

Practical problems in the diagnosis of thyroid tumours

FORPATH asbl Workshop
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Hospital of S. João & IPATIMUP

THYROID CARCINOMAS

WHO book on Endocrine Tumours, 2nd edition, Zurich, 1986

Follicular carcinoma
Papillary carcinoma
(Hürthle cell carcinoma)

Medullary carcinoma
Poorly differentiated ca

Undifferentiated ca



WHO book on Endocrine Tumours, 3rd edition, 2004

THYROID CARCINOMAS

Follicular carcinoma

Papillary carcinoma

Hyalinizing trabecular tumour

Mucoepidermoid carcinoma

Sclerosing mucoepidermoid ca
with eosinophilia

Medullary carcinoma

Poorly differentiated ca

Mixed medullary and follicular cell ca

Squamous cell carcinoma

Mucinous carcinoma

Undifferentiated ca

Practical Points

Age: Patients under 40/50 rarely, if ever, have follicular or anaplastic carcinoma

Function: Hyperfunctioning tumours are almost never malignant

Multinodular conditions – Tend to be benign unless there is a thick encapsulated tumour or it is a multinodular form of follicular variant PTC

Uninodular tumours – Crucial to evaluate thoroughly the entire capsule (If there is no capsule - characterize the growth pattern as expanding or infiltrative)

Strange lesions – Perform immunohistochemistry to clarify if it is a primary thyroid tumour and, if yes, if it is made of follicular or C-cells.

Most frequent diagnostic problems of thyroid pathology in a consultancy practice

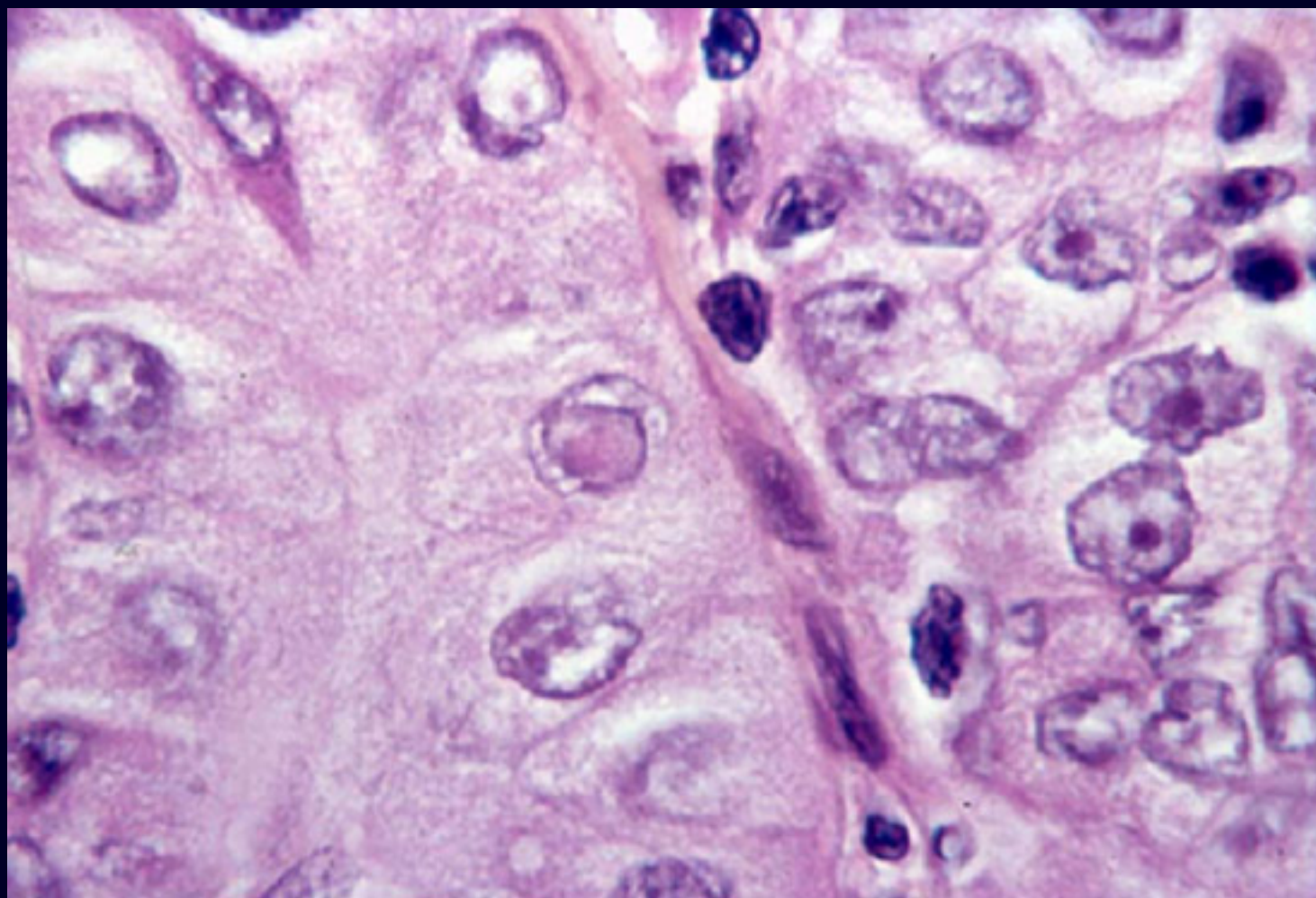
1. Is there a focus (or some foci) of papillary carcinoma in “this” Hashimoto’s thyroiditis or “this” nodular goiter?
2. Is this lesion an adenoma, a follicular carcinoma or an encapsulated follicular variant of papillary carcinoma?
3. How would you classify this Hürthle cell lesion?
4. Is this a well differentiated carcinoma with a solid pattern of growth or a poorly differentiated carcinoma?

12 cases suggested by Dr. H van Dick

9/12 fall into the 4 categories

- Incipient PTC – cases 1 and 2
- Diagnosis of encapsulated tumours – Cases 4,8,10 and 12
- Diagnosis of Hürthle cell tumour – Case 3
- Solid WDTC vs PDTC? – Cases 5 and 9

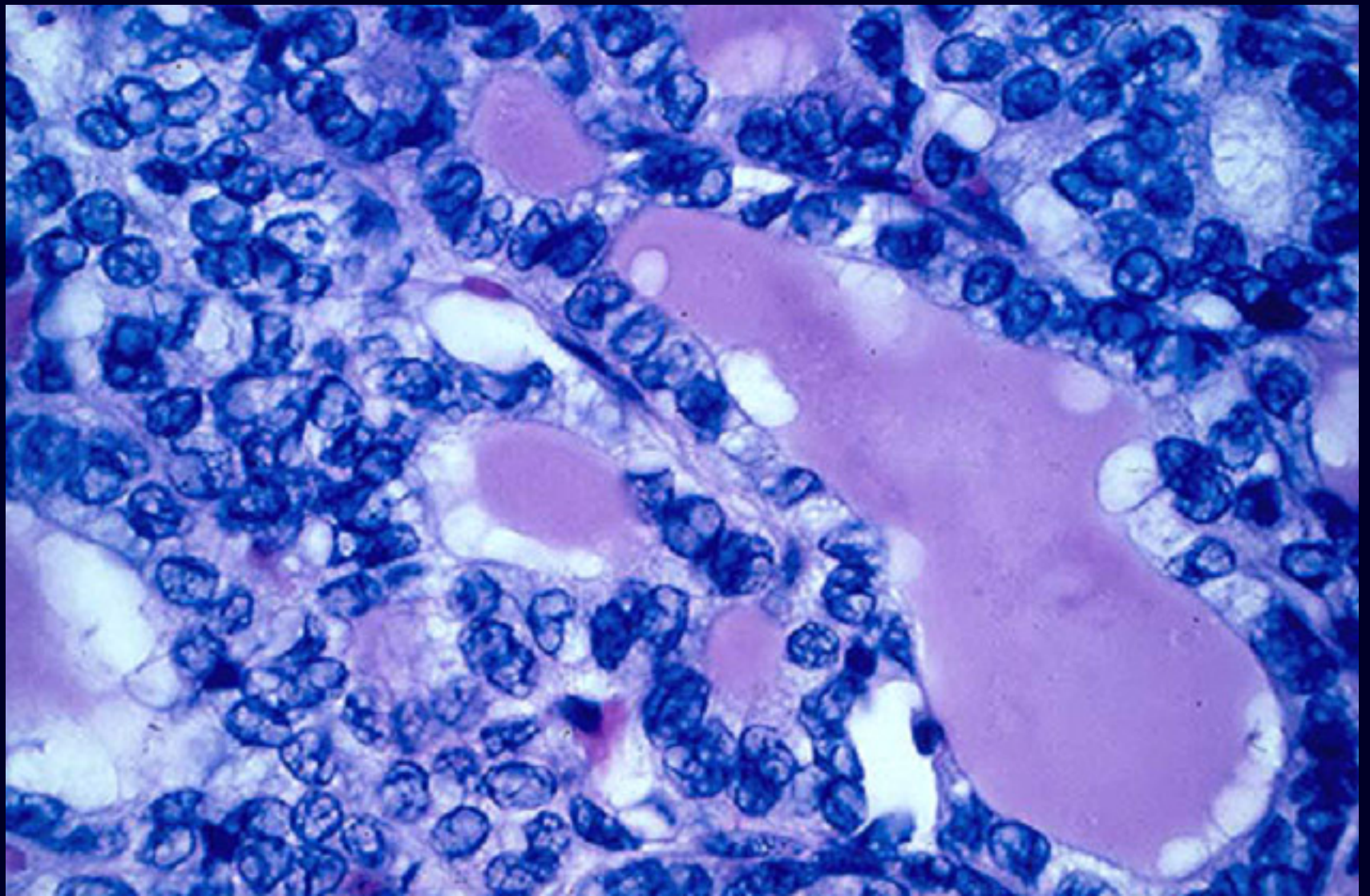
The remaining 3 cases fall into a 5th category of Rare flowers & Miscellaneous

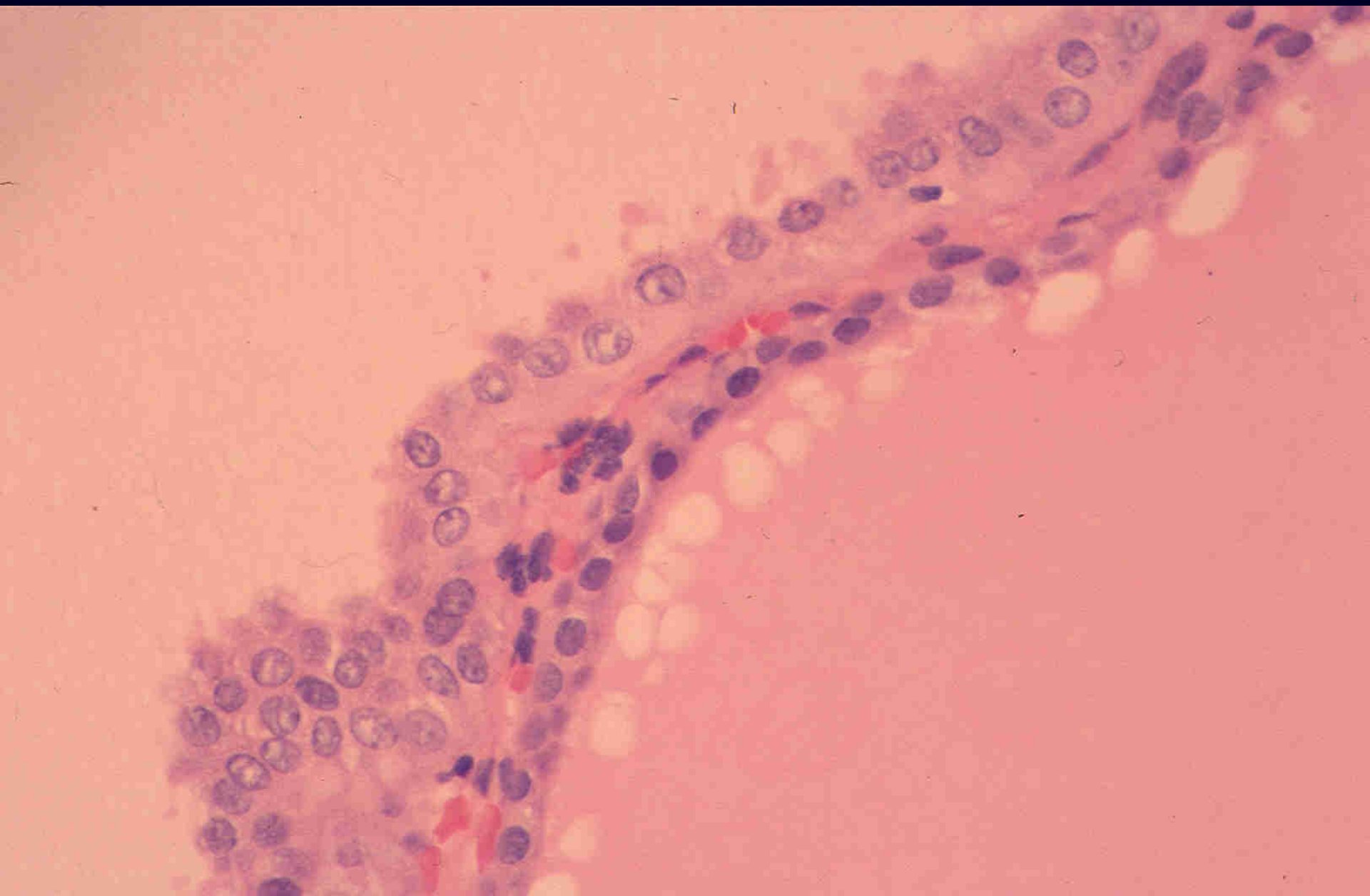


The optically clear nucleus: A reliable sign of papillary carcinoma of the thyroid?

Hapke MR & Dehner LP, Am J Surg Pathol 3:31, 1979



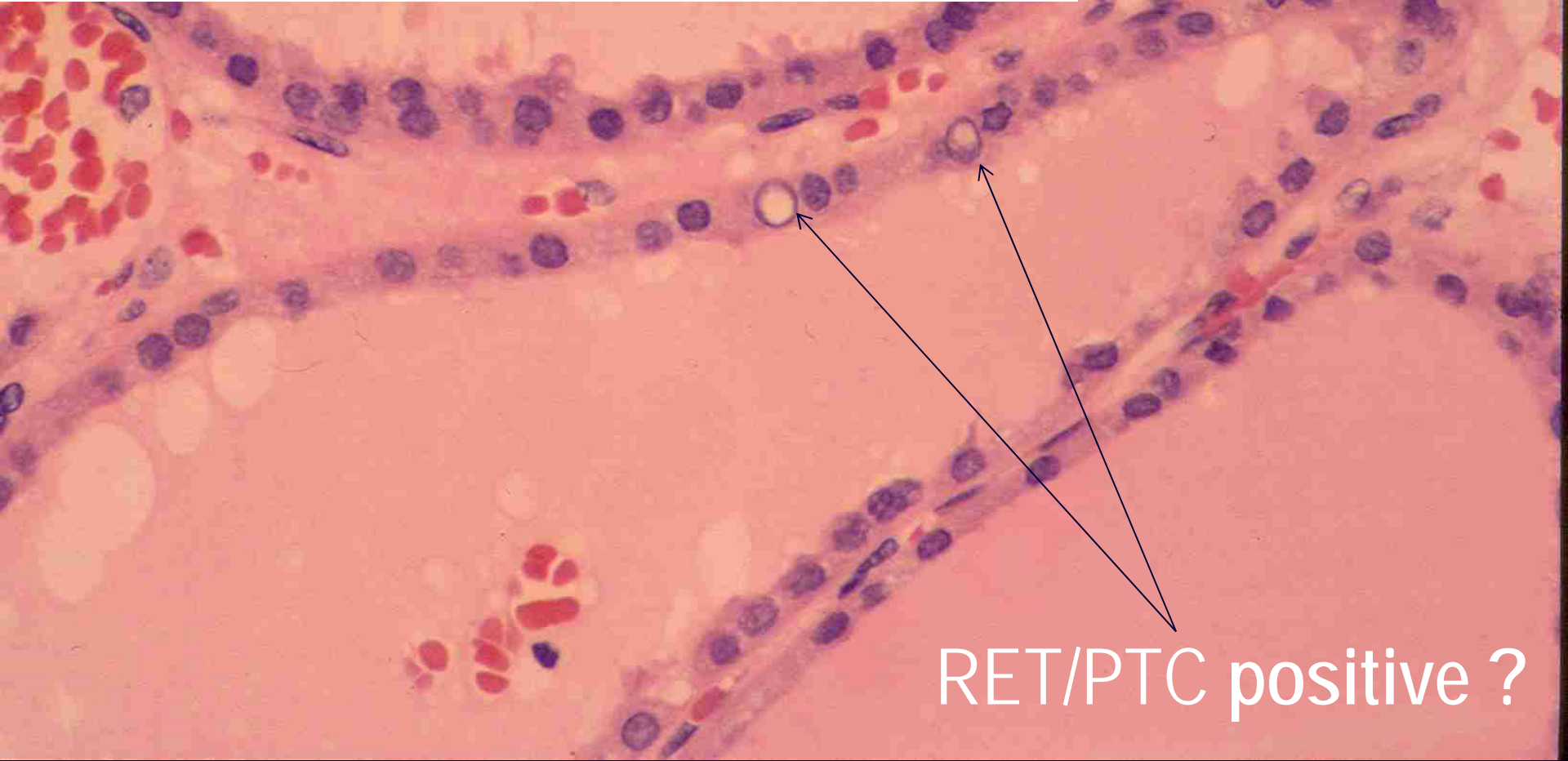


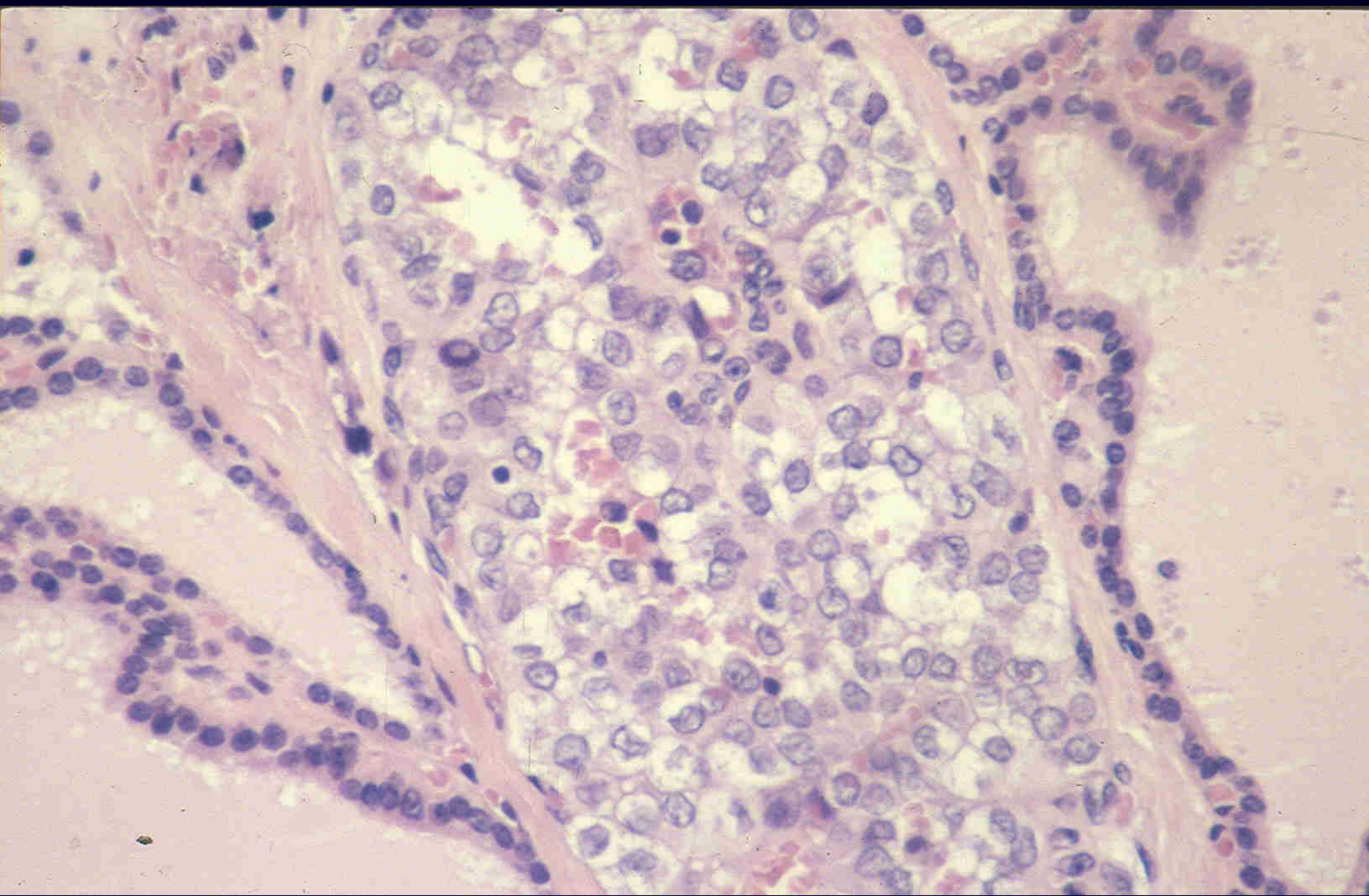


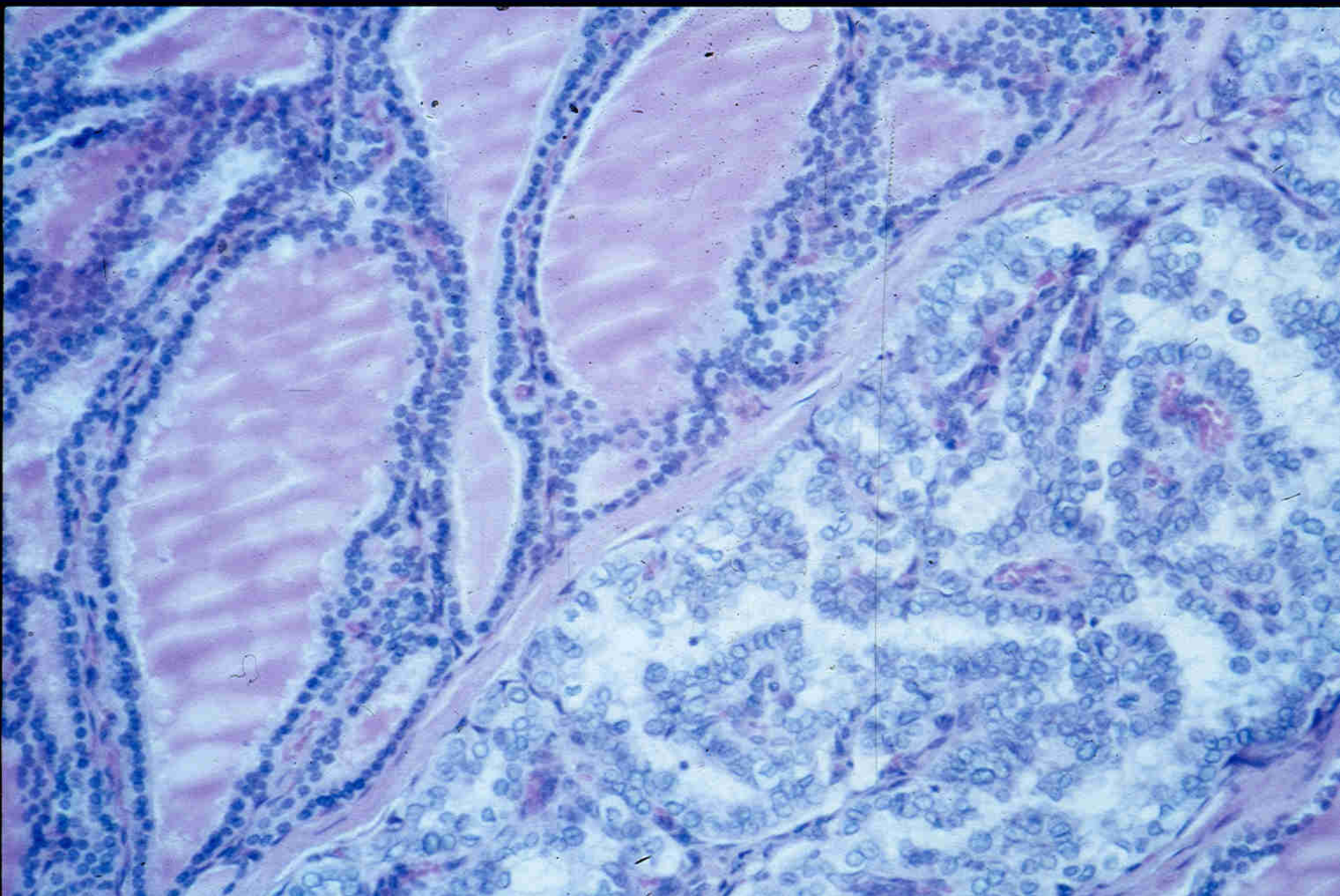


***RET*/PTC rearrangements arising from a small population of papillary thyroid carcinoma cells, possible candidate for passenger mutation**

Tadao Nakazawa • Shin-ichi Murata • Tetsuo Kondo • Dongfeng Niu •
Kunio Mochizuki • Tomonori Kawasaki • Tetsu Yamane • Nobuki Nakamura •
Ryohei Katoh







Diagnosis of (incipient) PTC

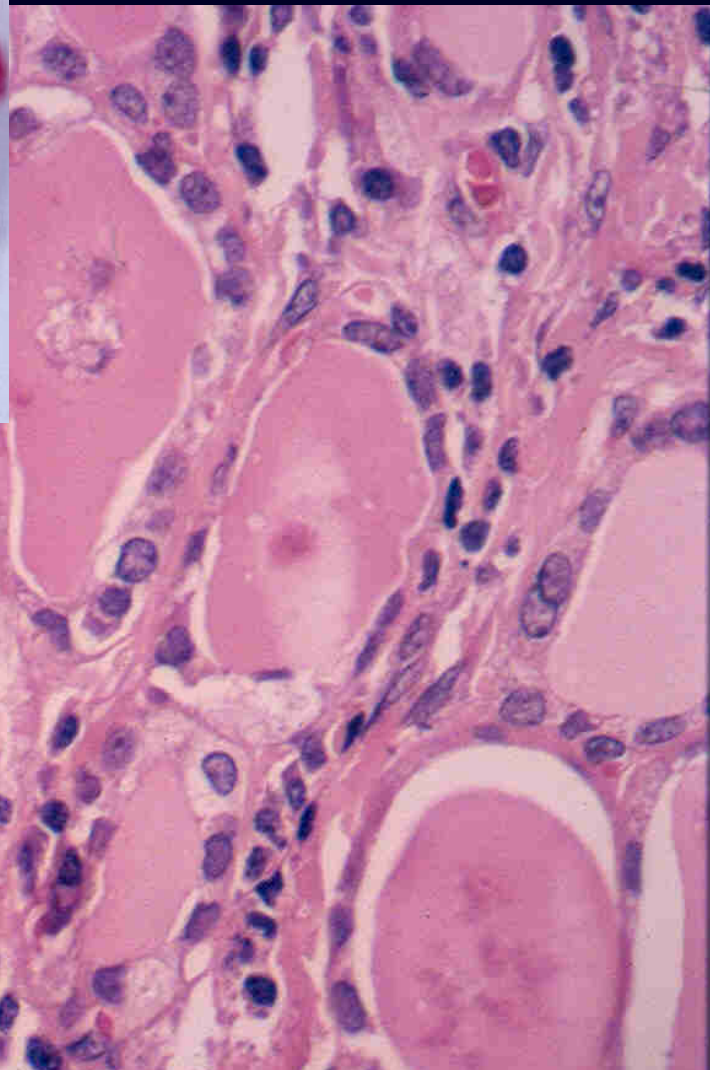
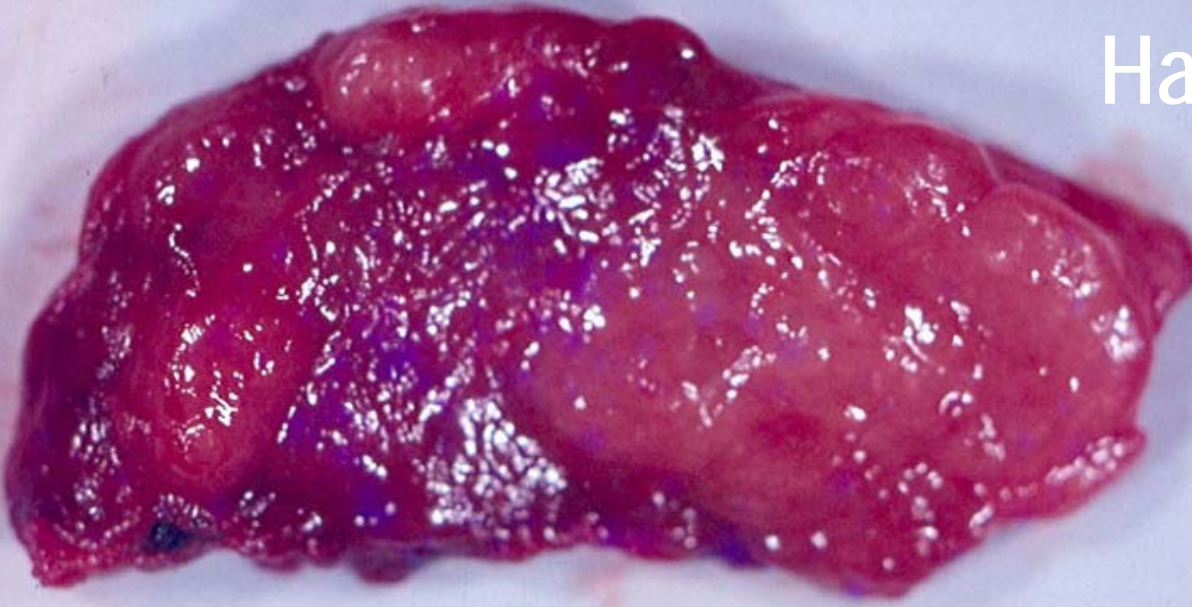
In our experience the most frequent doubts arise in four different settings:

- a. Hashimoto's thyroiditis
- b. Nodular (adenomatous) goiter
- c. Encapsulated well differentiated neoplasms
- d. Oncocytic (Hürthle cell) neoplasms

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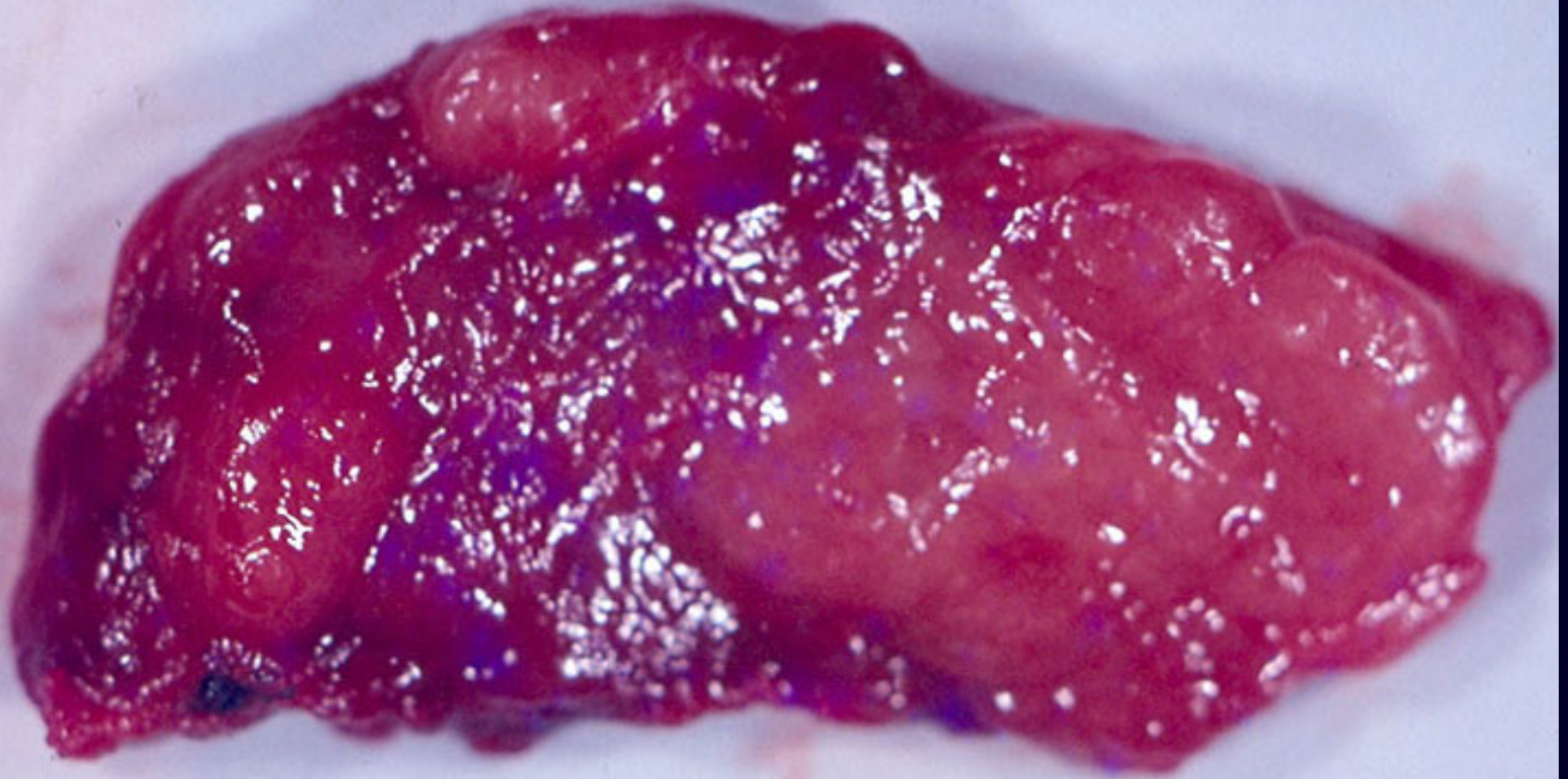


Hashimoto thyroiditis

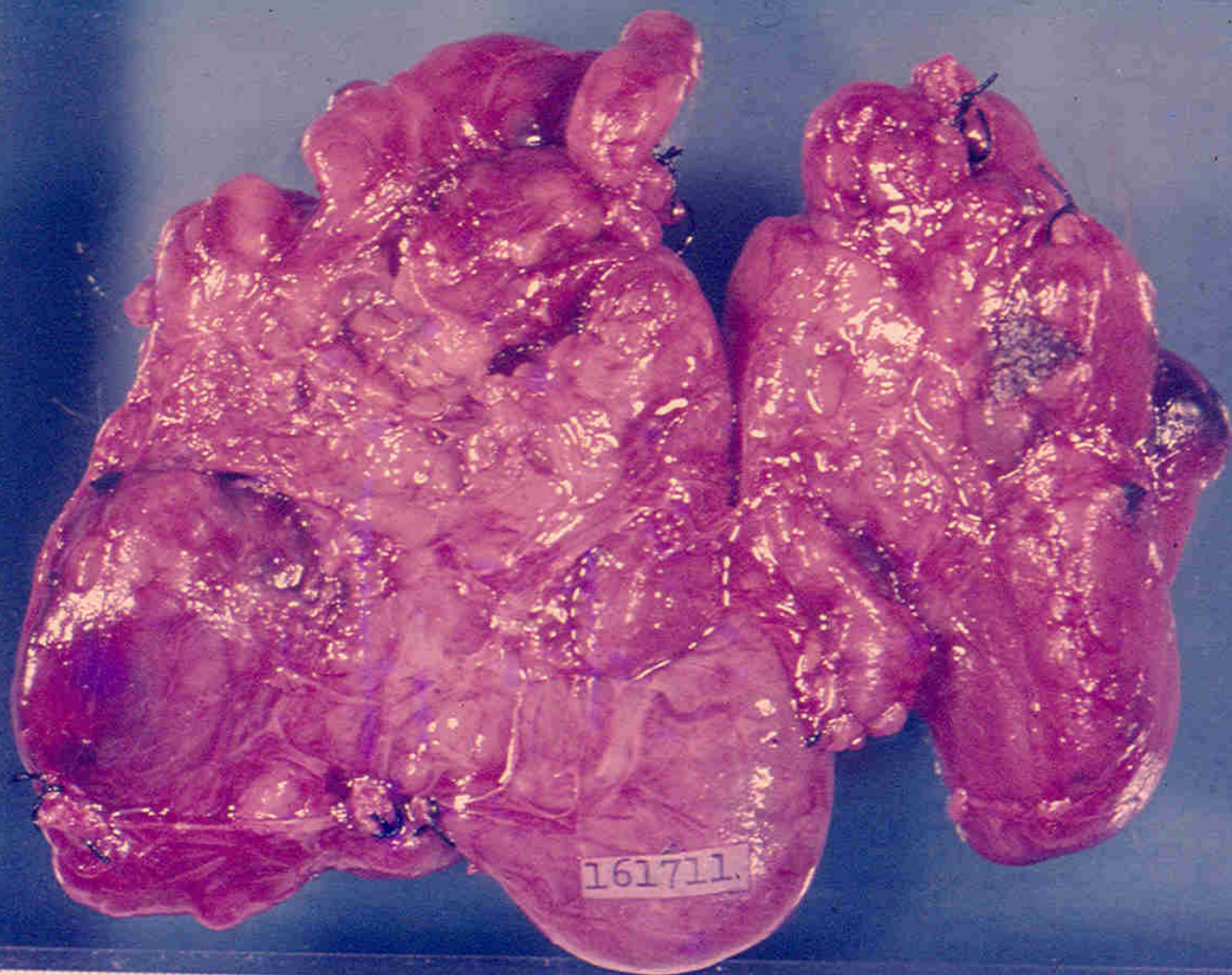


RET/PTC positive

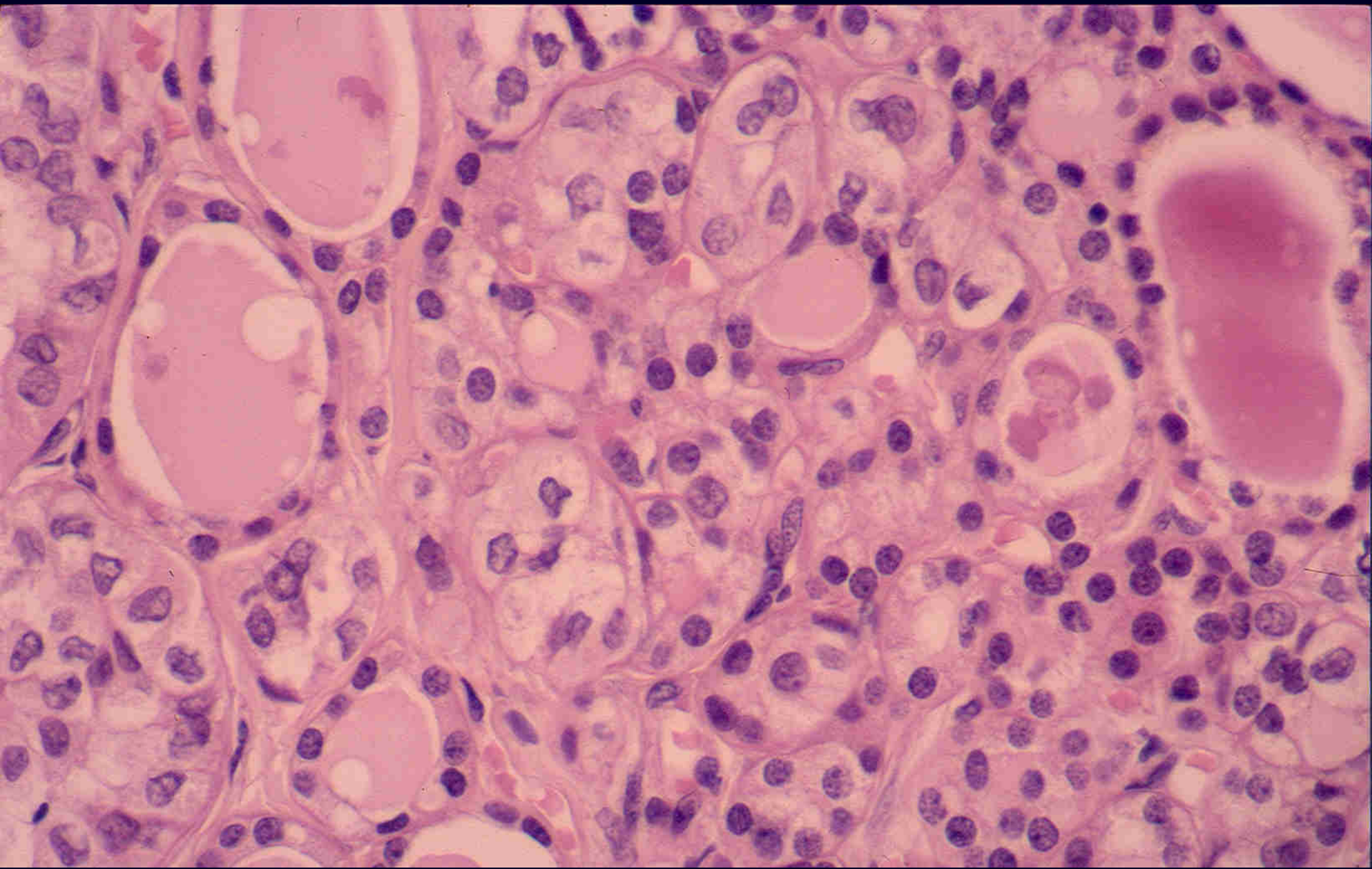
Hashimoto thyroiditis

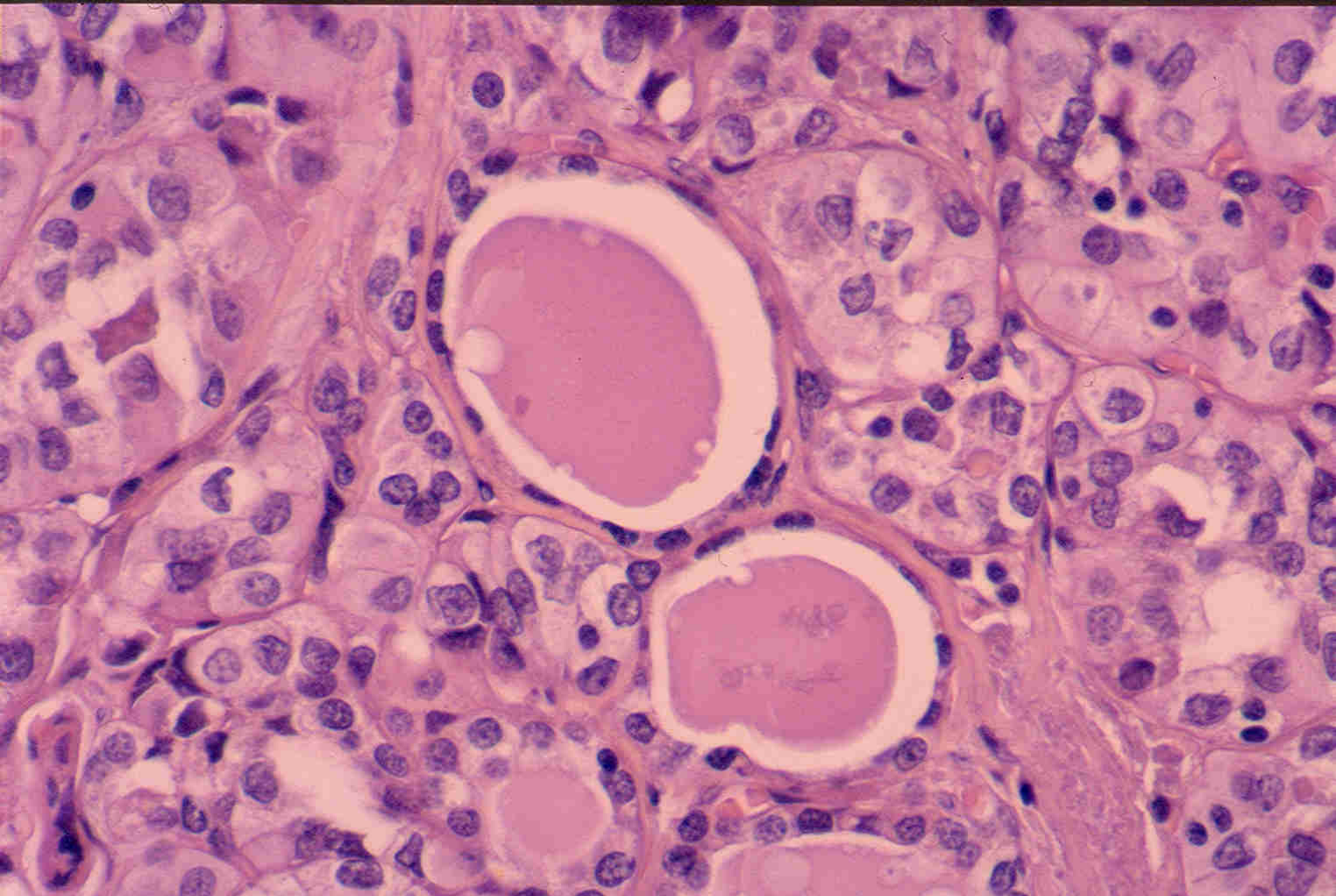


68% RET/PTC positivity



161711





Microdissected areas with PTC nuclei within
adenomas/nodular goiters

RET/PTC rearrangements – Yes

Fusco et al, Am J Surg Pathol, 2002

B-RAF mutations – no (?) (few cases)

Trovisco et al, 2005

CONCLUSION

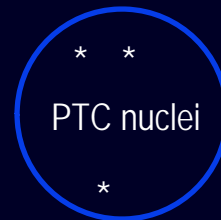
Hashimoto's thyroiditis and Adenoma/nodular goiter

Dispersed cells with PTC-nuclei
with or without molecular alterations → KEEP THE DIAGNOSIS

Clusters of cells with PTC-
nuclei forming a microtumour
with or without molecular alterations → PTC

Hashimoto thyroiditis/Adenoma/Nodular goiter
Cluster of cells with stroma and PTC
nuclei → Papillary microcarcinoma

Adenoma/nodular goiter

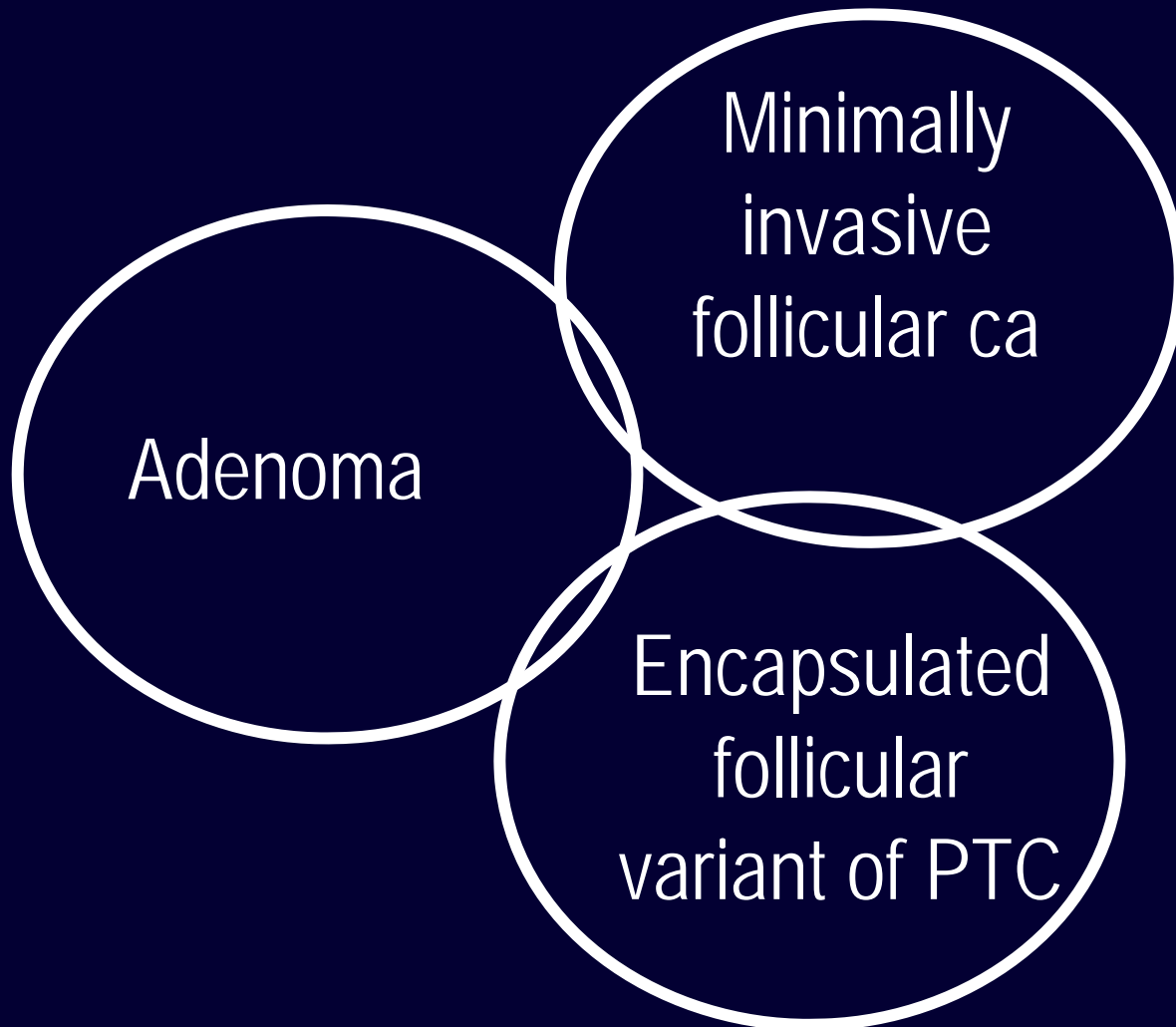


Consider the whole nodule as PTC

Most frequent diagnostic problems of thyroid pathology in a consultancy practice

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Follicular patterned, encapsulated neoplasms



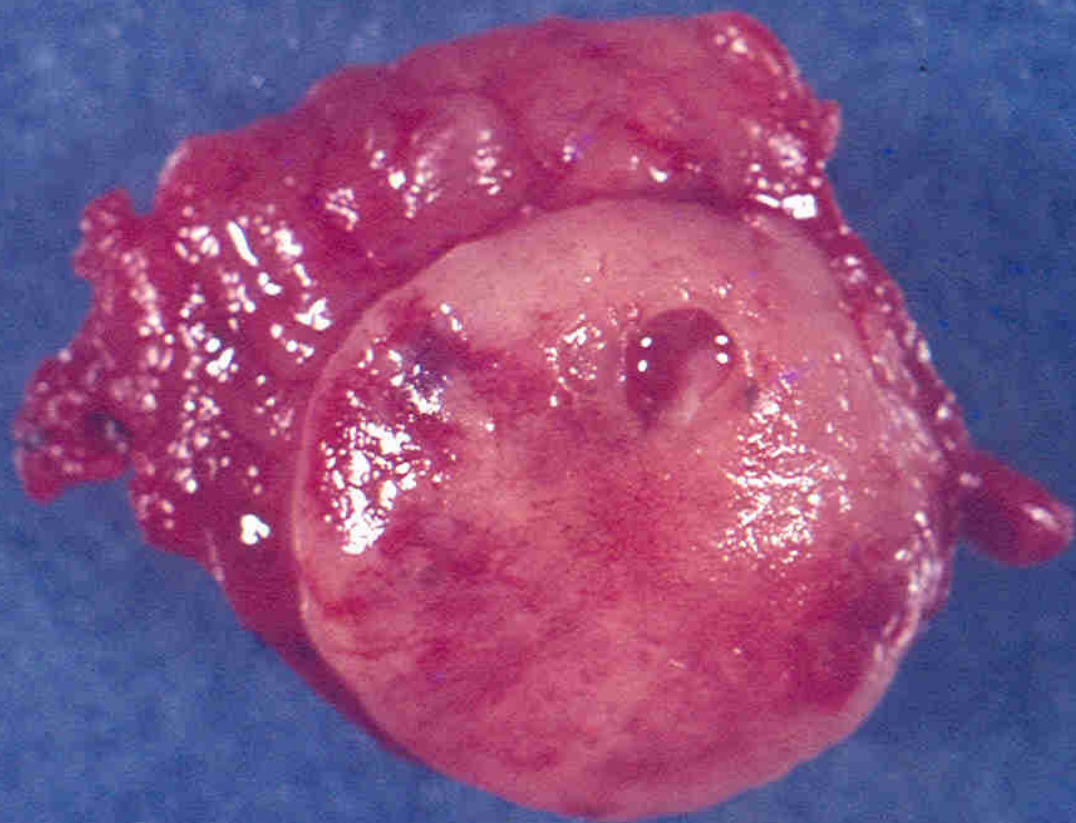
Nodular goiter & Adenoma

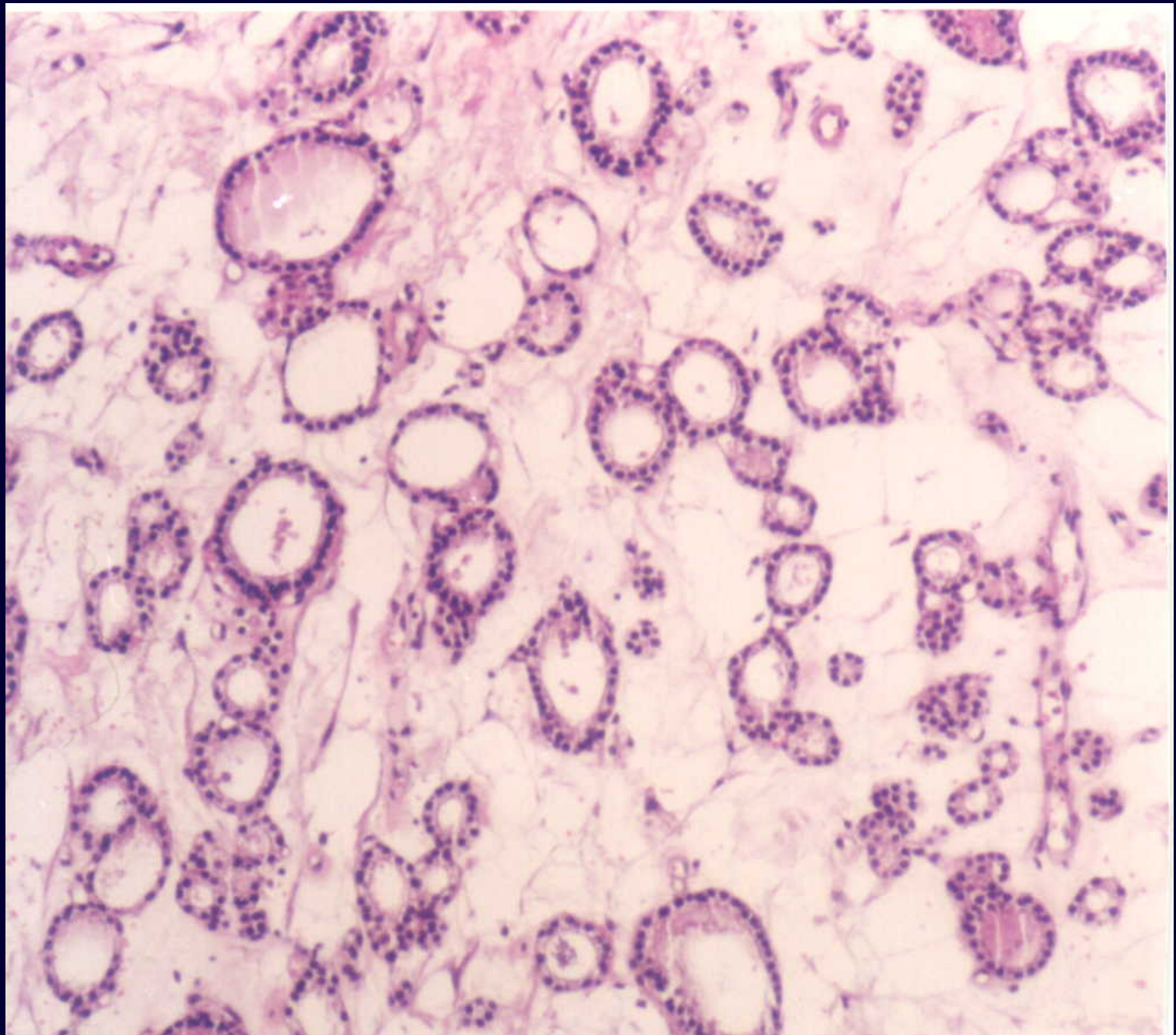
Thyroid nodule & Adenoma

Differential diagnosis:

Is it necessary? And, if yes, is it possible?

Up to 60% of nodules in multinodular goiters are monoclonal (WHO, 2nd ed)





Malignancy in follicular patterned thyroid tumours

Capsular and/or VASCULAR INVASION

Pattern of growth

Solid, insular, trabecular

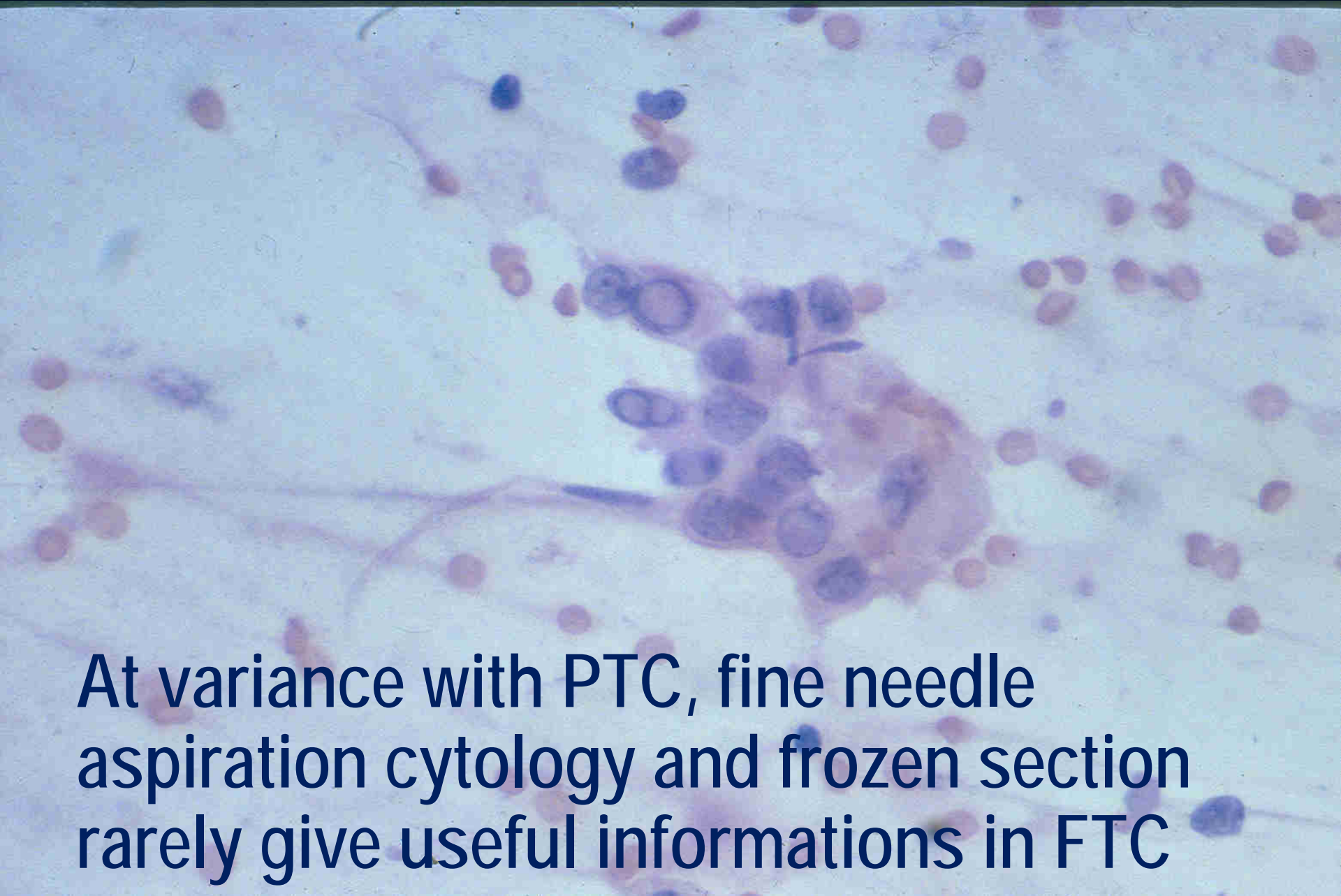
Embryonal, fetal

Normofollicular

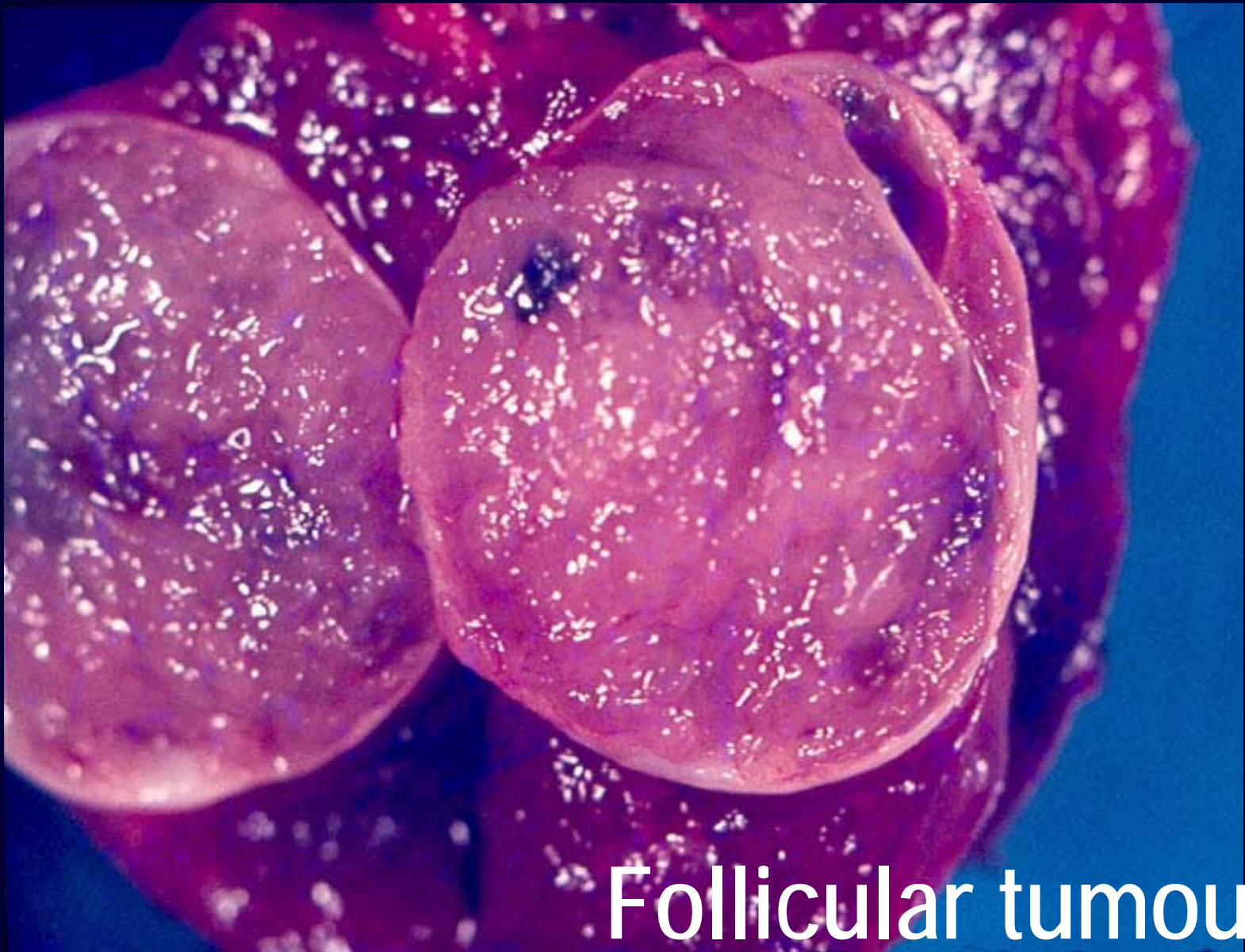
Macrofollicular

Nuclear features

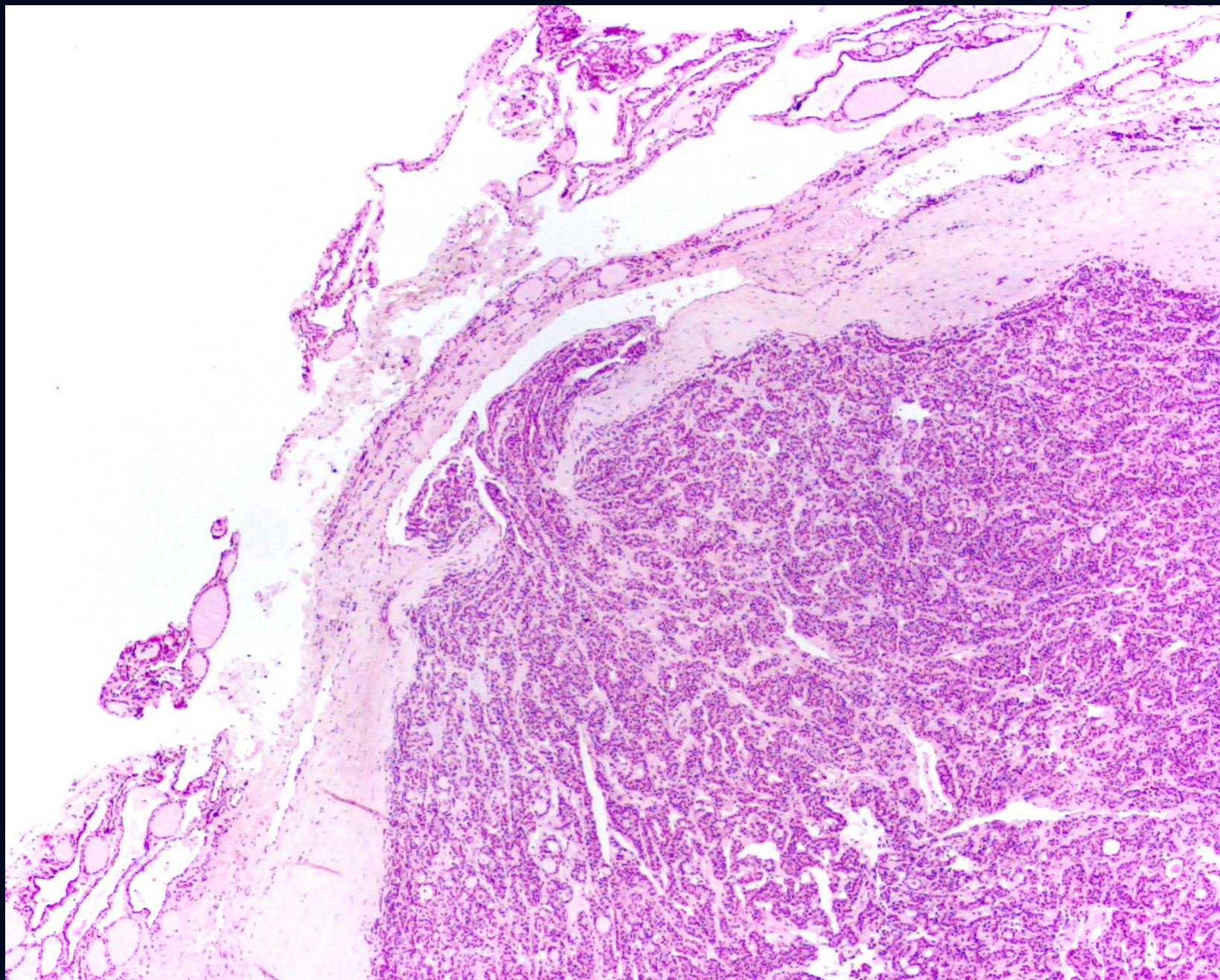
PTC NUCLEI

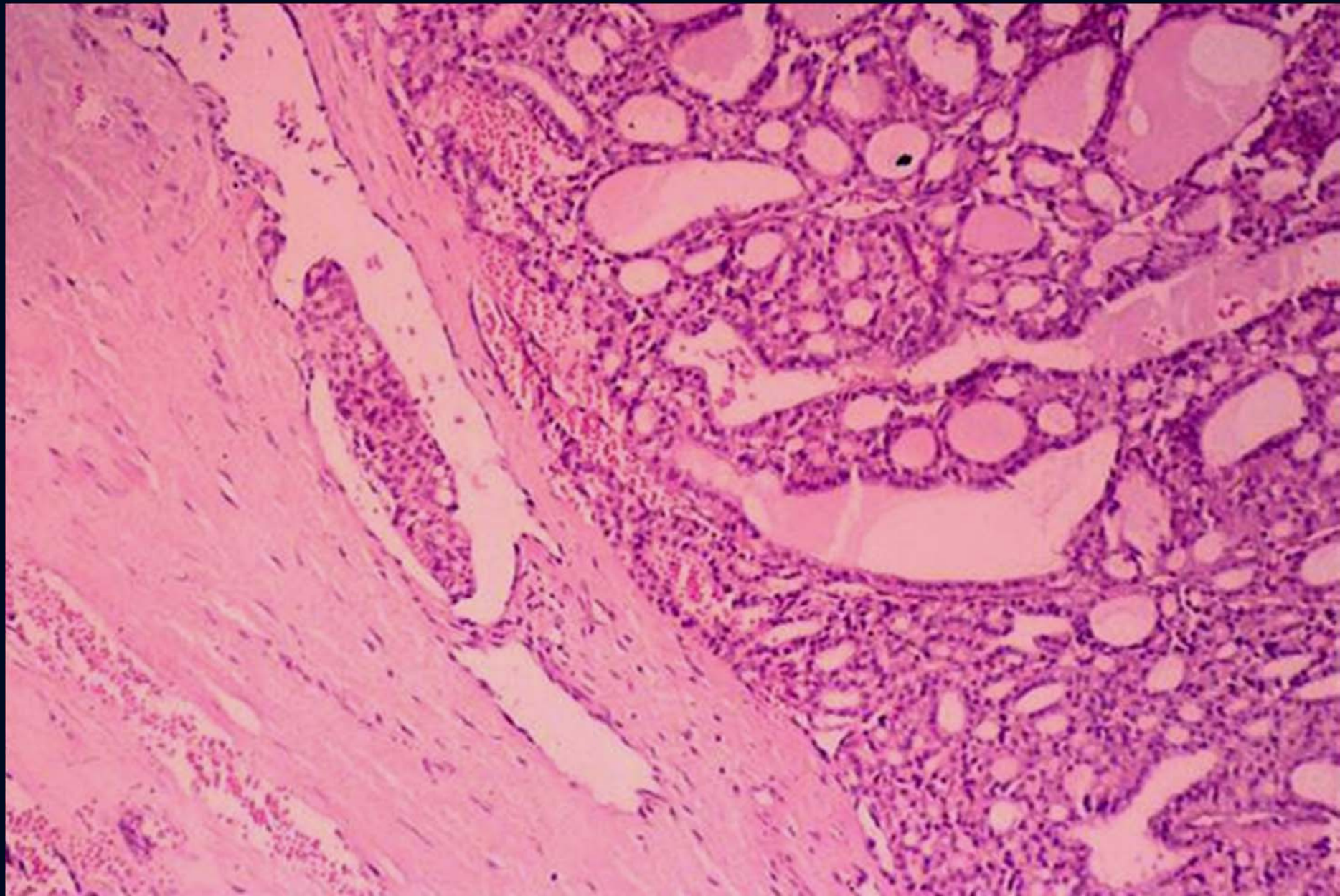


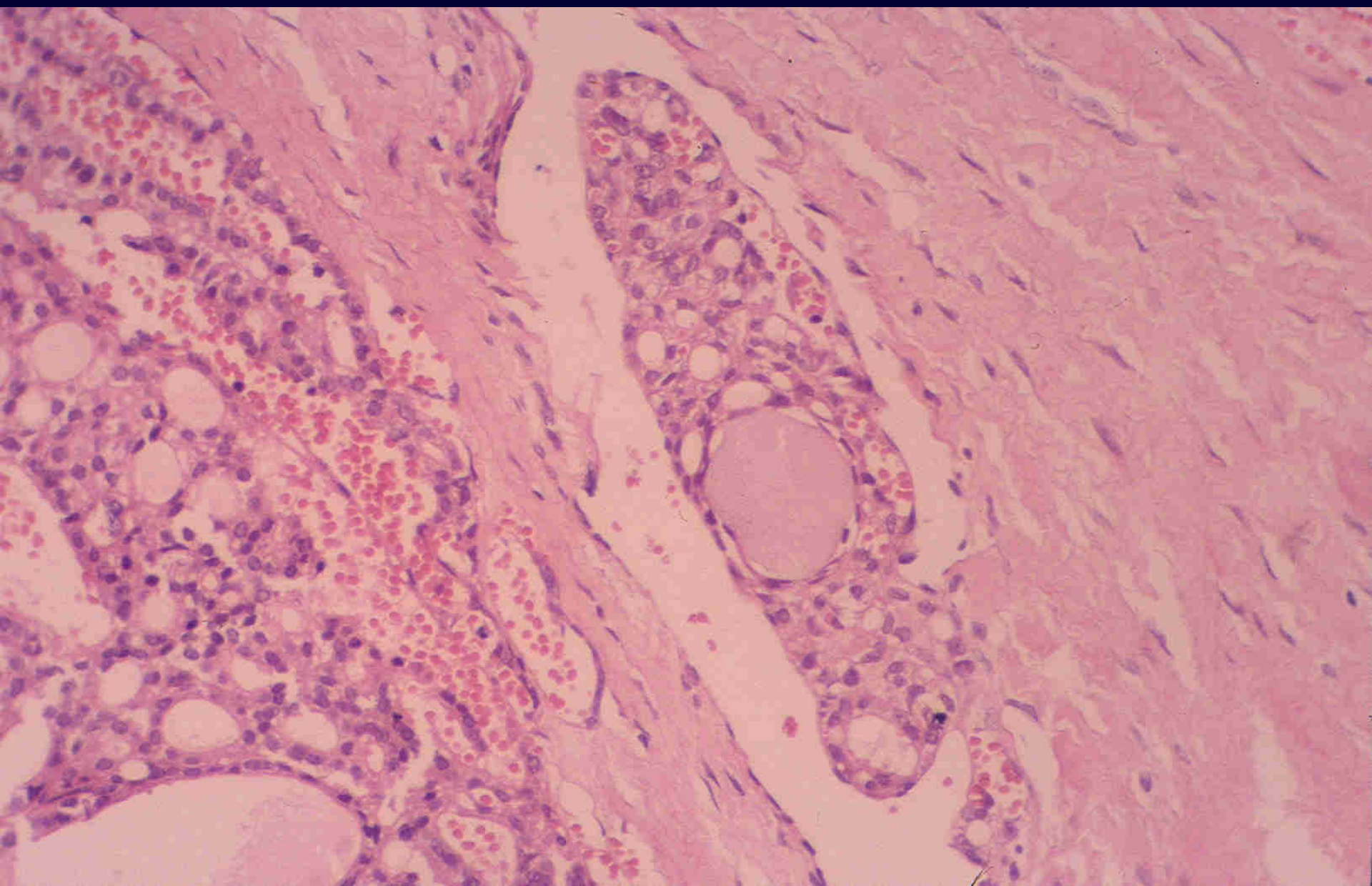
At variance with PTC, fine needle aspiration cytology and frozen section rarely give useful informations in FTC

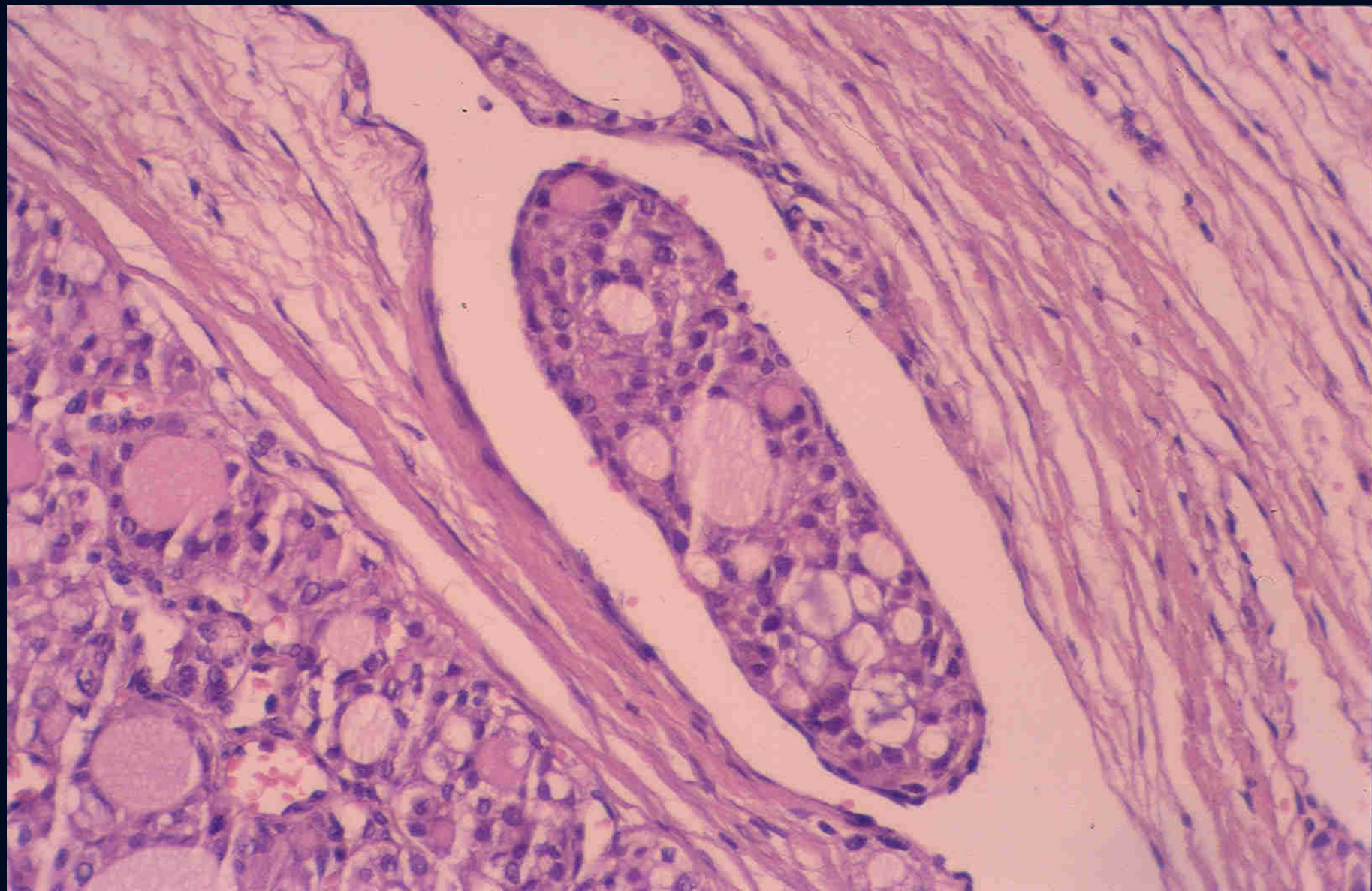


Follicular tumours

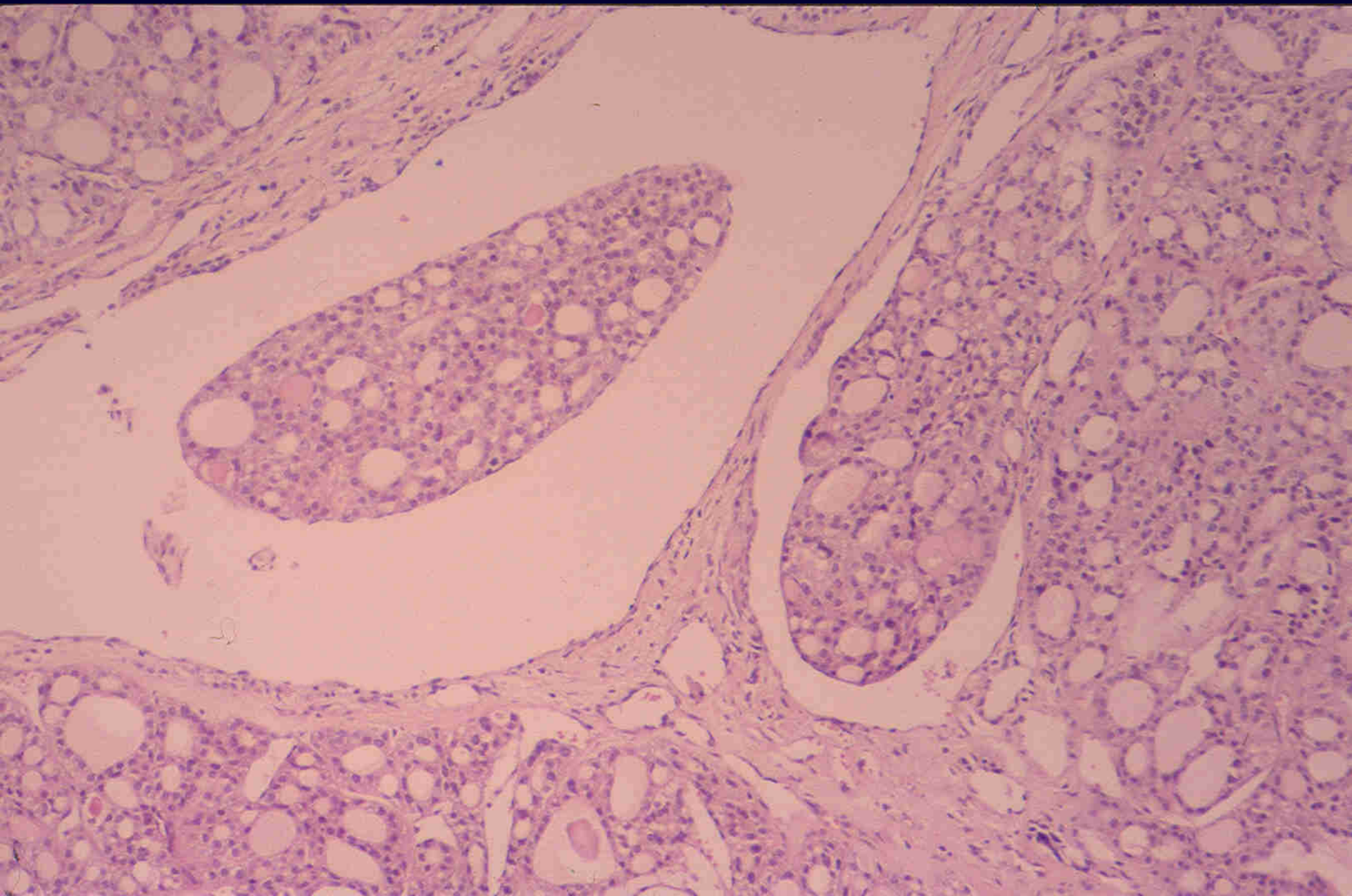


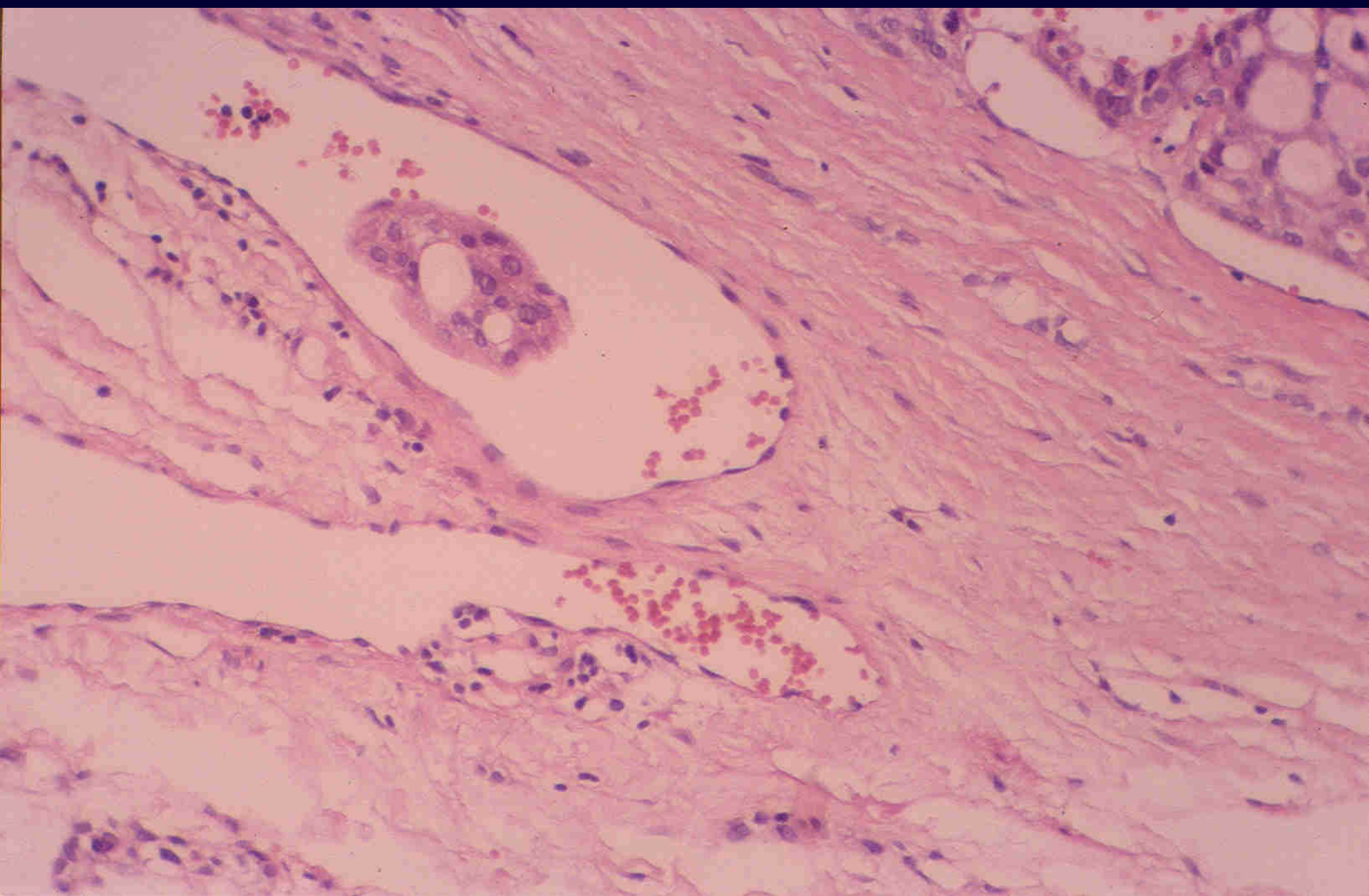






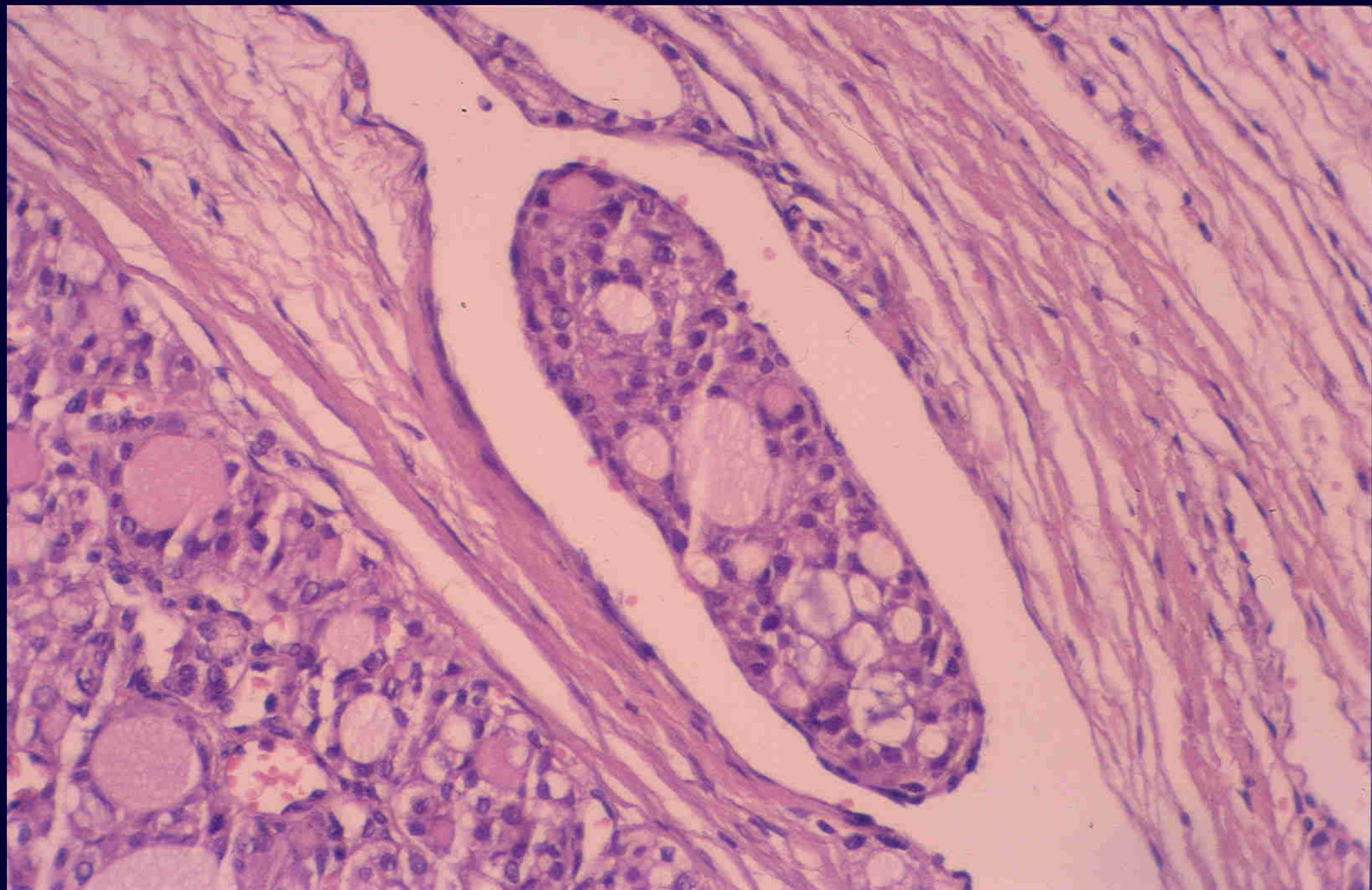
PITFALLS IN THE “VASCULAR INVASION” FRONT



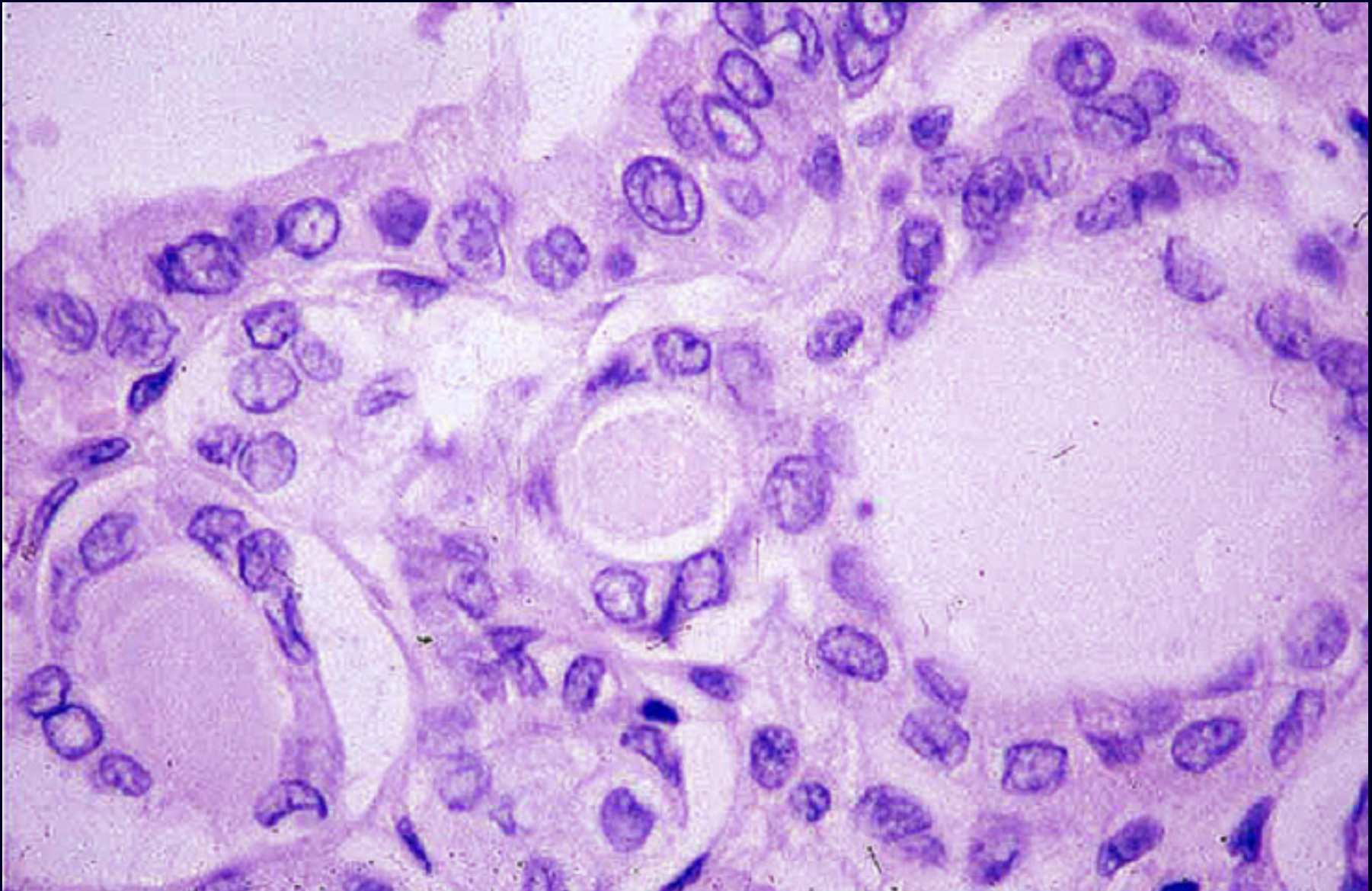


What is the best way to diagnose vascular invasion?

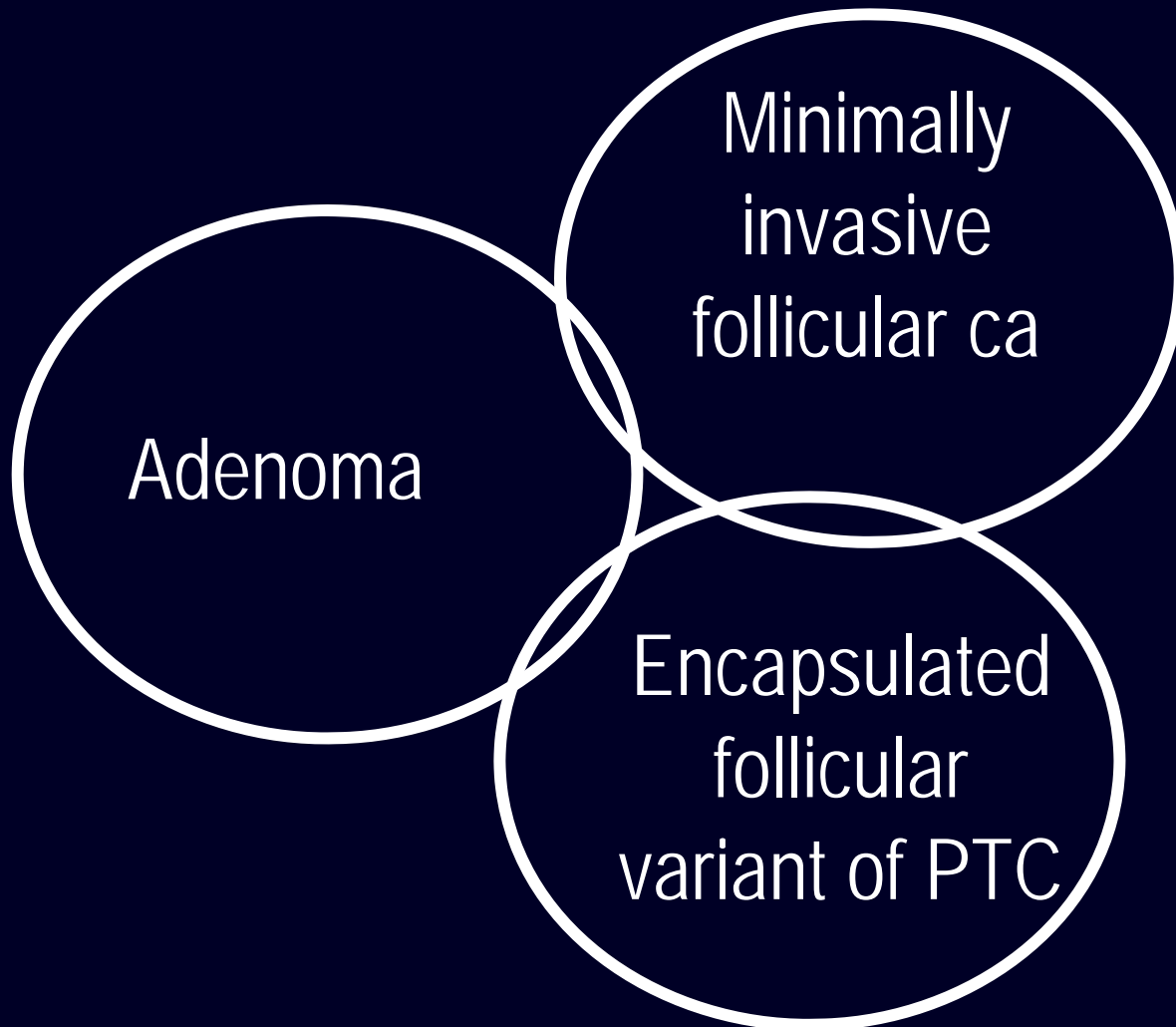
Cytopathology	No
Histopathology	Yes
Detection of biomarkers in the plasma/blood	May be
Conventional molecular pathology and high throughput approaches	No



Follicular variant of PTC



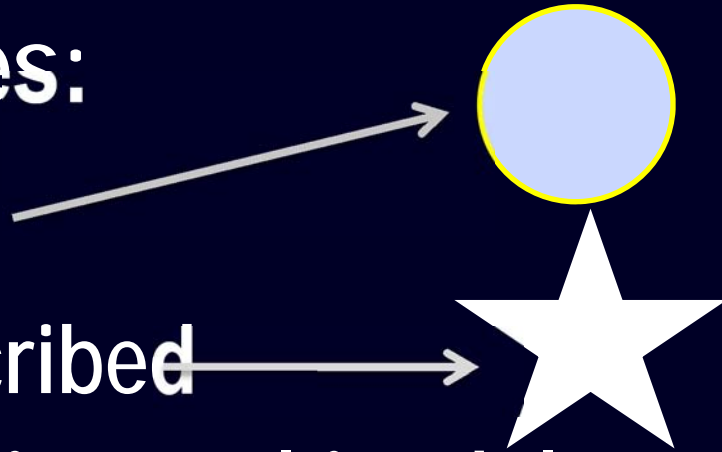
Follicular patterned, encapsulated neoplasms



Follicular variant of PTC

Three main types:

- Encapsulated
- Poorly circumscribed
- Diffuse, aggressive, multinodular



Multicentricity

Vascular invasiveness

Lung and bone metastases

Castro et al Endocr Pathol 13:313, 2002

Ivanova et al Virchows Archiv 440:418, 2002

Diffuse follicular variant of PTC

Sobrinho-Simões et al, Surg Pathol 3:189, 1990

Mikuzami et al, Histopathology 27:575, 1995

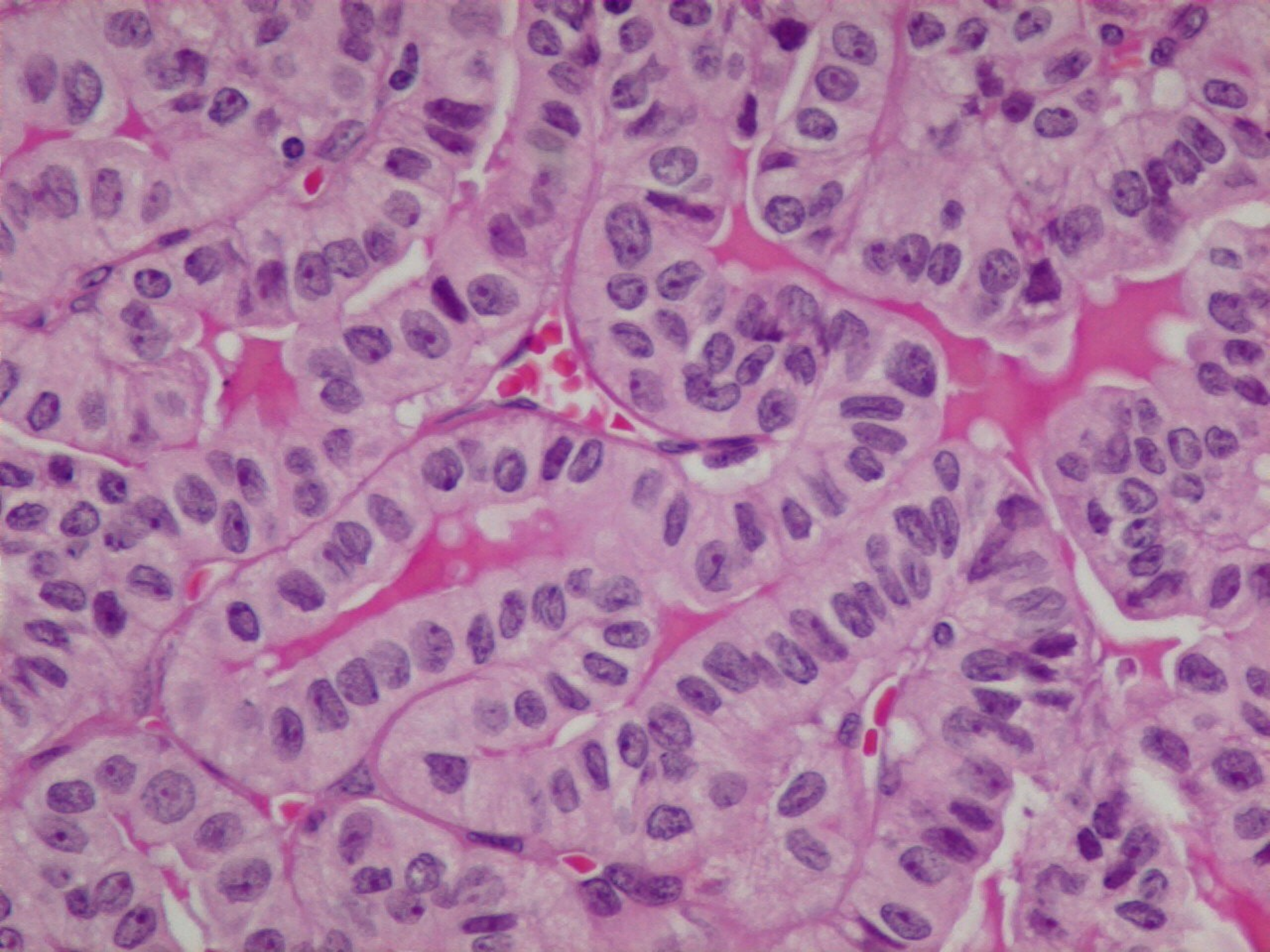
Aggressive follicular variant of PTC

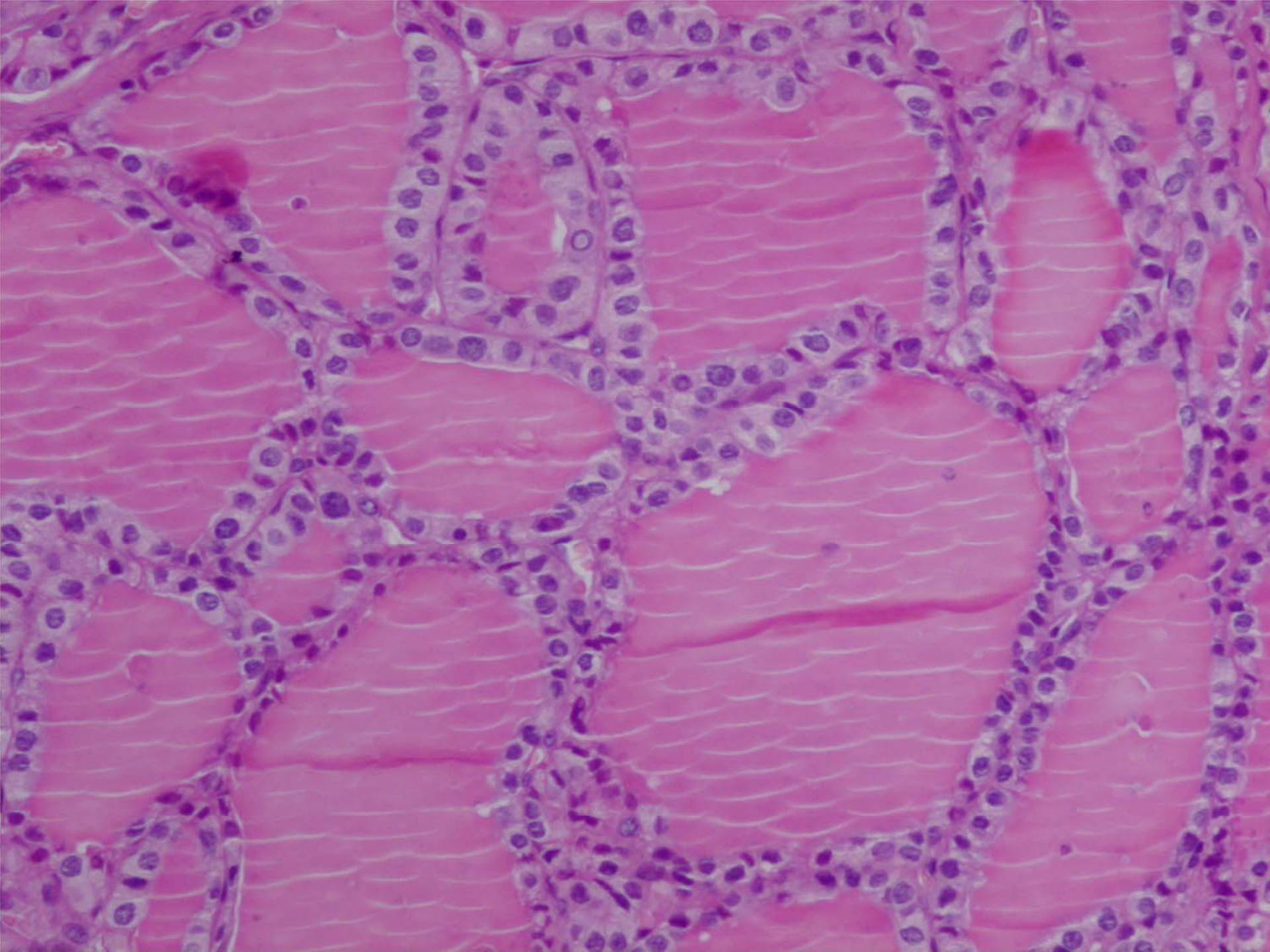
Guo et al, Lab Invest 79:67A, 1999

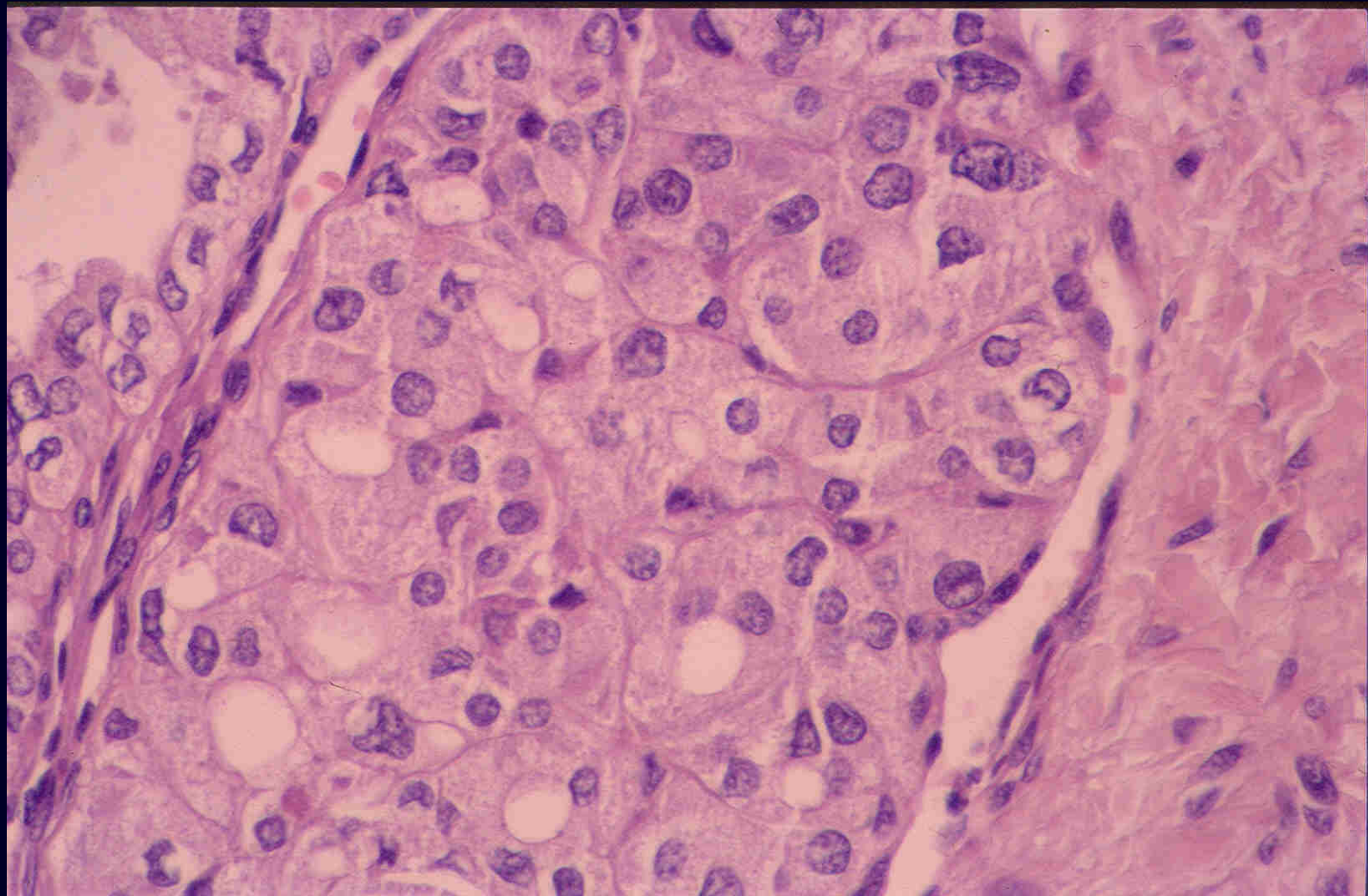
Multinodular follicular variant of PTC

Ivanova et al, Virchows Arch 440: 418, 2002









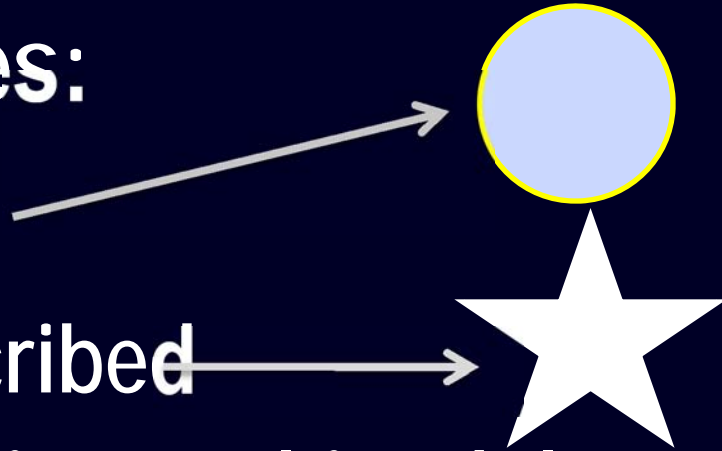
	Common PTC (n=25)	Diffuse/multinodular follicular variant of PTC (n=10)	Common follic variant of PTC (n=8)
Extrathyroid extension	12%	70%	0%
Lymph node metastases	36%	80%	13%
Vascular invasion	20%	80%	0%

Ivanova et al, Virchows Arch 440: 418, 2002_

Follicular variant of PTC

Three main types:

- Encapsulated
- Poorly circumscribed
- Diffuse, aggressive, multinodular

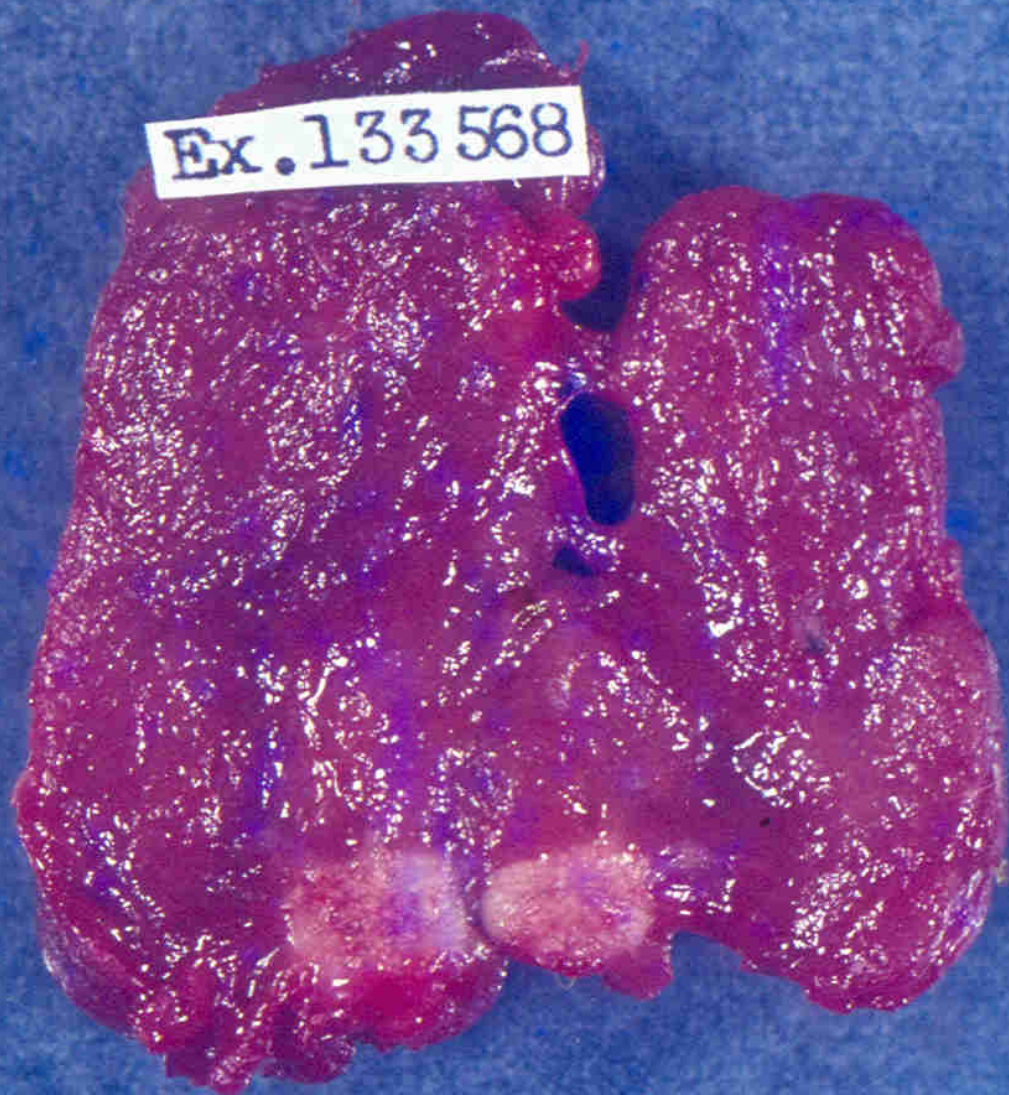


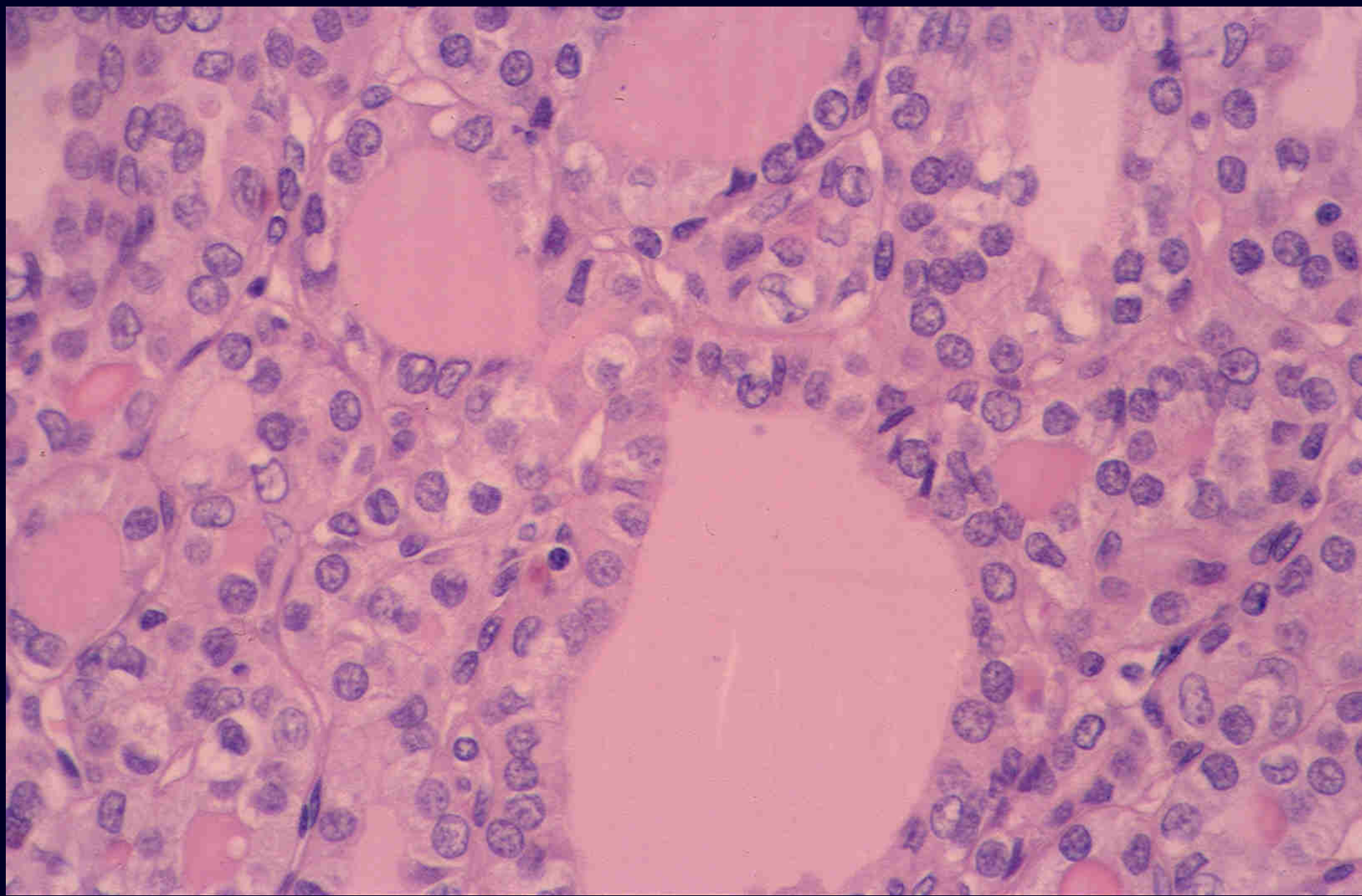
Multicentricity

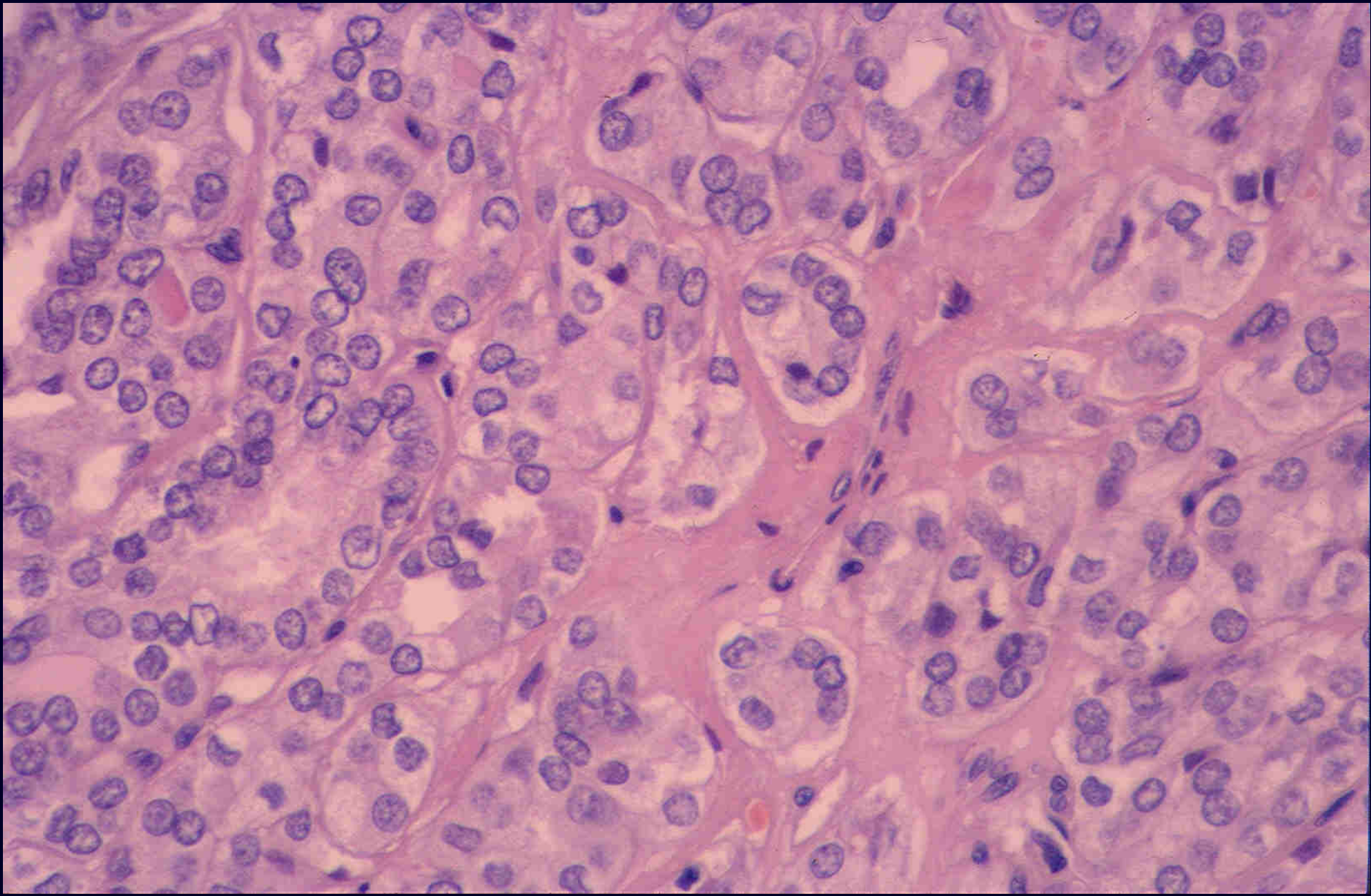
Vascular invasiveness

Lung and bone metastases

Ex. 133 568







DIAGNOSTIC HINTS

Capsular or, more importantly, vascular invasion

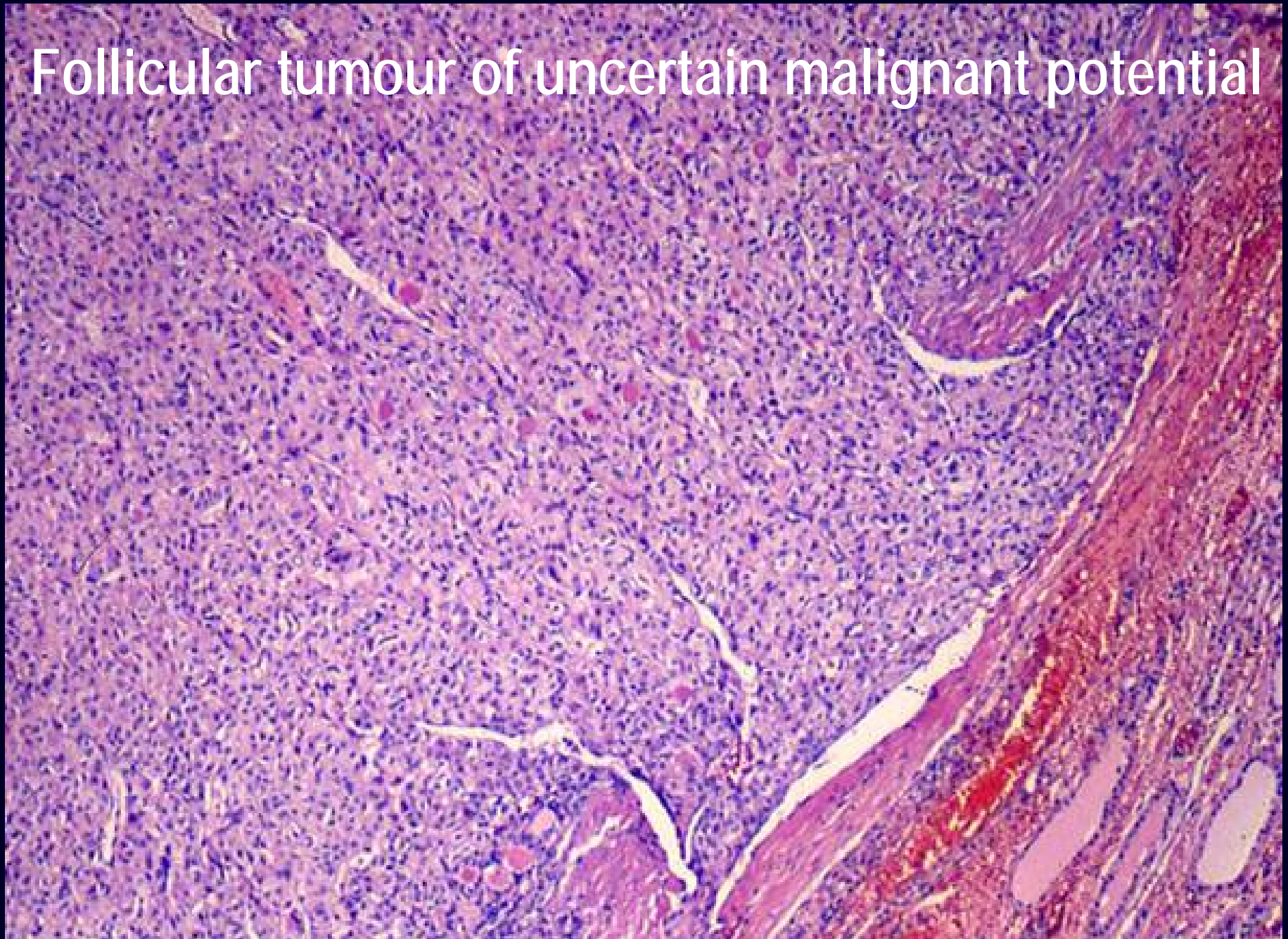
Nuclear features

WHAT ABOUT QUESTIONABLE CASES?

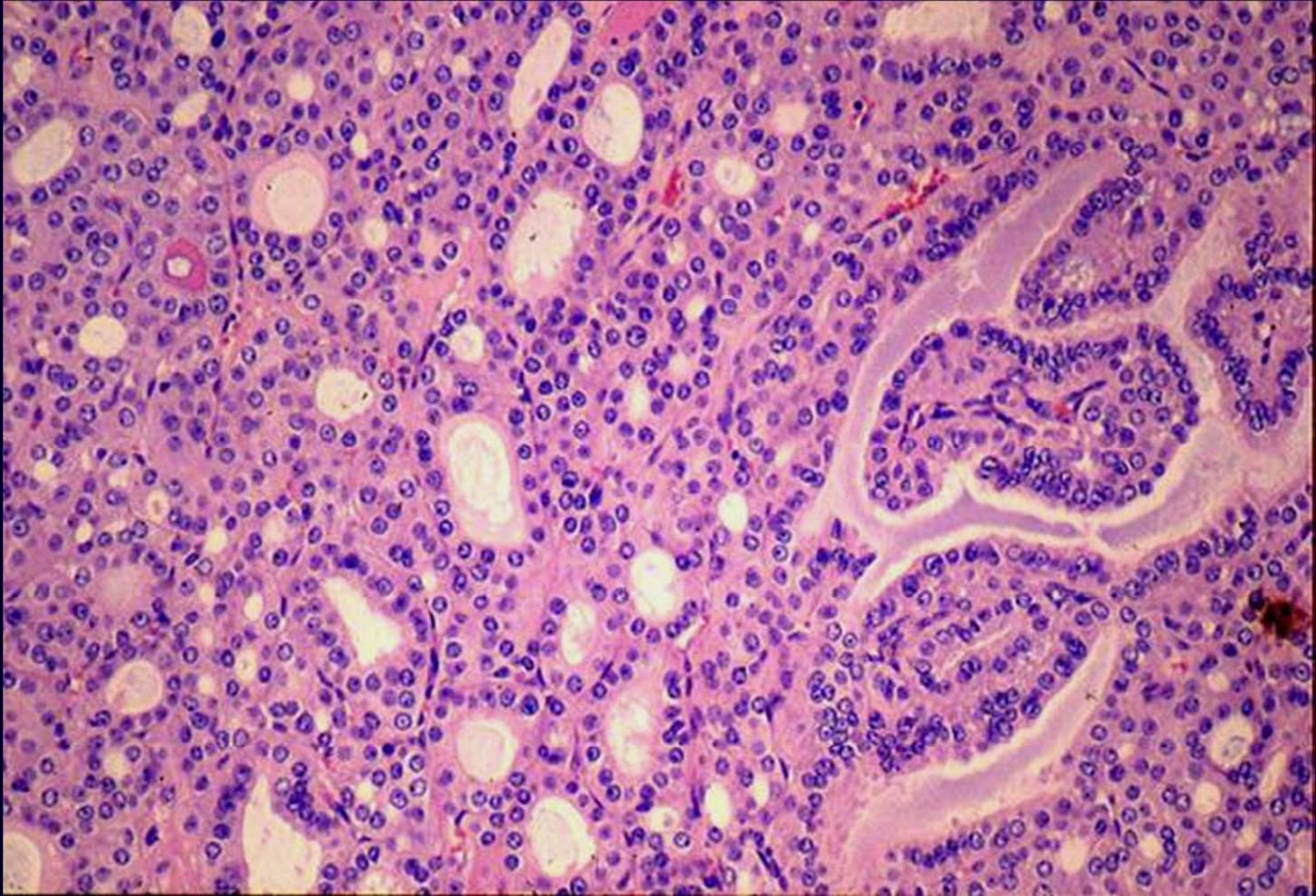
DOES IMMUNOHISTOCHEMISTRY OR
MOLECULAR BIOLOGY HELP?

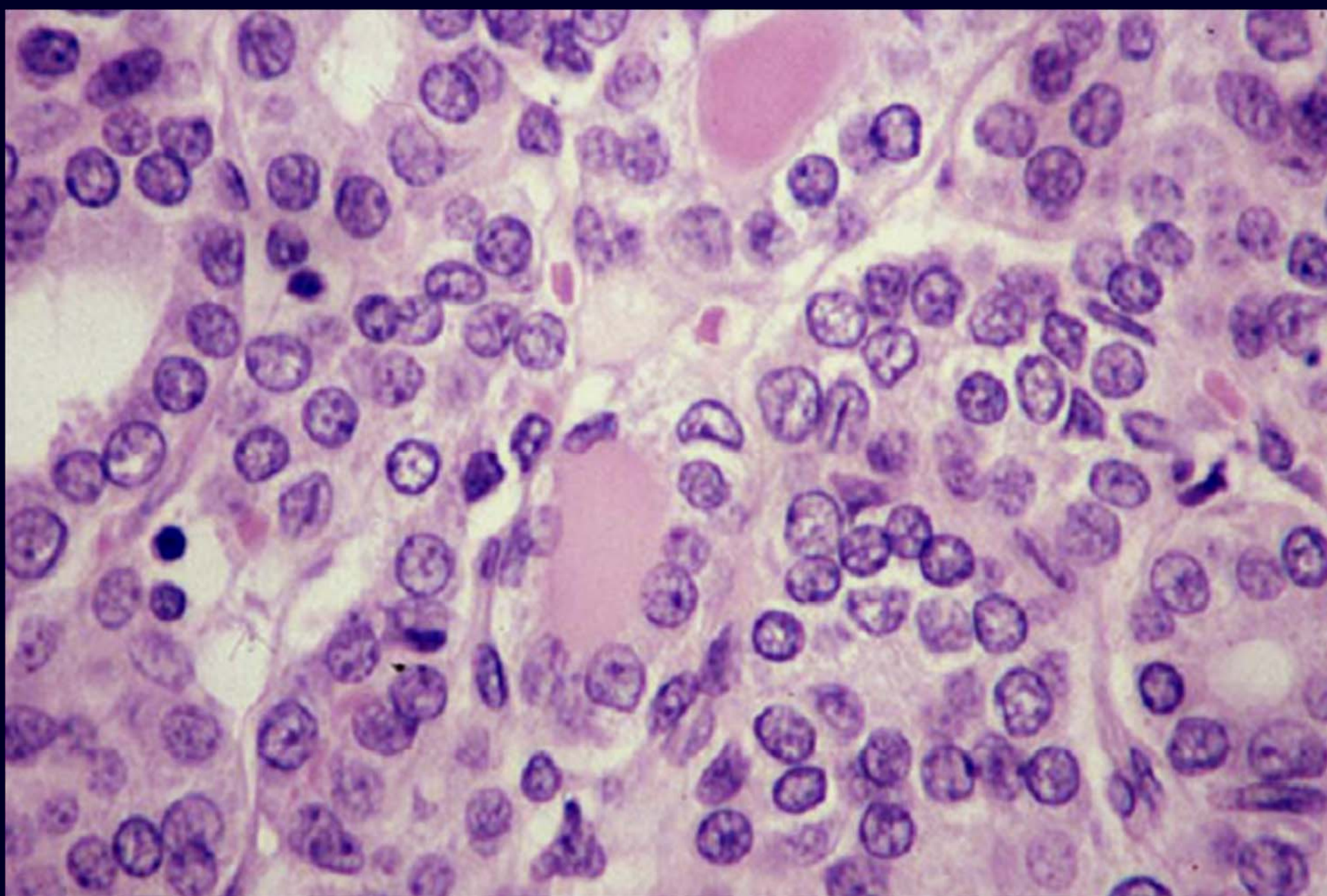


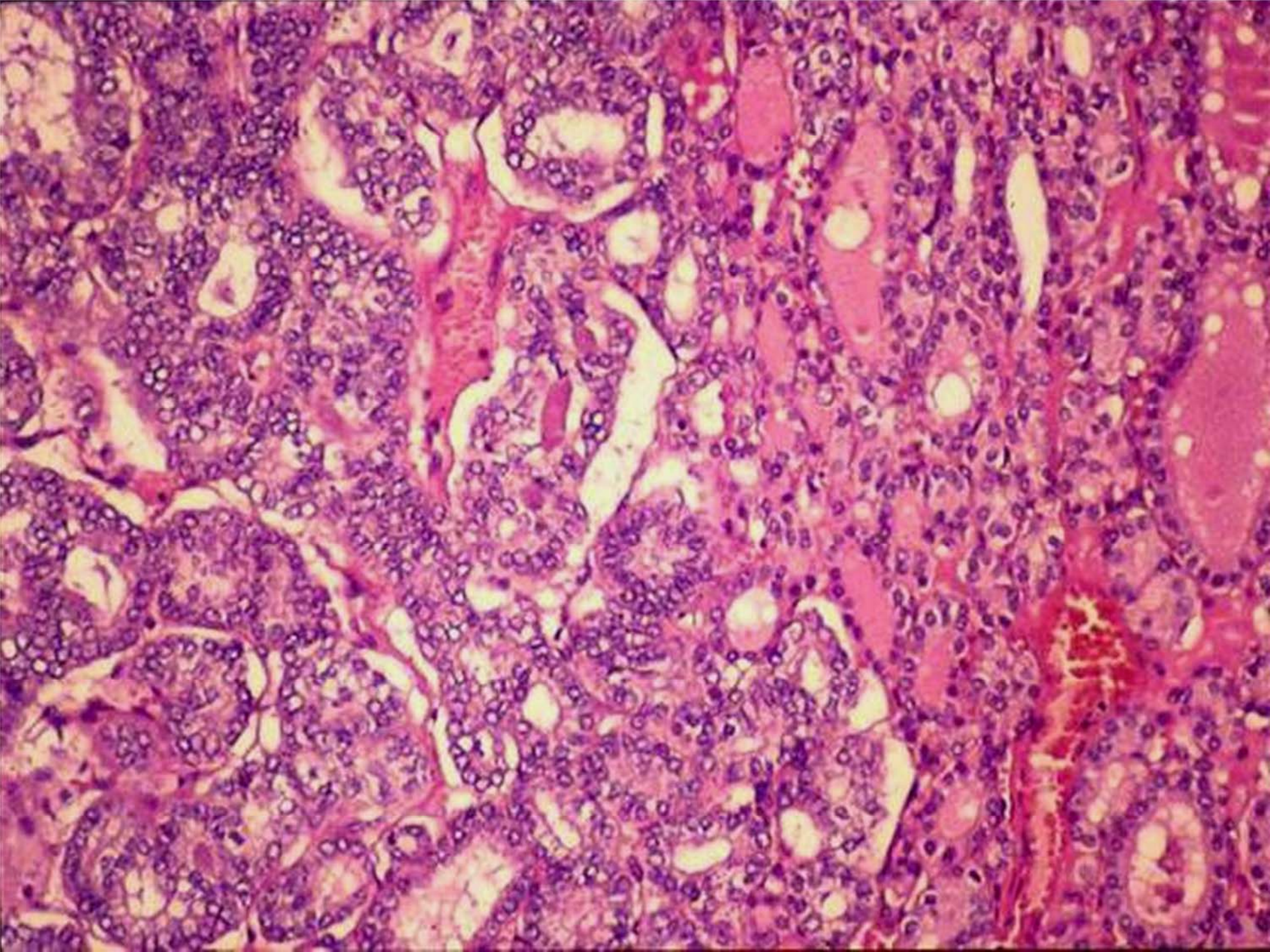
Follicular tumour of uncertain malignant potential

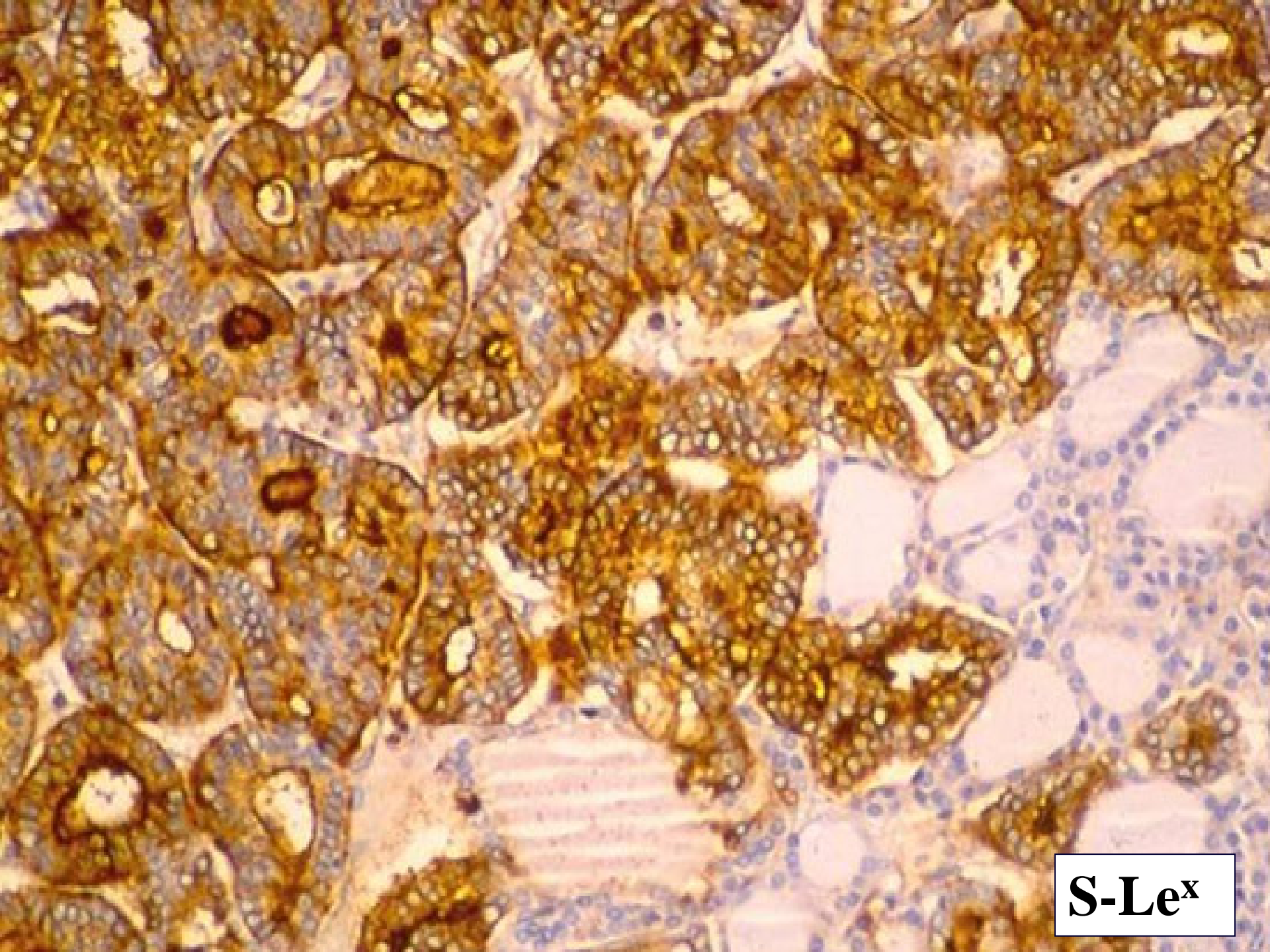


What about intermediate nuclei?









S-Le^x

IMMUNOHISTOCHEMICAL MARKERS OF PAPILLARY THYROID CARCINOMA

- Cytokeratin 19
- Lewis X and S Lewis X
- Galectin 3
- HBME1
-

B-RAF MUTATIONS IN 176 PAPILLARY THYROID CARCINOMAS

Warthin-like PTC	> 75%
Conventional PTC	~ 50%
Follicular variant PTC	< 5%

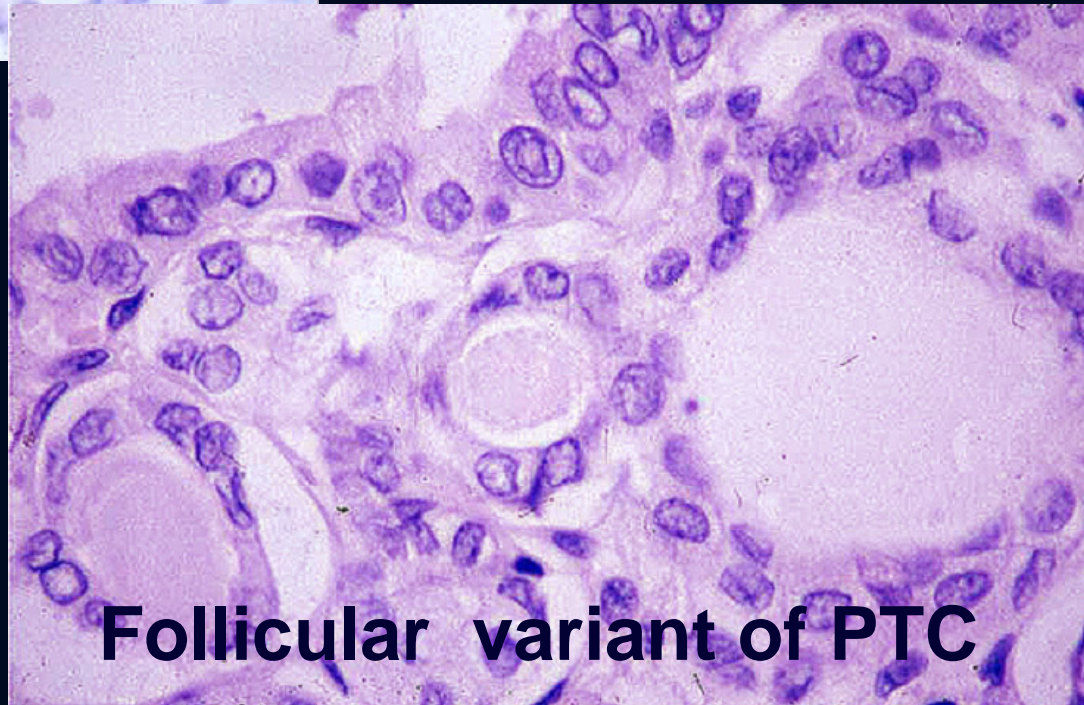
Soares et al, Oncogene 2003
Trovisco et al, J Pathol, 2004
Lima et al, JCEM 89:4267, 2004

Malignancy in papillary carcinoma

Conventional papillary carcinoma

Nuclear features

Follicular variant of PTC



In the large majority of cases the most important feature for diagnosing a PTC is the poor circumscription/infiltrative pattern rather than the nuclear characteristics

What about encapsulated,
non-invasive follicular
variant of PTC?

Is it clinically malignant?

"...we can only conclude that the morbidity and mortality associated with encapsulated follicular variant PTC (EFV-PTC) is practically zero. Therefore, whenever we reluctantly make the diagnosis of EFV-PTC, we add a note emphasizing the extremely high probability of a permanent cure following a conservative operation (usually a lobectomy) and the lack of indication for additional surgery"

Rosai J. Camino Santiago Meeting, 2010
Piana S et al. Am J Surg Pathol , 2010

A pathologic re-review of follicular thyroid neoplasms: The impact of changing the threshold for the diagnosis of the follicular variant of papillary thyroid carcinoma

Widder S et al. Surgery 144:80-85, 2008.

Problems of encapsulated follicular or papillary carcinoma

PARTIAL *vs* TOTAL THYROIDECTOMY

- Encapsulated, non-angioinvasive follicular variant of PTC (with or without BRAF mutation?) and encapsulated, non-angioinvasive follicular carcinoma **do not imply total thyroidectomy.**
(The same holds true for follicular and well differentiated tumours of uncertain malignant potential)
- It is mandatory to have very good sonography data & to study thoroughly the surgical specimens

Rosai, Sobrinho-Simões,... 2010

240 cases (1978-2003) with nodal and/or distant metastases [Excluding medullary, poorly diff and undiff ca]

- Classical and several variants of PTC
- Poorly circumscribed and multinodular follicular variant of PTC
- Angio- and/or widely invasive follicular carcinoma

Consortium IPO-IPATIMUP, 2012 (unpublished results)

240 cases (1978-2003) with nodal and/or distant metastases

NOT A SINGLE CASE OF:

Follicular tumour of uncertain malignant potential

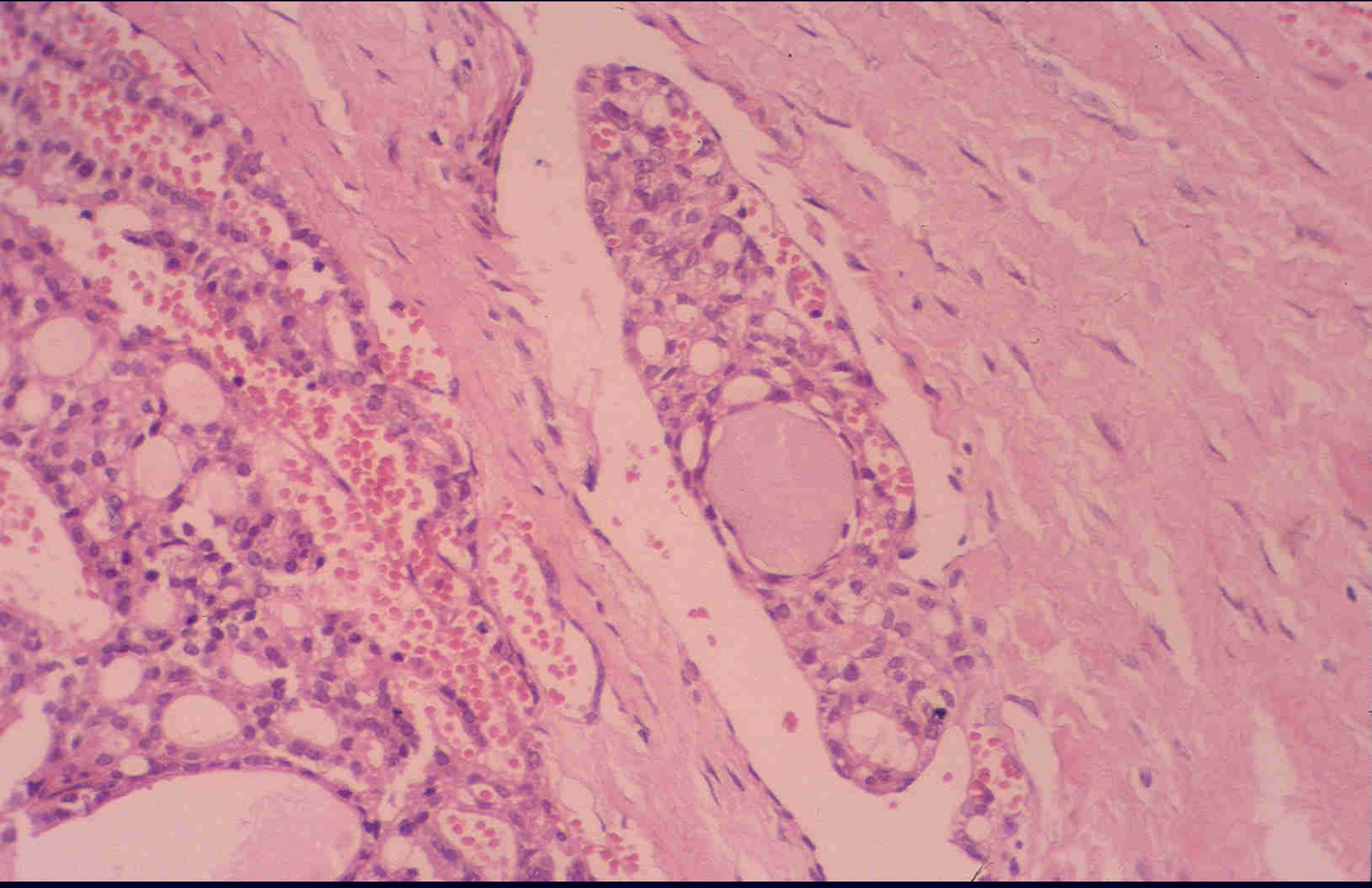
Well differentiated tumour of uncertain malignant potential

Minimally invasive follicular carcinoma without vascular invasion

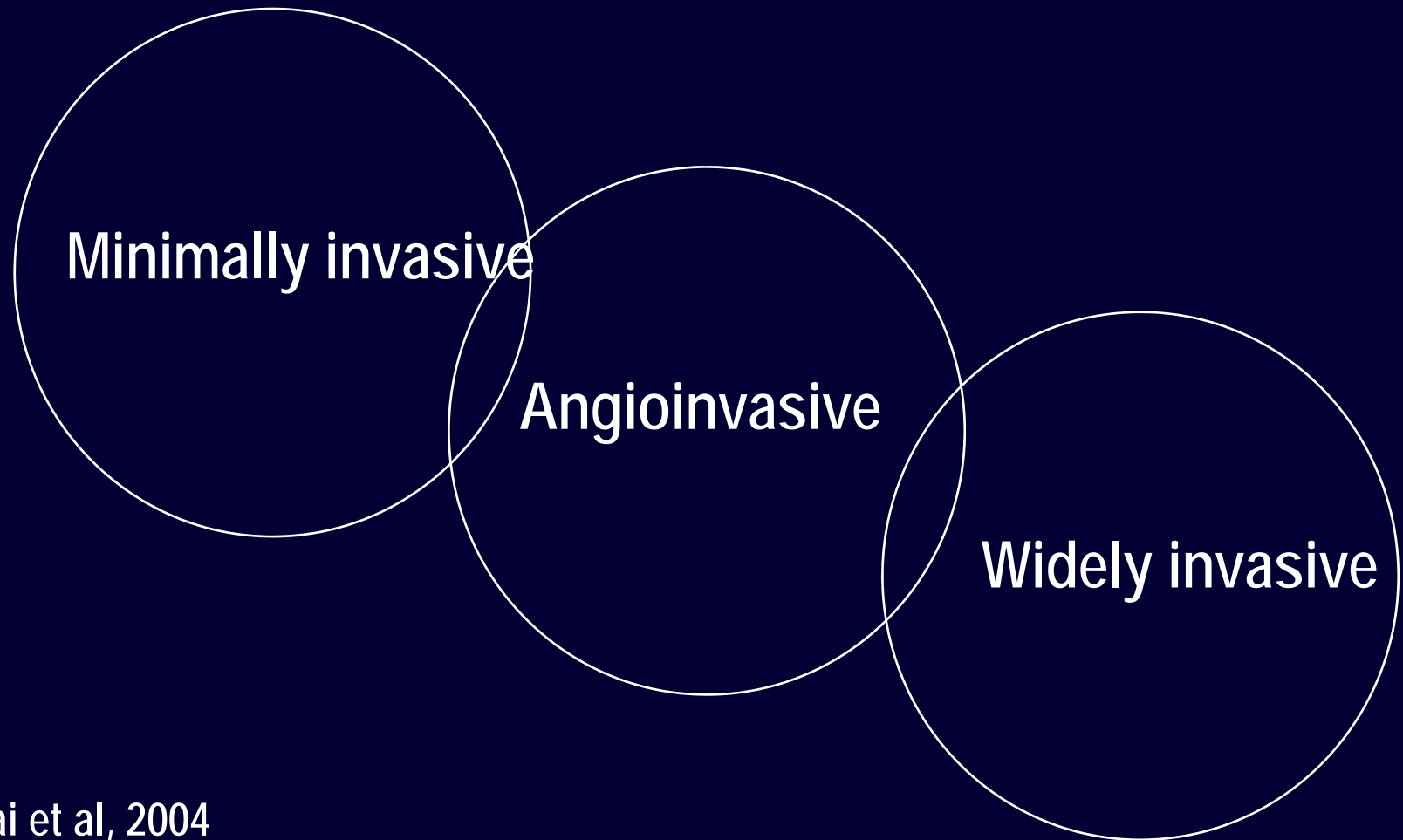
Encapsulated follicular variant of PTC without invasion

Consortium IPO-IPATIMUP, 2012 (unpublished results)

TAKE HOME LESSON: In every encapsulated lesion look for vascular invasion



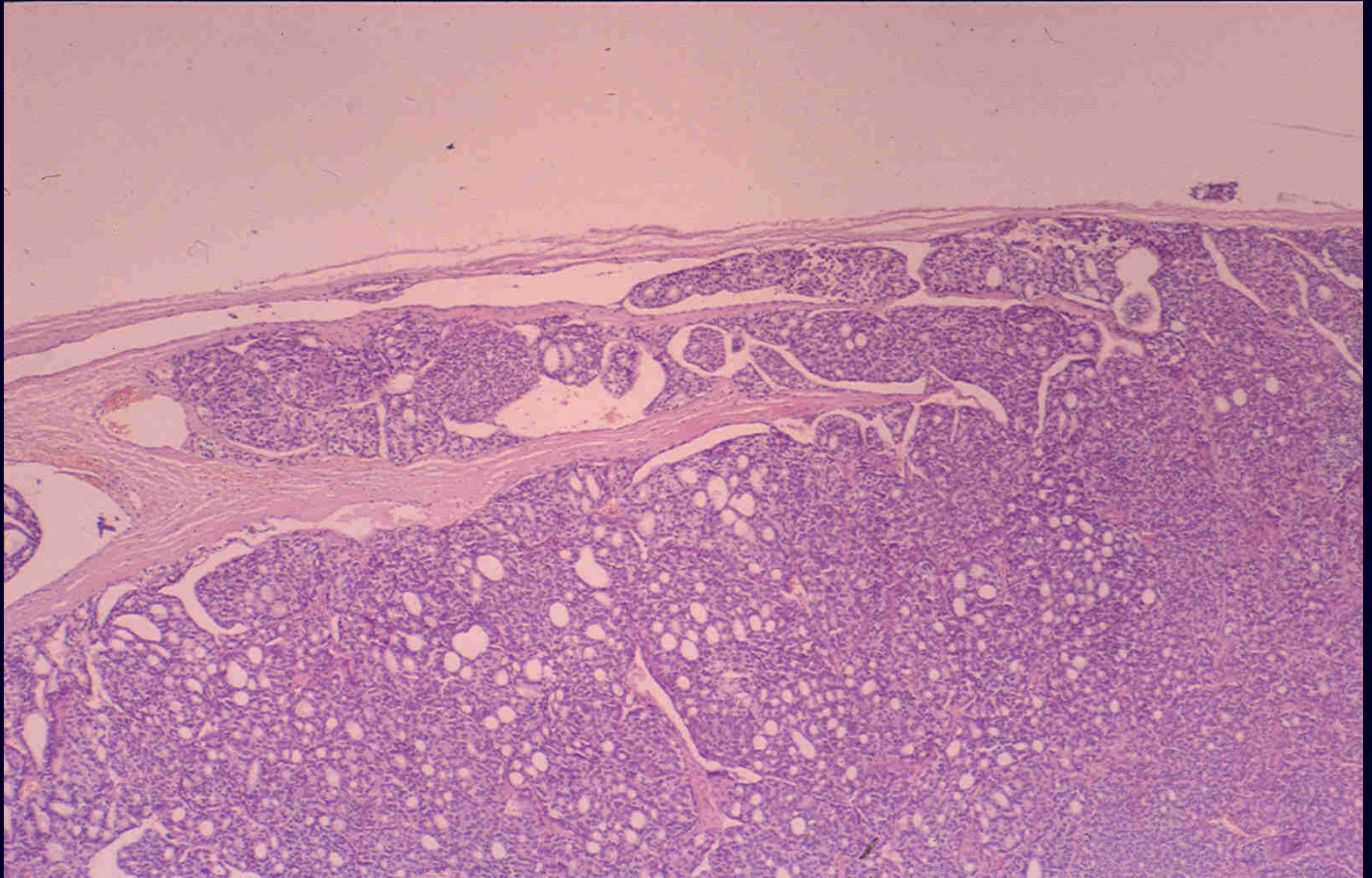
Follicular carcinoma



Rosai et al, 2004

WHO book on Endocrine Tumours, 2004

Minimally invasive and angioinvasive follicular carcinoma

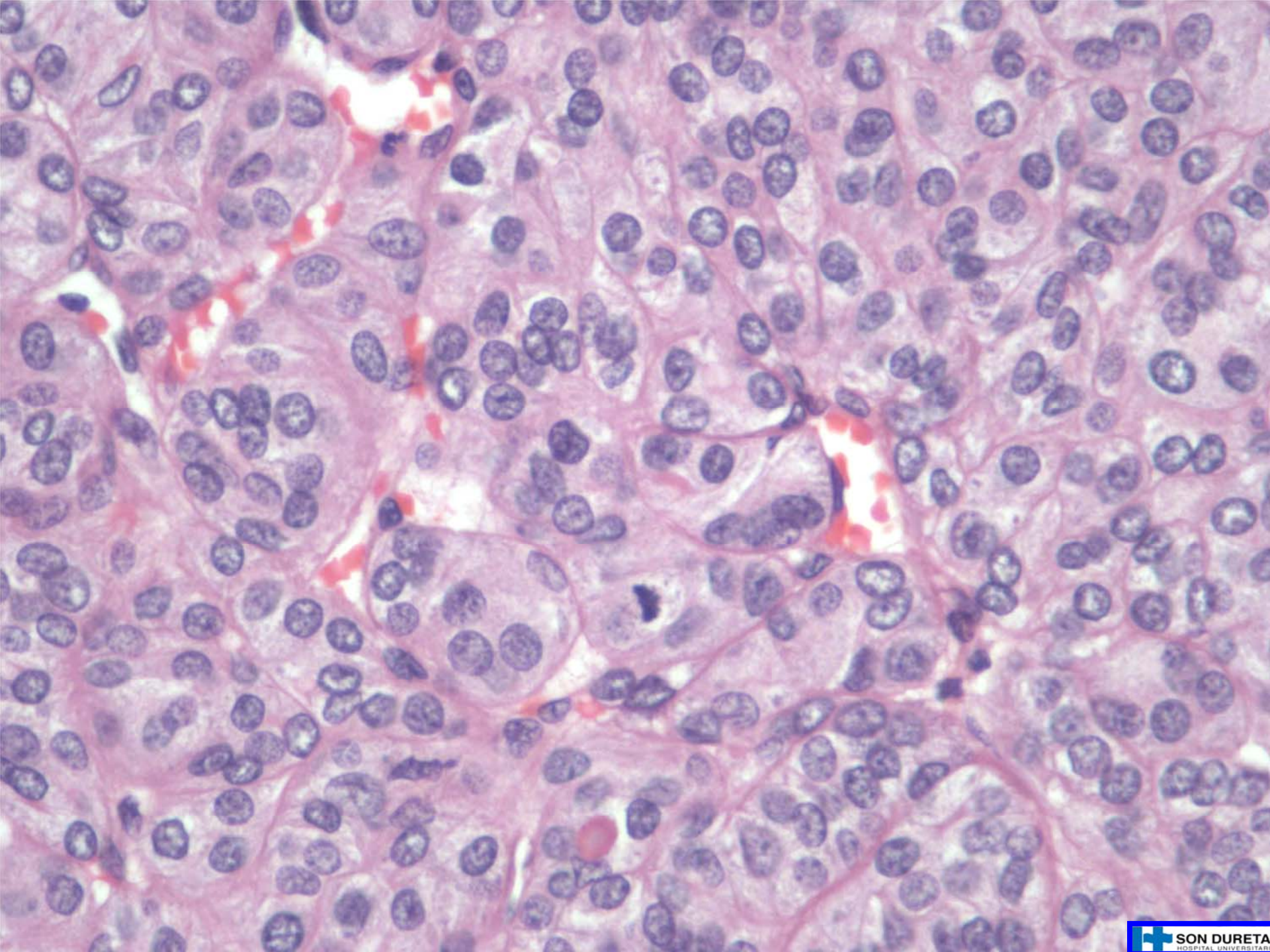


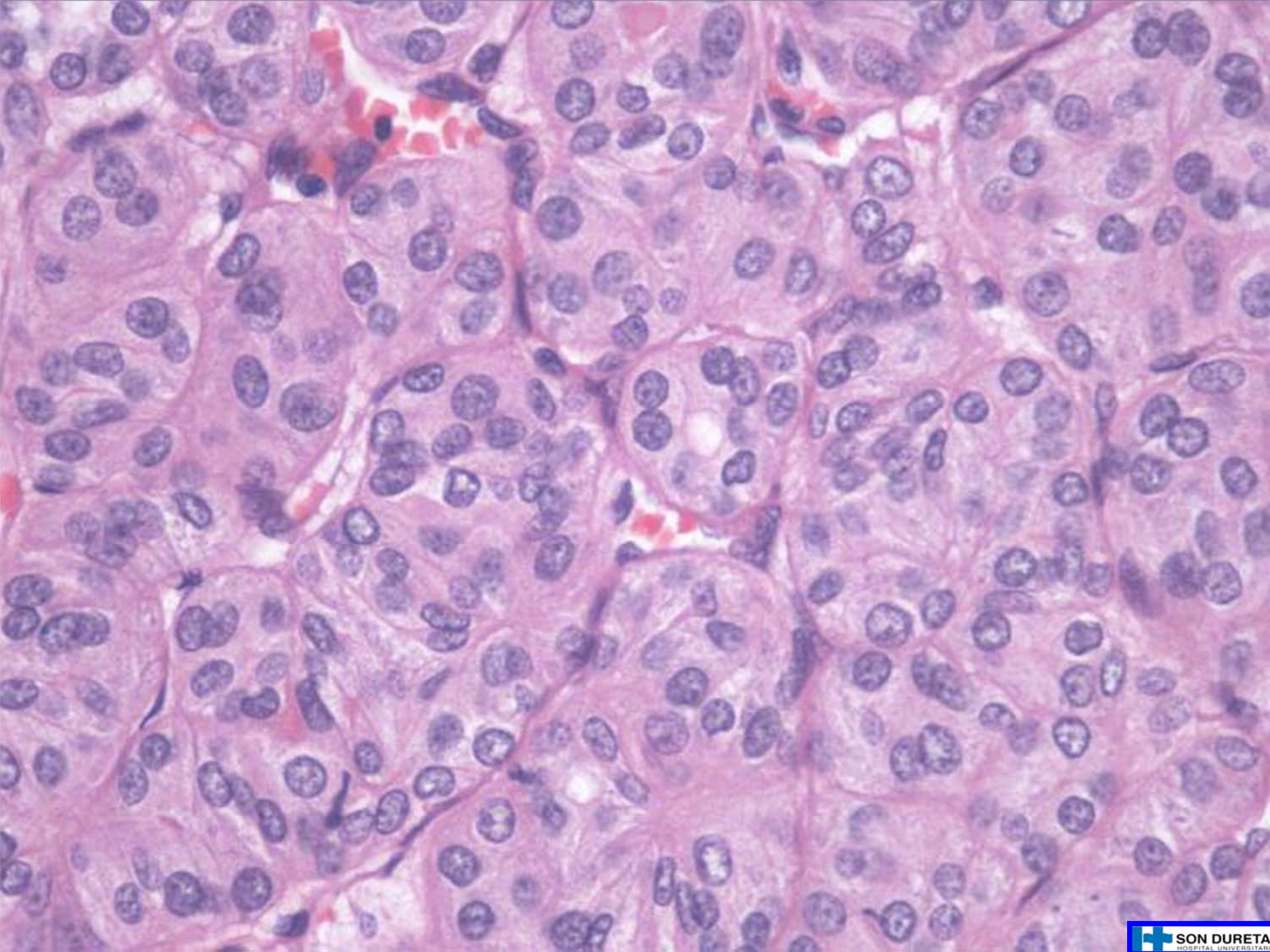
- Well differentiated tumor of uncertain malignant potential
- Well differentiated carcinoma, NOS

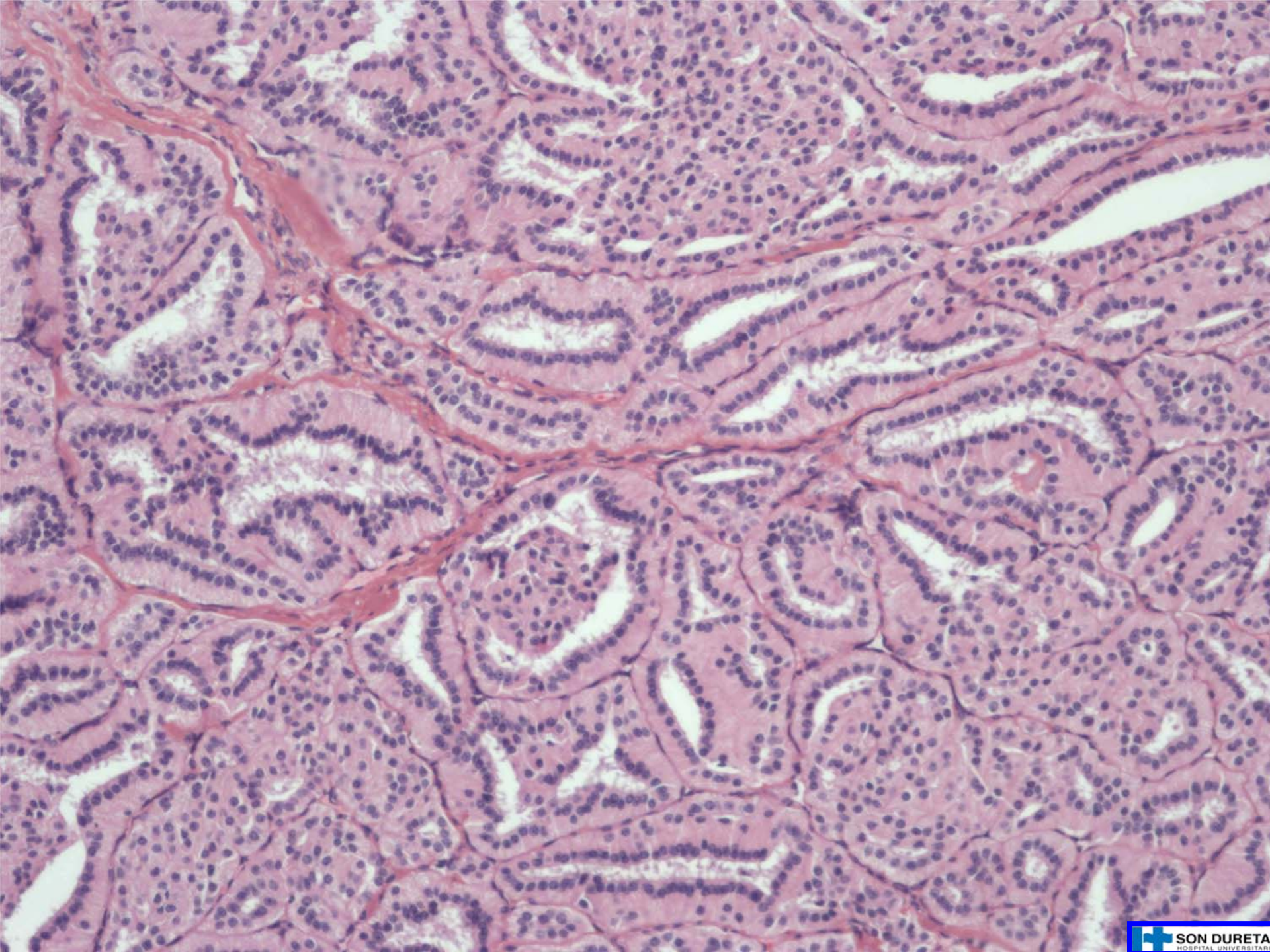
Williams et al, Int J Surg Pathol 8:181, 2000

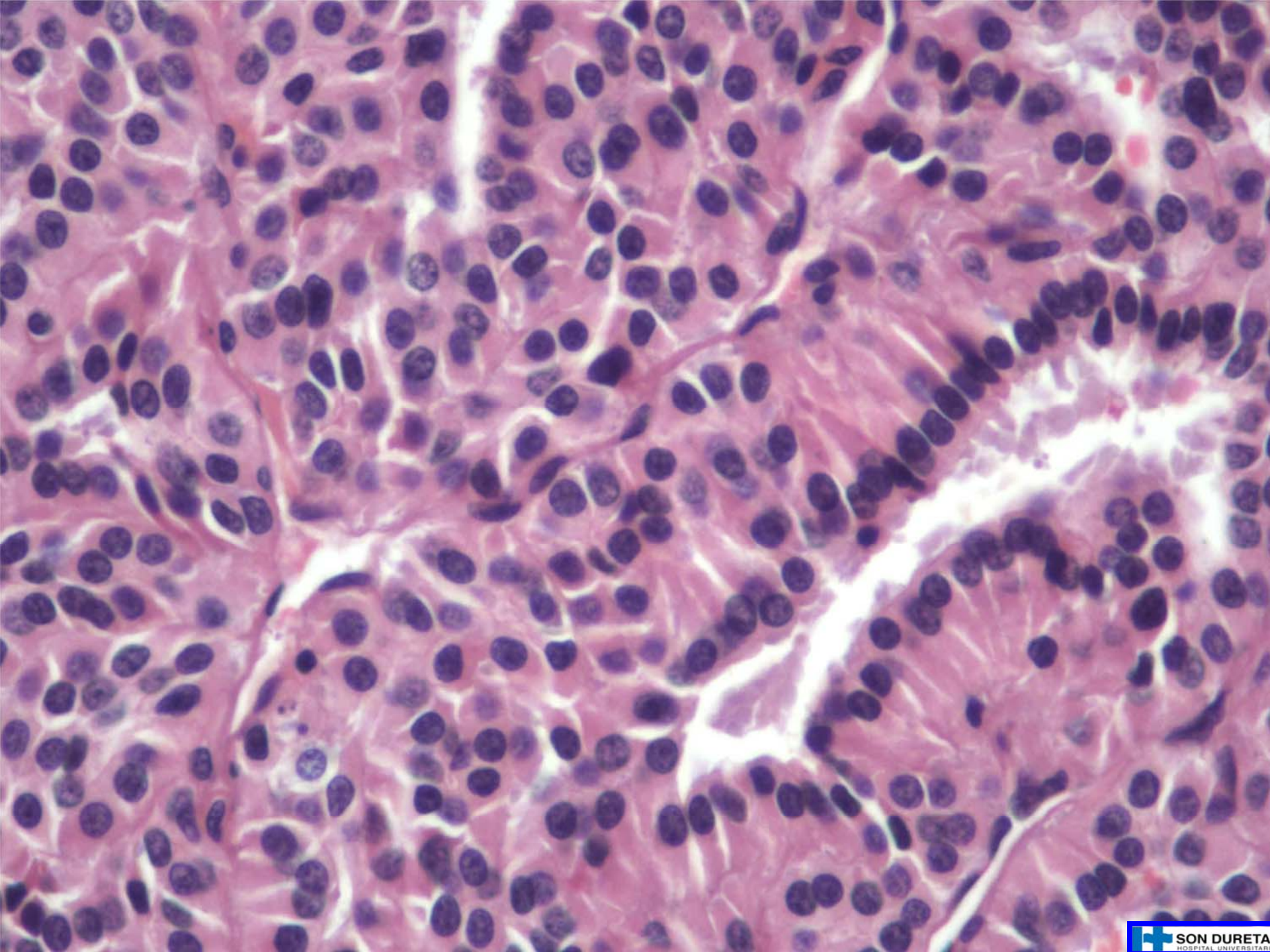
WHO book on Endocrine Tumours, 3rd edition, 2004

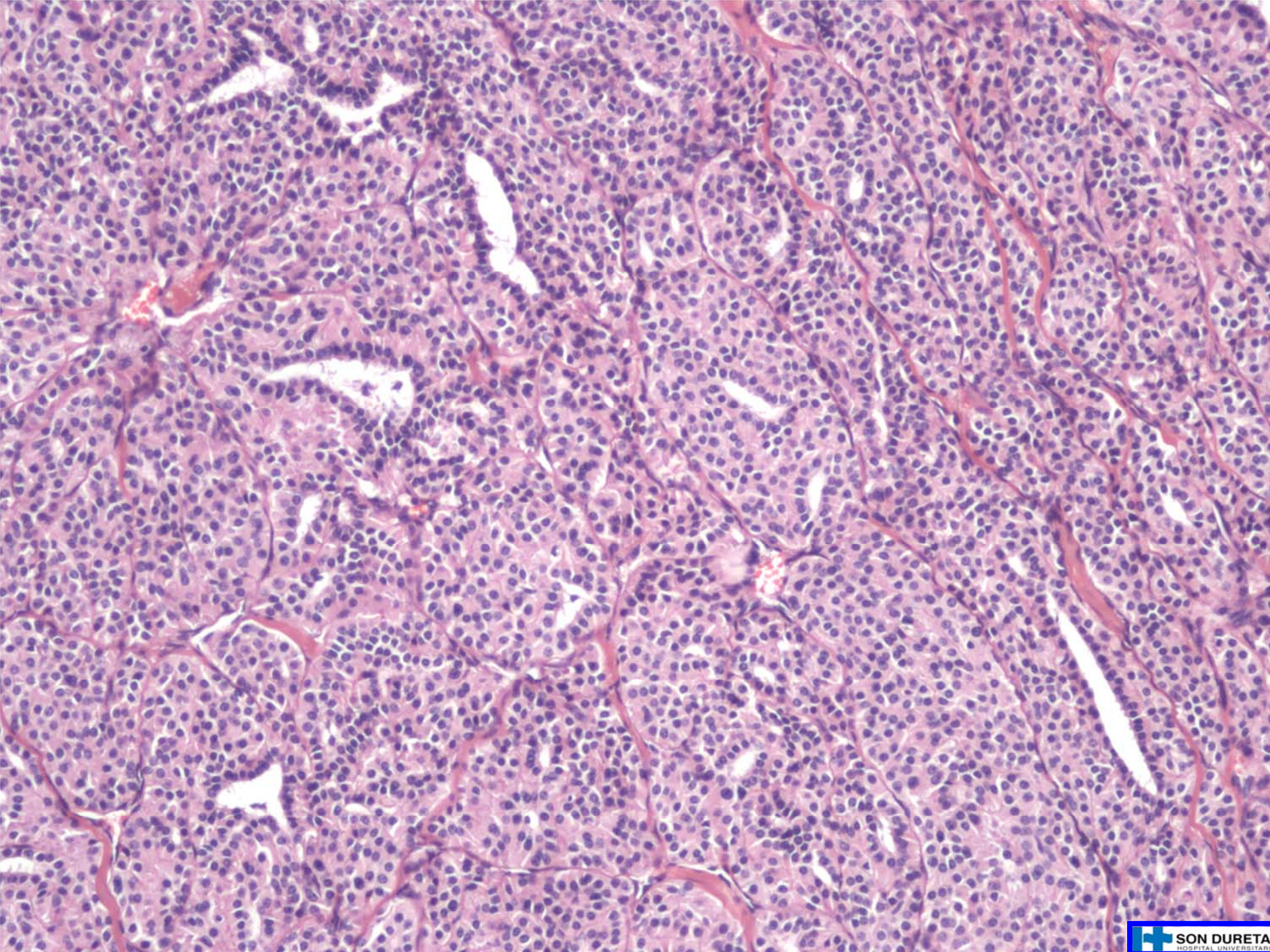
- 
- A histological slide of thyroid tissue stained with hematoxylin and eosin (H&E). The left side of the image shows normal thyroid follicles with pink-stained colloid and a single layer of cuboidal follicular cells. The right side shows a large, dense area of tumor tissue with a more cellular, purple-stained appearance, separated from the normal follicles by a thin layer of connective tissue.
- Consultation case
 - 71 y, man, 9cm thyroid tumour

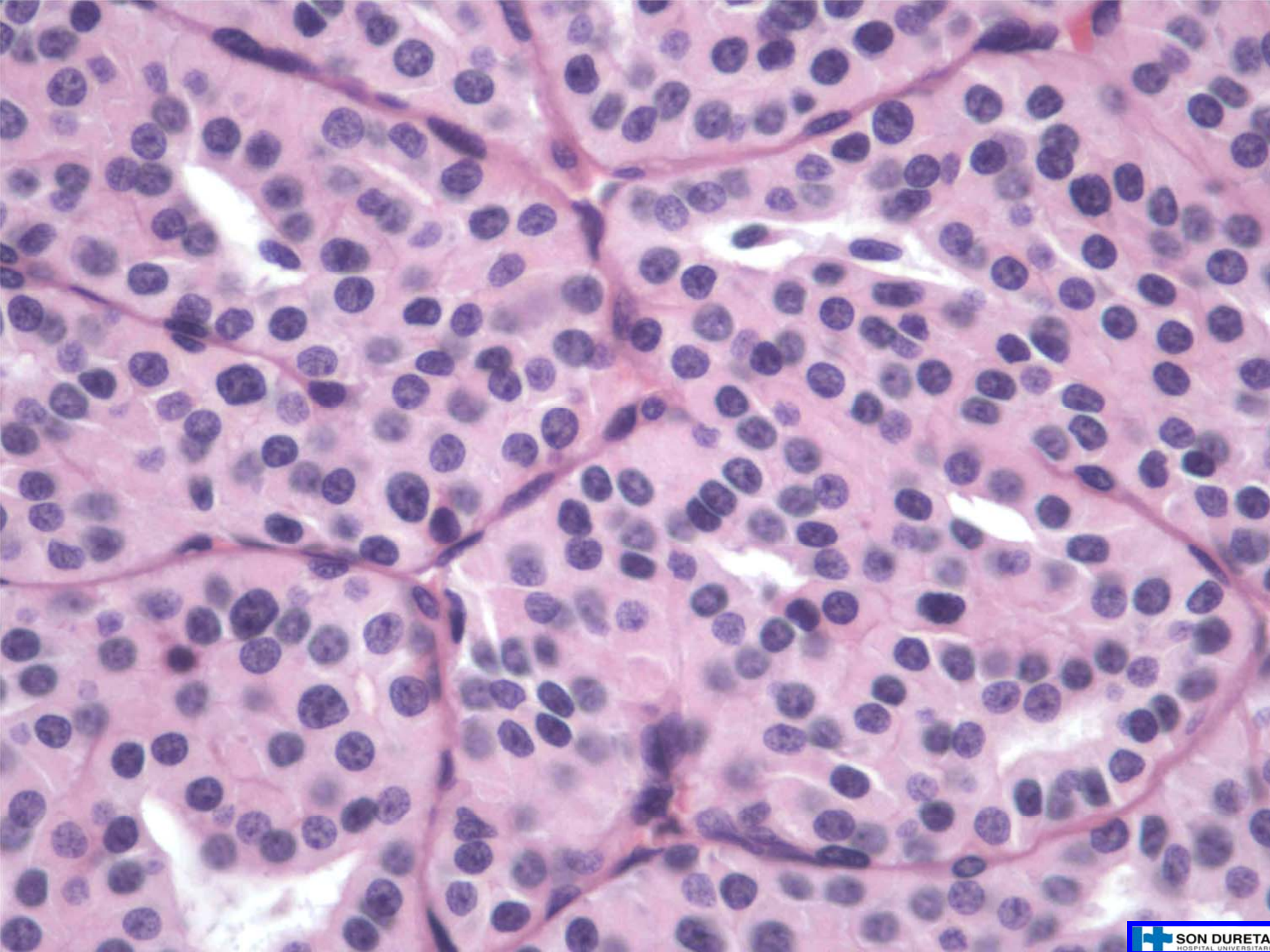


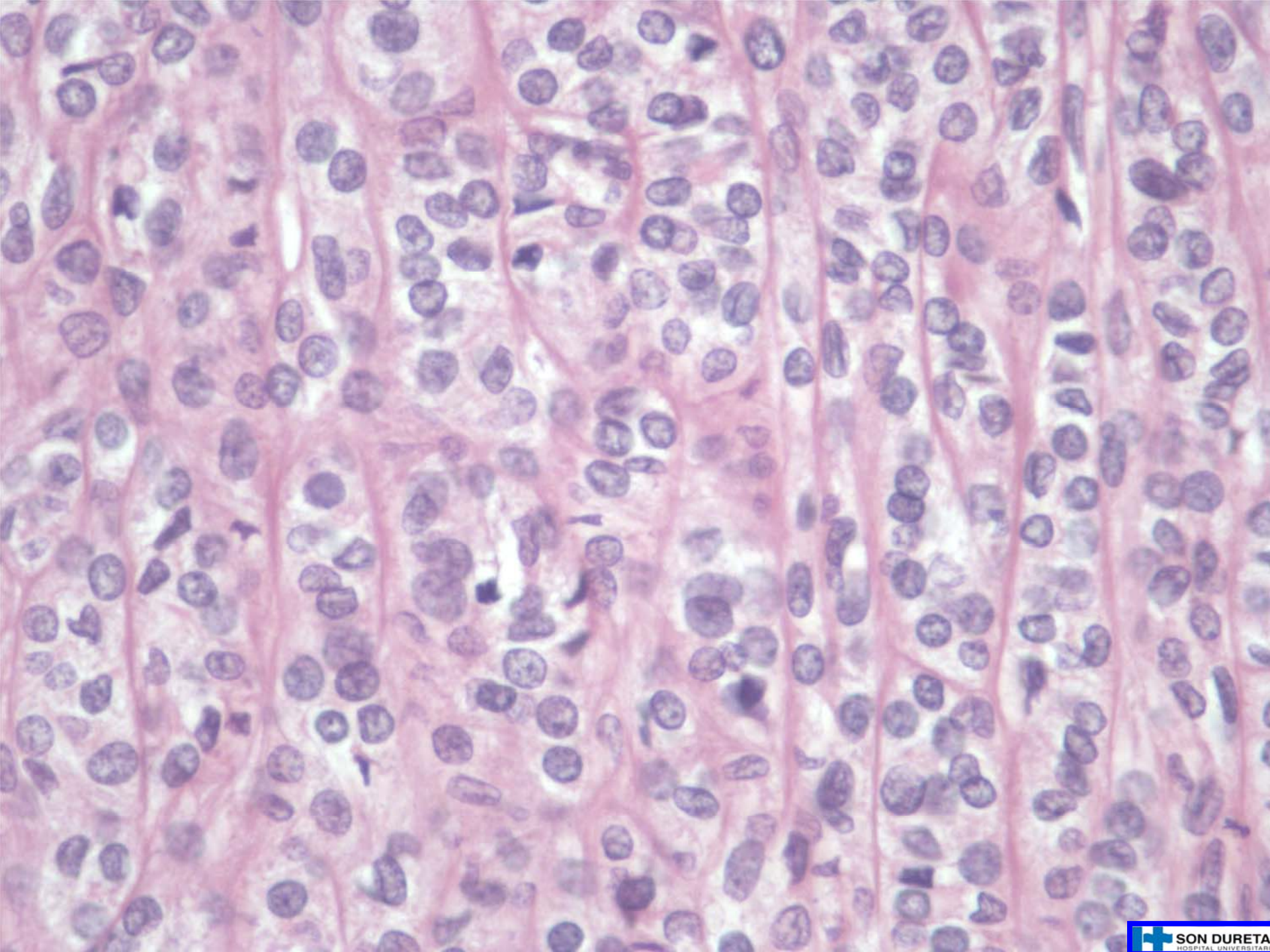


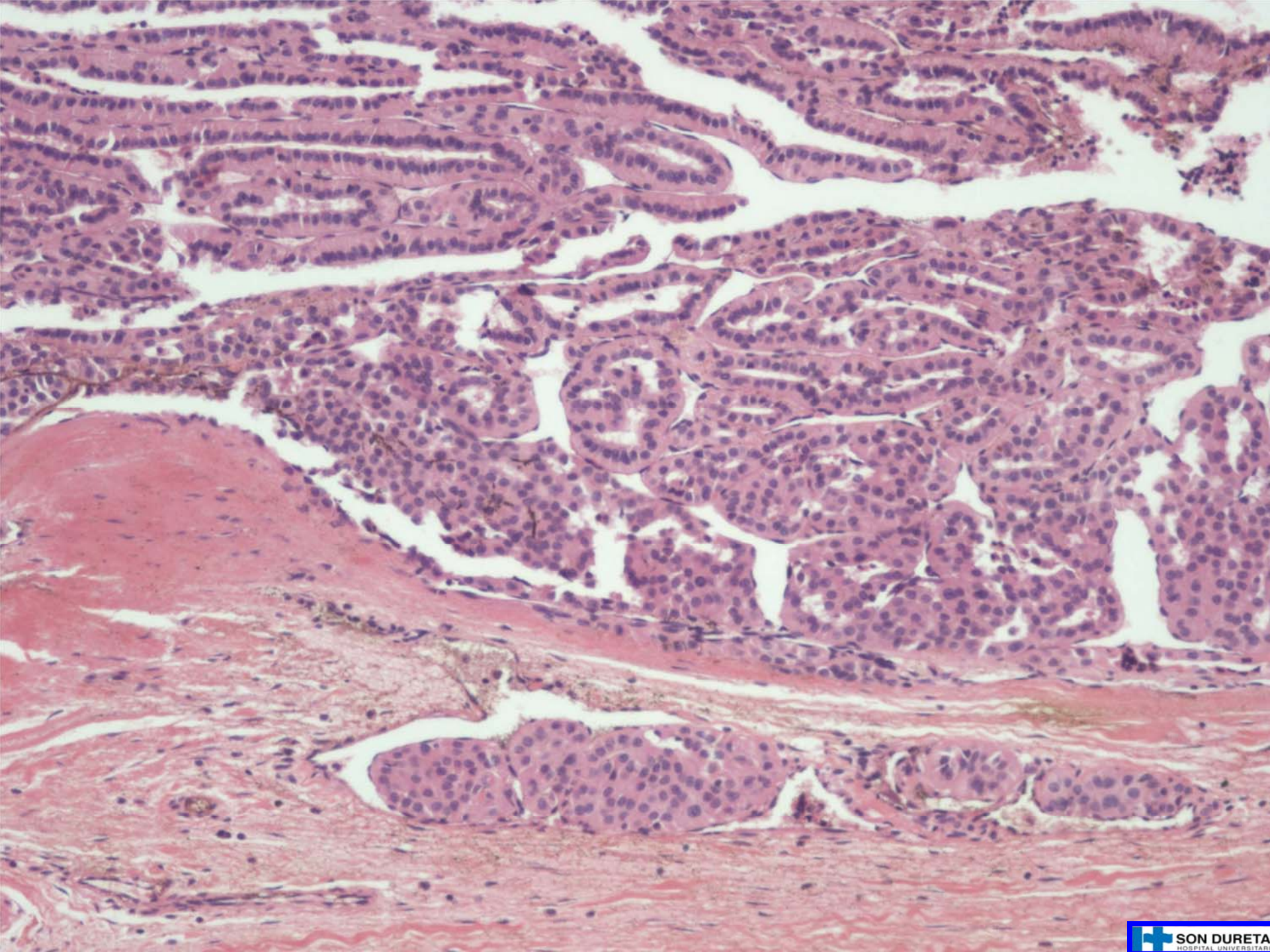


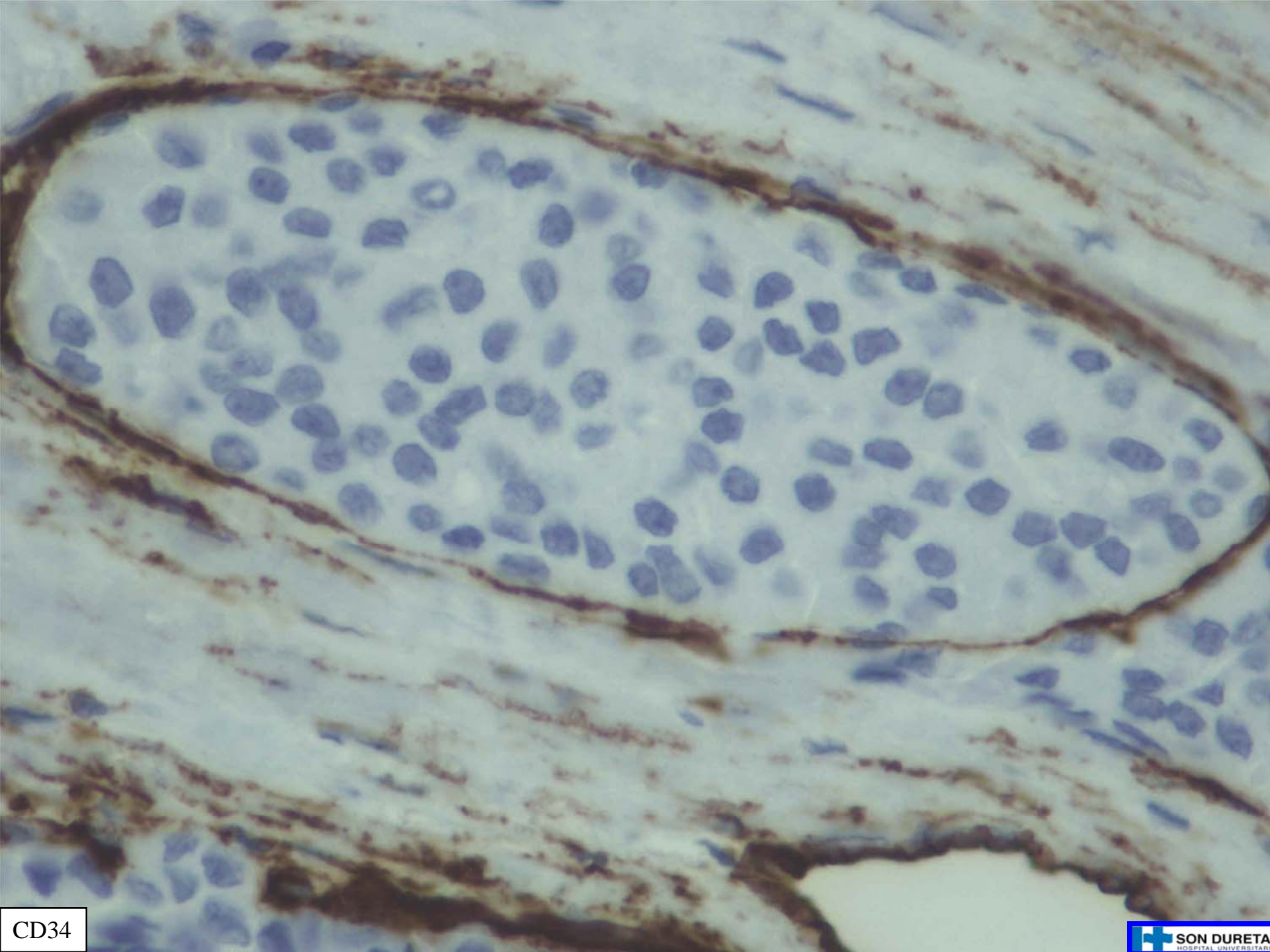












CD34

Follicular carcinoma can be difficult to distinguish from follicular variant of PTC. In a small number of follicular tumours with definite capsular or vascular invasion a minority of nuclei may show changes suggestive of a PTC



**Well differentiated carcinoma,
not otherwise specified**

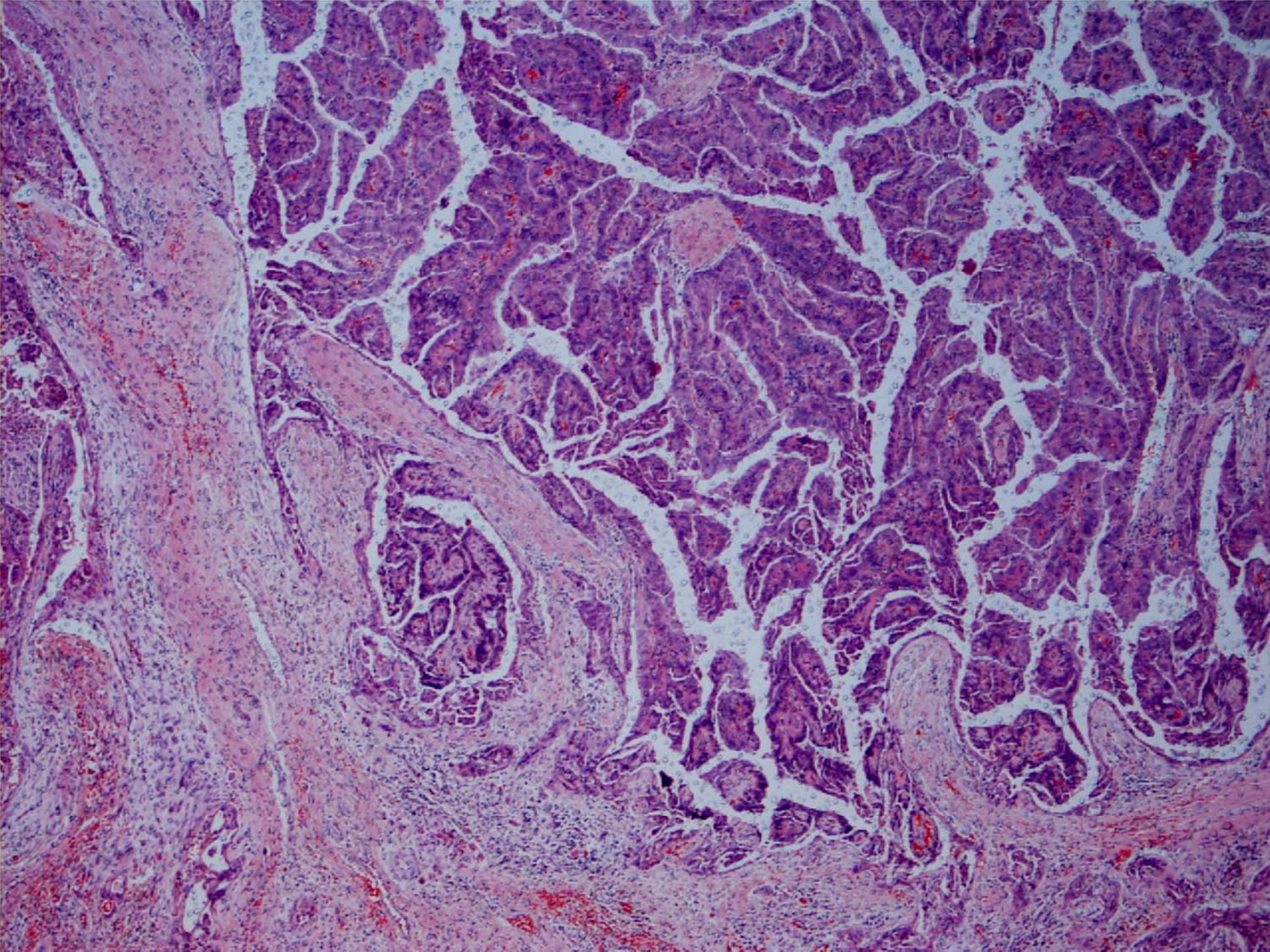
Most frequent diagnostic problems of thyroid pathology in a consultancy practice

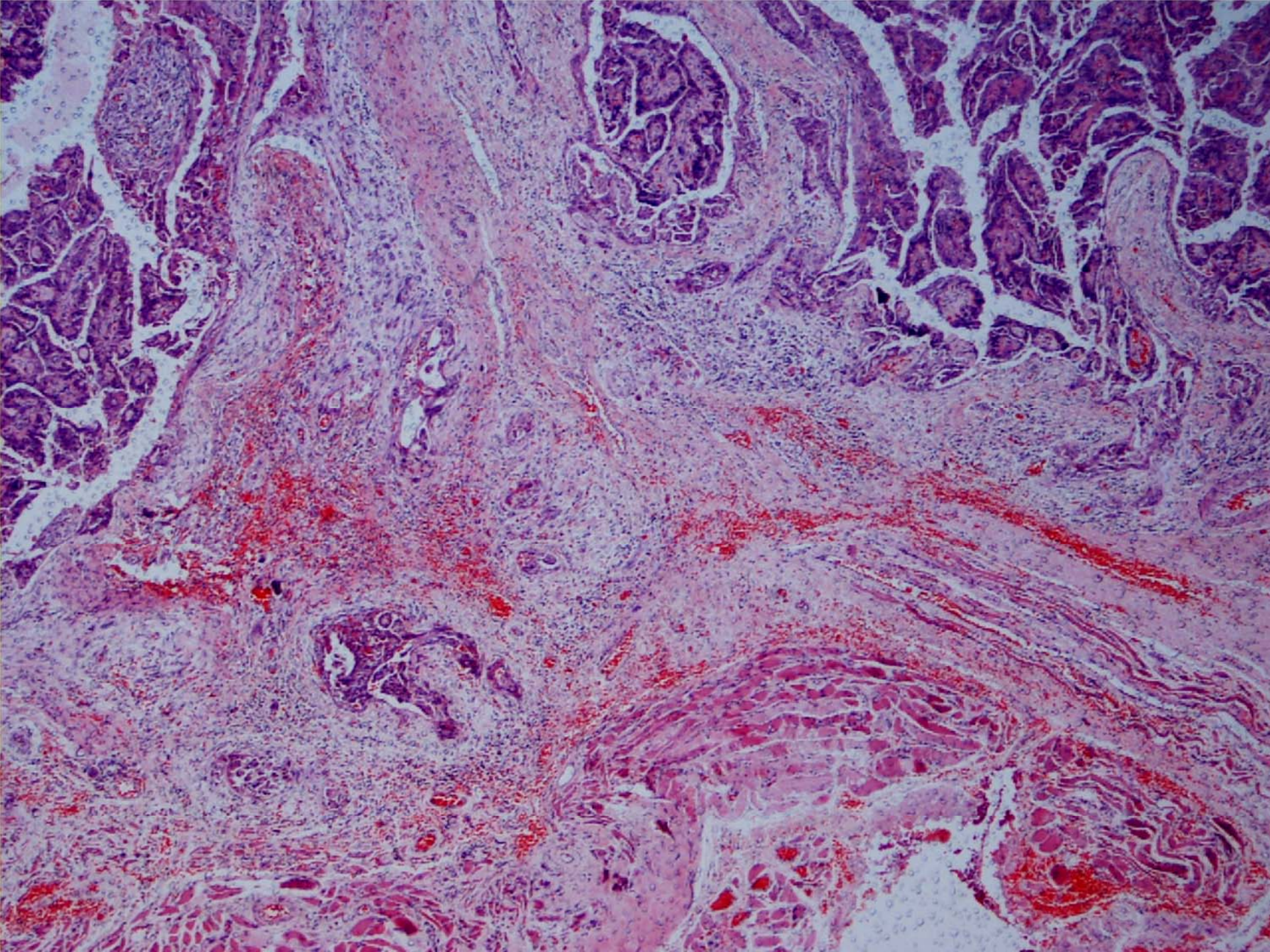
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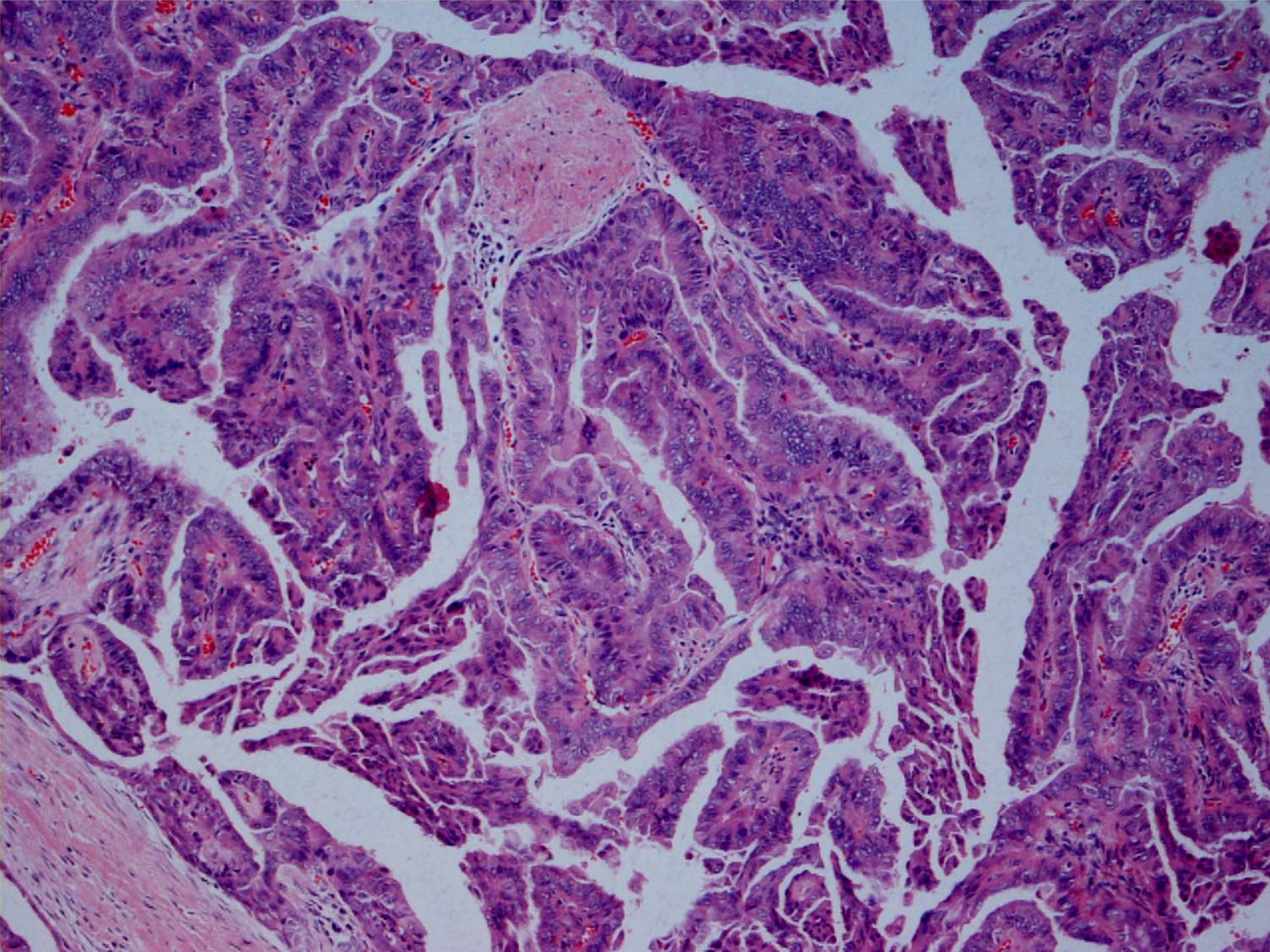
Case 1

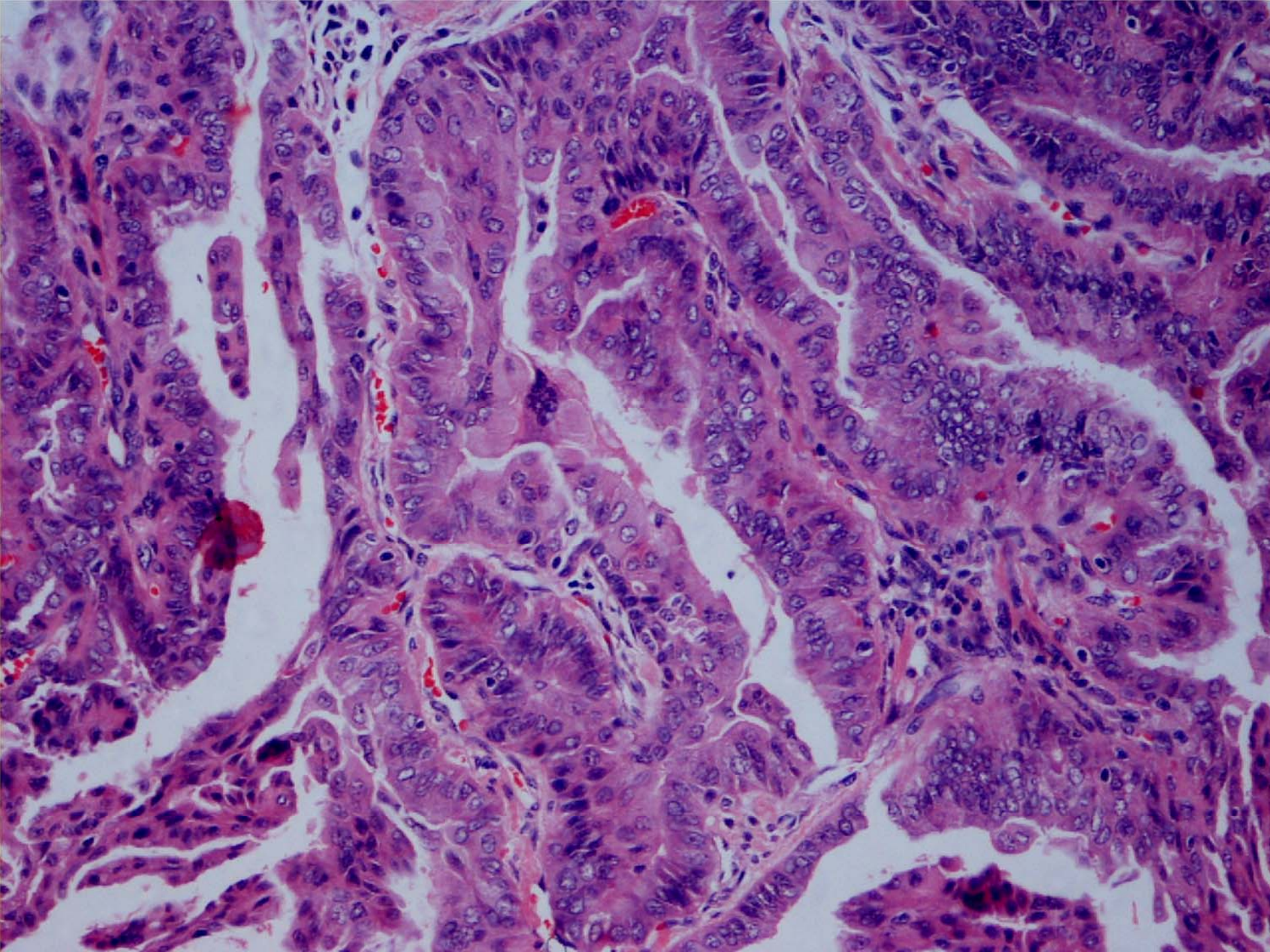
Female, 79-year-old.

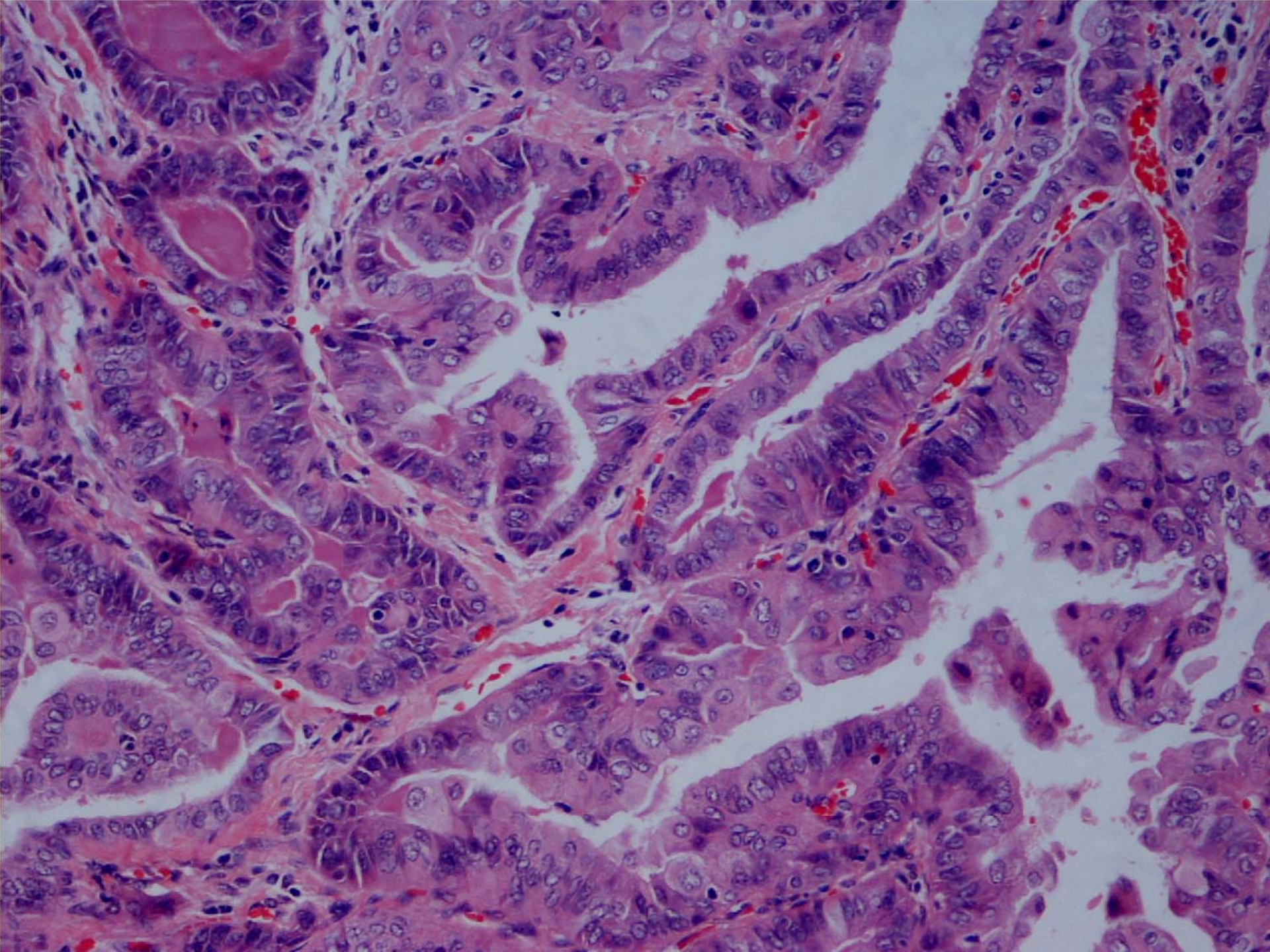
Right hemithyroidectomy specimen
measuring 6.0 cm x 4.8 cm x 3.7 cm, totally
occupied by a brown, firm nodule.

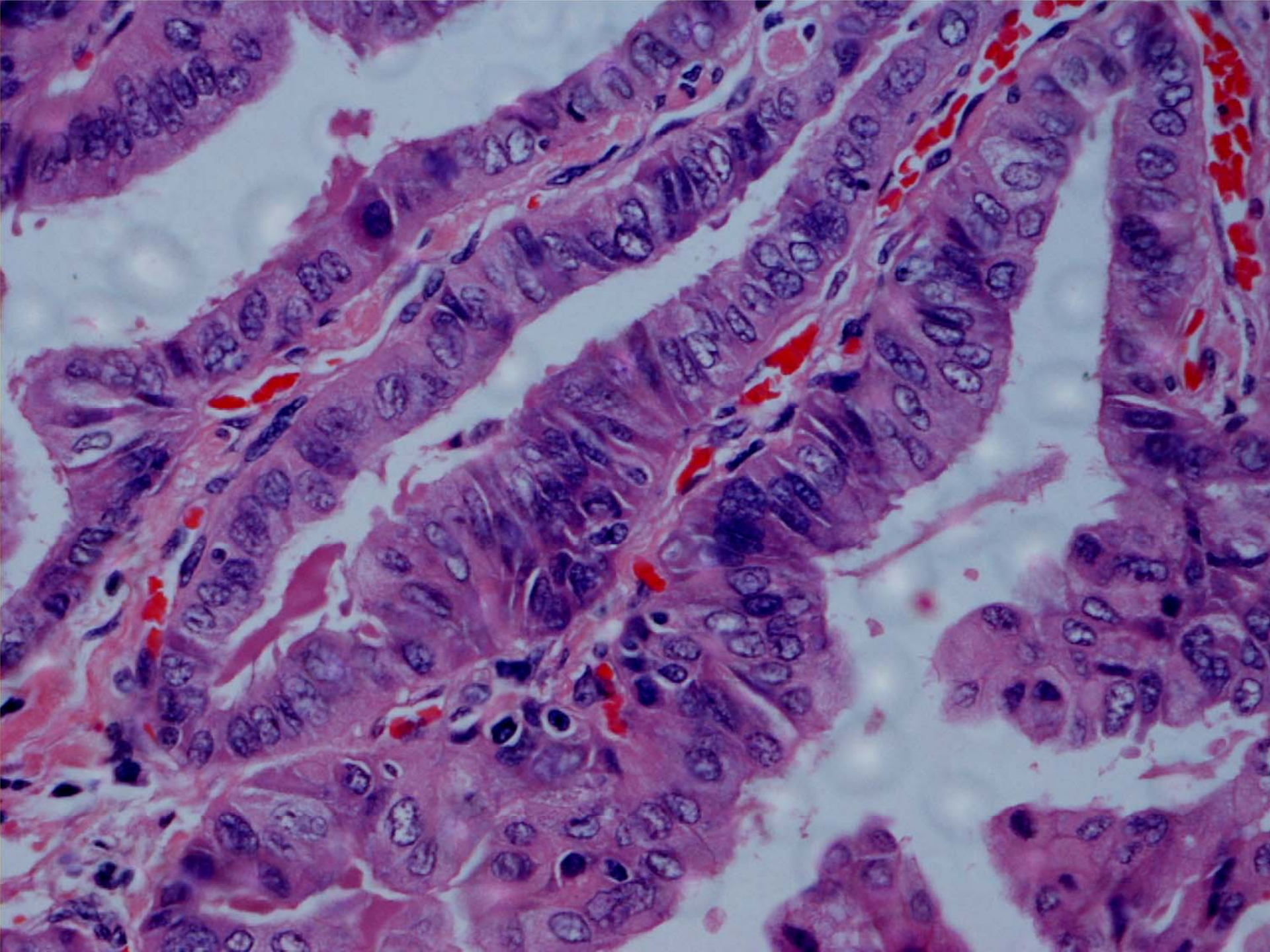


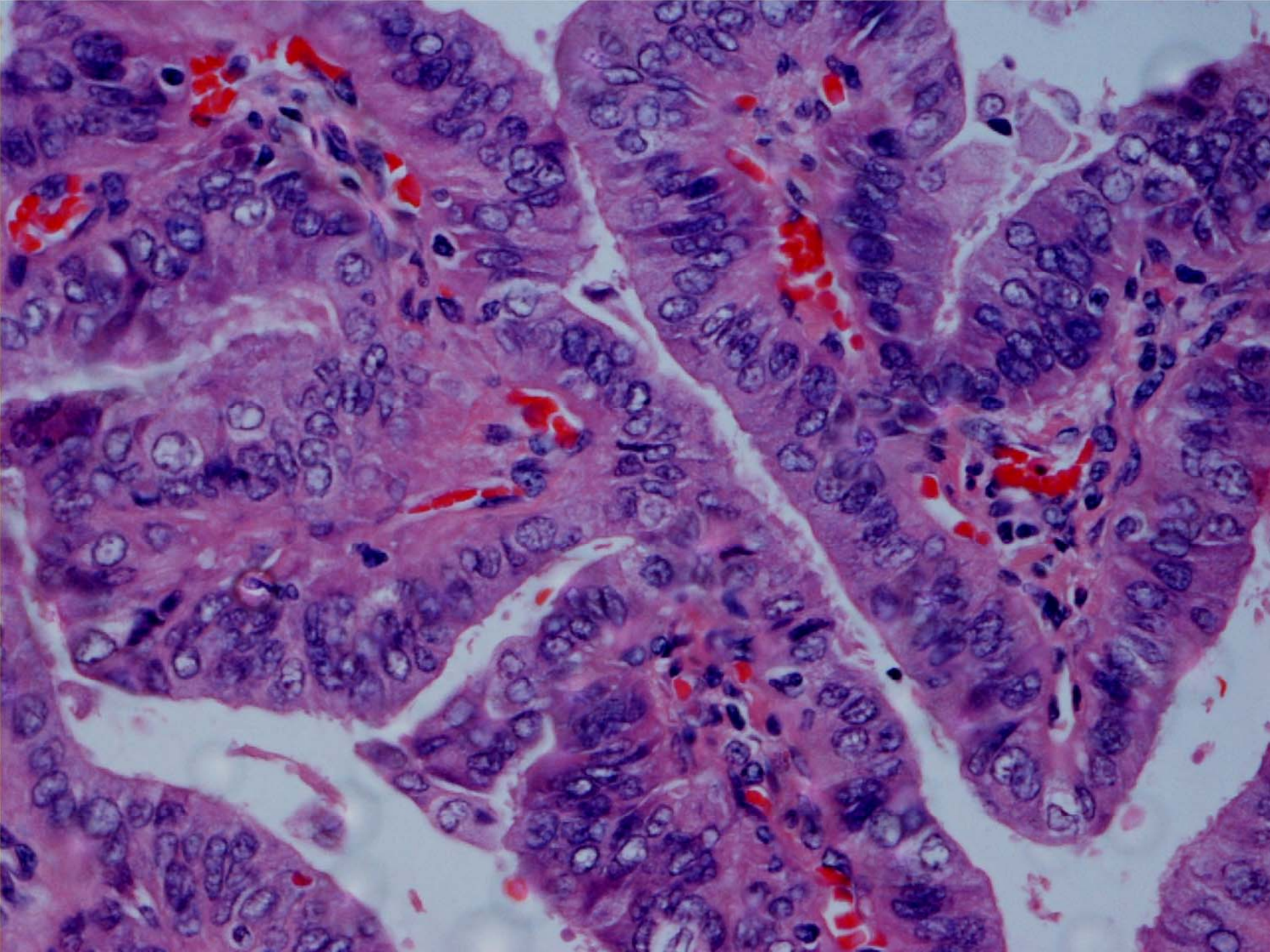


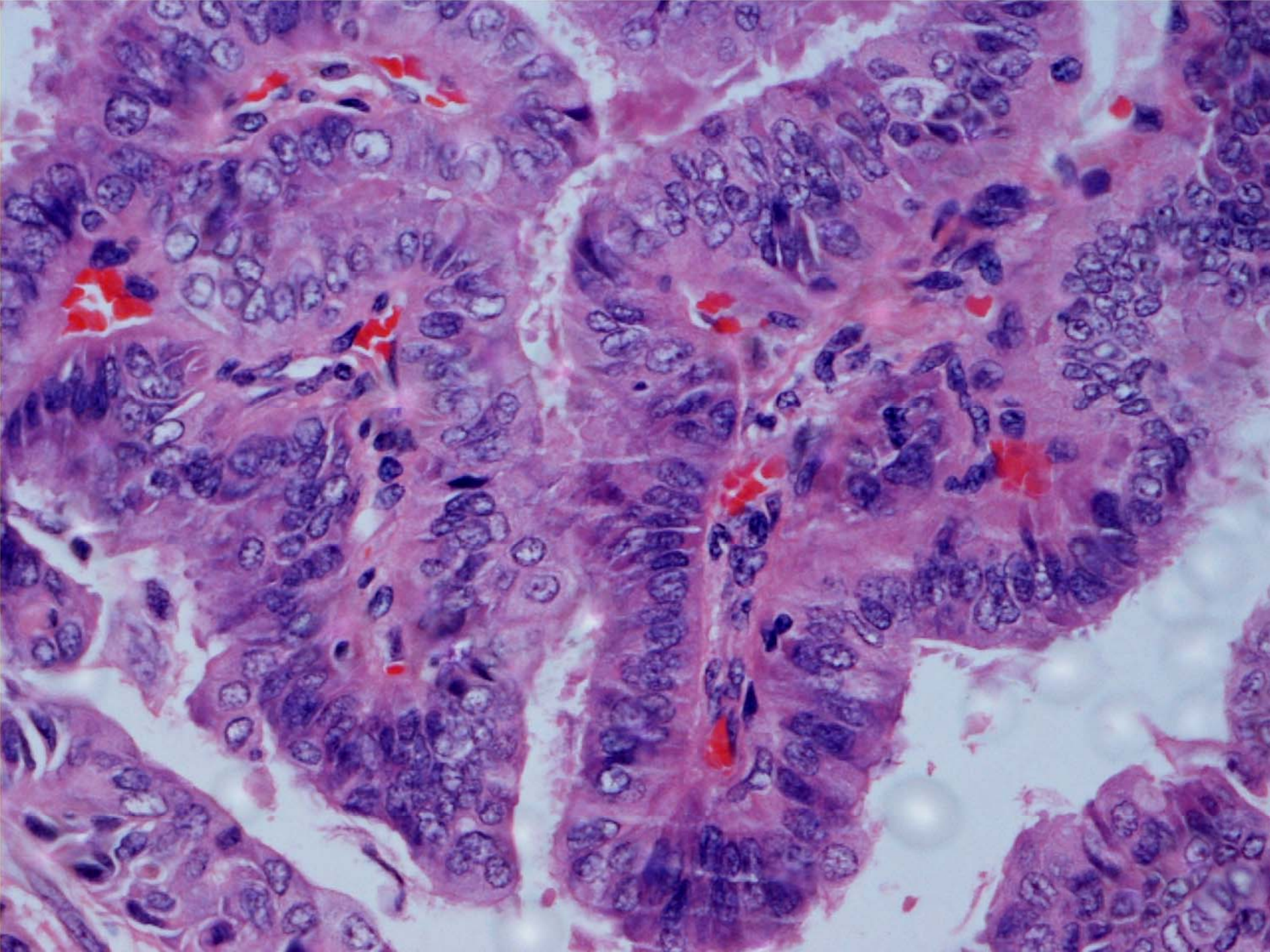




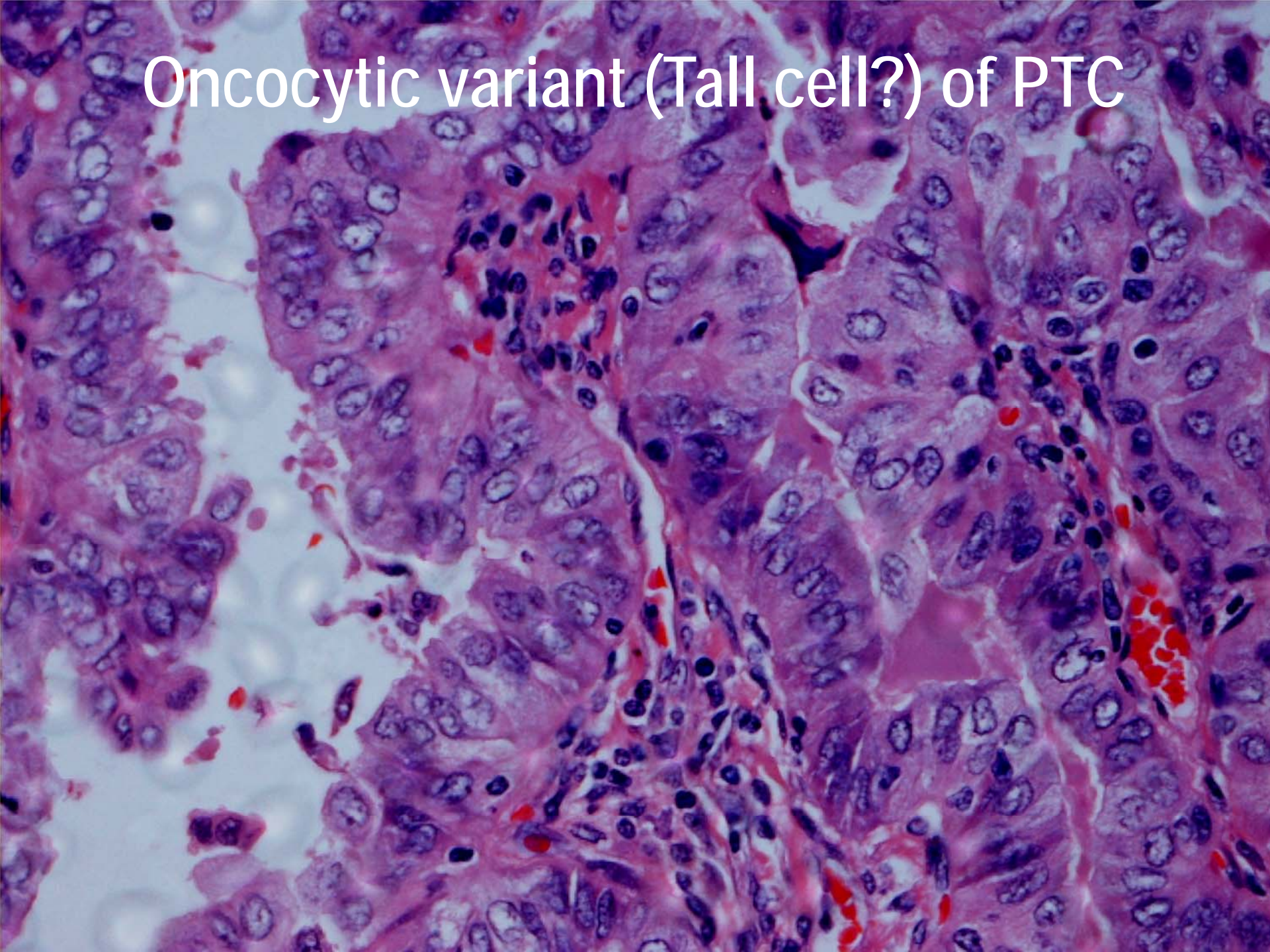








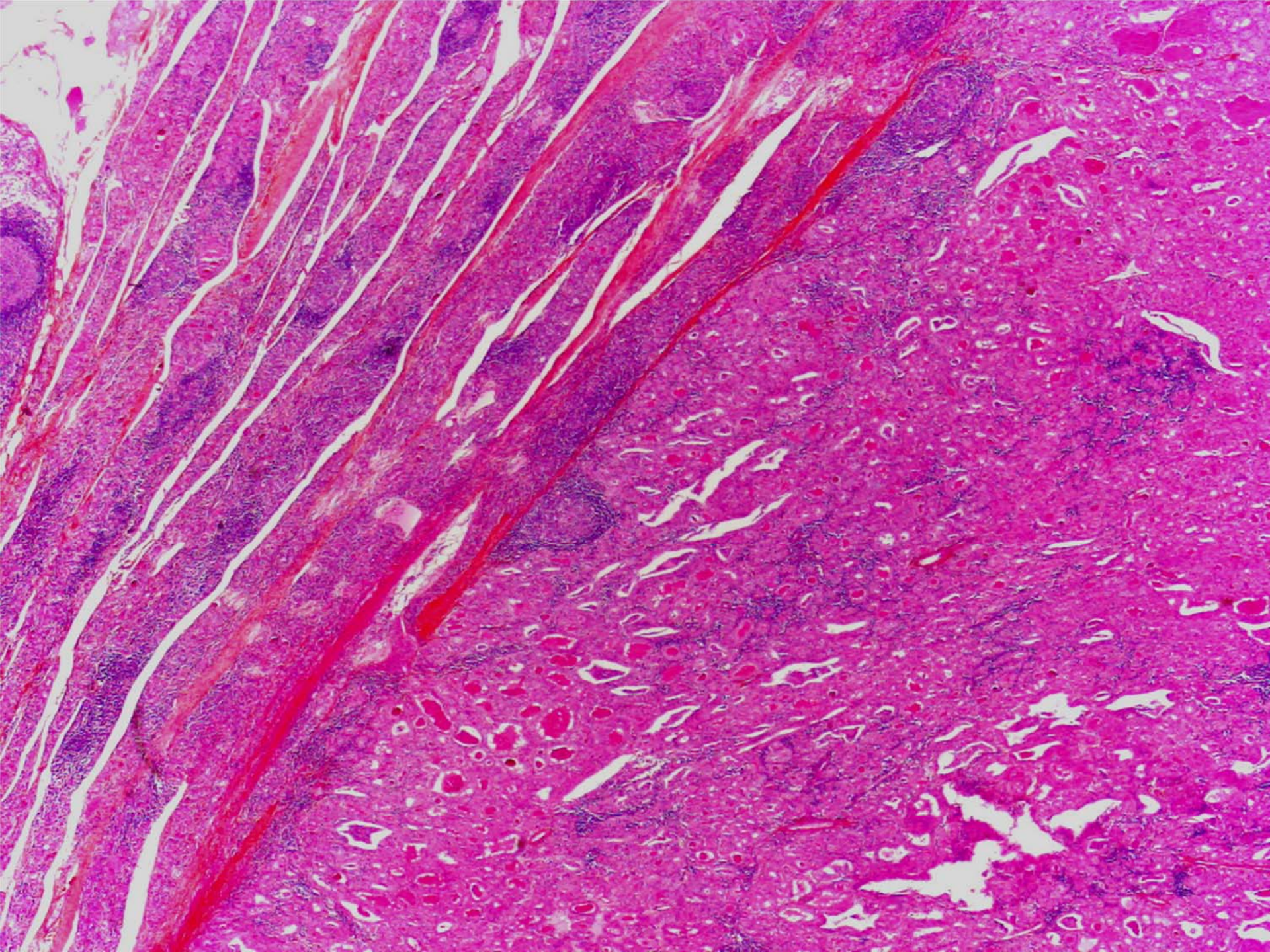
Oncocytic variant (Tall cell?) of PTC

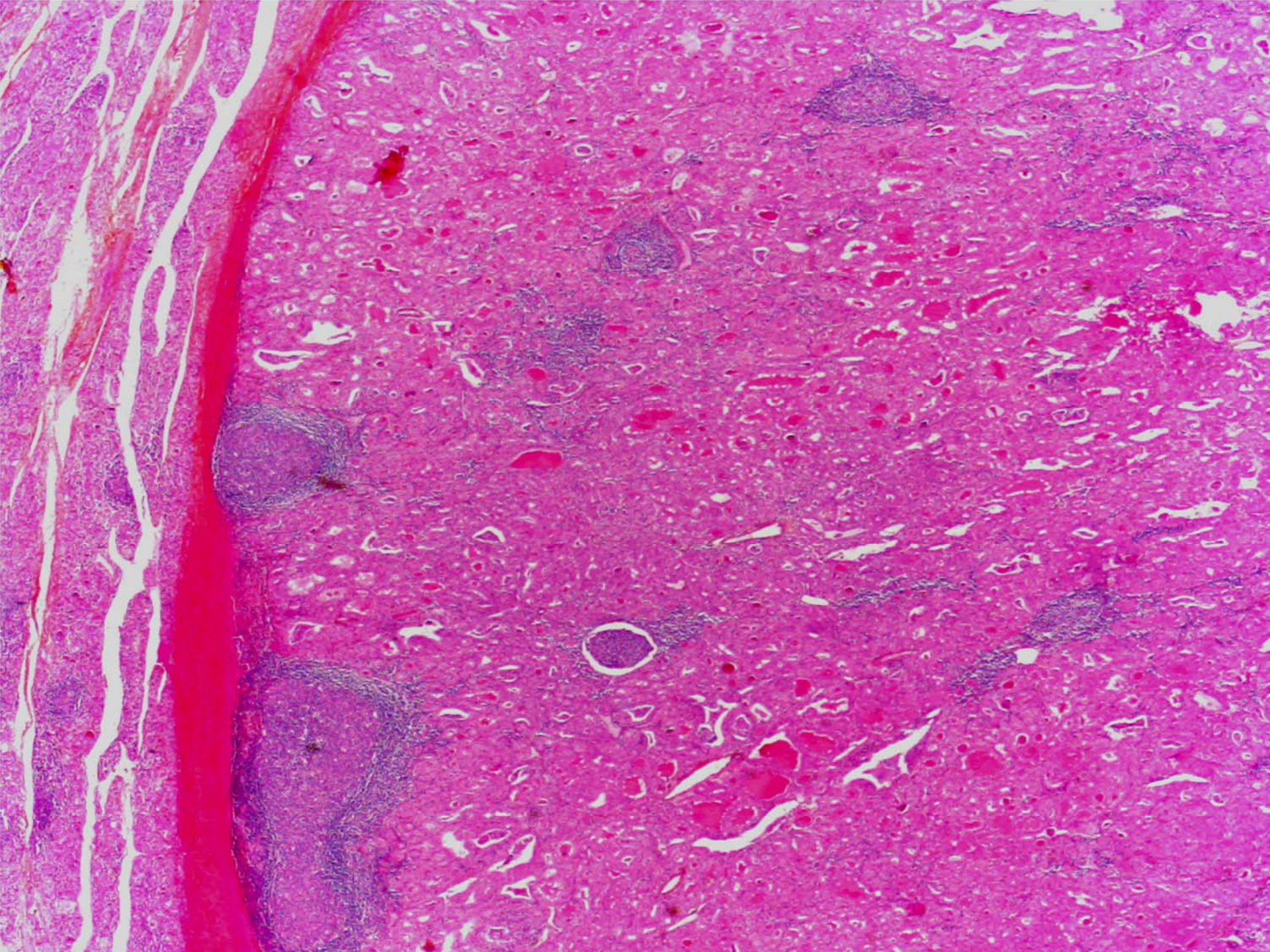


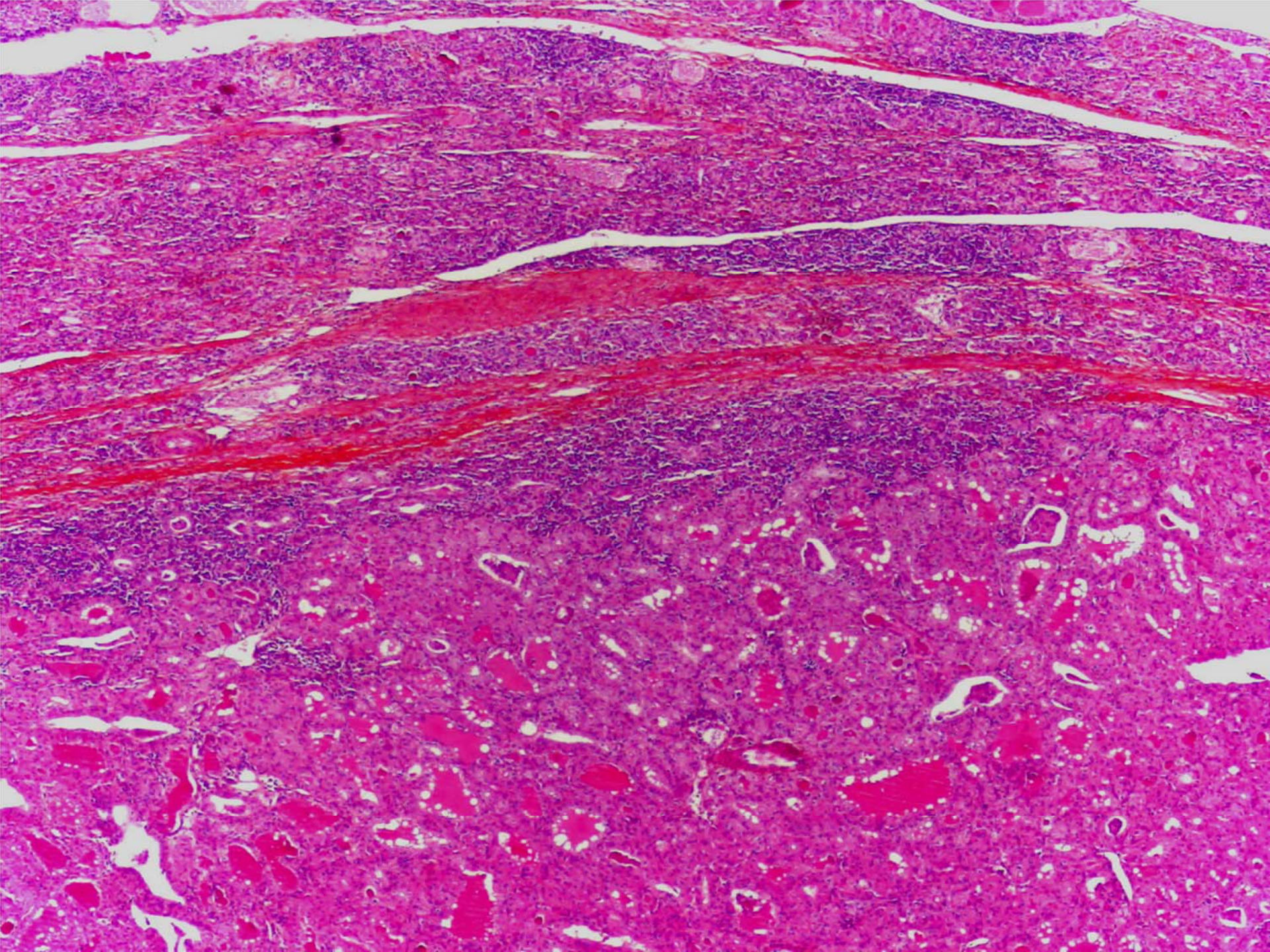
Case 2

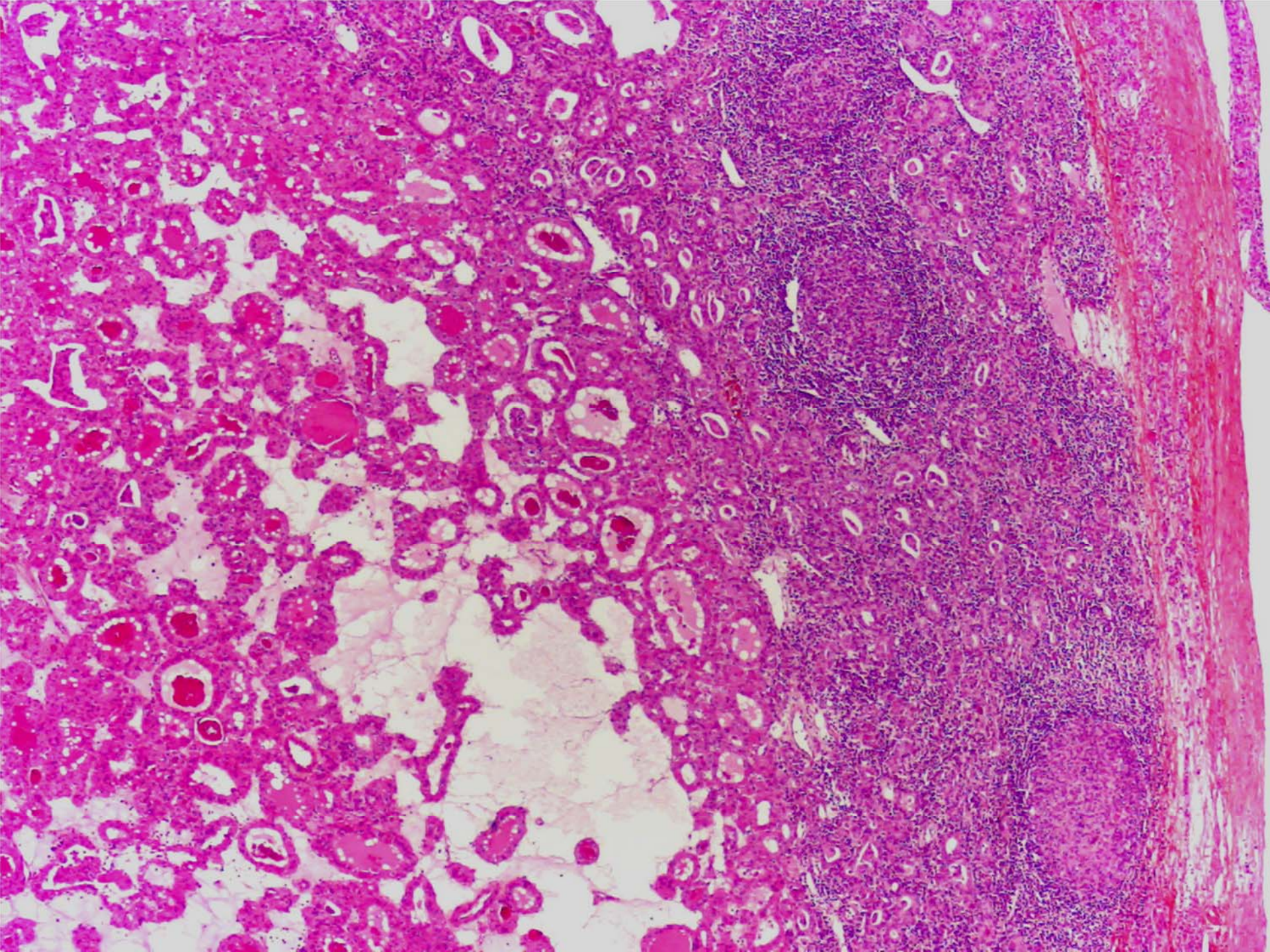
Female, 23-year-old.

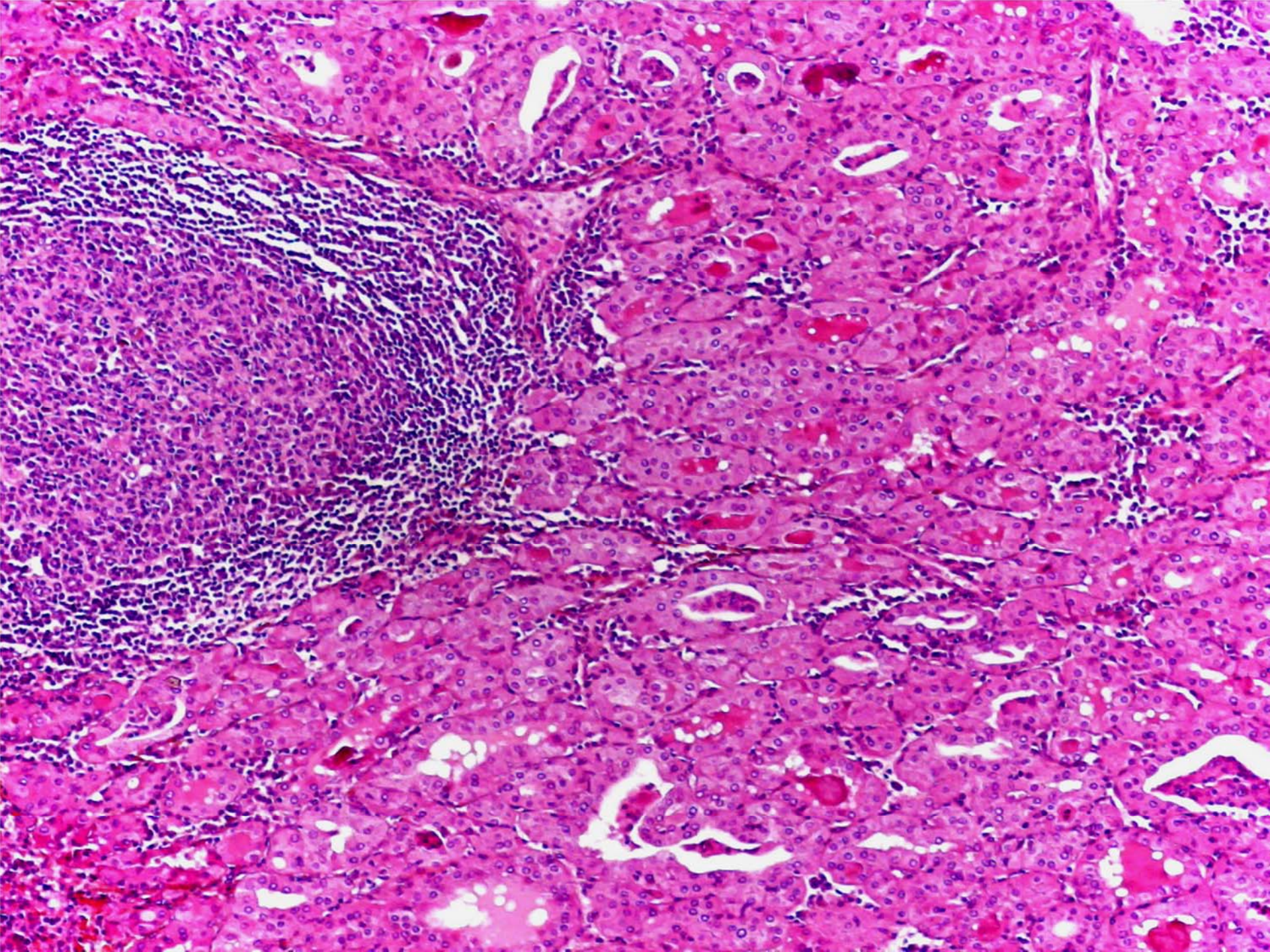
Solitary cold nodule measuring 3cm in the right lobe of the thyroid.

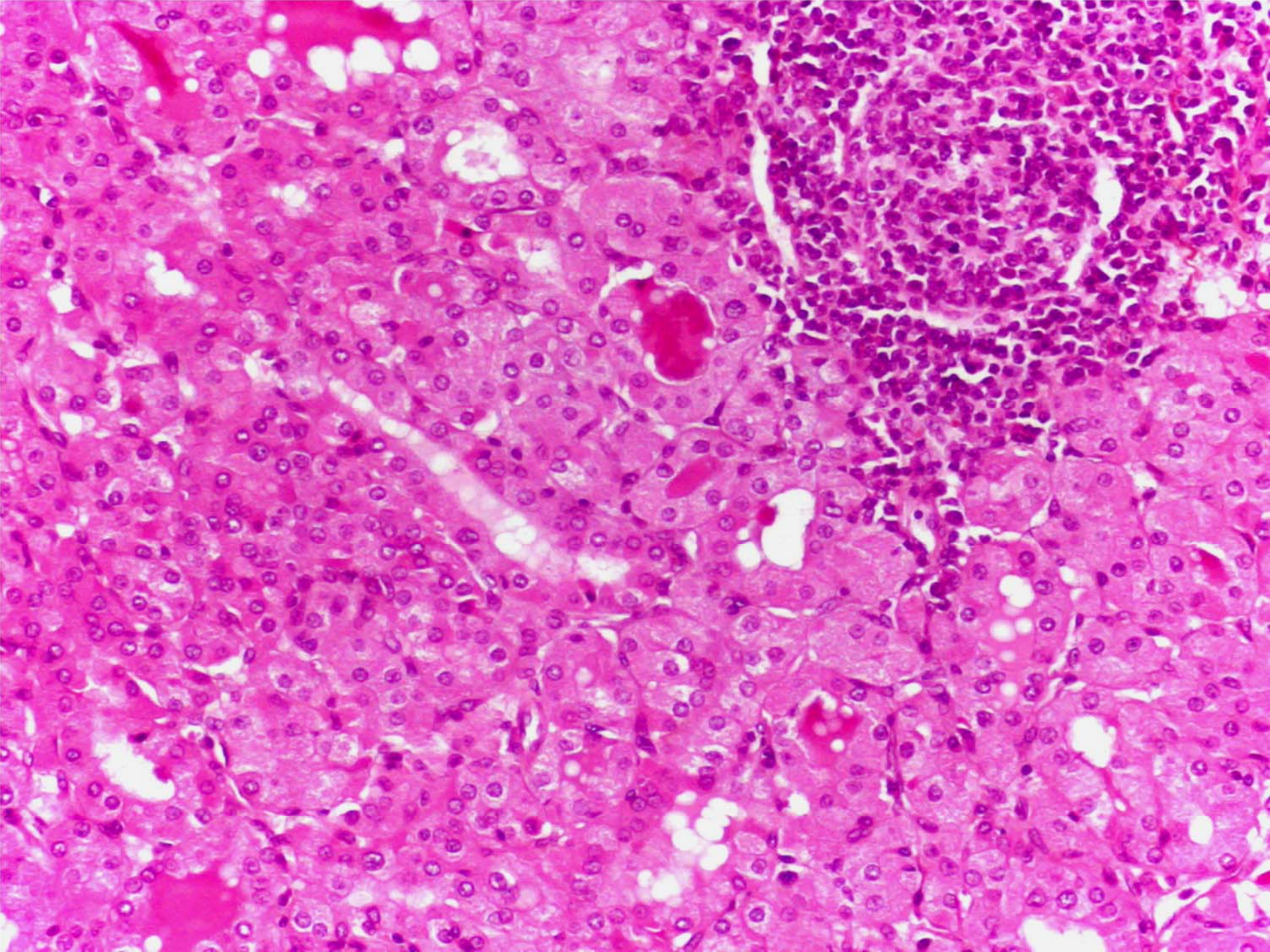




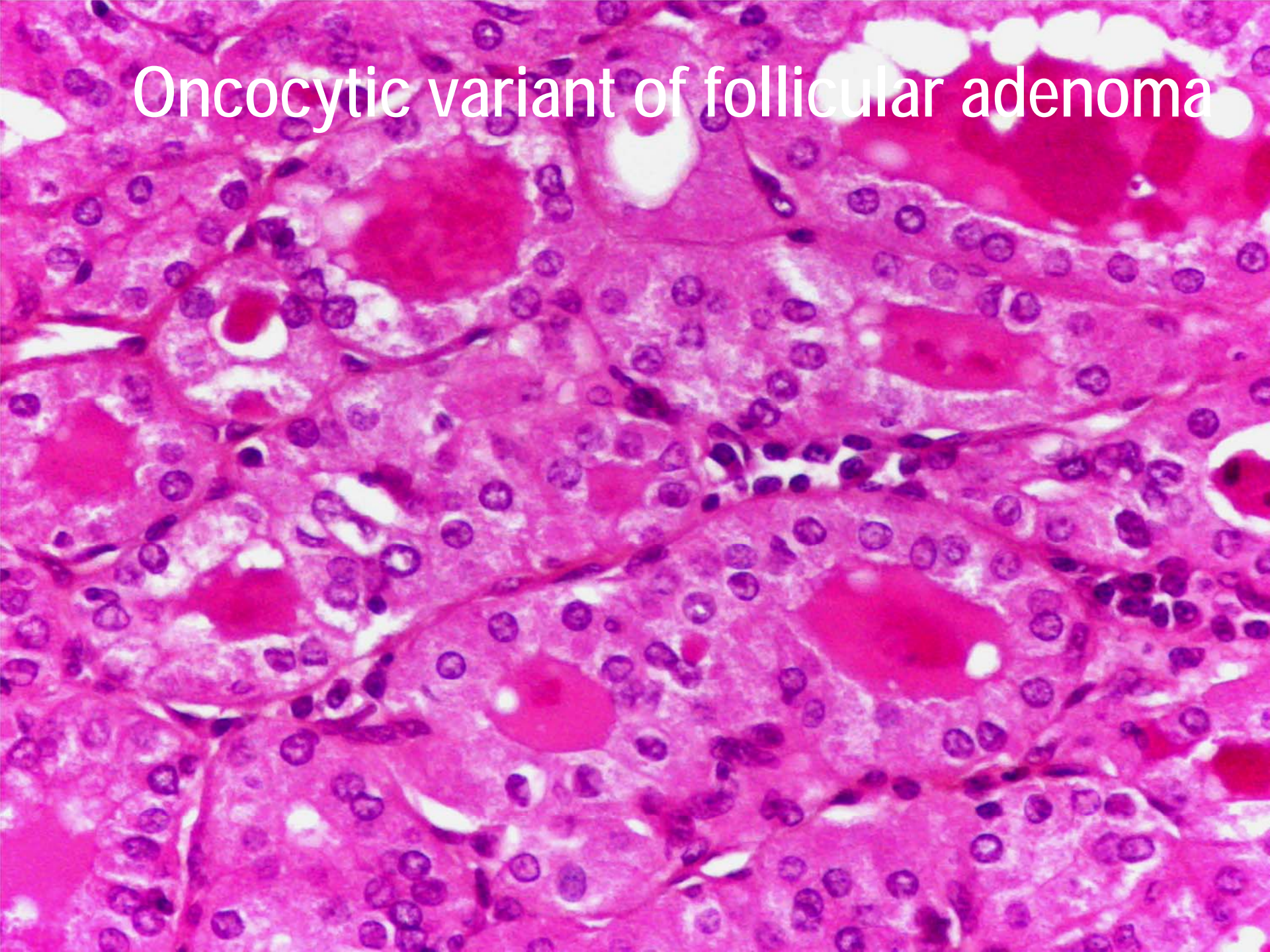








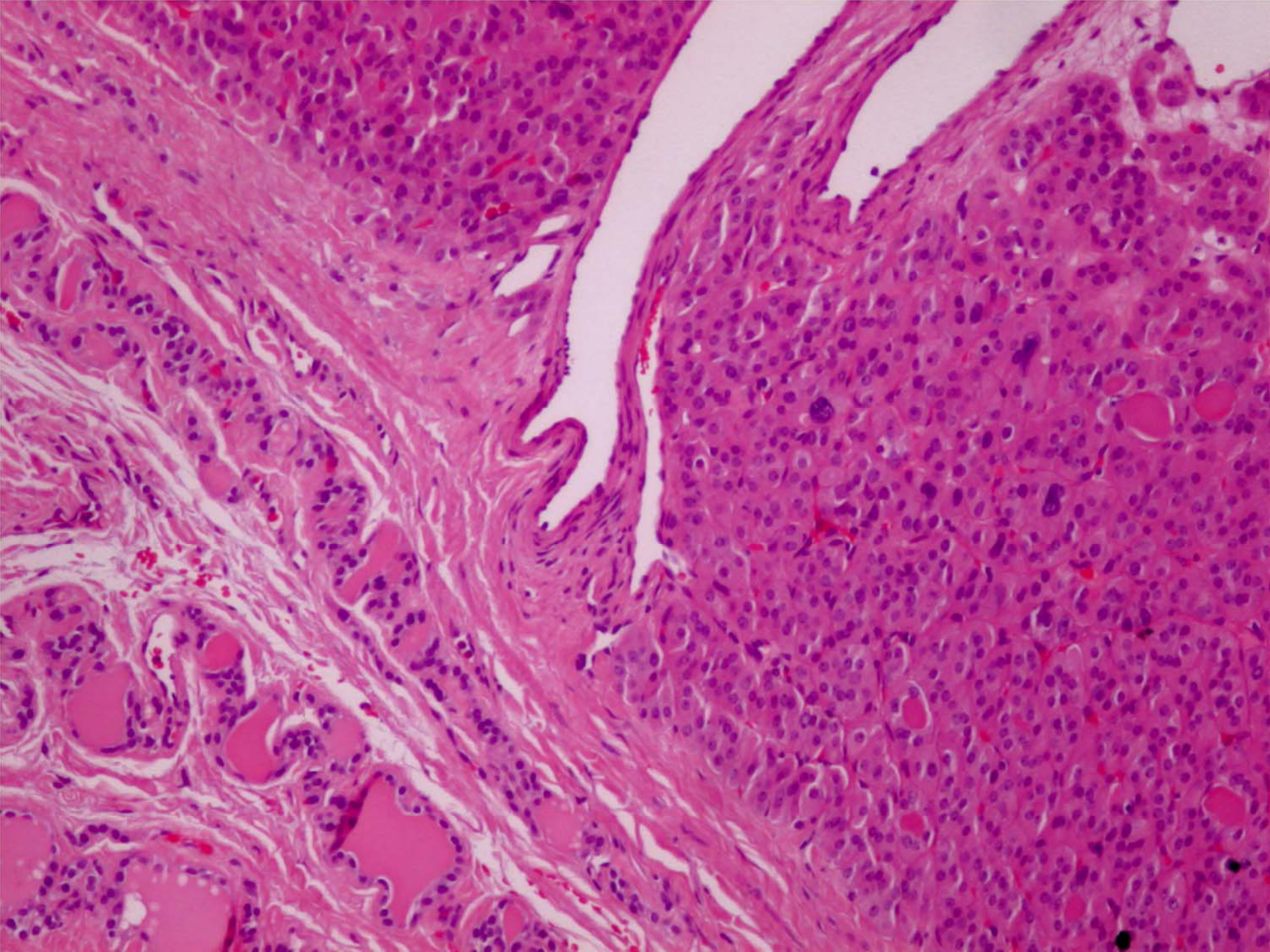
Oncocytic variant of follicular adenoma

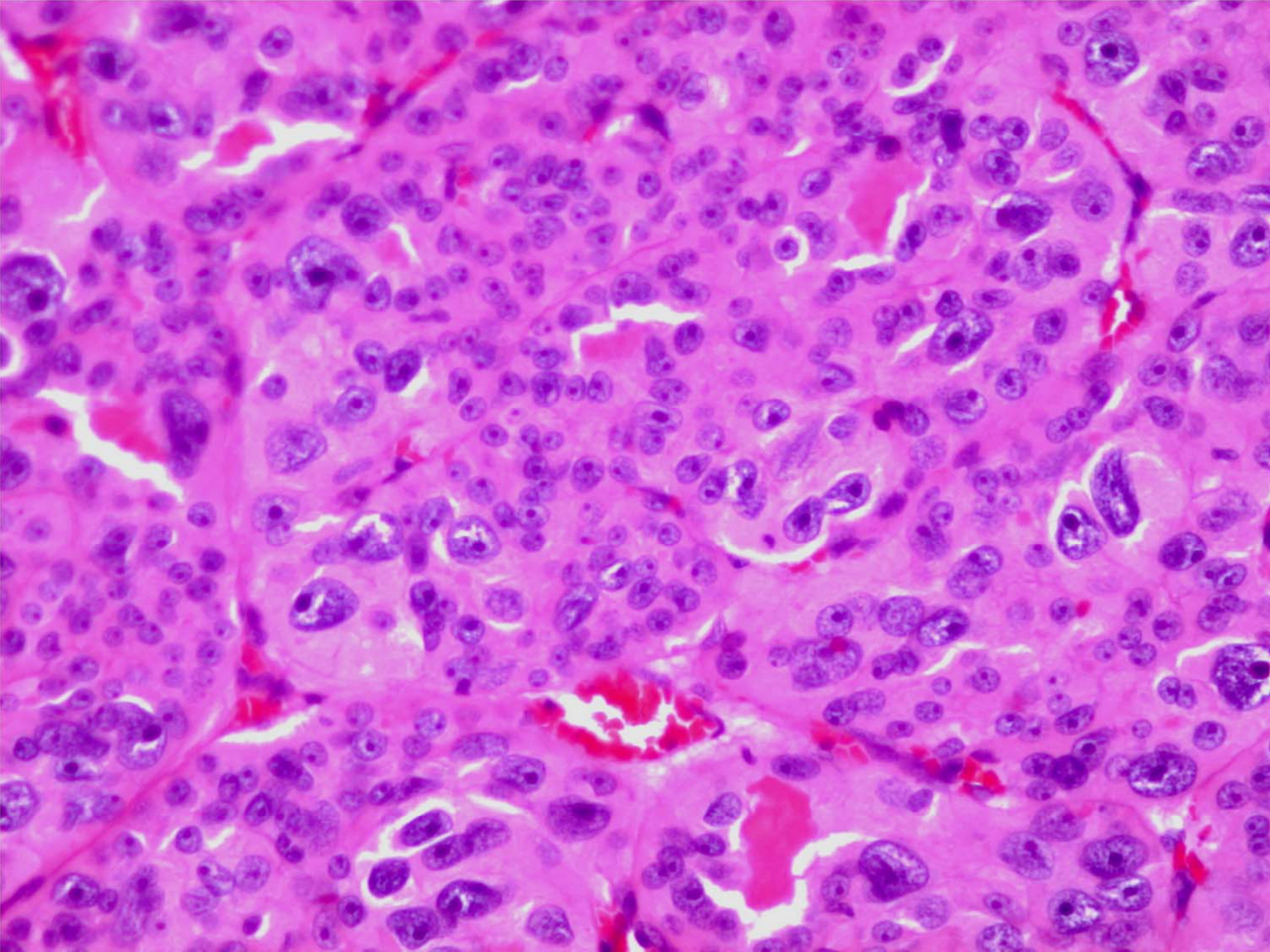


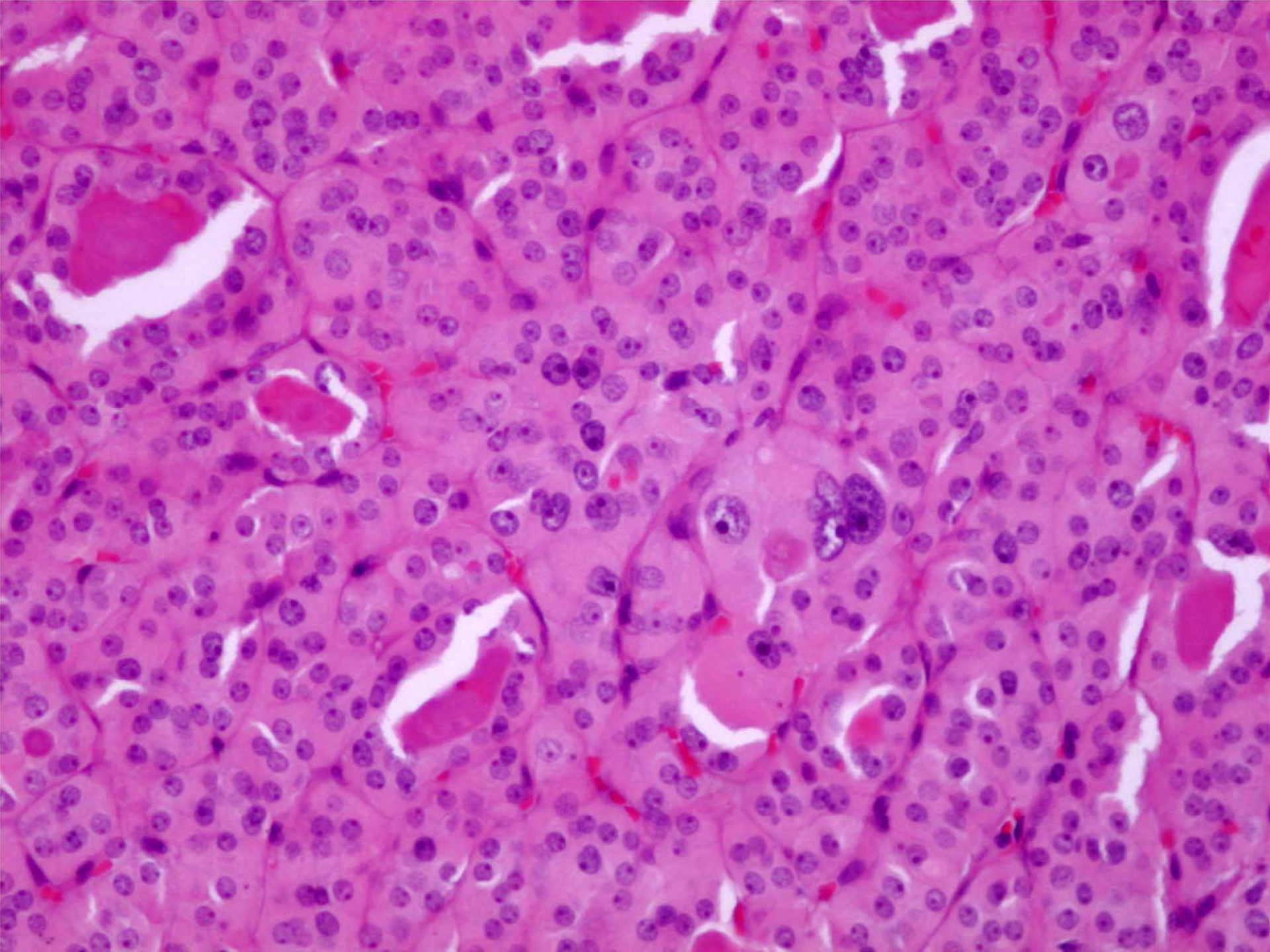
Case 3

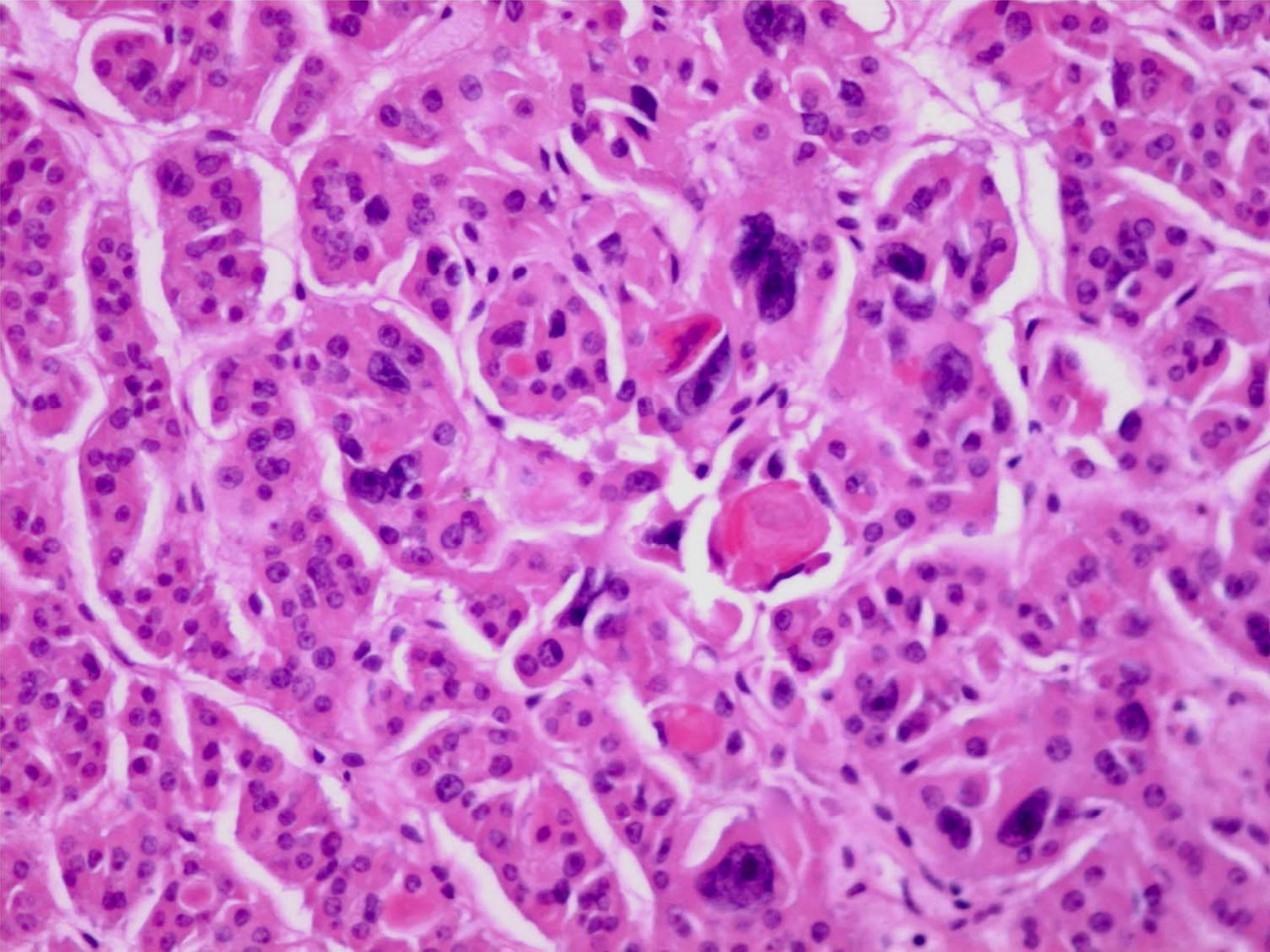
Female, 56-year-old.

Solitary nodule measuring 2cm, in the left lobe of the thyroid.

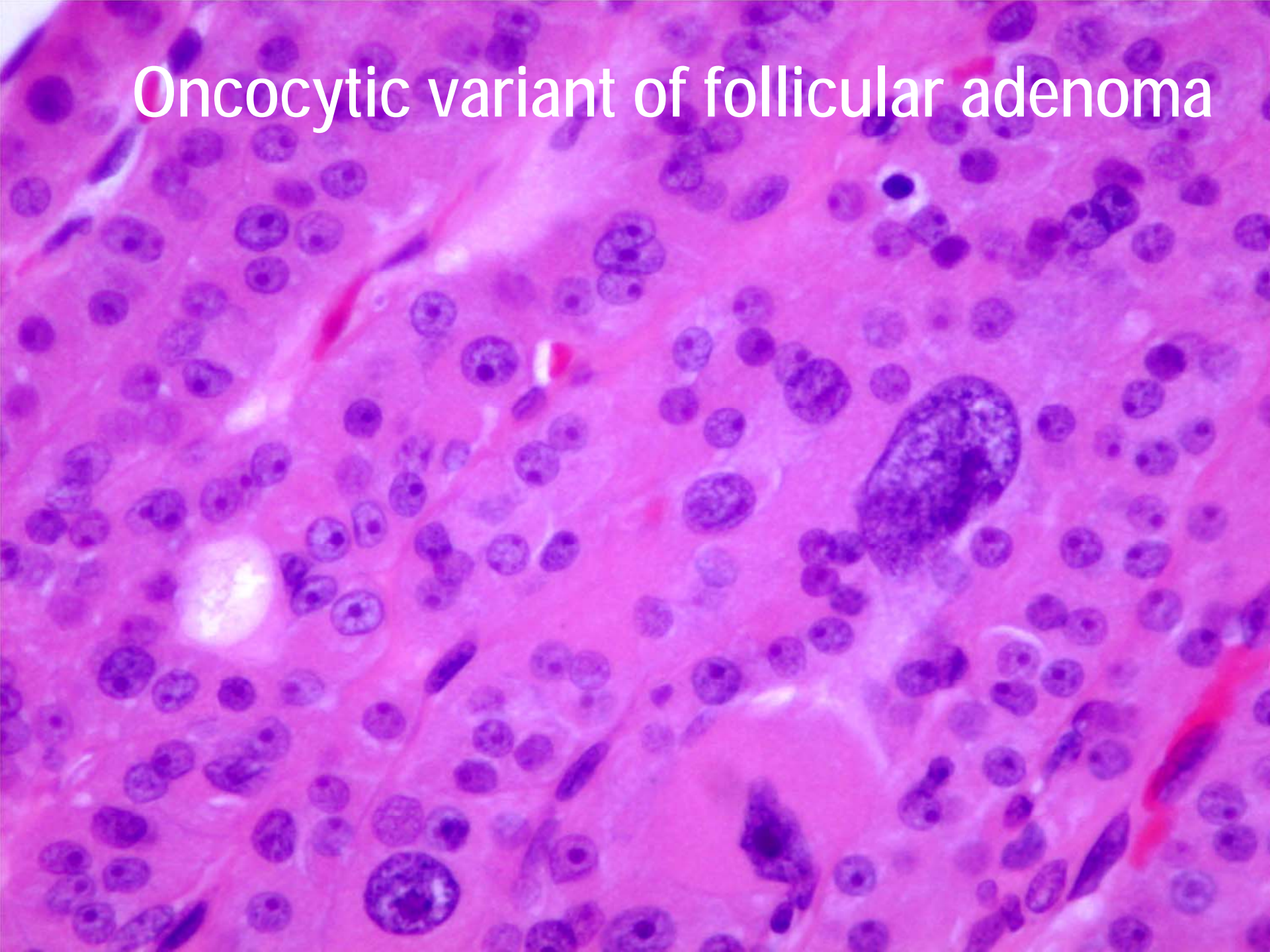








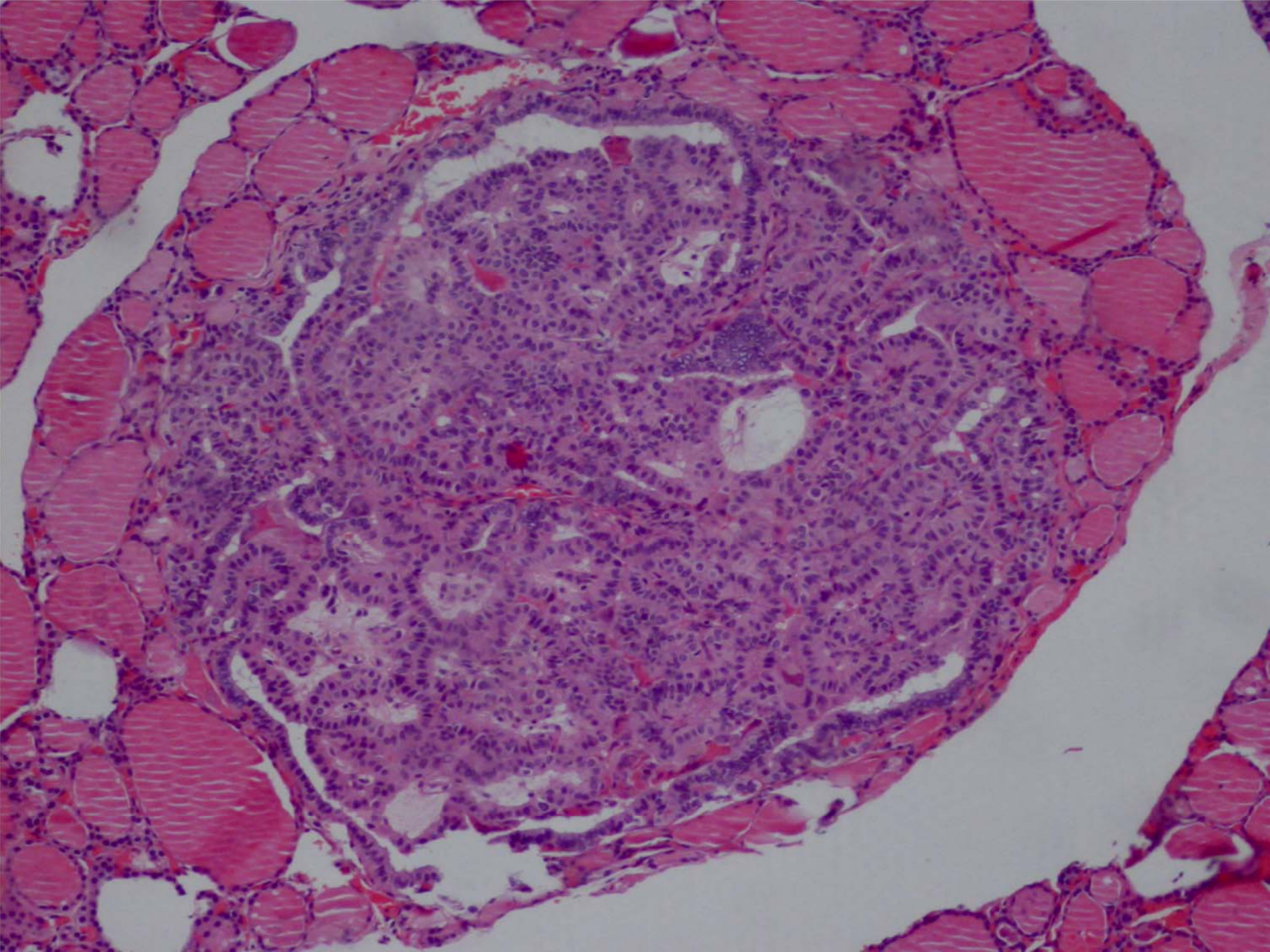
Oncocytic variant of follicular adenoma

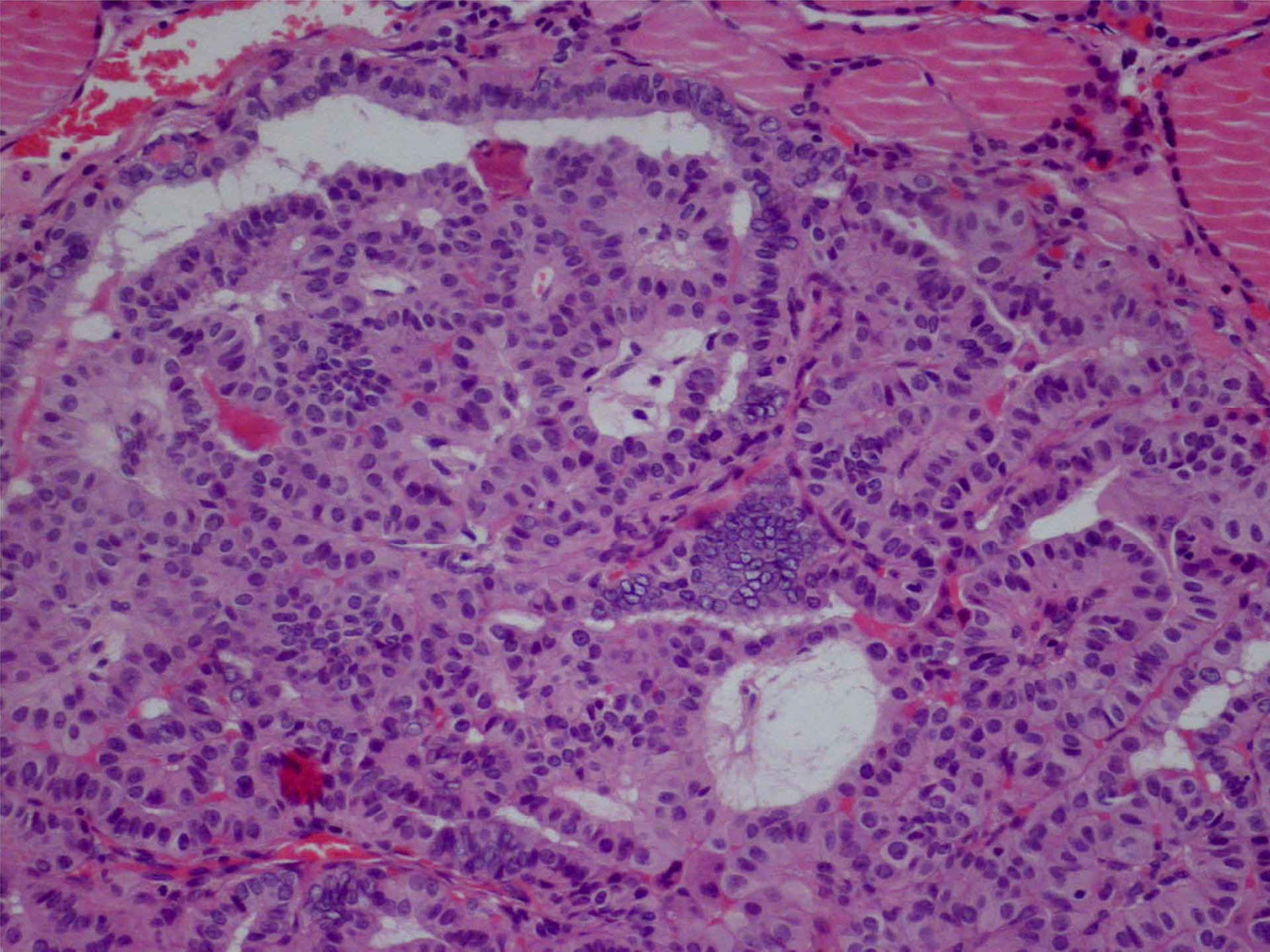


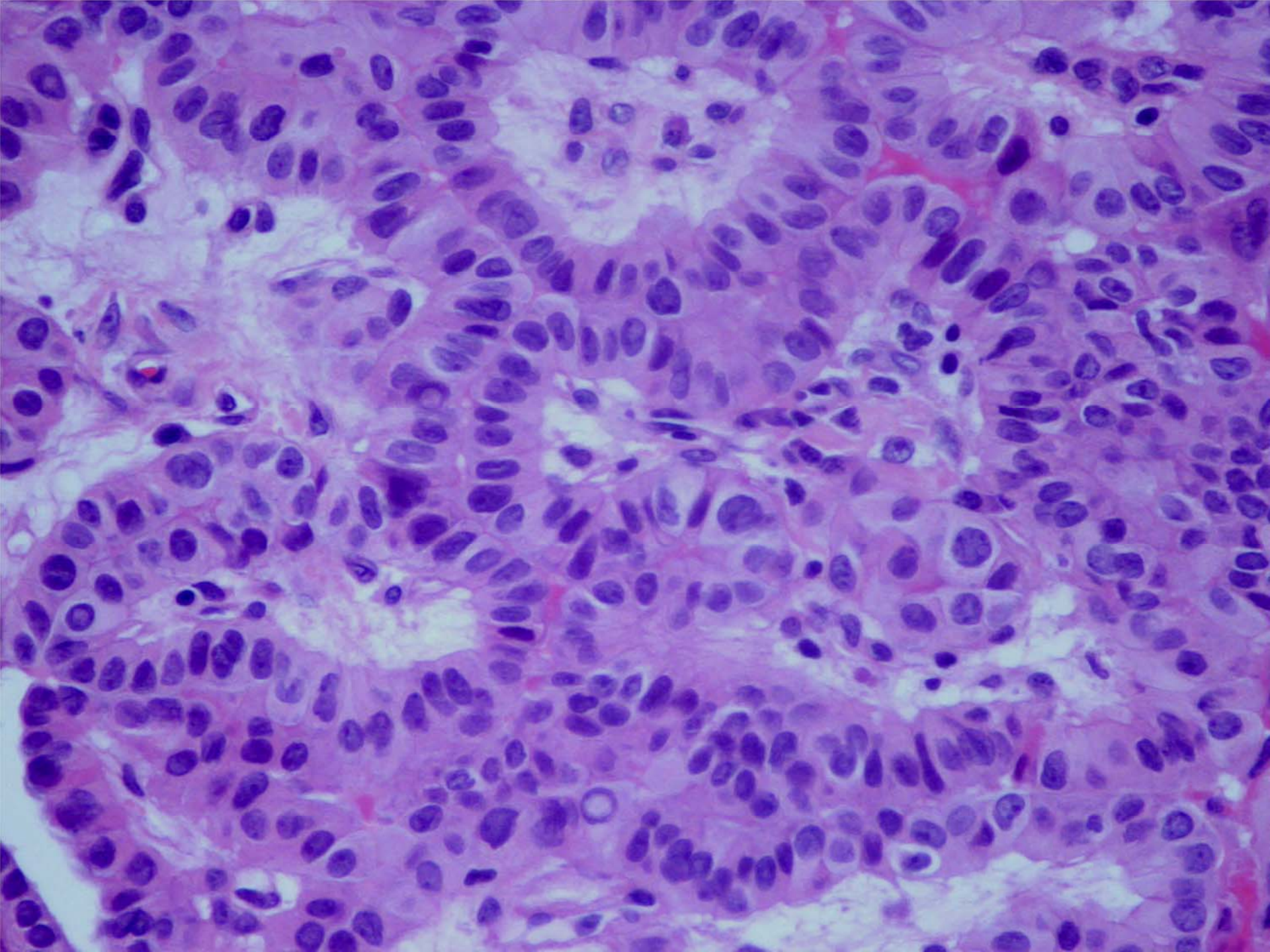
Case 4

Male, 45-year-old.

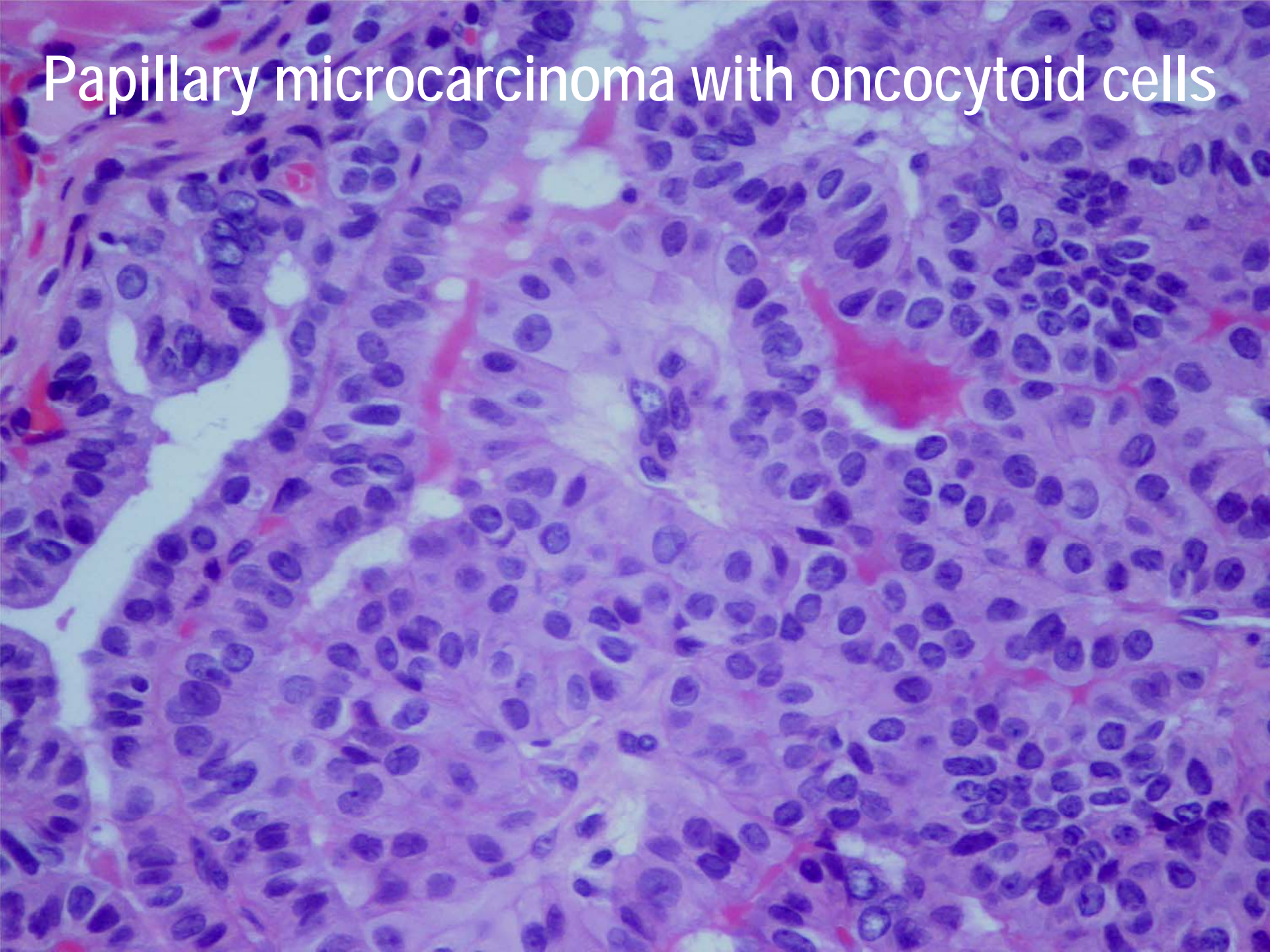
Multinodular goiter.



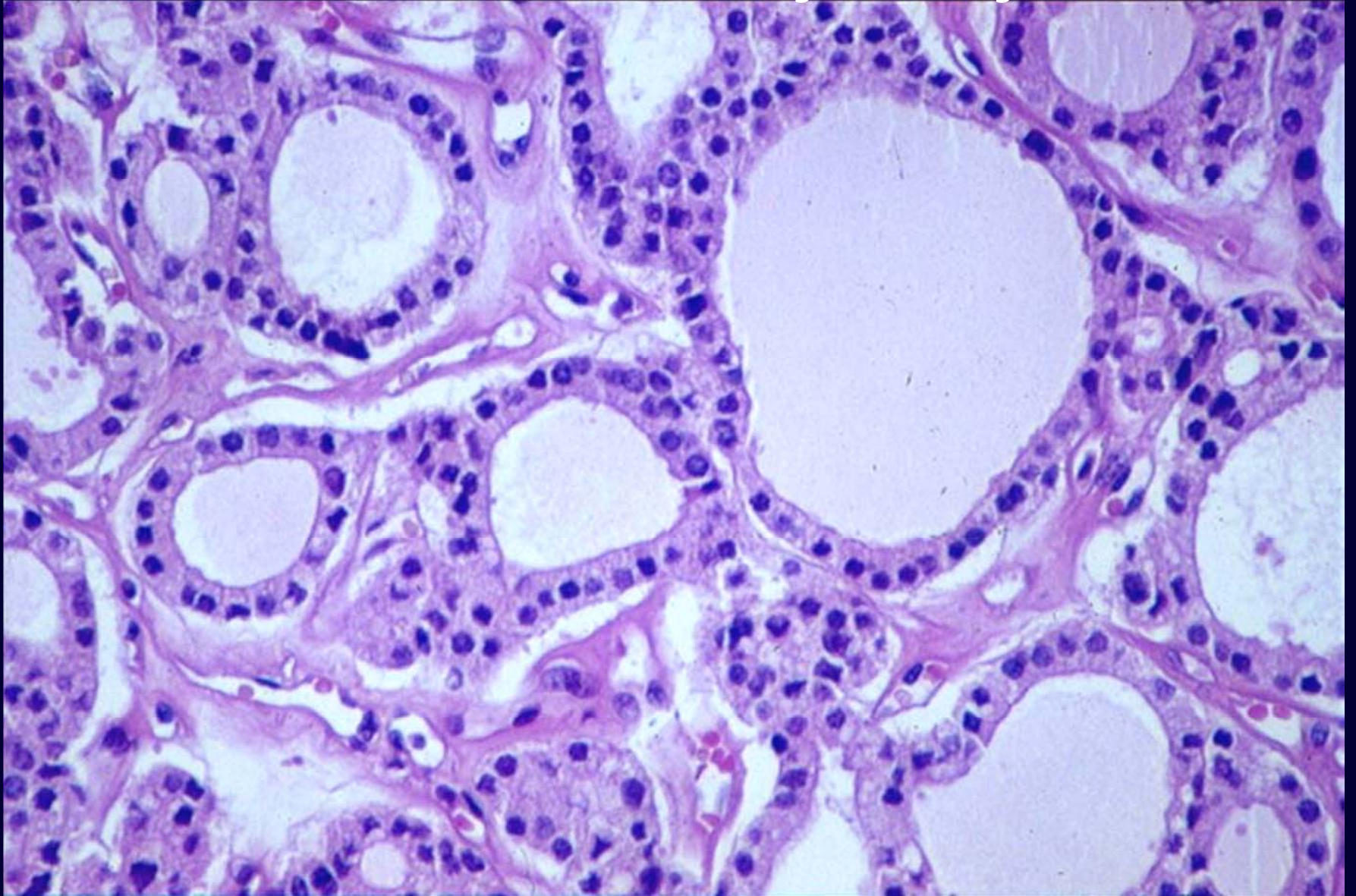




Papillary microcarcinoma with oncocytoid cells



There are many oncocytoid lesions

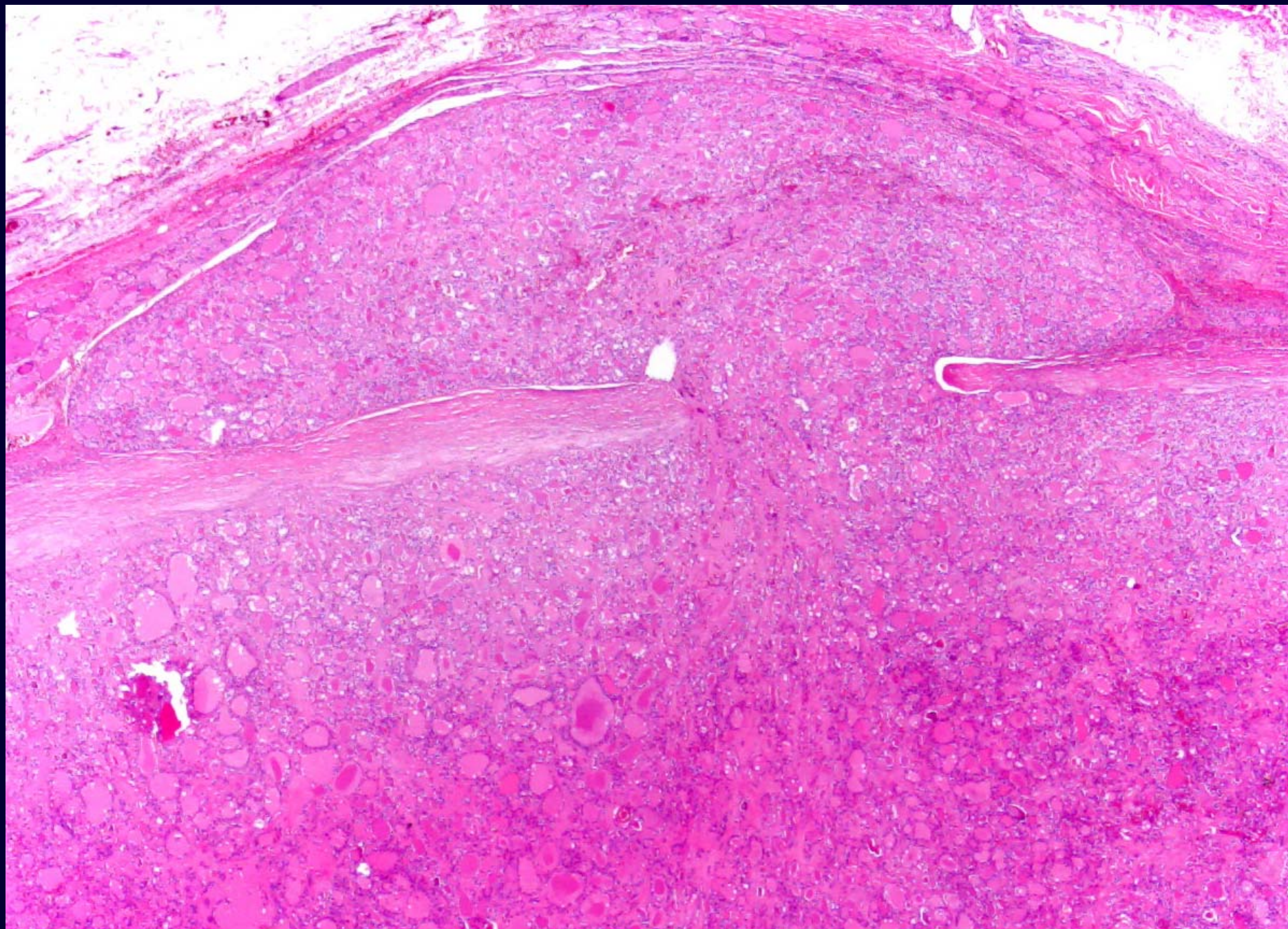


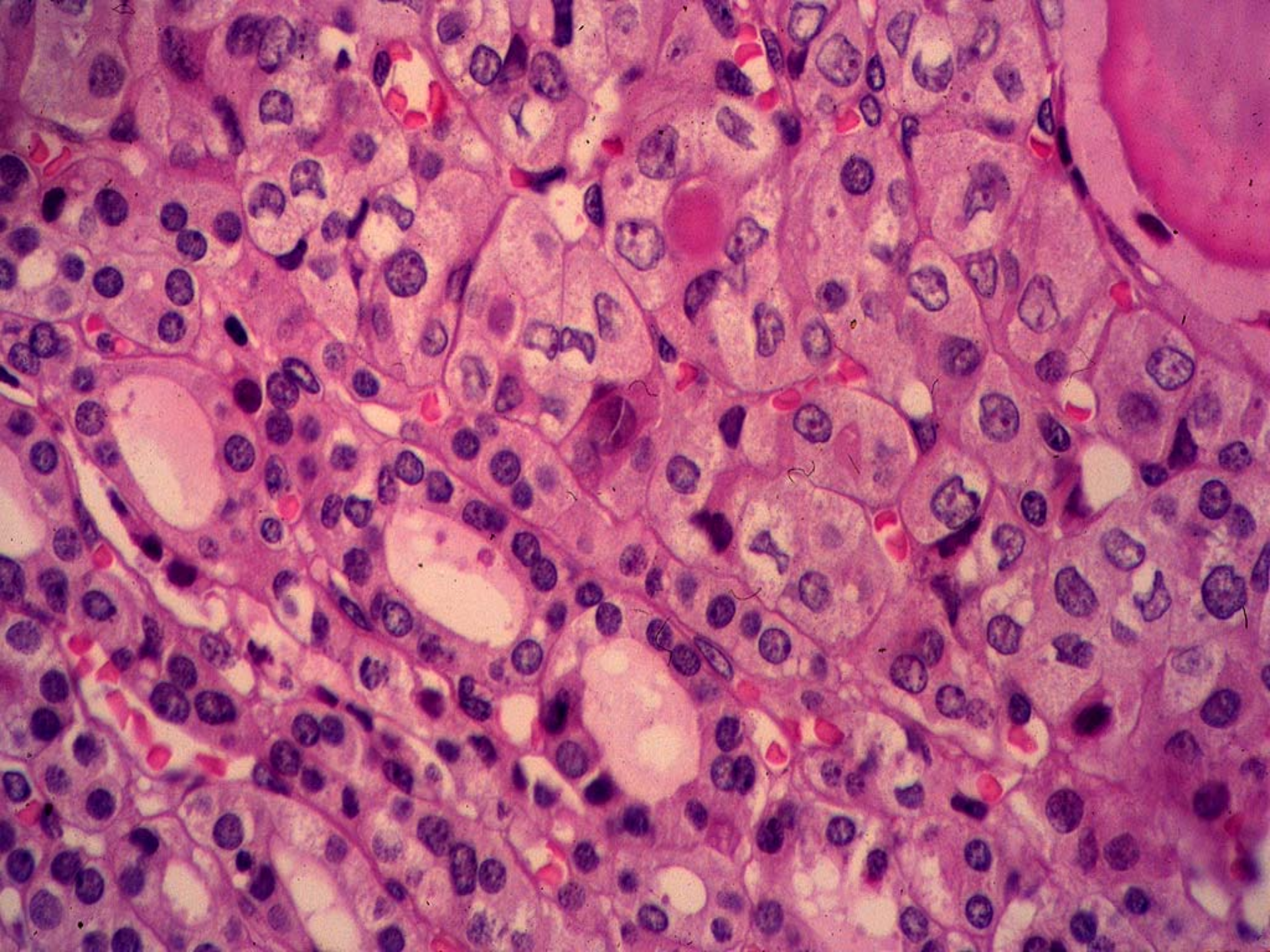
Malignancy in Hürthle cell tumours of follicular cells

Diagnostic hints

Capsular/vascular invasion

Nuclear features





Hürthle cell follicular tumour, UMP
Hürthle cell well diff tumour, UMP
Hürthle cell well diff carcinoma,
NOS

Adapted from WHO, Book on Endocrine
Tumours, 3rd ed, 2004

Hürthle cell tumours

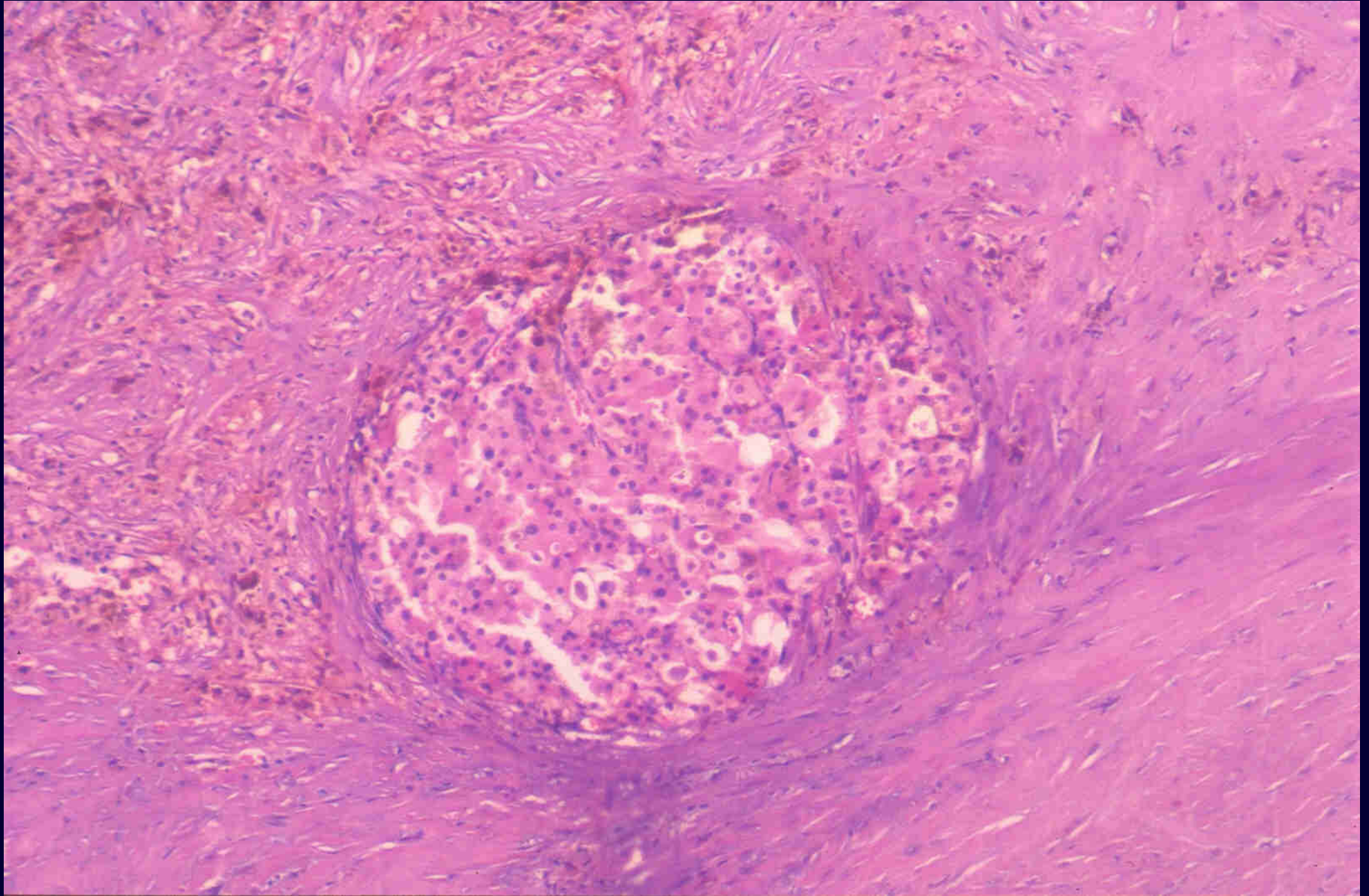
Additional problems

- Foci of necrosis and scars
- Partial oncocytic transformation
- Classification of “mixed” cases
- Treatment and prognosis

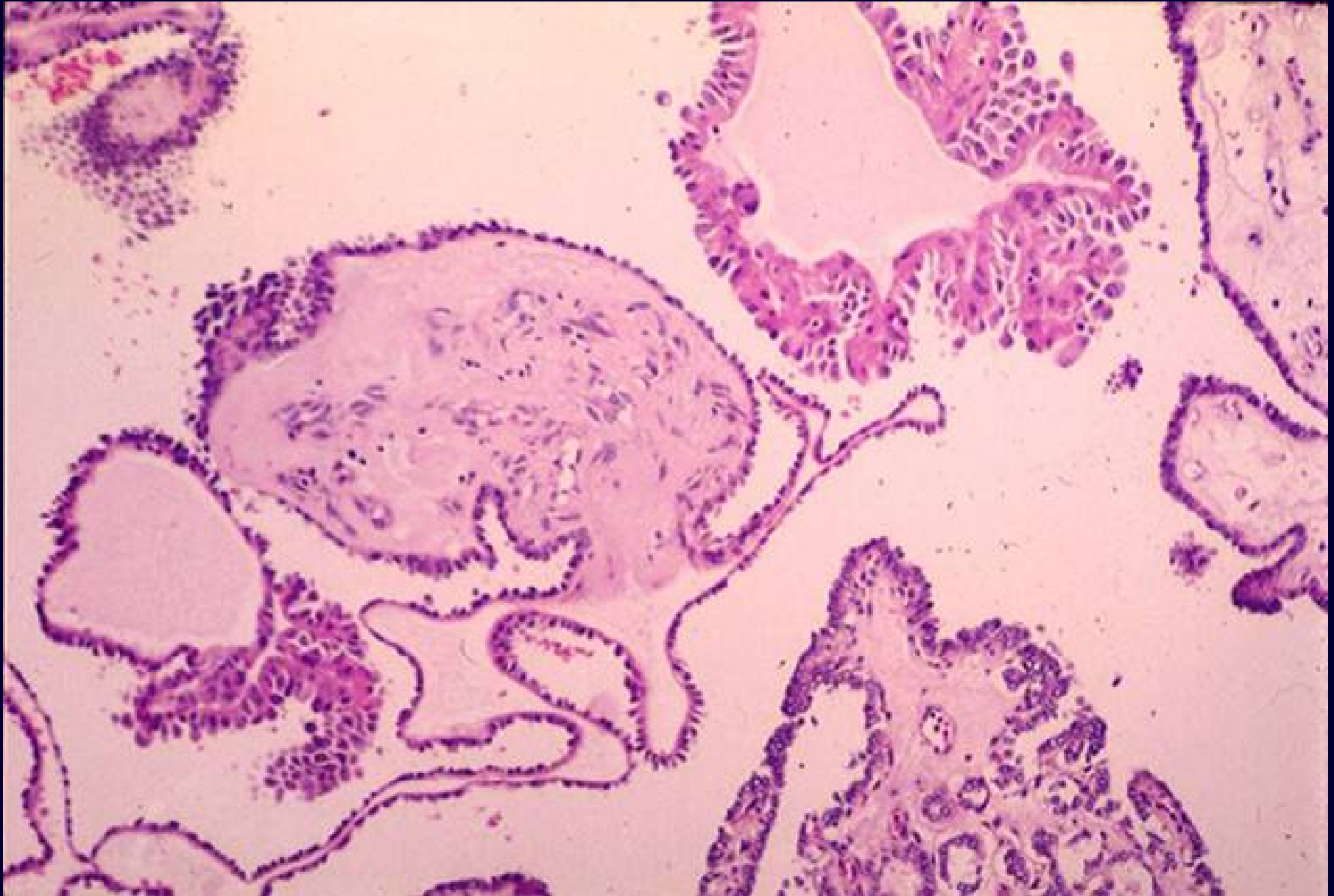
Oncocytic transformation



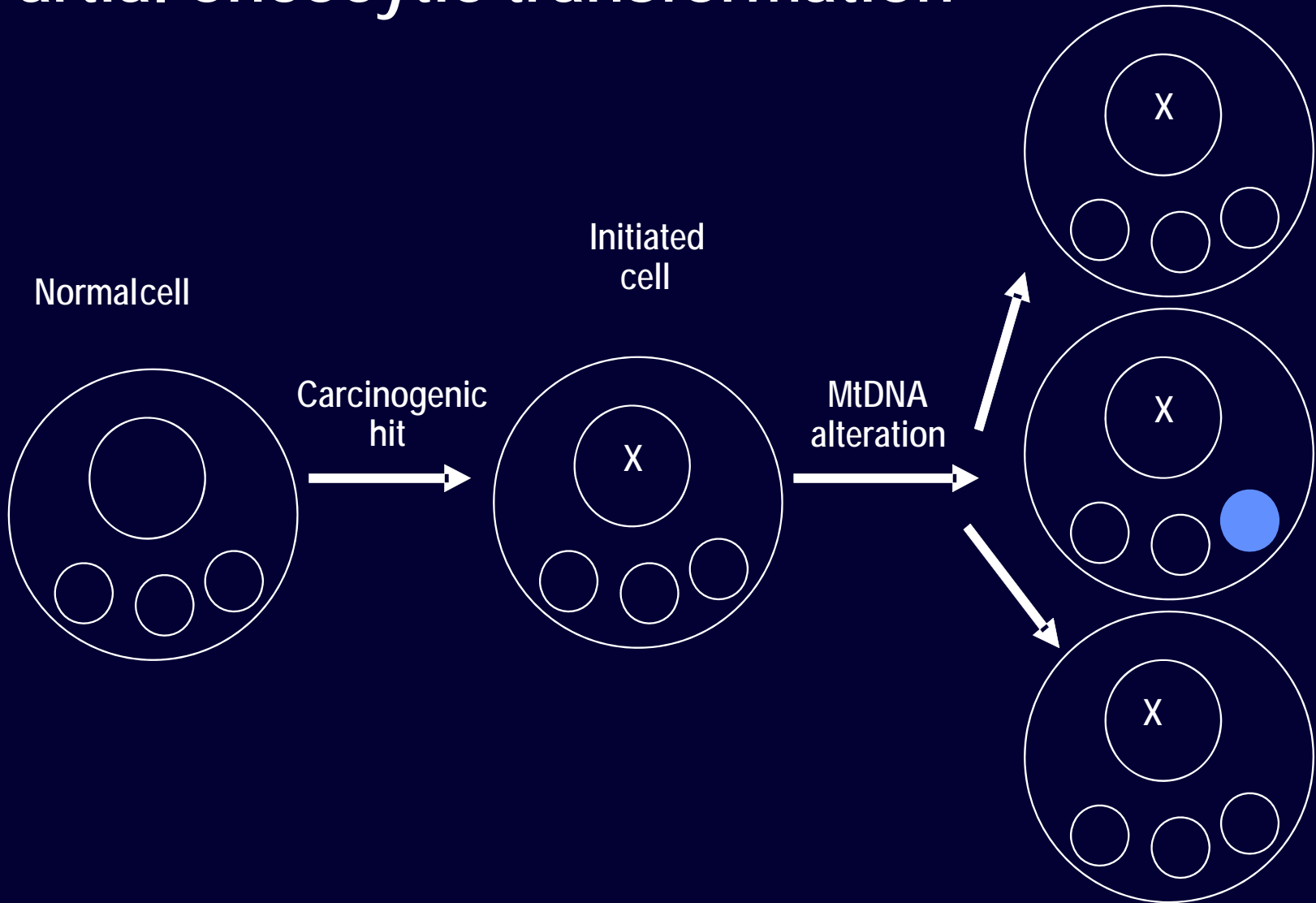
- Foci of necrosis and scars

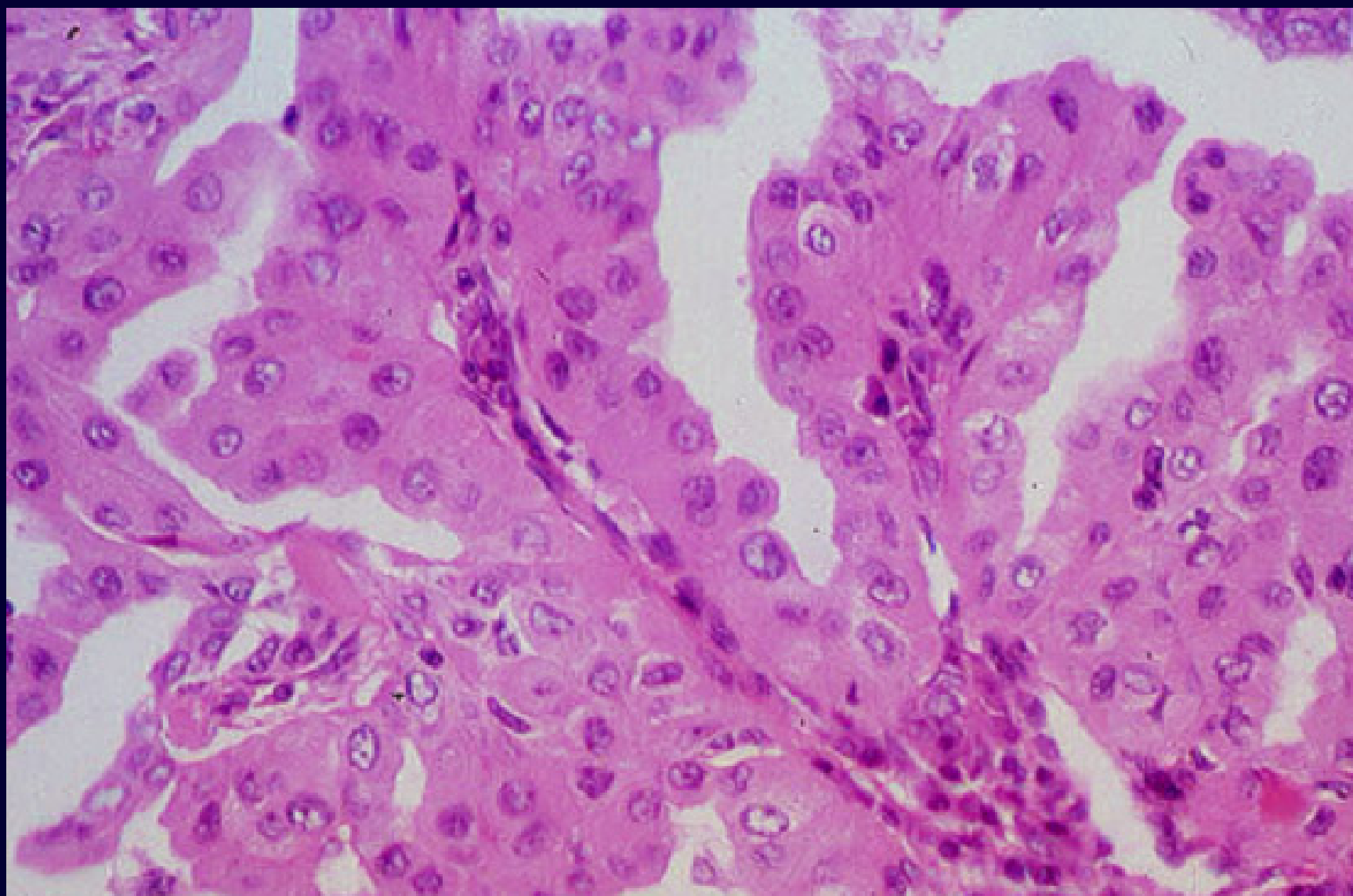


- Partial oncocytic transformation

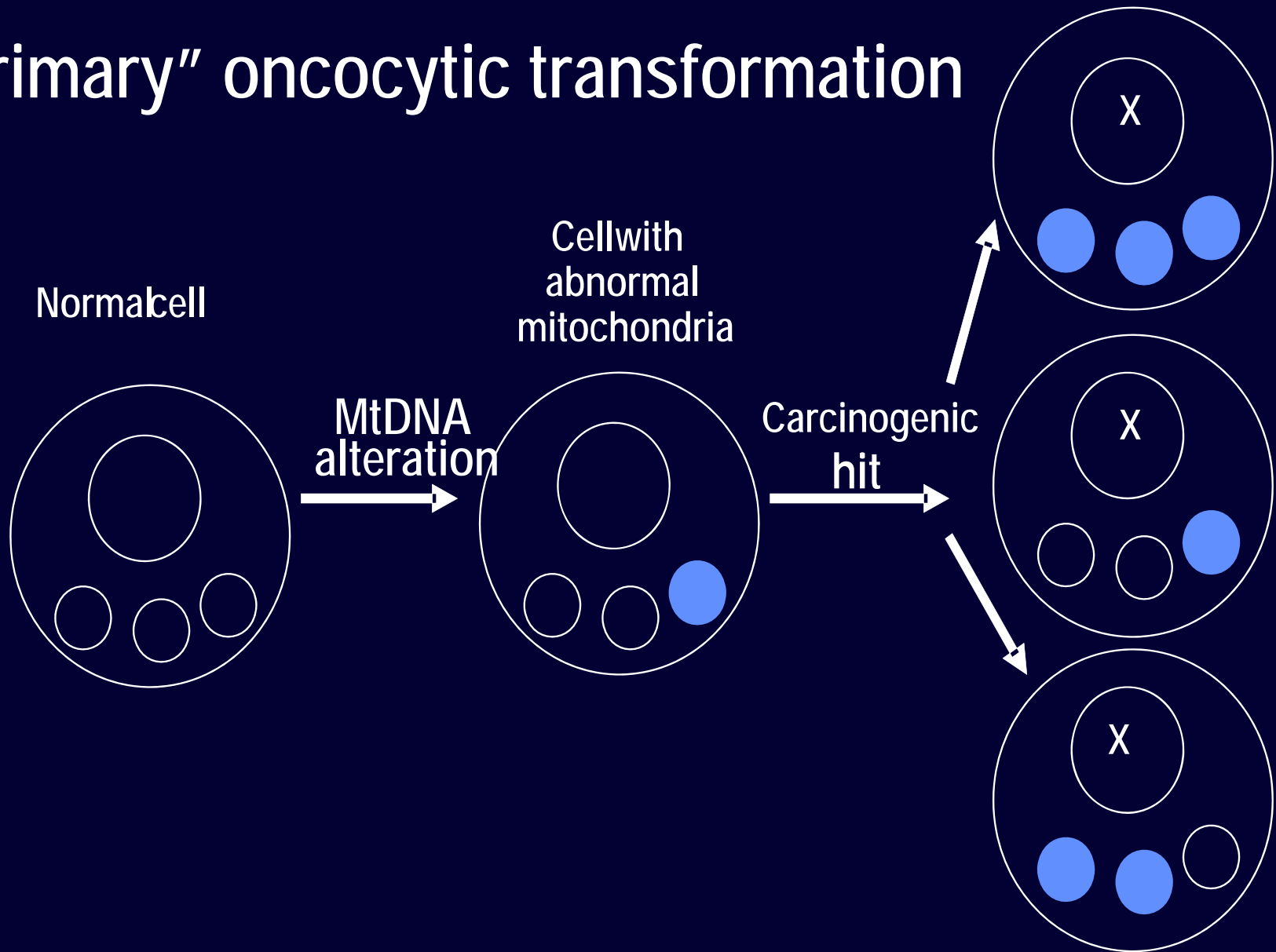


Partial oncocytic transformation





“Primary” oncocytic transformation



Revision of 401 cases of primary papillary and follicular carcinomas displaying increased clinical aggressiveness and not responding to radioactive iodine therapy

2/5 Oncocytic (Hürthle cell) variant of papillary carcinoma

1/5 Oncocytic (Hürthle cell) variant of follicular carcinoma

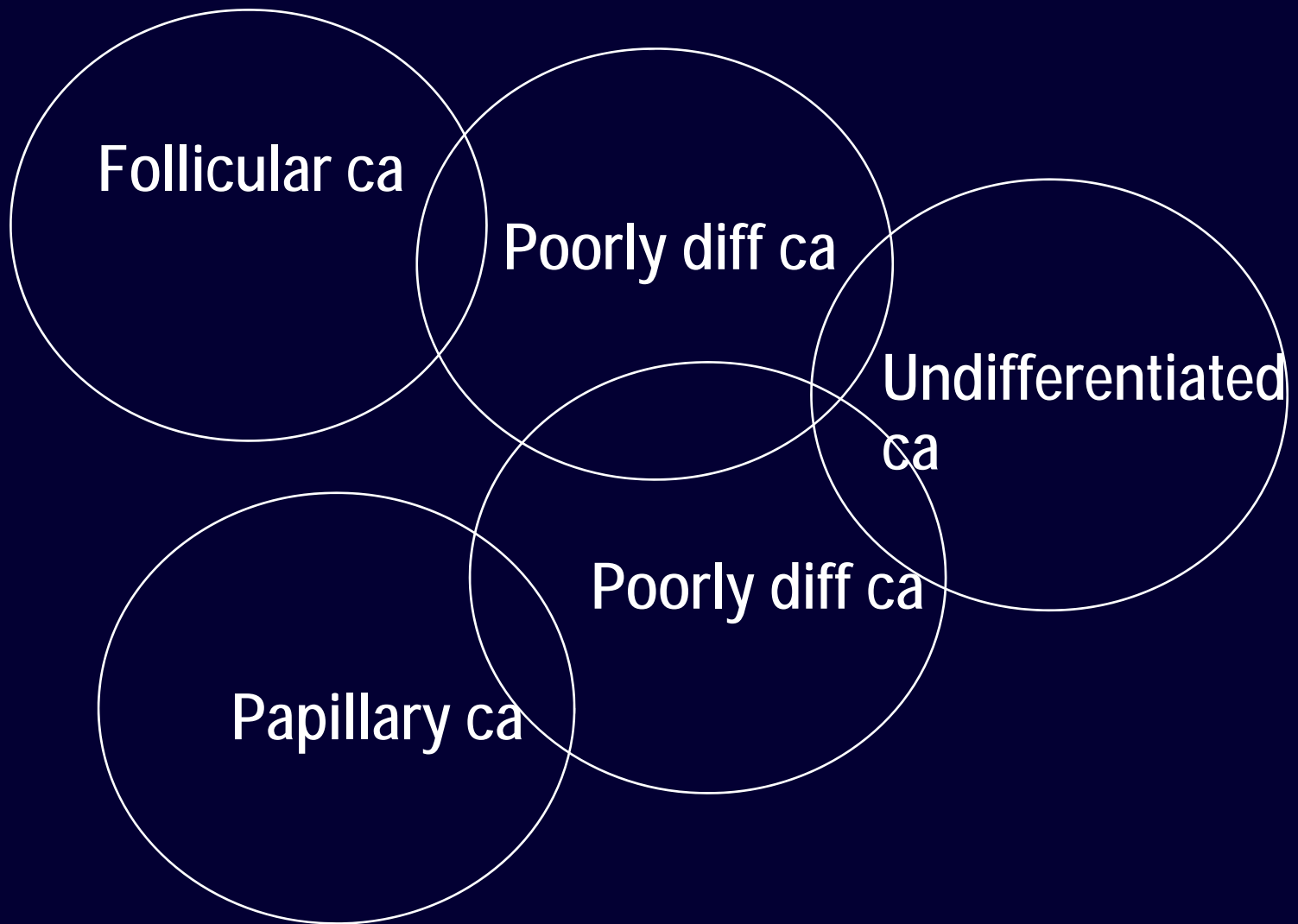
1/5 Poorly differentiated carcinoma

1/5 Other histotypes

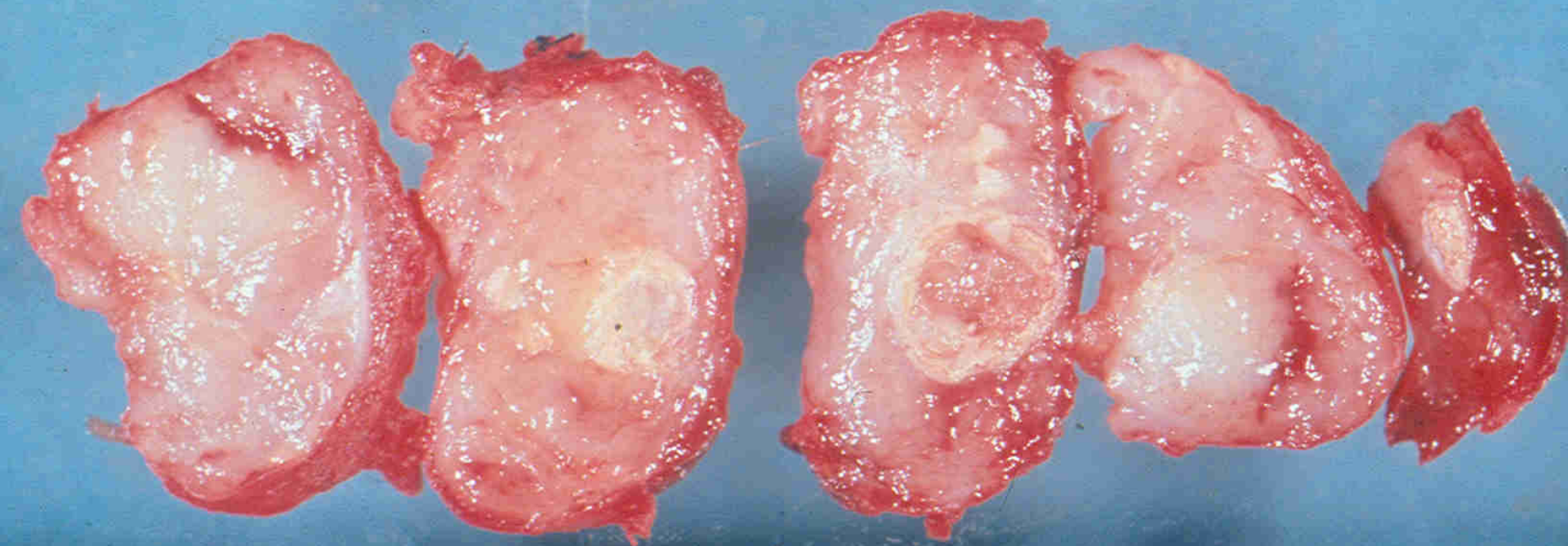
Sobrinho-Simões M, Unpublished observations, 2012

Most frequent diagnostic problems of thyroid pathology in a consultancy practice

1. Is there a focus (or some foci) of papillary carcinoma in “this” Hashimoto’s thyroiditis or “this” nodular goiter?
2. Is this lesion an adenoma, a follicular carcinoma or an encapsulated follicular variant of papillary carcinoma?
3. How would you classify this Hürthle cell lesion?
4. Is this a well differentiated carcinoma with a solid pattern of growth or a poorly differentiated carcinoma?



Soares et al, Virchows Arch 444:572, 2004



U352-84



16

17

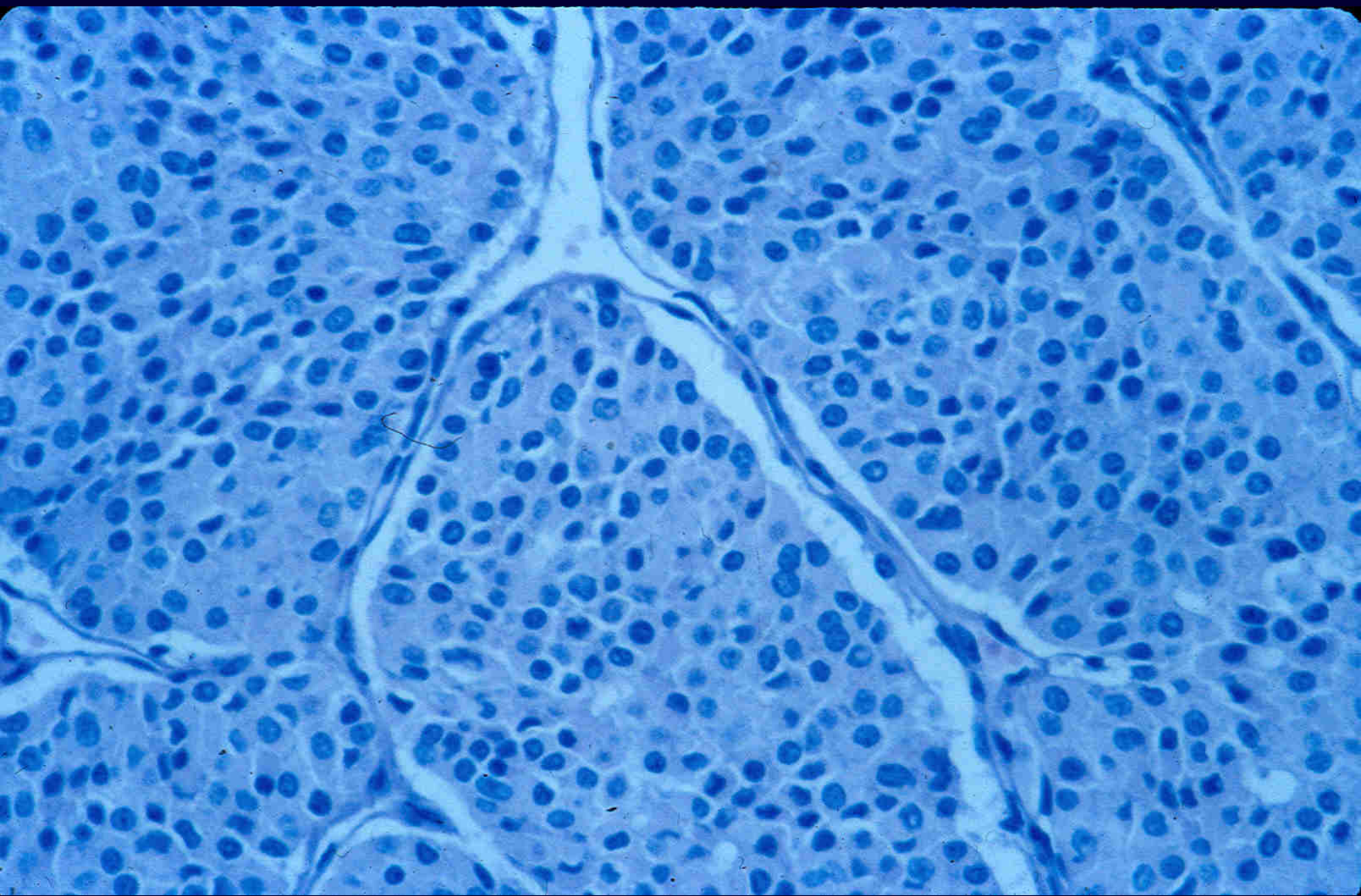
18

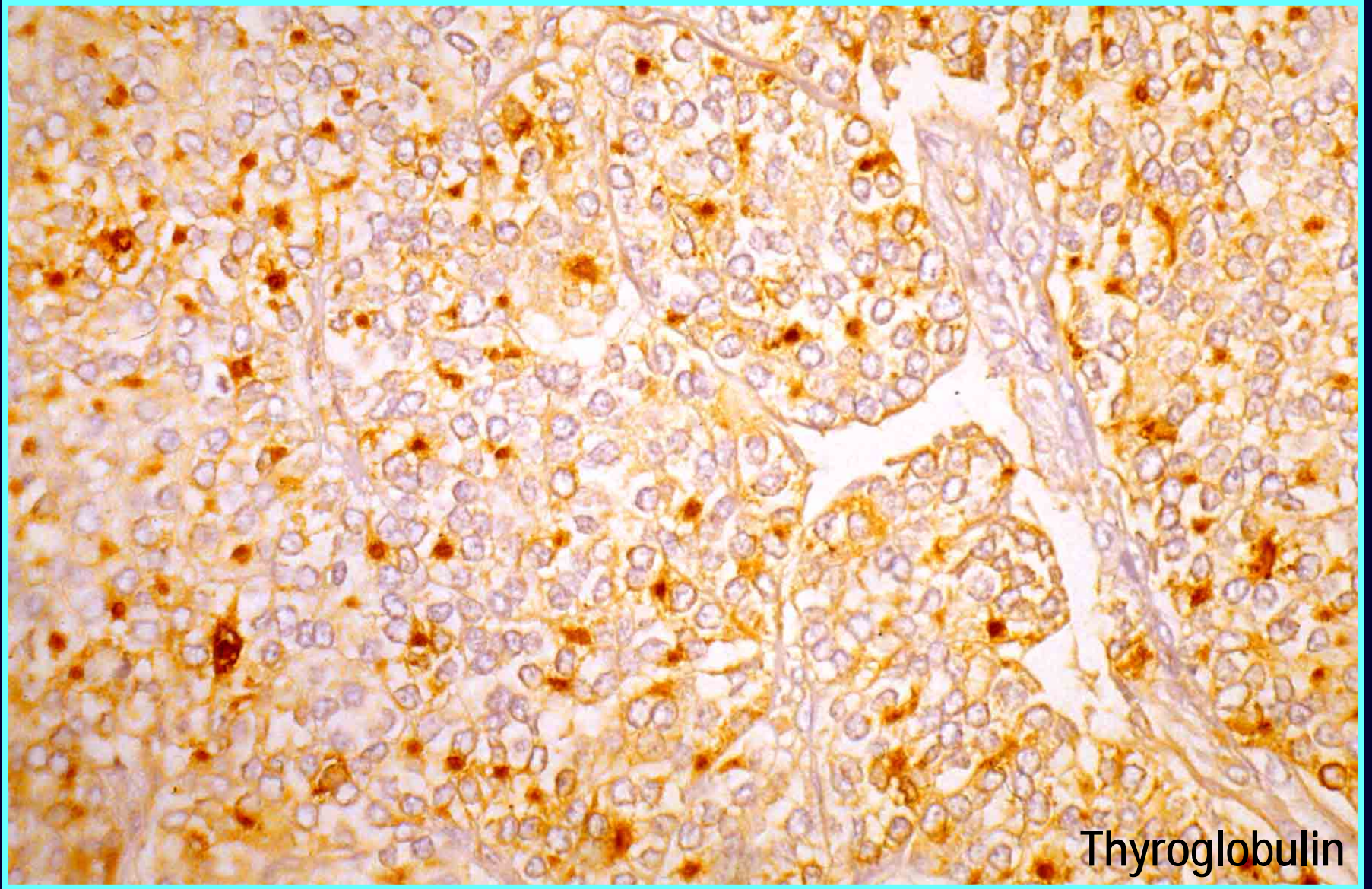
19

20

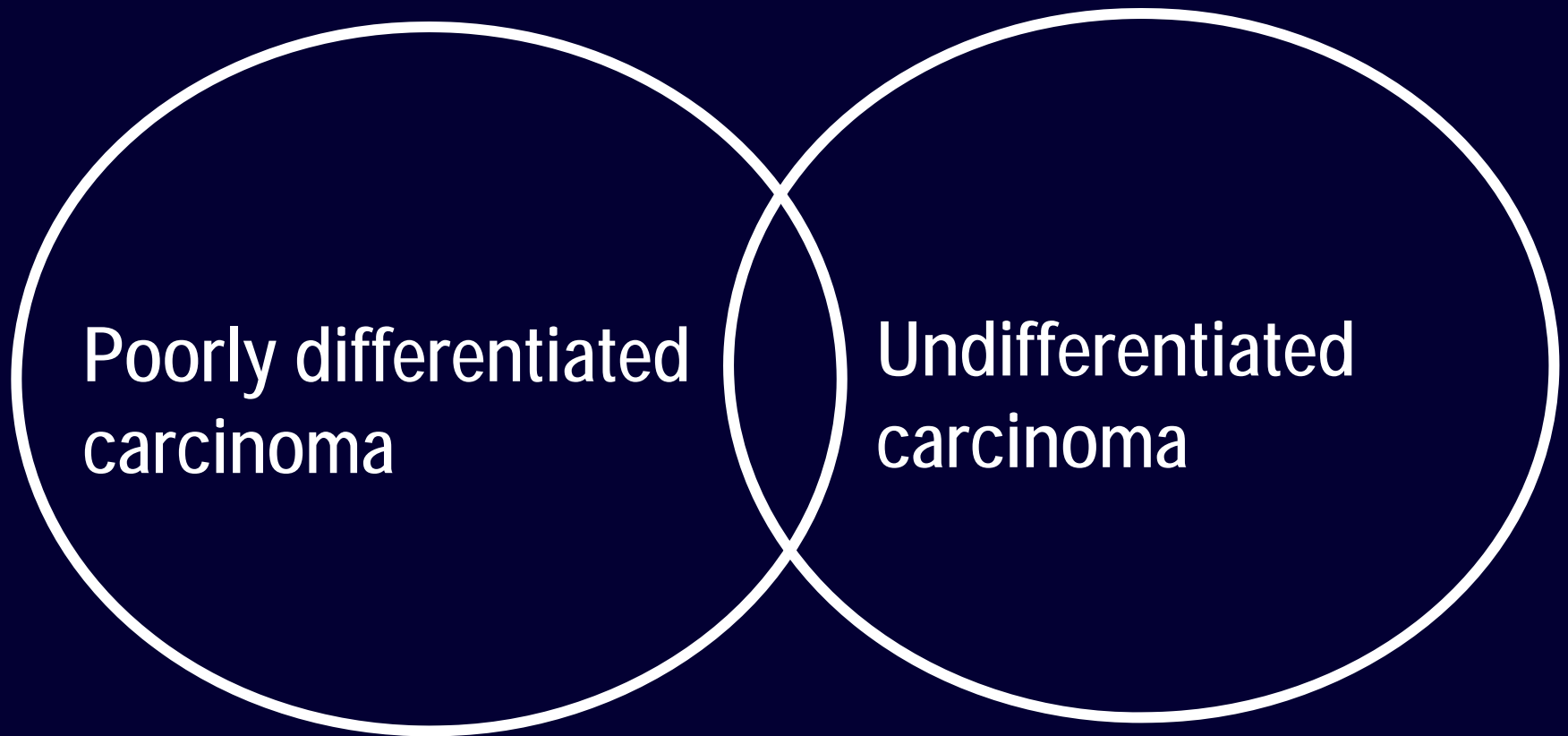
21

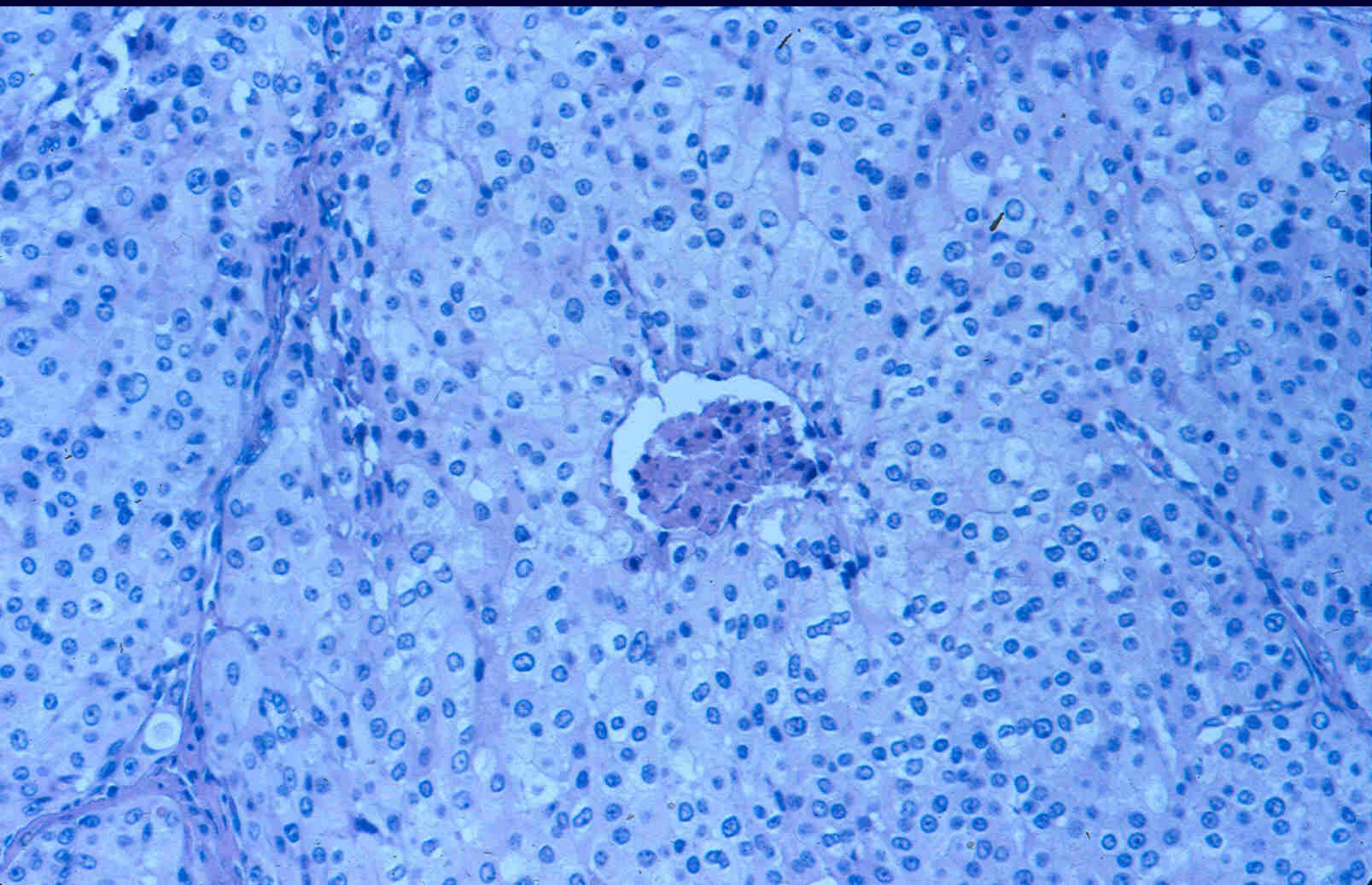
22

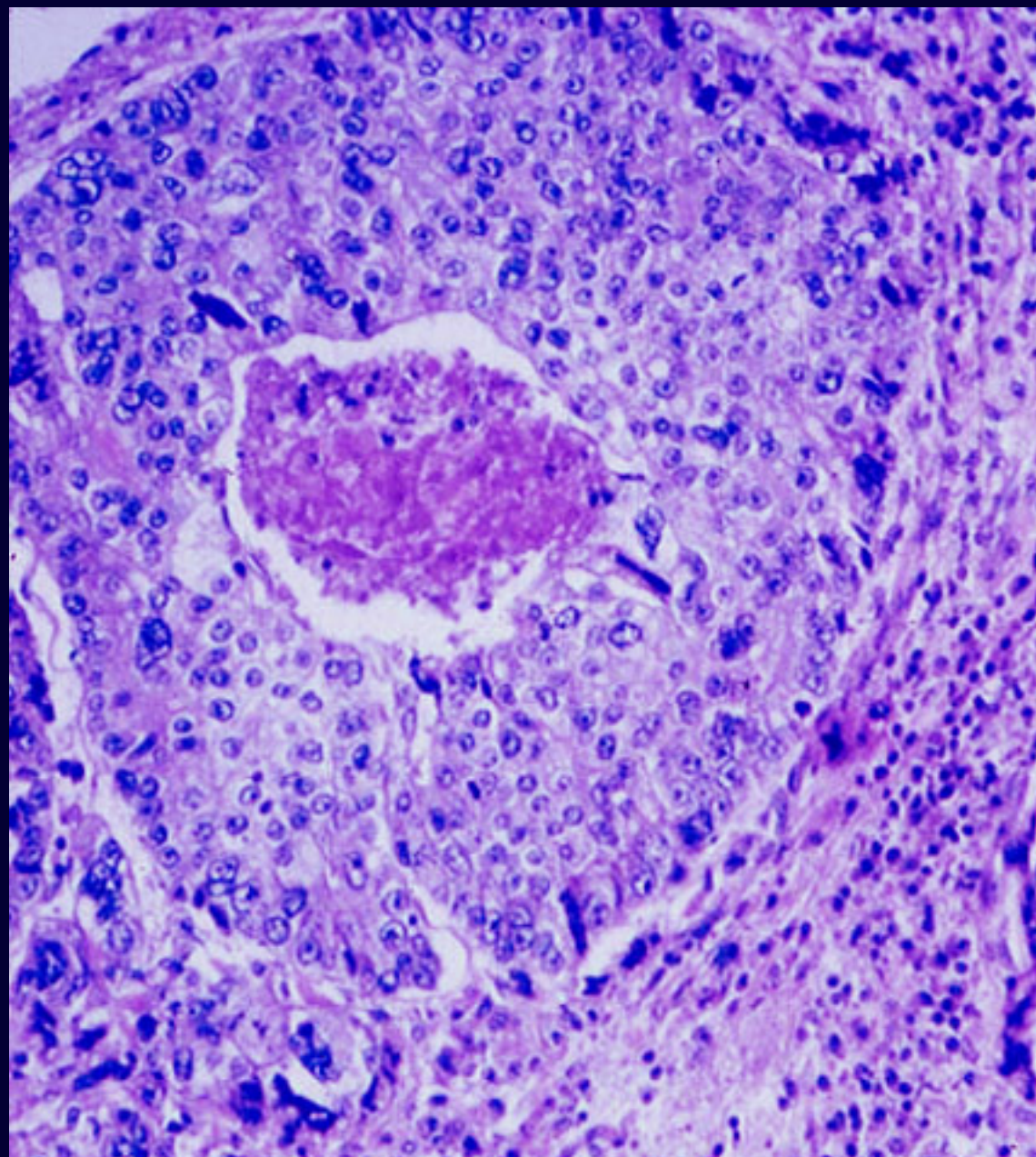


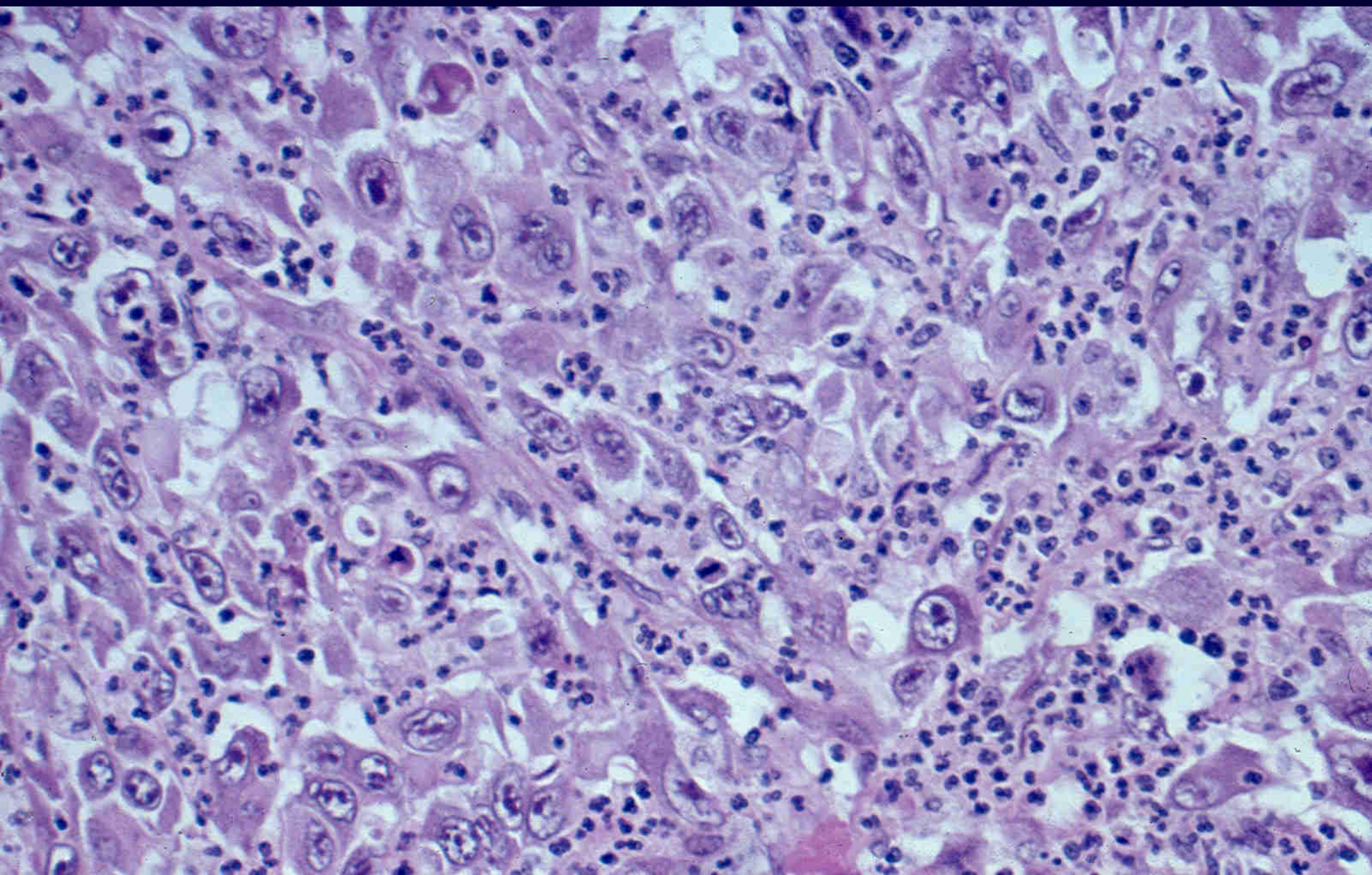


Thyroglobulin









p 53

P53 Mutations in Thyroid Carcinomas

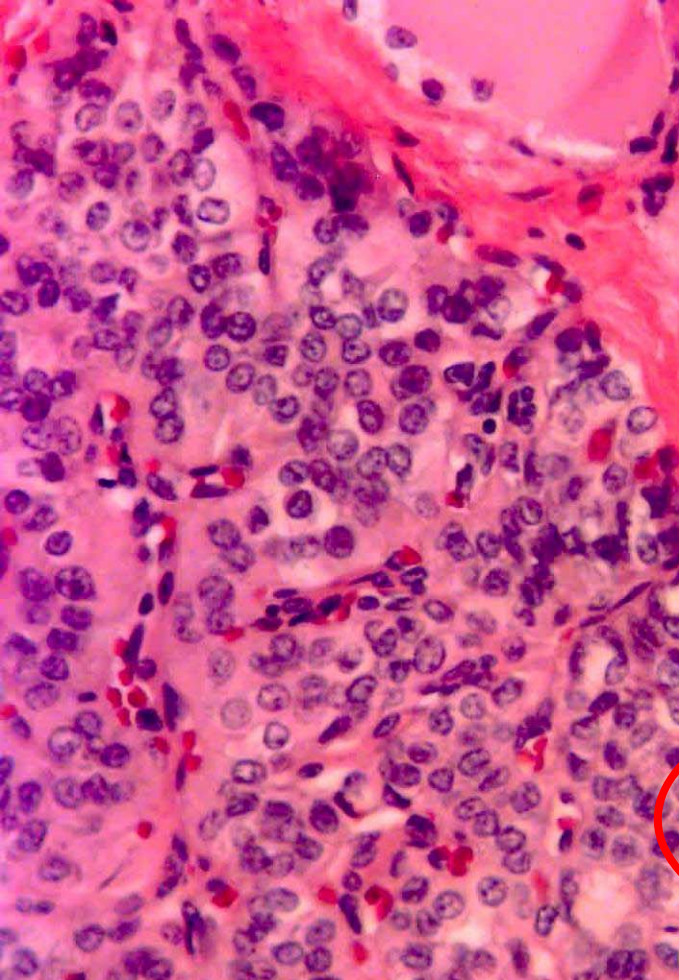
Papillary & Follicular ca	-	0%
Poorly differentiated ca	-	17-38%
Undifferentiated (anaplastic) ca	-	56-86%

Preto et al Oncogene 23:1316, 2004

Sobrinho-Simões et al Endocr Metab Clin N Am 37:333, 2008

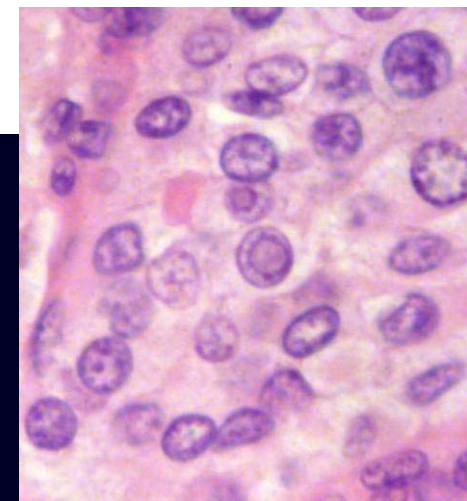
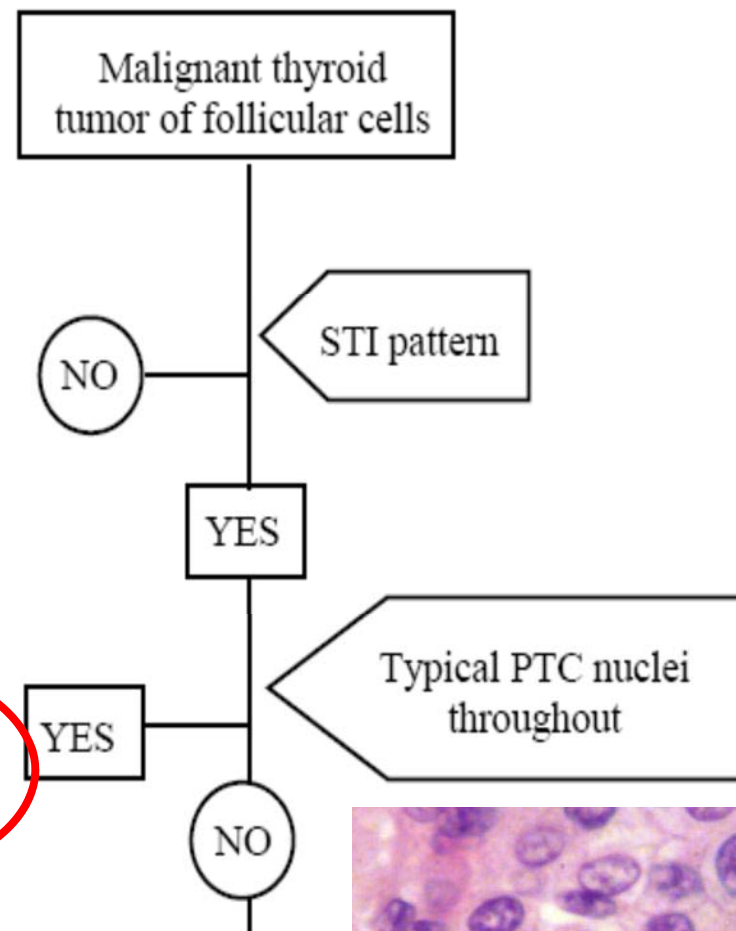


Volante M et al, Am J Surg Pathol, 2007 (Turin Proposal - Multicontinental study)

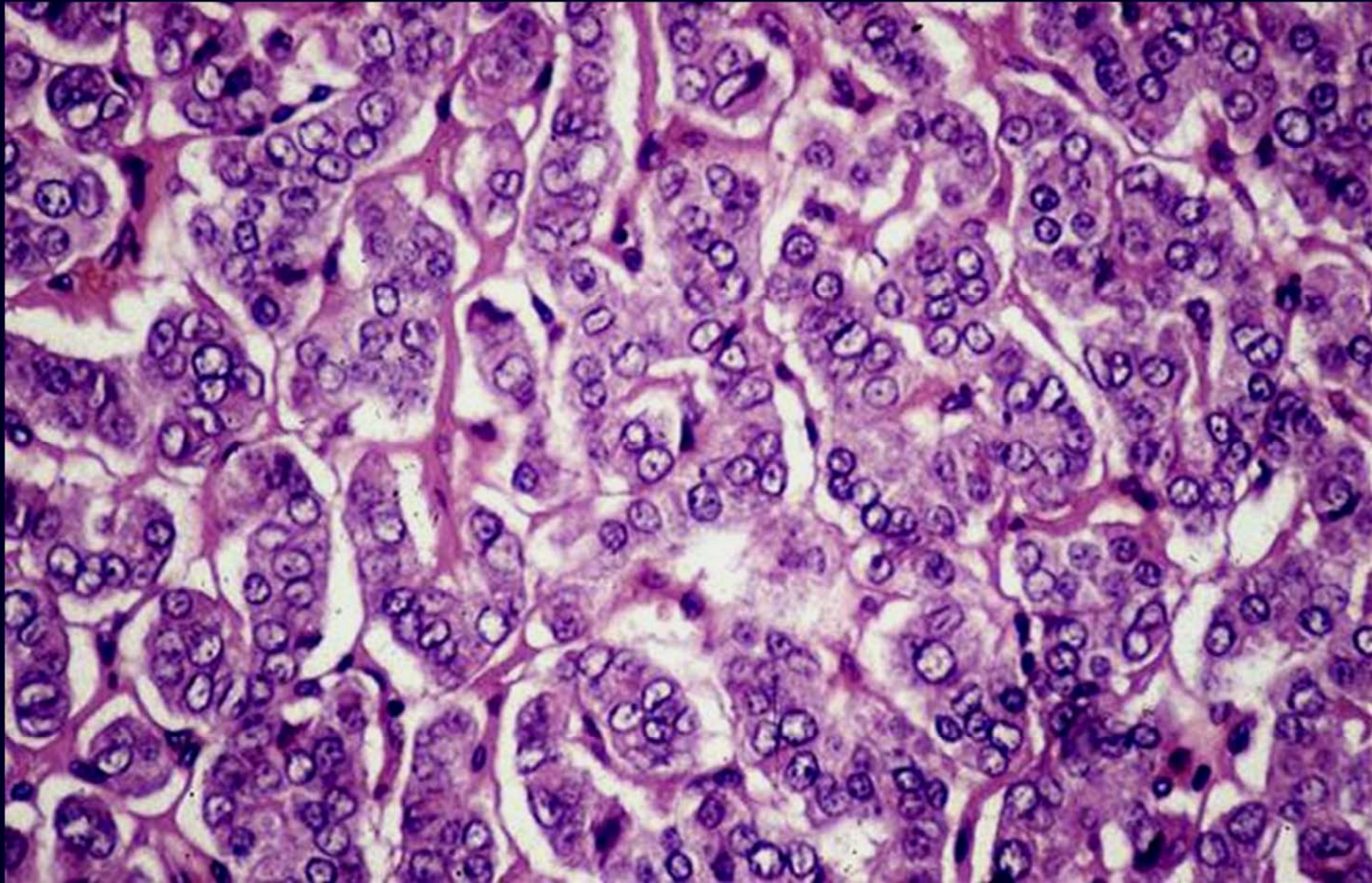


Follicular carcinoma
Papillary carcinoma
(etc)

Solid variant of
papillary carcinoma



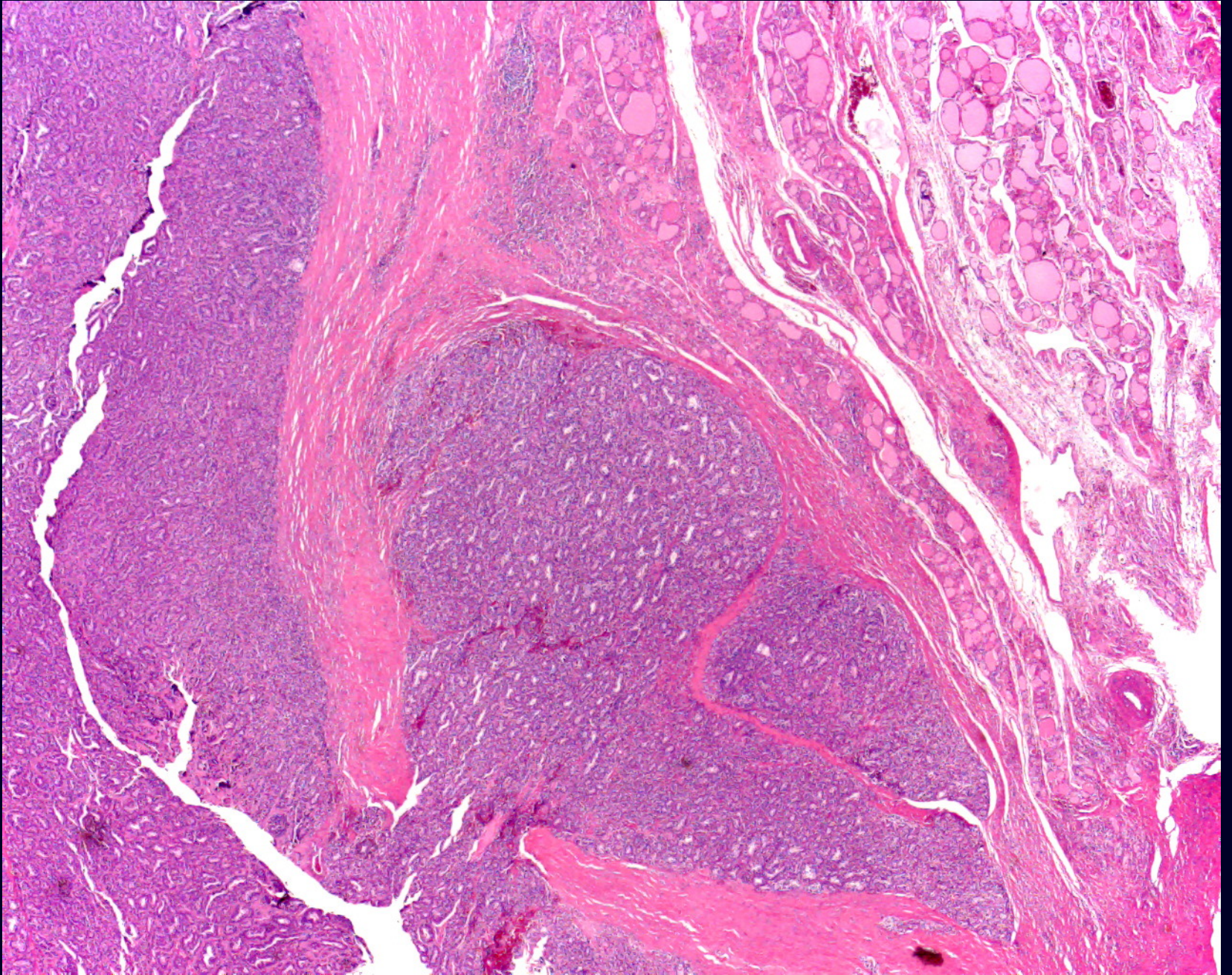
Solid/trabecular variant of PTC

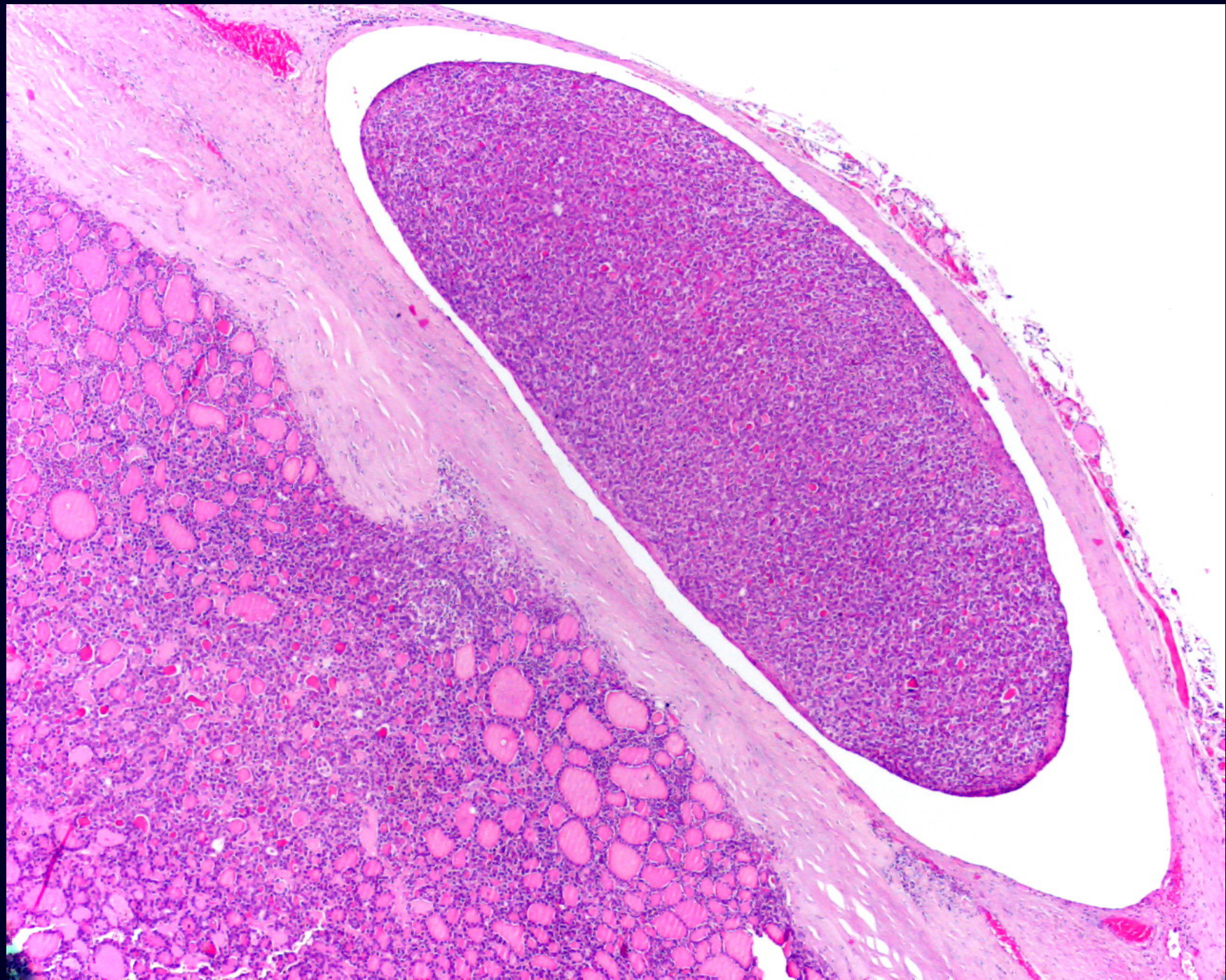


Widely invasive FTC



Widely invasive FTC







Volante M et al, Am J Surg Pathol, 2007 (Turin Proposal - Multicontinental study)

Rare flowers & Miscellaneous

Practical problems

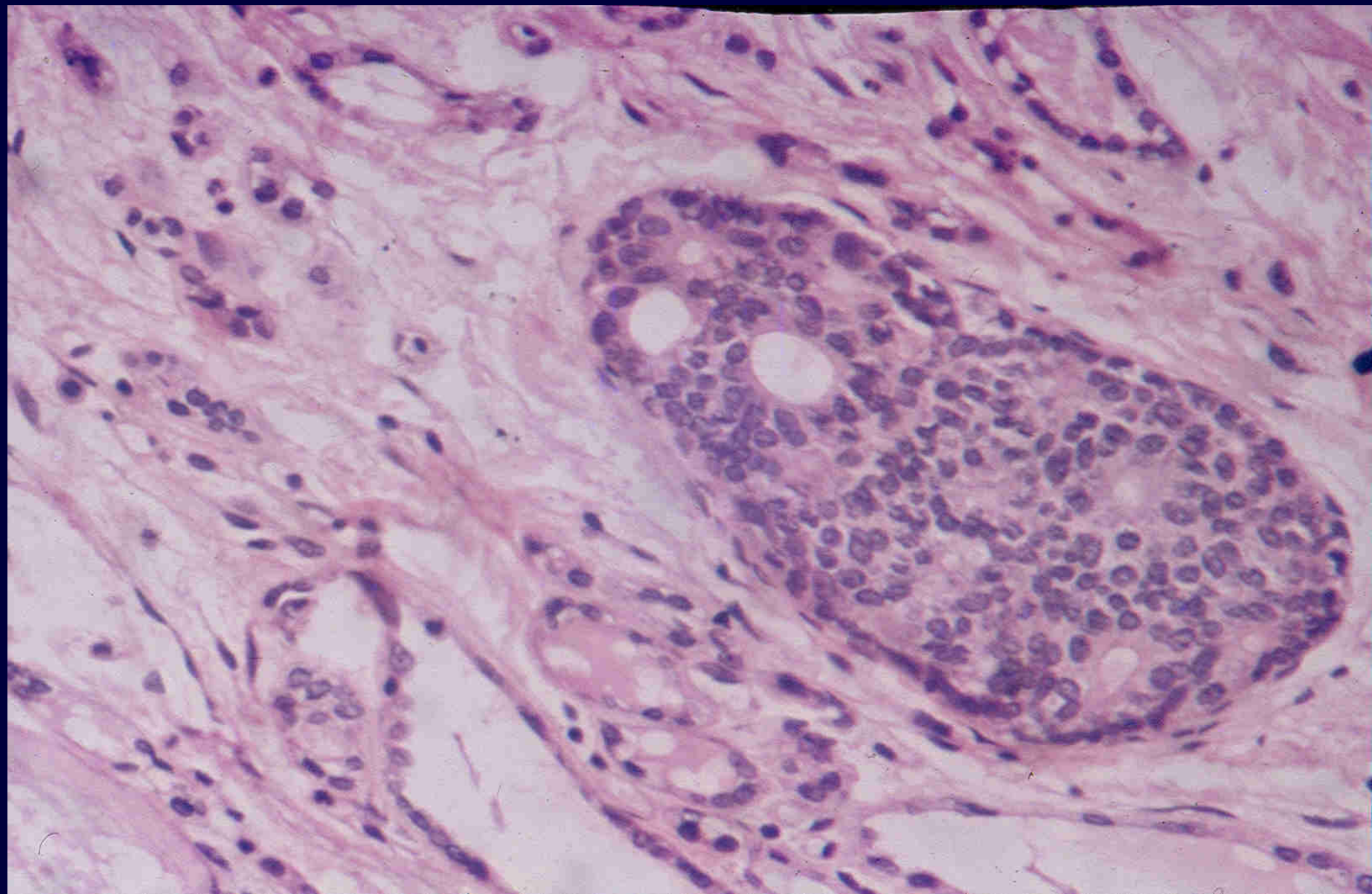
Questions to be made whenever facing a strange lesion in the thyroid

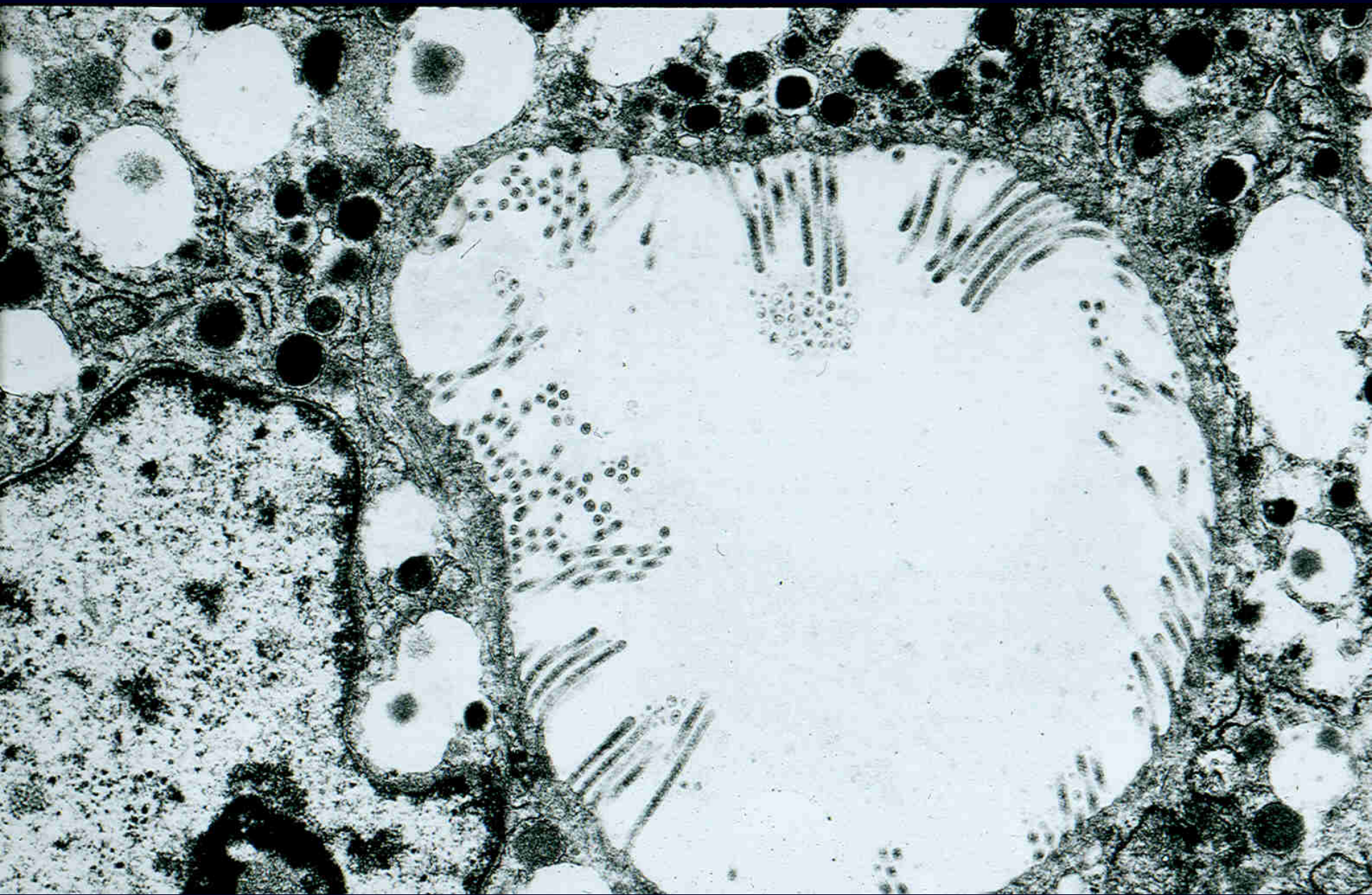
Is it a primary thyroid tumour?

If yes, is it made of follicular or C-cells?

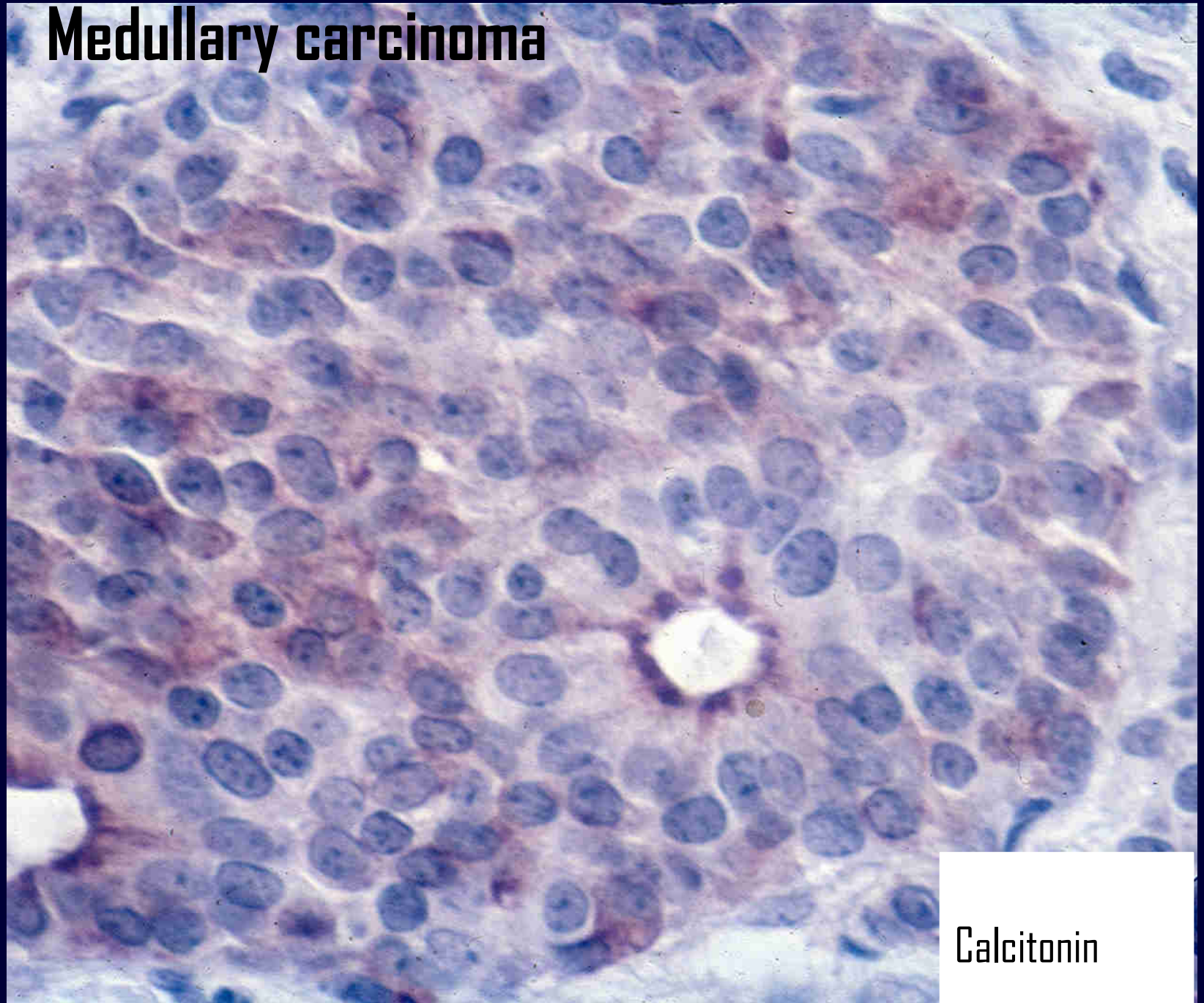
Immunohistochemistry is mandatory:
TG and calcitonin (and, if necessary,
TTF1)





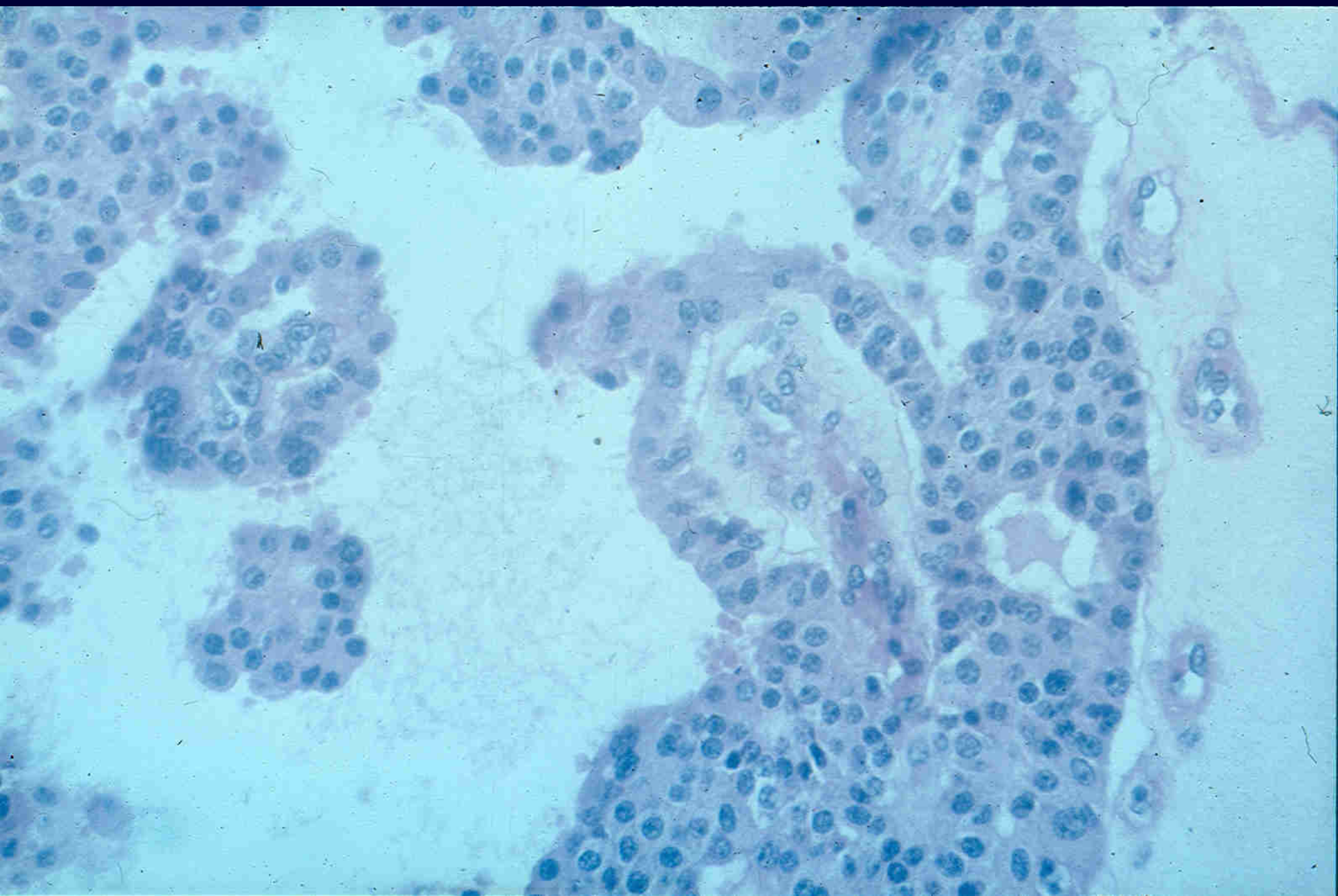


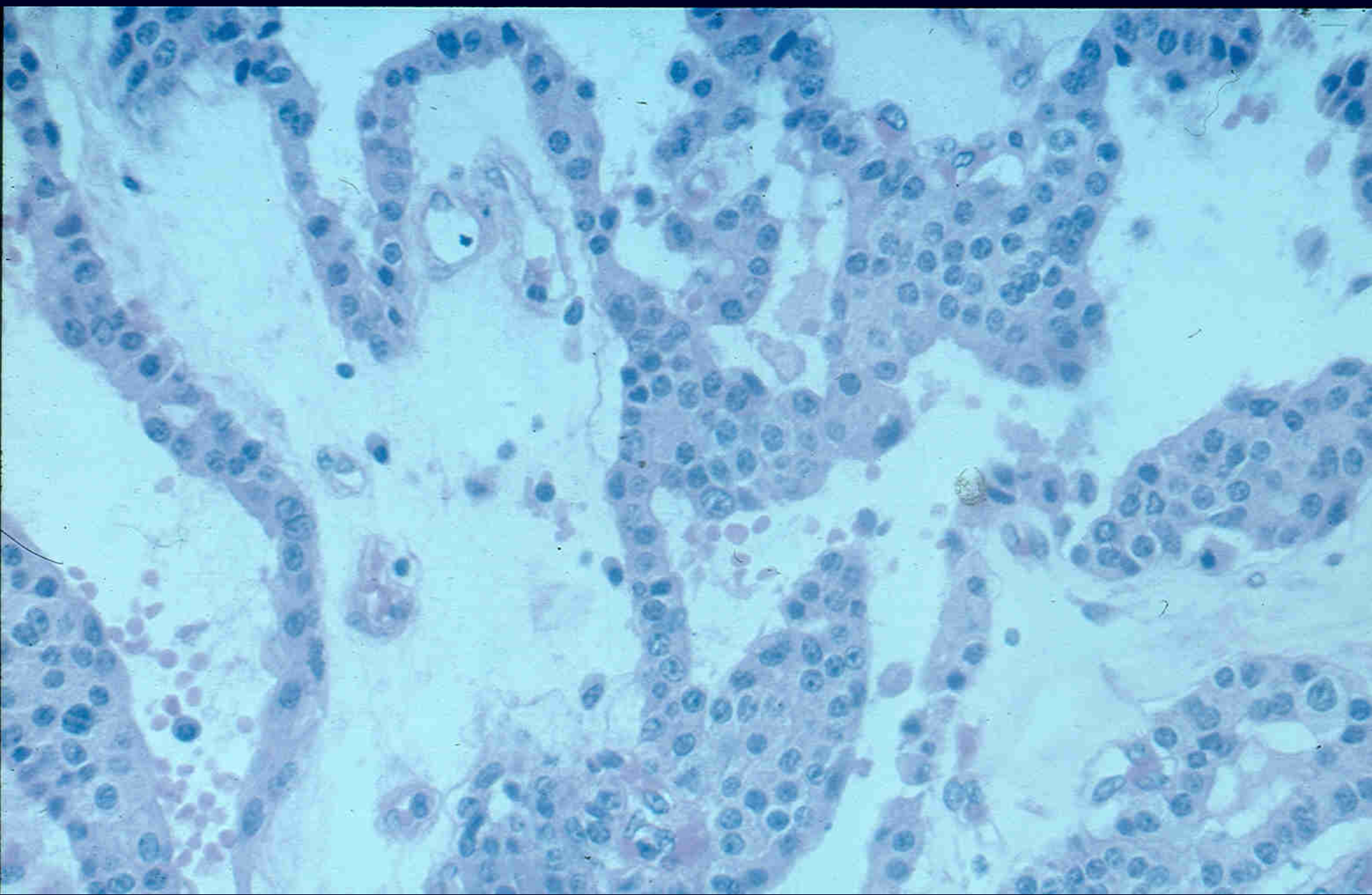
Medullary carcinoma



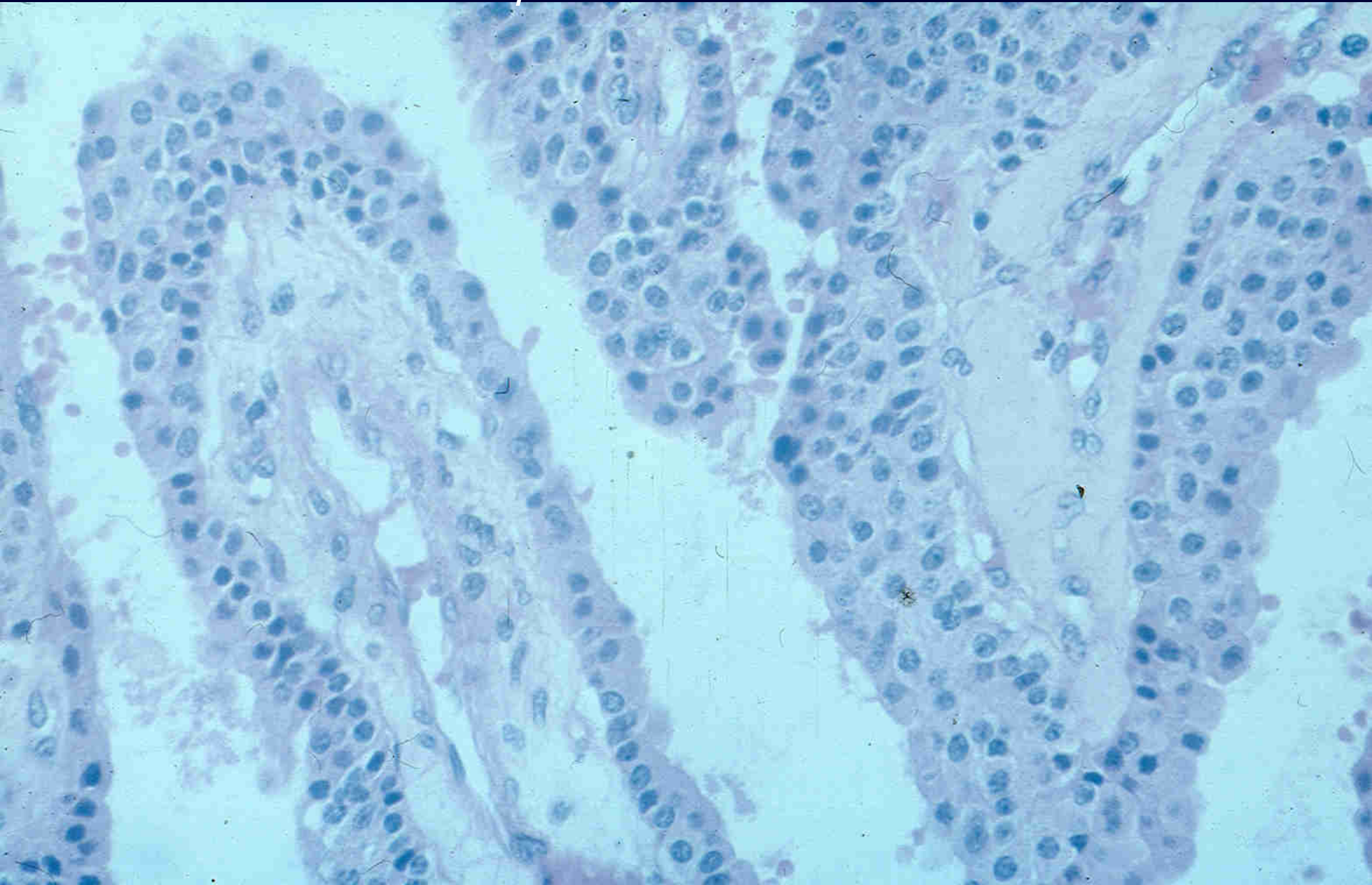
Calcitonin



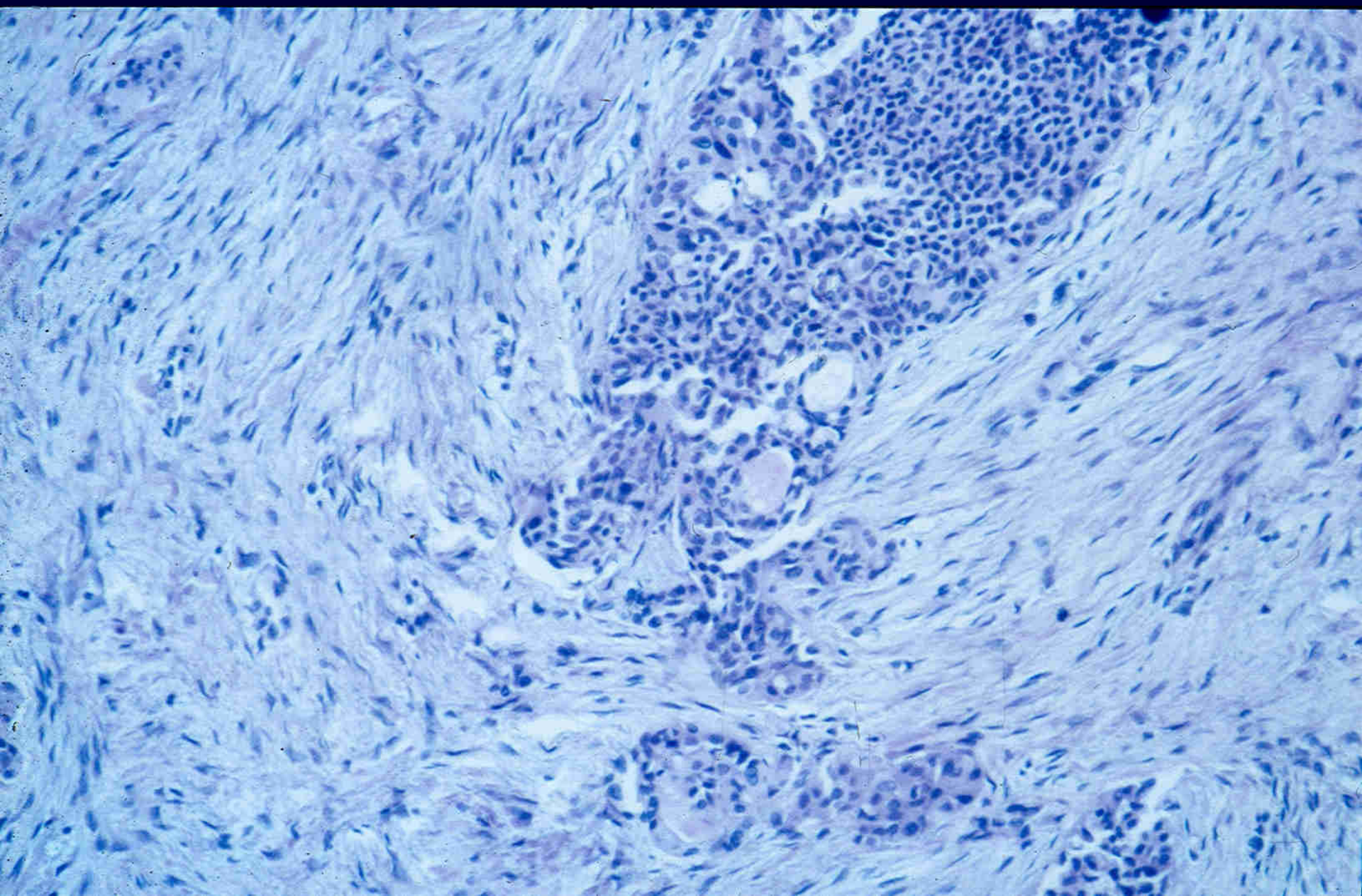


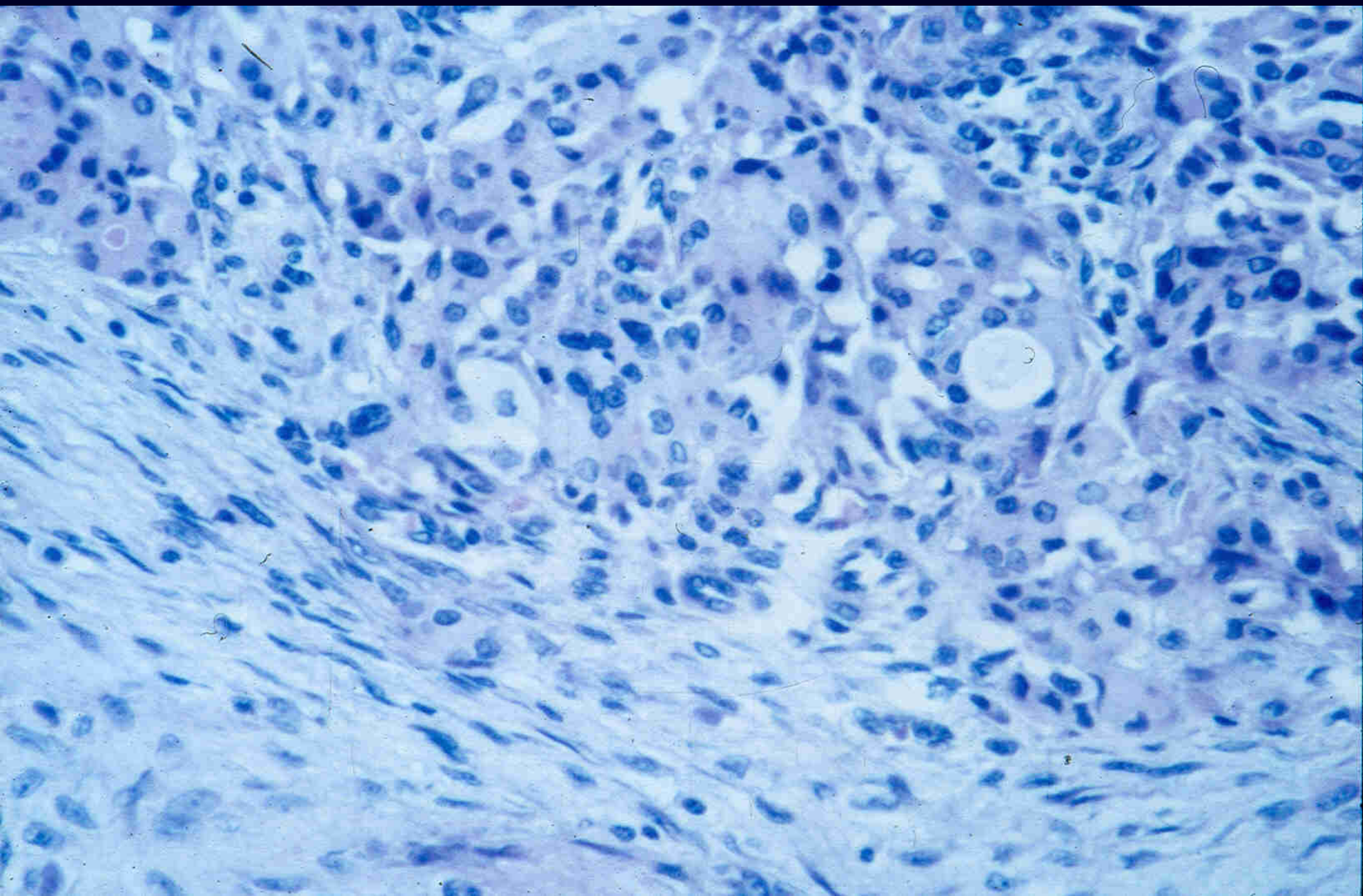


Calcitonin positive Medullary carcinoma

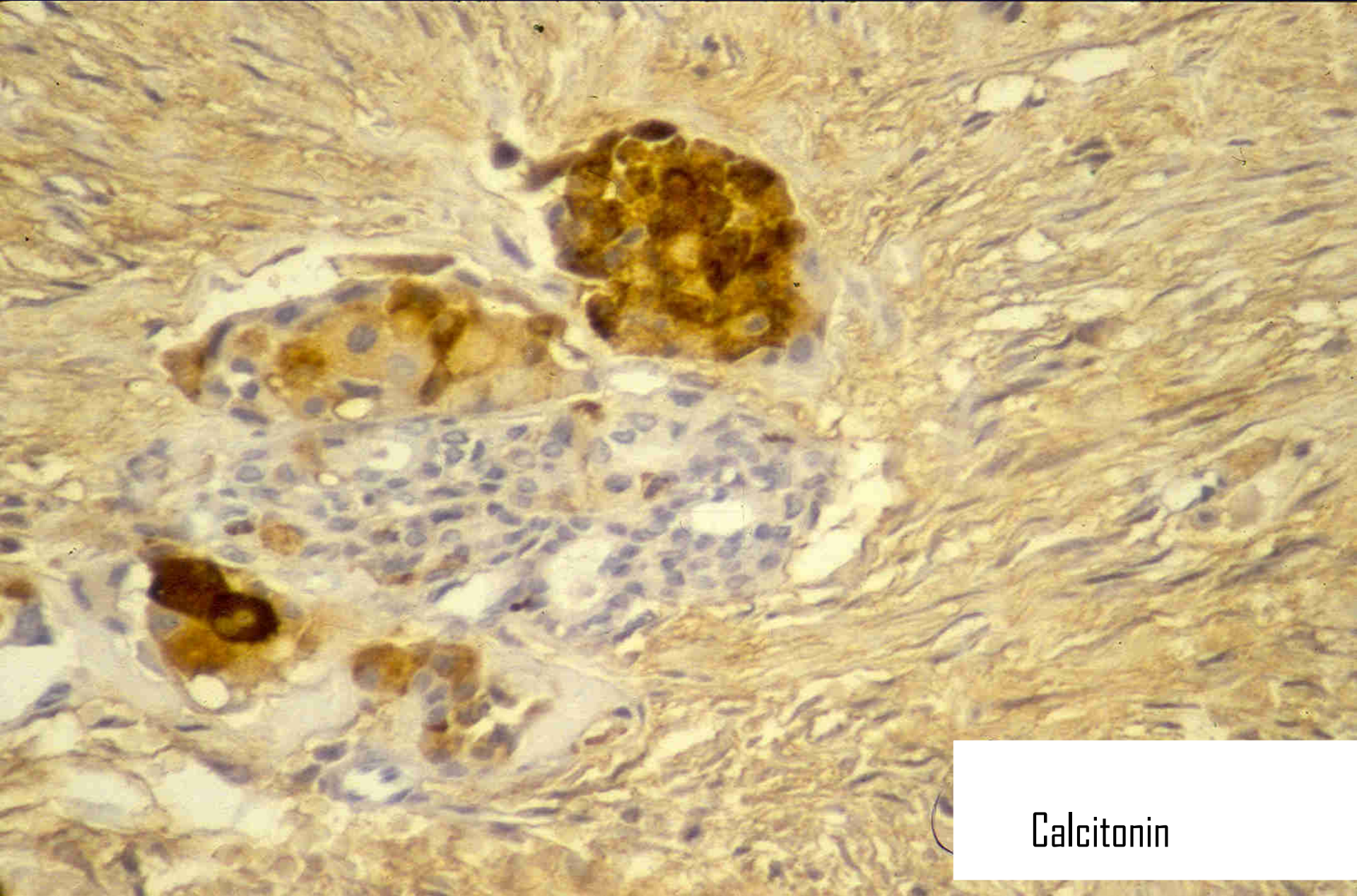








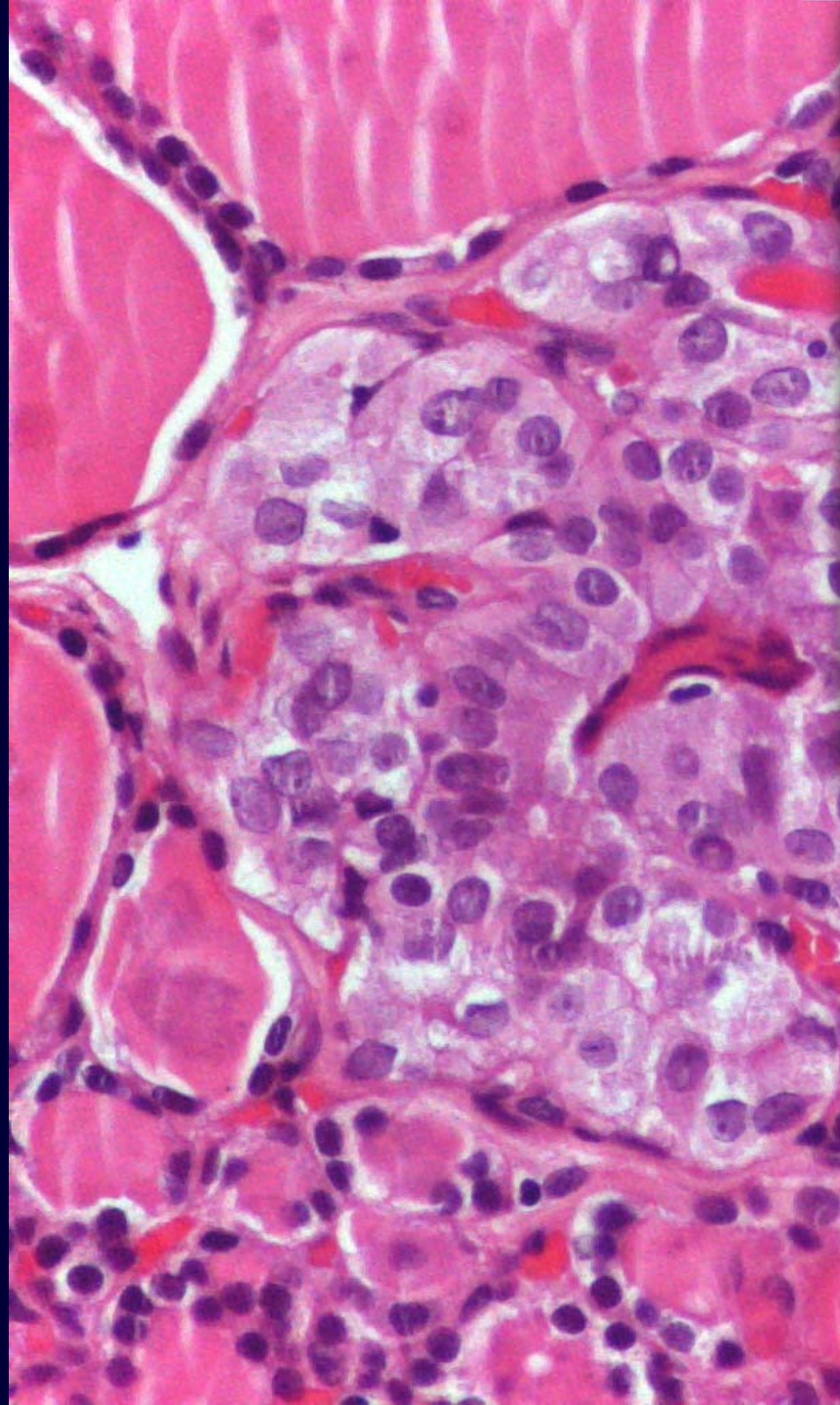
Mixed medullary – follicular carcinoma



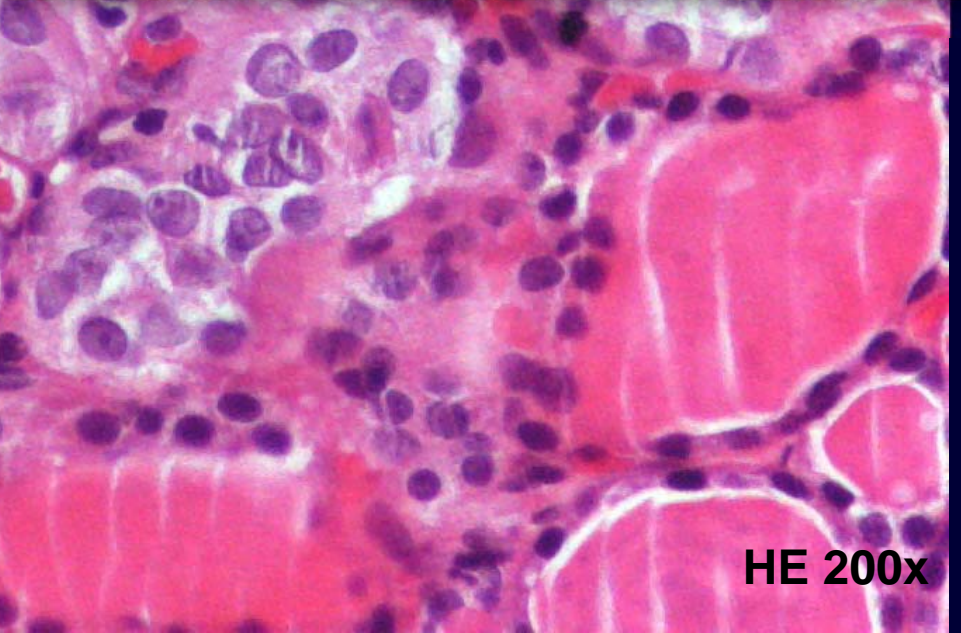
Calcitonin

Differential diagnosis of
reactive and neoplastic c-cell
hyperplasia

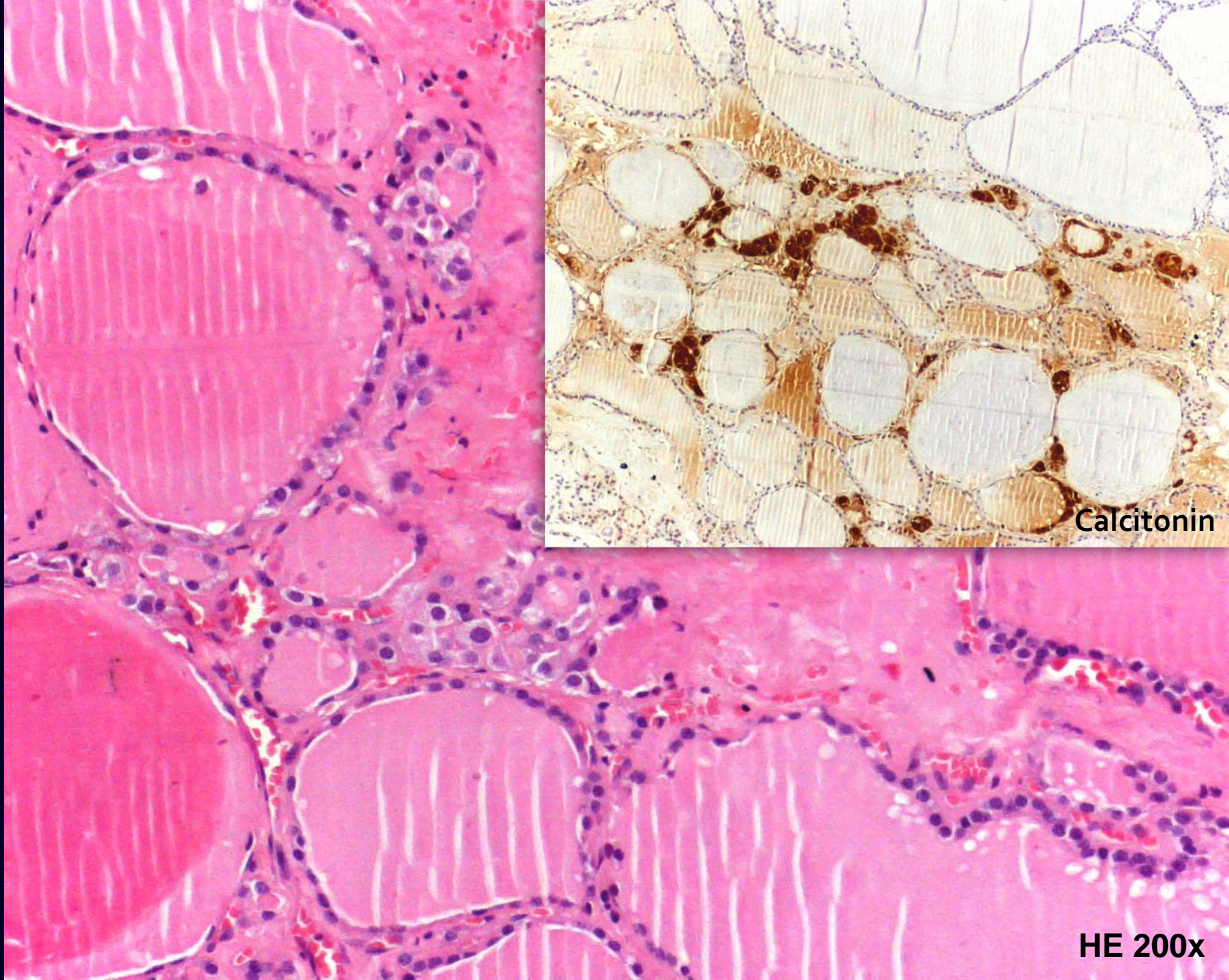
Differential diagnosis of
nodular c-cell hyperplasia and
medullary microcarcinoma



Calcitonin

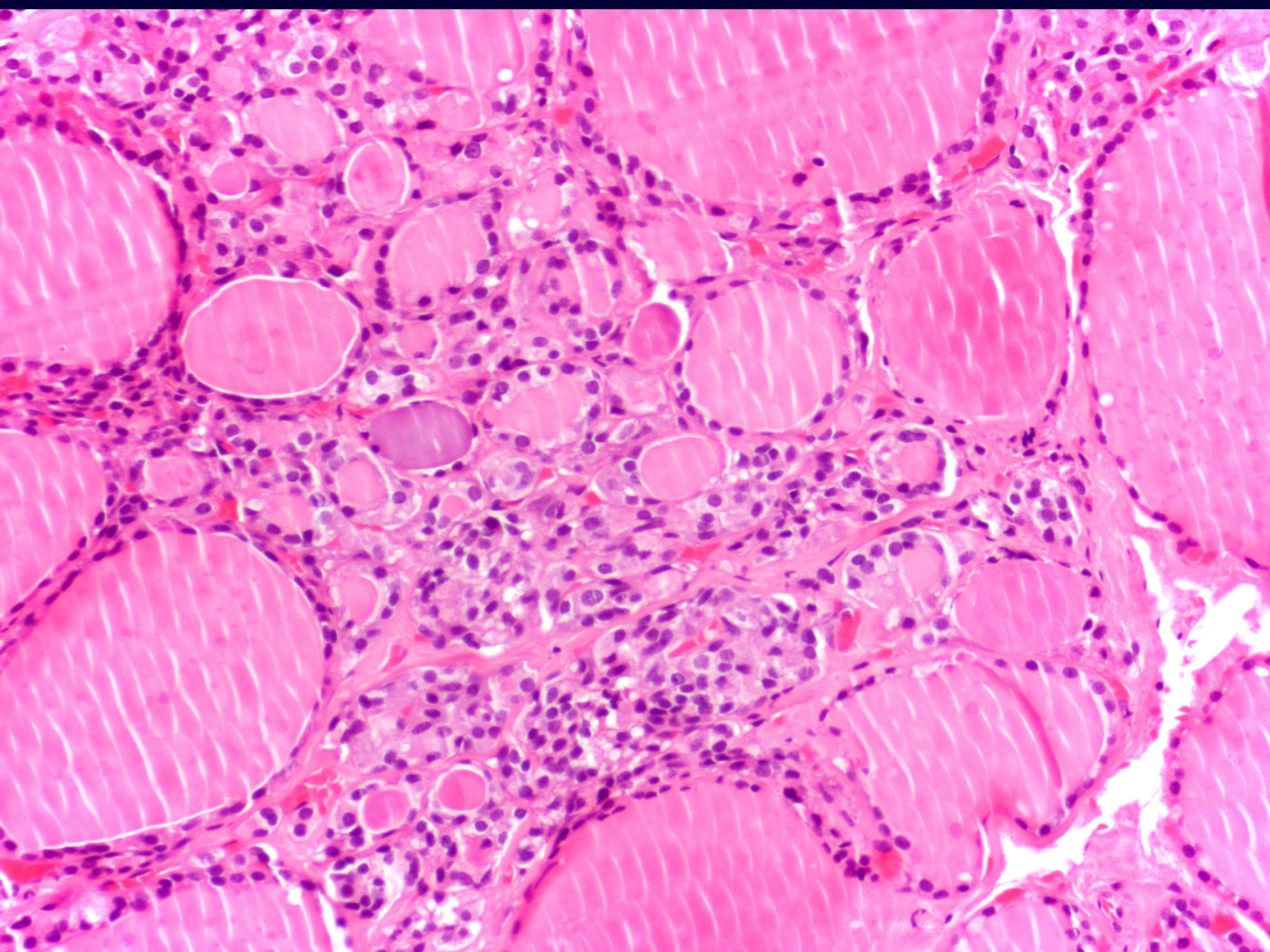


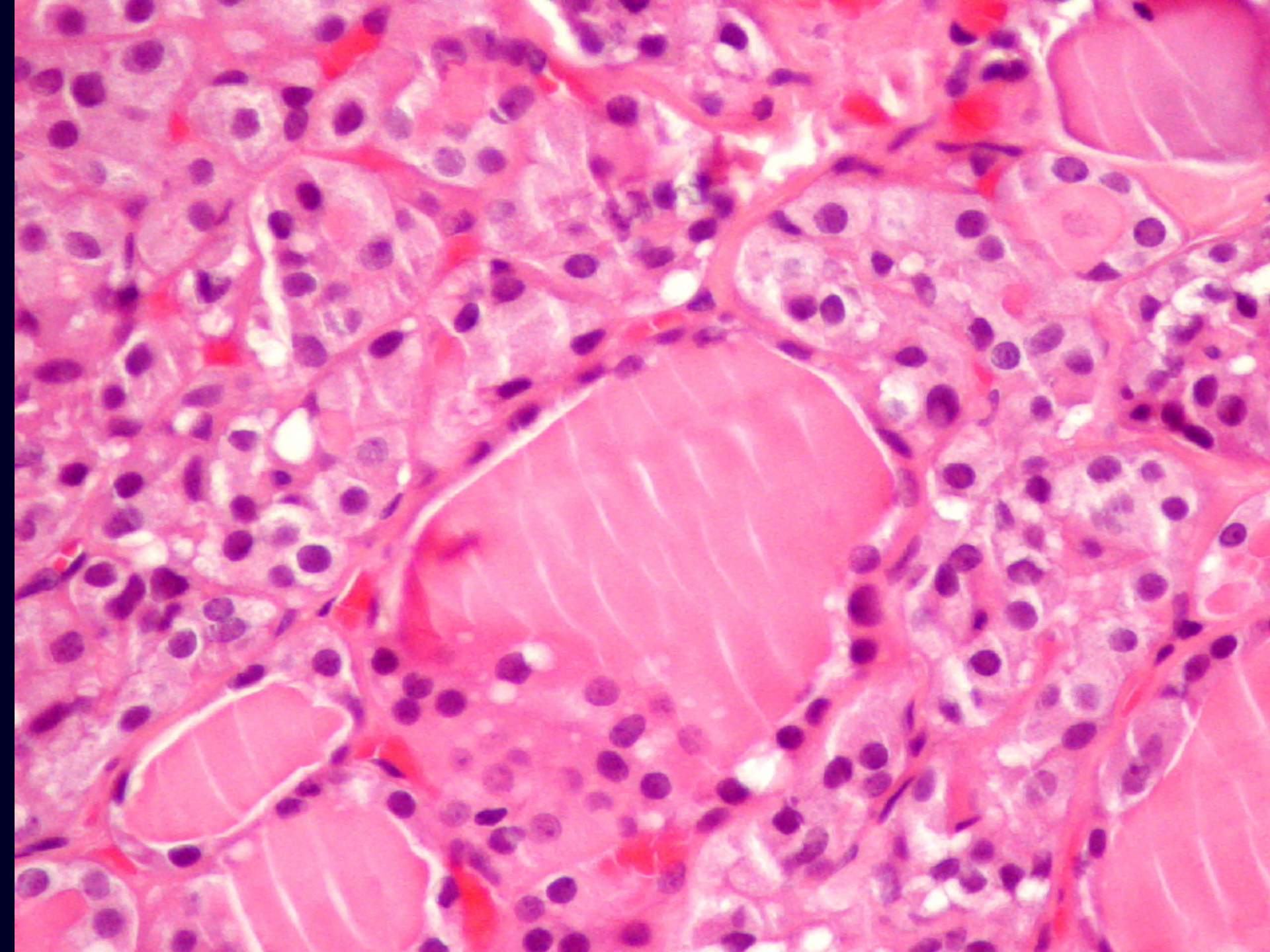
HE 200x

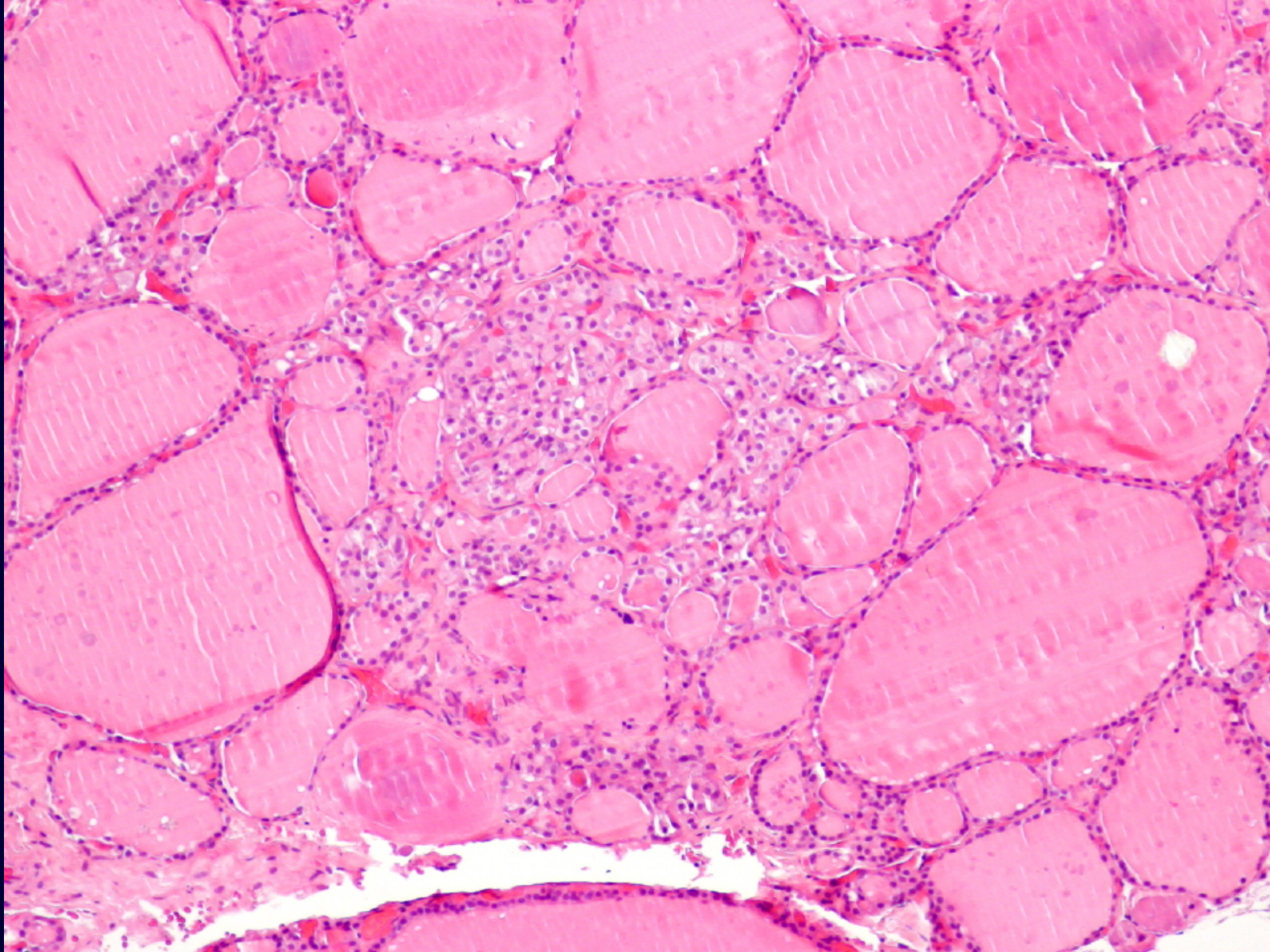


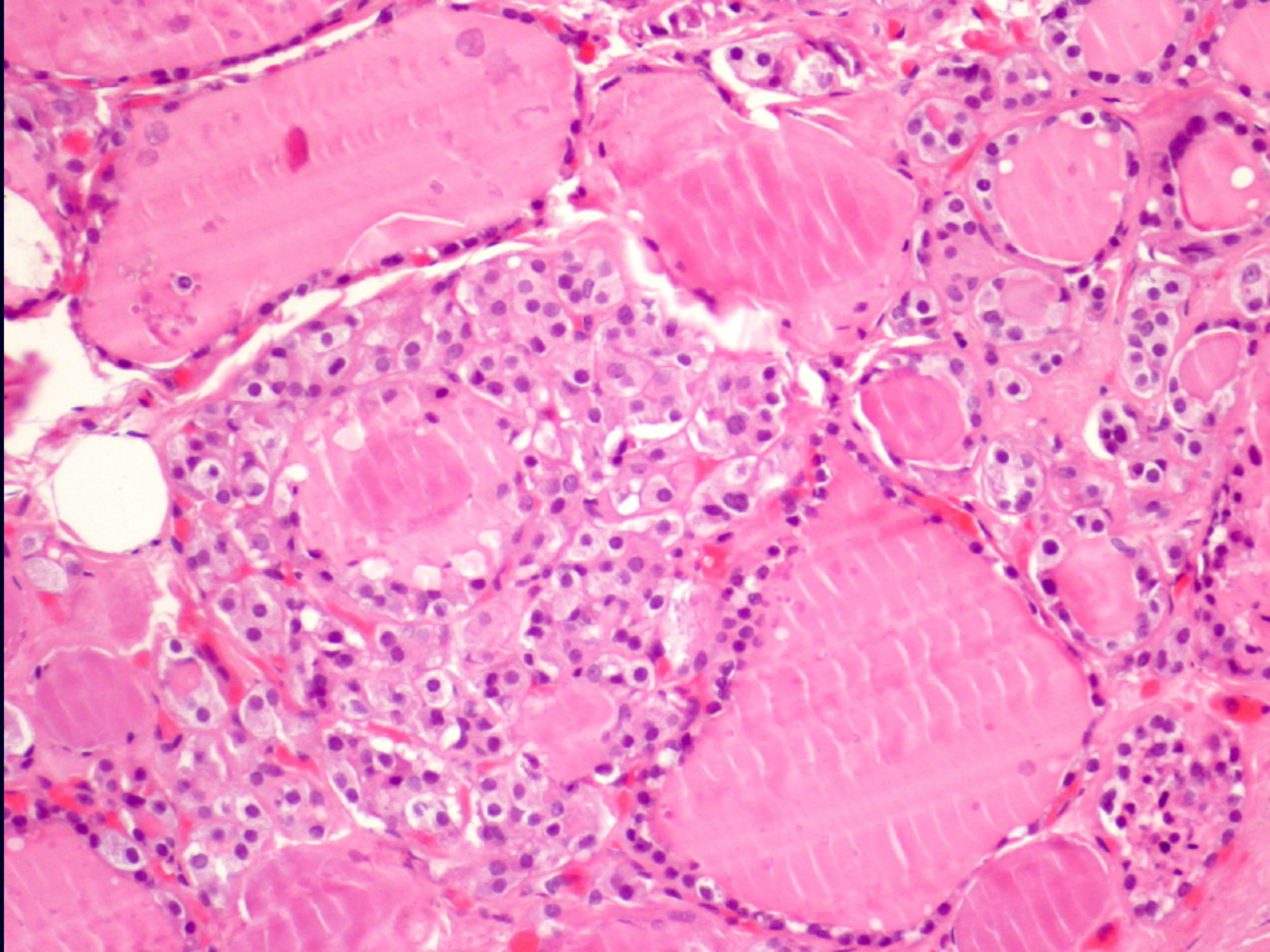
Calcitonin

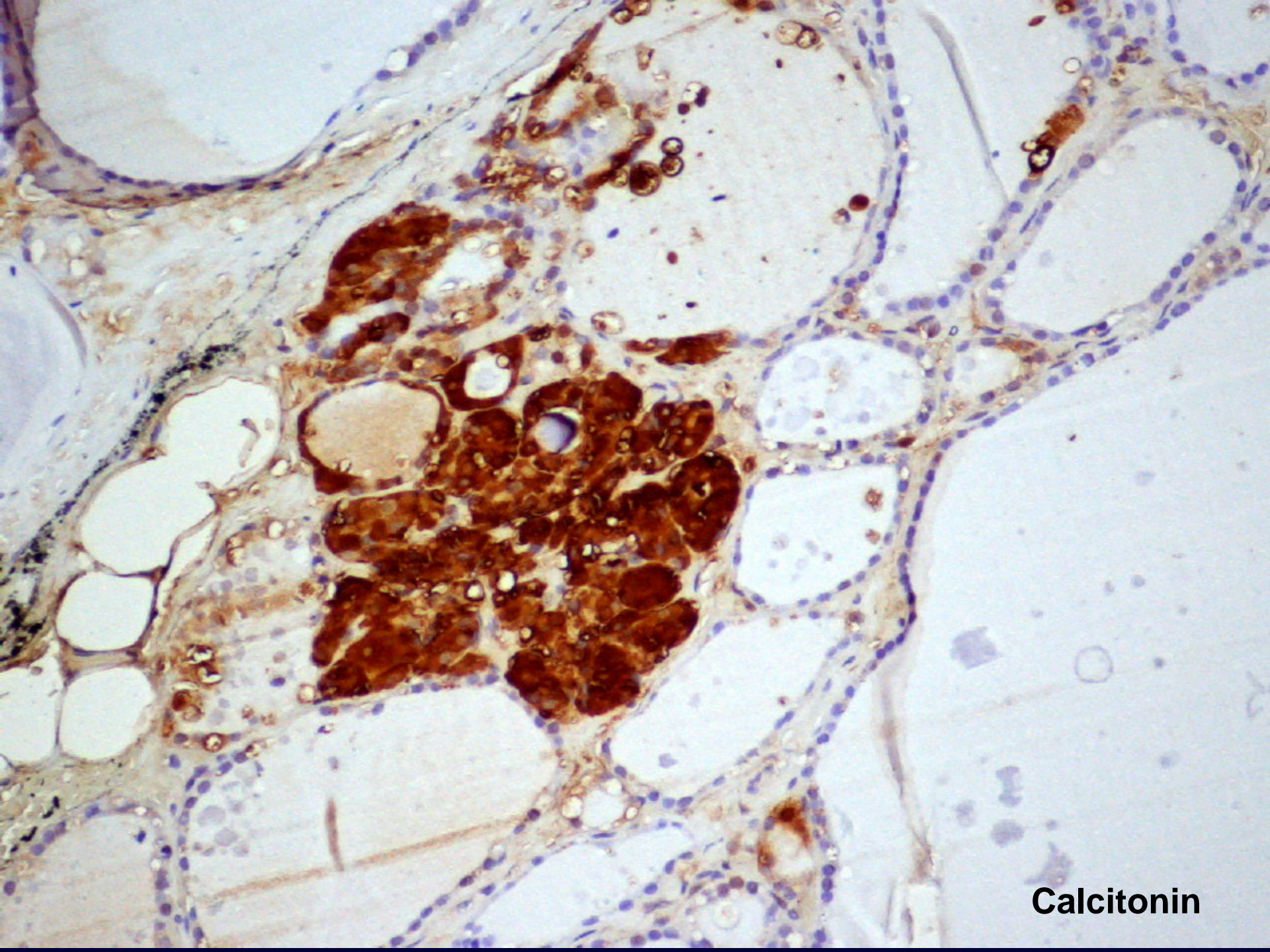
HE 200x



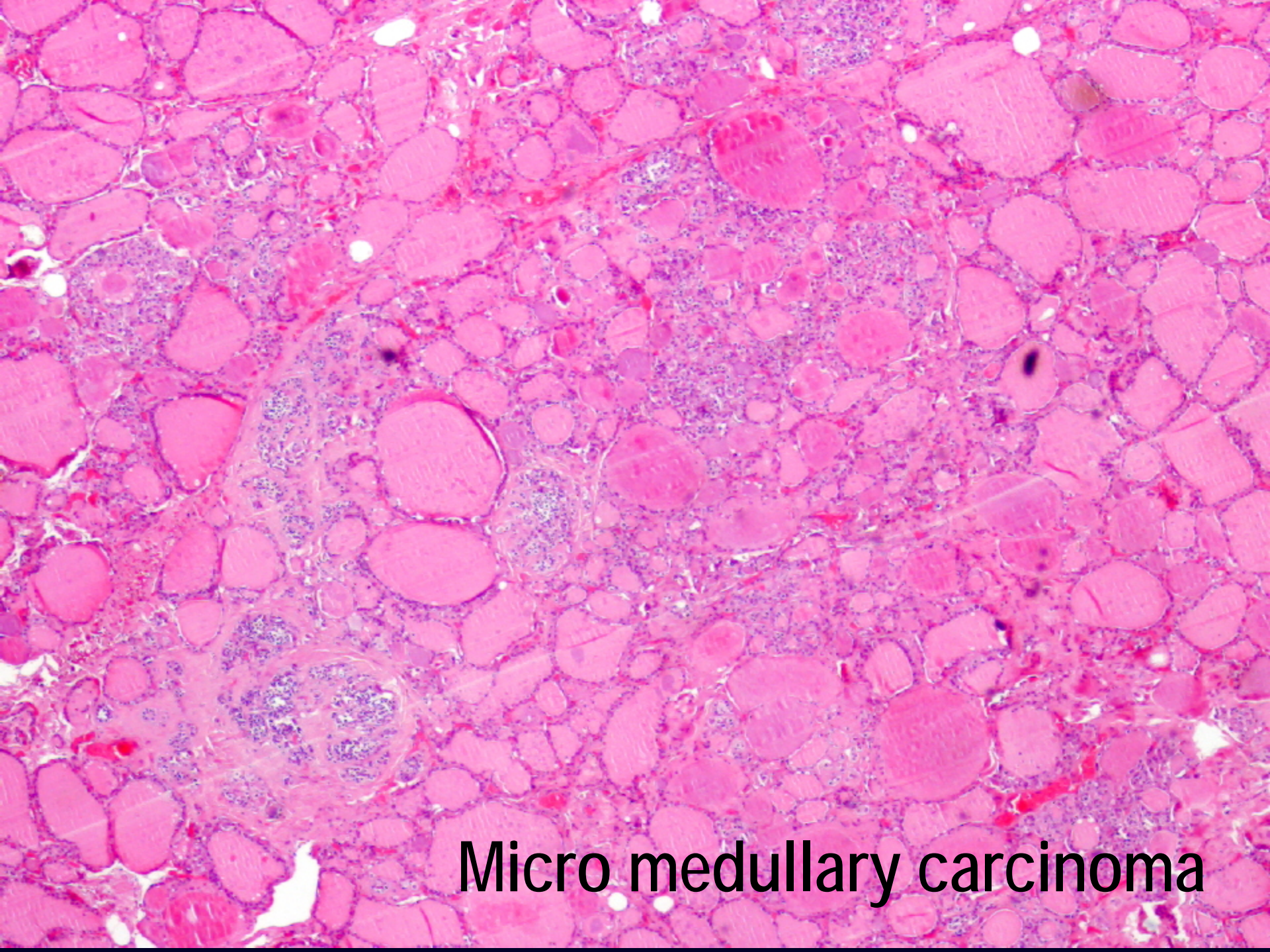




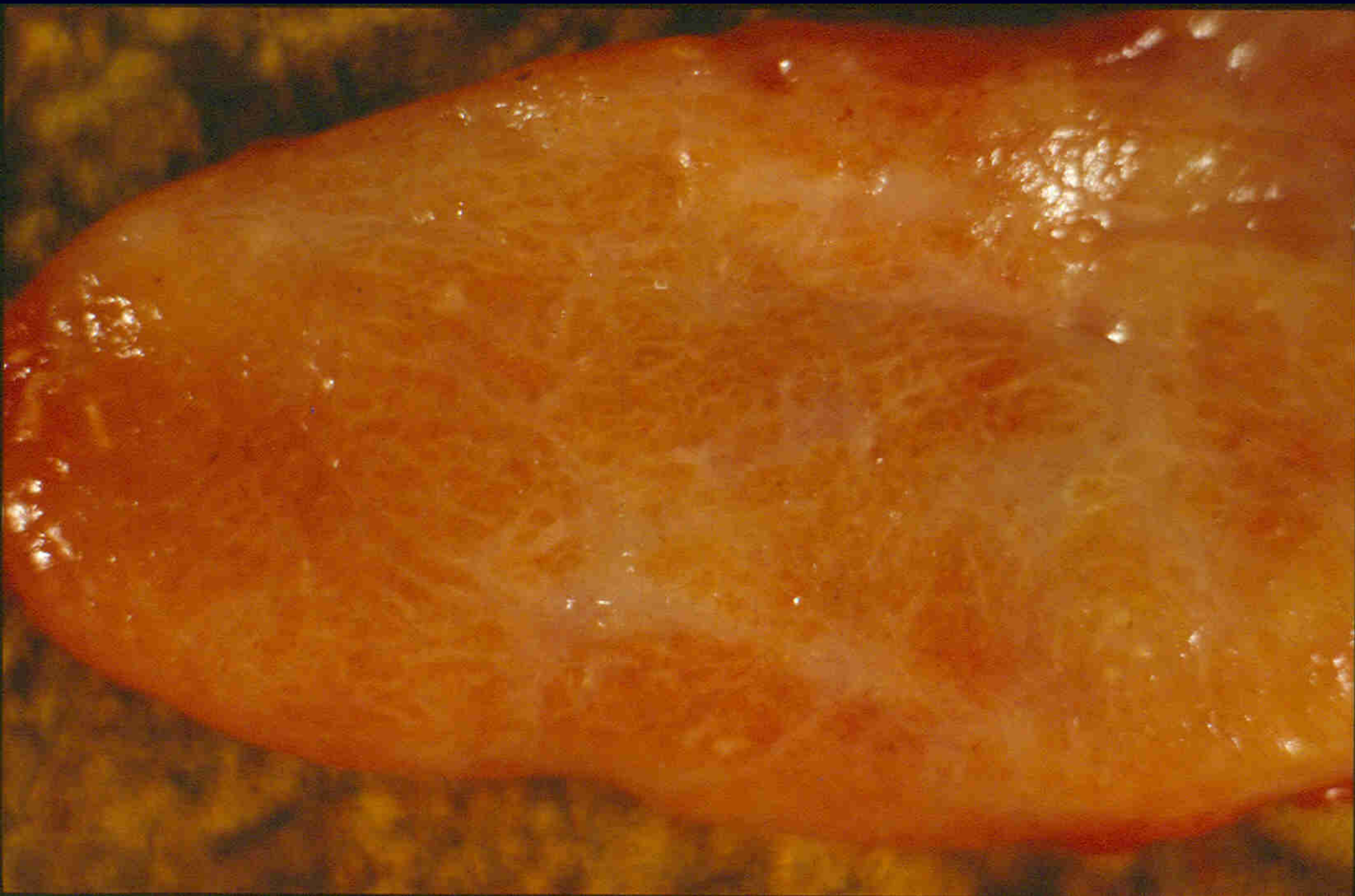


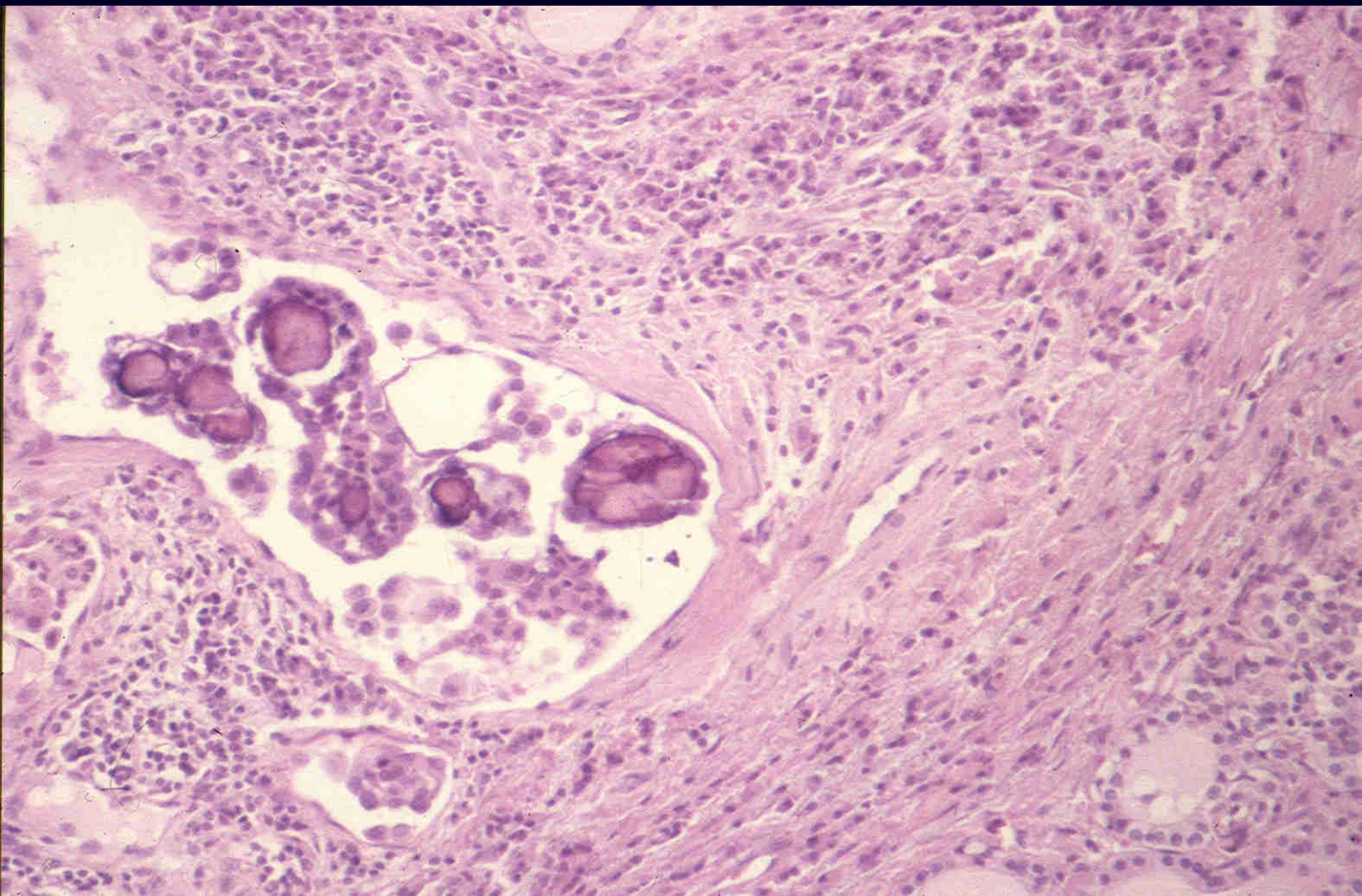


Calcitonin



Micro medullary carcinoma



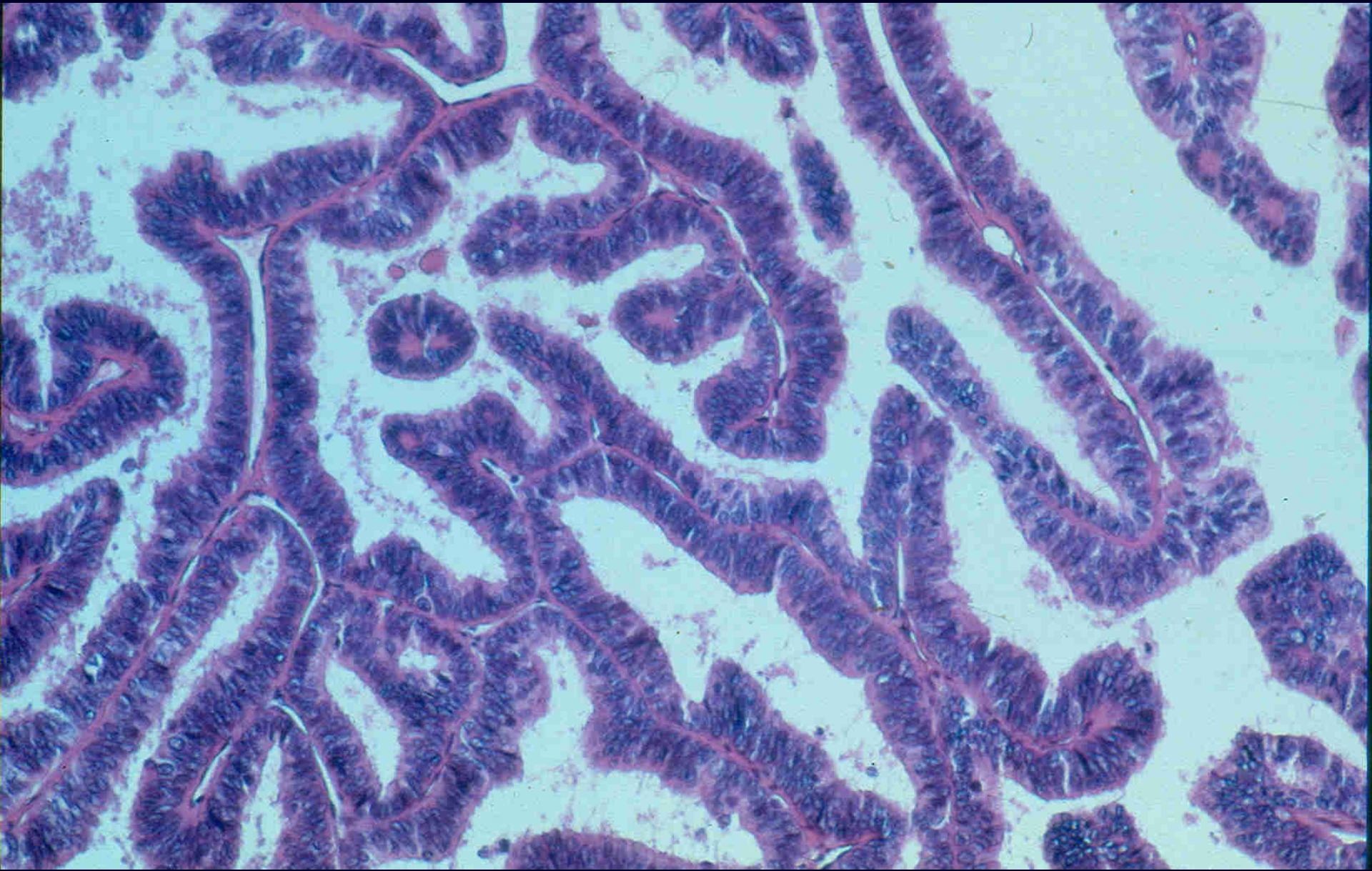




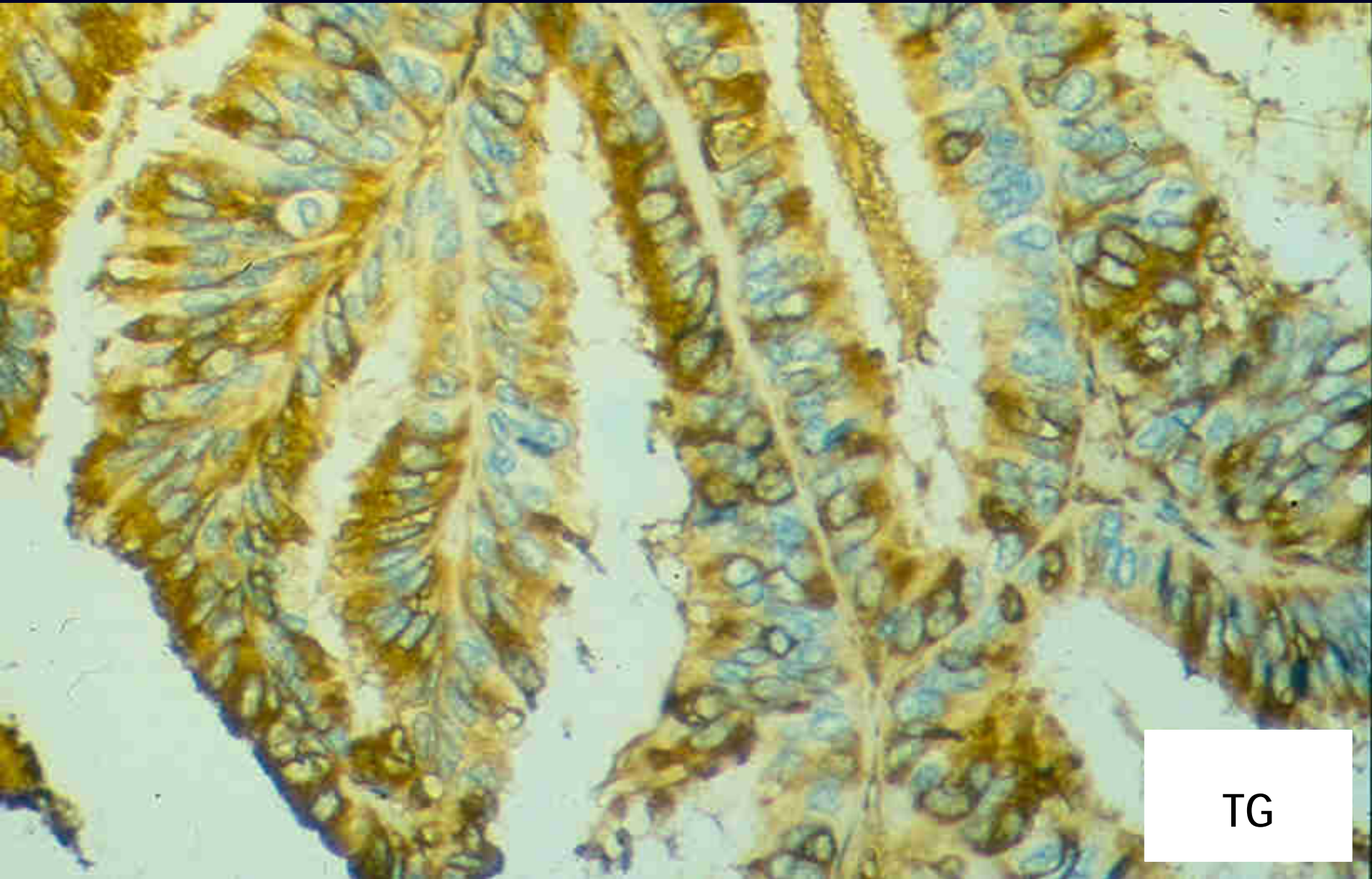
Thyroglobulin

Diffuse sclerosing variant of PTC

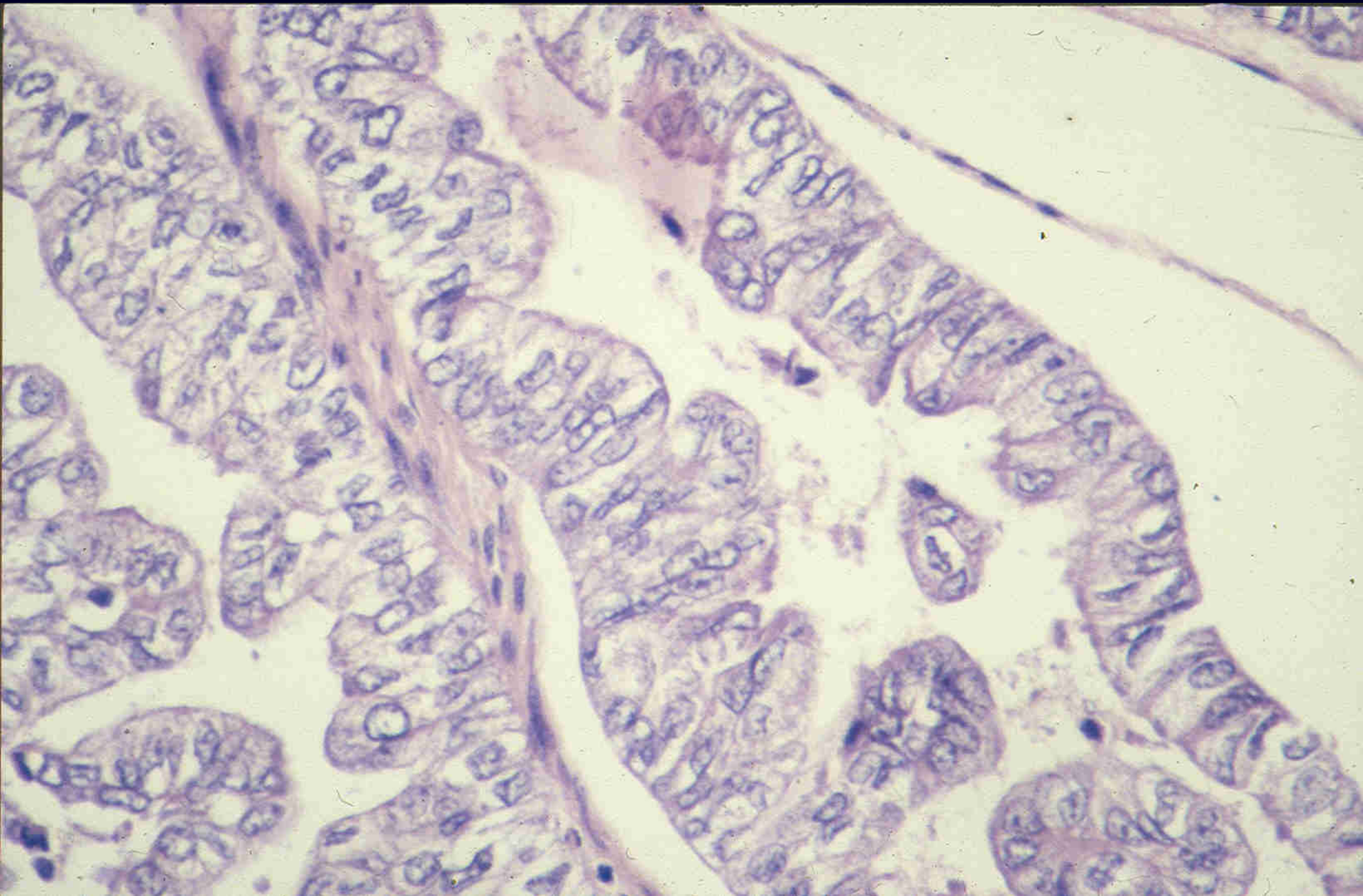
Thyroid tumour in a 56-year-old man with a history of colorectal cancer



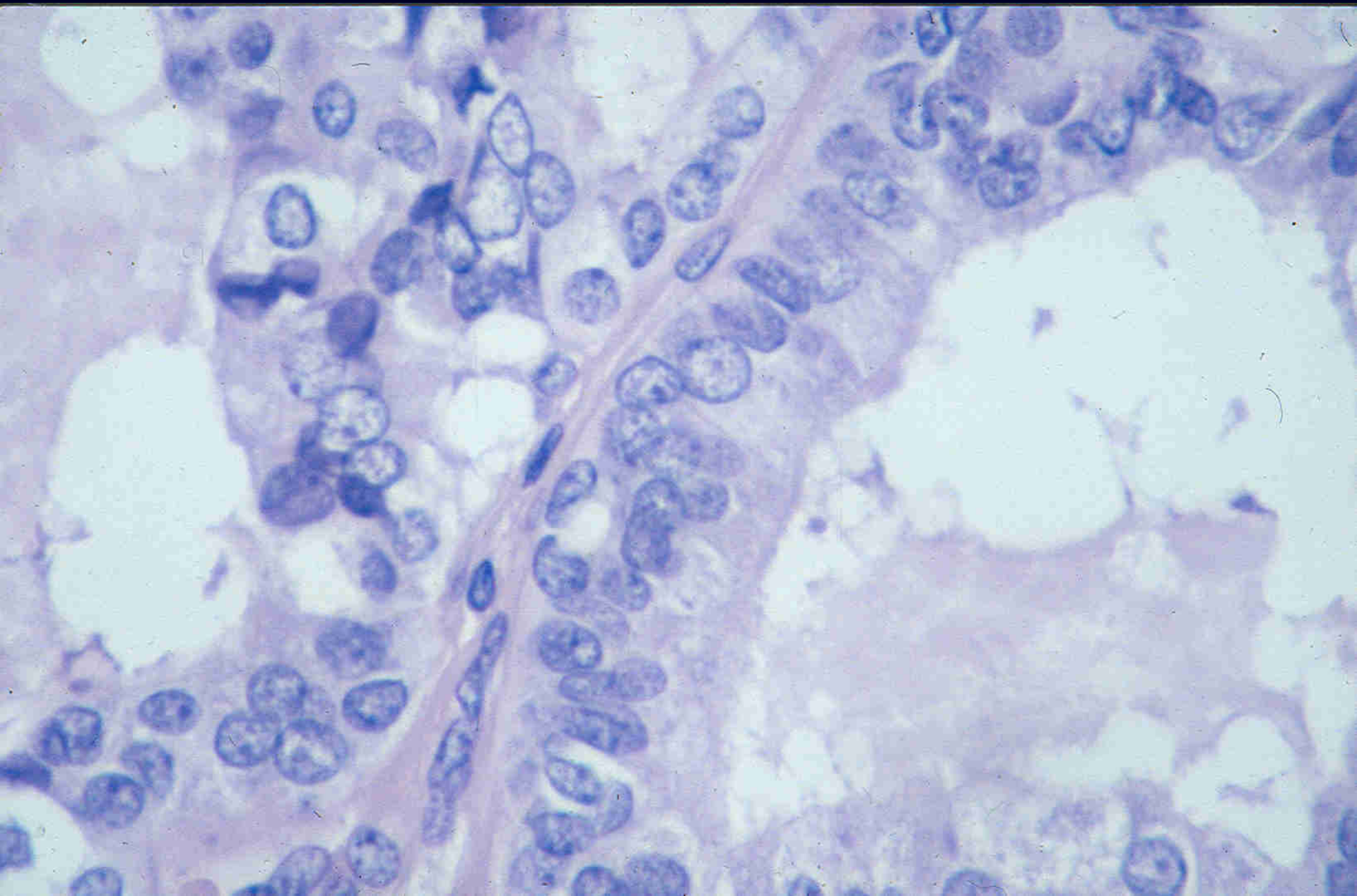
Columnar cell carcinoma



Columnar cell carcinoma



Tall cell/Columnar cell carcinoma/Oncocytic PTC?



PROGNOSTIC MEANING OF HISTOLOGICAL VARIANTS OF PTC

DIFFUSE SCLEROSING VARIANT

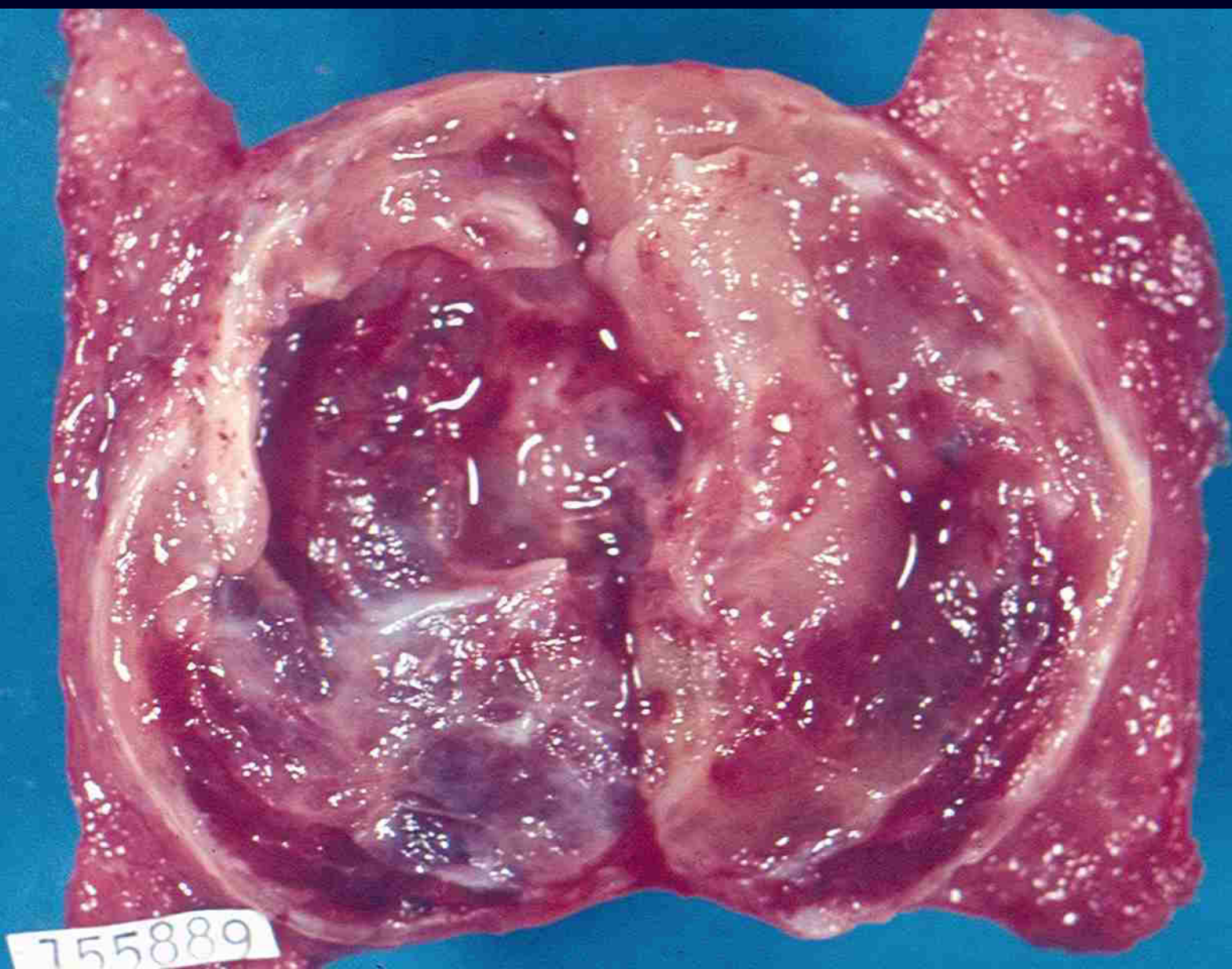
DIFFUSE/MULTINODULAR FVTPC

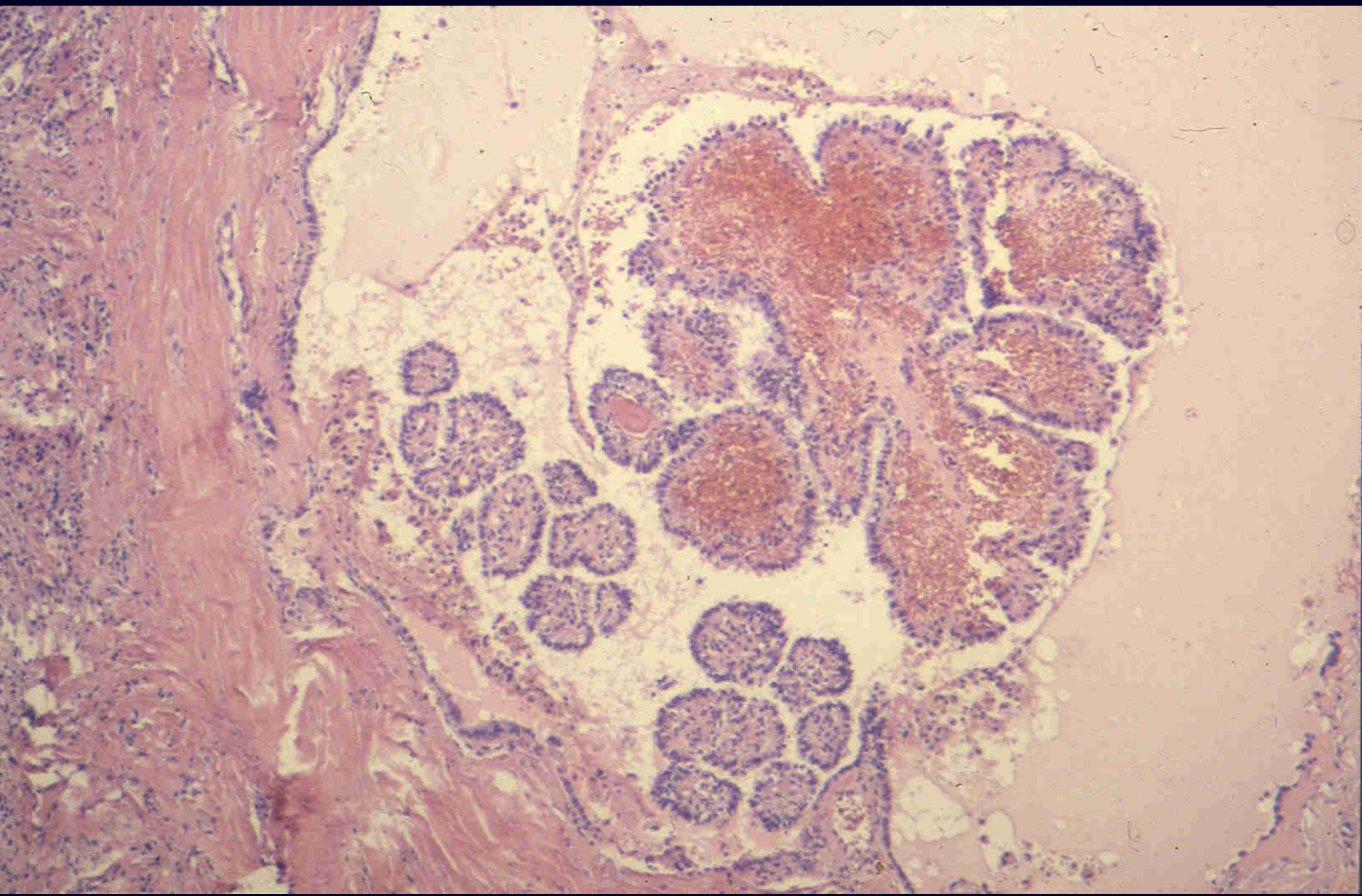
TALL CELL VARIANT

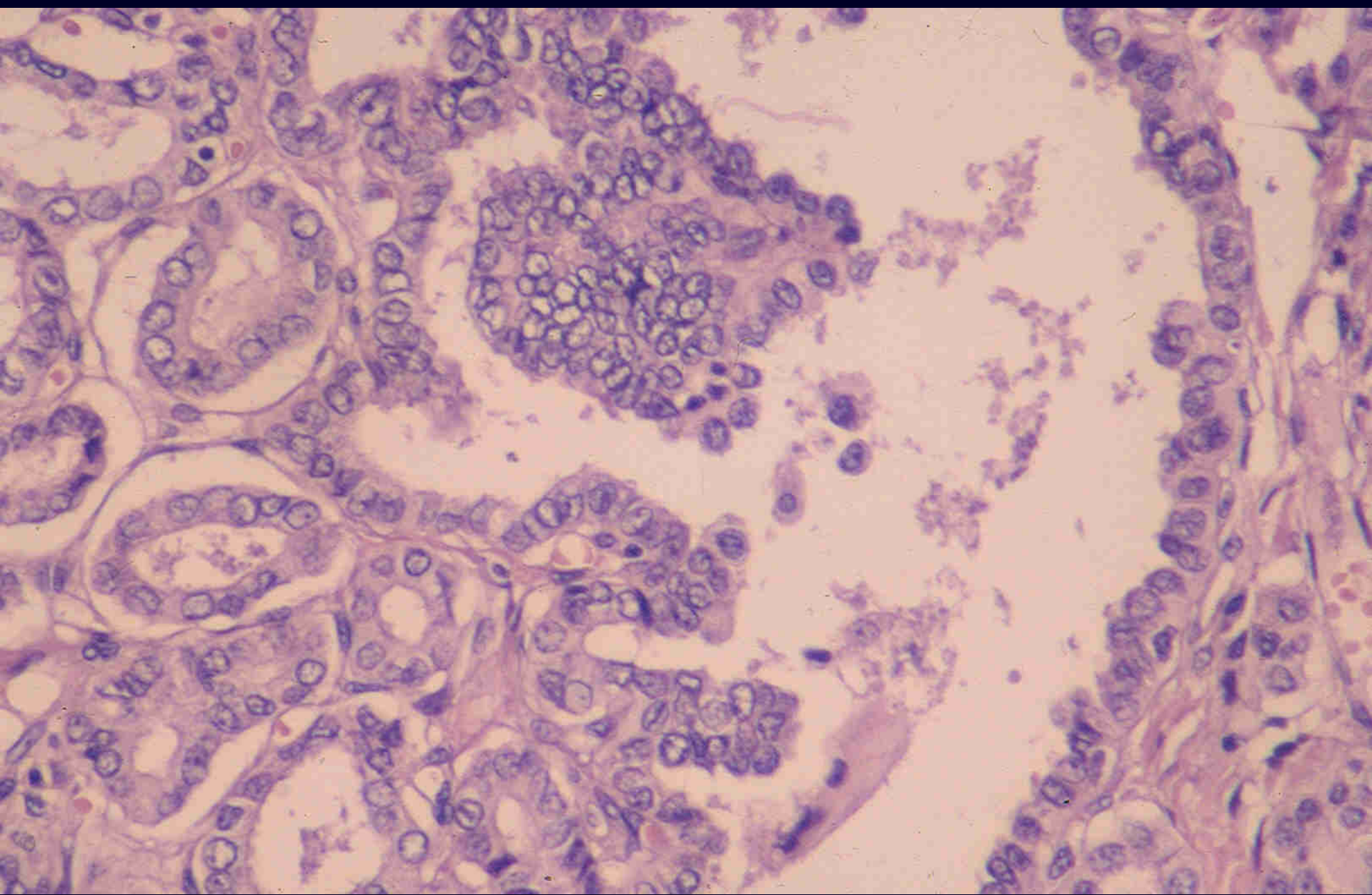
COLUMNAR CELL CARCINOMA

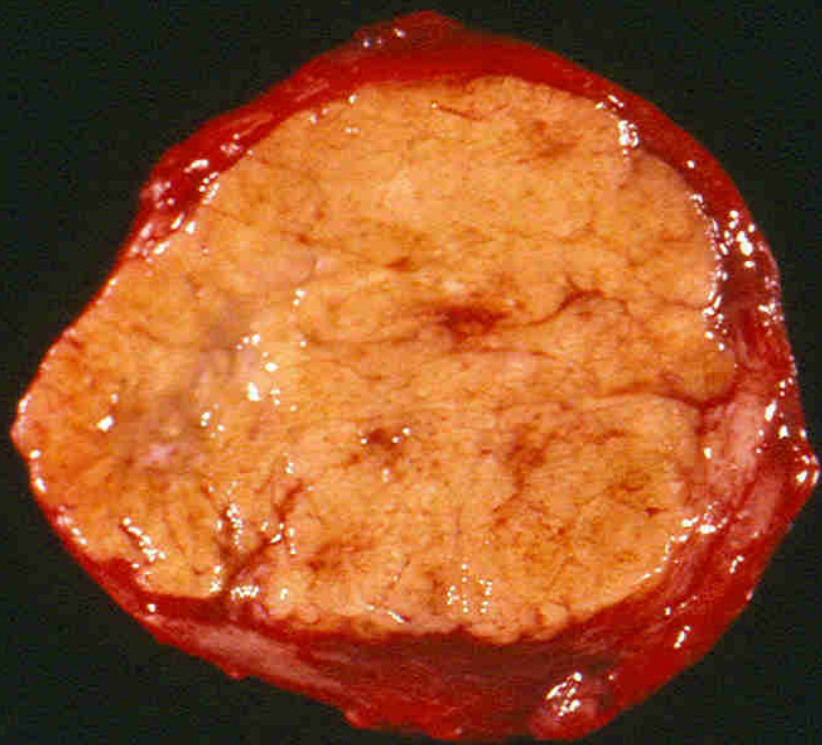
HOBNAIL VAR OF HÜRTHLE CELL PTC(?)

MICROCARCINOMA









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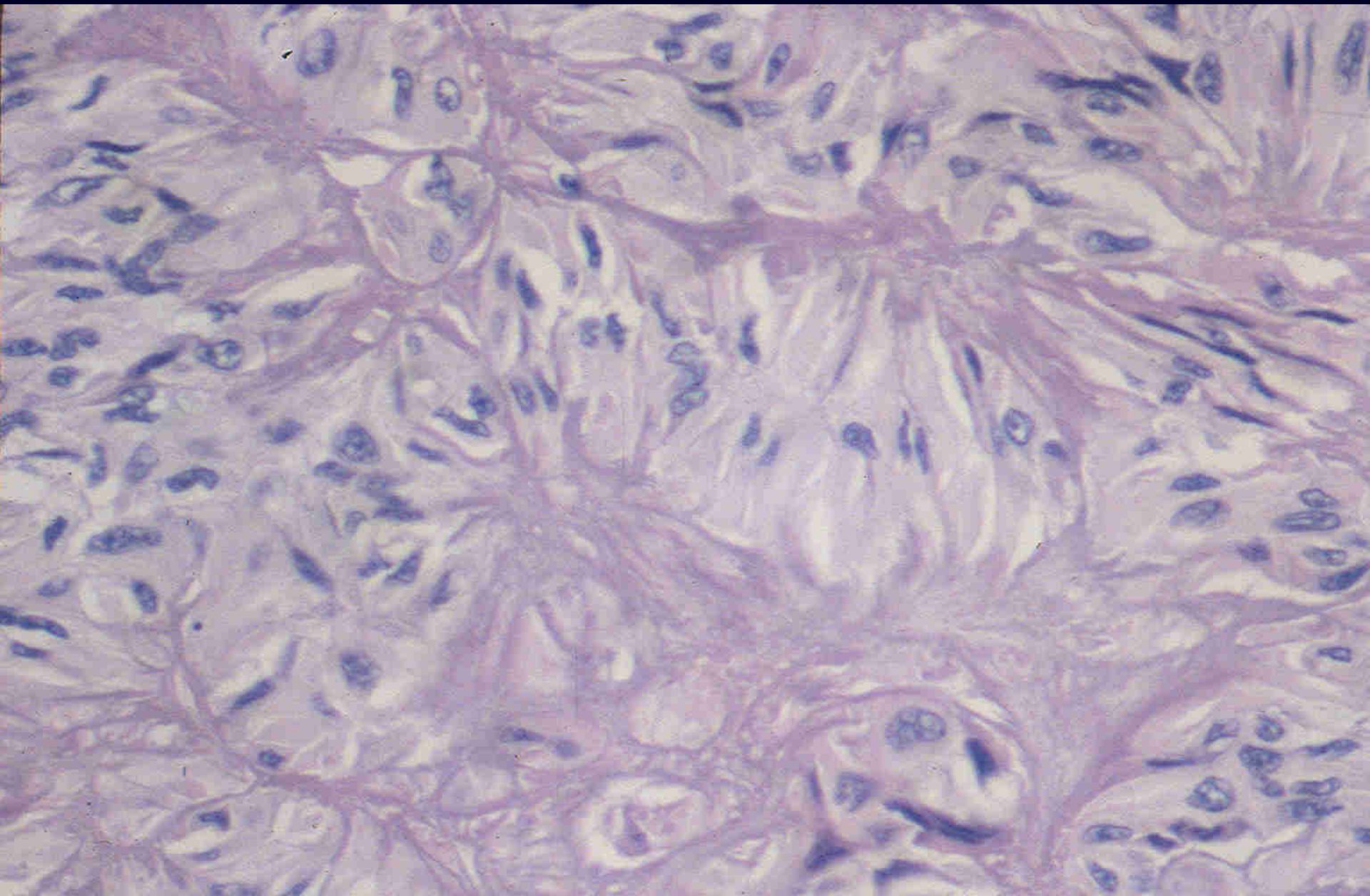
20

4098.87

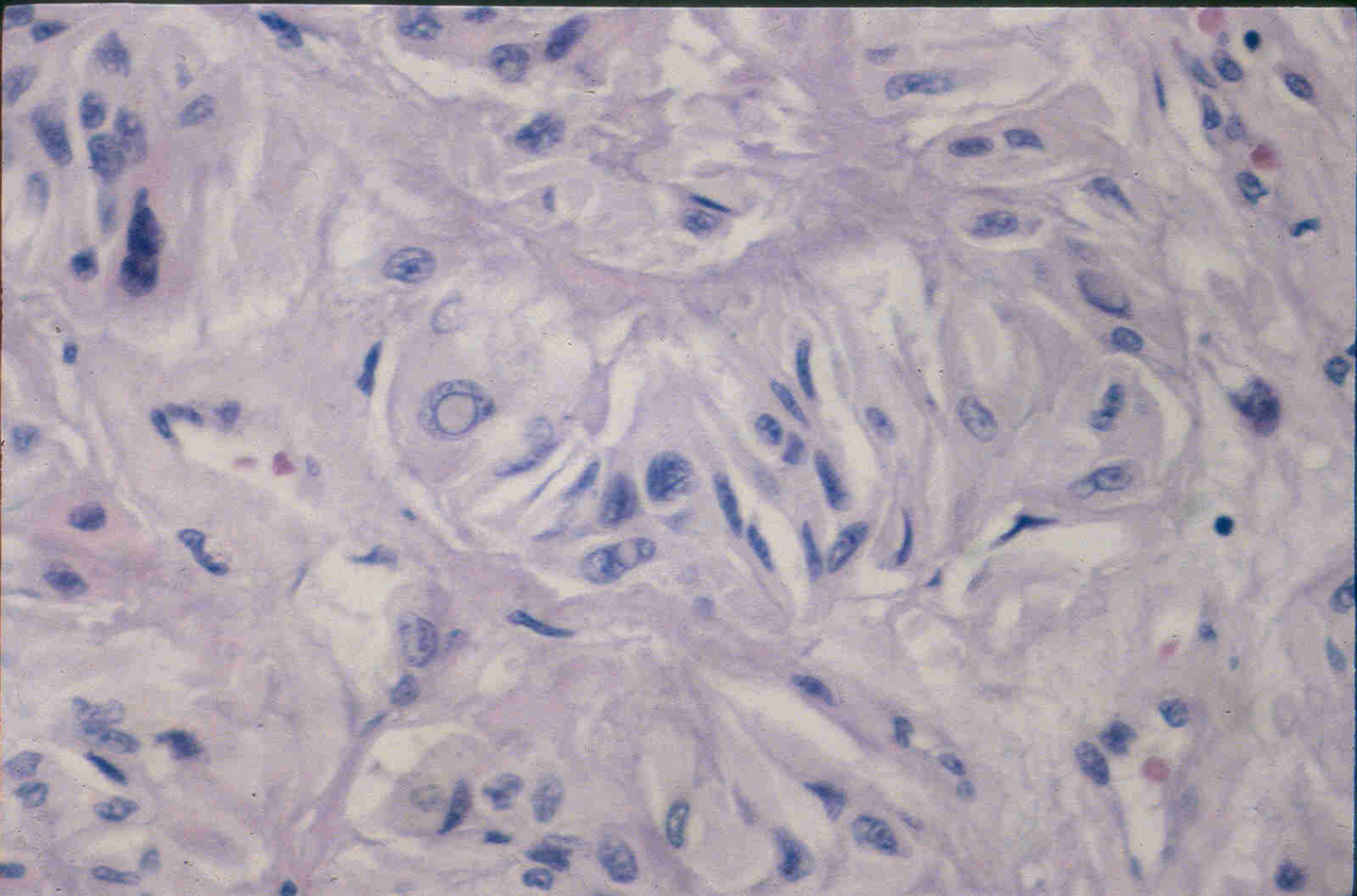


4098.87

Hyalinizing trabecular tumour



Hyalinizing trabecular tumour



PROGNOSTIC FACTORS IN PAPILLARY AND FOLLICULAR THYROID CARCINOMA

Completeness of surgery and responsiveness to radioactive iodine

A – Age

M – Distant metastases

E – Extrathyroid extension

S – Size of the tumours

Vascular invasion

Still debatable: aneuploidy (D...AMES) and molecular features (MIB1, p53, BRAF)

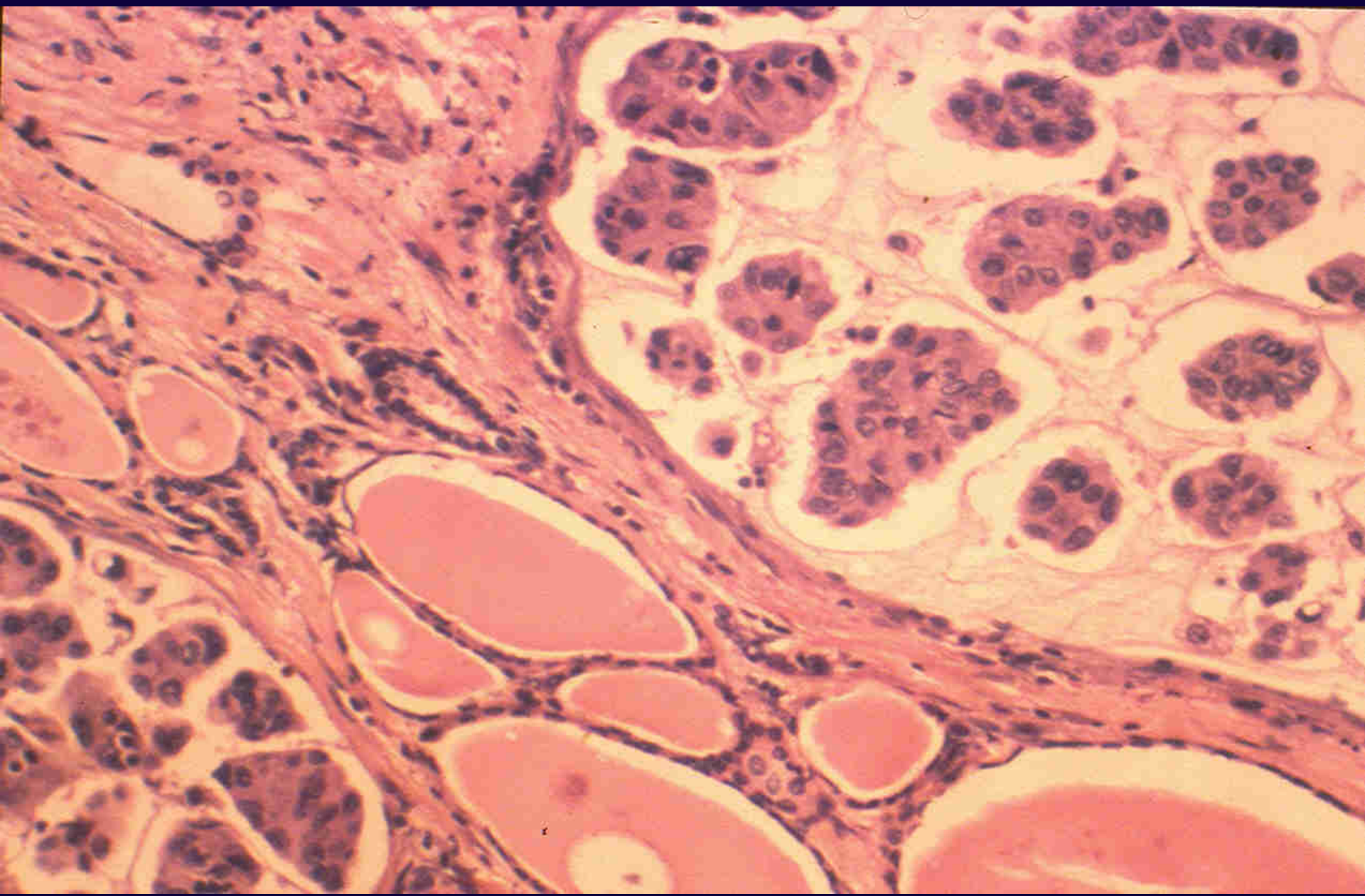
HISTOCHEMISTRY & MOLECULAR PATHOLOGY

Questions to be made whenever facing a strange lesion in the thyroid

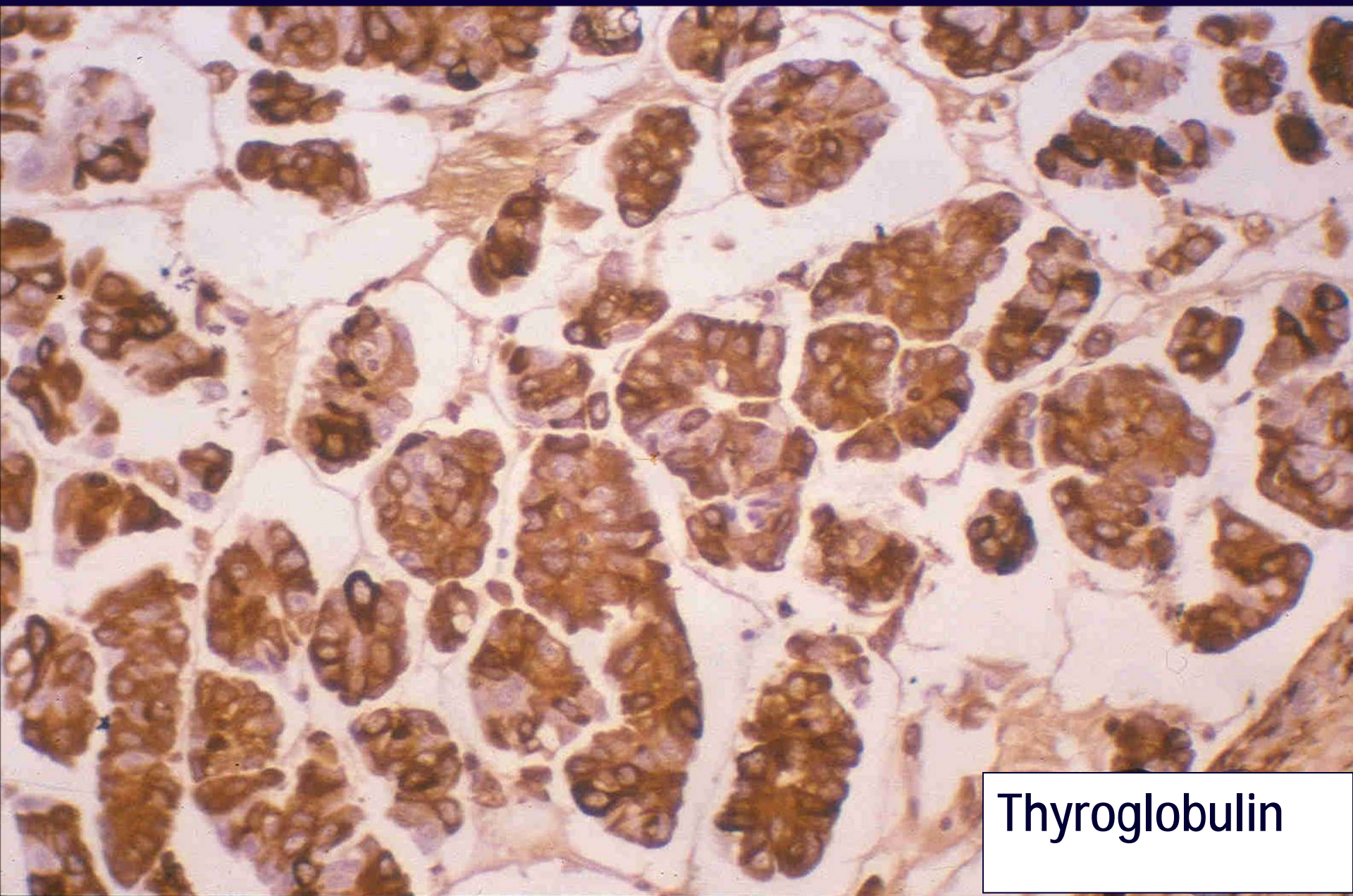
Is it a primary thyroid tumour?

If yes, is it made of follicular or C-cells?

Immunohistochemistry is mandatory: TG and calcitonin (and, if necessary, TTF1)

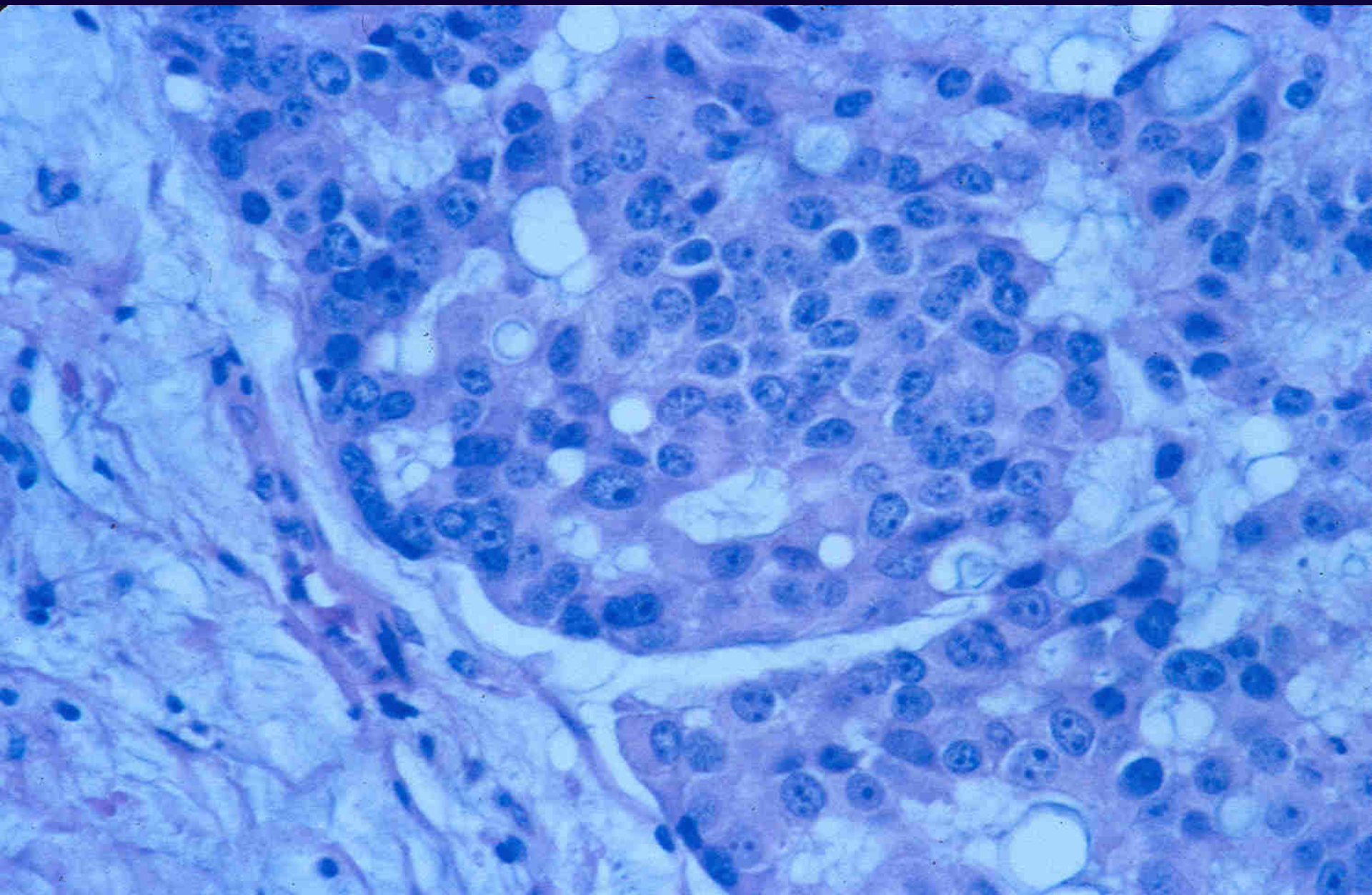


Mucinous tumour

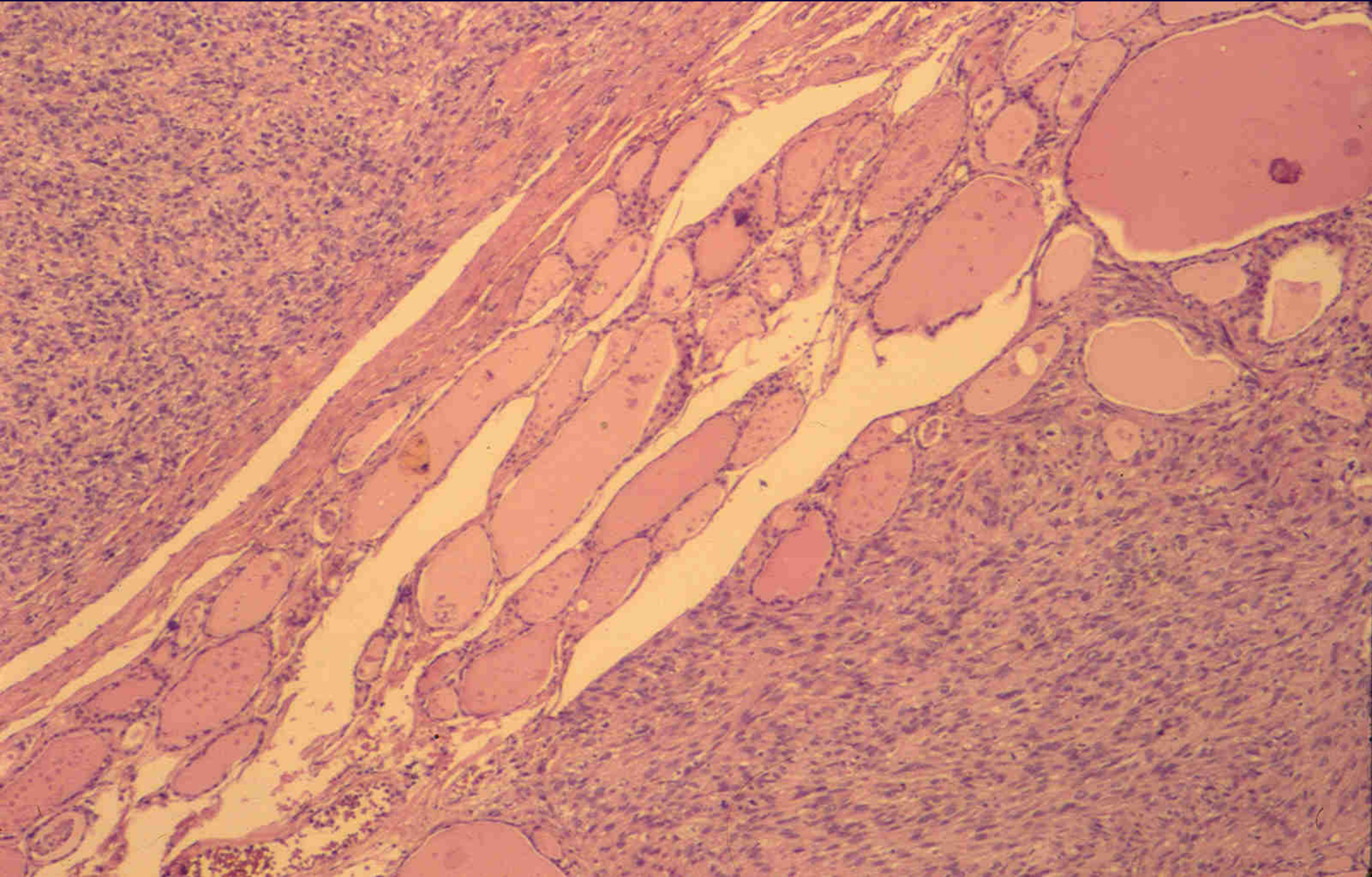


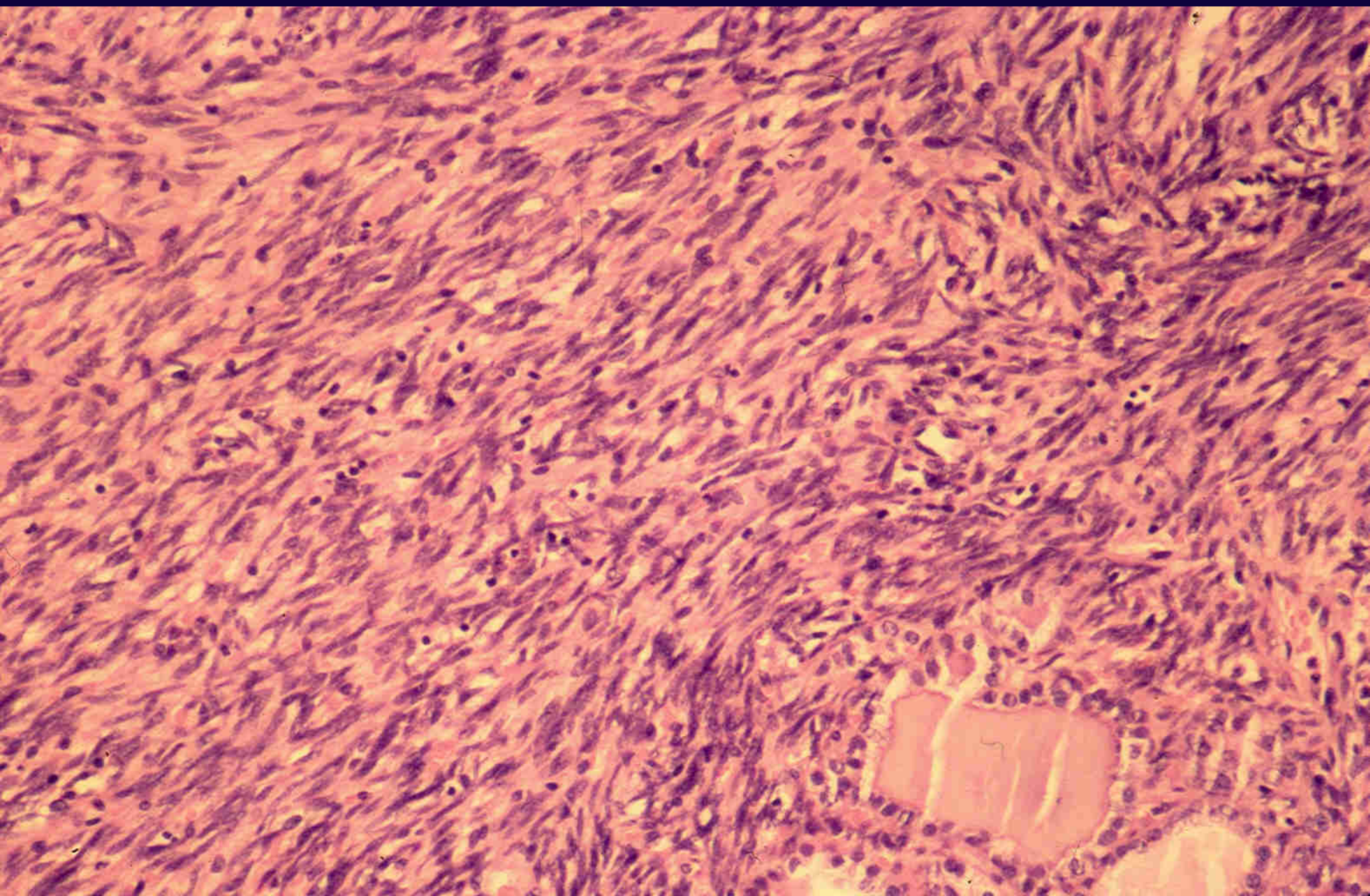
Thyroglobulin

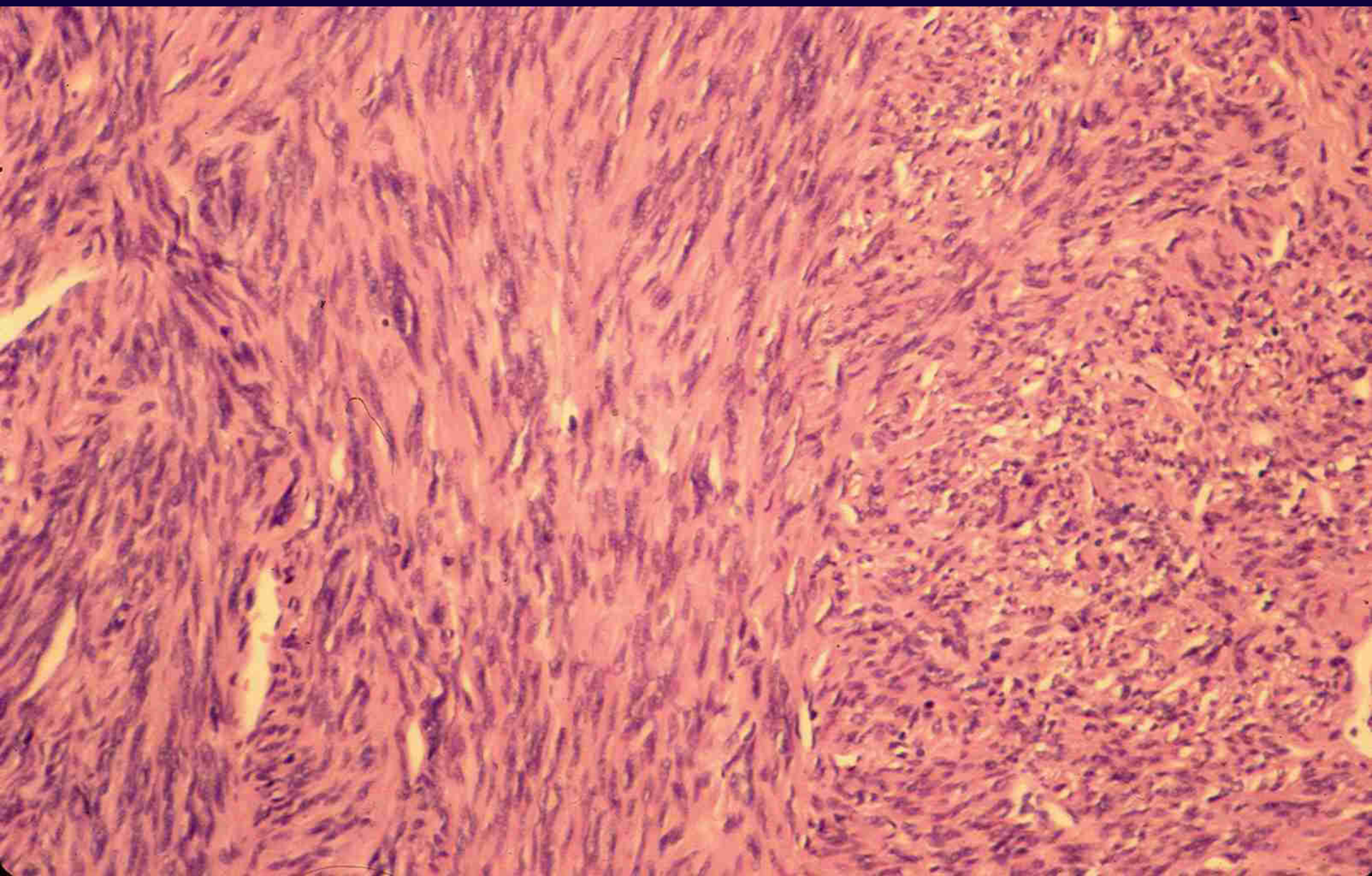
Mucinous tumour

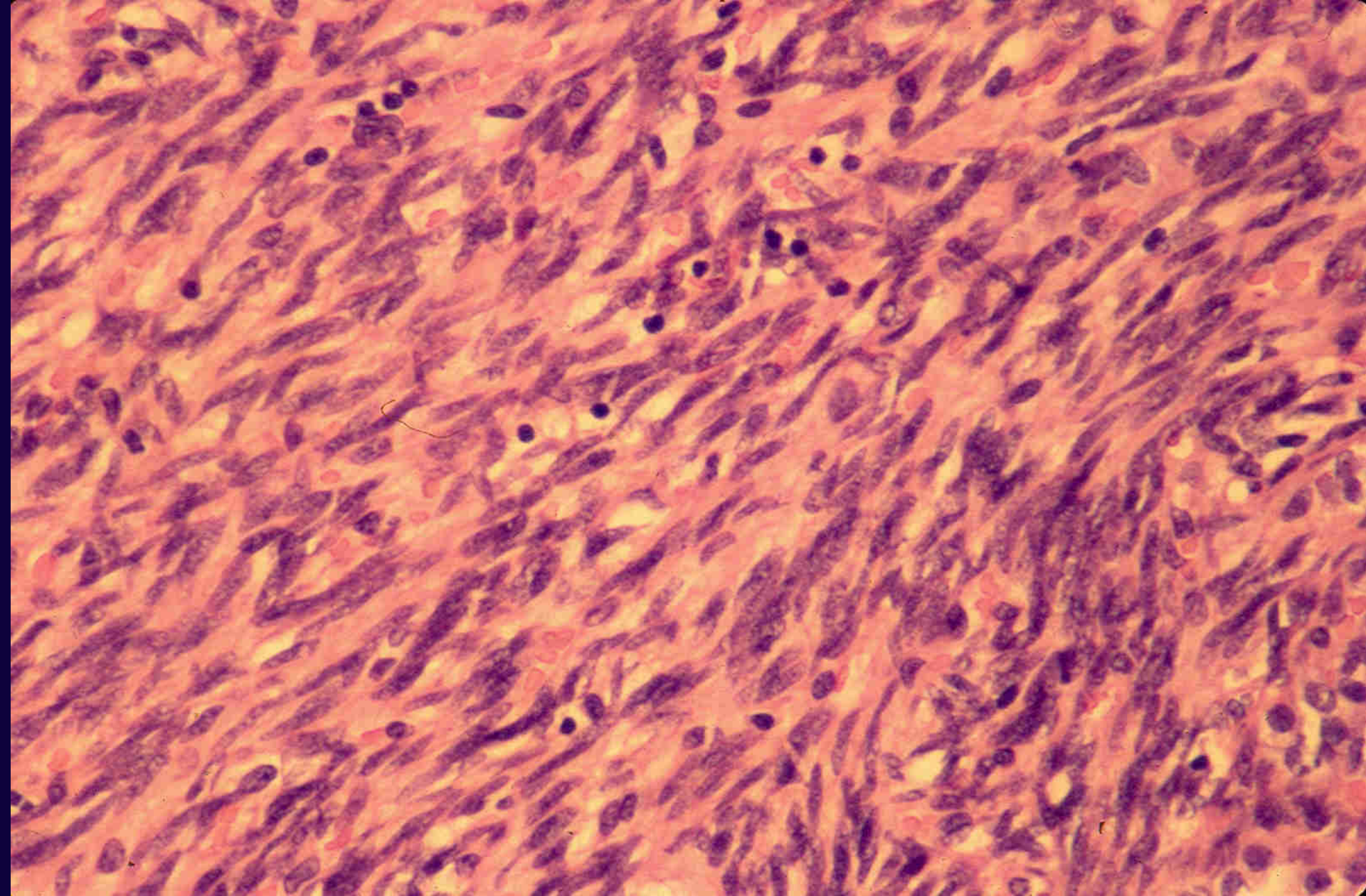


59y,man with a well circumscribed, unencapsulated tumour



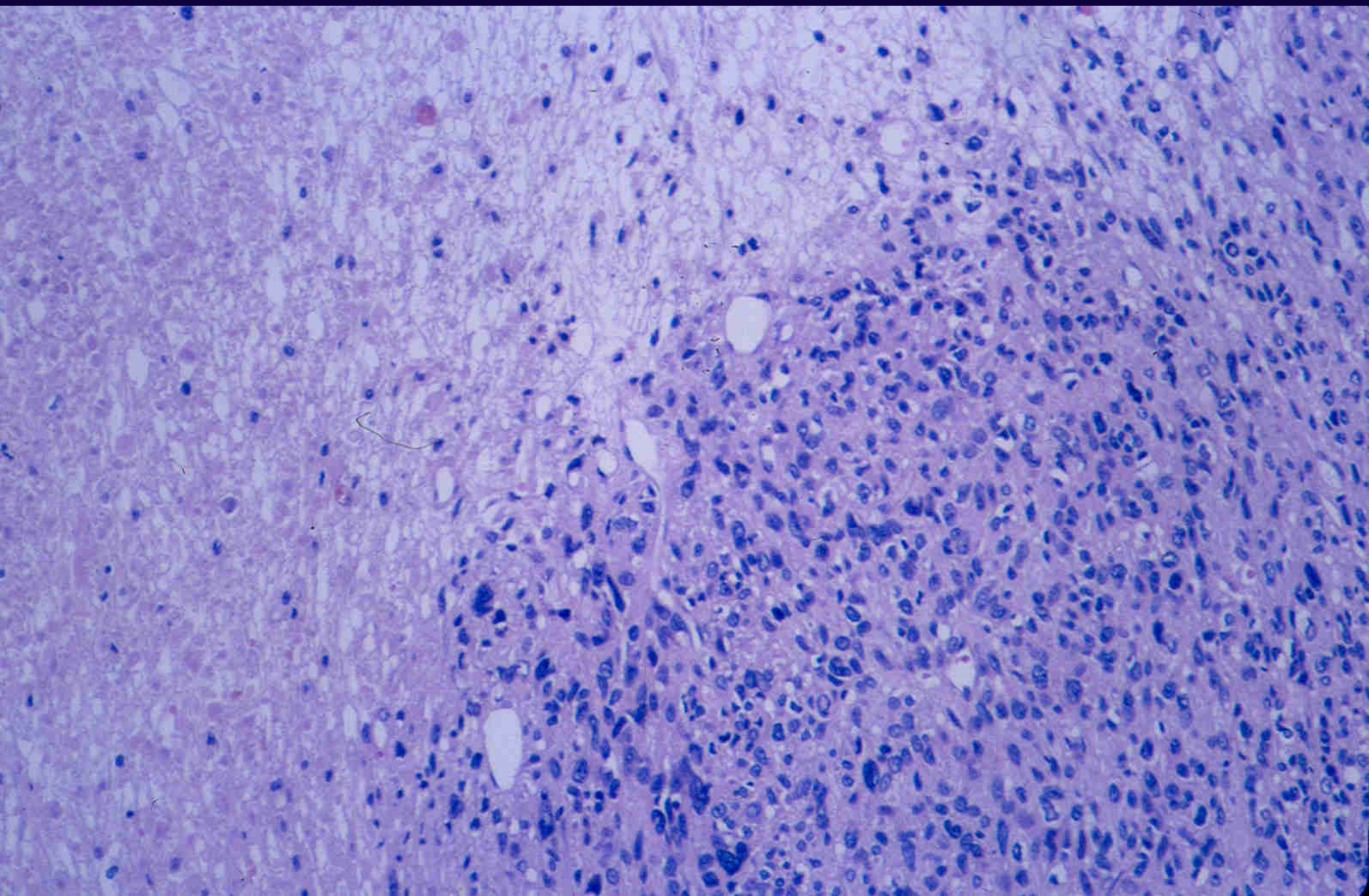


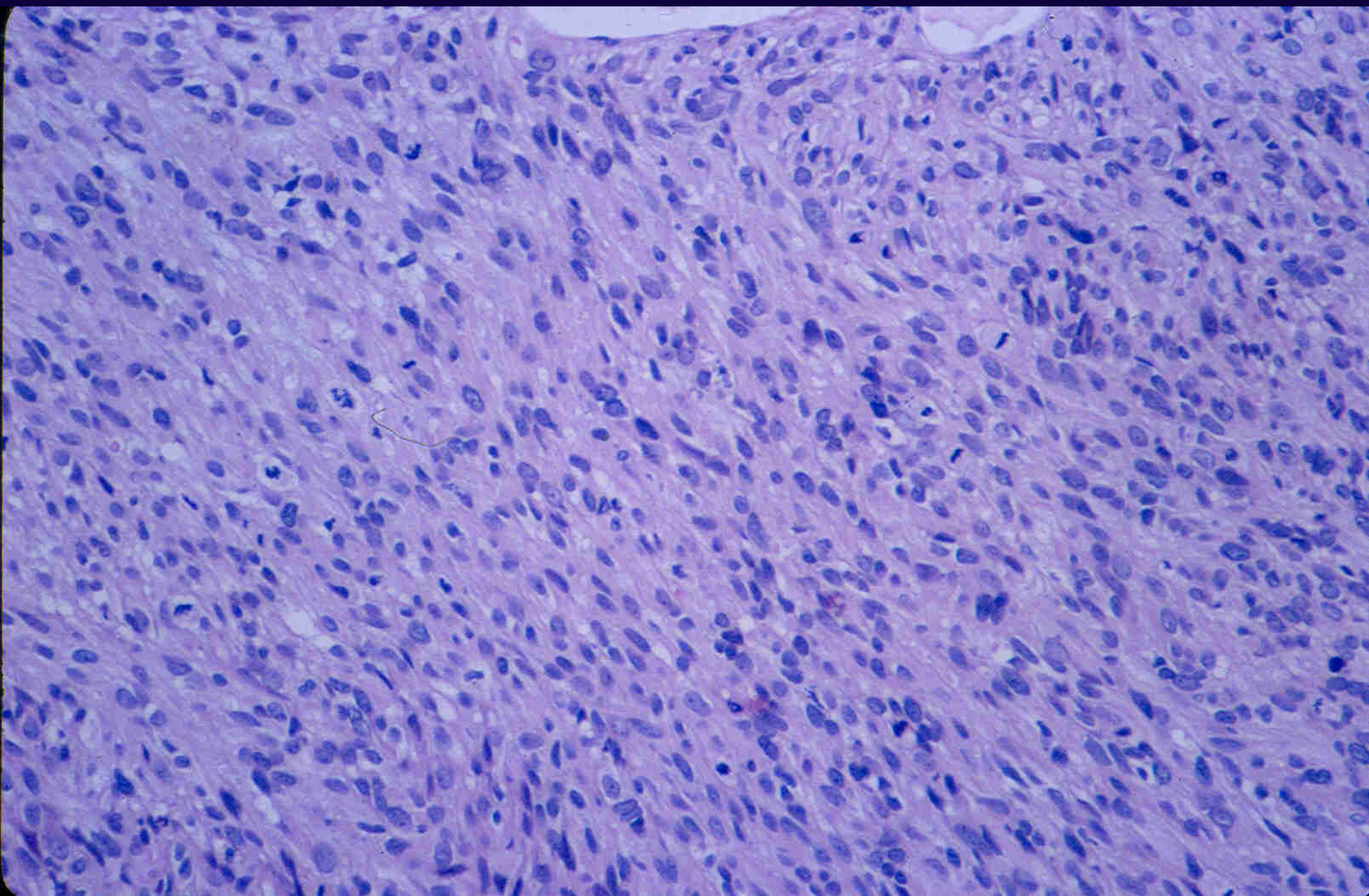


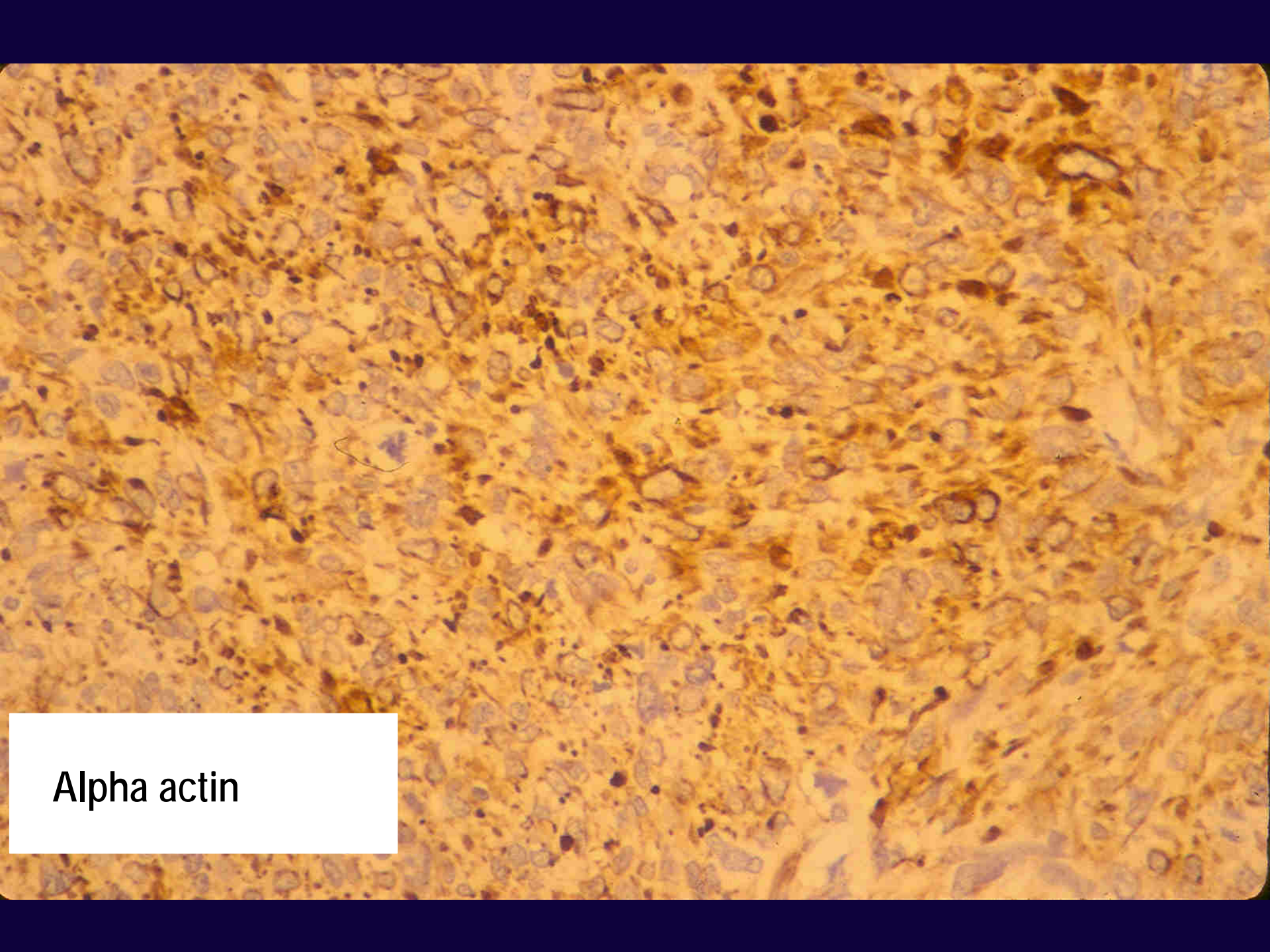


Cytokeratins negative and CD31 positive
Solitary fibrous tumour

58y, woman with an unencapsulated tumour with foci of necrosis



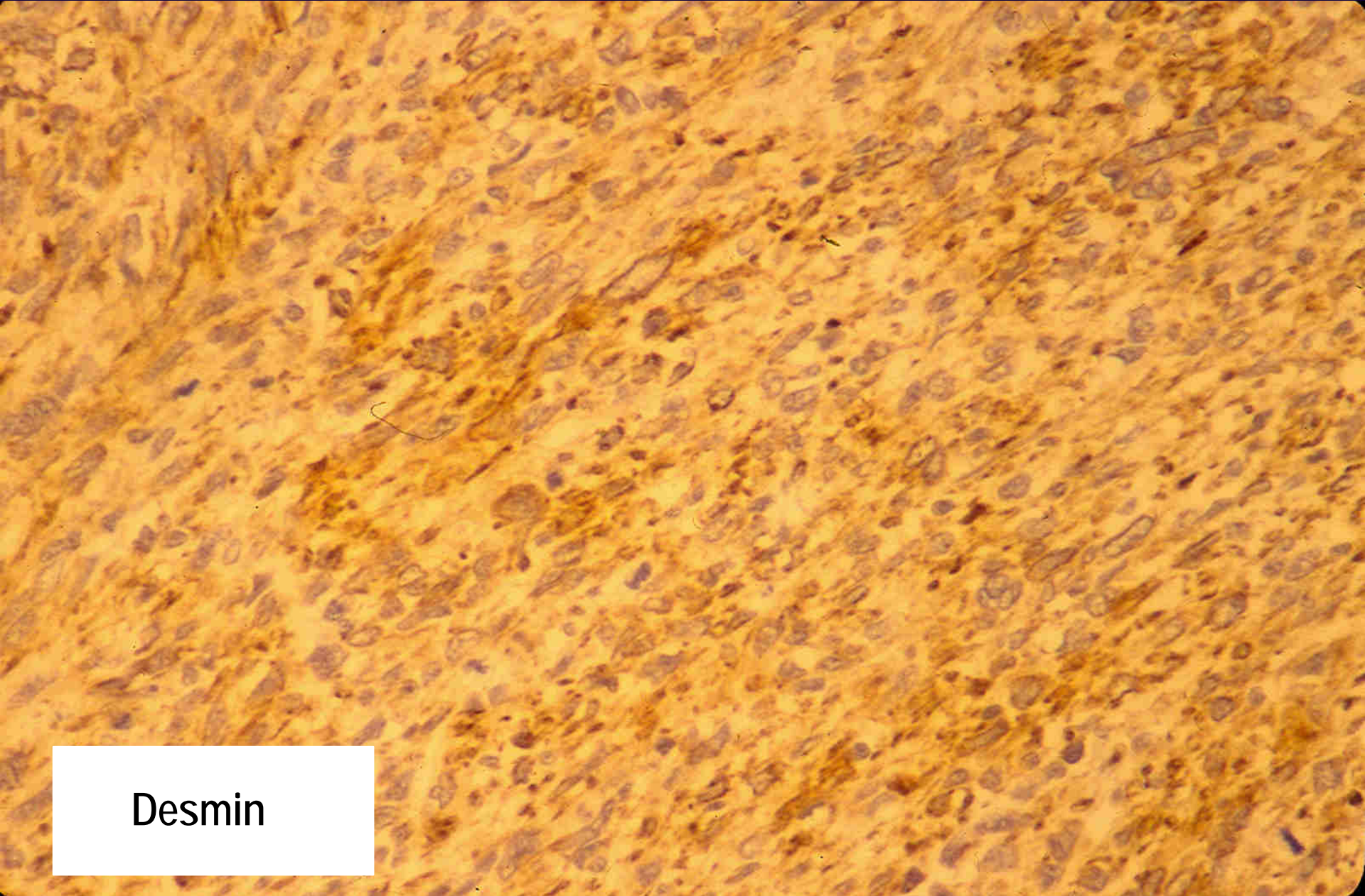




Alpha actin

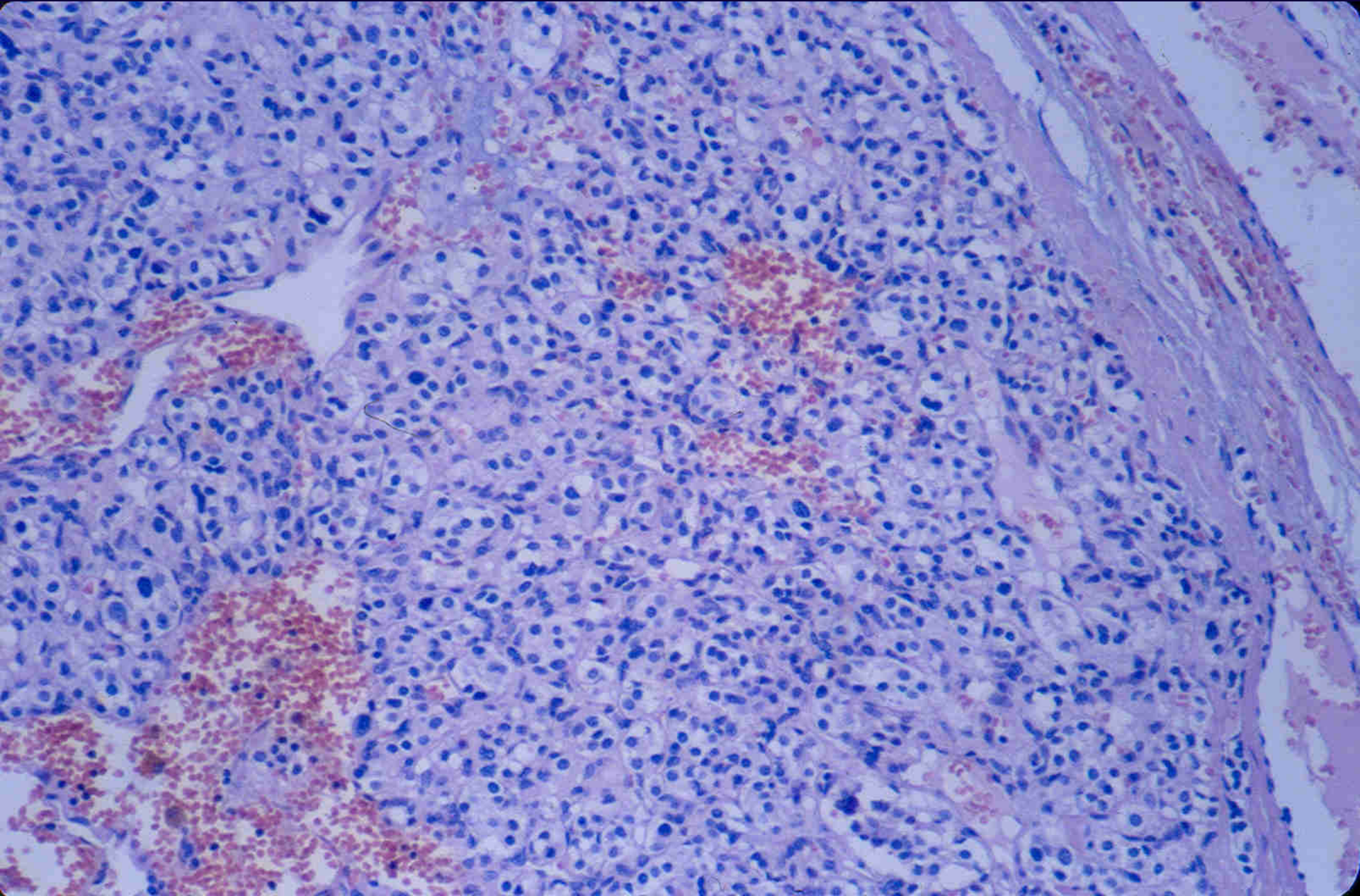
This histological image shows a tissue section stained for Alpha actin. The tissue is densely packed with cells, many of which exhibit prominent, dark brown cytoplasmic staining, indicating the presence of Alpha actin. The nuclei are stained a lighter, more uniform color, likely with hematoxylin. The overall appearance is that of a highly cellular, possibly neoplastic, tissue sample.

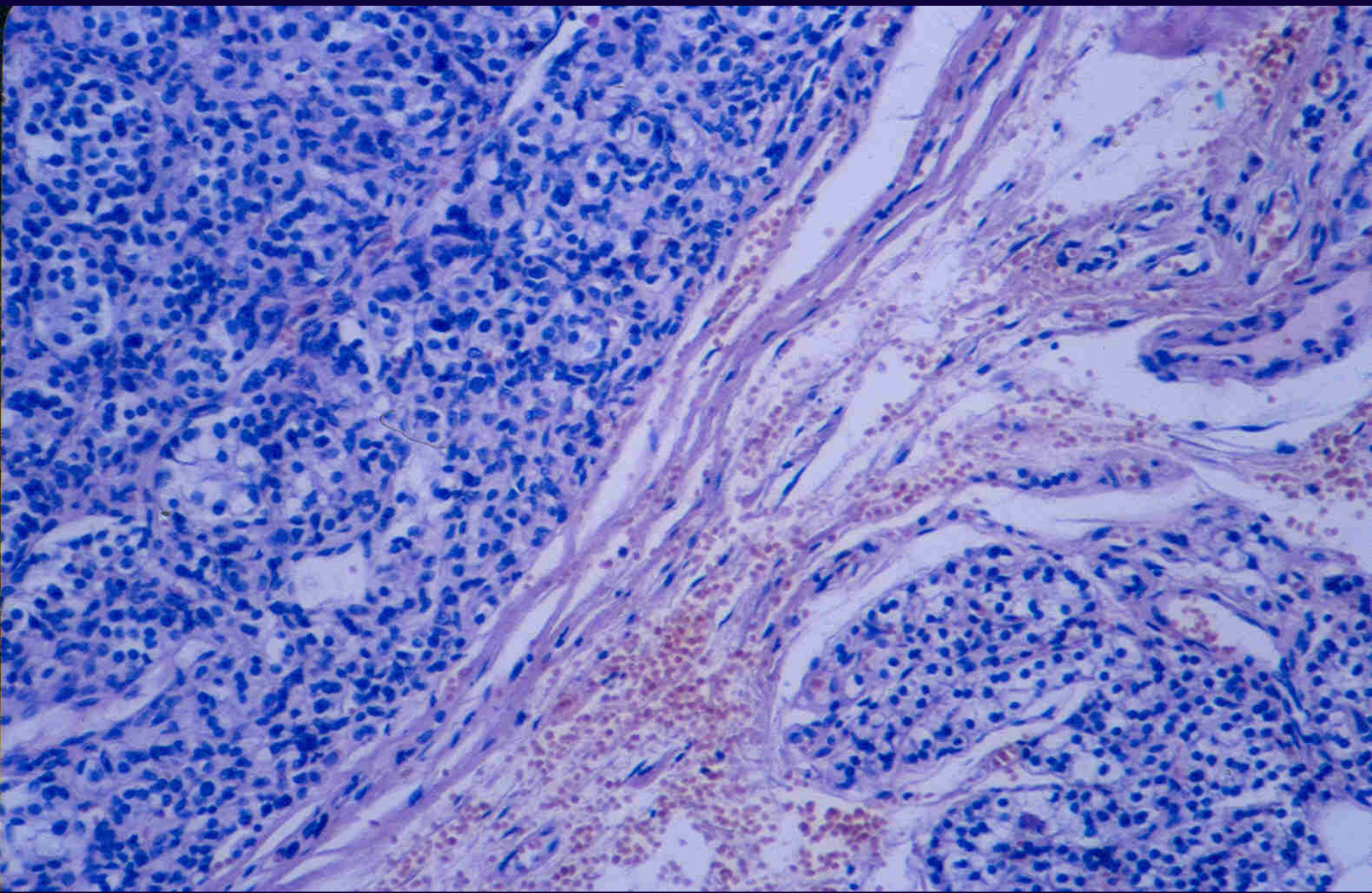
Metastasis from a retroperitoneal leiomyosarcoma

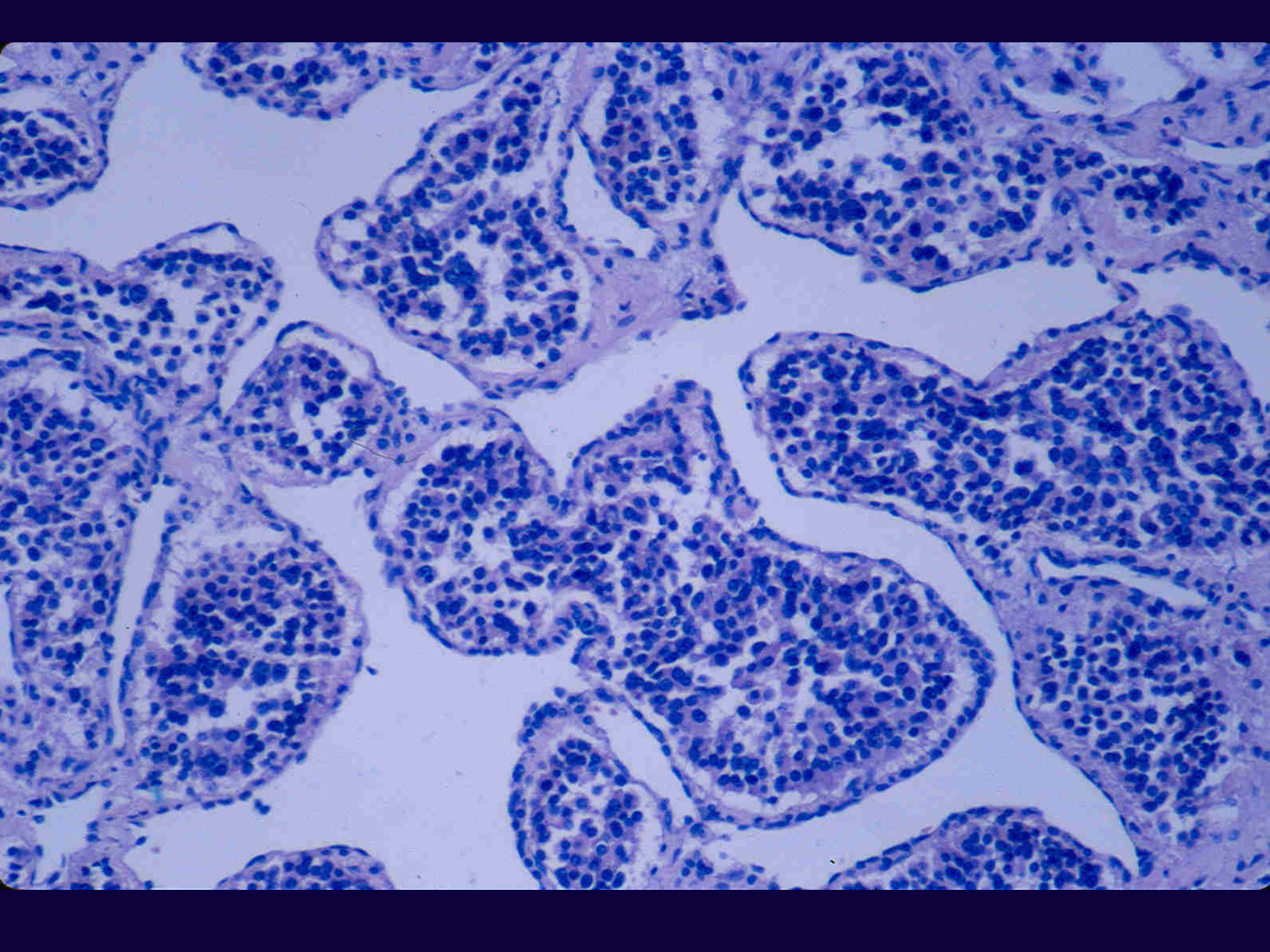


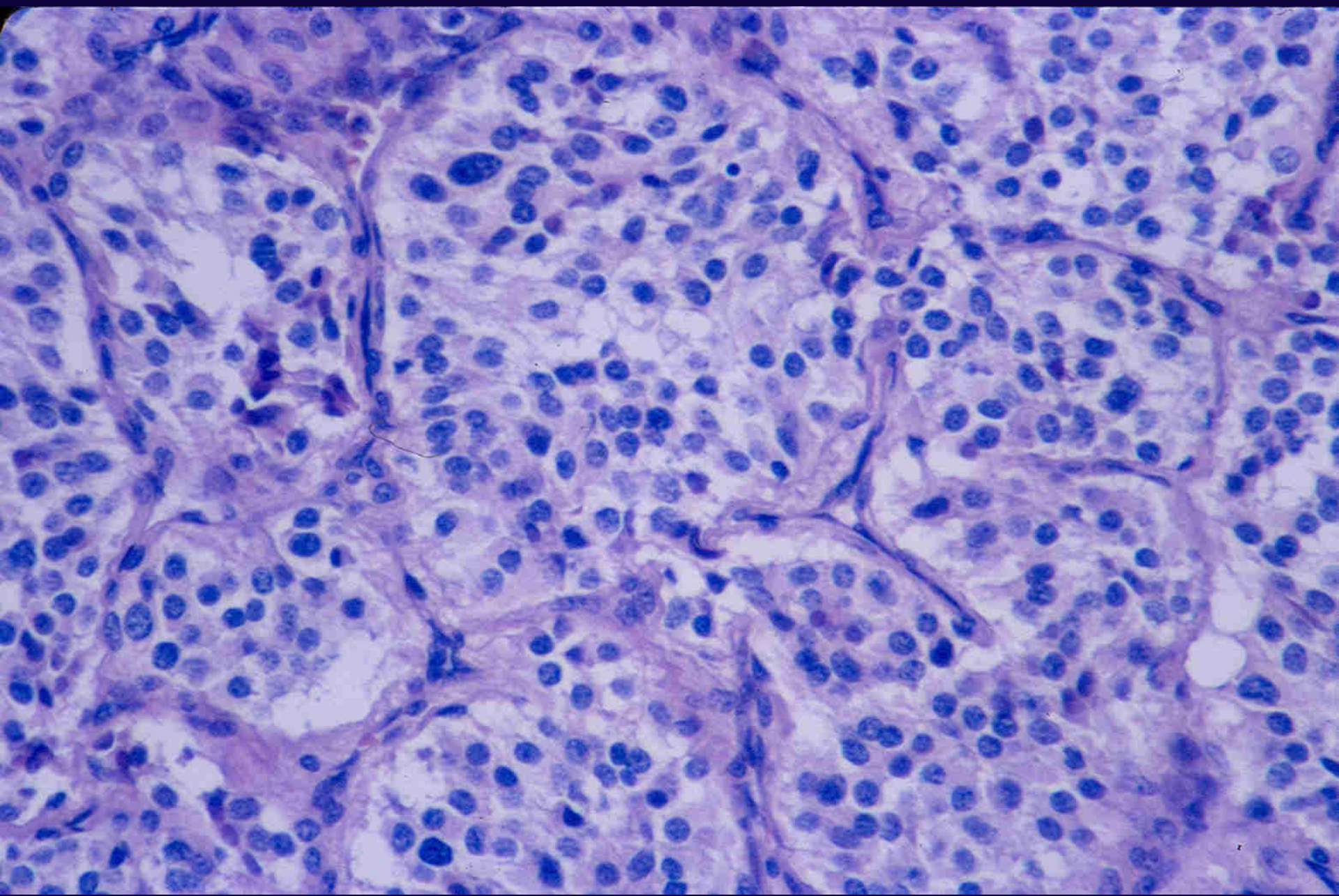
Desmin

Thyroid tumour in a 22 year-old woman

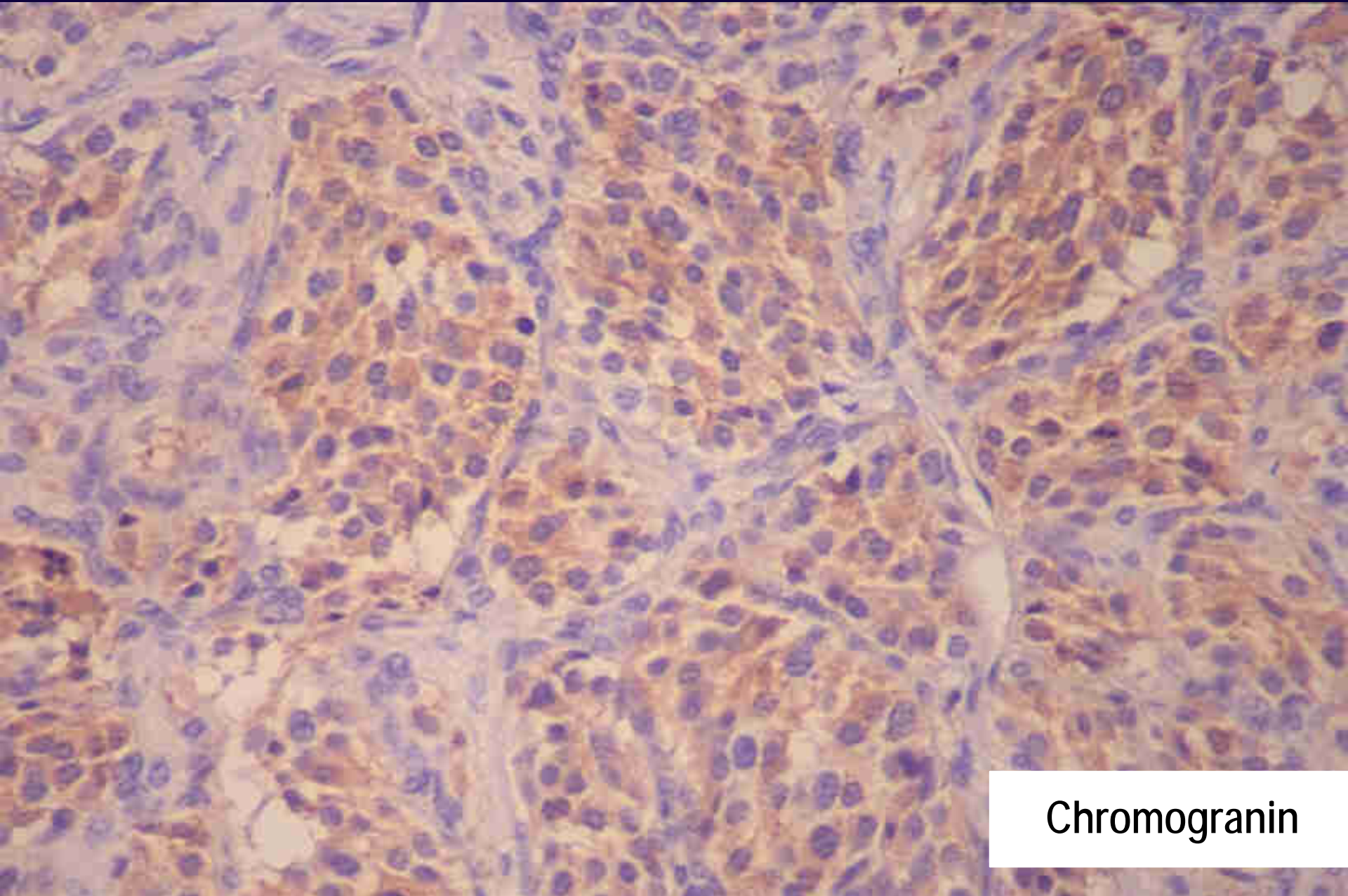






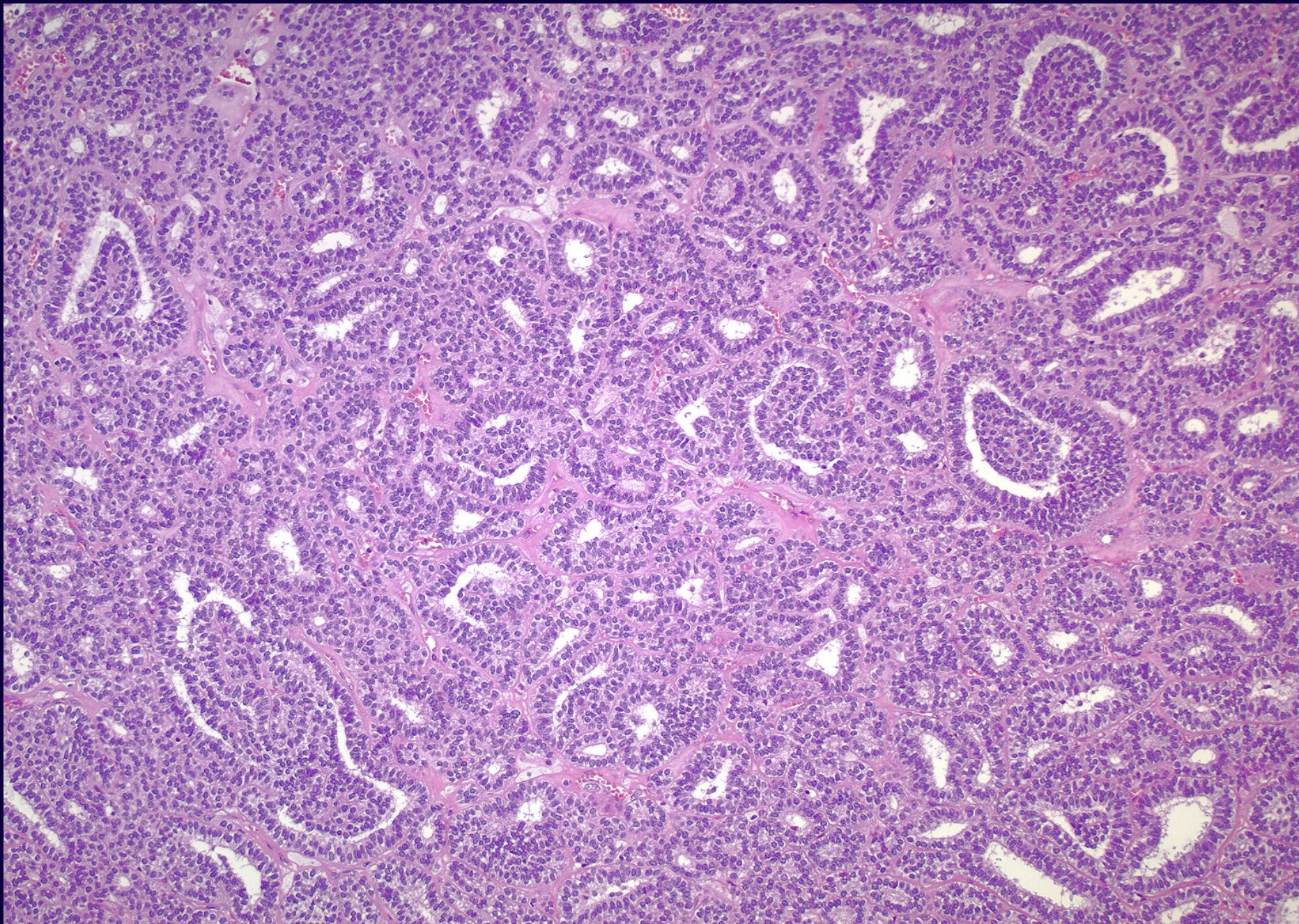


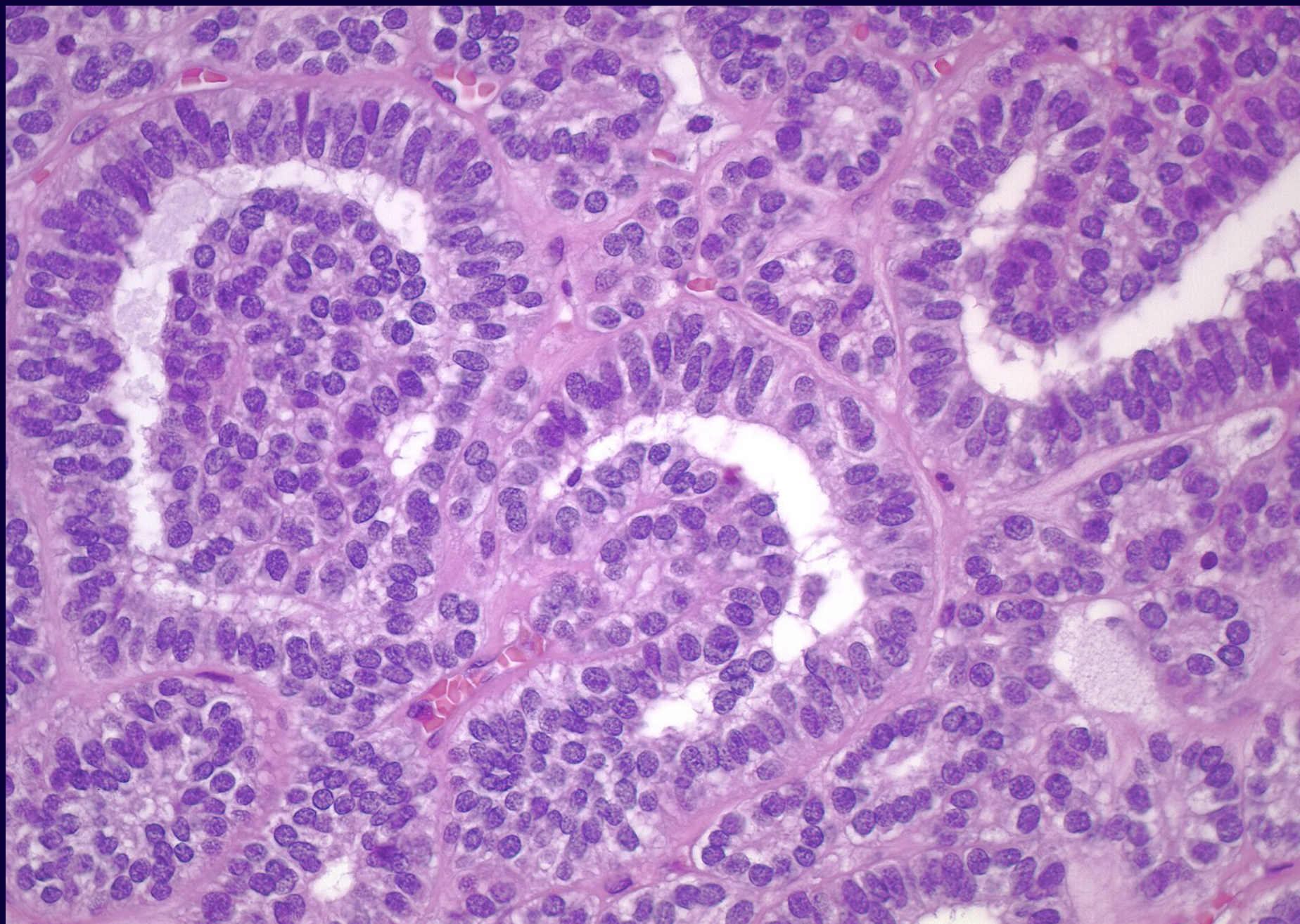
Paraganglioma

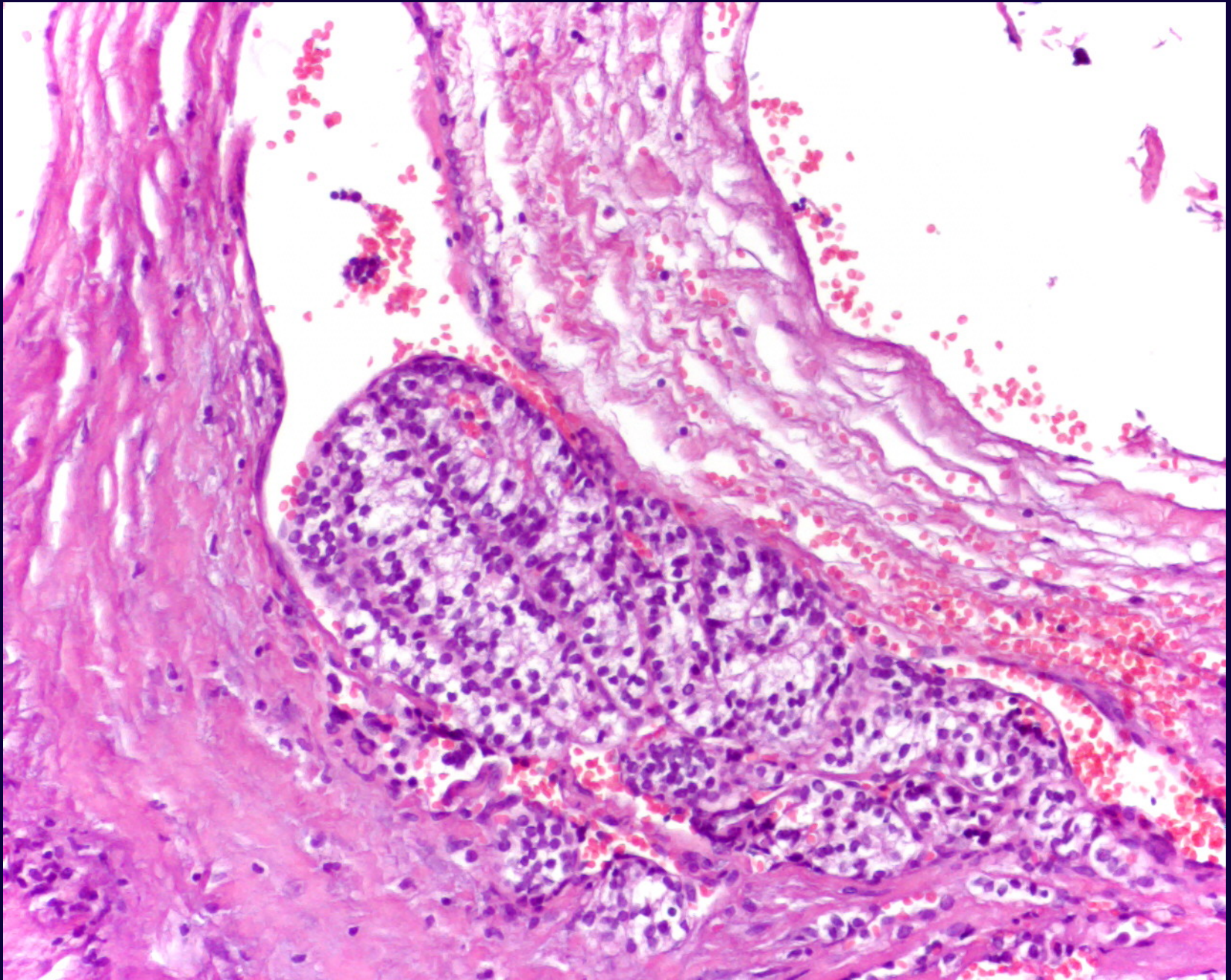


Chromogranin

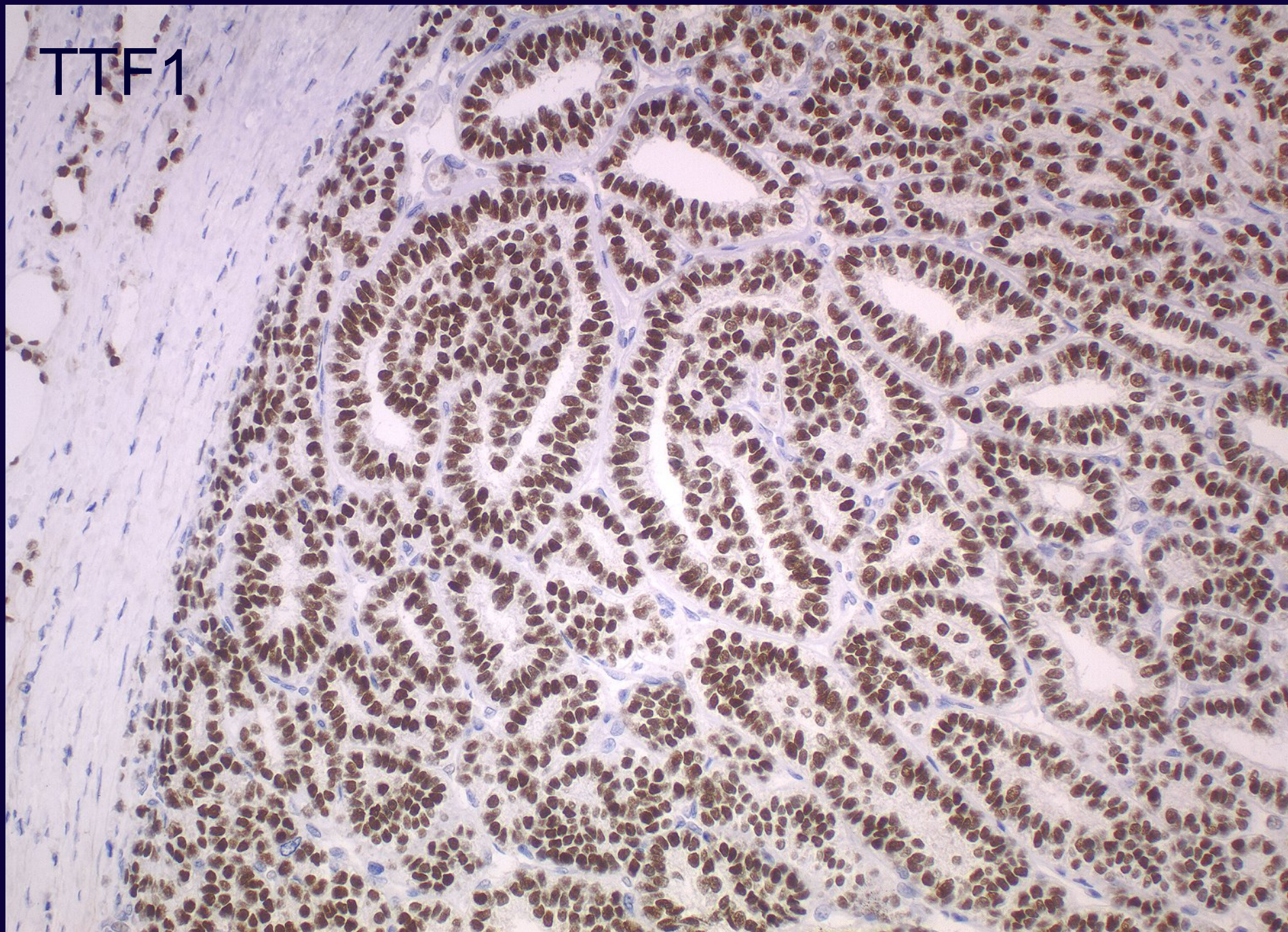
Thyroid tumour in a 56-year-old woman. No familial history







TTF1





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Case study

Follicular thyroid carcinoma with an unusual glomeruloid pattern of growth ☆

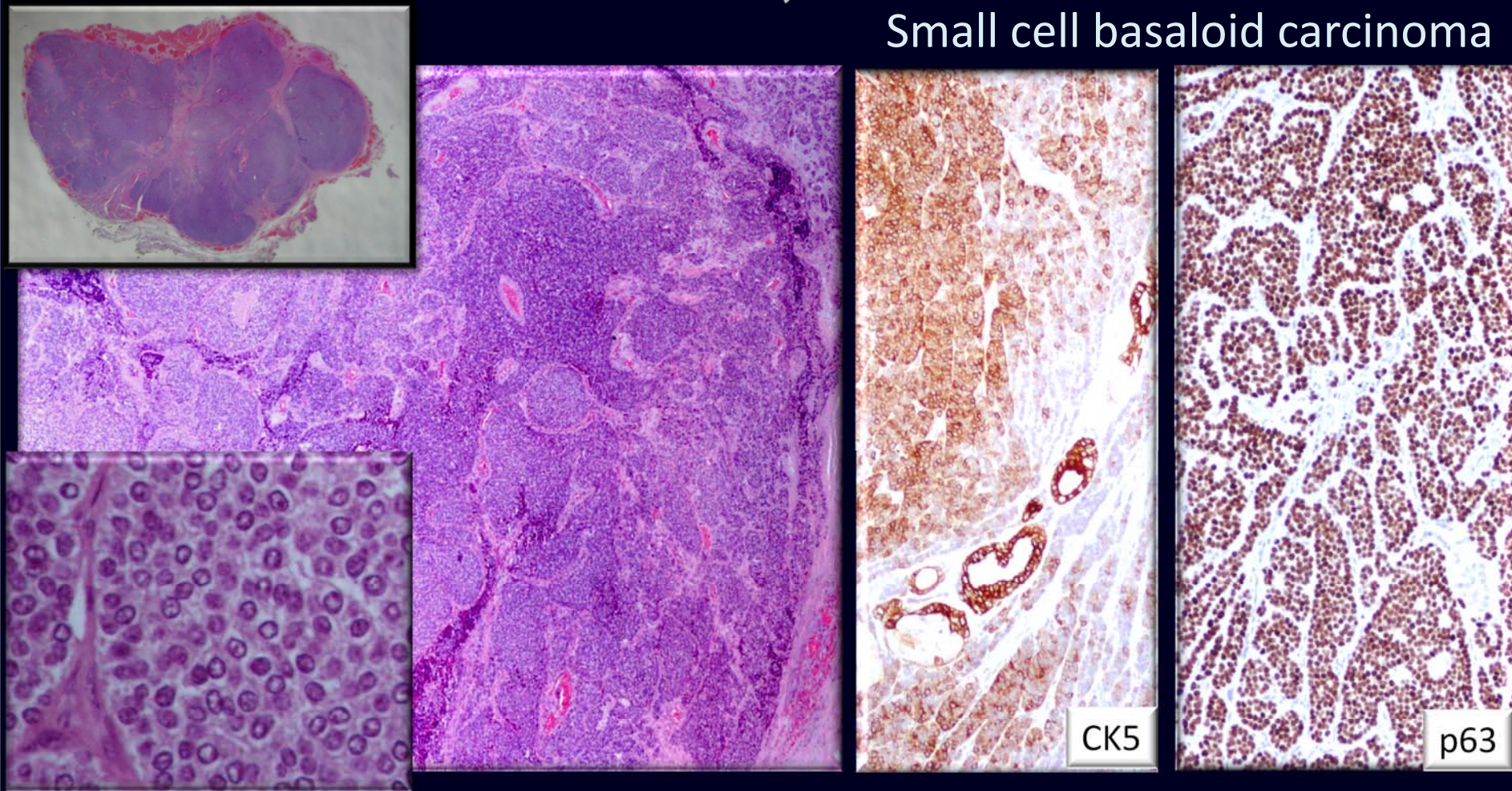
José Cameselle-Teijeiro MD, PhD^{a,*}, Fernando Pardal MD^b, Catarina Eloy MD^{d,e},
Clara Ruiz-Ponte PhD^c, Ricardo Celestino BSc^d, Patricia Castro BSc, PhD^d,
Paula Soares BSc, PhD^{d,f}, Manuel Sobrinho-Simões MD, PhD^{d,e,f}

Peculiar variants of TTF1 positive thyroid carcinomas

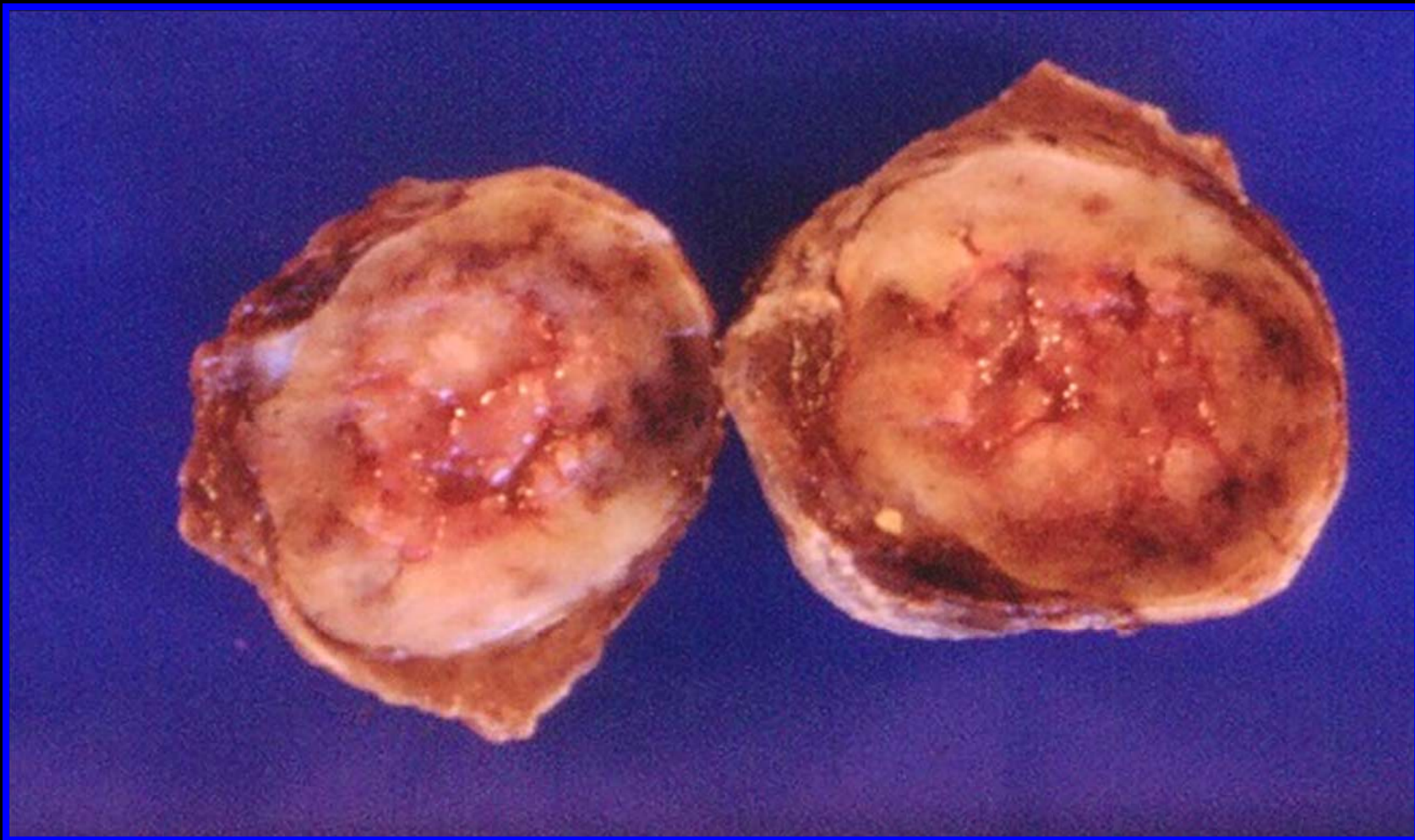
1. Cribriform morular variant (APC setting or sporadic)
2. Poorly differentiated CMV with or without neuroendocrine features
3. Columnar cell carcinoma with CDX2 positivity
4. Glomeruloid variant of follicular carcinoma
5.

Primary TTF1 negative rare flowers: SETTLE, CASTLE, Small cell basaloid tumours, PNET

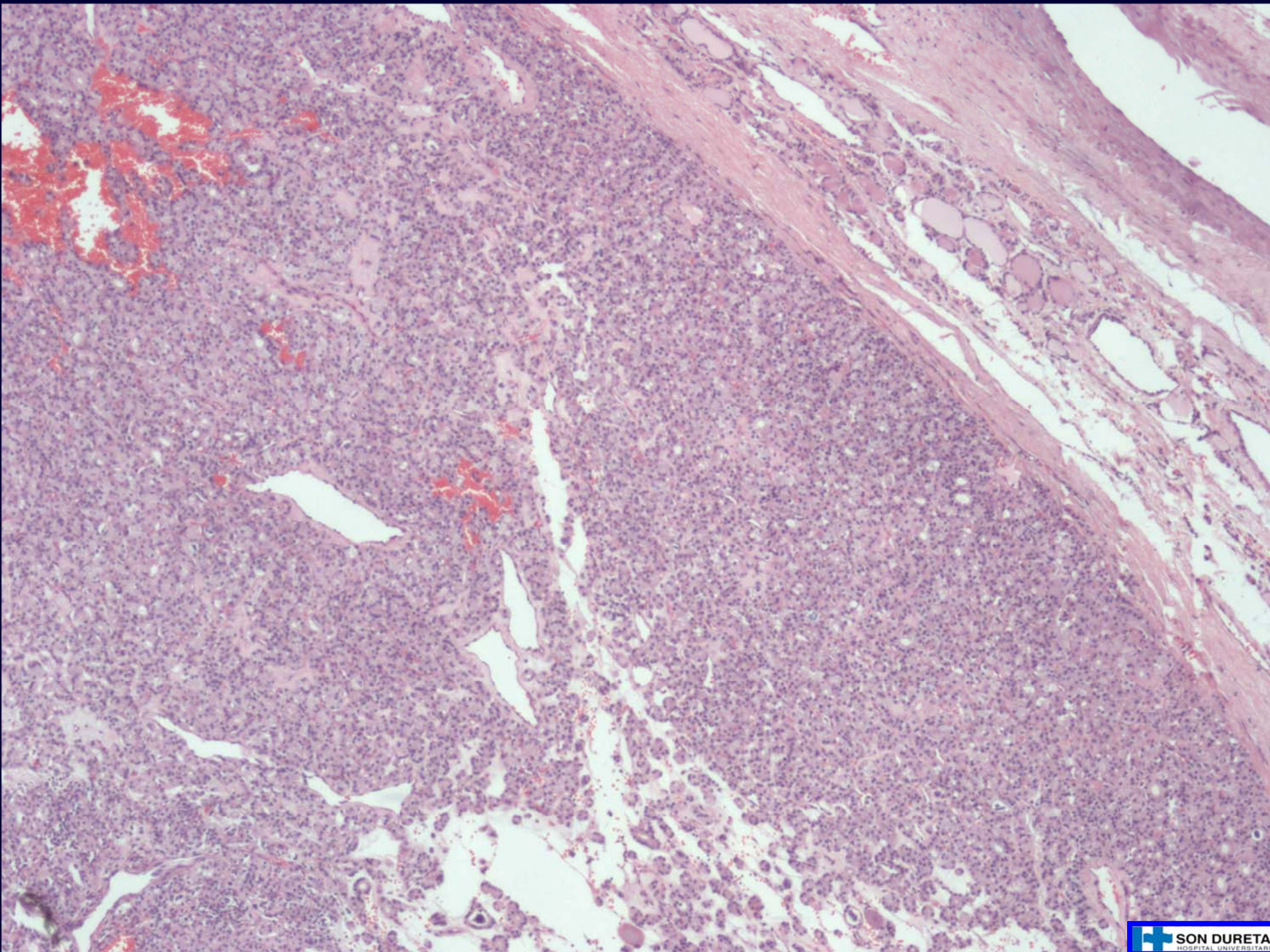
Small cell basaloid carcinoma

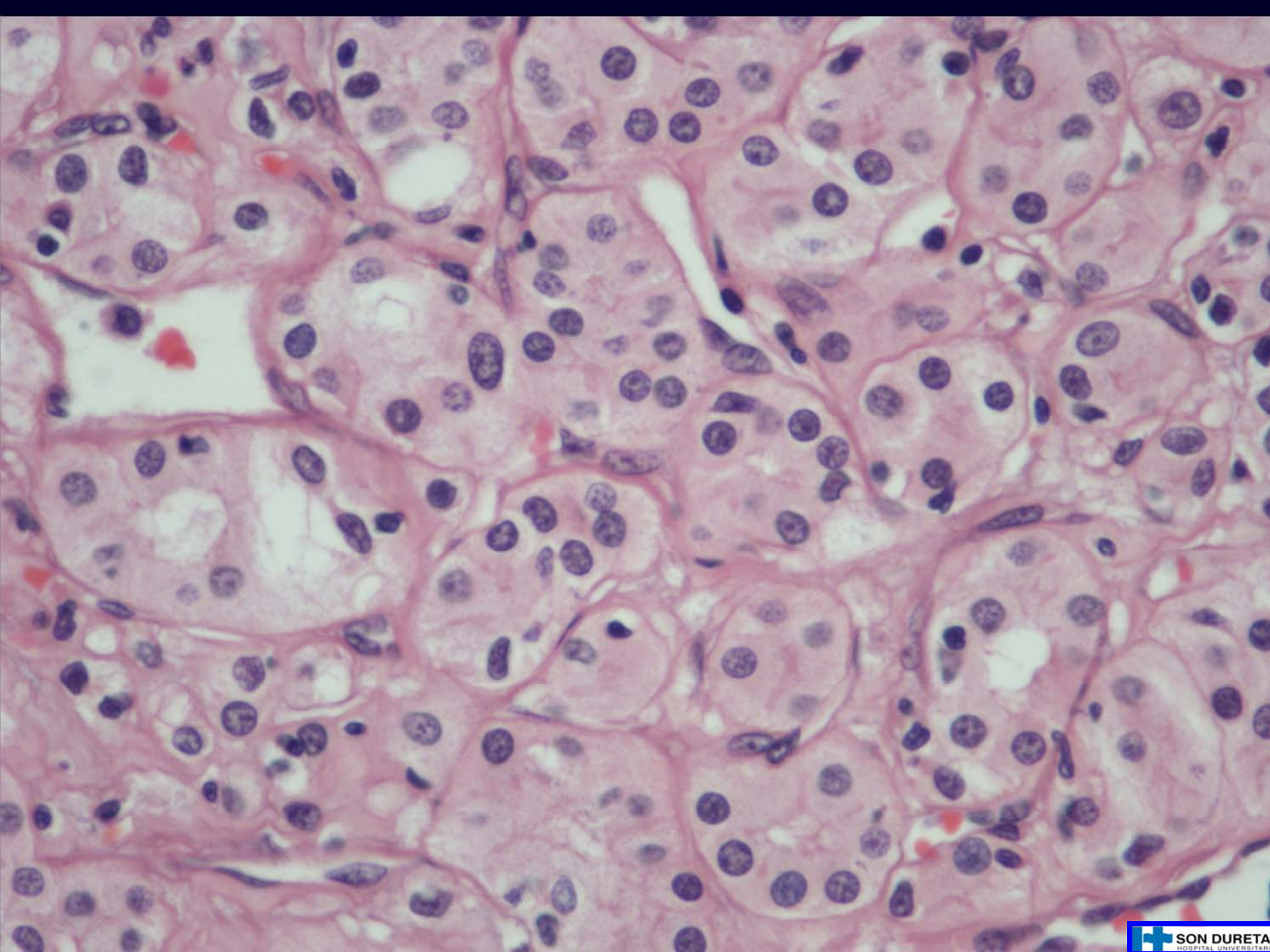


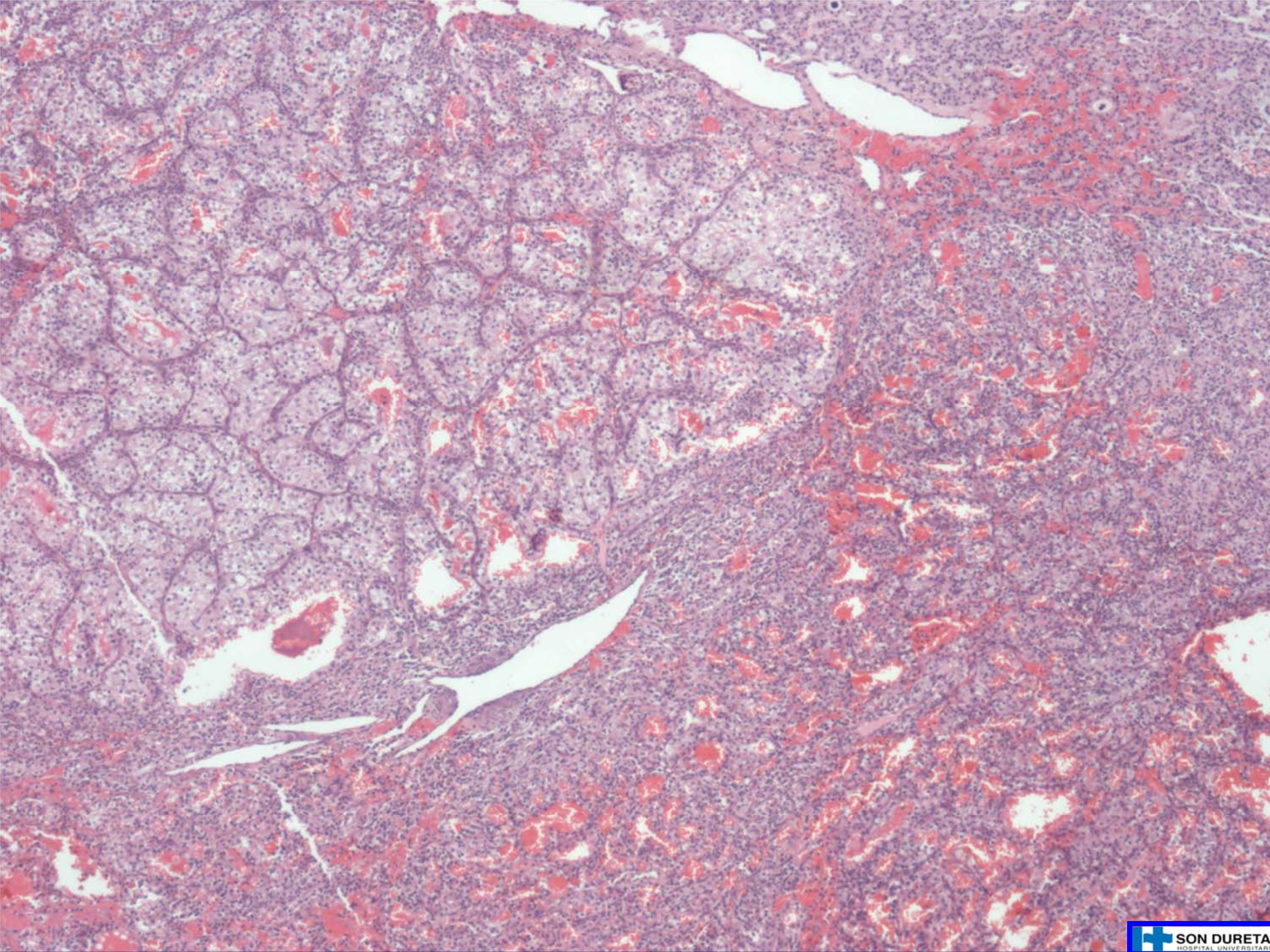
Hemitiroides derecho 81 g, 8x5x3 cm.

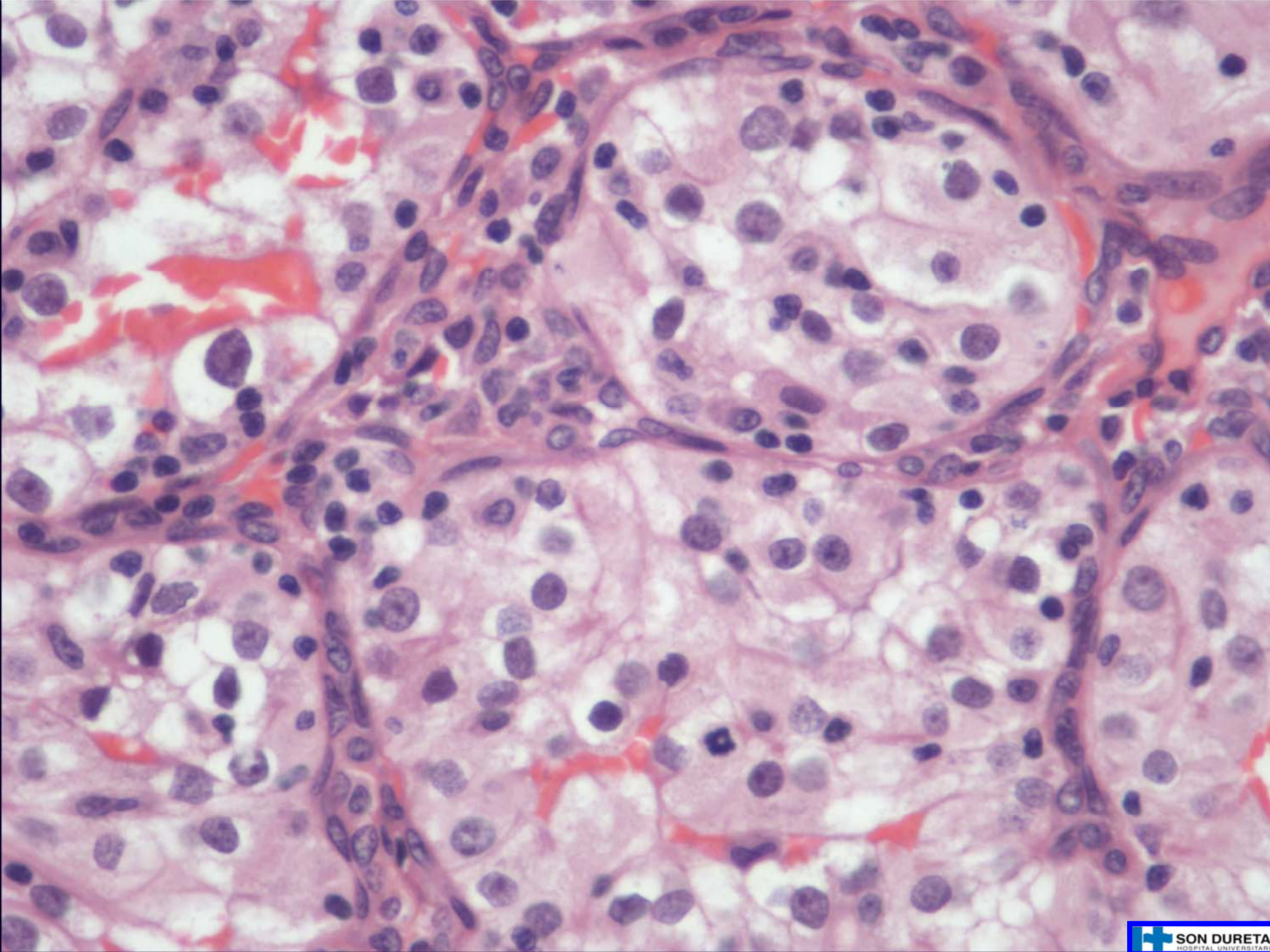


Nódulo encapsulado 6 cm diámetro

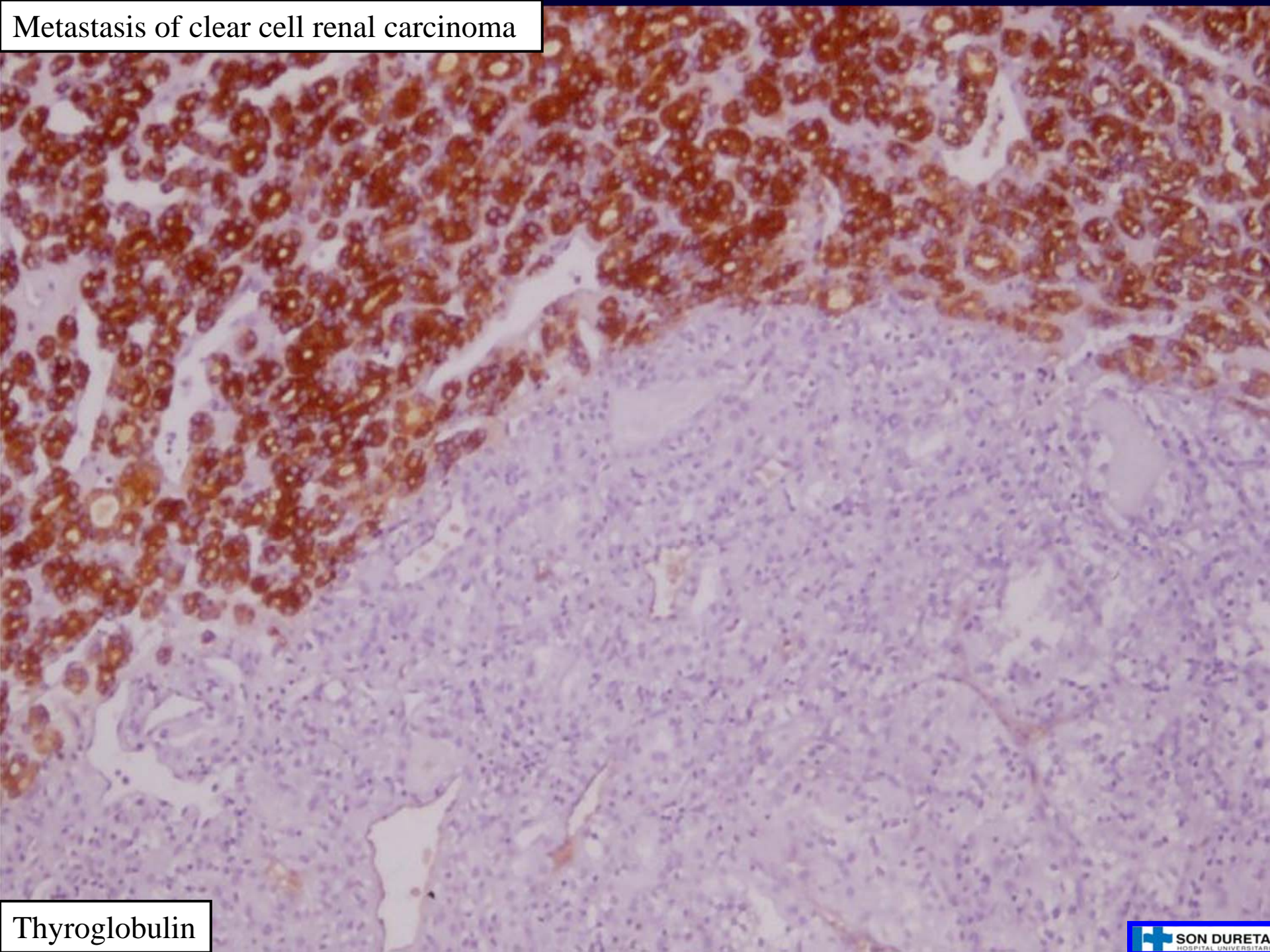




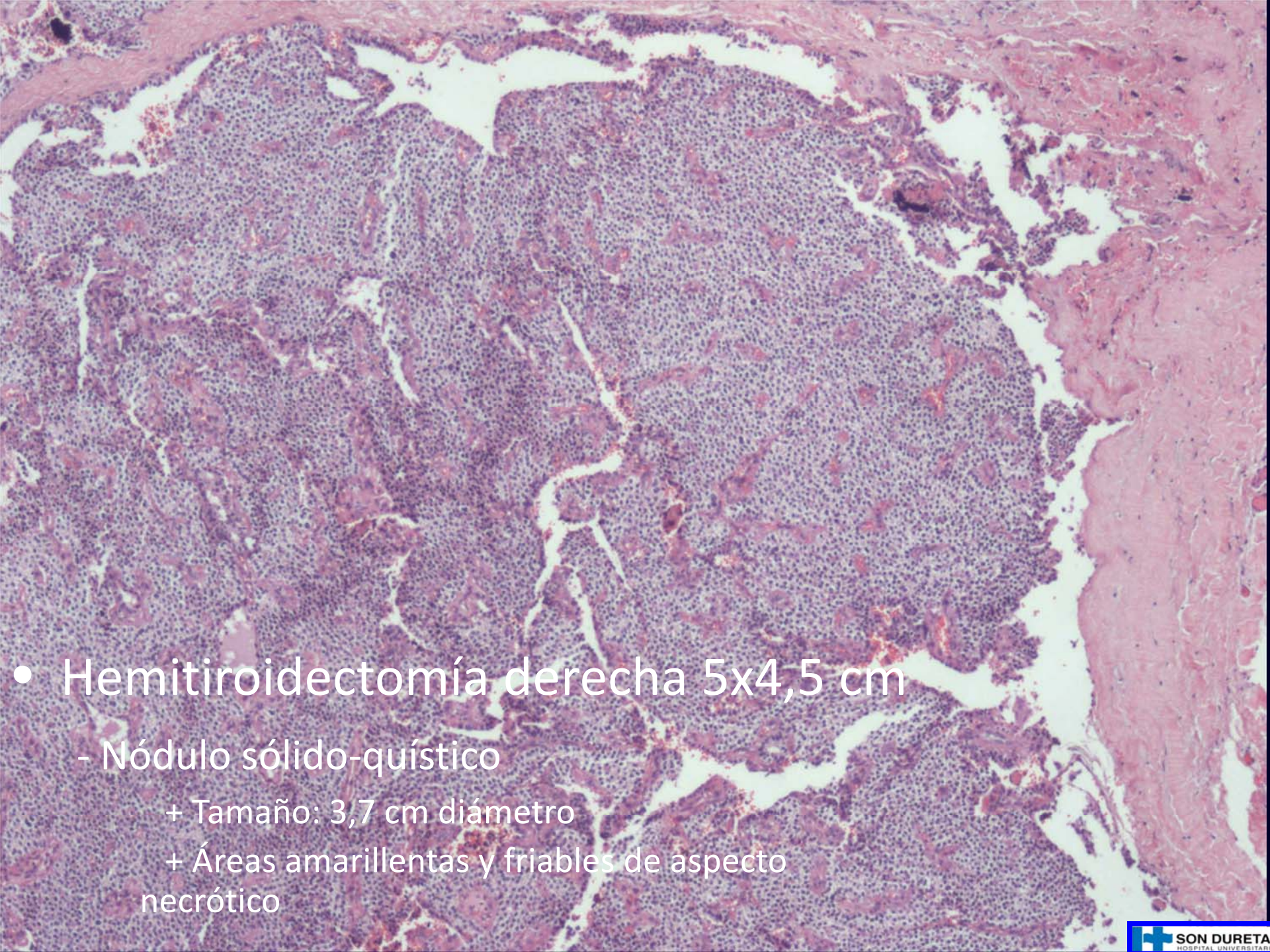




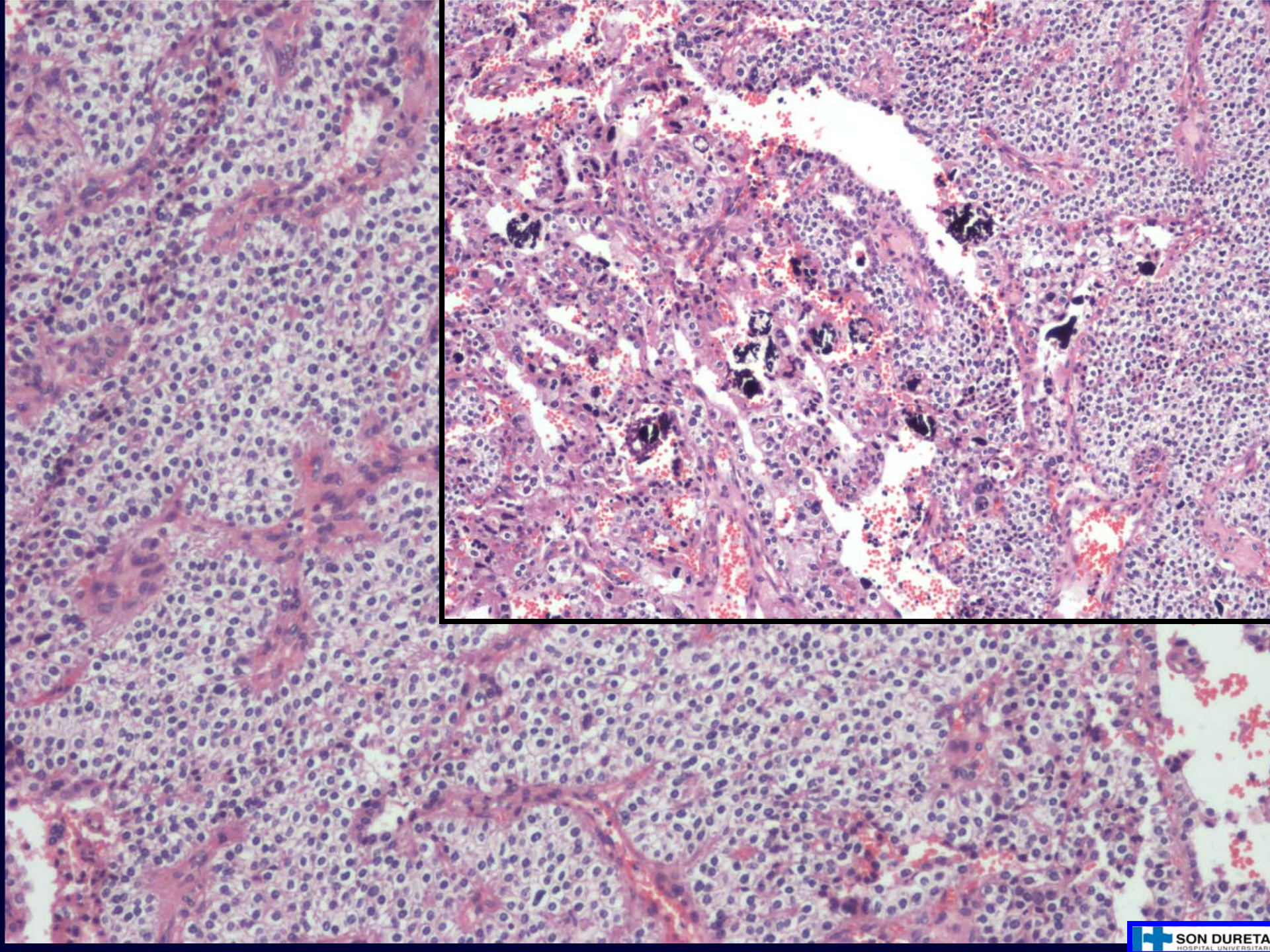
Metastasis of clear cell renal carcinoma

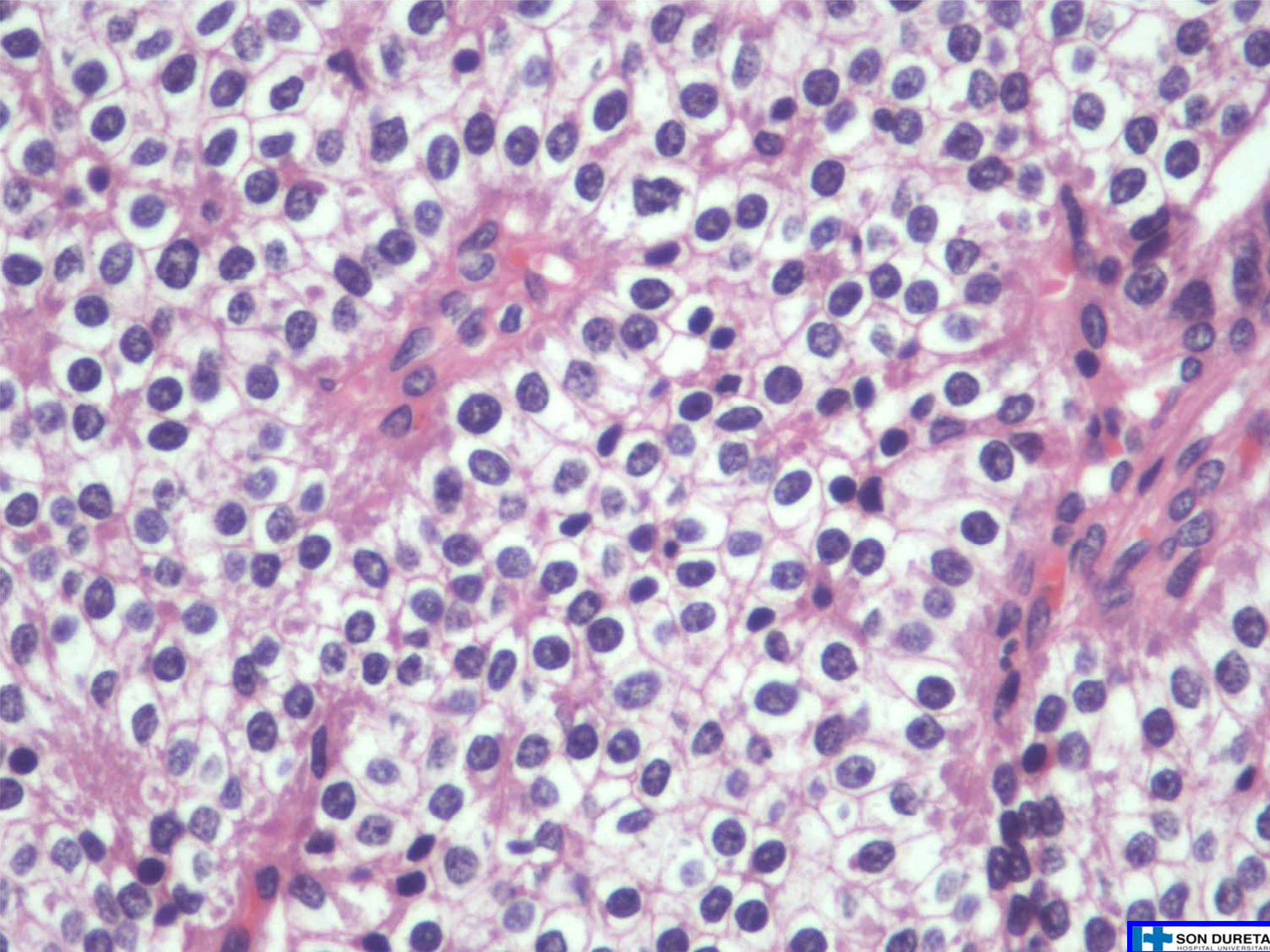


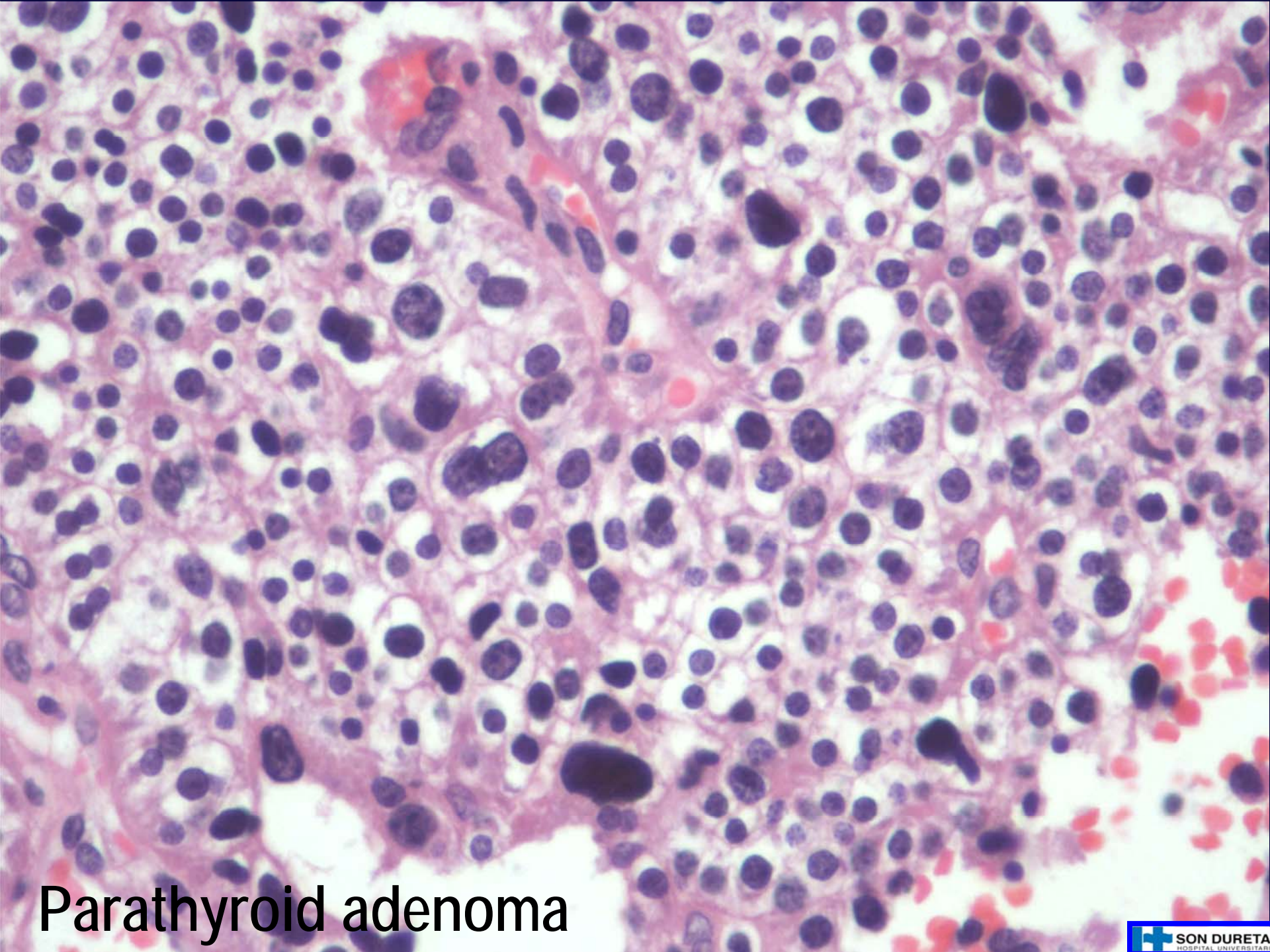
Thyroglobulin



- Hemitiroidectomía derecha 5x4,5 cm
 - Nódulo sólido-quístico
 - + Tamaño: 3,7 cm diámetro
 - + Áreas amarillentas y friables de aspecto necrótico

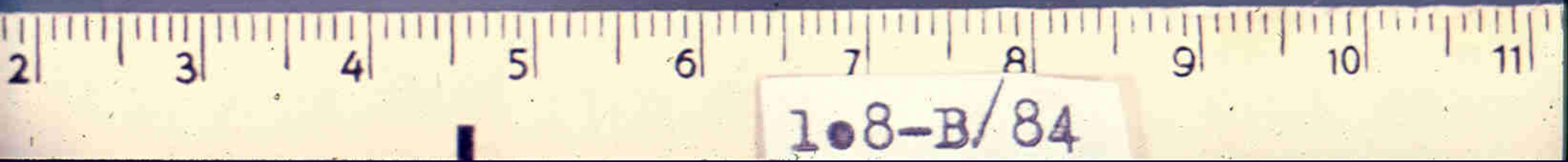
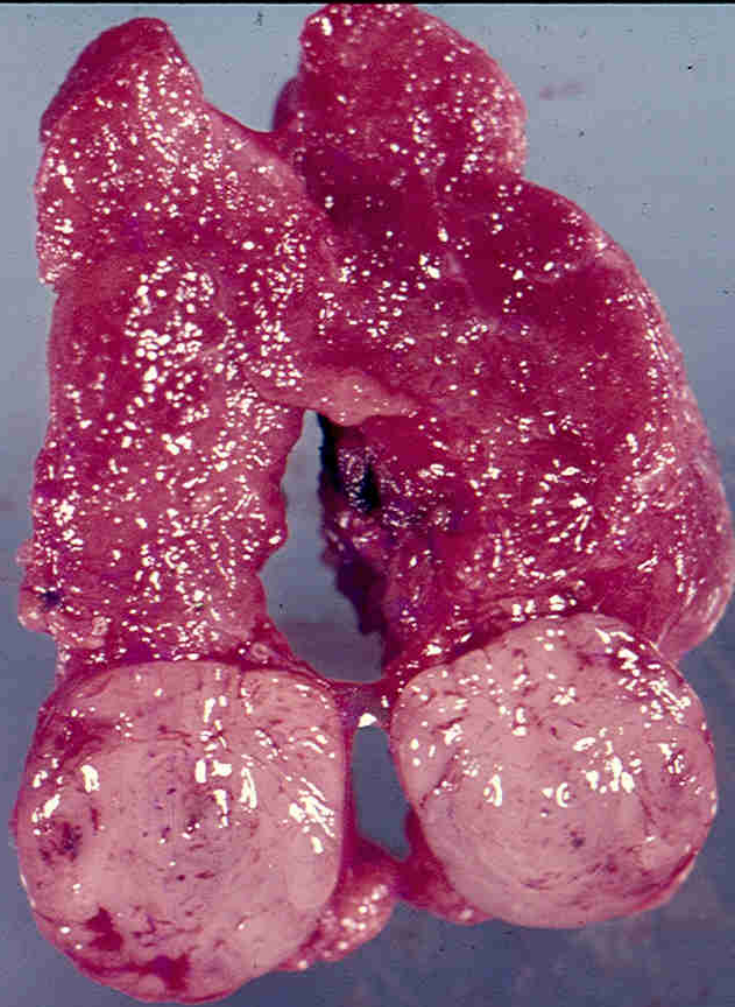






Parathyroid adenoma

Parathyroid adenoma





Save the Date



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31 August – 4 September 2013
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