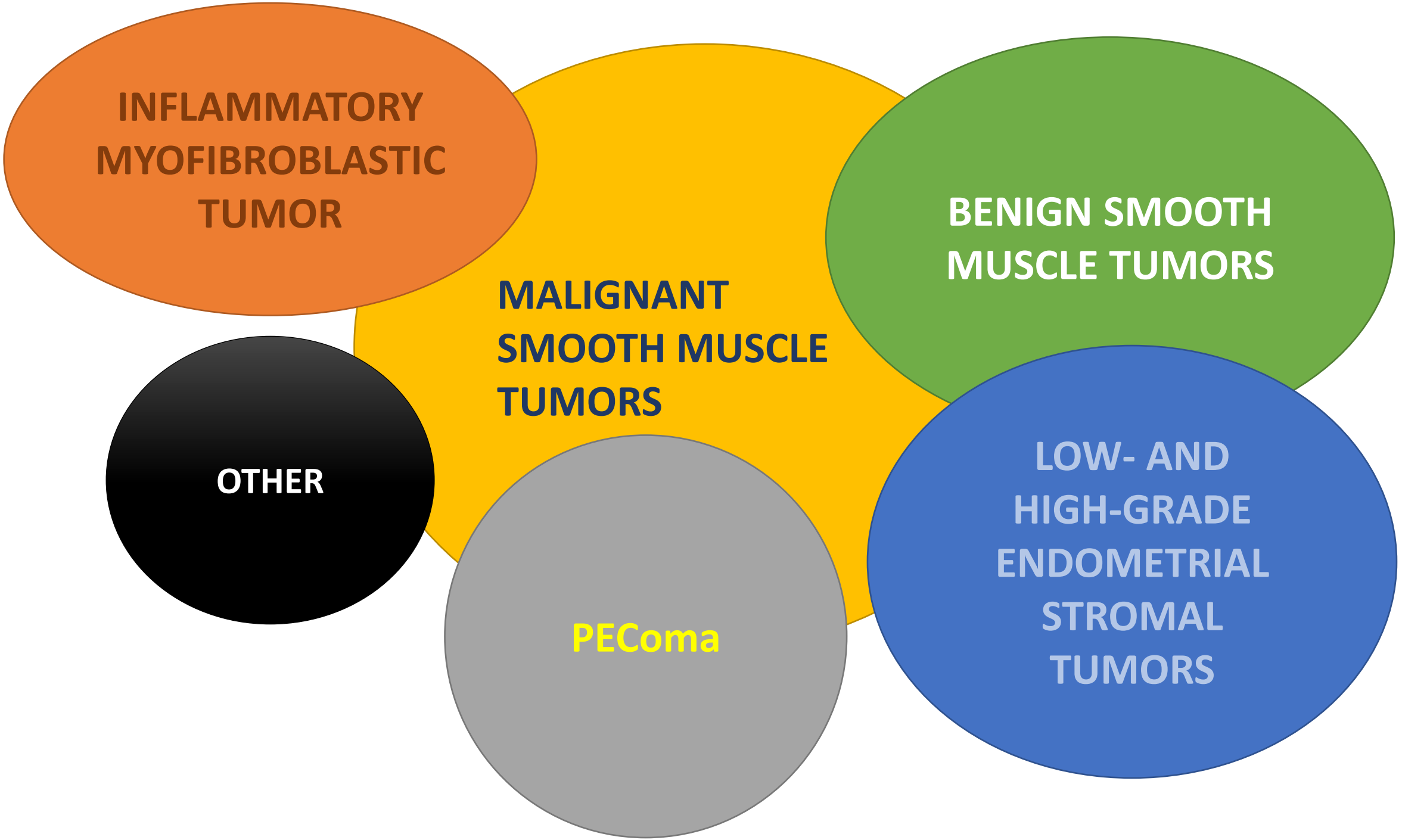
HOUSTON SOCIETY OF CLINICAL PATHOLOGISTS
63rd ANNUAL SPRING SYMPOSIUM
CURRENT CONCEPTS IN GYNECOLOGIC PATHOLOGY, APRIL 27th, 2024

An Integrated Approach to the Diagnosis of Mesenchymal Tumors of the Uterus

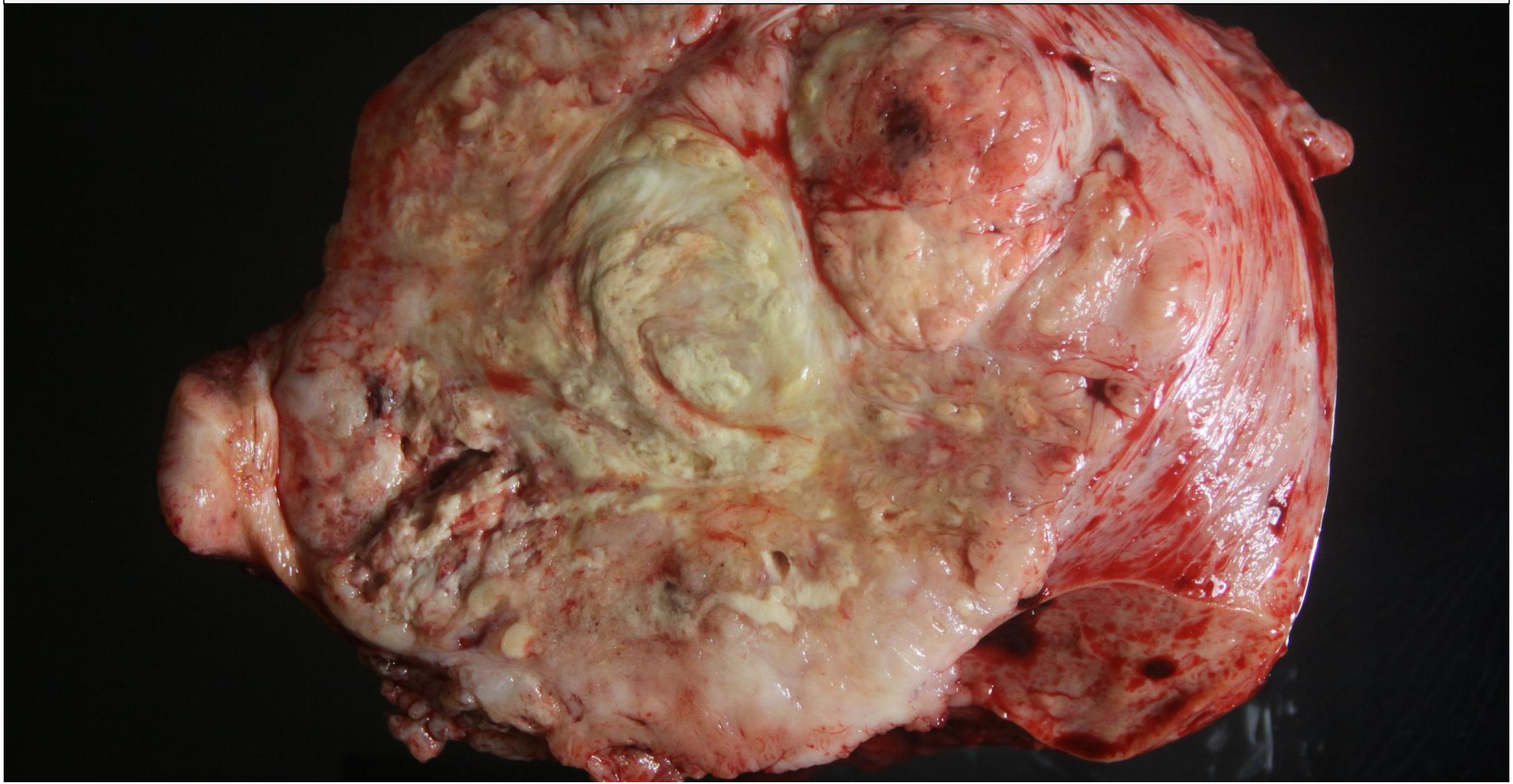
Esther Oliva
Massachusetts General Hospital and Harvard Medical School
eoliva@mgh.harvard.edu


INFLAMMATORY MYOFIBROBLASTIC TUMOR
MALIGNANT SMOOTH MUSCLE TUMORS
BENIGN SMOOTH MUSCLE TUMORS
OTHER
PEComa
LOW- AND HIGH-GRADE ENDOMETRIAL STROMAL TUMORS

SMOOTH MUSCLE TUMORS

- **Benign or malignant or STUMP?**
- **Cell type?**
- **What is in the differential diagnosis?**

LEIOMYOSARCOMA

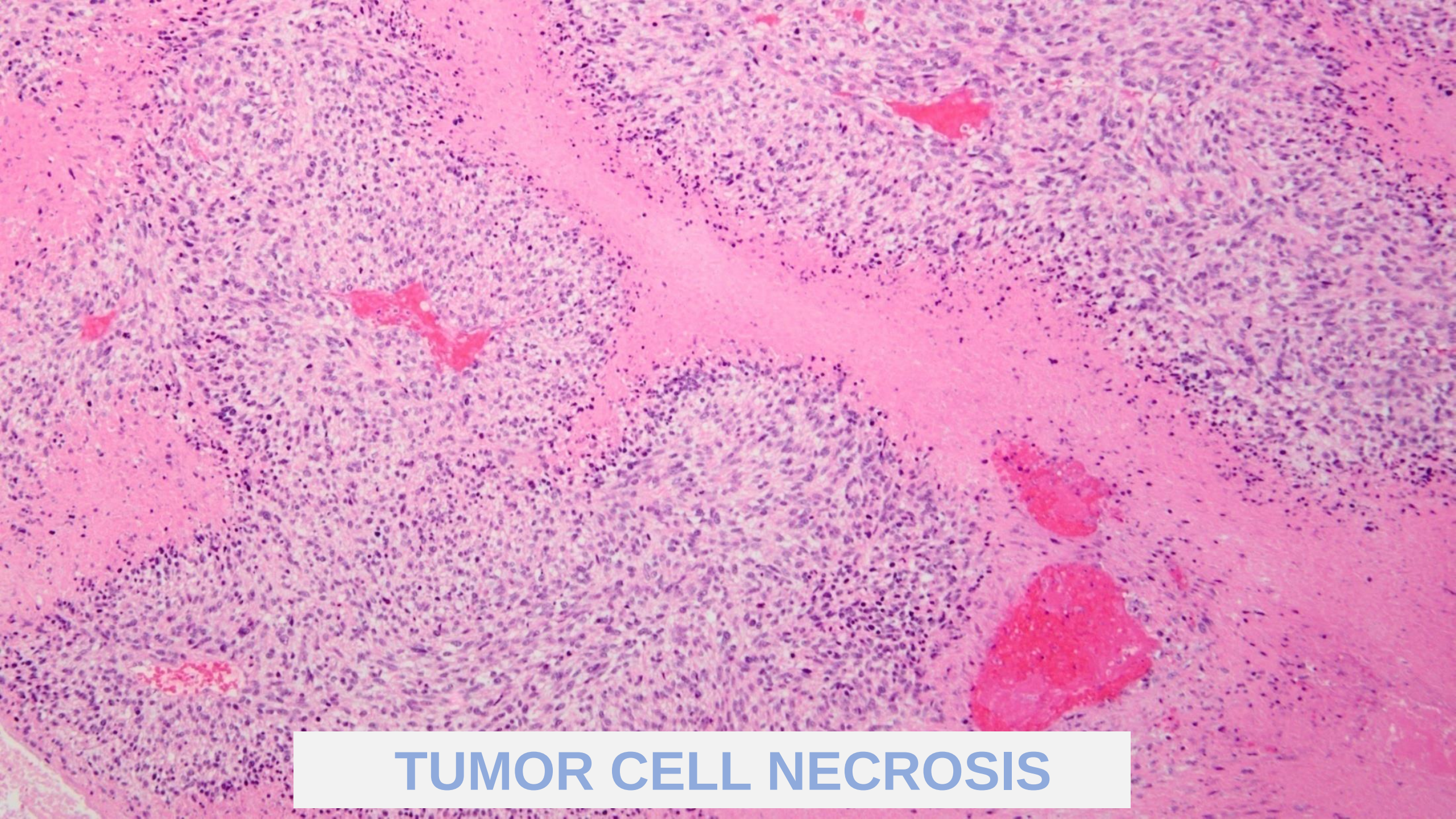


SPINDLE LEIOMYOSARCOMA

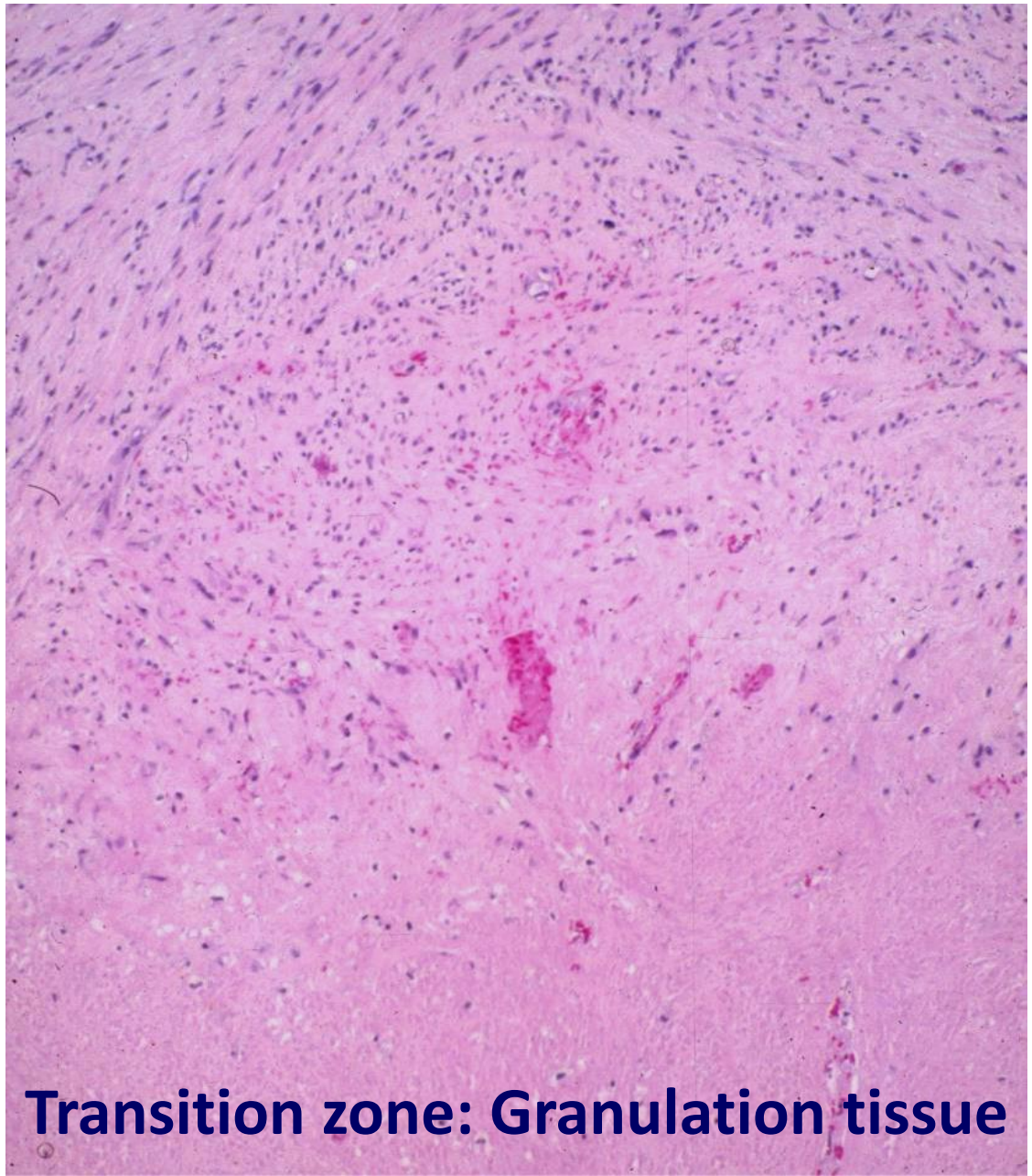
Bell et al, Am J Surg Pathol 1994;18:535

- **Tumor cell necrosis**
- **Diffuse moderate to marked atypia**
- **High mitotic rate (>10MFs/10HPFs)**

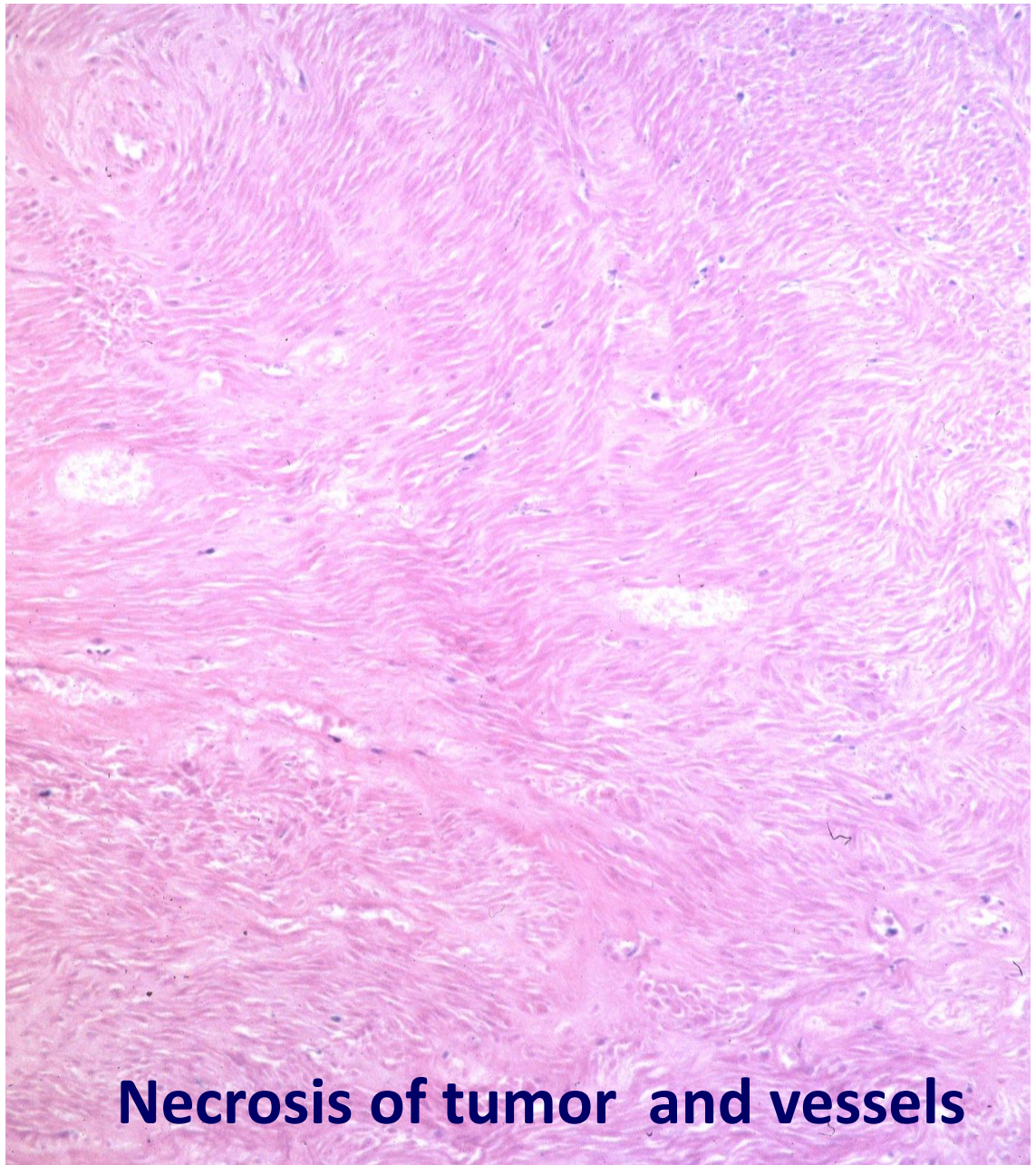
*** any two of these criteria diagnostic**


TUMOR CELL NECROSIS

INFARCT-TYPE NECROSIS

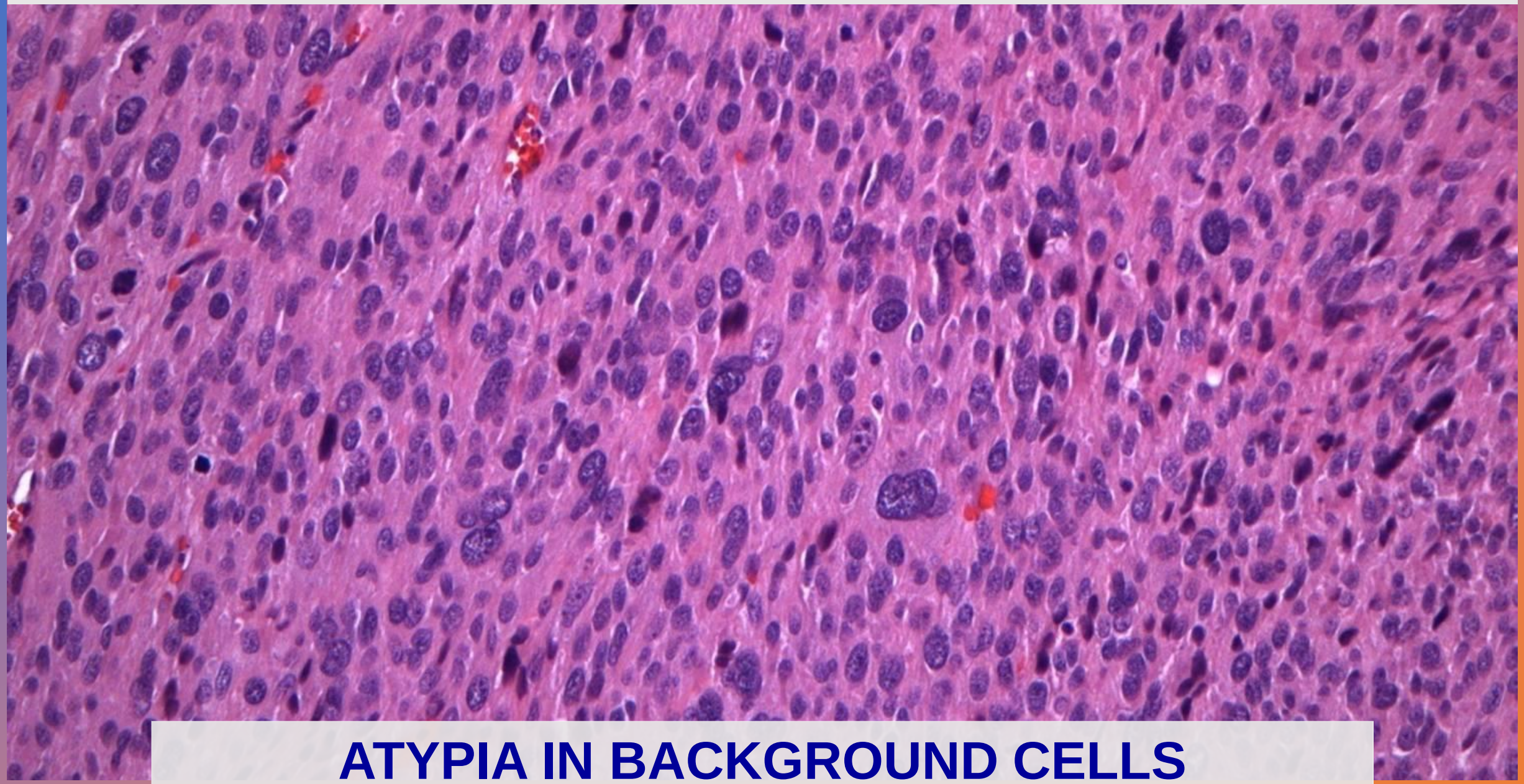


Transition zone: Granulation tissue



Necrosis of tumor and vessels

LEIOMYOSARCOMA



ATYPIA IN BACKGROUND CELLS

LEIOMYOSARCOMA GRADING
Low *vs* High grade

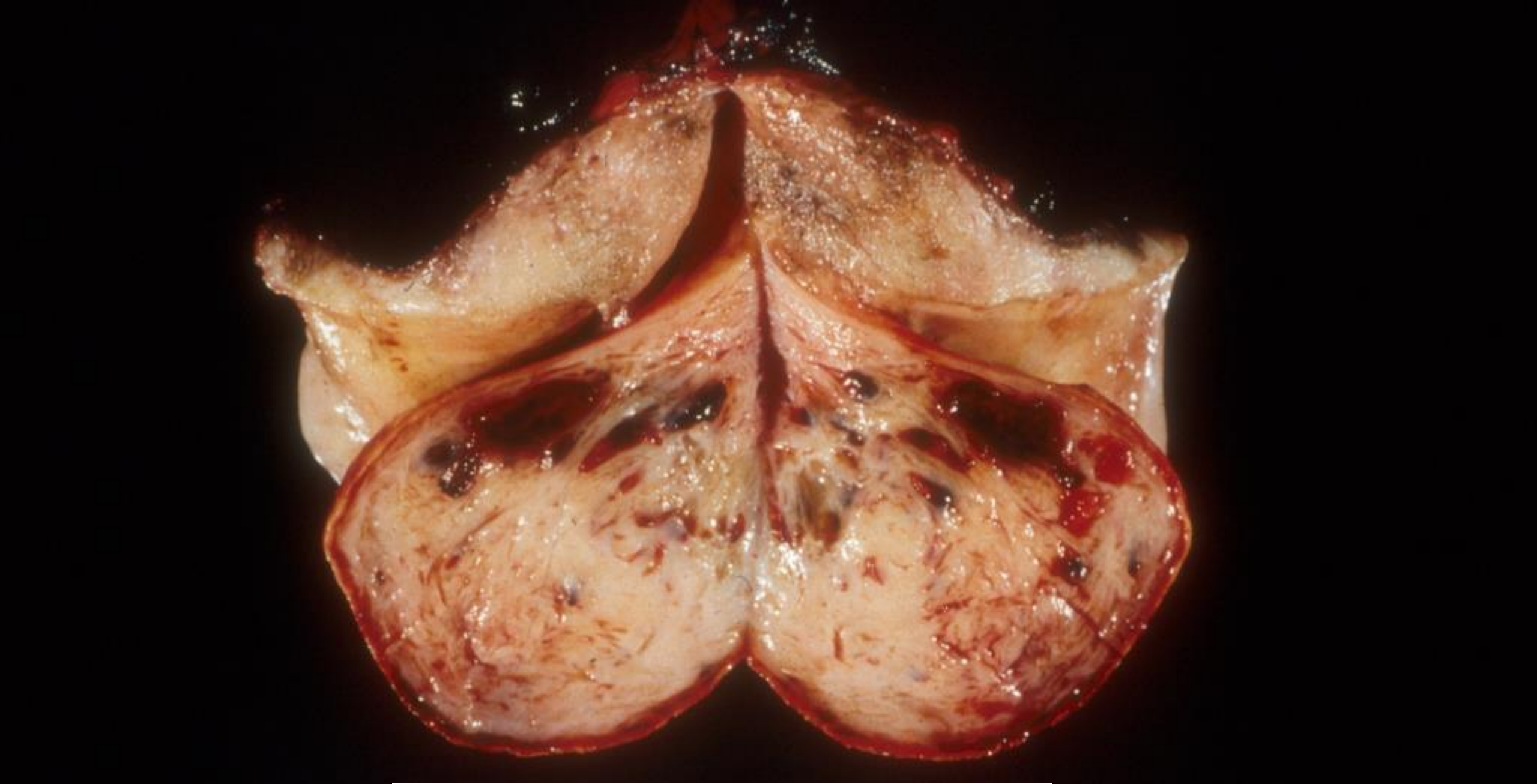
Based on current (Stanford) criteria all leiomyosarcomas are high-grade

…….Low-grade leiomyosarcomas exist, but criteria not well defined

SPINDLE LEIOMYOSARCOMA

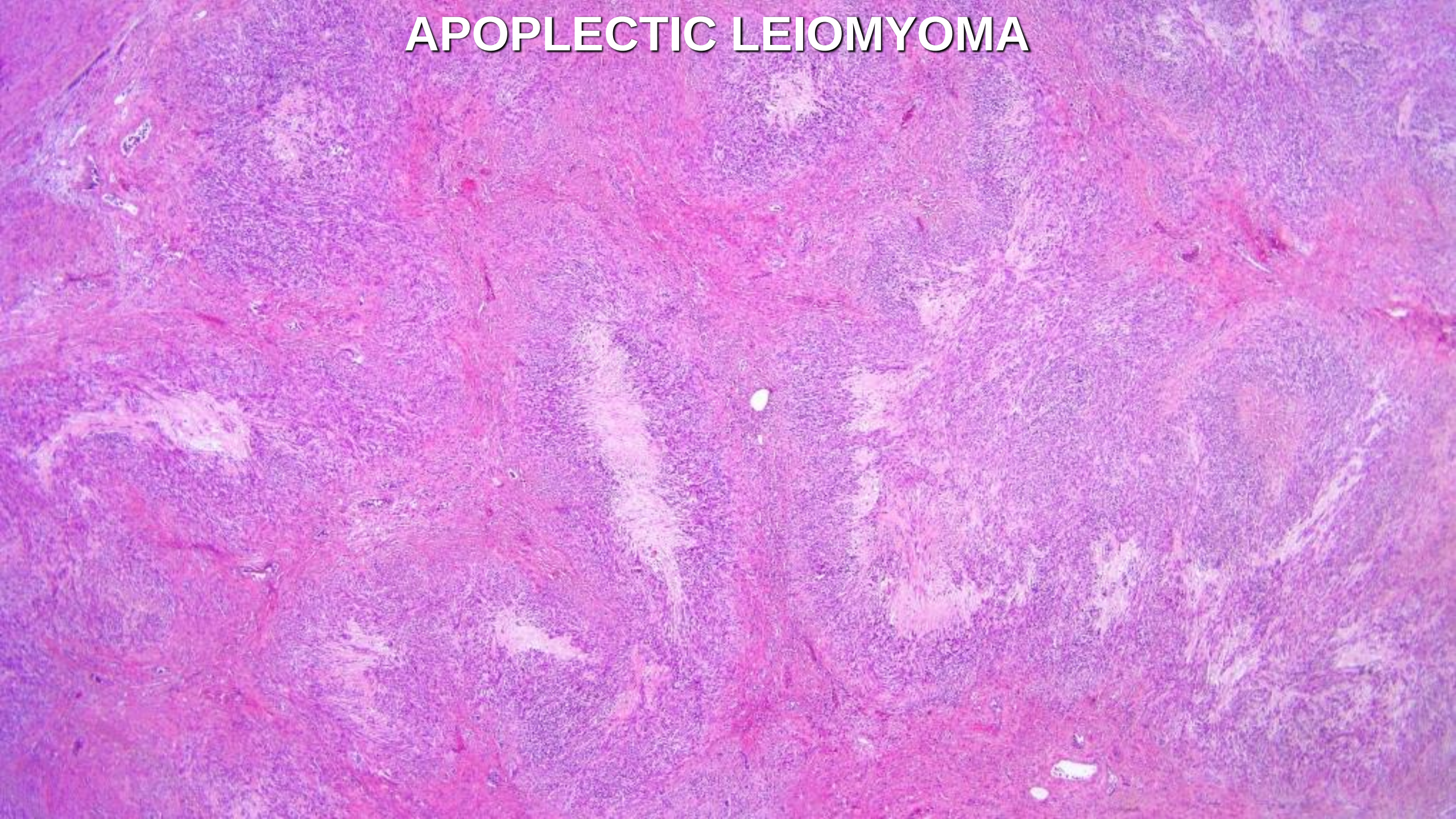
Differential Diagnosis

- Apoplectic leiomyoma
- Leiomyoma with bizarre nuclei
- Mitotically active leiomyoma
- Highly cellular leiomyoma
- Rhabdomyosarcoma
- Undifferentiated uterine sarcoma (Diagnosis of exclusion)

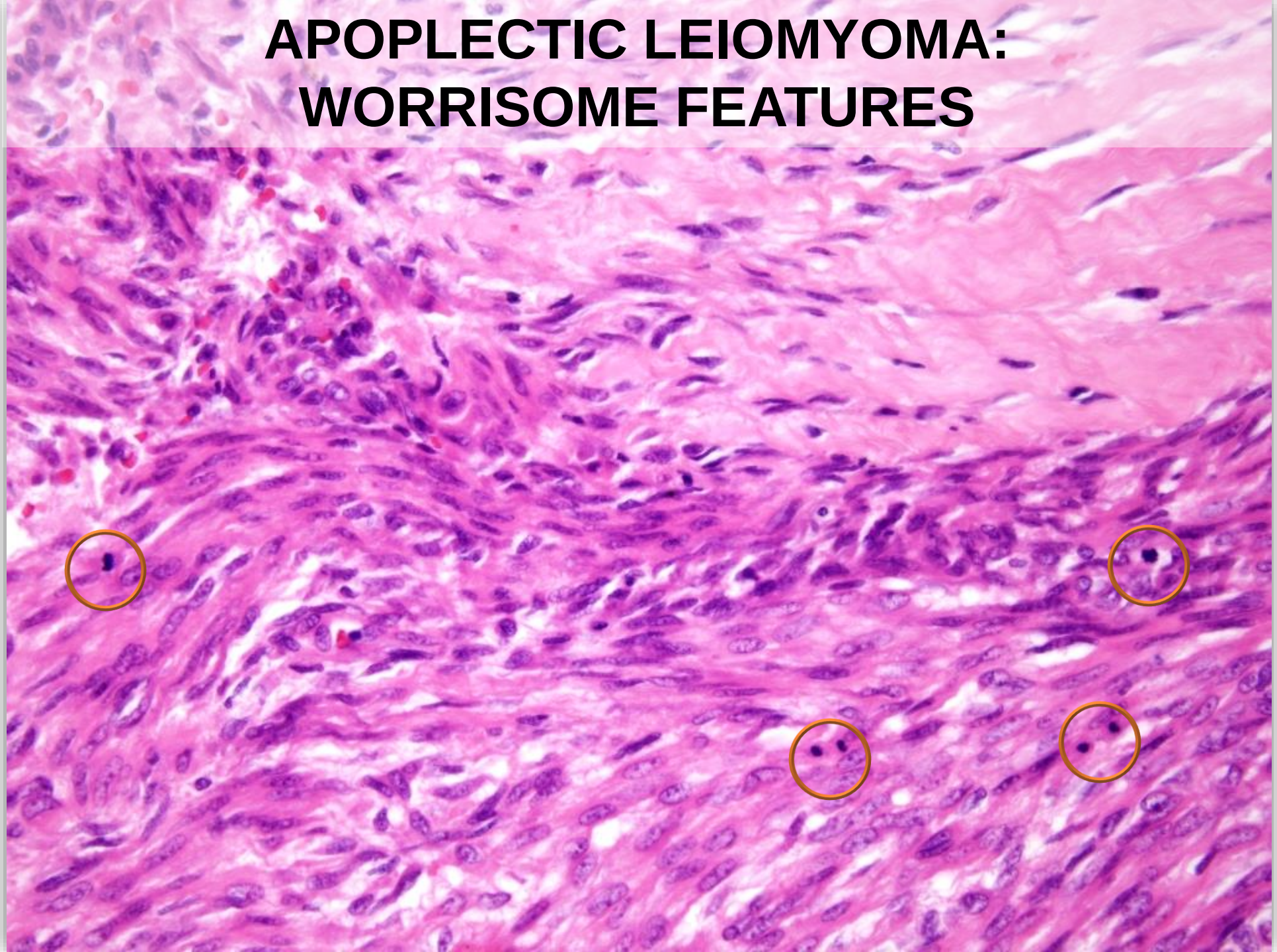


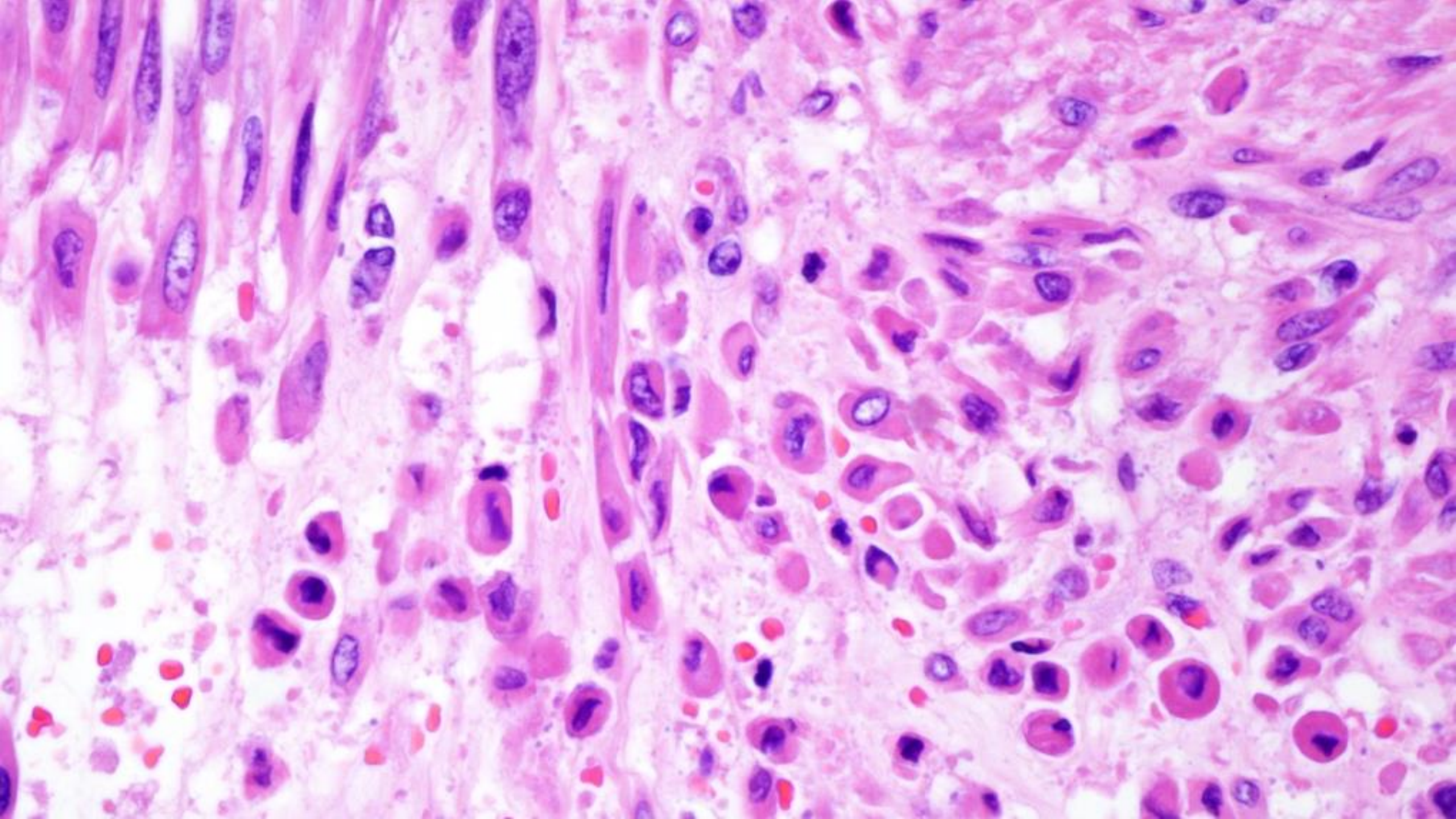
Apoplectic Leiomyoma

APOPLECTIC LEIOMYOMA

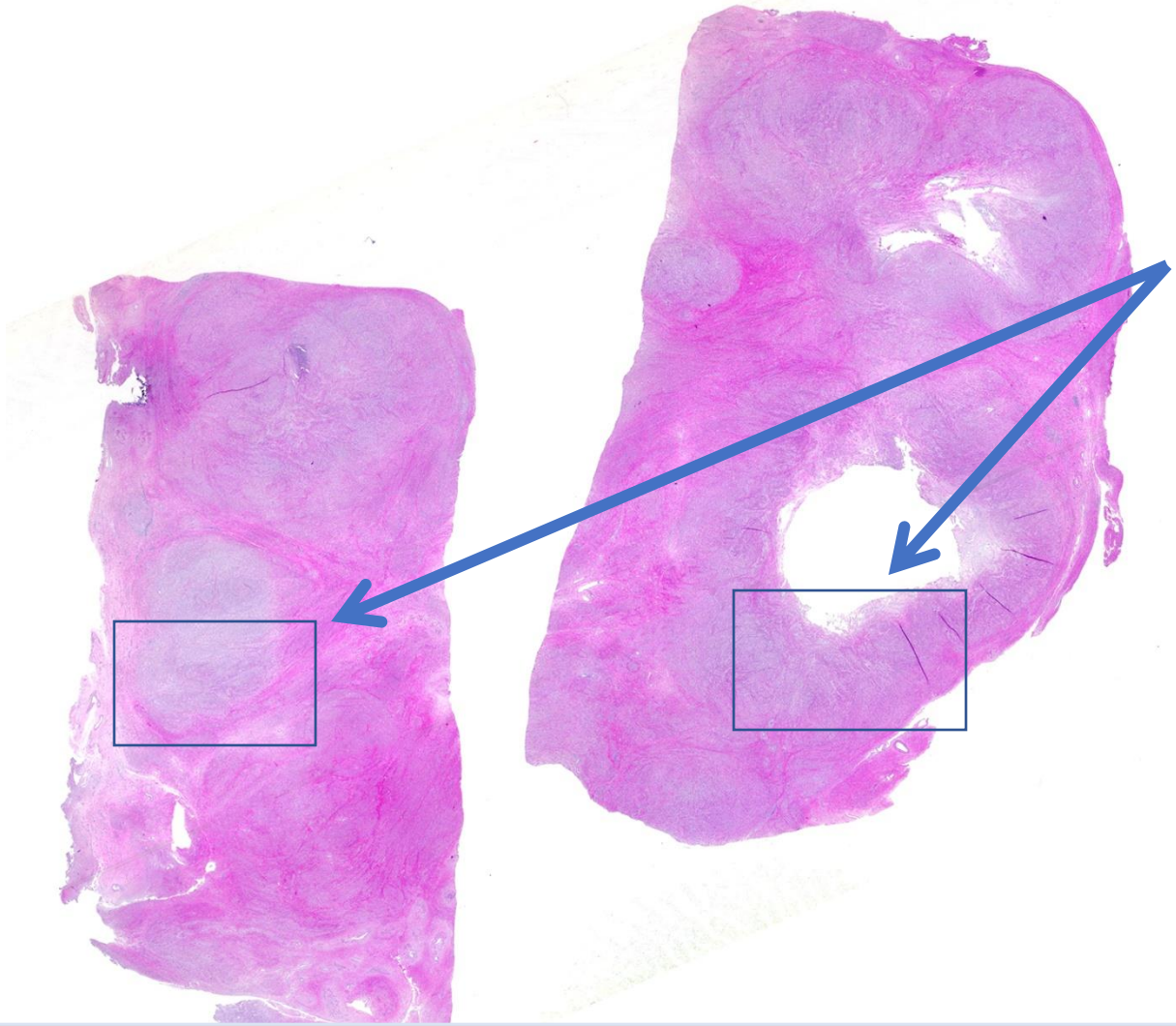


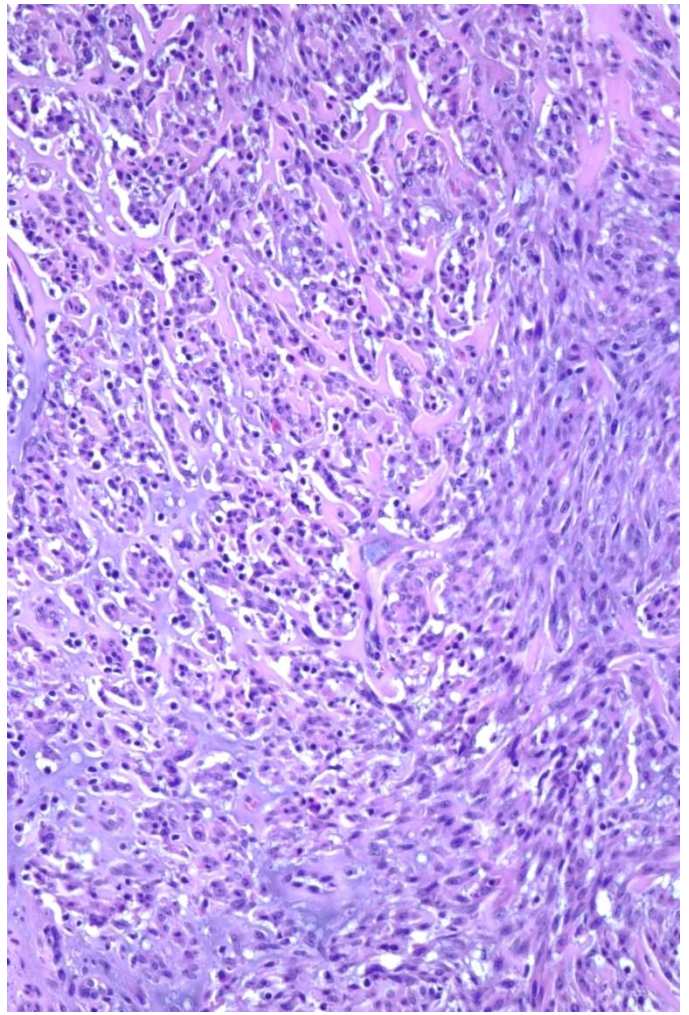
APOPLECTIC LEIOMYOMA: WORRISOME FEATURES



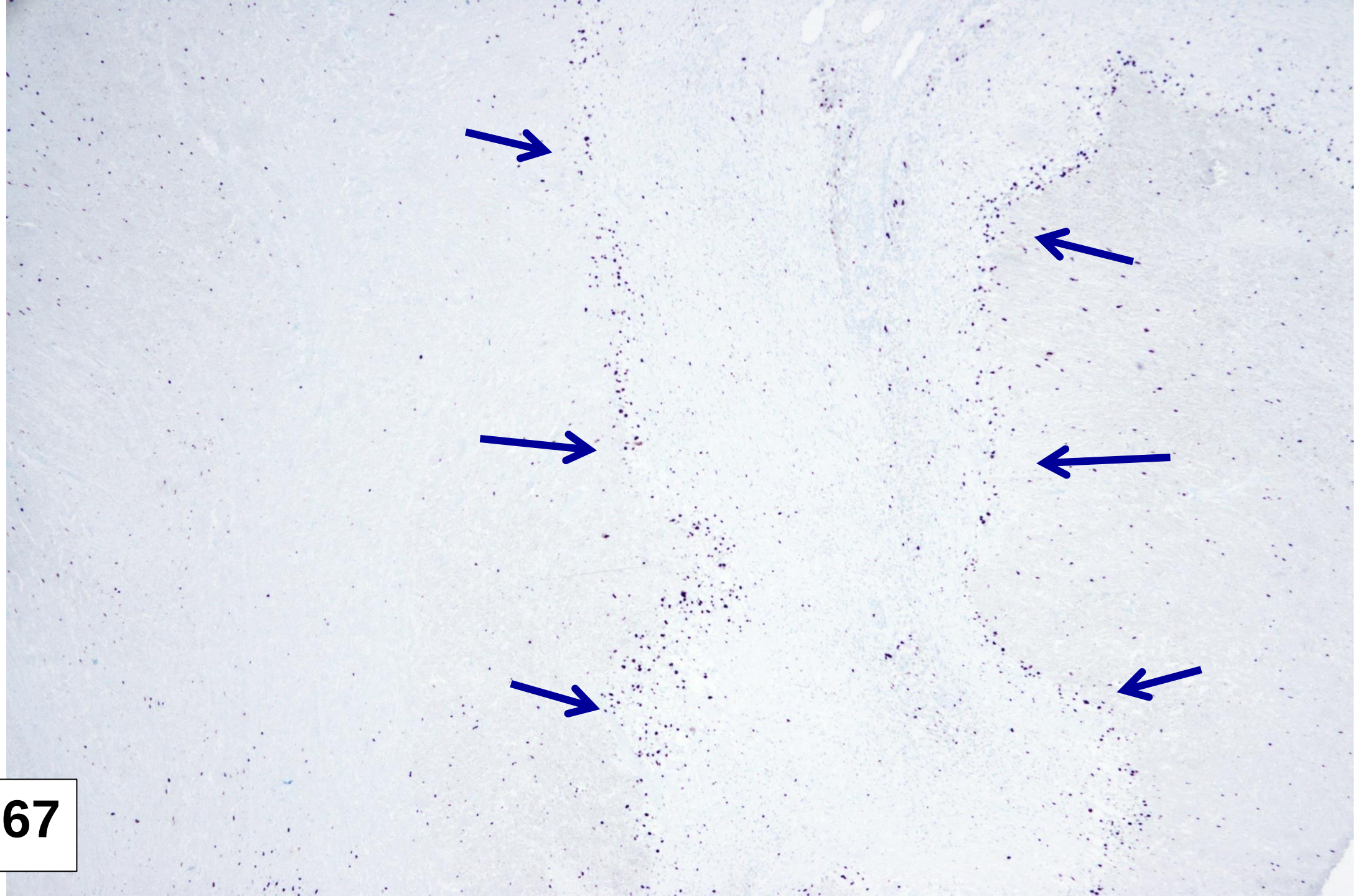


LEIOMYOMA with APOPLECTIC CHANGE

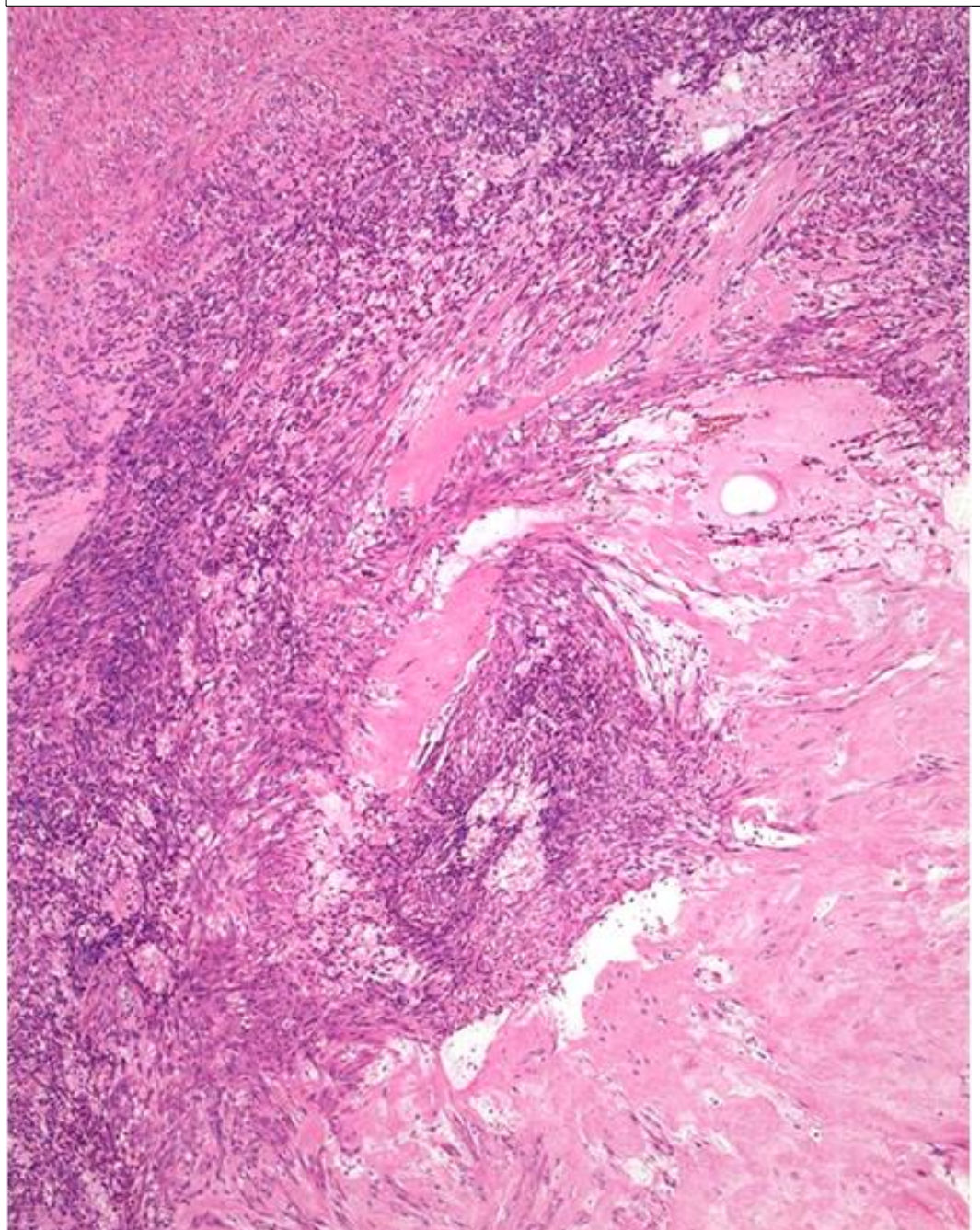


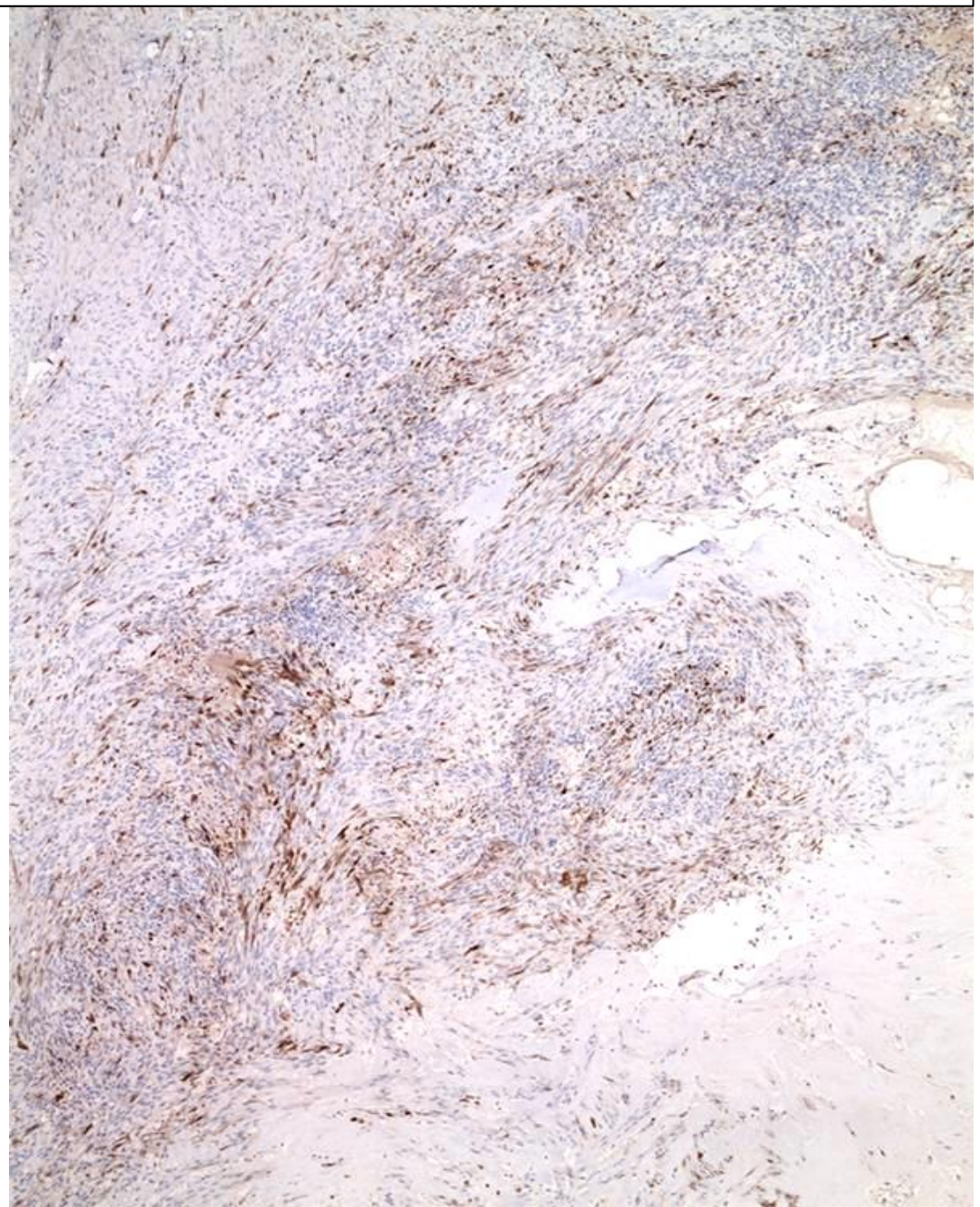


Evaluate tumor away from areas of infarction

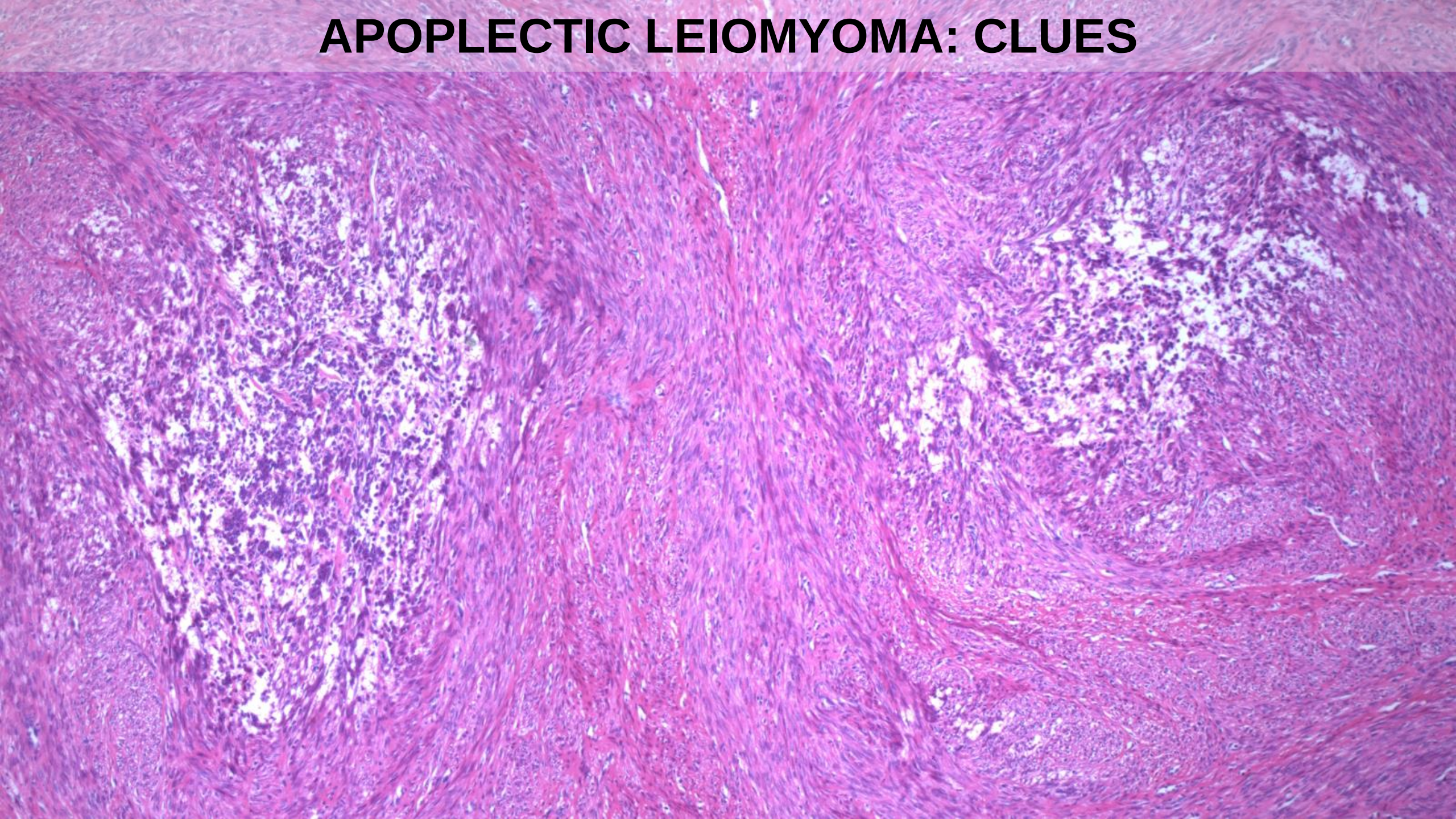

Ki67

APOPLECTIC LEIOMYOMA: p16 POSITIVE

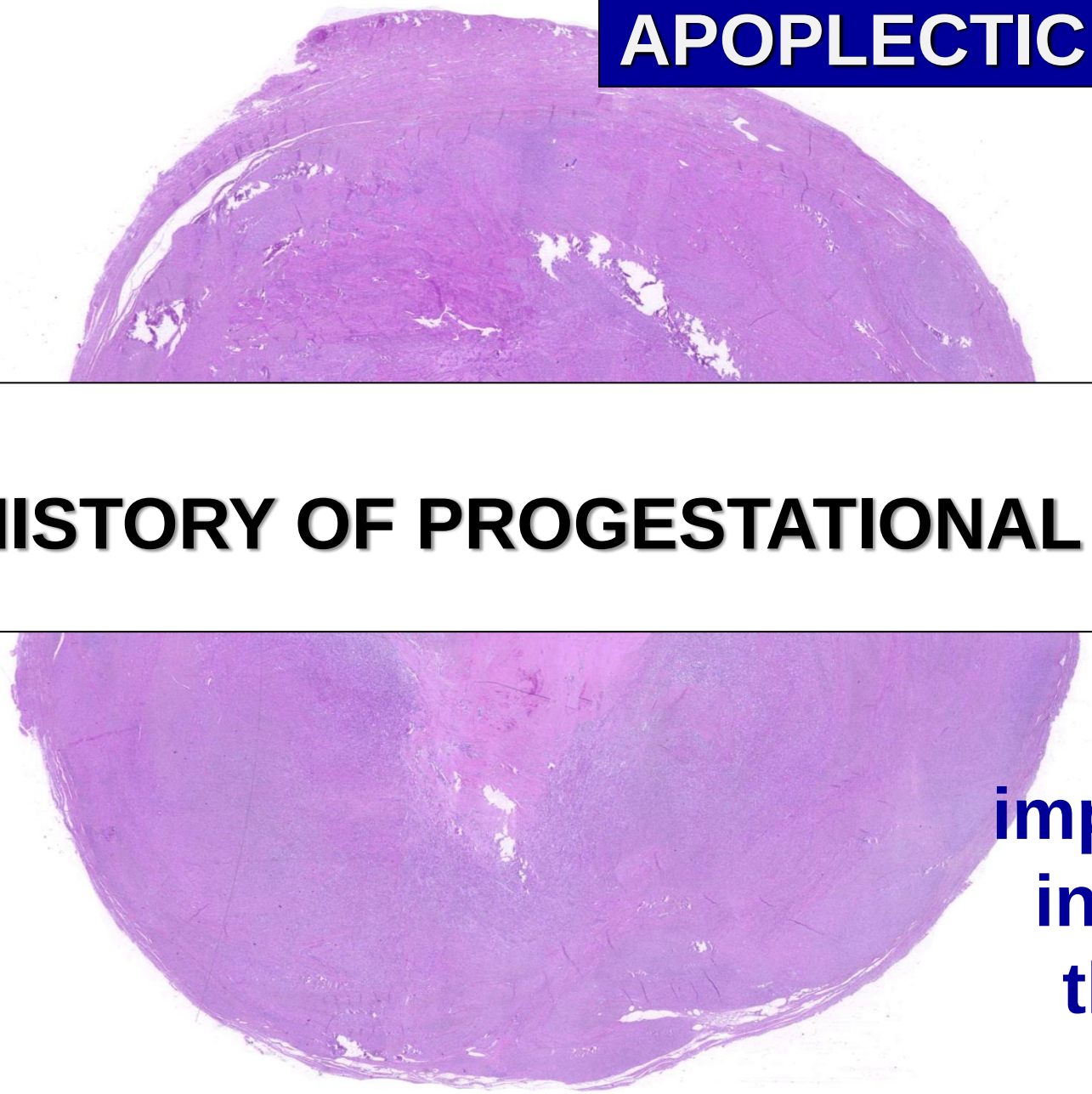




APOPLECTIC LEIOMYOMA: CLUES



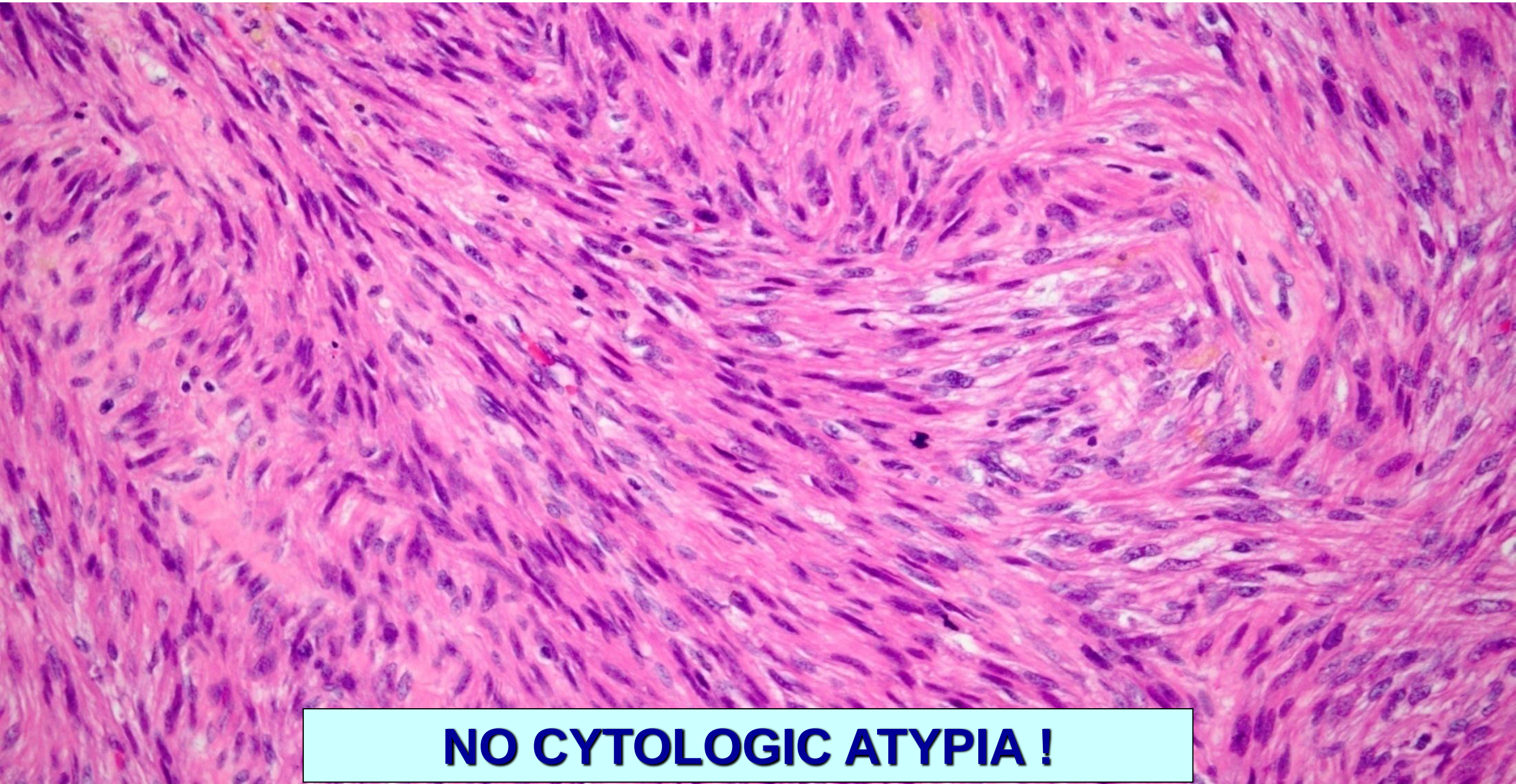
APOPLECTIC LEIOMYOMA



HISTORY OF PROGESTATIONAL THERAPY

“Zonation” important feature in recognizing the tumor as BENIGN

MITOTICALLY ACTIVE LEIOMYOMA

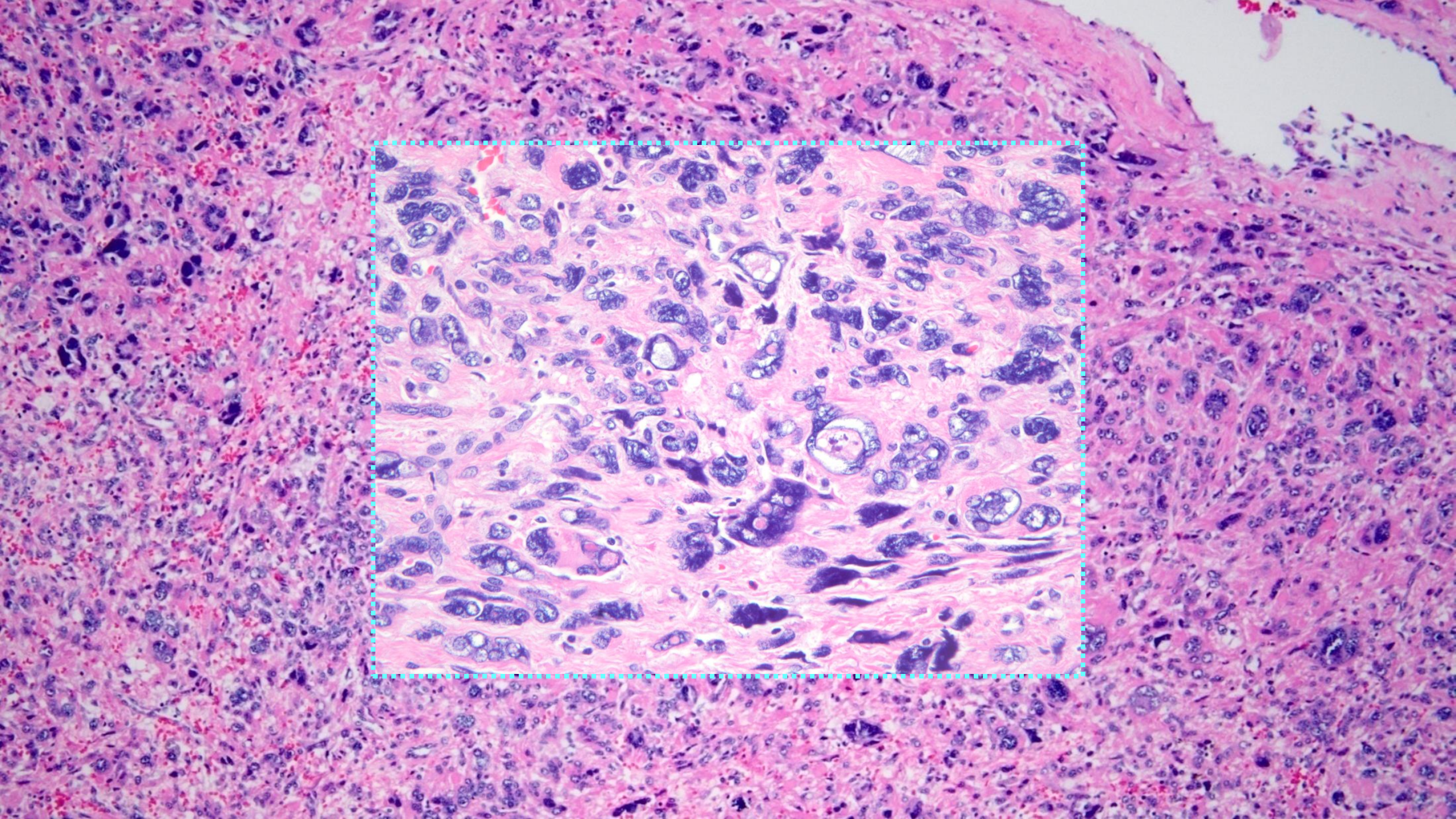


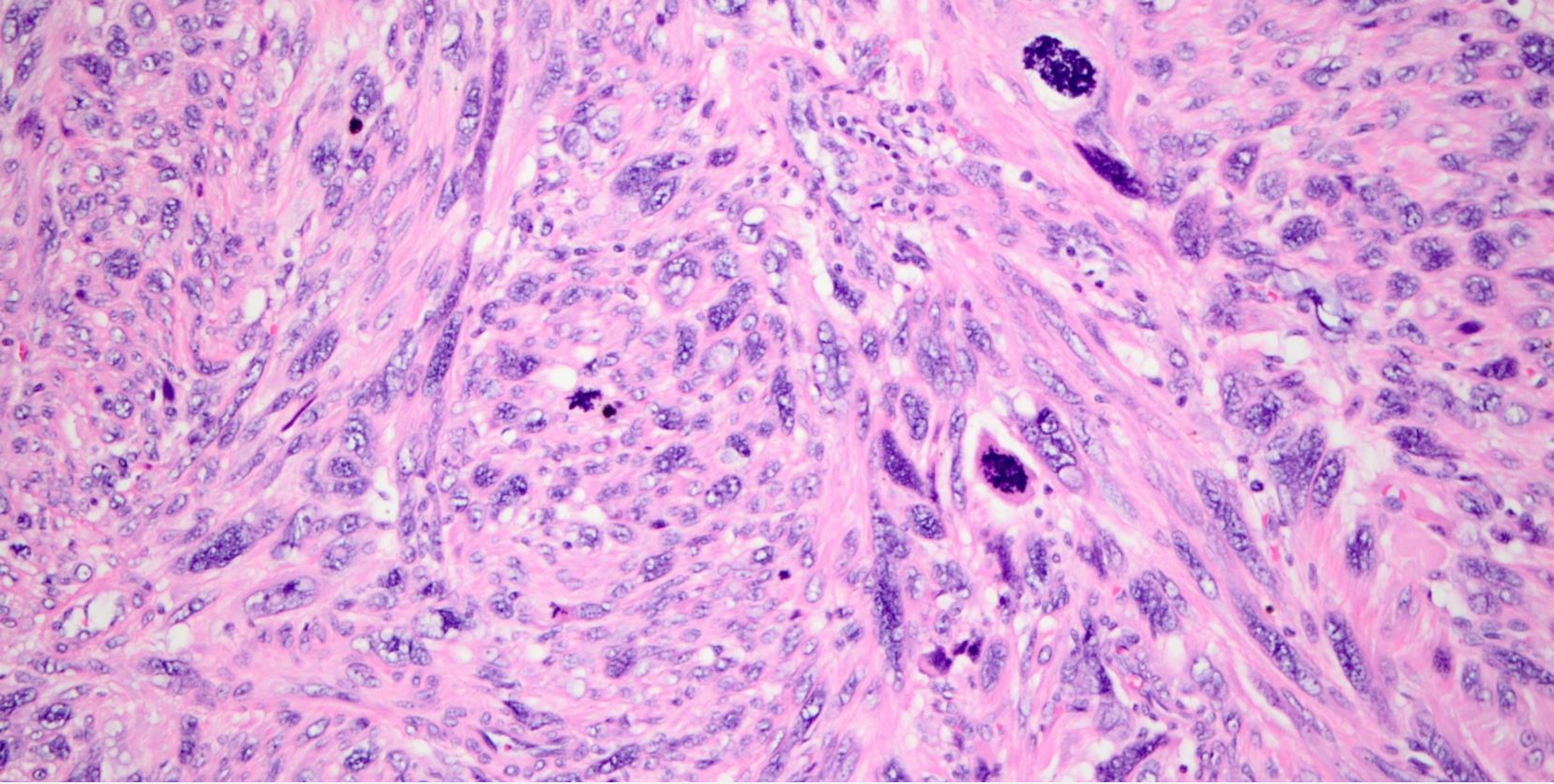
NO CYTOLOGIC ATYPIA !

Leiomyomas with Bizarre Nuclei (synonym: symplastic)

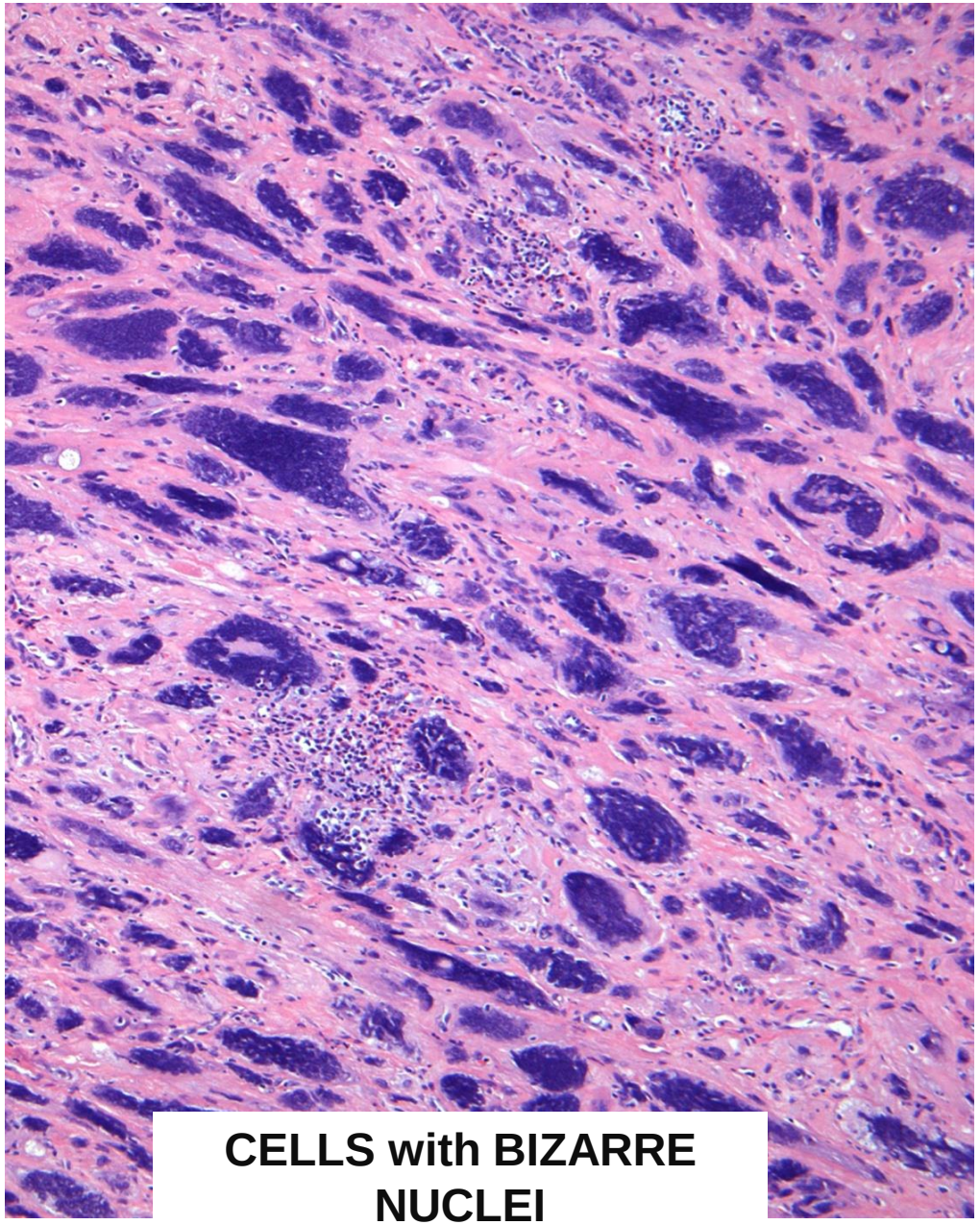
CONCERNING FEATURES :

- Bizarre mono or multinucleated cells with nuclear pseudoinclusions
- Diffuse distribution or high density of cells
- Karyorrhectic nuclei and coarse chromatin
- Prominent nucleoli
- Mitotic counts focally up to 7/10HPFs (average 1-2)

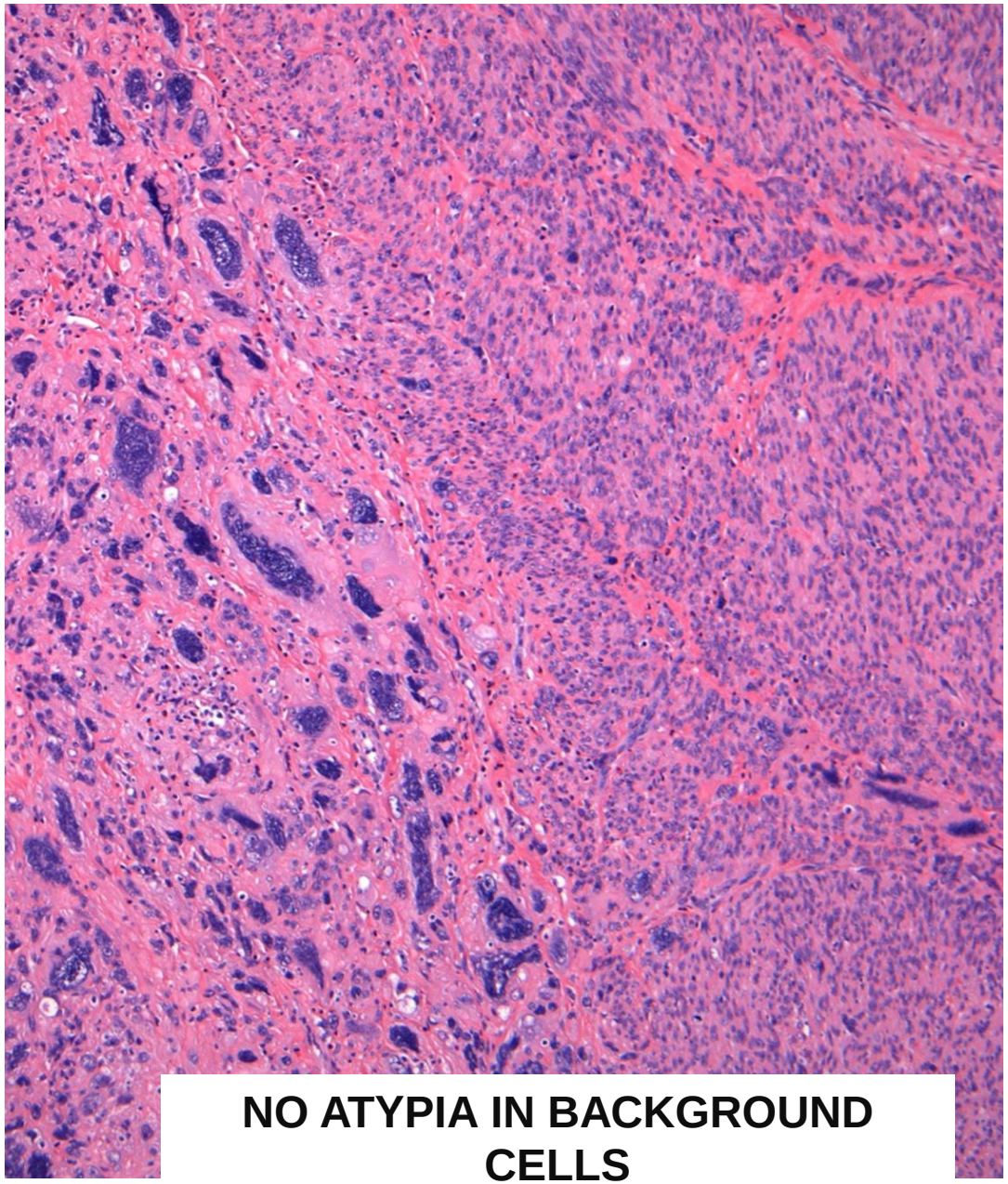




Karyorrhectic nuclei often counted as atypical mitoses



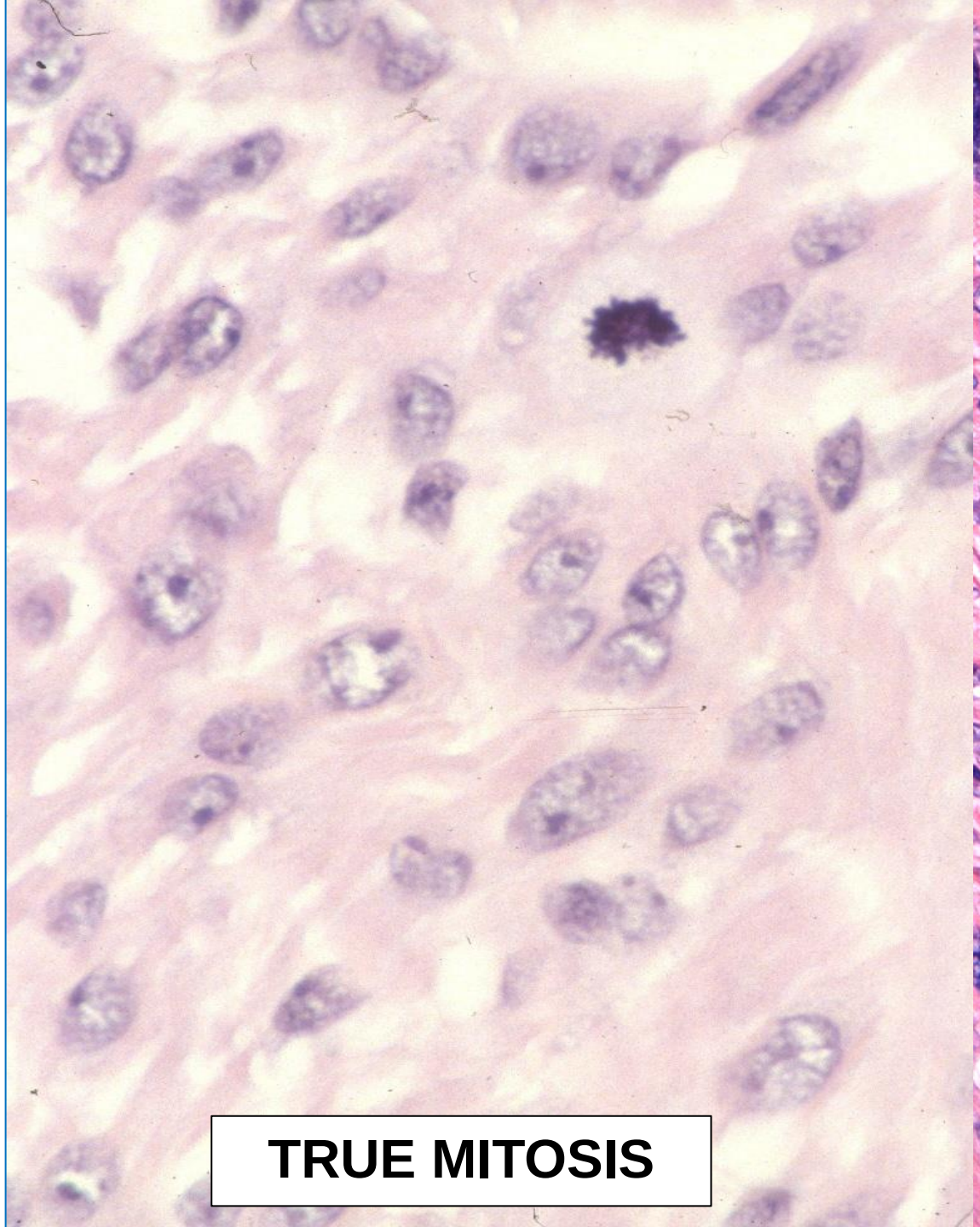
CELLS with BIZARRE NUCLEI

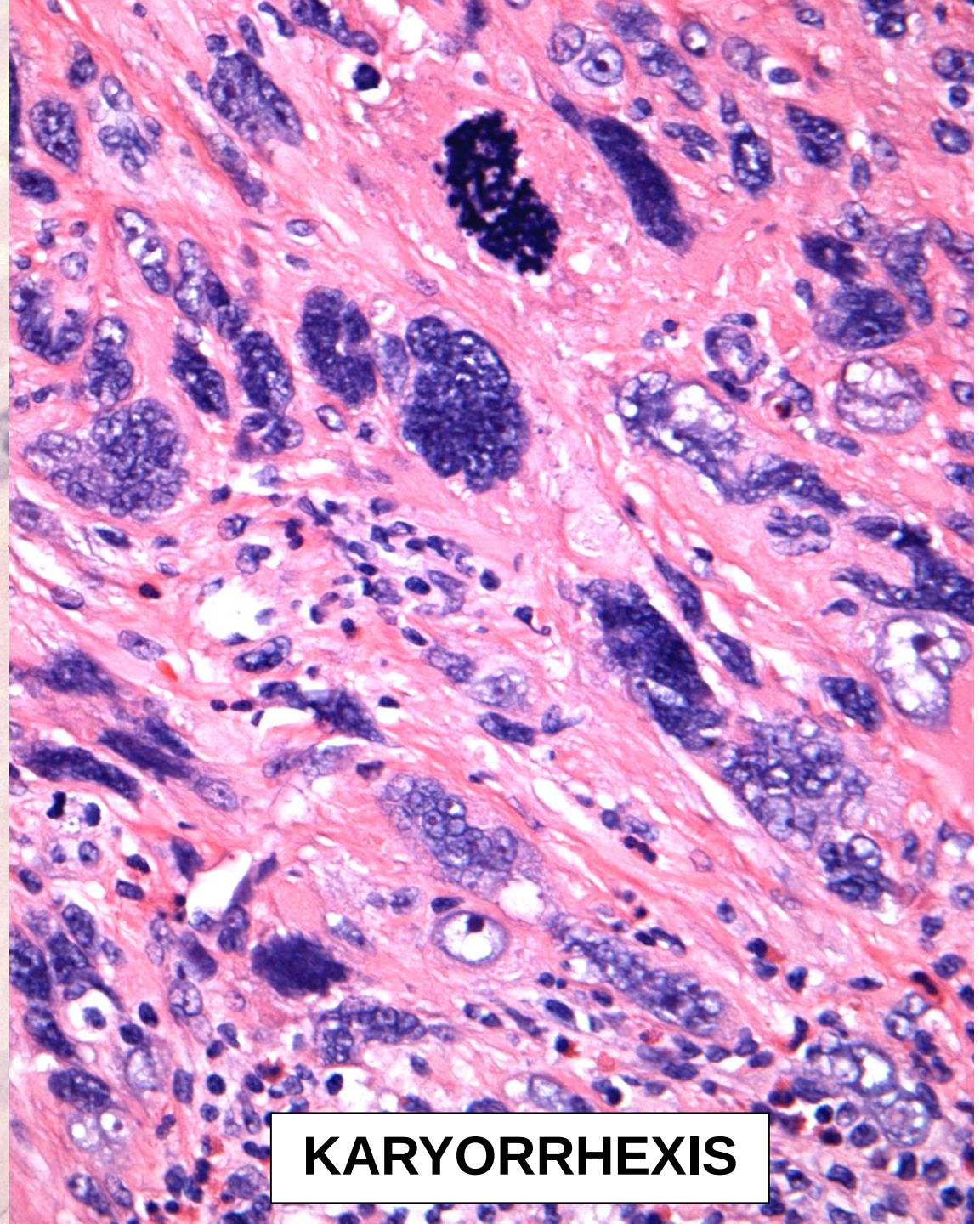


NO ATYPIA IN BACKGROUND CELLS

Leiomyoma with Bizarre Nuclei *vs* Leiomyosarcoma

	LMBN	LMS
Mitotic count	<10	>10
Tumor cell necrosis	-	+
DNA ploidy	Diploid	Aneuploid
MIB-1	Low	High
ER/PR	+	+ (~50%)
p53	-/+	+
p16	+/-	+
MED12 mutations	Uncommon	Rare


TRUE MITOSIS


KARYORRHEXIS

Leiomyoma with Bizarre Nuclei *vs* Leiomyosarcoma

- **Ki-67 is very often performed but is infrequently helpful as results show extensive overlap between leiomyoma with bizarre nuclei and leiomyosarcoma**

- **Ki-67 typically overestimates mitotic index**

Mills AM, et al, Am J Surg Pathol 2013

Histopathology

Histopathology 2018, 73, 284–298. DOI: 10.1111/his.13515

Predictors of adverse outcome in uterine smooth muscle tumours of uncertain malignant potential (STUMP): a clinicopathological analysis of 22 cases with a proposal for the inclusion of additional histological parameters

Mamta Gupta,[1,2] Anna L Laury,[3] Marisa R Nucci[2,4] & Bradley J Quade[2,4]

[1]*Department of Pathology, Beth Israel Deaconess Medical Center,* [2]*Harvard Medical School, Boston, MA,* [3]*Department of Pathology, Cedars-Sinai, Los Angeles, CA, and* [4]*Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA*

If adverse outcome, features included:

- moderate–severe nuclear atypia (7)
- Infiltrative or irregular margins (5)
- vascular intrusion (3)
- atypical mitoses (2)
- epithelioid features (1)

Necrosis not particularly associated with adverse outcomes

Evaluation of criteria to distinguish uterine smooth muscle tumors of uncertain malignant potential (STUMP) from mimics and improved prediction of patient outcome: A multi-institutional study of 51 cases

Philip P. Ip[1], Zehra Ordulu[2], Diana Lim[3], Robert A. Soslow[4], Robert H. Young[2], Liwei Jia[4], Sarah Chiang[4], Esther Oliva[2]

DepDepartments of Pathology: University of Hong Kong, Hong Kong. Department of Pathology, National University Hospital, Singapore, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York. Massachusetts General Hospital, Harvard Medical School, Boston. USCAP 2019

- Diagnostic criteria vary among pathologists. After consensus review by a panel of experienced gynecologic pathologists, original diagnosis changed in 49% cases to leiomyoma variants, high-grade leiomyosarcoma, others
- Combination of histologic features such as nuclear atypia, mitoses, tumor cell necrosis, infiltrative margins, vascular space intrusion/invasion, and focal myxoid or epithelioid differentiation present in tumors with +/- recurrences
- Prominent long sweeping fascicles significantly present in tumors followed by recurrence

STUMP-WHO (5th EDITION)
Guidelines for spindle cell tumors

1- Focal/multifocal/diffuse atypia with 7-9 mitoses/10HPFs without TCN

- 12-17% of these tumors have recurred but also some even with < mitoses

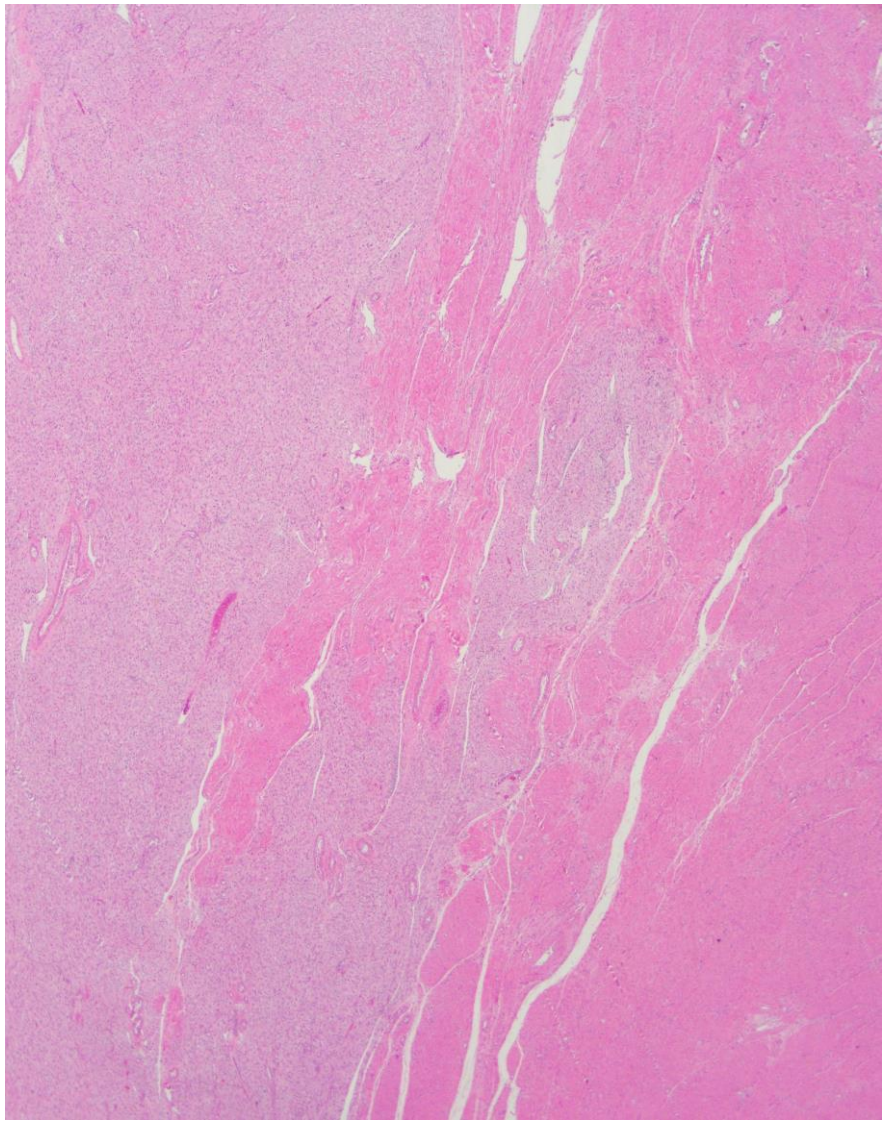
2- If TCN but no other worrisome features (~28%)

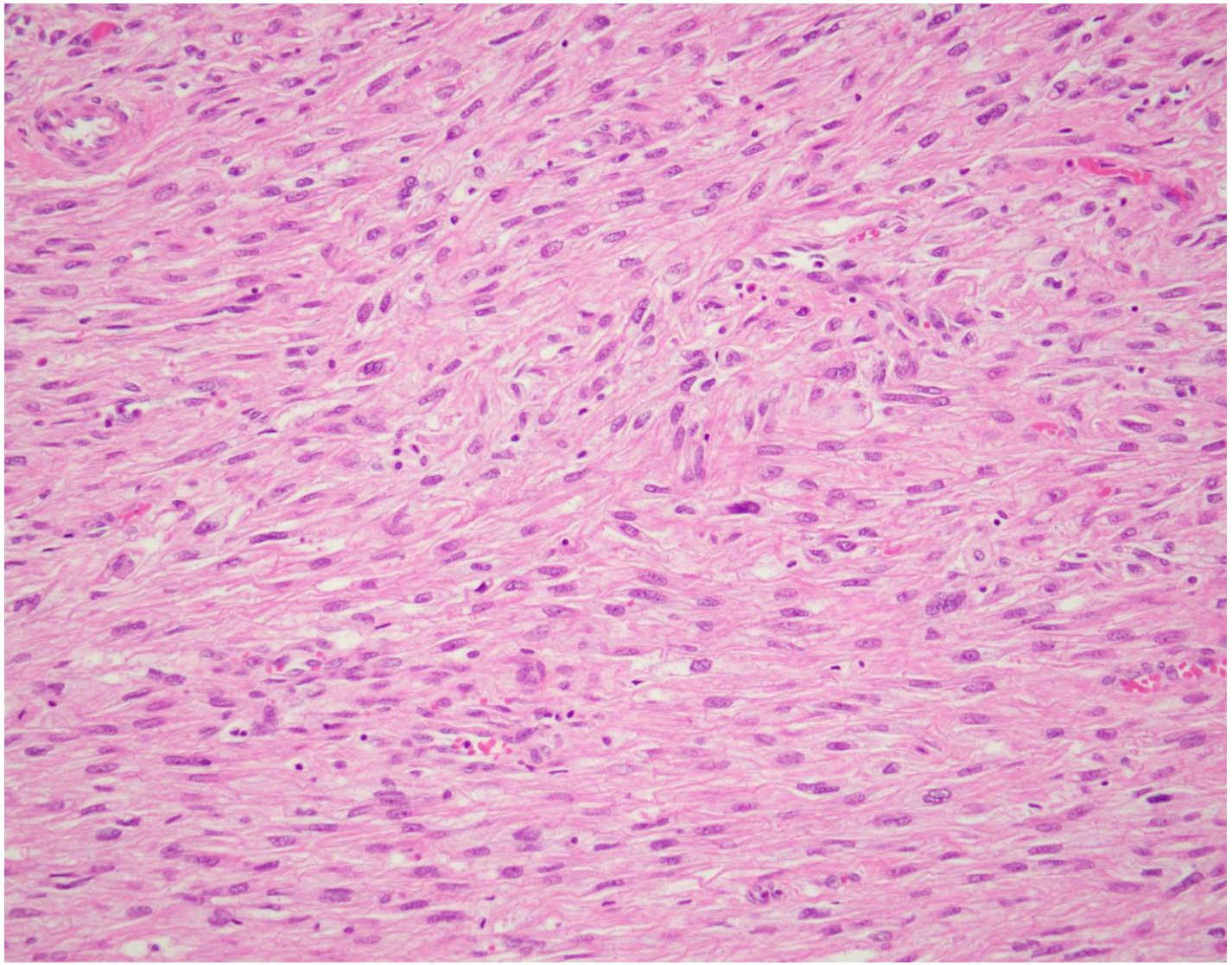
- These tumors have also recurred

3- Tumors with >15 mitoses/10HPFs without cytologic atypia or TCN

- None has recurred

4- If diffuse atypia and uncertain mitotic count (often due to karyorrhexis)

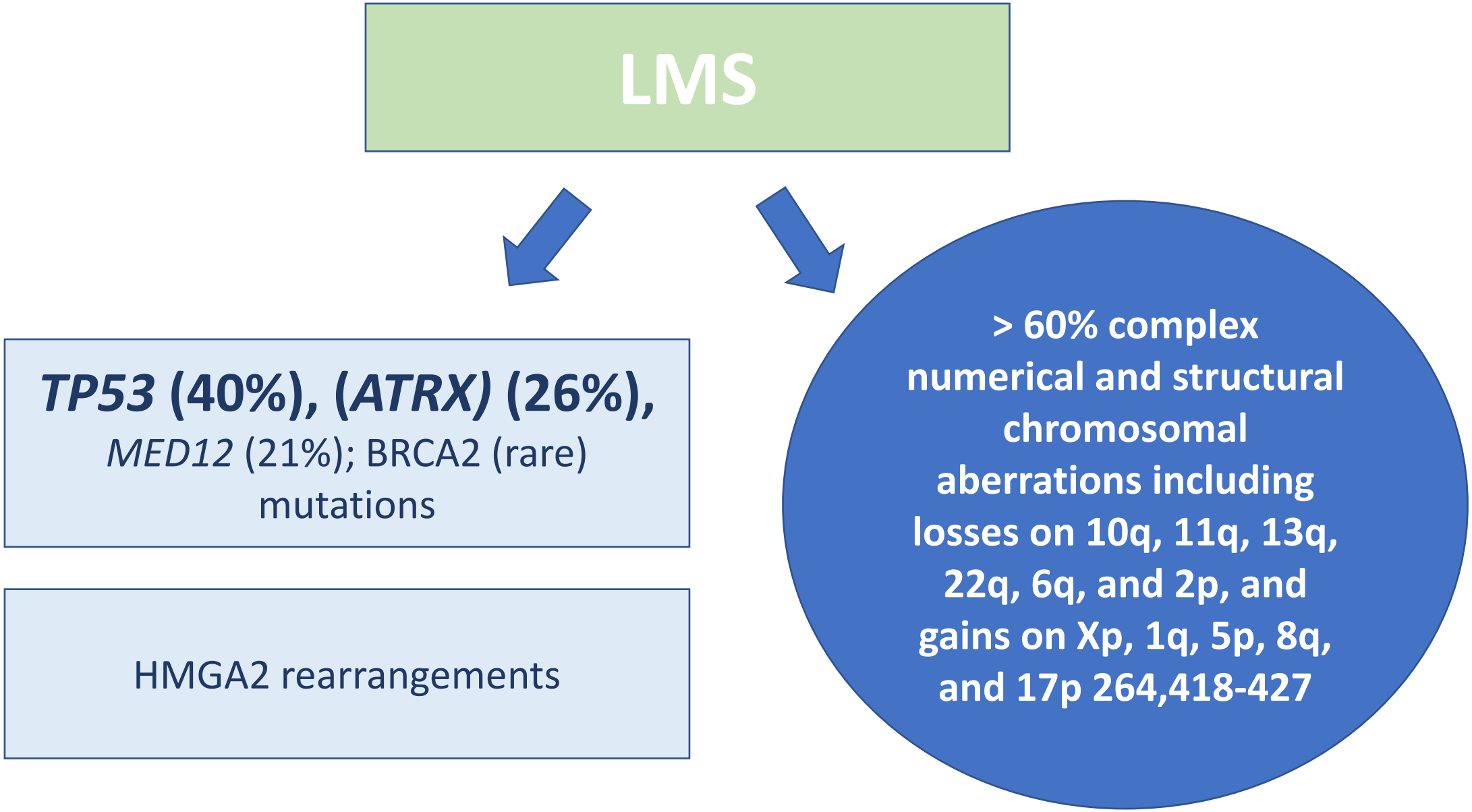




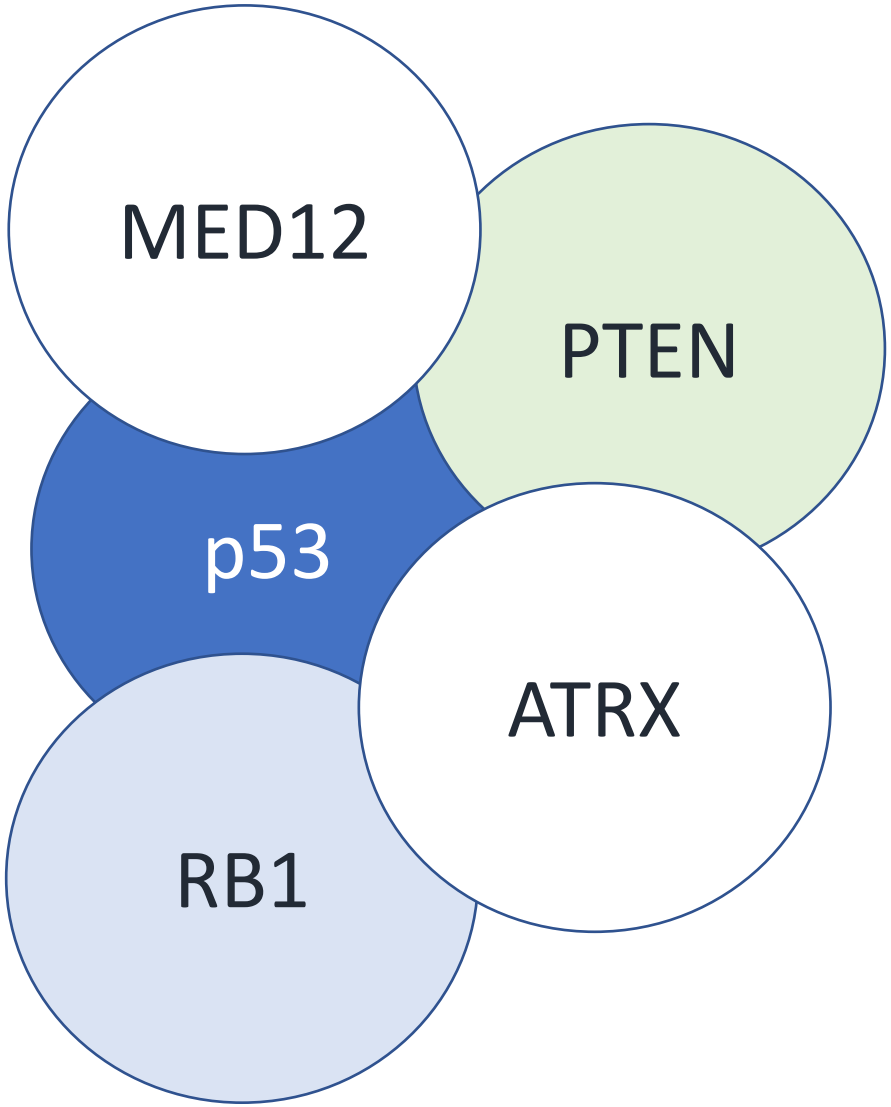
Diagnosed as STUMP with posterior omental metastases

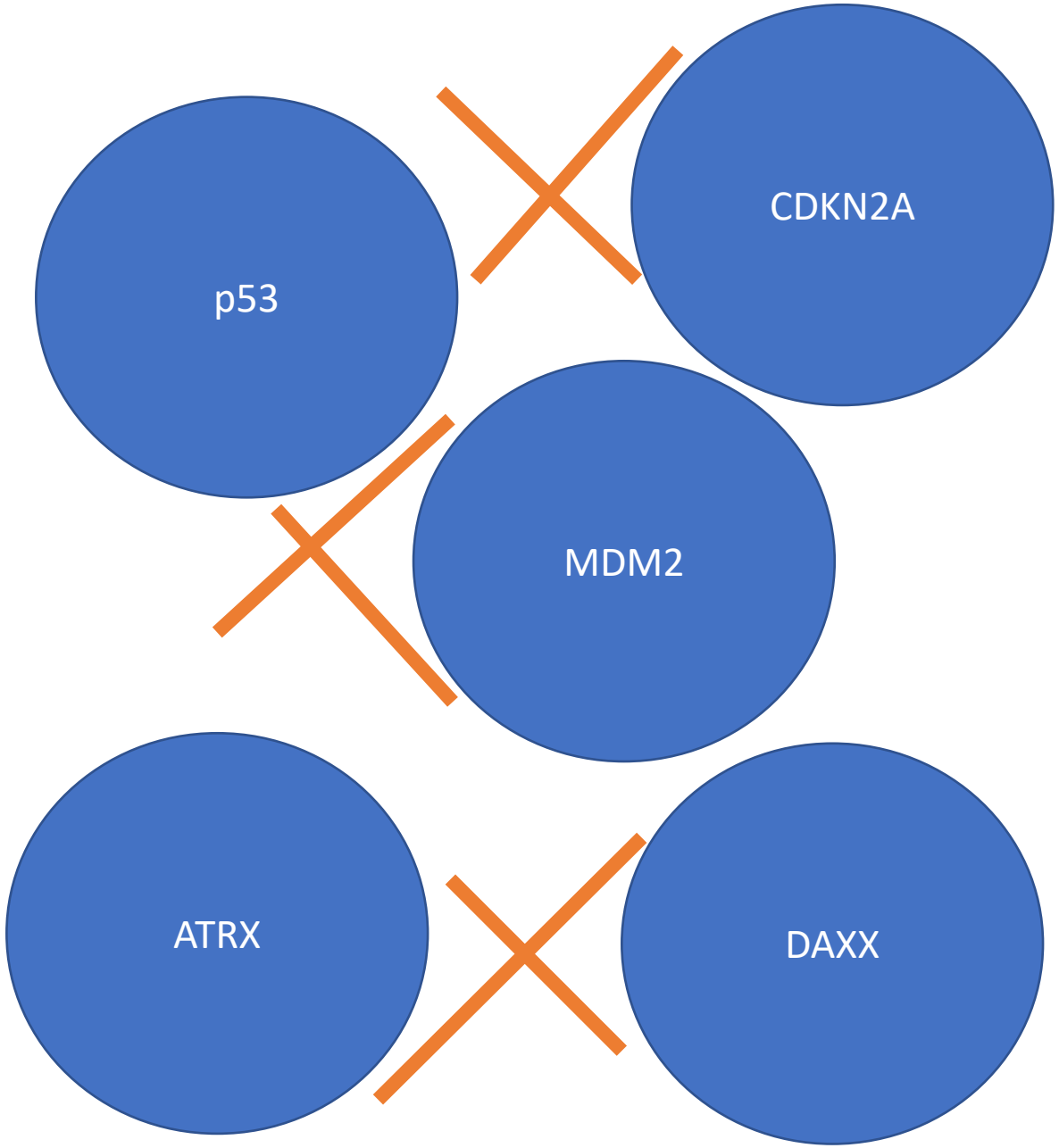
Smooth Muscle Tumor of Uncertain Malignant Potential "STUMP"

DO NOT USE FOR LEIOMYOMA VARIANTS!

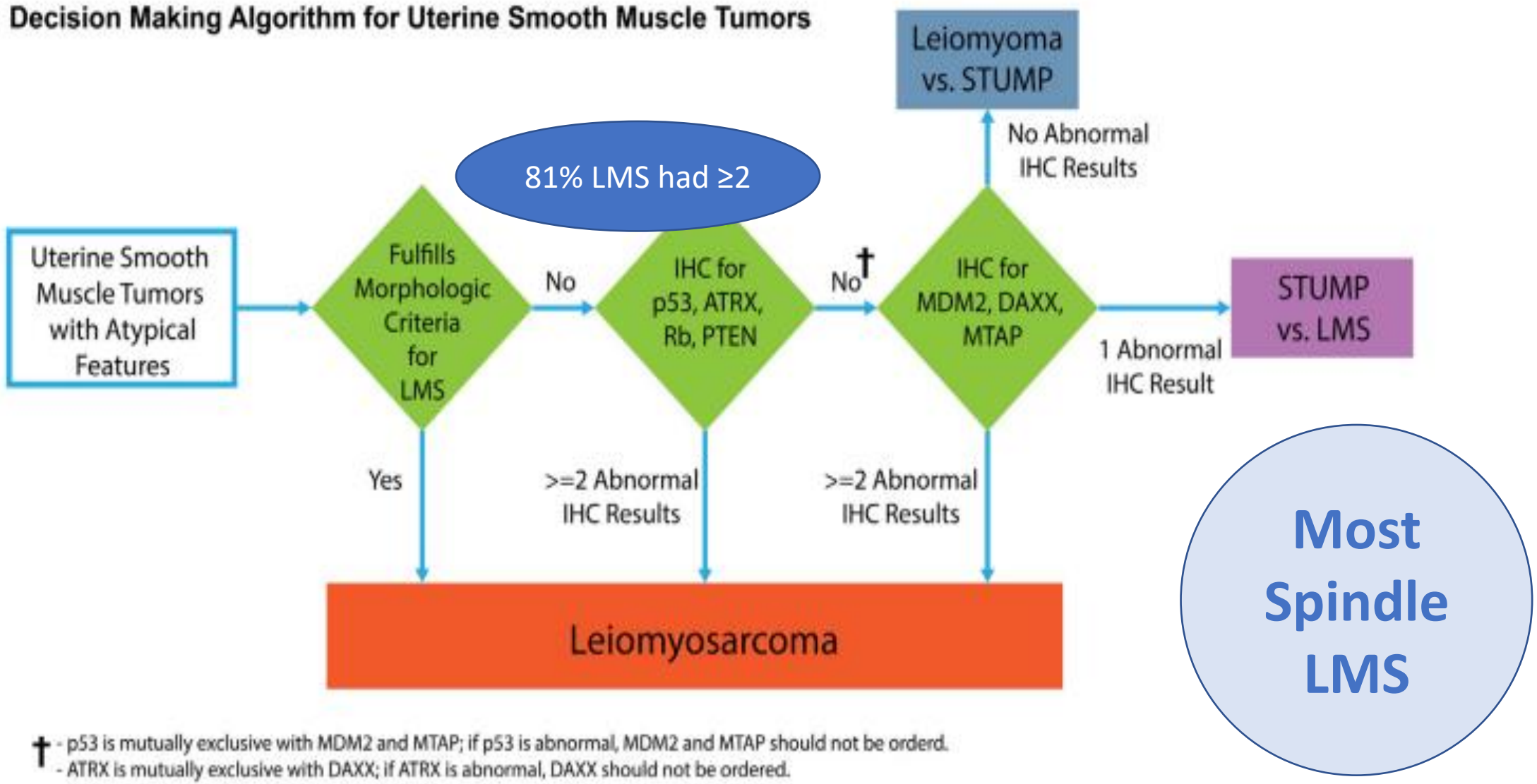

LMS
***TP53* (40%), (*ATRX)* (26%),**
MED12 (21%); BRCA2 (rare) mutations
HMGA2 rearrangements
> 60% complex numerical and structural chromosomal aberrations including losses on 10q, 11q, 13q, 22q, 6q, and 2p, and gains on Xp, 1q, 5p, 8q, and 17p 264,418-427

FREQUENTLY COEXIST





Momeni-Boroujeni A, et al. Mod Pathol. 2023 Jan 10;36(4)



Most Spindle LMS

94% (157/167) showed at least one genomic abnormality involving TP53, RB1, ATRX, PTEN,CDKN2A or MDM2 with 80% showing alterations in two genes

Uterine Leiomyoma

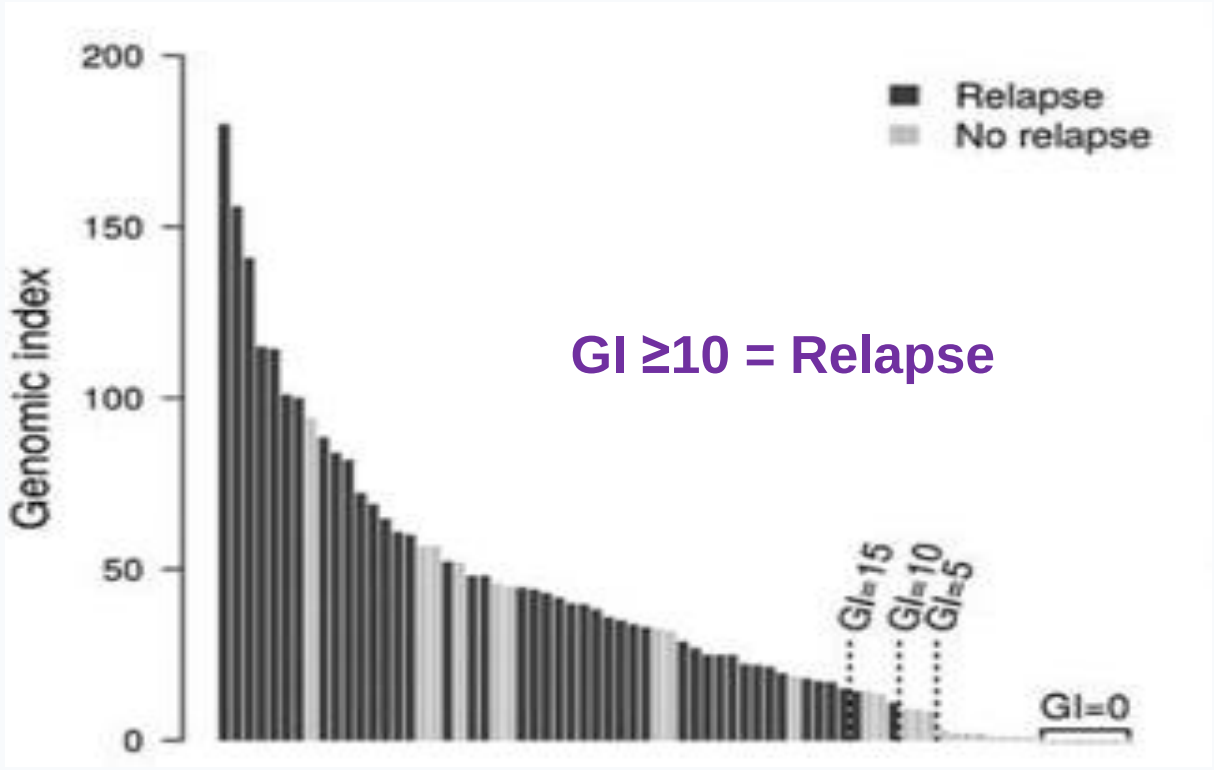
CNV: Stable genome

Uterine Leiomyosarcoma

CNV: Genome instability

(Genomic Scar/HRD)

Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP)



GI ≥10 = Relapse

- There is a gradient of **genomic complexity** that correlates with **outcome**
- STUMPs with **genomic index ≥ 10** are reclassified as **"molecular leiomyosarcoma"**

Croce S. Mod Pathol. 2018

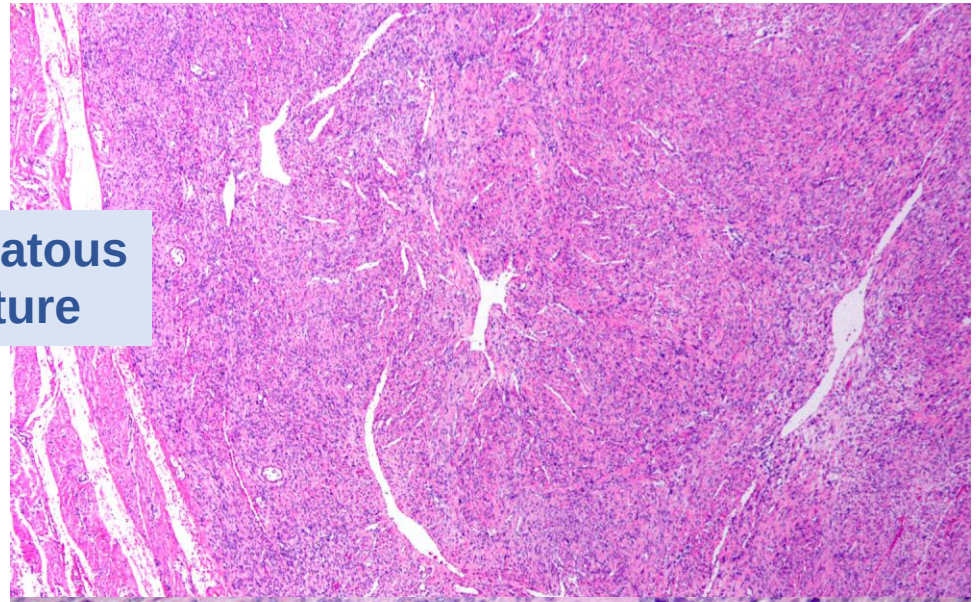
HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CARCINOMA SYNDROME

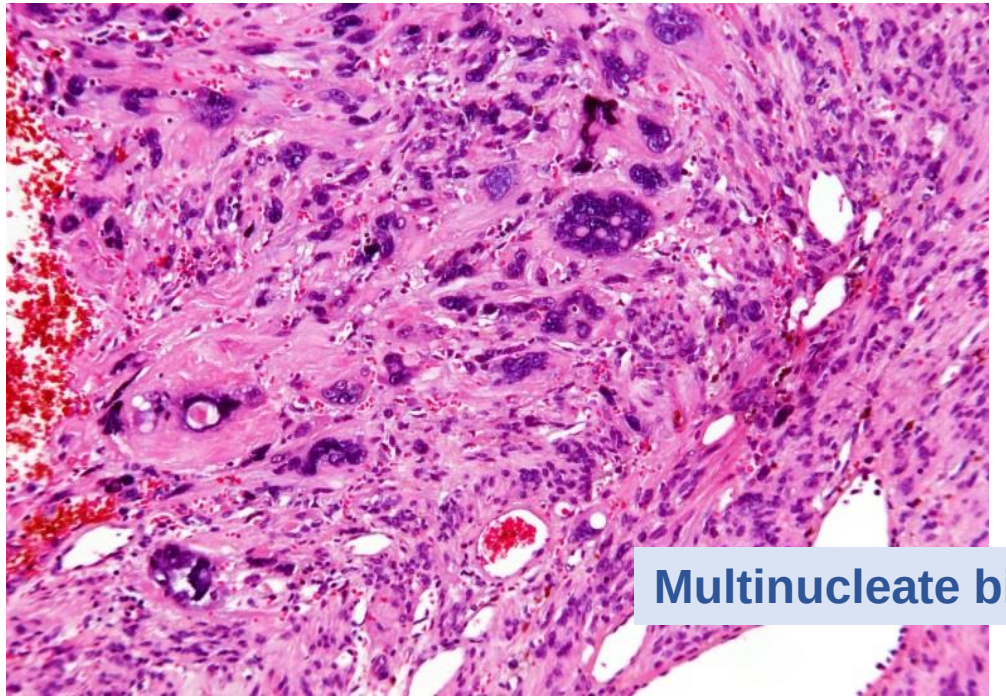
- Autosomic dominant
- Multiple pilar leiomyomas of skin
- Uterine leiomyomas (early onset)
- Papillary renal cell carcinoma, high-grade

- Most patients develop leiomyomas
- Only 15-20% develop renal cell carcinoma

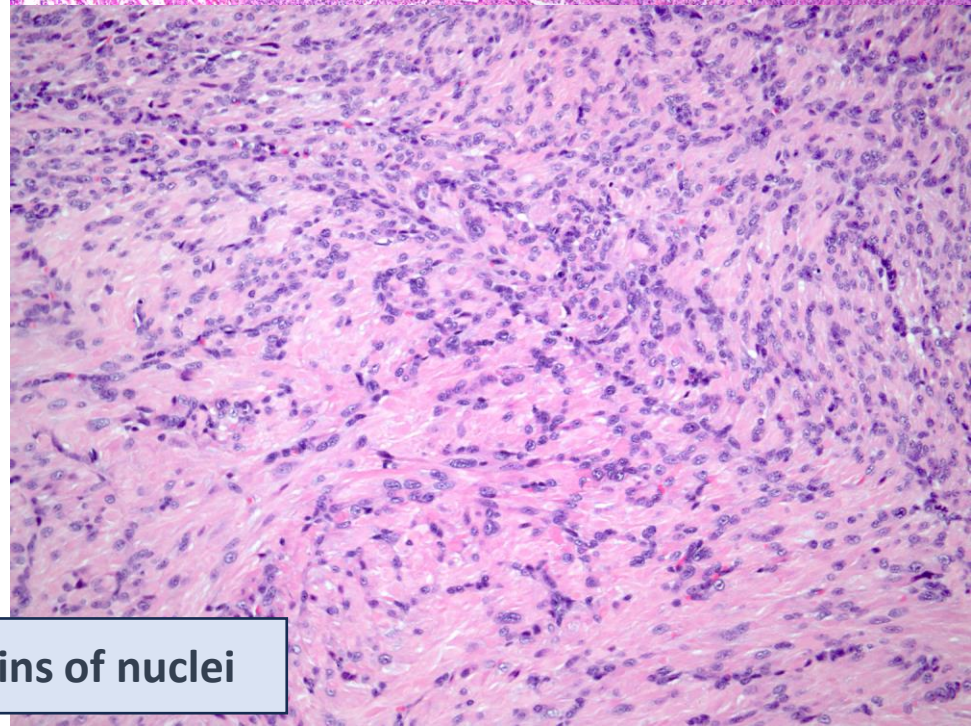
LEIOMYOMATOSIS-RENAL CELL CARCINOMA SYNDROME

Pericytomatous vasculature

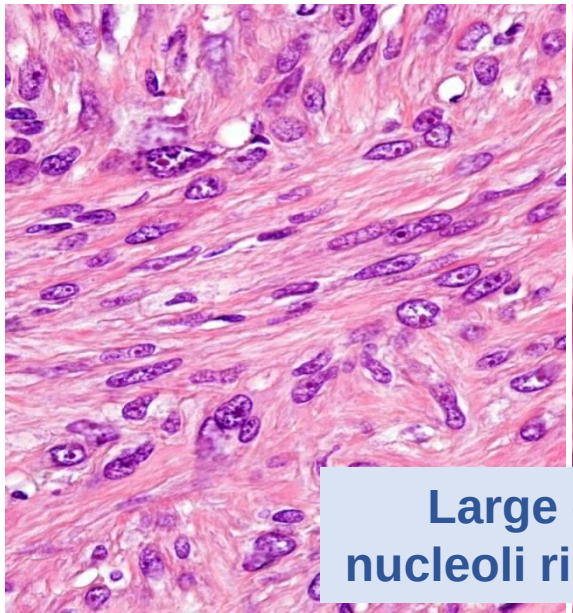


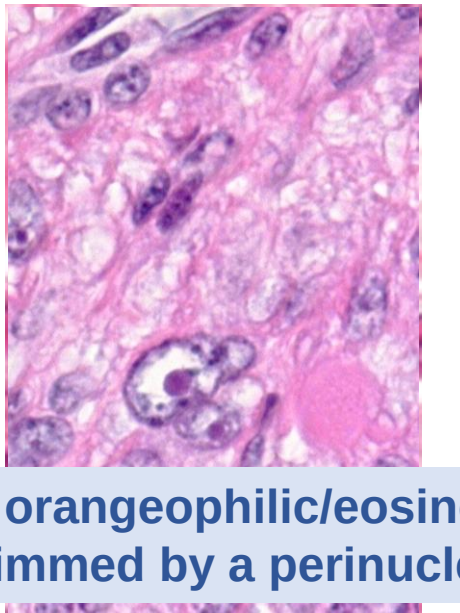


Multinucleate bizarre cells



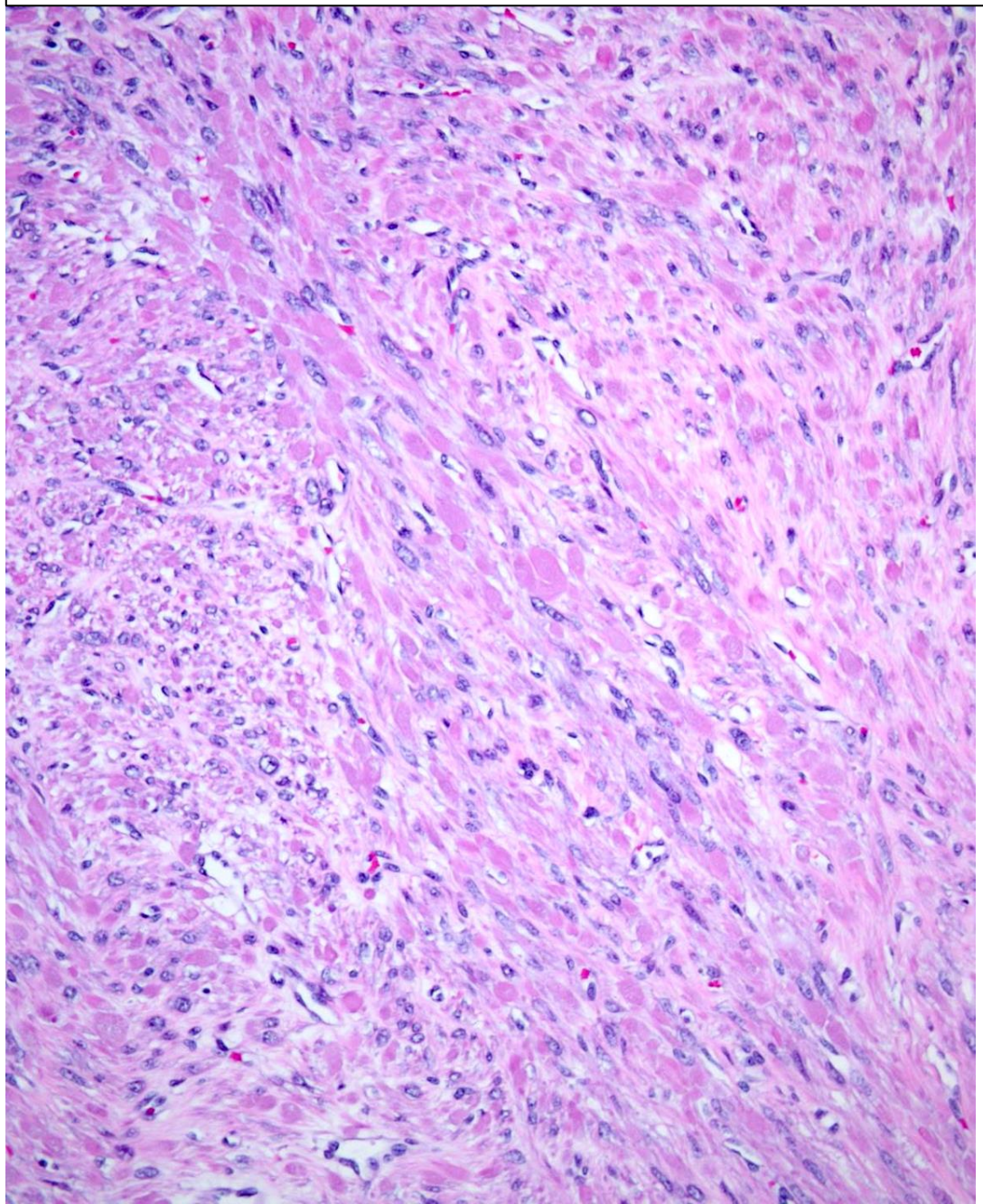
Small chains of nuclei

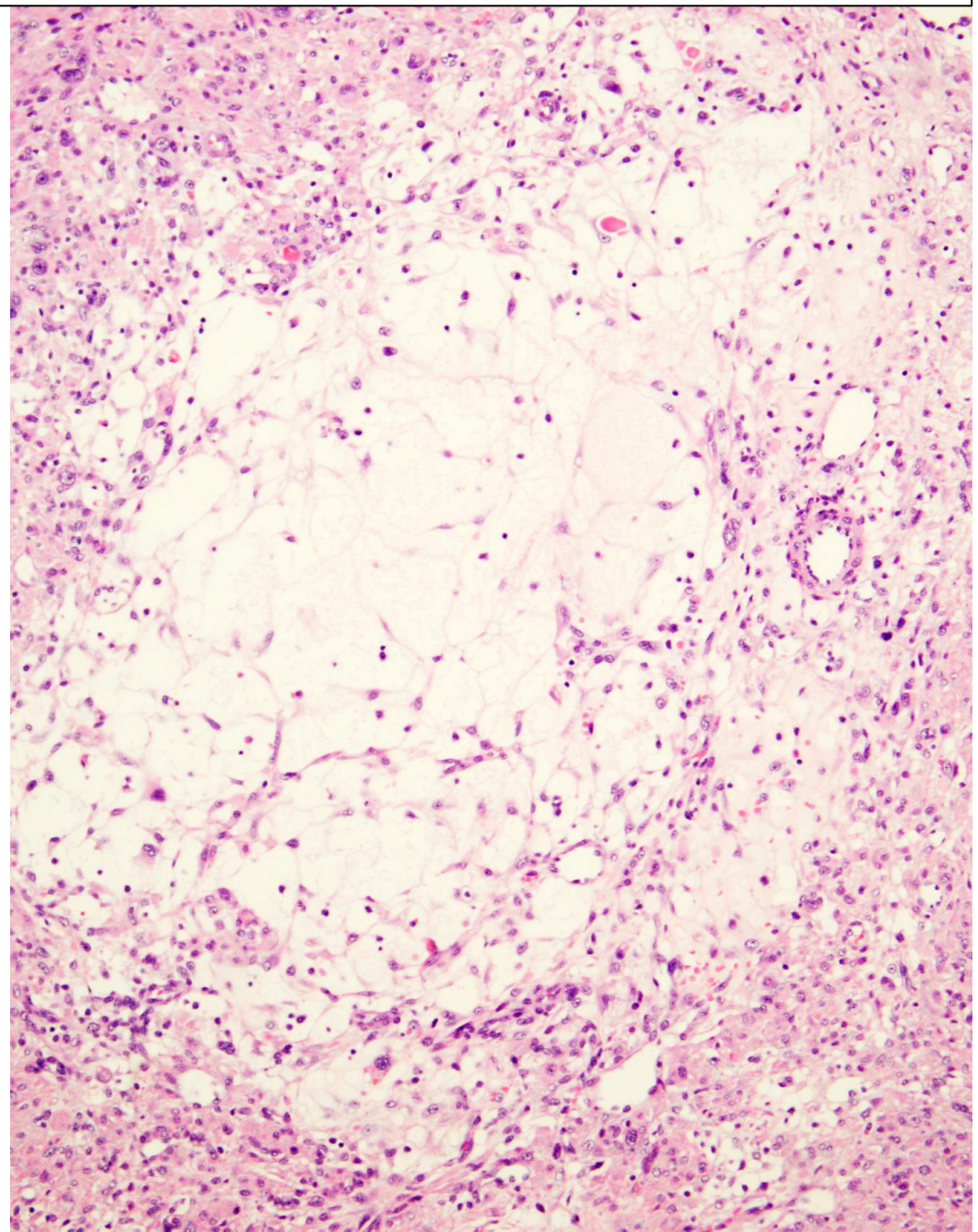




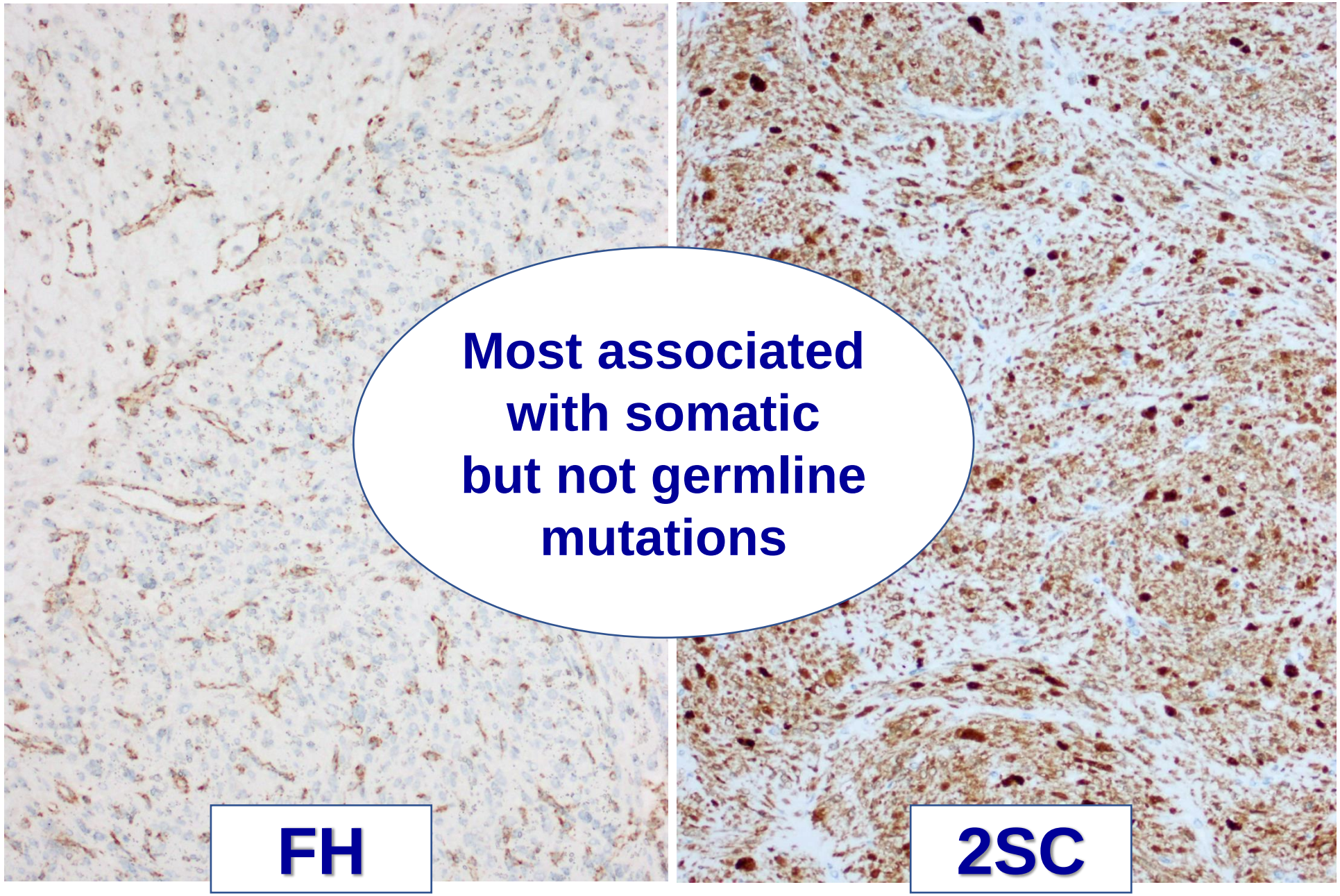
Large orangeophilic/eosinophilic nucleoli rimmed by a perinucleolar halo

Rhabdoid morphology and Alveolar-type edema





LEIOMYOMA WITH BIZARRE NUCLEI



Prospective Detection of Germline Mutation of *Fumarate Hydratase* in Women With Uterine Smooth Muscle Tumors Using Pathology-based Screening to Trigger Genetic Counseling for Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome

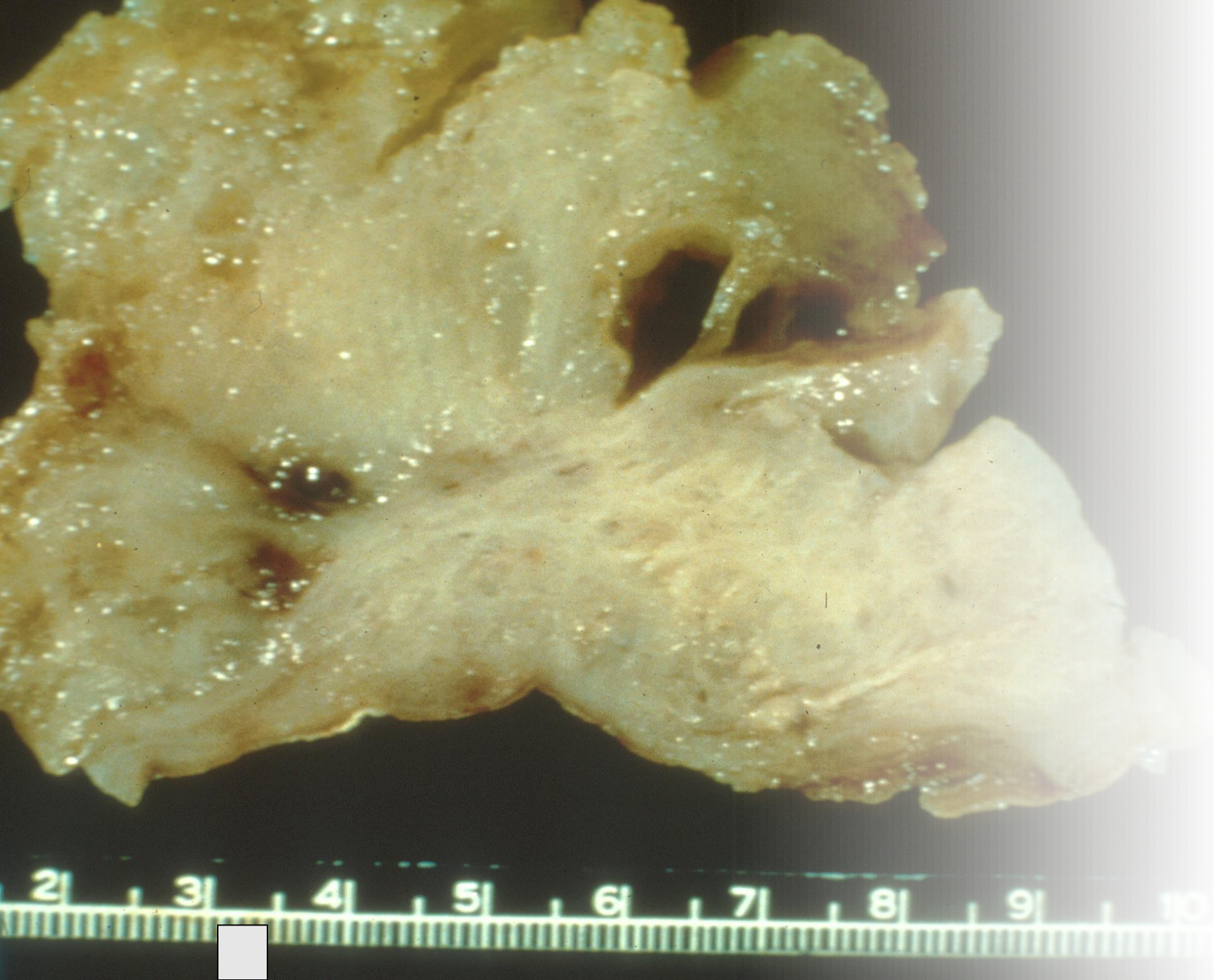
A 5-Year Single Institutional Experience

- U-SMT from 2060 women evaluated for FH-d morphology (staghorn vessels, macronucleoli surrounded by clear halo, eosinophilic globules) in a 5 year period and noted in 30 (1.4%)
- 10/30 elected FH genetic testing and 6/10 had a germline mutation
- Abnormal FH expression was not very reliable to trigger genetic counseling with no difference in incidence of pathogenic FH germline mutation between FH-d morphology U-SMT with abnormal *vs* normal FH expression
- Morphologic screening confirmed genetic diagnosis of HLRCC syndrome in 0.24% of all women (24-40 years) with any type of U-SMT (BN and conventional); thus, *morphology-based screening with genetic counseling referral can result in diagnosis of HLRCC syndrome in unselected women with U-SMT*

Rabban J, et al; Am J Surg Pathol 2019

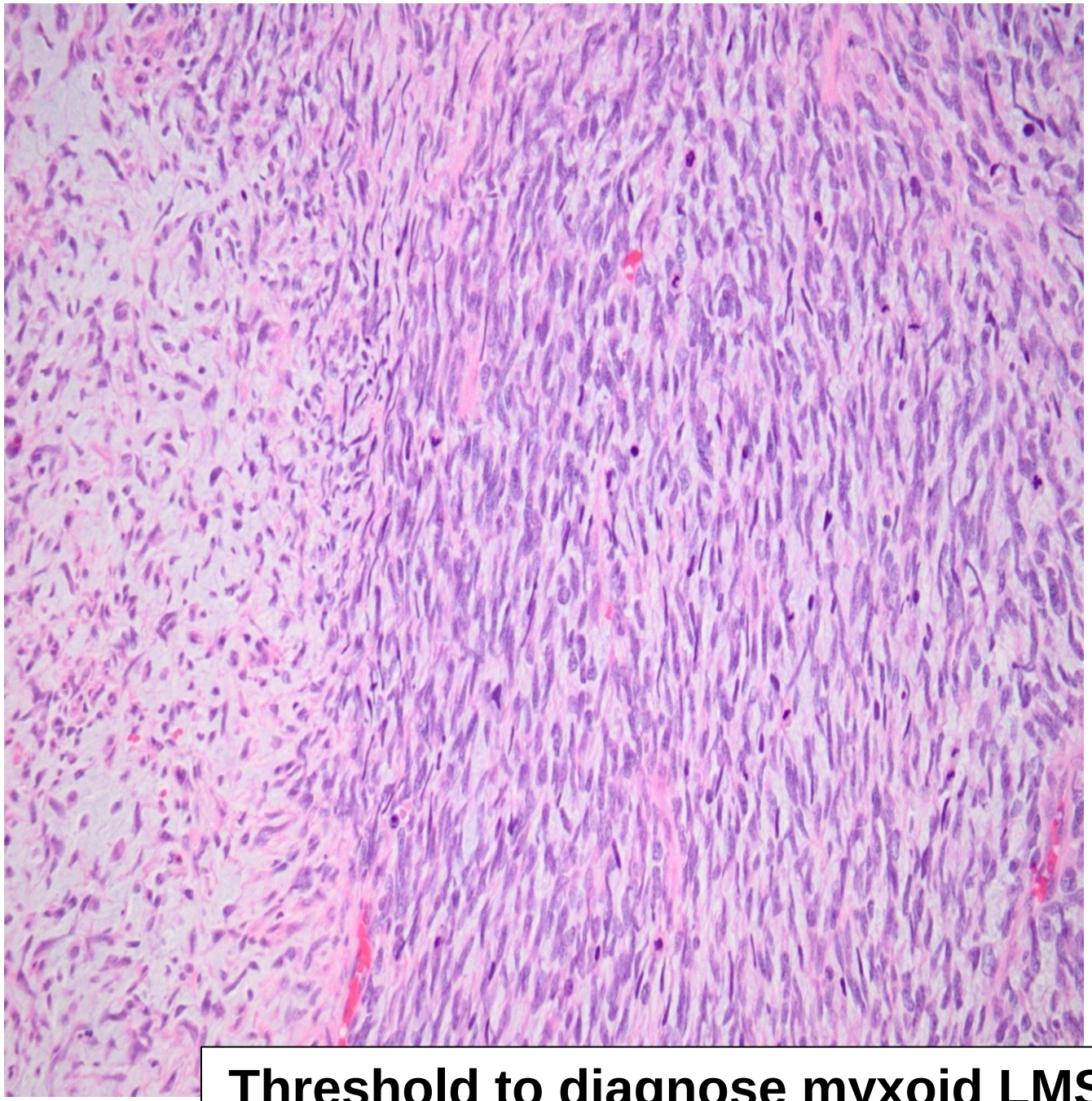
BLURB:

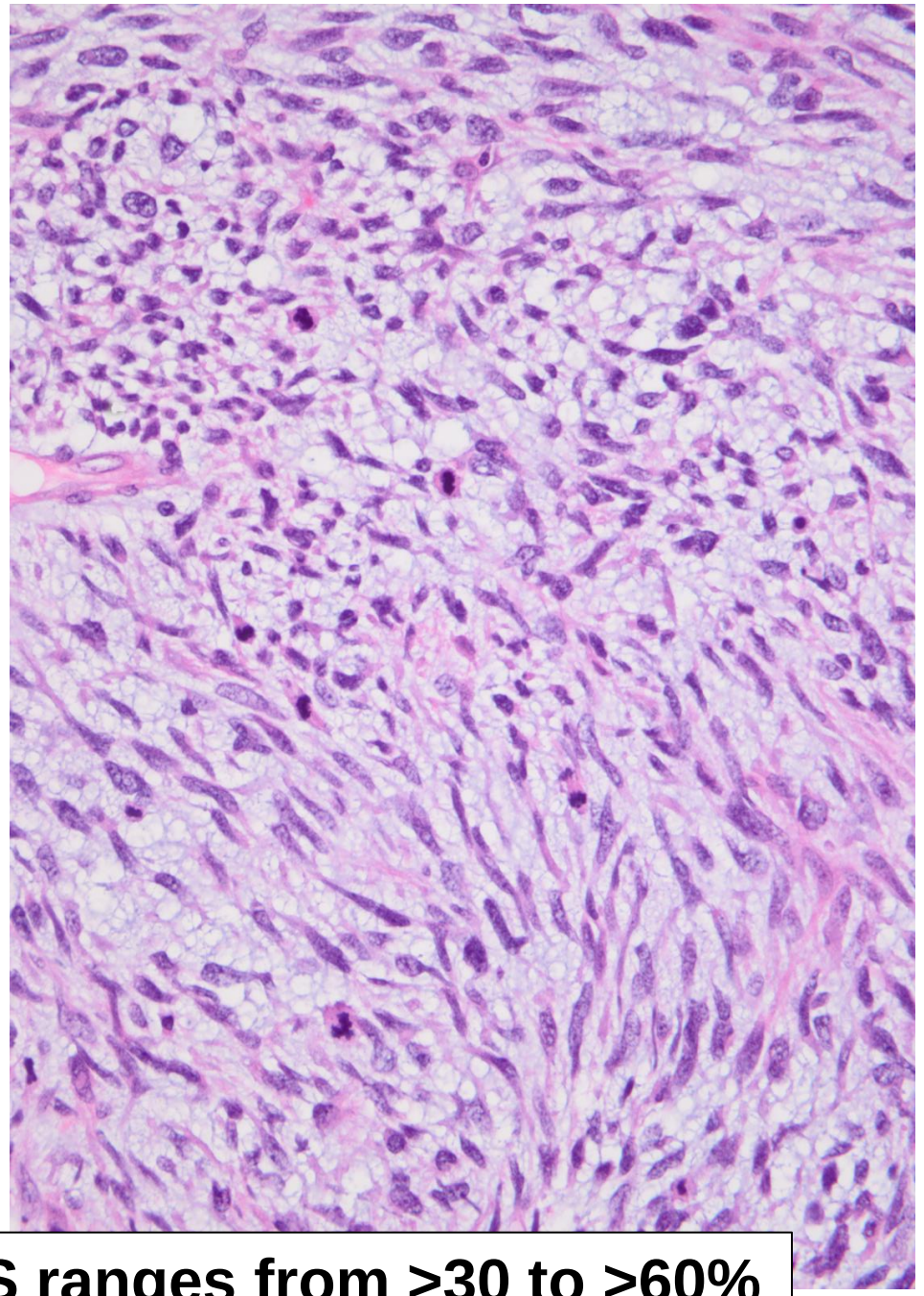
Although these features may be seen in leiomyomas that are part of Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Syndrome, in most cases tumors are sporadic. Genetic consultation and additional testing may be indicated if clinical suspicion is high.



MYXOID

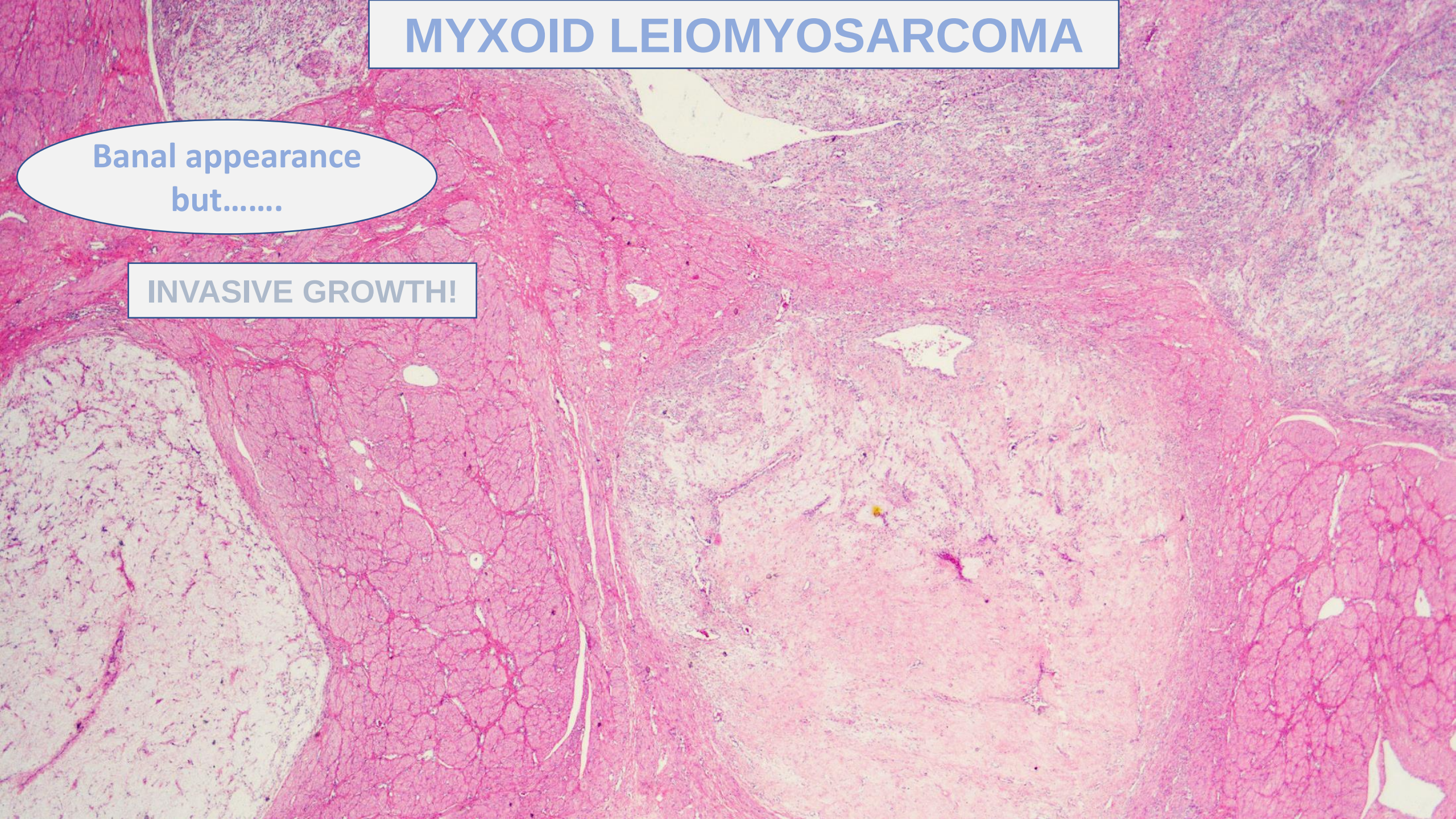
LEIOMYOSARCOMA





Threshold to diagnose myxoid LMS ranges from >30 to >60%

MYXOID LEIOMYOSARCOMA



Myxoid Smooth Muscle Tumors

Atkins K et al., Modern Pathol 132A, 2001

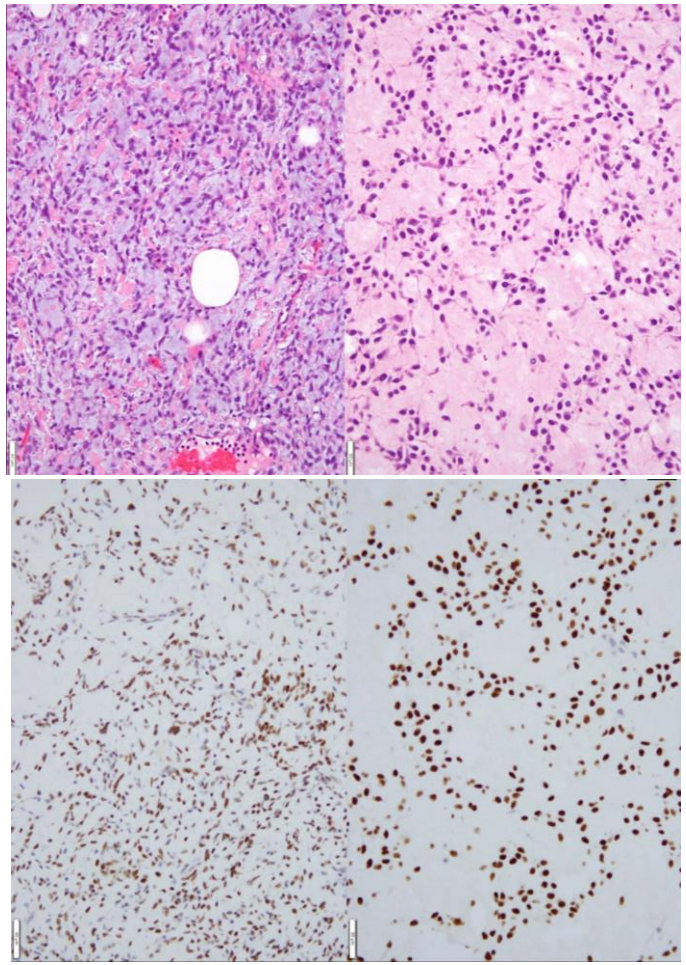
- **Presence of tumor cell necrosis or severe cytologic atypia warrant the diagnosis of malignancy**

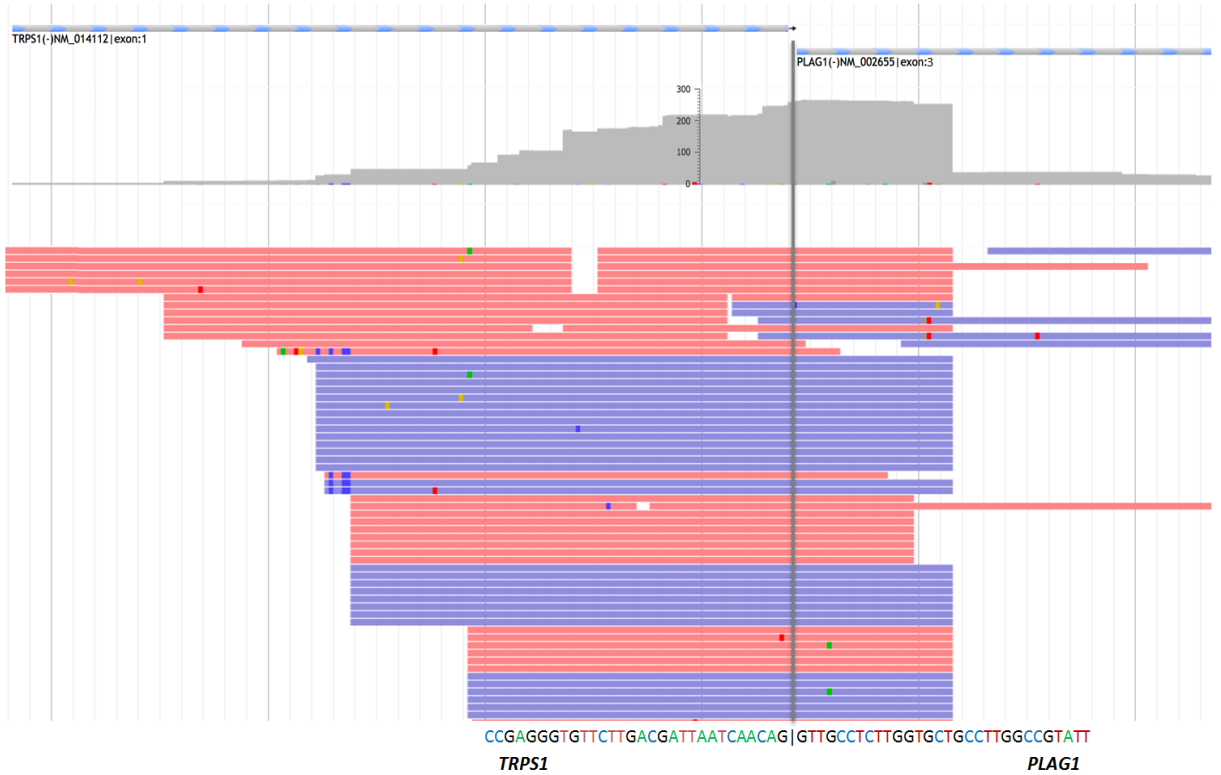
- **In the absence of tumor cell necrosis or severe cytologic atypia, a mitotic index of >2/10HPFs is indicative of malignant behavior**

Parra-Herran C et al, Am J Surg Pathol 2016;40:285
Goh R et al, Modern Pathol 2016, 29, suppl2, 285A

Tumors with < 2mitoses/10 HPFs may also be associated with an aggressive behavior

Novel PLAG1 Gene Rearrangement Distinguishes a Subset of Uterine Myxoid Leiomyosarcomas From Other Uterine Myxoid Mesenchymal Tumors





TRPS1-PLAG1 fusion>RAD51B-PLAG1 fusion (NGS/FISH)

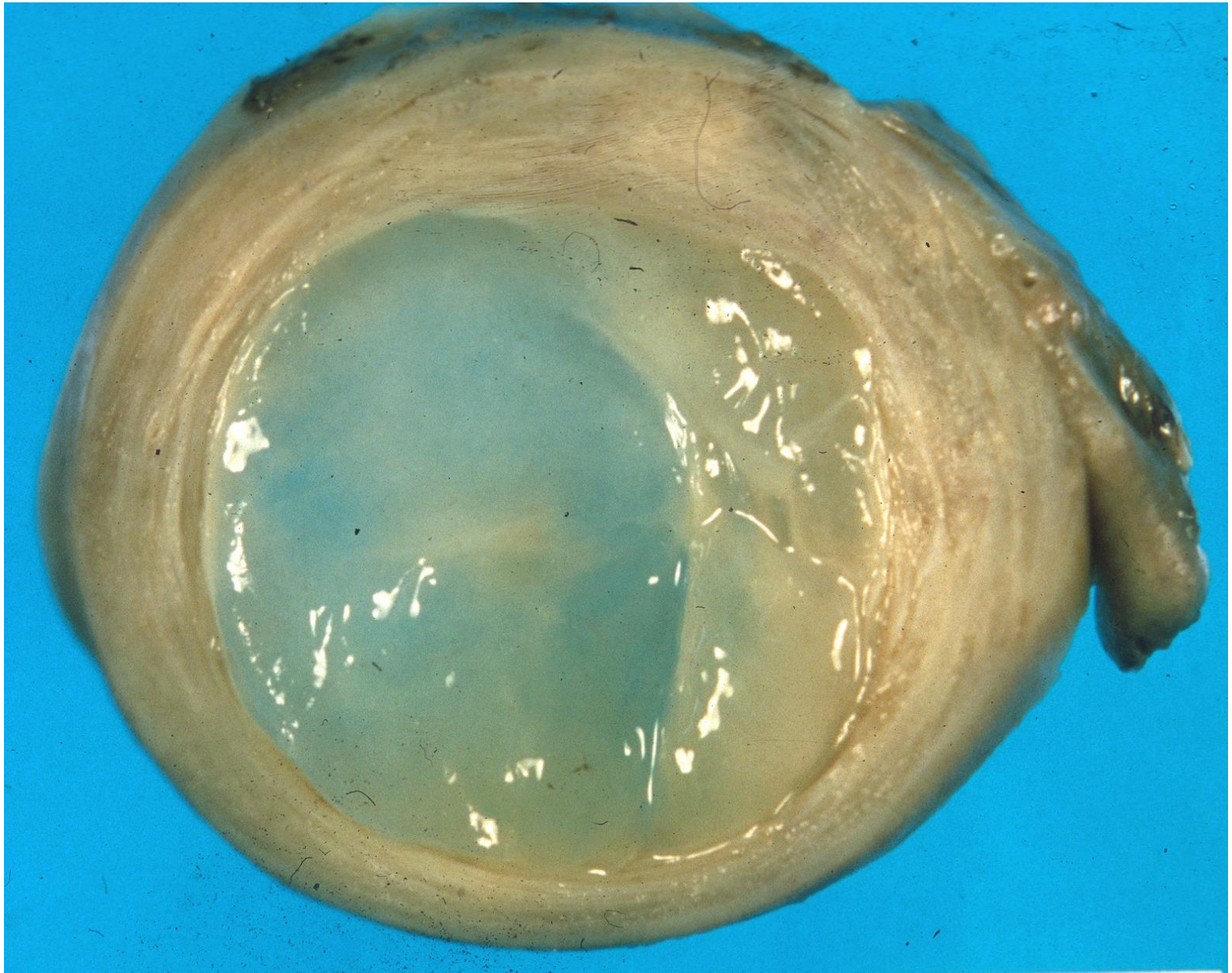
Arias Stella JA et al, Am J Surg Pathol 2019; 43:382-388

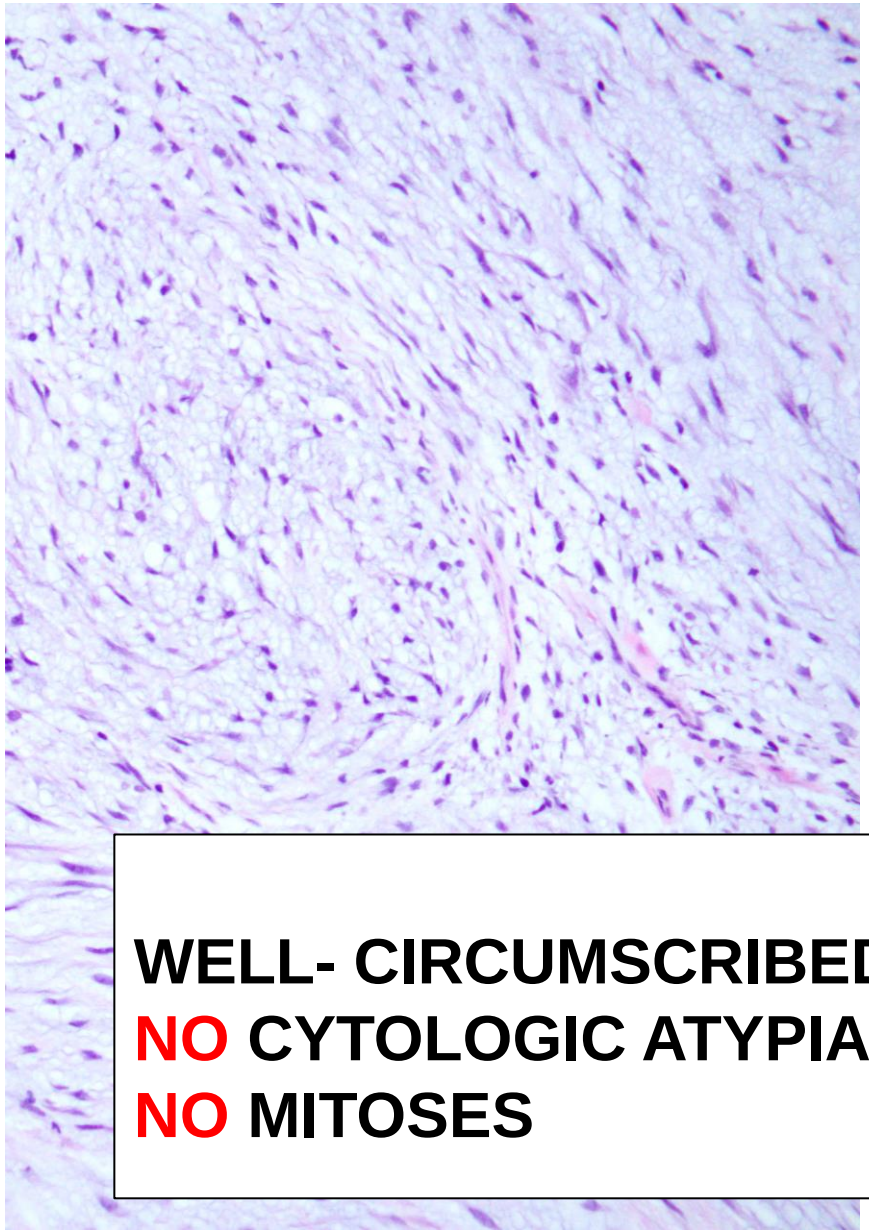
No distinctive morphologic features

UTERINE MYXOID LESIONS

- Myxoid change in leiomyoma (conventional, in pregnancy, or apoplectic)
- Myxoid smooth muscle tumors
  - Benign (rare)
  - Malignant (uncommon)
- Inflammatory myofibroblastic tumor
- Endometrial stromal tumors
  - Low-grade fibromyxoid (uncommon)
  - BCOR high-grade (rare)
- Other: Embryonal rhabdomyosarcoma, liposarcoma, solitary fibrous tumor, NTRK sarcomas, fibroblastic sarcomas with features of malignant nerve sheath tumor, sarcomas with GLI1 gene alterations….
- Myxoidosis or myxoid change in uterine wall

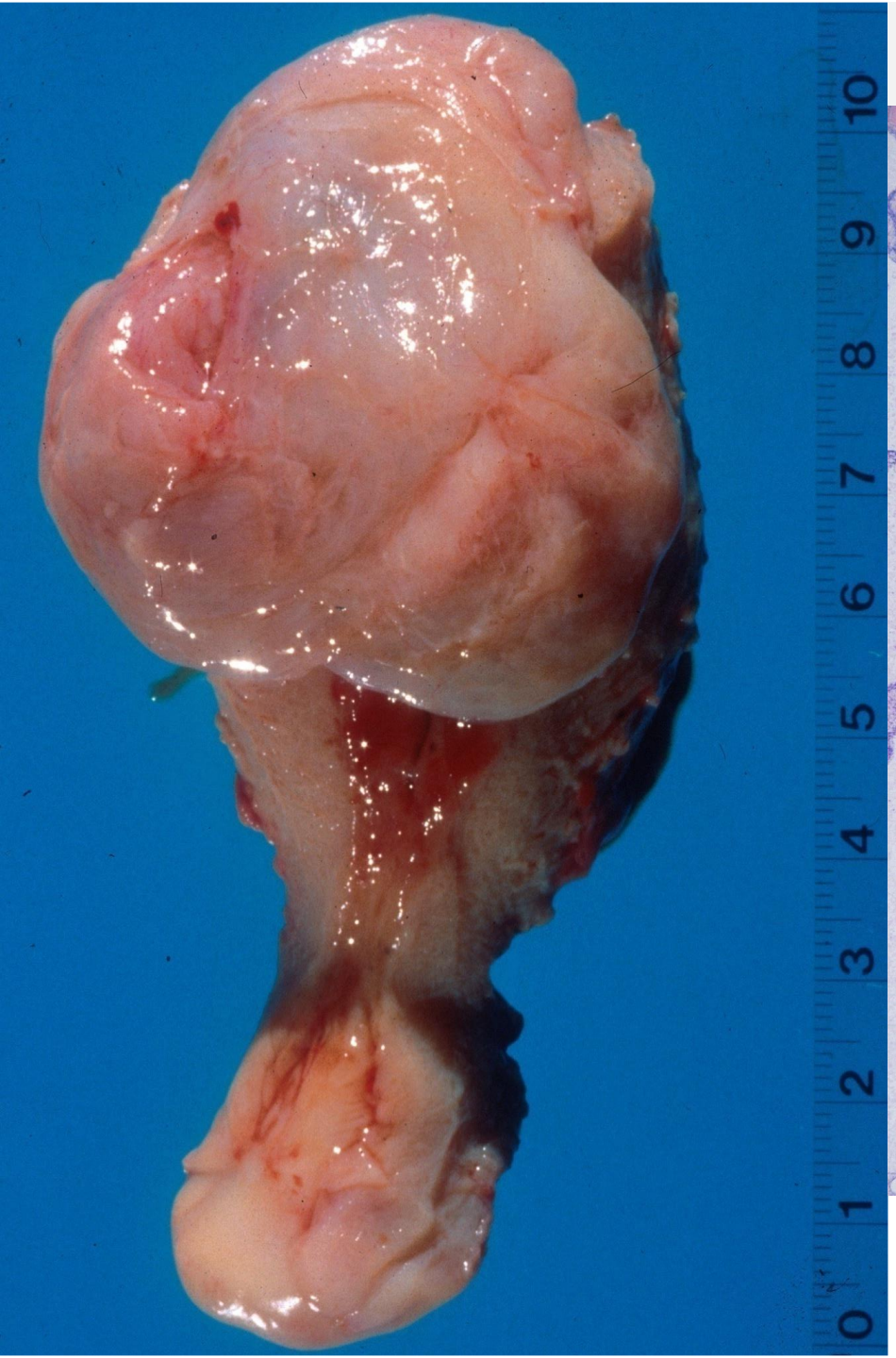
MYXOID LEIOMYOMA <5 cm

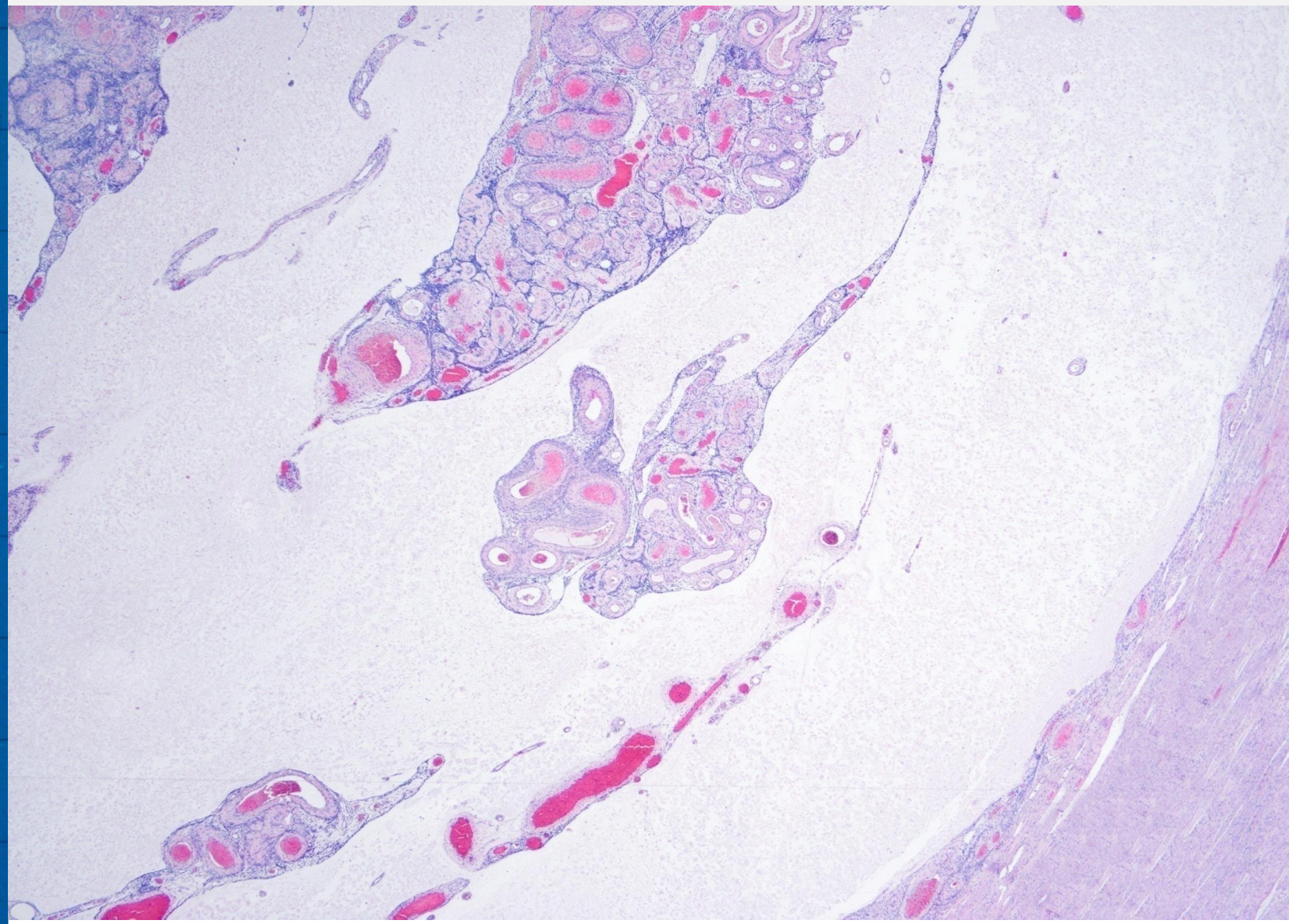




WELL- CIRCUMSCRIBED
NO CYTOLOGIC ATYPIA
NO MITOSES

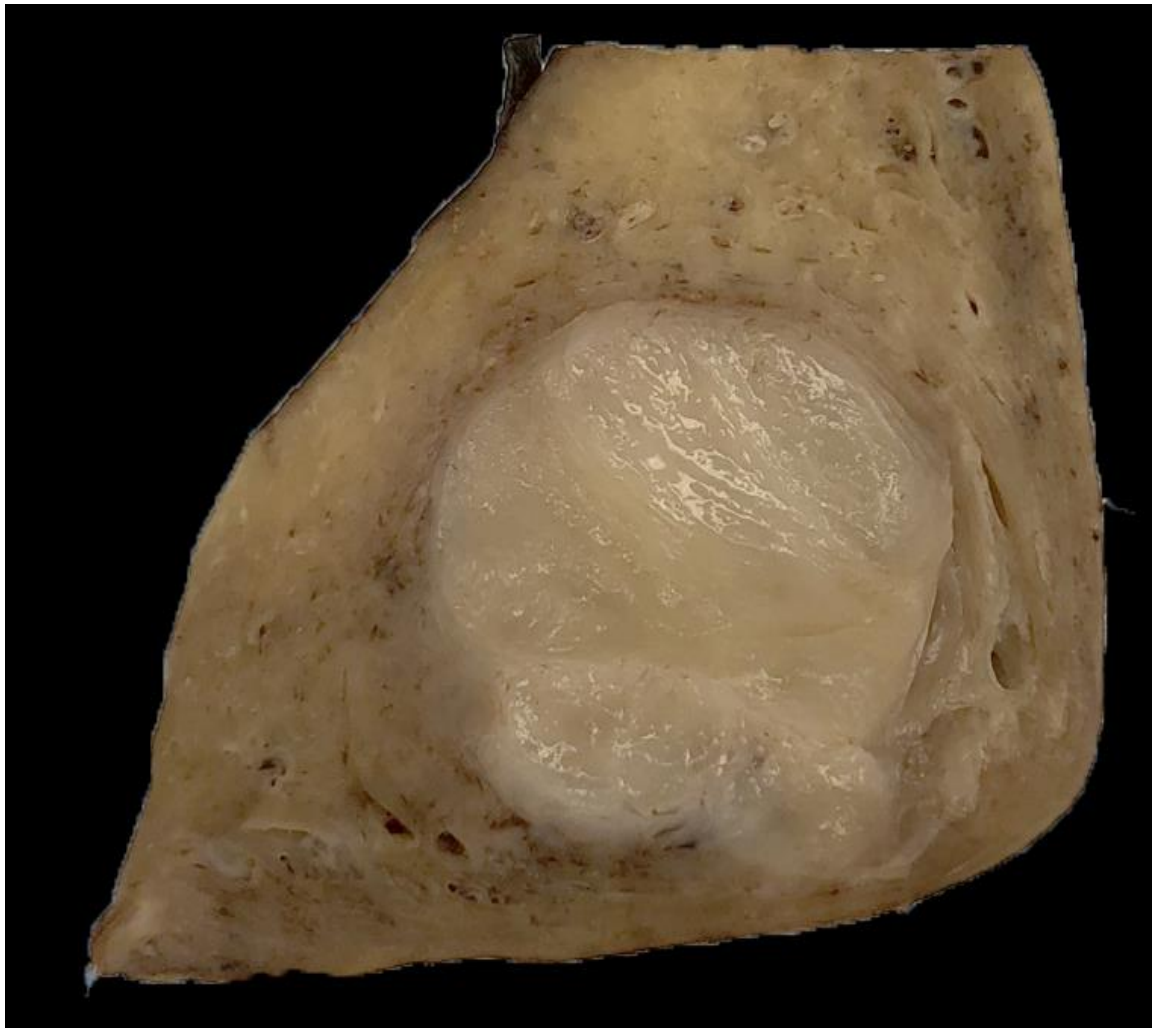
LEIOMYOMA WITH HYDROPIC CHANGE

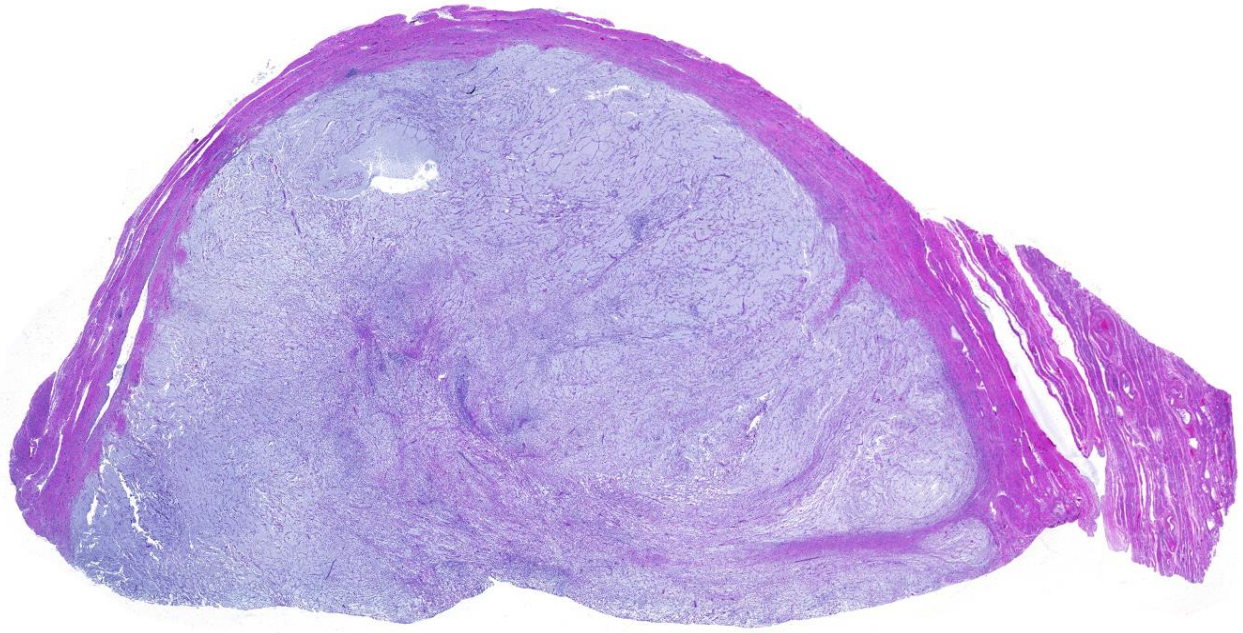




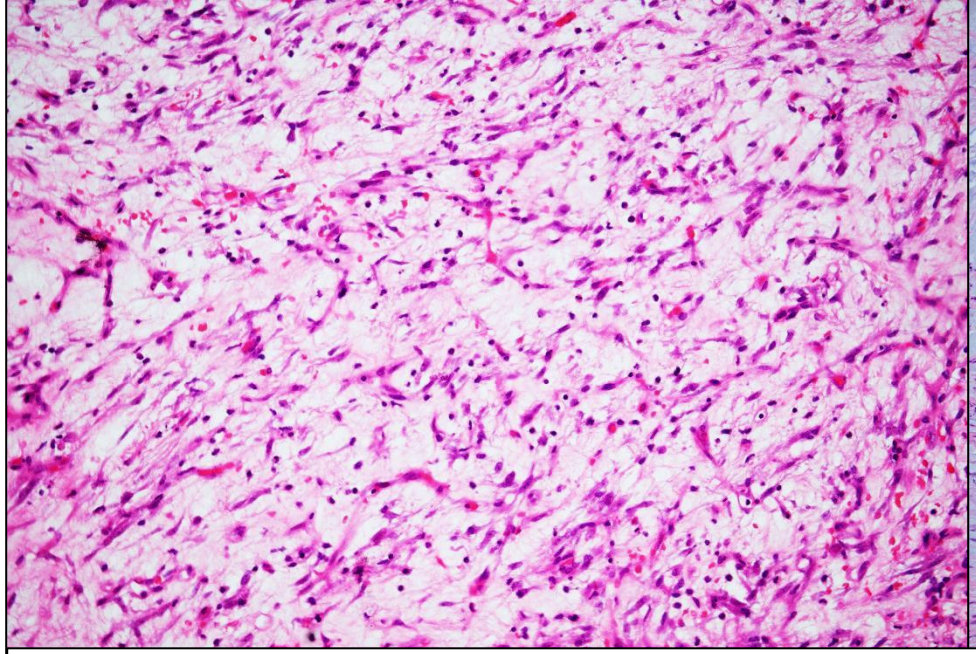
WATERY FLUID=EDEMA:
ALCIAN BLUE NEGATIVE

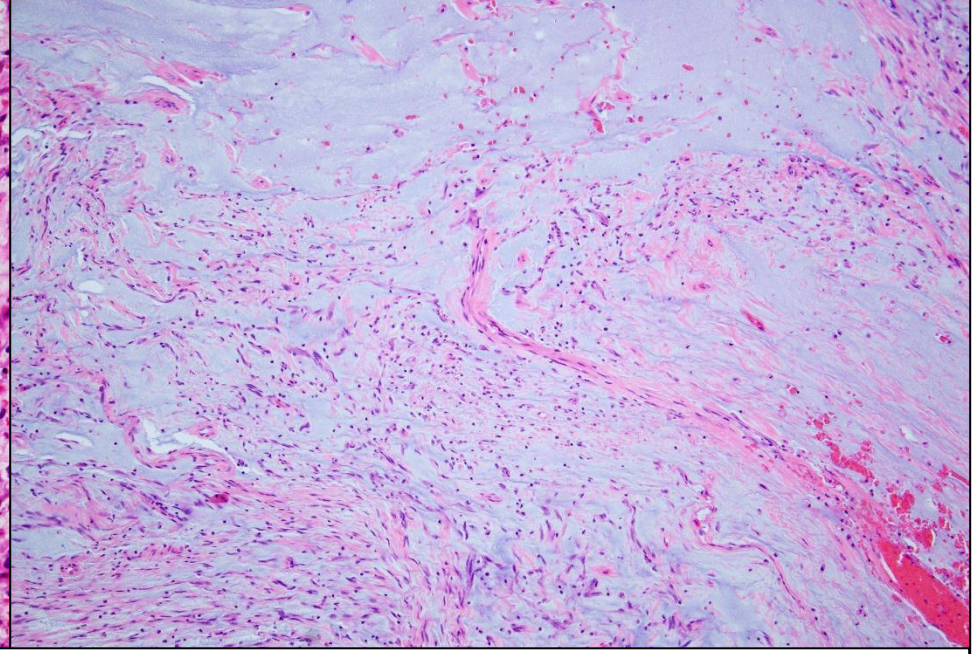
INFLAMMATORY MYOFIBROBLASTIC TUMOR



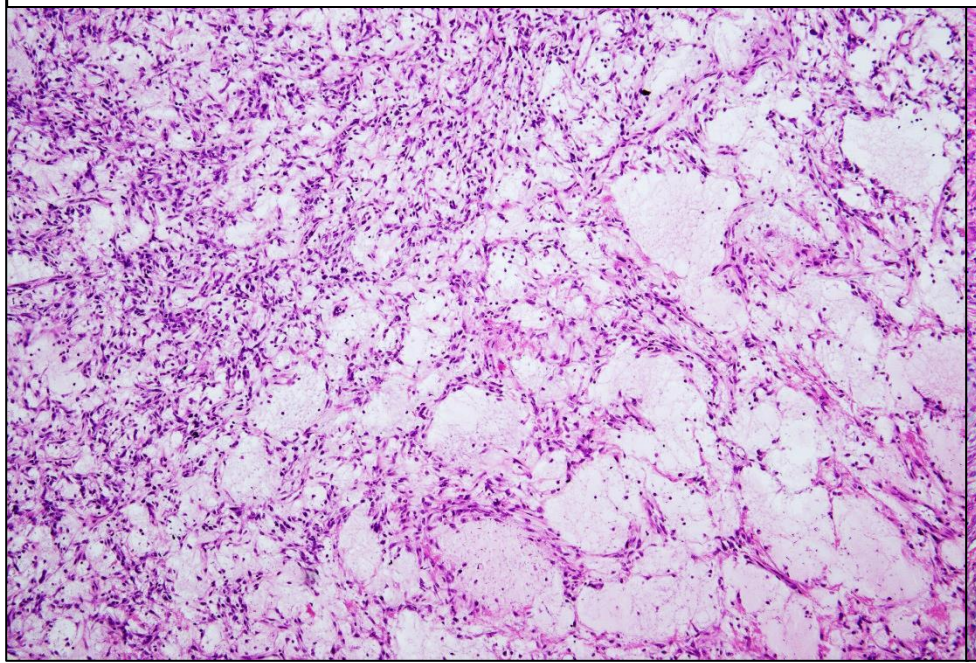


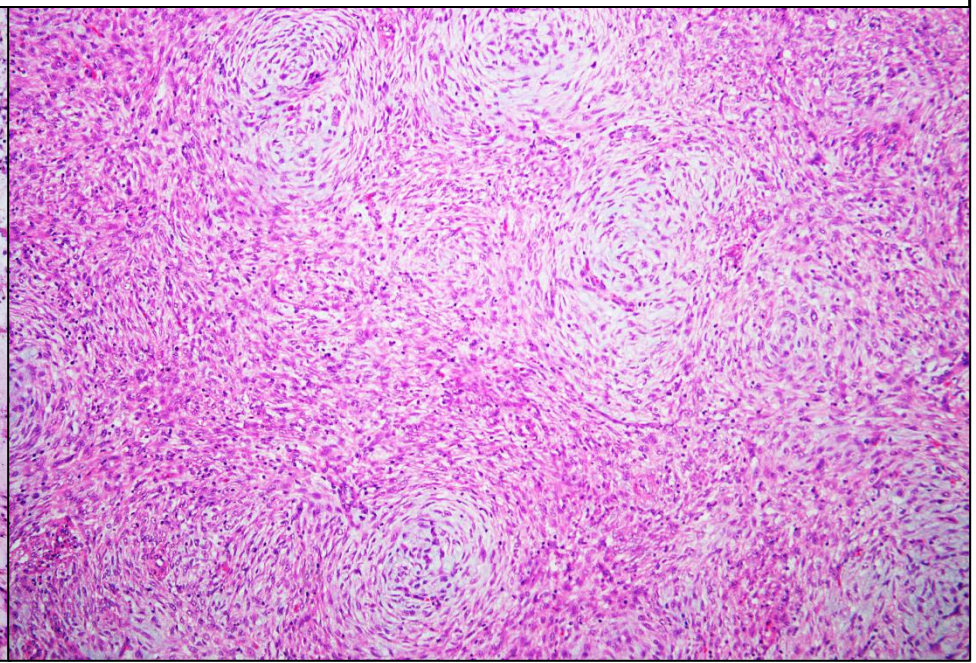
May be strikingly myxoid



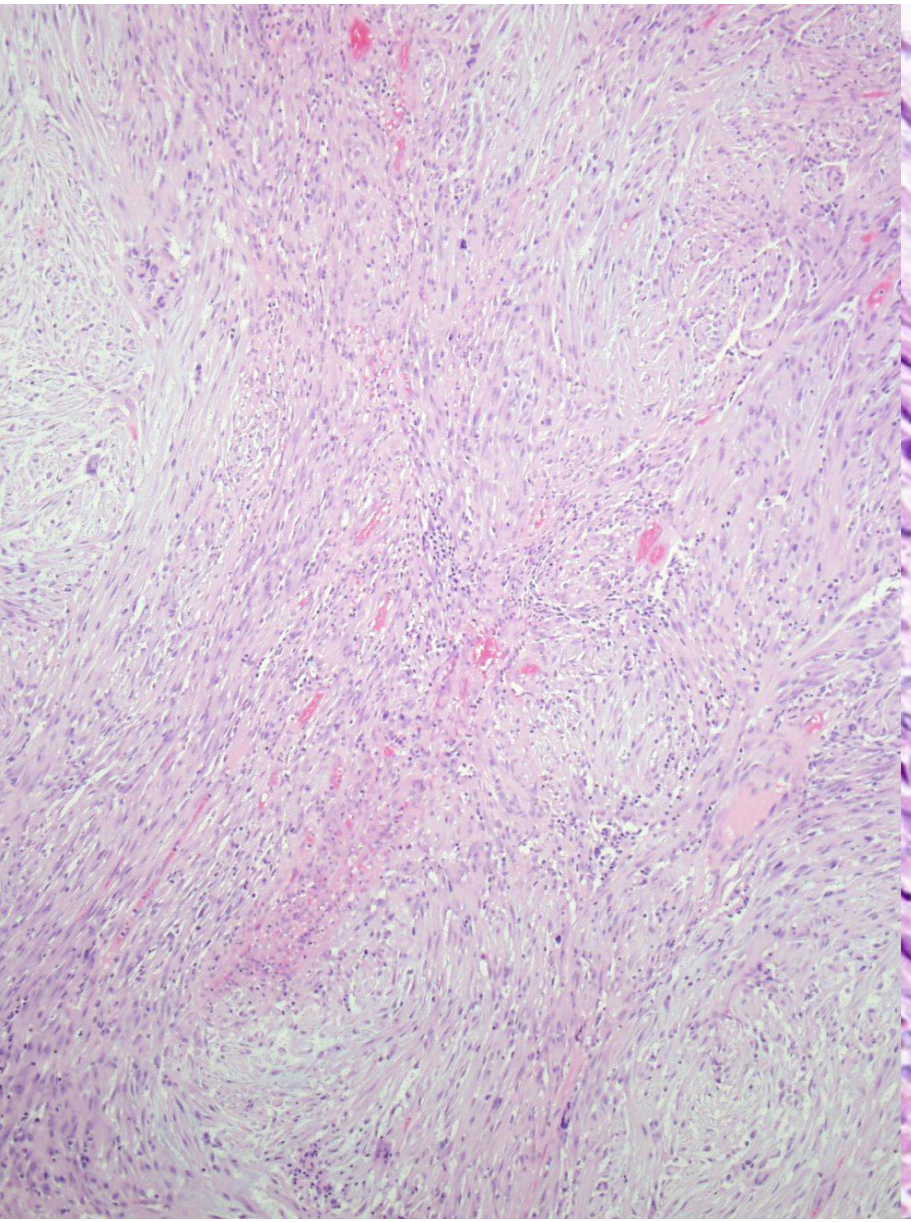


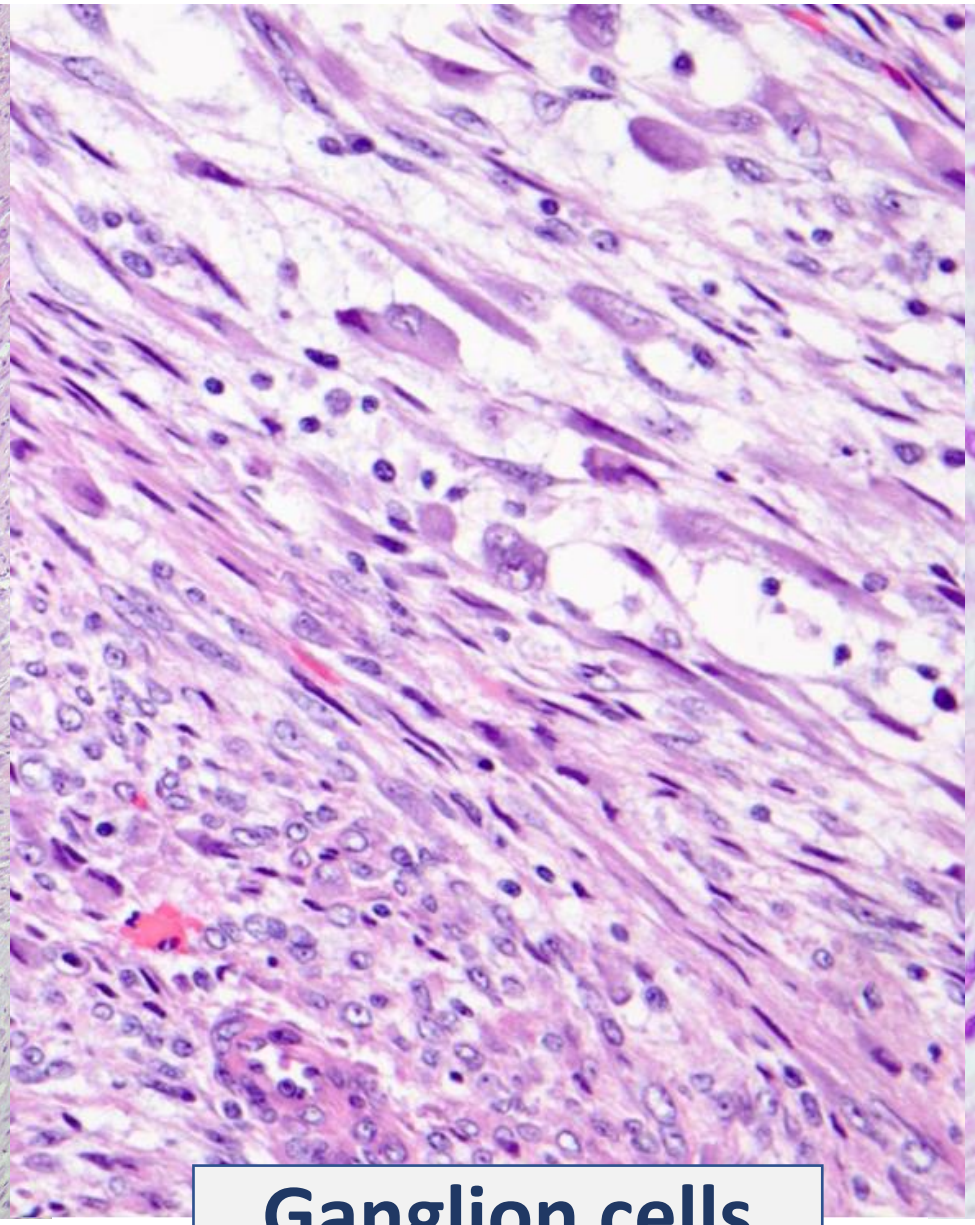
Myxoid appearances



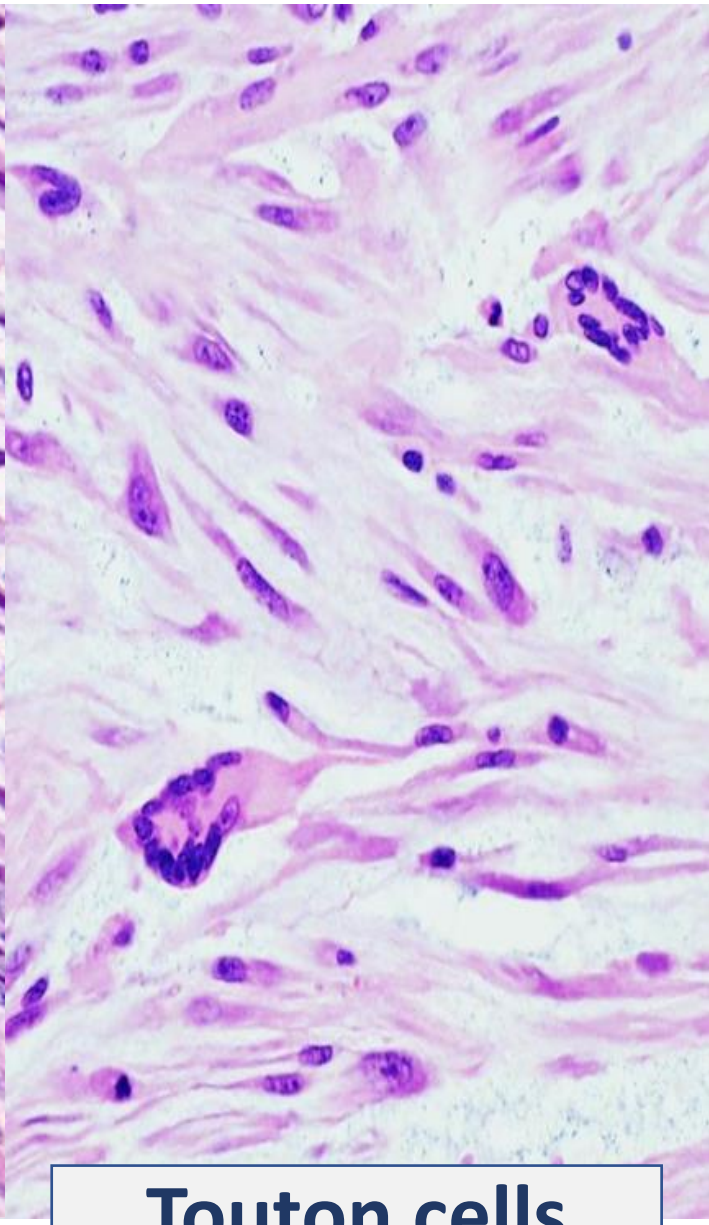


INFLAMMATORY MYOFIBROBLASTIC TUMOR

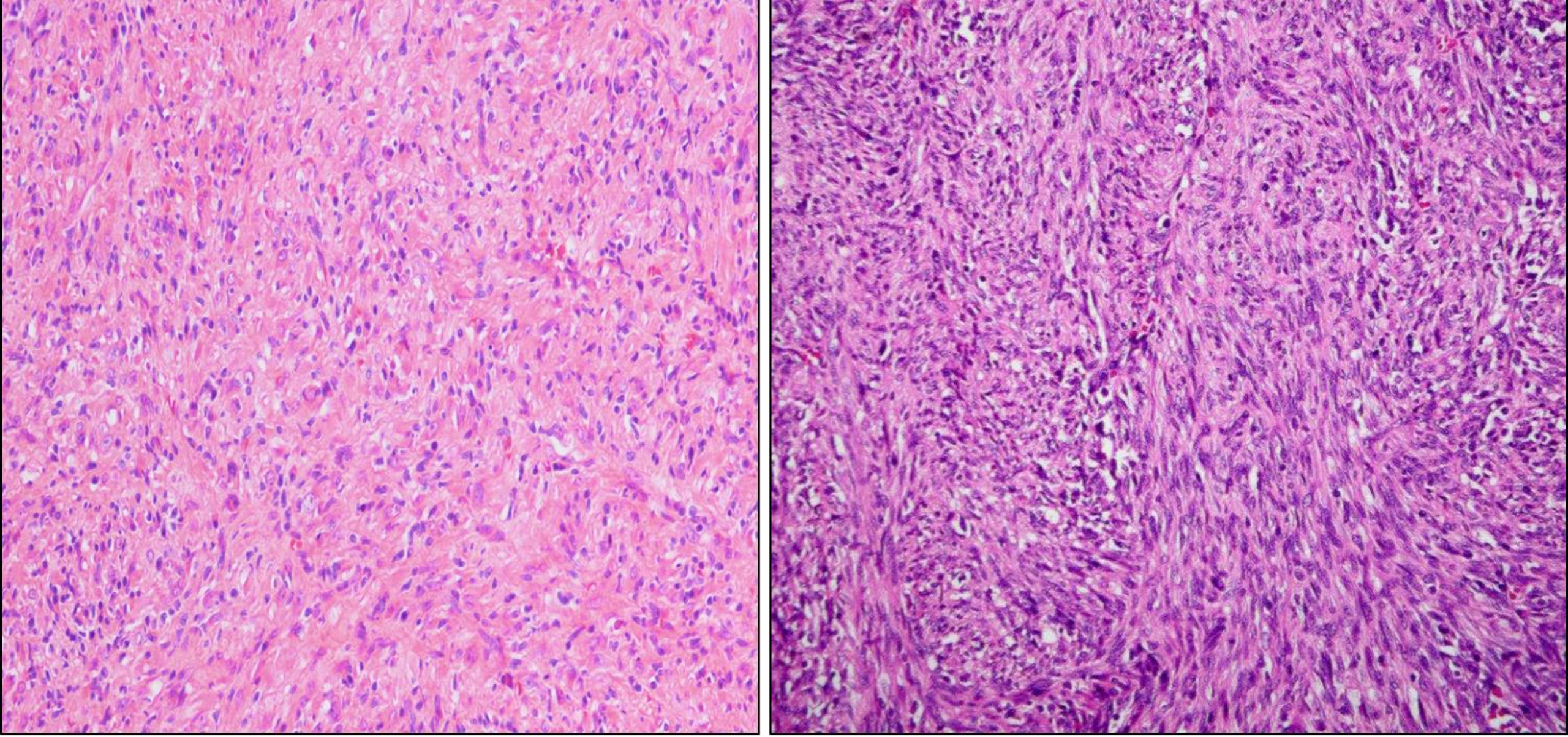




Ganglion cells



Touton cells



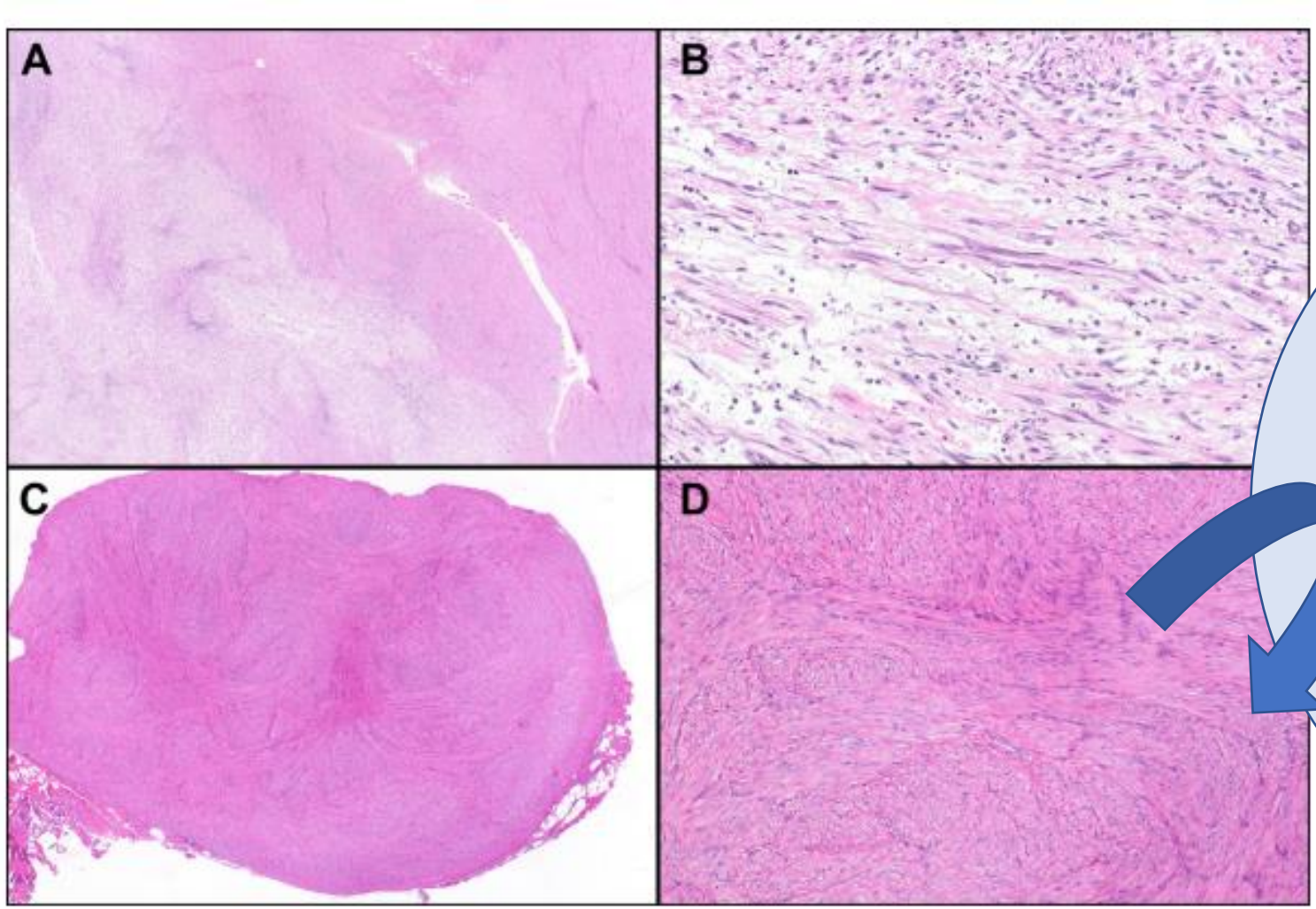
Be aware of smooth muscle-like appearance!

Leiomyoma-like Morphology in Metastatic Uterine Inflammatory Myofibroblastic Tumors

Kyle M. Devins[a,*], Wesley Samore[a], G. Petur Nielsen[a], Vikram Deshpande[b], Esther Oliva[a]

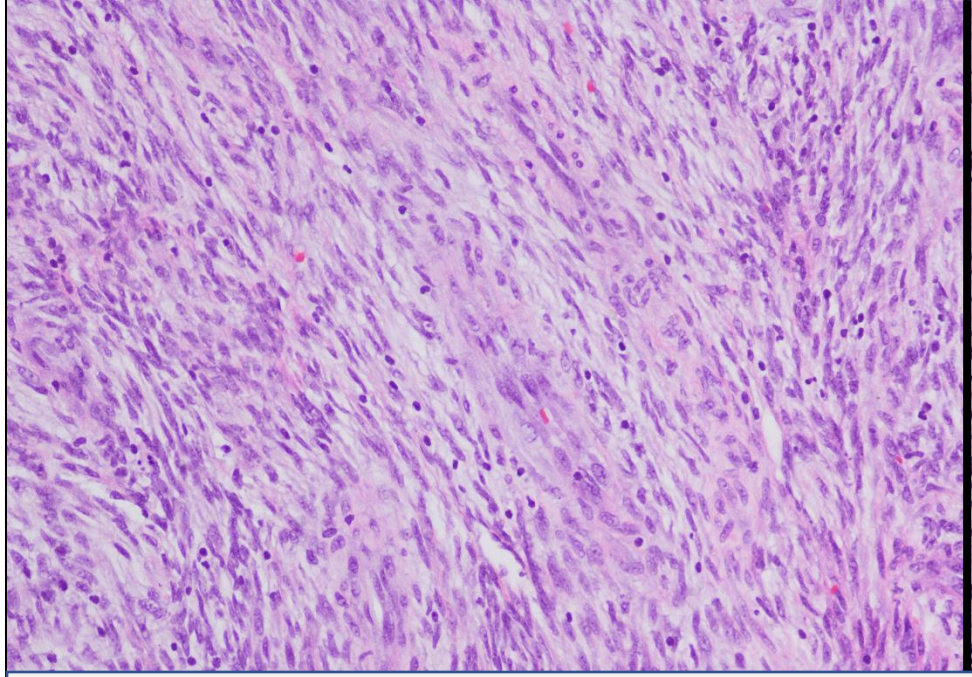
Modern Pathol 2023

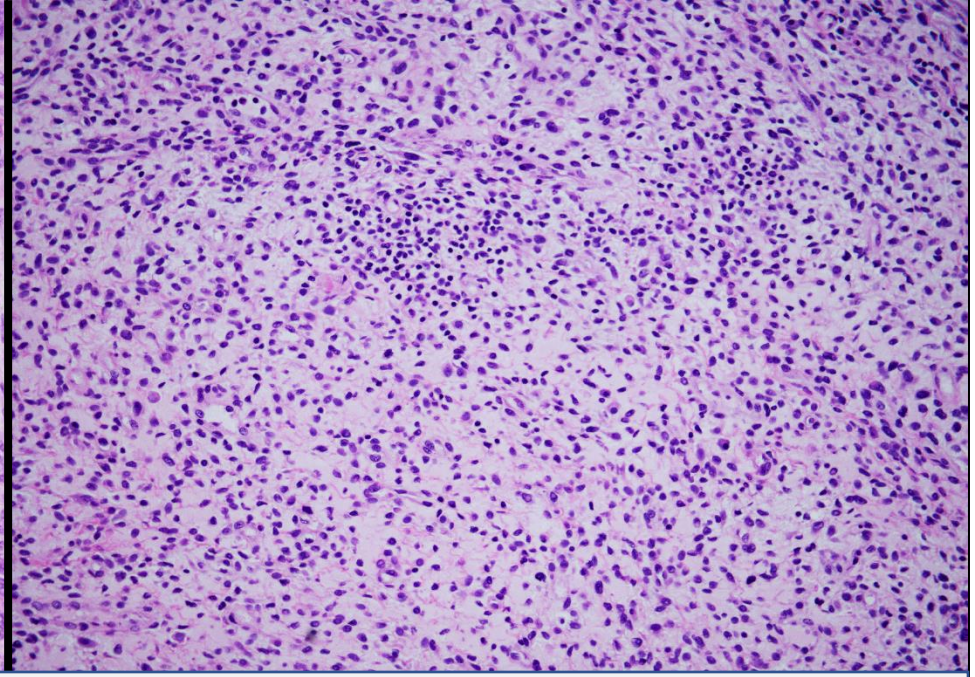
Also reported in primary tumors



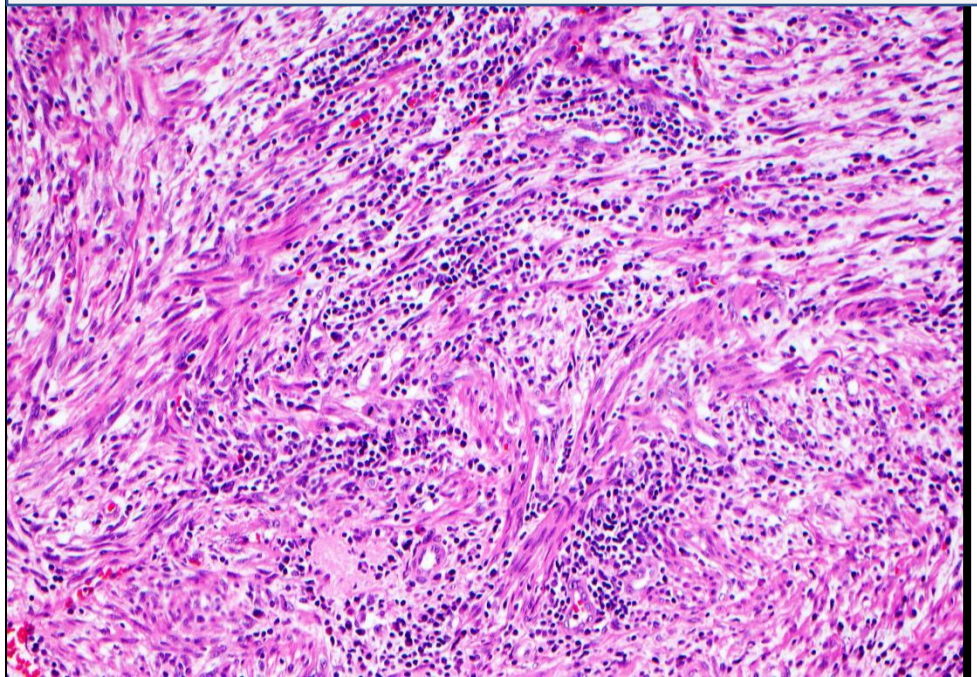
Recurrence-leiomyoma-like

ASK FOR PRIOR HISTORY AND REVIEW SLIDES IF POSSIBLE





INFLAMMATORY INFILTRATE

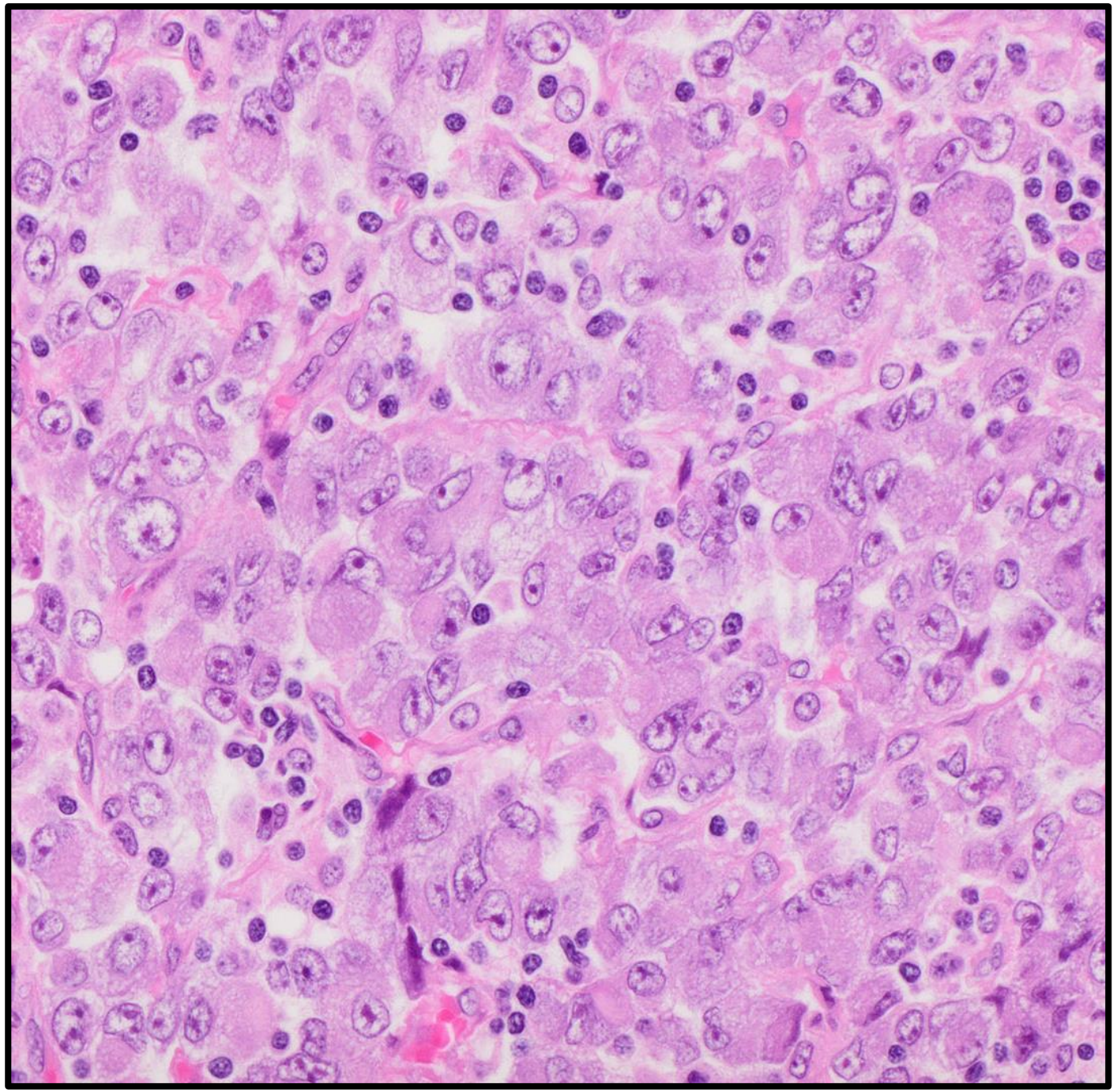


Location

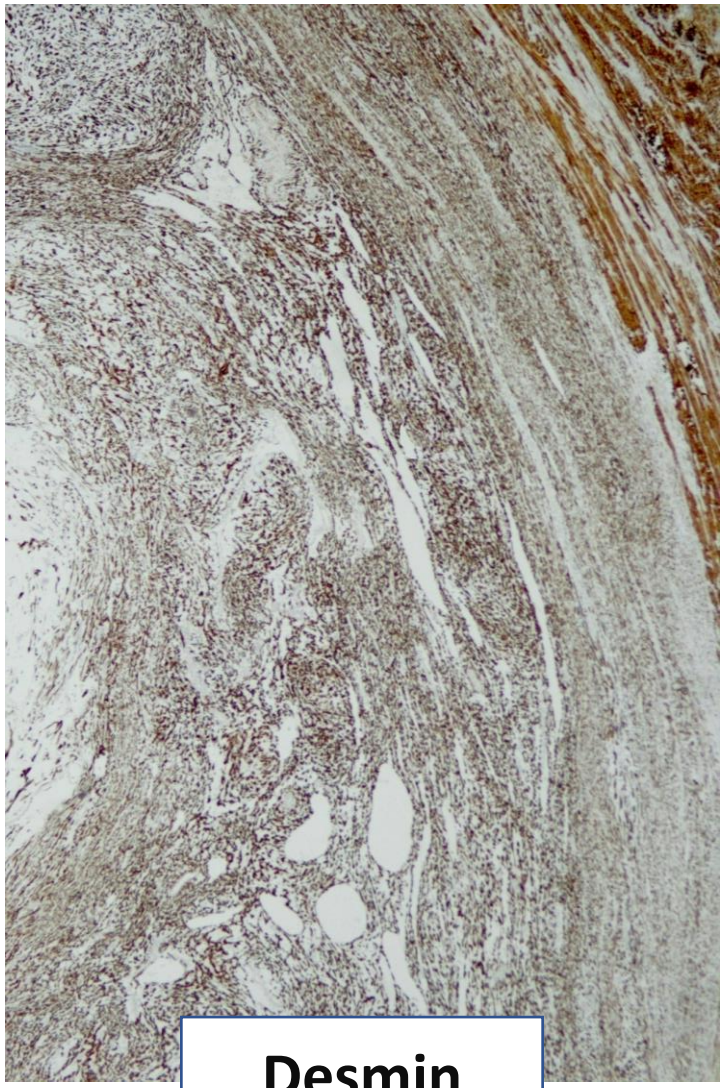
- Compact-Predominant: 46%
- Equally Distributed: 31%
- Myxoid-Predominant: 23%

Epithelioid Inflammatory Myofibroblastic Sarcoma

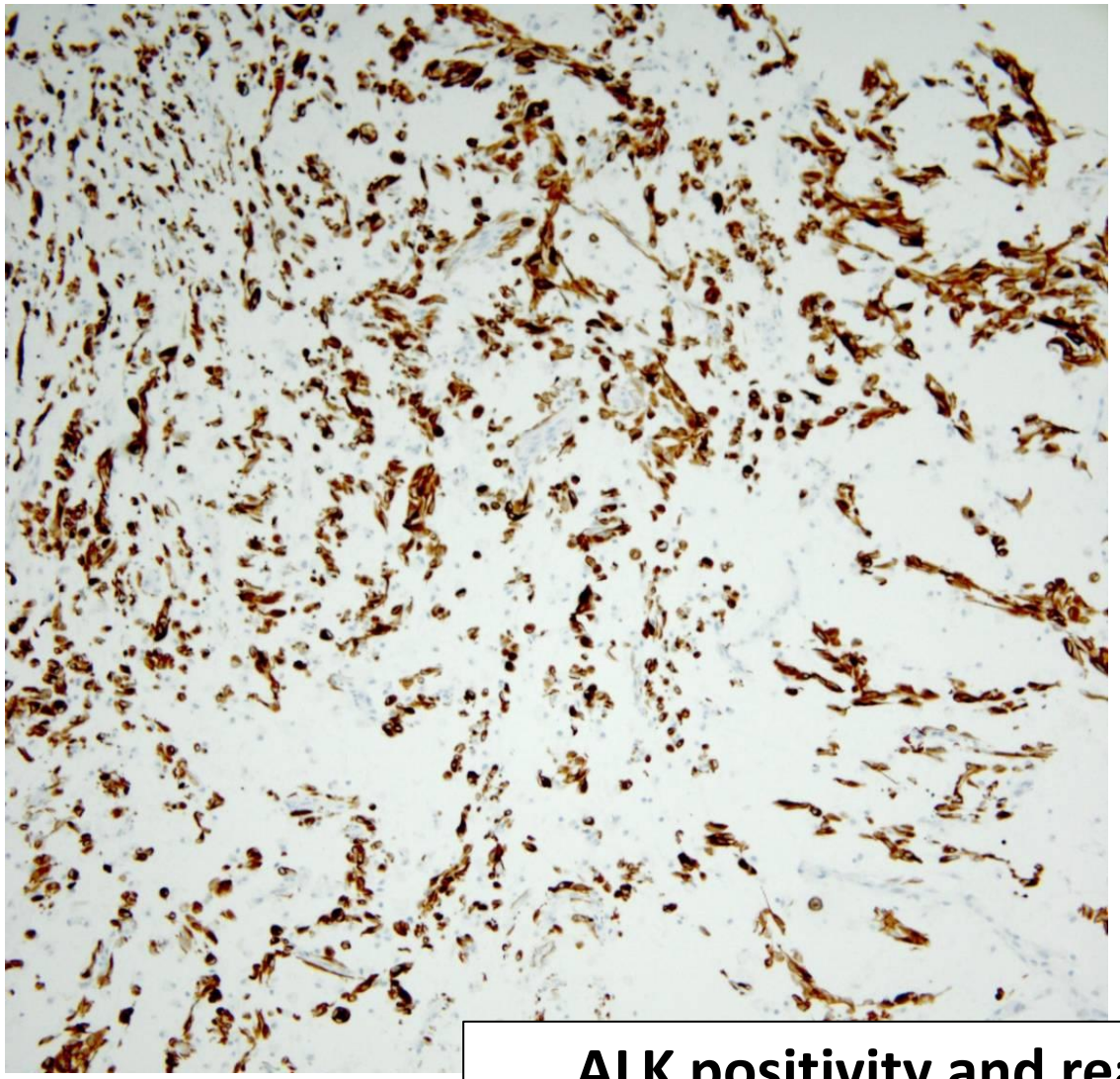
- Always malignant
- Rarely reported in uterus and ovary

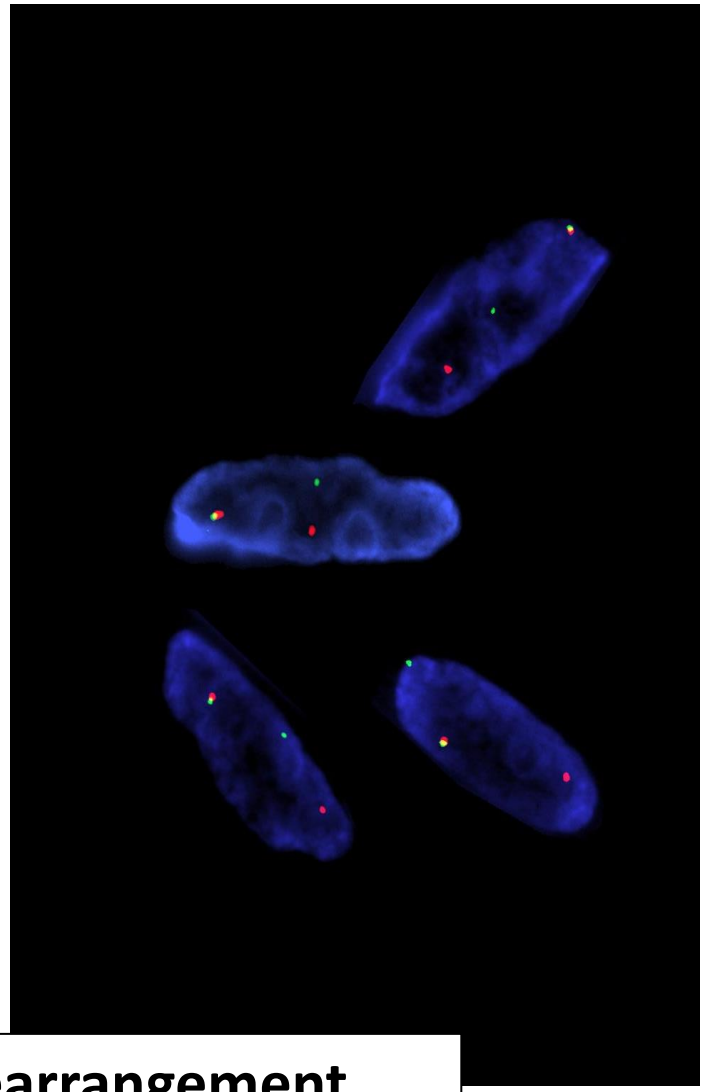


INFLAMMATORY MYOFIBROBLASTIC TUMOR



Desmin





ALK positivity and rearrangement

Smooth muscle tumors may have ALK amplifications but typically no rearrangements

INFLAMMATORY MYOFIBROBLASTIC TUMOR

Features associated with aggressive behavior:

- **Large size >7cm**
- **Tumor cell necrosis**
- **Cytologic atypia and brisk mitotic activity**
- **Lymphovascular invasion**

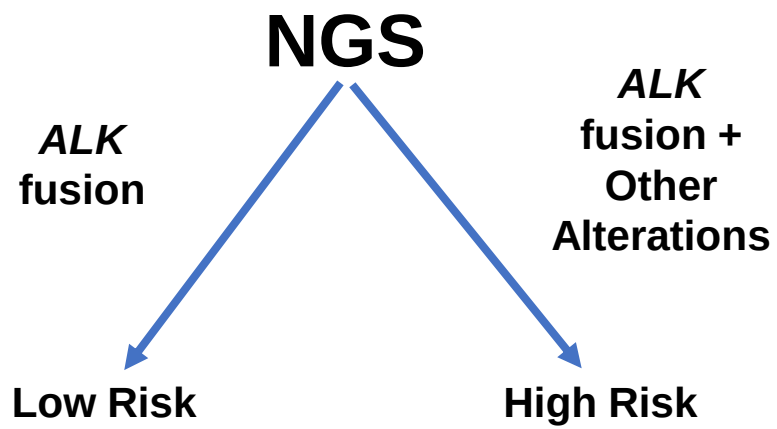
Parra-Herran C et al, Am J Surg Pathol 2015;39:157-68

**Bennett J et al , Modern Pathol 2017; 30:1489-1503*

New Proposed Risk Stratification Score

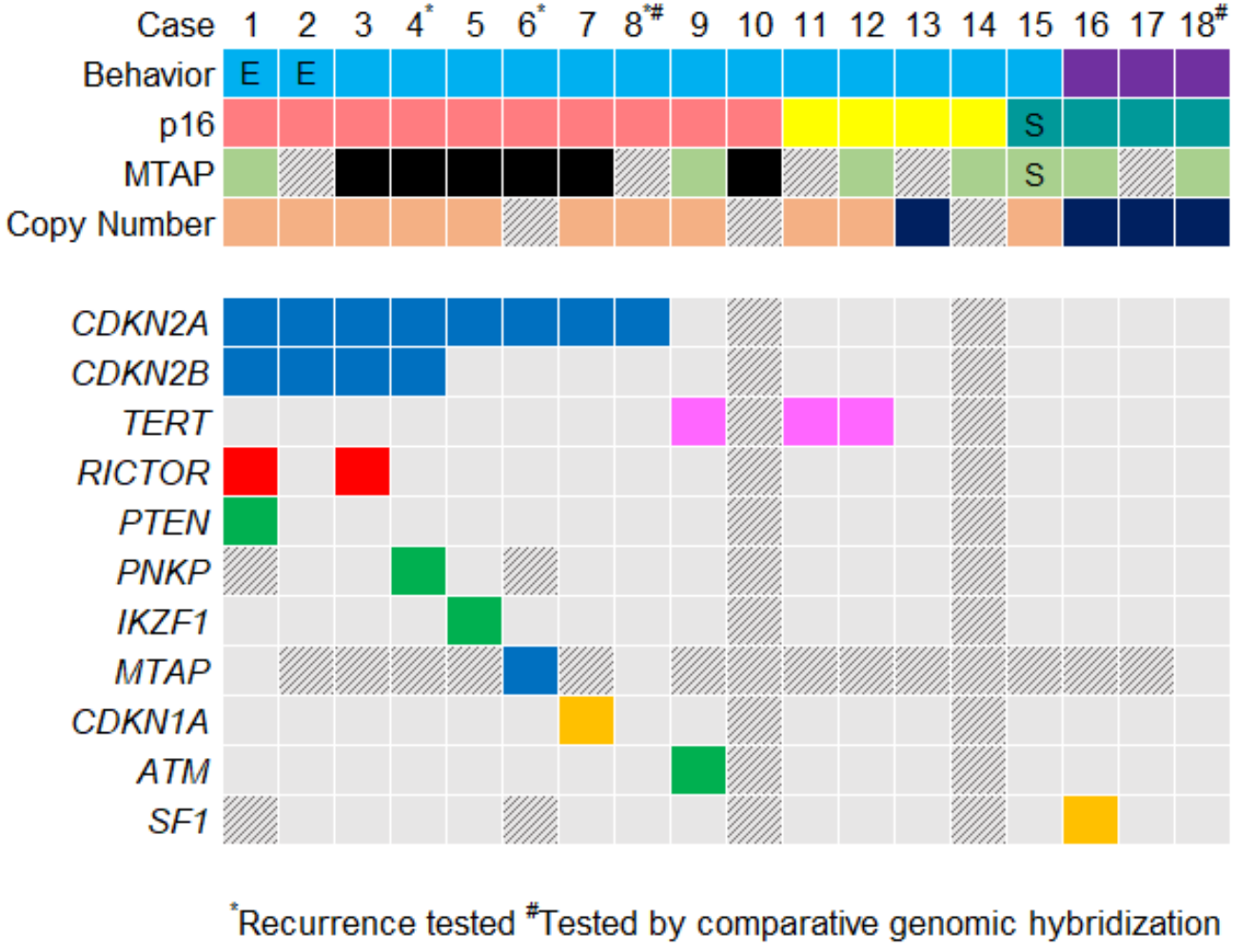
- Age > 45 years
- Size ≥ 5 cm
- Mitoses ≥ 4/10 HPFs
- Infiltrative Border

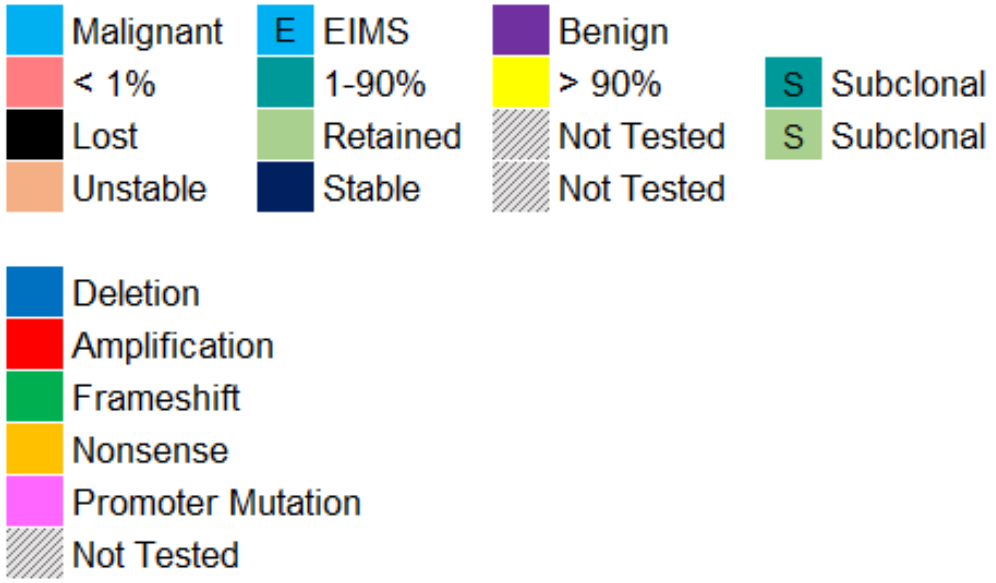
Outcome (n=52)	Low Risk (0 Points)	Intermediate Risk (1-2 Points)	High Risk (≥ 3 Points)
Benign (n=30)	11	19	0
Aggressive (n=22)	0	4	18



Ladwig et al. Am J Surg Pathol 2023

Abnormal p16 in Malignant IMTs





Devins K, et al, AM J Surg Pathol 2024

<u>Abnormal p16 expression in most malignant IMTs:</u>

<1%: Usually associated with *CDKN2A* *(+/- CDKN2B*) deletion

>90%: Often with *TERT* promoter mutations

KEEP IN MIND:

When a lymphoplasmacytic inflammatory infiltrate is noted within a spindle cell proliferation that resembles a smooth muscle neoplasm, think about the possibility of an inflammatory myofibroblastic tumor

When working up such differential diagnosis apply smooth muscle markers as well as ALK/ROS and perform FISH

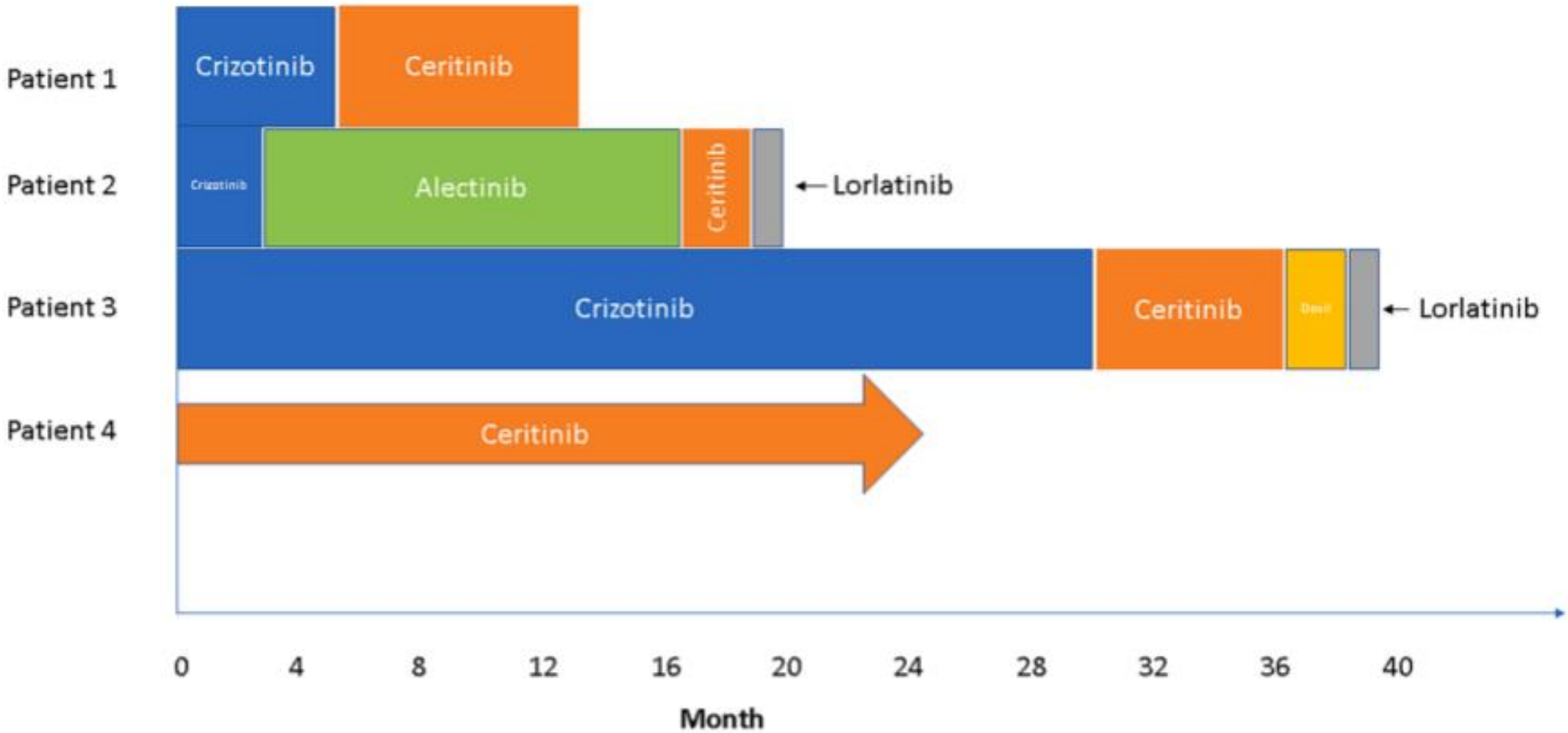
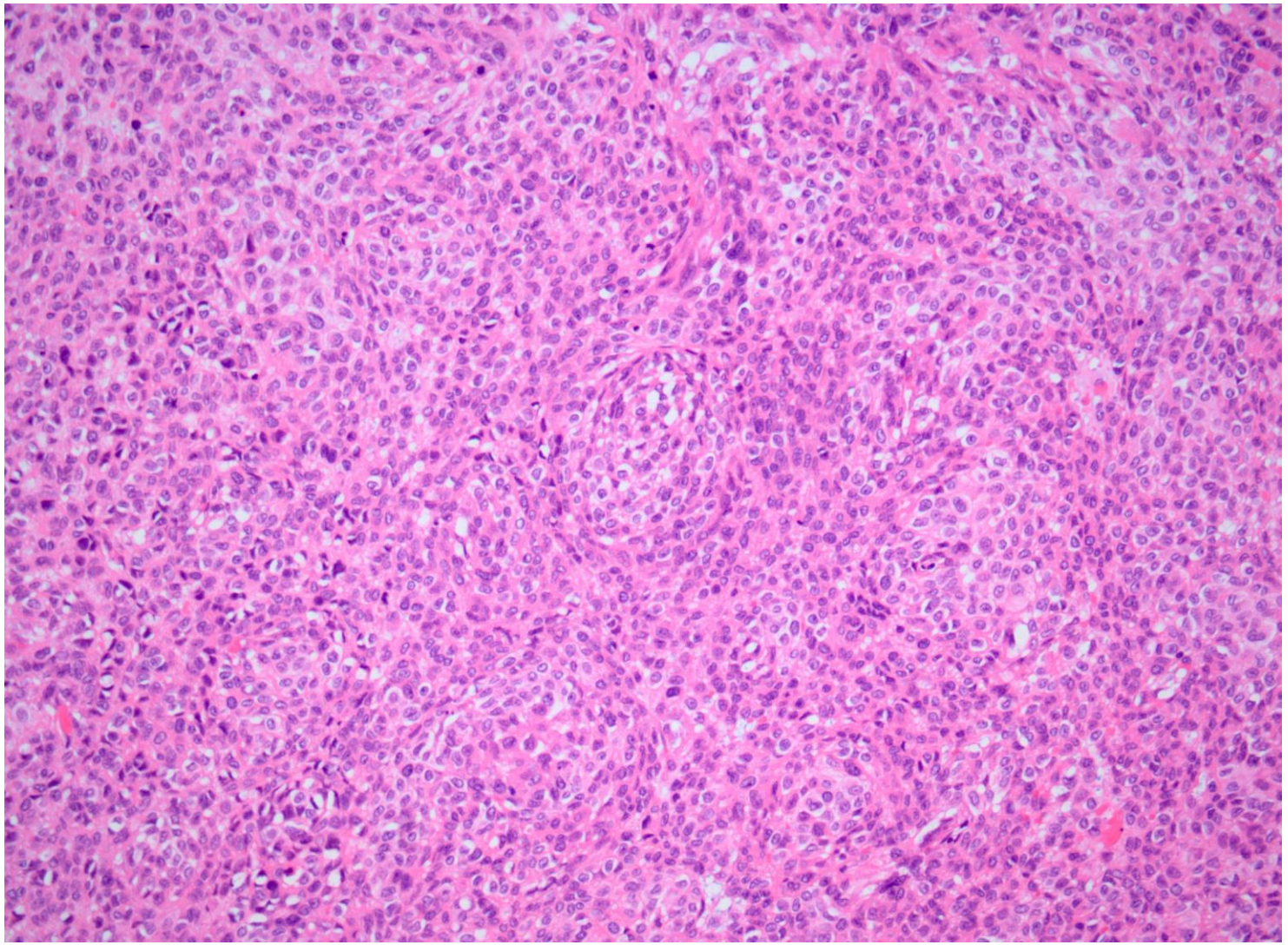
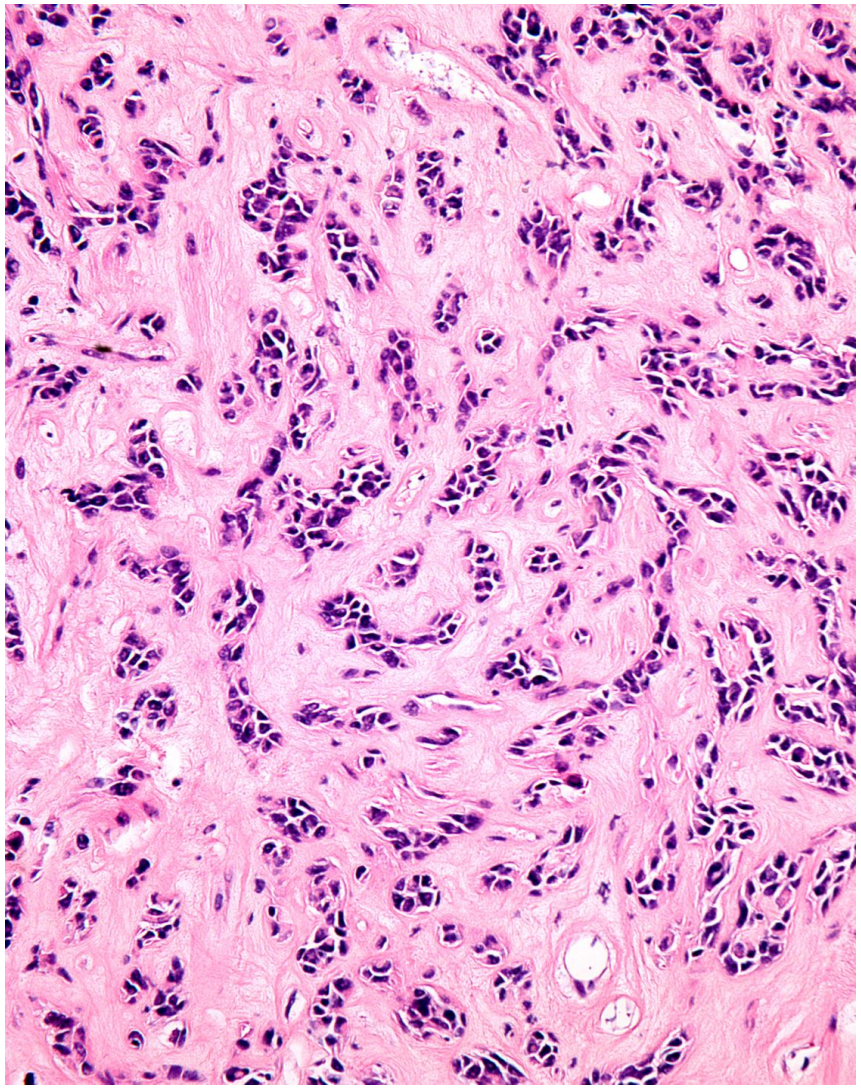


Fig. 2. Response to *ALK* inhibitors in uterine mesenchymal tumors harboring *ALK* fusions.

Gynecol Oncol Rep 2021 Sep 1;37:100852

EPITHELIOID LEIOMYOSARCOMA





EPITHELIOID SMOOTH MUSCLE Ts

- No widely accepted criteria for predicting behavior as rare

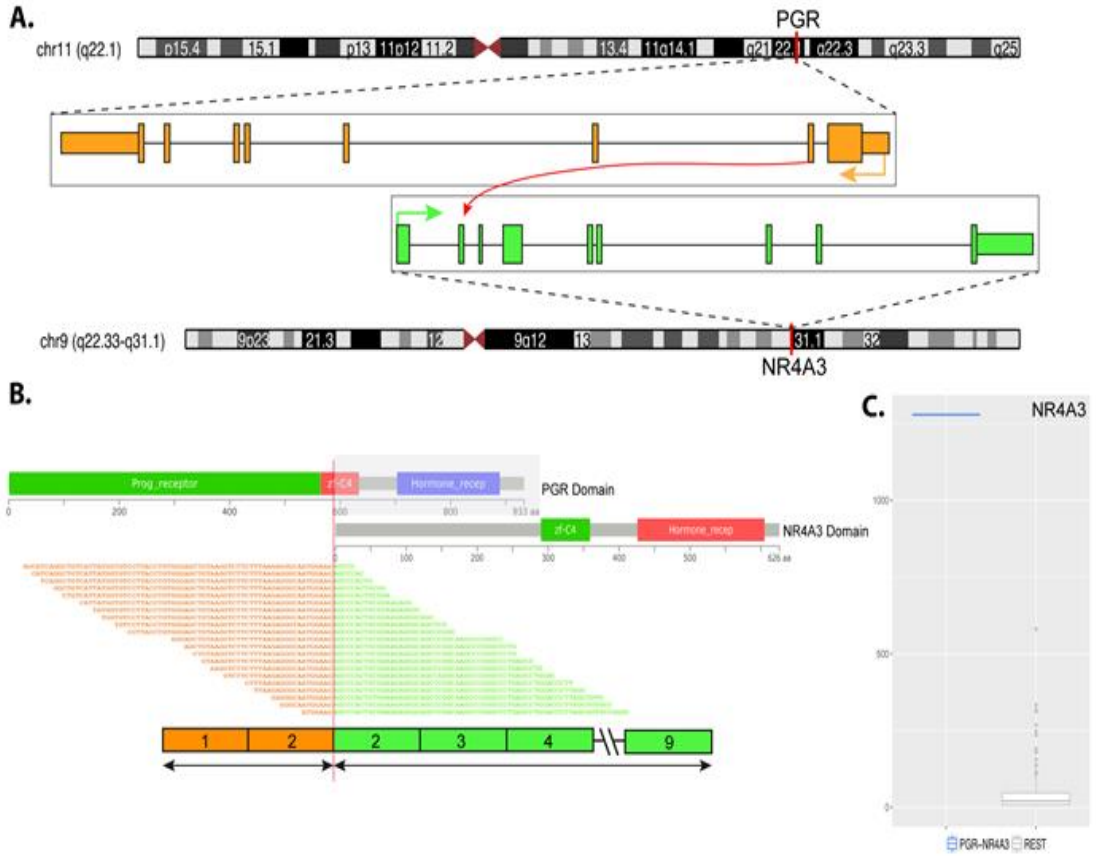
- Epithelioid Leiomyosarcoma:
  - ≥4 MFs/10HPFs & grade 2 or 3 nuclei

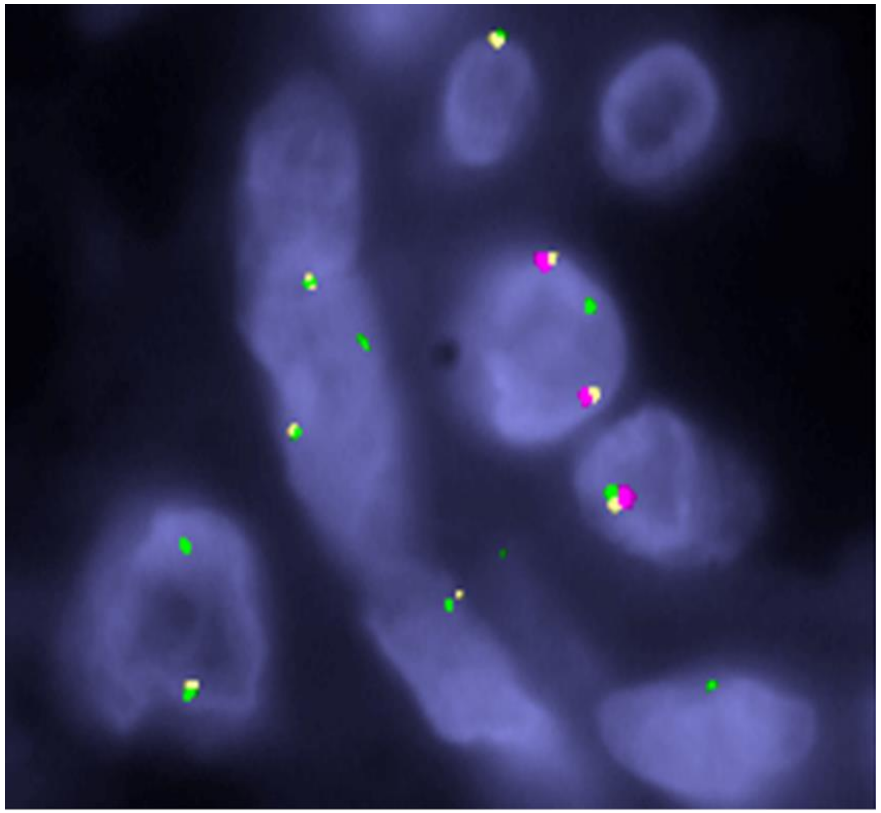
    or

  - Tumor cell necrosis
- Epithelioid Smooth Muscle Tumor, probably benign:
  - ≤2 MFs/10HPFs, no tumor cell necrosis

    and at most mild nuclear atypia

EPITHELIOID LEIOMYOSARCOMA (*PGR fusion* subset), with *t*(9,11)





PGR-NR4A3 fusion ----projected fusion protein including the progesterone receptor domain of PGR

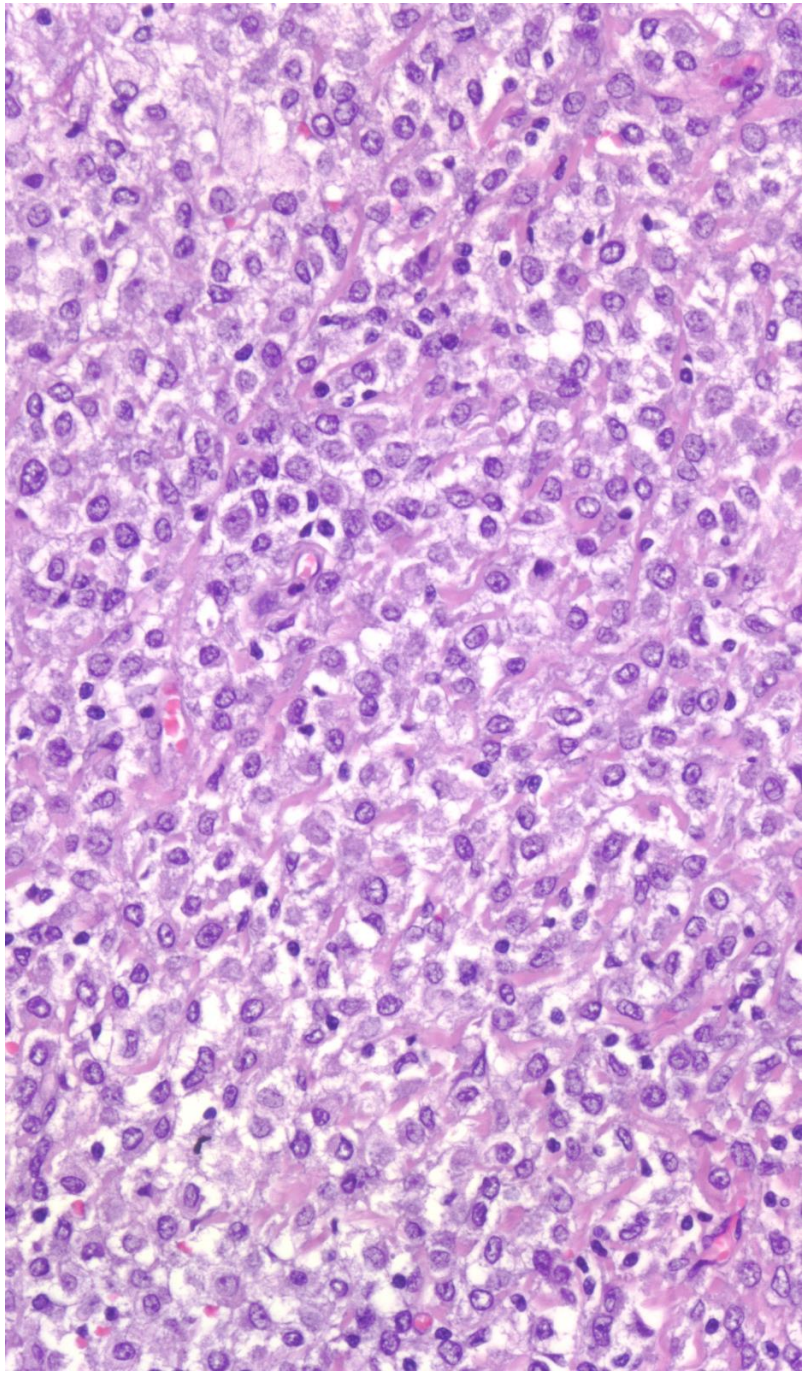
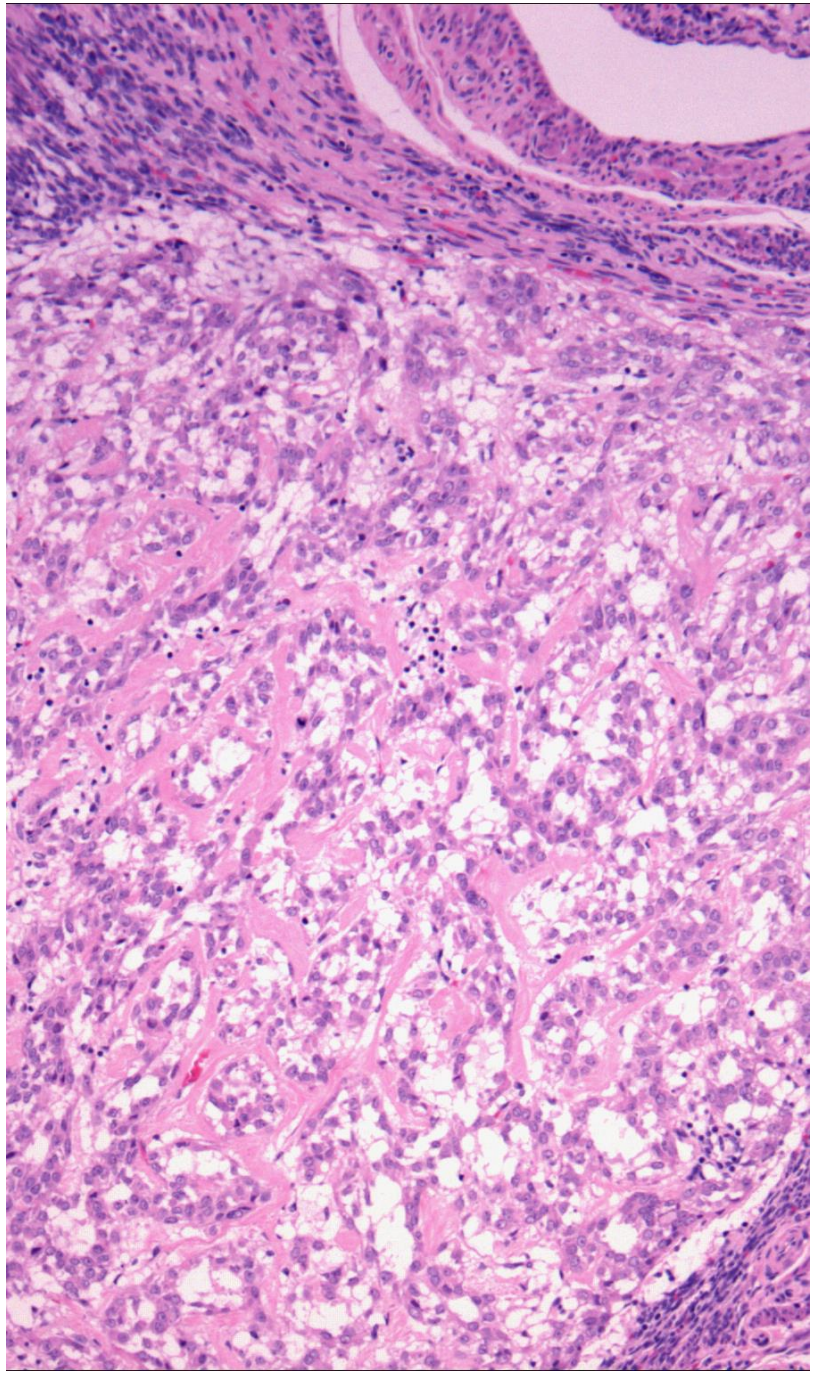
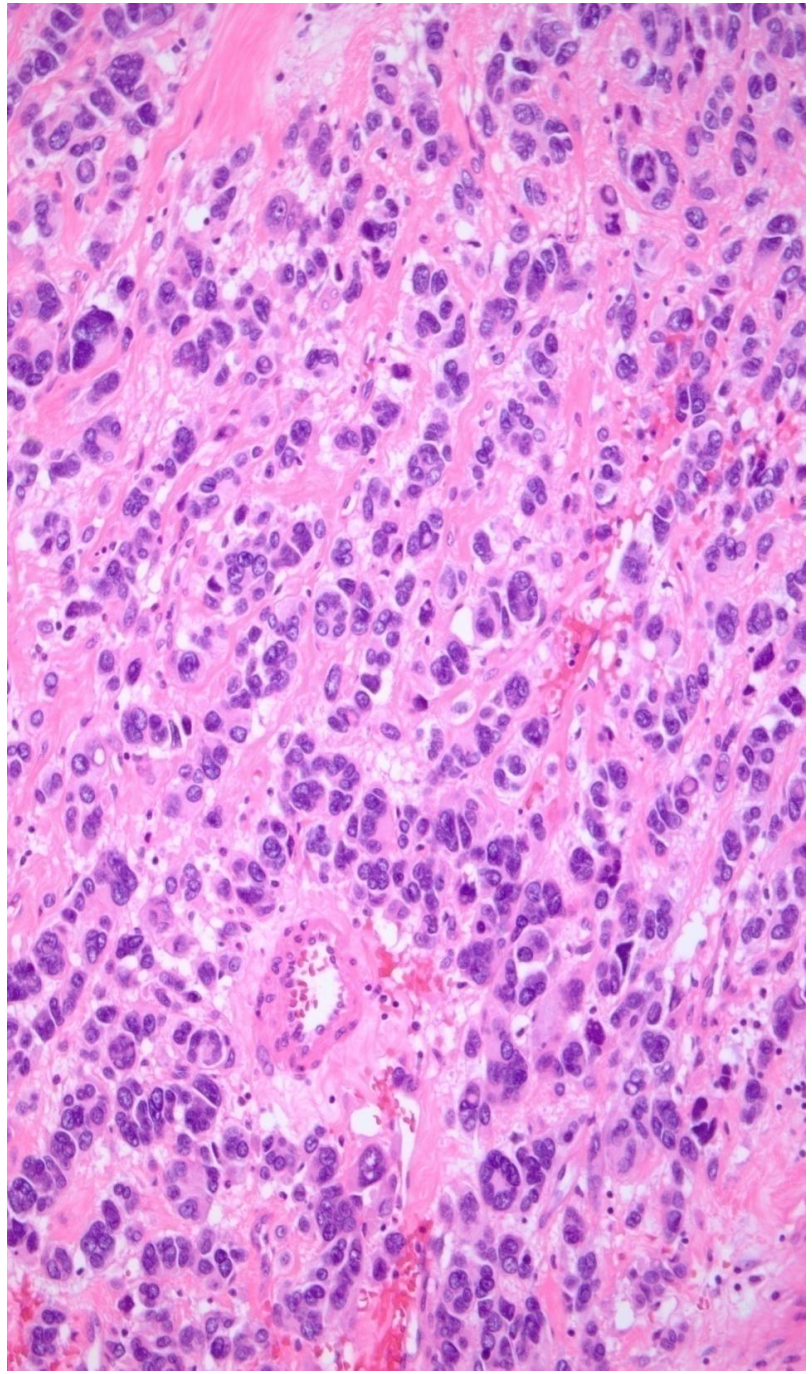
PGR mutations rare; seen in 2% of EC and 0.2% of high-grade serous carcinomas

EPITHELIOID LEIOMYOSARCOMA
Differential Diagnosis:

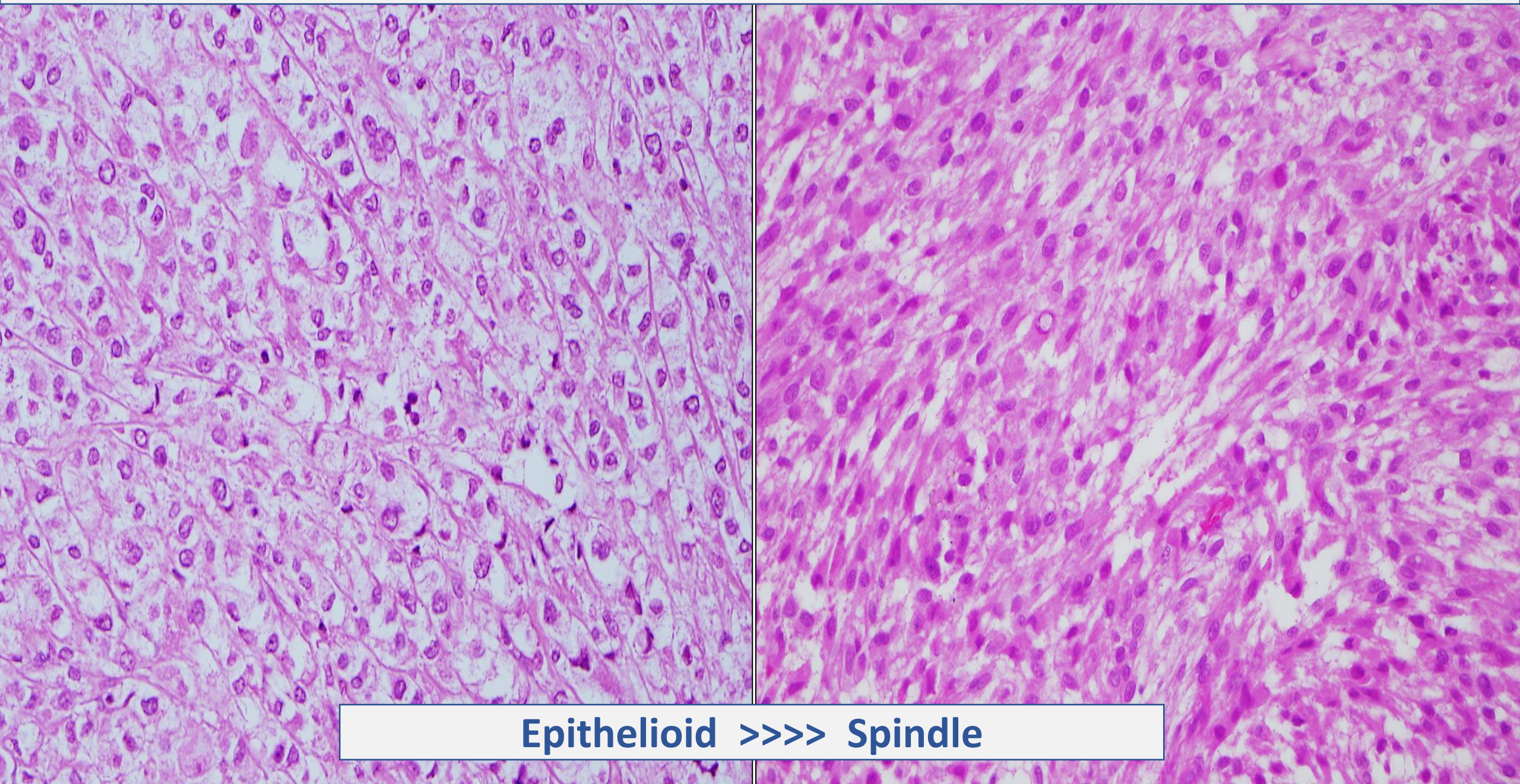
- Poorly differentiated carcinoma
- PEComa
- UTROSCT
- Epithelioid endometrial stromal sarcoma
- Intermediate-type trophoblastic tumors
- Melanoma
- Other (rhabdomyosarcoma, angiosarcoma, alveolar soft part sarcoma, GIST)
- SMARCA4 deficient uterine sarcoma
- Metastases

PERIVASCULAR EPITHELIOID CELL TUMOR (PEComa)

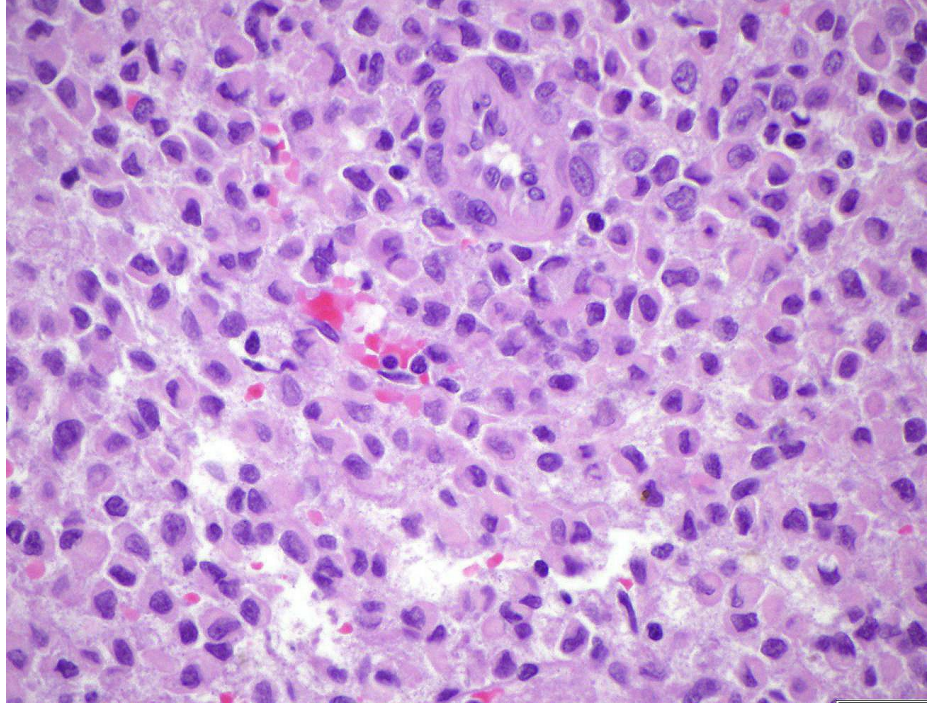
- Mesenchymal tumor composed of perivascular epithelioid cells (PECs) that express melanocytic and smooth muscle markers
- Uterine corpus > cervix > vagina > ovary > broad ligament
- Wide age range and clinical presentation non-specific
- Most sporadic but ~10% associated with tuberous sclerosis
- Potential treatment with mTOR inhibitors

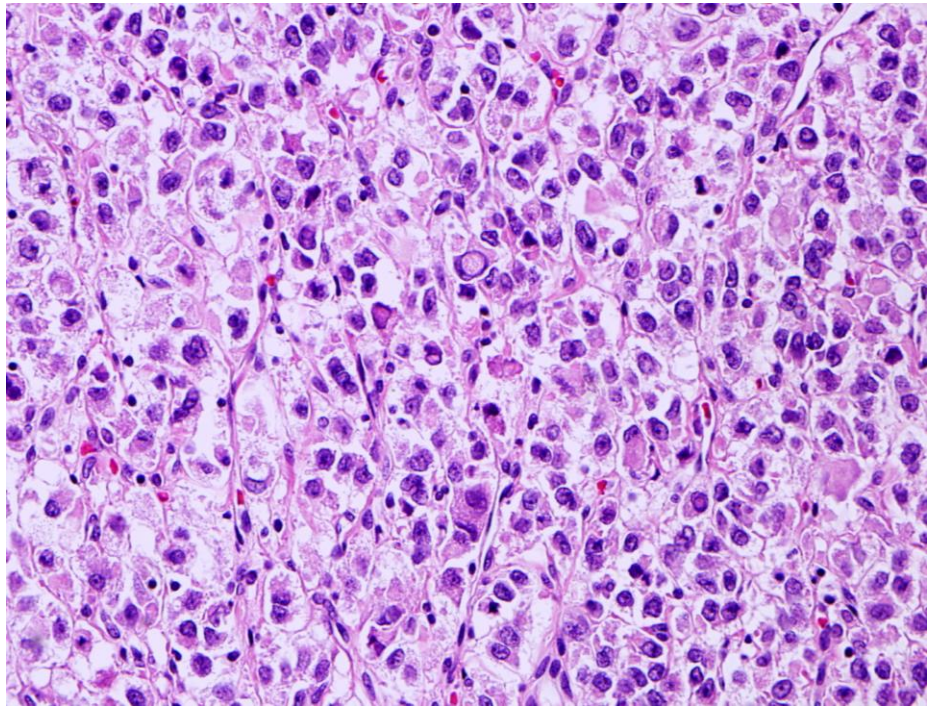




PECOMA

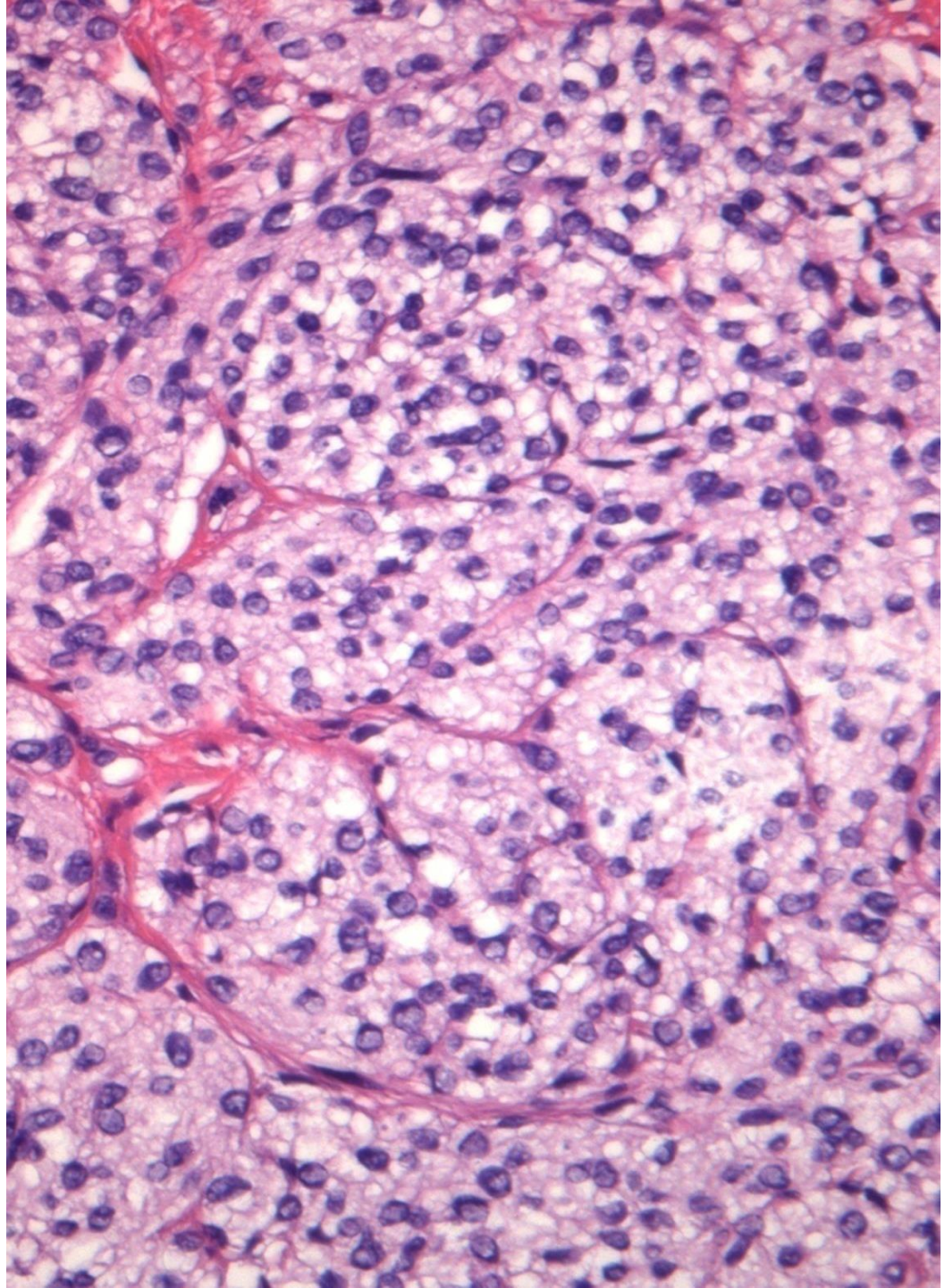


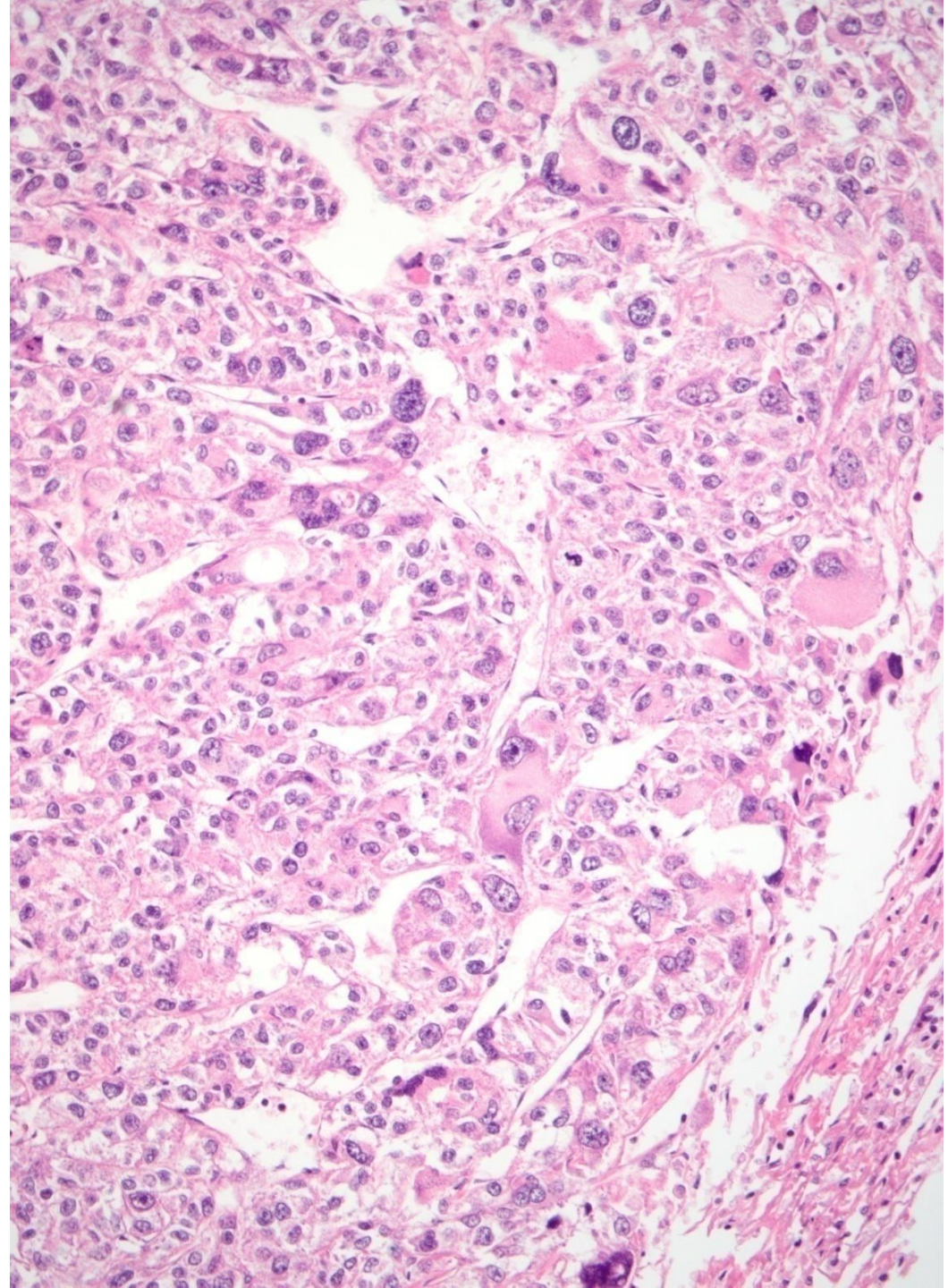
Epithelioid >>>> Spindle

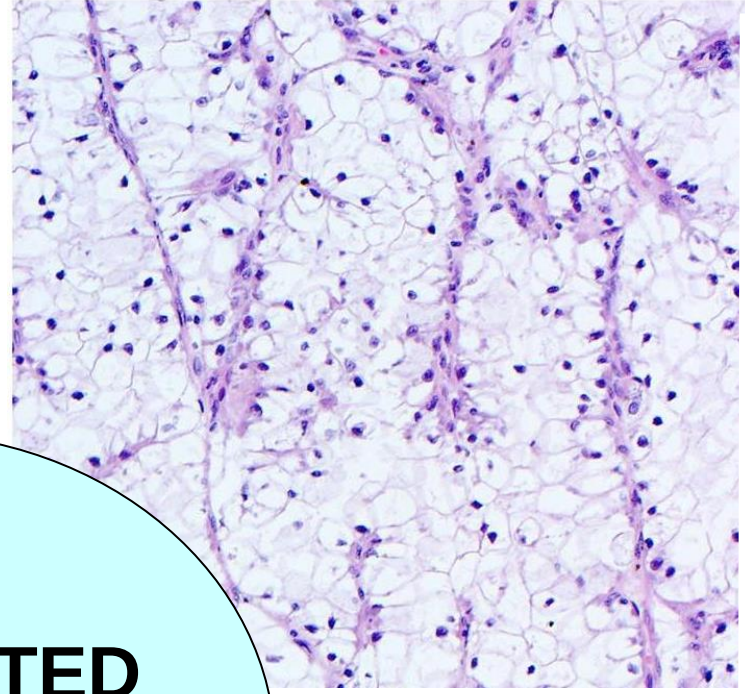


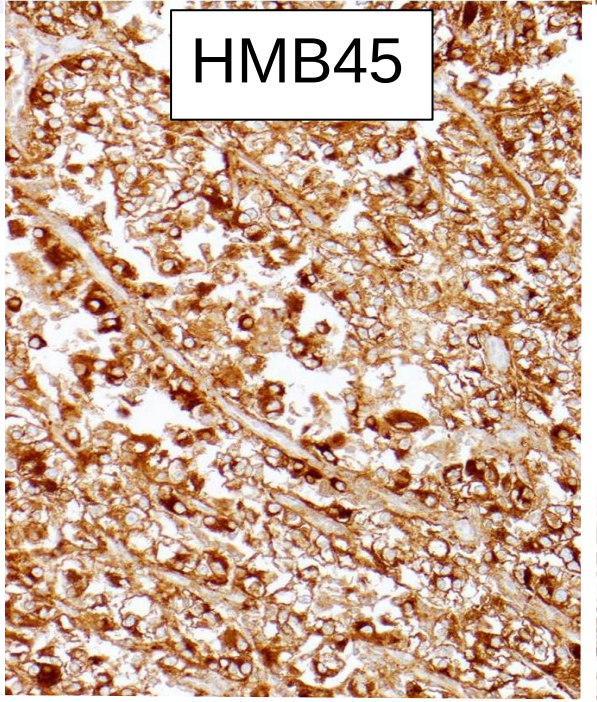


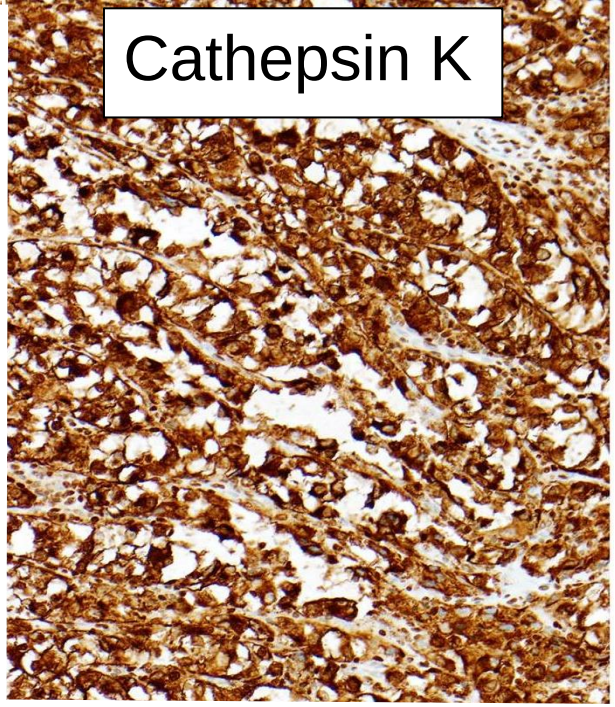
PEComa: CYTOLOGY



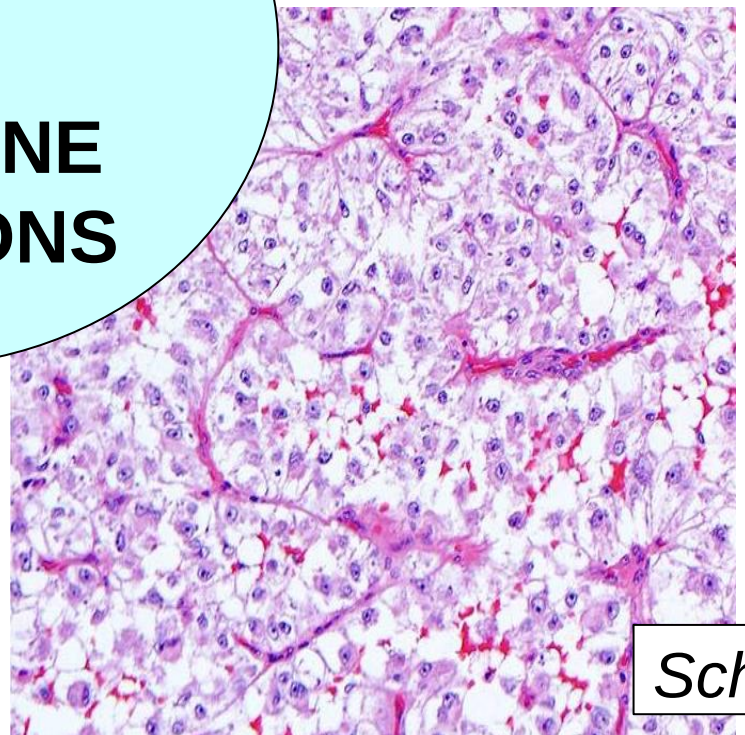


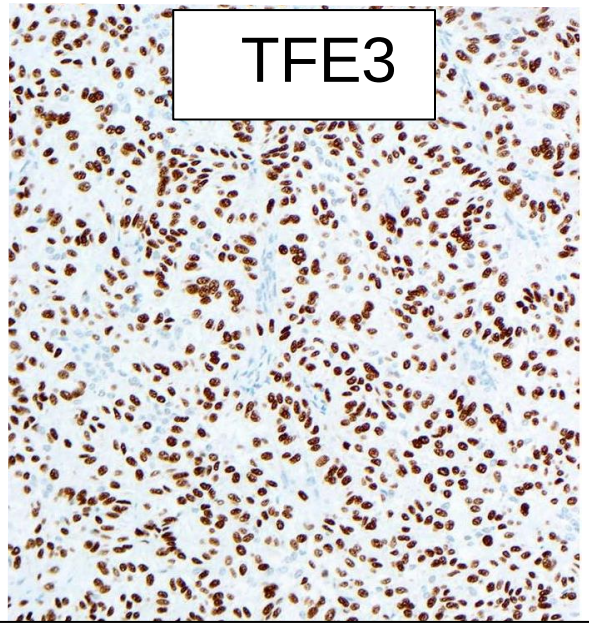


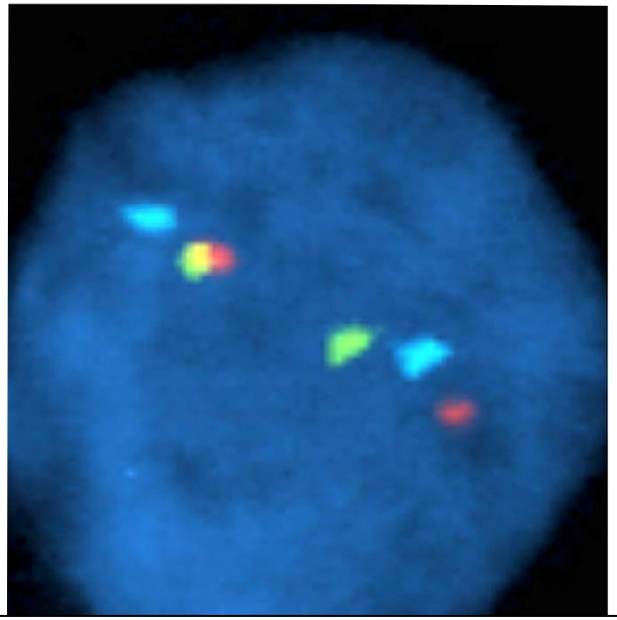




NOT ASSOCIATED WITH *TSC* GENE MUTATIONS







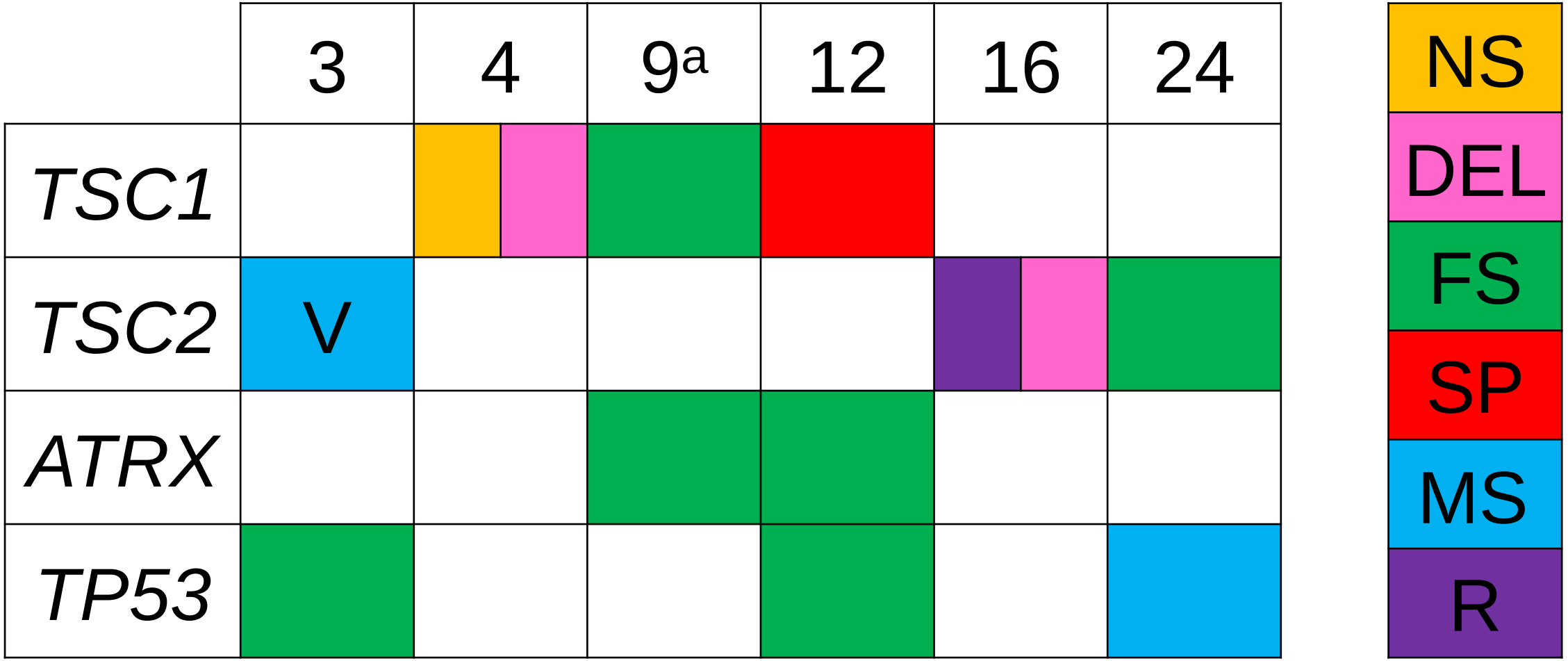
Schoolmeester JK, et al. Am J Surg Pathol 2015

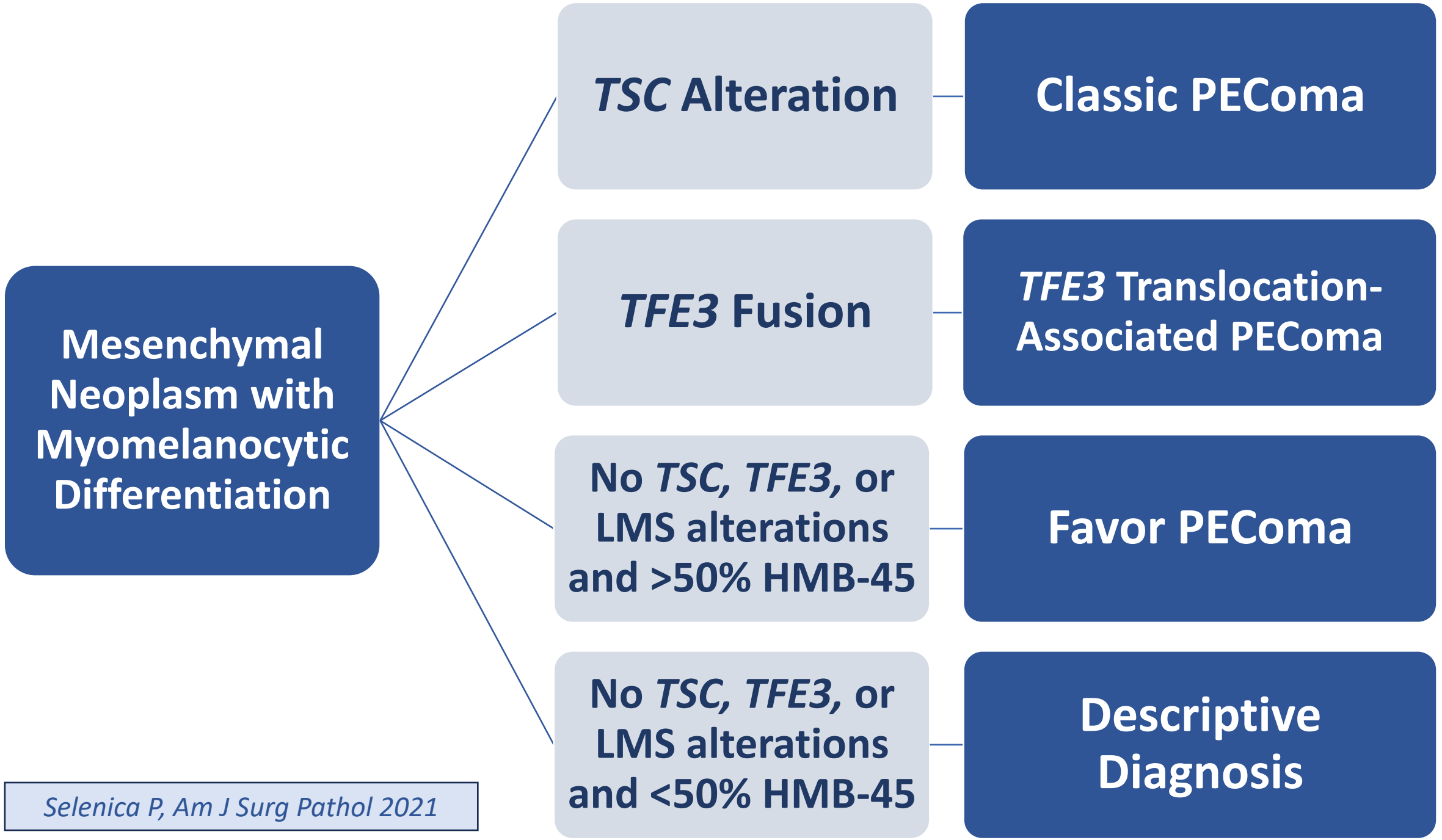
- **HMB45**: Variably expressed in 99% of PEComas
- **Melan-A**: Often focal and less extensive than HMB45
- MiTF: Not very reliable marker and non-specific
- Smooth muscle markers: Always positive at least for one
  - Smooth muscle actin (~90%) > desmin > caldesmon
  - More often positive in spindle areas
- Cathepsin K: Often strongly and diffusely positive
- PNL2: Variable cytoplasmic positivity
- **TFE3**: Positive in only tumors with fusion
- ER/PR: May be positive
- AE1/3, s100, and CD10: Rarely positive
- PAX8: Negative

TSC1/2 **alterations common**

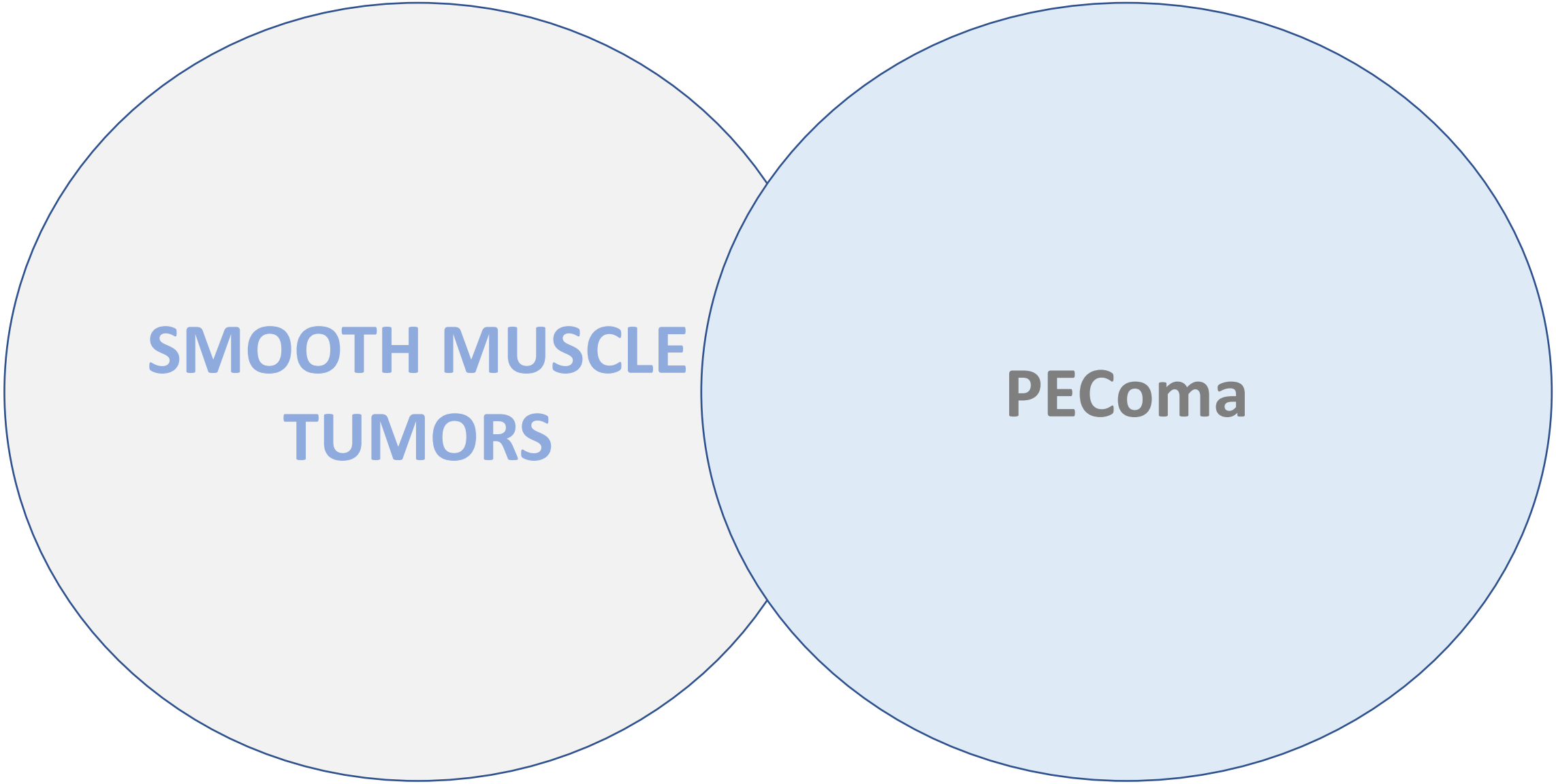
	WHO 2013	WHO 2020
Benign		< 3 features: ≥ 5 cm, high-grade atypia, >1 mitoses/50 HPFs, necrosis, LVI
Uncertain malignant behavior	Nuclear pleomorphism /multinucleated giant cells or >5 cm	
Malignant	≥ 2 features: >5 cm, infiltration, high-grade atypia, >1 mitoses/50 HPFs, necrosis, vascular invasion	≥ 3 features

Malignant PEComas Often Harbor *TP53* and/or *ATRX* Mutations





Selenica P, Am J Surg Pathol 2021


SMOOTH MUSCLE TUMORS
PEComa

A Clinicopathologic and Molecular Characterization of Uterine Sarcomas Classified as Malignant PEComa

William J. Anderson, MBChB, Fei Dong, MD, Christopher D.M. Fletcher, MD, Michelle S. Hirsch, MD, PhD, and Marisa R. Nucci, MD

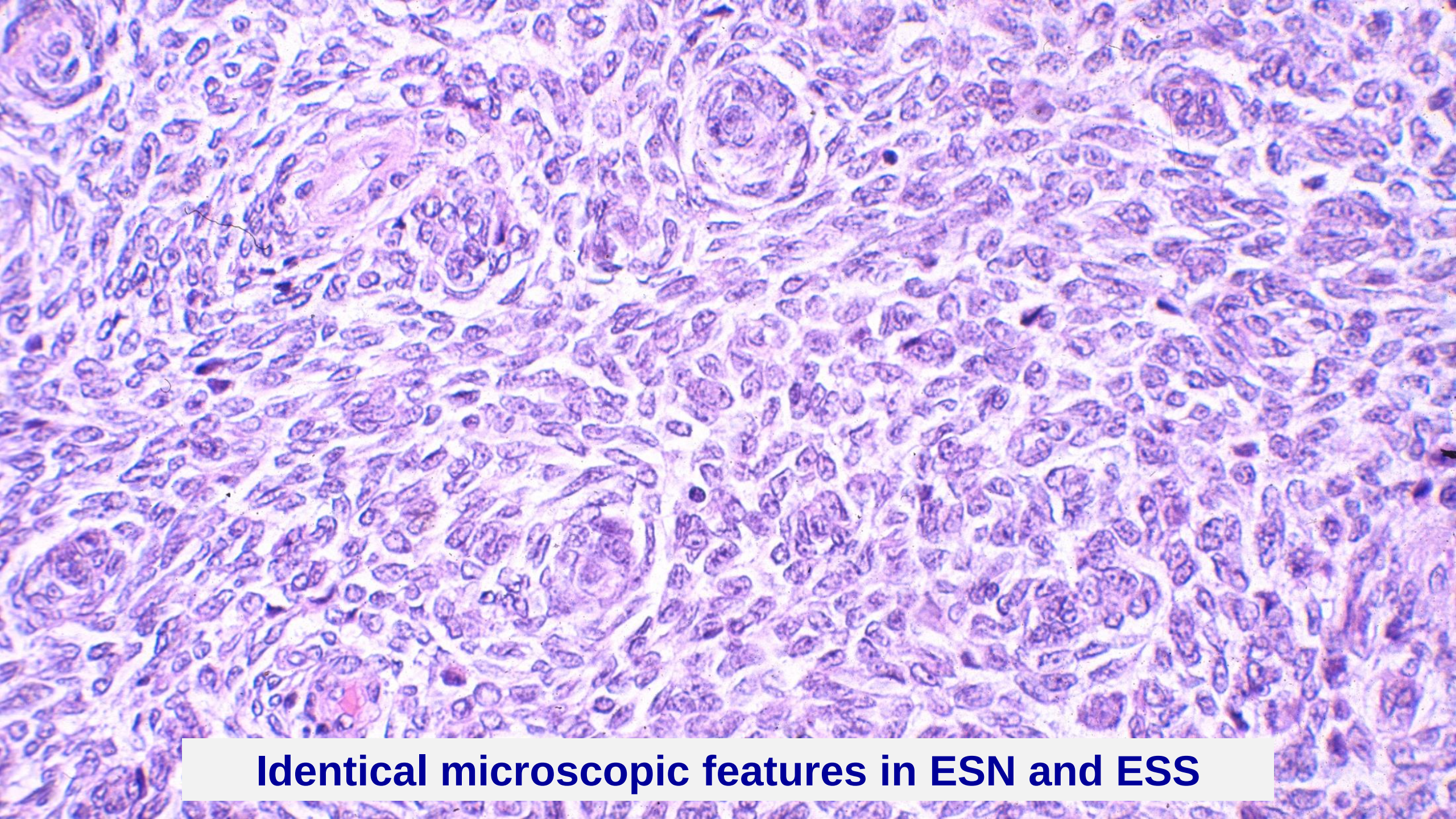
- 15 patients
- Mutually exclusive variants in TSC1 (27%) and TSC2 (20%)
- Recurrent alterations also identified in TP53 (53%), RB1 (30%), ATRX (33%), and BRCA2 (13%)
- Important role of targeted sequencing in tumors with focal melanocytic marker expression

Am J Surg Pathol 2023

ENDOMETRIAL STROMAL TUMORS
Classification

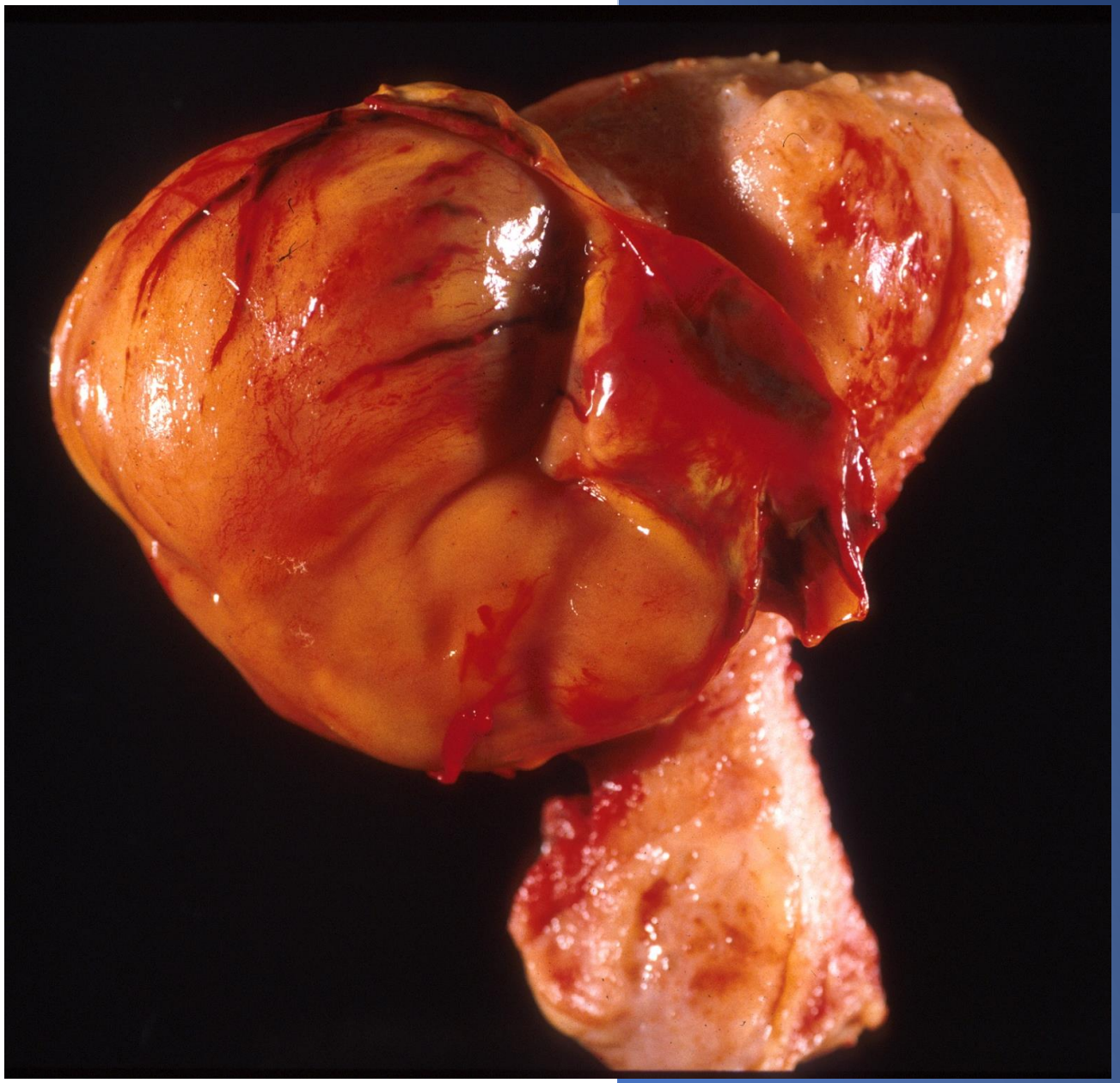
- **Endometrial Stromal Nodule**
- **Low-Grade Endometrial Stromal Sarcoma**
- **High-Grade Endometrial Stromal Sarcoma**

- **Undifferentiated Uterine (includes stromal) Sarcoma**



Identical microscopic features in ESN and ESS

ENDOMETRIAL STROMAL NODULE

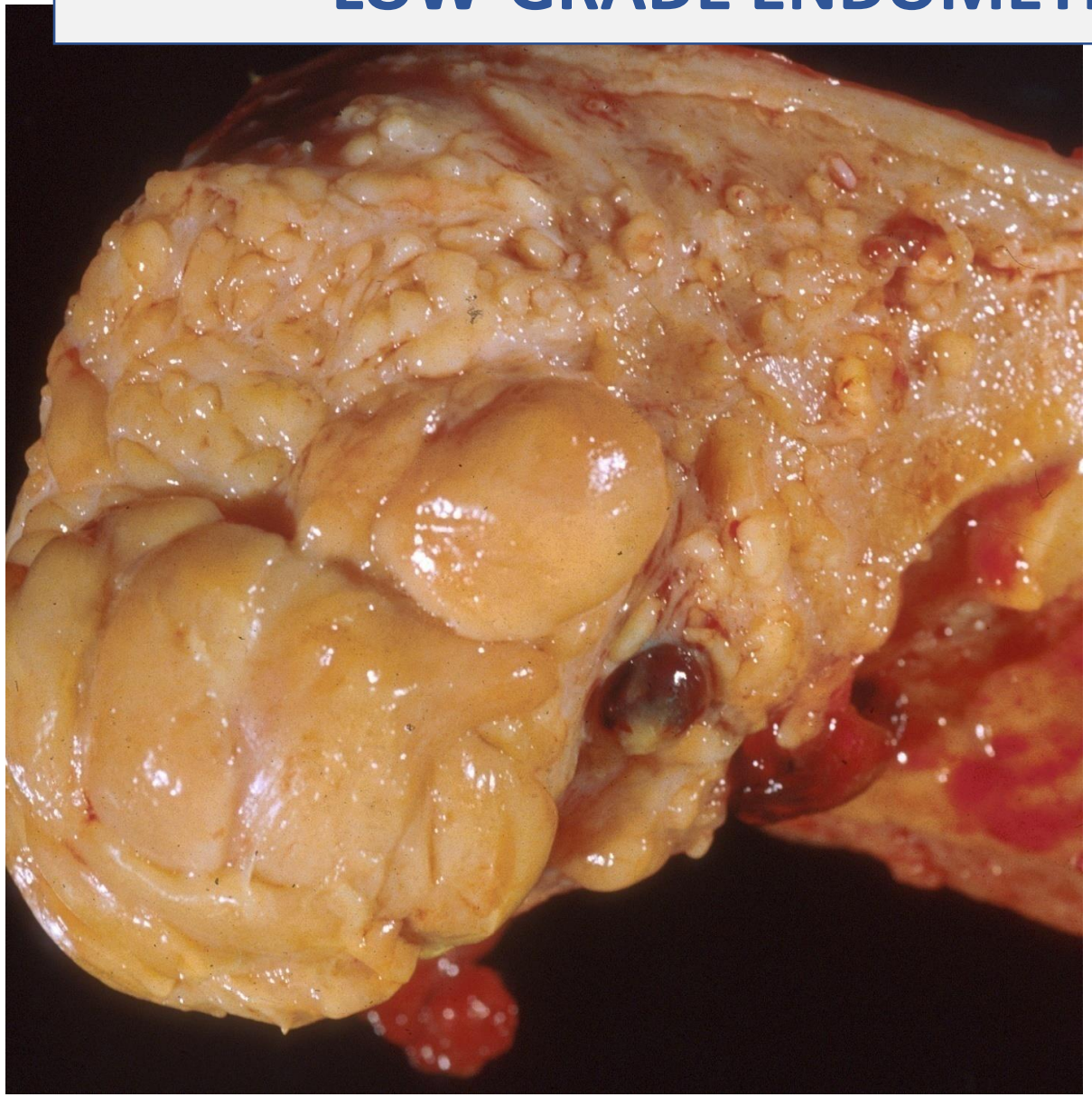


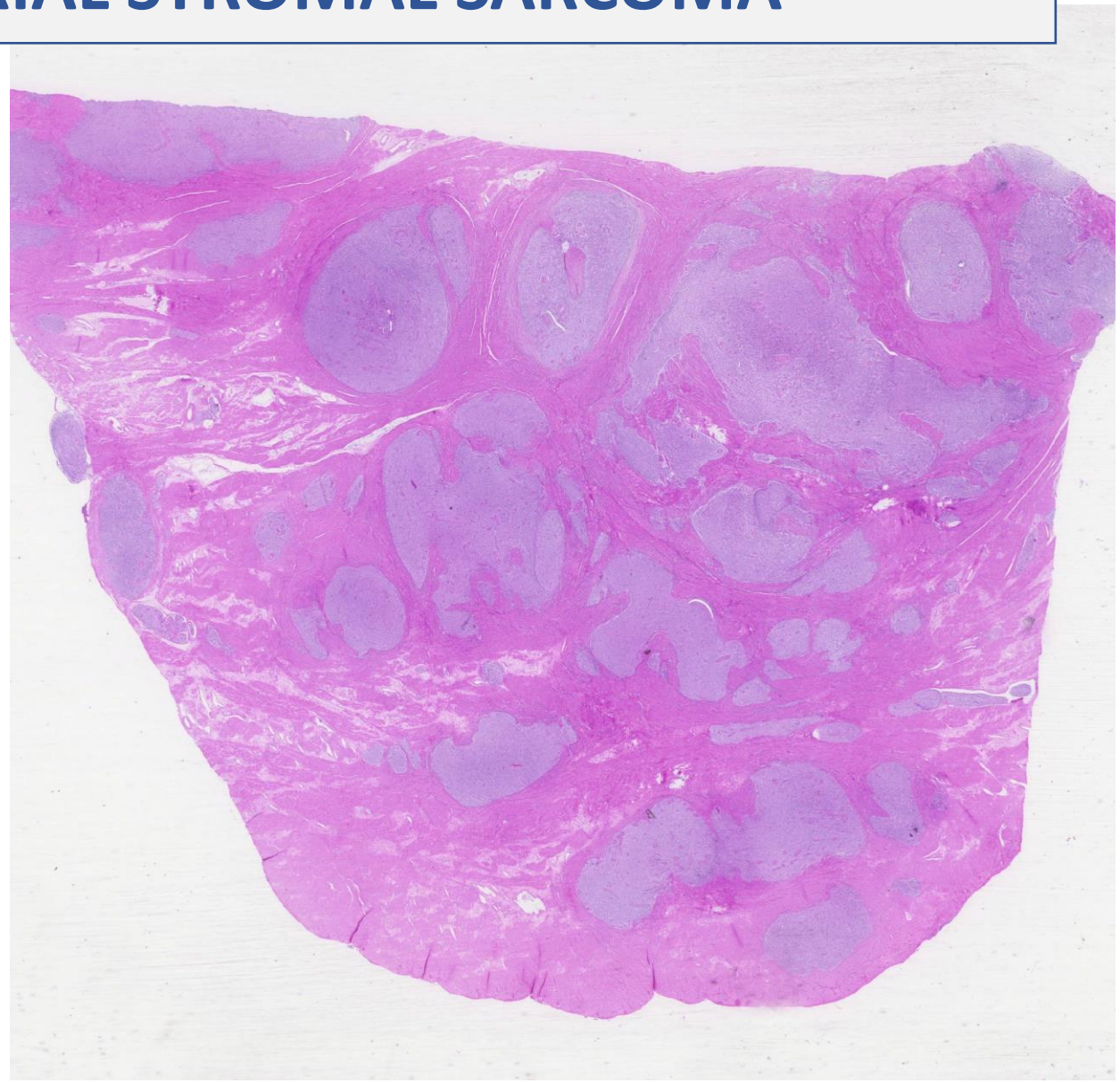
Well delineated, expansile margin on microscopic exam

Focal irregularities: lobulated or finger-like projections (< 3) into myometrium (≤ 3 mm) allowed

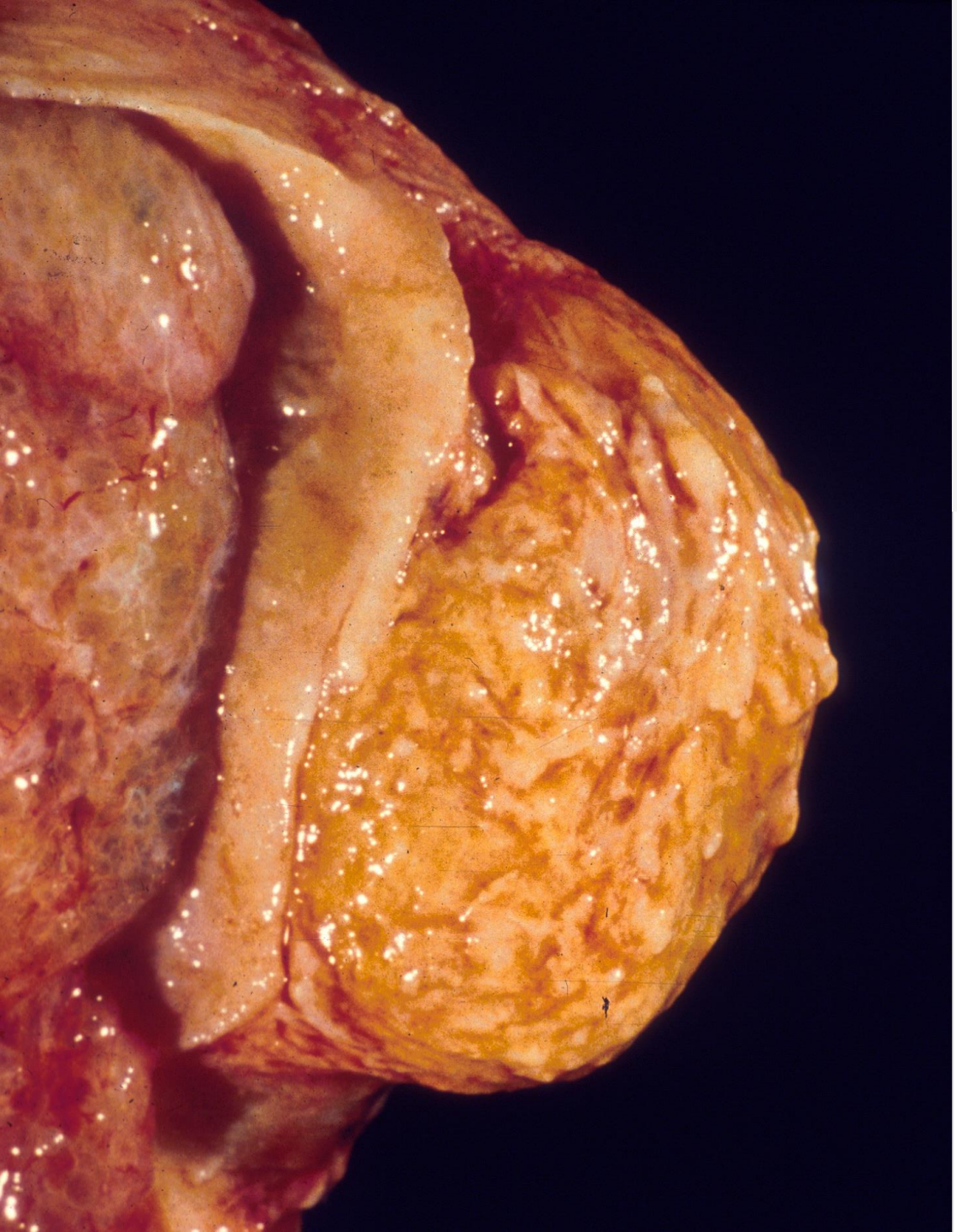
No vascular invasion

LOW-GRADE ENDOMETRIAL STROMAL SARCOMA





Permeative, not destructive, growth in myometrium



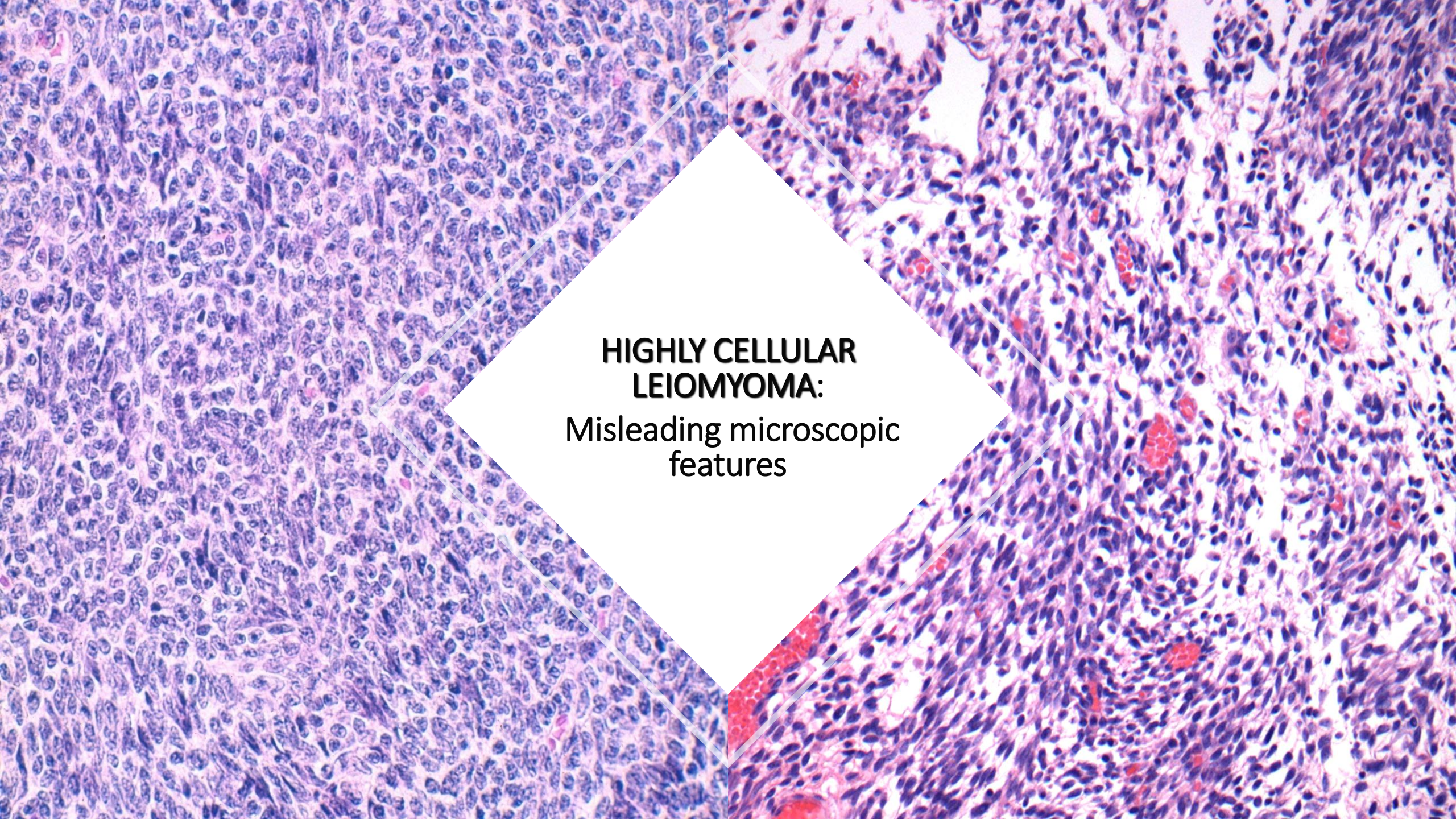
Highly Cellular Leiomyoma *vs* Endometrial Stromal Tumor

Shared features:

Dense cellularity

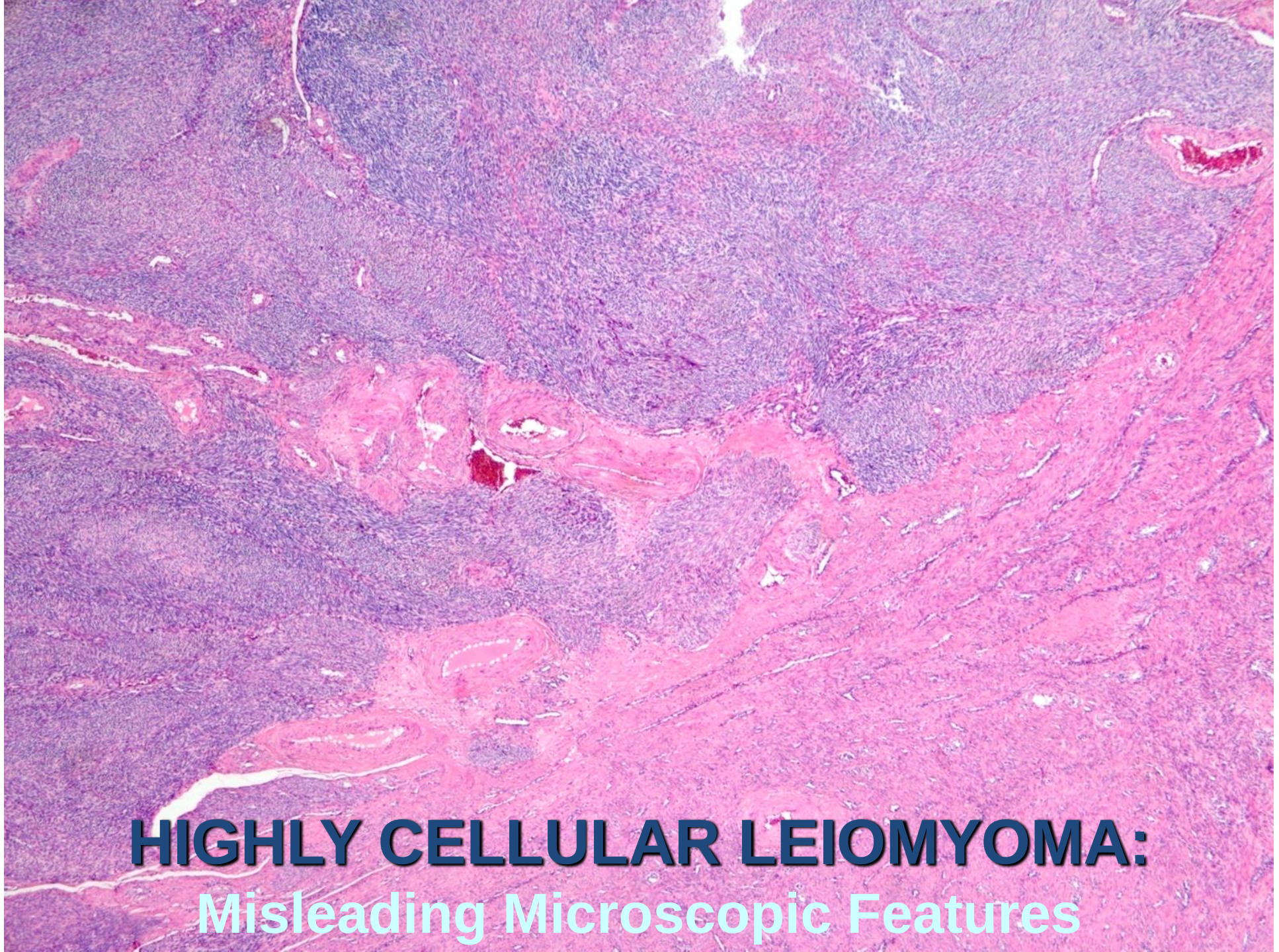
Prominent vascularity

Irregular margin



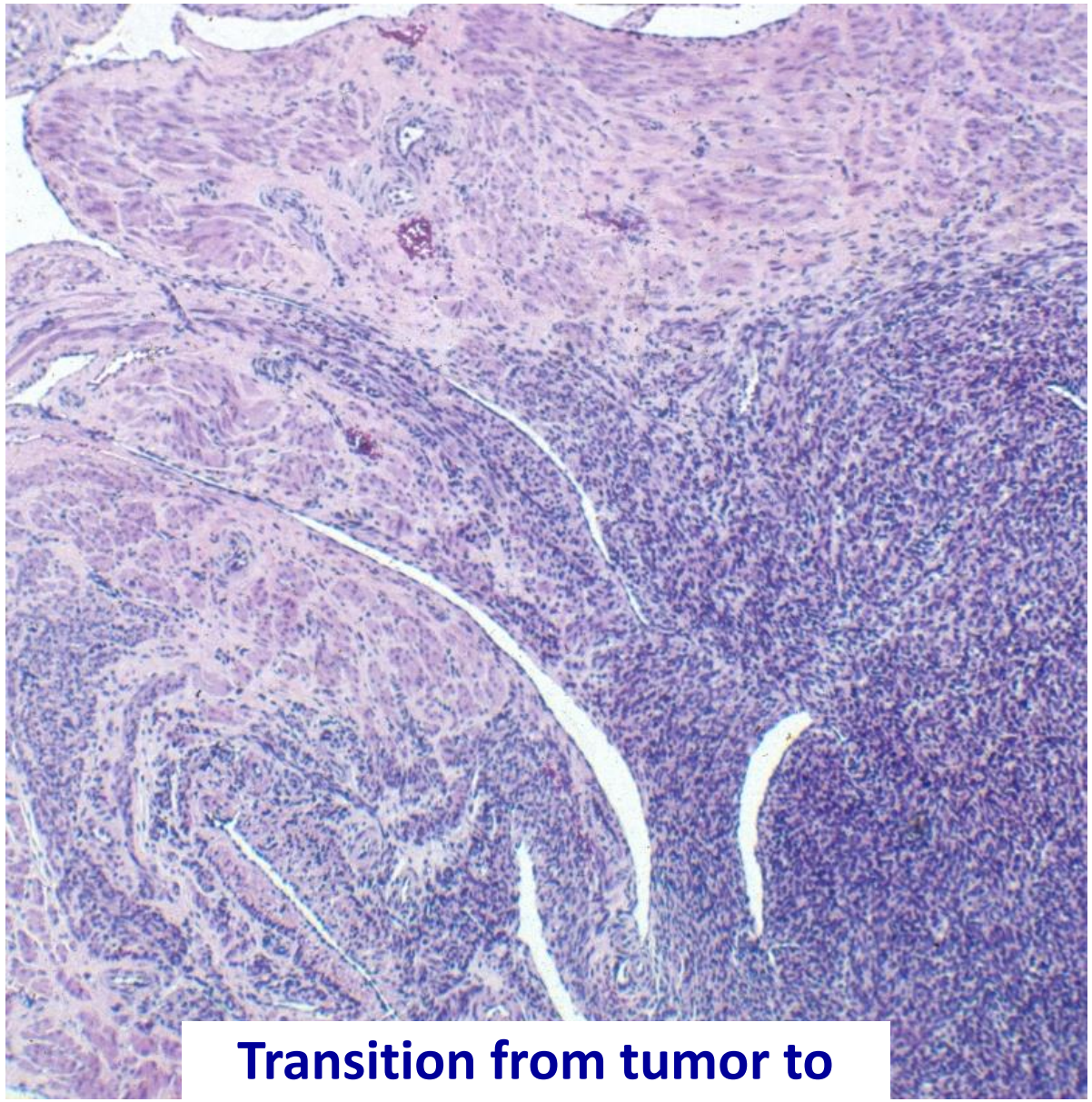
HIGHLY CELLULAR LEIOMYOMA:

Misleading microscopic features

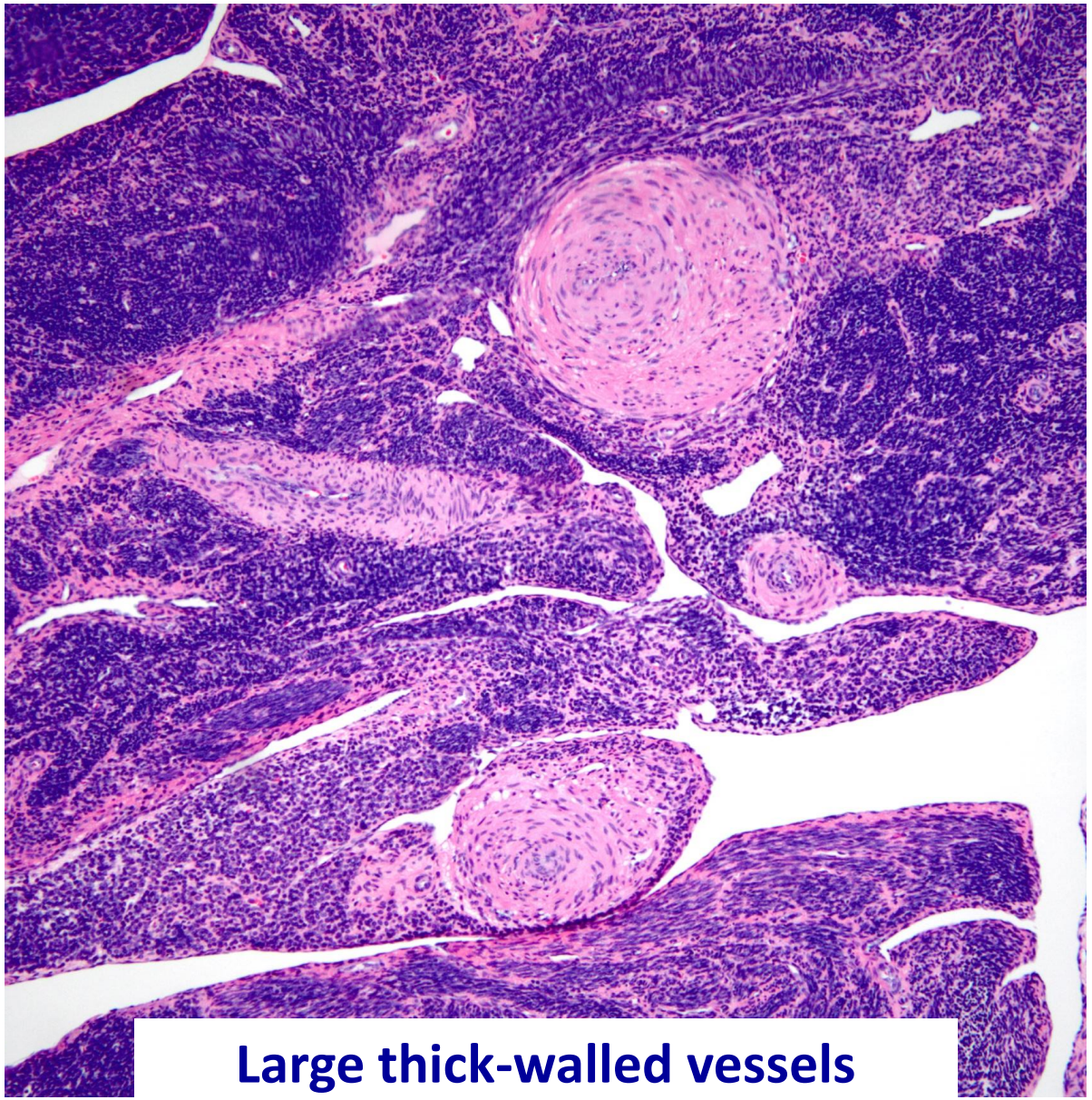


HIGHLY CELLULAR LEIOMYOMA:

Misleading Microscopic Features



Transition from tumor to surrounding myometrium



Large thick-walled vessels and cleft-like spaces

SMOOTH MUSCLE TUMOR *vs* ENDOMETRIAL STROMAL TUMOR

MOST HELPFUL PANEL:

CD10 + DESMIN + h-CALDESMON

Correlation with morphology is key

HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA

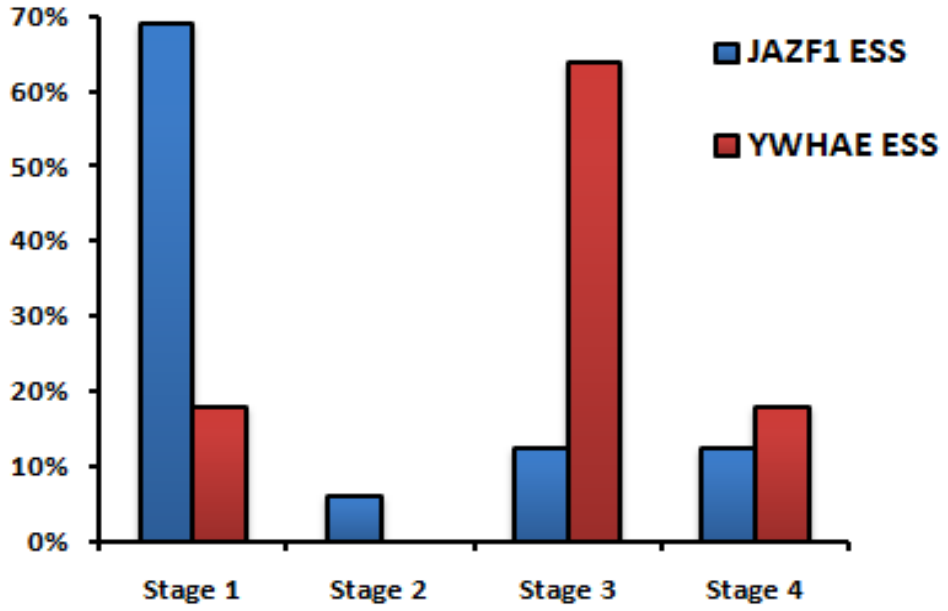
Definition:

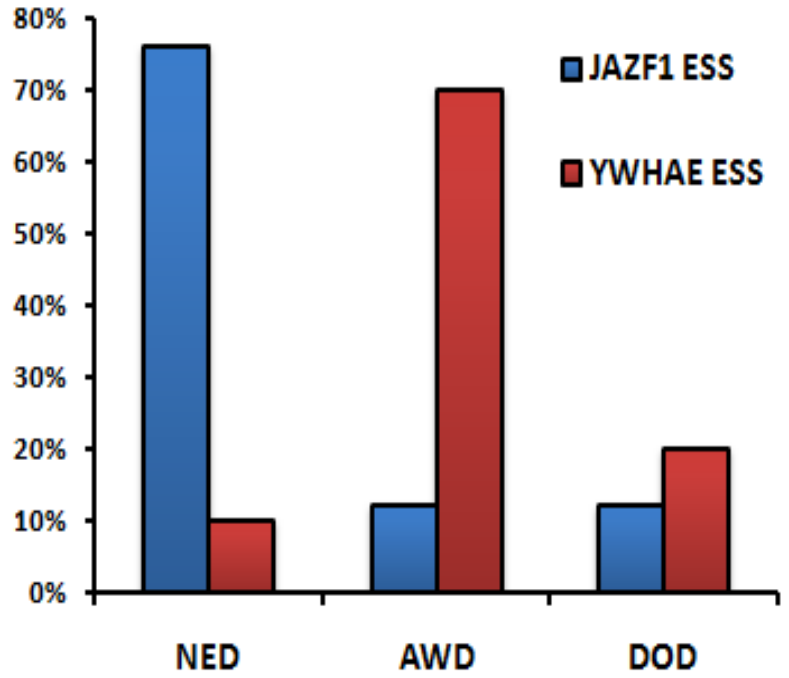
Tumor with morphologic features that differs from the "proliferative"-type morphology seen in typical endometrial stromal sarcomas although some are associated with a low-grade component

HIGH-GRADE YWHAE-FAM22 ENDOMETRIAL STROMAL SARCOMA

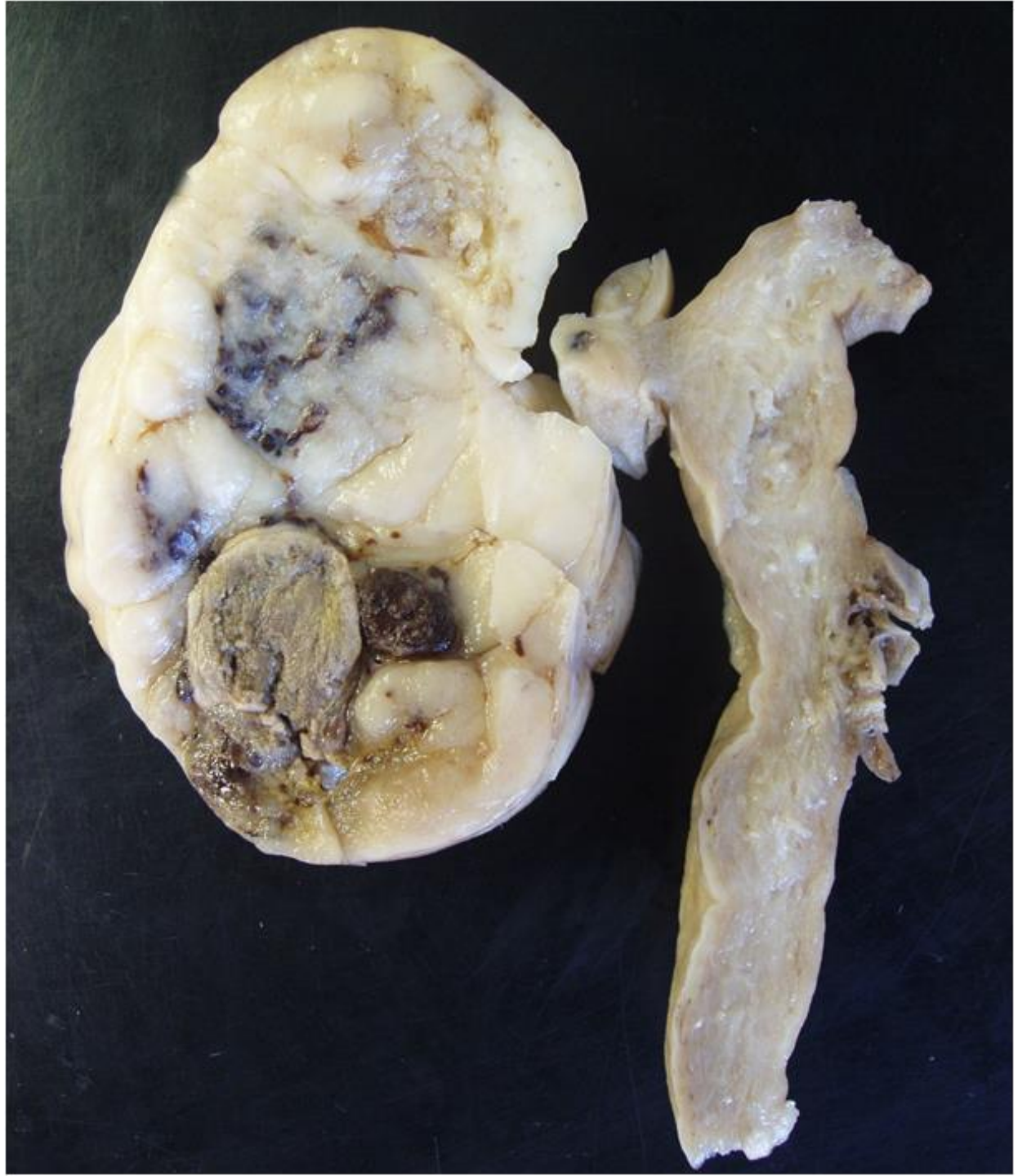
Clinical Features

Age at presentation: 28 to 67 years (median 50)

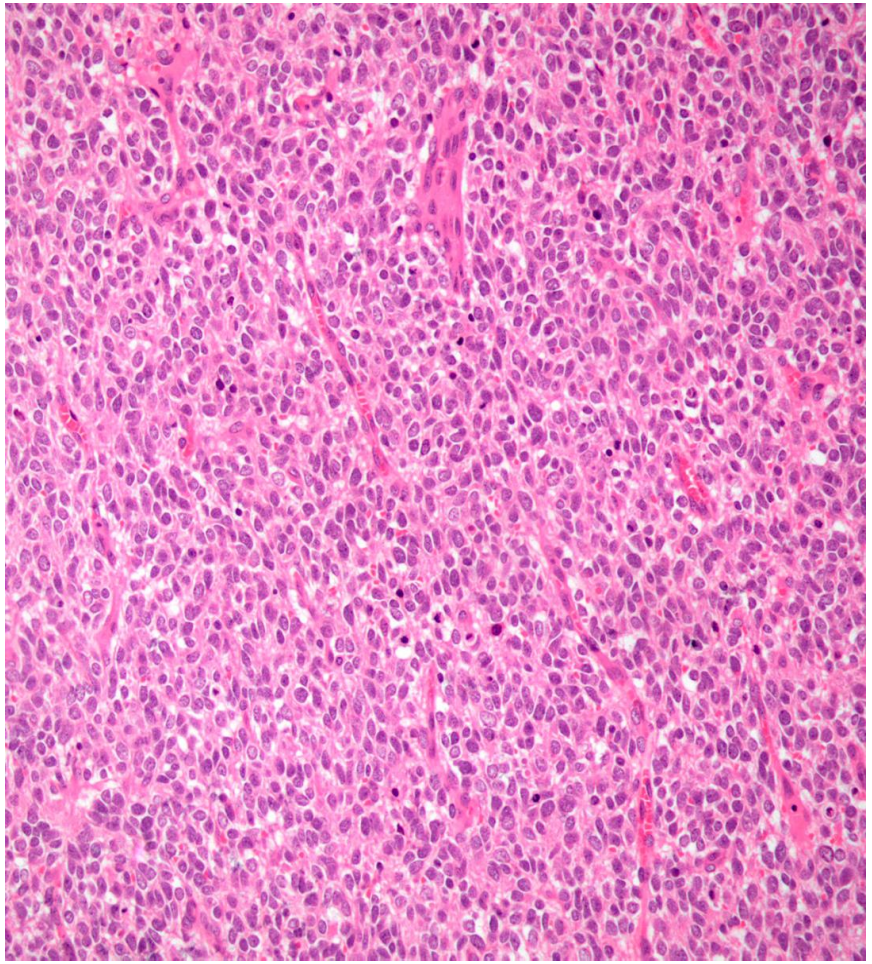
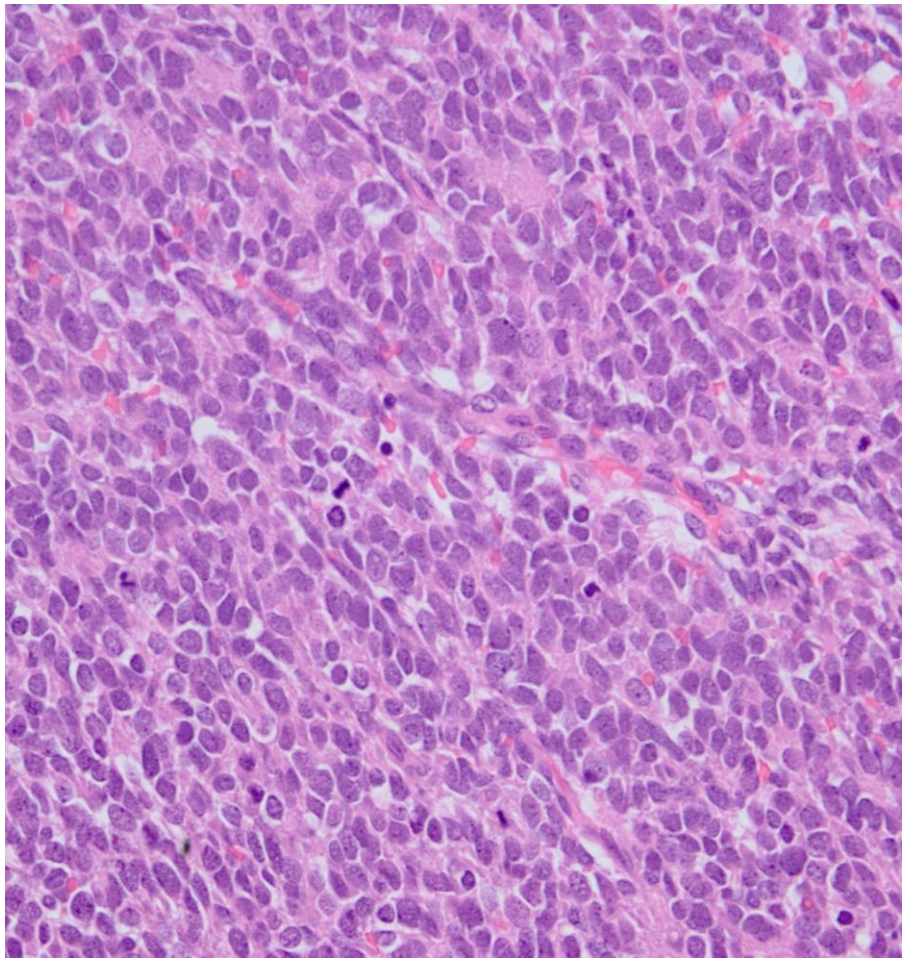
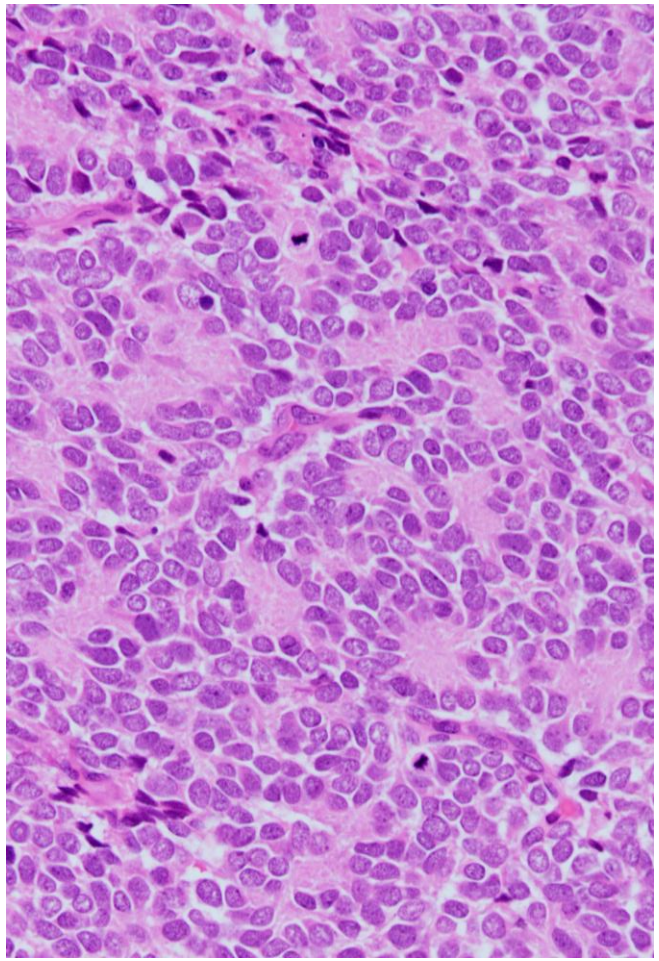




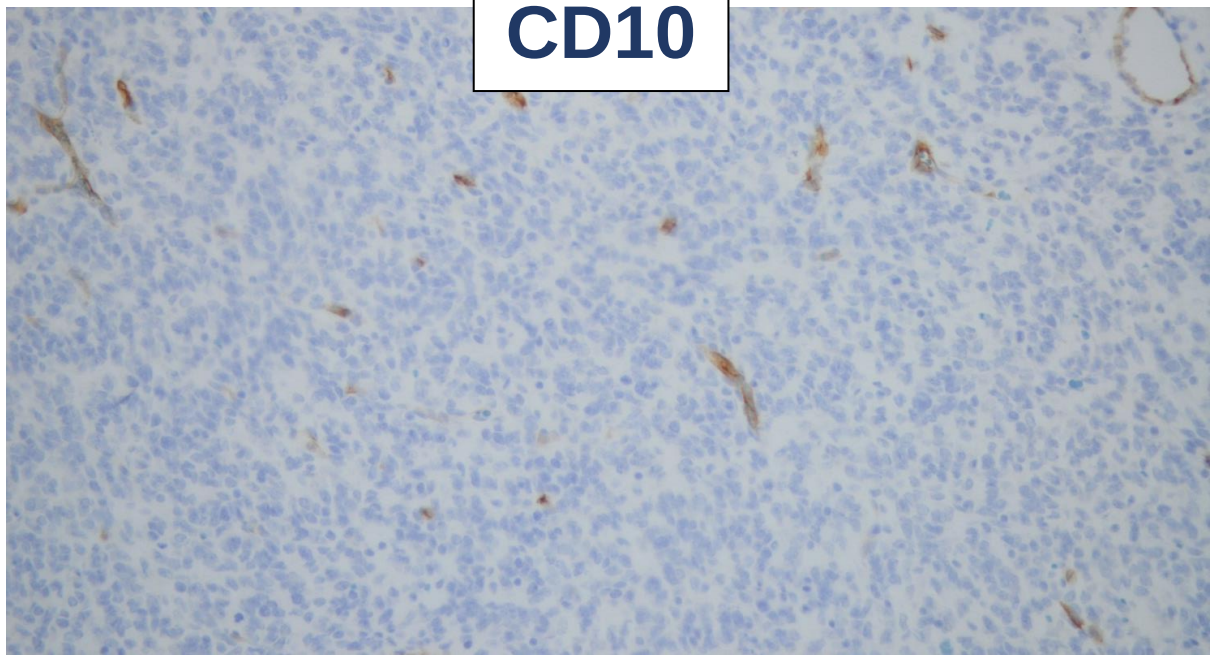
Cheng-Han Lee et al, Am J Surg Pathol 2012

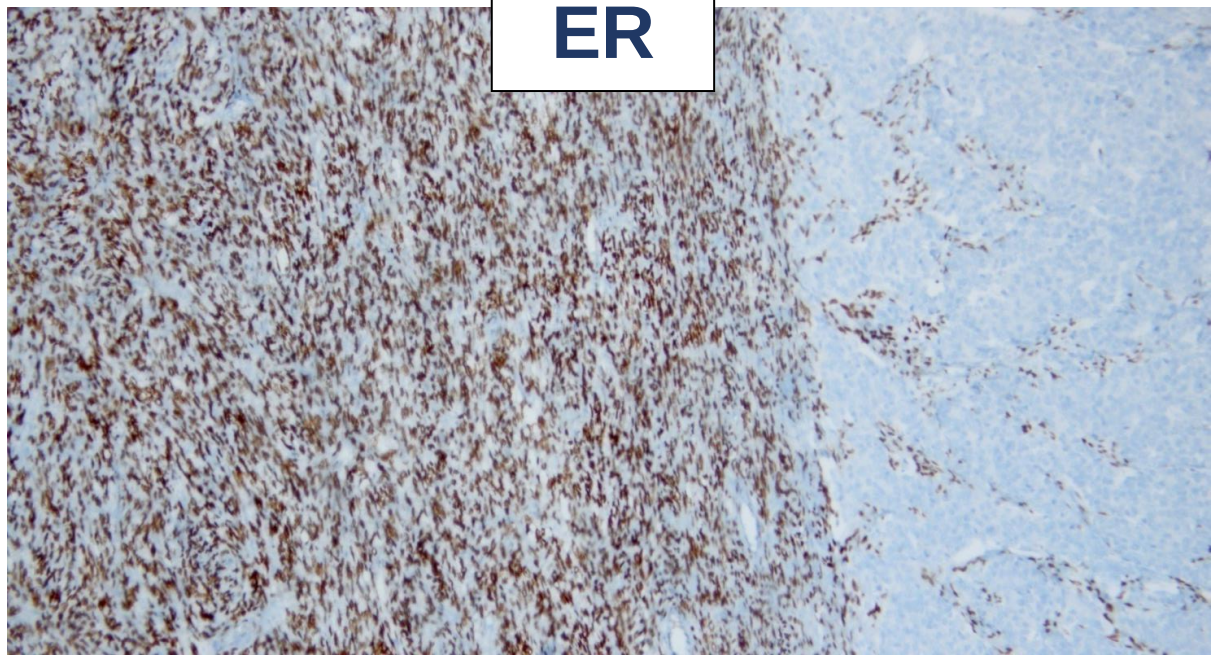


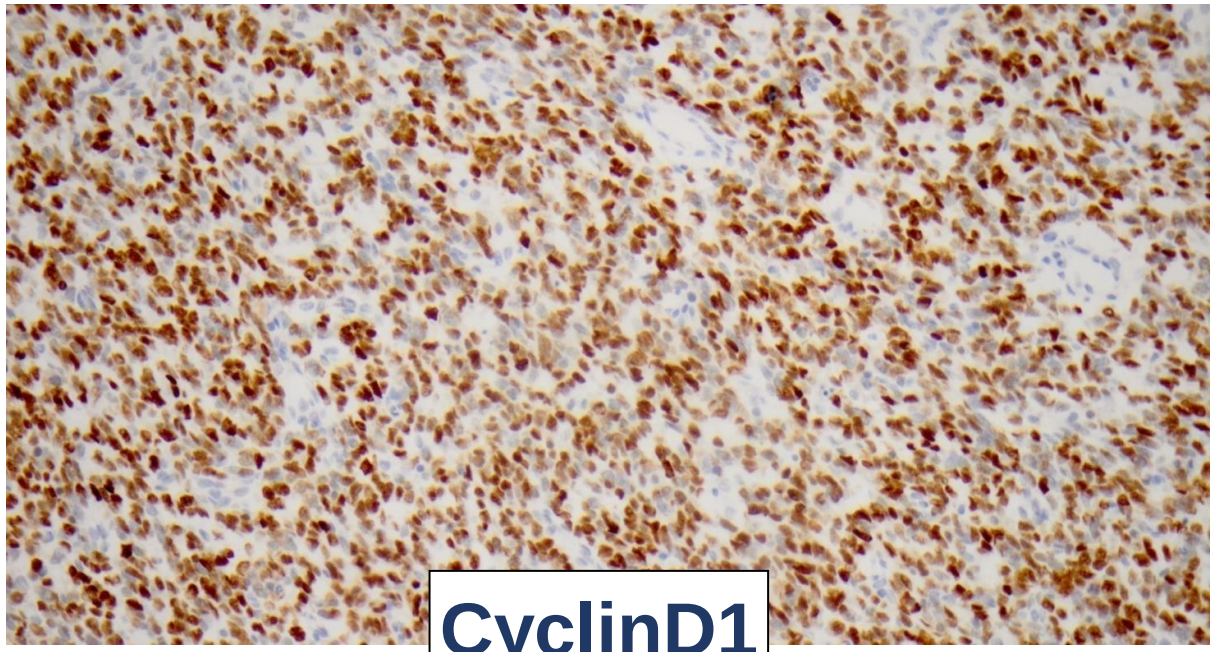
YWHAE-FAM22 High-Grade Endometrial Stromal Sarcoma *t(10,17)*

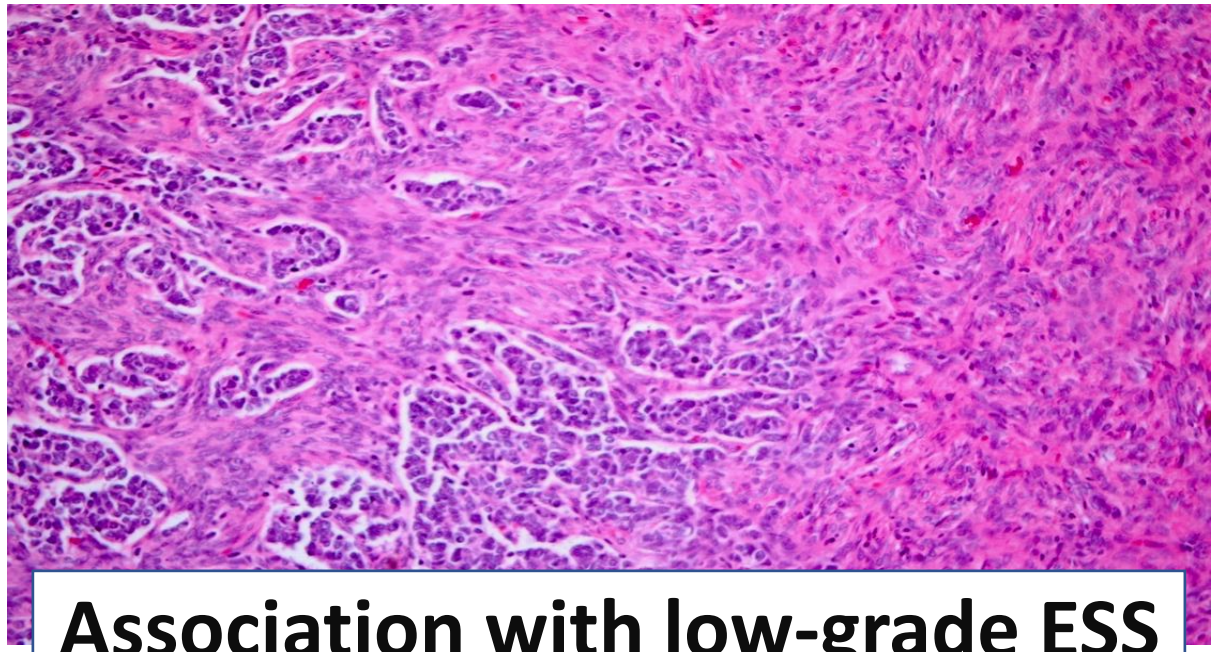




YWHAE-FAM22 HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA

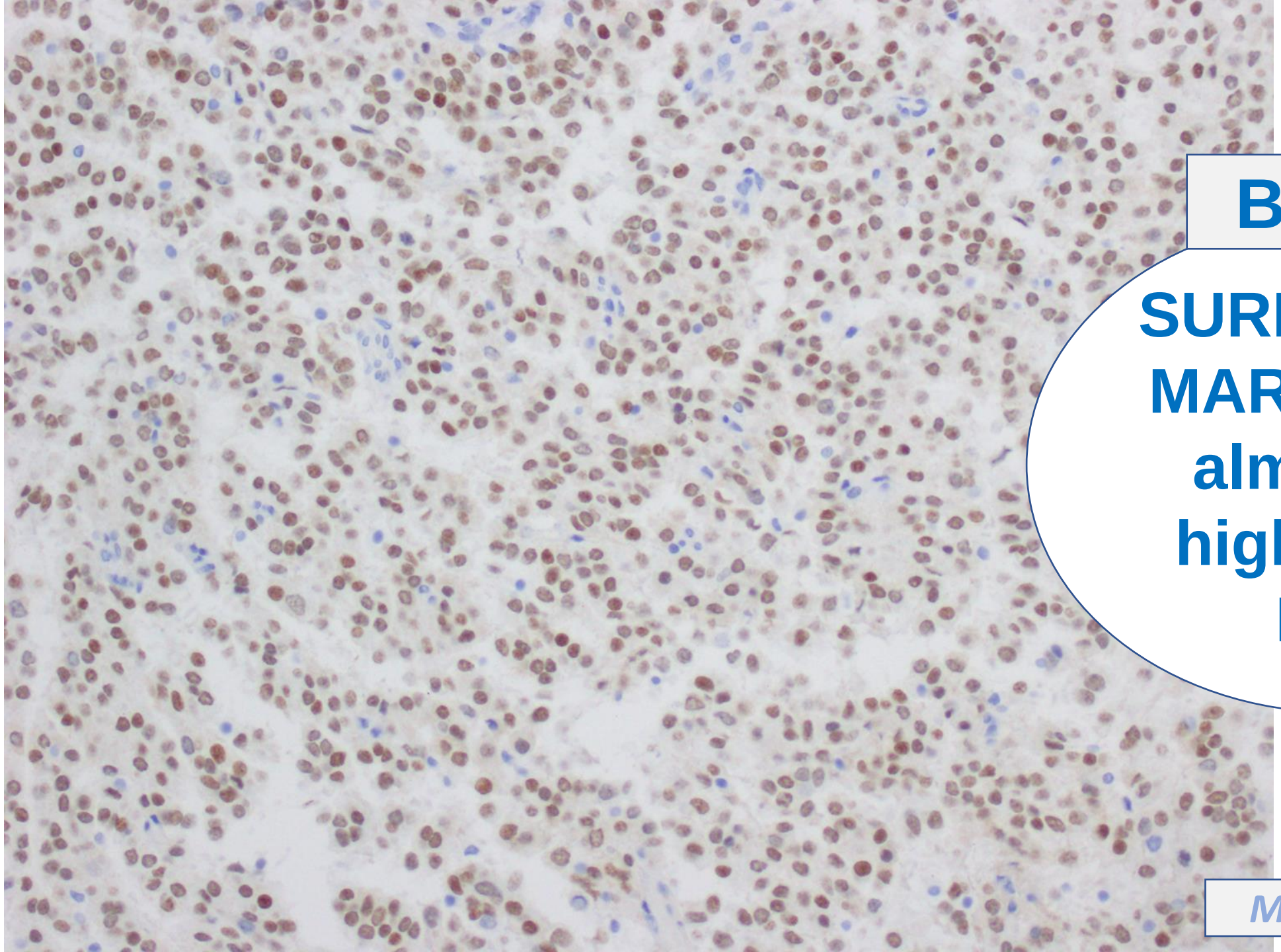








Association with low-grade ESS



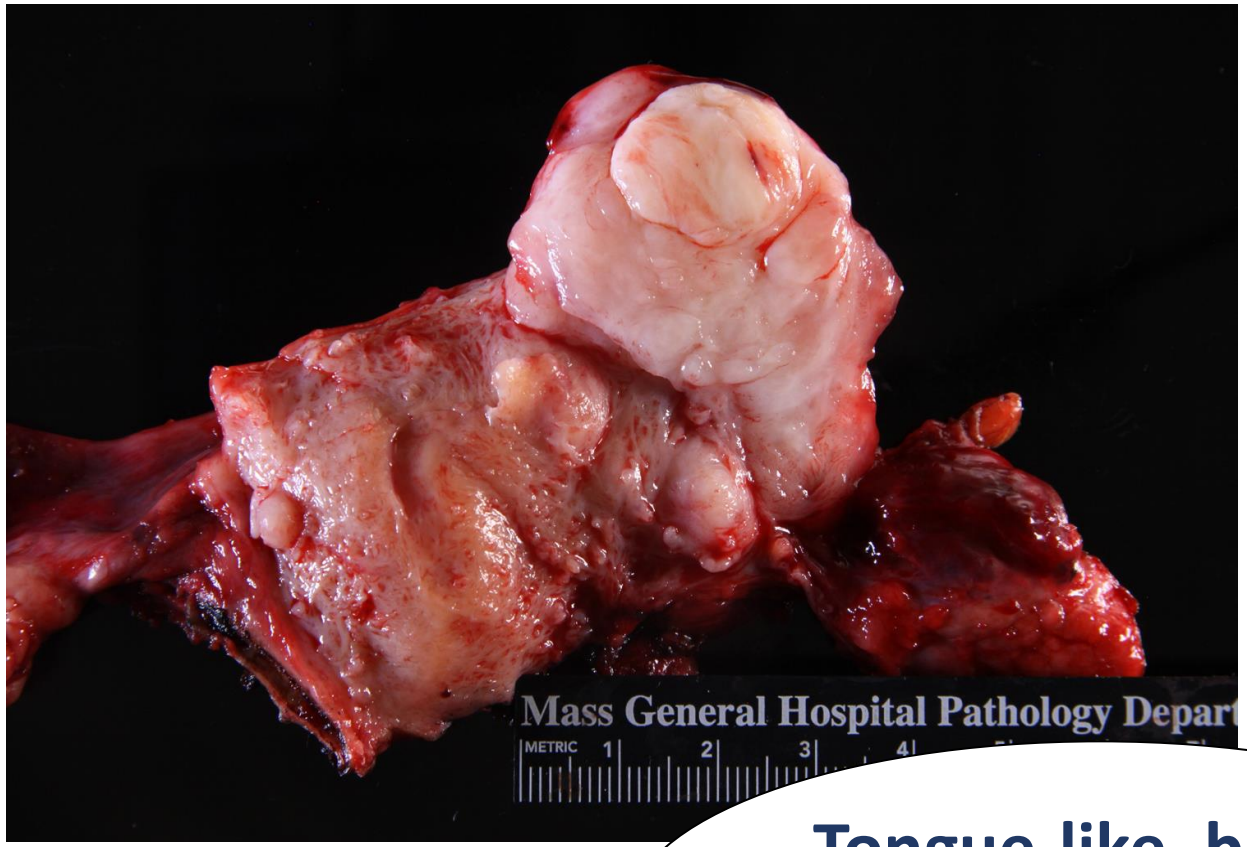
BCOR

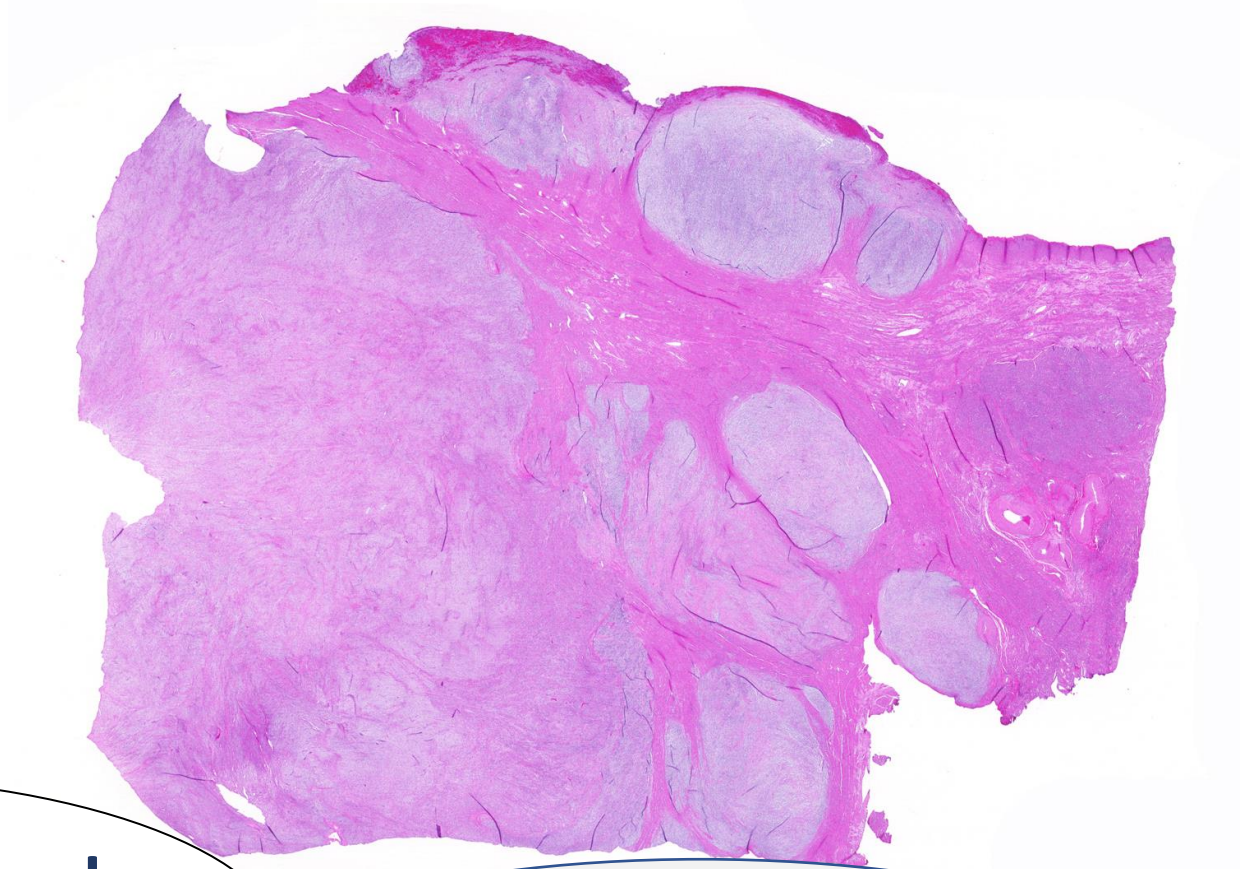
SURROGATE MARKER for almost all high-grade ESS

Modern Pathol 2017

ZC3H7B-BCOR HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA

Modern Pathol 2018

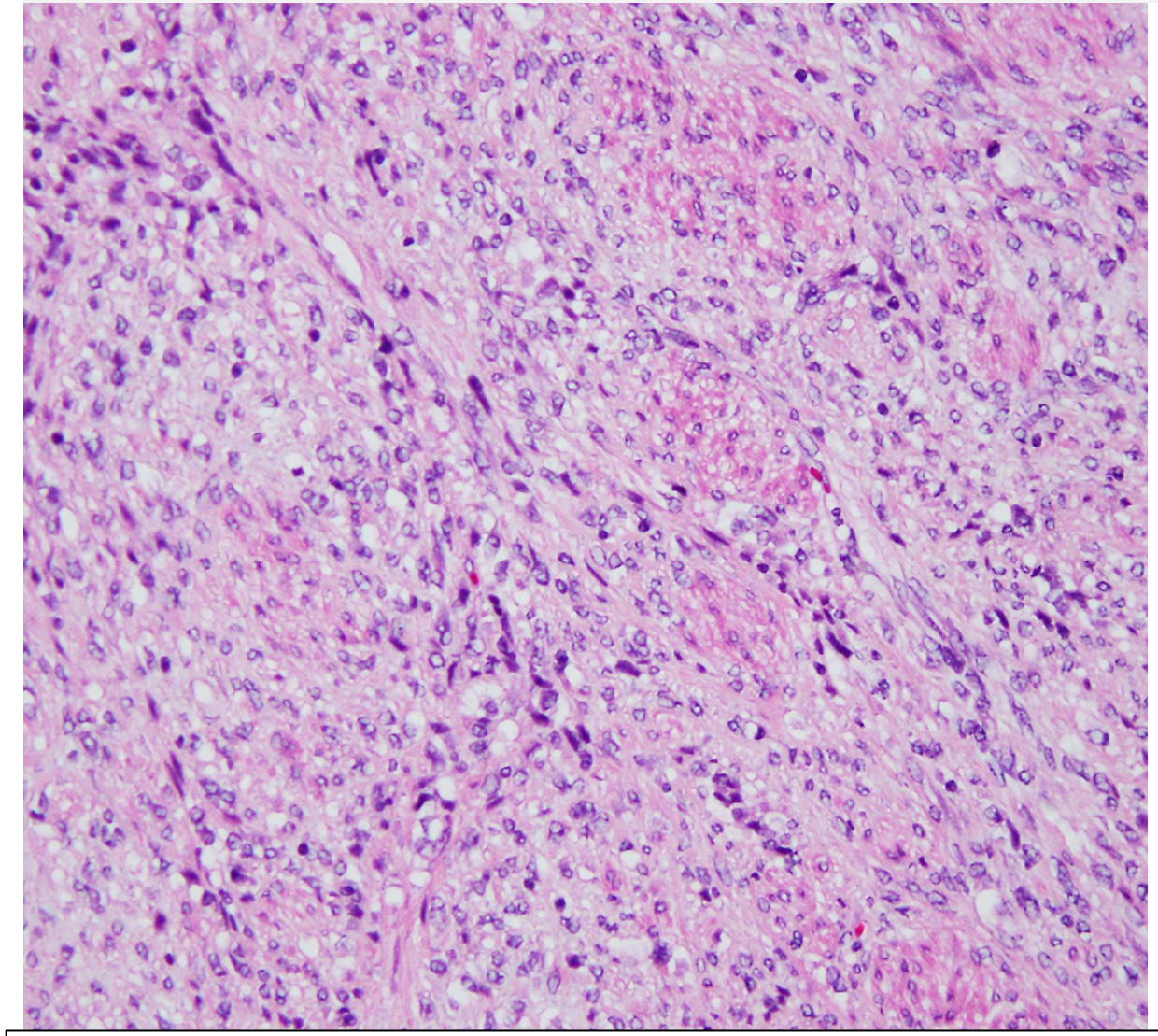


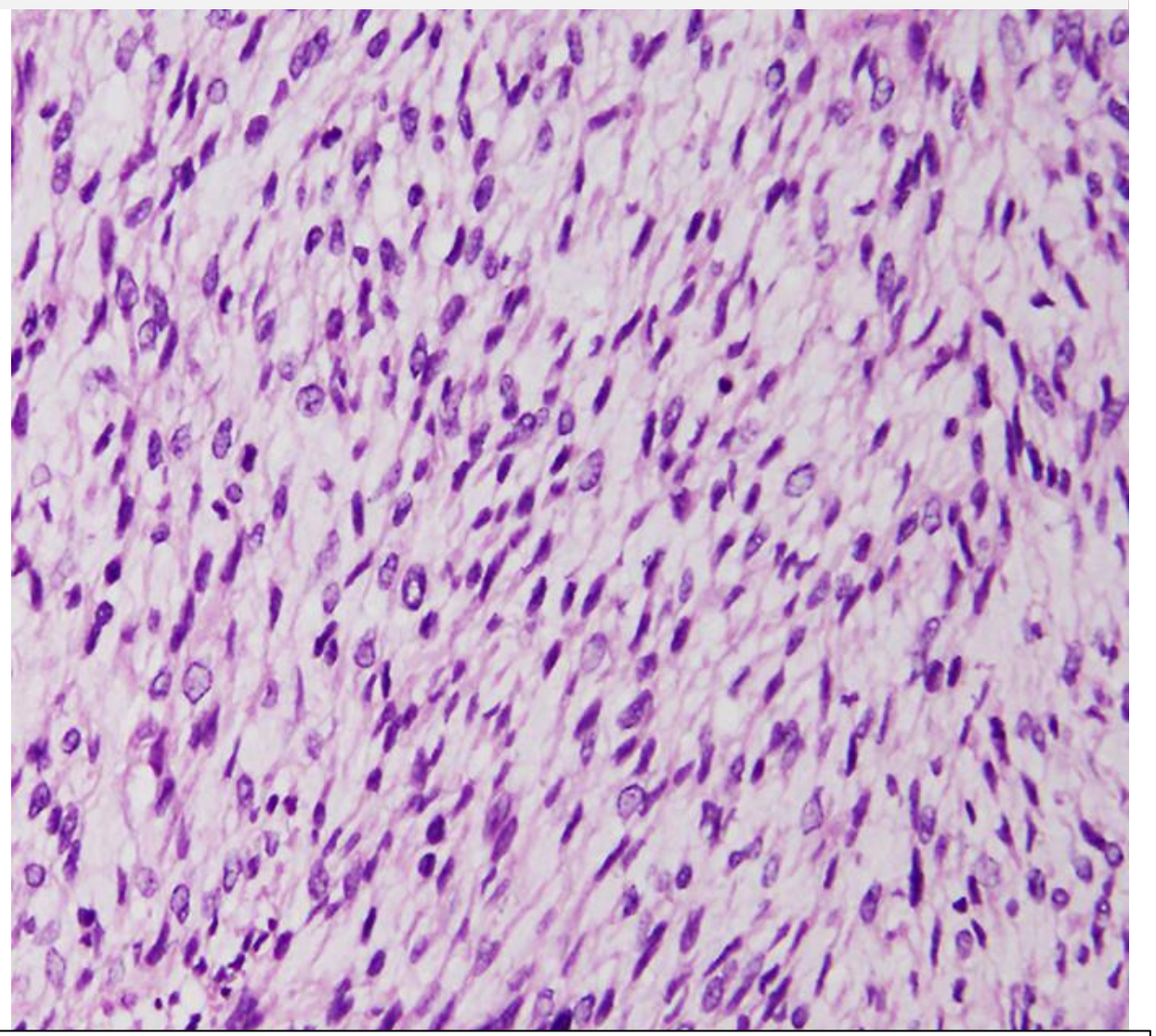


Tongue-like, broad front, or destructive

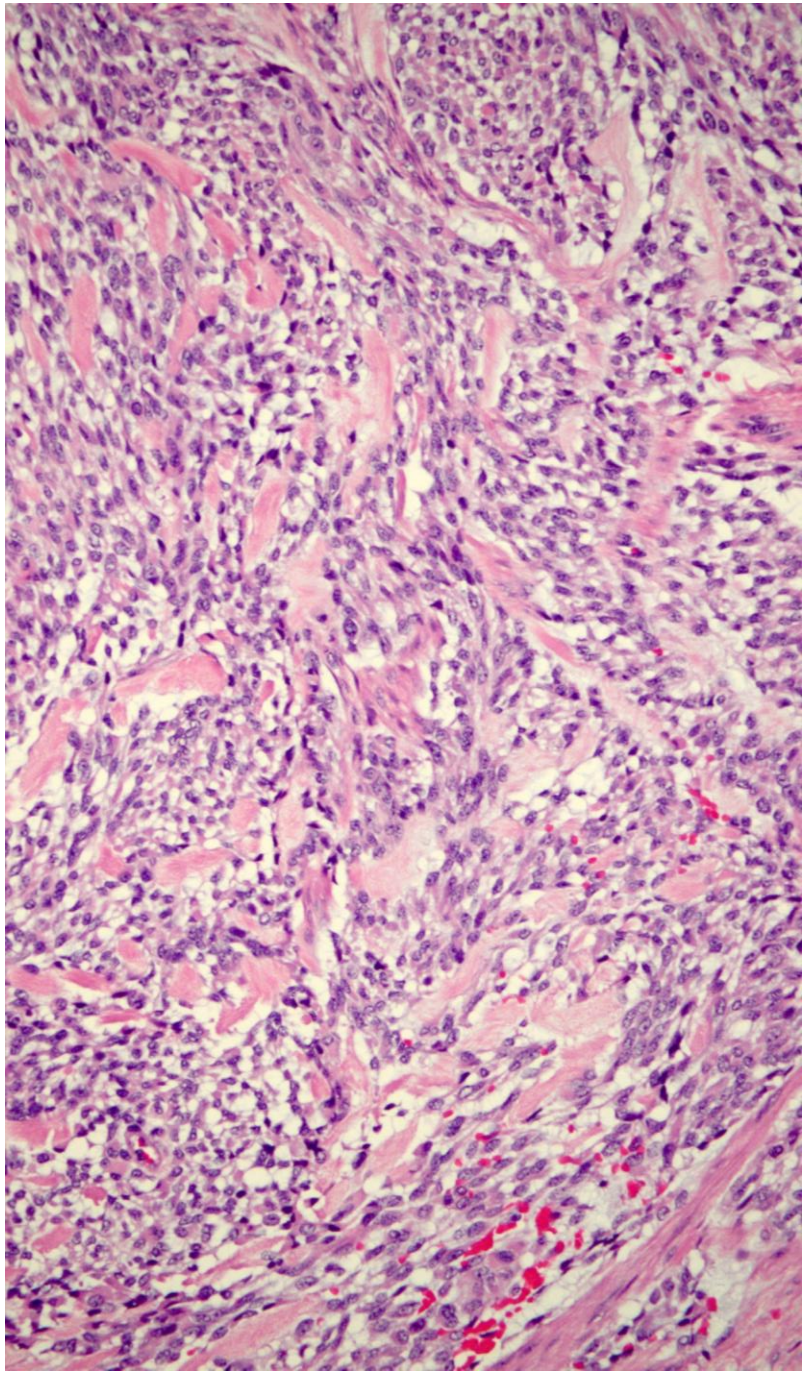
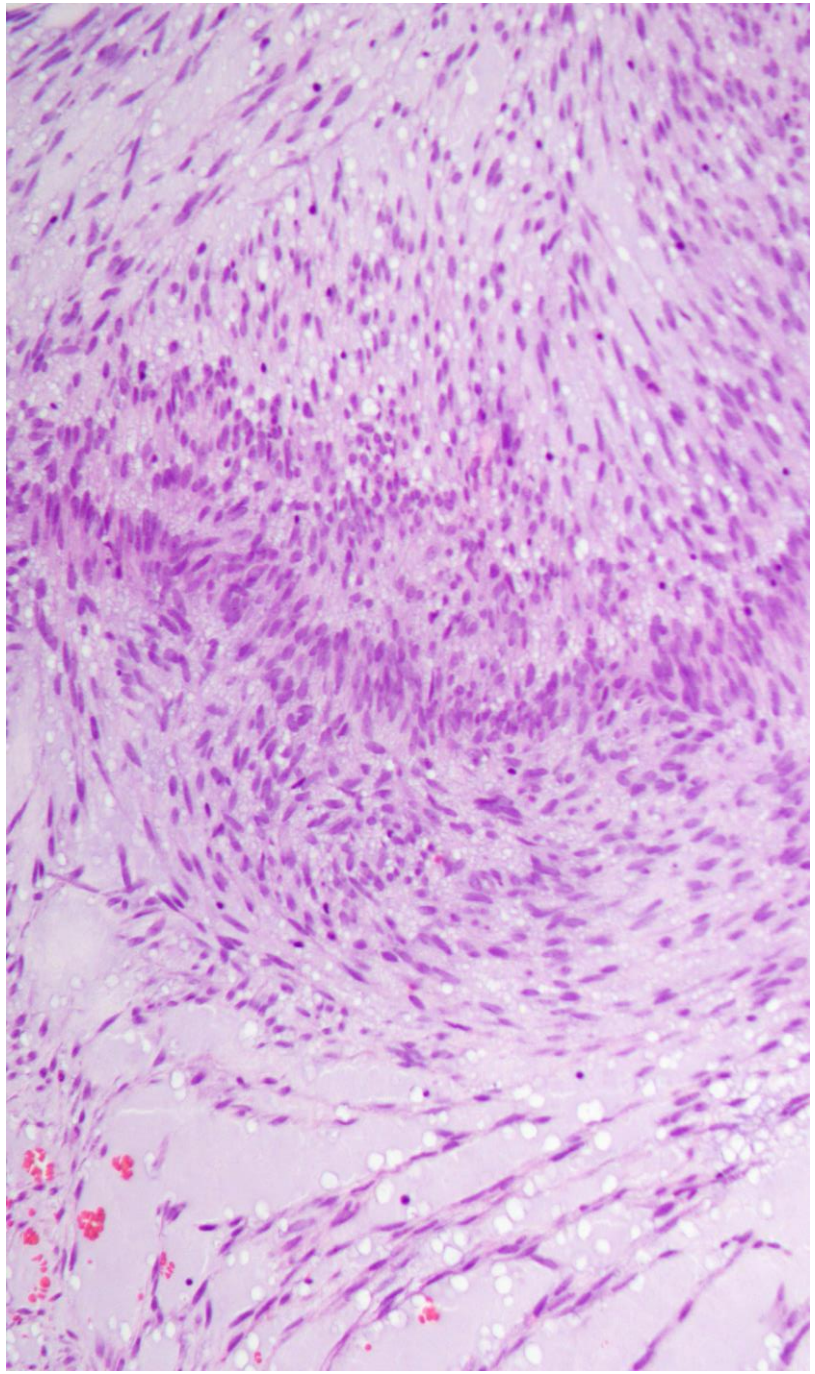
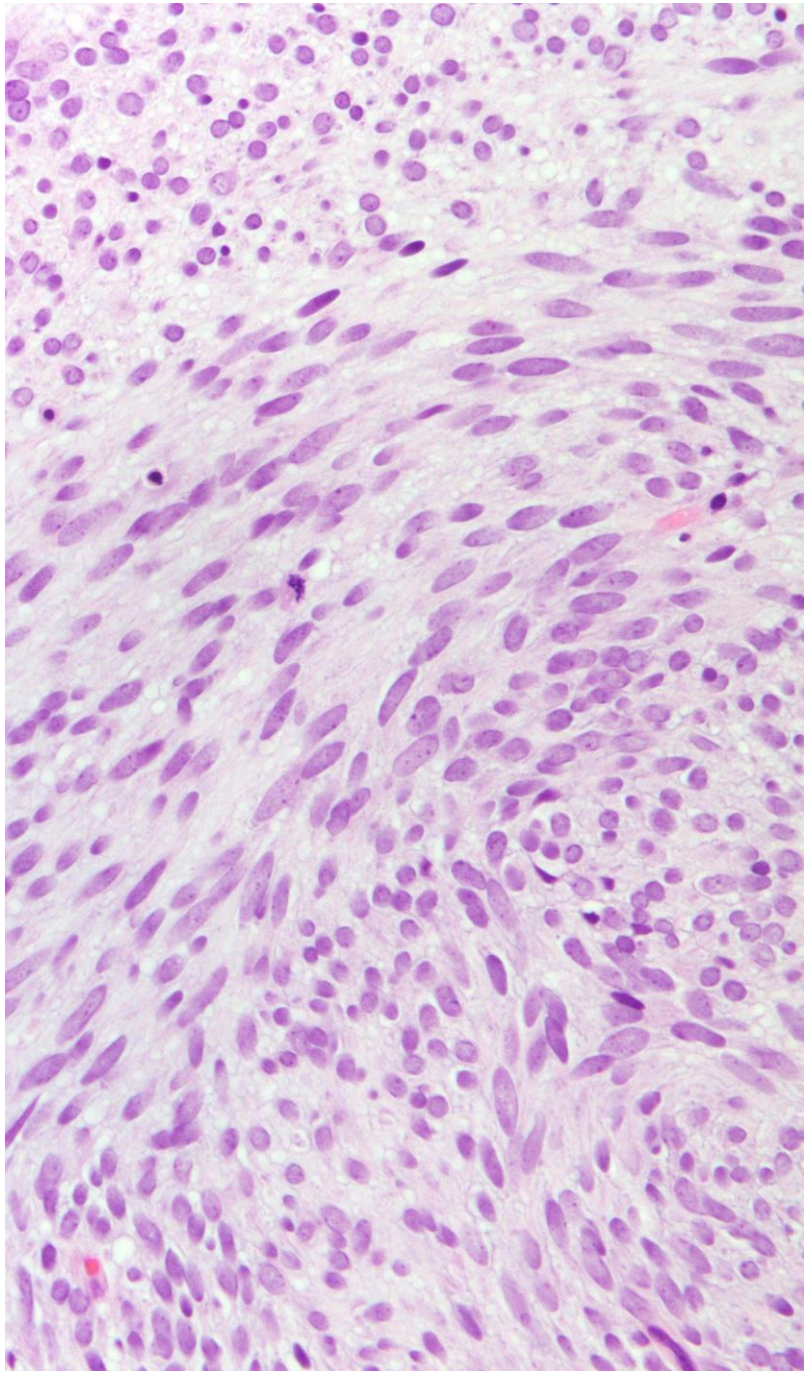
More aggressive behavior compared to low-grade tumors

BCOR-ZC3H7B HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA

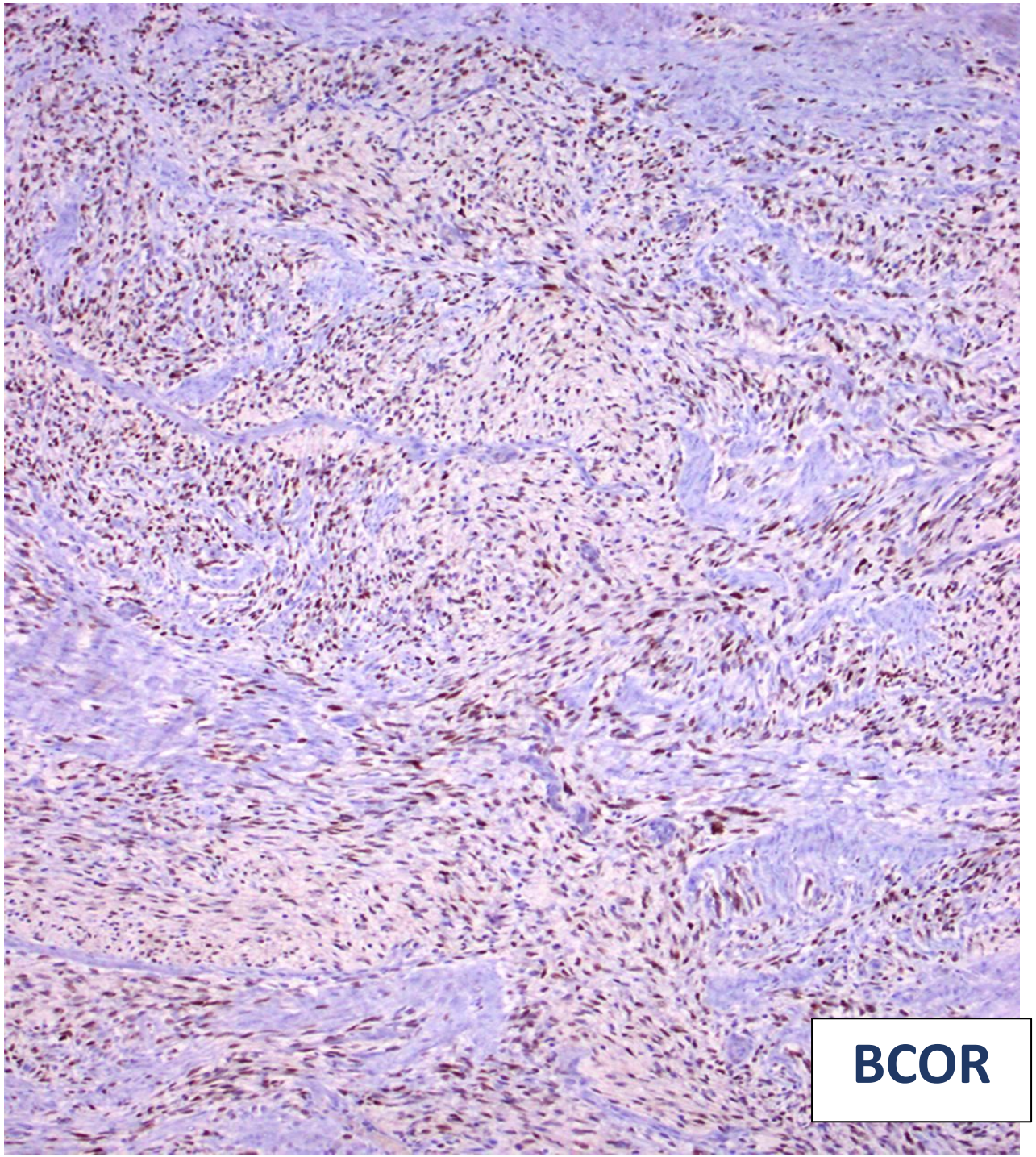




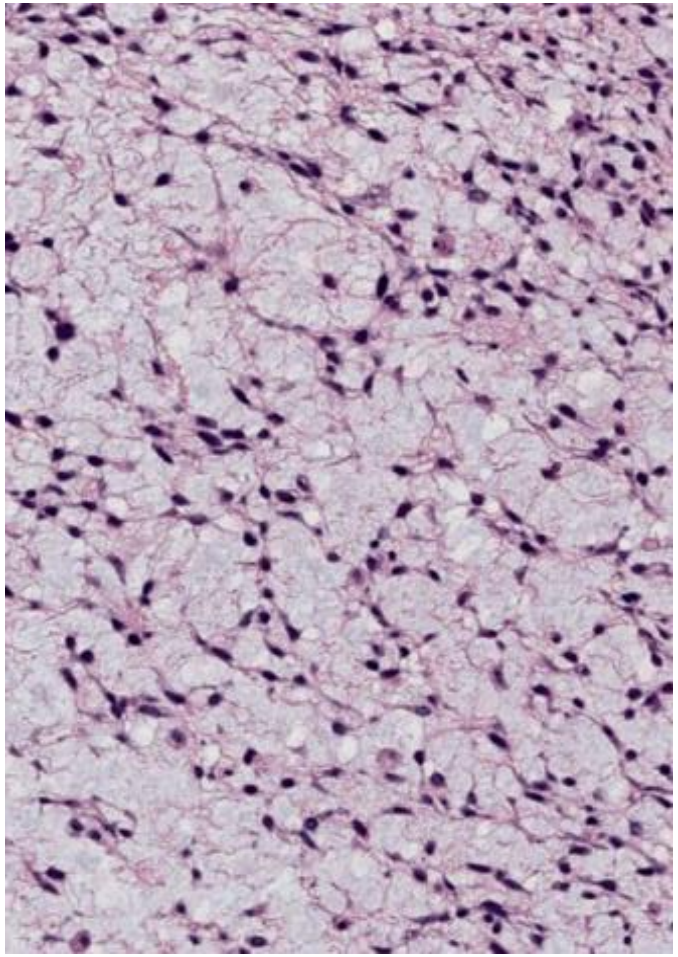
CLOSELY MIMICS MYXOID LEIOMYOSARCOMA,
up to 25% misdiagnosed as such in different series

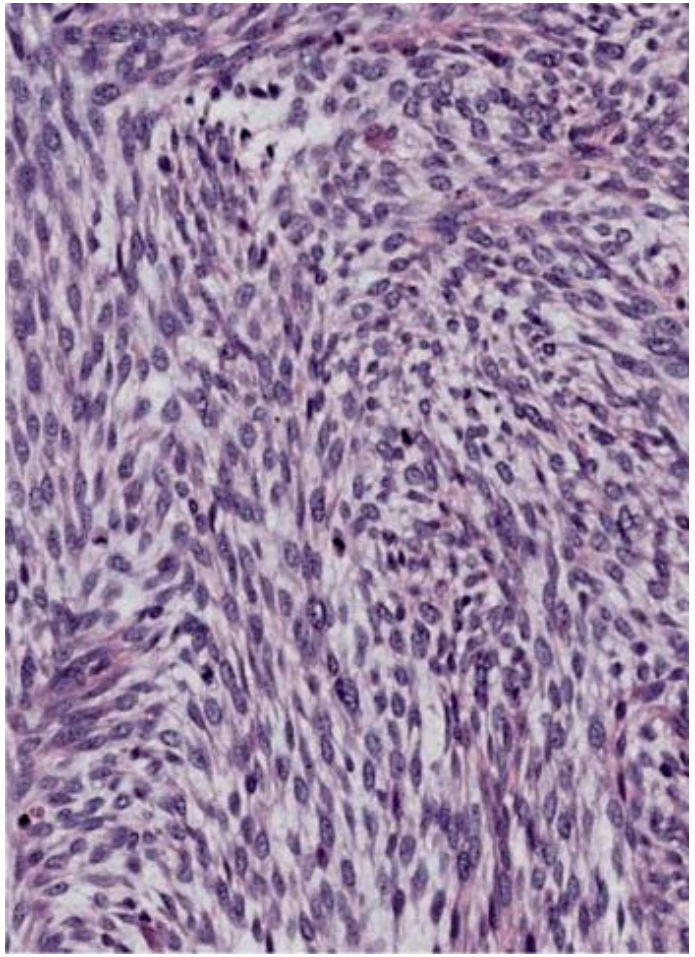




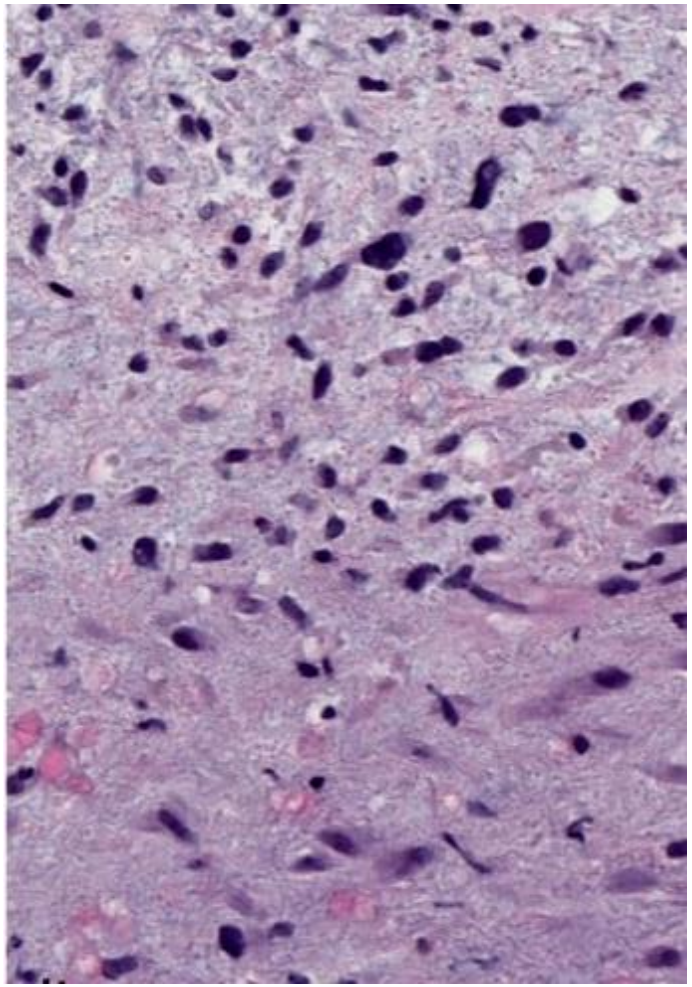
	CD10	ER	PR	CyclinD1	BCOR	Desmin	SMA	Caldesmon
ESN	+ D	+ D	+ D	-/+ F	-/+ F	-/+ F/D	+ D	+ F/D
LG-ESS	+ D	+ D	+ D	-/+ F	-/+ F	-/+ F/D	+ D	+ F/D
YWHAE-NUT2A/B HG-ESS Low-grade areas	+ D	+ D	+ D	-/+ F	-/+ F	-	-	-
YWHAE-NUT2A/B HG-ESS High-grade areas	-	-	-	+ D	+ D	-	-	-
ZC3H7B-BCOR HG-ESS	+ D	-/+ F	-/+ F	+ D	-/+ F/D	-	-/+ F	-/+ F
BCOR ITD HG-ESS	+ F/D	-	-	+ D	+ F/D	-/+ F	-	-



In a malignant myxoid spindle cell tumor negative for BCOR and muscle markers showing diffuse cyclinD1 expression perform MOLECULAR STUDIES







BCORL1 ENDOMETRIAL STROMAL SARCOMAS (Modern Pathol 2021)

Can I have other types of high-grade ESS?

YES

When can I make this diagnosis?

WHEN AN ASSOCIATED LOW-GRADE ESS IS SEEN

High-grade transformation of low-grade endometrial stromal sarcomas lacking *YWHAE* and *BCOR* genetic abnormalities

JAZF1-SUZ12 (n = 6), JAZF1-PHF1 (n = 3), EPC1-PHF1, (n = 1), or BRD8-PHF1 (n = 1) fusions were detected in 11/12 tumors

Modern Pathol 2020

***ESR1* hotspot mutations in endometrial stromal sarcoma with high-grade transformation and endocrine treatment**

Modern Pathol 2022

UNDIFFERENTIATED UTERINE SARCOMAS REPRESENT UNDERRRECOGNIZED HIGH-GRADE ENDOMETRIAL STROMAL SARCOMAS

Chiang S et al, Am J Surg Pathol 2020

10 "UNDIFFERENTIATED SARCOMAS"

BCOR IHC

FISH: BCOR, ZC3H7B, CCNB3, YWHAE, NUTM2, JAZF1, BCORL1

Targeted RNA sequencing if no rearrangement or lack of partner

---

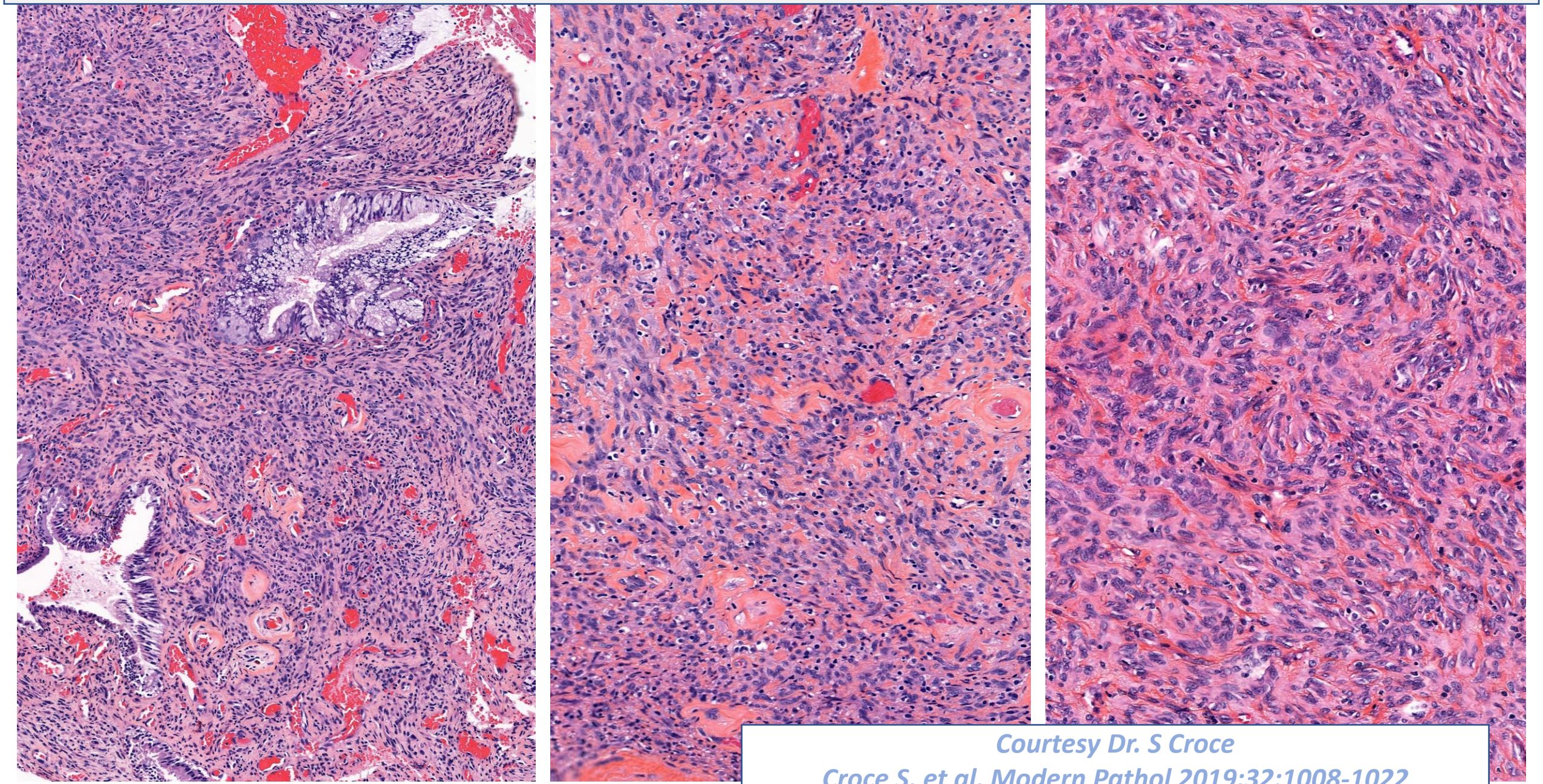
BCOR IHC in >50% of cells in 8/10 and <5% and negative in one each

FISH: ZC3H7B-BCOR and YWHAE-NUTM2 in 3 tumors with uniform features

YWHAE rearrangement with no partner in 2 pleomorphic sarcomas

Targeted RNA sequencing: BRD8-PHF1, YWHAE-NUTM2, and BCOR ITD in 4

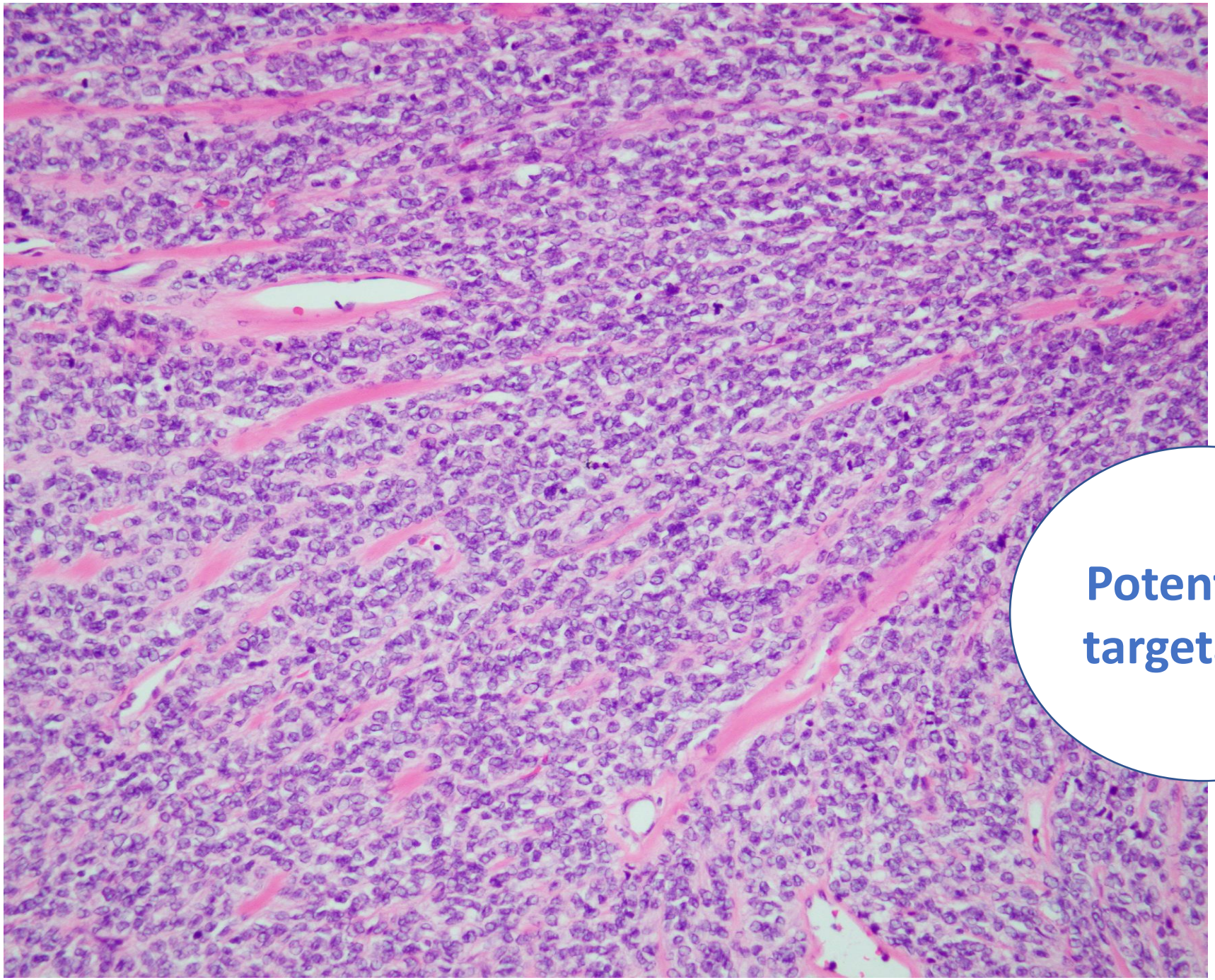
NTRK-REARRANGED CERVICAL SPINDLE CELL NEOPLASM

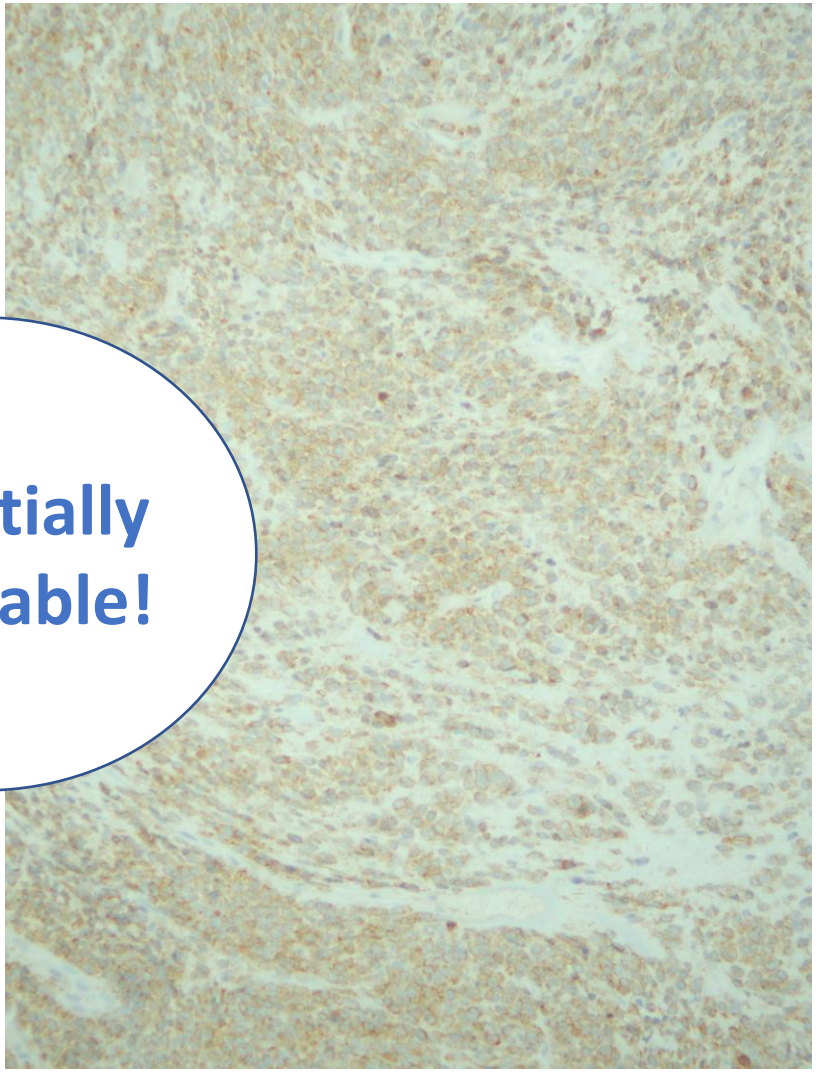


Courtesy Dr. S Croce

Croce S, et al, Modern Pathol 2019;32:1008-1022

NTRK-REARRANGED CERVICAL SPINDLE CELL NEOPLASM

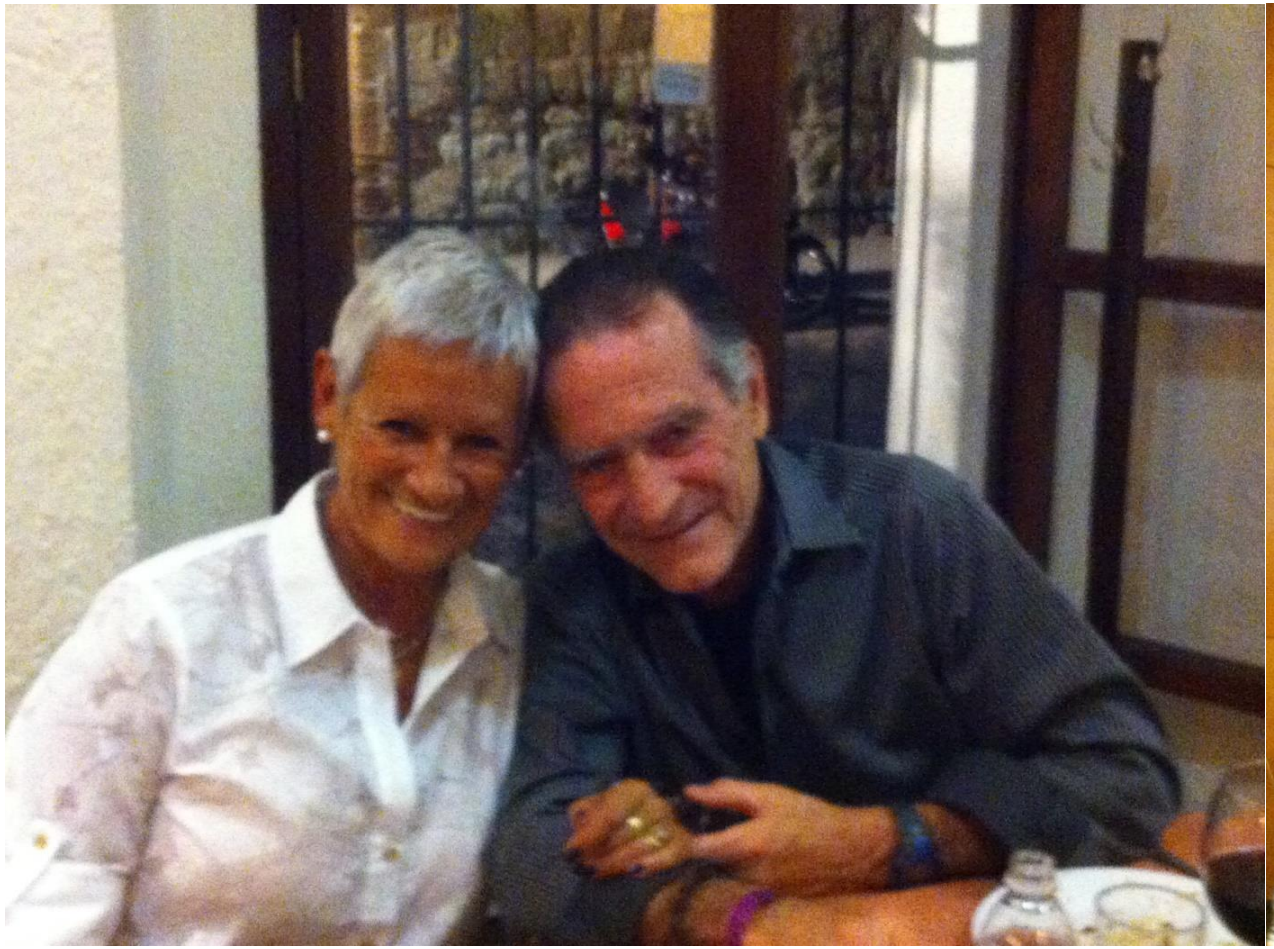




Potentially targetable!

CONCLUSIONS

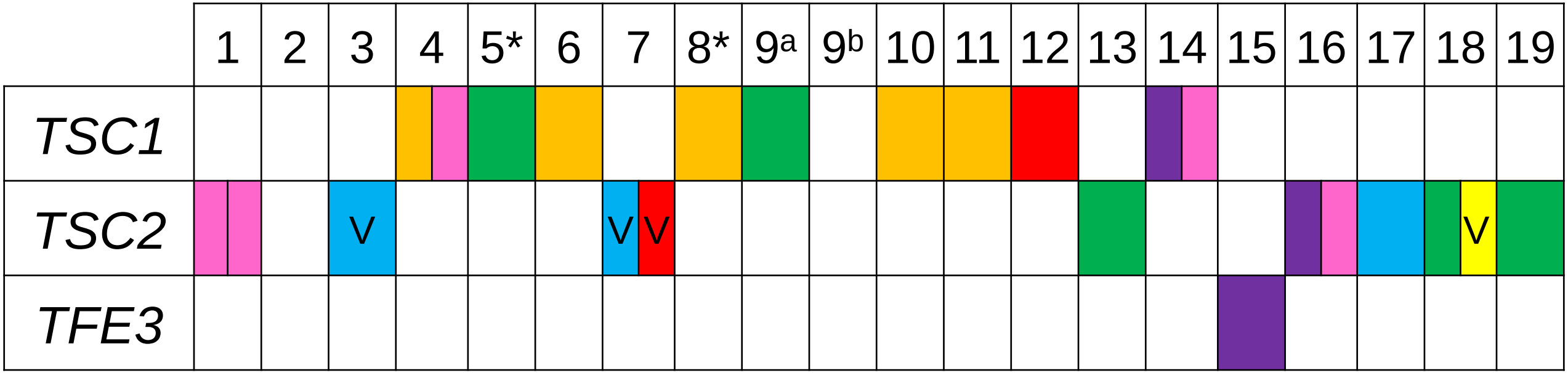
- Integration of gross, morphologic, immunohistochemical features key
- Panel of antibodies, but not a single stain should be used as the latter may lead to the incorrect diagnosis
- Overlapping morphologic features and immunohistochemical staining patterns exist within different tumors
- If unusual (morphology or immunohistochemical profile), molecular testing may be helpful
- Establishing correct diagnosis important as at least some mesenchymal tumors may be treated with specific targeted therapy

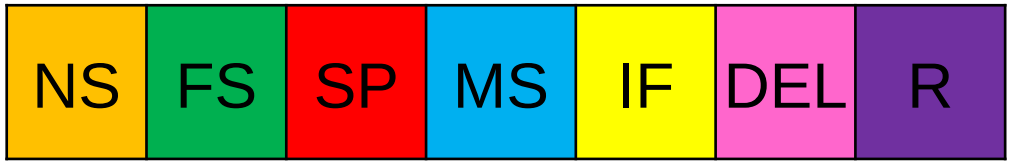



Parc
SORTIDA
D'EMERGÈNCIA

Thank you !!!!

TSC Alterations are Common in PEComas





*=tuberous sclerosis, V=VUS

TSC1: 9/19 (47%)
TSC2: 8/19 (42%)