THE ZEBRAS OF UTERINE MESENCHYMAL NEOPLASMS

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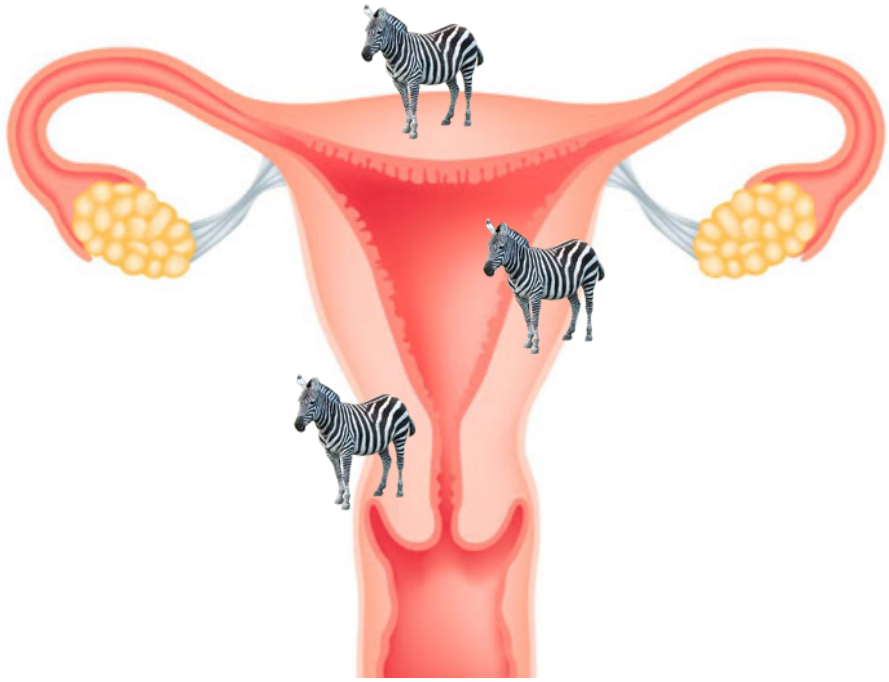


Why Should We Try to Classify the “Zebras”?

- Many mesenchymal neoplasms fail to respond to chemo/radiation therapy

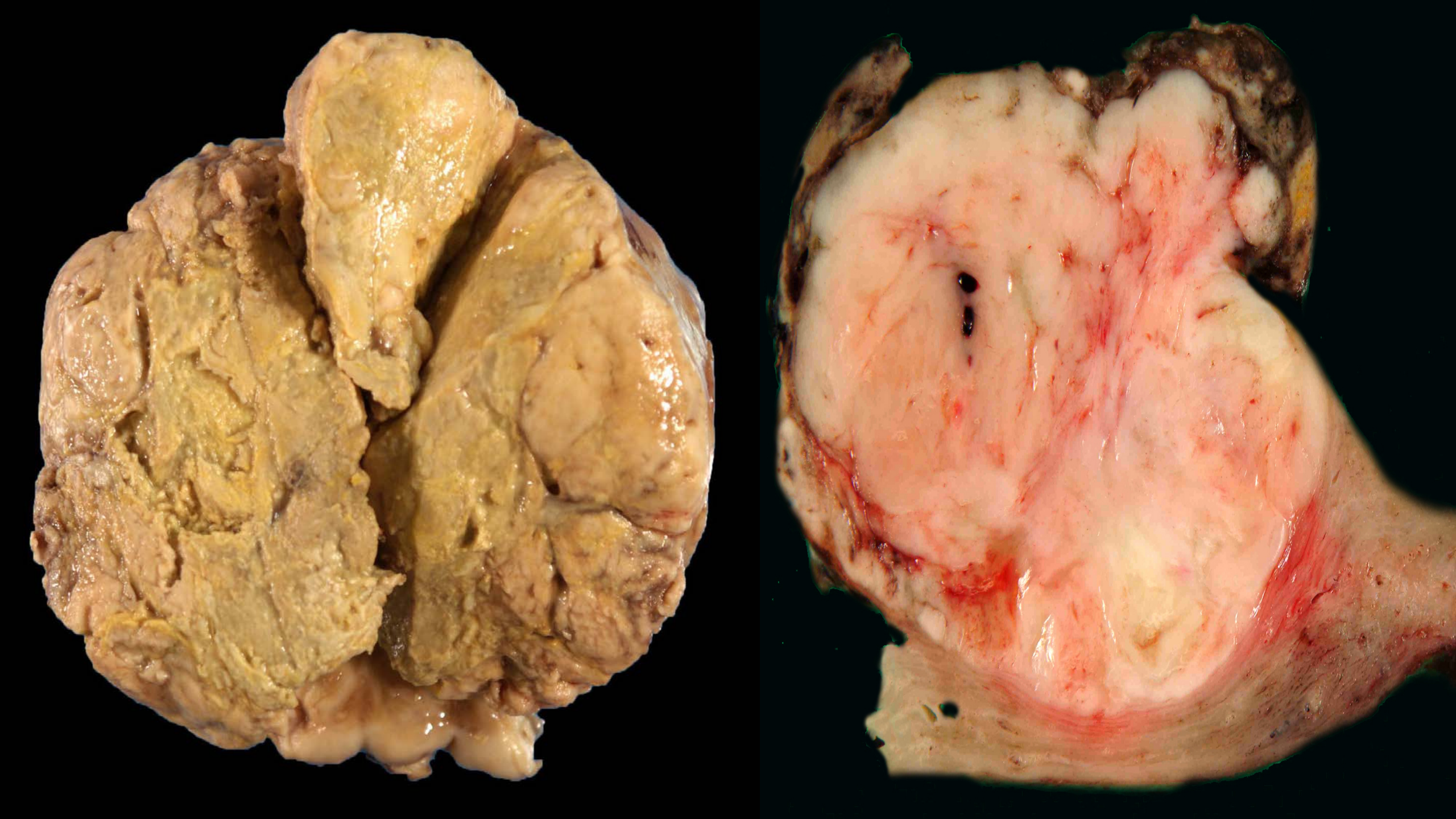
- Targeted therapy as an alternative treatment modality
  - Inflammatory myofibroblastic tumor – Tyrosine Kinase Inhibitors
  - PEComa – mTOR Inhibitors
  - *NTRK*-rearranged spindle cell sarcoma – NTRK Inhibitors
  - *SMARCA4*-deficient uterine sarcoma – EZH2 Inhibitors

What Molecular Test to Order

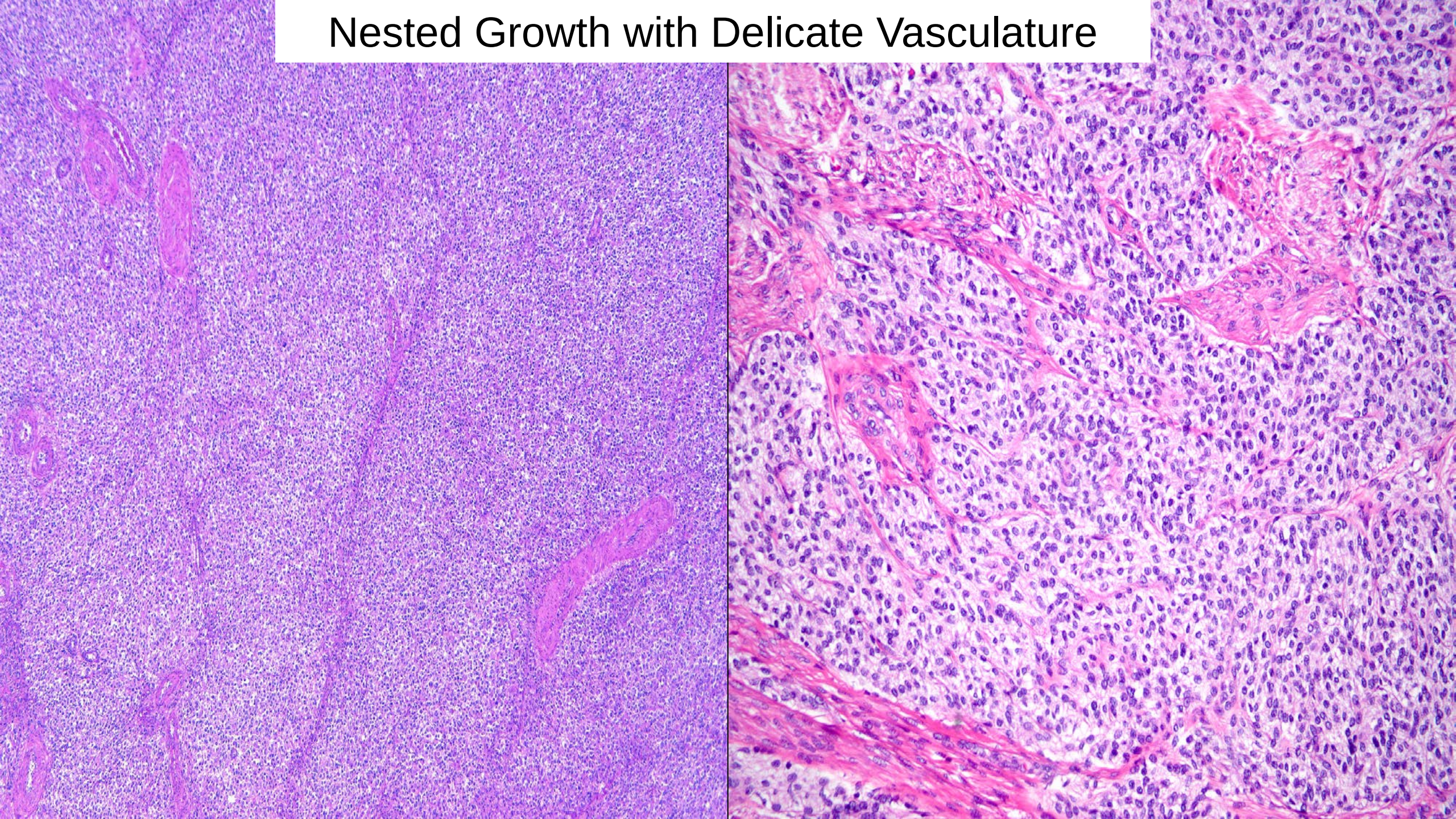
- Mutations: Next-Generation Sequencing (DNA)
  - *TSC* mutations in PEComa
  - *SMARCA4* mutations in SDUS

- Rearrangements: Next-Generation Sequencing (RNA Fusion Analysis) or FISH (DNA)
  - *ALK* fusion in IMT
  - *NTRK* fusion in *NTRK*-rearranged spindle cell sarcoma

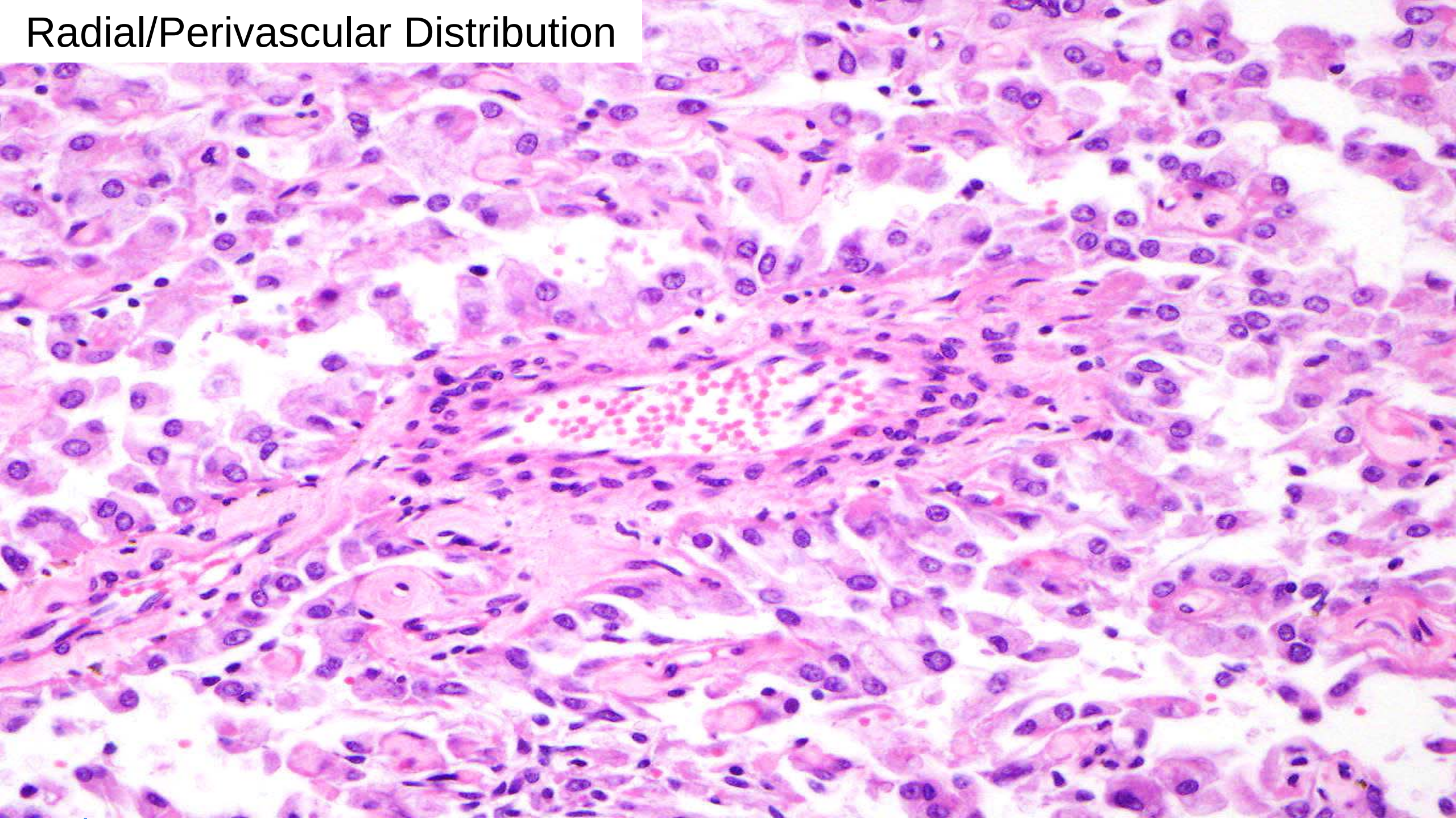
PERIVASCULAR EPITHELIOID CELL TUMOR (PECOMA)

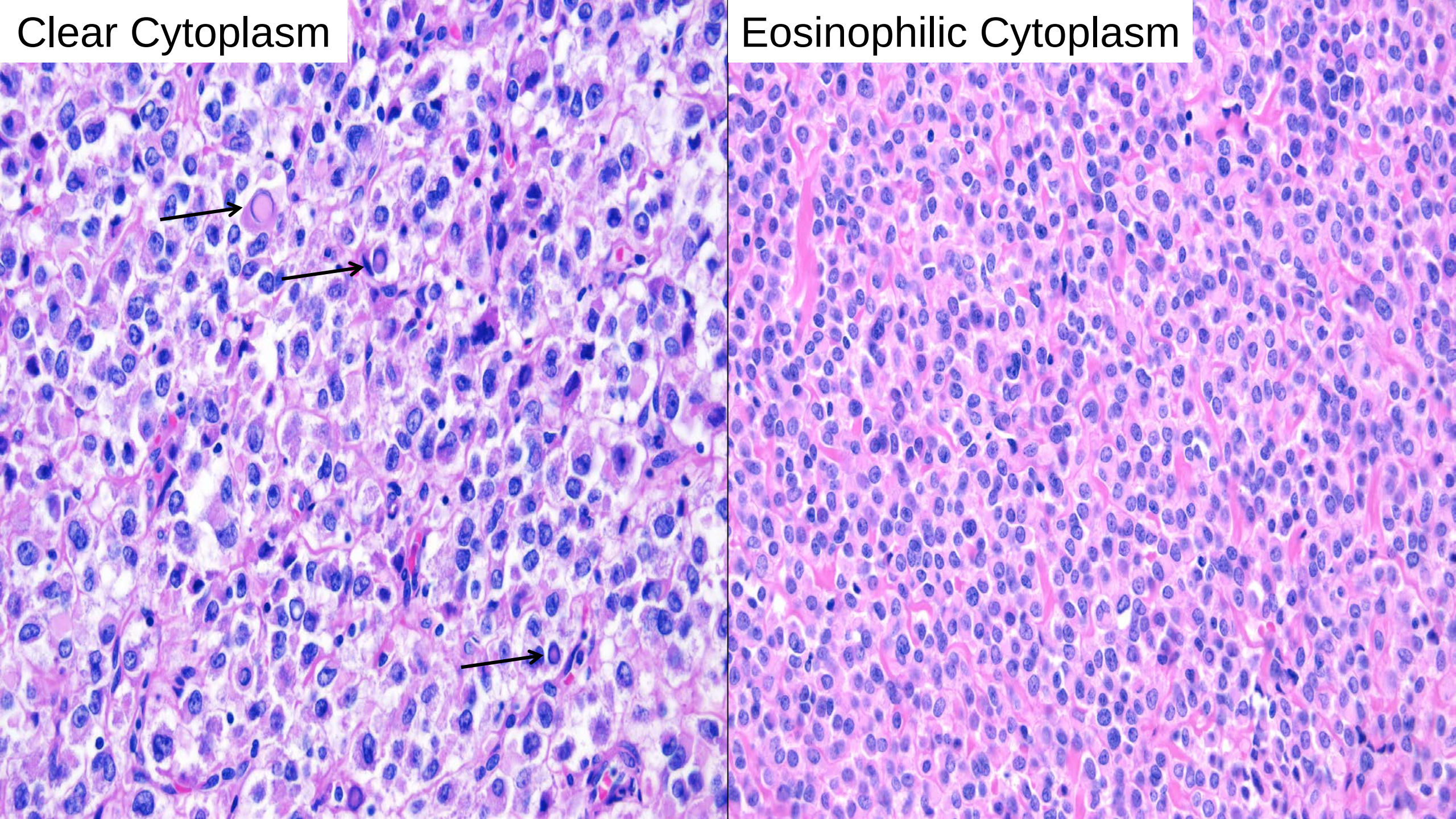


Nested Growth with Delicate Vasculature

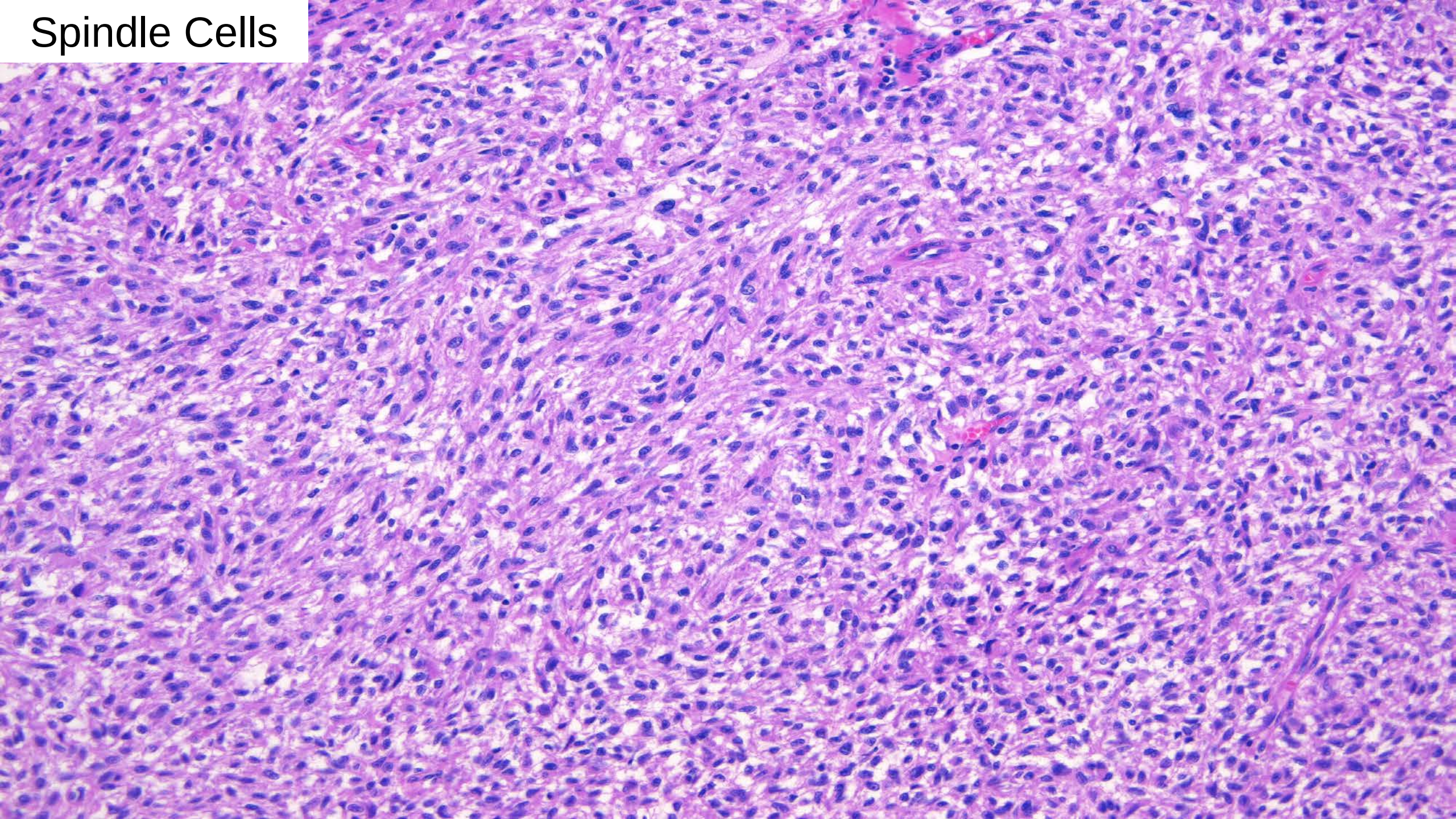


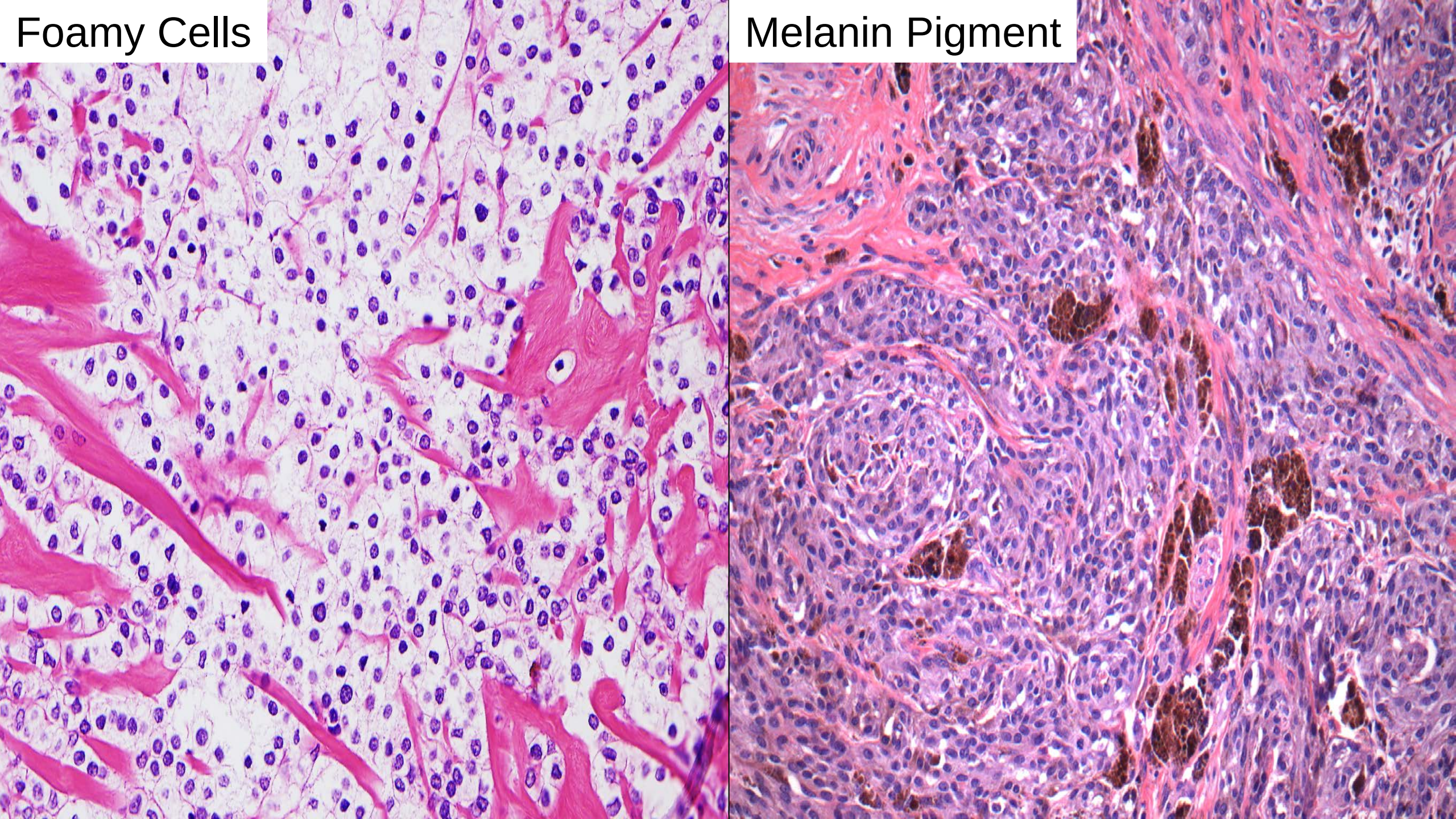
Radial/Perivascular Distribution



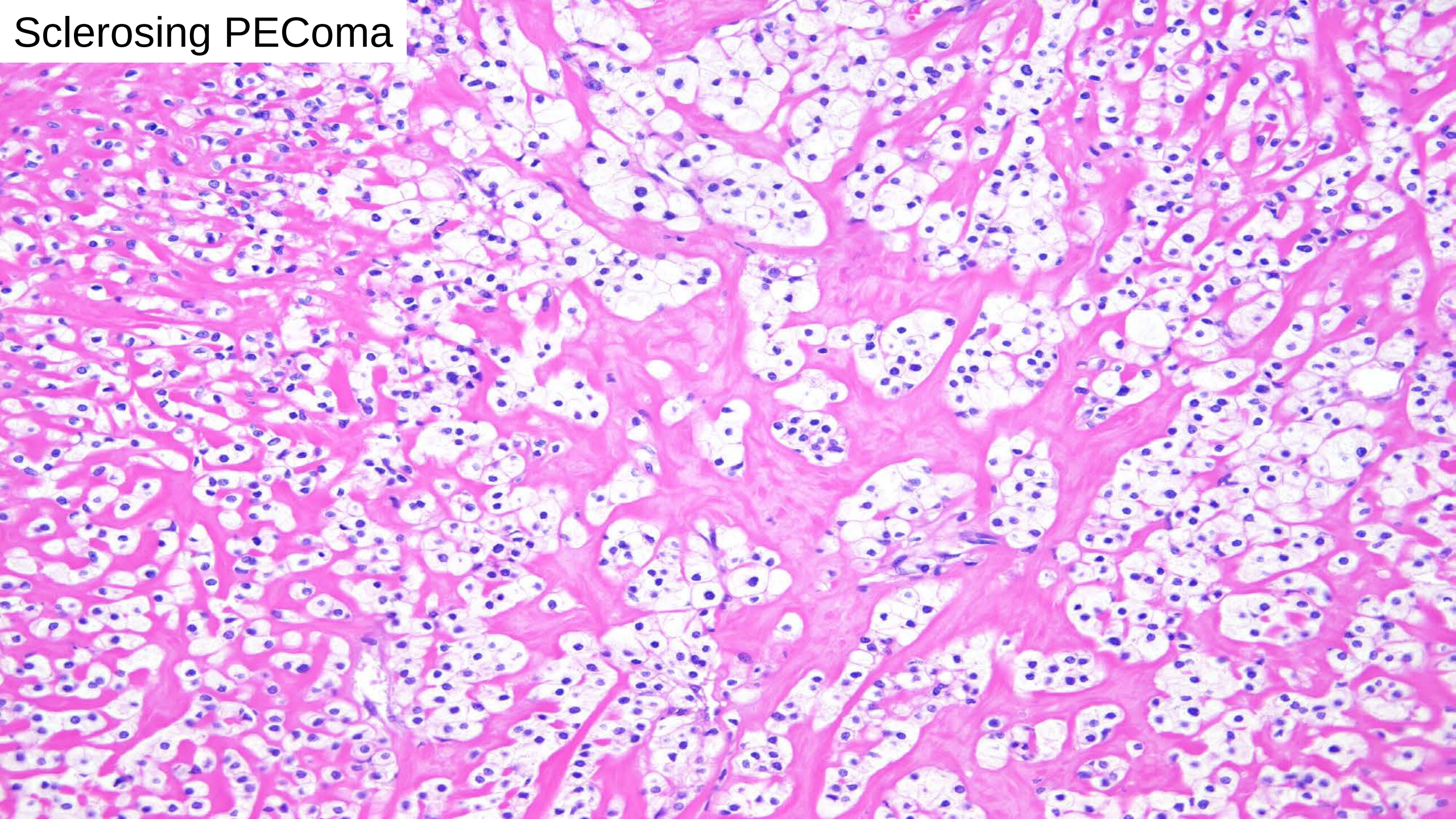

Clear Cytoplasm
Eosinophilic Cytoplasm

Spindle Cells

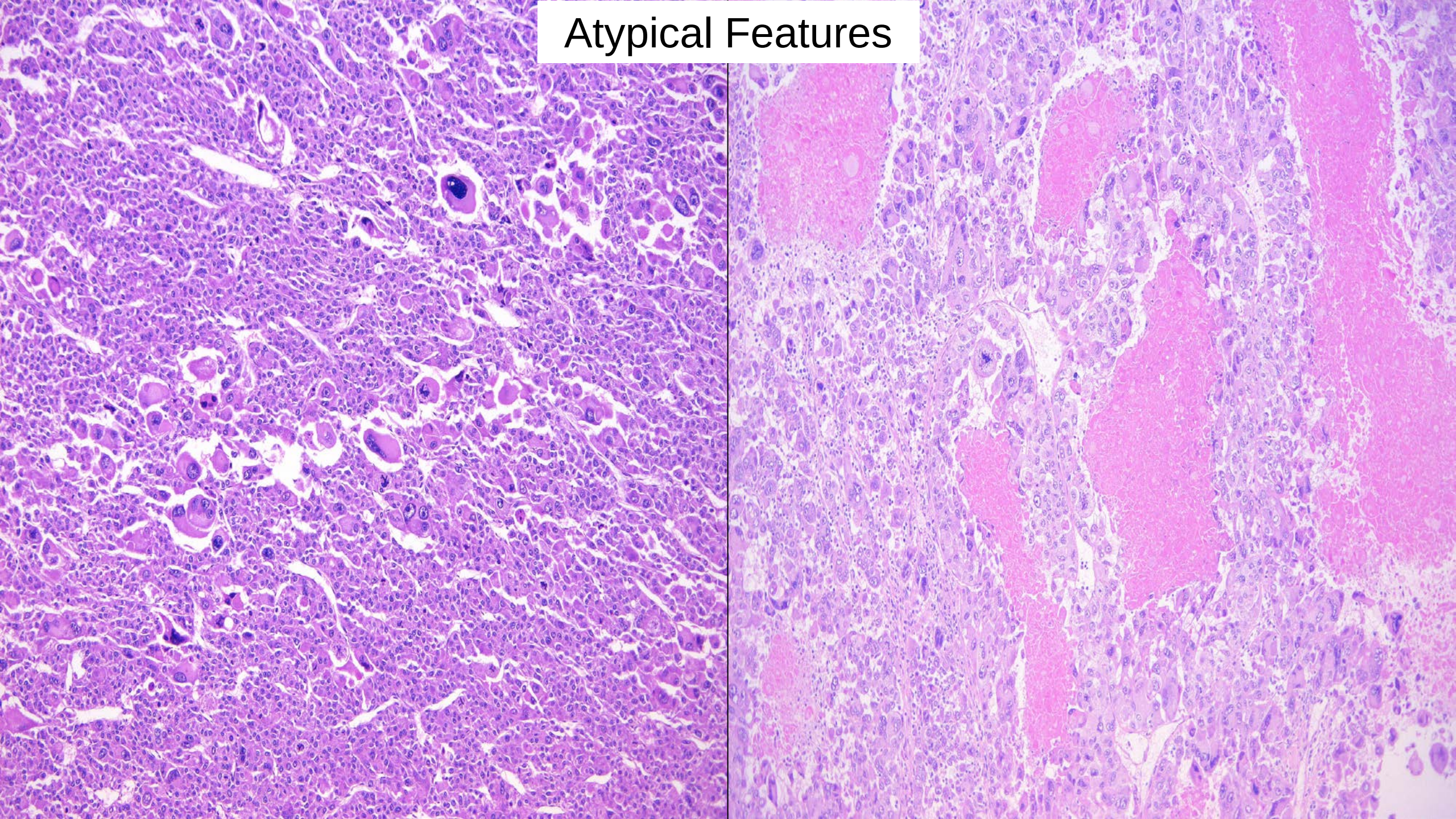



Foamy Cells
Melanin Pigment

Sclerosing PEComa



Atypical Features



Prognostic Features

	Folpe 2005	Schoolmeester 2014	Bennett 2018
Benign	< 5 cm, not infiltrative, no high-grade atypia, mitoses ≤ 1 / 50 HPFs, no necrosis, no LVI	< 4 features (≥ 5 cm, high-grade atypia, mitoses > 1 / 50 HPFs, necrosis, LVI)	
Uncertain Malignant Potential	Nuclear pleomorphism / multinucleated giant cells or > 5 cm		< 3 features (> 5 cm, high-grade atypia, mitoses > 1 / 50 HPFs, necrosis, LVI)
Malignant	2+ features (> 5 cm, infiltrative, high-grade atypia, mitoses > 1 / 50 HPFs, necrosis, LVI)	≥ 4 features	≥ 3 features

PEComas are Characterized by Expression of Myomelanocytic Markers

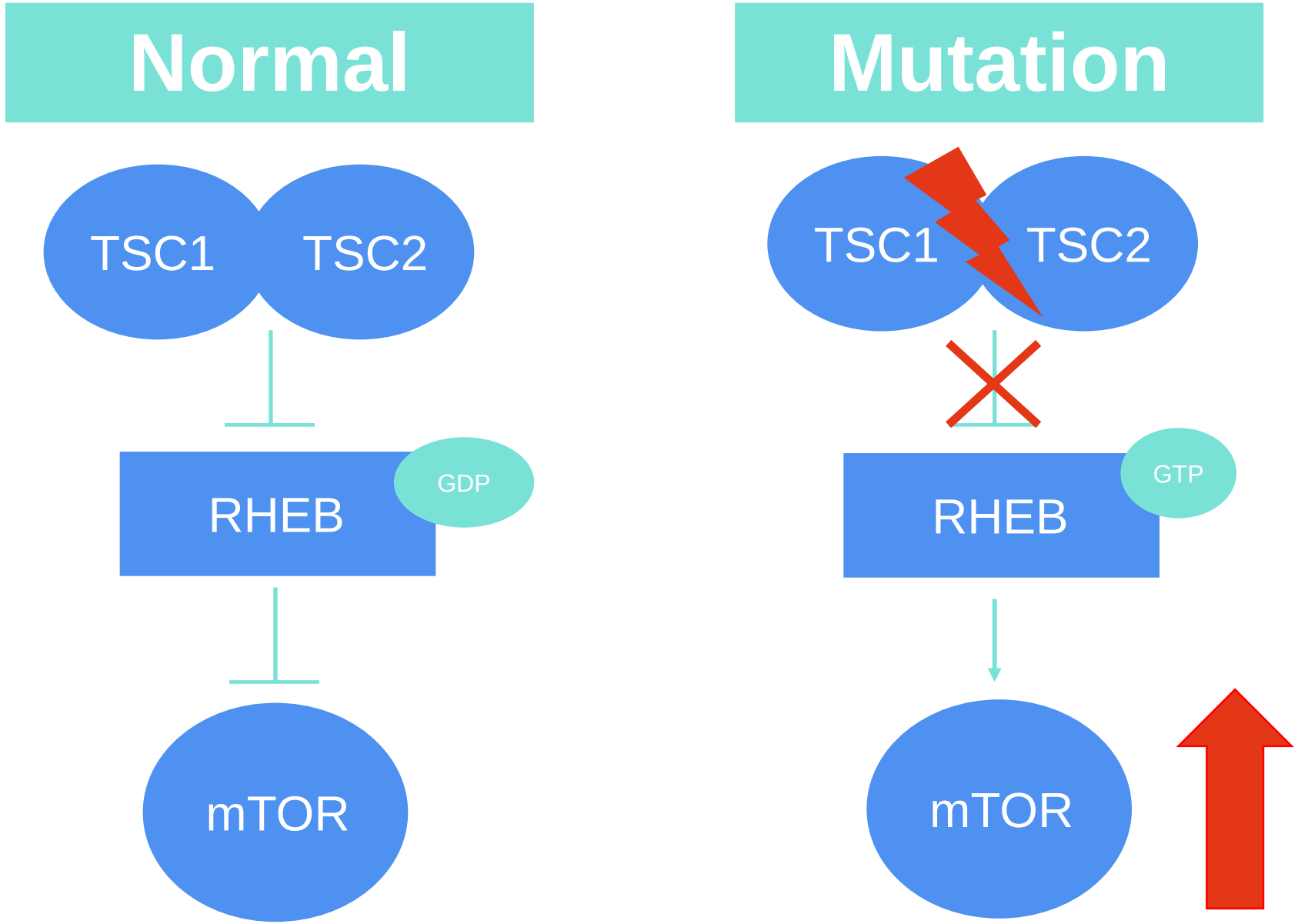
- Myogenic – SMA, desmin, caldesmon
- Melanocytic – HMB-45, Melan-A, MiTF

BUT, exactly how much staining for melanocytic markers is required to make the diagnosis remains controversial….

Molecular Features

- "Classic" PEComas
  - *TSC1* or *TSC2* mutations
  - Somatic or germline (~10%)
- *TFE3*-Translocation Associated PEComas

Argani 2010
Agaram 2015
Schoolmeester 2015
Bennett 2018


Normal
TSC1
TSC2
RHEB
GDP
mTOR
Mutation
TSC1
TSC2
RHEB
GTP
mTOR

Precision Medicine and Imaging

Clinical Cancer Research

Role of Chemotherapy, VEGFR Inhibitors, and mTOR Inhibitors in Advanced Perivascular Epithelioid Cell Tumors (PEComas)

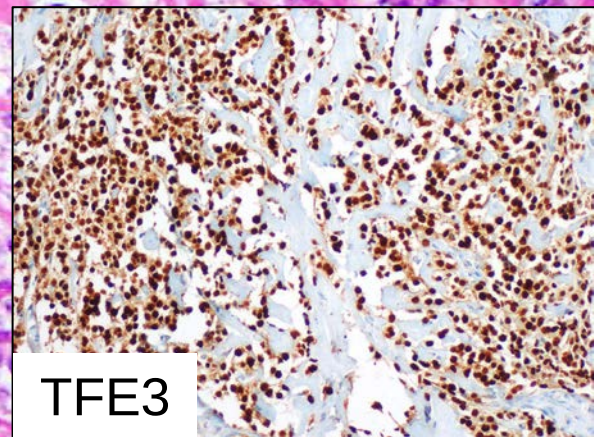
Roberta Sanfilippo[1], Robin L. Jones[2], Jean-Yves Blay[3], Axel Le Cesne[4], Salvatore Provenzano[1], Georgios Antoniou[2], Olivier Mir[4], Giovanni Fucà[1], Elena Fumagalli[1], Rossella Bertulli[1], Silvia Stacchiotti[1], Mehdi Brahmi[3], Federica Grosso[5], Armelle Dufresne[3], Nadia Hindi[6,7], Marta Sbaraglia[8], Alessandro Gronchi[9], Paola Collini[10], Angelo P. Dei Tos[8,11], and Paolo G. Casali[1,12]

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Addition of Antiestrogen Treatment in Patients with Malignant PEComa Progressing to mTOR Inhibitors

Roberta Sanfilippo[1], Chiara Fabbroni[1], Giovanni Fucà[1], Elena Fumagalli[1], Carlo Morosi[2], Marta Sbaraglia[3], Alessandro Gronchi[4], Paola Collini[5], Angelo P. Dei Tos[3,6], and Paolo G. Casali[1,7]

TFE3-Translocation Associated PEComa



TFE3-Translocation Associated PEComa

- Nested / alveolar growth
- Epithelioid cells with clear cytoplasm
- Variably cytological atypia and mitoses
- Strong and diffuse HMB-45, TFE3, cathepsin K
- Focal / negative Melan-A and myogenic markers

The Myomelanocytic Controversy…..

- Schoolmeester et al. (2014) proposed “that a tumor exhibiting morphologic features of PECs with at least focal IHC expression of 2 melanocytic markers, preferably HMB45 and MelanA, with concurrent expression of at least a single muscle marker such as SMA, desmin, or h-caldesmon should be classified as PEComa.”

- Selenica et al. (2020): 5/17 mesenchymal tumors with myomelanocytic differentiation harbored *TSC2* mutations and 1/12 had a *TFE3* rearrangement

TABLE 3. Key Immunohistochemical and Genomic Features of High-grade UMTs

Sample ID	Desmin	SMA	HMB45	Melan-A	TFE3	pS6	Other Positive	TFE3 FISH	RNA Sequencing	Key Mutations	Key CNAs	Best Diagnosis Based on Morphology, Immunophenotype, and Genomics
UMT01	+++60	++20	++-+++70	0	++70	++-+++90	MiTF	Neg	Fail	*TP53*, *RB1*, *BRD4*	*PRDM1*	Malignant PEComa
UMT02	++40	+++100	+++50	0	++40	++30	MiTF	Neg	Neg	***TP53***, ***MED12***	*TP53*	Leiomyosarcoma
UMT03	+++100	+++20	+5	0	+++100	++5		Neg	Fail	*ESR1*		Myogenic neoplasm, most likely leiomyosarcoma
UMT04	**+++100**	**+++100**	++1	0	++80	++40		Neg	*DNAJB6-PLAG1*	***TP53***, ***ATRX***	*RB1*, *RAD50* *FGFR3*	Myogenic sarcoma, most likely leiomyosarcoma
UMT05	0	0	++15	++20	0	+++100		Neg	Fail	*TP53*, *DAXX*, *DICER1*	*NTRK1*	Sarcoma, NOS
UMT06	**+++40***	**+++80**	**+++5†**	**0**	+70	+30		Neg	Neg	***TP53***, ***ATRX***		Sarcoma associated with leiomyosarcoma-like and PEComa-like features
UMT06-R	**0**	**+++30**	**+++20**	**0**	++100	+++15		Neg	Neg	***TSC2***, ***ATRX***		
UMT07	**0**	**0**	**+++100**	**+10**	+++100	++30		**Pos**	***SFPQ-TFE3***			Malignant PEComa, TFE3-rearranged
UMT08	**+++100**	**+++100**	0	+2	+30	+++70	MiTF	Neg	Fail	*KDM6A*, *NTRK3*, *JAK3*	*ERCC2*	Myogenic sarcoma, most likely leiomyosarcoma
UMT09	**Pos**	**Focal**	**Pos**	**Focal**	Very focal					***TSC2***	*ROS1*	Sarcoma associated with LGESS-like and PEComa-like features
UMT09-R	**++50**	**+++20**	**+++100**	**0**	++90	+++30		Neg	***JAZF1-SUZ12***	***TSC2***		
UMT10	**Pos**	**Pos**	Focal	Neg	Patchy weak					***TP53***, ***MED12***	*RB1*, *BRCA2*	Leiomyosarcoma
UMT11	Neg	Neg	Pos	Neg						***TSC2***	*TP53*	Malignant PEComa
UMT12	**+++100**	**+++100**	+++5	0	0	++10	MiTF	Neg	Neg		*ERBB3*, *NCOR1*	Myogenic sarcoma, most likely leiomyosarcoma
UMT13	Neg	Patchy	Focal strong	Focal strong						*ATRX*	*TP53*, *BRCA2*	Sarcoma, NOS
UMT14	**Pos**	**Pos**	Focal	Focal						***TSC2***, *ASXL1*	*CDKN2A*	Sarcoma associated with leiomyosarcoma-like and PEComa-like features
UMT15	0	0	**+++15**	**++100**	+++100	+++100		Neg	Neg	*TP53*	***TSC2***, *RB1*	Malignant PEComa

Immunohistochemistry: Results described as a combination of staining intensity (+ weak, ++ moderate, +++ strong) and percentage of tumor cells exhibiting expression; for UMT09, UMT10, UMT11, UMT13, and UMT14, unstained slides for immunohistochemistry were not available; immunohistochemical findings are as described in original report. Desmin: *expression in spindle and part of round cell areas, negative in other round cell areas; HMB45: *mainly in cells in septa separating nests of epithelioid cells; †positive in bizarre large cells, negative everywhere else.

Bold font - Key immunohistochemical and genetic findings that (in combination with the histopathologic features) contributed to the diagnosis.

fail indicates sequencing failure due to poor RNA quality; neg, negative for gene rearrangements; NOS, not otherwise specified; pos, positive.

TABLE 5. Suggested Integrated Phenotypic-Genotypic Diagnostic Approach to High-grade UMTs With Ambiguous Histologic Appearances

Histopathologic evaluation				
One or more morphologic features seen in part or all of tumor	Spindle cells with round-ended nuclei, diffuse, moderate-to-severe nuclear atypia and coagulative tumor necrosis	Epithelioid and/or spindled cells with variably clear cytoplasm, variable nuclear pleomorphism, nested or corded architecture, stromal hyalinization	Tongue-like growth, small round to oval cells with scant cytoplasm	No specific morphologic features, or a combination of features typical of >1 entity
Favored diagnosis	Leiomyosarcoma	PEComa	ESS	Sarcoma, NOS
Confirm morphologic impression with immunohistochemistry				
Myogenic markers	+	+	+/−	Other combinations
Melanocytic markers	− (may be focal)	+ (2 or more)	−	
ESS markers	−	−	+	
Favored diagnosis	Suggestive of leiomyosarcoma	Suggestive of PEComa	Suggestive of ESS	Consider hybrid tumor or sarcoma NOS with a descriptive diagnosis
If immunophenotype is inconsistent with morphologic impression or the diagnosis remains in question, proceed to molecular profiling				
Mutations/rearrangements identified	*TP53*, *MED12*, *FH*, *ATRX*, *DAXX*, *RB1*	*TSC2*, *TFE3*, *RAD51B*	*JAZF1-JJAZ1*, *JAZF1-SUZ12*, *JAZF1-PHF1*, *YWHAE-FAM22*, *ZC3H7-BCOR*	Various combinations
Favored diagnosis	Leiomyosarcoma	PEComa	ESS	Consider hybrid tumor or sarcoma NOS with a descriptive diagnosis

Clearly the spectrum of tumors in the differential diagnosis, the number of immunohistochemical markers that are used to aid diagnosis of UMTs and the number of genetic alterations that may be found is much larger in reality, but this highly simplified approach is presented to illustrate one possible scheme for integrated phenotypic-genotypic classification.

ESS indicates endometrial stromal sarcoma; NOS, not otherwise specified.

In a Nutshell

- Perform a thorough morphological and immunohistochemical evaluation

- If cannot make a definitive diagnosis:
  - Sign out descriptively
  - In comment, discuss differential and recommend genetic testing in clinically indicated cases
    - **Do not want to miss a potential TSC diagnosis or the opportunity for treatment with mTOR inhibitors!**

INFLAMMATORY MYOFIBROBLASTIC TUMOR (IMT)

International Journal of Gynecological Pathology
6:275–286, Raven Press, Ltd., New York

Brief Communication

Inflammatory Pseudotumor of the Uterus

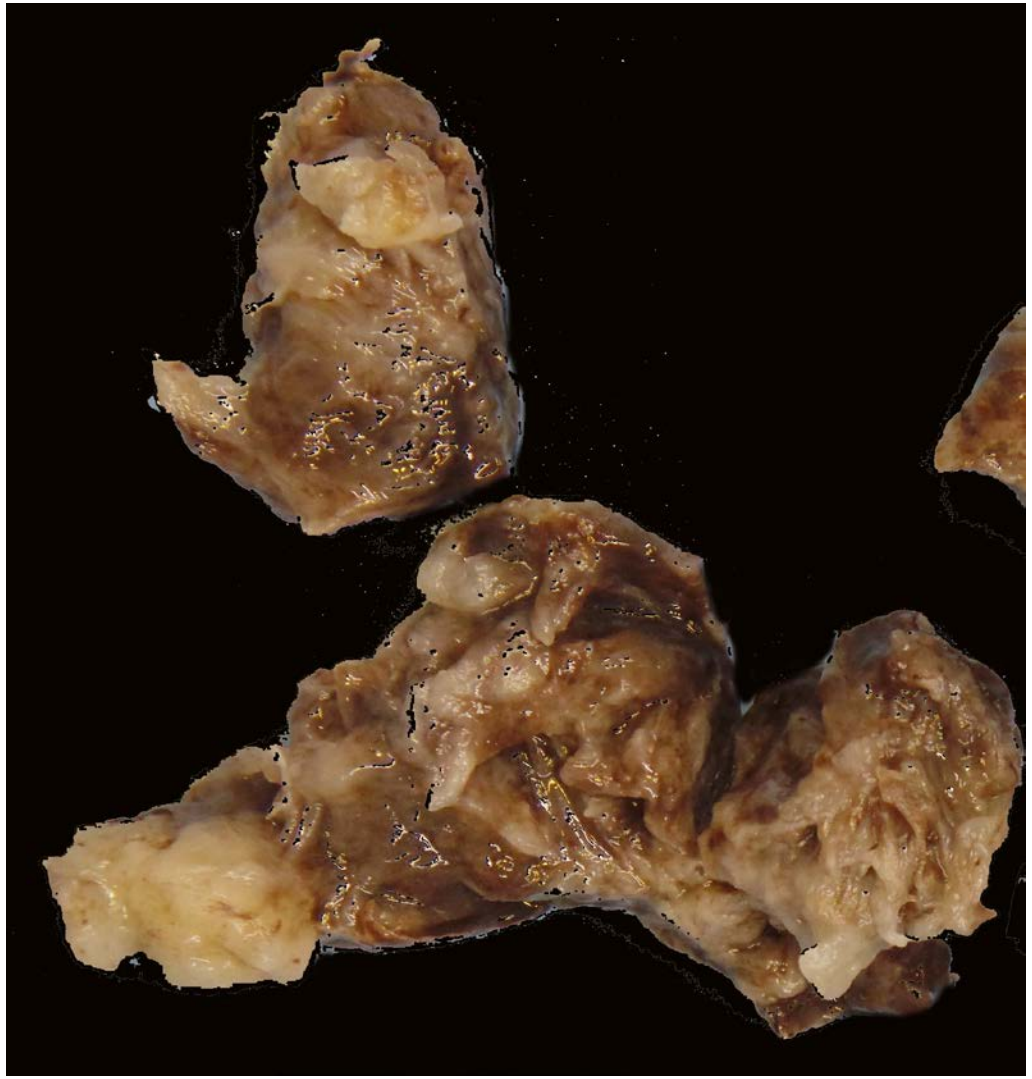
*C. Blake Gilks, *†Glenn P. Taylor, and *‡Philip B. Clement

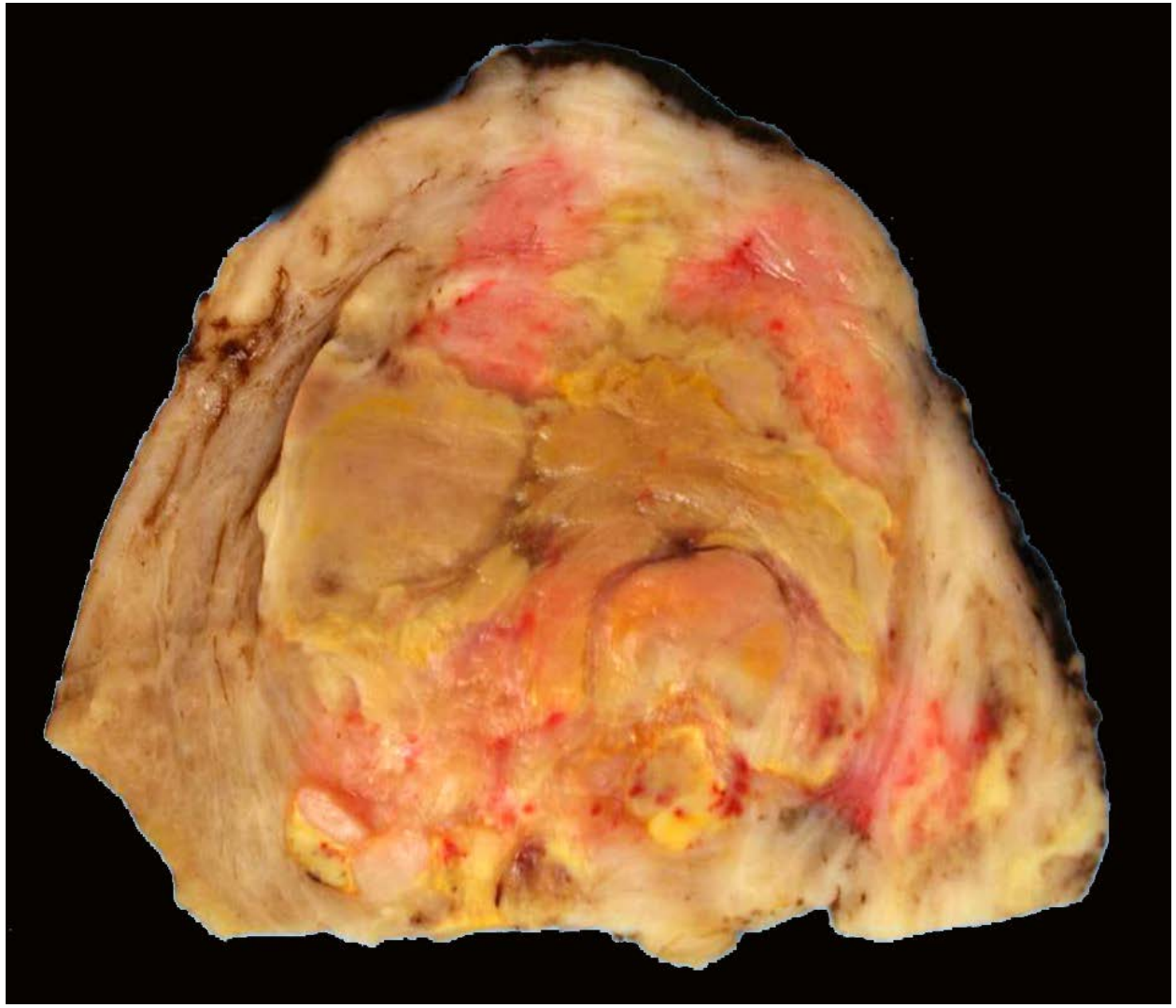
18 years later

Inflammatory Myofibroblastic Tumor of the Uterus

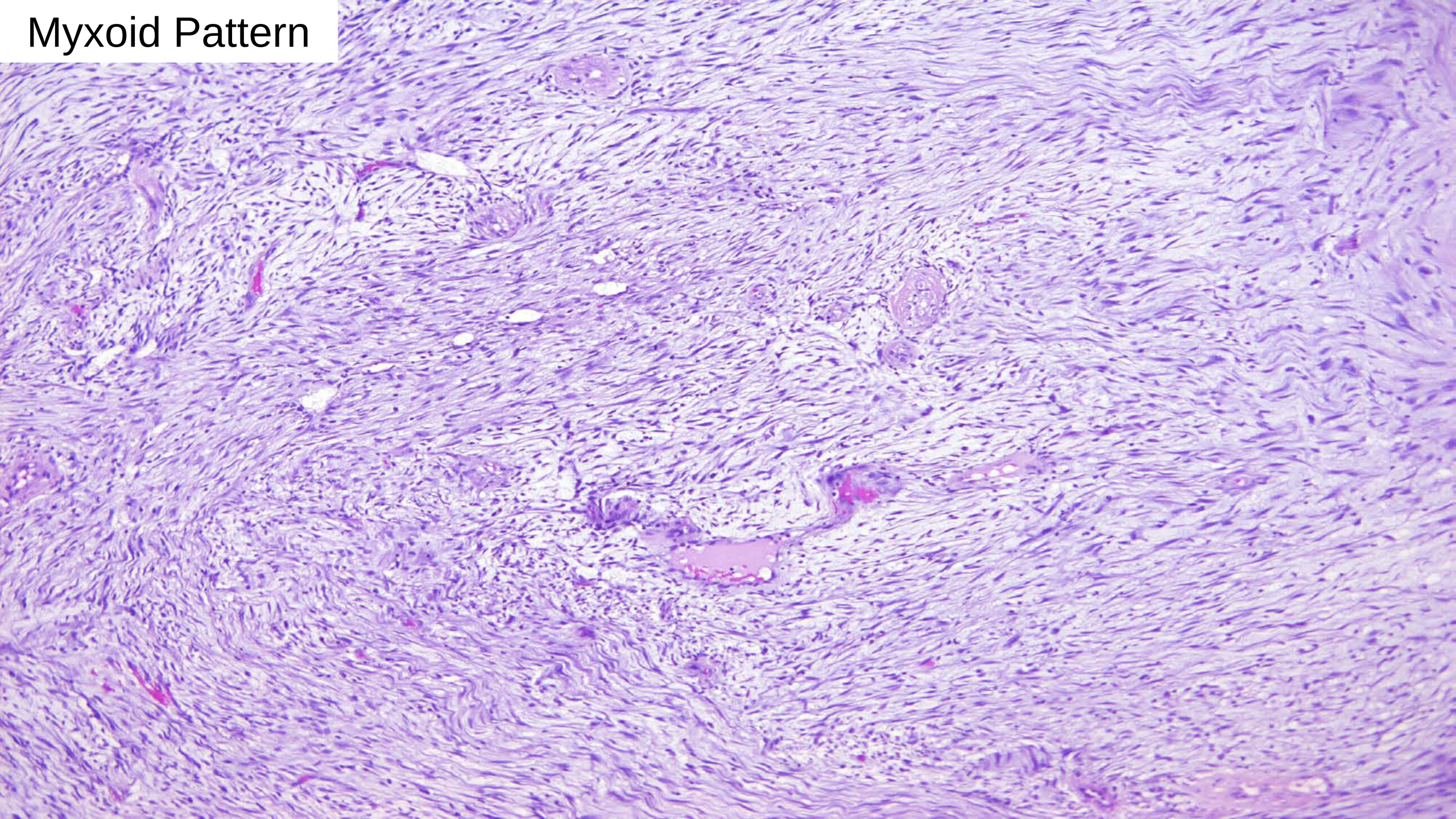
A Clinicopathologic Study of 6 Cases Emphasizing Distinction From Aggressive Mesenchymal Tumors

Joseph T. Rabban, MD, MPH, Charles J. Zaloudek, MD,* Kris M. Shekitka, MD,† and Fattaneh A. Tavassoli, MD‡*

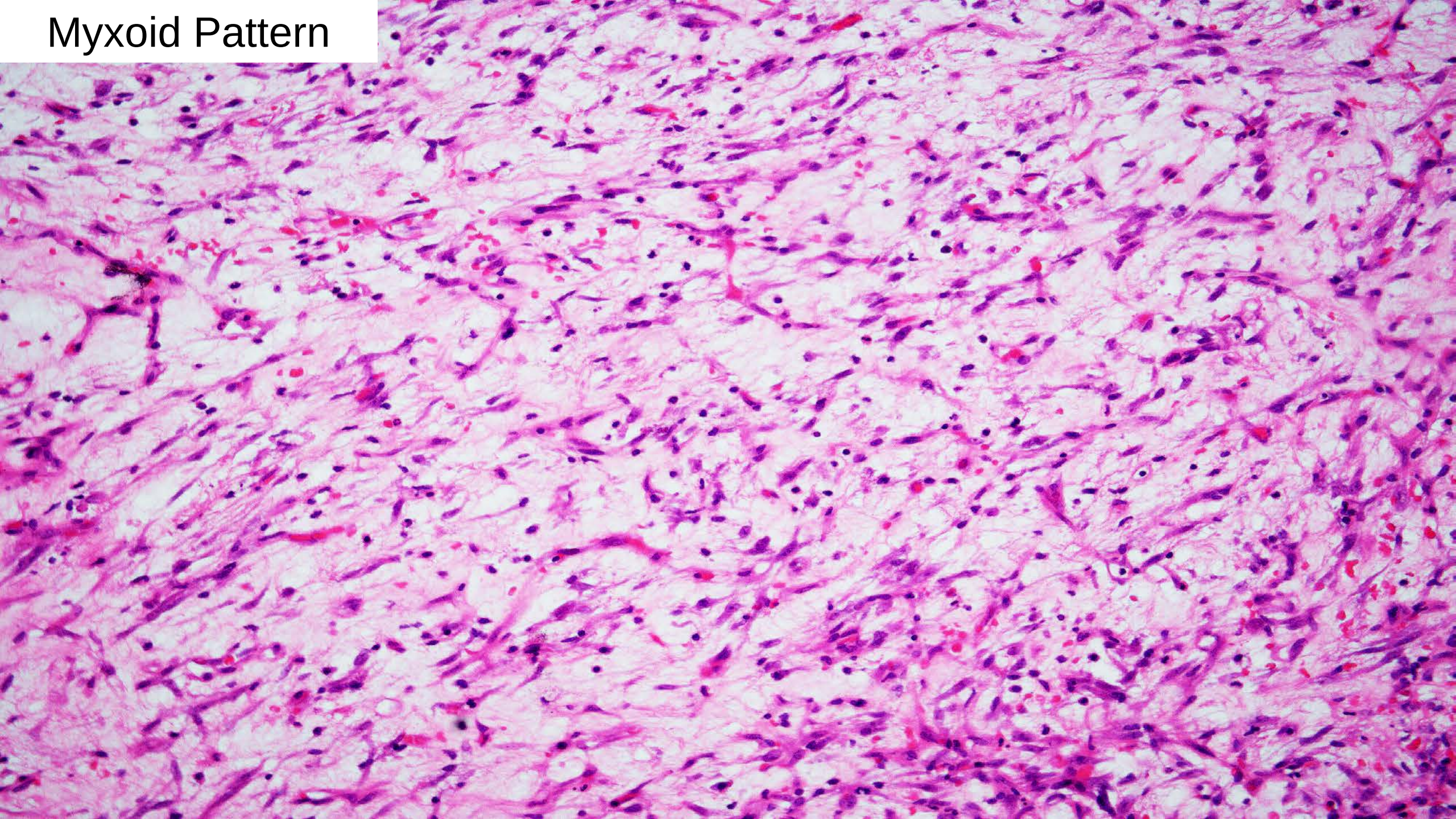




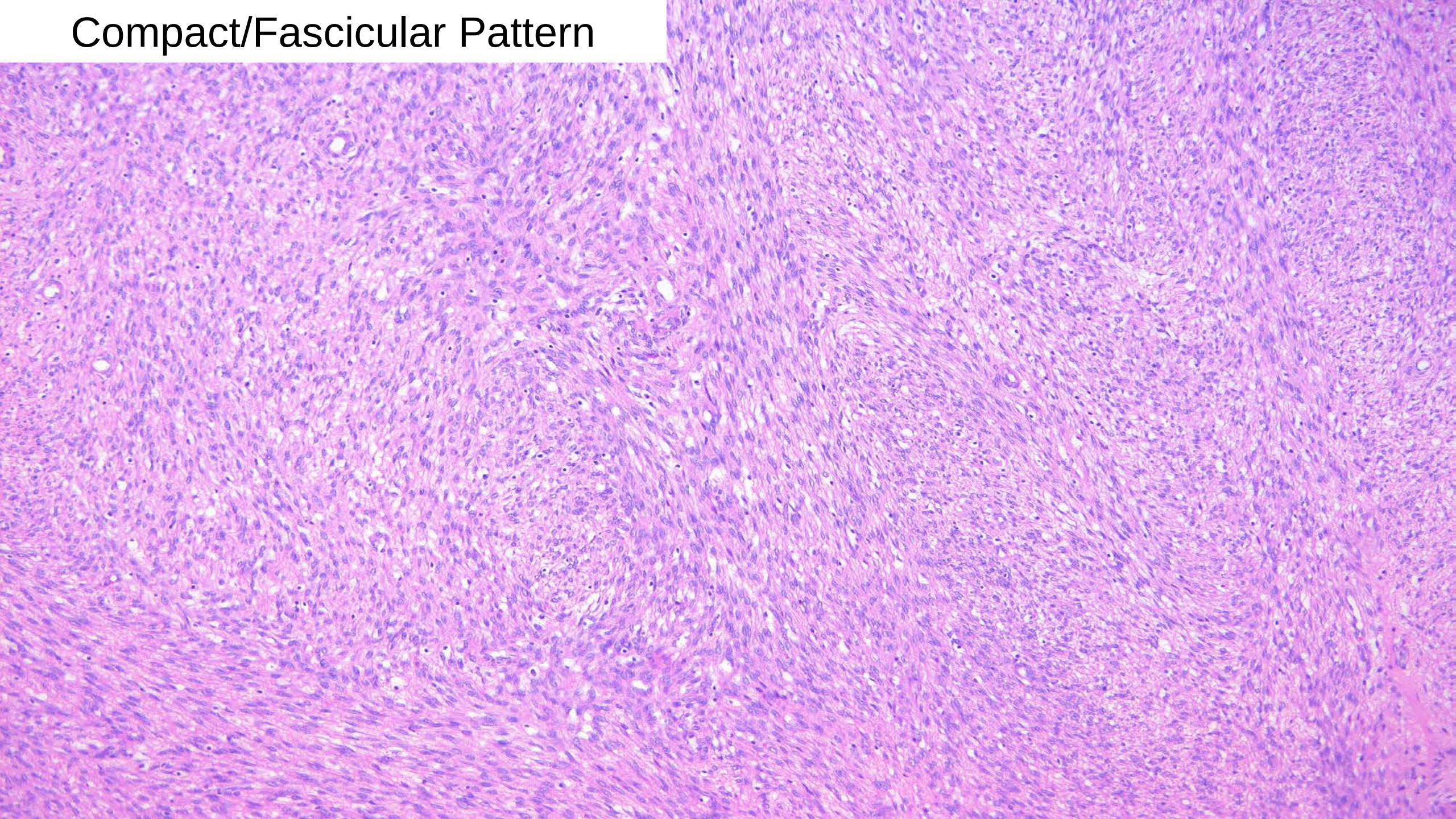
Myxoid Pattern



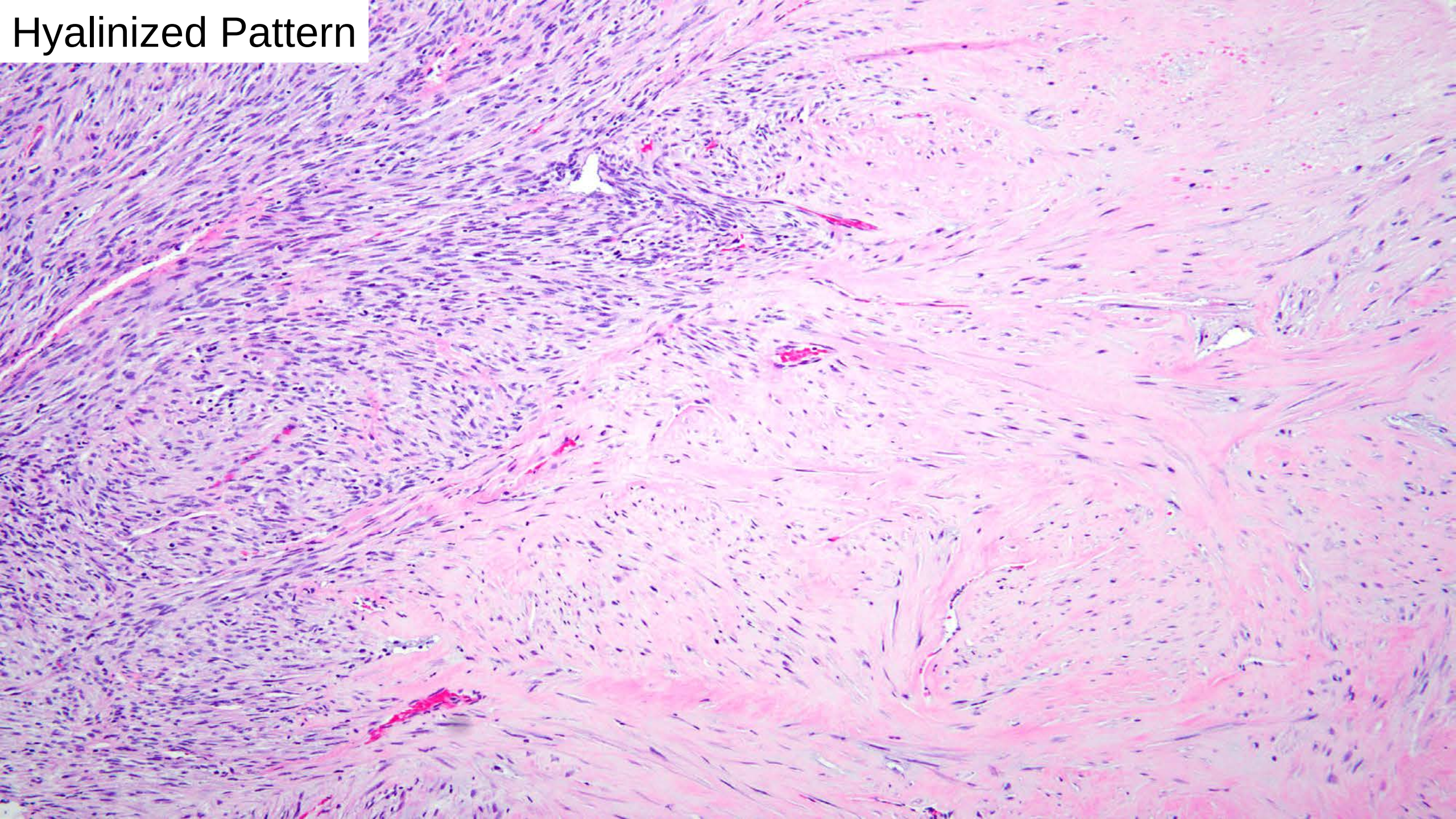
Myxoid Pattern

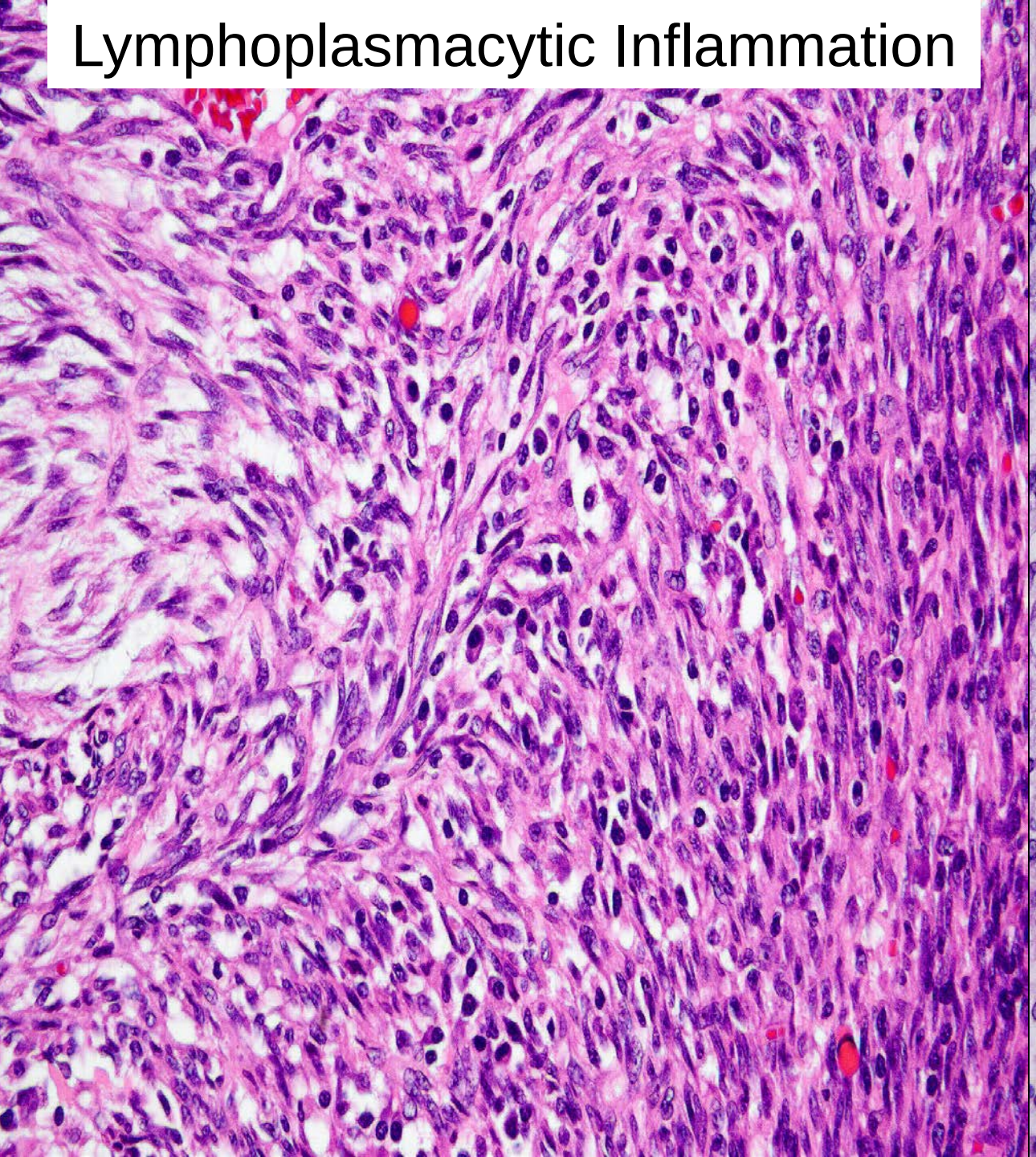


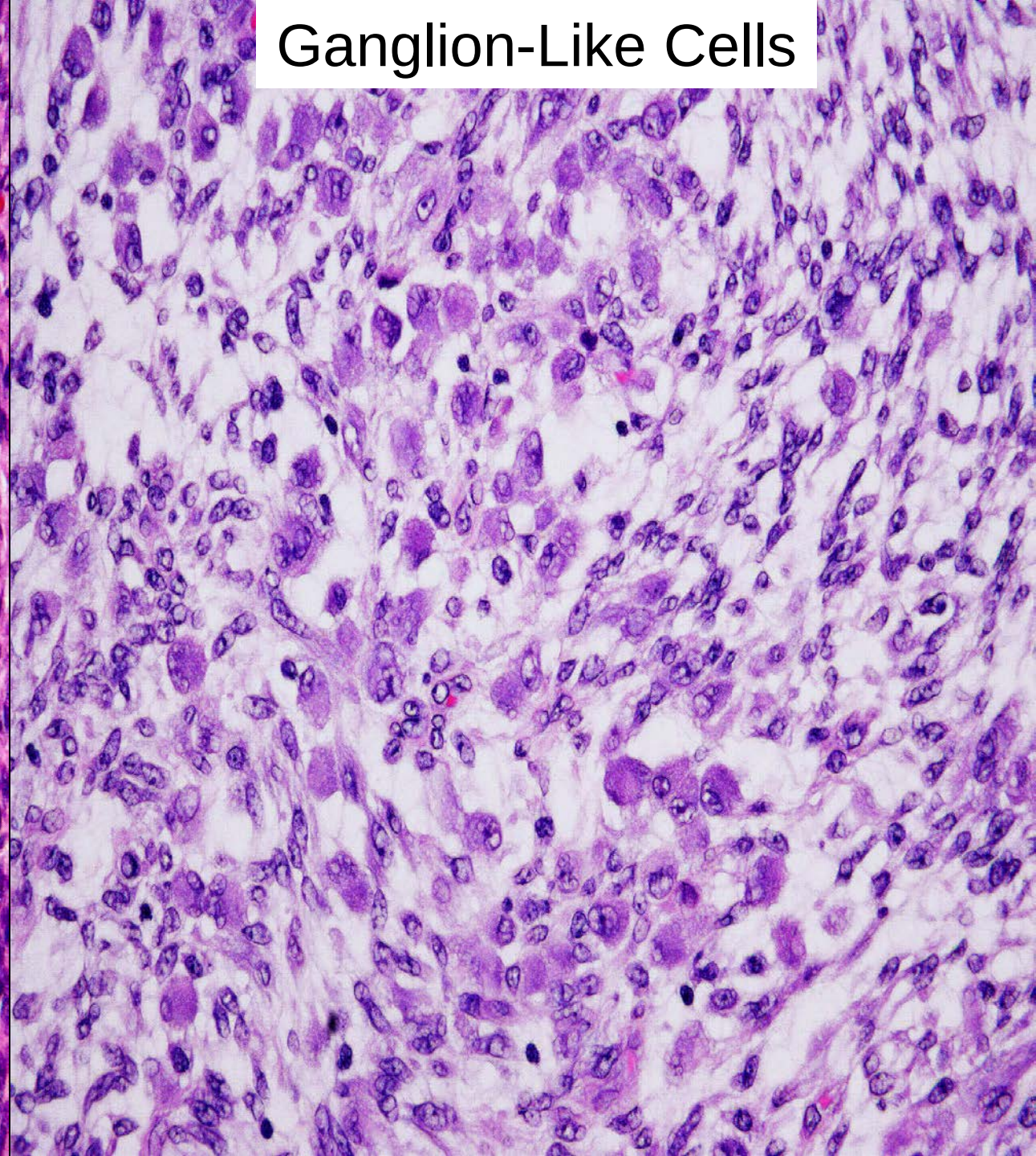
Compact/Fascicular Pattern

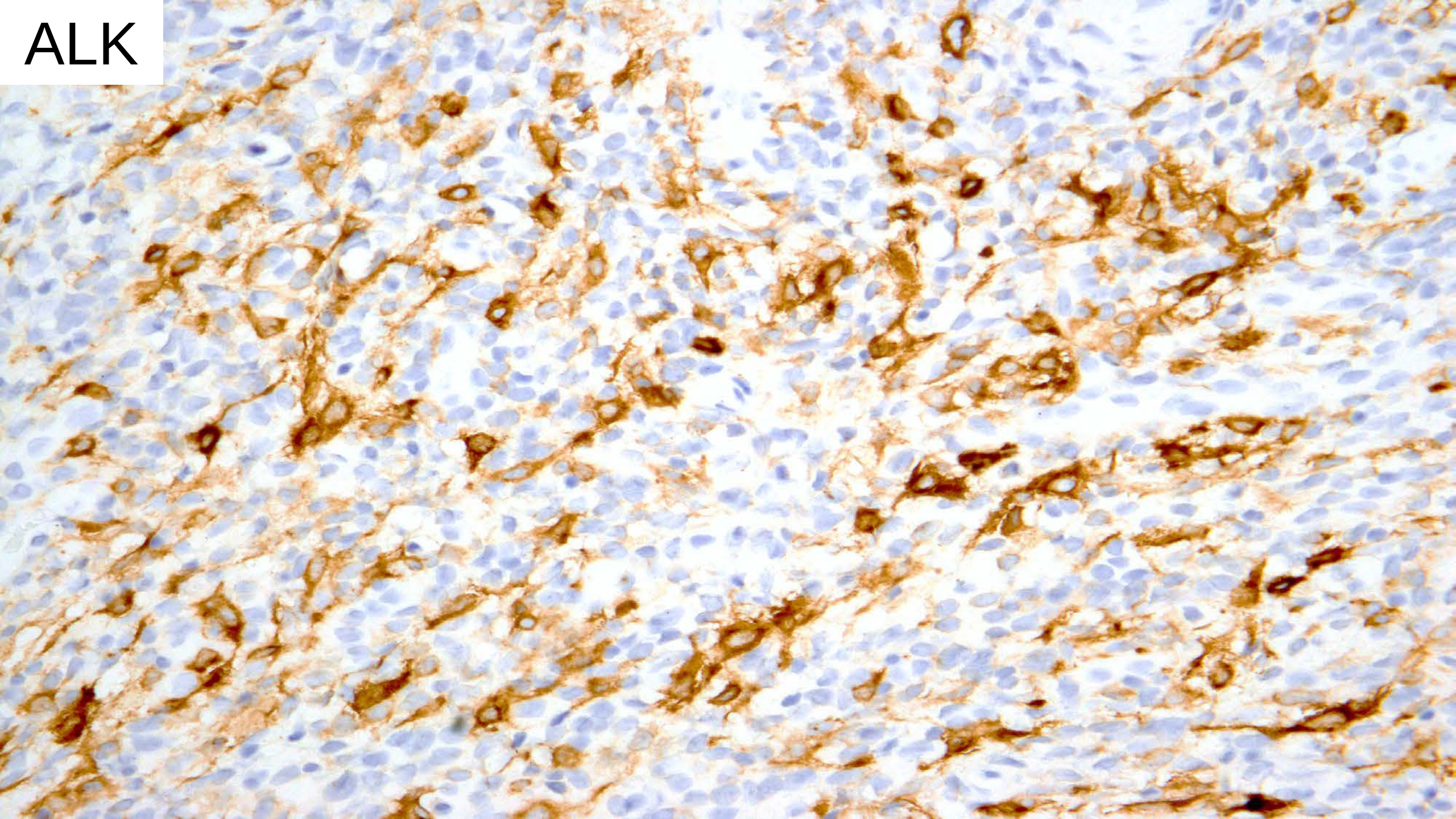


Hyalinized Pattern




Lymphoplasmacytic Inflammation


Ganglion-Like Cells


ALK

Immunohistochemistry

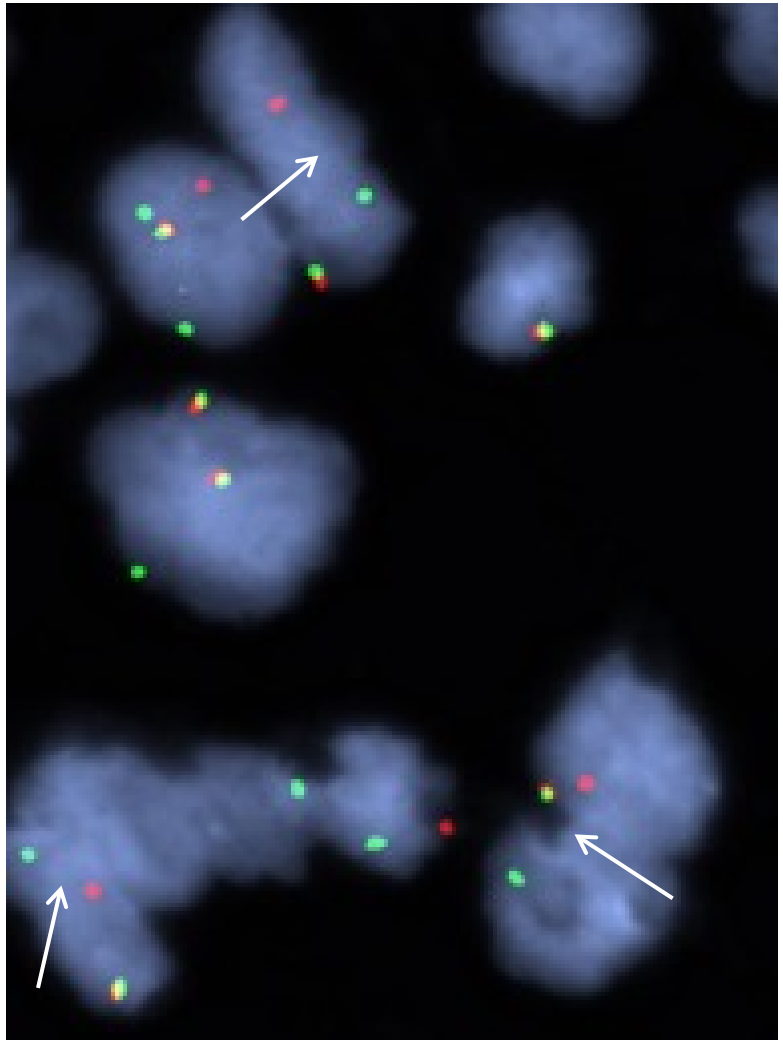
Study	SMA	Desmin	CD10	Caldesmon
Rabban 2005	100%, often weak/focal	67%, often weak/focal	NP	NP
Parra-Herran 2014	89%	90%	100%	43%, often weak/focal
Bennett 2017	NP	91%	85%	42%
Pickett 2017	100%	100%	33%	NP
Devereaux 2019	NP	67%	100%, often focal/patchy	67%
	95% (20/21)	85% (33/39)	81% (25/31)	48% (12/25)

IFITM1 positive in 19/23 (83%), BCOR weakly positive in 8/20 (40%), and transgelin in 22/23 (96%)

Bennett 2020

FISH

- 5’-end (green) of partner gene fused to 3’-end (red) of ALK tyrosine kinase domain
- Abnormal signals have been reported
- **PITFALL** – may get false negative result if intrachromosomal inversion present



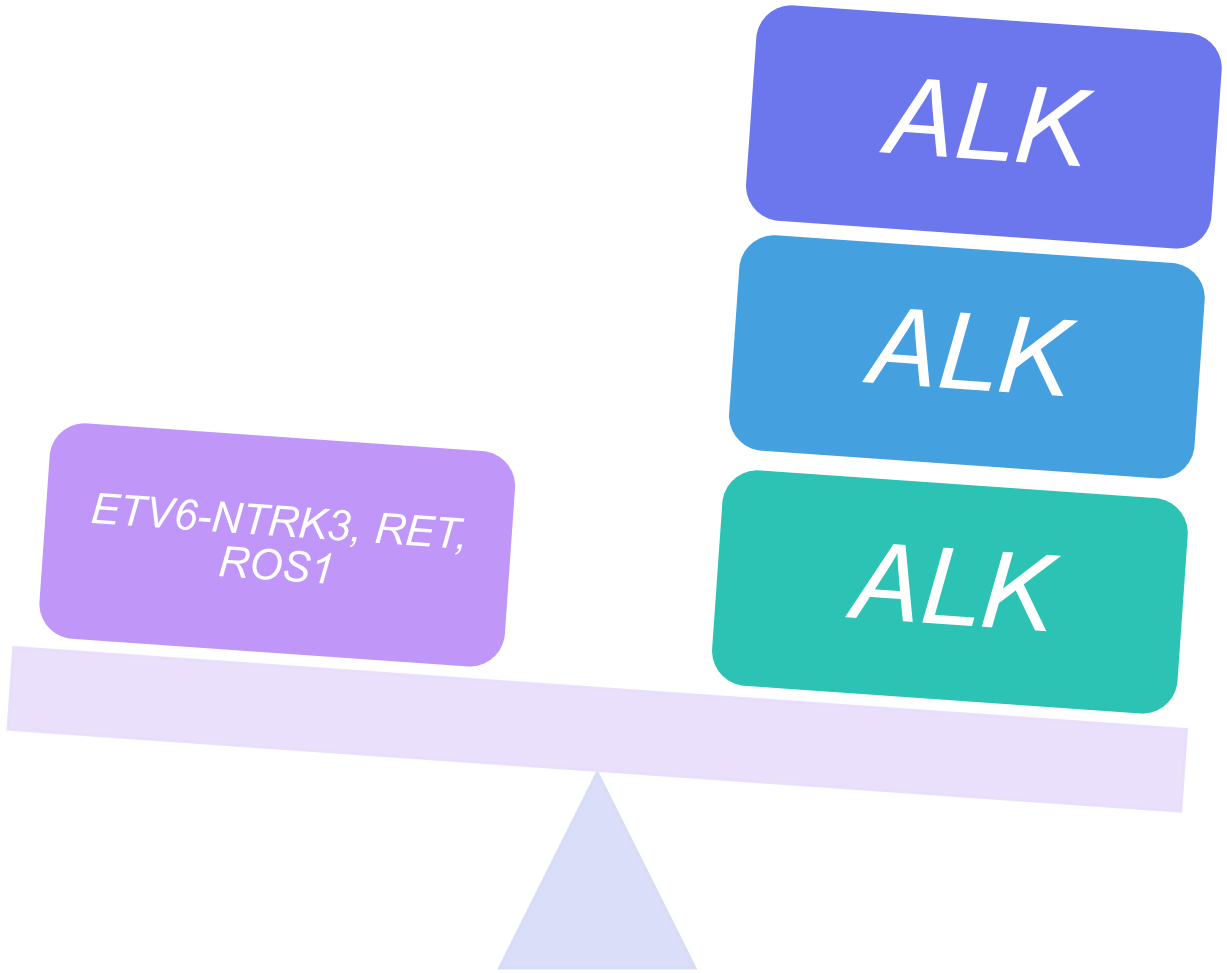
Haimes 2017
Bennett 2017
Devereaux 2019

RNA Fusion Analysis

Study	*TIMP3*	*THBS1*	*IGFBP5*	*DES*	*FN1*	*SEC31*	*TPM3*	*TNS1*
Bennett 2017	1	3	2	2	0	1	1	0
Haimes 2017 / Mohammed 2018	1	4	6	0	2	0	0	1
Cheek 2020	4	1	0	0	0	0	0	0
Devereaux 2020	5	2	0	0	0	0	0	0
	11	10	8	2	2	1	1	1

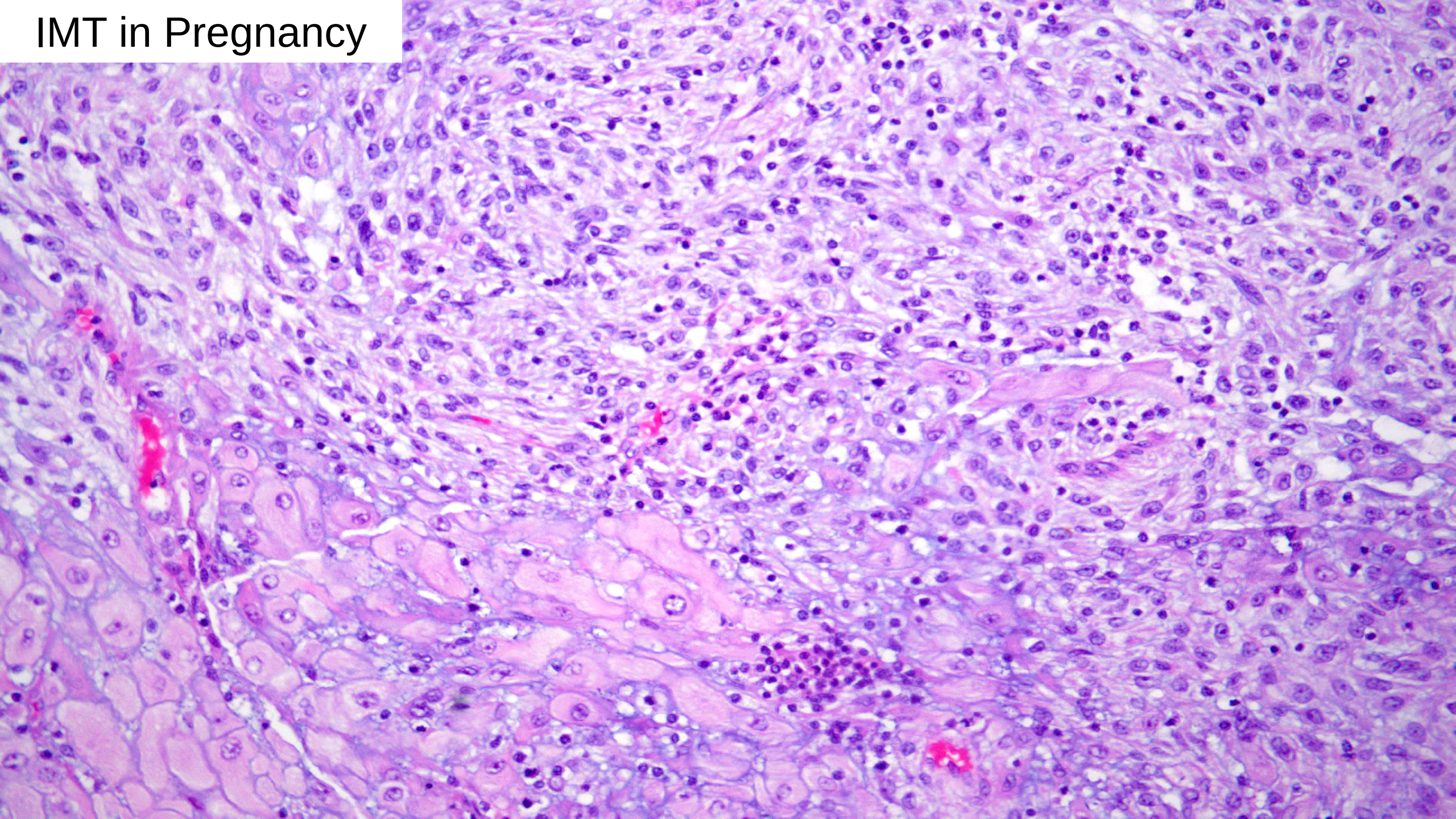
PITFALL: Not sequencing the entire *ALK* gene can result in a false negative result as fusions outside of exons 17-20 have been reported!

Non-ALK Fusions Are Rare in Uterine IMTs



Ladwig 2018
Takahashi 2018
Cheek 2020

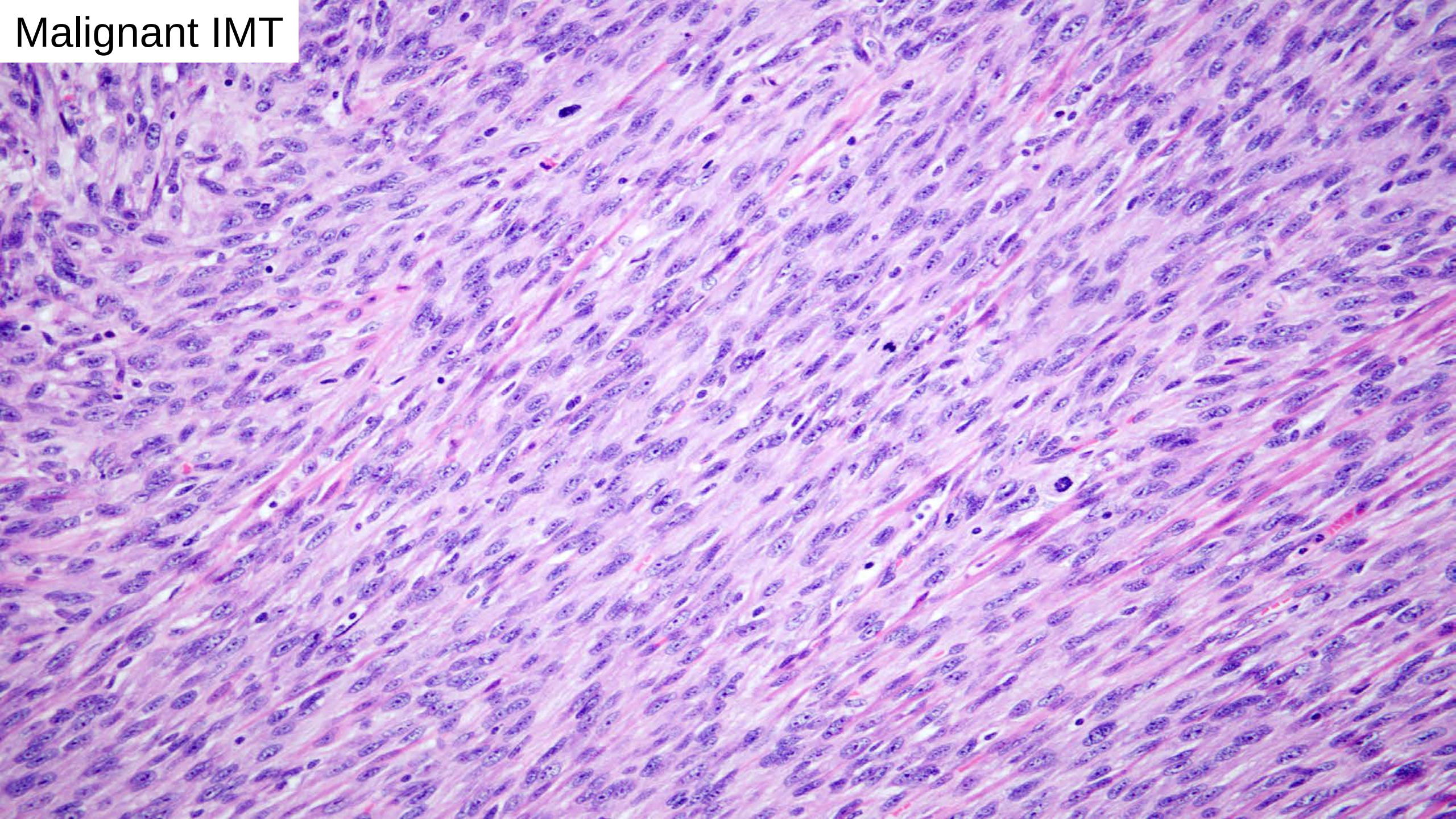
IMT in Pregnancy



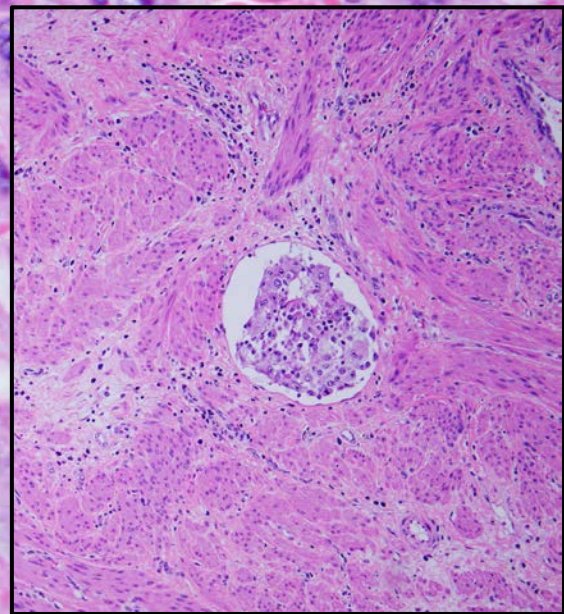
IMT in Pregnancy

- Setting of prenatal complications
- Location:
  - Detached
  - Adherent to placental disc/extraplacental membranes
  - Within placental disc
- Maternal origin
- ER weak to negative, PR strong
- *TIMP3* and *THBS1* fusions (*ALK, RET, ROS1)*
- Appear to have a favorable prognosis

Banet 2015
Ladwig 2018
Cheek 2020
Devereaux 2020

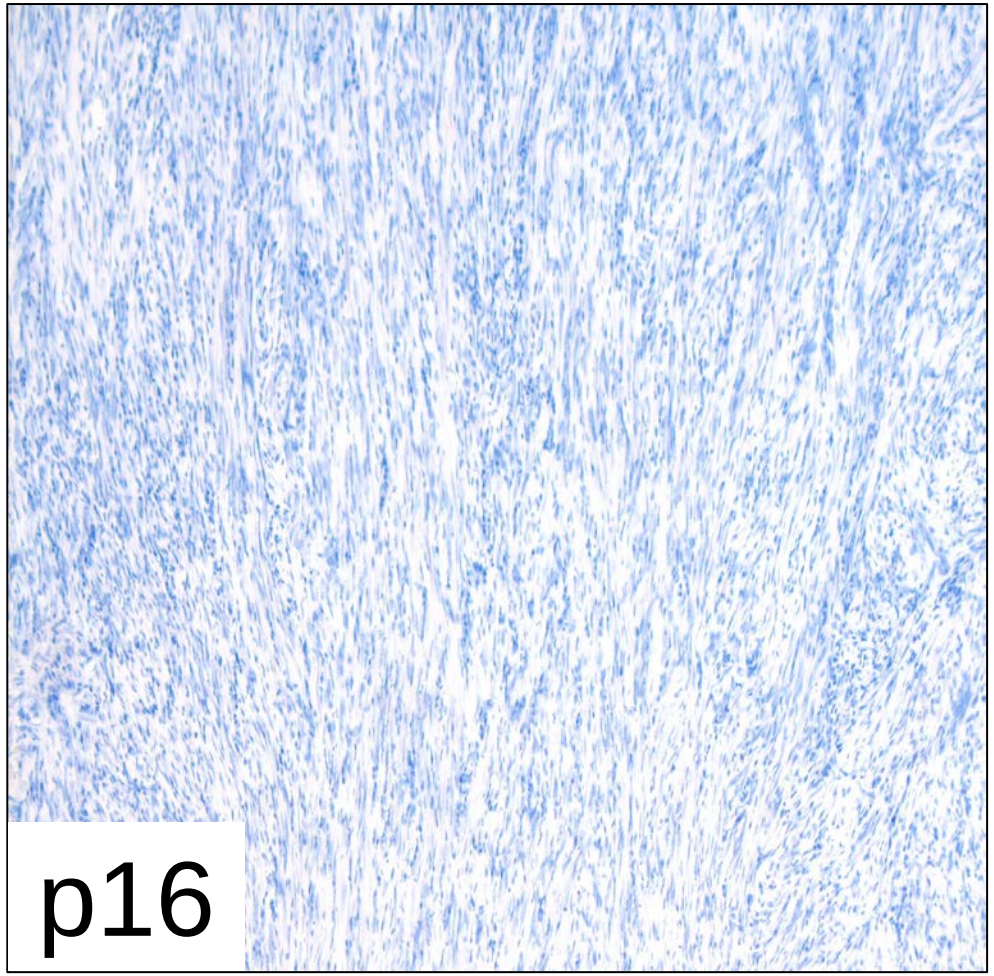

Malignant IMT

Malignant IMT



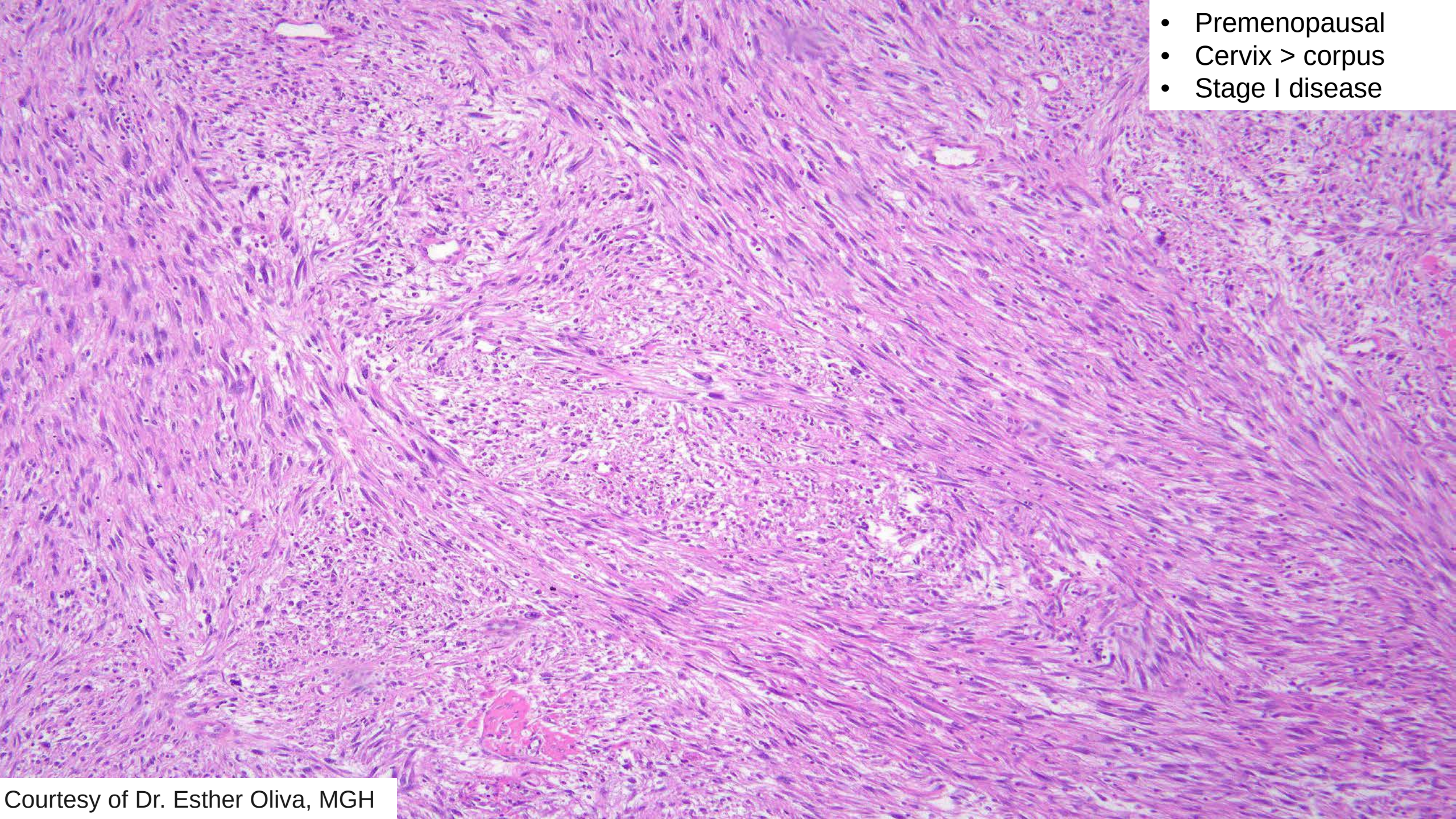
Malignant IMT

- Tumor cell necrosis
- Large tumor size (> 7 cm)
- Moderate to severe atypia
- High mitotic activity (> 10/10 HPF)
- Infiltrative borders
- ? Complete loss of p16 staining
  - *CDKN2A* deletion
- ? *TP53* mutation



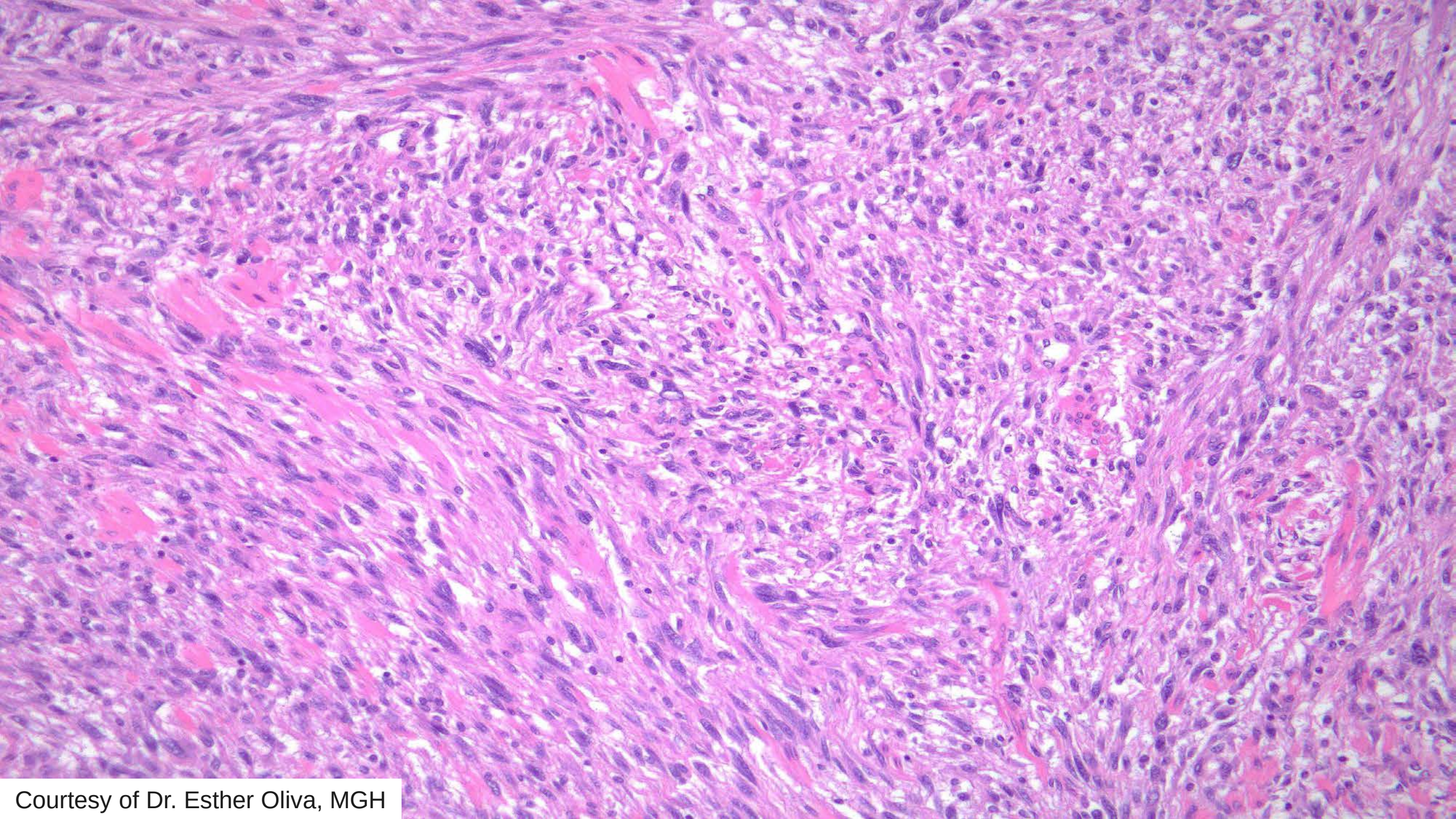
Busca 2018
Bennett 2020

NTRK-REARRANGED SPINDLE CELL SARCOMA (FIBROSARCOMA-LIKE UTERINE SARCOMA)

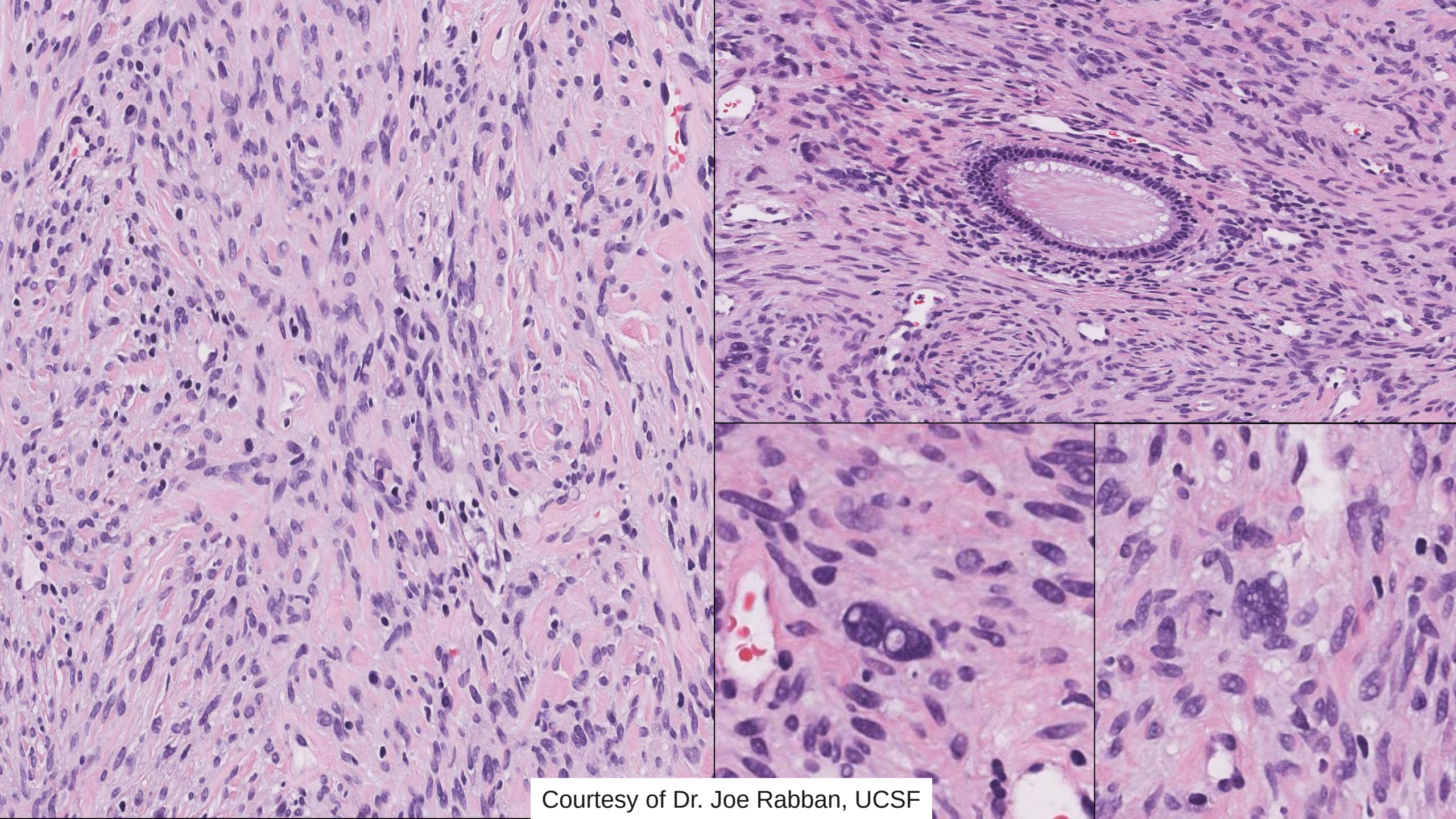


- Premenopausal
- Cervix > corpus
- Stage I disease

Courtesy of Dr. Esther Oliva, MGH



Courtesy of Dr. Esther Oliva, MGH



Courtesy of Dr. Joe Rabban, UCSF

Immunohistochemistry

Study	# of Cases	Pan-Trk	S100	CD34	SMA	Desmin	ER	PR
Chiang 2018	4	Cytoplasmic	< 10%	Neg	Focal	Neg	Neg	Neg
Croce 2019	7	Cytoplasmic	Diffuse (1 focal)	Diffuse (1 focal)	Not done	Neg	Neg	Neg
Rabban 2020	3	Cytoplasmic	Diffuse (1 focal)	Neg	Neg	Neg	Neg	Neg

PITFALL: Leiomyosarcomas and normal smooth muscle may also be Pan-Trk positive in the absence of *NTRK* fusion

Molecular Findings

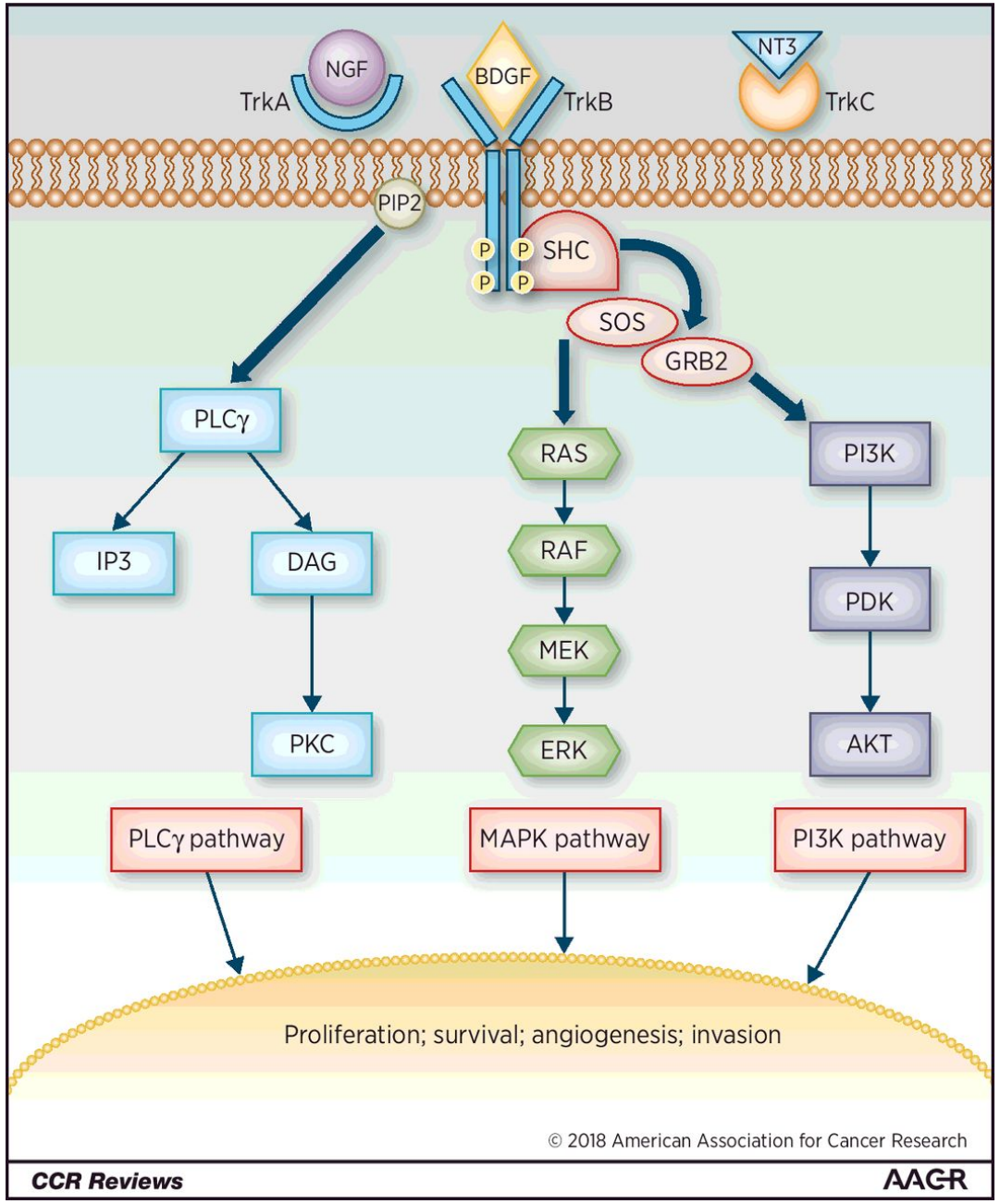
NTRK Gene	Fusion Partner
NTRK1	***TPM3***, *TPR, LMNA*
NTRK3	*RBPMS, EML4, SPECC1L*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman



I have a uterine tumor that is morphologically identical to a *NTRK* sarcoma, but besides being desmin, ER, and PR negative, S100 and pan-Trk are also negative. Negative for *NTRK* fusion. What now?

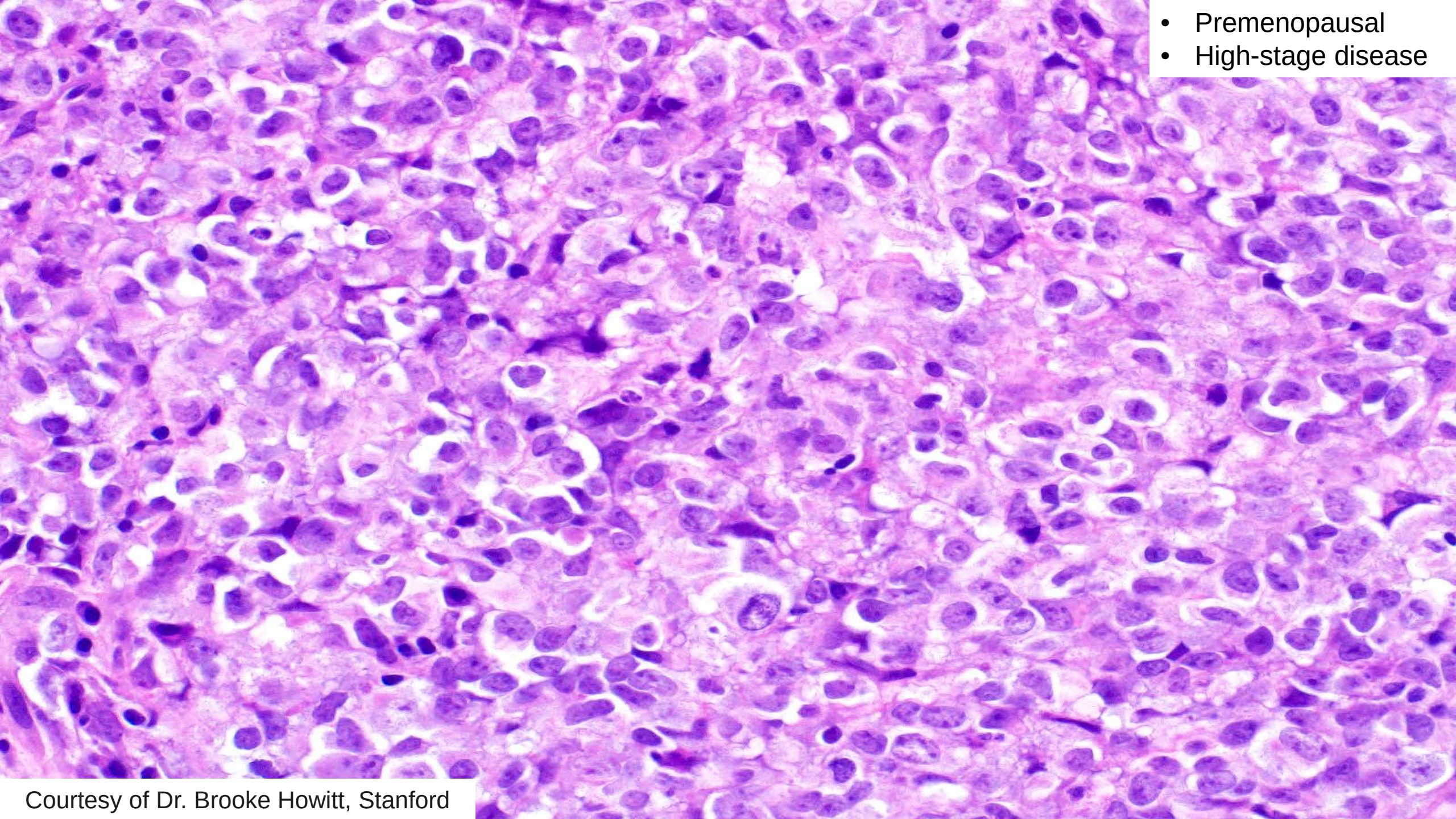
Test for *COL1A1-PDGFB* fusion and if positive → *COL1A1-PDGFB* rearranged sarcoma

Uterine and vaginal sarcomas resembling fibrosarcoma: a clinicopathological and molecular analysis of 13 cases showing common *NTRK*-rearrangements and the description of a *COL1A1-PDGFB* fusion novel to uterine neoplasms

Sabrina Croce[1,2] · Isabelle Hostein[1] · Teri A. Longacre[3] · Anne M. Mills[4] · Gaëlle Pérot[1] · Mojgan Devouassoux-Shisheboran[5] · Valérie Velasco[1] · Anne Floquet[6] · Frédéric Guyon[7] · Camille Chakiba[6] · Denis Querleu[7] · Emmanuel Khalifa[1] · Laetitia Mayeur[1] · Flora Rebier[1] · Sophie Leguellec[8] · Isabelle Soubeyran[1] · W. Glenn McCluggage[9]

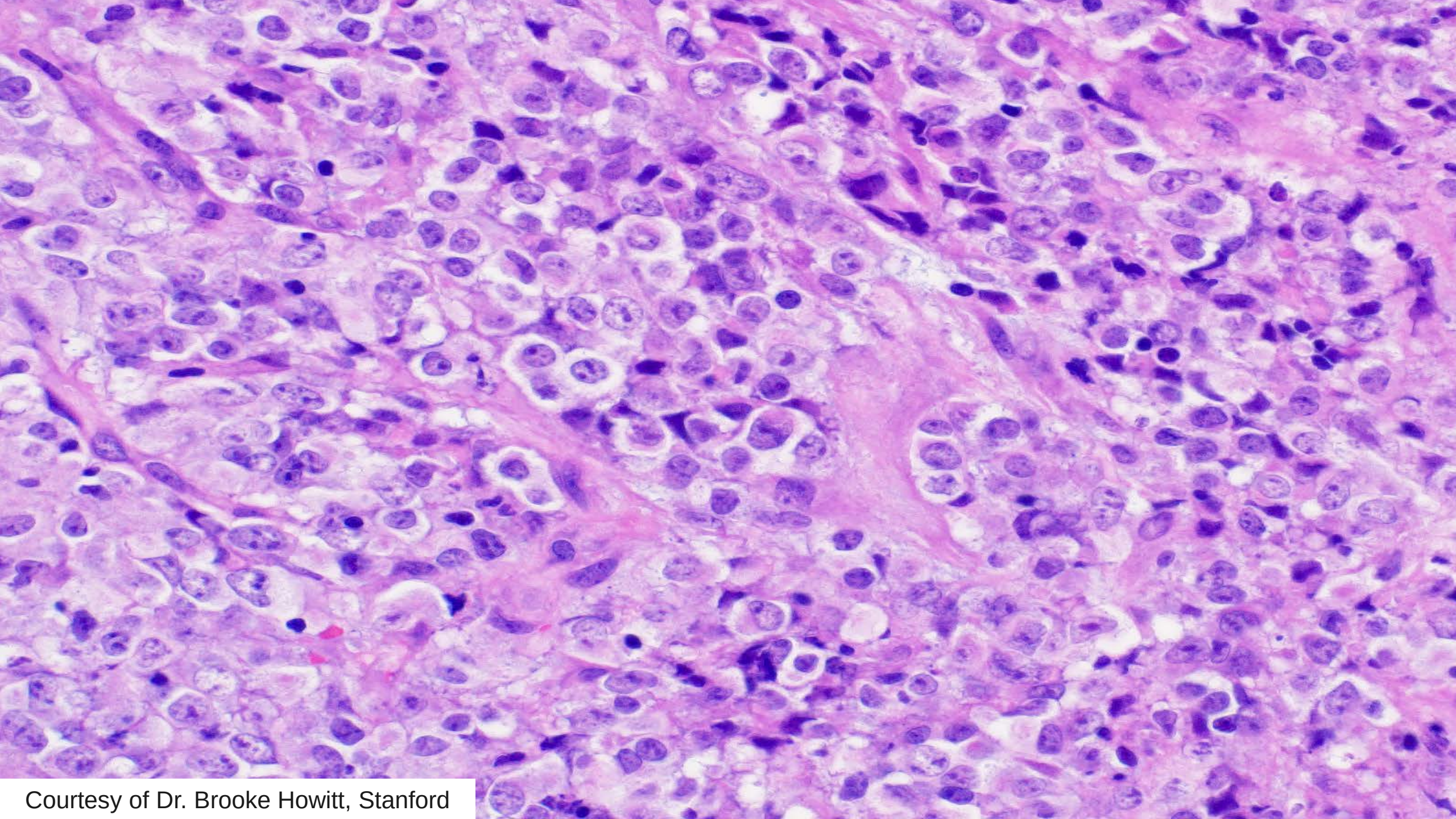
- 48, 60, 82 years
- 2 cervix, 1 corpus
- 1 DOD, 1 NED, 1 recent
- ? Imatinib

SMARCA4-DEFICIENT UTERINE SARCOMA (SDUS)



- Premenopausal
- High-stage disease

Courtesy of Dr. Brooke Howitt, Stanford



Courtesy of Dr. Brooke Howitt, Stanford

Infrequent Morphological Features

- Cords or vague nests
- Focal myxoid stroma
- Stromal hyalinization
- Focal phyllodiform architecture
- Biphasic (small and large cells)
- Spindle cells

Lin 2019
Kolin 2020

Overall, SDUS is Characterized by NEGATIVE Immunohistochemistry

- BRG-1 loss (rarely INI-1)
- Claudin-4
- Keratins
- EMA
- Myogenic markers
- Hormone receptors
- WT1
- HMB-45

MMR retained
p53 wildtype

Kolin 2018
Lin 2019
Kolin 2020

Main DDX: Undifferentiated Carcinoma

Parameter	SDUS	Undifferentiated Carcinoma
Age	Mean: 36 years Median: 34 years	Mean/median: 61 years
Claudin-4	0%	45%
MMRD/MSI	0%	44%
***TP53* Mutation**	0%	34%
Other Mutations (non *SMARCA4/SMARCB1)*	Rare	*PTEN, PIK3CA, CTNNB1, ARID1A/B*
CNV	45% (few)	84%
Disease-Specific Survival	Median: 9 mo	Median: 36 mo

PITFALL: BRG-1 and INI-1 loss can be seen in undifferentiated carcinomas!

Kolin 2020

Hereditary Basis?

- Rhabdoid Tumor Predisposition Syndrome Type 2 is characterized by *SMARCA4* germline mutations
- Daughter diagnosed with SCCOHT at 31 years
- Mother diagnosed with SDUS at 55 years

Connor 2020

Role of Targeted Therapy?

MOLECULAR CANCER THERAPEUTICS

Home About Articles For Authors Alerts News Search

Small Molecule Therapeutics

Selective Killing of SMARCA2- and SMARCA4-deficient Small Cell Carcinoma of the Ovary, Hypercalcemic Type Cells by Inhibition of EZH2: *In Vitro* and *In Vivo* Preclinical Models

Elayne Chan-Penebre, Kelli Armstrong, Allison Drew, Alexandra R. Grassian, Igor Feldman, Sarah K. Knutson, Kristy Kuplast-Barr, Maria Roche, John Campbell, Peter Ho, Robert A. Copeland, Richard Chesworth, Jesse J. Smith, Heike Keilhack, and Scott A. Ribich

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-06958-9 OPEN

CDK4/6 inhibitors target SMARCA4-determined cyclin D1 deficiency in hypercalcemic small cell carcinoma of the ovary

Yibo Xue et al.#

OXFORD

JNCI J Natl Cancer Inst (2018) 110(7): djx277

doi: 10.1093/jnci/djx277
First published online January 22, 2018
Brief Communication

BRIEF COMMUNICATION

Immune-Active Microenvironment in Small Cell Carcinoma of the Ovary, Hypercalcemic Type: Rationale for Immune Checkpoint Blockade

Petar Jelinic*, Jacob Ricca*, Elke Van Oudenhove, Narciso Olvera, Taha Merghoub, Douglas A. Levine*, Dmitriy Zamarin*

RHABDOMYOSARCOMA (RMS)

Rhabdomyosarcoma in the Uterus

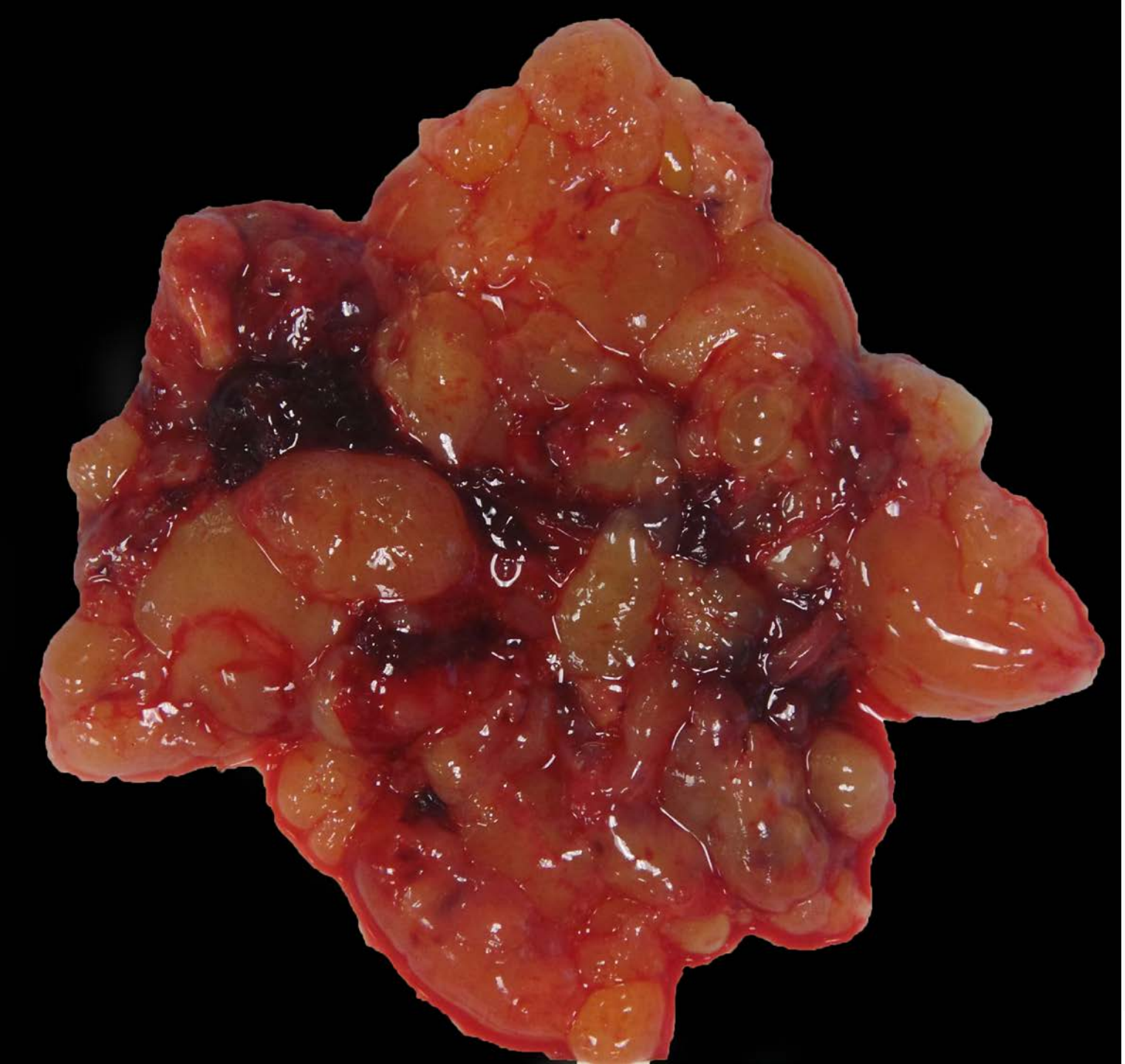
- Embryonal Rhabdomyosarcoma
- Alveolar Rhabdomyosarcoma
- Pleomorphic Rhabdomyosarcoma

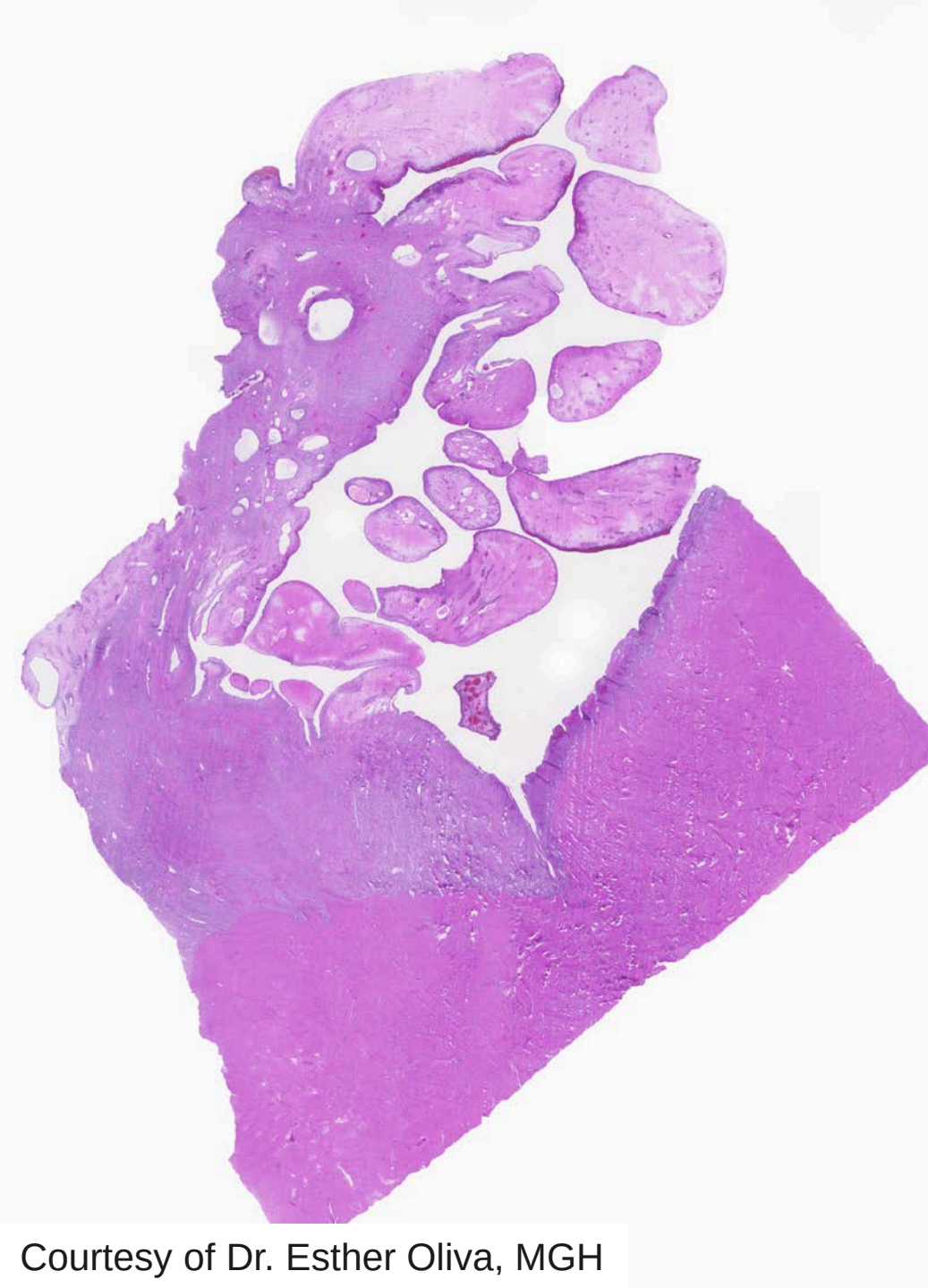
Alveolar RMS

- Nests or alveoli separated by collagenous stroma
- Small round blue cells and admixed rhabdomyoblasts
- Adhere to septa peripherally and non-cohesive centrally
- *PAX3-FOXO1* or *PAX7-FOXO1* fusions

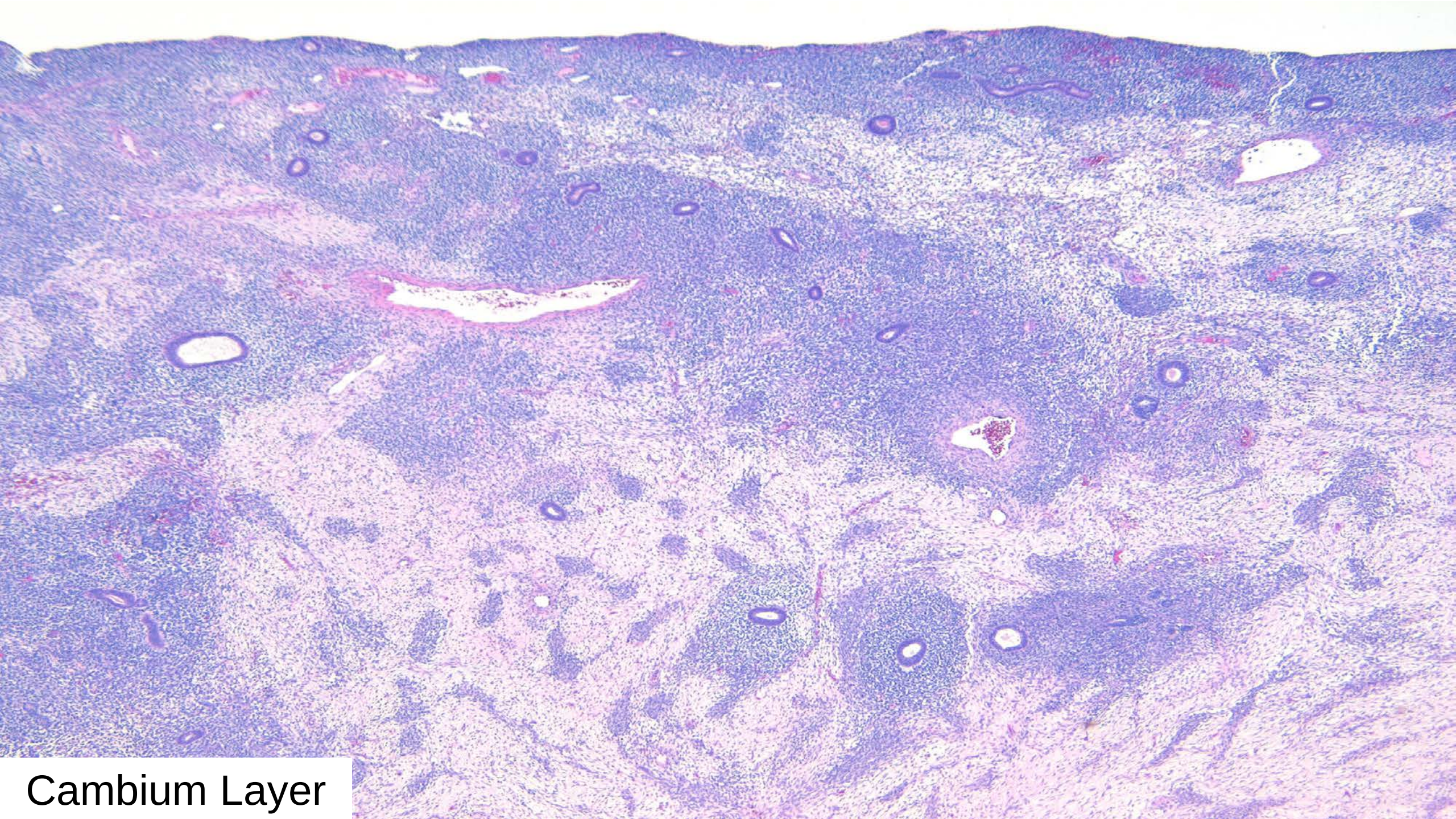
Pleomorphic RMS

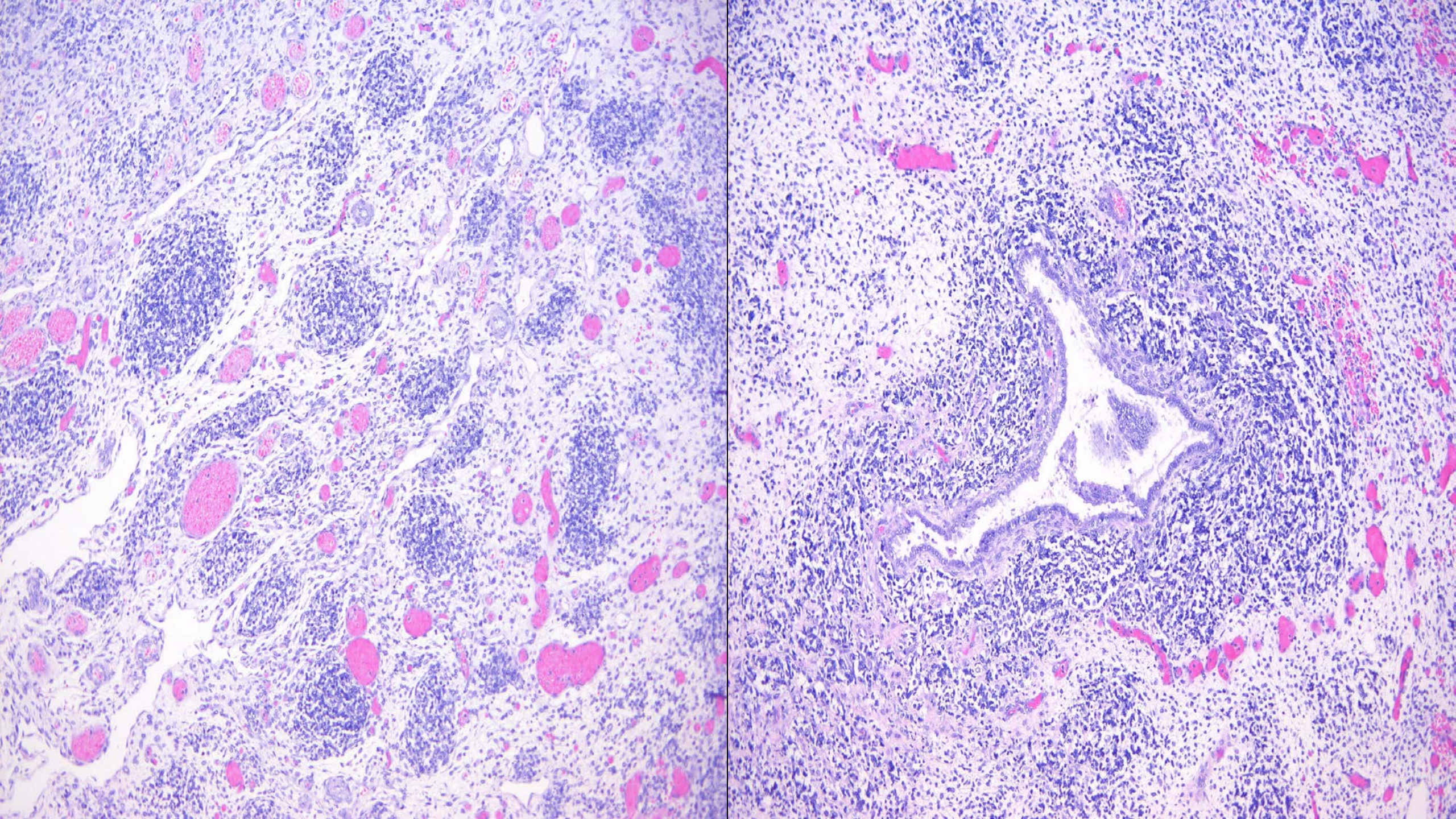
- Markedly atypical polygonal, spindle, and giant cells with brisk mitoses
- May be difficult to visualize cross striations
- **PITFALL**: Sample thoroughly to exclude carcinosarcoma/ adenosarcoma with rhabdomyosarcomatous differentiation!

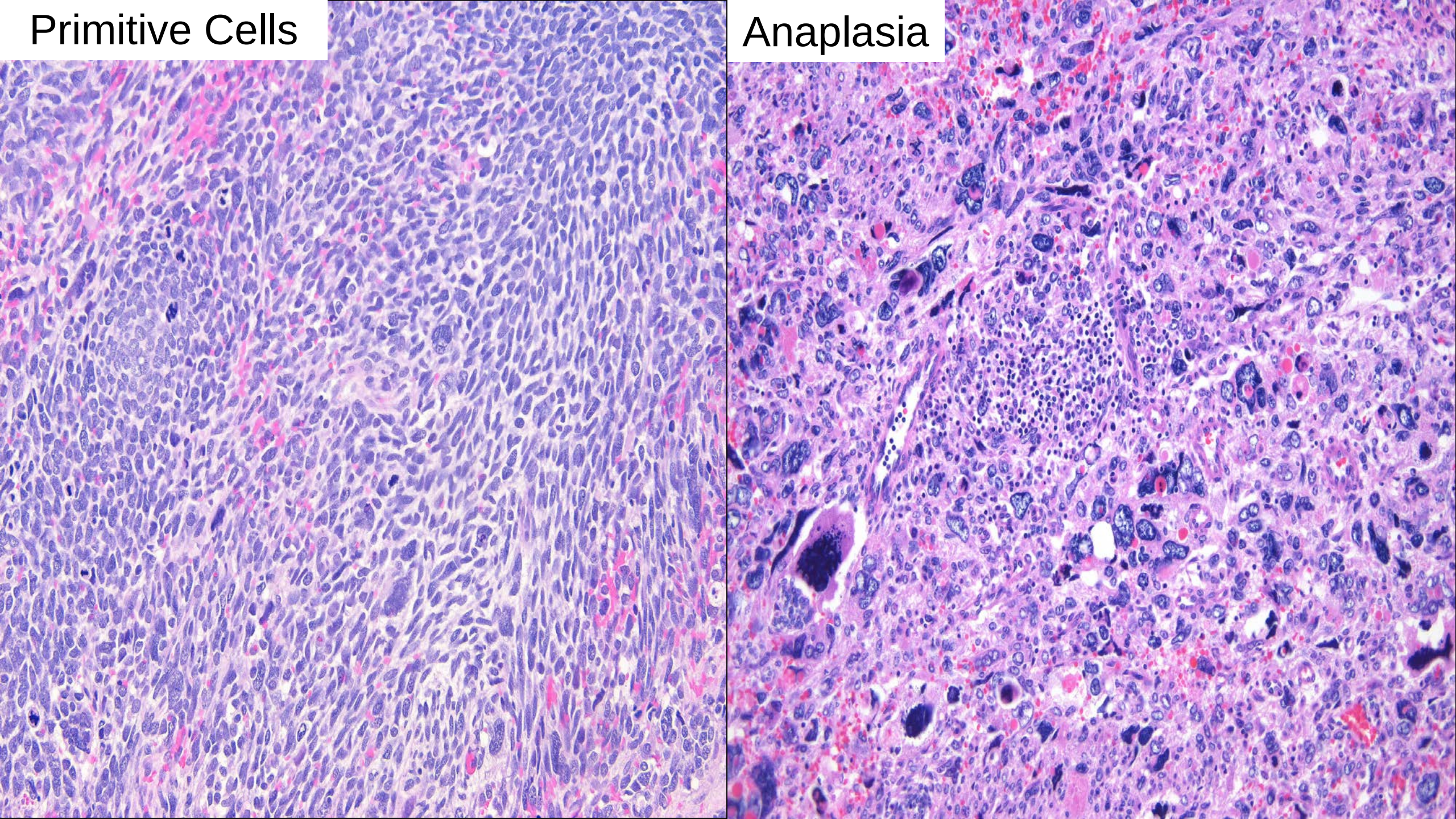




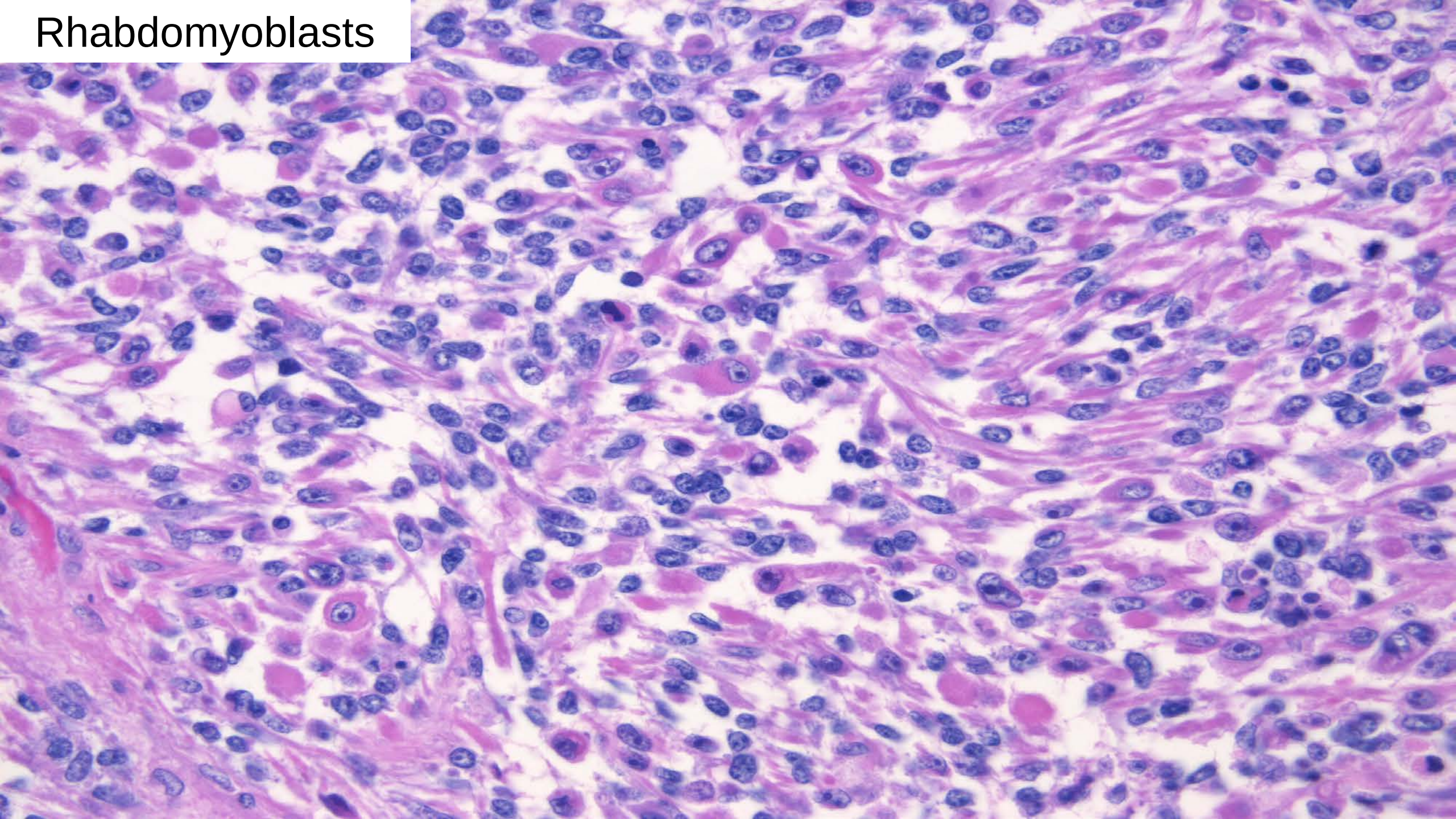
Courtesy of Dr. Esther Oliva, MGH


Cambium Layer

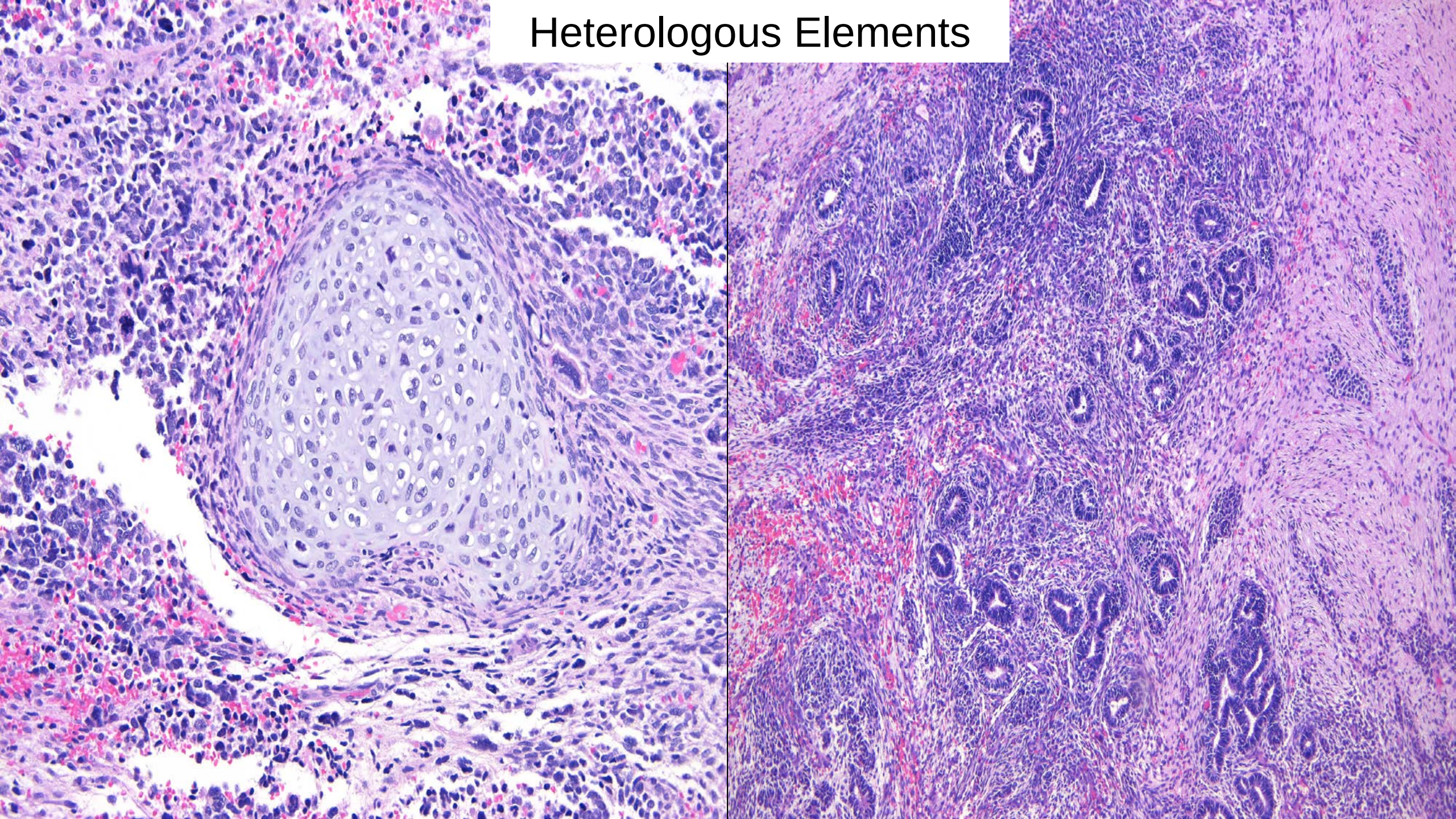



Primitive Cells
Anaplasia

Rhabdomyoblasts



Heterologous Elements



BRIEF REPORT

Human Mutation

OFFICIAL JOURNAL

HGVS

HUMAN GENOME VARIATION SOCIETY

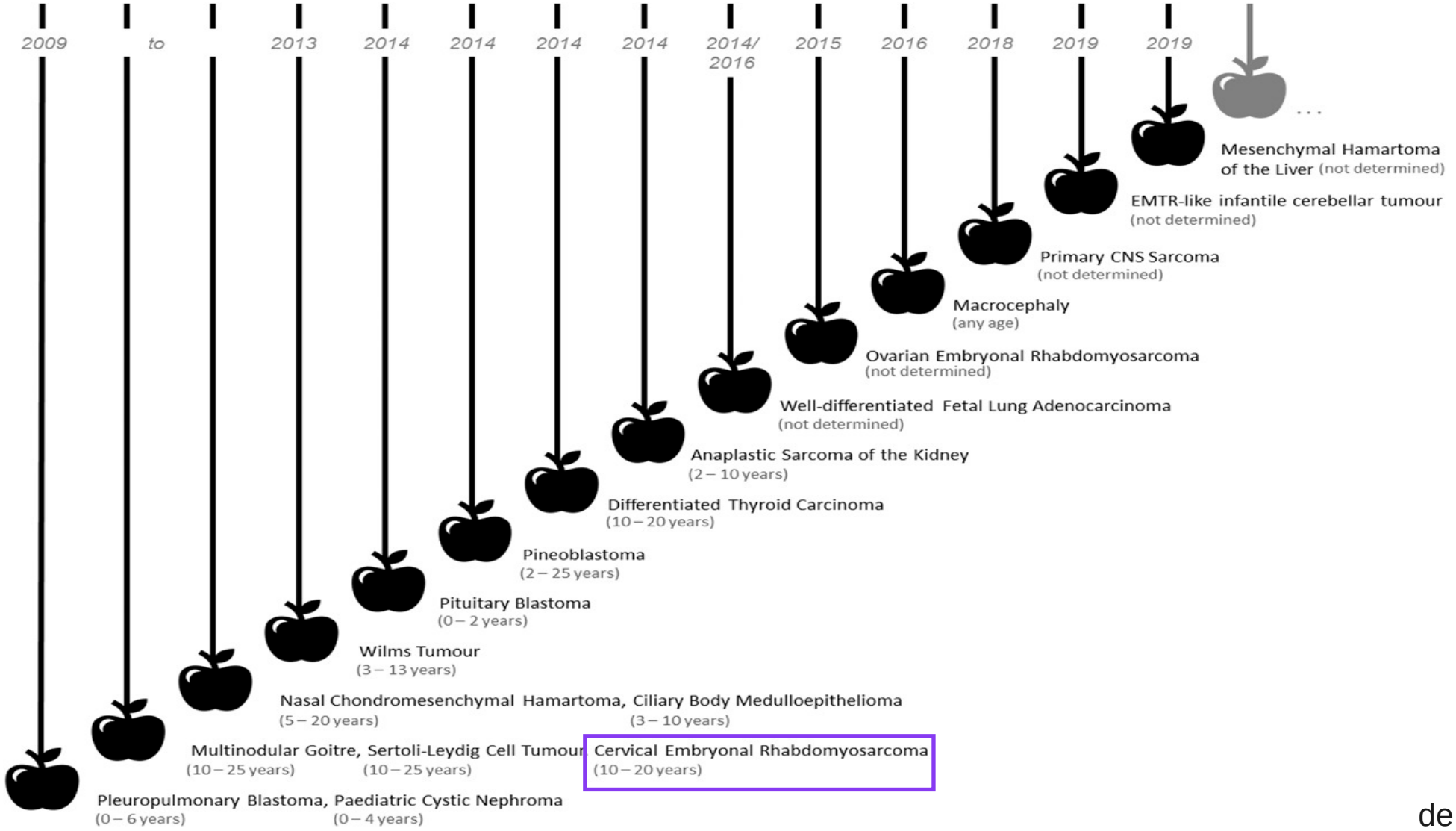
www.hgvs.org

Extending the Phenotypes Associated with *DICER1* Mutations

William D. Foulkes,[1–3]* Amin Bahubeshi,[1,2] Nancy Hamel,[1,3] Barbara Pasini,[4] Sofia Asioli,[5] Gareth Baynam,[6,7] Catherine S. Choong,[7,8] Adrian Charles,[9] Richard P. Frieder,[10] Megan K. Dishop,[11] Nicole Graf,[12] Mesiha Ekim,[13] Dorothée Bouron-Dal Soglio,[14] Jocelyne Arseneau,[15] Robert H. Young,[16] Nelly Sabbaghian,[1,2] Archana Srivastava,[1,2] Marc D. Tischkowitz,[1,2] and John R. Priest[17]

Cervical ERMS found to be associated with germline *DICER1* mutations

The Spectrum of DICER1 Syndrome



de Kock 2019

Not all *DICER1* Mutations in ERMS are Germline

SHORT COMMUNICATION

BJC

British Journal of Cancer (2017) 116, 1621–1626 | doi: 10.1038/bjc.2017.147

Keywords: sarcoma; DICER1; mutations; biallelic; embryonal rhabdomyosarcoma

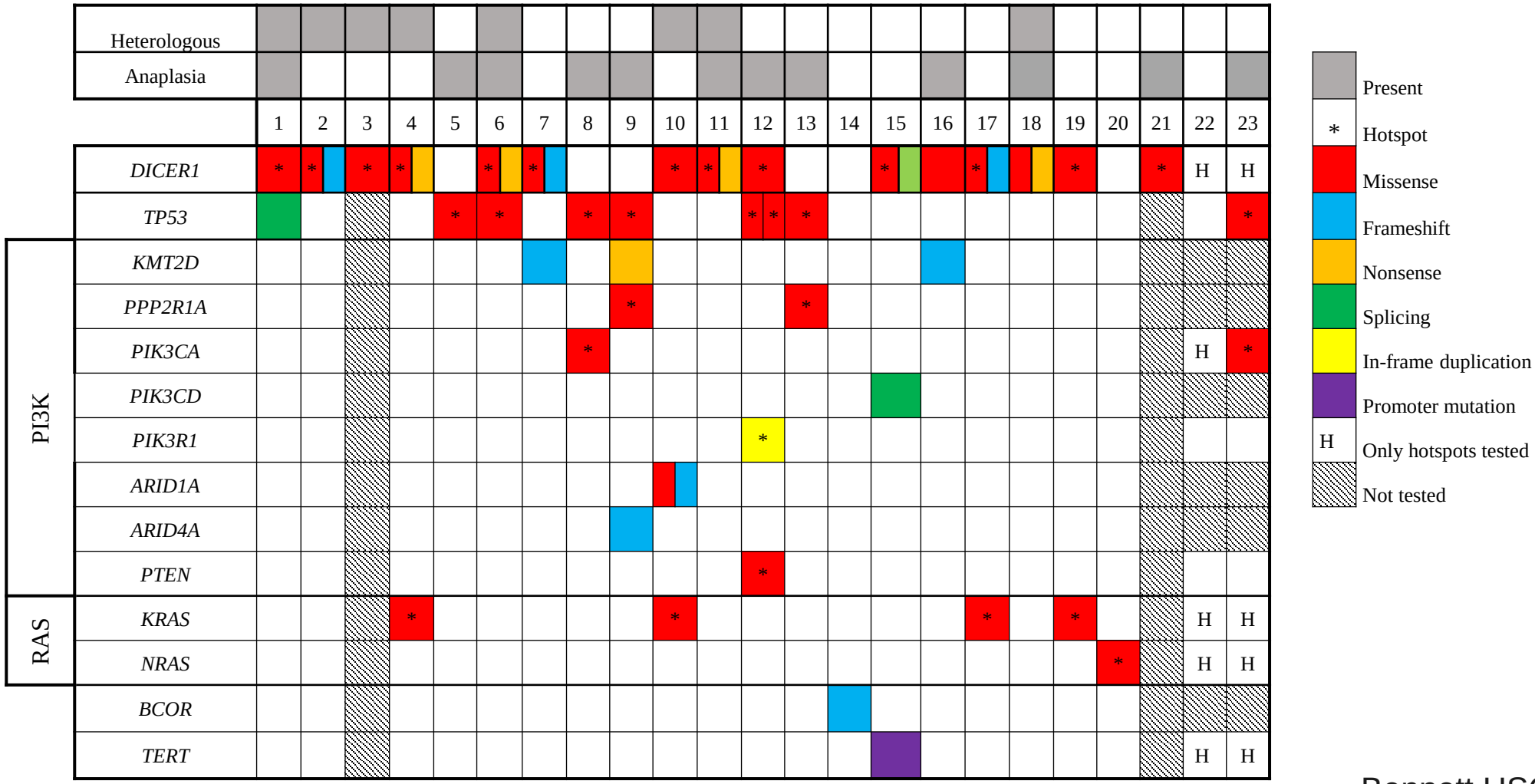
Sequencing of *DICER1* in sarcomas identifies biallelic somatic *DICER1* mutations in an adult-onset embryonal rhabdomyosarcoma

Leanne de Kock[1,2], Barbara Rivera[1,2], Timothée Revil[3], Paul Thorner[4,5], Catherine Goudie[6], Dorothée Bouron-Dal Soglio[7], Catherine S Choong[8,9], John R Priest[10], Paul J van Diest[11], Jantima Tanboon[12,13], Anja Wagner[14], Jiannis Ragoussis[3], Peter FM Choong[15] and William D Foulkes*[,1,2,16]

Case #	Age at Dx	Tumor Type	Tumor Site	*DICER1* RNase IIIb Status	*DICER1* LOF Status
E01	12			S	G
E02	13			S	G
E03	13			S	G
E04	14			S	G
E05	53			S	G
E06	14			S	S
E07	41			S	S
E08	44			S	S
E09	19			–	–
E10	53			–	–
E11	29			–	≈
E12	30			–	≈
E13	41			–	≈
E14	3		*		
E15	53			S	G
E16	52			S	S
E17	69			S	S
E18	44			–	≈
E19	23			S	≈

de Kock 2020

ERMS in the Uterine Corpus also Harbor *DICER1* Mutations

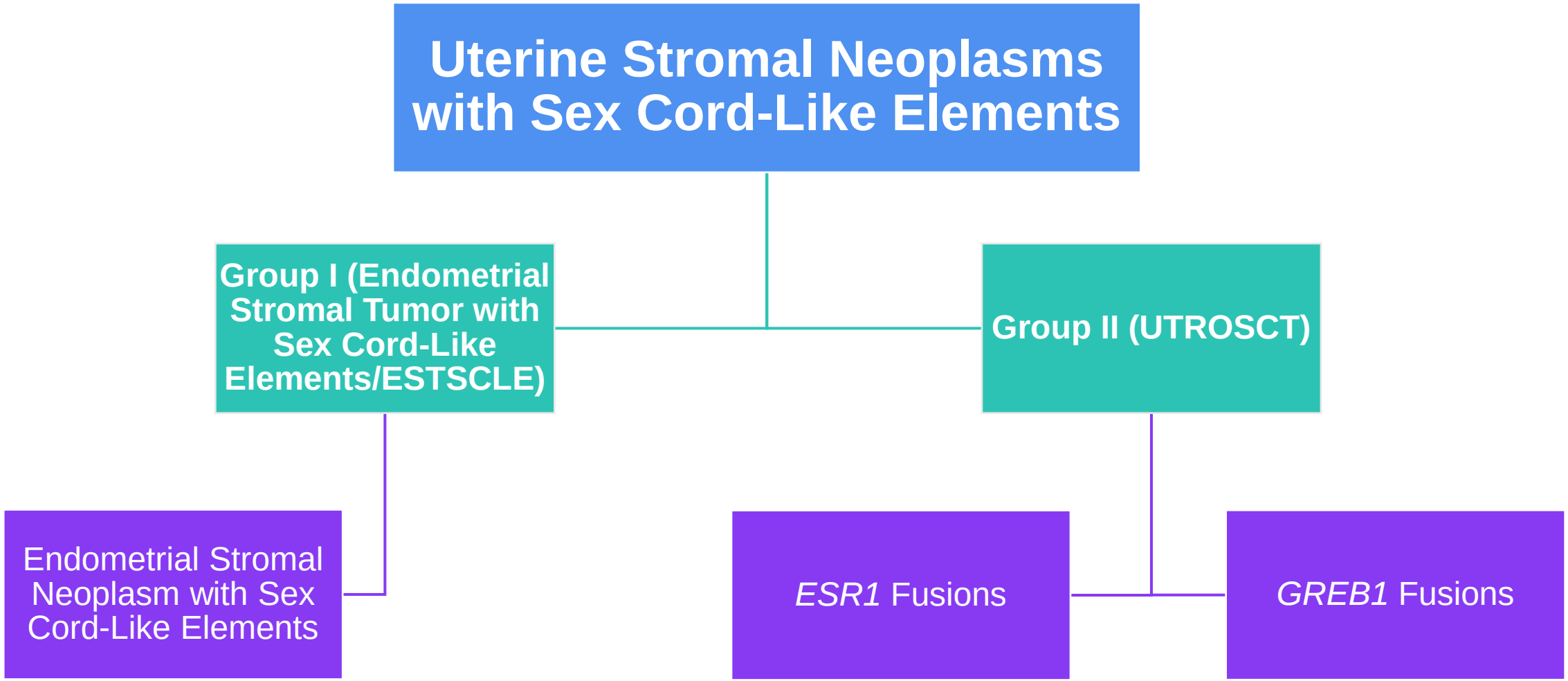


Bennett USCAP 2020

ERMS Pearls

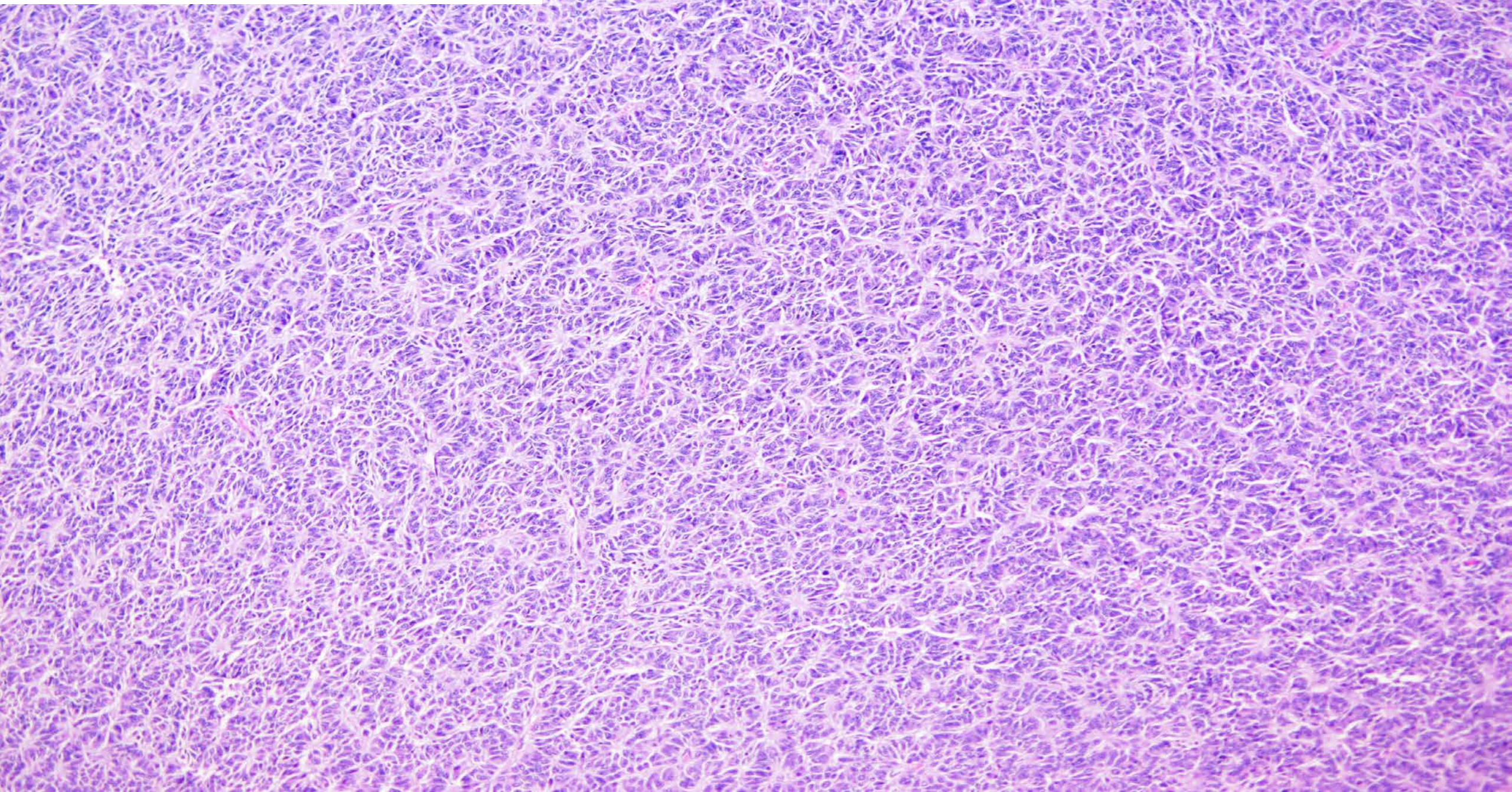
- Occur in all ages in the corpus and cervix
- Sample generously to look for cartilage/heterologous elements
- Inquire about personal/family history in all patients
- If history suspicious and/or young patient, recommend molecular testing!

UTERINE TUMOR RESEMBLING OVARIAN SEX CORD TUMOR (UTROSCT)

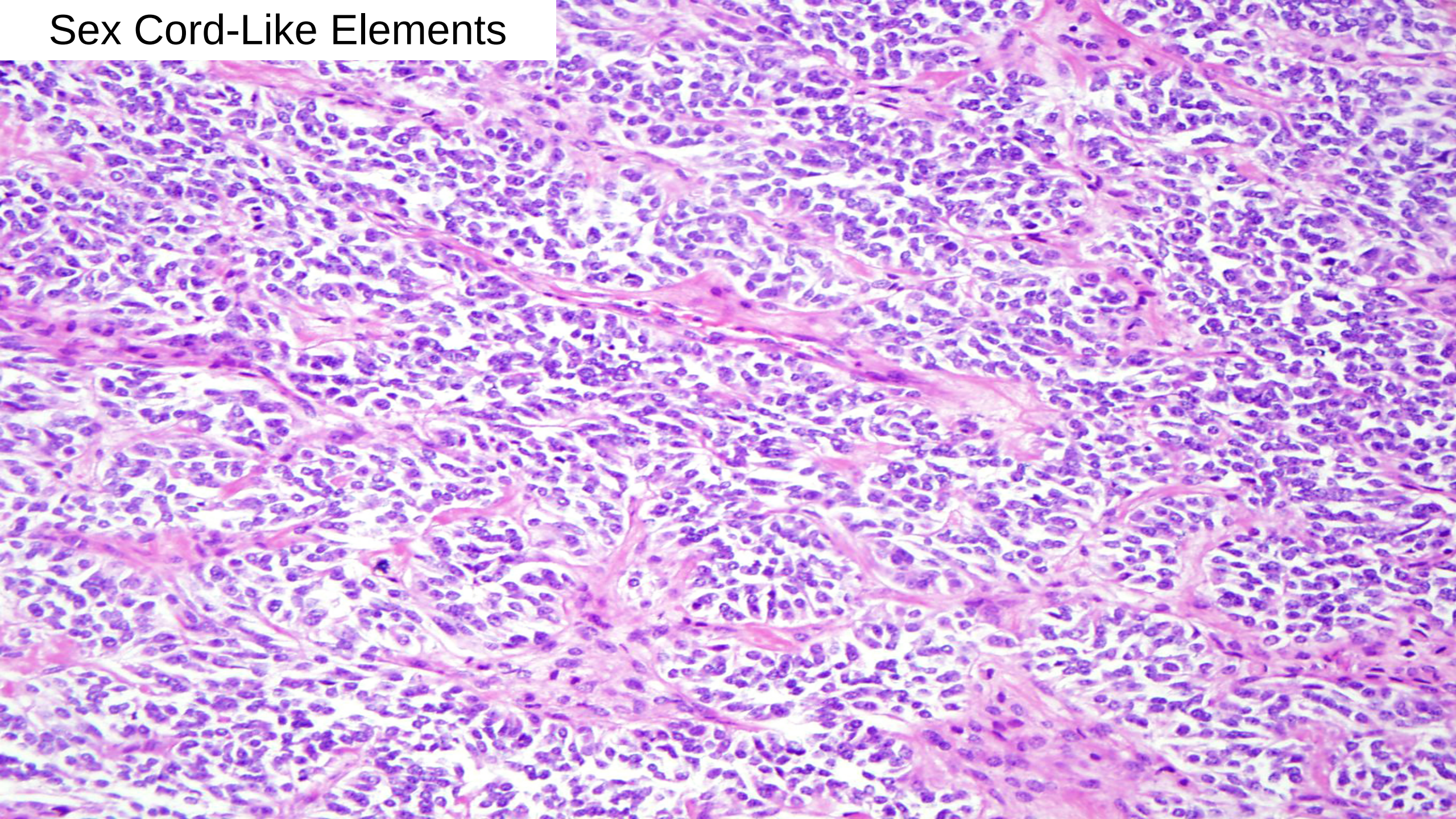


Clement and Scully 1976

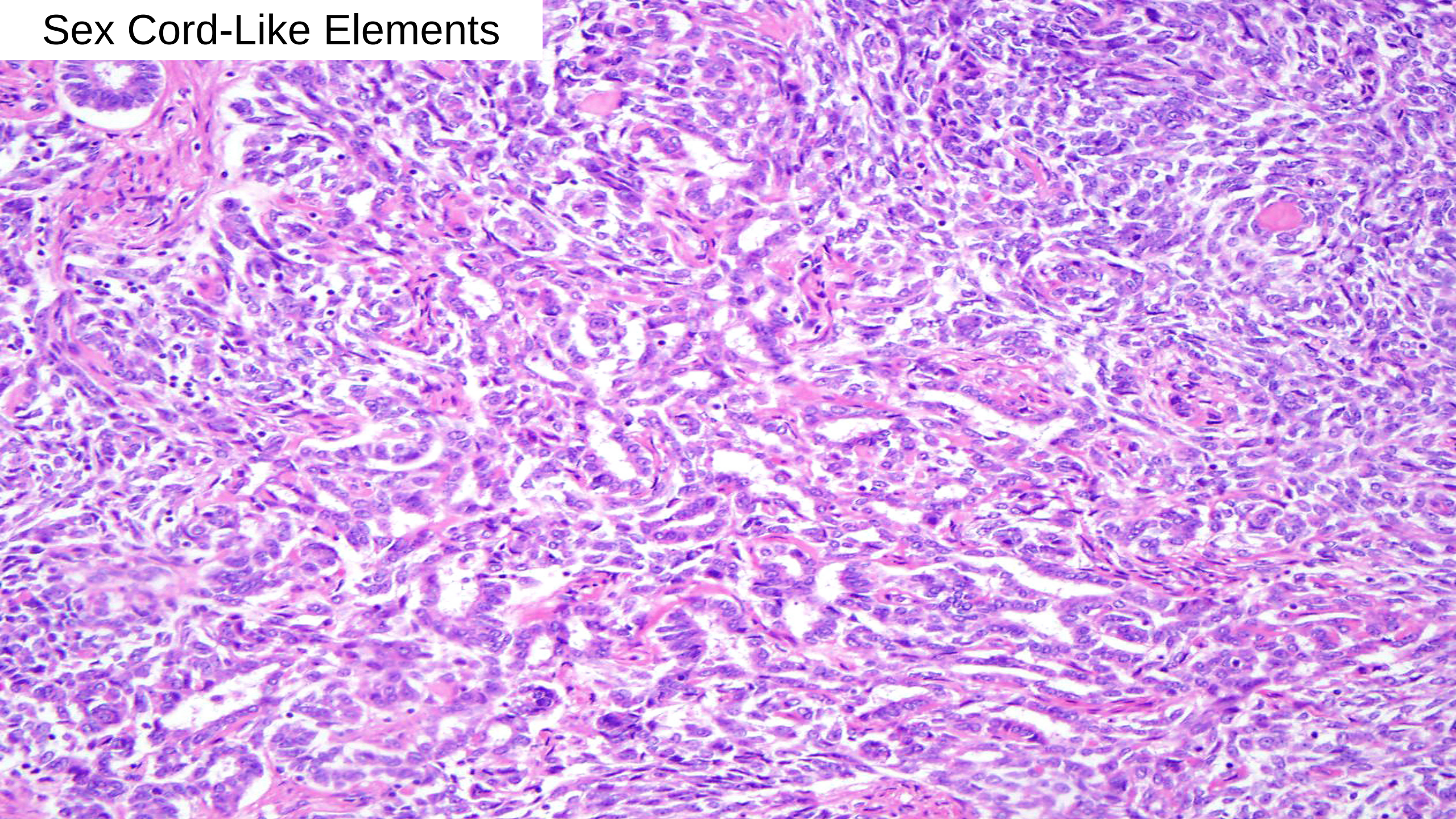
Sex Cord-Like Elements

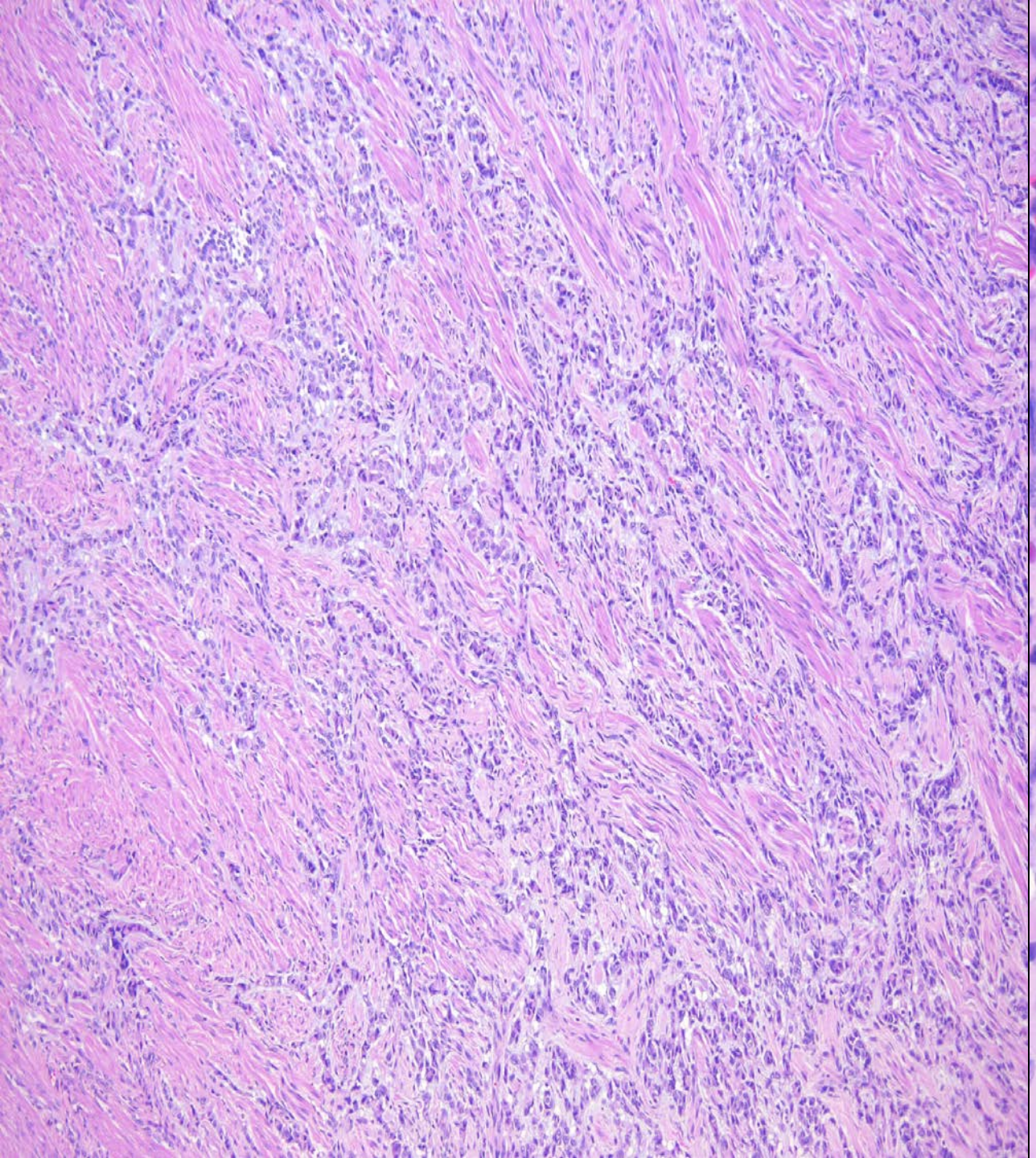
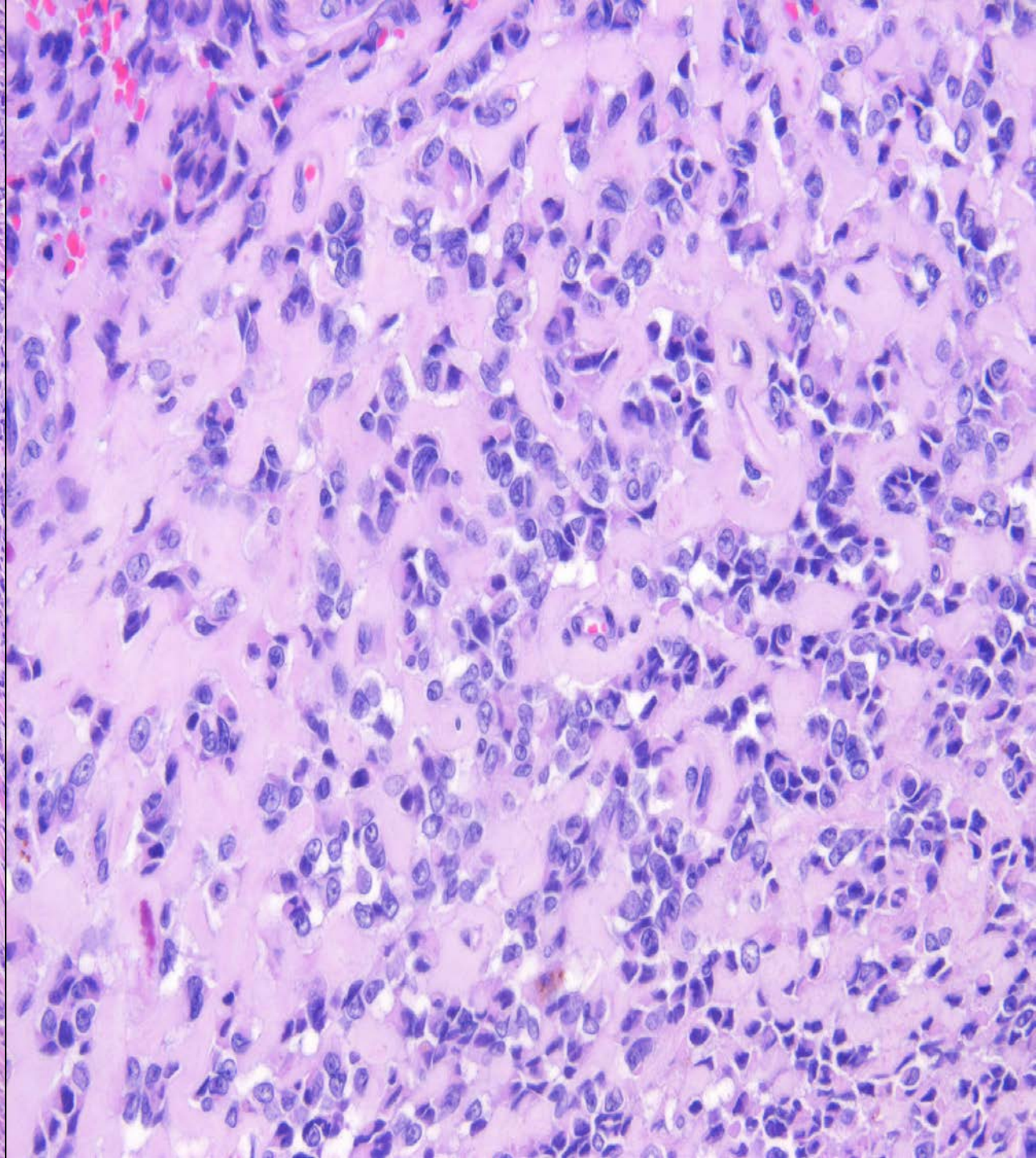


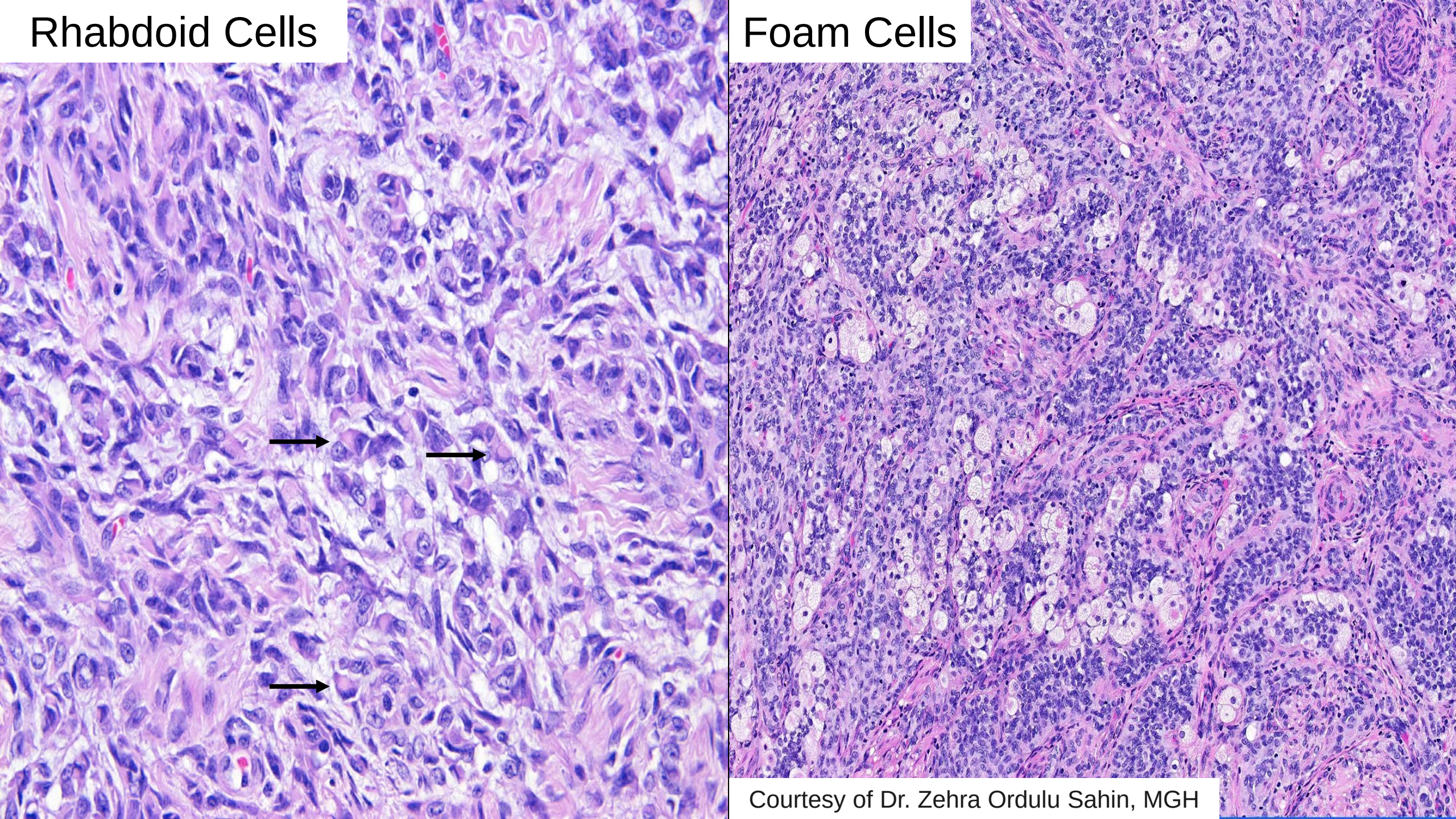
Sex Cord-Like Elements



Sex Cord-Like Elements




Rhabdoid Cells
Foam Cells
Courtesy of Dr. Zehra Ordulu Sahin, MGH

Variably express sex cord markers, myogenic markers, epithelial markers, hormone receptors, and CD10

Lack *JAZF1-SUZ12* fusions as well as *FOXL2* and *DICER1* mutations

Irving 2006
Hurrell 2007
Staats 2009
De Leval 2010
Chiang 2015
Croce 2016
Stewart 2016

Uterine Tumor Resembling Ovarian Sex Cord Tumor

A Distinct Entity Characterized by Recurrent NCOA2/3 Gene Fusions

Brendan C. Dickson, MSc, MD,† Timothy J. Childs, MD,‡ Terrence J. Colgan, MD,*†
Yun-Shao Sung, MSc,§ David Swanson, BSc,*† Lei Zhang, MD,§
and Cristina R. Antonescu, MD§*

GREB1-CTNNB1 fusion transcript detected by RNA-sequencing in a uterine tumor resembling ovarian sex cord tumor (UTROSCT): A novel *CTNNB1* rearrangement

Sabrina Croce[1] | Tom Lesluyes[2,3,4,5] | Lucile Delespaul[3,4] | Benjamin Bonhomme[1] | Gaëlle Pérot[1] | Valérie Velasco[1] | Laetitia Mayeur[1] | Flora Rebier[1] | Houda Ben Rejeb[1] | Frédéric Guyon[6] | W Glenn McCluggage[7] | Anne Floquet[8] | Denis Querleu[3,6] | Camille Chakiba[8] | Mojgan Devouassoux-Shisheboran[9] | Eliane Mery[5] | Laurent Arnould[10] | Gerlinde Averous[11] | Isabelle Soubeyran[1] | Sophie Le Guellec[4,5] | Frédéric Chibon[4,5]

Clinicopathologic Characterization of *GREB1*-rearranged Uterine Sarcomas With Variable Sex-Cord Differentiation

Cheng-Han Lee, MD, PhD, FRCPC, Yu-Chien Kao, MD,† Wan-Ru Lee, BS,‡
Yi-Wen Hsiao, MS,§ Tzu-Pin Lu, PhD,§ Chia-Ying Chu, MD,‖ Yi-Jia Lin, MD,¶
Hsuan-Ying Huang, MD,# Tsung-Han Hsieh, PhD,** Yun-Ru Liu, PhD,**
Cher-Wei Liang, MD,†† Tom Wei-Wu Chen, MD,‡‡ Stephen Yip, MD, PhD, FRCPC,§§
Amy Lum, BS,§§ Kuan-Ting Kuo, MD,‡ Yung-Ming Jeng, MD, PhD,‡ Shih-Chen Yu, MS,#
Yung-Chuan Chung, MS,‡ and Jen-Chieh Lee, MD, PhD‡*

Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT)

A Morphologic and Molecular Study of 26 Cases Confirms Recurrent NCOA1-3 Rearrangement

Emily A. Goebel, MD, FRCPC,† Silvia Hernandez Bonilla, MD,‡ Fei Dong, MD,†
Brendan C. Dickson, MSc, MD, FRCPC,§‖ Lien N. Hoang, MD, FRCPC,¶
David Hardisson, MD, PhD,‡ Maribel D. Lacambra, MD,# Fang-I Lu, MD, FRCPC,‖**
Christopher D.M. Fletcher, MD, FRCPath,† Christopher P. Crum, MD,*†
Cristina R. Antonescu, MD,†† Marisa R. Nucci, MD,*† and David L. Kolin, MD, PhD*†*

Uterine Tumor Resembling Ovarian Sex Cord Stromal Tumor (UTROSCT)

A Series of 3 Cases With Extensive Rhabdoid Differentiation, Malignant Behavior, and ESR1-NCOA2 Fusions

Jennifer A. Bennett, MD, Ricardo R. Lastra, MD,* Julieta E. Barroeta, MD,†
Megan Parilla, MD,* Filippo Galbo, BS,* Pankhuri Wanjari, MS,* Robert H. Young, MD,‡
Thomas Krausz, MD,* and Esther Oliva, MD‡*

ESR1 UTROSCTs

- Partners: *NCOA2/3*
- Often premenopausal
- Sex cord-like elements
- Foam cells, Leydig-like cells
- More often positive for sex cord markers
- No known recurrences*

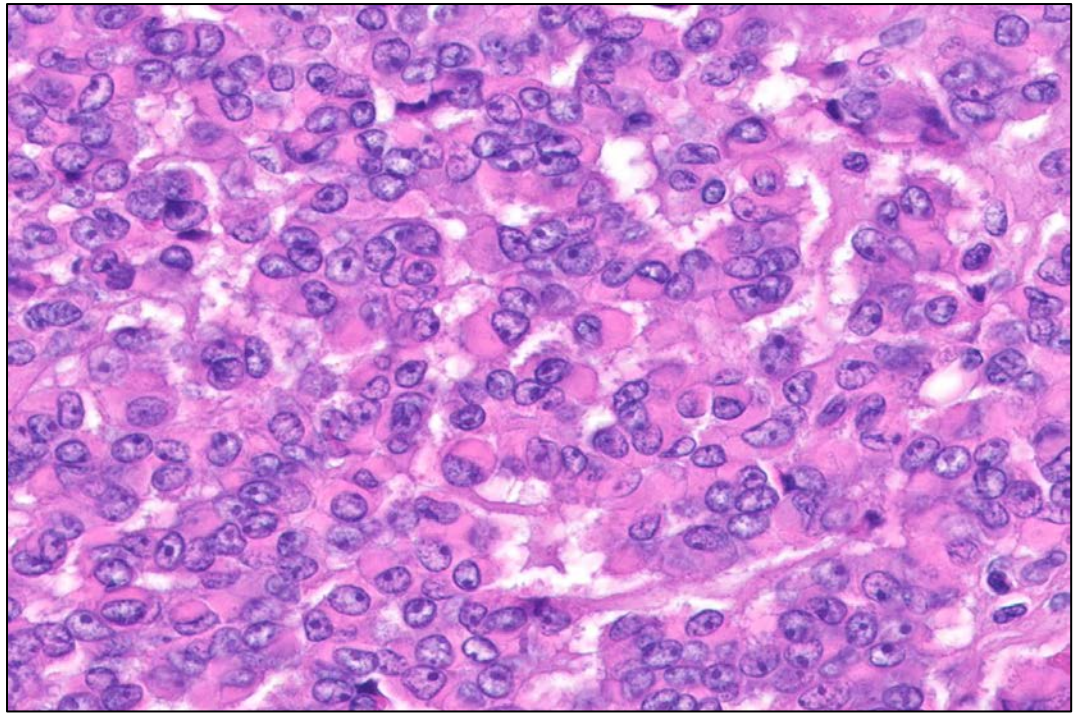
GREB1 Sarcomas

- Partners: *NCOA1/2/3, CTNNB1, NR4A3, SS18*
- Often peri/postmenopausal
- +/- sex cord-like elements
- +/- fascicular growth
- +/- sex cord markers
- Rare tumors have recurred

Uterine Tumor Resembling Ovarian Sex Cord Stromal Tumor (UTROSCT)

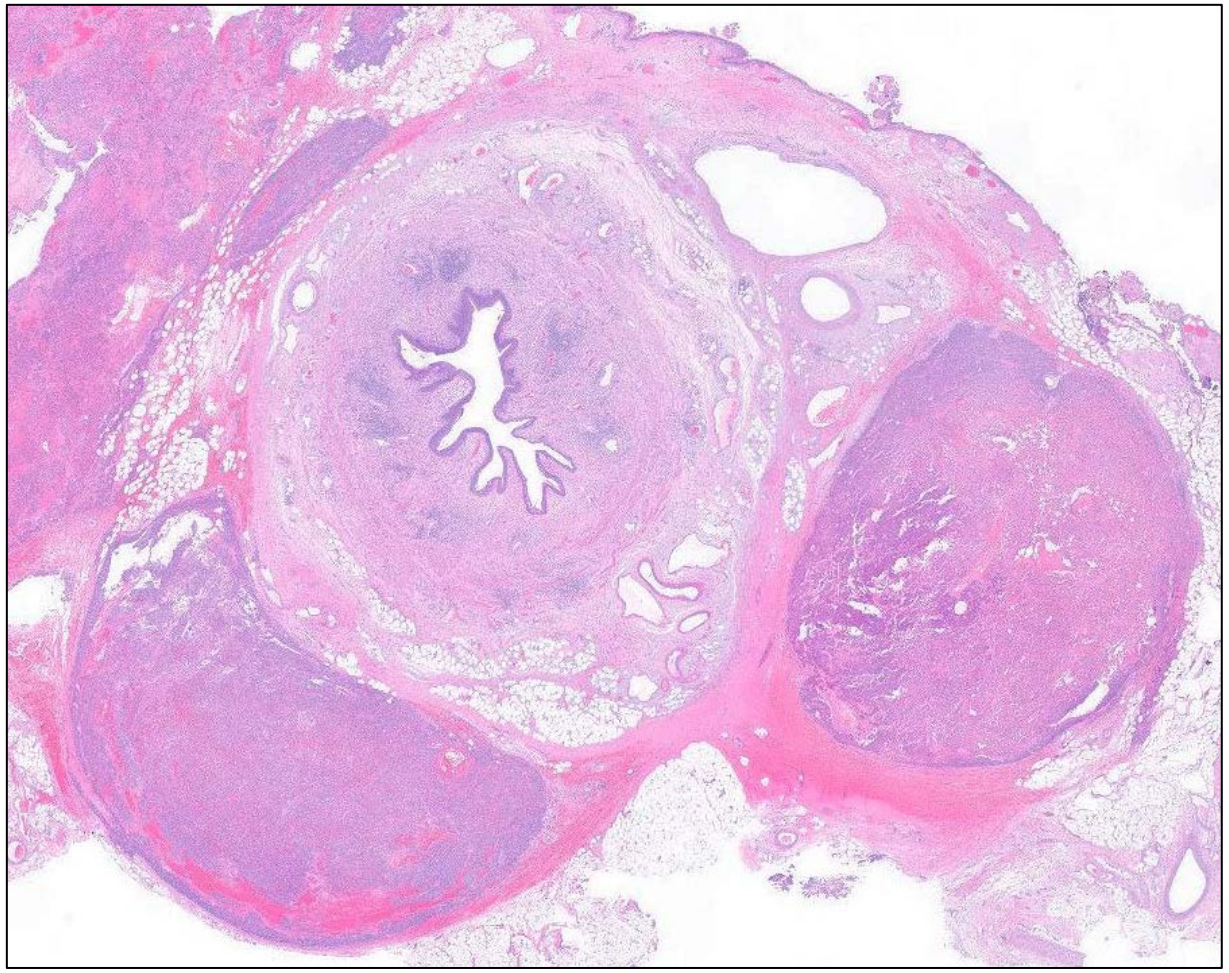
A Series of 3 Cases With Extensive Rhabdoid Differentiation, Malignant Behavior, and ESR1-NCOA2 Fusions

Jennifer A. Bennett, MD, Ricardo R. Lastra, MD,* Julieta E. Barroeta, MD,† Megan Parilla, MD,* Filippo Galbo, BS,* Pankhuri Wanjari, MS,* Robert H. Young, MD,‡ Thomas Krausz, MD,* and Esther Oliva, MD‡*



Case	Time to First Recurrence	Hysterectomy	Metastases	Sex Cord Markers	Myogenic Markers	Epithelial Markers	ER/PR
1	7 years	Uniformly rhabdoid, no appreciable mitoses	Uniformly rhabdoid, 16/10 HPF	Only WT1+	-	AE1/AE3+ CAM5.2+	+
2	9 years	Uniformly rhabdoid, 4/10 HPF	Uniformly rhabdoid, 17/10 HPF	Only WT1+	-	CAM5.2+ AE1/AE3-	+
3	32 years	N/A	#1: 50% rhabdoid, 2/10 HPF #2: Uniformly rhabdoid	Calretinin+ WT1+ Melan-A+ Inhibin-	Desmin+	CAM5.2+	+

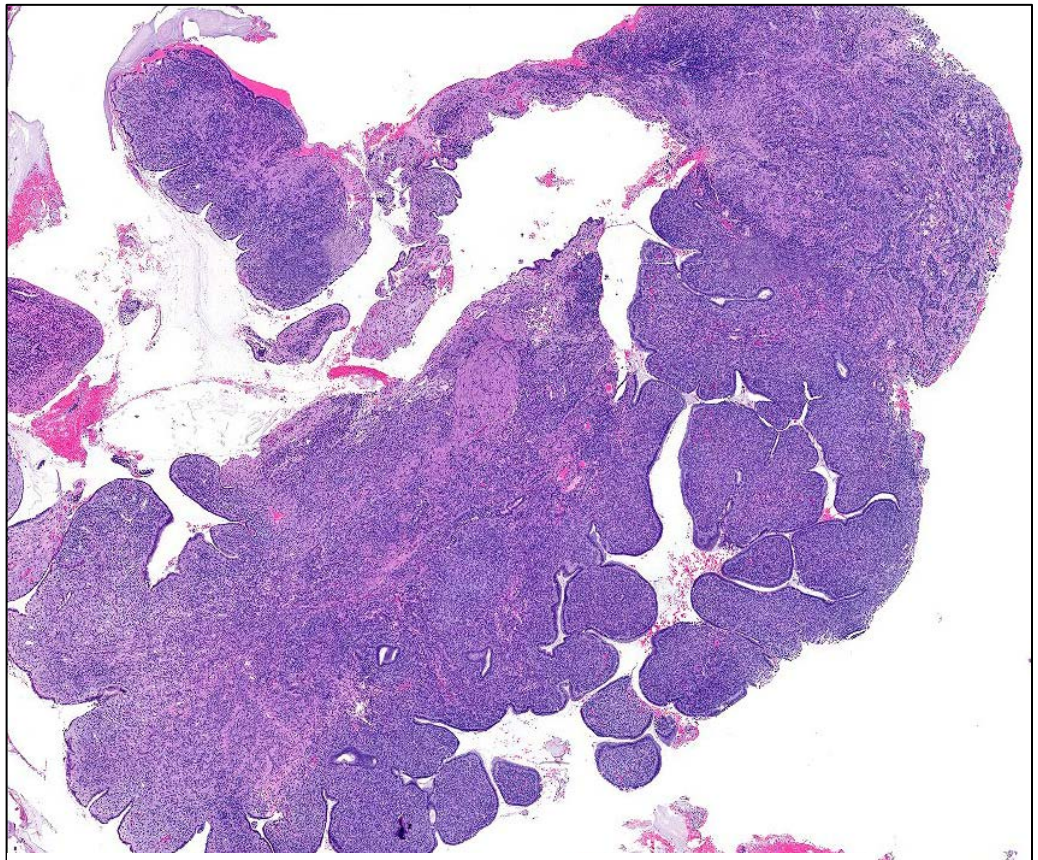
Are there features associated with recurrence?



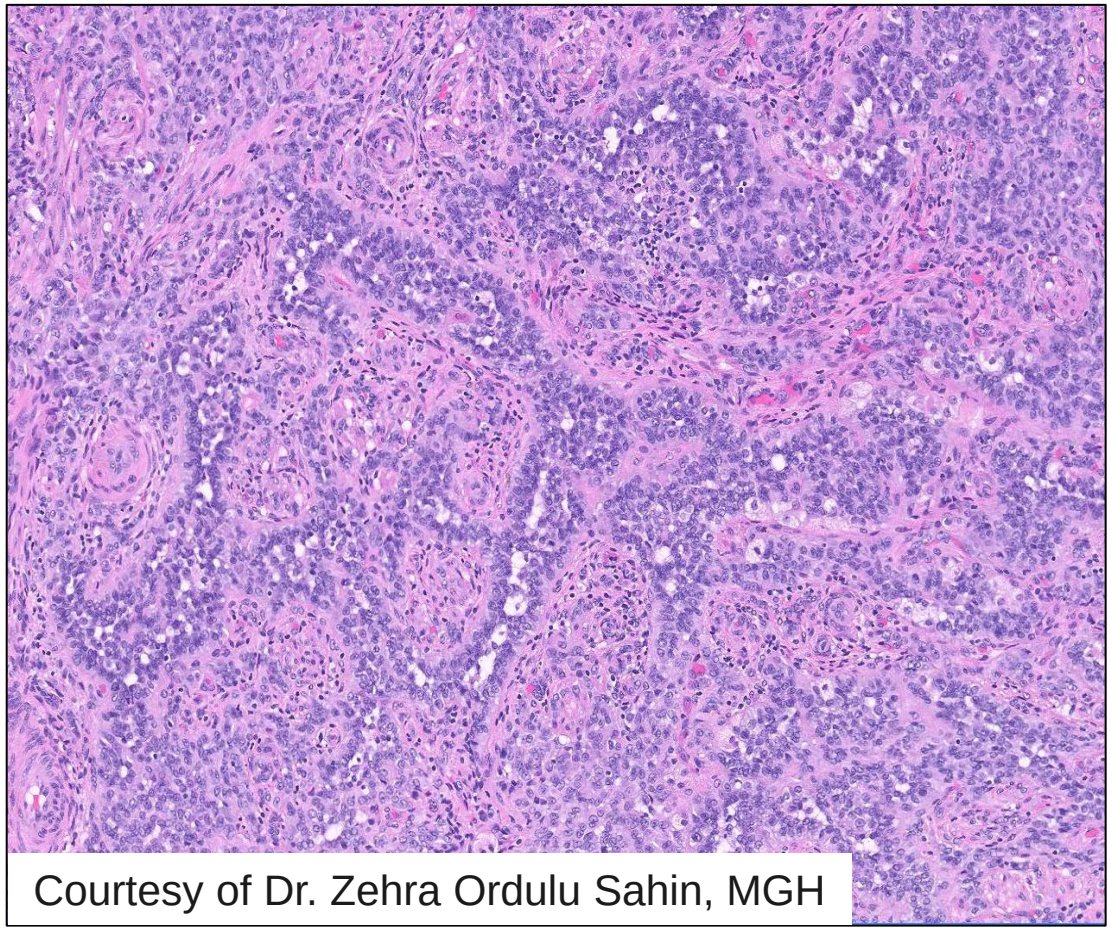
- Mitoses ≥ 2/10 HPFs
- Necrosis
- *GREB1* fusion
- *ESR1-NCOA2* fusion with extensive rhabdoid differentiation

Moore 2017
Brunetti 2018
Croce 2019
Goebel 2020
Bennett 2020

PITFALL: *ESR1-NCOA2/3* fusions have also been detected in several adenosarcomas



Courtesy of Dr. Zehra Ordulu Sahin, MGH



Courtesy of Dr. Zehra Ordulu Sahin, MGH

Piscuoglio 2016
Bean 2019

UNDIFFERENTIATED UTERINE SARCOMA (UUS)

When to Use the Diagnosis of UUS

- Minimal expression of desmin/caldesmon or focal SMA expression in isolation
- Lack of molecular alterations diagnostic of other mesenchymal neoplasms
- Ruled out non-sarcoma diagnoses
  - Undifferentiated carcinoma, melanoma, lymphoma, plasmacytoma, metastasis, etc

THANK YOU!