Seminar of Young Pathologists
Litomysl, Czech Republic
April 12-13, 2024

Follicular-derived/patterned thyroid tumors

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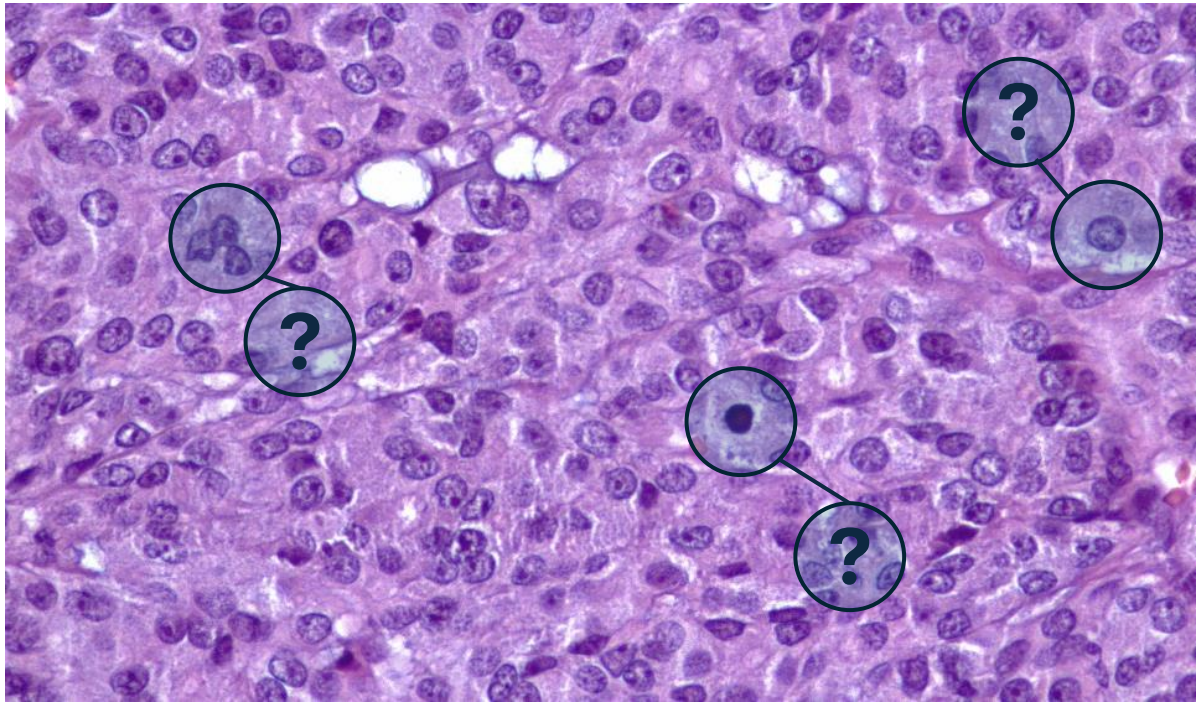
WHO Classification - 5th edition Thyroid Tumors



Major changes

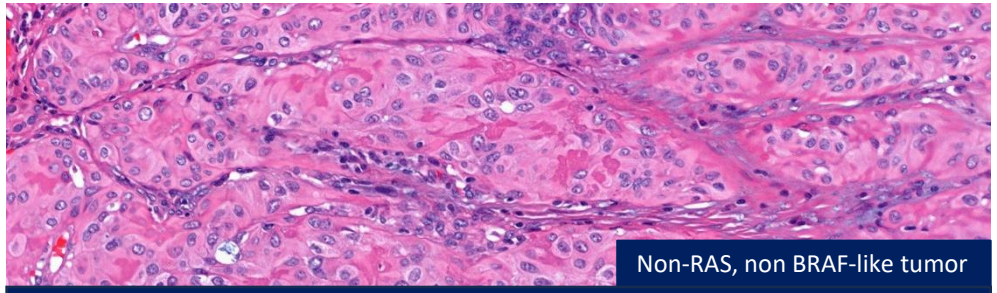
- Increased value of **molecular features**
- Decreased value of **nuclear features** and **tumour size**
- Increased value of **invasion** (vascular) and **high-grade features** (necrosis and mitosis)
- Alterations in the classification of **rare tumours**

News! 5th Edition of the WHO

Endocrine Pathology (2022) 33:27–63
https://doi.org/10.1007/s12022-022-09707-3

Overview of the 2022 WHO Classification of Thyroid Neoplasms

Zubair W. Baloch[1] · Sylvia L. Asa[2] · Justine A. Barletta[3] · Ronald A. Ghossein[4] · C. Christofer Juhlin[5,6] · Chan Kwon Jung[7] · Virginia A. LiVolsi[1] · Mauro G. Papotti[8] · Manuel Sobrinho-Simões[9] · Giovanni Tallini[10,11] · Ozgur Mete[12]



Non-RAS, non BRAF-like tumor

PAX8-GLIS3 gene fusion is a pathognomonic alteration of hyalinizing trabecular tumours of the thyroid. Marchiò et al, 2019

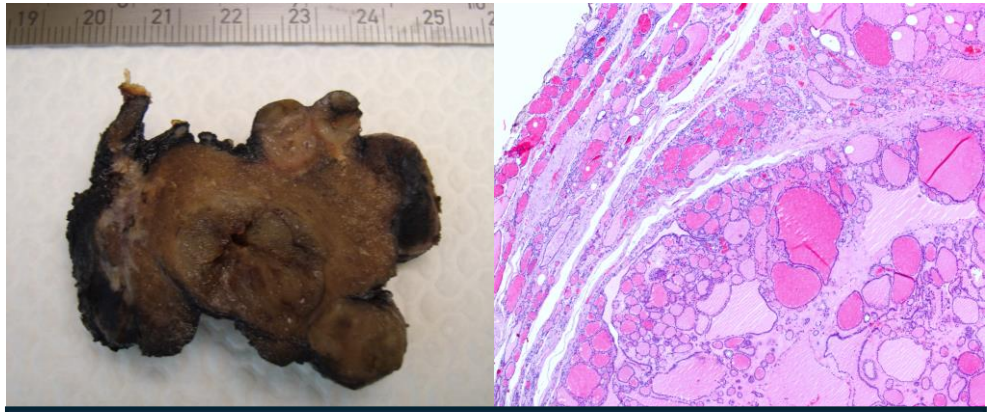
Table 1 WHO classification scheme of thyroid neoplasms, 5th edition

Developmental abnormalities	
1. Thyroglossal duct cyst	
2. Other congenital thyroid abnormalities	
Follicular cell–derived neoplasms	
1. Benign tumors	
a. Thyroid follicular nodular disease	
b. Follicular adenoma	RAS-like tumors
c. Follicular adenoma with papillary architecture	Non-RAS, non BRAF-like tumors
d. Oncocytic adenoma of the thyroid	
2. Low-risk neoplasms	
a. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features	RAS-like tumors
b. Thyroid tumors of uncertain malignant potential	
c. Hyalinizing trabecular tumor	Non-RAS, non BRAF-like tumors
3. Malignant neoplasms	
a. Follicular thyroid carcinoma	RAS-like tumors
b. Invasive encapsulated follicular variant papillary carcinoma	
c. Papillary thyroid carcinoma	BRAF-like tumors
d. Oncocytic carcinoma of the thyroid	Non-RAS, non BRAF-like tumors
e. Follicular-derived carcinomas, high-grade	
i. Differentiated high-grade thyroid carcinoma	
ii. Poorly differentiated thyroid carcinoma	
f. Anaplastic follicular cell–derived thyroid carcinoma	

(…)

Follicular derived benign tumours

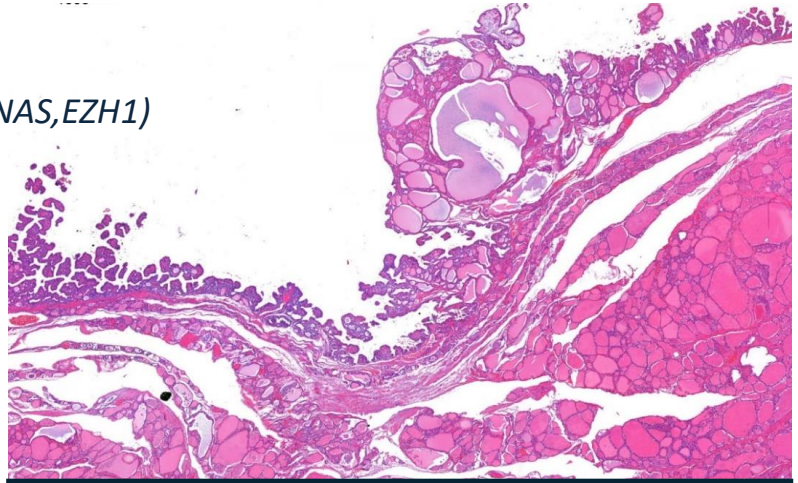
- Thyroid follicular nodular disease
  - Previous mixed terminology: “colloid nodules”, “hyperplasia”, “adenomatous nodules” and “adenomatoid nodules”
  - Not always clonal
  - The separation between these designations has no clinical meaning



FND diagnosis at the cytological setting requires mapping and ultrasound correlation

- Follicular adenoma
- Follicular adenoma with papillary architecture
  - Associated with autonomous hyperfunction after activating intracellular cyclic AMP (*TSHR, GNAS,EZH1)*
- Oncocytic adenoma

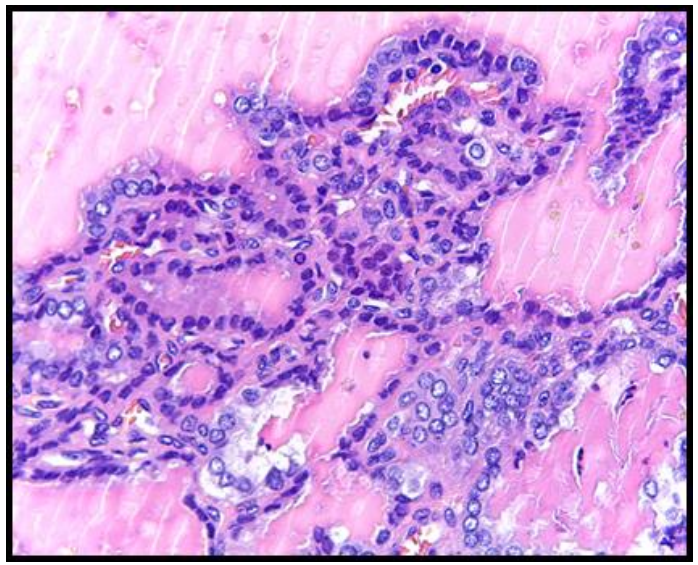
- > 75% oncocytic cytology
- Associated with alterations in the mitochondrial genome or in the related *GRIM19* (*NDUFA13*) gene

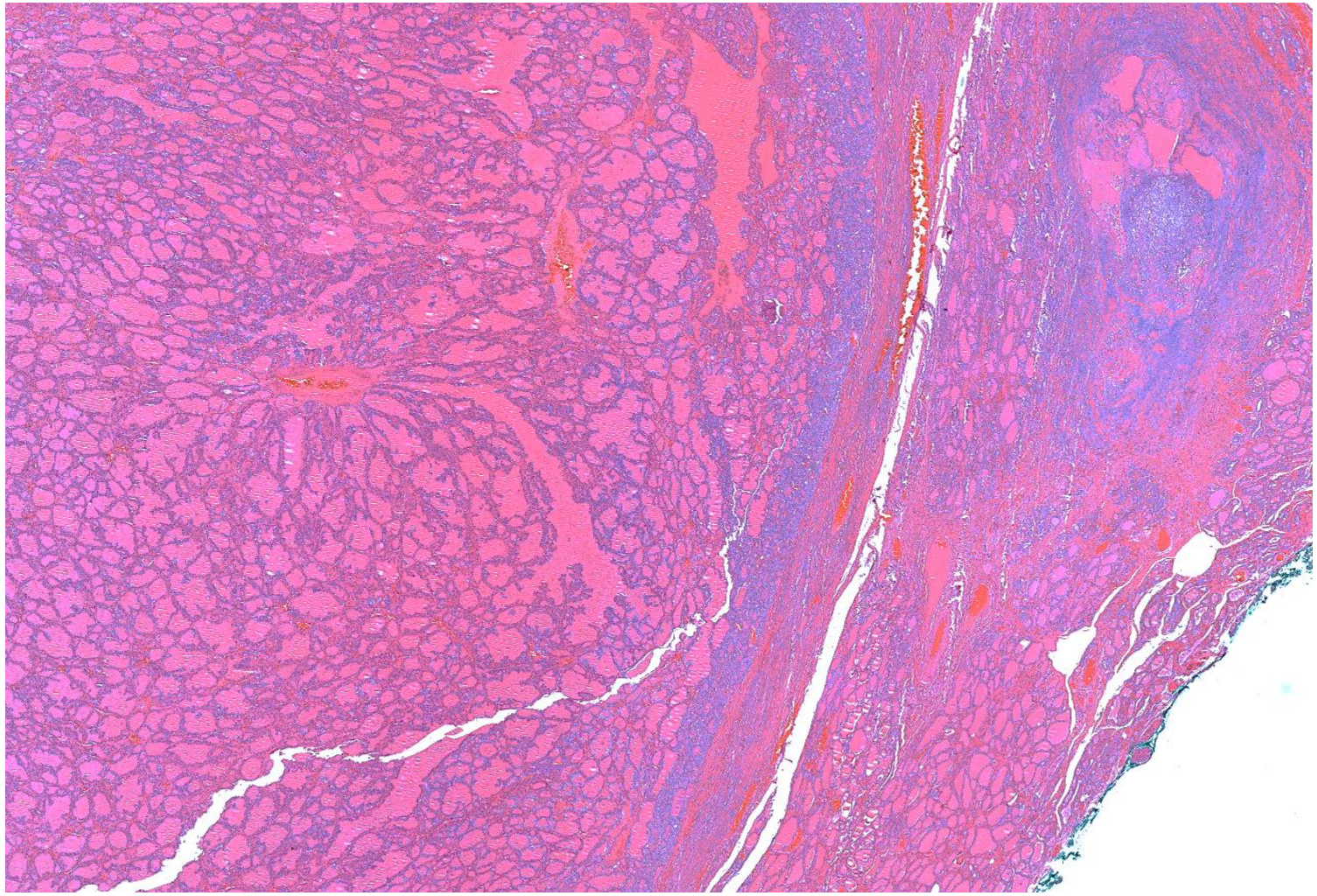


Follicular adenoma with papillary architecture

DICER1 mutated tumours

Young patients
Macrofolicular & papillary centripetal growth
Intermediate type-nuclei
Somatic *versus* germline mutations

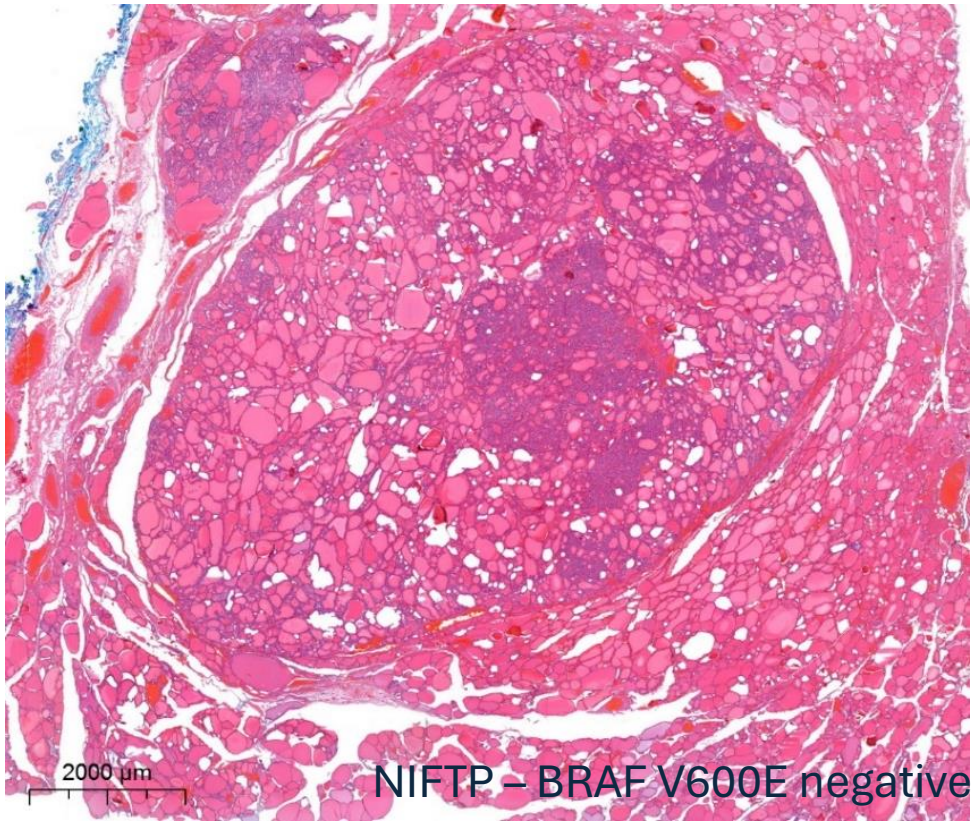




Low-risk follicular cell–derived neoplasms

- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
- Thyroid tumors of uncertain malignant potential
- Hyalinizing trabecular tumor

Cytology: Bethesda IV, V or VI
Treatment: lobectomy or lobectomy + isthmectomy

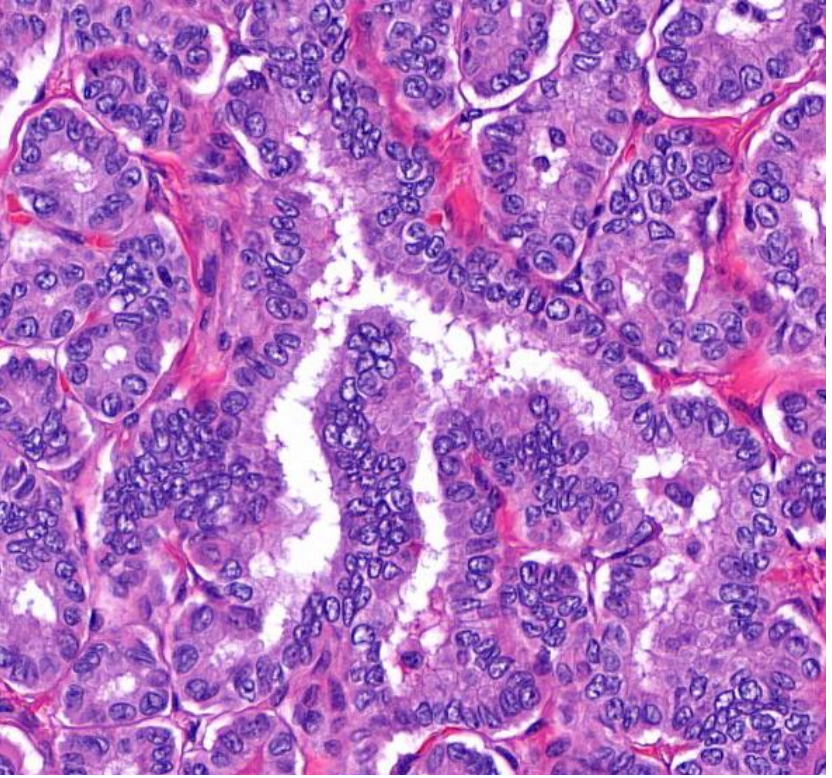


NIFTP – BRAF V600E negative

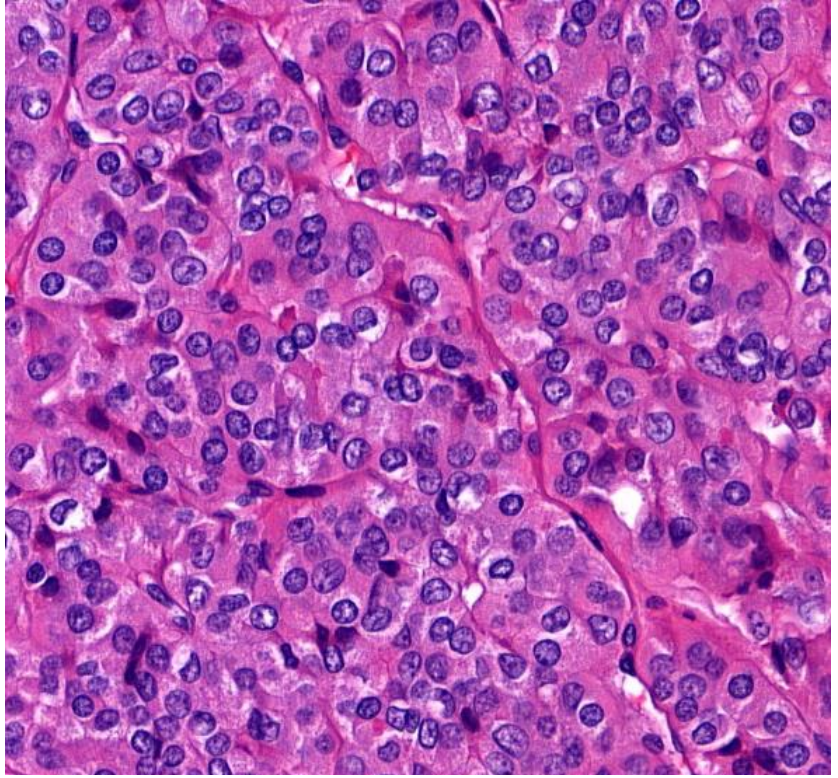
Oncocytic NIFTPs (>75% oncocytic cells)

Subcentimeter NIFTP (< 1 cm & ≥2 mm)

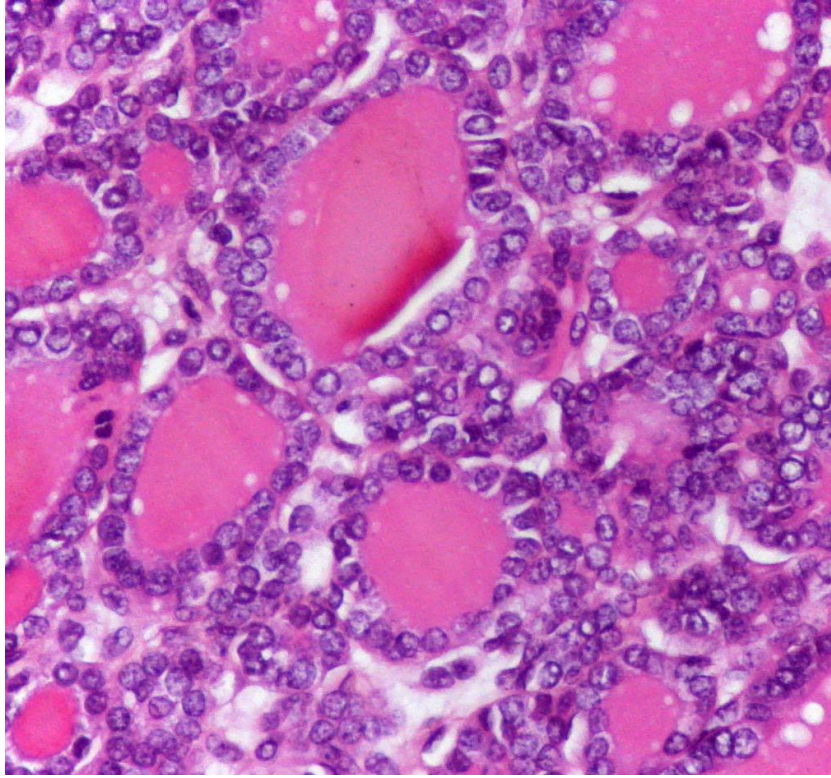
Solid NIFTP? – differential diagnosis with HTT?



Papillary thyroid carcinoma (PTC), classic



Invasive encapsulated FV-PTC



Follicular adenoma with artifacts

The PTC-type nuclear features paradox

A broad spectrum of alterations that is deeply affected (also) by analytic conditions

Endocrine Pathology (2023) 34:484–486
https://doi.org/10.1007/s12022-023-09791-z

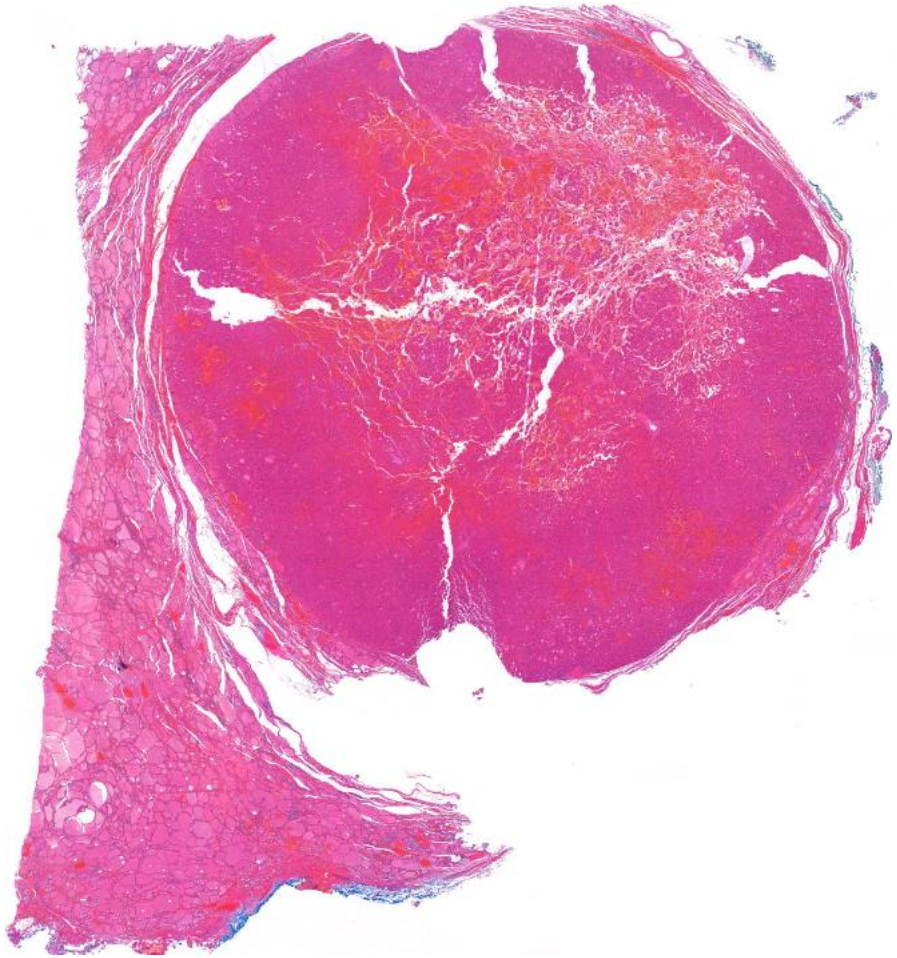
CORRESPONDENCE

Obstacles to Tumor Capsule Assessment in Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)

Ivan J. Stojanov[1] · Ozgur Mete[2] · Sylvia L. Asa[3]

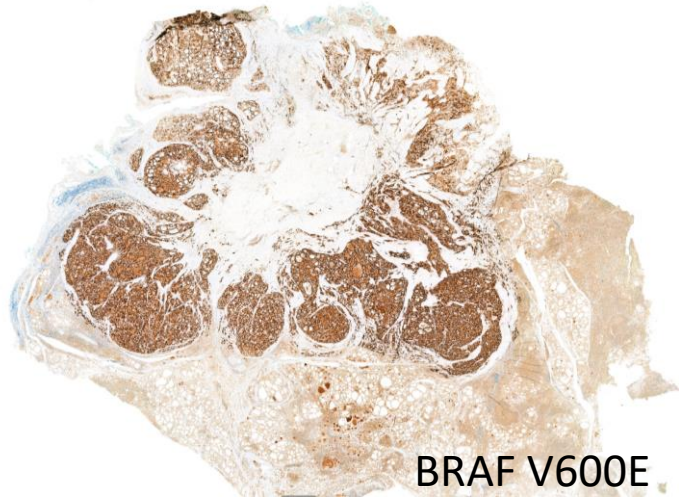
Accepted: 13 November 2023 / Published online: 18 November 2023

Comparing the capsular surface area on 6 glass slides (0.0188496 cm^2) to the overall capsular surface area (12.56637 cm^2) demonstrates that 0.15% of the capsule is microscopically evaluated in routine cases. If a patholo-

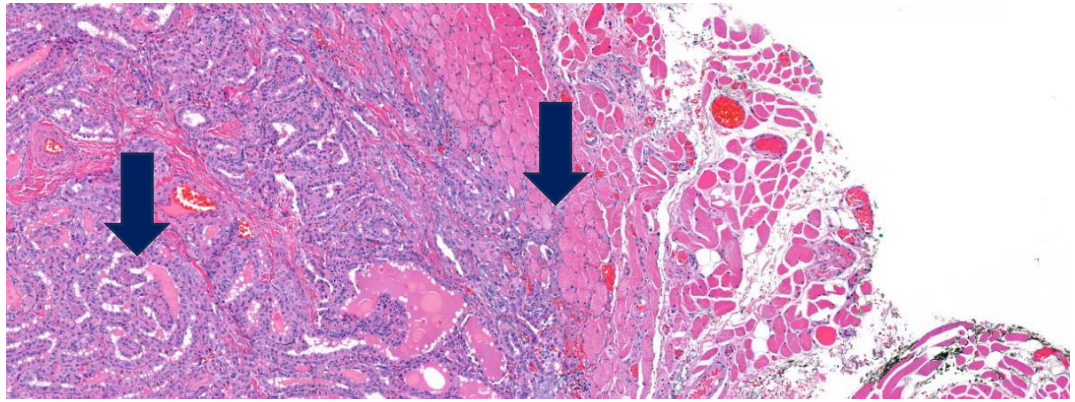


Molecular testing in thyroid tumors

There are no absolut molecular markers of invasion



If BRAF is mutated/expressed in otherwise-looking NIFTP, then review histology!



Lobectomy or lobectomy plus isthmectomy is the recommended treatment, regardless of the immunohistochemical or molecular markers

Follicular patterned tumor
Follicular adenoma
Oncocytic adenoma
NIFTP
Well differentiated tumour, UMP
Follicular tumour, UMP
Minimally invasive FTC (without angioinvasion)
Encapsulated follicular variant of PTC (without angioinvasion)

Int J Surg Pathol. 2010 Jun;18(3 Suppl):209S-212S. doi: 10.1177/1066896910370886.

Molecular pathology of thyroid tumors: diagnostic and prognostic relevance.

Sobrinho-Simões M[1], Eloy C, Vinagre J, Soares P.

Am J Surg Pathol. 2010 Jun;34(6):868-72. doi: 10.1097/PAS.0b013e3181dbee07.

Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma.

Piana S[1], Frasoldati A, Di Felice E, Gardini G, Tallini G, Rosai J.

Author information

Abstract

A cohort of 1039 consecutive cases of thyroid carcinoma treated at a single institution and followed for an average of 11.9 years or until death included 102 encapsulated well-differentiated follicular-patterned tumors that had been diagnosed as carcinoma because of complete capsular invasion and/or papillary carcinoma-type nuclei. None of these cases were among the 67 patients from the cohort who died as a result of their thyroid carcinoma. The results of this study and a critical review of the pertinent literature indicate that tumors with these features are associated with an extremely favorable outcome and that they do not play a significant role in the fatality rate of thyroid carcinoma.

THYROID
Volume 33, Number 5, 2023

DOI: 10.1089/thy.2023.0032

THYROID SURGERY

Open camera or QR reader and scan code to access this article and other resources online.

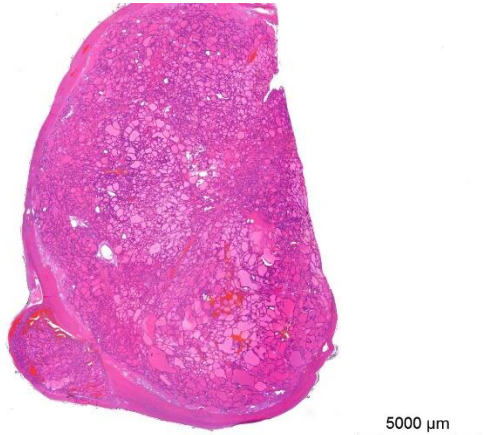
Large (>4 cm) Intrathyroidal Encapsulated Well-Differentiated Follicular Cell-Derived Carcinoma Without Vascular Invasion May Have Negligible Risk of Recurrence Even When Treated with Lobectomy Alone

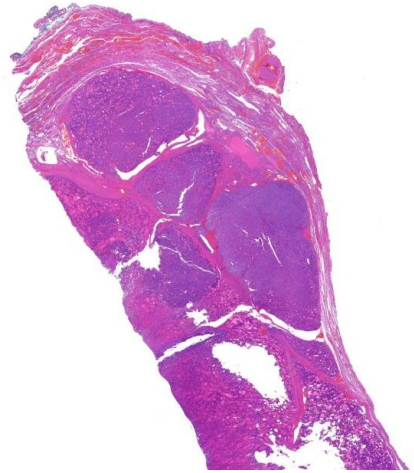
Ronald Ghossein,[1] Ian Ganly,[2] R. Michael Tuttle,[3] and Bin Xu[1]

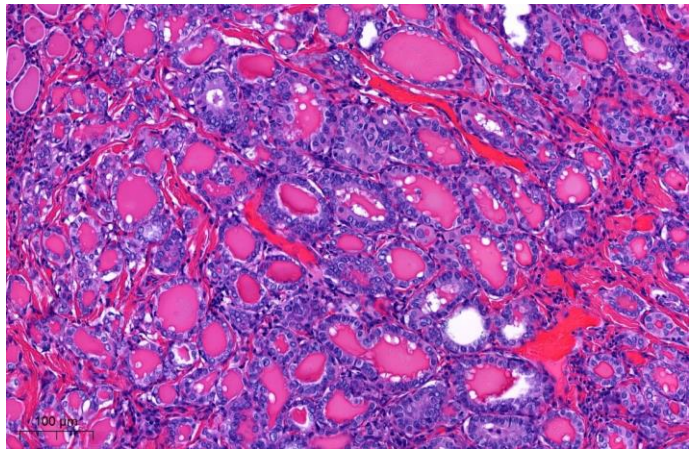
Malignant follicular cell–derived neoplasms are stratified based on molecular profiles and invasiveness

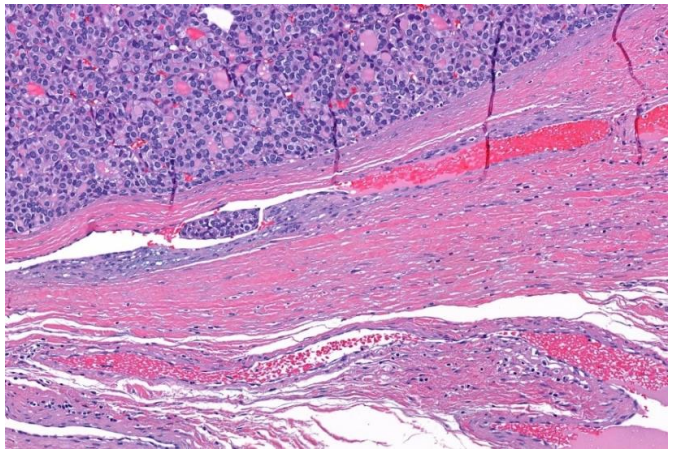
- PTC subtypes: **BRAF-like**
- Invasive encapsulated follicular variant PTC and follicular thyroid carcinoma: ***RAS*-like**

The importance of capsular & **vascular invasion**

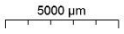




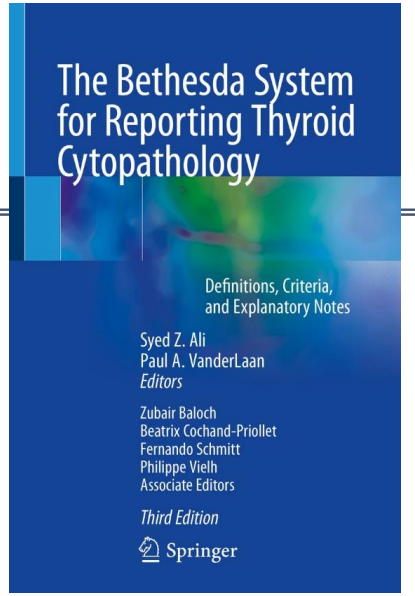




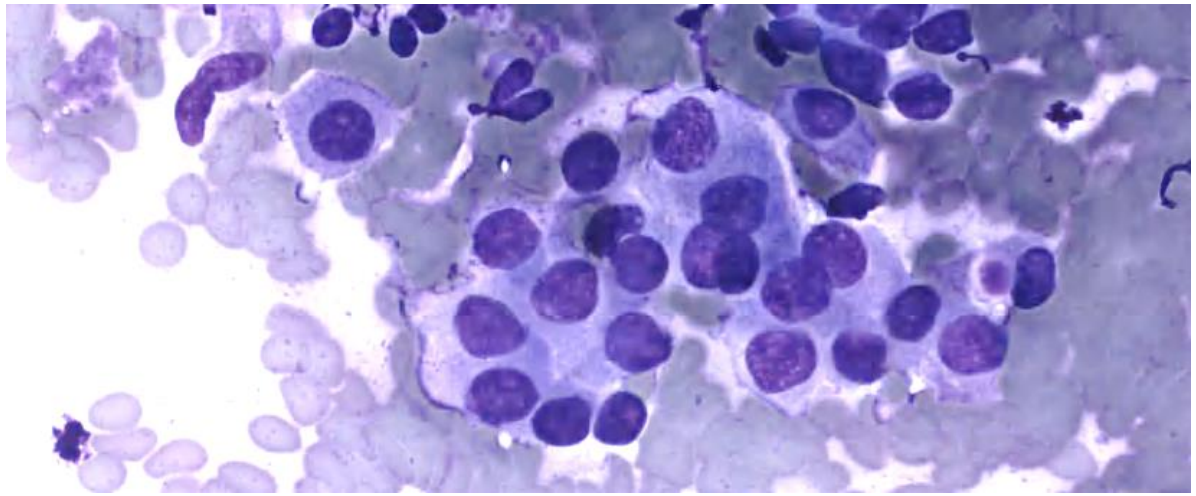
The negative impact on preoperative cytology



The Bethesda System – Follicular neoplasm



- Follicular patterned lesions with mild nuclear changes are included (NIFTP)
- Papillae or nuclear pseudoinclusions are not allowed



Invasion (capsular or vascular) **is a problem!**

- it is a sign of malignancy
- can not be evaluated in cytological samples
- can not be excluded in “core biopsies”/ frozen sections
- can be difficult to evaluate in the surgical sample
- is not detected by any molecular biomarker

The introduction of NIFTP decreased the positive predictive value of cytology examination of fine-needle aspiration of thyroid nodules

The 2017 Bethesda system for reporting thyroid cytopathology
Implied risk of malignancy and recommended clinical management (simplified)

Diagnostic category	Risk of malignancy		Usual management
	NIFTP ≠ cancer	*NIFTP = cancer*	
I. **Nondiagnostic**	5–10%	5–10%	Repeat FNA with ultrasound guidance
II. **Benign**	0–3%	0–3%	Clinical and sonographic follow-up
III. **AUS/FLUS**	6–18%	≈ 10–30%	Repeat FNA, molecular testing, or lobectomy
IV. **FN/SFN**	10–40%	25–40%	Molecular testing, lobectomy
V. **Suspicious for malignancy**	45–60%	50–75%	Near–total thyroidectomy or lobectomy
VI. **Malignant**	94–96%	97–99%	Near–total thyroidectomy or lobectomy

Endocrine-Related Cancer | I Amendoeira, T Maia *et al.* | NIFTP, impact on the reclassification | 25:4 | R247–R258

REVIEW

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): impact on the reclassification of thyroid nodules

Isabel Amendoeira[1,2,3,*], **Tiago Maia**[1,2,*] and **Manuel Sobrinho-Simões**[1,2,3,4]

Table 3 Distribution of NIFTP (non-invasive follicular tumor with papillary-like nuclear features) according to Bethesda system in the indeterminate categories.

	AUS/FLUS (%)	**SFN/FN** (%)	**SM** (%)
Brandler *et al.* (2017)		82.10	
Maletta *et al.* (2016)	15	56	27
Bizzarro *et al.* (2016)	13.50	40.60	35.10
Faquin *et al.* (2016)	31.20	26.60	24.30
Strickland *et al.* (2015)	14.80	13.40	14.40
Lee *et al.* (2017)	57		19
Maia & Amendoeira*	23.80	25.60	13.70

*Unpublished observations.
AUS/FLUS, atypia of unknown significance/follicular lesion of unknown significance; SFN/FN, suspicious for follicular neoplasm/follicular neoplasm; SM, suspicious of malignancy.

Well-differentiated, invasive, follicular patterned neoplasms with PTC-nuclei

Infiltrative follicular subtype PTC

BRAF-like

Lymph node metastases/ local recurrence

Similar to classic PTC

Encapsulated follicular variant PTC with invasion

Minimally invasive

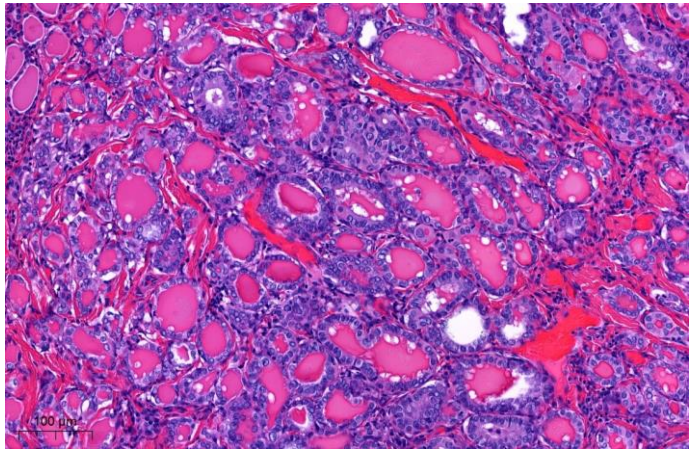
Angioinvasive

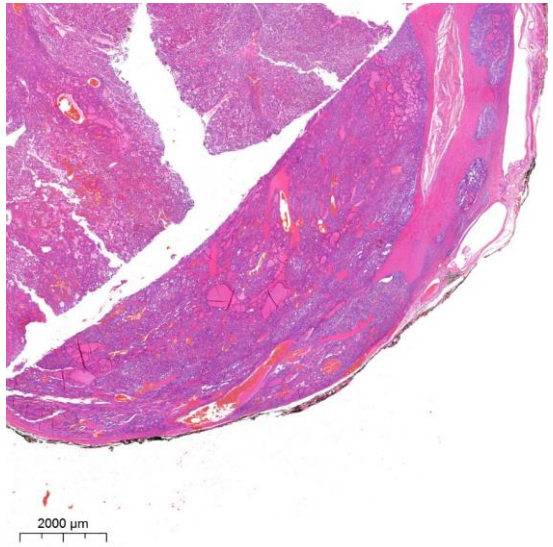
Widely invasive

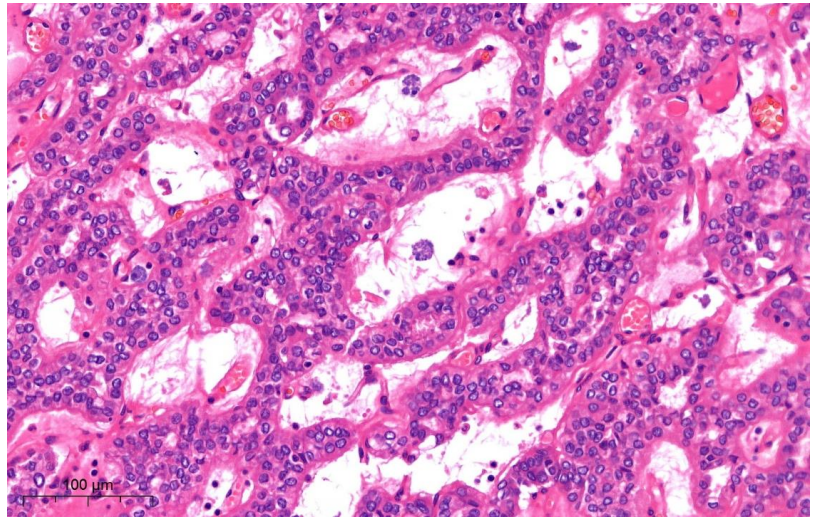
RAS-like

Distant metastases

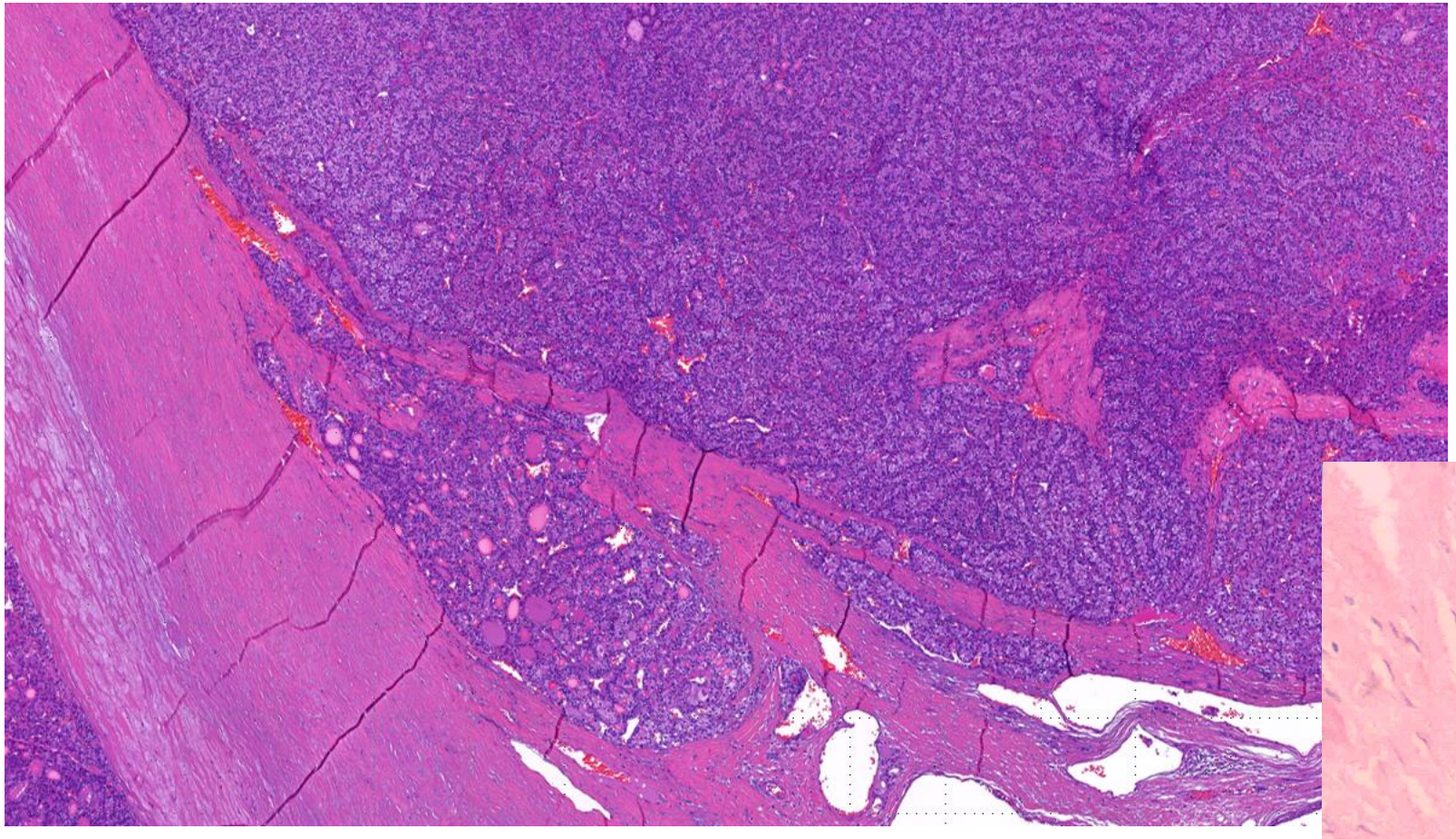
Similar to FTC

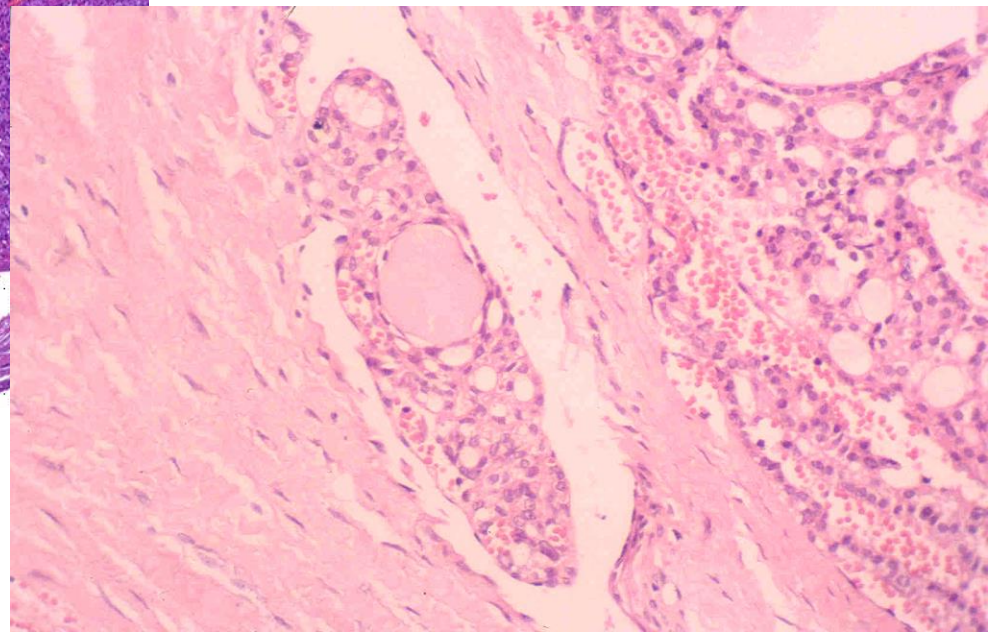






Vascular invasion? Capsular invasion?





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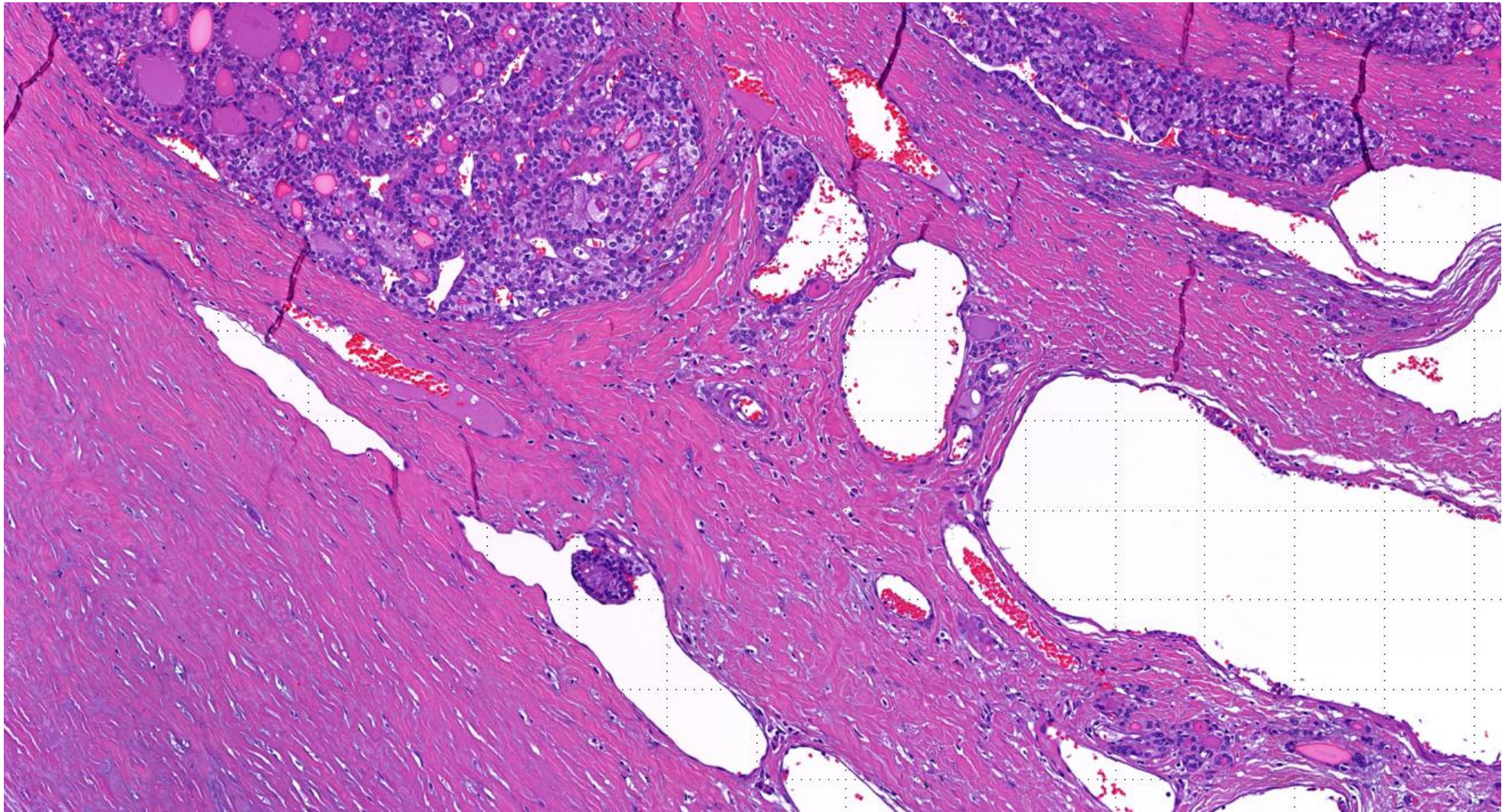

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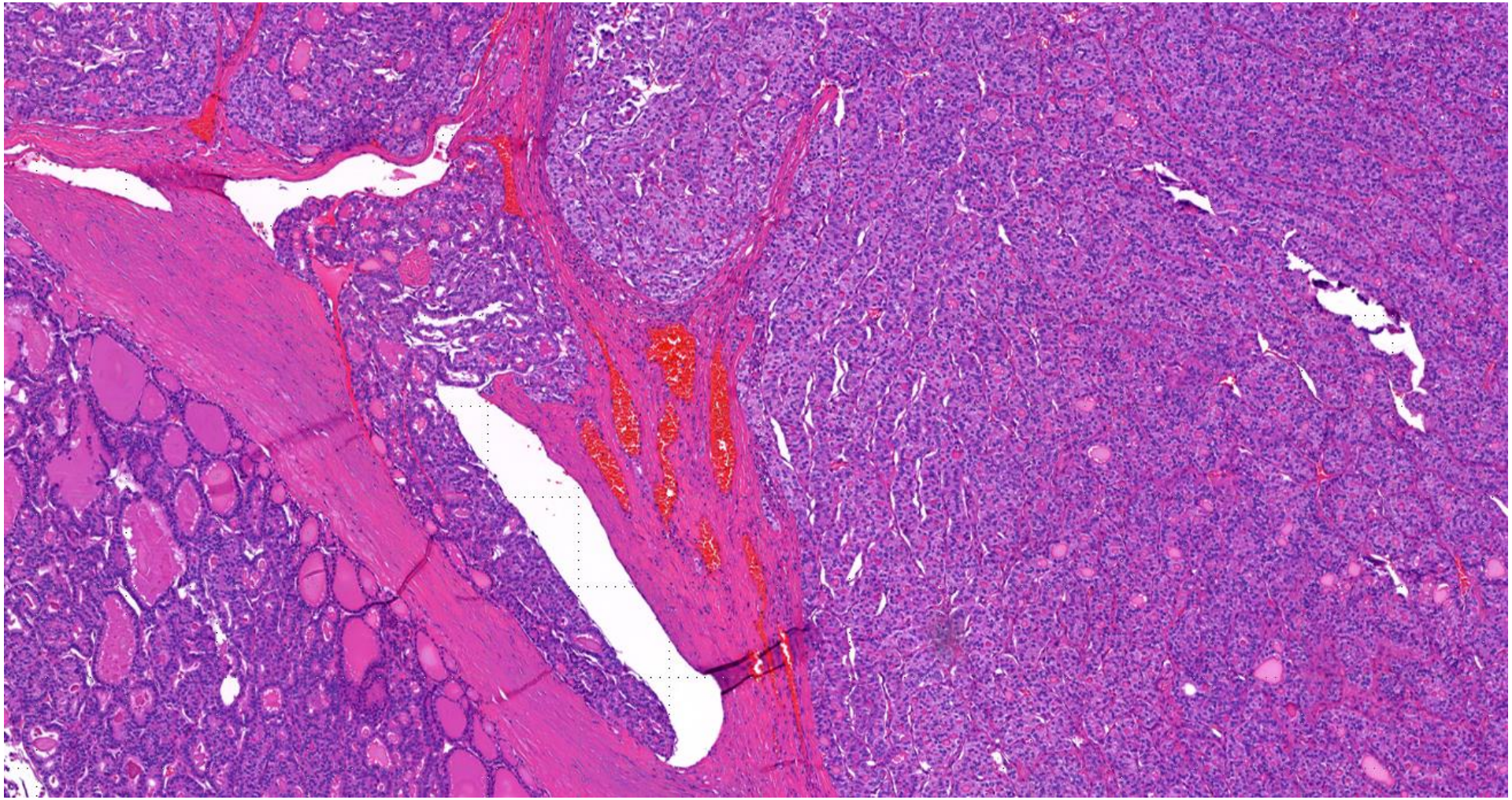

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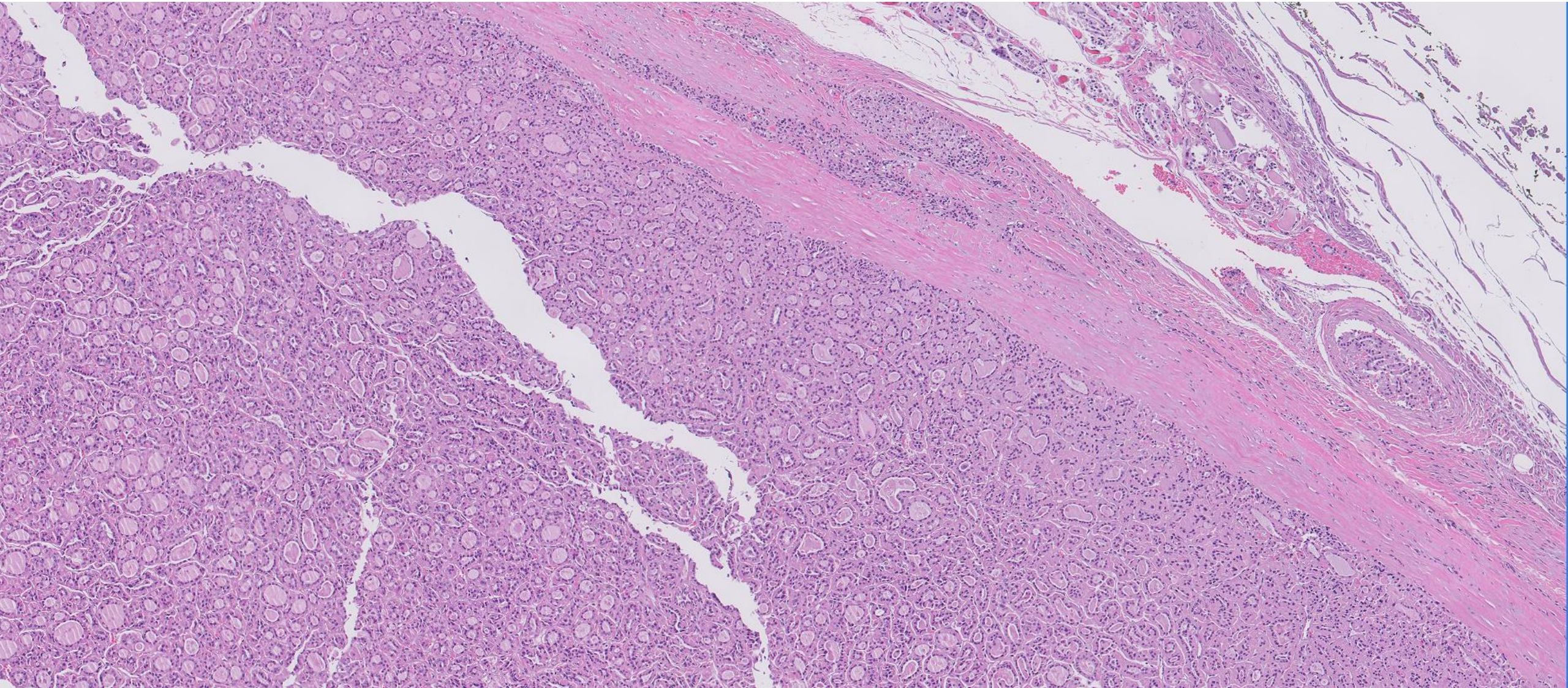
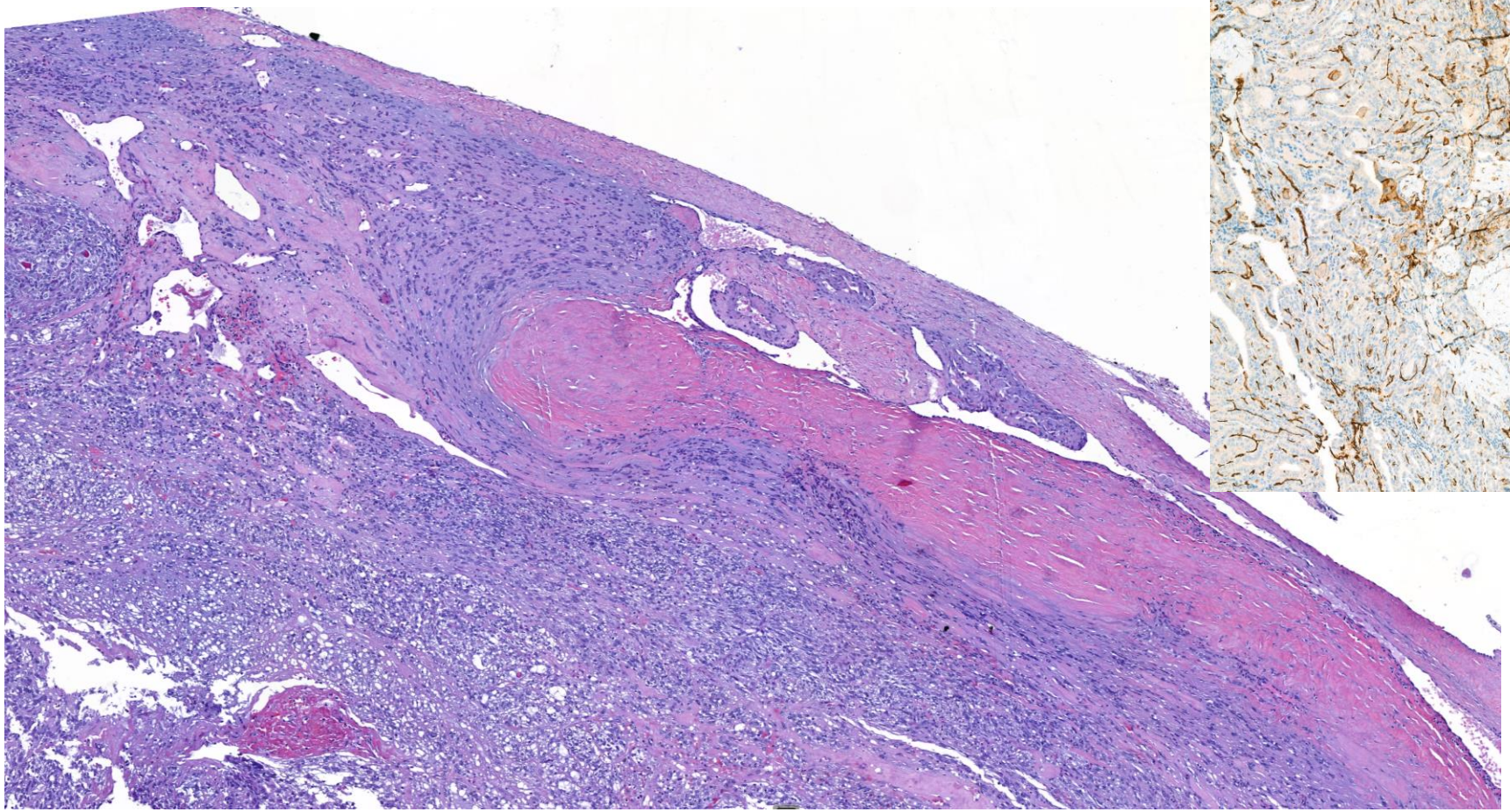
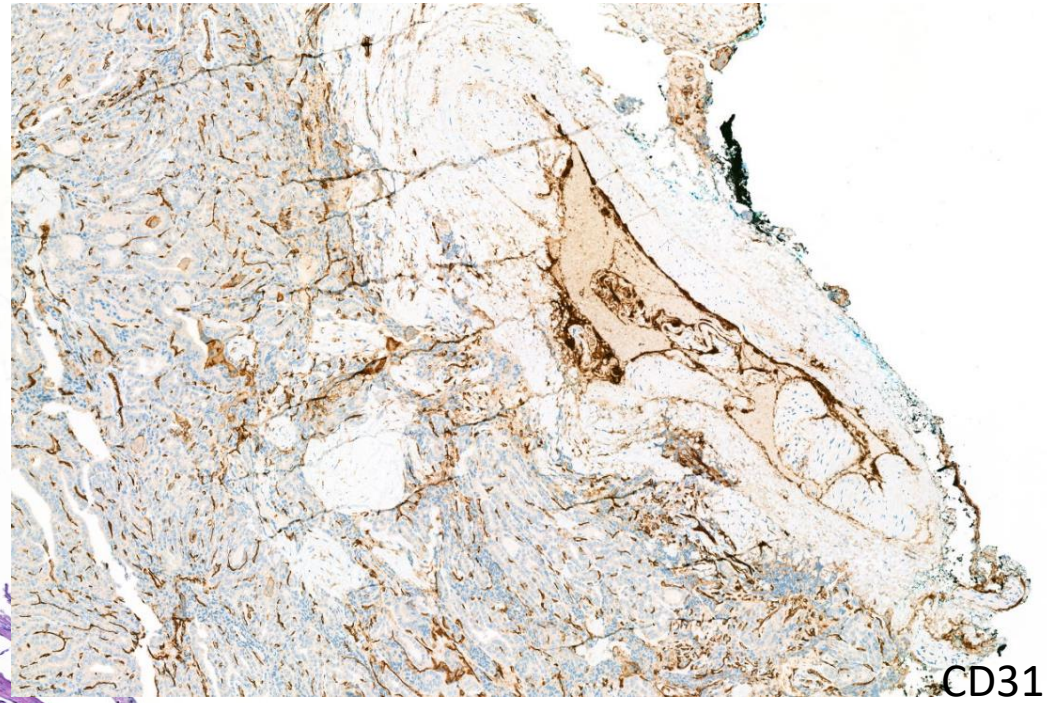


Vascular endotelial hyperplasia





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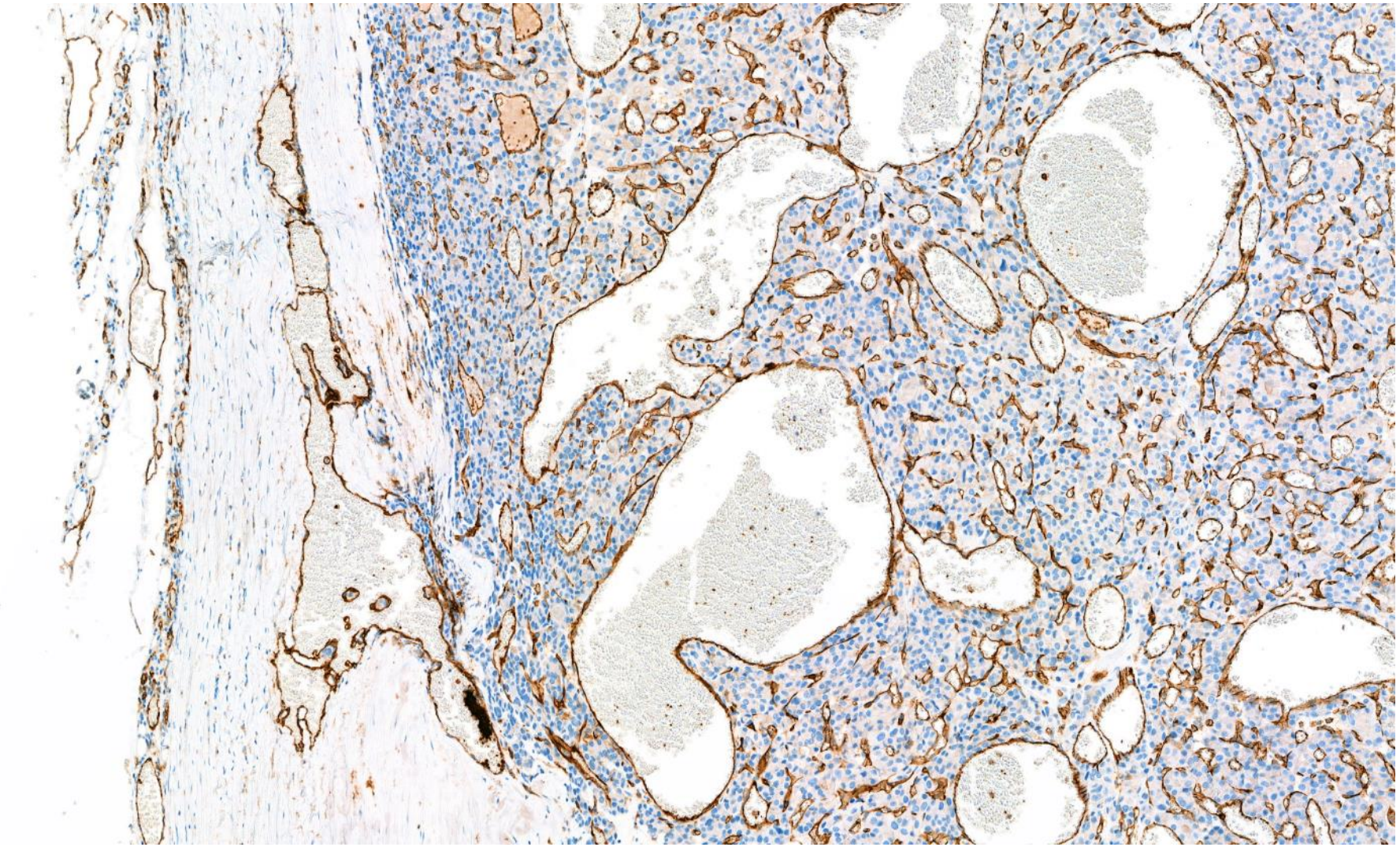

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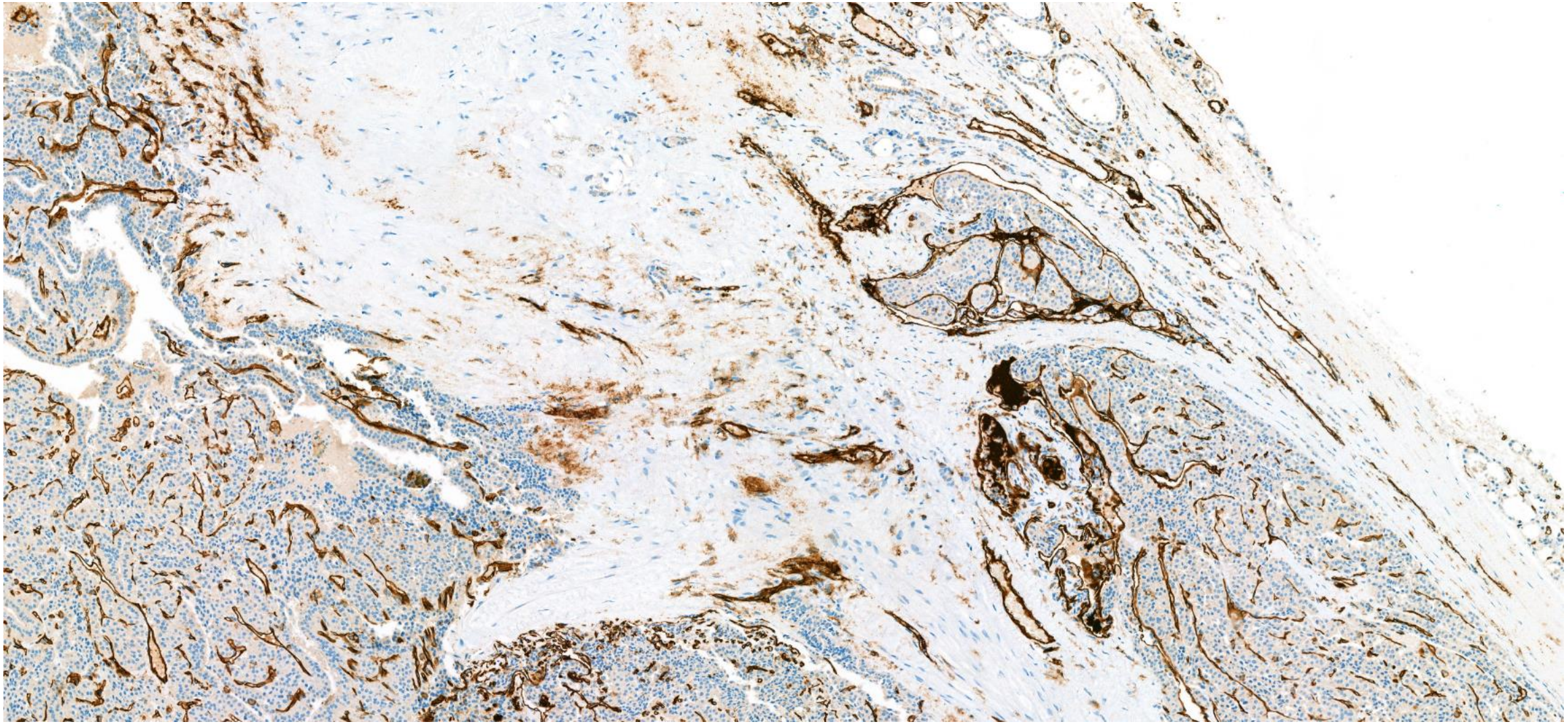

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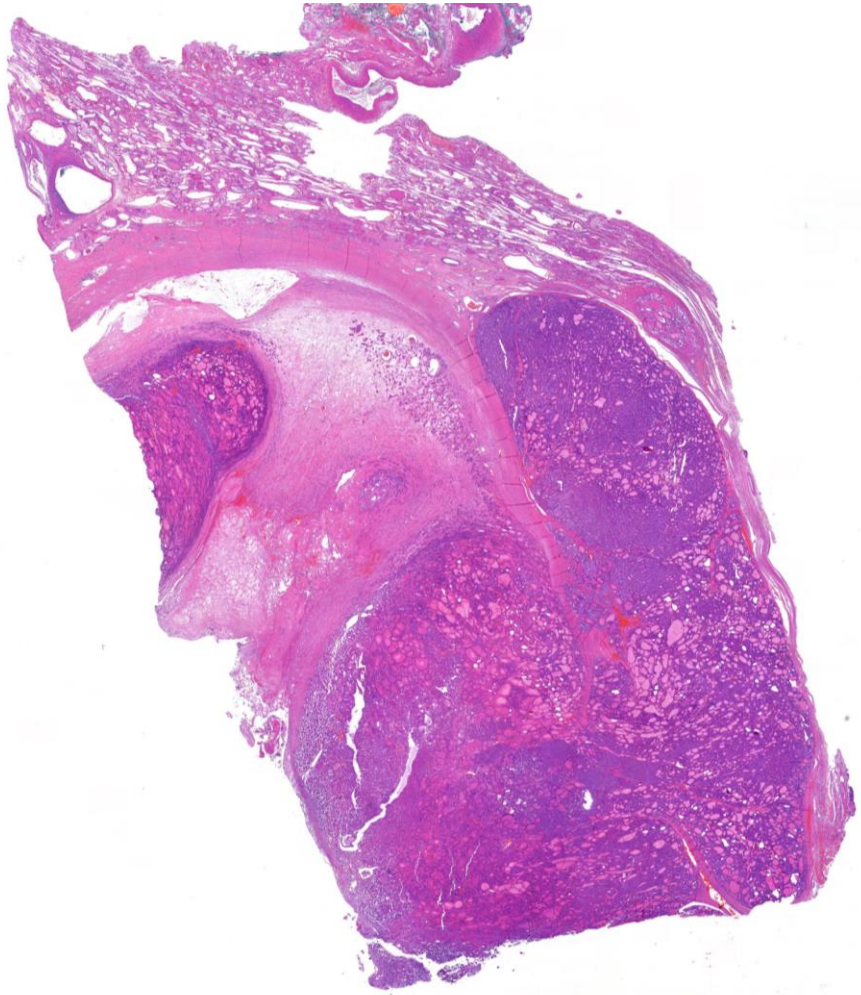

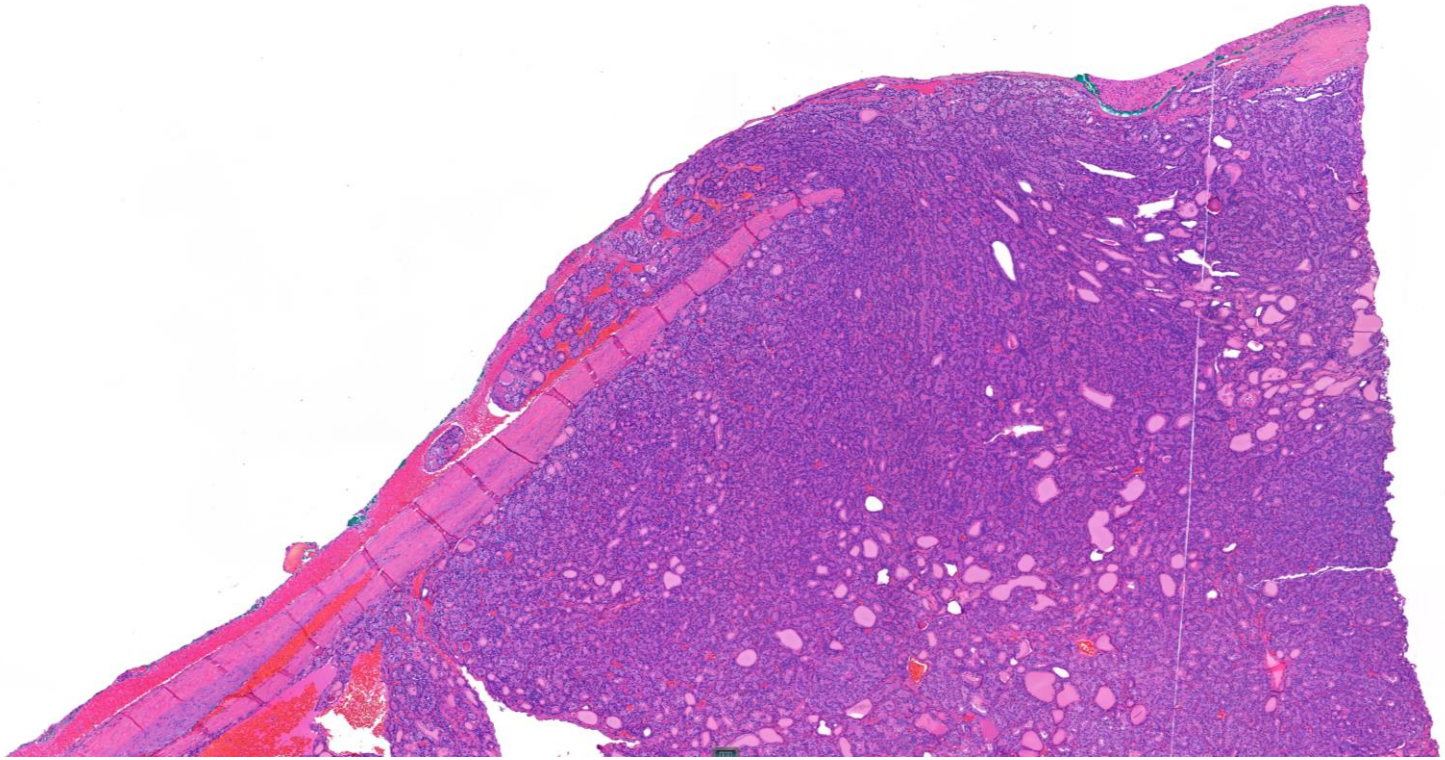

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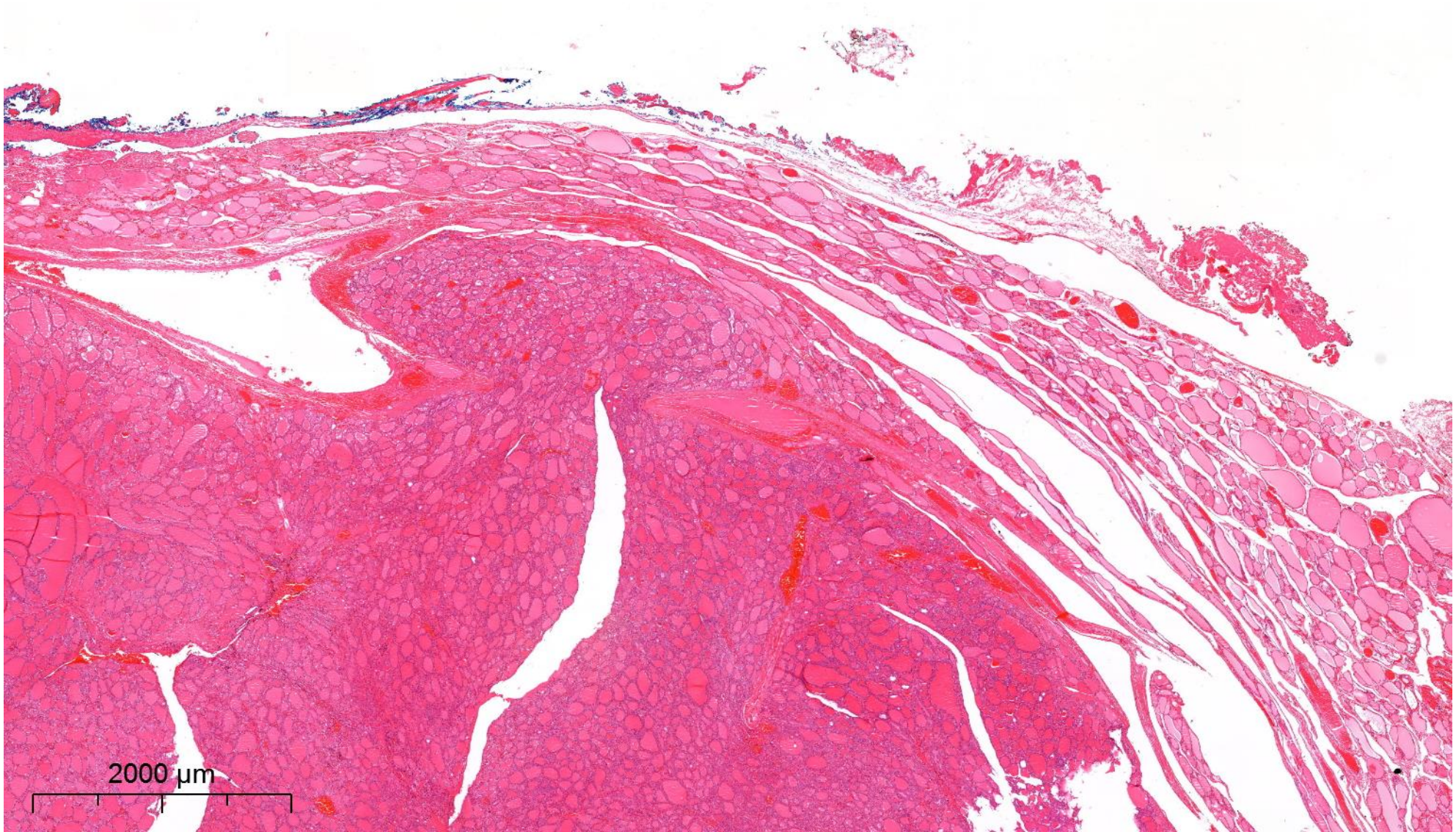

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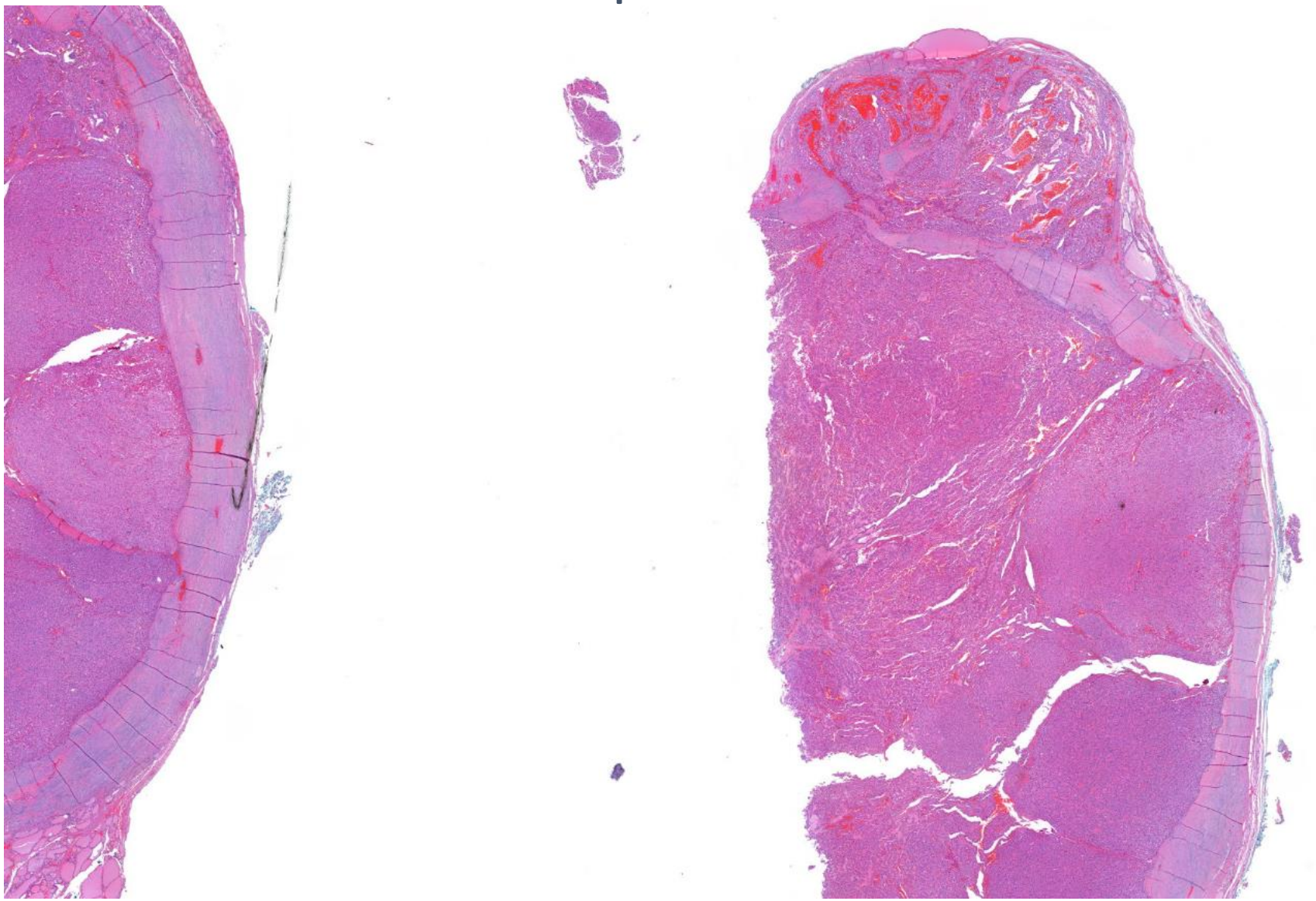
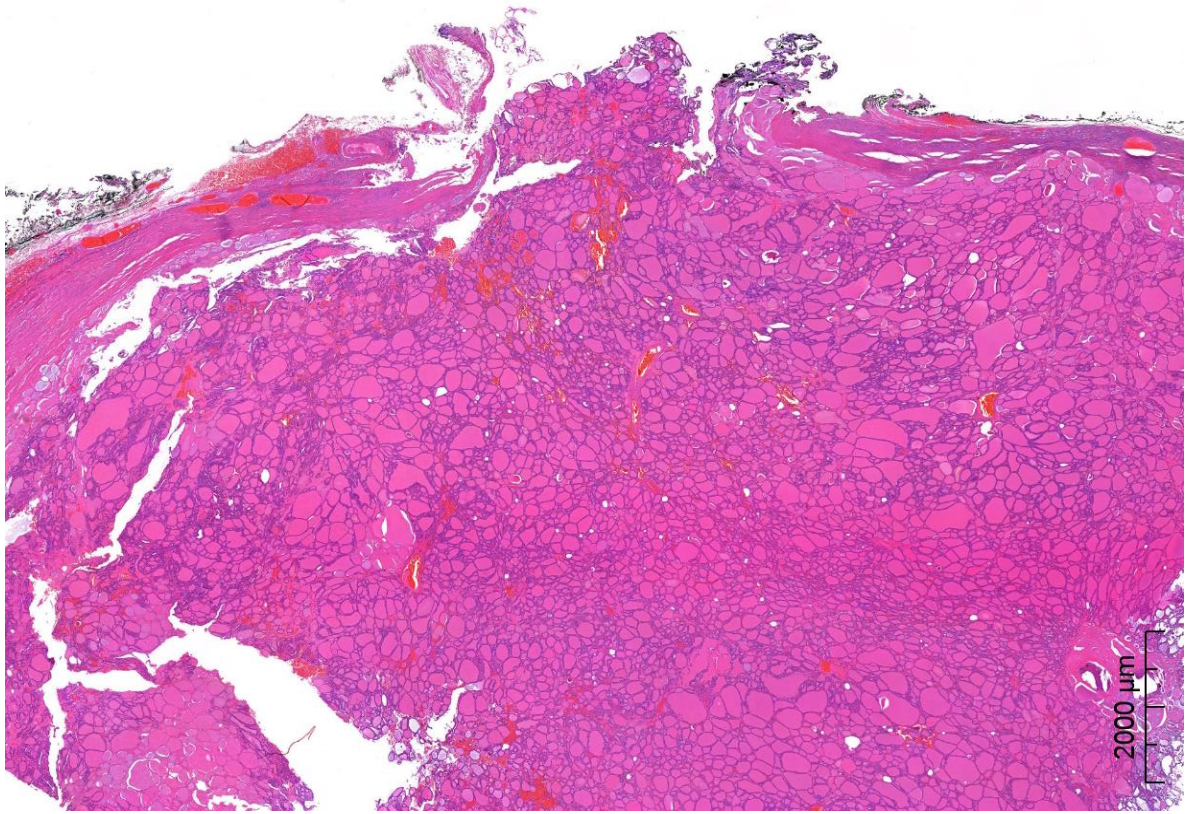
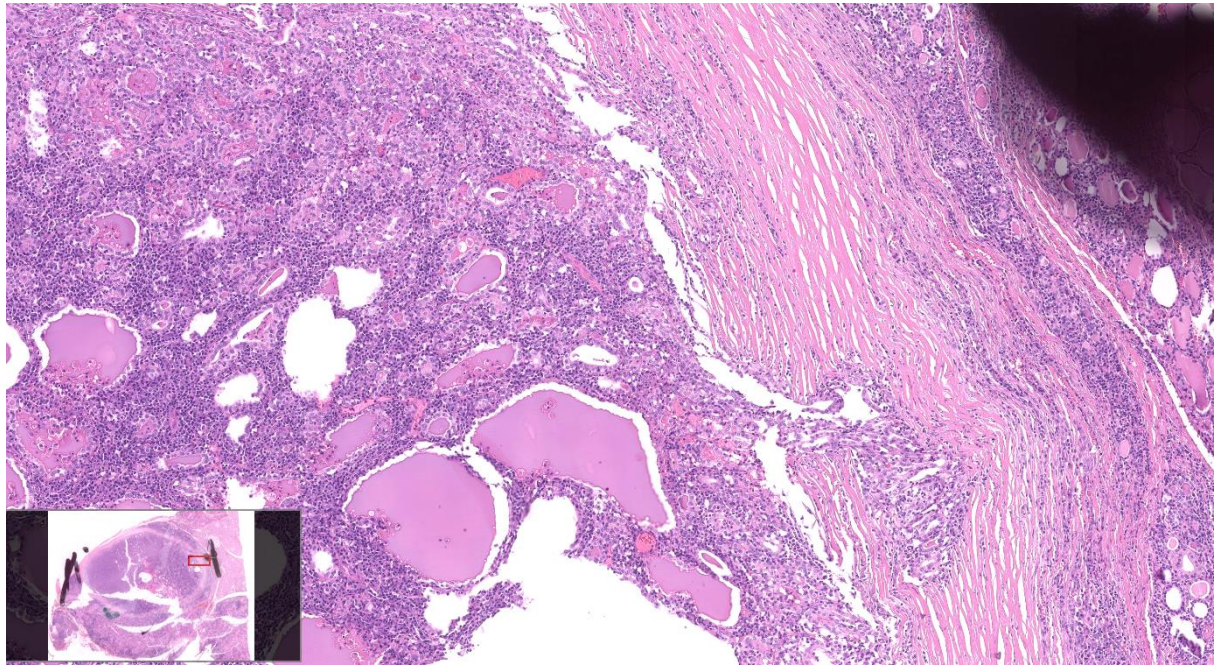


Vascular invasion? Capsular invasion?



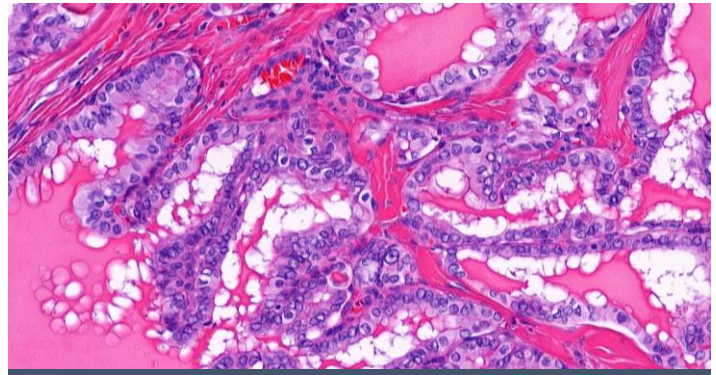


PTC subtypes *BRAF*-like family of malignancies

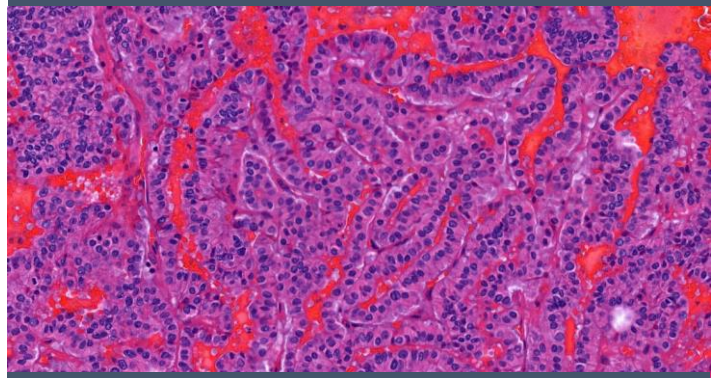
Table 3 Key histopathologic criteria and molecular profiles of subtypes of papillary thyroid carcinoma (Figs. 4–10)

PTC subtype	Proportion of subtype features	Key histopathologic features	Key molecular profile
Infiltrative follicular	≥ 90% neoplastic follicles	• Infiltrative growth • Sclerosis • Multicentric tumor foci	• *BRAF* V600E and K601E, *NRAS**, *CTNNB1**mutations • *RET* translocation, *NTRK* and *ALK* fusions
Tall cell	≥ 30% tall cells	• Tightly packed follicles and papillae — AKA "tram track appearance." • Tumor cell height at least 3× the width [279]** • Eosinophilic cytoplasm with distinct cytoplasmic border • Easily identifiable nuclear features of PTC	• *BRAF* V600E, *TERT* promoter and *TP53* mutations
Columnar cell	NA	• Papillary growth admixed with follicles • Columnar cells with pale to eosinophilic cytoplasm and prominent pseudostratification • Subnuclear vacuoles	• *BRAF* V600E, *RAS**, *TERT* promoter*, and *TP53** • *BRAF* fusions, activating *BRAF* deletions, loss of *CDKN2A* and copy number alterations (recurrent gain of chromosome 1q)
Hobnail	≥ 30% hobnail cells	• Complex papillary or micropapillary growth pattern, rare presence of follicular architecture • Tumor cells with enlarged nuclei, bulging from the apical surface	• *BRAF* V600E, *TP53*, *TERT* promoter, *PIK3CA* mutations • Rarely, *RET* rearrangements, moleular *CTNNB1*, *EGFR*, *ATK1*, *ATM*, *ARID2*, and *NOTCH1*
Solid	> 50% solid trabecular growth	• Solid, trabecular or nested growth pattern with intervening thin and delicate fibrovascular bands, rarely foci of dense sclerosis • Lack of tumor necrosis (including single cell necrosis) and high mitotic rate	• *CCD6::RET* and *NCOA4::RET* rearrangements (later in radiation indiuced tumors), and *BRAF* V600E* • *ETV6::NTRK3* fusions
Diffuse sclerosing	100% diffuse unilateral or bilateral involvement, without dominant tumor mass	• Dense sclerosis, extensive lympahtic permeation, numerous psammoma bodies and ssociated chronic lymphocytic thyroiditis • Tumor cells arranged in solid nests and papillary formations with squamous metaplasia	• *RET* rearrangements (especially *NCOA4::RET* in radiation induced cases), *BRAF* V600E mutations (20% of cases) and *ALK* rearrangements (10% of cases) • High frequency of *LOH* of 3p24, 9p21, 17q21, 21q22, and 22q13
Warthin-like	NA	• Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis • Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate	• *BRAF* V600E mutation
Oncocytic***	NA	• Well-developed papillae lined by oncocytic cells	• *BRAF* V600E mutations • *GRIM-19* (germline mutations) and *RET* rearrangements*

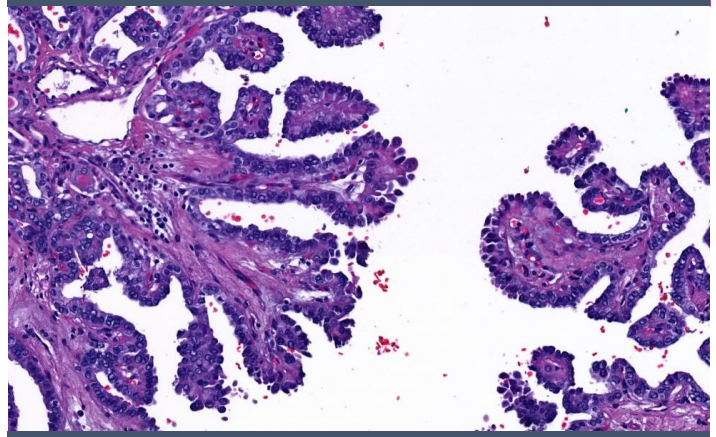
*Rare molecular alteration; **The new criterion for the diagnosis of tall cell subtype as compared to 4th edition; ***For oncocytic-FVPTC refer to question #3



Classic PTC



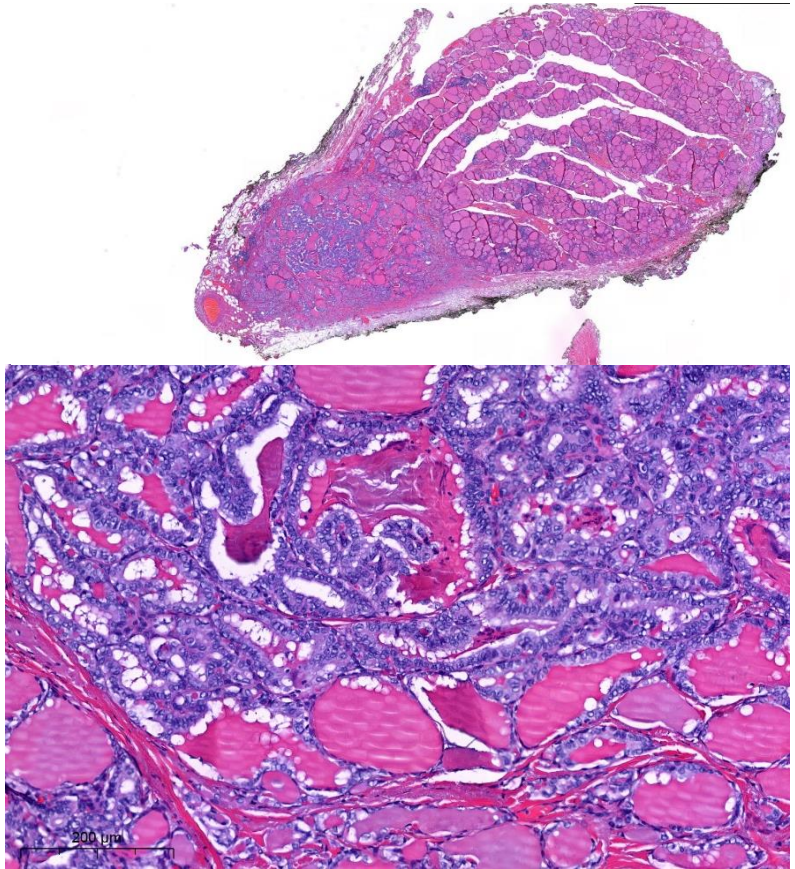
Tall-cell PTC



Hobnail PTC

The relevance of staging

- Papillary microcarcinoma is not a variant/subtype of PTC
  - Subtyping small papillary carcinomas



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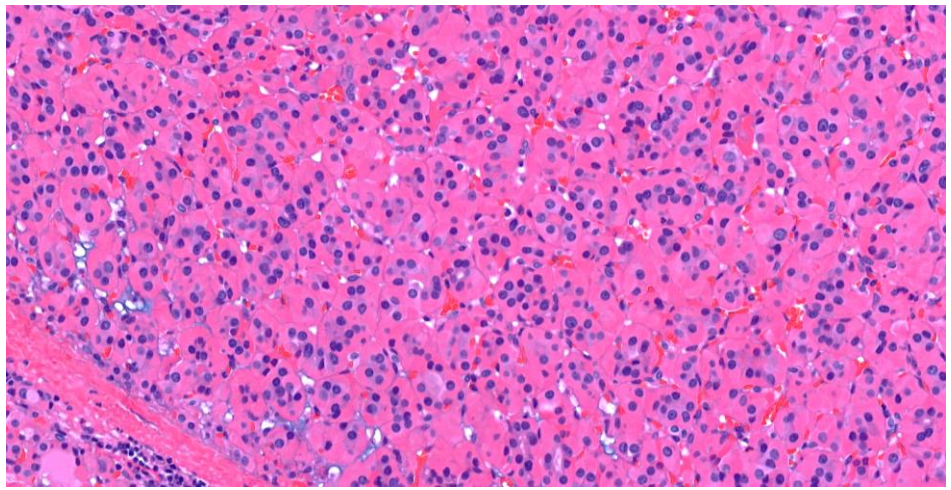
Progression of Low-Risk Papillary Thyroid Microcarcinoma During Active Surveillance: Interim Analysis of a Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma in Korea

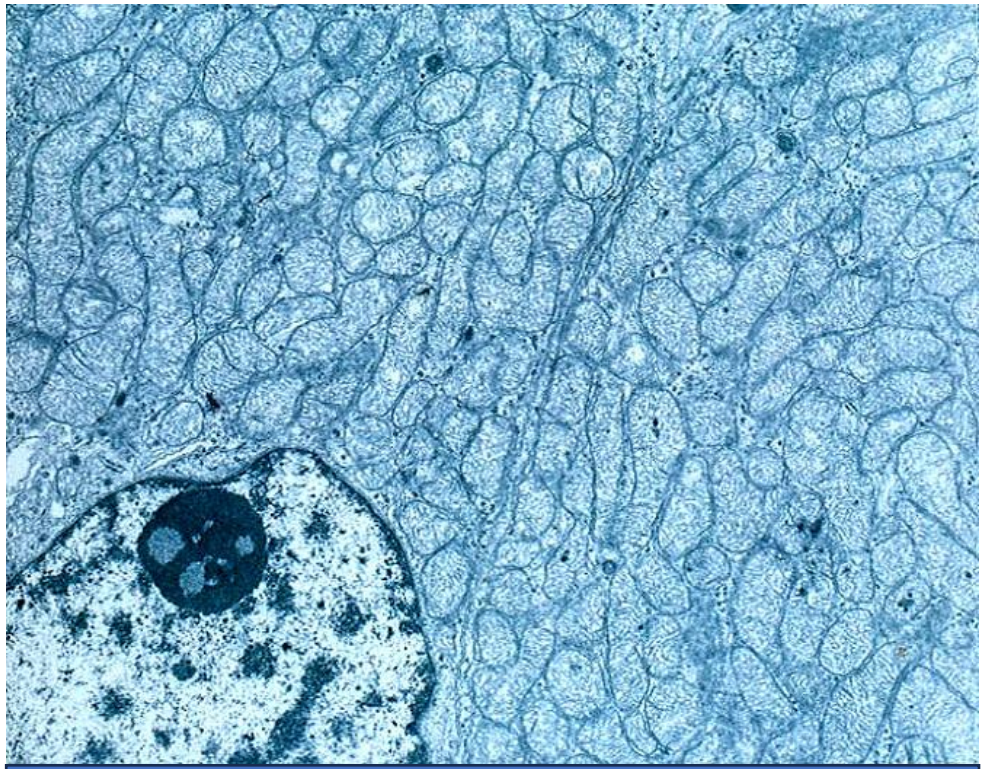
Eun Kyung Lee,[1,*] Jae Hoon Moon,[2,*] Yul Hwangbo,[1] Chang Hwan Ryu,[3] Sun Wook Cho,[4,5] June Young Choi,[6] Eun-Jae Chung,[7] Woo-Jin Jeong,[8] Yuh-Seog Jung,[3] Junsun Ryu,[3] Su-jin Kim,[9] Min Joo Kim,[4] Yeo Koon Kim,[10] Chang Yoon Lee,[11] Ji Ye Lee,[12] Hyeong Won Yu,[6] Jeong Hun Hah,[7] Kyu Eun Lee,[5,9,13] You Jin Lee,[1] Sue K. Park,[11,13,14] Do Joon Park,[4,5] Ji-hoon Kim,[12] and Young Joo Park[4,5,14]

every 6–12 months to monitor for disease progression. Progression under AS was evaluated by a criterion of tumor size increment by 3 mm in one dimension (3 mm), 2 mm in two dimensions (2×2 mm), new extrathyroidal extension (ETE), or new lymph node metastasis (LNM), and a composite outcome was defined using all four criteria. ***Results:*** A total of 1177 eligible patients with PTMC (919 female, 78.1%) with a median age of 48 years (range 19–87) were enrolled; 755 (64.1%) patients chose AS and 422 (35.9%) underwent surgery. Among 755 patients under AS, 706 (female 537, 76.1%) underwent at least two ultrasound examinations and were analyzed. Over a follow-up period of 41.4 months (standard deviation, 16.0), 163 AS patients (23.1%) underwent surgery. Progression defined by the composite outcome was observed in 9.6% (68/706) of patients, and the 2- and 5-year progression estimates

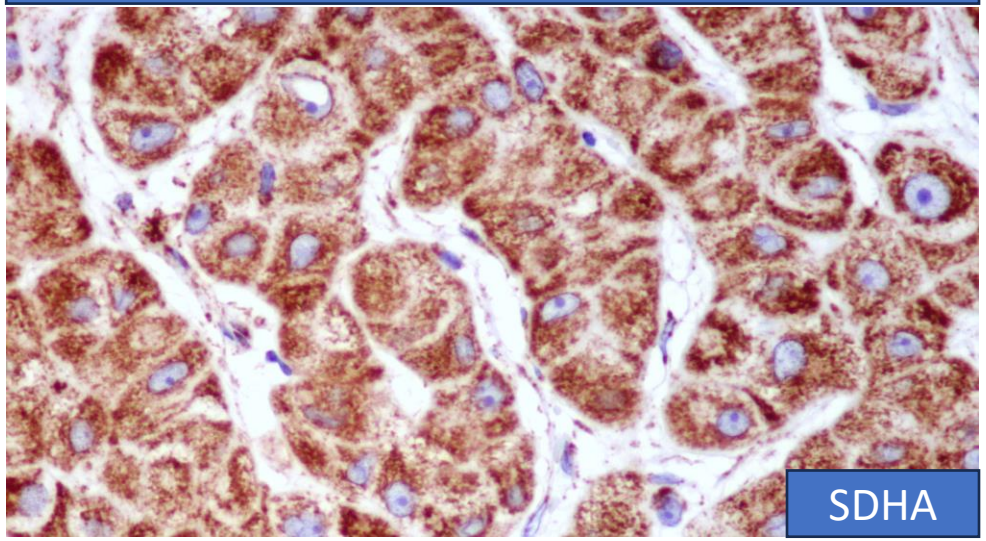
Oncocytic tumours

- Oncocytic adenoma
- Oncocytic carcinoma
- Oncocytic papillary carcinoma
- Oncocytic poorly differentiated carcinoma
- Oncocytic medullary carcinoma



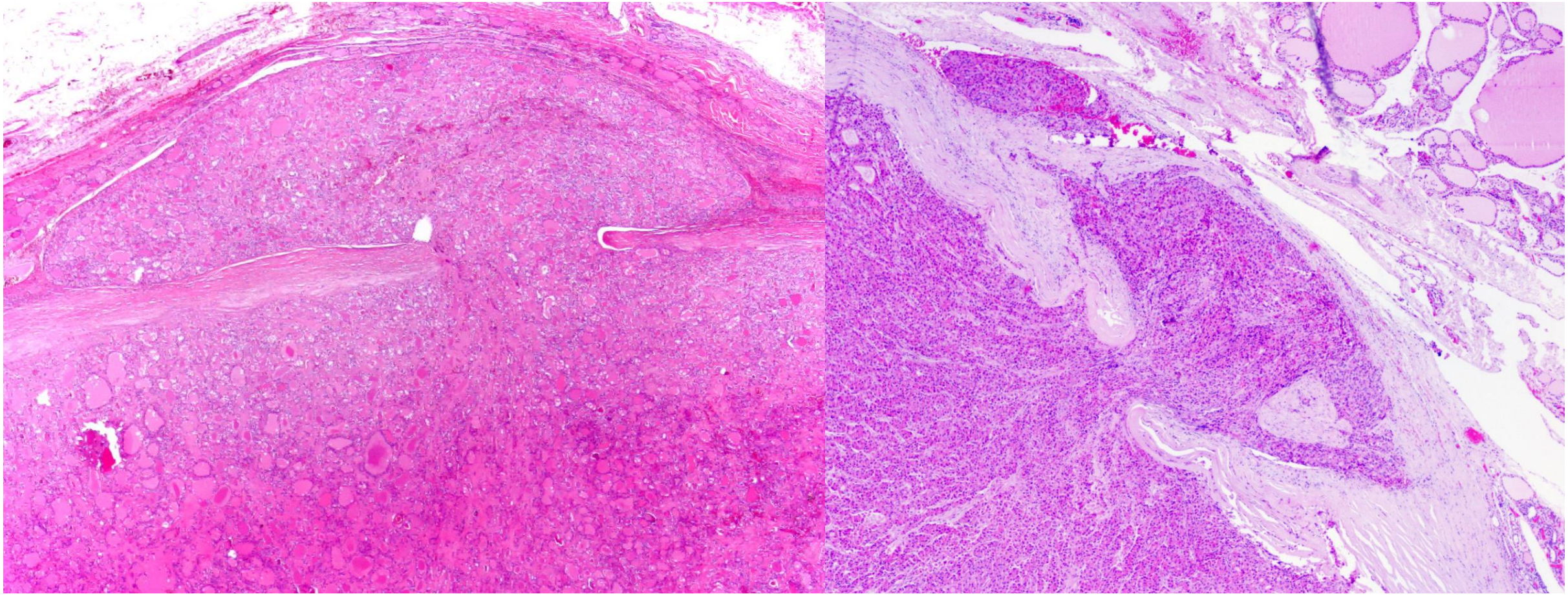


Courtesy of Prof. Manuel Sobrinho Simões



SDHA

Oncocytic carcinoma



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Follicular-derived/patterned thyroid tumors

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