Fibroepithelial tumours I
what's in the new blue

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New sections in WHO 2019

- Definition
- ICD-O code
- ICD-11
- Synonyms /Related terminology
- Subtypes (WHO2012: in histopathology)
- Localization
- Epidemiology
- Etiology (WHO2012: discussed in various sections)
- Histogenesis (PT)/ Pathogenesis
- Clinical features
- Macroscopy
- Histopathology
- Cytology
- Diagnostic molecular pathology
- Differential diagnosis (in Histopathology)
- Grading (PT) (in Histopathology)
- Genetics (in Pathogenesis)
- Essential diagnostic criteria
- Staging
- Prognosis and predictive factors

Red new in WHO 2019

Grey removed in WHO 2019

Fibroepithelial lesions (FEL)

- Biphasic neoplasms that exhibit a proliferation of both epithelial and stromal components
- Two main entities
  - Fibroadenoma (FA): complex FA, cellular FA and juvenile FA
  - Phyllodes tumor (PT): benign PT, borderline PT and malignant PT, periductal stromal tumor
- Hamartomas are not strictly FEL
  - They are circumscribed lesions, possessing lobular glands and fibroadipose stroma, with some resemblance to FEL
  - Included in the section of FEL

Fibroadenoma

- Definition:
  - A circumscribed benign neoplasm of the terminal duct-lobular unit (TDLU) with biphasic proliferation of epithelial and stromal components.
- The term of “adenofibroma” is not recommended
- Occurs in any region within the breast - may be multifocal or bilateral
- Rare before menarche and most common in adolescent girls and women ≤35 years
  - except complex FA which occur about two decades later
  - may develop in men with gynecomastia
- Usually presents as a well defined nodules <3mm, but giant FA (>5cm), though uncommon, can occur

Fibroadenoma

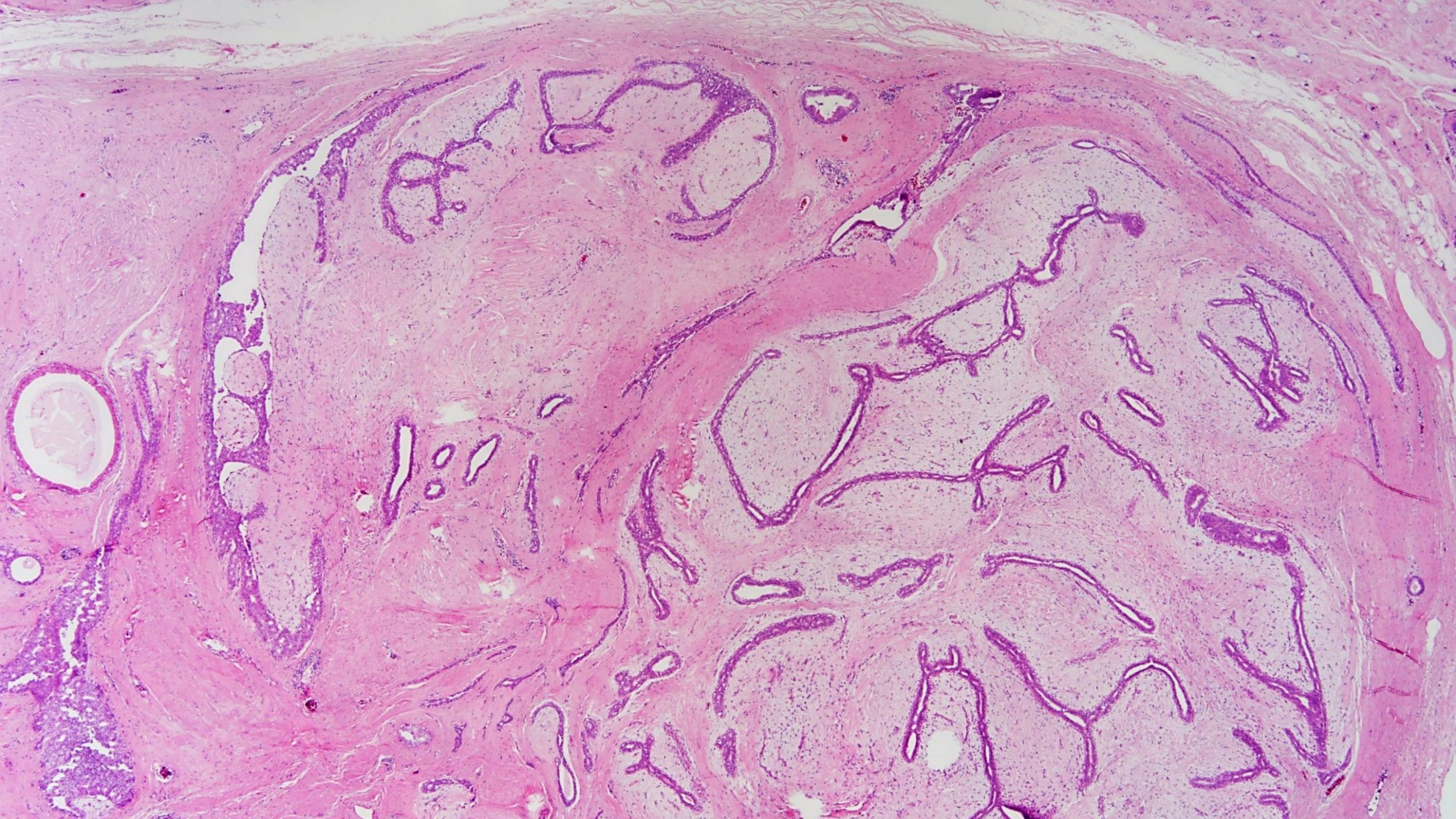
- Hormone sensitive and may grow rapidly during pregnancy
- Most FA are sporadic
  - myxoid FA occur in women with Carney syndrome
  - multiple large FA in adolescent/ young women has been associated with cyclosporine immune suppression
- Most FA do not recur after complete surgical excision
- In adolescent, there is tendency for one or more new lesions to develop at another site or close to the site of previous surgery

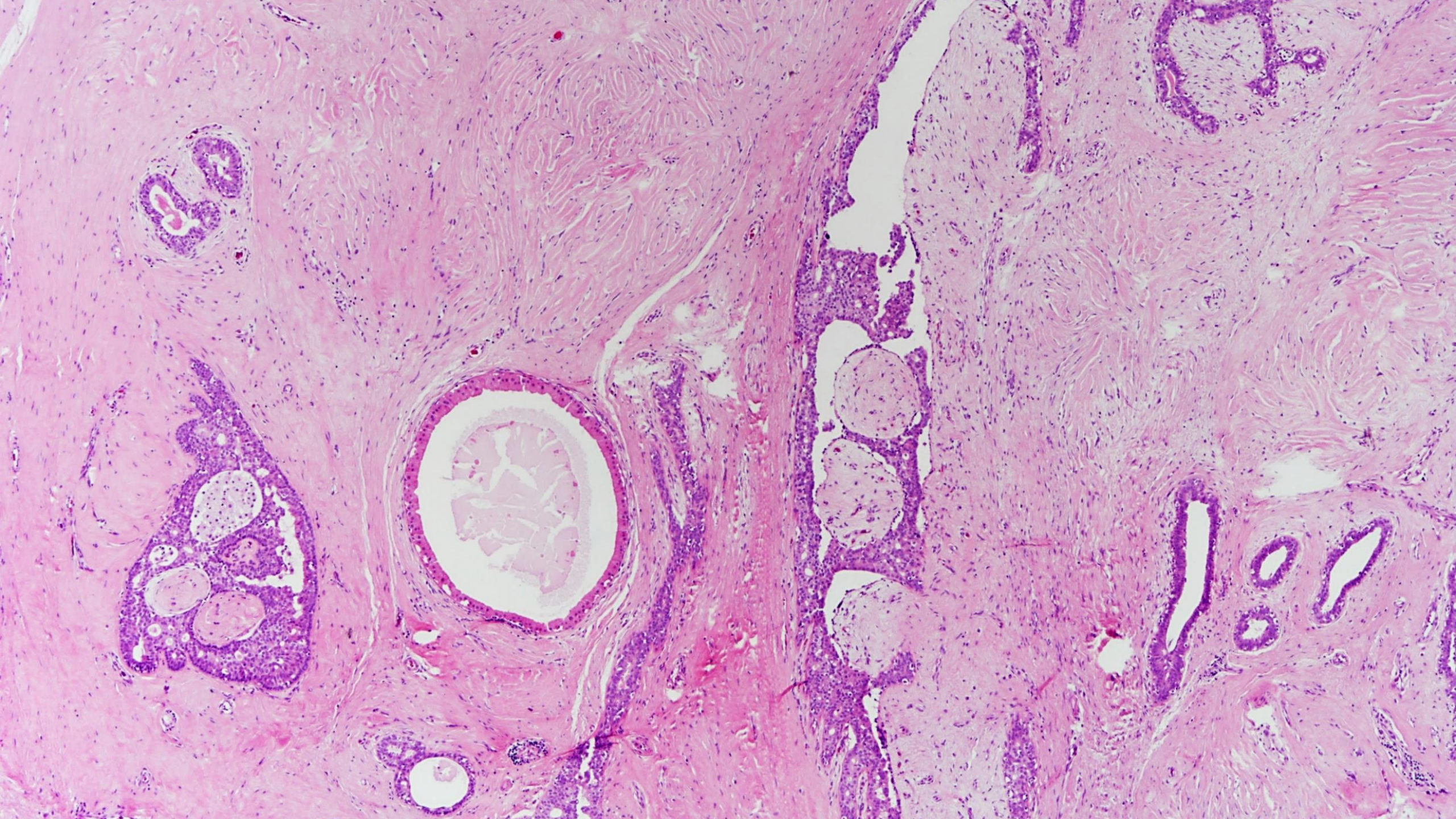
Fibroadenoma

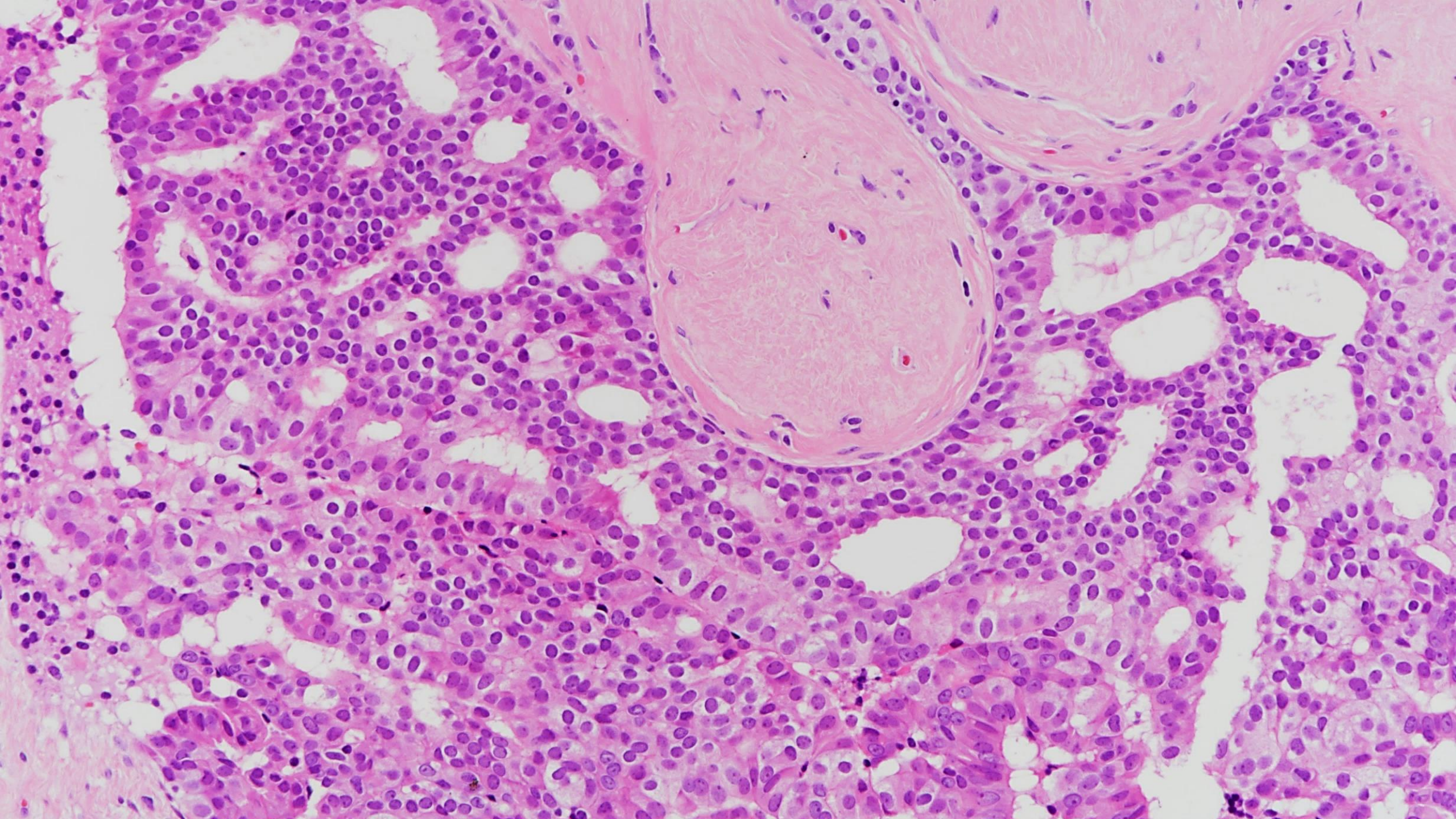
- Macroscopically solid, ovoid and well-circumscribed with a uniform rubbery, lobulated, whorled, grey-white cut surface with intervening slit-like spaces
- Show pericanalicular or intracanalicular pattern
  - pericanalicular pattern more common in juvenile FA
- Stromal components are uniformly low cellularity, lack atypia and with uncommon mitosis
  - however FA in young women : focal /diffuse hyper-cellularity and some mitoses
- Bizarre multinucleated giant cells, extensive myxoid change or hyalinization with dystrophic calcifications, and rarely ossification in postmenopausal women can sometimes be observed

Fibroadenoma

- Epithelial squamous and apocrine metaplasia, epithelial apical snouts, focal fibrocystic changes, sclerosing adenosis, usual ductal hyperplasia and even extensive myoepithelial proliferation can occur
  - ADH, ALH, DCIS, LCIS may infrequently involve FA
  - no increased cancer risk, if hyperplasia confined to FA
- Epithelium and stroma are non-clonal, but monoclonality had been demonstrated in areas of stromal expansion







FA subtypes

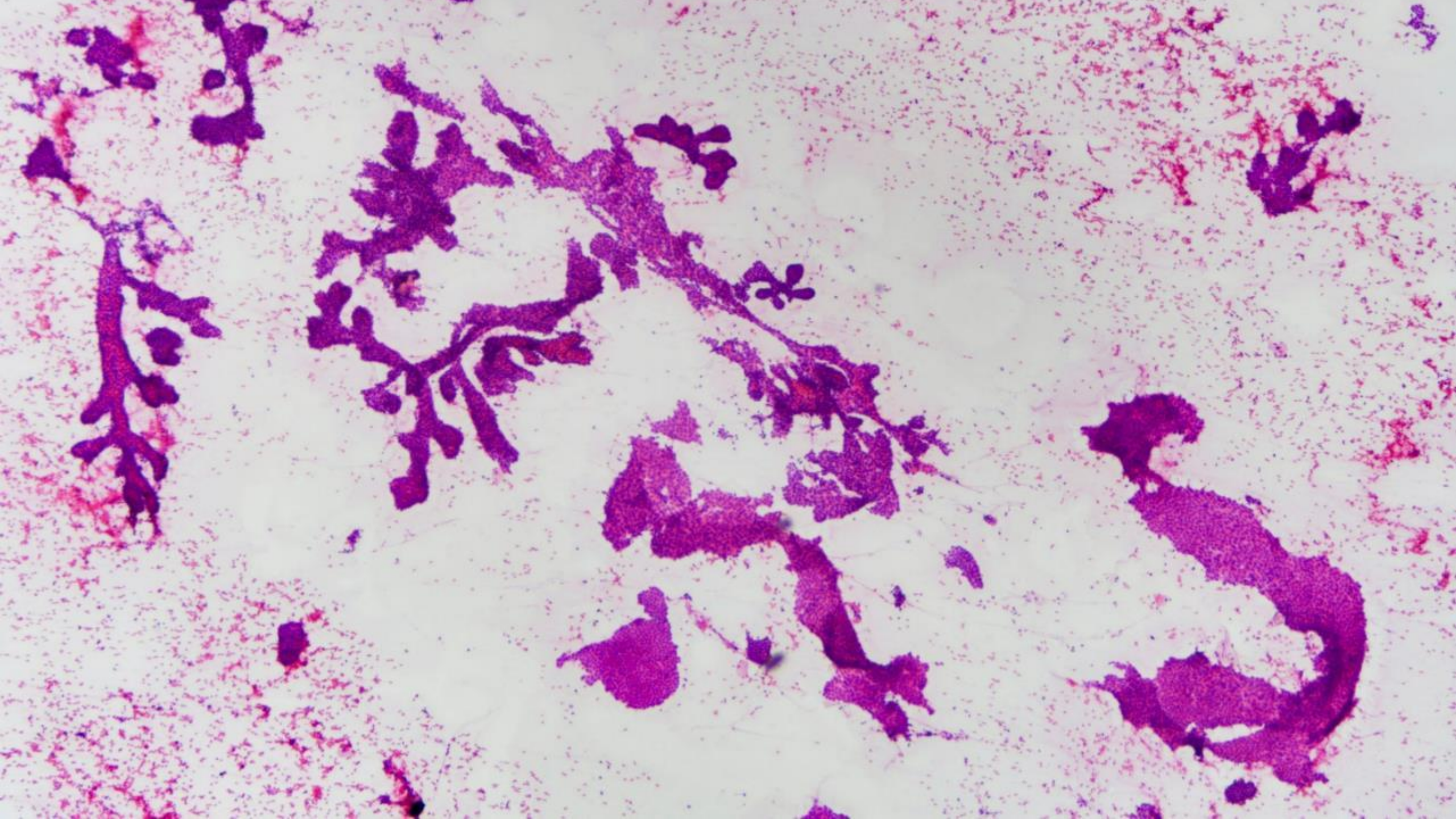
- Complex FA
  - one or more of the following features:
    - cysts >3mm
    - sclerosing adenosis
    - epithelial calcifications and/or papillary apocrine metaplasia
- Cellular FA
  - pericanalicular growth pattern
  - mildly to moderately increased stromal cellularity
  - usually <2 stromal mitoses/10HPFs (<0.87 mitoses/mm^2)
  - lack stromal nuclear atypia, exaggerated intracanalicular architecture, periductal subepithelial stromal condensation and intratumoral heterogeneity
- Juvenile FA
  - stromal cellularity is mild to moderate with fascicular arrangement and no nuclear atypia
  - stromal mitoses usually are <2/HPFs (<0.87 mitoses/mm^2), but can be up to 6/10HPF (2.61 mitoses/mm^2)

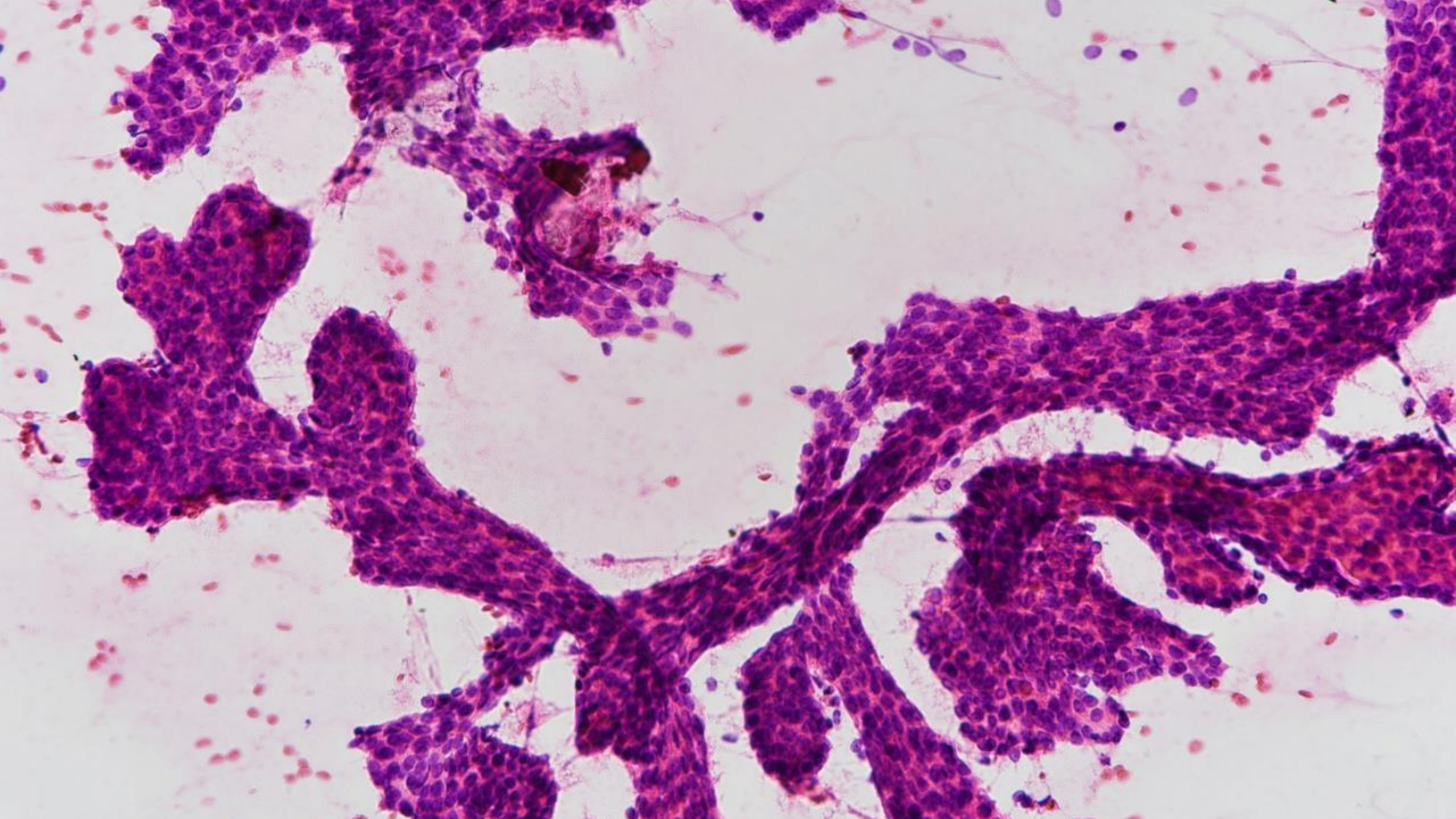
FA subtypes

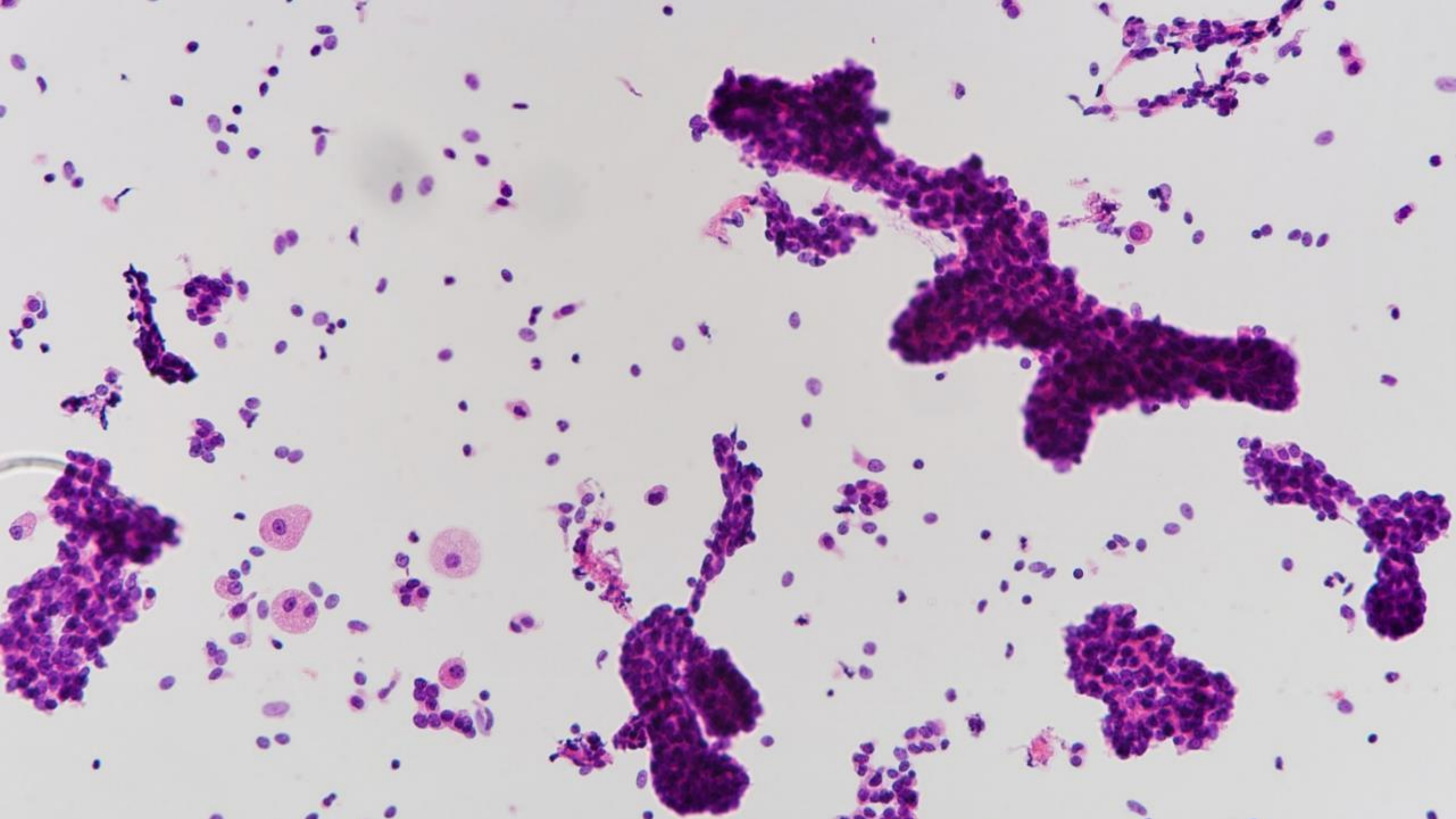
- More detailed and precise definitions on the FA subtypes
- Myxoid FA now not included as a FA subtype

FA cytology

- Typically cellular sheets with antler or staghorn shaped epithelial clusters, with a clean background containing bipolar nuclei, giving an appearance of sesame seeds strewn among epithelial fragments
- Epithelial clusters often show admixed myoepithelial nuclei
- Stromal clumps can be associated with myxoid material
- Rarely, multinucleated giant cells may be discerned
- Usual ductal hyperplasia within FA can lead to the presence of larger branched proliferative epithelial aggregates in the aspirates
- Occasionally the aspirates may show high cellularity, and isolated single epithelial cells with mild nuclear atypia
  - resulting in an atypical or even malignant diagnosis







Essential and desirable diagnostic criteria: FA

- Circumscribed biphasic tumor
- Intra- and/or pericanalicular growth pattern
- No stromal overgrowth
- Absence of well-developed fronds
- No stromal atypia
- Low mitotic activity in stromal component

Phyllodes tumor

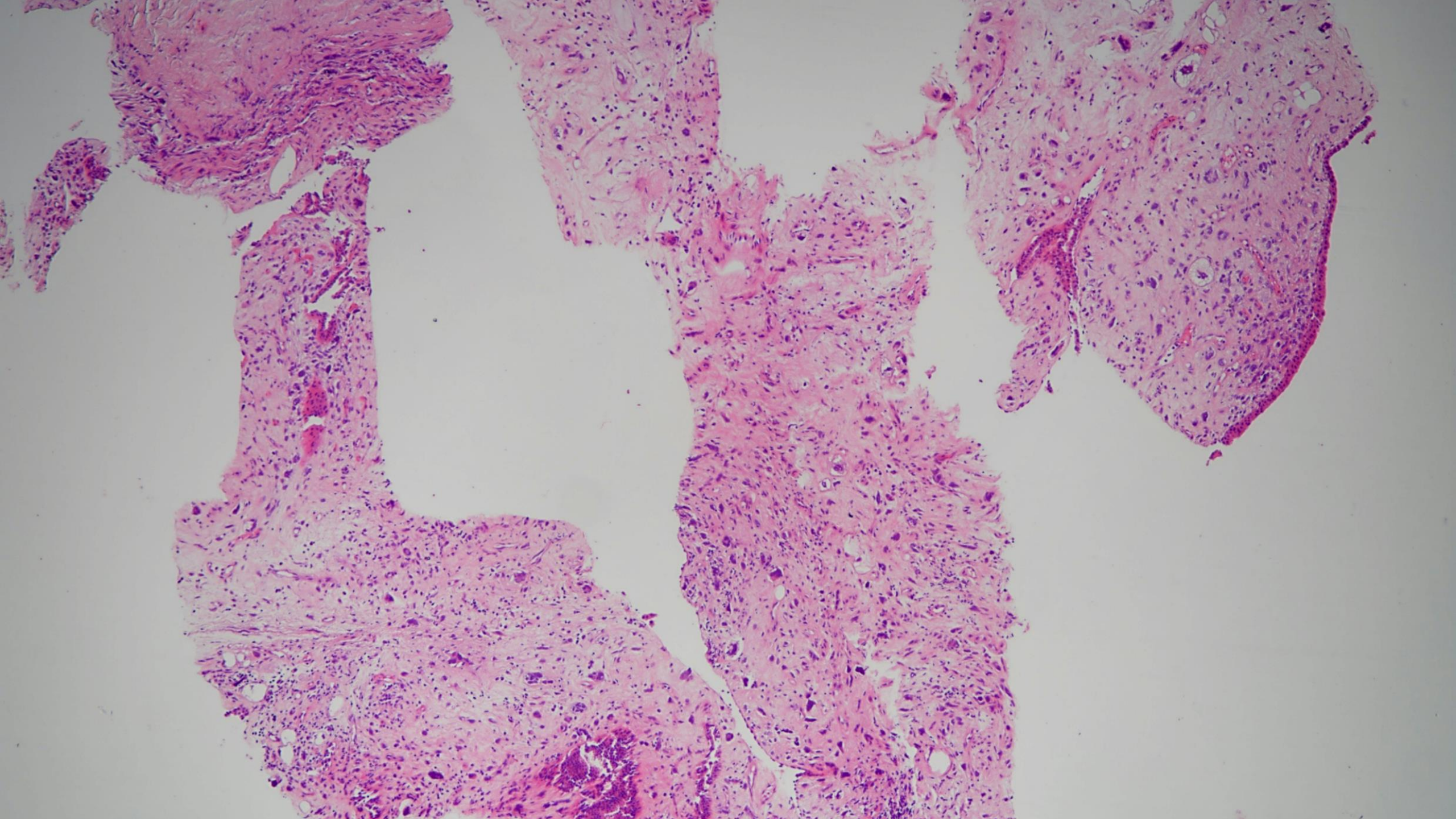
- Definition
  - a group of generally circumscribed fibroepithelial neoplasms, showing prominent intracanalicular architectural patterns with leaf-like fronds capped by bilayered epithelium (luminal epithelial and myoepithelial layers) accompanied by stromal hypercellularity
- The term “cystosarcoma phylloides” is not recommended
- May arise in any part of the breast, including the nipple and ectopic breast tissue
- Accounts for 0.3-1% of all primary tumor of the breast and 2.5% FEL

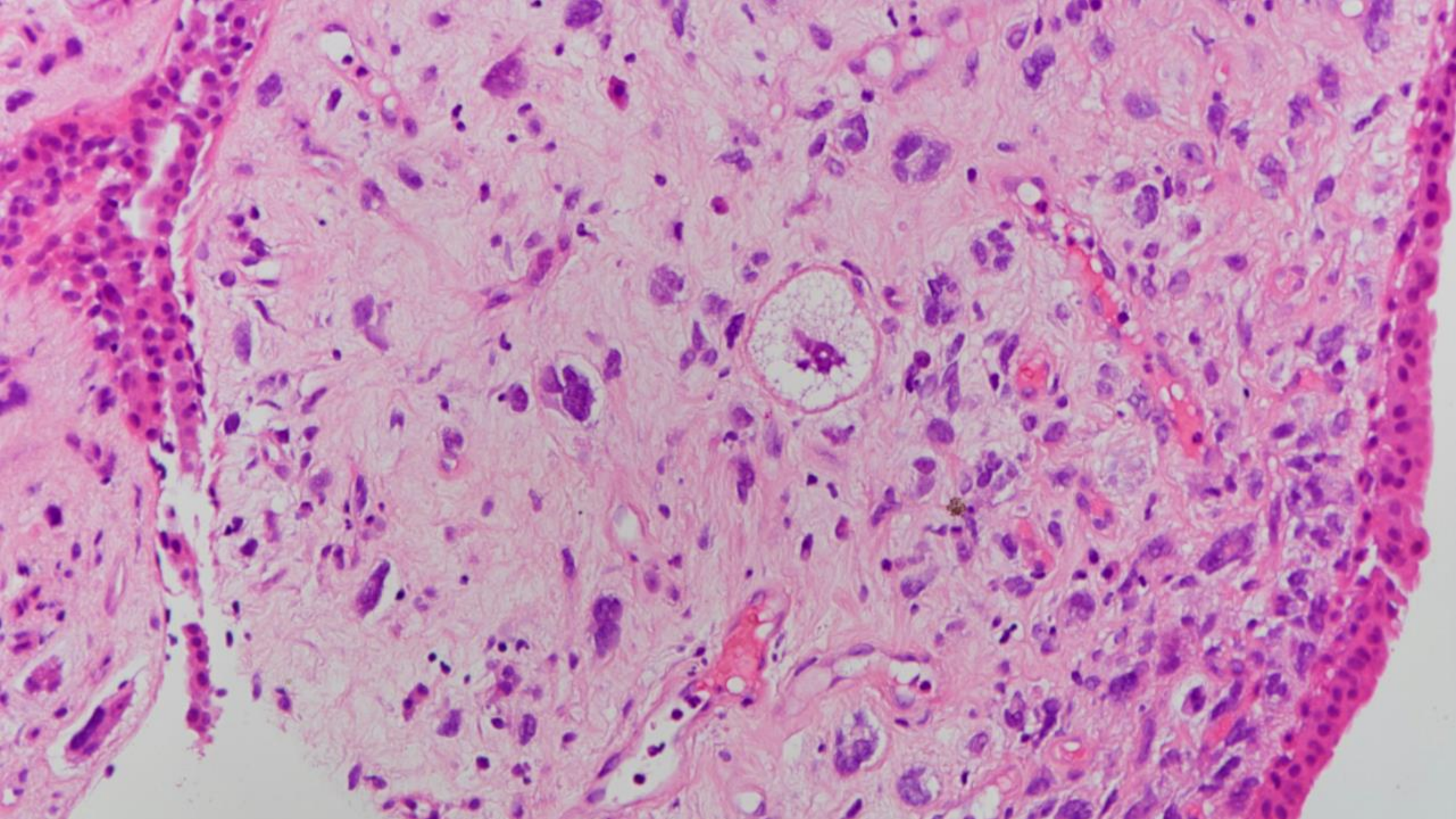
Phyllodes tumor

- Higher incidence in Asian women
- Occur predominantly in older women (average 40-50 years), about 15-20 years later than FA
- Malignant PT develops on average 2-5 years later than benign PT
- Etiology of PT is unclear, but PT have been described in Li-Fraumeni syndrome patients

Phyllodes tumor

- Macroscopically, circumscribed firm bulging masses with curved clefts resembling leaf buds and hemorrhage/ necrosis
- Microscopically, exhibited an exaggerated intracanalicular growth pattern, with leaf-life projections extending into variably dilated elongated lumina
- Stromal cellularity is higher in the zone immediately adjacent to epithelium (subepithelial accentuation)
  - also areas of sparse stromal cellularity , hyalinization or myxoid change, reflecting stromal heterogeneity
- Monomorphic stromal nuclei with rare mitosis (<2.55 mitoses/mm^2)
- Bizarre or multinucleated stromal giant cells may be present, and should not be interpreted as a marker of malignancy
- Apocrine or squamous metaplasia and UDH can be present
  - ADH / DCIS, LN and invasive carcinoma can rarely occur within the tumor





WHO2012

ICD-O code	
Phyllodes tumour, not otherwise specified (NOS)	9020/1
Phyllodes tumour, benign	9020/0
Phyllodes tumour, borderline	9020/1
Phyllodes tumour, malignant	9020/3
Periductal stromal tumour, low grade	9020/3

WHO2019

ICD-O coding

9020/1 Phyllodes tumour NOS

9020/0 Phyllodes tumour, benign

9020/1 Phyllodes tumour, borderline

9020/3 Phyllodes tumour, malignant

Subtype(s)

Periductal stromal tumour

Periductal stromal tumor

- Benign ductal elements in a cellular spindle stroma, with spindle cells displaying varying degrees of atypia and mitotic activity
- Lacks the fronded architecture of typical PT
- Unlike PT, its incidence is higher in peri- and post-menopausal women, a decade older than PT (55.3 median and 45)

- WHO 2003 : classified as a distinct entity
- WHO 2012 : classification was not very clear
  - Under the ICD-O code for PT, but is an entity for differential diagnosis with PT
- WHO 2019 : included in the same spectrum, as a PT subtype

Periductal stromal tumor

- Tendency to local recur if not completely excised
- Histological grading depends on atypia and mitotic counts ranges from low to high grade
- Tumor cells are positive for CD34, CD10; but lacks CD117, S-100, ER and PR
- However, focal PT features could be found in recurrences and morphologic coexistence of periductal tumor in some PT favors it being regarded as a PT subtype

TABLE 3. *Comparison of CD34, CD117, and HHF35 in FA, PT, and PDSS*

Tumor type	CD34	CD117	HHF35	Dominant growth pattern
Fibroadenoma	4/4	0/4	2/4* (1)	Intracanalicular
Phyllodes tumor	3/3	0/3	2/3	Intracanalicular & leaf-like processes
Periductal stromal sarcoma	13/15† (4)	6/15† (2)	2/15	Pericanalicular
MPT (Chen et al.)†	3/12	8/12	10/12	

* Focal in the number of cases in parentheses.
† Data retrieved from Chen et al. (*J Surg Res,* 2000).
MPT, malignant phyllodes tumor; FA, fibroadenoma; PT, phyllodes tumor; PDSS, periductal stromal sarcoma.

Tomas D et al 2009 Pathol Int 59:588

Grading

Histological feature	Fibroadenoma	Phyllodes tumours		
		Benign	Borderline	Malignant[a]
Tumour border	Well defined	Well defined	Well defined, may be focally permeative	Permeative
Stromal cellularity	Variable, scant to uncommonly cellular, usually uniform	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal atypia	None	Mild or none	Mild or moderate	Marked
Mitotic activity	Usually none, rarely low	Usually low (< 5 mitoses per 10 HPFs)	Usually frequent (5–9 mitoses per 10 HPFs)	Usually abundant (≥ 10 mitoses per 10 HPFs)
Stromal overgrowth	Absent	Absent	Absent (or very focal)	Often present
Malignant heterologous elements	Absent	Absent	Absent	May be present
Distribution relative to all breast tumours	Common	Uncommon	Rare	Rare
Relative proportion of all phyllodes tumours	n/a	60–75%	15–26%	8–20%

Similar to WHO 2012, except updates on the relative proportions

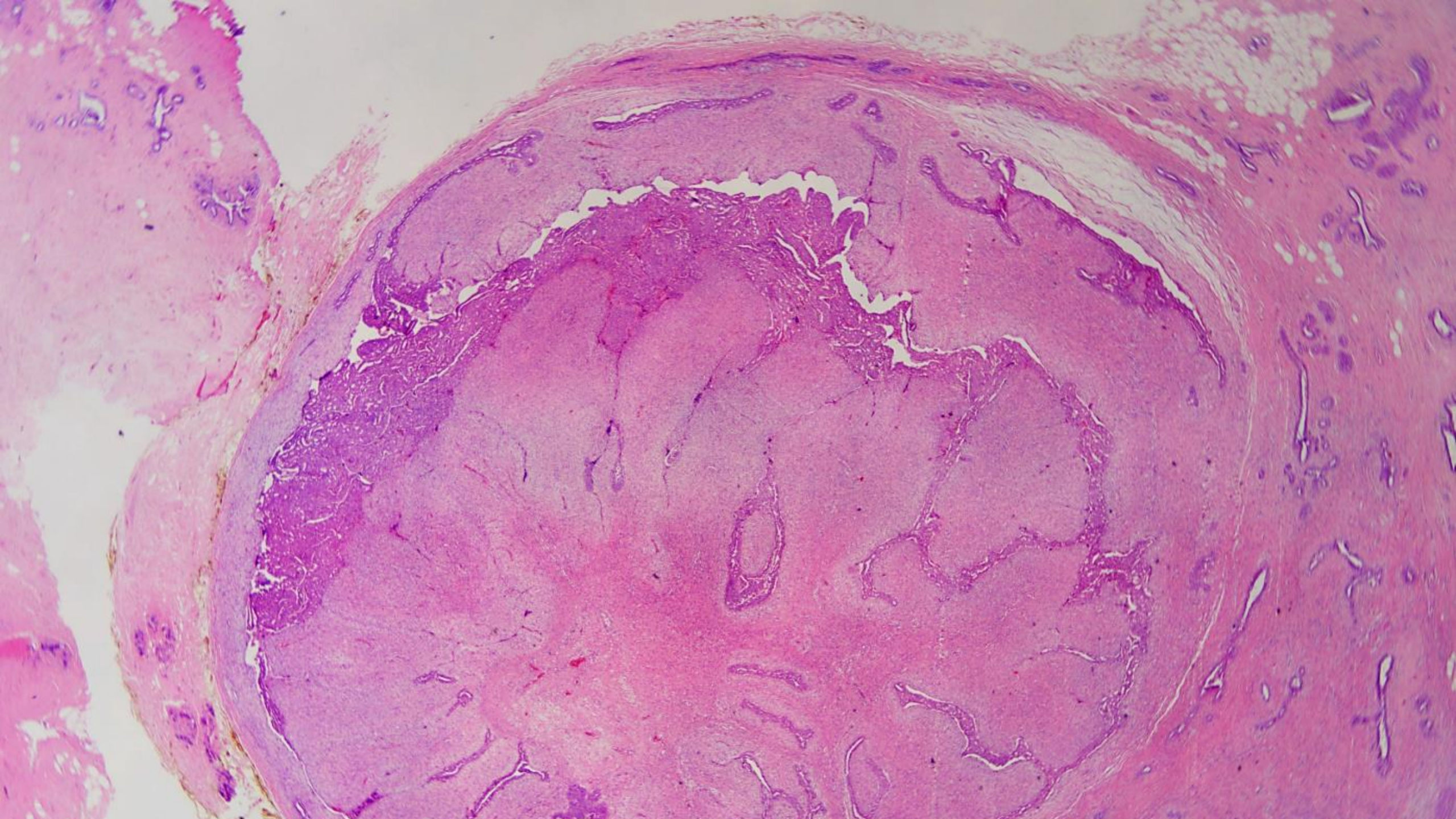
Histologic grading for malignancy

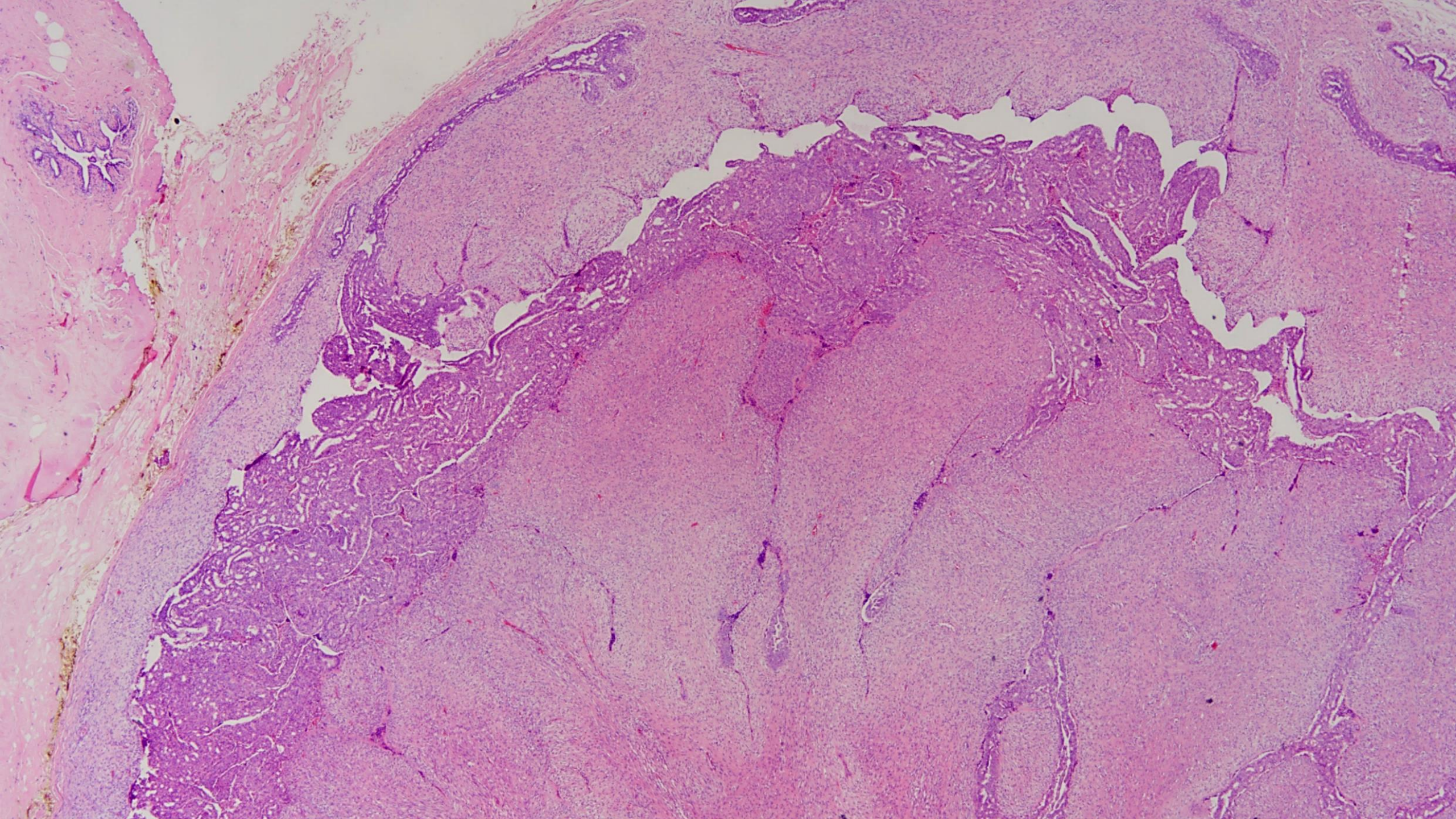
- Marked stromal nuclear pleomorphism
- Stromal overgrowth
- Increased mitoses
- Increased stromal cellularity
- Infiltrative border
- The presence of heterologous element, even in the absence of other features

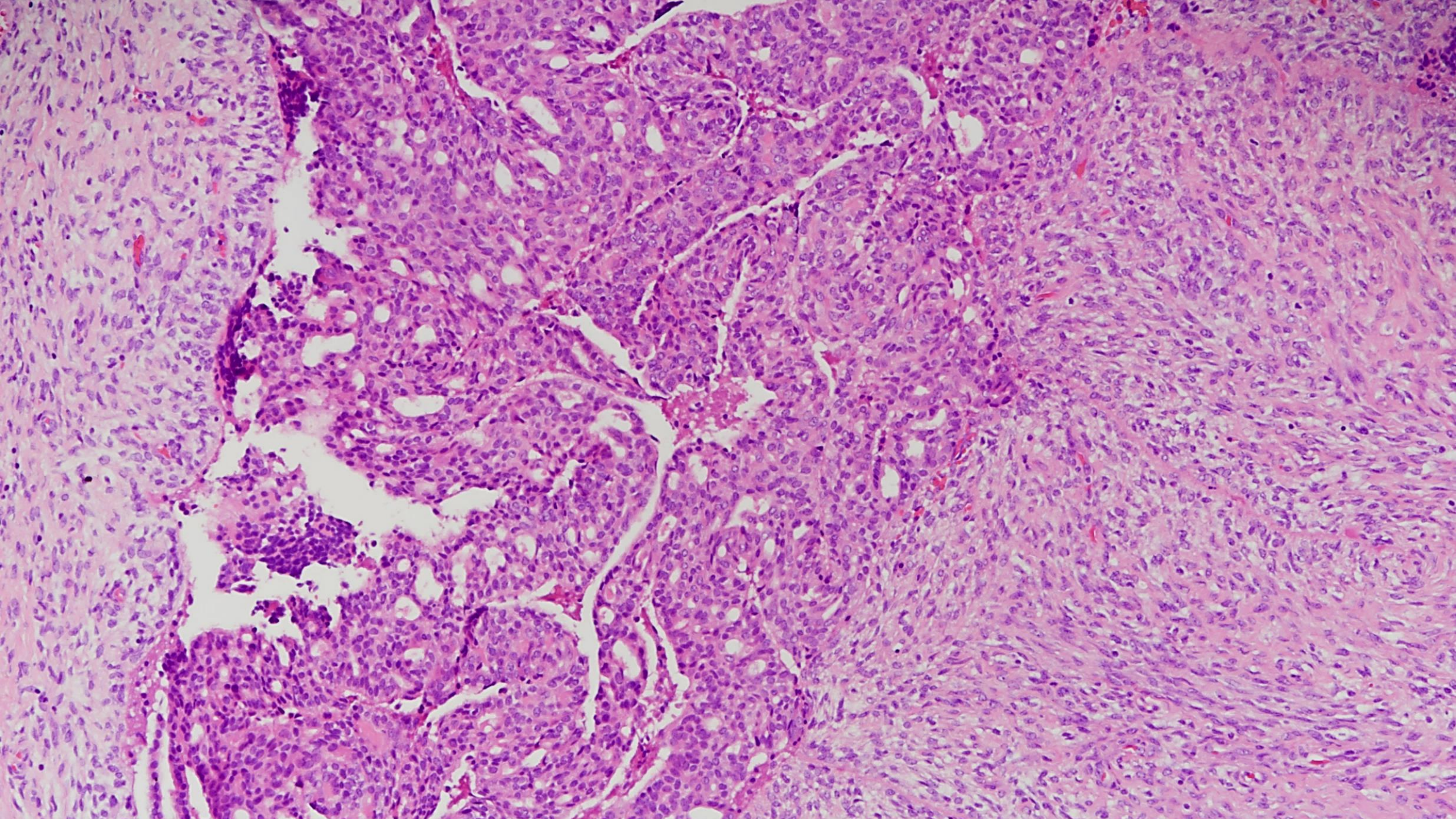
Histologic grading for malignancy

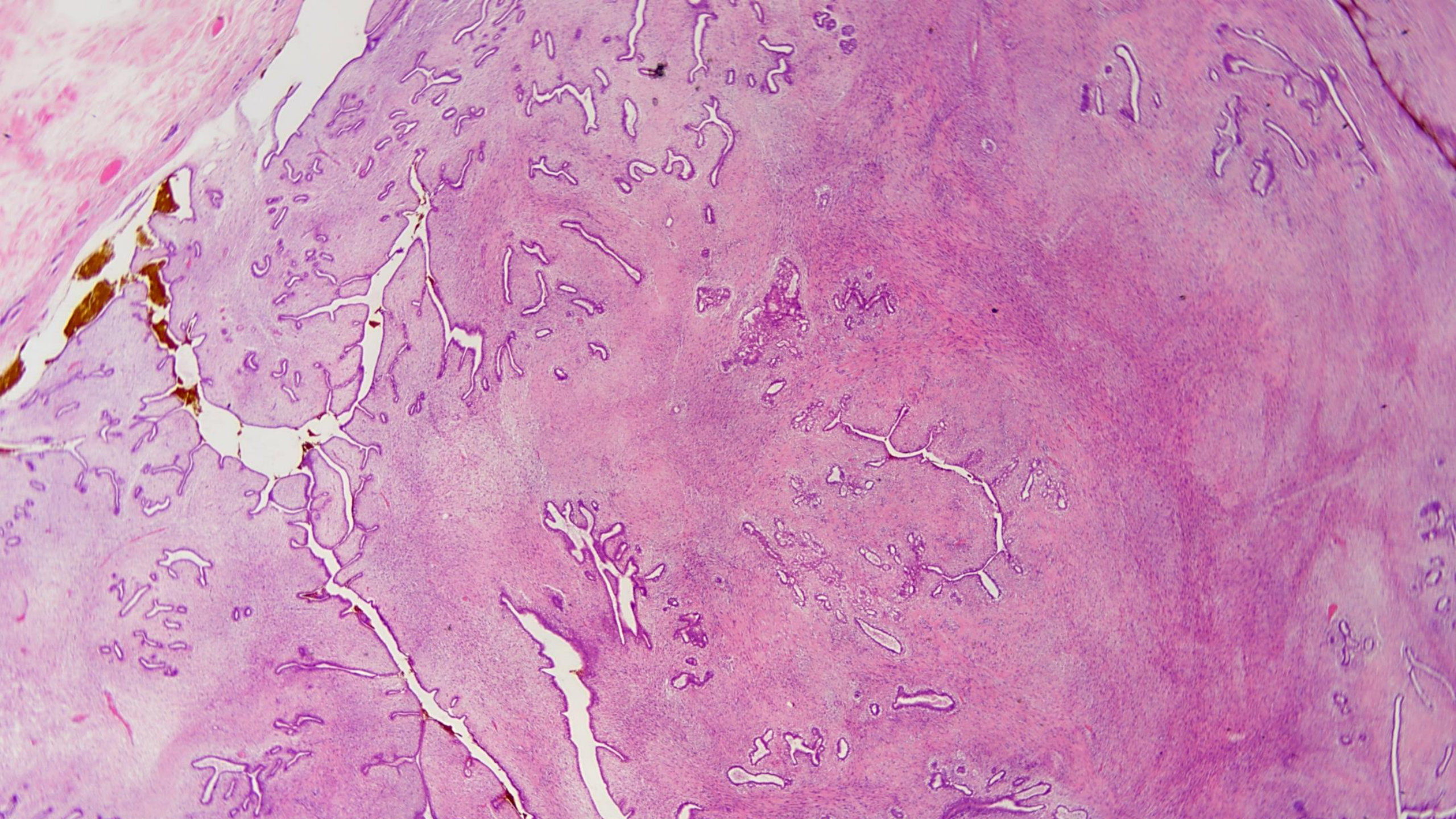
- WHO 2019 : malignant diagnosis is made based on the presence of all malignant histologic features

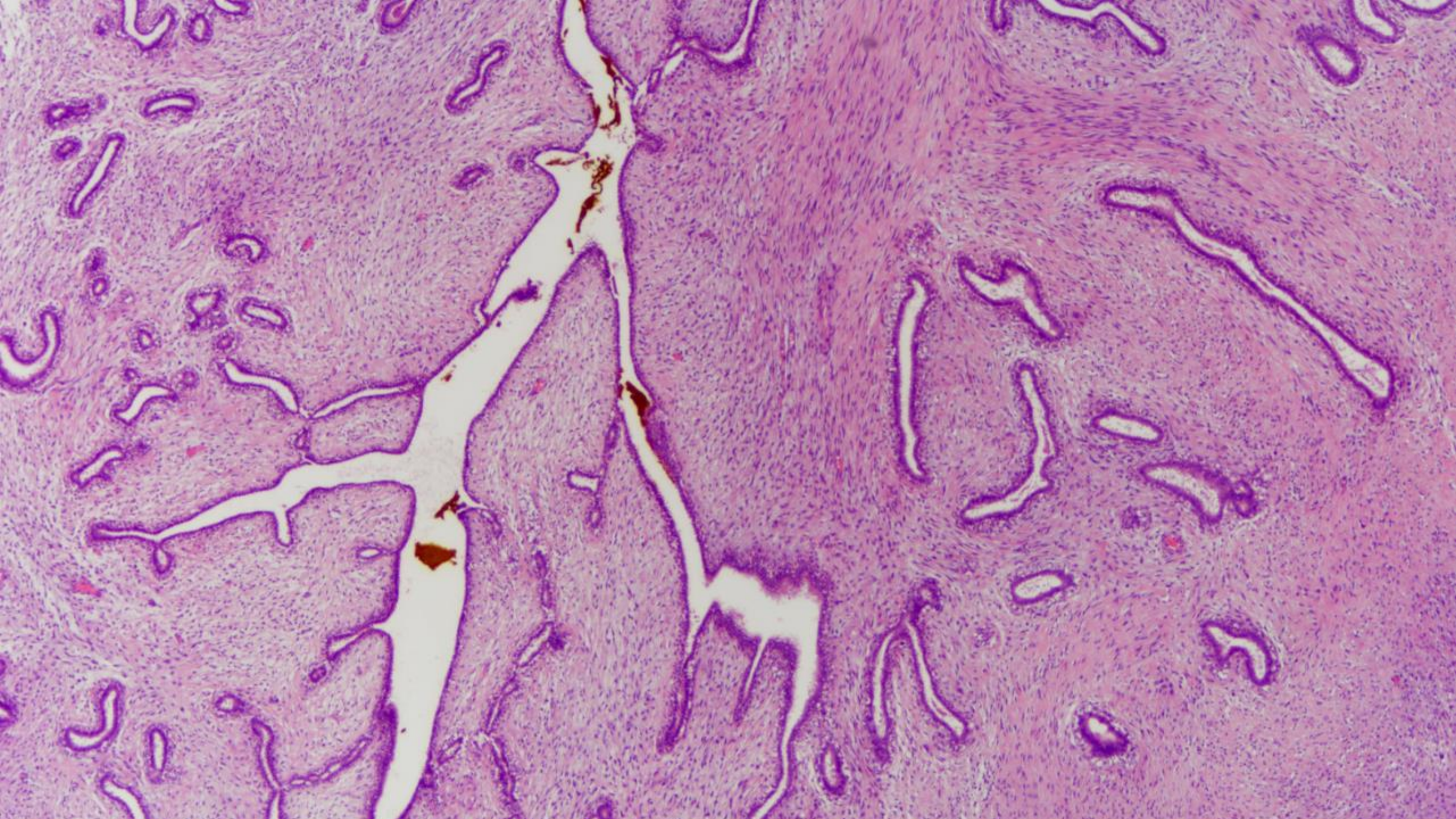
  "Malignant phyllodes tumors are diagnosed when all of the following features are present."
- More details on assessment are provided:
  - Marked stromal nuclear pleomorphism
  - Stromal overgrowth : absence of an epithelial element in one LPF (40x) (4x objective and 10x eyepiece) containing only stroma
  - Increased mitoses : (≥5.1 mitoses/mm^2; 10 mitoses per 10 HPF of 0.5mm^2)
  - Increased stromal cellularity
  - Infiltrative border
  - The presence of heterologous element, even in the absence of other features
    - but not on the finding of well-differentiated liposarcoma
- Details on sampling and area for diagnosis was removed

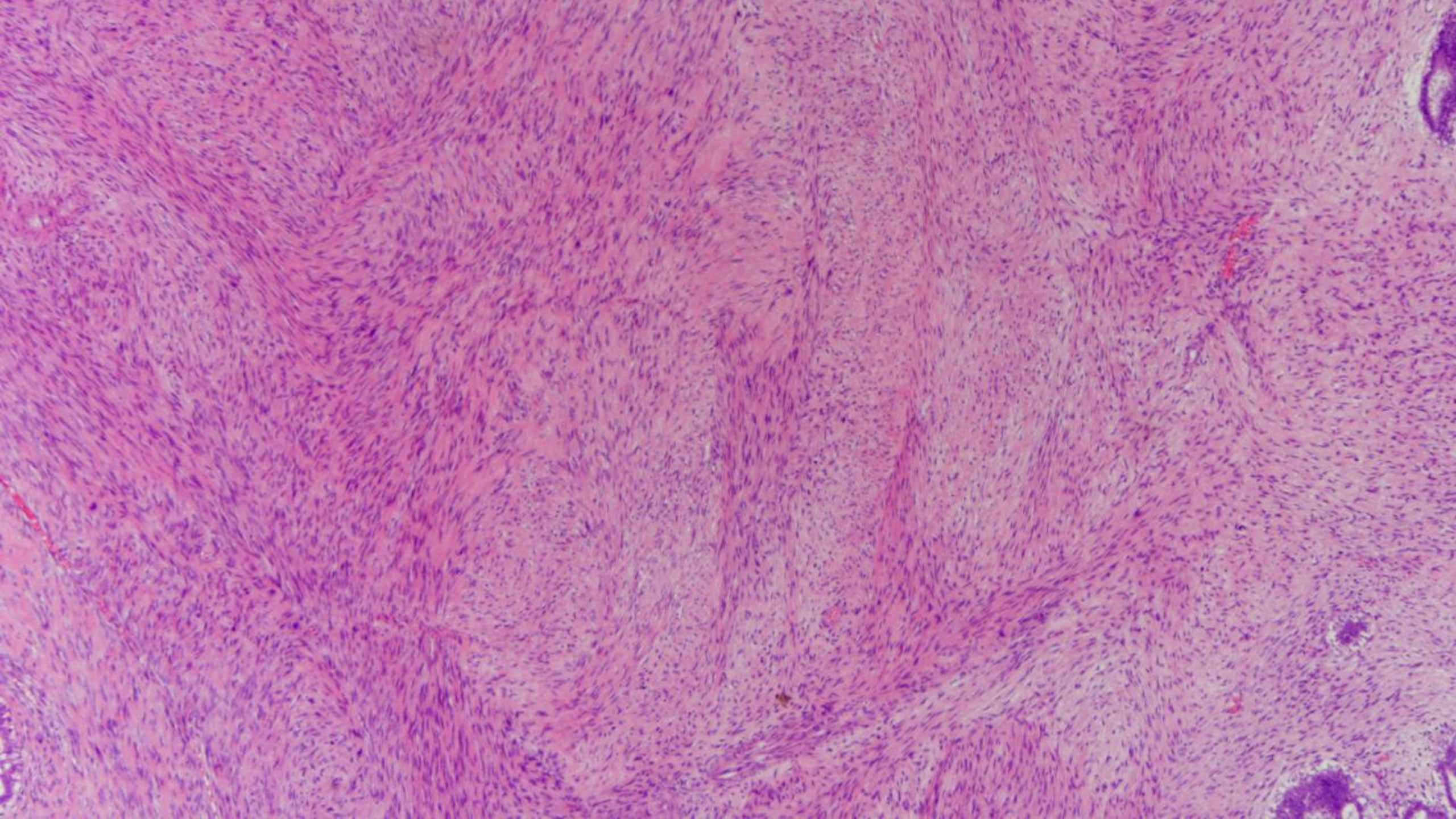


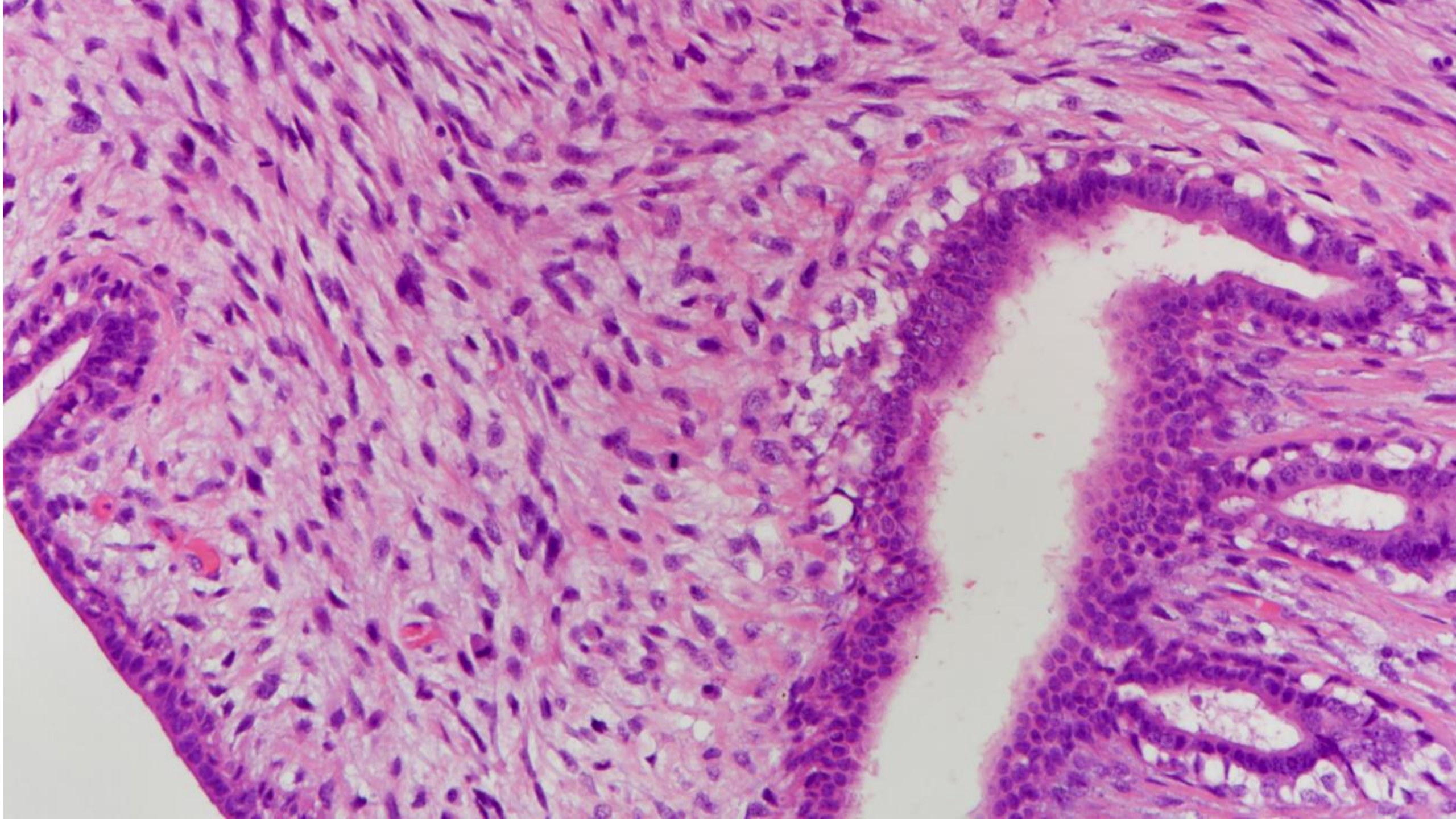


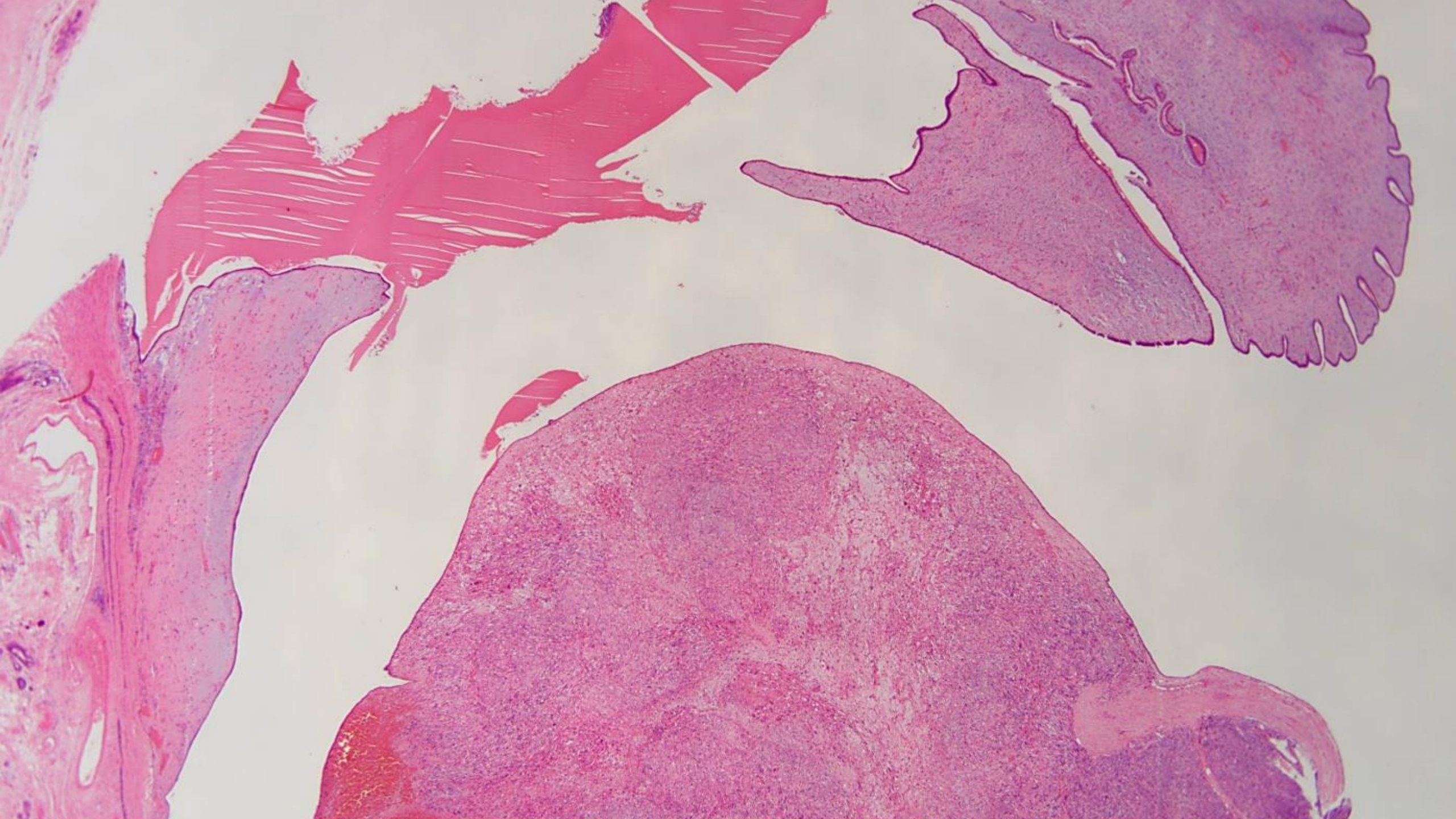


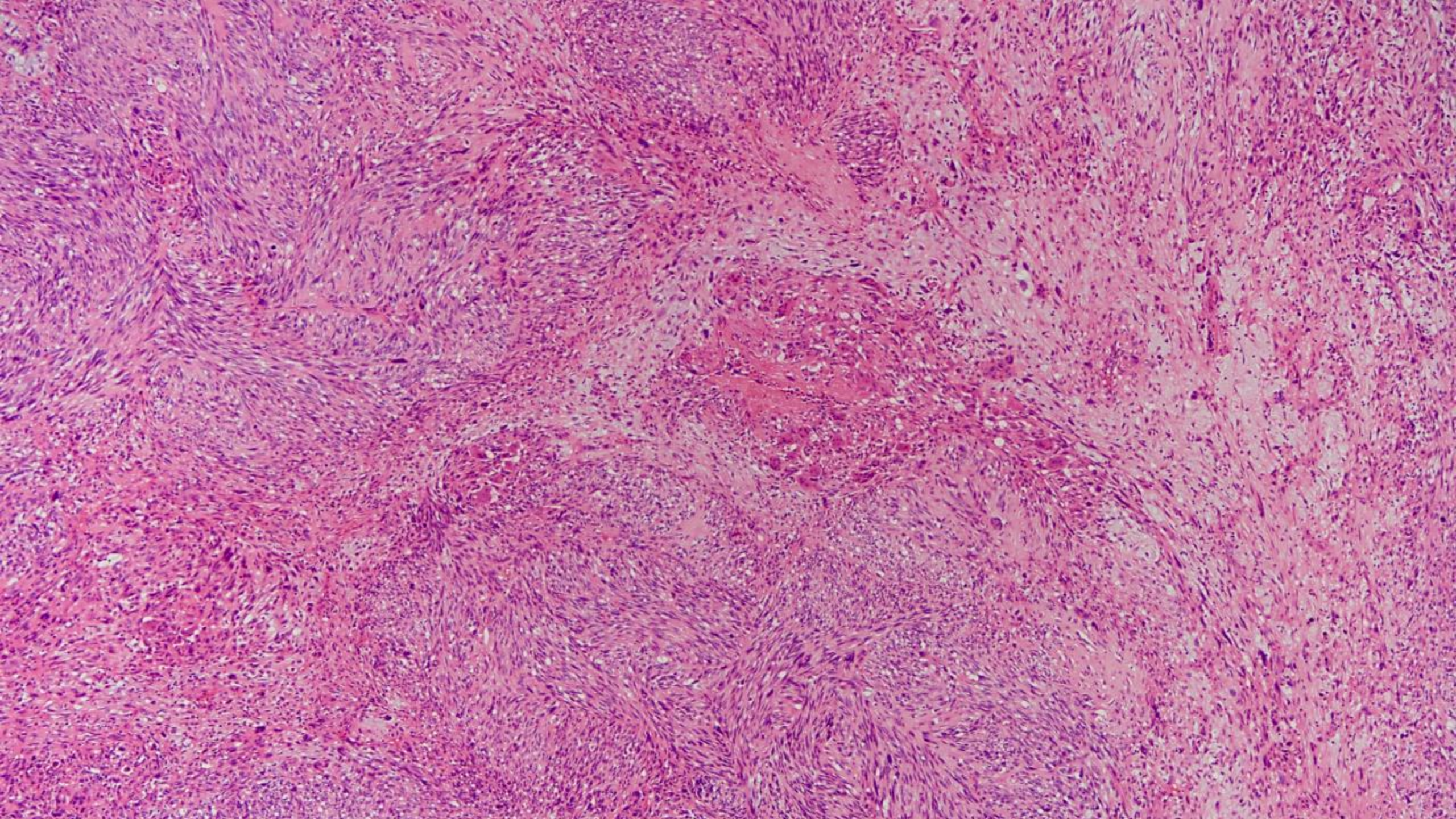


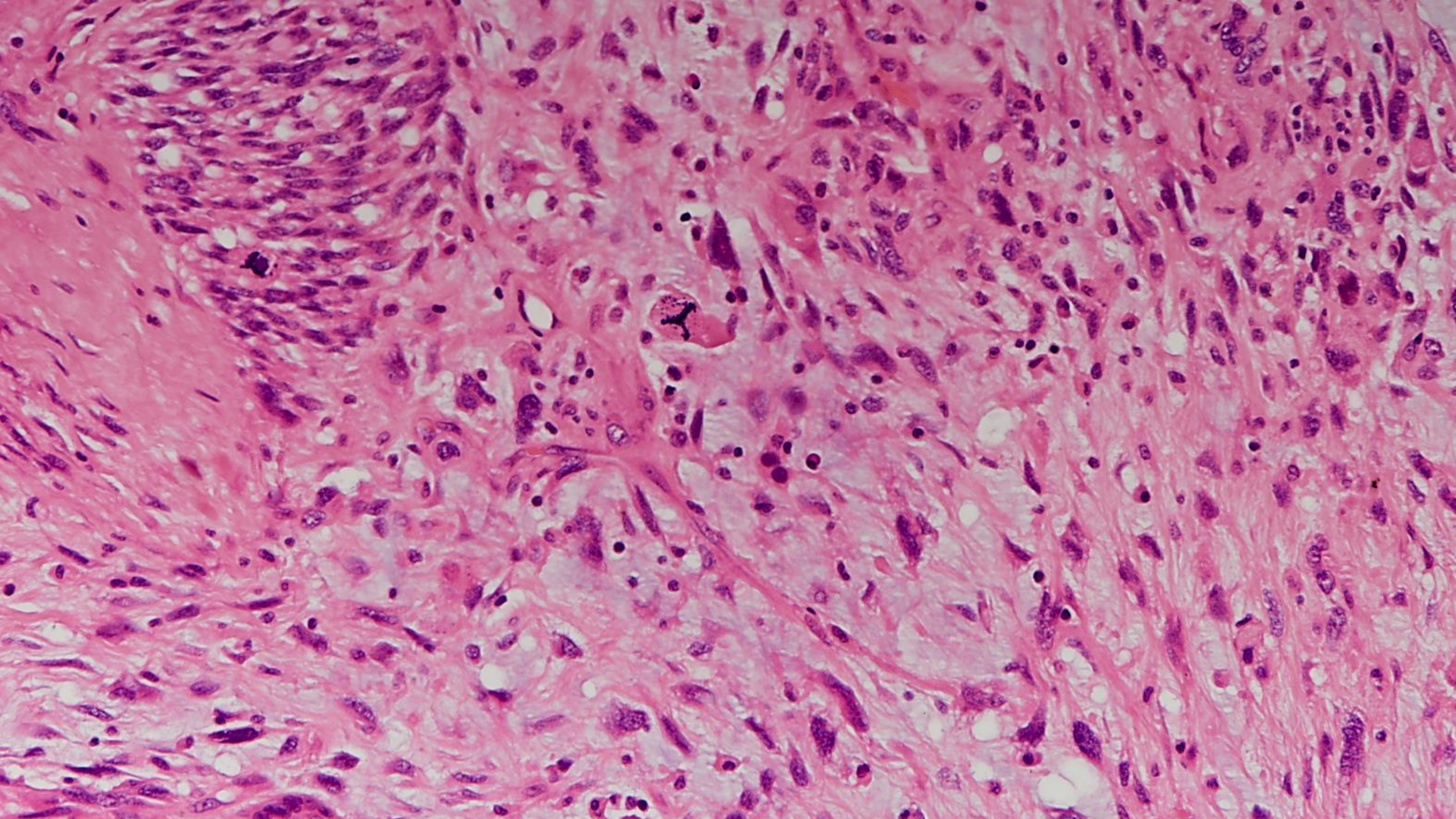


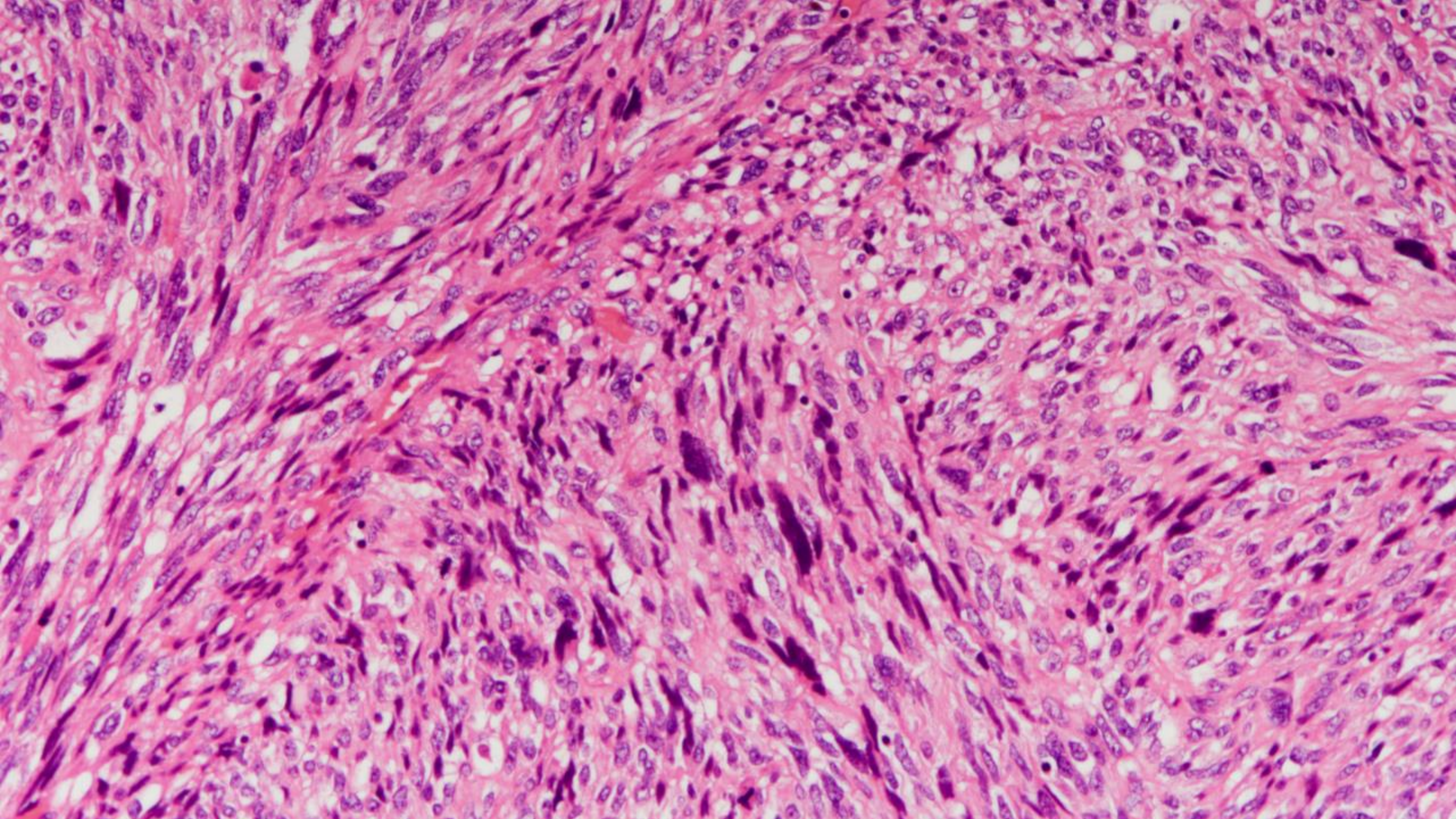








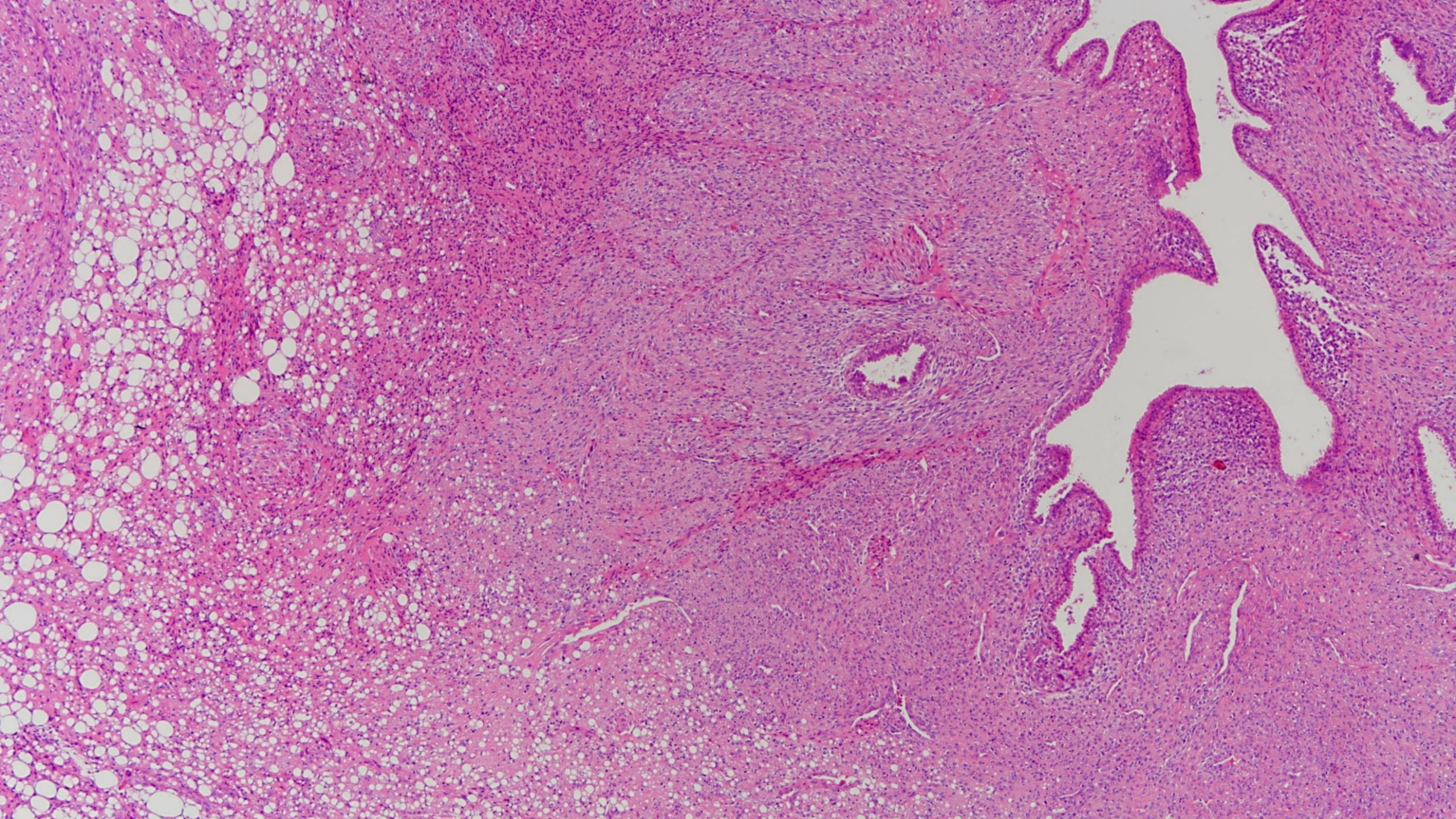


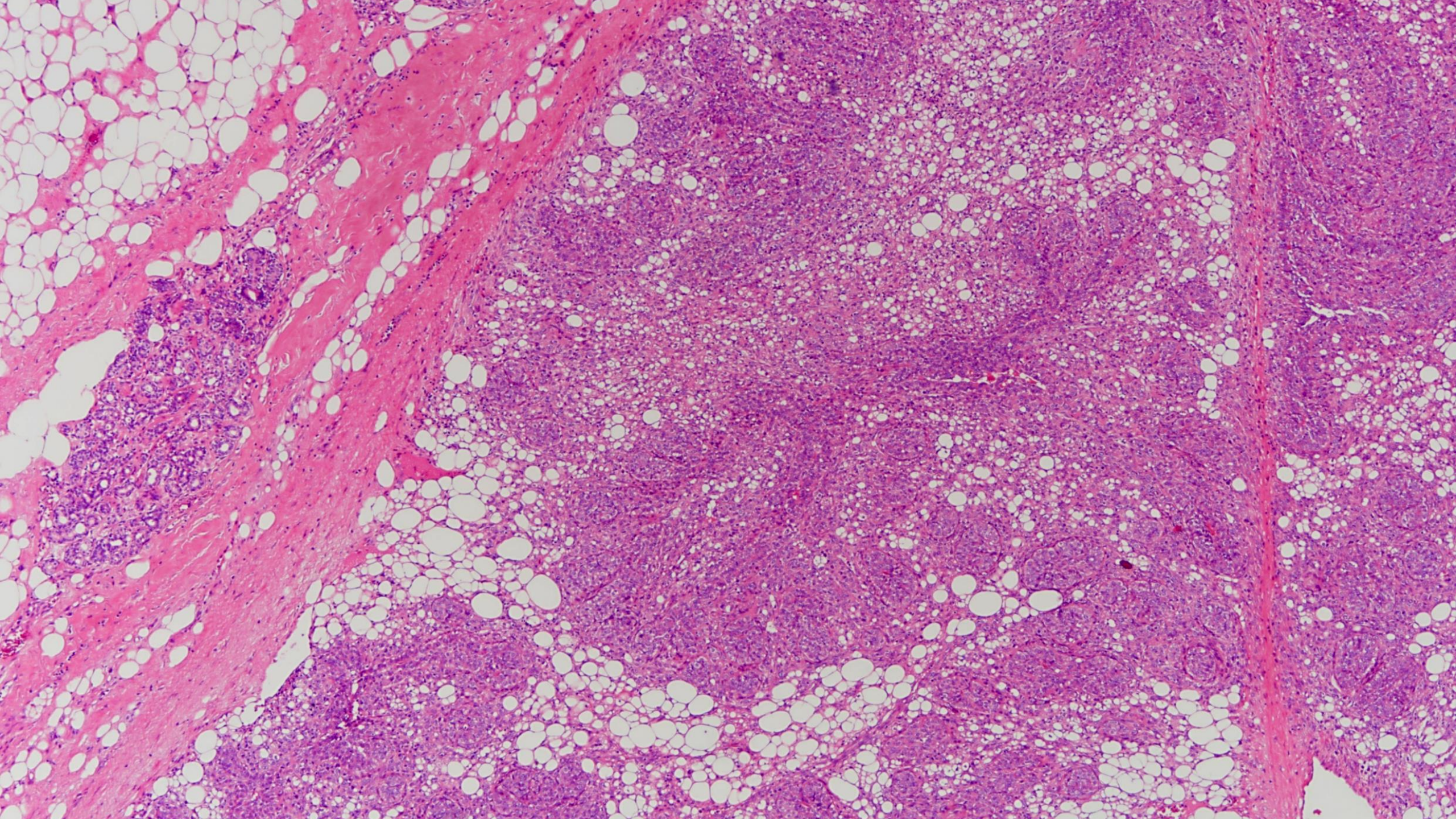


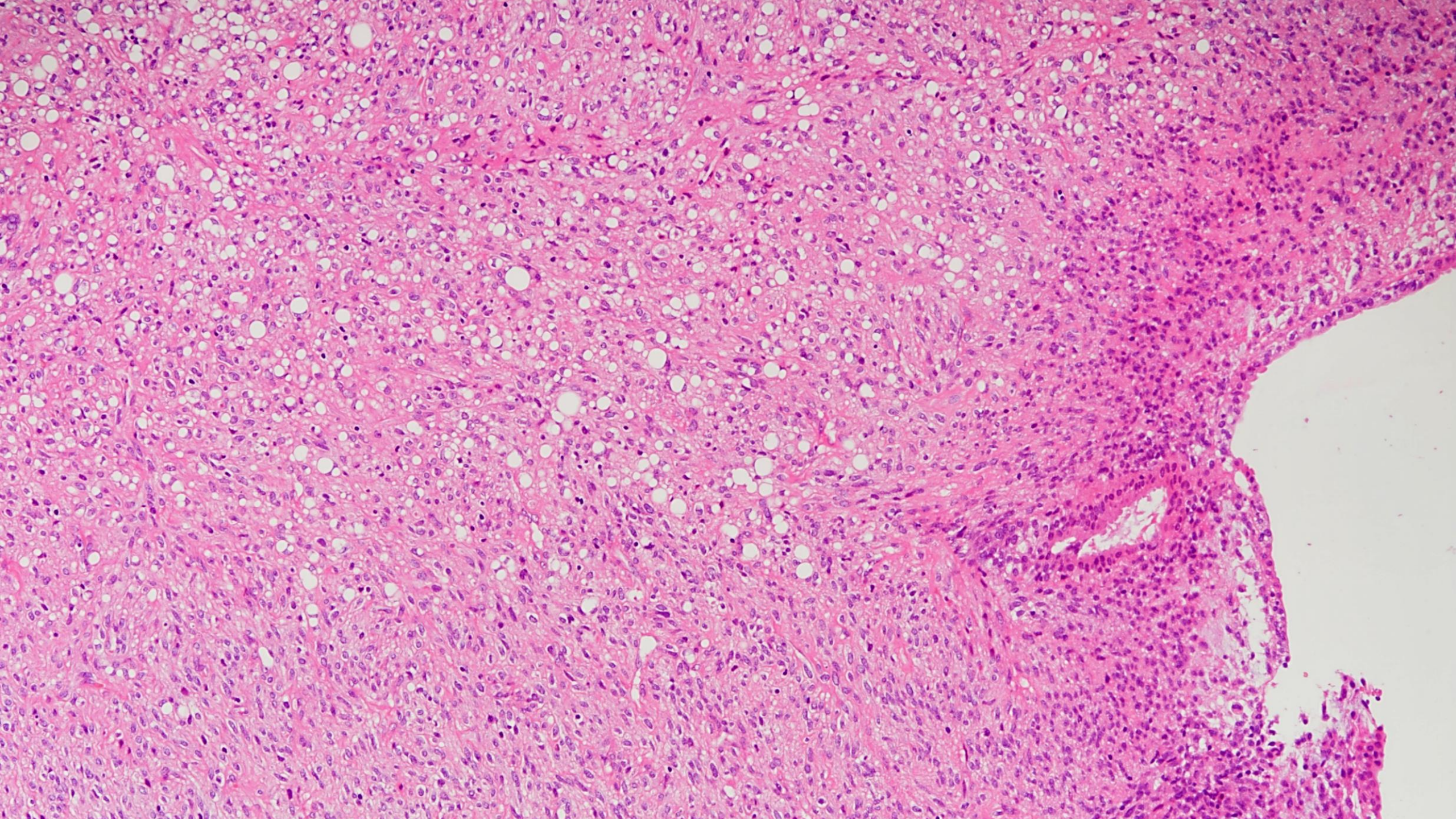
Liposarcomatous elements in PT

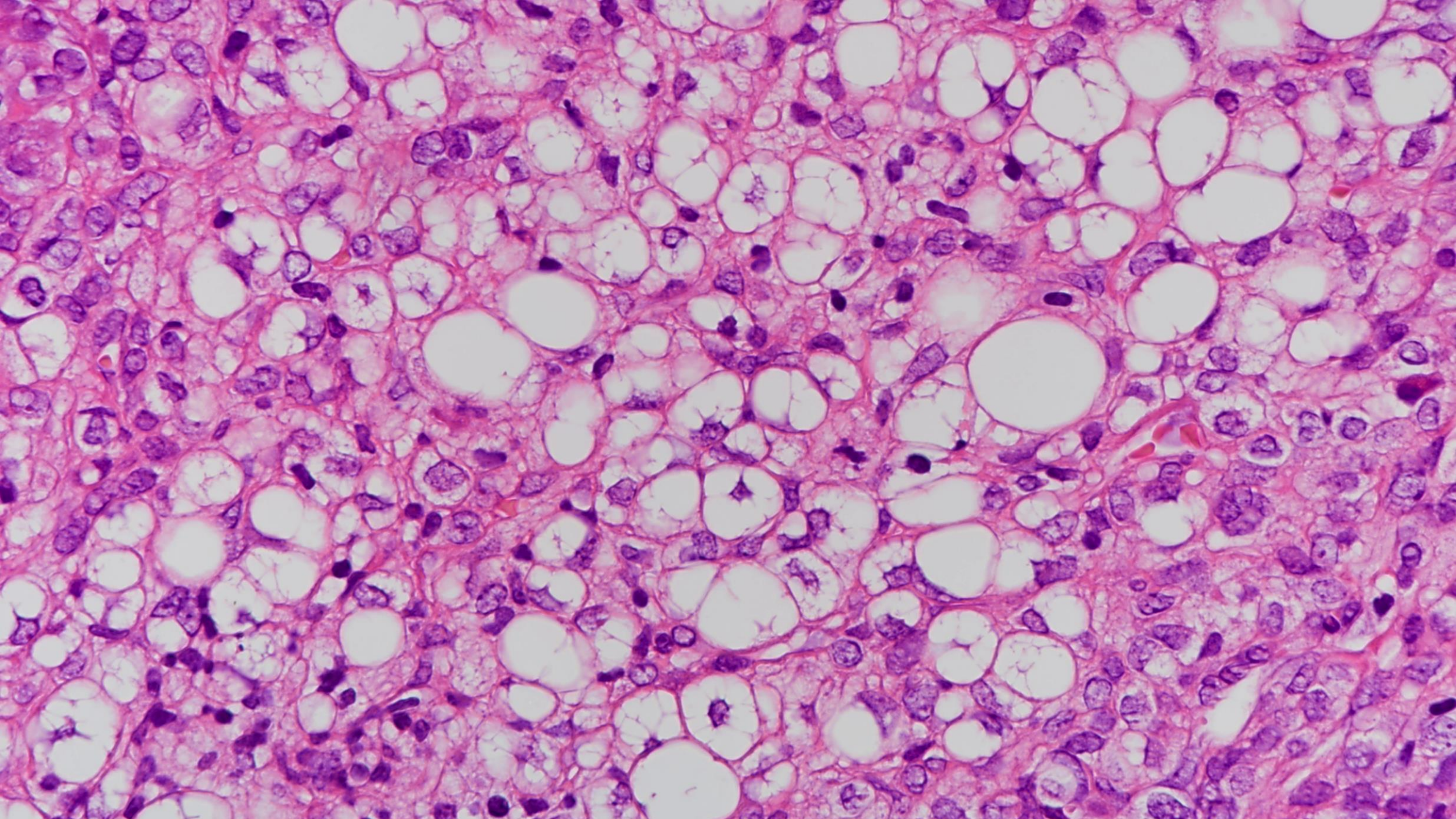
- Despite the histologic similarity, liposarcomatous differentiation in PT lacks MDM2 or CDK4 amplifications in contrast to extramammary WD liposarcoma
- Lower metastatic risk for well differentiated liposarcoma occurs as the sole heterologous element in PT
  - in 8 PT with liposarcomatous elements, 2/2 pleomorphic and 2/4 myxoid subtypes had metastases, but not in 2/2 well-differentiated subtype
- Diagnosis of malignant PT should not be made purely based on the presence of WD liposarcoma
- Pleomorphic liposarcoma in PT is rare and may have worse outcome
- Myxoid liposarcoma in PT lacks the associated characteristic molecular aberrations and its true existence needs to be confirmed

Inyang A et al 2016 Breast 22:282
Lyle P et al 2016 Histopath 68:1040
Bacchi CE et al 2016 Annals Diag Path 21:1









Differential diagnosis

- Benign PT and FA with a prominent intracanalicular growth pattern
- Malignant PT and primary and metastatic sarcomas
- Malignant PT and metaplastic carcinoma

Differential diagnosis: PT Vs FA

Benign PT

- More cellular stroma and well developed leaf like processes
- If no fronds observed, the presence of elongated branching and cleft-like ducts within cellular stroma may be clue
- Stromal cellularity is difficult to define, but should be fairly uniform or closely accompanying leafy fronds, particularly adjacent to epithelium

FA with intracanalicular pattern

- Shows leaf like processes
- Fewer and poorly formed
- No increased stromal cellularity

Differential diagnosis: PT Vs FA

- Rare mitosis could be seen in both
- Cellular FA could have mitotic activity as high as 3.57 mitoses/mm^2 (7 mitoses per HPF)
- Both with similar recurrence rate, but differences in clinical management
- In the event of uncertainty in CNB setting, a diagnosis of benign FEL is preferable
- Prompt consideration of PT and surgical excision is advised

Differential diagnosis: vs sarcoma

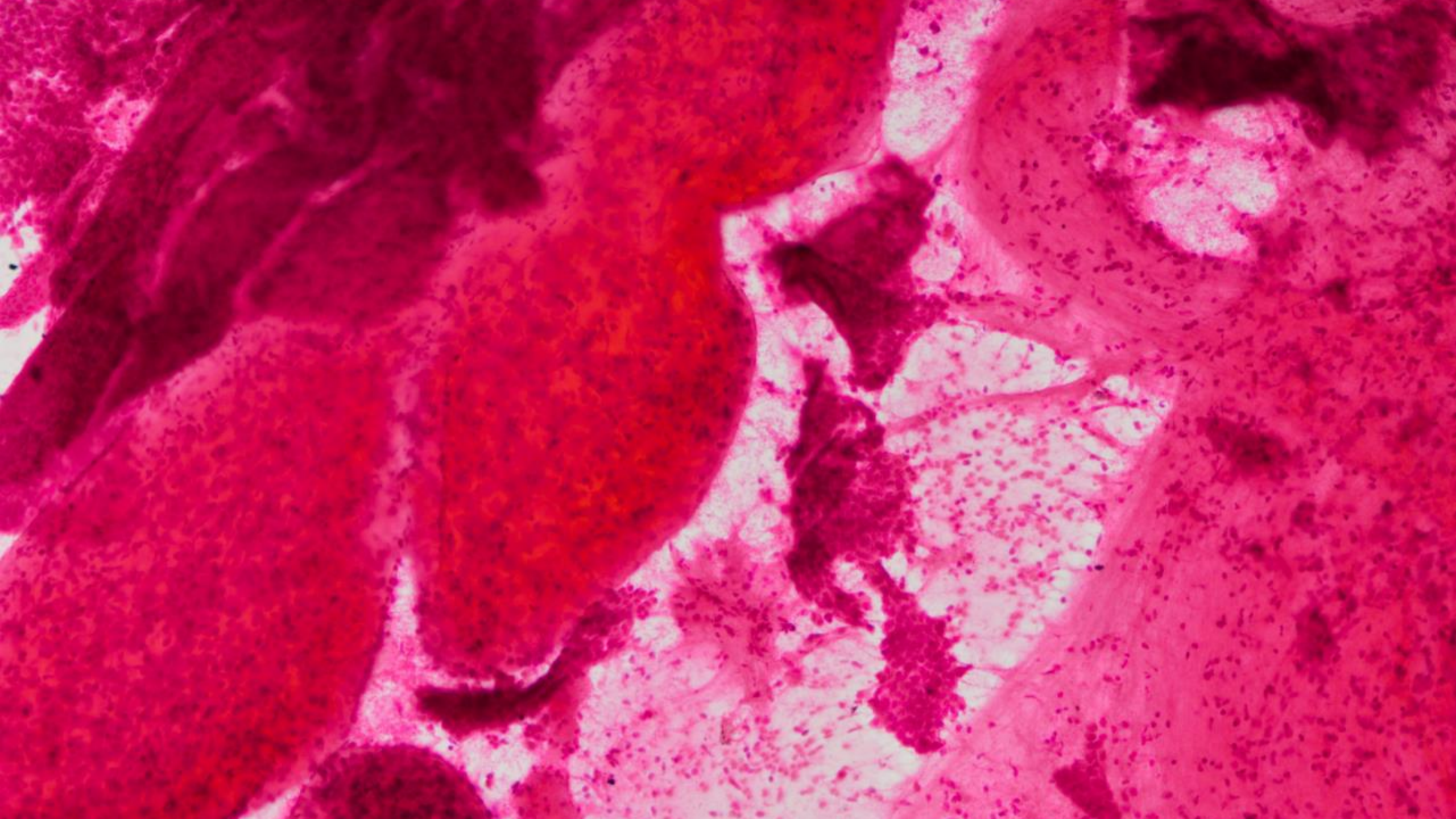
- PT diagnosis depends on residual epithelial structure by extensive sampling
- Knowledge of clinical history may aid in the distinction of primary vs metastatic sarcoma
- Clinical outcomes of primary breast sarcoma and malignant PT appear to be similar

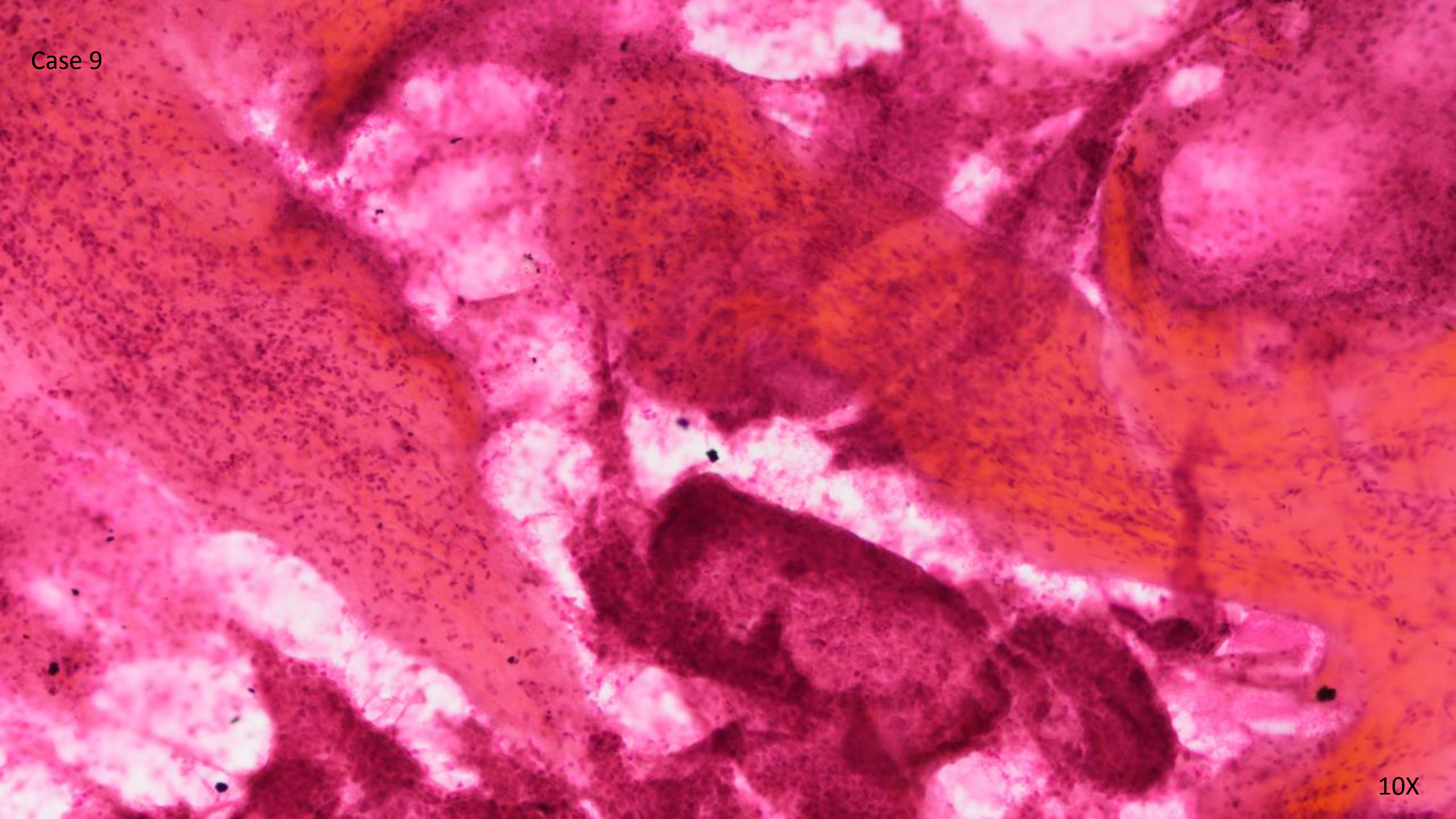
Differential diagnosis: vs metaplastic CA

- Malignant epithelial components and IHC demonstration (cytokeratin/ p63 staining) of diffuse epithelial differentiation of metaplastic carcinoma
- Caution should be taken for very focal keratin expression and p63 positivity in limited samples
- Distinct genetic alterations

PT Cytology

- Contains cellular stromal fragments and sheets of benign epithelial cells with admixed myoepithelial cells
- Features overlap with FA
- Diagnostic clues for PT
  - presence of large cellular stromal fragments
  - moderate to large numbers of dissociated stromal cells admixed with fibromyxoid material
  - a lower epithelial-to-stromal ratio
  - rounded epithelial fragments with mild atypia and columnar cells
- Malignant PT may show a higher degree of stromal nuclear atypia, mitotic activity, more atypical single cells and sacromatous elements
  - cytologically PT grading remains difficult

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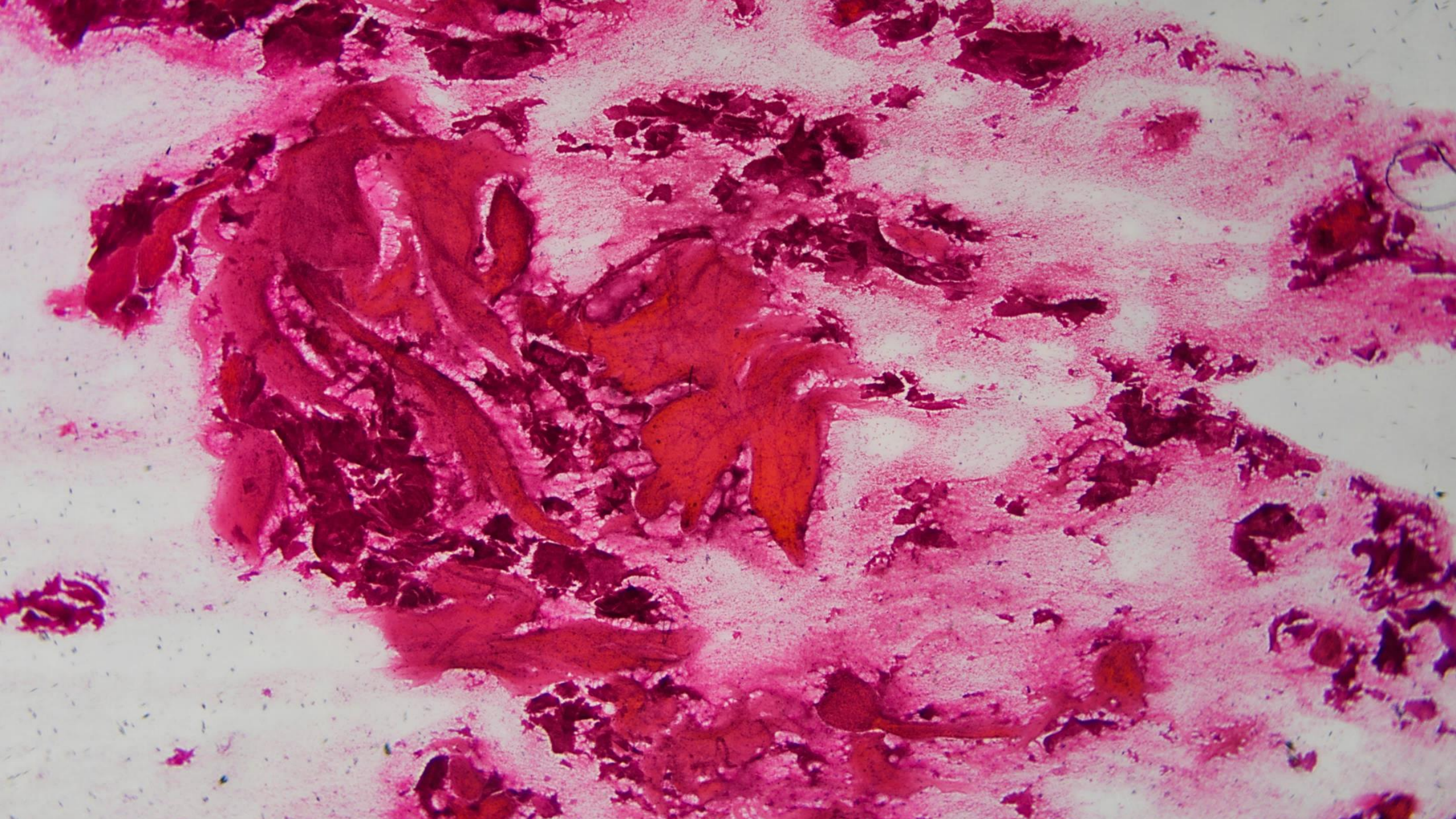
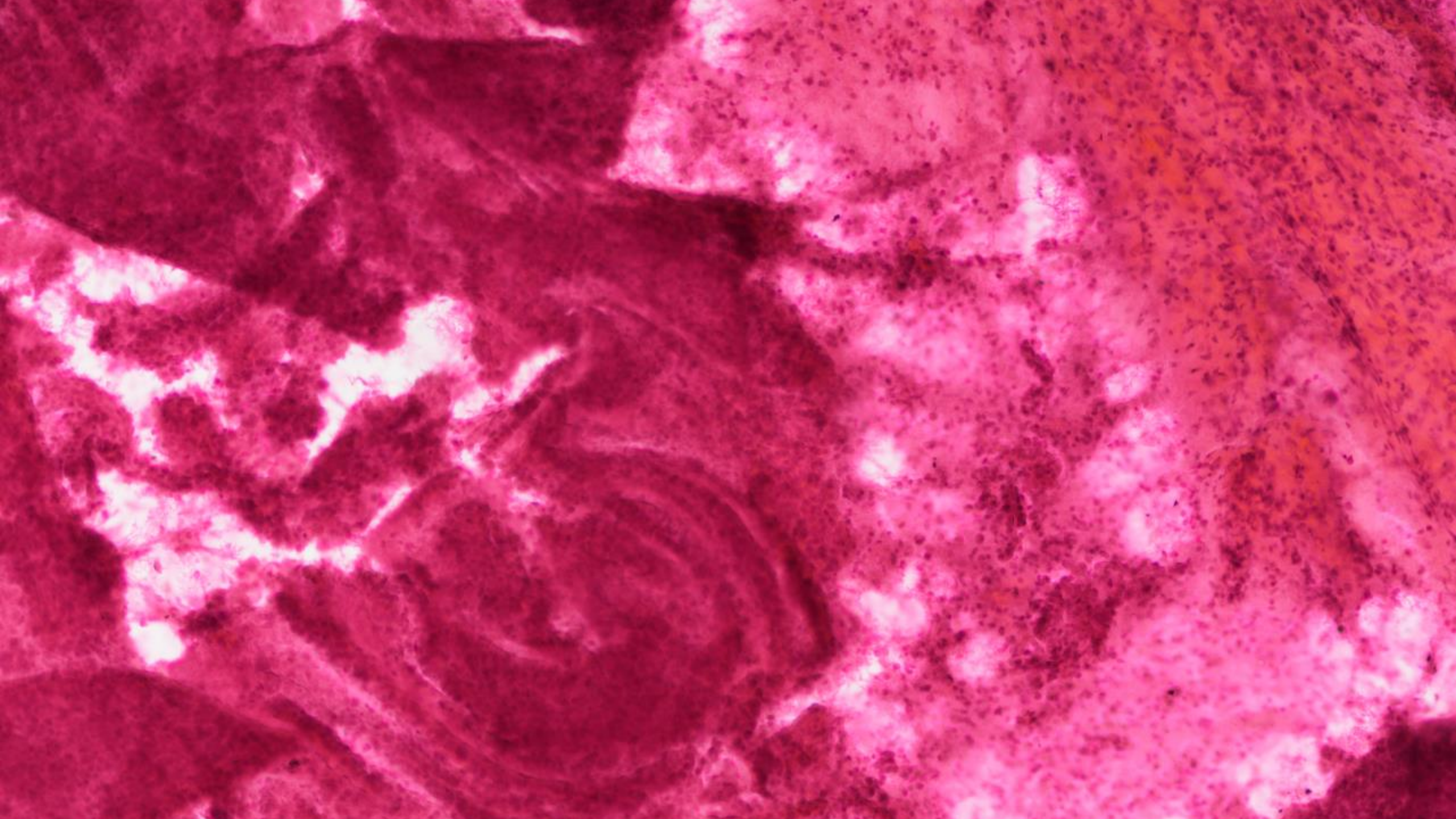




Essential and desirable diagnostic criteria: PT

- Essential criteria
  - stromal fronds and hypercellularity
  - dominant intracanalicular growth pattern with stromal fronds capped by luminal/myoepithelial cell layers
- Essential for malignant diagnosis:
  - high power field for mitotic count should be defined
  - degree of stromal cellularity
  - stromal atypia
  - stromal overgrowth : absence of epithelial elements in at least one LPF
  - Infiltrative tumor border
  - malignant heterologous elements (excludes WD liposarcoma)

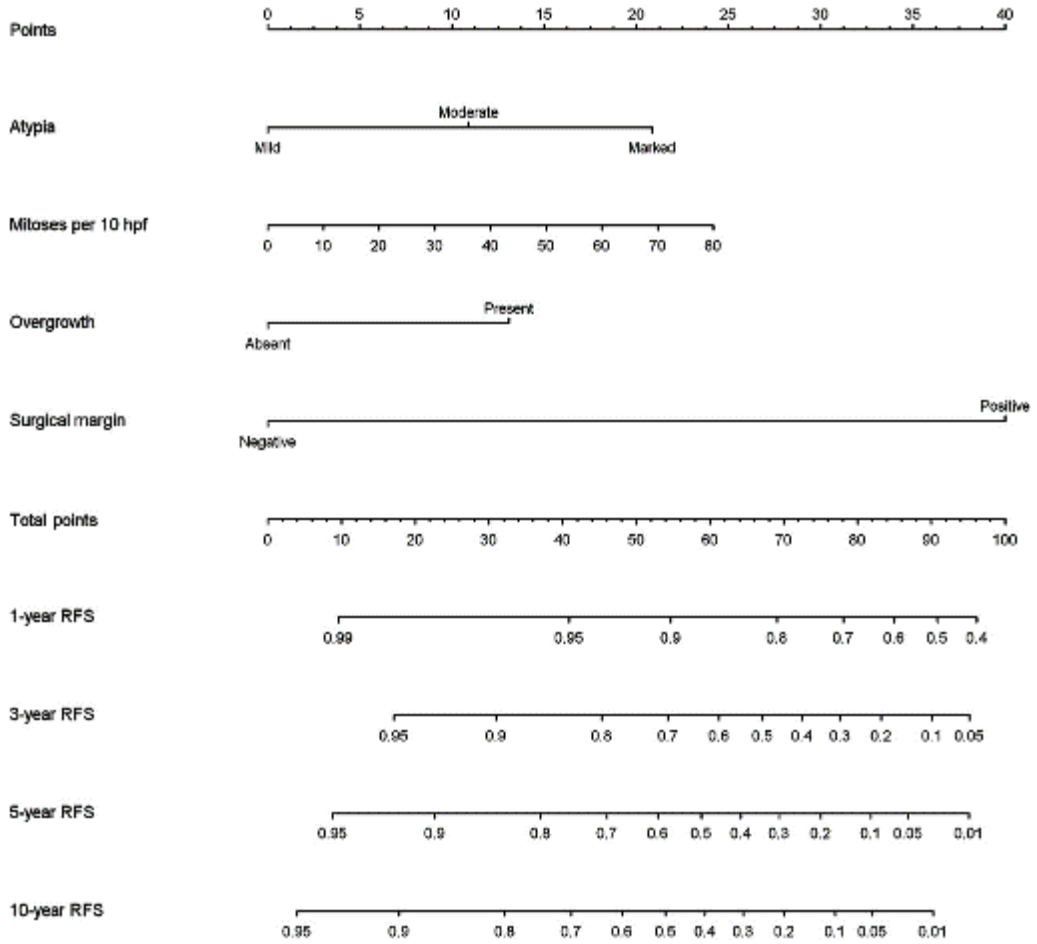
Prognosis

- Most PT are benign
- Local recurrence usually occurs within 2-3 years of diagnosis
  - overall rate : 21%
  - benign, borderline, malignant : 10-17%, 14-25%, 23-30%
  - recurrences could be of similar or higher grade (31.5%) than the original tumor
- Axillary nodal metastases rare
- Distant metastases (around 2%), exclusively in malignant PT
  - usually occur within 5-8 years of diagnosis
  - metastases reported in nearly all internal organs, esp lung and skeleton
  - most metastases consist of stromal element only
- Margin status at excision appears to be the most reliable predictor of recurrence, except for benign tumors

Prognosis

- PT grading might correlate with outcome, but the different parameters on grading may not have equal impact on outcome

- SGH nomogram
  - predicts recurrence free survival using : stromal atypia, stromal mitotic count, stromal overgrowth and surgical margin status (AMOS)
  - border and cellularity are not included
  - validated in several independent studies
  - local vs distant recurrences

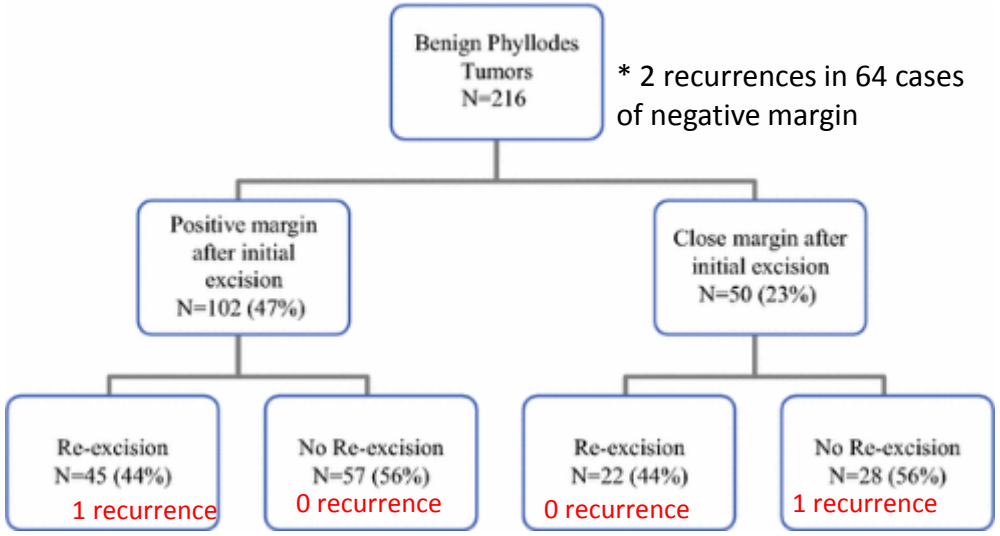


Tan PH et al 2012 J Clin Pathol 65:69
Chng T et al 2018 J Clin Pathol 71:125

Margin status in benign PT recurrence

- 2 recent studies : margin status may not be relevant for benign PTs

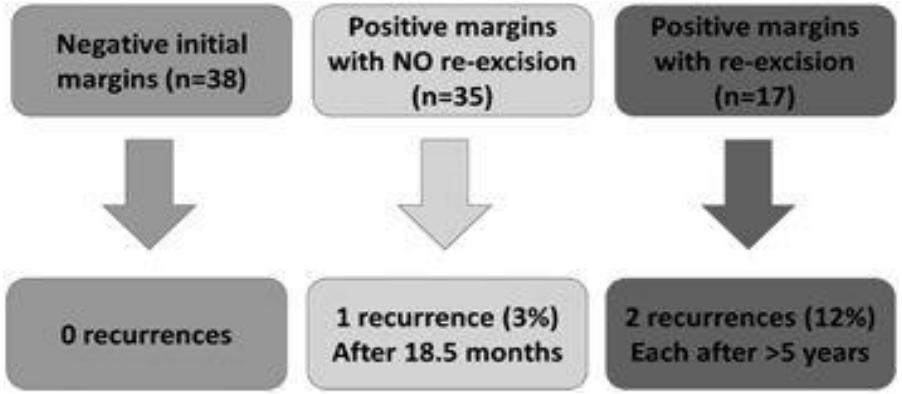
  - Negative margin: >2mm from ink
  - Close margin: ≤2mm form ink
  - Positive margin: tumor on ink
  - all patients with local excision
  - Median FU 35.5 months



* 2 recurrences in 64 cases of negative margin

Moo T et al 2017 Ann Surg Oncol 24:3088

  - Positive margin: tumor on ink
  - Low grade FEL or benign PT (52 benign PT, 19 borderline and 19 FA with phyllodal features)
  - One borderline PT with mastectomy, others either excisional biopsy or lumpectomy
  - Median FU 40.5 months



Cowan M et al 2016 Mod Pathol 29:259

Heterologous element in PT

- Heterologous elements such as metaplastic cartilage, bone, or exceptionally skeletal muscle may be present in malignant PT
- PT are classified as malignant in the presence of malignant heterologous elements even when other features are absent
- The presence of heterologous element together with large tumor size predicted distance metastasis in malignant PTs

Clinicopathological parameters	HR	95% CI	p-value
Age			
≥ mean age versus <mean age	0.477	0.164 to 1.385	0.173
Tumour size			
≥ mean size versus <mean size	0.731	0.235 to 2.270	0.588
Large tumours harbouring malignant heterologous elements			
yes versus no	2.434	1.041 to 12.517	0.049

Koh V et al 2018 Virchow Archiv 472:615

Staging

- Not applicable for FA
- Malignant PT may be staged as sarcomas using the 8th UICC TNM classification