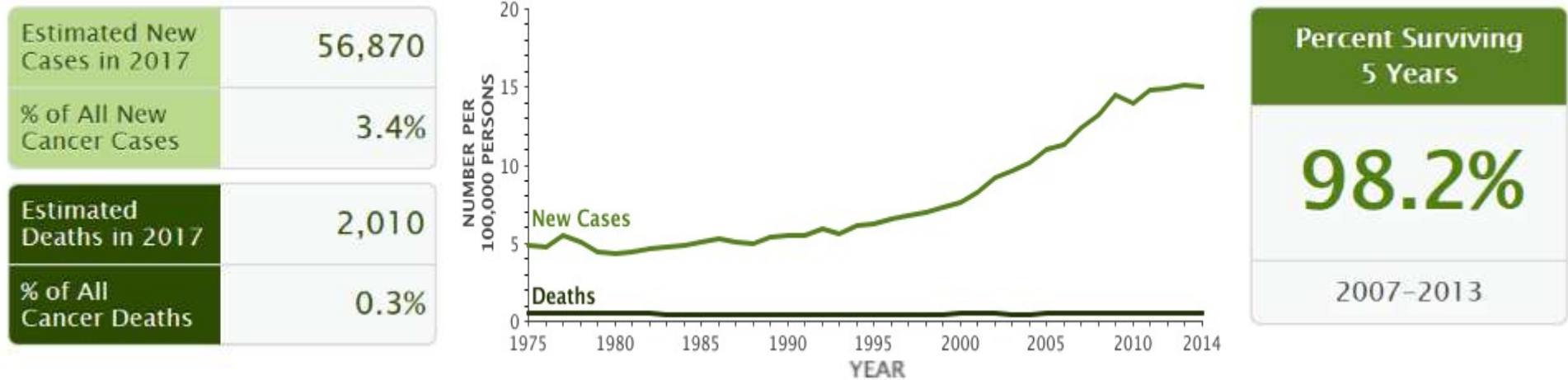


2018 KOPANA 17th Spring Seminar

**Critical Review and Appraisal of the
Latest AJCC System and WHO
Classification of **Thyroid Tumors****

Chan Kwon Jung, MD, PhD
Department of Hospital Pathology,
The Catholic University of Korea
Seoul St. Mary's Hospital

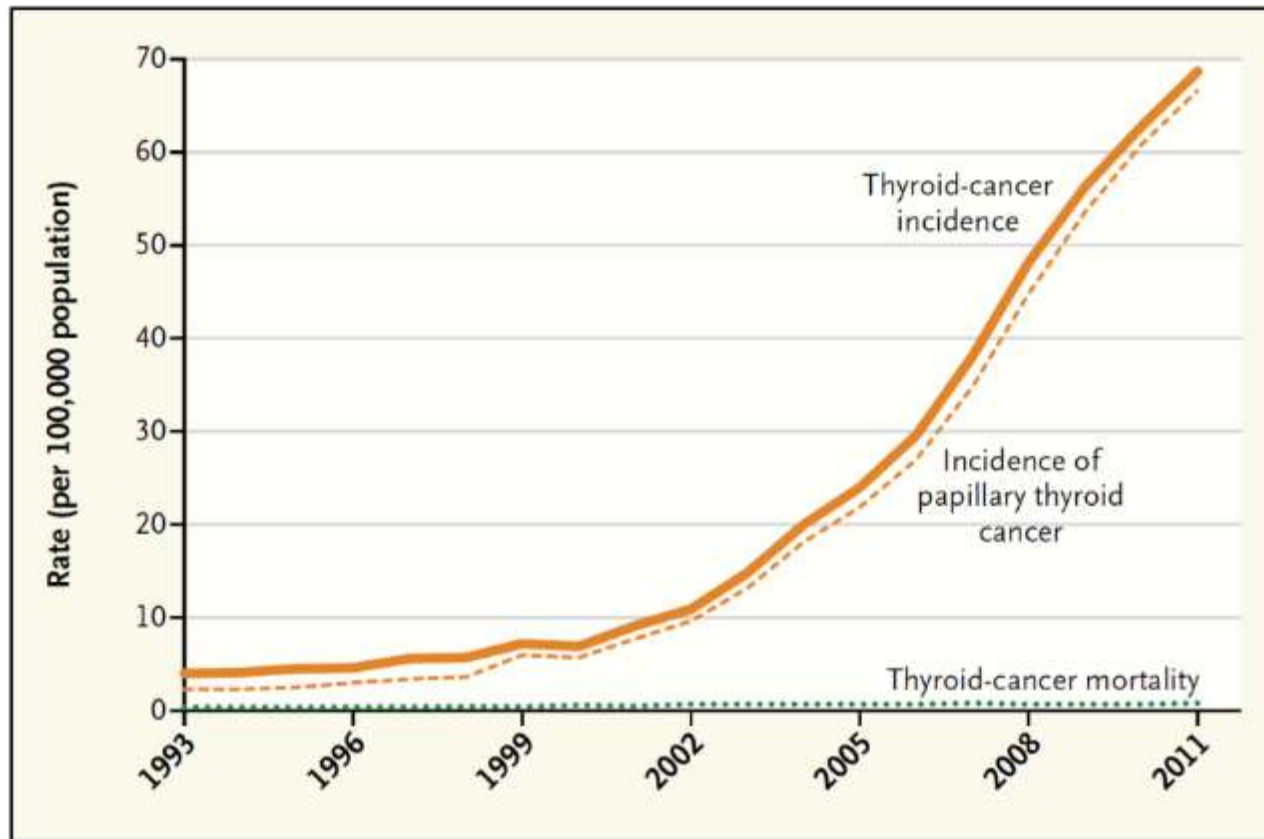
Cancer Stat Facts: Thyroid Cancer



rates for new thyroid cancer cases have been rising on average 3.8% each year over the last 10 years

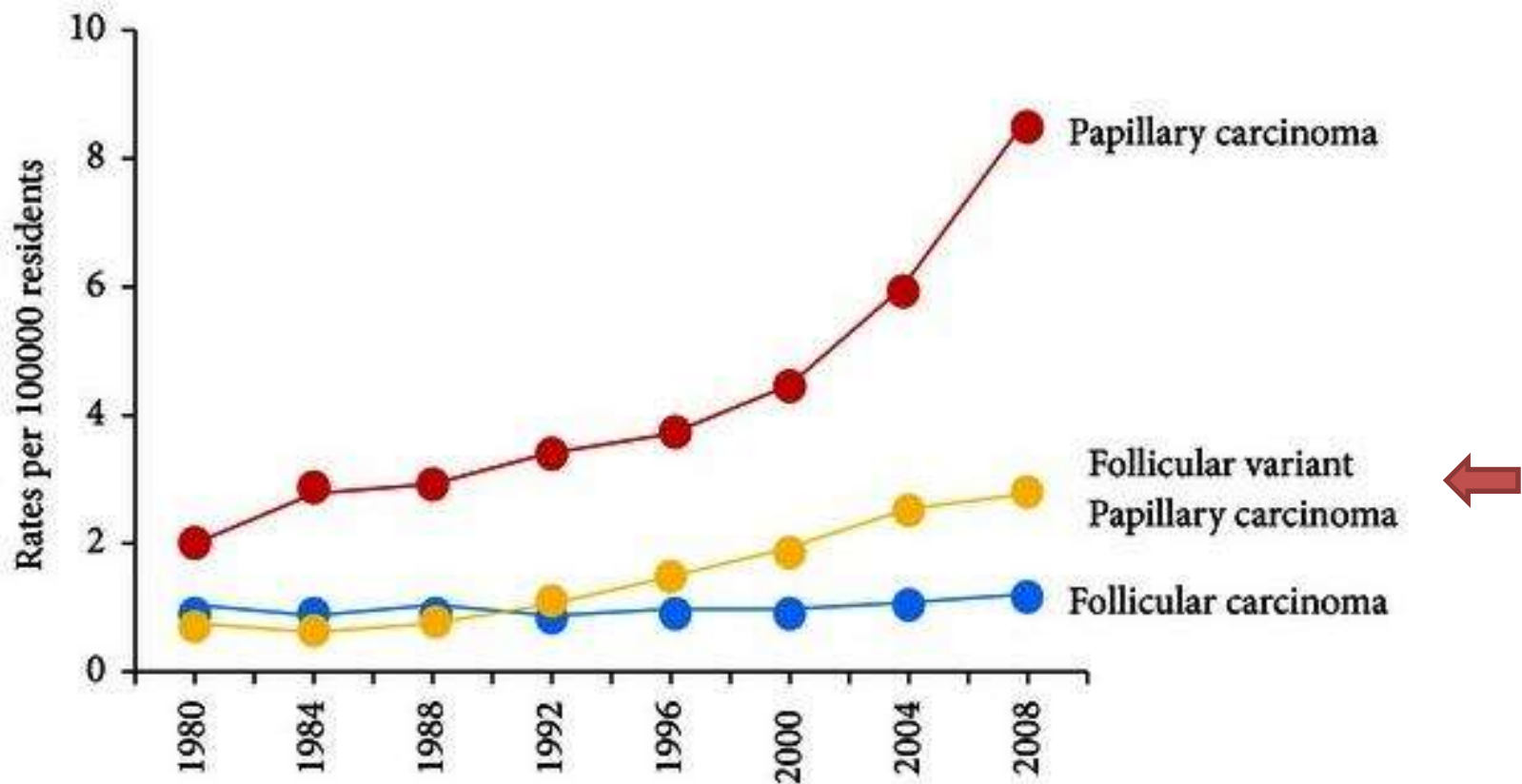
<https://seer.cancer.gov/statfacts/html/thyro.html>

Korea's Thyroid-Cancer “Epidemic” — Screening and Overdiagnosis



N Engl J Med 2014;371:1765-7

The trend in thyroid cancer incidence in the United States from 1980 to 2009



J Cancer Epidemiol. 2013; 2013: 965212.

Historical aspects of FVPTC

1953

Crile & Hazard, first described FVPTC

Ann Surg 1953;138:33-8

1960

Lindsay S. recognized the entity

1977

Chen KT and Rosai J. defined the FVTPC

Am J Surg Pathol 1977;1:123-30

1988

WHO classification 2nd Ed.

1998

more accurate diagnosis

Am J Clin Pathol 1999;111:216-222

2016

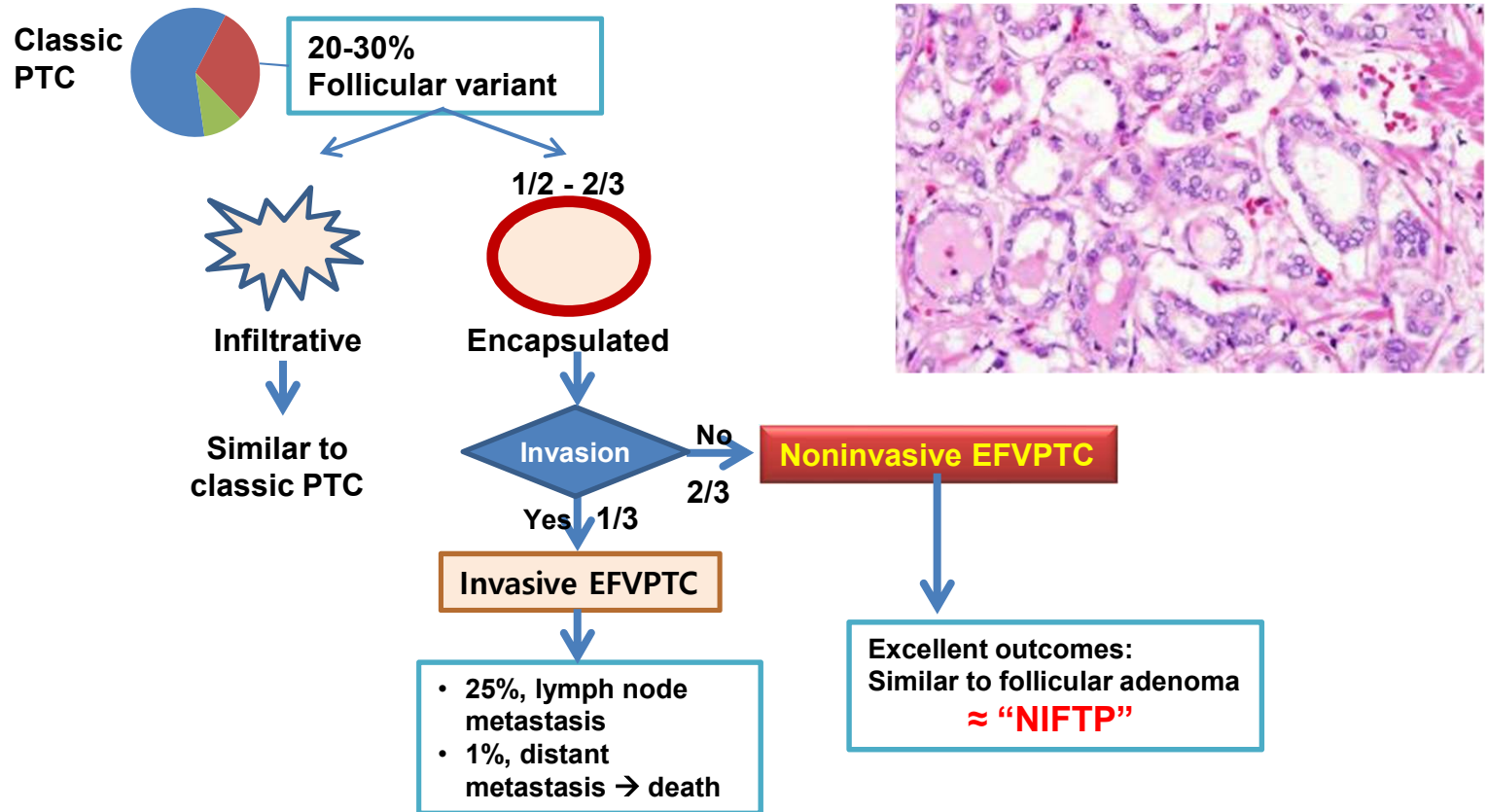
NIFTP

EFVPTC with distant metastasis

- 3 follicular adenomas → bone metastases 7 to 17 yrs after thyroid resection
- 2 presented initially with bone metastases

Baloch ZW and LiVolsi VA. Mod Pathol 2000;13:861–5

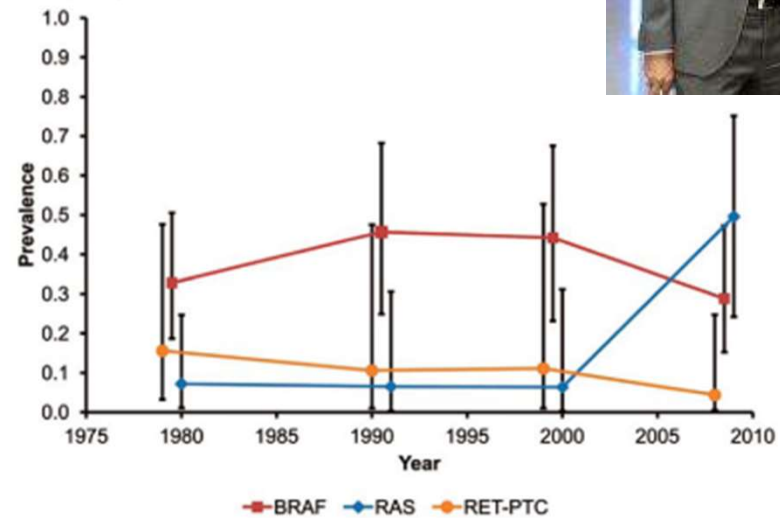
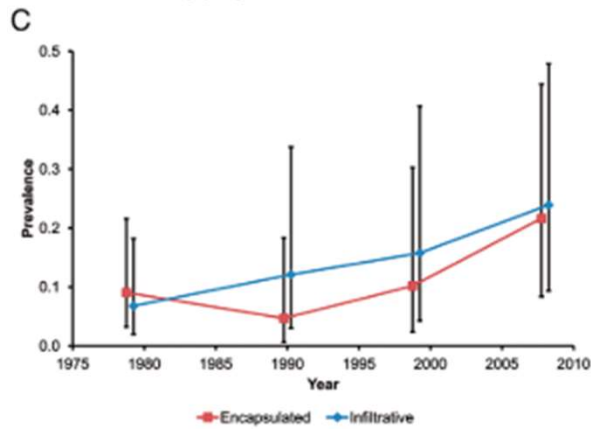
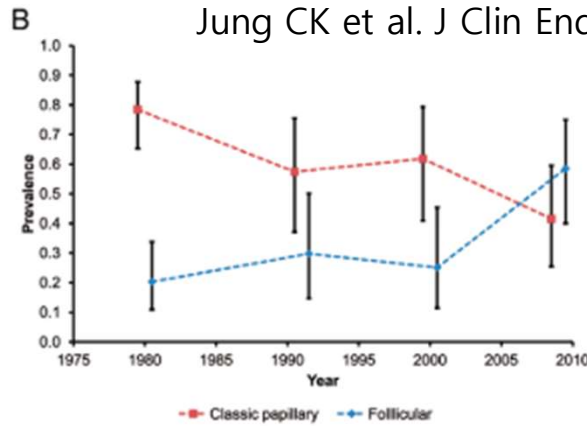
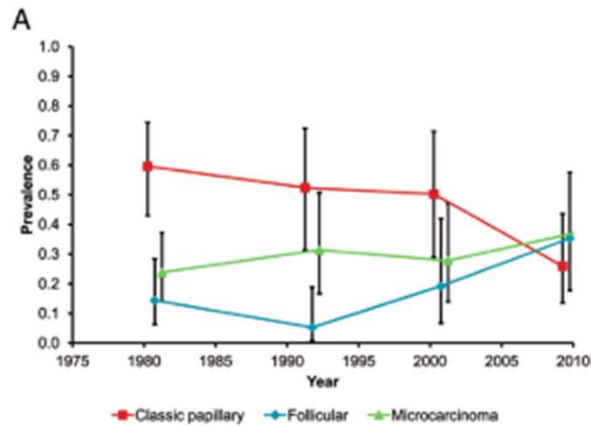
Risk stratification of follicular variant of papillary thyroid carcinoma



“noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP)

The Increase in Thyroid Cancer Incidence During the Last Four Decades Is Accompanied by a High Frequency of *BRAF* Mutations and a Sharp Increase in *RAS* Mutations

Jung CK et al. J Clin Endocrinol Metab. 2014 Feb;99(2):E276-85

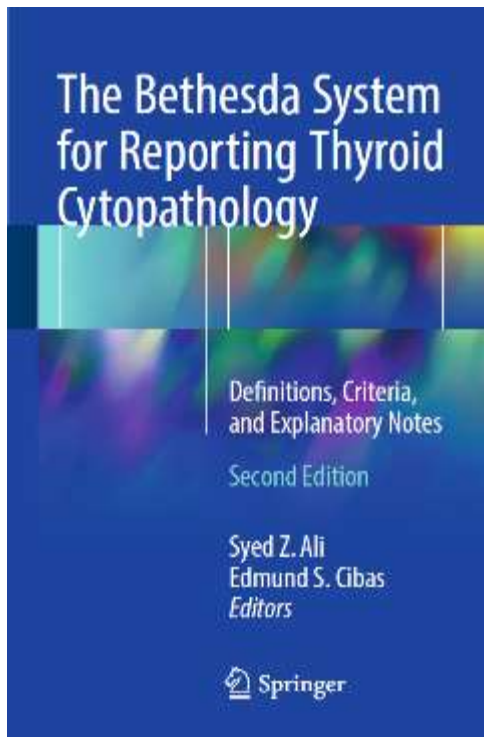


“Less is More”

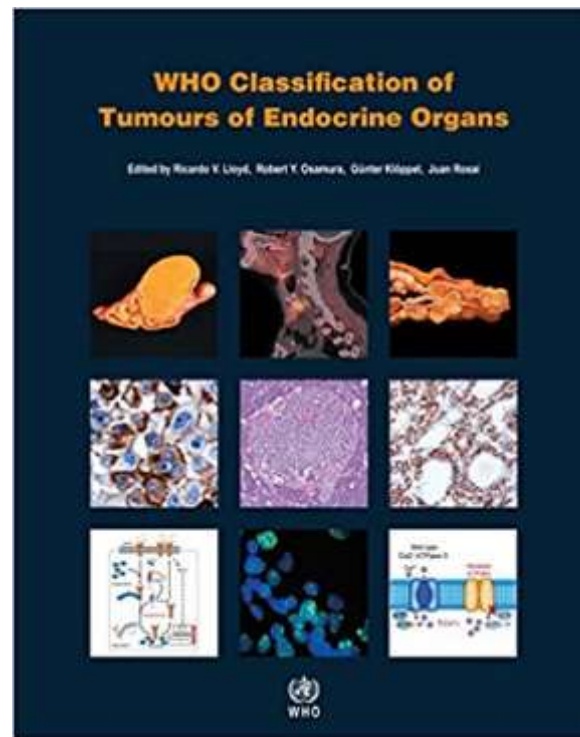
- **Less diagnosis:** sub-centimeter nodules should not be routinely selected for FNA
- **Lobectomy as the initial surgical approach**
- **Less radioactive iodine treatment**
- **Less stimulated thyroglobulin testing**

2017 Update

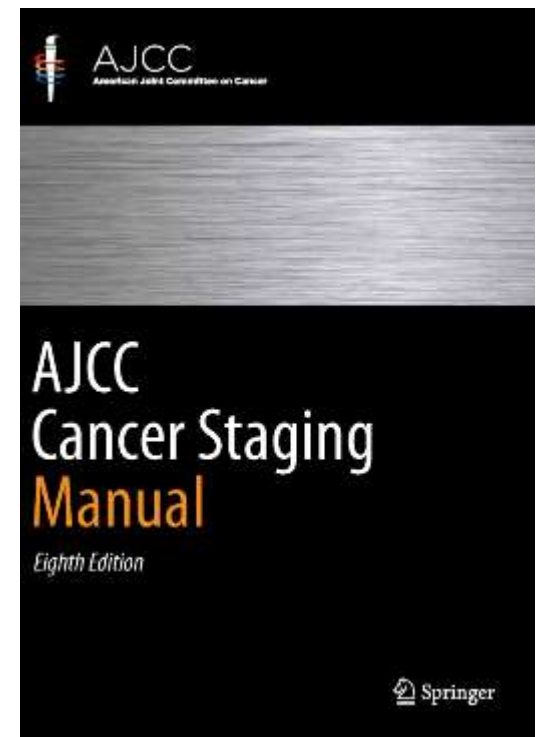
2nd Edition



4th Edition



8th Edition



The 3rd Edition WHO Classification of Thyroid Tumors

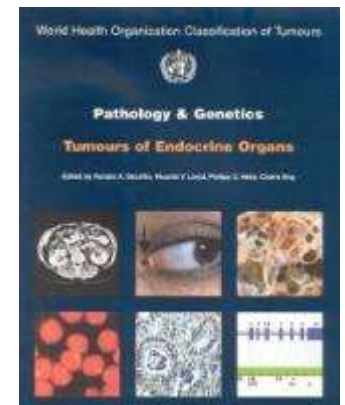
Malignant

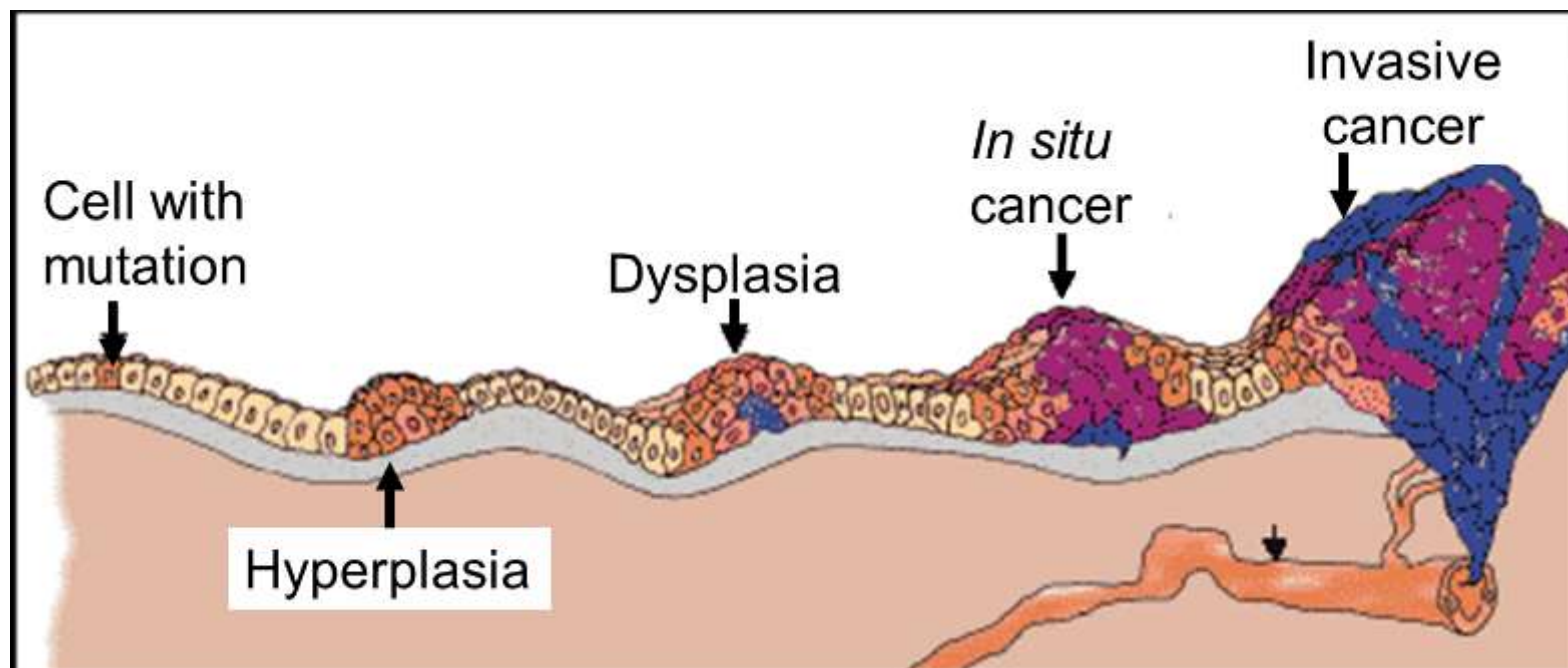
- Papillary carcinoma
- Follicular carcinoma
- Poorly differentiated carcinoma
- Undifferentiated (anaplastic) carcinoma
- Squamous cell carcinoma
- Sclerosing mucoepidermoid carcinoma with eosinophilia
- Mucinous carcinoma
- Medullary thyroid carcinoma
- Mixed medullary and follicular cell carcinoma
- Spindle cell tumor with thymus-like differentiation
- Carcinoma showing thymus-like differentiation

Benign

- Follicular adenoma
- Hyalinizing trabecular tumor
- ...
- Secondary tumor of the thyroid

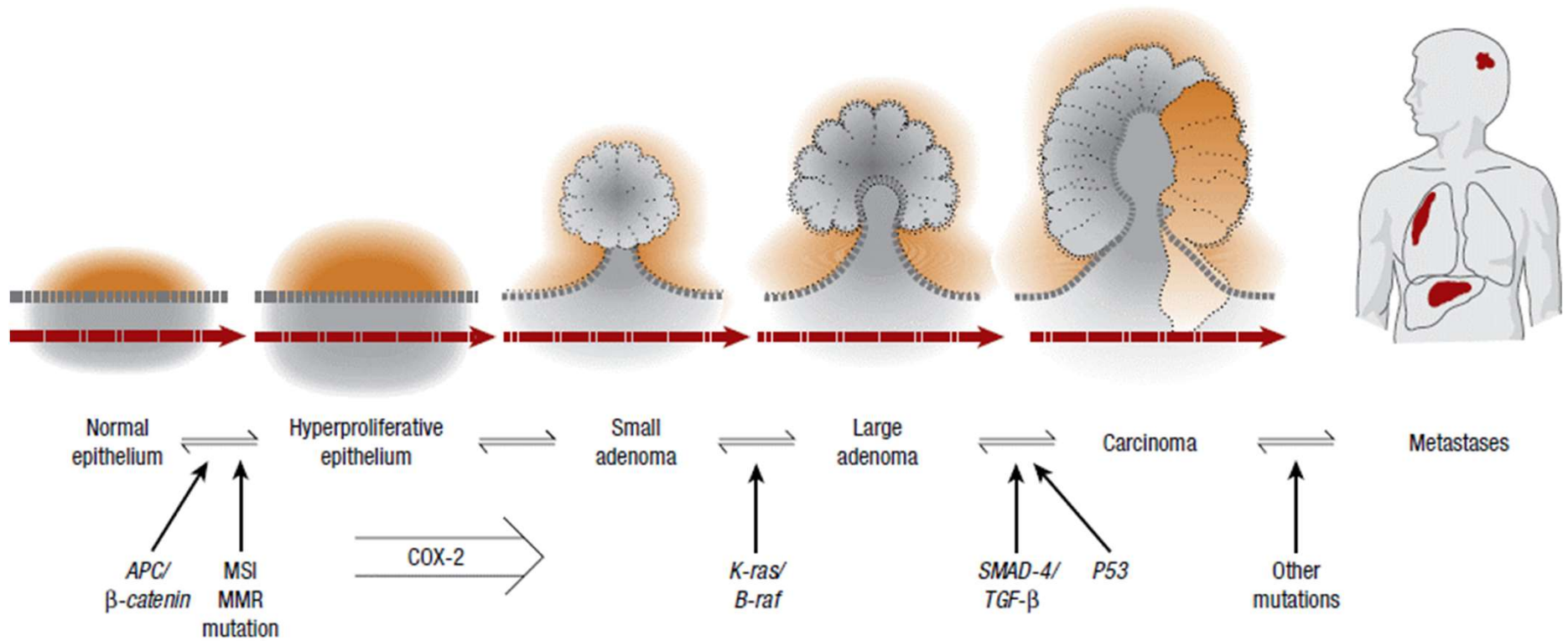
2004





← 10-15 years →

Adenoma-Carcinoma Sequence



The 4th Edition WHO Classification of Thyroid Tumors

ICD-O

Benign:

Follicular adenoma	8330/0
Hürthle cell adenoma	8290/0

Borderline, uncertain:

Hyalinizing trabecular tumor	8336/1
Other Encapsulated Follicular Patterned Thyroid Tumors	
Follicular Tumor of Uncertain Malignant Potential (FT-UMP)	8335/1
Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP)	8348/1
Non-invasive Follicular Thyroid neoplasm with Papillary-like nuclear features (NIFTP)	8349/1

Malignant:

Papillary thyroid carcinoma	8260/3
Follicular thyroid carcinoma	8330/3
Hürthle cell carcinoma	8290/3
Poorly differentiated thyroid carcinoma	8337/3
Anaplastic thyroid carcinoma	8020/3
Squamous cell carcinoma	8070/3
Medullary thyroid carcinoma	8345/3

The 4th Edition WHO Classification of Thyroid Tumors

Follicular thyroid carcinoma (FTC), NOS	8330/3
FTC, minimally invasive	8335/3
FTC, encapsulated angioinvasive	8339/3
FTC, widely invasive	8330/3
Hürthle (oncocytic) cell tumors	
Hürthle cell adenoma	8290/0
Hürthle cell carcinoma	8290/3
Poorly differentiated thyroid carcinoma	8337/3
Anaplastic thyroid carcinoma	8020/3
Squamous cell carcinoma	8070/3
Medullary thyroid carcinoma	8345/3

New codes

• Hyalinizing trabecular tumor	8336/1
• Follicular Tumor of Uncertain Malignant Potential (FT-UMP)	8335/1
• Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP)	8348/1
• Non-invasive Follicular Thyroid neoplasm with Papillary-like nuclear features (NIFTP)	8349/1
• FTC, encapsulated angioinvasive	8339/3

Renaming entities

2004, 3 rd edition	2017, 4 th edition
Follicular adenoma, oncocytic type	Hürthle cell adenoma
Follicular carcinoma, oncocytic type	Hürthle cell carcinoma
Poorly differentiated carcinoma	Poorly differentiated thyroid carcinoma
Undifferentiated (anaplastic) carcinoma	Anaplastic thyroid carcinoma
Mixed medullary and follicular cell carcinoma	Mixed medullary and follicular thyroid carcinoma
Carcinoma showing thymus-like differentiation (CASTLE)	Intrathyroid thymic carcinoma

Hürthle (oncocytic) cell tumors

>75% of the tumor is composed of Hürthle cells

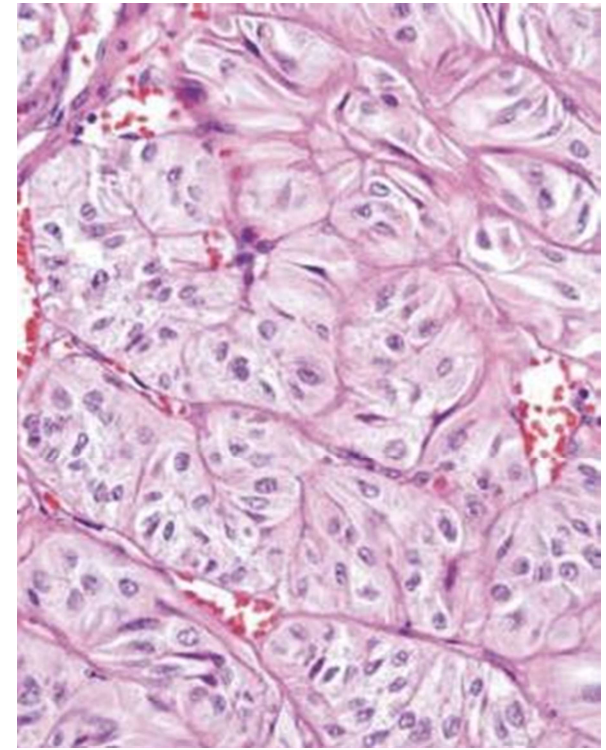
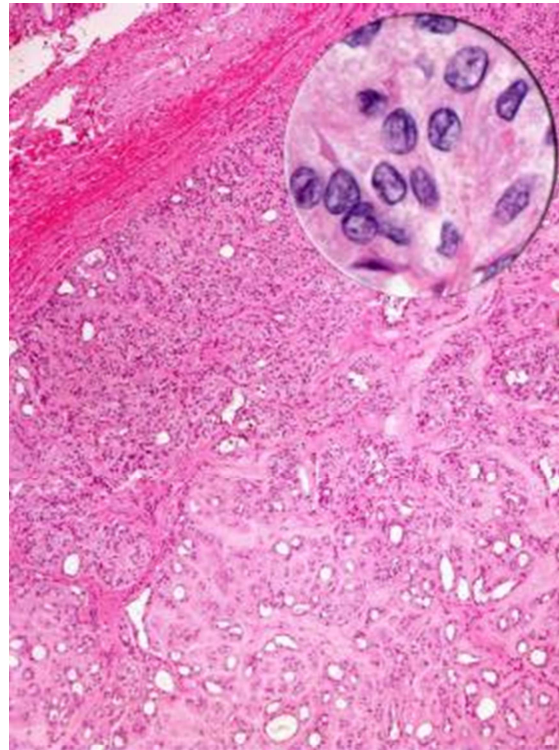
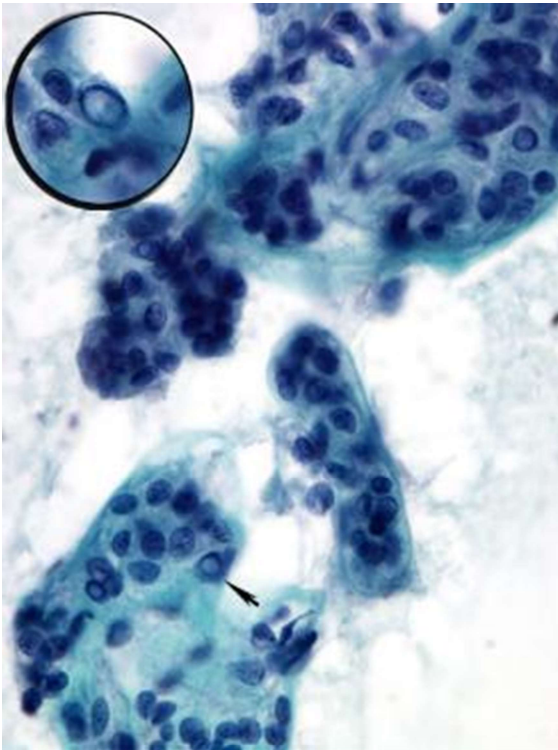
Hürthle cell adenoma	8290/0
Hürthle cell carcinoma	8290/3

Different from non- Hürthle cell thyroid carcinomas

- HCC can spread to cervical nodes
- HCC had larger tumors, higher-stage disease, and lower survival rates
- More common in men
- Older age

Hyalinizing trabecular tumor

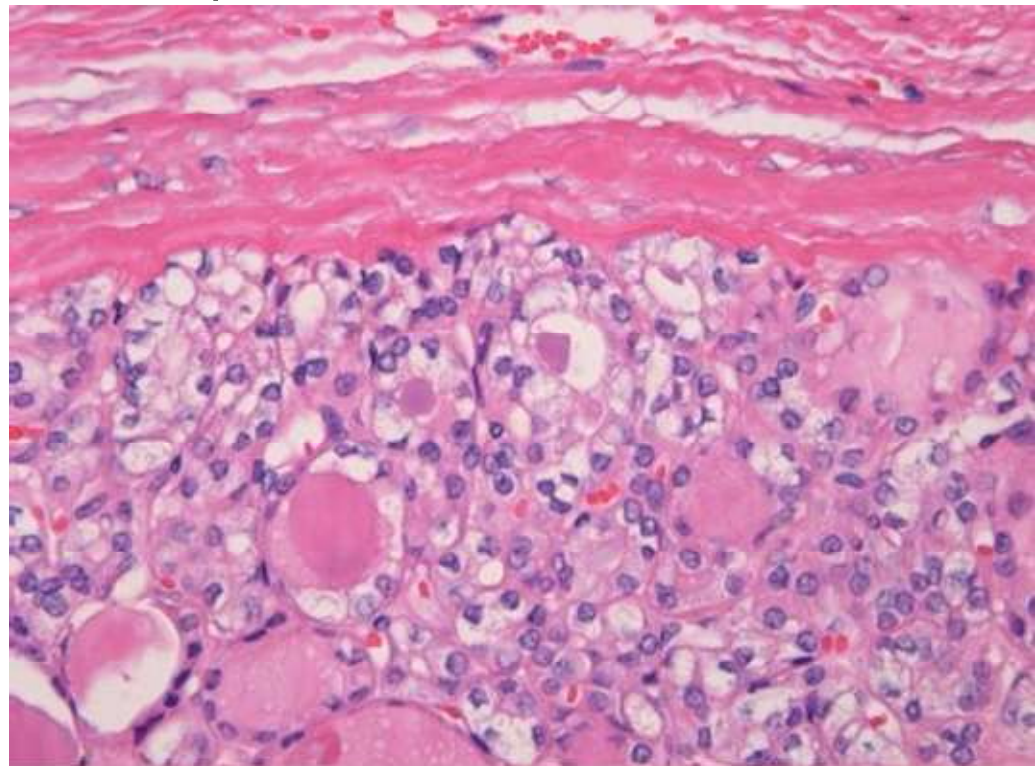
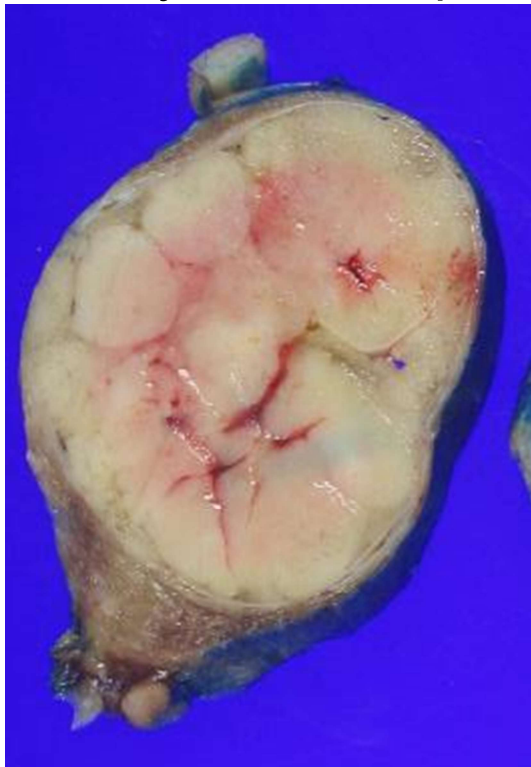
- ICD-O code 8336/1
- Benign course, only one case of distant metastasis, rare lymph node metastasis
- Detection of RET/PTC1 rearrangement and RET immunoreactivity



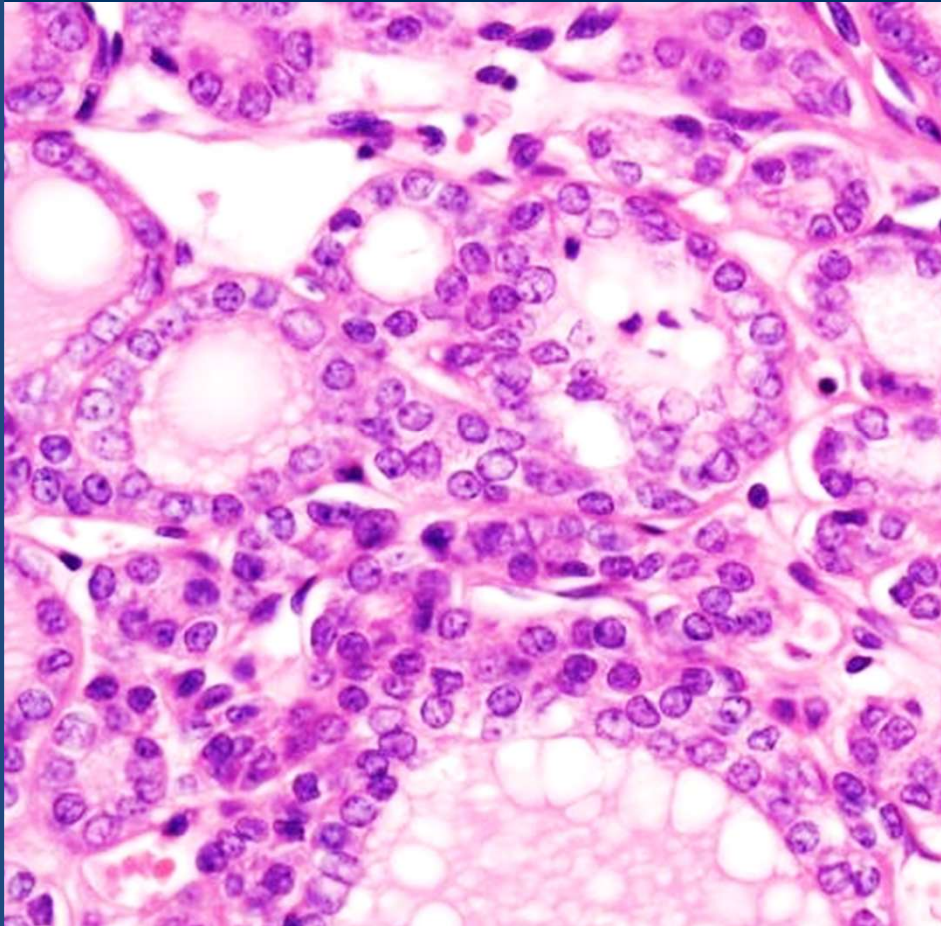
Encapsulated follicular-patterned thyroid tumors

Diagnostic difficulties

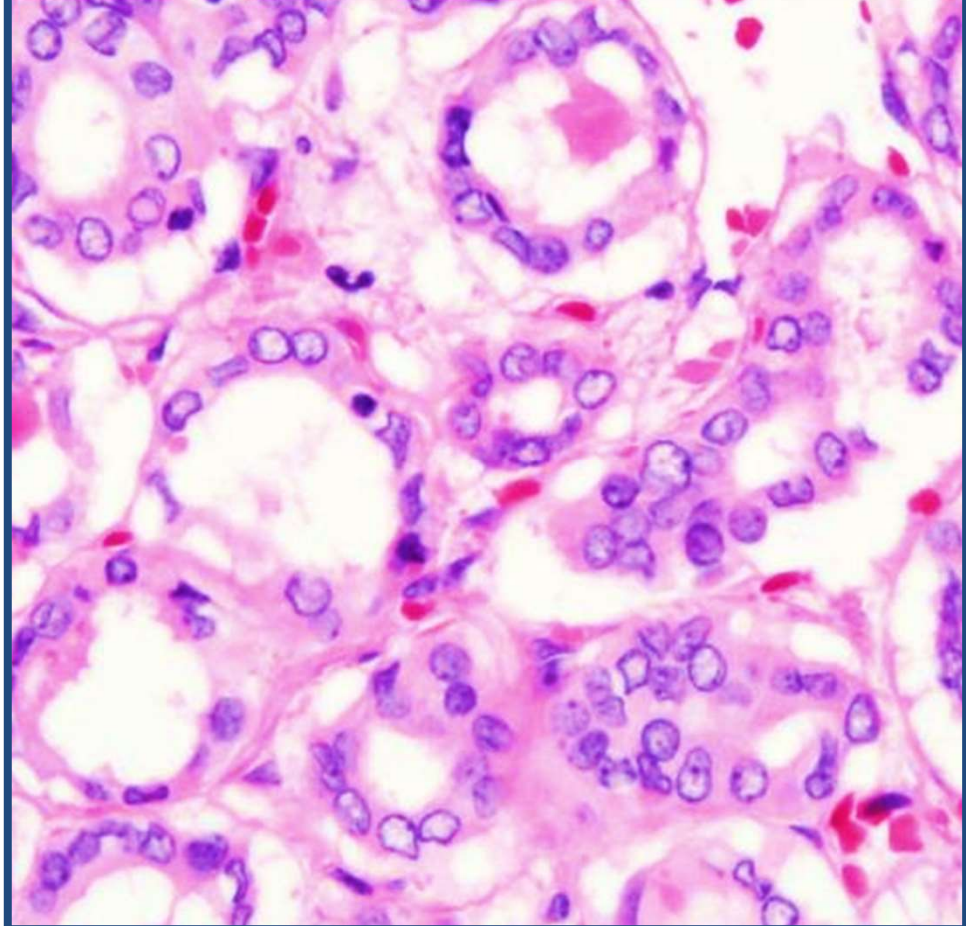
- whether the nuclear changes are sufficient to justify a diagnosis of PTC
- uncertainty about the presence of capsular or vascular invasion

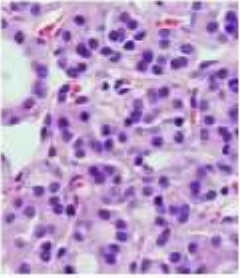
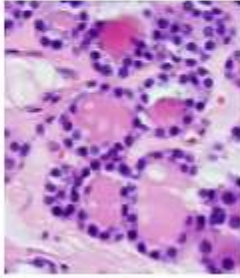
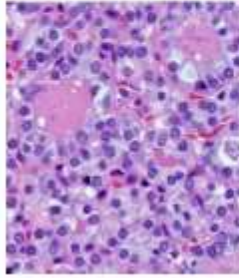
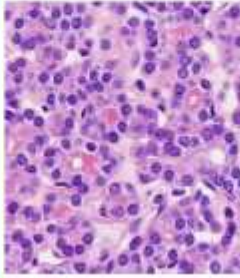
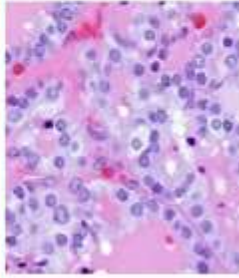


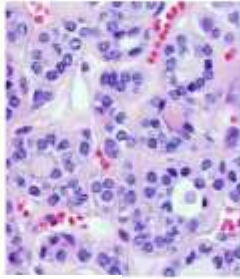
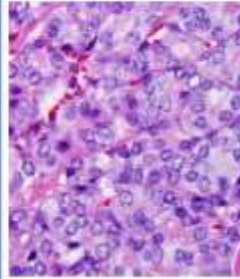
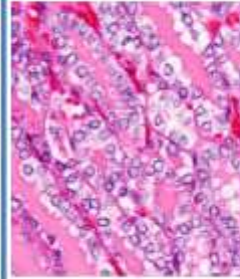
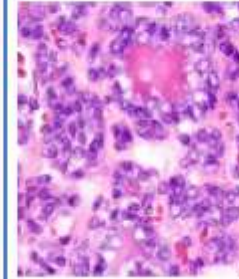
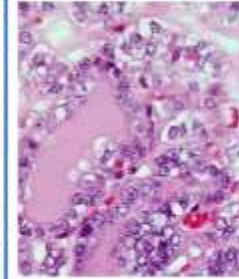
**Uncertainty about the presence of
PTC-type nuclear changes**



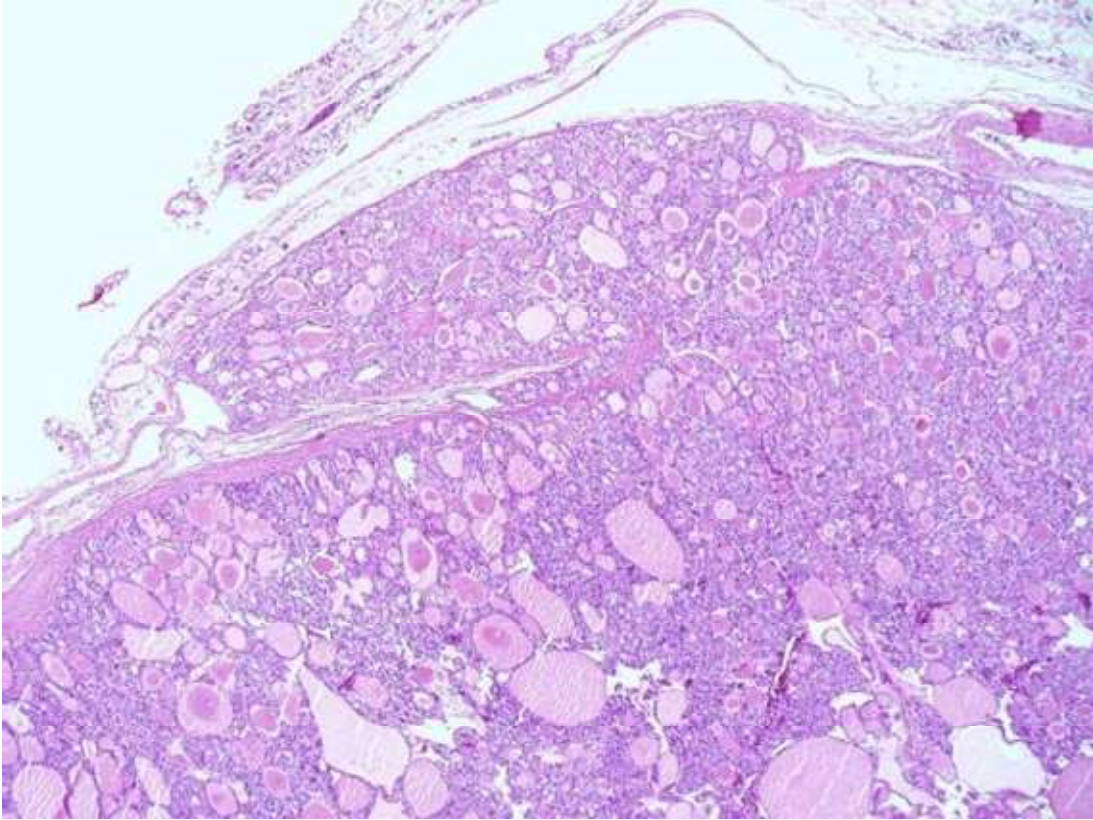
**Follicular variant of papillary
thyroid carcinoma**



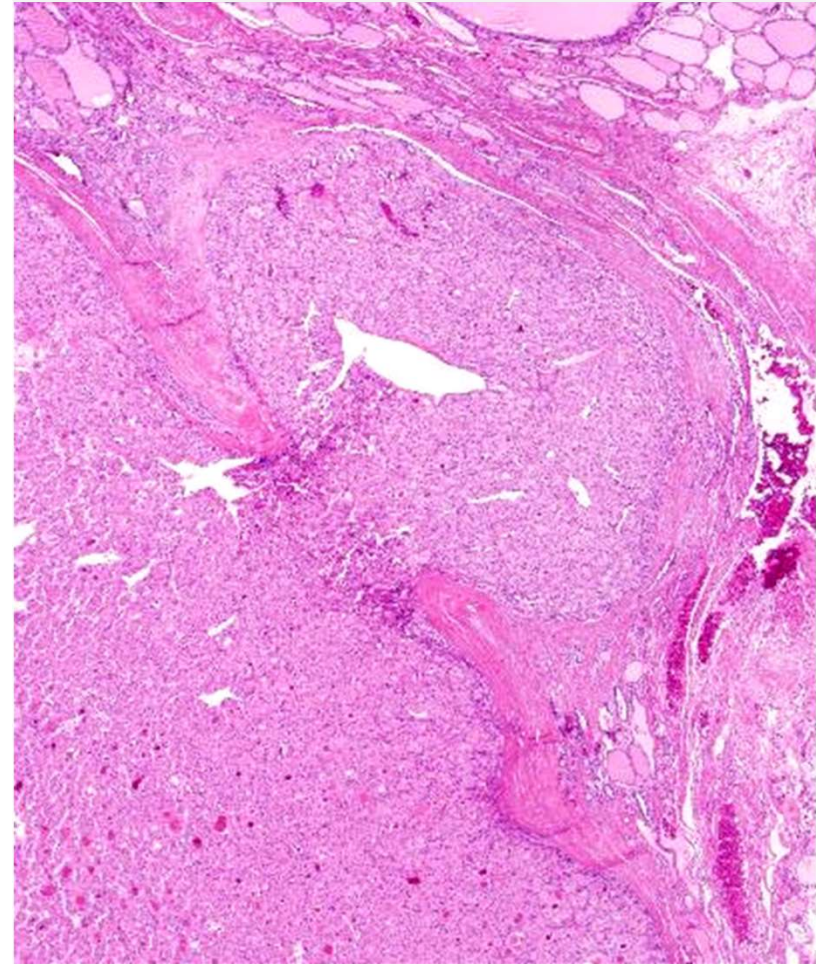
% of pathologists	0-9%	10-19%	20-29%	30-39%	40-49%
Number of cases (out of 138 total)	1	1	12	10	9
Representative image					

% of pathologists diagnosing	50-59%	60-69%	70-79%	80-89%	90-99%
Number of cases (out of 138 total)	15	34	29	19	8
Representative image					

Uncertainty about the presence of capsular or vascular invasion



Minimally invasive follicular thyroid carcinoma



Uncertainty

Poor interobserver concordance

Encapsulated tumor		Capsular or vascular invasion		
		Present	Questionable	Absent
Nuclear features of PTC	Present	Malignancy		Benign
	Questionable			
	Absent			

Regarding the Terminology

2017 WHO classification: Encapsulated follicular-patterned thyroid tumors on the basis of presence or absence of nuclear features of PTC and capsular or vascular invasion

Encapsulated tumor		Capsular or vascular invasion		
		Present	Questionable	Absent
Nuclear features of PTC	Present	Invasive EFVPTC	WDT-UMP	NIFTP
	Questionable	WDC, NOS		
	Absent	FTC	FT-UMP	Follicular adenoma

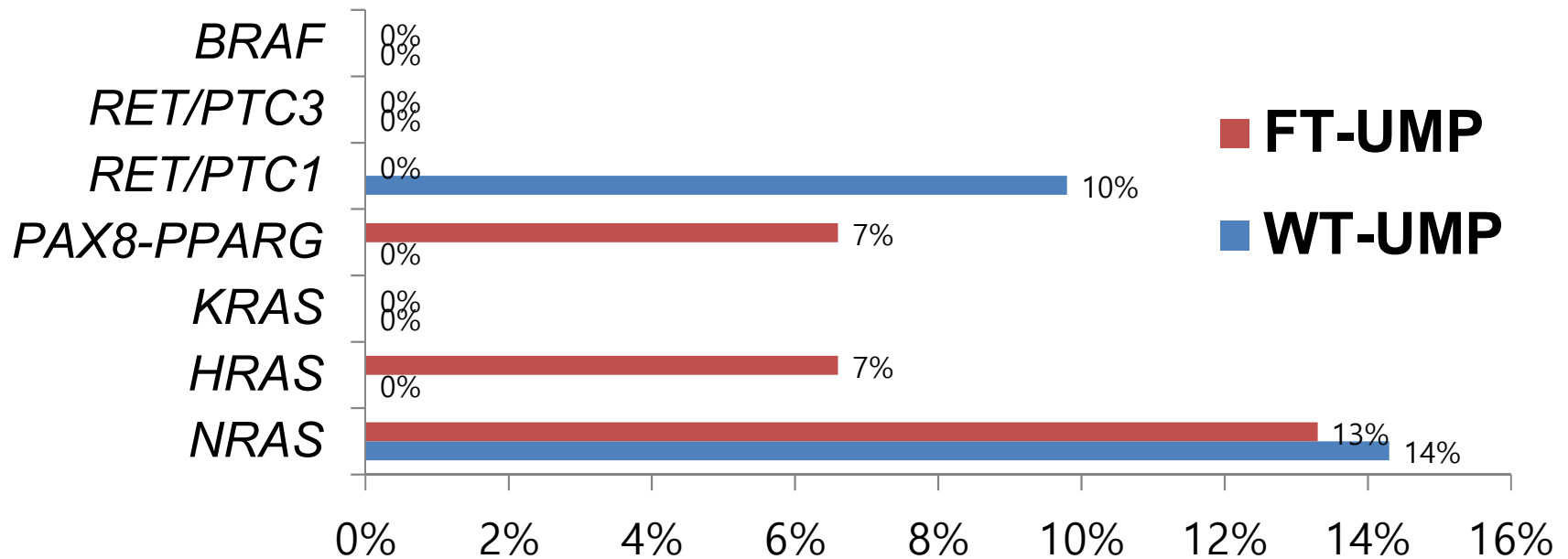
Tumors of Uncertain Malignant Potential

Encapsulated or well-circumscribed follicular-patterned thyroid tumors with **questionable capsular or vascular invasion**

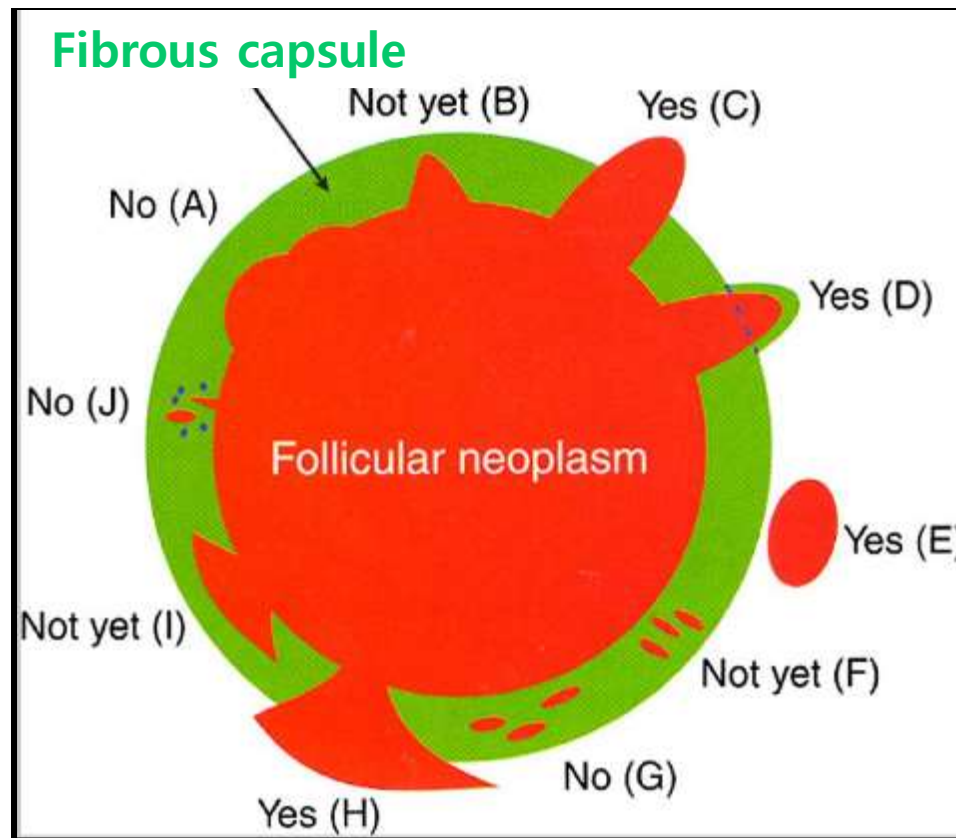
ICD-O codes

- 1) Follicular tumor of uncertain malignant potential **8335/1**
- 2) Well-differentiated tumor of uncertain malignant potential **8348/1**

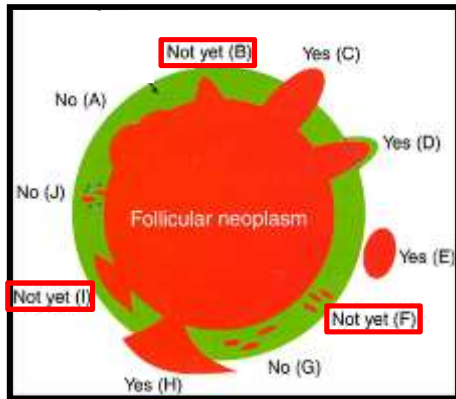
	Immunohistochemistry	Genetic profile
FT-UMP	similar to those of follicular adenoma, hyperplasia, minimally invasive FTC	similar to those of follicular neoplasms
WDT-UMP	may be positive for HBME1, Galectin 3, CK19	intermediate between benign follicular nodule and PTC



Criteria for Capsular Invasion



Chan JKC. The thyroid gland. In: Fletcher CDM, ed. *Diagnostic Histopathology of Tumours*. Edinburgh: Churchill Livingstone Elsevier; 2007:1018.

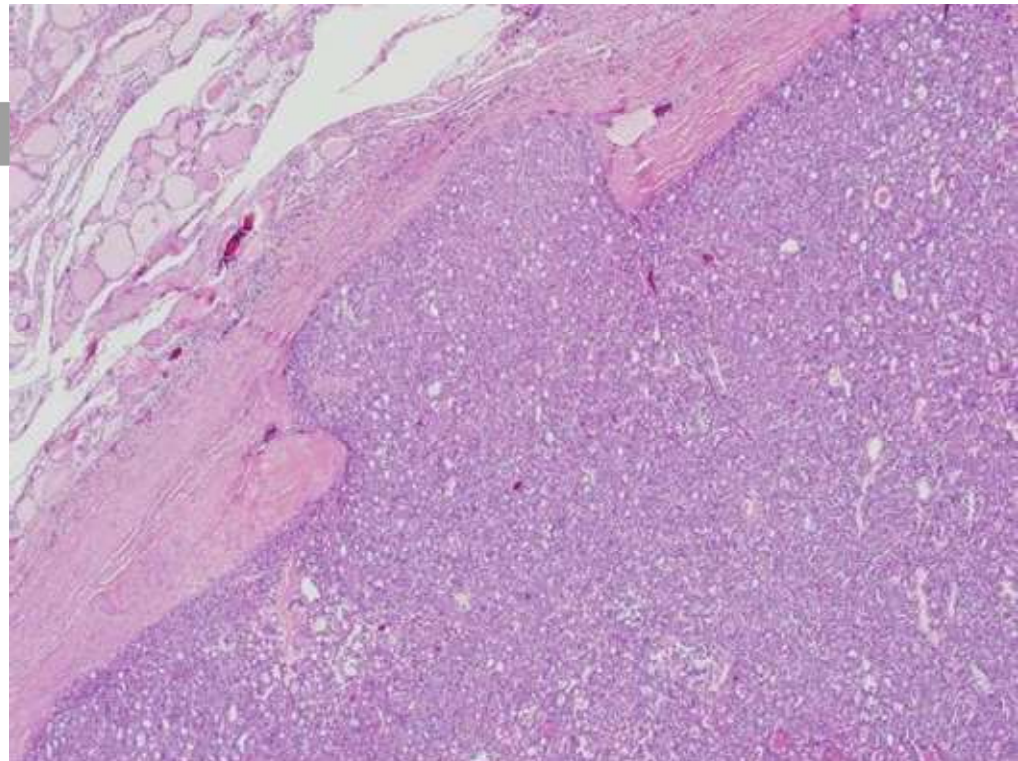


Not yet (B) Sharp tumor bud invades into but not through the capsule suggesting invasion **requiring deeper sections to exclude.**

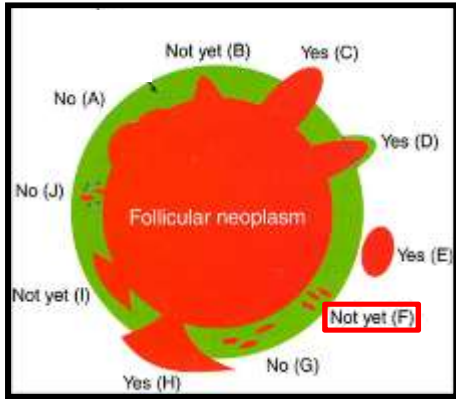
Not yet (F) Follicles aligned perpendicular to the capsule suggesting invasion **requiring deeper sections to exclude.**

Not yet (I) Mushroom-shaped tumor within but not through the capsule suggests invasion **requiring deeper sections to exclude invasion.**

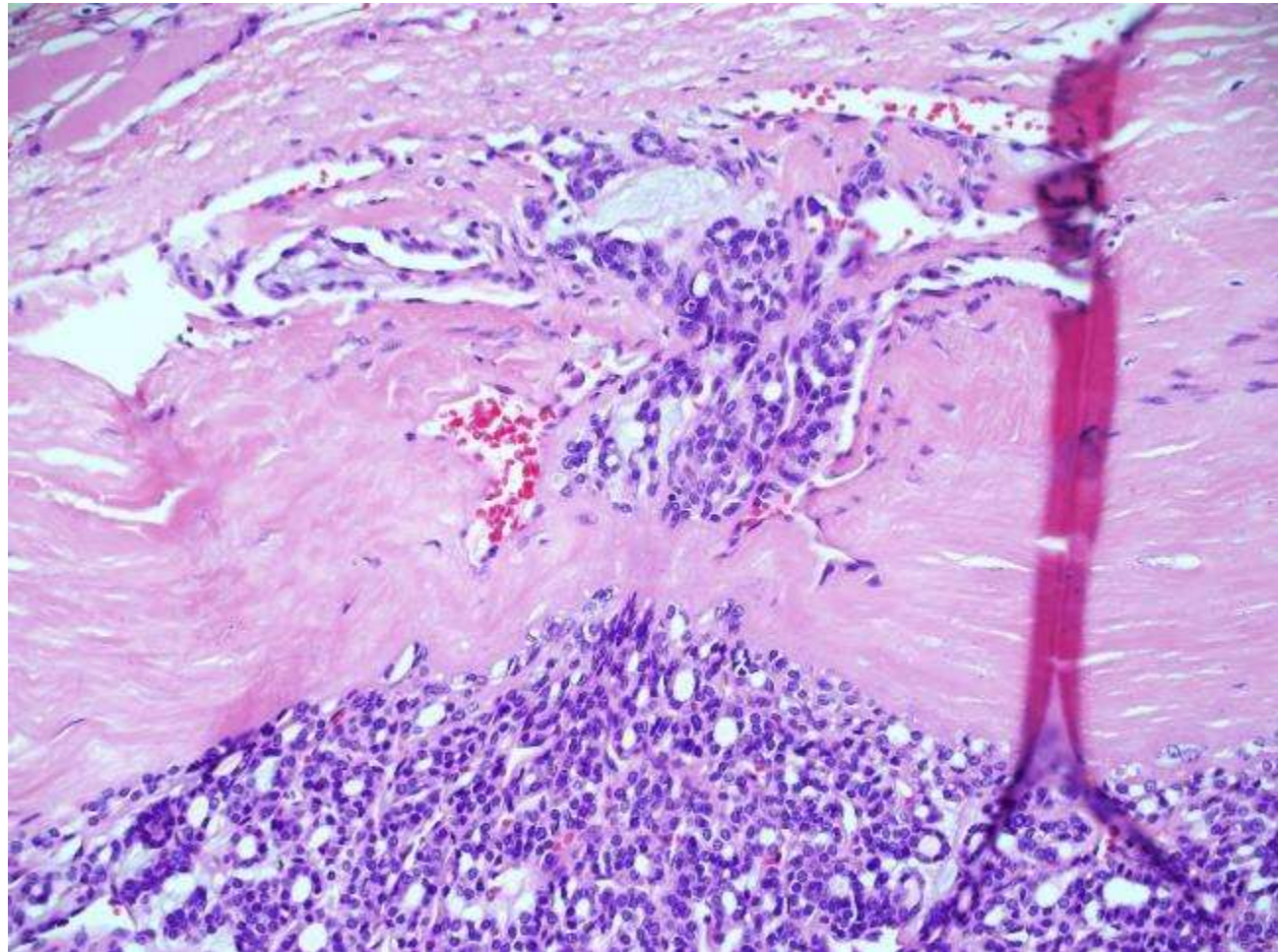
Not yet (I)



“Not yet” (eg, F, G, I) may be acceptable to some pathologists as representing capsular invasion

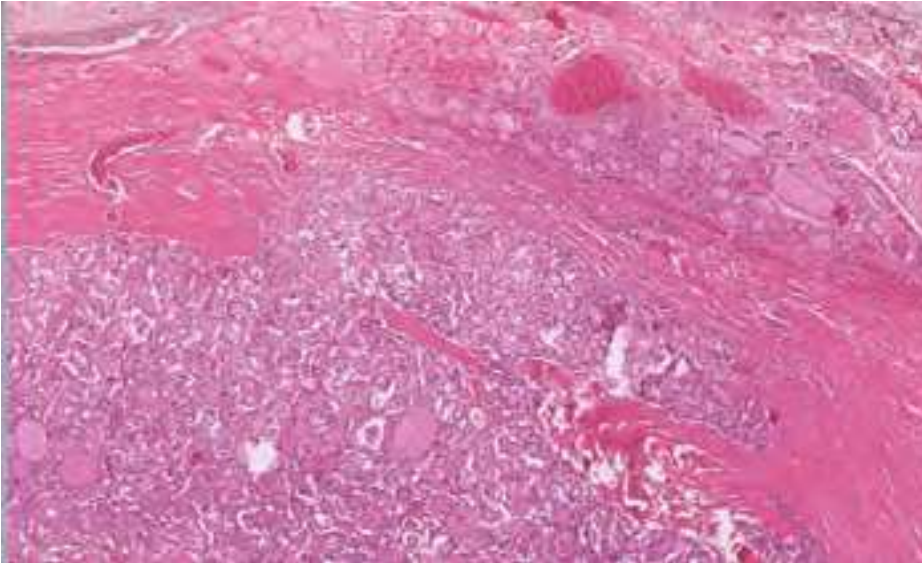


Not yet (F) Follicles aligned perpendicular to the capsule suggesting invasion requiring deeper sections to exclude.



Questionable capsular invasion

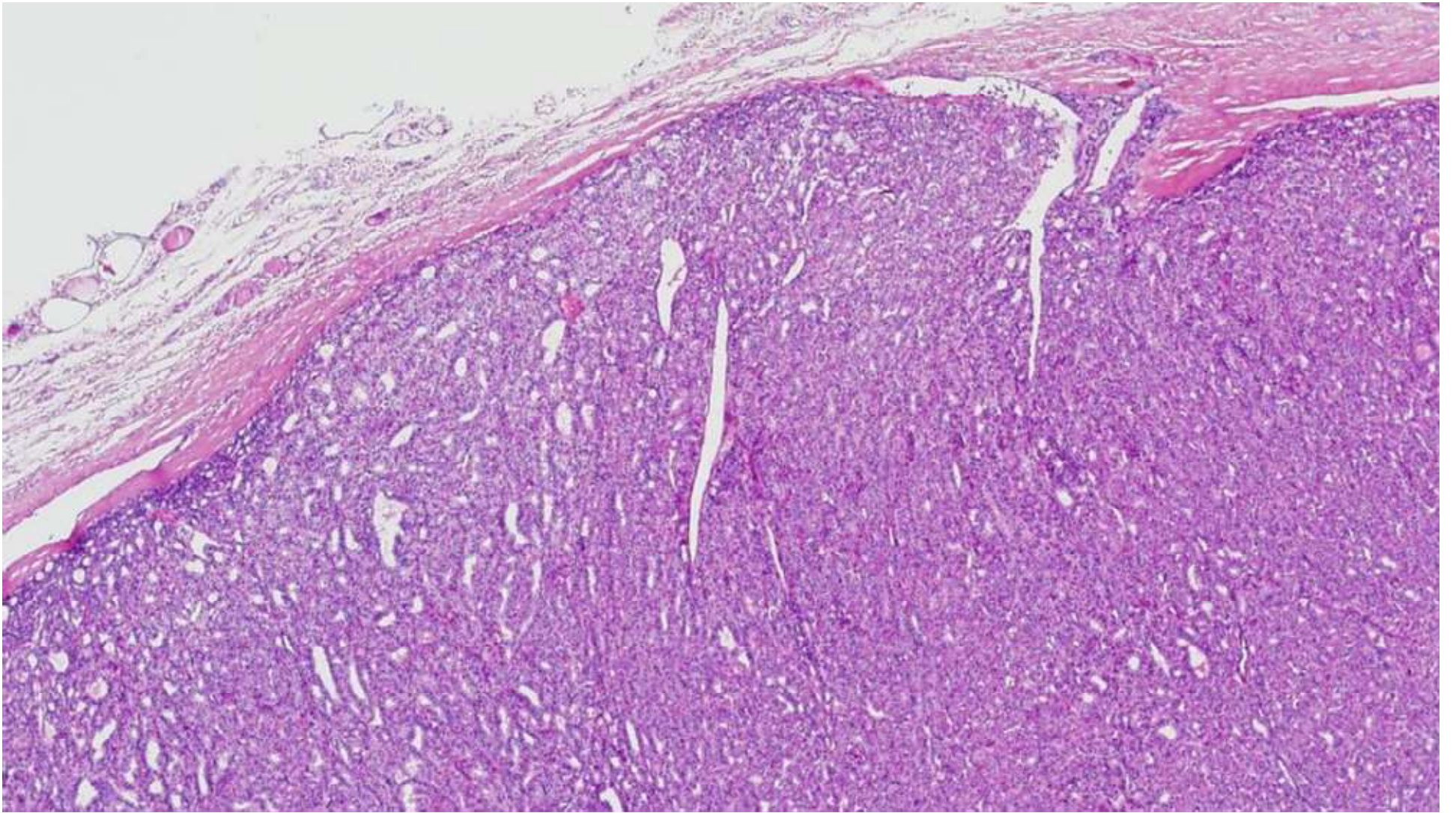
Fig. 2.16



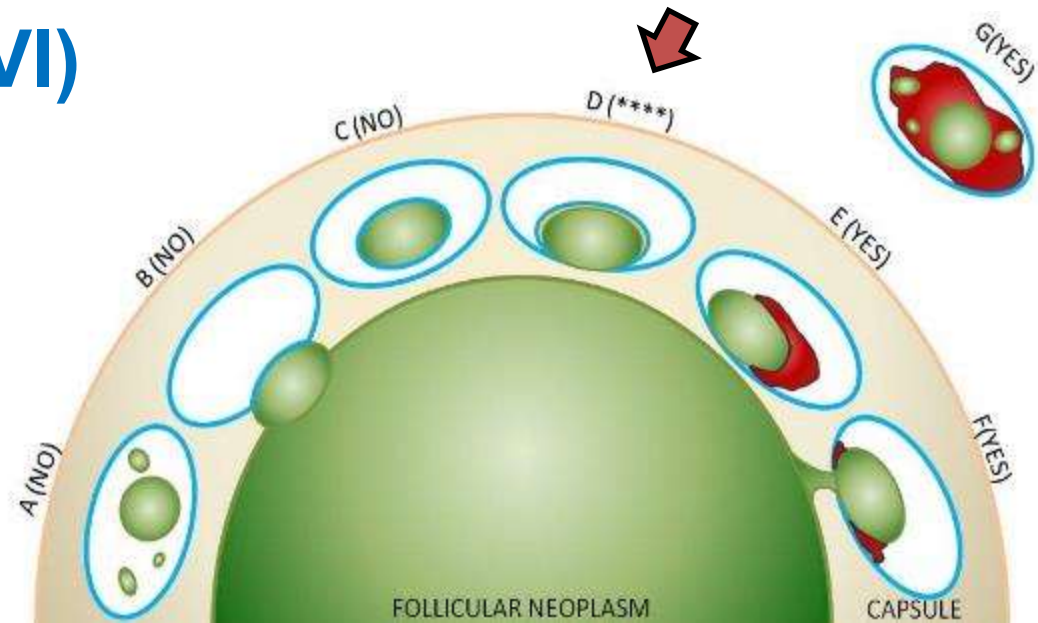
Hook-like protrusion of tumor cells deeply into but not completely through the capsule



Broad-based bulge of tumor cells into the capsule that does not extend beyond its outer contour



Vascular invasion (VI)



**** D represents a common but contentious scenario among experts, in light of these new proposed criteria for significant VI. This **endothelialized tumor deposit** is juxta-posed to the vessel wall. As this is somewhat similar to C, and **there is no obvious thrombus, technically this would not count as significant VI**. One counterargument is that the endothelialized appearance represents “organization” of a tumor thrombus and is thus still significant. While deeper levels may help, this scenario may still be considered a **“judgment call”** based on current level of evidence.

Criteria for vascular invasion in 2017 WHO classification

Intravascular tumor cells should be adherent to the vessel walls, either covered by endothelium or in a context of thrombus or fibrin.

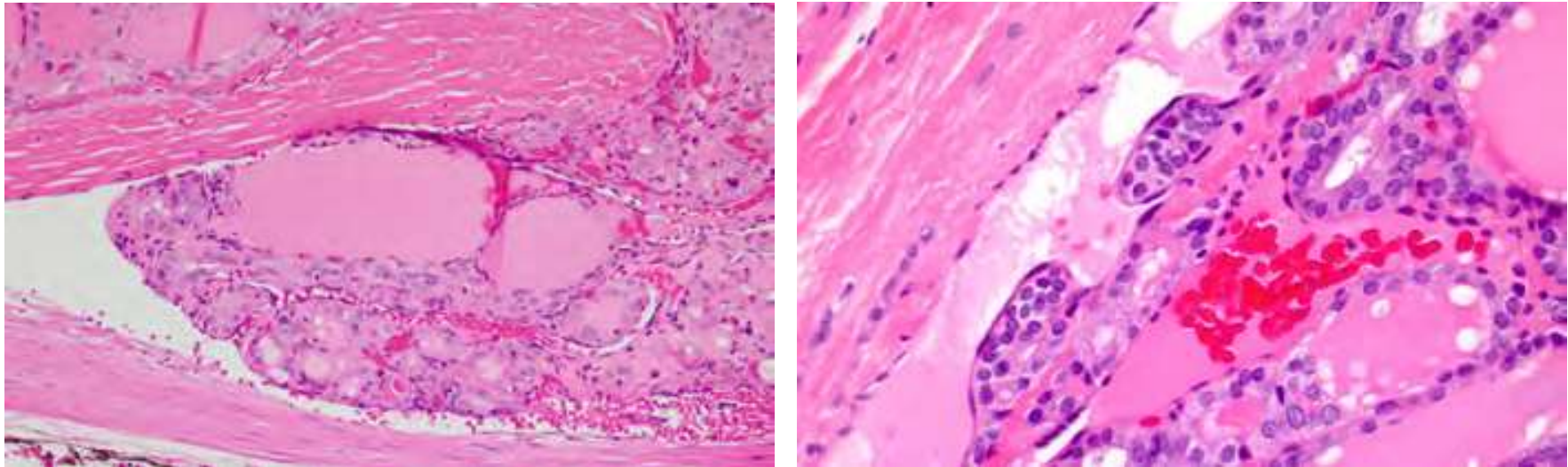
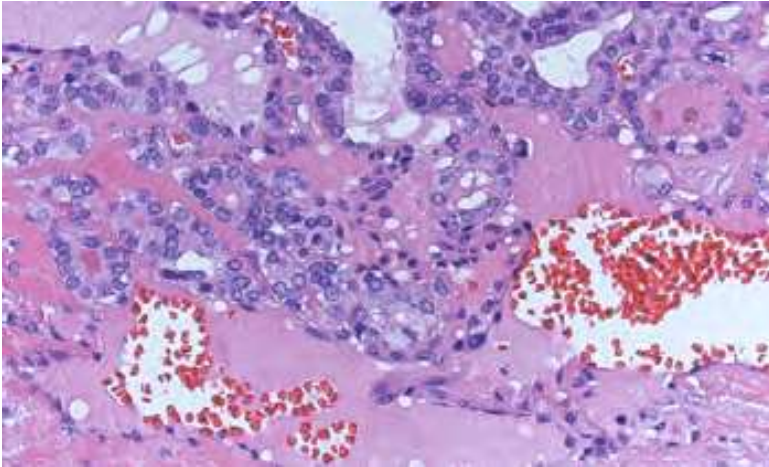


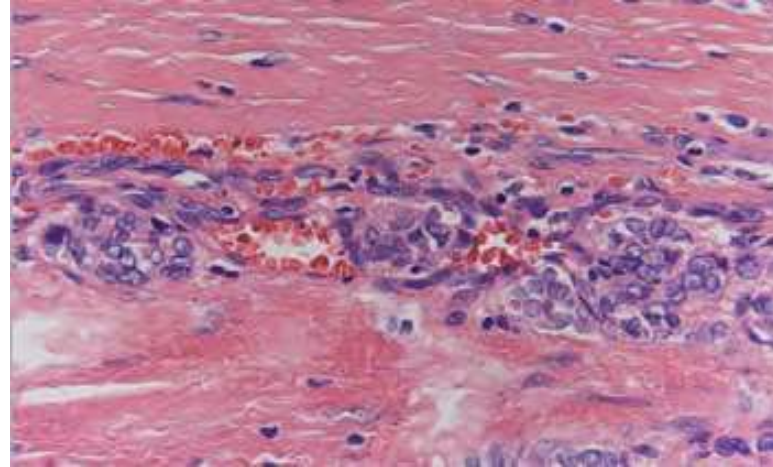
Fig. 2.52 Follicular thyroid carcinoma with vascular invasion

Questionable vascular invasion

Fig. 2.17



Irregular outgrowth of neoplastic cells within vascular spaces of the tumor capsule



Tumor cells closely intermixed with vascular spaces of the tumor capsule

Vascular invasion is considered questionable

- when a smooth-contoured tumor cell nest located within a vascular space of the tumor capsule lacks endothelial covering and associated thrombus,
- when a tumor nest in the fibrous capsule abuts a blood vessel

“Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP)”

- by the Chernobyl Pathologists Group in 2000
- Encapsulated tumor composed of well-differentiated follicular cells with questionable PTC-type nuclear changes, no blood vessel invasion, and capsular invasion that is either absent or questionable

“WDT-UMP, however, is not widely accepted as it is not linked to a define clinical management for these patients”
Instead, it is important to designate these tumors in the diagnostic line as “EFVPTC” and state if the tumor has vascular or tumor capsule invasion – by Nikiforov YE

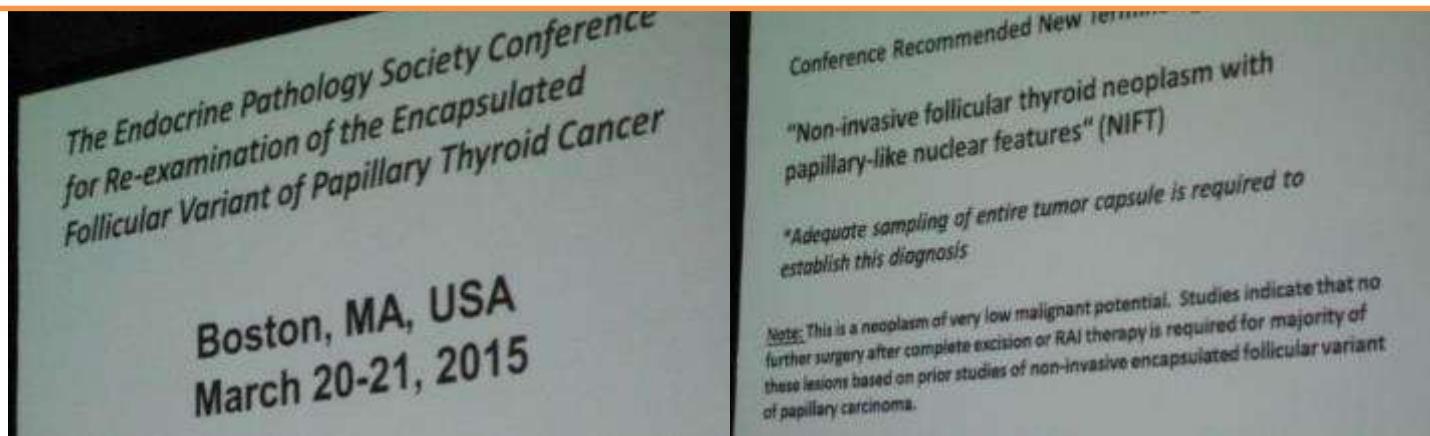
**Table 2. Encapsulated Thyroid Tumors with Follicular Architecture:
A Diagrammatic Scheme**


PTC-Type Nuclear Changes	Capsular Invasion		Diagnosis
Obvious	Definite	}	PTC-FV
	Questionable		
	Absent		
Questionable	Definite	}	WDC-NOS
	Questionable		WDT-UMP
	Absent		
Absent	Definite		FC
	Questionable		FT-UMP
	Absent		FA

“Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)”

- by international Endocrine Pathology Society working group
- Removing the word “carcinoma” from the nomenclature in an attempt to reduce overtreatment of this indolent tumor
- encompasses non-invasive encapsulated follicular-patterned tumors previously called encapsulated FVPTC as well as WDT-UMP

The International Working Group for re-examination of the encapsulated follicular variant of papillary thyroid cancer





Research

Original Investigation

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

JAMA Oncol.

doi:10.1001/jamaoncol.2016.0386

Published online April 14, 2016.

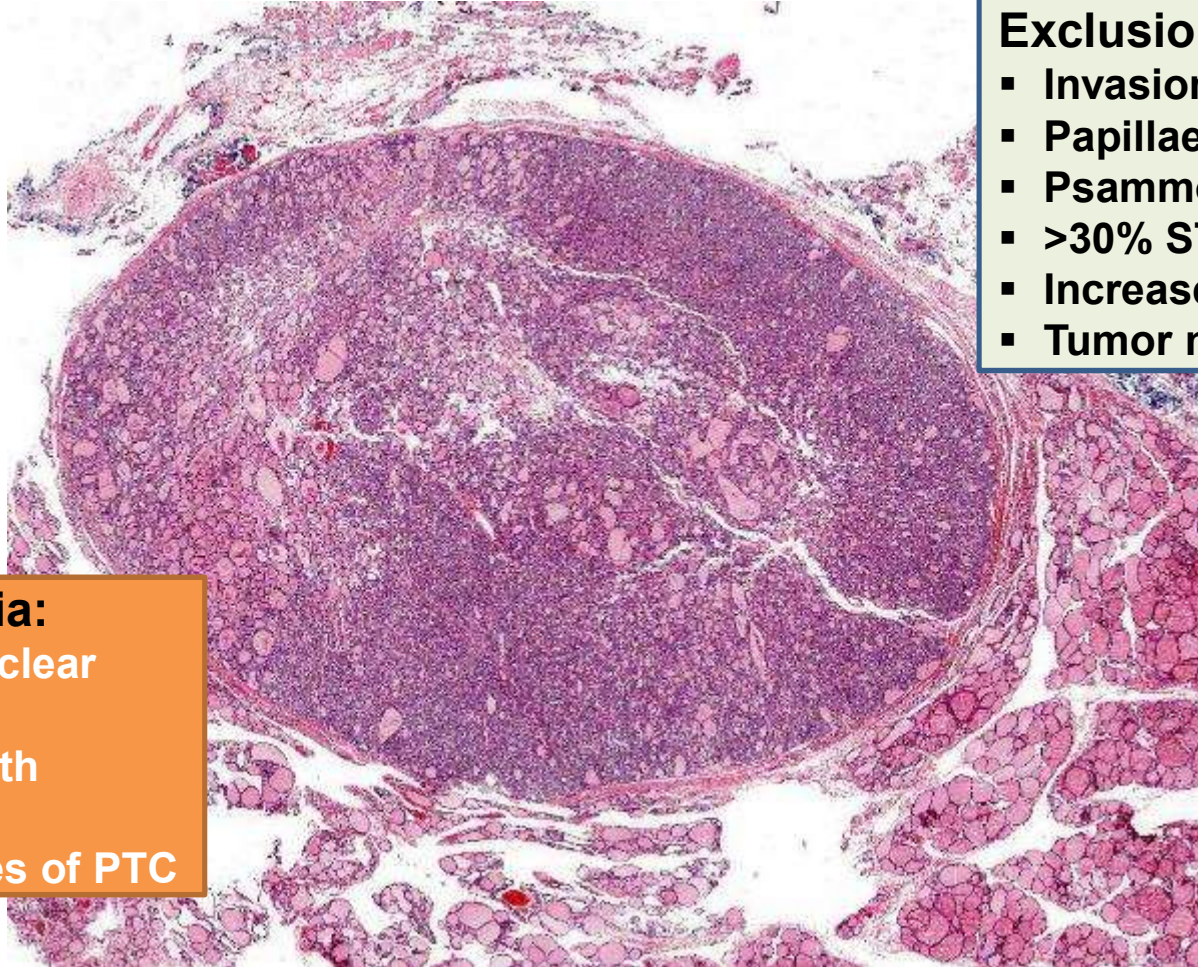
2015 AFIP fascicle

		Capsular invasion		
		Present	Questionable	Absent
Nuclear features of PTC	Present	Follicular variant of PTC		
	Questionable	Well-differentiated carcinoma, NOS	Well-differentiated tumour of uncertain malignant potential	
	Absent	Follicular carcinoma	Follicular tumour of uncertain malignant potential	Follicular adenoma

2017 WHO classification

		Capsular or vascular invasion		
		Present	Questionable	Absent
Nuclear features of PTC	Present	Invasive encapsulated follicular variant of PTC	Well-differentiated tumour of uncertain malignant potential	Non-invasive follicular neoplasm with papillary-like nuclear features
	Questionable	Well-differentiated carcinoma, NOS		
	Absent	Follicular carcinoma	Follicular tumour of uncertain malignant potential	Follicular adenoma

NIFTP



Inclusion criteria:

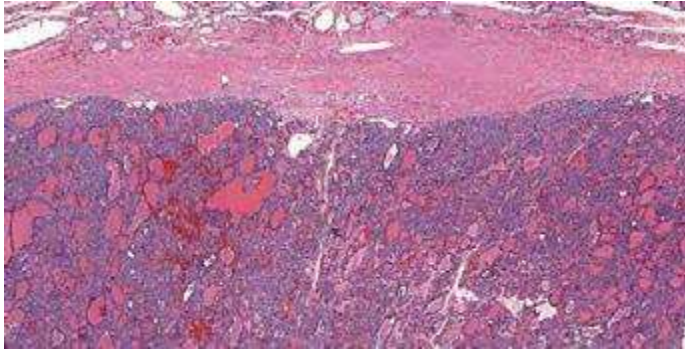
- Encapsulation/clear demarcation
- Follicular growth pattern
- Nuclear features of PTC

Exclusion criteria:

- Invasion
- Papillae > 1%
- Psammoma bodies
- >30% STI growth
- Increased mitoses
- Tumor necrosis

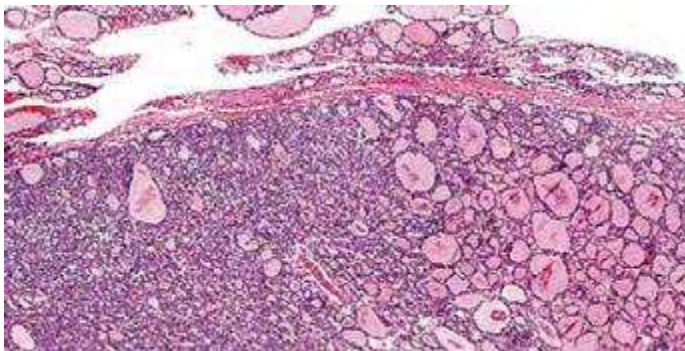
Image and diagnostic criteria for NIFTP from Nikiforov YE, et al. JAMA Oncol 2016

Fig. 2.21

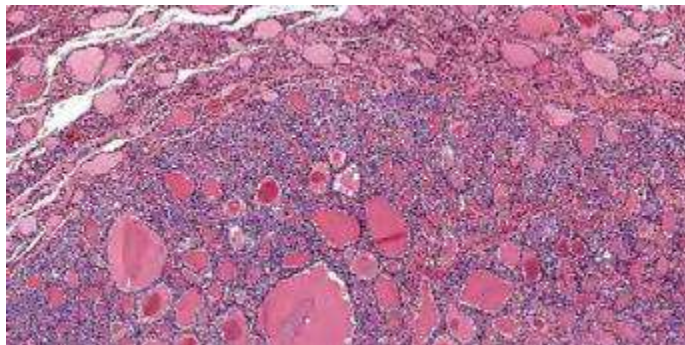


thick capsule

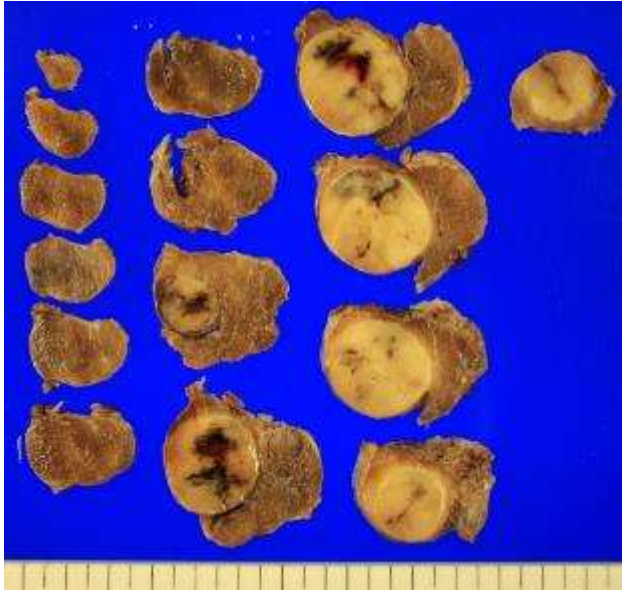
1. Encapsulation or clear demarcation



thin capsule



no capsule but be sharply demarcated

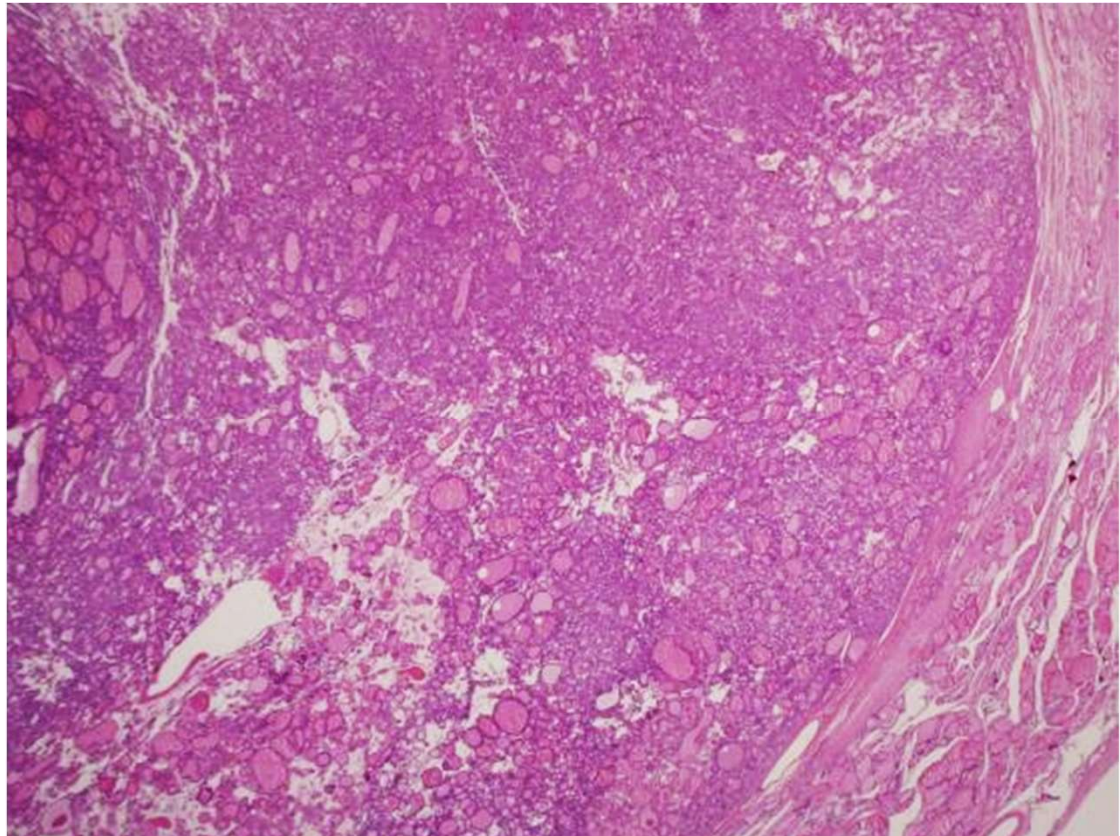


2. Follicular growth pattern with

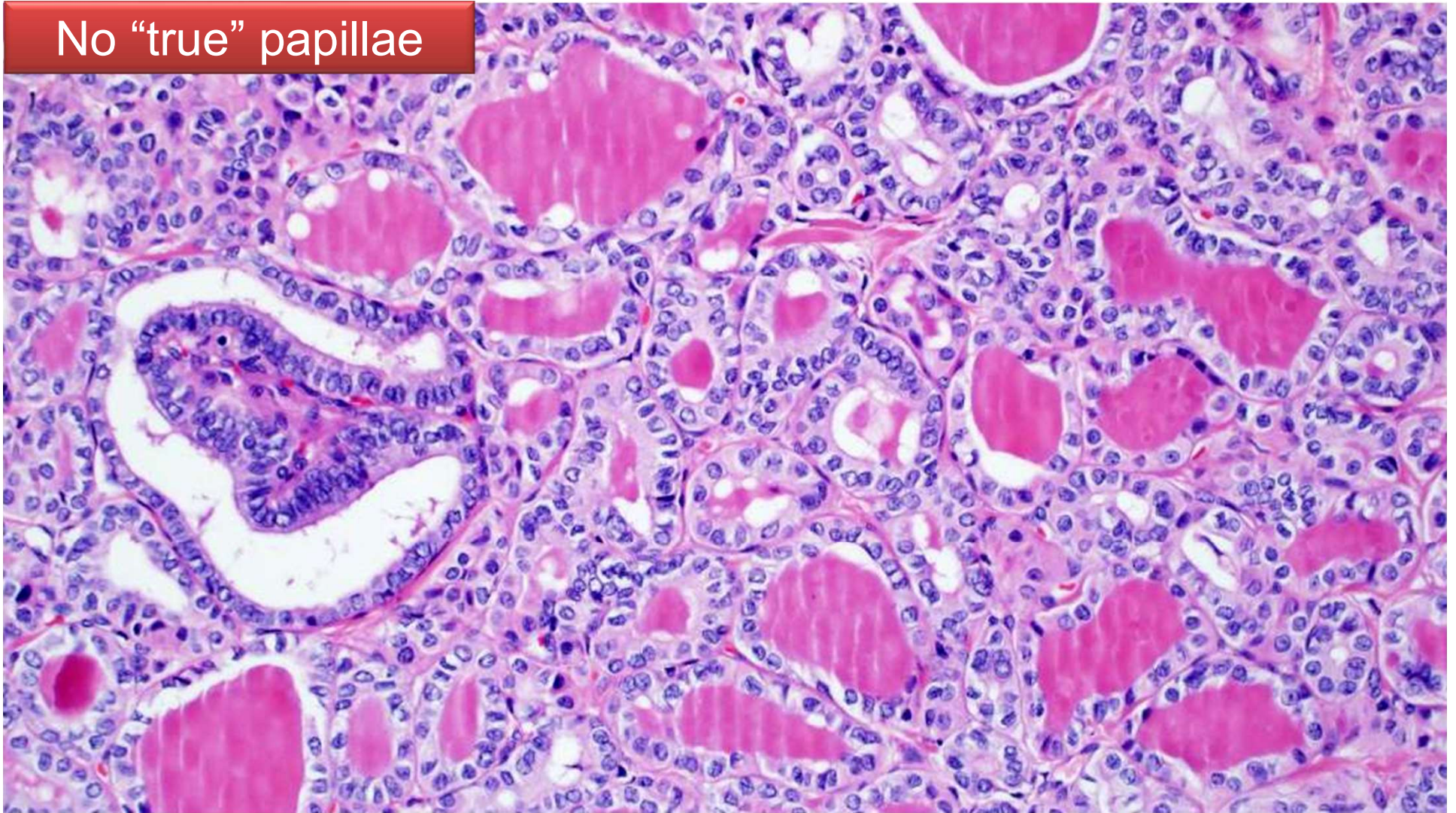
<1% Papillae

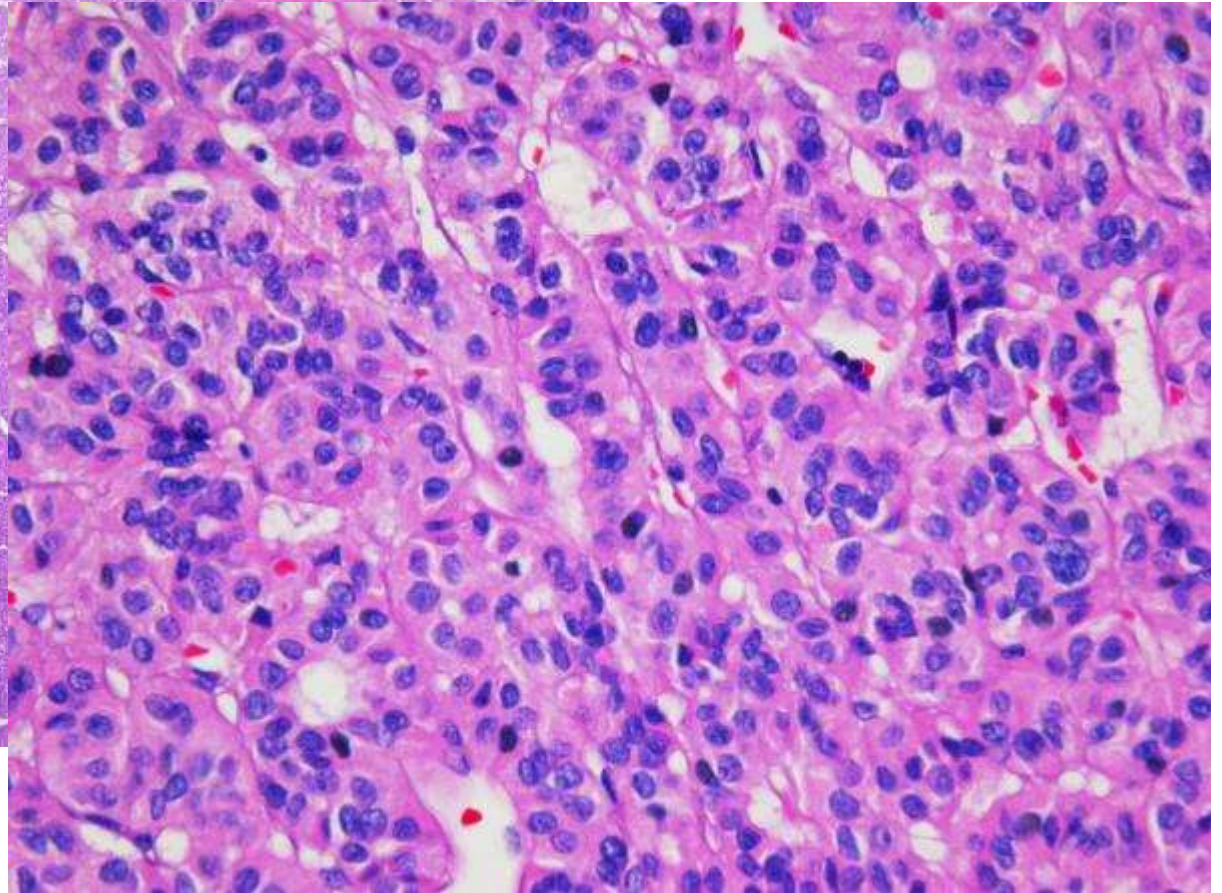
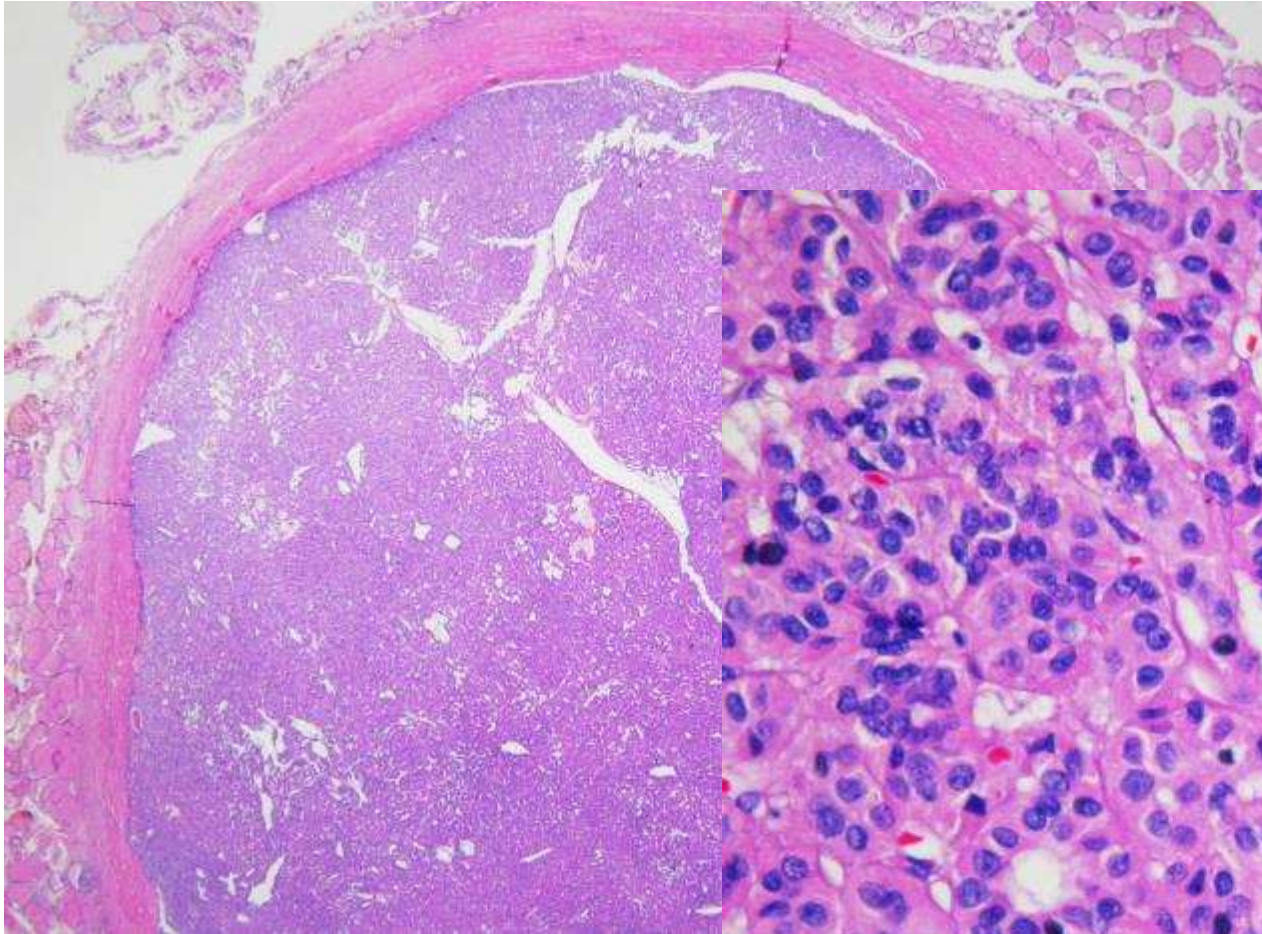
No psammoma bodies

<30% solid/trabecular/insular growth pattern



No "true" papillae





3. Nuclear score

Nuclear features:

1. Nuclear Size and Shape

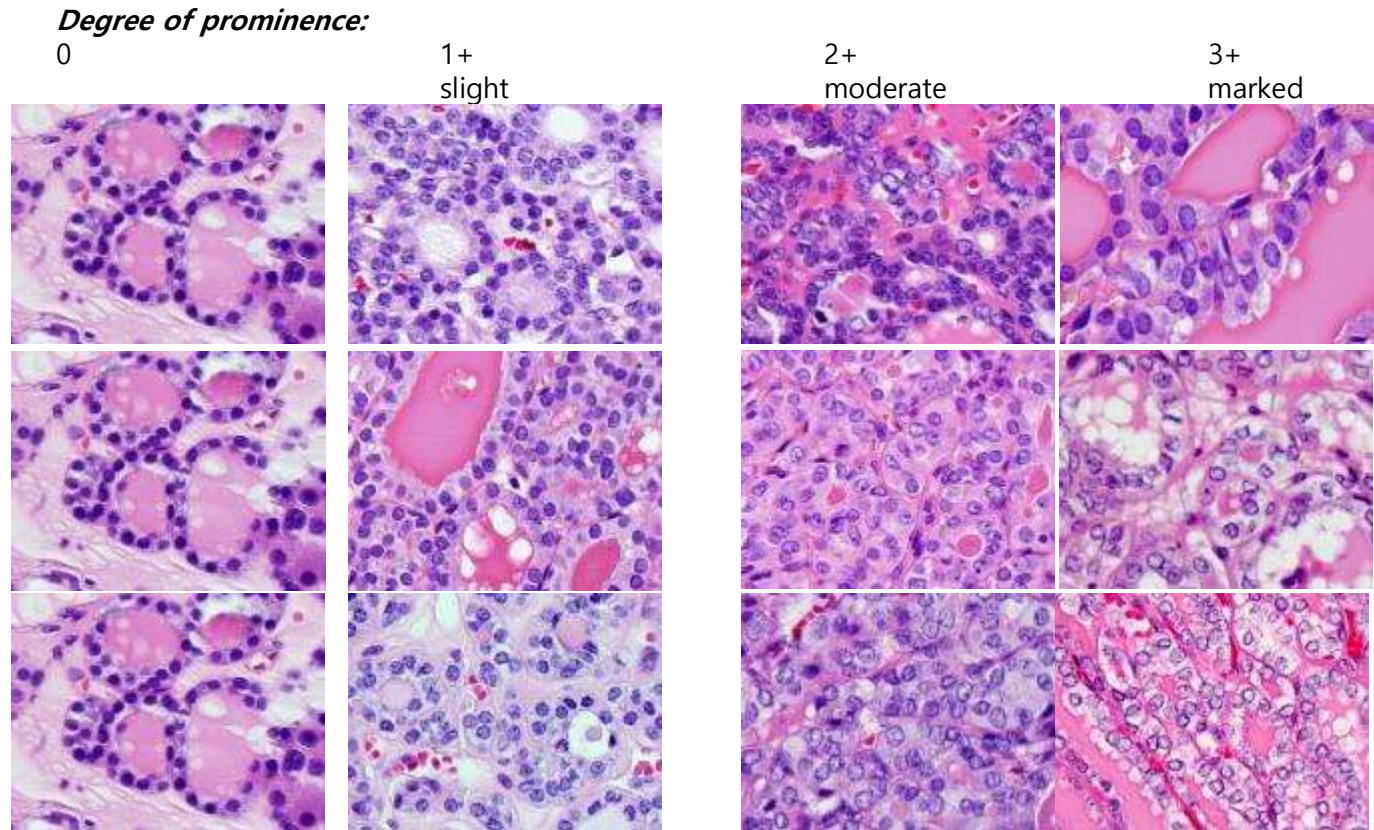
- Enlargement
- Elongation
- Overlapping

2. Membrane Irregularities

- Irregular contours
- Grooves
- Pseudoinclusions

3. Chromatin Characteristics

- Chromatin clearing
- Margination of chromatin to membrane
- Glassy nuclei



Nuclear features of PTC (nuclear score of 2-3)

3-point scoring scheme

Nuclear features:

1. Nuclear Size and Shape

- Enlargement
- Elongation
- Overlapping

2. Membrane Irregularities

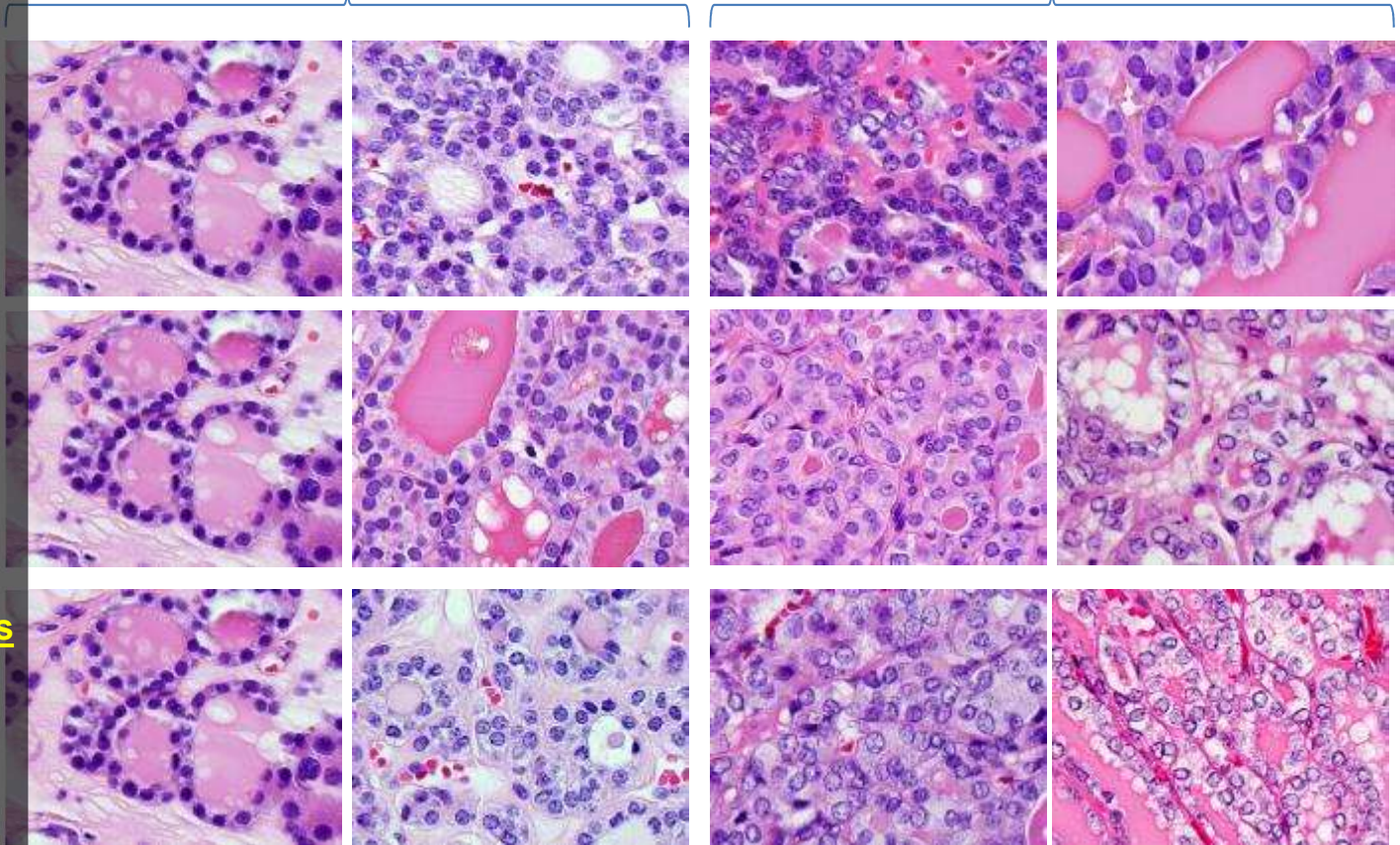
- Irregular contours
- Grooves
- Pseudoinclusions

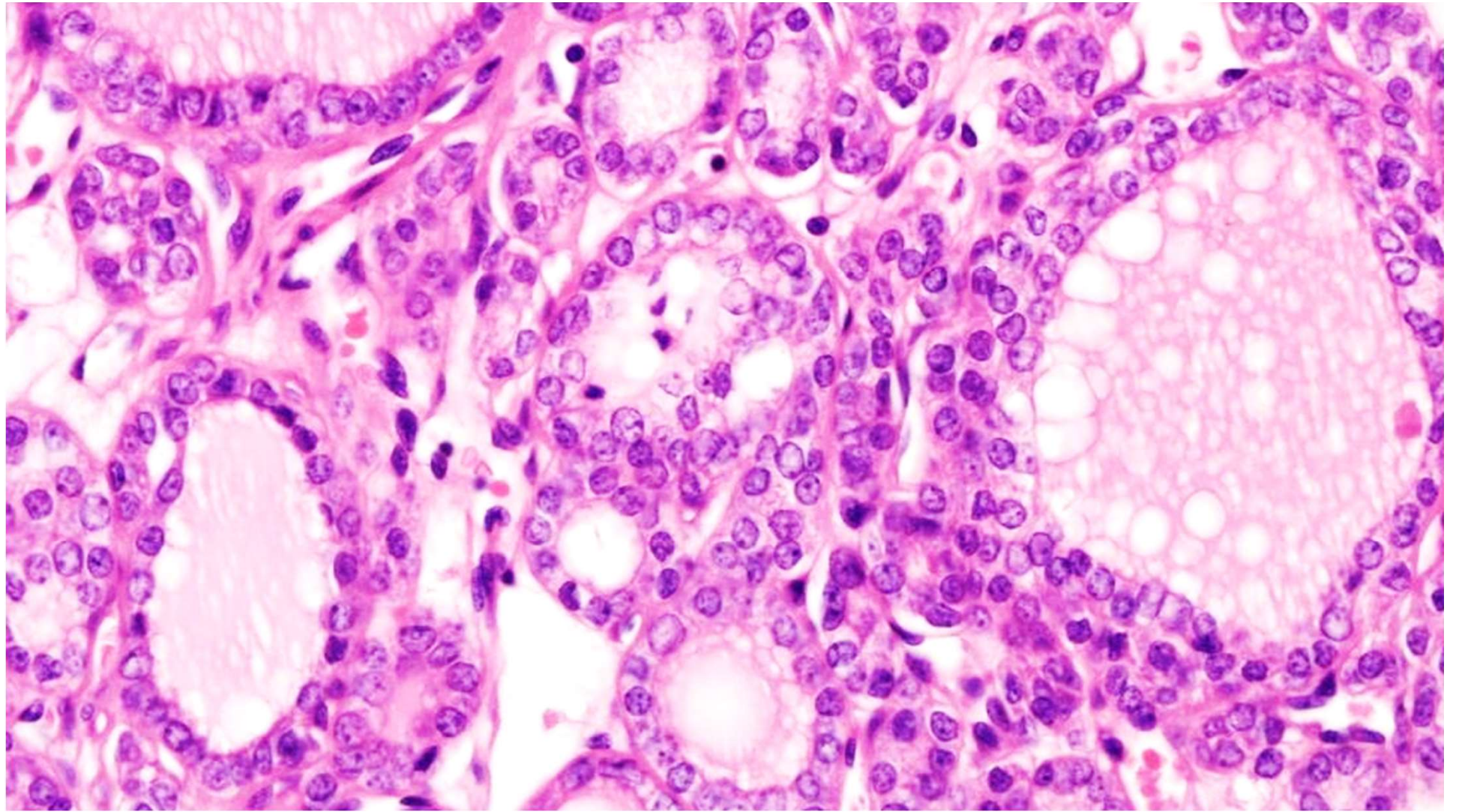
3. Chromatin Characteristics

- Chromatin clearing
- Margination of chromatin to membrane
- Glassy nuclei

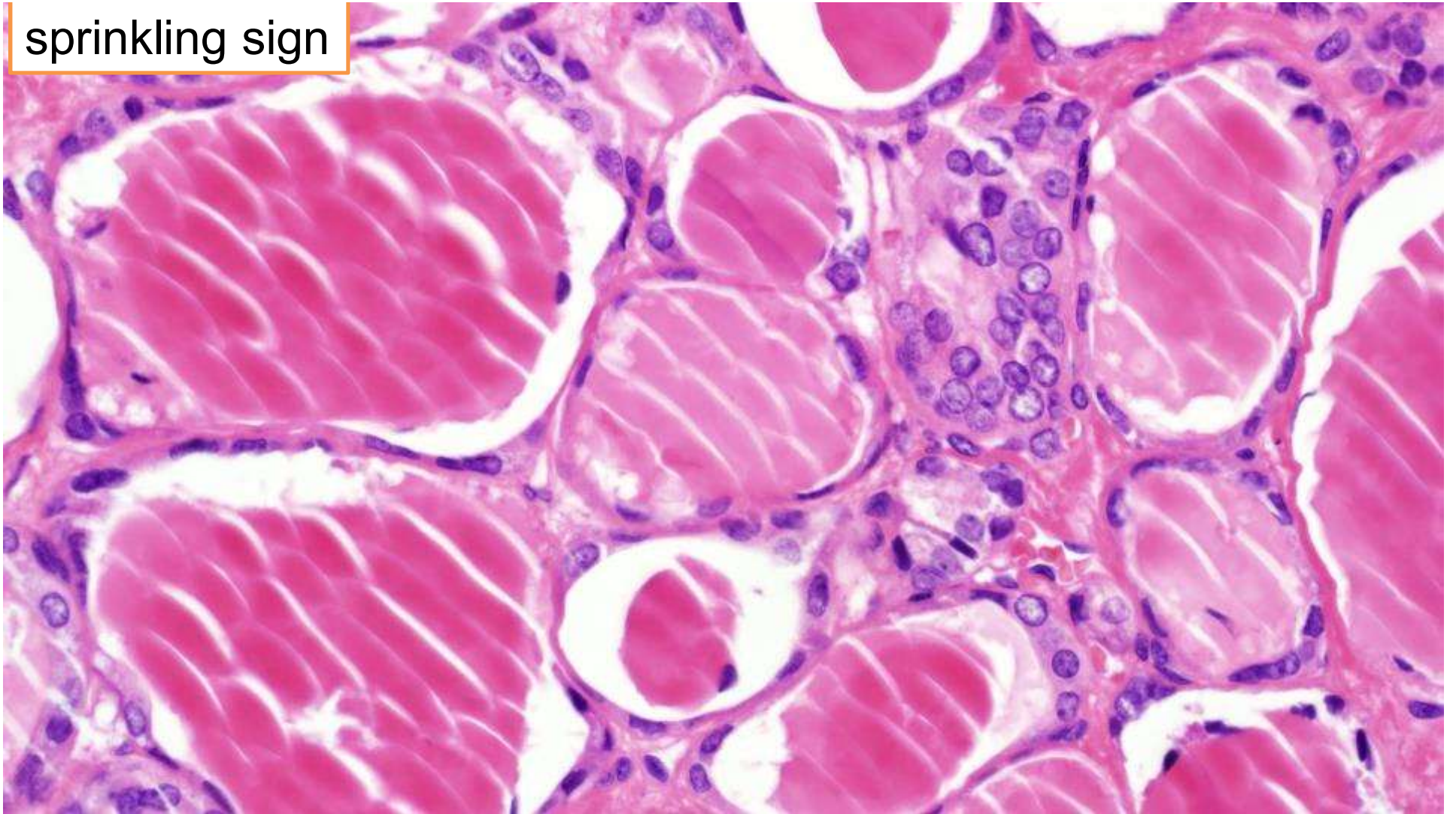
Absent/insufficiently expressed (0)

Present/Sufficient (1)





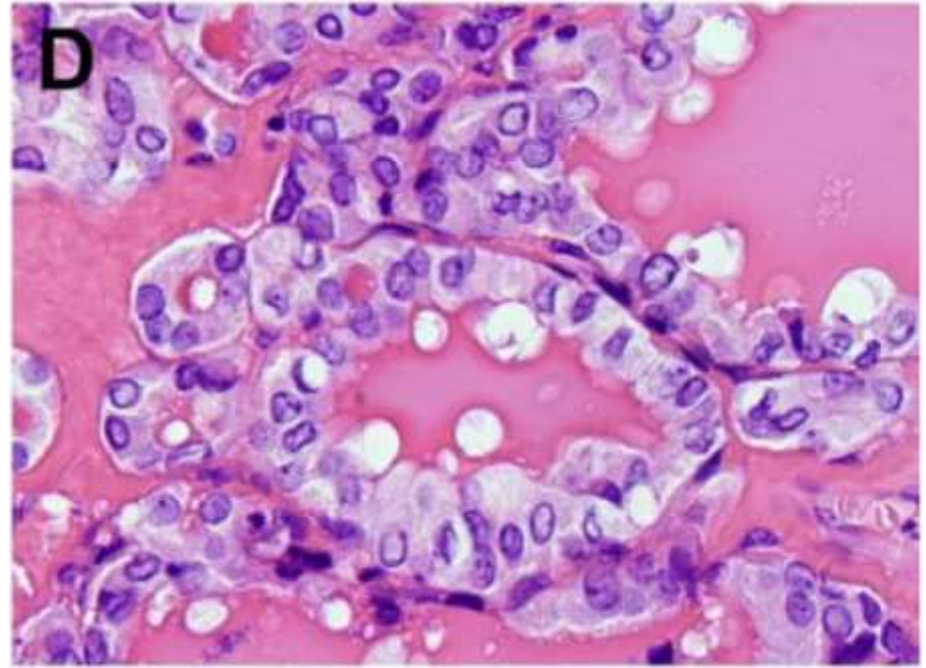
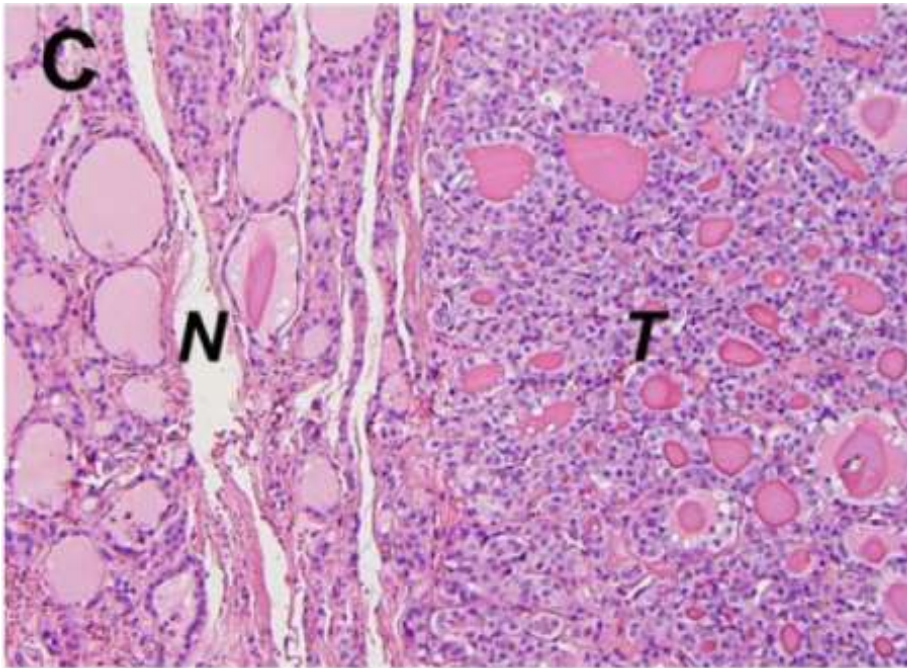
sprinkling sign



Minor diagnostic features:

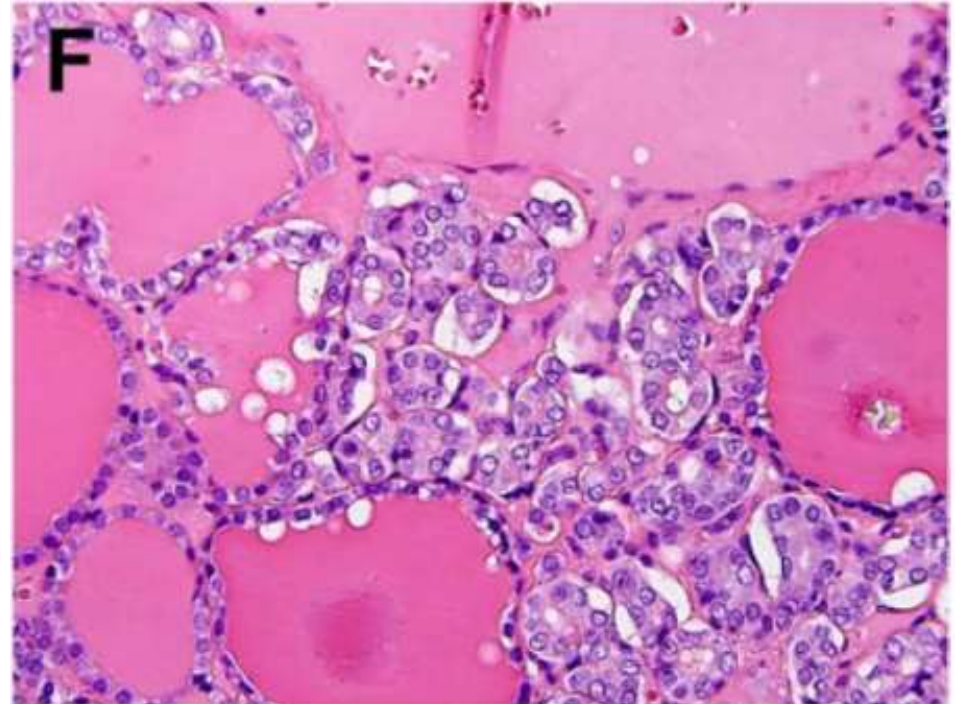
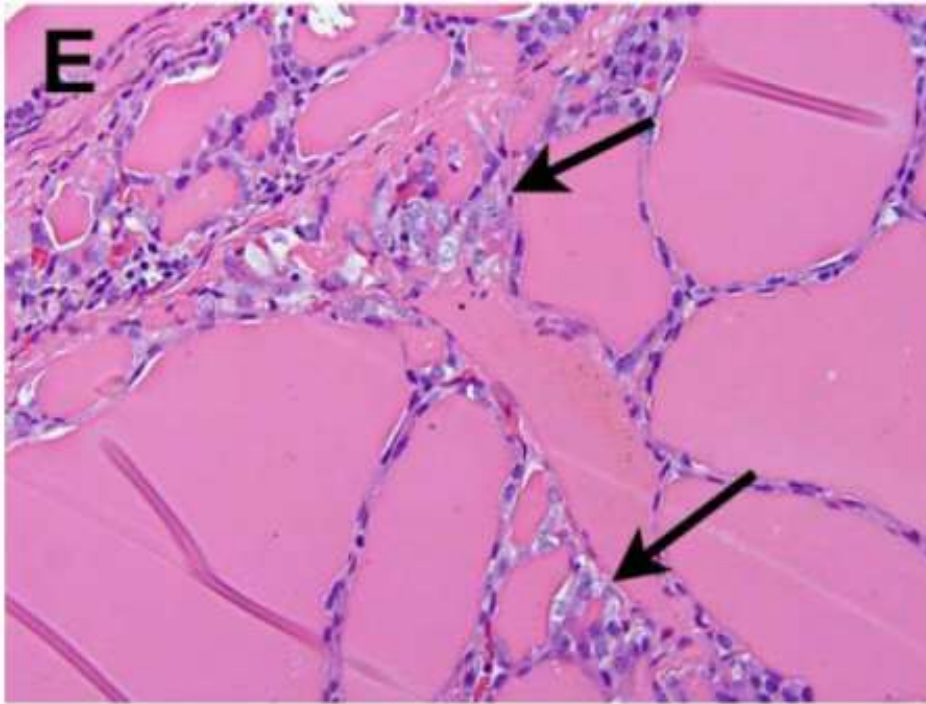
(C) – **Dark colloid** in the tumor follicles (T) as compared to the adjacent normal tissue follicles (N);

(D) – **Irregularly-shaped follicles** with haphazard placement of follicular cell nuclei along the basement membrane of the follicle;



Minor diagnostic features:

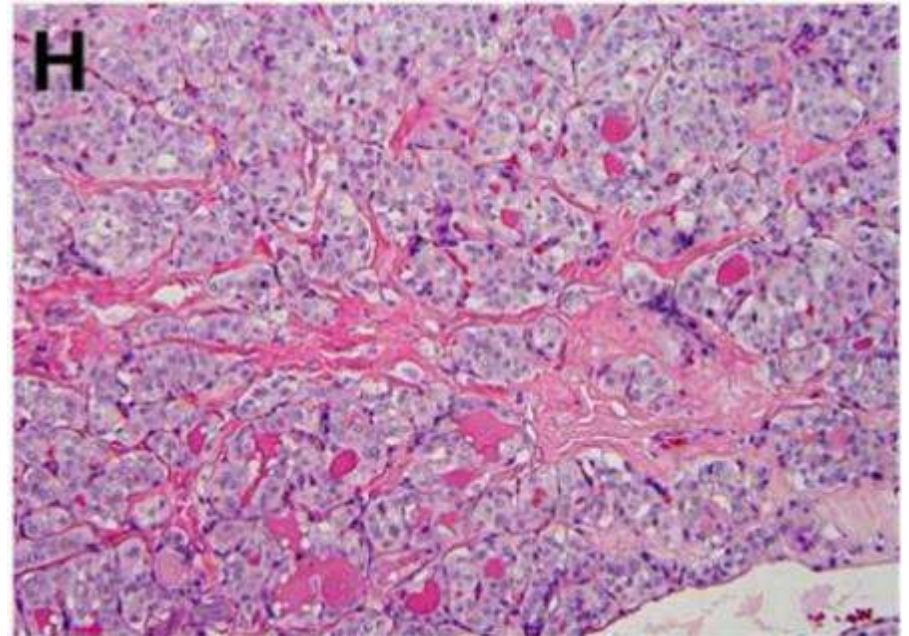
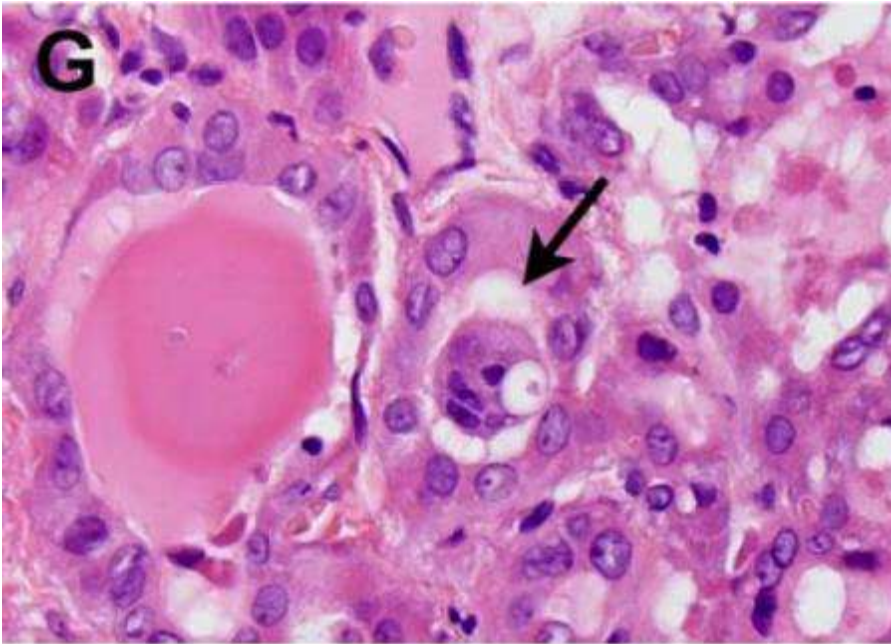
(E) – “**Sprinkling**” of the **follicles** lined by cells showing the characteristic nuclear features of PTC (arrows) on the background of follicles with benign appearing cells; **(F)** – **Follicles clef from stroma**;

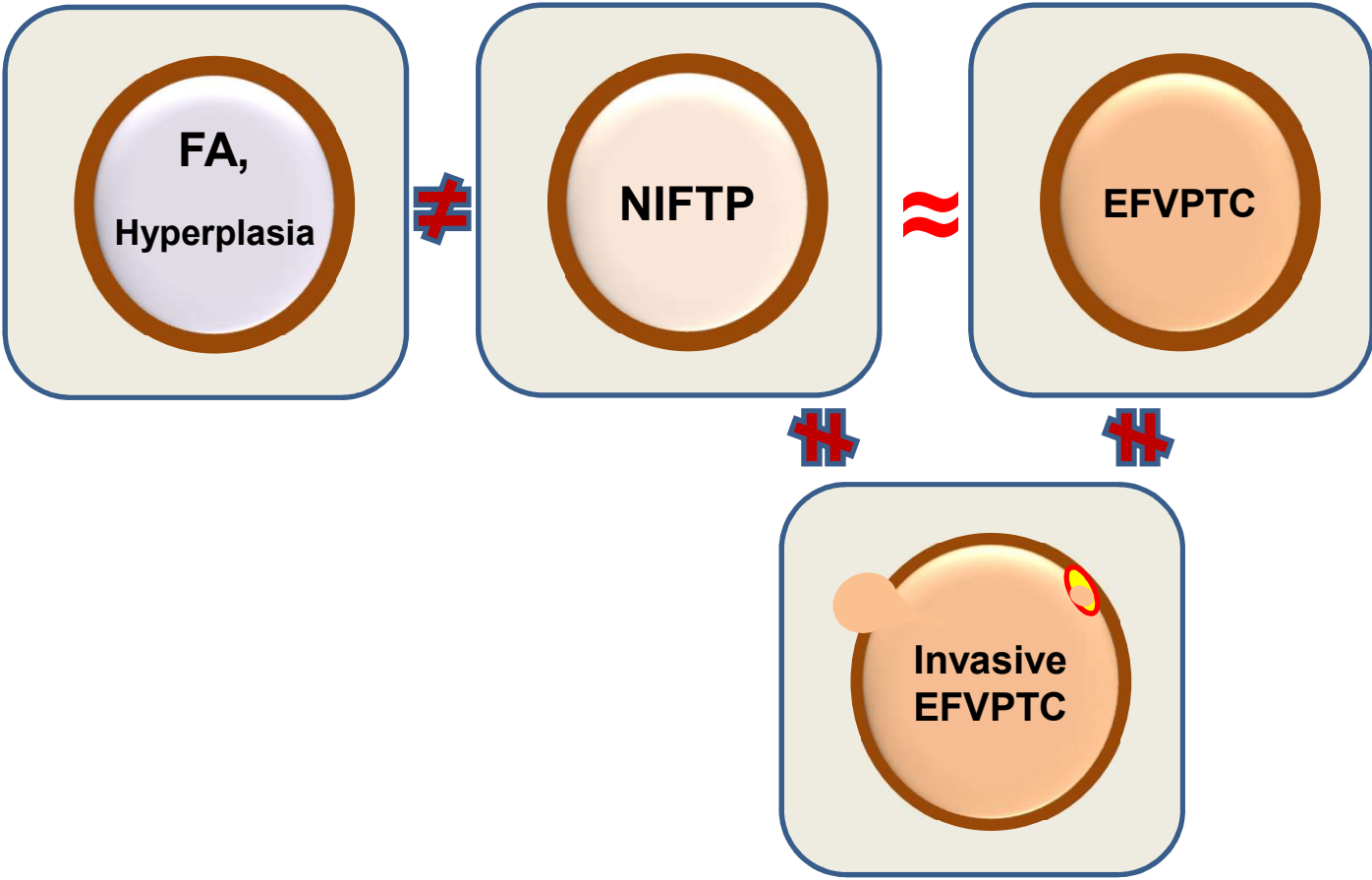


Minor diagnostic features:

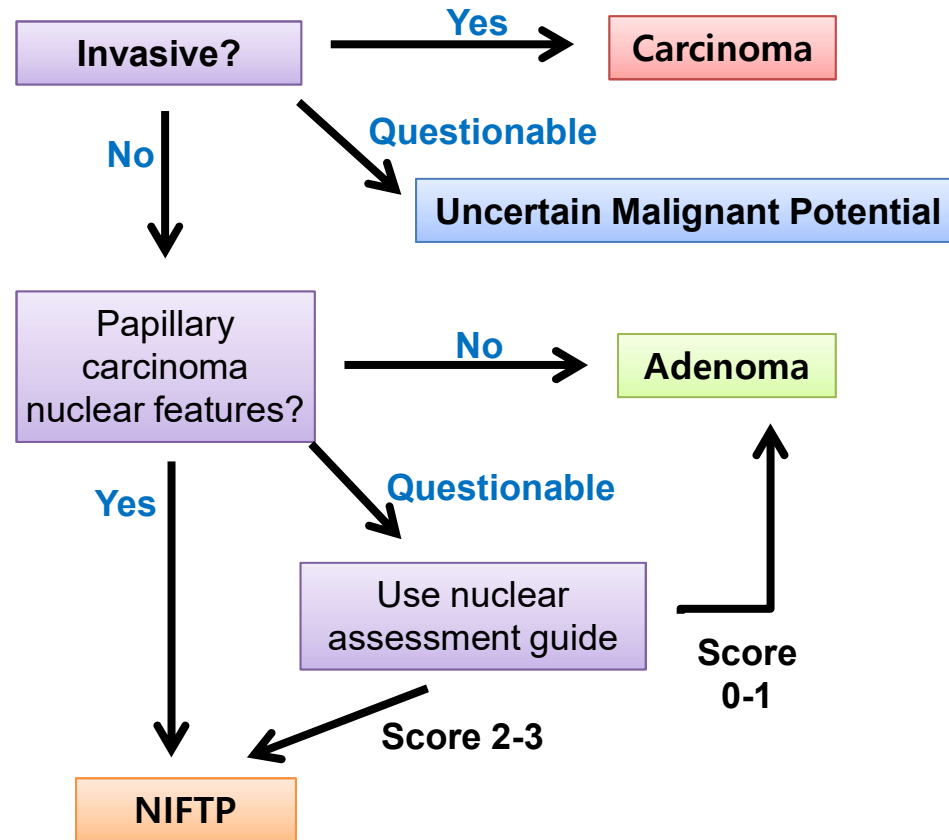
(G) – Multinucleated giant cells within follicles;

(H) – Intratumoral fibrosis.





Algorithm for the evaluation of encapsulated/well circumscribed follicular tumors (with no papillae)



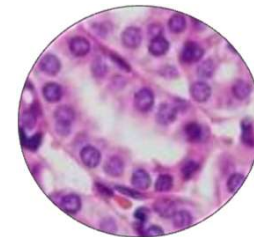
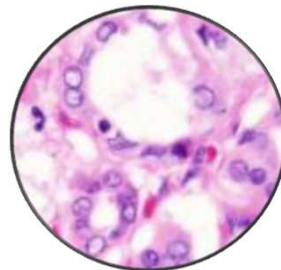
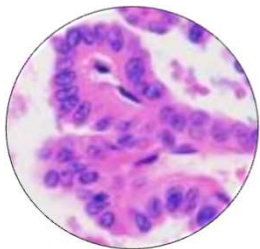
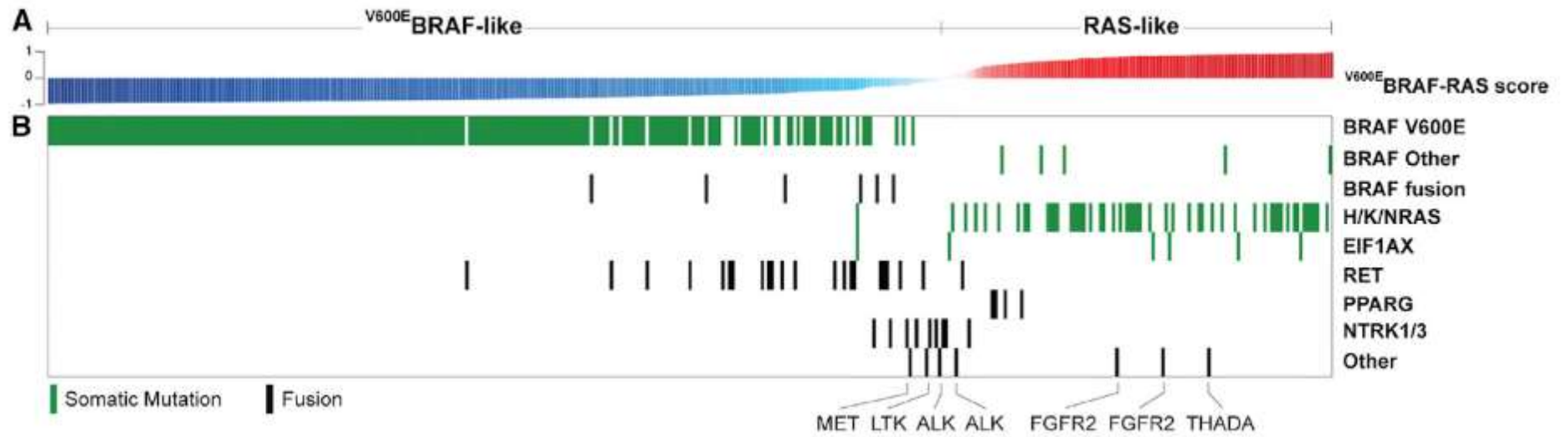
A meticulous histopathologic examination is of paramount importance, since a deviation from these criteria may affect outcomes

Exclusion criteria:

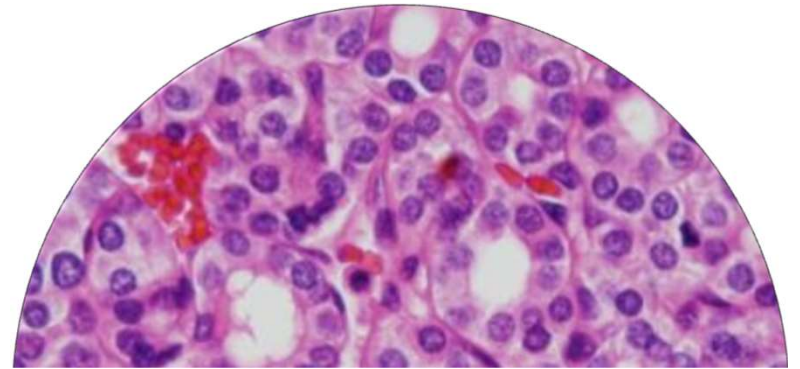
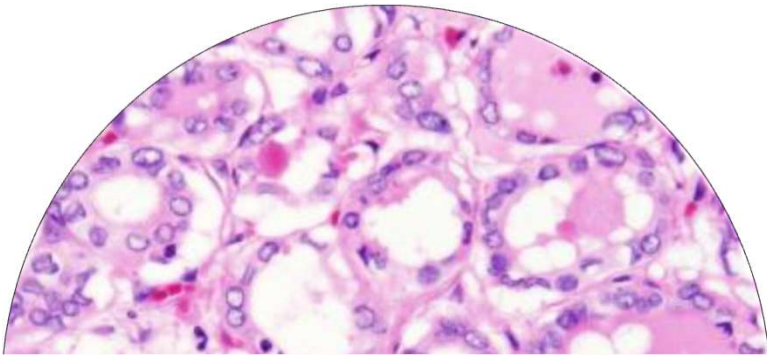
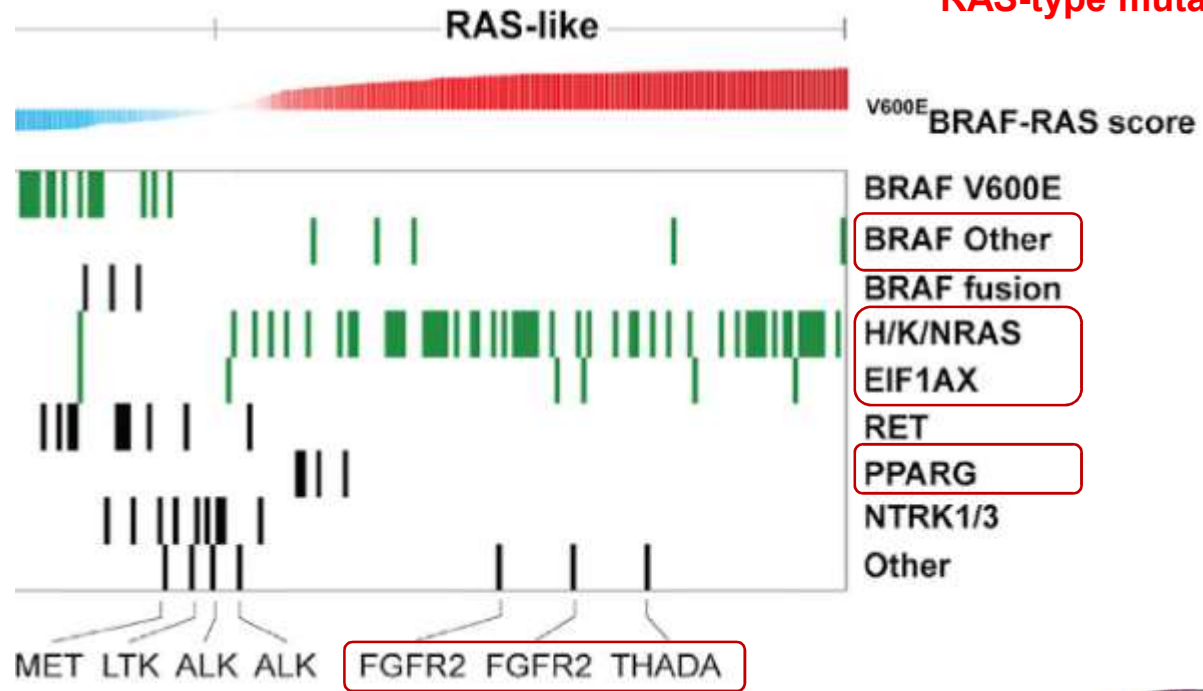
- **Invasion** → Invasive EFV PTC
- **Papillae > 1%** → Encapsulated classic PTC
- **Psammoma bodies**
- **>30% STI growth** → Encapsulated solid variant of PTC
- **Increased mitoses** → Poorly differentiated thyroid carcinoma
- **Tumor necrosis**

BRAF^{V600E}-like PTC

RAS-like PTC

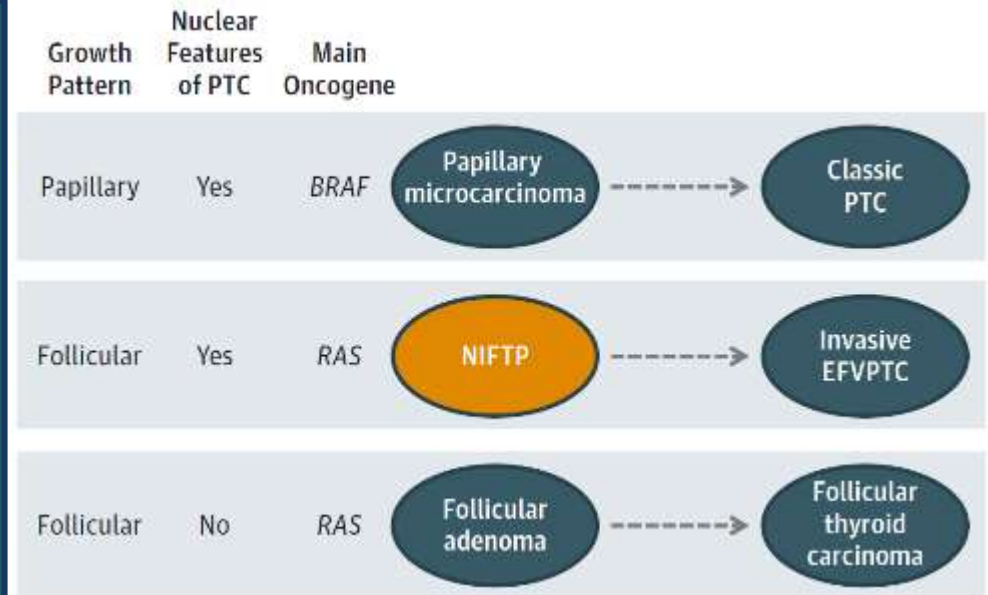


RAS-type mutations



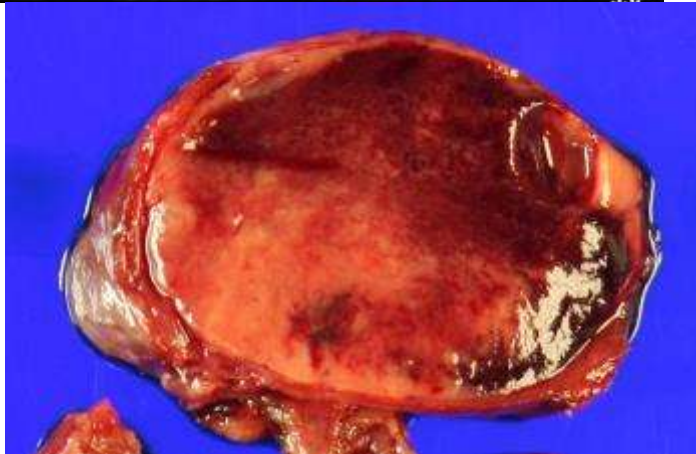
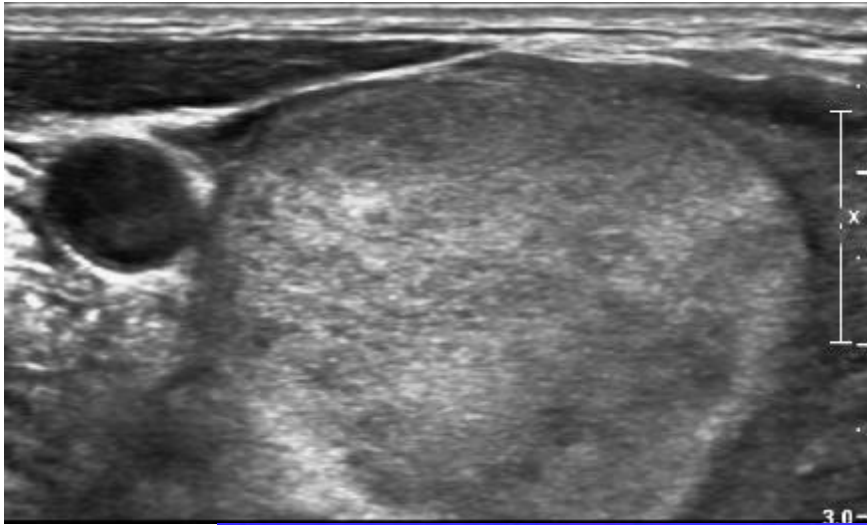
Molecular phenotype of NIFTP

- **RAS**
- **BRAF K601E**
absence of **BRAF V600E**
- **PPARG fusion**
- **THADA fusion**



- Most of NIFTPs are driven by clonal genetic alterations → biologically a neoplasm
- NIFTP likely represents the “benign” counterpart or precursor of the invasive EFVPTC

Case 1



Male / 59 years
5.0 cm indeterminate nodule

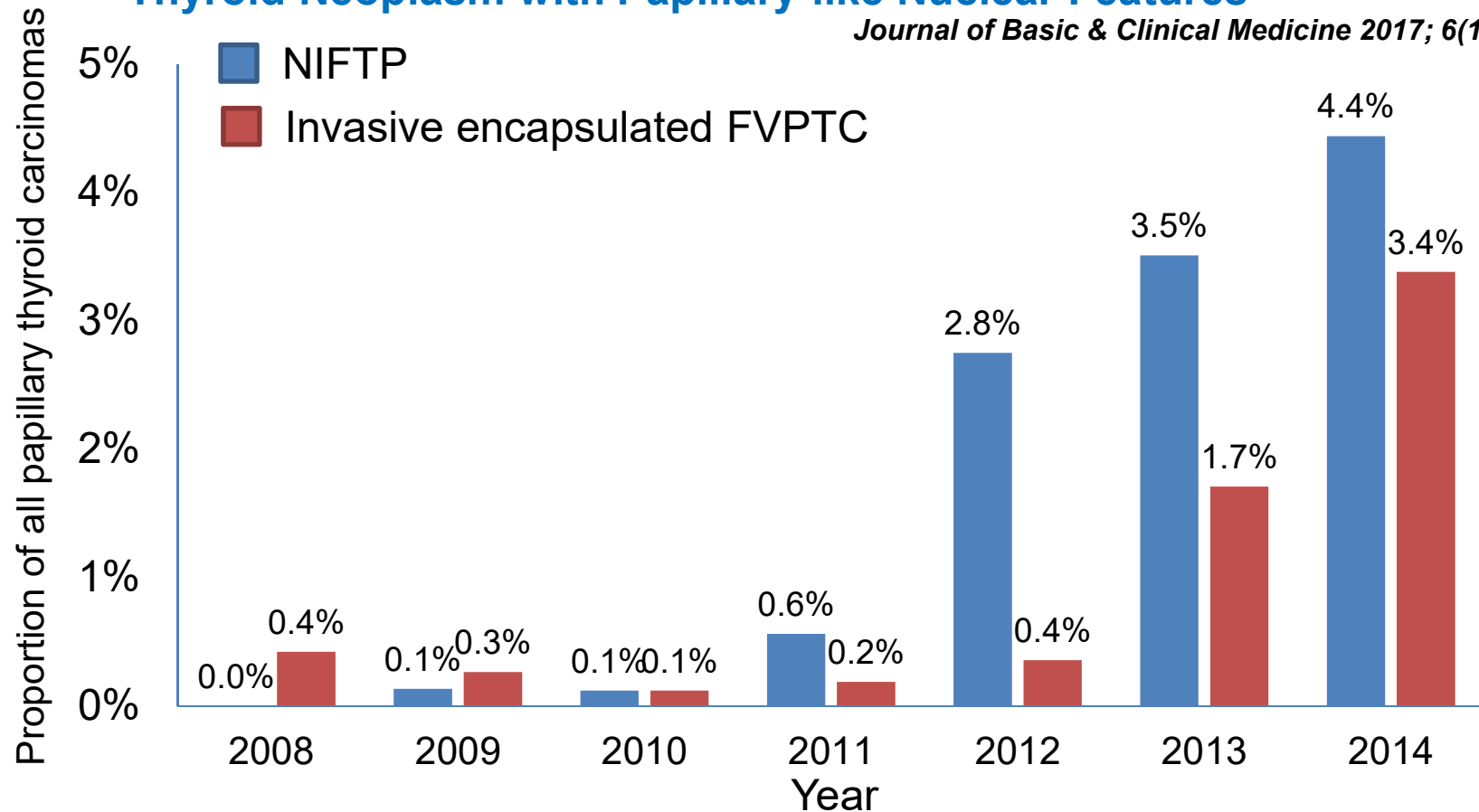
➔ FNA: follicular neoplasm
↓
Lobectomy
Frozen section: follicular neoplasm

↓
➔ **> 4 cm
Noninvasive EFVPTC
(NIFTP)**

↓
➔ **No completion thyroidectomy
No RAI**

Effect of Lowering the Diagnostic Threshold for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma on the Prevalence of Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

Journal of Basic & Clinical Medicine 2017; 6(1):26-28



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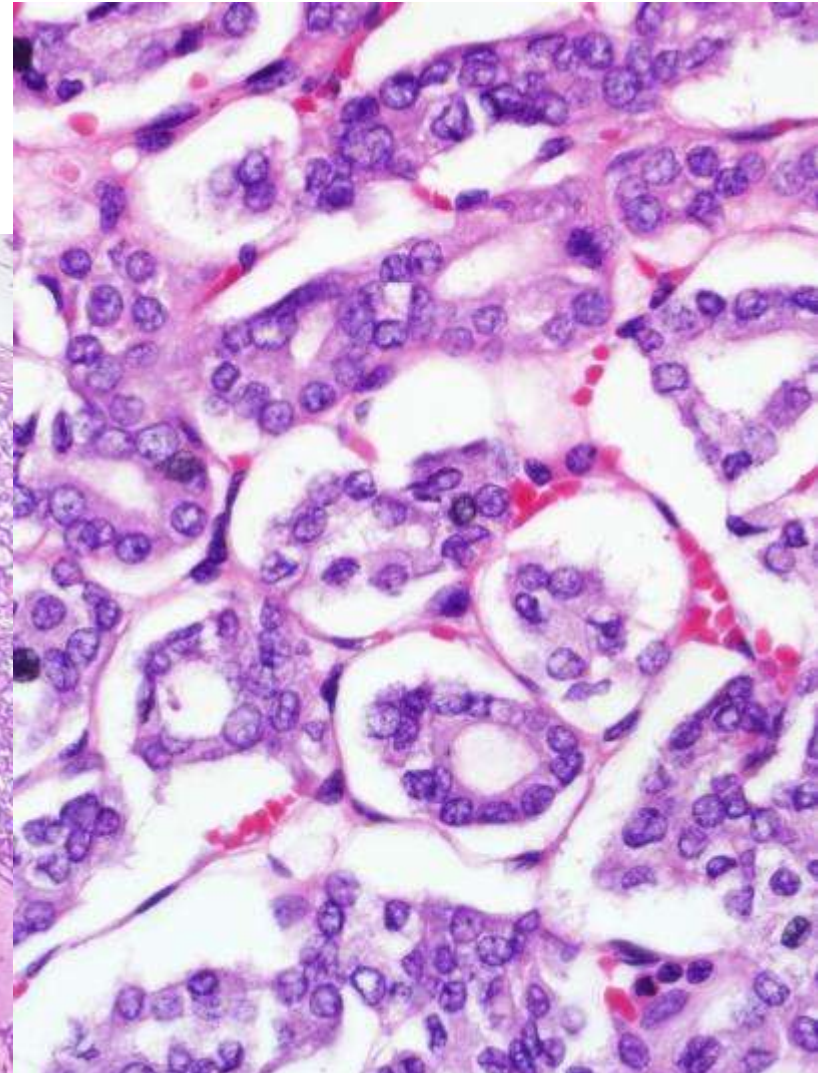
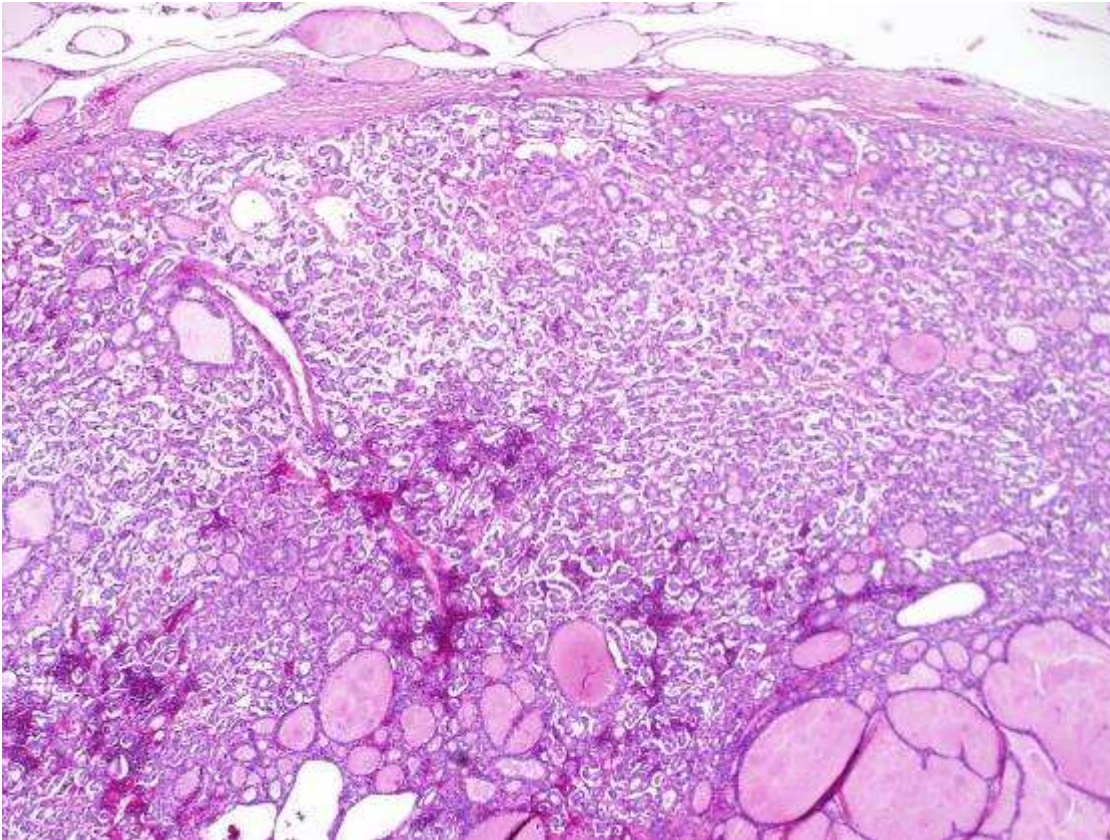
Osaka Aoki, M.D., Ph.D.





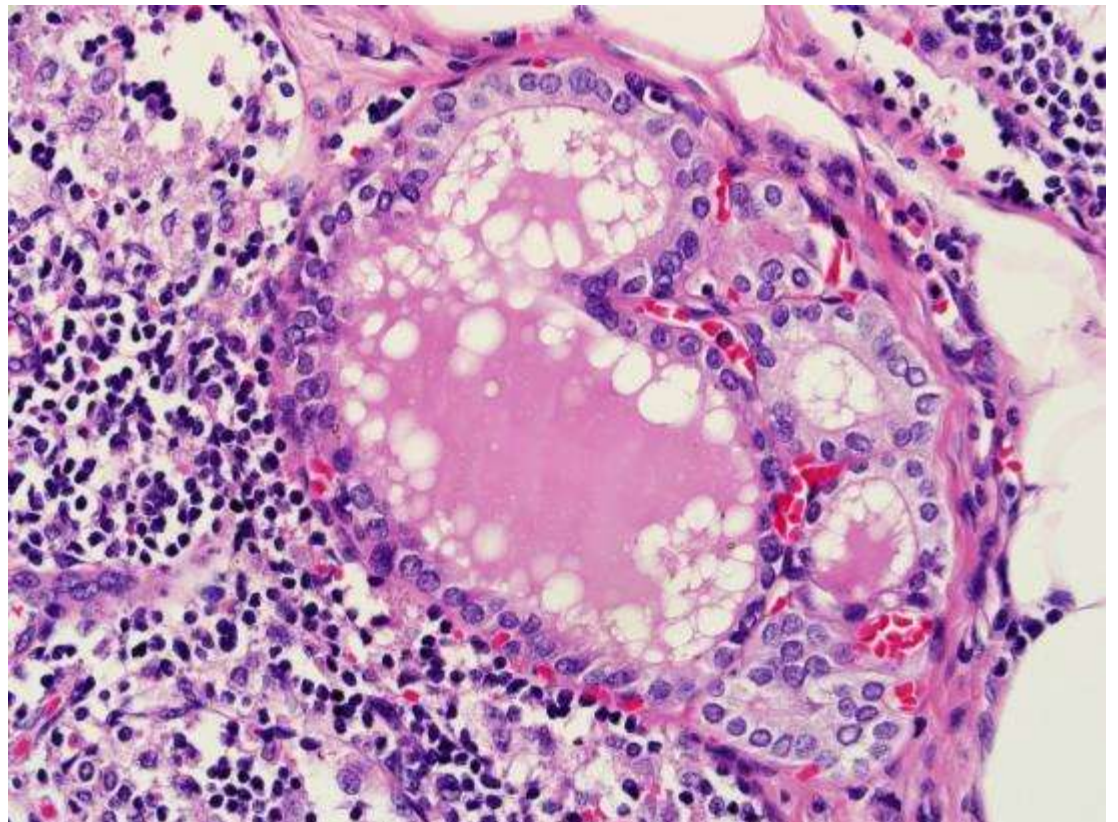
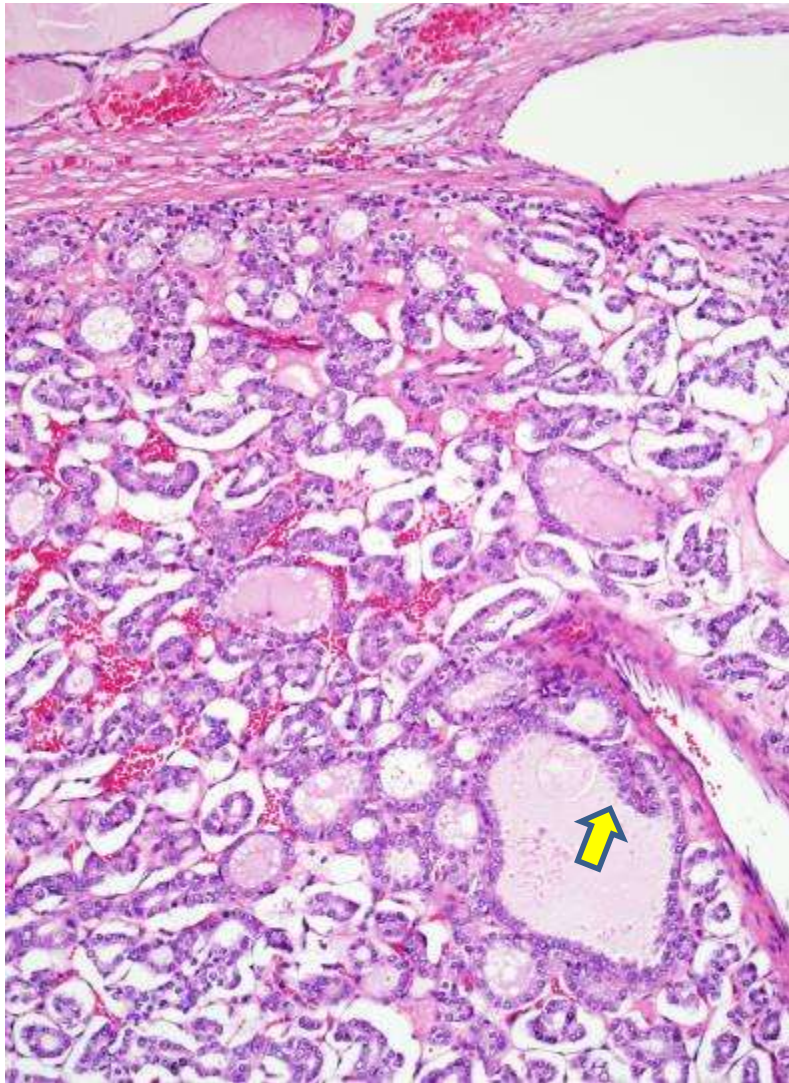
Case 2

- 37 y/o male
- 1.4 cm nodule



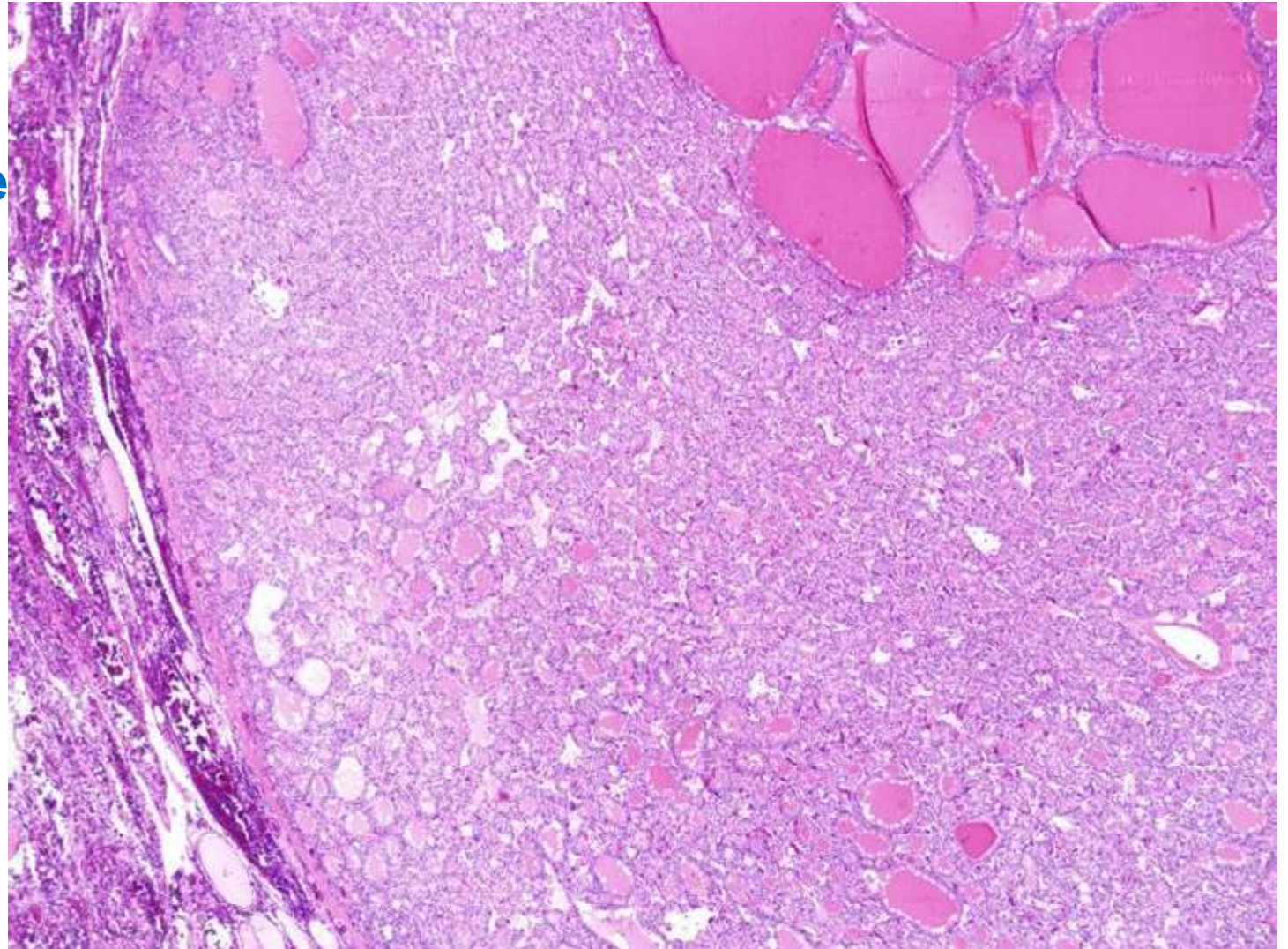
BRAF V600E

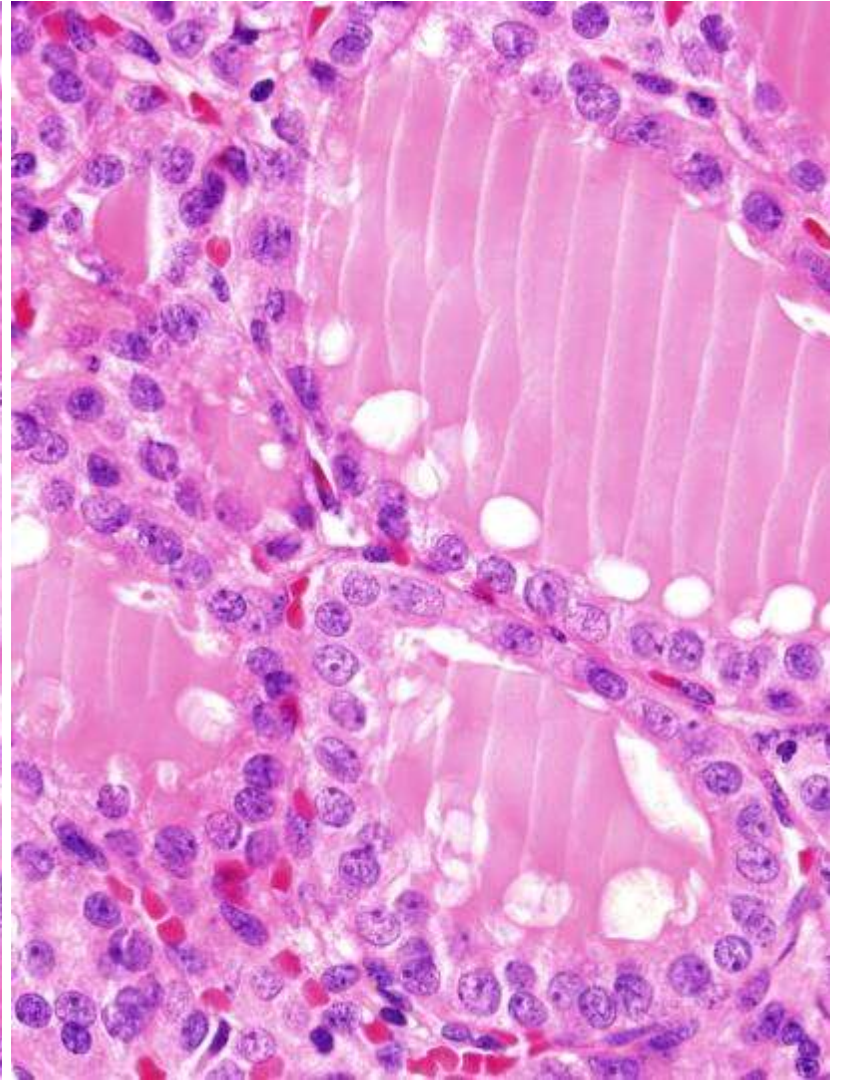
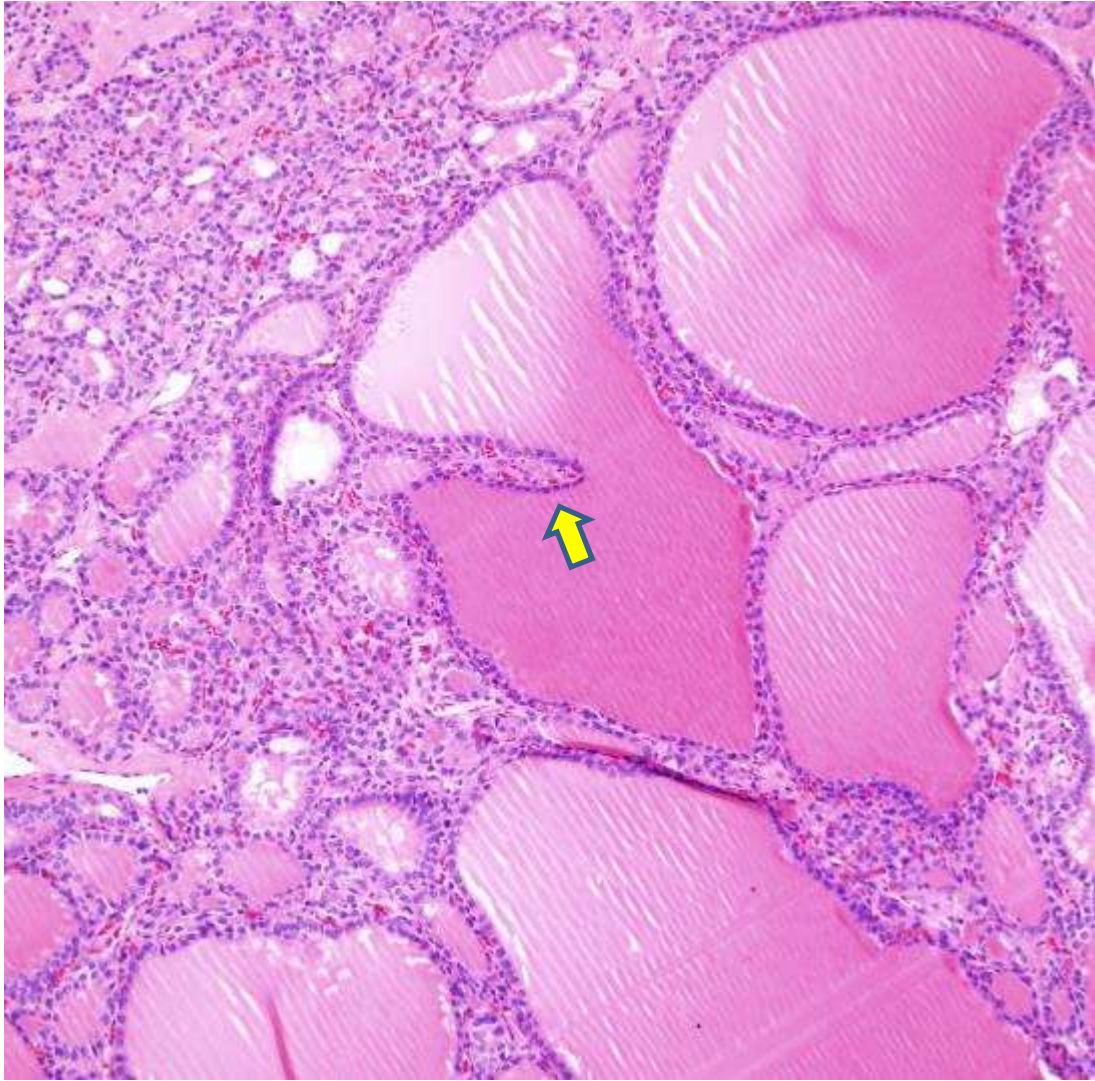
Lymph node metastasis



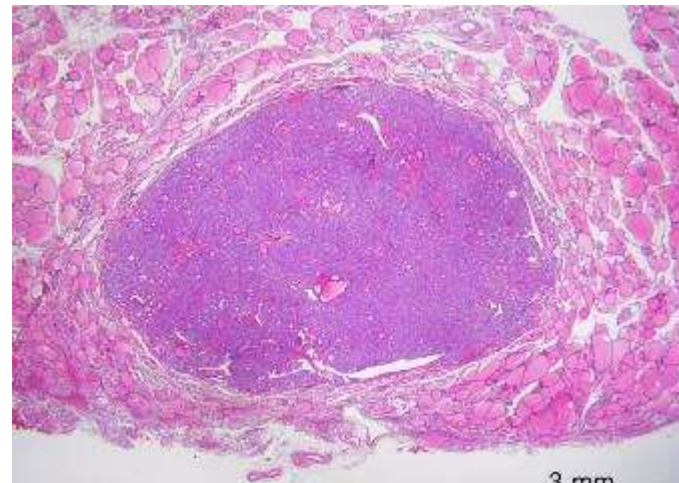
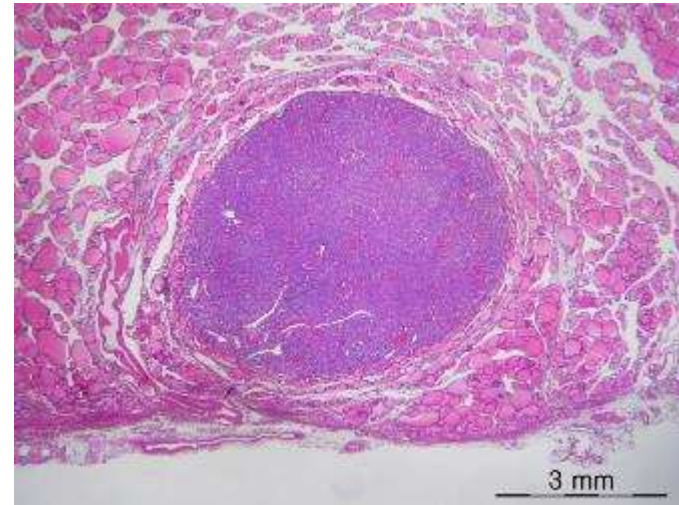
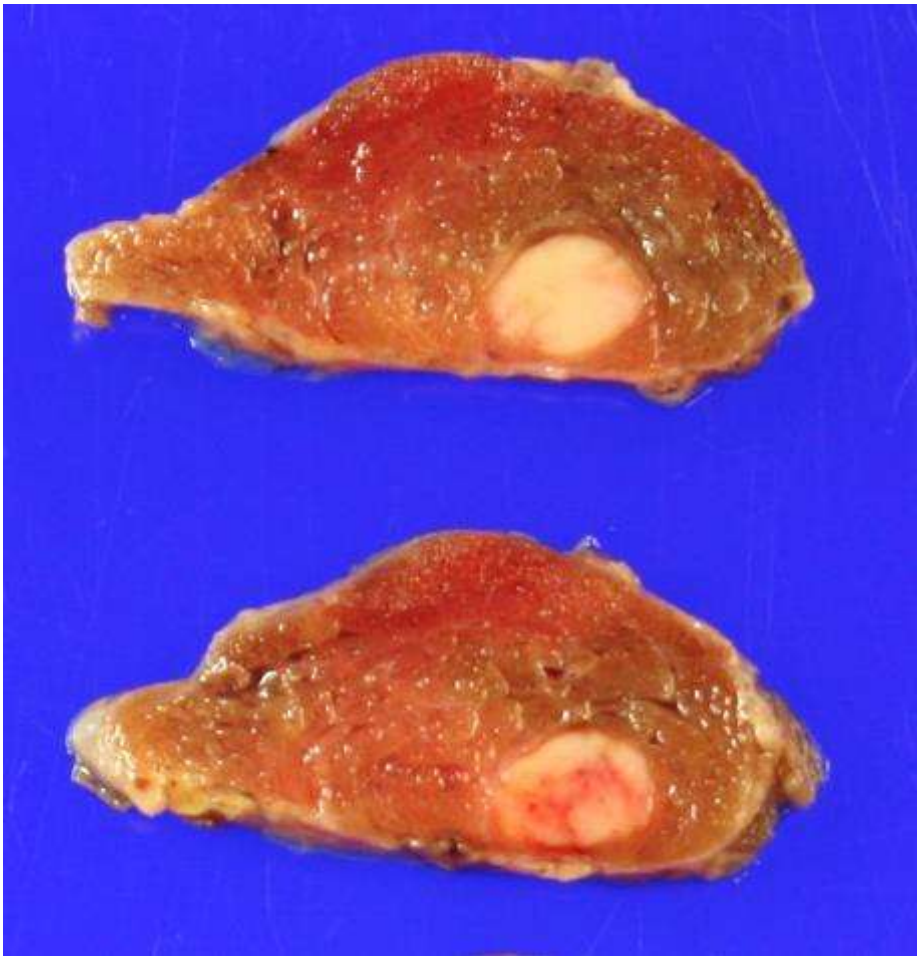
Case 3

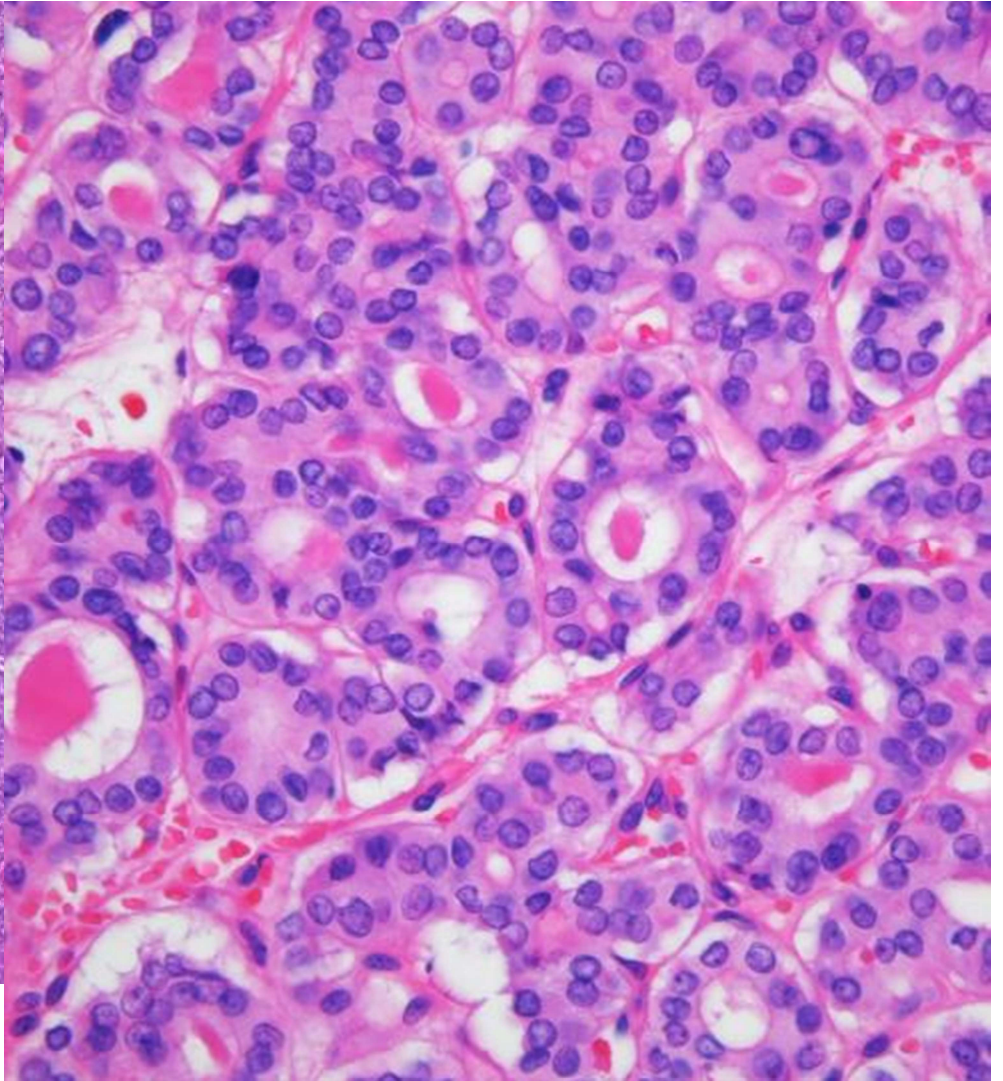
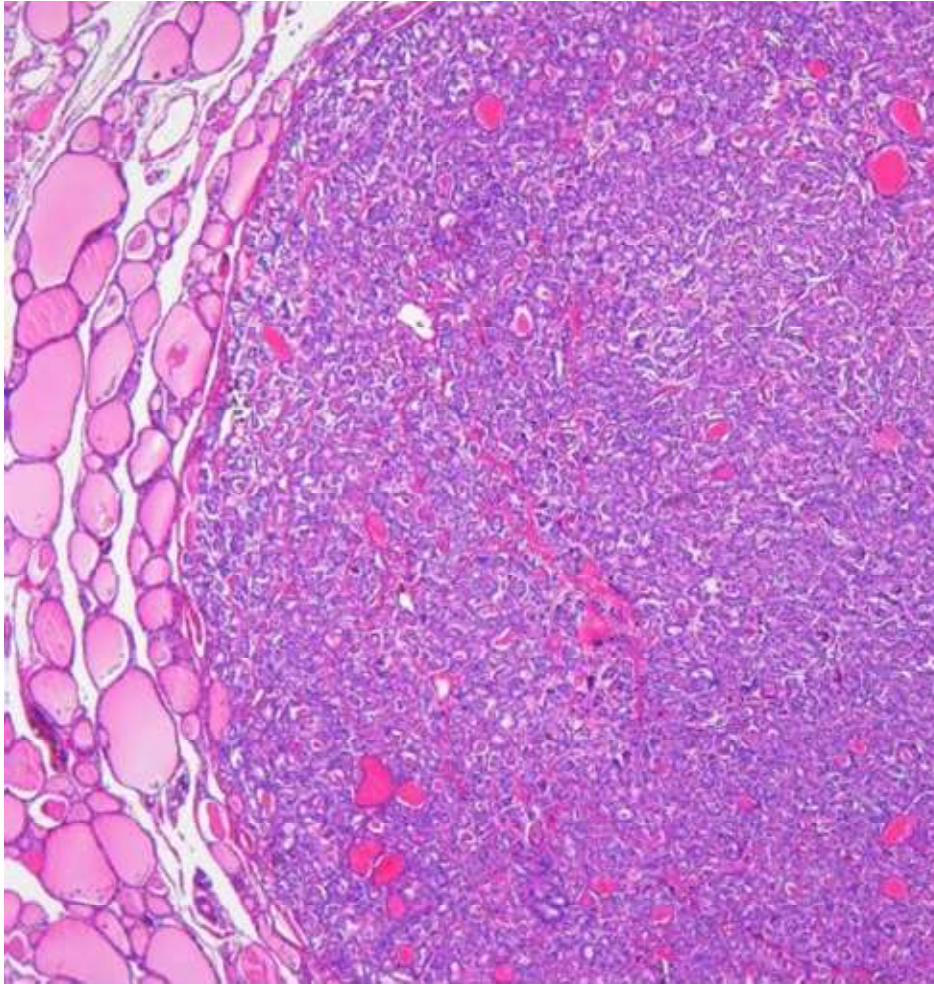
- 33 y/o female
- 0.9 cm nodule
- ***BRAF V600E***

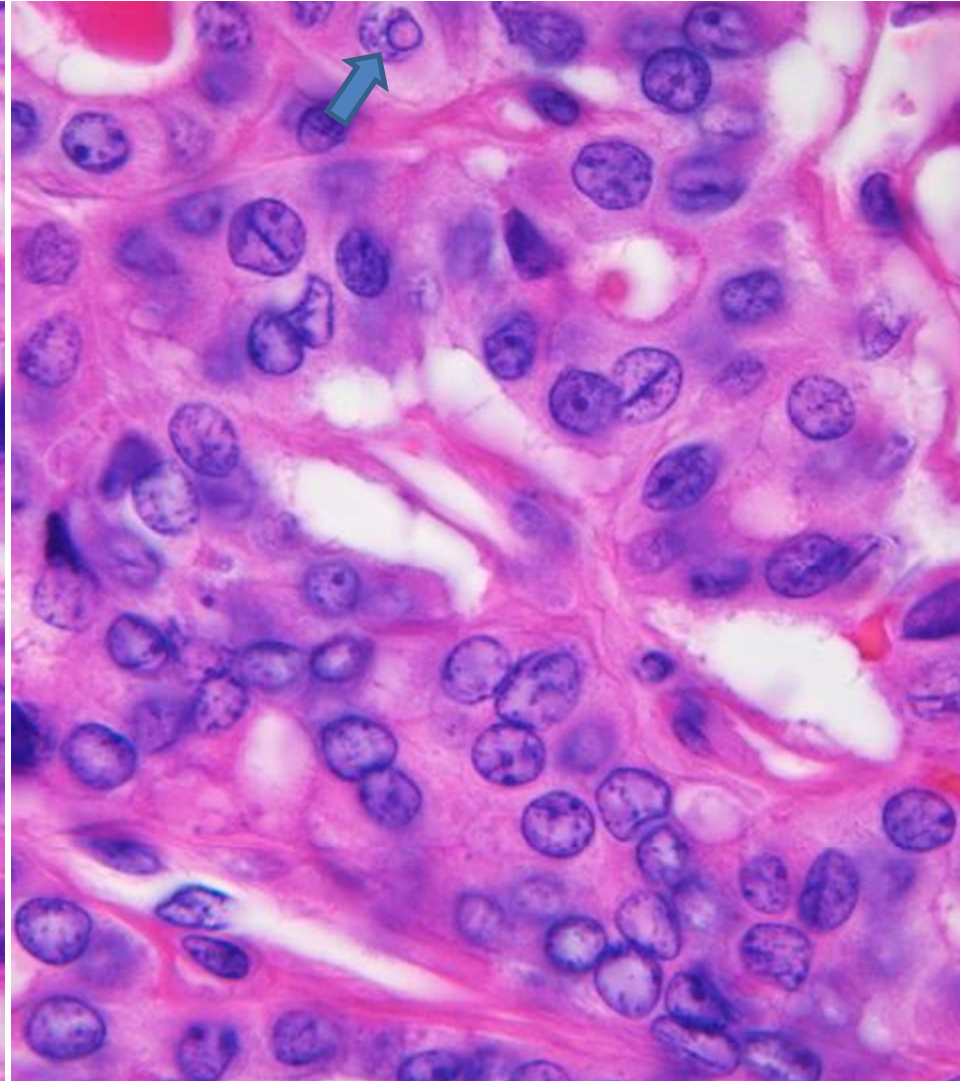
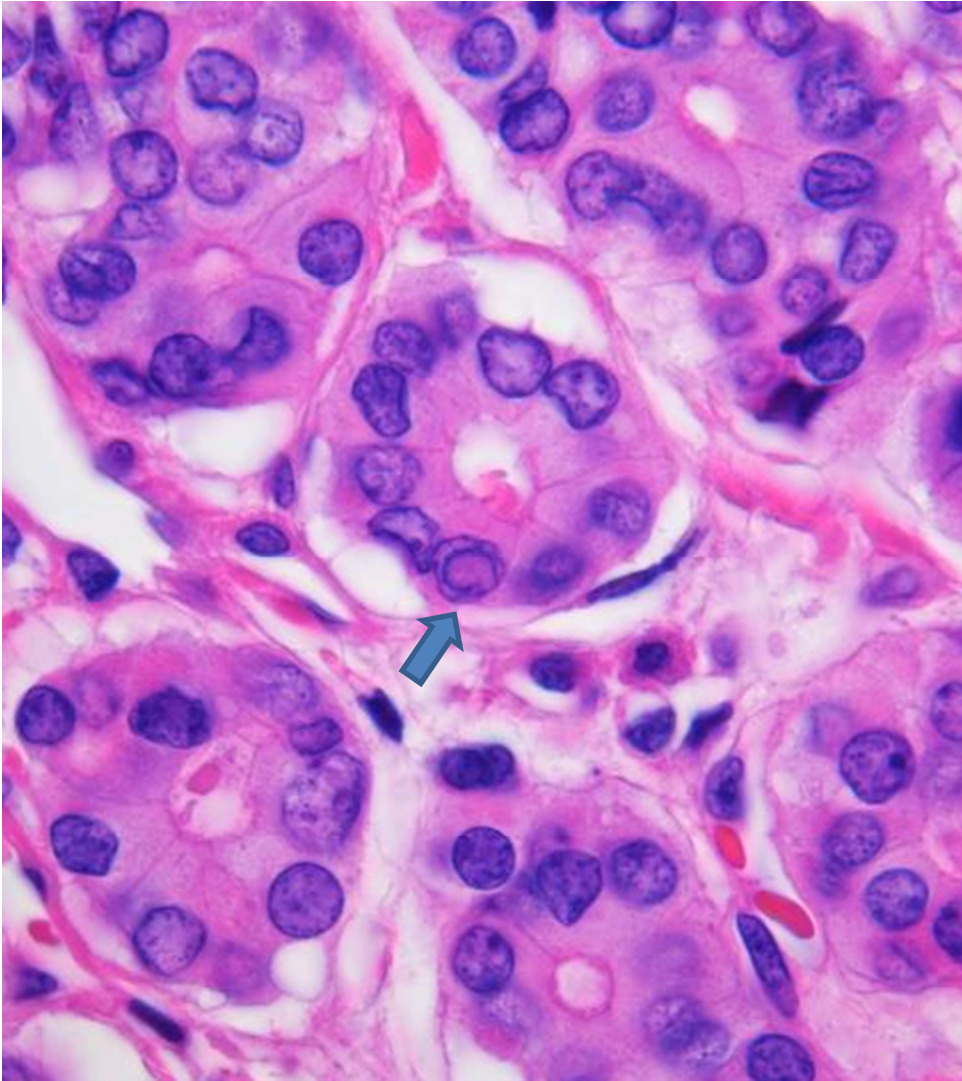




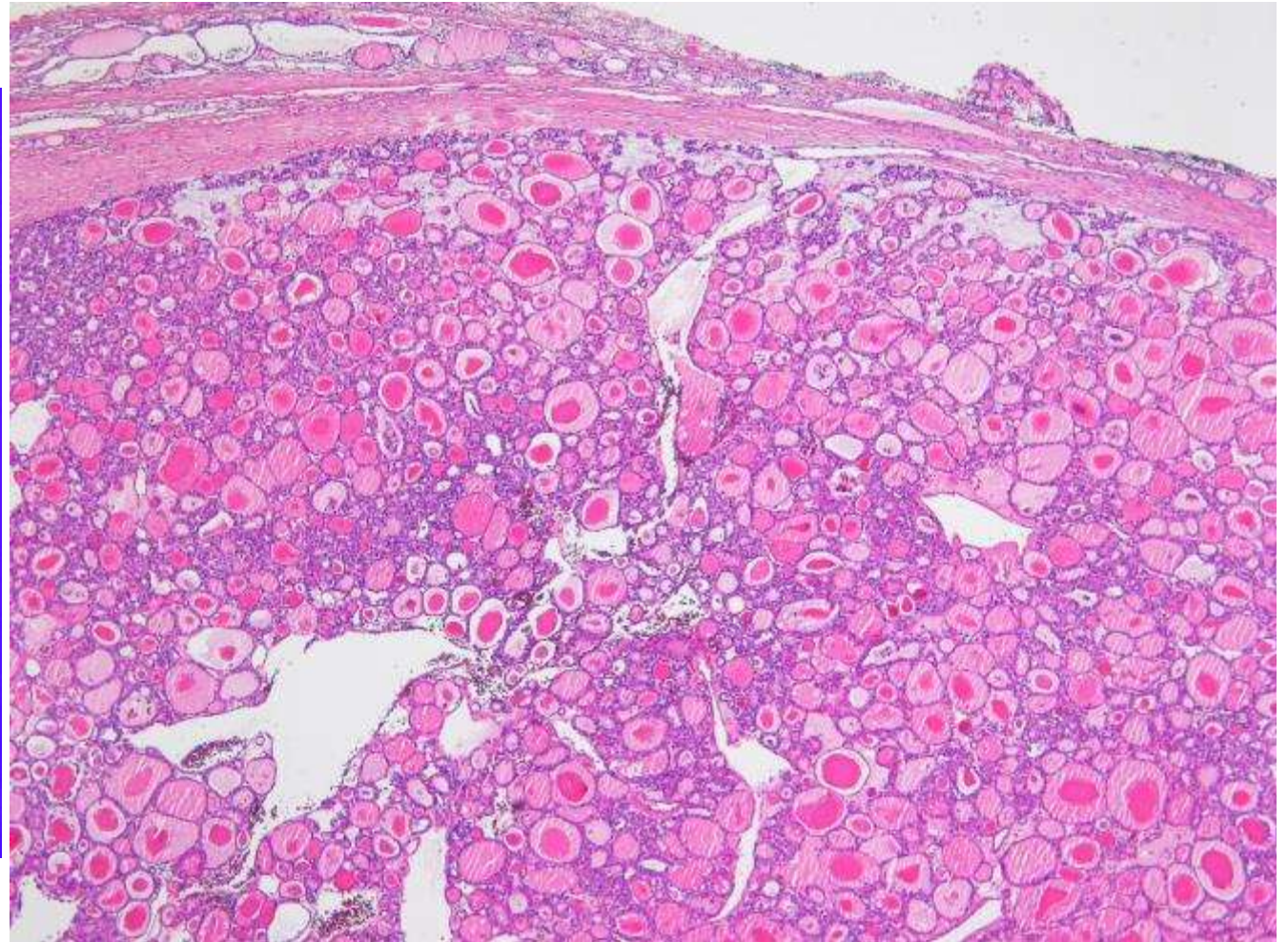
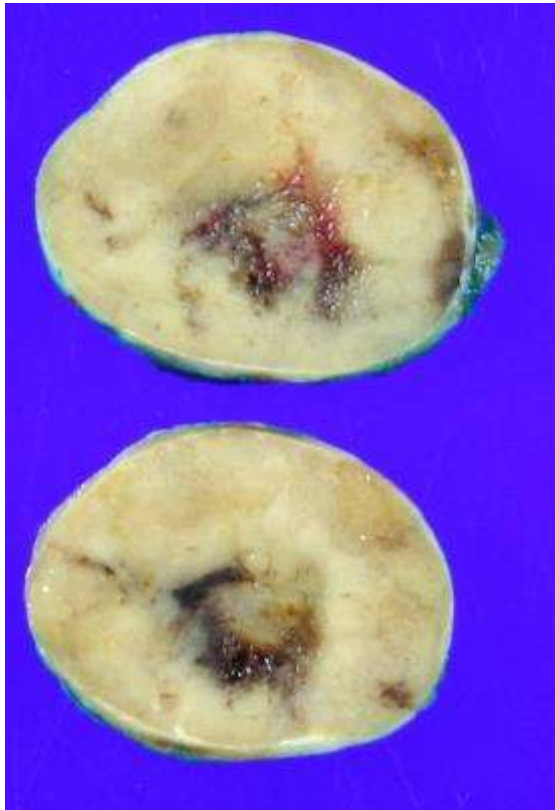
Case 4. 67 y/o male, 0.9 cm nodule, *BRAF V600E*

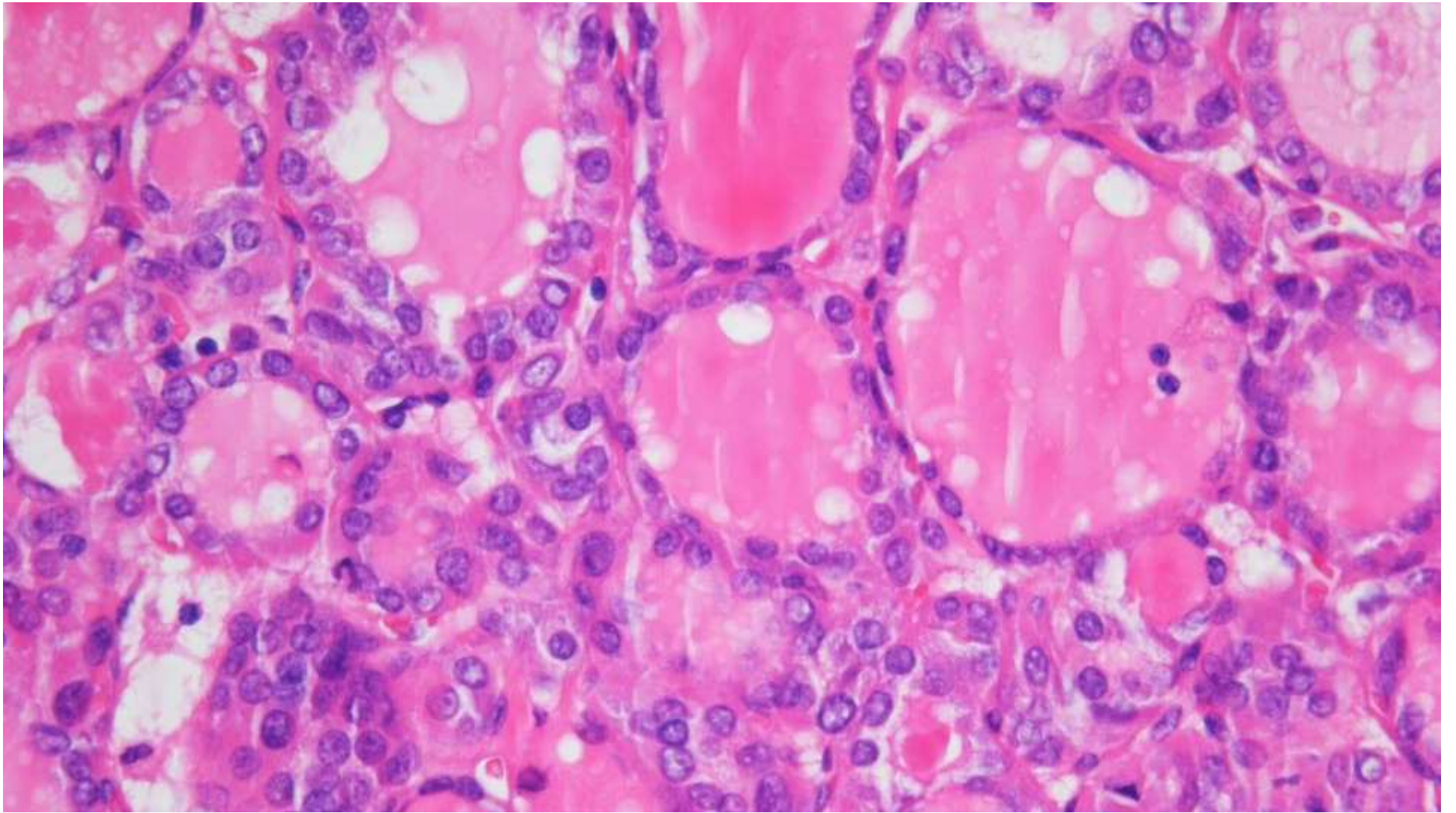


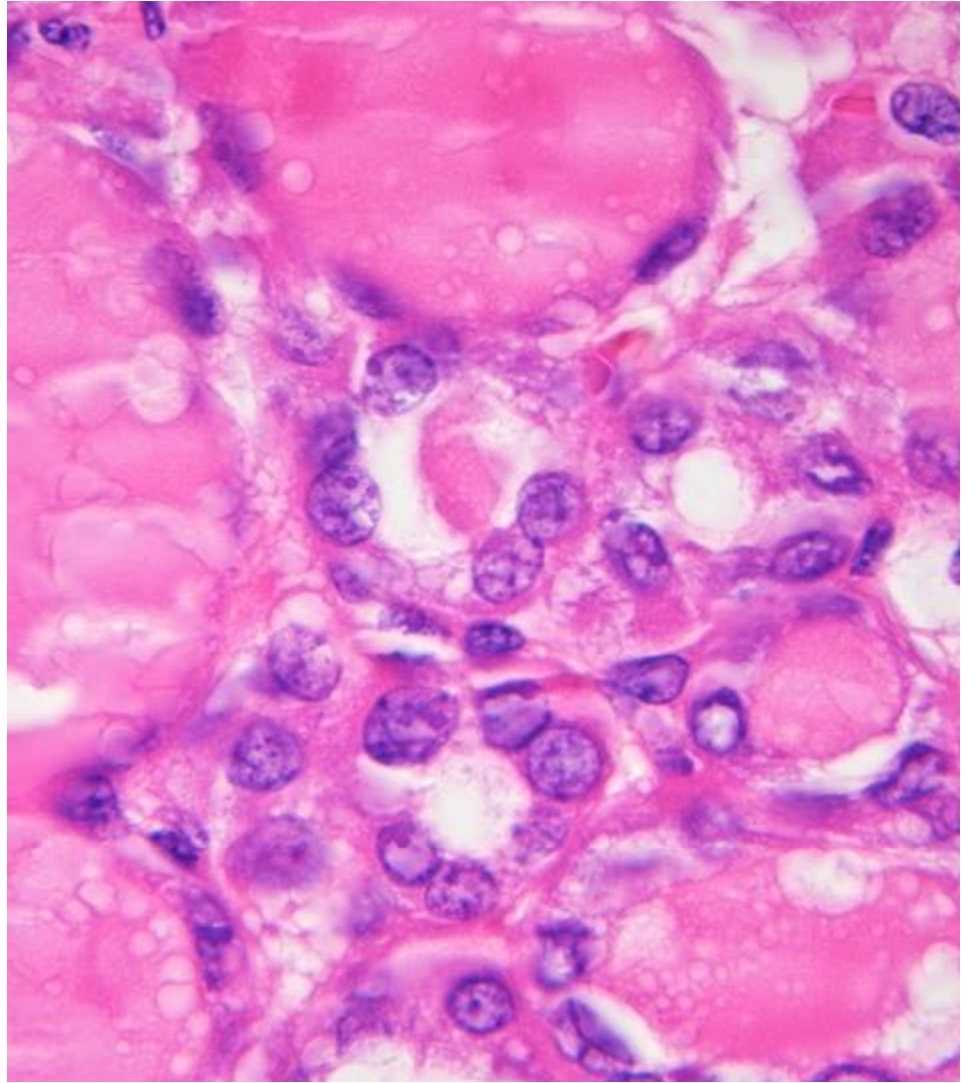
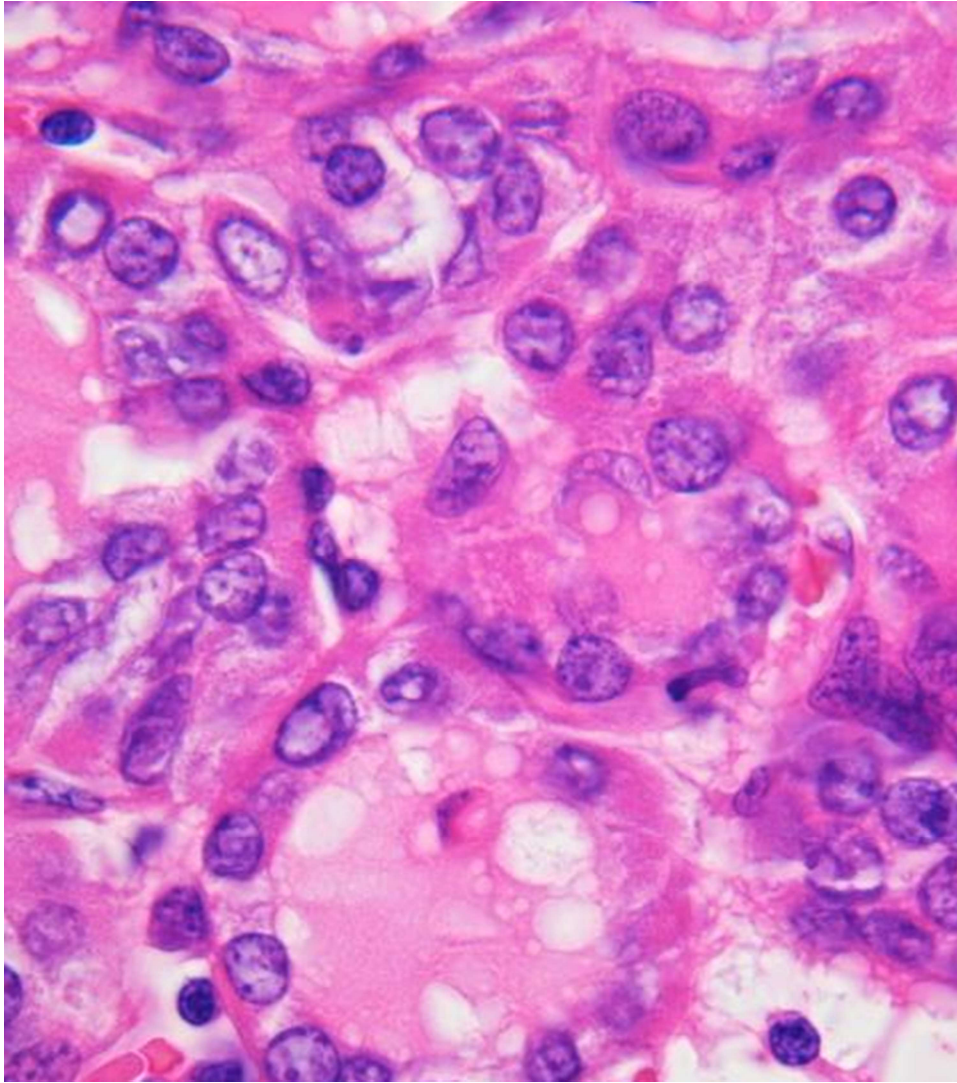




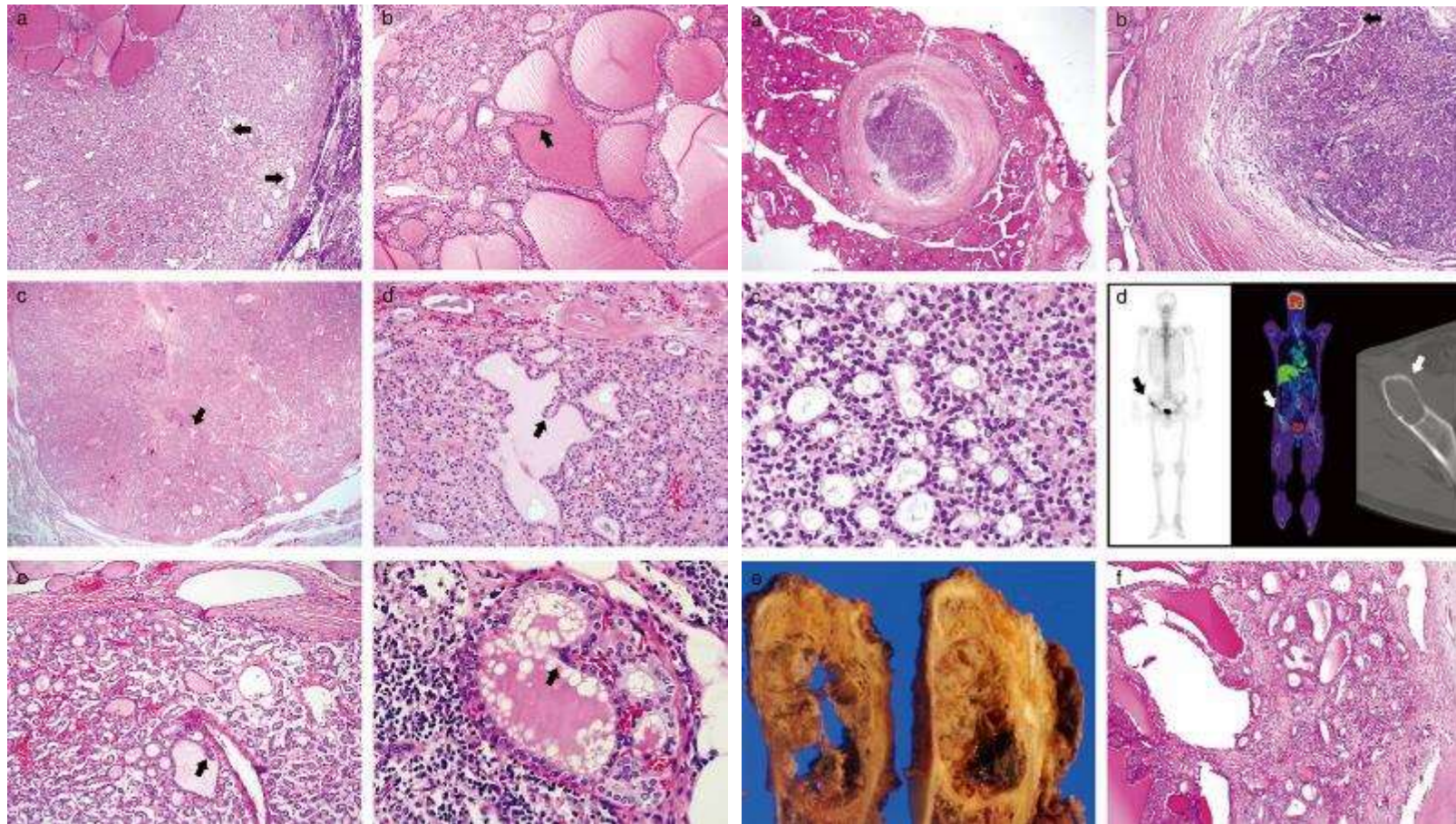
Case 5. 37 y/o male, 3.5 cm nodule, *NRAS* Q61R



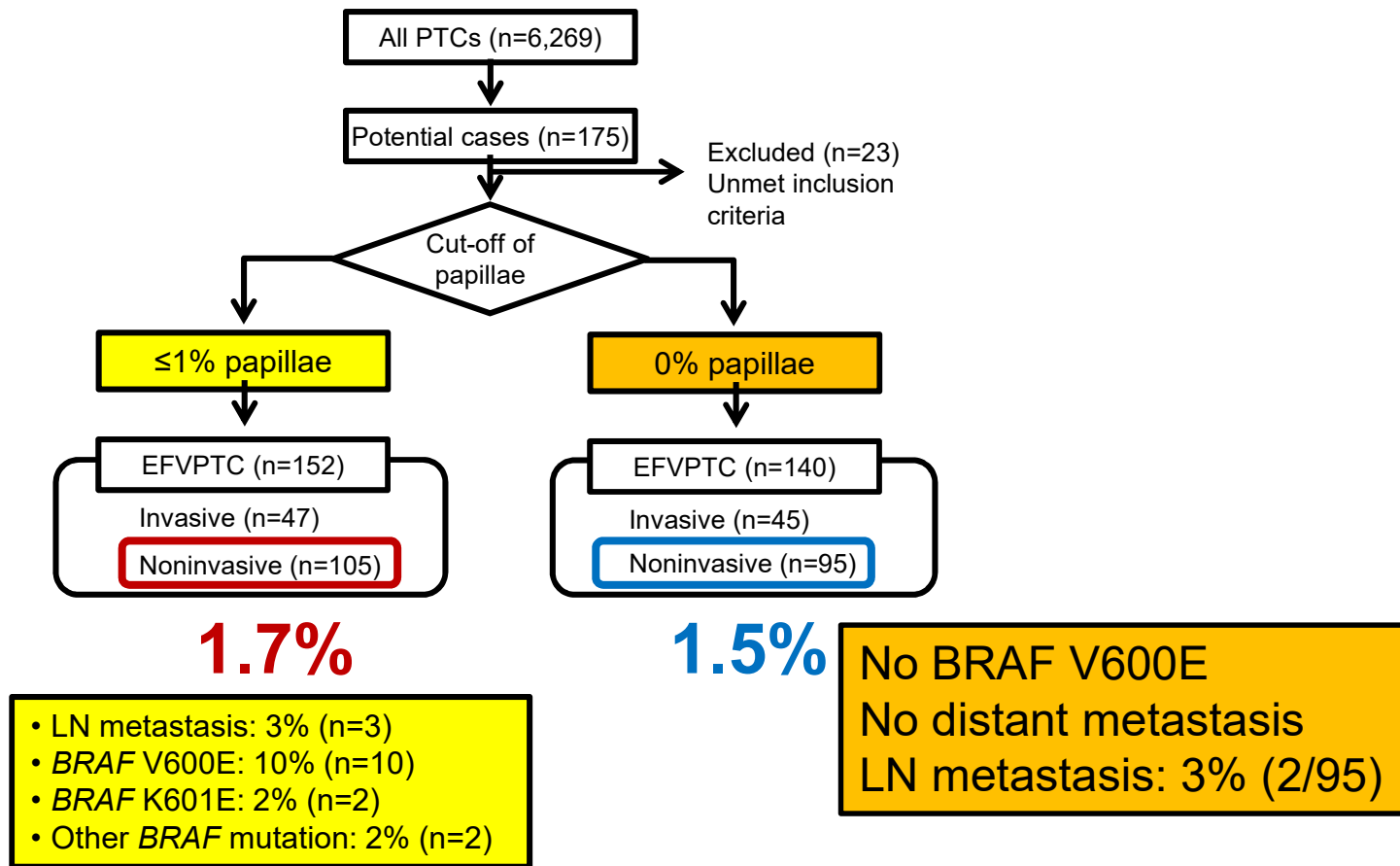




NIFTP (?) with *BRAF* V600E mutation

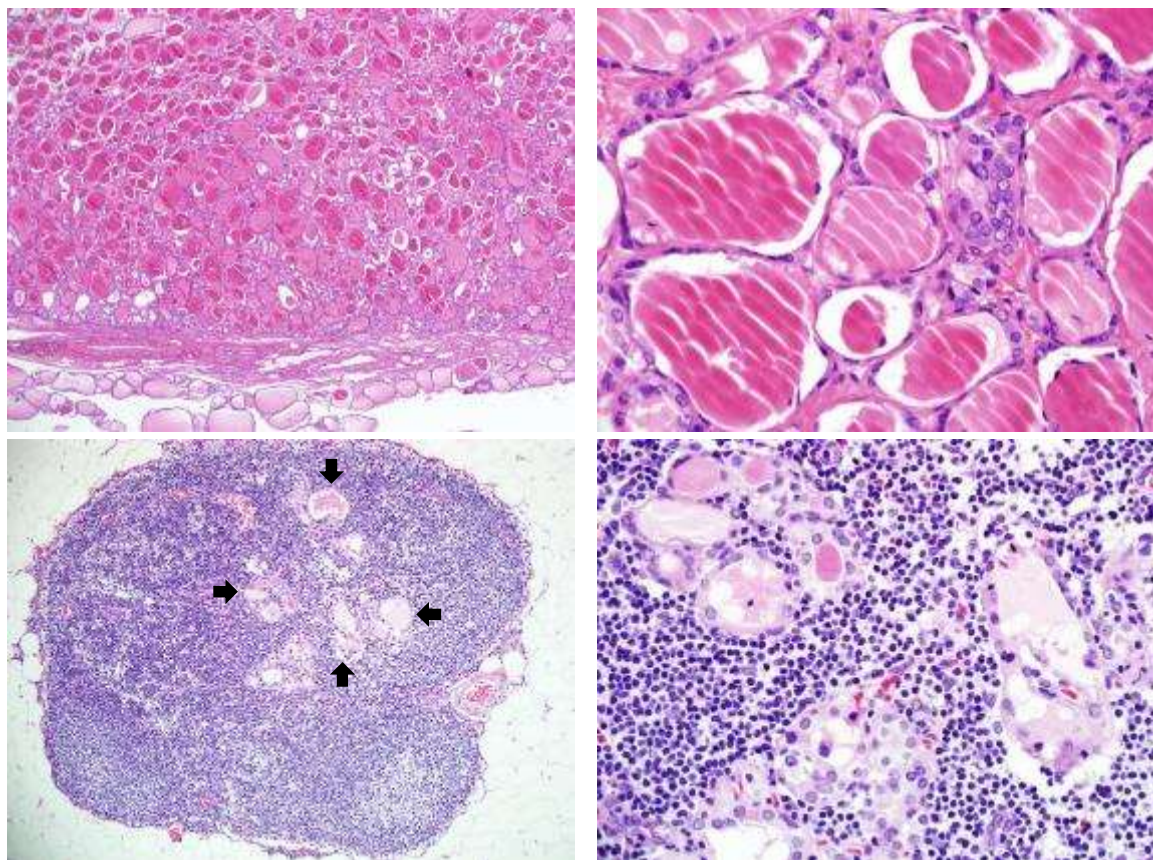


Mod Pathol. 2017 Mar 10. doi: 0.1038/modpathol.2017.9



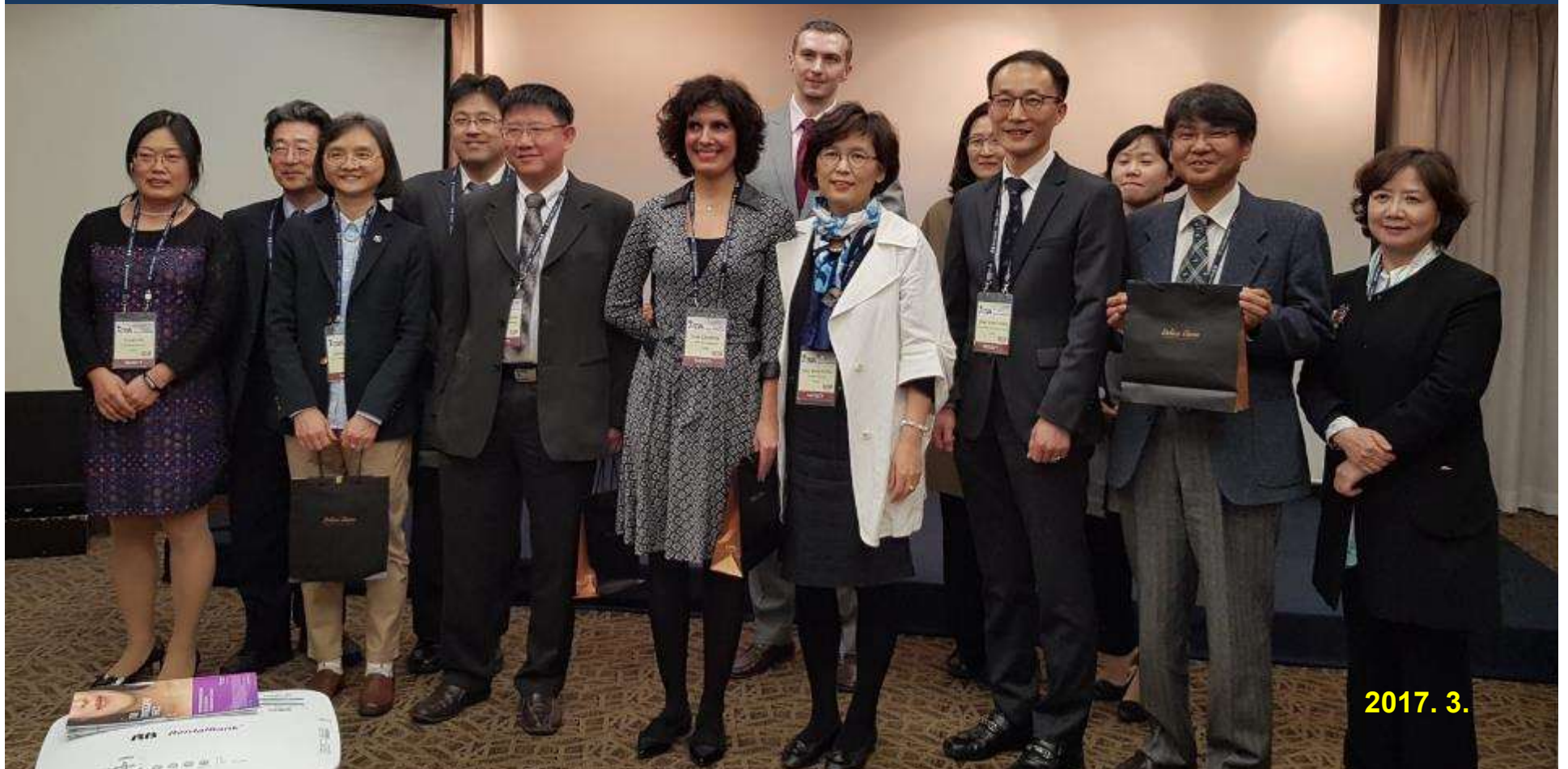
Seoul St. Mary's Hospital study 2008 -2014

NIFTP (?) with lymph node metastasis



Mod Pathol. 2017 Mar 10. doi: 0.1038/modpathol.2017.9

Working Group of Asian thyroid FNA cytology



Joint Symposium of the Working Group of Asian Thyroid FNA Cytology
25th Thai-Japanese Workshop in Diagnostic Cytopathology
Le Meridien, Chiang Mai, Thailand, January 19, 2018



First row, left-to-right: C.K. Jung (Korea), A. Salillas (Philippines), S.W. Hong (Korea), K. Kakudo (Japan), S. Rangdaeng (Thailand), C.R. Lai (Taiwan), S. Maeda (Japan), S. Hiroi (Japan), P. Sampatanukul (Thailand)

Second row, left-to-right: J.Y. Pyo (Korea), J.F. Hang (Taiwan), S. Watcharadetwittaya (Thailand), P. Srimunta (Thailand), A. Abelardo (Philippines), S. Shrestha (Nepal), A. Bychkov (Thailand), C. Y. Liu (Taiwan), S. Keelawat (Thailand), T. Hayashi (Japan)

Low Rate of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features in Asian Practice

Andrey Bychkov,¹ Mitsuyoshi Hirokawa,² Chan Kwon Jung,³ Zhiyan Liu,⁴ Yun Zhu,⁵ Soon Won Hong,⁶ Shinya Satoh,⁷ Chiung-Ru Lai,⁸ Lien Huynh,⁹ and Kennichi Kakudo¹⁰

TABLE 1. INCIDENCE OF FV-PTC AND NIFTP IN ASIAN INSTITUTIONS

<i>PI</i>	<i>Site</i>	<i>Period</i>	<i>PTC, n</i>	<i>FV-PTC</i>		<i>eFV-PTC</i>		<i>NIFTP</i>	
				<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
M. Hirokawa	Japan, Kobe	2007–2015	9727	271	2.8%	167	1.7%	50	0.5%
S. Satoh, K. Kakudo	Japan, Fukuoka	2015	386	25	6.5%	20	5.2%	12	3.1%
C.K. Jung	South Korea, Seoul	2008–2014	6269	240	3.8%	140	2.2%	95	1.5%
S.W. Hong	South Korea, Seoul	2014	2111	171	8.1%	55	2.6%	5	0.2%
Z. Liu	China, Shandong	2011–2016	5113	113	2.2%	36	0.7%	16	0.3%
Y. Zhu	China, Wuxi	2012–2014	2190	187	8.5%	19	0.9%	6	0.3%
C.R. Lai	Taiwan, Taipei	2010–2011	380	22	5.8%	20	5.3%	18	4.7%
A. Bychkov	Thailand, Bangkok	2013–2014	163	16	9.8%	9	5.5%	4	2.5%
L. Huynh	Vietnam, Ho Chi Minh City	2016	265	25	9.4%	10	3.8%	0	0%
Total			26,604	1070	4.0%	476	1.8%	206	0.8%

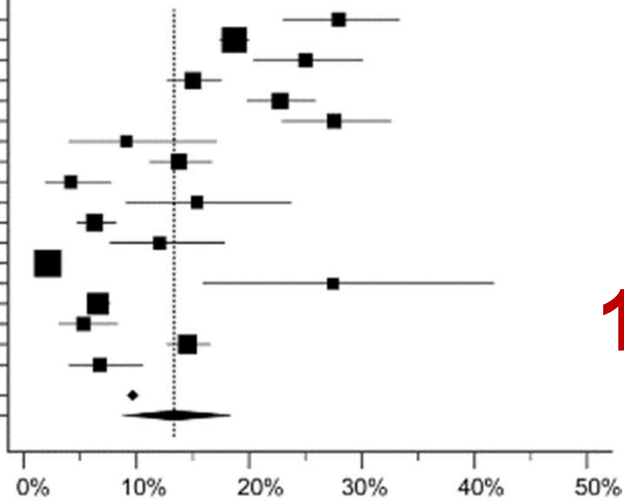
PTC = all primary PTC, including NIFTP; FV-PTC = all PTC follicular variant, including infiltrative and encapsulated (both invasive and noninvasive); eFV-PTC = encapsulated invasive and noninvasive FV-PTC; NIFTP = noninvasive eFV-PTC.

PI, principal investigator; PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of PTC; eFV-PTC, encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

Endocr Pathol. 2018
Feb 23. [Epub ahead
of print]

Non-Asian Studies	N	%	95% CI	Weight (%)
Strickland et al., 2015	304	28.0	23.0-334	5.6
Nikiforov et al., 2016	3,432	18.7	17.4-20.0	5.8
Thompson, 2016	324	25.0	20.4-30.1	5.6
Rosario et al., 2016	860	15.0	12.7-17.6	5.7
Faquin et al., 2016	756	22.8	19.8-25.9	5.7
Canberk et al., 2016	341	27.6	22.9-32.6	5.6
Godley et al., 2016	88	9.1	4.0-17.1	5.1
Pusztaszeri et al., 2017	625	13.8	11.2-16.7	5.7
Saglietti et al., 2017	216	4.2	1.9-7.8	5.5
Layfield et al., 2017	104	15.4	9.1-23.8	5.2
Golding et al., 2017	796	6.3	4.7-8.2	5.7
Singh et al., 2017	174	12.1	7.6-17.9	5.4
Parente et al., 2017	4,790	2.1	1.7-2.6	5.8
Jaconi et al., 2017	51	27.5	15.9-41.7	4.7
Zhou et al., 2017	2,283	6.6	5.9-7.7	5.8
Kiernan, 2017	321	5.3	3.1-8.3	5.6
Mainthia, 2017	1,335	14.5	12.7-16.5	5.8
Li et al., 2017	252	6.7	4.0-10.6	5.6
Total (fixed effects)	17,052	9.7	9.2-10.1	100
Total (random effects)	17,052	13.3	9.0-18.3	100

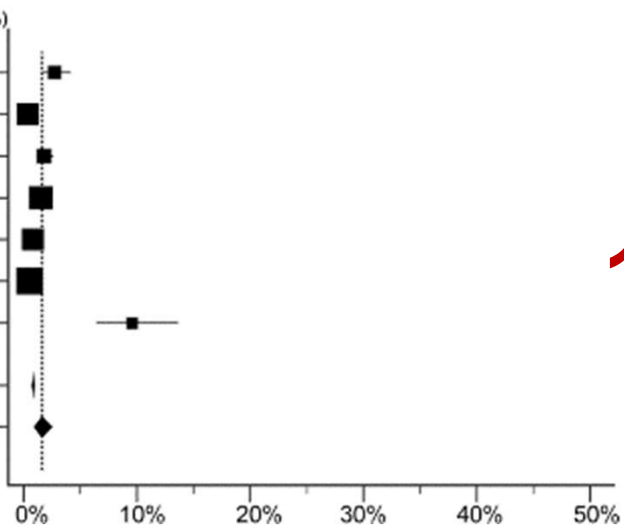
$I^2=98.6\%$, $P<0.0001$



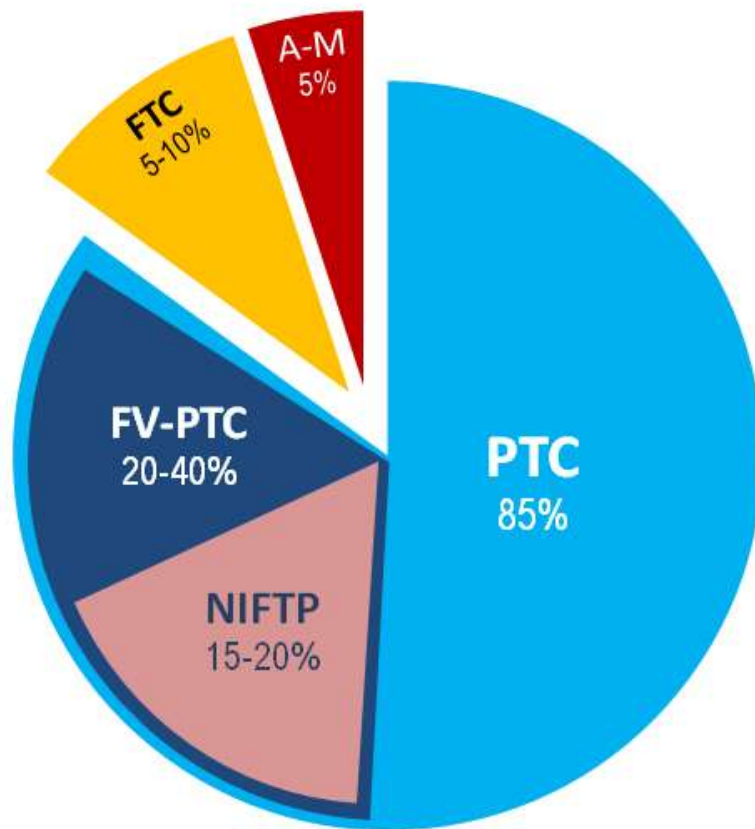
17%

Asian studies	N	%	95% CI	Weight (%)
Lee et al., 2017	769	2.7	1.7-4.1	13.2
Liu et al., 2017	5,561	0.4	0.2-0.6	15.5
Song et al., 2017	1,444	1.8	1.2-2.6	14.4
Cho et al., 2017	6,269	1.5	1.2-1.8	15.6
Bychkov et al., 2017*	5,495	0.8	0.6-1.1	15.5
Hirokawa et al., 2017	10,076	0.5	0.4-0.7	15.7
Bychkov et al., 2018**	282	9.6	6.4-13.6	10.1
Total (fixed effects)	29,896	0.9	0.8-1.0	100
Total (random effects)	29,896	1.6	0.9-2.5	100

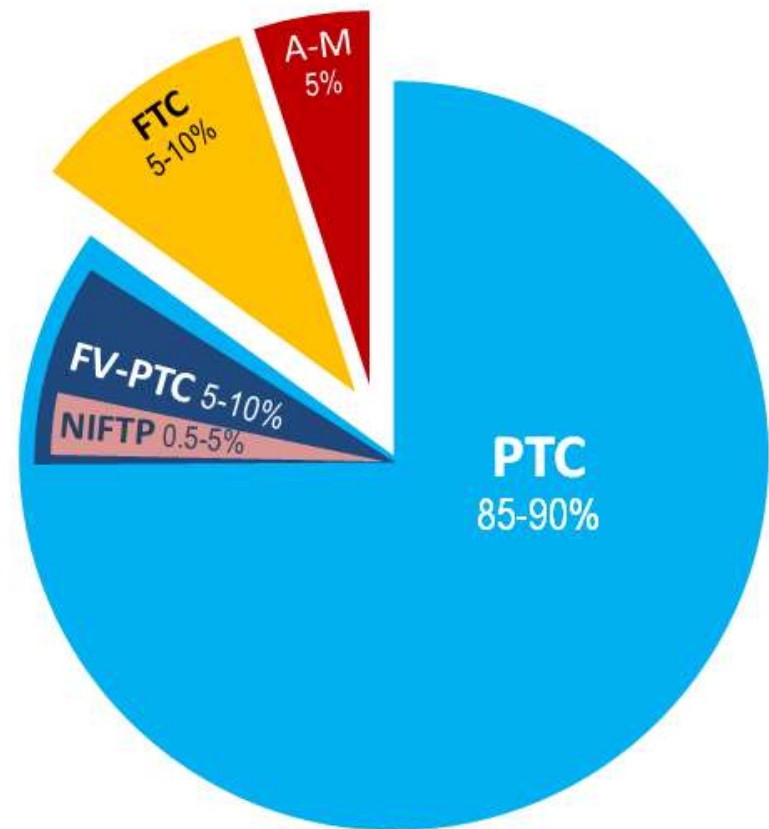
$I^2=95.9\%$, $P<0.0001$



1.6%



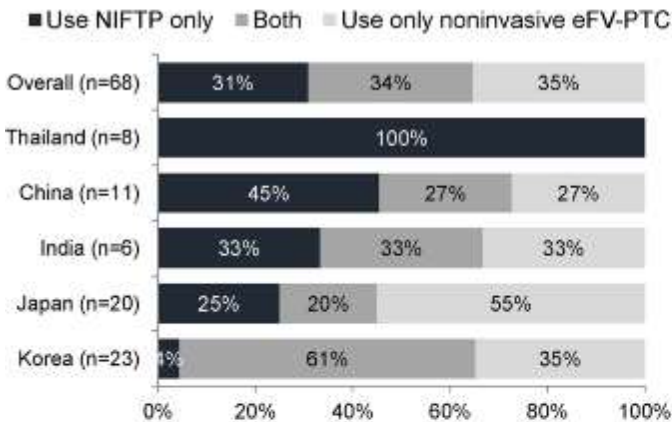
Western series



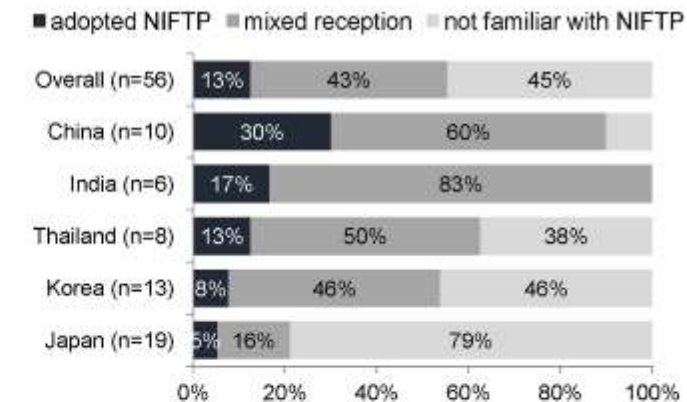
Asian series

Endocr Pathol. 2018 Feb 23. [Epub ahead of print]

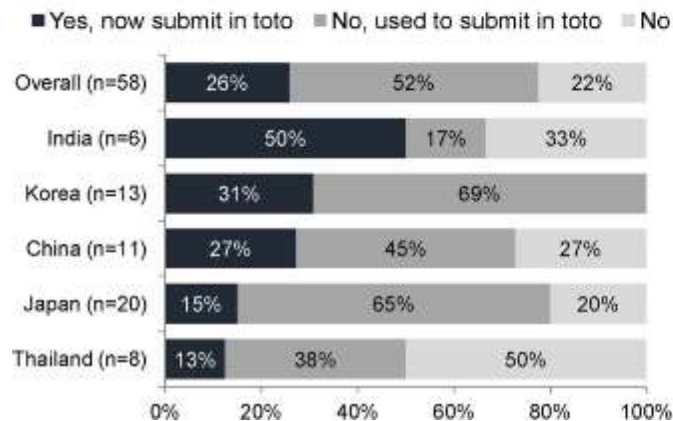
Q1. Have you adopted NIFTP terminology in your practice?



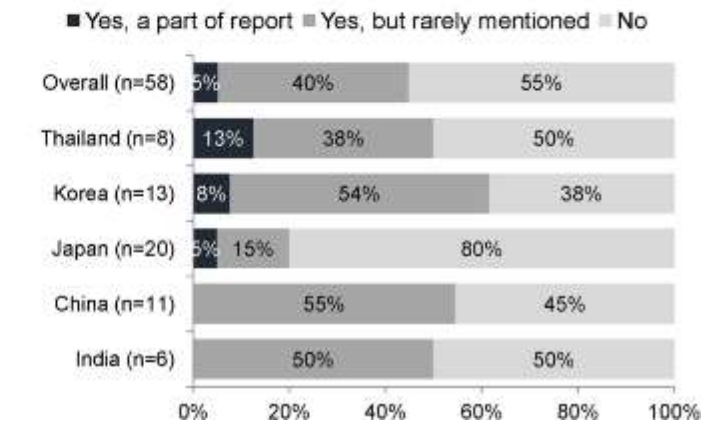
Q2. What is opinion of your clinicians about NIFTP?

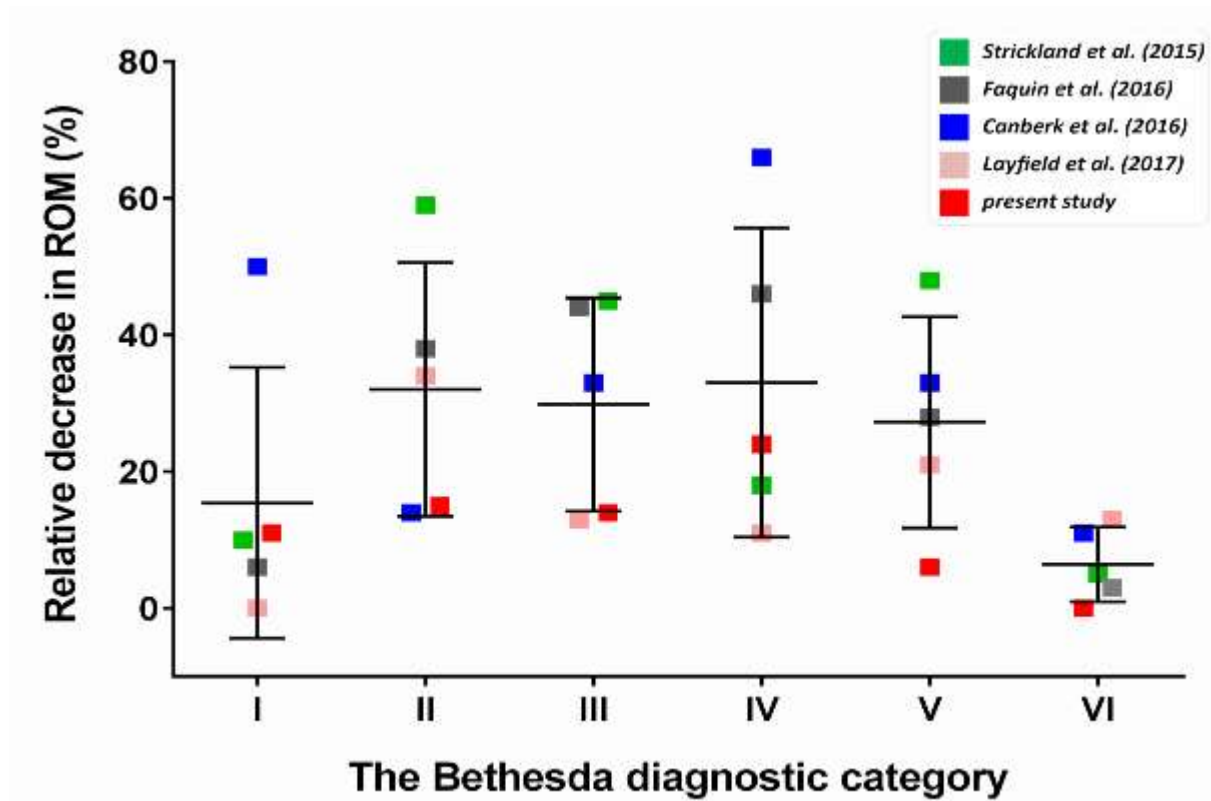


Q3. Did you change a sampling technique of the capsule of encapsulated thyroid lesions after NIFTP implementation?



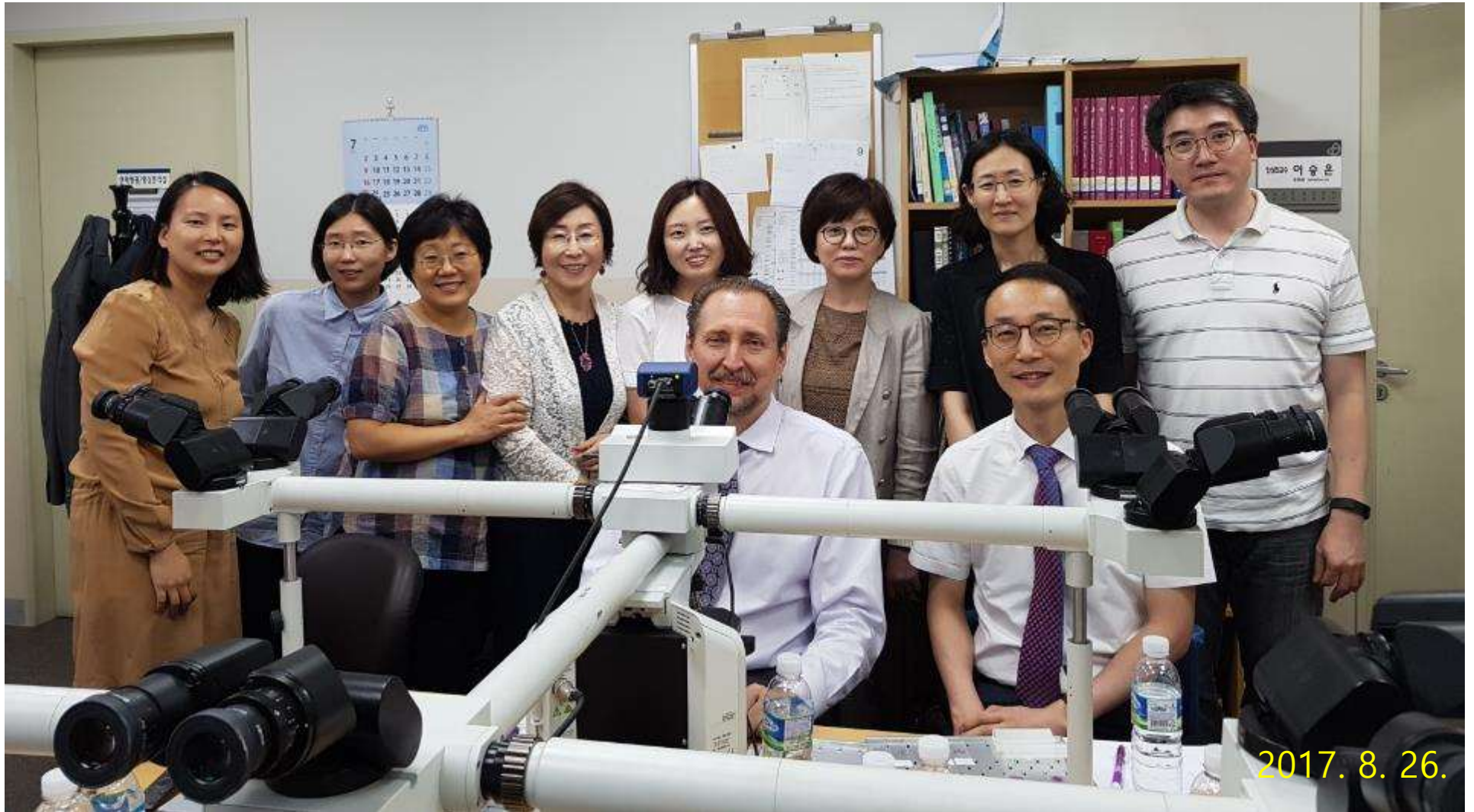
Q4. Do you use papillary thyroid carcinoma nuclear score proposed by the NIFTP working group?





The impact of NIFTP on the relative decrease in ROM for the Bethesda diagnostic categories

Pathology 2018 in press



Limitations and challenges

NIFTP is not a 'finished product'
it is still evolving and the
concepts outlined here require
validation and if needed,
modification

Modifications of Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation
2. Follicular growth pattern with
 - <1% Papillae → 0% Papillae
 - No psammoma bodies
 - <30% solid/trabecular/insular growth pattern
3. Nuclear score 2 - 3
4. No vascular or capsular invasion
5. No tumor necrosis
6. No high mitotic activity (<3 mitoses per 10 HPF)

Florid nuclear features of PTC is not an exclusion criterion, but is rarely seen without true papillae. If such nuclear features are seen, examination of the entire tumor, not just the capsule, with optional, but recommended analyses for *BRAF* V600E using either IHC or molecular techniques may be necessary

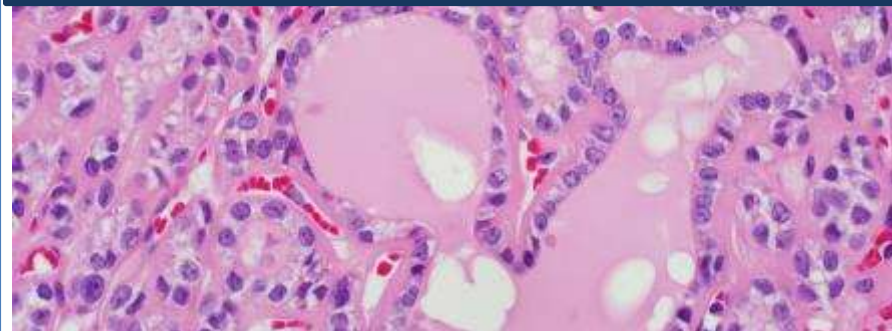
Modifications of Diagnostic Criteria for NIFTP

- Misclassification of invasive infiltrative FVPTC with *BRAF*V600E mutation as NIFTP should be avoided.
- With detailed histological examination of the entire tumor, most NIFTPs with suggested metastasis and/or *BRAF* V600E mutation can be eliminated.
- If genotyping is available, *BRAF* V600E mutation, *RET/PTC* rearrangements, and *TERT* mutations should be used to exclude NIFTP.
- Needless to say, any tumors with histologically confirmed metastasis should not be classified in the borderline tumor category.

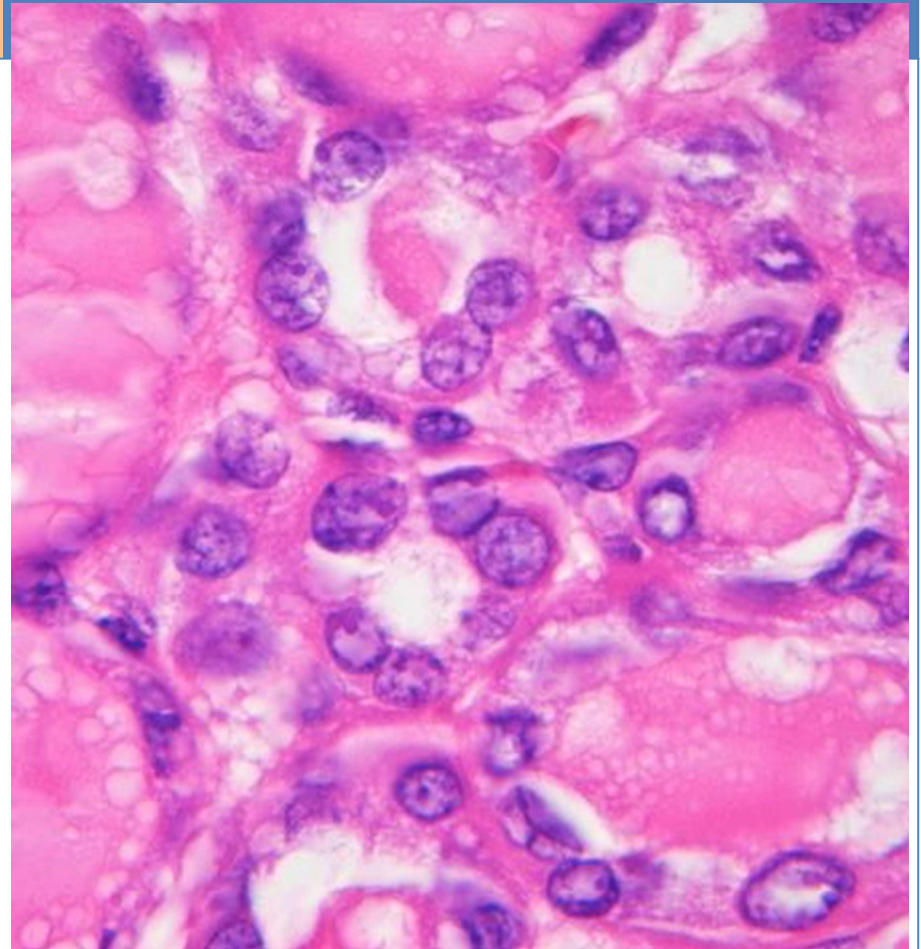
BRAF V600E EFVPTC



**Exclusion criteria:
BRAF V600E, RET/PTC, TERT
promoter mutations**



RAS (+) or BRAF K601E NIFTP

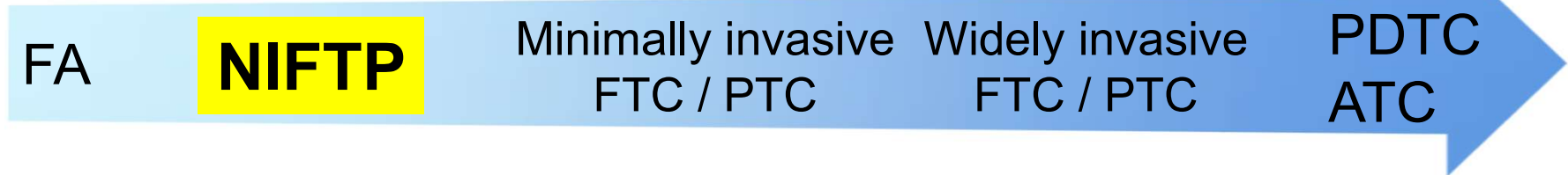


RAS mutations in thyroid cancer

FA	FTC / EFVPTC	PDTC	ATC
20-25%	30-45%	20-40%	10-20%

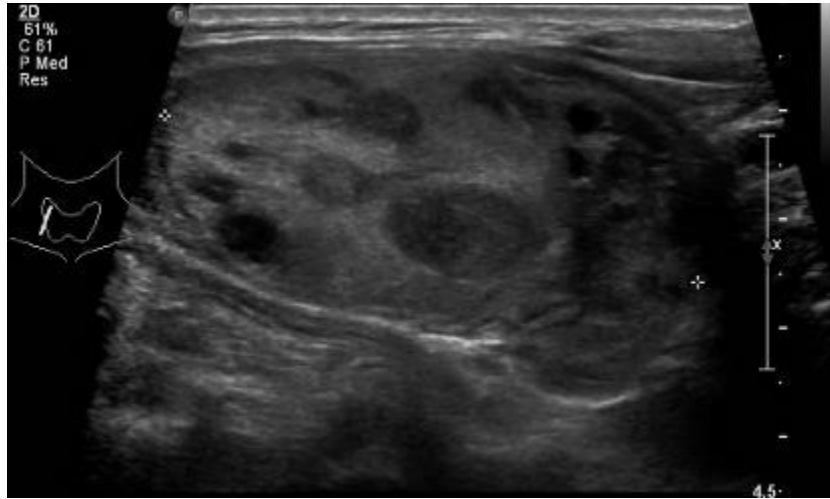
BMC Medicine (2016) 14:12

Putative progression of *RAS*-driven follicular-patterned thyroid tumors



Accumulation of secondary mutations as a result of chronic *RAS* activation

Case 6

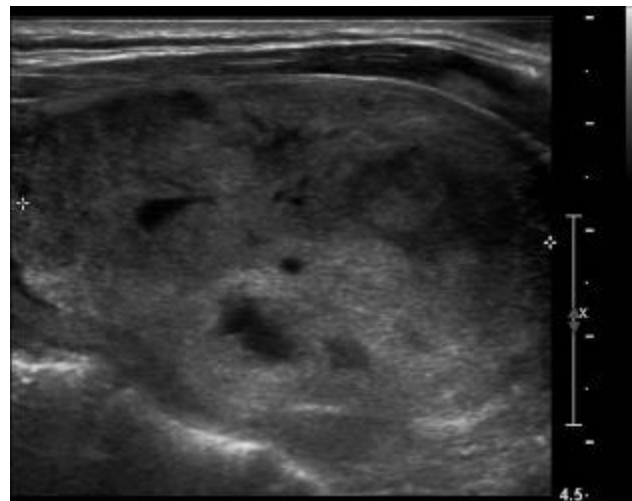
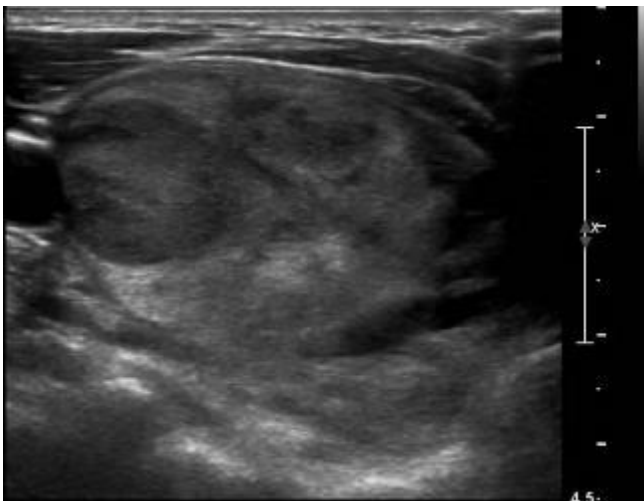


2013. 1.

F/74

24 x 36 x 51 mm

FNA: **Benign**

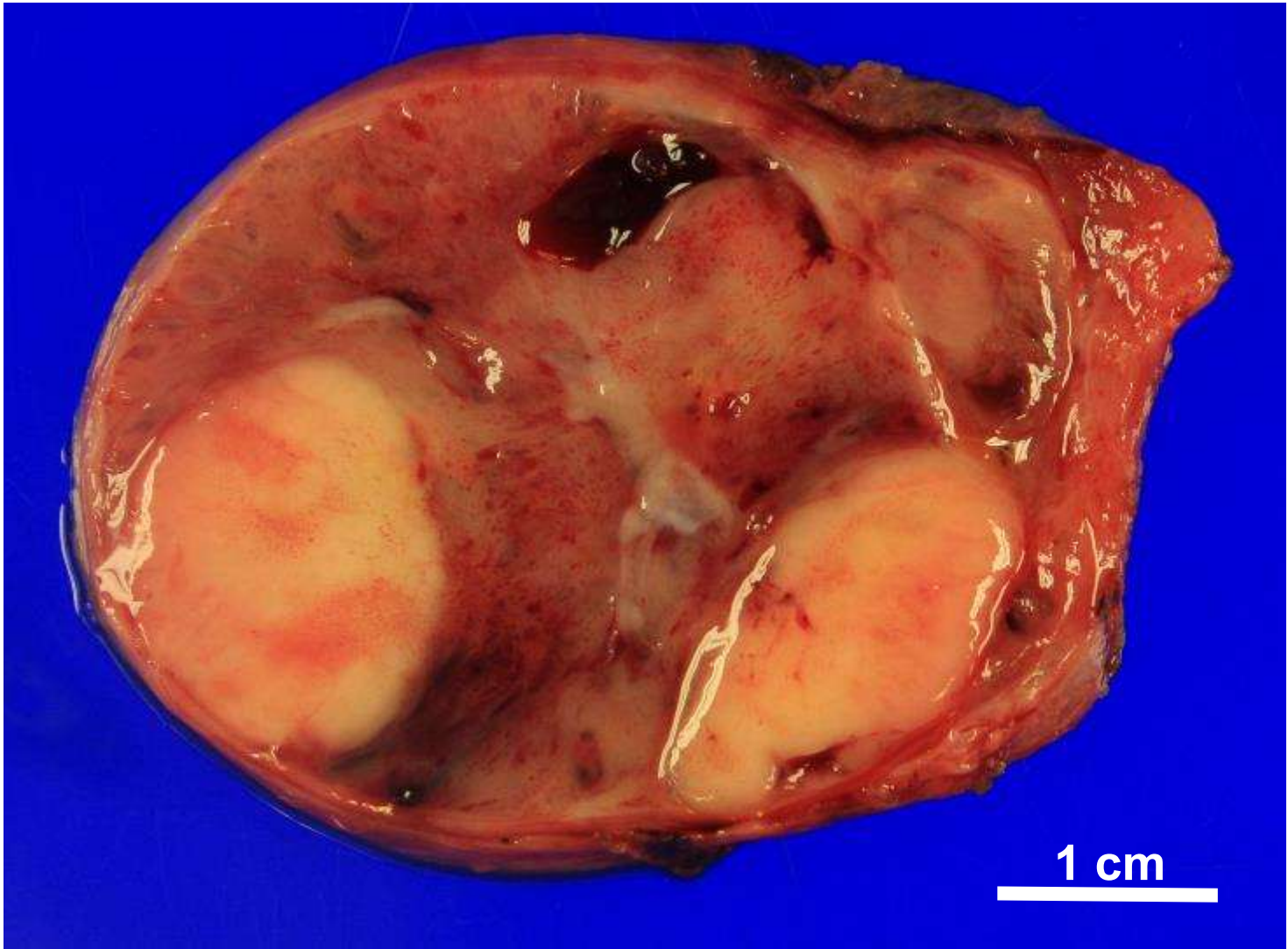


2014. 9.

40 x 32 x 50 mm

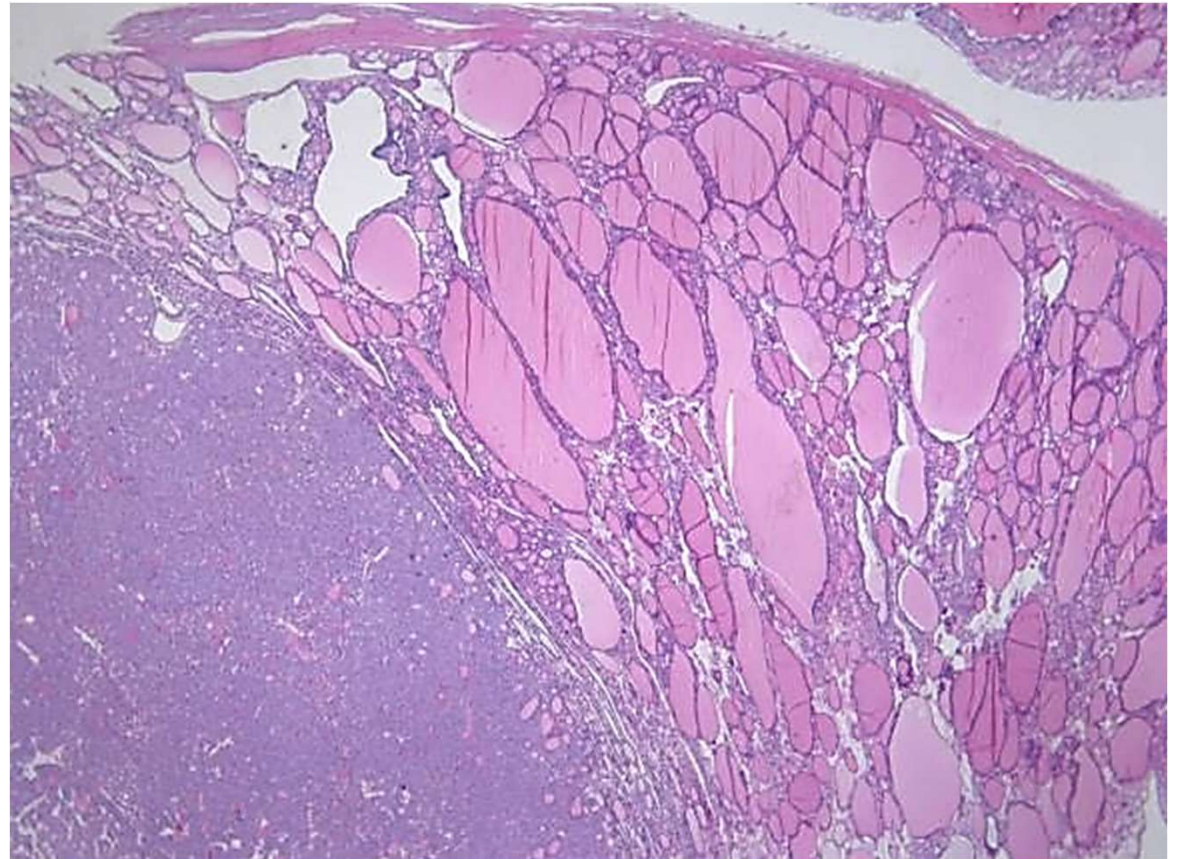
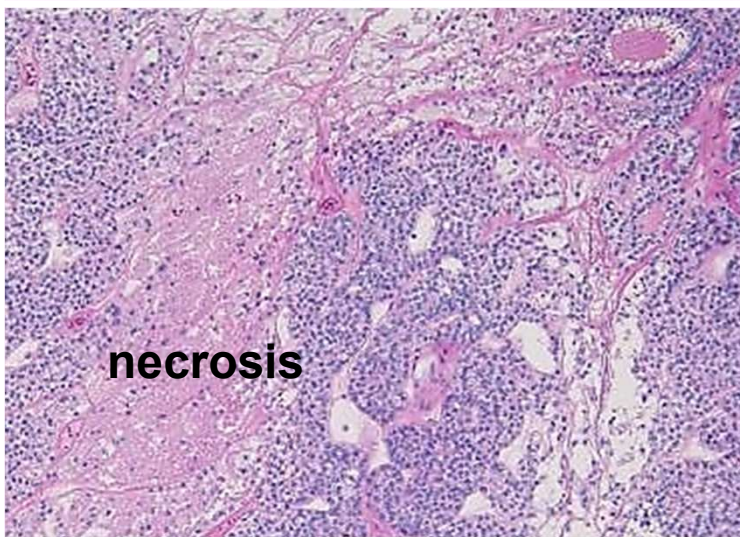
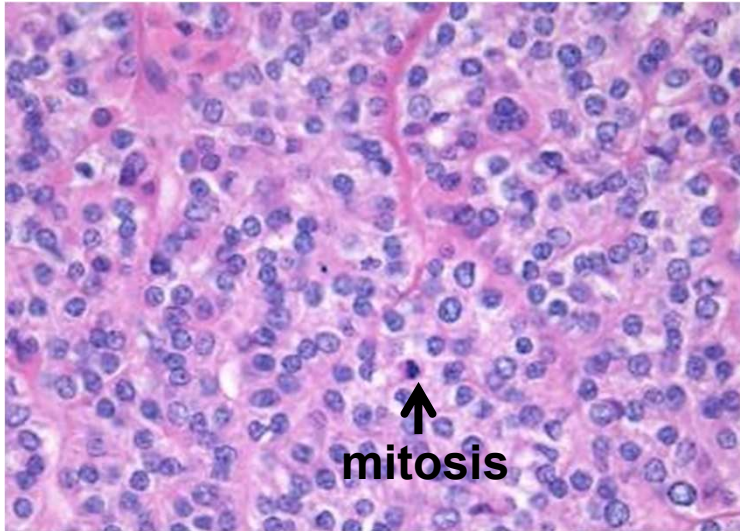
CNB:

Follicular neoplasm



**Poorly
differentiated
thyroid ca.**

- *NRAS* mutation
- *TERT* promoter mutation



Papillary thyroid carcinoma

- Malignant epithelial tumor showing evidence of follicular cell differentiation and a set of distinctive nuclear features.
- PTC is usually invasive.
- **Papillae, invasion or cytological features of papillary thyroid carcinoma are required.**

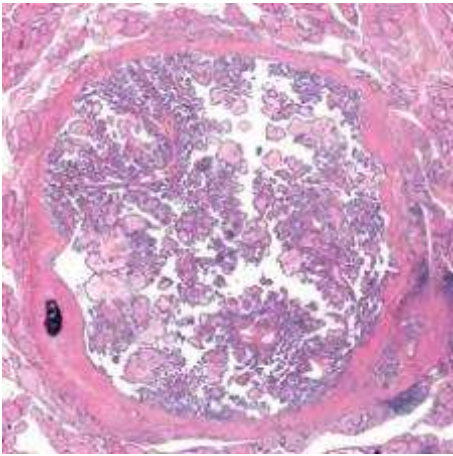
ICD-O codes

1) Papillary carcinoma	8260/3
2) Follicular variant of PTC	8340/3
3) Encapsulated variant of PTC	8343/3
4) Papillary microcarcinoma	8341/3
5) Columnar cell variant of PTC	8344/3
6) Oncocytic variant of PTC	8342/3

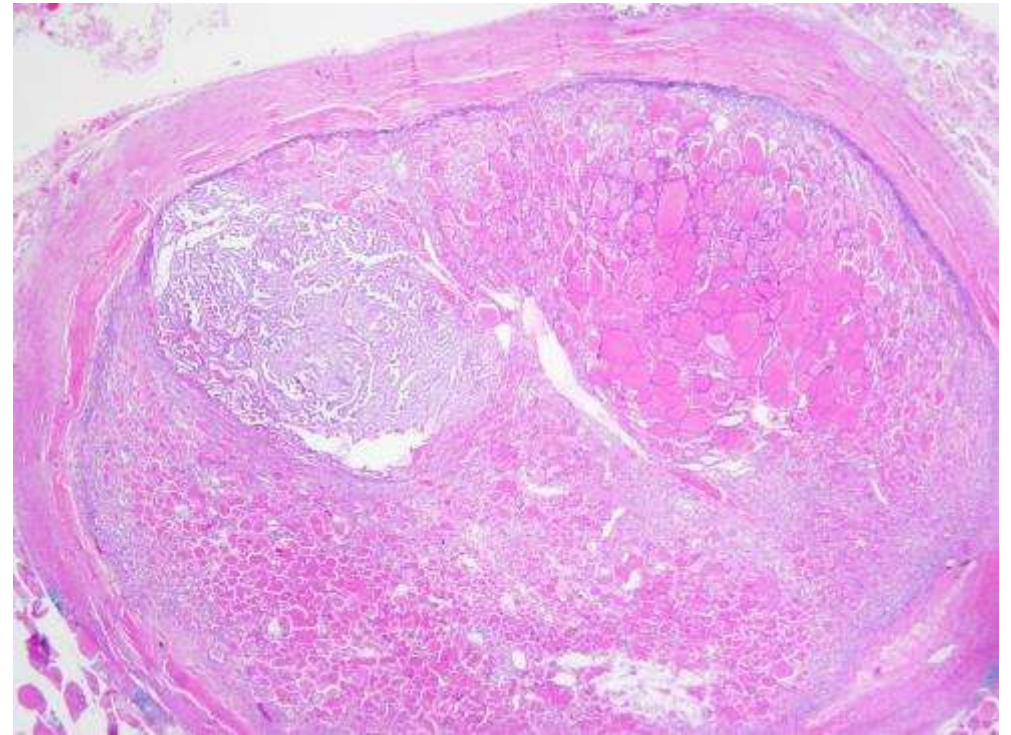
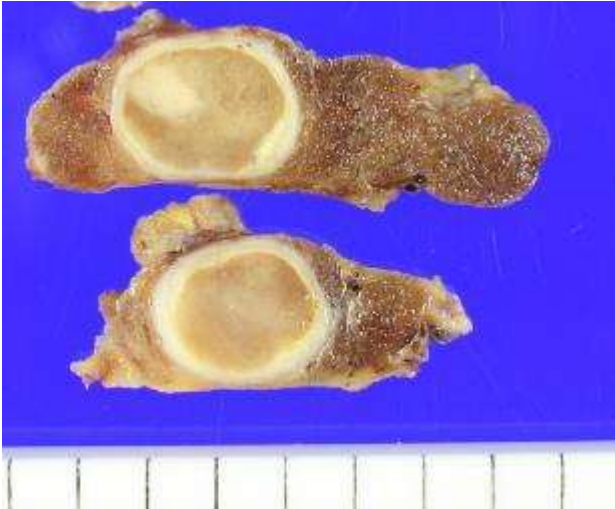
Variants of papillary thyroid carcinoma

- 1) Papillary microcarcinoma
- 2) Encapsulated variant
- 3) Follicular variant
- 4) Diffuse sclerosing variant
- 5) Tall cell variant
- 6) Columnar cell variant
- 7) Cribriform-morular variant
- 8) Hobnail variant
- 9) Papillary thyroid carcinoma with fibromatosis/fasciitis-like stroma
- 10) Solid/trabecular variant
- 11) Oncocytic variant
- 12) Spindle cell variant
- 13) Warthin-like variant

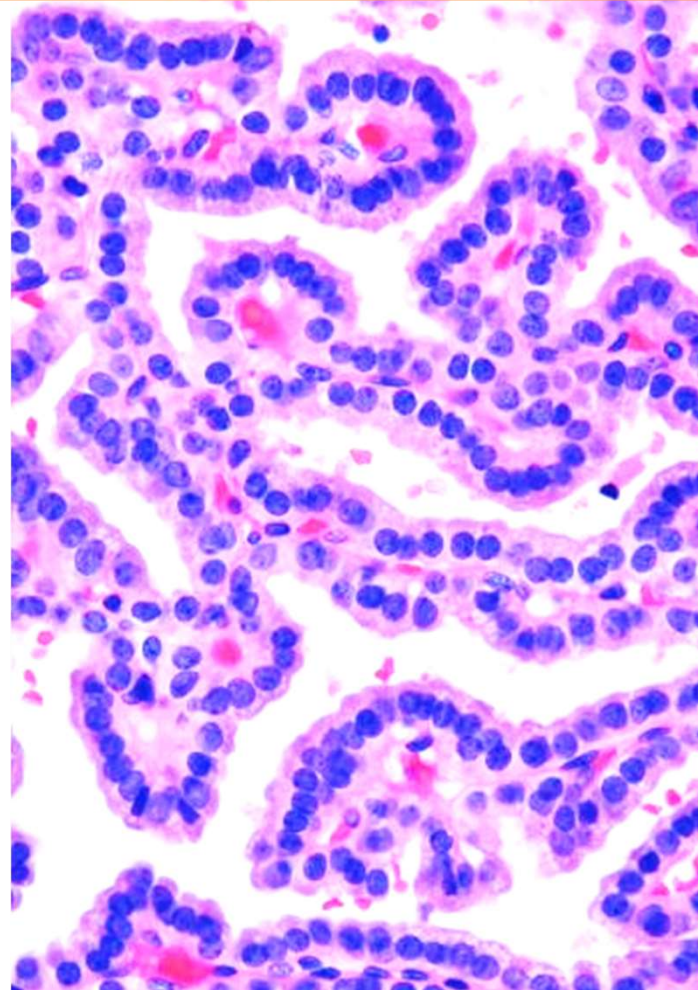
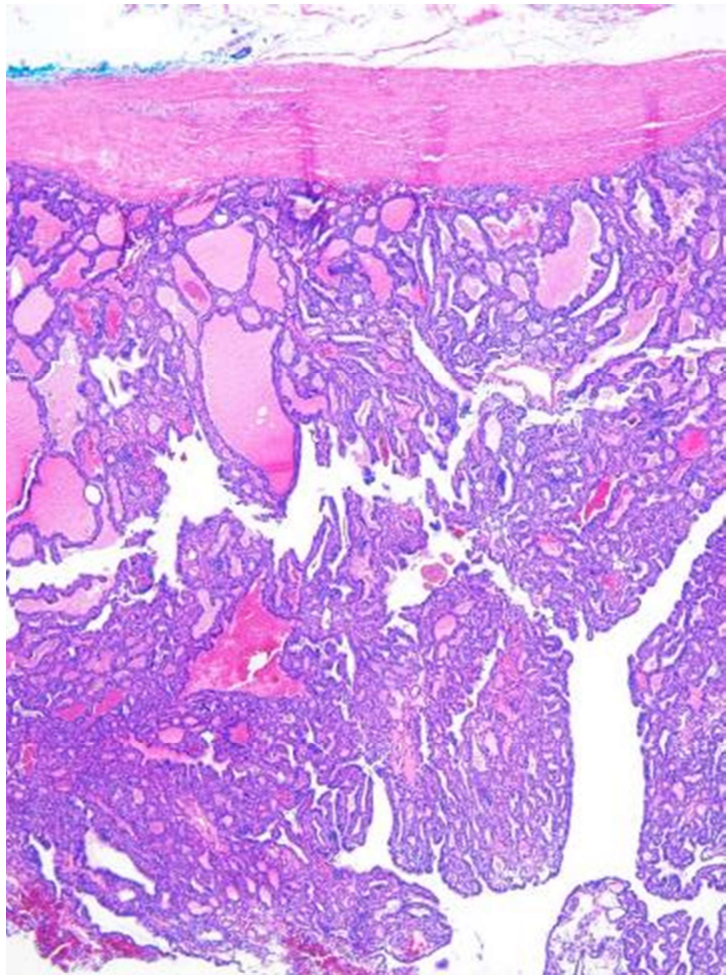
Encapsulated variant of PTC



- about 10% of all cases of PTC
- Blood borne metastases are rare
- Survival rate is nearly 100%



Main DDX: Follicular adenoma with papillary hyperplasia

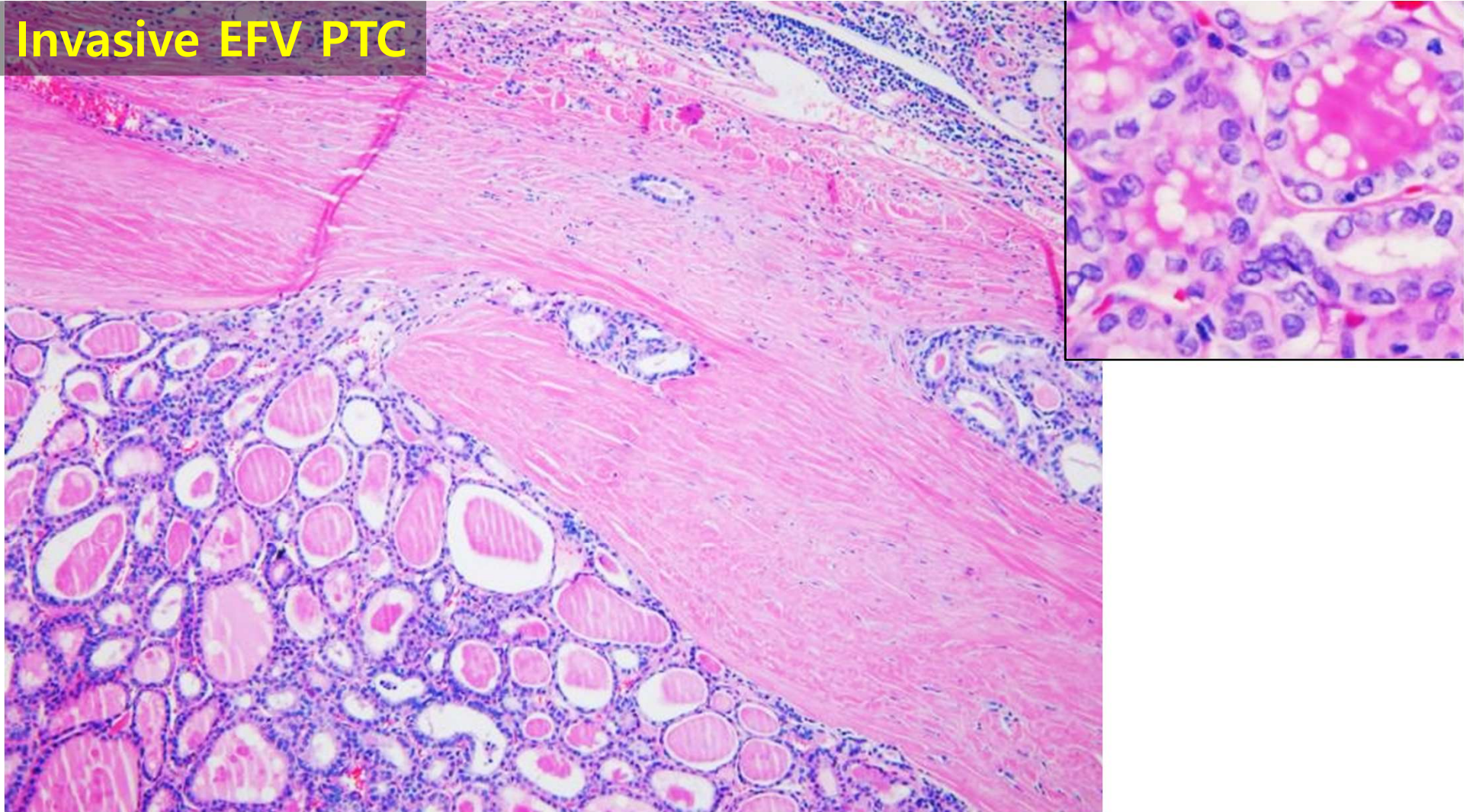


Follicular variant of PTC

Exclusively or almost exclusively follicular growth pattern

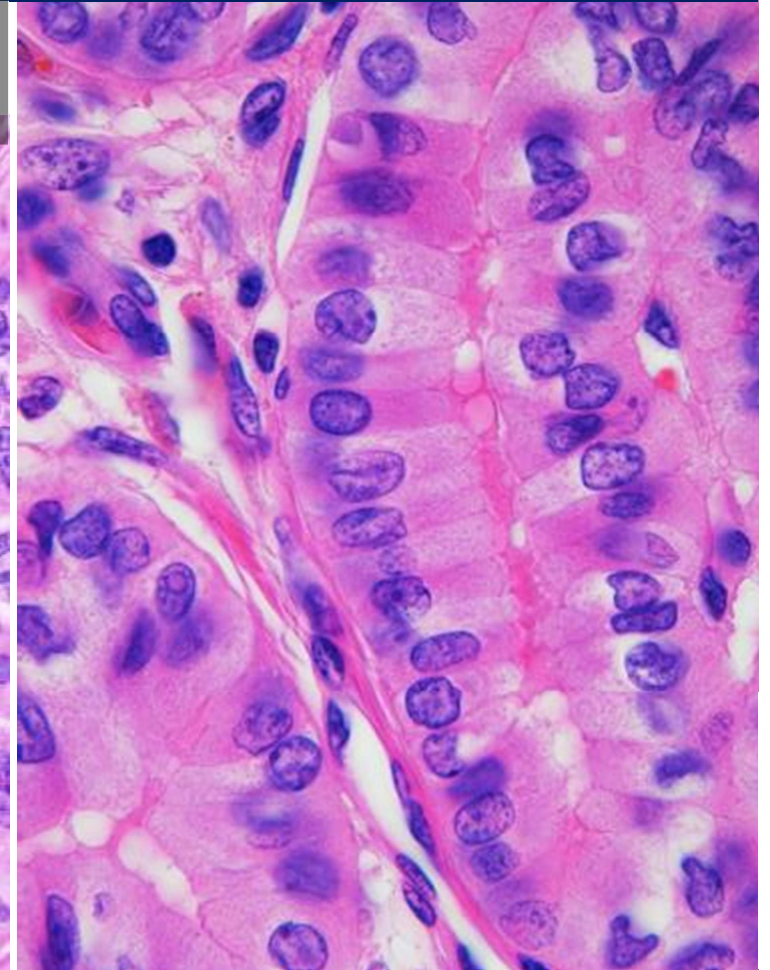
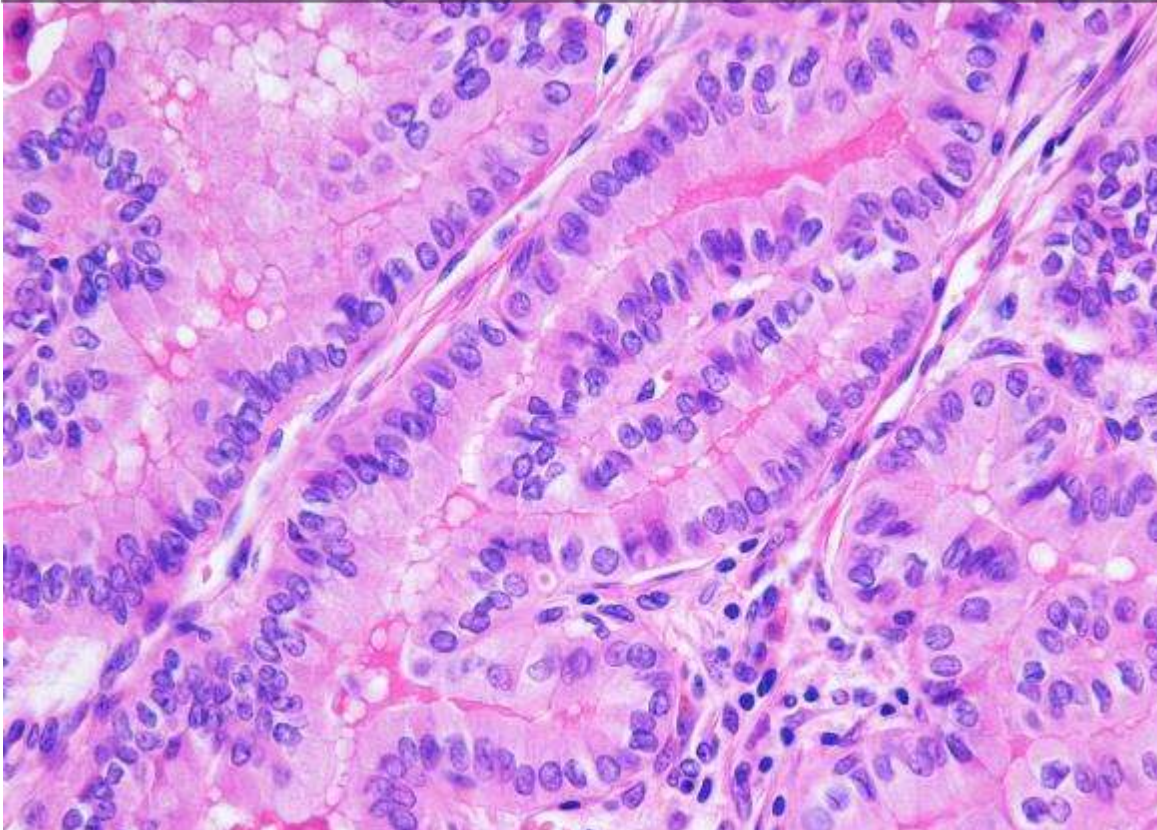
- 1) Infiltrative subtype**
- 2) Encapsulated subtype with invasion**
- 3) Macrofollicular variant
- 4) Diffuse or multinodular follicular variant

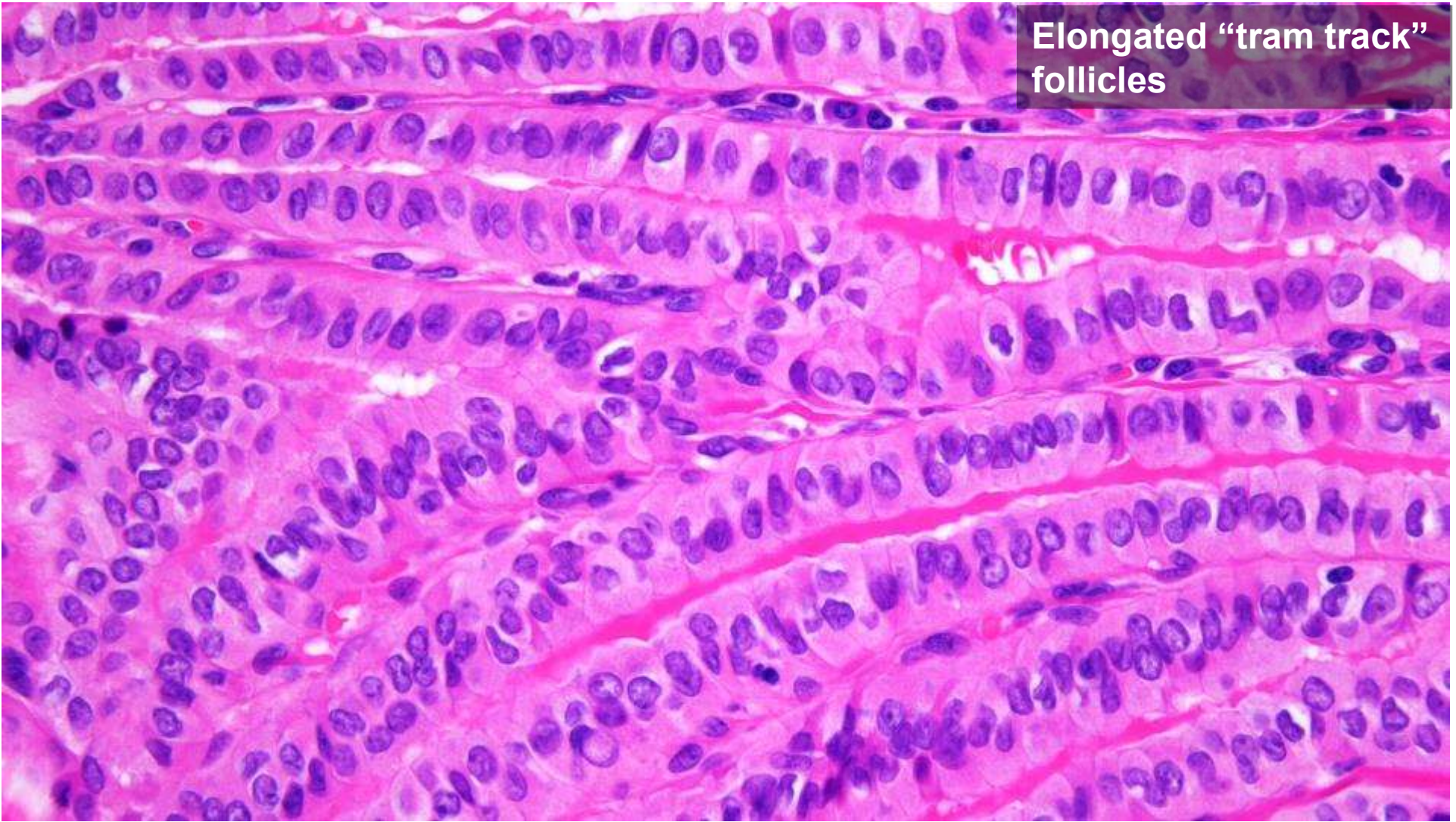
Invasive EFV PTC



Tall cell variant of PTC

- Two to three times taller
- Eosinophilic (oncocytic-like) cytoplasm, Distinct cell borders
- $\geq 30\%$ of all tumor cells

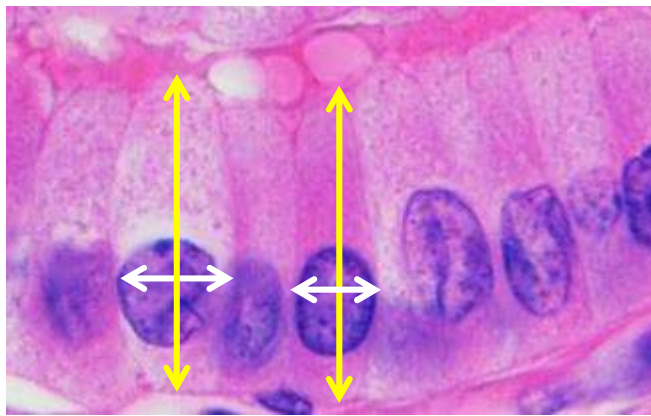




Elongated "tram track" follicles

Tall cells: Height to width ratio

two to three times taller



2.8:1

3.5:1

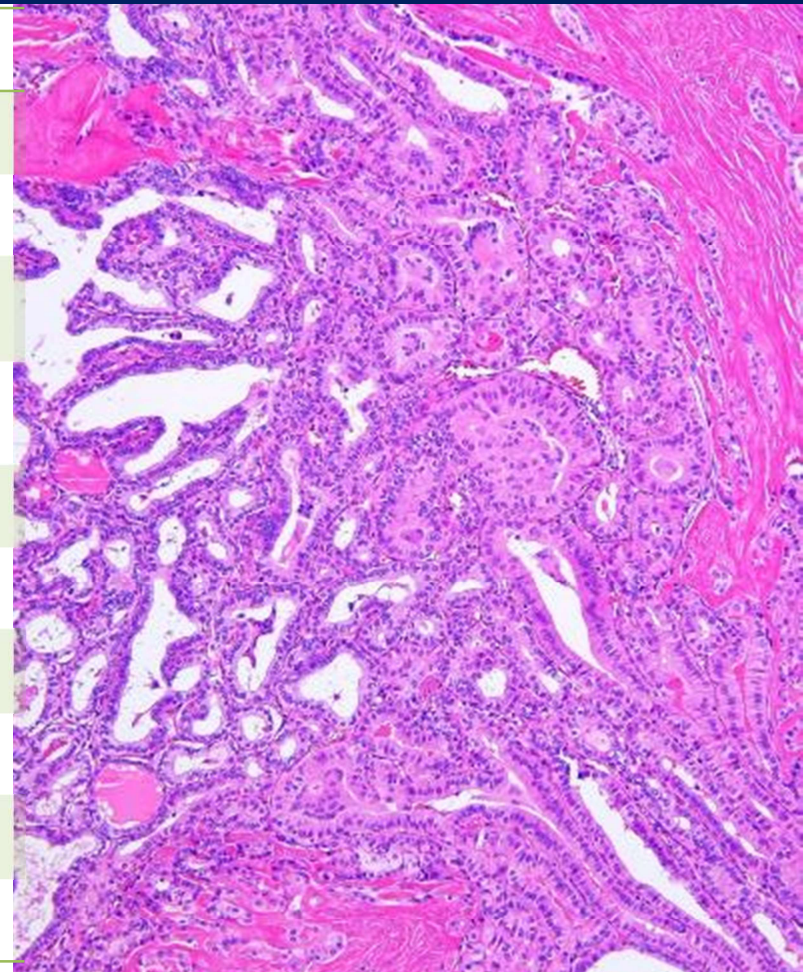


2.3:1

Variation depending on the plane of section

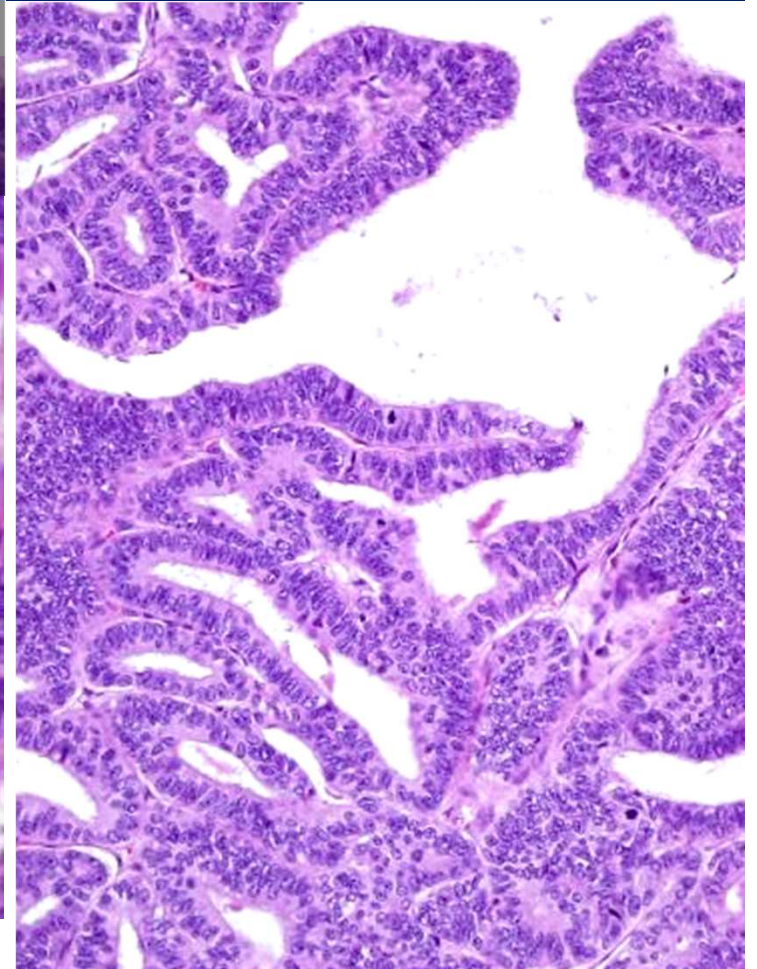
Historical evolution of the diagnostic criteria for TCV

Year	Author	H:W ratio	Tall cells %
2017	WHO	2~3:1	>30%
2015	ATA	3:1	>50%
2014	Jung CK et al.	3:1	> 50% TCV, 10-50% TCF
2014	Ganly et al.	2:1	>50% TCV, 30-49% TCF
2008	Ito et al	3:1	>50%
2007	Ghossein & LiVolsi	2:1	>50%
2004	WHO	3:1	No %
1996	Ostrowski & Merino	2:1	>70%
1988	Johnson et al.	2:1	>30%
1976	Hawk & Hazard	2:1	No %

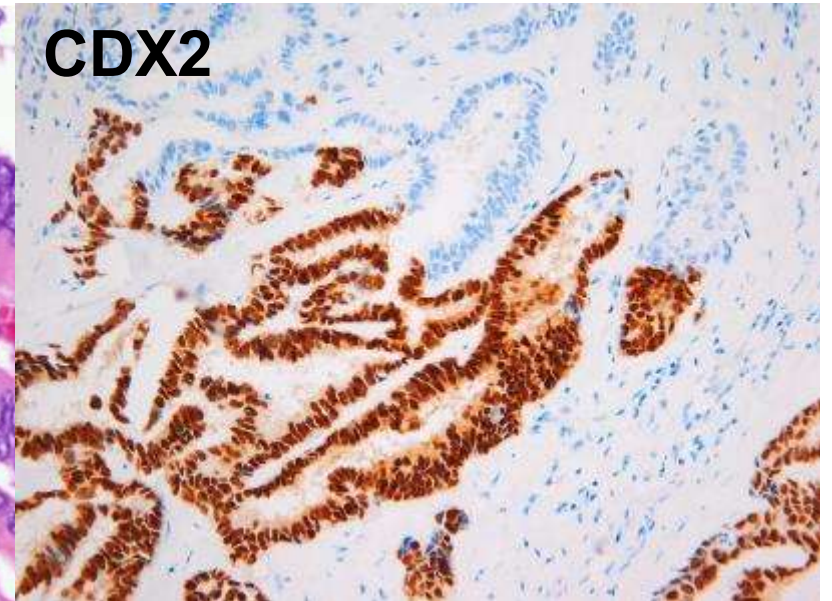
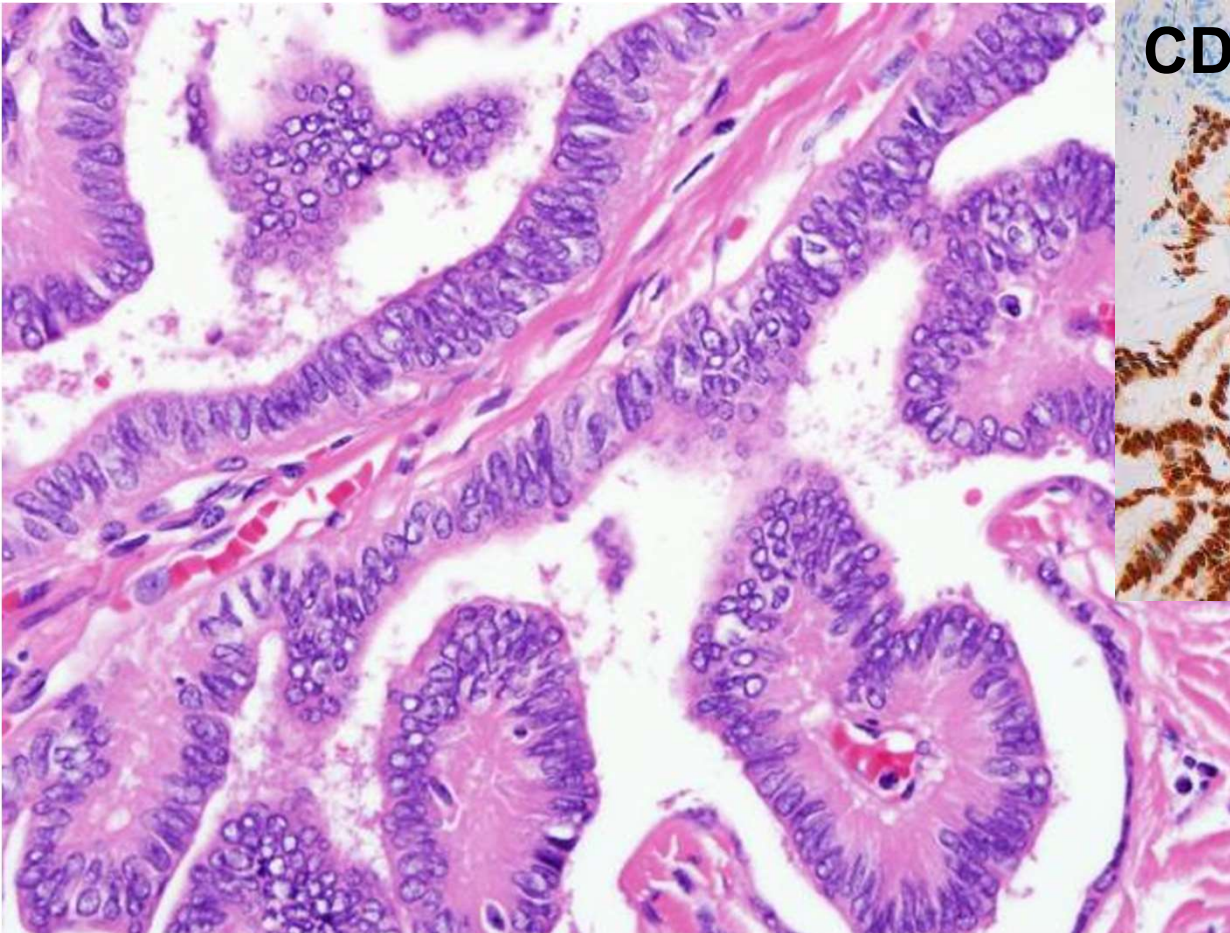


Columnar cell variant of PTC

- lack the conventional nuclear features of PTC
- pseudostratified epithelium,
- subnuclear vacuolization or clear cytoplasm
- CDX2(+)

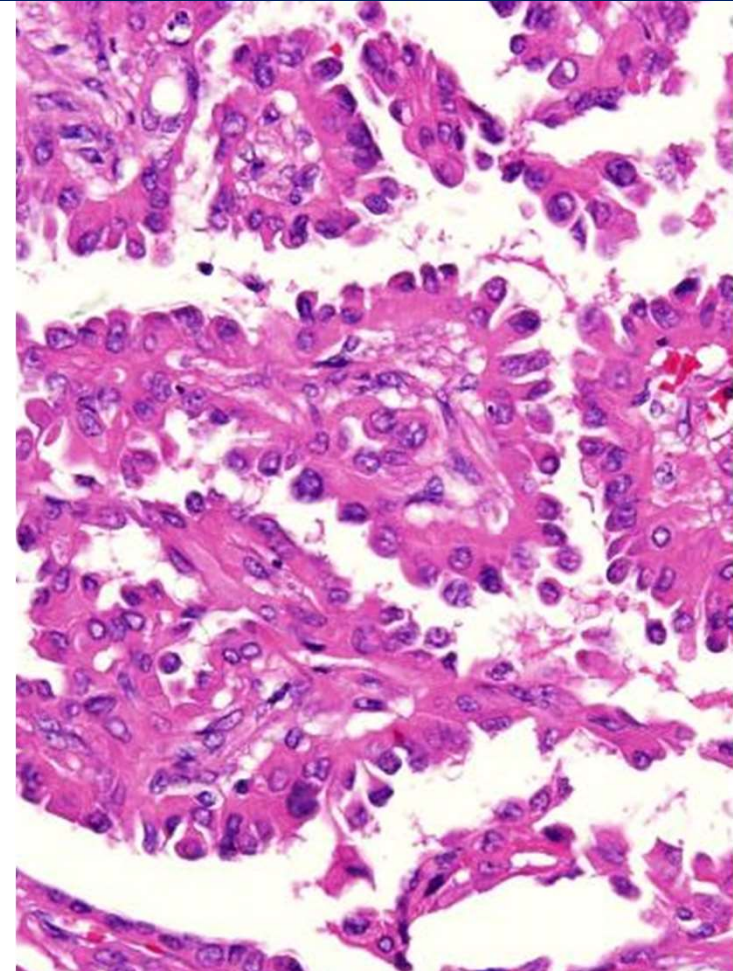
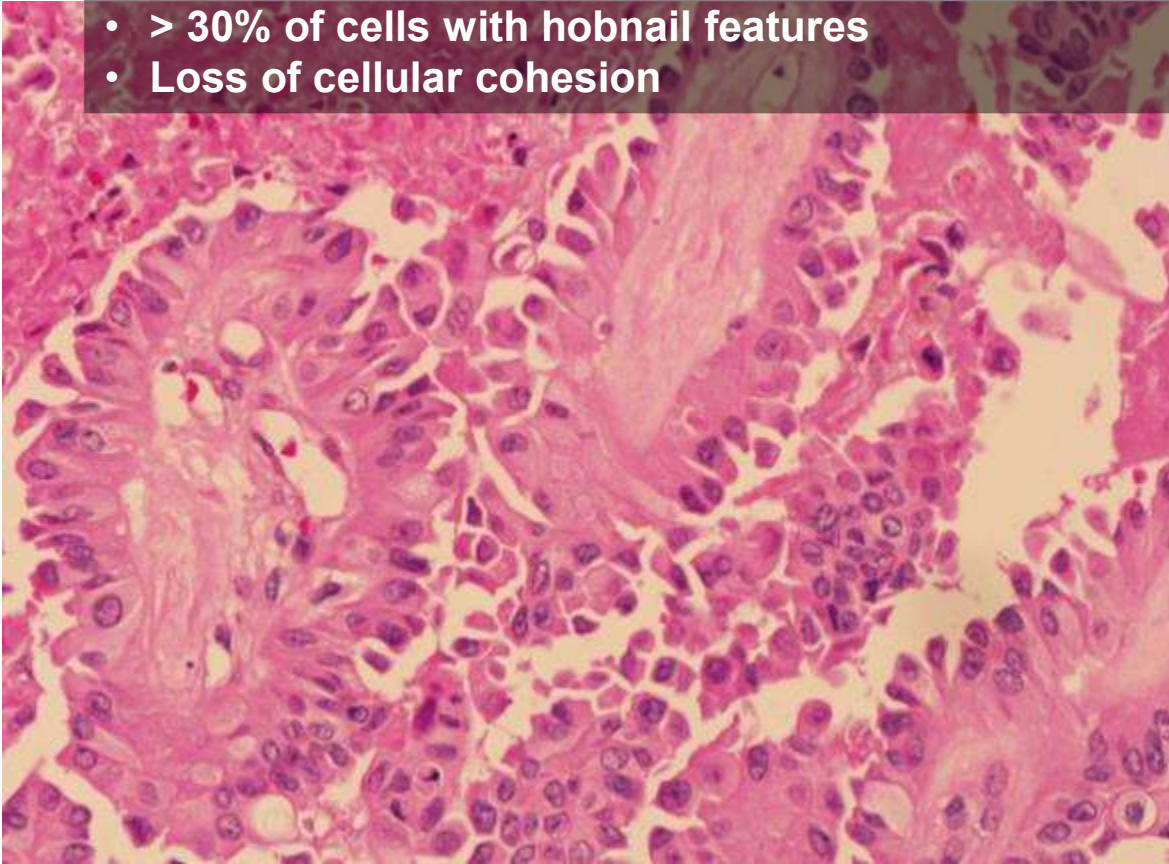


Columnar cell variant of PTC



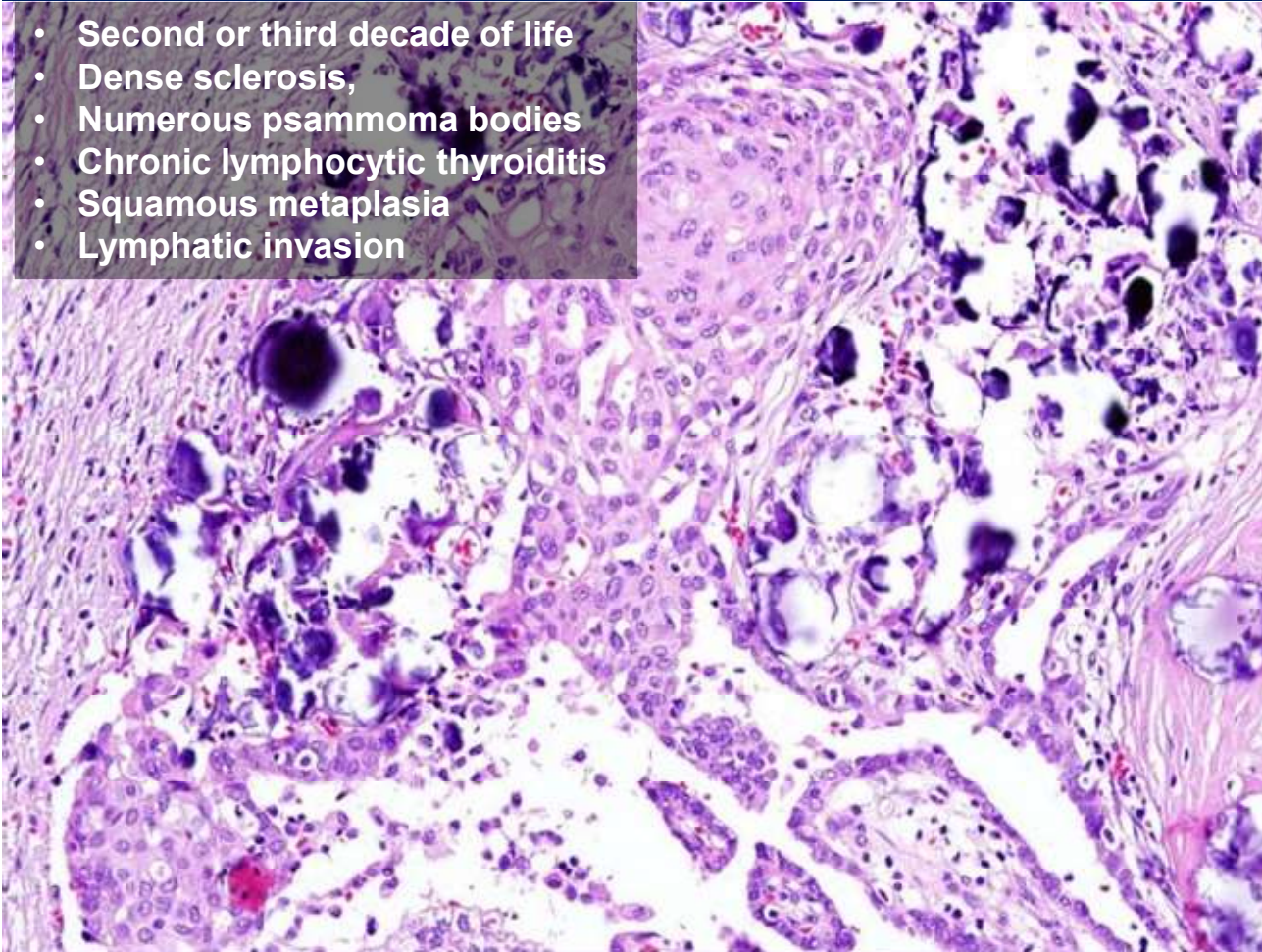
Hobnail variant

- Apically located nuclei with prominent nucleoli
- Eosinophilic cytoplasm
- > 30% of cells with hobnail features
- Loss of cellular cohesion

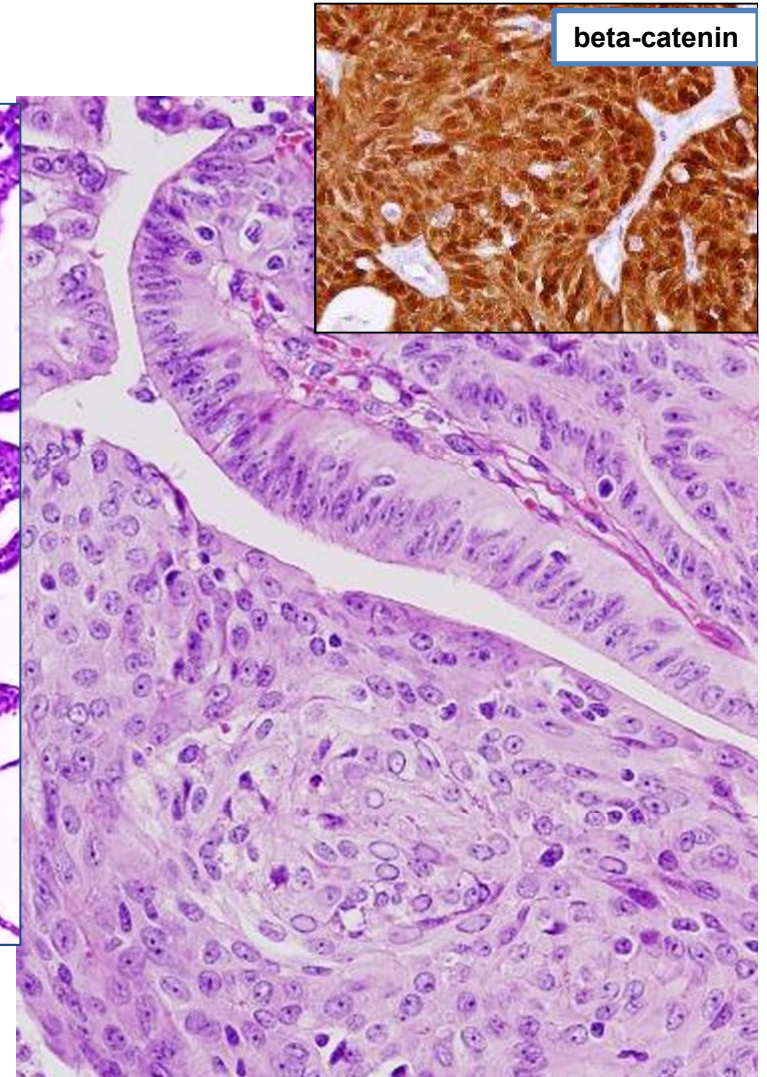
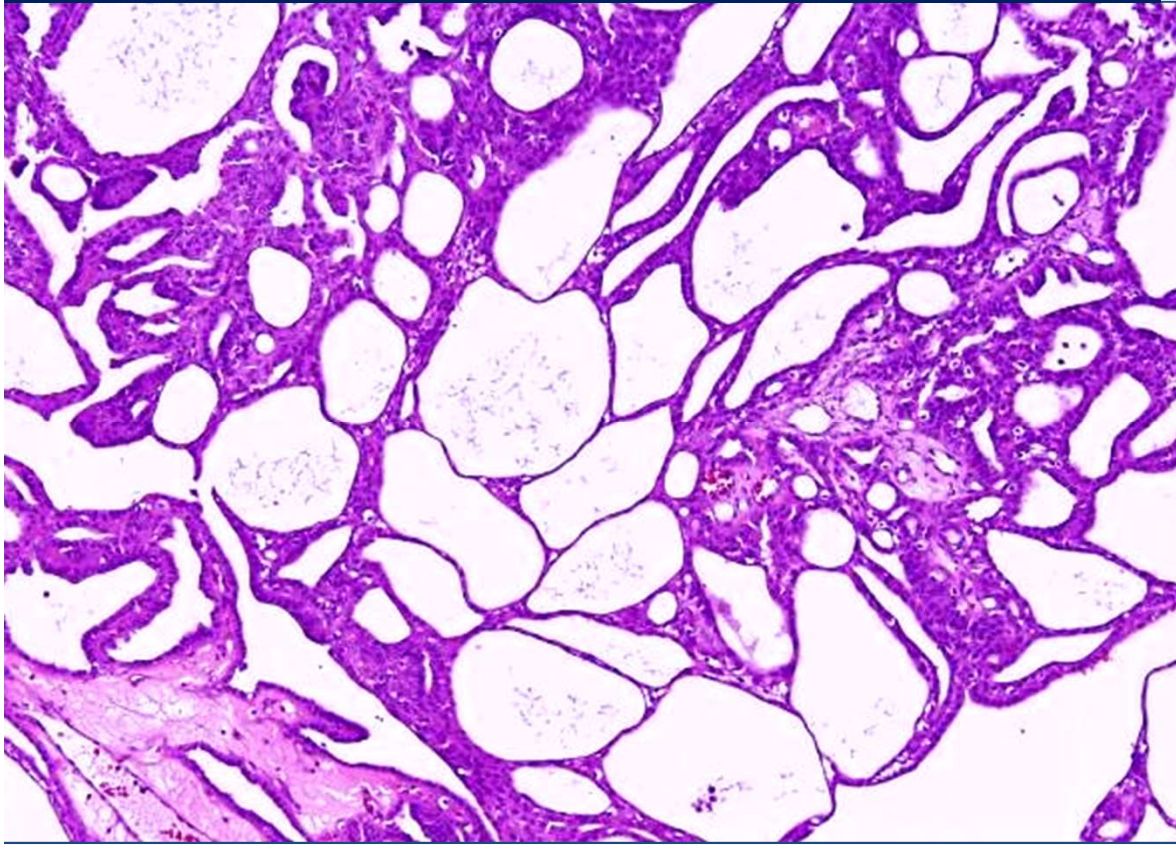


Diffuse sclerosing variant

- Second or third decade of life
- Dense sclerosis,
- Numerous psammoma bodies
- Chronic lymphocytic thyroiditis
- Squamous metaplasia
- Lymphatic invasion

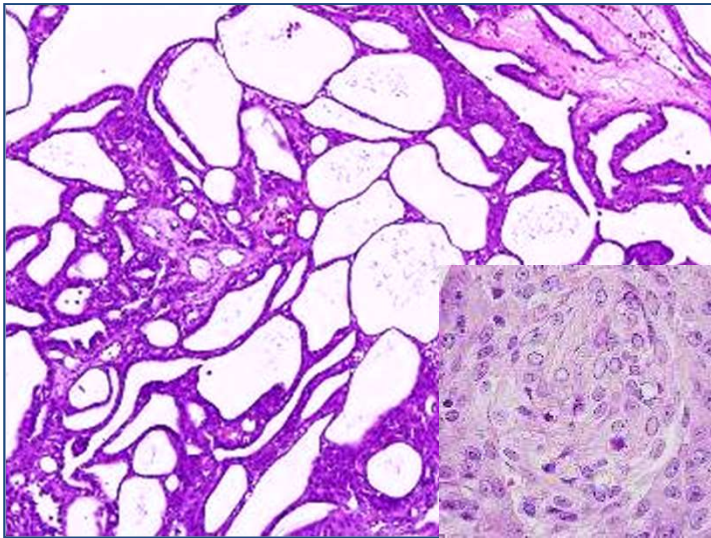


Cribriform-morular variant



Hereditary Thyroid cancer

- Medullary thyroid cancer
- Familial non-medullary thyroid cancer
- Familial adenomatous polyposis , Cowden's disease , Werner's syndrome and Carney complex



Cribriform-Morular Variant of PTC

- Young women
- **FAP: ~40%**
- ***APC*, *CTNNB1*** mutations
- no *BRAF* mutation

Risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy

High Risk
*Gross extrathyroidal extension,
 incomplete tumor resection, distant metastases,
 or lymph node >3 cm*

Intermediate Risk
*Aggressive histology, minor extrathyroidal
 extension, vascular invasion,
 or > 5 involved lymph nodes (0.2-3 cm)*

Low Risk
*Intrathyroidal DTC
 ≤ 5 LN micrometastases (< 0.2 cm)*



- FTC, extensive vascular invasion (≈ 30-55%)
- pT4a gross ETE (≈ 30-40%)
- pN1 with extranodal extension, >3 LN involved (≈ 40%)
- PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)
- pN1, any LN > 3 cm (≈ 30%)
- PTC, extrathyroidal, BRAF mutated* (≈ 10-40%)
- PTC, vascular invasion (≈ 15-30%)
- Clinical N1 (≈20%)
- pN1, > 5 LN involved (≈20%)
- Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈10%)
- pT3 minor ETE (≈ 3-8%)
- pN1, all LN < 0.2 cm (≈5%)
- pN1, ≤ 5 LN involved (≈5%)
- Intrathyroidal PTC, 2-4 cm (≈ 5%)
- Multifocal PTMC (≈ 4-6%)
- pN1 without extranodal extension, ≤ 3 LN involved (2%)
- Minimally invasive FTC (≈ 2-3%)
- Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
- Intrathyroidal unifocal PTMC, BRAF mutated*, (≈ 1-2%)
- Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
- Unifocal PTMC (≈ 1-2%)

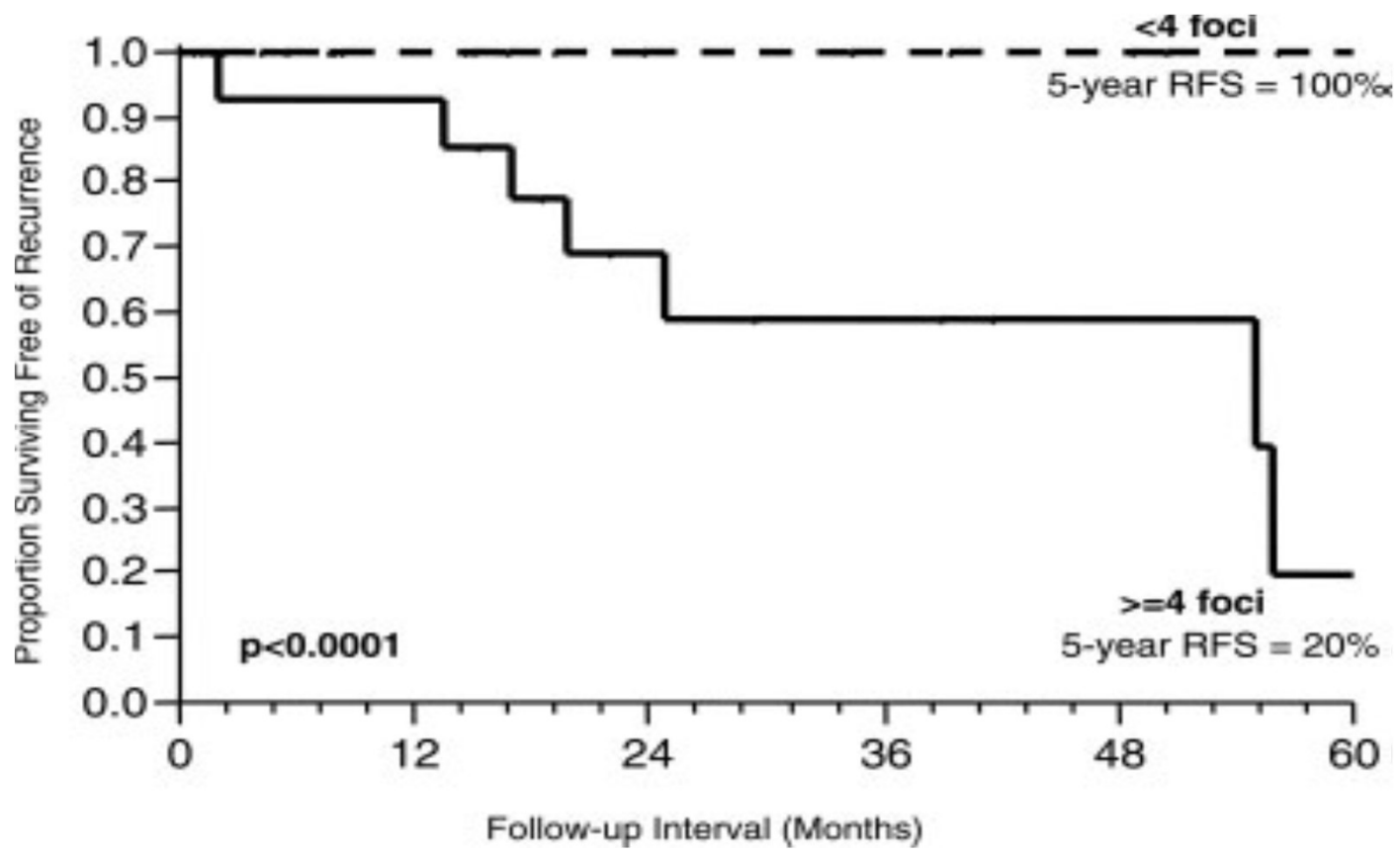
Follicular thyroid carcinoma

	ICD-O codes
Follicular thyroid carcinoma	8330/3
• Minimally invasive	8335/3
• Encapsulated angioinvasive	8339/3
• Widely invasive	8338/3

Classification follicular thyroid carcinoma

Traditional	AFIP 2014		WHO 2017
Minimally invasive	Minimally invasive	With capsular invasion	Minimally invasive
		With limited vascular invasion (< 4 vessels)	Encapsulated angioinvasive
		With extensive vascular invasion (≥ 4 vessels)	
Widely invasive	Widely invasive		Widely invasive

AFIP, Armed Forces Institute of Pathology



Cancer 2006;106:1669-76

Extensive vascular invasion (≥ 4 foci)

- Tumors with **limited invasion of vessels (< 4)** have a better prognosis than do those with **extensive vascular invasion**

Risk of structural disease recurrence

High Risk
*Gross extrathyroidal extension,
incomplete tumor resection, distant metastases,
or lymph node >3 cm*

Intermediate Risk
*Aggressive histology, minor extrathyroidal
extension, vascular invasion,
or > 5 involved lymph nodes (0.2-3 cm)*

FTC, extensive vascular invasion ($\approx 30-55\%$)

pT4a gross ETE ($\approx 30-40\%$)

pN1 with extranodal extension, >3 LN involved ($\approx 40\%$)

PTC, > 1 cm, TERT mutated \pm BRAF mutated* ($>40\%$)

pN1, any LN > 3 cm ($\approx 30\%$)

PTC, extrathyroidal, BRAF mutated* ($\approx 10-40\%$)

PTC, vascular invasion ($\approx 15-30\%$)

Clinical N1 ($\approx 20\%$)

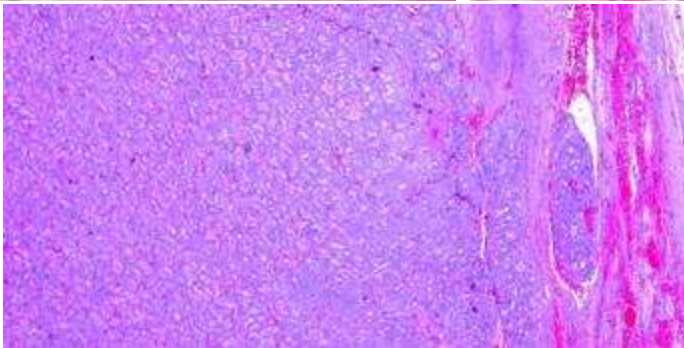
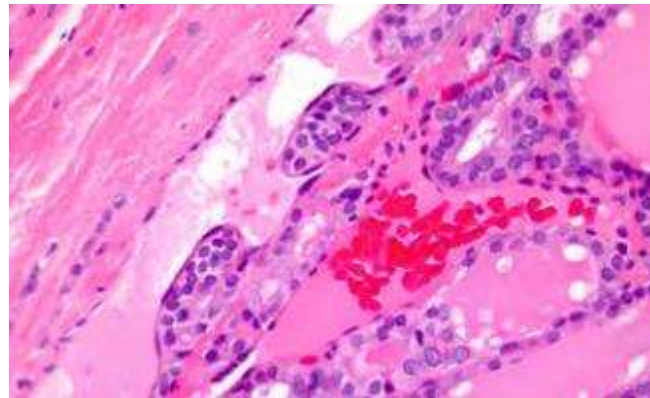
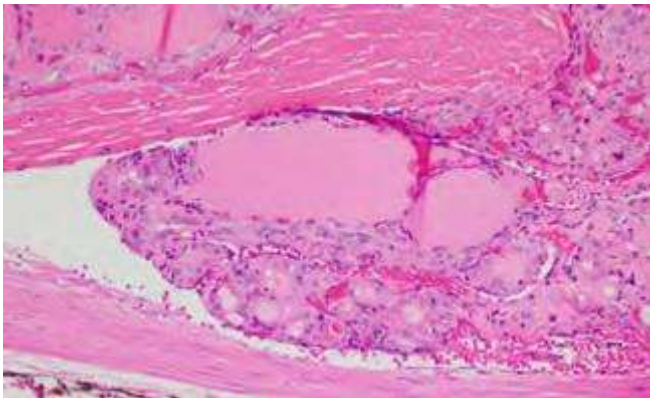
pN1, > 5 LN involved ($\approx 20\%$)

Intrathyroidal PTC, < 4 cm, BRAF mutated* ($\approx 10\%$)

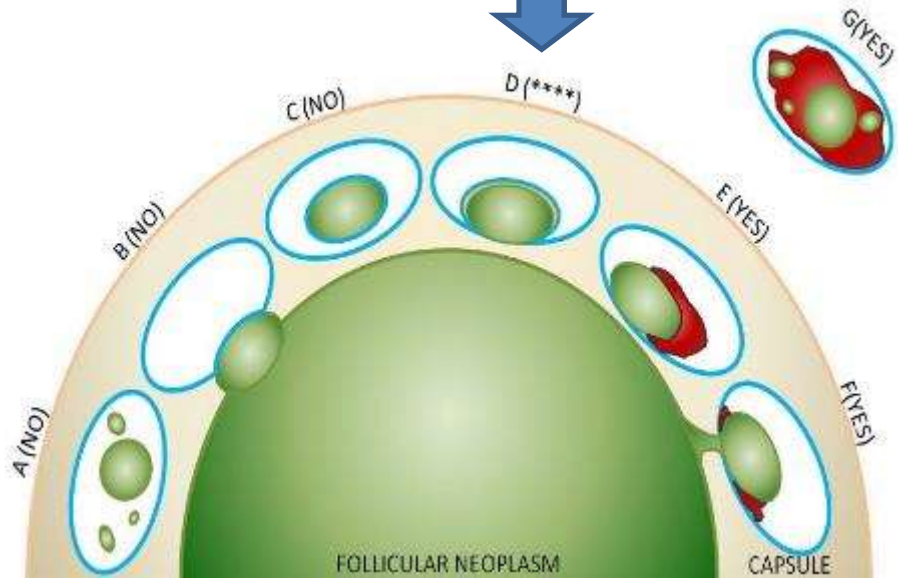
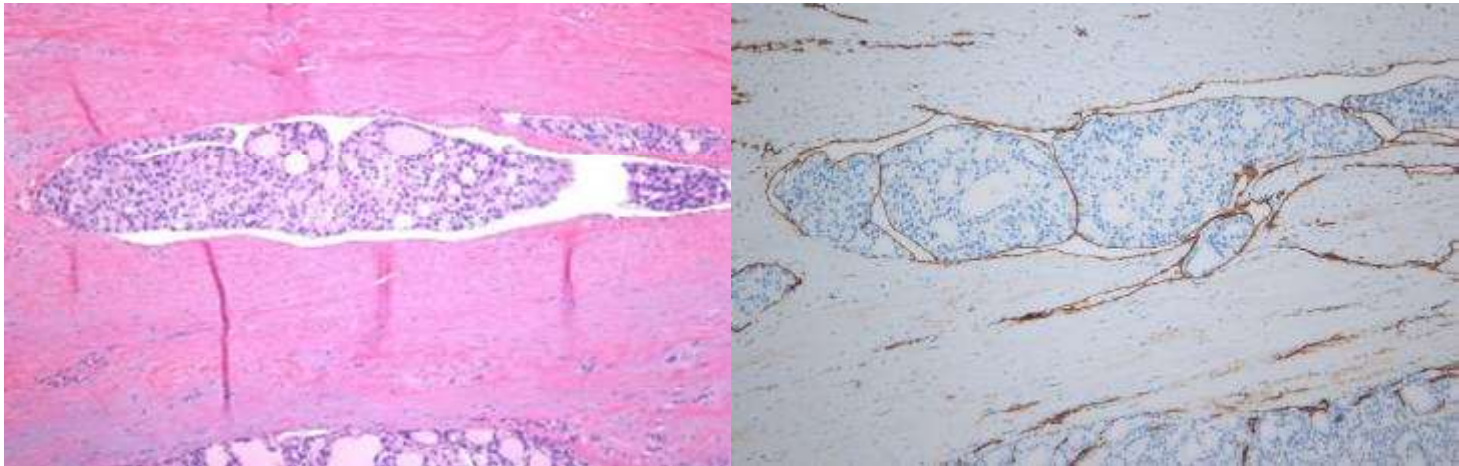
pT3 minor ETE ($\approx 3-8\%$)

Histopathology of FTC

- Capsular and/or vascular invasion
- Microfollicular, normofollicular, macrofollicular, and other patterns (e.g. cribriform)
- No nuclear features of PTC

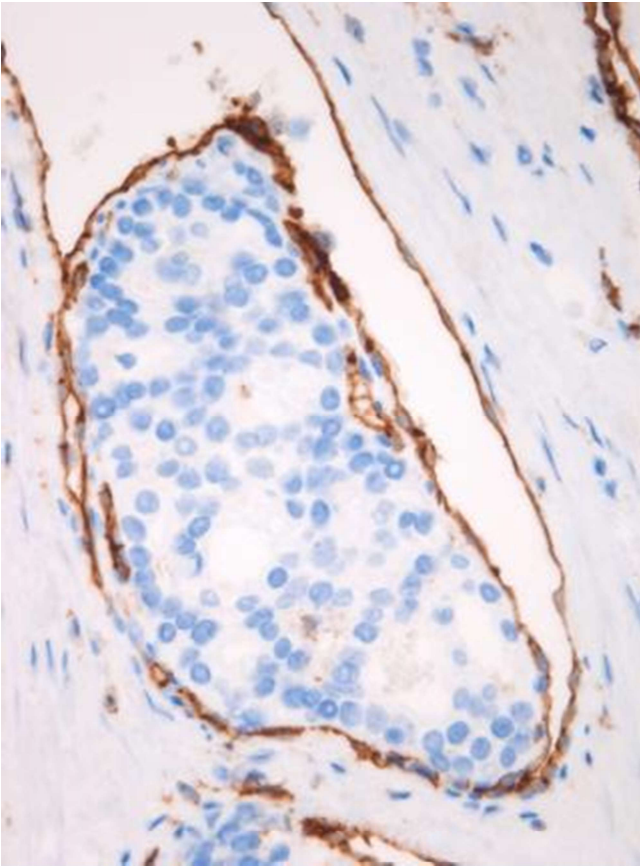


Intravascular tumor cells should be **adherent to the vessel walls**, either **covered by endothelium** or **in a context of thrombus or fibrin**

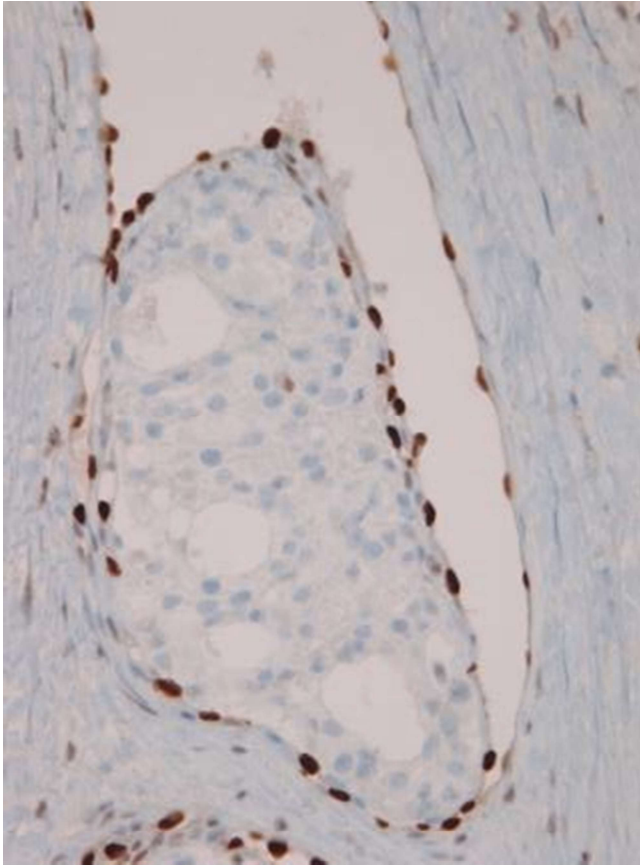


Endothelial Cell Markers

CD31/CD34



ERG/Fli-1



Encapsulated angioinvasive FTC

- Tumors with **limited invasion of vessels (< 4)** have a better prognosis than do those with **extensive vascular invasion**

Vascular invasion

- Armed Forces Institute of Pathology fascicle, 1992

: **focal (<4 invasive foci) and extensive (≥4 foci)**

- WHO

: vascular invasion is often prominent in widely invasive FTC, but alone, does not categorize an FTC as “widely invasive”

Widely invasive FTC

- **Extensive invasion of the thyroid and extrathyroidal soft tissues.**
- **Vascular invasion is often prominent, but alone, does not categorize an FTC as “widely invasive”**
- **More important than the extent of thyroid or soft tissue invasion is the identification of extensive angioinvasion**

Multinodular invasive growth



Variants of FTC

- 1) Clear cell variant: >50% clear cells**
- 2) Signet-ring cell type**
- 3) FTC with a glomeruloid pattern: round to oval epithelial tufts growing within them, mimicking a renal glomerulus**
- 4) Spindle cell FTC**

Hürthle (oncocytic) cell tumors

>75% of the tumor is composed of Hürthle cells

Hürthle cell adenoma	8290/0
Hürthle cell carcinoma	8290/3

Different from non- Hürthle cell thyroid carcinomas

- HCC can spread to cervical nodes
- HCC had larger tumors, higher-stage disease, and lower survival rates
- More common in men
- Older age

The revised Bethesda System

Diagnostic category		Risk of malignancy (%)
I. Nondiagnostic or Unsatisfactory		5-10
II. Benign		0-3
III. AUS/FLUS	~5-15 →	~10-30
IV. FN/SFN	15-30 →	25-40
V. Suspicious for malignancy		50-75
VI. Malignant		97-99

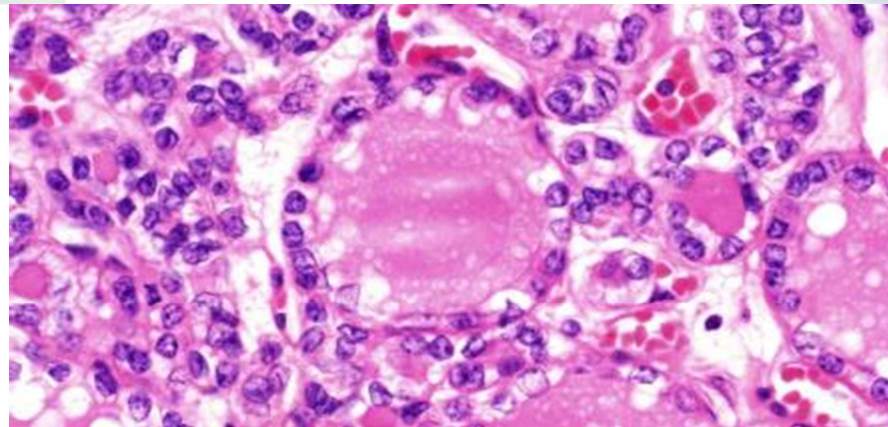
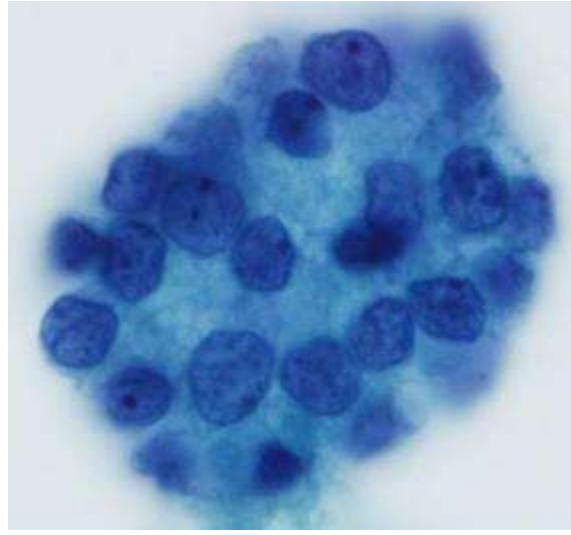
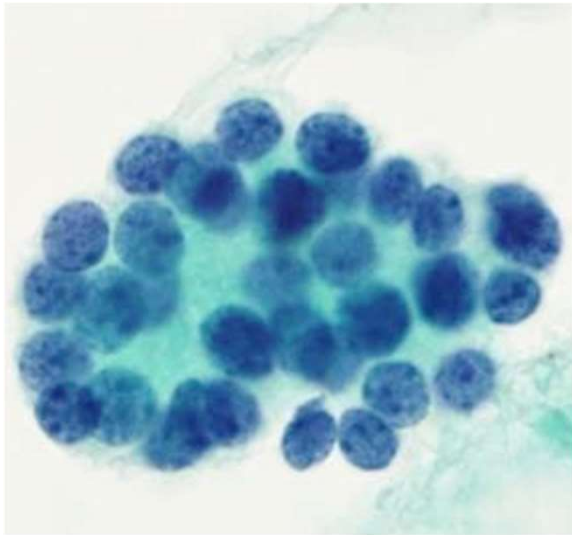
The revised Bethesda System

Diagnostic category	Risk of malignancy (%)	Risk of malignancy If NIFTP is not CA (%)
I. Nondiagnostic or Unsatisfactory	5-10	No change
II. Benign	0-3	No change
III. AUS/FLUS	~10-30	6-18
IV. FN/SFN	25-40	10-40
V. Suspicious for malignancy	50-75	45-60
VI. Malignant	97-99	94-96

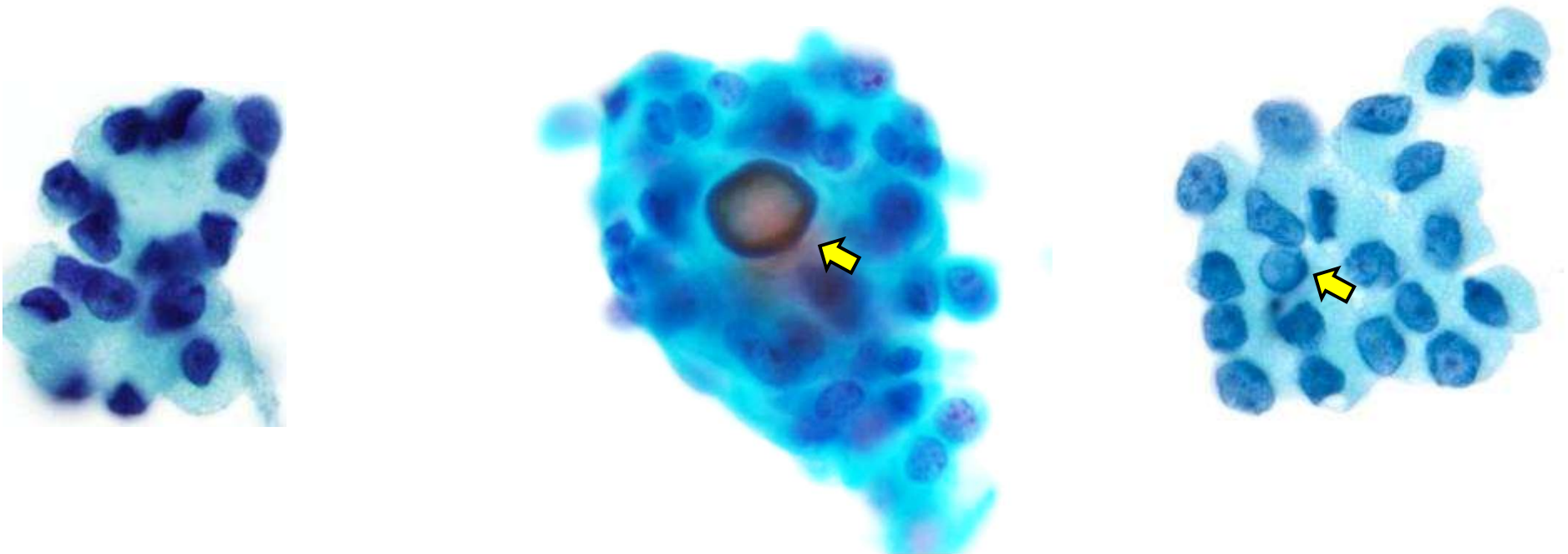
Anticipated changes in the implied risk of malignancy of TBSRTC diagnostic categories and recommendations for comments due to the surgical pathology diagnosis of NIFTP

Diagnostic category	Risk of malignancy with NIFTP (%)	Optional note
Nondiagnostic or Unsatisfactory	No significant change	None
Benign	No significant change	None
AUS or FLUS	6-18	None
Follicular neoplasm or Suspicious for a FN	10-40	The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma, including its recently described indolent counterpart NIFTP.
Suspicious for malignancy	45-60	The cytomorphic features are suspicious for a follicular variant of papillary thyroid carcinoma and its recently described indolent counterpart NIFTP.
Malignant	94-96	A small proportion of cases (~3–4%) diagnosed as malignant – compatible with papillary thyroid carcinoma – may prove to be NIFTP on histopathologic examination.

AUS/FLUS, FN/SFN, or suspicious for PTC?



- It is desirable to eliminate from the malignant category tumors likely to harbor a NIFTP.
- A suspected PTC with an exclusively follicular architecture, especially one that lacks intranuclear cytoplasmic **pseudoinclusions** and **psammoma bodies** (e.g., many follicular variants of PTC), is best interpreted as “suspicious for malignancy” rather than malignant.



Updated AJCC/TNM system

downstages a significant number of patients by

- 1) raising the age cutoff from 45 to 55 years of age at diagnosis
- 2) removing microscopic extrathyroidal extension from the definition of T3 disease

Extrathyroidal extension (ETE)

Minor extrathyroid extension was removed from the definition of T3 disease

Minor ETE: not clinically appreciated

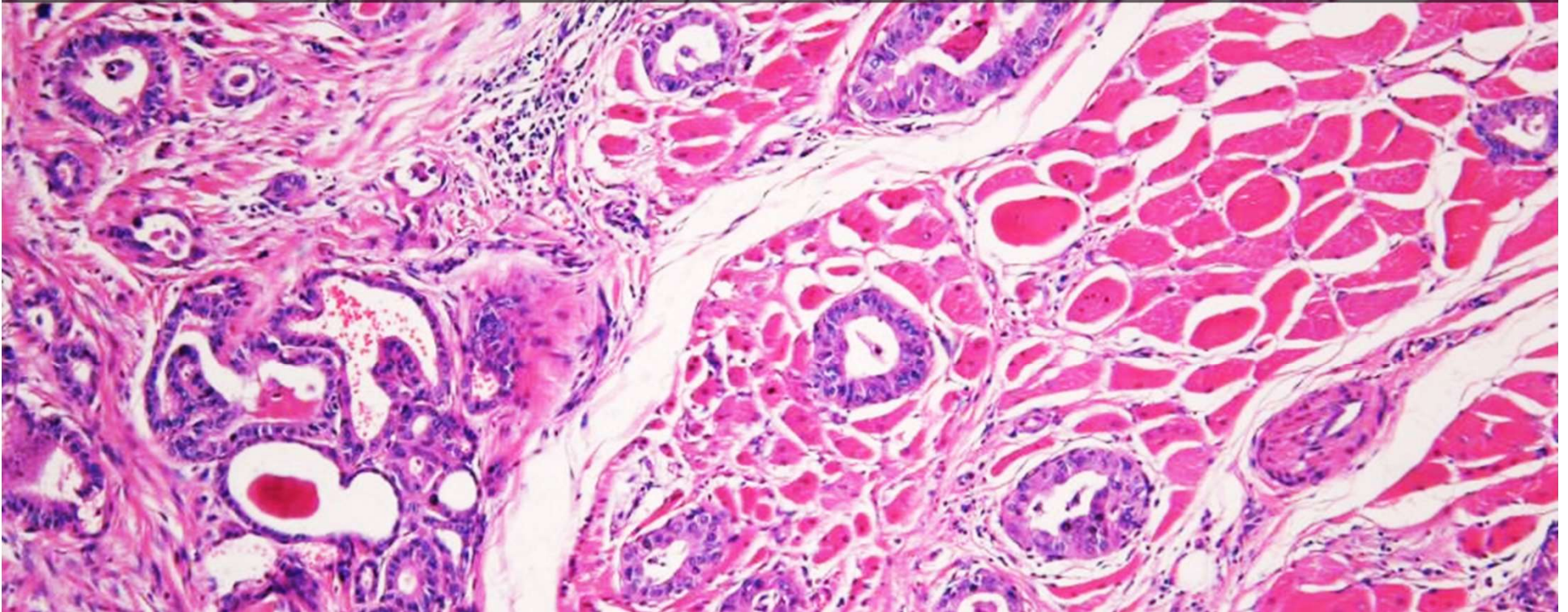
- Involvement of perithyroidal adipose tissue, strap muscles, nerves, or small vascular structures detected **only by microscopy**
- Lack of prognostic significance
- T1 or T2 disease

Gross ETE: grossly evident

- Identified by imaging or **intraoperative findings**
- T3b disease
- T4a disease
- T4b disease

Gross extrathyroidal extension

a clinical finding based on **radiologic and/or clinical evidence** of macroscopic tumor extending outside the thyroid gland



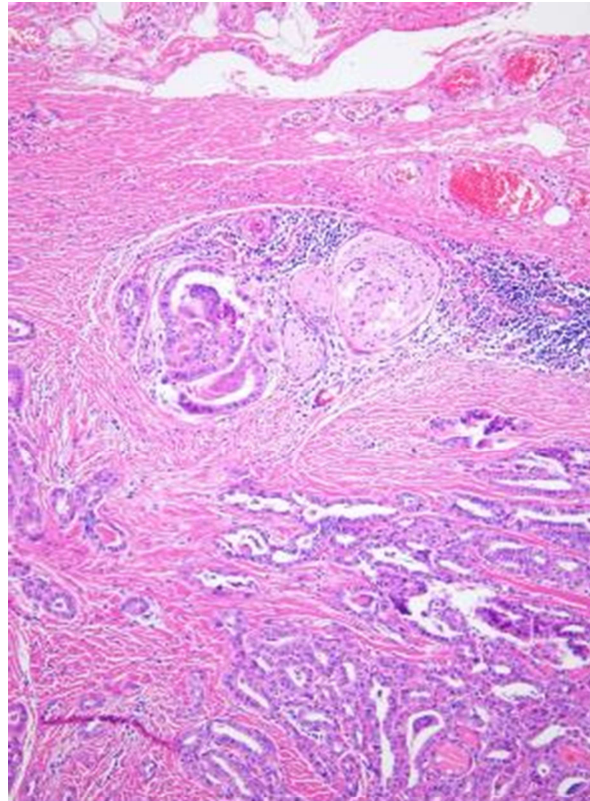
Tumor size: 1.5 x 1.4 cm

OP record: presence of
strap muscle invasion

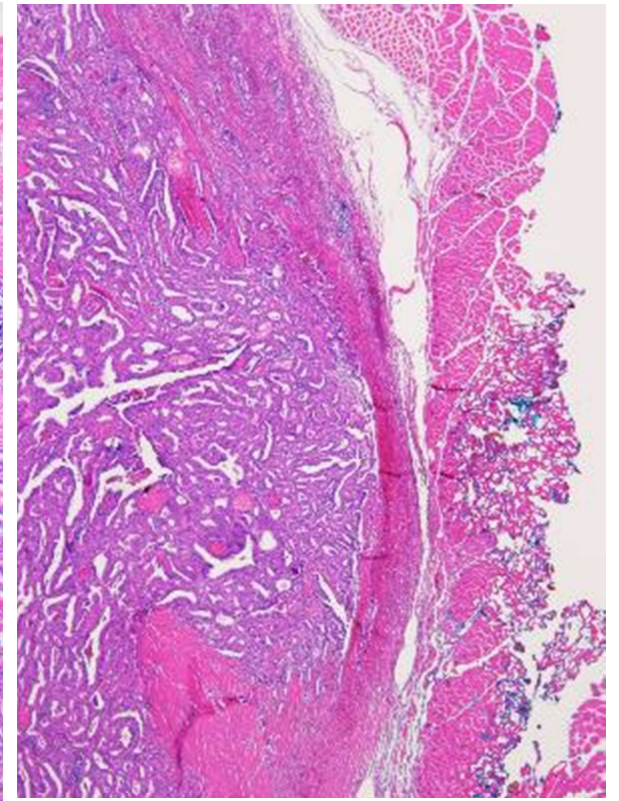
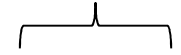


T1 or T3 ?

Microscopic ETE



Strap muscle



Gross extrathyroidal extension

Identified by imaging or intraoperative findings

- T3b disease – gross ETE involving only strap muscles
- T4a disease – gross ETE involving the subcutaneous soft tissues, larynx, trachea, esophagus, muscle, or recurrent laryngeal nerve
- T4b disease – gross ETE involving prevertebral fascia or encasing the carotid artery or mediastinal vessels

Pathological staging requires the use of all information obtained during clinical staging, as well as histologic study of the surgically resected specimen.

Primary tumor (T) for papillary, follicular, poorly differentiated, Hürthle cell and anaplastic thyroid carcinomas

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1: Tumor \leq 2 cm in greatest dimension limited to the thyroid

T1a: Tumor \leq 1 cm in greatest dimension limited to the thyroid

T1b: Tumor $>$ 1 cm but \leq 2 cm in greatest dimension limited to the thyroid

T2: Tumor $>$ 2 cm but \leq 4 cm in greatest dimension limited to the thyroid

T3*: Tumor $>$ 4 cm limited to the thyroid or **gross** extrathyroidal extension invading only strap muscles

T3a*: Tumor $>$ 4 cm limited to the thyroid

T3b*: Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid or omohyoid muscles) from a tumor of any size

T4: Includes gross extrathyroidal extension into major neck structures

T4a: Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve from a tumor of any size

T4b: Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size

Regional lymph node (N)

NX: Regional lymph nodes cannot be assessed

N0: No evidence of regional lymph node metastasis

N0a*: One or more cytologic or histologically confirmed benign lymph nodes

N0b*: No radiologic or clinical evidence of locoregional lymph node metastasis

N1*: Metastasis to regional nodes

N1a*: Metastasis to level VI or VII (pretracheal, paratracheal, prelaryngeal / Delphian or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease

N1b*: Metastasis to unilateral, bilateral or contralateral lateral neck lymph nodes (levels I, II, III, IV or V) or retropharyngeal lymph nodes

Pathologic confirmation of lymph node status is not required, and patients can be classified as having N0 disease, as long as there is no evidence of lymph node metastasis on routine preoperative and intraoperative evaluations (**clinical examination, imaging, and intraoperative findings**).

Differentiated thyroid cancer

<i>When age at diagnosis is...</i>	<i>And T is...</i>	<i>And N is...</i>	<i>And M is...</i>	<i>Then the stage group is...</i>
< 55 yrs	Any T	Any N	M0	I
	Any T	Any N	M1	II
≥ 55 yrs	T1	N0/NX	M0	I
	T1	N1	M0	II
	T2	N0/NX	M0	I
	T2	N1	M0	II
	T3a/T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
Any T	Any N	M1	IVB	

Anaplastic thyroid cancer

<i>T is...</i>	<i>And N is...</i>	<i>And M is...</i>	<i>Then the stage group is...</i>
T1-T3a	N0/NX	M0	IVA
T1-T3a	N1	M0	IVB
T3b	Any N	M0	IVB
T4	Any N	M0	IVB
Any T	Any N	M1	IVC

Differentiated thyroid cancer

Age at diagnosis < 55 years			
Stage I:	any T	any N	M0
Stage II:	any T	any N	M1
Age at diagnosis ≥ 55 years			
Stage I:	T1	N0 / NX	M0
	T2	N0 / NX	M0
Stage II:	T1	N1	M0
	T2	N1	M0
	T3a / T3b	any N	M0
Stage III:	T4a	any N	M0
Stage IVA:	T4b	any N	M0
Stage IVB:	any T	any N	M1

Medullary thyroid carcinoma

Stage I:	T1	N0	M0
Stage II:	T2	N0	M0
	T3	N0	M0
Stage III:	T1 - 3	N1a	M0
Stage IVA:	T4a	any N	M0
	T1 - 3	N1b	M0
Stage IVB:	T4b	any N	M0
Stage IVC:	any T	any N	M1

Anaplastic thyroid carcinoma

Stage IVA:	T1 - T3a	N0 / NX	M0
Stage IVB:	T1 - T3a	N1	M0
	T3b	any N	M0
	T4	any N	M0
Stage IVC:	any T	any N	M1

Thank you

