A Cased-Based Tour of Thyroid Pathology: From the Basics to the Latest

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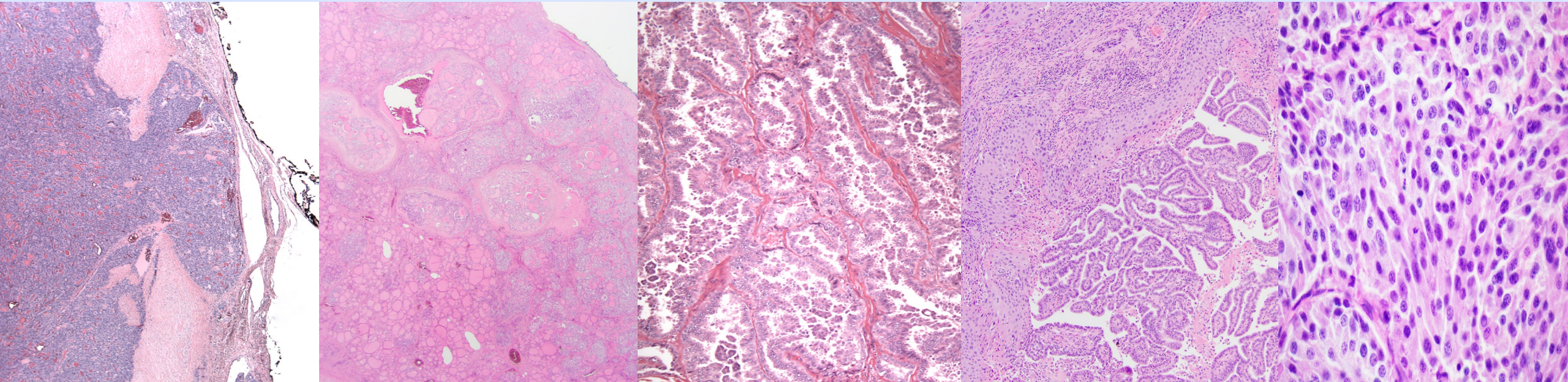

Disclosures

- I have no financial disclosures or conflicts of interest to report.

Goal of the Session

Present cases that highlight:

- clinically significant diagnostic challenges in thyroid pathology
- updates from the 2022 World Health Organization Classification of Endocrine and Neuroendocrine Tumours
- advances in our understanding of risk stratification, tumor classification, and molecular pathogenesis of thyroid carcinomas
- how the molecular underpinnings of thyroid carcinomas may impact treatment

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- how the molecular underpinnings of thyroid carcinomas may impact treatment

Focus on follicular-patterned tumors for first hour.

Case

The patient is a 39-year-old woman with multinodular goiter (MNG) with a dominant 4.6 cm nodule in the left lobe of the thyroid.

FNA was performed of the dominant nodule, and an indeterminate FNA diagnosis was obtained.

ThyroSeq v3 was performed, and an *NRAS* Q61R mutation was detected.

What is the significance of a *RAS* mutation detected on molecular analysis of a nodule with an indeterminate FNA result?

RAS mutations are the most frequent molecular alterations detected in nodules with indeterminate FNA results.

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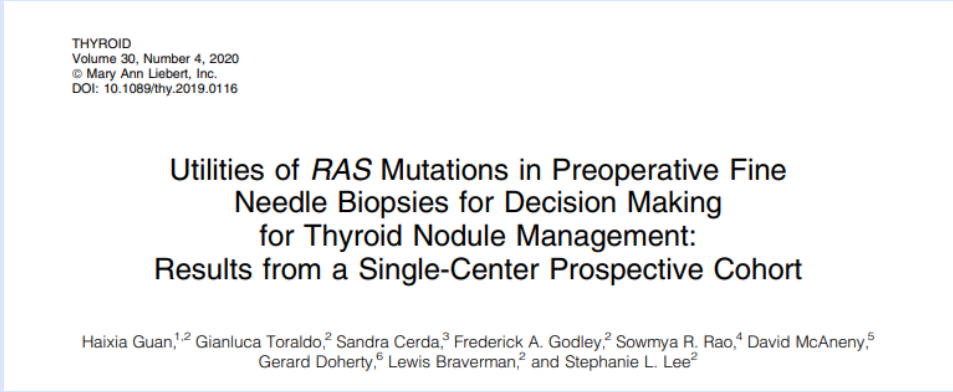
DOI: 10.1089/thy.2019.0116

Utilities of *RAS* Mutations in Preoperative Fine Needle Biopsies for Decision Making for Thyroid Nodule Management: Results from a Single-Center Prospective Cohort

Haixia Guan,[1,2] Gianluca Toraldo,[2] Sandra Cerda,[3] Frederick A. Godley,[2] Sowmya R. Rao,[4] David McAneny,[5] Gerard Doherty,[6] Lewis Braverman,[2] and Stephanie L. Lee[2]

504 nodules (73% with indeterminate FNA dx) and ThyroSeq results.

46% harbored *RAS* mutations: *NRAS (66%)*, *HRAS (21%)* or *KRAS* mutations (13%).



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The PPV of *RAS* mutations for identifying **NIFTP or carcinoma** among Bethesda III/IV nodules was 30%.

The 12 *RAS*-only-positive carcinomas all showed low-risk features and favorable prognosis.

In the ThyroSeq v3 validation study, reported rates of cancer or NIFTP for specific RAS mutations were: 72% for *HRAS*, 52% for *NRAS*, and 40% for *KRAS.*

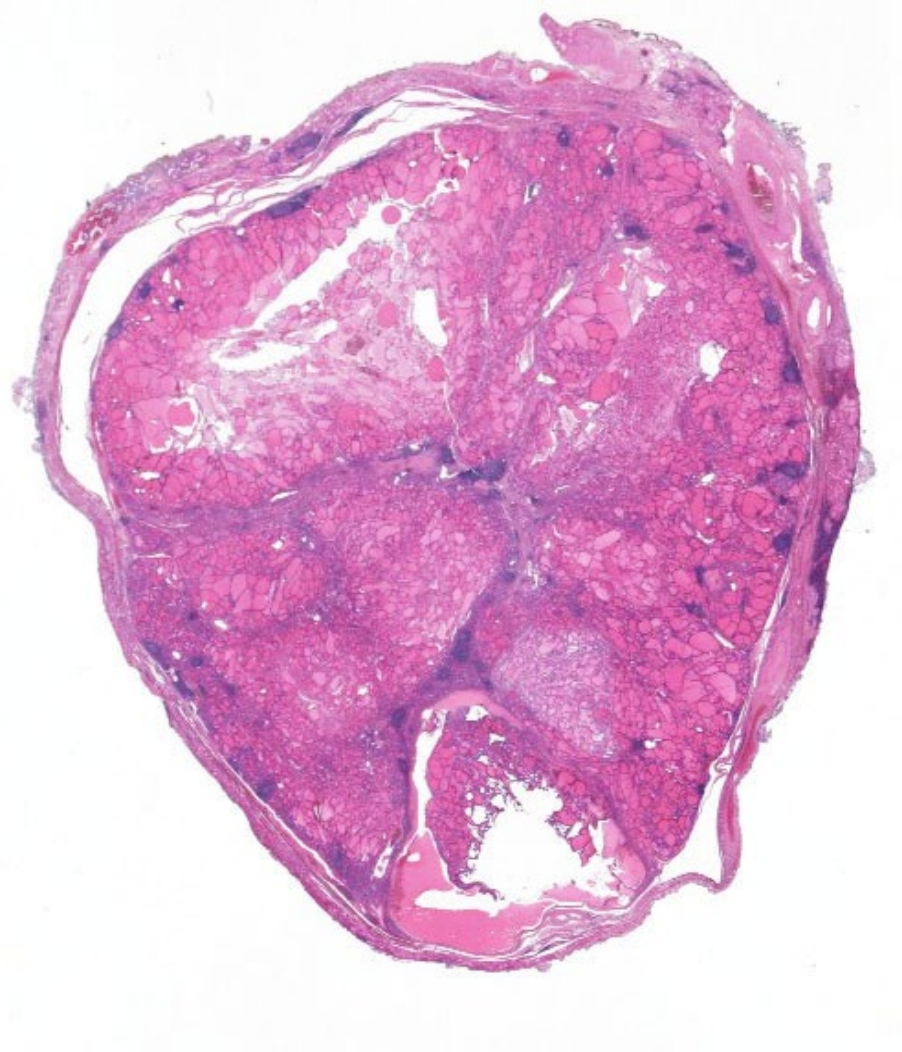
RAS and *RAS*-like alterations (such as *BRAF* K601E mutation, *PTEN* mutations, *EIF1AX* mutations, *PPARG* fusions, and *THADA* fusions) are associated with a spectrum of encapsulated/well-circumscribed, follicular-patterned thyroid tumors, that includes:

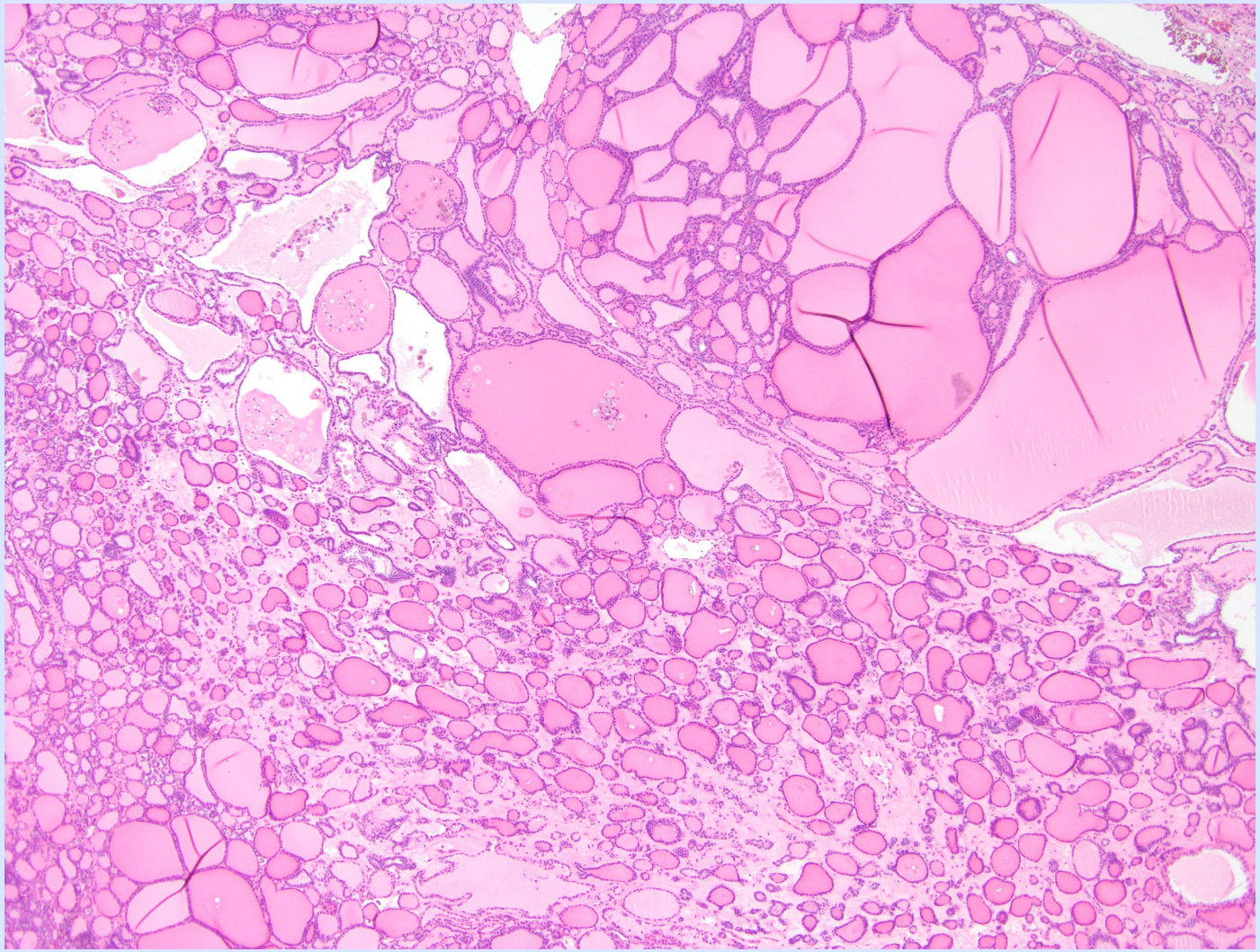
- follicular adenoma/follicular thyroid carcinoma

- NIFTP/invasive encapsulated follicular variant of papillary thyroid carcinoma

- Poorly differentiated thyroid carcinoma and even anaplastic thyroid carcinoma can also have *RAS* mutations; however, they usually harbor additional molecular alterations as well

Back to our patient…





Some nodules with *RAS* mutations have morphologic overlap with hyperplastic nodules.

Thyroid - Follicular-cell Derived Benign Tumors
Thyroid follicular nodular disease
Follicular adenoma of the thyroid
Follicular adenoma with papillary architecture
Oncocytic adenoma of the thyroid

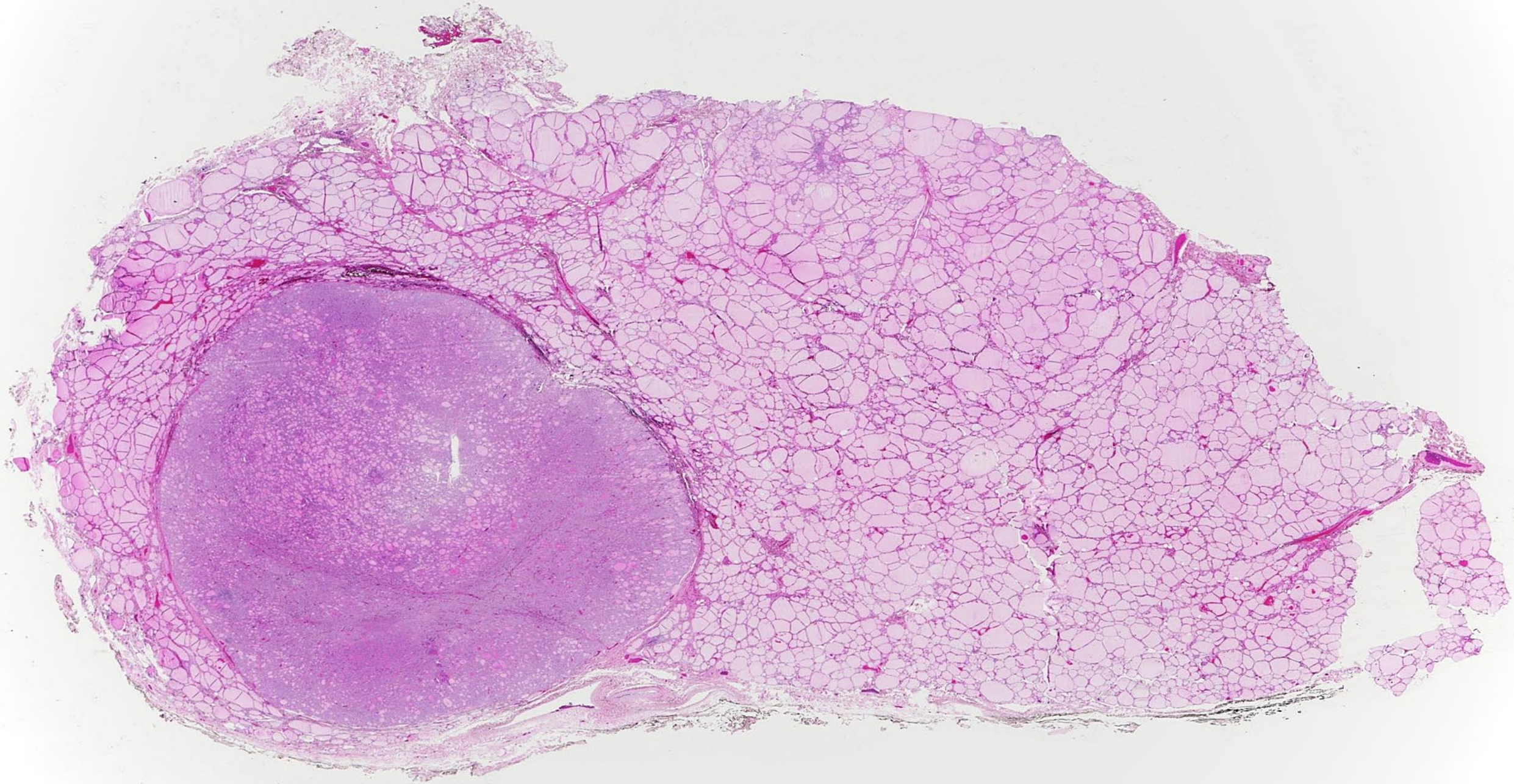
To reflect the fact that some nodules within MNG are clonal, the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours has introduced the terminology thyroid follicular nodular disease.

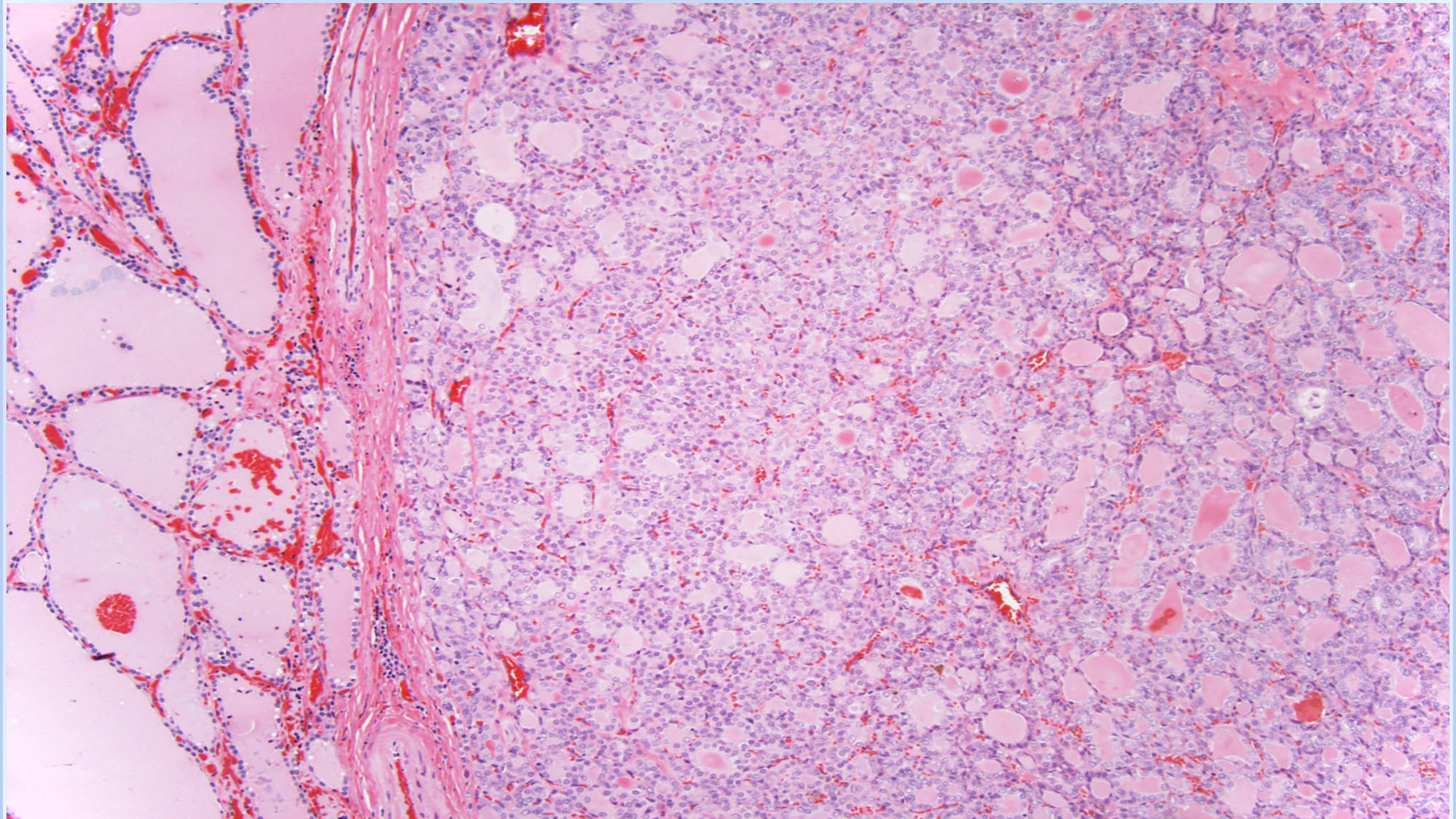
Case

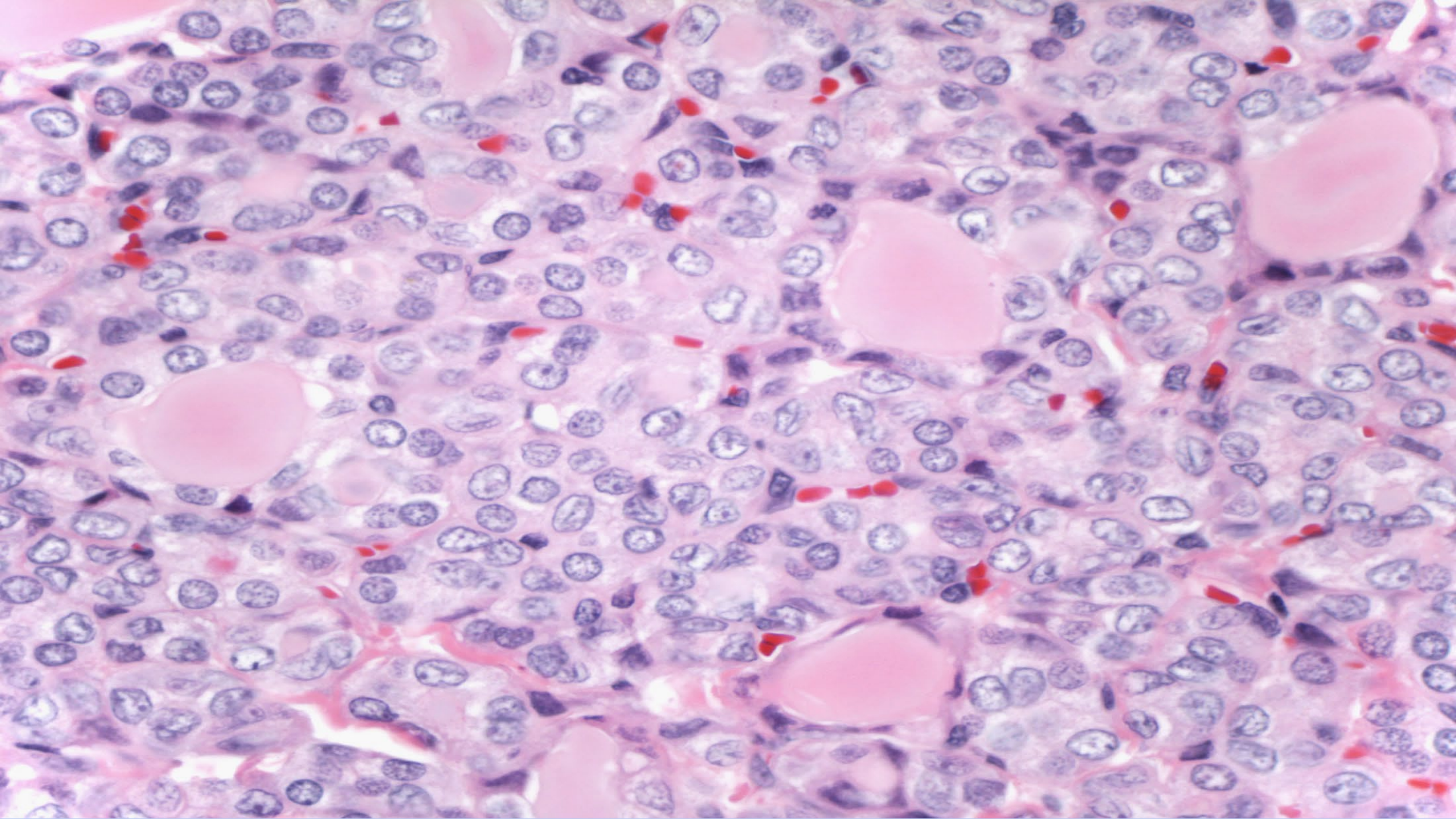
The patient is a 49-year-old woman who was incidentally found to have a 2.2 cm thyroid nodule.

An FNA was performed and interpreted as atypia of undetermined significance with a note indicating the presence of both cytologic and architectural atypia. Afirma testing came back with a "suspicious result“ and Afirma Xpression Atlas revealed an *NRAS* Q61R mutation.

A diagnostic lobectomy was performed.





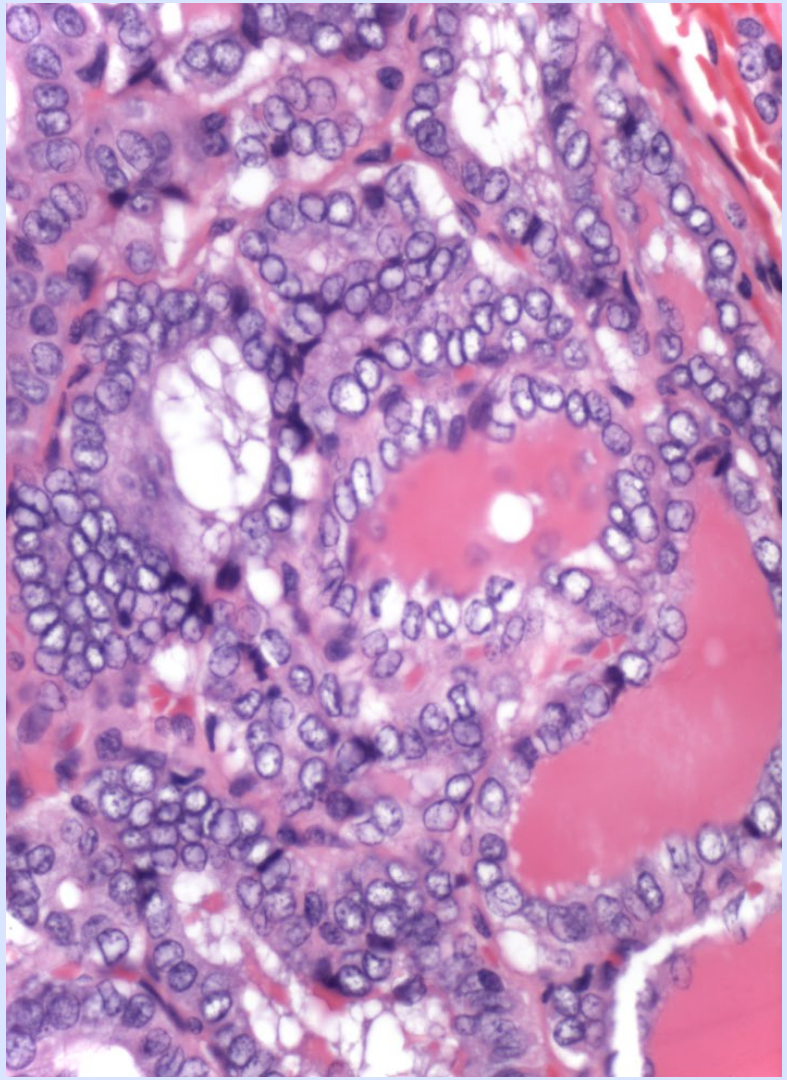


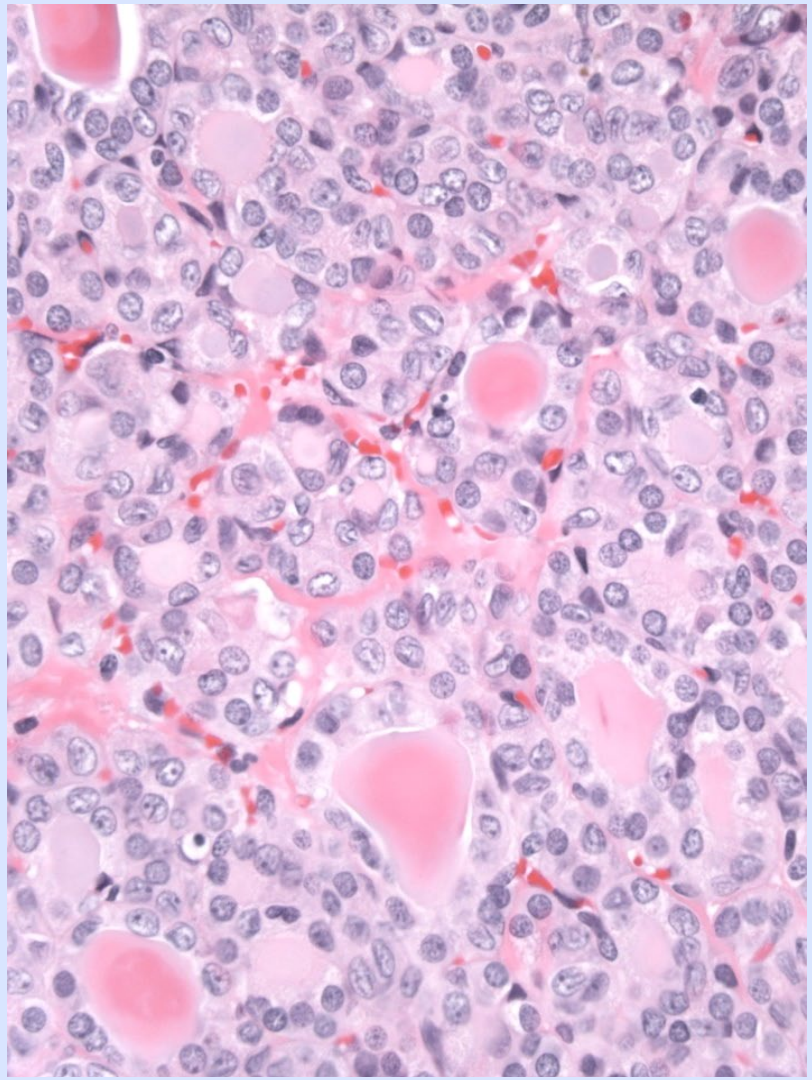
Rendering a Diagnosis of NIFTP

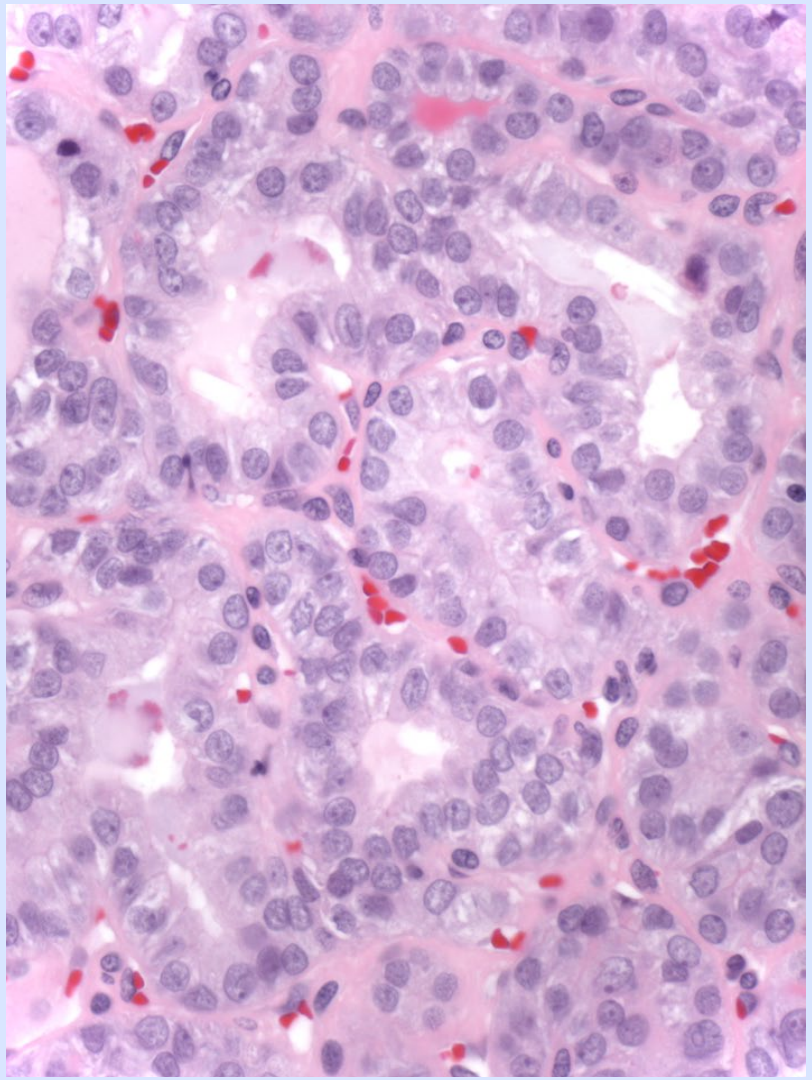
1. Nuclear features of papillary thyroid carcinoma are present.
2. The tumors should have a nearly entirely follicular architecture (<1% papillae).
3. The capsule can be variably thick.
4. The capsule must be thoroughly examined for invasion in a fashion similar to FA/FTC.
5. Cases with any indication of invasive/infiltrative growth should be excluded.
6. Cases with greater than 30% solid growth or high-grade features, such as increased mitotic activity or necrosis should be excluded.

Spectrum of Nuclear Atypia

Marked/ diffuse → Moderate/ multifocal







Nuclear Scoring System

To provide simplified and reproducible criteria for the nuclear features that could assist in the diagnosis of NIFTP.

Features were grouped into 3 categories:

1. Size and shape: nuclear enlargement/overlapping/crowding and elongation.

2. Nuclear membrane irregularities (irregular contours, grooves, and pseudoinclusions).

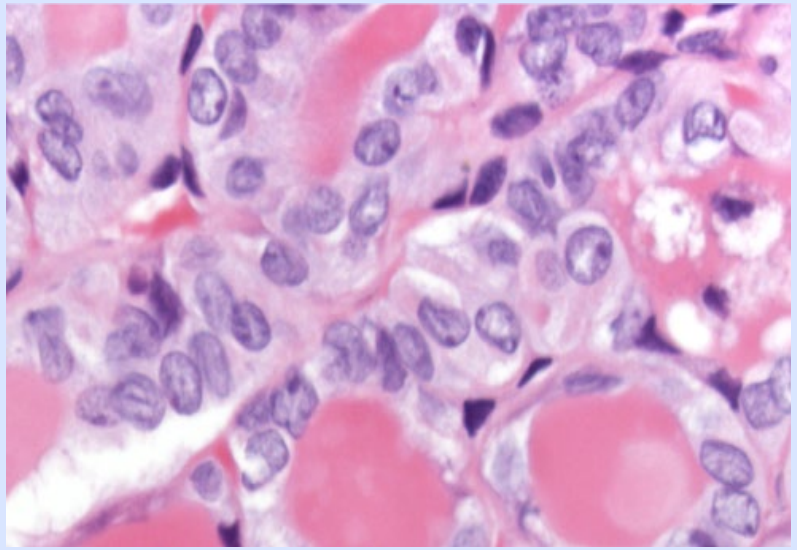
3. Chromatin characteristics (clearing with margination/glassy nuclei).

Nuclear Score

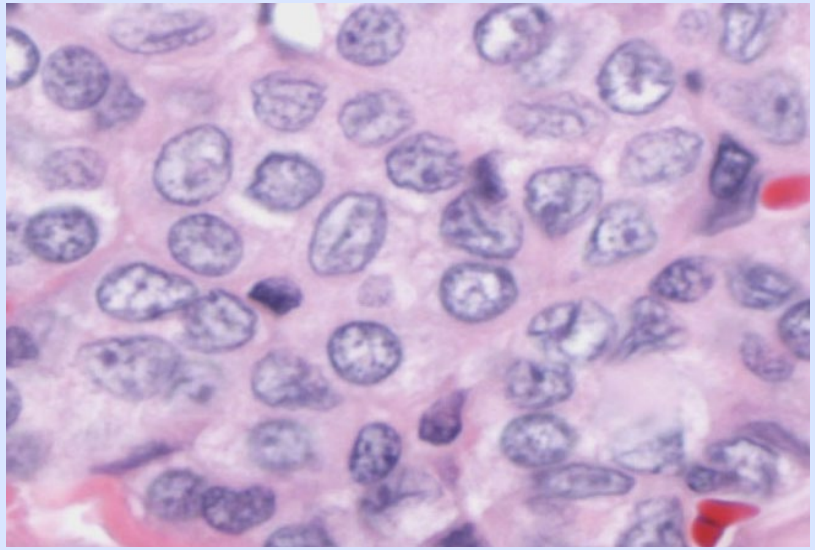
<u>Can get a total of 3 points:</u>

A score of 0 or 1= benign

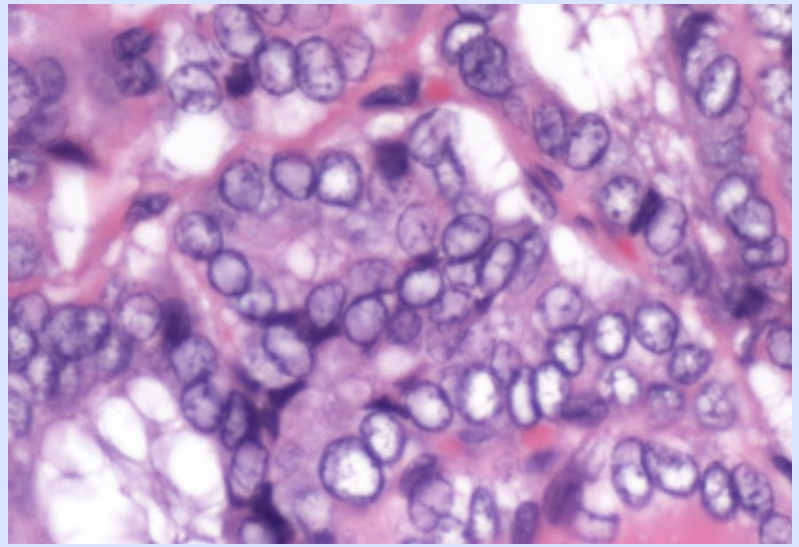
A score of 2 or 3=NIFTP (given correct growth pattern/architecture)



Nuclear enlargement, crowding, elongation→ 1 point



Nuclear membrane irregularities→ 1 point

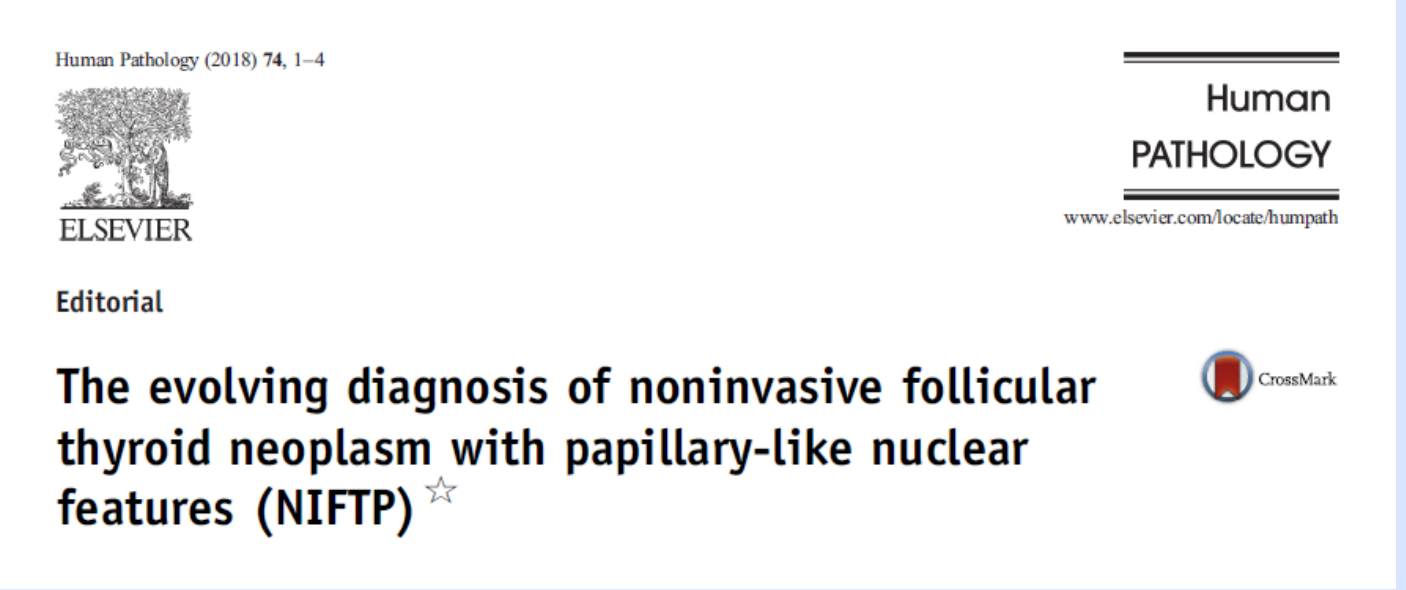


Chromatin characteristics → 1 point

Papillary Architecture

Initial definition of NIFTP allowed for <1% papillae.

Subsequent studies reporting *BRAF* V600E and lymph node metastasis in a small subset of NIFTPs with <1% papillae led to many in the consensus group to advocate a change in definition to allow no well-formed papillae.


Human Pathology (2018) 74, 1–4

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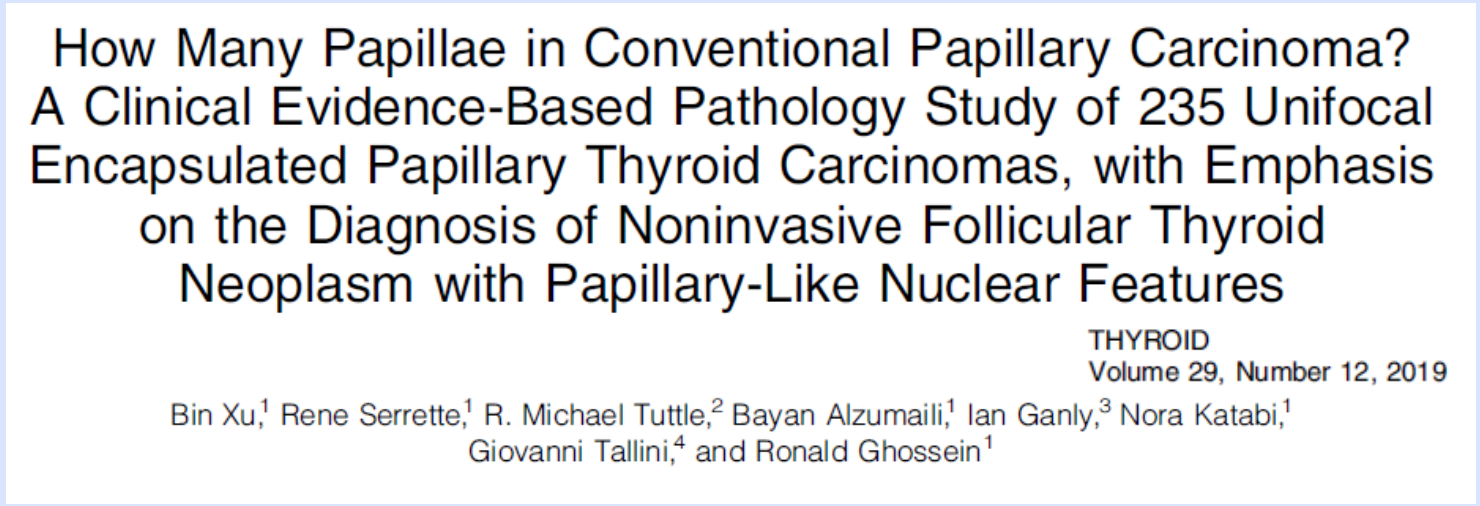
Editorial

The evolving diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) ☆

Papillary Architecture

In subsequent studies using the original criteria of <1% true papillae, no adverse events were reported.



How Many Papillae in Conventional Papillary Carcinoma? A Clinical Evidence-Based Pathology Study of 235 Unifocal Encapsulated Papillary Thyroid Carcinomas, with Emphasis on the Diagnosis of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

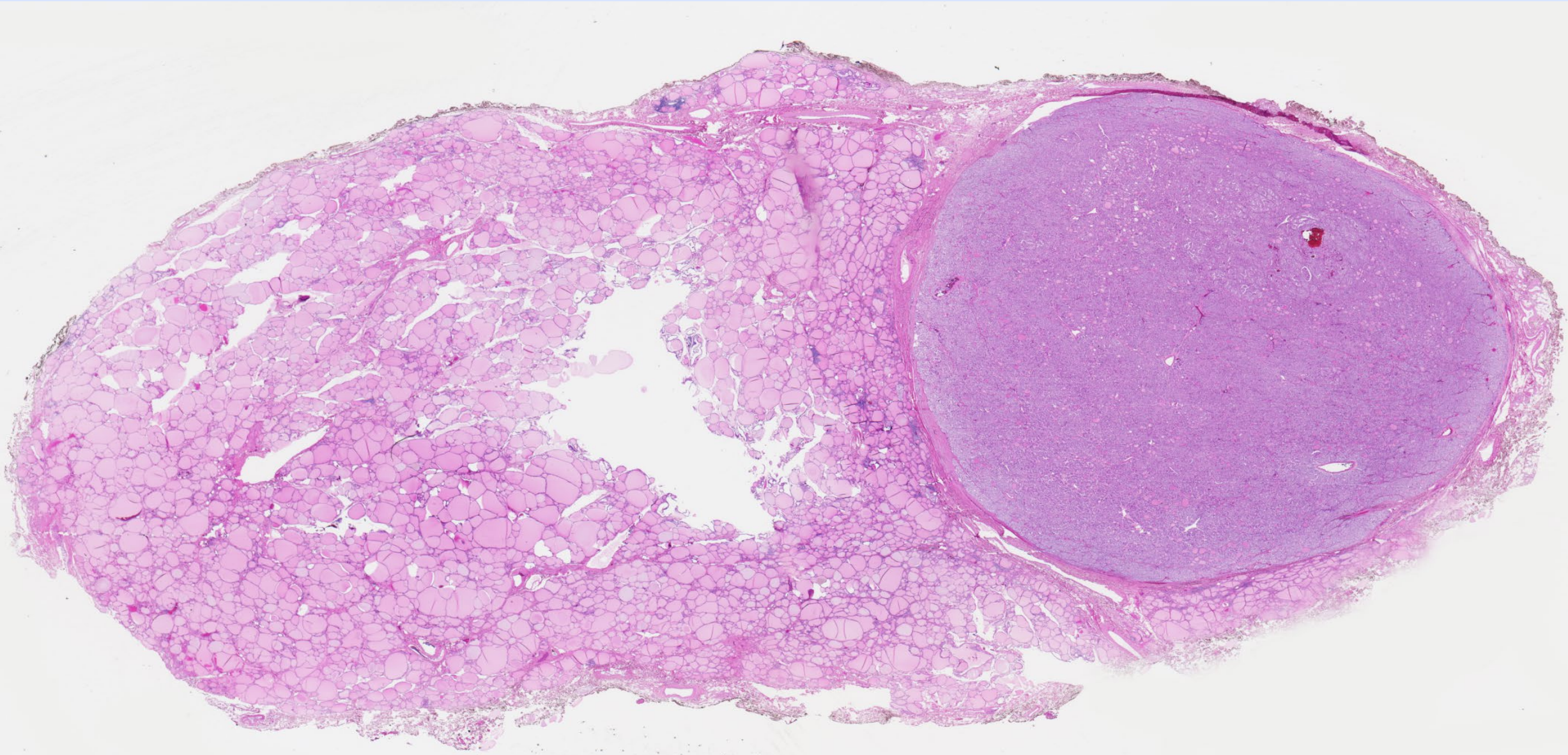
THYROID
Volume 29, Number 12, 2019

Bin Xu,[1] Rene Serrette,[1] R. Michael Tuttle,[2] Bayan Alzumaili,[1] Ian Ganly,[3] Nora Katabi,[1] Giovanni Tallini,[4] and Ronald Ghossein[1]

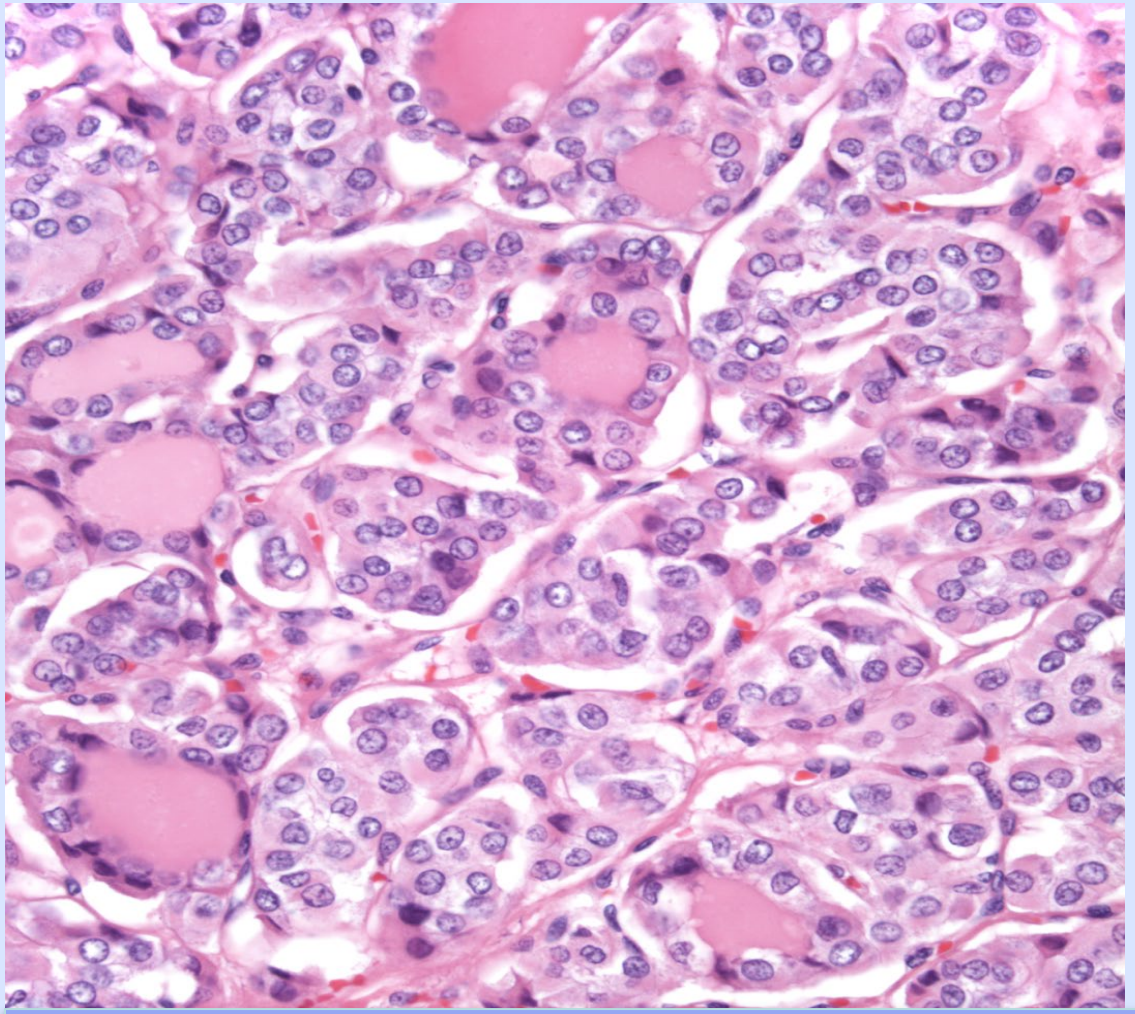
235 cases of unifocal encapsulated PTC. In the noninvasive group, N1 disease was seen only in tumors with ≥10% papillae. "These findings indicate that the initial criterion of <1% papillae is still valid for the diagnosis of NIFTP."

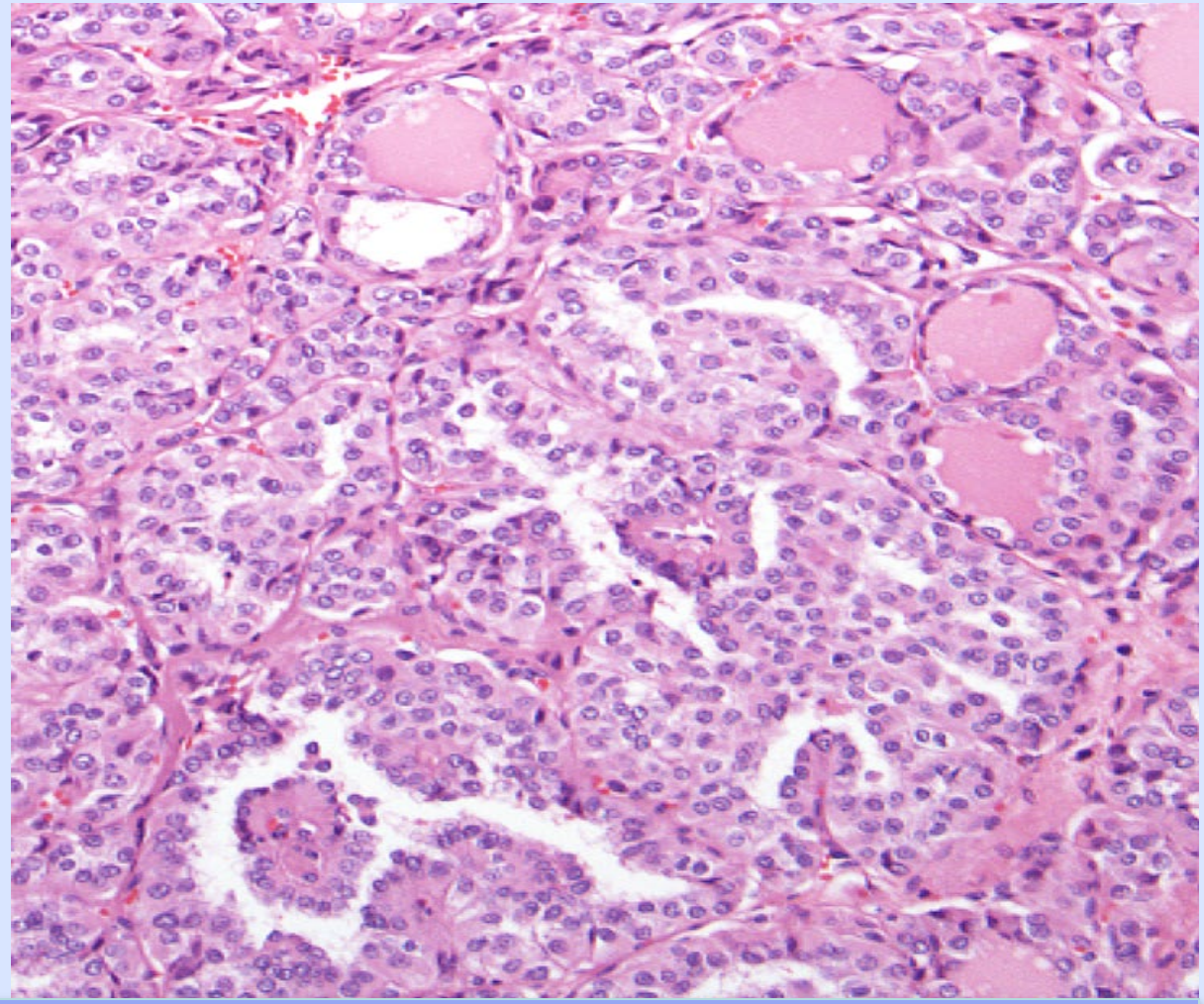
As a result of studies like this one, the original criterion allowing less than 1% true papillae is unchanged in the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours.

Nearly Entirely Follicular Architecture



Exclude Papillary Architecture





NOTE: Although the tumor has a predominantly follicular architecture, scattered papillae warrant characterization of the tumor as classic PTC.

Evaluating for Papillae

MODERN PATHOLOGY (2018) 31, 39–55

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a review for pathologists

Raja R Seethala, Zubair W Baloch, Justine A Barletta, Elham Khanafshar, Ozgur Mete, Peter M Sadow, Virginia A LiVolsi, Yuri E Nikiforov, Giovanni Tallini and Lester DR Thompson

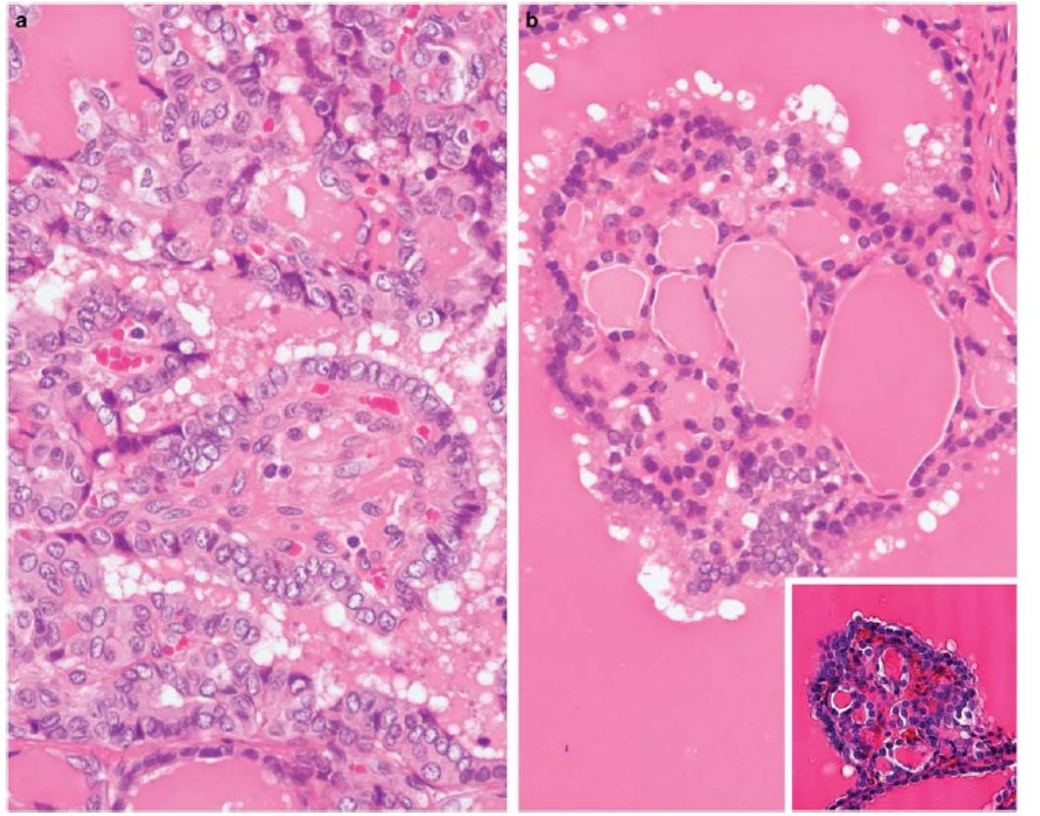


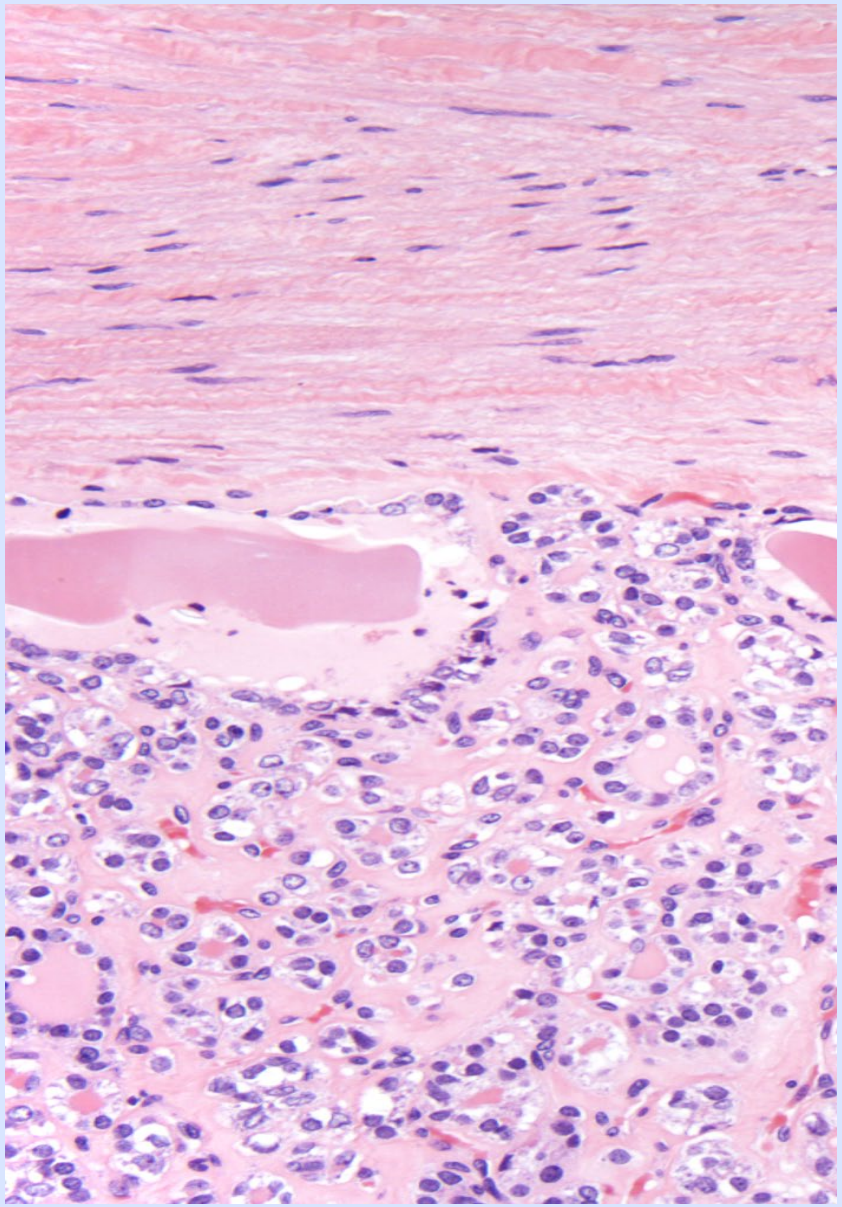
Figure 6 (**a**) Despite a predominant follicular pattern, there is a well-developed papilla with a fibrovascular core in the center of this classic papillary thyroid carcinoma. (**b**) This NIFTP shows a pseudopapillary structure, with follicles rather than vessels within the connective tissue core, recapitulating the features of the Sanderson polster seen in this hyperplastic nodule (inset).

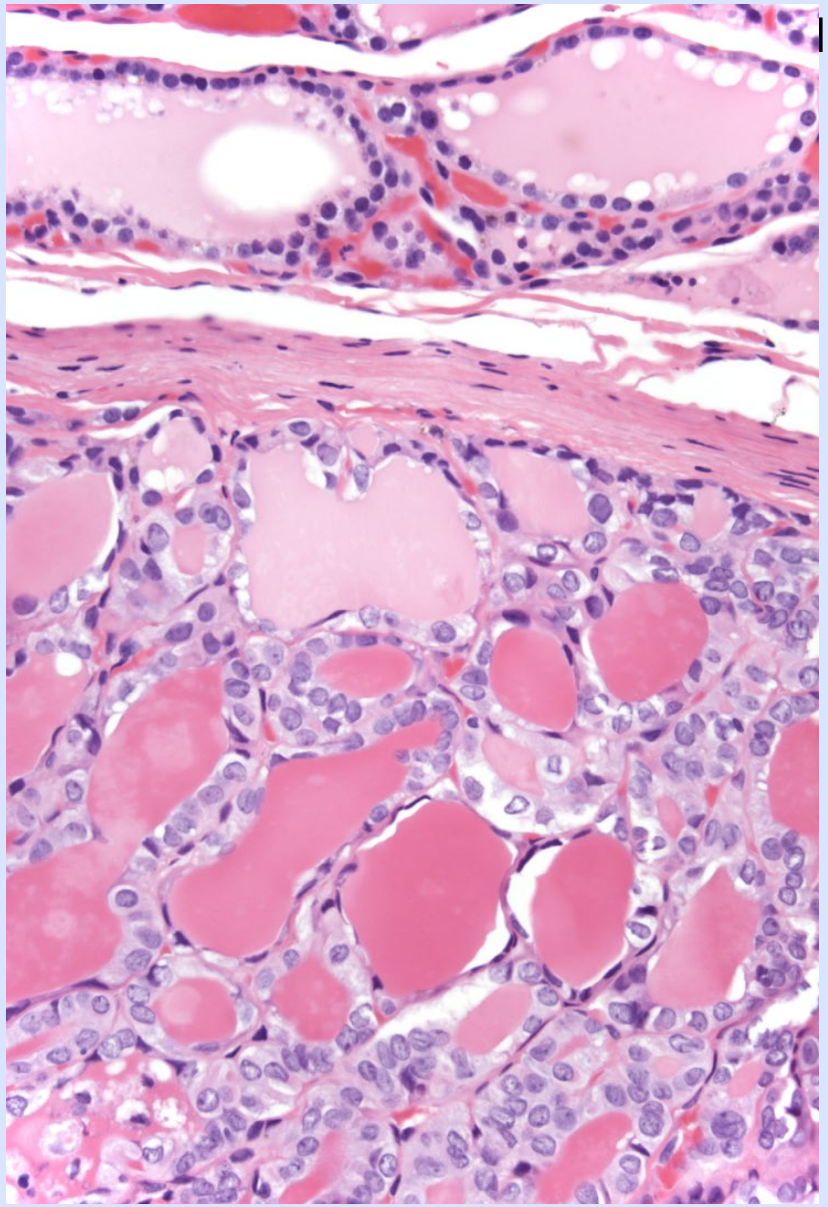
By definition, papillae have fibrovascular cores lined by neoplastic follicular cells.

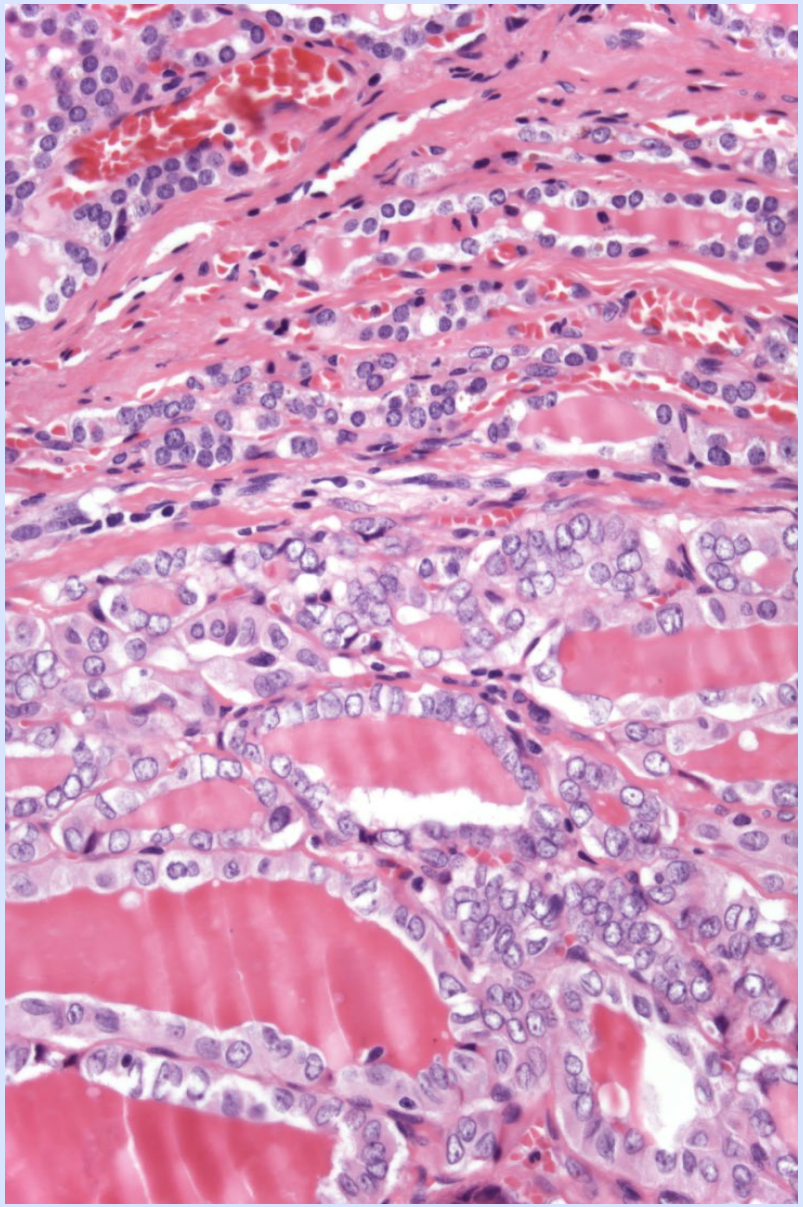
Sanderson polsters - collections of small follicles that project into the lumen of a larger follicles (but lack true fibrovascular cores), do not qualify as true papillae.

Tumor with psammomatous calcifications should also be excluded because psammomatous calcifications represent mummified papillae that have undergone concentric lamination by calcium.

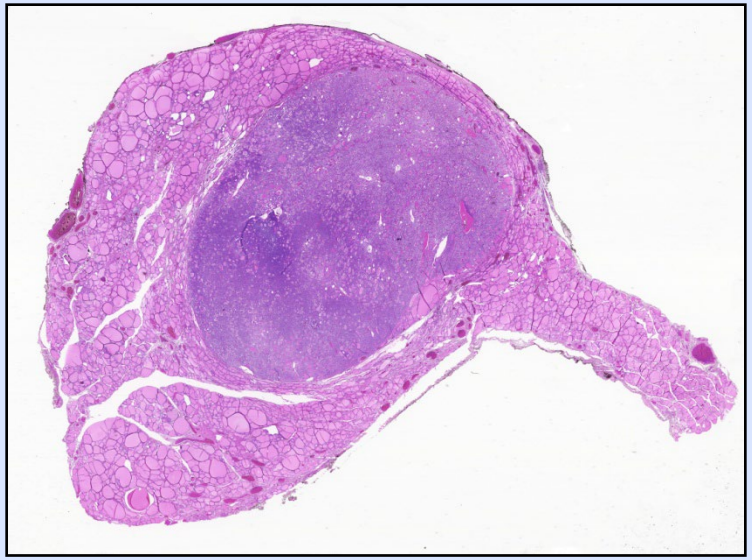
Capsule Thickness Can Vary







Partially-encapsulated/ Well-circumscribed Tumors



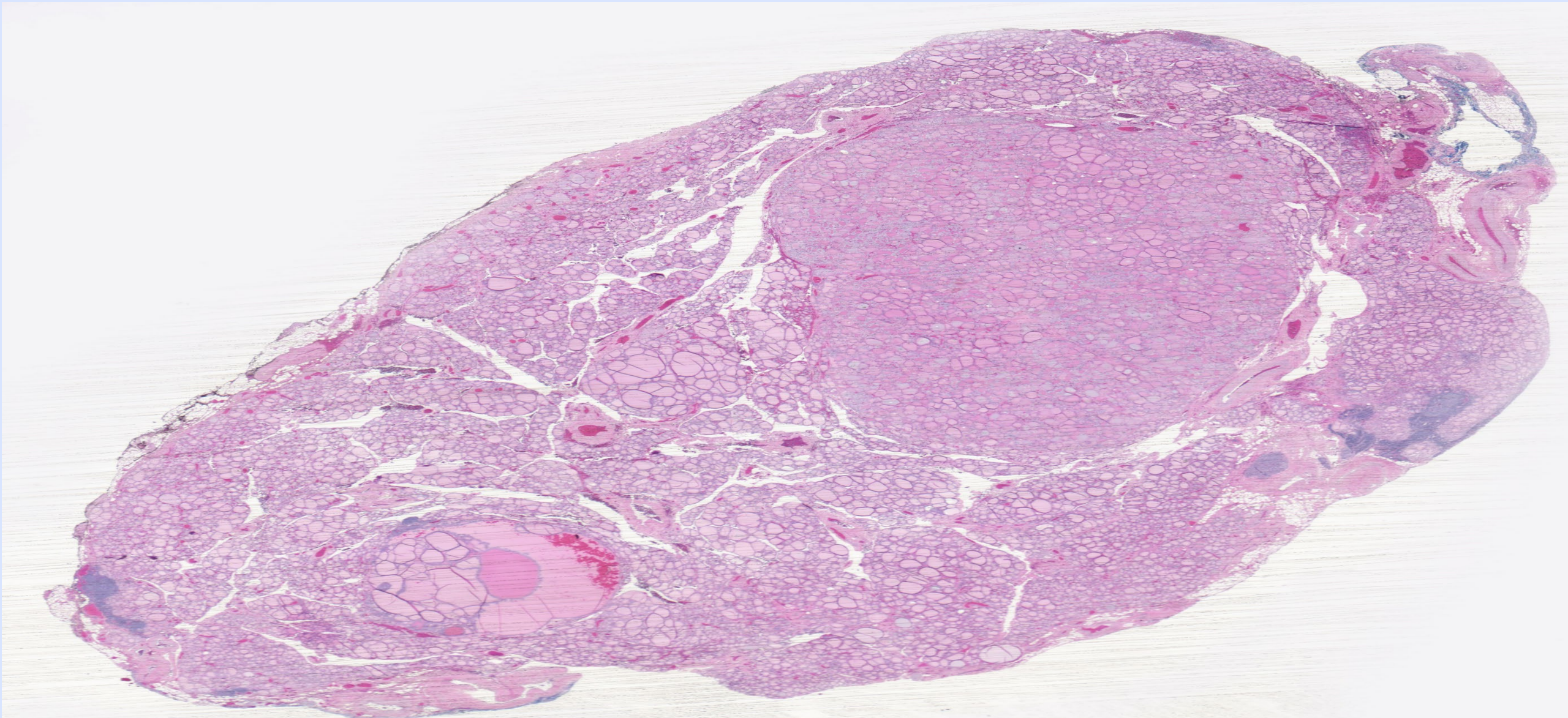
PE/WC FVPTC behave similarly to encapsulated FVPTC (no metastatic or recurrence potential if completely excised) and should be distinguished from infiltrative FVPTC.

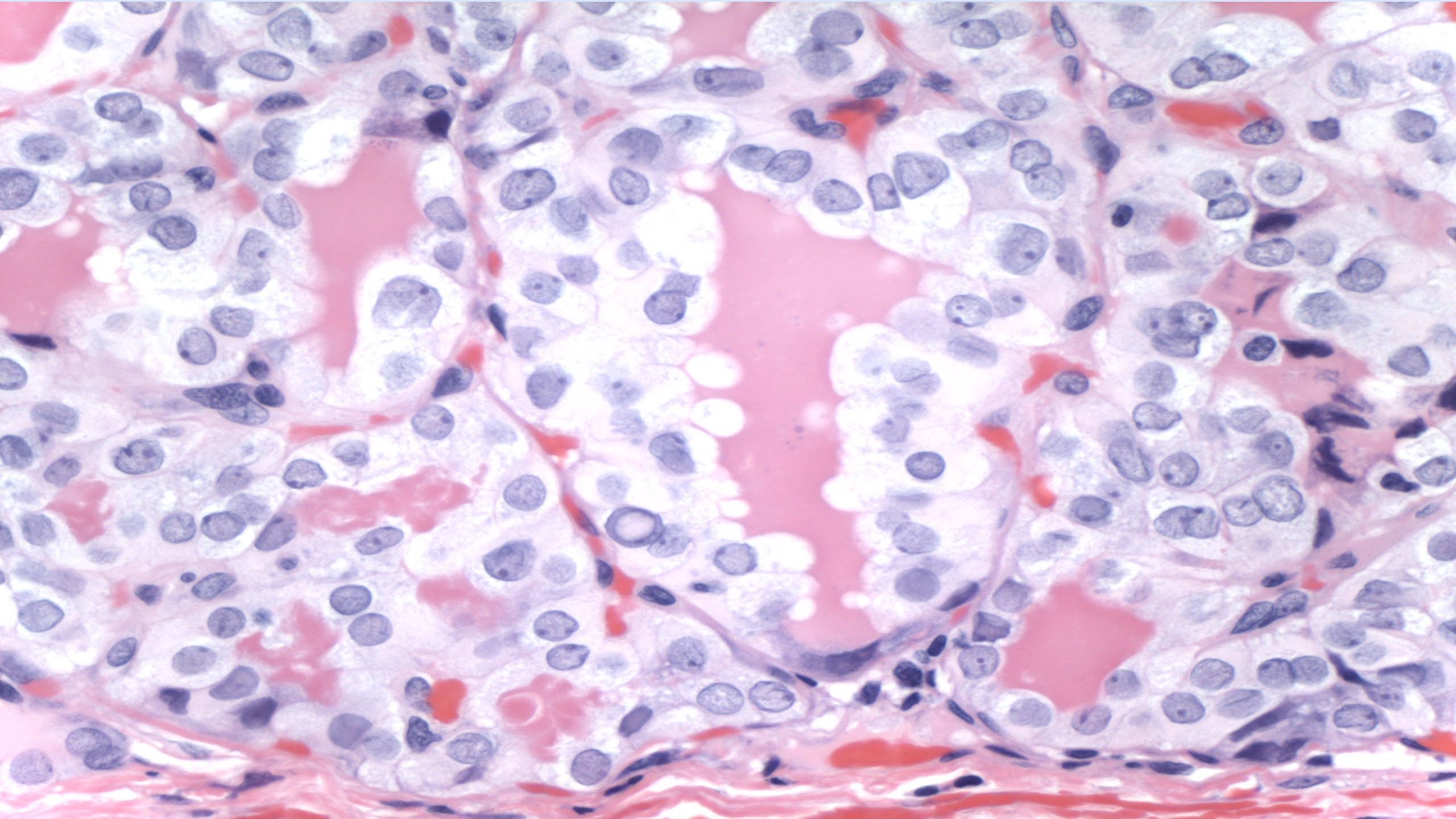
Vivero, *Thyroid*, 2013; 23(3): 273-279.

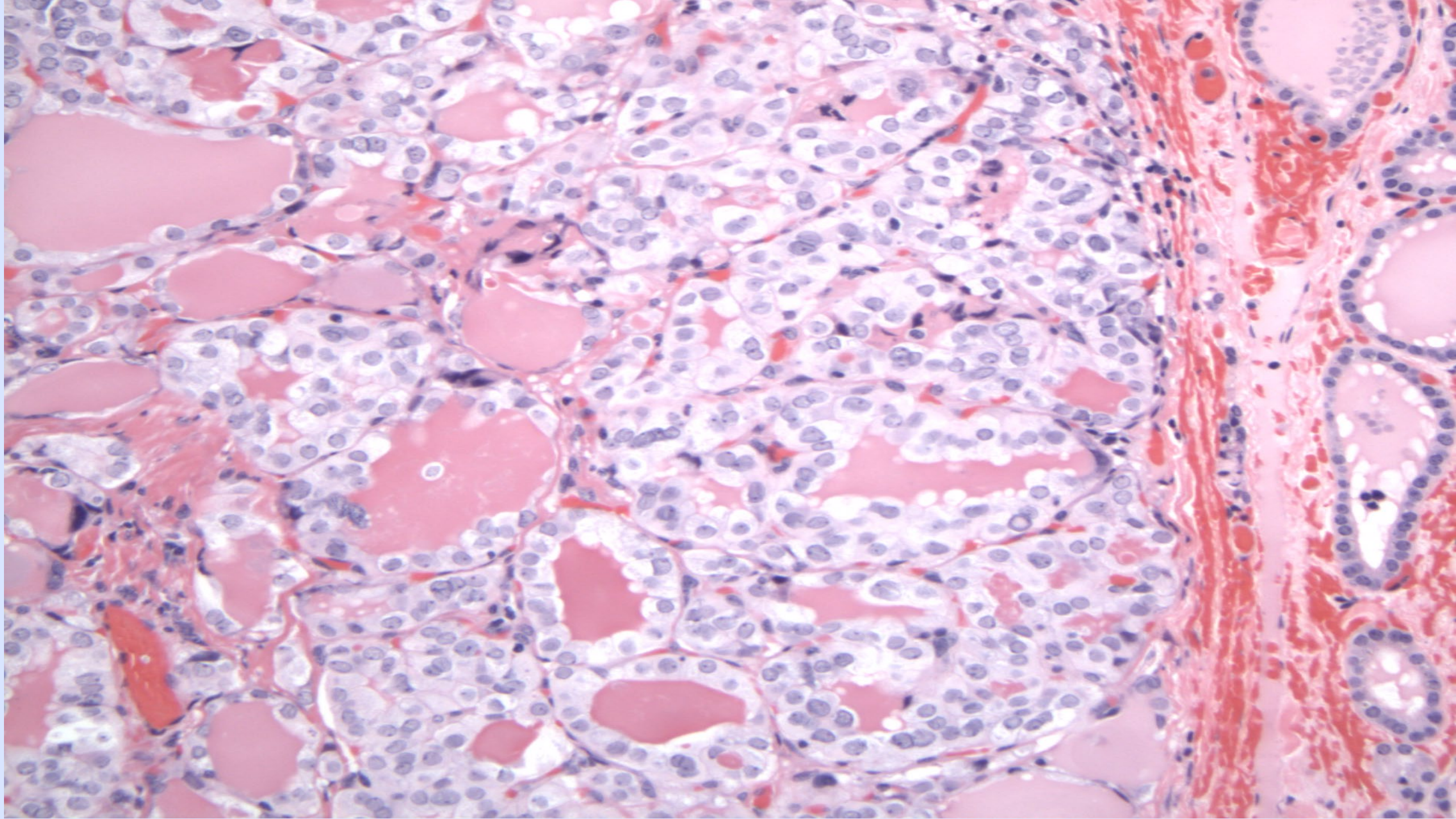
PE/WC FVPTC have molecular alterations similar to encapsulated tumors (with *RAS* mutations and no *BRAF* V600E mutations) - molecular alterations support clinical data indicating that tumors are similar to encapsulated FVPTC.

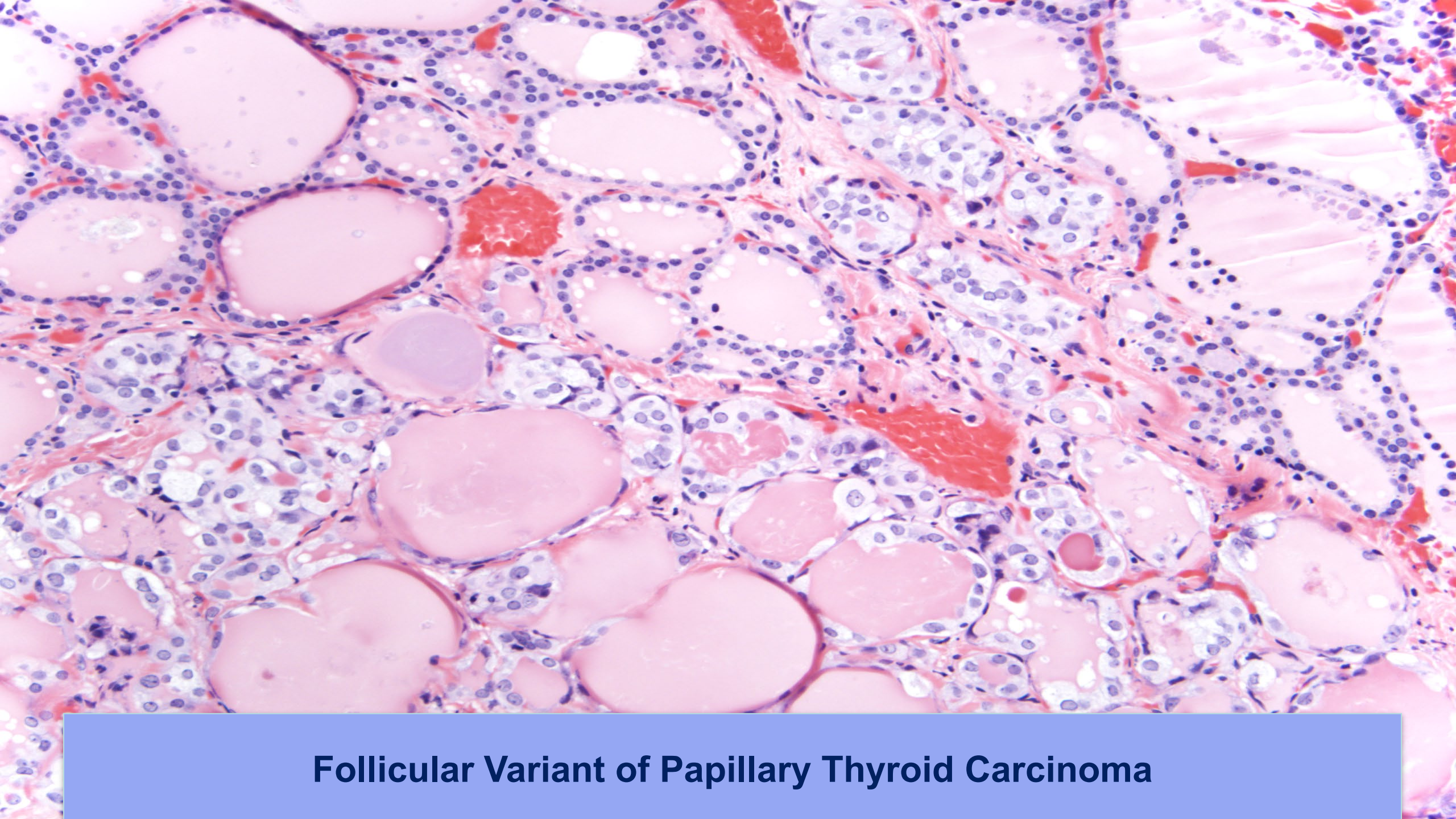
Howitt, *Thyroid*, 2013; 23(10): 1257-1262

Exclude Invasive/Infiltrative Growth



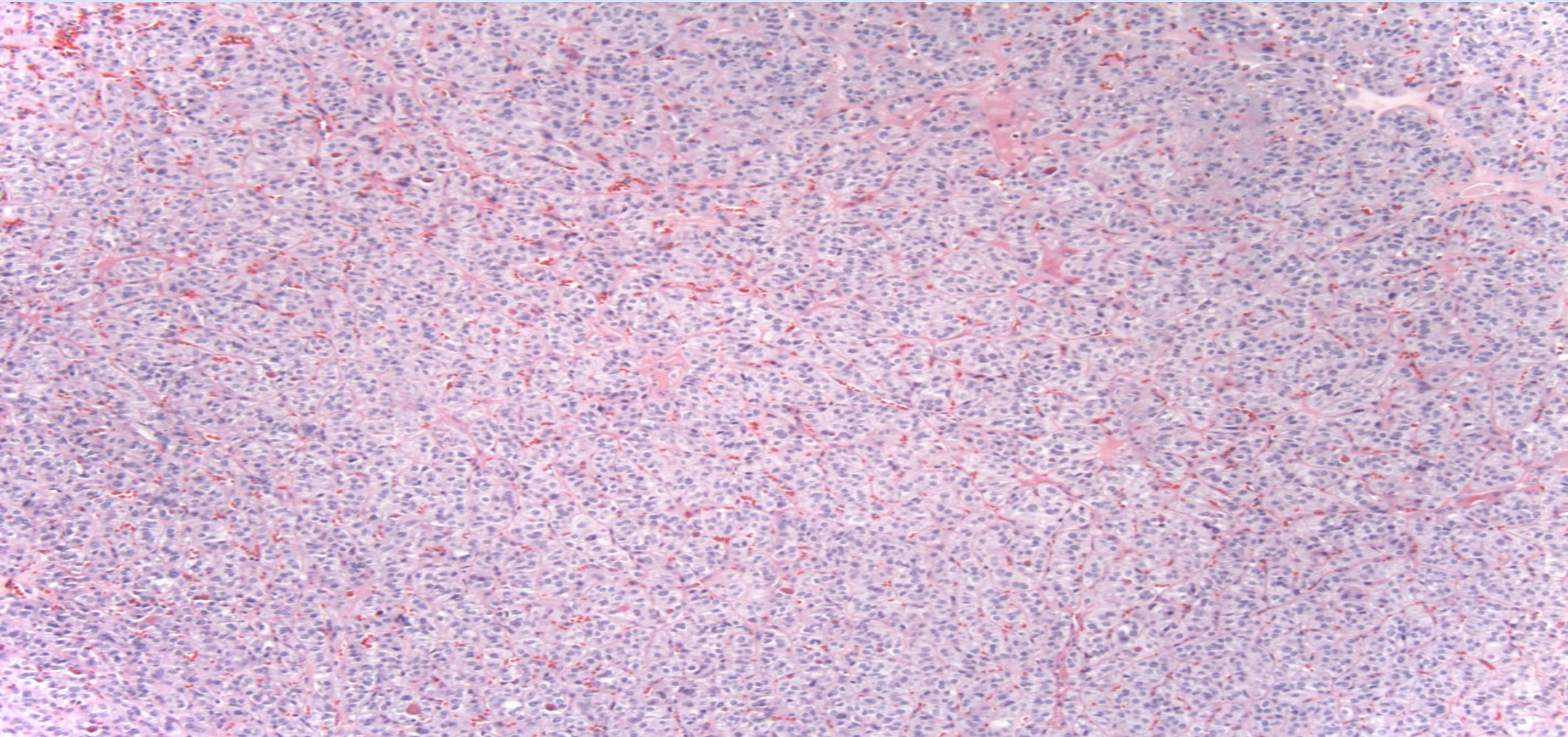




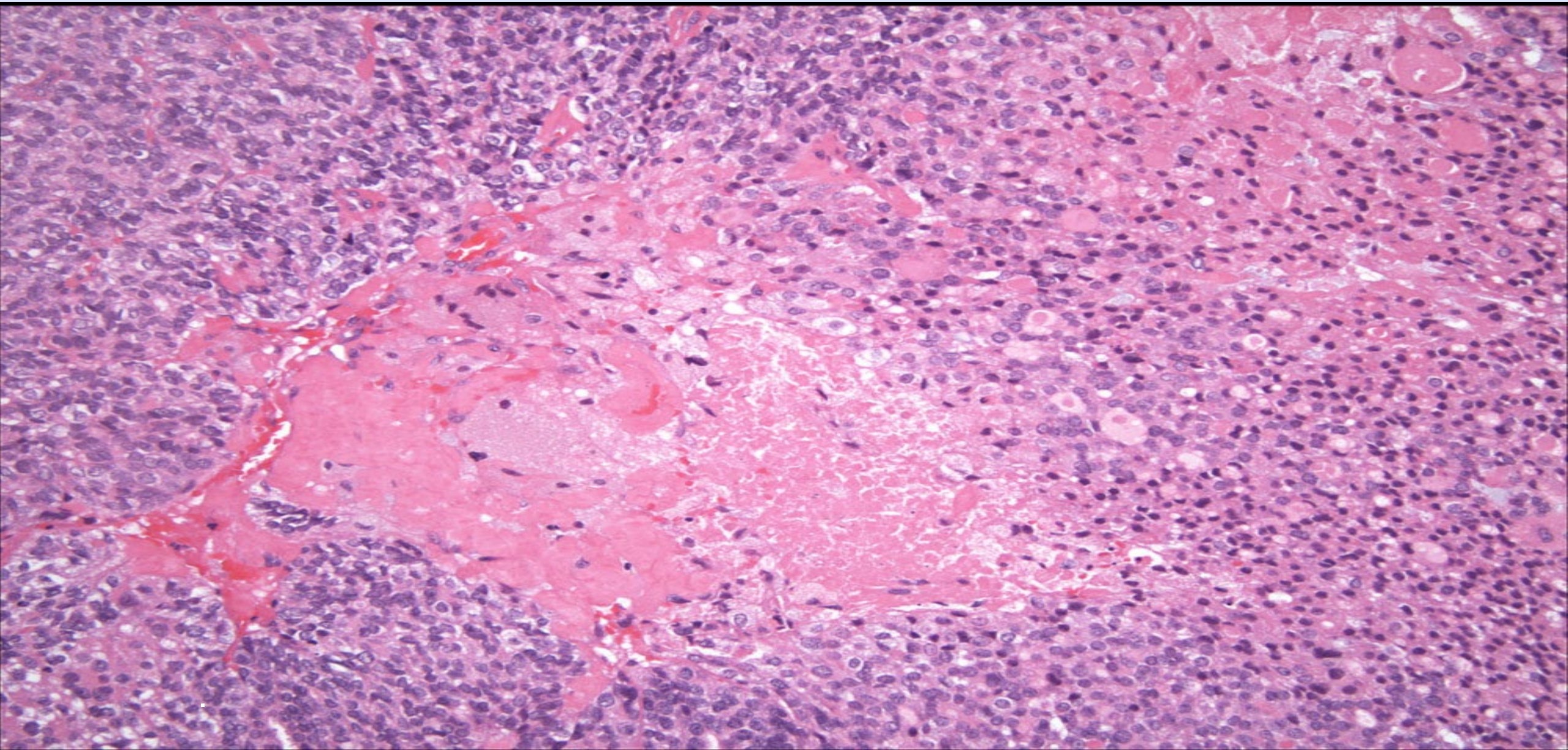


Follicular Variant of Papillary Thyroid Carcinoma

Exclude Cases with >30% Solid Growth

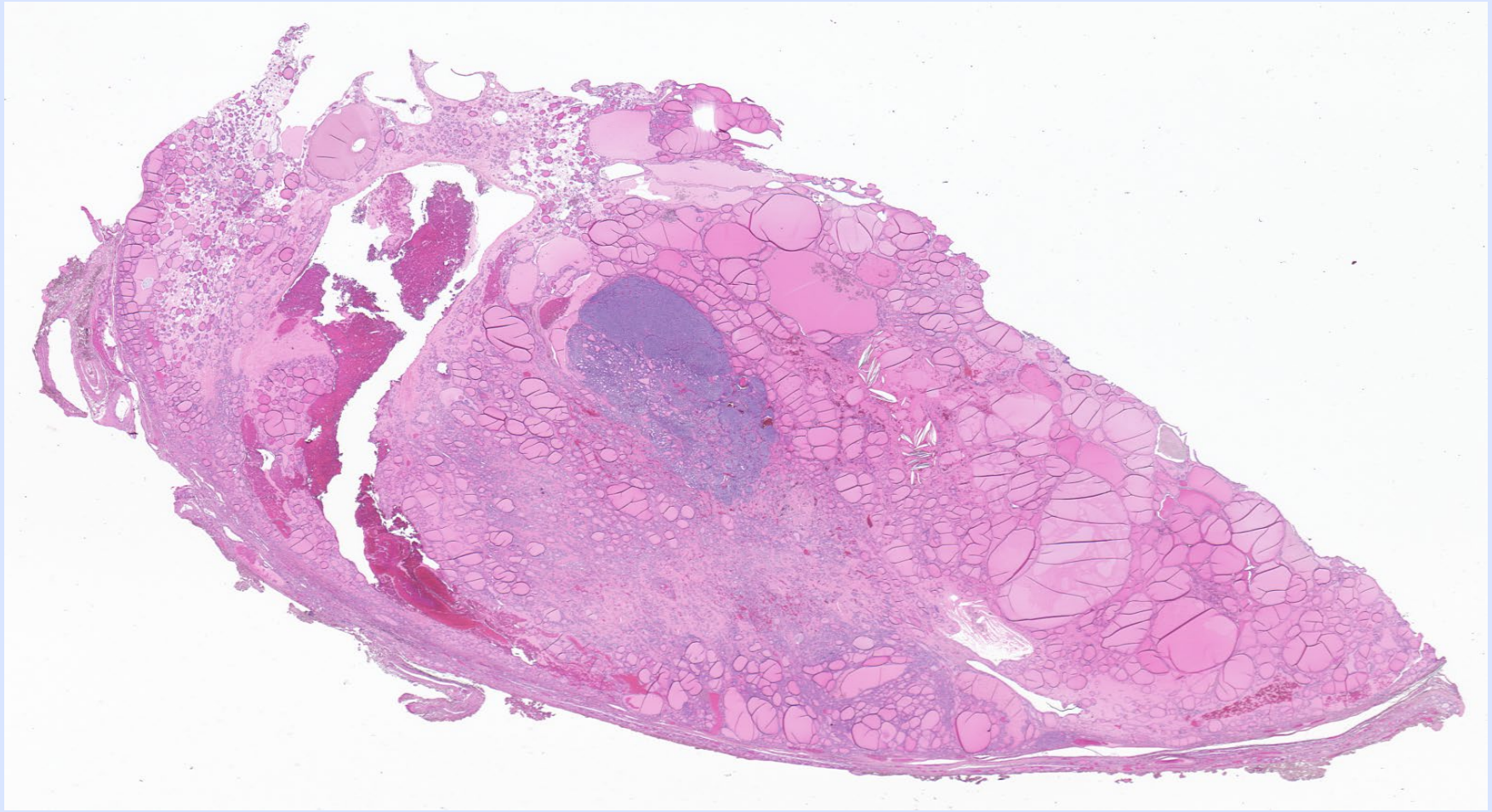


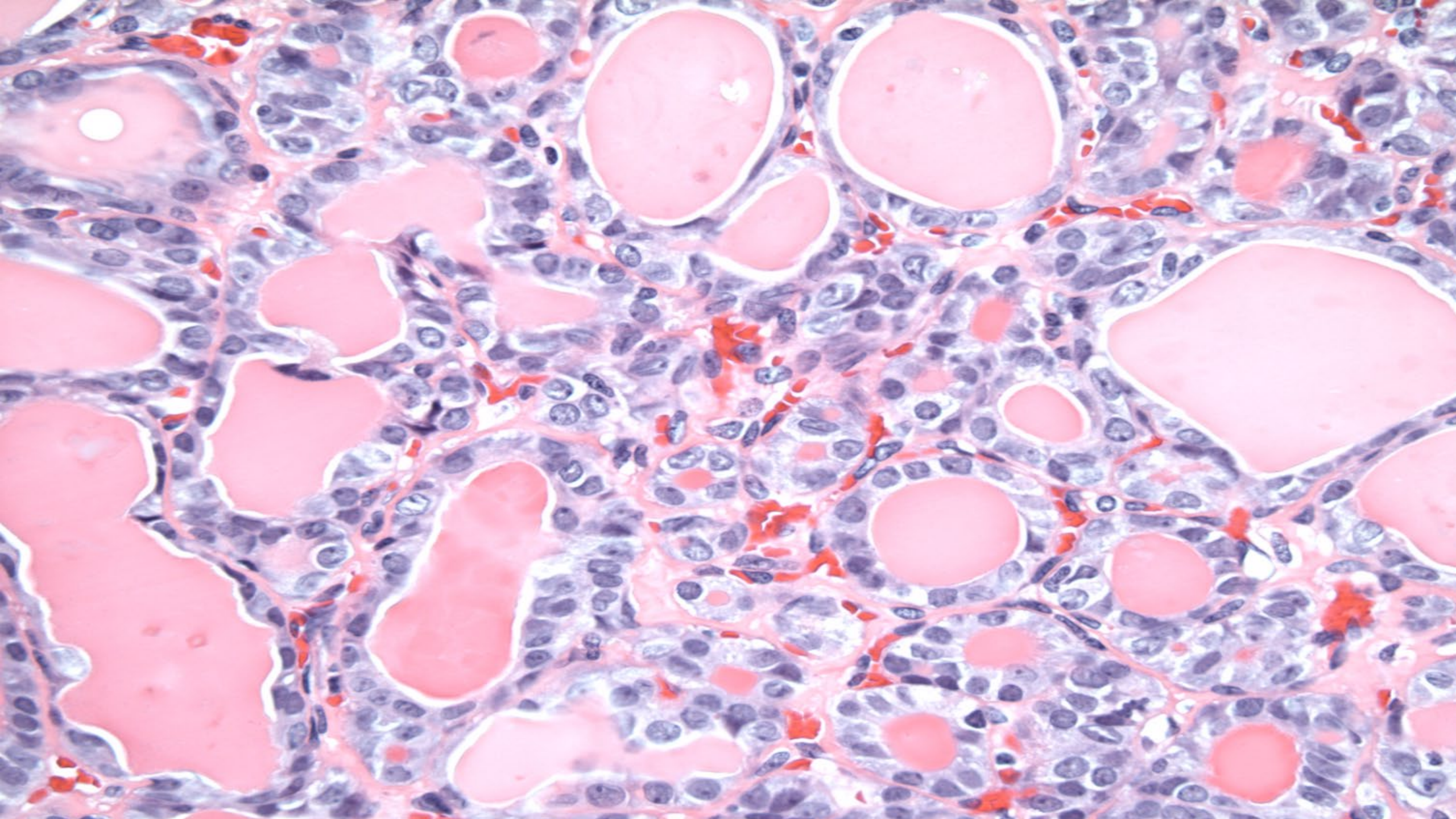
Exclude High-Grade Features

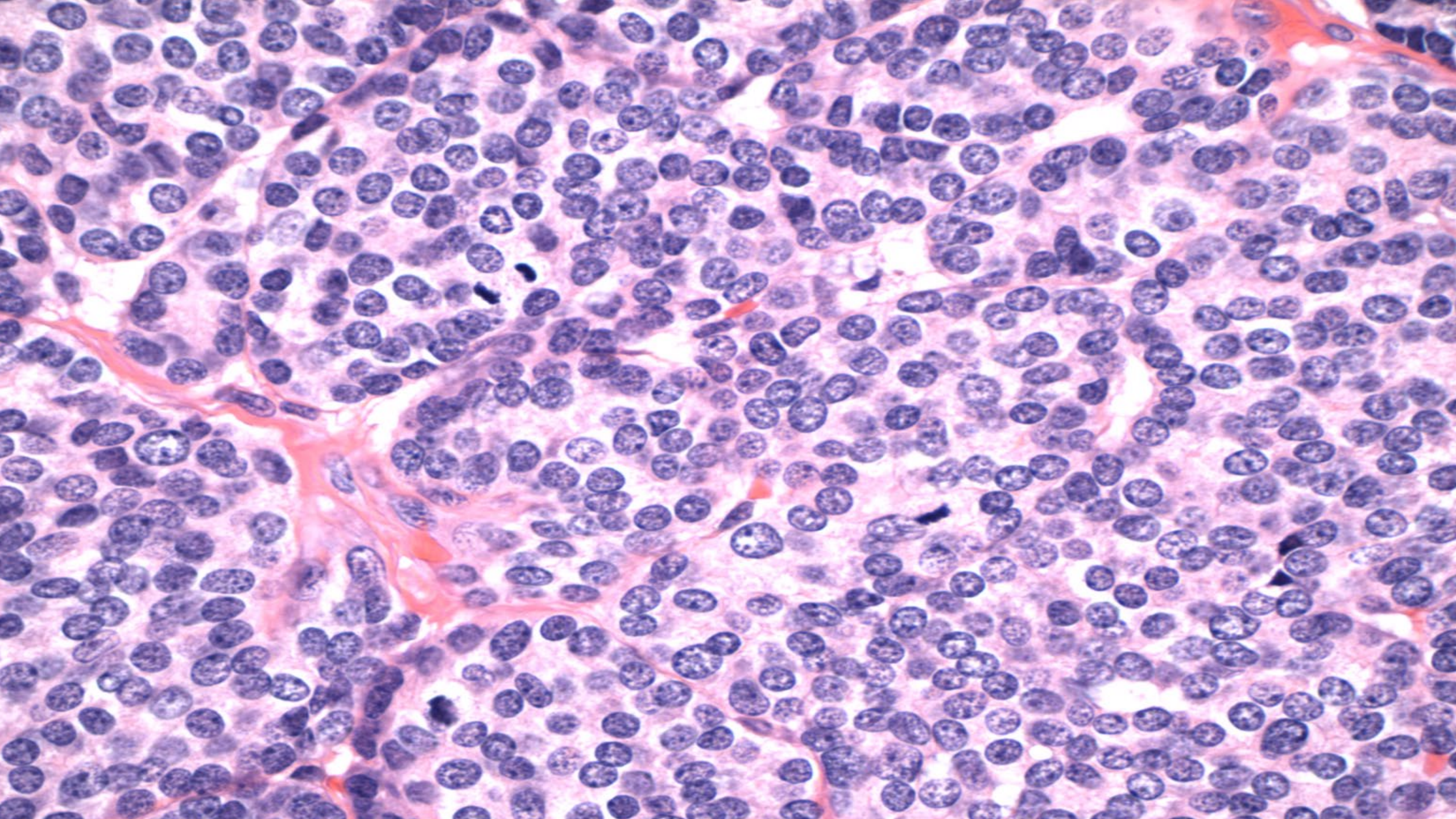


Exclude High Grade Features

Case sent in consult, with question – is this a NIFTP? The patient is a 49-year-old woman with a 4.9 cm thyroid nodule.







A. THYROID, TOTAL THYROIDECTOMY:
FOLLICULAR NEOPLASM OF UNCERTAIN MALIGNANT POTENTIAL (4.6 cm, by report), see NOTE.

NOTE: Focally (<5% of the tumor), the tumor demonstrates solid growth and increased mitotic activity (8 mitoses per 10 HPFs, Ki67 proliferative index 10-15%). Based on this focus, the tumor does not qualify as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Encapsulated tumors with high-grade features without capsular penetration or vascular invasion are rare. Although there is some evidence that these tumors pursue an indolent clinical course (see reference), given the lack of significant outcome data in the literature, this tumor should be considered of uncertain biologic potential. Clinical follow up is advised.

Reference:
Rivera M, Ricarte-Filho J, Patel S, Tuttle M, Shaha A, Shah JP, Fagin JA, Ghossein RA. Encapsulated thyroid tumors of follicular cell origin with high grade features (high mitotic rate/tumor necrosis): a clinicopathologic and molecular study. Hum Pathol. 2010 Feb;41(2):172-80.

The Tumor Can Be Large

Outcome of Large Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

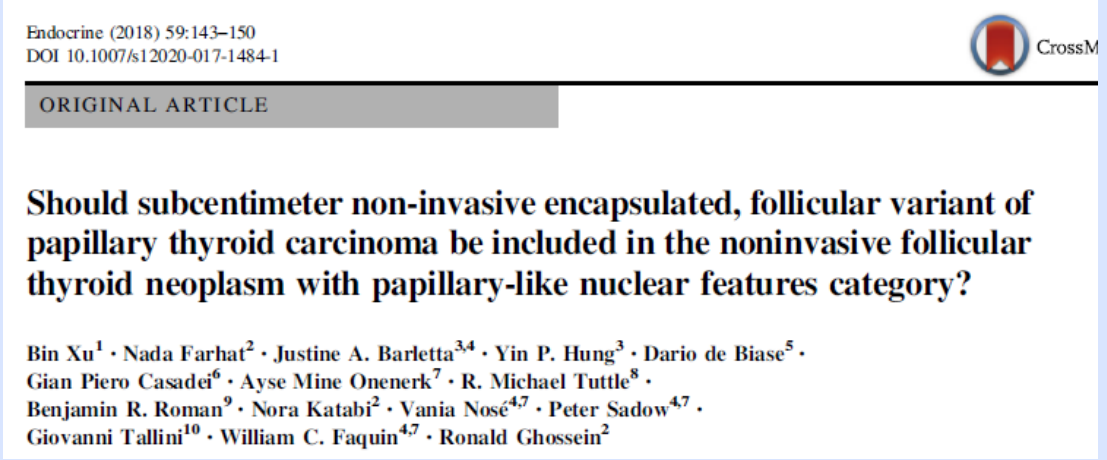
Bin Xu,[1] Giovanni Tallini,[2] Theresa Scognamiglio,[3] Benjamin R. Roman,[4] R. Michael Tuttle,[5] and Ronald A. Ghossein[6]

THYROID
Volume 27, Number 4, 2017

Evaluated 79 cases of NIFTP ≥ 4cm (mean, 4.0–8.0 cm). No lymph node metastases and no recurrences (33%, underwent lobectomy alone). Similar to their small counterparts, large NIFTP appear to have an extremely low risk of recurrence (zero in this cohort), even when treated conservatively. Surgical treatment alone, including lobectomy, appears to be adequate for large NIFTP.

What About Small NIFTP?

Although most studies on NIFTP used a minimum size cutoff of 1 cm, a 2019 study of 52 subcentimeter NIFTP showed that they have the same indolent behavior as larger tumors with the same morphology.



Endocrine (2018) 59:143–150
DOI 10.1007/s12020-017-1484-1

ORIGINAL ARTICLE

Should subcentimeter non-invasive encapsulated, follicular variant of papillary thyroid carcinoma be included in the noninvasive follicular thyroid neoplasm with papillary-like nuclear features category?

Bin Xu[1] · Nada Farhat[2] · Justine A. Barletta[3,4] · Yin P. Hung[3] · Dario de Biase[5] · Gian Piero Casadei[6] · Ayse Mine Onenerk[7] · R. Michael Tuttle[8] · Benjamin R. Roman[9] · Nora Katabi[2] · Vania Nosé[4,7] · Peter Sadow[4,7] · Giovanni Tallini[10] · William C. Faquin[4,7] · Ronald Ghossein[2]

If a diagnosis of NIFTP is rendered for a subcentimeter tumor, must be confident that the tumor is well circumscribed and lacks papillae.

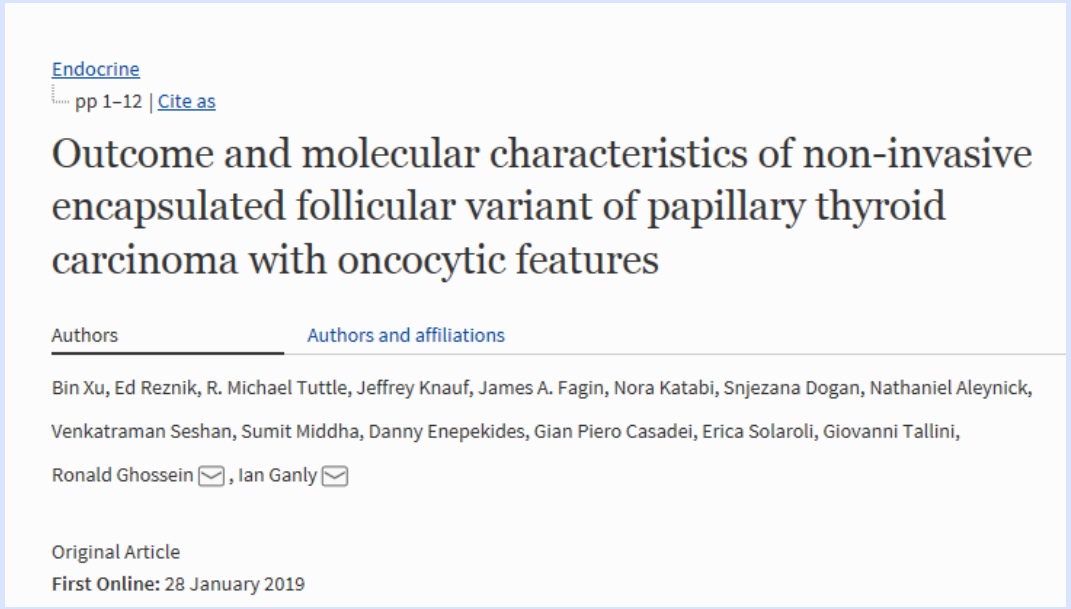
These features may be especially challenging to assess when the tumor is <0.5 cm; hence, caution is advised for rendering a diagnosis of NIFTP for tumors under half a centimeter.

What About NIFTP with Oncocytic Features?

Original NIFTP study did not mention tumors with oncocytic features.

61 patients with oncocytic EFVPTC.

No distant metastasis, lymph node metastases, or structural recurrence in the entire cohort (10.2 yr median follow-up time).



Endocrine
pp 1–12 | Cite as

Outcome and molecular characteristics of non-invasive encapsulated follicular variant of papillary thyroid carcinoma with oncocytic features

Authors | Authors and affiliations

Bin Xu, Ed Reznik, R. Michael Tuttle, Jeffrey Knauf, James A. Fagin, Nora Katabi, Snjezana Dogan, Nathaniel Aleynick, Venkatraman Seshan, Sumit Middha, Danny Enepekides, Gian Piero Casadei, Erica Solaroli, Giovanni Tallini, Ronald Ghossein, Ian Ganly

Original Article
First Online: 28 January 2019

Fine to use NIFTP terminology for tumors with oncocytic cytoplasm.

Consider BRAF V600E IHC

IHC (or molecular analysis) interrogating the *BRAF* V600E mutation status could be considered for cases of potential NIFTP with unusual histologic features (such as readily identifiable pseudo-inclusions or potential papillae).

IHC for BRAF V600E has demonstrated a high concordance rate with molecular methods.

Table – Correlation between BRAF V600E immunohistochemistry and BRAF mutation status assessed by molecular testing.

Study	Tumor	# of cases	Antibody	Sensitivity	Specificity
Bullock et al.[56]	Thyroid	96	VE1 hybridoma	100%	90%
Capper et al.[21]	Thyroid	21	VE1 hybridoma	100%	100%
Crescenzi et al.[57]	Thyroid	21	VE1 (Spring Bio)	100%	100%
Fisher et al., 2014[58]	Thyroid	41	VE1 (Spring Bio)	100%	62%
Ghossein et al.[46]	Thyroid	91	VE1 (Spring Bio)	100%	91%
Ilie et al.[59]	Thyroid	194	VE1 hybridoma	99%	100%
Kim et al.[60]	Thyroid	91	VE1 (Spring Bio)	n/a[a]	n/a[a]
Koperek et al.[61]	Thyroid	39	VE1 hybridoma	100%[b]	100%[b]
McKelvie et al.[62]	Thyroid	71	VE1 (Spring Bio)	100%	94%
Routhier et al.[39]	Thyroid	23	VE1 (Spring Bio)	100%	100%
			V600E (NewEast Bio)	100%	70%
Zagzag et al.[63]	Thyroid	37	VE1 (Spring Bio)	89%	100%
Zimmermann et al.[64]	Thyroid	48	VE1 (Spring Bio)	94%	94%

Modified from Ritterhouse, *Semin Diagn Pathol*, 2015.

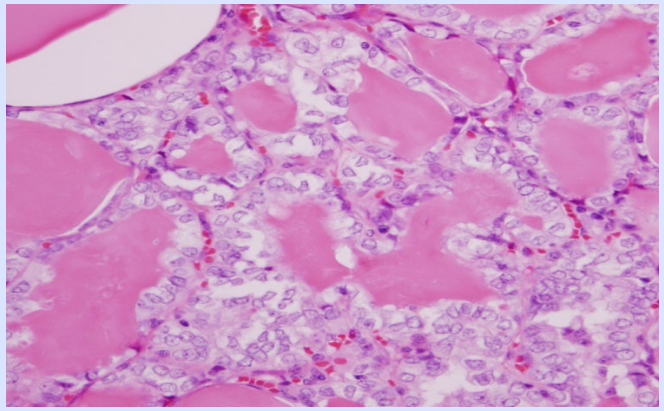
Consider BRAF V600E IHC

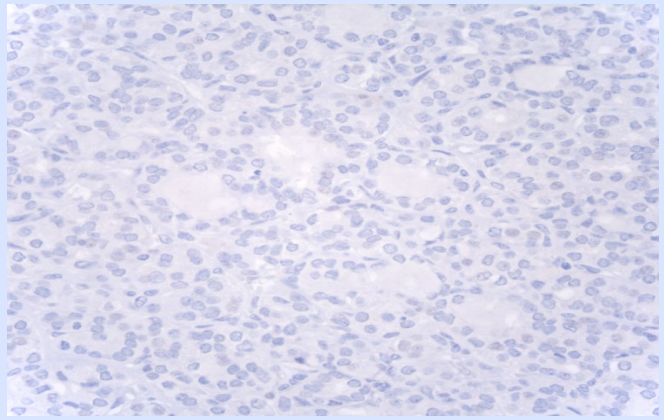
Histopathology

Correspondence 579

Howitt, Paulson, *Histopathology*, 2015.

Absence of BRAF V600E in non-infiltrative, non-invasive follicular variant of papillary thyroid carcinoma





Human Pathology (2018) **82**, 32–38

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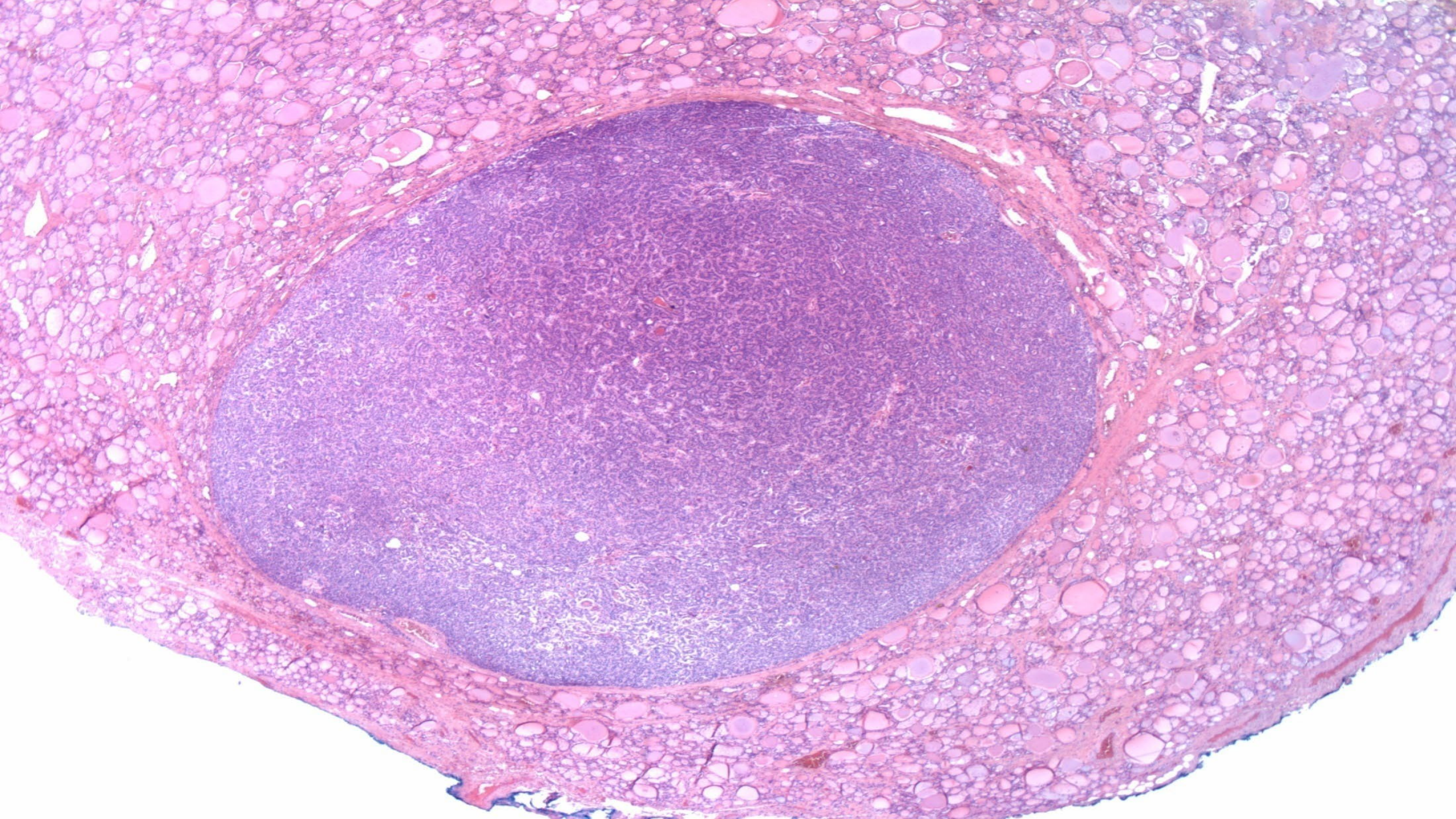
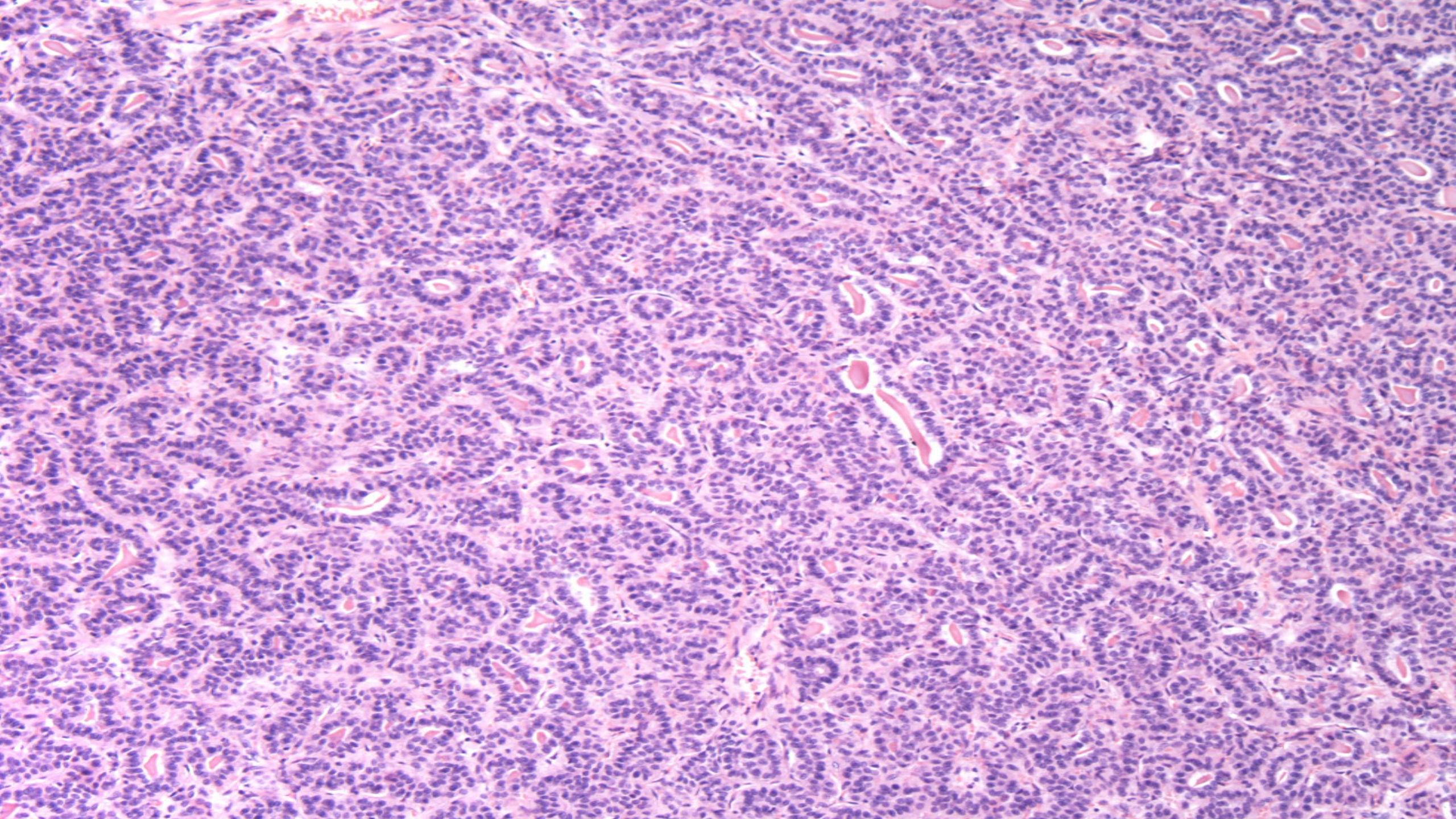
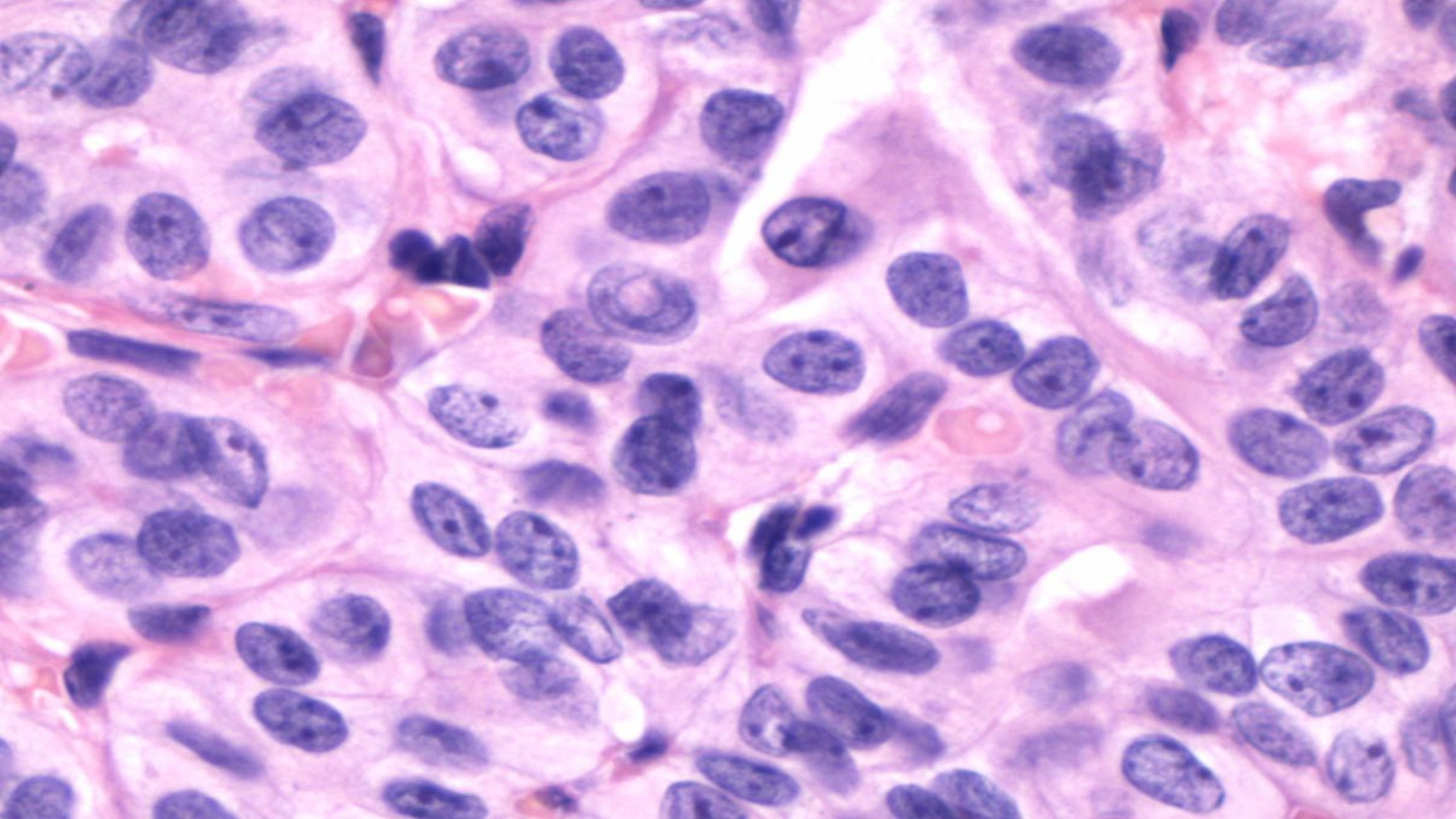
In this issue

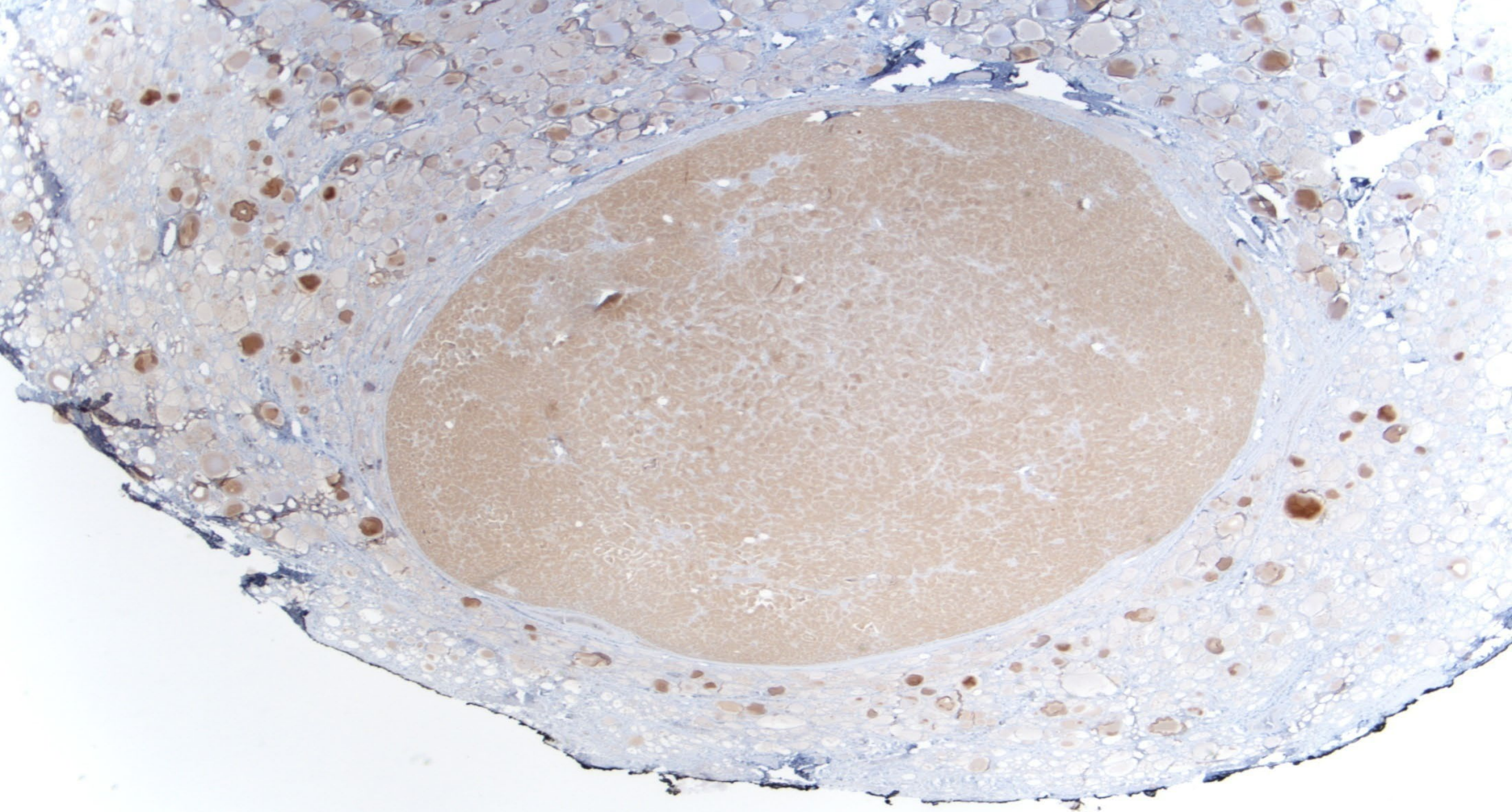
Exploration of BRAFV600E as a diagnostic adjuvant in the non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) ☆

Daniel N. Johnson MD[a,b], Peter M. Sadow MD, PhD[a,b,c,*]









Diagnosis

PAPILLARY THYROID CARCINOMA , see NOTE.

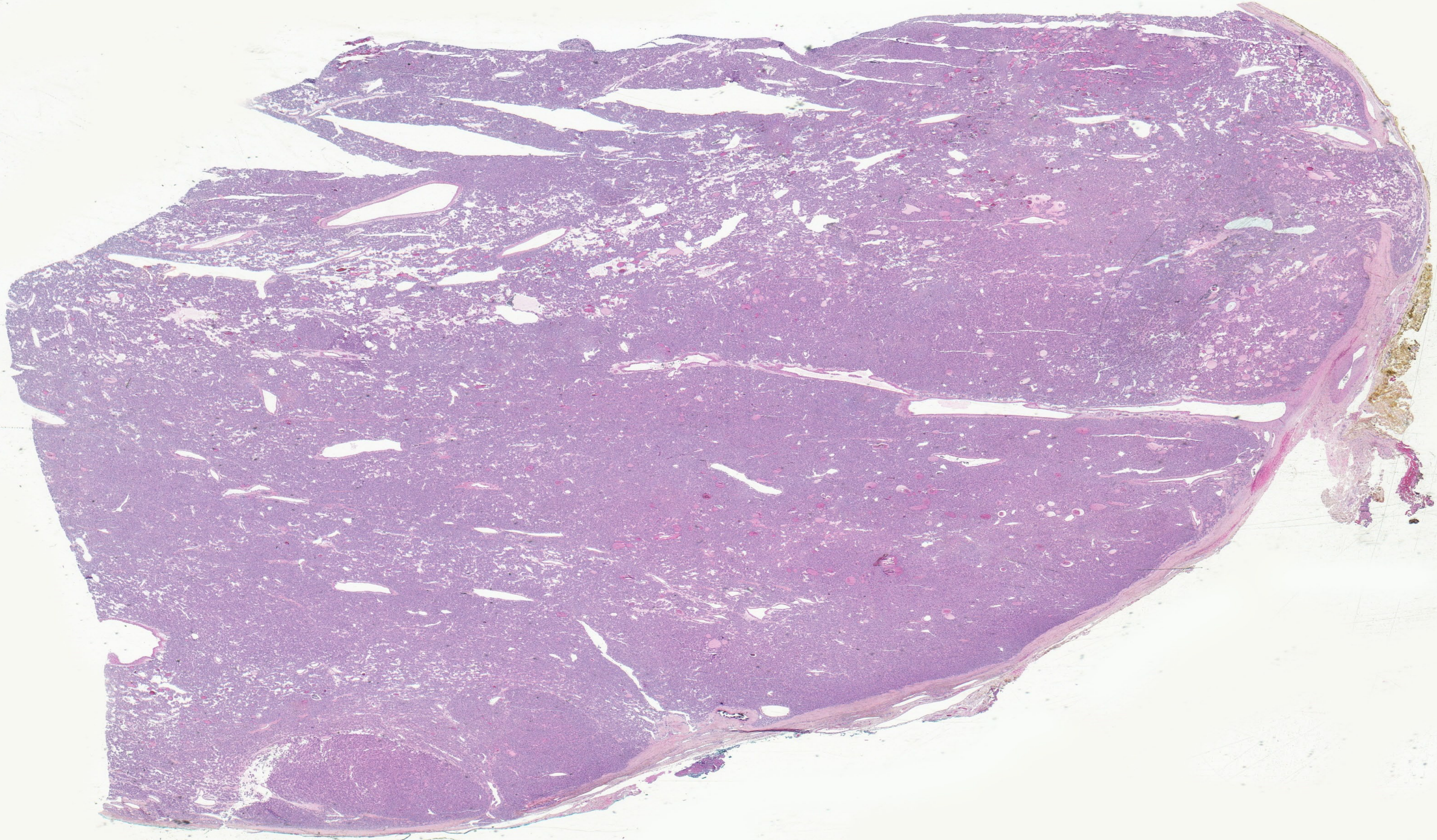
NOTE: Although the tumor appears to have a predominantly follicular architecture, the scattered nuclear pseudoinclusions and positivity for BRAF V600E by immunohistochemistry suggests that this tumor is best considered a classic papillary thyroid carcinoma with a predominantly follicular architecture.

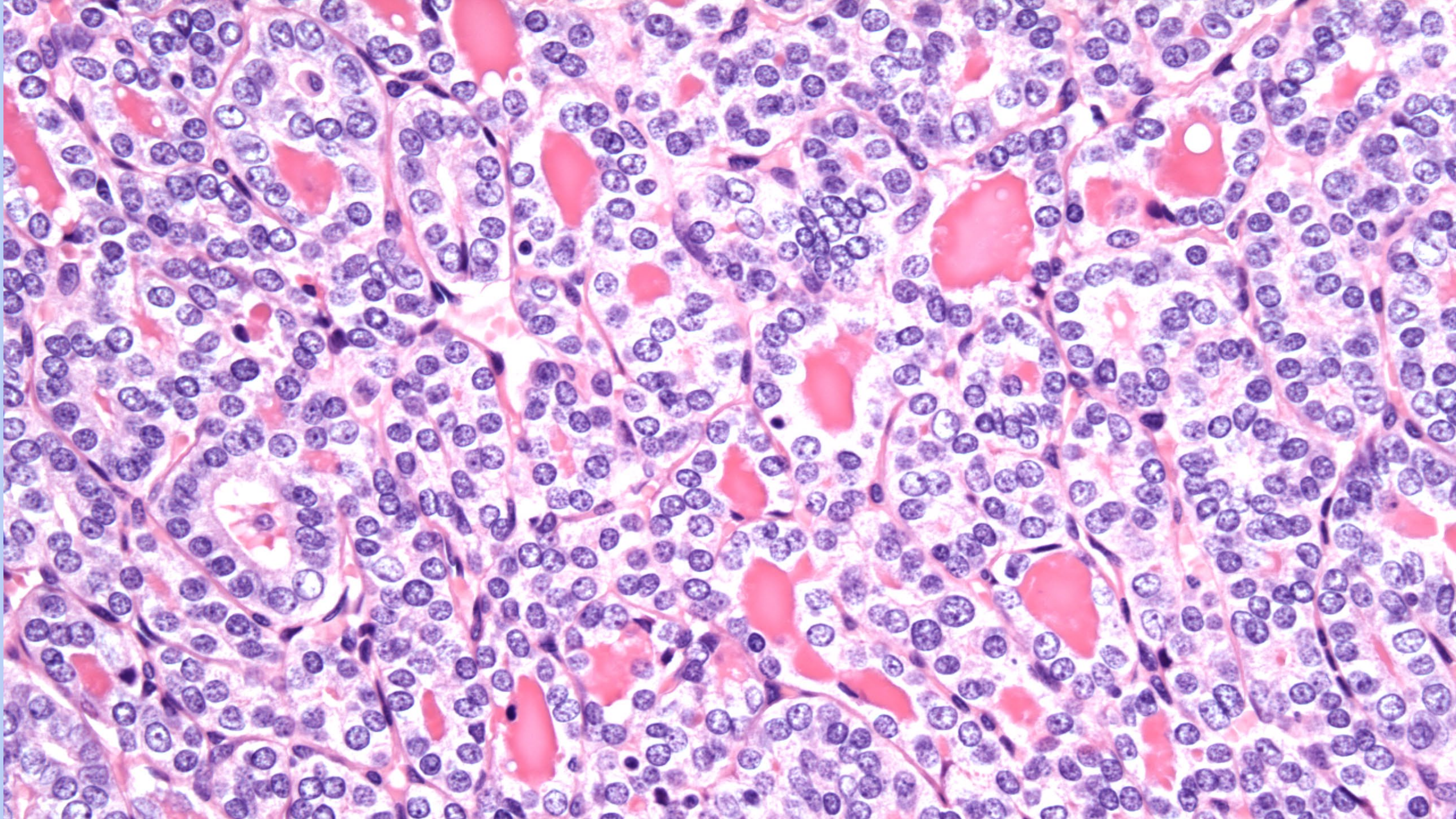
Case

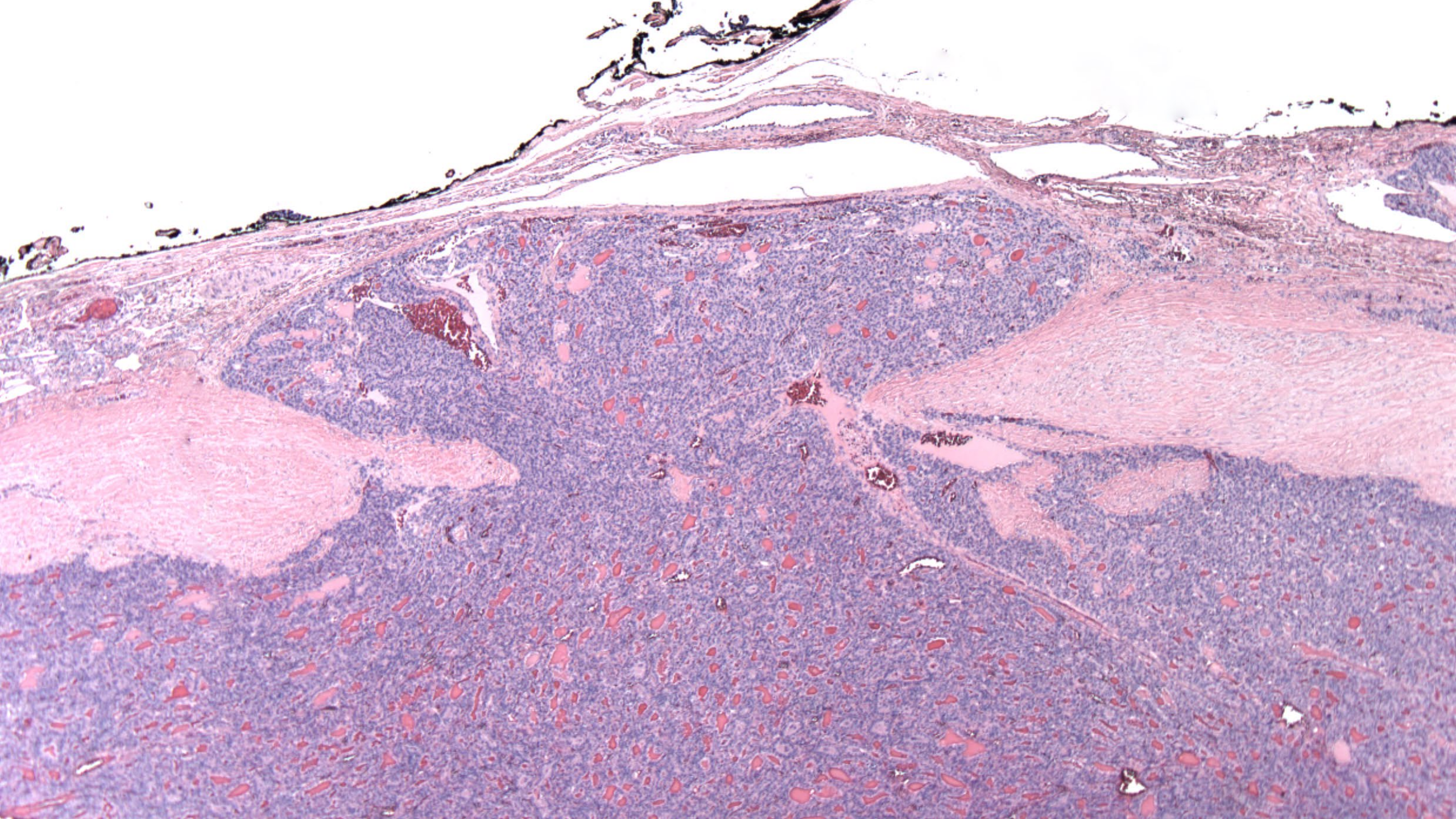
The patient is a 43-year-old man who detected a thyroid nodule on self examination. Ultrasound revealed a 3.9 cm nodule in the left lobe.

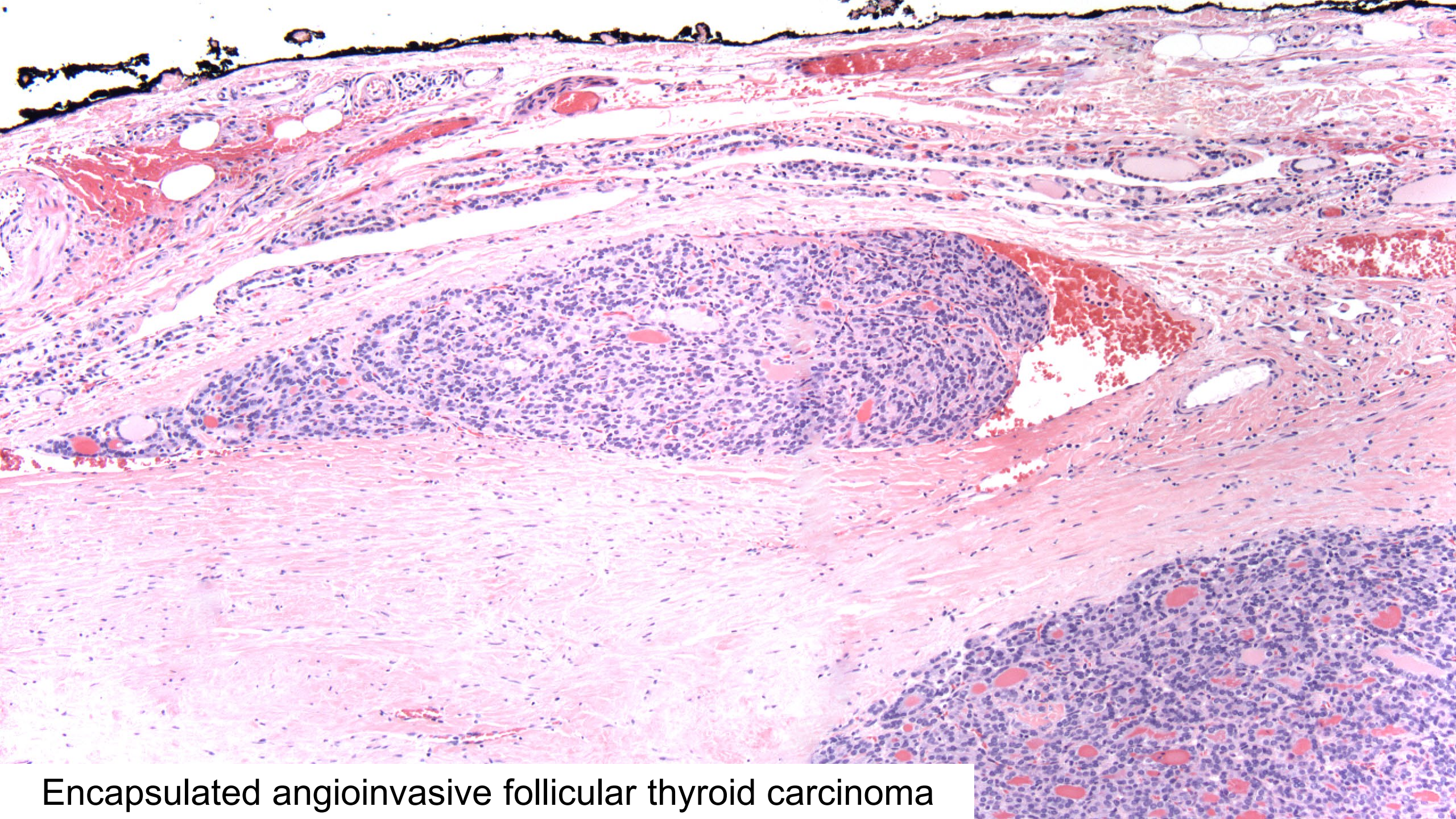
A fine needle aspiration (FNA) was performed and interpreted as suspicious for a follicular neoplasm.

A diagnostic lobectomy was performed.









Encapsulated angioinvasive follicular thyroid carcinoma

Follicular Thyroid Carcinoma

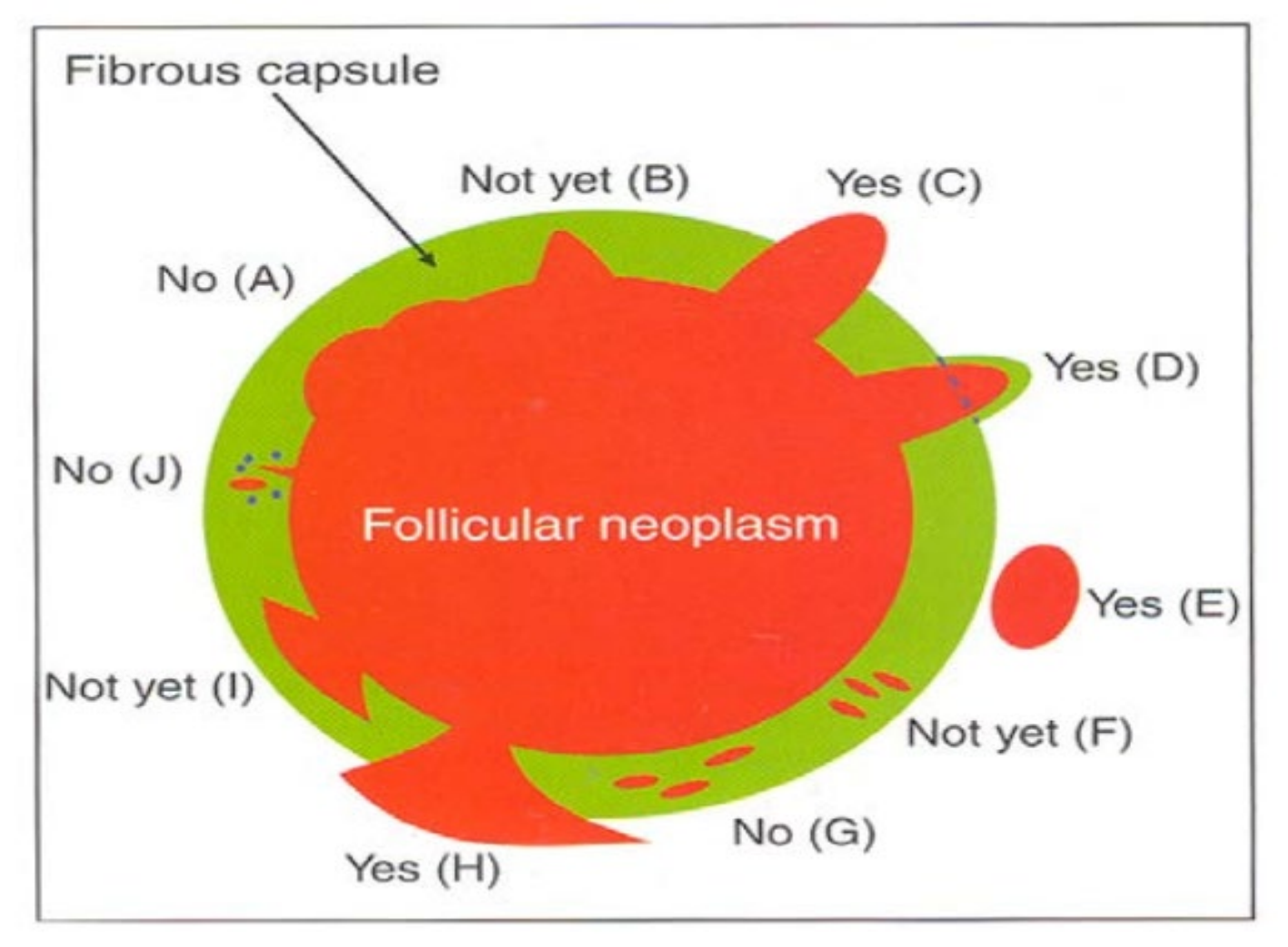
The distinction between follicular adenoma and follicular thyroid carcinoma (FTC) is based on the presence of capsular and/or vascular invasion.

Diagnostically challenging aspect of diagnosis/area of controversy:

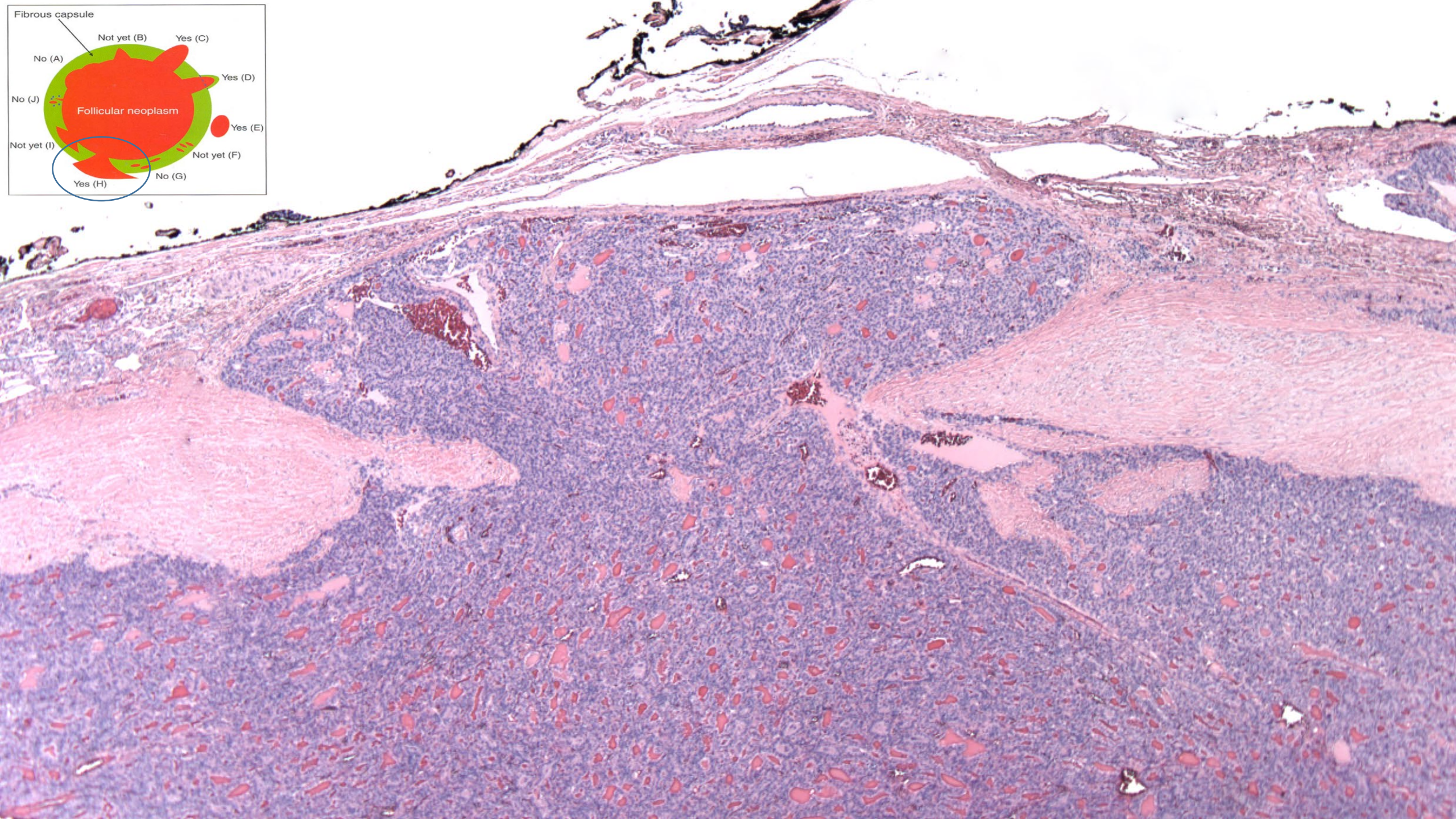
- Capsular invasion

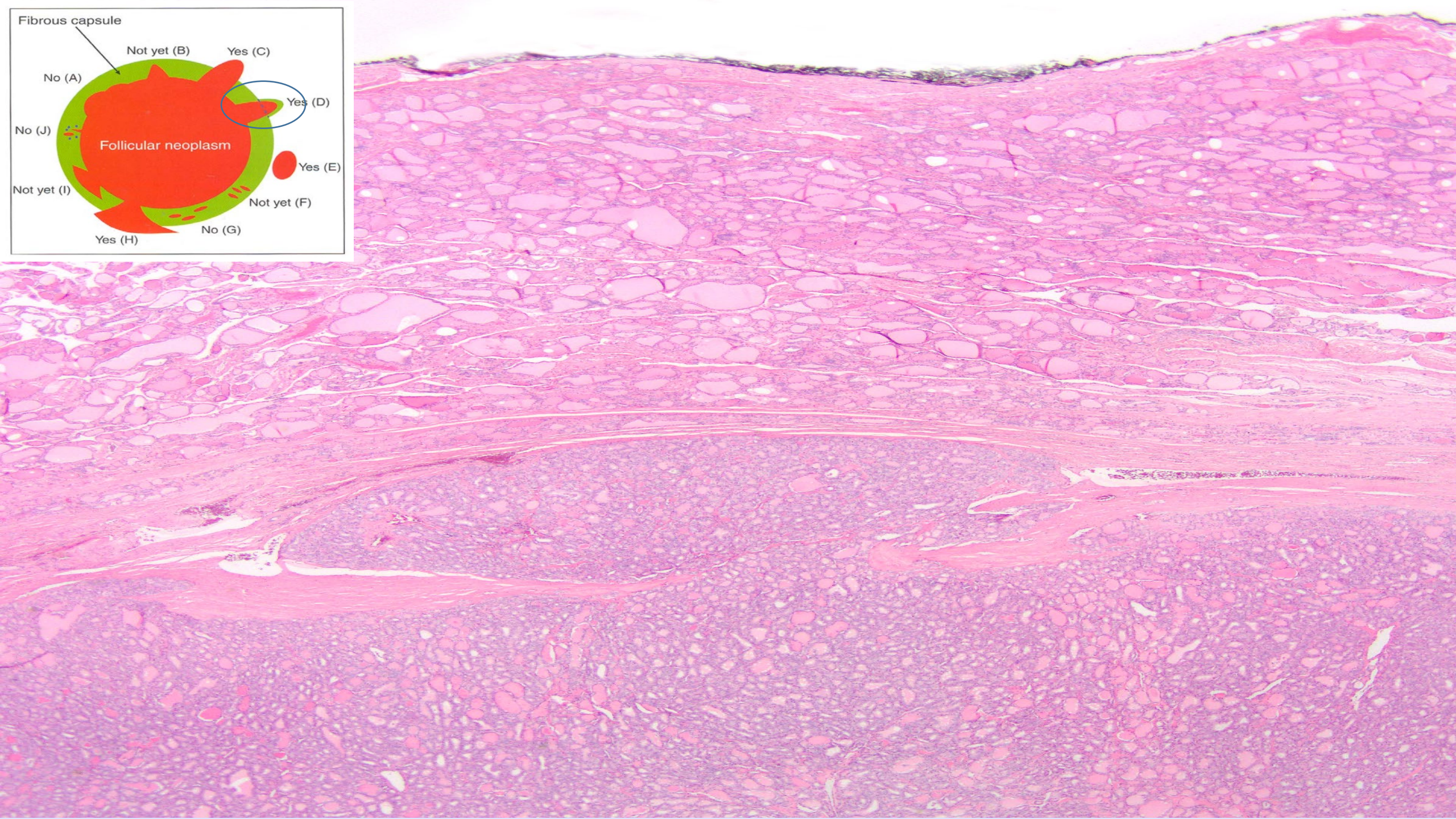
- Vascular invasion

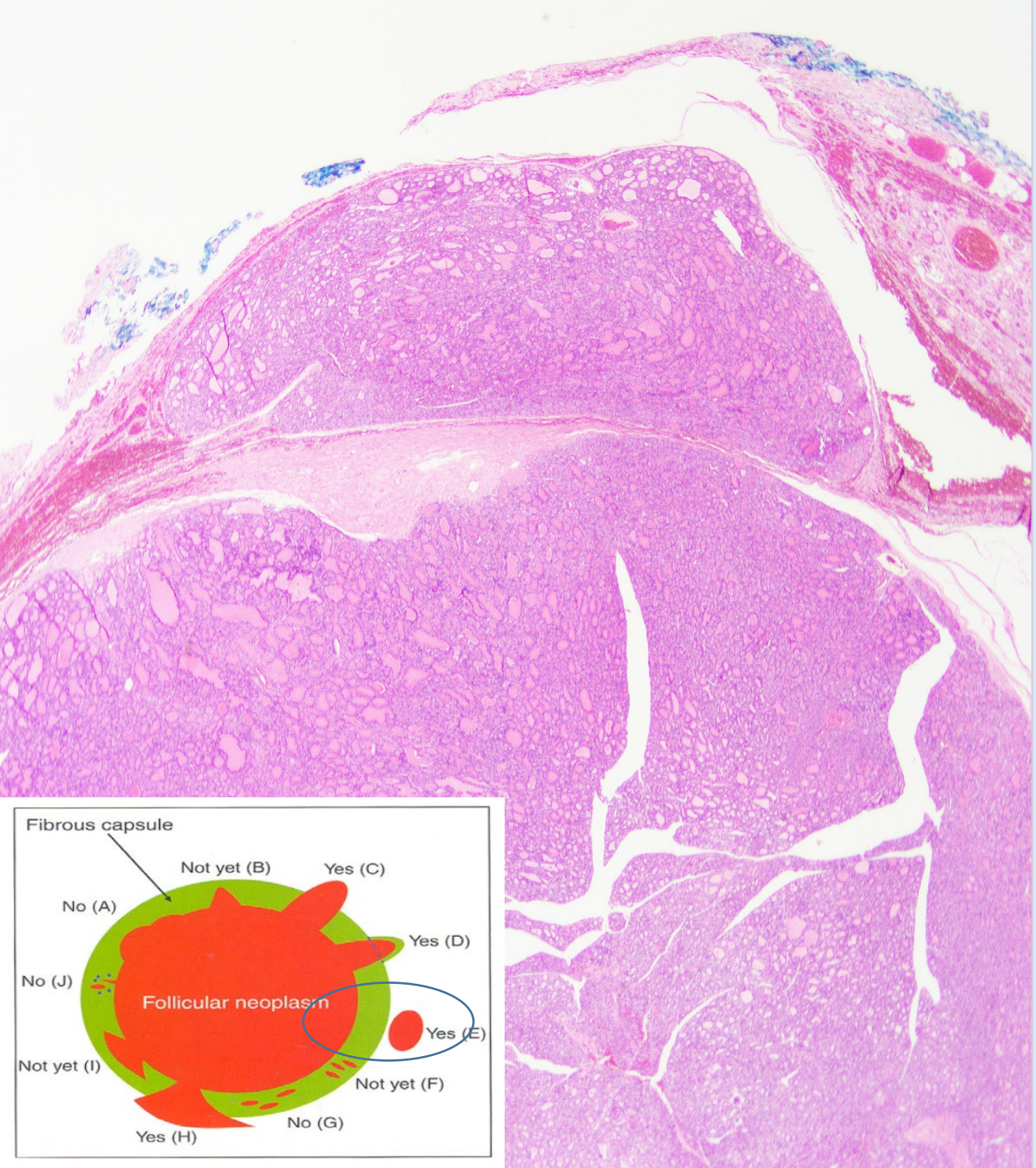
Criteria for Capsular Invasion

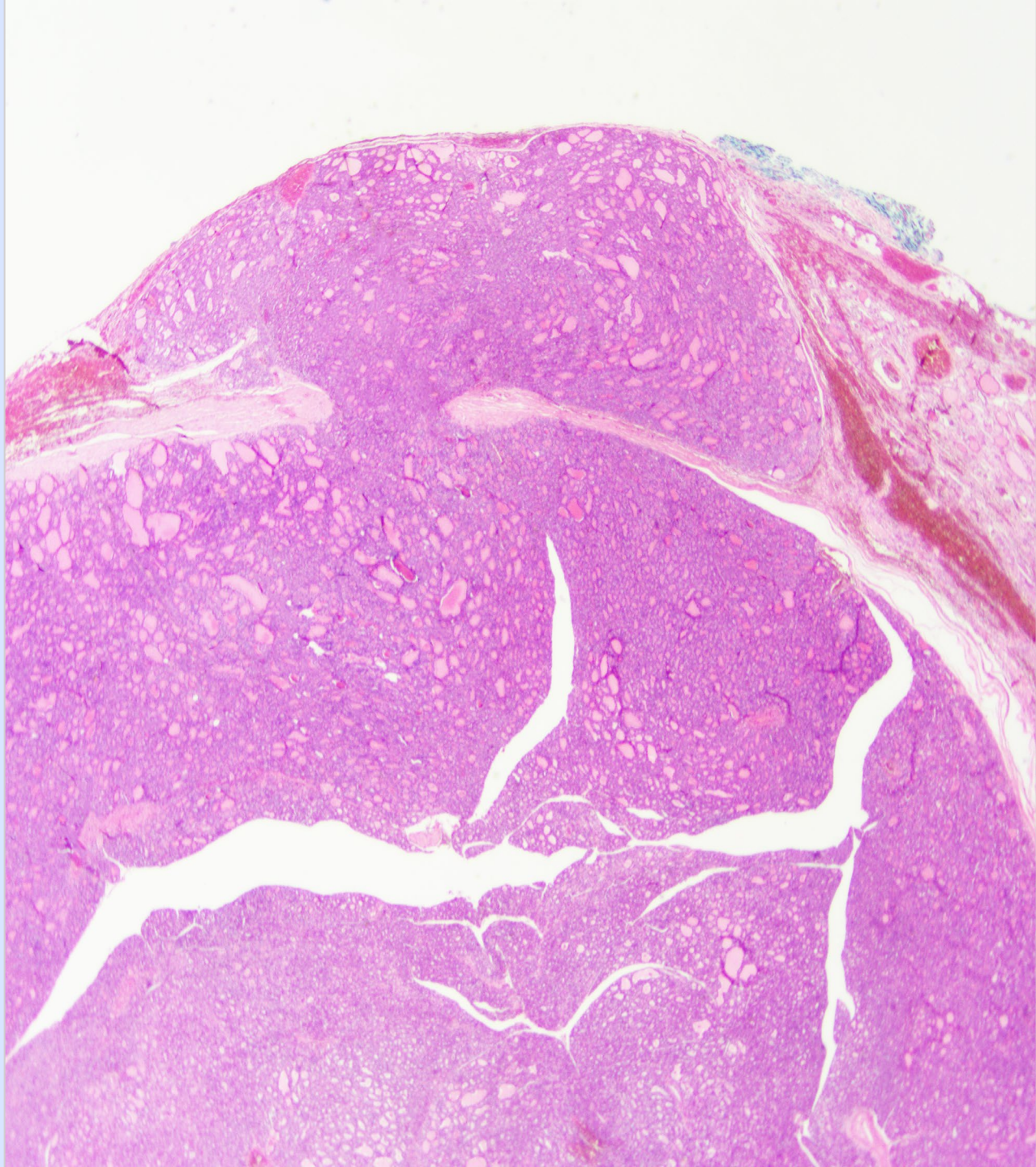


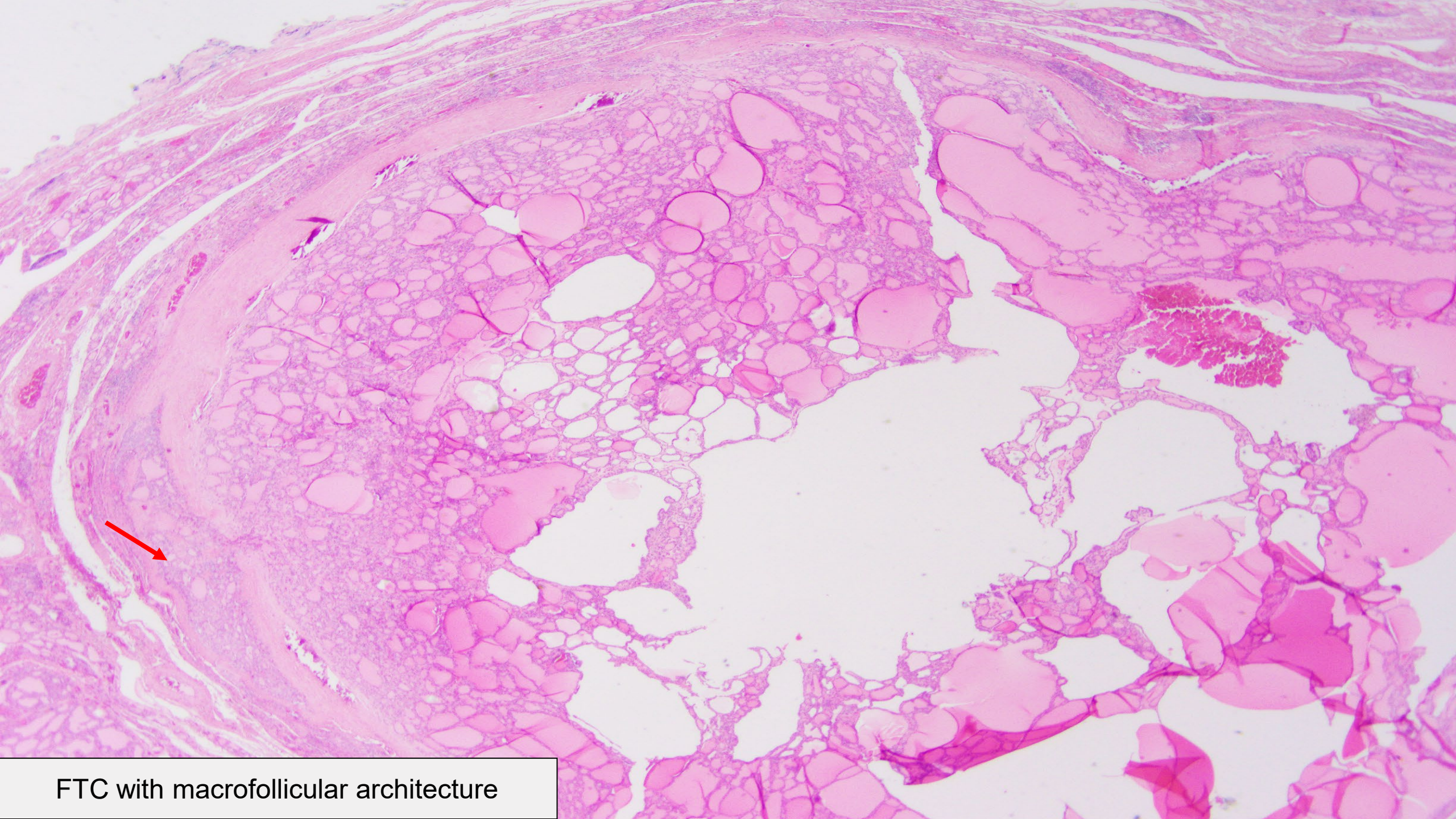
Fletcher CDM, ed. Diagnostic Histopathology of Tumours. 3rd ed. Edinburgh: Churchill Livingstone Elsevier; 2007.


Fibrous capsule
Not yet (B)
Yes (C)
No (A)
Yes (D)
No (J)
Follicular neoplasm
Yes (E)
Not yet (I)
Not yet (F)
No (G)
Yes (H)

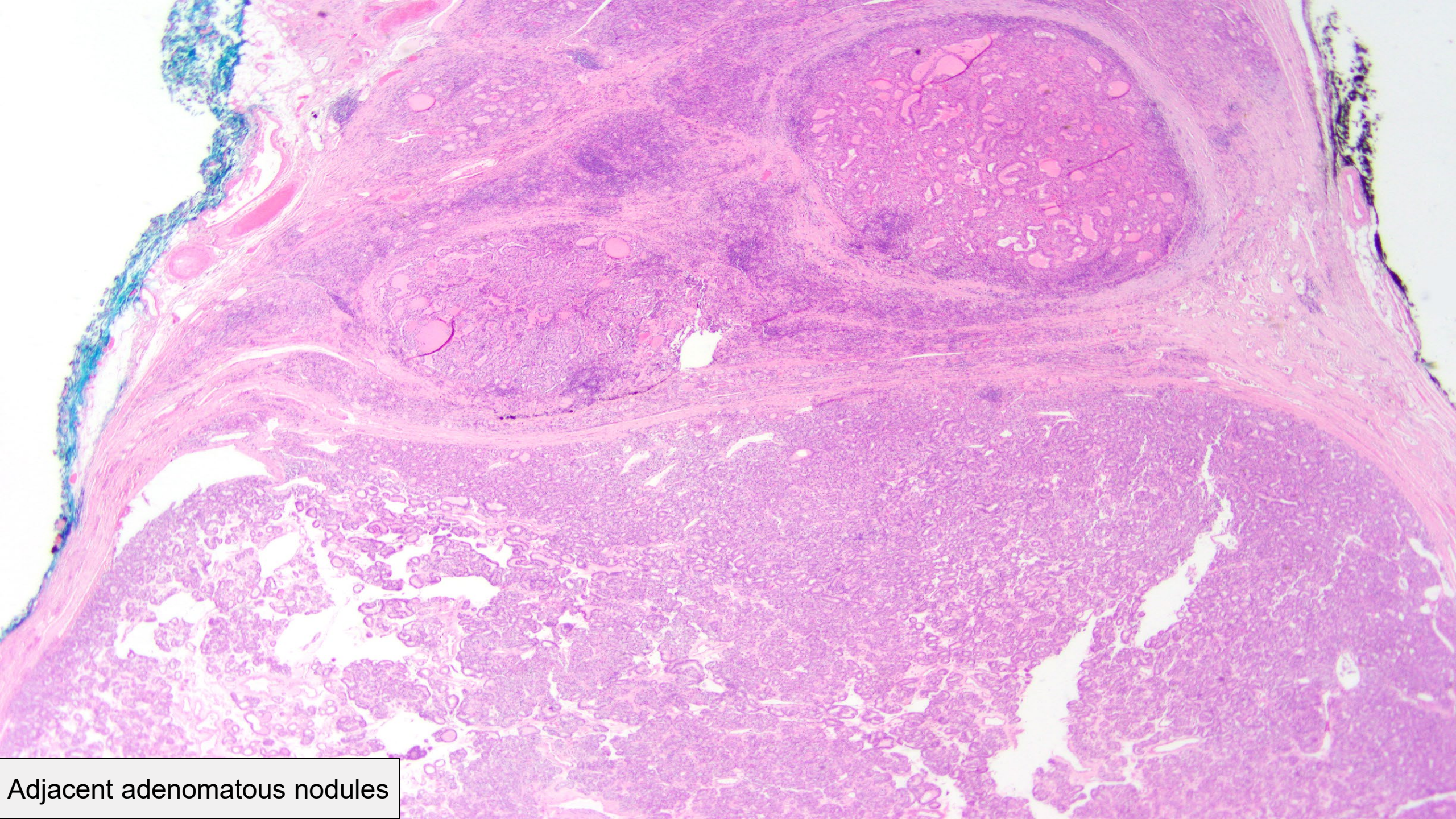

Fibrous capsule
Not yet (B)
Yes (C)
No (A)
Yes (D)
No (J)
Follicular neoplasm
Yes (E)
Not yet (I)
Not yet (F)
No (G)
Yes (H)


Fibrous capsule
Not yet (B)
Yes (C)
No (A)
Yes (D)
No (J)
Follicular neoplasm
Yes (E)
Not yet (I)
Not yet (F)
No (G)
Yes (H)

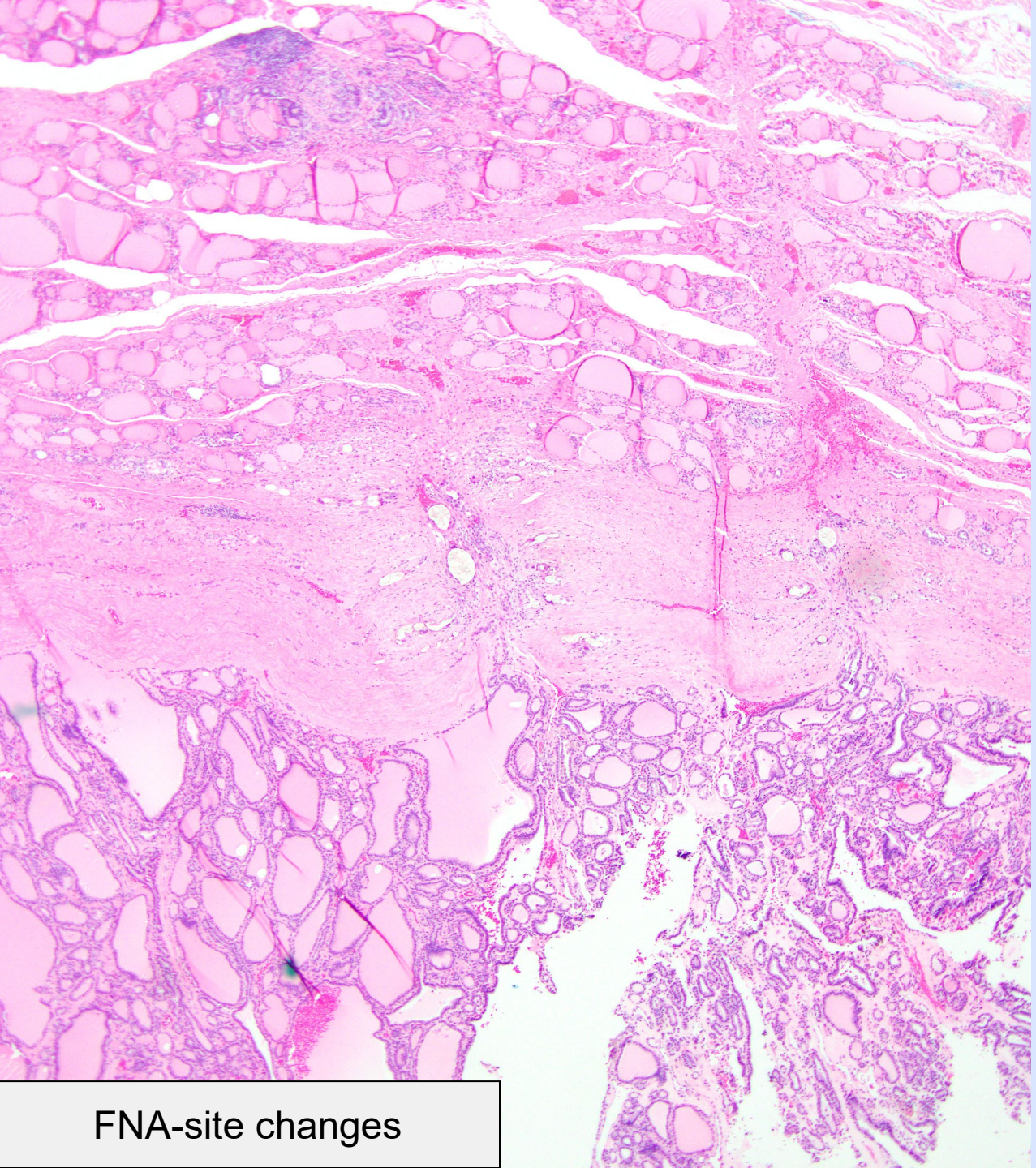




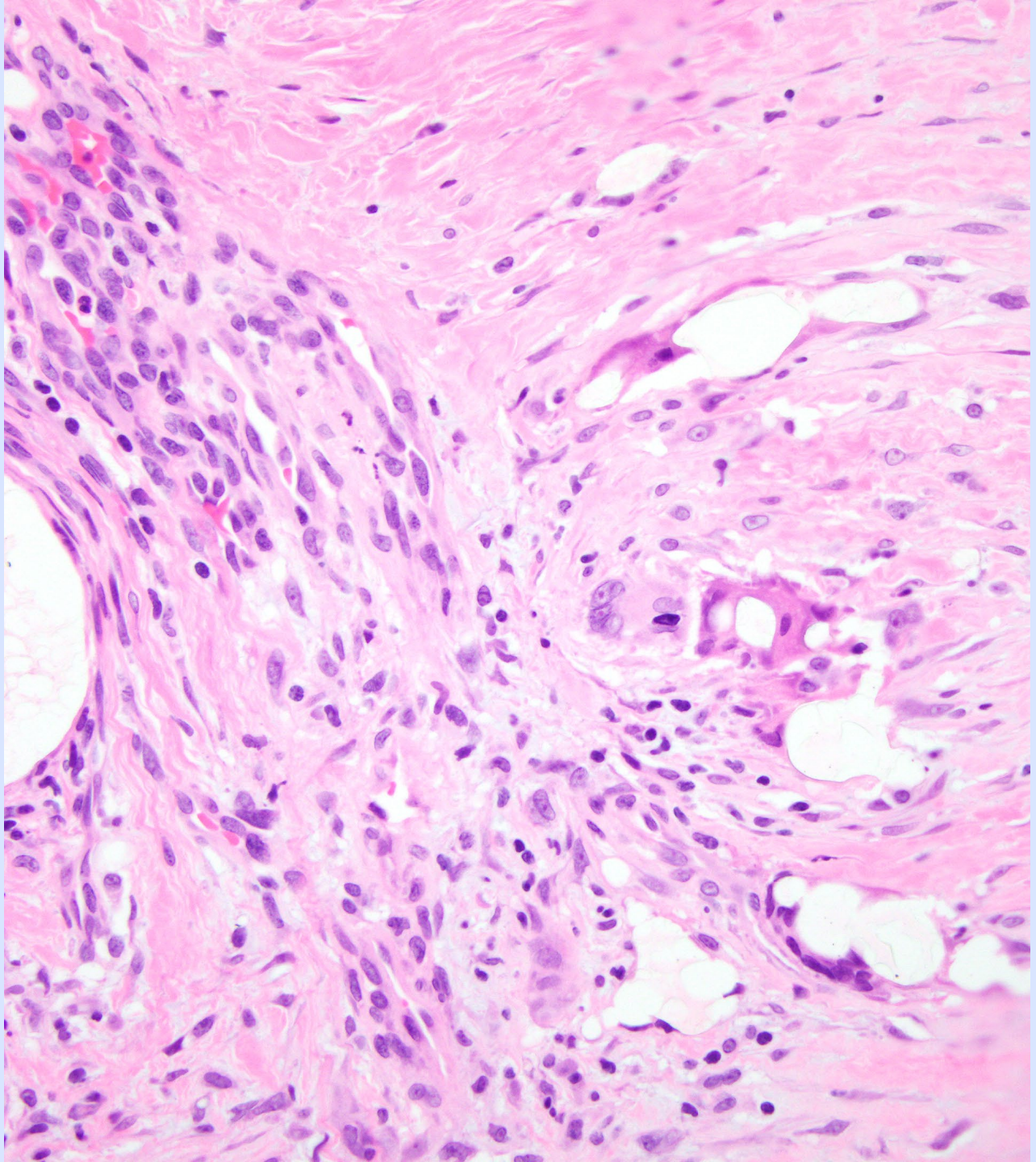
FTC with macrofollicular architecture

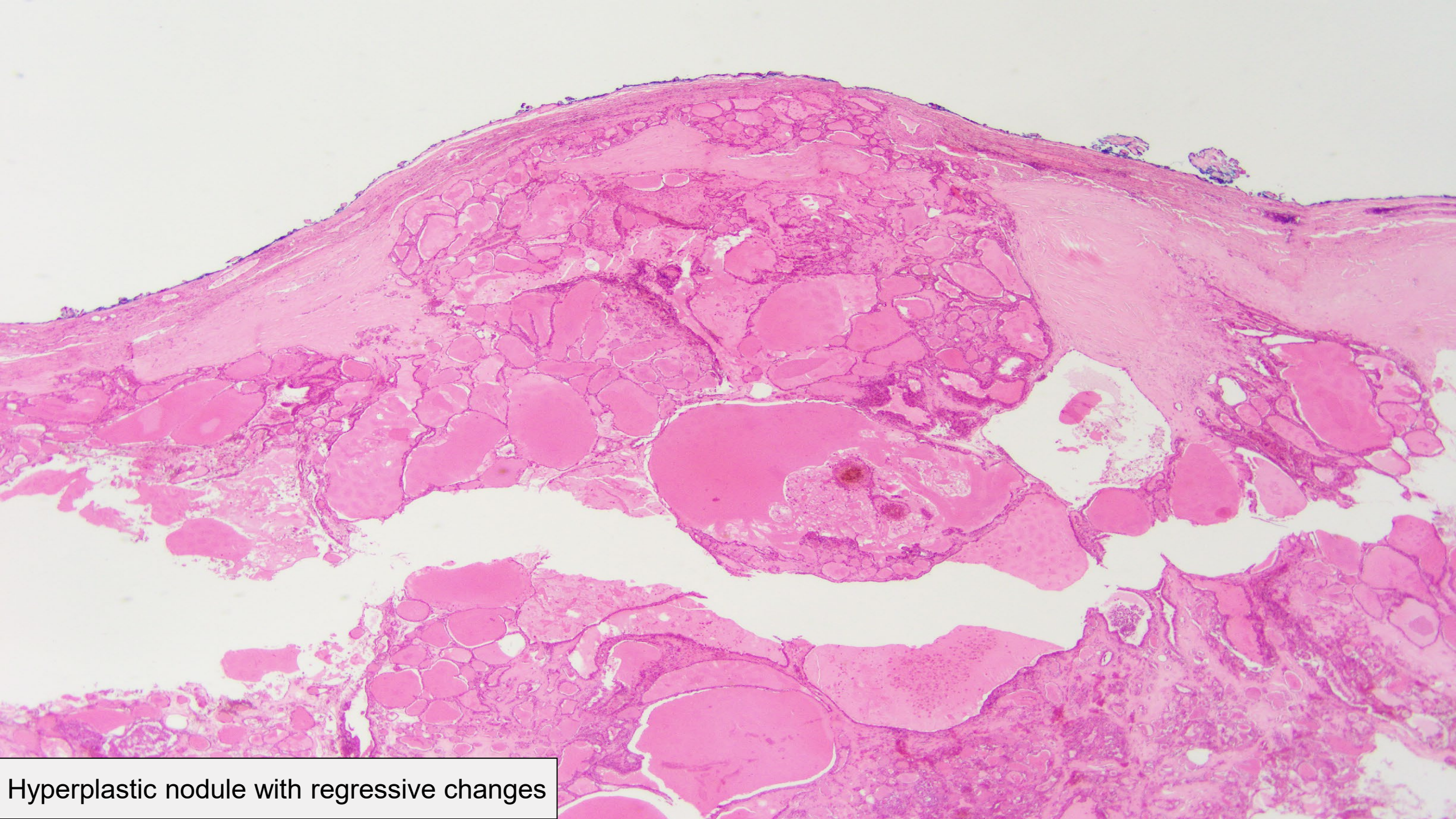


Adjacent adenomatous nodules



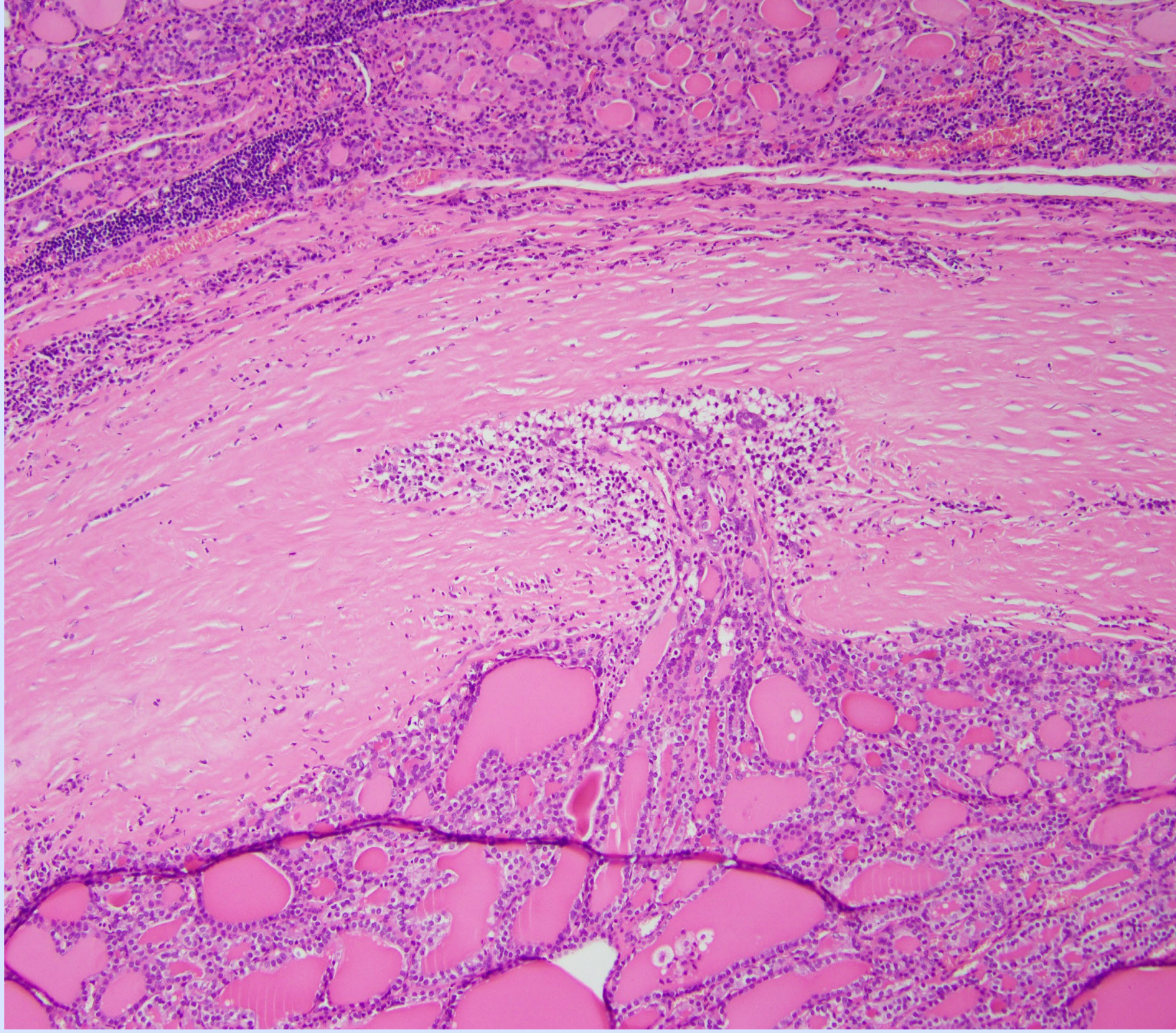
FNA-site changes





Hyperplastic nodule with regressive changes

What to do if invasion into, but not through, capsule?



Definition of Vascular Invasion

2015 AFIP Fascicle and 2022 WHO require:

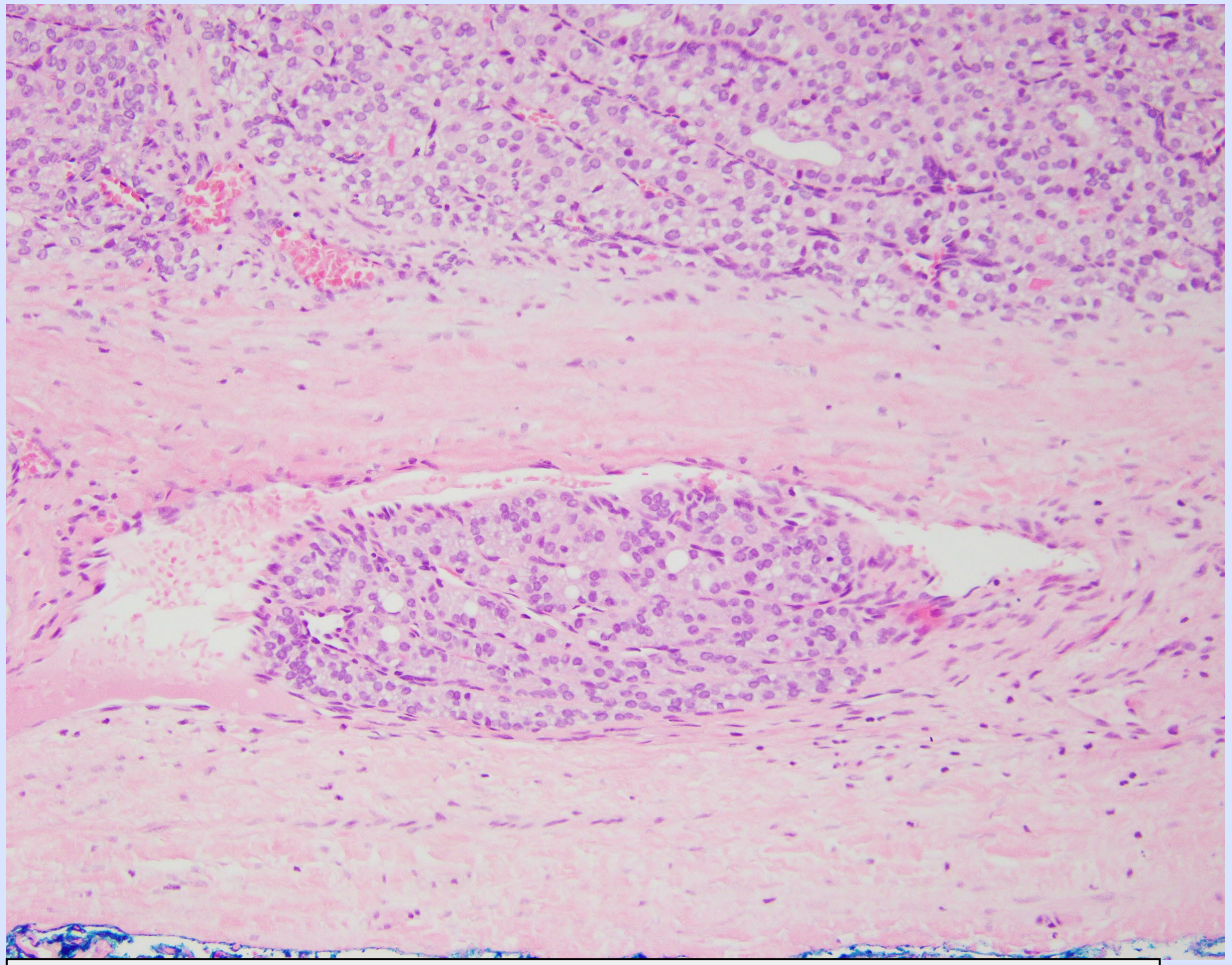
- Invasion of vessels in tumor capsule or beyond
- Intravascular tumor must be attached to the vessel wall, admixed with fibrin or covered by endothelium.

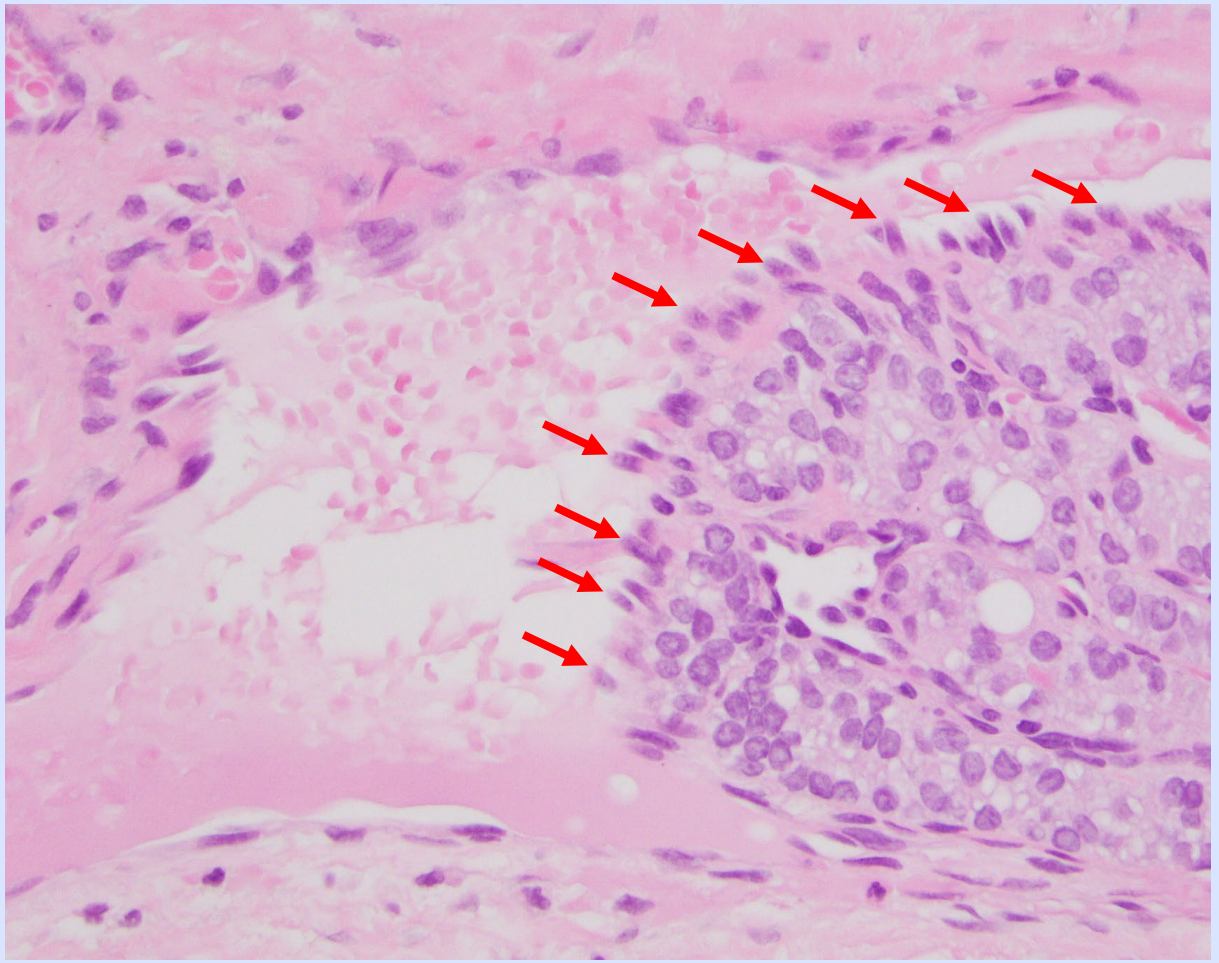
Mete and Asa, *Mod Pathol*, 2011

- Required association of fibrin thrombus – 35% of these cases were associated with distant metastases.

Most publications (and pathologists) use the AFIP/WHO definition.

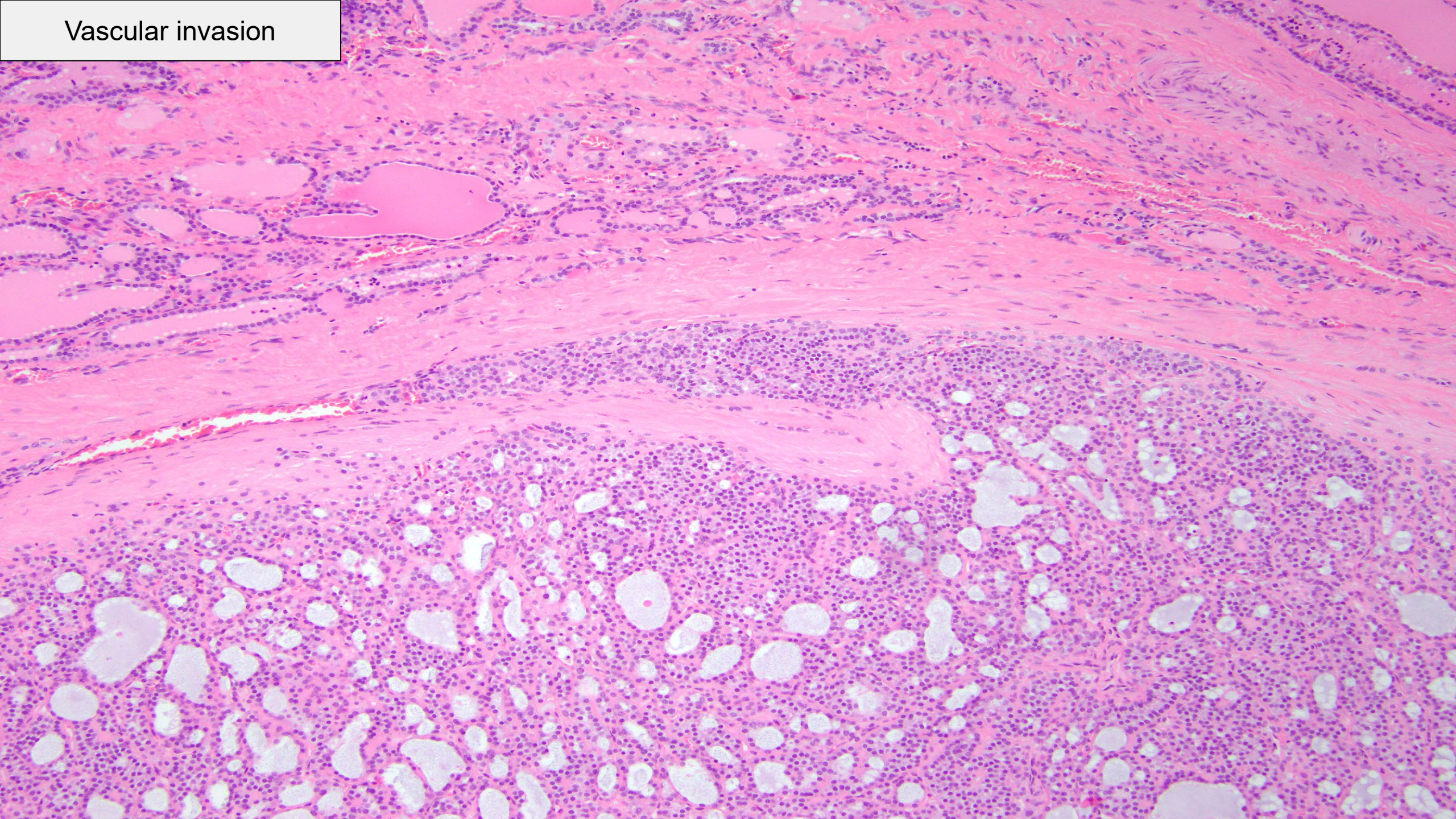
Risk of using more stringent criteria is that tumors with metastatic potential are not identified.



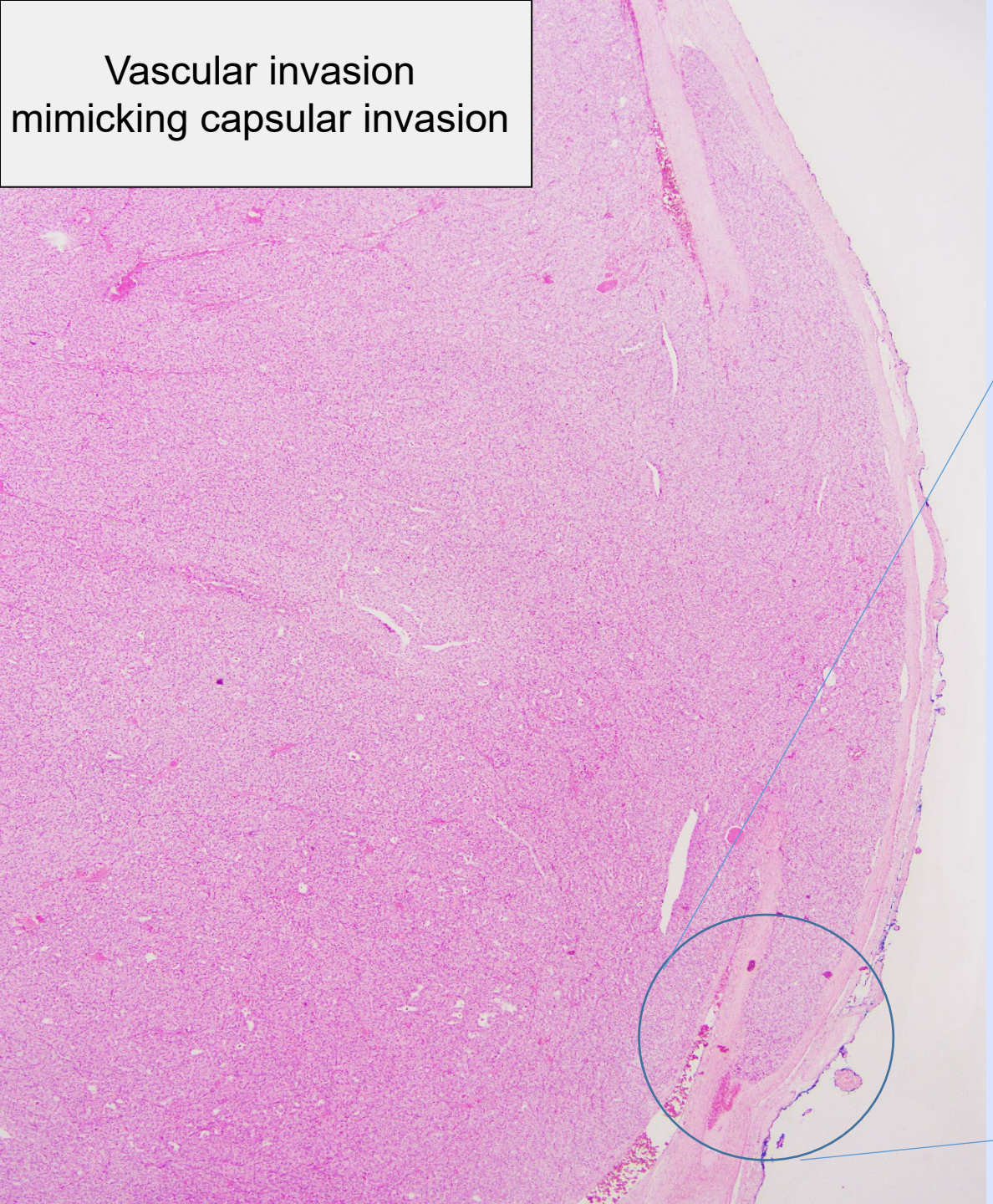


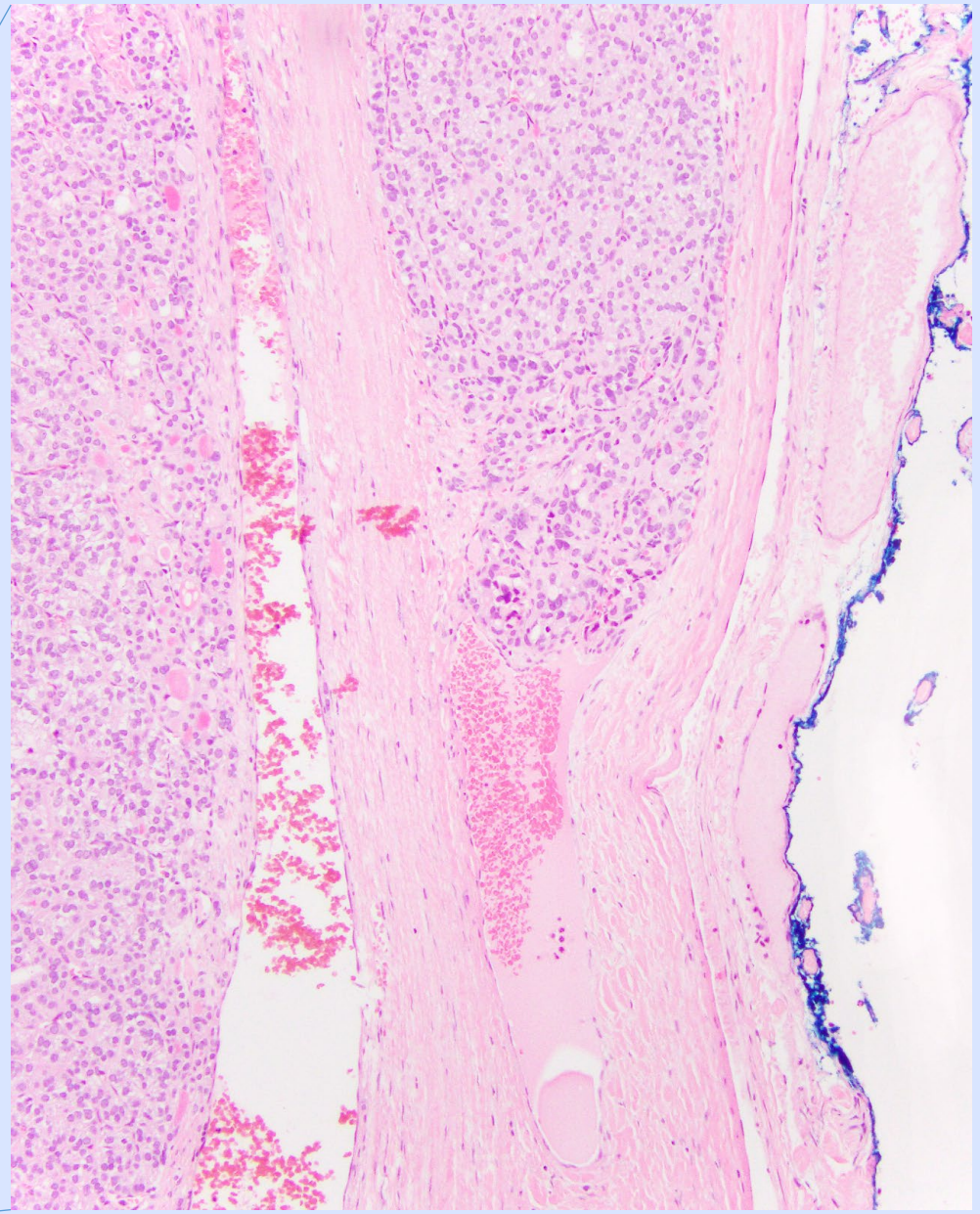
Vascular invasion with endothelial wrapping

Vascular invasion

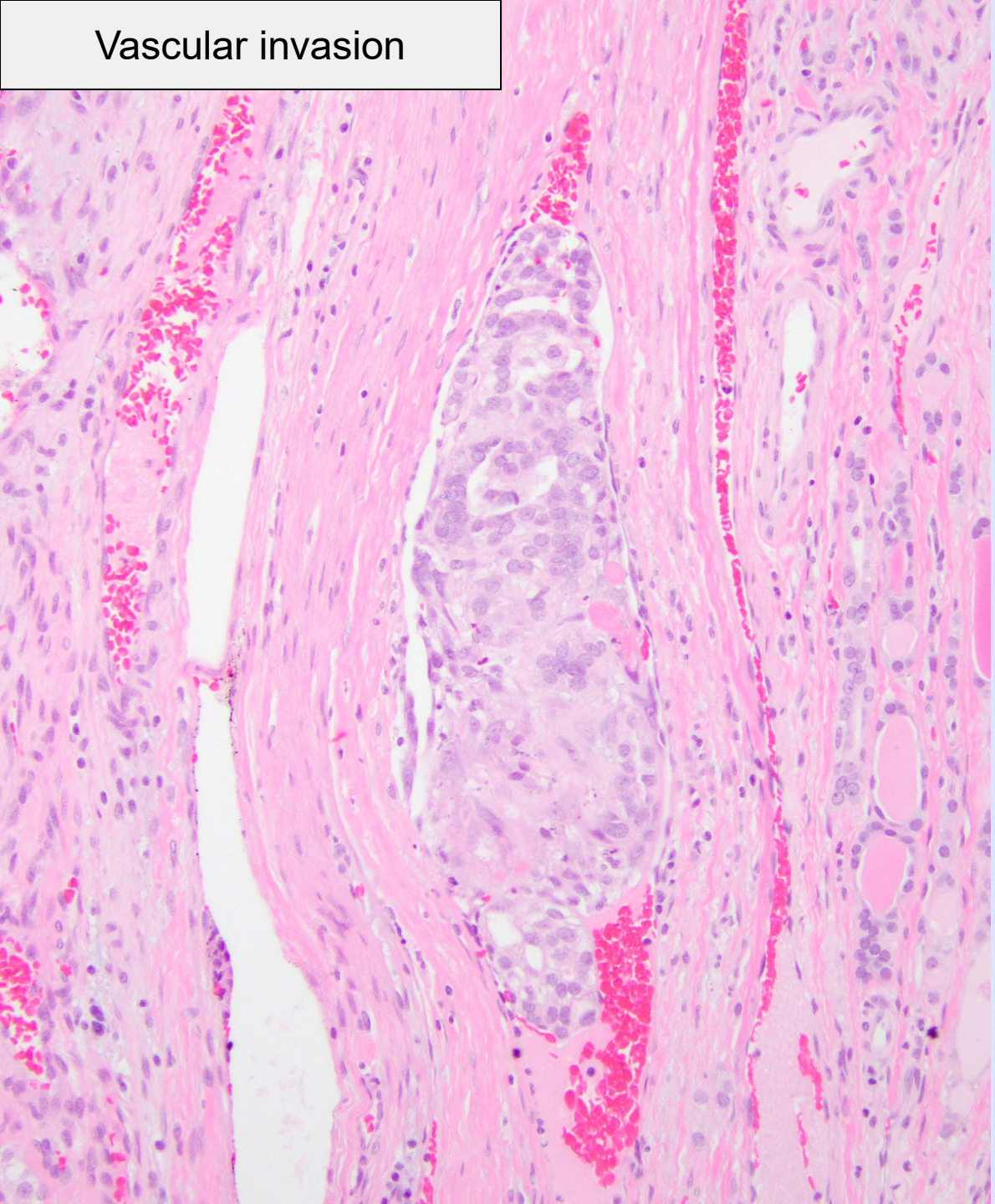


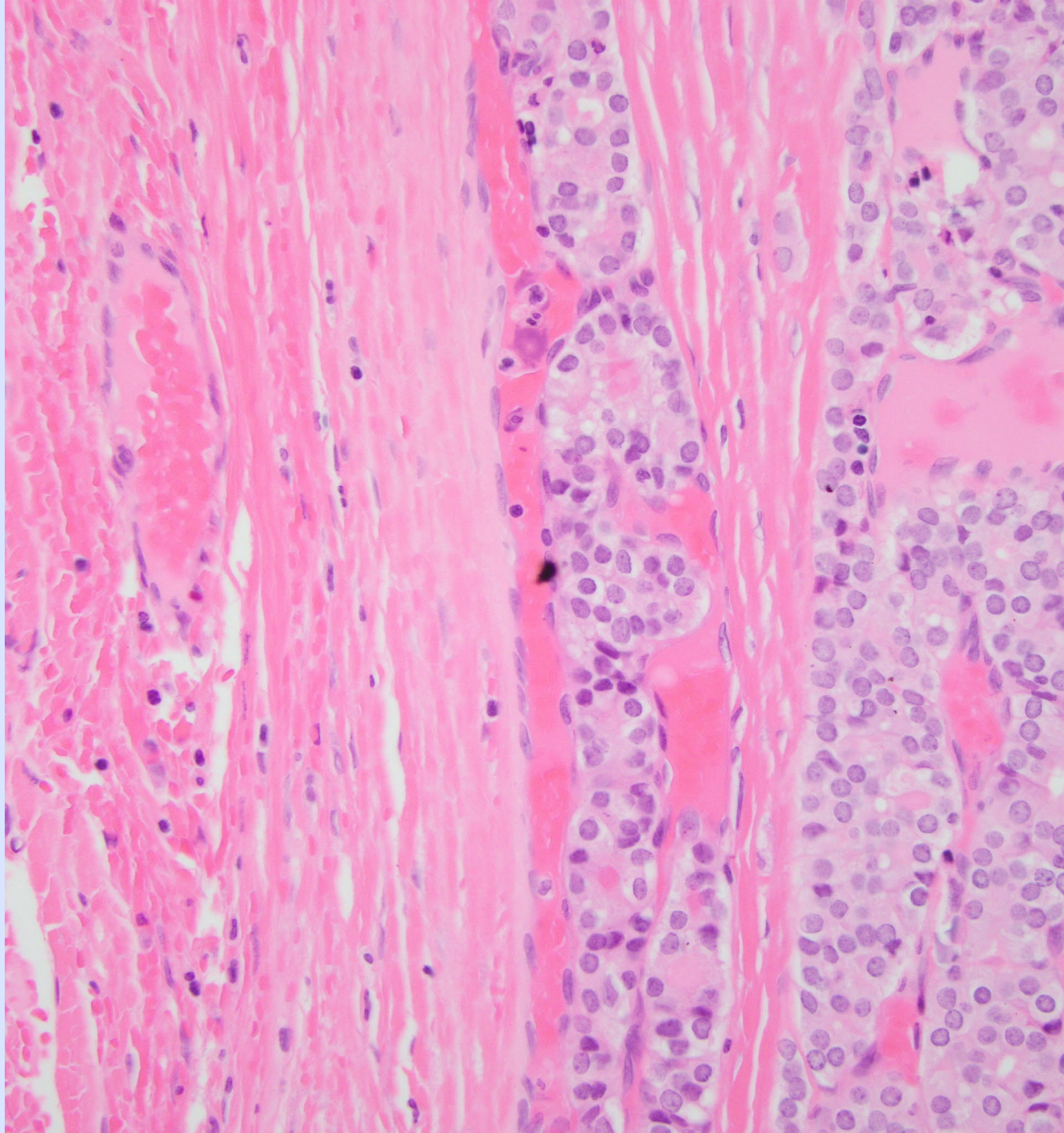
Vascular invasion
mimicking capsular invasion

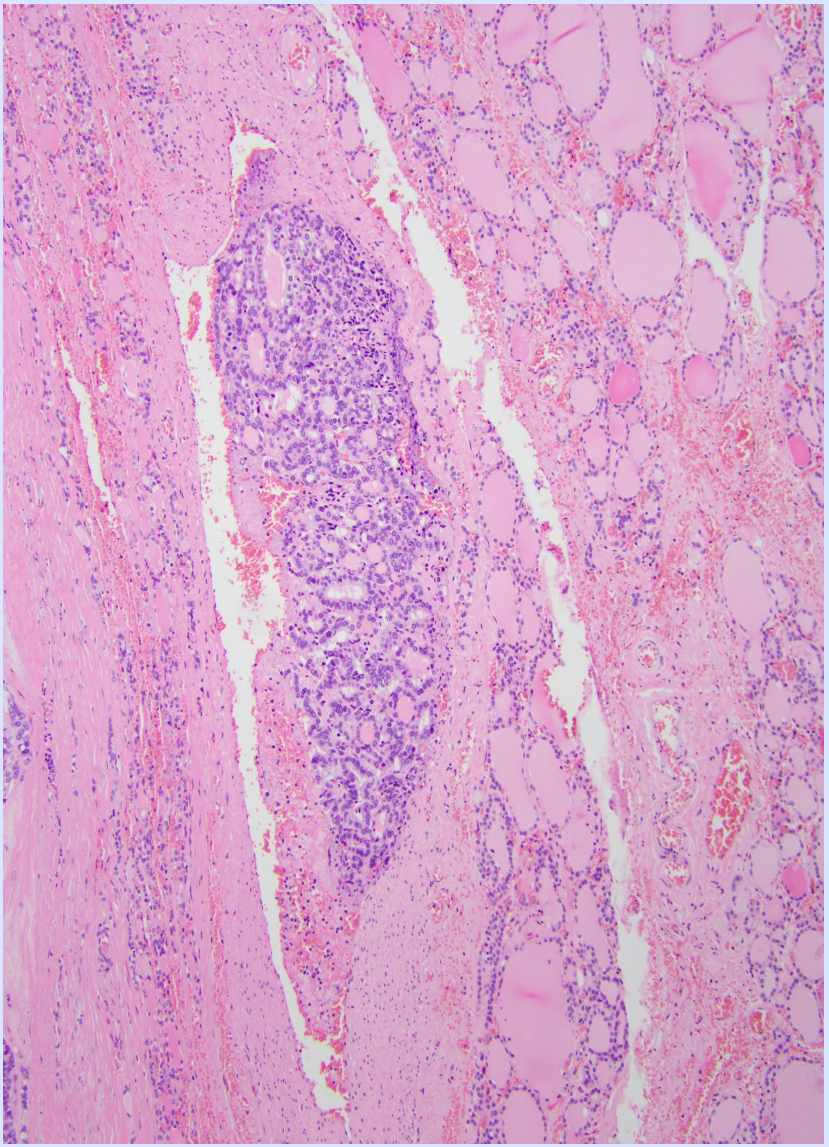


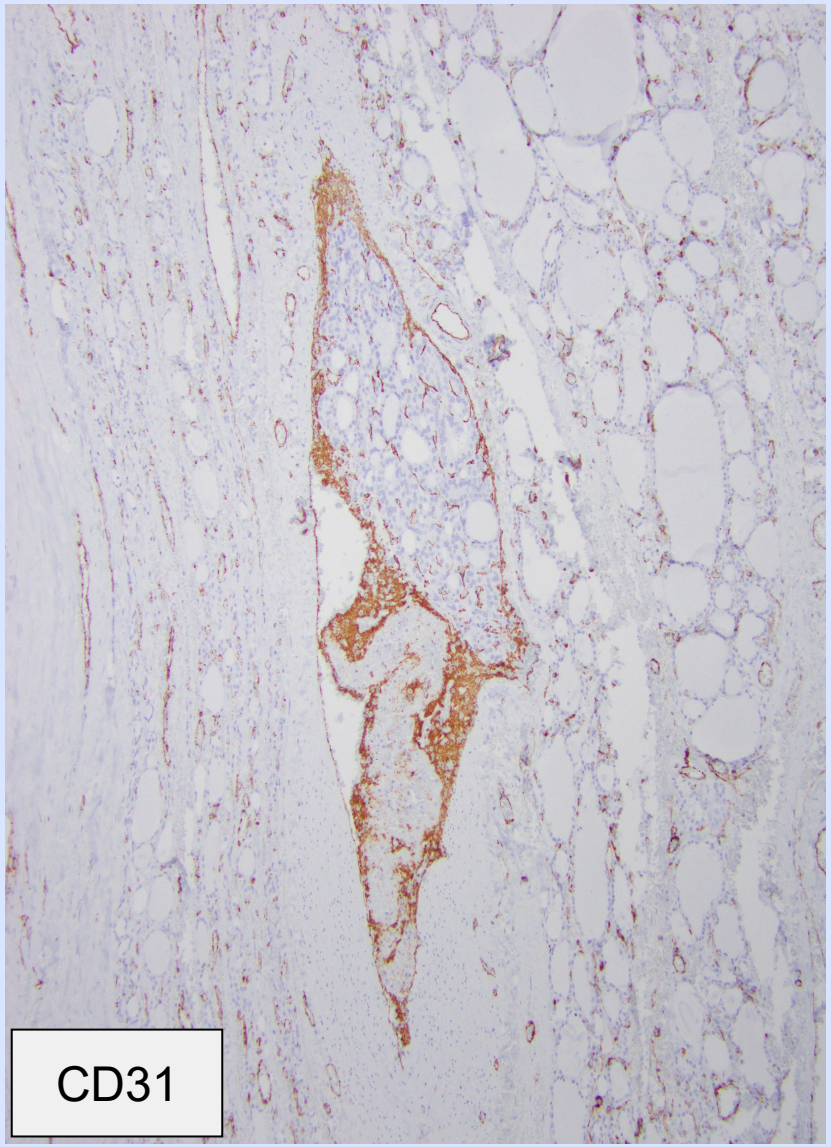


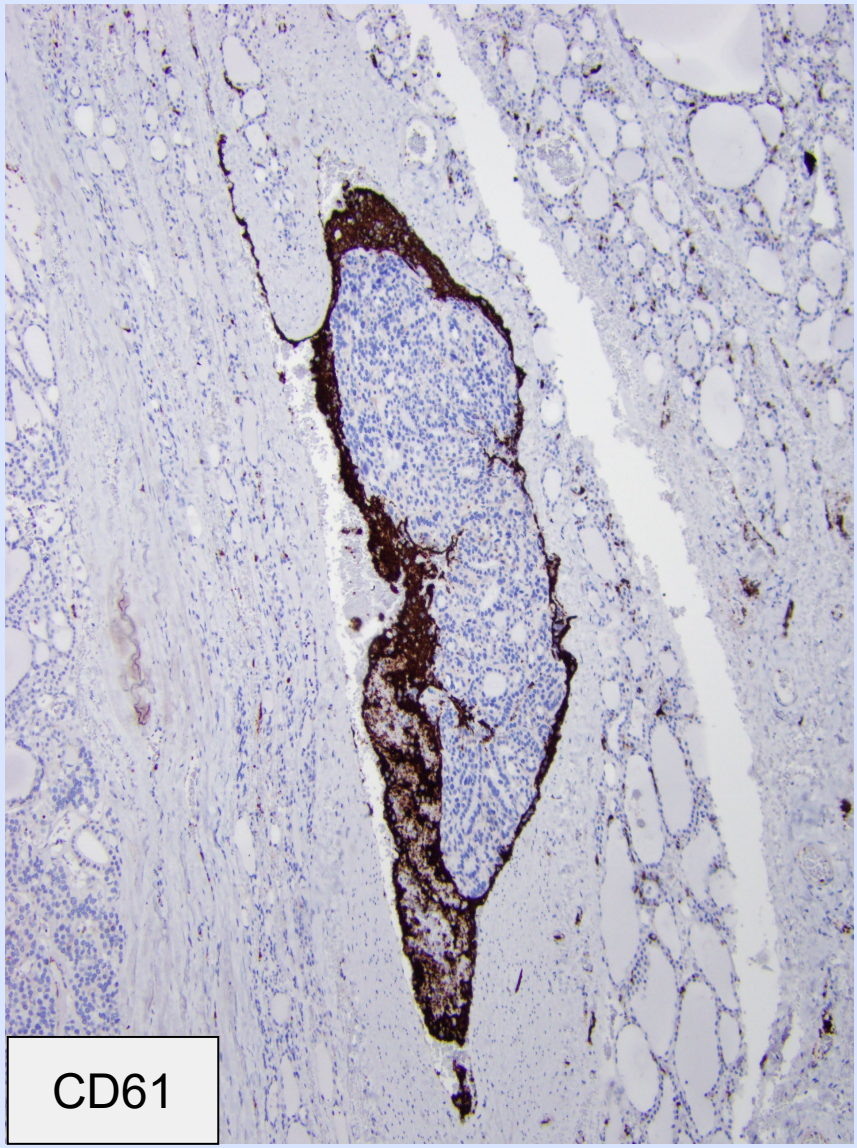
Vascular invasion








CD31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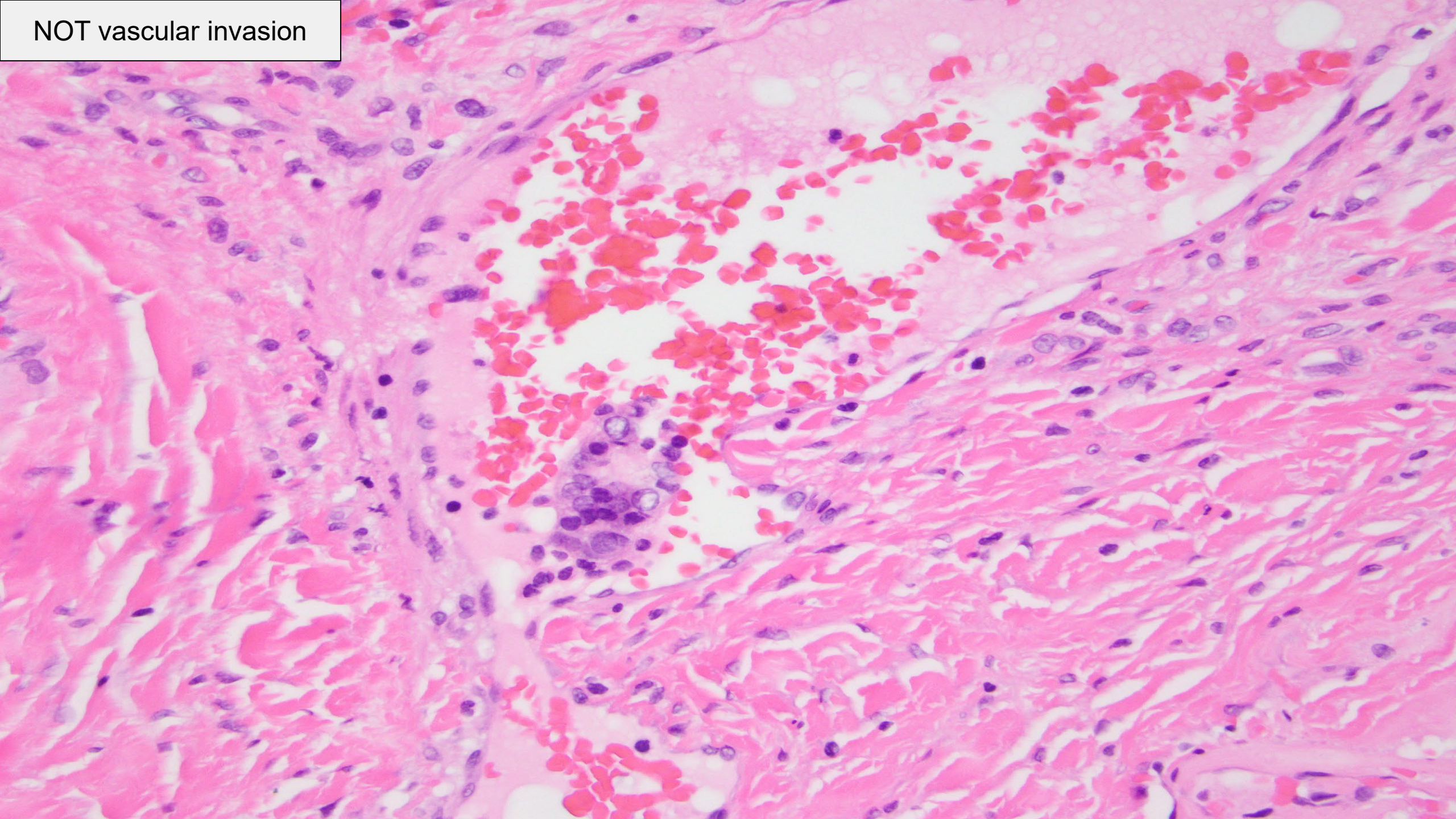
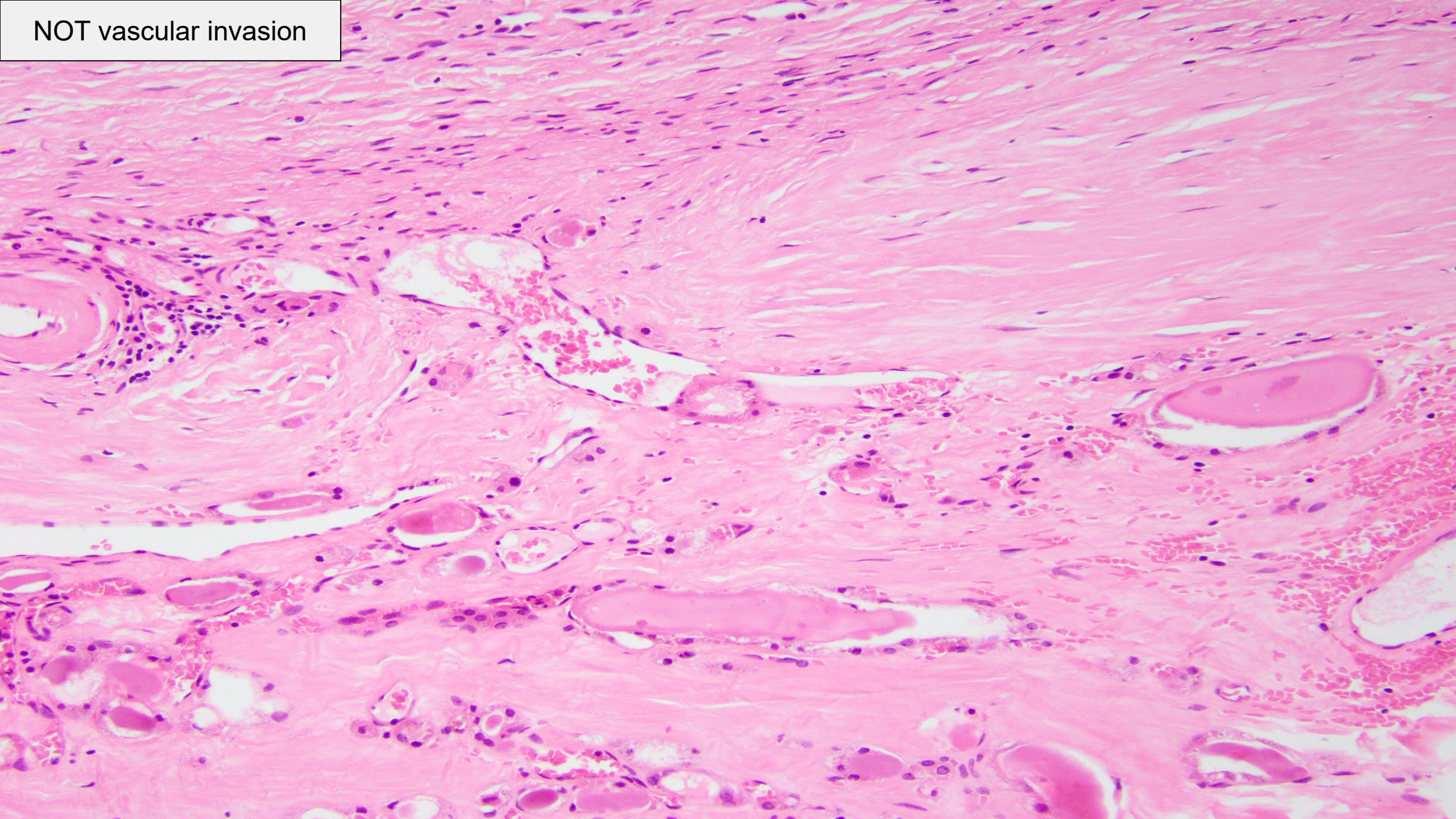
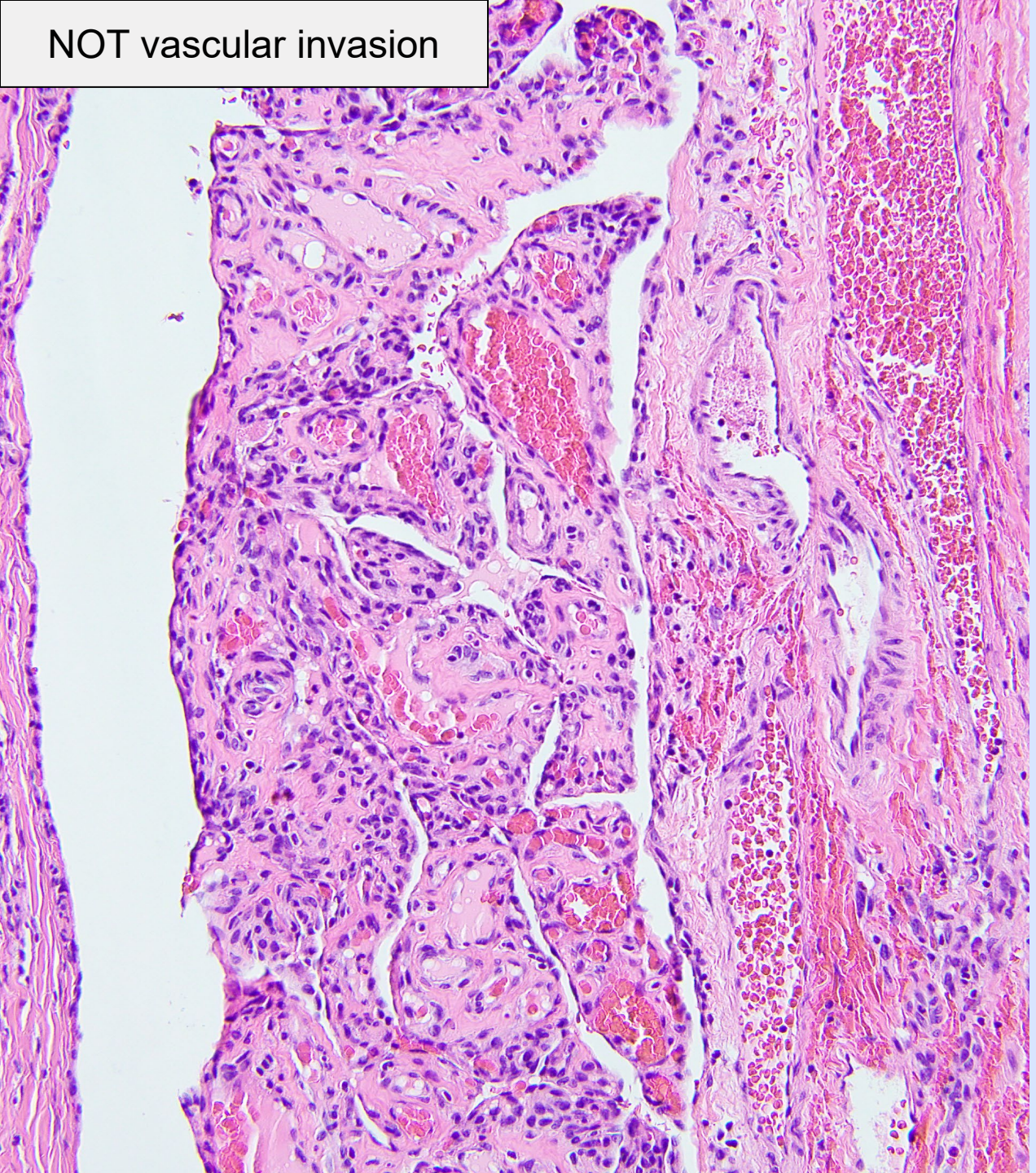
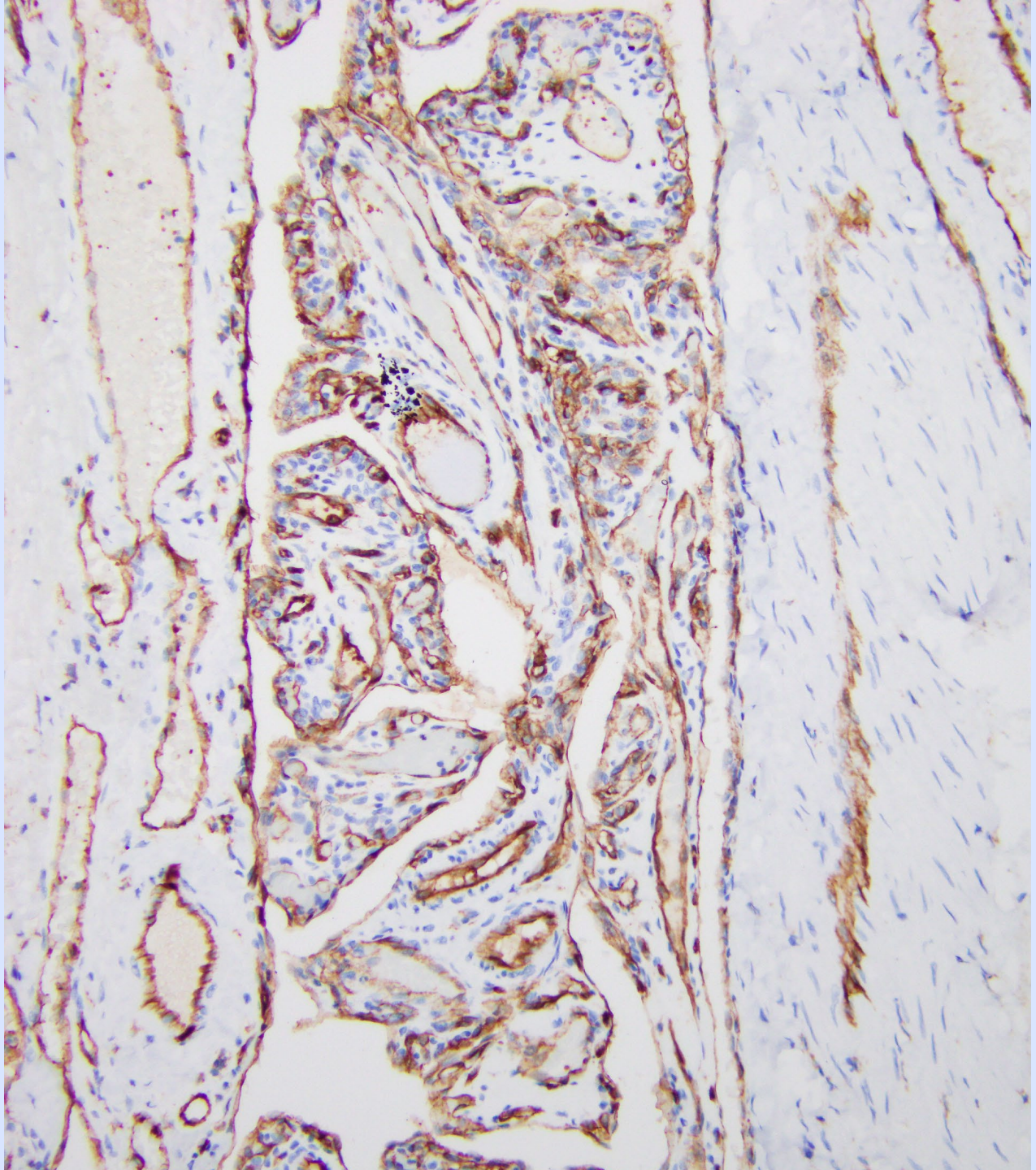

NOT vascular invasion


NOT vascular invasion

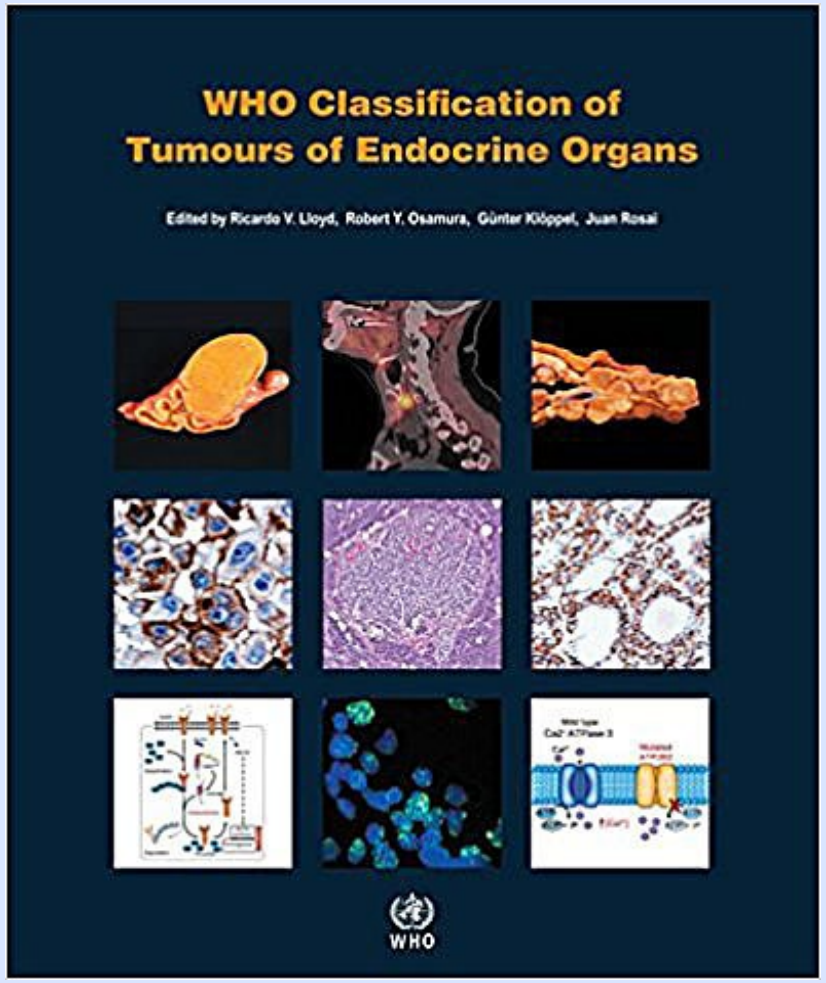

NOT vascular invasion



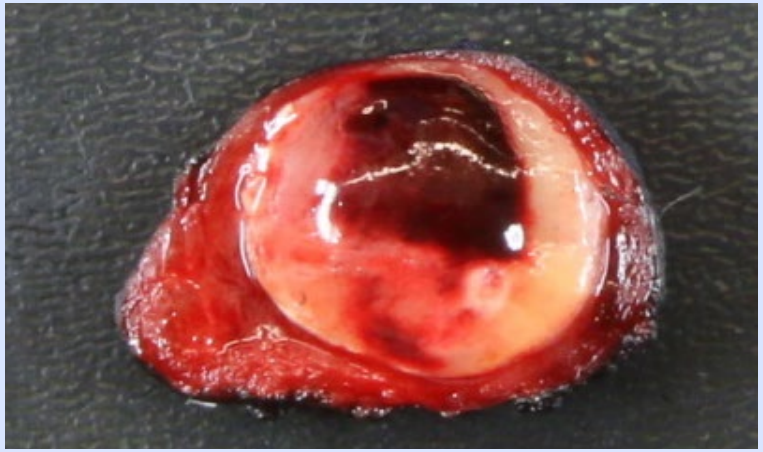
Follicular Thyroid Carcinoma

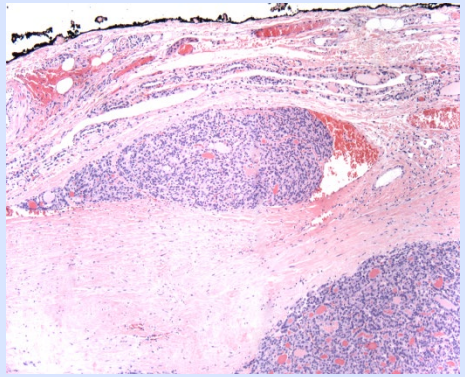
The 2017 Endocrine WHO (same in 2022 WHO) moved from classifying follicular thyroid carcinoma and oncocytic thyroid carcinoma as minimally and widely invasive to:

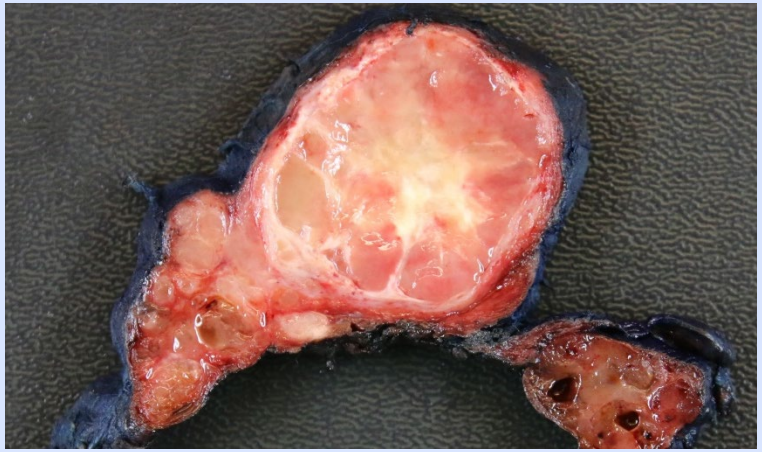
- Minimally invasive (capsular invasion only)
- Encapsulated angioinvasive
- Widely invasive

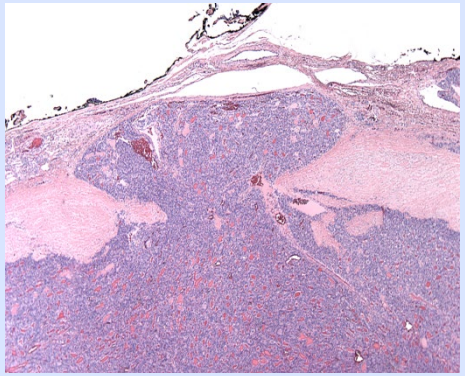


Extent of Invasion









- Minimally invasive (capsular invasion only)

- Encapsulated angioinvasive: vascular invasion present with/without capsular invasion

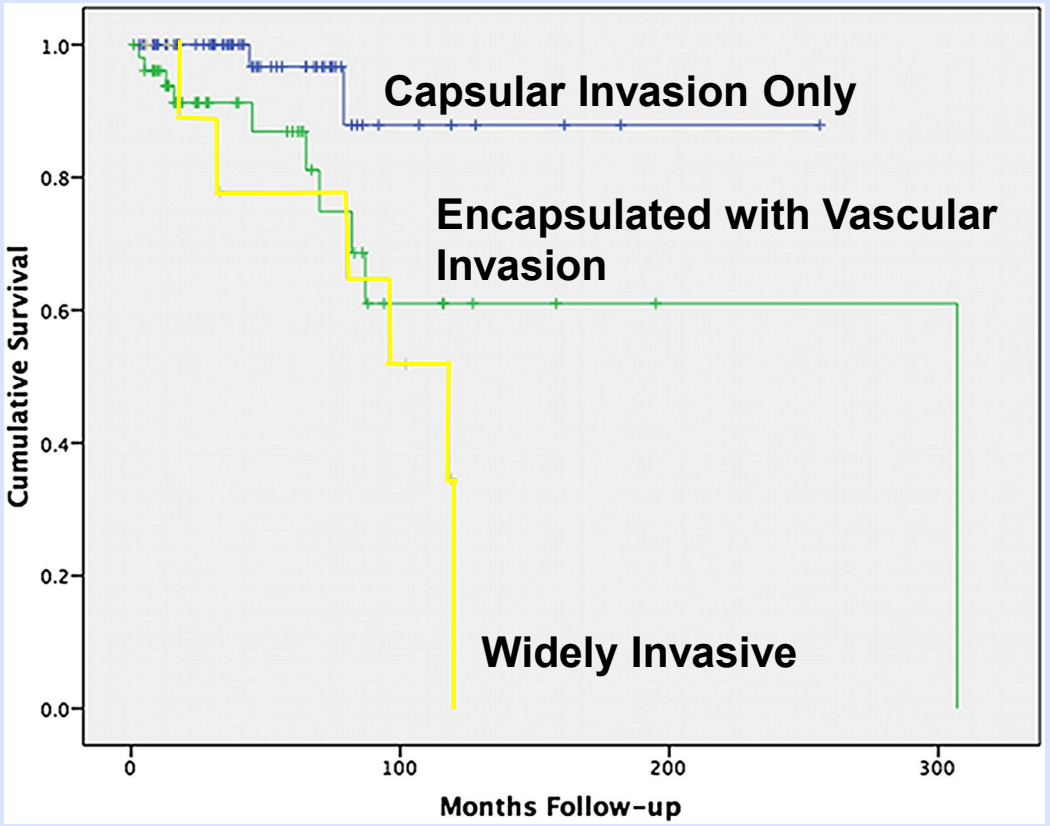
- Widely invasive: grossly see tumor invading through parenchyma, usually also have extensive vascular invasion

Vascular Invasion in Follicular Thyroid Carcinoma (FTC)

Cohort of 124 patients with FTC:
- Capsular invasion only (~49%)
- Encapsulated angioinvasive (~42%)
- Widely invasive (9%)

Disease-free survival (DFS) was significantly improved in patients with less invasive tumors.

40-month DFS: 97%, 81% and 45%, respectively (P= 0.007).



O'Neill, *European Journal of Surgical Oncology*, 2011.

Follicular Thyroid Carcinoma (FTC)

The only two patients with an adverse outcome that had FTC with capsular invasion only had the distant metastases at presentation.

For the rare aggressive tumors with capsular invasion only, the biologic potential is usually clinically evident at time of initial diagnosis due to presence of distant metastases at the time of presentation.

Table 2
Factors influencing the occurrence of distant metastases.

	No distant metastases, $n = 111$	Distant metastases, $n = 13$	Univariate p-value	Multivariate p-value
Age				
≤45 years	54	1	$p = 0.02$	$p = 0.03$
>45 years	57	12		
Gender				
Male	33	3	$p = 0.62$	$p = 0.68$
Female	78	10		
Tumour diameter				
≤20 mm	33	5		
21–40 mm	52	4	$p = 0.55$	$p = 0.86$
>40 mm	26	4		
Vascular invasion				
Absent	60	2	$p = 0.02$	$p = 0.03$
Present	51	11		
Nodal metastasis				
Absent	110	10	$p = 0.004$	$p = 0.01$
Present	1	3		

O'Neill, *European Journal of Surgical Oncology*, 2011.

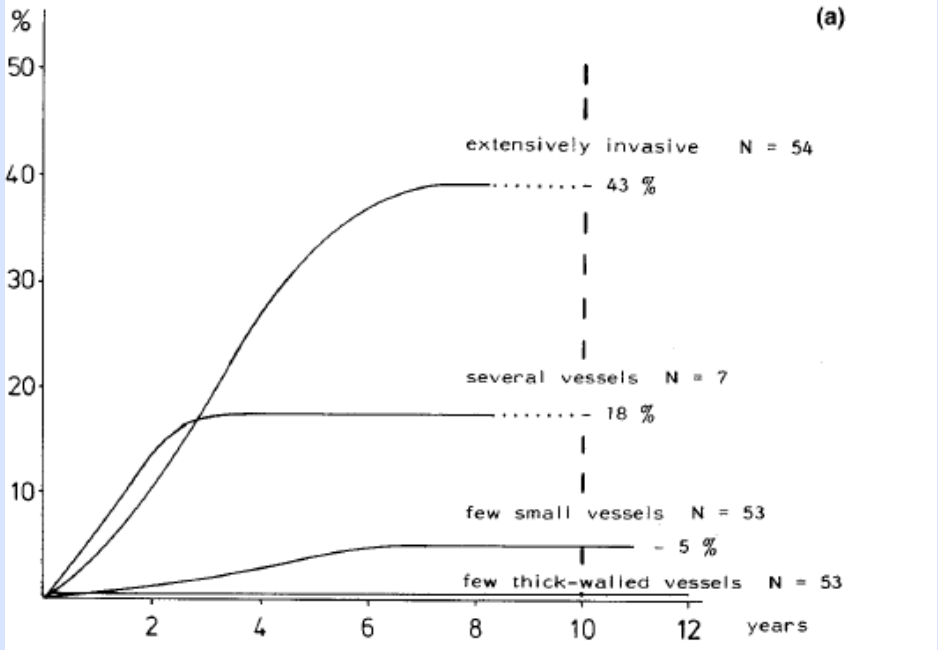
Extent of Vascular Invasion

Risk Factors in Follicular Thyroid Carcinomas

A Retrospective Follow-up Study Covering a 14-Year Period with Emphasis on Morphological Findings

Walter Lang, M.D., Harald Choritz, and Heinz Hundeshagen, M.D.

The American Journal of Surgical Pathology *10(4): 246–255, 1986*



Cumulative death rate depended on extent of vascular invasion

Endocrine Journal 2013, **60** (5), 637-642

Prognostic factors of minimally invasive follicular thyroid carcinoma: Extensive vascular invasion significantly affects patient prognosis

Yasuhiro Ito[1)], Mitsuyoshi Hirokawa[2)], Hiroo Masuoka[1)], Tomonori Yabuta[1)], Minoru Kihara[1)], Takuya Higashiyama[1)], Yuuki Takamura[1)], Kaoru Kobayashi[1)], Akihiro Miya[1)] and Akira Miyauchi[1)]

Table 3 Multivariate analysis of CSS in 292 patients

Variables	*p* values	Odds ratio (95% *CI)
M1	< 0.0001	456.900 (47.619-1007.500)
Age ≥ 45 yrs	0.4637	2.555 (0.208-31.416)
Male gender	0.4707	0.413 (0.037-4.566)
Size > 4 cm	0.0474	25.641 (1.037-50.000)
Duplication and/or satellite nodule	0.8719	1.213 (0.116-12.658)
Definite capsular invasion	0.5222	2.915 (0.110-76.923)
Extensive vascular invasion	0.0430	13.699 (1.085-166.667)

Extent of Vascular Invasion

Focal vascular invasion: <4 foci Extensive vascular invasion: ≥4 foci

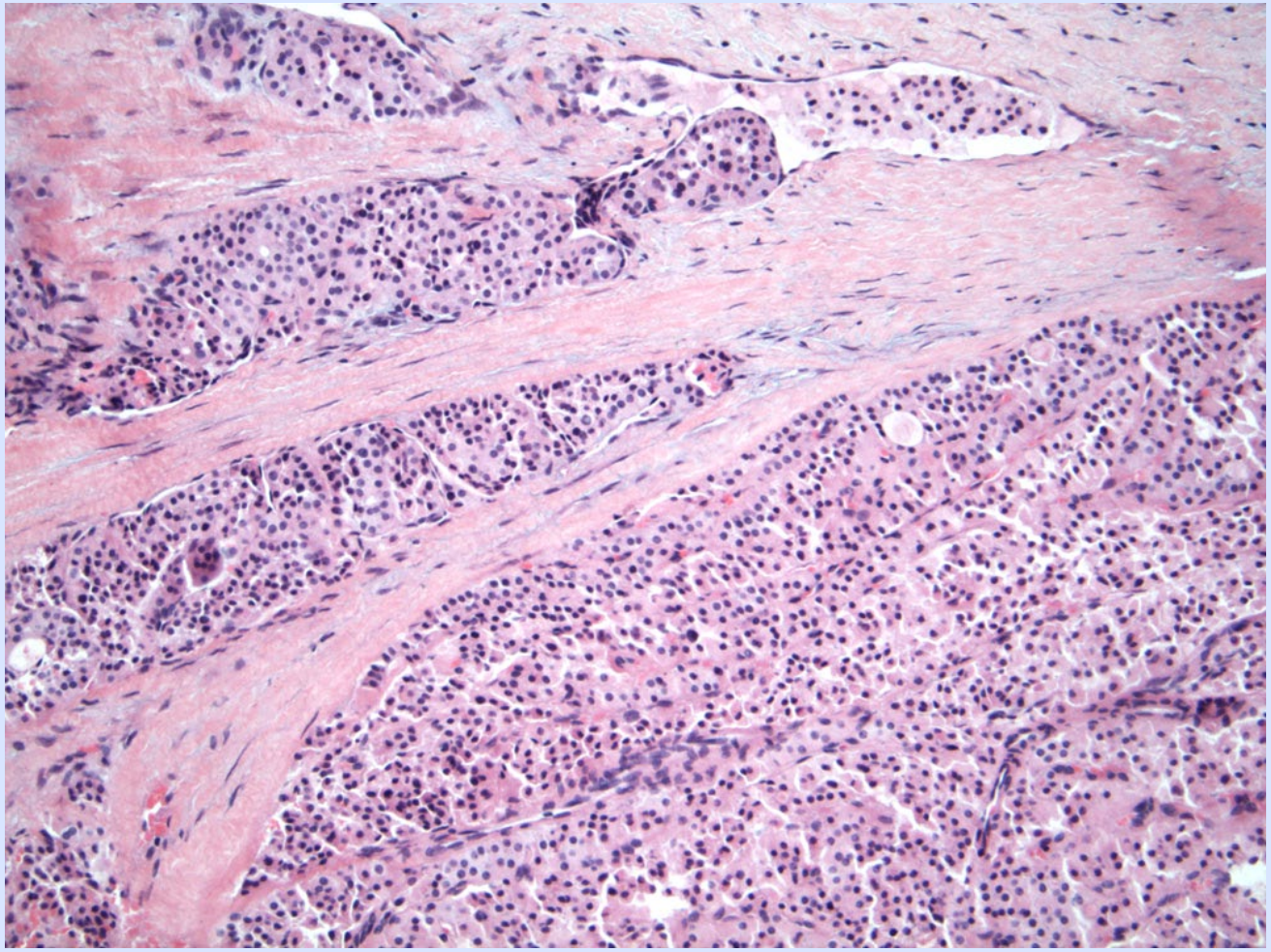
COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland

Version: 4.4.0.0
Protocol Posting Date: March 2023

 # Historically, less than 4 vessels have been considered as focal and involvement of 4 or more vessels has been referred to extensive angioinvasion in follicular cell-derived thyroid carciniomas. However, the 5th edition of the WHO classification questioned the validity of the cut-off point applied for this distinction. For this reason, pathologists are encouraged to document the extent of angioinvasion based on the number of vessels involved.

___ Present (specify extent)#: _____
___ Present, extent not specified
___ Present, extent cannot be specified (explain): _____
___ Cannot be determined: _____



Foci of vascular invasion that are closely adjacent to one another are counted as separate foci.

NCCN Guidelines Version 1.2023
Thyroid Carcinoma – Follicular Carcinoma

NCCN Guidelines Index
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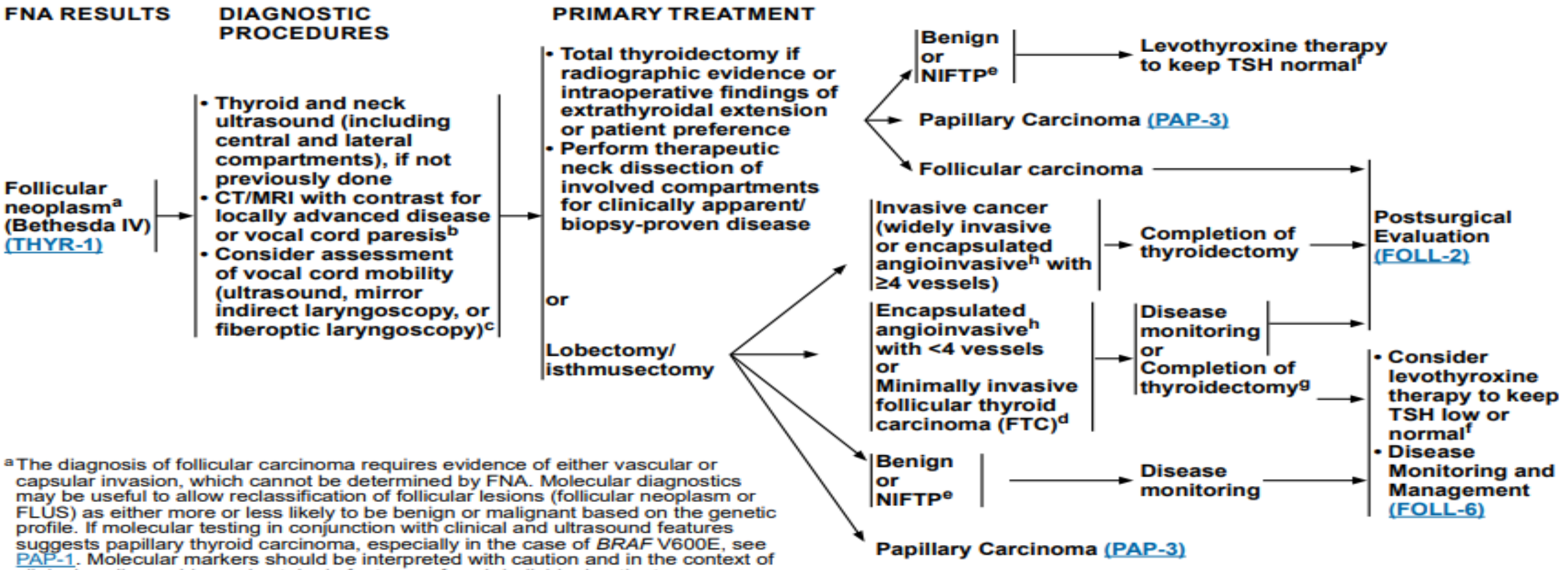
Discussion



[a] The diagnosis of follicular carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (follicular neoplasm or FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing in conjunction with clinical and ultrasound features suggests papillary thyroid carcinoma, especially in the case of *BRAF* V600E, see PAP-1. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.

[b] Use of iodinated contrast is required for optimal cervical imaging using CT; potential delay in RAI treatment will not cause harm.

[c] Vocal cord mobility should be examined in patients if clinical concern for involvement, including those with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck. Evaluation is imperative in those with voice changes.

[d] Minimally invasive FTC is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion.

[e] Formerly called encapsulated follicular variant of PTC, NIFTP has been reclassified and only lobectomy is needed. Ongoing surveillance is recommended.

[f] Principles of TSH Suppression (THYR-A).

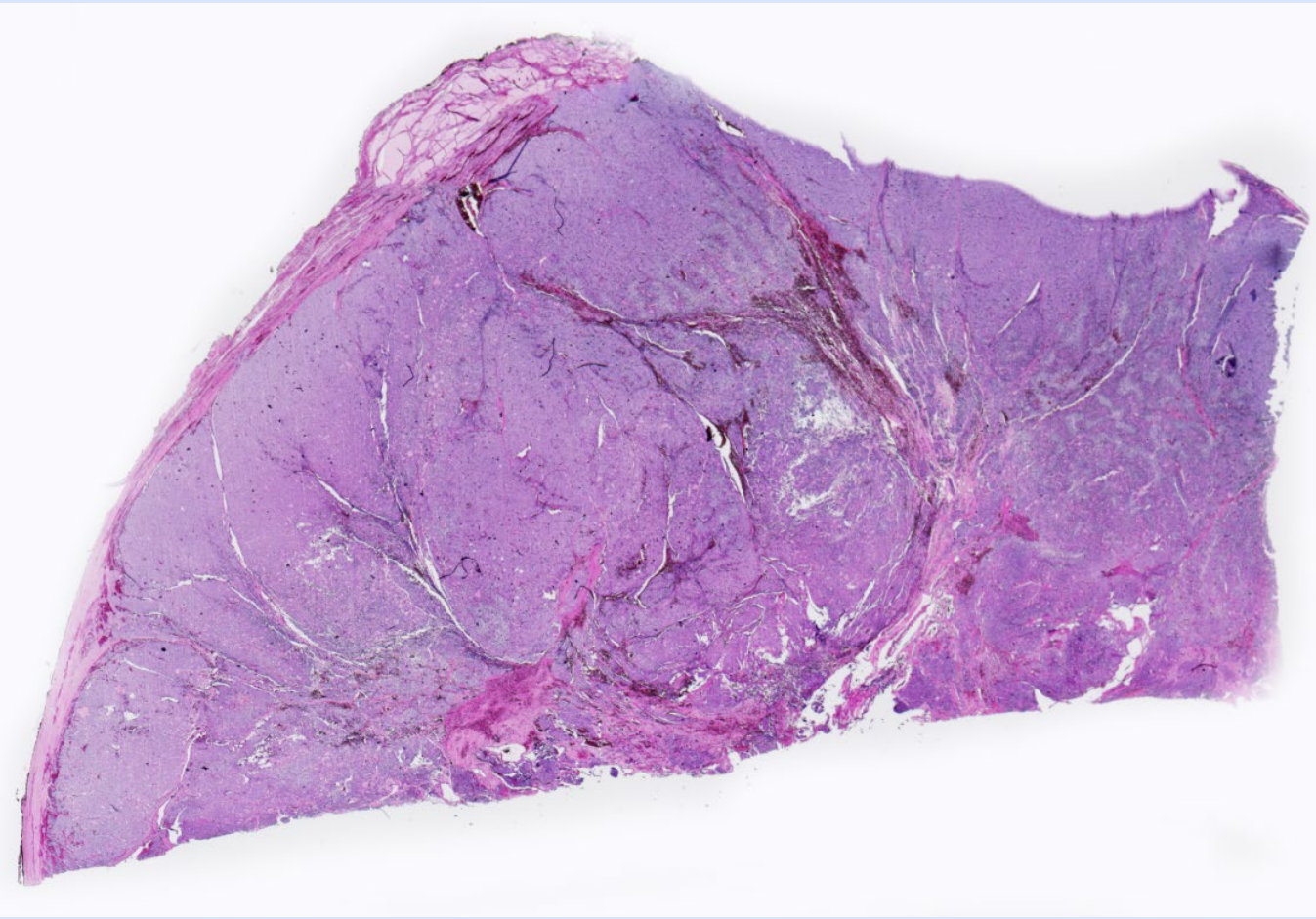
[g] Disease monitoring is preferred in most circumstances. However, there are certain clinical scenarios in which completion of thyroidectomy may be appropriate.

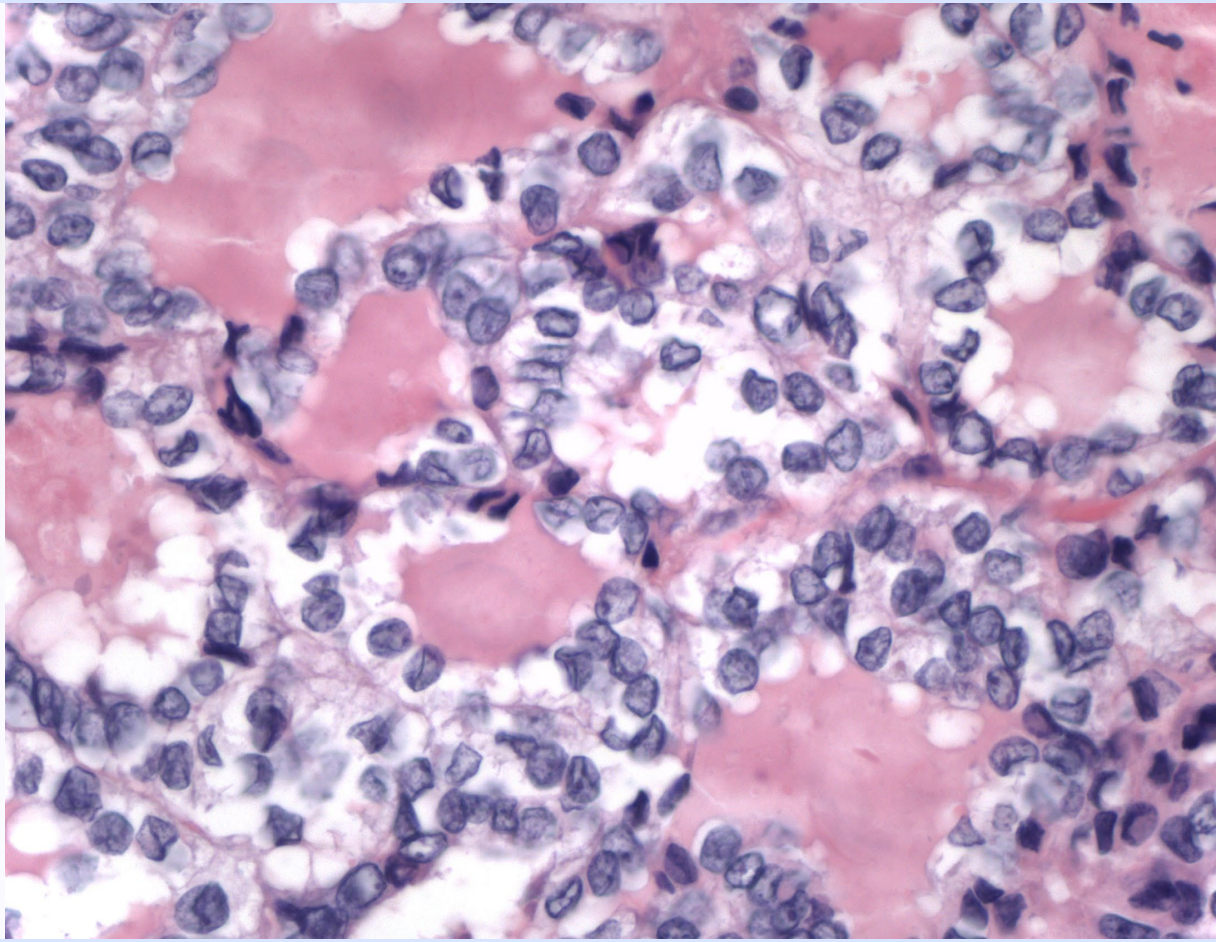
[h] Blood vessel invasion fewer than 4 vessels does not require completion thyroidectomy.

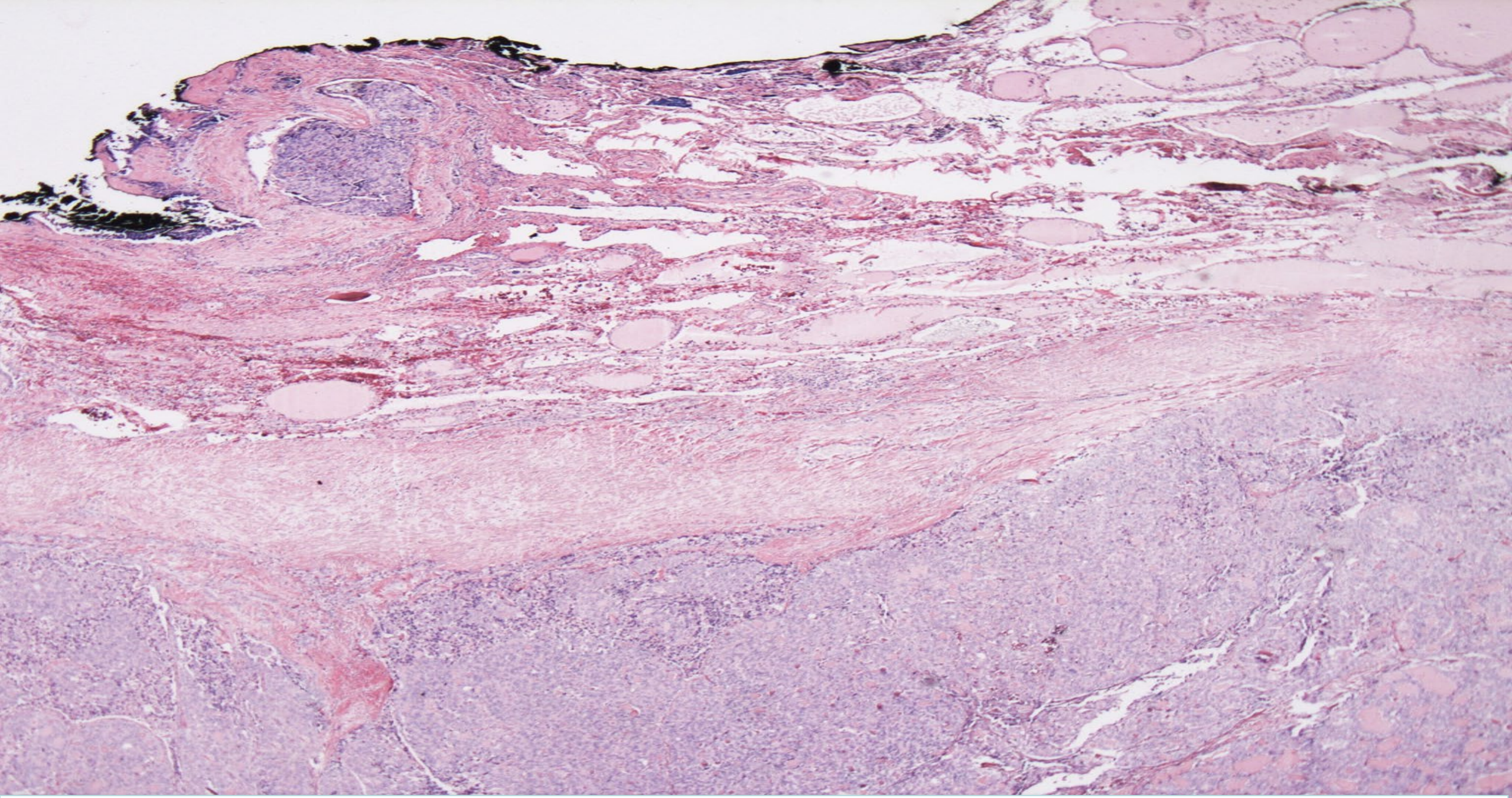
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Case

The patient is a 53-year-old man who was found to have a 5.0 cm thyroid nodule with an indeterminate FNA result and an *NRAS* Q61R mutation.







Encapsulated Angioinvasive Follicular Variant of Papillary Thyroid Carcinoma.

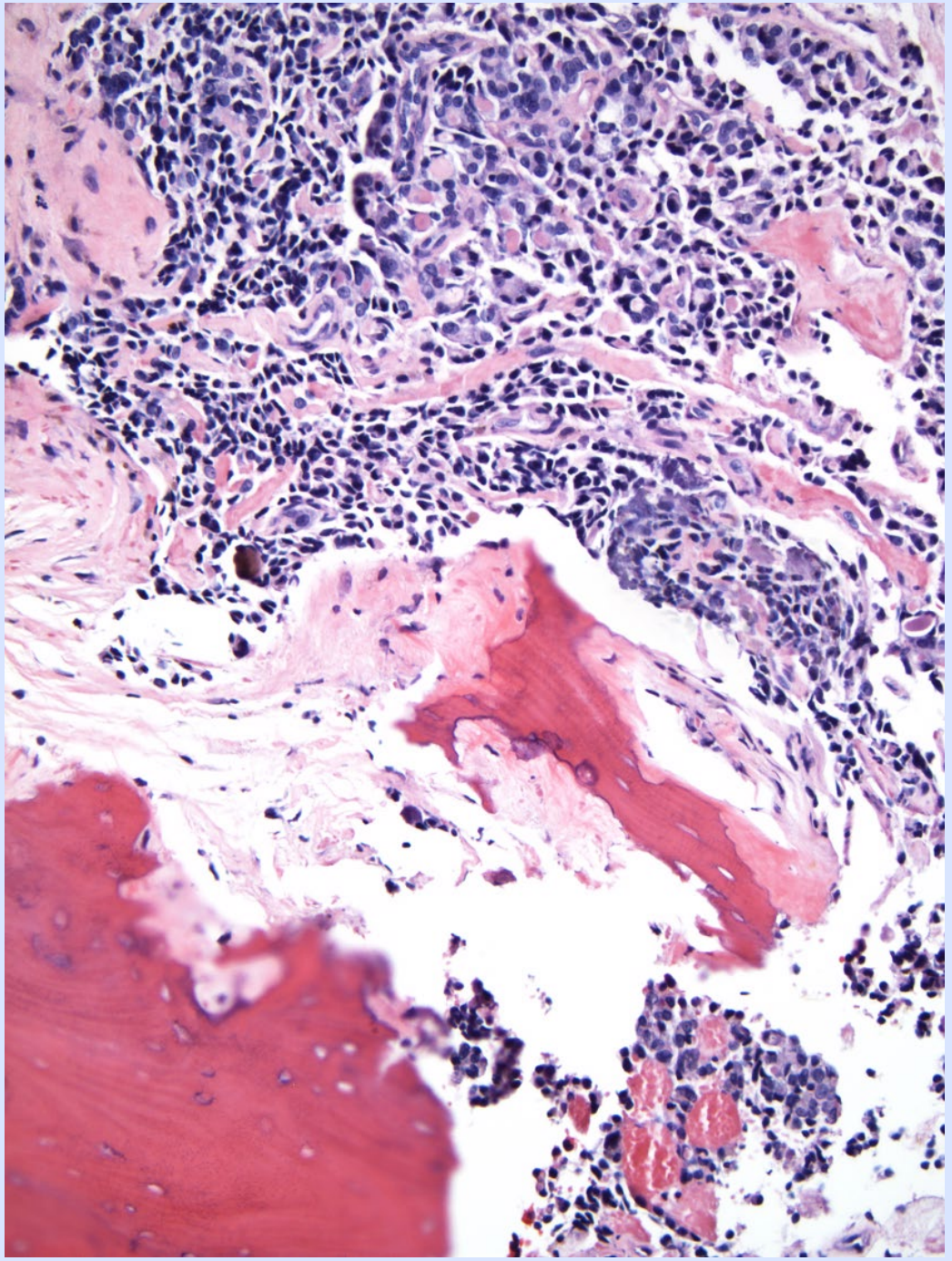
A tumor bed recurrence was detected one year later, and a metastasis to the right femur was detected 5 years later.

Roughly 50 lymph nodes were resected at various time points that were negative for tumor.

These tumors:

- Spread in a similar fashion as FTC not PTC.

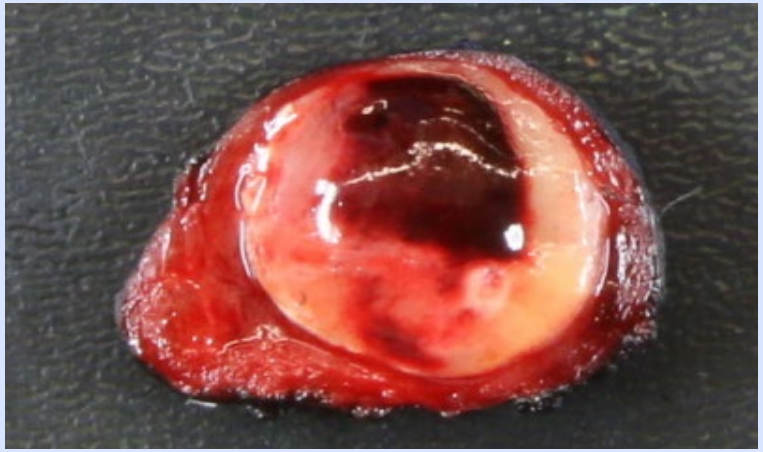
- Have a molecular profile similar to FTC (*RAS*-like).

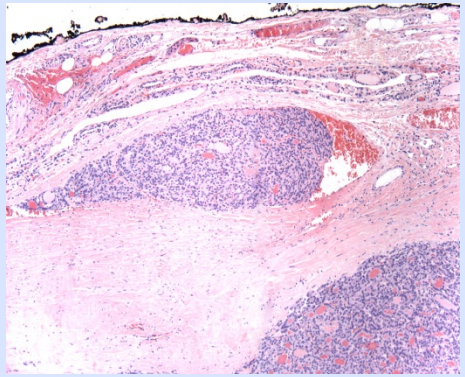


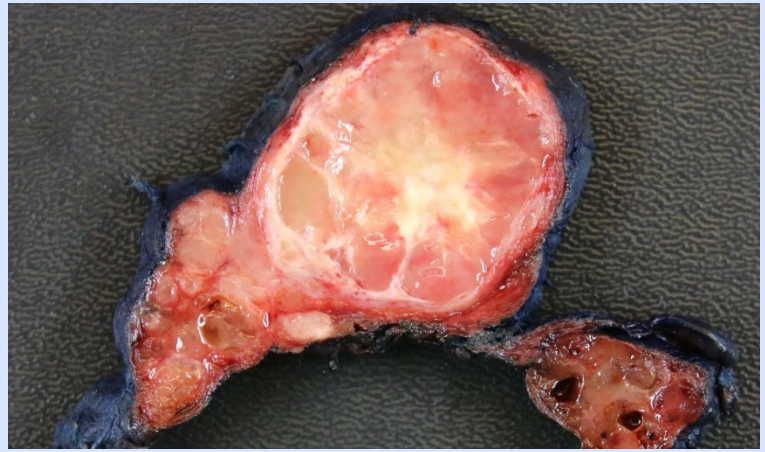
Thyroid - Follicular-cell Derived Malignant Neoplasms
Follicular thyroid carcinoma
Invasive encapsulated follicular variant of papillary thyroid carcinoma
Papillary thyroid carcinoma
Oncocytic carcinoma of the thyroid
Follicular-derived carcinoma, high-grade
Anaplastic thyroid carcinoma

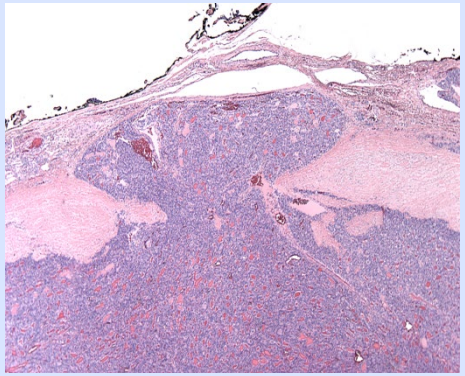
To reflect that the biology of invasive encapsulated FVPTC is more similar to FTC, it was taken out of the PTC section of the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours and given its own section between FTC and PTC.

Invasive encapsulated FVPTC is subdivided in a similar fashion to FTC.







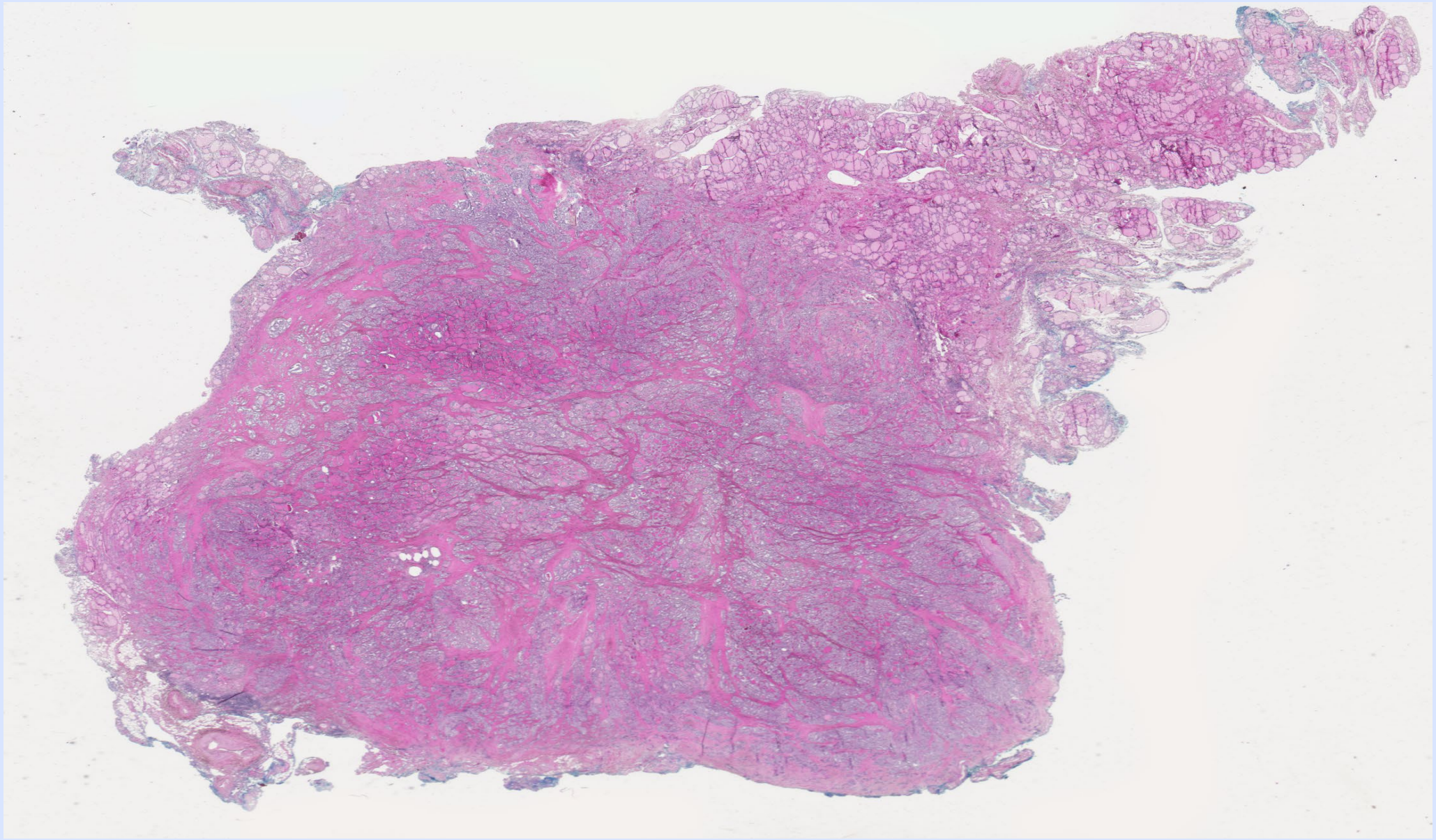


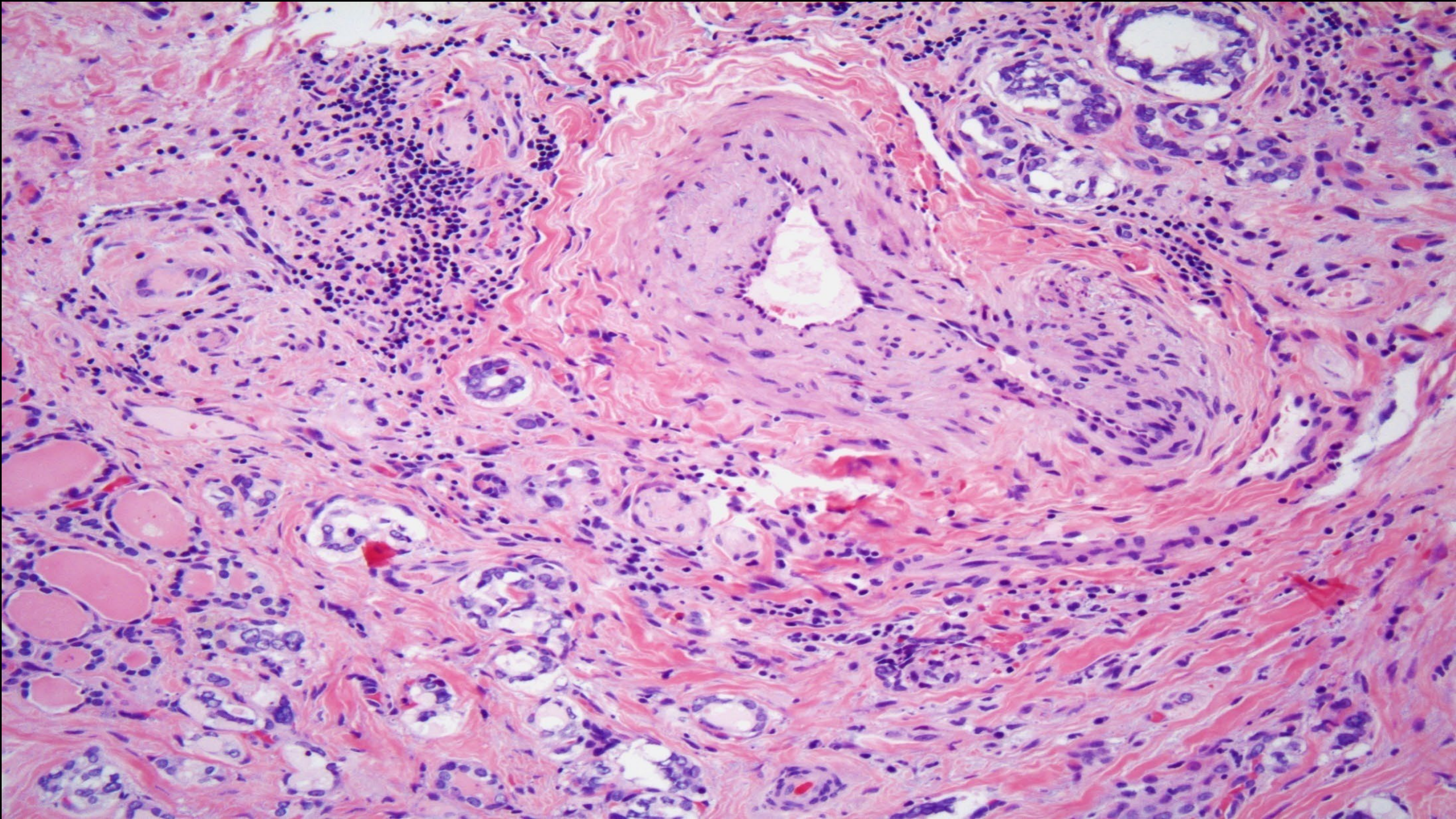
- Minimally invasive (capsular invasion only)

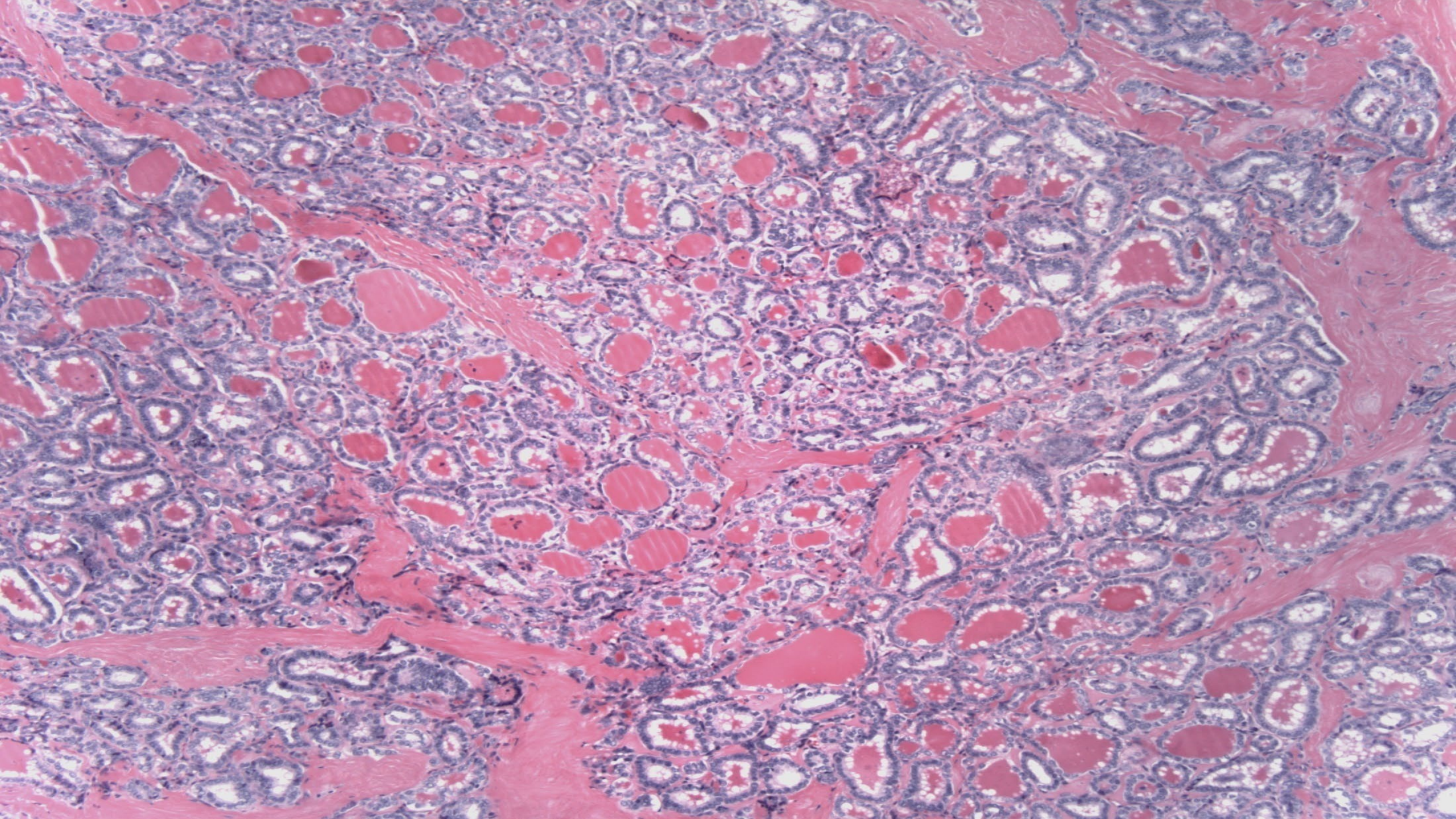
- Encapsulated angioinvasive: vascular invasion present with/without capsular invasion

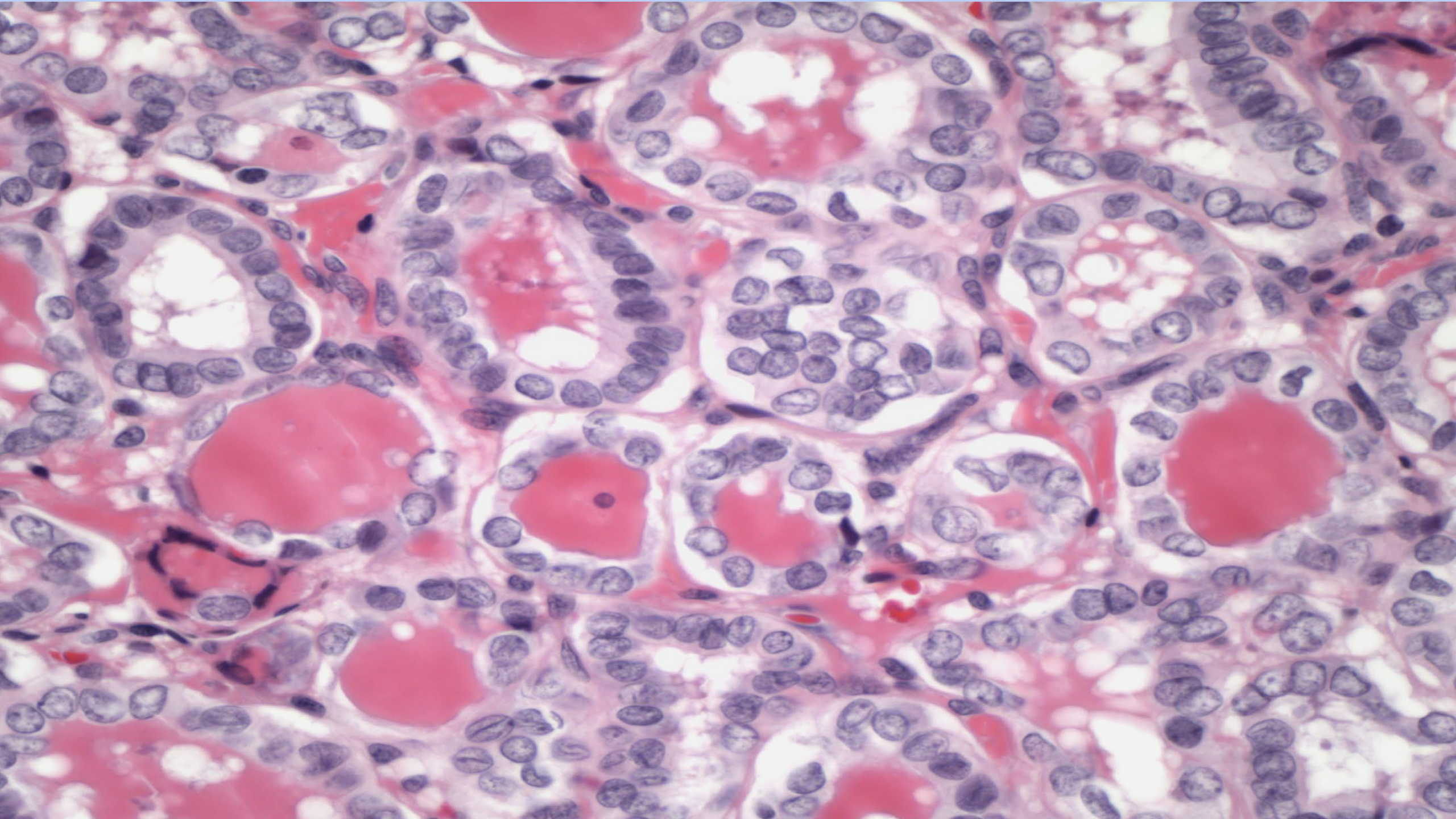
- Widely invasive: grossly see tumor invading through parenchyma, usually also have extensive vascular invasion

Infiltrative FVPTC









Infiltrative FVPTC

- Spread to lymph nodes in a similar fashion as classic PTC

- Approximately 25% have a *BRAF* V600E mutation

Because the biology of infiltrative FVPTC is similar to that of classic PTC, it is in the PTC section of the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours.

Case

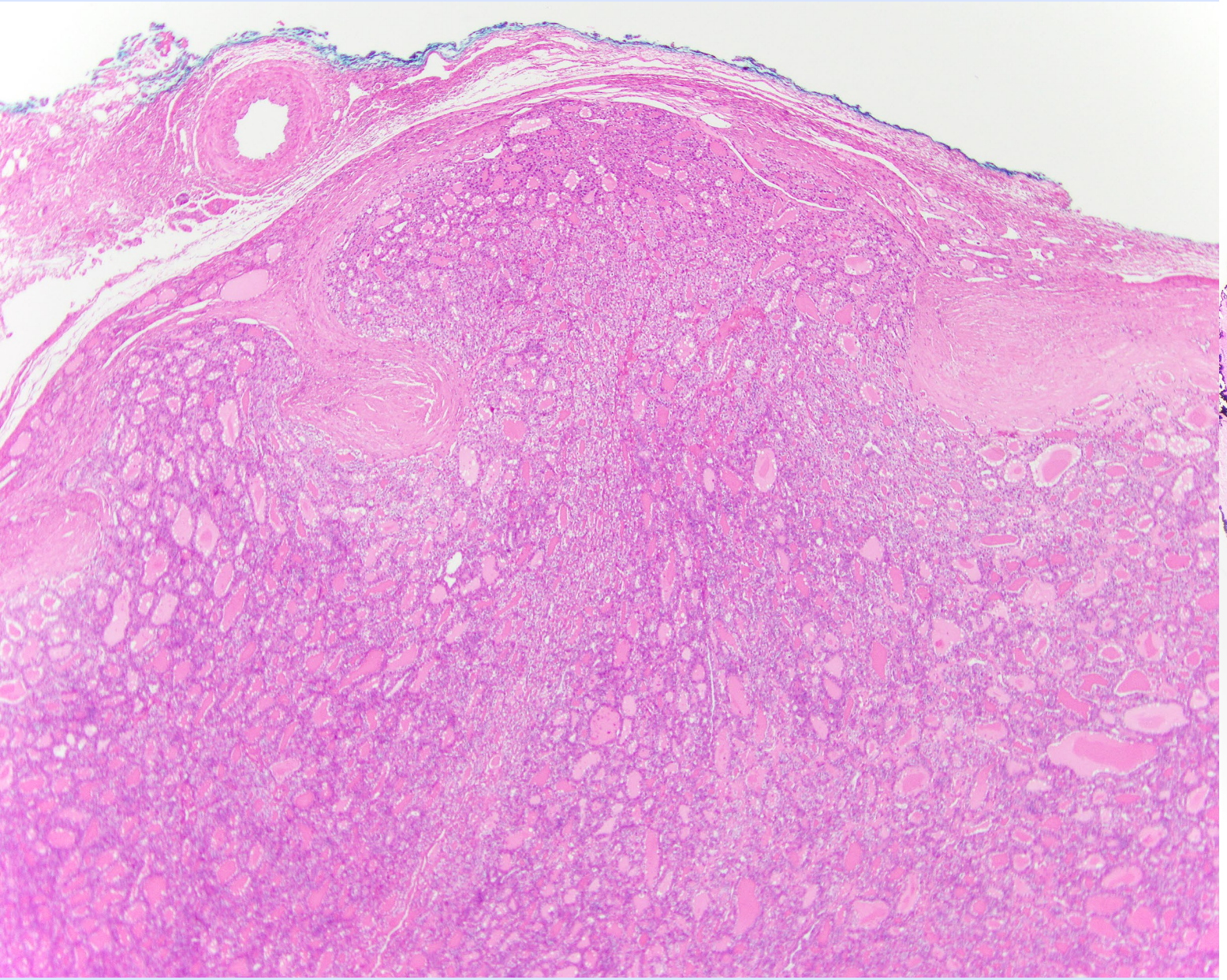
The patient is a 33-year-old woman with a known germline *DICER1* mutation.

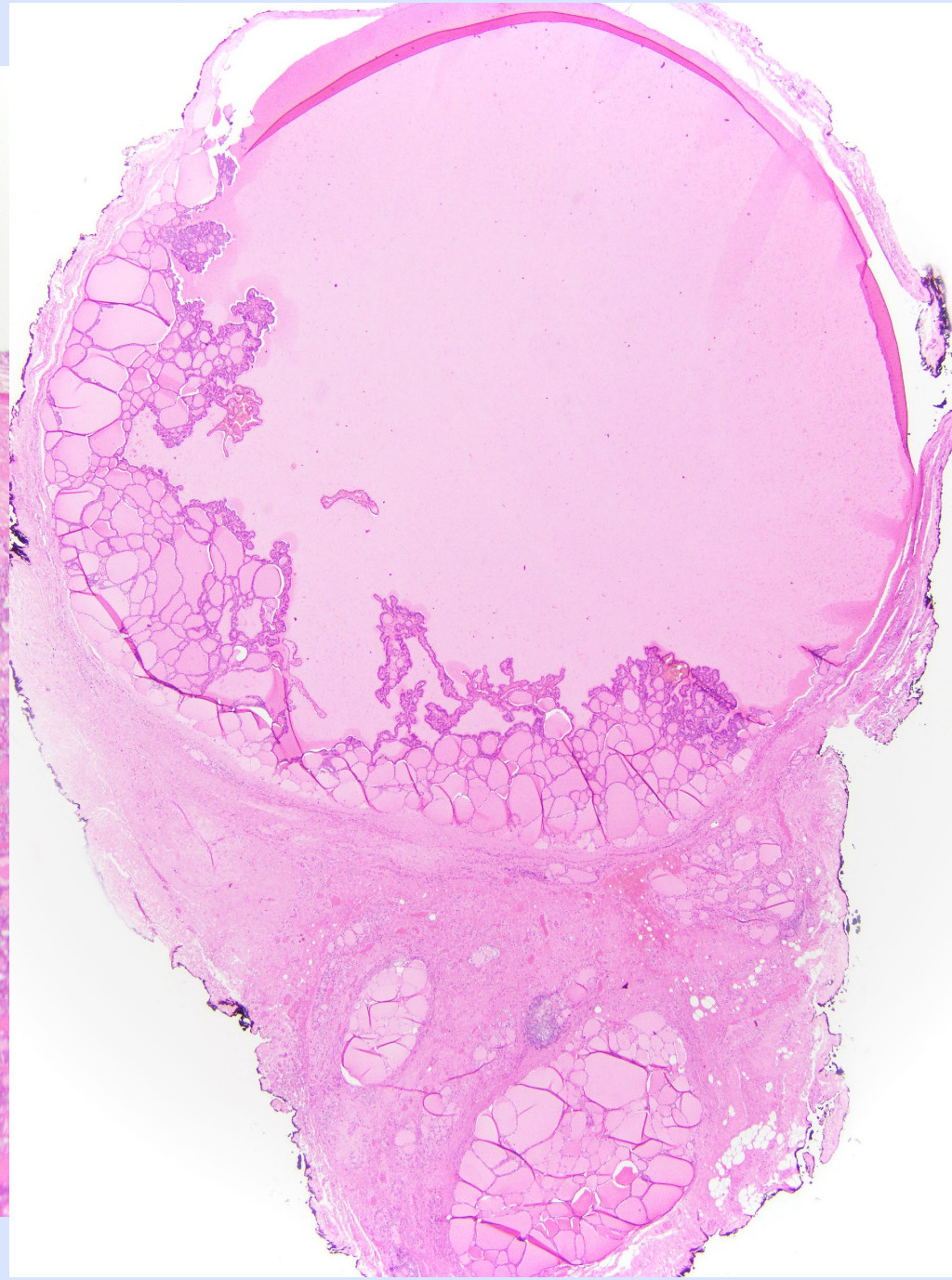
She had 2 prior thyroid operations when she was age 16 and 20 for multinodular goiter (MNG).

A small amount of thyroid tissue was left behind, and she subsequently developed recurrent thyroid nodules.

Fine needle aspiration (FNA) of one of the nodules was performed and was suspicious for a follicular neoplasm.

Completion thyroidectomy was performed.

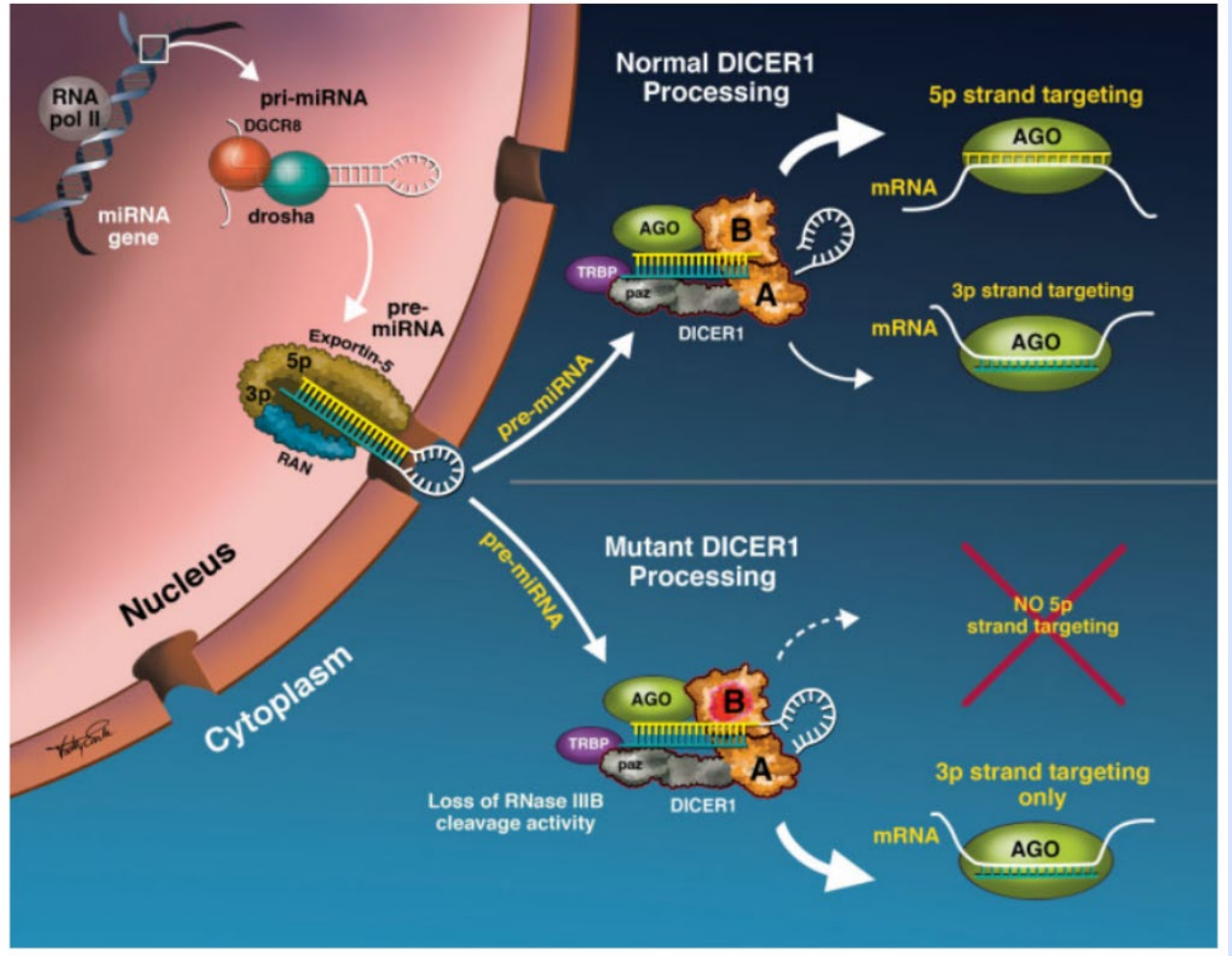




DICER1 activity is central to the synthesis of microRNA (miRNA).

Tumors typically harbor a hotspot mutation in the RNase IIIB domain along with a loss of function mutation that may be germline (in the setting of DICER1 syndrome) or somatic.

Mutations lead to an altered miRNA ratio that results in dramatic shifts in mRNA profiles and subsequent dysregulation of gene expression.



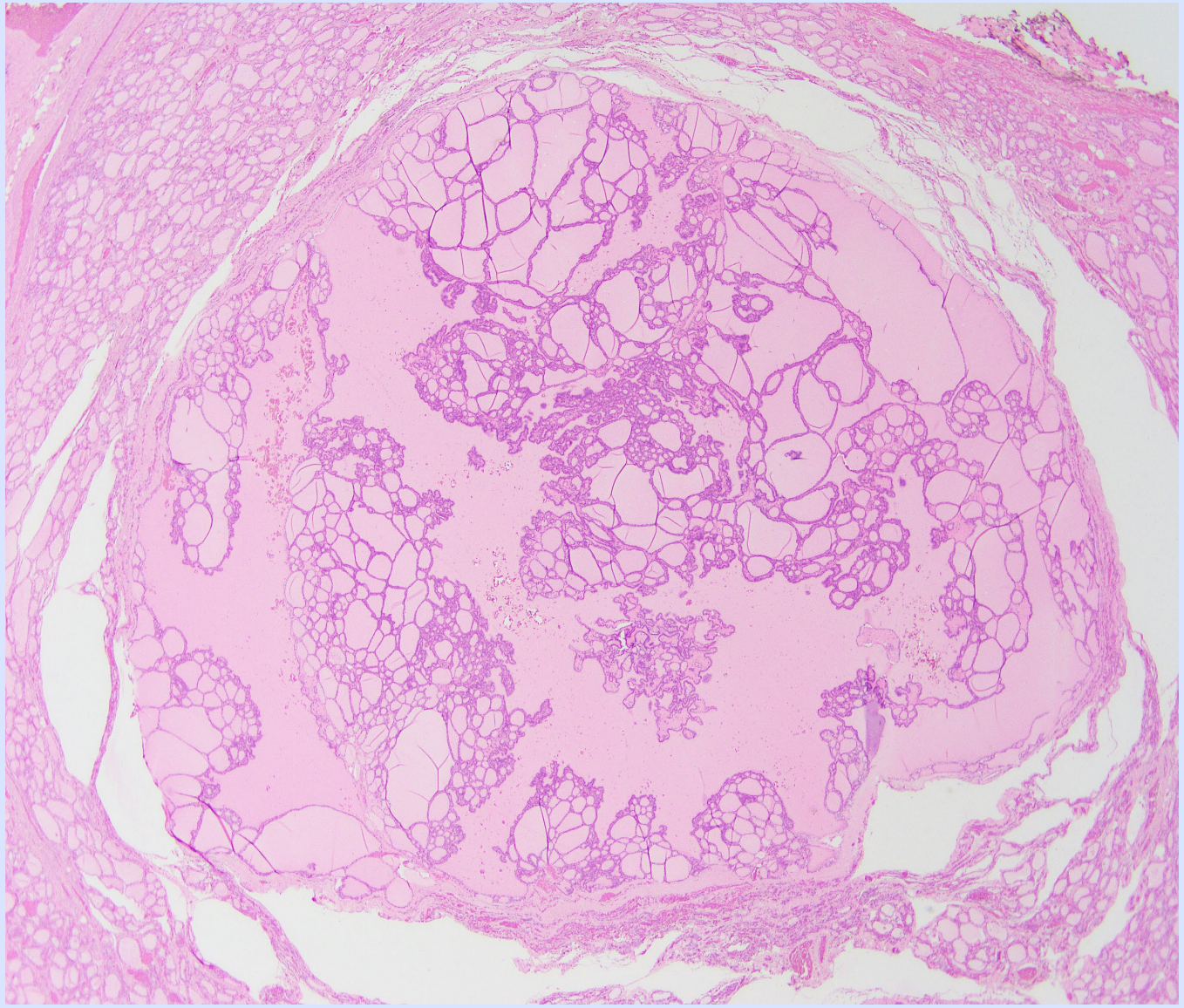
Anglesio et al. J Pathol 2013; 229: 400–409

Thyroid Manifestations of DICER1 Syndrome

Most frequent manifestation is multinodular goiter or follicular nodular disease.

Many of these nodules have histologic features of hyperplastic nodules (though they can have an adenomatous appearance).

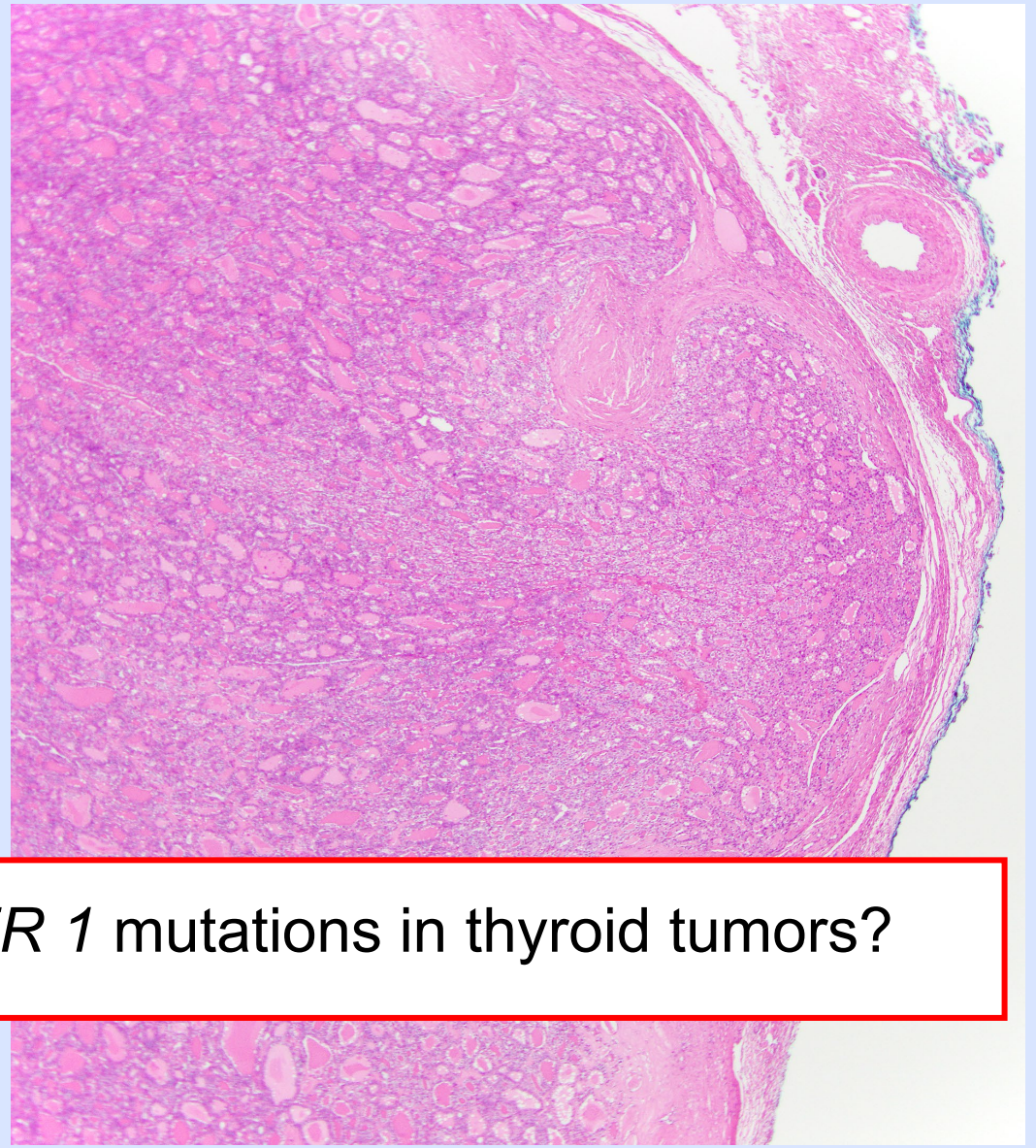
These are clonal neoplasms.



Thyroid Manifestations of DICER1 Syndrome

Patients with DICER1 syndrome are at increased risk of developing thyroid carcinomas.

These are usually indolent follicular-patterned tumors (minimally invasive FTC or minimally invasive encapsulated FVPTC most common).



How common are somatic *DICER 1* mutations in thyroid tumors?

DICER1 Mutations in Thyroid Carcinoma

In adults, follicular-patterned thyroid tumors are *RAS*-mutant predominant and have a low rate of *DICER1* mutations (present in about 1% of nodules undergoing FNA).

DICER1 mutations are enriched in follicular-patterned thyroid tumors children, pediatric poorly differentiated thyroid carcinoma and in macrofollicular variants of FTC.

DICER1 mutations can be sporadic or germline.

DICER1 Mutations in Thyroid Carcinoma

In adults, follicular-patterned thyroid tumors are *RAS*-mutant predominant and have a low rate of *DICER1* mutations (present in about 1% of nodules undergoing FNA).

D
c
m

For follicular-patterned tumors (with or without invasion and with or without nuclear features of PTC) with a background of follicular nodular disease consider DICER1 syndrome (especially if patient is young).

DICER1 mutations can be sporadic or germline.

Case

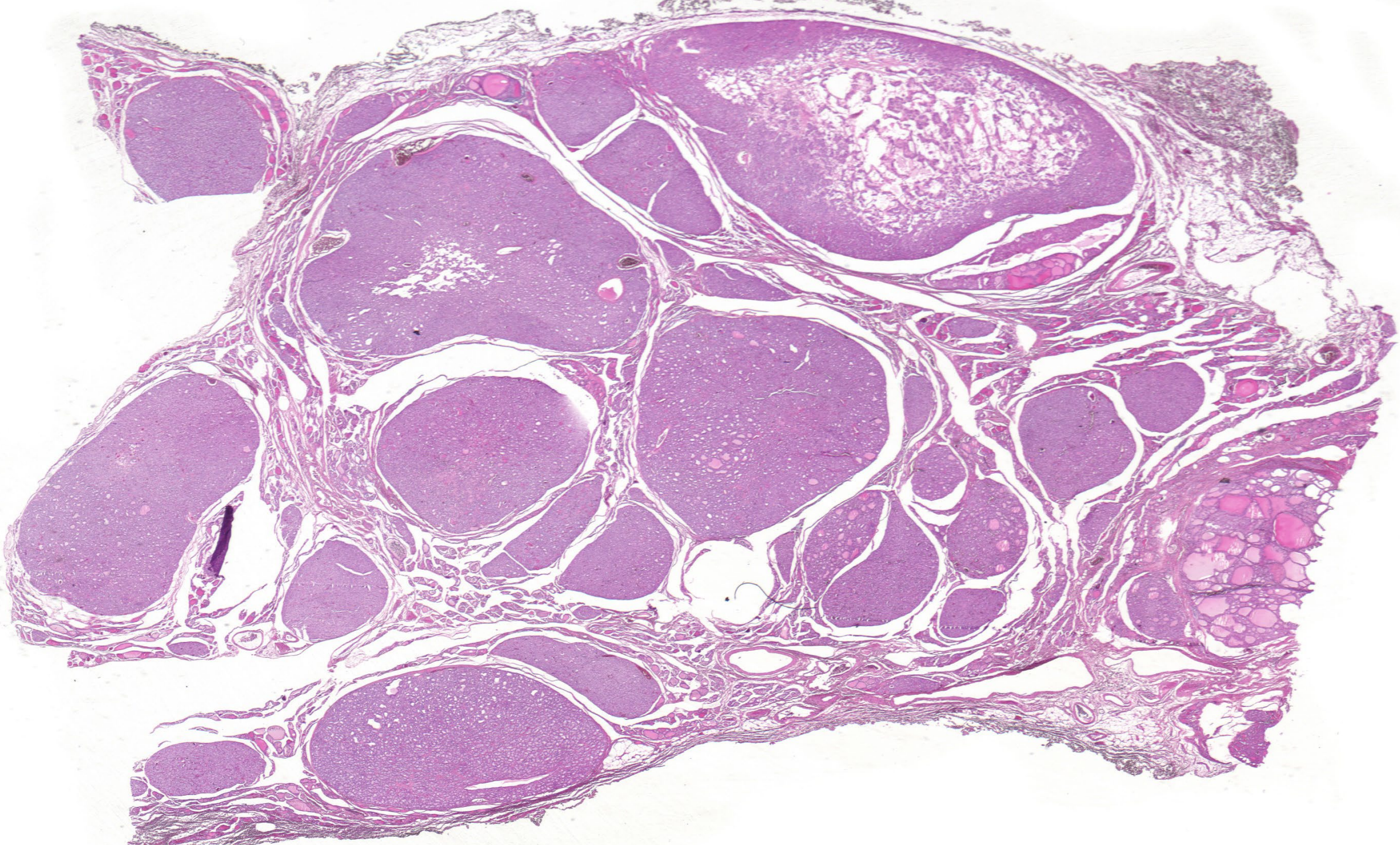
A 52-year-old woman with a clinical history of thyroid issues for over 20 years presents because her thyroid is leading to uncomfortable fullness in her neck.

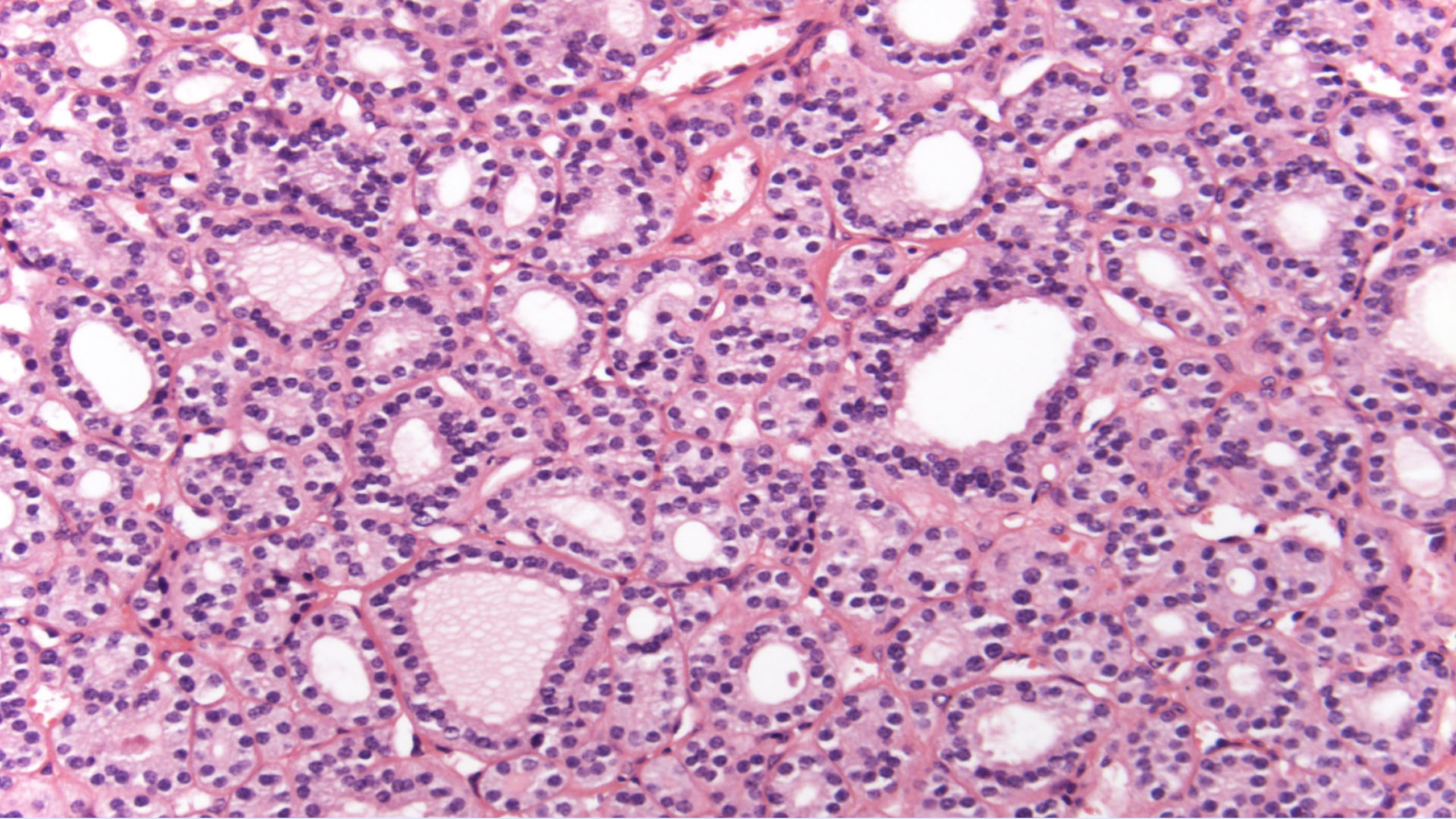
Ultrasound findings are suggestive of goiter.

An FNA of one of the nodules was diagnosed as suspicious for a follicular neoplasm.

A total thyroidectomy was performed for compressive symptoms.

The thyroid was 92 grams and demonstrated over 100 discrete nodules.





Multiple Adenomatous Nodules in the Setting of Cowden Syndrome

Cowden syndrome (CS) is an autosomal dominant disorder most frequently caused by a germline mutation in *PTEN.*

Characterized by the development of multiple hamartomas and carcinomas of the thyroid, breast, and uterus.

Recognition of CS is important so that genetic counseling and cancer screening and can be initiated (for women with CS, the lifetime risk of breast cancer of 50%).

Multiple Adenomatous Nodules in the Setting of Cowden Syndrome

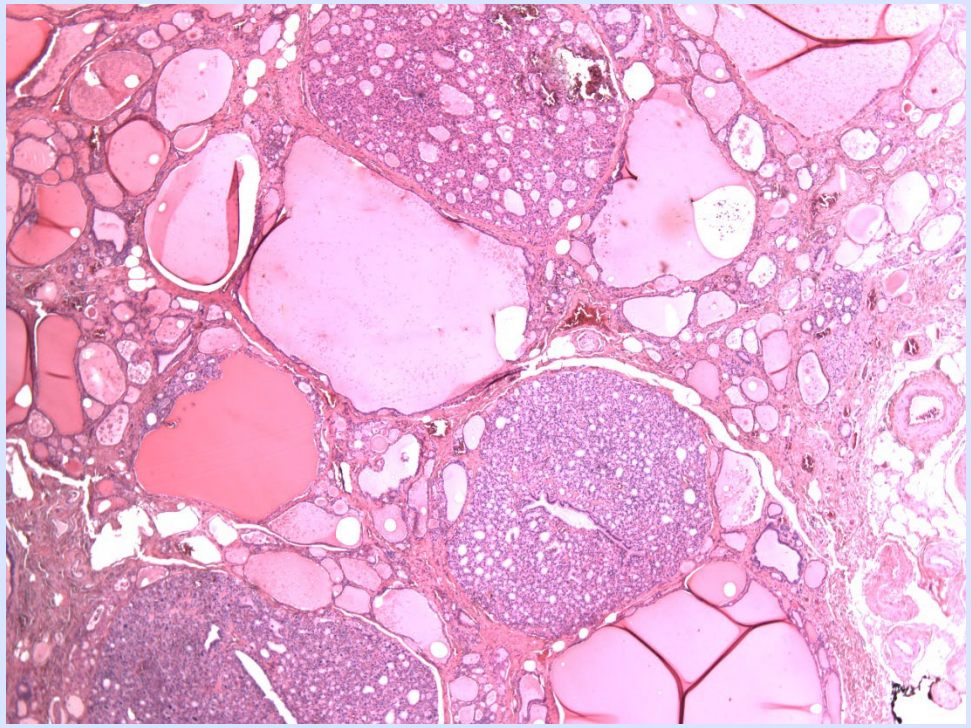
Pathologic findings in thyroidectomy specimens:

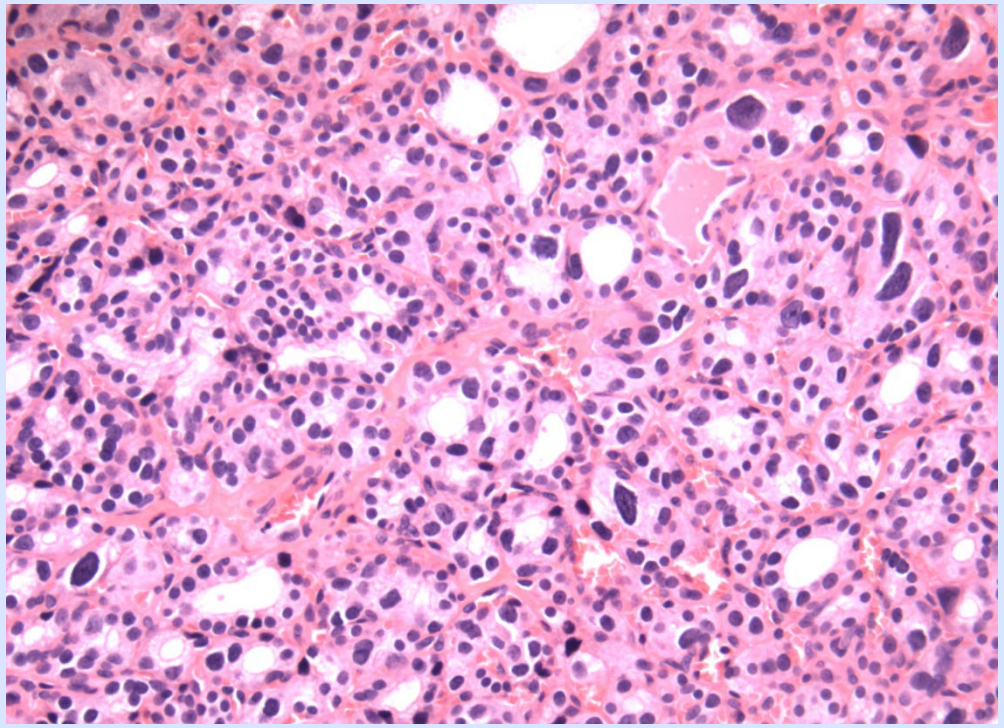
- Multiple adenomatous nodules
- Follicular adenomas
- Nodular hyperplasia
- Can also have follicular or papillary thyroid carcinoma

Although the constellation of histologic findings in thyroidectomy specimens from CS is unusual and should raise the possibility of a diagnosis of CS, the findings are not entirely specific for CS.

Multiple Adenomatous Nodules in the Setting of Cowden Syndrome

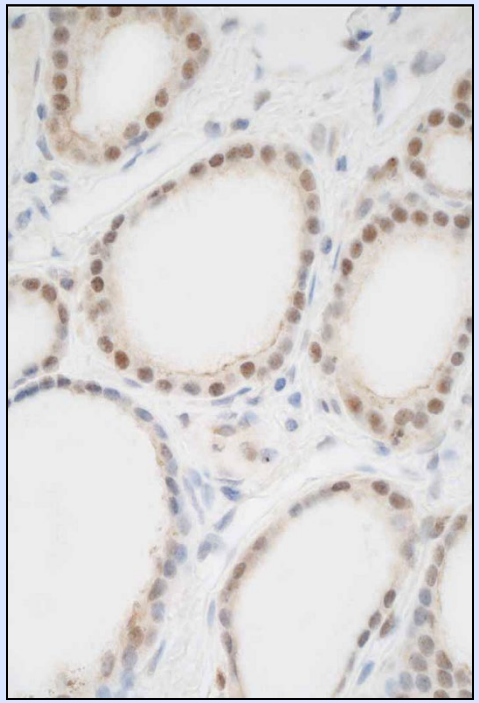
External beam radiation can produce similar findings (though there is usually more fibrosis and atrophy in the gland). In other cases with similar findings, the etiology is unclear.

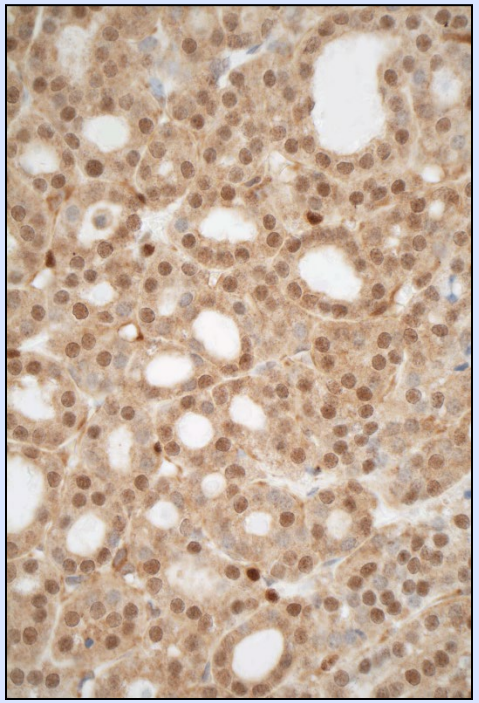


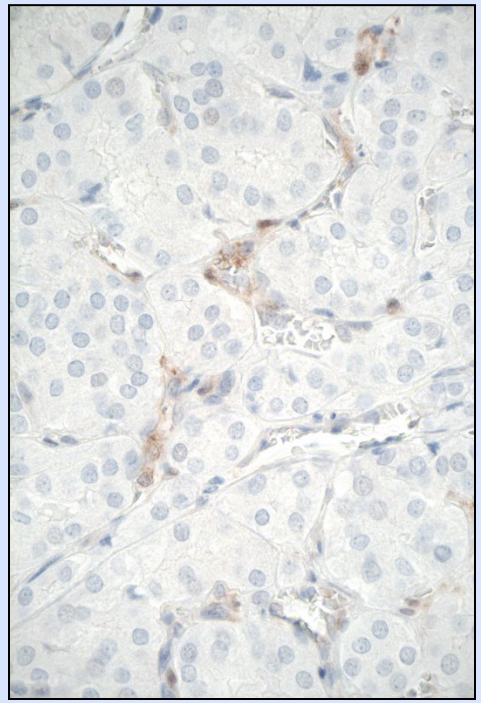


Multiple Adenomatous Nodules in the Setting of Cowden Syndrome

Immunohistochemical staining for PTEN can be used to aid in the diagnosis. The sensitivity and specificity of loss of PTEN staining in adenomatous nodules for CS is 100% and 92.3%, respectively (Barletta *et al*, *Am J Surg Pathol*, 2011).

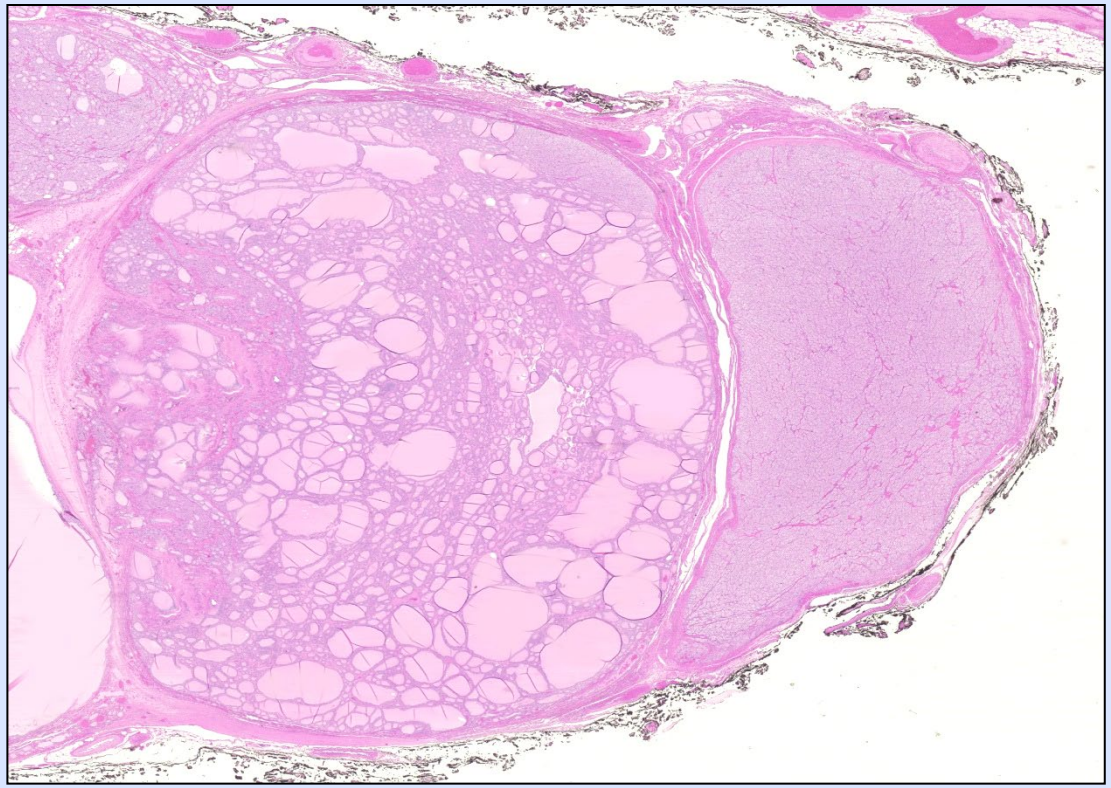


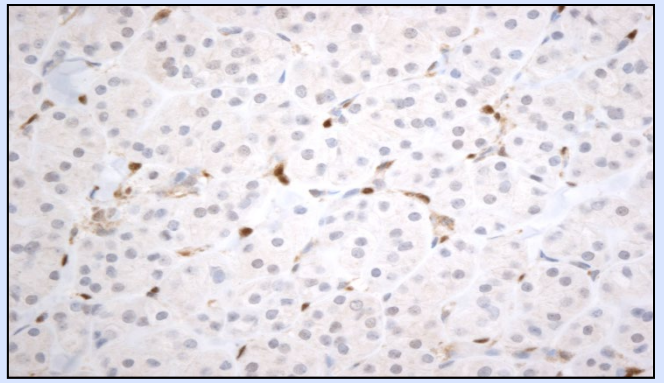


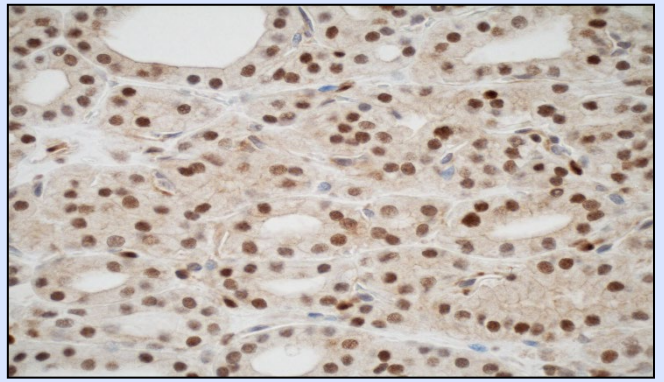


Multiple Adenomatous Nodules in the Setting of Cowden Syndrome

Loss of PTEN staining may be heterogeneous. Roughly a third of CS cases show intact expression in some nodules and complete loss of expression in other nodules.







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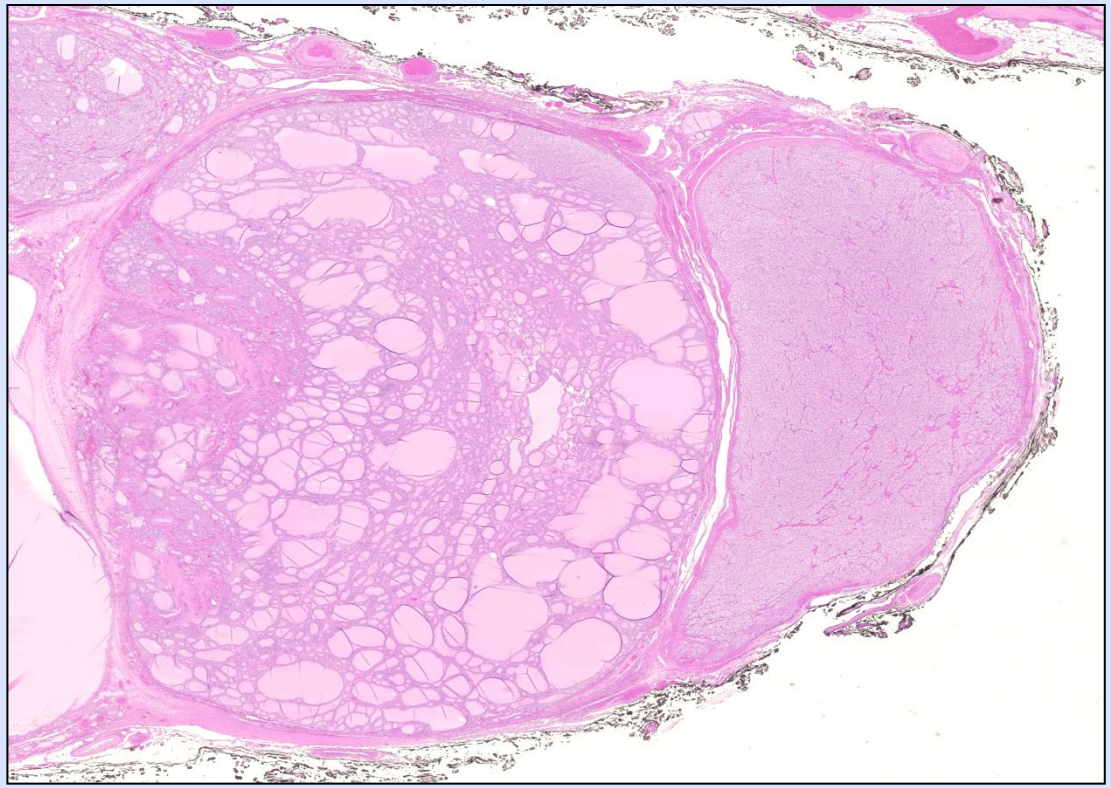

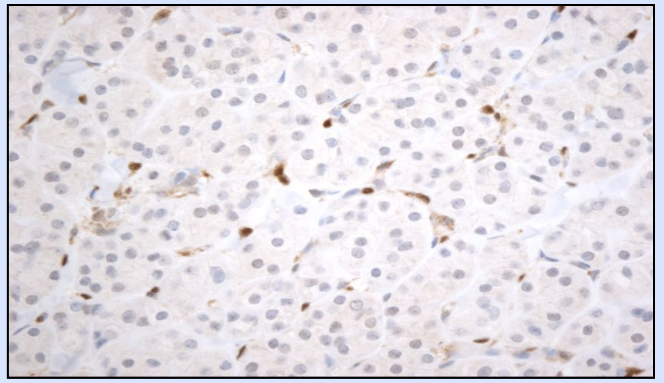

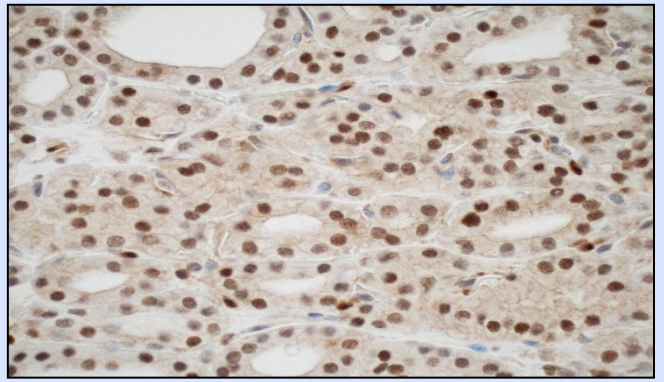

Multiple Adenomatous Nodules in the Setting of Cowden Syndrome

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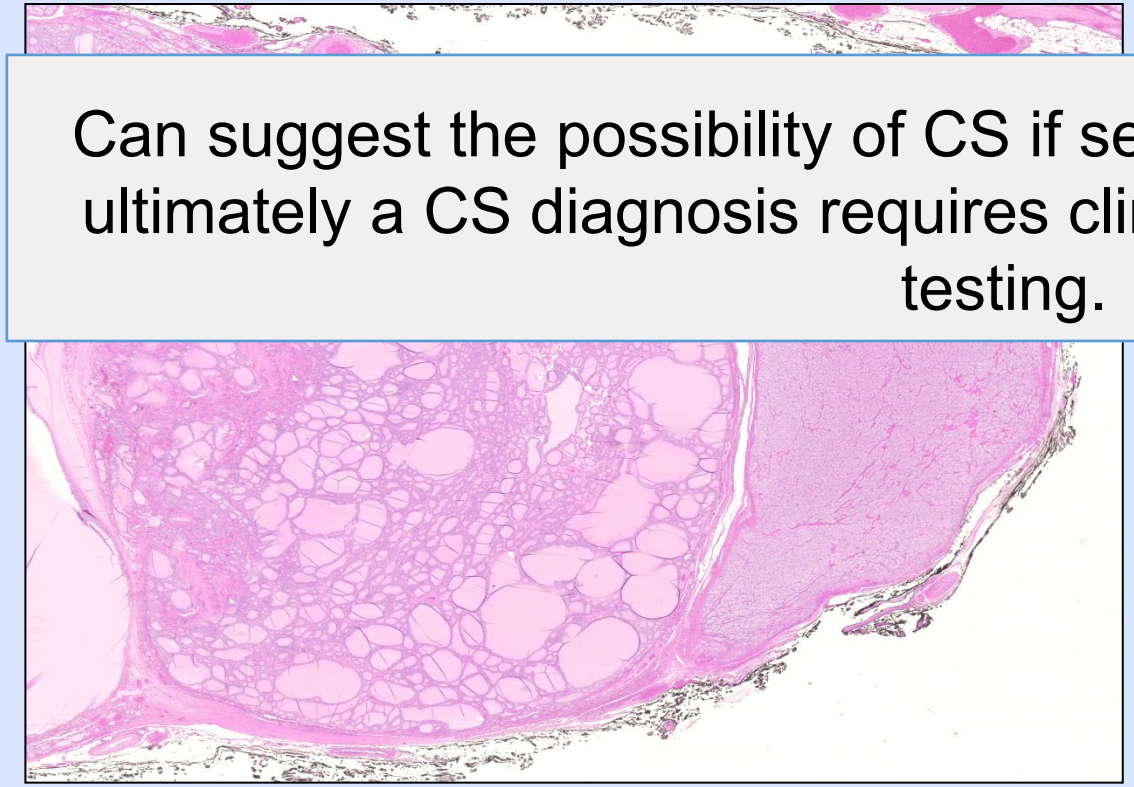
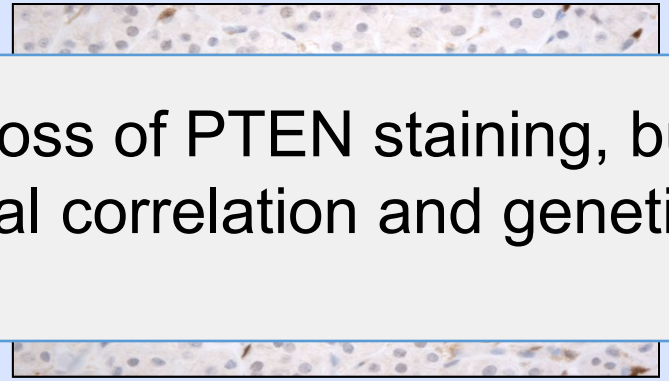
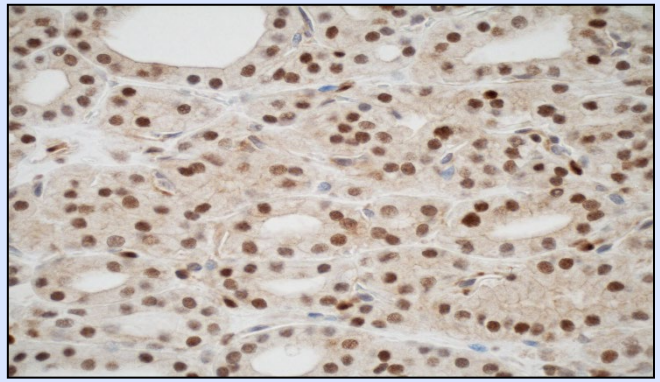






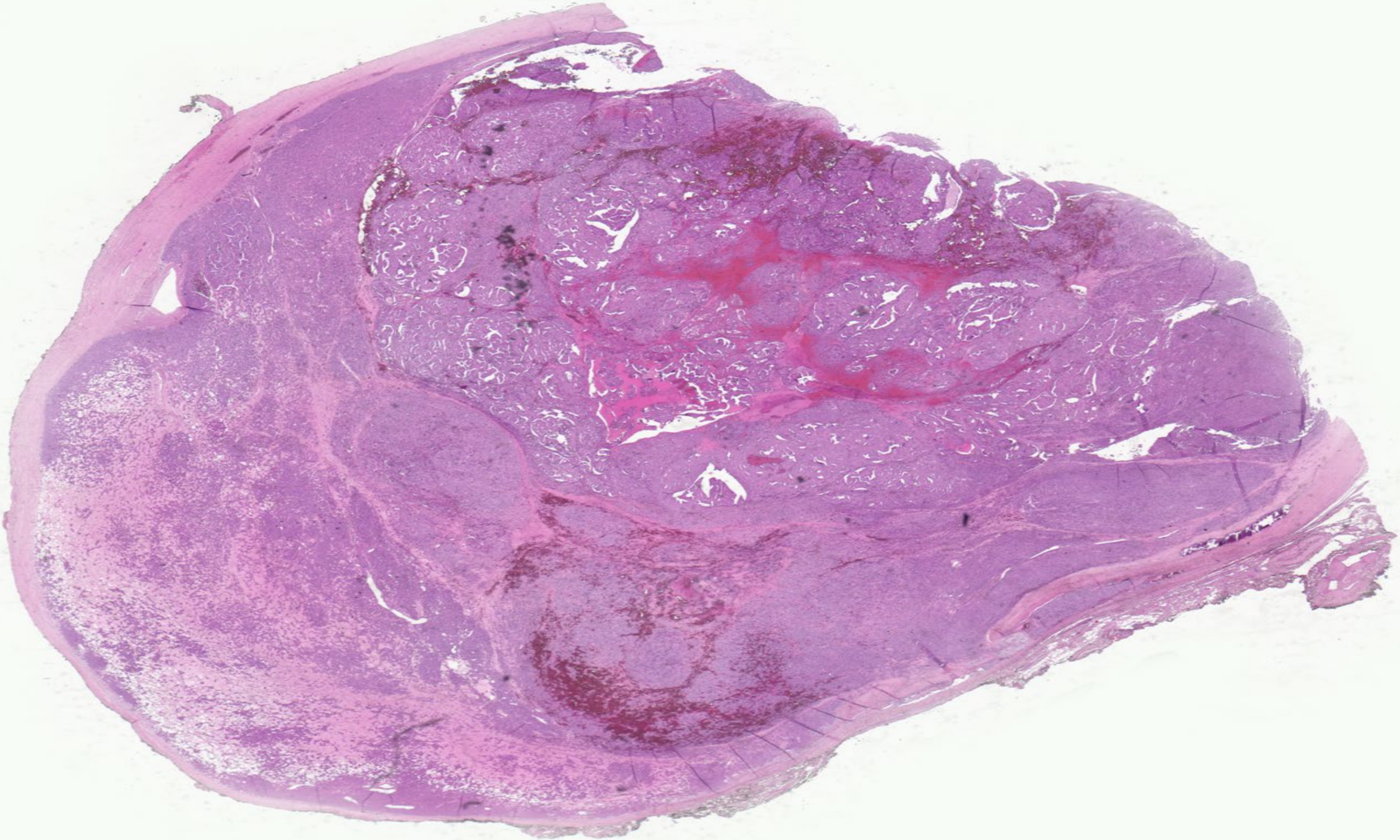
Can suggest the possibility of CS if see loss of PTEN staining, but ultimately a CS diagnosis requires clinical correlation and genetic testing.

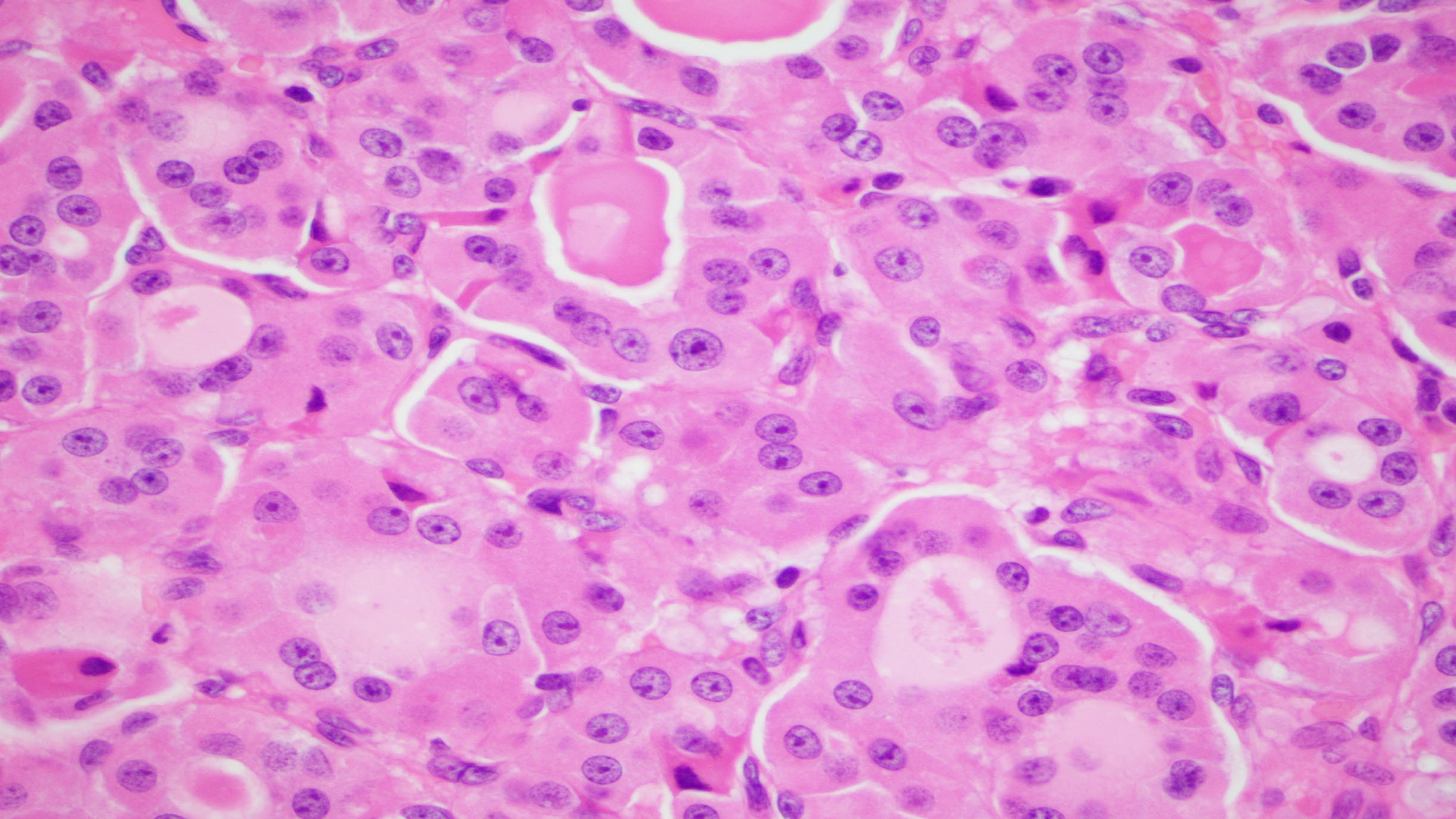
Case

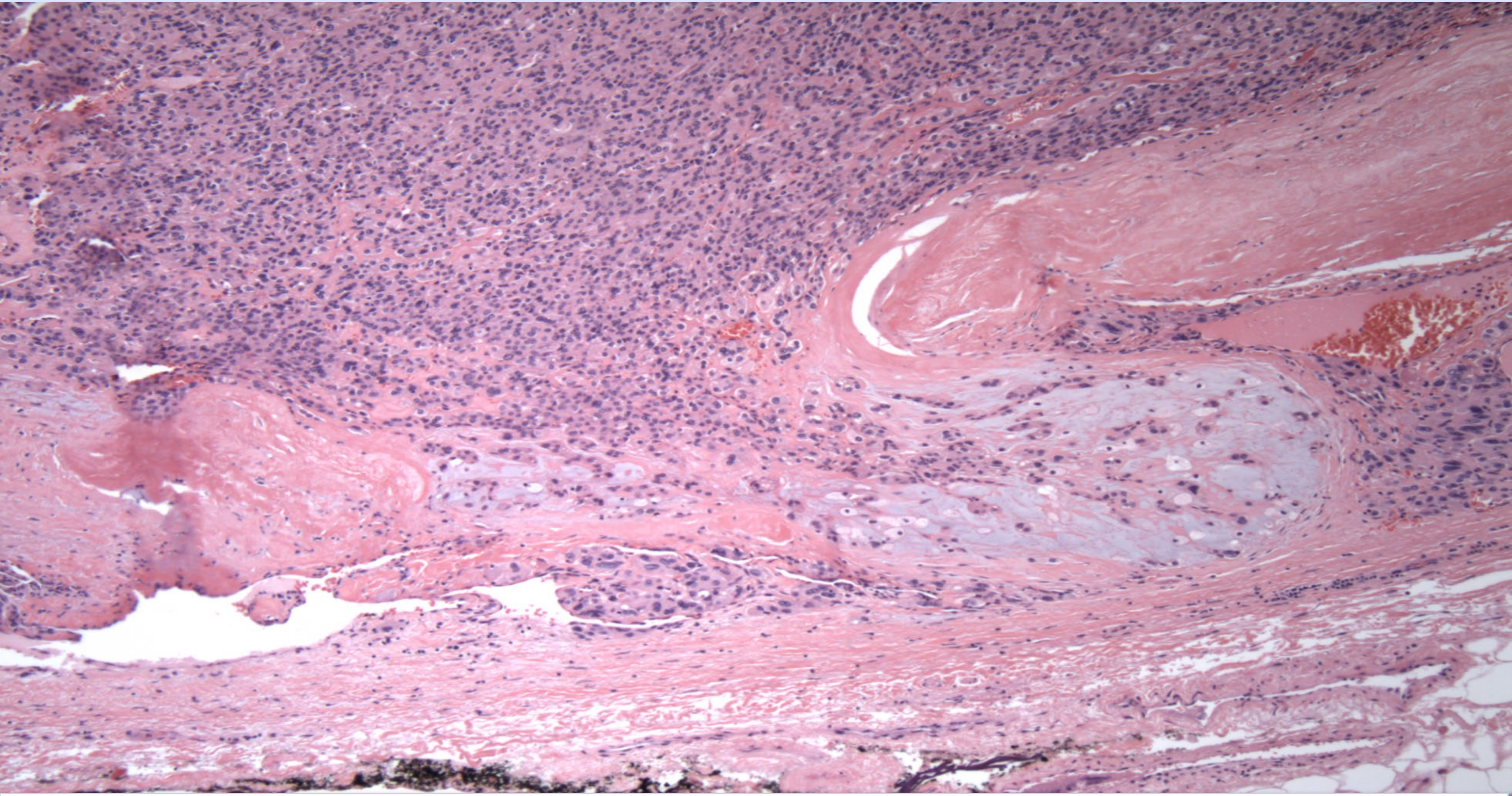
The patient is a 59-year-old woman who palpated a thyroid nodule.

Imaging demonstrated a 3 cm nodule in the left lobe.

A diagnostic hemithyroidectomy was performed after an indeterminate FNA diagnosis and a suspicious Afirma result.







Encapsulated Angioinvasive Oncocytic Thyroid Carcinoma

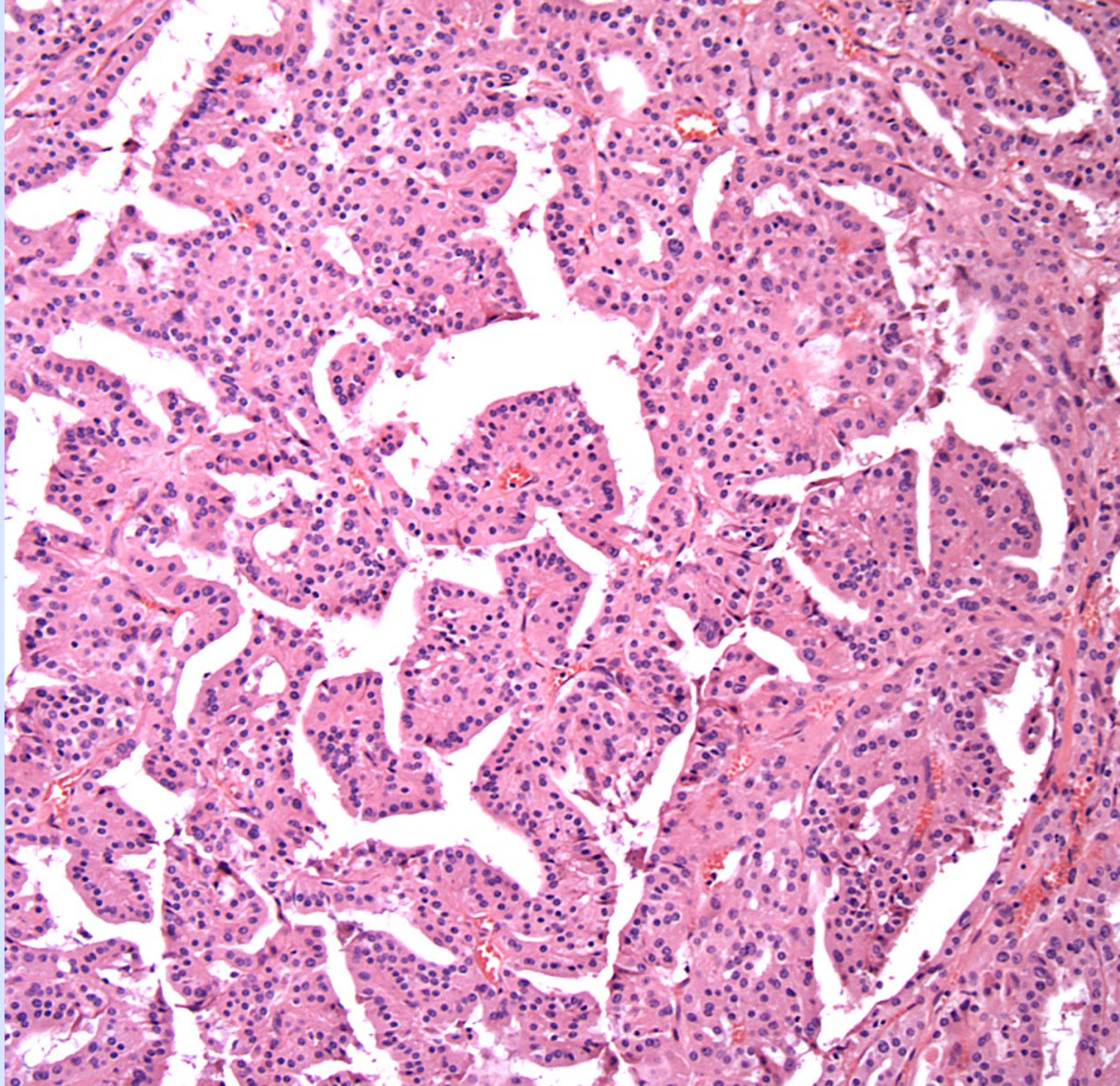
Oncocytic tumors can occasionally have areas of papillary architecture!

Encapsulated Papillary Oncocytic Neoplasms of the Thyroid: Morphologic, Immunohistochemical, and Molecular Analysis of 18 Cases

Randall Lyndon Woodford, MD, Yuri E. Nikiforov, MD, PhD,† Jennifer L. Hunt, MD,‡ Andrew M. Bellizzi, MD,§ Xiaotang Zhang,‖ Stacey E. Mills, MD,* and Edward B. Stelow, MD**

(*Am J Surg Pathol* 2010;34:1582–1590)

Just as in any other oncocytic neoplasm, malignancy is based on the presence of invasion.

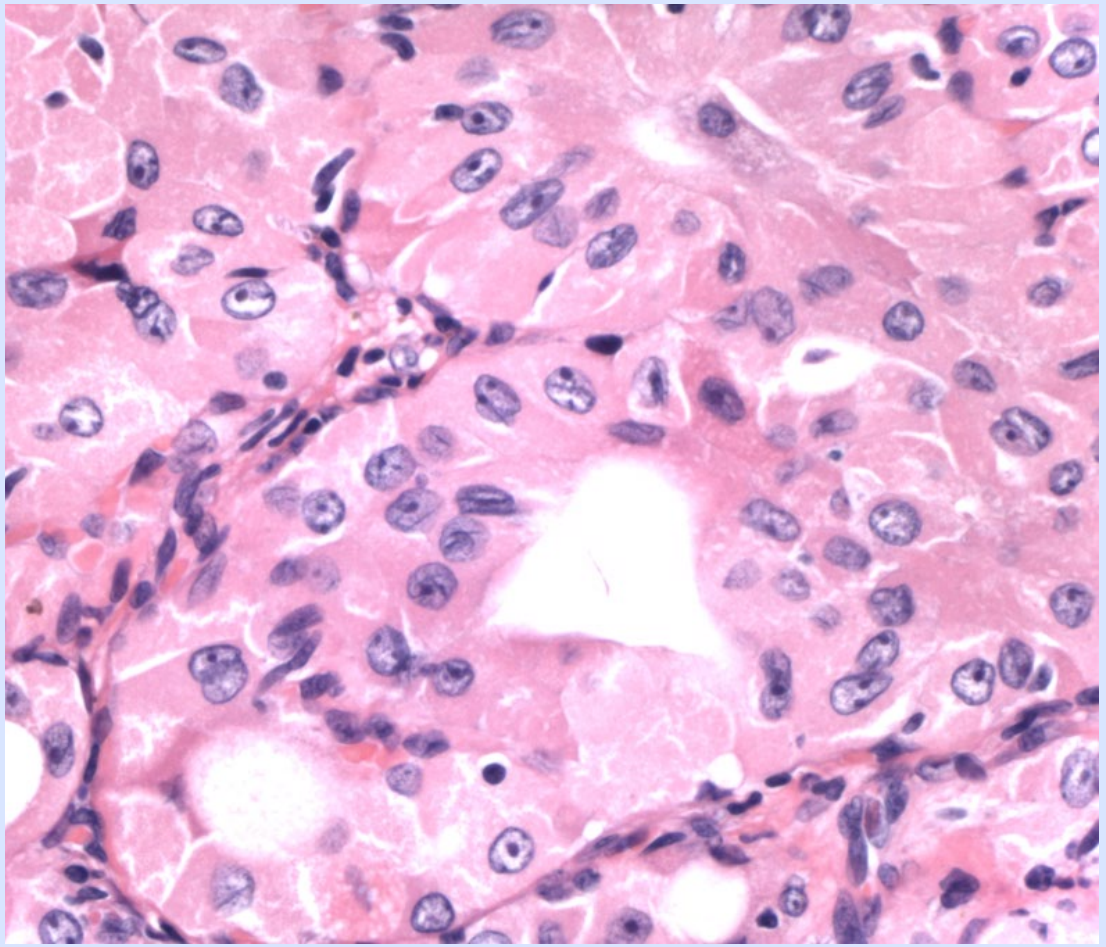


Pitfall

Think you are looking at a PTC based on the papillary architecture.

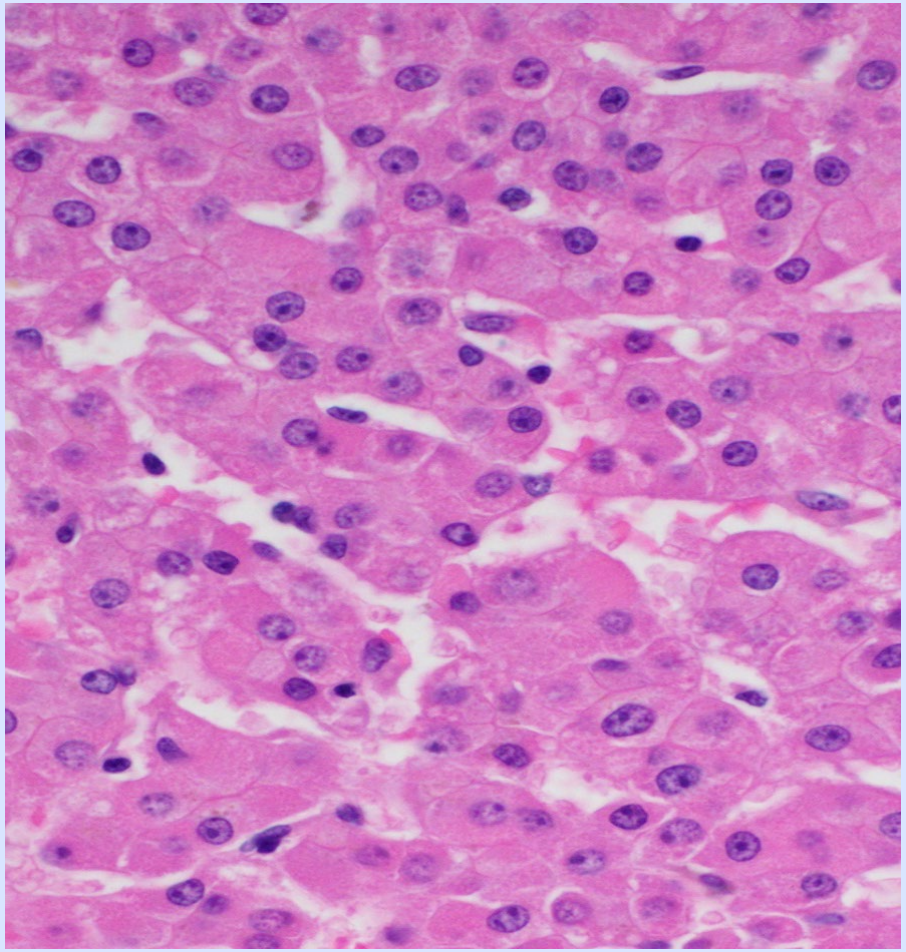
Some oncocytic neoplasms have nuclear contour irregularities.

Once you decide a tumor is oncocytic (pay attention to macronucleoli in addition to the oncocytic cytoplasm) ignore atypia such as contour irregularity.



Oncocytic Thyroid Carcinoma (OTC)

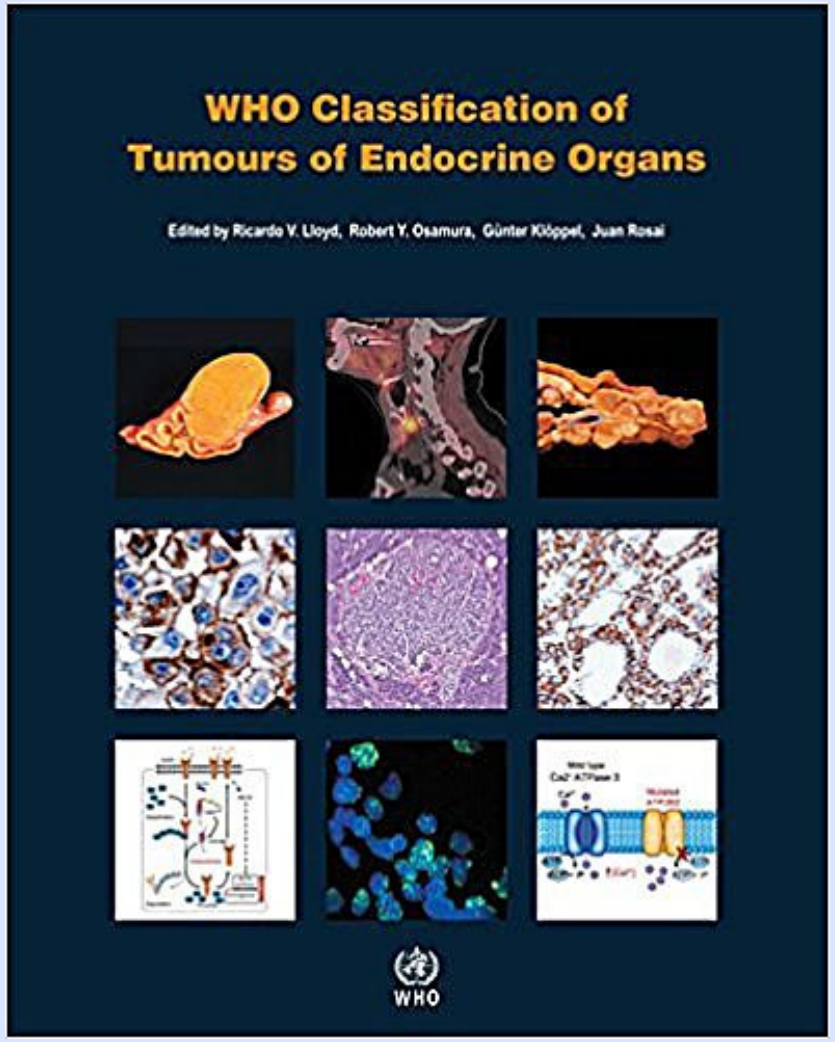
- OTC accounts for 3-4% of thyroid carcinomas (defined as having >75% oncocytic cells).
- Cells have abundant granular eosinophilic cytoplasm and prominent nucleoli.
- The risk of malignancy increases with size for oncocytic nodules.
- Prone to infarction after FNA.



Hurthle cell carcinoma

- No longer considered a subtype of FTC in the 2017 Endocrine WHO.

- Based on differences in clinicopathologic features and molecular alterations.



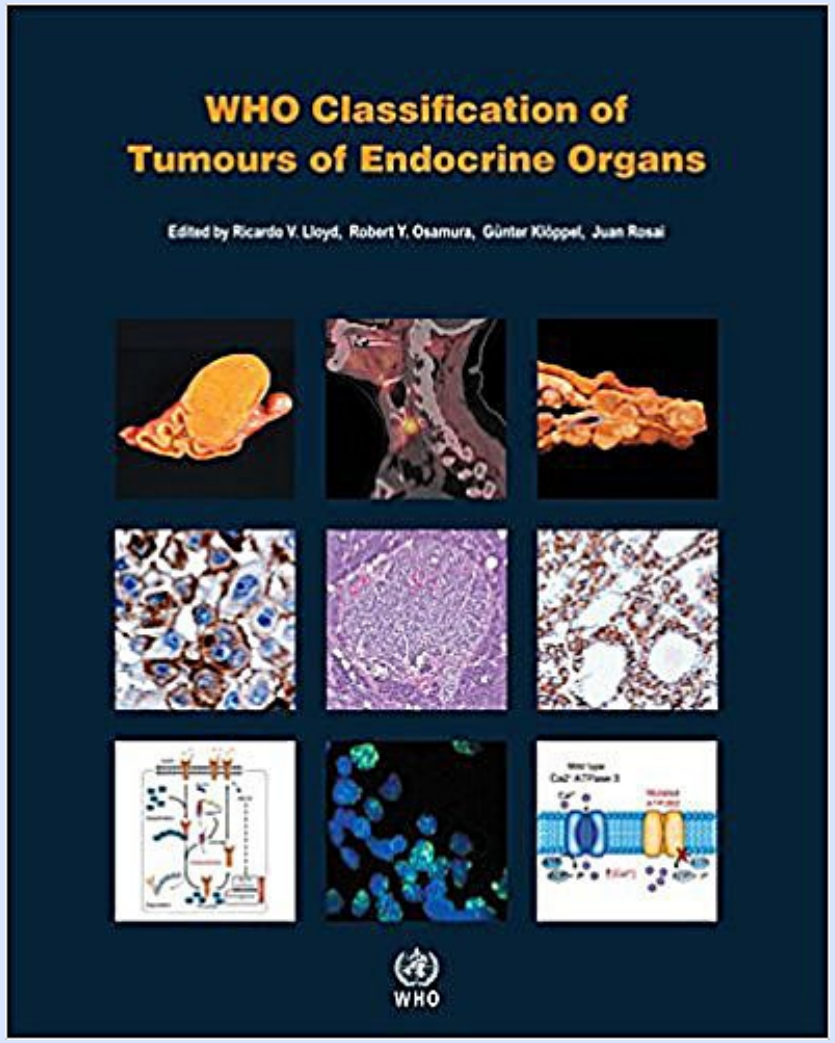
~~Hurthle cell carcinoma~~

Oncocytic thyroid carcinoma

- No longer considered a subtype of FTC in the 2017 Endocrine WHO.

- Based on differences in clinicopathologic features and molecular alterations.

- Referred to as oncocytic thyroid carcinoma in 2022 WHO



Clinical Features of Patients with OTC

- Patients with OTC are diagnosed at an older age than patients with FTC, and there is less of a dramatic female to male ratio (1.6:1 versus 2.6:1, SEER data).

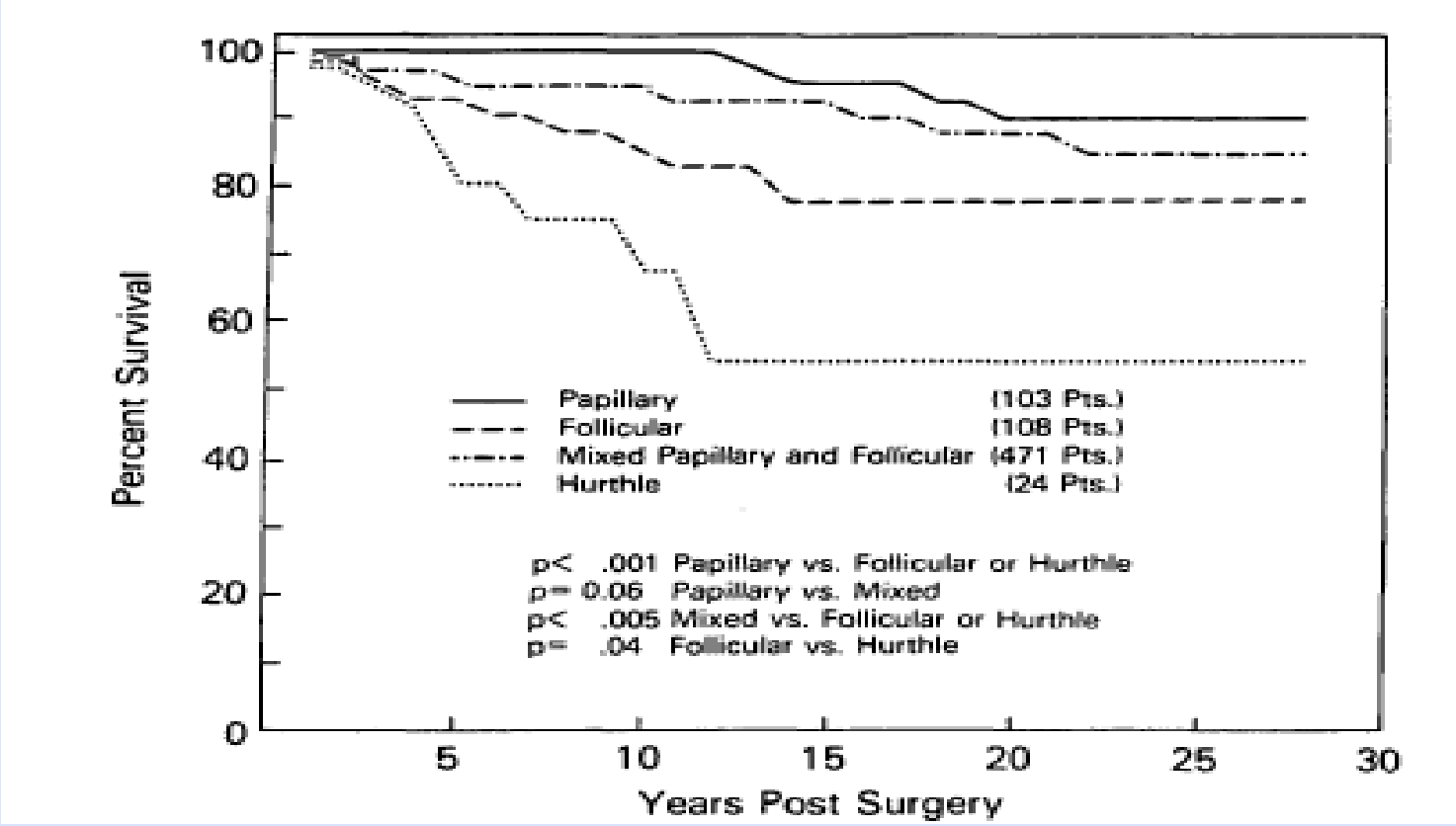
Table II. Characteristics of patients, stratified into HCFC or non-HCFC histologic condition

Characteristic	*HCFC (n)**	*Non-HCFC (n)†*	P *value*
Age (y)			<.001
<50	67 (39%)	369 (55%)	
≥50	105 (61%)	304 (45%)	
Gender			.005
Female	105 (61%)	486 (72%)	
Male	67 (39%)	187 (28%)	

Modified from Haigh et al, *Surgery*, 2005

Clinical Course of OTC

OTC was historically considered to be an aggressive differentiated thyroid CA.



Samaan et al, *J Clin Endocrinol Metab*, 1983

Clinical Course of OTC vs FTC

- OTC may not be more aggressive than FTC when adjusting for other variables.

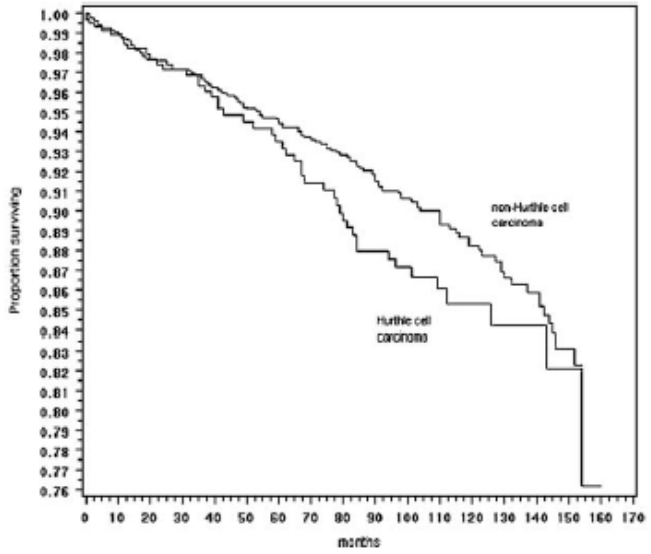
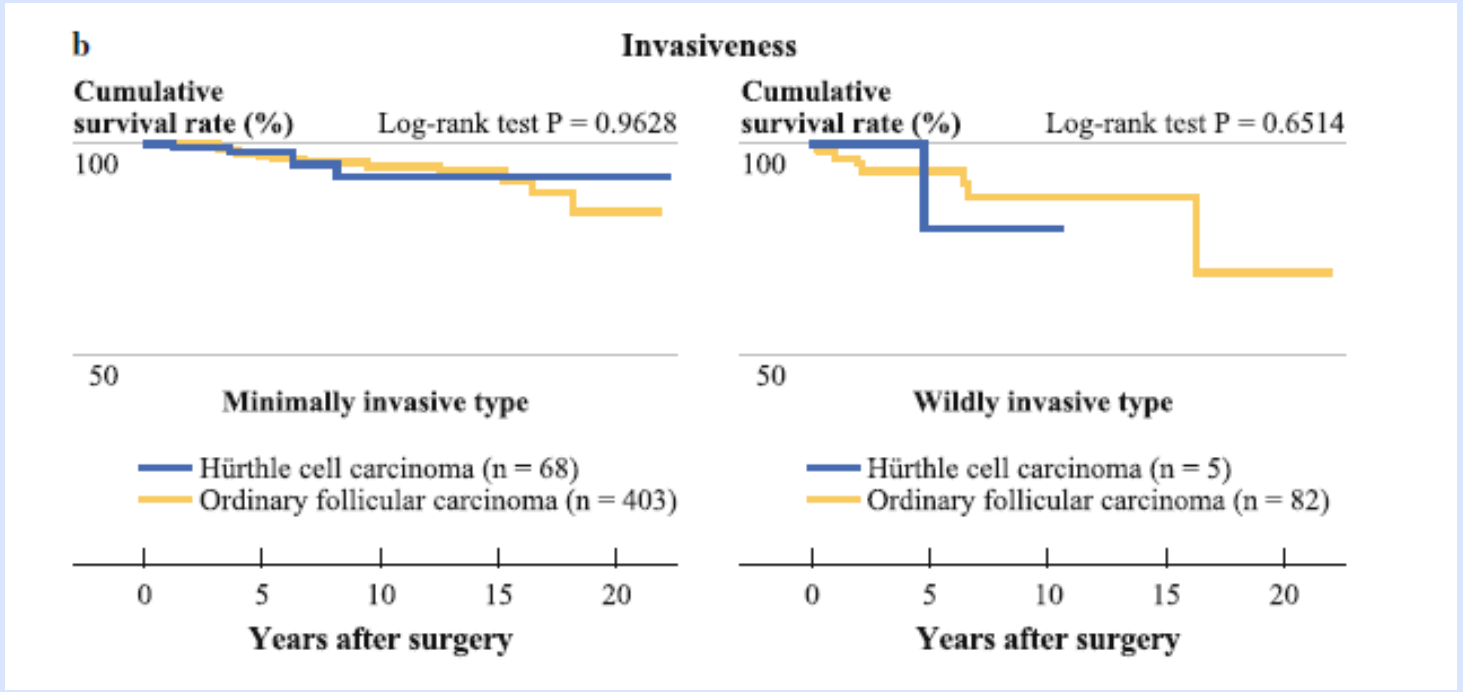


Figure. Adjusted survival of patients with HCFC compared with non-HCFC. There was no difference in survival between the 2 histologic conditions ($P = .34$).

Haigh et al, *Surgery*, 2005.
Utilized SEER data from 1988 to 1993 followed until 2001

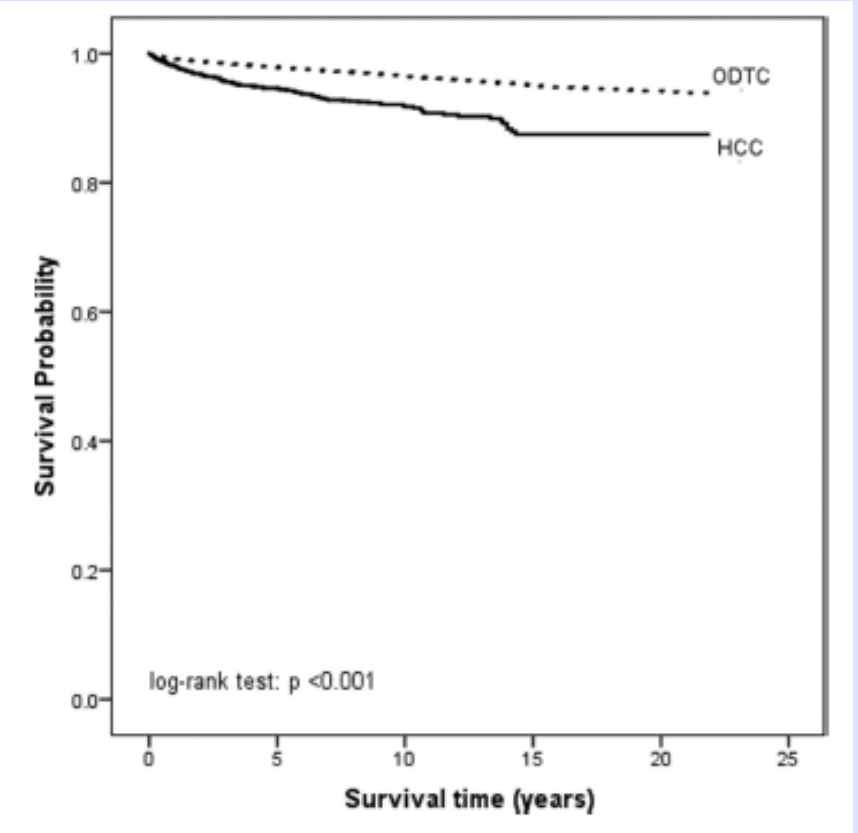


Sugino, *Ann Surg Oncol*, 2013
Evaluated 73 HCC and 558 FTC treated at a single institution from 1989 to 2010.

OTC Compared with Other Differentiated Thyroid Carcinomas

Has a higher rate of distant metastases (lung, bone).

OTC has a decreased disease-specific survival even when controlling for stage ($p<0.001$).



Goffredo et al, *Cancer*, 2013

Radioactive Iodine (RAI)

- In contrast to follicular thyroid carcinoma, most OTC lack RAI uptake (<10% of bone and lung metastases of OTC show radioactive iodine uptake, Lopez-Penabad, *Cancer*, 2003).

- High rate of false negative RAI scans with OTC (78% false negative, Chindris, *J Clin Endocrinol Metab*, 2015).

- OTC accounts for a significant percentage of patients with RAI refractory (RAIR) disease.

TABLE 1
Clinicopathologic Characteristics of 70 Cases of Metastatic Radioactive Iodine-Refractory, PET-Positive Thyroid Carcinoma

	PD	PTC	TCV	HCC	ANA
No. of cases	33 (47.1%)	16 (22.9%)	14 (20.0%)	6 (8.6%)	1 (1.4%)
Median age at diagnosis, y	62	46.5	53	42.5	53
Gender ratio, M:F	15:18	8:8	6:8	6:0	1:0
No. DOD	24 (73%)	3 (19%)	3 (21%)	2 (33%)	1 (100%)
No. AWD	9 (27%)	8 (50%)	7 (50%)	4 (67%)	0
No. AND	0	5 (31%)	4 (29%)	0	0

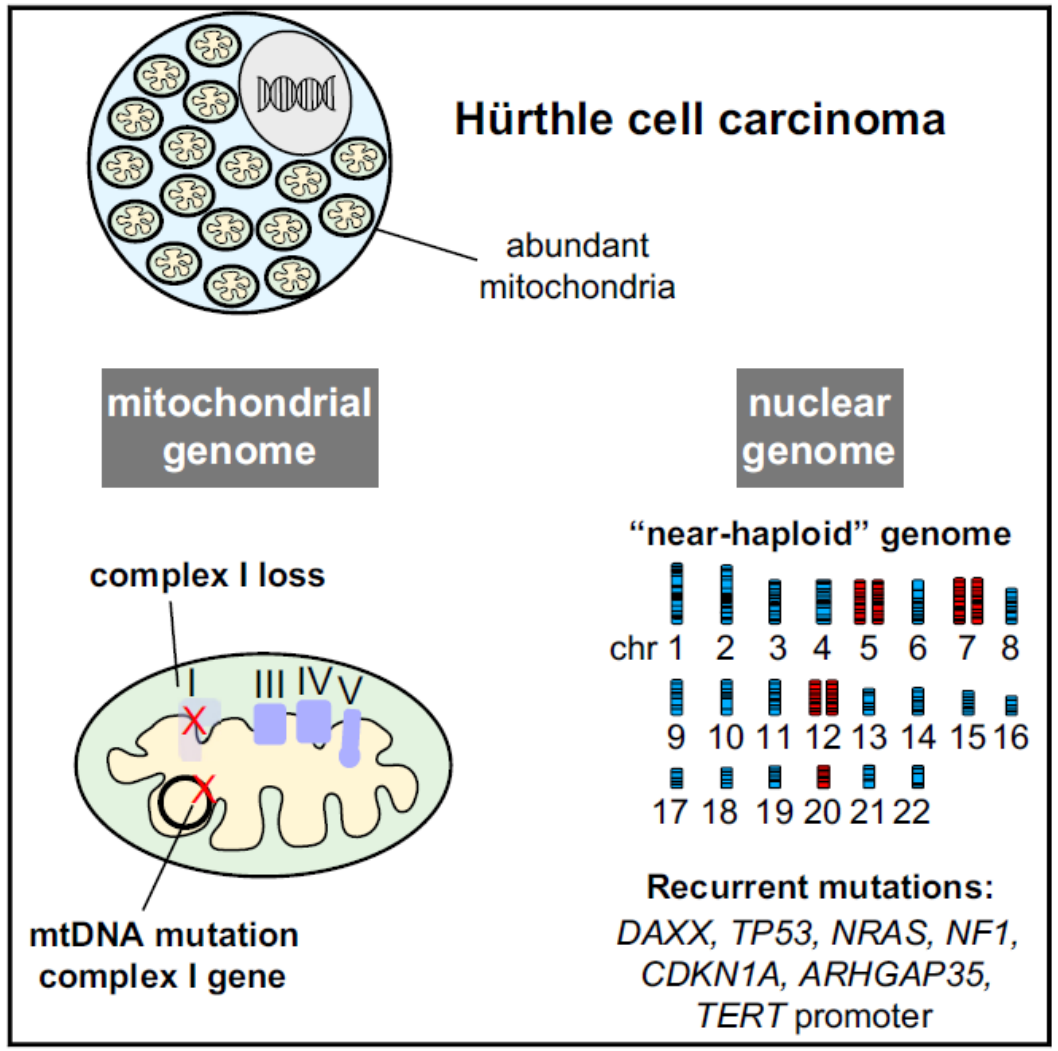
Rivera et al. Cancer, 2008

Molecular Alterations

Molecular profile of OTC and FTC are distinct.

Genetic alterations in Hurthle cell tumors comared to other thyroid cancers					
Gene	**Prevalence stratified by thyroid histology**				
	PTC	**FTC**	**PDTC**	**ATC**	**HCC**
RET point mutation RET rearrangements	0% Sporadic 20% Radiation induced 50-80%				0%
BRAF mutations	30-70%	0%	0-15%	10-35%	0%
RAS mutations	10%	45%	20-35%	50-60%	16%
PIK3CA point mutation or amplification		10-30%		25-45%	0%
PPARG rearrangement		25-60%			0%

Ganly et al, *J Clin Endocr Metab*, 2013.



Gopal et al., 2018, Cancer Cell *34*, 242–255

- Early widespread loss of chromosomes leading to a stable near-haploid state.*
- mtDNA mutations in complex I of the electron transport chain.
- *TERT, TP53, NRAS, DAXX, NF1*, and *CDKN1A*, are recurrently altered in OTC.

* Often chromosome 7 is maintained, subset also show uniparental disomy.

Highlights

- Hyperplastic appearing nodules may be clonal.

- The diagnosis of NIFTP must be rendered carefully in order to preserve the fact that it is a tumor with virtually no metastatic or recurrence potential.

- Invasive encapsulated FVPTC has a biology similar to FTC.

Highlights

- Extent of invasion determines the prognosis and treatment for follicular thyroid carcinoma, encapsulated FVPTC, and oncocytic thyroid carcinoma.

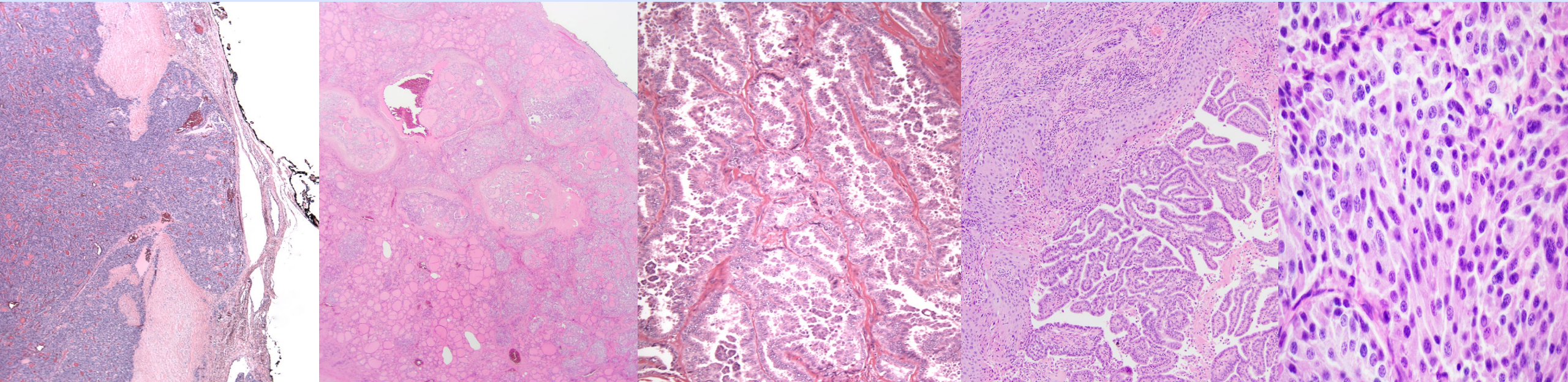
- For patients (especially young ones) with a follicular-patterned tumor in the background of follicular nodular disease, consider DICER1 syndrome and Cowden syndrome.

- Oncocytic tumors are clinically distinct from follicular adenoma and FTC. They occasionally have papillary architecture and may have some nuclear contour irregularities.

A Cased-Based Tour of Thyroid Pathology: From the Basics to the Latest

Justine A. Barletta, M.D.

Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA



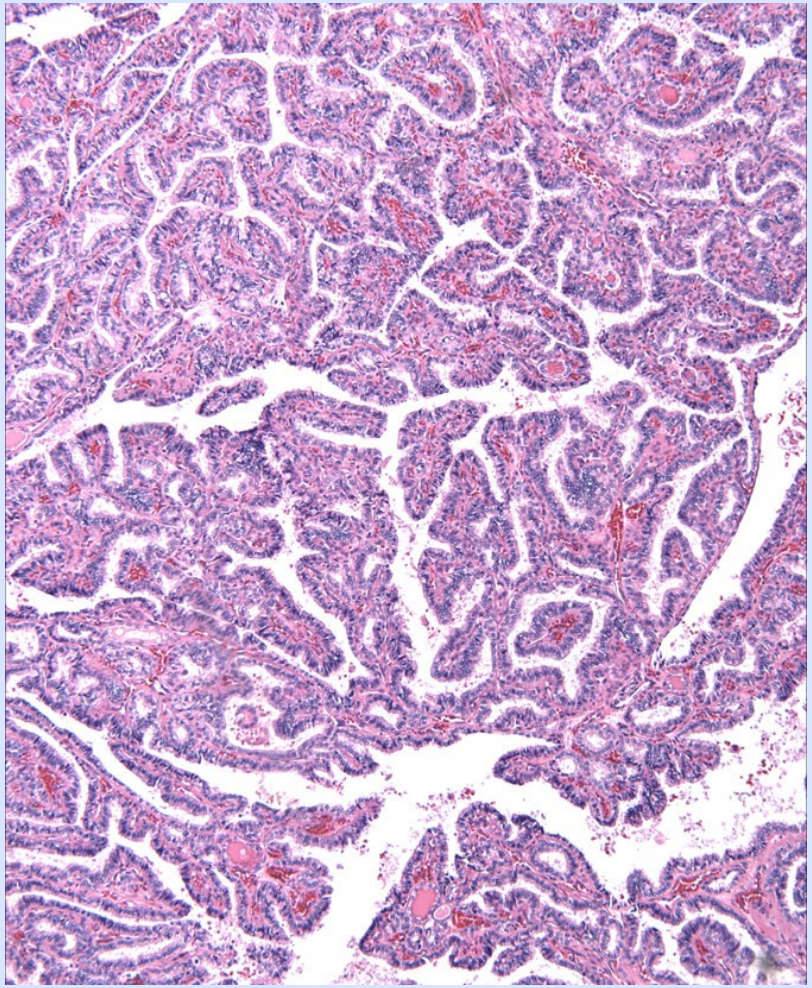
Case

The patient is a 37-year-old woman who was found to have a thyroid nodule on physical examination. Ultrasound revealed a 1.8 cm mass.

An FNA was performed and was read as positive for papillary thyroid carcinoma (PTC).

A hemithyroidectomy was performed and showed classic PTC.

The patient asks whether her tumor has a *BRAF* V600E mutation.



BRAF V600E

The *BRAF* V600E mutation is present in 70% of PTC.

Based on the results of large PTC studies, the American Thyroid Association (ATA) concluded that *BRAF* V600E mutation status considered in the context of other clinicopathologic parameters incrementally improves risk stratification.

However, because the clinical implications of this incremental difference are not clear, the ATA does not recommend routine assessment of *BRAF* V600E mutation status for initial post-operative risk stratification of PTC.

At BWH, we don't routinely determine *BRAF* V600E mutation status.

When might I perform BRAF V600E IHC?

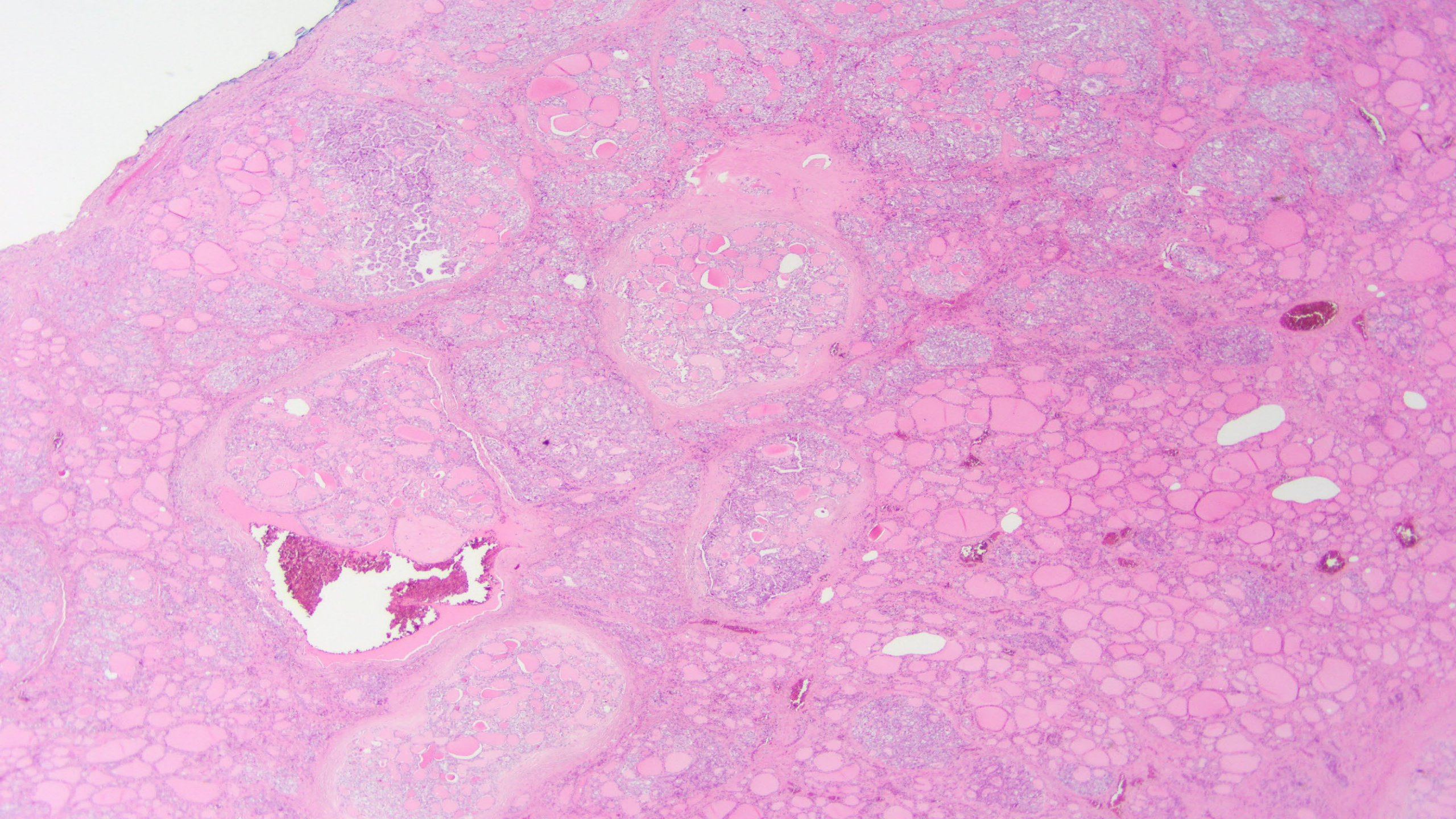
Case

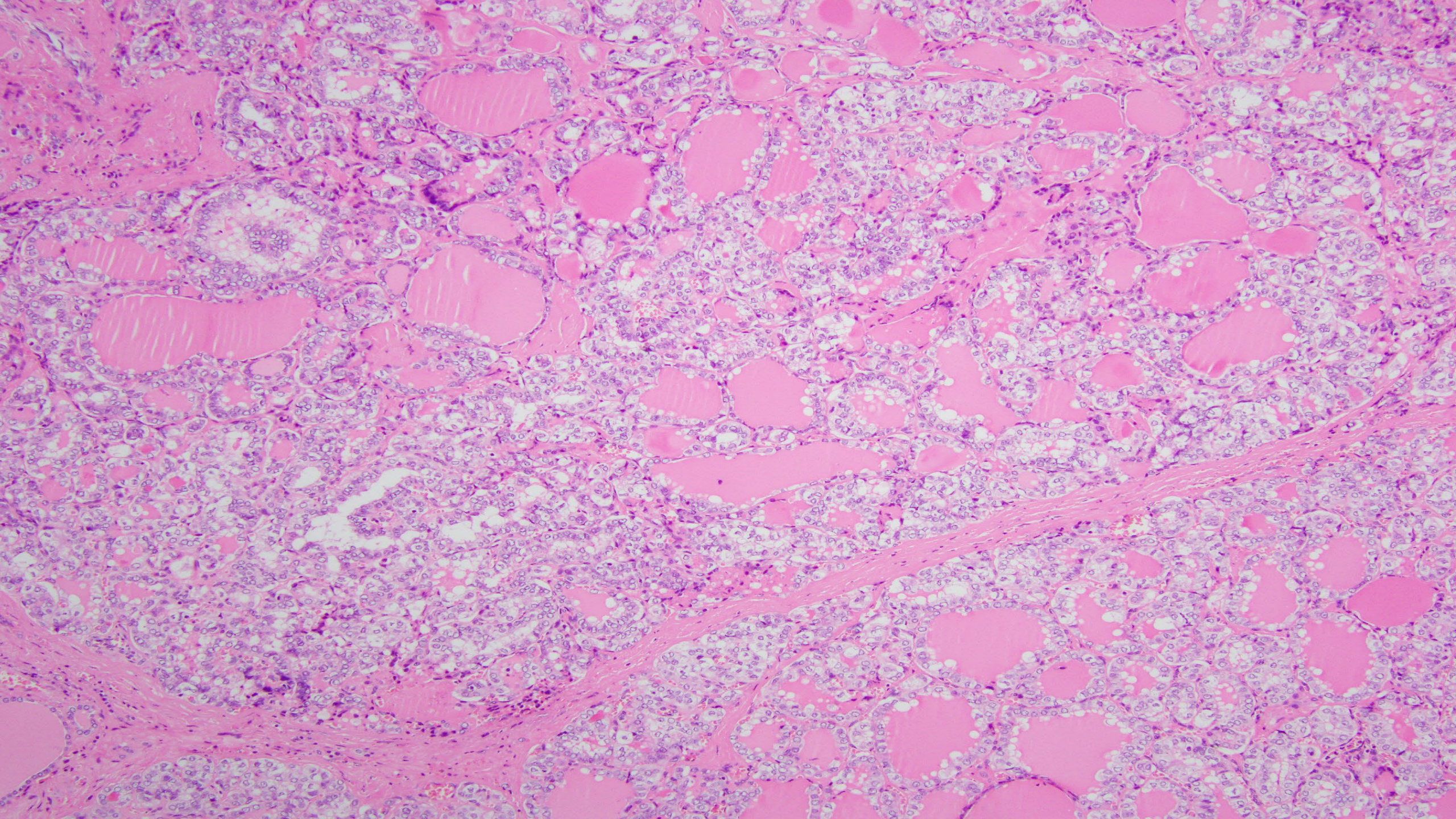
The patient is a 51-year-old man with a thyroid mass.

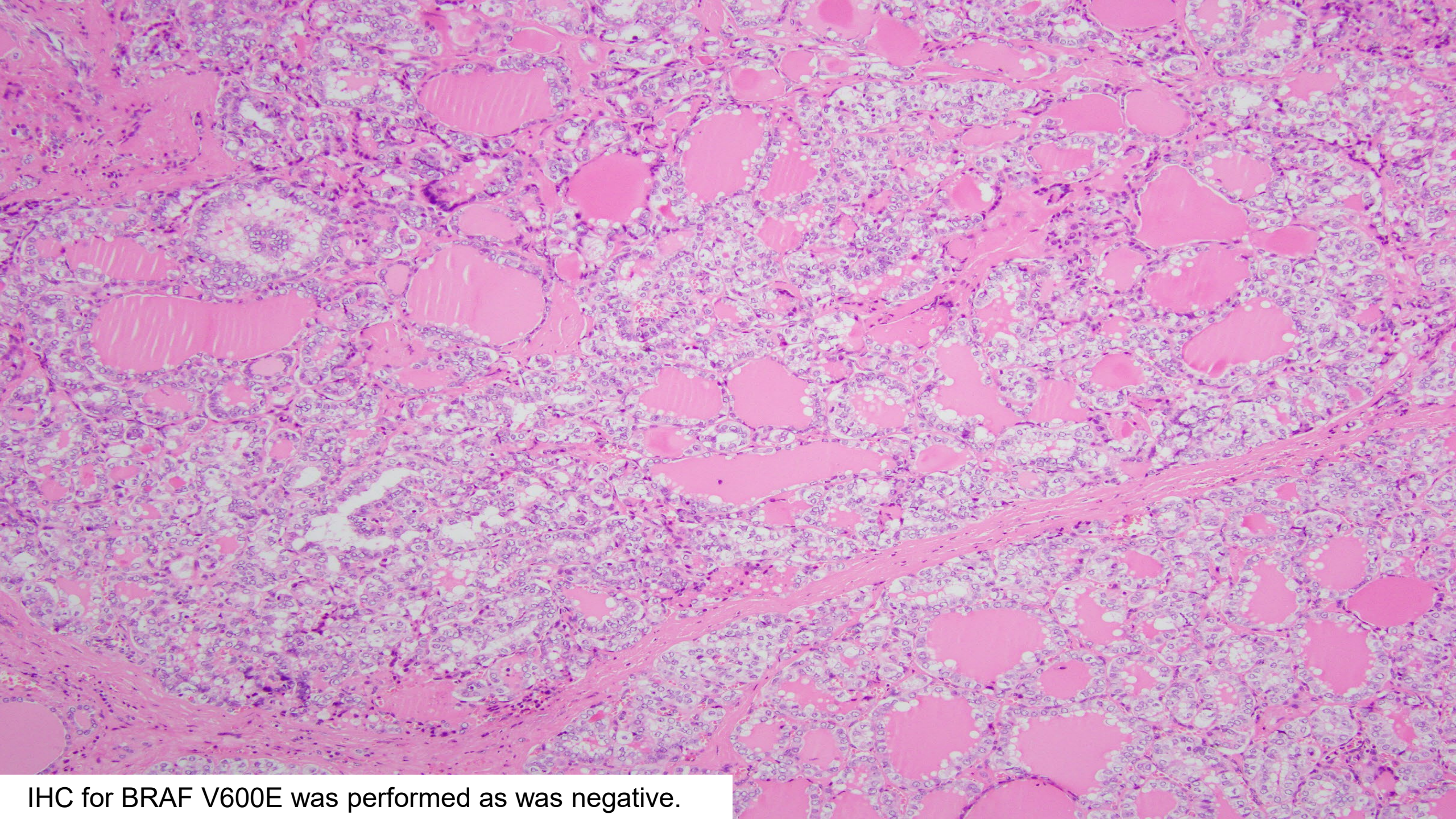
Resection demonstrated a 4.2 cm classic PTC with multiple associated foci of intrathyroidal spread of tumor and gross extrathyroidal extension with involvement recurrent laryngeal nerve.

The patient was treated with radioactive iodine post-operatively, but subsequently developed both locoregional recurrences and distant metastatic disease which became refractory to radioactive iodine.

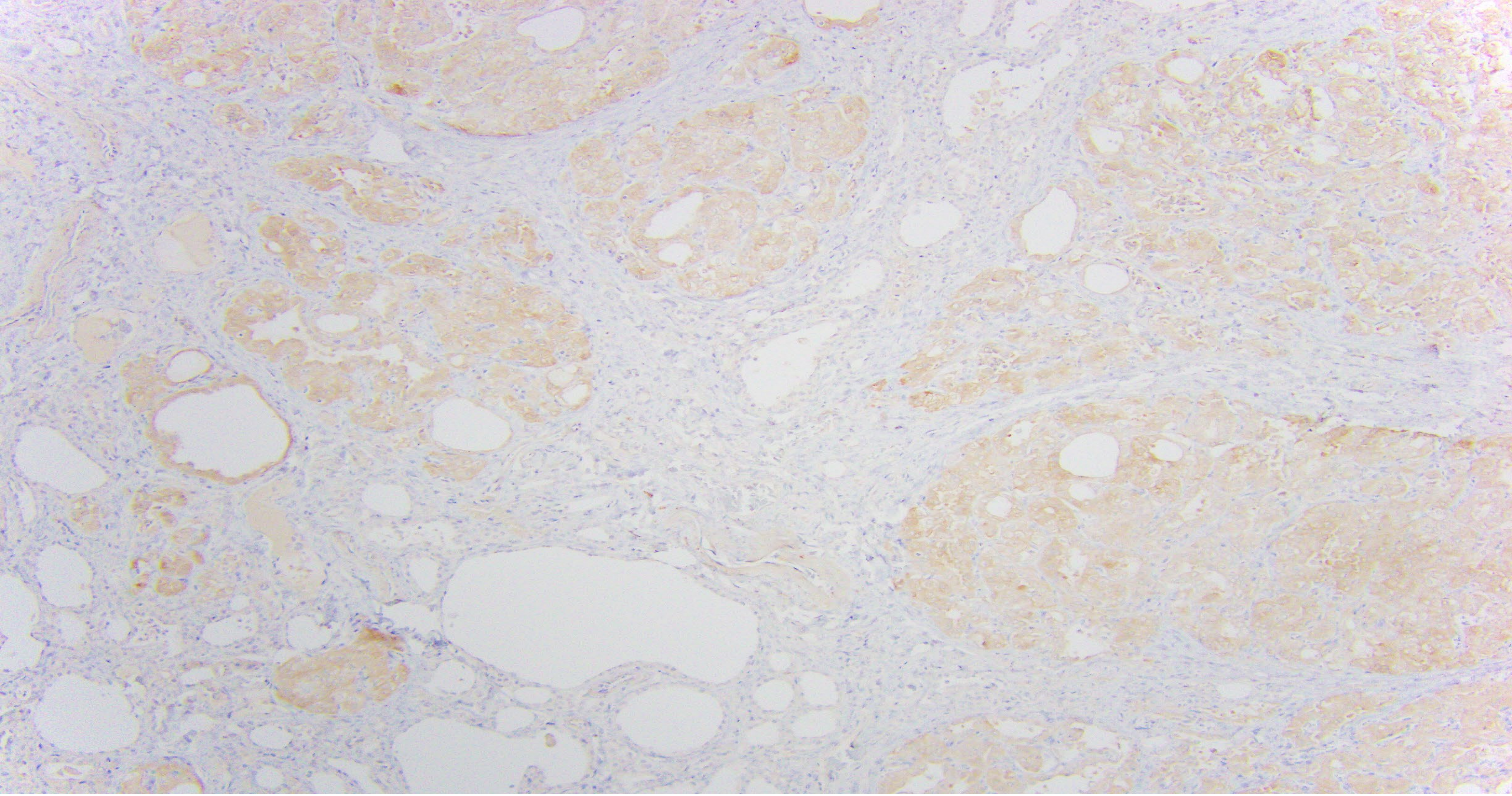
Due to disease progression, other systemic therapy options were being considered.







IHC for BRAF V600E was performed as was negative.



PAN-TRK Molecular analysis → *TPR-NTRK1* rearrangement

NTRK-Rearranged Thyroid Carcinomas

Modern Pathology (2020) 33:2186–2197
https://doi.org/10.1038/s41379-020-0574-4

USCAP

ARTICLE

Check for updates

Clinicopathologic and molecular characterization of *NTRK*-rearranged thyroid carcinoma (NRTC)

Ying-Hsia Chu[1] · Dora Dias-Santagata[1] · Alexander A. Farahani[1] · Baris Boyraz[1] · William C. Faquin[1] · Vânia Nosé[1] · Peter M. Sadow[1]

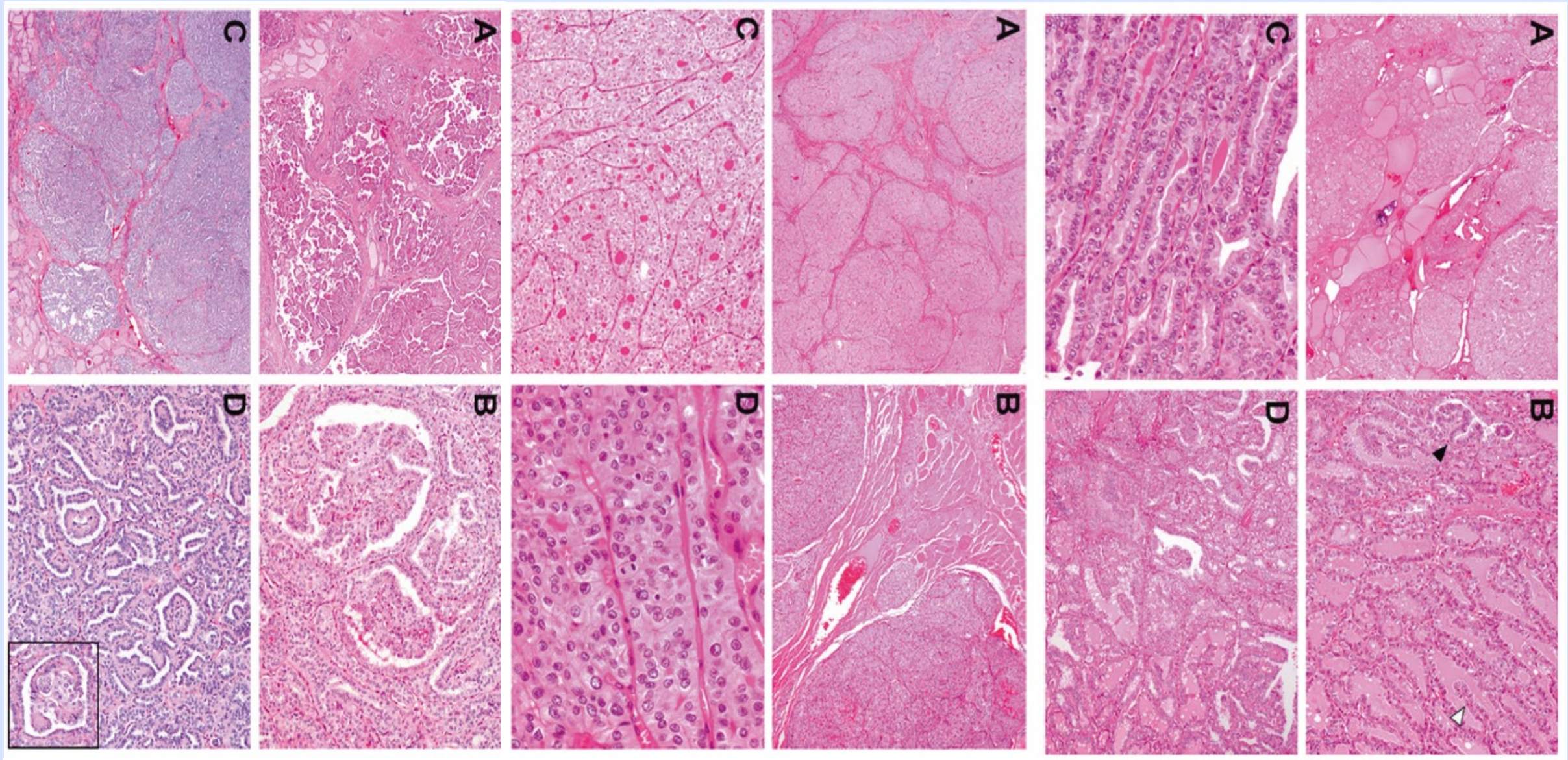
11 *NTRK*-rearranged thyroid carcinomas: 10 PTC and one secretory carcinoma (SC), in 10 adults and one adolescent.

NTRK-rearranged thyroid carcinomas were characterized by multinodular growth pattern, extensive lymphovascular invasion, and cervical lymph node metastases.

Observed gene rearrangements included *ETV6-NTRK3* (n = 4, including the SC), *TPR-NTRK1* (n = 2), *RBPMS-NTRK3* (n = 2), *SQSTM1-NTRK1* (n = 1), *SQSTM1-NTRK3* (n = 1), and *EML4-NTRK3* (n = 1).

Despite frequent development of recurrent disease and distant metastases, no tumor-related death occurred over a median follow-up of 44 months (range 11 to 471).

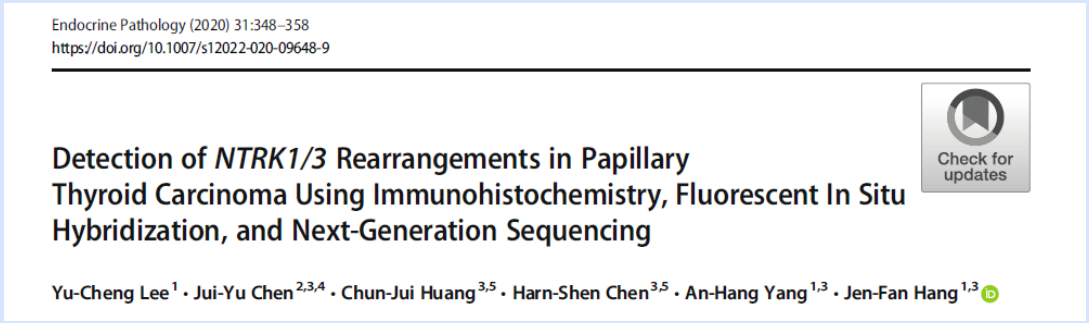
Three patients received NTRK inhibitor therapy, with one patient showing complete resolution of disease and two other patients experiencing significant decrease of disease burden, highlighting the importance of identifying these cases so that NTRK inhibitor therapy can be utilized.



Clinicopathologic and molecular characterization of *NTRK*-rearranged thyroid carcinoma (NRTC)

Edited from Chu et al, *Mod Pathol*, 2020.

PAN-TRK Immunohistochemistry

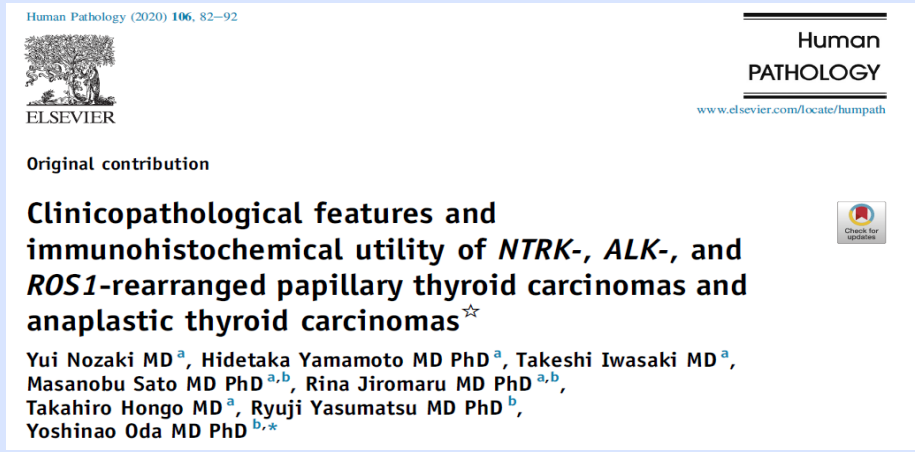


Endocrine Pathology (2020) 31:348–358
https://doi.org/10.1007/s12022-020-09648-9

Detection of *NTRK1/3* Rearrangements in Papillary Thyroid Carcinoma Using Immunohistochemistry, Fluorescent In Situ Hybridization, and Next-Generation Sequencing

Yu-Cheng Lee[1] · Jui-Yu Chen[2,3,4] · Chun-Jui Huang[3,5] · Harn-Shen Chen[3,5] · An-Hang Yang[1,3] · Jen-Fan Hang[1,3]

PAN-TRK IHC showed a sensitivity of 58% and specificity of 100% for *NTRK1/3* rearrangements in BRAF V600E-negative PTC.



Human Pathology (2020) 106, 82–92

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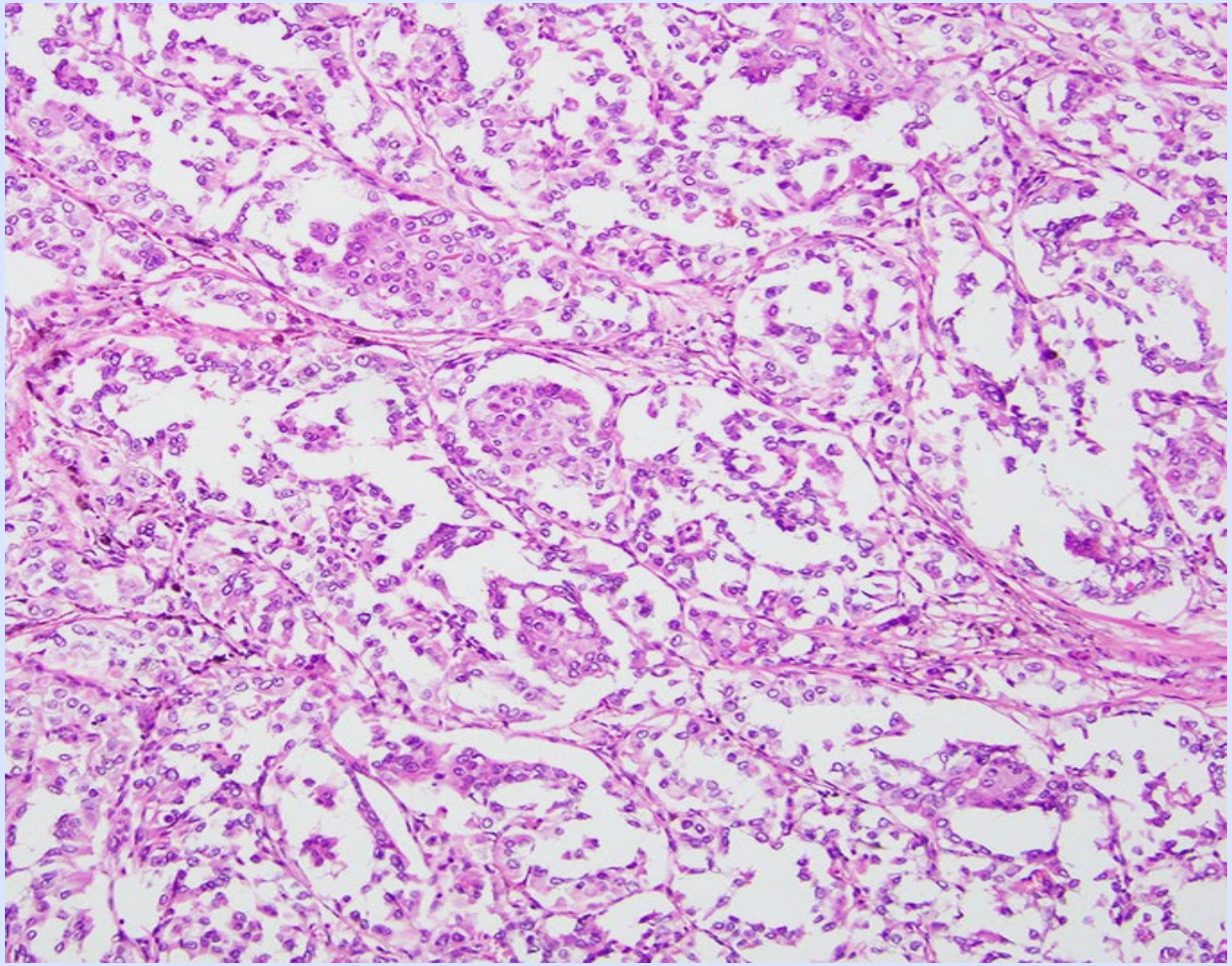
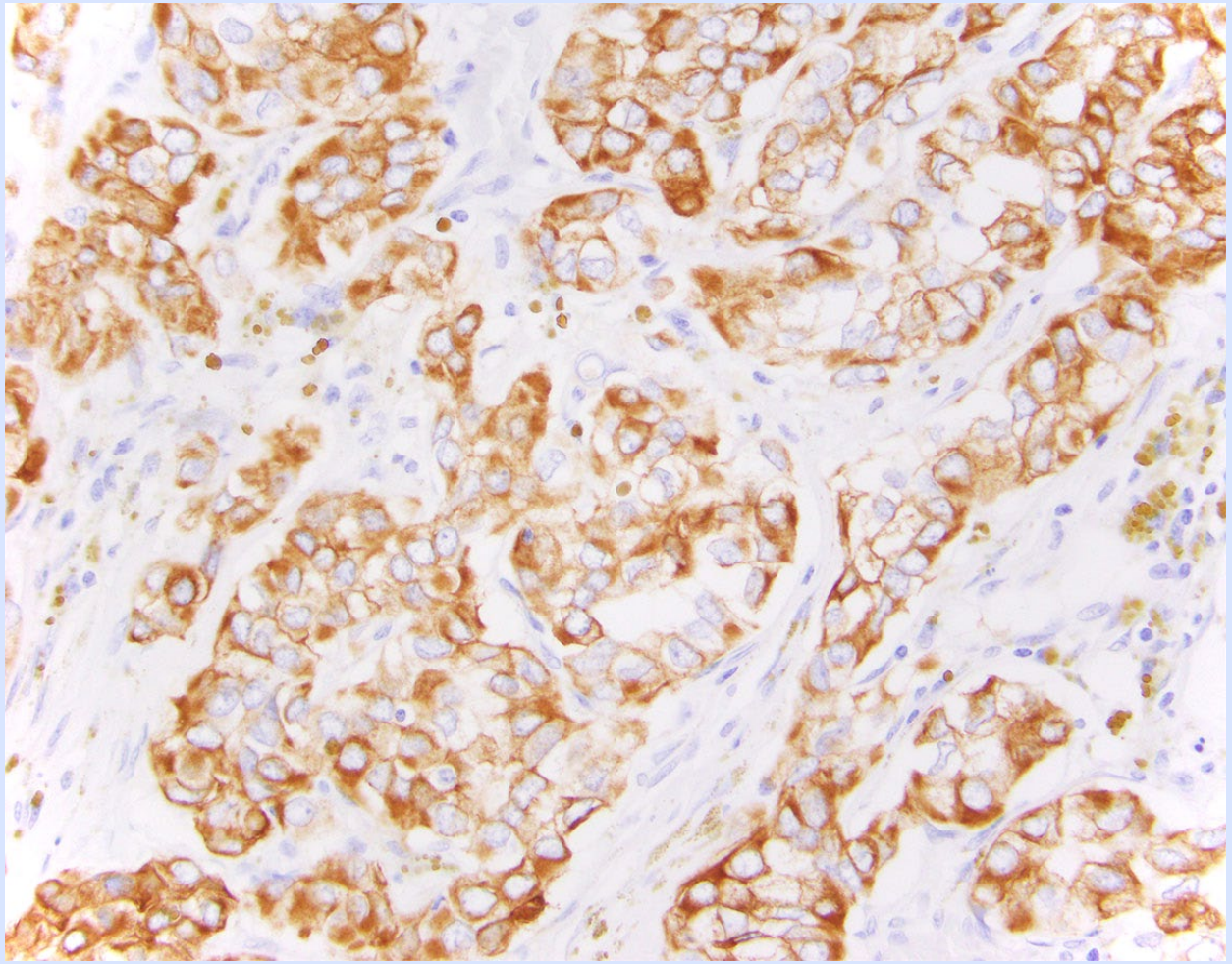
Original contribution

Clinicopathological features and immunohistochemical utility of *NTRK*-, *ALK*-, and *ROS1*-rearranged papillary thyroid carcinomas and anaplastic thyroid carcinomas☆

Yui Nozaki MD[a], Hidetaka Yamamoto MD PhD[a], Takeshi Iwasaki MD[a], Masanobu Sato MD PhD[a,b], Rina Jiromaru MD PhD[a,b], Takahiro Hongo MD[a], Ryuji Yasumatsu MD PhD[b], Yoshinao Oda MD PhD[b,*]

PAN-TRK IHC showed a positive predictive value of only 11% (for the detection of an underlying *NTRK* fusion)…. FISH or molecular analysis likely the best way to interrogate *NTRK* fusions.





IHC for PAN-TRK was focally strong but molecular detected a *RET/PTC3* fusion, indicating a lack of specificity of PAN-TRK IHC.

Fusion-Related Thyroid Carcinomas

Thyroid carcinomas can harbor other fusions besides *NTRK* fusions (*RET, ALK, MET, BRAF*).

Fusion-associated thyroid carcinomas show multinodular growth with prominent intratumoral fibrosis and high rates of lymphovascular invasion, extrathyroidal extension, cervical lymph node metastases, and an associated aggressive clinical course.

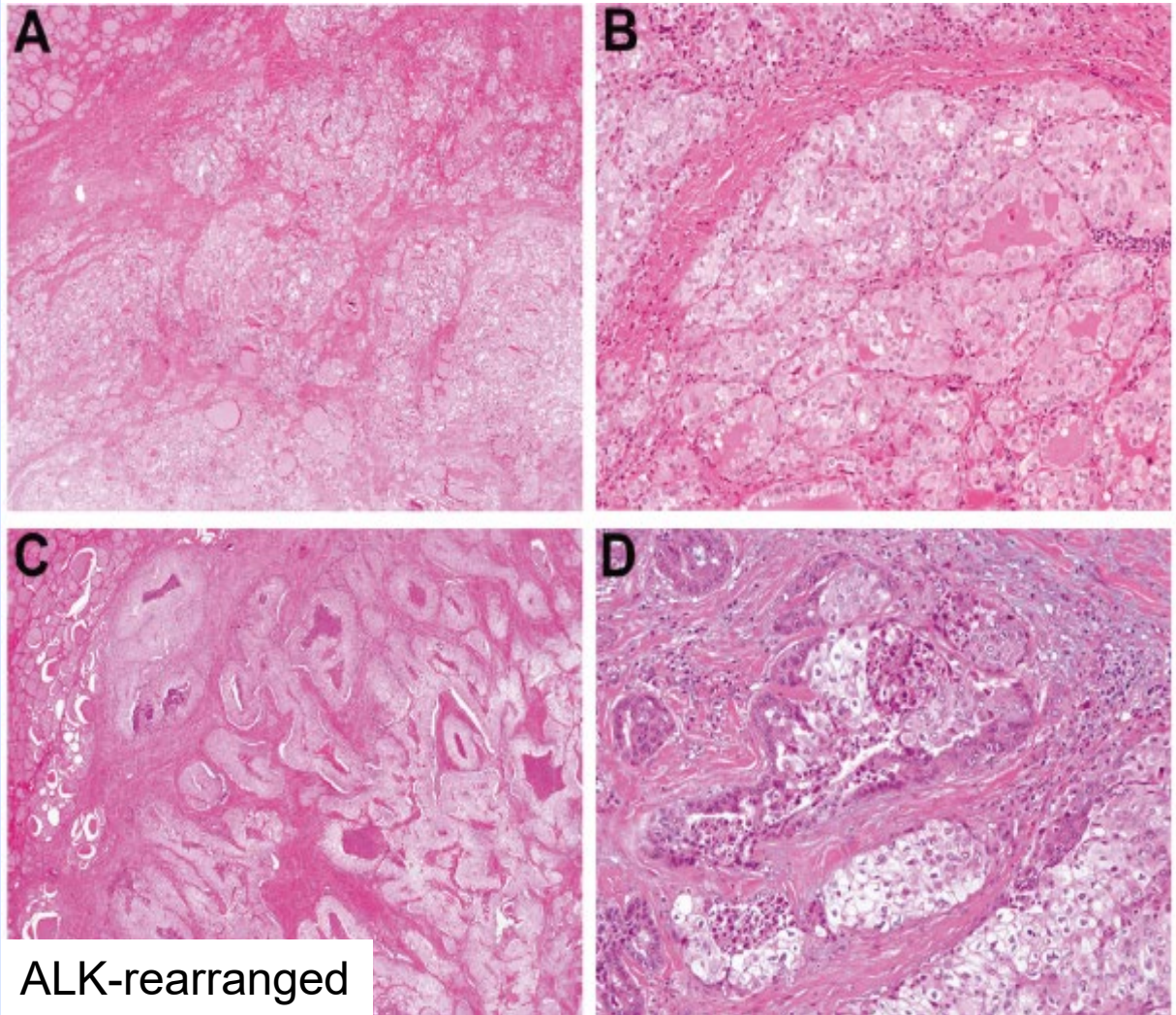
Modern Pathology (2020) 33:2458–2472
https://doi.org/10.1038/s41379-020-0638-5

USCAP

ARTICLE

Clinicopathologic features of kinase fusion-related thyroid carcinomas: an integrative analysis with molecular characterization

Ying-Hsia Chu[1] · Lori J. Wirth[2] · Alexander A. Farahani[1] · Vânia Nosé[1] · William C. Faquin[1] · Dora Dias-Santagata[1] · Peter M. Sadow[1]



ALK-rearranged

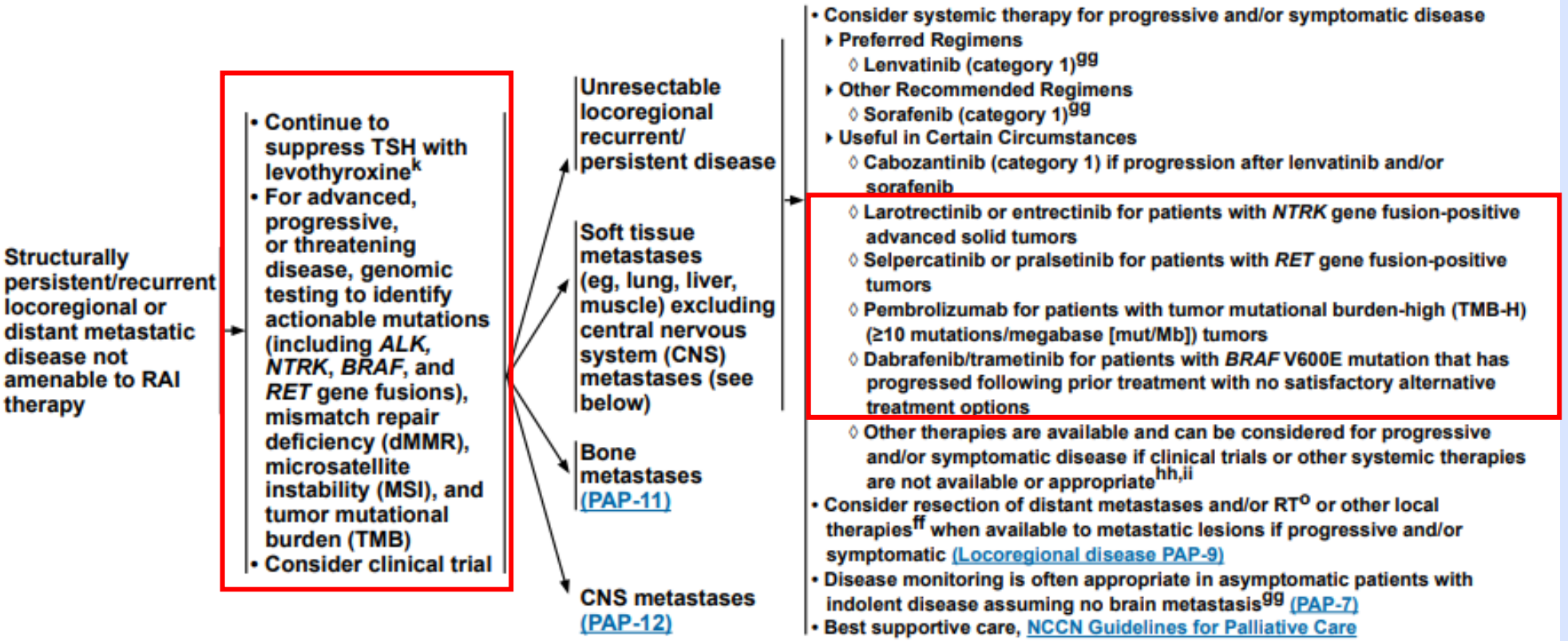
Not all PTCs need to have molecular analysis; however, it becomes important for patients with advanced disease who require systemic therapy.

If you have BRAF V600E IHC start with that. If BRAF V600E is negative, molecular analysis is warranted since selective agents may be used depending on the alteration found:

- larotrectinib (anti-TRK)
- entrectinib (anti-ALK, ROS1, and TRK),
- selpercatinib and pralsetinib (both anti-RET),

These therapies have demonstrated significant efficacy with more favorable side effect profiles compared with lenvatinib.

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY



[k] Principles of TSH Suppression (THYR-A).
[o] Principles of Radiation and RAI Therapy (THYR-C).
[ff] Ethanol ablation, cryoablation, RFA, etc.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy (THYR-B).
[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.
[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Case

The patient is a 57-year-old man who found a thyroid nodule on self examination.

Ultrasound revealed a 4.5 cm nodule.

An FNA was performed and was read as suspicious for a follicular neoplasm.

Thyroseq was performed and showed and *NRAS* mutation and a *TERT* promoter mutation.

TERT Promoter Mutations

The frequency of *TERT* promoter mutations increases with the aggressiveness of thyroid tumors.

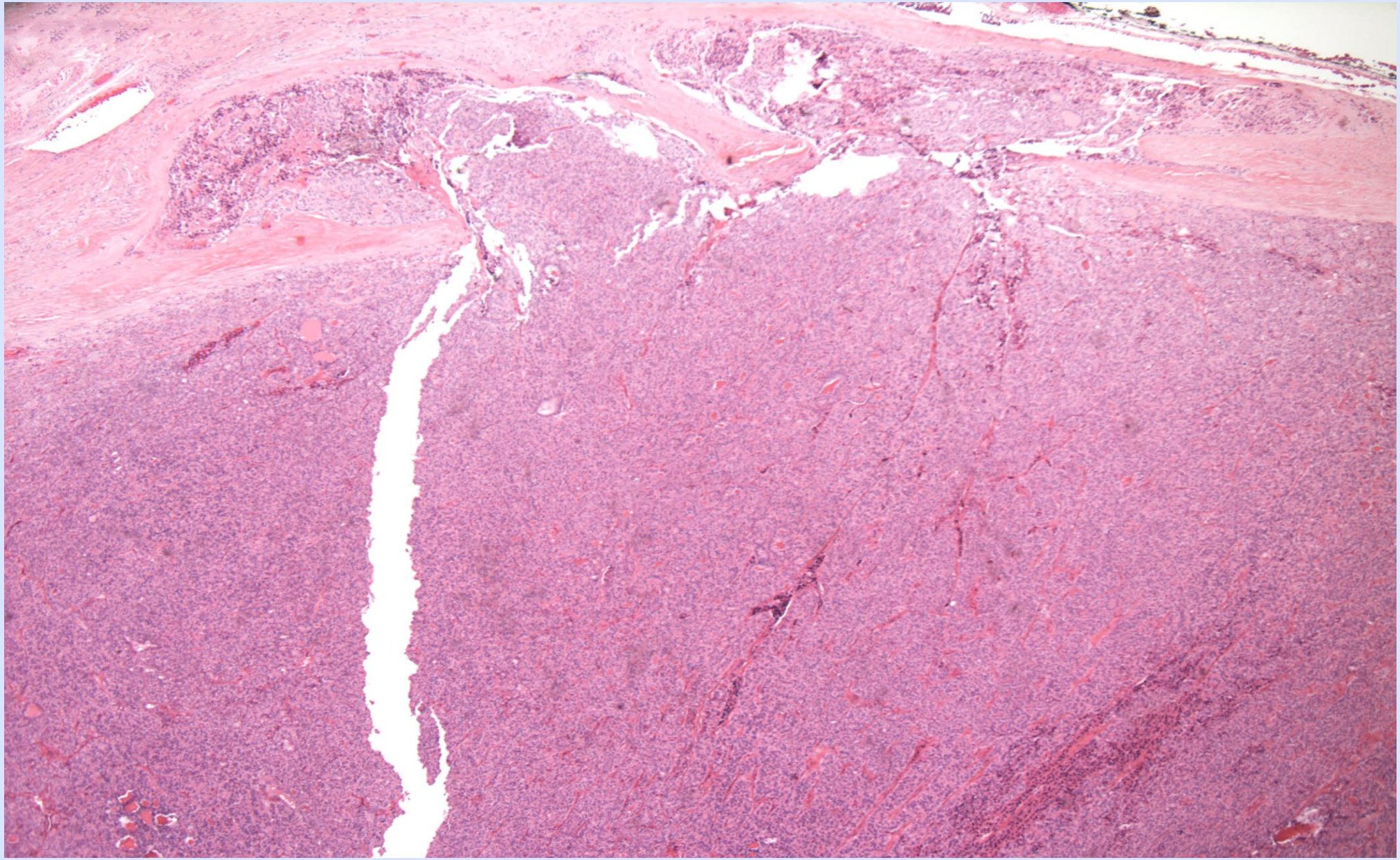
A *TERT* promoter mutation along with a *RAS* mutation, suggests the tumor is most likely a follicular thyroid carcinoma, invasive encapsulated FVPTC, poorly differentiated thyroid carcinoma, or an anaplastic thyroid carcinoma.

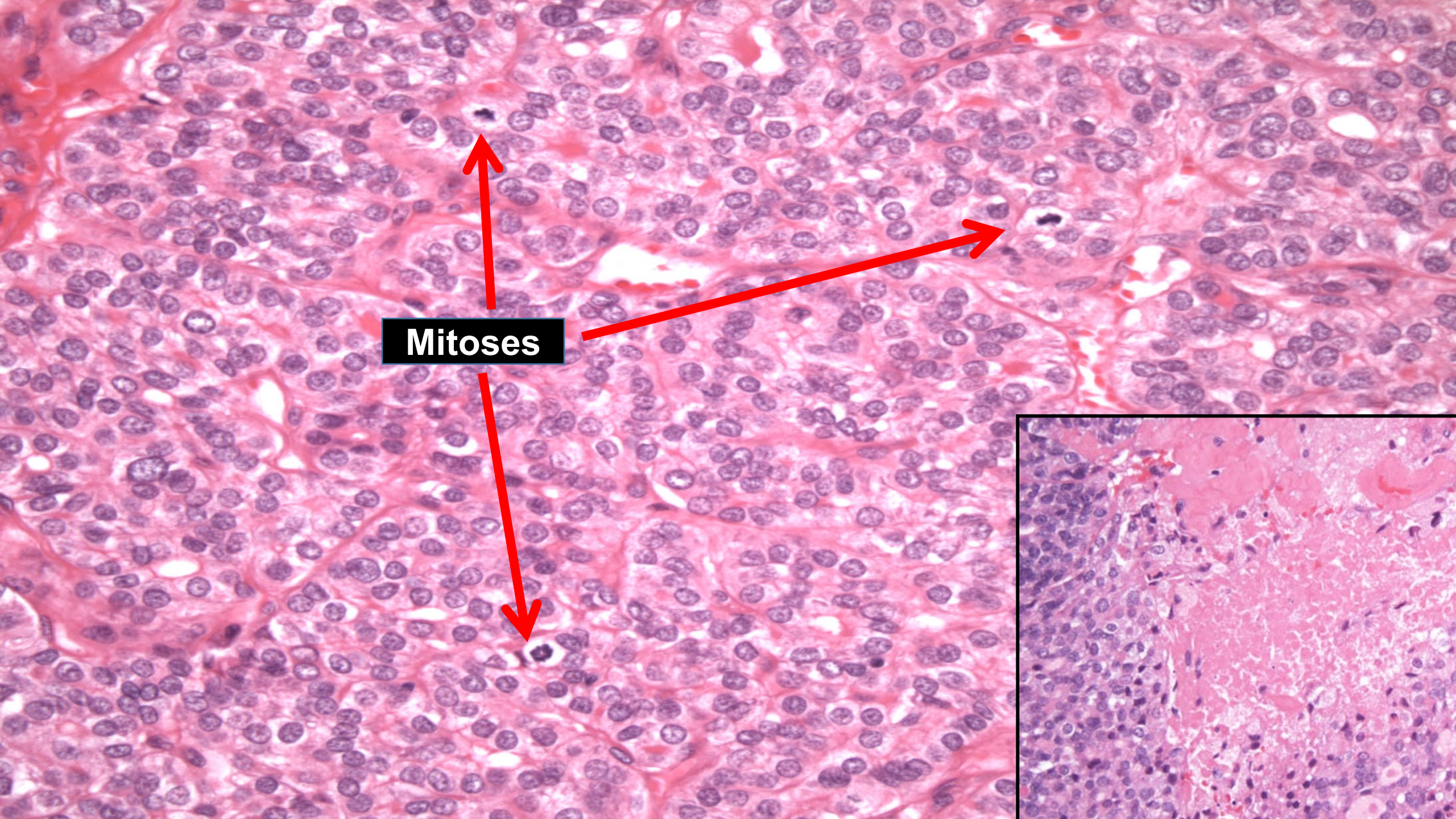
Table 2 *TERT* promoter mutations in thyroid tumors

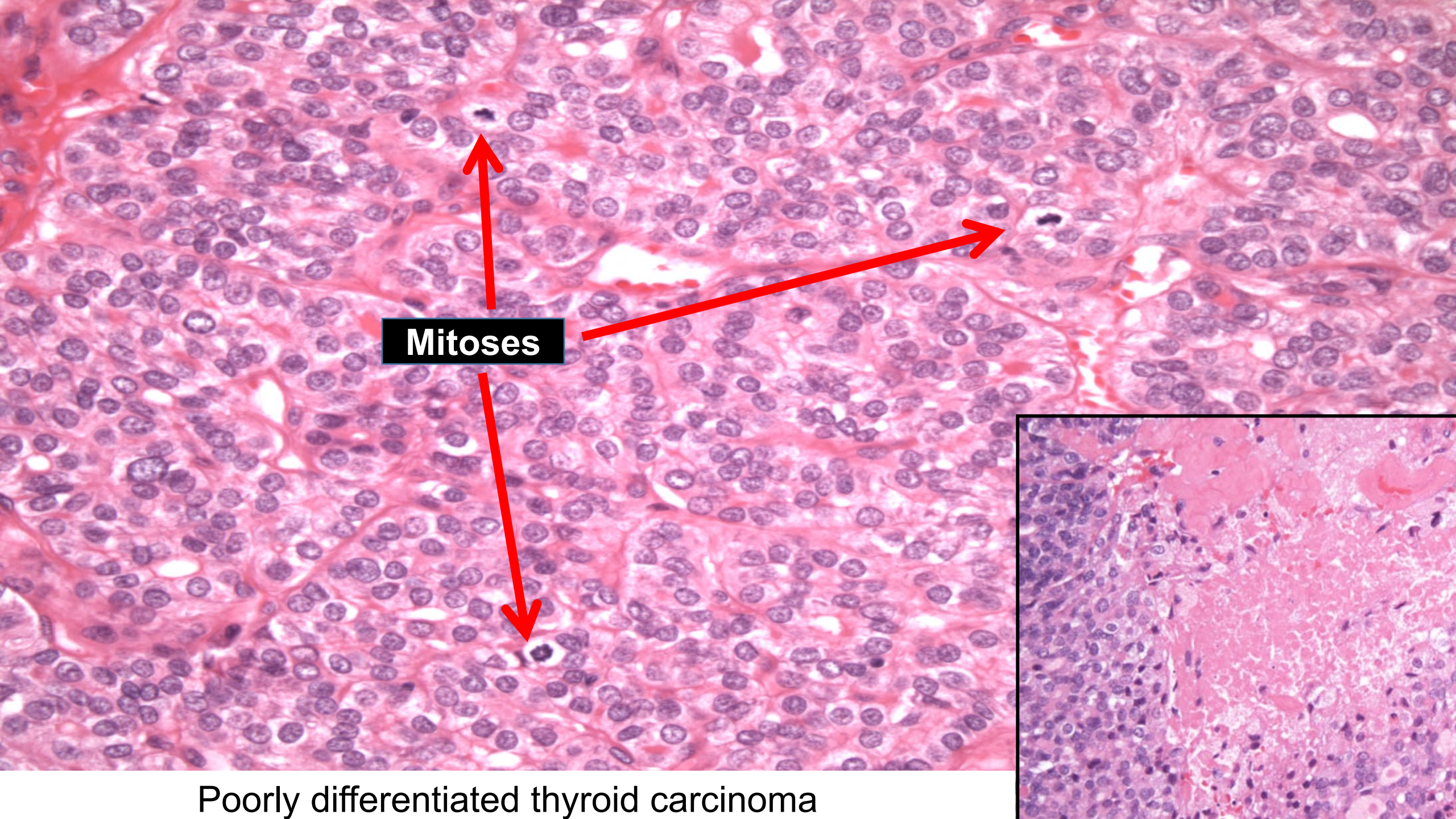
Samples	Mutation C228T (*n*/*N* (%))	Mutation C250T (*n*/*N* (%))	Collective mutations (*n*/*N* (%))
Thyroid cancer cell lines			
PTC	3/3 (100.0)	0/3 (0.0)	3/3 (100.0)
FTC	1/2 (50.0)	0/2 (0.0)	1/2 (50.0)
ATC	4/7 (57.1)	3/7 (42.9)	7/7 (100.0)
All	8/12 (66.7)	3/12 (25.0)	11/12 (91.7)
Thyroid tumors			
Benign tumor	0/85 (0.0)	0/85 (0.0)	0/85 (0.0)
PTC			
CPTC	23/187 (12.3)	0/187 (0.0)	23/187 (12.3)
FVPTC	2/56 (3.6)	0/56 (0.0)	2/56 (3.6)
TCPTC	4/13 (30.8)	0/13 (0.0)	4/13 (30.8)
Columnar	1/1 (100.0)	0/1 (0.0)	1/1 (100.0)
All	30/257 (11.7)	0/257 (0.0)	30/257 (11.7)
FTC	9/79 (11.4)	2/79 (2.5)	11/79 (13.9)
DTC	39/336 (11.6)	2/336 (0.6)	41/336 (12.2)
PDTC	3/8 (37.5)	0/8 (0.0)	3/8 (37.5)
ATC	23/54 (42.6)	2/54 (3.7)	25/54 (46.3)
MTC	0/16 (0.0)	0/16 (0.0)	0/16 (0.0)

PTC, papillary thyroid cancer; CPTC, conventional PTC; FVPTC, follicular variant PTC; TCPTC, tall-cell PTC; FTC, follicular thyroid cancer; DTC, differentiated thyroid cancer (combination of PTC and FTC); PDTC, poorly DTC; ATC, anaplastic thyroid cancer; MTC, medullary thyroid cancer.

Liu, *Endocr Relat Cancer*, 2013




Mitoses



Poorly differentiated thyroid carcinoma

Poorly Differentiated Thyroid Carcinoma (PDTC)

PDTC was added to WHO in 2004 but had a general description (lacked specific criteria). The 2017 WHO endorsed the Turin consensus criteria for PDTC:

1. Has conventional criteria of malignancy (capsular penetration or vascular invasion)
2. Has solid, insular, or trabecular growth
3. Lacks nuclear features of PTC
4. Presence of one of the three:
   - Convoluted nuclei
   - Mitotic count $\geq$3 per 10 HPFs
   - Necrosis

No change in criteria for PDTC in the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours.

Poorly Differentiated Thyroid Carcinoma (PDTC)

PDTC accounts for roughly ~3% of thyroid malignancies.

The 5- and 10-year survival of patients with PDTC as defined by the Turin criteria is approximately 70 and 50%, respectively.

Distant metastases are common, with lung and bone being the most frequent sites.

No change in criteria for PDTC in the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours.

Pitfalls

1. Don’t notice solid growth and increased mitotic activity – diagnosis of FTC rendered. All thyroid tumors should be assessed for solid/trabecular/insular growth, increased mitotic activity, and necrosis.

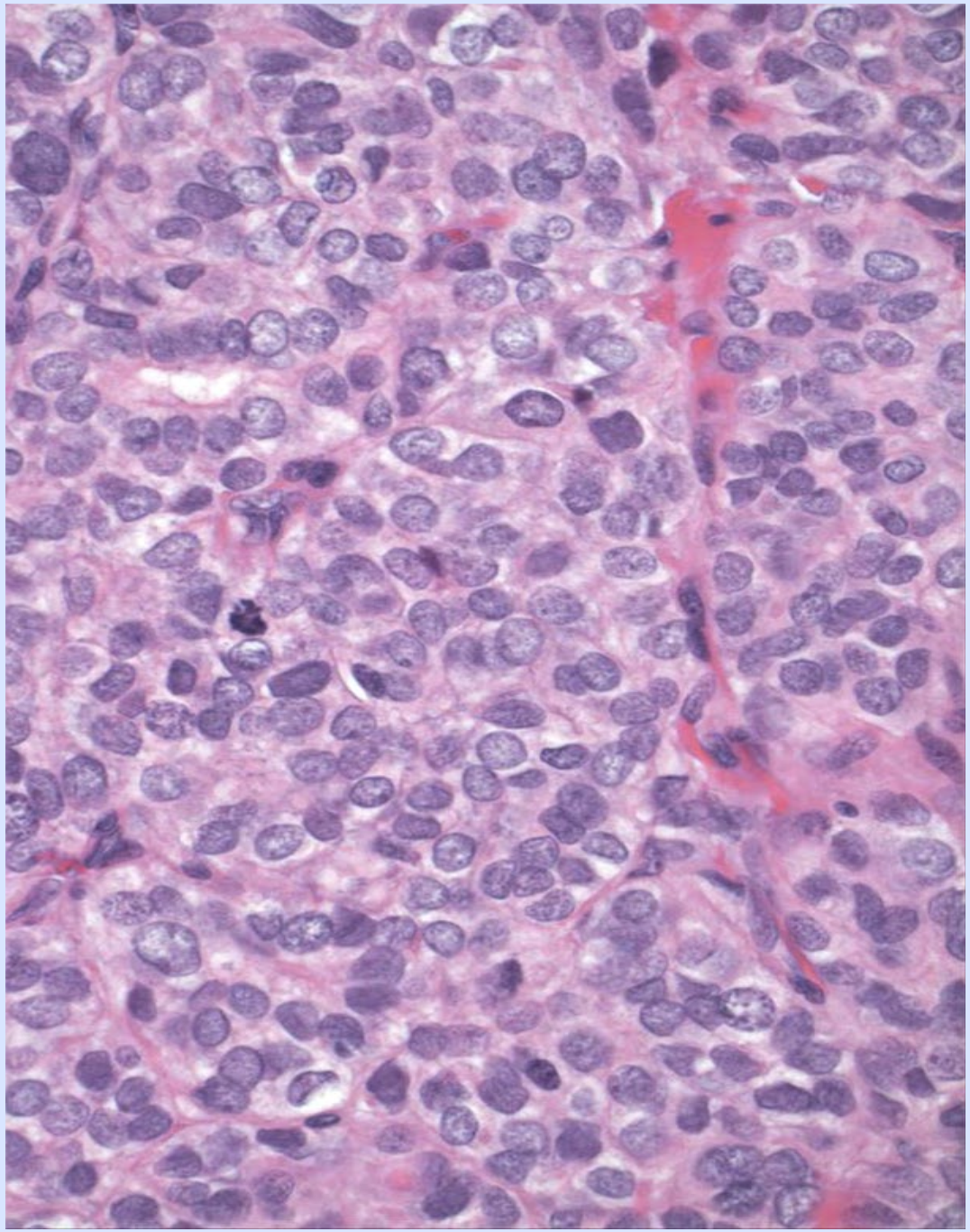
   Poorly differentiated thyroid carcinoma often is preceded by a suspicious for follicular neoplasm diagnosis on FNA.

2. Mistake a case of solid variant of PTC for PDTC. In contrast to PDTC, solid variant of PTC has maintained nuclear features of PTC.

What are convoluted nuclei?

The nuclei of PDTC are uniform, small, and dark.

While there may be irregular contours, the chromatin is evenly dispersed (not clear) and there are no pseudoinclusions.



A note on convoluted nuclei: although many PDTC have convoluted nuclei, it is not clear that convoluted nuclei alone (along with solid architecture and lack of nuclear features of PTC) warrant a diagnosis of PDTC.

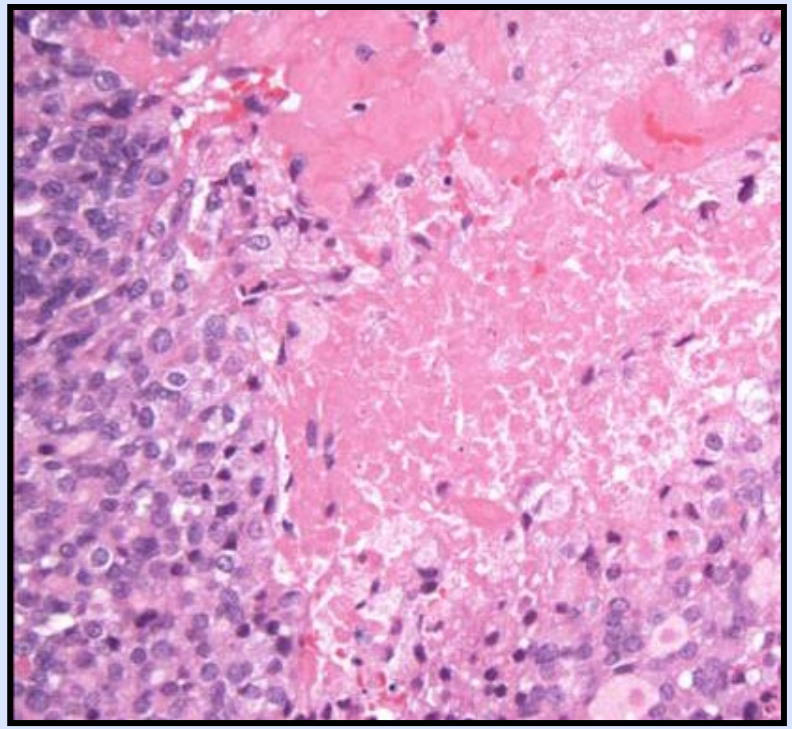
A study published after the Turin proposal did not find convoluted nuclei to be prognostically significant.

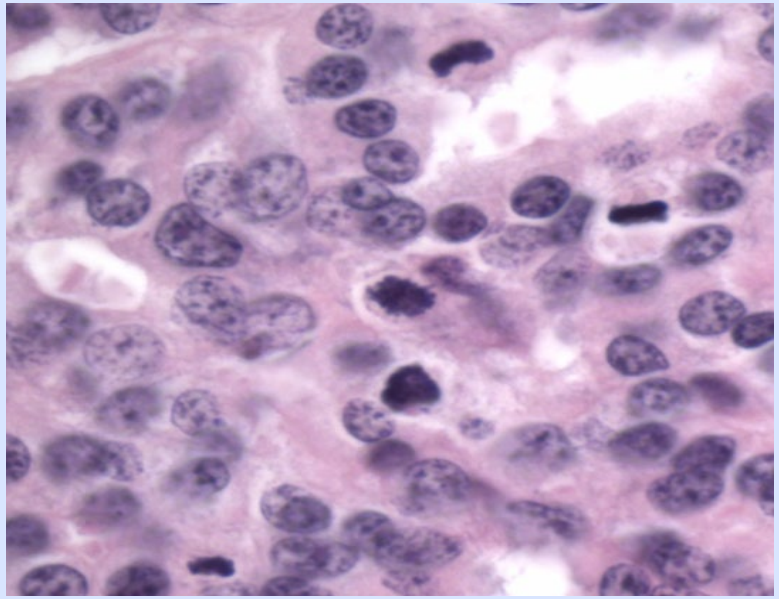
Many endocrine pathologists don't render a diagnosis of PDTC on the basis of convoluted nuclei alone – require mitoses and/or necrosis.

The necrosis of PDTC is coagulative necrosis - in the area of necrosis you can still see the outlines of tumor cells that were previously viable.

Necrosis secondary to fine needle aspiration (especially common in oncocytic tumors) must be excluded.

A mitotic count should be generated using the area of highest mitotic activity. Often the area of highest mitotic activity is adjacent to the areas of tumor necrosis.





Immunohistochemistry (IHC)

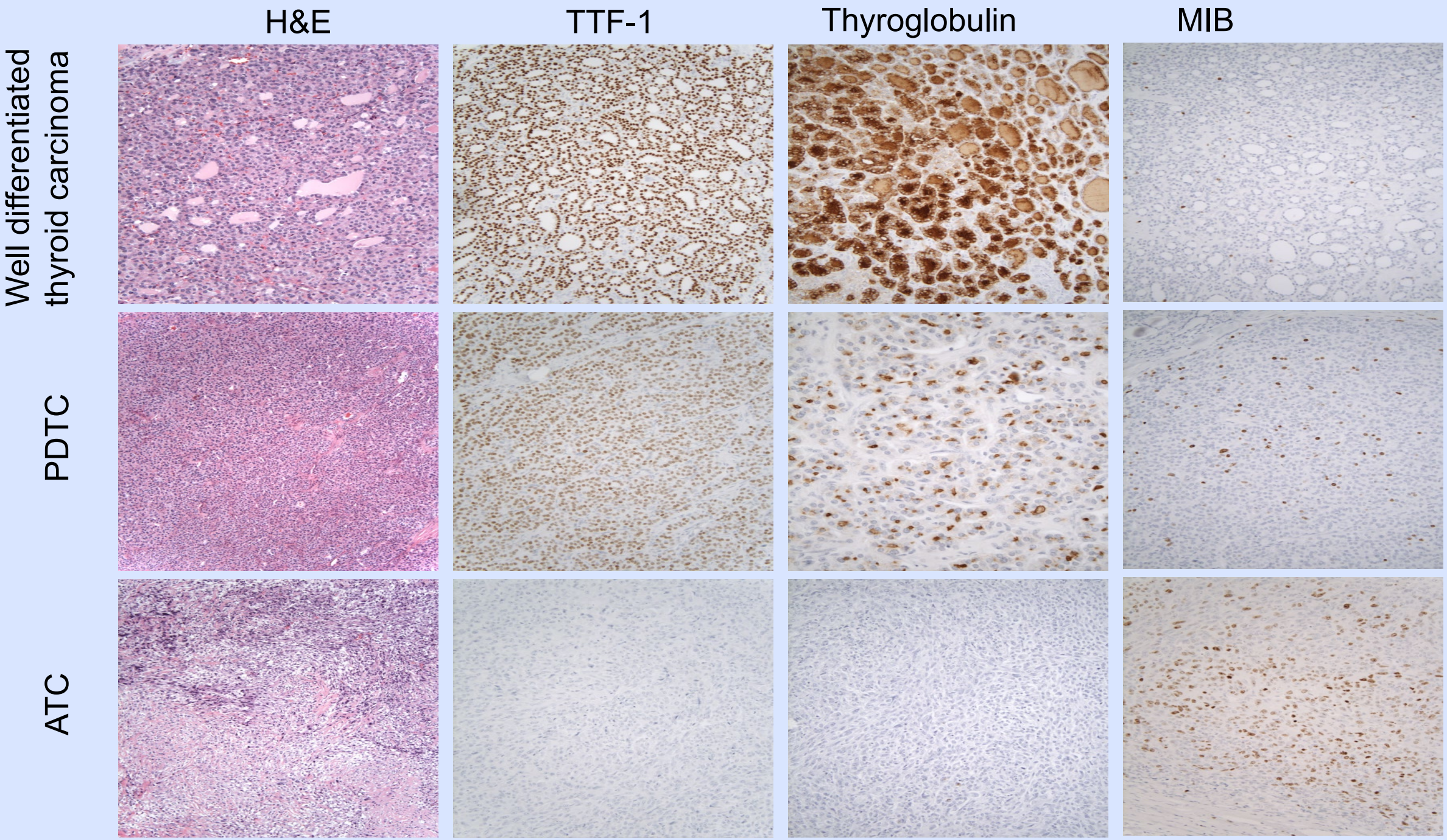
IHC is not required to render a diagnosis of PDTC; however, IHC can be used to support the diagnosis.

PDTC are positive for PAX8, TTF-1, and thyroglobulin.

As compared to well-differentiated tumors, TTF-1 and thyroglobulin staining is generally weaker in PDTCs.

Thyroglobulin staining often has a dot-like paranuclear pattern.

MIB-1: The Ki-67 proliferative index has been reported to be below 5% in 95% of well-differentiated thyroid carcinomas. Most PDTCs have a Ki67 proliferative index >10% (per Asioli et al, the mean Ki67 for PDTCs is 13%) – PDTC tend to have a Ki-67 index of 10-30% (ATC >30%).

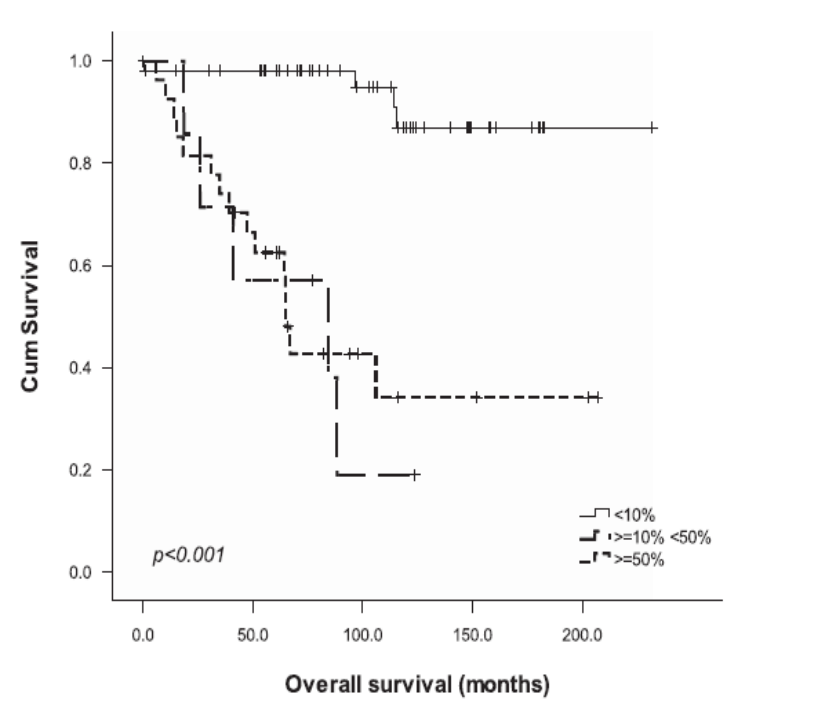

H&E
TTF-1
Thyroglobulin
MIB
Well differentiated thyroid carcinoma
PDTC
ATC

PDTC – How much is enough?

Dettmer et al Am J Surg Pathol • Volume 35, Number 12, December 2011

Aimed to evaluate the percentage of a tumor that needs to show poorly differentiated features for it to be regarded as PDTC.

Tumors with a poorly differentiated component amounting to at least 10% of the tumor had significantly worse outcome by Kaplan-Meier analysis compared with those in the control group (for overall survival, tumor–specific survival, and relapse-free survival).



PDTC – How much is enough?

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Tumors with a poorly differentiated
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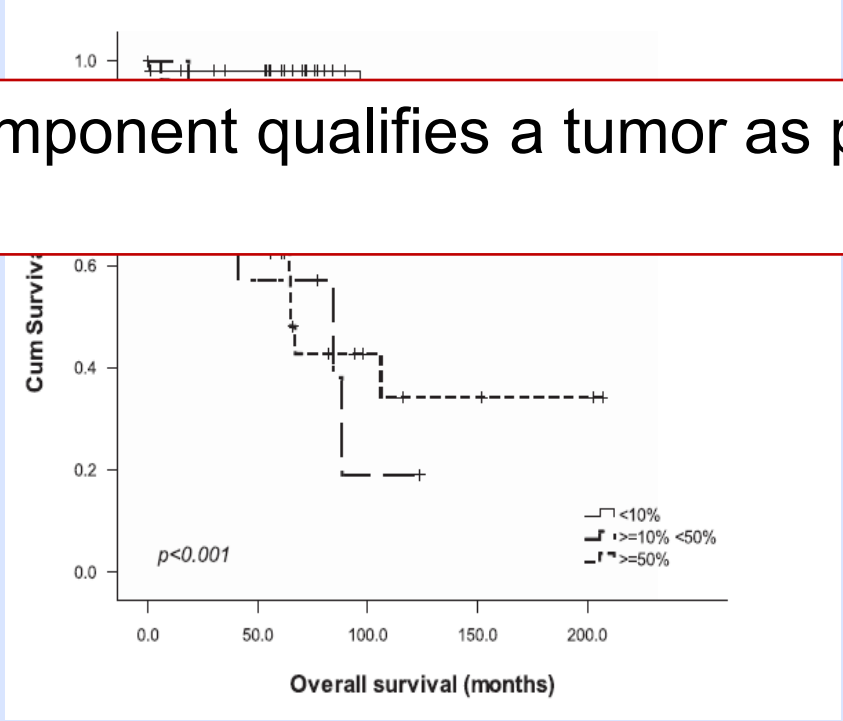
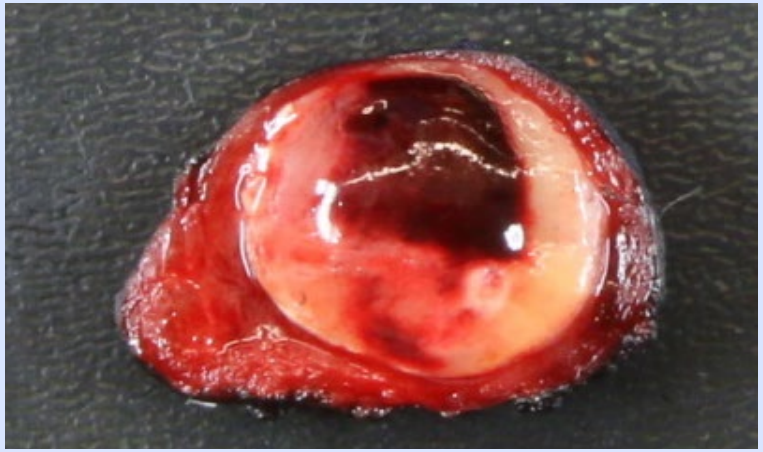
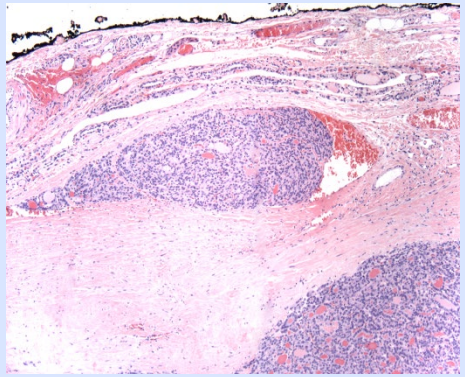
outcome by Kaplan-Meier analysis compared with those in the control group (for overall survival, tumor–specific survival, and relapse-free survival).

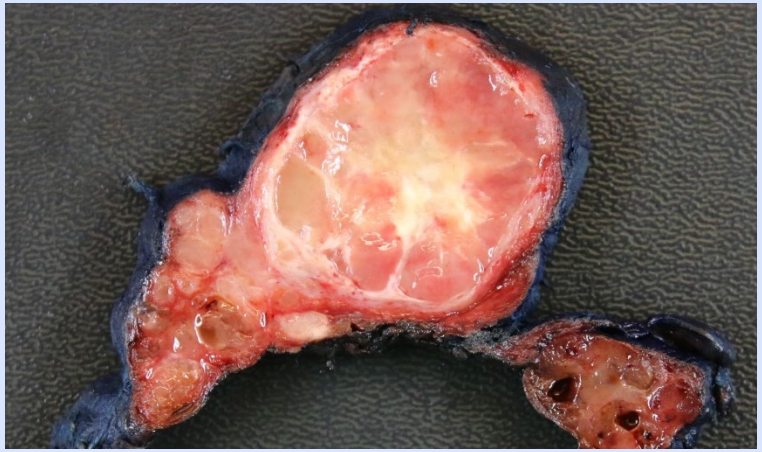
Any amount of a poorly differentiated component qualifies a tumor as poorly differentiated thyroid carcinoma.

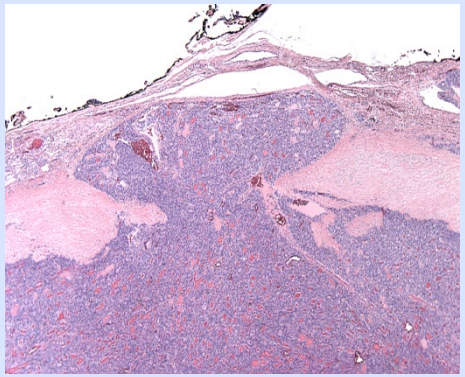


What is the prognostic significance of extent of invasion in PDTC









- Minimally invasive (capsular invasion only)

- Encapsulated angioinvasive: vascular invasion present
  + focal (<4 foci)
  + extensive (≥ foci)

- Widely invasive: grossly see tumor invading through parenchyma, usually also have extensive vascular invasion

Prognostic Significance of Extent of Invasion in Poorly Differentiated Thyroid Carcinoma

Kristine S. Wong,[1] Jochen H. Lorch,[2] Erik K. Alexander,[3] Ellen Marqusee,[3] Nancy L. Cho,[4] Matthew A. Nehs,[4] Gerard M. Doherty,[4] and Justine A. Barletta[1]

THYROID
Volume 29, Number 9, 2019

DOI: 10.1089/thy.2019.0263

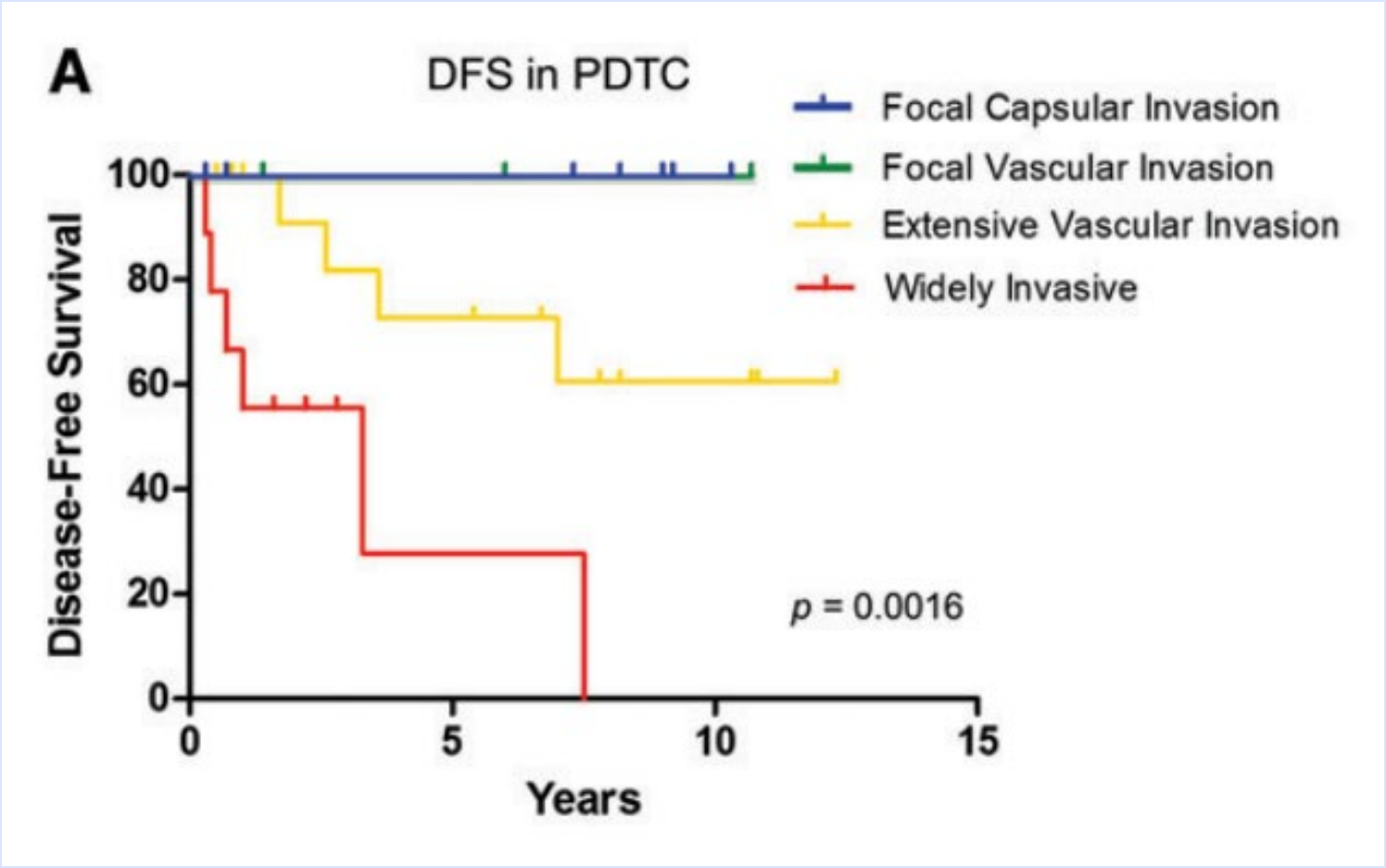
Evaluated the outcome of a cohort of 47 PDTC. Mean patient age 57, mean tumor size 4.3 cm, T4 disease 13%, N1 disease 38%, M1 disease at presentation in 19%, mitoses average 8 per 10 HPFs, 45% of cases had necrosis, 32% were oncocytic, 64% PD component >50% of tumor.

- 8 (17%) had capsular penetration only

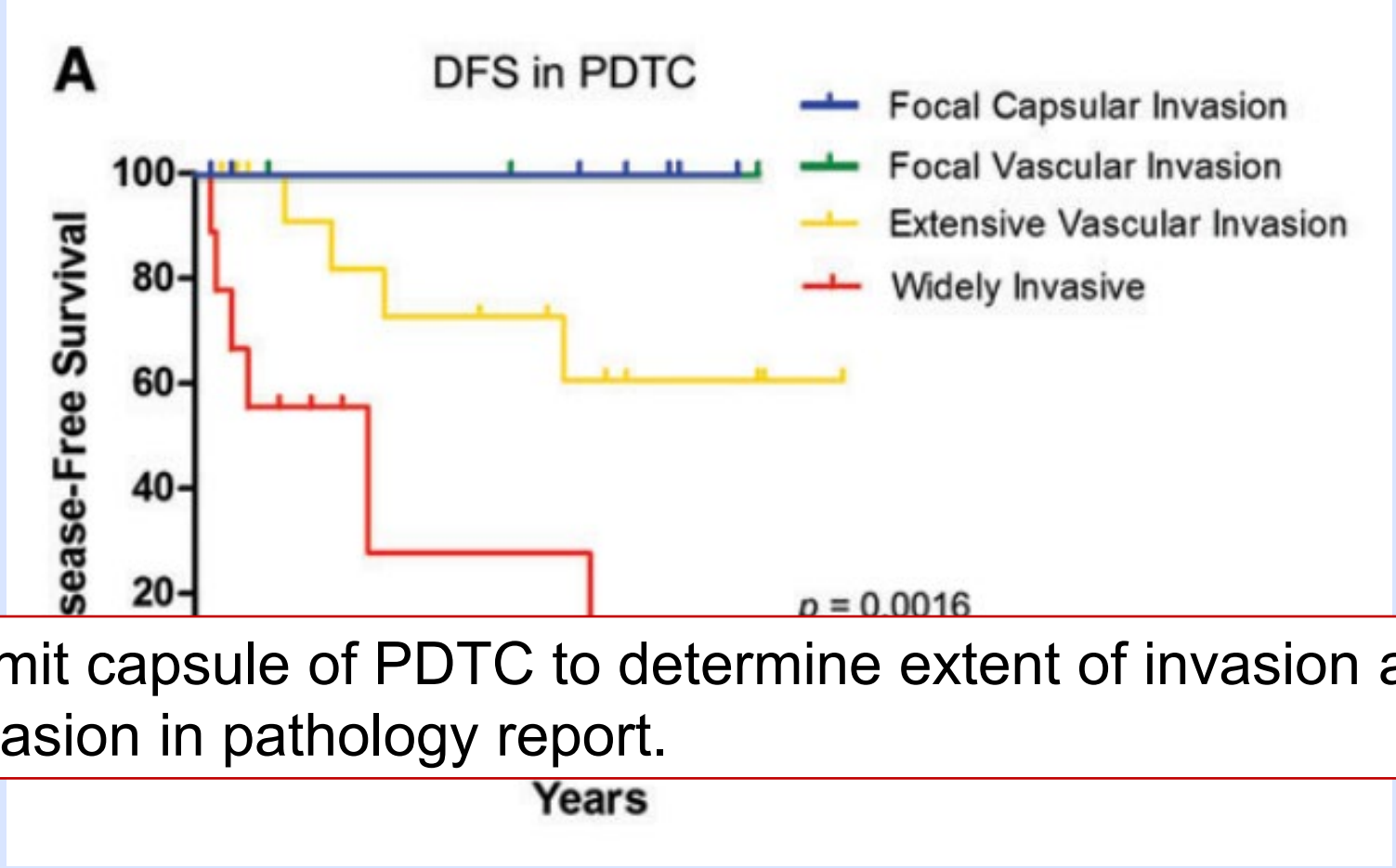
- 5 (11%) had focal vascular invasion (< 4 foci)

- 18 (38%) had extensive vascular invasion (4 or more foci)

- 16 (34%) were widely invasive



Significant difference in DFS in PDTC subgroups among patients with M0 disease at diagnosis. The 5-year DFS was 100% in patients with tumors with focal invasion (capsular or focal vascular invasion), 73% in patients with tumors with extensive vascular invasion, and 17% in patients with widely invasive disease.



Entirely submit capsule of PDTC to determine extent of invasion and document extent of invasion in pathology report.

Significant difference in DFS in PDTC subgroups among patients with M0 disease at diagnosis. The 5-year DFS was 100% in patients with tumors with focal invasion (capsular or focal vascular invasion), 73% in patients with tumors with extensive vascular invasion, and 17% in patients with widely invasive disease.

Case

The patient is a 73-year-old woman who was found to have a neck mass on physical examination.

Ultrasound revealed a 4 cm mass.

An FNA was performed and was read as positive for PTC and pre-operative molecular testing revealed a *BRAF* V600E mutation and a *TERT* promoter mutation.

A total thyroidectomy was performed.

TERT Promoter Mutations

If a tumor has a *BRAF* V600E mutation and a *TERT* promoter mutation, the tumor is most likely an aggressive PTC or an anaplastic thyroid carcinoma.

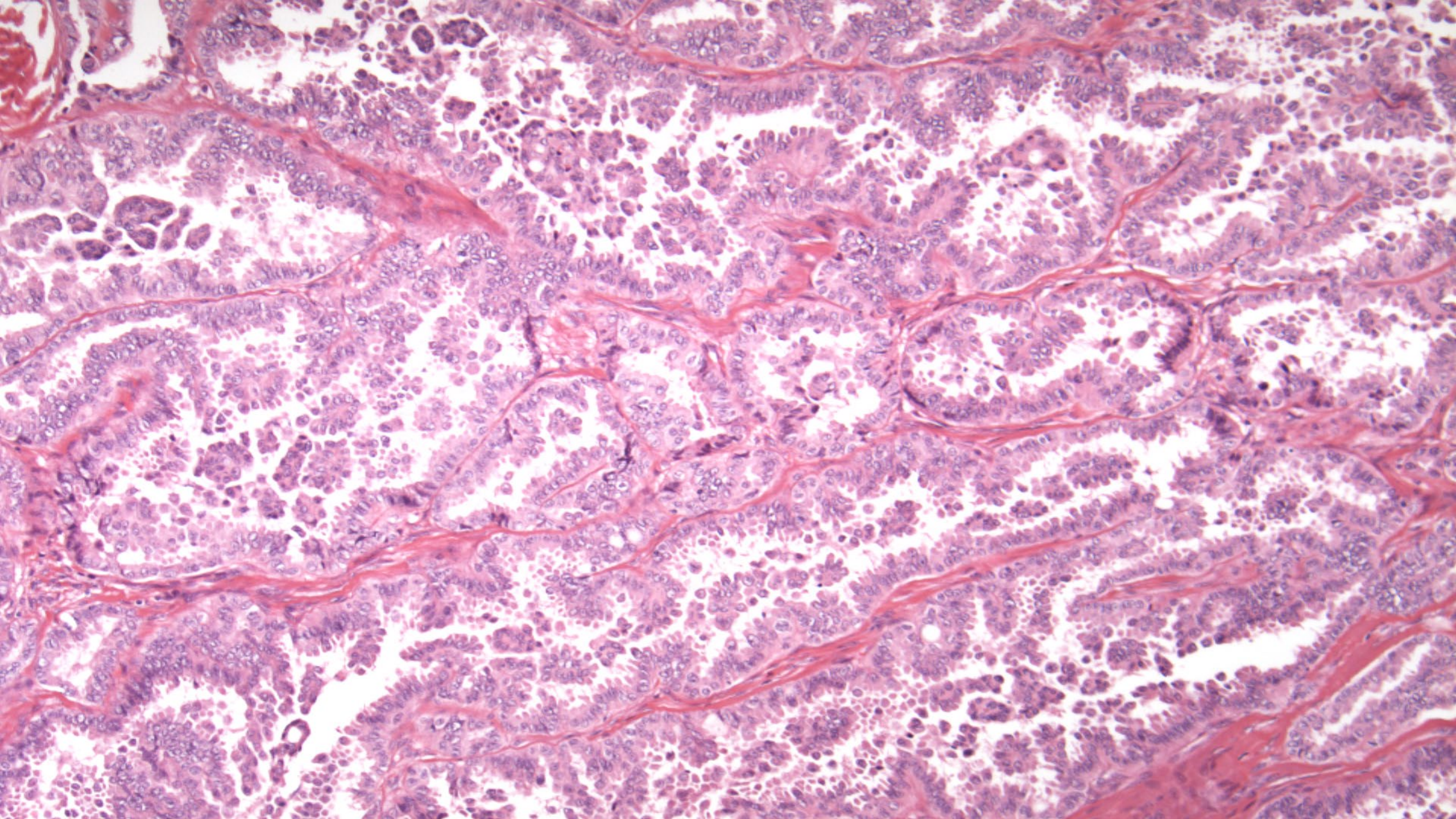
PTC with *BRAF* and *TERT* mutations are at increased risk for dedifferentiation.

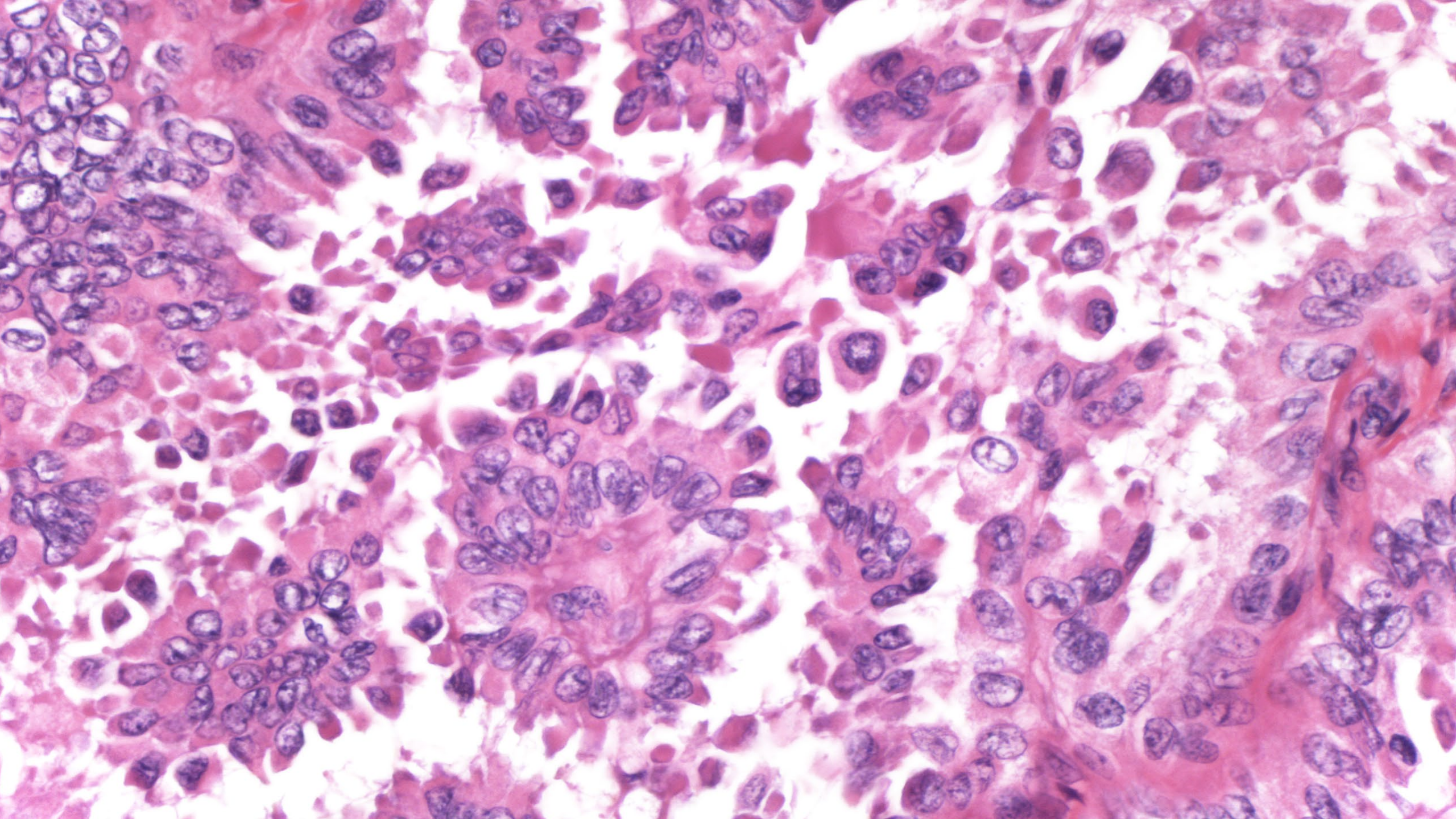
Table 2 *TERT* promoter mutations in thyroid tumors

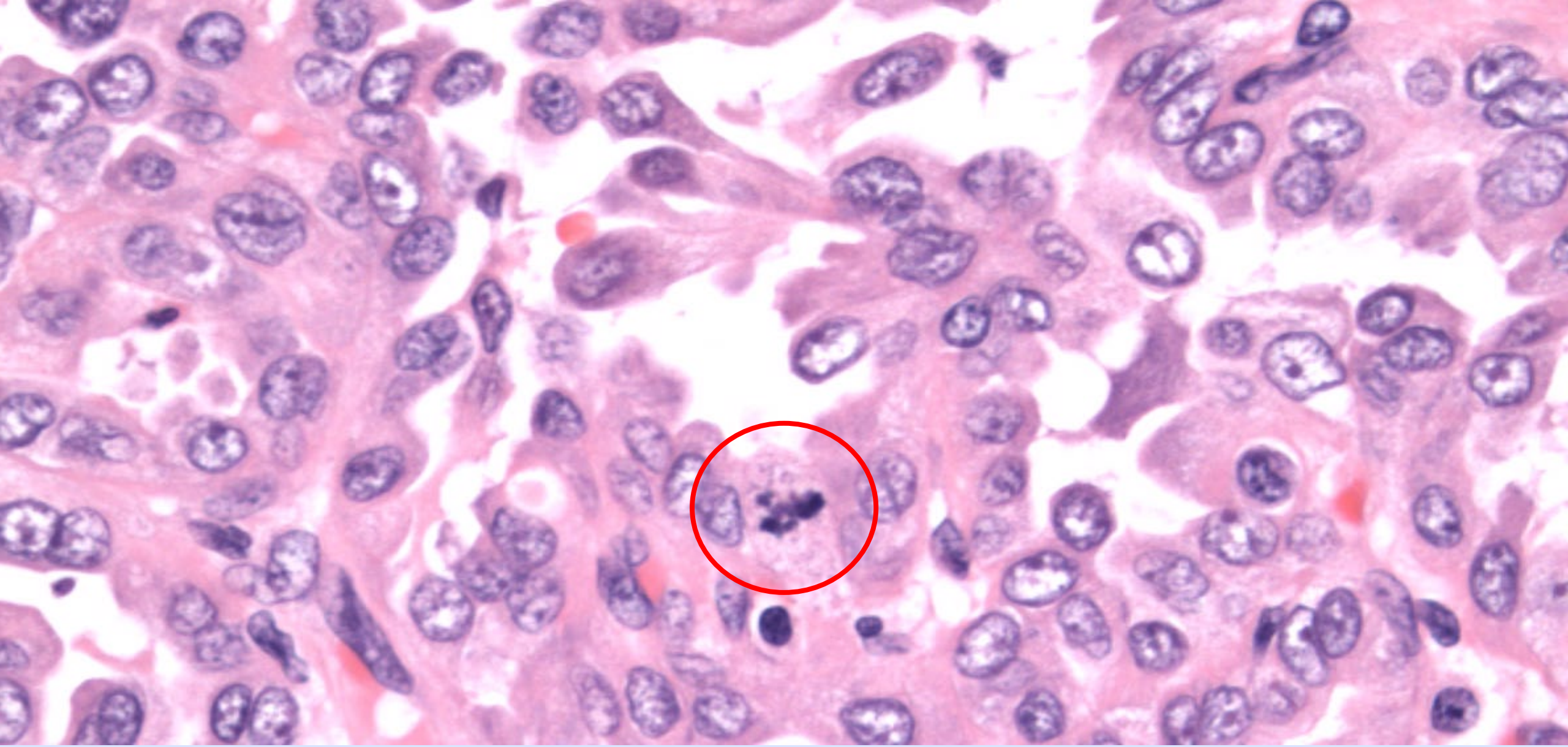
Samples	Mutation C228T (*n*/*N* (%))	Mutation C250T (*n*/*N* (%))	Collective mutations (*n*/*N* (%))
Thyroid cancer cell lines			
PTC	3/3 (100.0)	0/3 (0.0)	3/3 (100.0)
FTC	1/2 (50.0)	0/2 (0.0)	1/2 (50.0)
ATC	4/7 (57.1)	3/7 (42.9)	7/7 (100.0)
All	8/12 (66.7)	3/12 (25.0)	11/12 (91.7)
Thyroid tumors			
Benign tumor	0/85 (0.0)	0/85 (0.0)	0/85 (0.0)
PTC			
CPTC	23/187 (12.3)	0/187 (0.0)	23/187 (12.3)
FVPTC	2/56 (3.6)	0/56 (0.0)	2/56 (3.6)
TCPTC	4/13 (30.8)	0/13 (0.0)	4/13 (30.8)
Columnar	1/1 (100.0)	0/1 (0.0)	1/1 (100.0)
All	30/257 (11.7)	0/257 (0.0)	30/257 (11.7)
FTC	9/79 (11.4)	2/79 (2.5)	11/79 (13.9)
DTC	39/336 (11.6)	2/336 (0.6)	41/336 (12.2)
PDTC	3/8 (37.5)	0/8 (0.0)	3/8 (37.5)
ATC	23/54 (42.6)	2/54 (3.7)	25/54 (46.3)
MTC	0/16 (0.0)	0/16 (0.0)	0/16 (0.0)

PTC, papillary thyroid cancer; CPTC, conventional PTC; FVPTC, follicular variant PTC; TCPTC, tall-cell PTC; FTC, follicular thyroid cancer; DTC, differentiated thyroid cancer (combination of PTC and FTC); PDTC, poorly DTC; ATC, anaplastic thyroid cancer; MTC, medullary thyroid cancer.

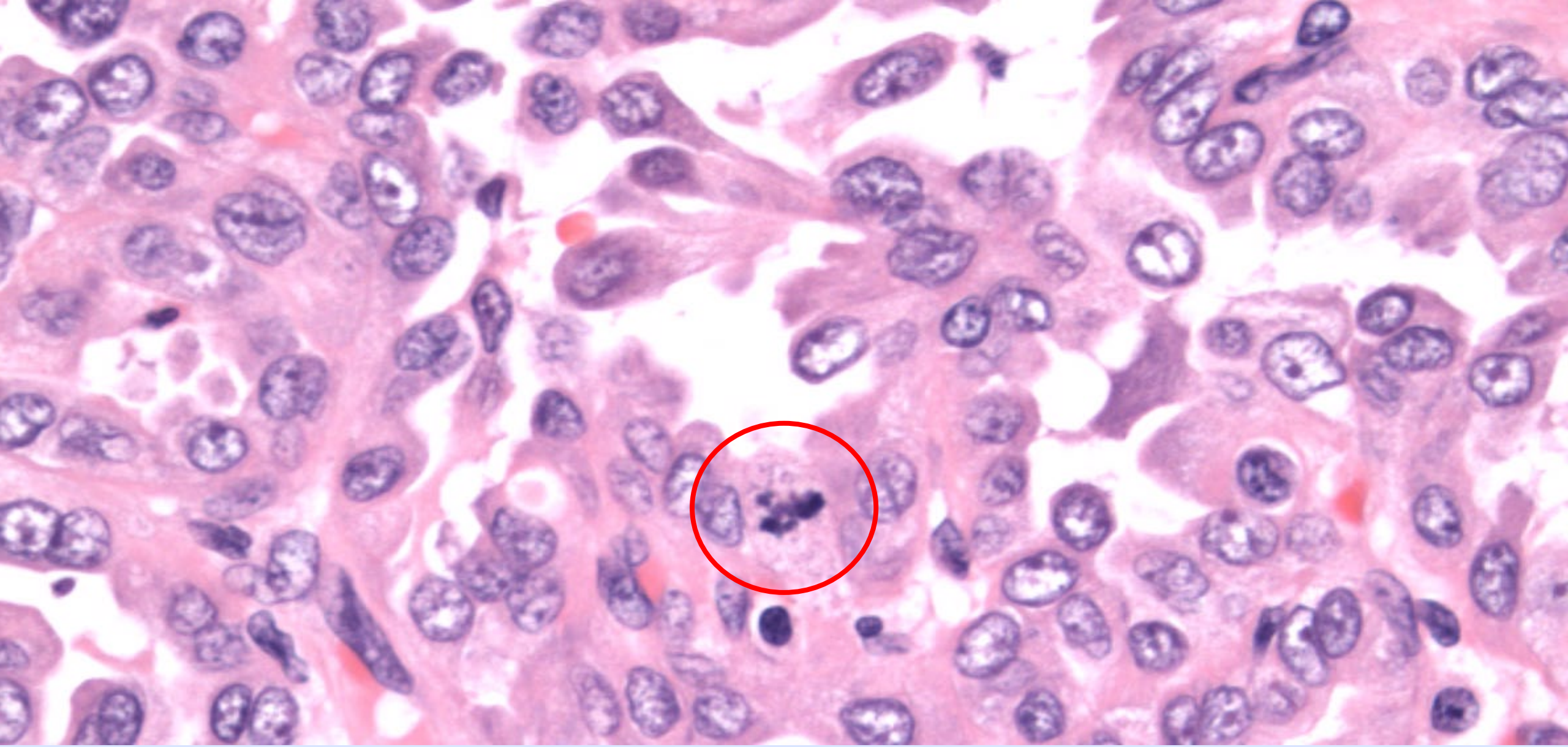
Liu, *Endocr Relat Cancer*, 2013







Mitoses numbered 8 per 10 HPF. No tumor necrosis.



High-grade papillary thyroid carcinoma, hobnail subtype*

* In 2022 WHO subtype is replacing variant.

High-Grade Papillary Thyroid Carcinoma

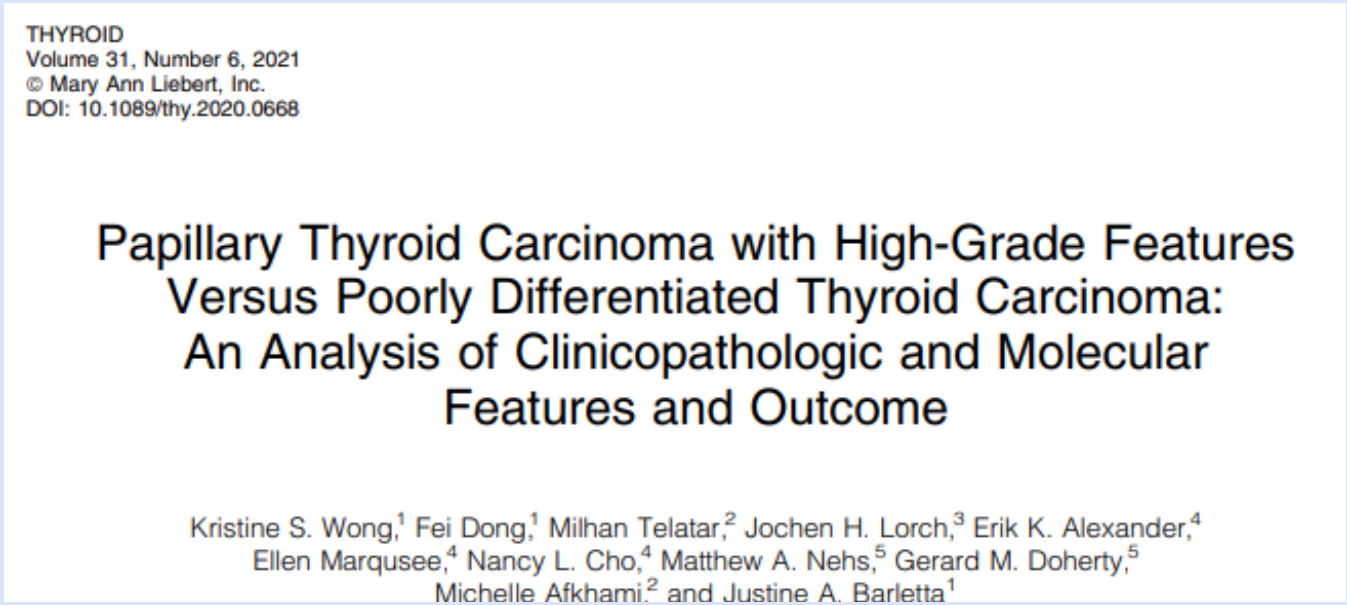
For many years at MSKCC different criteria were used to render a diagnosis of PDTC (Hiltzik, *Cancer*, 2006).

They defined PDTC as a follicular cell-derived tumor:

- necrosis and/or ≥5 mitoses per 10 HPFs
- regardless of the tumor growth pattern
- regardless of presence of nuclear features of PTC

2017 Endocrine WHO indicated tumors with maintained nuclear features of PTC should not be included in the PDTC category.

Some endocrine pathologists used the terminology PTC with high-grade features.



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Volume 31, Number 6, 2021

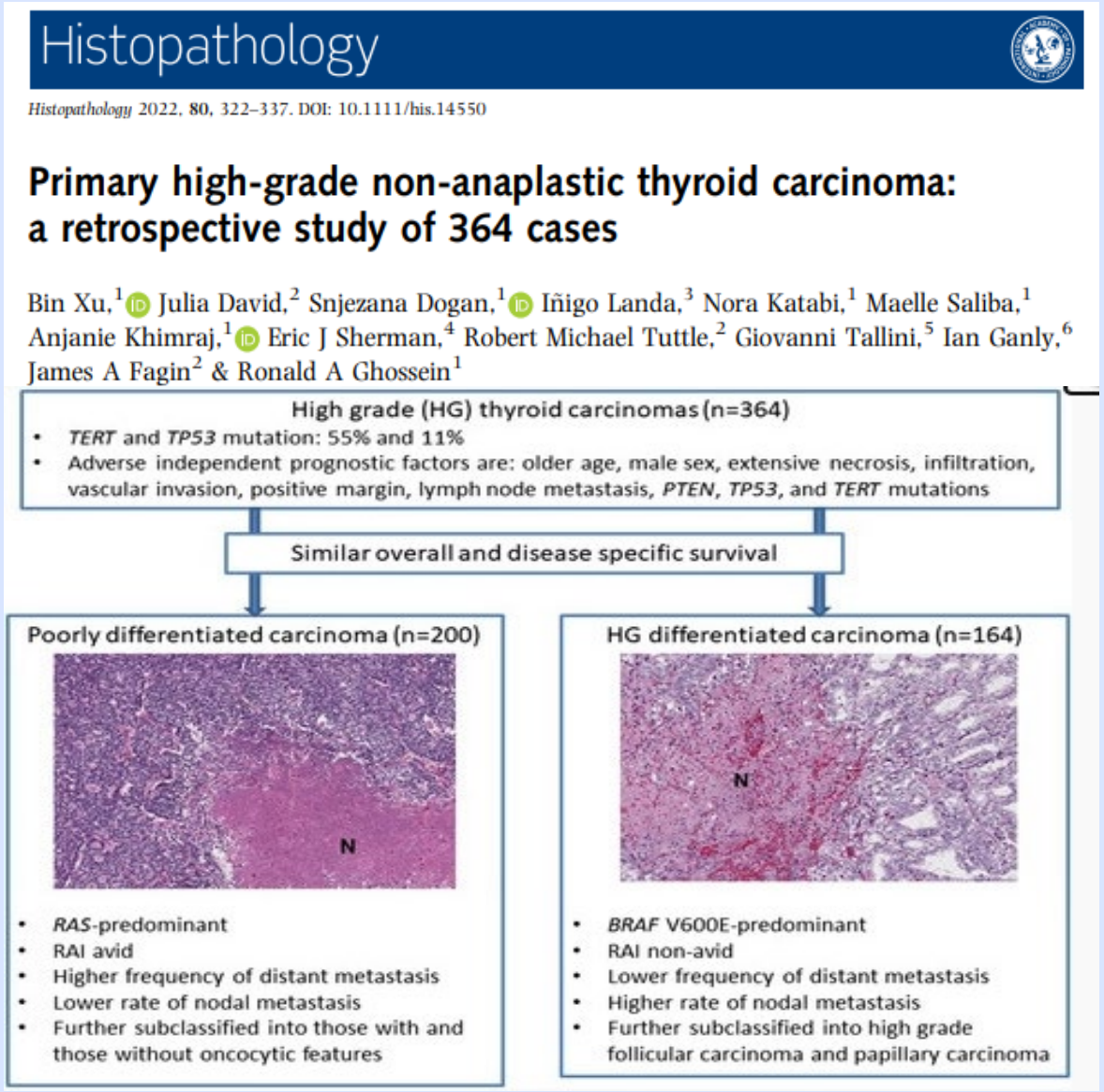
DOI: 10.1089/thy.2020.0668

Papillary Thyroid Carcinoma with High-Grade Features Versus Poorly Differentiated Thyroid Carcinoma: An Analysis of Clinicopathologic and Molecular Features and Outcome

Kristine S. Wong,[1] Fei Dong,[1] Milhan Telatar,[2] Jochen H. Lorch,[3] Erik K. Alexander,[4] Ellen Marqusee,[4] Nancy L. Cho,[4] Matthew A. Nehs,[5] Gerard M. Doherty,[5] Michelle Afkhami,[2] and Justine A. Barletta[1]

PTC with high-grade features pursue an aggressive clinical course – more aggressive than PDTC in our small cohort (in terms of DFS and DSS).

PTC with high-grade features are molecular distinct with a higher rate of *BRAF* V600E mutations compared to PDTC which is *RAS*-mutant predominant.



Differentiated high-grade thyroid carcinoma:

- predominantly HG-PTC

- pursues an aggressive clinical course similar to PDTC

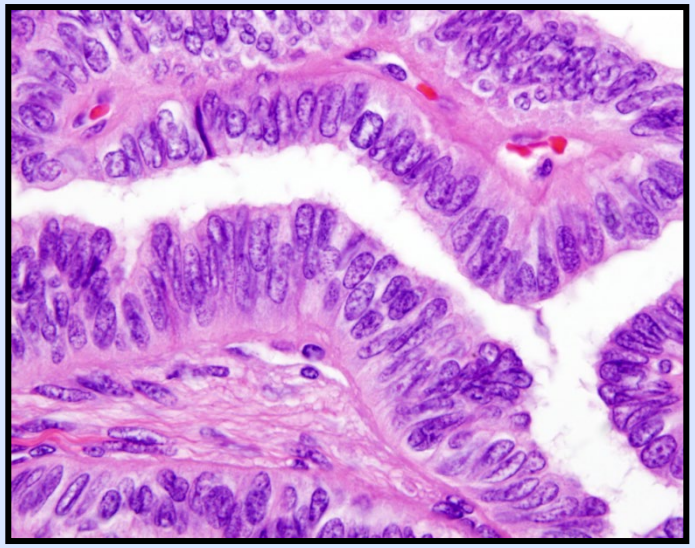
- higher *BRAF* V600E mutation rate

- higher rate of LN metastases

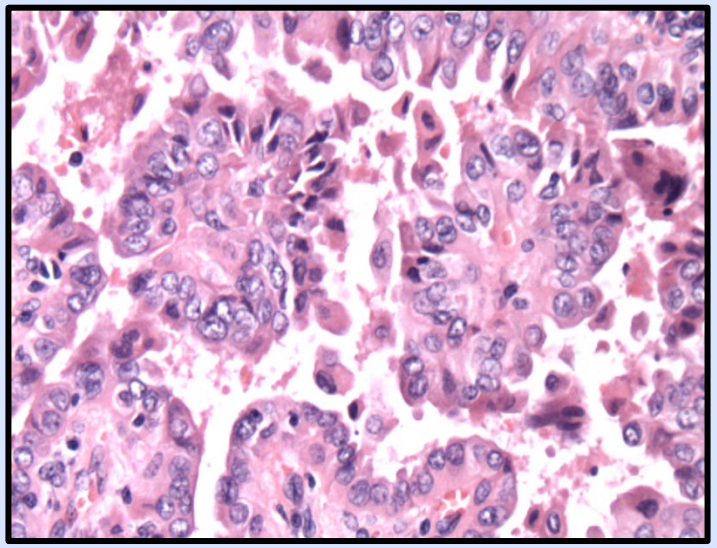
- more likely to be RAI non-avid

High-Grade Papillary Thyroid Carcinoma

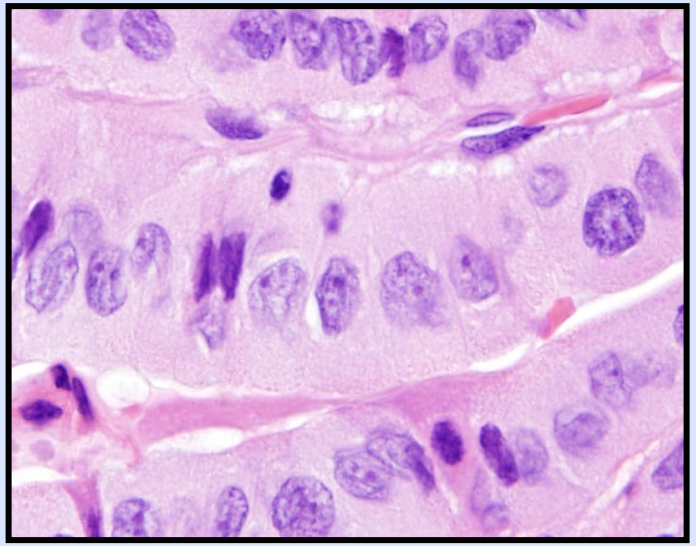
Many are known aggressive subtypes of PTC, but they can also be classic PTC (18% in MSK study).



Columnar cell subtype



Hobnail subtype



Tall cell subtype

2022 WHO Classification of Endocrine and Neuroendocrine Tumours has a new chapter on high-grade follicular cell-derived non-anaplastic thyroid carcinoma that includes:

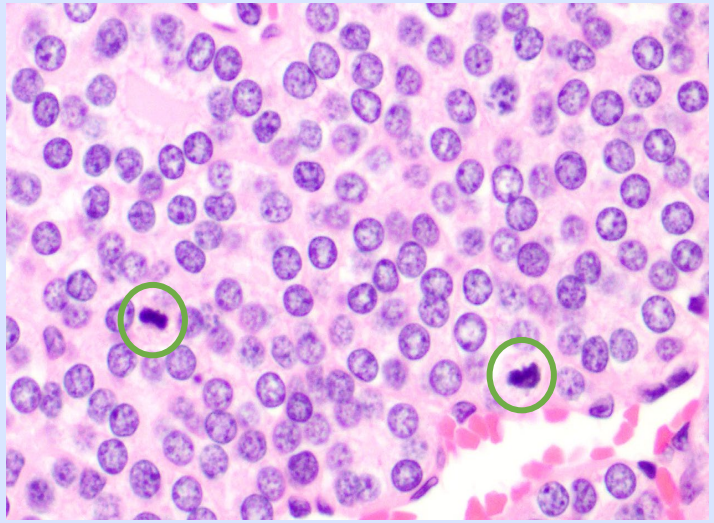
- PDTC: defined based on Turin criteria

- Differentiated high-grade thyroid carcinoma: defined as PTC or FTC with ≥5 mitoses per 10 HPFs and/or tumor necrosis

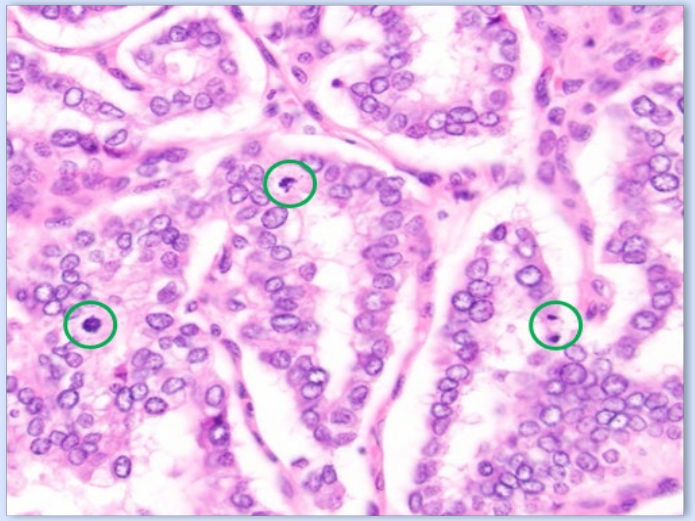
Most differentiated high-grade thyroid carcinomas represent high-grade PTCs.

Mitotic count and presence/absence of tumor necrosis needs to be evaluated in all thyroid tumors in order to identify high-grade follicular cell-derived non-anaplastic thyroid carcinomas.

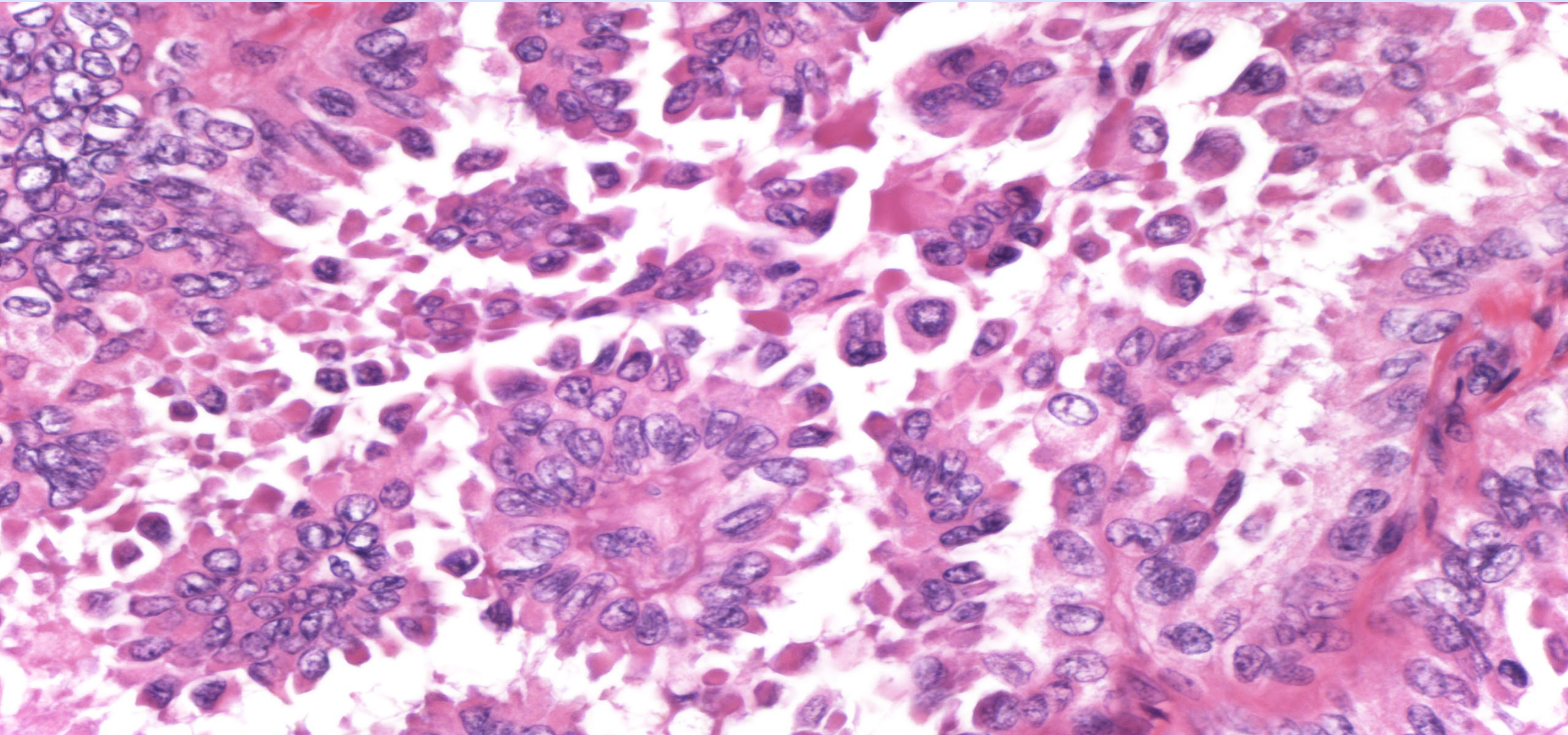
If the tumor has high-grade features and has solid/trabecular/insular (STI) growth AND lacks nuclear features of PTC, then it is a poorly differentiated thyroid carcinoma/



If the tumor has high-grade features and has maintained nuclear features of PTC or lacks STI growth, then it is a differentiated high-grade thyroid carcinoma (usually high-grade PTC).



Back to the case



Hobnail Subtype of PTC

Described by Dr. Lloyd in 2010 (Asioli, Am J Surg, Pathol, 2010). Rare (<1% of PTC) aggressive subtype of PTC. In Dr. Lloyd's original cohort, distant metastases were present in 5 of 8 patients and 4 died of disease after a mean time of 42.8 months.

<u>Subsequent work has shown that these tumors are:</u>

- Often tumor also has a tall cell component.

- Have a tendency to dedifferentiate (Amacher et al, Am J Surg Pathol, 2015).

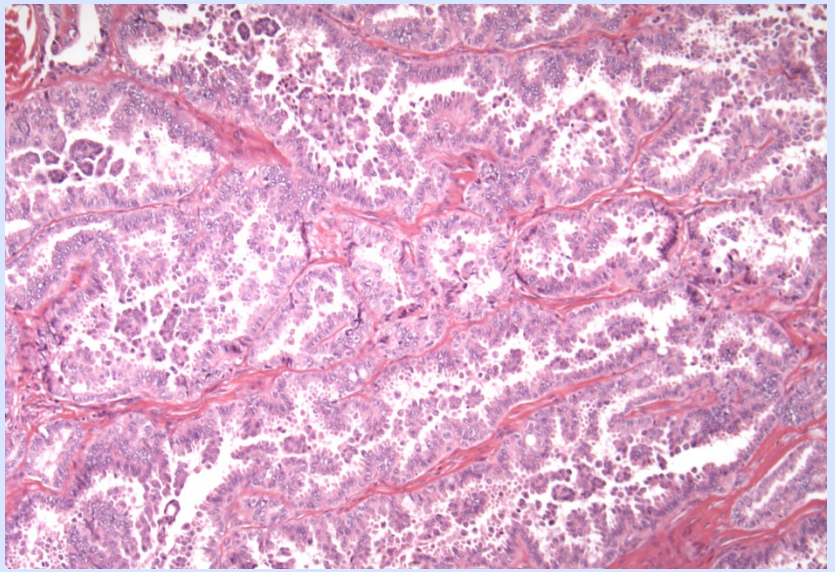
- Frequently harbor the *BRAF* V600E mutation (80%) (Lubitz, Thyroid, 2014) and secondary mutations such as *TP53* (15-55%), *TERT* (45%) and *PIK3CA* mutations (28%) (Morandi, Endocr Relat Cancer, 2017).

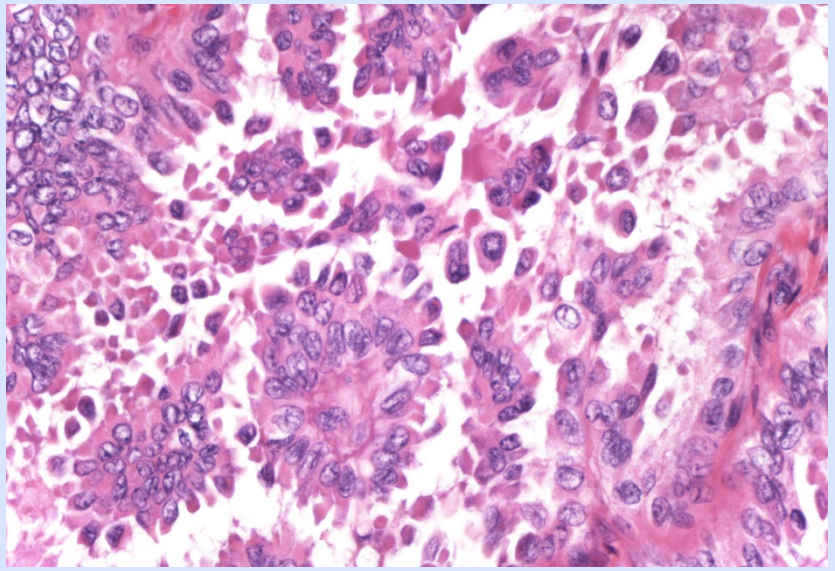
Hobnail Subtype of PTC

Making the diagnosis:

- Usually occur in older patients
- Large, invasive tumors
- Architecture can be papillary, micropapillary, cribriform, or follicular
- Higher power - cells with nuclear pseudo-stratification with nuclei jutting out from the apical surface. The nuclei show more atypia than most PTC. Mitoses usually readily identified.

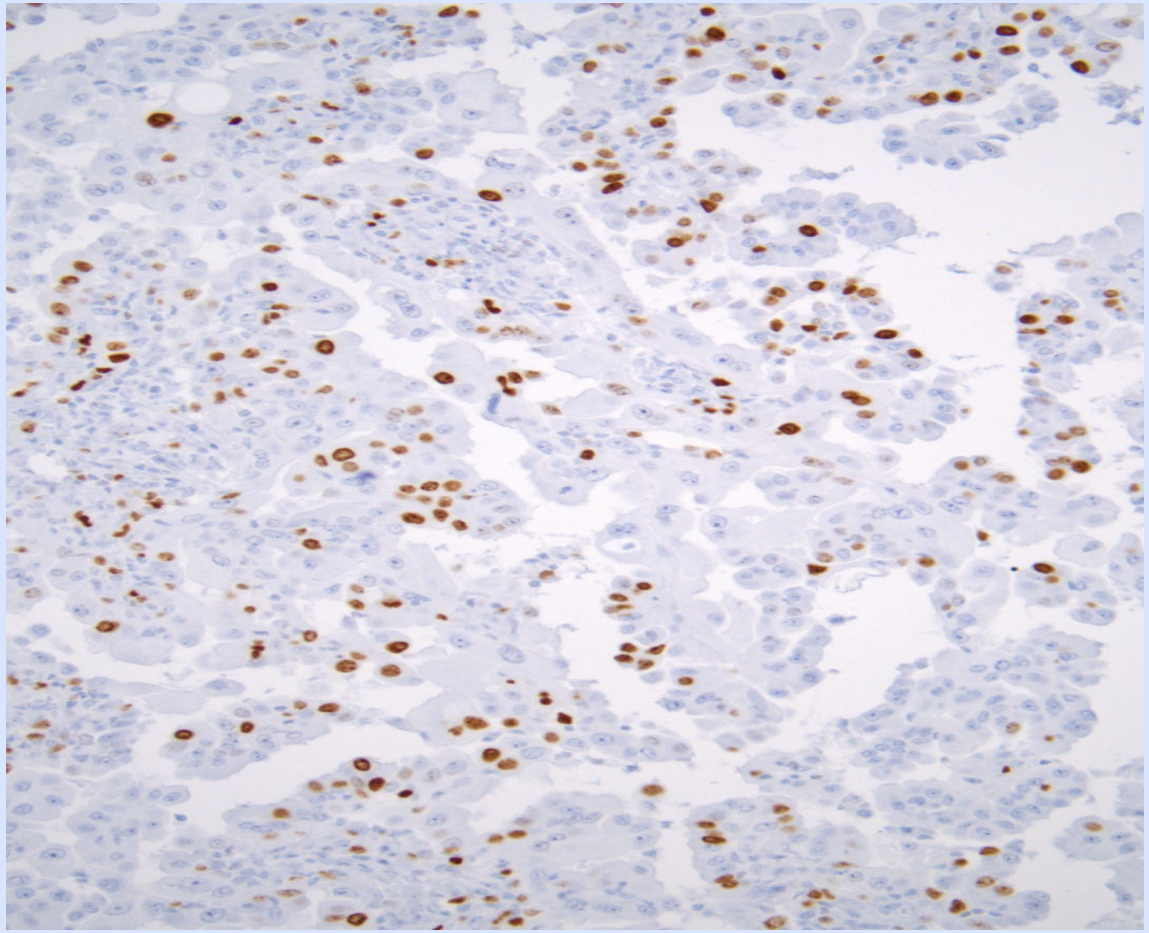
- Pitfall: Mistake it for classic PTC



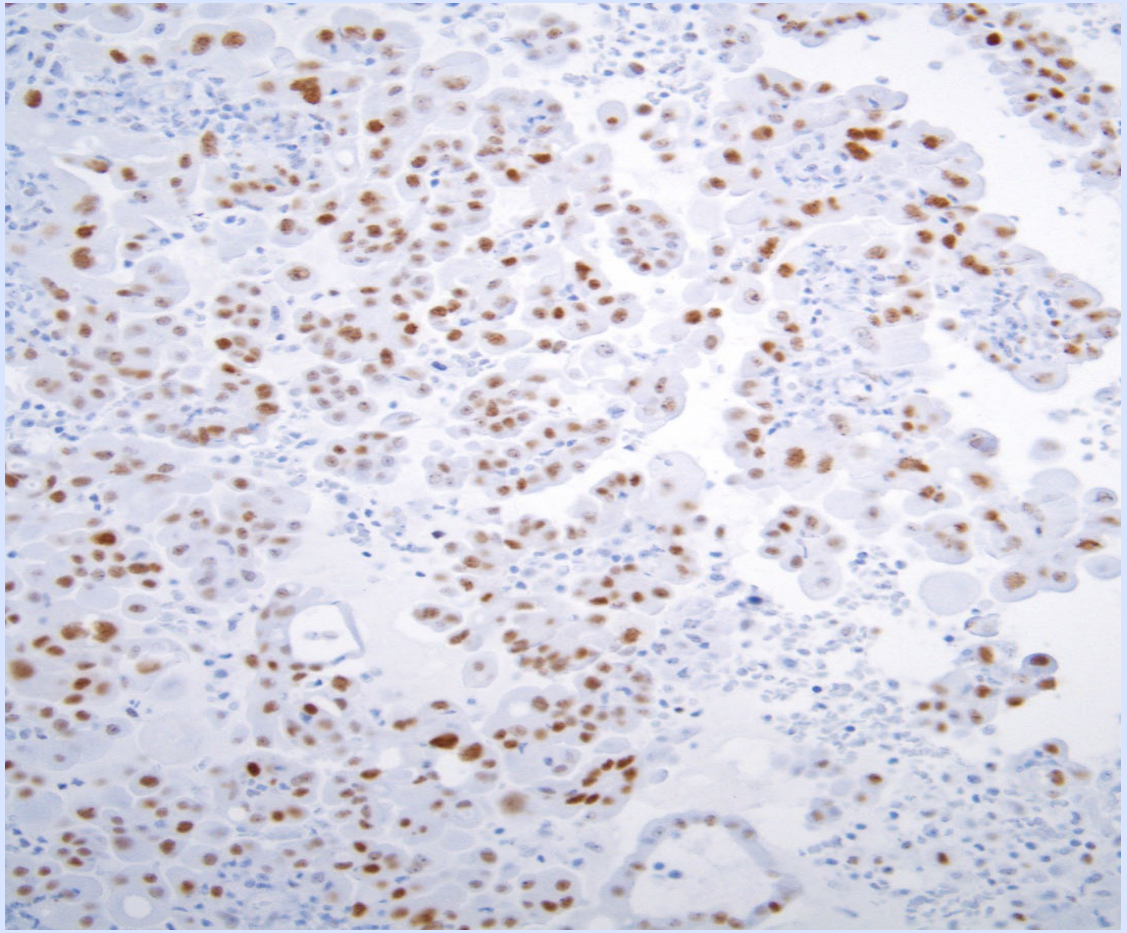


Hobnail Variant of PTC

Ki67 averages 8-10%



May have upregulated p53



Hobnail Subtype of PTC

The presence of a hobnail component should always be indicated in the pathology report.

- 30% or more top line as hobnail

- <30% focal hobnail features with note indicating less clear prognostic significance but potential to pursue an aggressive clinical course.

Histopathology

Histopathology 2020, **76**, 707–713. DOI: 10.1111/his.14042

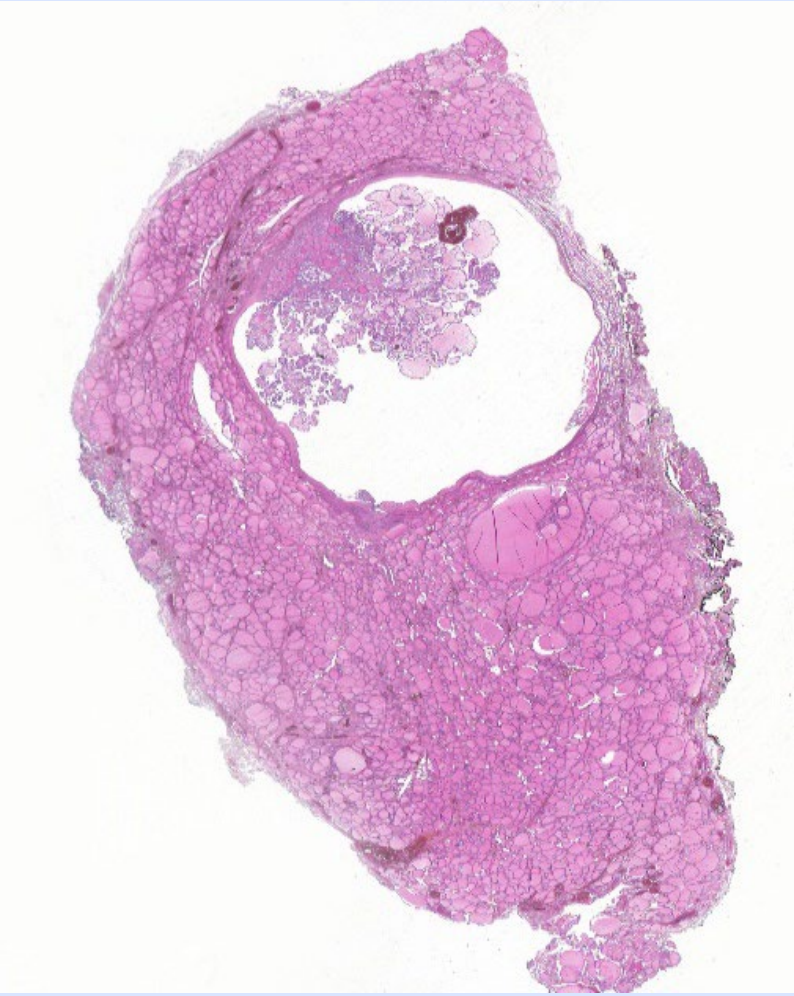
A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma

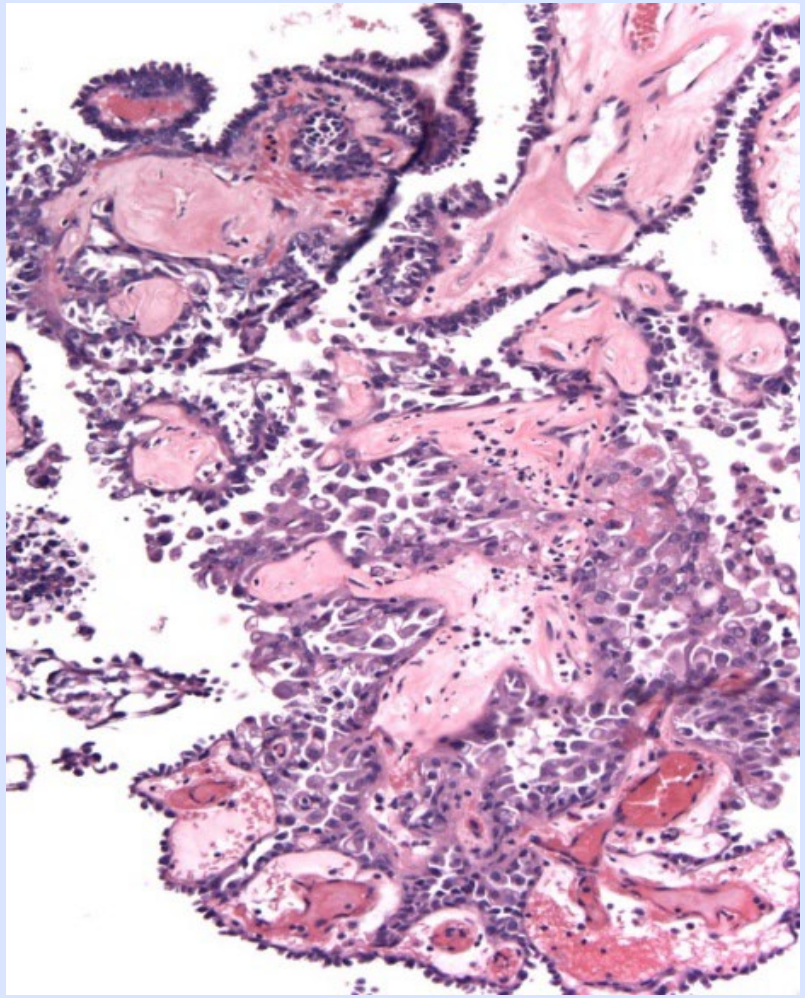
Kristine S Wong,[1] Tiffany Y Chen,[1] Sara E Higgins,[1] Brooke E Howitt,[2] Jochen H Lorch,[3] Erik K Alexander,[4] Ellen Marqusee,[4] Nancy L Cho,[5] Matthew A Nehs,[5] Gerard M Doherty[5] & Justine A Barletta[1]

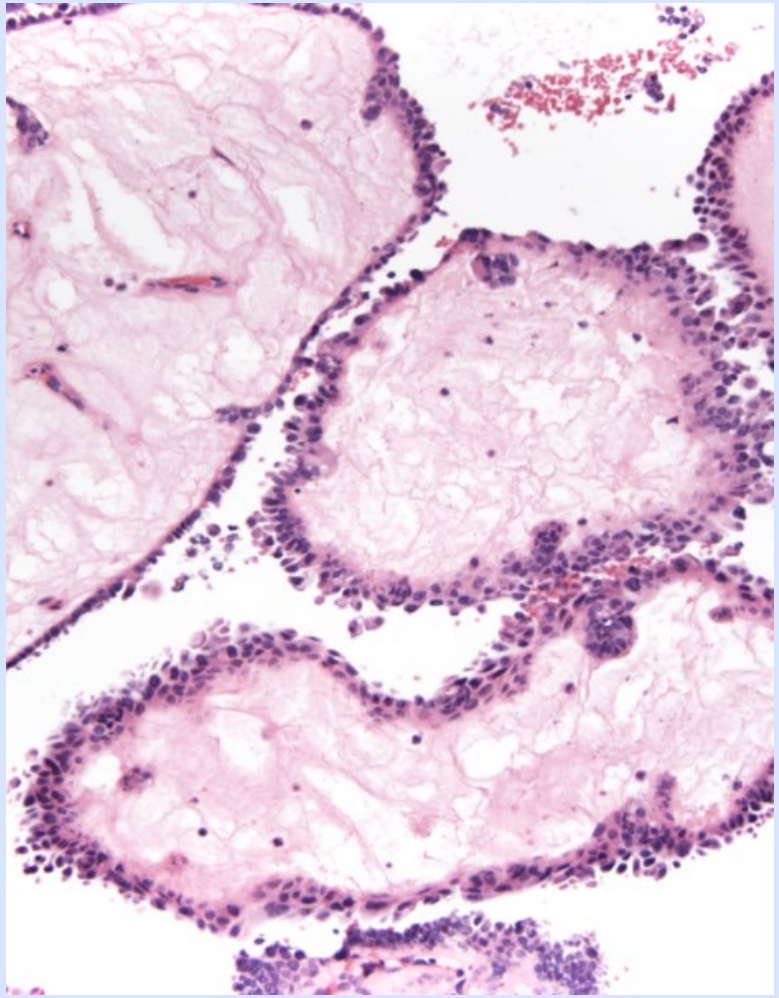
- ~15% of classic PTC have a hobnail cytomorphology secondary to degenerative/ischemic change.

- Found that these tumors have an outcome similar to classic PTC and lack secondary molecular alterations that are frequently associated with true hobnail subtype.

Hobnail-like classic PTC are often encapsulated and partially cystic and have hyalinized and variably edematous cores.







“Hobnail-like” classic PTC vs True Hobnail Subtype

Can be distinguished from true hobnail subtype based on:

1. Patient age: diagnosed in younger patients (mean age 40 vs 68 yrs)
2. Tumor size: smaller tumors (mean tumor size 2.1 cm vs 4.0 cm)
3. Invasive growth: lower rate of gross extrathyroidal extension (0 vs 71%)
4. Mitotic activity: all had <3 mitoses per 10 HPF (0 vs 71%)
5. No areas of dedifferentiation
6. Ki-67 proliferative rate: <5% in all cases (hobnail 85% had Ki67 PI >5%)
7. Lack mutant p53 staining pattern
8. Lack of secondary oncogenic mutations (found in all true hobnail subtype in our cohort)

“Hobnail-like” classic PTC vs True Hobnail Subtype

Can be distinguished from true hobnail subtype based on:

1. Patient age: diagnosed in younger patients (mean age 40 vs 68 yrs)
2. Tumor size: smaller tumors (mean tumor size 2.1 cm vs 4.0 cm)
3. Inv[illegible]1%)
4. Mit[illegible]
5. No[illegible]
6. Ki-67 proliferative rate: <5% in all cases (hobnail 85% had Ki67 PI >5%)
7. Lack mutant p53 staining pattern
8. Lack of secondary oncogenic mutations (found in all true hobnail subtype in our cohort)

Don’t use terminology hobnail-like classic PTC, just diagnose as classic PTC.

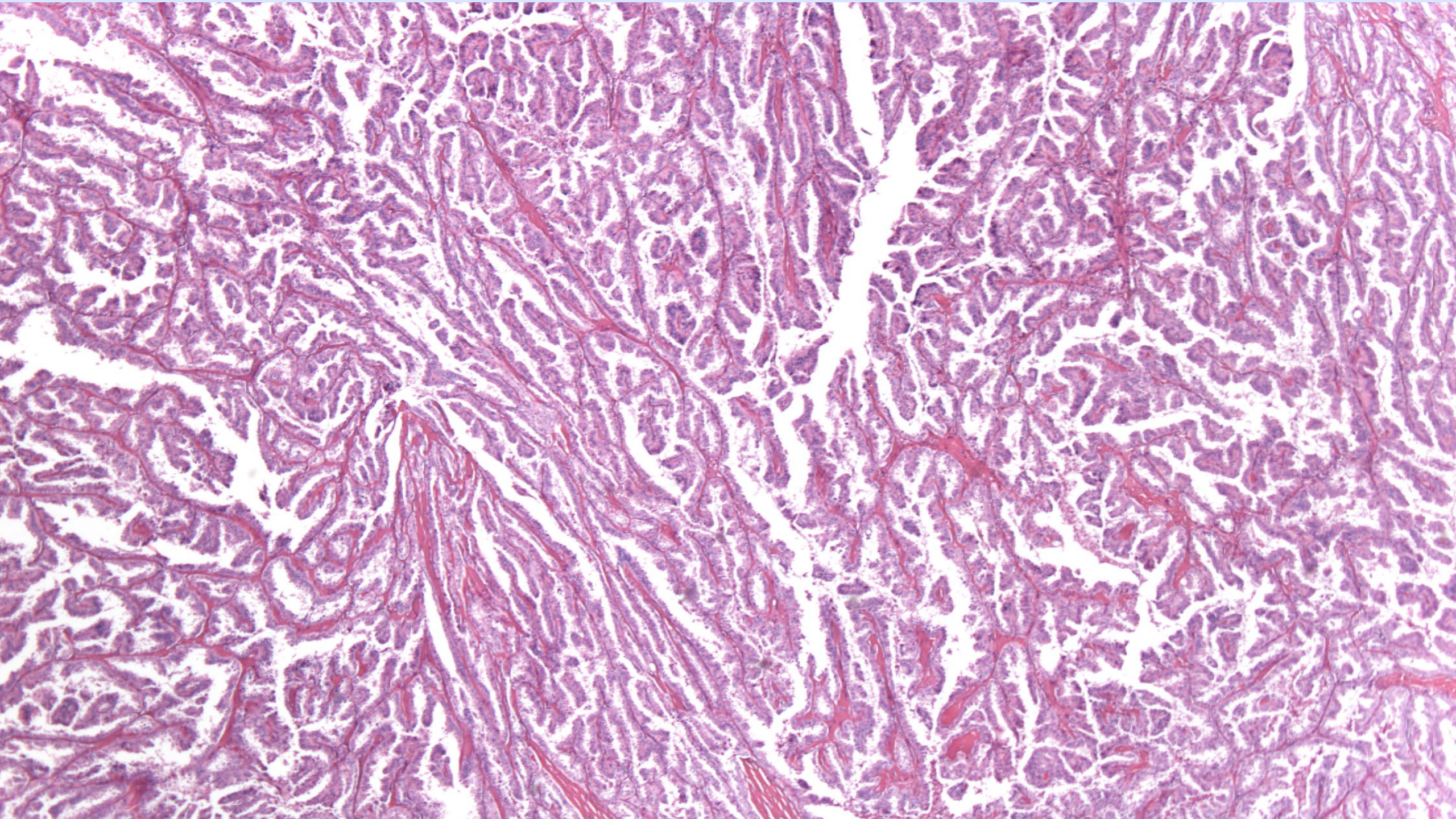
Case

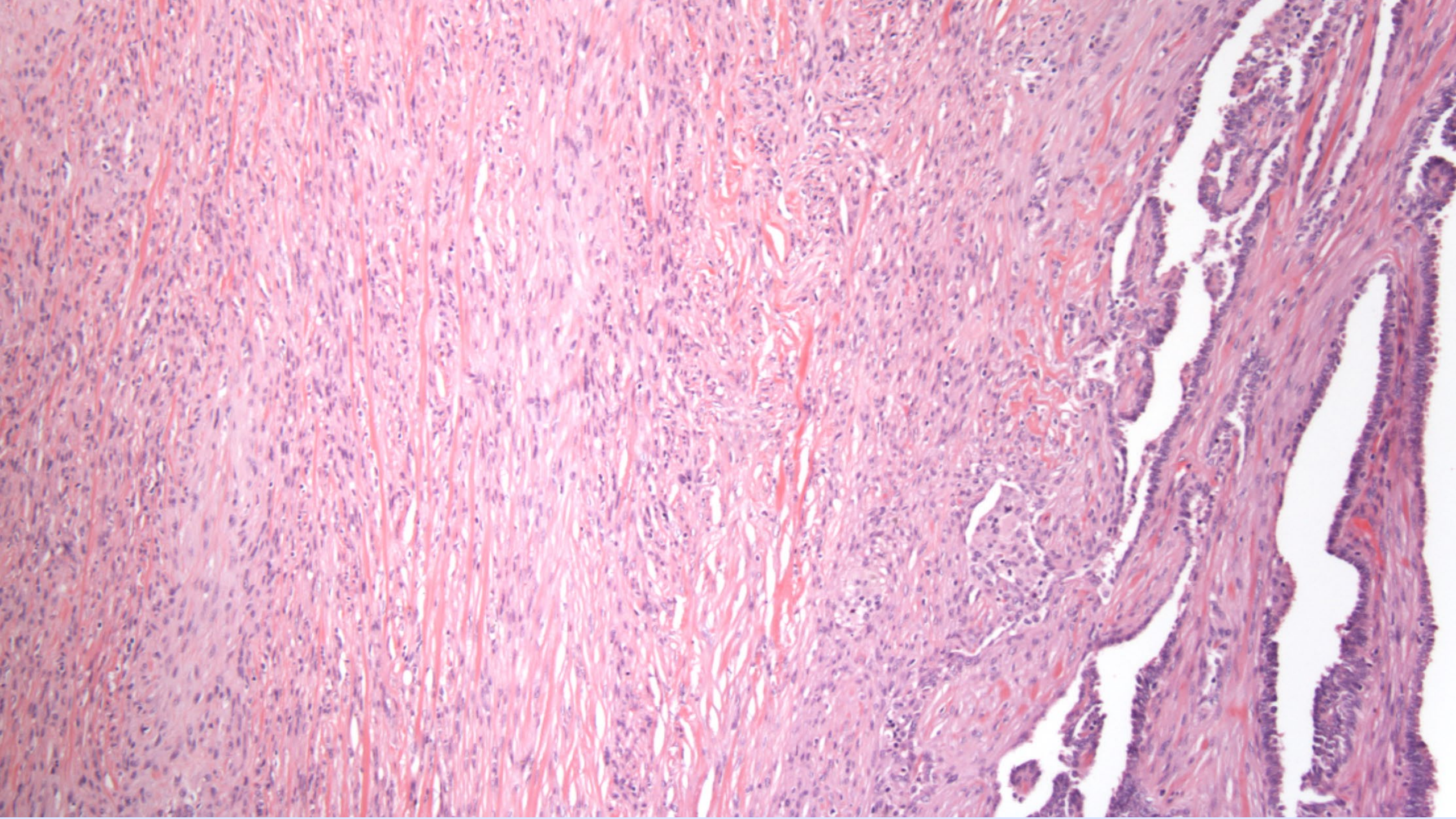
The patient is a 73-year-old woman who was found to have a neck mass on physical examination.

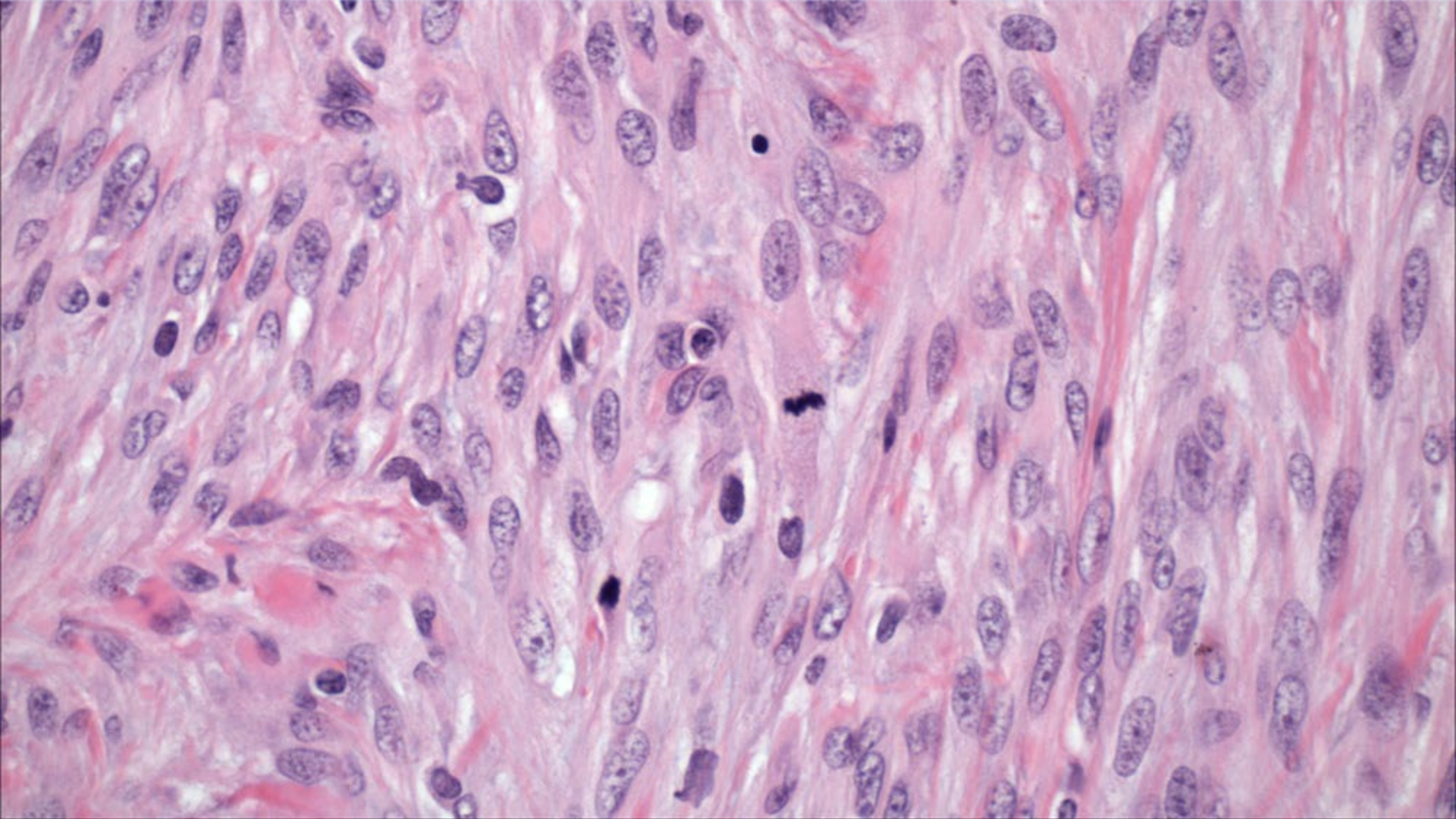
Ultrasound revealed a 4 cm mass.

An FNA was performed and was read as positive for papillary thyroid carcinoma.

A total thyroidectomy was performed.







Diagnosis

Anaplastic thyroid carcinoma arising in a background papillary thyroid carcinoma, see NOTE.

NOTE: The anaplastic component comprised <5% of the tumor.

Anaplastic Thyroid Carcinoma

Although there is variation in the microscopic appearance of ATC.
Most ATC are:

1. Spindle cell
2. Pleomorphic giant cell
3. Epithelioid
4. Squamoid

<u>Characteristic features:</u>

- Marked pleomorphism
- High proliferative rate
- Infiltrative growth
    + extensive extrathyroidal extension
    + extensive vascular invasion

ATC - Immunohistochemistry

Keratin positivity is seen in ~80% of ATCs.

PAX8 is positive in roughly 80% of ATCs.

TTF-1 is usually negative with occasional cases that are positive (~10%).

Thyroglobulin is negative in ATC.

BRAF V600E present in ~30%.

MIB-1 proliferative index is high (>30%).

P53 accumulation by IHC in ~70%.

To confirm that the tumor is epithelial and coming from the thyroid: keratins, PAX8 and BRAF V600E.

To confirm progression to ATC: MIB-1, TTF-1 (utilizing TTF-1 to see reduced expression compared to the better differentiated component), and p53.

To guide treatment: BRAF V600E and PDL1.

ATC - Pitfalls

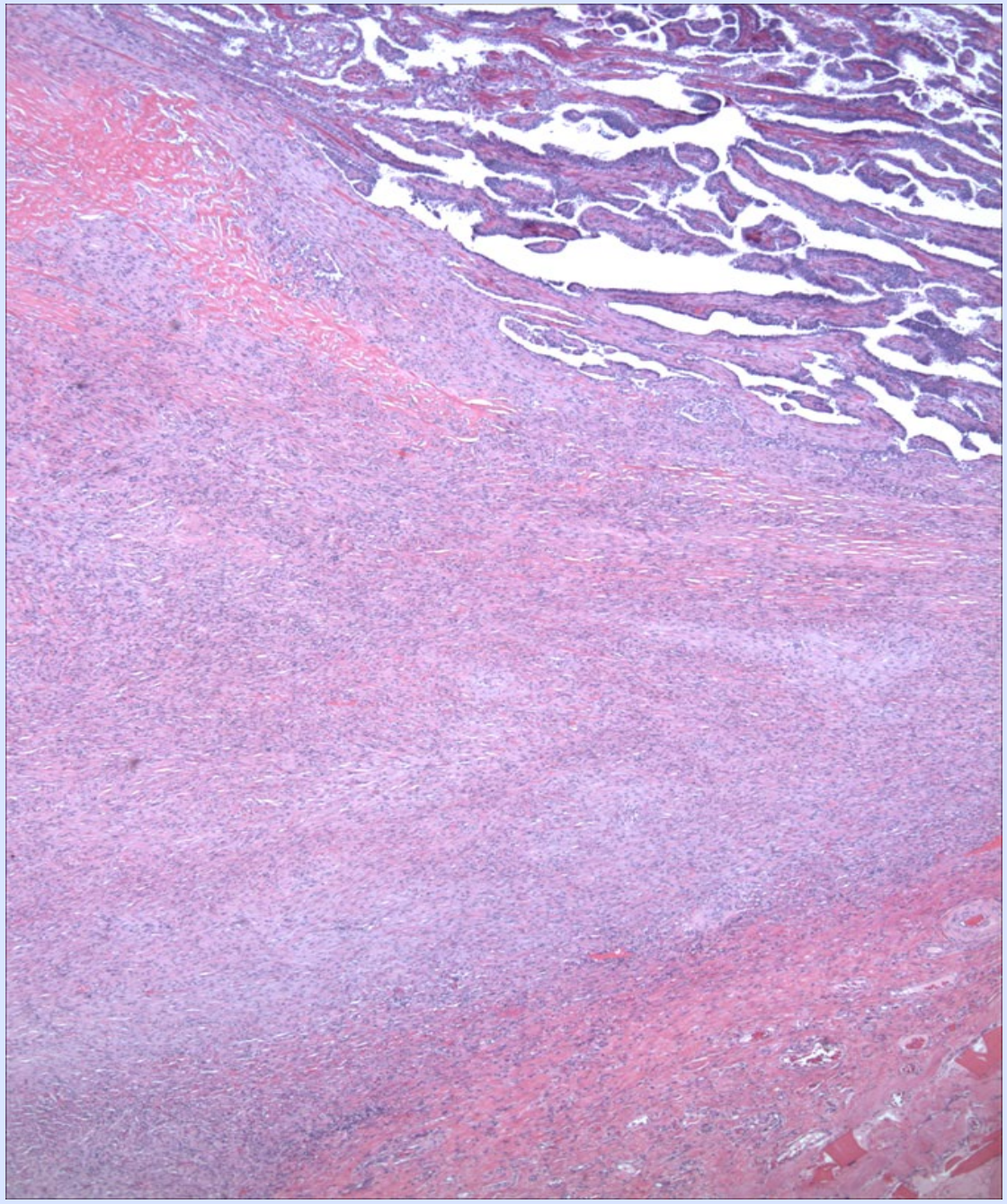
How could the diagnosis of ATC potentially be missed?

When the tumor is large and the ATC component comprises a small percentage of the tumor.

- ATC not suspected clinically
- Easy to miss when reviewing the slides

Make sure areas that you think represent fibrosis, are fibrosis and not spindle cell ATC.

Be especially vigilant when looking at aggressive tumors like tall cell and hobnail subtype.

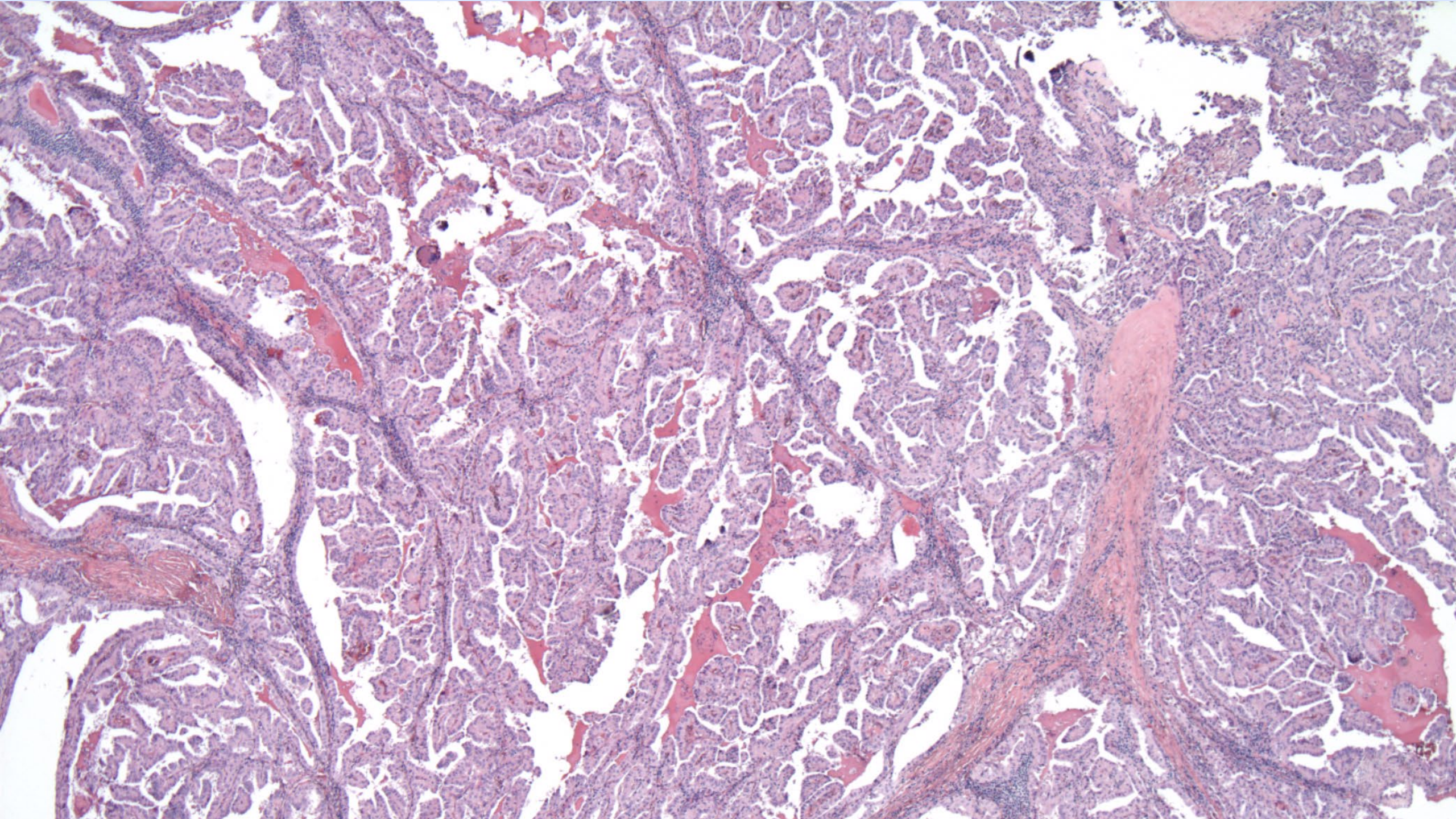


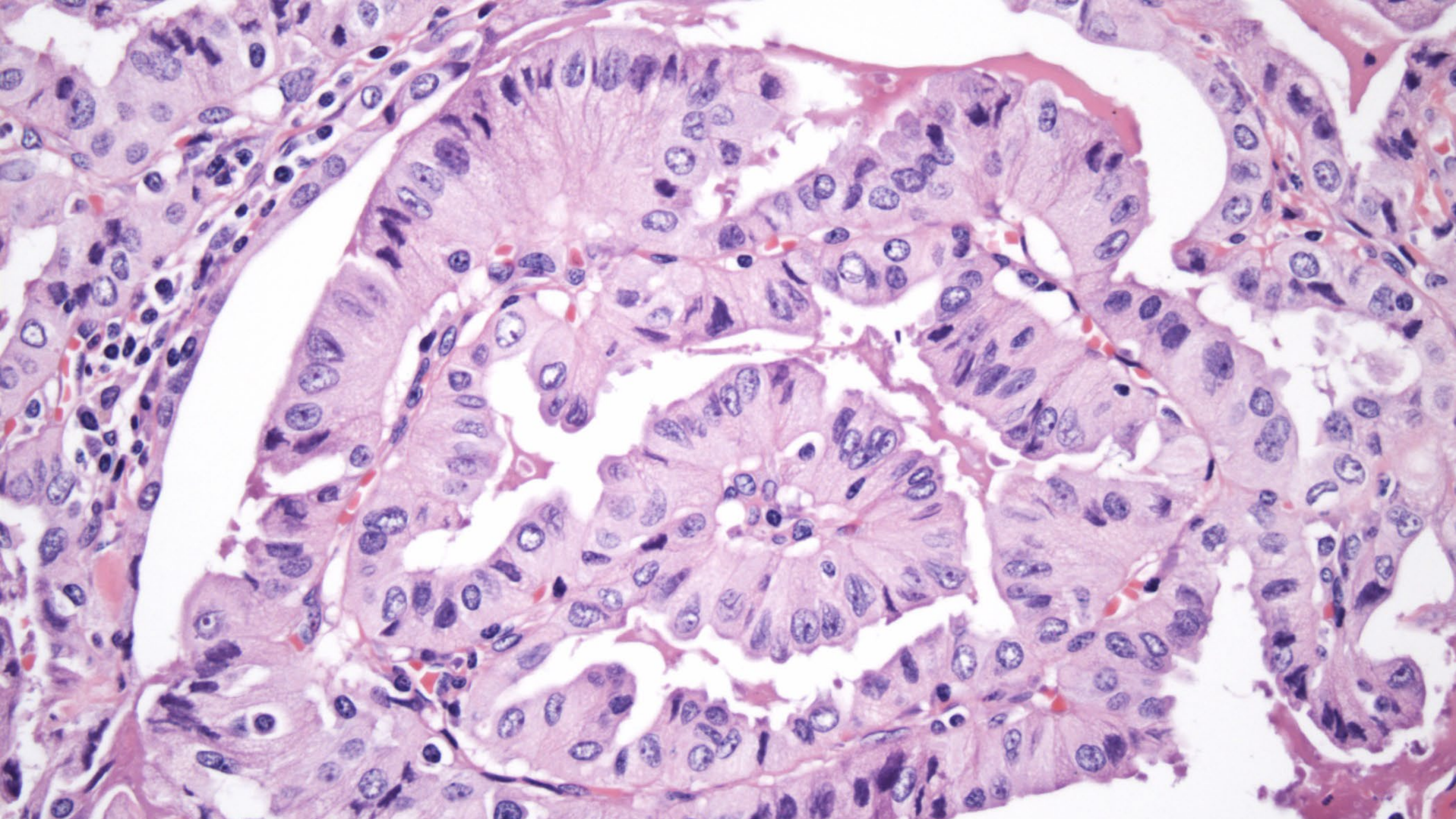
A similar scenario

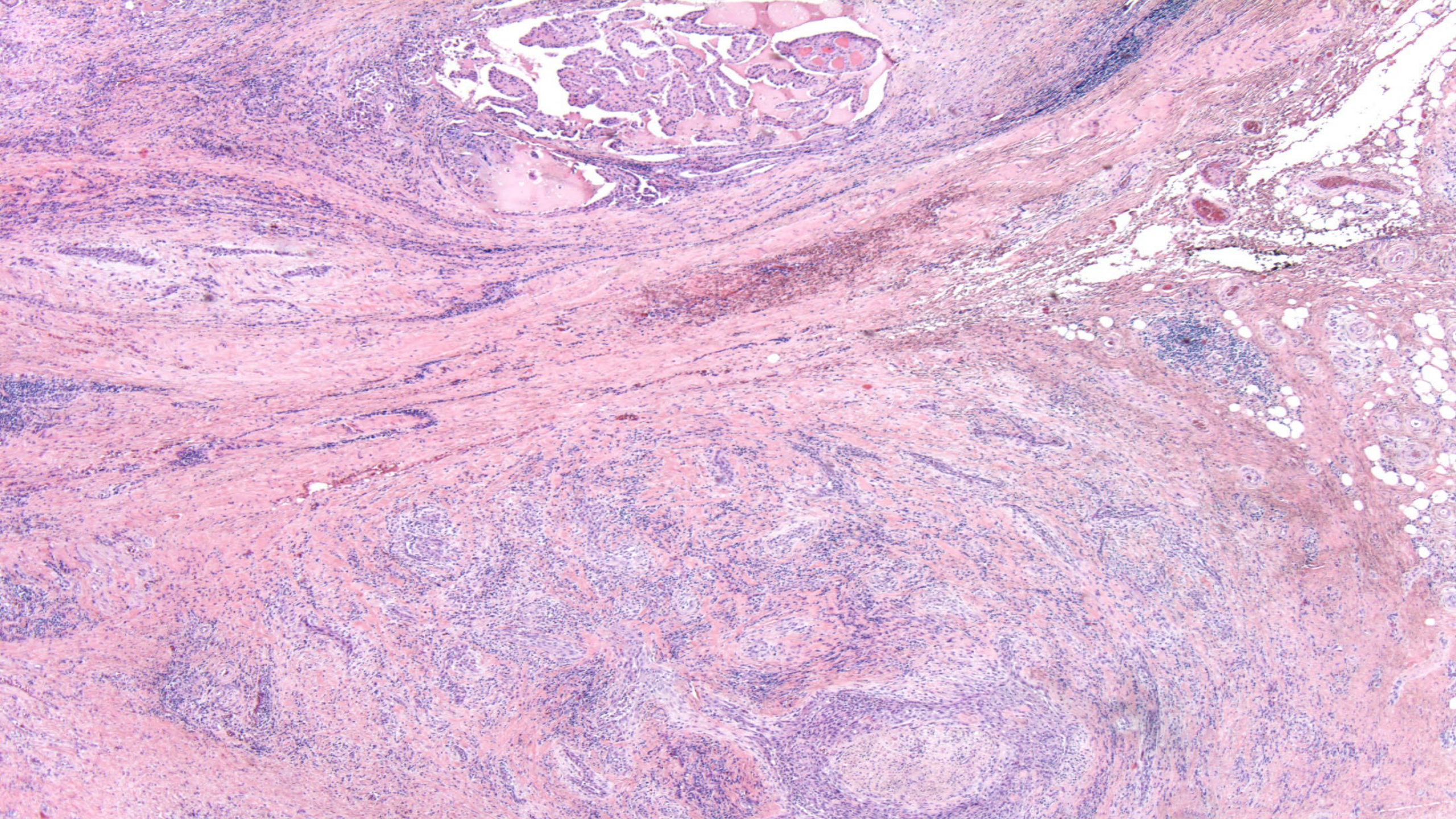
The patient is a 65-year-old woman who was found to have a neck mass by physical examination.

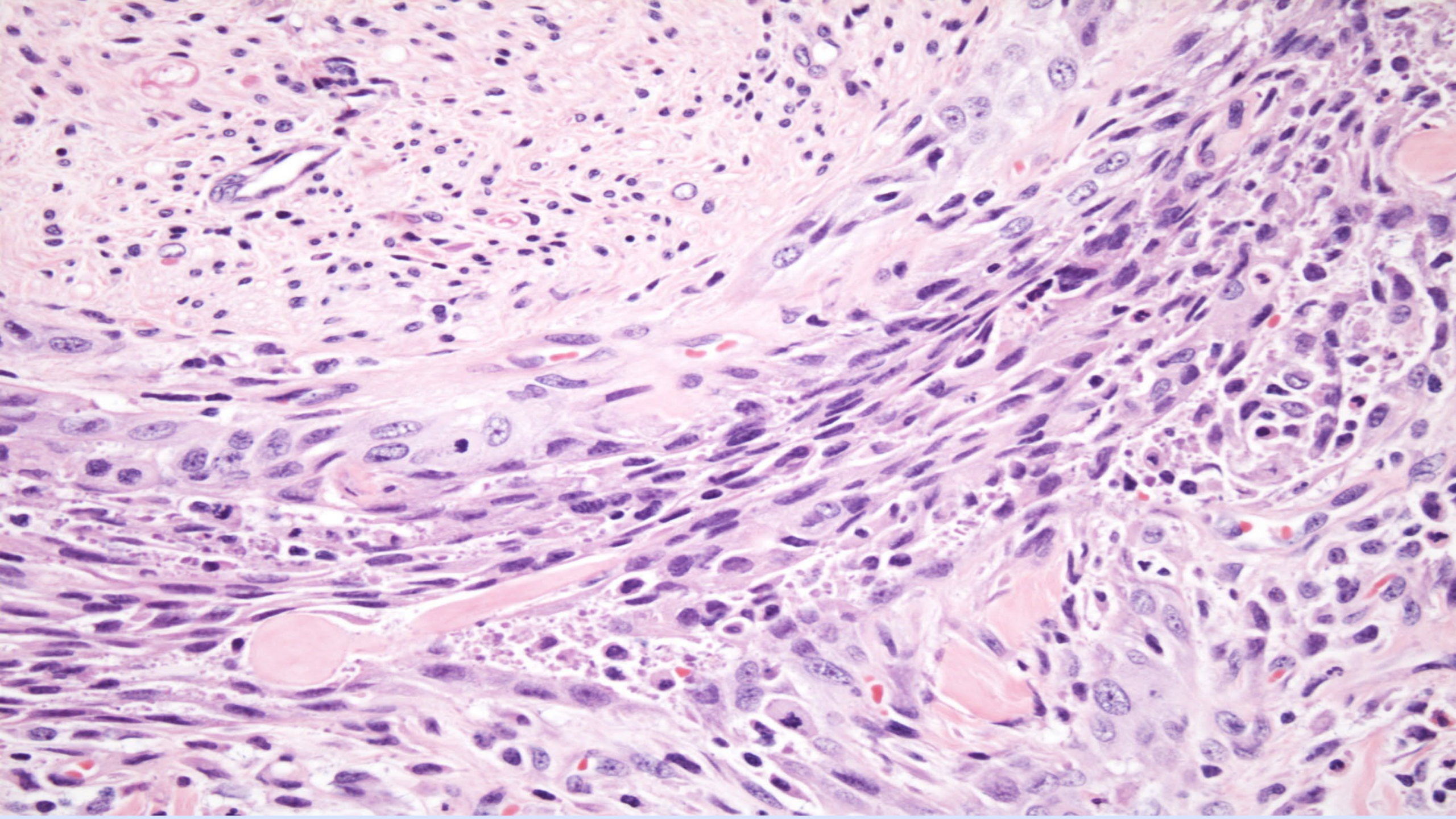
Ultrasound revealed a 3.2 cm mass.

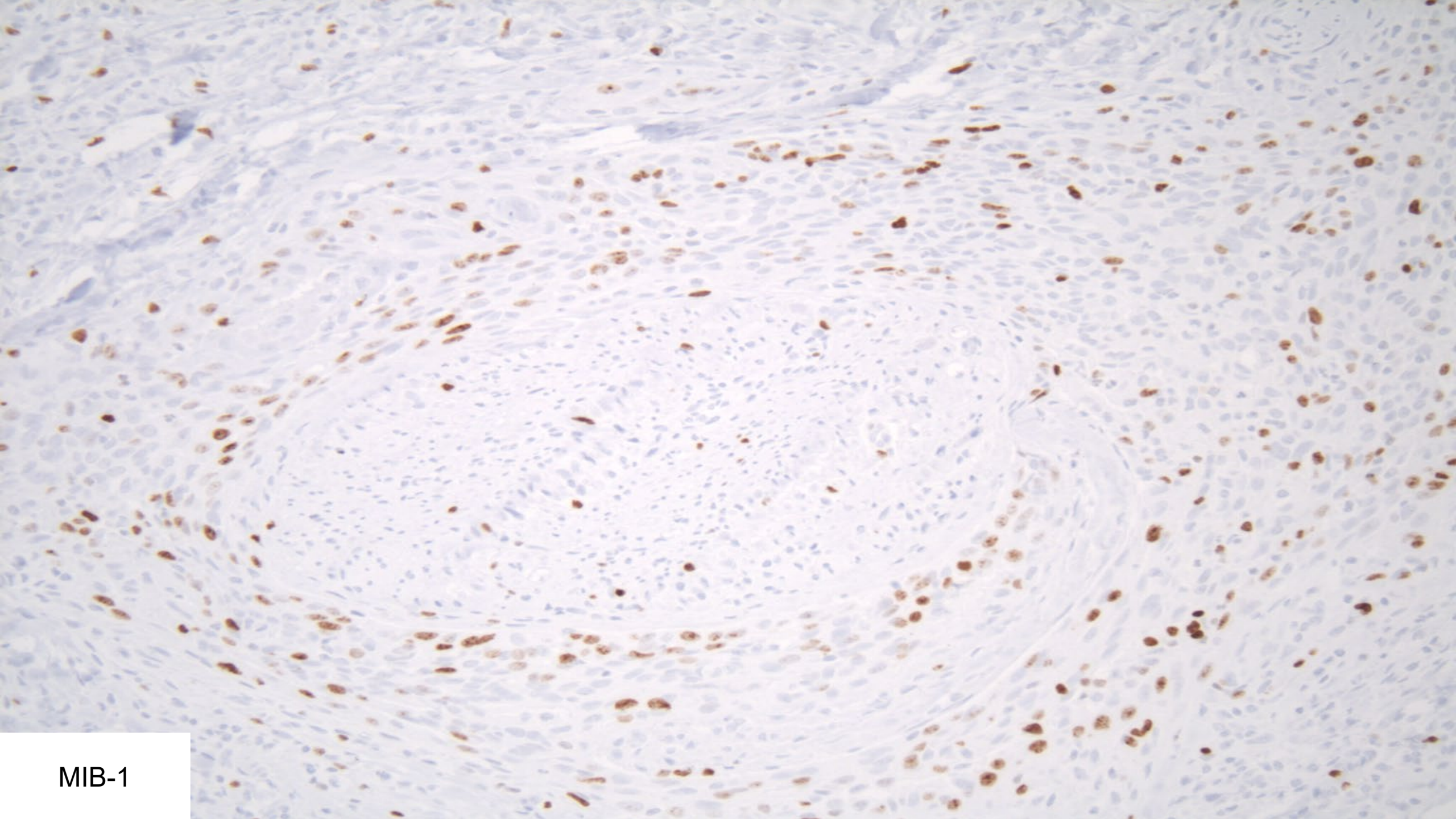
An FNA was performed and was read as positive for papillary thyroid carcinoma.

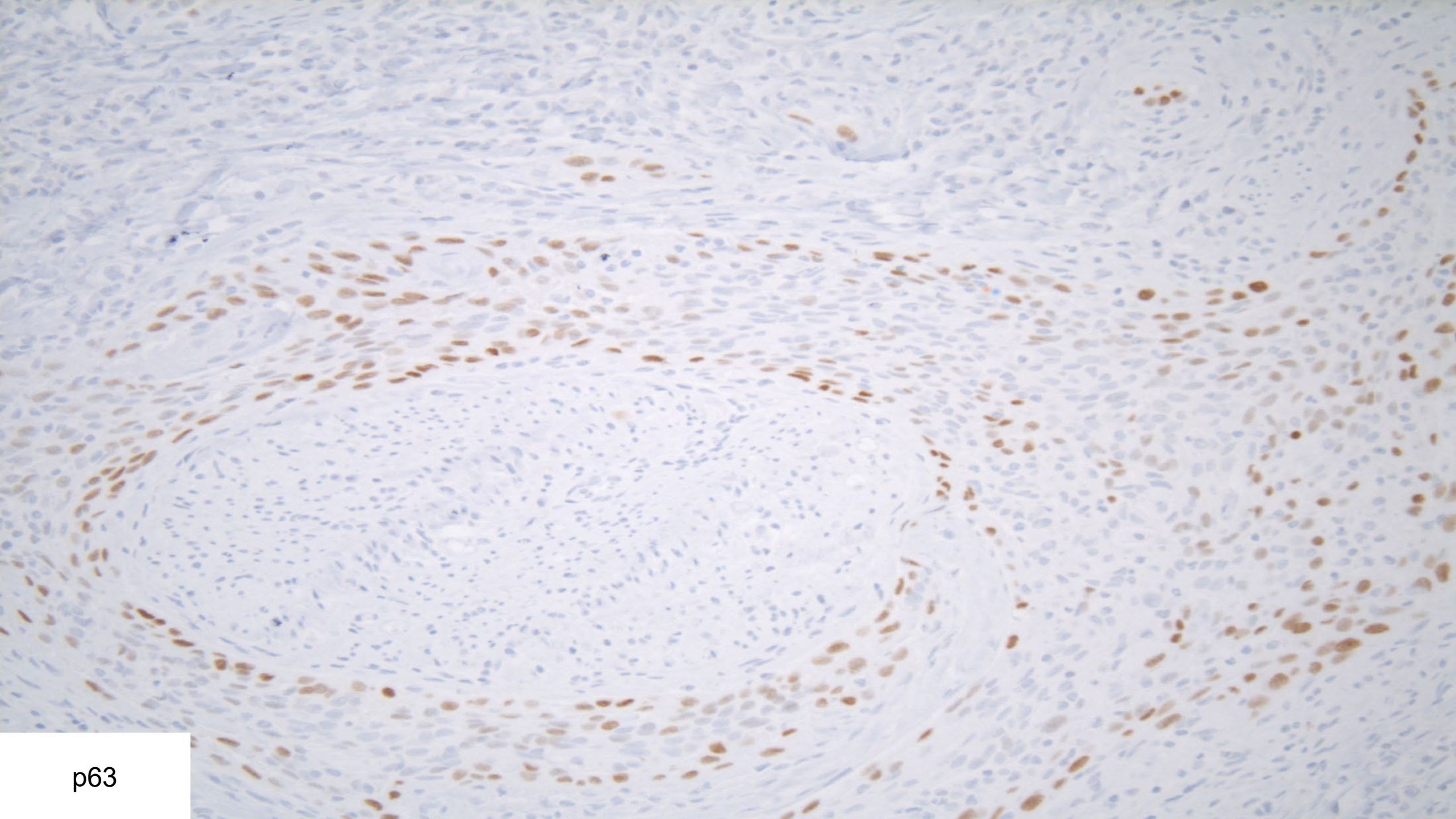









MIB-1


p63

Diagnosis

Anaplastic thyroid carcinoma (spindle cell squamous type) arising in a background of tall cell subtype of PTC, see NOTE.

NOTE: The anaplastic component comprises 5% of the tumor.

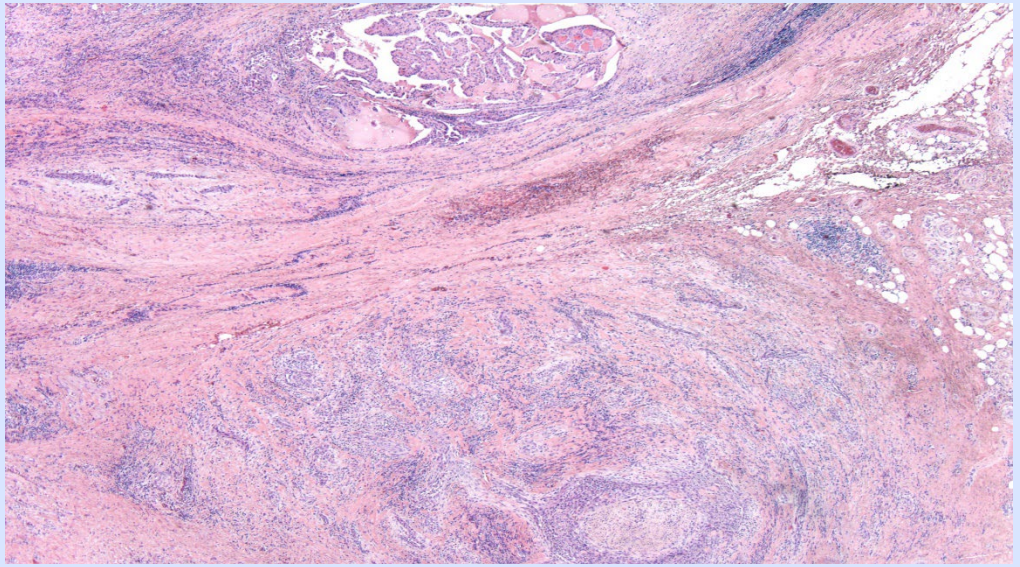
Spindle Cell Squamous ATC

Spindle cell squamous cell ATC is often associated with tall cell subtype.

The Variable Presentations of Anaplastic Spindle Cell Squamous Carcinoma Associated with Tall Cell Variant of Papillary Thyroid Carcinoma

THYROID
Volume 21, Number 5, 2011

Pallavi P. Gopal,[1] Kathleen T. Montone,[1] Zubair Baloch,[1] Madalina Tuluc,[2] and Virginia LiVolsi[1]



When looking at a tall cell or other aggressive PTC always look at the periphery of the tumor for dedifferentiation.

Make sure that any squamous metaplasia isn't mitotically active, infiltrative, etc.

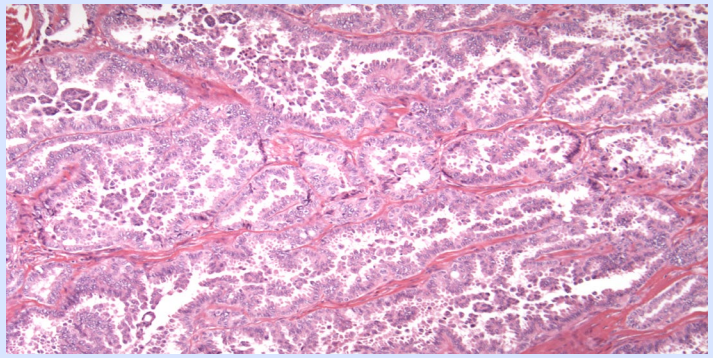
Make sure that nuclear features of PTC are maintained at the periphery of the tumor.

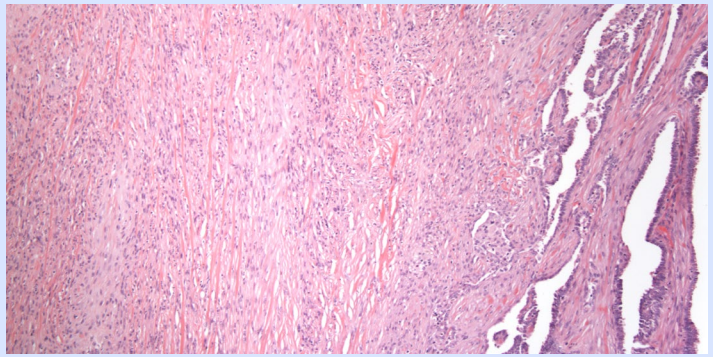
Notice mitotic activity.

What is the prognosis for patients with tumors with a small anaplastic component?

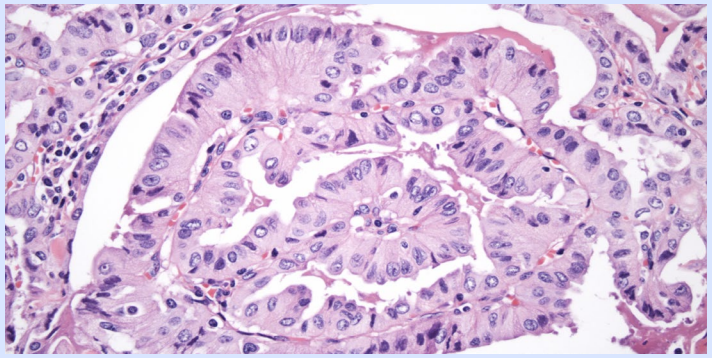
Course is highly variable: although some patients with tumors with a small anaplastic component have extended survival (account for the majority of “long-term” survivors), others have rapid disease progression.

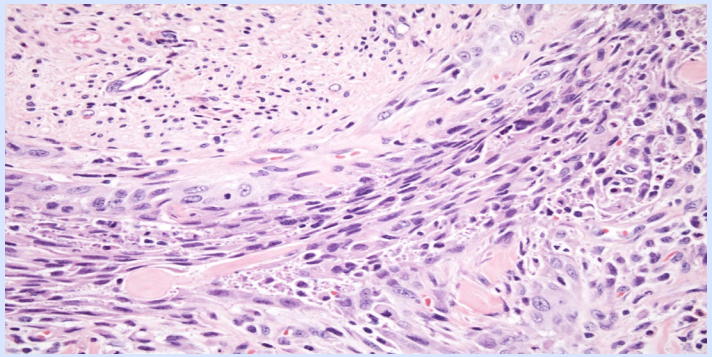
Case 1: patient died in 9 months.





Additional case: patient still alive at last follow up (3 years after dx)





CAP Guidelines on ATC

Indicate that ATC should be characterized as:

- Comprising a major component of the tumor
- Comprising a minor component without extrathyroidal extension

Based on studies showing improved survival for intrathyroidal ATC and on studies demonstrating that patients with intrathyroidal tumors with a minor ATC component have improved survival compared to patients with tumors in which the ATC component comprises the majority of the tumor.

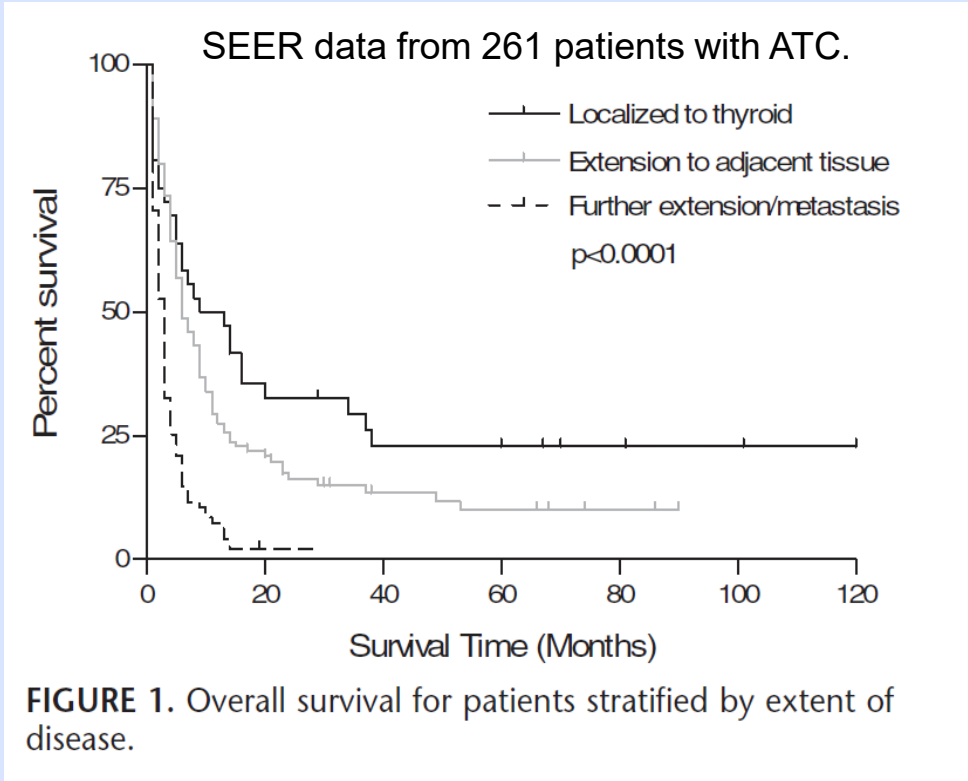


FIGURE 1. Overall survival for patients stratified by extent of disease.

Chen et al, *Am J Clin Oncol*, 2008.

ATC - Pitfalls

How could the diagnosis of ATC potentially be missed?

When the tumor is large and the ATC component comprises a small percentage of the tumor.

- ATC not suspected clinically
- Easy to miss when reviewing the slides

ATC - Pitfalls

How could the diagnosis of ATC potentially be missed?

When the tumor is large and the ATC component comprises a small percentage of the tumor.

- ATC not suspected clinically
- Easy to miss when reviewing the slides

When the anaplastic component is present in lymph nodes only (either at the time of the initial thyroidectomy or as recurrent disease).

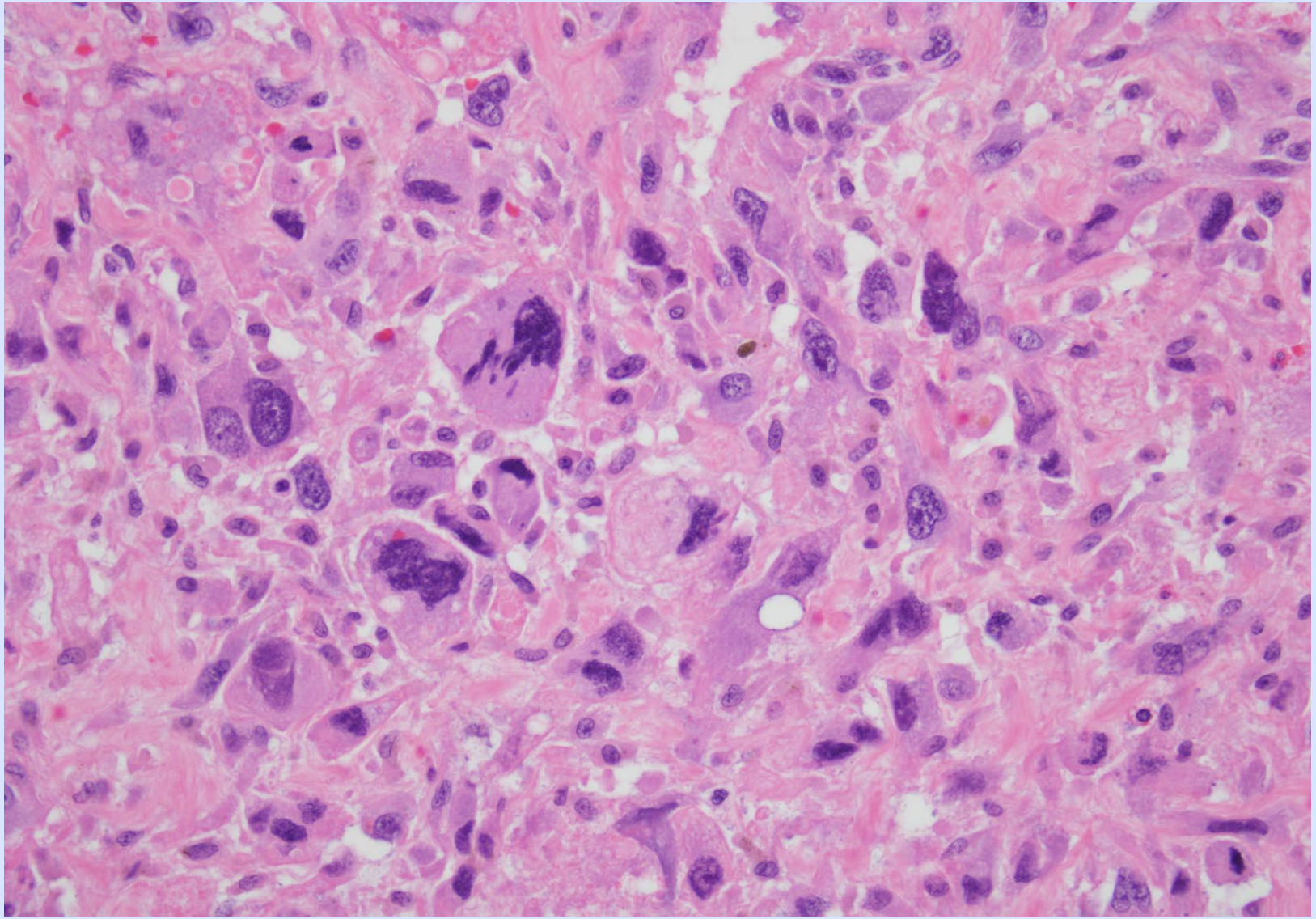
Case

The patient is a 46-year-old woman who has a history of papillary thyroid carcinoma 7 years prior (PTC was multifocal with positive lymph nodes at time of diagnosis) now with recurrence in cervical lymph nodes.

An FNA of one of the lymph nodes was positive for metastatic PTC.

A lymph node dissection was performed removing >20 lymph nodes.

All other lymph nodes showed metastatic PTC, but one showed this. The patient subsequently died of ATC.



Molecular Alterations of Anaplastic Thyroid Carcinoma

Rapid increase in knowledge of the molecular landscape of ATC.

ORIGINAL ARTICLE

Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing

John W. Kunstman[1,2,†], C. Christofer Juhlin[1,6,†], Gerald Goh[3,4,†], Taylor C. Brown[1,2], Adam Stenman[6], James M. Healy[1,2], Jill C. Rubinstein[1,2], Murim Choi[3,4], Nimrod Kiss[6], Carol Nelson-Williams[3,4], Shrikant Mane[3], David L. Rimm[5], Manju L. Prasad[5], Anders Höög[6], Jan Zedenius[7], Catharina Larsson[6], Reju Korah[1,2], Richard P. Lifton[3,4] and Tobias Carling[1,2,*]

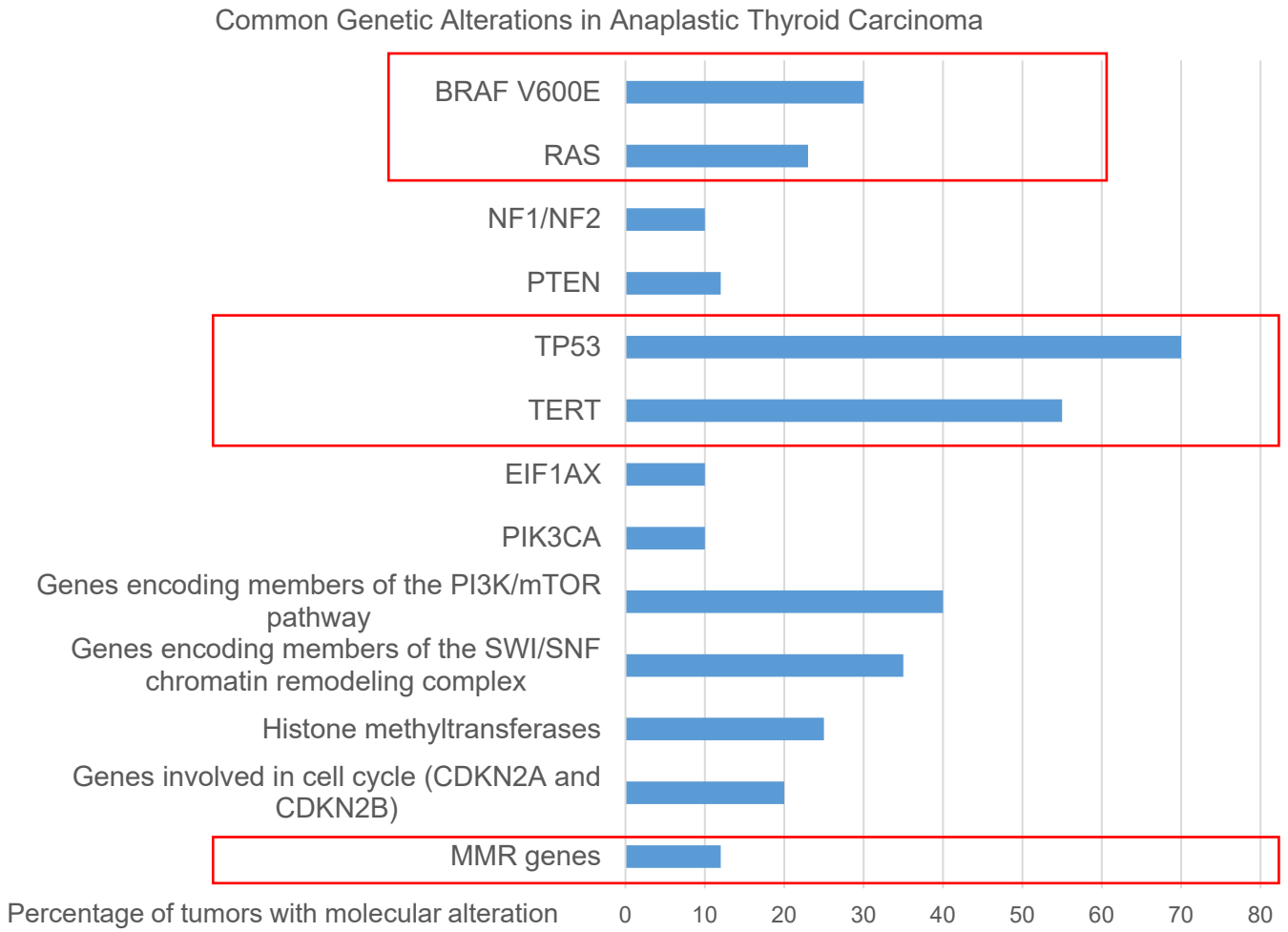
Human Molecular Genetics, 2015, Vol. 24, No. 8 2318–2329

CLINICAL MEDICINE The Journal of Clinical Investigation

Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers

Iñigo Landa,[1] Tihana Ibrahimpasic,[2] Laura Boucai,[3] Rileen Sinha,[4,5] Jeffrey A. Knauf,[1,3] Ronak H. Shah,[1] Snjezana Dogan,[6] Julio C. Ricarte-Filho,[1] Gnana P. Krishnamoorthy,[1] Bin Xu,[6] Nikolaus Schultz,[7,8] Michael F. Berger,[1,6,8] Chris Sander,[4] Barry S. Taylor,[1,7,8] Ronald Ghossein,[6] Ian Ganly,[1,2] and James A. Fagin[1,3]

Volume 126 Number 3 March 2016

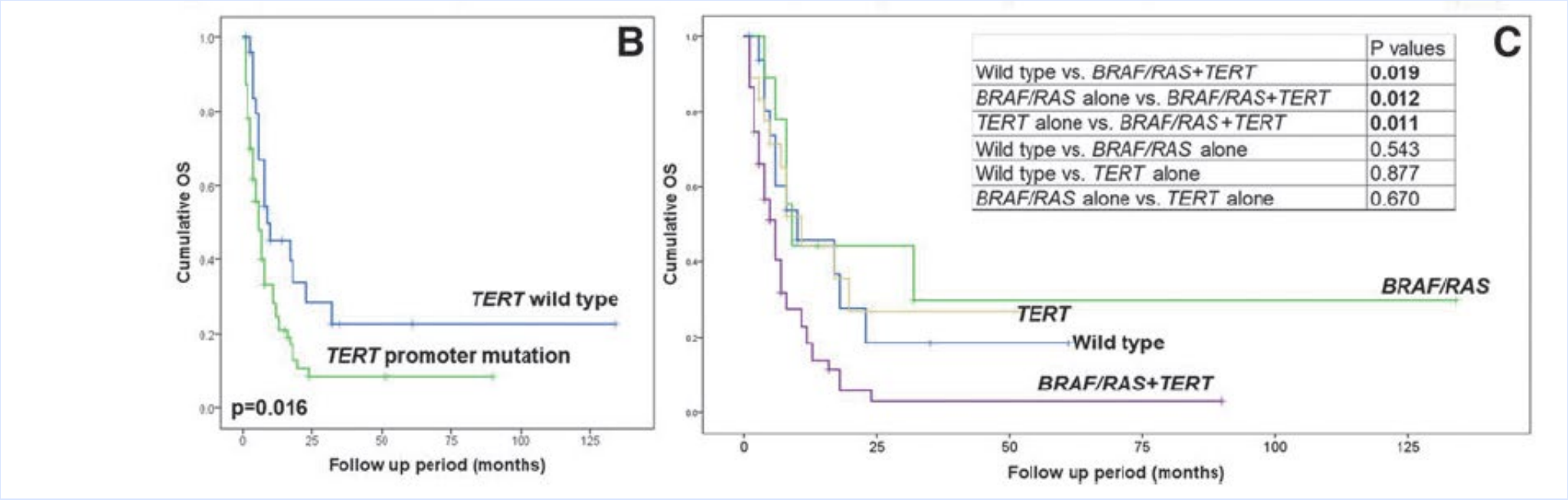


Dissecting Anaplastic Thyroid Carcinoma: A Comprehensive Clinical, Histologic, Immunophenotypic, and Molecular Study of 360 Cases

Bin Xu,[1] Talia Fuchs,[2] Snjezana Dogan,[1] Iñigo Landa,[3] Nora Katabi,[1] James A. Fagin,[3,4] R. Michael Tuttle,[4] Eric Sherman,[4] Anthony J. Gill,[2] and Ronald Ghossein[1]

Thyroid. 2020 Oct;30(10):1505-1517.

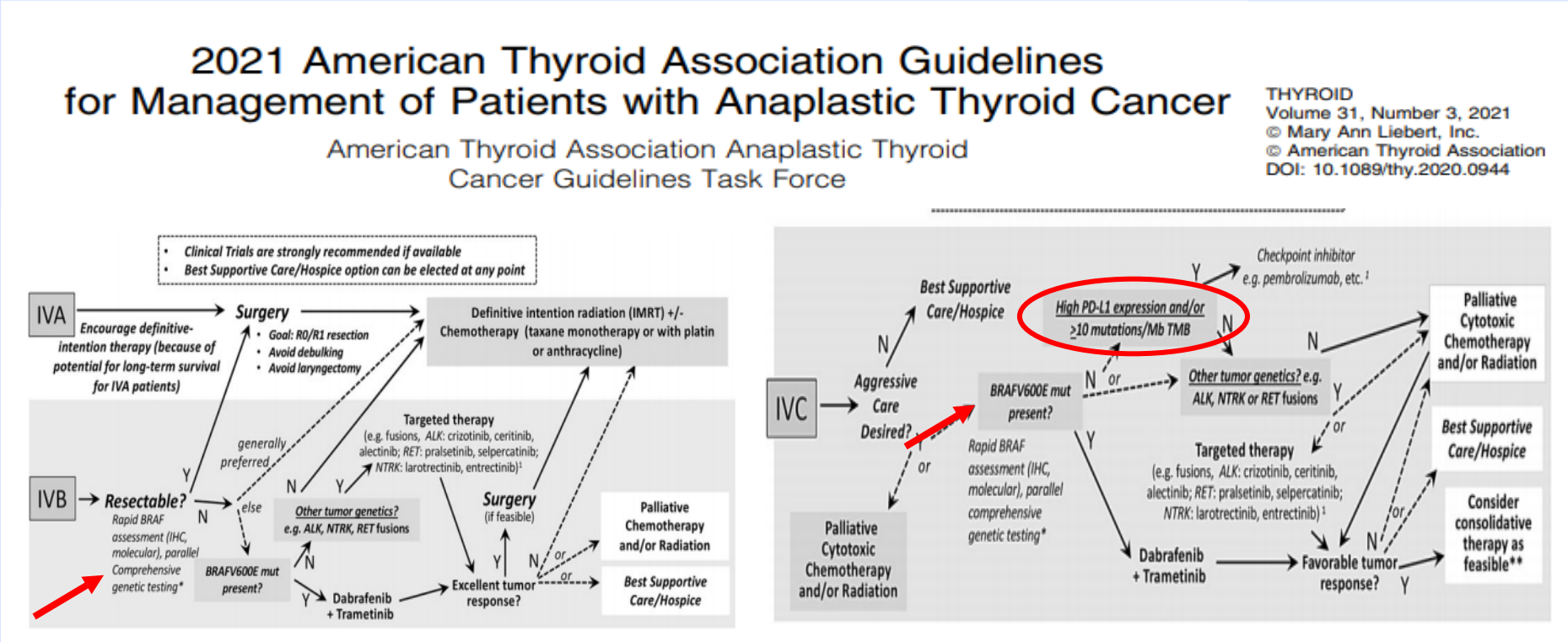
Presence of a *TERT* promoter mutation, especially when combined with a *BRAF* or *RAS* mutation, was associated with a worse survival.



	P values
Wild type vs. *BRAF/RAS+TERT*	**0.019**
BRAF/RAS alone vs. *BRAF/RAS+TERT*	**0.012**
TERT alone vs. *BRAF/RAS+TERT*	**0.011**
Wild type vs. *BRAF/RAS* alone	0.543
Wild type vs. *TERT* alone	0.877
BRAF/RAS alone vs. *TERT* alone	0.670

BRAF V600E Mutant ATC

- In 2018 the FDA approved dabrafenib (BRAF inhibitor) and trametenib (MEK inhibitor) for the treatment of *BRAF* V600E-mutant ATC.



BRAF V600E Mutant ATC

- *BRAF* mutation status can be determined by molecular techniques or by IHC; however, there are also histologic clues to *BRAF* status.

Dissecting Anaplastic Thyroid Carcinoma:
A Comprehensive Clinical, Histologic,
Immunophenotypic, and Molecular Study of 360 Cases

Bin Xu,[1] Talia Fuchs,[2] Snjezana Dogan,[1] Iñigo Landa,[3] Nora Katabi,[1] James A. Fagin,[3,4]
R. Michael Tuttle,[4] Eric Sherman,[4] Anthony J. Gill,[2] and Ronald Ghossein[1]

Thyroid. 2020 Oct;30(10):1505-1517.

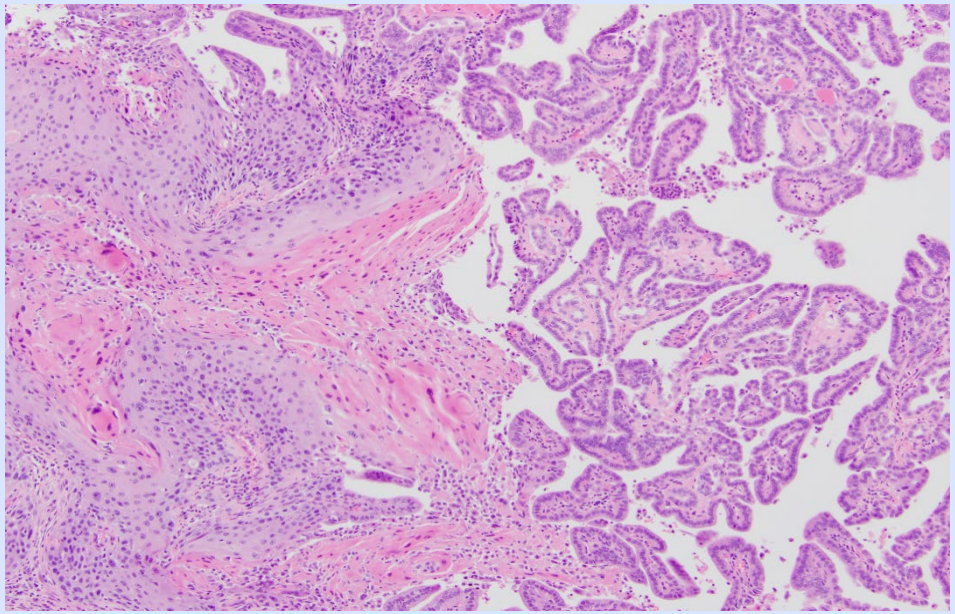
Histopathology

Histopathology 2020, 77, 314–320. DOI: 10.1111/his.14144

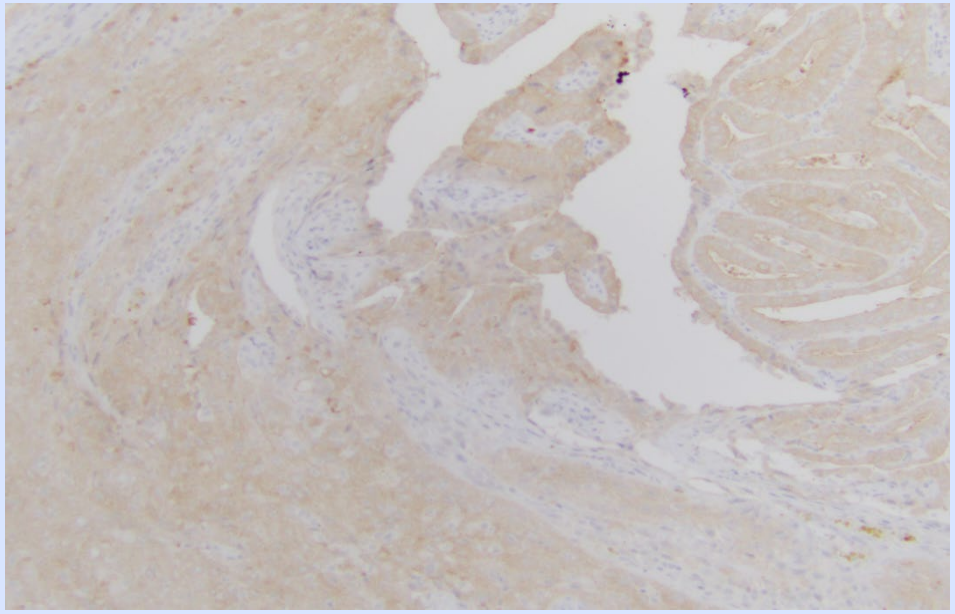
Histological features of *BRAF* V600E-mutant anaplastic thyroid carcinoma

Tiffany Y Chen,[1] Jochen H Lorch,[2] Kristine S Wong[1,*] & Justine A Barletta[1,*]
[1]*Department of Pathology, Brigham and Women's Hospital,Harvard Medical School, Boston, MA, USA, and*
[2]*Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*

BRAF V600E mutant-ATC have a high frequency of associated PTC (or a history of PTC).



Squamoid ATCs (with or without a PTC component) often harbor a *BRAF* V600E mutation.



2022 WHO Classification of Endocrine and Neuroendocrine Tumours

The chapter on primary squamous cell carcinoma of the thyroid has been removed, instead they are considered a type of ATC. Based on:

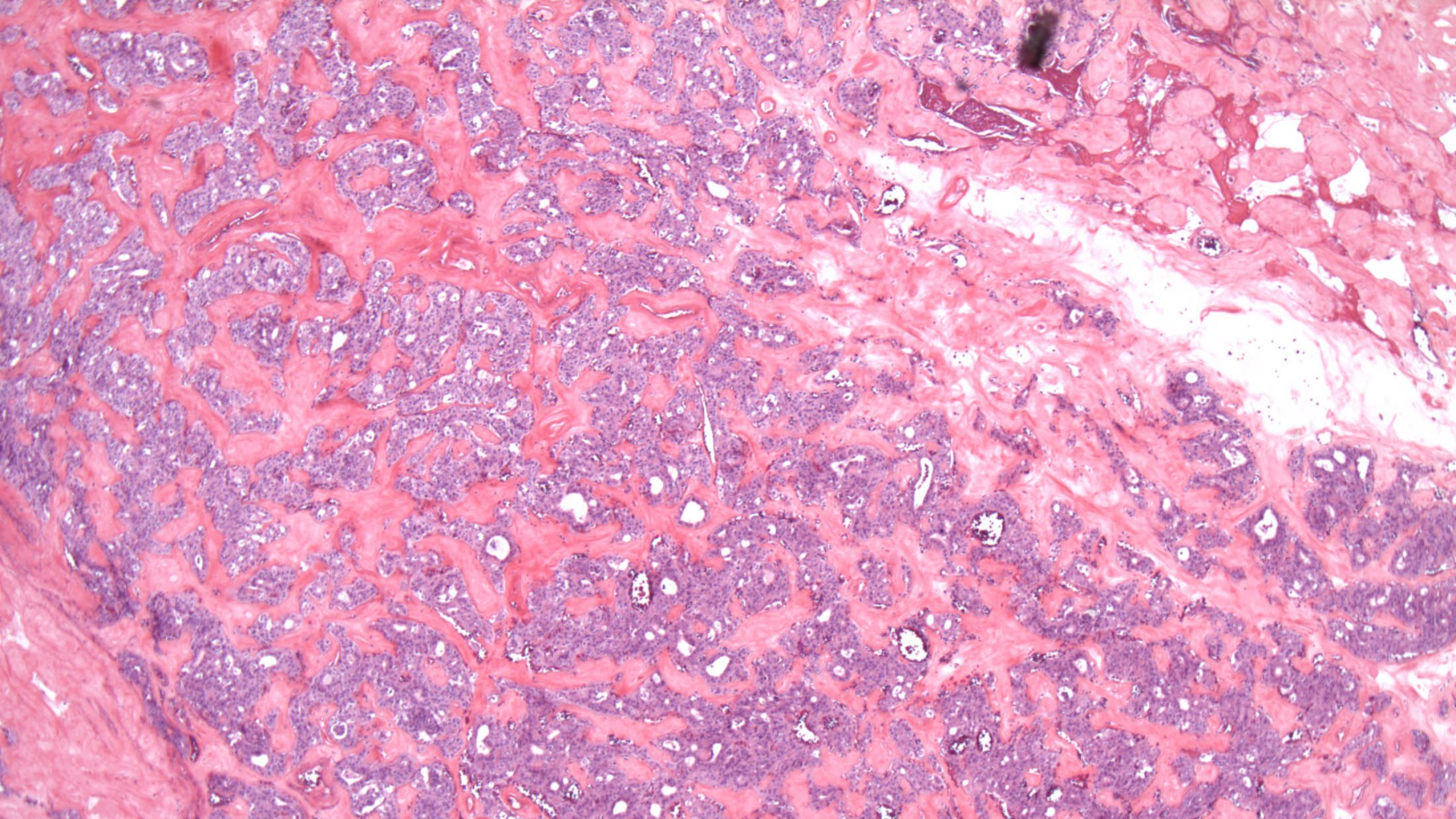
- High rate of PAX8 expression
- High rate of *BRAF* V600E mutation
- Similar clinical behavior

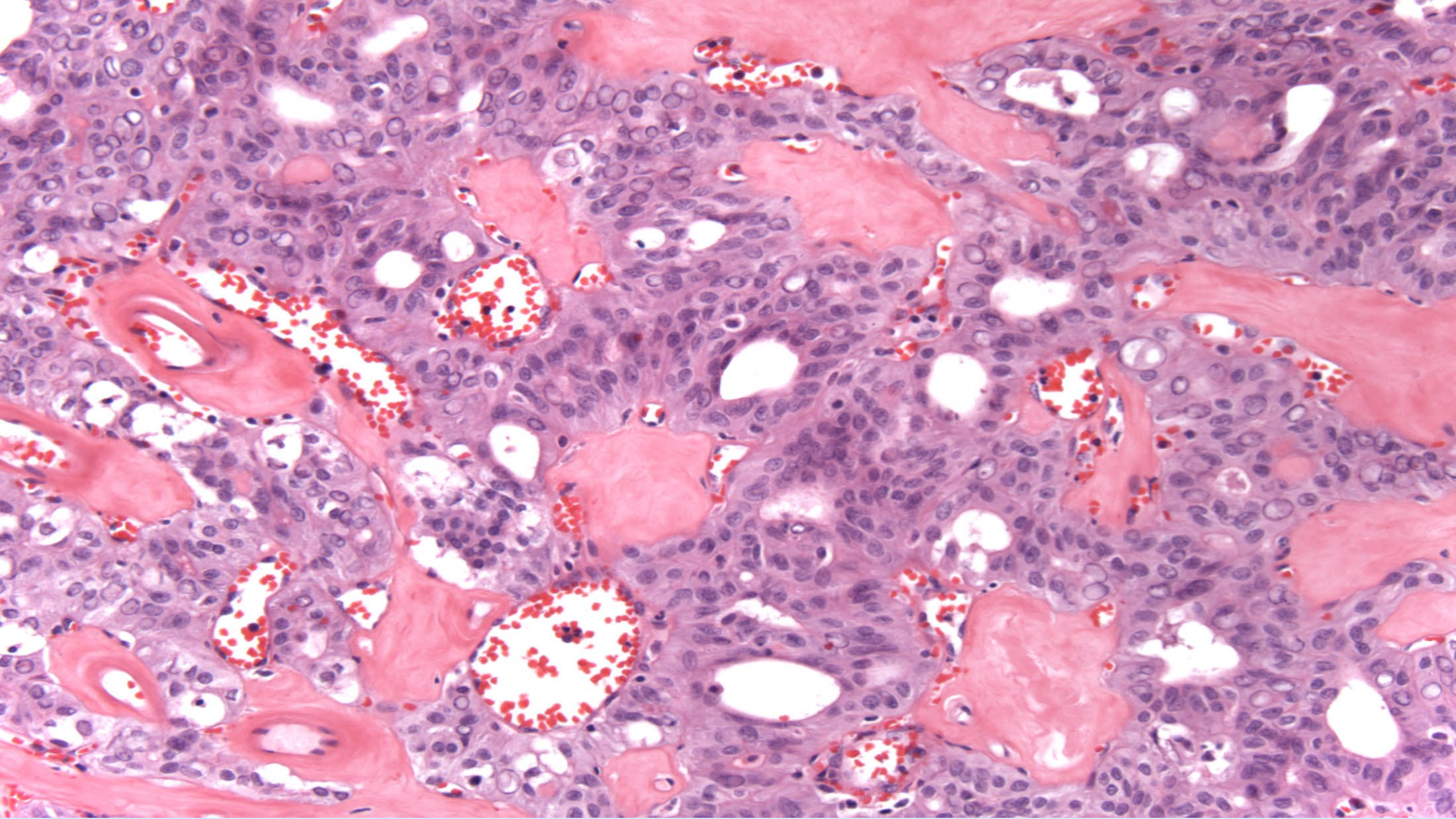
Case

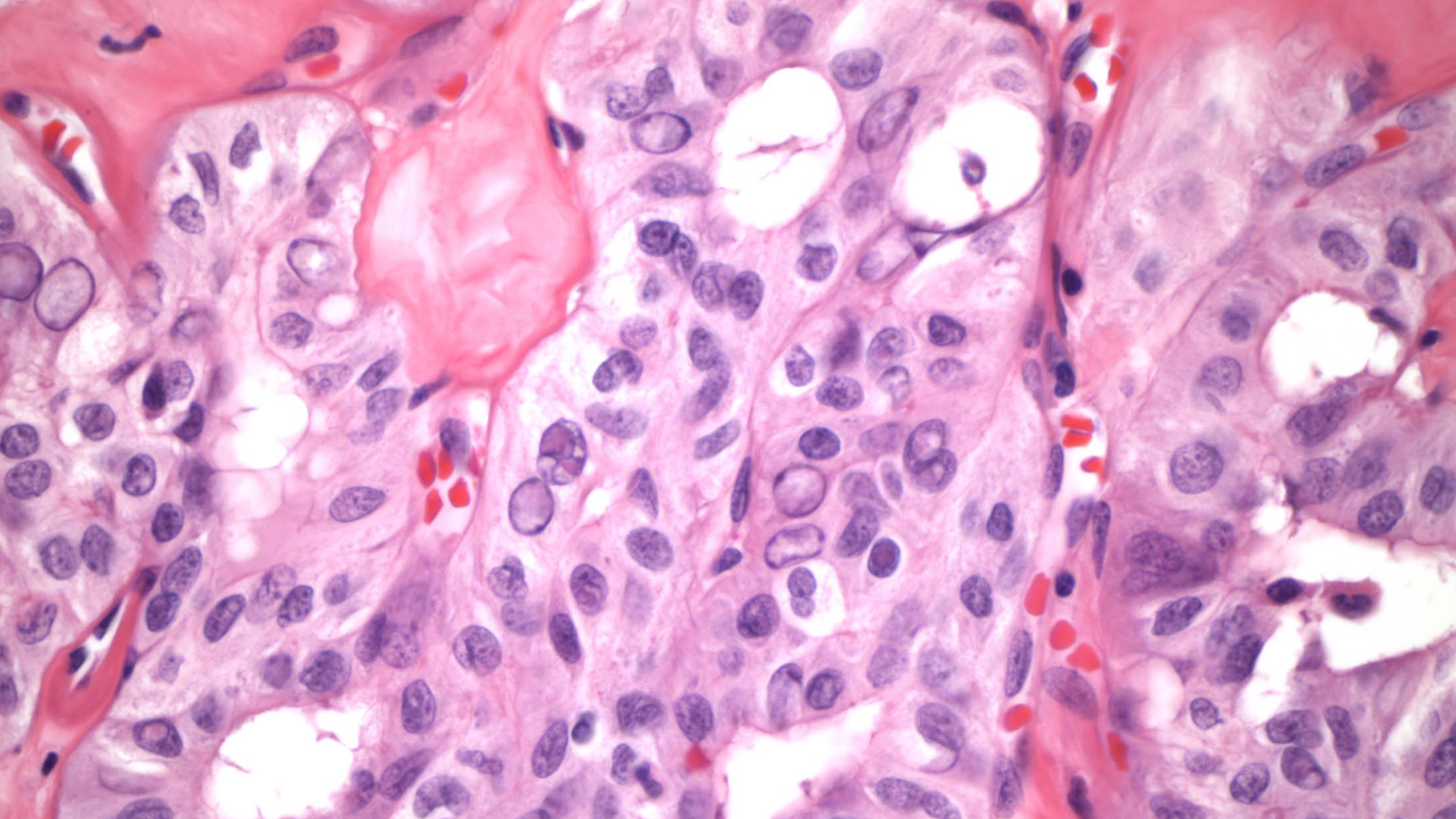
The patient is a 35-year-old woman who was noted to have thyroid enlargement about half a decade ago. She was diagnosed with Hashimoto thyroiditis.

A recent ultrasound revealed a 3.0 cm left-sided nodule.

An FNA was performed that was read as consistent with papillary thyroid carcinoma.







Cribriform Morular Thyroid Carcinoma

~50% of cribriform morular thyroid carcinoma are associated with familial adenomatous polyposis (FAP); therefore, its identification should raise the possibility of this familial tumor syndrome.

In the series by Ito and colleagues, the diagnosis of cribriform morular thyroid carcinoma was the first detected manifestation of FAP in ~40% of the cohort (Ito et al, Endocr J, 2011).

Cases of cribriform morular thyroid carcinoma that are associated with FAP are usually multifocal and occur at an earlier age than sporadic cases.

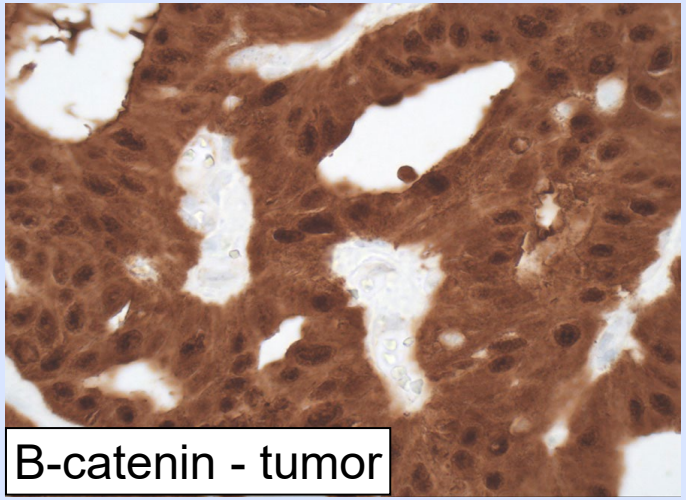
Rare sporadic cases can be aggressive and show high-grade features.

Cribriform Morular Thyroid Carcinoma

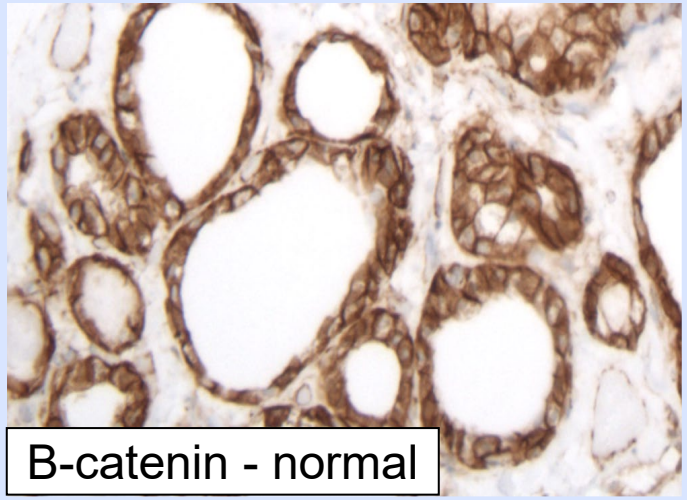
When cribriform morular thyroid carcinoma is associated with FAP, a germline adenomatous polyposis coli (*APC*) gene mutation is almost always detected.

Sporadic cases may have somatic *APC* gene mutations or another mutation in the pathway (such as *CTNNB1* or *AXIN1* mutations).

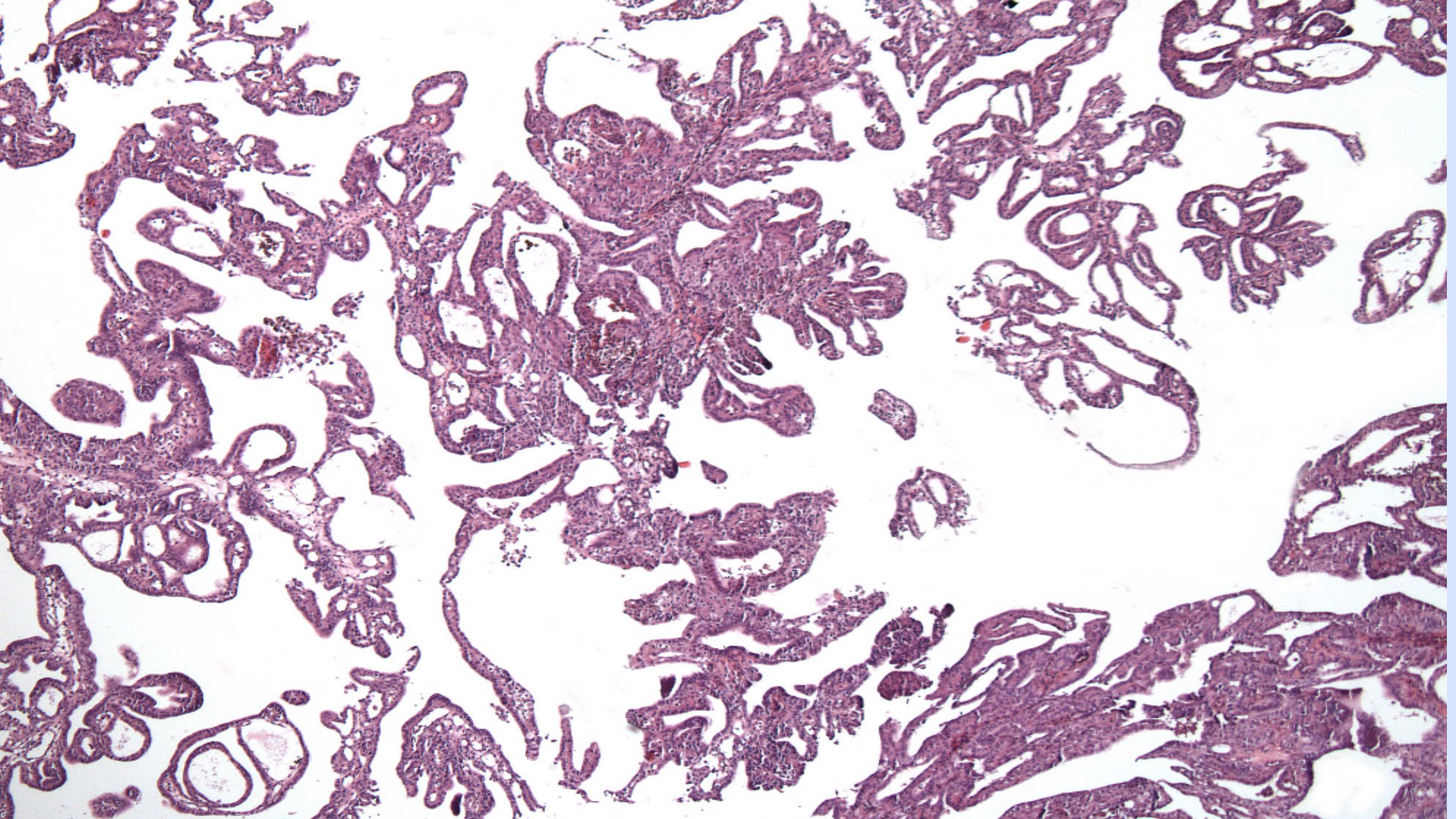
IHC for B-catenin can be used to confirm the diagnosis.

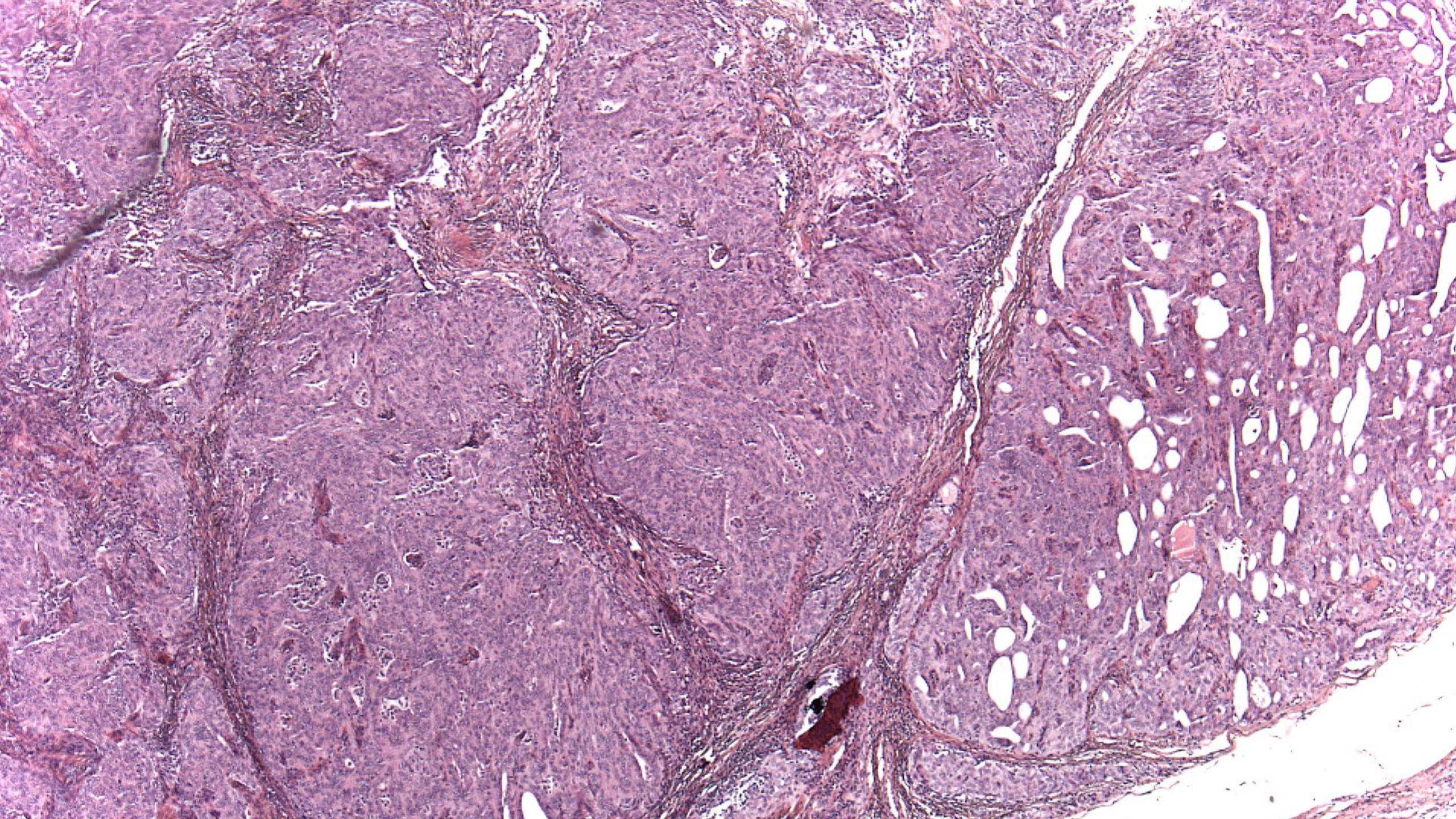


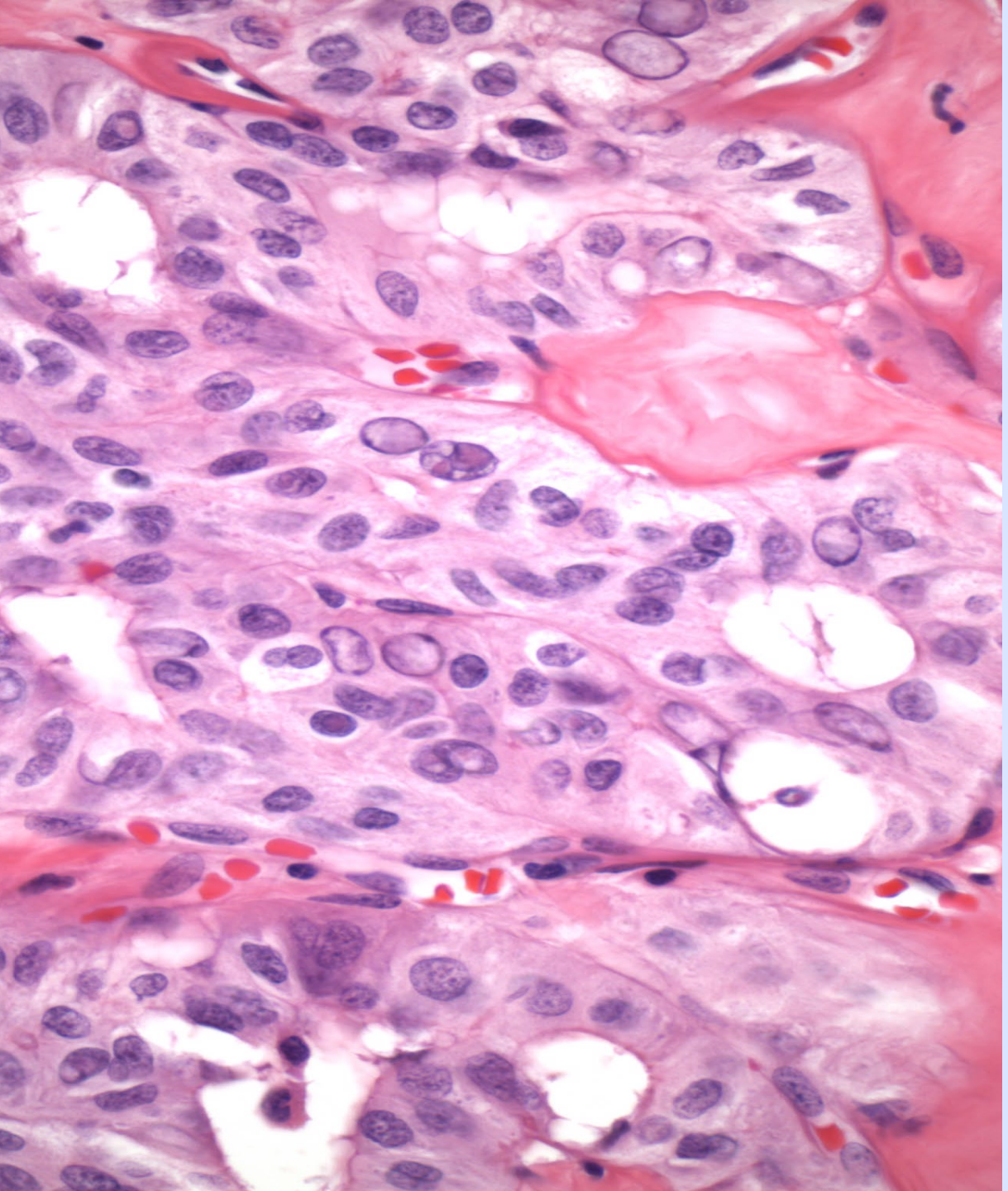
B-catenin - tumor

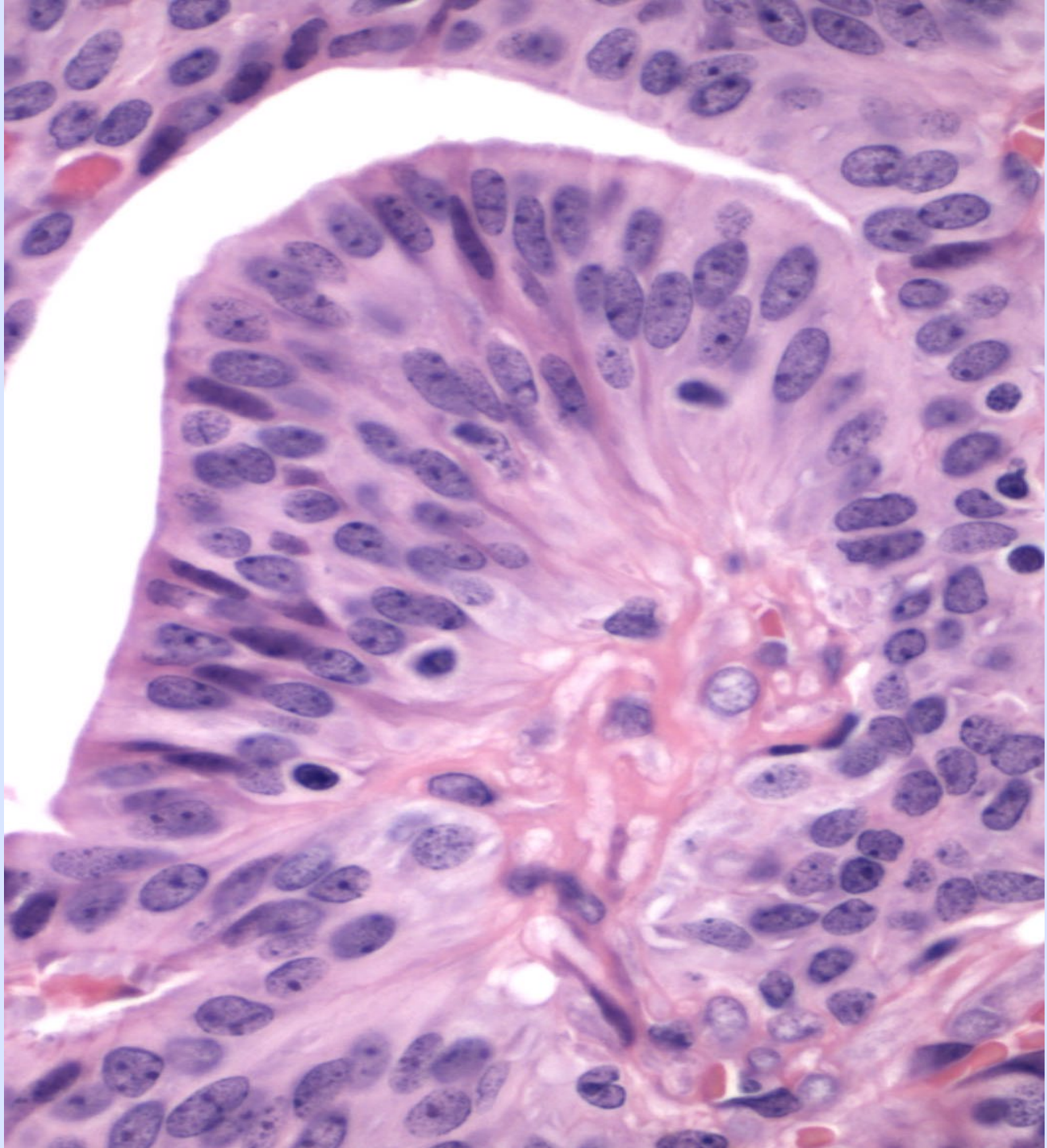


B-catenin - normal









Cribriform Morular Thyroid Carcinoma

Endocrine Pathology (2021) 32:327–335
https://doi.org/10.1007/s12022-021-09683-0

Check for updates

Cribriform-Morular Thyroid Carcinoma Is a Distinct Thyroid Malignancy of Uncertain Cytogenesis

Baris Boyraz[1] · Peter M. Sadow[1] · Sylvia L. Asa[2] · Dora Dias-Santagata[1] · Vania Nosé[1] · Ozgur Mete[3,4,5]

Tumors were positive for TTF1; however, PAX8 immunoreactivity was weak, focal or negative, and all tumors lacked thyroglobulin reactivity.

Cribriform Morular Thyroid Carcinoma

Endocrine Pathology (2021) 32:327–335
https://doi.org/10.1007/s12022-021-09683-0

Check for updates

Cribriform-Morular Thyroid Carcinoma Is a Distinct Thyroid Malignancy of Uncertain Cytogenesis

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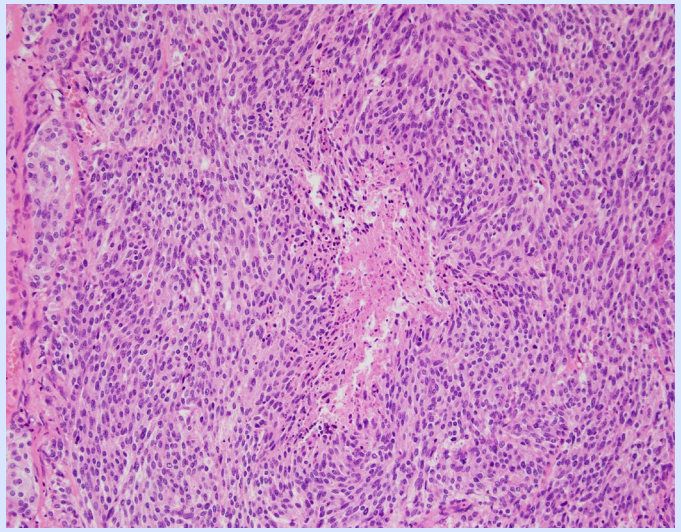
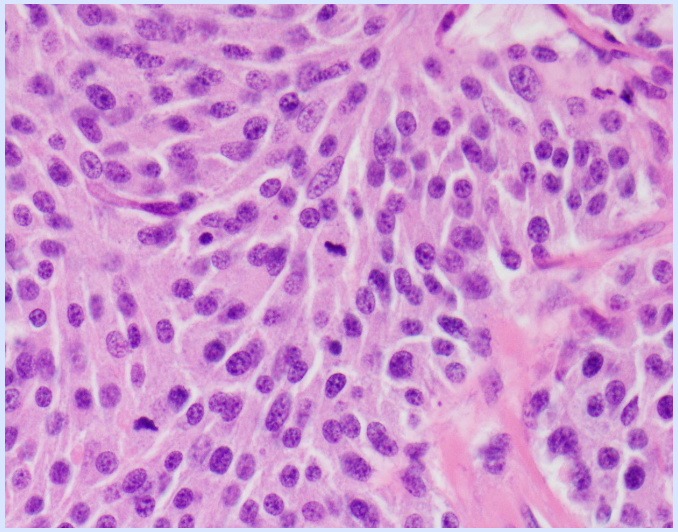
In the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours, cribriform morular thyroid carcinoma was taken out of the PTC chapter and is in a section for tumors of uncertain histogenesis.

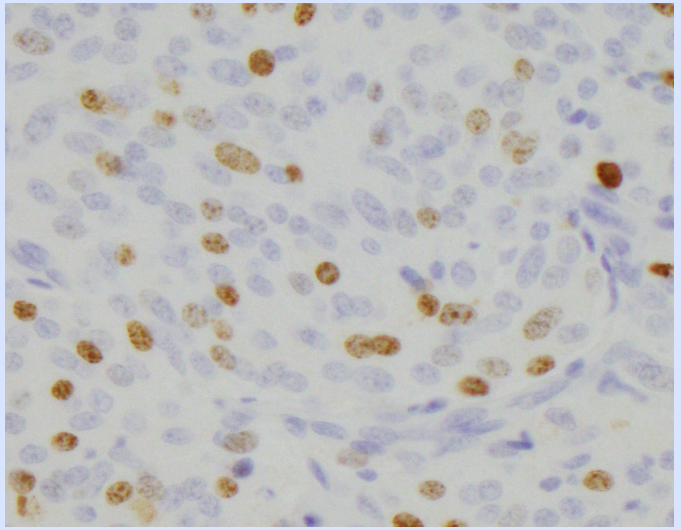
Case

The patient is a 55-year-old woman with 4.4 cm medullary thyroid carcinoma (MTC) with gross extrathyroidal extension (pT3b) and multiple lymph node metastases (N1b).

Tumor necrosis was present, mitoses numbered 8 per 10 HPF, and the Ki-67 proliferative index was 13%.







Medullary Thyroid Carcinoma (MTC)

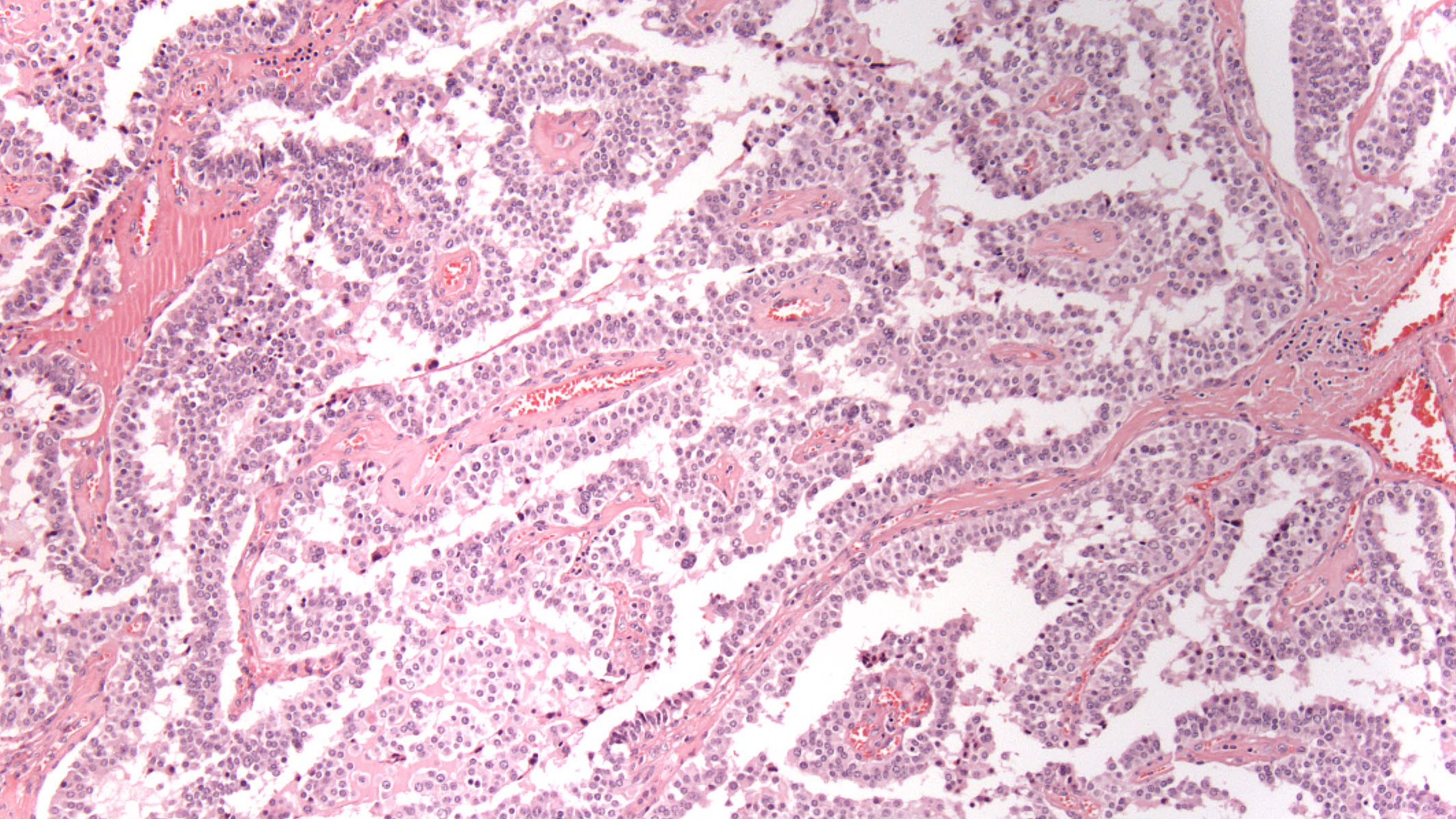
MTC can exhibit a broad range of histologic features.

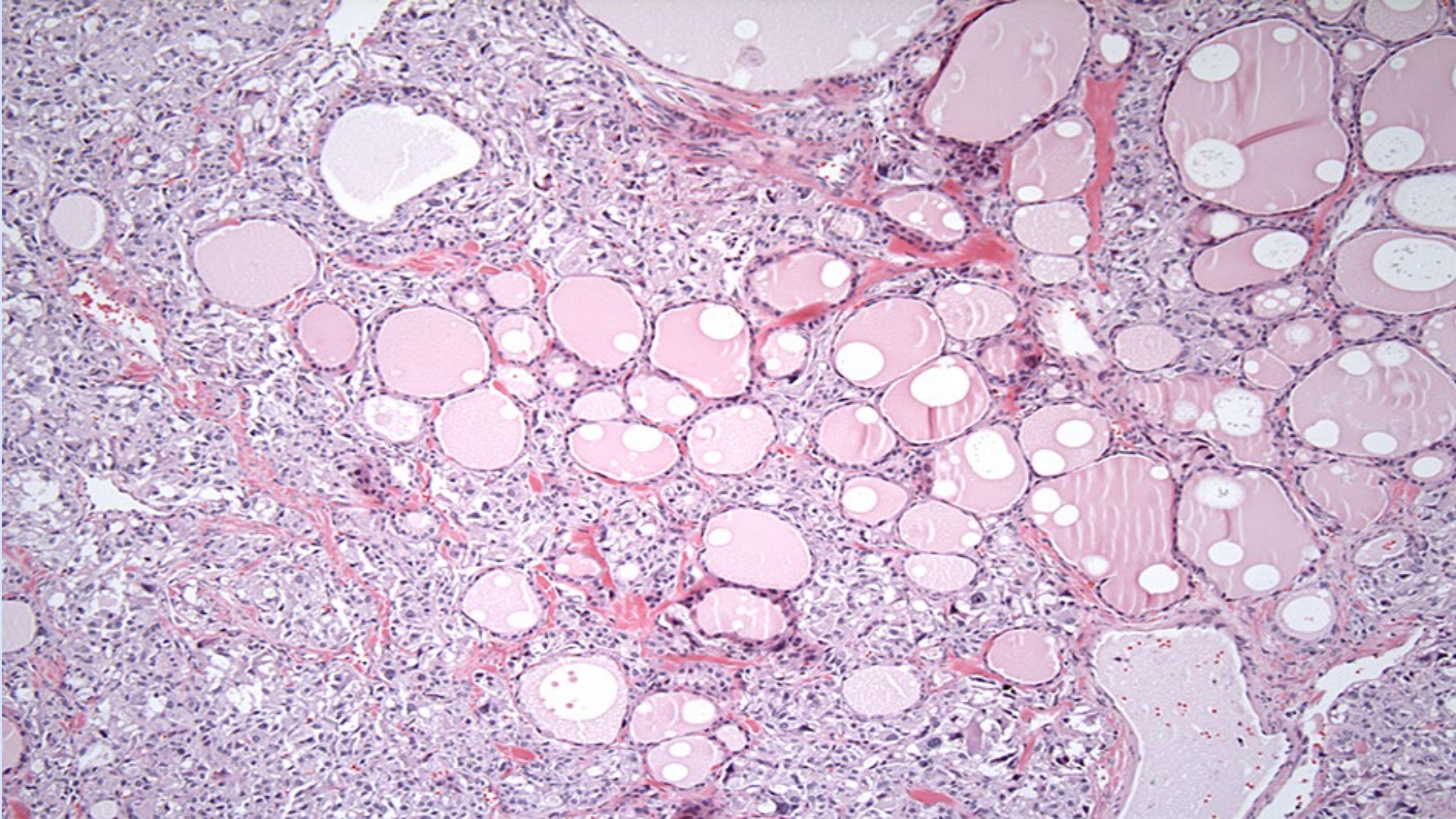
Usually solid with round/polyhedral, plasmacytoid, or spindled cells.

Variants include: papillary, oncocytic, clear-cell variant, paraganglioma-like, small cell variant, giant cell variant, angiosarcoma-like variant and glandular/tubular/follicular variant.

Can entrap non-neoplastic thyroid follicles.

Positive for chromogranin, synaptophysin, calcitonin, TTF-1, PAX8, and mCEA.



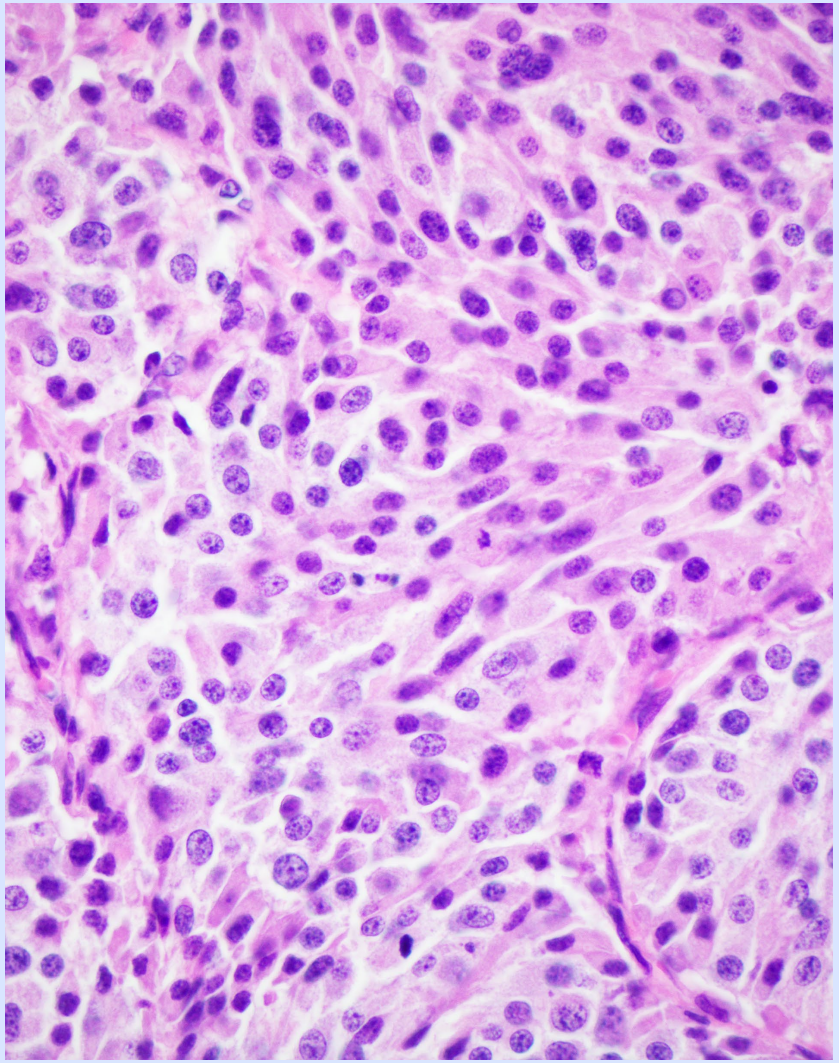


Medullary Thyroid Carcinoma

MTC accounts for approximately 2% of thyroid malignancies and approaching 15% of thyroid-cancer related deaths in the U.S.

A quarter of MTC occurs in the setting of MEN2 (therefore all patients with MTC require genetic testing). 75% of MTC is sporadic. For these patients:

- average age at diagnosis is 50 years
- ~50% have LN metastases at dx
- 15% have distant metastases at dx



Medullary Thyroid Carcinoma

Stage is the strongest independent predictor of survival on multivariate analysis.

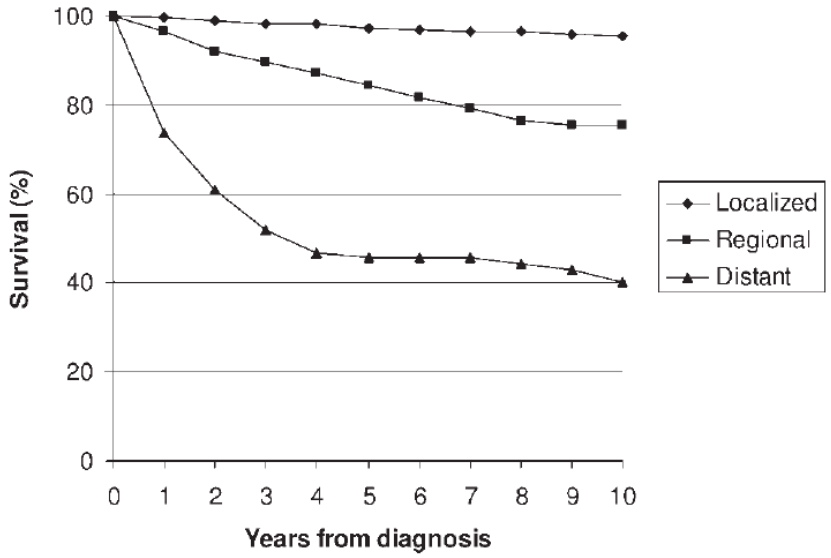


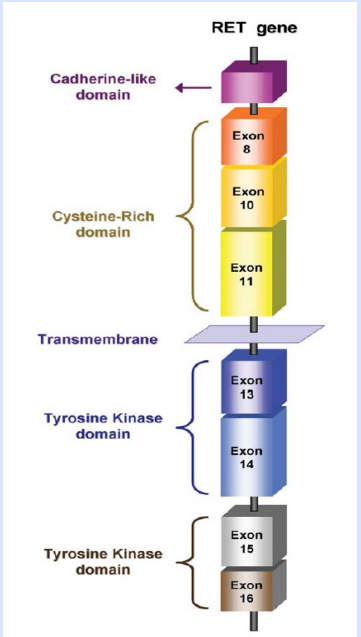
FIGURE 2. Ten-year, disease-specific survival by Surveillance, Epidemiology, and End Results (SEER) stage for patients with histologically confirmed medullary thyroid cancer. SEER, 1973–2002.

Roman et al, Cancer, 2006

Molecular Alterations of MTC

RET mutations are present in virtually all cases of hereditary MTC and they are the most frequent mutations detected in sporadic MTC (~50% of cases).

The *RET* M918T mutation (the mutation associated with MEN2B) accounts for up to 80% of *RET* mutations in sporadic MTC.



Elisei et al, Thyroid, 2005

RET status has been shown to be prognostically significant in sporadic MTC, with the presence of a *RET* mutation shown to be an independent predictor of decreased survival on multivariate analysis.

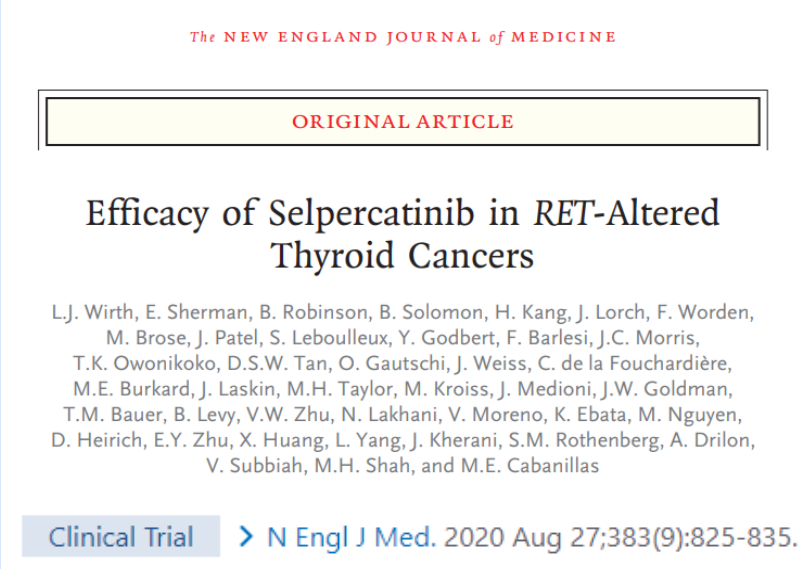
An understanding of the genomics has informed systemic treatment for MTC patients that require systemic therapy – those with significant tumor burden and symptomatic or progressive metastatic disease.

Two FDA approved multi-kinase inhibitors (inhibit RET and other kinases) :

- vandetanib
- cabozantinib

Although MKI therapy was a major advance, these drugs have overall modest response rates and significant toxicities. With time virtually all patients cease to respond to these drugs.

Now there are two selective RET inhibitors selpercatinib and pralsetinib.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

L.J. Wirth, E. Sherman, B. Robinson, B. Solomon, H. Kang, J. Lorch, F. Worden, M. Brose, J. Patel, S. Leboulleux, Y. Godbert, F. Barlesi, J.C. Morris, T.K. Owonikoko, D.S.W. Tan, O. Gautschi, J. Weiss, C. de la Fouchardière, M.E. Burkard, J. Laskin, M.H. Taylor, M. Kroiss, J. Medioni, J.W. Goldman, T.M. Bauer, B. Levy, V.W. Zhu, N. Lakhani, V. Moreno, K. Ebata, M. Nguyen, D. Heirich, E.Y. Zhu, X. Huang, L. Yang, J. Kherani, S.M. Rothenberg, A. Drilon, V. Subbiah, M.H. Shah, and M.E. Cabanillas

Clinical Trial > N Engl J Med. 2020 Aug 27;383(9):825-835.

Pralsetinib for patients with advanced or metastatic *RET*-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study

Vivek Subbiah, Mimi I Hu*, Lori J Wirth, Martin Schuler, Aaron S Mansfield, Giuseppe Curigliano, Marcia S Brose, Viola W Zhu, Sophie Leboulleux, Daniel W Bowles, Christina S Baik, Douglas Adkins, Bhumsuk Keam, Ignacio Matos, Elena Garralda, Justin F Gainor, Gilberto Lopes, Chia-Chi Lin, Yann Godbert, Debashis Sarker, Stephen G Miller, Corinne Clifford, Hui Zhang, Christopher D Turner, Matthew H Taylor*

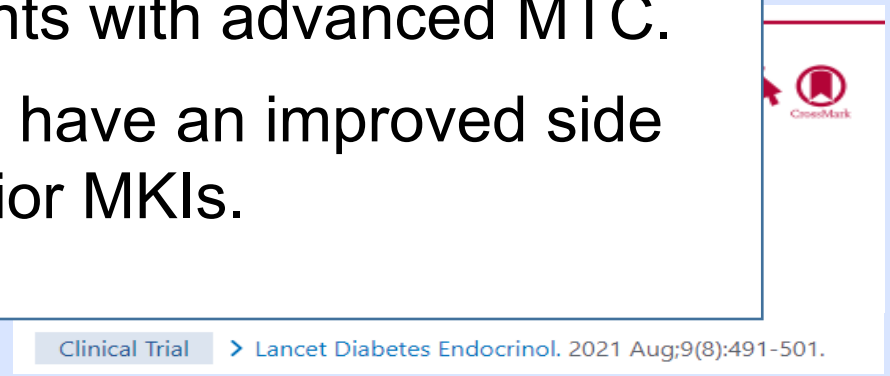
Clinical Trial > Lancet Diabetes Endocrinol. 2021 Aug;9(8):491-501.

Although MKI therapy was a major advance, these drugs have overall modest response rates and significant toxicities. With time virtually all patients cease to respond to these drugs.

Now there are two selective RET inhibitors selpercatinib and pralsetinib

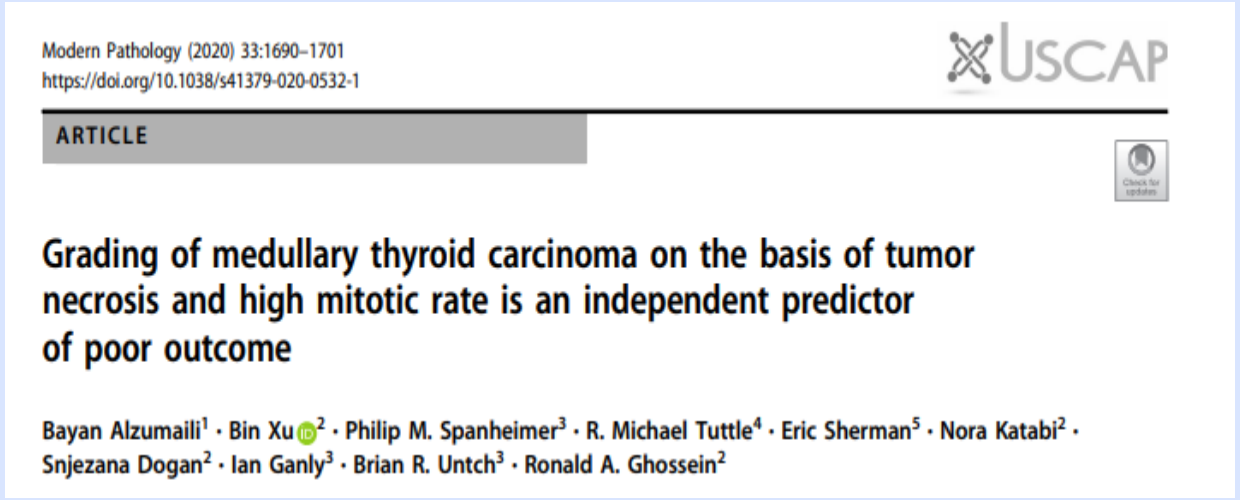
RET status now informs treatment for patients with advanced MTC.

RET selective inhibitors are efficacious and have an improved side effect profile compared to prior MKIs.



Medullary Thyroid Carcinoma Grading

Two groups proposed grading schemes for MTC, with grading based on proliferative rate and presence of tumor necrosis.



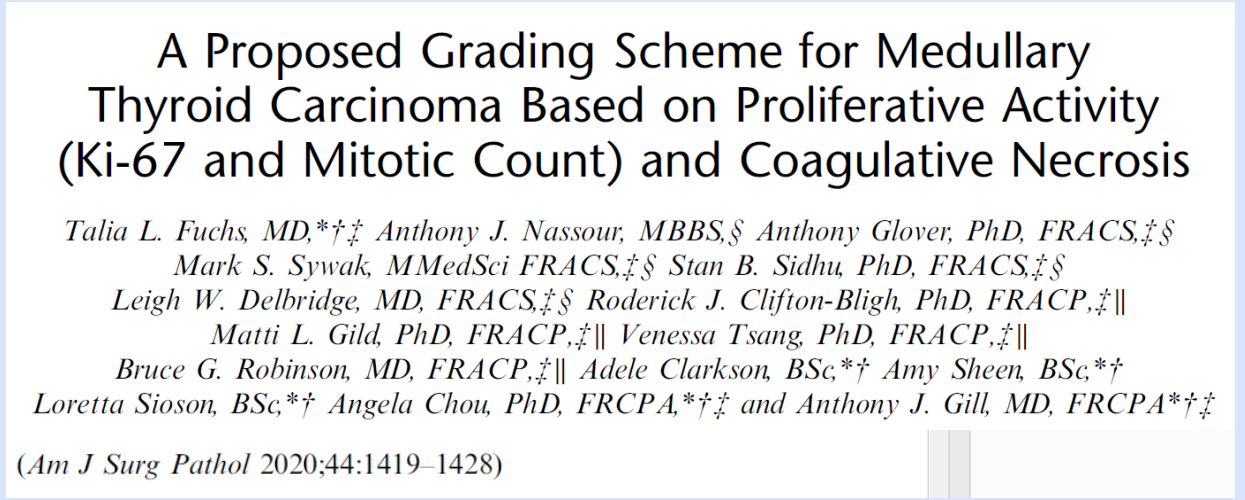
Modern Pathology (2020) 33:1690–1701
https://doi.org/10.1038/s41379-020-0532-1

USCAP

ARTICLE

Grading of medullary thyroid carcinoma on the basis of tumor necrosis and high mitotic rate is an independent predictor of poor outcome

Bayan Alzumaili[1] · Bin Xu[2] · Philip M. Spanheimer[3] · R. Michael Tuttle[4] · Eric Sherman[5] · Nora Katabi[2] · Snjezana Dogan[2] · Ian Ganly[3] · Brian R. Untch[3] · Ronald A. Ghossein[2]



A Proposed Grading Scheme for Medullary Thyroid Carcinoma Based on Proliferative Activity (Ki-67 and Mitotic Count) and Coagulative Necrosis

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(*Am J Surg Pathol* 2020;44:1419–1428)

Two-tiered system based on mitotic count and necrosis.

Three-tiered system based on mitotic count, Ki-67 proliferative index, and necrosis.

International Medullary Thyroid Carcinoma Grading System: A Validated Grading System for Medullary Thyroid Carcinoma

Bin Xu, MD, PhD[1]; Talia L. Fuchs, MD[2,3]; Sara Ahmadi, MD[4]; Mohammed Alghamdi, MD[1]; Bayan Alzumaili, MD[1]; Mohamed-Amine Bani, MD[5]; Eric Baudin, MD[6]; Angela Chou, MD[2,3]; Antonio De Leo, MD[7]; James A. Fagin, MD[8]; Ian Ganly, MD, PhD[9]; Anthony Glover, MD[3,10]; Dana Hartl, MD[11]; Christina Kanaan, MD[5]; Pierre Khneisser, MD[5]; Fedaa Najdawi, MD[12]; Aradhya Nigam, MD[9]; Alex Papachristos, MD[3,10]; Andrea Repaci, MD[13]; Philip M. Spanheimer, MD[9]; Erica Solaroli, MD[14]; Brian R. Untch, MD[9]; Justine A. Barletta, MD[12]; Giovanni Tallini, MD[7]; Abir Al Ghuzlan, MD[5]; Anthony J. Gill, MD[2,3]; and Ronald A. Ghossein, MD[1]

Multicenter Study > J Clin Oncol. 2022 Jan 1;40(1):96-104. doi: 10.1200/JCO.21.01329.

Epub 2021 Nov 3.

International MTC Grading Scheme

327 MTC from 5 centers from the USA, Europe, and Australia with data on mitotic count, Ki67 proliferative index, and necrosis.

Extensive statistical analysis performed to determine best cut-offs values and strength of a two-tiered vs three-tiered system.

International MTC Grading Scheme

IMTCGS Low-grade

- < 5 mitoses per 2 mm^2
- Ki-67 proliferative index < 5%
- AND no tumor necrosis

IMTCGS High-grade

At least one of the following:

- ≥ 5 mitoses per 2 mm^2
- Ki-67 proliferative index ≥ 5%
- OR tumor necrosis

International MTC Grading Scheme

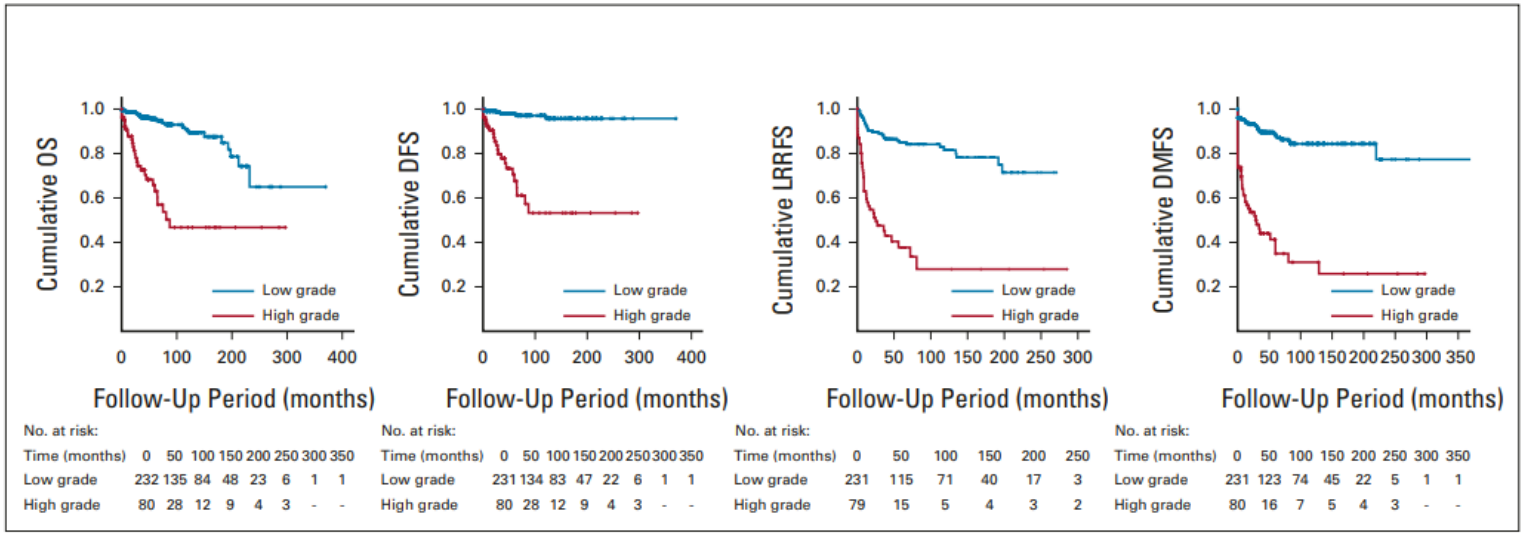
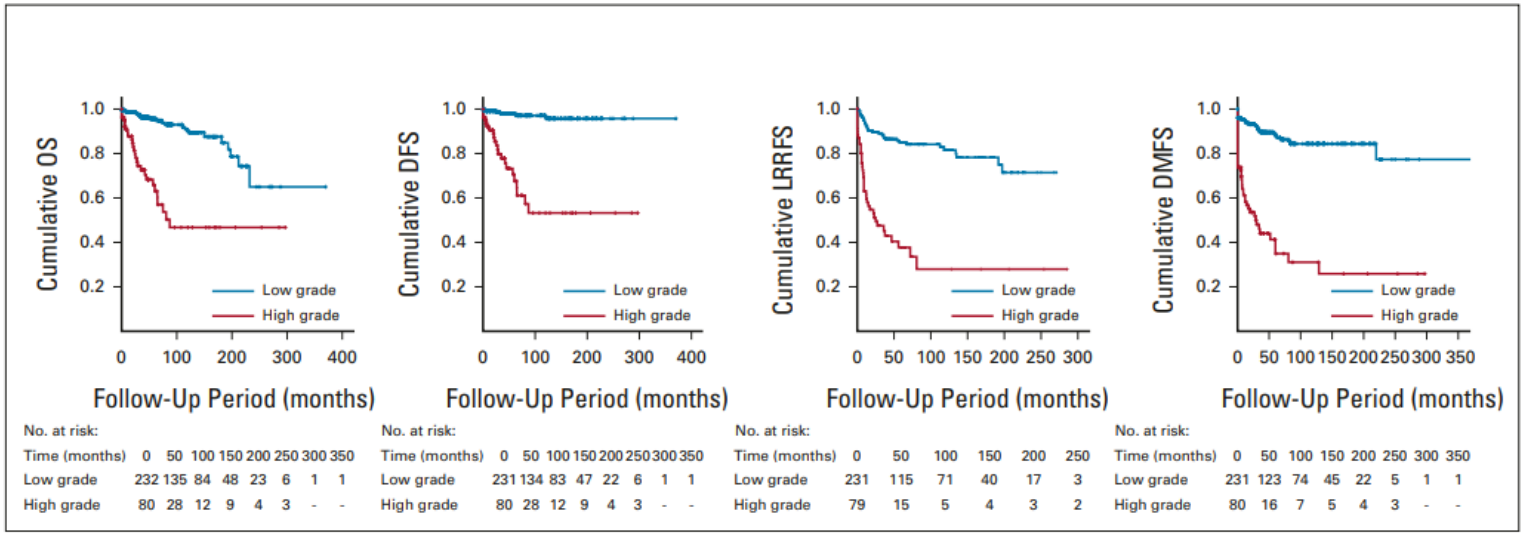


FIG 2. Kaplan-Meier curves for survival according to the international medullary thyroid carcinoma grading system. DMFS, distant metastasis-free survival; DSS, disease-specific survival; LRRFS, locoregional recurrence-free survival; OS, overall survival.

XU et al, *J Clin Oncol*, 2021.

IMTCGS grade was an independent predictor of outcome in multivariate analyses that included patient age, gender, tumor size, margin status, AJCC stage group, and post-operative calcitonin and CEA serum levels.

International MTC Grading Scheme



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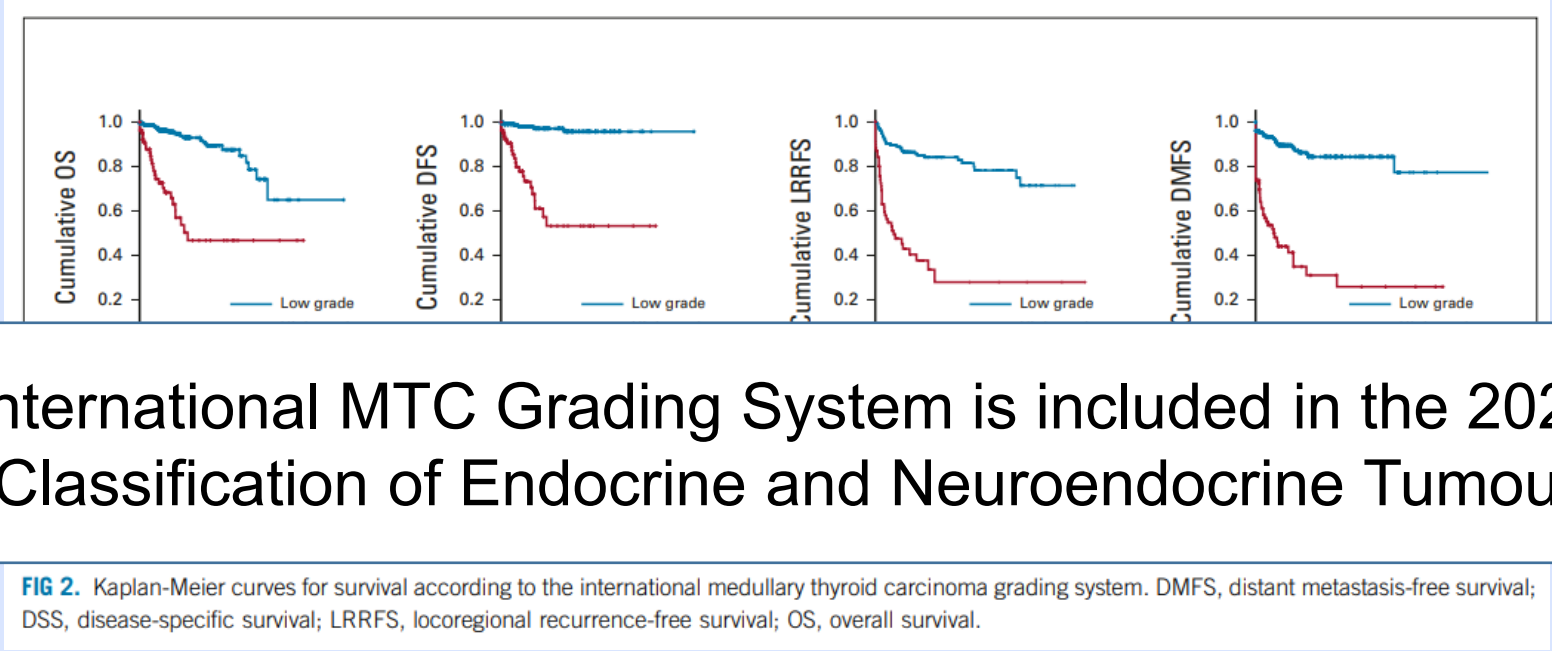
XU et al, *J Clin Oncol*, 2021.

Patients with high-grade MTC (which accounted for 25% of patients in the study) had a 10-year disease-specific survival of 53% compared to 97% for patients with low-grade tumors.

International MTC Grading Scheme



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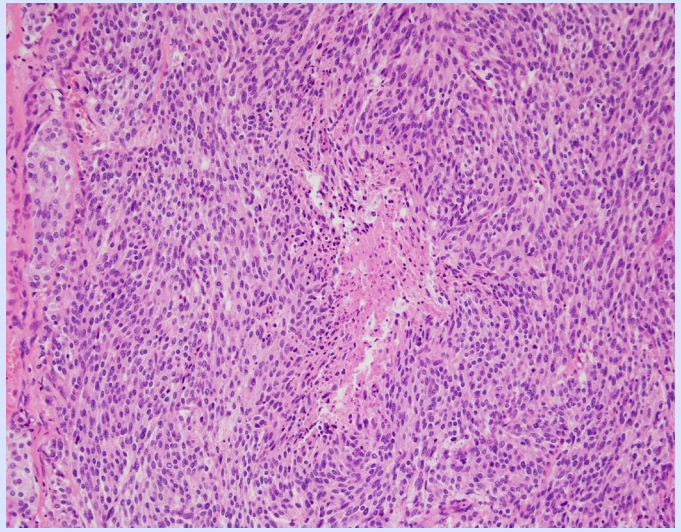
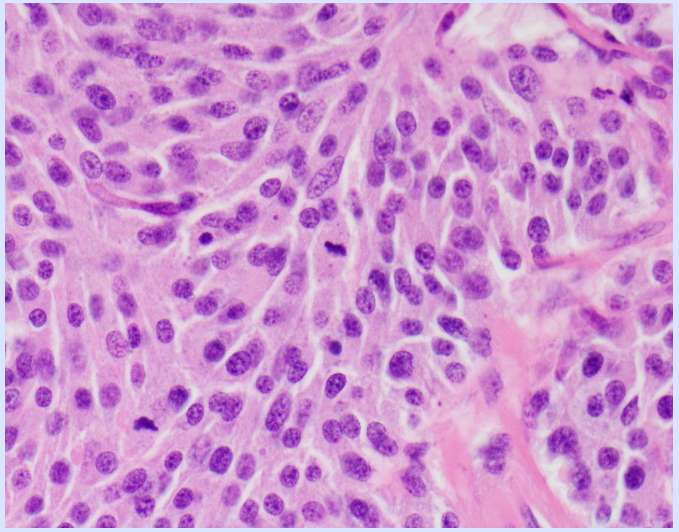
XU et al, *J Clin Oncol*, 2021.

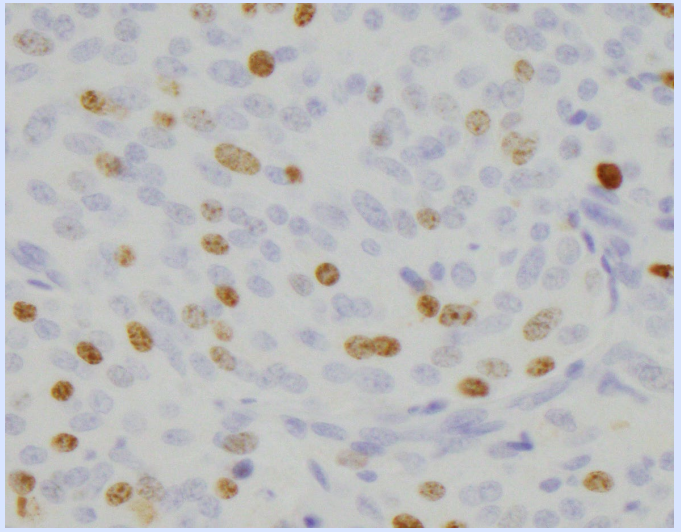
The International MTC Grading System is included in the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours.

Patients with high-grade MTC (which accounted for 25% of patients in the study) had a 10-year disease-specific survival of 53% compared to 97% for patients with low-grade tumors.

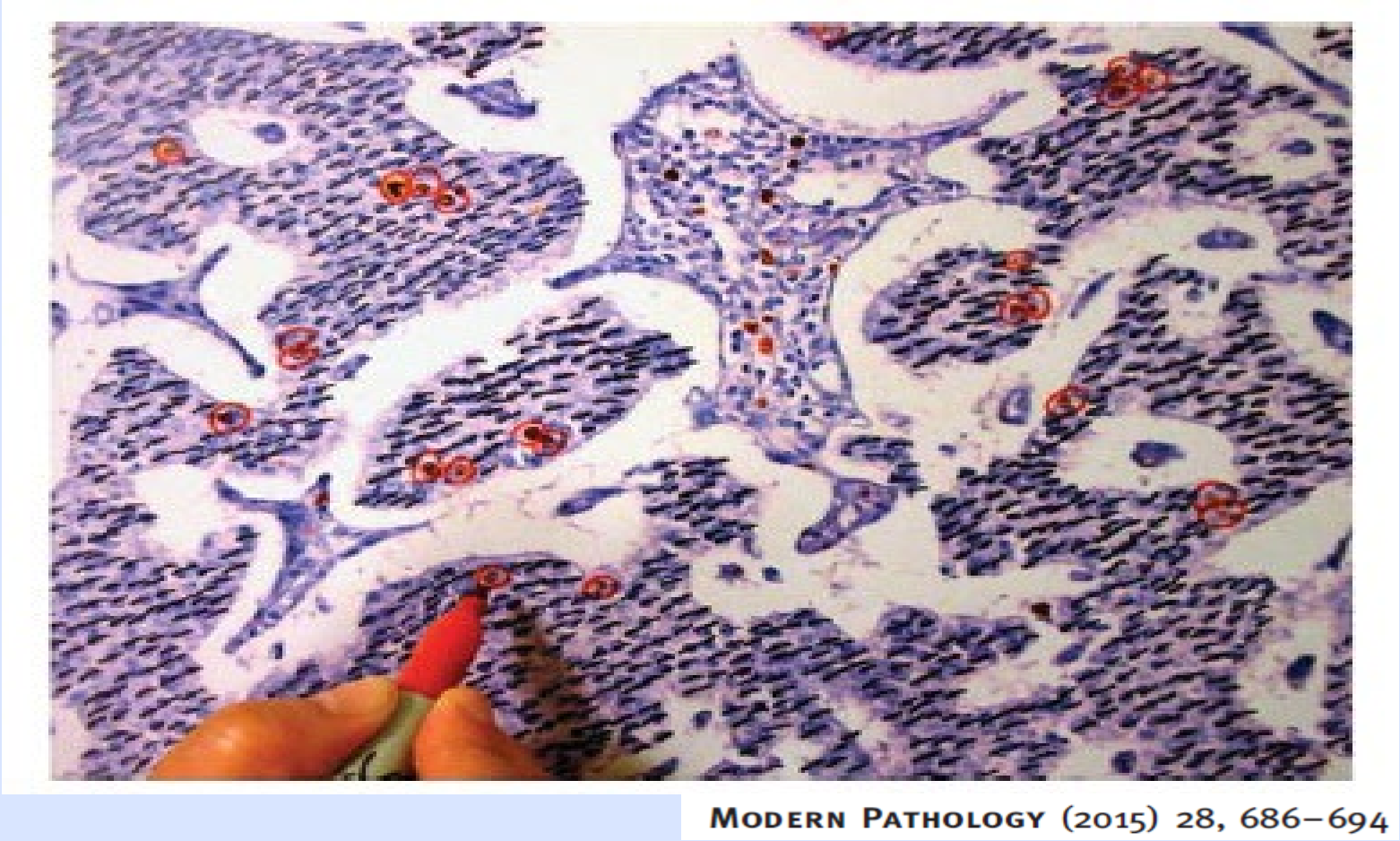
Back to our case: High-grade MTC - based on tumor necrosis, mitoses numbering 8 per 10 HPF, and a Ki-67 proliferative index was 13%.





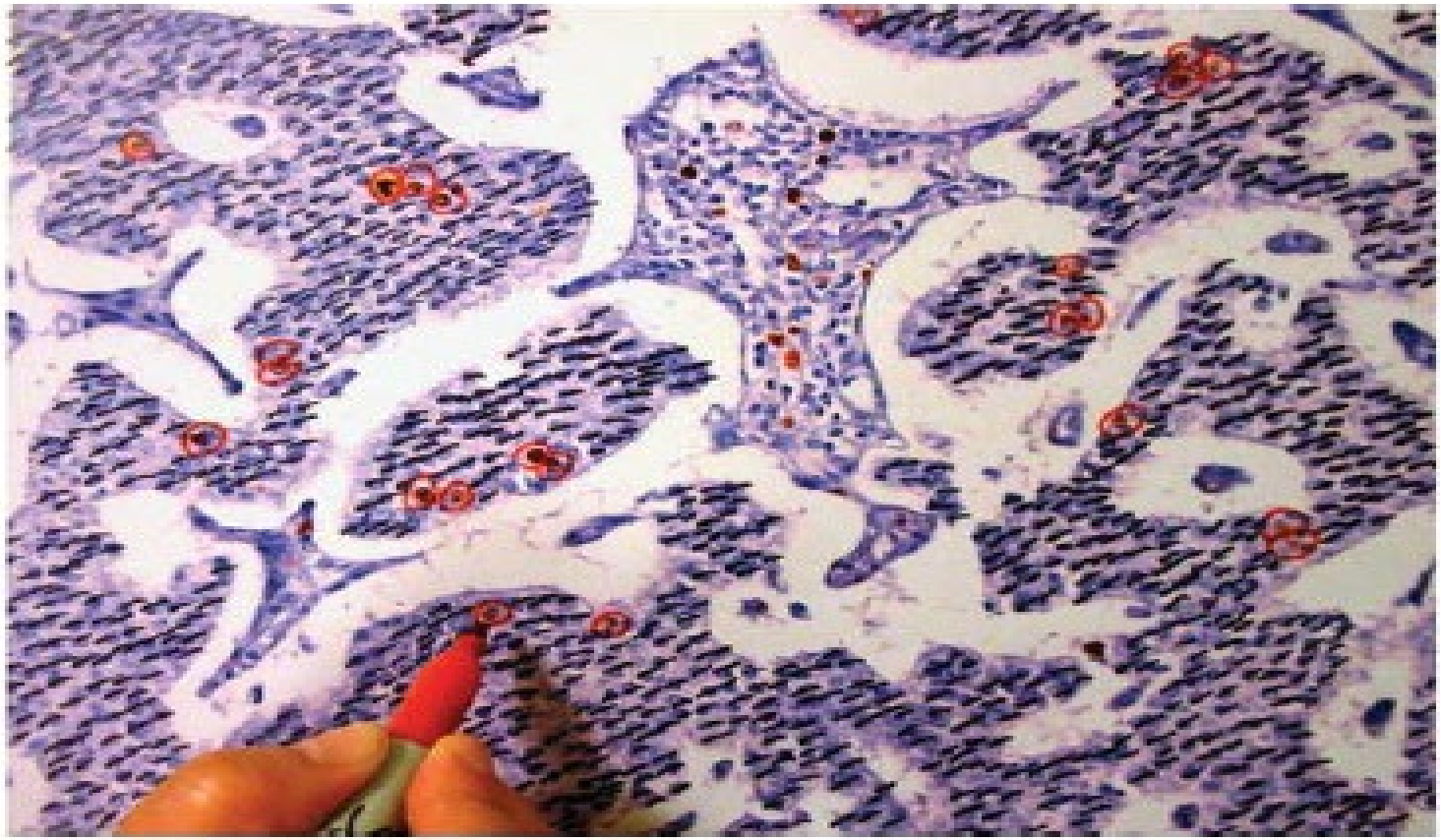


Mitotic count and Ki-67 proliferative index based on hotspots. Necrosis is often focal, so must carefully examine all tumor slides for necrosis.



MODERN PATHOLOGY (2015) 28, 686–694

Take picture at 20X and count all cells and Ki-67 positive cells. Divide number of Ki-67-positive cells by number of total cells. Takes roughly 8 minutes per case.



MODERN PATHOLOGY (2015) 28, 686–694

A precise mitotic count and Ki-67 proliferative index should be reported because in the IMTCGS study it was found that as these continuous variables increased, the prognosis decreased.

Endocrine Pathology
https://doi.org/10.1007/s12022-022-09718-0

Grading of Medullary Thyroid Carcinoma: an Interobserver Reproducibility Study

Jessica F. Williams[1,3] · Melissa Zhao[1,3] · Fedaa Najdawi[1,3] · Sara Ahmadi[2,3] · Jason L. Hornick[1,3] · Kristine S. Wong[1,3] · Justine A. Barletta[1,3]

Accepted: 3 May 2022

	Mitotic count	Ki-67 proliferative index	Tumor necrosis	IMTCGS grade
Fleiss' kappa	0.68	0.86	0.89	0.87
% agreement	93.0%	93.0%	95.5%	93.2%

IMTCGS = International Medullary Thyroid Carcinoma Grading System

Summary

- For aggressive PTC, consider whether the tumor may harbor a gene rearrangement, such as *NTRK*. These tumors tend to have a multinodular growth pattern. Detecting the fusion could guide treatment.

- The 2022 WHO Classification of Endocrine and Neuroendocrine Tumours has a new section on high-grade follicular cell-derived tumors that includes PDTC (defined by Turin criteria) and high-grade differentiated thyroid carcinoma (predominantly high-grade PTC)… remember to look for mitoses and necrosis in thyroid carcinomas.

- Cribriform morular thyroid carcinoma is associated with FAP, is negative for thyroglobulin, and often weak or negative for PAX8; therefore, it is now considered to be a tumor of uncertain histogenesis.

Summary

- The *BRAF* V600E mutation is present in about a third of ATC, and *BRAF* V600E status is used to guide treatment.

- There is no longer a primary thyroid squamous cell carcinoma section in WHO. These tumors are now considered as ATC.

- MTC should be graded according to the IMTCGS.

Thank you!

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