Welcome to ScOPE

-School of Open Pathology Education-

www.scope-us.org

Endocrine Pathology Fundamentals

Daniel Rosen, MD. MEd.
Professor of Pathology
Baylor college of Medicine

openflexure microscope

OPEN RESEARCH COMMUNITY ACCELERATOR

Multiplier

Goals

Learn basic concepts in endocrine pathology.

Learning objectives

- Describe relevant clinical and pathological characteristics of benign and malignant tumors of the thyroid
- Describe the different histological variants of papillary and follicular thyroid carcinomas
- Describe special types of thyroid carcinomas
- Describe differences between parathyroid adenoma, carcinoma, and parathyromatosis
- Describe clinical characteristics and histological findings of benign and malignant tumors of the adrenal gland and pituitary gland

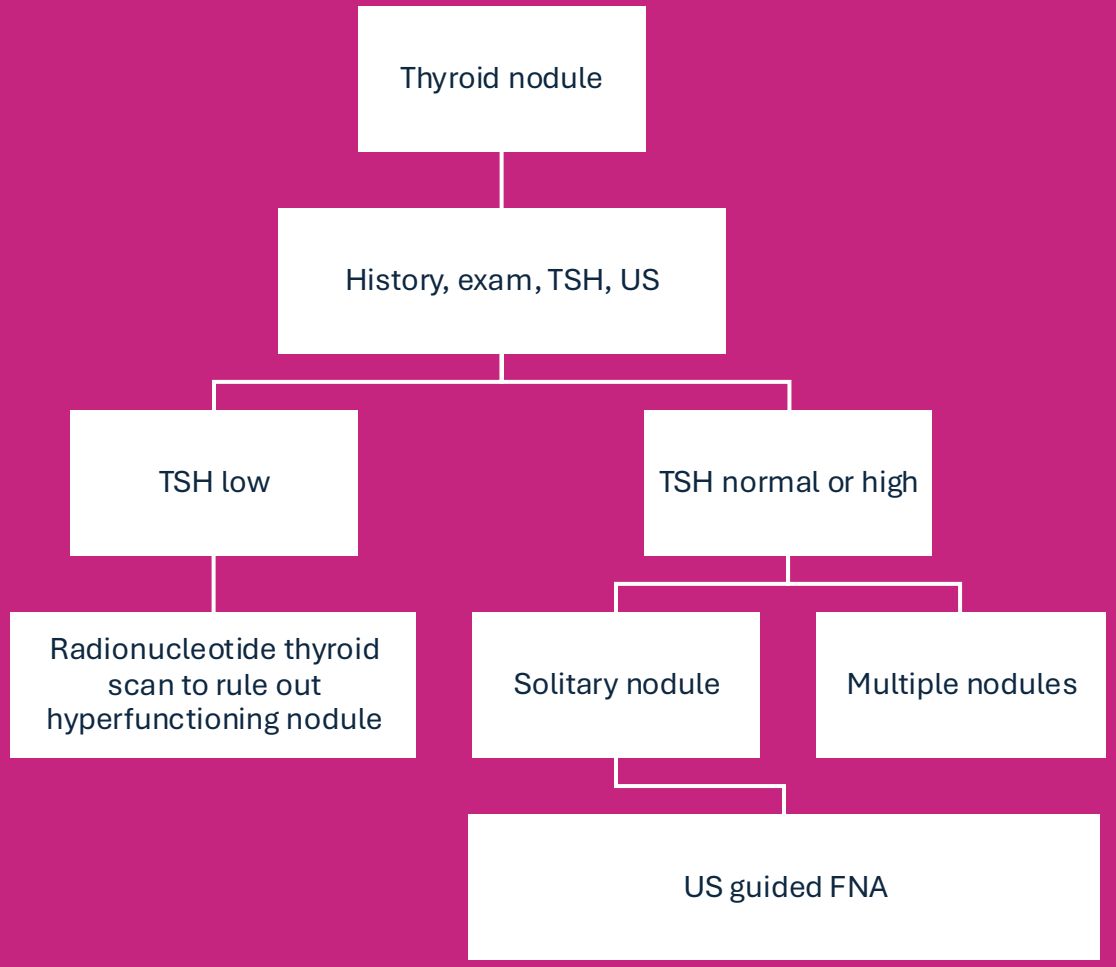
CASE 1

45-year-old female with a 2.5 cm solitary thyroid nodule discovered on routine physical examination. Ultrasound shows a hypoechoic nodule with microcalcifications. Serum TSH is within normal limits. Fine needle aspiration performed.

WHY IS THIS PATIENT HAVING A BIOPSY?

WHAT IS EXPECTED FROM THE PATHOLOGIST?

Thyroid gland disease



Thyroid imaging reporting and data system (TI-RADS)

Risk stratification systems for thyroid lesions, usually based on **ultrasound** features, with a structure modelled off BI-RADS.

- American College of Radiology: ACR TI-RADS
- European Thyroid Association: EU-TIRADS
- Korean Society of Thyroid Radiology: K-TIRADS

EU-TIRADS system has sensitivity 83-86% and specificity 32-79%. The rate of unnecessary FNA was 25%. Good interobserver agreement regarding decision to biopsy has also been shown (kappa 0.68).

Endocrine. 64 (2): 299; 2019
The Journal of Clinical Endocrinology & Metabolism. 104 (1): 95; 2019
Endocrine Connections. 7 (1): 1; 2018

ACR TI-RADS

COMPOSITION (Choose 1)	
Cystic or almost completely cystic	0 points
Spongiform	0 points
Mixed cystic and solid	1 point
Solid or almost completely solid	2 points

ECHOGENICITY (Choose 1)	
Anechoic	0 points
Hyperechoic or isoechoic	1 point
Hypoechoic	2 points
Very hypoechoic	3 points

SHAPE (Choose 1)	
Wider-than-tall	0 points
Taller-than-wide	3 points

MARGIN (Choose 1)	
Smooth	0 points
Ill-defined	0 points
Lobulated or irregular	2 points
Extra-thyroidal extension	3 points

ECHOGENIC FOCI (Choose All That Apply)	
None or large comet-tail artifacts	0 points
Macrocalcifications	1 point
Peripheral (rim) calcifications	2 points
Punctate echogenic foci	3 points

Add Points From All Categories to Determine TI-RADS Level

0 Points	2 Points	3 Points	4 to 6 Points	7 Points or More
TR1 Benign — No FNA	**TR2** Not Suspicious — No FNA	**TR3** Mildly Suspicious — FNA if ≥ 2.5 cm; Follow if ≥ 1.5 cm	**TR4** Moderately Suspicious — FNA if ≥ 1.5 cm; Follow if ≥ 1 cm	**TR5** Highly Suspicious — FNA if ≥ 1 cm; Follow if ≥ 0.5 cm*

COMPOSITION	ECHOGENICITY	SHAPE	MARGIN	ECHOGENIC FOCI
Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. *Mixed cystic and solid:* Assign points for predominant solid component. Assign 2 points if composition cannot be determined because of calcification.	*Anechoic:* Applies to cystic or almost completely cystic nodules. *Hyperechoic/isoechoic/hypoechoic:* Compared to adjacent parenchyma. *Very hypoechoic:* More hypoechoic than strap muscles. Assign 1 point if echogenicity cannot be determined.	*Taller-than-wide:* Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. This can usually be assessed by visual inspection.	*Lobulated:* Protrusions into adjacent tissue. *Irregular:* Jagged, spiculated, or sharp angles. *Extrathyroidal extension:* Obvious invasion = malignancy. Assign 0 points if margin cannot be determined.	*Large comet-tail artifacts:* V-shaped, >1 mm, in cystic components. *Macrocalcifications:* Cause acoustic shadowing. *Peripheral:* Complete or incomplete along margin. *Punctate echogenic foci:* May have small comet-tail artifacts.

*Refer to discussion of papillary microcarcinomas for 5-9 mm TR5 nodules.

https://radiogyan.com/tirads-calculator/#tirads-calculator

CASE 1

https://www.digitalscope.org/ViewerUI/?SlideId=1eef36d3-bffa-4ab0-b3e3-5bde25729013

https://radiogyan.com/tirads-calculator/#tirads-calculator

FOLLICULAR LESIONS OF THE THYROID

Benign or malignant based on:

1. encapsulation,
2. lack or presence of invasion
3. nuclear features of papillary thyroid carcinoma

Differential diagnosis

- Adenomatoid nodules and adenomas
- Follicular carcinoma
- Follicular variant of papillary thyroid carcinoma
- Follicular tumours of uncertain malignant potential (rare)

J Clin Pathol. 2006 Jun 23;60(3):244–250.

Follicular Adenoma

- Predominantly young to middle women
- Presents as a painless solitary thyroid nodule
- Typically euthyroid
- Little or no I131 uptake

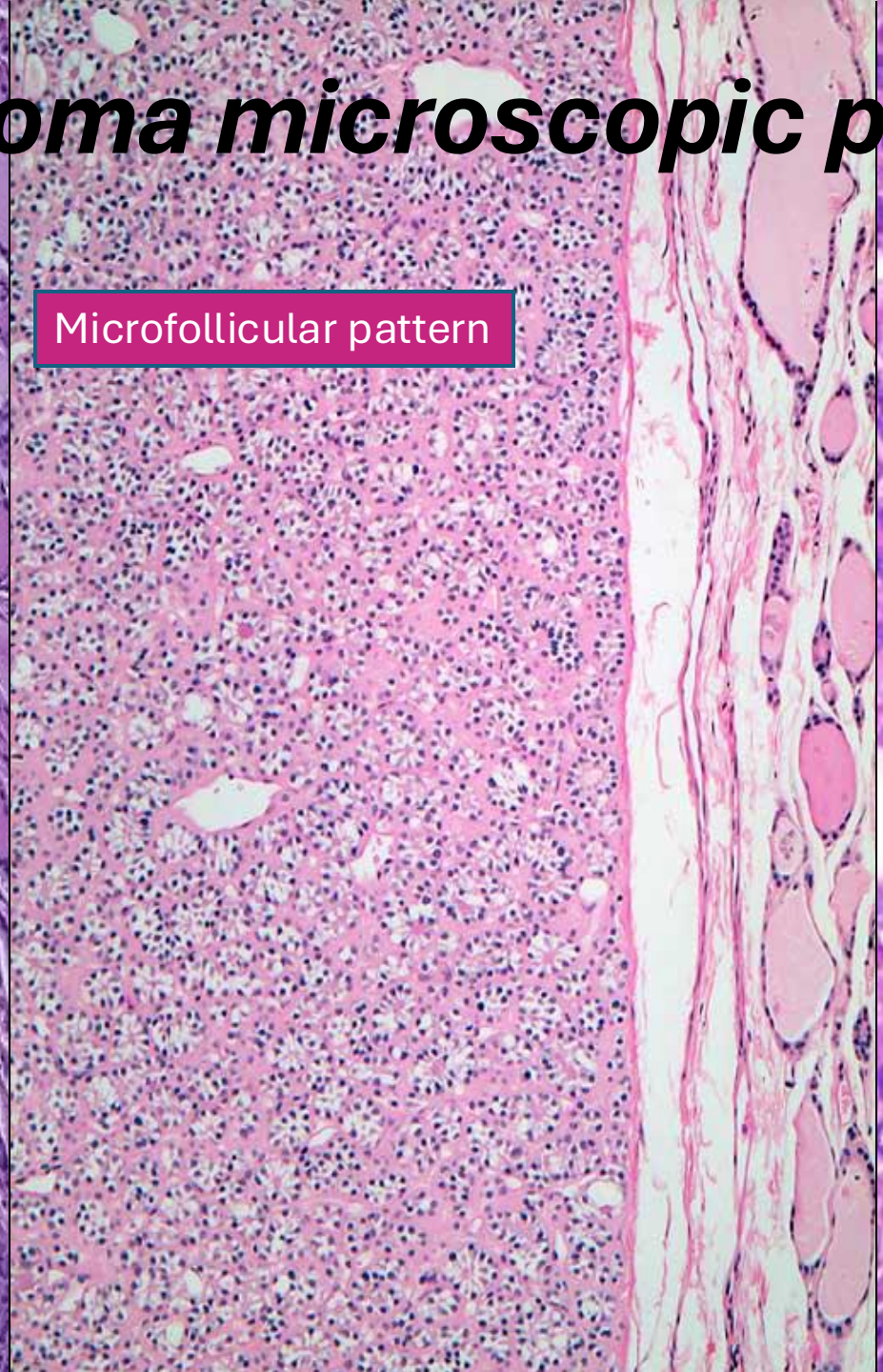
Follicular Adenoma

Complete **thin** capsule and compression of surrounding thyroid tissue

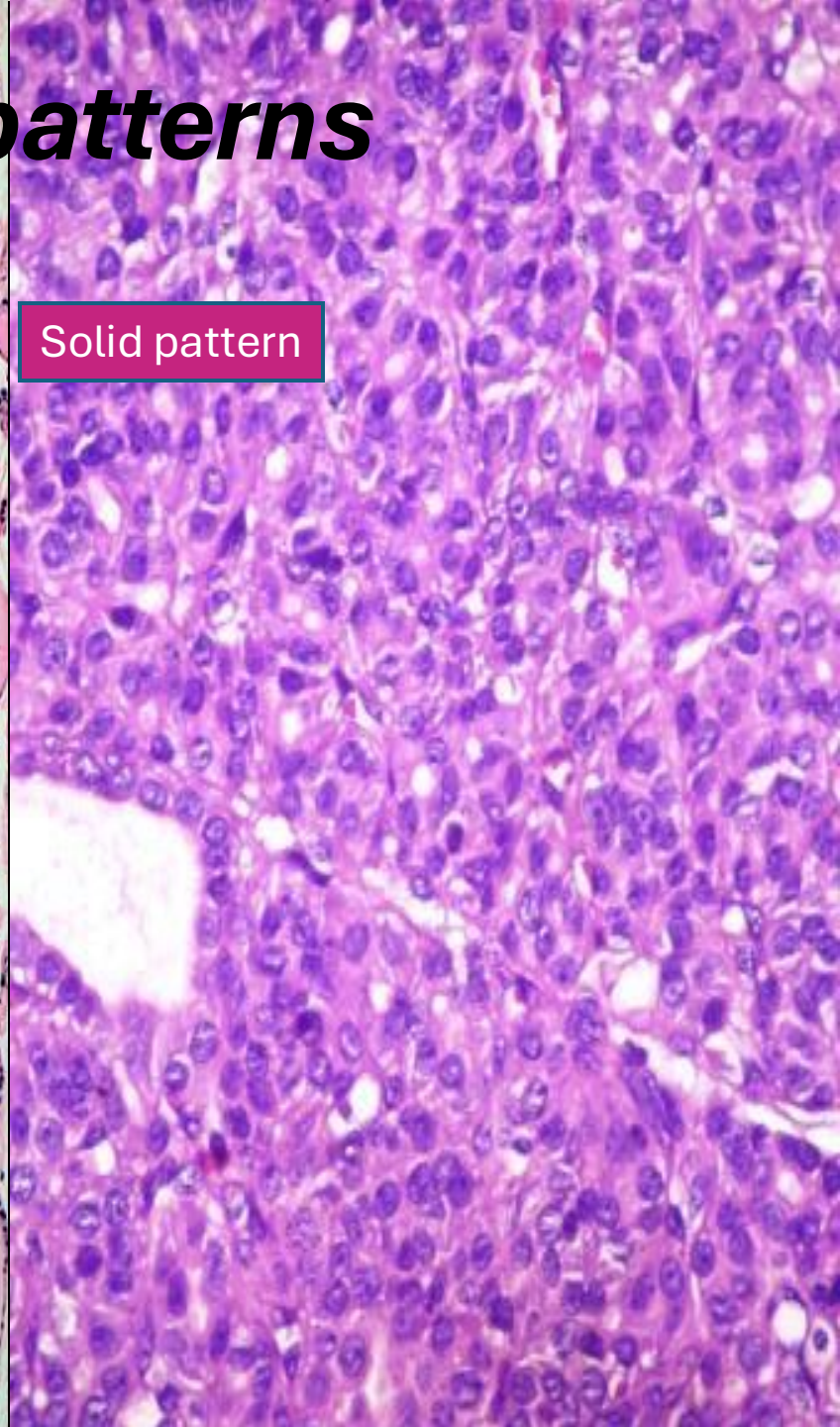
Follicular Adenoma microscopic patterns

Normofollicular and colloid

Complete **thin** capsule and compression of surrounding thyroid tissue



Microfollicular pattern



Solid pattern

Follicular Carcinoma

Second most common tumor (~20%)

Females > Males, (45 – 55 Y/O)

single palpable neck mass

Higher incidence in iodine-deficient regions

Follicular Carcinoma

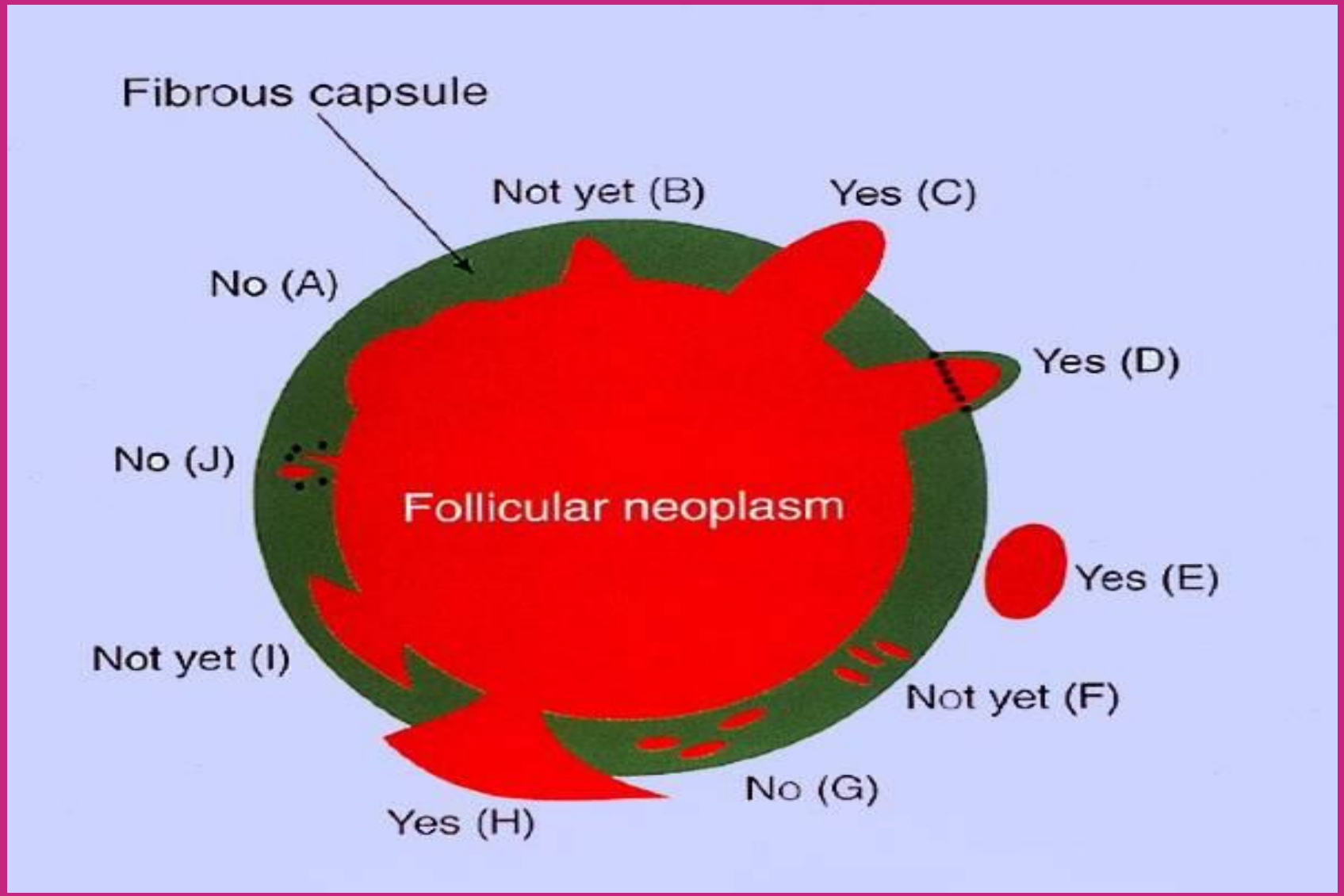
Hematogenous spread

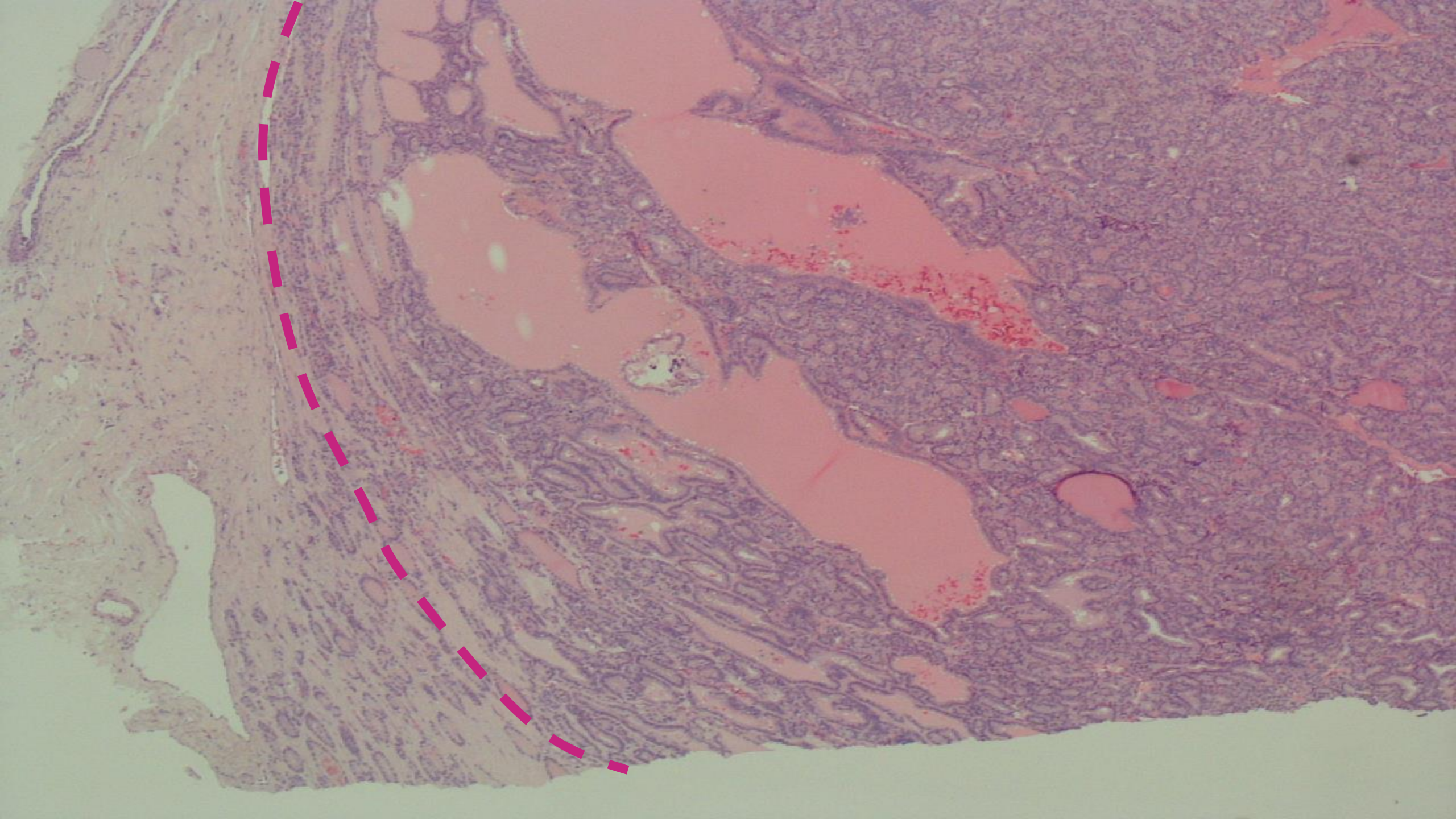
Malignancy determined by vascular invasion or capsular invasion

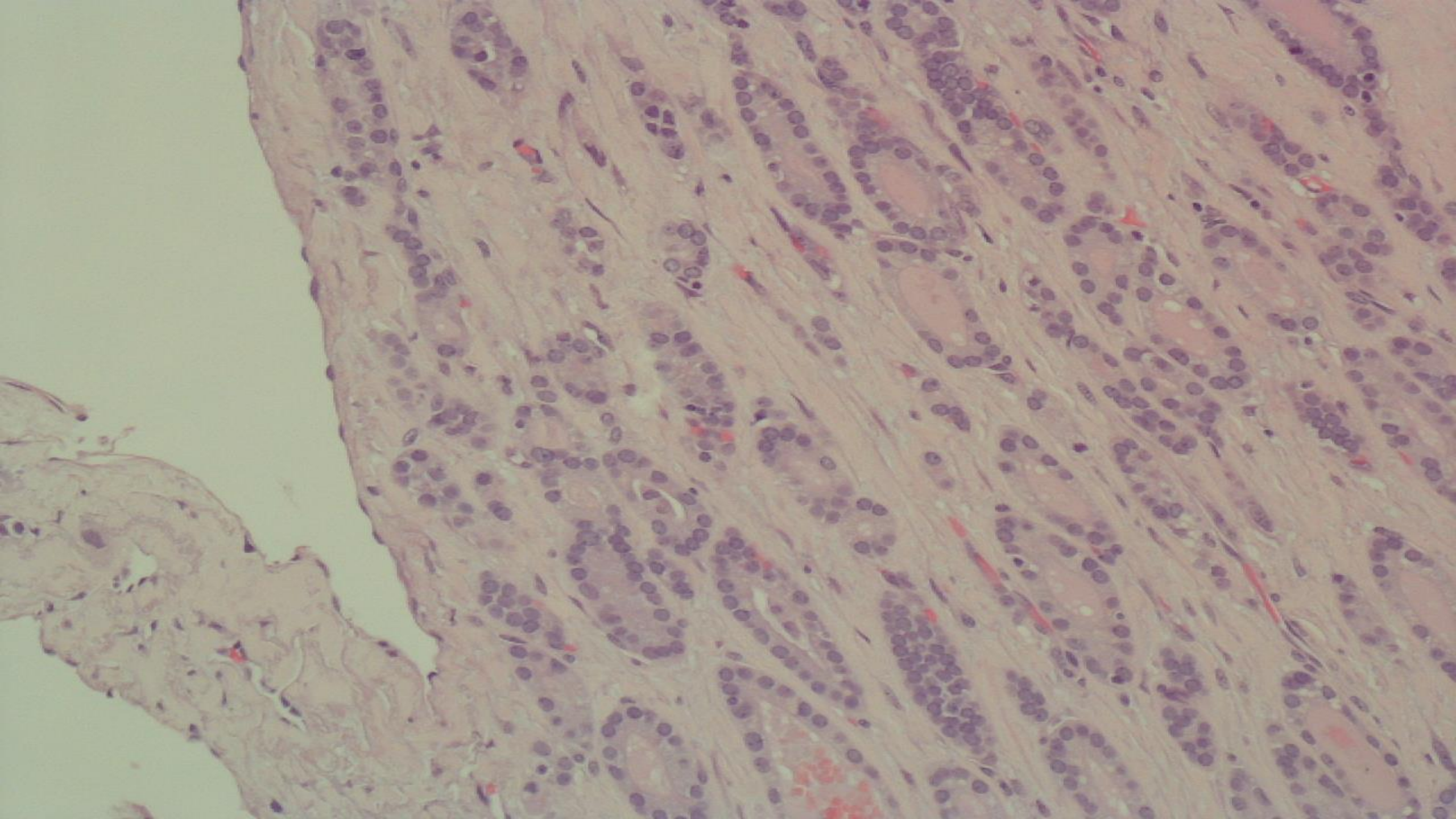
Follicular Carcinoma

- Classical type
- Oncocytic (hurtle cell)
- Clear cell
- Mimimaly invasive
- Widely invasive

Follicular Thyroid Carcinoma: Capsular Invasion





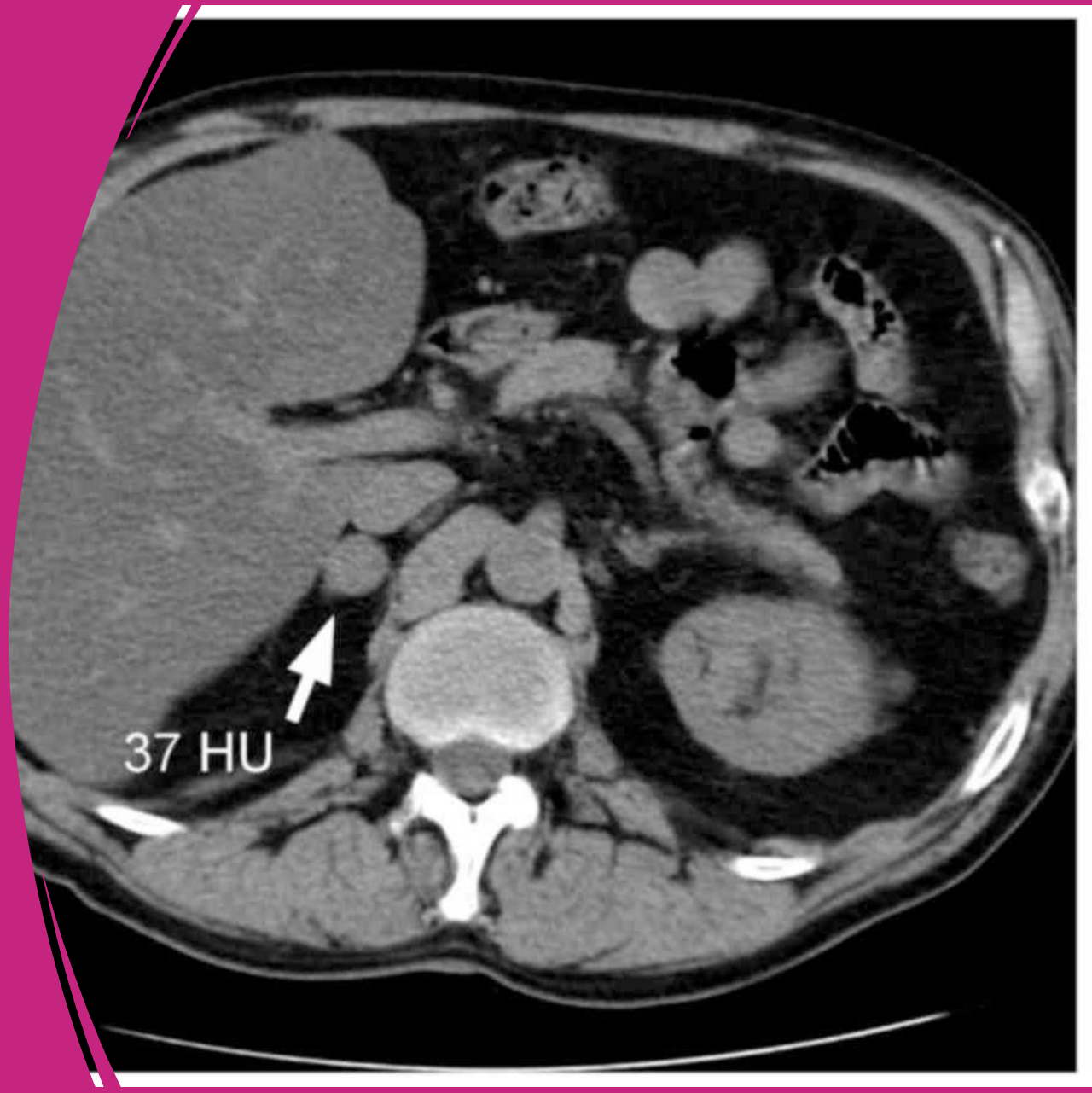


CASE 1

- DIAGNOSIS
  - FOLLICULAR CARCINOMA

CASE 2

38-year-old male with hypertension and episodic palpitations. CT scan reveals a 4 cm right adrenal mass with heterogeneous enhancement. Elevated 24-hour urinary catecholamines and metanephrines. Surgical resection performed.



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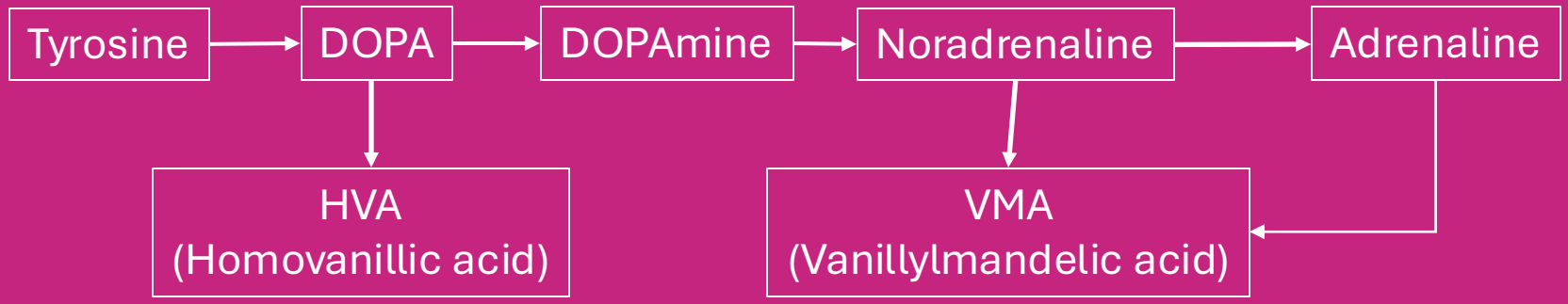
CASE 2

- What is the significance of these findings?



- Adrenal gland produces both norepinephrine and epinephrine
- Paragangliomas only NE
- Neubroblastoma both VMA and HVA
- Antihypertensive drugs will interfere with the test

Adrenal lesions

Benign

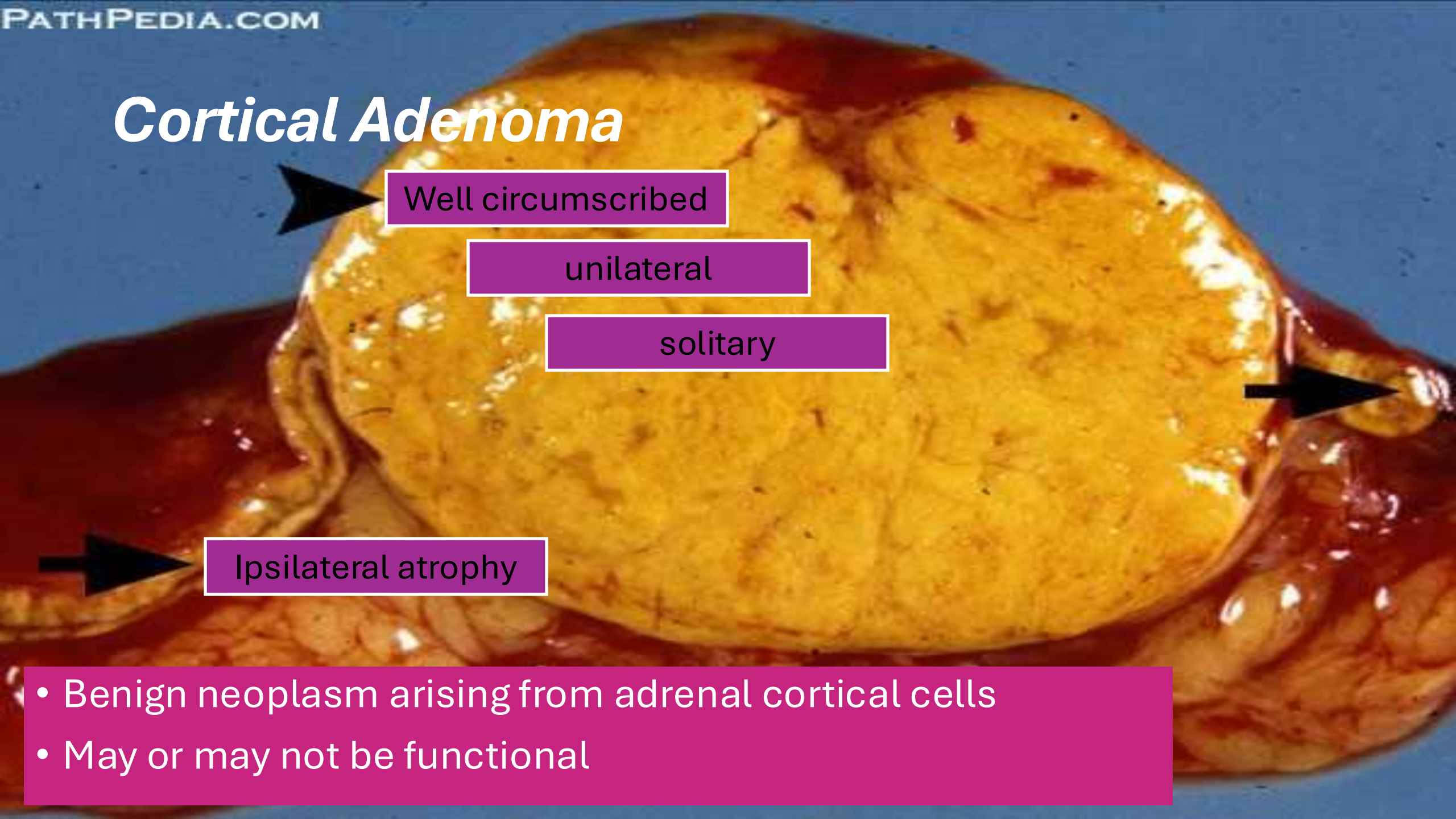
- Adenoma
- Myelolipoma
- Pheochromocytoma
- Ganglioneuroma

Malignant

- Adrenal cortical carcinoma
- Ganglioneuroblastoma

IMPORTANT

- The adrenal gland is the 4th most common site of mets after lung, liver, bone
- Mets indicates Stage IV disease
- Presence of mets always influences treatment management…except in ipsilateral RCC
- Most common sites
  - Lung: 30%
  - Breast: 30%
  - Melanoma: 50%
  - Renal: 10%
  - Thyroid: rare
  - Colon:10%



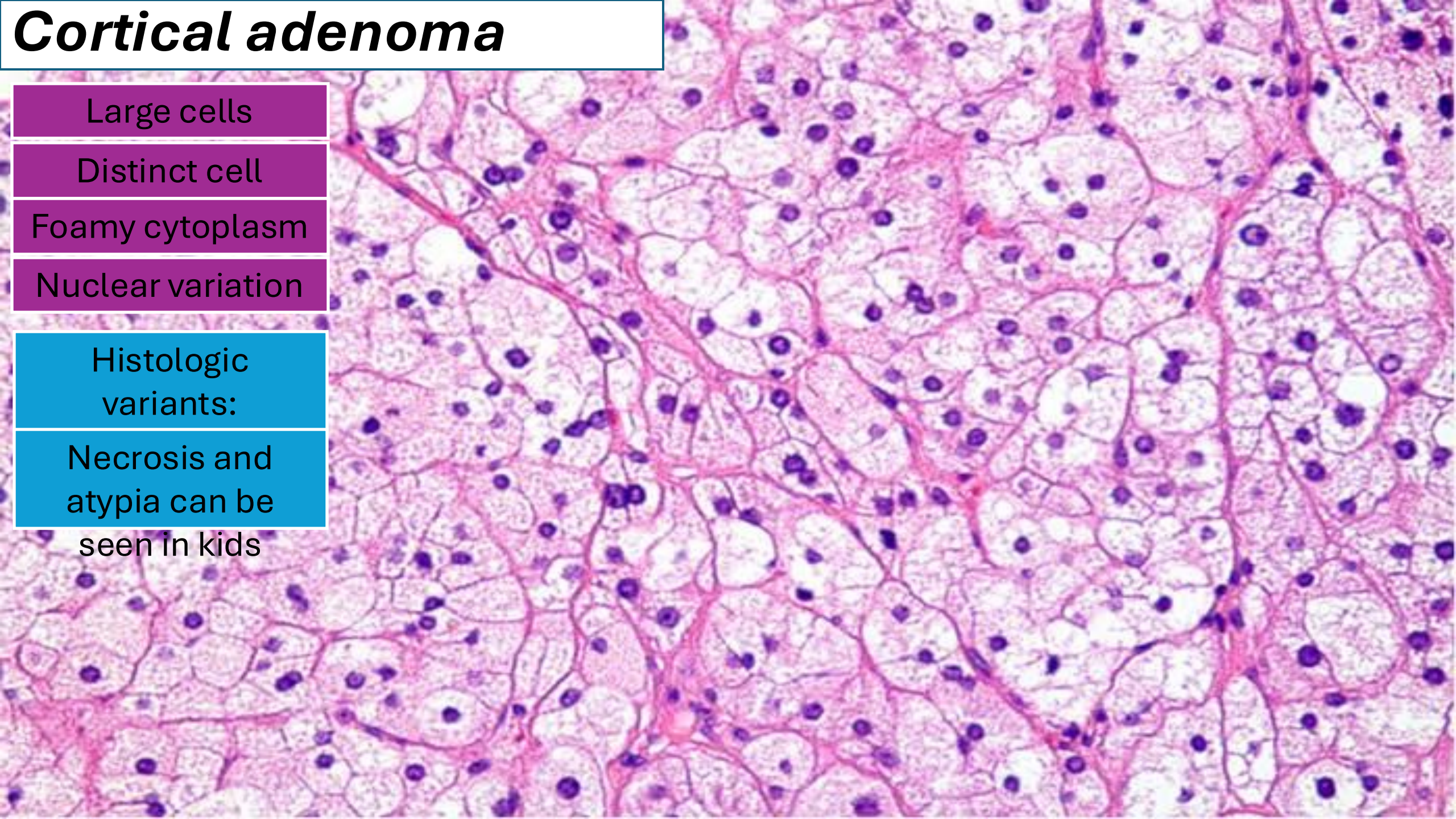
- Benign neoplasm arising from adrenal cortical cells
- May or may not be functional

Cortical adenoma

- Large cells
- Distinct cell
- Foamy cytoplasm
- Nuclear variation

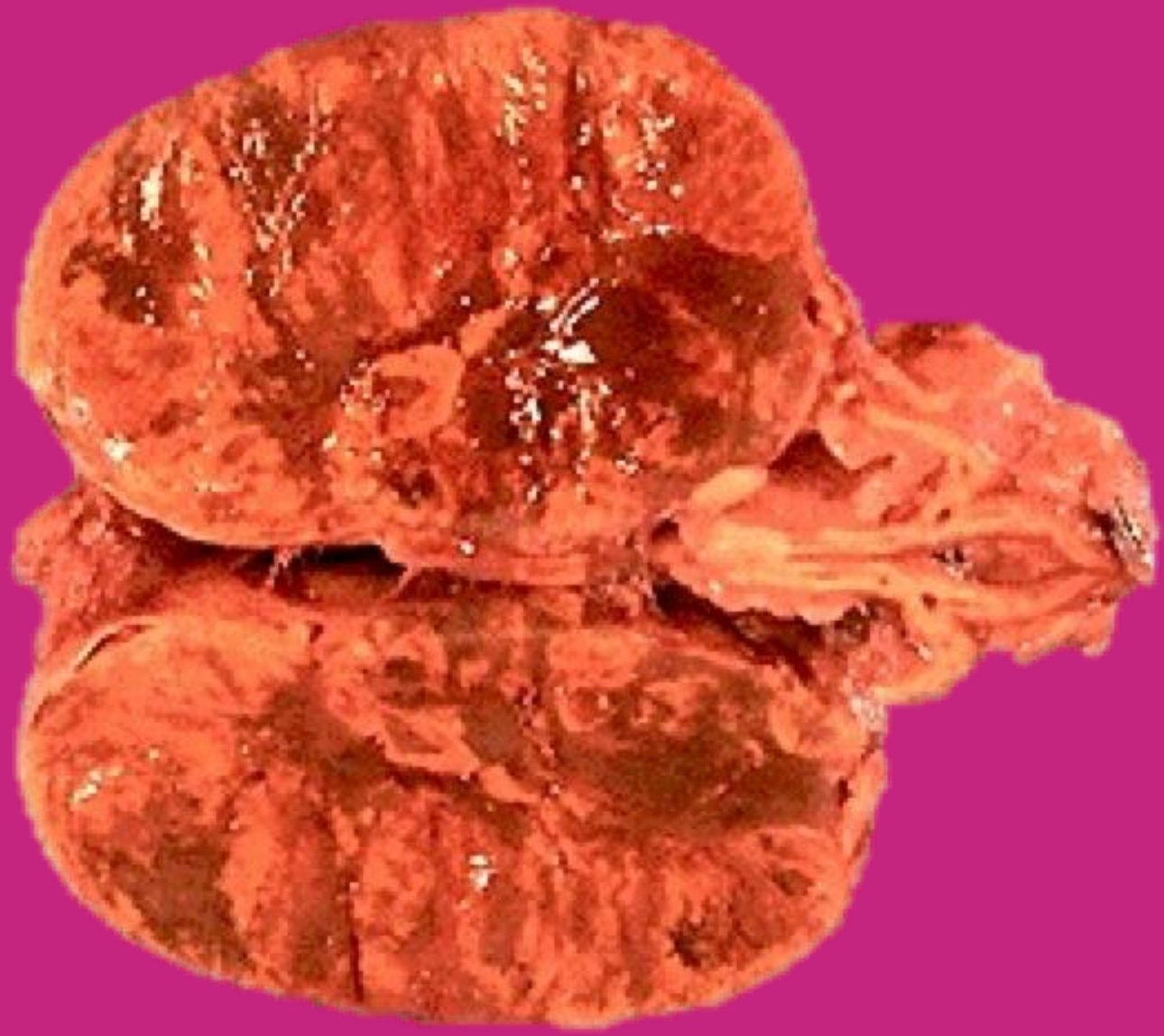
Histologic variants:

Necrosis and atypia can be seen in kids



Adenoma in Cushing

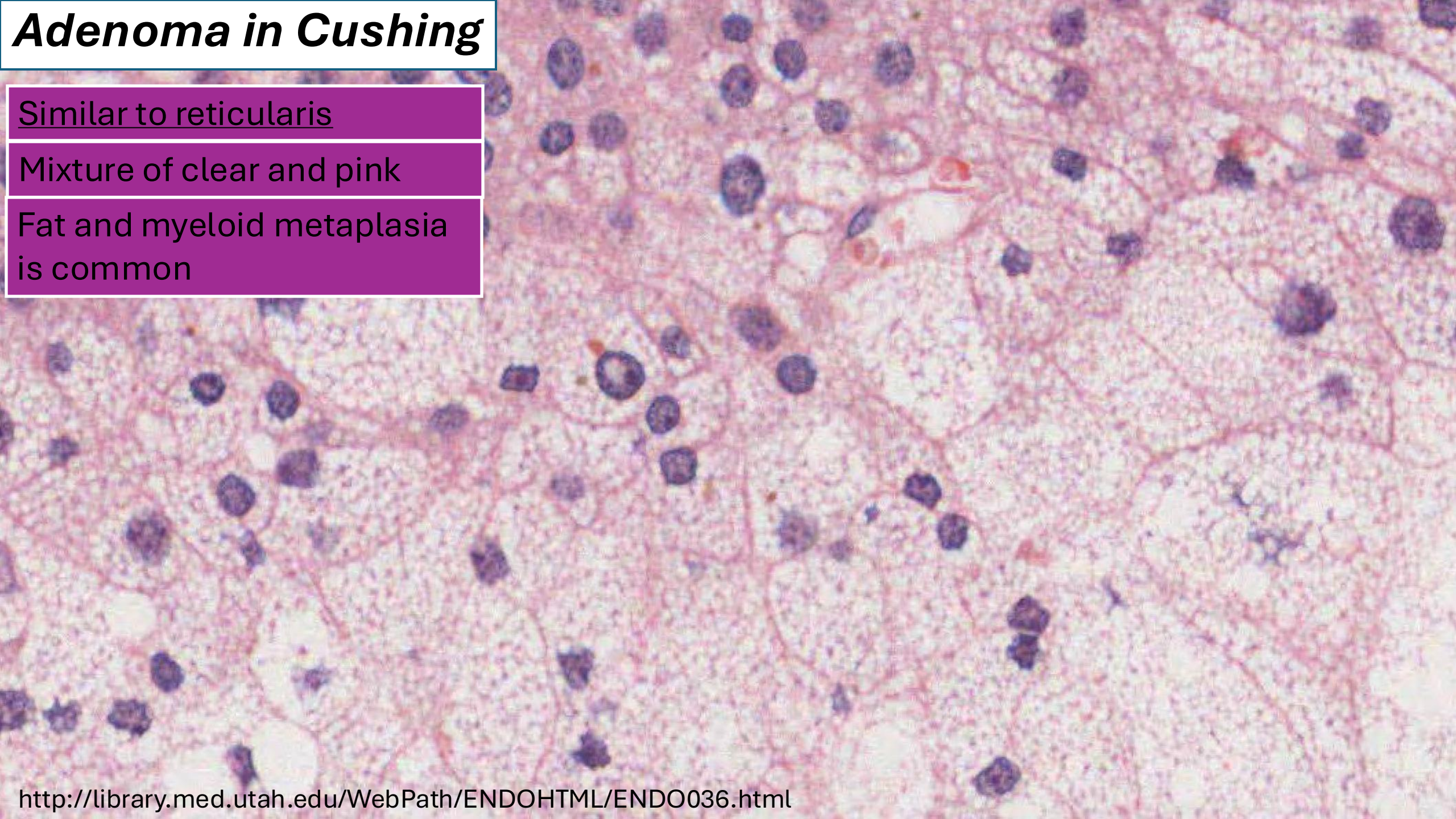
Yellow and
brown or black



http://library.med.utah.edu/WebPath/ENDOHTML/ENDO036.html

Adenoma in Cushing

- Similar to reticularis
- Mixture of clear and pink
- Fat and myeloid metaplasia is common

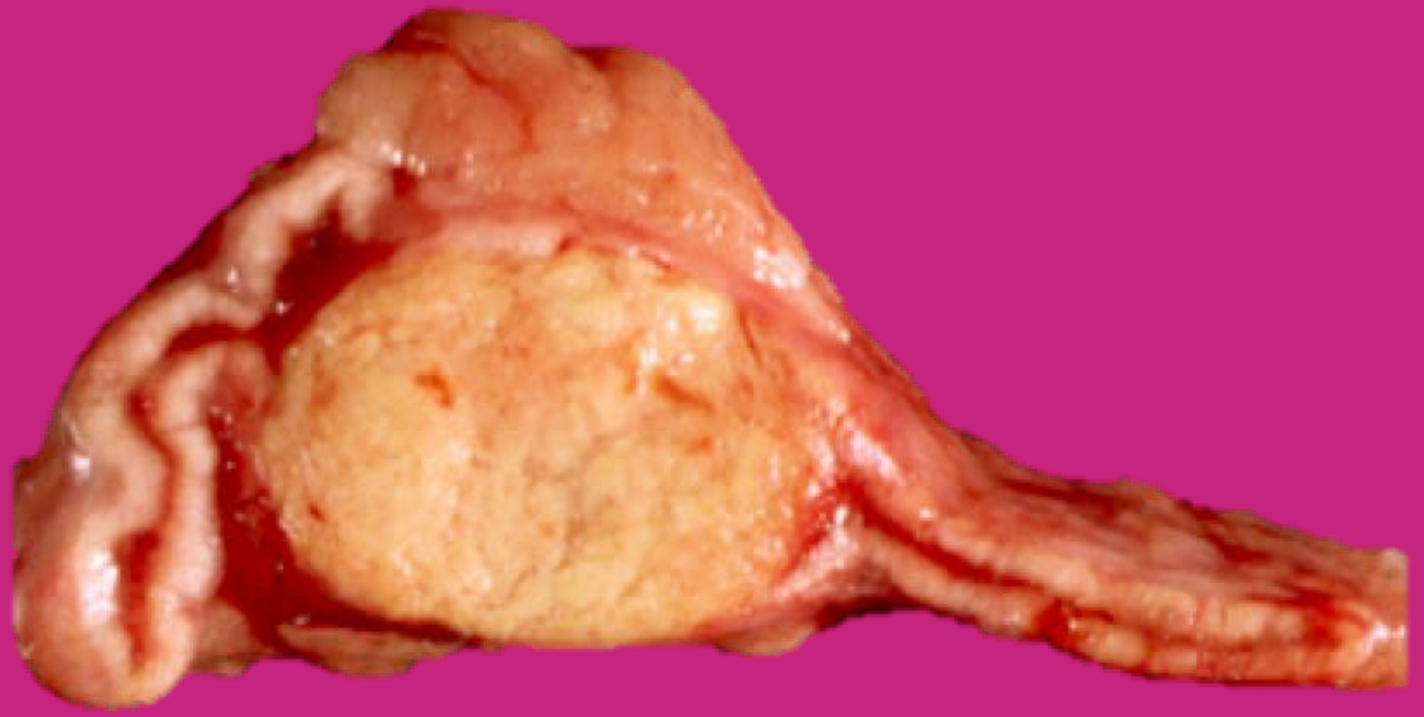


http://library.med.utah.edu/WebPath/ENDOHTML/ENDO036.html

Adenoma in Conn's Syndrome

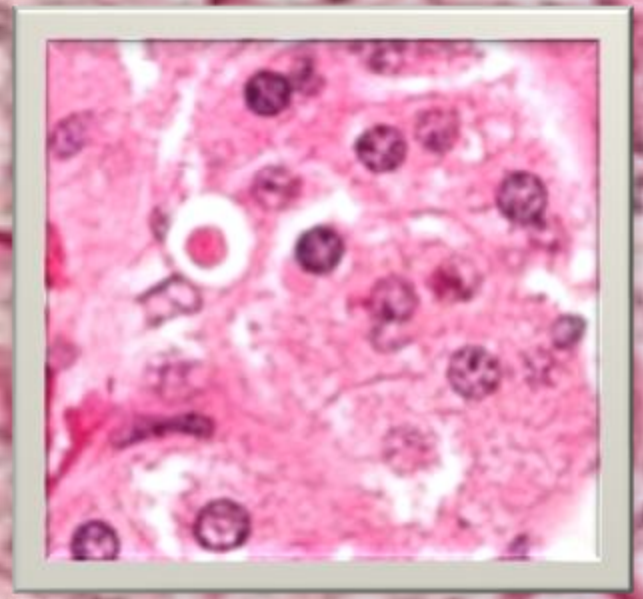
Usually less than 2 cm in size

Yellow on cut surface.



Adenoma in Conn's Syndrome

- Similar to granulosa and/or fasciculata
- Spironolactone bodies



Cortical adenomas

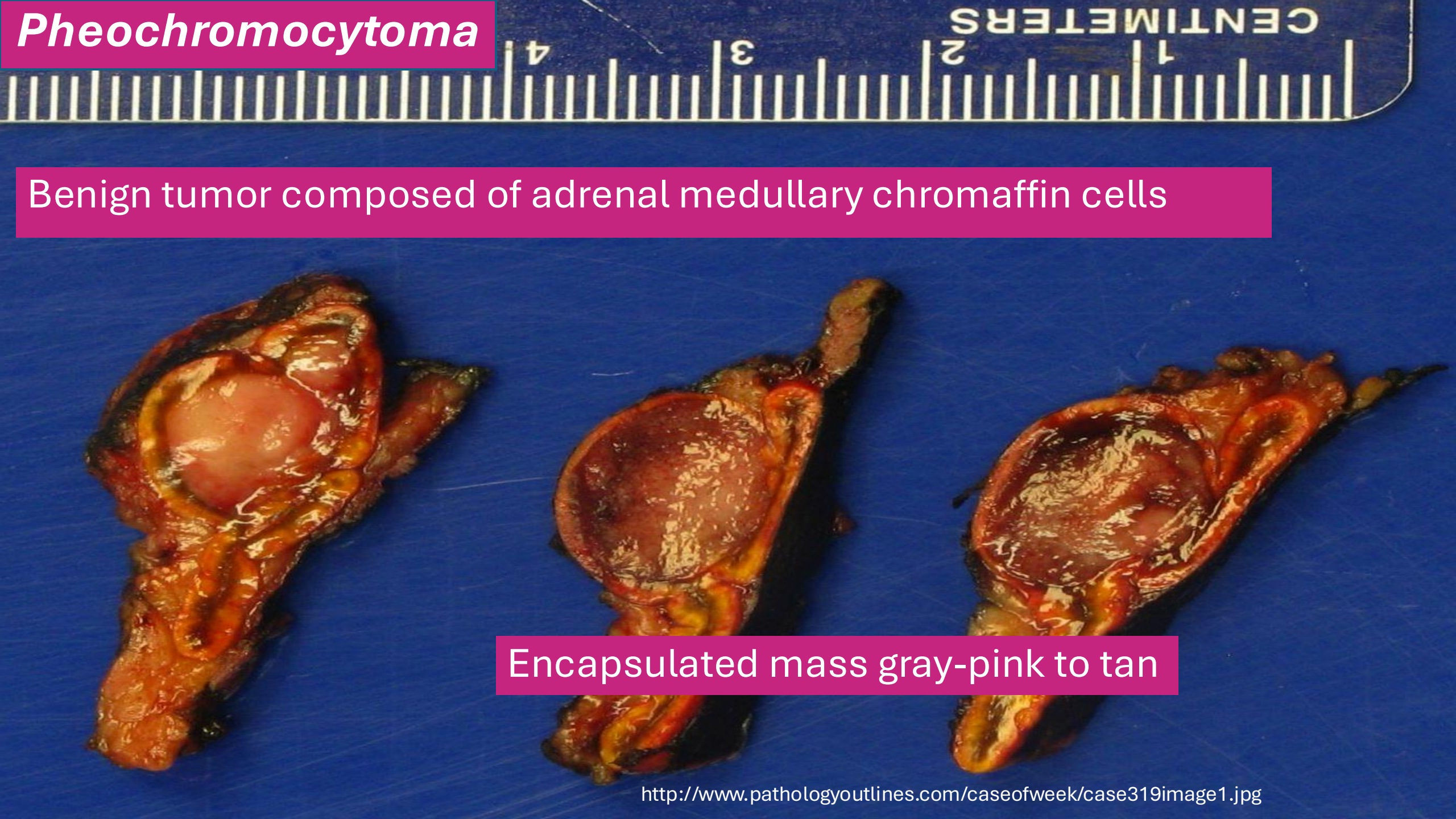
(+)	(±)	(-)
• α-inhibin, Melan-A/Mart-1, steroidogenic factor-1 (SF-1), calretinin	• SYN	• VIM (rarely (+)) • S100 (no subtentacular cells)

Incidentaloma

- ~1cm adrenal mass discovered on exam for non-adrenal cause in the absence of signs or symptoms of adrenal disorder
- 0.5 – 5% of abdominal CTs show abnormal adrenal glands
- **85%** are nonfunctional and **BENIGN**

Pheochromocytoma

Benign tumor composed of adrenal medullary chromaffin cells



Encapsulated mass gray-pink to tan

http://www.pathologyoutlines.com/caseofweek/case319image1.jpg

Pheochromocytoma

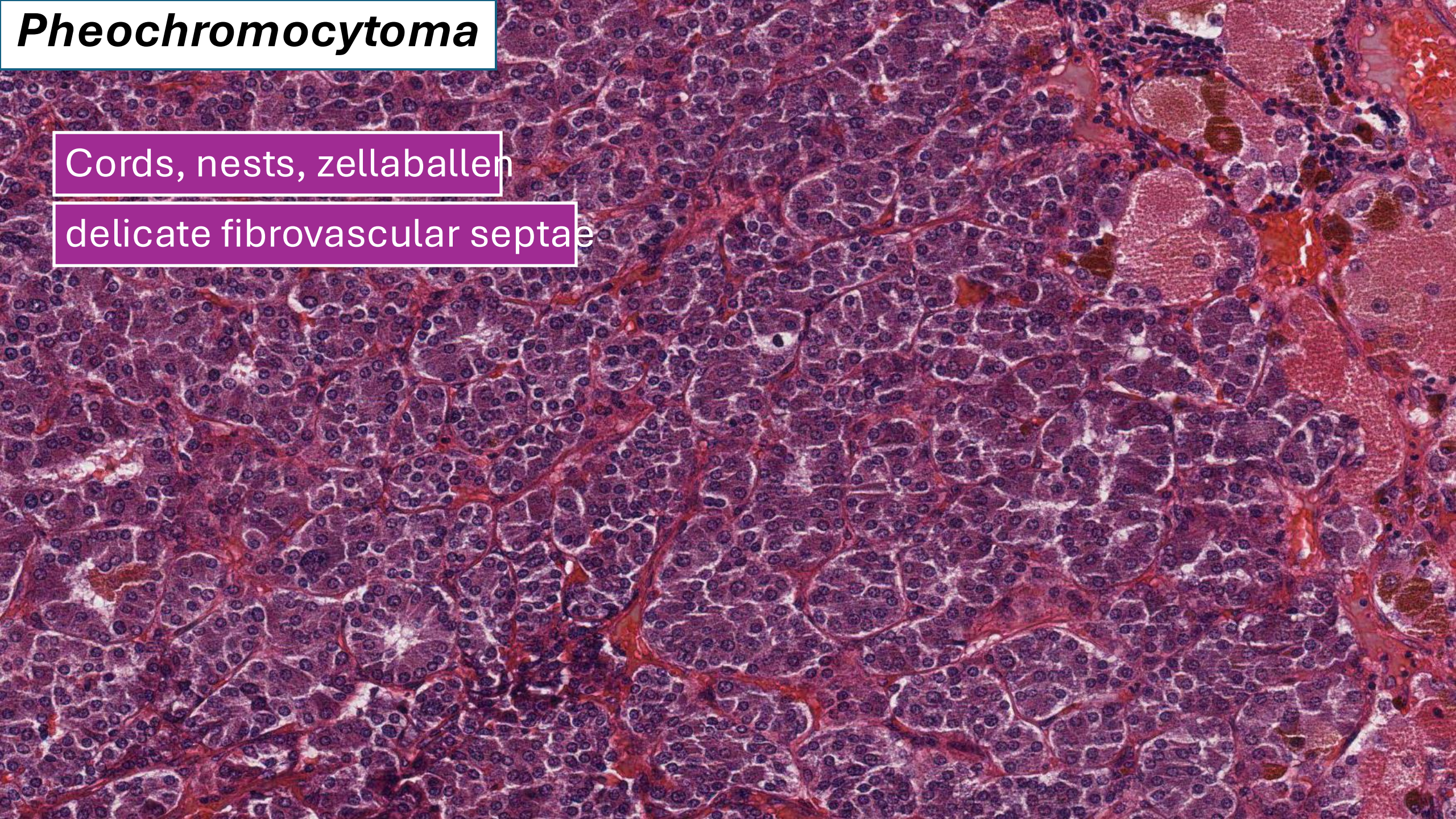
- Rule of 10s (for familial cases):
  - 40-50s. 10% in kids
  - 10% extraadrenal (paraganglioma)
  - 10% familial
  - 10% bilateral

Pheochromocytoma

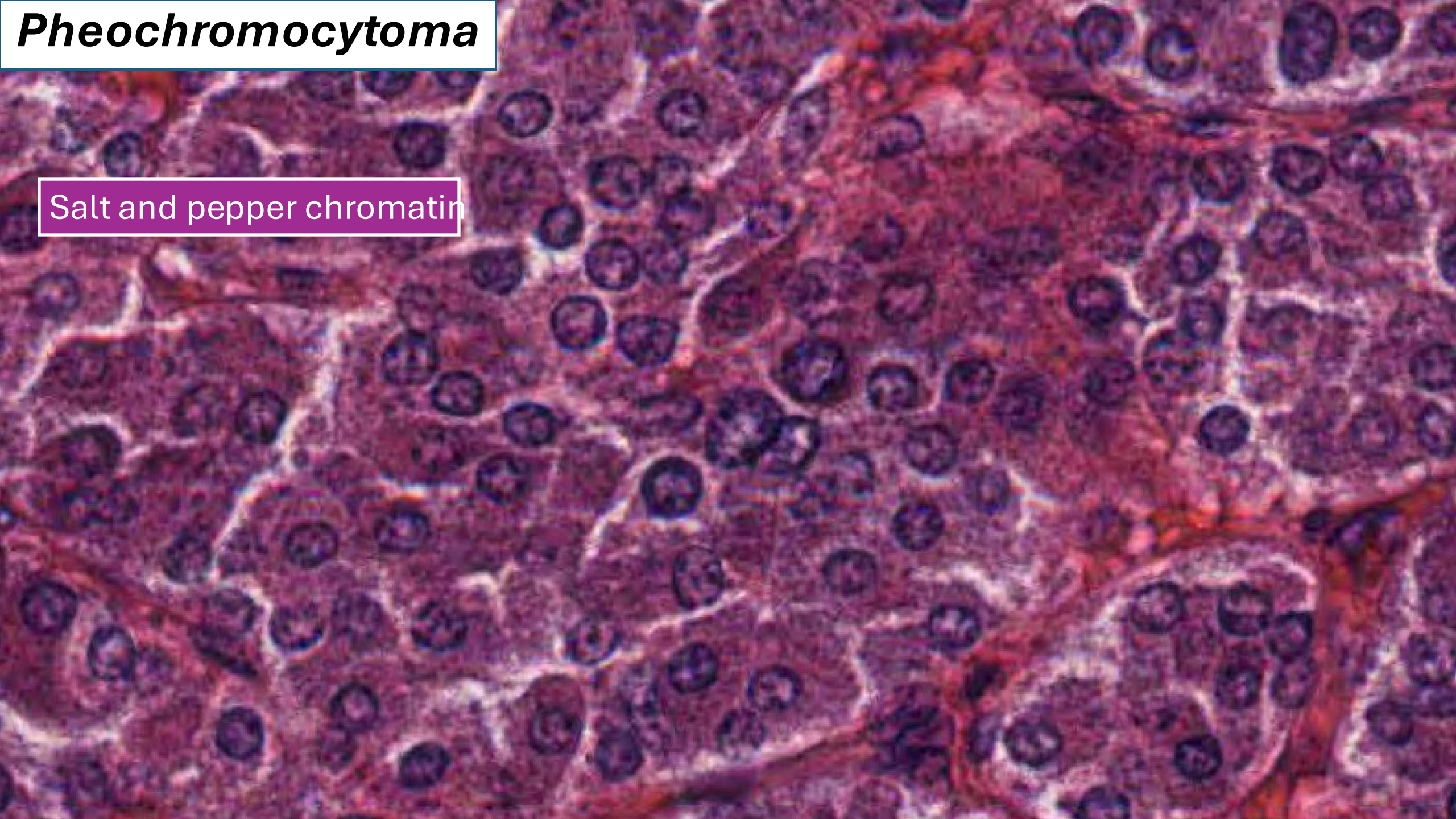
- Occasionally associated with melanoma, adrenal cortical tumors, and paragangliomas
- Up to 25% of cases have germ line mutations:
  - RET gene →type 2 MEN syndrome
  - GNAQ (?) → Sturge-Weber
  - VHL → Von Hippel Lindau
  - NF1 → Neurofibromatosis type 1 (Von Recklinghausen)
  - SDHB, SDHC, SDHD → no name yet *

* succinate dehydrogenase complex

Pheochromocytoma



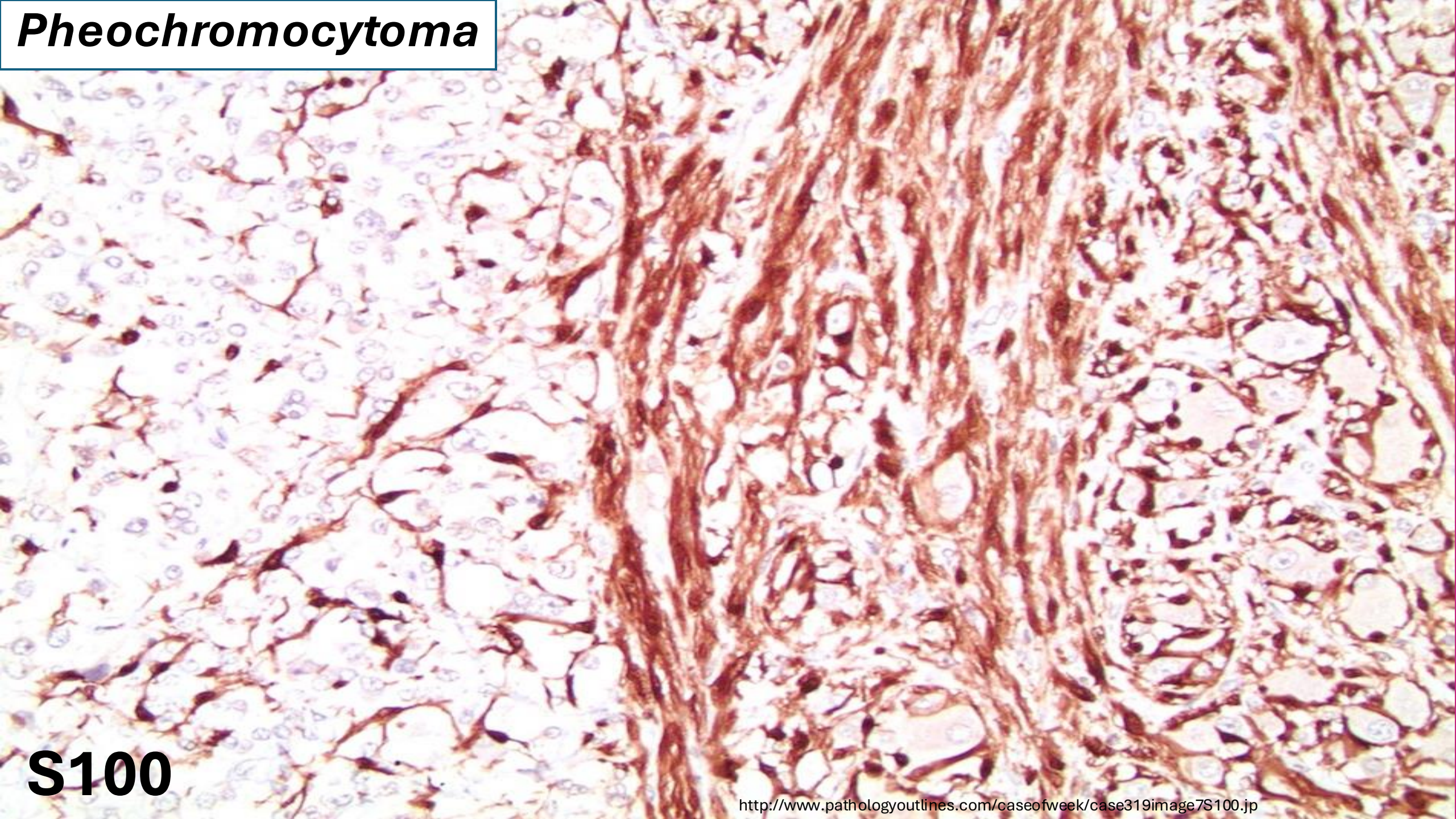
Pheochromocytoma



Pheochromocytoma

(+)	(-)
• Chr, Syn, Neurofilament, S100 in spindled subtentacular cells	• CK, VIM

Pheochromocytoma



S100

http://www.pathologyoutlines.com/caseofweek/case319image7S100.jp

Pheochromocytoma

Criteria for malignancy

- Metastasis
  - most reliable
  - lymph nodes, liver, lung or bone
- PASS Score (Pheochromocytoma of the Adrenal gland Scaled Score)

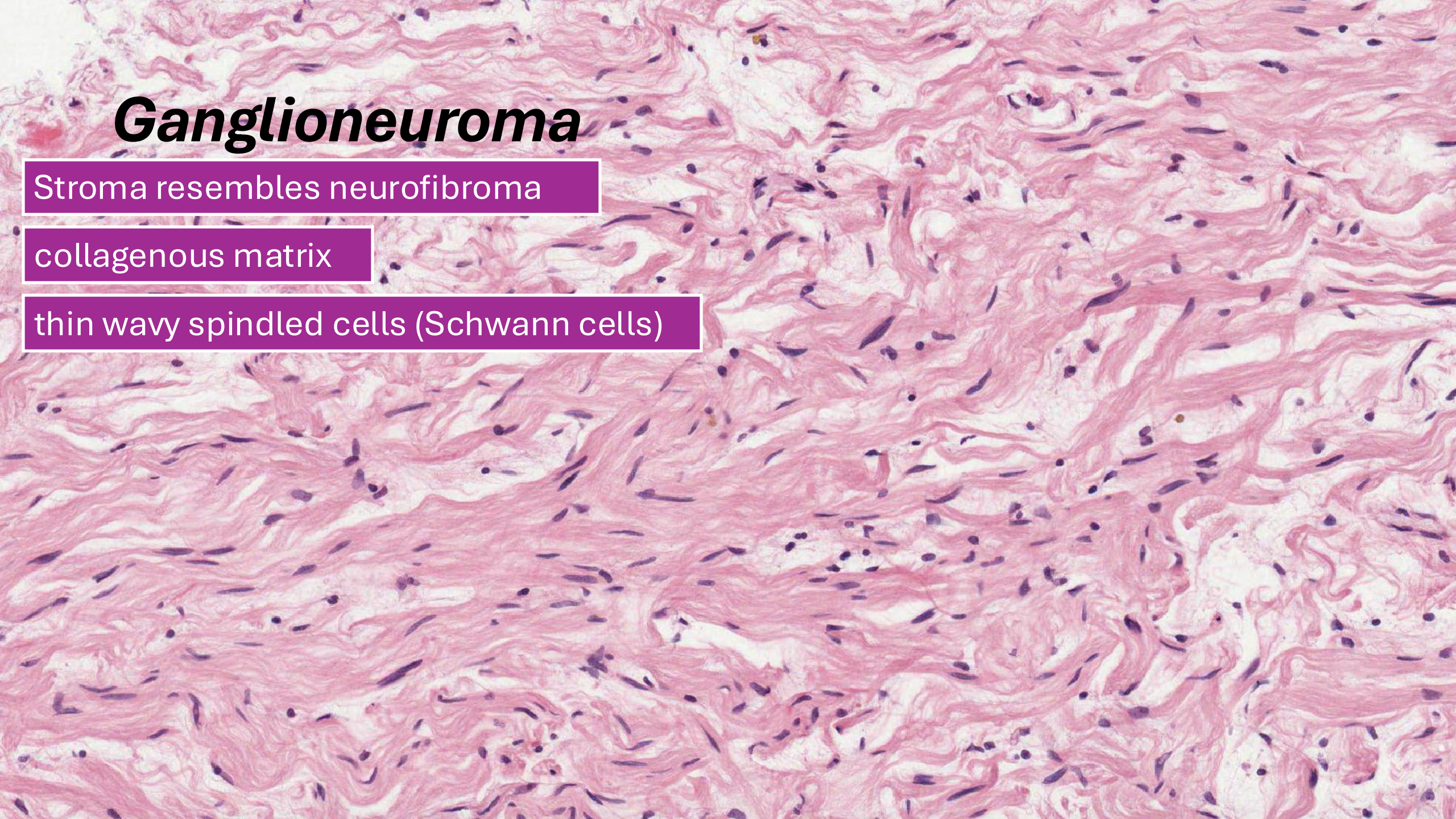
1 point	2 points
• vascular invasion • capsular invasion • profound nuclear pleomorphism or hyperchromasia	• invasion of periadrenal adipose tissue • large nests or diffuse growth, focal or confluent necrosis • high cellularity • tumor cell spindling • cellular monotony • 4+ mitotic figures per 10 high power fields • atypical mitotic figures

0-3= Benign
>4= Potential for malignant

Surgery 2008;143:759

Ganglioneuroma

- Arise in adrenal medulla and ganglia
- Kids and young adults
- May evolve to MPNST



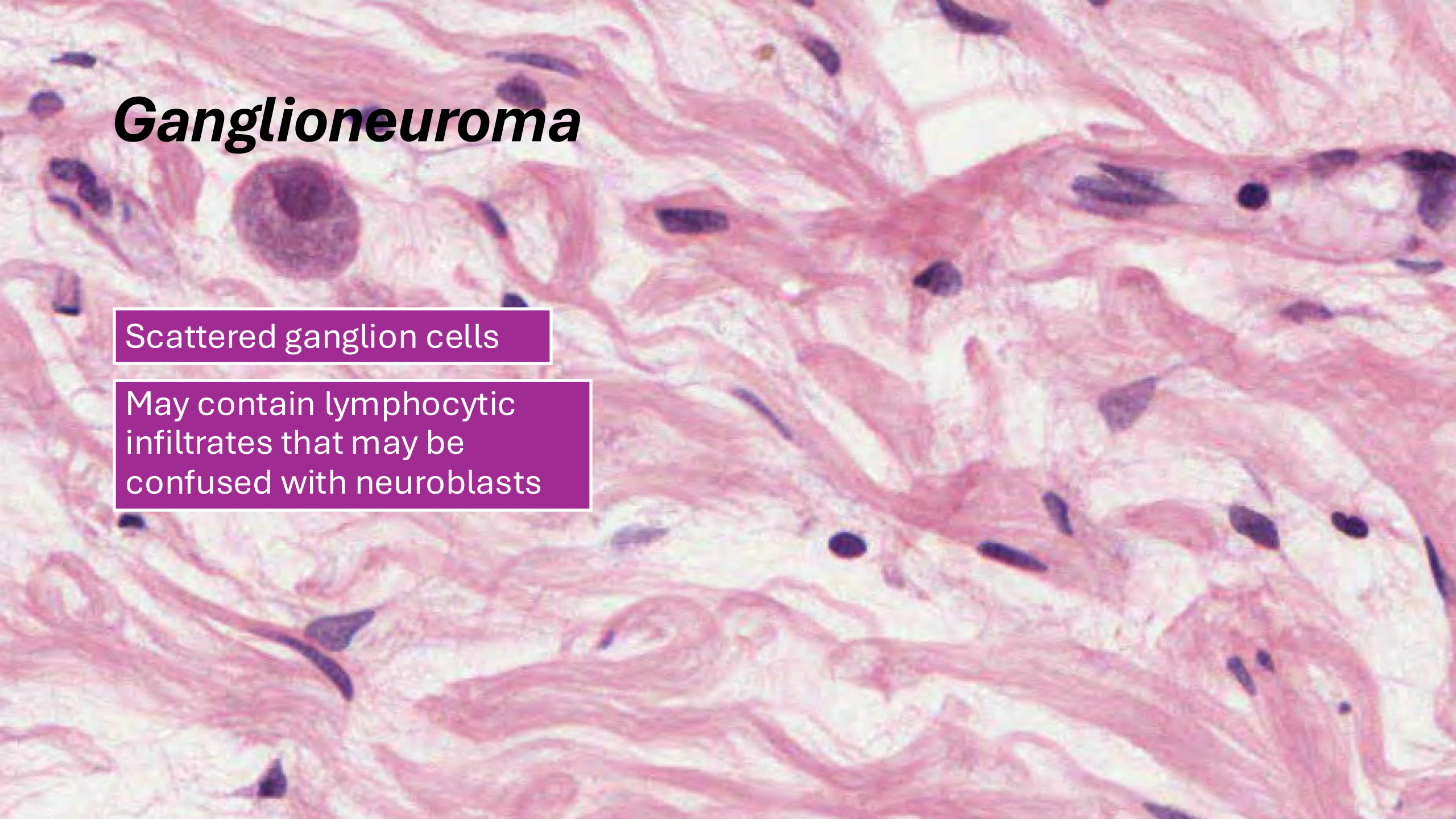
Ganglioneuroma

Stroma resembles neurofibroma

collagenous matrix

thin wavy spindled cells (Schwann cells)

Ganglioneuroma



- Scattered ganglion cells
- May contain lymphocytic infiltrates that may be confused with neuroblasts

Ganglioneuroma

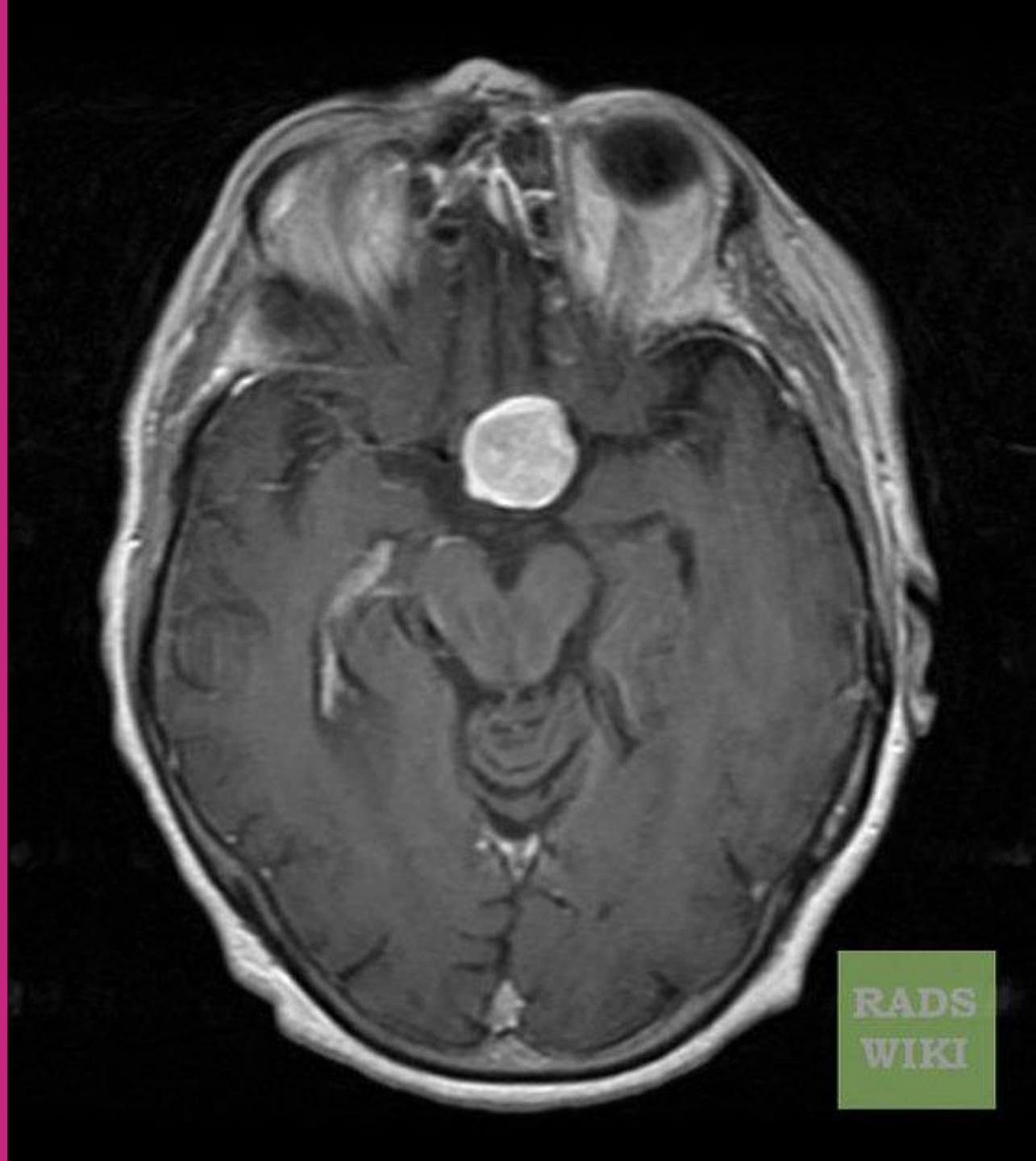
(+)
•S100 in stroma •neurofilament, Chr, NSE in ganglion cells

CASE 2

- DIAGNOSIS
  - PHEOCHROMOCYTOMA

CASE 3

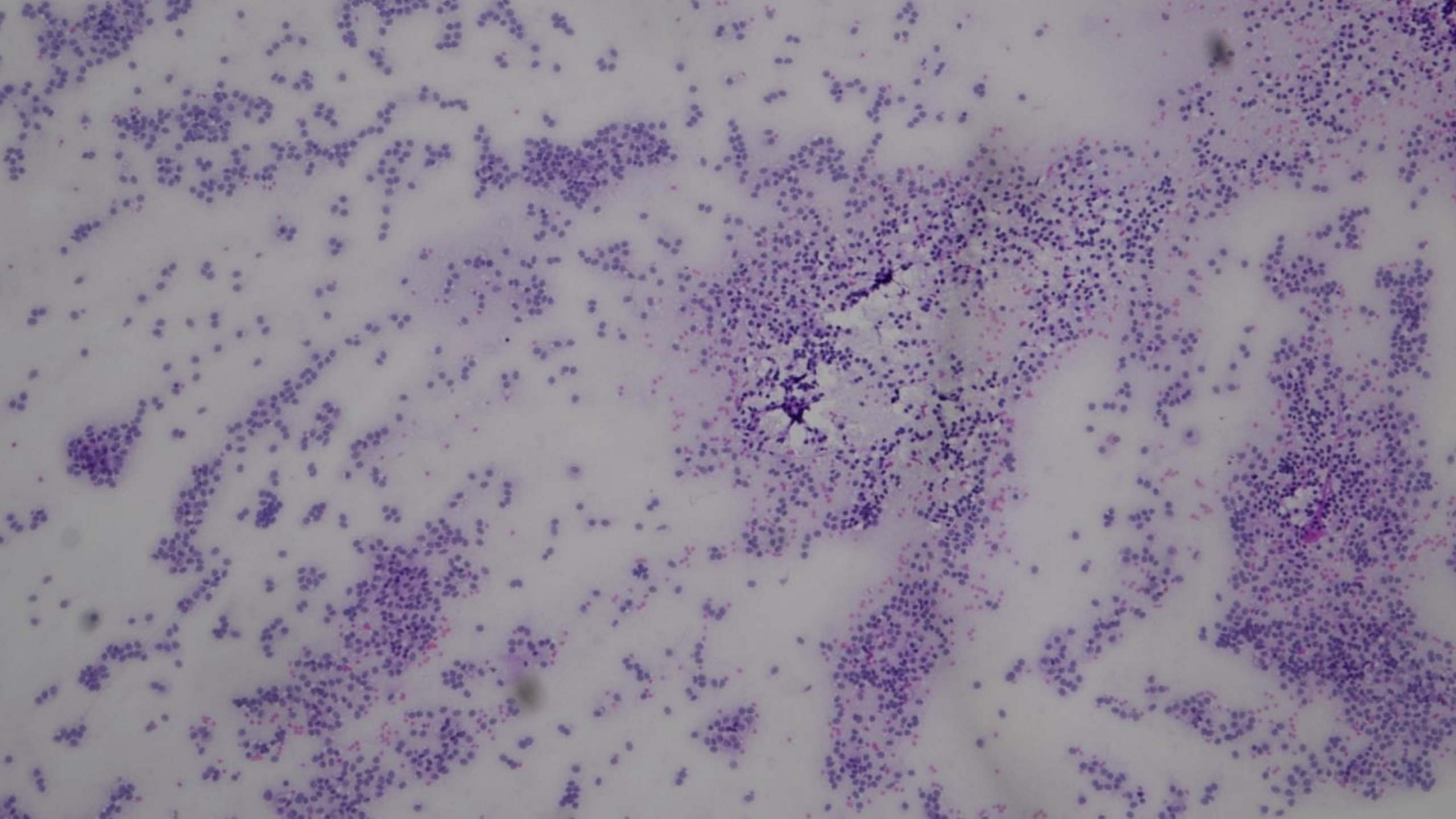
29-year-old female with amenorrhea and galactorrhea for 8 months. MRI shows a 1.2 cm sellar mass with suprasellar extension. Elevated serum prolactin (180 ng/mL). Transsphenoidal resection performed due to visual field defects.

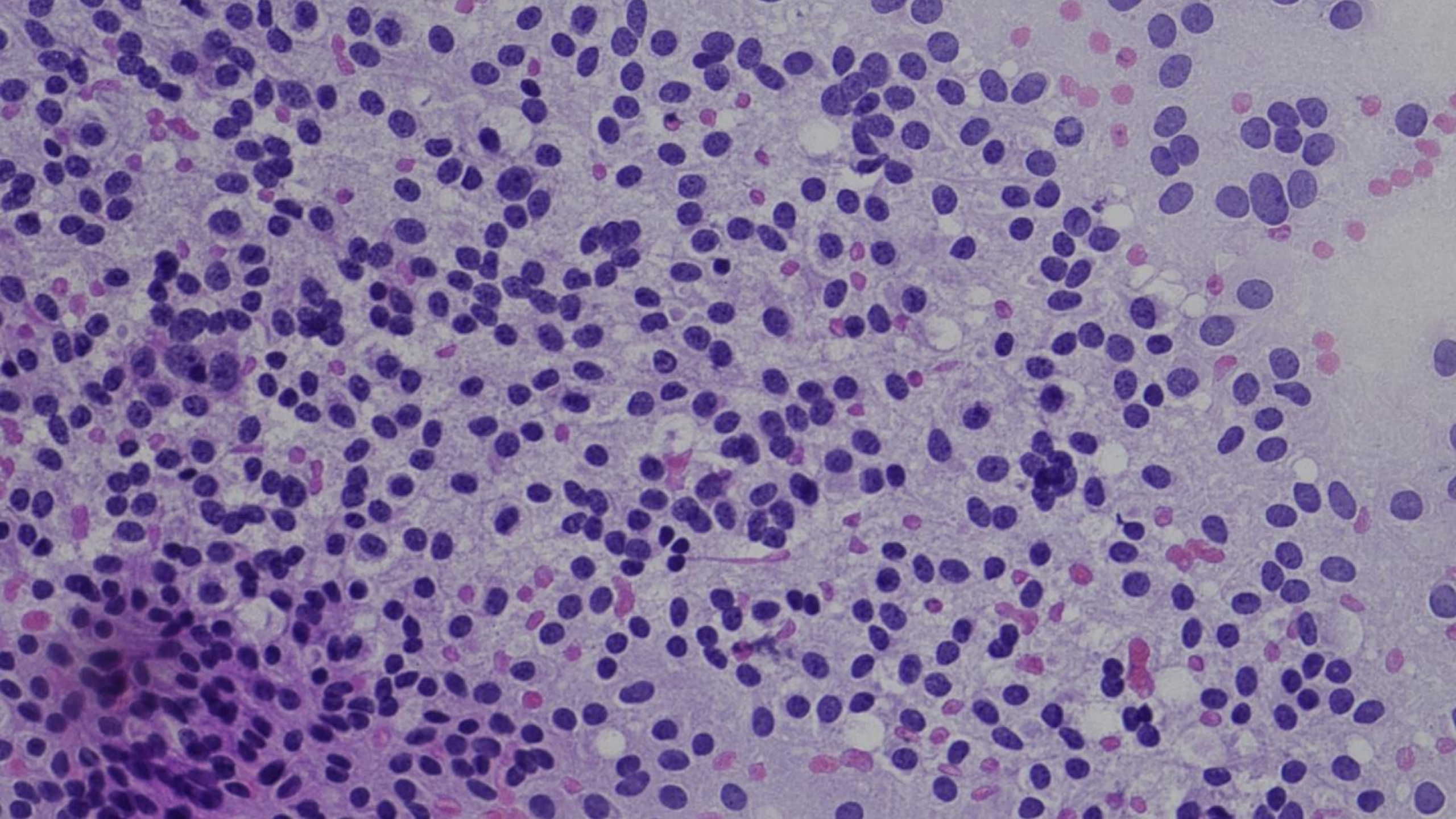


Case 3

The patient is scheduled for surgery the day you are on frozen section. You received 2 small fragments of soft tan tissue.

What would you do next?





CASE 3

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https://www.digitalscope.org/ViewerUI/?SlideId=d2e7604f-0e3d-4b1f-aaf3-e173fe3b5d81

Endocrine Pituitary gland tumors

Adenoma (pituitary neuroendocrine tumor)

Carcinoma

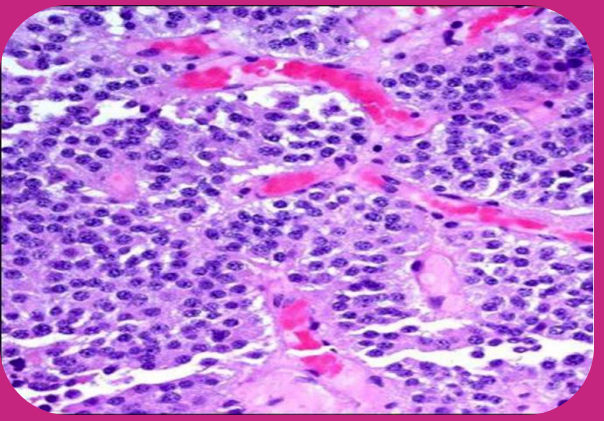
Pituitary adenoma (pituitary neuroendocrine tumor)

- Microadenoma: <1cm, usually functional
- Macroadenoma: >1cm, usually non-functional. Mass effect
- “Stalk effect” mild prolactin (PRL) elevation
- “Invasive adenoma” = gross intraoperative or radiologic descriptor;

Pituitary adenoma (pituitary neuroendocrine tumor)

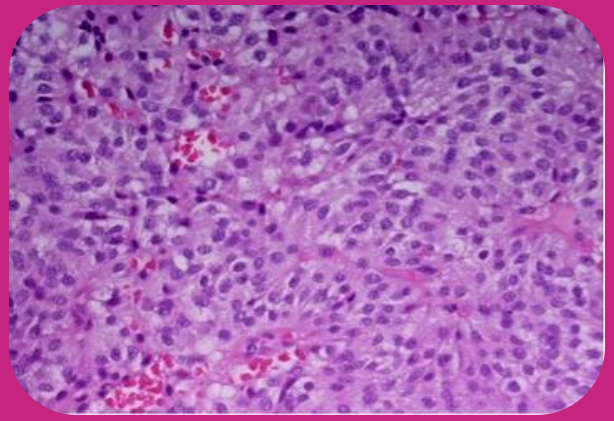
- **Loss of acinar architecture** and the presence of prominent nucleoli are helpful in distinguishing adenoma from normal pituitary
- **Reticulin stain** helpful to highlight architecture. Adenomas are reticulin poor
- Simple microscopic invasion of dura alone is unimportant

Pituitary adenoma (pituitary neuroendocrine tumor)



Prolactinomas

- **<u>50% of pituitary adenomas</u>**
- Chromophone cells with central nucleus
- Psammoma bodies, lamelar bodies
- High N/C and fibrosis if treated with dopamine agonist

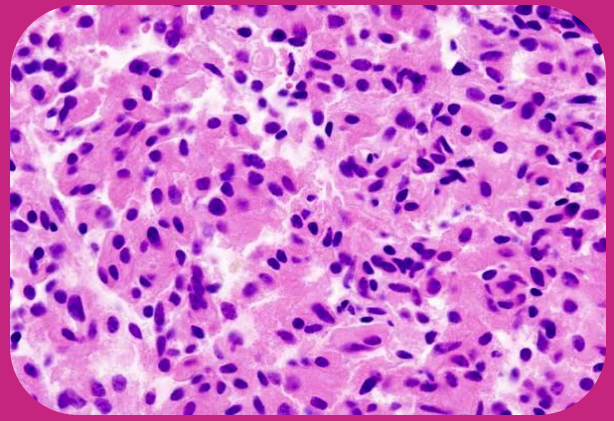


Gonadotroph adenoma (Null cell):

<u>Most indolent</u>

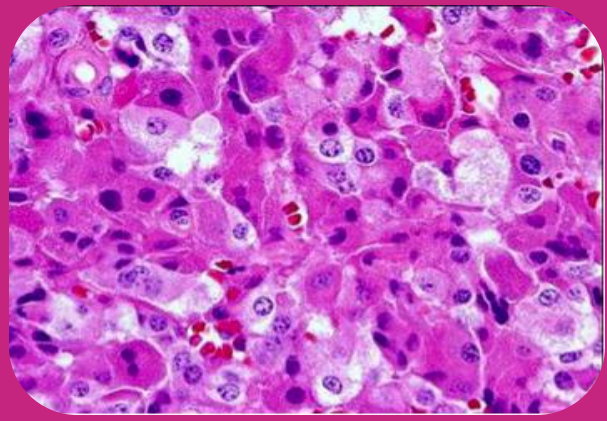
Chromophobic cells

perivascular rosettes or papillae.



Growth hormone adenoma

- 20% of pituitary adenomas
- Acromegaly
- **<u>Up to 50% are invasive</u>**



Corticotroph adenoma

- 10% of pituitary adenomas
- strong PAS (+). Cushing Sdr.

http://radiopaedia.org/cases/pituitary-macroadenoma-prolactinoma
http://radiopaedia.org/cases/silent-gonadotroph-cell-adenoma
https://commons.wikimedia.org/wiki/File:Pituitary_adenoma_(2)_GH_production.jpg
http://emedicine.medscape.com/article/1868045-overview#a3

Pituitary adenoma (pituitary neuroendocrine tumor)

- Includes categories like null cell adenomas and plurihormonal tumors and uses histological markers like Ki-67 (>3%) to assess risk and invasion potential.
- **PIT1 Lineage:** GH, Prolactin, TSH adenomas, as well as mixed tumors.
- **TPIT Lineage:** ACTH adenomas
- **SF1 Lineage:** FSH and LH adenomas

Table 1 The 2022 WHO classification of pituitary neuroendocrine tumors (PitNETs)

PitNET Type	Subtype	Transcription factors	Hormones	LMWK
PIT1-lineage PitNETs				
Somatotroph tumors	Densely granulated somatotroph tumor	PIT1	GH, α-subunit	Perinuclear
	Sparsely granulated somatotroph tumor	PIT1	GH	Fibrous bodies (> 70%)
Lactotroph tumors	Sparsely granulated lactotroph tumor	PIT1, ERα	PRL (paranuclear dot-like)	Weak or negative
	Densely granulated lactotroph tumor		PRL (diffuse cytoplasmic)	Weak or negative
Mammosomatotroph tumor		PIT1, ERα	GH (predominant), PRL, α-subunit	Perinuclear
Thyrotroph tumor		PIT1, GATA3	α-subunit, βTSH	Weak or negative
Mature plurihormonal PIT1-lineage tumor		PIT1, ERα, GATA3	Monomorphic tumor cells with predominant GH expression and variable PRL, βTSH, and α-subunit	Perinuclear
Immature PIT1-lineage tumor		PIT1 (ERα, GATA3)	Monomorphic tumor cells with focal/variable staining for no hormones, or one or more of GH, PRL, βTSH, and/or α-subunit	Focal/variable
Acidophil stem cell tumor		PIT1, ERα	Monomorphic tumor cells with PRL (predominant) and GH (focal/variable)	Scattered fibrous bodies
Mixed somatotroph and lactotroph tumor*		PIT1, ERα**	Somatotroph tumor component: GH ± α-subunit depending on tumor subtype; lactotroph tumor component: PRL (diffuse or paranuclear depending on the subtype)	Tumor subtype characteristics
TPIT-lineage PitNETs				
Corticotroph tumors	Densely granulated corticotroph tumor	TPIT	ACTH and other POMC derivates	Strong, always diffuse
	Sparsely granulated corticotroph tumor			Variable (often diffuse)
	Crooke cell tumor			Perinuclear ring–like cytoplasmic
SF1-lineage PitNETs				
Gonadotroph tumor		SF1, ERα, GATA3	α-subunit, βFSH, βLH, or none	Variable or negative
PitNETs with no distinct cell lineage				
Plurihormonal tumor		Multiple combinations	Multiple combinations in a monomorphous tumor population	Variable
Null cell tumor		None	None	Variable

Endocr Pathol. 2022 Mar;33(1):6-26.

Pituitary carcinoma

- <1% of pituitary neoplasms
- Brain invasion (exceptional finding) or intracranial (CSF) and/or extracranial metastases
- Most PRL+ or ACTH+. (latter often occur in setting of Nelson's syndrome)
- High morbidity/mortality

CASE 3

- DIAGNOSIS
  - PITUITARY ADENOMA (PITUITARY NEUROENDOCRINE TUMOR)

CASE 4

62-year-old male with nephrolithiasis and bone pain. Laboratory studies show elevated serum calcium (11.2 mg/dL) and parathyroid hormone (95 pg/mL). Sestamibi scan localizes to the right lower parathyroid gland. Surgical exploration performed.

Case 4

The patient is scheduled for surgery the day you are on frozen section. You received 1 small fragment of soft tissue.

What would you do next?

https://www.digitalscope.org/ViewerUI/?SlideId=2423f83d-9dab-4ac7-bc65-d6149a3a132c

Histopathologic Findings at the Time of First Surgery

Histologic characteristic	Parathyroid carcinoma	Atypical adenoma	Parathyromatosis	Adenoma
Capsular invasion	+++	0	0	0
Fibrous trabeculae	+++	++	+	0
Trabecular pattern	+++	+	+	+
Mitotic figures (>1 mitoses/10 HPF)	+++	+	+	0
Nuclear pleomorphism	++	+	+	+
Vascular invasion	++	0	0	0
Lymph node invasion	+	0	0	0

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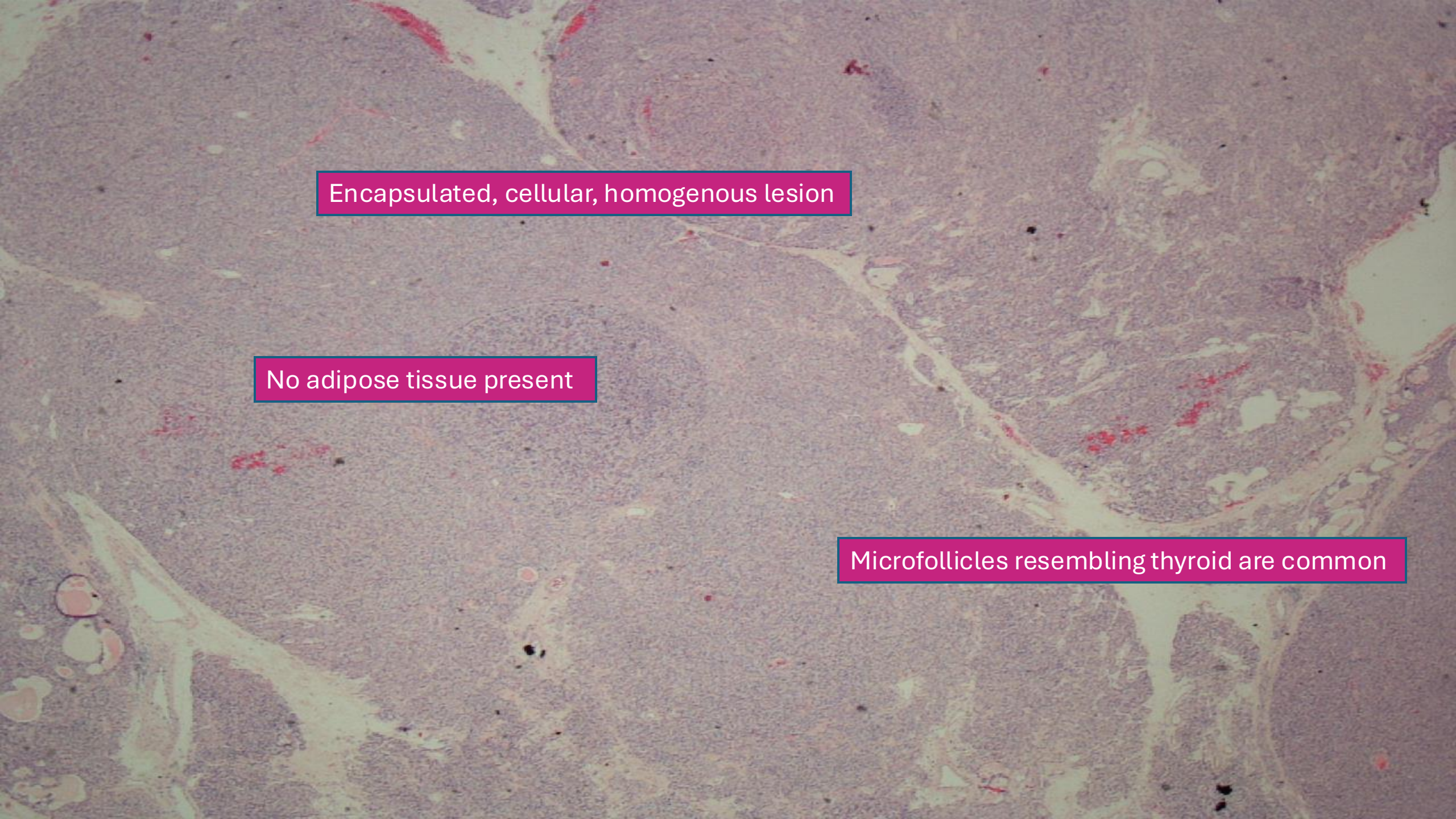
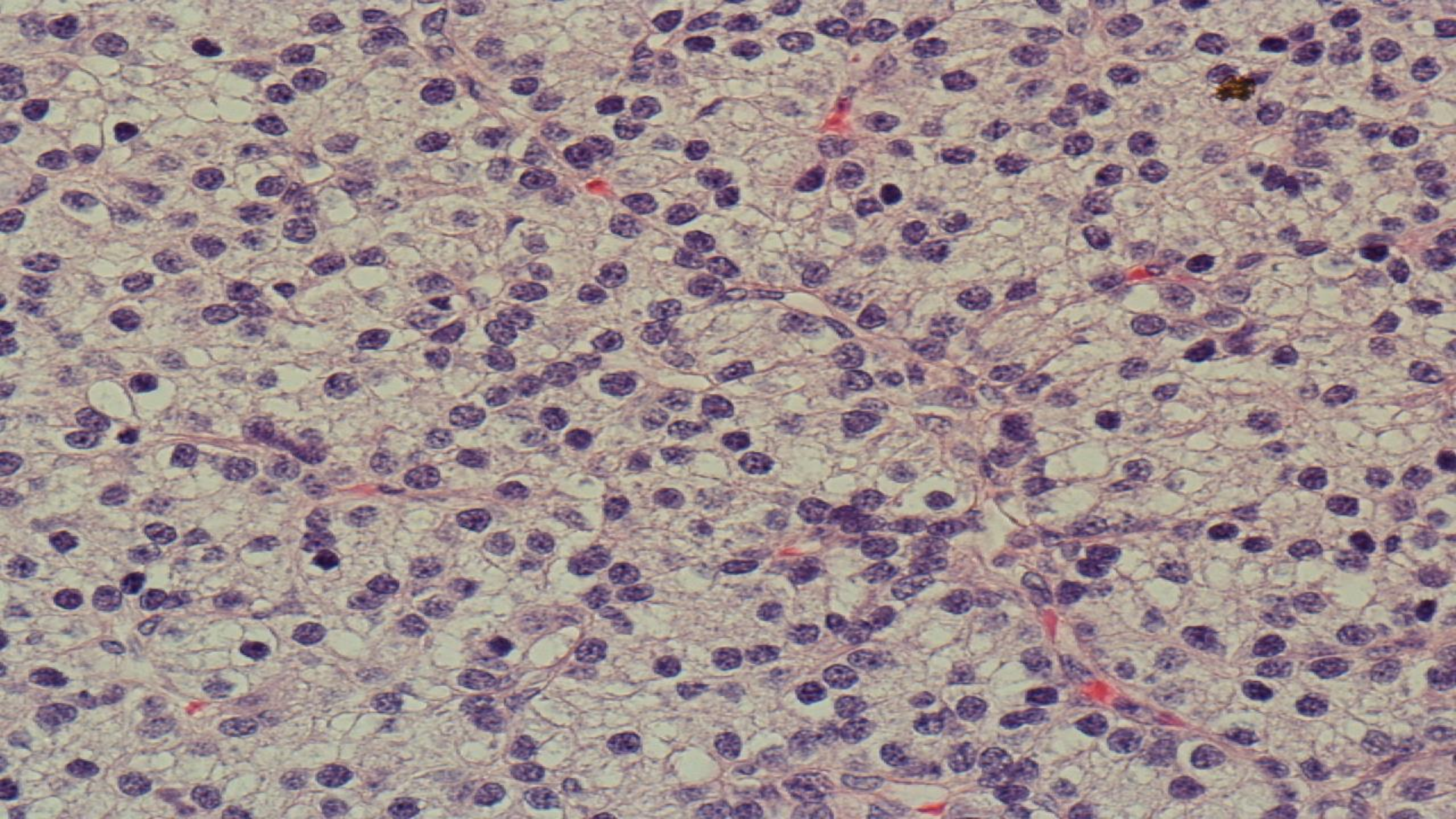

Encapsulated, cellular, homogenous lesion
No adipose tissue present
Microfollicles resembling thyroid are common


chief cells with some oxyphil cells in delicate capillary network



CASE 4

- FROZEN SECTION DIAGNOSIS
  - HYPERCELLULAR PARATHYROID TISSUE IDENTIFIED

- FINAL DIAGNOSIS
  - PARATHYROID ADENOMA

Welcome to ScOPE

-School of Open Pathology Education-

THANKS FOR YOUR ATTENTION

FOR ADDITIONAL COMMENTS ABOUT THIS SESSION

https://forms.office.com/r/exz9K52ubm