

# UPDATE OF THYROID NEOPLASMS IN THE MOLECULAR DIAGNOSTICS ERA

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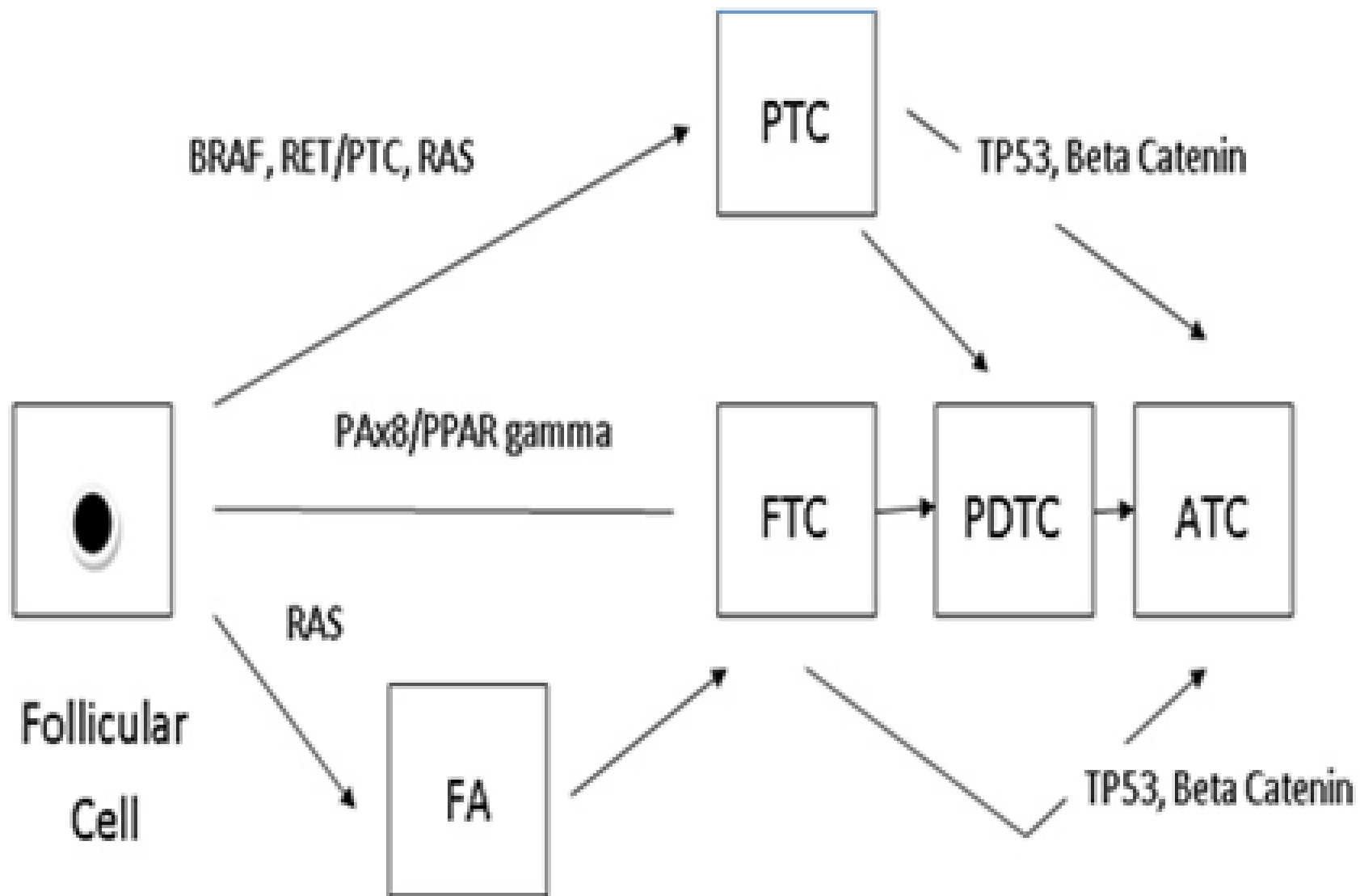
September 18, 2021

# Methodological ERAS in Pathology

- Histochemical/Electron Microscopic
- Immunohistochemical
- Molecular
- Digital Pathology/Artificial Intelligence

# Thyroid Carcinoma

Type	%
Papillary CA	80
Follicular CA	5-10
Medullary Thyroid CA	5-10
Poorly Differentiated CA	1-2
Anaplastic CA	1-2



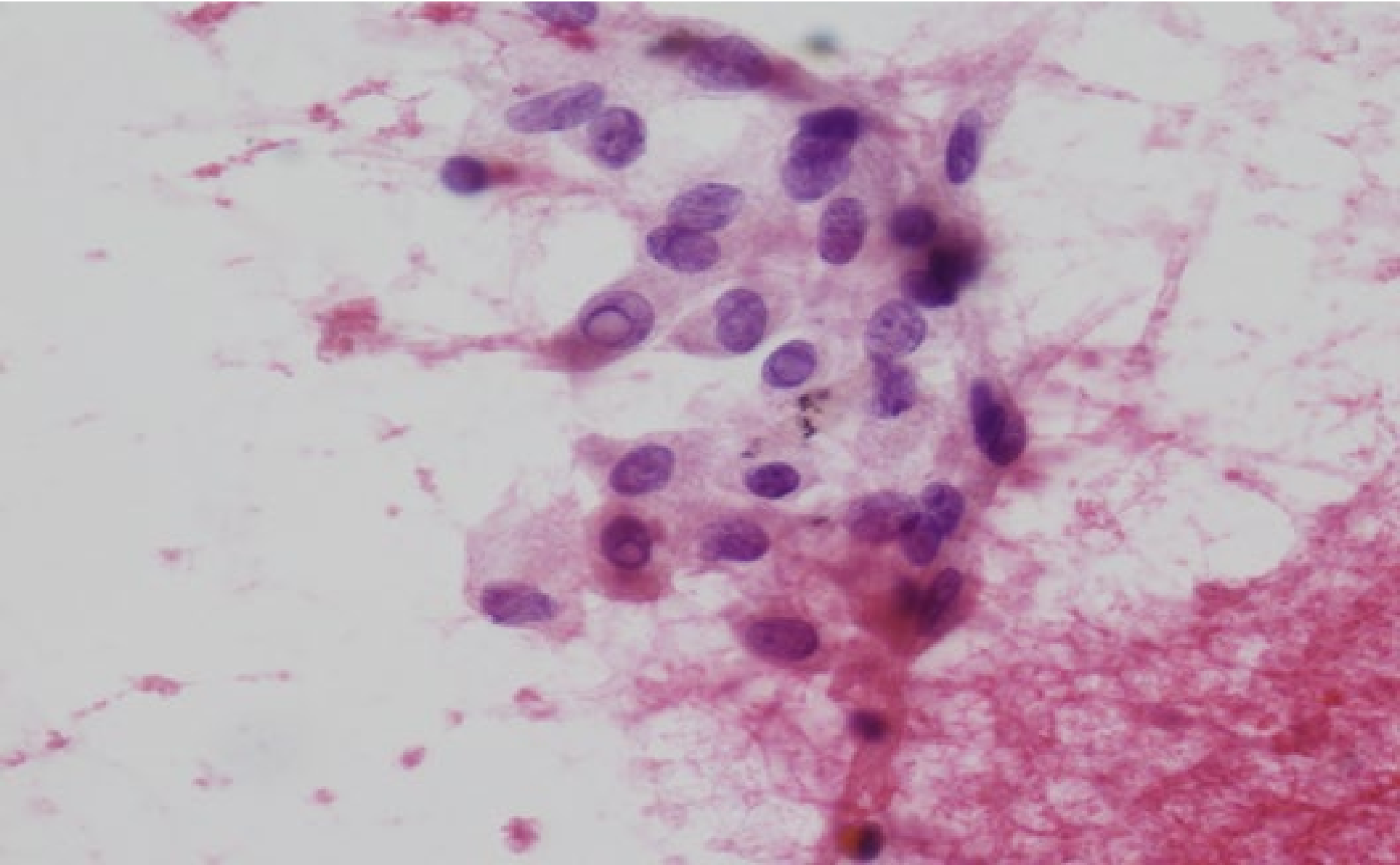
# Telomerase (TERT) Promoter Mutations (C228T and C250T)

• Benign Thyroid Tumors	0%
• Medullary Thyroid Carcinomas	0%
• PTC	11.7%
• FTC	11.4%
• PDTC	37.5%
• ATC	42.6%

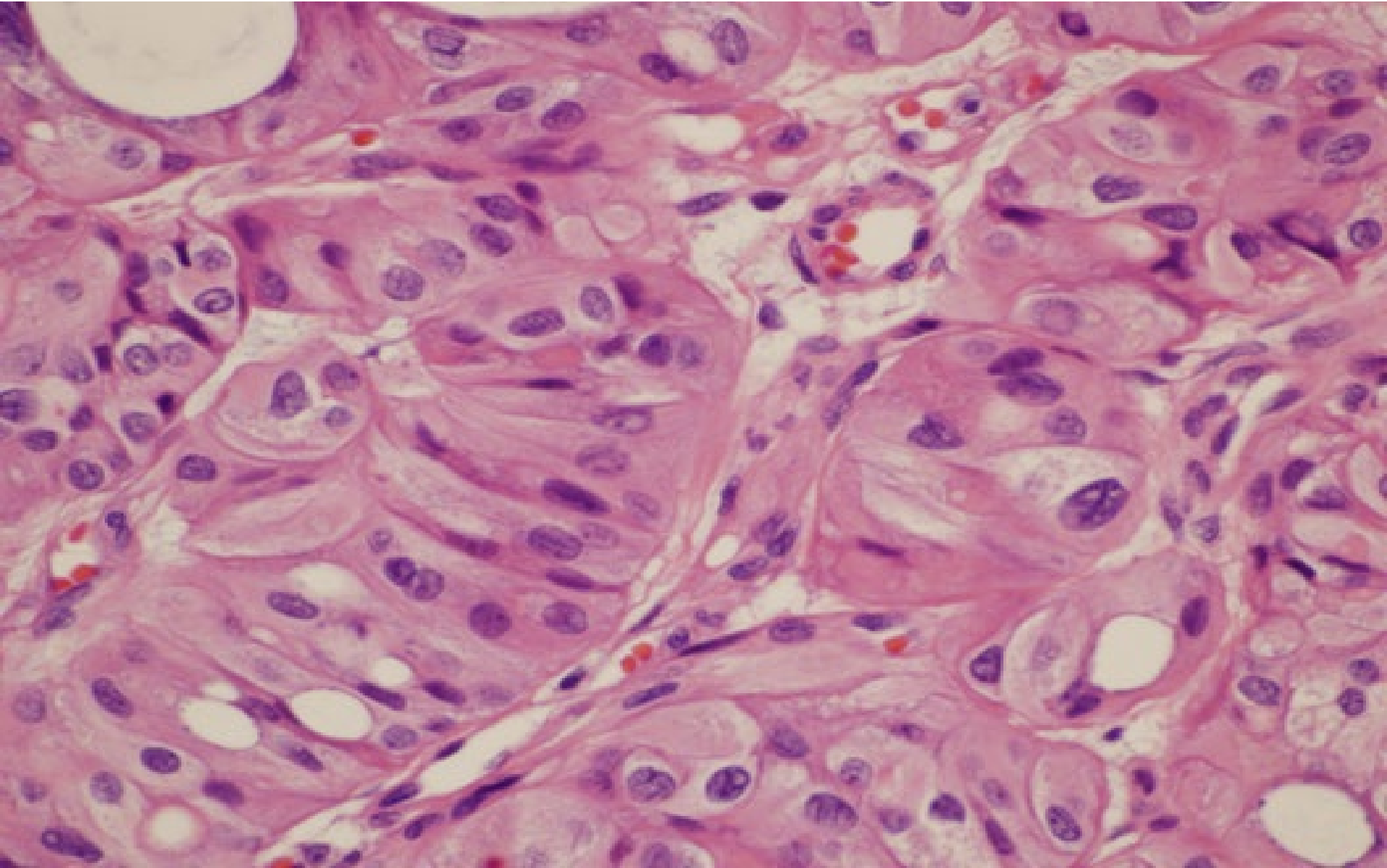
# Commonly Used CytoMolecular Tests

- Affirma Gene Expression Classifier (GEC)
- Affirma Genomic Sequencing Classifier (GSC)
- Thyroseq v.3

# Hyalinizing Trabecular Tumor

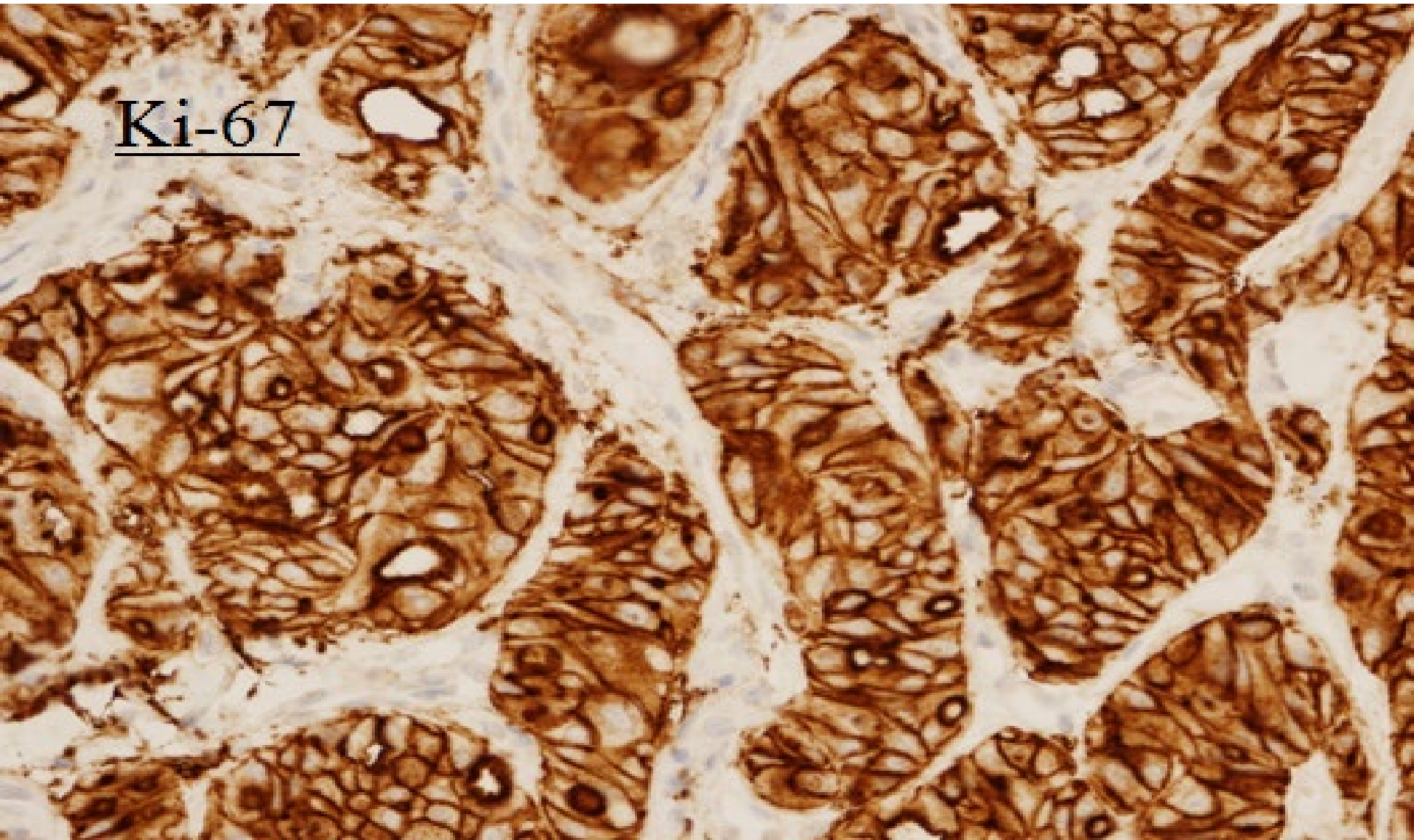


# Hyalinizing Trabecular Tumor





# Ki-67 in Hyalinizing Trabecular Tumor



# Hyalinizing Trabecular Tumor

- GLIS rearrangement as a genomic hallmark of HTT by Nikiforov et al in 2019.
- PAX8-GLIS3 in HTT, but not in PTC

Nikiforov et al. Thyroid 29:161, 2019

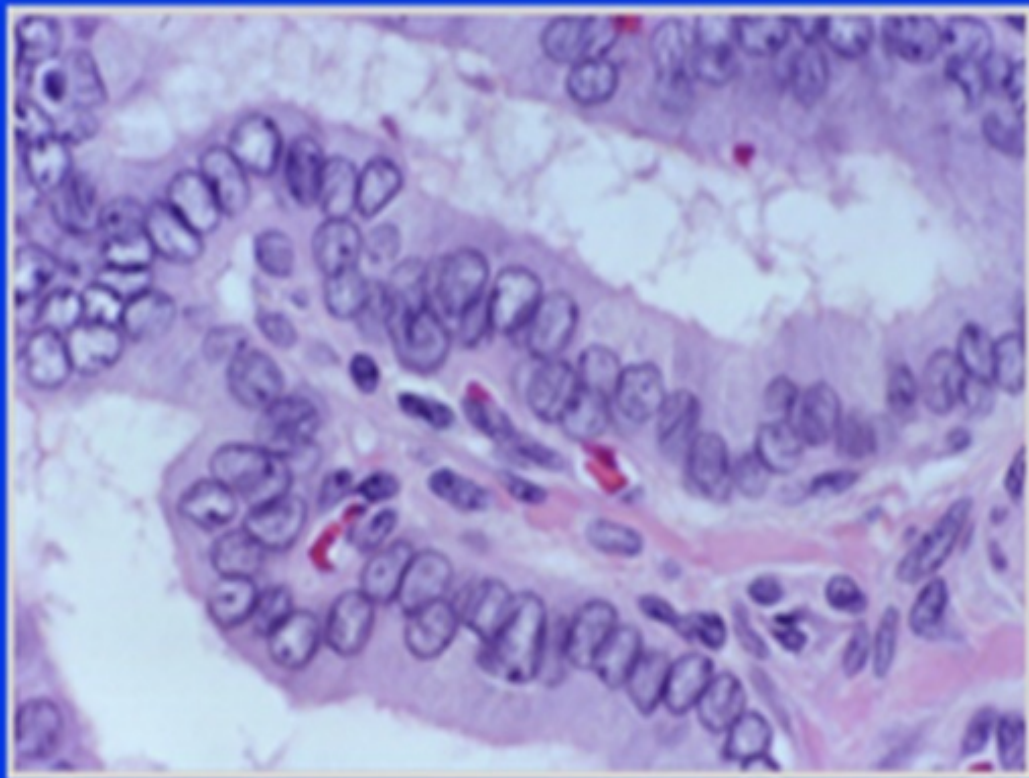
Marchio et al. Modern Pathol 32:1734, 2019

# Are HTT Ever Malignant

- Carney JA, Hirokawa M, Lloyd RV, Papotti M, Sebo TJ. Hyalinizing trabecular tumors of the thyroid are almost all benign. Am J Surg Pathol 32:1877,2008

# HTT Ever Malignant?

- Examined 119 neoplasms
- Follow up in 96%
- 118 No evidence of aggressive behavior
- 1 with vascular and capsular invasion
- Most benign tumors



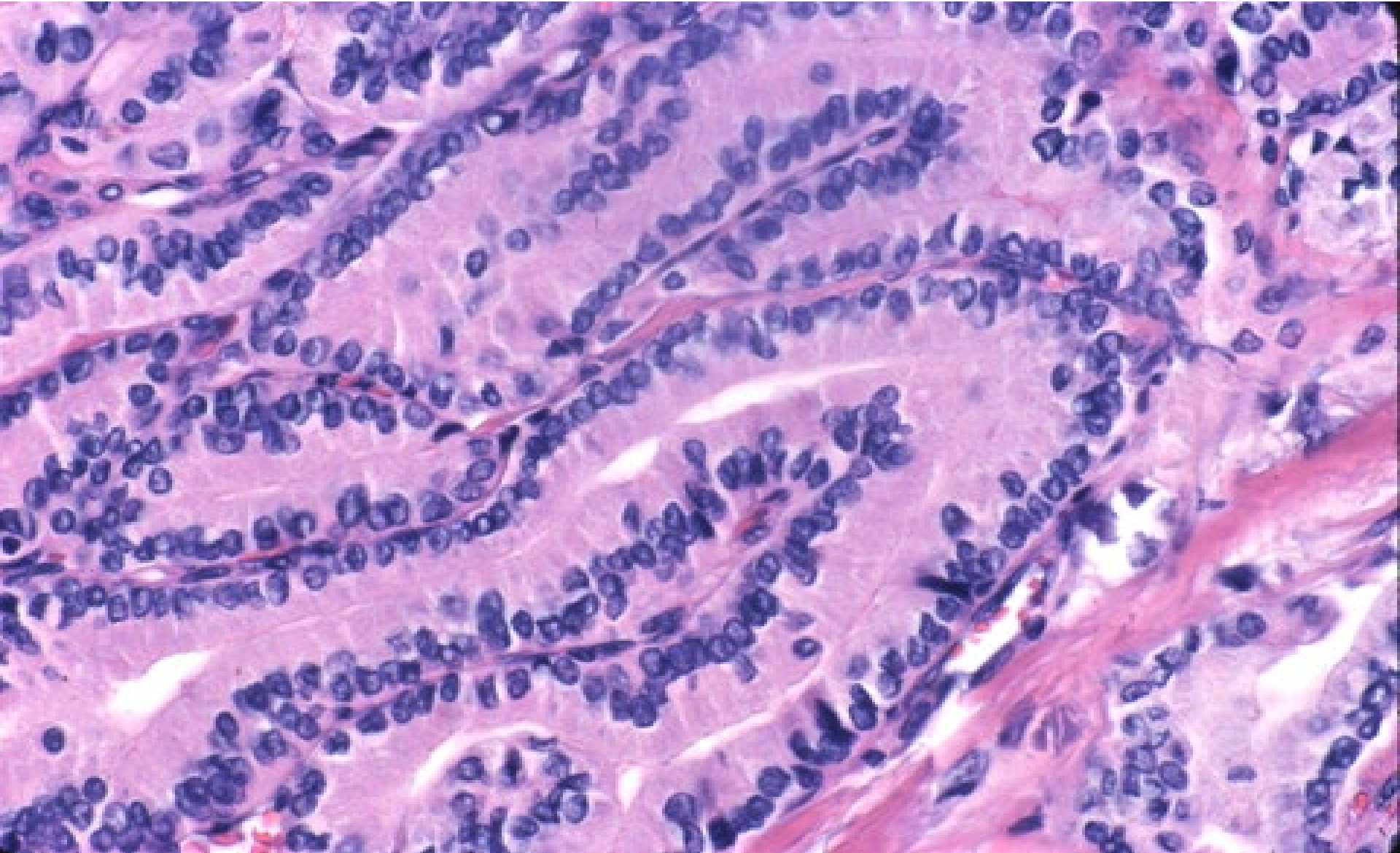
# Aggressive Variants of Papillary Thyroid Carcinoma

- Tall Cell
- Columnar Cell
- Solid Variant
- Diffuse Sclerosing Variant
- PTC with Hobnail Features (Micropapillary)

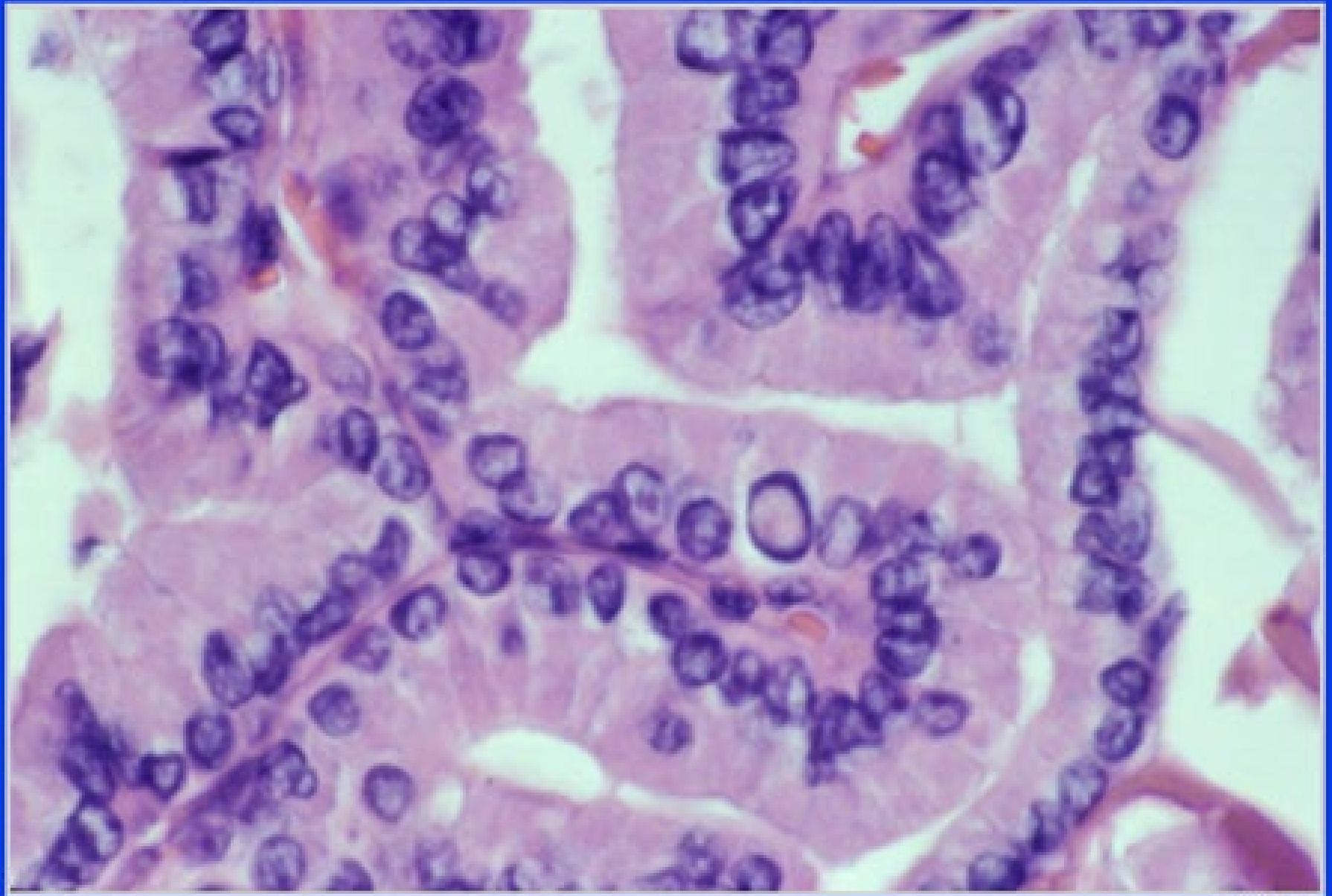
# Tall Cell Variant

- Cells 2 to 3 times as tall as they are wide
- Prominent nuclear pseudo-inclusions
- Most patients older and have larger tumors.

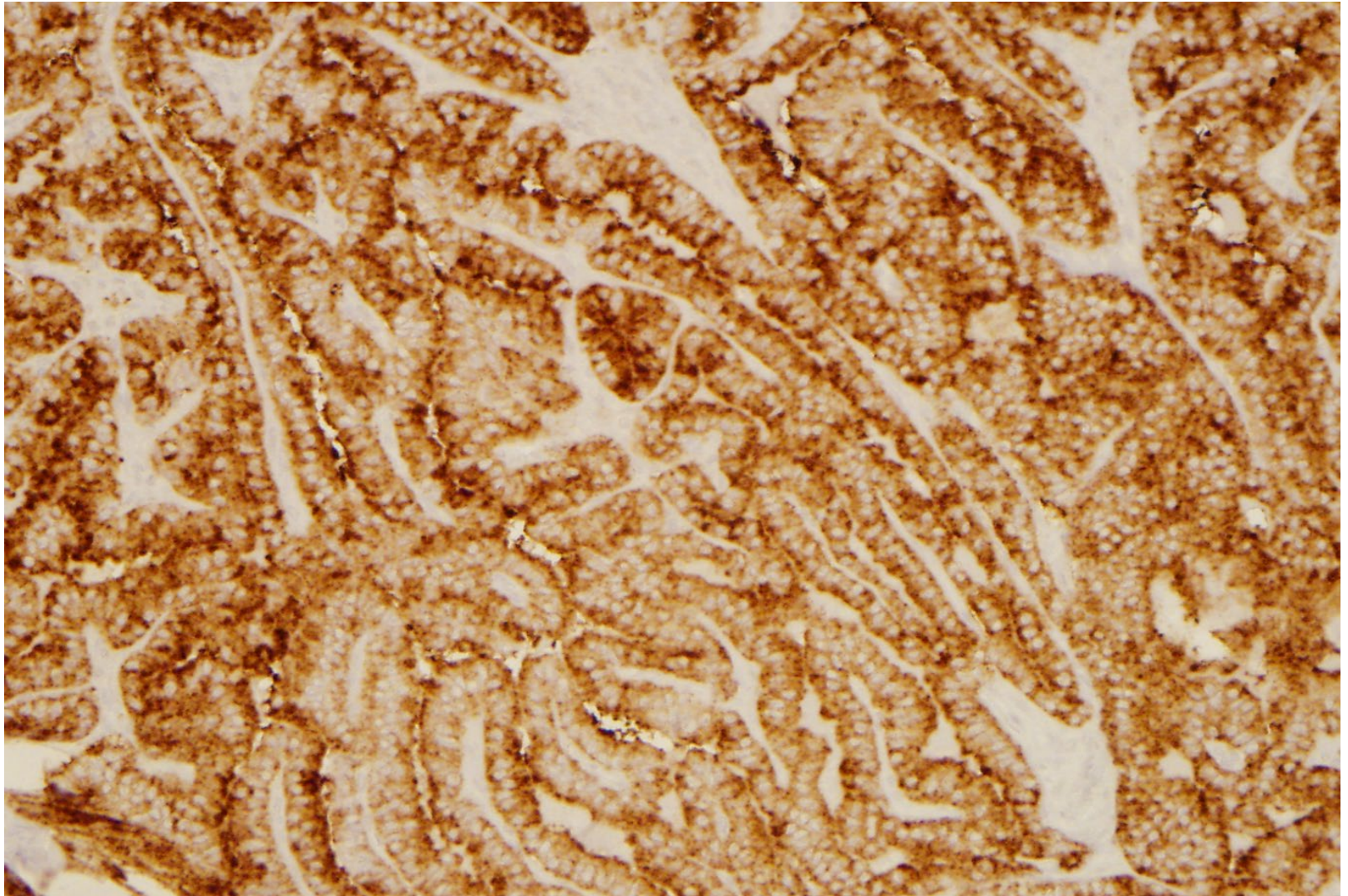
# Tall Cell Variant of PTC







# BRAFV600E IHC



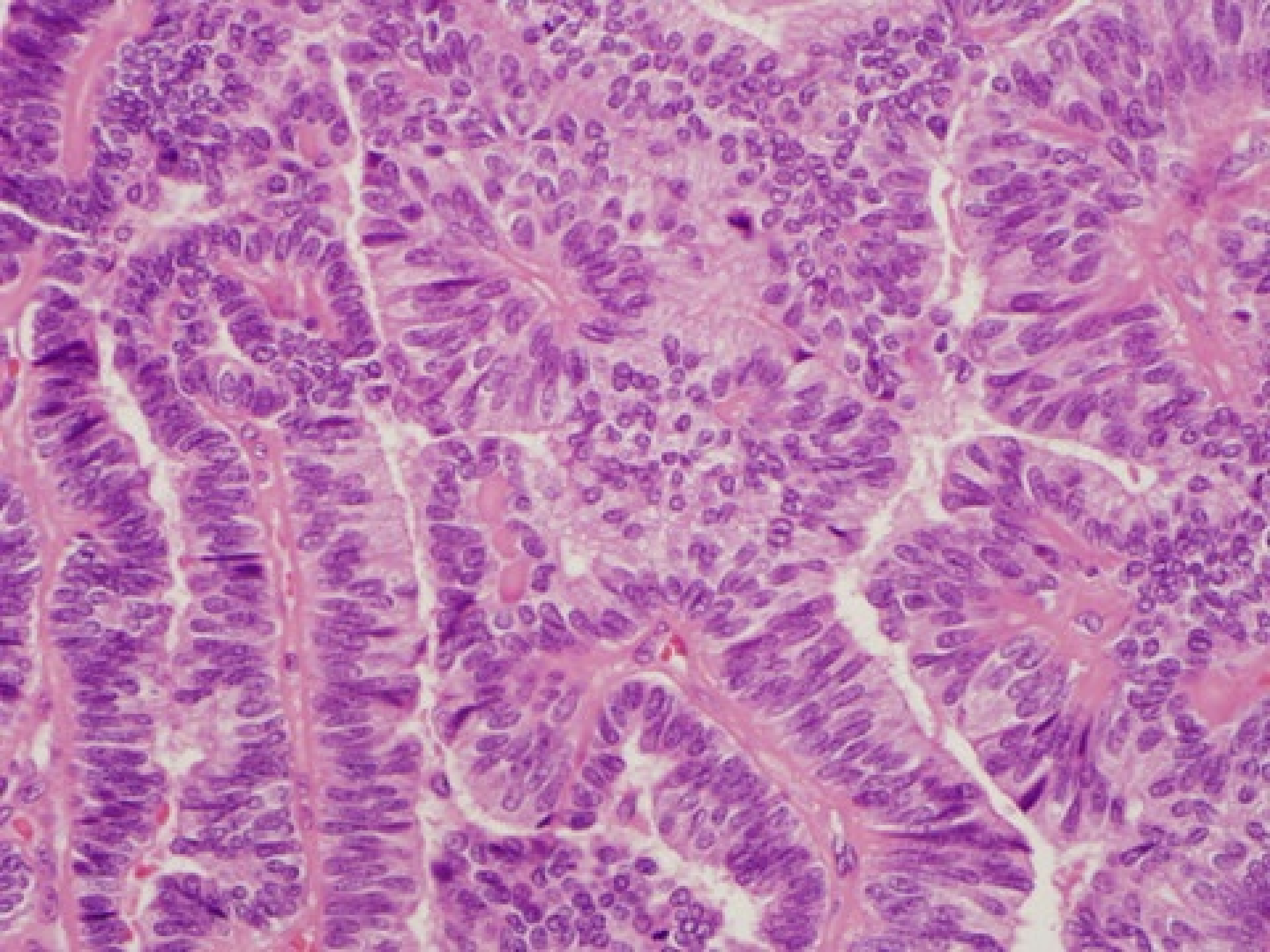
# Tall Cell Variant of PTC

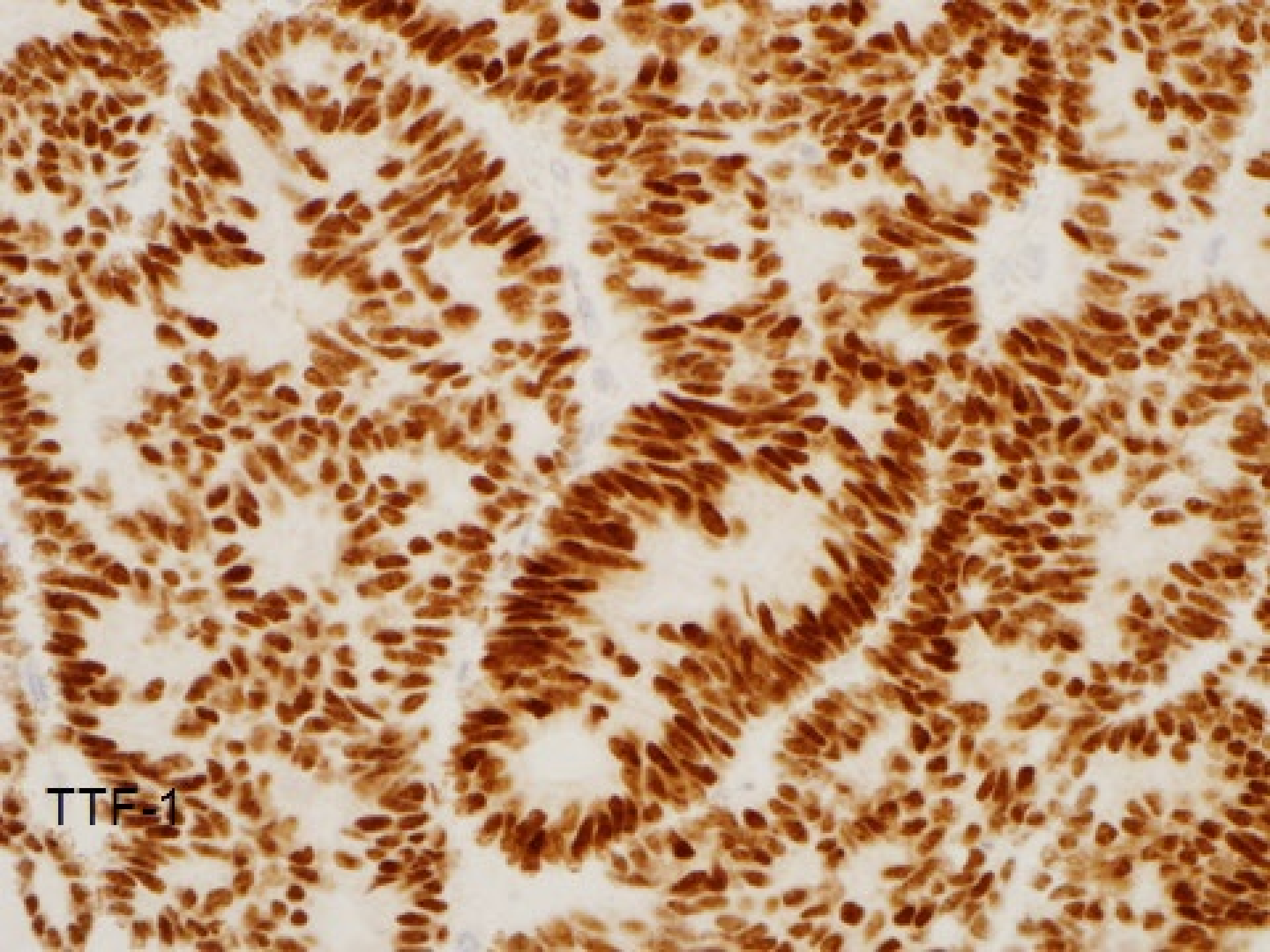
	Tall Cell PTC	Usual PTC
Age	49.4 yrs	48.3 yrs
Sex (F/M)	10/2	10/2
Tumor Size (mean)	2.8 cm	2.3 cm
Follow-up (mean)	68 months	80 months
Extrathyroidal – CLN	9/12 (75%)	5/12 (42%)
Extrathyroidal – soft tissue	5/12 (42%)	0/12
Distant metastases	2/12 (17%)	0/12
Recurrent disease	7/12	1/12
DOD	3/12 (25%)	0/12

Johnson et al, Am J Surg Pathol, 1988

# Columnar Cell Variant

- Look like endometrial or colonic carcinoma
- Nuclear features of conventional PTC usually not present
- Usually positive for TTF-1
- Variably positive for thyroglobulin



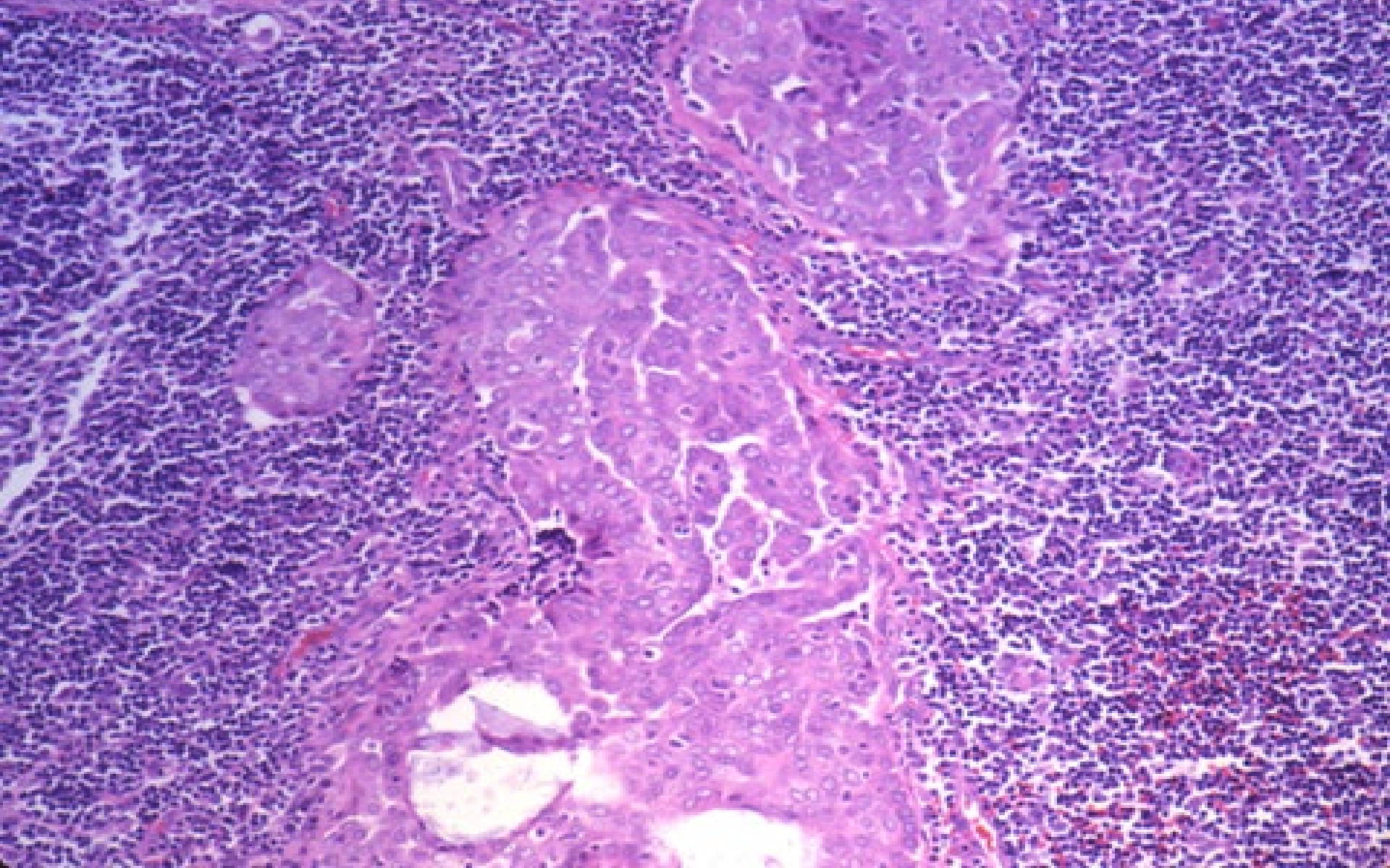


TTF-1

# Diffuse Sclerosing Variant

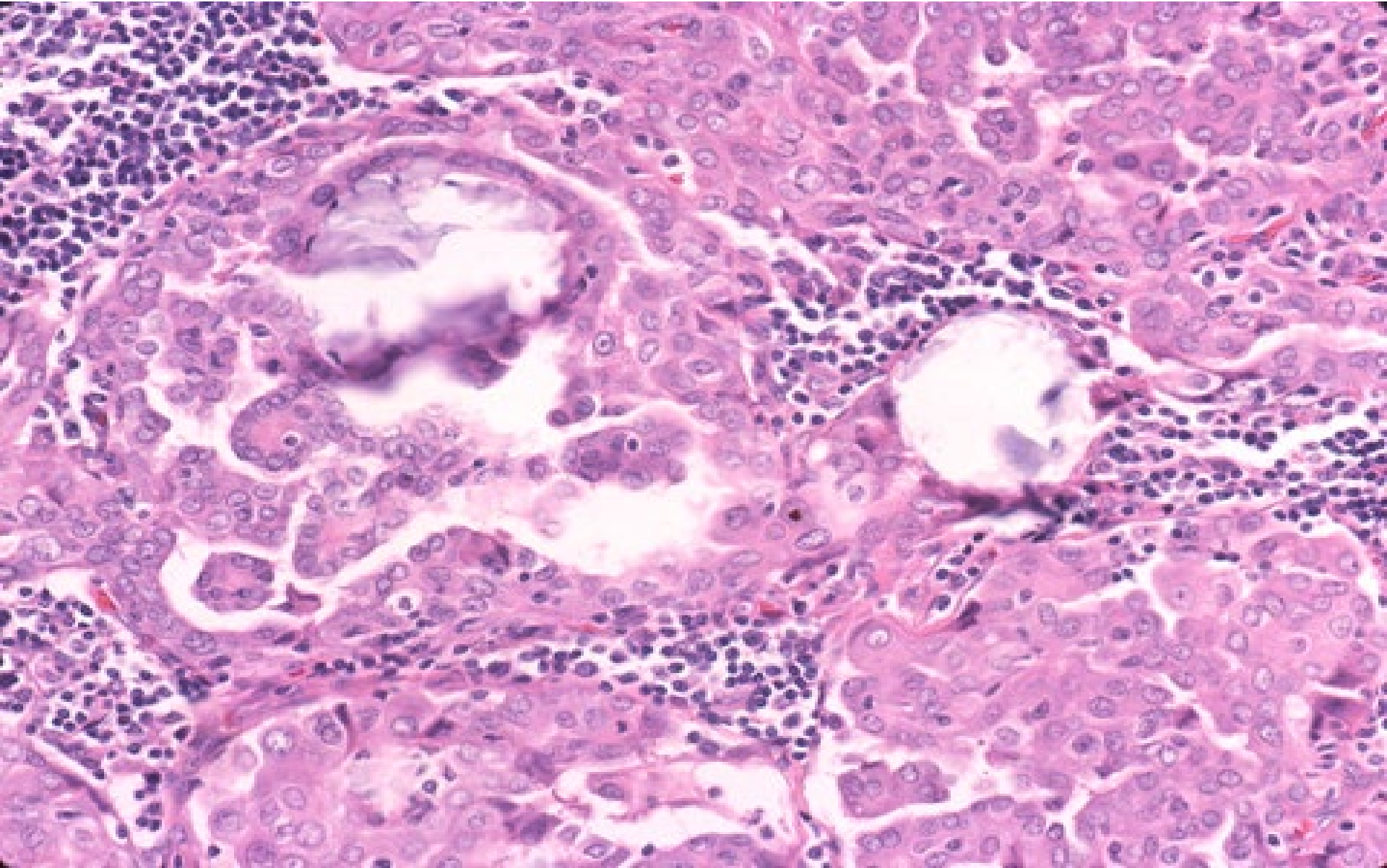
- Young people (< 40 years old)
- Usually involves both thyroid lobes
- Lymph node metastases common
- Lung metastasis not uncommon
- Patients rarely die of their disease

# Diffuse Sclerosing Variant of PTC

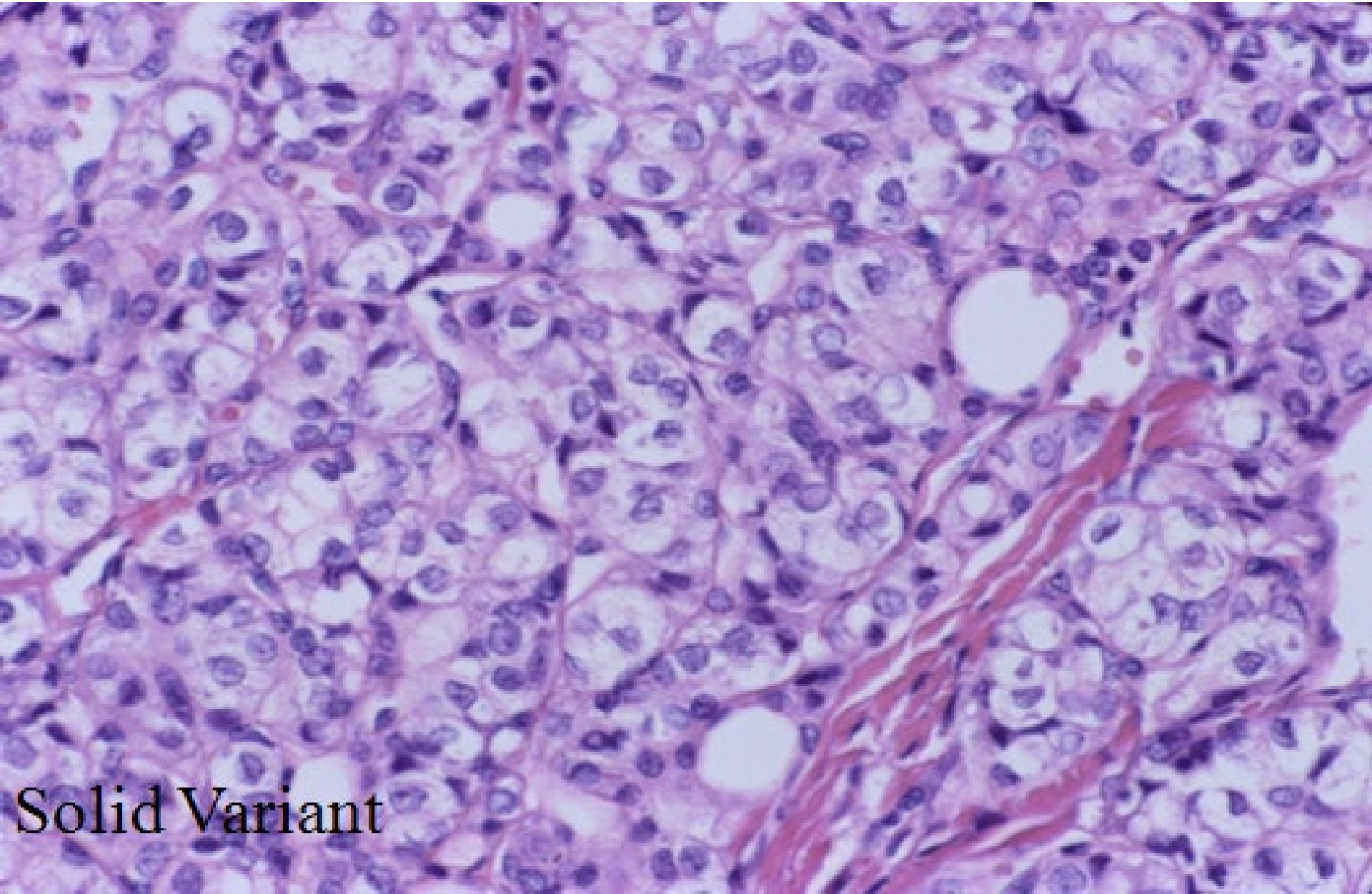




# Diffuse Sclerosing Variant of PTC



# Solid Variant of PTC

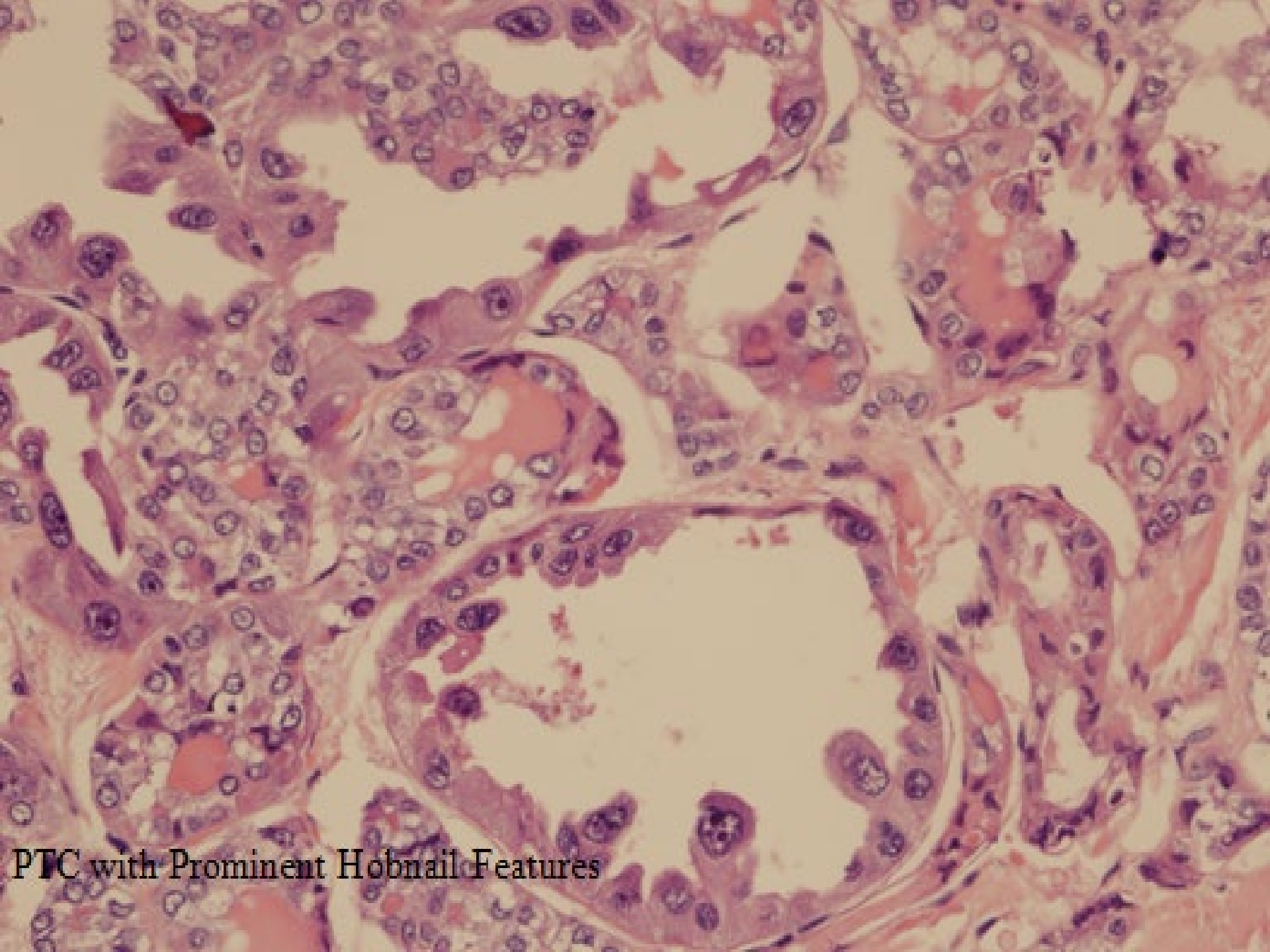


Solid Variant

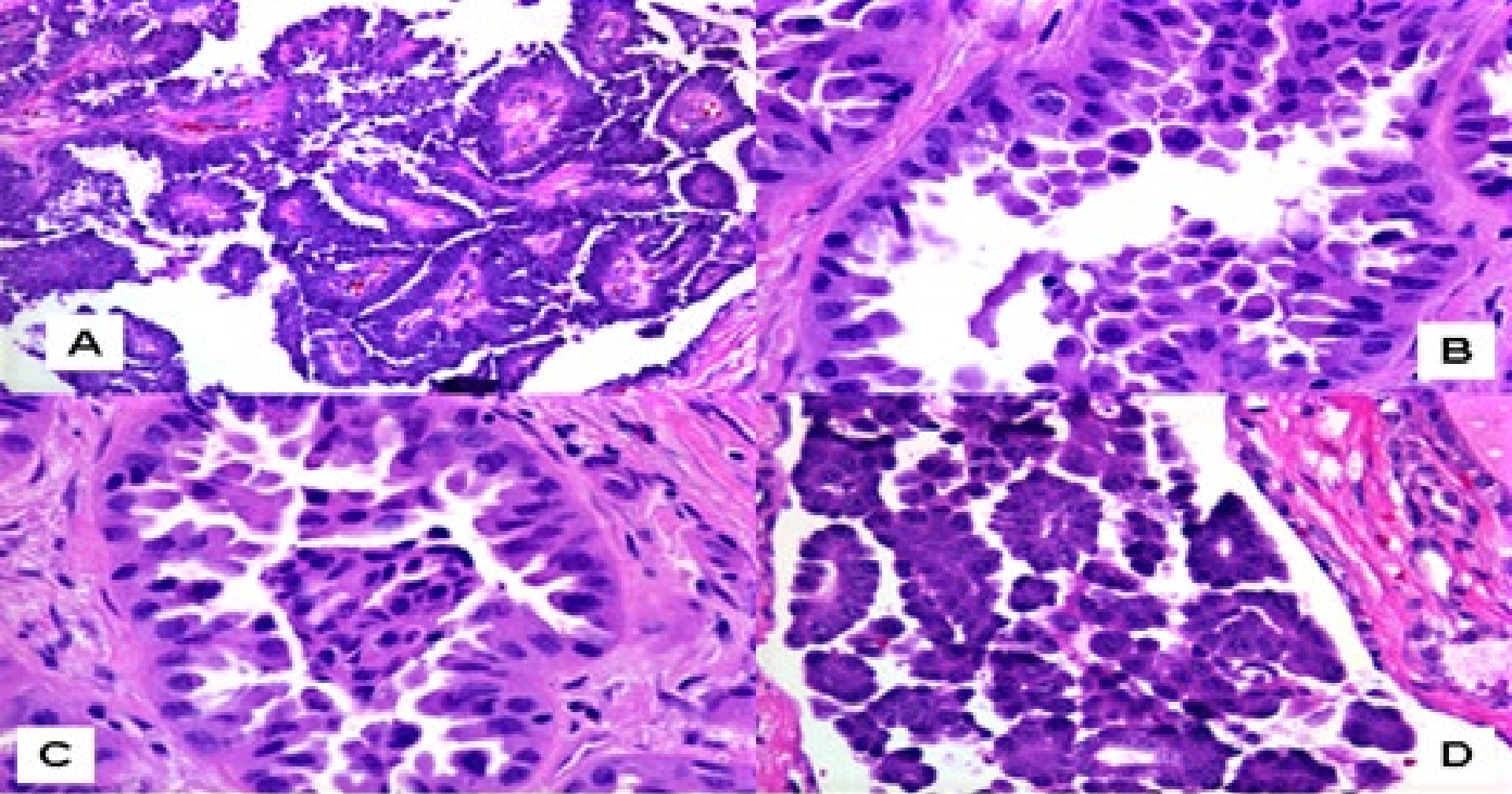
**Papillary thyroid carcinoma with prominent hobnail features: a new aggressive variant of moderately differentiated papillary carcinoma. A clinicopathologic, immunohistochemical, and molecular study of eight cases.**

[Asioli S](#), [Erickson LA](#), [Sebo TJ](#), [Zhang J](#), [Jin L](#),  
[Thompson GB](#), [Lloyd RV](#).

Am J Surg Pathol. 2010 Jan;34(1):44-52



PTC with Prominent Hobnail Features



PTC--Hobnail

p53

TTF1



# PTC with Prominent Hobnail Features

Case	Age/Sex	pTMN	BRAF	F/U (no)
1	51/F	T <sub>2</sub> N1M1	WT	DOD (6)
2	78/F	T <sub>3</sub> N1M0	NA	DOD (10)
3	63/F	T <sub>1</sub> N1M1	MUT	DOD (31)
4	28/F	T <sub>3</sub> N0M0	WT	AND (120)
5	58/M	T <sub>3</sub> N1M1	MUT	AWD (87)
6	53/F	T <sub>2</sub> N0M0	MUT	AND (236)
7	65/F	T <sub>3</sub> N1M1	MUT	DOD (124)
8	65/M	T <sub>3</sub> N1M1	WT	AWD (4)

Asioli et al, AJSP, 2010

# General Molecular Pathways for PTCs

## **BRAF-V600E-Like-**

- Classical PTC
- Tall Cell Variant
- Hobnail variant

## **RAS-Like**

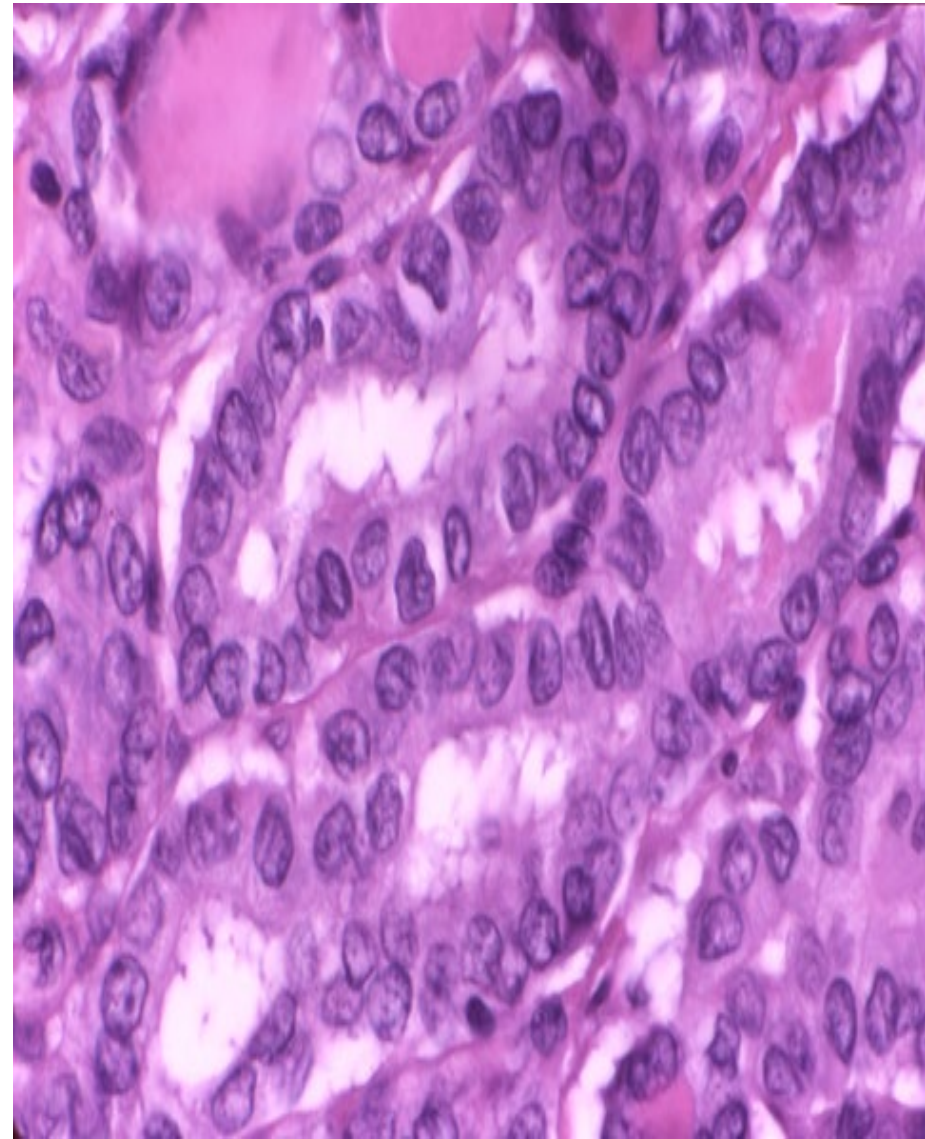
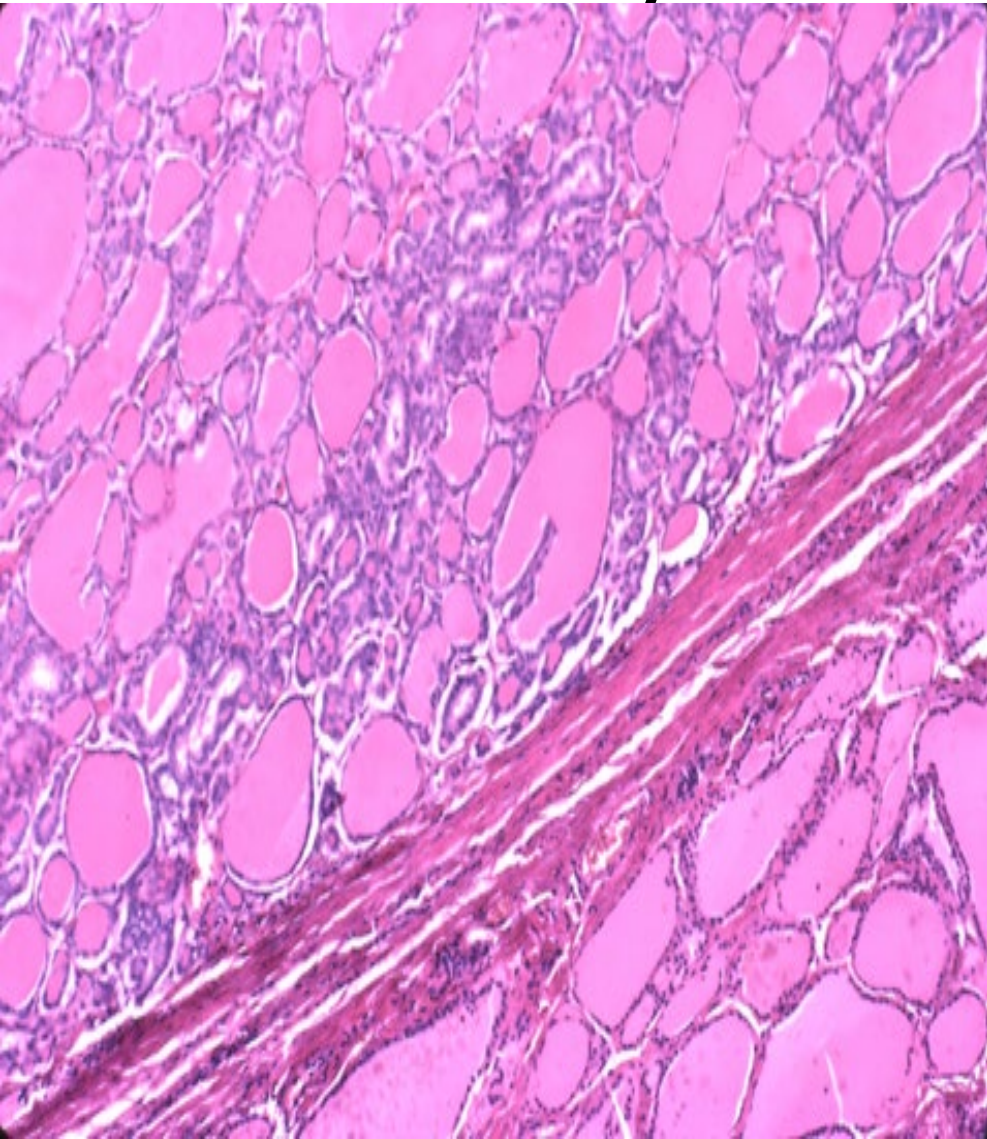
- NIFTP
- FVPTC

# Other Mutations in PTCs

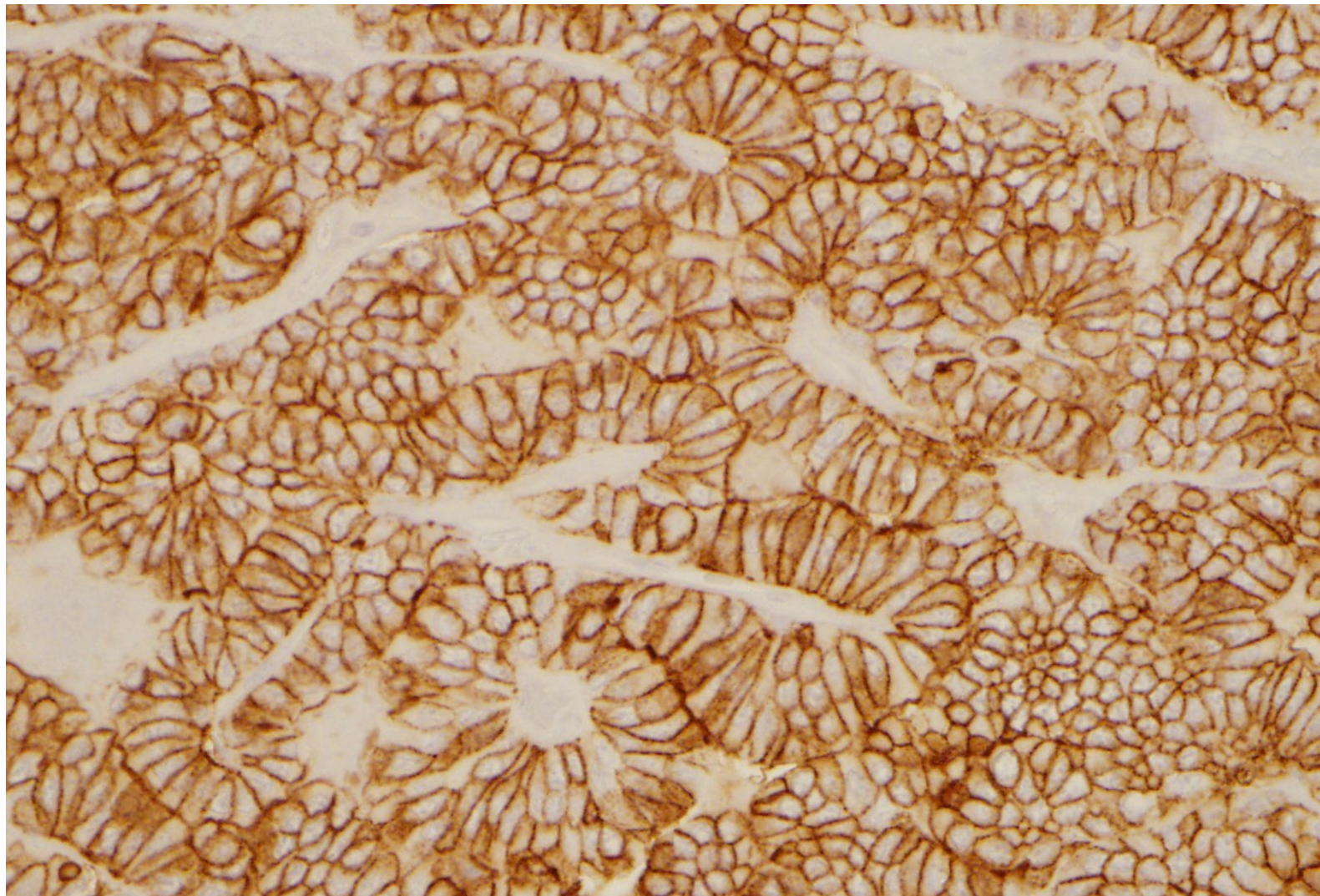
- H/K/NRAS
- BRAF indels
- BRAF K601E
- PAX8-PPARGamma fusions
- FGFR2 fusions
- THADA fusions



# Follicular Variant of Papillary Thyroid Carcinoma



# HBME1 in PTC



# NIFTP

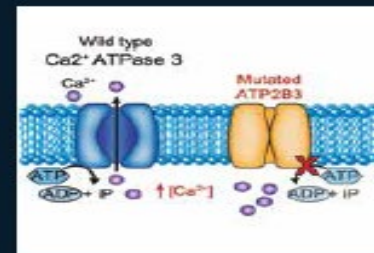
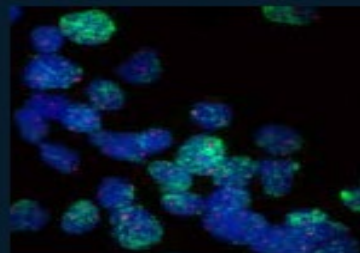
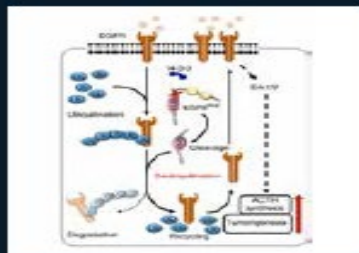
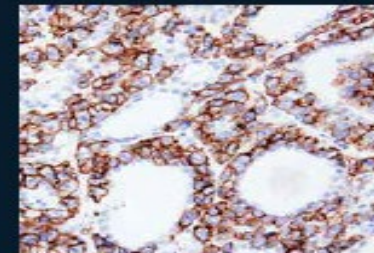
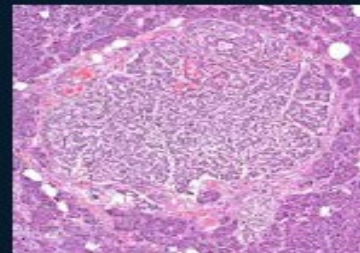
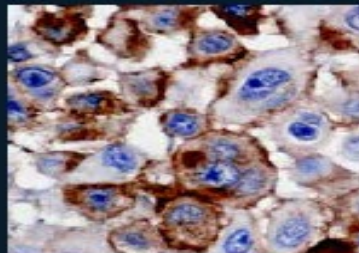
Non-Invasive Follicular Thyroid Neoplasm with  
Papillary Like Features



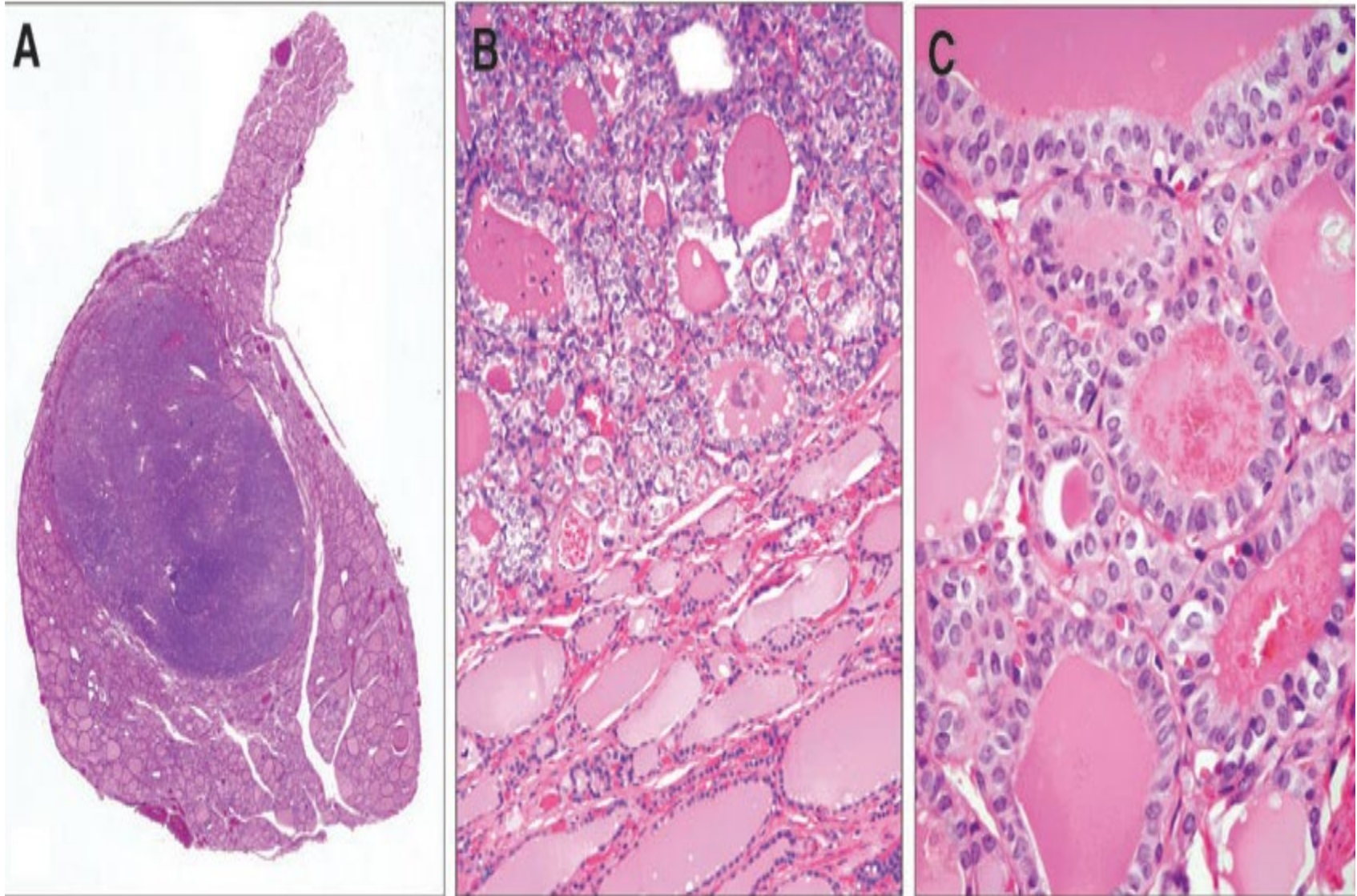
# WHO Classification of Tumours of Endocrine Organs

Edited by Ricardo V. Lloyd, Robert Y. Osamura, Günter Klöppel, Juan Rosai

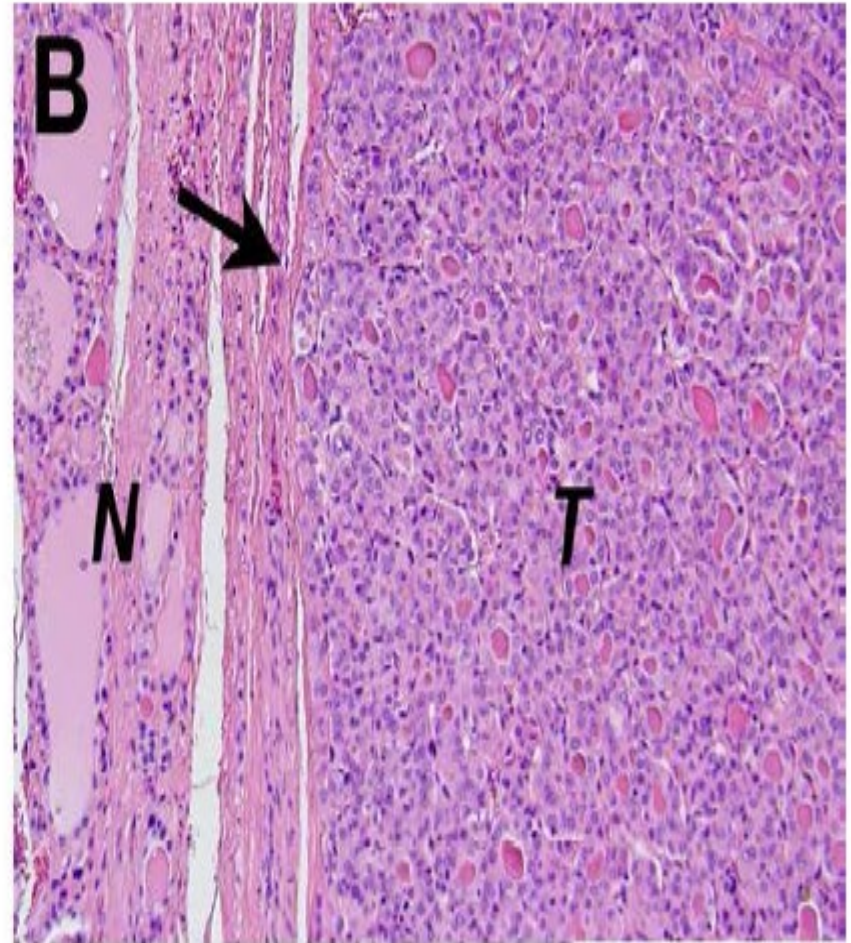
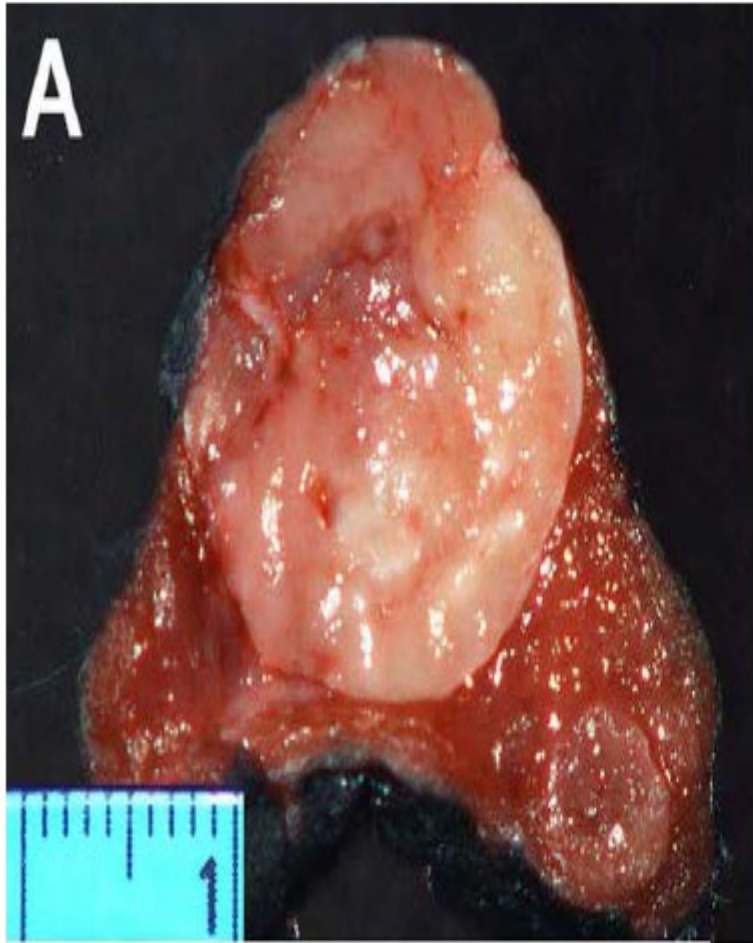
WHO Classification of Tumours of Endocrine Organs



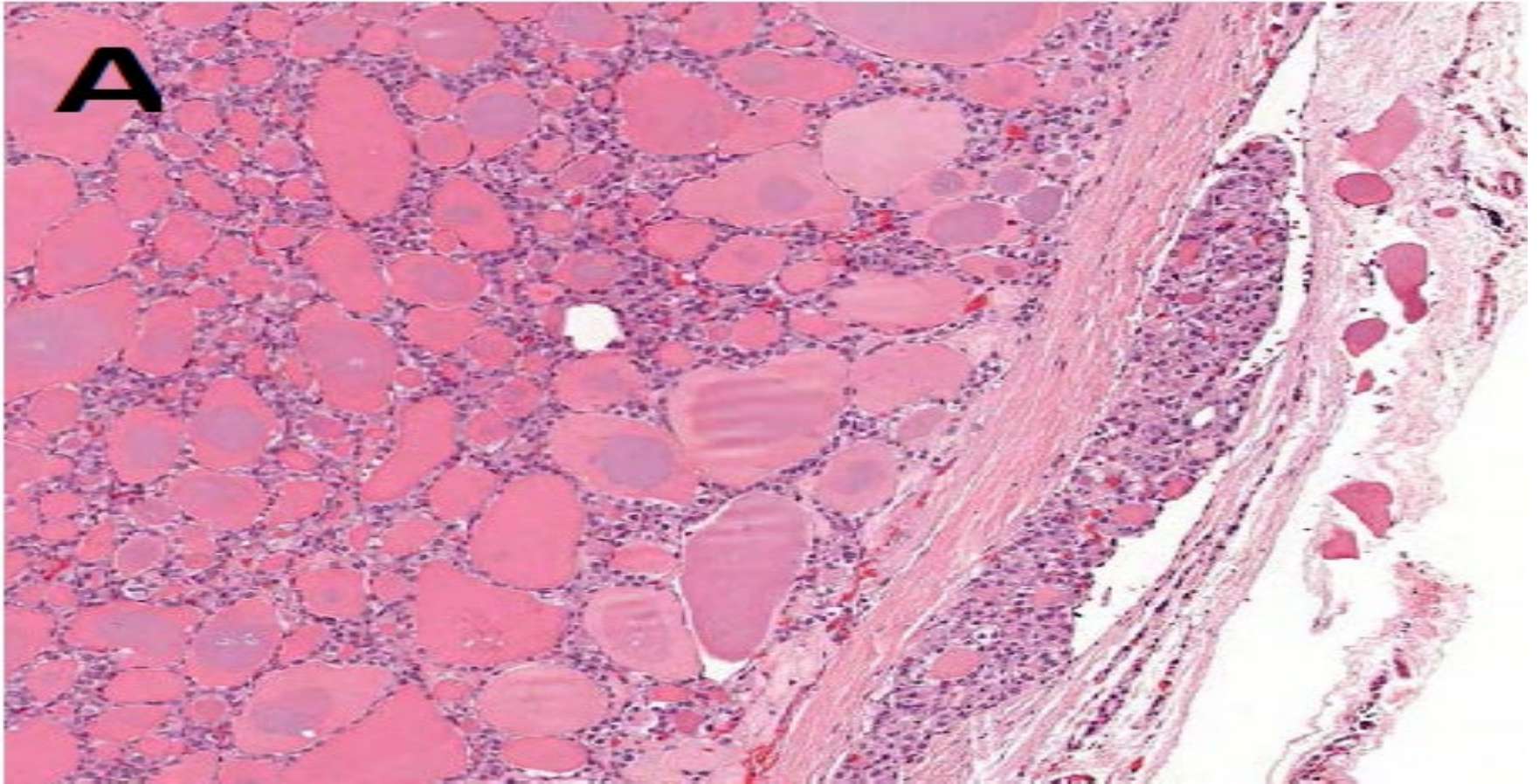
# Howitt et al Thyroid 23, 2013



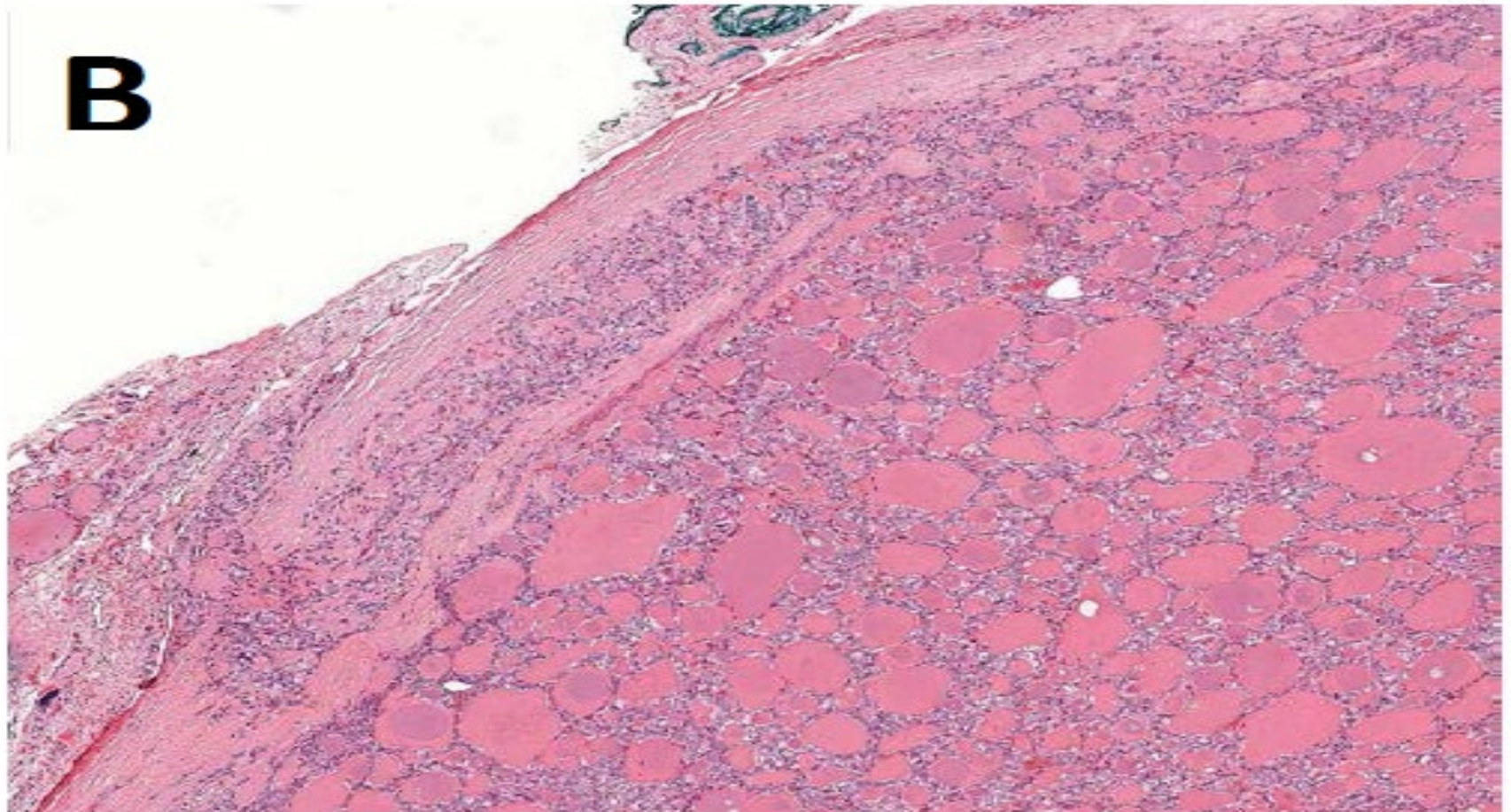
# NIFTP-Gross and Microscopic



# Invasive FVPTC

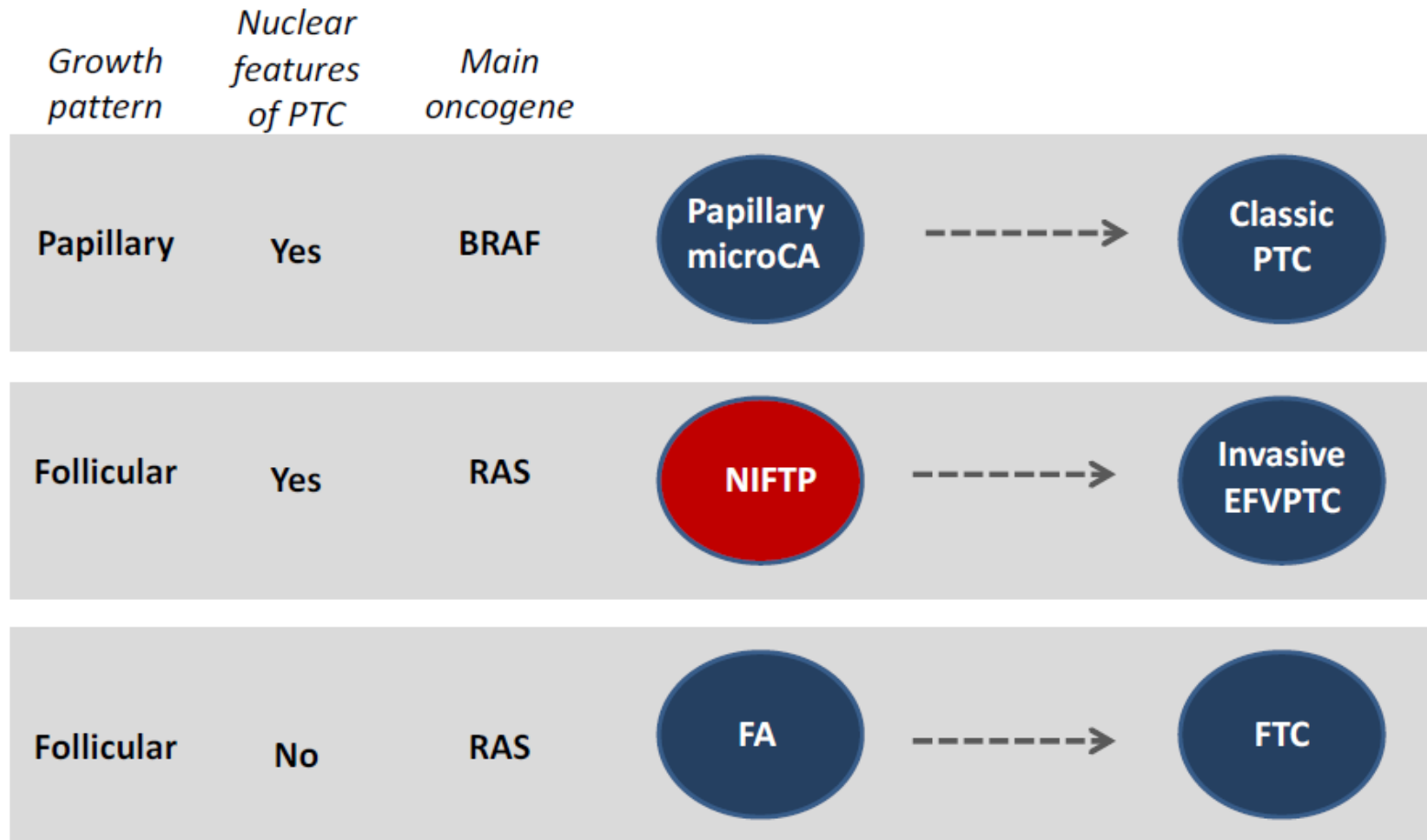


# Invasive FVPTC





# NIFTP



Based on the JAMA Oncology publication (April 2016) the following should probably not be designated as NIFTP

- -Encapsulated non-invasive follicular variant of papillary thyroid with papillae
- -Thyroid tissue with psammoma bodies should not be classified as NIFTP
- -Tumors with some features of NIFTP (follicular variant nuclear features), but the majority of the lesion has a solid variant pattern of PTC
- -Presence of capsular or vascular invasion

# Utility of NIFTP Diagnosis

- Decrease the incidence of overtreatment for some thyroid tumors—surgery and radioactive iodine.
- Regional variation in the NIFTP diagnosis. From 2% in Far East and Canada to around 10% in USA.

# Molecular Findings in NIFTP

- Affirma GEC -usually classified as FLUS or suspicious
- Mutations: RAS (30%),PPARgamma (22%), THADA fusion (22%),BRAF K601E (4%)
- BRAF V600E is usually negative

# Molecular Alterations in Encapsulate Follicular Variant of Papillary Thyroid Carcinoma

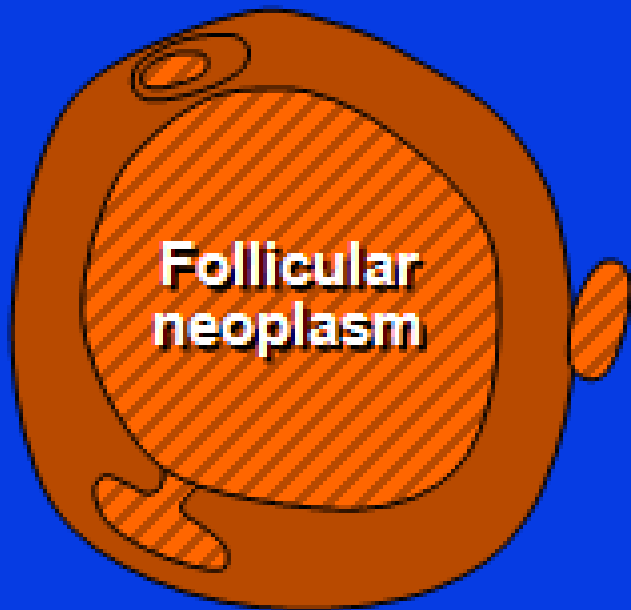
- RAS (HRAS,KRAS,NRAS) -25-45%
- TERT Promoter -5-15%
- BRAF V600E -0-10%

# Variants of Papillary Thyroid Carcinoma

- Conventional
- Micropapillary
- Follicular Variant
- Tall Cell
- Oncocytic
- Columnar Cell
- Diffuse Sclerosing
- Clear Cell
- Cribriform-Morular
- Macrofollicular
- PTC with Hobnail features
- PTC with Fasciitis-Like Stroma
- PTC with dedifferentiation

# Follicular Thyroid Carcinoma

Yes



Yes

Not yet

**J.K.C. Chan**

Yes



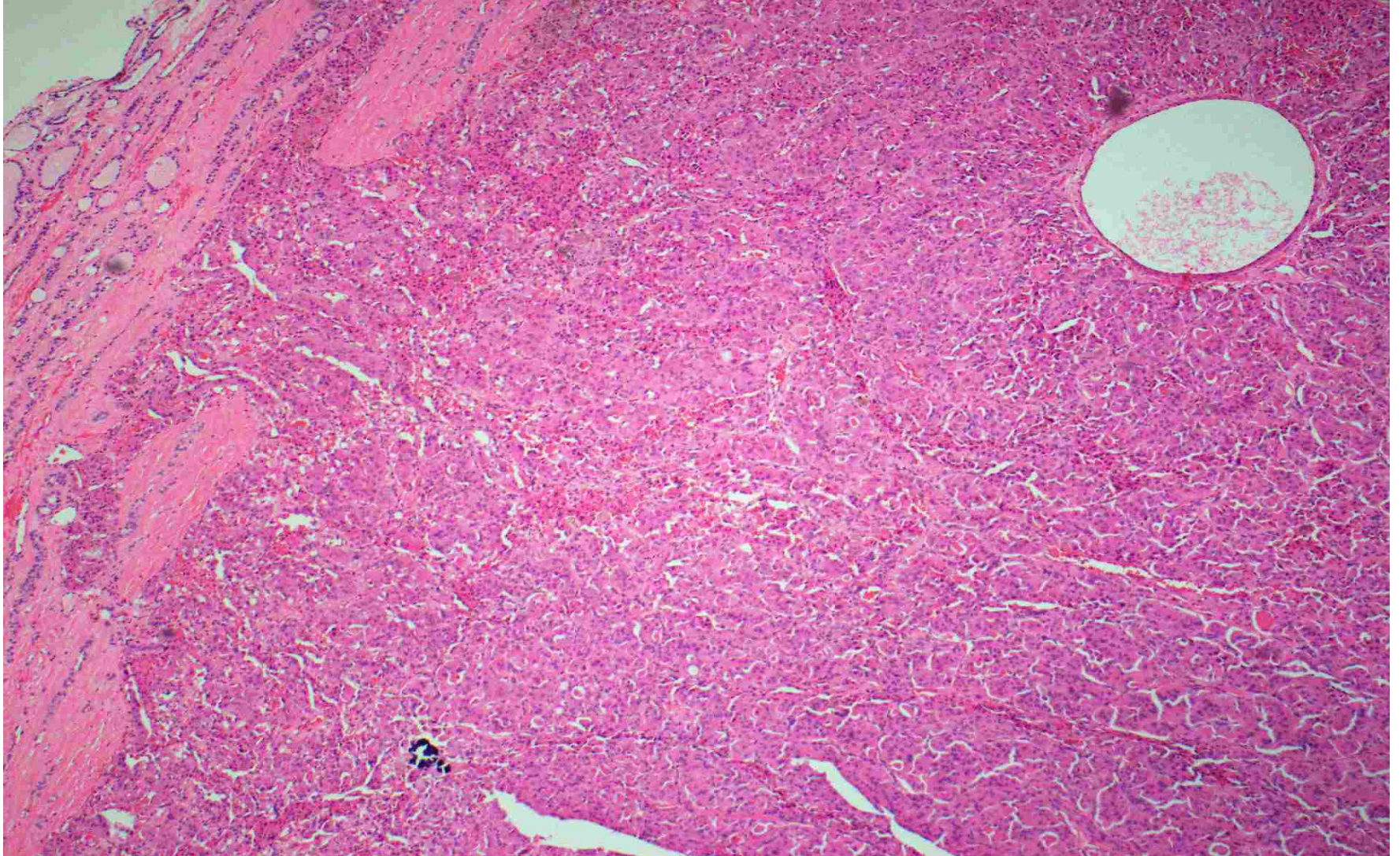
Yes

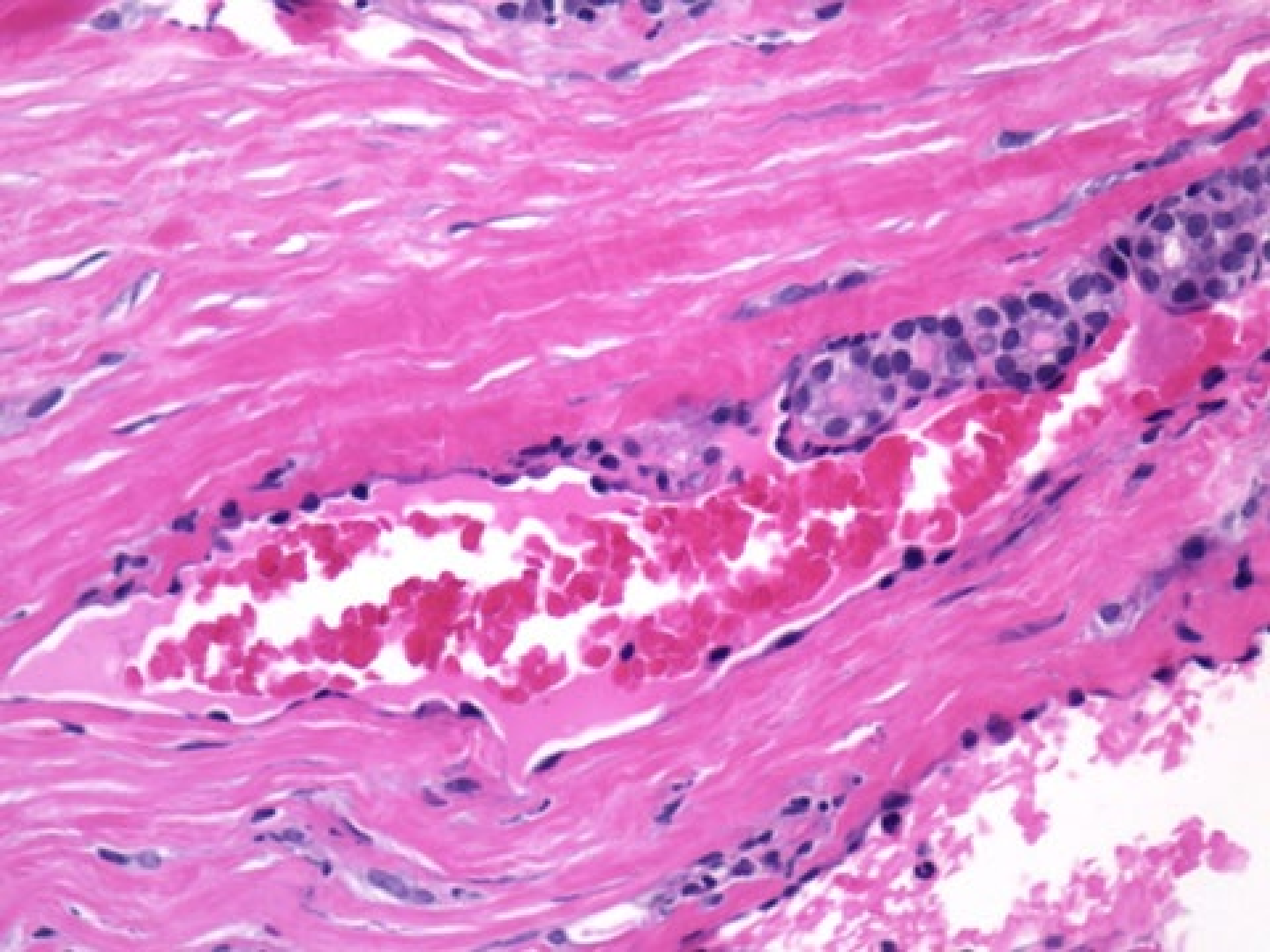
Yes

**V.A. LiVolsi**

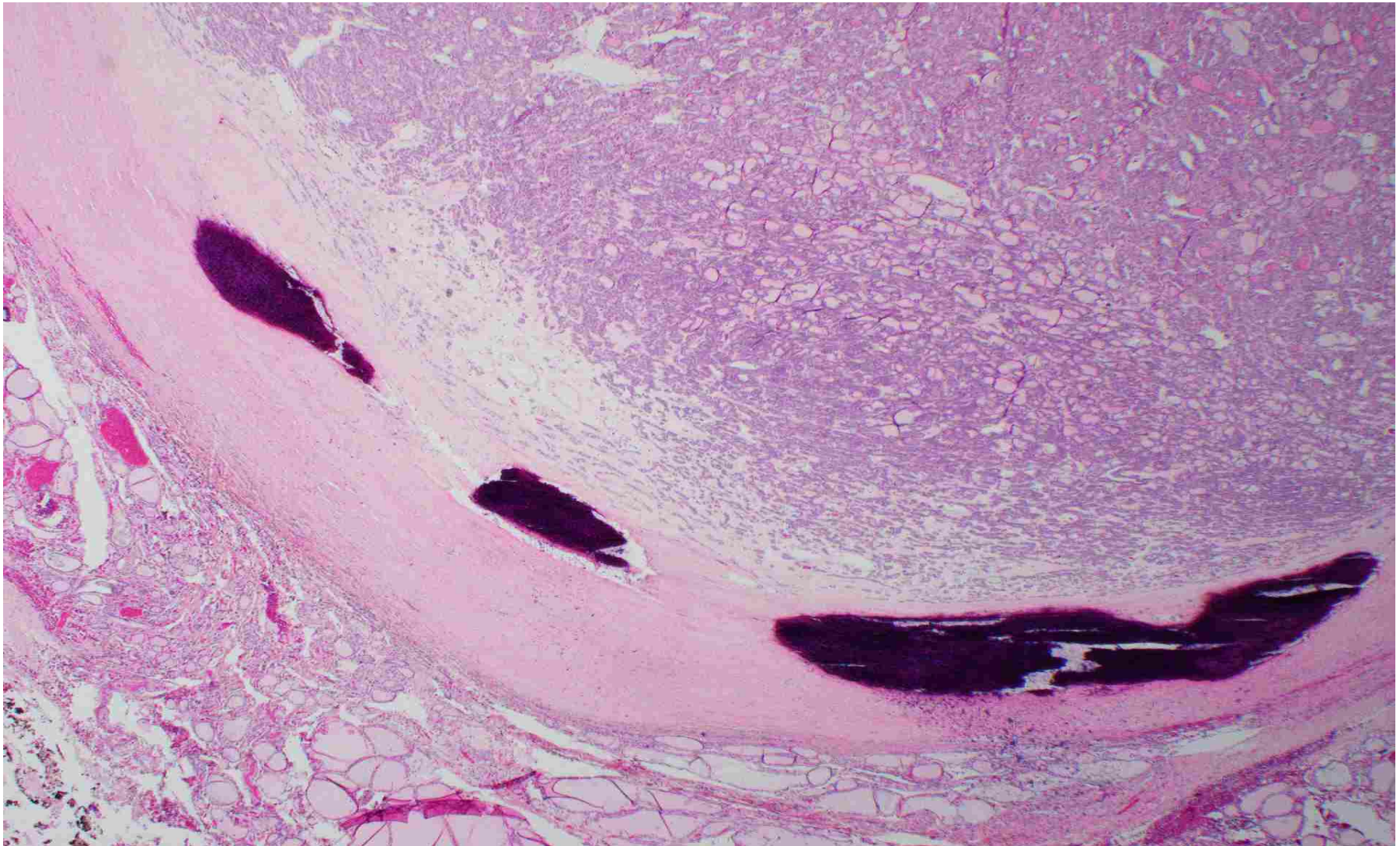


# FTC—“Mushrooming” in Capsule





# Follicular Thyroid Carcinoma With Intracapsular Calcification



# Follicular Carcinoma

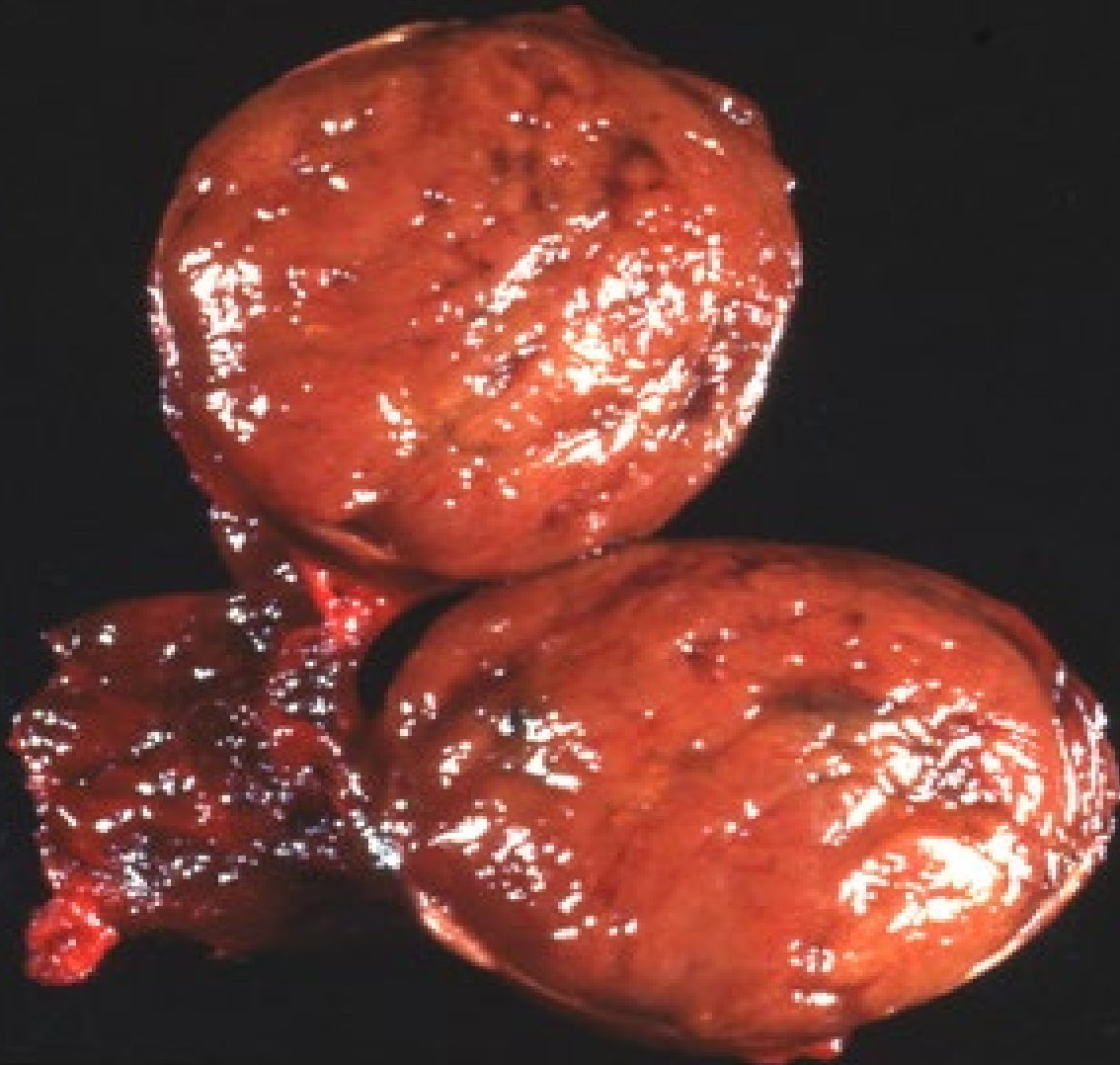
WHO 2017

- Minimally Invasive
- Encapsulated Angioinvasive
- Widely Invasive

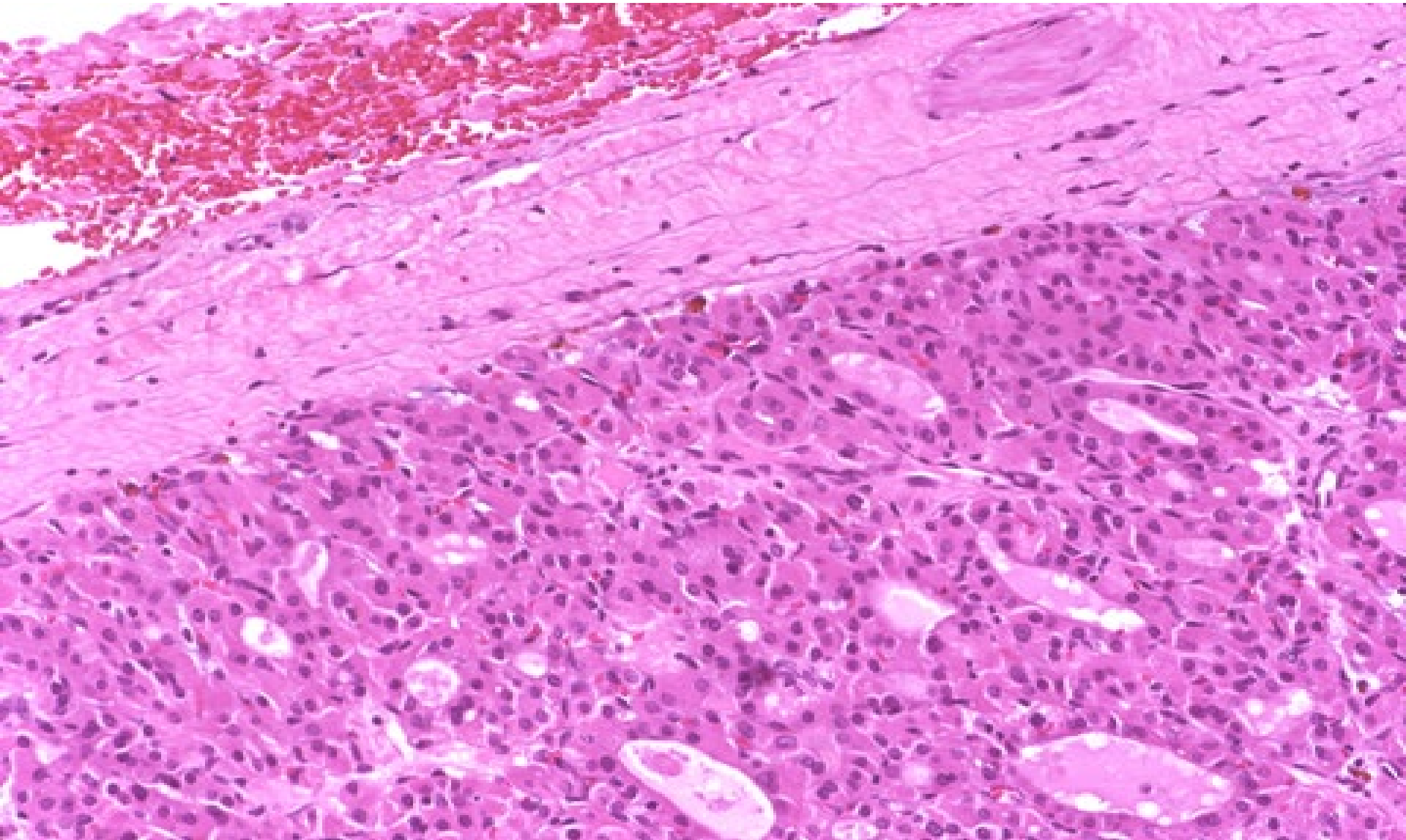
# Molecular Alterations in Follicular Carcinomas

- PAX8-PPARGamma -30-35%
- TERT Promoter -10-35%
- RAS (HRAS,KRAS,NRAS) -30-50%

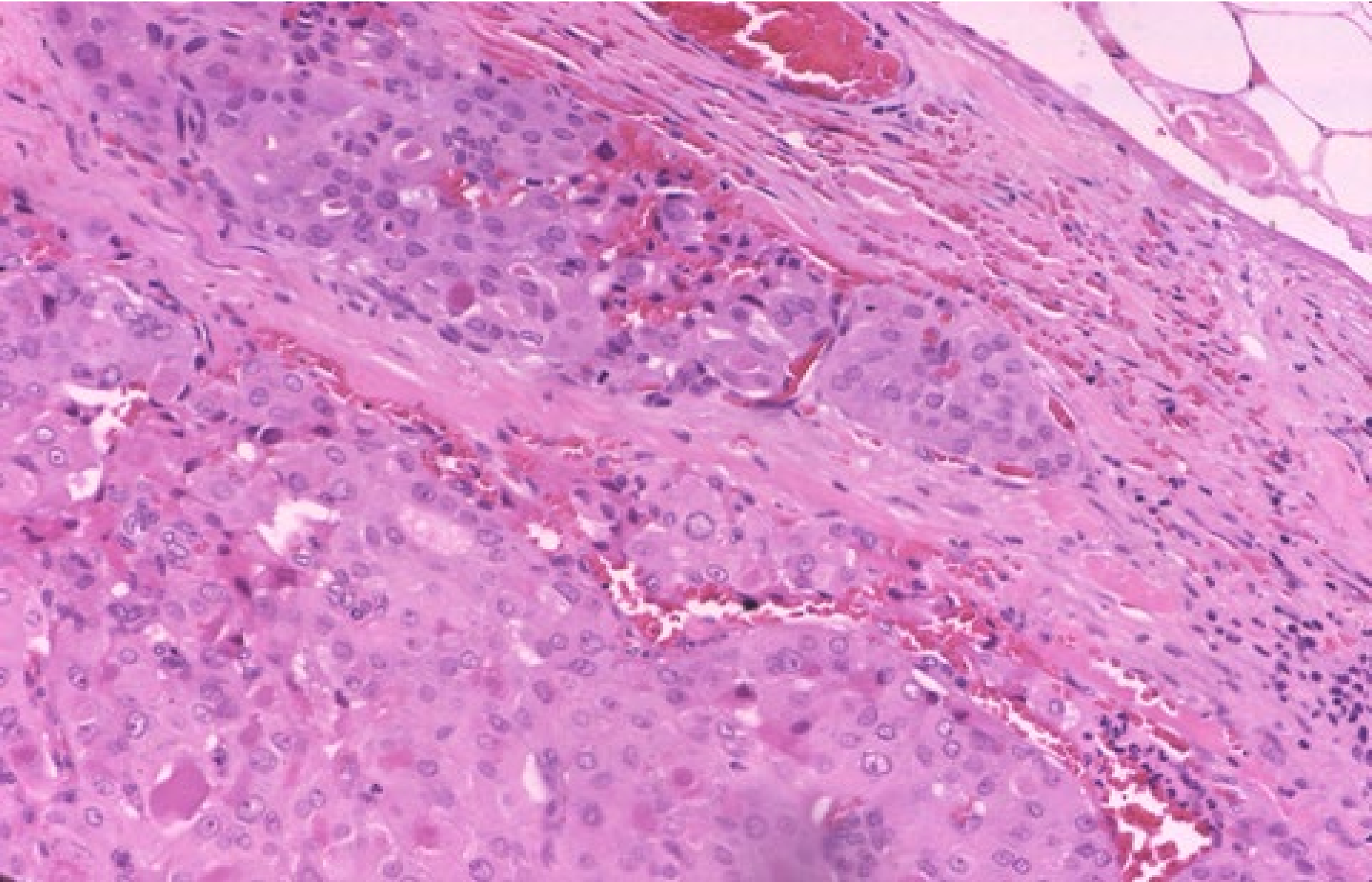
# Hurtele Cell Tumor



# Hurthle Cell Adenoma



# Hurthle Cell Carcinoma





# Hurthle Cell Neoplasms

- **Mitochondrial Gene:**

-**GRIM-19**-Complex I nuclear gene-Nuclear gene mutations specific for Hurthle cell tumors.

## **Oncogenes/Tumor Suppressor Genes-**

**HCFTC**-RET/PTC (35%),PAX8/PPARgamma (5%)

BRAF(V600E) (0%),RAS (17%)

**HCPTC**-RET/PTC (96%),PAX8/PPARgamma (0%)

BRAF(21%), RAS (0%)

# Poorly Differentiated Thyroid Carcinoma: The Turin Proposal for the Use of Uniform Diagnostic Criteria and an Algorithmic Diagnostic Approach

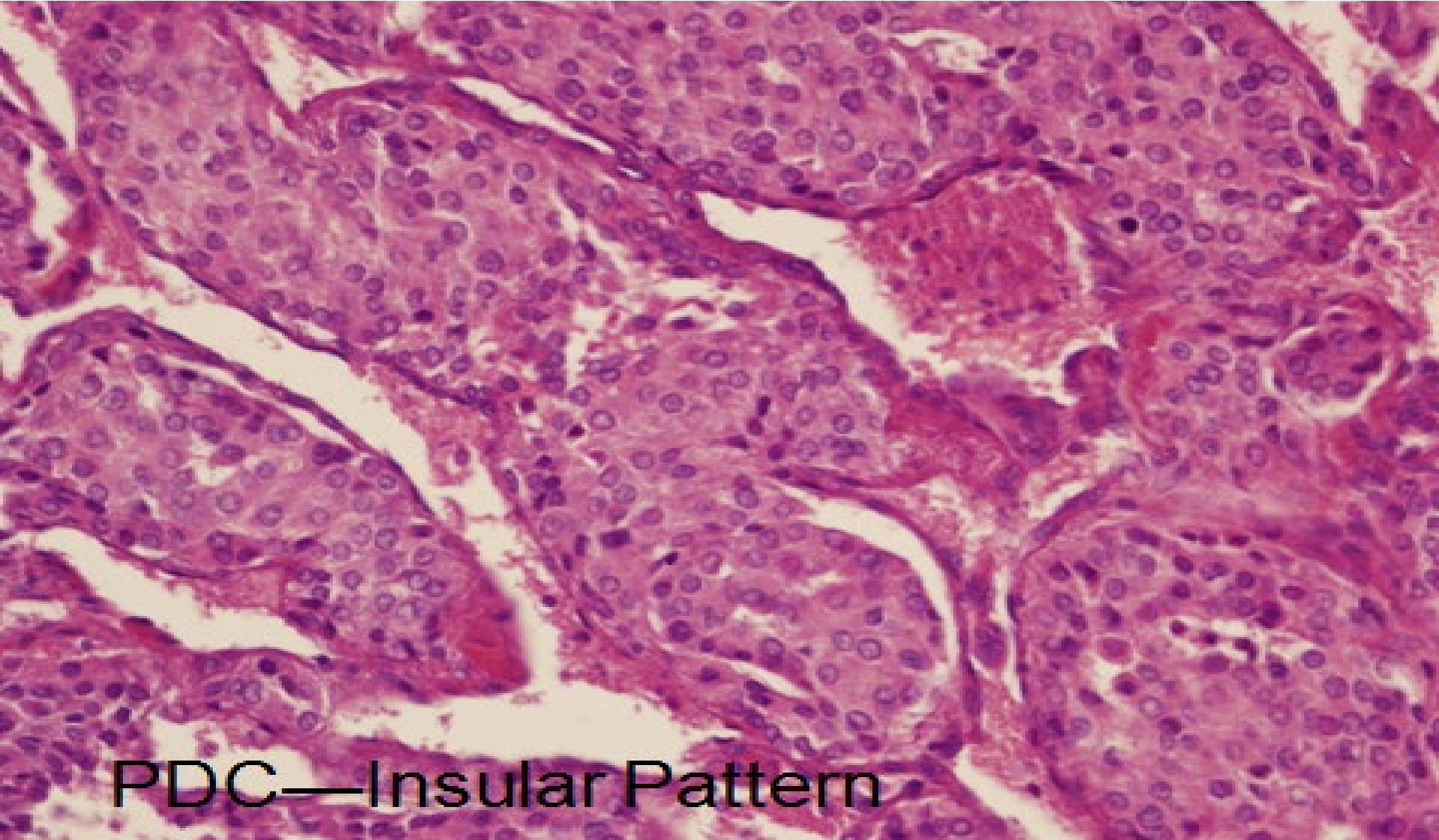
Marco Volante, MD,\* Paola Collini, MD,w Yuri E. Nikiforov, MD, PhD,z  
Atsuhiko Sakamoto, MD,y Kennichi Kakudo, MD, PhD,J Ryohei Katoh, MD,z  
Ricardo V. Lloyd, MD,# Virginia A. LiVolsi, MD,\*\* Mauro Papotti, MD,\*  
Manuel Sobrinho-Simoes, MD, PhD,ww  
Gianni Bussolati, MD, FRCPath,zz and Juan Rosai, Mdyy

Am J Surg Pathol 31: 1256-1264, 2009

# Poorly Differentiated Thyroid Carcinoma

- Presence of solid/trabecular/insular growth pattern
- Absence of conventional nuclear features of PTC
- Convoluted nuclei or mitotic activity  $>/$ or 3 mitoses/10 HPF or tumor necrosis

# Poorly Differentiated Carcinoma Insular pattern



PDC—Insular Pattern

# Poorly Differentiated Thyroid Carcinoma

- Insular is one subtype
- Behavior is between well-differentiated thyroid carcinoma and undifferentiated (anaplastic) carcinoma

Poorly differentiated carcinoma of  
the thyroid:  
validation of the Turin proposal and  
analysis  
of IMP3 expression

Sofia Asioli<sup>1,2</sup>, Lori A Erickson<sup>1</sup>, Alberto Righi<sup>1,2</sup>, Long Jin<sup>1</sup>,  
Marco Volante<sup>3</sup>, Sarah Jenkins<sup>4</sup>,  
Mauro Papotti<sup>3</sup>, Gianni Bussolati<sup>3</sup> and Ricardo V Lloyd<sup>1</sup>

Modern Pathol 23:1269-1278, 2010

# Poorly Differentiated Thyroid Carcinoma

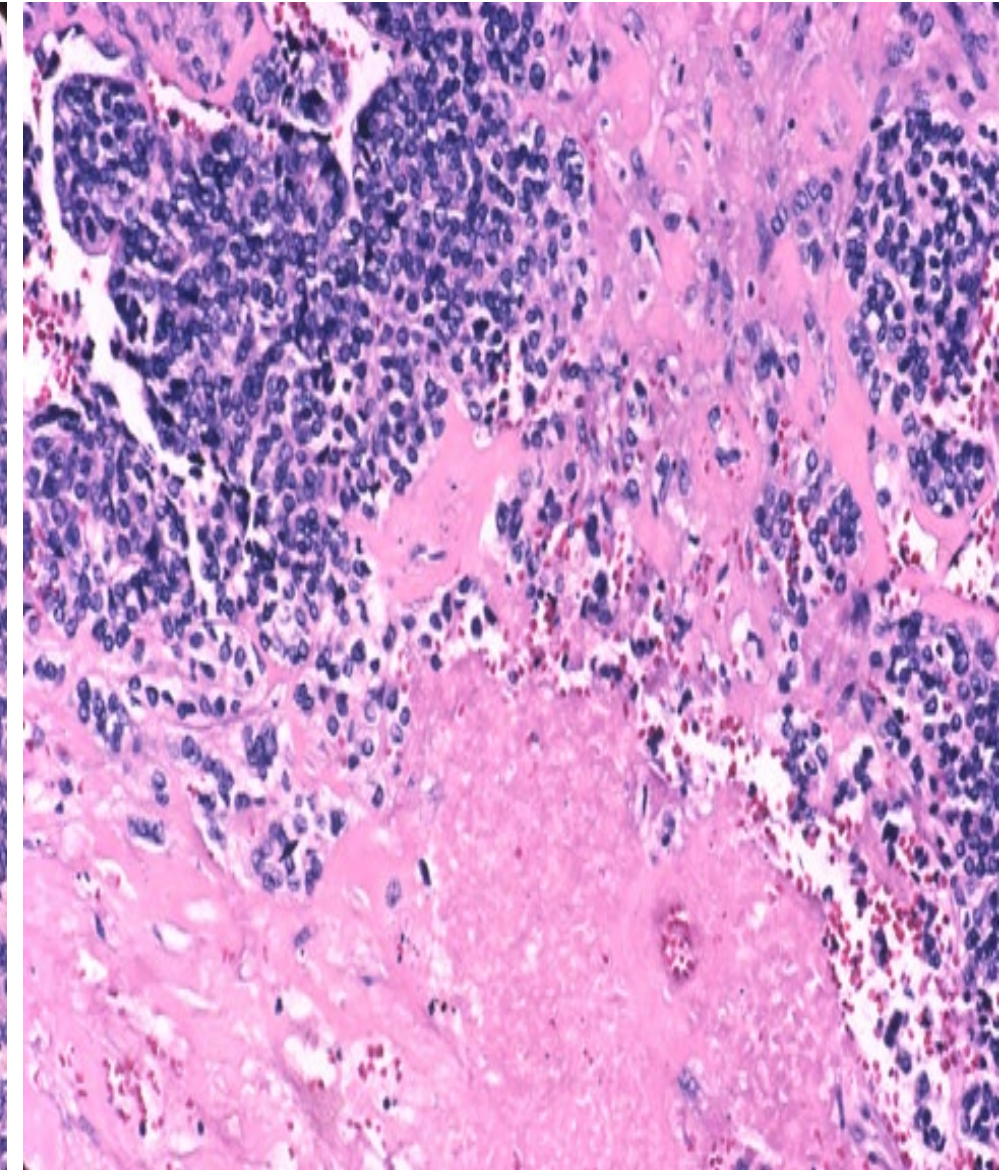
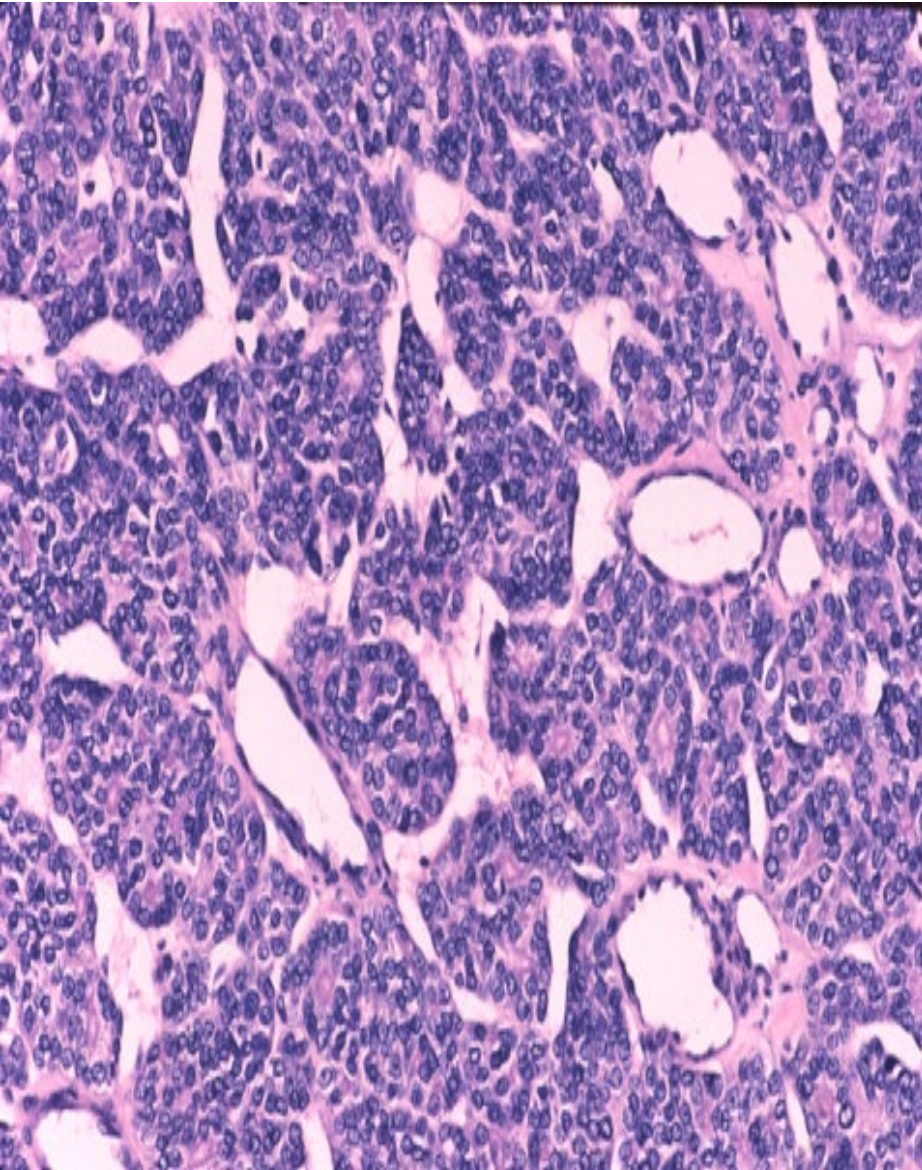
Turin, Italy      6.7%

Rochester, MN    1.8%

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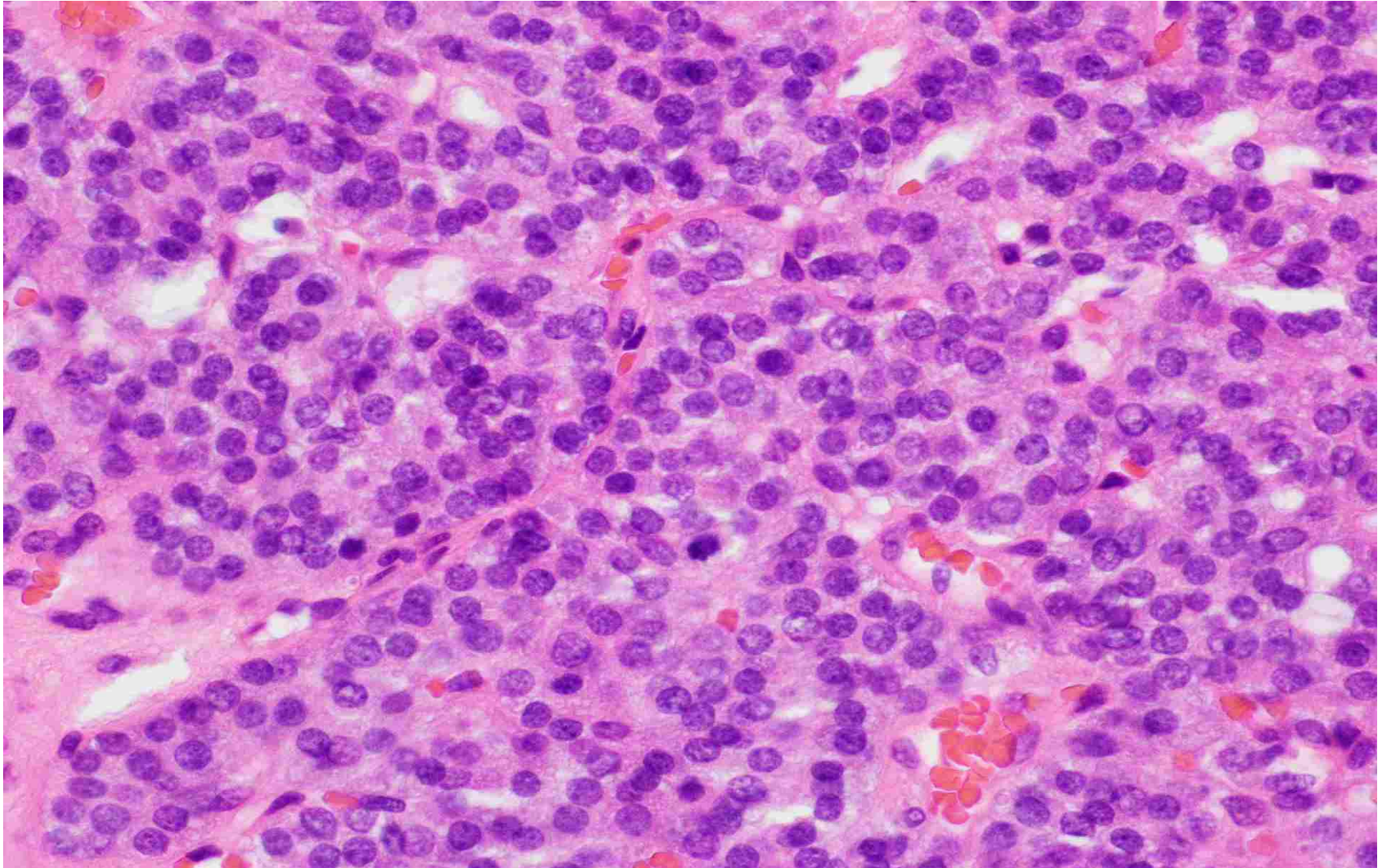
Asioli, Modern Pathology, 2010

# Poorly Diff Carcinoma

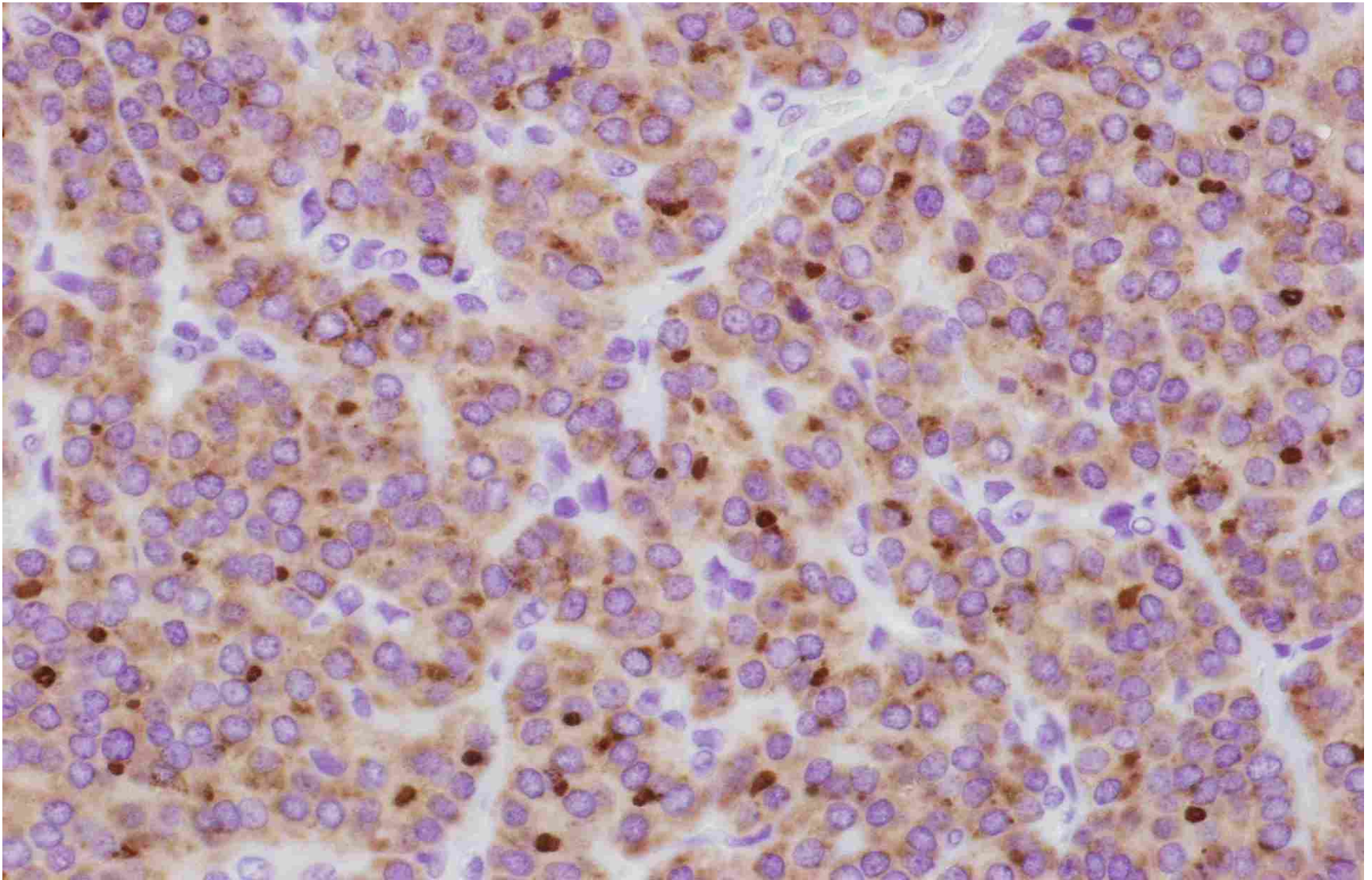




# Follicular Carcinoma Dedifferentiating to Poorly Differentiated Carcinoma



# Juxtannuclear Thyroglobulin

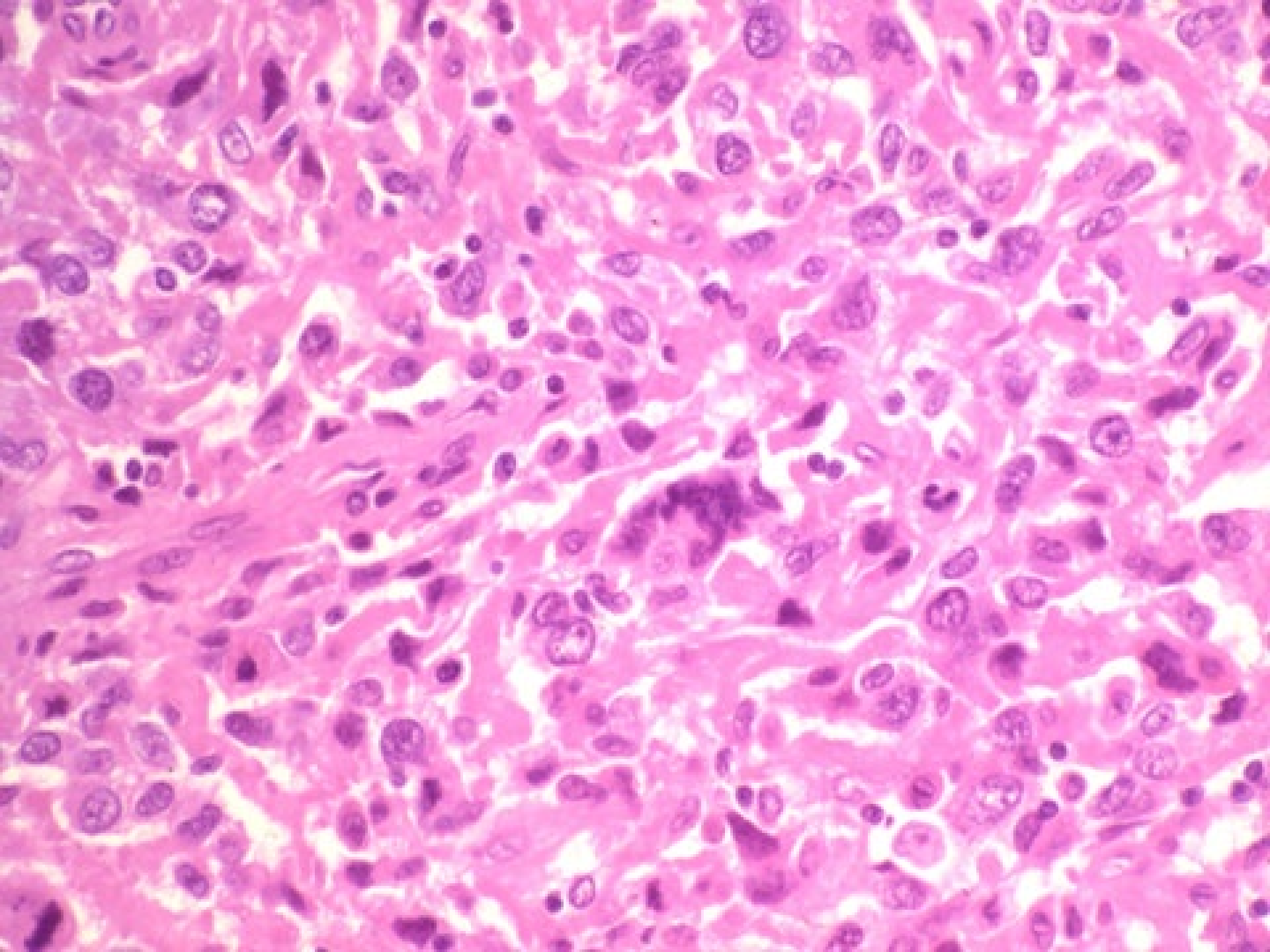


# Molecular Alterations in Poorly Differentiated Thyroid Carcinomas

- TERT Promoter -40%
- BRAFV600E -27%
- RAS -24%
- EIF1AX -11%
- TP53 -10%

# Anaplastic Thyroid Carcinoma

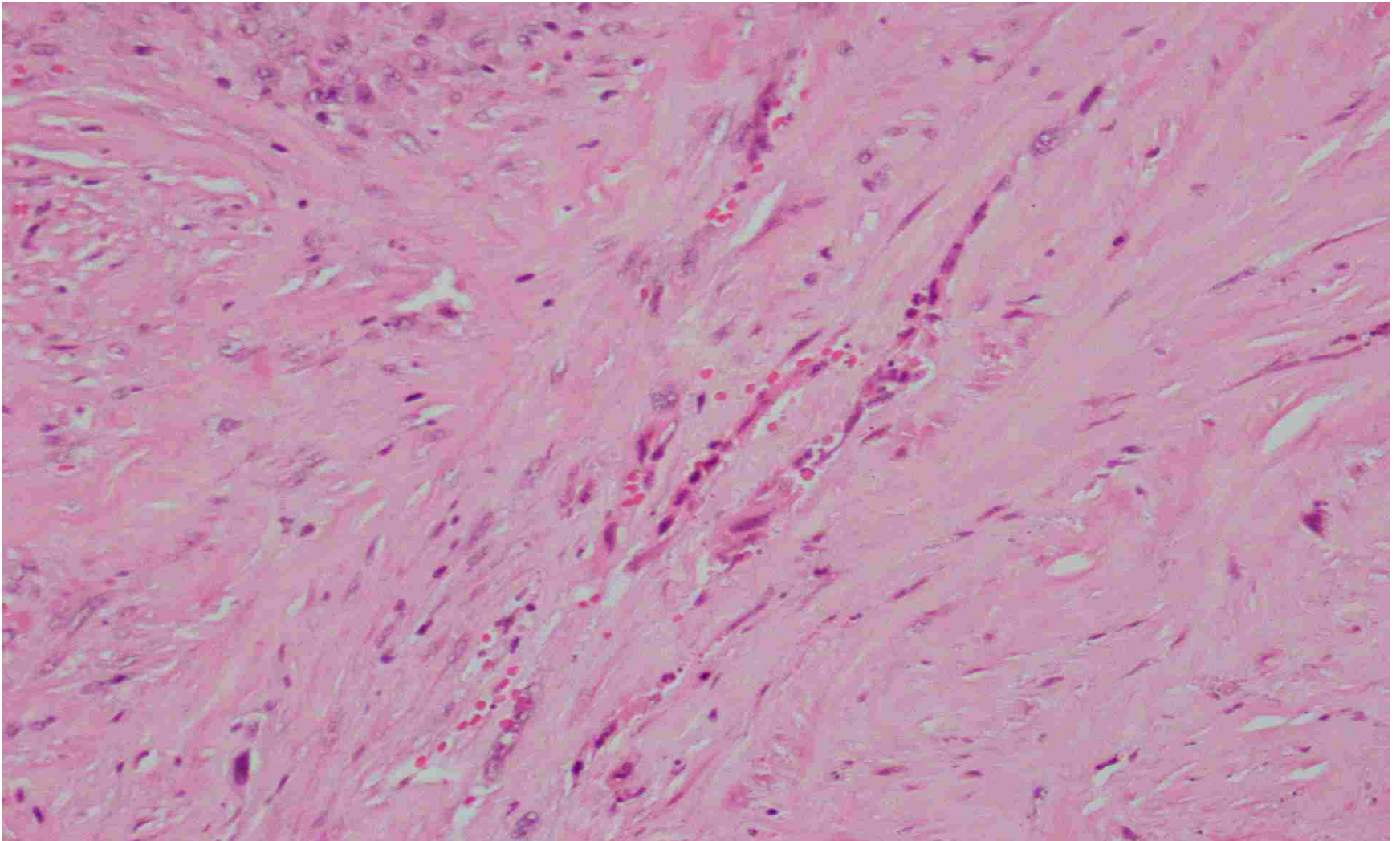




# Anaplastic Thyroid Carcinoma

- Giant Cell (Pleomorphic Variant)
- Spindle Cell Variant
- Squamoid Variant
- Paucicellular Variant

# Paucicellular Variant of ATC





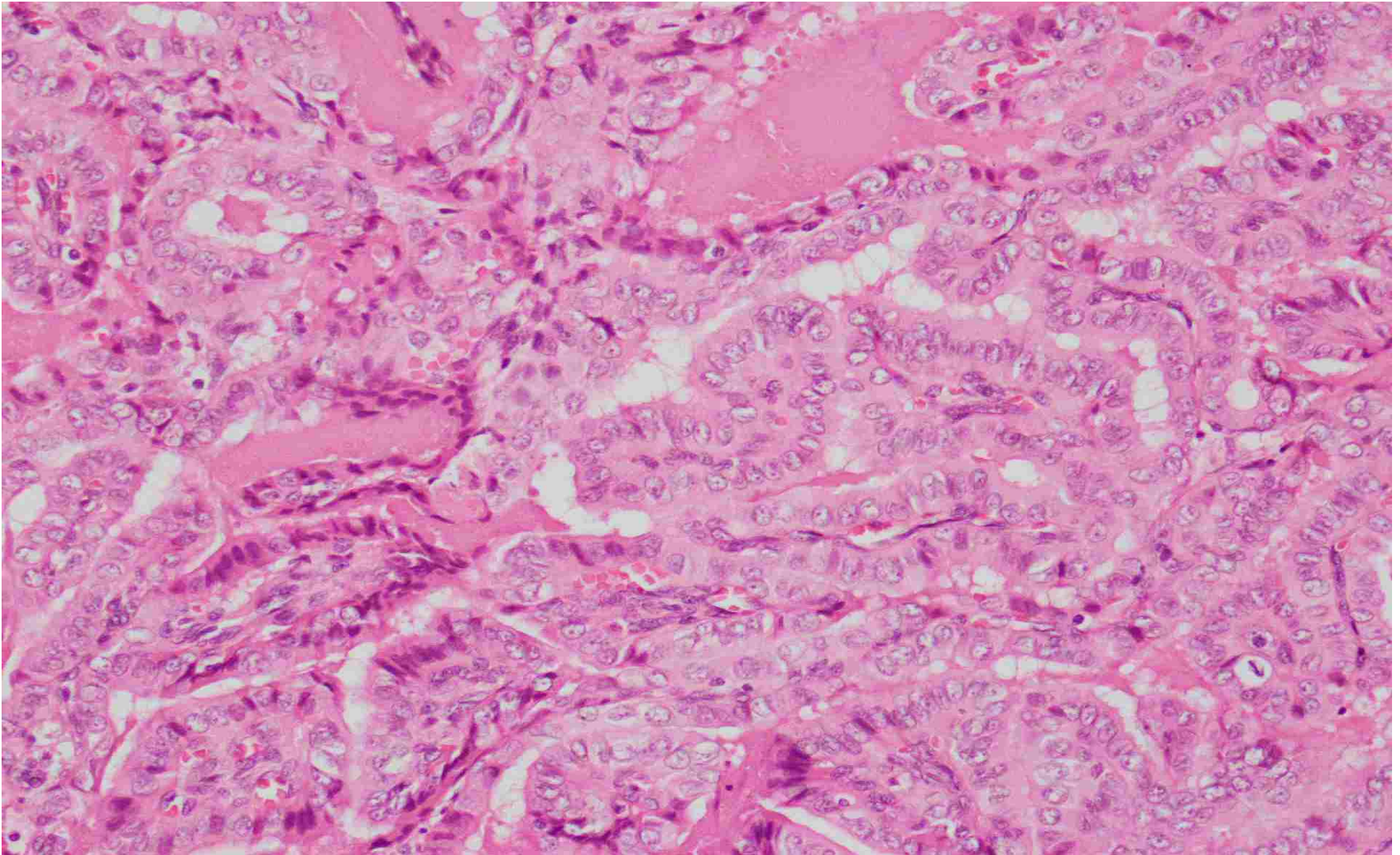
# Molecular Alterations in Anaplastic Thyroid Carcinomas

- TERT Promoter -75%
- TP53 -63%
- BRAF (V600E) -45%
- RAS -24%
- PIK3CA -18%
- EIF1AX -14%
- PTEN -14%

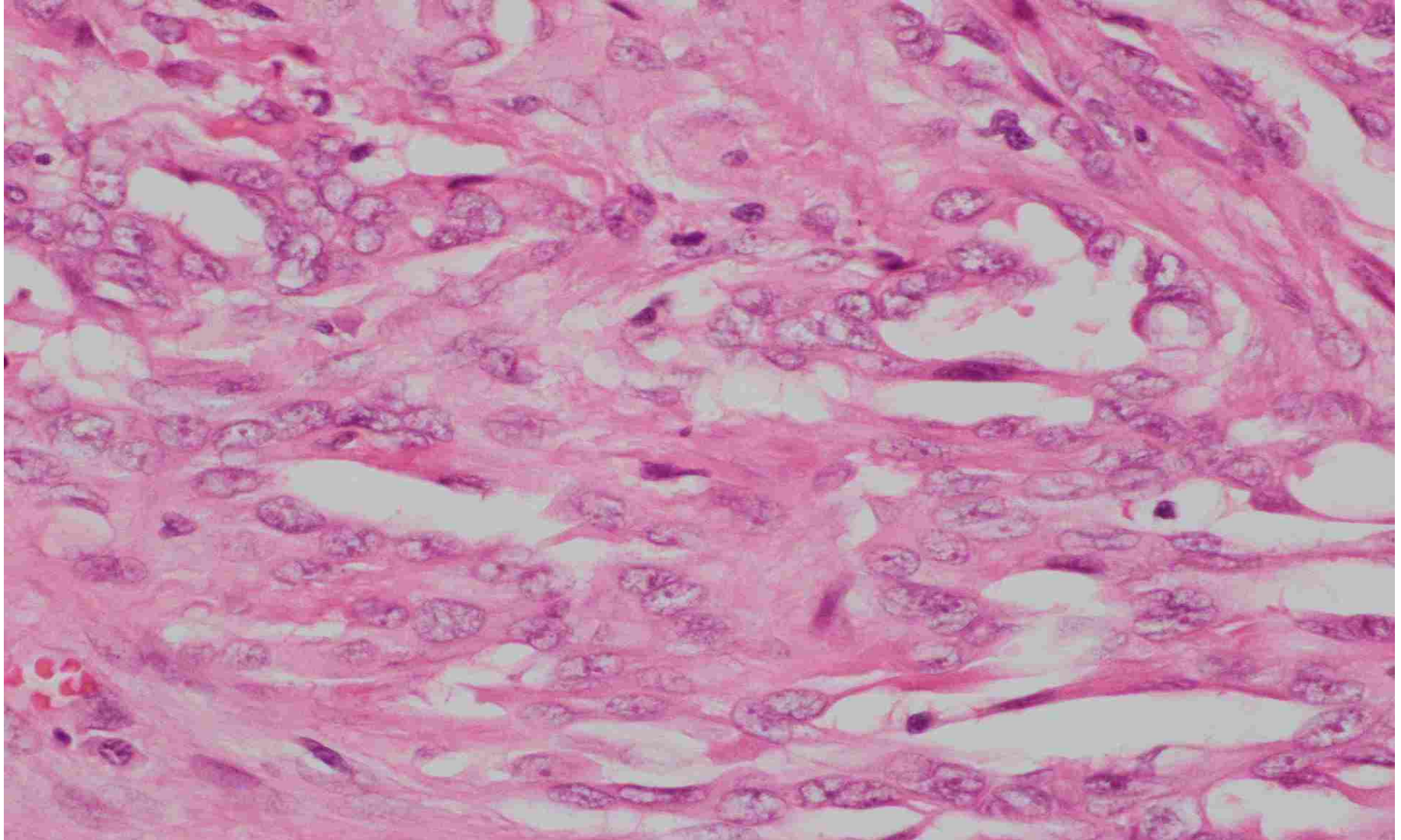
Concomitant mutations of BRAF or RAS with TERT Promoter associated with a worse prognosis.

Xu et al. *Thyroid* 30:1505-1517, 2020

# Mixed TCV of PTC with Dedifferentiation to ATC



# PTC-ATC in Epithelial-Mesenchymal Transition



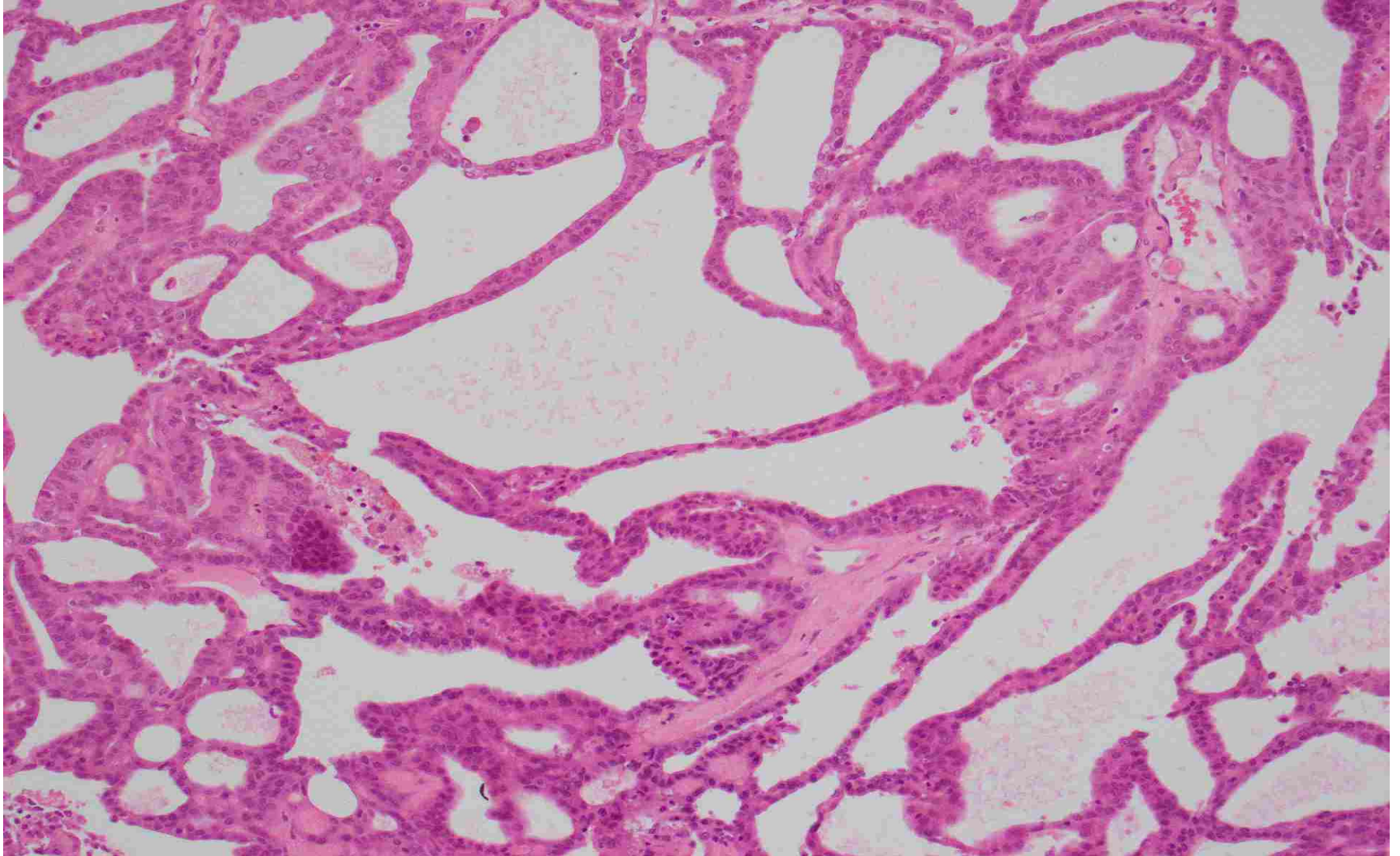
# Epithelial-Mesenchymal Transition (EMT)

- Transition from an epithelial morphology to a spindle cell morphology
- PTC dedifferentiates to ATC
- Seen in about 50-60% of ATCs
- Behavior of these tumors similar to other ATCs

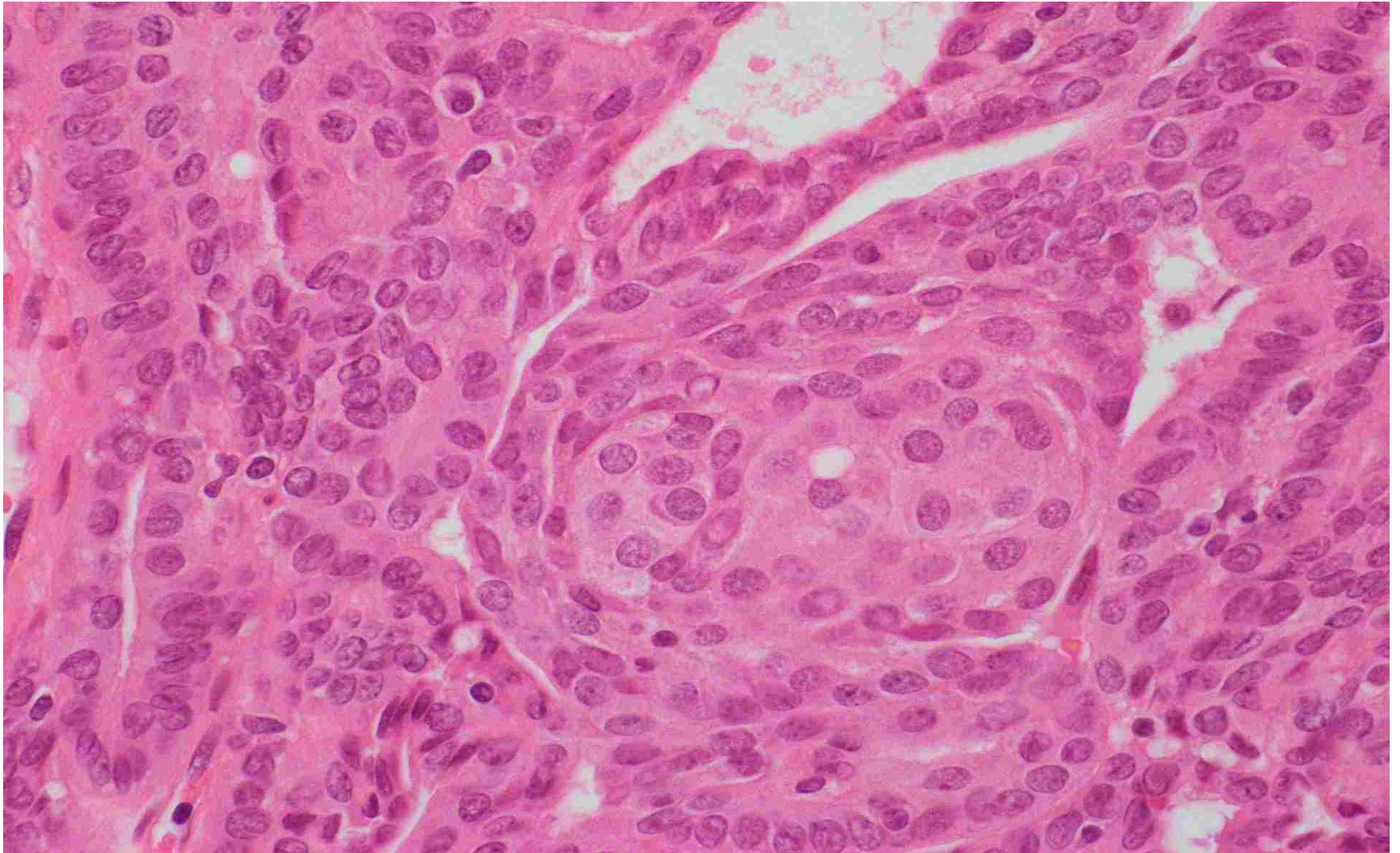
# Cribriform-Morular Variant of PTC

- Marked female predominance (30:1)
- Familial subtype associated with familial adenomatous polyposis (FAP)
- Cribriform and Morular histologic features
- Nuclear beta catenin by IHC
- Very good prognosis (only a small percentage metastasize to lymph nodes -10%)

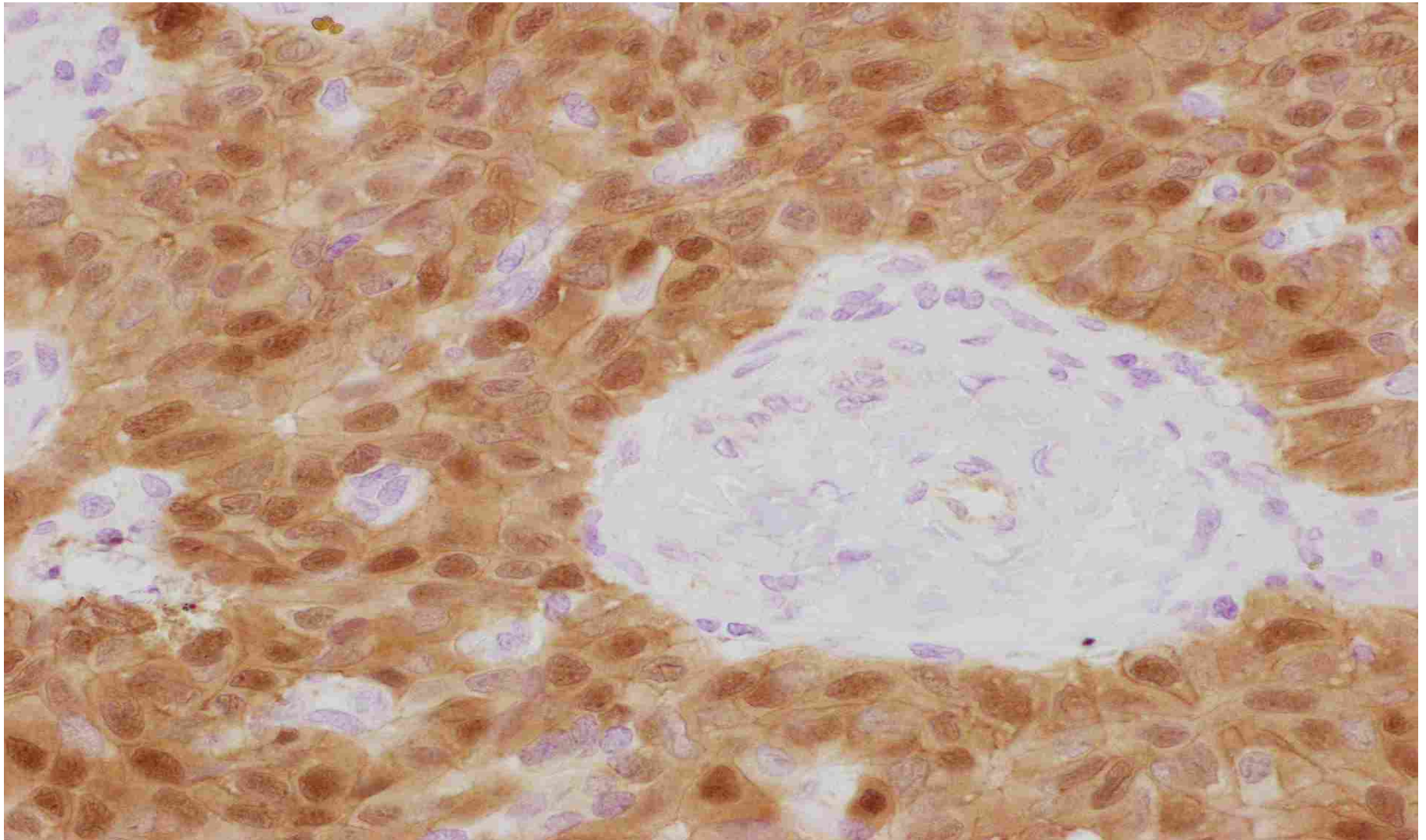
# Cribriform-Morular Variant of PTC



# Morular focus in CMV of PTC

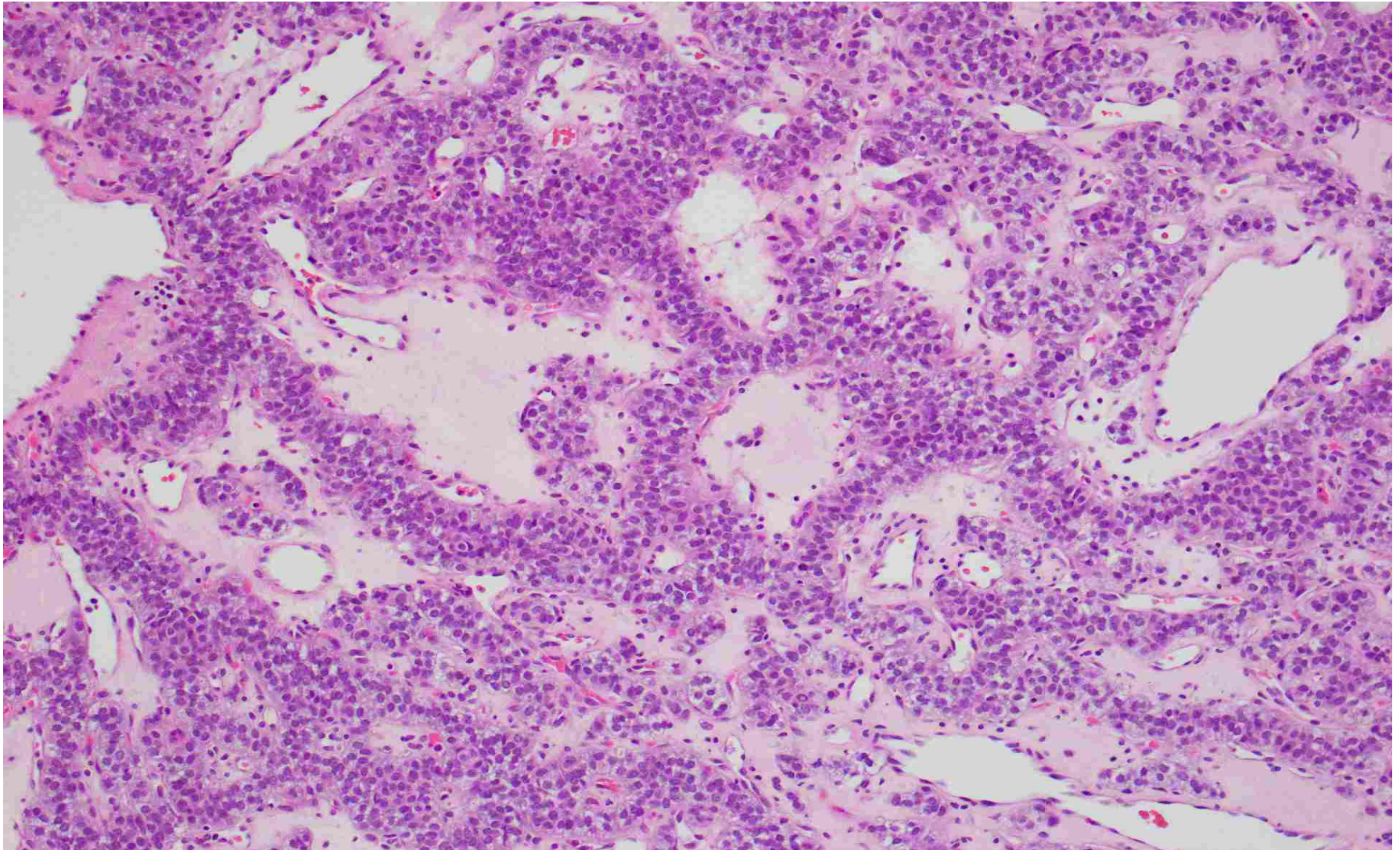


# CMV of PTC—Beta Catenin IHC

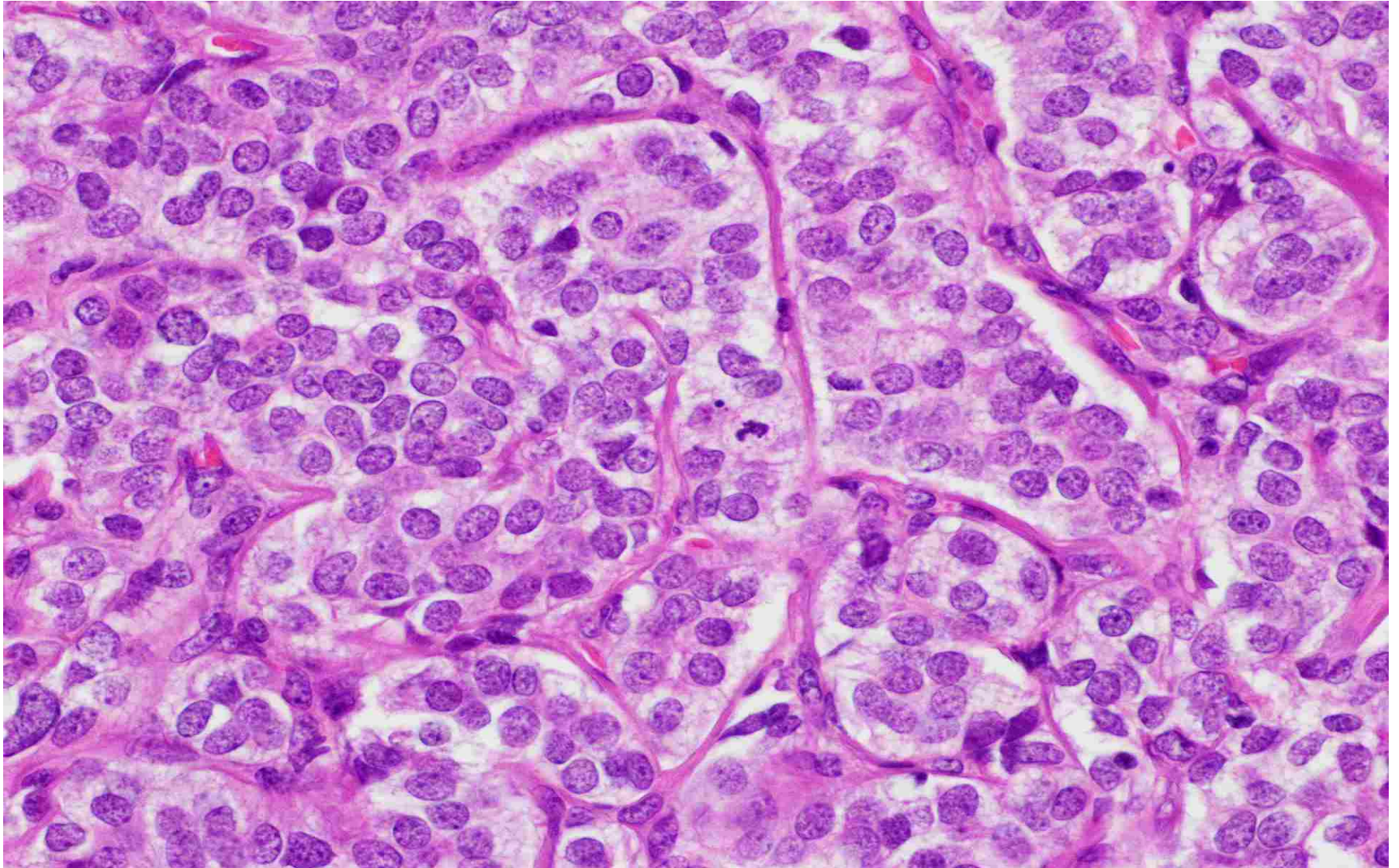




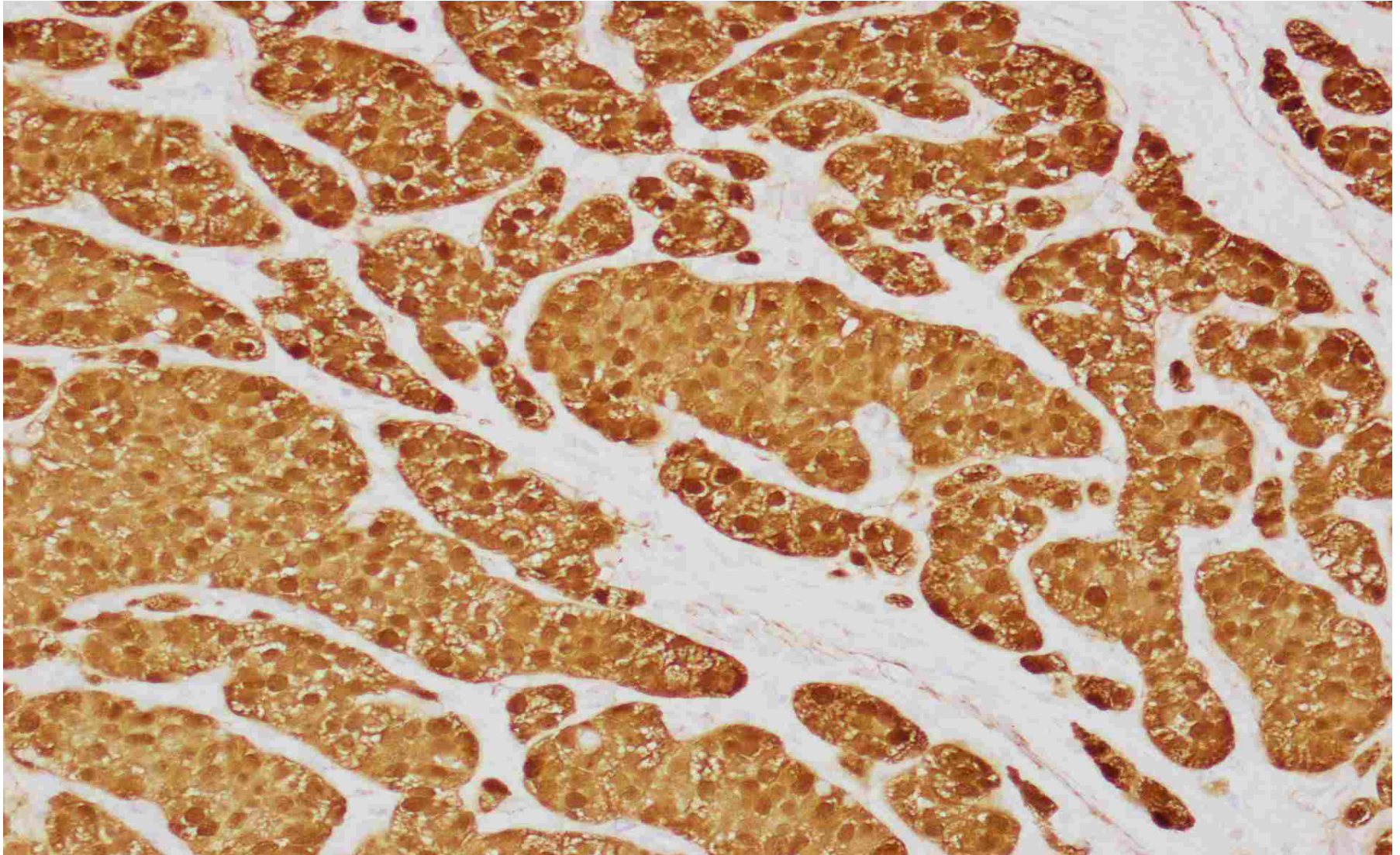
# CMV of PTC with Poorly Differentiated Features



# CMV of PTC with Poorly Differentiated Features



# CMV of PTC with Poorly Differentiated Features-Beta Catenin



# CMVPTC with Undifferentiated Features

<u>Reference</u>	<u>Age</u>	<u>Sex</u>	<u>FAP</u>	<u>Metastasis</u>
• Nakazawa, et al	35	F	-	lung, bone
• Oh, et al	45	F	-	bone, lymph node
•				
•				
• Tsuji, et al	28	F	-	lung
• Corean, et al	29	F	- <sup>b</sup>	none
•				
• Present Case	49	F	-	none

# Summary

- Molecular analyses have been helpful in the diagnosis, prognosis and therapeutics of thyroid carcinomas.
- Although PTCs are not graded, the specific subtypes are predictive of tumor behavior
- The diagnosis of NIFTP has been helpful in guiding the diagnosis and treatment of some low grade PTCs.

# References

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