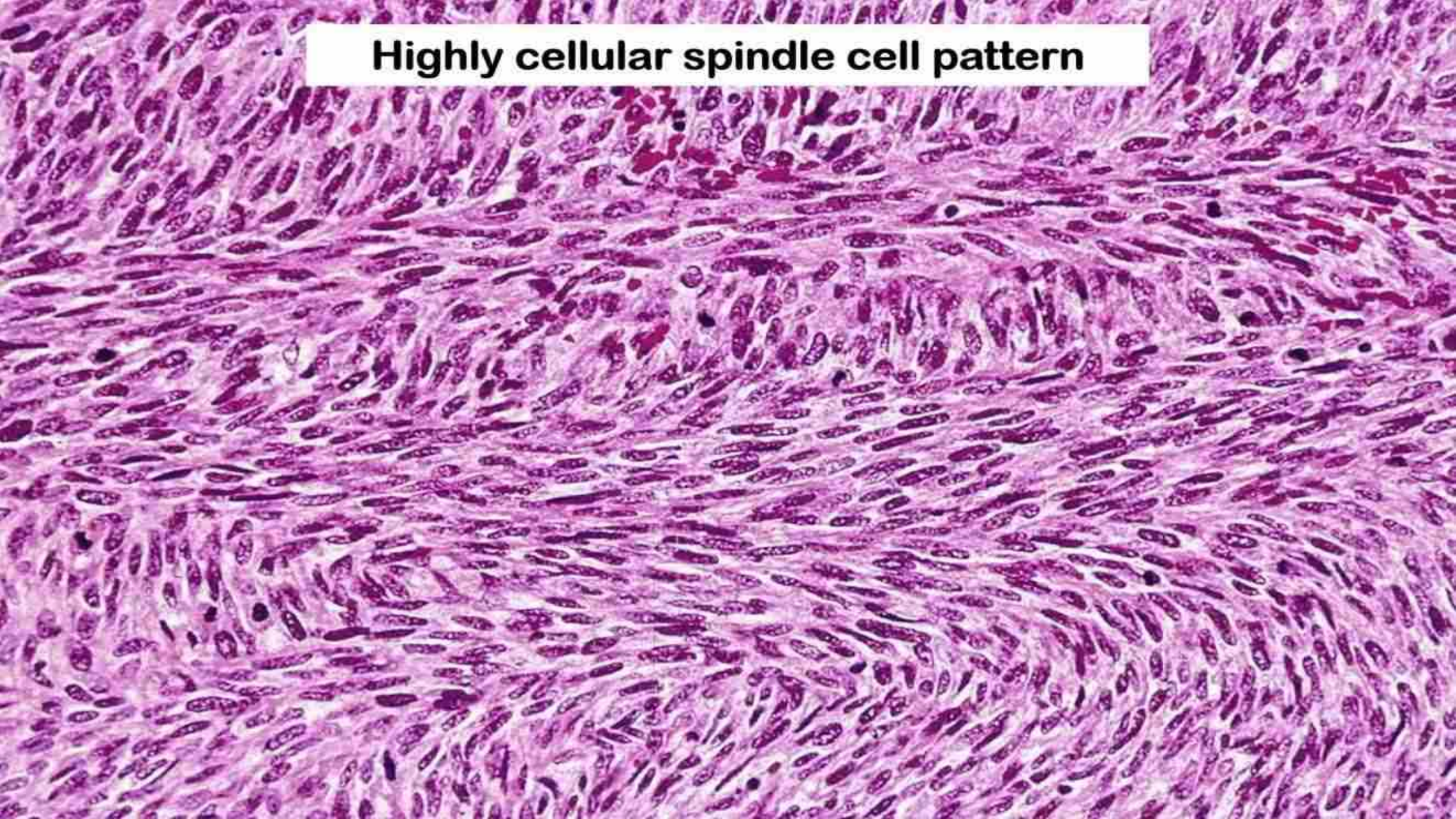
- Elderly patients
- Deep soft tissues of extremities
  (rare in retroperitoneum)
- Diagnosis of exclusion
- Metastatic rate 50%
- IHC: +/- SMA



Dedifferentiated Liposarcoma

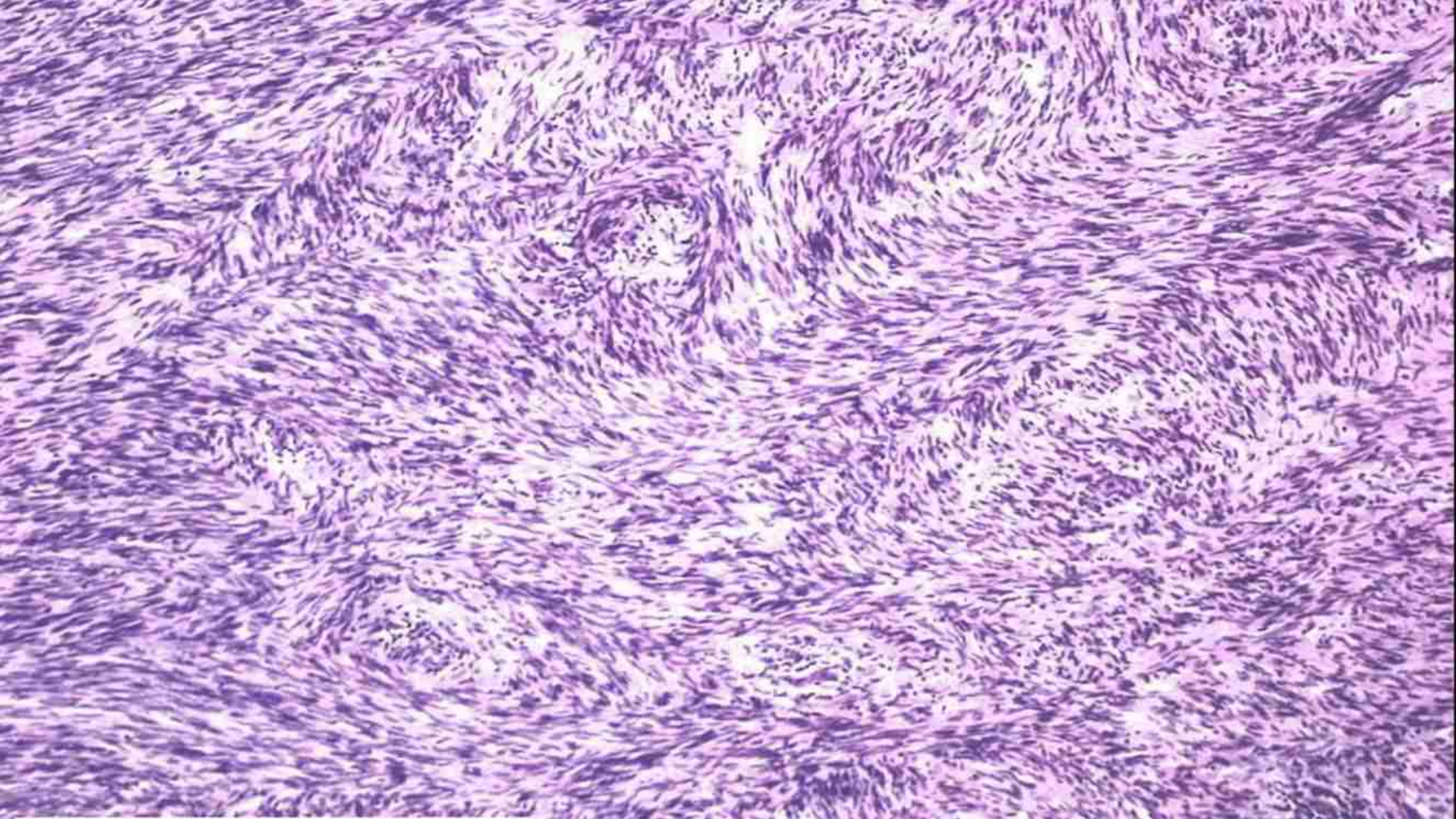
- Middle-aged to elderly patients
- Retroperitoneum >> abdominal cavity, mediastinum >> extremities
- Very high local recurrence rate
- Metastatic rate: 15-25% (but many die in 5-20 years)
- IHC/molecular: MDM2 (and CDK4)




Highly cellular spindle cell pattern

Highly Cellular Spindle Cell Tumors

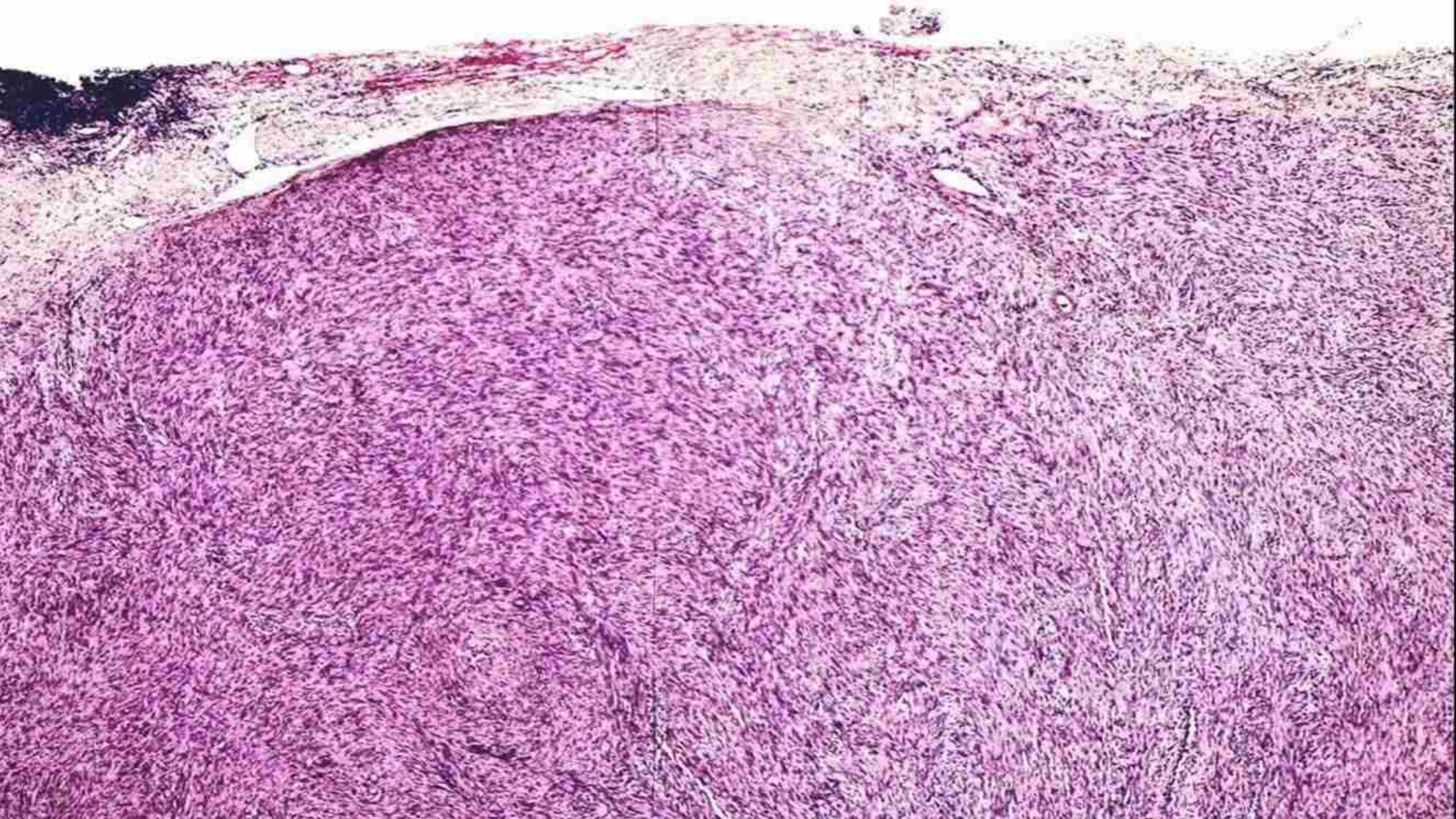
- Cellular schwannoma
- MPNST
- Fibrosarcoma
- Leiomyosarcoma
- Monophasic synovial sarcoma

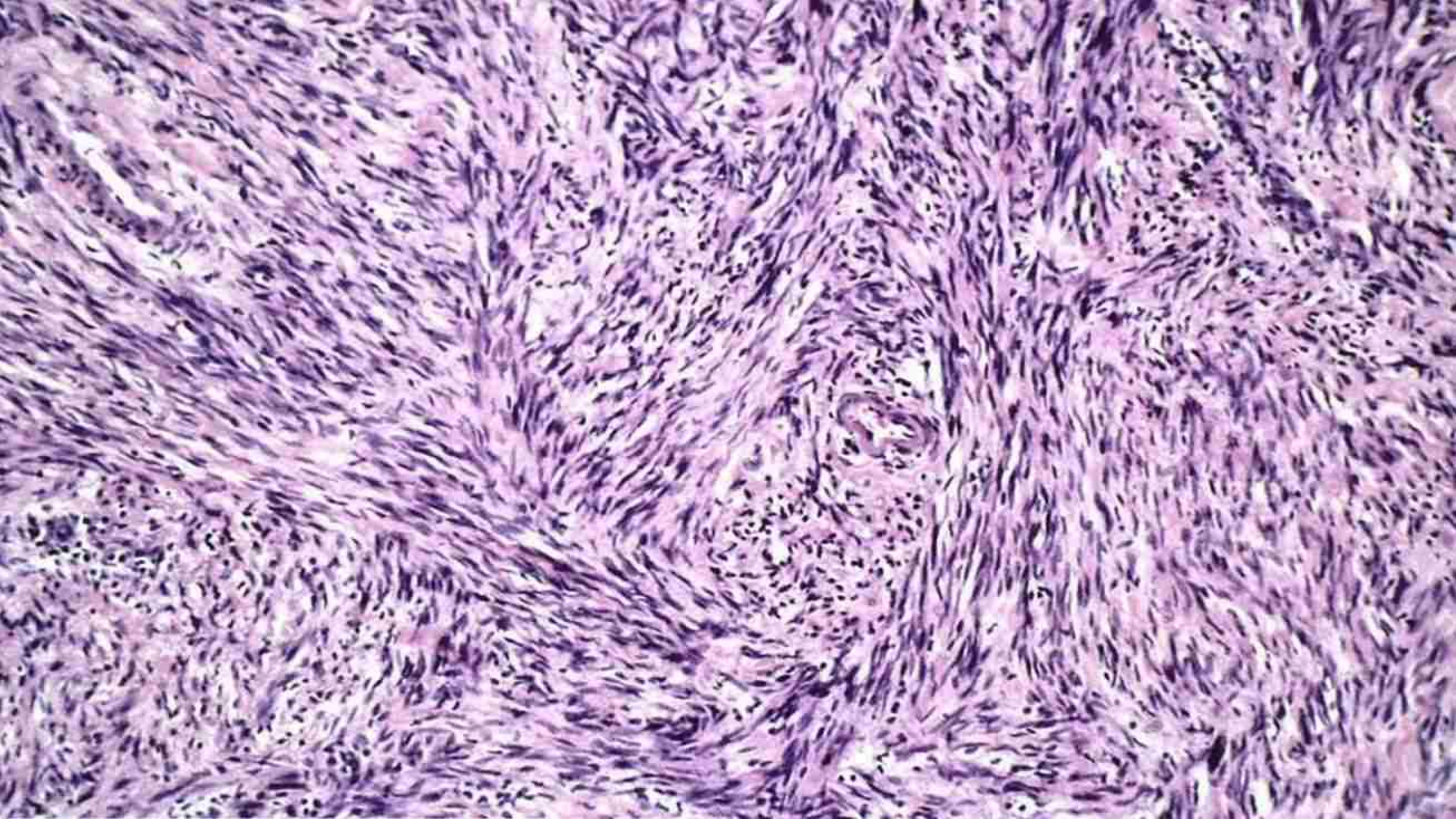


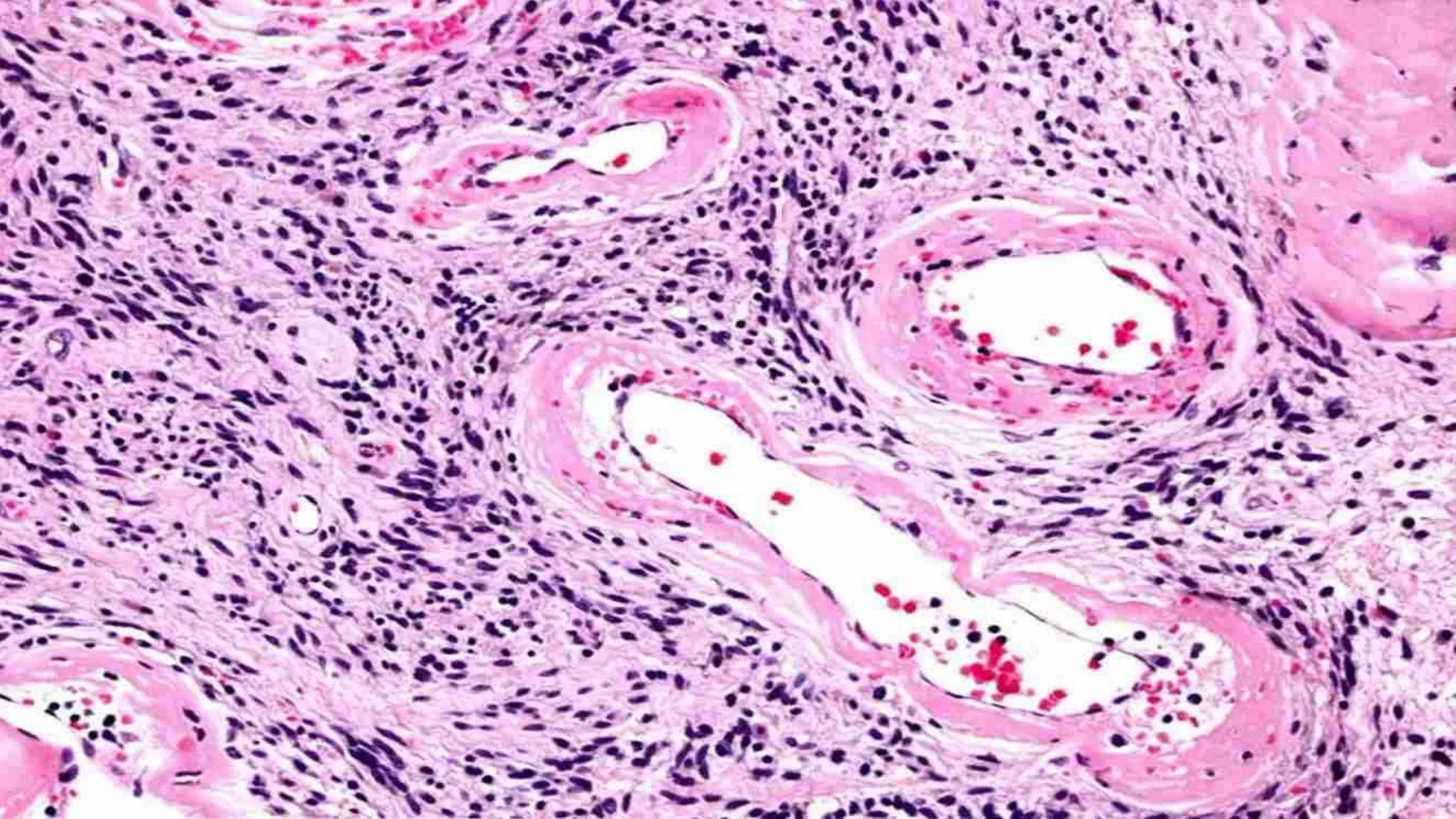
Cellular Schwannoma
Definition

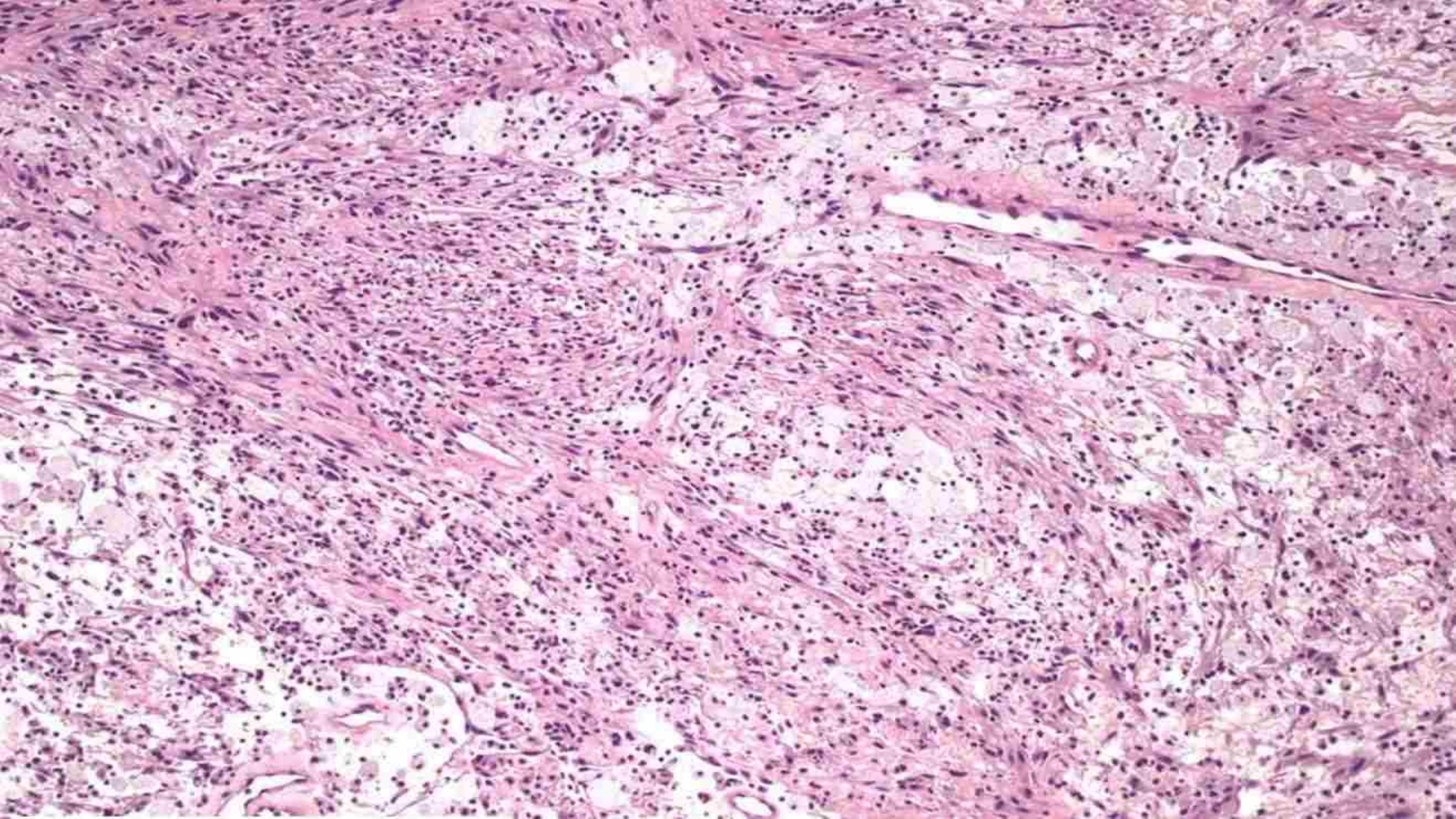
- Highly cellular schwann cell proliferation composed predominantly/ exclusively of Antoni A areas

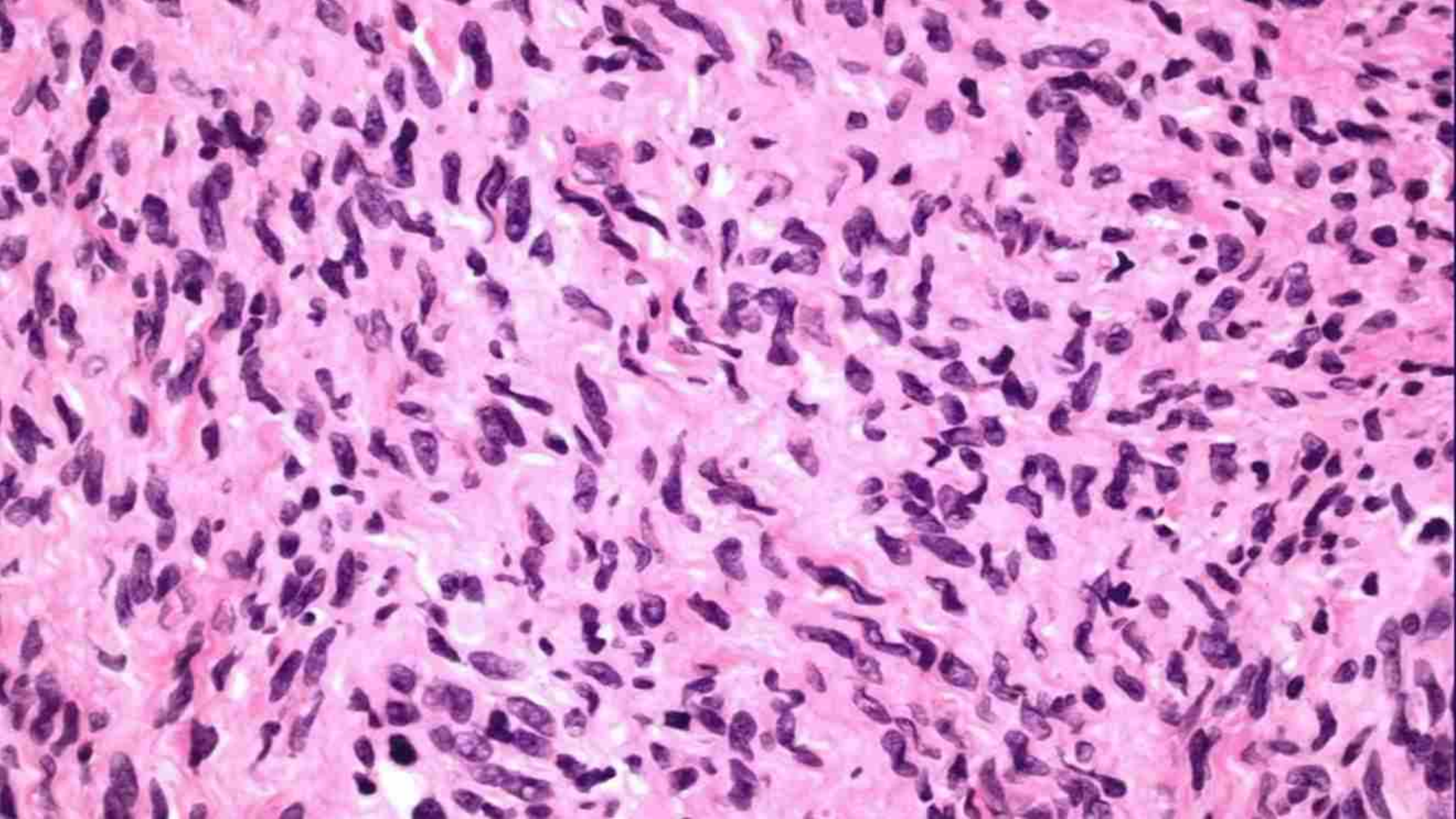
- Absence of well-formed Verocay bodies

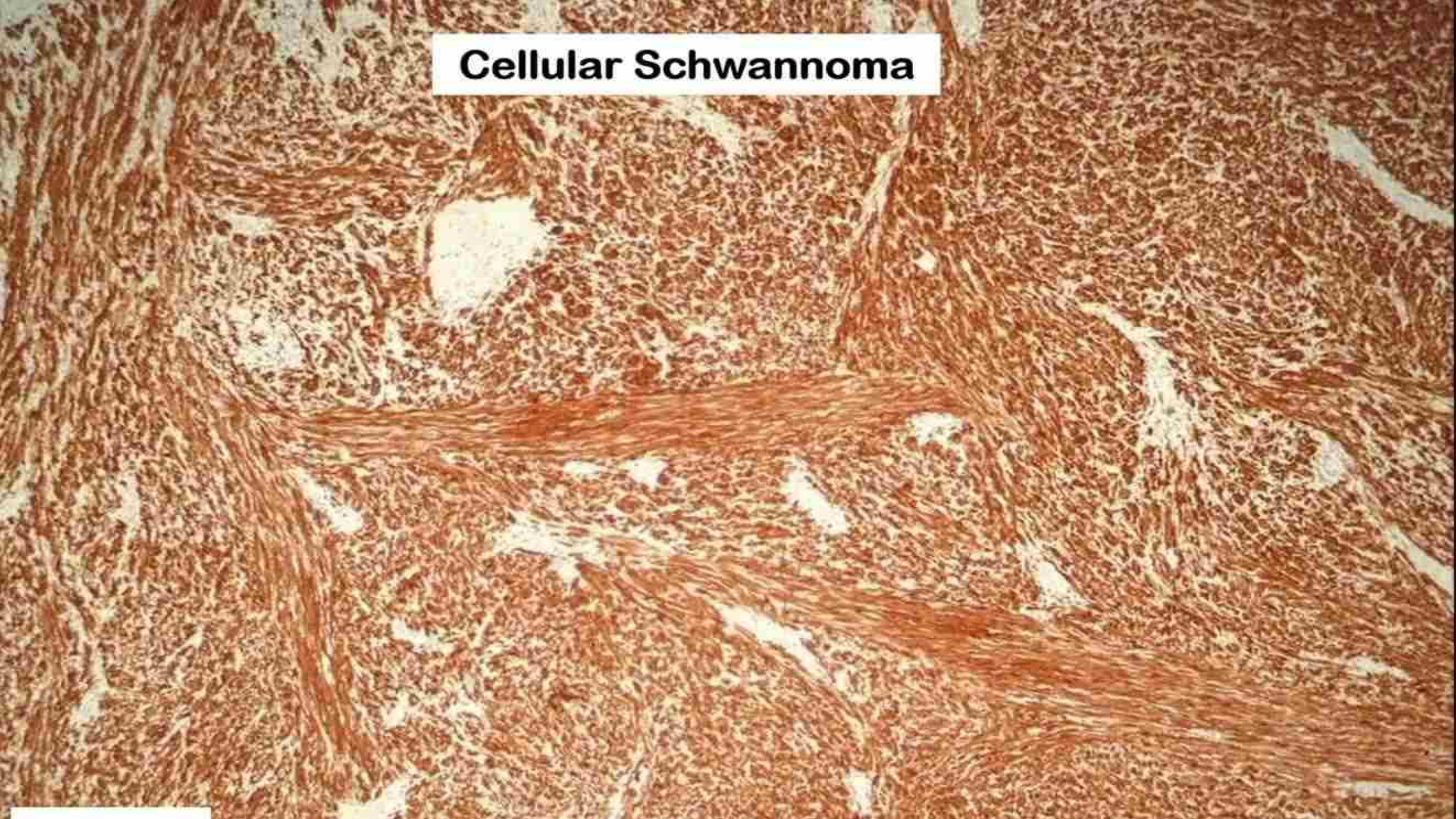











Cellular Schwannoma

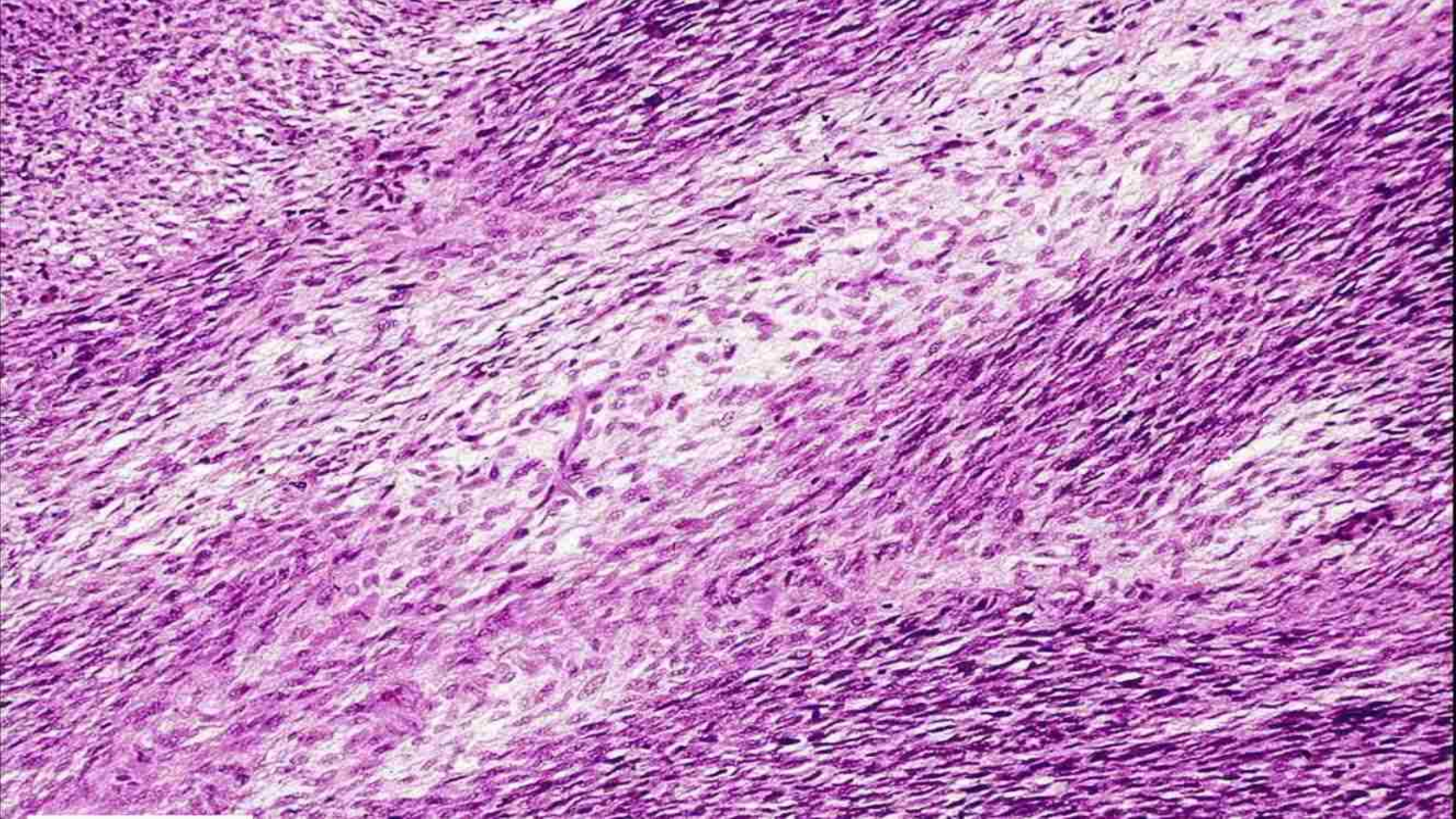
Cellular Schwannoma
Worrisome Features

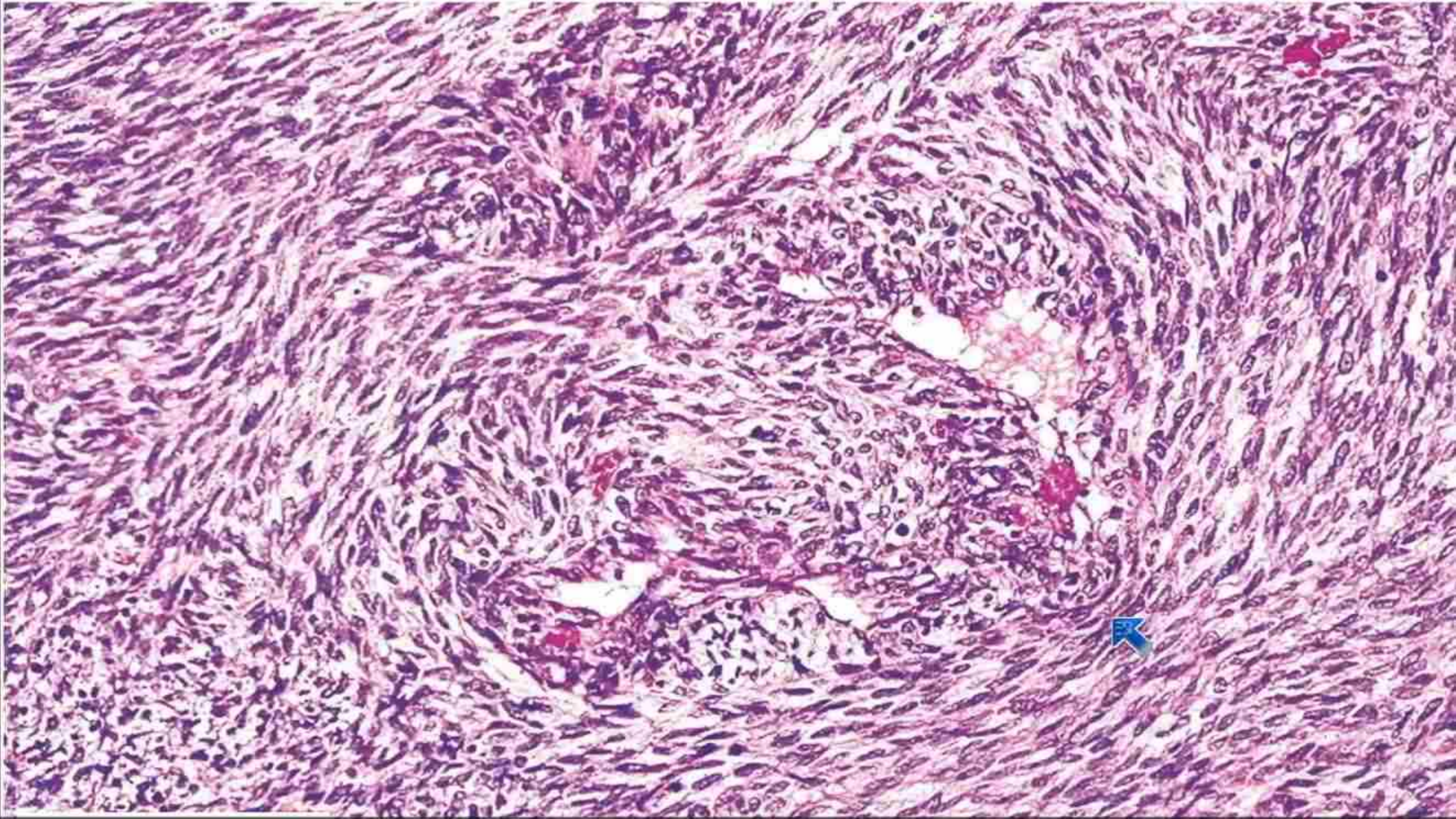
- High cellularity
- Mitotically active (usual < 4/10HPF)
- Nuclear atypia
- Focal necrosis
- Bony erosion

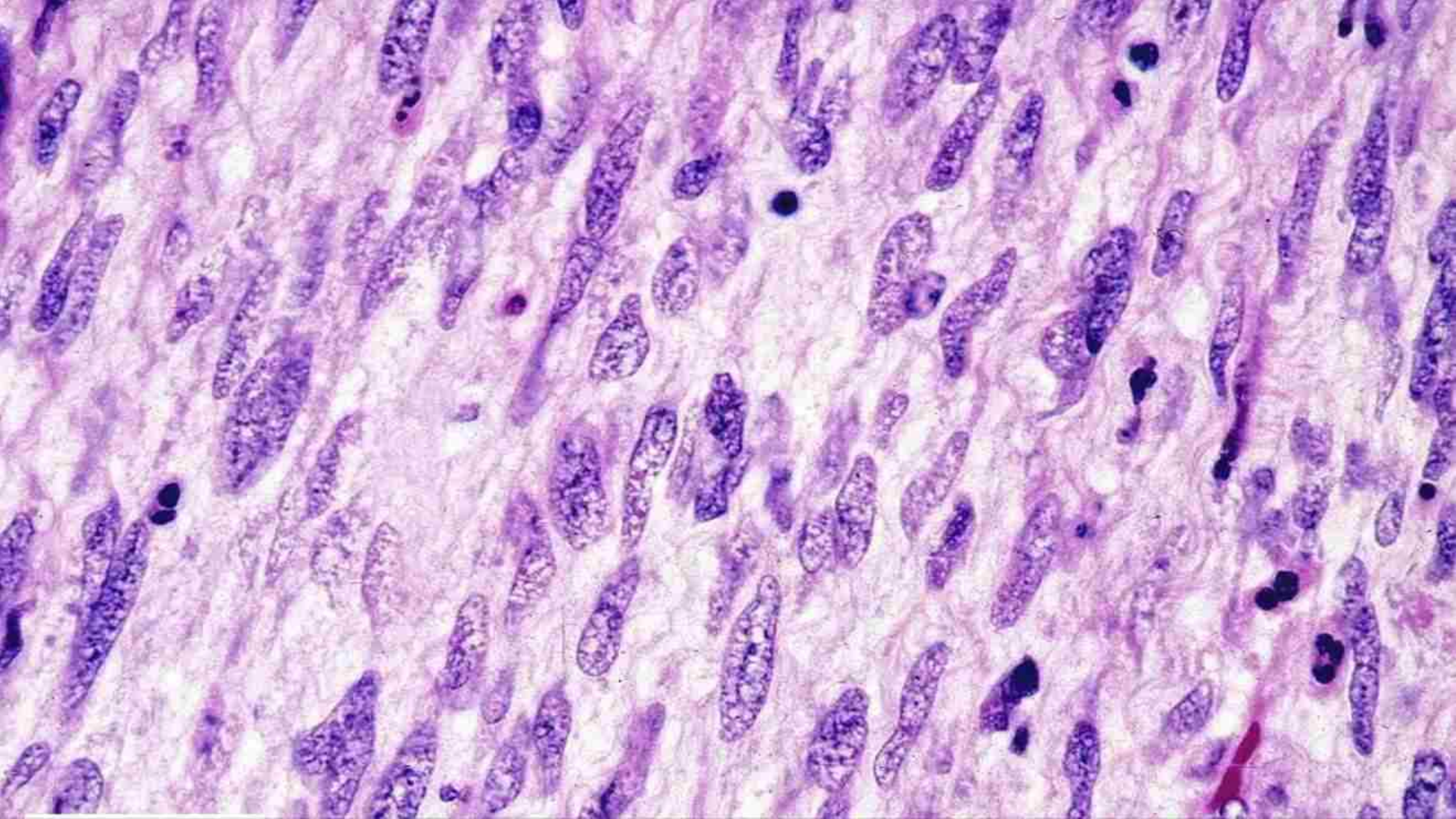
** THE PERFECT PSEUDOSARCOMA **

MPNST

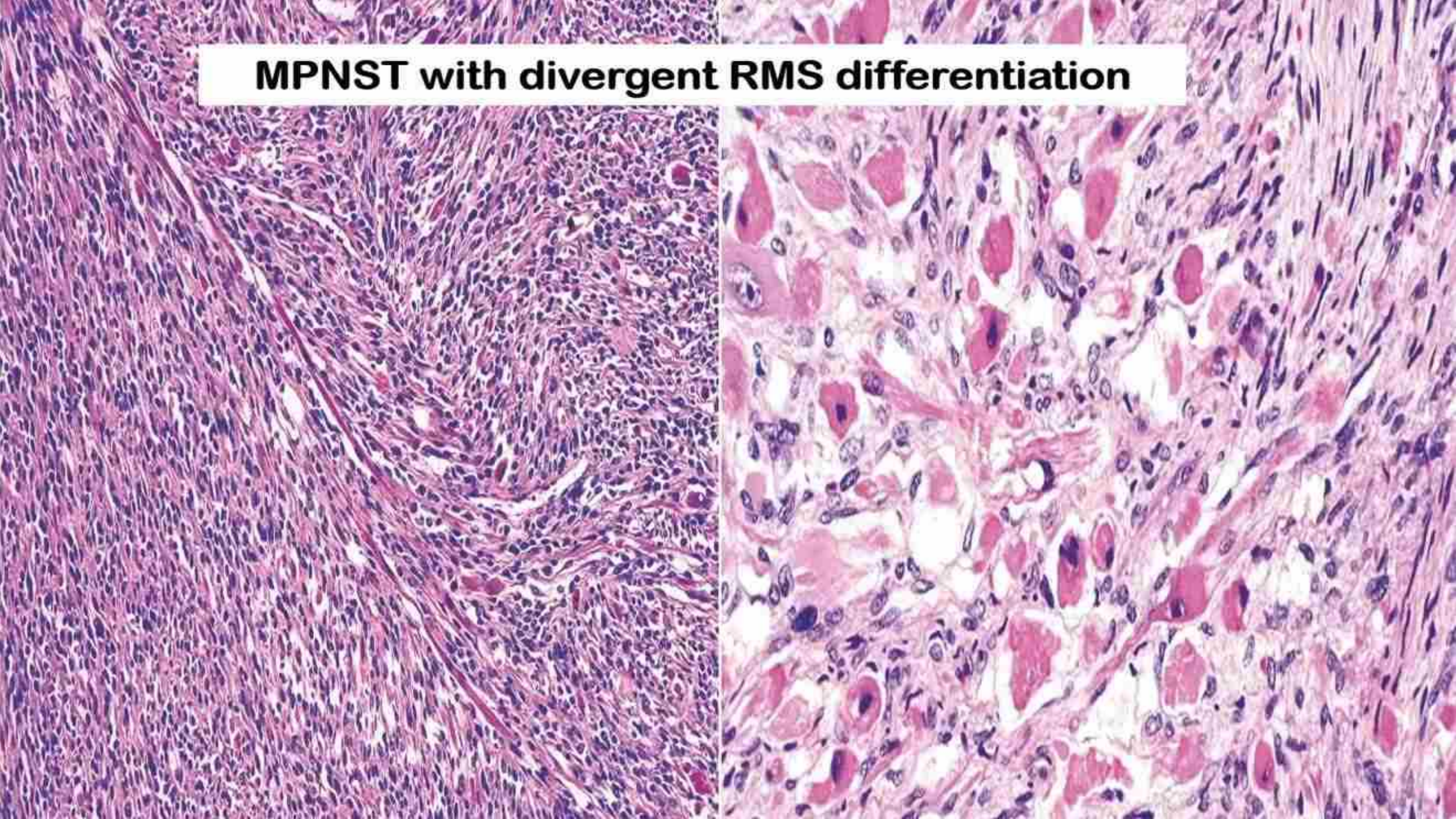
- Middle-aged adults
- Proximal extremities (lower>upper); paraspinal
- Sporadic, post-RT or NF1 (5-10% lifetime risk)
- High risk of metastasis (↑ grade → ↑ risk)
- Diagnostic challenge when not arising from a large nerve or in NF1



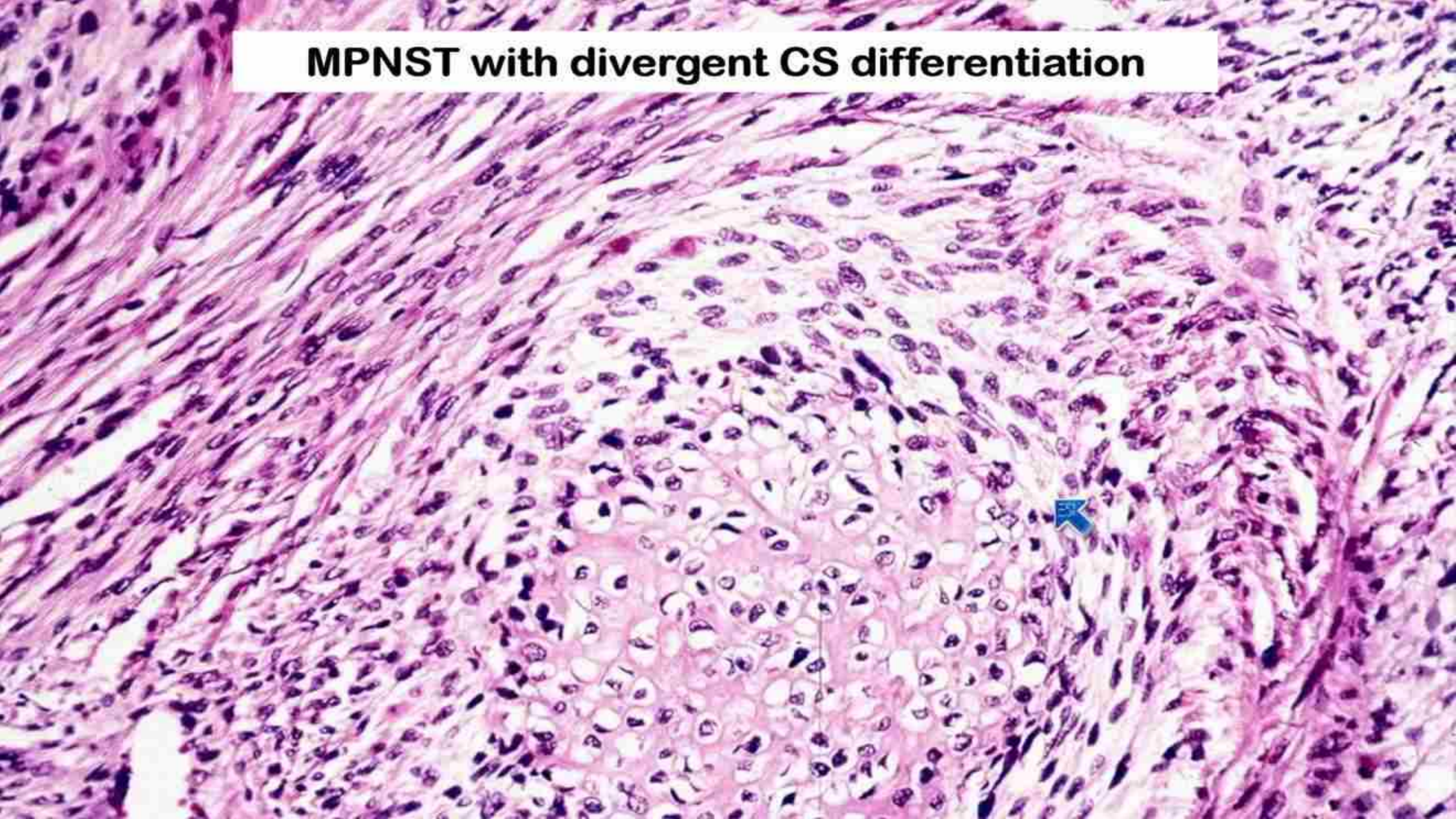


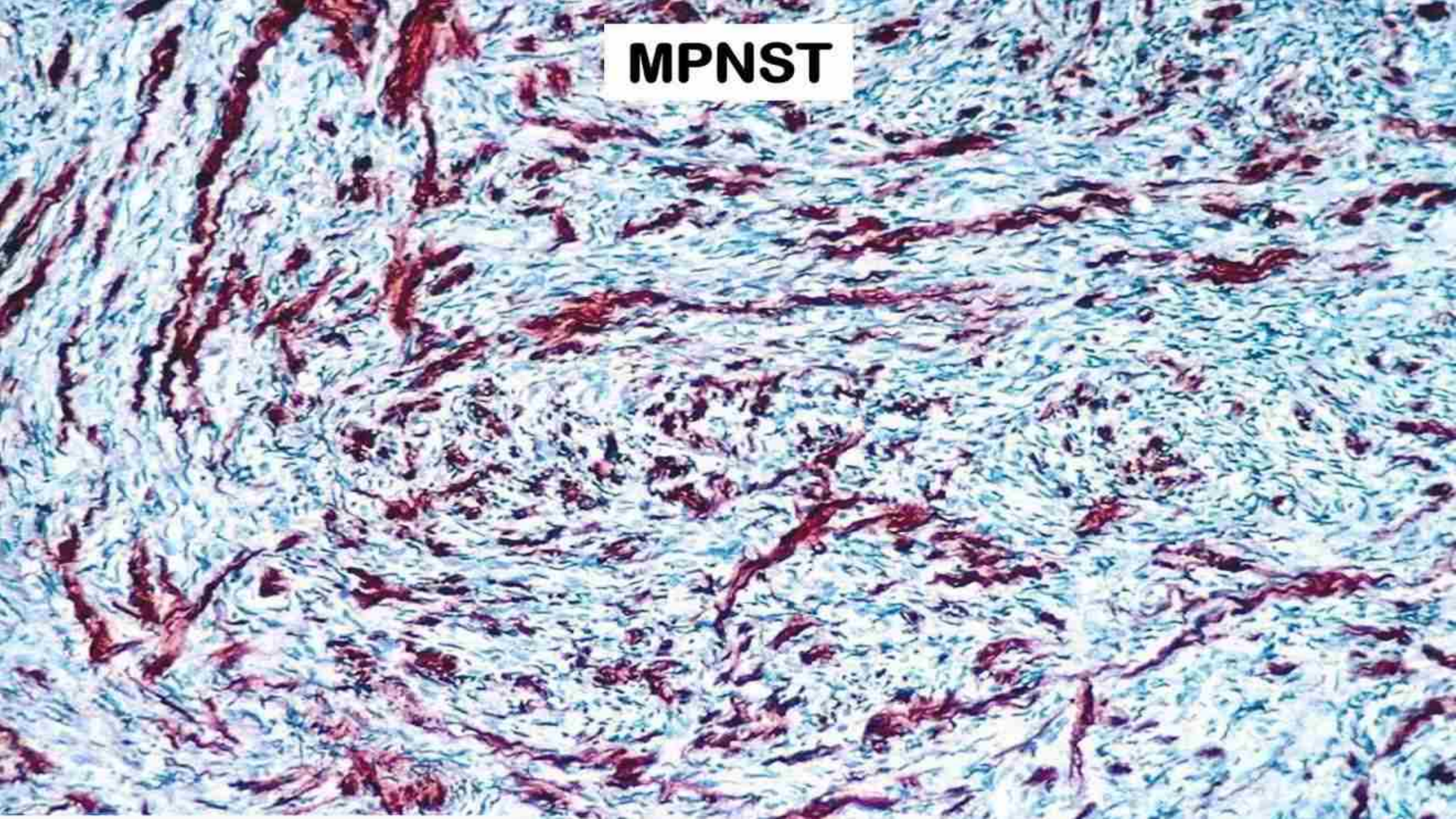


MPNST with divergent RMS differentiation



MPNST with divergent CS differentiation



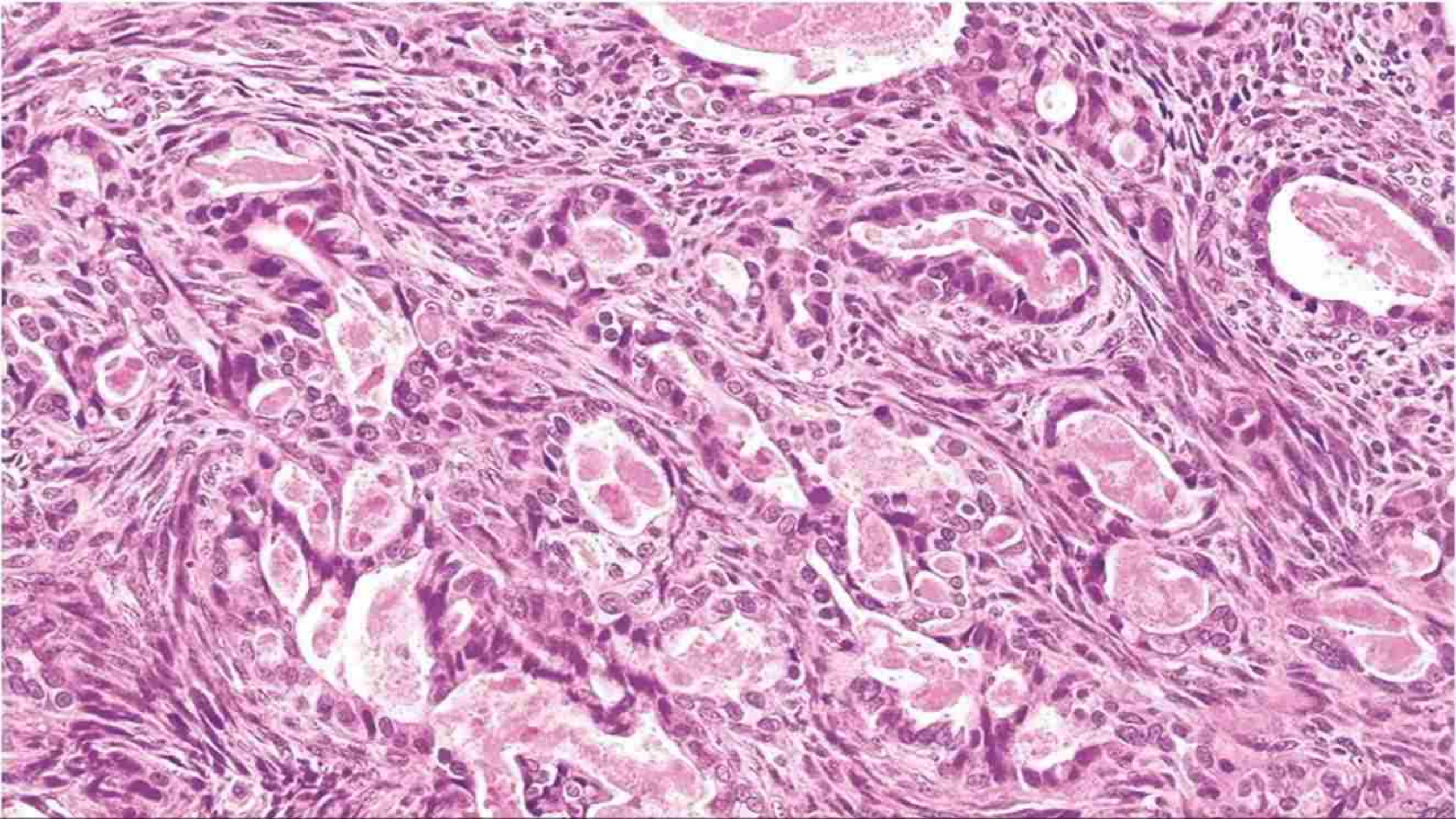

MPNST

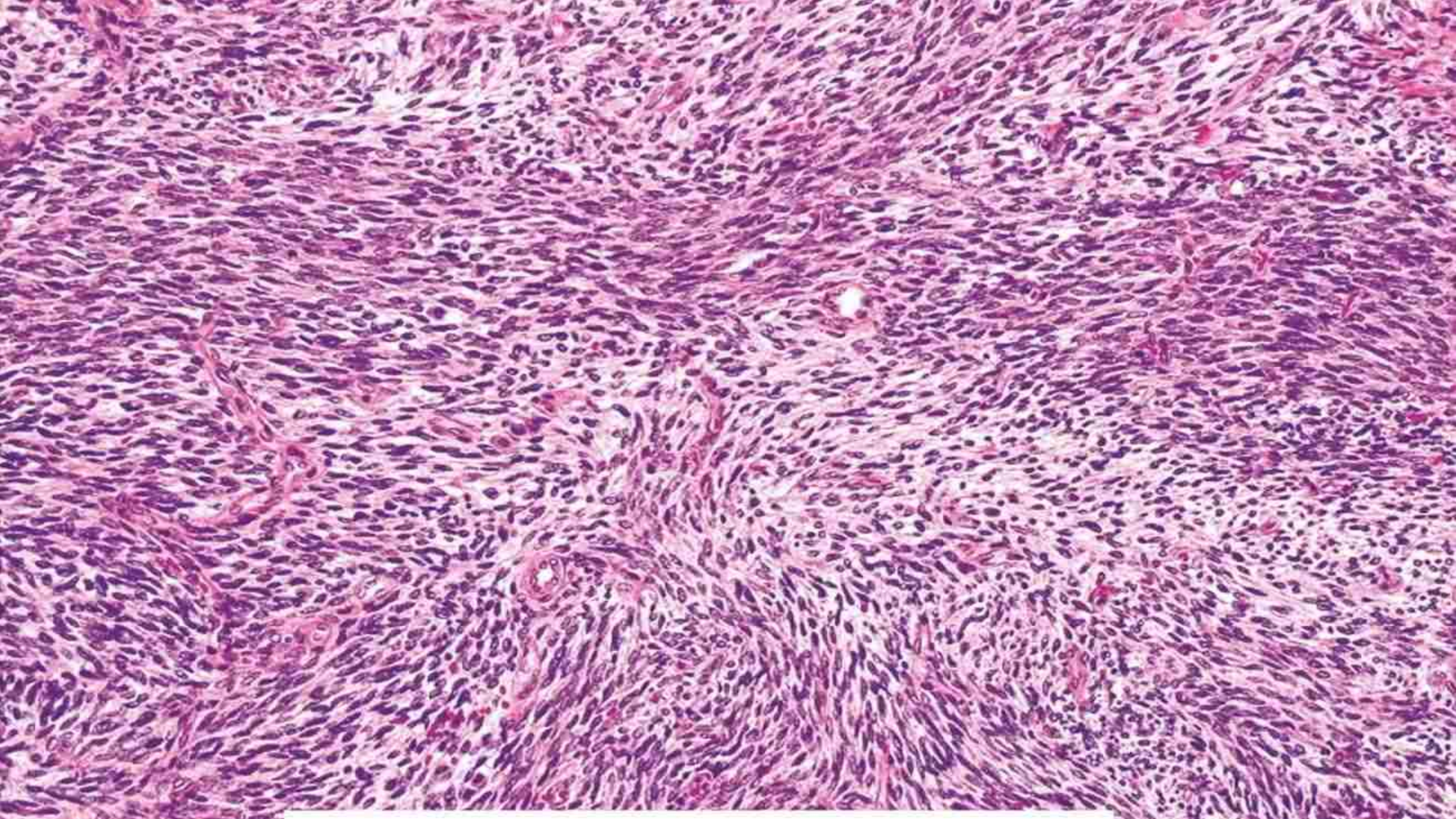
MPNST: IHC Profile

- S100: focal in 40-50%
- SOX10: focal in 30-40%
- CK or EMA: focal in 30-40%
- H3K27me^3: potentially useful

Cellular Schwannoma vs MPNST

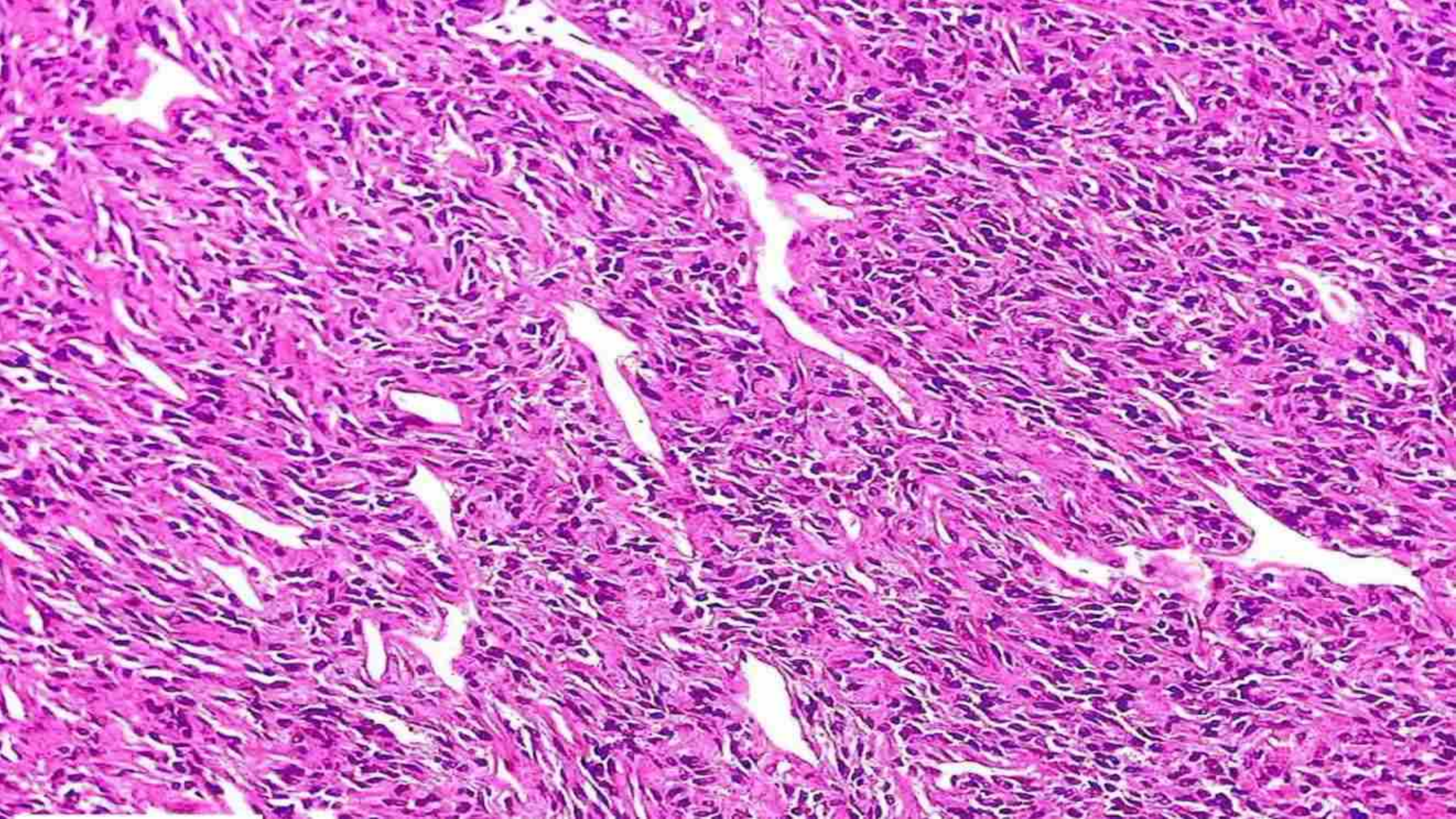
	Cellular schwannoma	*MPNST*
Encapsulated	+	-
Cellularity	3+	3+
Necrosis	rare	common
Pleomorphism	1+ - 2+	3+
Mitoses	1+ - 2+	3+
Divergent diff.	-	+ (10%)
S-100	diffuse	focal (40-50%)

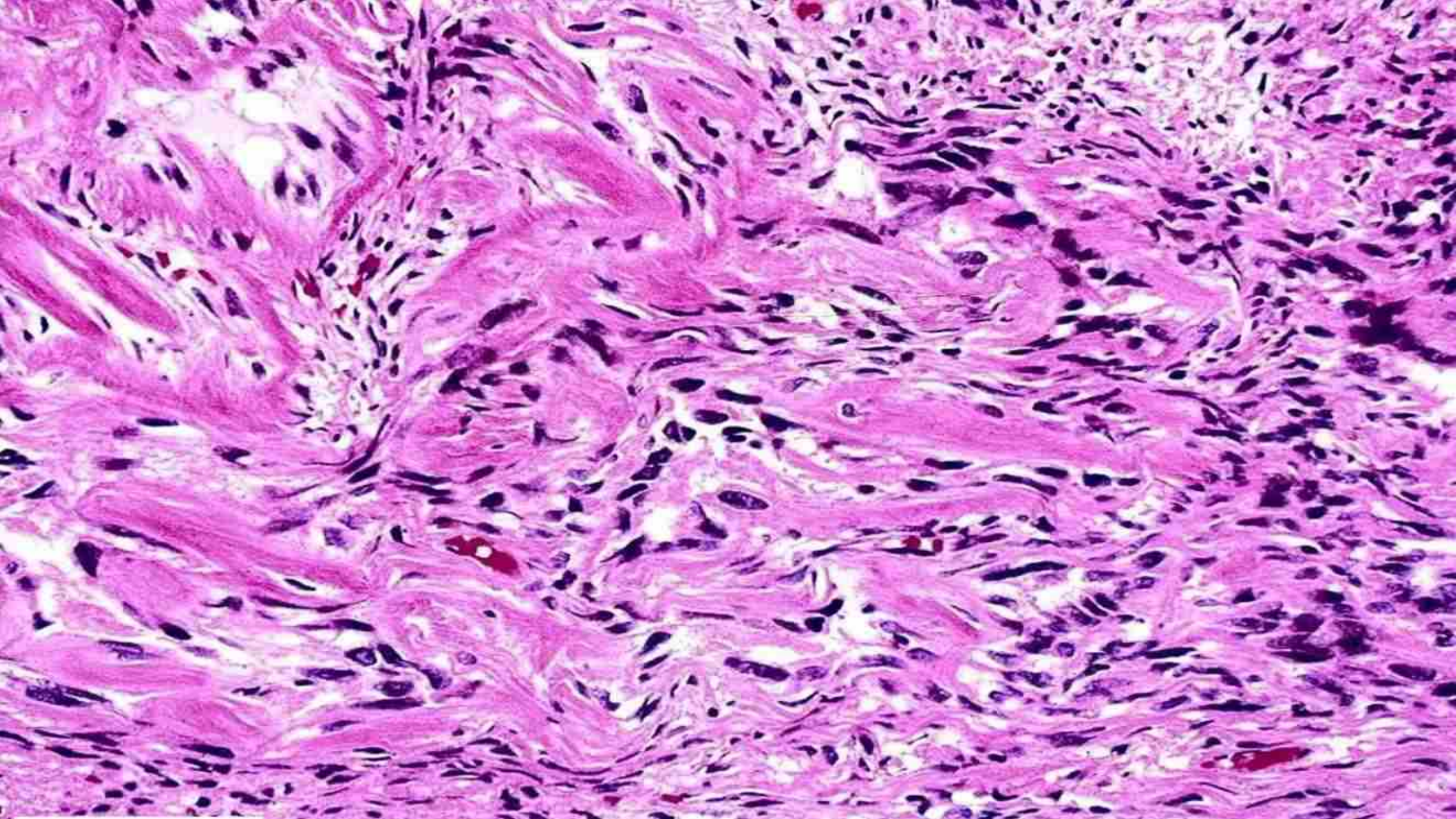


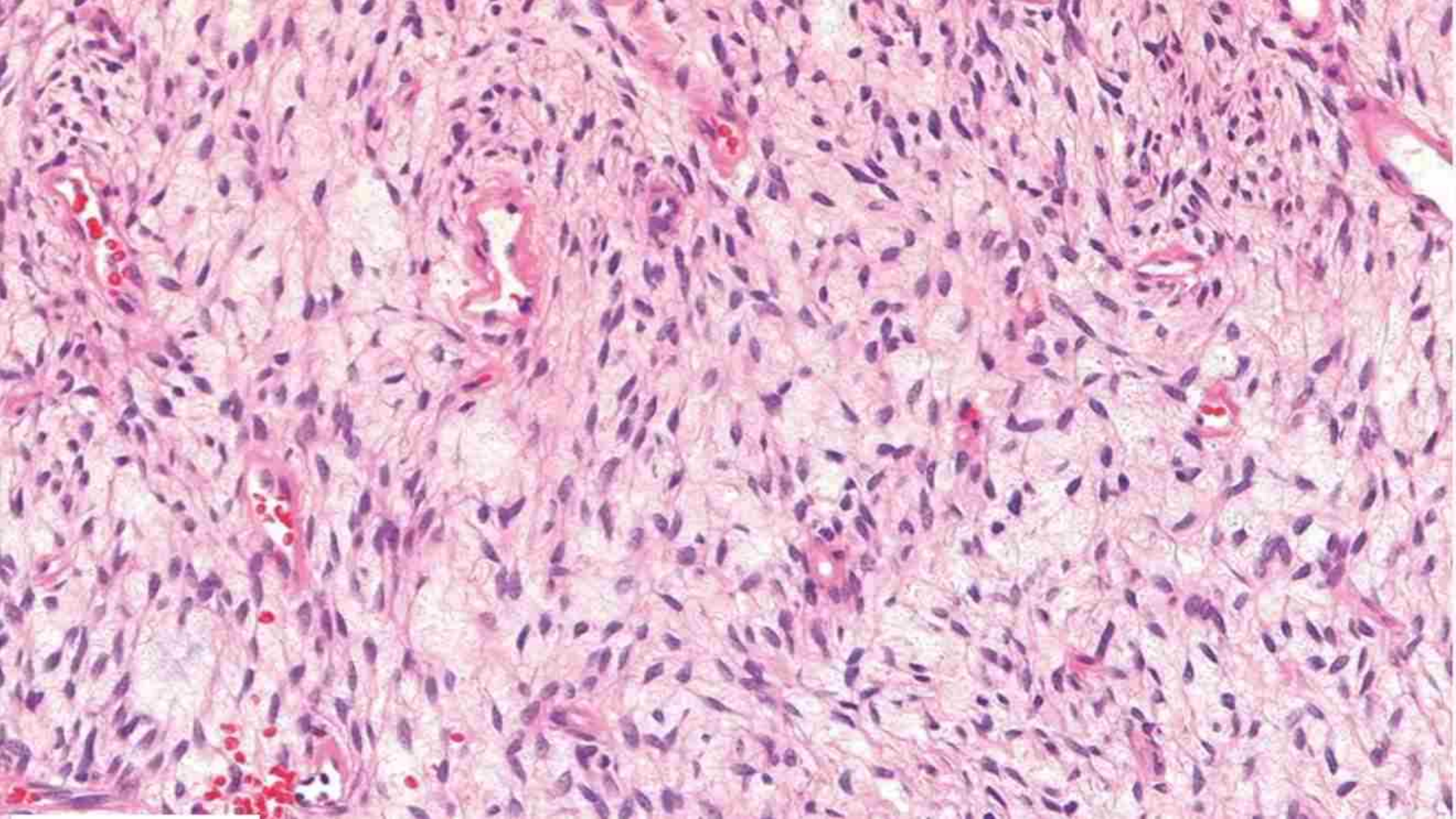


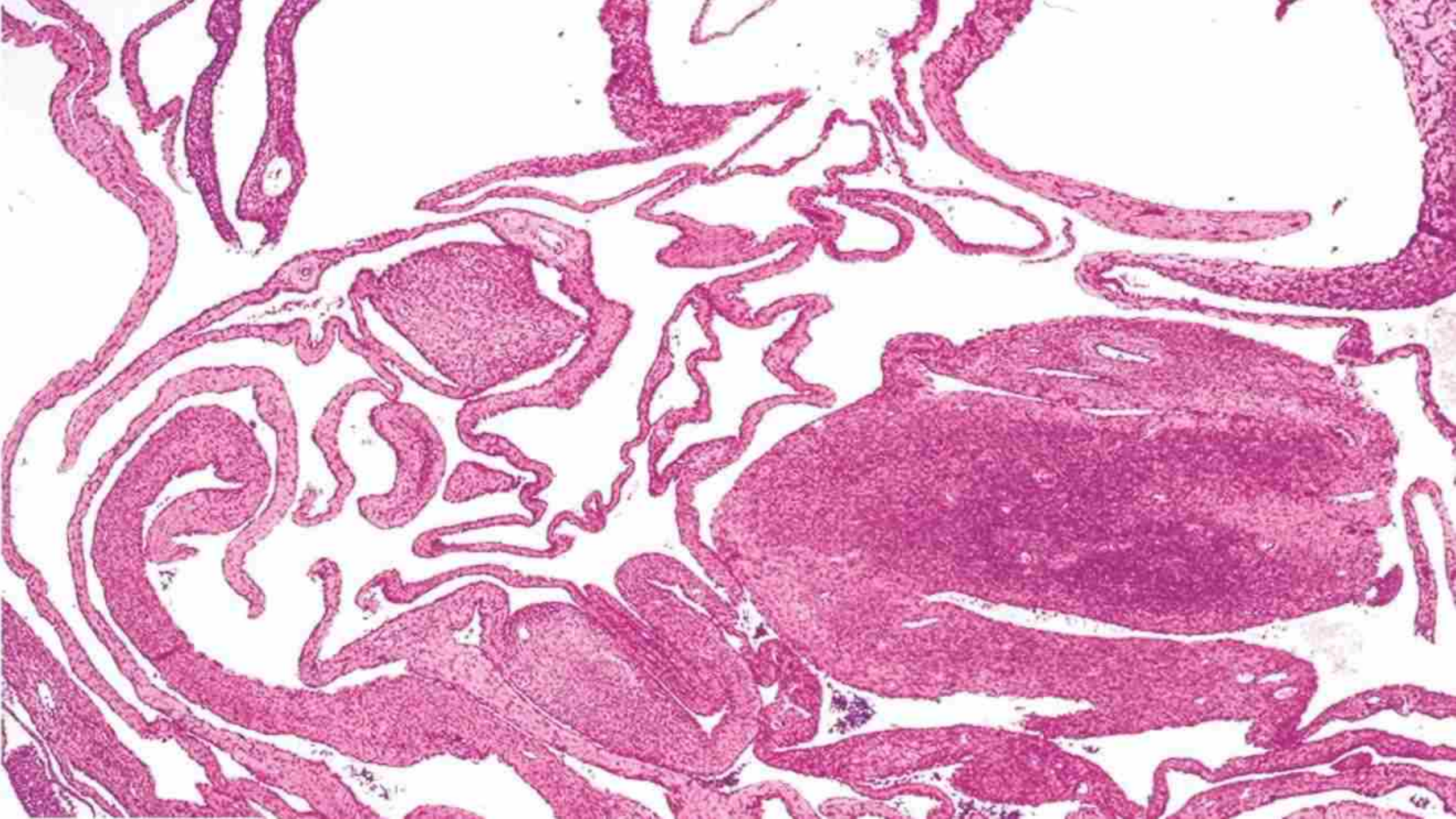
Synovial Sarcoma

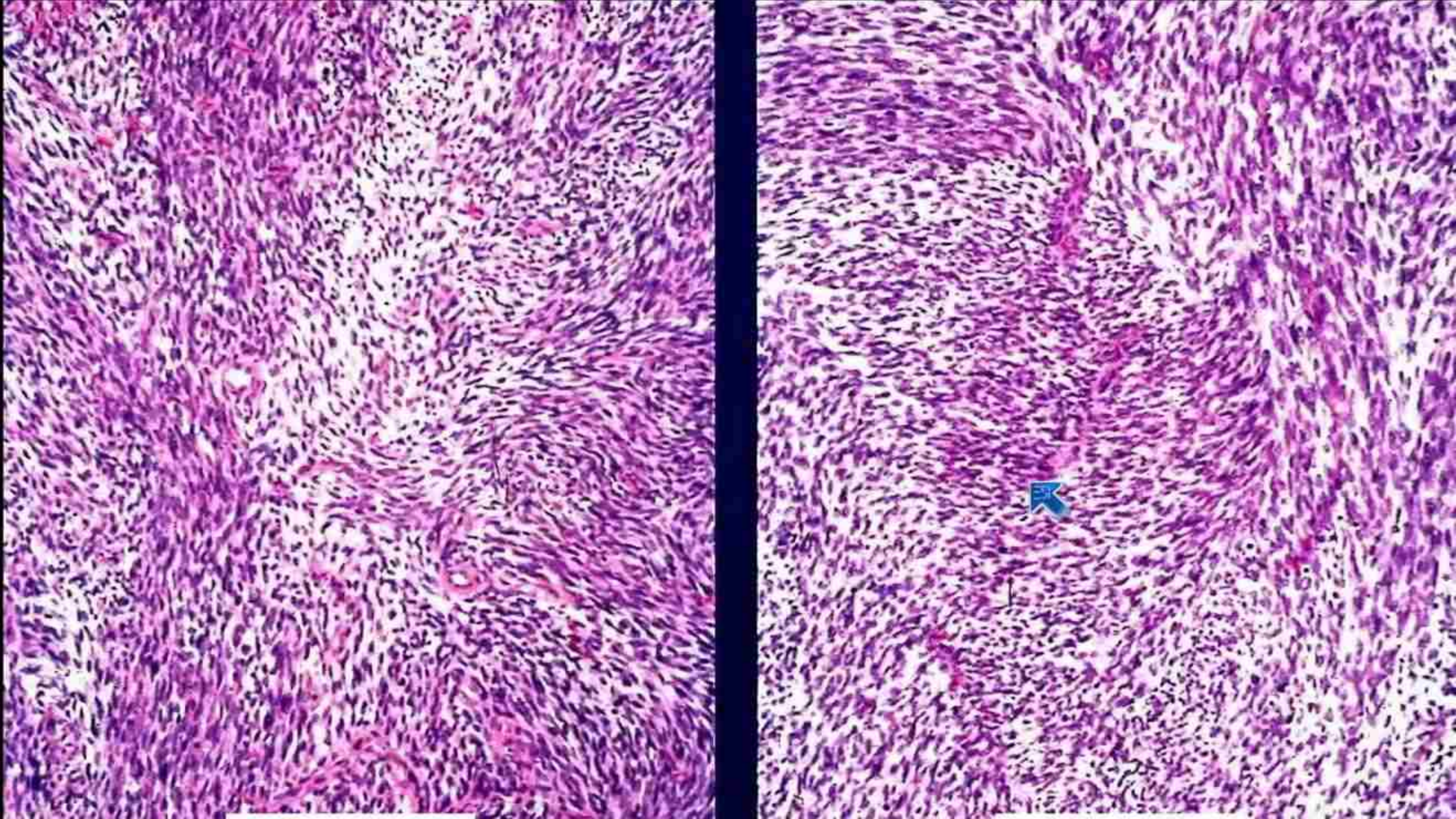
- Adolescents & young adults (>older adults)
- Proximal > distal extremities > head and neck, abd wall
- Painful; Ca^{++} on imaging
- Prognosis: grade, tumor size, older age
- High rate of recurrence and metastasis (lungs, bone)

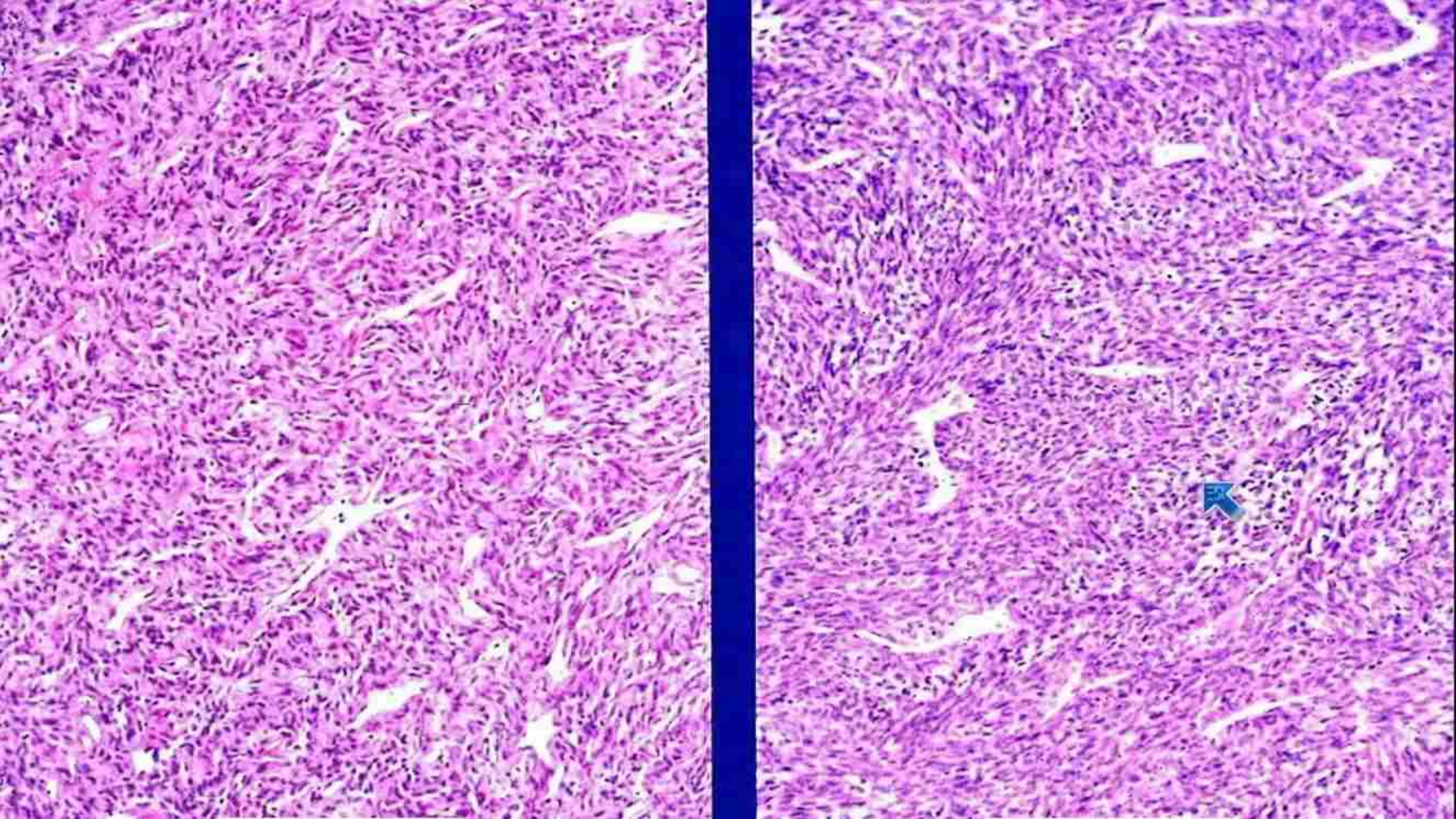






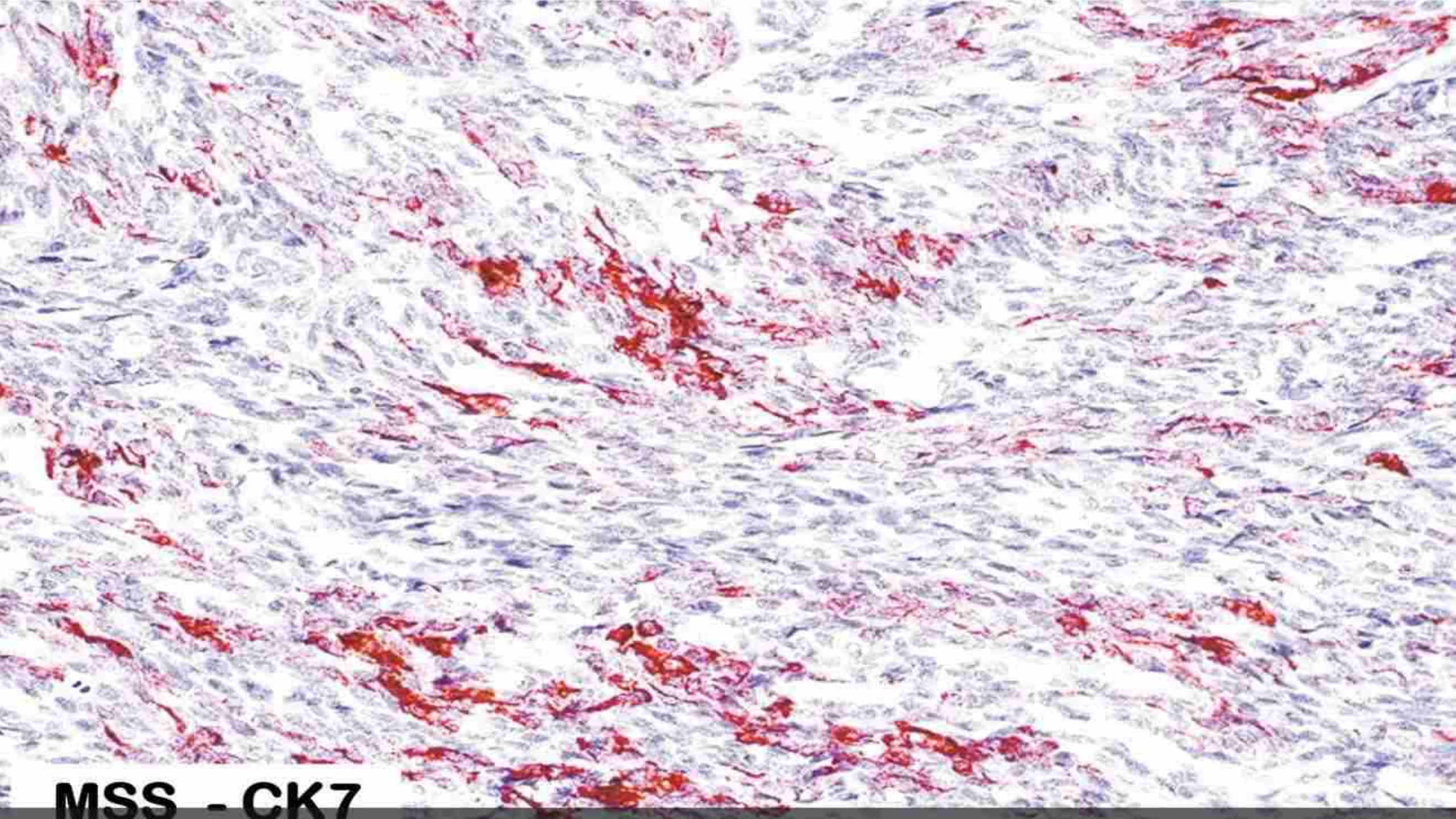






MSS vs MPNST
Immunohistochemical Quandary

	MSS	MPNST
S-100	30% (f)	40-50% (f)
Epithelial markers (EMA, AE1/AE3)	70-90% (f)	30% (f)


MSS - CK7

MPNST: loss of H3K27me^3

MPNST grade	H3K27me^3 loss
Low-grade	30%
Intermediate-grade	60%
High-grade	85%

Schaefer et al. Mod Pathol 2016
Prieto-Granada et al. AJSP 2016

H3K27me^3: Specificity

Tumor Type	H3K27me^3 loss
Benign PNST	0%
SFT	0%
LGFMS	0%
GIST	0%
Synovial sarcoma (MSS)	0%-60%
Spindle cell melanoma	10%

Schaefer et al. Mod Pathol 2016
Cleven et al. Mod Pathol 2016
Prieto-Granada et al. AJSP 2016

SS18: SSX fusion-specific antibody

Tumor type	SS18:SSX+
Synovial sarcoma (233)	94%
MPNST (128)	0%
SFT (52)	0%
Dediff liposarcoma (87)	0%
Sarcomatoid carcinoma (19)	0%

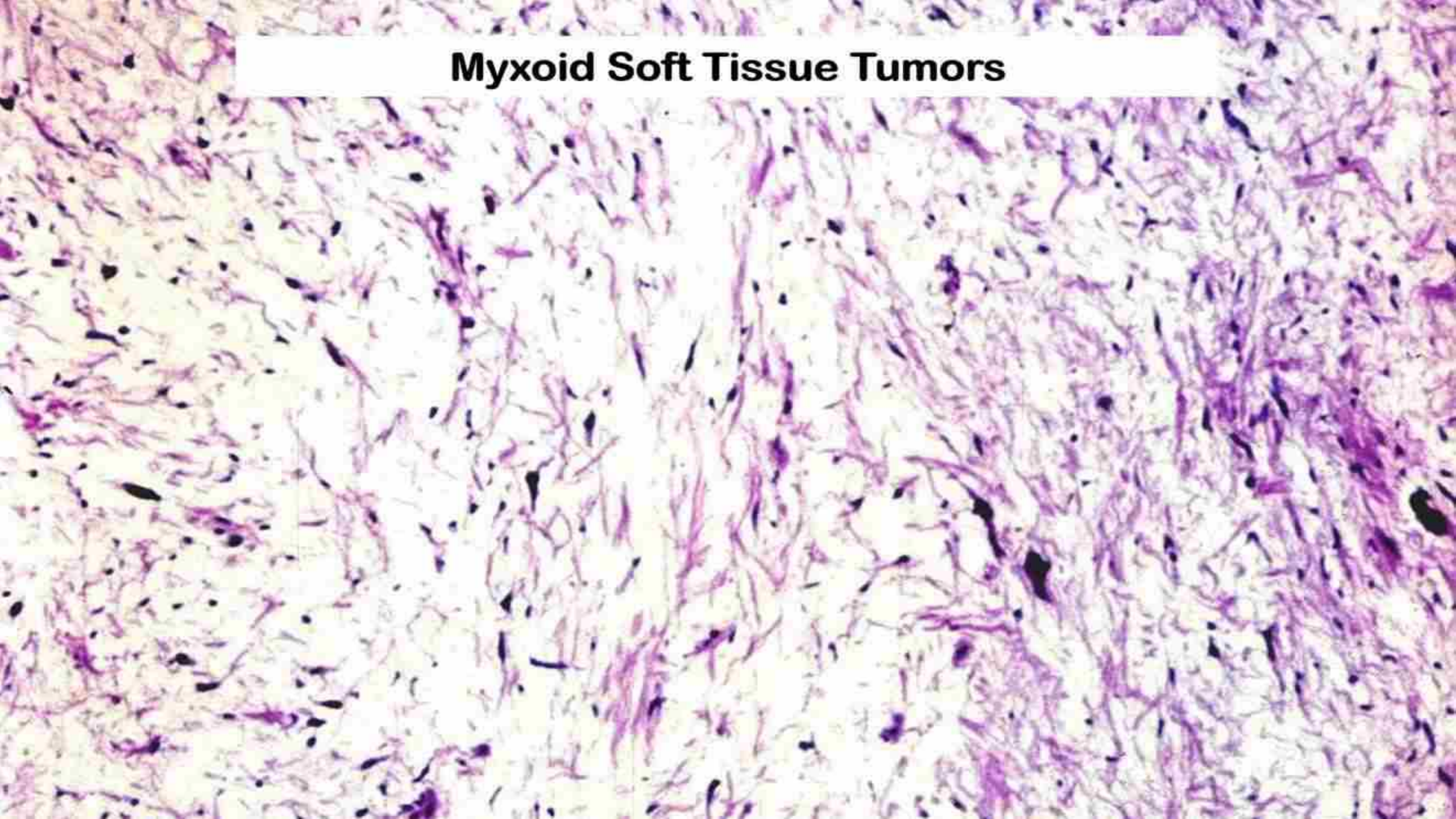
	Sensitivity	Specificity
SS18:SSX	95%	100%
SSX	100%	96%

Baranov et al. AJSP 2020

Cellular Spindle Cell Pattern

	S-100	CK7	SMA	SS18:SSX	H3K27
Cellular schwannoma	+ (diffuse)	-	-	-	Retained
MPNST	60% (focal)	-	-	-	Loss (62%)
MSS	30% (focal)	+	-	+	Retained?
Leiomyosarcoma	-	-	+	-	Retained
Fibrosarcoma	-	-	+/-	-	?

Myxoid Soft Tissue Tumors



Myxoid Soft Tissue Lesions

Benign

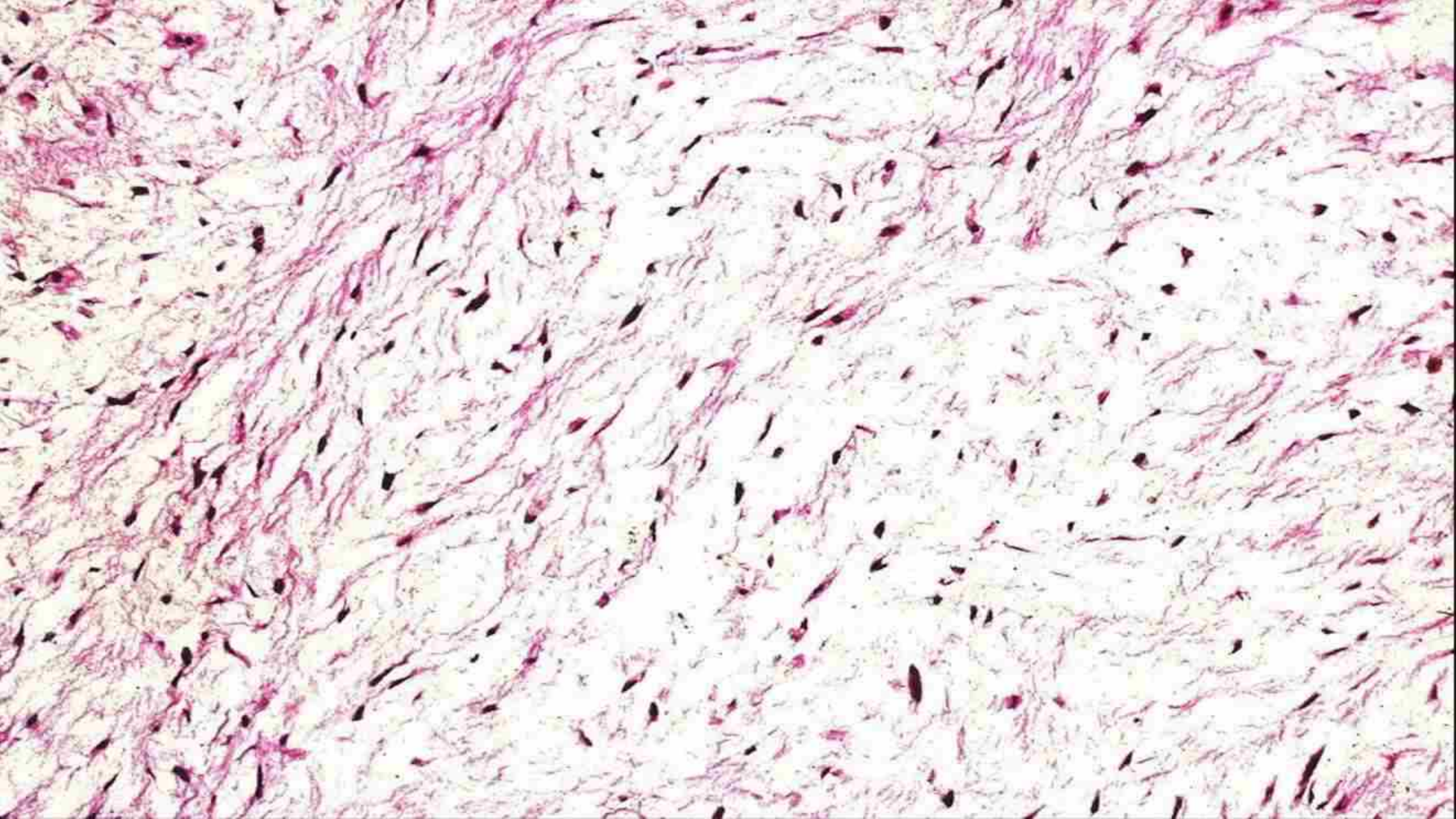
- Nodular fasciitis
- Myxoma
  - intramuscular
  - juxta-articular
  - cutaneous
- Nerve sheath tumors
  - neurofibroma
  - neurothekeoma
  - schwannoma

Malignant

- Myxoid liposarcoma
- Myxofibrosarcoma (myxoid MFH)
- Myxoid chondrosarcoma
- Low-grade fibromyxoid sarcoma
- All other sarcomas

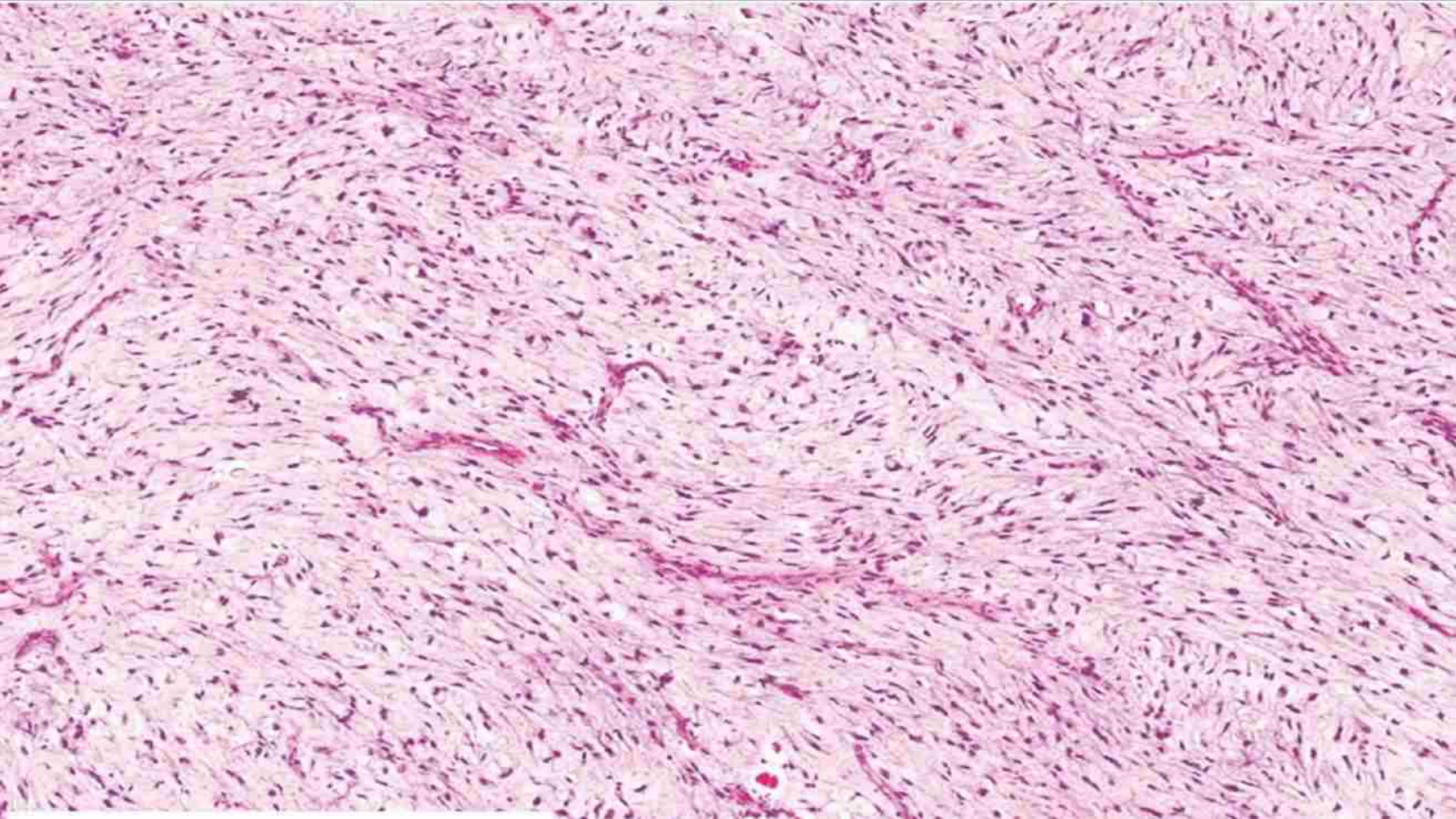
Myxoid Soft Tissue Tumors

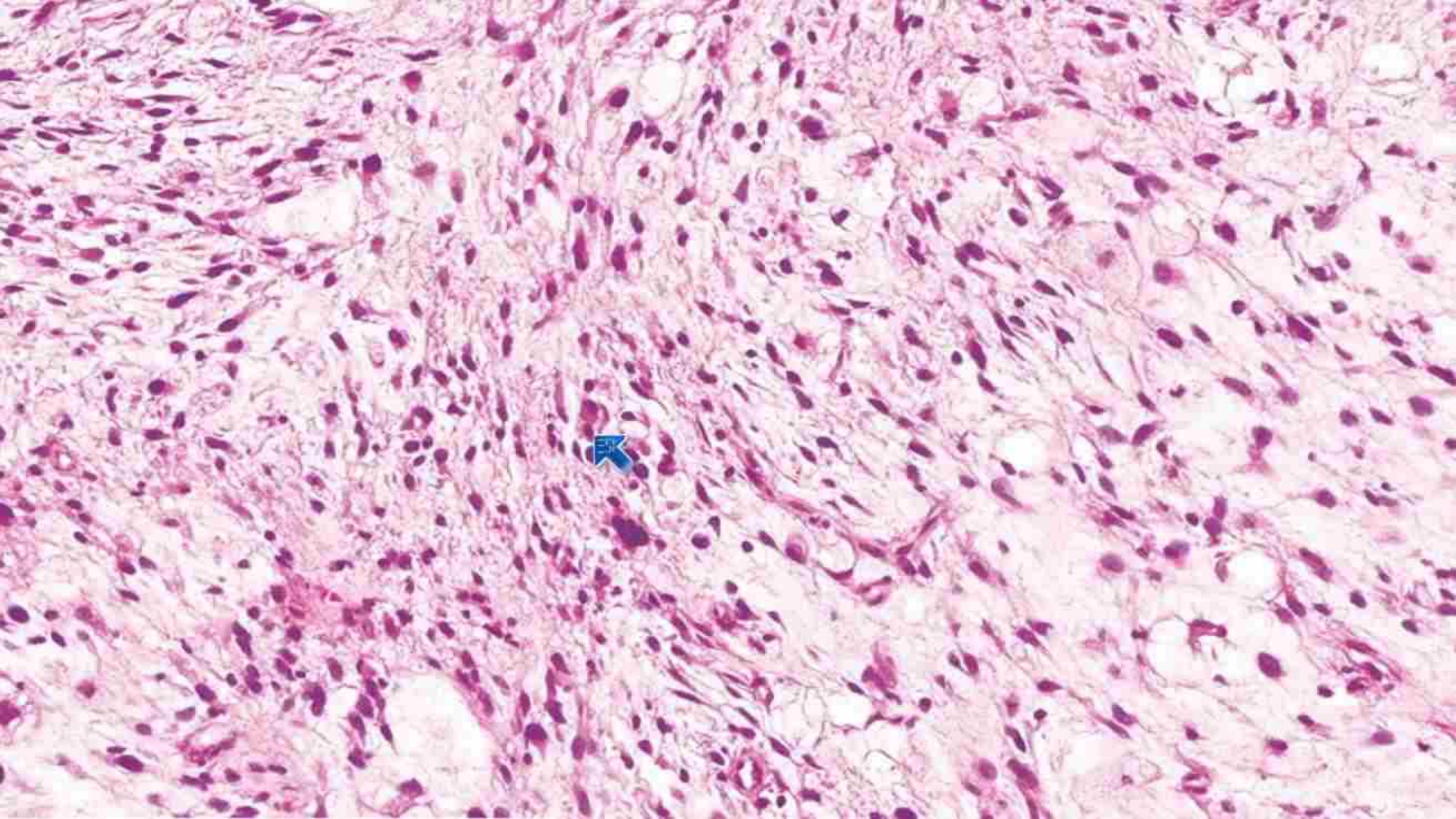
- Morphology is most useful
  - Cellularity and cellular arrangement
  - Atypia
  - Vascular pattern
- Limited use of IHC (S100; MUC4)
- FISH useful in selected cases



Intramuscular Myxoma

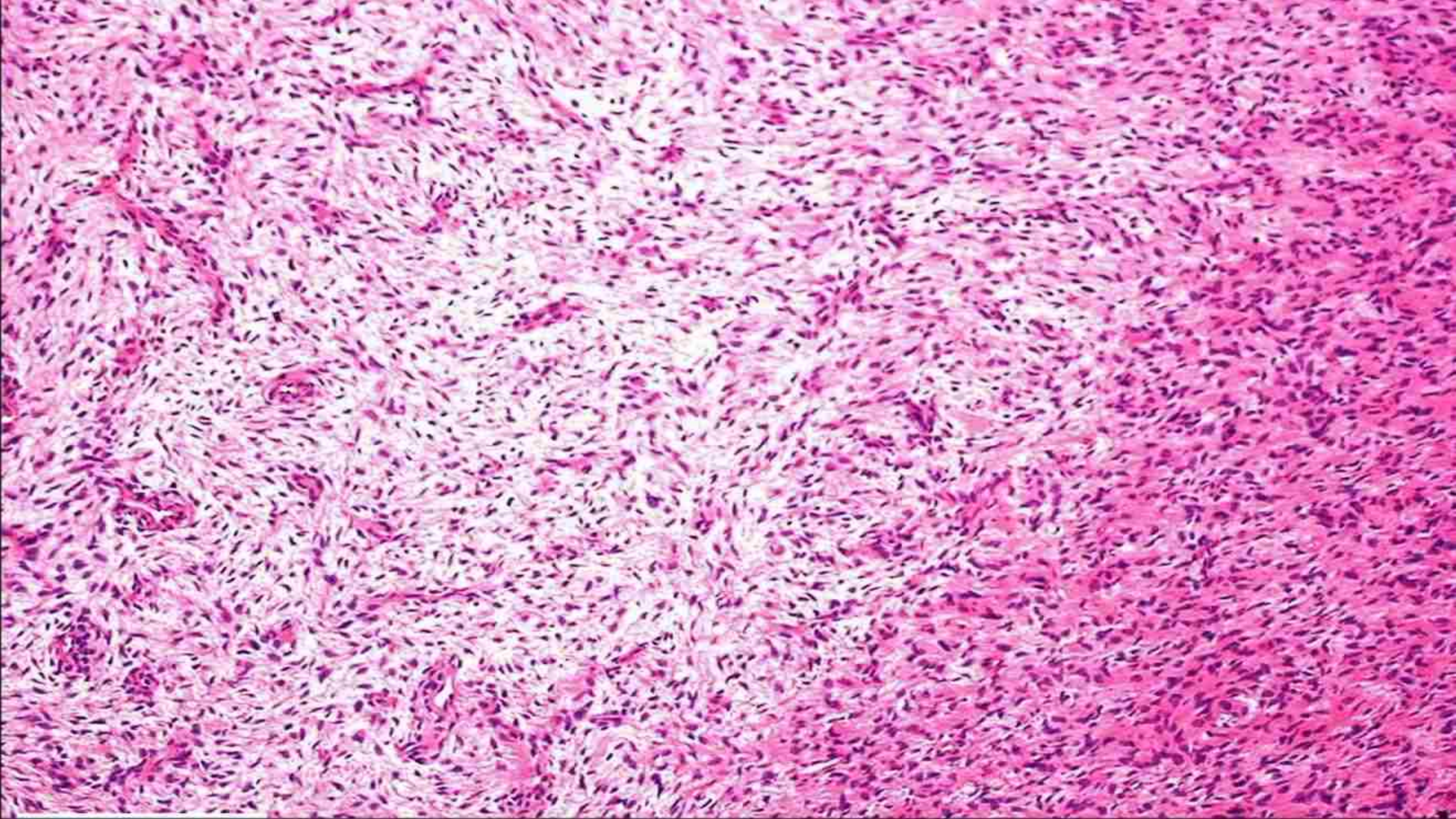
- Middle-aged/elderly adults (F>M)
- Large muscles of thigh, shoulder, buttock (usually 5-10 cm)
- May be associated with fibrous dysplasia (Mazabraud syndrome)
- Activating mutations in *GNAS1*
- Very low risk of local recurrence

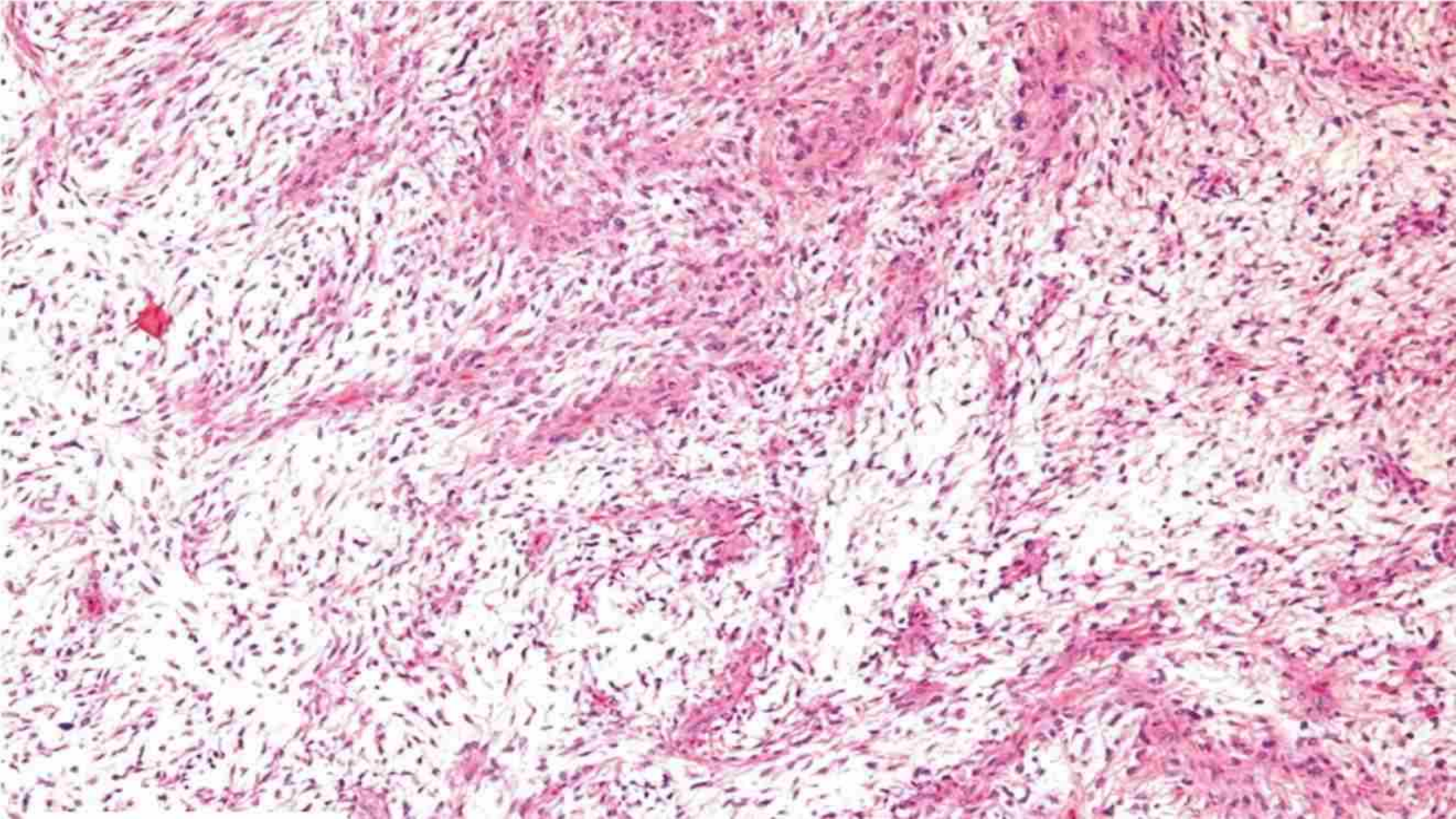


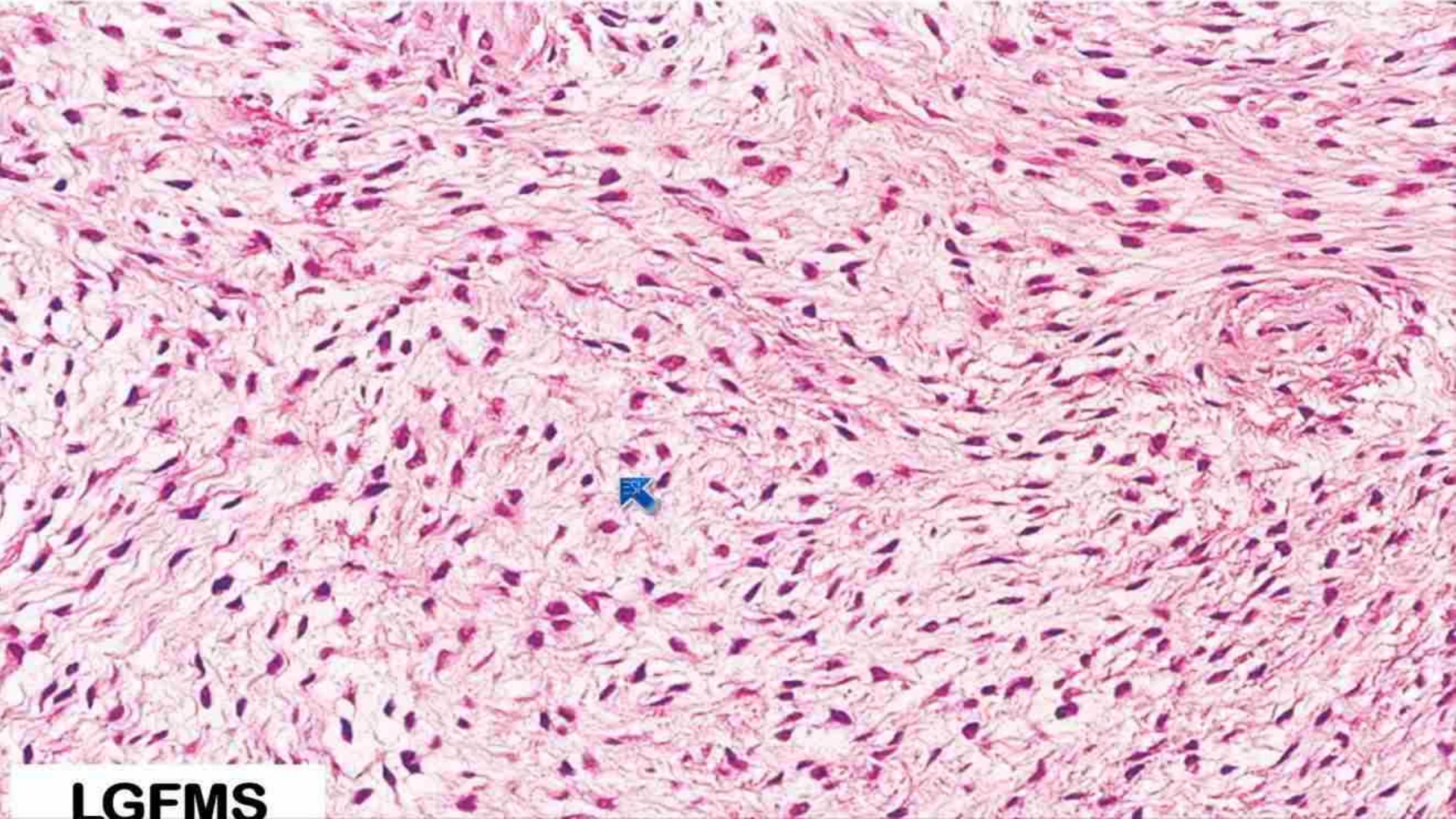


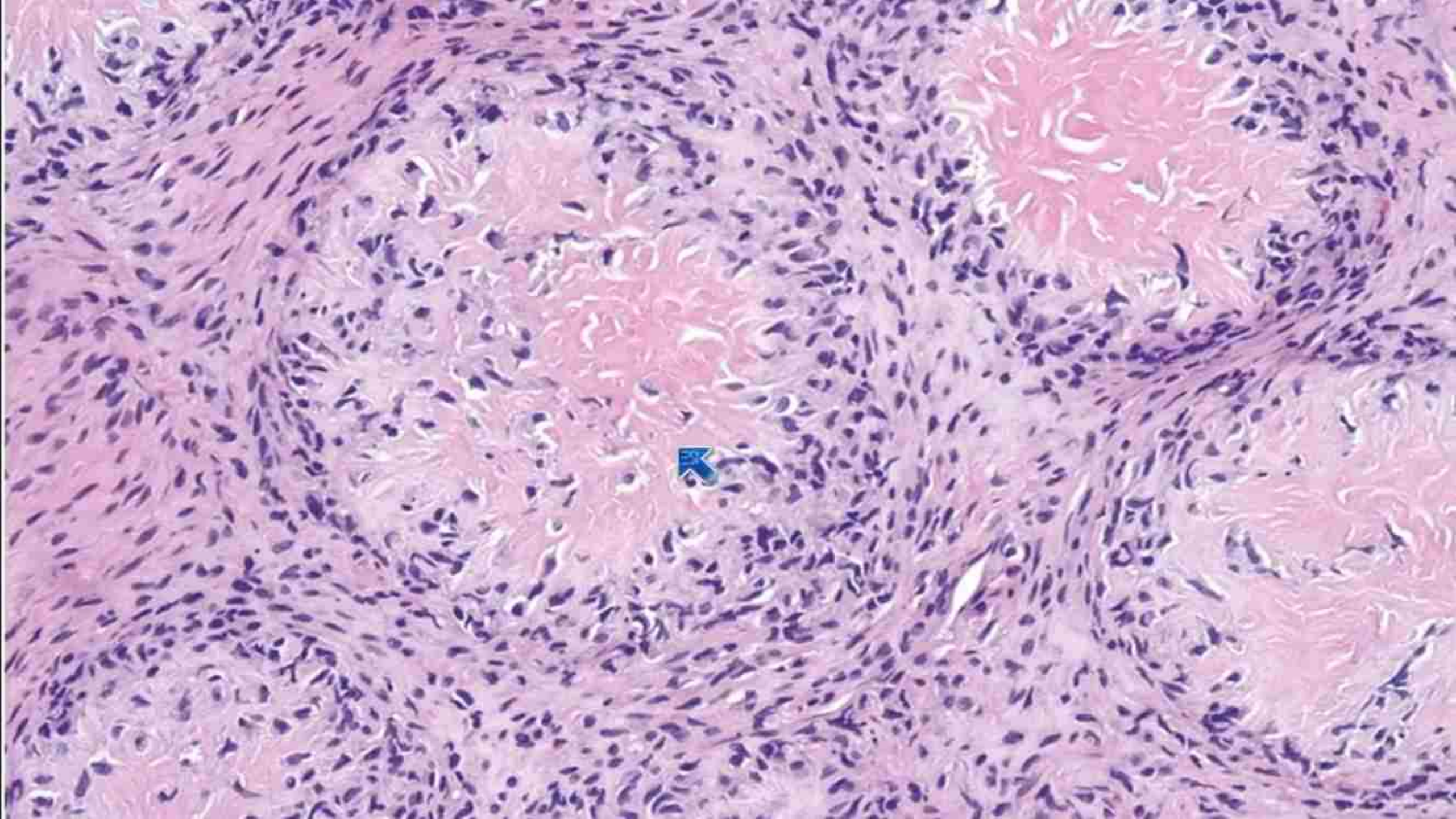
Myxofibrosarcoma

- Elderly patients (Peak: 5^{th} – 7^{th} decades)
- Slow growing, painless mass, usually in extremities (lower > upper)
- Most (~70%) centered in subcutis; infiltrative pattern
- High risk of recurrence; some progress to higher grade and can metastasize

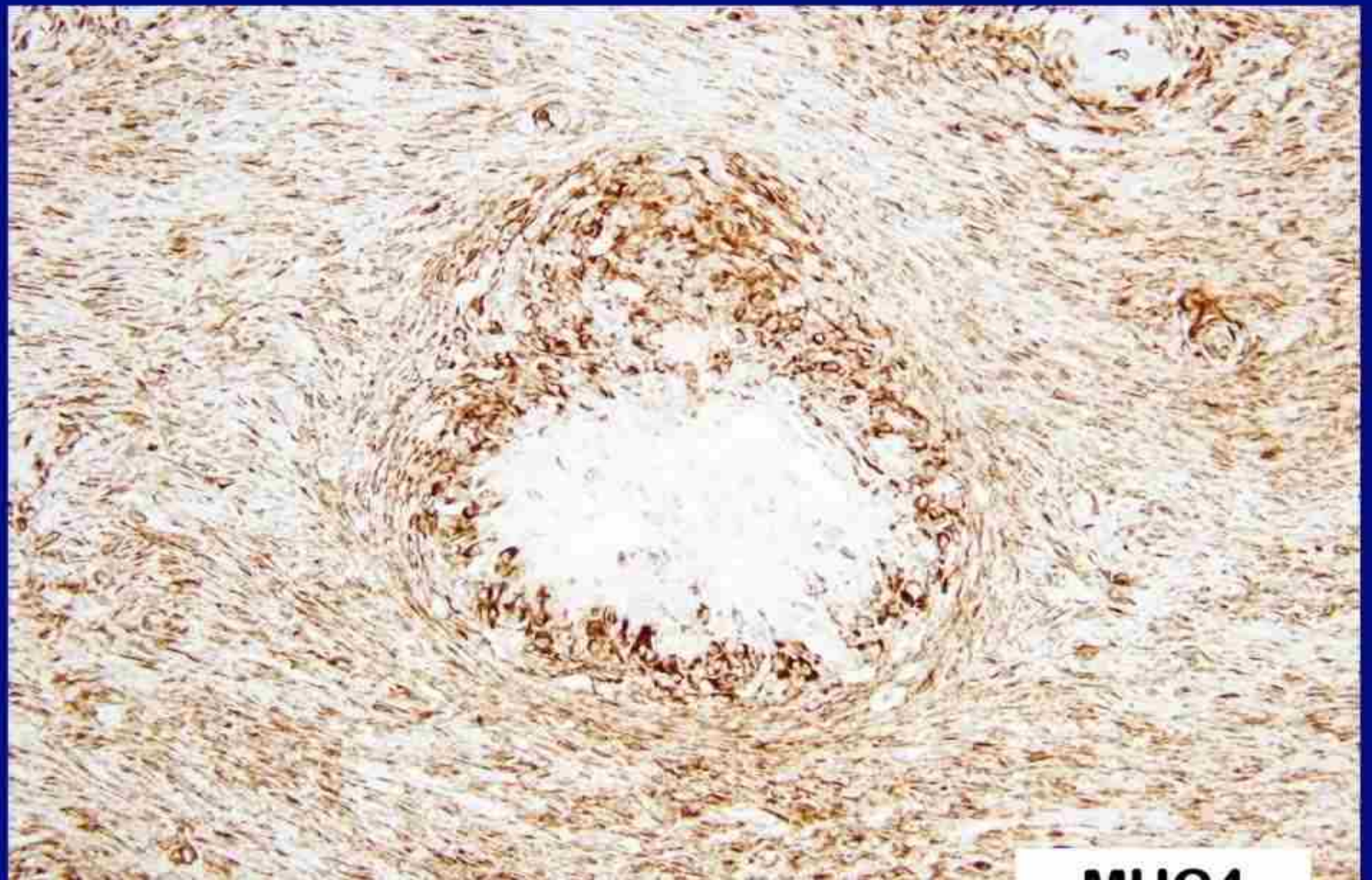





LGFMS

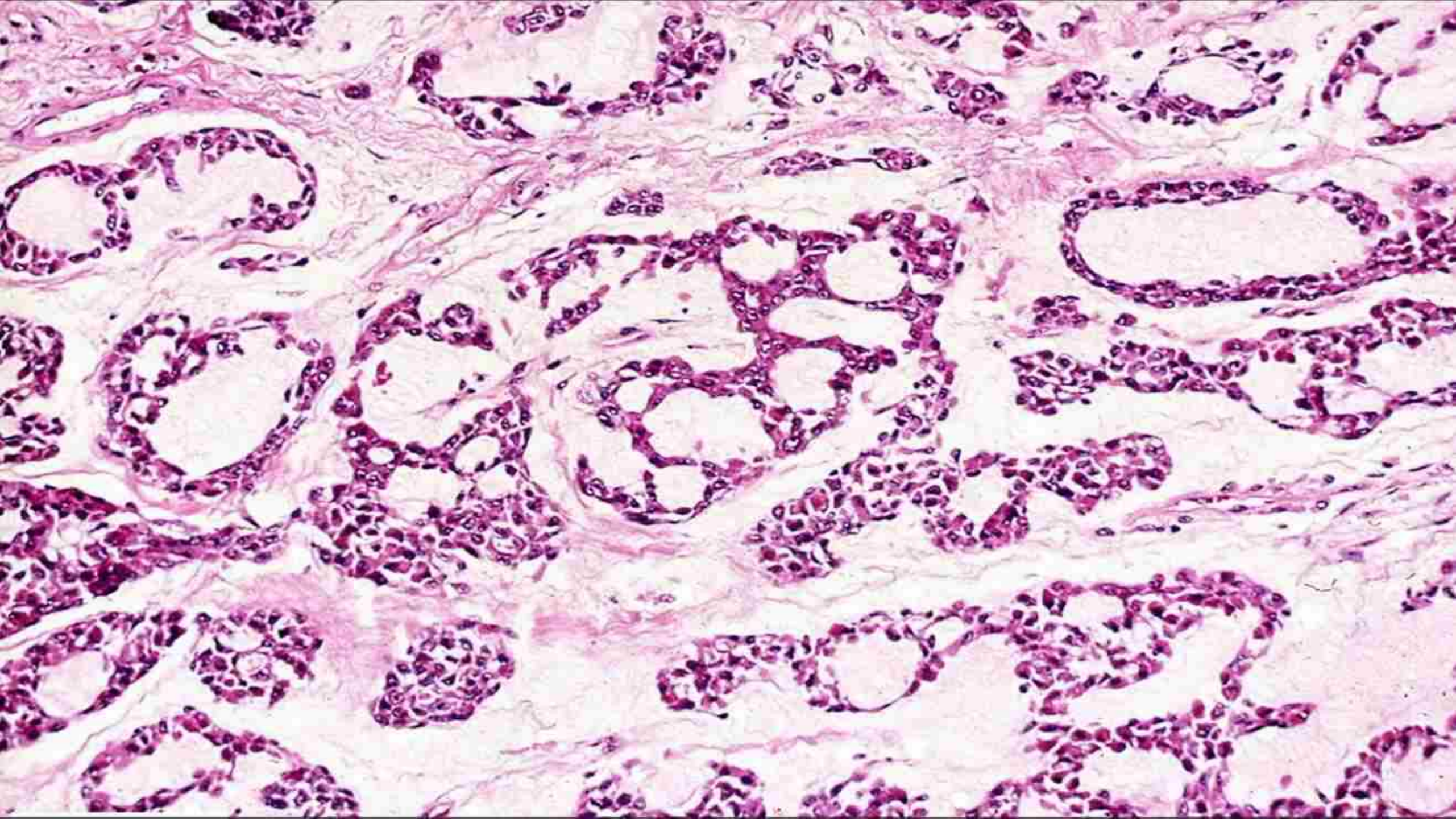


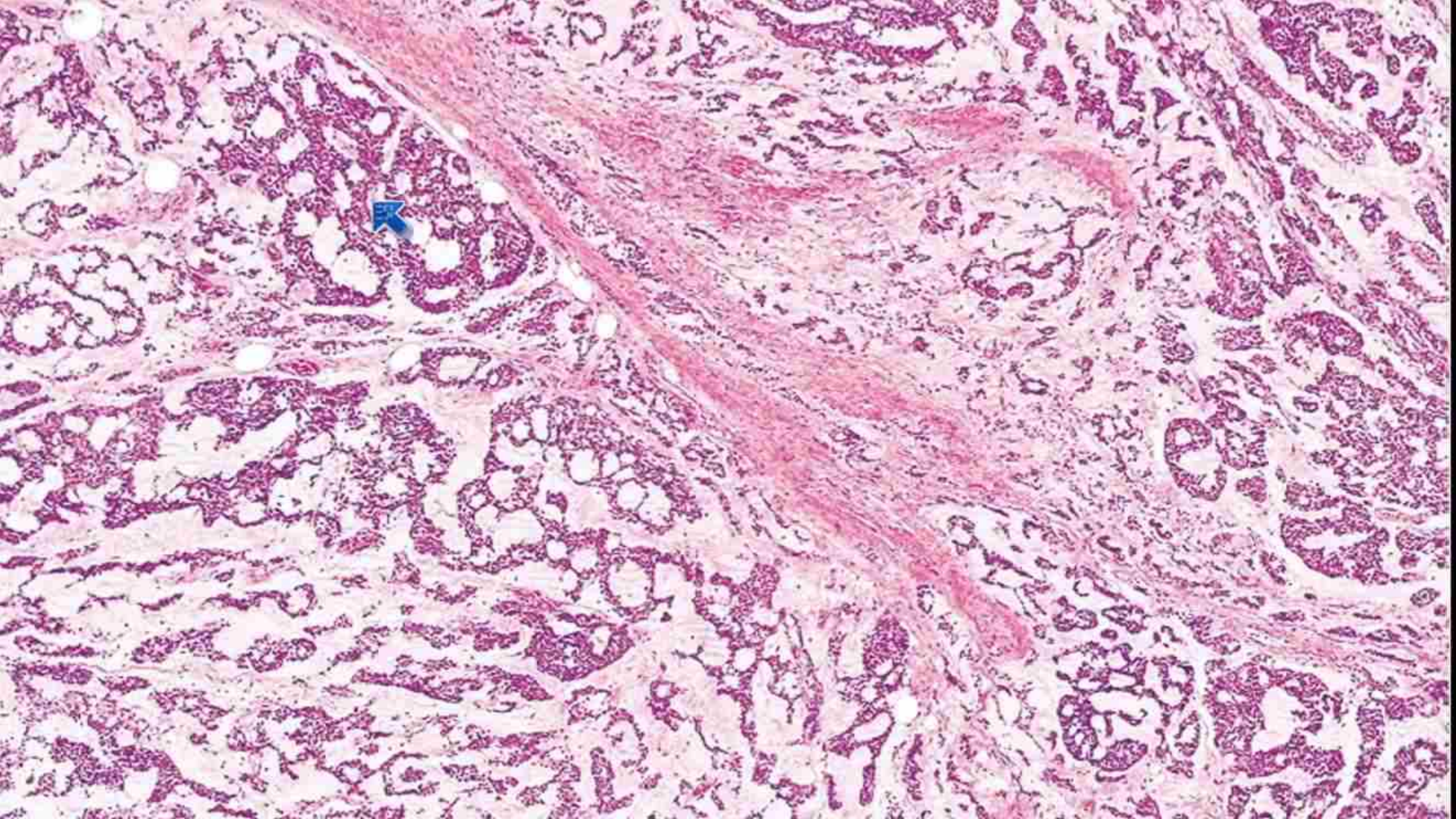
LGFMS (with rosettes)

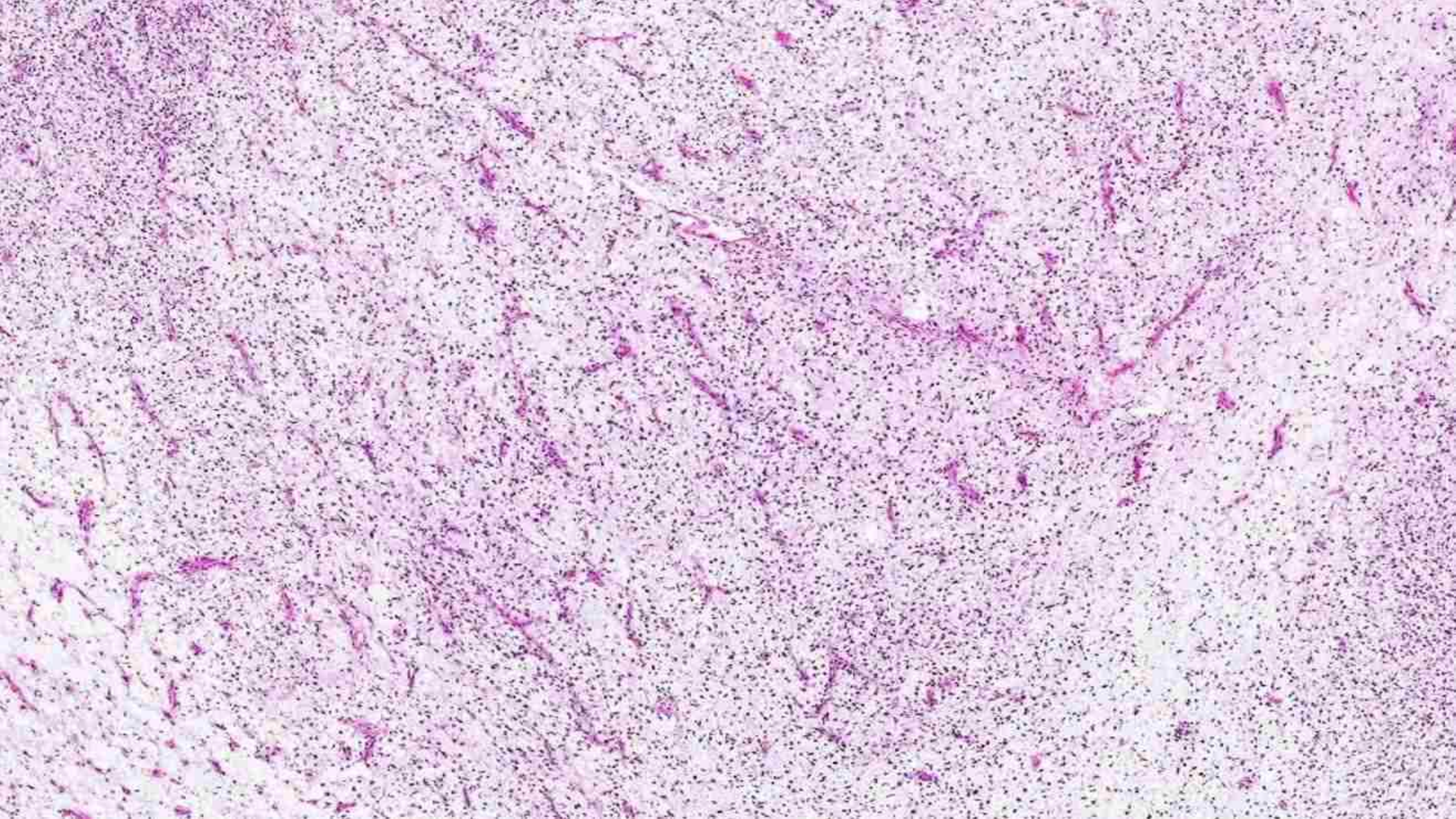


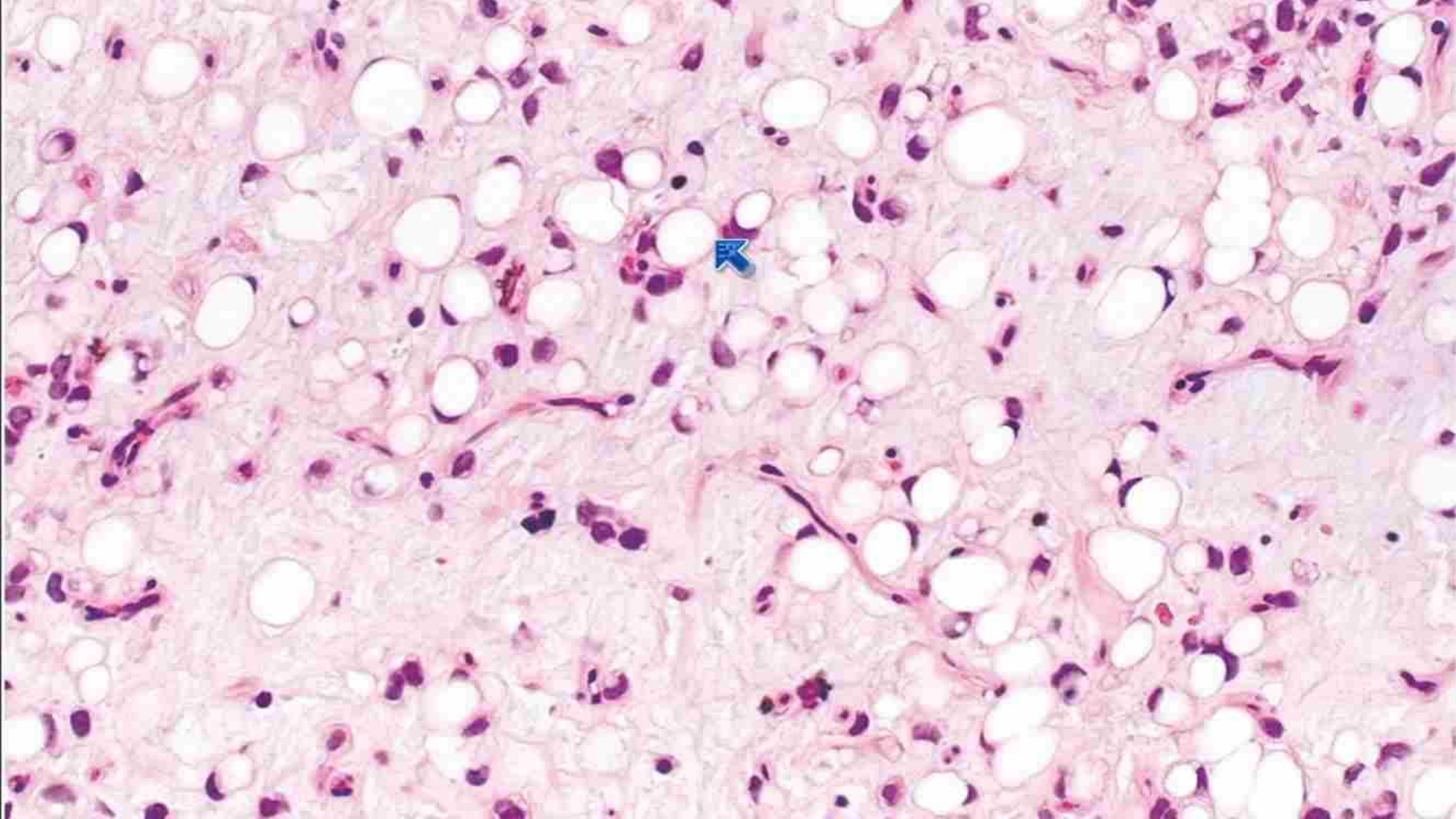
Low-Grade Fibromyxoid Sarcoma (Evans' Tumor)

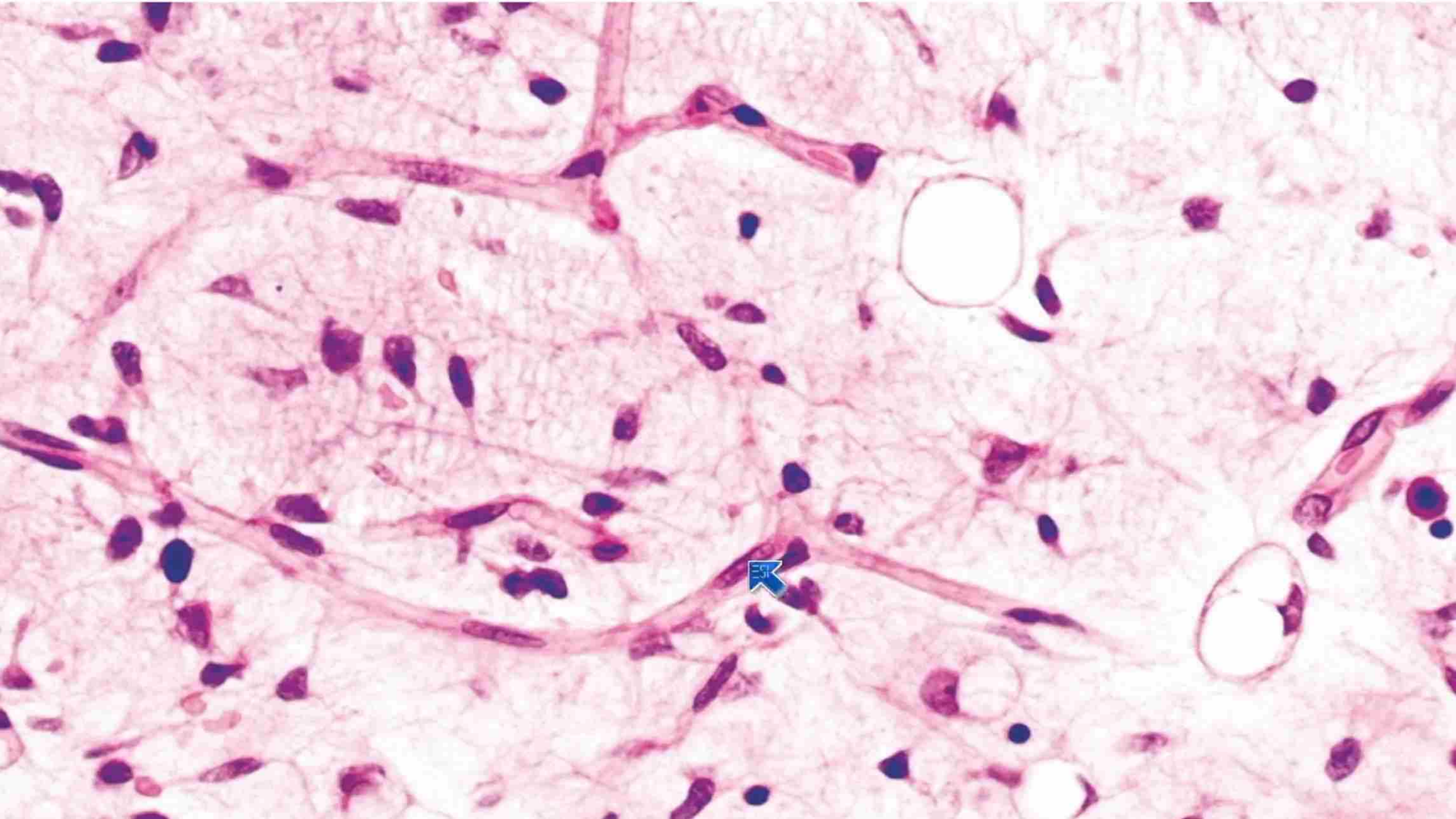
- Young adults/adults
- Deep-seated mass, most common in proximal extremities or trunk
- MUC4 immunoreactivity
- *FUS-CREB3L2* [t(7;16)] or *FUS-CREB3L1* [t(11;16)]
- Low risk of local recurrence or late metastases if adequately treated initially





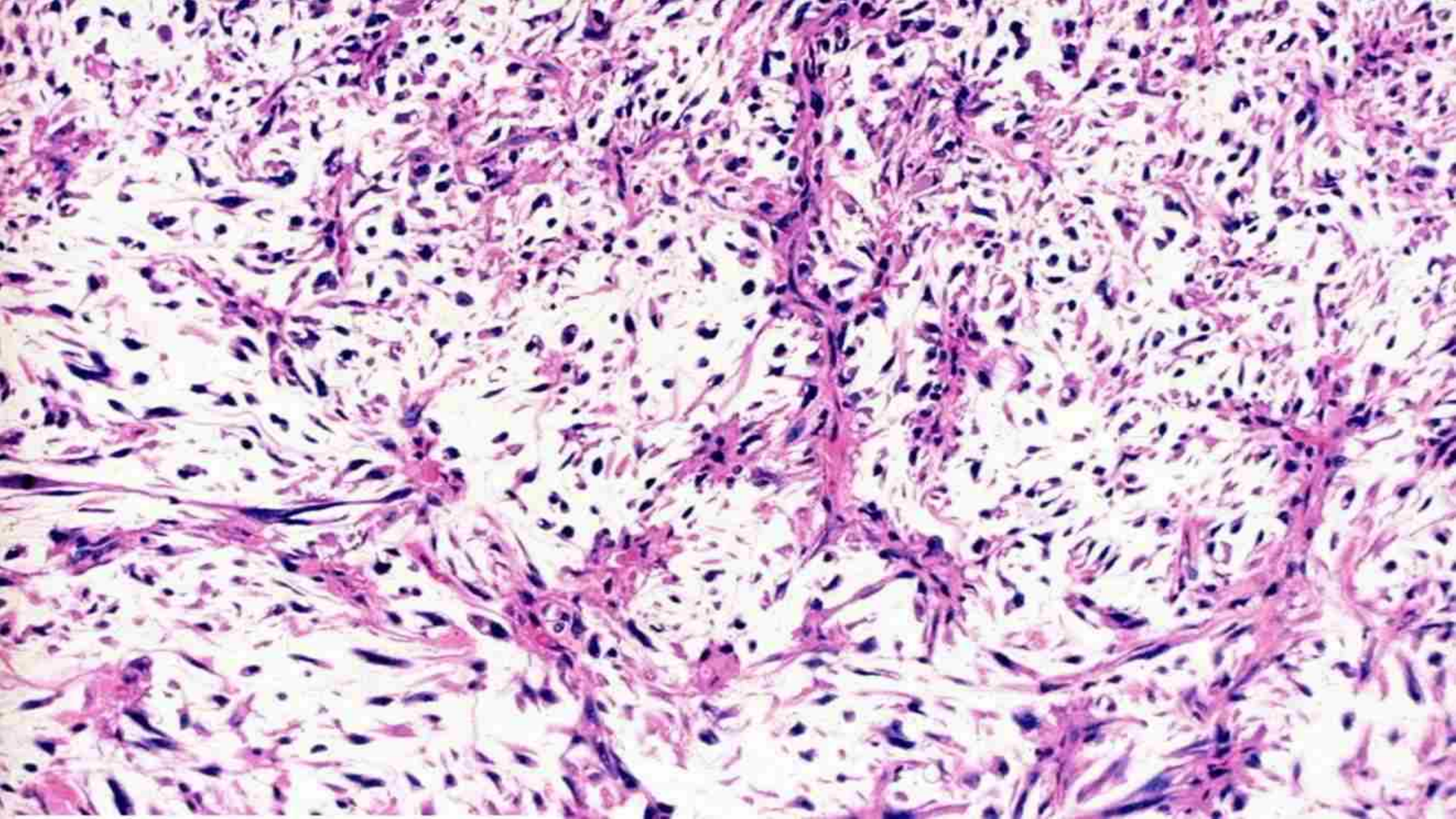




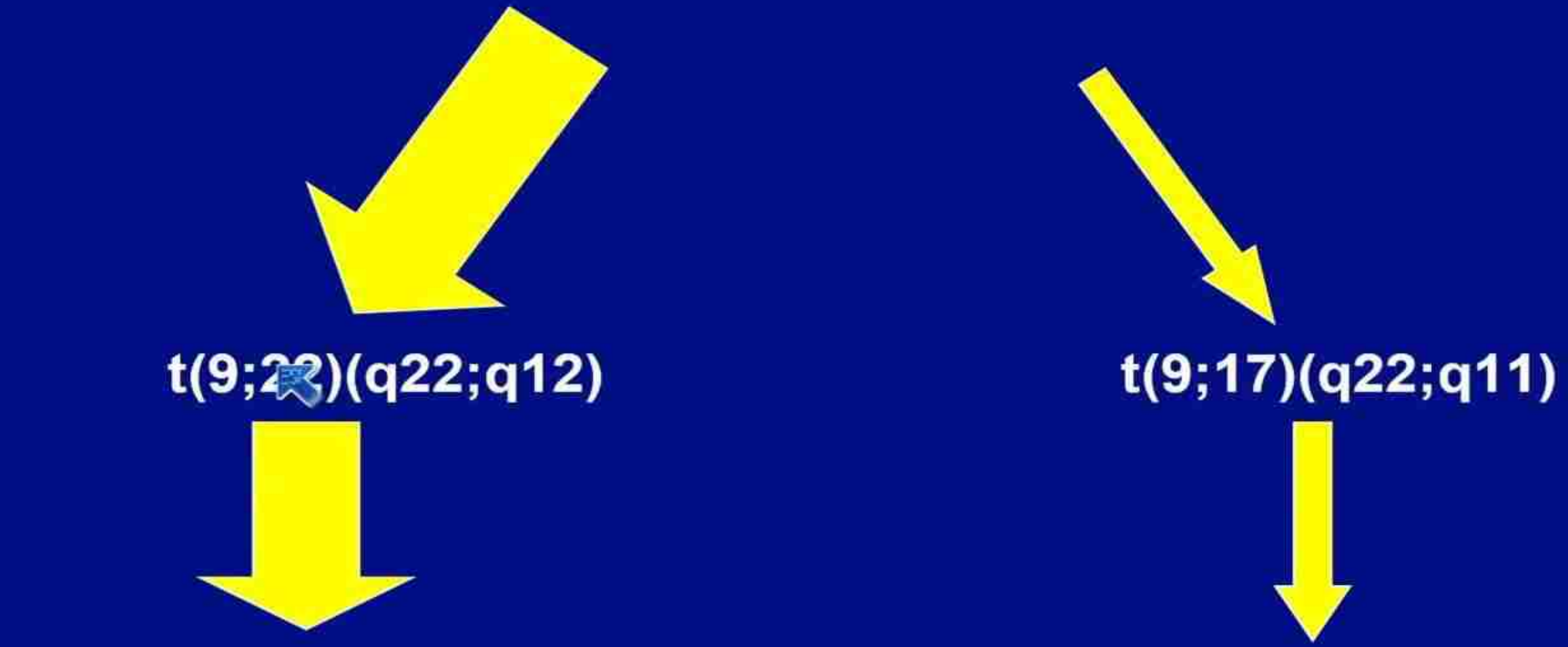


Myxoid/Round Cell Liposarcoma

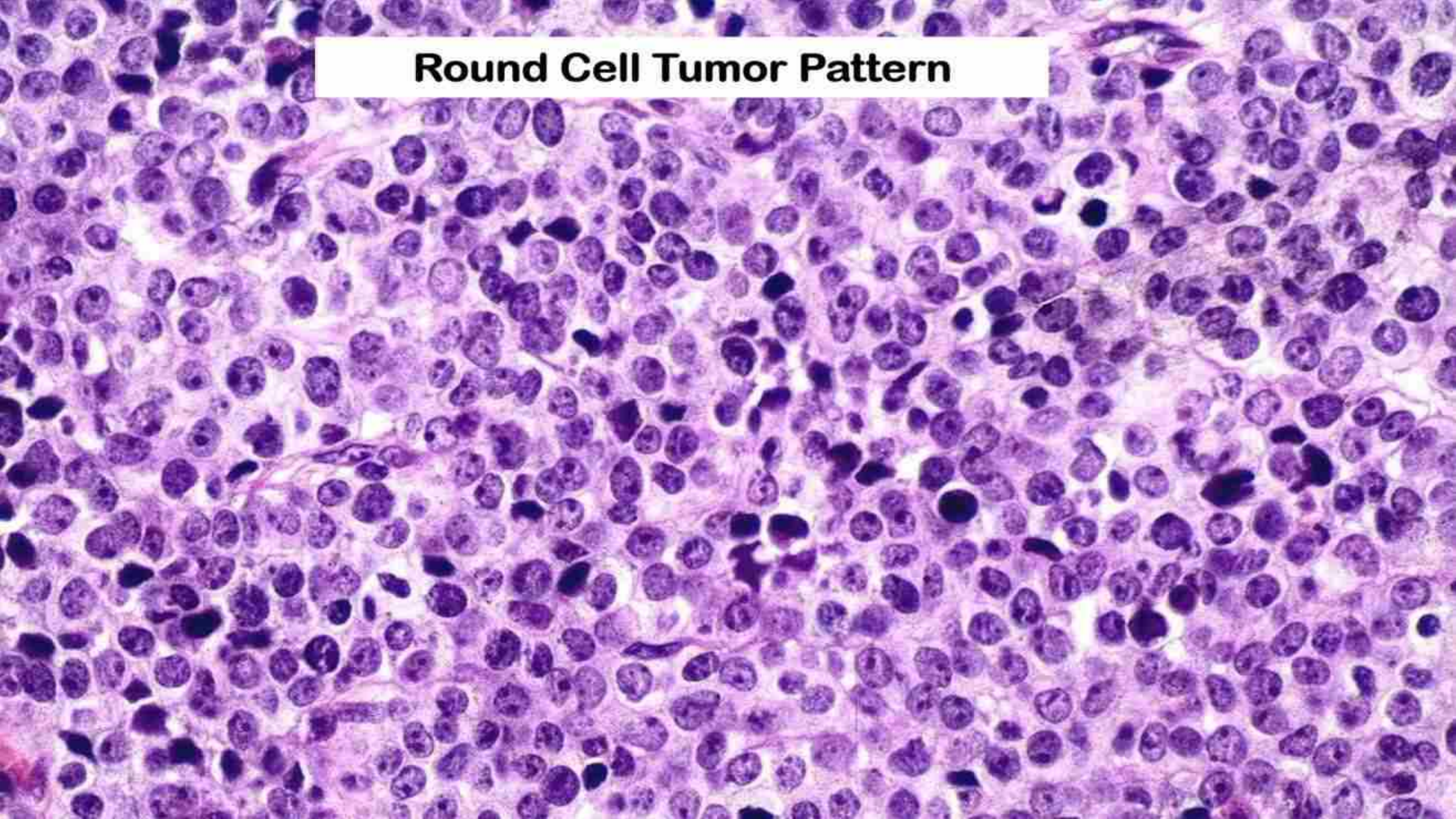
- Middle-aged adults (peak in 5th decade)
- Deep soft tissues of extremities (medial thigh, popliteal fossa); very rare in retroperitoneum
- *FUS-DDIT3* [t(12;16)] or *DDIT3-EWSR1* [t(12;22)]
- Frequent local recurrence and metastasis (↑with ↑round cell component)



Extraskeletal Myxoid Chondrosarcoma



Round Cell Tumor Pattern

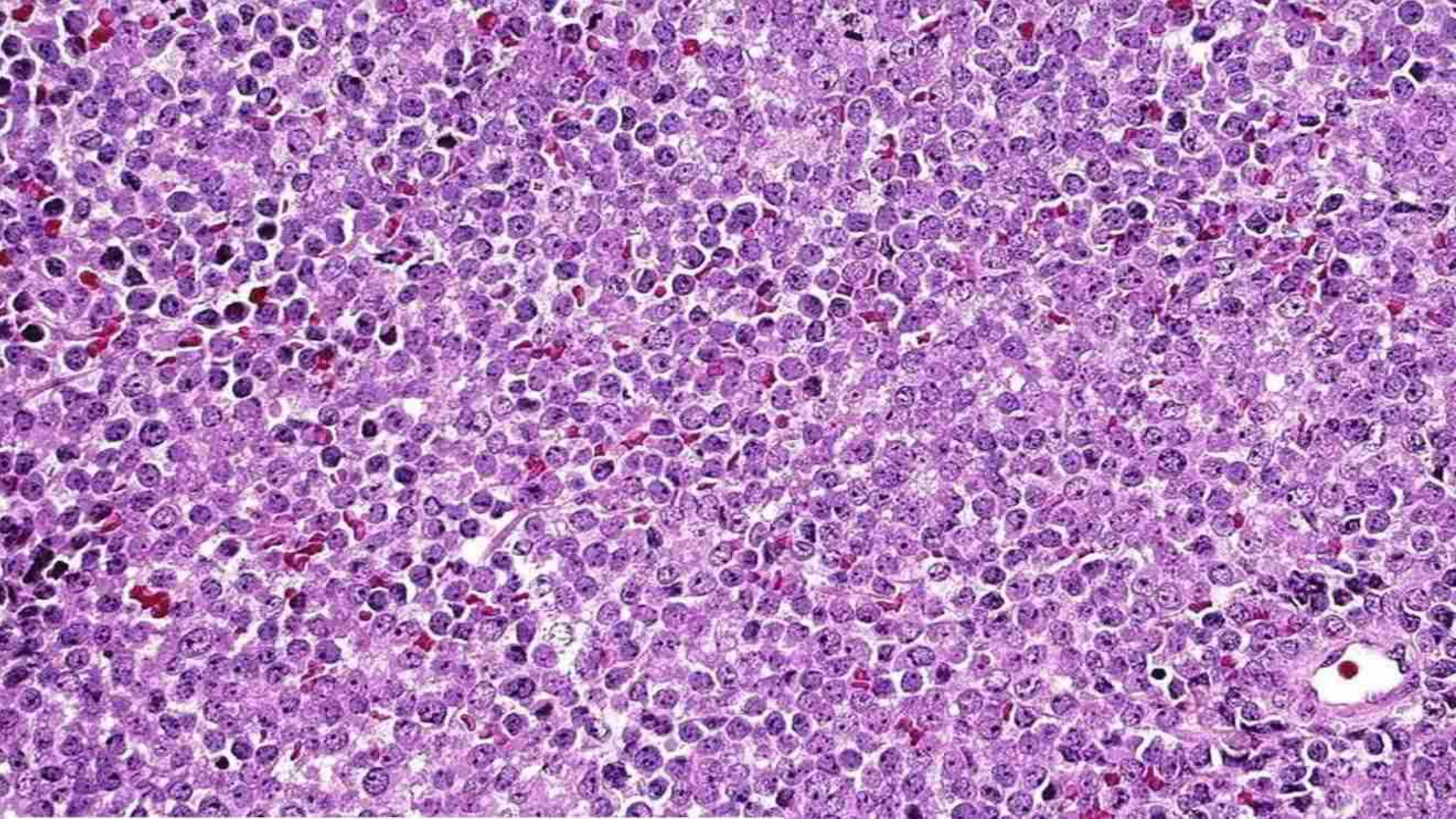


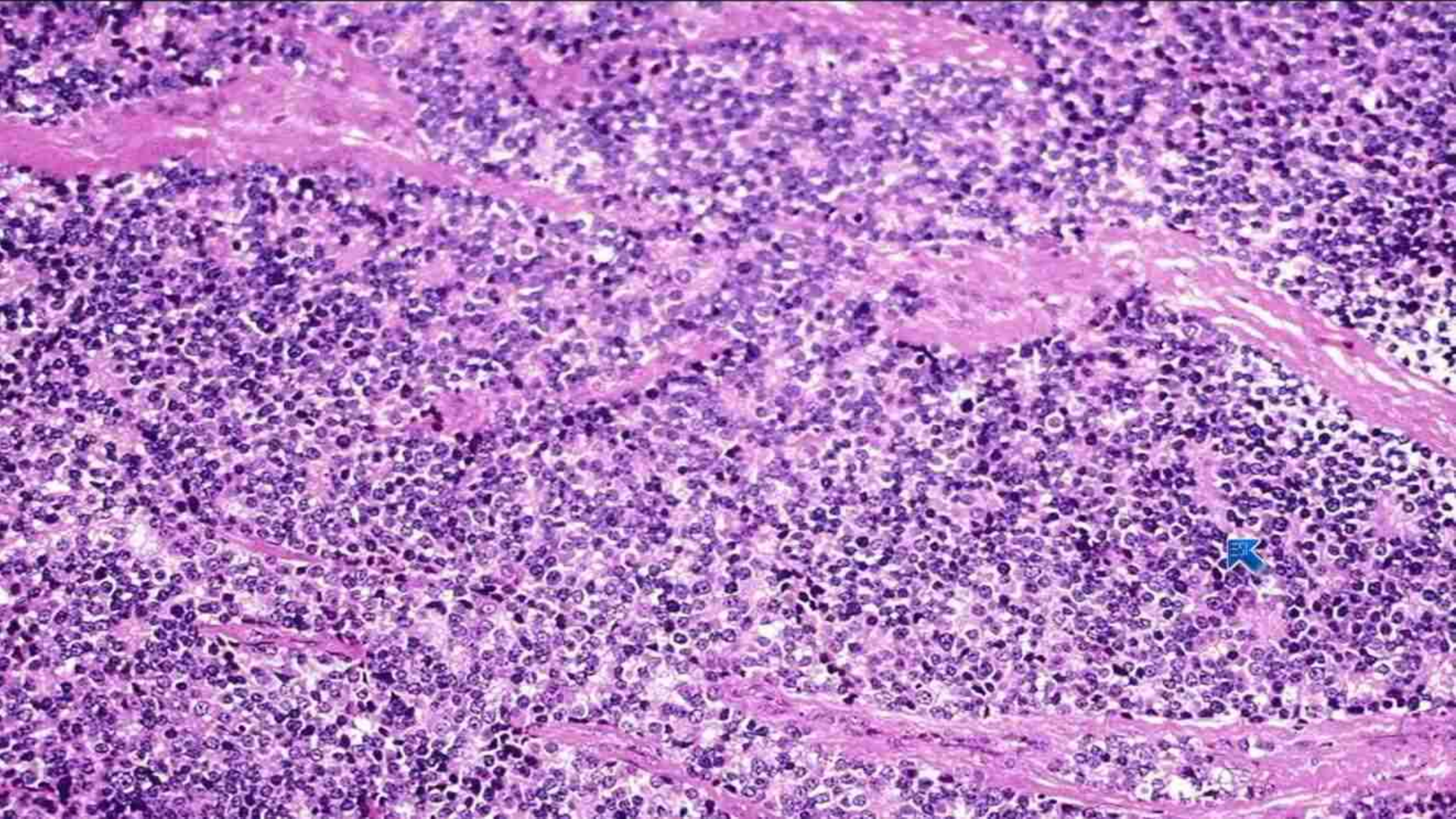
Round Cell Tumors
Benign

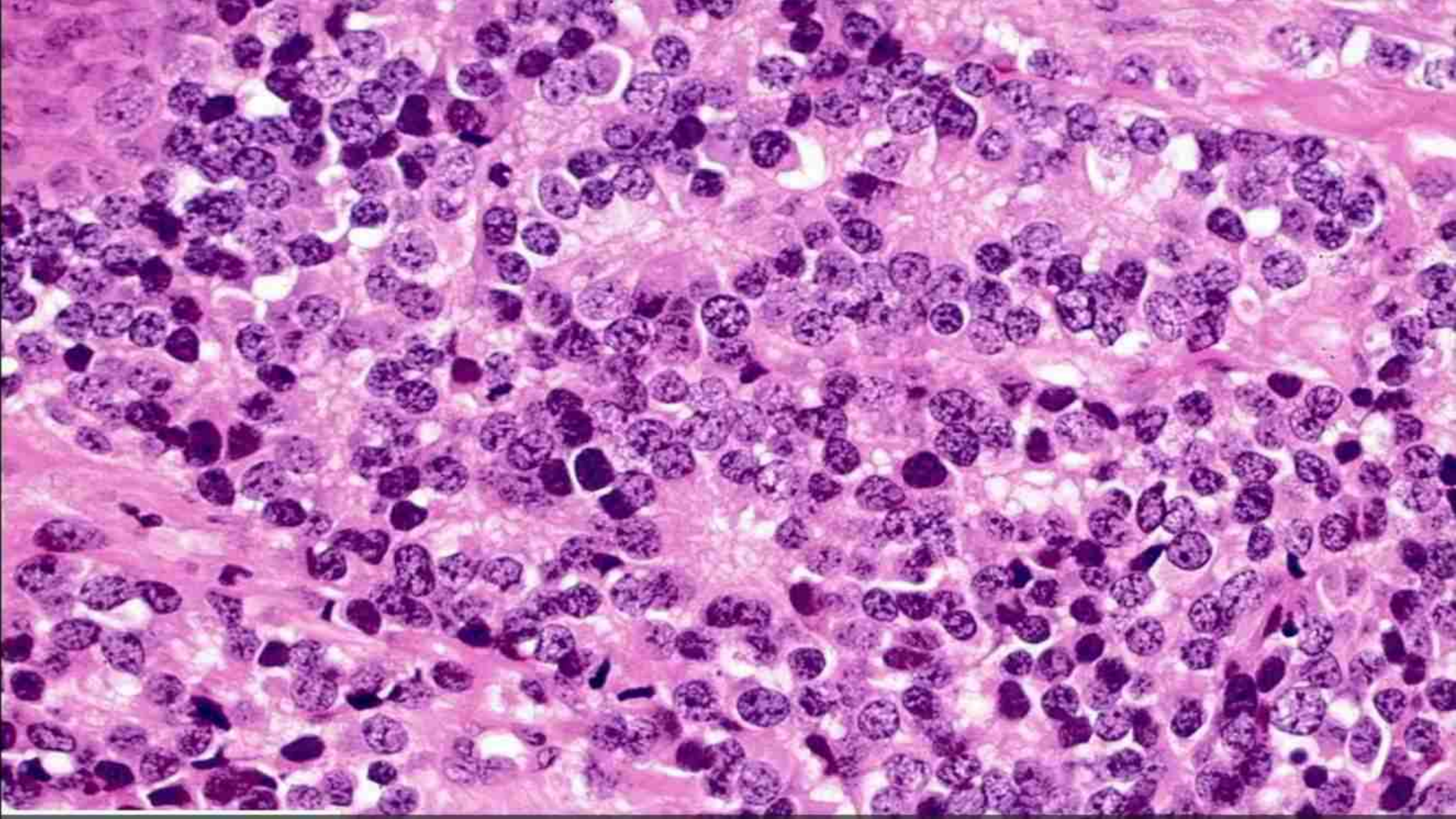
- Glomus Tumor
- Eccrine Spiradenoma
- Giant Cell Tumor

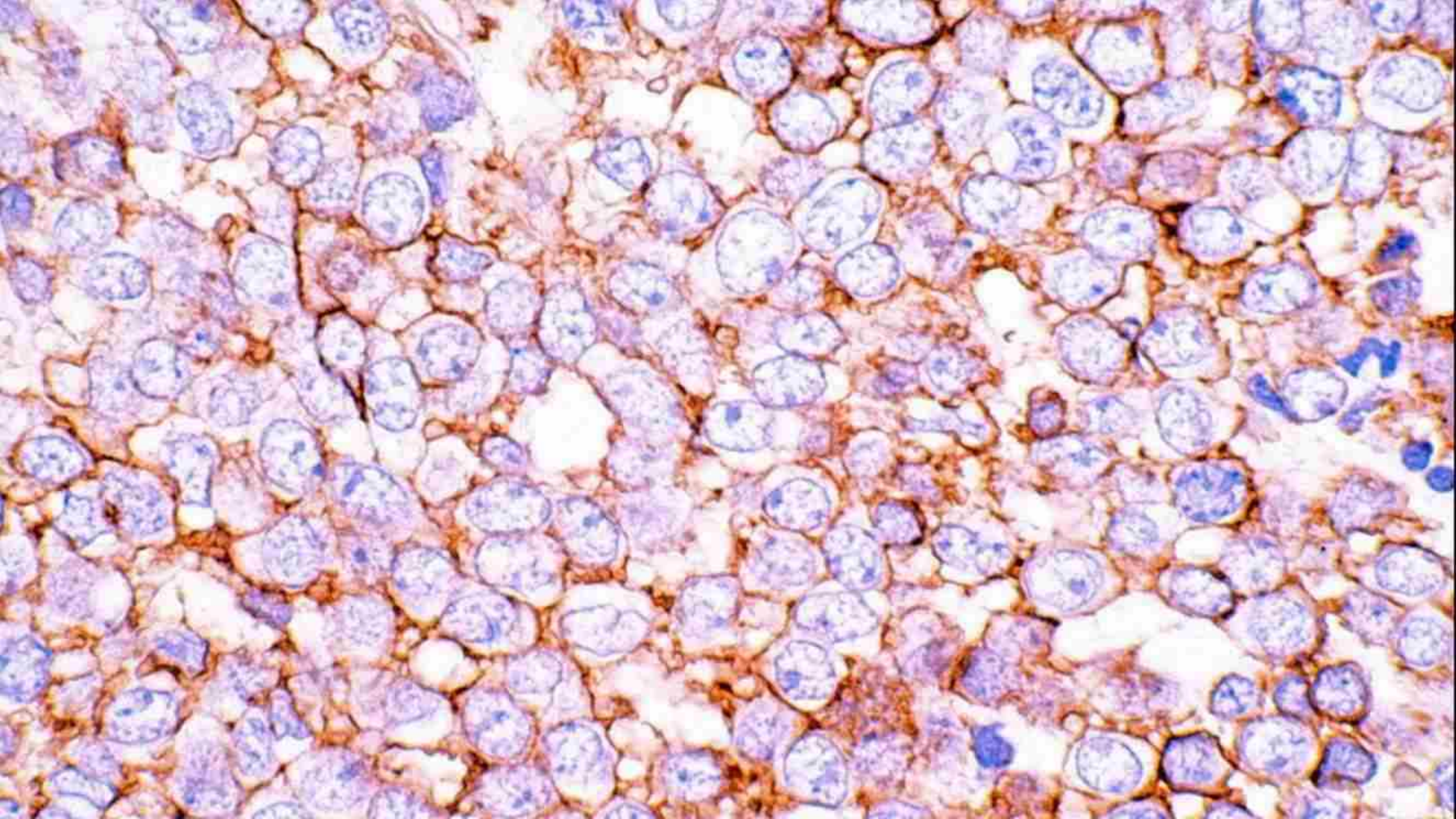
Round Cell Pattern

- ES/PNET (EFT)
- Alv RMS
- DSRCT
- Neuroblastoma
- Small cell/Merkel cell
- Lymphoma
- Mesenchymal CS
- Round cell LS
- Poorly diff SS
- "Ewing-like"
  - CIC-DUX4
  - BCOR-CCNB3



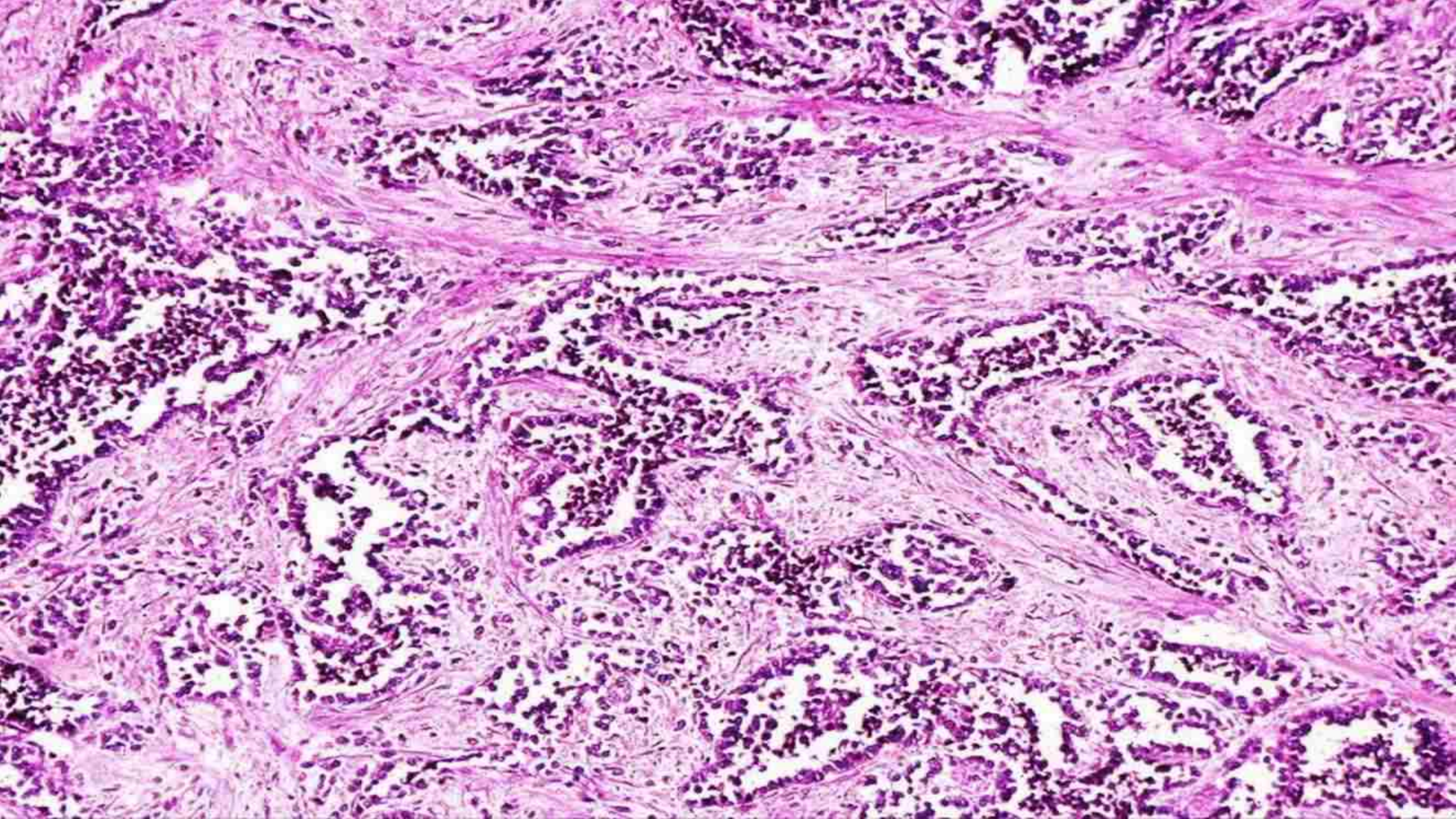


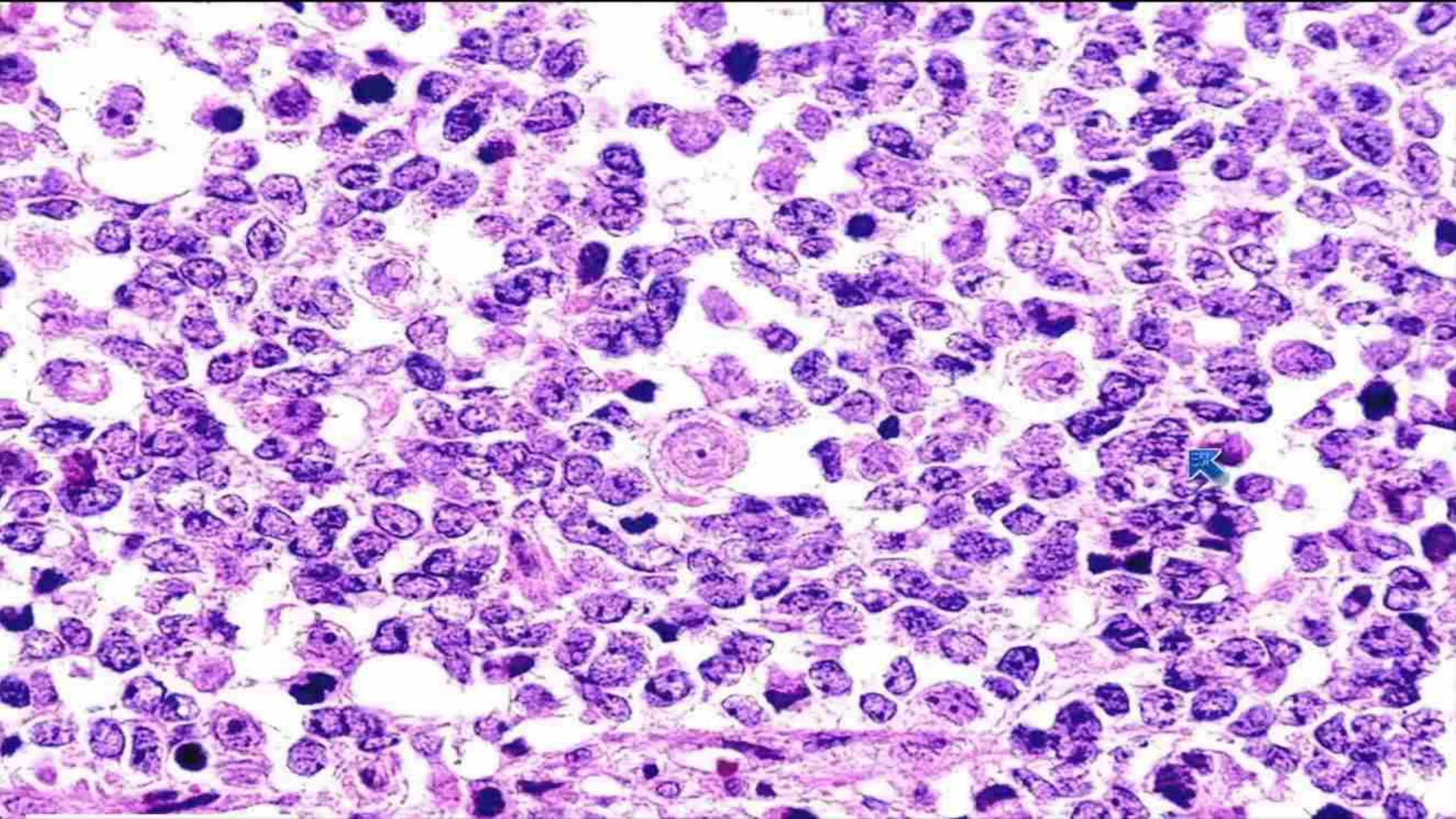


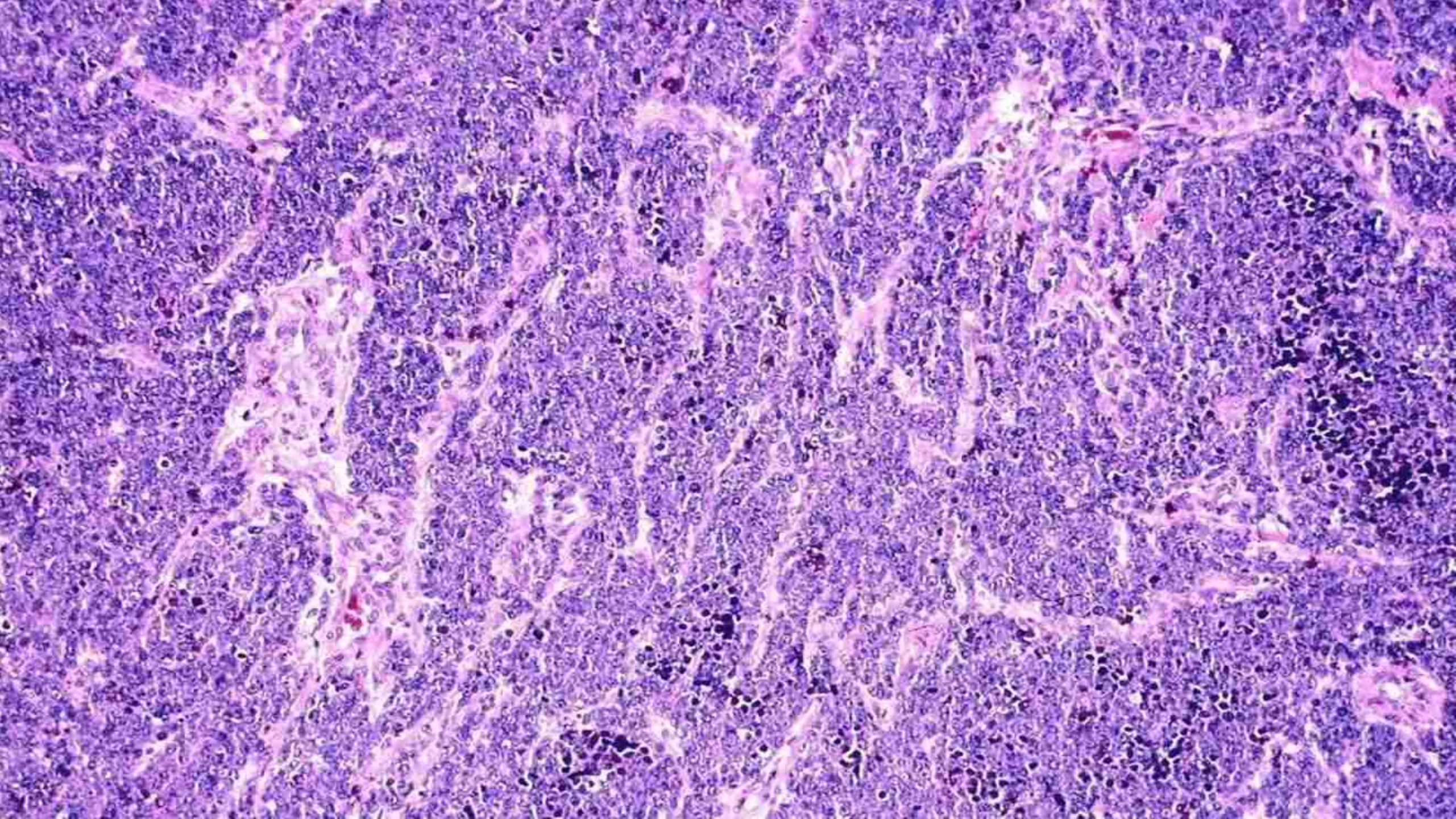


NKX2-2: Sensitivity/Specificity

Tumor	Cases staining (nuclear)
• EFT (genetically confirmed)	37/40 (93%)
• Non-EFT round cell tumors	
CIC-DUX4 sarcoma	1/20 (%)
BCOR-CCNB3 sarcoma	0/5 (0%)
PD synovial sarcoma	1/10 (10%)
Lymphoblastic lymphoma	0/10 (0%)
A-RMS	0/10 (0%)
E-RMS	0/10 (0%)
Melanoma	0/20 (0%)
Mesenchymal CS	9/12 (75%)

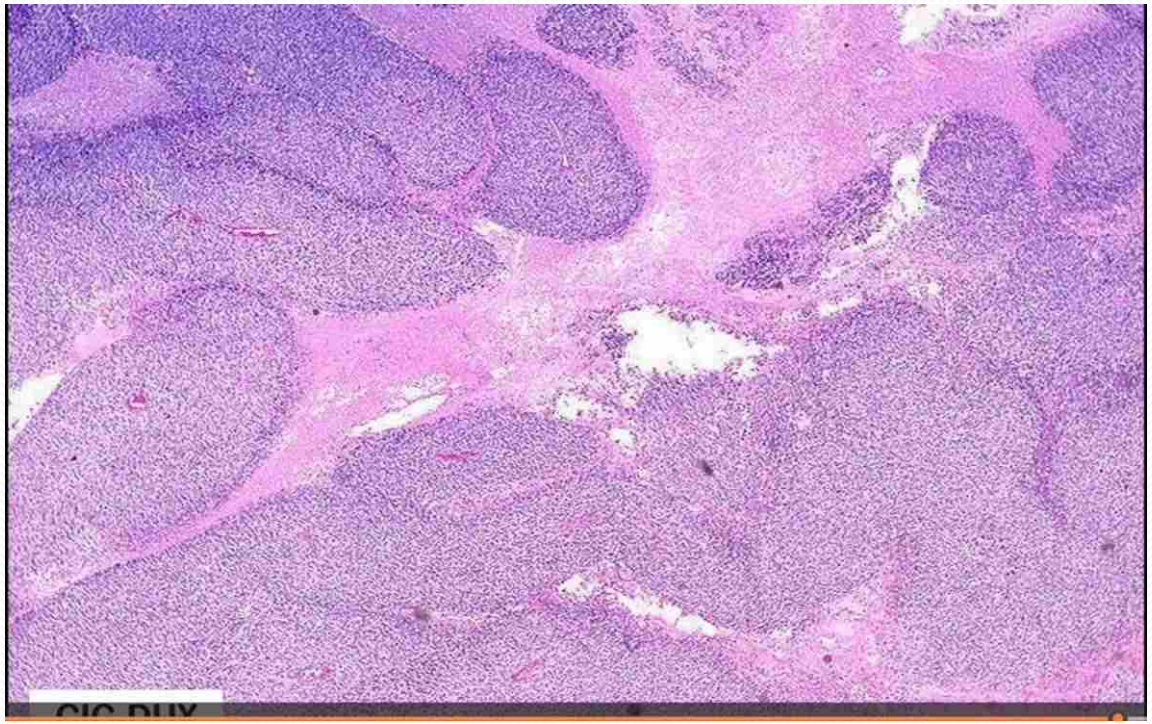




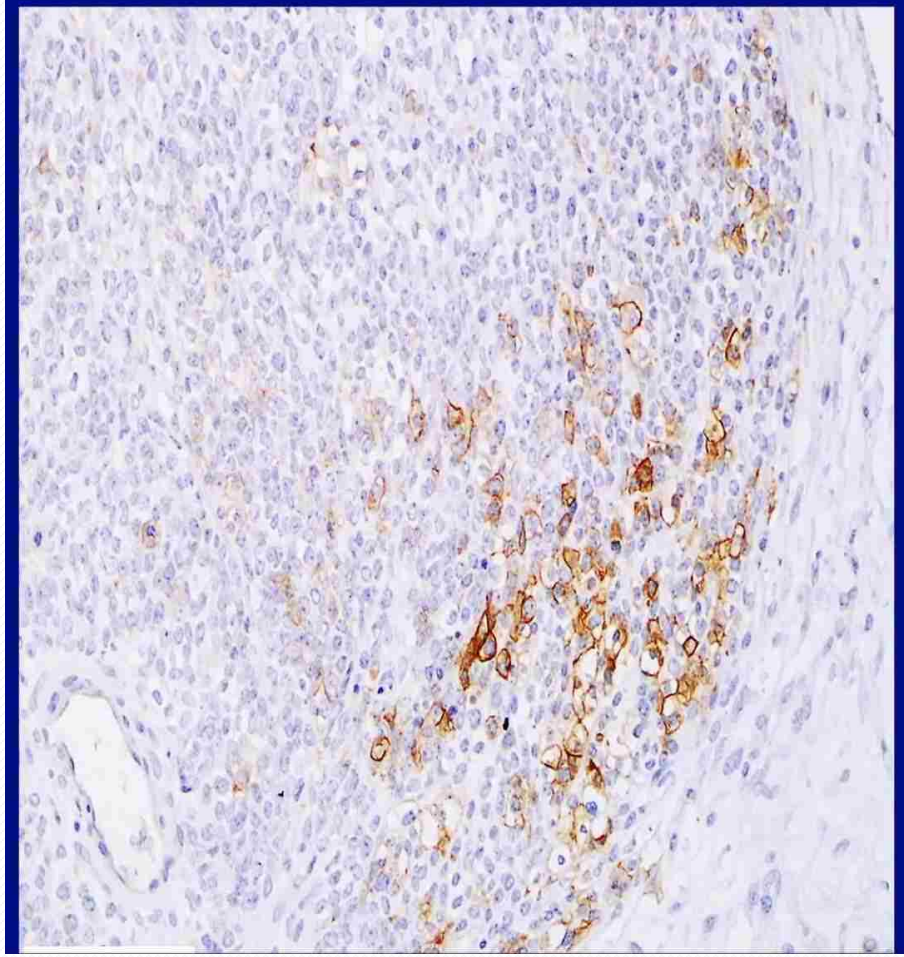


CIC-rearranged Sarcoma

- Most common "Ewing-like" round cell sarcoma that lacks *EWSR1* fusions (most are *CIC-DUX4*)
- Wide age range (peak in young adults)
- Most common in deep soft tissue of extremities and trunk (rare in visceral sites and bone)
- Much more aggressive clinical course and poorer survival than Ewing sarcoma



CIC-Rearranged Sarcoma (19q13)



CD99	focal (70-80%)
S-100	-
Desmin	-
Myogenin	-
CK	focal (10-15%)
ETV4	95% (nuclear)
WT1	90% (nuclear +/- cyt
EWSR1 FISH	-