Uterine mesenchymal tumors

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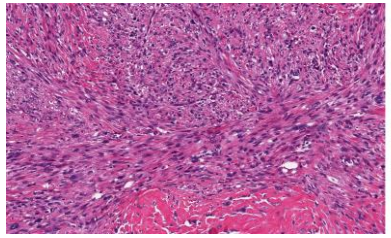
Outline

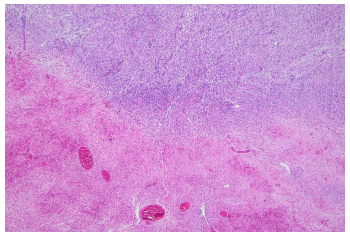
- Desmin-positive mesenchymal tumors and differential diagnosis
    - Leiomyosarcoma
    - Leiomyoma variants
    - Inflammatory myofibroblastic tumor
    - Perivascular epithelioid cell tumor
    - STUMP
- Selected, rare desmin-negative spindle cell tumors

Tricky desmin-positive uterine mesenchymal tumors

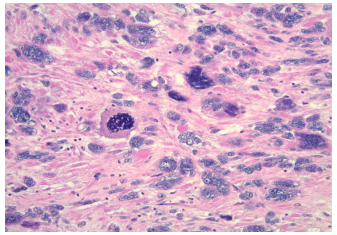
Leiomyosarcoma



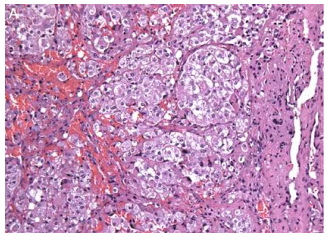
Apoplectic leiomyoma



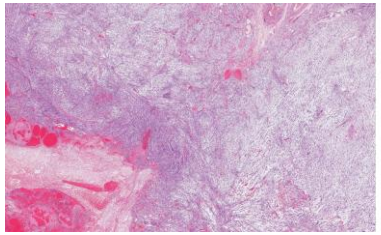
Leiomyoma with bizarre nuclei



Perivascular epithelioid cell tumor



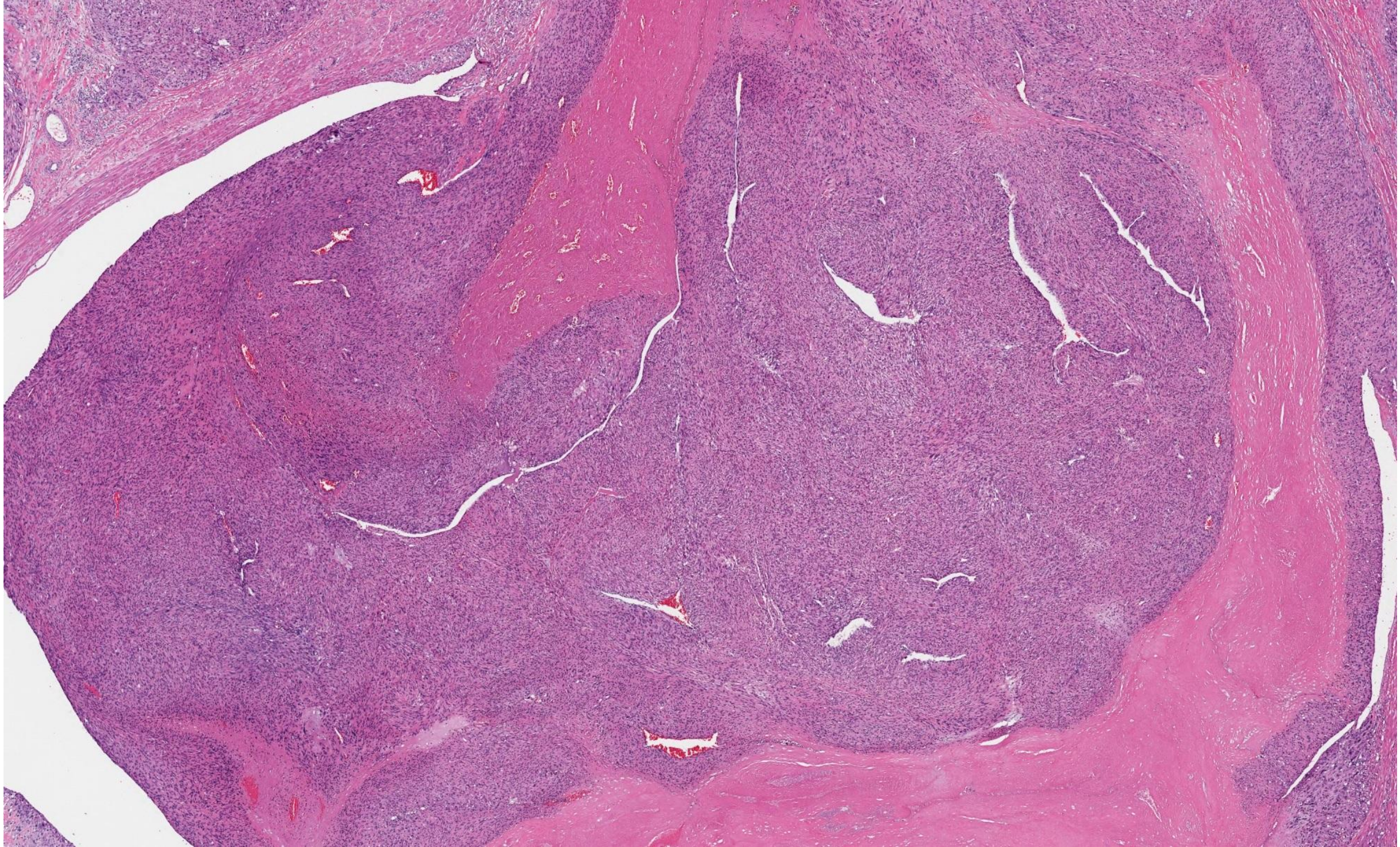
Inflammatory myofibroblastic tumor

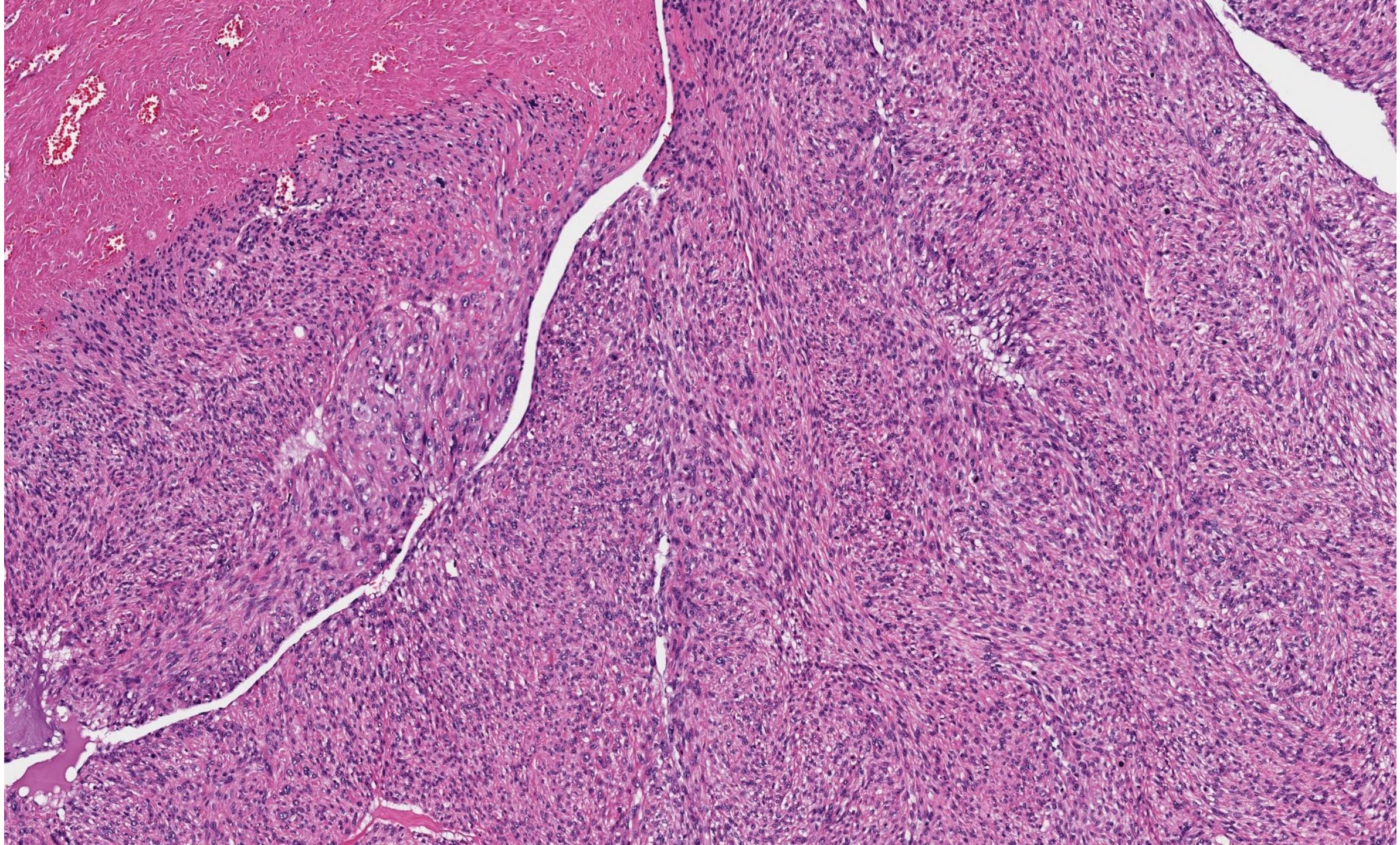


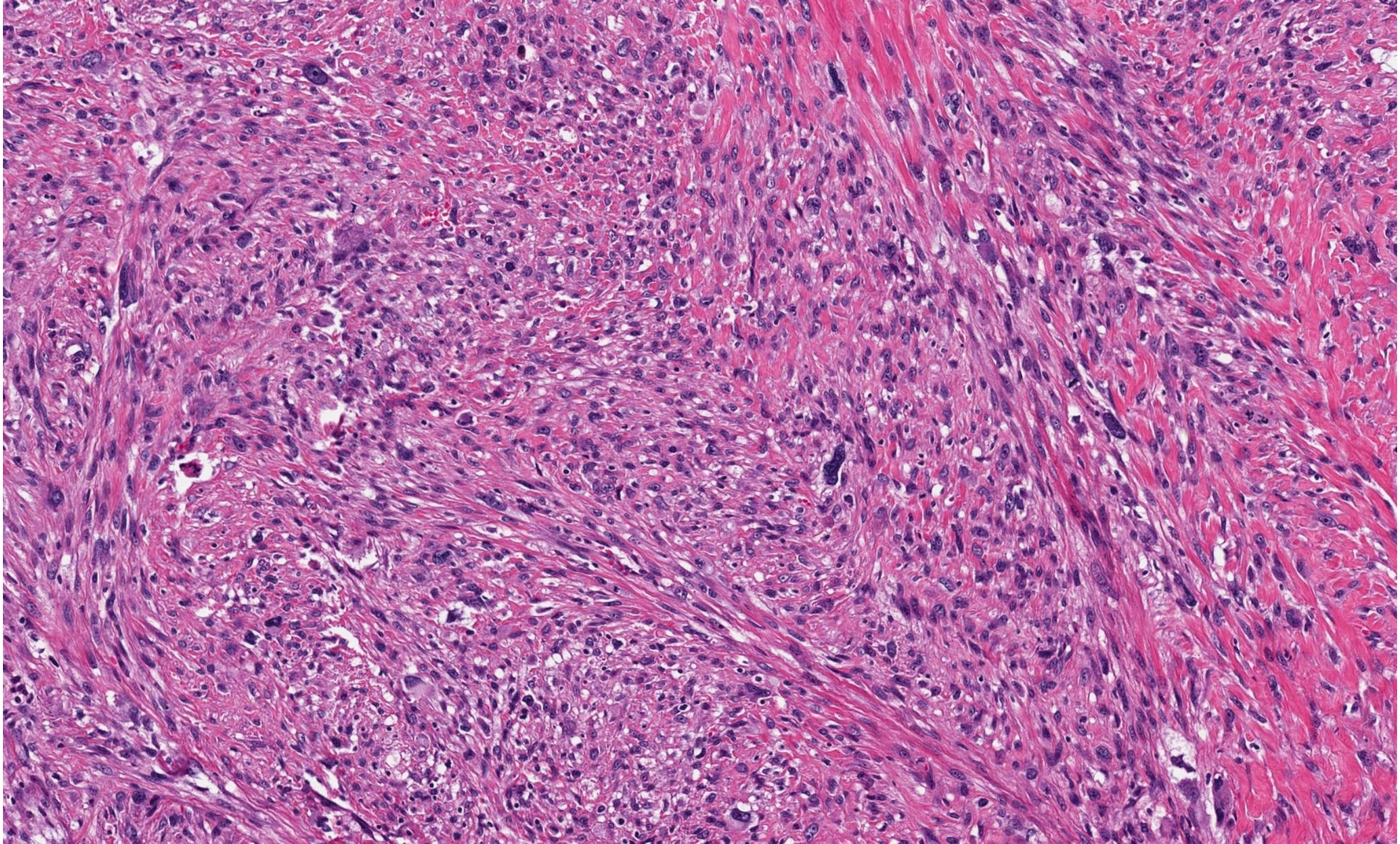
Leiomyosarcoma

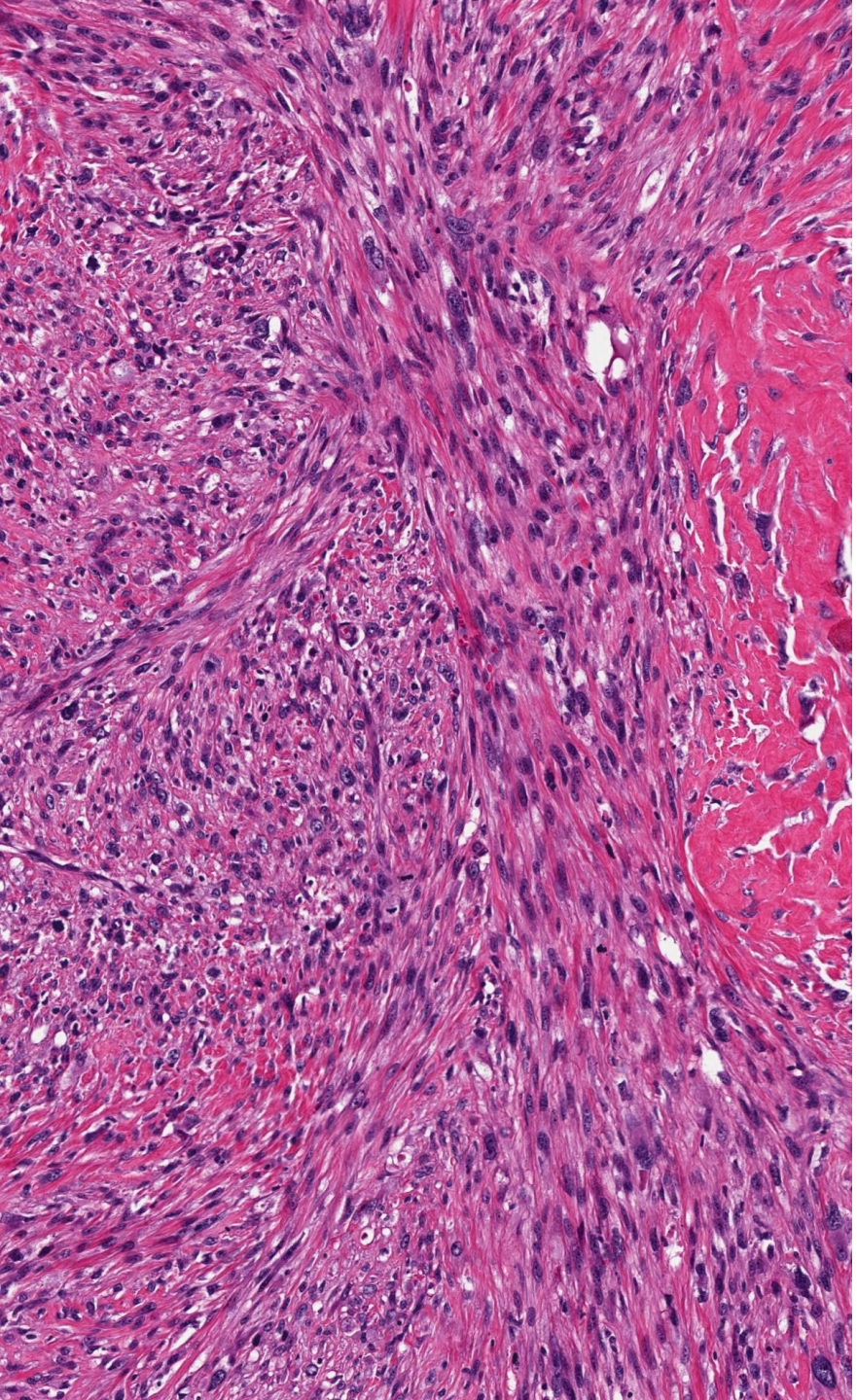
- Spindle/conventional
  - High-grade tumor, histologically and clinically
  - 2 of 3: diffuse moderate-severe atypia, tumor necrosis, ≥10 MF/HPF

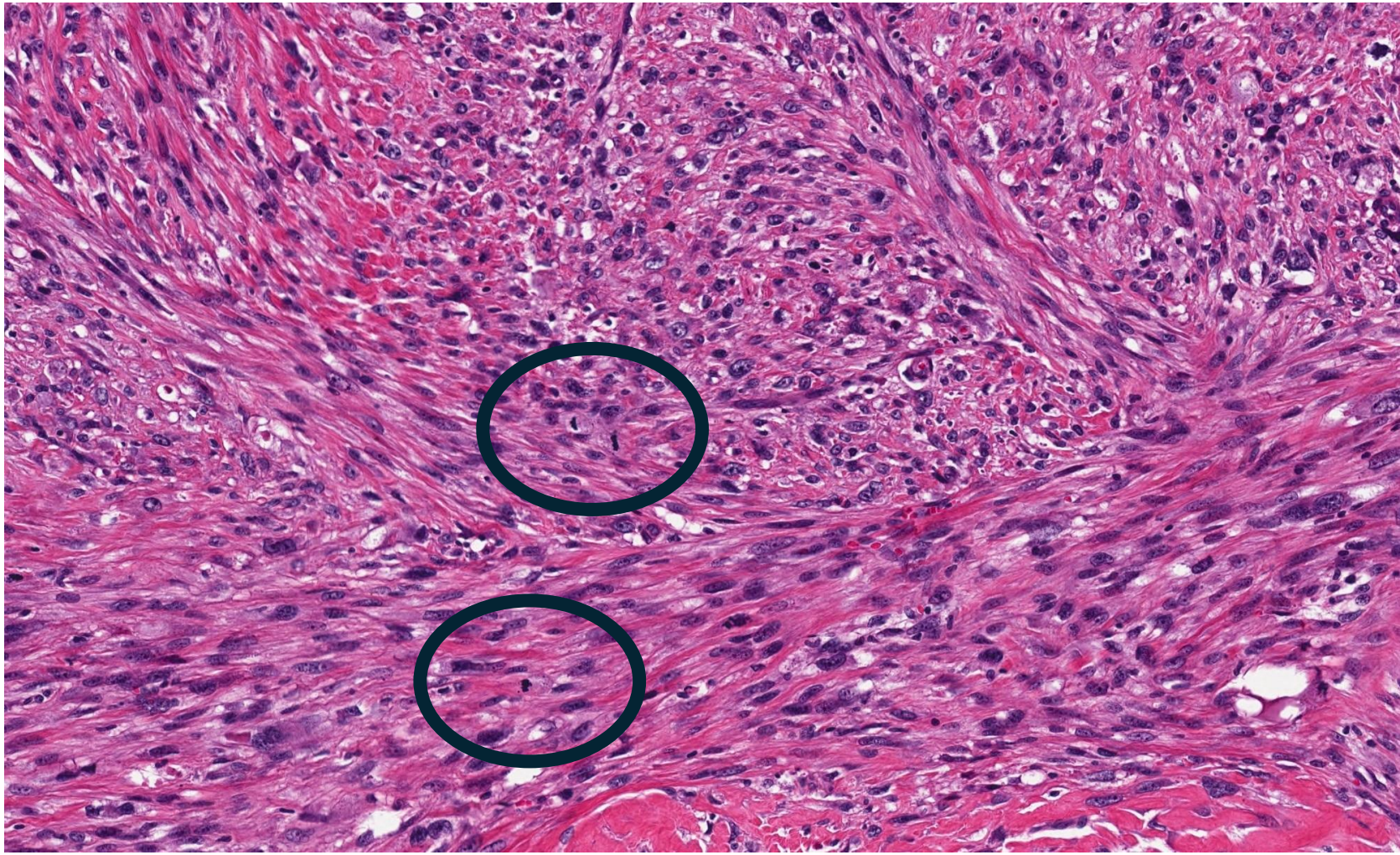
- Epithelioid (**diagnosis of exclusion**)
  - 2 of 3: diffuse moderate-severe atypia, tumor necrosis, ≥4 MF/HPF
- Myxoid (**diagnosis of exclusion**)
  - 2 of 3: at least focal moderate atypia, tumor necrosis, ≥2 MF/HPF

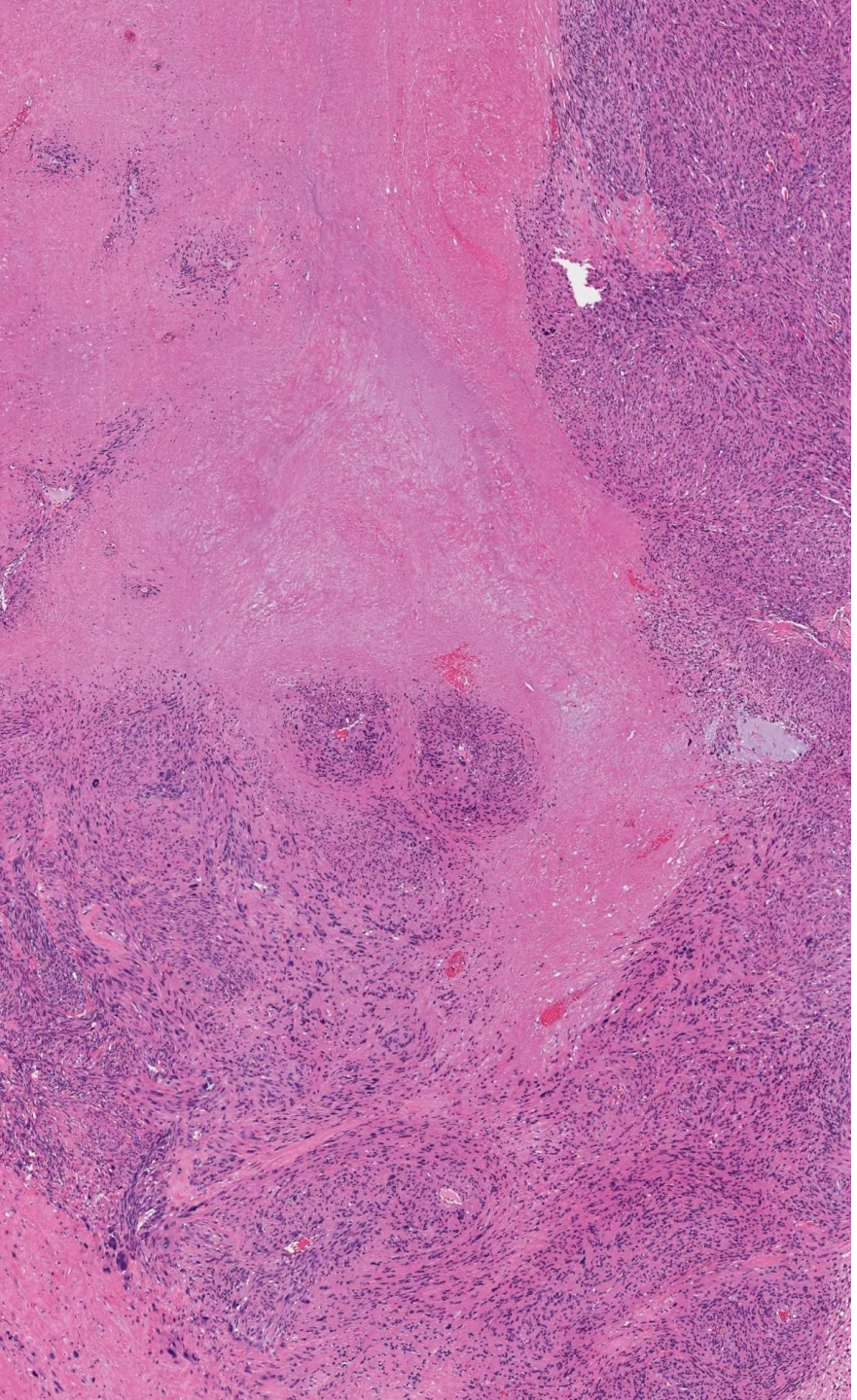


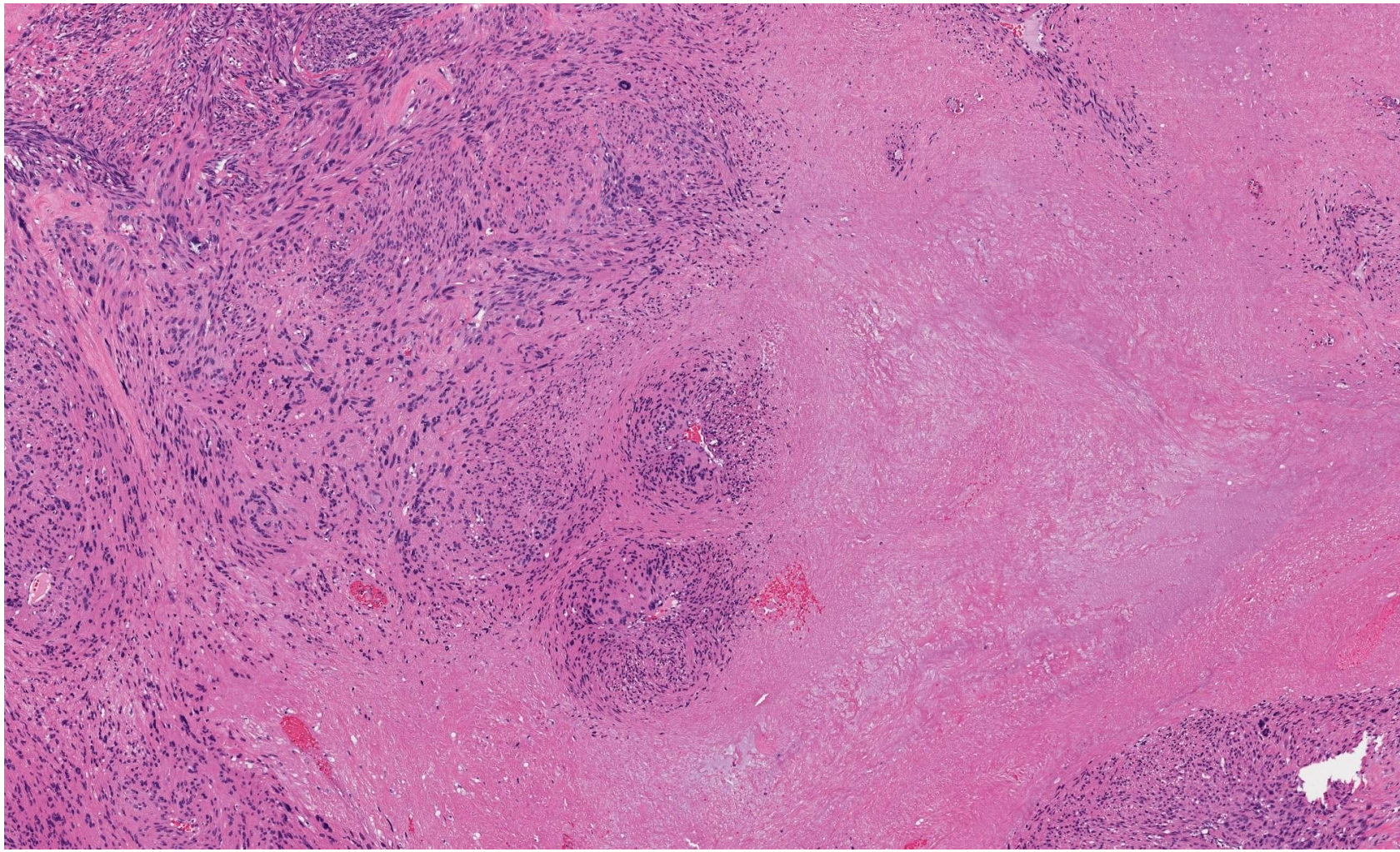


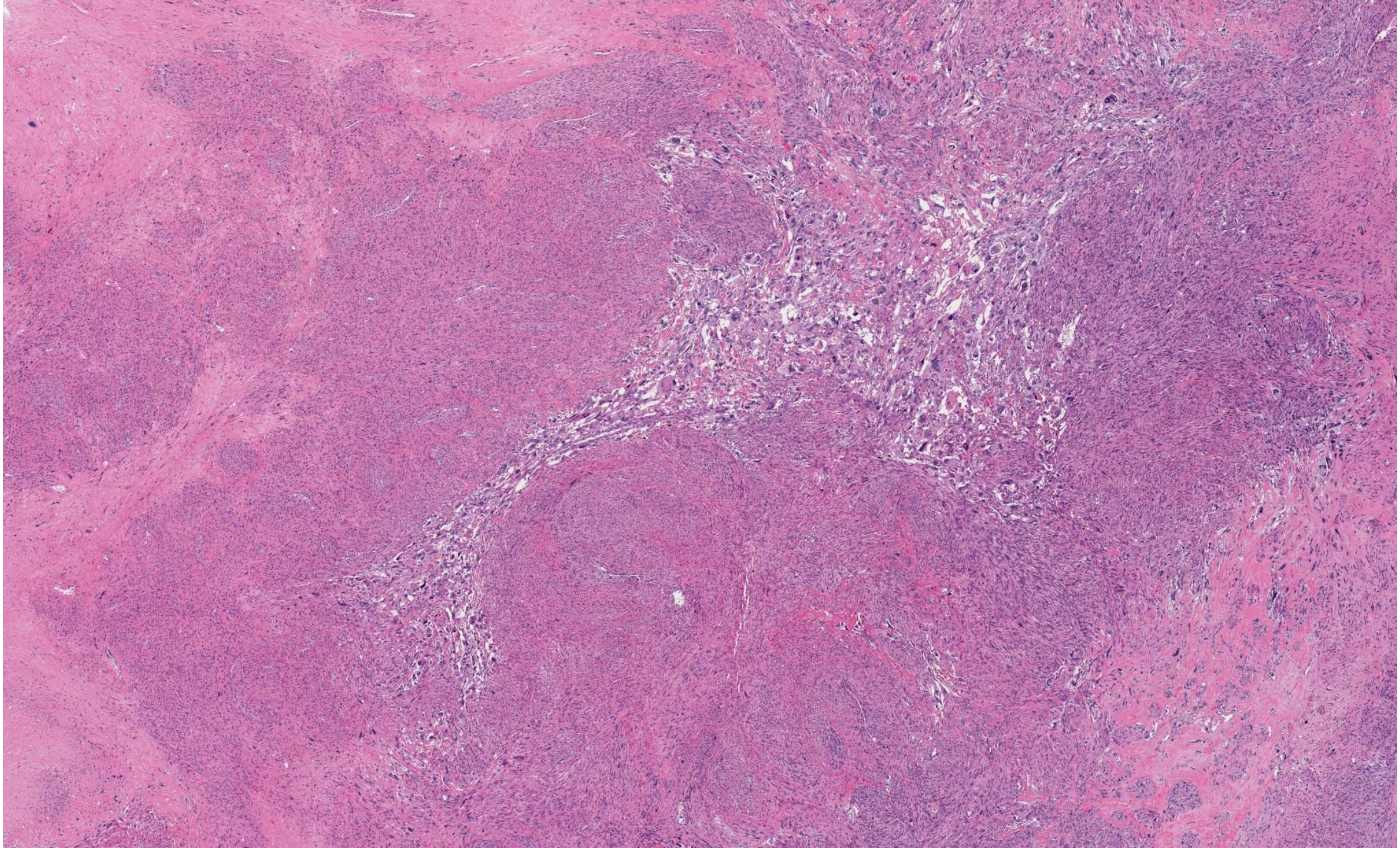


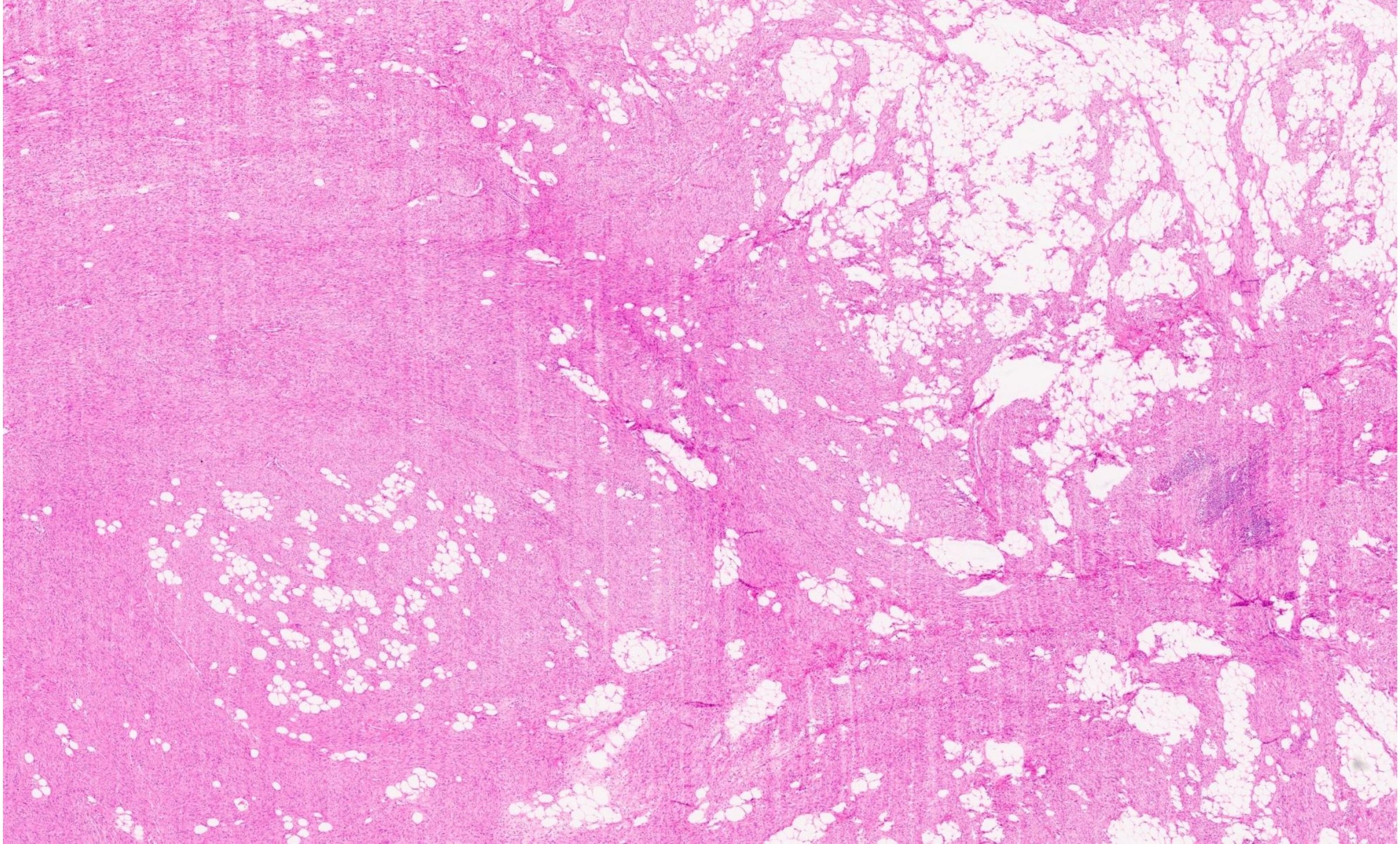


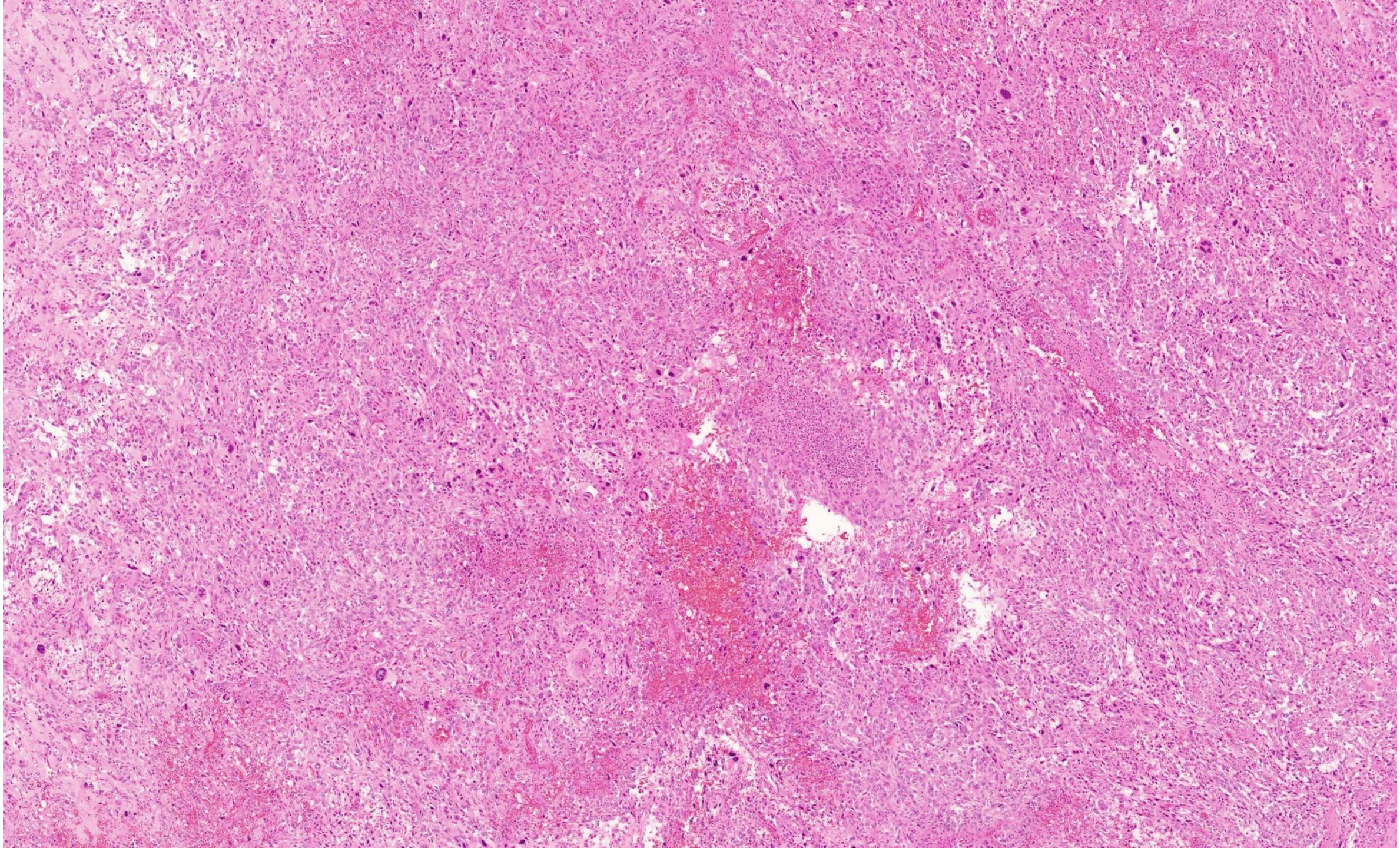






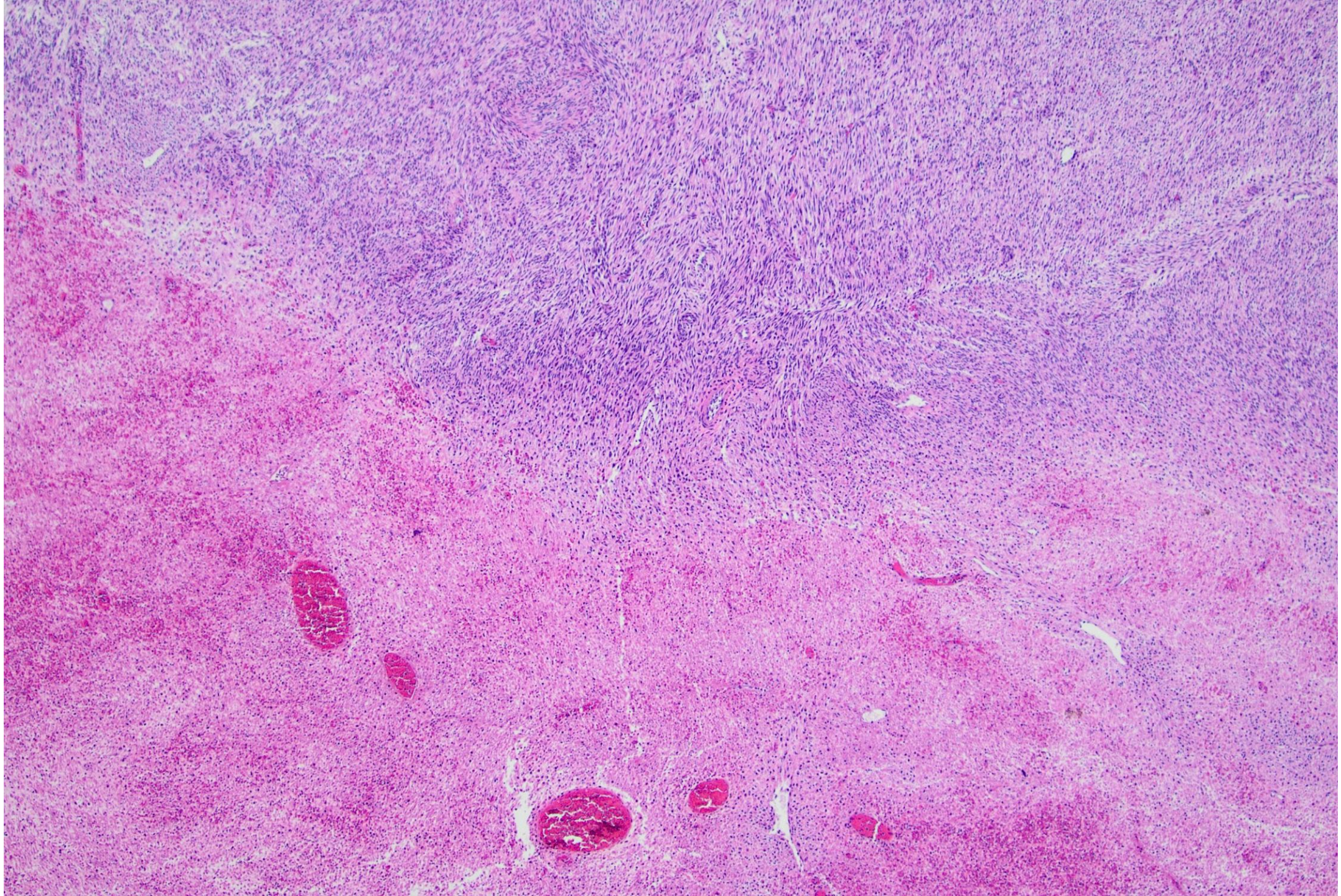


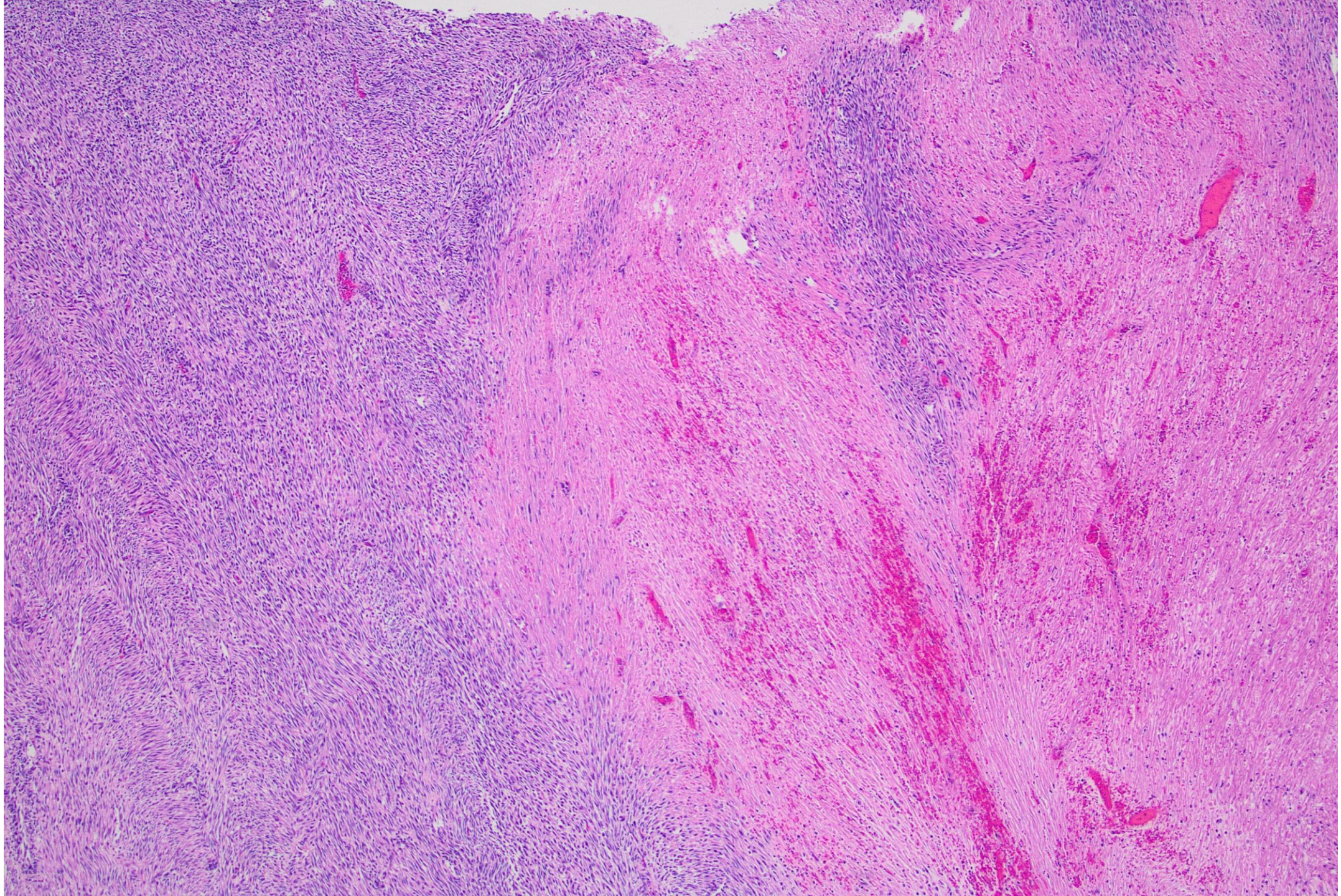


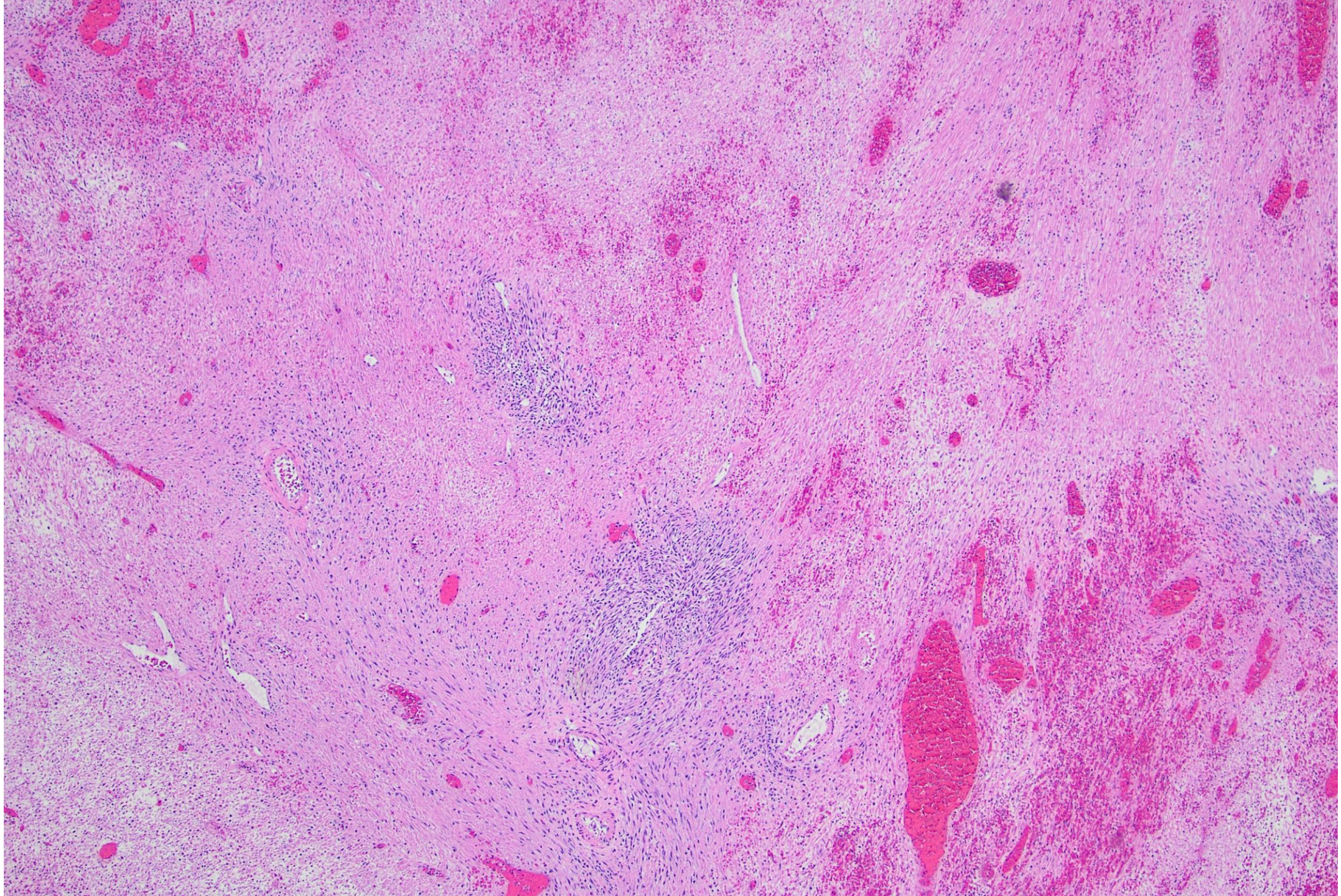


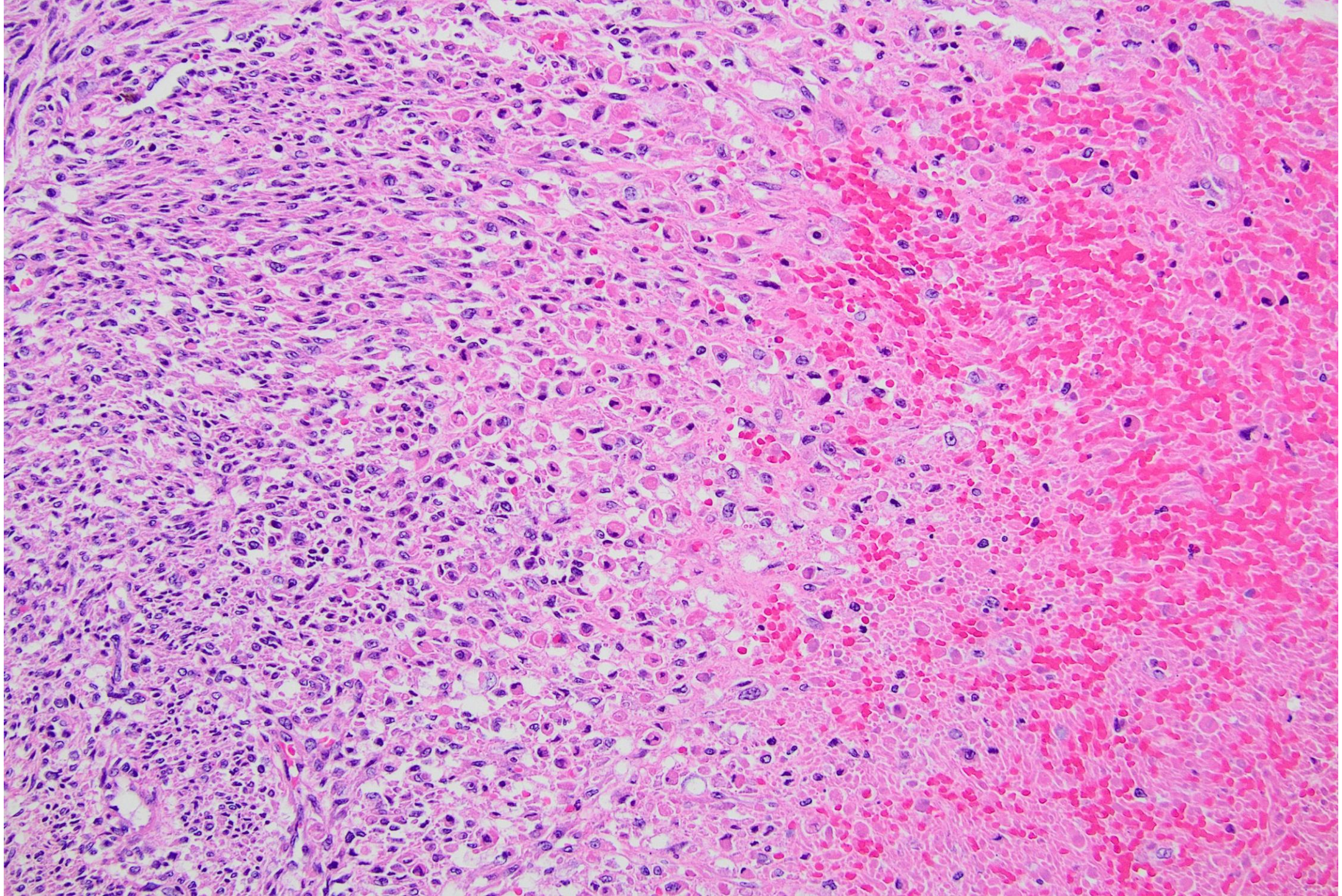
Apoplectic leiomyoma

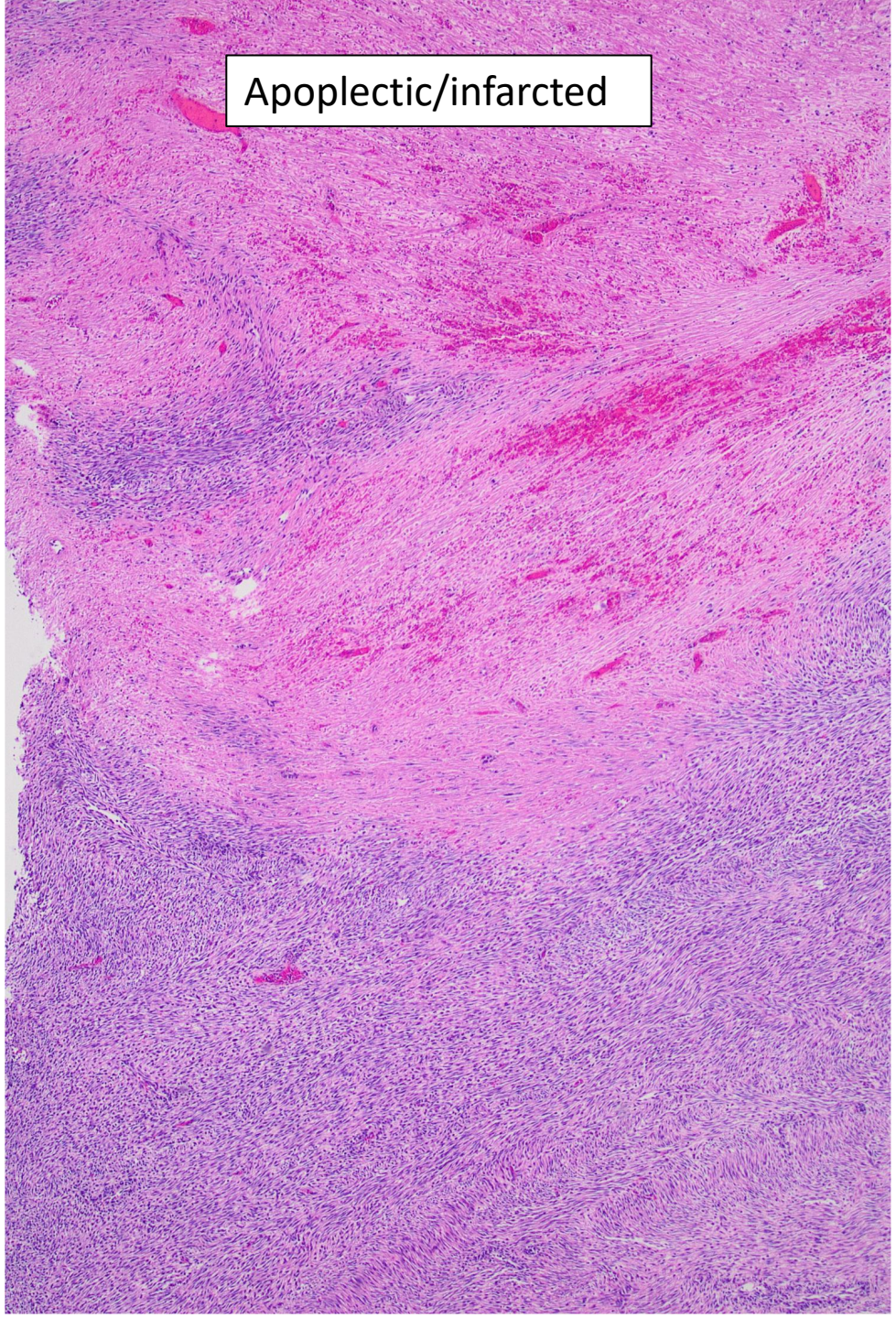
- Hemorrhagic infarct
- Zonation
- Leiomyoma background

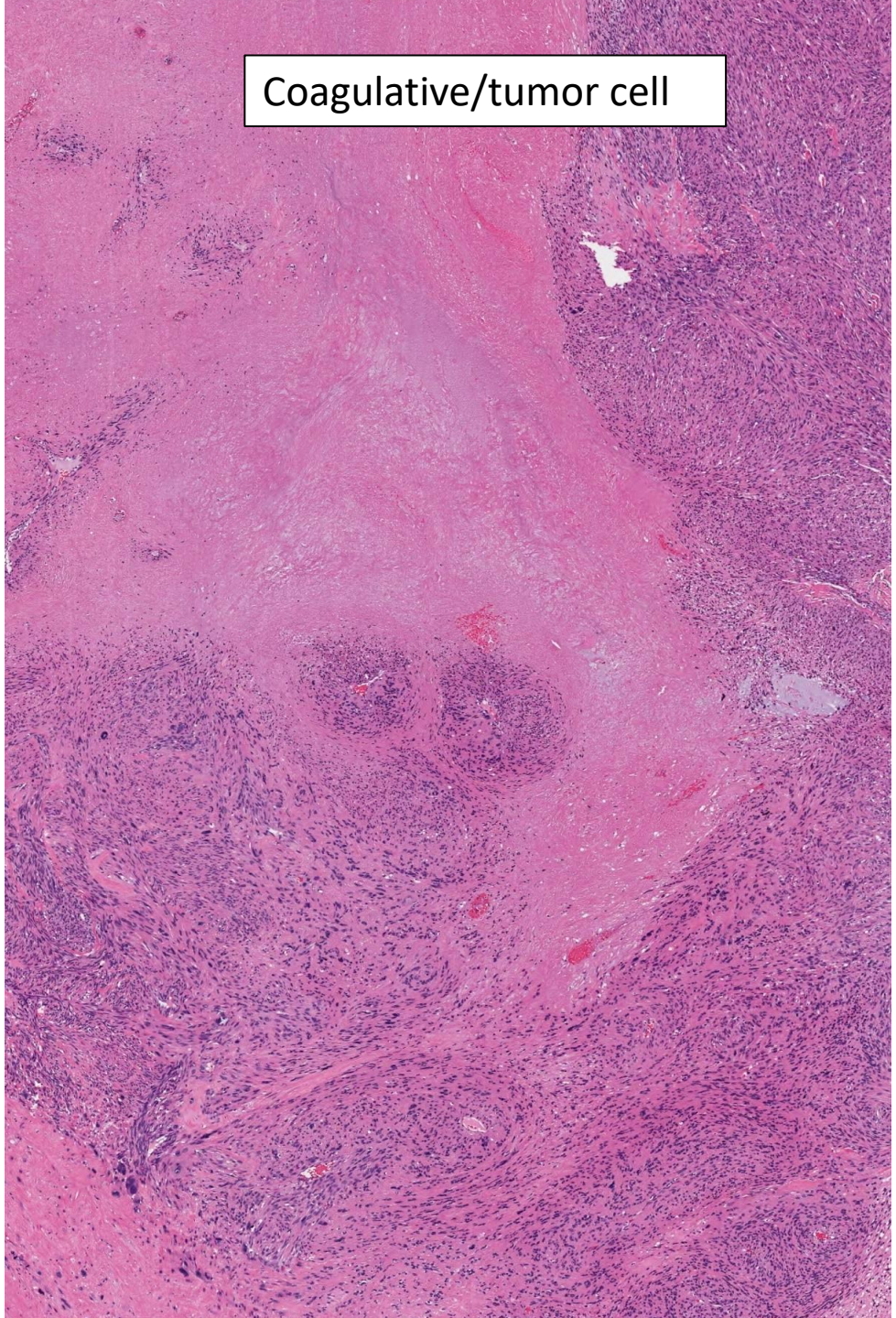






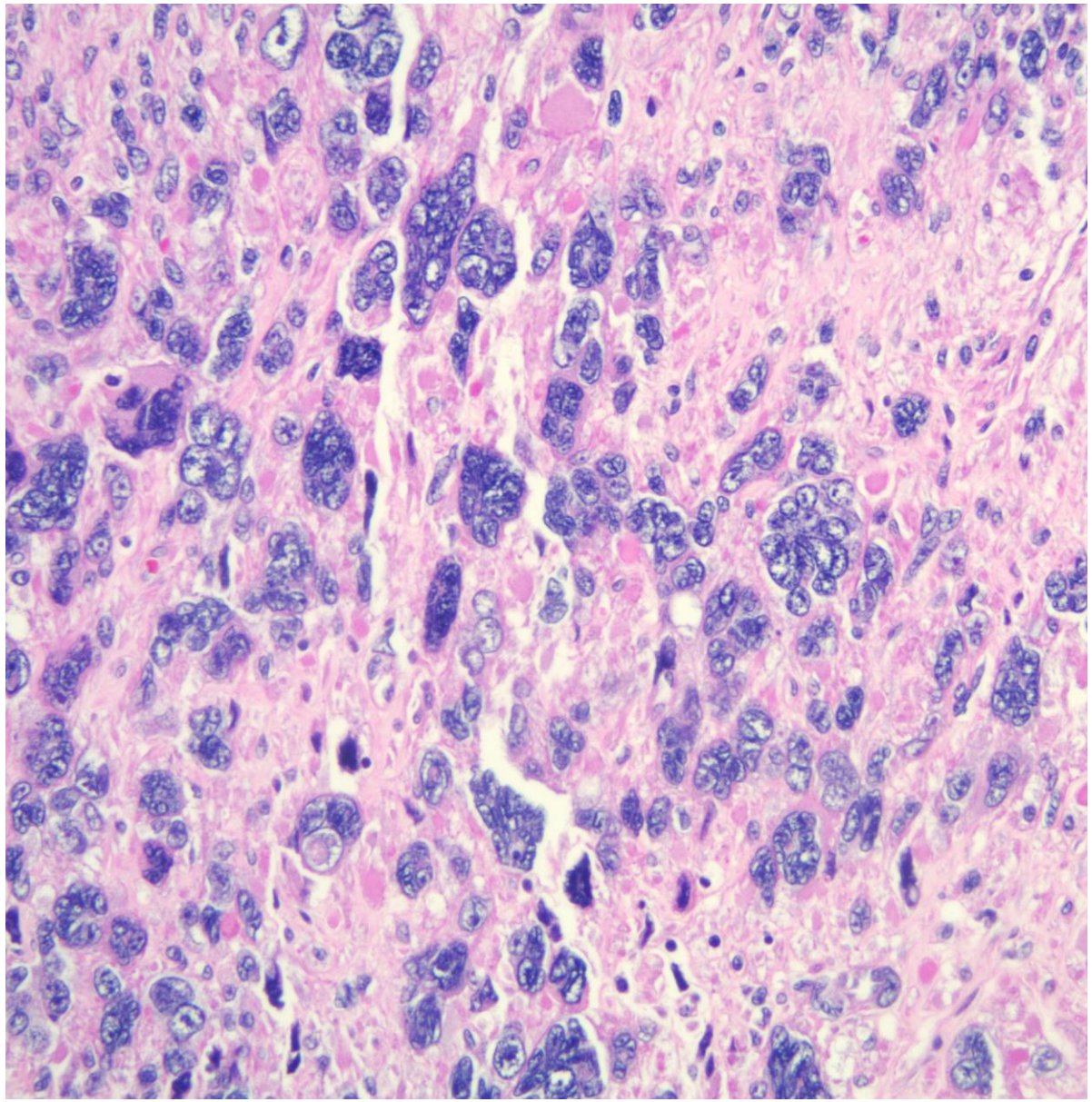



Apoplectic/infarcted

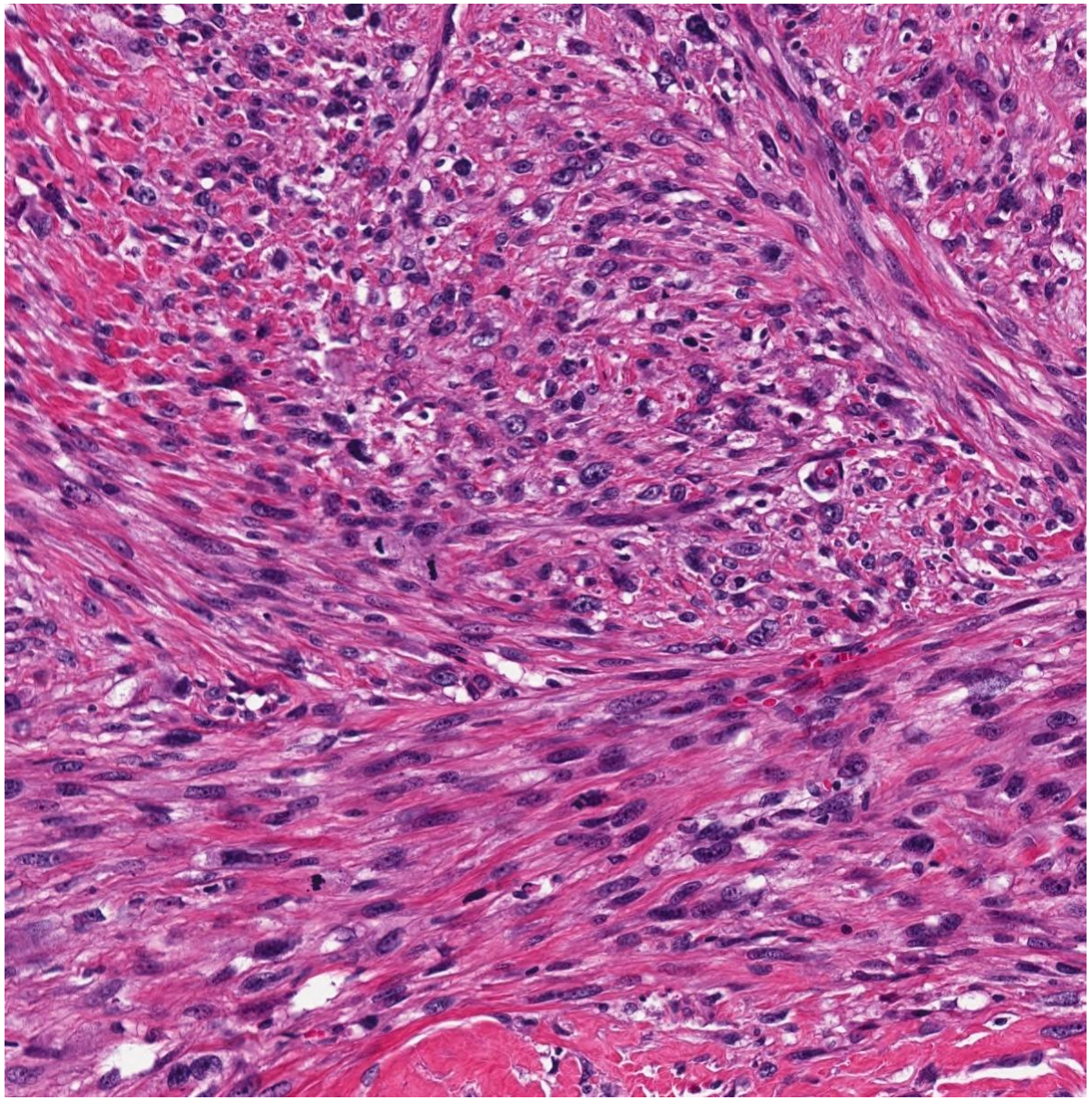

Coagulative/tumor cell

Leiomyoma with bizarre nuclei (LBN)

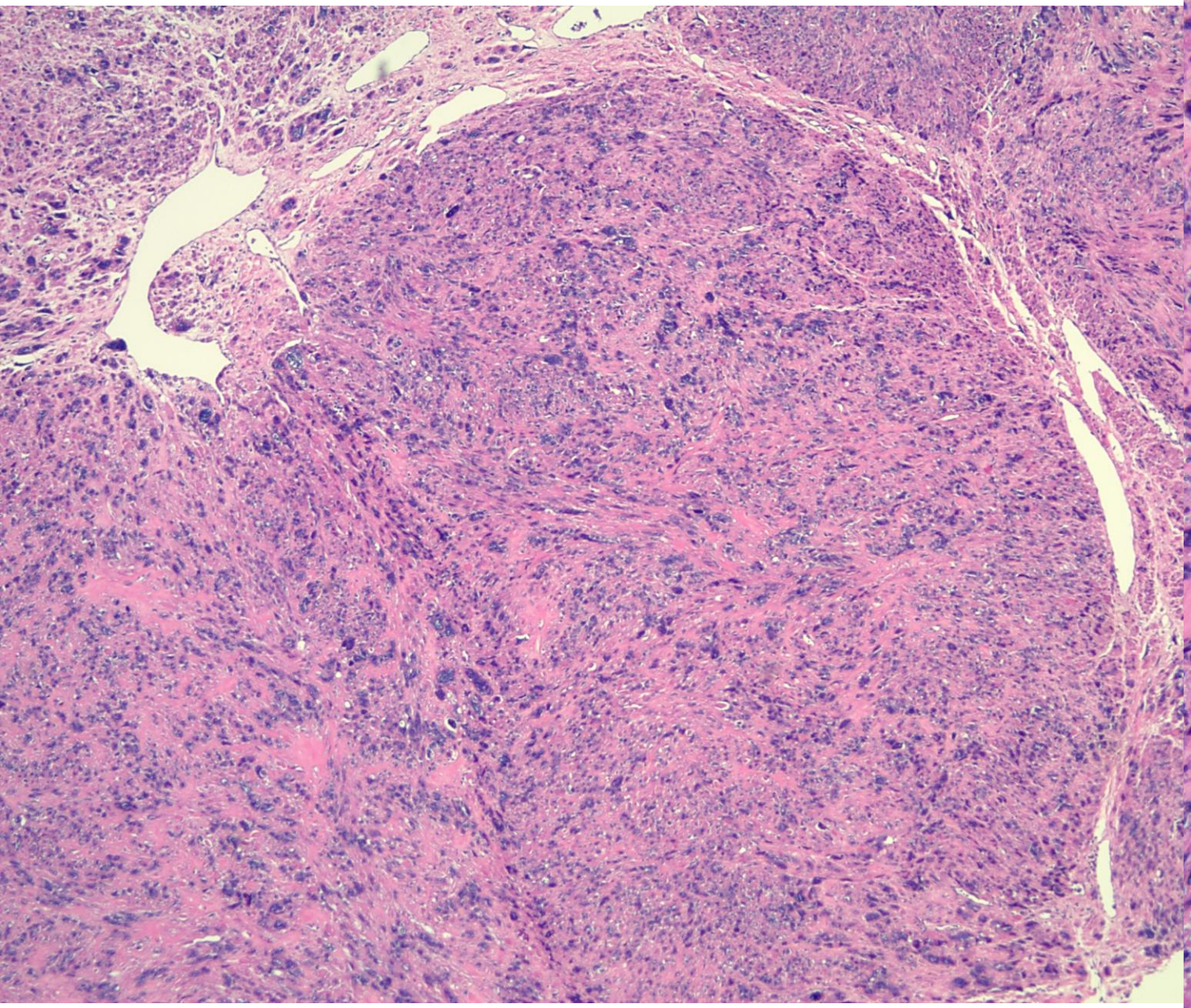
- Bizarre nuclei
- No tumor necrosis
- ≤5 MF/10HPF

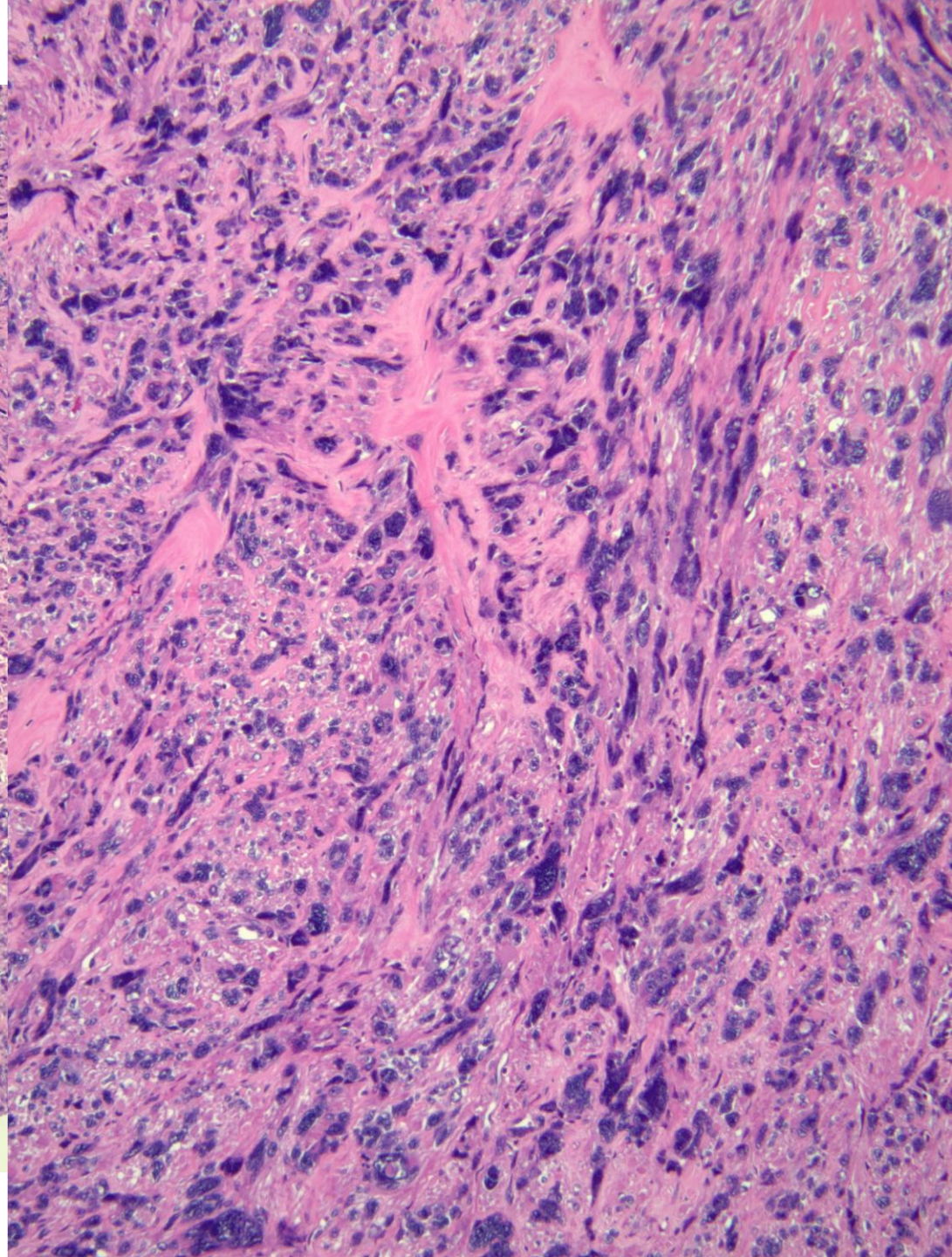


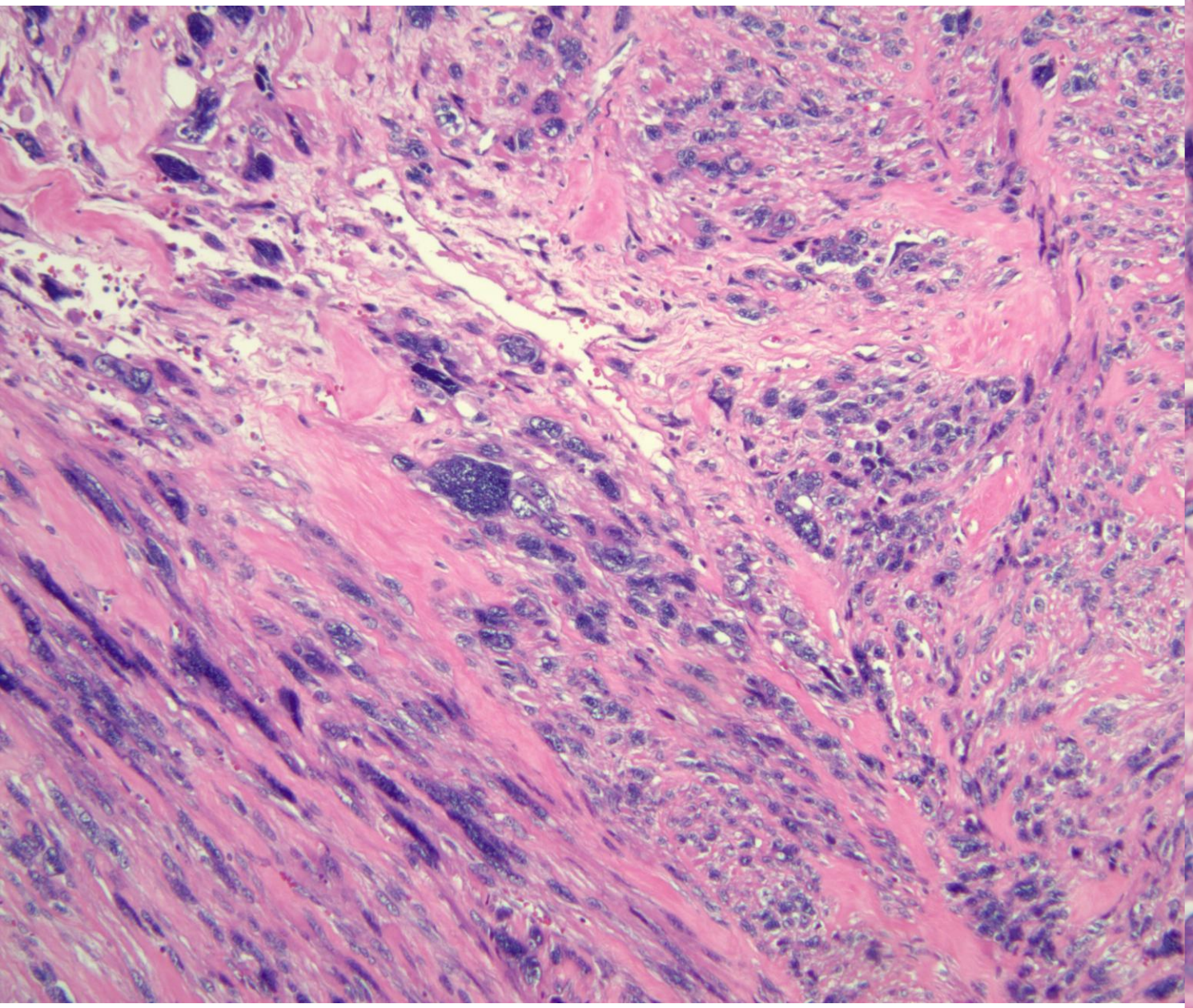
Leiomyoma with bizarre nuclei

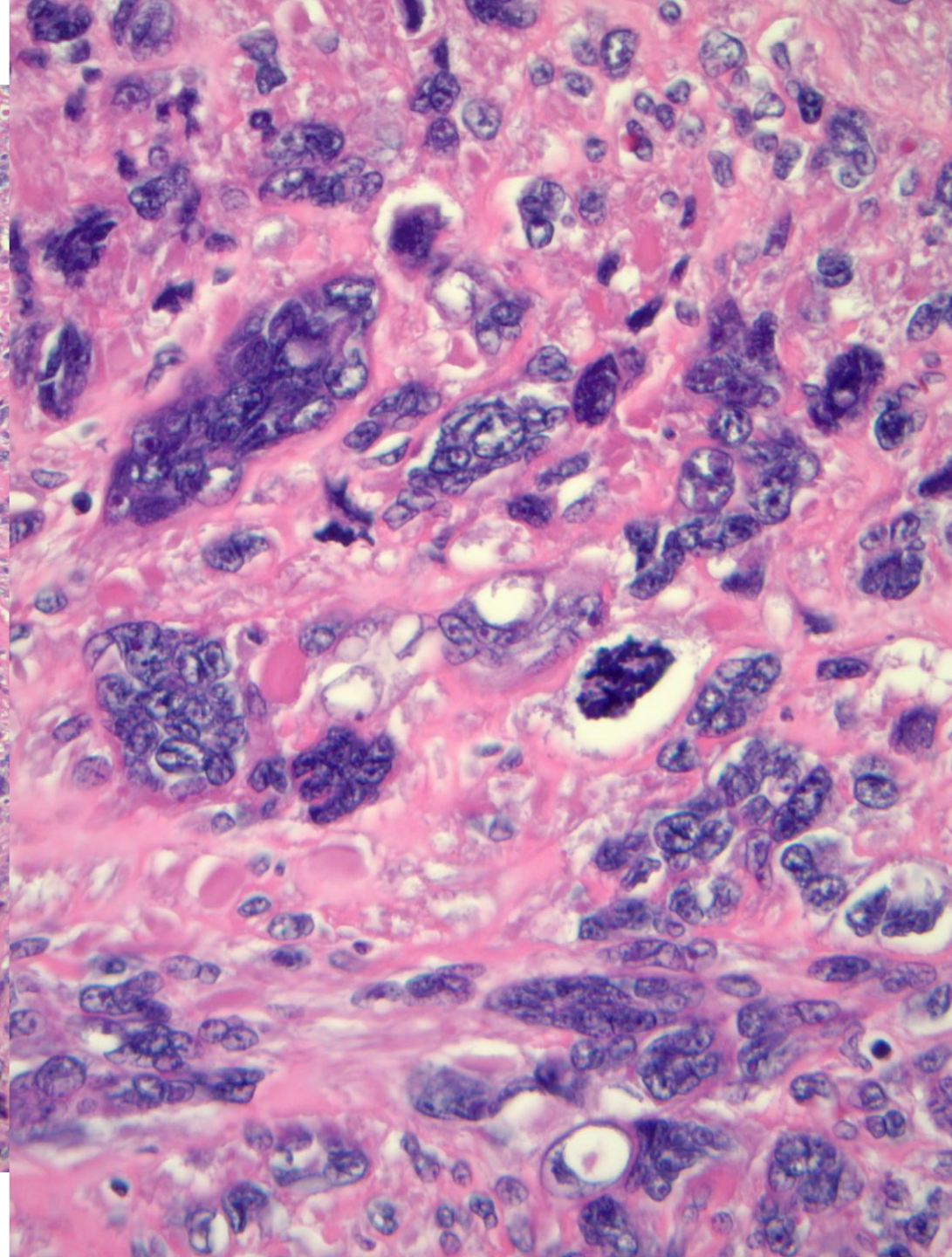


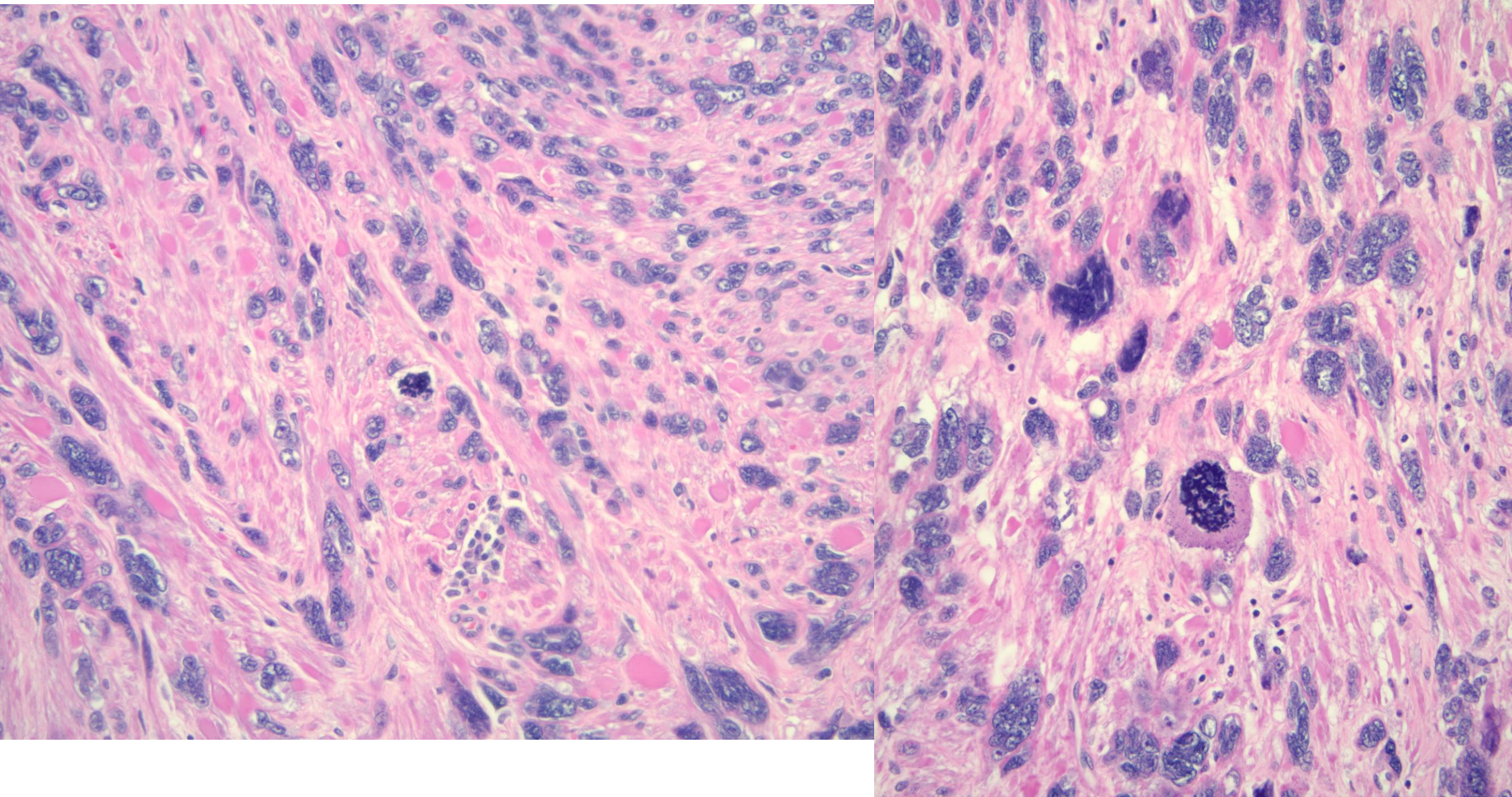
Leiomyosarcoma











Leiomyoma with bizarre nuclei (LBN)

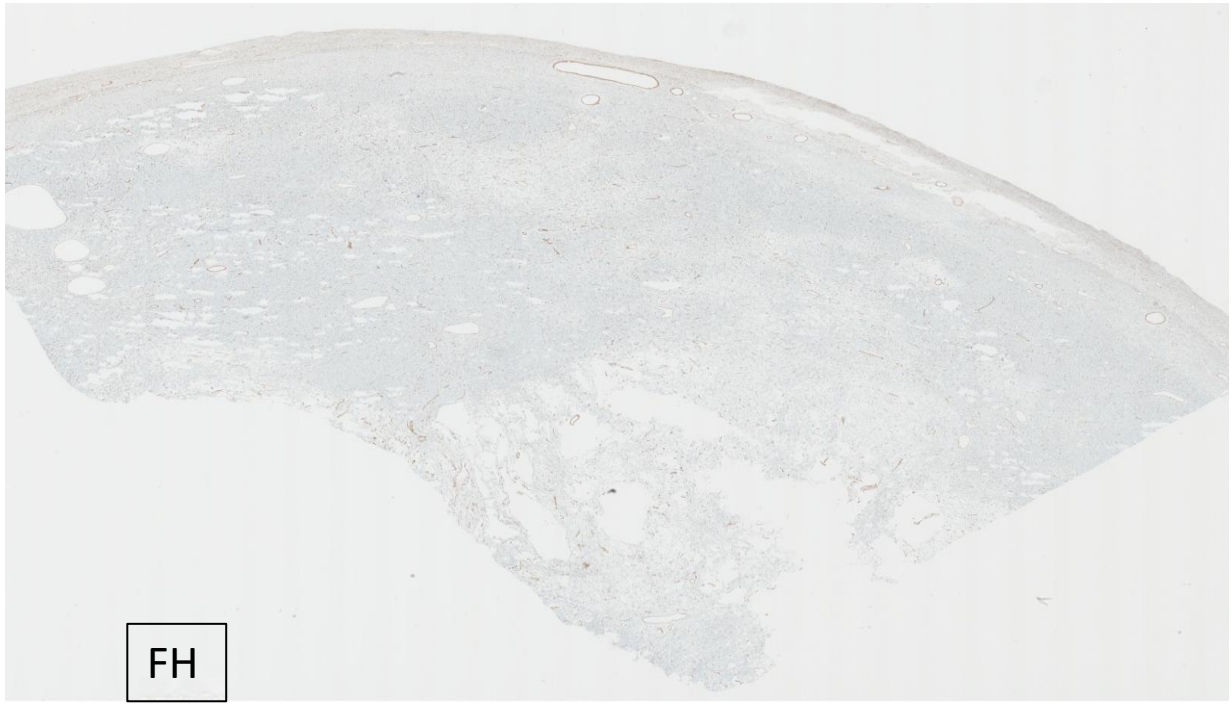
- 60% have *fumarate hydratase* (*FH)* abnormalities, mostly somatic

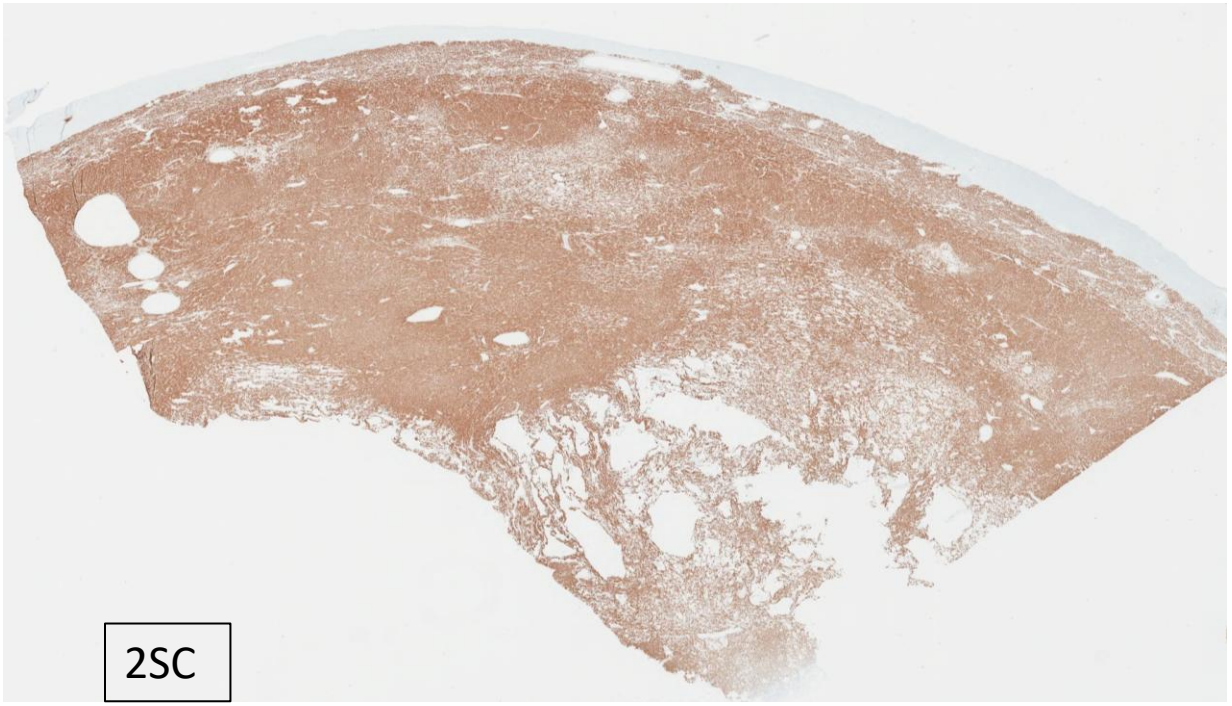
- ~40% have *TP53* mutation or *Rb1* mutation/deletion
  - **p53 and Rb1 immunohistochemistry has no role in the diagnosis of leiomyosarcoma when the tumor resembles LBN

Fumarate hydratase (FH) deficient-leiomyoma and LBN

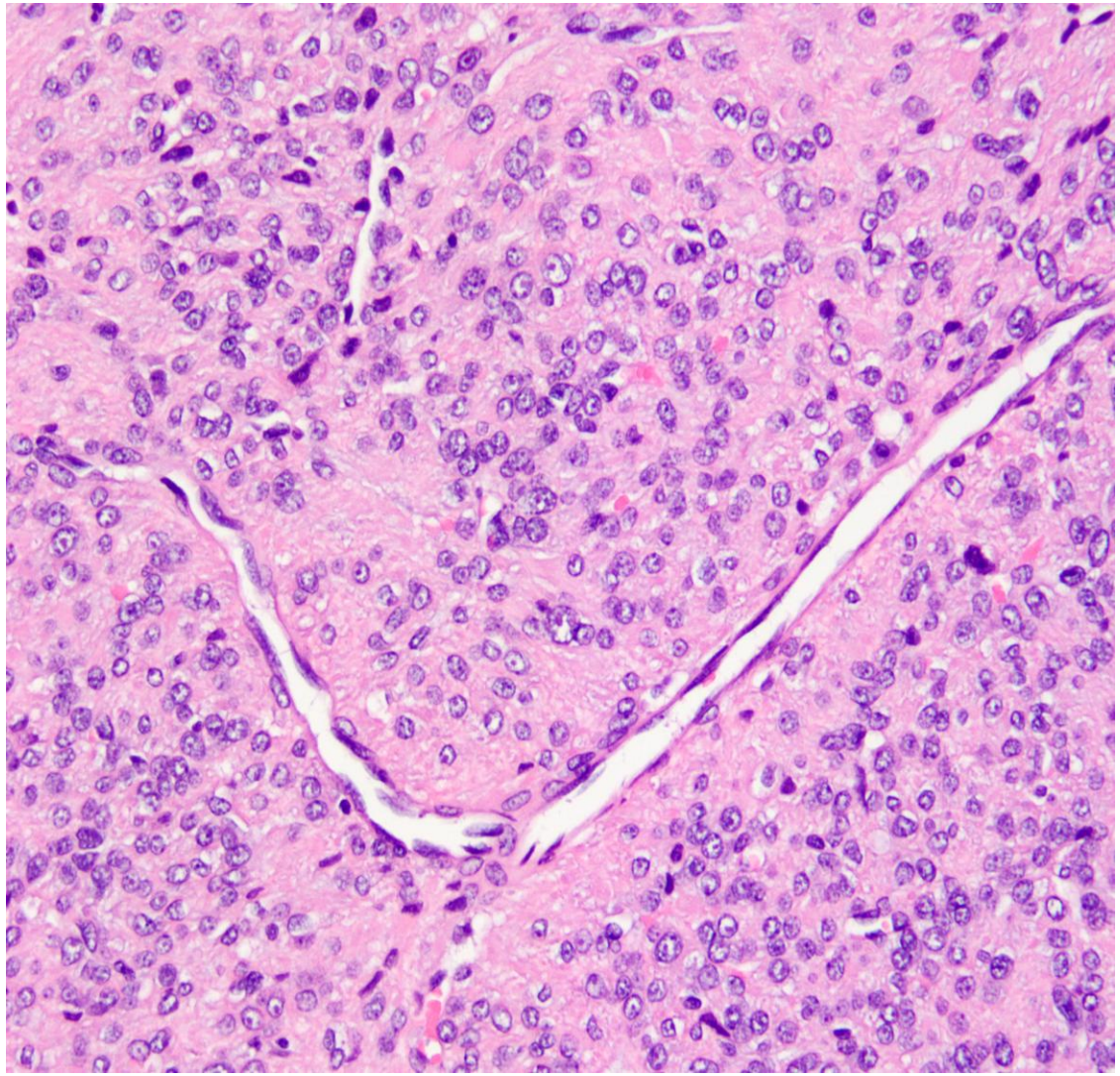
- Characteristic morphology
- Positive 2 succinyl-cysteine (2SC) IHC; Loss of FH staining
  - Glycolosis >> Oxidative phosphorylation (Warburg effect)
- Significance
  - Rare, germline *FH* mutation
    - Hereditary leiomyoma/RCC syndrome
    - Opportunity to intervene before development of RCC

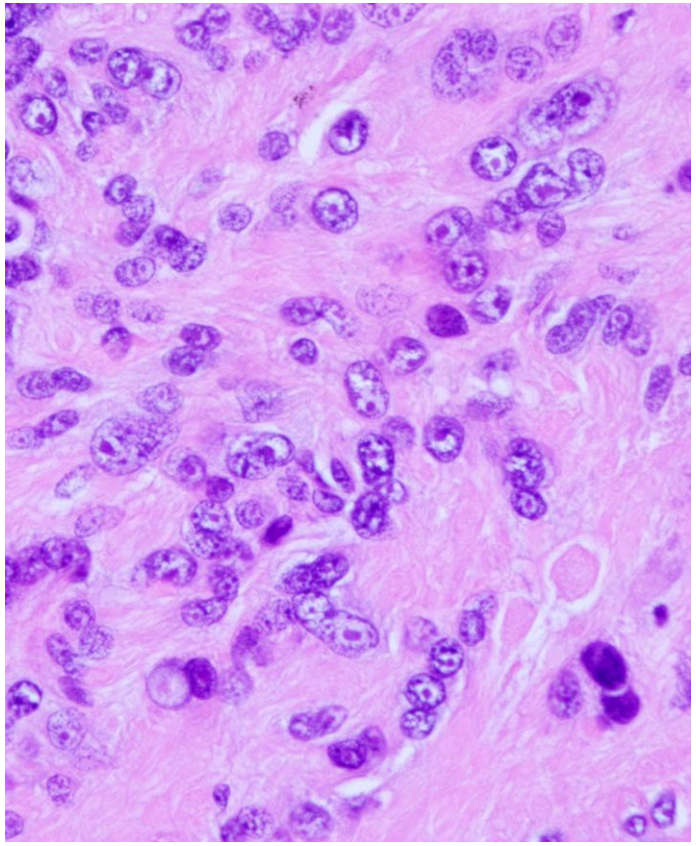
FH deficient immunohistochemistry

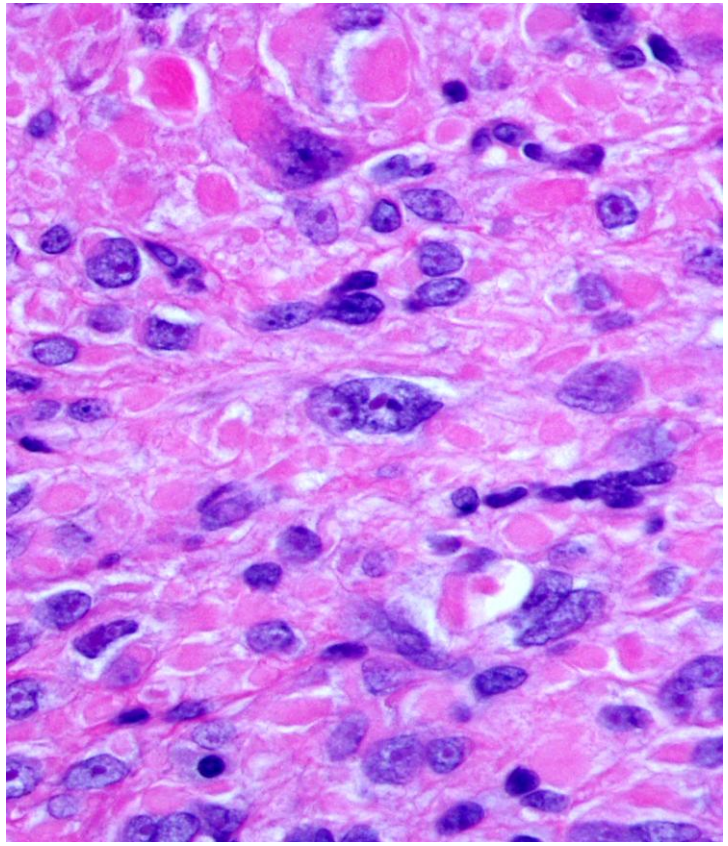




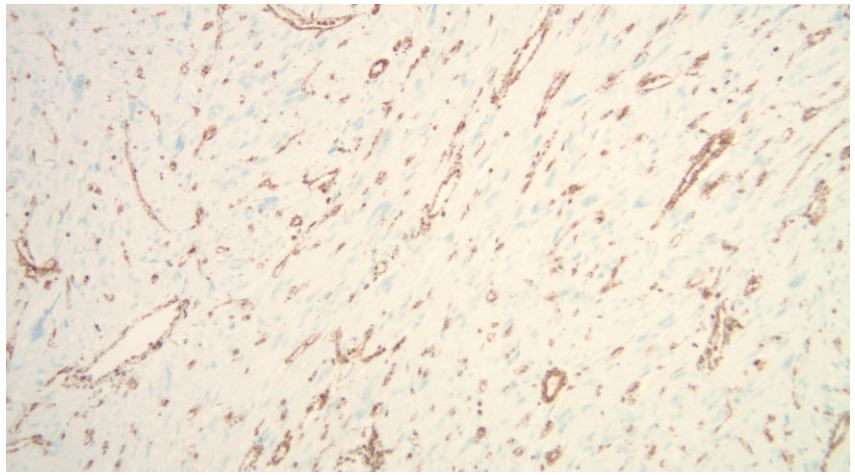
Fumarate hydratase (FH) deficient-leiomyoma

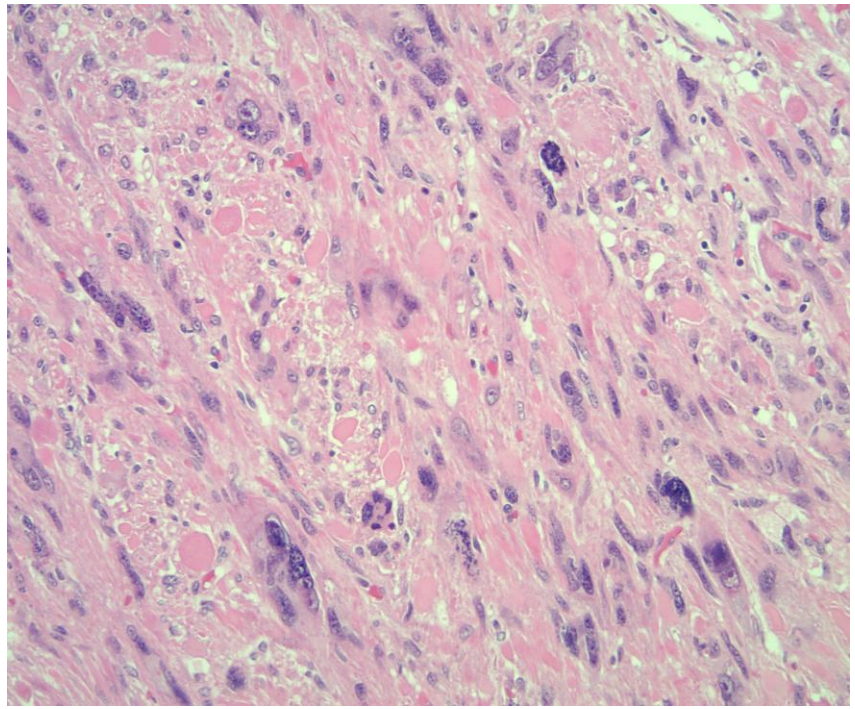


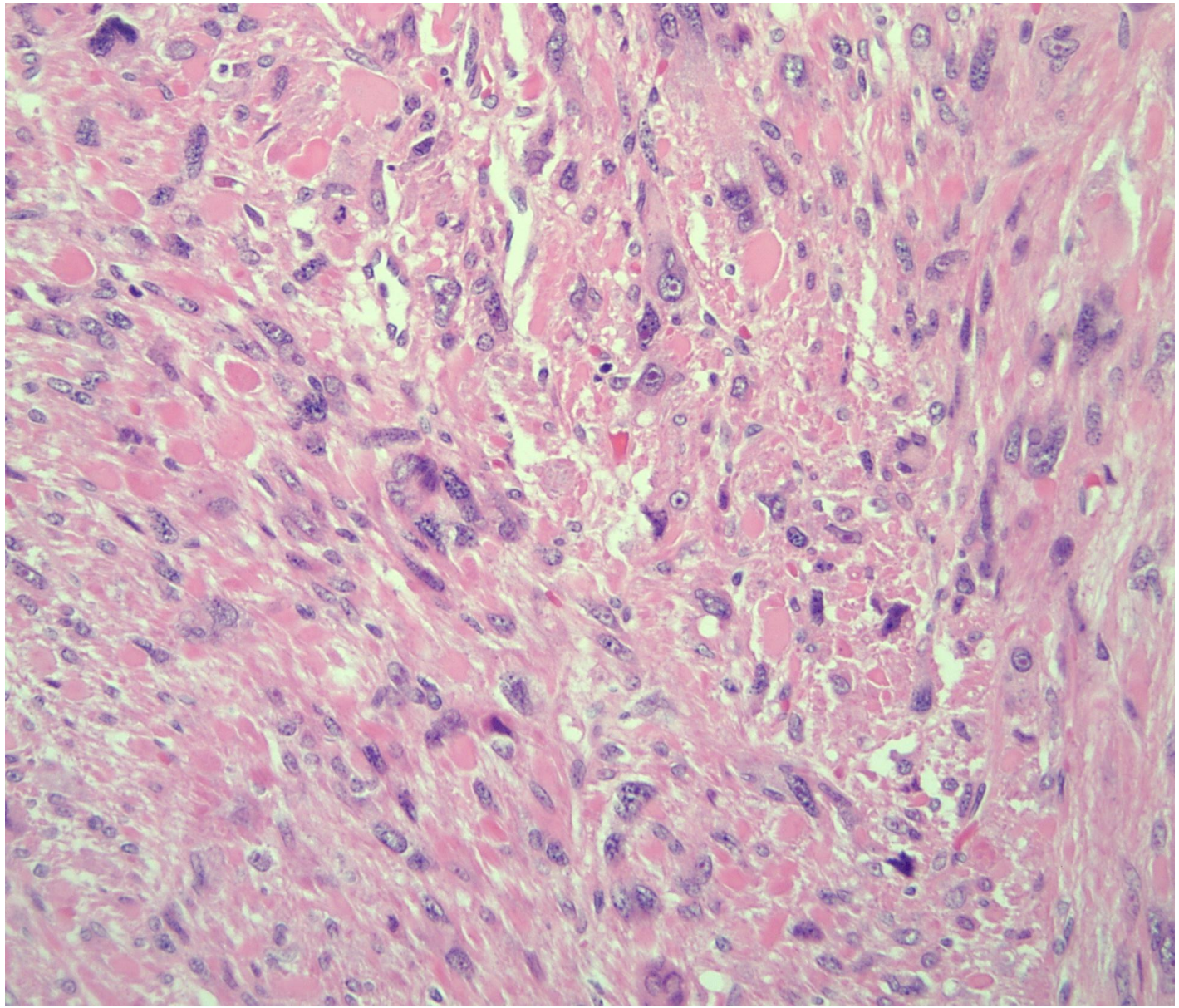


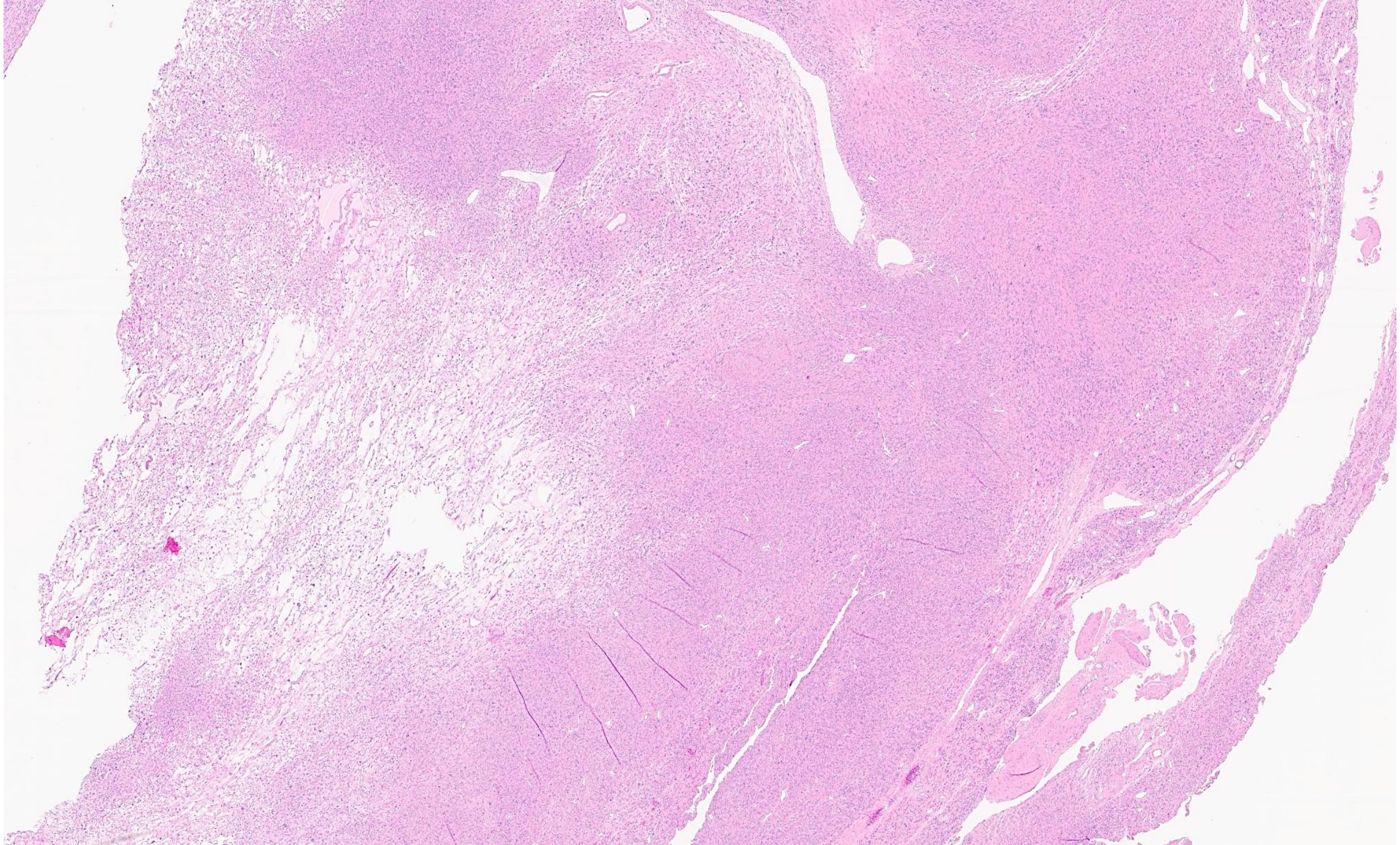


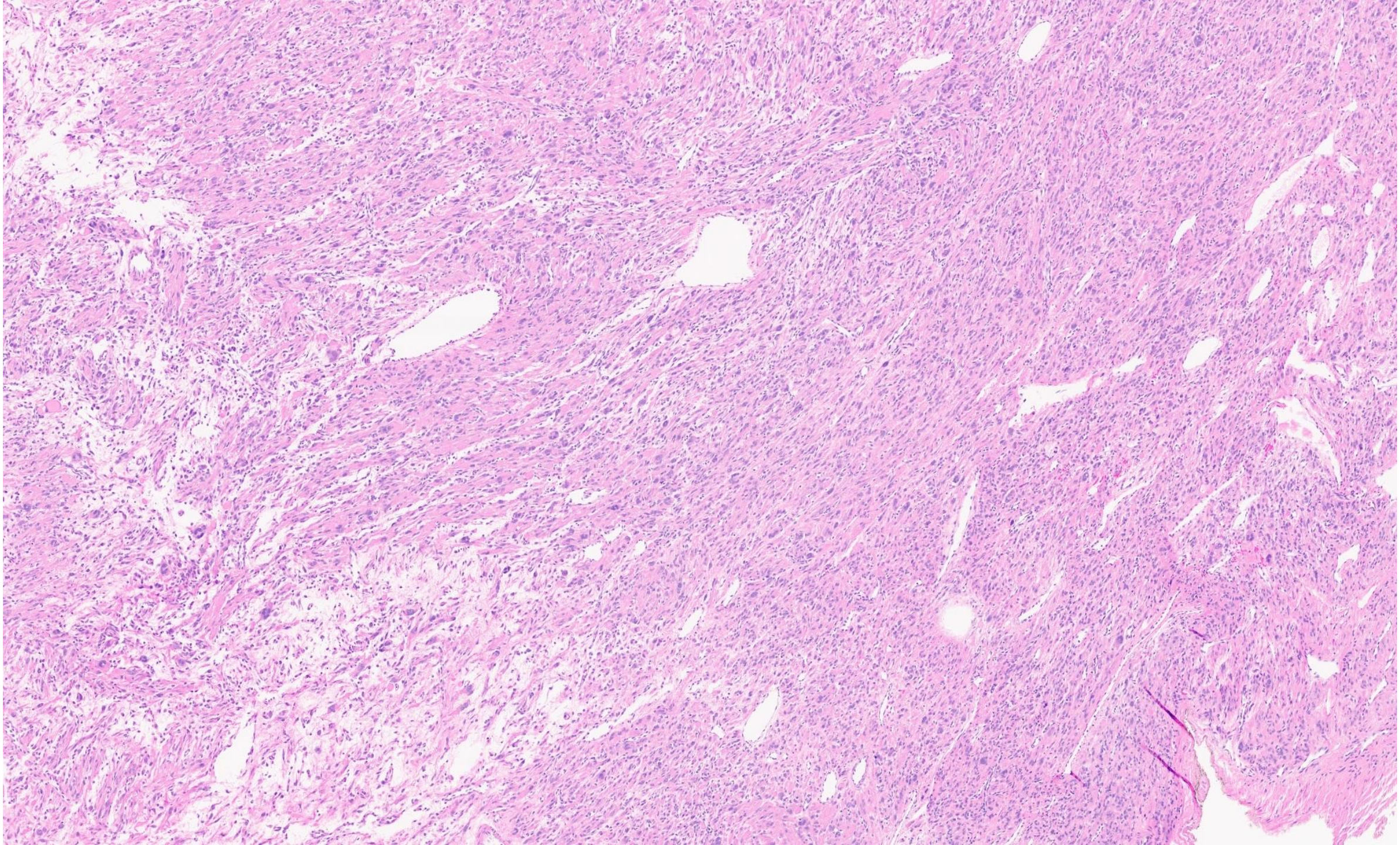
FH

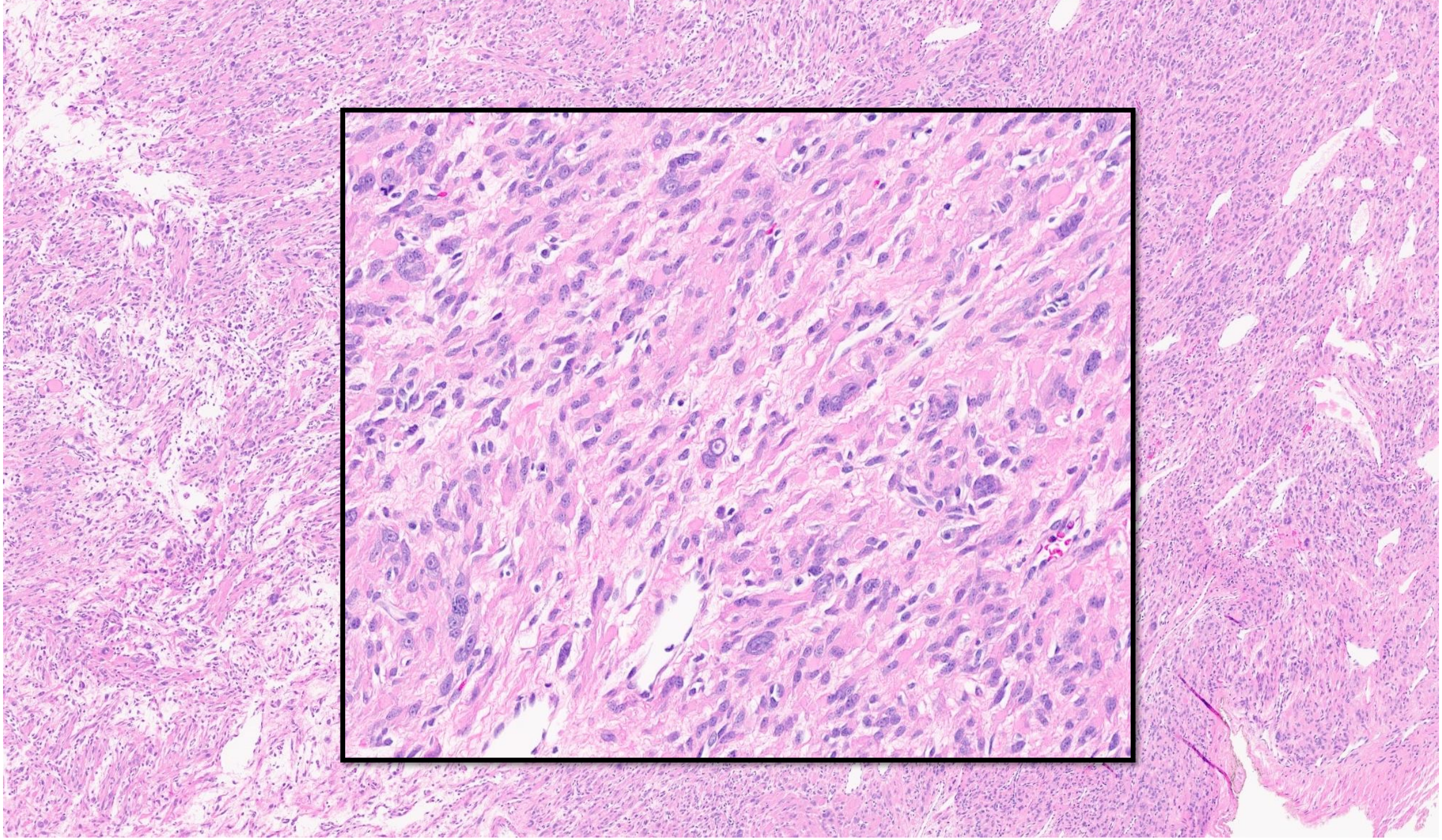






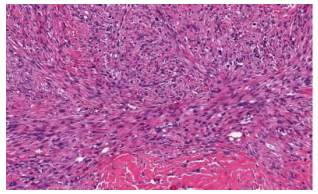




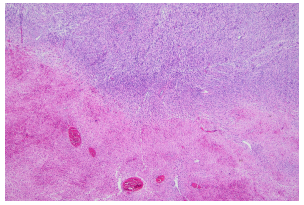


Smooth muscle tumor of uncertain malignant potential (STUMP): A diagnosis of exclusion

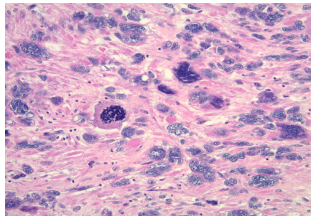
Leiomyosarcoma



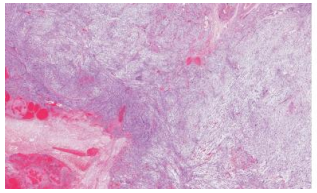
Apoplectic leiomyoma



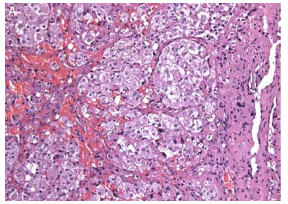
Leiomyoma with bizarre nuclei



Inflammatory myofibroblastic tumor

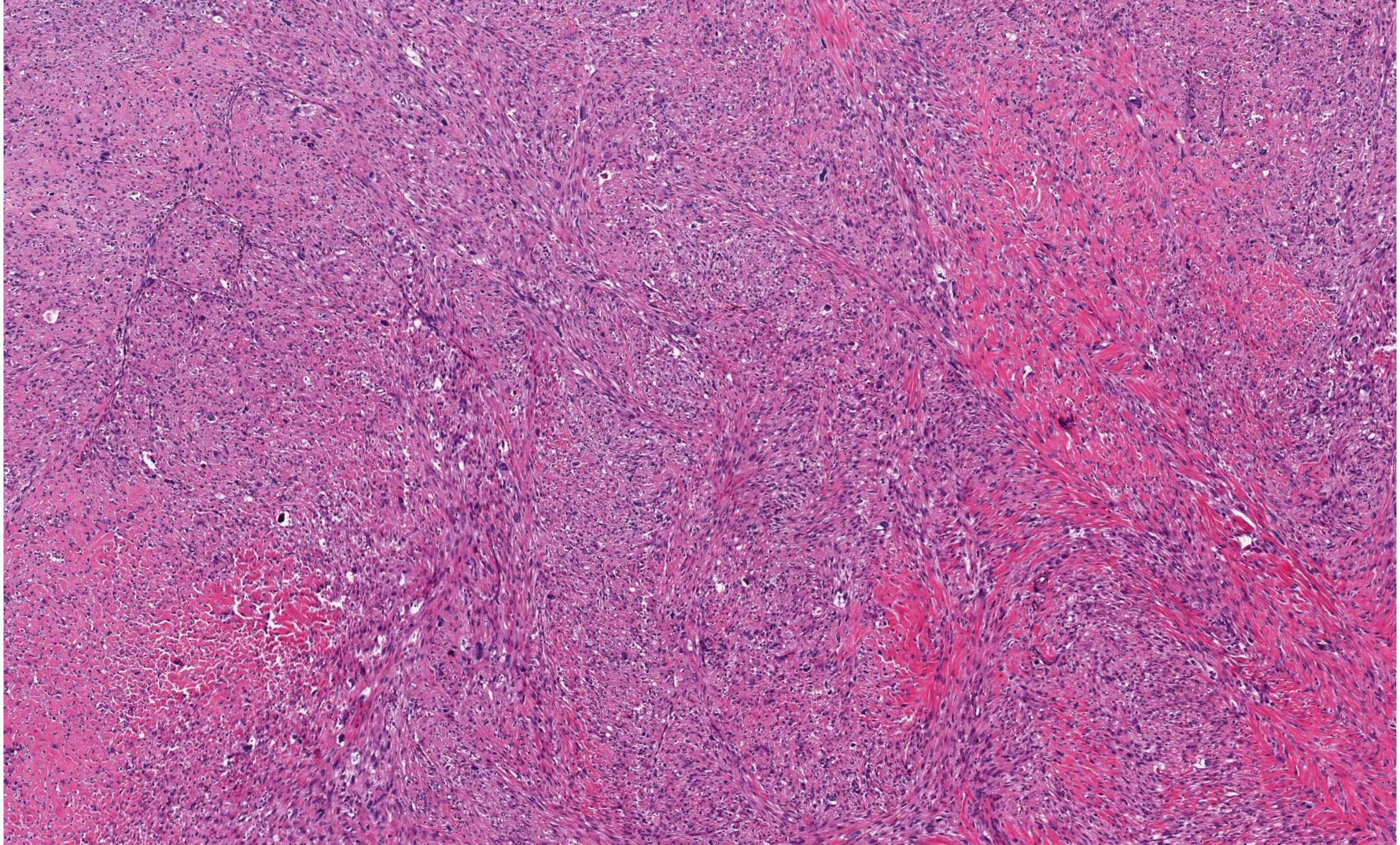


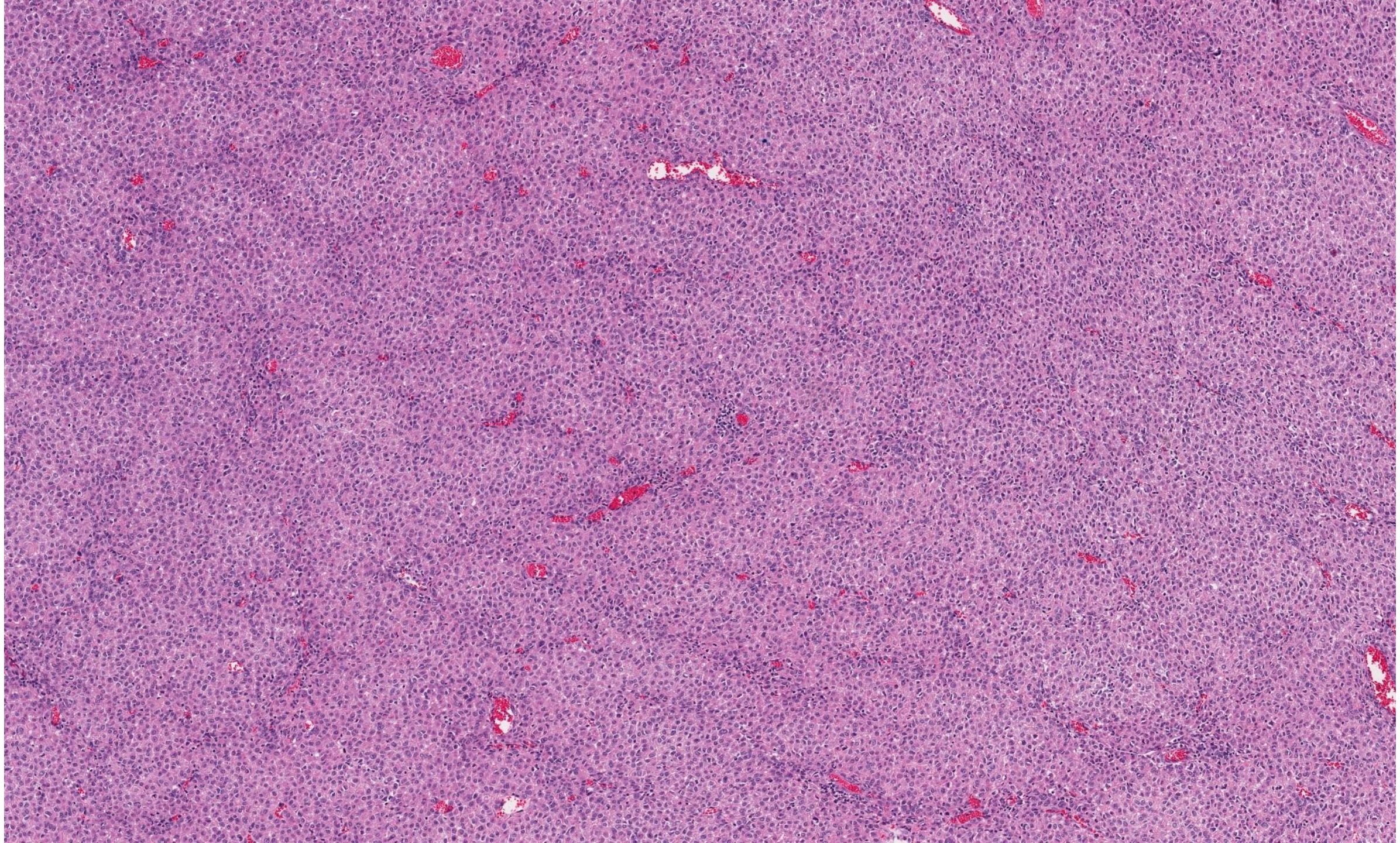
Perivascular epithelioid cell tumor

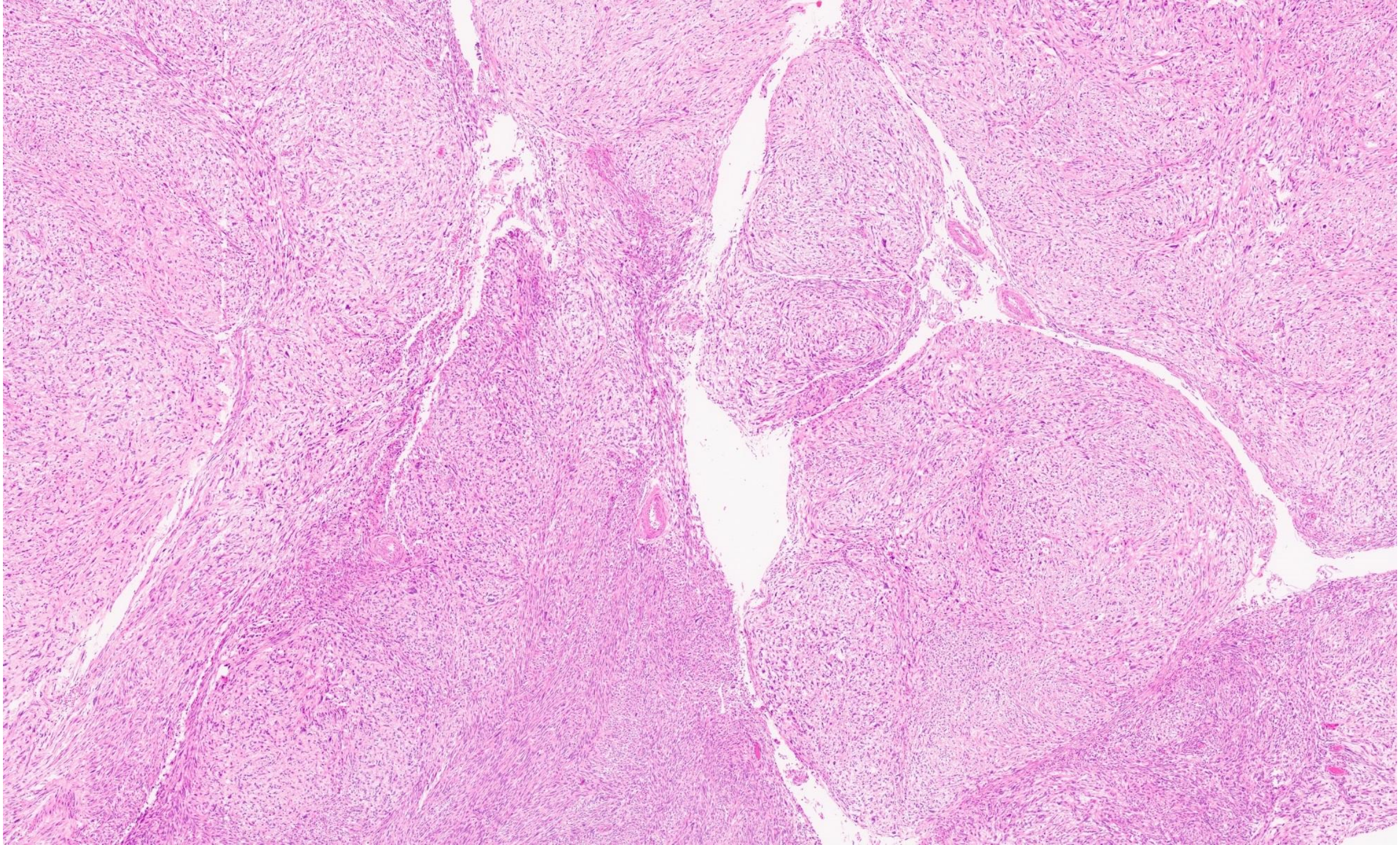


STUMP examples

- Leiomyoma with bizarre nuclei, but 5-9 MF/10HPF
  - 15% recurrence
- Almost meets criteria for leiomyosarcoma
- Tumor necrosis alone
- High mitotic counts (≥20 MF/10HPF) alone
- Uncertainty about necrosis, degree of atypia or mitotic count
- Uncertainty about myxoid or epithelioid features (qualitative or quantitative)







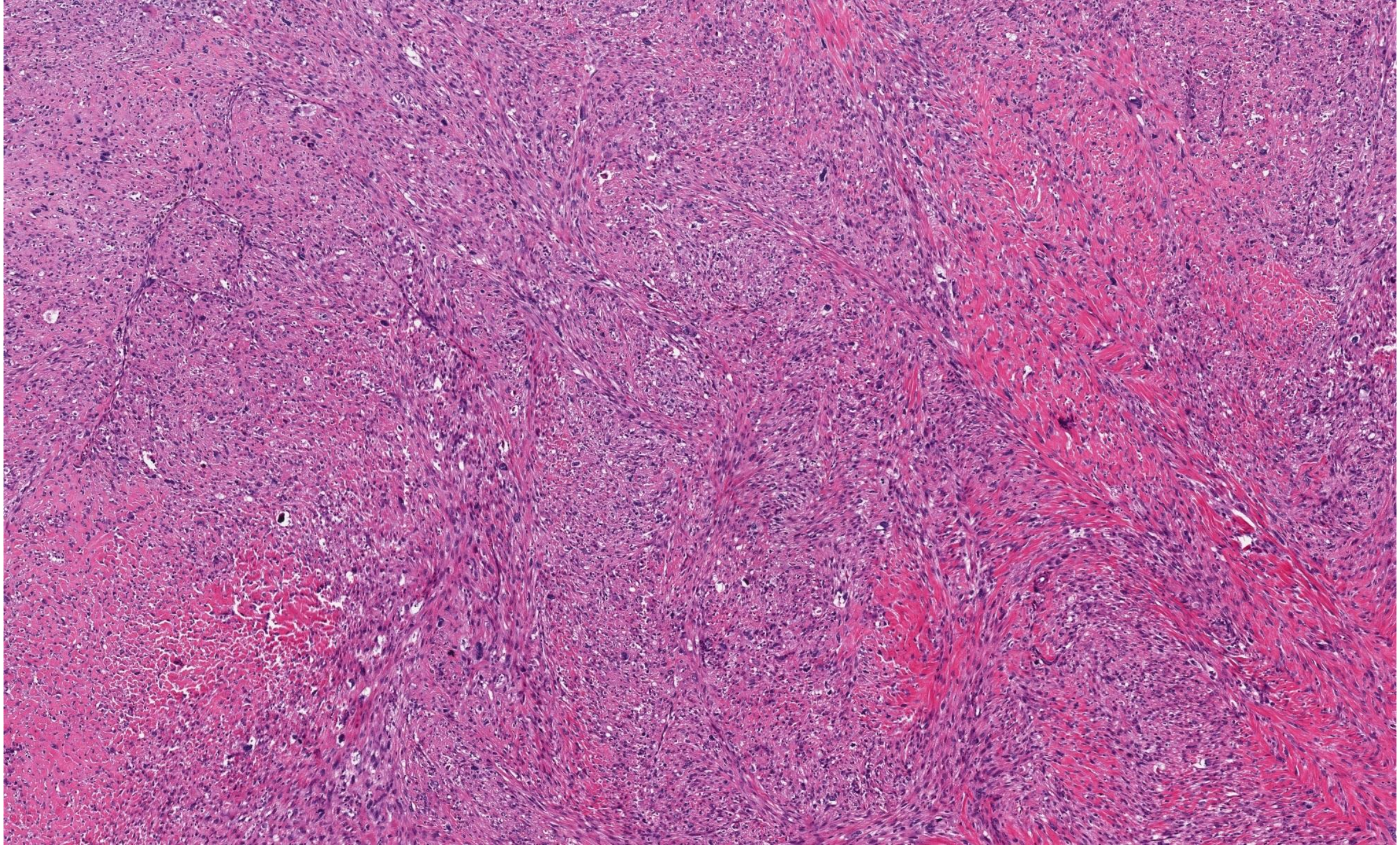
Smooth muscle tumor of uncertain malignant potential (STUMP)

- STUMPs encompass
  - Benign tumors
  - Recurring smooth muscle tumors other than leiomyoma (“low-grade leiomyosarcoma”) with an indolent clinical course
  - Leiomyosarcomas, clinically high-grade

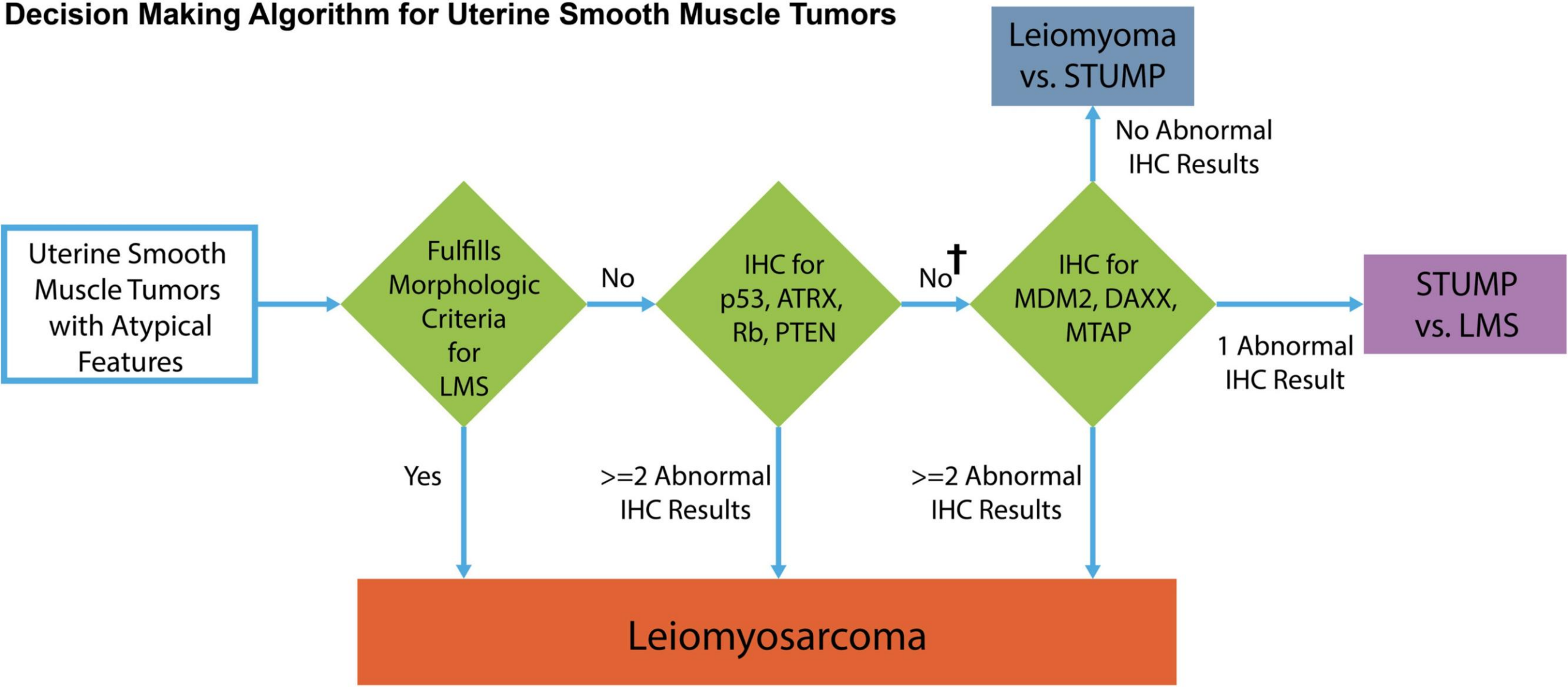
How can we predict clinical outcomes for STUMPs?

- STUMPs encompass
  - Benign tumors
  - Recurring smooth muscle tumors other than leiomyoma (“low-grade leiomyosarcoma”) with an indolent clinical course

- Leiomyosarcomas, clinically high-grade
  - Almost meets criteria for conventional leiomyosarcoma
    - Immunohistochemistry, but
      - Not epithelioid, myxoid or “leiomyoma with bizarre nuclei”



Decision Making Algorithm for Uterine Smooth Muscle Tumors



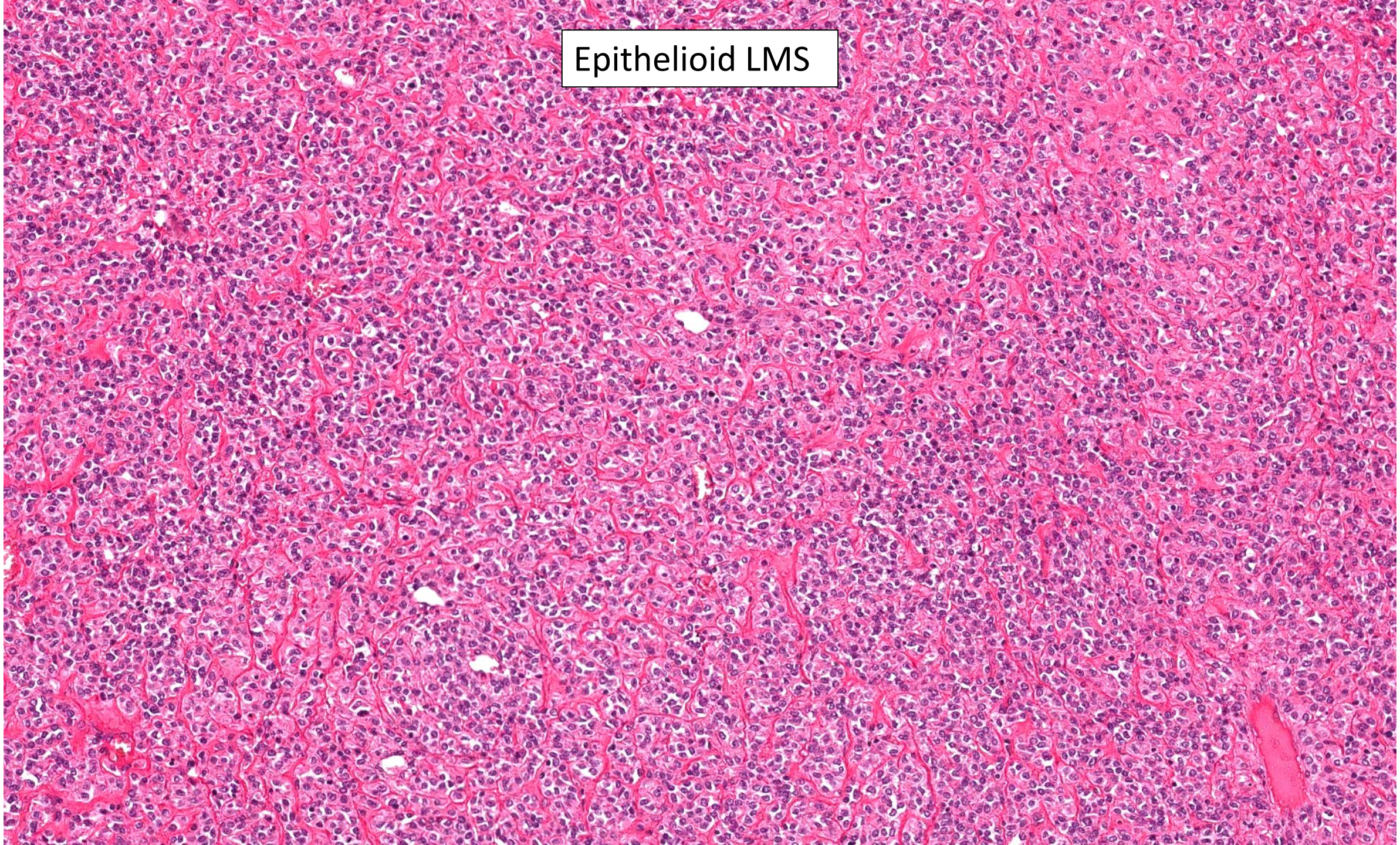
† - p53 is mutually exclusive with MDM2 and MTAP; if p53 is abnormal, MDM2 and MTAP should not be orderd.
- ATRX is mutually exclusive with DAXX; if ATRX is abnormal, DAXX should not be ordered.

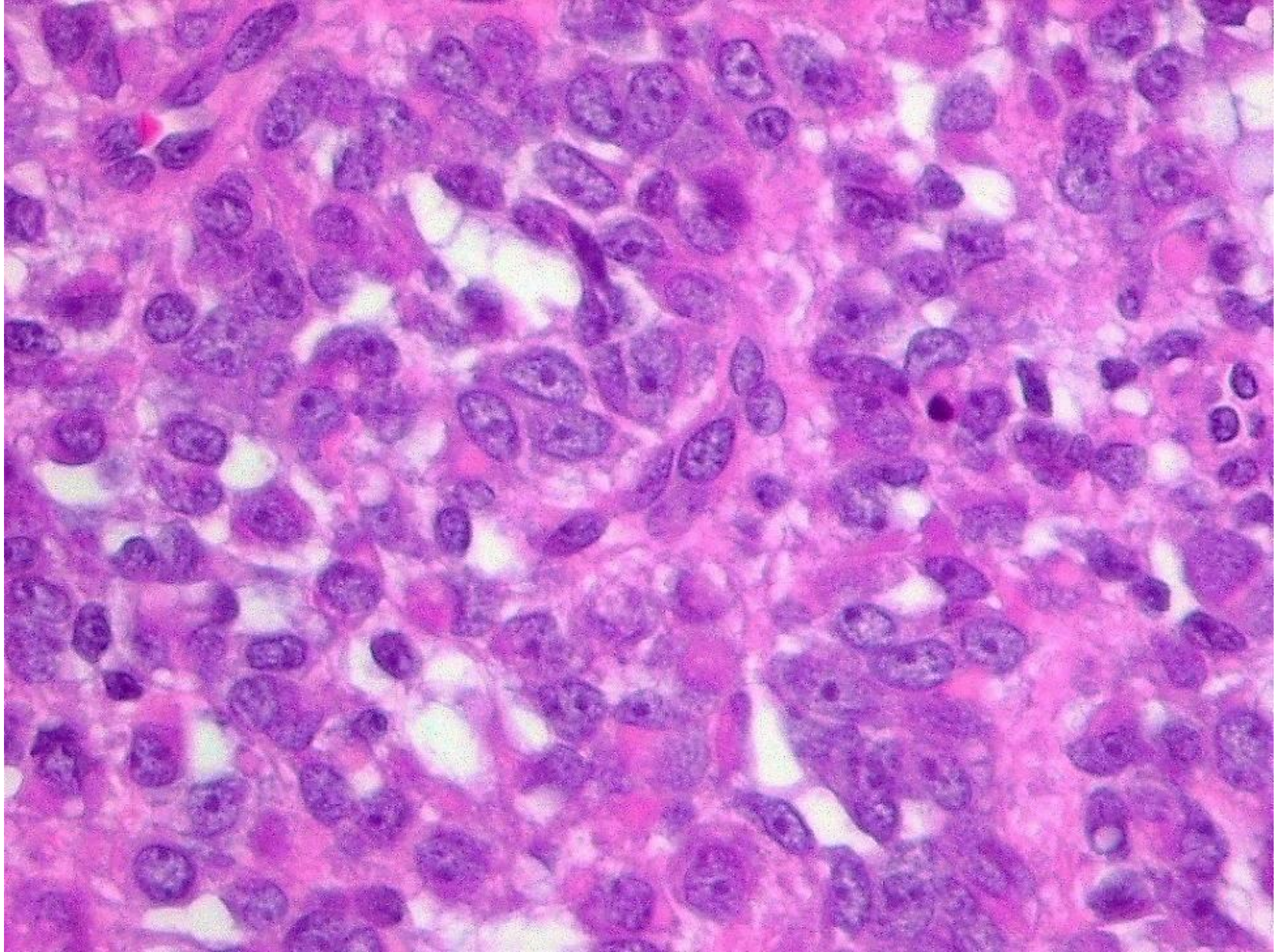
Momeni-Boroujeni A, et al.
https://doi.org/10.1016/j.modpat.2022.100084

Immunohistochemistry and differential diagnosis of spindled tumors

	Des	CD10	p53	C-kit	STAT6	Trk/PDGF
LMS	++	-/+	-/+	variable	-	-
ESS-BCOR	-	+	-	++	-	+ Trk*
GIST	-	-/+	-/+	++	-	-
SFT	-	+/-	-	-	++	-
Sarcoma-undiff	-	-/+	++	-	-	-
Fibro-NTRK	-	-	-		-	+ Trk*
Fibro-PDGFR	-	-	-	-/+	-	+ PDGFR*

Epithelioid tumors


Epithelioid LMS



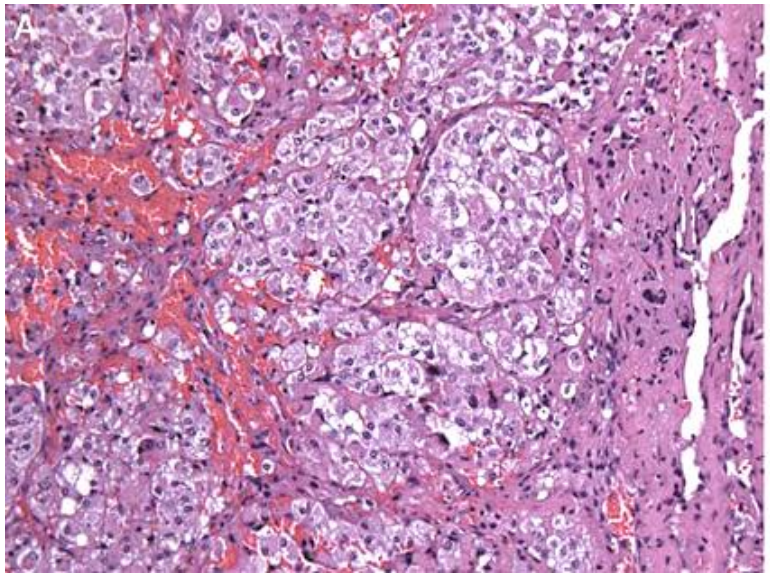
Perivascular epithelioid cell tumors (PEComas)

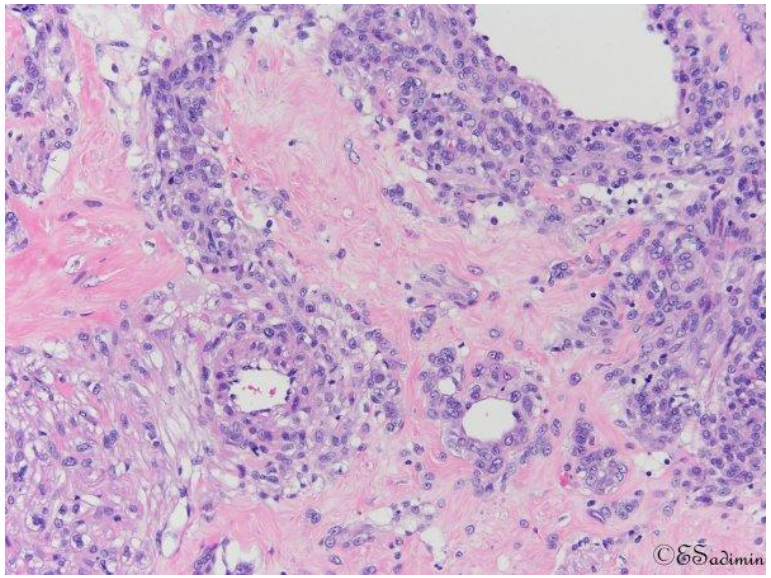
- Heterogeneous collection of tumors
  - Usually epithelioid
  - Usually resemble “epithelioid predominant angiomyolipoma”
  - Usually desmin positive
  - Usually positive with some melanocytic markers
  - Usually *TSC1* or *TSC2* mutation

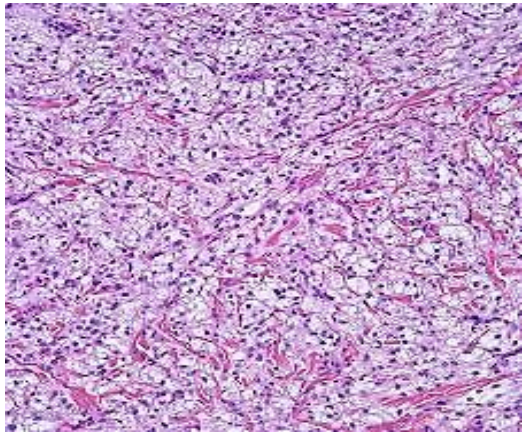
Genetic diversity of PEComa

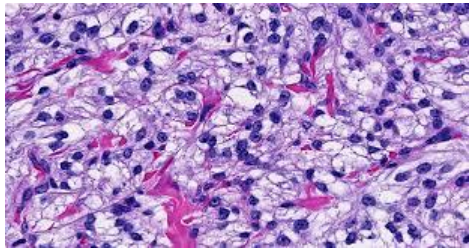
- *TSC1/2* mutation (“classic” PEComas)
- *TFE3* fusions (“Xp11” PEComas)
- PEComas with hybrid features
  - With leiomyosarcoma or STUMP
  - With LG-ESS and/or *JAZF1* rearrangement

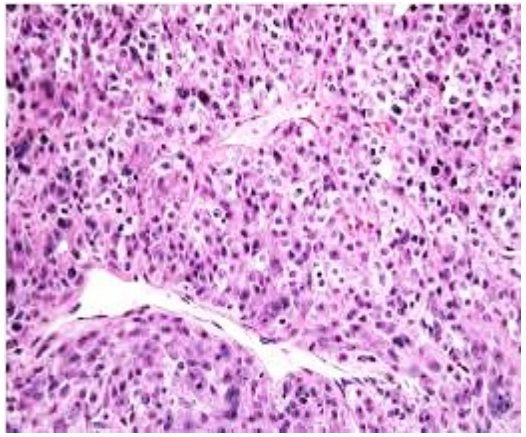
Classic PEComa









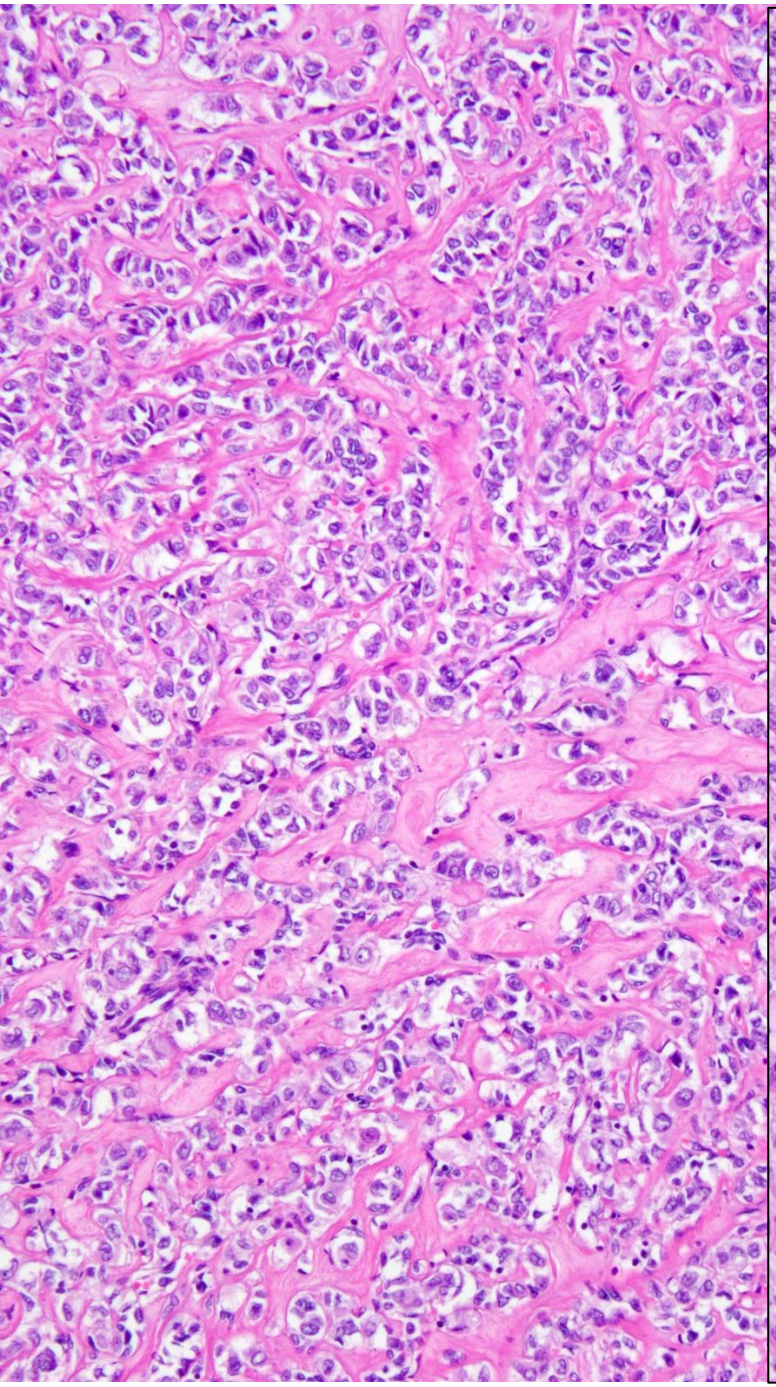


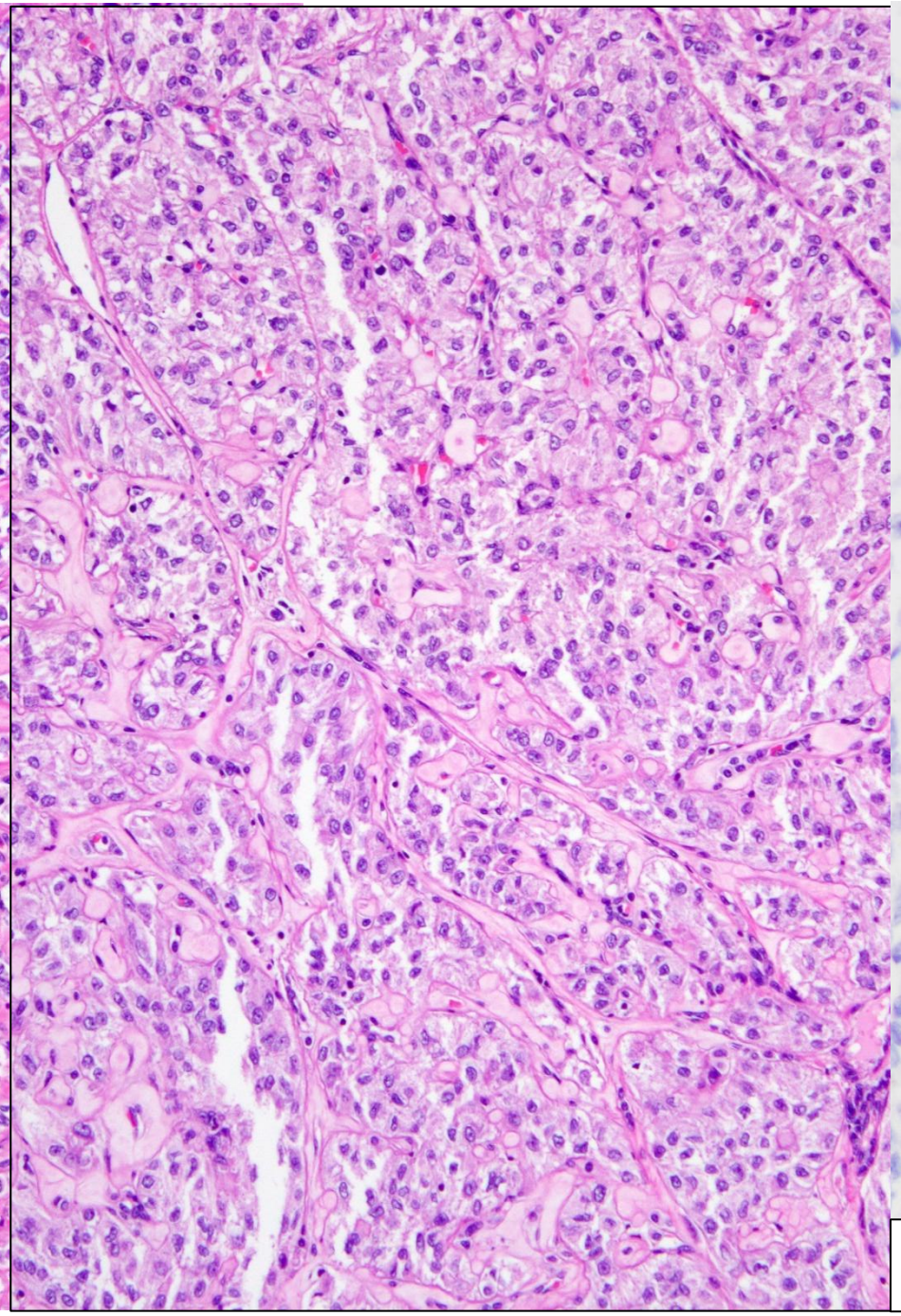
researchgate.net
dermpedia.org

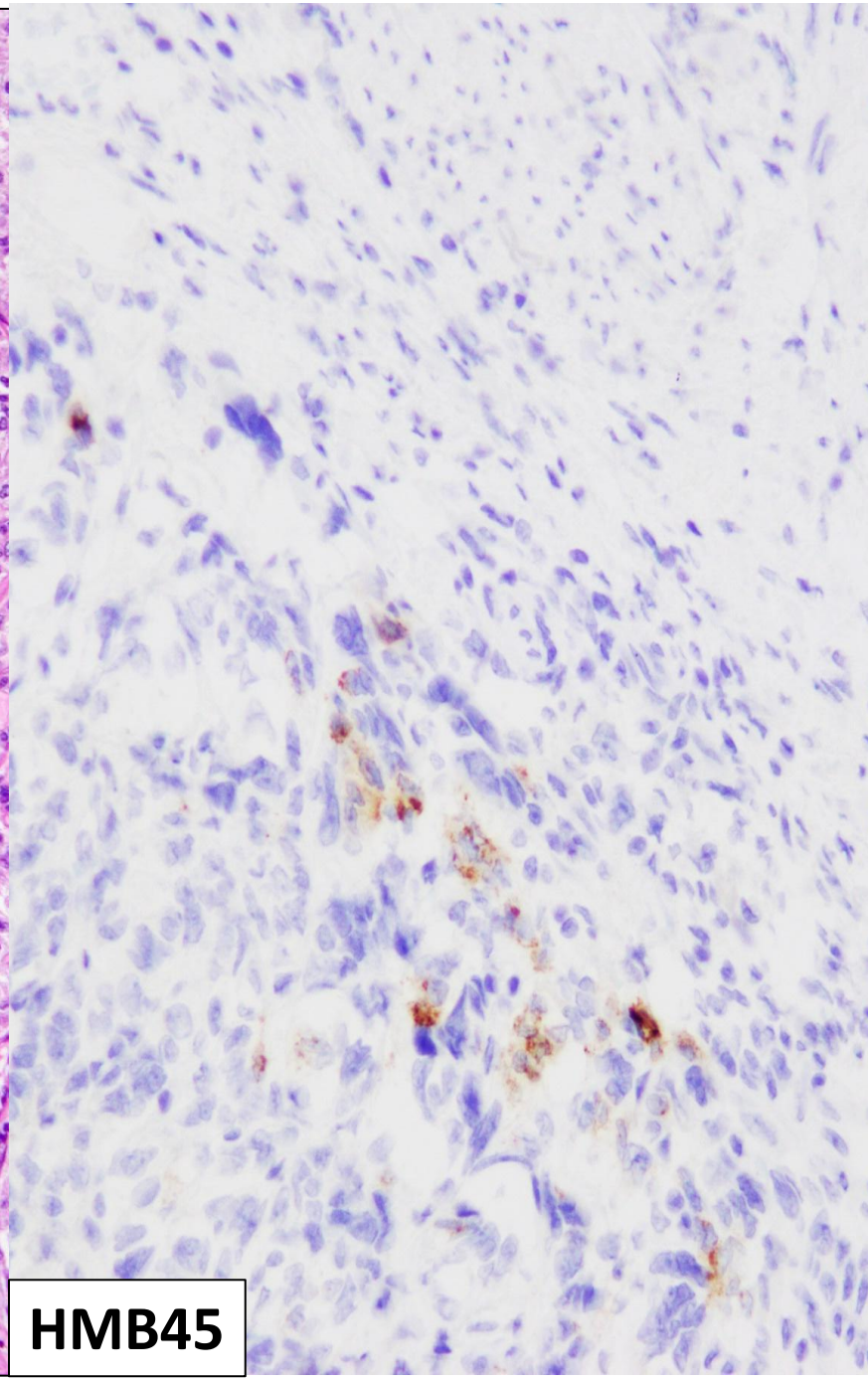
Classic PEComa

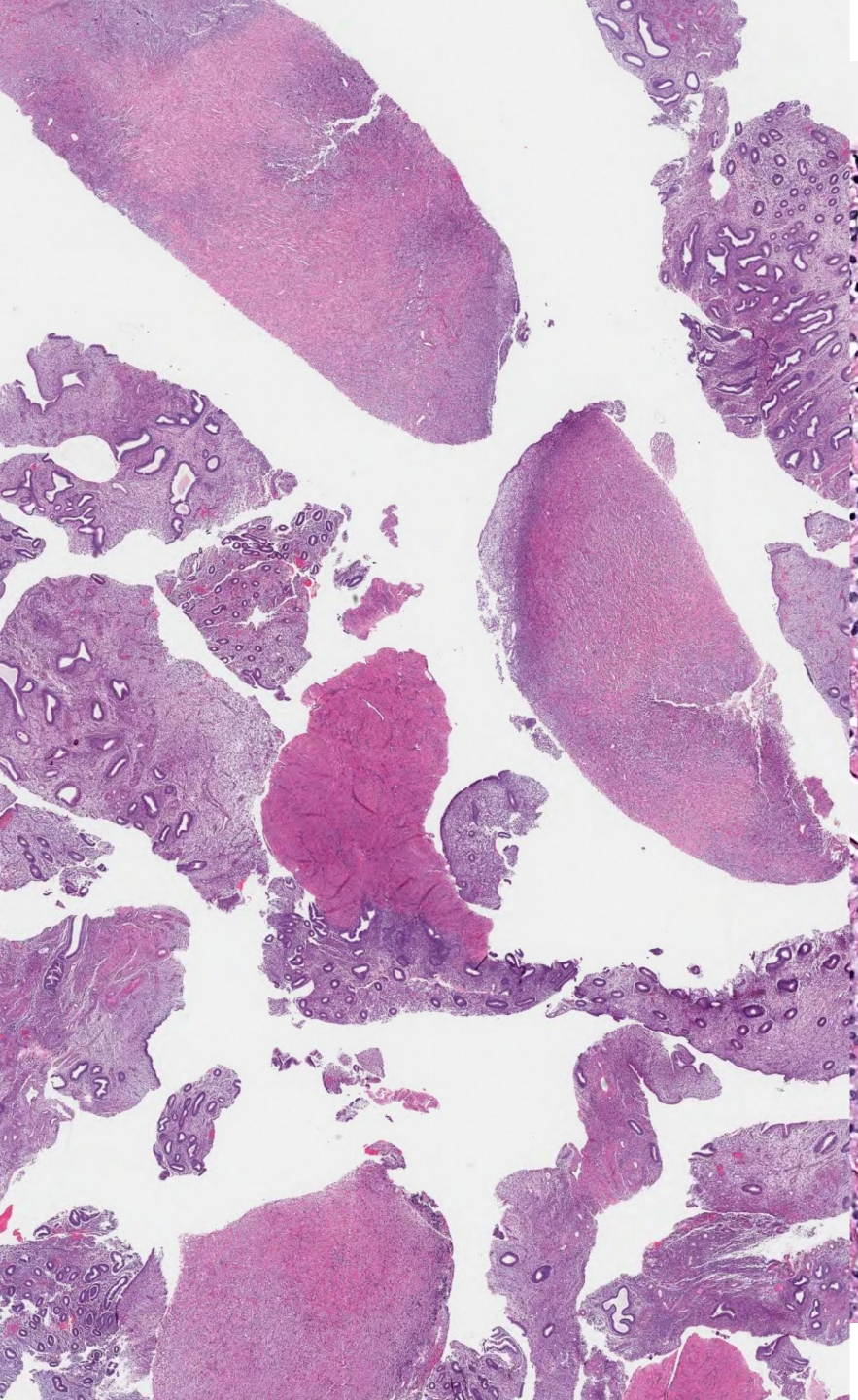
- At least 2 melanocytic markers, usually at least HMB45
- Oliva et al.:
  - 79% of tumors--diffuse HMB45 expression in > 50% of cells
  - 79% of tumors--variable expression of Melan-A and MiTF
- When in doubt, perform sequencing

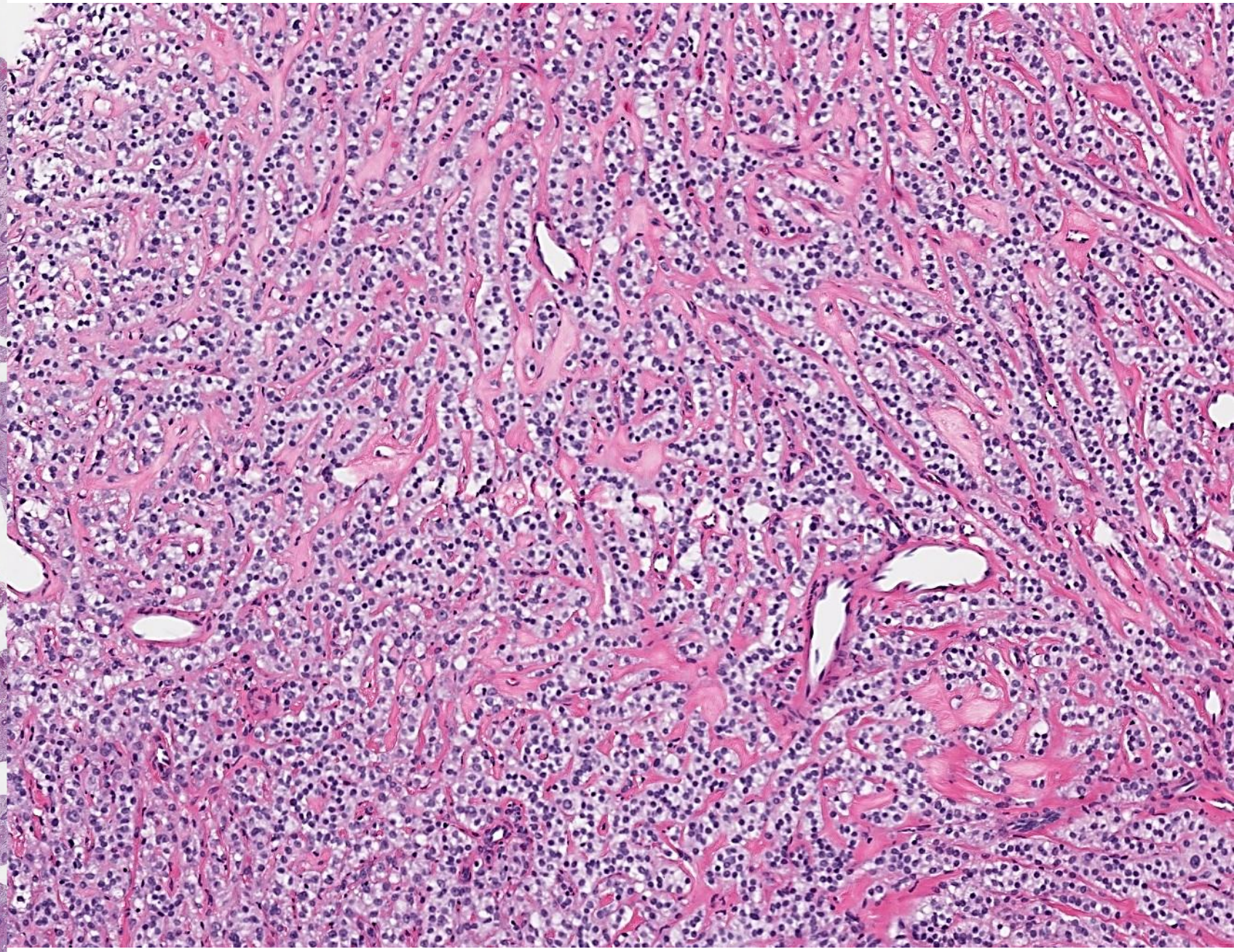
Mod Pathol 2022 Apr;35(4):515-523






HMB45

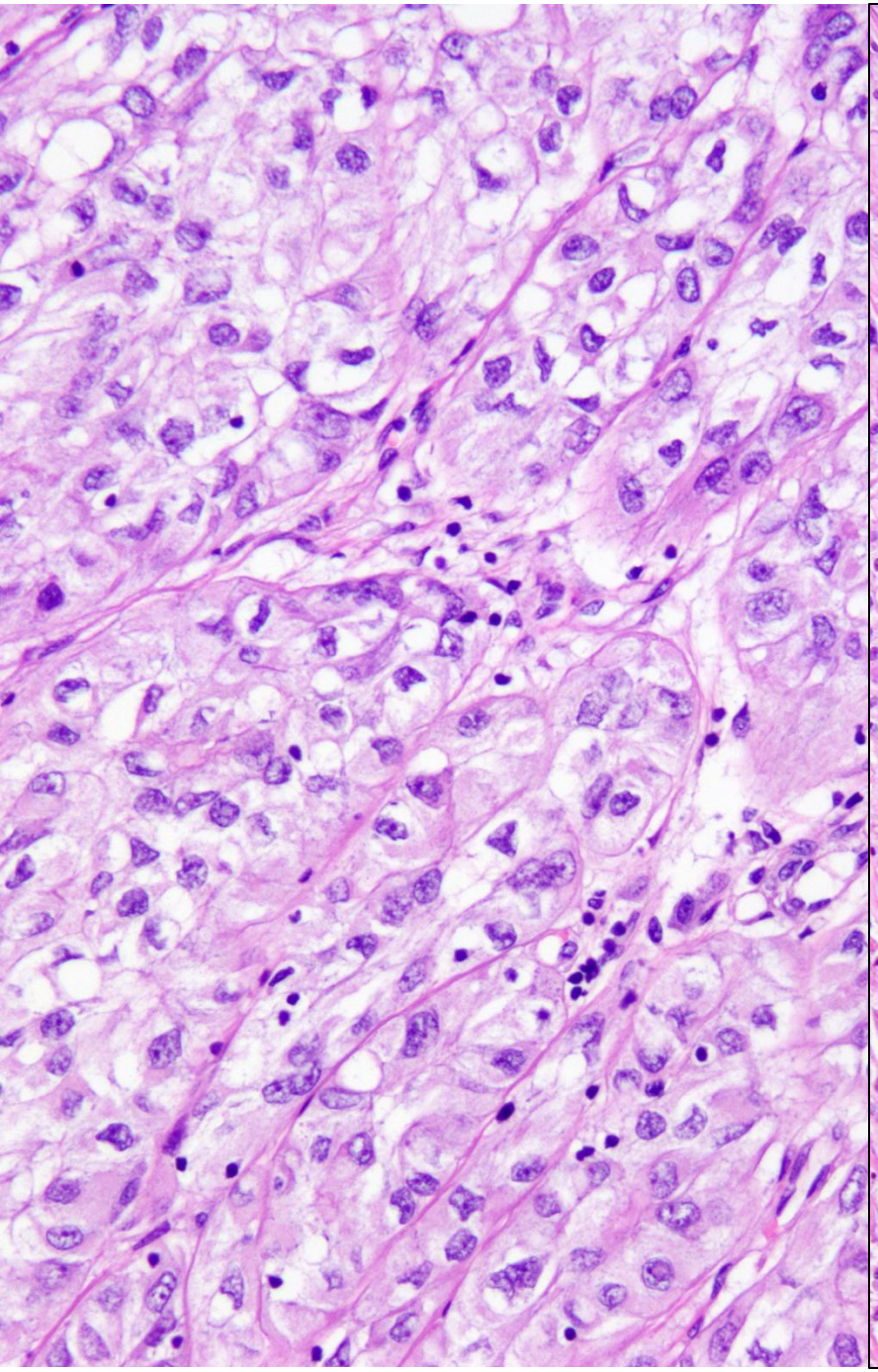
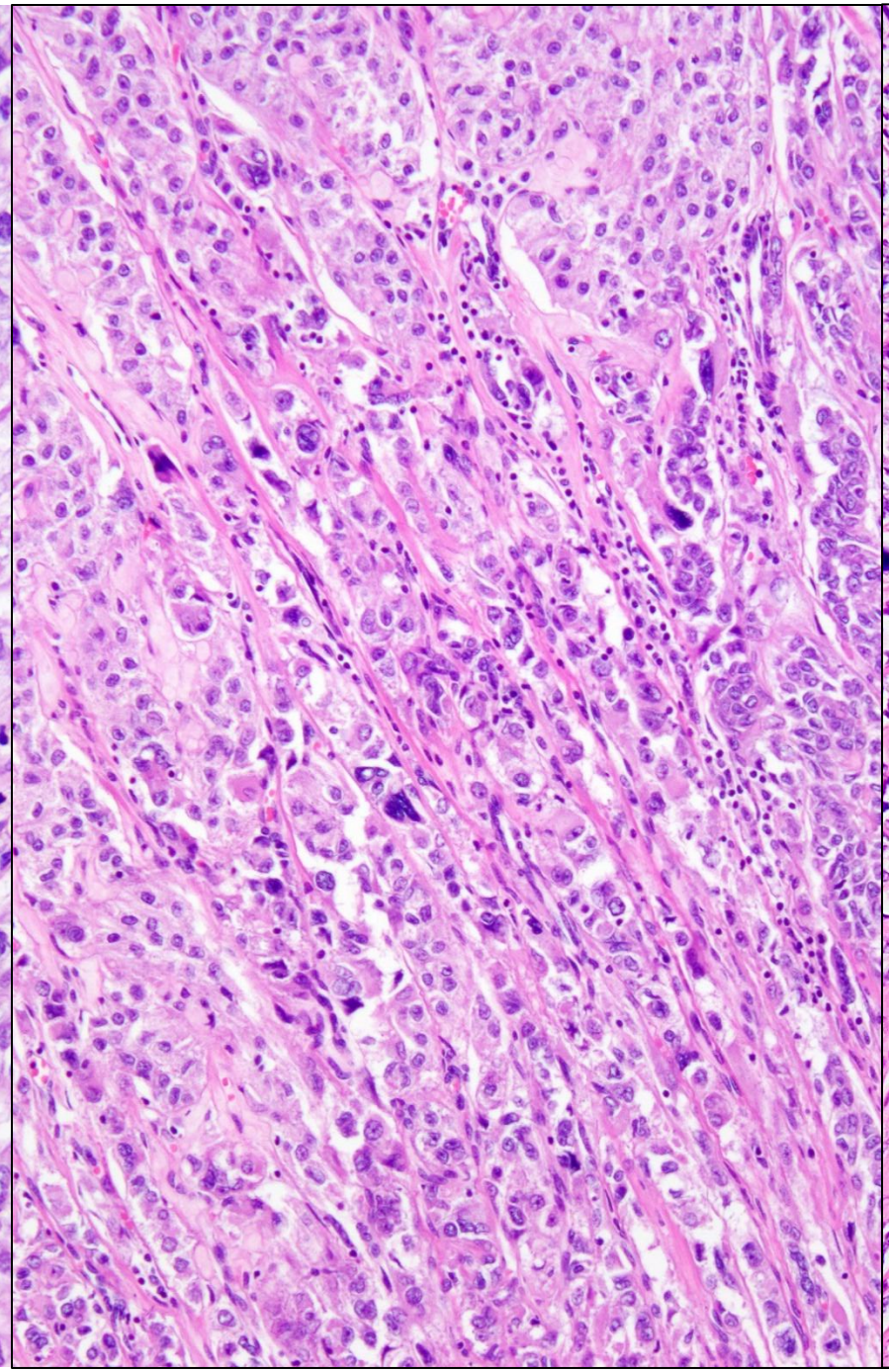
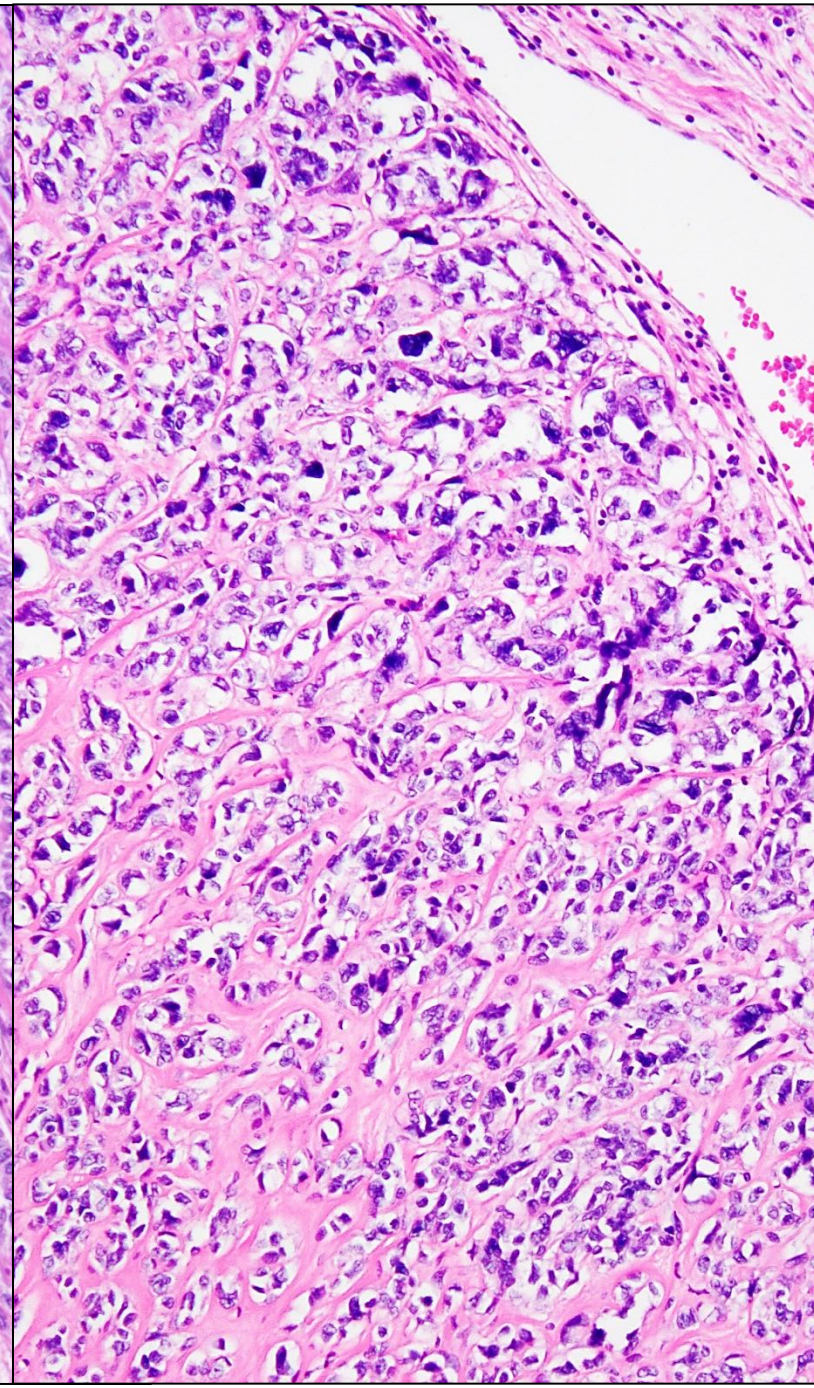


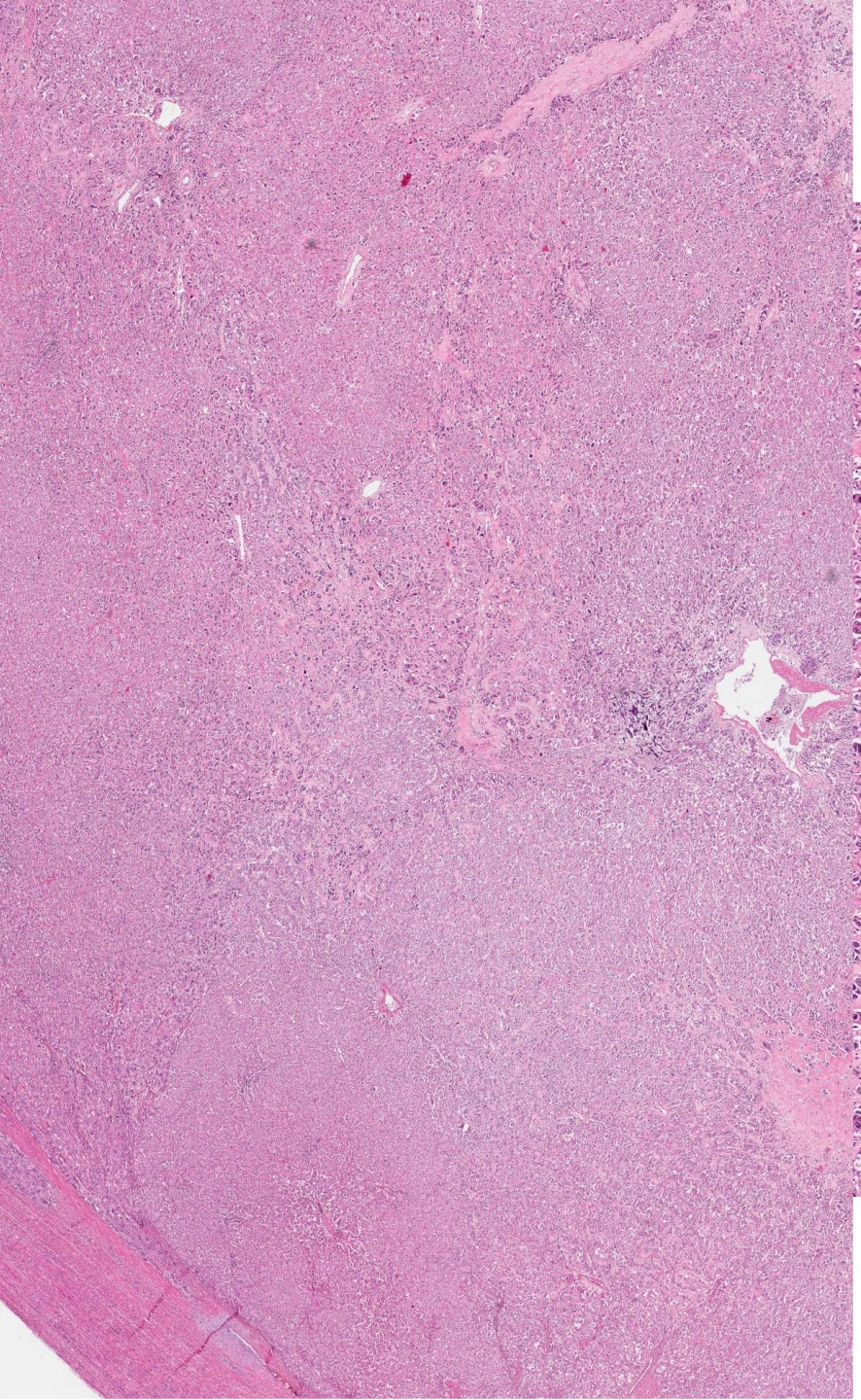


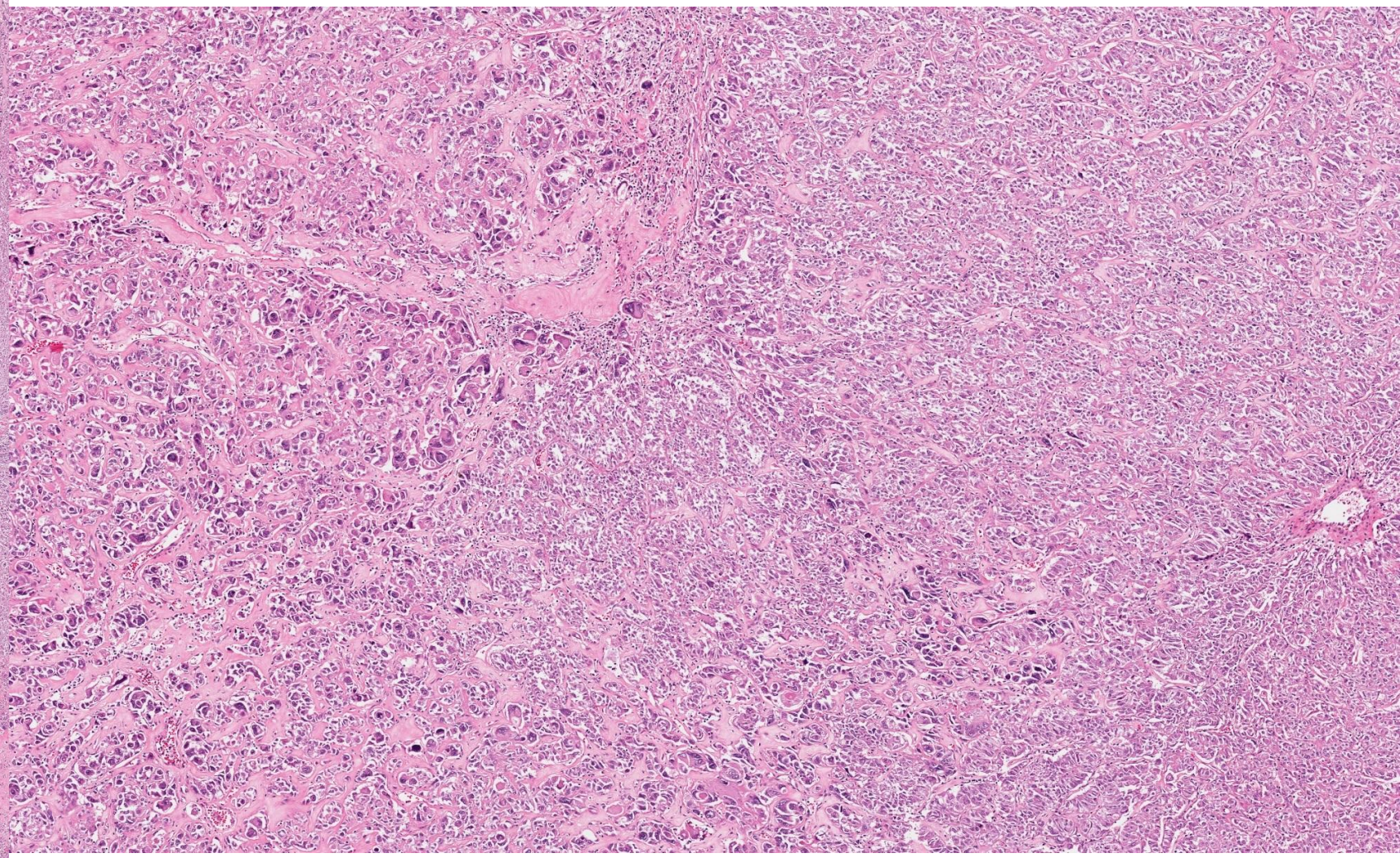
Criteria for malignancy

	Modified (GYN) criteria
Benign	
Uncertain malignant potential	< 3 of the following: ≥ 5 cm; high nuclear grade; >1 mf/50 hpf; necrosis; vascular invasion
Malignant	≥ 3 features

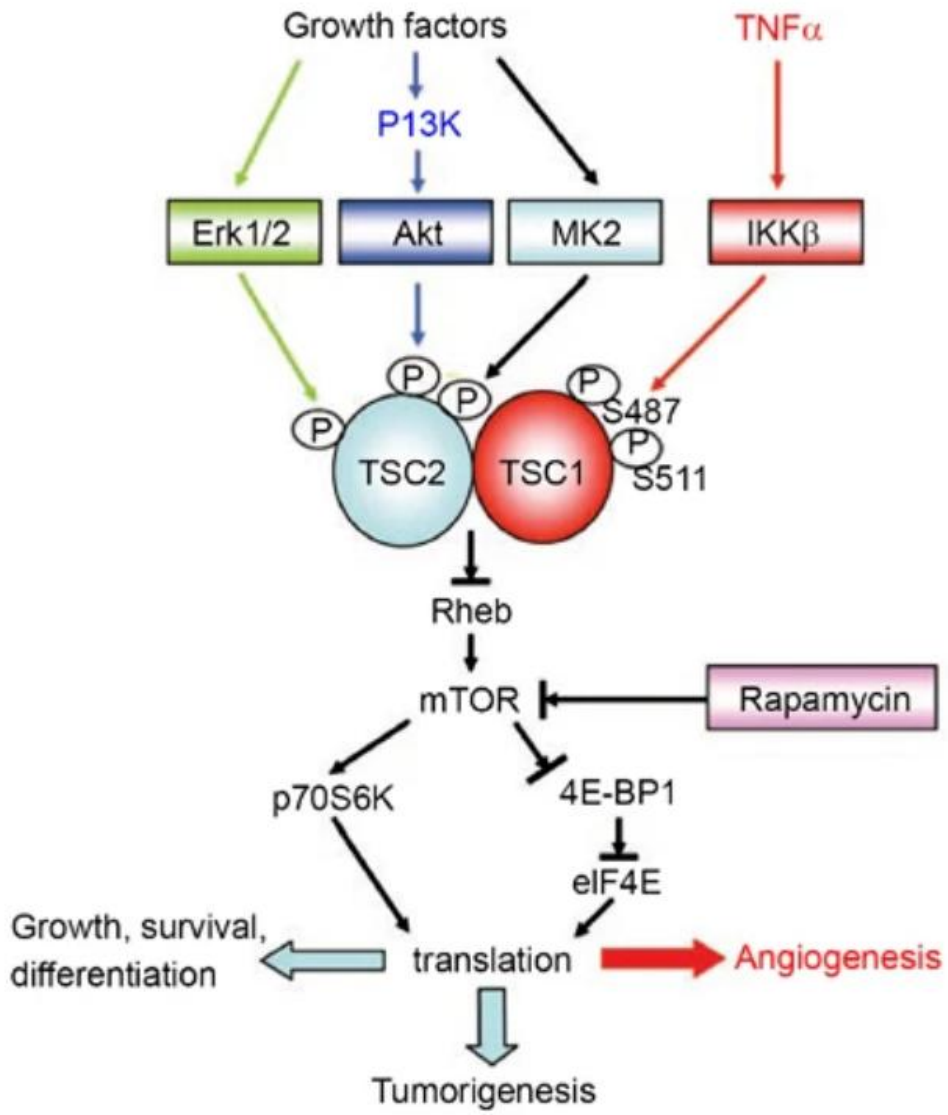
WHO 2020



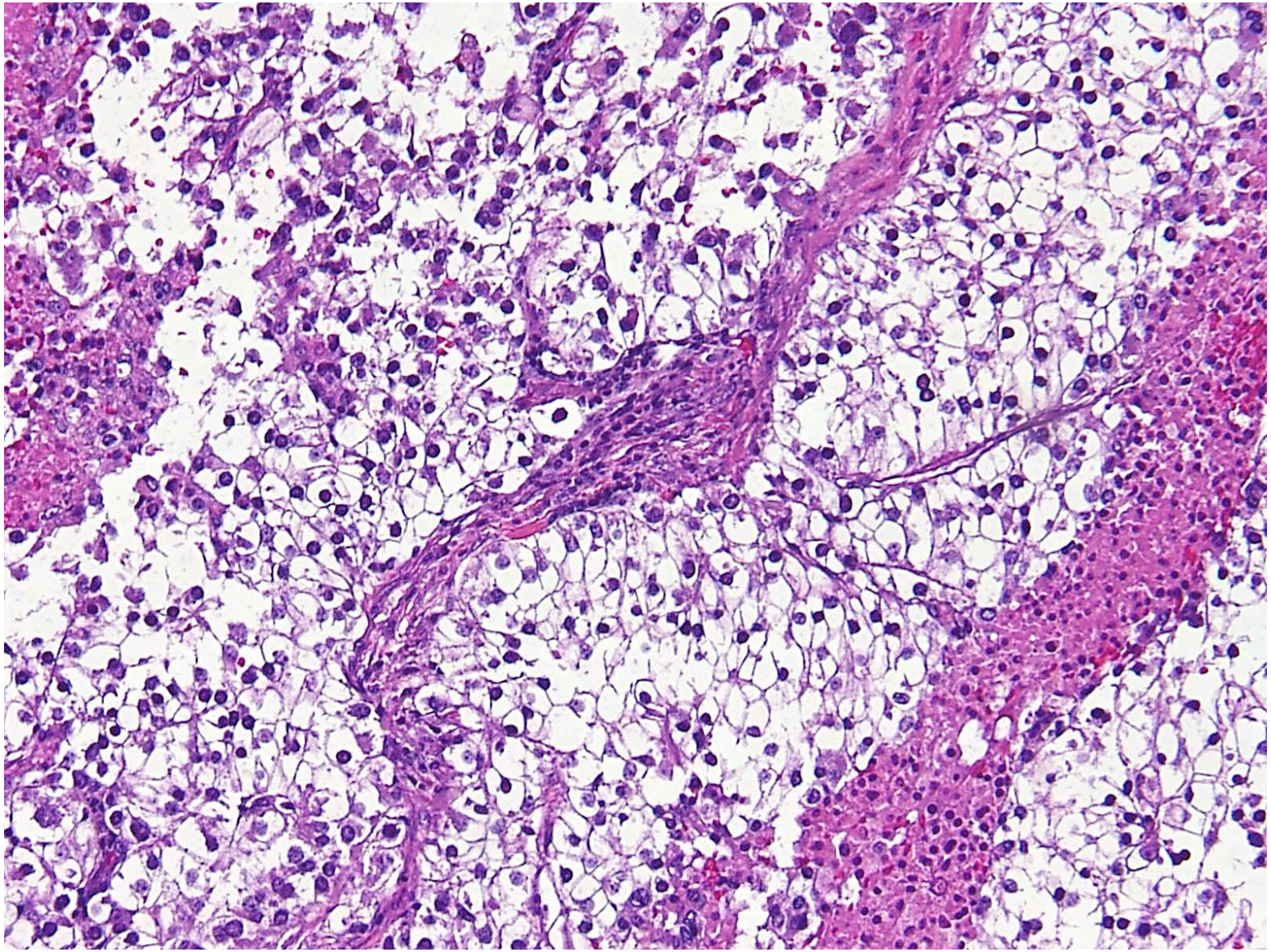


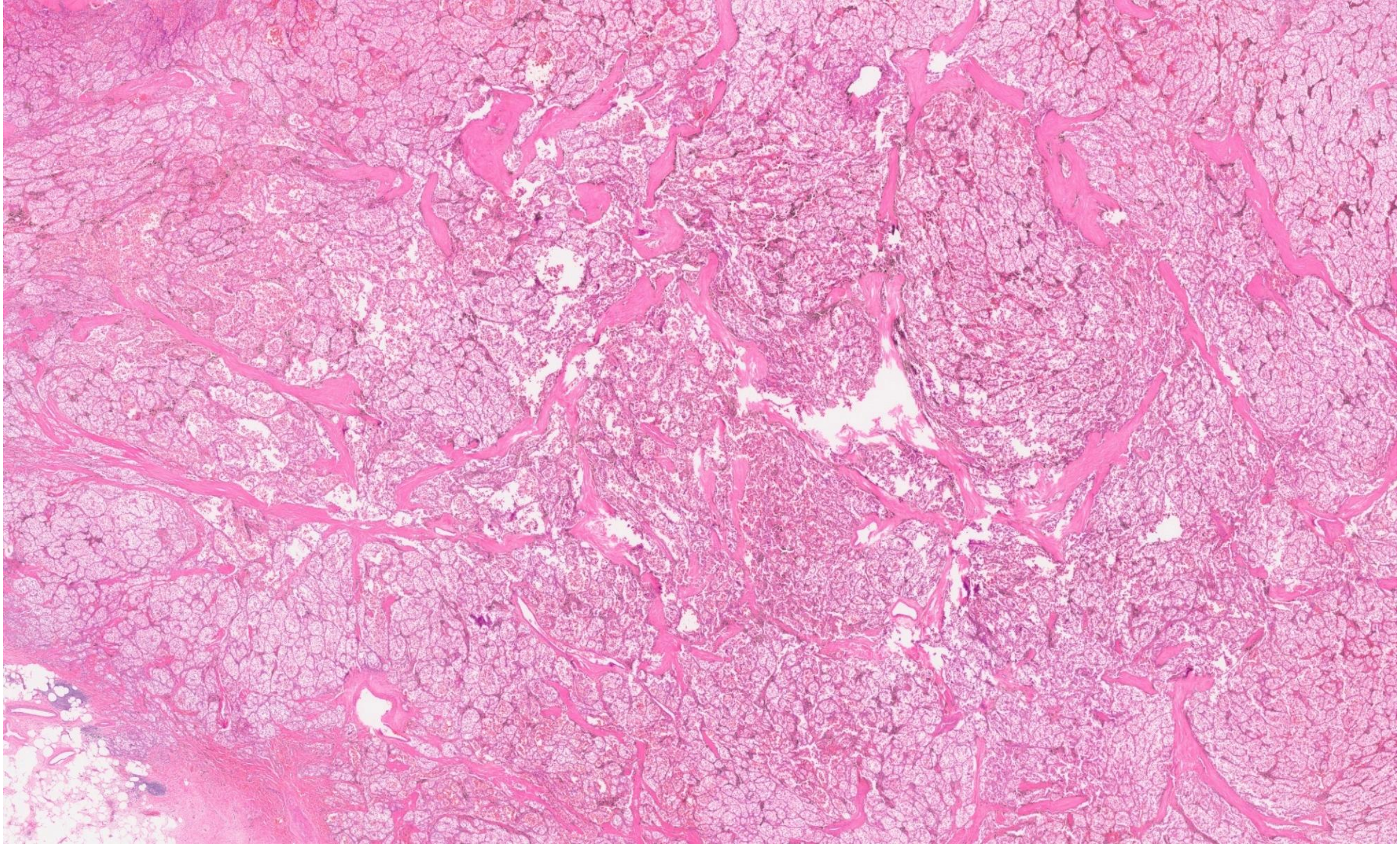
Mammalian target of rapamycin (mTOR)

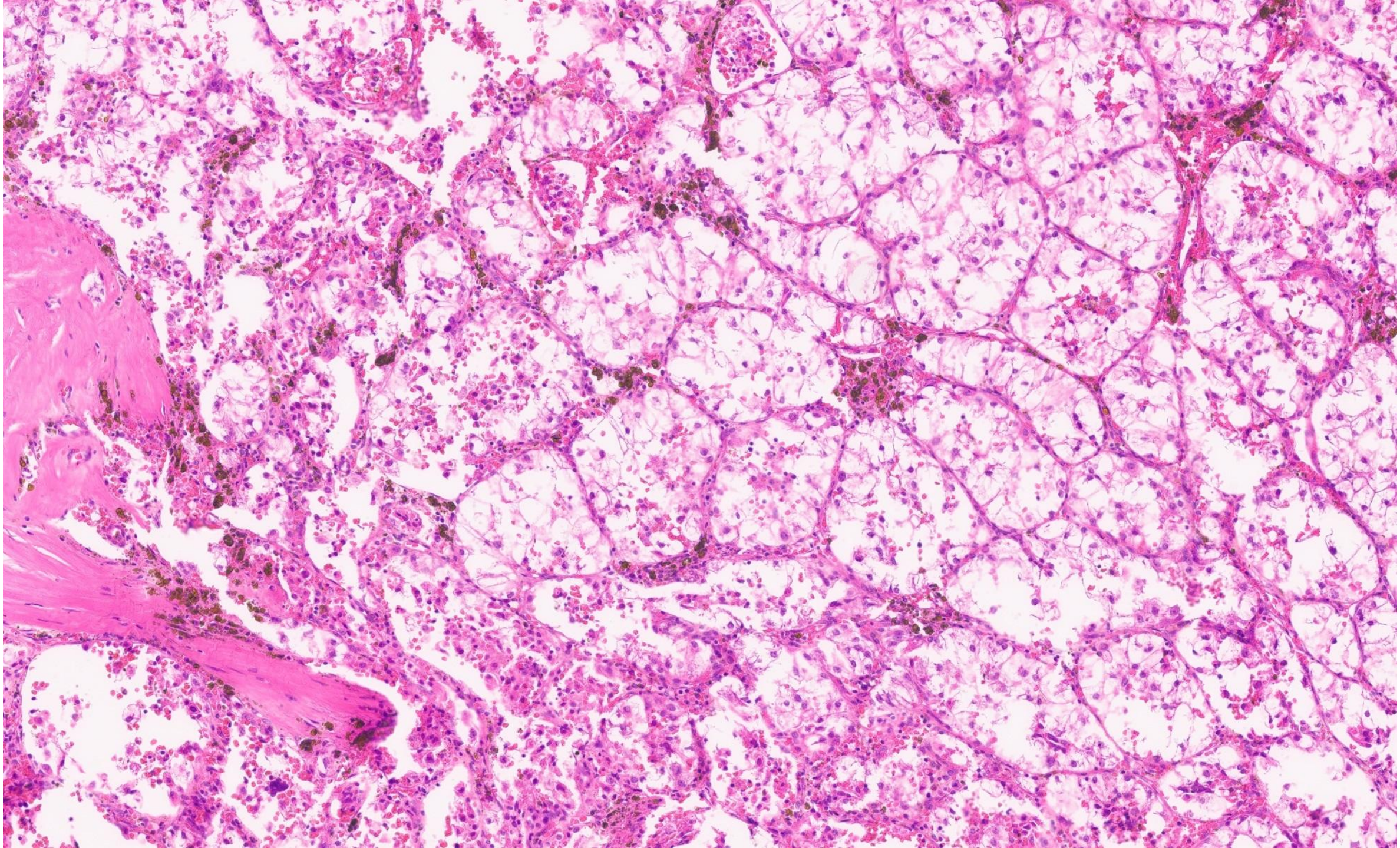


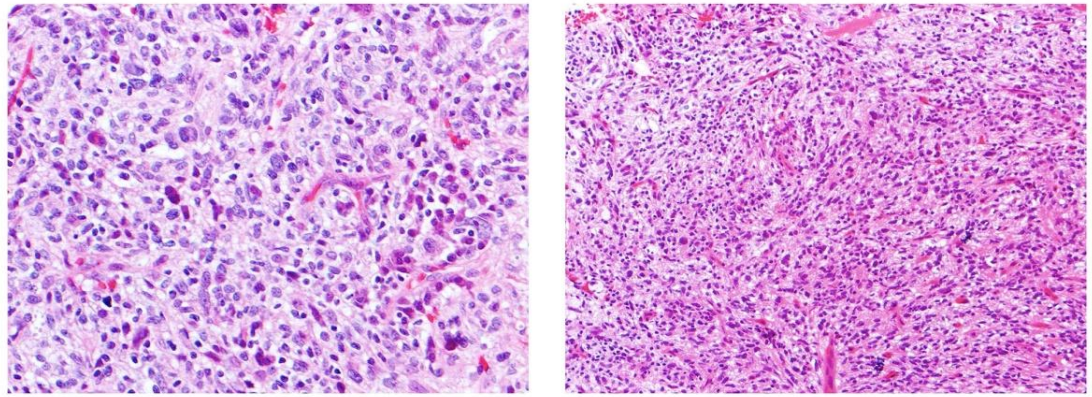
Cell Research (*Cell Res*) ISSN 1748-7838 (online)

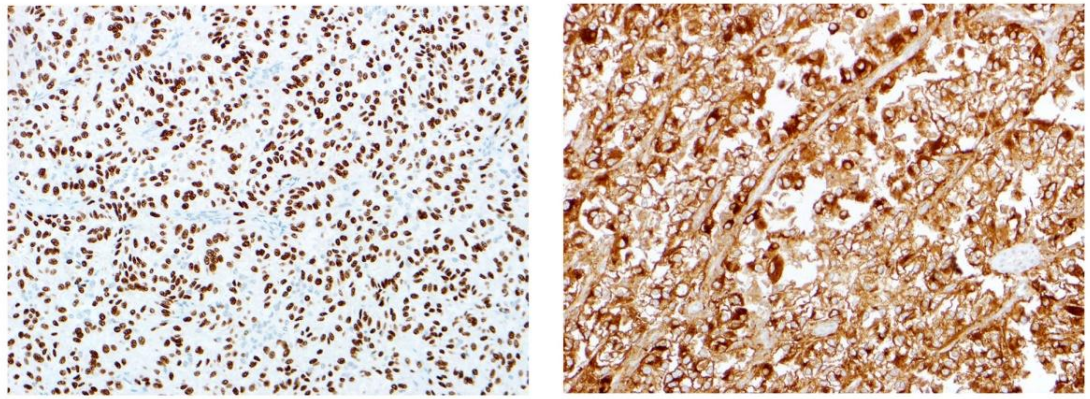
Xp11 PEComa









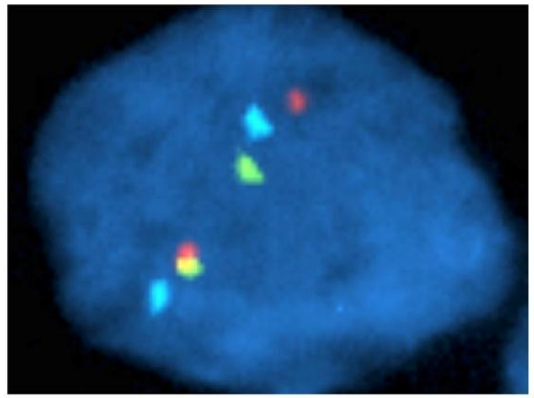


TFE3

HMB45

Desmin

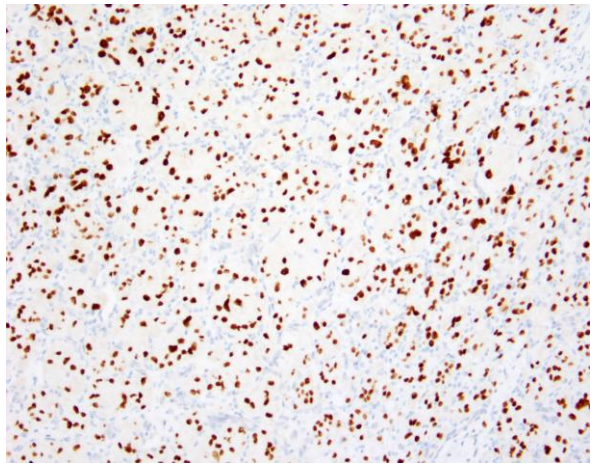
Negative



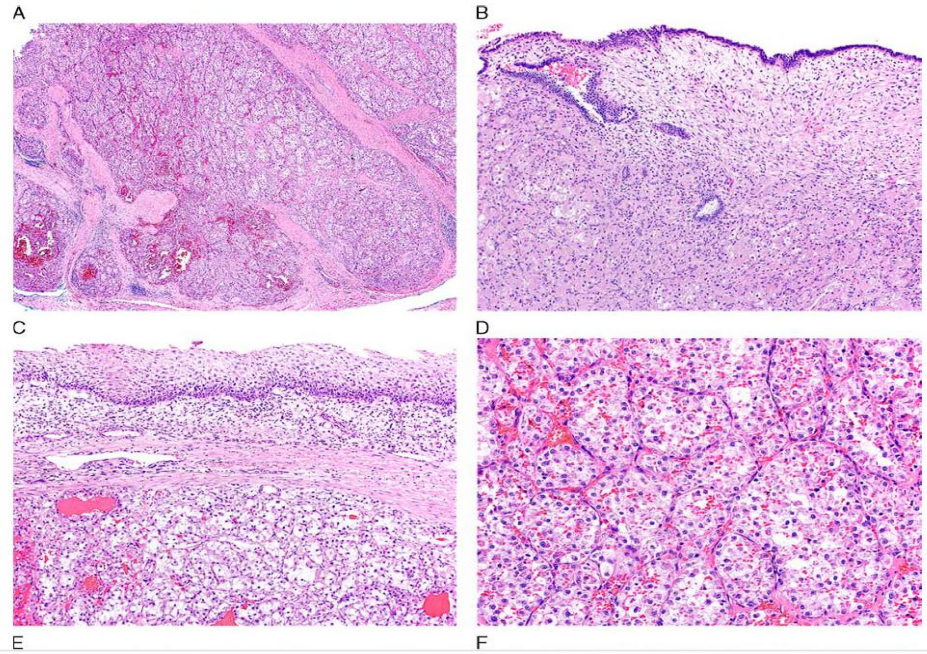
Schoolmeester JK, et al. *Am J Surg Pathol* 2015 Mar;39(3):394-404

Other well-known tumors with *TFE-3* fusions

- Alveolar soft part sarcoma
- Xp11 translocation-associated RCC

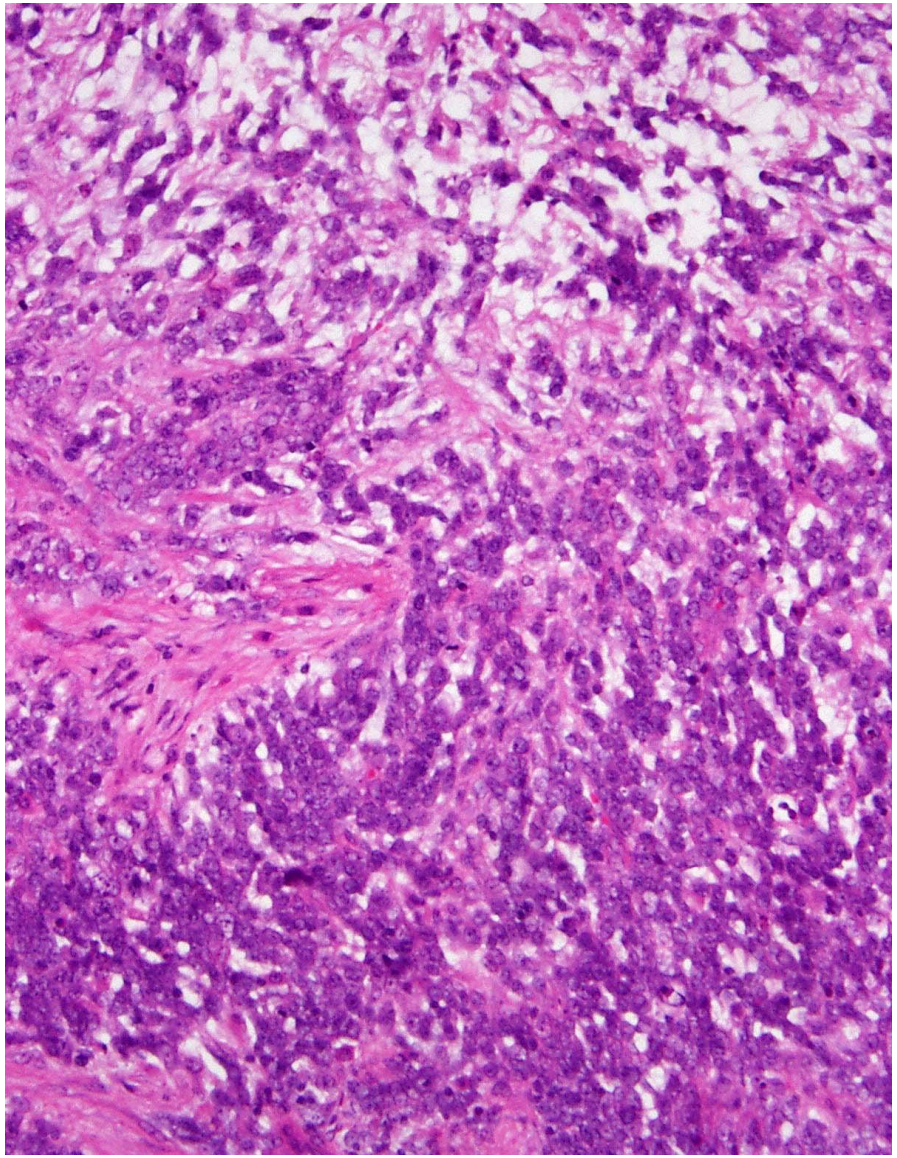


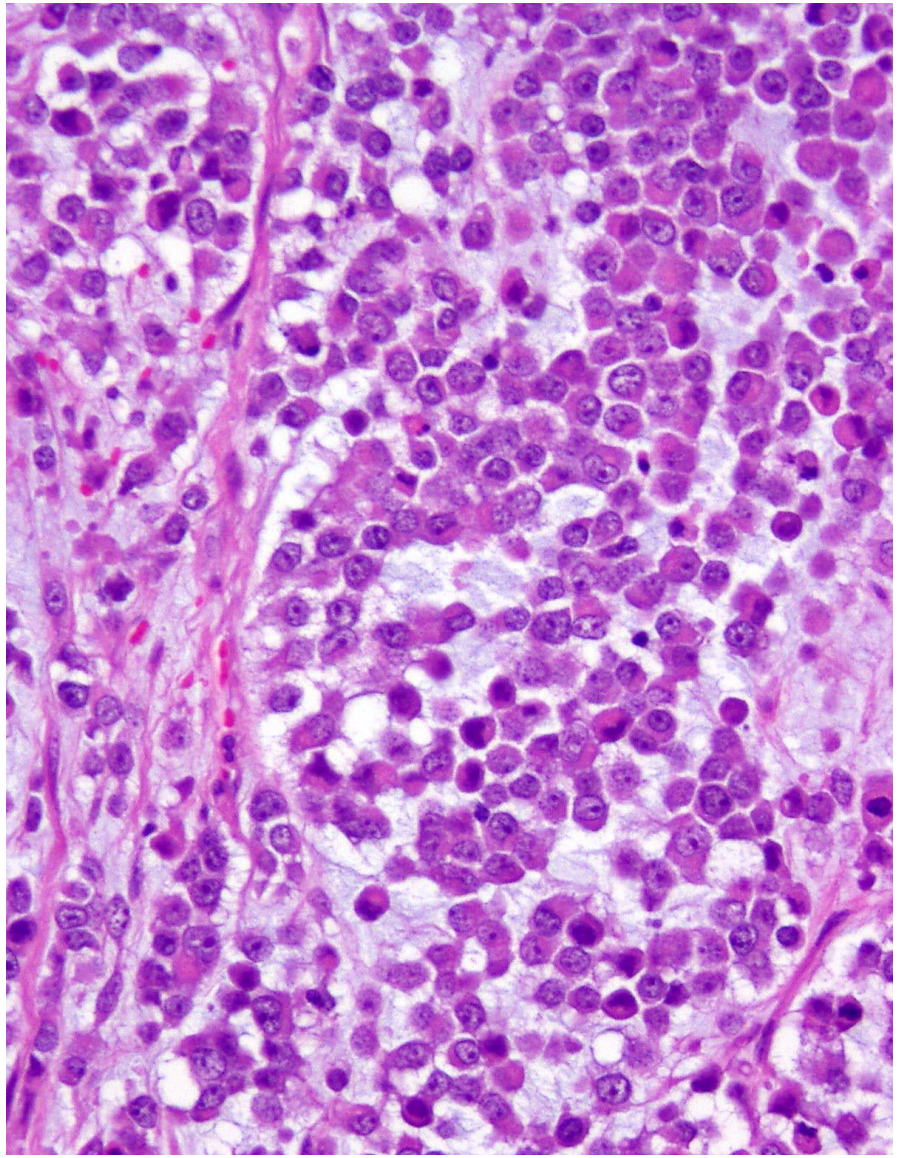
TFE3

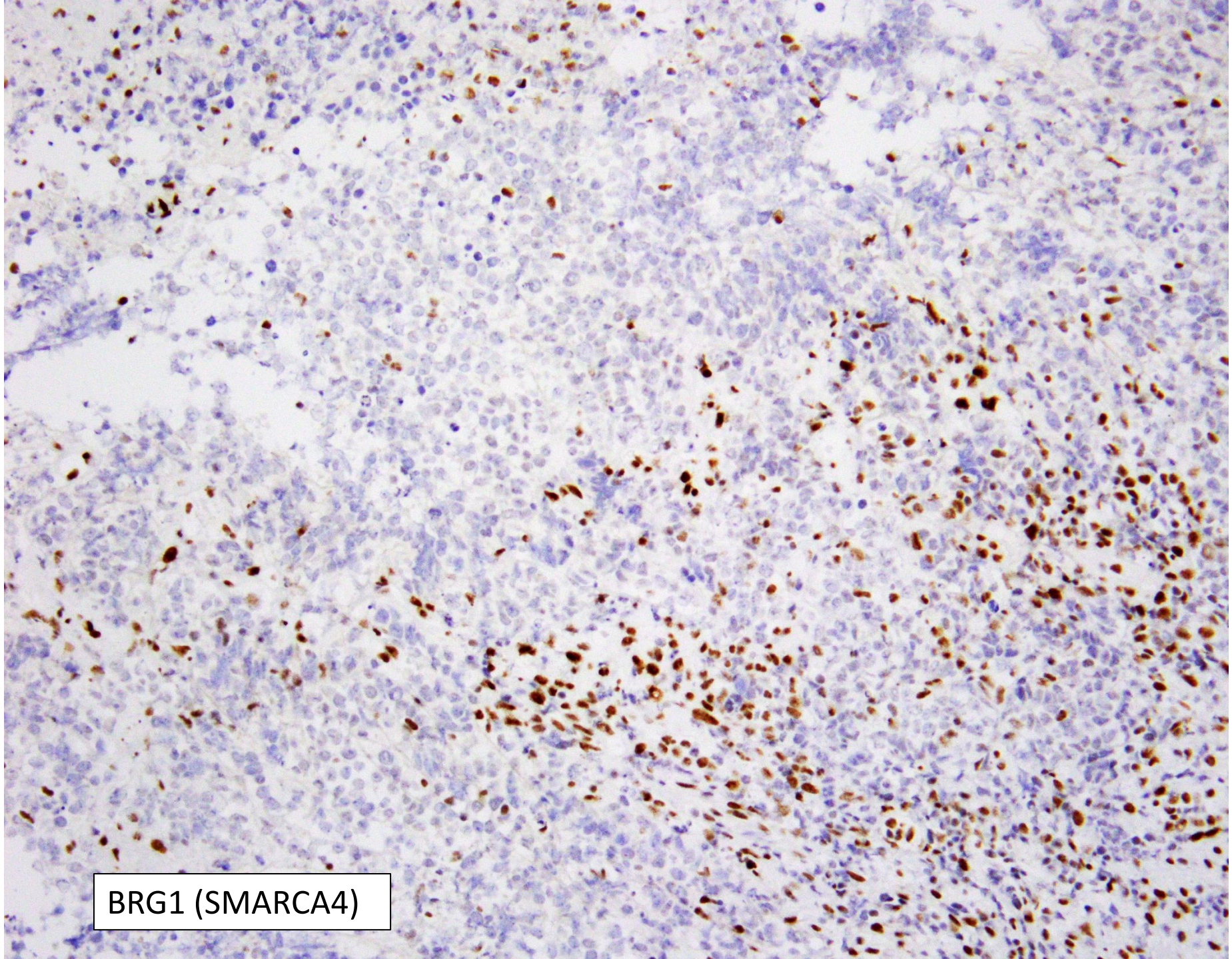


Am J Surg Pathol 2017 May;41(5):622-632

SMARCA4-deficient sarcoma






BRG1 (SMARCA4)

SMARCA4-deficient sarcoma

- *SMARCA4* mutation, somatic or germline; loss of *SMARCA4* (BRG-1) nuclear staining
  - No MSI-H or mutation in *KRAS, PTEN, CTNNB1, PIK3CA*
- Median age: 33yrs
- May resemble
  - Adenosarcoma
  - Undifferentiated endometrial carcinoma
- Survival: ~100% DOD at a median time of < 1 year

SMARCA4 and SMARCB1-deficient tumors

Table 3 Comparison of clinicopathologic features of SWI/SNF complex-deficient tumors

From: SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma

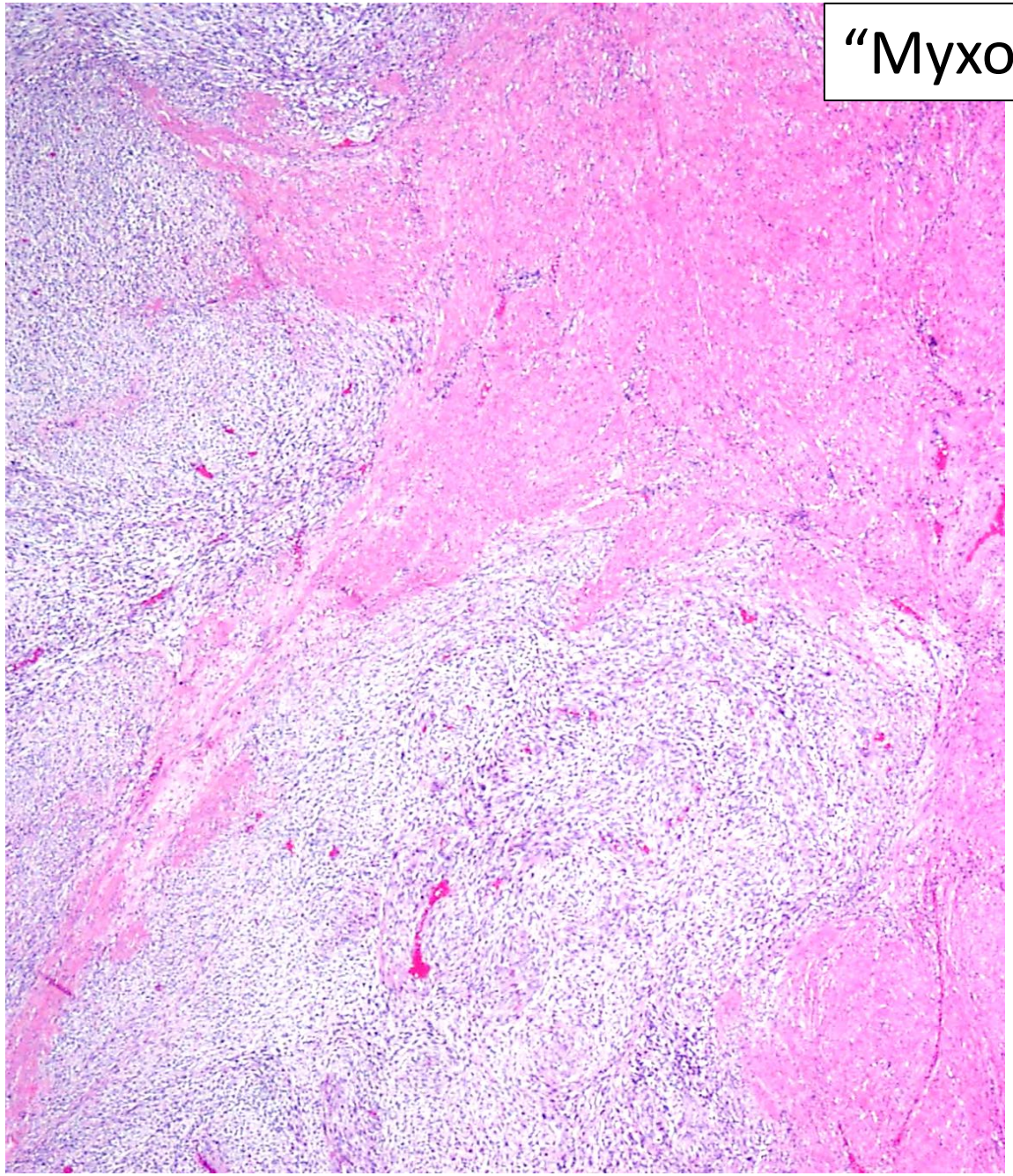
	Age	Location	Main molecular abnormality	Germline association	Prognosis	Non-germline risk factors
Malignant rhabdoid tumor [31, 32]	Usually infants <1 year, rarely adolescents and adults	Kidney, liver, head and neck	*SMARCB1* in 95%, rare cases with *SMARCA4*	*SMARCB1* deletion in 15–30%	Poor; 31% of patients survive 1 year	Low birthweight, preterm birth
Small cell carcinoma of the ovary, hypercalcemic type [1,2,3,4, 33,34,35]	Mean 24 years (range 14 months–71 years)	Ovary	*SMARCA4*	*SMARCA4* mutation in 8%-50%	Poor; almost all patients greater than stage 1A die from disease; 10–20% overall survival	None
Atypical teratoid/rhabdoid tumor [32, 36,37,38]	Usually under 3 years, rarely adolescents and adults	CNS	Usually *SMARCB1*, rarely *SMARCA4*	*SMARCB1* mutation in 35%	Poor; median survival 8 months	Low birthweight, increased maternal age, higher parental socioeconomic status
Proximal-type epithelioid sarcoma [39]	Median 40 years (range 13–80 years)	Inguinal region, thigh, vulva	*SMARCB1*	None	Local recurrences common; median survival 6 years	History of trauma in some cases
SMARCA4-deficient thoracic sarcoma [7, 40]	Median 39 years (27–82 years)	Thorax	*SMARCA4* mutations and LOH; *TP53* mutations	None	Poor; median survival 7 months	Heavy smoking
Undifferentiated endometrial carcinoma [14, 20]	Mean 59 years (range 40–69 years)	Endometrium	*KRAS, PTEN, CTNNB1,* MMR proteins, *ARID1A SMARCA4, SMARCB1*	None	Stage dependent; survival of months to years	Unknown
SMARCA4-deficient uterine sarcoma	Mean 36 years (range 25–58 years)	Uterus	*SMARCA4*	Unknown	Poor; average survival ~6 months	Unknown, possibly radiation therapy

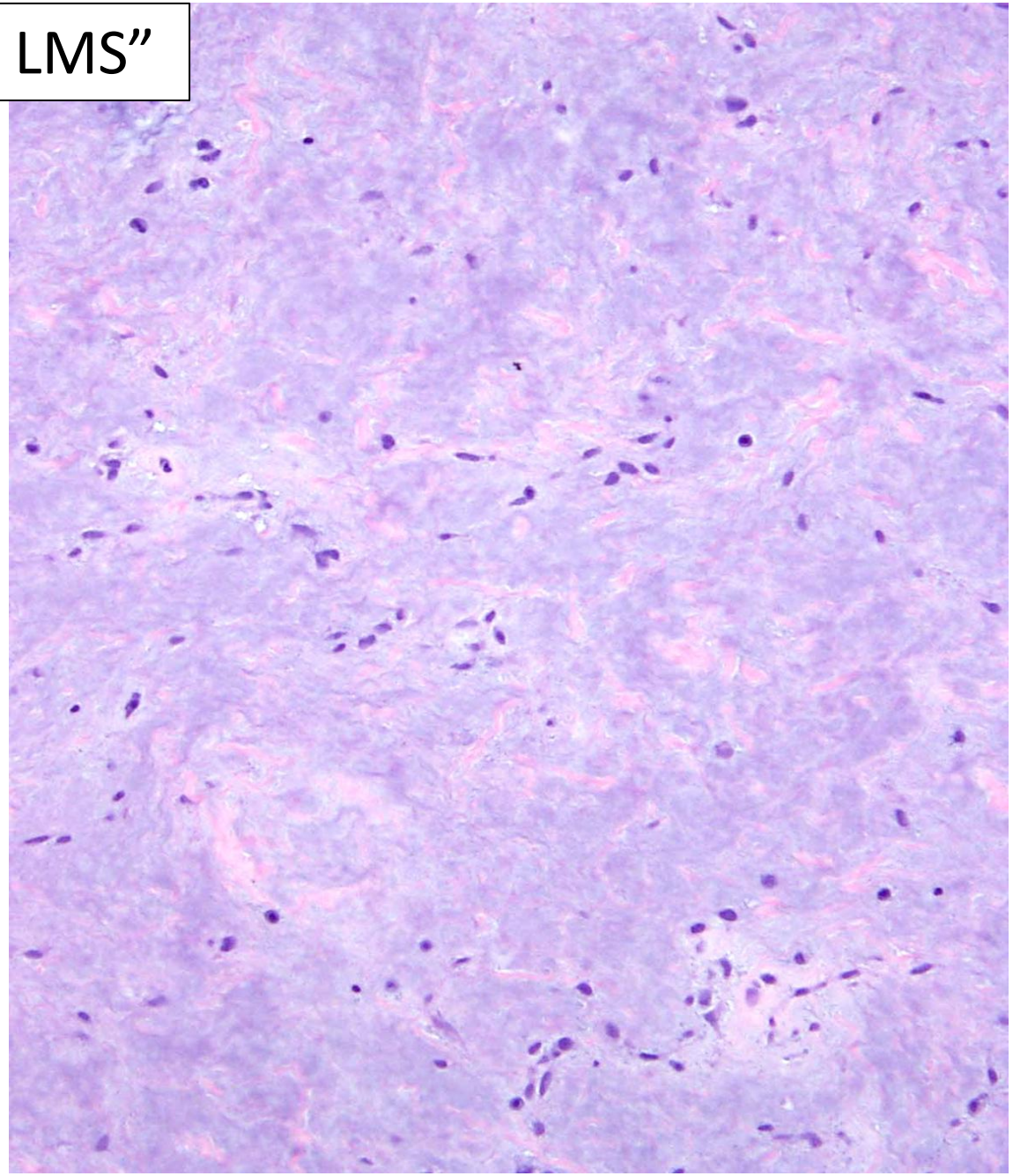
Immunohistochemistry and differential diagnosis of epithelioid tumors

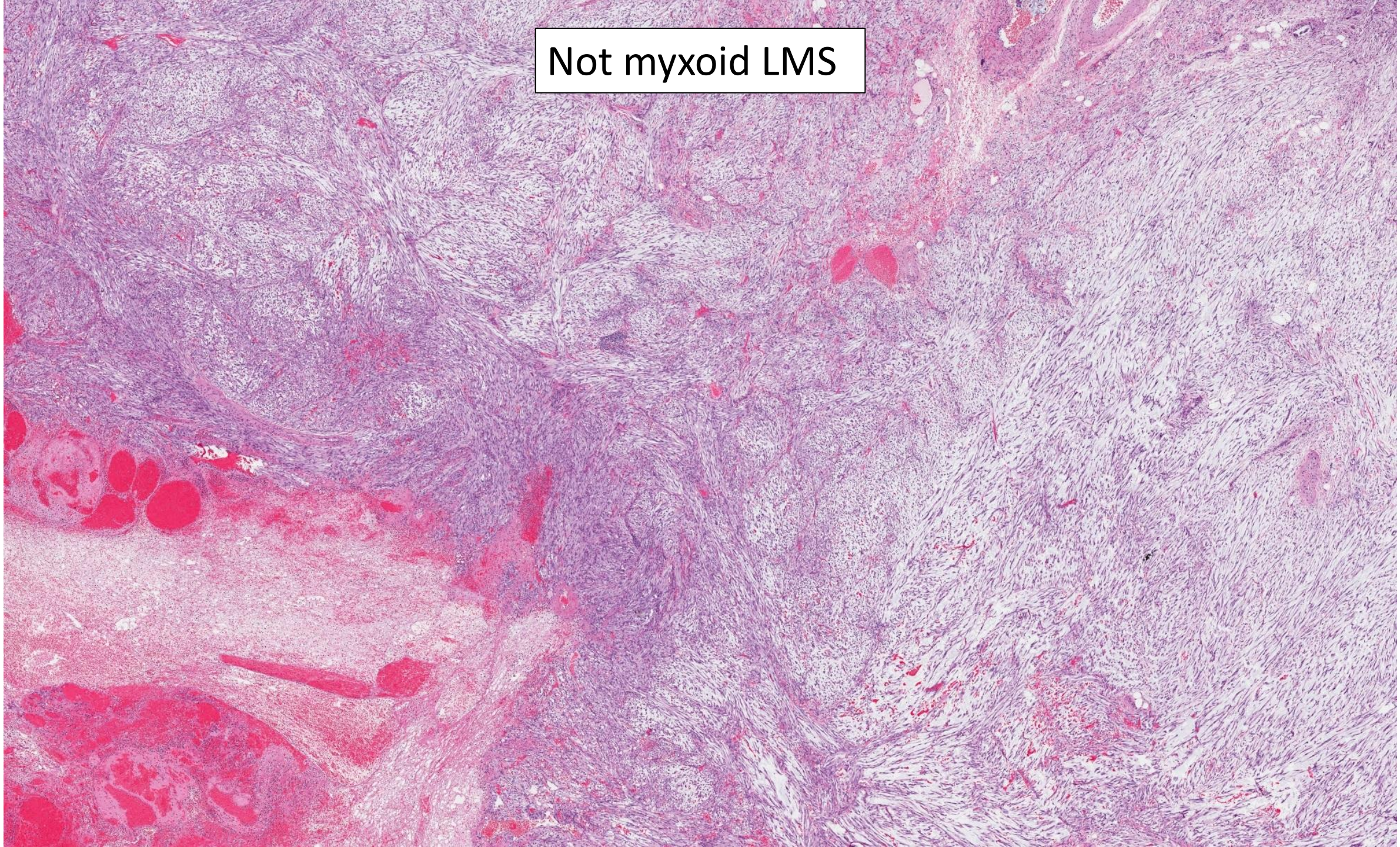
	Des	HMB45	TFE3	CD10	Inh	CyclD1 BCOR/TRK	Ker	BRG1
LMS-epi	++	-/+	-	-/+	-	-	-/+	-
PEComa (*TSC*)	+/-	+	-	-/+	-	-	-	NA
PEComa (*TFE3*)	-	++	++	NA	-	-	-	NA
ESS-YWHAE (HG)	-	-	-	-	-	++	-	NA
UTROSCT	+/-	-	-	+	++	-	+/-	NA
Carcinoma-undiff	-	-	-	-	-	-/+	+/-	+/- Loss
SMARCA4-def sarcoma	-	-	-	-	-	?	-	++ Loss

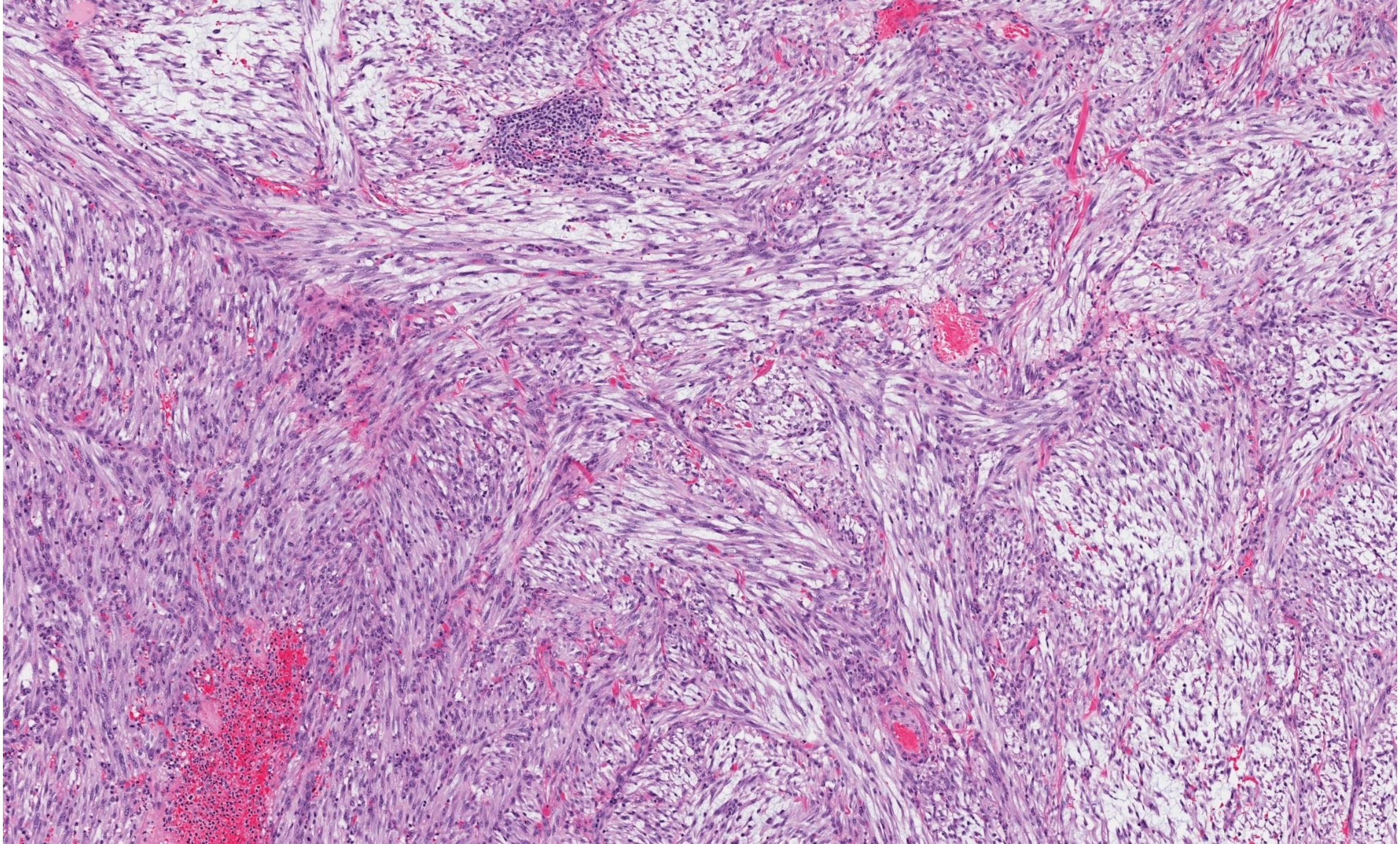
Spindled tumors

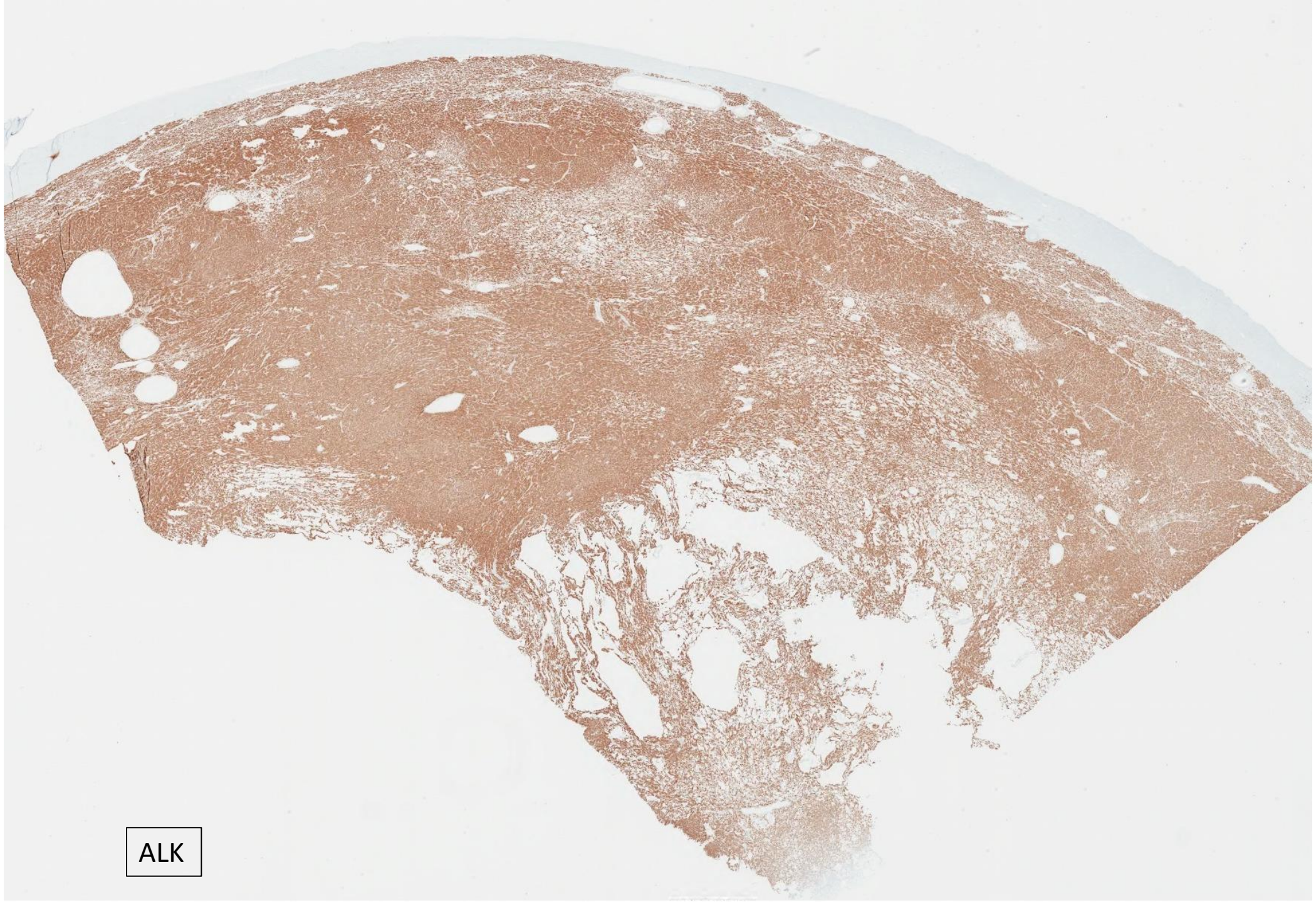
“Myxoid LMS”






Not myxoid LMS




ALK

Inflammatory myofibroblastic tumor (IMT)

- Mimic of hydropic leiomyoma and myxoid leiomyosarcoma
- >95% have *ALK* rearrangements and cytoplasmic ALK by IHC
- Should confirm diagnosis with ALK IHC and/or FISH

Inflammatory myofibroblastic tumor (IMT)

- Histologic patterns
  - Fasciitis-like with lymphoplasmacytic inflammation
  - Leiomyoma-like (risk features guide decision to perform ALK IHC)*
  - Hylanized
- Malignant tumors
  - High-risk IMT
  - Epithelioid inflammatory myofibroblastic sarcoma (EIMS)

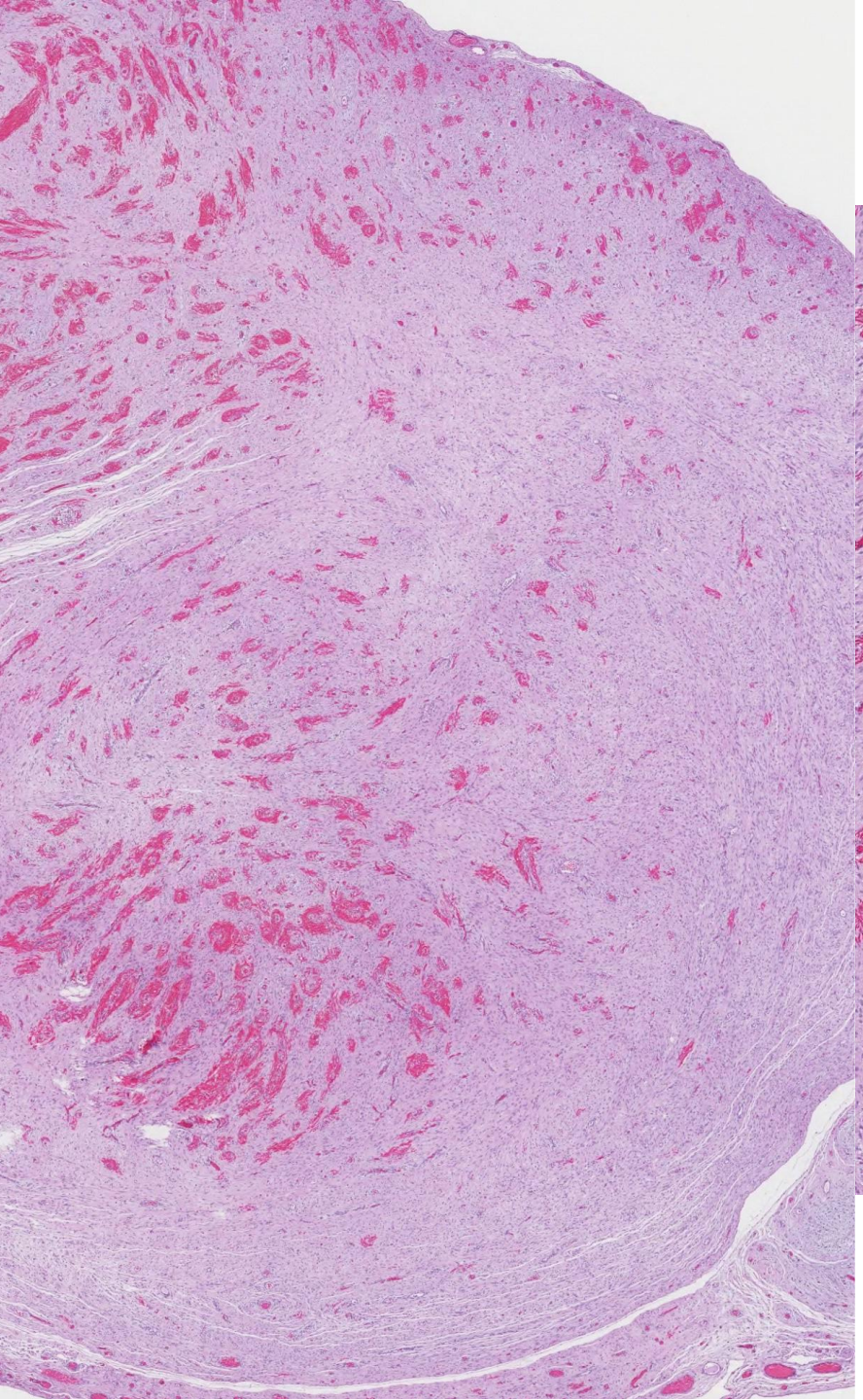
Risk stratification for IMT and EIMS definition

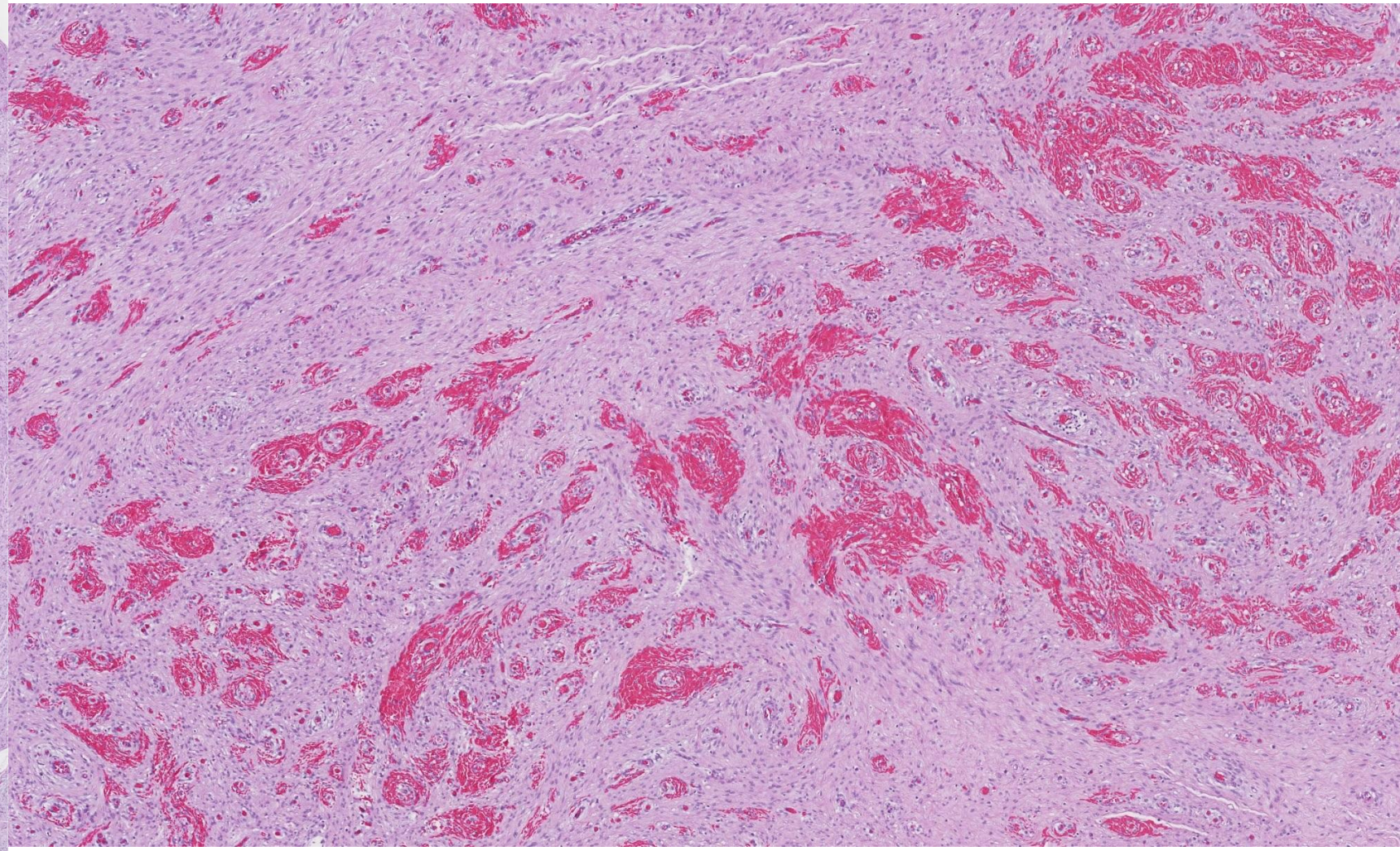
- IMT risk stratification: 1 point each for the following:
  - Age > 45 years
  - Size ≥ 50 mm
  - ≥ 4 MF/ 2.5 mm2
  - Infiltrative borders

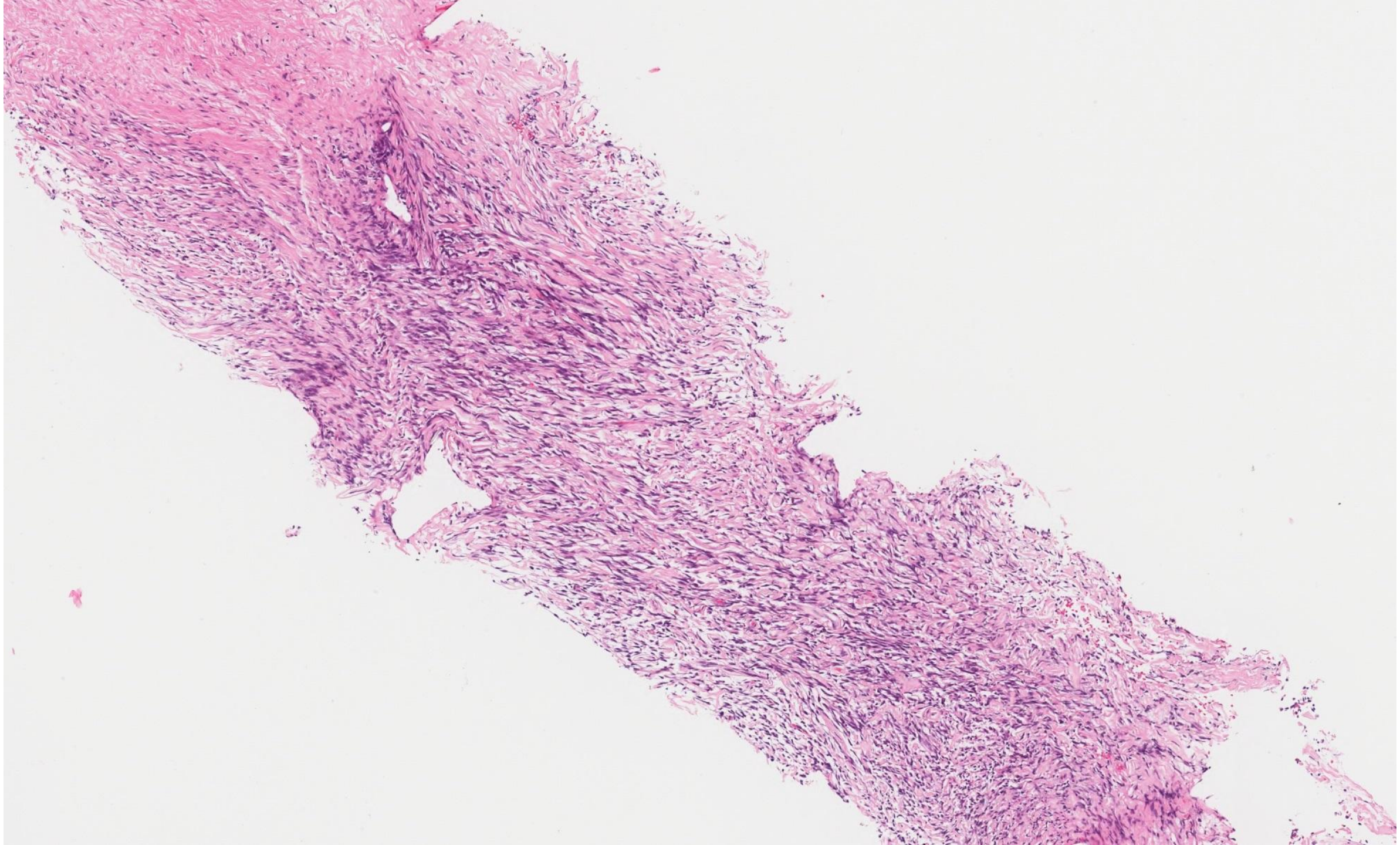
0 Points	**1-2 Points***	**3-4 Points**
Low-Risk	Intermediate-Risk	High-Risk

- EIMS
  - Sheets of epithelioid cells with large nucleoli; amphophilic to eosinophilic cytoplasm
  - Prominent myxoid stroma and inflammation (often neutrophilic); infrequent mits
  - ALK may be cytoplasmic or nuclear membrane

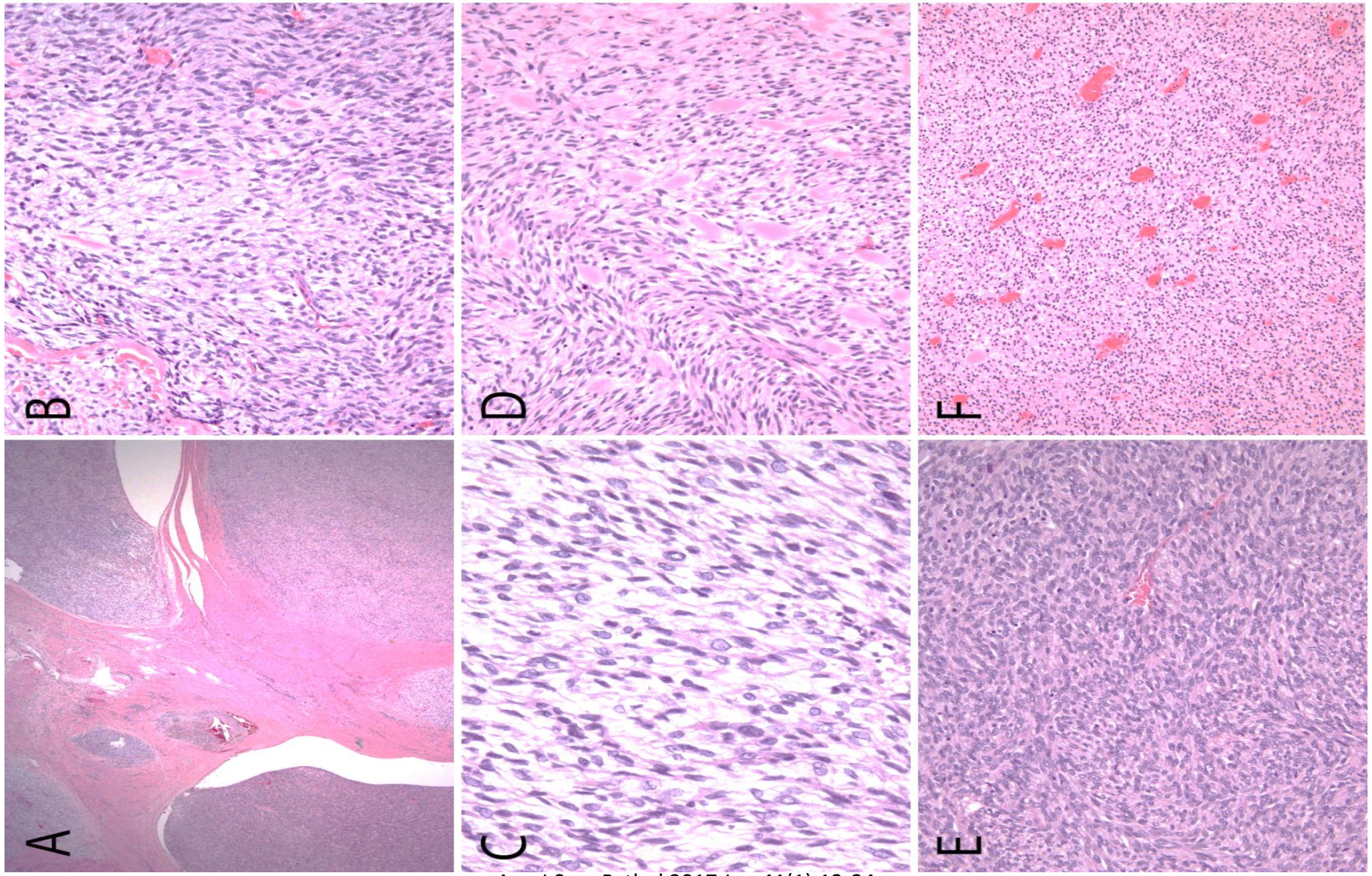
Not myxoid LMS







BCOR translocated high-grade ESS



Am J Surg Pathol 2017 Jan;41(1):12-24
Mod Pathol. 2018 Apr;31(4):674-684

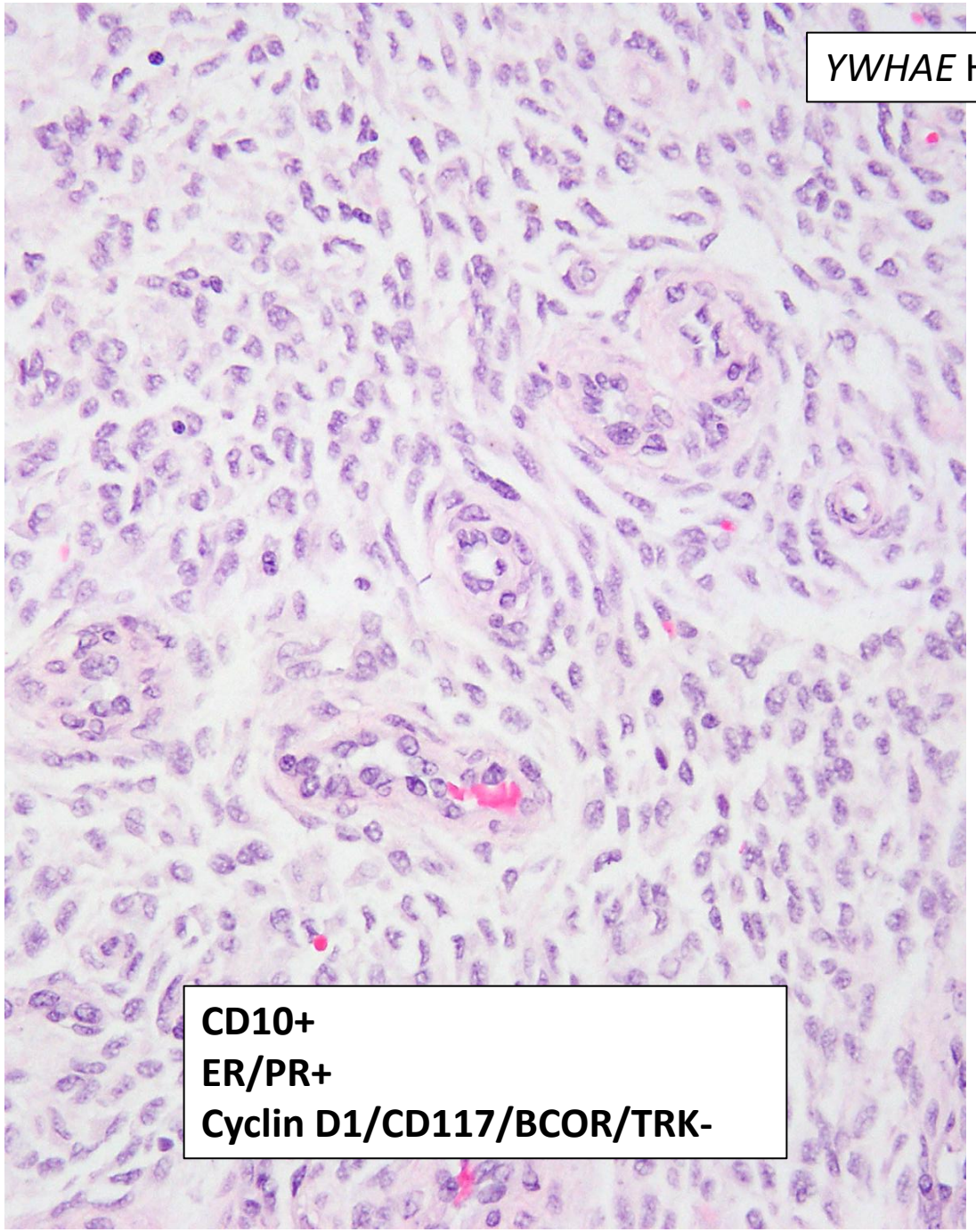
High-grade endometrial stromal sarcoma

- *BCOR* rearrangement or internal tandem duplication (HG-ESS)
- *YWHAE* rearrangement (HG-ESS)
- *JAZF1* or *PHF1* rearrangement (transformation of LG to HG-ESS)

BCOR translocated high-grade ESS

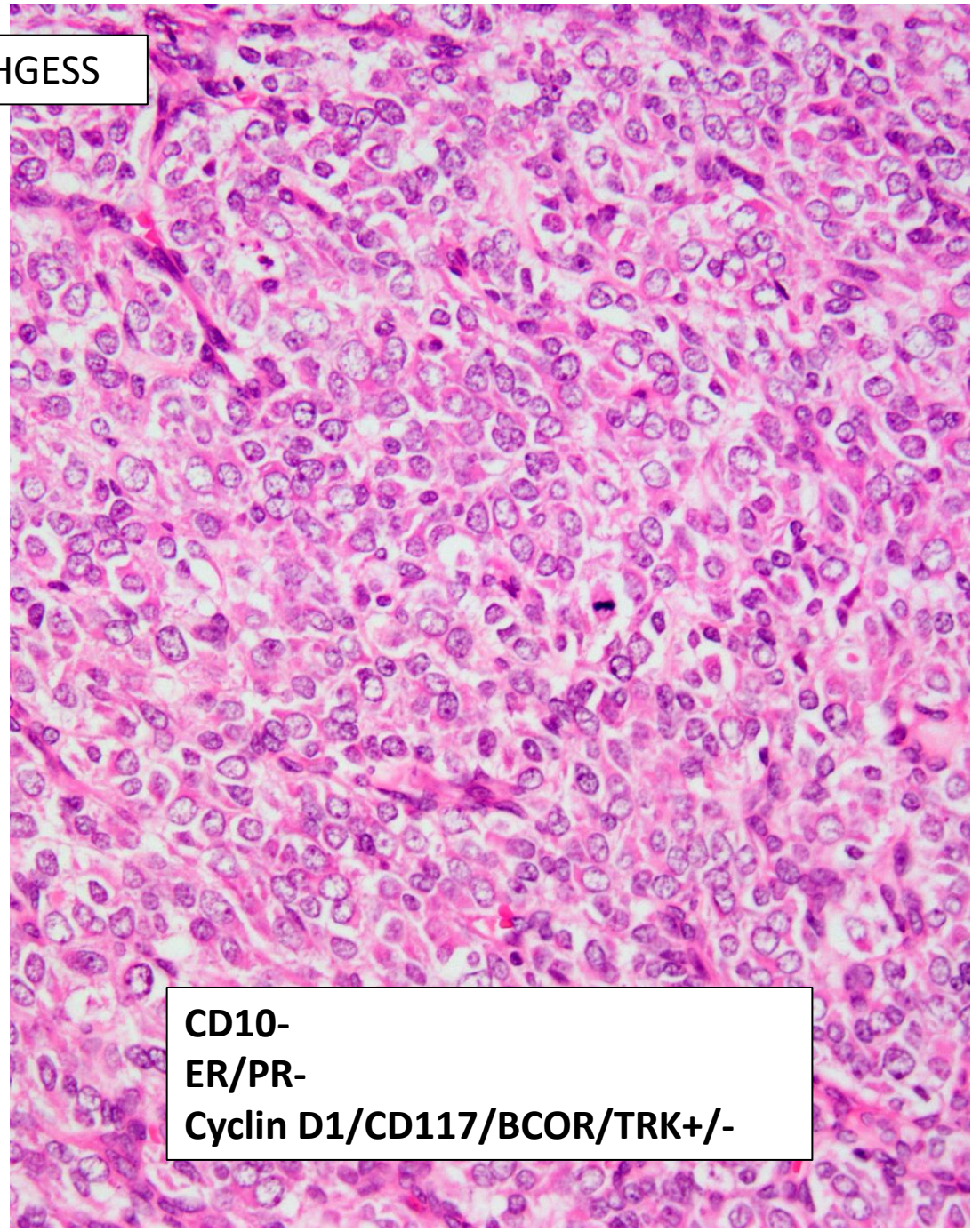
- High-grade ESS (mimicking other myxoid tumors)
- t(X;22) involving *ZC3H7B and BCOR*
- Median age: 54 yrs
- Stage/Recurrence: Low or high/Not uncommon
- Survival: Pace of disease may be slower than pleomorphic undifferentiated uterine sarcoma

Am J Surg Pathol 2017 Jan;41(1):12-24
Mod Pathol. 2018 Apr;31(4):674-684



YWHAE HGESS

CD10+
ER/PR+
Cyclin D1/CD117/BCOR/TRK-

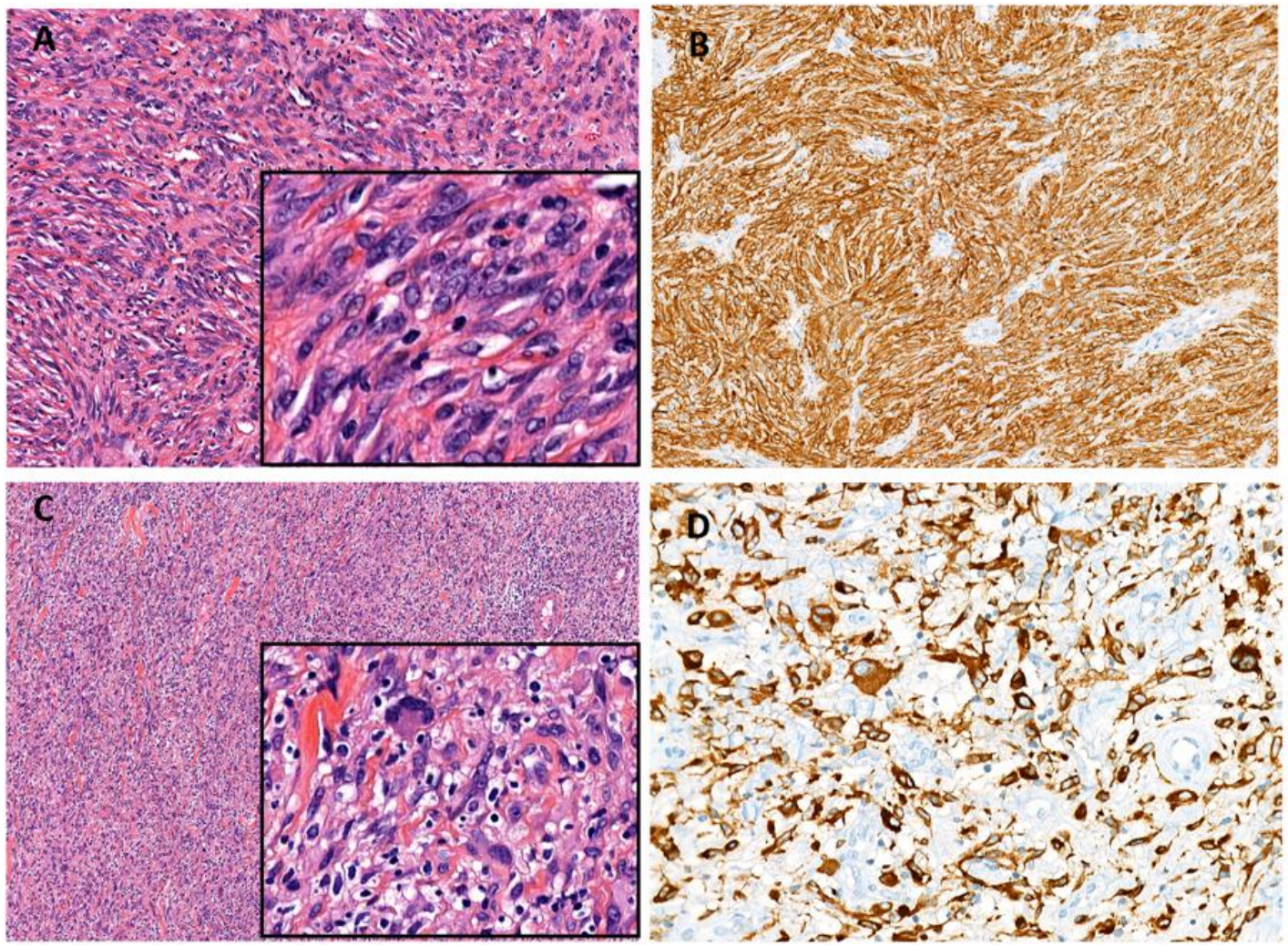


CD10-
ER/PR-
Cyclin D1/CD117/BCOR/TRK+/-

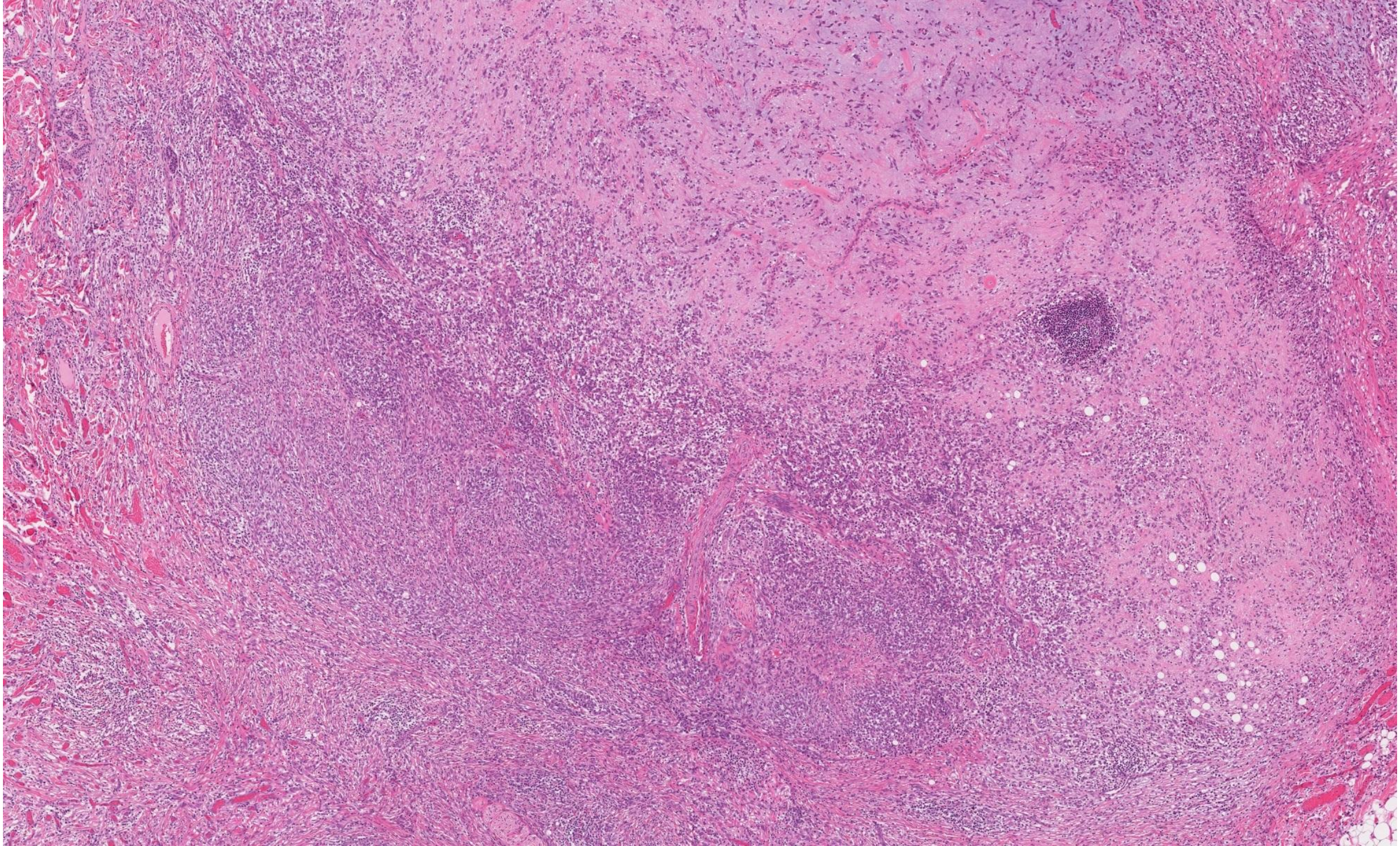
Immunohistochemistry and differential diagnosis of myxoid tumors

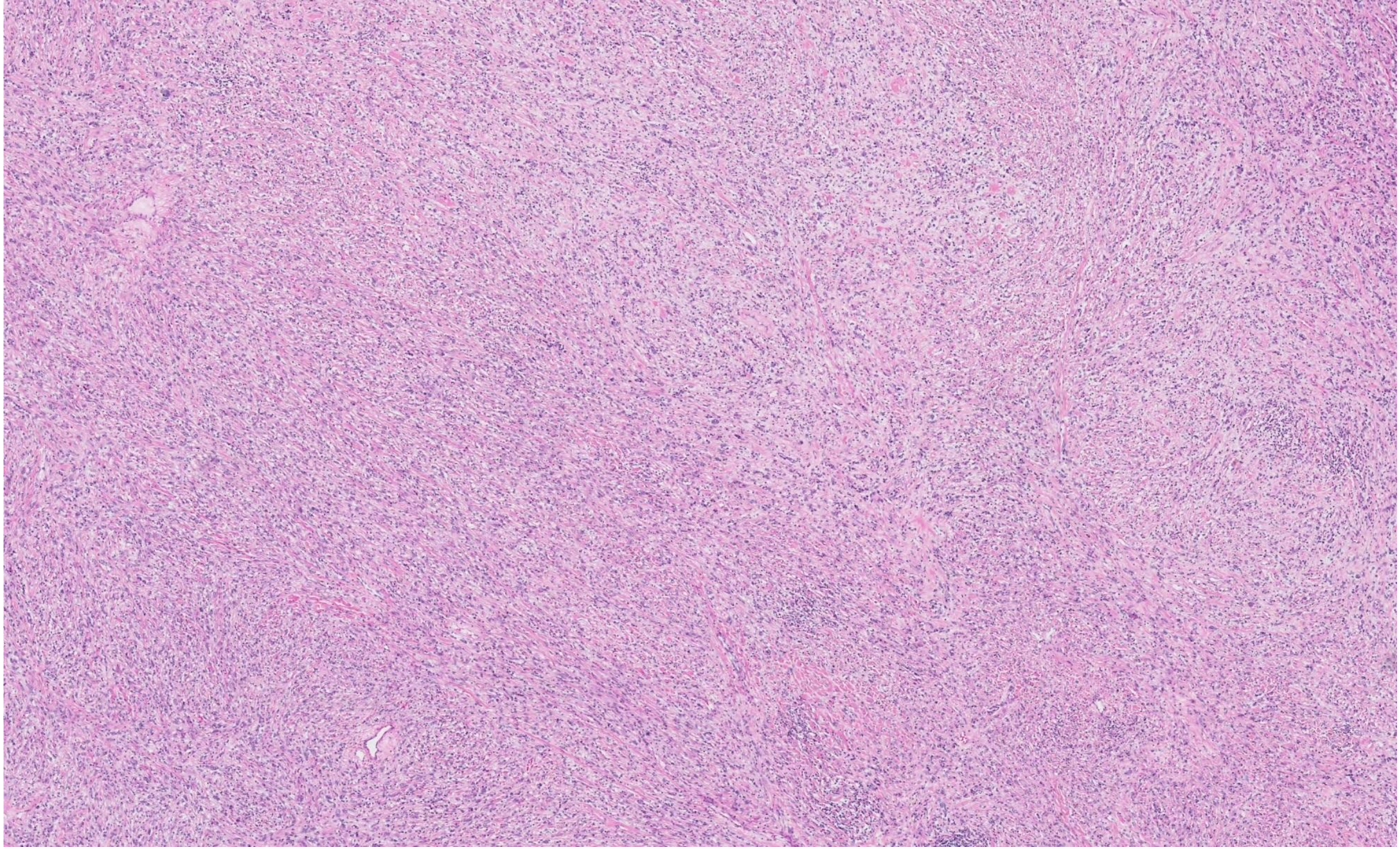
	Des	SMA	ALK	CD10	Cycl D1	BCOR	TRK	Ker
LMS-myx	+	+	-	-	-	-	-	-
IMT	+/-	+/-	++	+/-	-	-	-	-/+
LGESS-myx	-	+/-	-	+	-	-/+	-	-
HGESS-BCOR	-	+/-	-	+	+/-	-/+	+	-
ESS-YWHAE (HG)	-	-	-	-	+/-	+/-	+/-	-

NTRK rearranged spindle cell neoplasm



Chiang S, et al. *Am J Surg Pathol* 2018 Jun;42(6):791-798



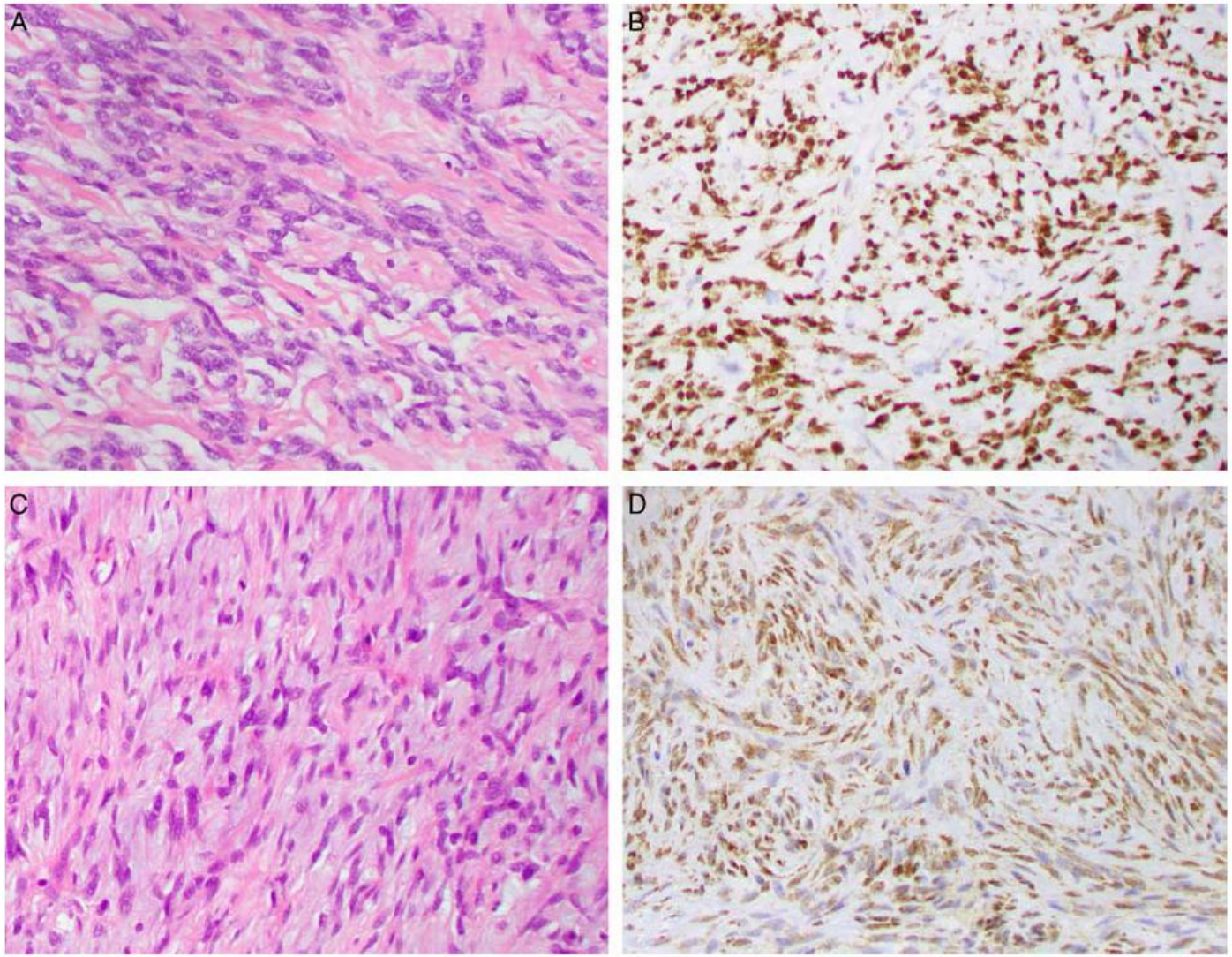


NTRK rearranged spindle cell neoplasm

- Translocations involve *NTRK1* or *NTRK3*
- Median age of 30 yrs (23-44)
- Cervix > Uterus
- May resemble adenosarcoma
- Stage 1B disease or higher with recurrences

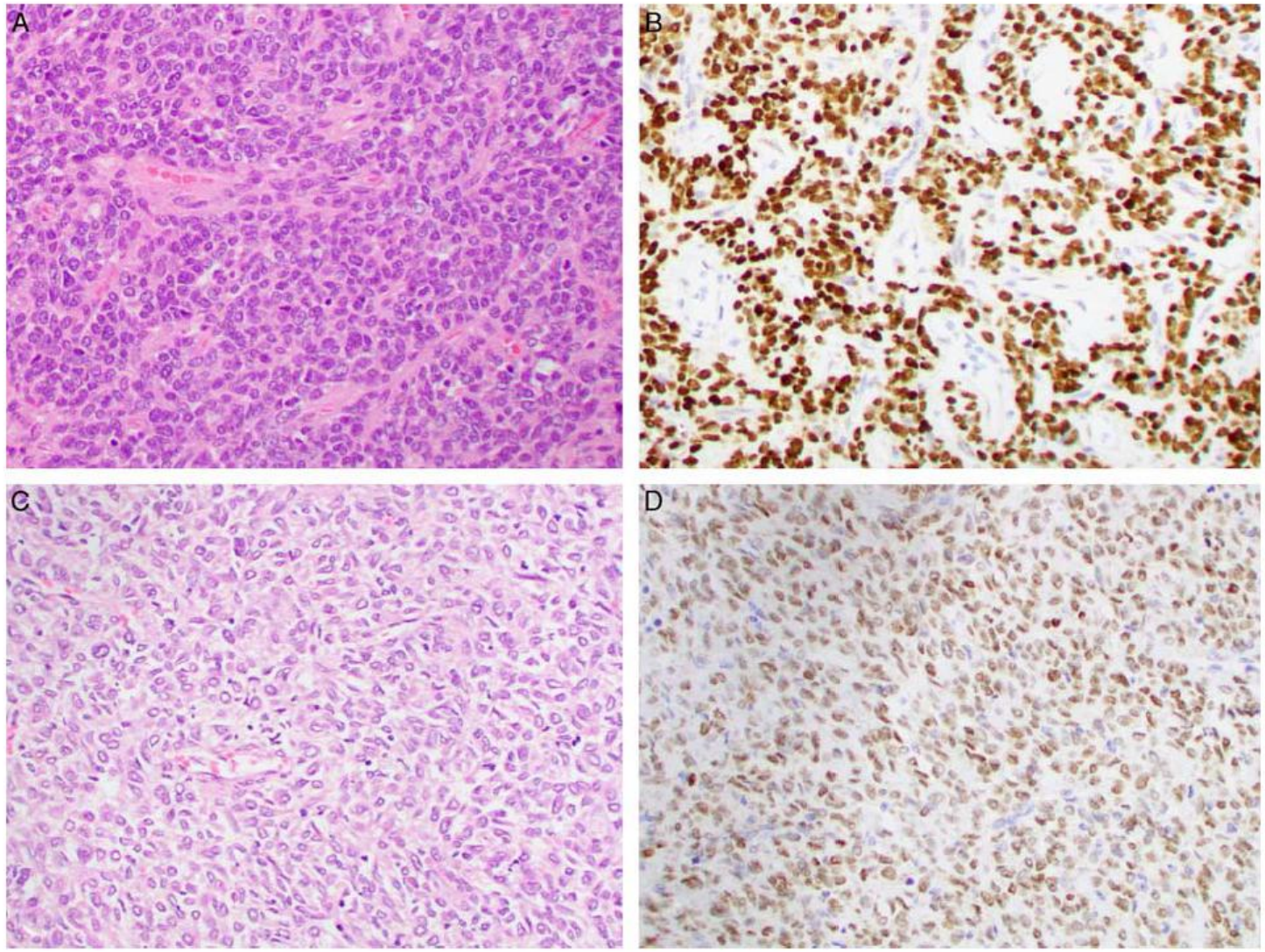
Croce S, et al. *Mod Pathol*, volume 32, pages1008–1022 (2019)

Solitary fibrous tumor (*NAB2-STAT6* fusion)



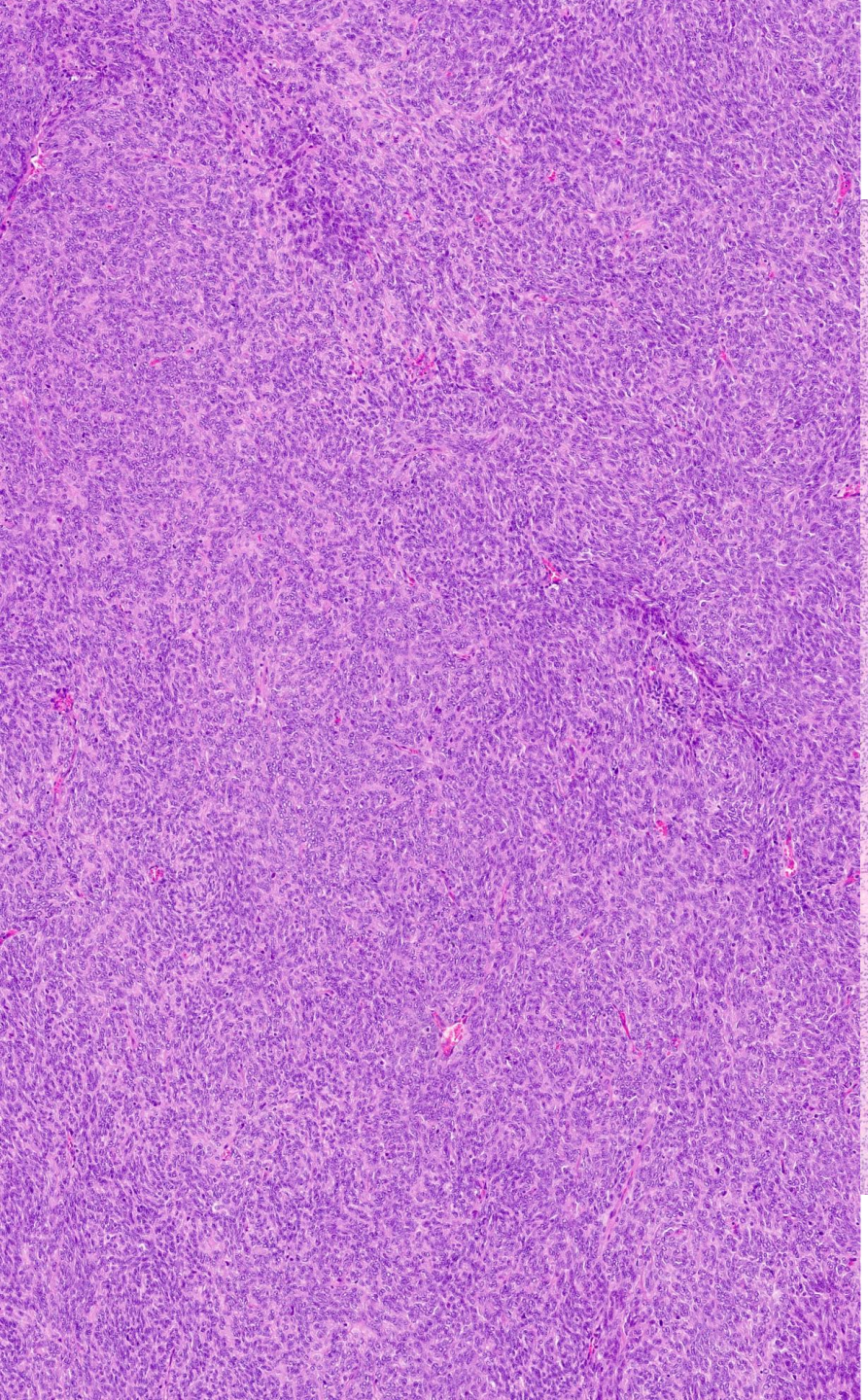
Devins KM, et al. *Am J Surg Pathol* 2022 Mar 1;46(3):363-375

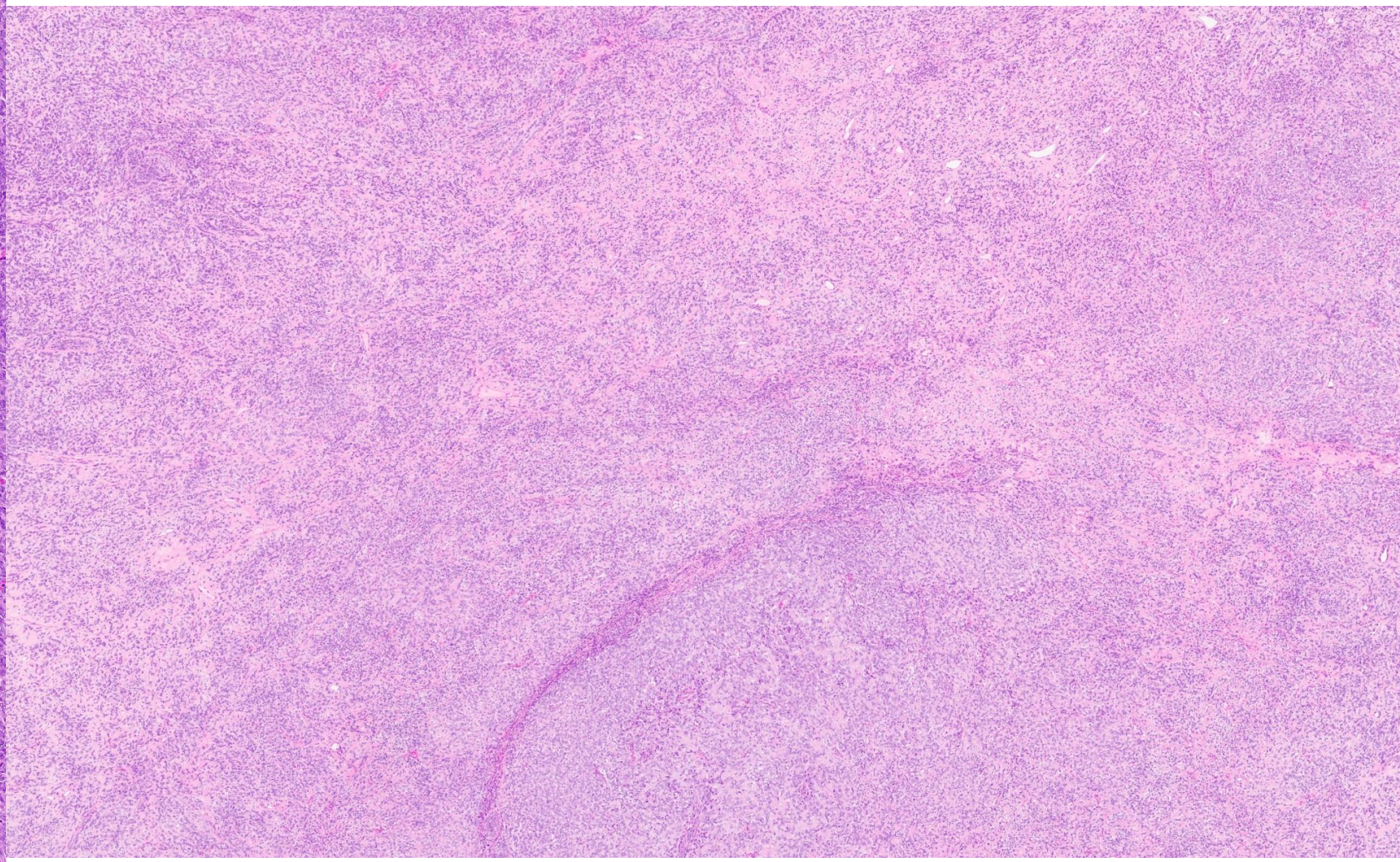
Malignant solitary fibrous tumor

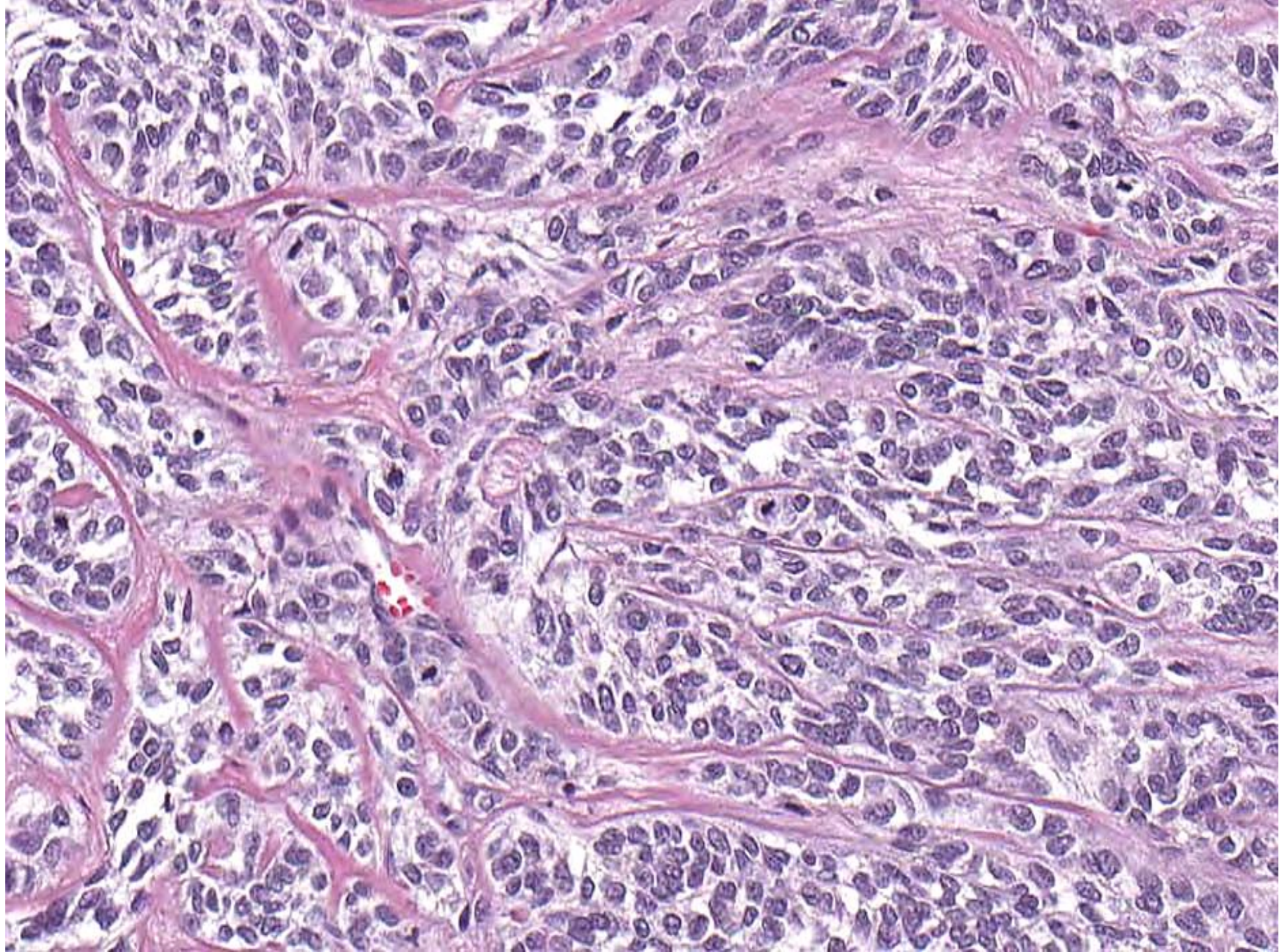


Devins KM, et al. *Am J Surg Pathol* 2022 Mar 1;46(3):363-375

GREB-1 translocated tumor





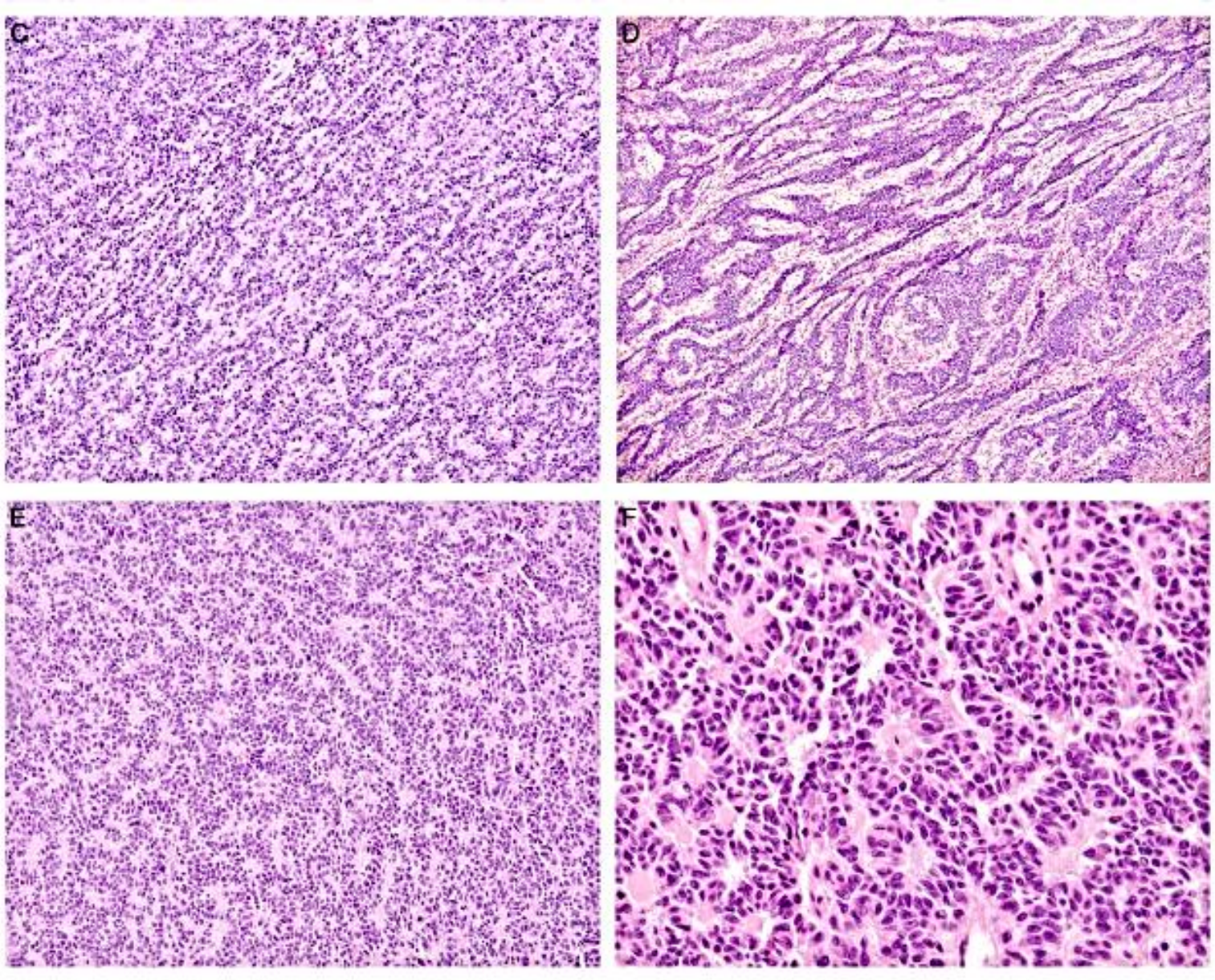


GREB-1 translocated tumor

- Family of uterine tumor resembling ovarian sex cord tumor (UTROSCT)
- *GREB-1* rearrangements
  - *GREB1-NCOA1* or *2* most common
- Variable sex cord differentiation
- Compared to UTROSCT
  - Patients older
  - More mitotic activity
  - More aggressive clinical course

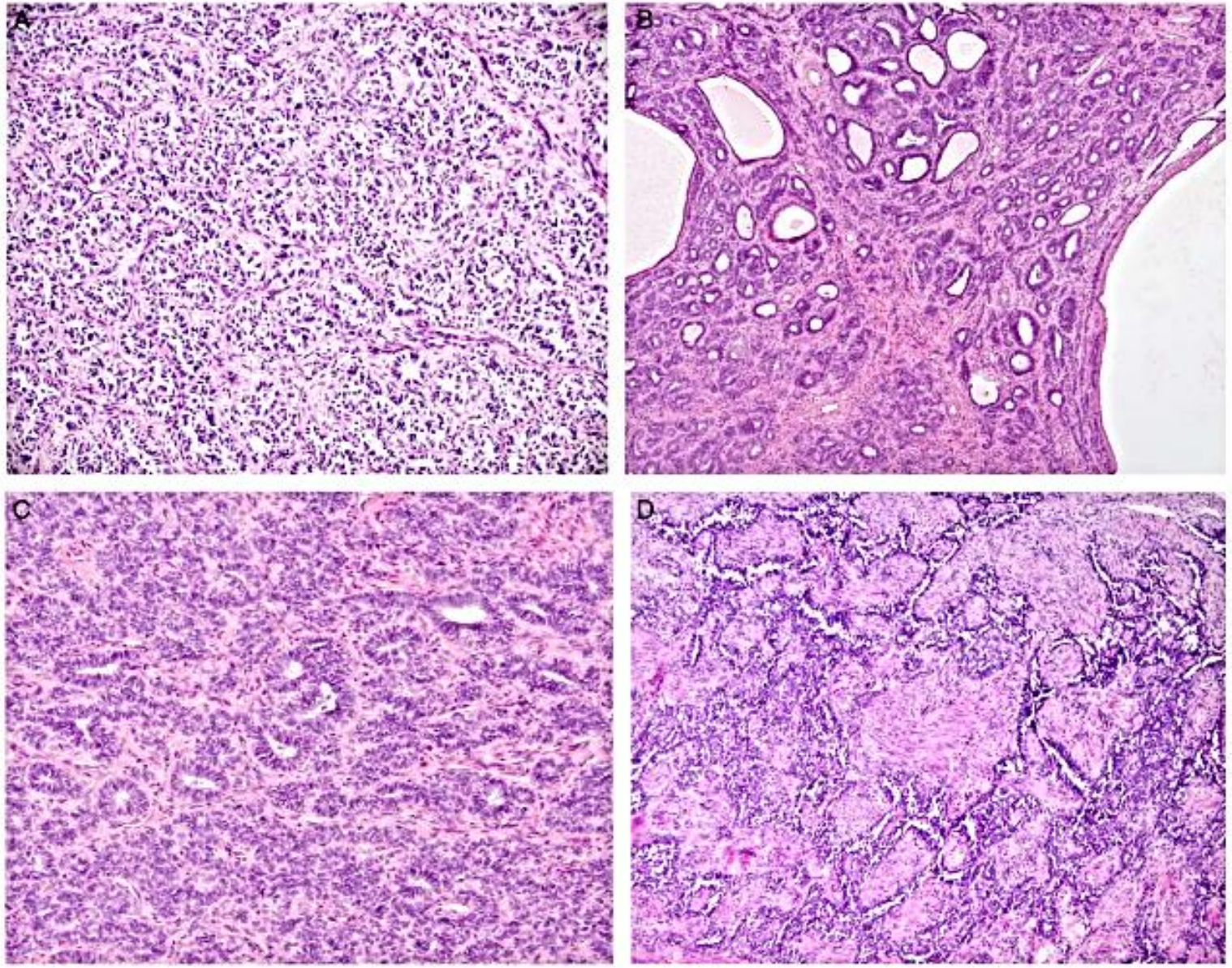
Lee C-H, et al. *Am J Surg Pathol* 2019; 43(7): 928-42

Conventional UTROSCT



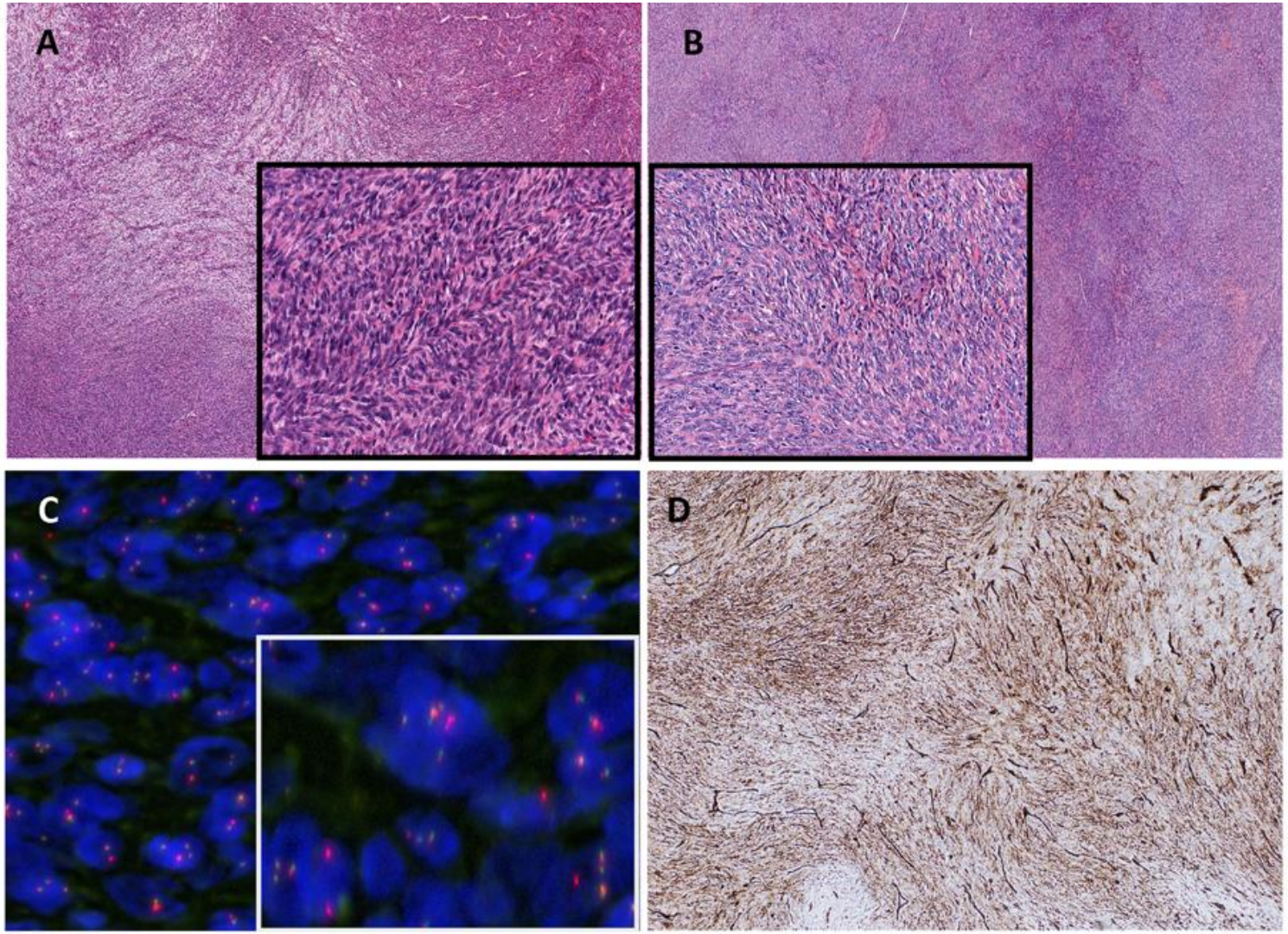
Boyraz B, et al. Am J Surg Pathol 2023;47 (2); 234-47

Conventional UTROSCT

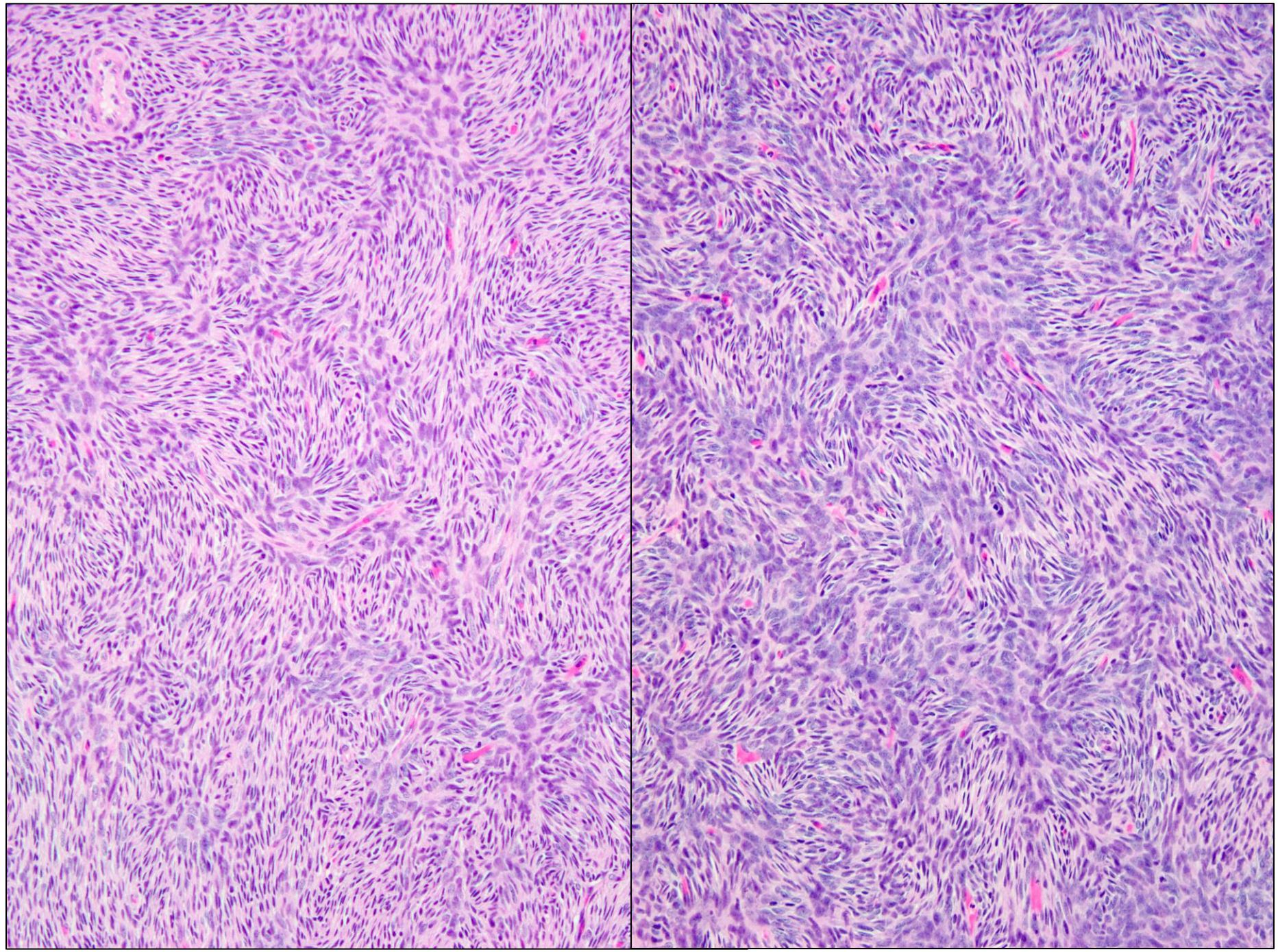


Boyraz B, et al. Am J Surg Pathol 2023;47 (2); 234-47

PDGFB rearranged spindle cell neoplasm



Croce S, et al. *Mod Pathol* 2019 Jul;32(7):1008-1022



How to decide which ancillary tests to perform?

- Is there prognostic relevance?
- Is there a therapeutic target?
- Does subclassification affect clinical trial eligibility?

Immunohistochemistry for directed therapy, germline screening and diagnosis

- Primary importance:
  - Desmin, CD10, p53, CD117, HMB45, Melan A, S100, cyclin D1, cytokeratin, EMA, ALK1, ER/PR, SMARCA4, CD34
- Also important (but may not be available):
  - 2SC or FH, STAT6
- Not entirely sensitive or specific (and may not be available):
  - TRK, BCOR, TFE3, PDGFR

Which genetic tests are important?

- Primary importance (directed therapy available):
  - Fusions involving ***NTRK, PDGFR*** (Fibrosarcoma)***, ALK1*** (IMT), ***STAT6*** (SFT)
  - ***TSC1/2*** **mutation** (PEComa); ***SMARCA4*** **mutation** (SMARCA4 deficient sarcoma)

- Primary importance (germline screening for hereditary cancers)
  - ***Fumarate hydratase*** mutation (Hereditary leiomyomatosis-renal cell carcinoma syndrome)
  - ***SMARCA4*** mutation
  - ***TSC1/2*** mutation

Take home messages

- Not every mesenchymal tumor is smooth muscle or stromal-derived
- Have a low threshold for performing desmin to confirm smooth muscle differentiation
- Many tumor types are now considered diagnoses of exclusion

Take home messages

- Not every mesenchymal tumor is smooth muscle or stromal-derived
- Have a low threshold for performing desmin to confirm smooth muscle differentiation
- Be aware of the wide spectrum of uterine mesenchymal tumors
  - Use available ancillary testing when relevant, ***especially to find therapeutic targets in recurrent setting***

Many thanks

- Patients
- Colleagues
- Audience
- Organizers

Thank you for your interest