Is it a fibroadenoma or a benign phyllodes tumour?

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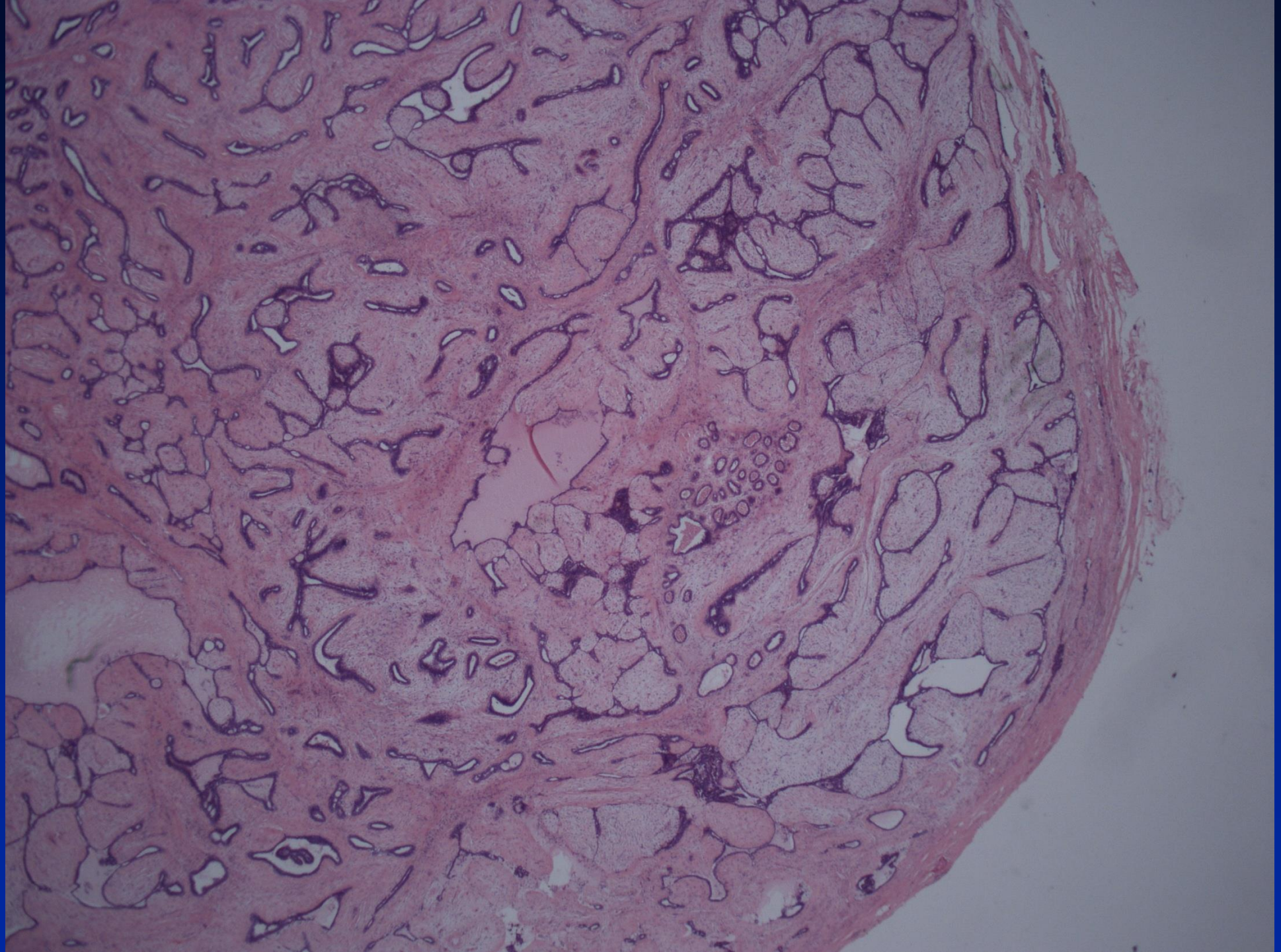
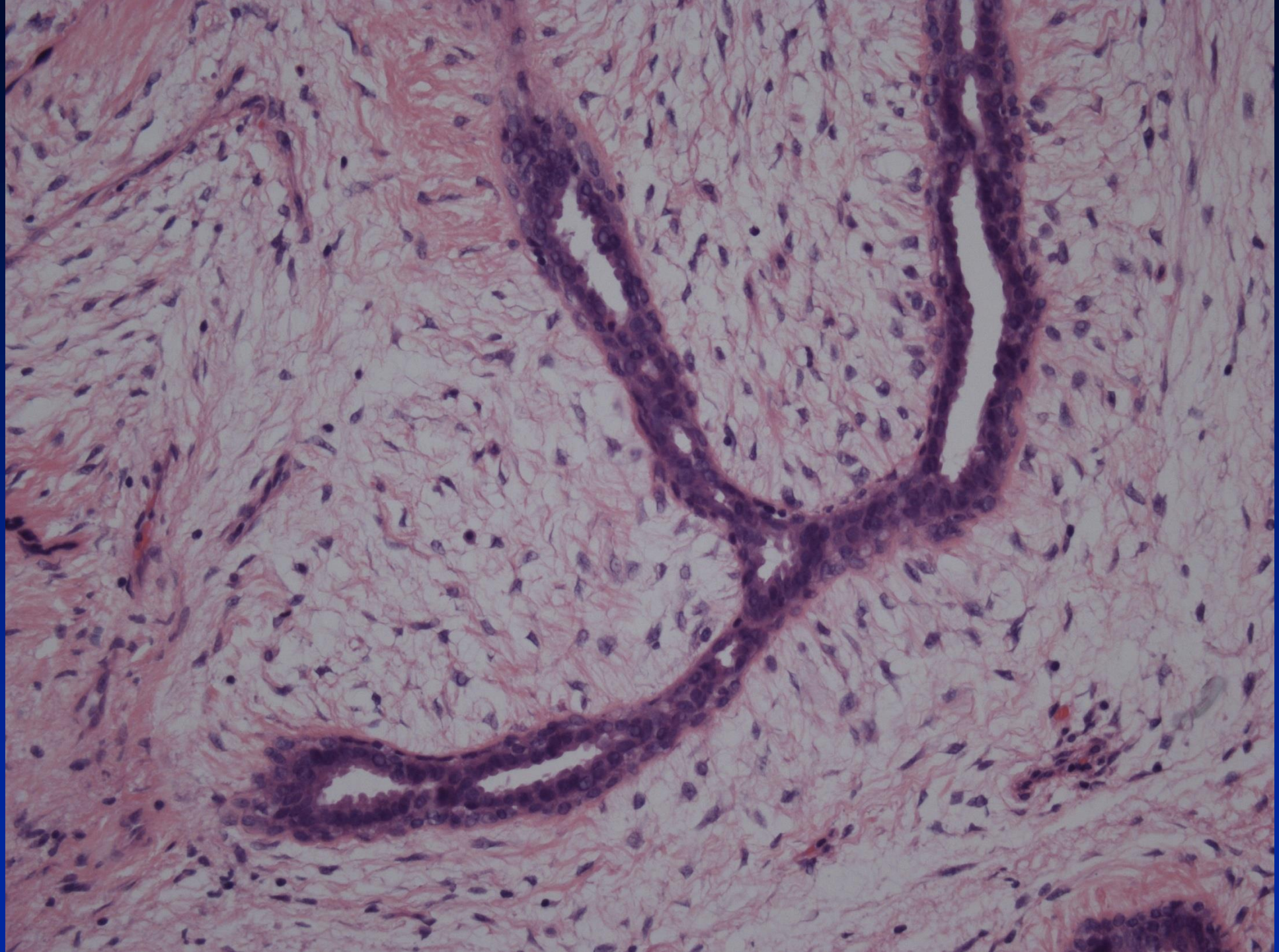
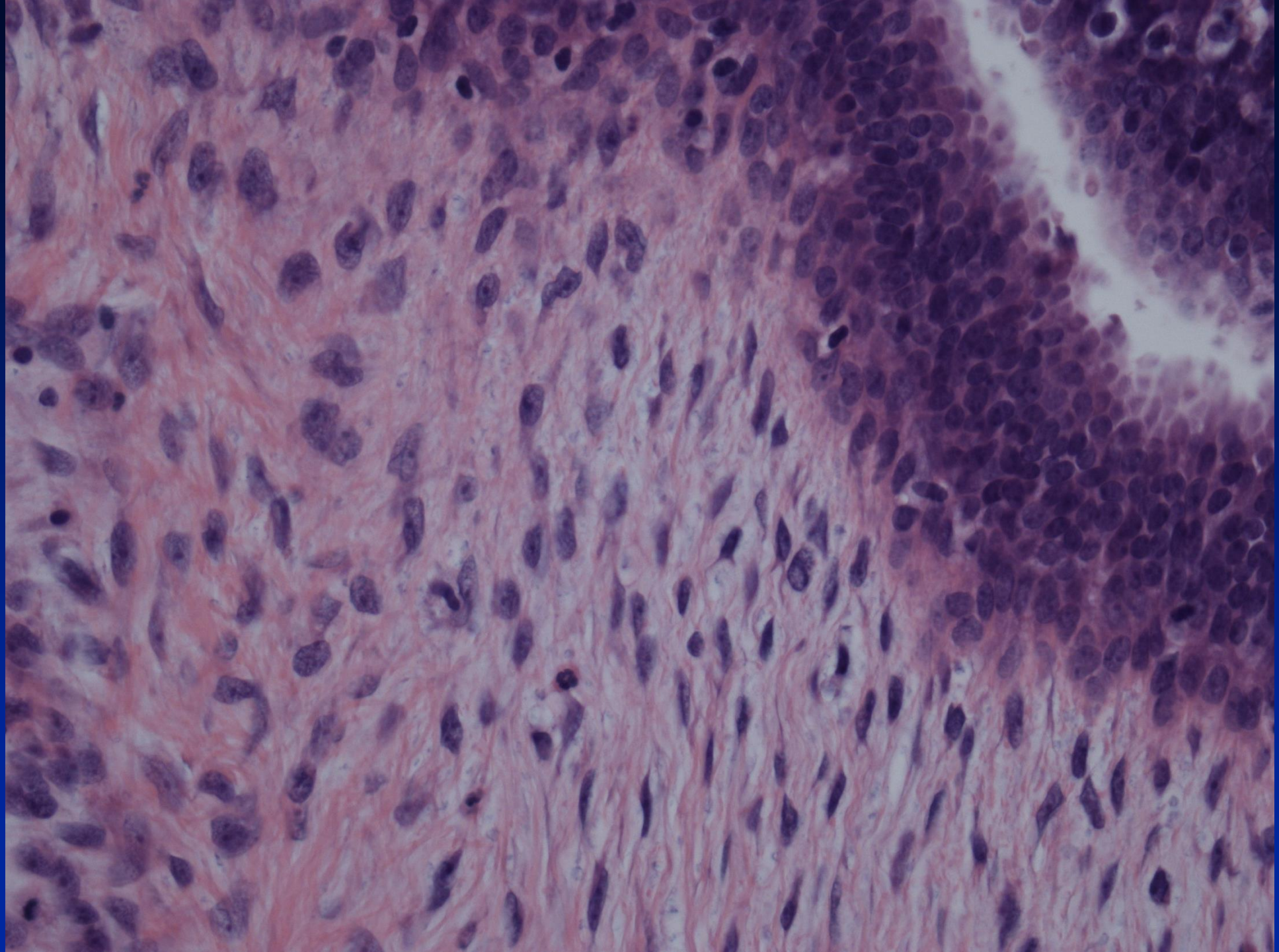






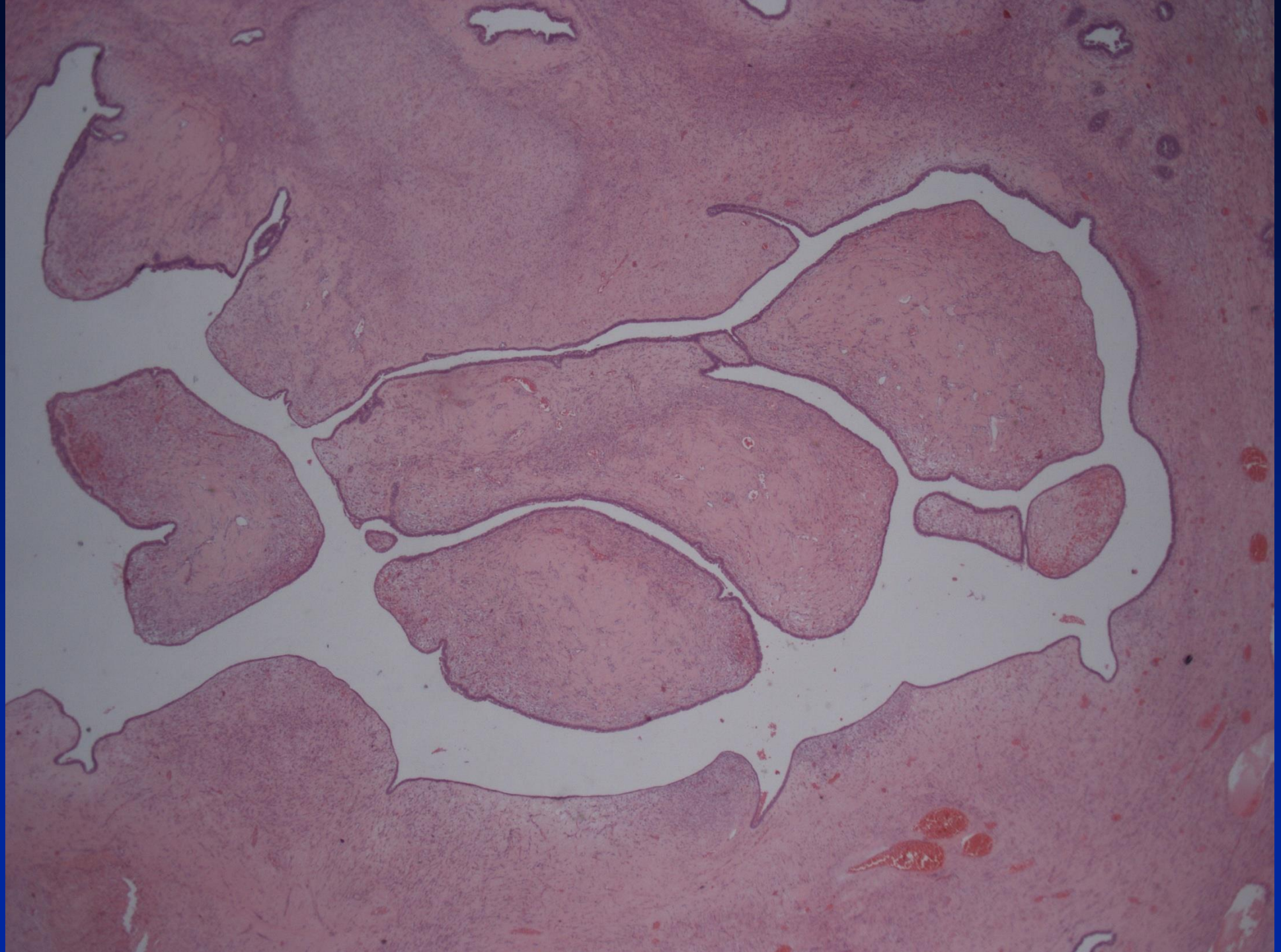
Phyllodes tumour v fibroadenoma

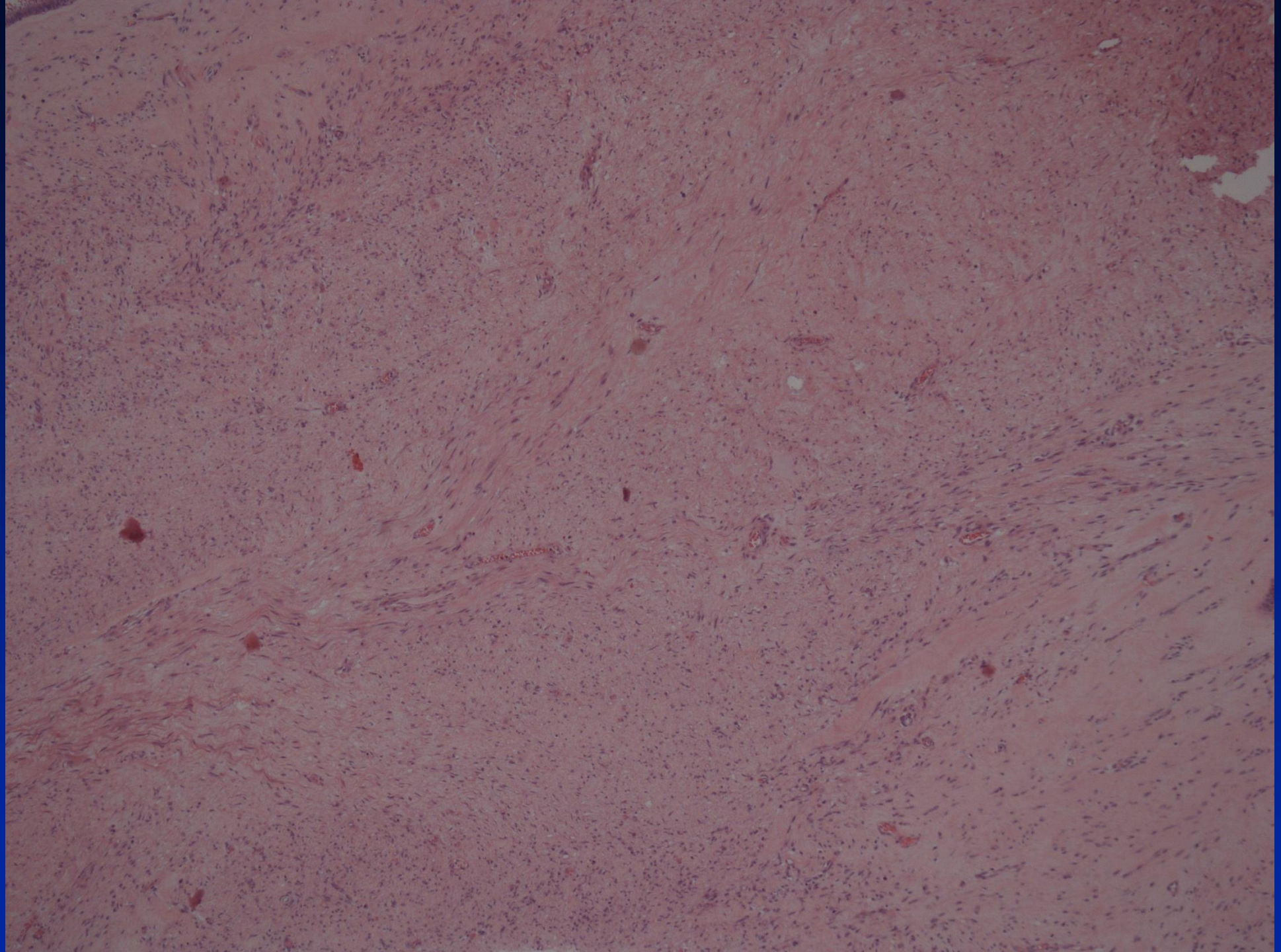
Stroma

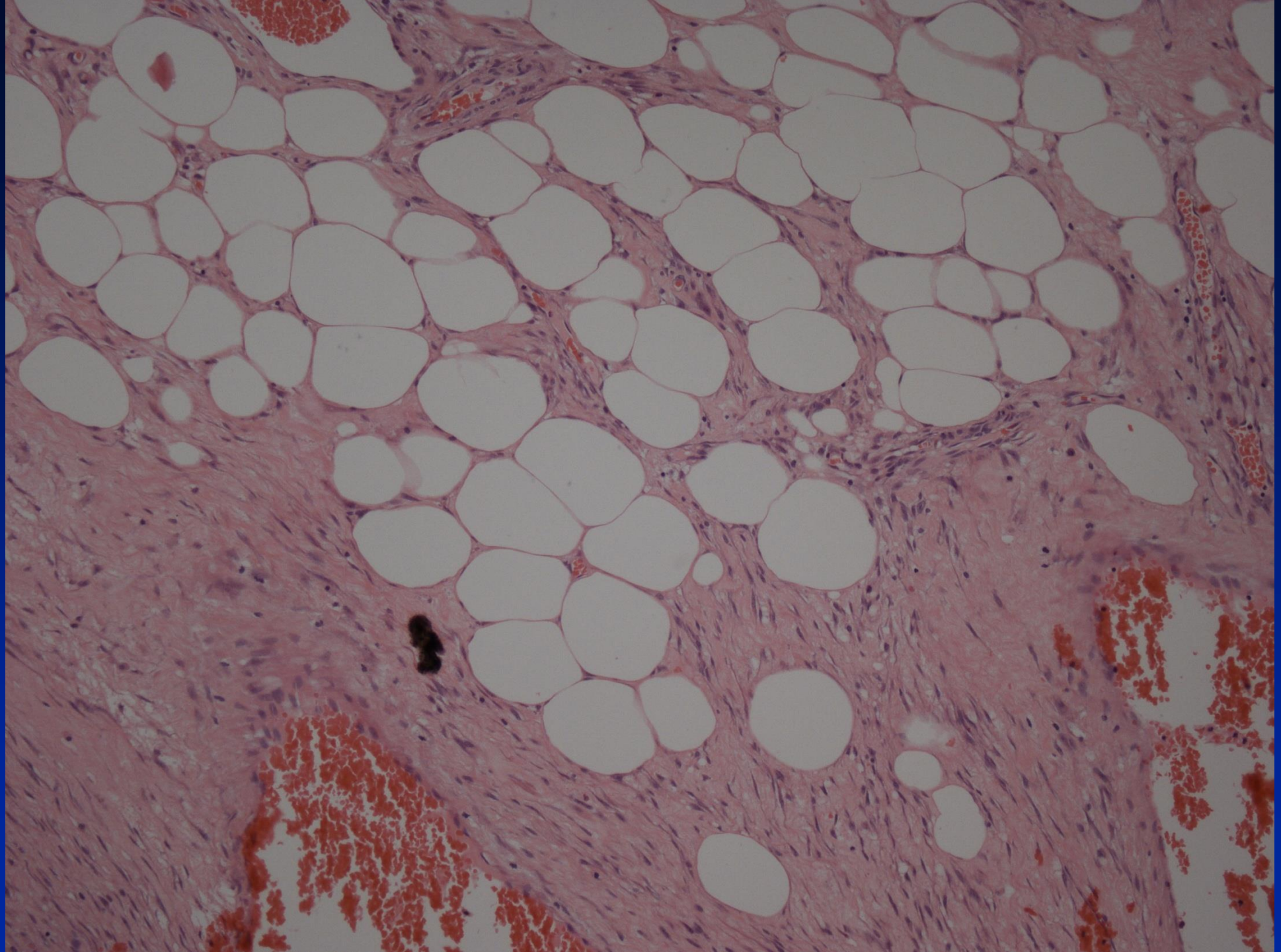
- Cellularity
- Nuclear pleomorphism
- Stromal overgrowth (x5 field with no glands)
- Mitotic rate

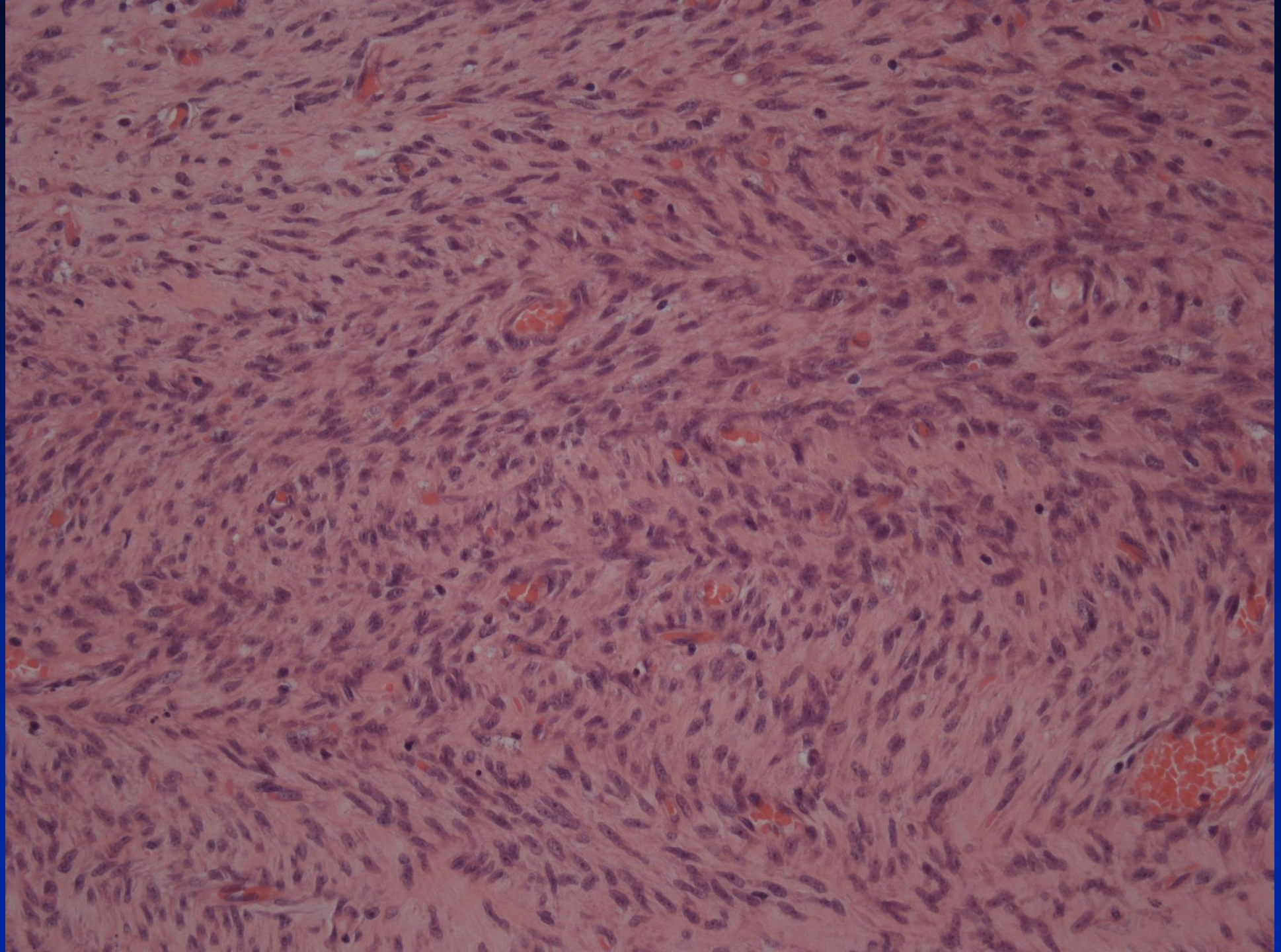
Leaf-like architecture

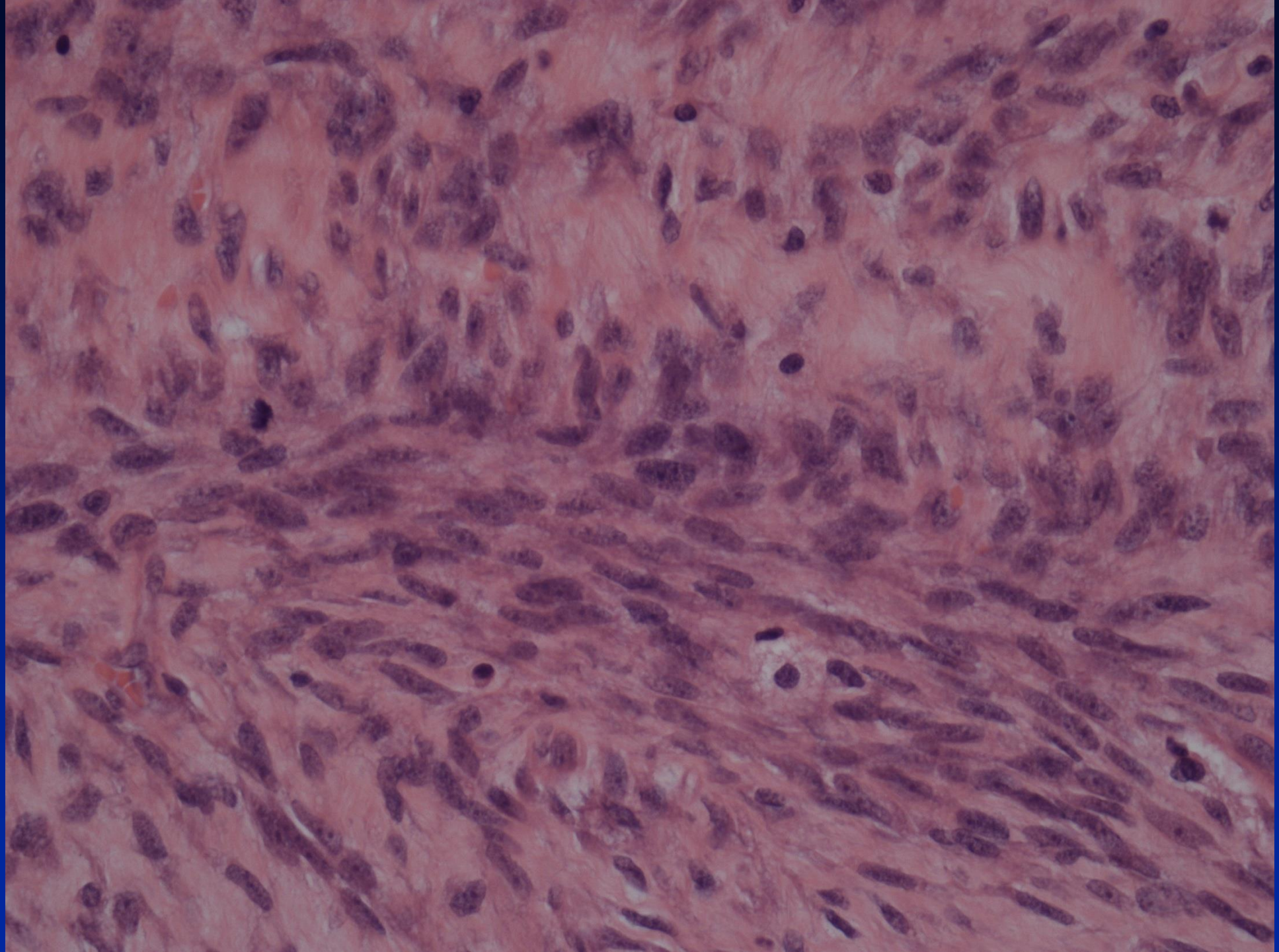
Irregular edge











Fibroepithelial lesion

Partly infiltrative edge

Leaf-like architecture

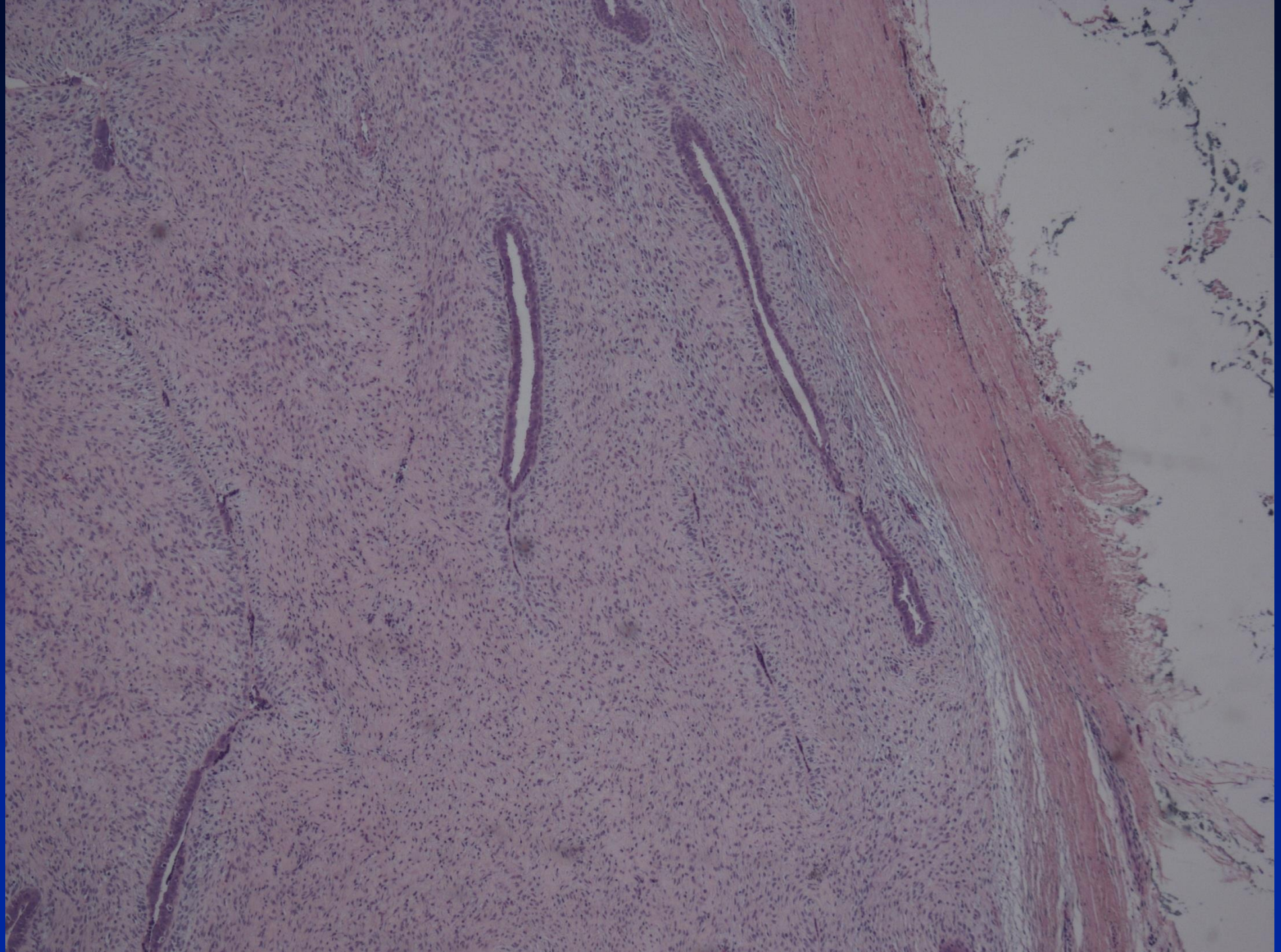
A little stromal overgrowth

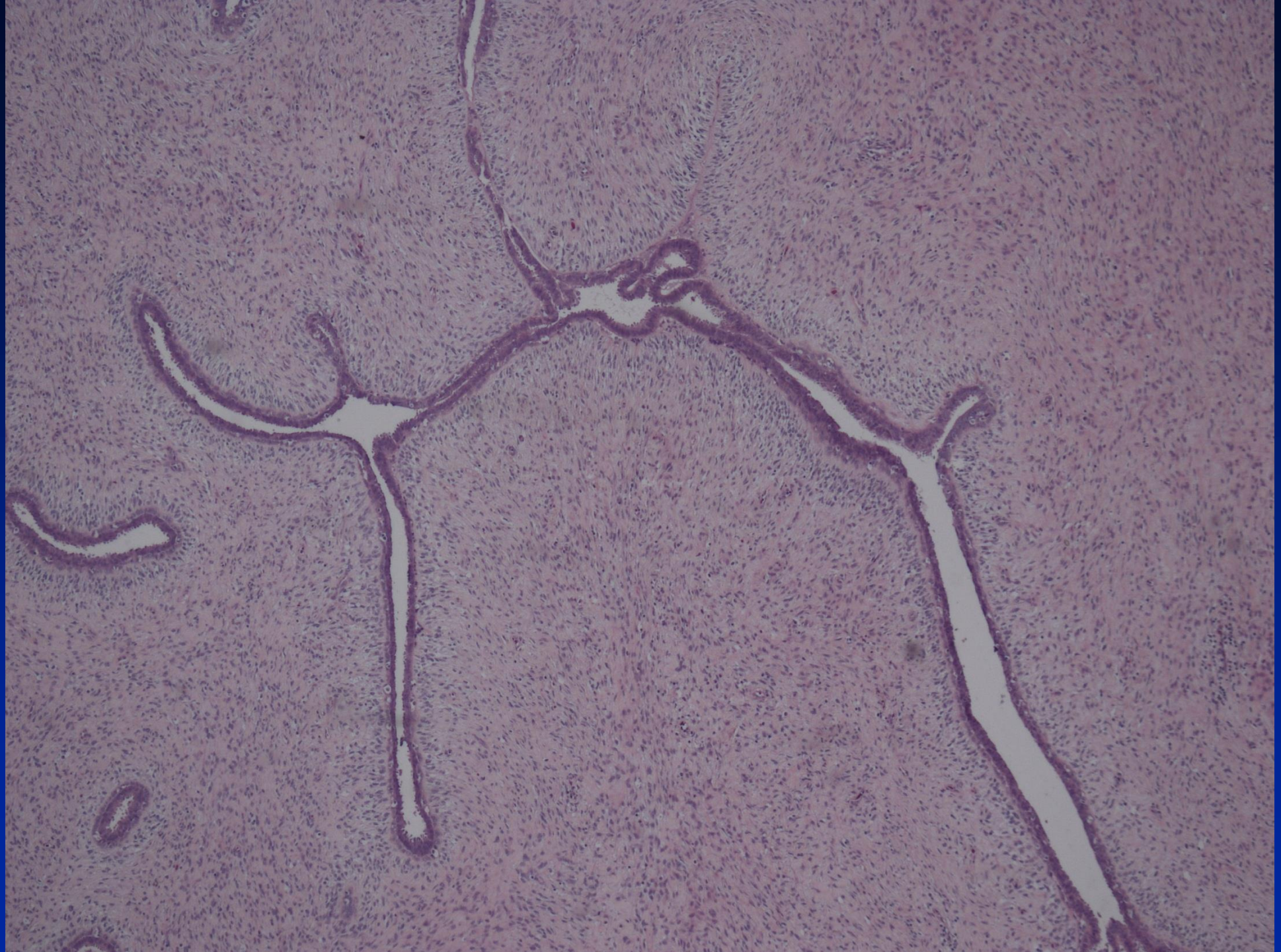
Moderate/marked increase in stromal cellularity

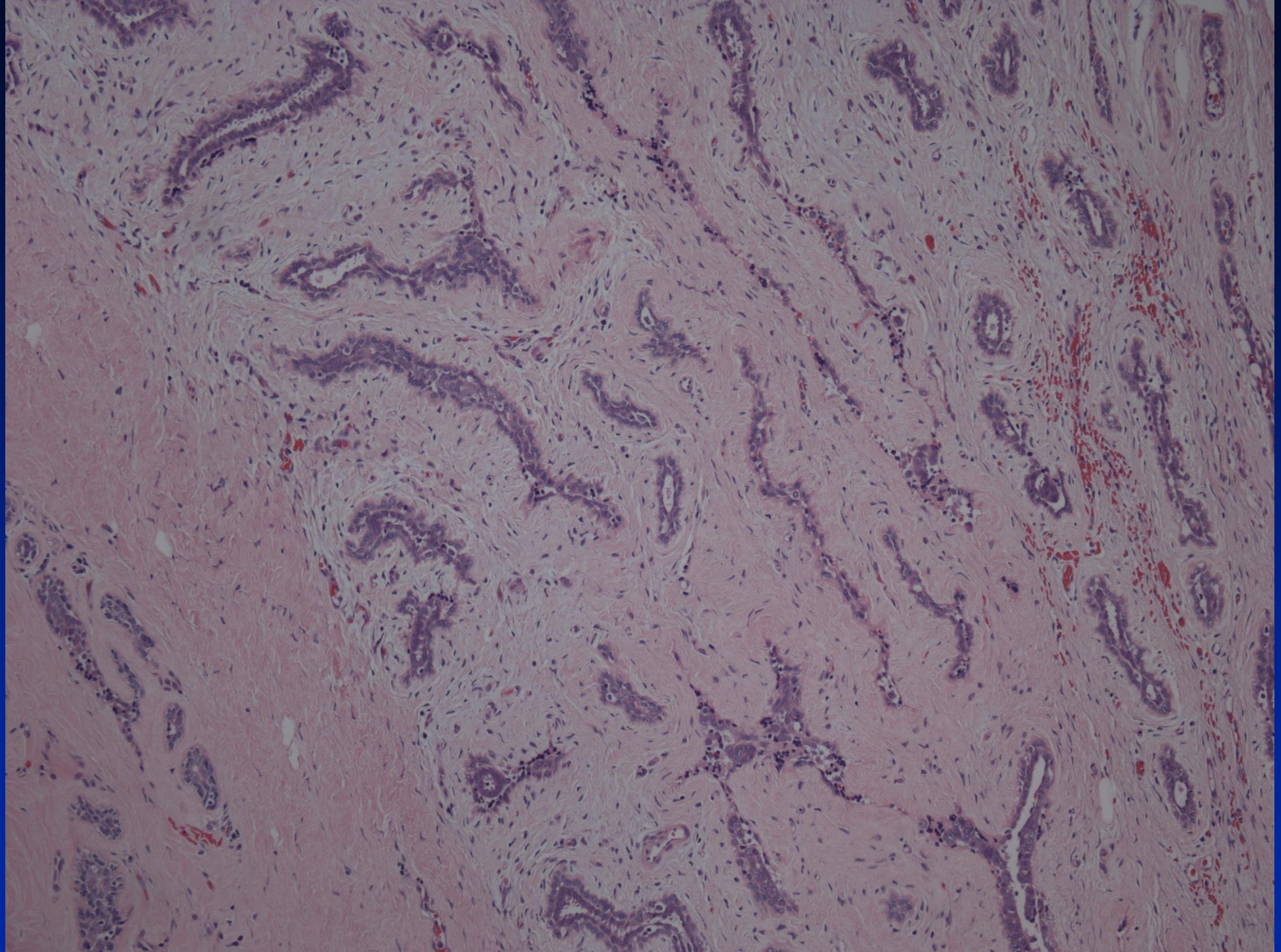
Mild/moderate stromal atypia

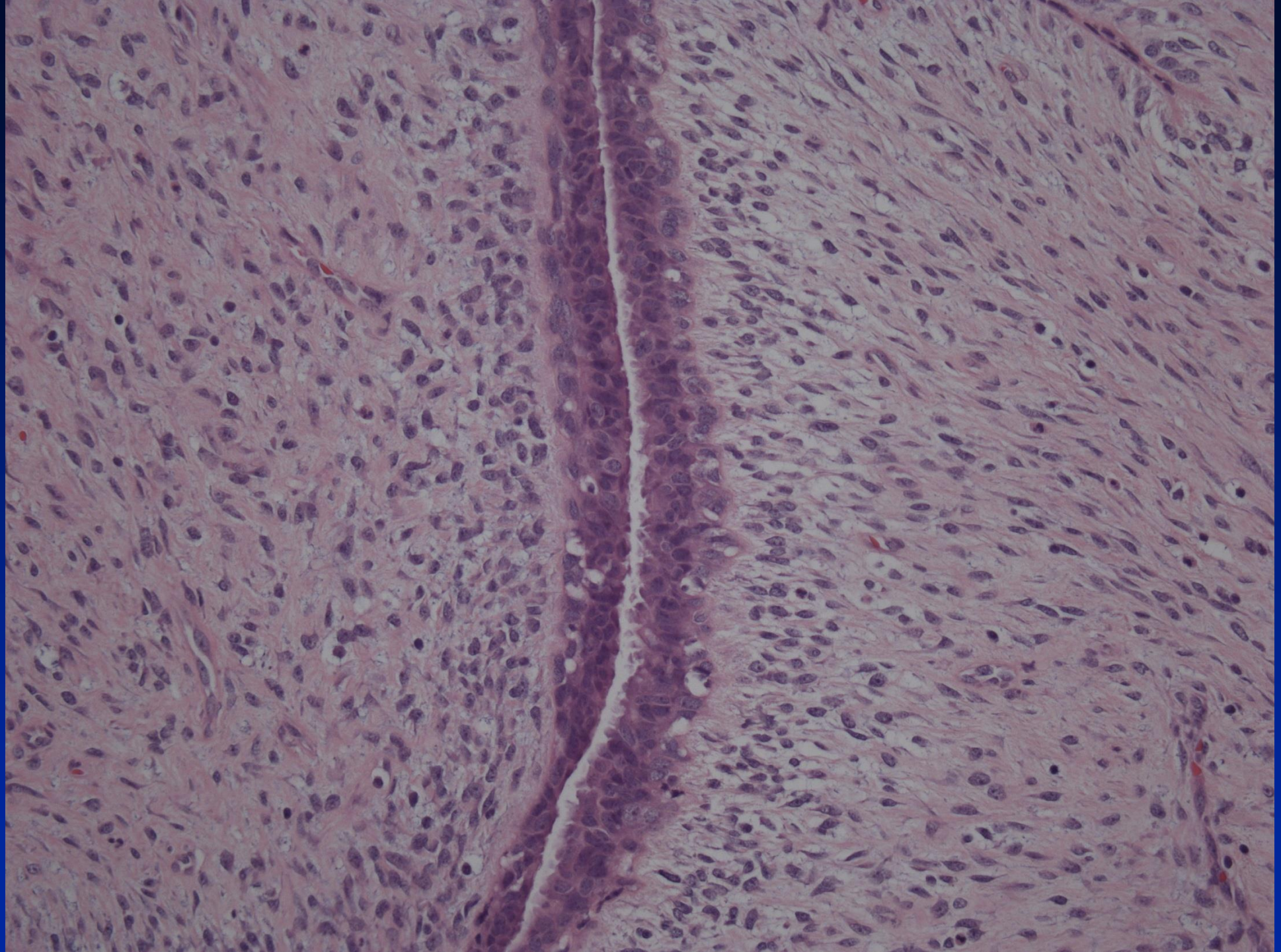
12 mitoses/10 high power fields

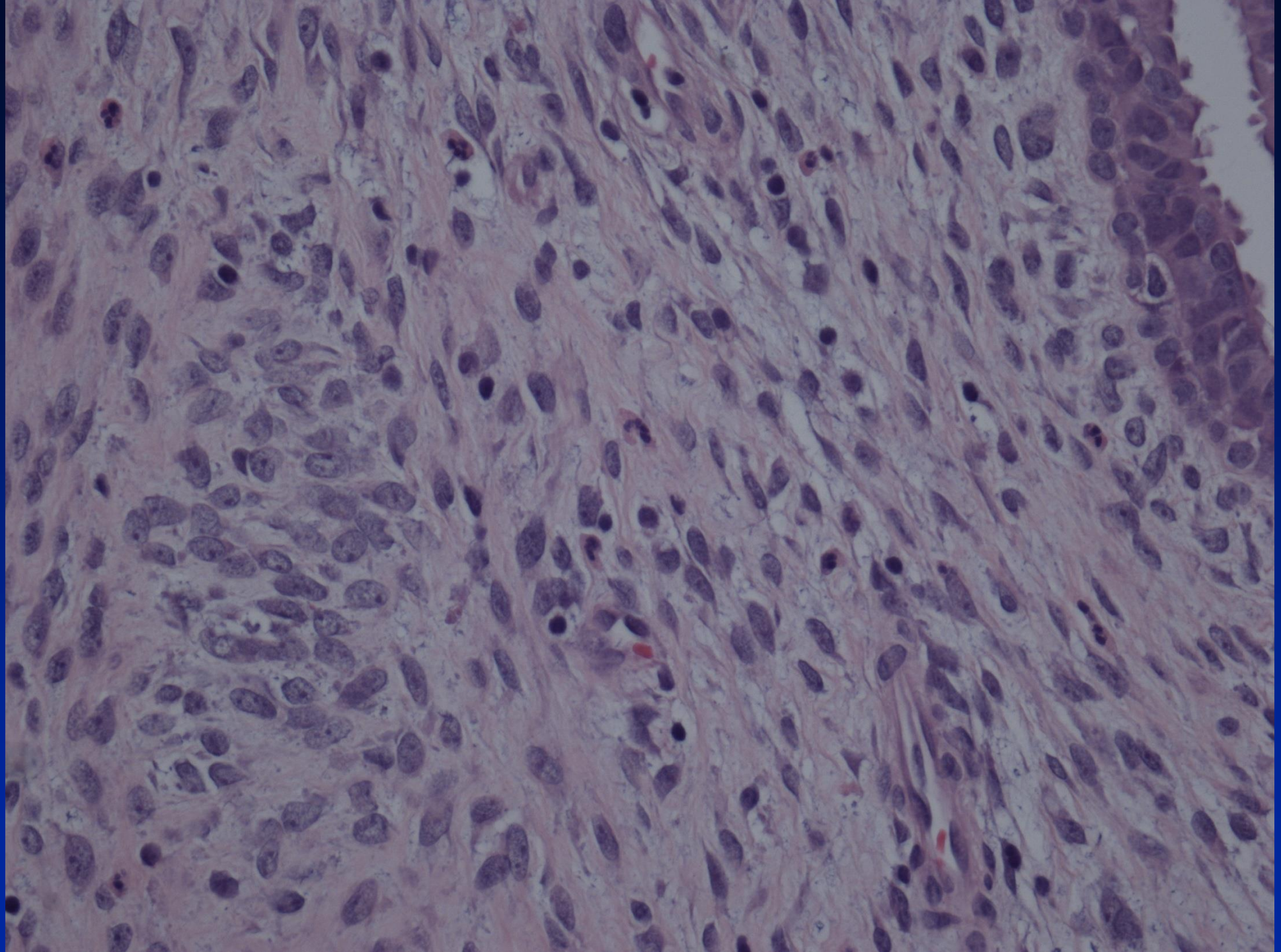
Conclusion: borderline phyllodes tumour











Fibroepithelial lesion

Circumscribed edge

Leaf-like areas

High proportion of stroma

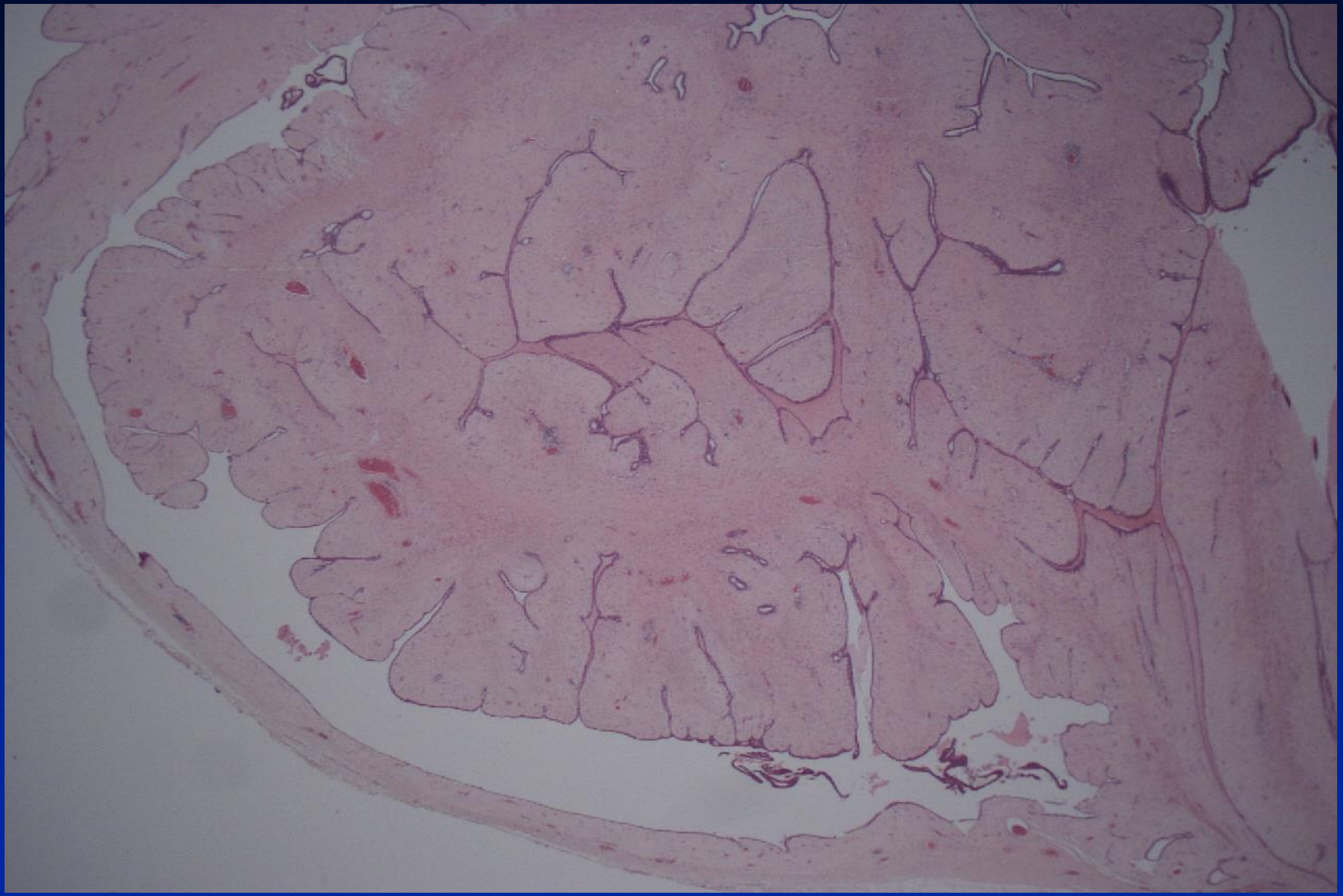
Increased stromal cellularity

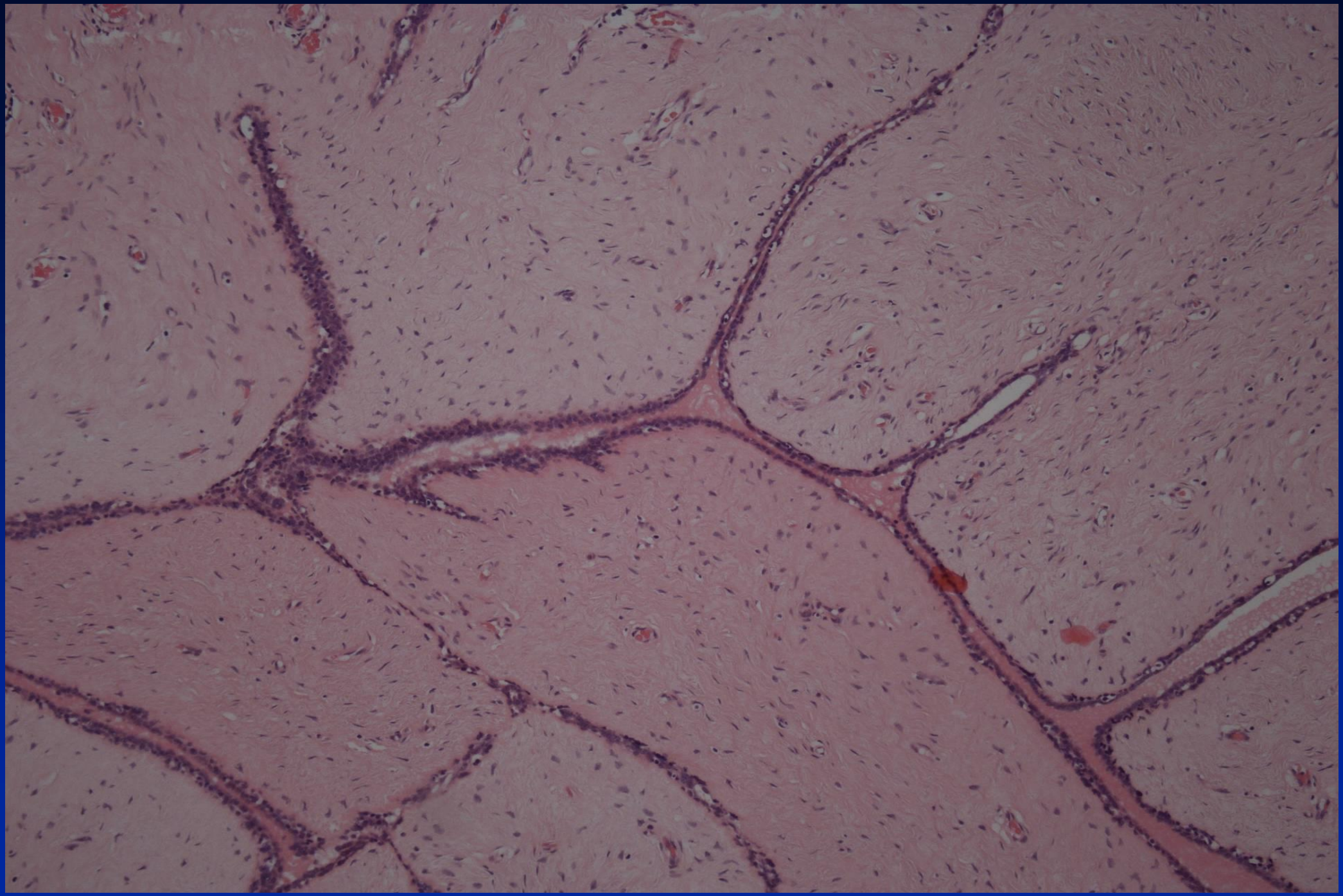
Focal area resembling fibroadenoma

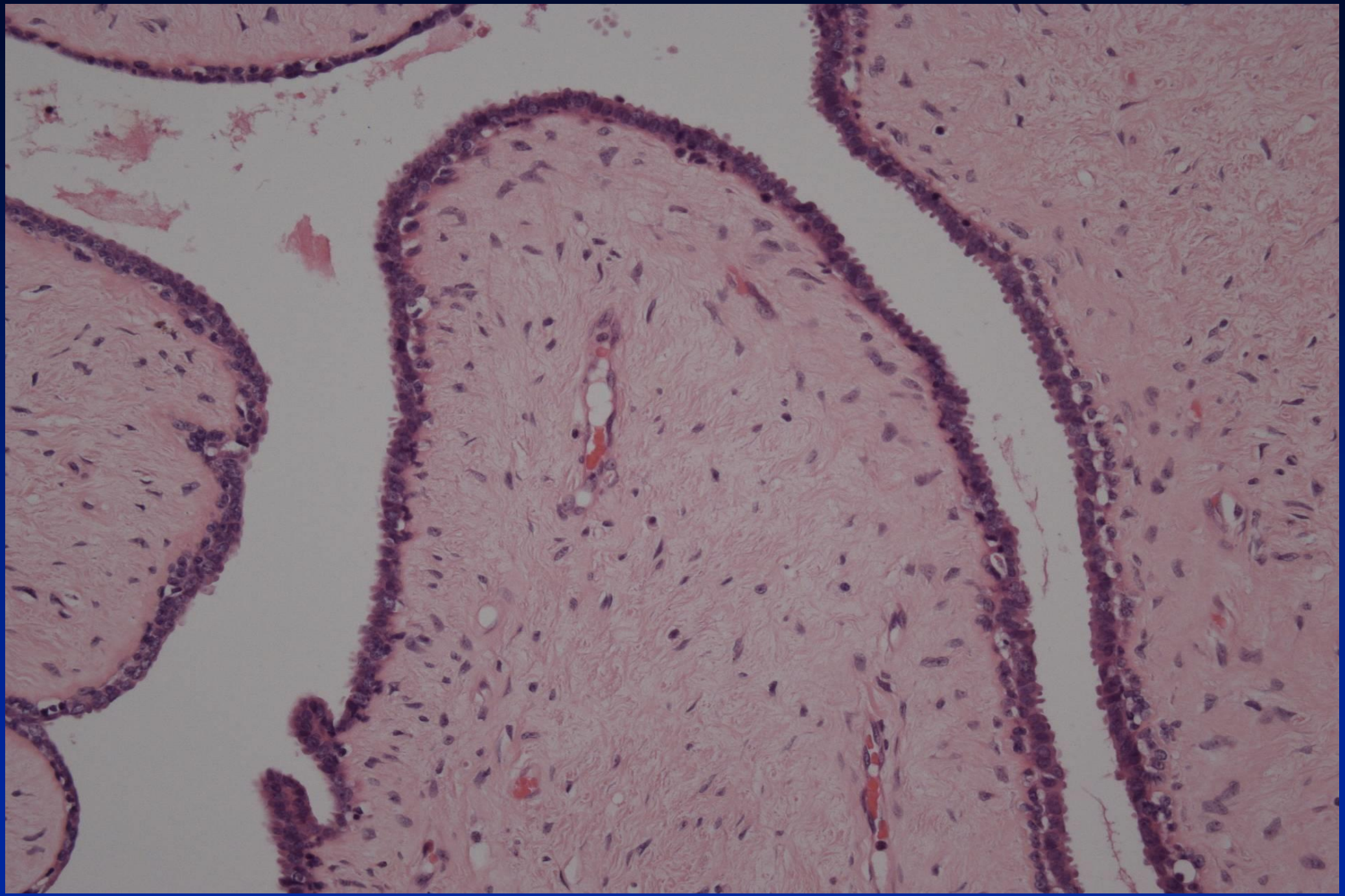
Mild atypia (moderate in other sections)

Mitoses 3/10 high power fields

Conclusion: benign phyllodes







Fibroepithelial lesion

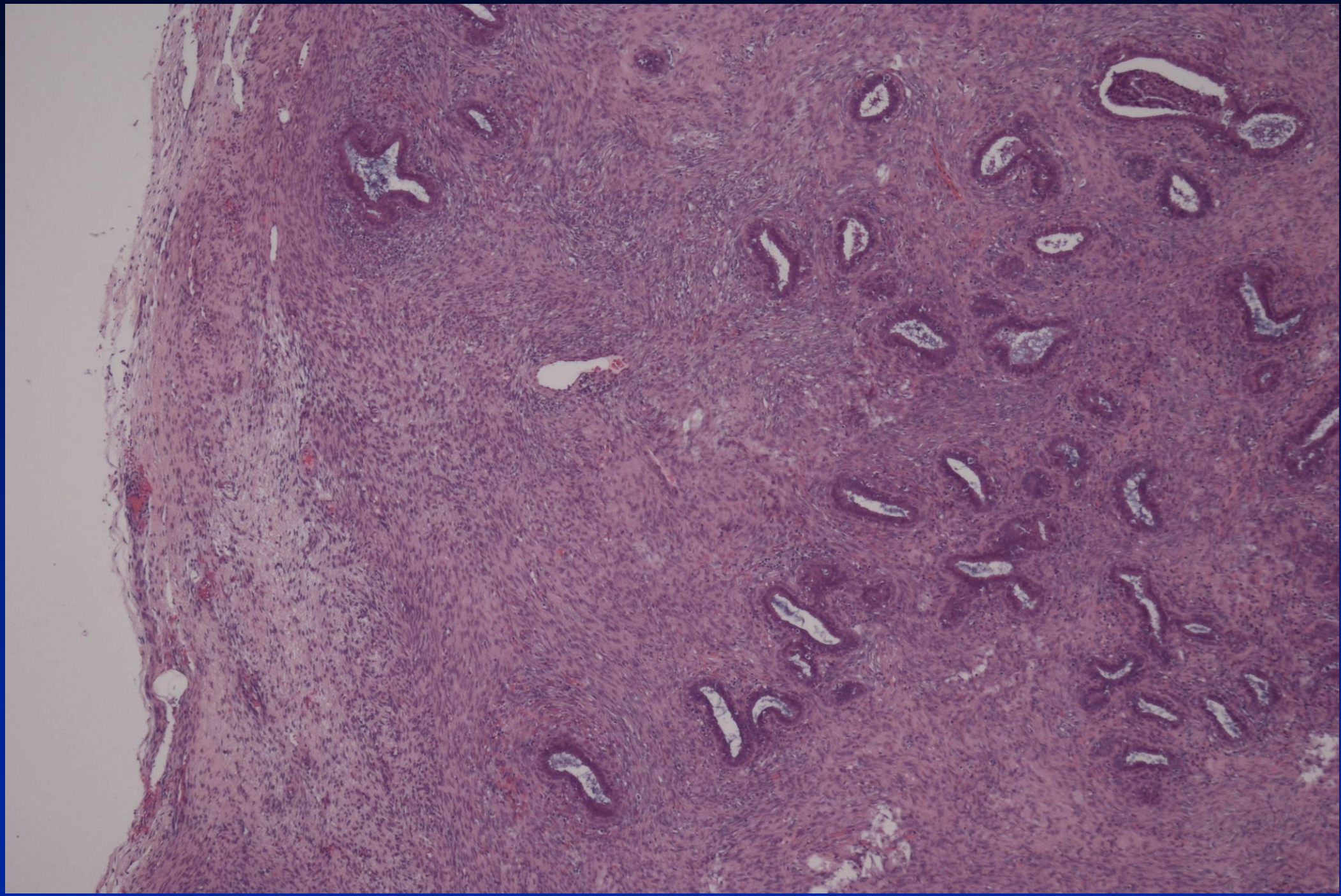
Circumscribed

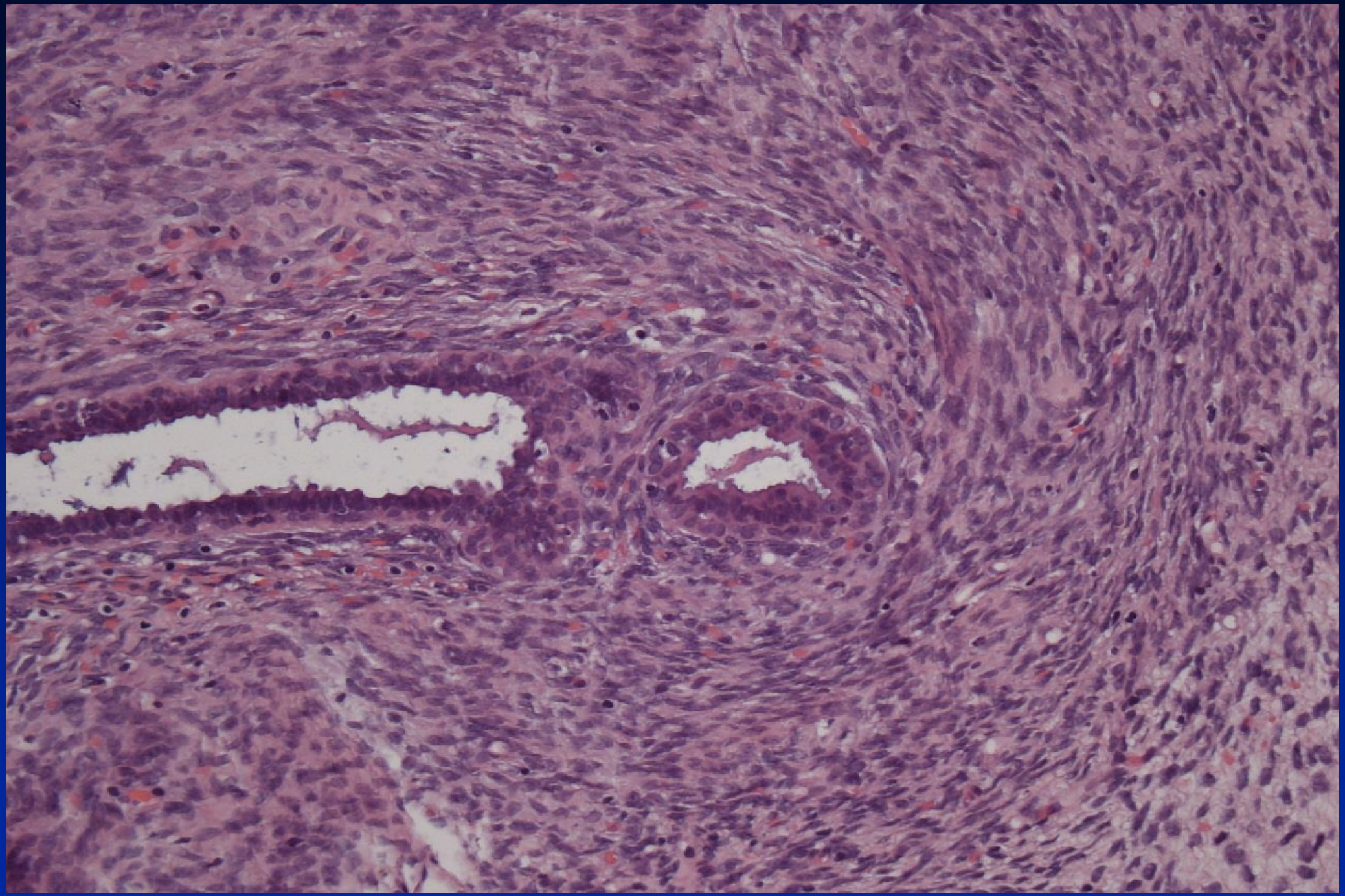
Leaf-like architecture

No increase in stromal cellularity

No atypia or mitoses

Conclusion: fibroadenoma

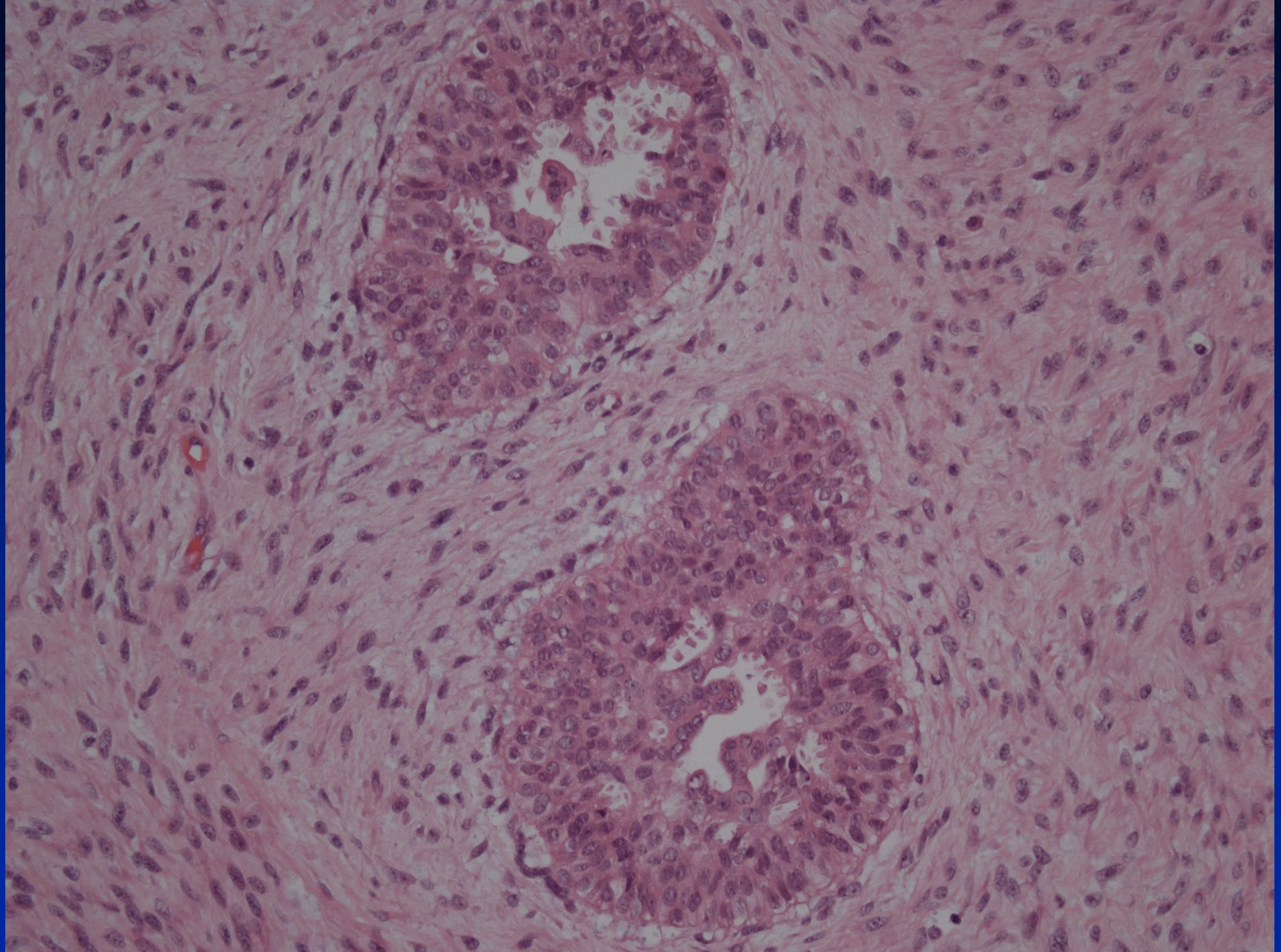


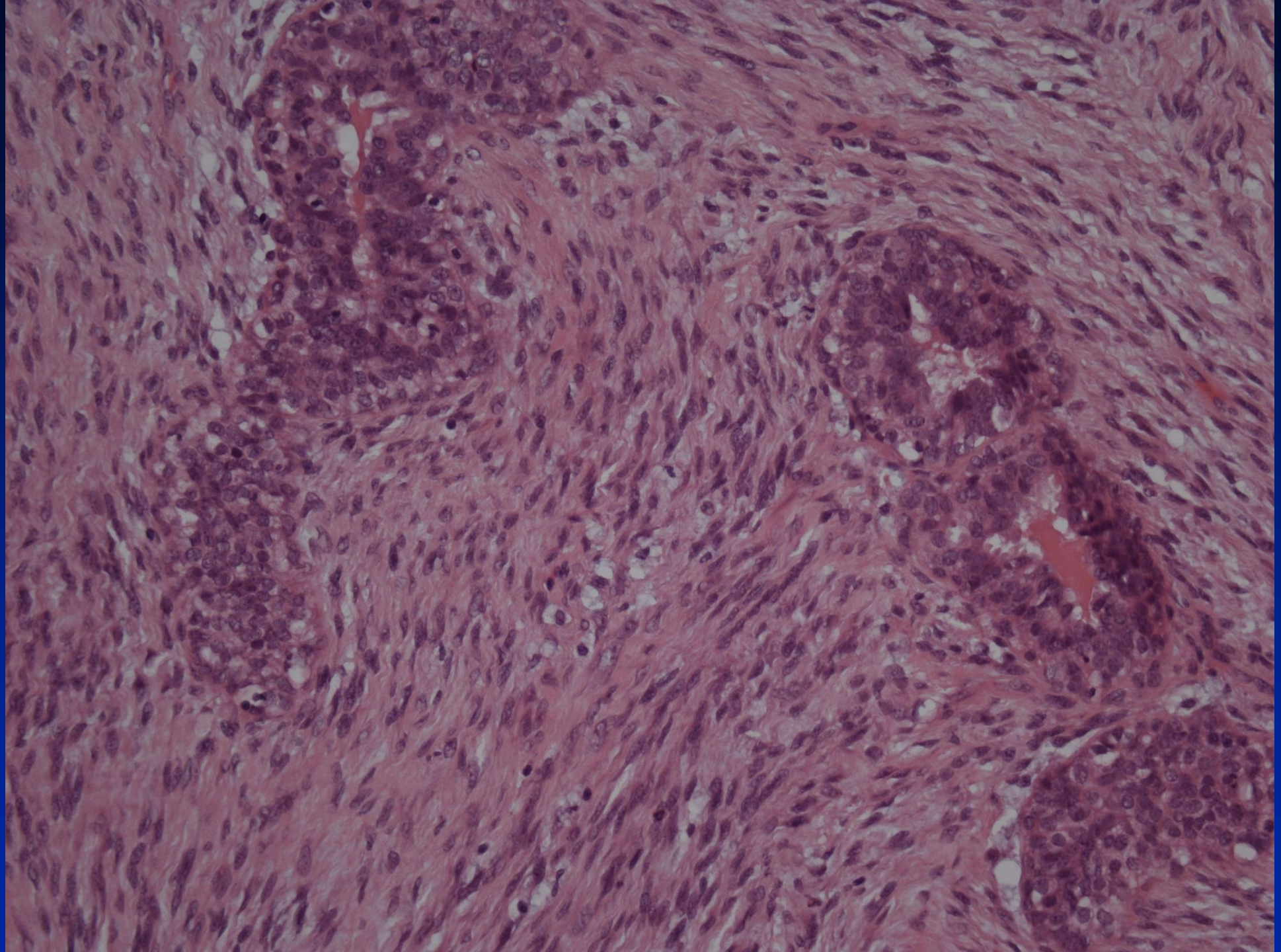


- Fibroepithelial lesion
- Circumscribed
- Pericanalicular
- Stromal expansion, but no overgrowth
- Moderate/marked increase in stromal cellularity
- Conclusion: benign phyllodes tumour

Juvenile fibroadenoma

- May be large
- May grow rapidly
- Pericannalicular
- Stromal cellularity mildly increased
- Rarely stromal overgrowth
- Epithelial hyperplasia of usual type
- Occasional mitoses may be present





Benign phyllodes tumour

- A key feature is increased stromal cellularity
- A leaf-like architecture is usually present (and can be seen in fibroadenoma)
- The following are often absent
- Nuclear pleomorphism
- Stromal overgrowth
- High mitotic count

- The margin is circumscribed

Diagnosis of benign phyllodes tumour

- No single feature can be relied on
- The more features present the more likely the diagnosis (increased stromal cellularity, leaf-like architecture, nuclear pleomorphism, stromal overgrowth, mitoses)
- Immunohistochemistry – no value

Benign phyllodes v fibroadenoma

- Poor reproducibility of diagnosis at the margin between these entities
- Pathol Oncol Res 2006;12:216
- Int J Surg Pathol 2014;22:695
- Where there is uncertainty WHO recommends categorisation as fibroadenoma

Sampling

- Heterogeneity is common
- If uncertain consider taking more blocks

Genetics

MED12 mutations

- Phyllodes tumours 70 - 80%
- Common in fibroadenoma esp intracanalicular
- Most often missense mutations in codon 44

TERT promotor mutations

- Phyllodes tumours 50 - 60%
- Fibroadenoma 0 – 7%

Mutations in cancer driver genes TP3, RB1, EGFR etc

- Restricted to borderline and malignant phyllodes

Grade of local recurrences

Original tumour	Recurrent tumour	Number
Benign	Benign	27
Benign	Borderline	17
Benign	Malignant	4
Borderline	Borderline	10
Borderline	Malignant	2
Borderline	Benign	4
Malignant	Malignant	9

Total 73 (Tan J Clin Pathol 2012;65:69)

Wait and see approach for incompletely excised benign phyllodes tumours

- Many phyllodes tumours not diagnosed preoperatively
- As a result incomplete excision common
- Local recurrence not inevitable
- Most recurrences benign
- Wait and see approach is an option if benign
- NOT appropriate for borderline and malignant
- Eur J Cancer 1992;28:654

Distinction of cellular fibroadenoma and benign phyllodes tumour

- Does it matter?
- No studies of wait and see policy of lesions that are difficult to classify
- Need large prospective studies with central review
- Is the diagnosis of borderline and malignant phyllodes more important?

WHO grading

	Benign	Borderline	Malignant
Border	Well-defined	Well-defined (focal infiltration)	Infiltrative
Stroma:			
Cellularity	Mild	Moderate	Marked
Atypia	Mild/none	Mild/moderate	Marked
Mitoses (10 hpf, 0.196 mm^2)	<5	5 to 9	>10
Overgrowth	No	No/very focal	Often

Phyllodes grading

- Not all tumours fall neatly into one of three WHO categories.
- More flexible systems eg Nottingham (Moffat 1995)
- Should each feature be given equal weight?
- Some evidence that stromal overgrowth is a particularly important feature suggesting malignant behaviour
- Lack of objective criteria for cellularity and atypia
- Wide variation of the proportion of benign, borderline and malignant phyllodes tumours in different series.
- Numerous biological markers have been shown to correlate with histological grade, but they are not of use in routine practice (reviewed in Karim J Clin Pathol 2013)

Benign phyllodes tumours

- Pushing margin > 90%
- Stromal overgrowth +/++
- Cellularity +/++
- Nuclear pleomorphism +/++
- Mitoses <10/10hpf (0.152 mm^2)
- If four features present = benign

Moffat Histopathology 1995;27:205-18

Malignant phyllodes tumour

- Infiltrative margin > 50%
- Stromal overgrowth ++/+++
- Cellularity ++/+++
- Nuclear pleomorphism ++/+++
- Mitoses >10/10hpf (0.152 mm^2)
- If four features present = malignant
- Necrosis & heterologous elements only seen malignant

Moffat Histopathology 1995;27:205-18

Fibroepithelial lesions

Value of preoperative diagnosis

- **Fibroadenoma – usually need not be excised**
- **Phyllodes tumour – excise**
- **Hamartoma - need not be excised**

Excision diagnosis after core showing cellular fibroepithelial lesion

Proportion of phyllodes tumours

5/32 (16%) El-Sayed et al. 2008
19/52 (37%) Rakha et al. 2011
12/29 (41%) Jacobs et al. 2005
25/57 (44%) Komenaka et al. 2003
11/16 (69%) Rakha et al. 2011
10/14 (71%) Bode et al. 2007
36/50 (72%) Lee et al. 2007
39/51 (76%) Abdulcadir et al. 2014

Studies of fibroadenoma v phyllodes tumour on core biopsy

Cellular fibroepithelial lesions on core

Jacobs et al. Am J Clin Pathol 2005;124:342

Resetkova et al. Breast J 2010;6:573

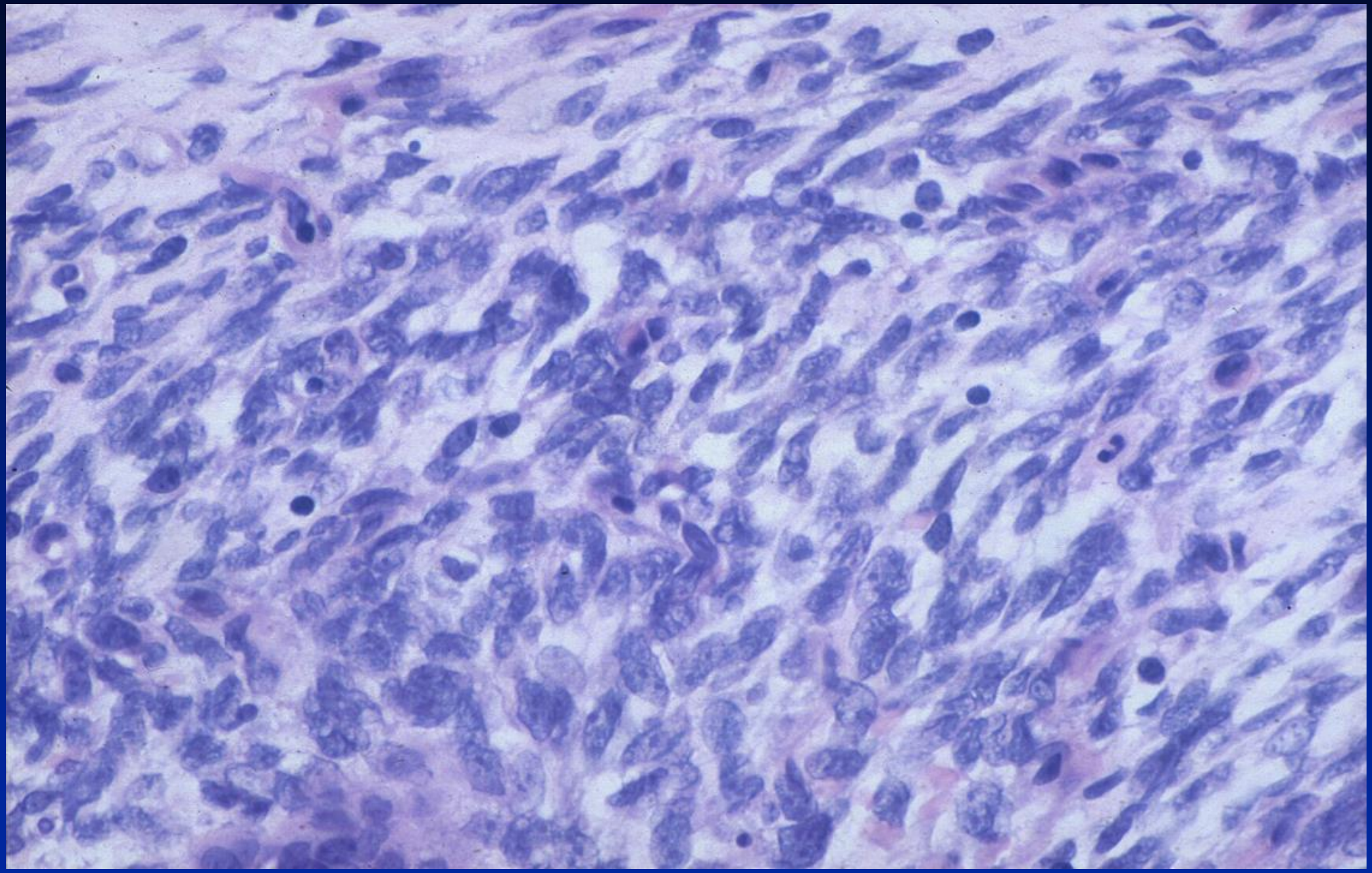
Jara-Lazaro et al. Histopathology 2010;57:220

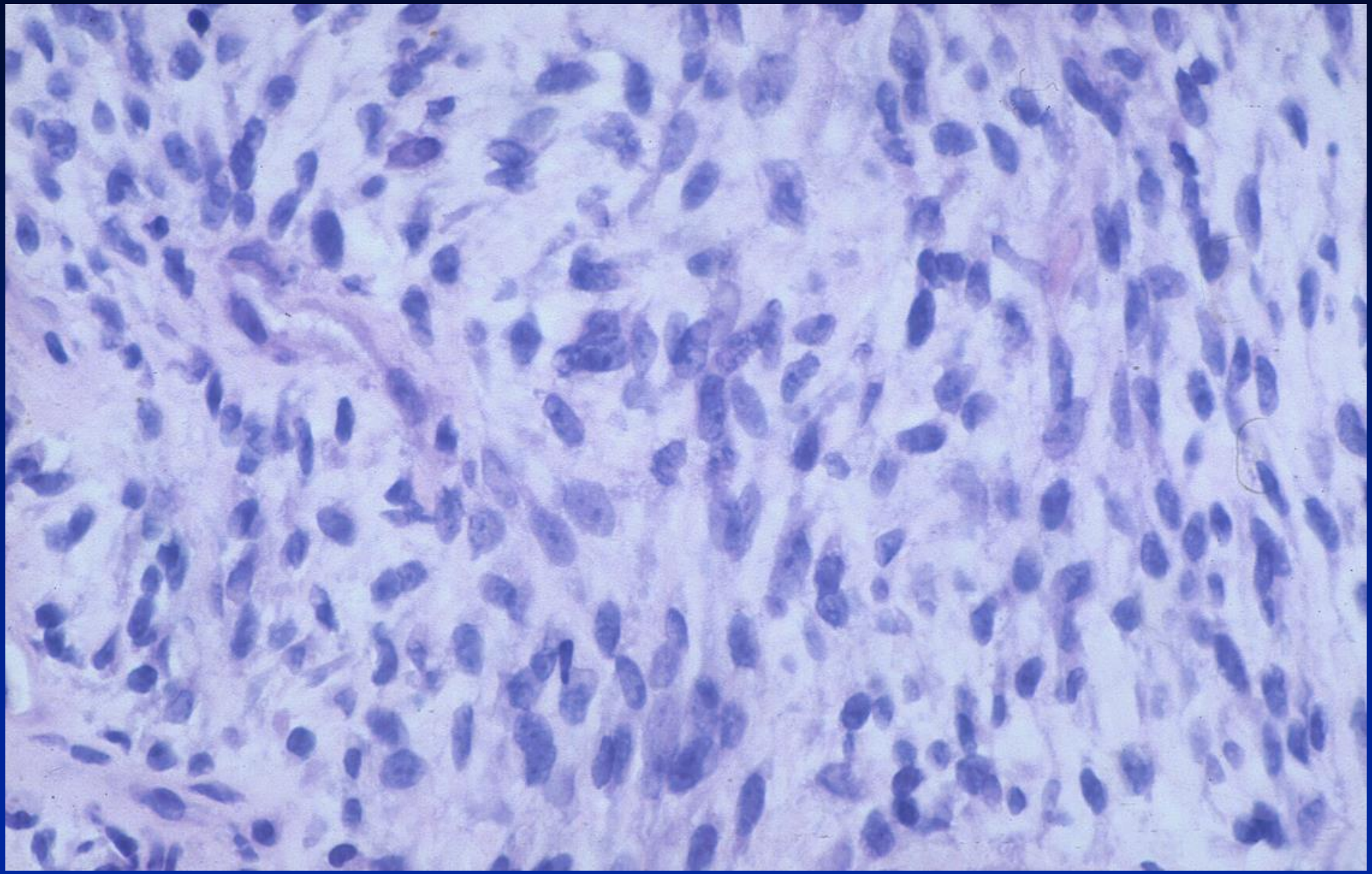
Excision diagnosis then look at core

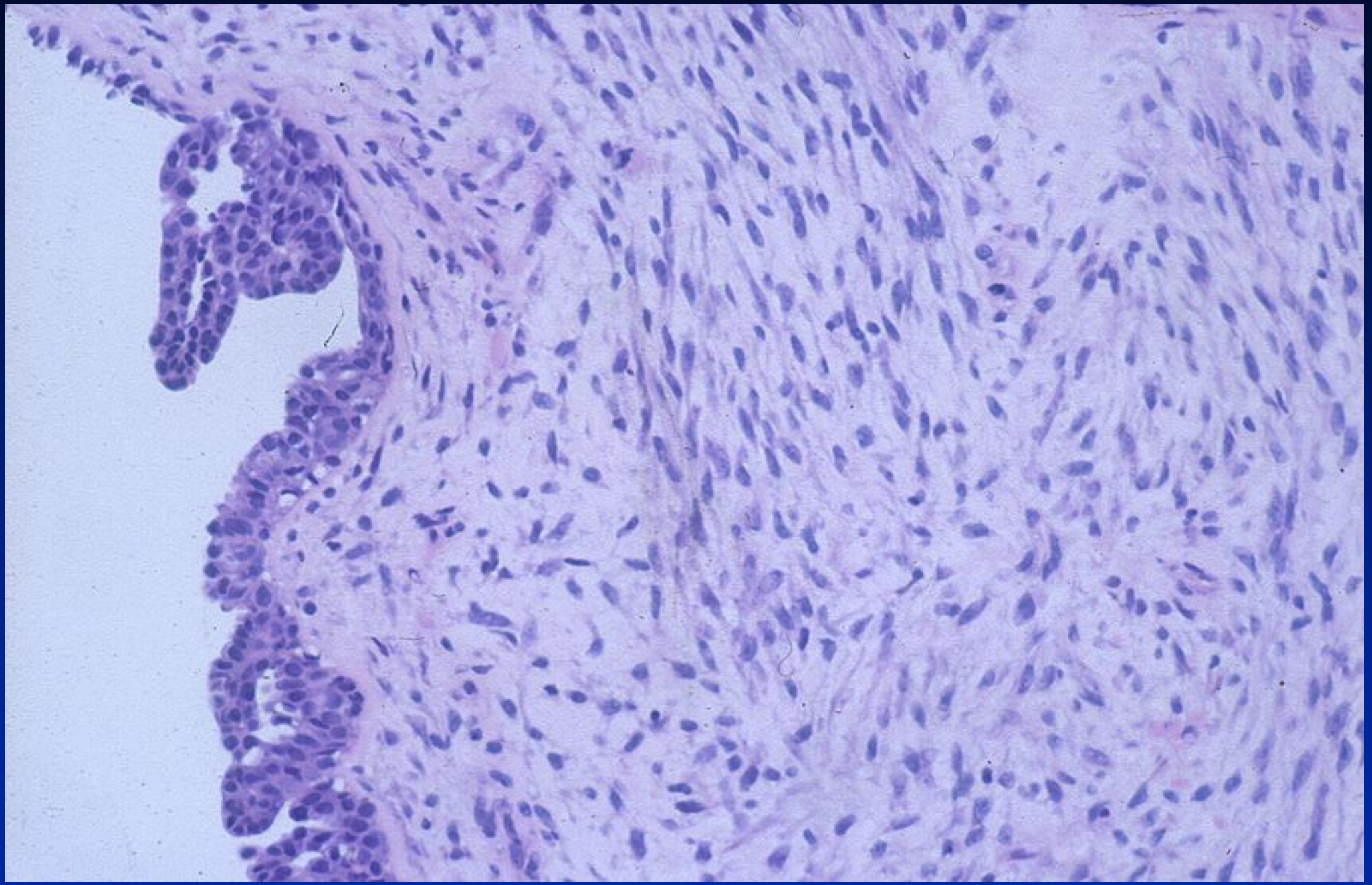
Lee et al. Histopathology 2007;51:336

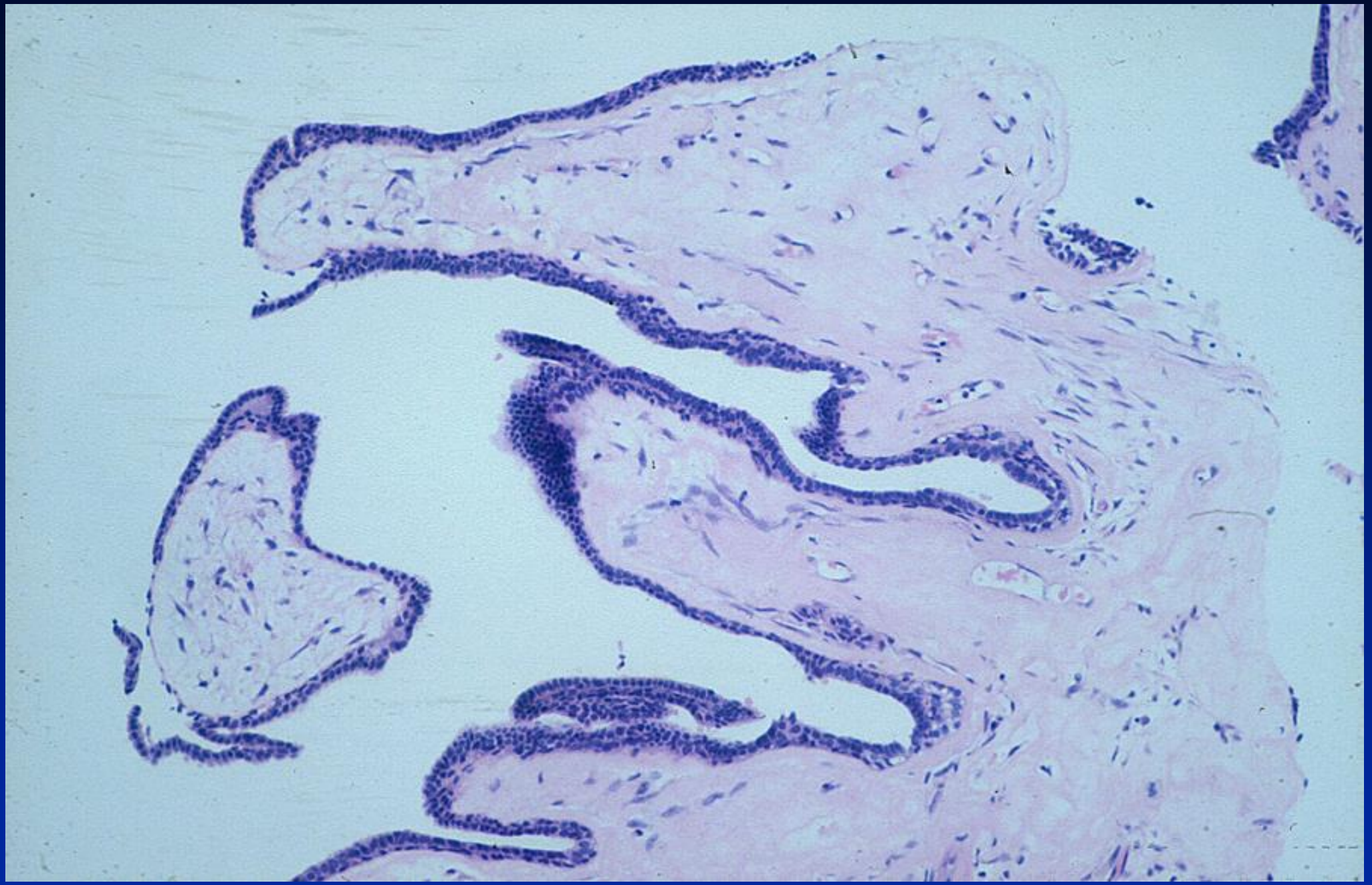
Morgan et al. Histopathology 2010;56:489

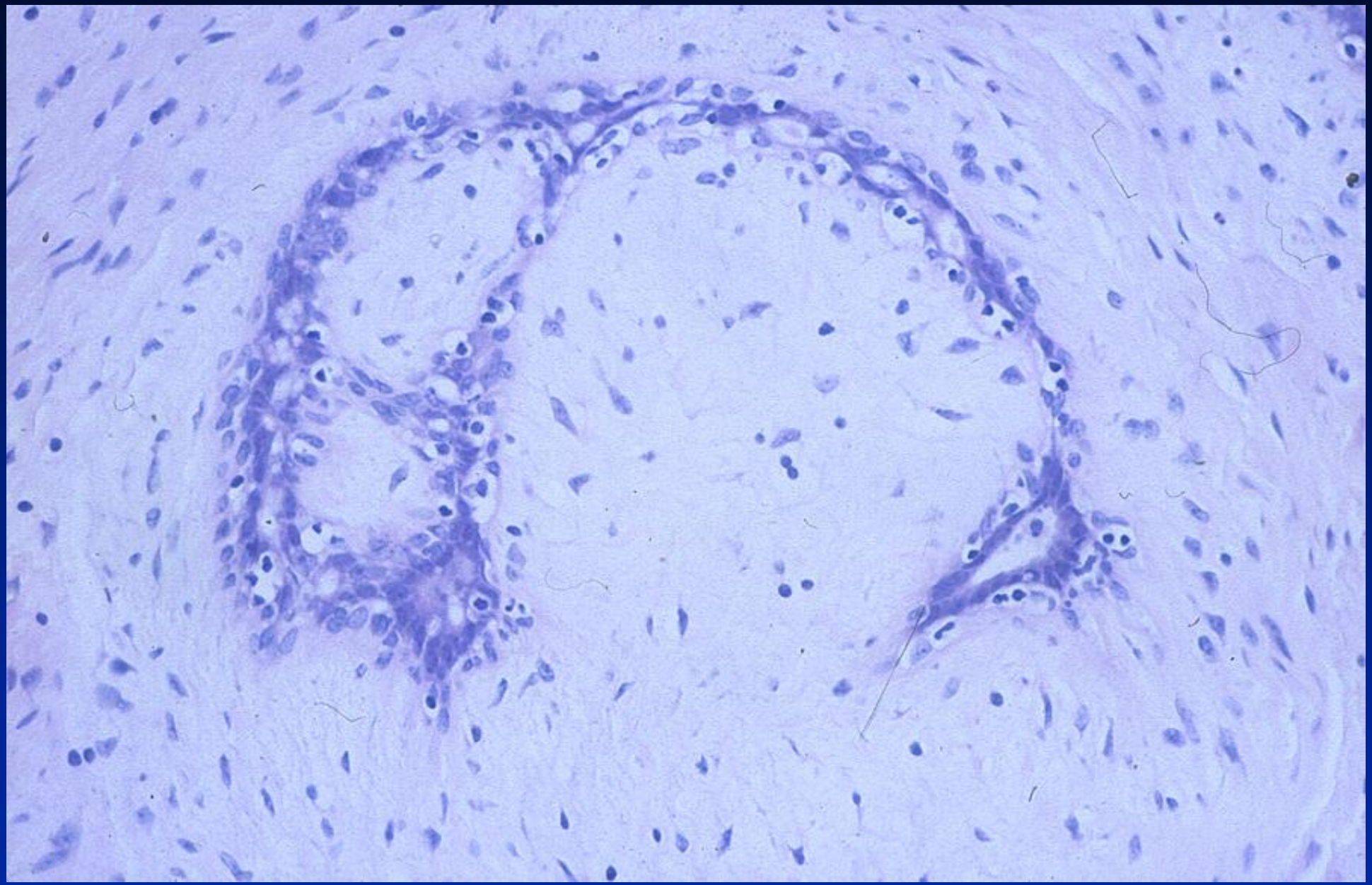
Tsang et al. Histopathology 2011;59:600

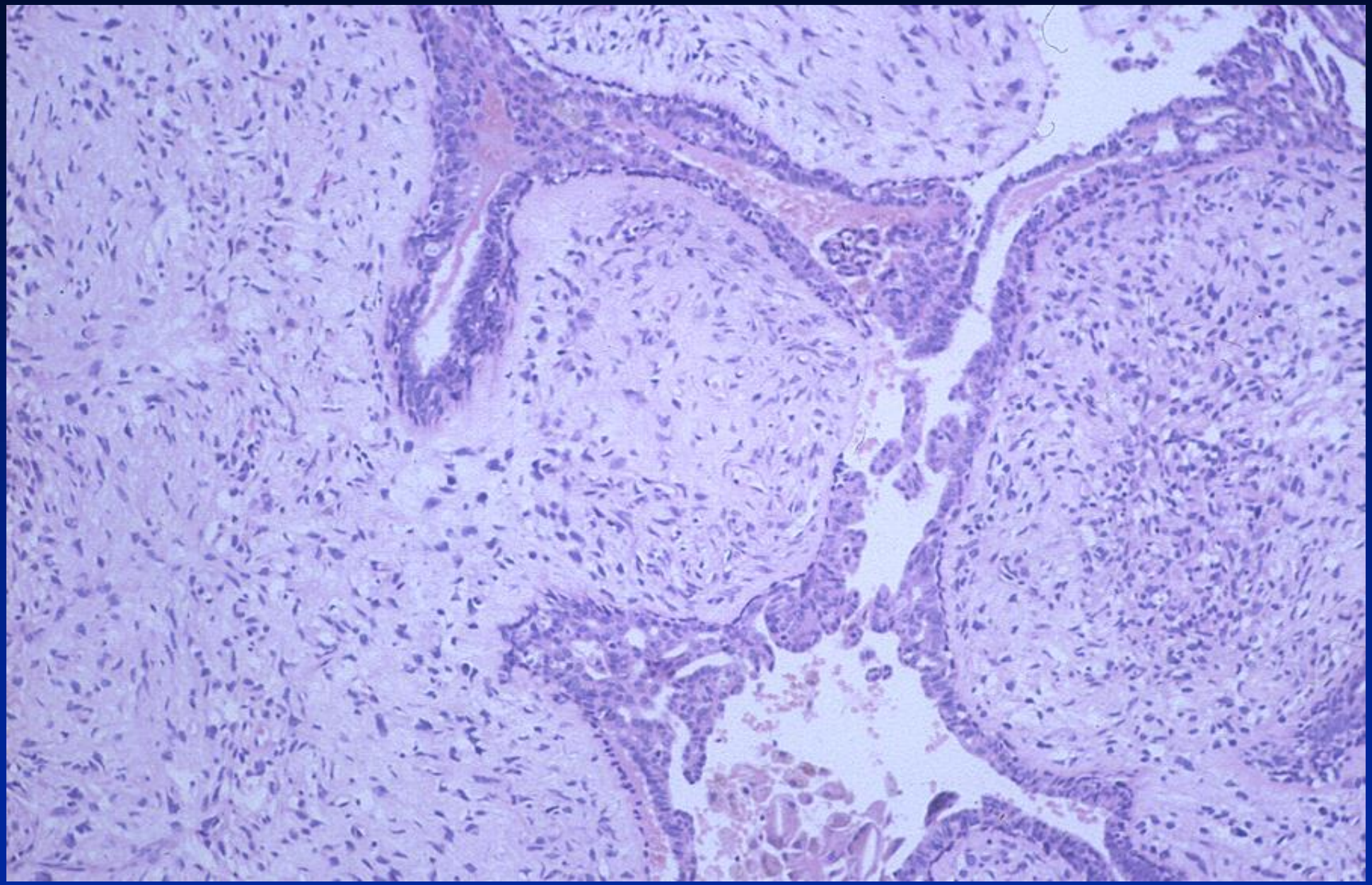


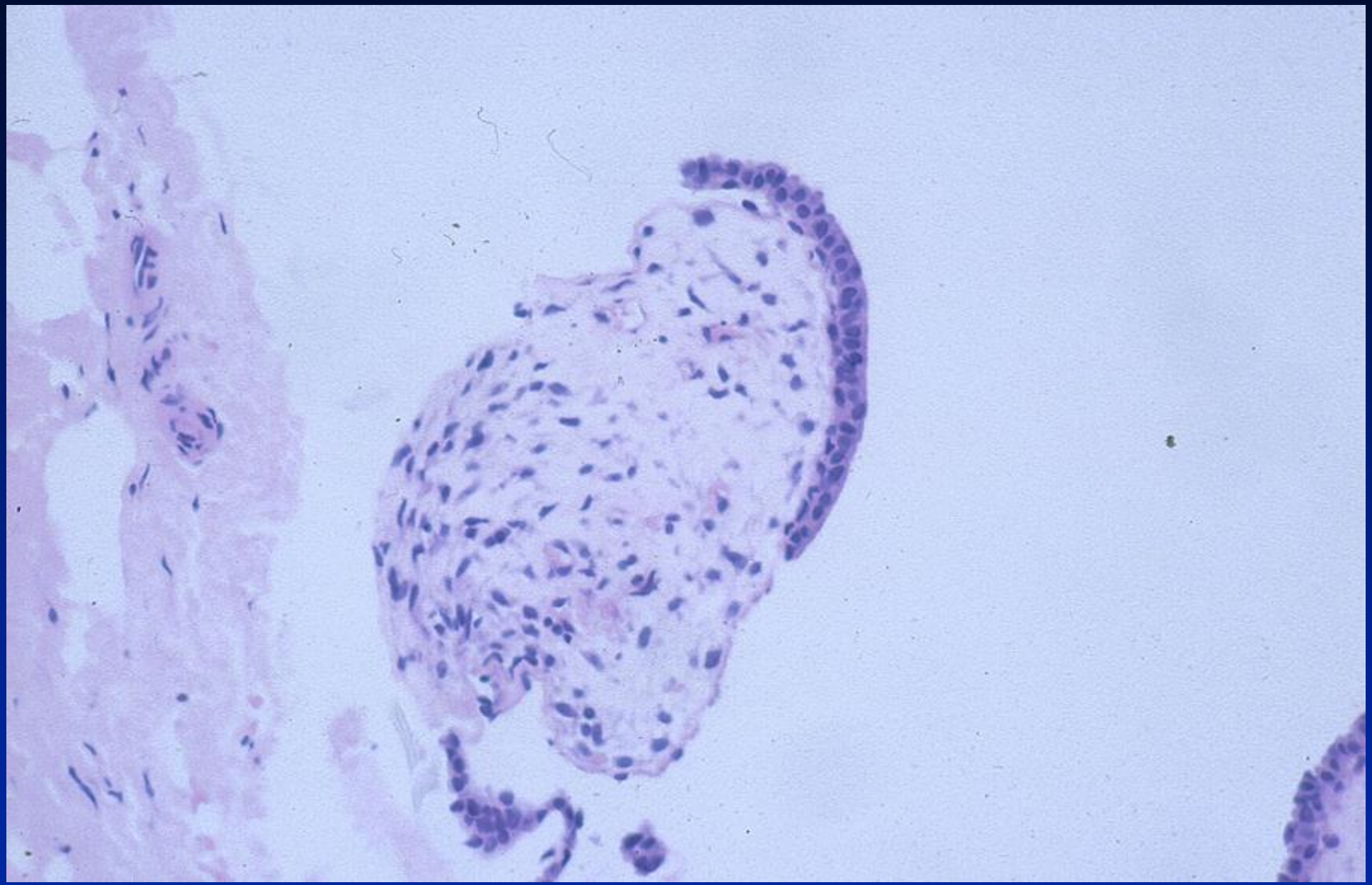


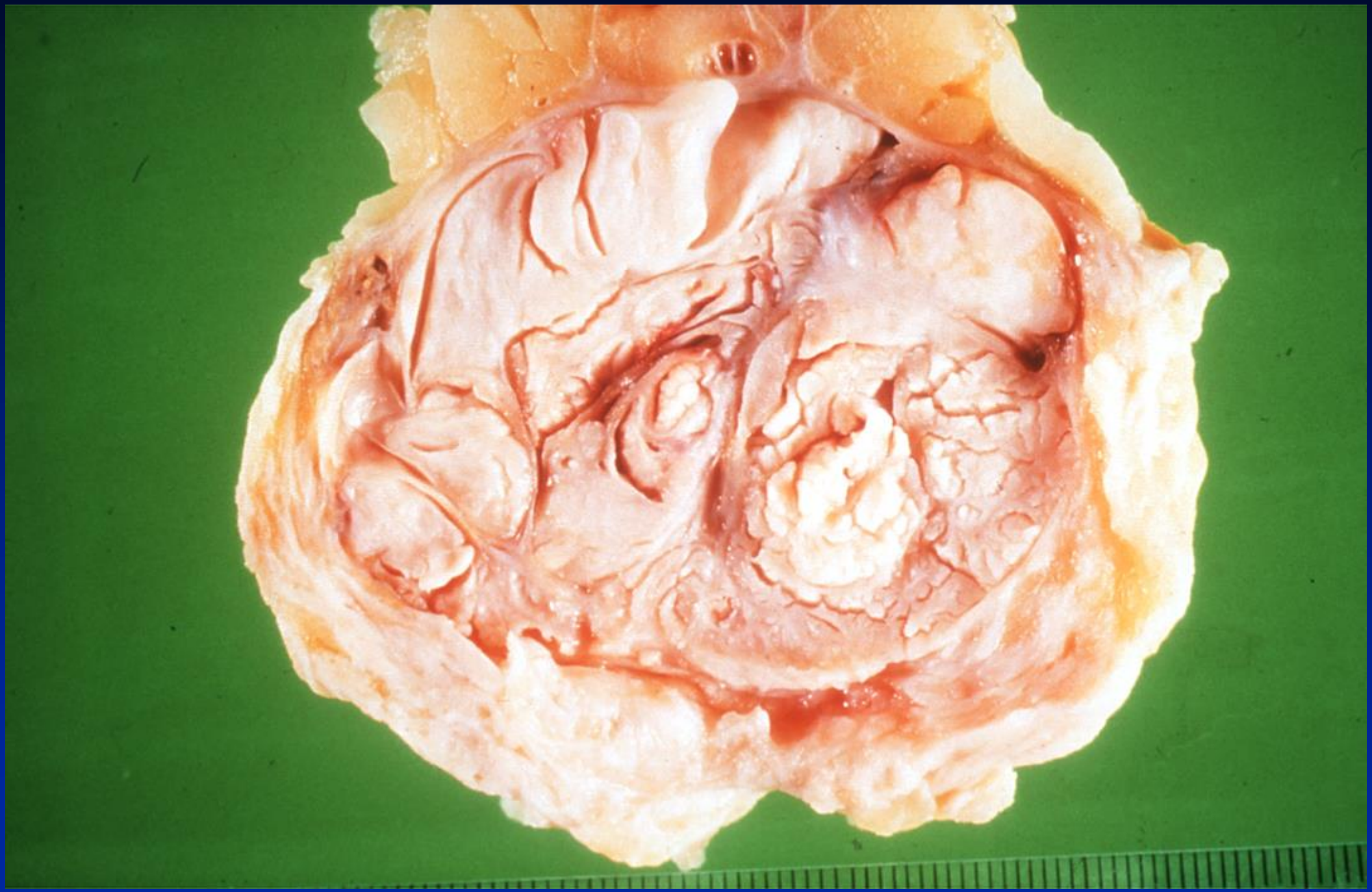


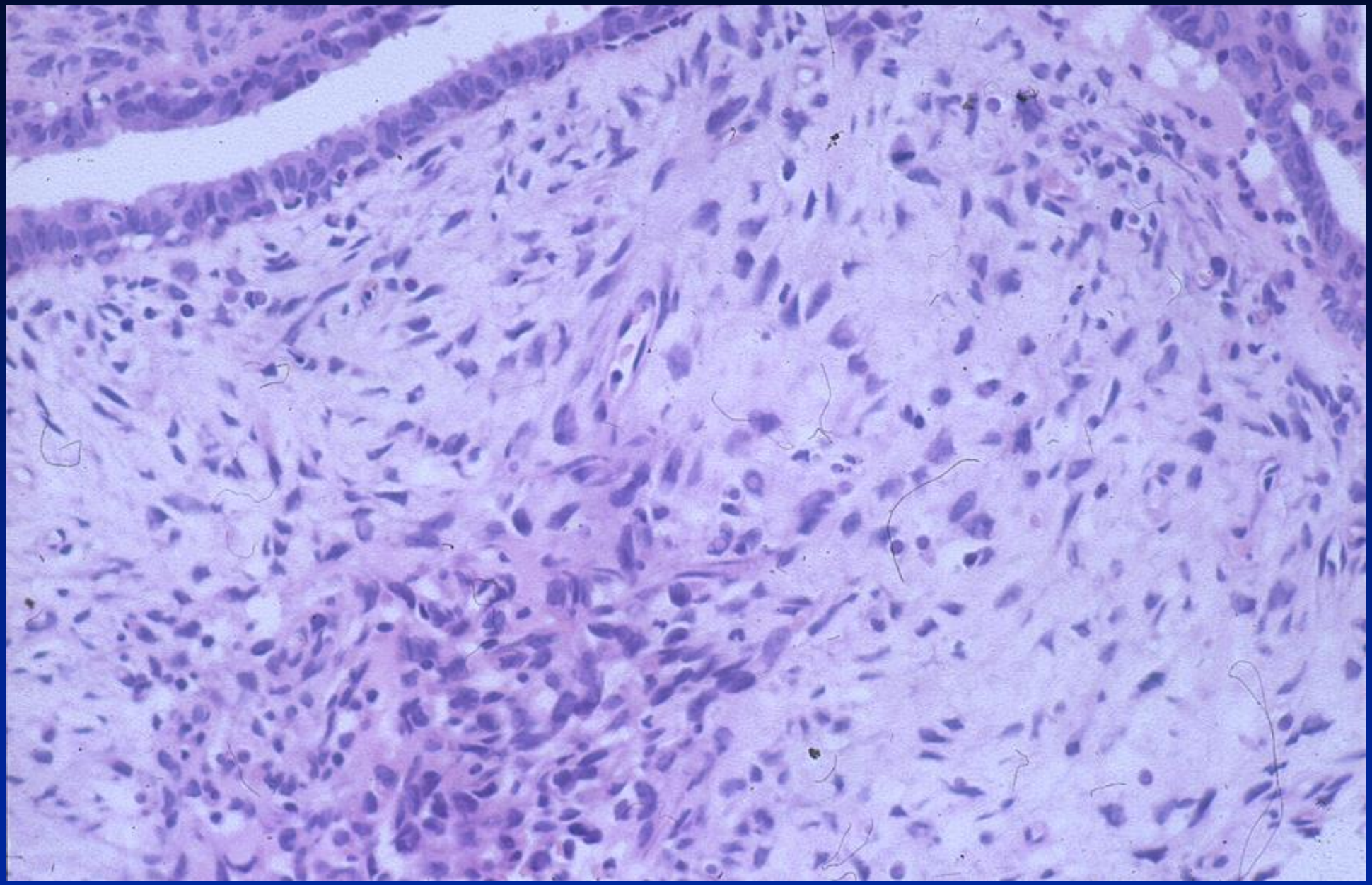


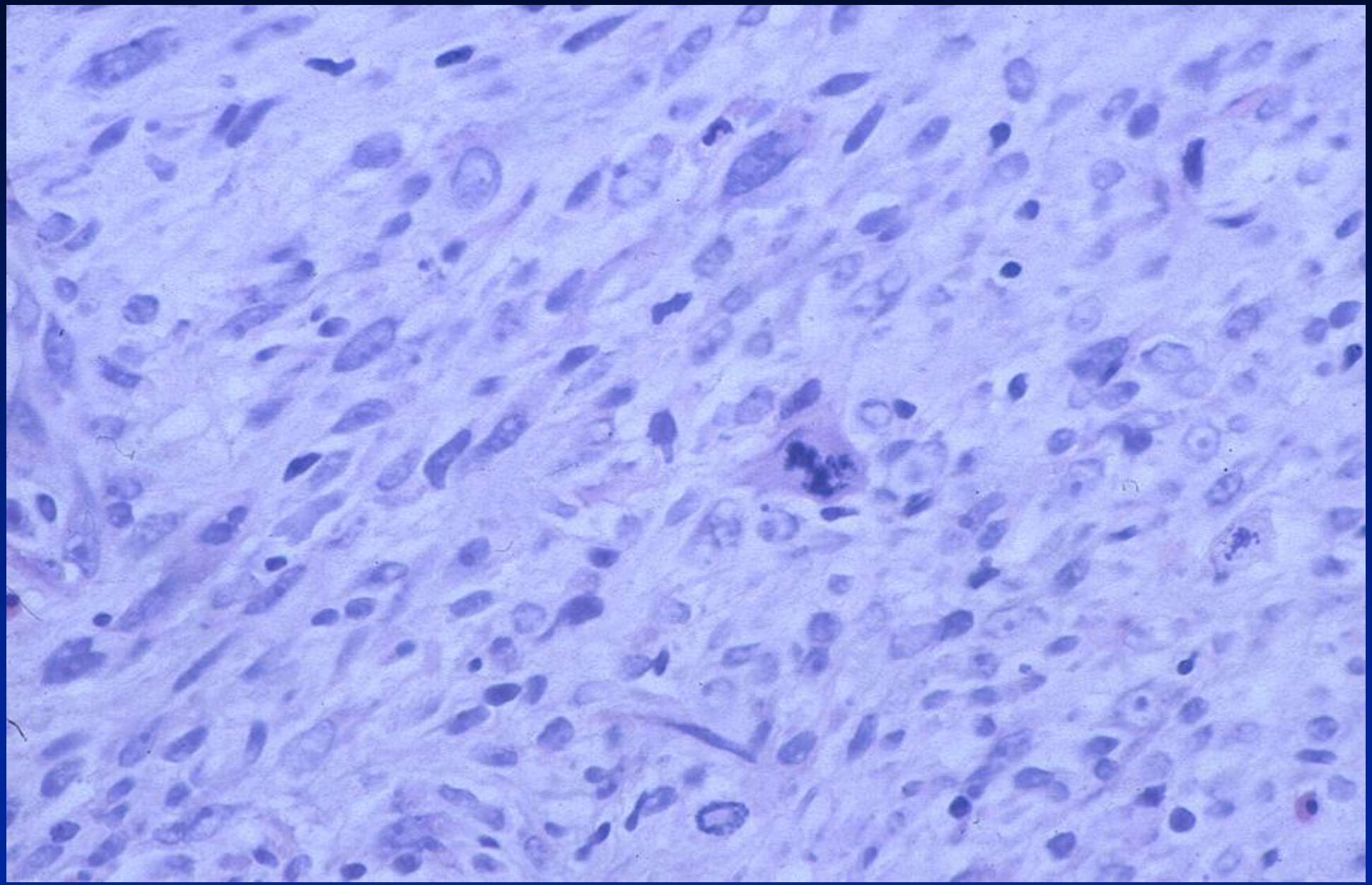


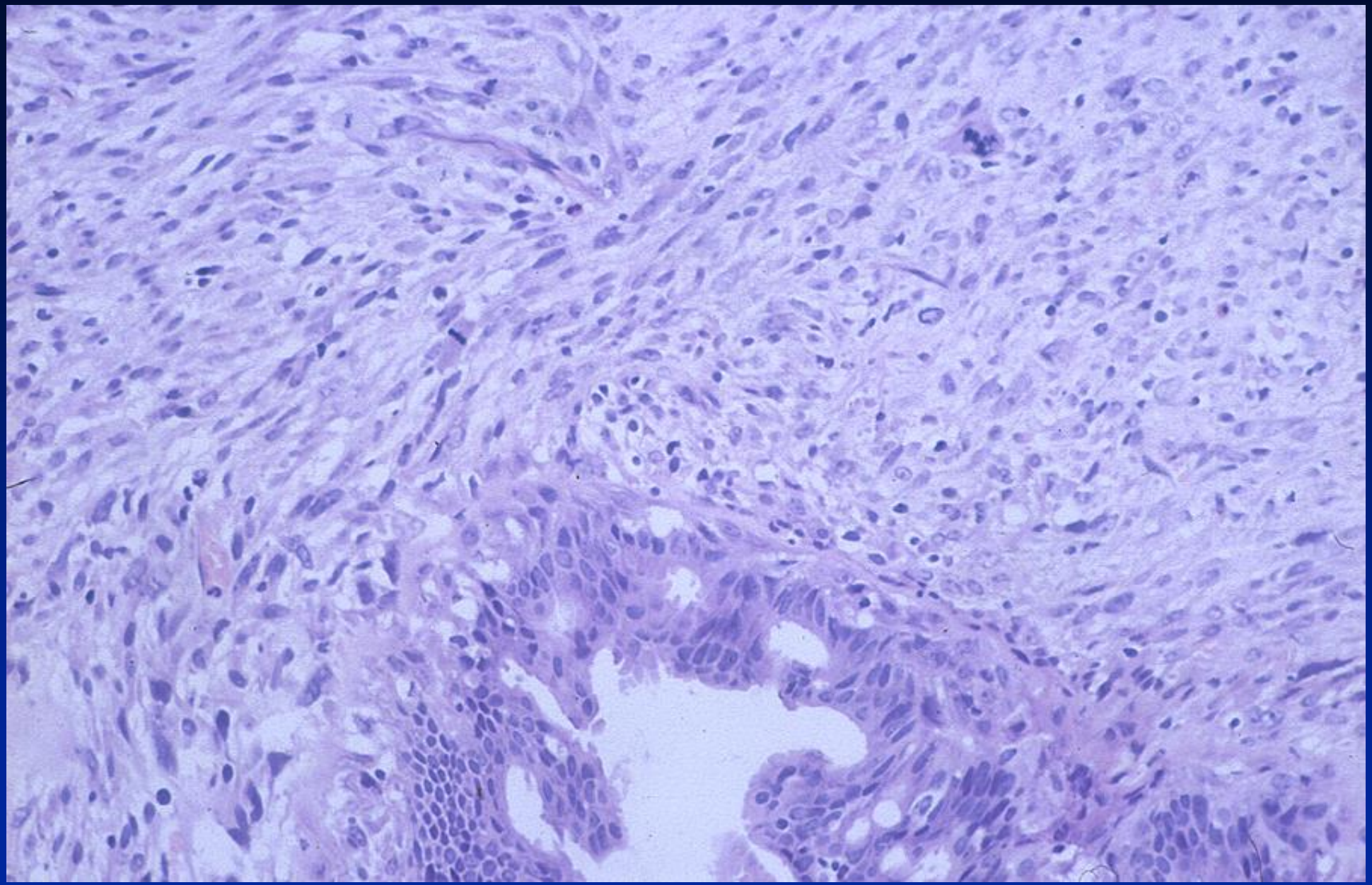












Features favouring phyllodes on core biopsy

Consistently of value in different studies

- Stromal cellularity
- Stromal overgrowth (x10 field with no epithelium)
- Stromal mitoses (3 or more/10hpf)
- Marked stromal pleomorphism
- Fragmentation

Of value in only some studies

- Irregular edge
- Entrapped fat
- Increased stromal cellularity adjacent to epithelium
- Absence of epithelial hyperplasia

Consistently NOT of value

- Intracanalicular growth pattern/leaf-like architecture

Features favouring phyllodes on core biopsy

Most not completely specific
Best used in combination (further research needed)

κ > 0.6 (Histopathology 2007;51:136)
Stromal cellularity (mild increase in 50%+)
Stromal overgrowth (x10 field with no epithelium)
Fragmentation

False-negative core biopsy (excision = phyllodes previous core = fibroadenoma etc)

- Tsang 2011 3/49 (7%)
- Bode 2007 2/12 (17%)
- Choi 2012 25/129 (19%)
- Lee 2007 11/44 (25%)
- Foxcroft 2007 5/17 (29%)
- Guillot 2011 16/54 (30%)
- Youn 2013 54/168 (32%)
- Dillon 2006 9/23 (39%)
- Reasons: heterogeneity, missed lesion, occasionally diagnostic error

Core = fibroadenoma
Excision = phyllodes

- **BUT < 1% of lesions called fibroadenoma on core are later found to be phyllodes**
- **Balance between sensitivity of diagnosis of phyllodes and too low a threshold for reporting minor changes**

Breast 2007;16:27 Surgery 2006;140:779 Histopathology 2007;51:136 Acta Radiol 2007;48:708

B3 cellular fibroepithelial lesion

- Repeat core biopsy not useful

Fibroepithelial lesions

Indications for excision

- Phyllodes in differential on core
- Size 30mm+
- Growing
- Ultrasound shows septae
- Patient wishes
- Age ? of value

  Breast 2007;16:27 Surgery 2006;140:779
  Histopathology 2007;51:136