34th Pezcoller Seminar
Surgical Pathology of the Thyroid and Salivary Glands:
Hot topics and slide seminars
October 26th -27th 2023, Trento - Italy

Papillary carcinoma and indolent follicular patterned tumors

Giovanni Tallini, MD
Anatomic Pathology, University of Bologna School of Medicine
giovanni.tallini@unibo.it

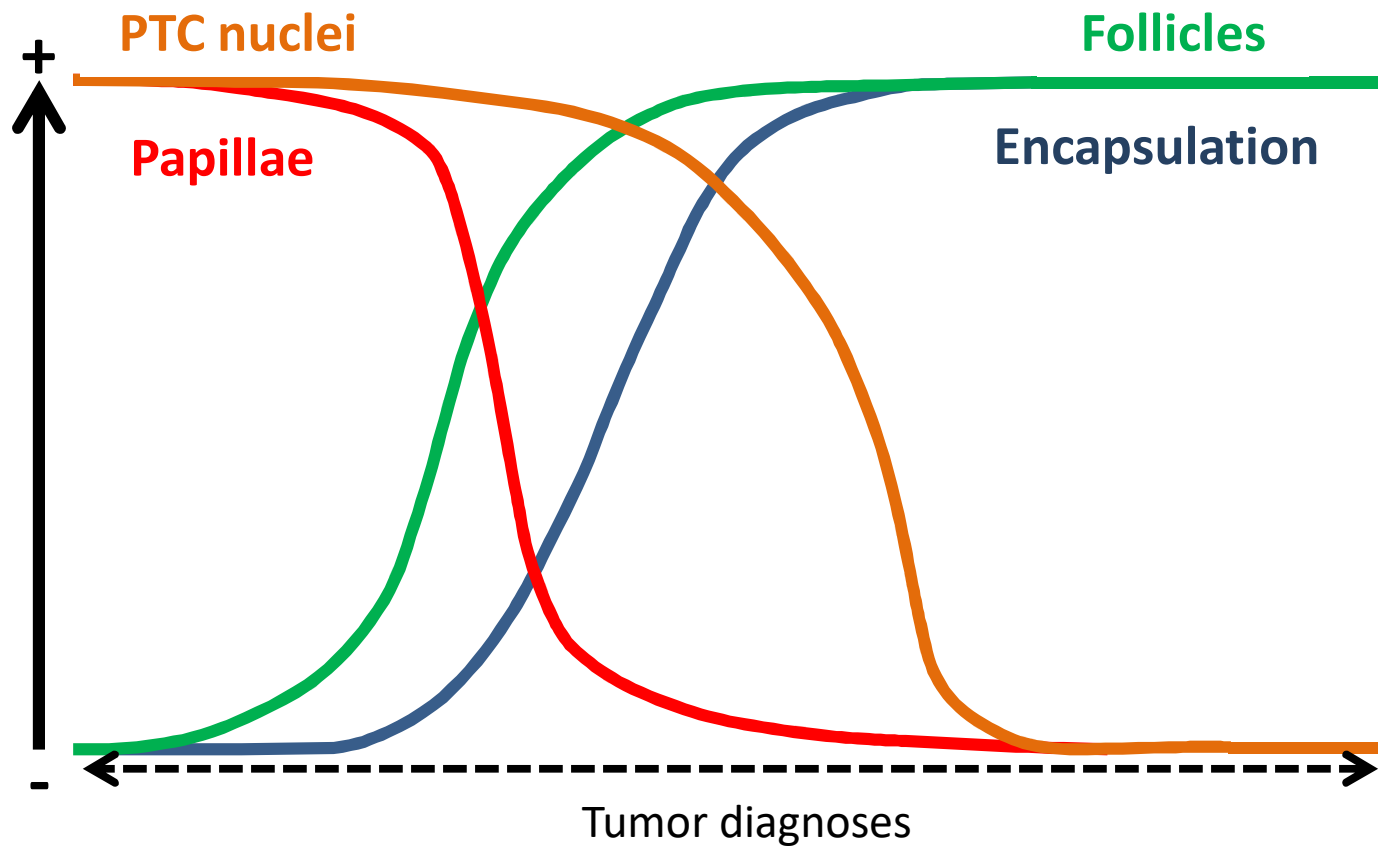
Topics

- Overview of current classification and lessons learnt from follicular-patterned lesions: Follicular variant papillary carcinoma, Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Tumors of uncertain malignant potential (UMP)
- Papillary carcinoma: subtypes and “Farewell to microcarcinoma”
- Thyroid follicular nodular disease
- Follicular thyroid adenoma with papillary architecture
- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic carcinoma): Minimally invasive (capsular invasion only); encapsulated angioinvasive; widely invasive

Topics

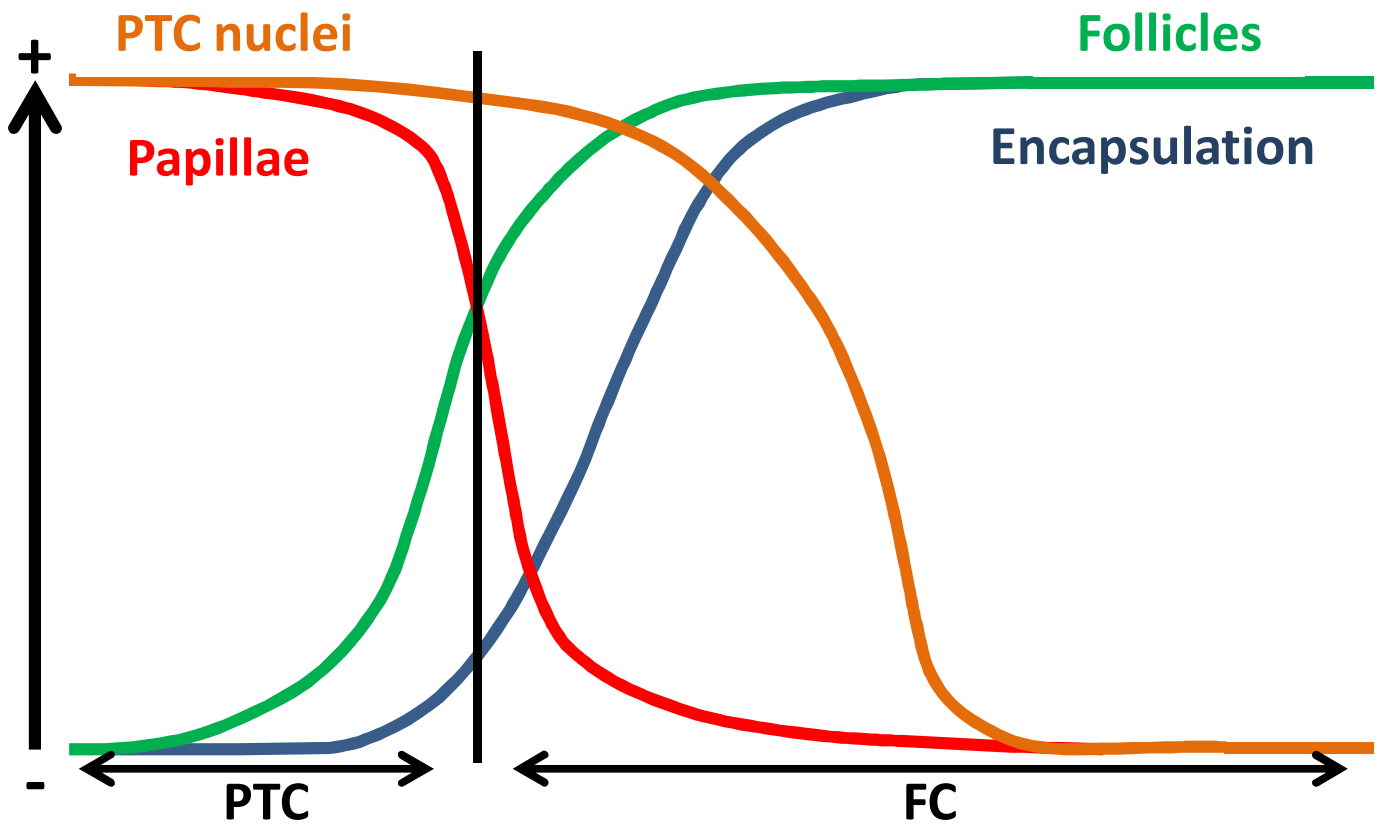
- Overview of current classification and lessons learnt from follicular-patterned lesions: Follicular variant papillary carcinoma, Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Tumors of uncertain malignant potential (UMP)
- Papillary carcinoma: subtypes and “Farewell to microcarcinoma”
- Thyroid follicular nodular disease
- Follicular thyroid adenoma with papillary architecture
- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic carcinoma): Minimally invasive (capsular invasion only); encapsulated angioinvasive; widely invasive

Differentiated Thyroid Carcinoma



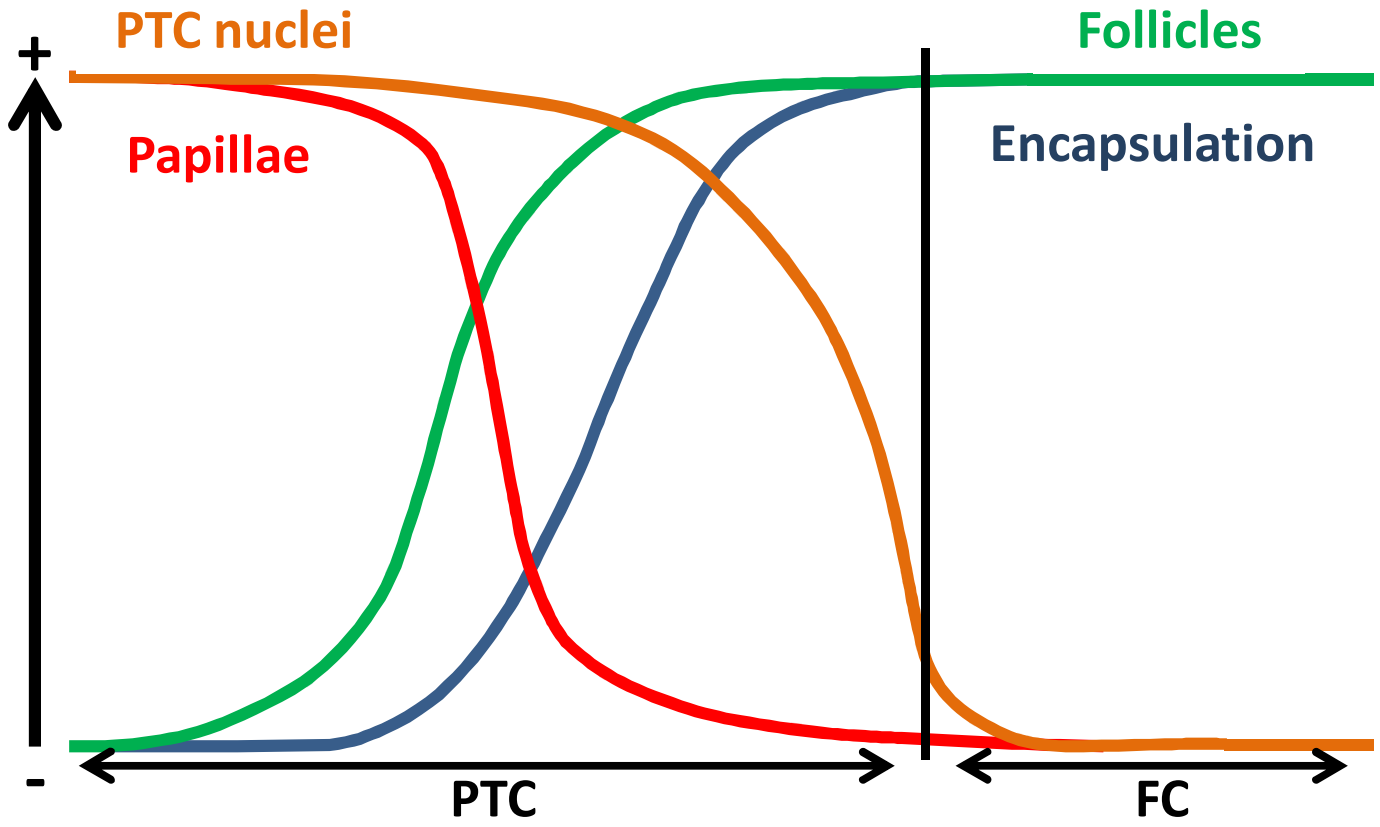
Tallini G, Tuttle RM, Ghossein RA. The History of the Follicular Variant of Papillary Thyroid Carcinoma. JCEM 2017. doi: 10.1210/jc.2016-2976

Differentiated Thyroid Carcinoma

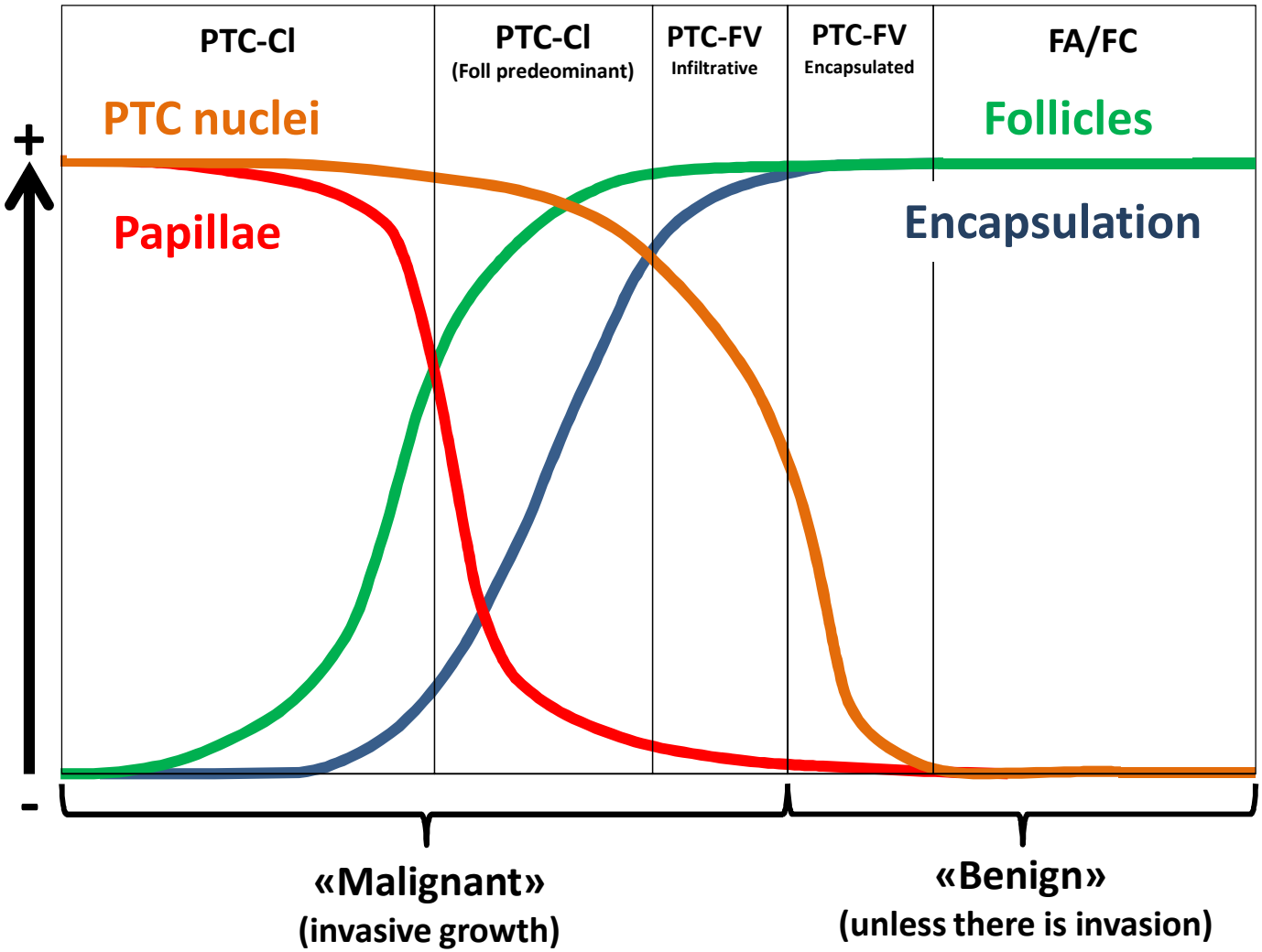


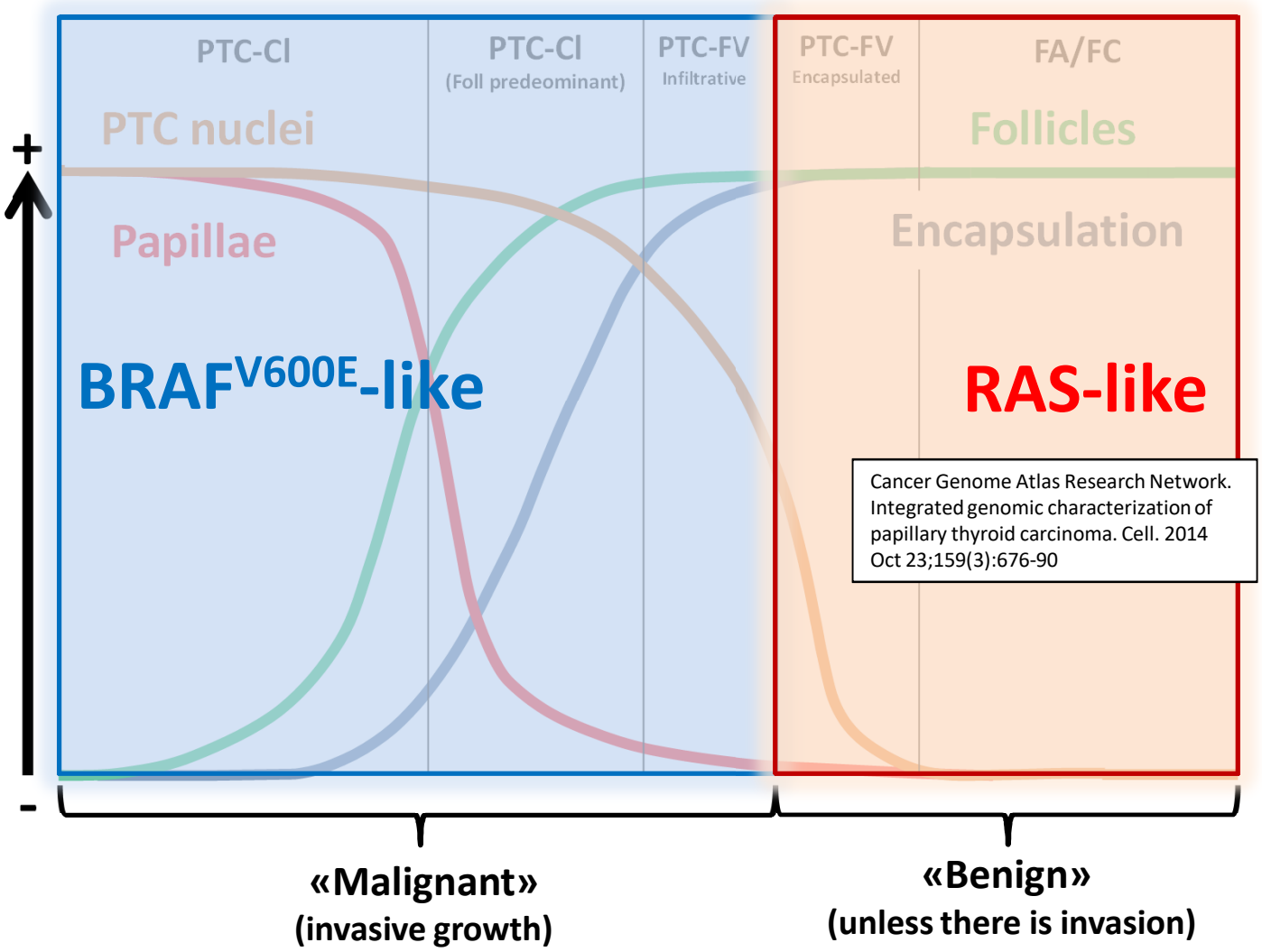
Dominance of follicular carcinoma diagnosis (up to the 1980s)

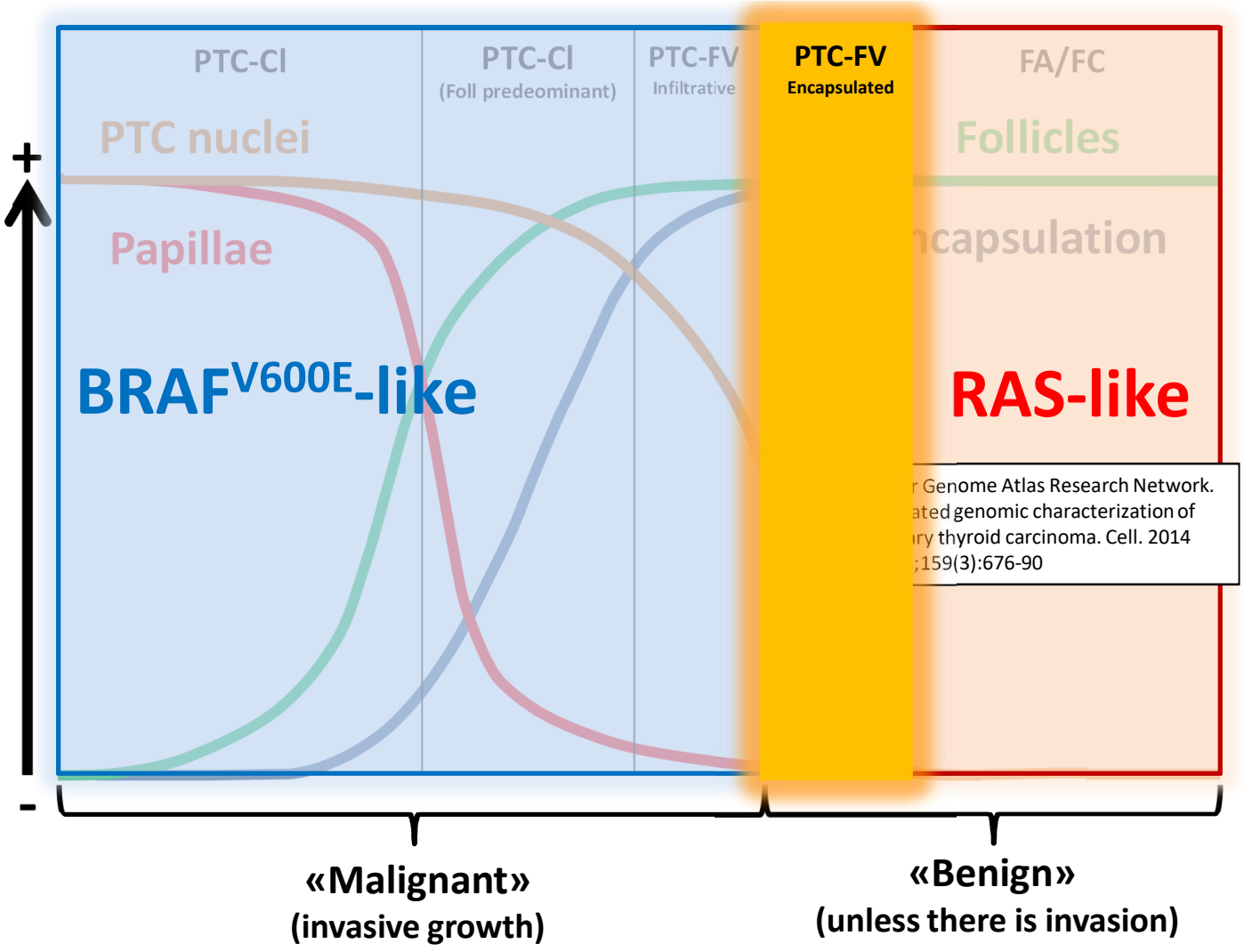
Differentiated Thyroid Carcinoma

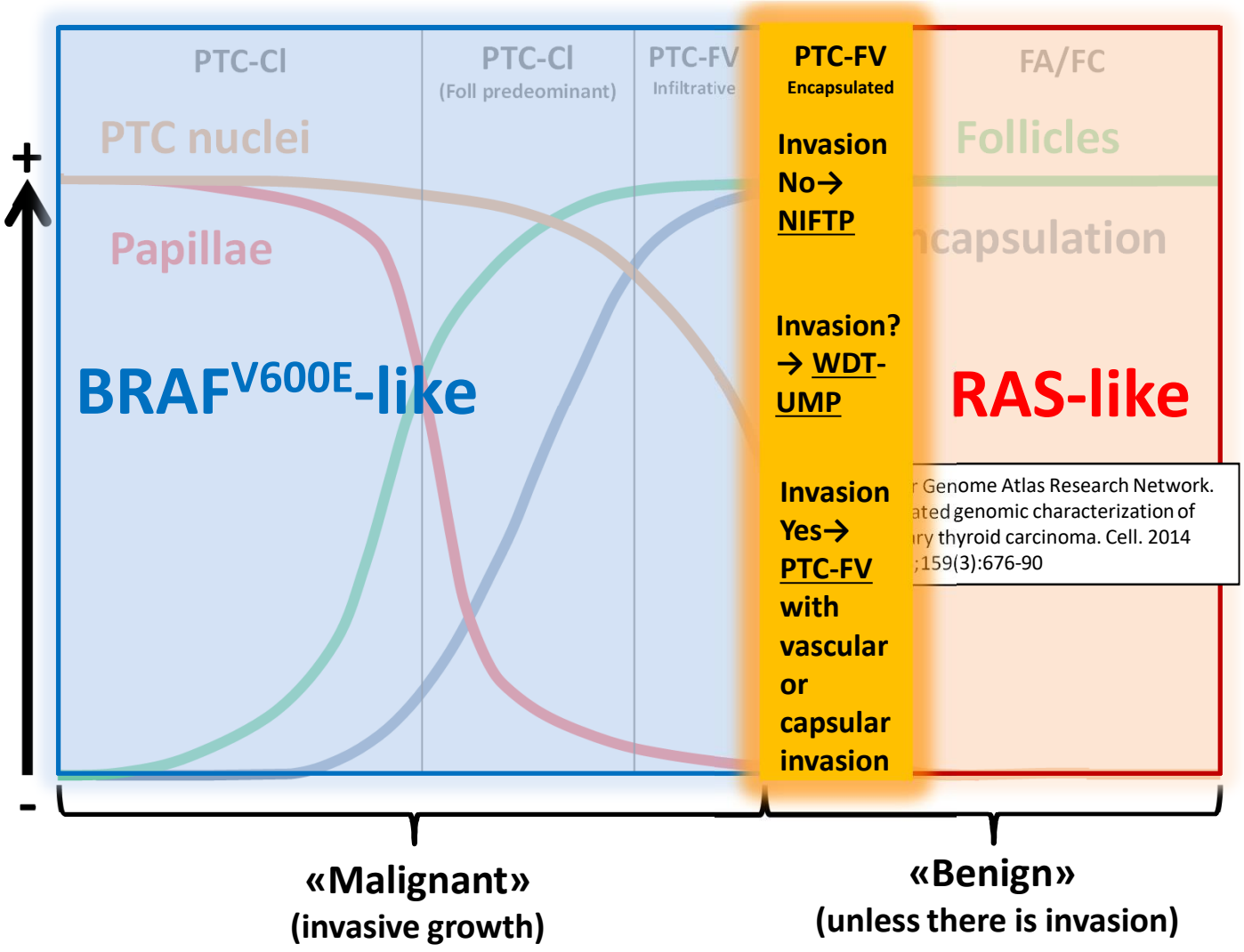


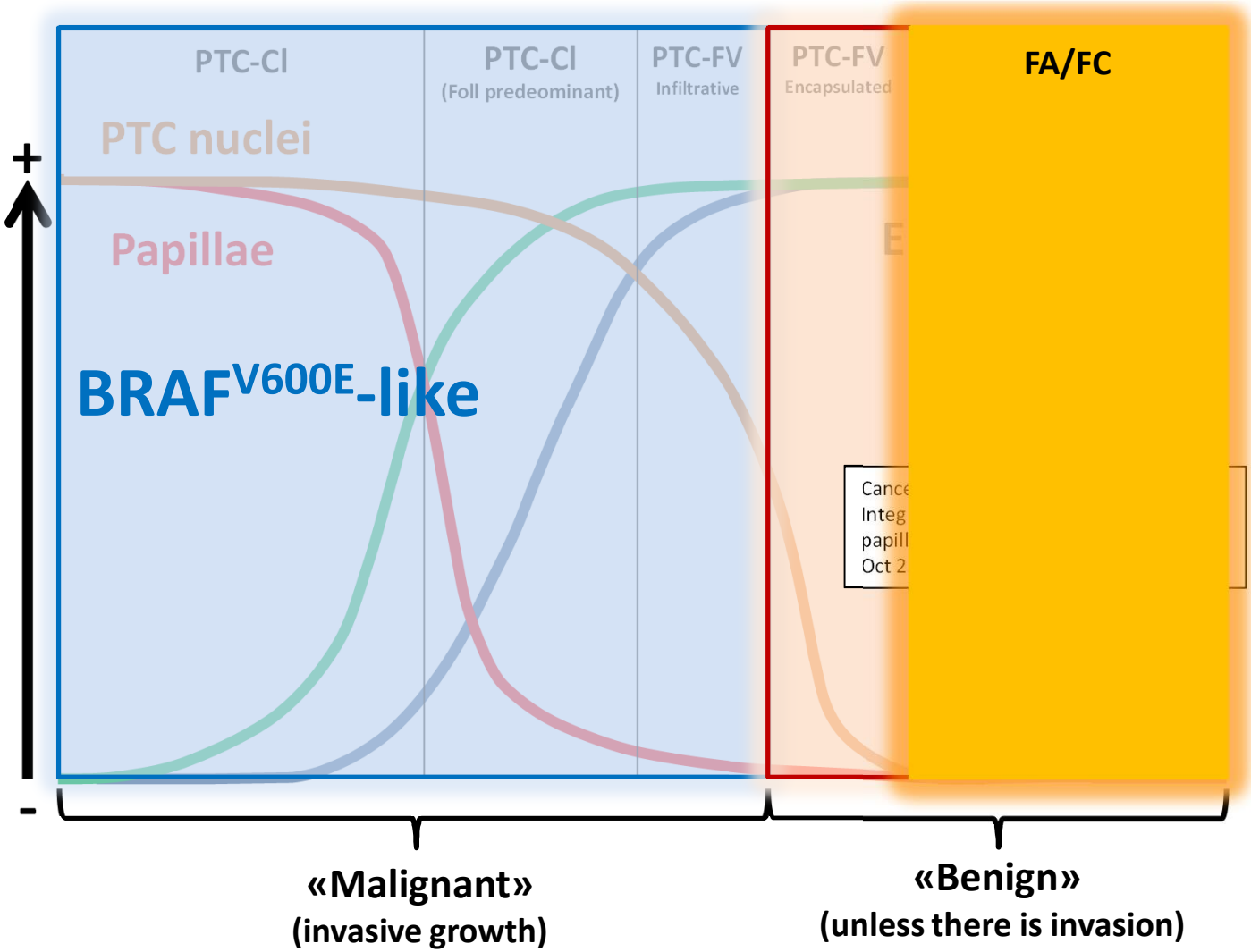
Dominance of papillary carcinoma diagnosis (after the 1980s)

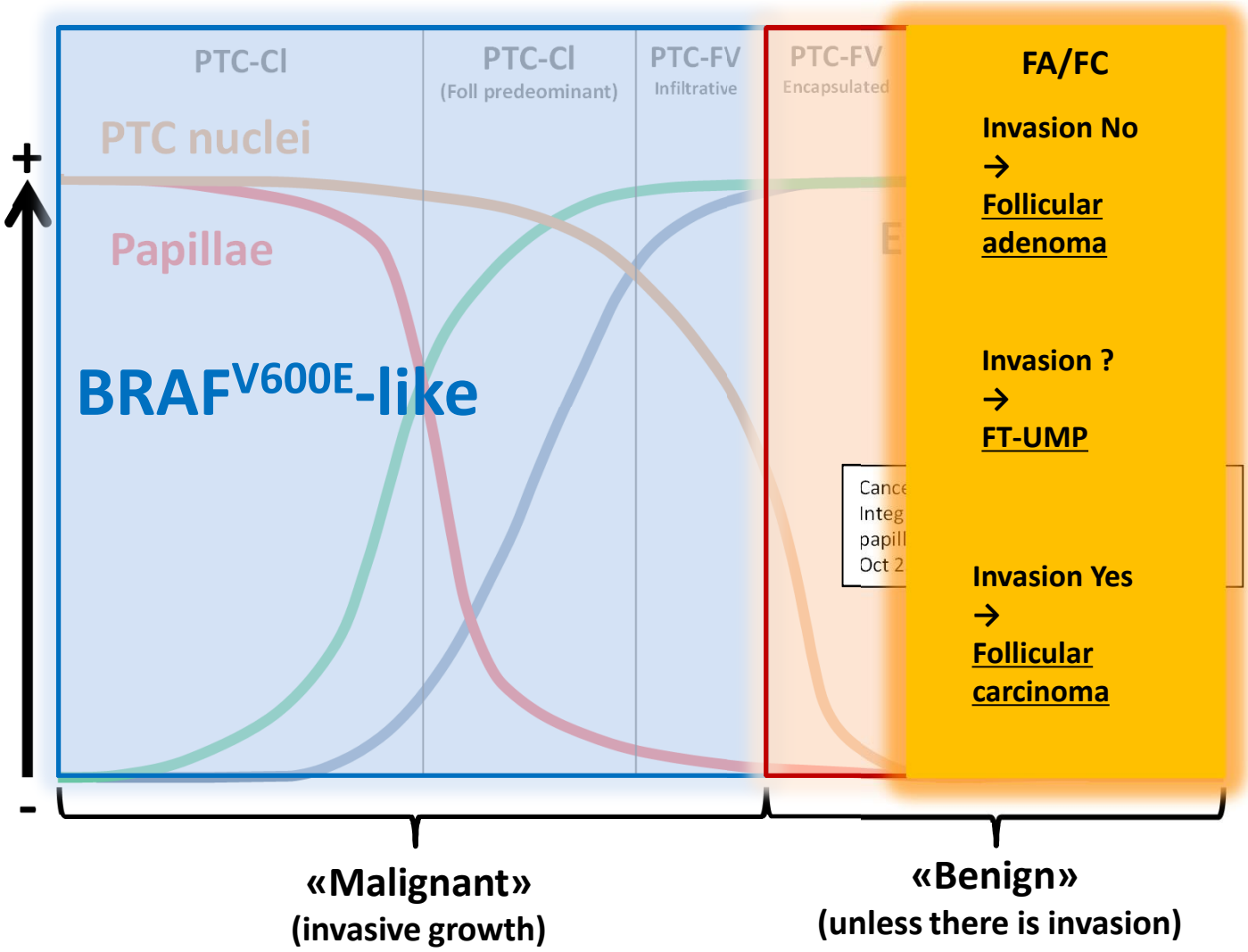

PTC-Cl
PTC-Cl
(Foll predeominant)
PTC-FV
Infiltrative
PTC-FV
Encapsulated
FA/FC
PTC nuclei
Follicles
Papillae
Encapsulation
+
-
«Malignant»
(invasive growth)
«Benign»
(unless there is invasion)


PTC-Cl
PTC-Cl
(Foll predeominant)
PTC-FV
Infiltrative
PTC-FV
Encapsulated
FA/FC
PTC nuclei
Follicles
+
Papillae
Encapsulation
BRAF V600E -like
RAS-like
Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014 Oct 23;159(3):676-90
-
«Malignant»
(invasive growth)
«Benign»
(unless there is invasion)


PTC-Cl
PTC-Cl
(Foll predeominant)
PTC-FV
Infiltrative
PTC-FV
Encapsulated
FA/FC
PTC nuclei
Follicles
Papillae
ncapsulation
+
-
BRAF V600E -like
RAS-like
r Genome Atlas Research Network.
ated genomic characterization of
ıry thyroid carcinoma. Cell. 2014
;159(3):676-90
«Malignant»
(invasive growth)
«Benign»
(unless there is invasion)


PTC-Cl
PTC-Cl
(Foll predeominant)
PTC-FV
Infiltrative
PTC-FV
Encapsulated
FA/FC
PTC nuclei
Follicles
Papillae
ncapsulation
+
-
BRAF V600E -like
RAS-like
Invasion
No→
NIFTP
Invasion?
→ WDT-
UMP
Invasion
Yes→
PTC-FV
with
vascular
or
capsular
invasion
r Genome Atlas Research Network.
ated genomic characterization of
ıry thyroid carcinoma. Cell. 2014
;159(3):676-90
«Malignant»
(invasive growth)
«Benign»
(unless there is invasion)

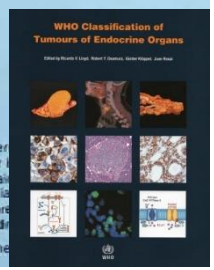

PTC-Cl
PTC-Cl
(Foll predeominant)
PTC-FV
Infiltrative
PTC-FV
Encapsulated
FA/FC
PTC nuclei
Papillae
BRAFV600E-like
+
-
«Malignant»
(invasive growth)
«Benign»
(unless there is invasion)


PTC-CI
PTC-CI
(Foll predeominant)
PTC-FV
Infiltrative
PTC-FV
Encapsulated
FA/FC
PTC nuclei
Papillae
BRAFV600E-like
+
-
Invasion No
→
Follicular adenoma
Invasion ?
→
FT-UMP
Invasion Yes
→
Follicular carcinoma
«Malignant»
(invasive growth)
«Benign»
(unless there is invasion)

Follicular adenoma	8330/0
Hyalinizing trabecular tumour	8336/1*
Other encapsulated follicular-patterned thyroid tumours	
Follicular tumour of uncertain malignant potential	8335/1*
Well-differentiated tumour of uncertain malignant potential	8348/1*
Non-invasive follicular thyroid neoplasm with papillary-like nuclear features	8349/1*
Papillary thyroid carcinoma (PTC)	
Papillary carcinoma	8260/3
Follicular variant of PTC	8340/3
Encapsulated variant of PTC	8343/3
Papillary microcarcinoma	8341/3
Columnar cell variant of PTC	8344/3
Oncocytic variant of PTC	8342/3
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 tumours	
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
Mixed medullary and follicular thyroid carcinoma	8346/3
Mucoepidermoid carcinoma	8430/3
Sclerosing mucoepidermoid carcinoma with eosinophilia	8430/3
Mucinous carcinoma	8480/3
Ectopic thymoma	8580/3
Spindle epithelial tumour with thymus-like differentiation	8588/3
Intrathyroid thymic carcinoma	8589/3
Paraganglioma and mesenchymal/stromal tumours	
Paraganglioma	8693/3
Peripheral nerve sheath tumours (PNSTs)	
Schwannoma	9560/0
Malignant PNST	9540/3
Benign vascular tumours	
Haemangioma	9120/0
Cavernous haemangioma	9121/0
Lymphangioma	9170/0
Angiosarcoma	9120/3
Smooth muscle tumours	
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Solitary fibrous tumour	8815/1
Haematolymphoid tumours	
Langerhans cell histiocytosis	9751/3
Rosai-Dorfman disease	
Follicular dendritic cell sarcoma	9758/3
Primary thyroid lymphoma	
Germ cell tumours	
Benign teratoma (grade 0 or 1)	9080/0
Immature teratoma (grade 2)	9080/1
Malignant teratoma (grade 3)	9080/3
Secondary tumours	

The morphology codes are from the Inter
for Oncology (ICD-O) (8936A). Behaviour
/1 for unspecified, borderline, or uncerta
situ and grade III intraepithelial neoplas
The classification is modified from the pr
into account changes in our understandi

*These new codes were approved by the



tumourclassification.iarc.who.int/chapters/53

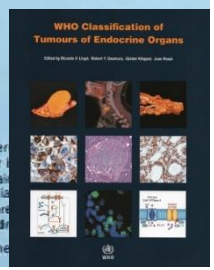
3. Thyroid gland

- Introduction
- **Developmental abnormalities**
  - Thyroglossal duct cyst
  - Other congenital thyroid abnormalities
- **Follicular cell-derived neoplasms**
  - *Benign tumours*
    - Thyroid follicular nodular disease
    - Follicular thyroid adenoma
    - Follicular thyroid adenoma with papillary architecture
    - Oncocytic adenoma of the thyroid
  - *Low risk neoplasms*
    - Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
    - Thyroid tumours of uncertain malignant potential
    - Hyalinizing trabecular tumour of thyroid
  - *Malignant neoplasms*
    - Follicular thyroid carcinoma
    - Invasive encapsulated follicular variant papillary carcinoma
    - Papillary thyroid carcinoma
    - Oncocytic carcinoma of the thyroid
    - Follicular-derived carcinomas, high-grade
    - Anaplastic follicular cell derived thyroid carcinoma
- **Thyroid C-cell derived carcinoma**
  - Medullary thyroid carcinoma
- **Mixed medullary and follicular-cell derived carcinomas**
  - Mixed medullary and follicular cell-derived thyroid carcinoma
- **Salivary gland-type carcinomas of the thyroid**
  - Mucoepidermoid carcinoma of the thyroid
  - Secretory carcinoma of salivary gland type
- **Thyroid tumours of uncertain histogenesis**
  - Sclerosing mucoepidermoid carcinoma with eosinophilia
  - Cribriform morular thyroid carcinoma
- **Thymic tumours within the thyroid**
  - Thymoma family
  - Spindle epithelial tumour with thymus-like elements
  - Thymic carcinoma family
- **Embryonal thyroid neoplasms**
  - Thyroblastoma

Follicular adenoma	8330/0
Hyalinizing trabecular tumour	8336/1*
Other encapsulated follicular-patterned thyroid tumours	
Follicular tumour of uncertain malignant potential	8335/1*
Well-differentiated tumour of uncertain malignant potential	8348/1*
Non-invasive follicular thyroid neoplasm with papillary-like nuclear features	8349/1*
Papillary thyroid carcinoma (PTC)	
Papillary carcinoma	8260/3
Follicular variant of PTC	8340/3
Encapsulated variant of PTC	8343/3
Papillary microcarcinoma	8341/3
Columnar cell variant of PTC	8344/3
Oncocytic variant of PTC	8342/3
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 tumours	
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
Mixed medullary and follicular thyroid carcinoma	8346/3
Mucoepidermoid carcinoma	8430/3
Sclerosing mucoepidermoid carcinoma with eosinophilia	8430/3
Mucinous carcinoma	8480/3
Ectopic thymoma	8580/3
Spindle epithelial tumour with thymus-like differentiation	8588/3
Intrathyroid thymic carcinoma	8589/3
Paraganglioma and mesenchymal/stromal tumours	
Paraganglioma	8693/3
Peripheral nerve sheath tumours (PNSTs)	
Schwannoma	9560/0
Malignant PNST	9540/3
Benign vascular tumours	
Haemangioma	9120/0
Cavernous haemangioma	9121/0
Lymphangioma	9170/0
Angiosarcoma	9120/3
Smooth muscle tumours	
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Solitary fibrous tumour	8815/1
Haematolymphoid tumours	
Langerhans cell histiocytosis	9751/3
Rosai-Dorfman disease	
Follicular dendritic cell sarcoma	9758/3
Primary thyroid lymphoma	
Germ cell tumours	
Benign teratoma (grade 0 or 1)	9080/0
Immature teratoma (grade 2)	9080/1
Malignant teratoma (grade 3)	9080/3
Secondary tumours	

The morphology codes are from the Inter
for Oncology (ICD-O) (8936A). Behaviour
/1 for unspecified, borderline, or uncerta
situ and grade III intraepithelial neoplasi
The classification is modified from the pre
into account changes in our understandi

*These new codes were approved by the



tumourclassification.iarc.who.int/chapters/53

3. Thyroid gland

- Introduction
- **Developmental abnormalities**
  - Thyroglossal duct cyst
  - Other congenital thyroid abnormalities
- **Follicular cell-derived neoplasms**
  - *Benign tumours*
    - Thyroid follicular nodular disease
    - Follicular thyroid adenoma
    - Follicular thyroid adenoma with papillary architecture
    - Oncocytic adenoma of the thyroid
  - *Low risk neoplasms*
    - Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
    - Thyroid tumours of uncertain malignant potential
    - Hyalinizing trabecular tumour of thyroid
  - *Malignant neoplasms*
    - Follicular thyroid carcinoma
    - Invasive encapsulated follicular variant papillary carcinoma
    - Papillary thyroid carcinoma
    - Oncocytic carcinoma of the thyroid
    - Follicular-derived carcinomas, high-grade
    - Anaplastic follicular cell derived thyroid carcinoma
- **Thyroid C-cell derived carcinoma**
  - Medullary thyroid carcinoma
- **Mixed medullary and follicular-cell derived carcinomas**
  - Mixed medullary and follicular cell-derived thyroid carcinoma
- **Salivary gland-type carcinomas of the thyroid**
  - Mucoepidermoid carcinoma of the thyroid
  - Secretory carcinoma of salivary gland type
- **Thyroid tumours of uncertain histogenesis**
  - Sclerosing mucoepidermoid carcinoma with eosinophilia
  - Cribriform morular thyroid carcinoma
- **Thymic tumours within the thyroid**
  - Thymoma family
  - Spindle epithelial tumour with thymus-like elements
  - Thymic carcinoma family
- **Embryonal thyroid neoplasms**
  - Thyroblastoma

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, Barletta JA, Wenig BM, Al Ghuzlan A, Kakudo K, Giordano TJ, Alves VA, Khanafshar E, Asa SL, El-Naggar AK, Gooding WE, Hodak SP, Lloyd RV, Maytal G, Mete O, Nikiforova MN, Nosé V, Papotti M, Poller DN, Sadow PM, Tischler AS, Tuttle RM, Wall KB, LiVolsi VA, Randolph GW, Ghossein RA

JAMA Oncol. 2016 Aug 1;2(8):1023-9. doi: 10.1001/jamaoncol.2016.0386

Follicular patterned tumor with PTC nuclear features is ~benign when not invasive

1. Encapsulation or clear demarcation[a]
2. Follicular growth pattern[b] with
   - <1% Papillae
   - No psammoma bodies
   - <30% Solid/trabecular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion[c]
5. No tumor necrosis
6. No high mitotic activity[d]

[a] Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue.

[b] Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid.

[c] Requires adequate microscopic examination of the tumor capsule interface.

[d] High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400×).

1. Consensus on the minimal criteria for the definition of follicular variant papillary carcinoma.
2. Analyzed follow up (median, 13 years) in a considerable number of cases: 109 non-invasive E-PTCFV → no recurrence/metastases/deaths
3. Correlated morphology with molecular alterations
4. Consensus terminology: "Non-invasive follicular thyroid neoplasms with papillary-like nuclear features" (NIFTP)

Change in Diagnostic Criteria for Noninvasive Follicular Thyroid Neoplasm With Papillarylike Nuclear Features

Nikiforov YE, Baloch ZW, Hodak SP, Giordano TJ, Lloyd RV, Seethala RR, Wenig BM

JAMA Oncol. 2018 Aug 1;4(8):1125-1126. doi: 10.1001/jamaoncol.2018.1446

Follicular patterned tumor with PTC nuclear features is ~benign when not invasive

Box. Revised Diagnostic Criteria for NIFTP

Primary

- Encapsulation or clear demarcation[a]
- Follicular growth pattern with:
  - No well-formed papillae
  - No psammoma bodies
  - <30% solid/trabecular/insular growth pattern
- Nuclear score 2-3[b]
- No vascular or capsular invasion[c]
- No tumor necrosis or high mitotic activity[d]

Secondary[e]

- Lack of *BRAF* V600E mutation detected by molecular assays or immunohistochemistry
- Lack of *BRAF* V600E-like mutations or other high-risk mutations (TERT, TP53)

Abbreviation: NIFTP, noninvasive follicular thyroid neoplasm with papillarylike nuclear features.

[a] Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid parenchyma.

[b] Typically nuclear score 2 (moderately expressed nuclear features of papillary thyroid carcinoma). In tumors with florid nuclear features of papillary thyroid carcinoma (nuclear score 3), the entire tumor should be examined to exclude the presence of papillae. Molecular testing for *BRAF* V600E and other mutations or immunohistochemistry for *BRAF* V600E is advisable but not required for tumors with nuclear score 3.

[c] Requires microscopic examination of the entire tumor capsule interface.

[d] High mitotic activity, defined as 3 or more mitoses per 10 high-power fields (×400).

[e] Secondary criteria are helpful but not required for NIFTP diagnosis.

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a non-invasive encapsulated/well demarcated follicular cell derived tumour with a follicular growth pattern and nuclei resembling papillary thyroid carcinoma (PTC) that has an extremely low malignant potential (previously: non invasive encapsulated follicular variant papillary thyroid carcinoma)

- RAS-like molecular alterations (mostly NRAS, but also EIF1AX, BRAF p.K601E and other BRAF non-V600E mutations, PPARG and THADA rearrangements
- Prevalence much lower in Asia (0.5-5%) compared to Western countries (up to 15-20%, especially North America), but also significant variation between different institutions within the same geographical location due to variable use of the term

➢ **Essential and desirable diagnostic criteria**

Essential:

1. Encapsulation or clear demarcation
2. Follicular growth pattern with all of the following: <1% true papillae; No psammoma bodies; <30% solid/trabecular/insular growth pattern
3. Nuclear features of papillary carcinoma (nuclear score of 2-3)
4. No vascular or capsular invasion
5. No tumour necrosis
6. Low mitotic count (<3 mitosis / $2mm^2$)
7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant (tall cell features, cribriform-morular variant, solid variant, etc)

Desirable:

Immunohistochemistry or molecular testing for *BRAF* and *NRAS* mutation: *BRAF* p.V600E excludes the diagnosis

- NIFTP terminology can be applied to subcentimeter (<10 mm NIFTP) and oncocytic tumors (Oncocytic NIFTP)

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a non-invasive encapsulated/well demarcated follicular cell derived tumour with a follicular growth pattern and nuclei resembling papillary thyroid carcinoma (PTC) that has an extremely low malignant potential (previously: non invasive encapsulated follicular variant papillary thyroid carcinoma)

- RAS-like molecular alterations (mostly NRAS, but also EIF1AX, BRAF p.K601E and other BRAF non-V600E mutations, PPARG and THADA rearrangements
- Prevalence much lower in Asia (0.5-5%) compared to Western countries (up to 15-20%, especially North America), but also significant variation between different institutions within the same geographical location due to variable use of the term

➢ **Essential and desirable diagnostic criteria**

Essential:

1. Encapsulation or clear demarcation
2. Follicular growth pattern with all of the following: **<1% true papillae**; No psammoma bodies; <30% solid/trabecular/insular growth pattern
3. Nuclear features of papillary carcinoma (nuclear score of 2-3)
4. No vascular or capsular invasion
5. No tumour necrosis
6. Low mitotic count (<3 mitosis / $2mm^2$)
7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant (tall cell features, cribriform-morular variant, solid variant, etc)

Desirable:

Immunohistochemistry or molecular testing for *BRAF* and *NRAS* mutation: *BRAF* p.V600E excludes the diagnosis

- NIFTP terminology can be applied to subcentimeter (<10 mm NIFTP) and oncocytic tumors (Oncocytic NIFTP)

How many papillae in conventional papillary carcinoma? A clinical evidence-based pathology study of 235 unifocal encapsulated papillary thyroid carcinomas, with emphasis on the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

Xu B, Serrette R, Tuttle RM MD, Alzumaili B, Ganly I, Katabi N, Tallini G, Ghossein R MD

Thyroid. 2019 Aug 27. doi: 10.1089/thy.2019.0328. [Epub ahead of print] PubMed PMID: 31452453

235 cases previously diagnosed as unifocal encapsulated PTC (U-EPTC)…27 patients (12%) had lymph node metastasis (N1)…Nodal metastases were only present in tumors with ≥1% papillae. In noninvasive U-EPTC (n=161), N1 disease was seen only in tumors with ≥10% papillae…Among 216 patients with follow-up (median: 5.2 years), 3 patients (1.5%) had distant metastases, all detected at the initial presentation. All three tumors displayed 100% follicular growth, and capsular or vascular invasion… U-EPTC, there is a strong correlation between high percentage of papillary growth, presence of nodal metastasis, and BRAF+/RAS- genotype regardless of invasive status

Non-invasive cases (capsular and/or vascular)

		All patients (n=156)	N0/Nx (n=144)	N1 (n=12)	P values
Percentage of papillae	0%	100 (64%)	100 (69%)	0 (0%)	<0.001
	0.1-0.9%	20 (13%)	20 (14%)	0 (0%)	
	1-9%	9 (6%)	9 (6%)	0 (0%)	
	10-24%	3 (2%)	2 (1%)	1 (8%)	
	25-49%	2 (1%)	2 (1%)	0 (0%)	
	50%	22 (14%)	11 (8%)	11 (92%)	

Cases with Invasion (capsular and/or vascular)

		All patients (n=79)	N0/Nx (n=64)	N1 (n=15)	P values
Percentage of papillae	0%	27 (34%)	27 (42%)	0 (0%)	0.001
	0.1-0.9%	11 (14%)	11 (17%)	0 (0%)	
	1-9%	5 (6%)	4 (6%)	1 (7%)	
	10-24%	3 (4%)	2 (3%)	1 (7%)	
	25-49%	3 (4%)	3 (5%)	0 (0%)	
	≥50%	30 (38%)	17 (27%)	13 (87%)	

Noninvasive encapsulated PTC with LN metastases
N1 tumor with the lowest proportion of papillae: **10% papillae**

Encapsulated PTC with invasion and LN metastases
N1 tumor with the lowest proportion of papillae: **5% papillae** (the tumor has capsular invasion only, no angioinvasion, and is BRAF V600E and NRAS Q61R negative by IHC)

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy

Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J

Cancer. 1985 Feb 15;55(4):805-28

"The features of greatest prognostic value were patient's age at presentation, small tumor size, total encapsulation, extrathyroid extension, multicentricity, and presence of distant metastases"

The encapsulated papillary carcinoma of the thyroid. A morphologic subtype of the papillary thyroid carcinoma

Schröder S, Böcker W, Dralle H, Kortmann KB, Stern C

Cancer. 1984 Jul 1;54(1):90-3

"The excellent prognosis for the encapsulated variant of papillary thyroid carcinoma was confirmed by a long follow-up period in which no evidence of recurrences or further metastasis was registered as compared with the time of initial diagnosis, whatever the mode of therapy"

Encapsulated papillary neoplasms of the thyroid. A study of 14 cases followed for a minimum of 10 years

Evans HL

Am J Surg Pathol. 1987 Aug;11(8):592-7

"The only evidence of malignant behavior in the entire series was a cervical lymph node metastasis in one case of encapsulated papillary carcinoma"

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy

Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J

Cancer. 1985 Feb 15;55(4):805-28

"The features of greatest prognostic value were patient's age at presentation, small tumor size, total encapsulation, extrathyroid extension, multicentricity, and presence of distant metastases"

TABLE 2. Tumor Encapsulation and Its Influence on Prognosis and Metastatic Behavior

	Absent Capsule	Partial Capsule	Total Capsule	
	92 (42.0%)	106 (48.4%)	21 (9.6%)	
Alive & well	67 (72.8%)	86 (81.1%)	19 (90.5%)	$P < 0.05$*
Alive with tumor	19 (20.6%)	9 (8.5%)	2 (9.5%)	
Dead of tumor	3 (3.3%)	6 (5.7%)	0 (0%)	
Node metastases	52 (56.5%)	49 (46.2%)	8 (38%)	
Lung metastases	13 (14.1%)	16 (15.1%)	0 (0%)	$P < 0.25$*

* The chi-square calculations were made between tumors with absent capsule and tumors with total capsule.

Patients who died of causes other than papillary carcinoma have been excluded.

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a non-invasive encapsulated/well demarcated follicular cell derived tumour with a follicular growth pattern and nuclei resembling papillary thyroid carcinoma (PTC) that has an extremely low malignant potential (previously: non invasive encapsulated follicular variant papillary thyroid carcinoma)

- RAS-like molecular alterations (mostly NRAS, but also EIF1AX, BRAF p.K601E and other BRAF non-V600E mutations, PPARG and THADA rearrangements
- Prevalence much lower in Asia (0.5-5%) compared to Western countries (up to 15-20%, especially North America), but also significant variation between different institutions within the same geographical location due to variable use of the term

➢ **Essential and desirable diagnostic criteria**

Essential:

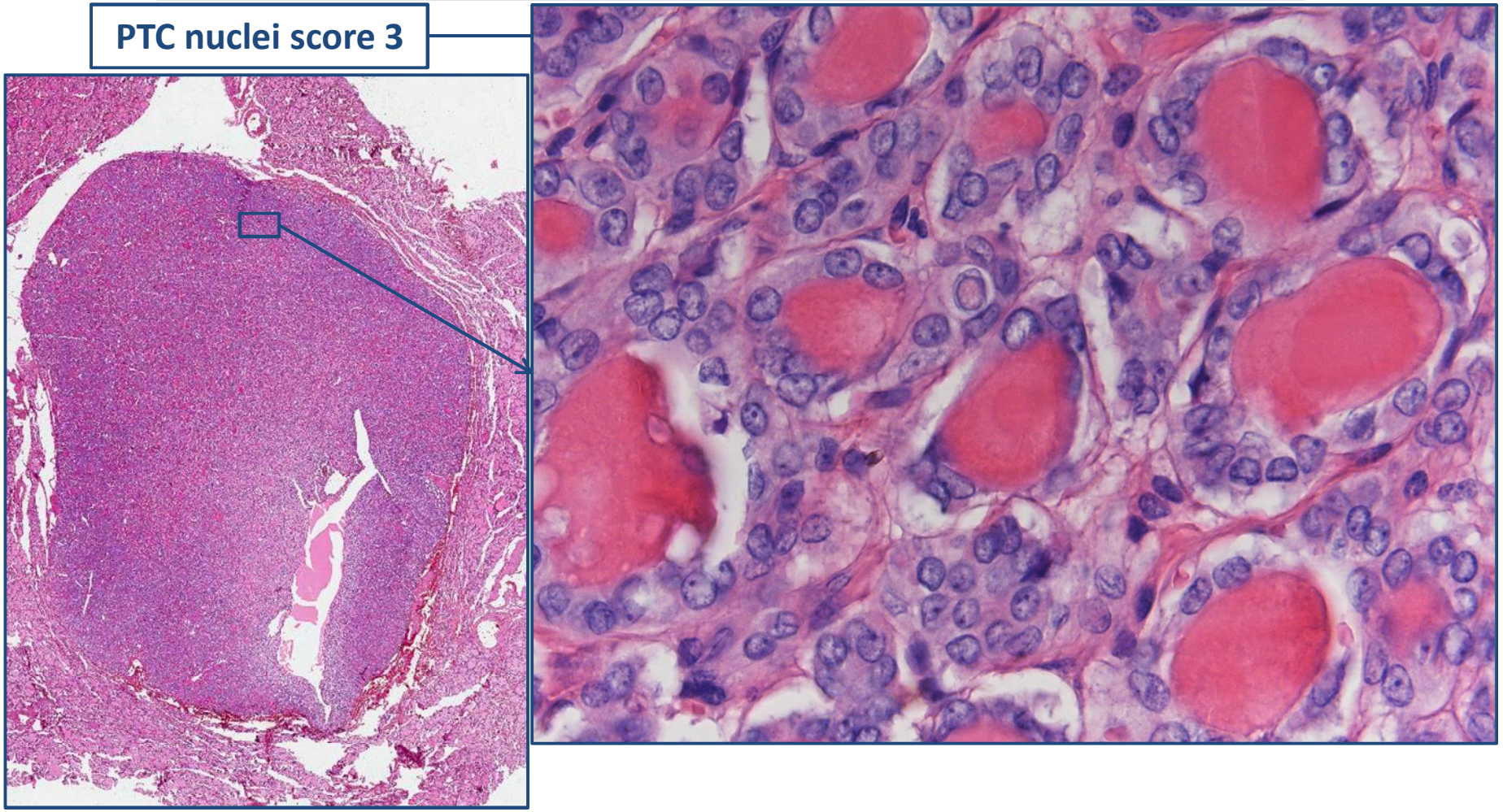
1. Encapsulation or clear demarcation
2. Follicular growth pattern with all of the following: <1% true papillae; No psammoma bodies; <30% solid/trabecular/insular growth pattern
3. Nuclear features of papillary carcinoma (nuclear score of 2-3)
4. No vascular or capsular invasion
5. No tumour necrosis
6. Low mitotic count (<3 mitosis / $2mm^2$)
7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant (tall cell features, cribriform-morular variant, solid variant, etc)

***Desirable*:**

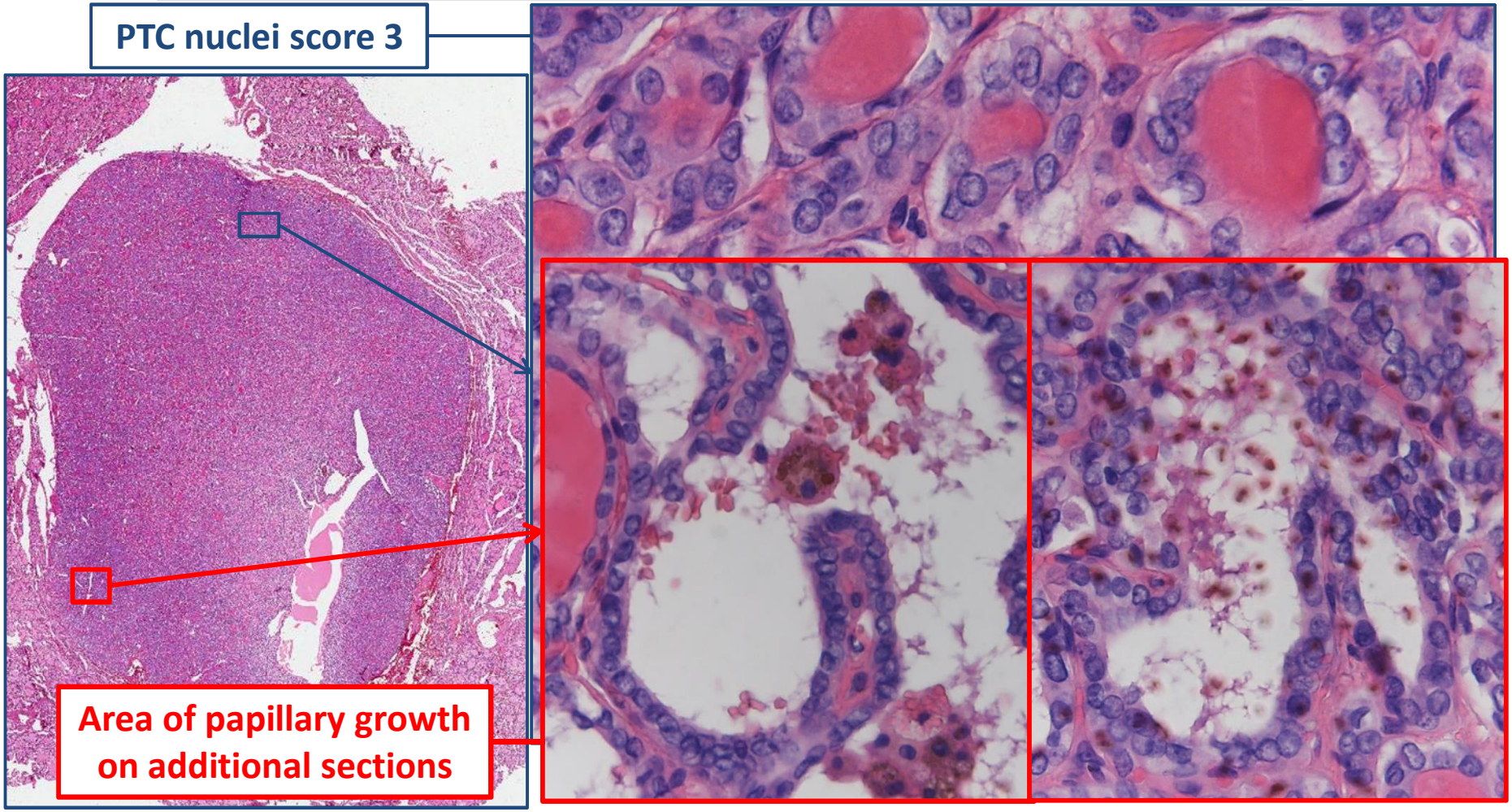
Immunohistochemistry or molecular testing for *BRAF* and *NRAS* mutation: *BRAF* p.V600E excludes the diagnosis

- NIFTP terminology can be applied to subcentimeter (<10 mm NIFTP) and oncocytic tumors (Oncocytic NIFTP)

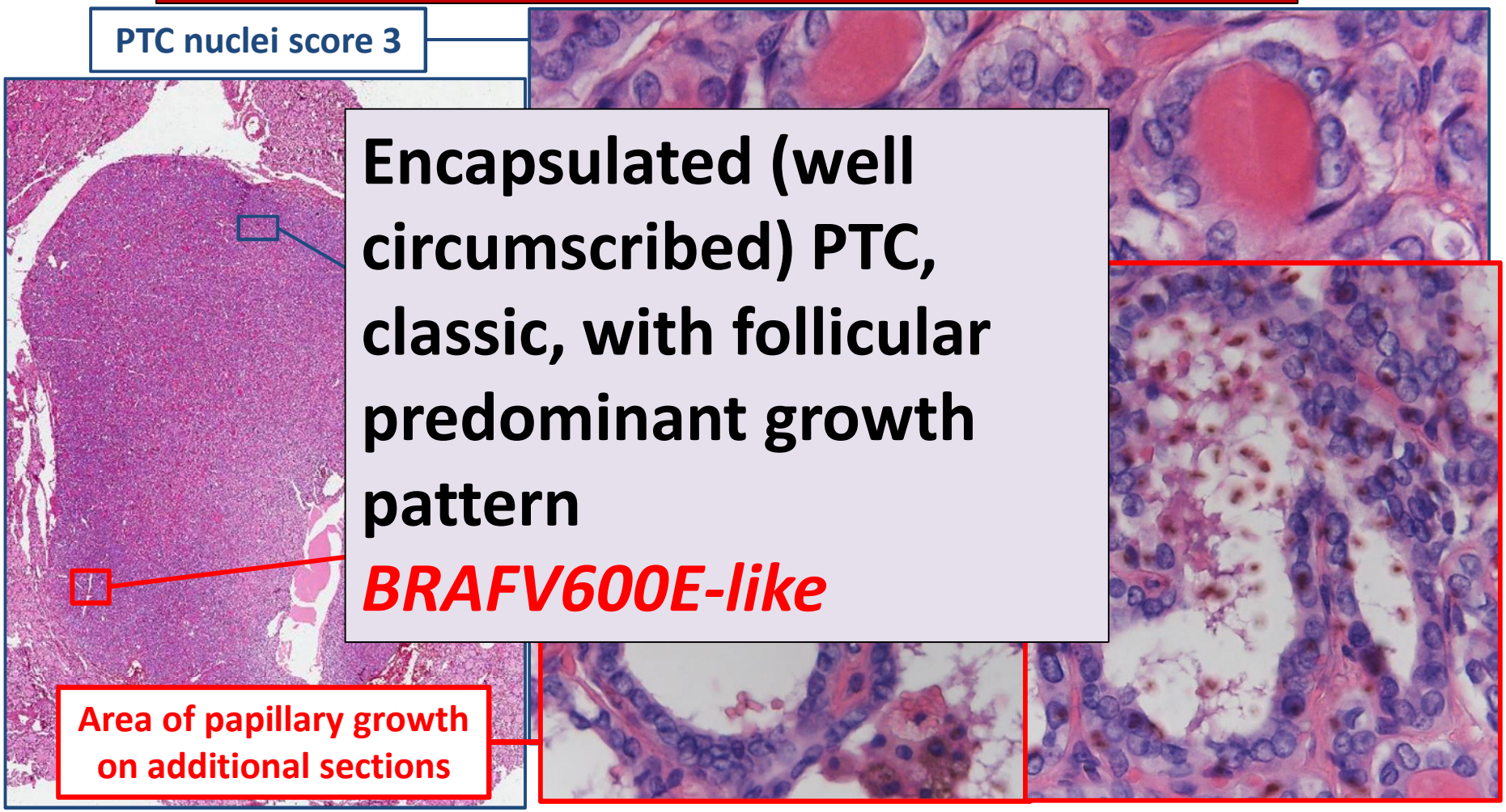
NIFTP exclusion criteria: nuclear alterations as a marker for classic PTC



NIFTP exclusion criteria: nuclear alterations as a marker for classic PTC



NIFTP exclusion criteria: nuclear alterations as a marker for classic PTC



Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a non-invasive encapsulated/well demarcated follicular cell derived tumour with a follicular growth pattern and nuclei resembling papillary thyroid carcinoma (PTC) that has an extremely low malignant potential (previously: non invasive encapsulated follicular variant papillary thyroid carcinoma)

- RAS-like molecular alterations (mostly NRAS, but also EIF1AX, BRAF p.K601E and other BRAF non-V600E mutations, PPARG and THADA rearrangements
- Prevalence much lower in Asia (0.5-5%) compared to Western countries (up to 15-20%, especially North America), but also significant variation between different institutions within the same geographical location due to variable use of the term

NIFTP is still a histopathologic diagnosis!

4. No vascular or capsular invasion
5. No tumour necrosis
6. Low mitotic count (<3 mitosis / 2mm^2)
7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant (tall cell features, cribriform-morular variant, solid variant, etc)

***Desirable*:**

Immunohistochemistry or molecular testing for *BRAF* and *NRAS* mutation: *BRAF* p.V600E excludes the diagnosis

- NIFTP terminology can be applied to subcentimeter (<10 mm NIFTP) and oncocytic tumors (Oncocytic NIFTP)

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

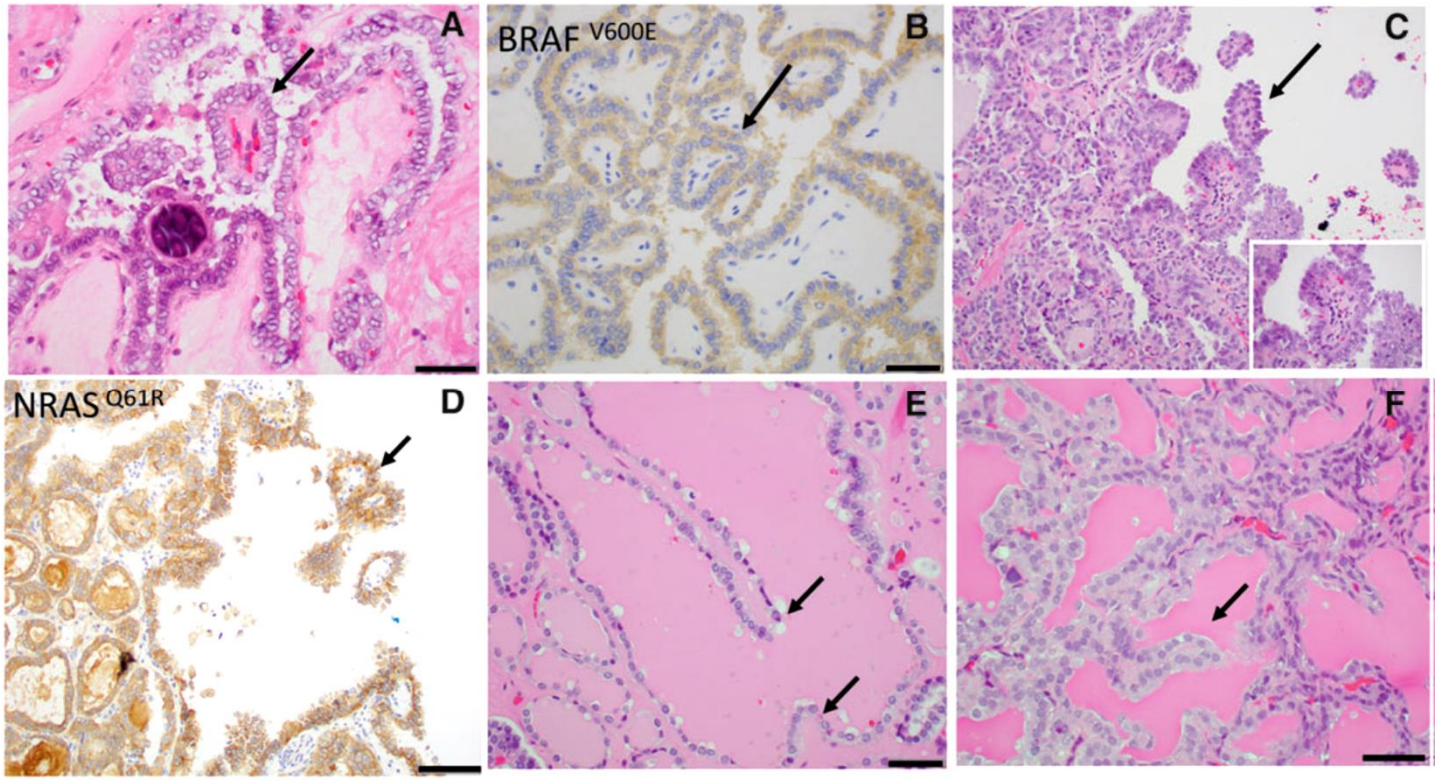


FIG. 1. Papillae in U-EPTC. (A, B) True papillae with fibrovascular cores (arrows) (A, H&E) in a classical PTC almost completely composed of papillae BRAFV600E-positive by immunohistochemistry (B). (C, D) An encapsulated PTC with follicular predominant growth pattern containing occasional (<1%) papillary structures (arrows). Inset shows typical PTC nuclei (C, H&E); neoplastic cells are positive for NRASQ61R by immunohistochemistry (D). (E) Pseudopapillae not fulfilling the definition of true papillae since they lack fibrovascular core (arrows) (F) Pseudopapilla not fulfilling the definition of true papillae since it lacks fibrovascular core and appears to represent an artefactually ruptured septa. H&E, hematoxylin and eosin; PTC, papillary thyroid carcinoma; U-EPTC, unifocal encapsulated PTC [Xu B et al. How Many Papillae in Conventional Papillary Carcinoma? A Clinical Evidence-Based Pathology Study of 235 Unifocal Encapsulated Papillary Thyroid Carcinomas, with Emphasis on the Diagnosis of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features. Thyroid. 2019 Dec;29(12):1792-1803. doi: 10.1089/thy.2019.0328]

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a non-invasive encapsulated/well demarcated follicular cell derived tumour with a follicular growth pattern and nuclei resembling papillary thyroid carcinoma (PTC) that has an extremely low malignant potential (previously: non invasive encapsulated follicular variant papillary thyroid carcinoma)

- RAS-like molecular alterations (mostly NRAS, but also EIF1AX, BRAF p.K601E and other BRAF non-V600E mutations, PPARG and THADA rearrangements
- Prevalence much lower in Asia (0.5-5%) compared to Western countries (up to 15-20%, especially North America), but also significant variation between different institutions within the same geographical location due to variable use of the term

➢ **Essential and desirable diagnostic criteria**

Essential:

1. Encapsulation or clear demarcation
2. Follicular growth pattern with all of the following: <1% true papillae; No psammoma bodies; <30% solid/trabecular/insular growth pattern
3. Nuclear features of papillary carcinoma (nuclear score of 2-3)
4. No vascular or capsular invasion
5. No tumour necrosis
6. Low mitotic count (<3 mitosis / $2mm^2$)
7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant (tall cell features, cribriform-morular variant, solid variant, etc)

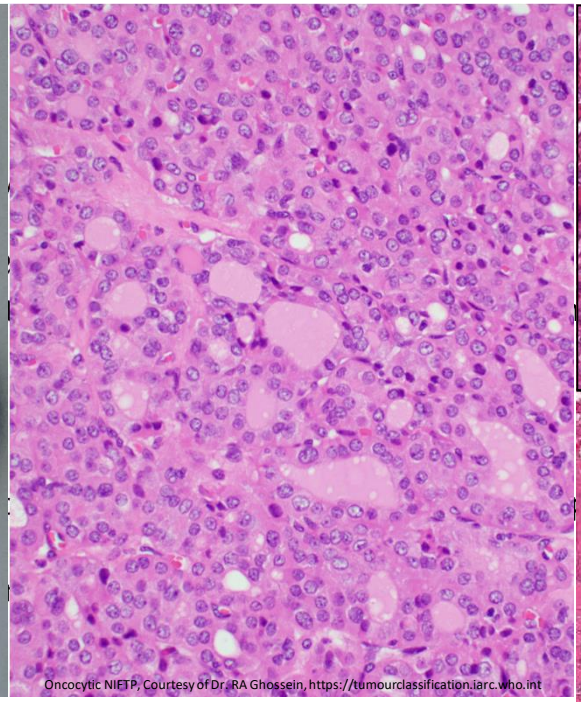
Desirable:

Immunohistochemistry or molecular testing for *BRAF* and *NRAS* mutation: *BRAF* p.V600E excludes the diagnosis

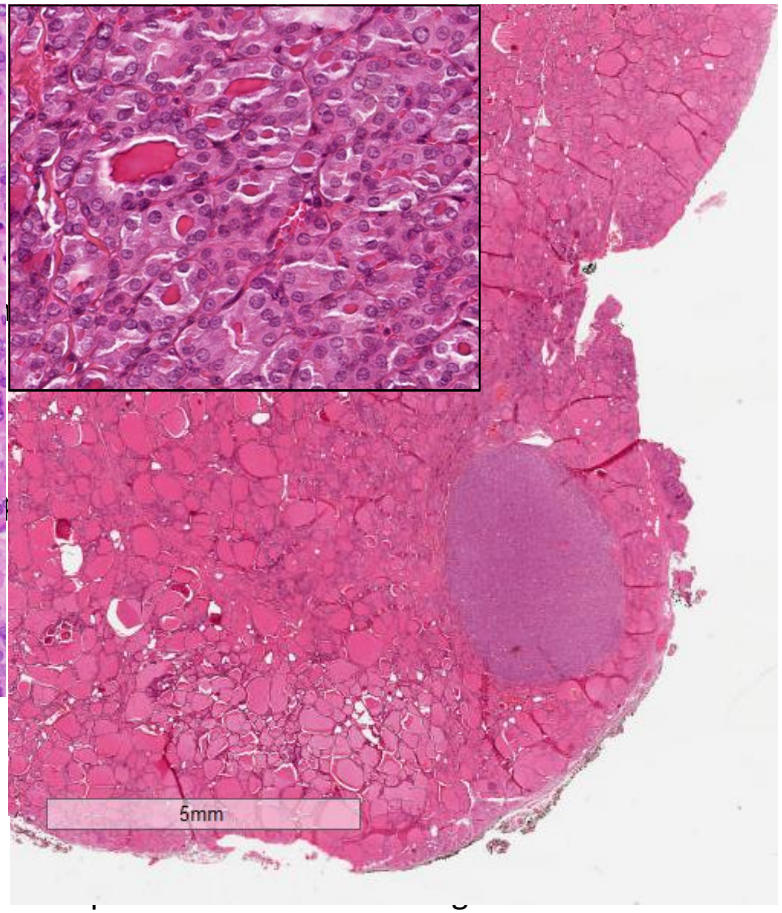
- **NIFTP terminology can be applied to subcentimeter (<10 mm NIFTP) and oncocytic tumors (Oncocytic NIFTP)**

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP

Courtesy of Dr. RA Ghossein, https://tumourclassification.iarc.who.int



Oncocytic NIFTP, Courtesy of Dr. RA Ghossein, https://tumourclassification.iarc.who.int



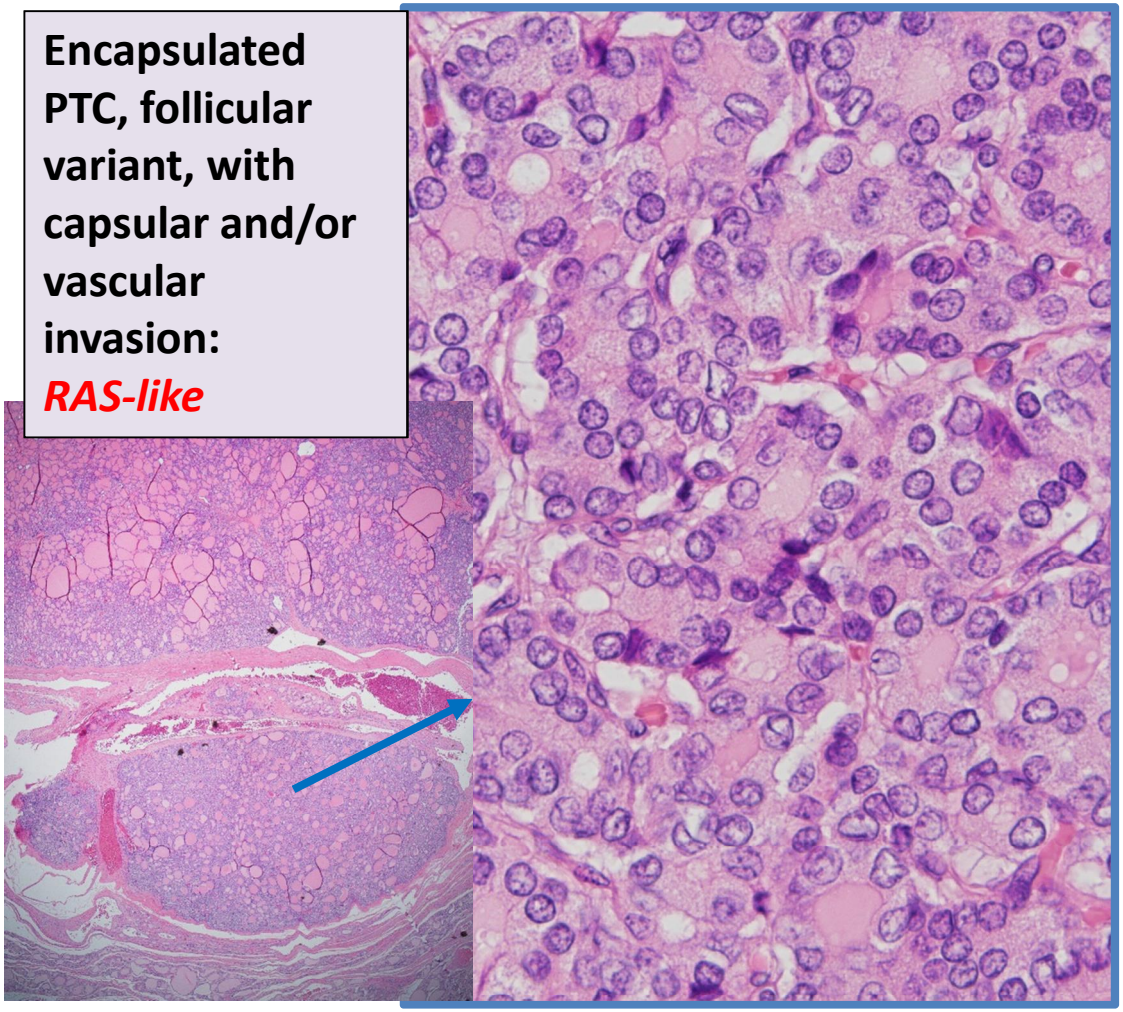
Xu B, Reznik E, Tuttle RM, Knauf J, Fagin JA, Katabi N, Dogan S, Aleynick N, Seshan V, Middha S, Enepekides D, Casadei GP, Solaroli E, Tallini G, Ghossein R, Ganly I. Outcome and molecular characteristics of non-invasive encapsulated follicular variant of papillary thyroid carcinoma with oncocytic features. Endocrine. 2019 Apr;64(1):97-108

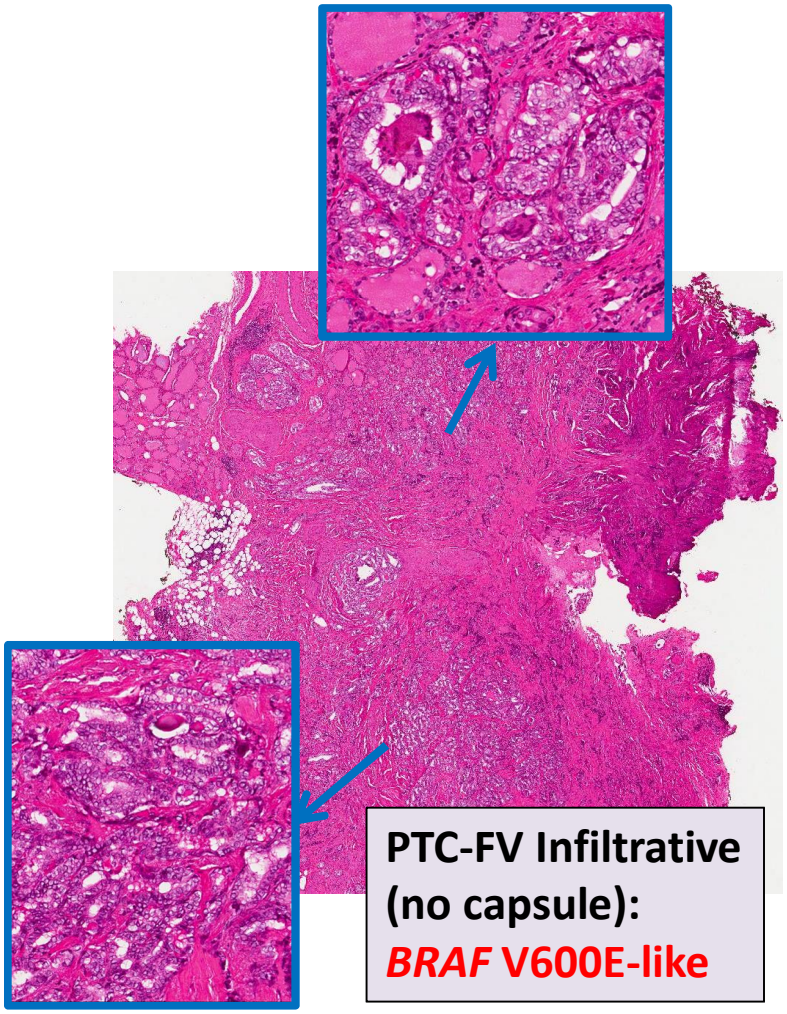
Xu B, Farhat N, Barletta JA, Hung YP, Biase D, Casadei GP, Onenerk AM, Tuttle RM, Roman BR, Katabi N, Nosé V, Sadow P, Tallini G, Faquin WC, Ghossein R. Should subcentimeter non-invasive encapsulated, follicular variant of papillary thyroid carcinoma be included in the noninvasive follicular thyroid neoplasm with papillary-like nuclear features category? Endocrine. 2018 Jan;59(1):143-150

- **NIFTP terminology can be applied to subcentimeter (<10 mm NIFTP) and oncocytic tumors (Oncocytic NIFTP)**

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP

Encapsulated PTC, follicular variant, with capsular and/or vascular invasion:
RAS-like

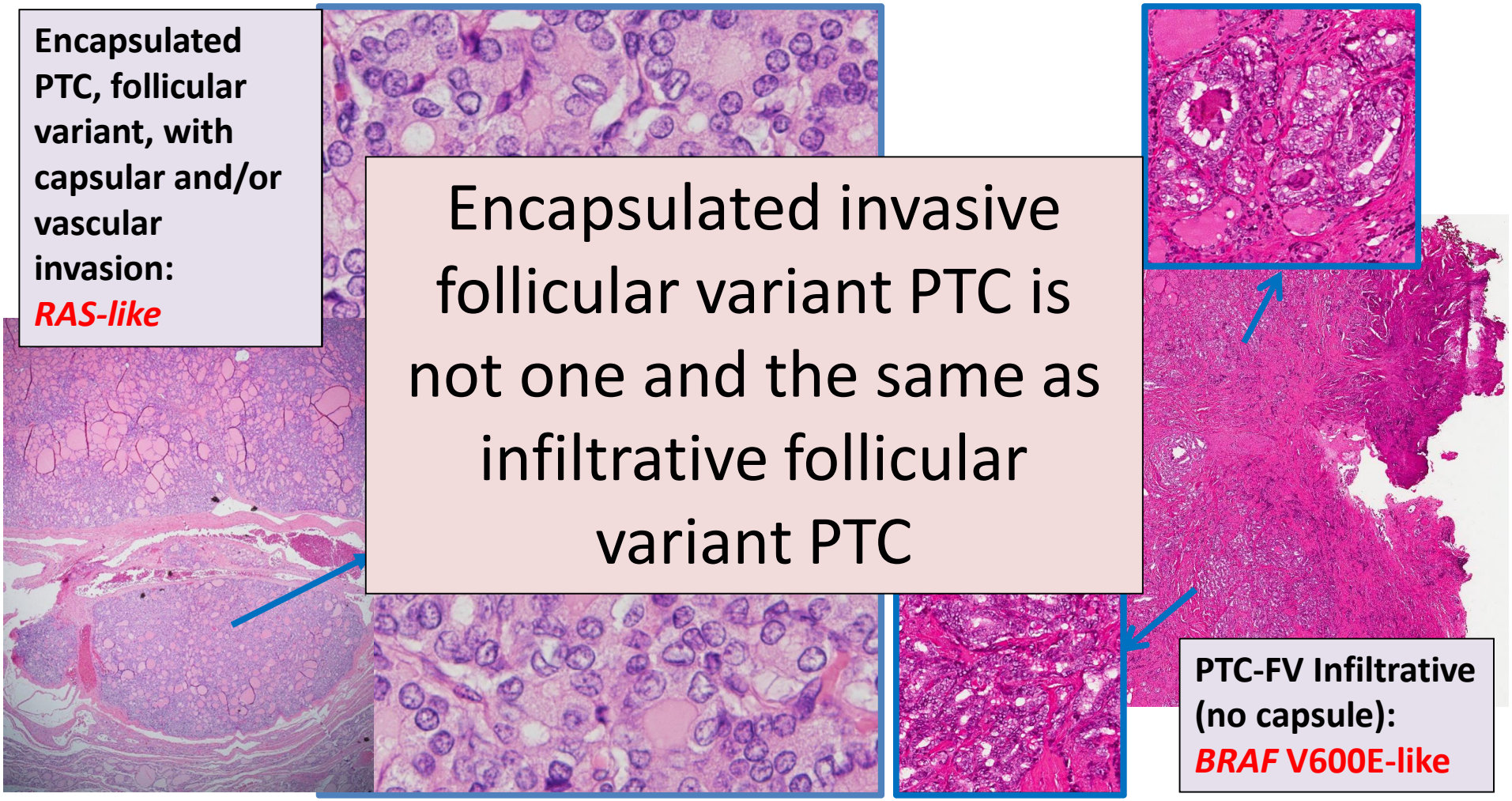




PTC-FV Infiltrative (no capsule):
***BRAF* V600E-like**

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP

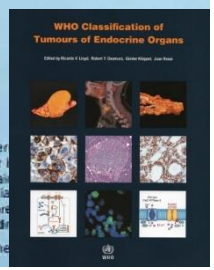
Encapsulated PTC, follicular variant, with capsular and/or vascular invasion:
RAS-like



Encapsulated invasive follicular variant PTC is not one and the same as infiltrative follicular variant PTC

PTC-FV Infiltrative (no capsule):
***BRAF* V600E-like**

Follicular adenoma	8330/0
Hyalinizing trabecular tumour	8336/1*
Other encapsulated follicular-patterned thyroid tumours	
Follicular tumour of uncertain malignant potential	8335/1*
Well-differentiated tumour of uncertain malignant potential	8348/1*
Non-invasive follicular thyroid neoplasm with papillary-like nuclear features	8349/1*
Papillary thyroid carcinoma (PTC)	
Papillary carcinoma	8260/3
Follicular variant of PTC	8340/3
Encapsulated variant of PTC	8343/3
Papillary microcarcinoma	8341/3
Columnar cell variant of PTC	8344/3
Oncocytic variant of PTC	8342/3
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 tumours	
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
Mixed medullary and follicular thyroid carcinoma	8346/3
Mucoepidermoid carcinoma	8430/3
Sclerosing mucoepidermoid carcinoma with eosinophilia	8430/3
Mucinous carcinoma	8480/3
Ectopic thymoma	8580/3
Spindle epithelial tumour with thymus-like differentiation	8588/3
Intrathyroid thymic carcinoma	8589/3
Paraganglioma and mesenchymal/stromal tumours	
Paraganglioma	8693/3
Peripheral nerve sheath tumours (PNSTs)	
Schwannoma	9560/0
Malignant PNST	9540/3
Benign vascular tumours	
Haemangioma	9120/0
Cavernous haemangioma	9121/0
Lymphangioma	9170/0
Angiosarcoma	9120/3
Smooth muscle tumours	
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Solitary fibrous tumour	8815/1
Haematolymphoid tumours	
Langerhans cell histiocytosis	9751/3
Rosai-Dorfman disease	
Follicular dendritic cell sarcoma	9758/3
Primary thyroid lymphoma	
Germ cell tumours	
Benign teratoma (grade 0 or 1)	9080/0
Immature teratoma (grade 2)	9080/1
Malignant teratoma (grade 3)	9080/3
Secondary tumours	



The morphology codes are from the Inter
for Oncology (ICD-O) (8936A). Behaviour
/1 for unspecified, borderline, or uncerta
situ and grade III intraepithelial neoplas
The classification is modified from the pr
into account changes in our understandi

*These new codes were approved by the

tumourclassification.iarc.who.int/chapters/53

3. Thyroid gland

- Introduction
- **Developmental abnormalities**
  - Thyroglossal duct cyst
  - Other congenital thyroid abnormalities
- **Follicular cell-derived neoplasms**
  - *Benign tumours*
    - Thyroid follicular nodular disease
    - Follicular thyroid adenoma
    - Follicular thyroid adenoma with papillary architecture
    - Oncocytic adenoma of the thyroid
  - *Low risk neoplasms*
    - Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
    - Thyroid tumours of uncertain malignant potential
    - Hyalinizing trabecular tumour of thyroid
  - *Malignant neoplasms*
    - Follicular thyroid carcinoma
    - Invasive encapsulated follicular variant papillary carcinoma
    - Papillary thyroid carcinoma
    - Oncocytic carcinoma of the thyroid
    - Follicular-derived carcinomas, high-grade
    - Anaplastic follicular cell derived thyroid carcinoma
- **Thyroid C-cell derived carcinoma**
  - Medullary thyroid carcinoma
- **Mixed medullary and follicular-cell derived carcinomas**
  - Mixed medullary and follicular cell-derived thyroid carcinoma
- **Salivary gland-type carcinomas of the thyroid**
  - Mucoepidermoid carcinoma of the thyroid
  - Secretory carcinoma of salivary gland type
- **Thyroid tumours of uncertain histogenesis**
  - Sclerosing mucoepidermoid carcinoma with eosinophilia
  - Cribriform morular thyroid carcinoma
- **Thymic tumours within the thyroid**
  - Thymoma family
  - Spindle epithelial tumour with thymus-like elements
  - Thymic carcinoma family
- **Embryonal thyroid neoplasms**
  - Thyroblastoma

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

Tumours of uncertain malignant potential (UMP) are well-differentiated thyroid tumours with follicular architecture that are encapsulated or unencapsulated but well circumscribed, in which invasion remains questionable after thorough sampling and exhaustive examination.

Subtype(s)

- Follicular tumour of uncertain malignant potential (FT-UMP);
- Well-differentiated tumour of uncertain malignant potential (WDT-UMP)

➢ **Essential and desirable diagnostic criteria**

Essential:

Questionable invasion; the feature of concern, i.e. invasion of vessels and/or of the tumour capsule must be specified. No pseudo invasive artifacts. No high grade morphology.

Desirable:

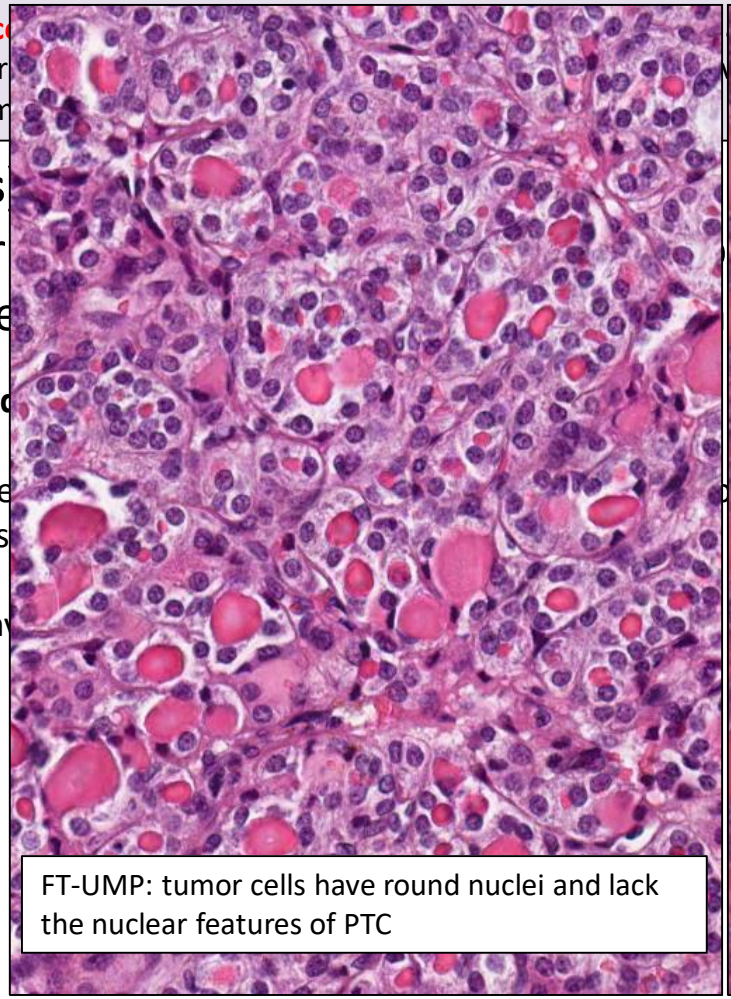
Molecular investigation for HRAS, KRAS, or NRAS mutations; BRAF p.V600E, TP53 or TERT promoter mutation

Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5TH edition

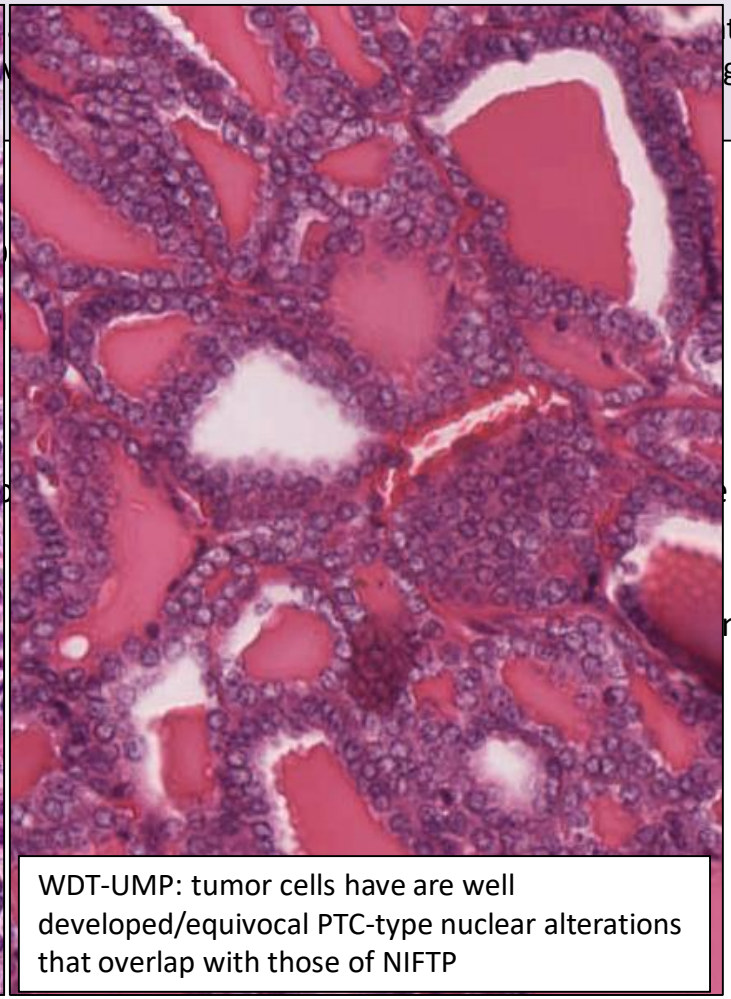
Tumours of unc t are
encapsulated or g and
exhaustive exam

Subtype(s
- Follicular
- Well-diffe

➢ **Essential and**
Essential:
Questionable specified. No
pseudo invas
Desirable:
Molecular in n

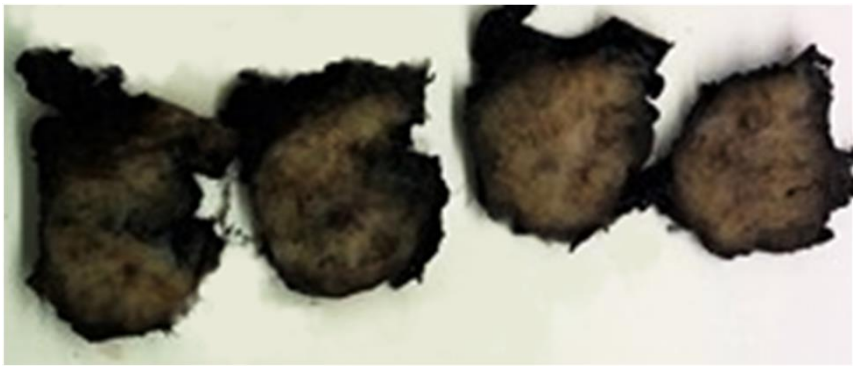


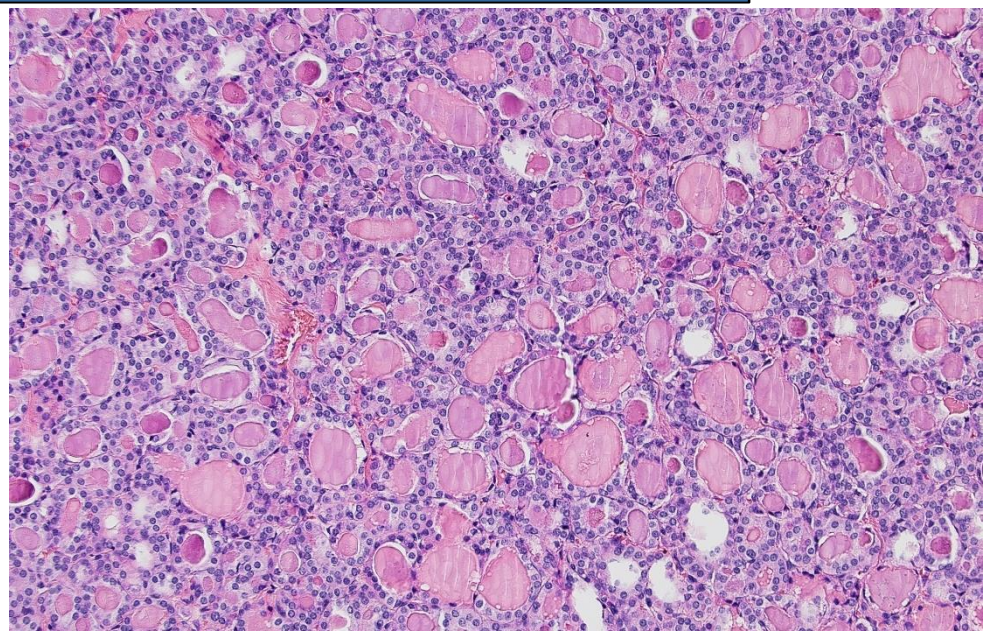
FT-UMP: tumor cells have round nuclei and lack the nuclear features of PTC



WDT-UMP: tumor cells have are well developed/equivocal PTC-type nuclear alterations that overlap with those of NIFTP

Tumors of uncertain malignant potential (UMP)





Iatrogenic laceration artifacts: not a tumor uncertain malignant potential, but report as:

Follicular tumor/well differentiated tumor Not otherwise specified *(FT-UMP/WDT-UMP NAS), extensive discontinuation of tumor to non-neoplastic interface precludes adequate assessment of invasion*

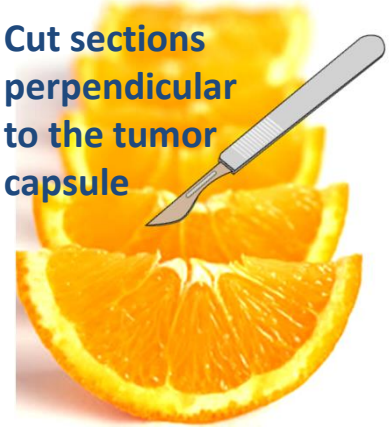
Tumors of uncertain malignant potential (UMP)

- Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**
- *For a diagnosis of carcinoma the burden of proof in on the pathologist who makes the diagnosis (Avoid overdiagnosis: Primum non nocere, Innocent unless proven guilty…)*

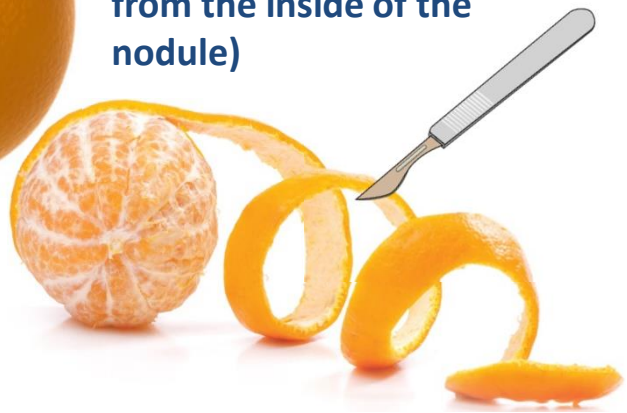
La Giustizia in trono (Trittico della Giustizia),
Jacobello del Fiore (1370 – 1439),
Gallerie dell'Accademia di Venezia.

Tumors of uncertain malignant potential (UMP): proper sampling to rule out invasion

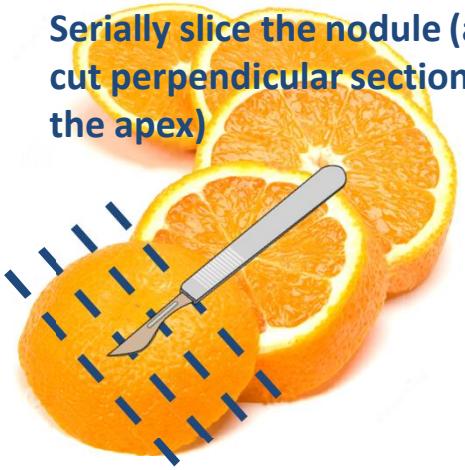
Cut sections perpendicular to the tumor capsule

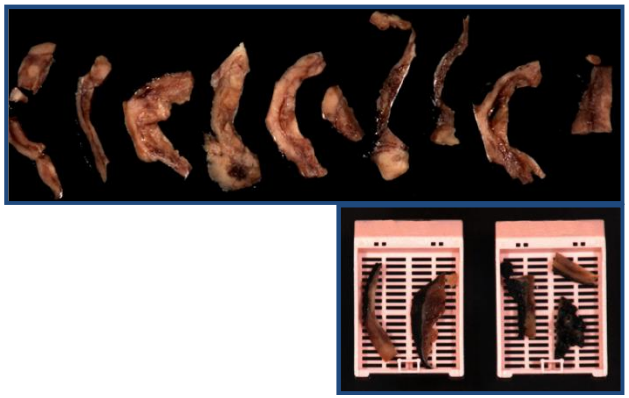


”peel ” the capsule (and submit additional sections from the inside of the nodule)



Serially slice the nodule (and cut perpendicular sections at the apex)



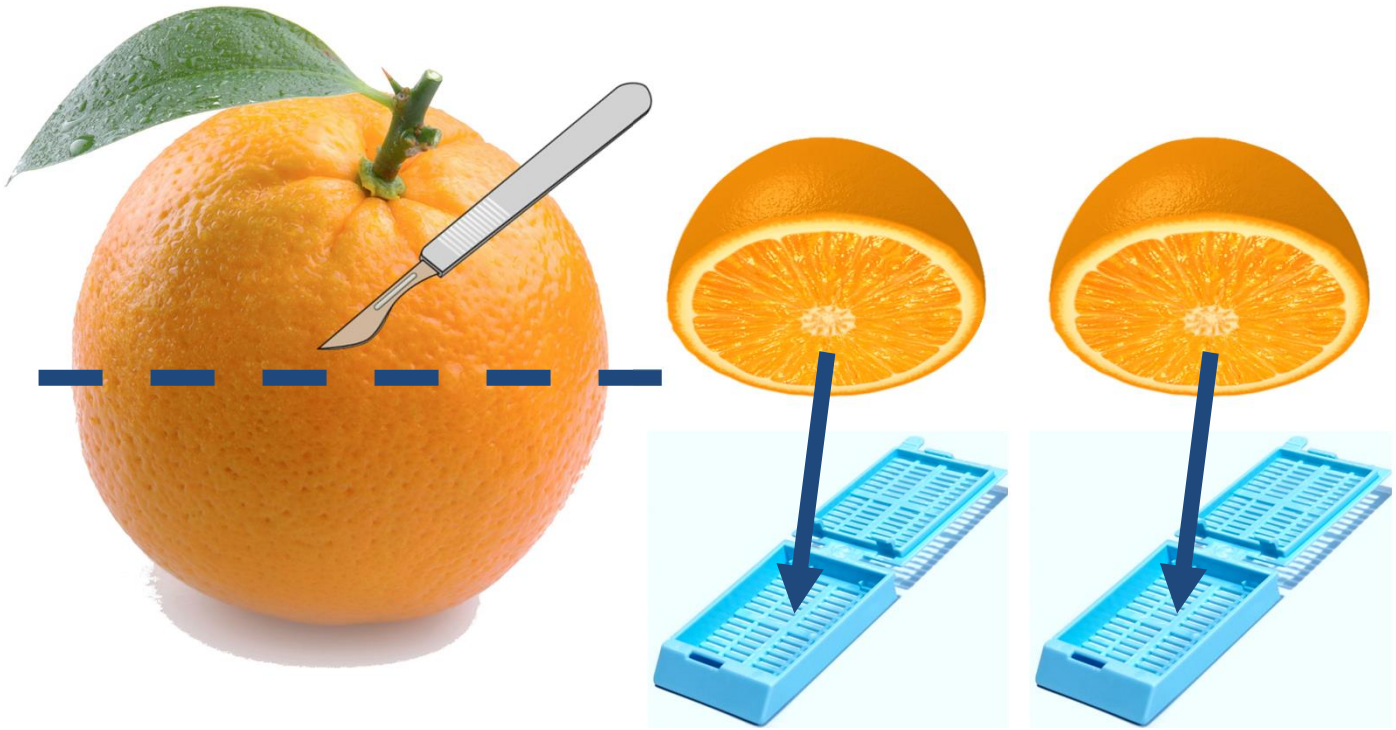


Tumors of uncertain malignant potential (UMP): proper sampling to rule out invasion

Alternative «Mango recepy» (Courtesy of Dr. O. Tsybrovskyy): formalin fixation flattens the tumor capsule…

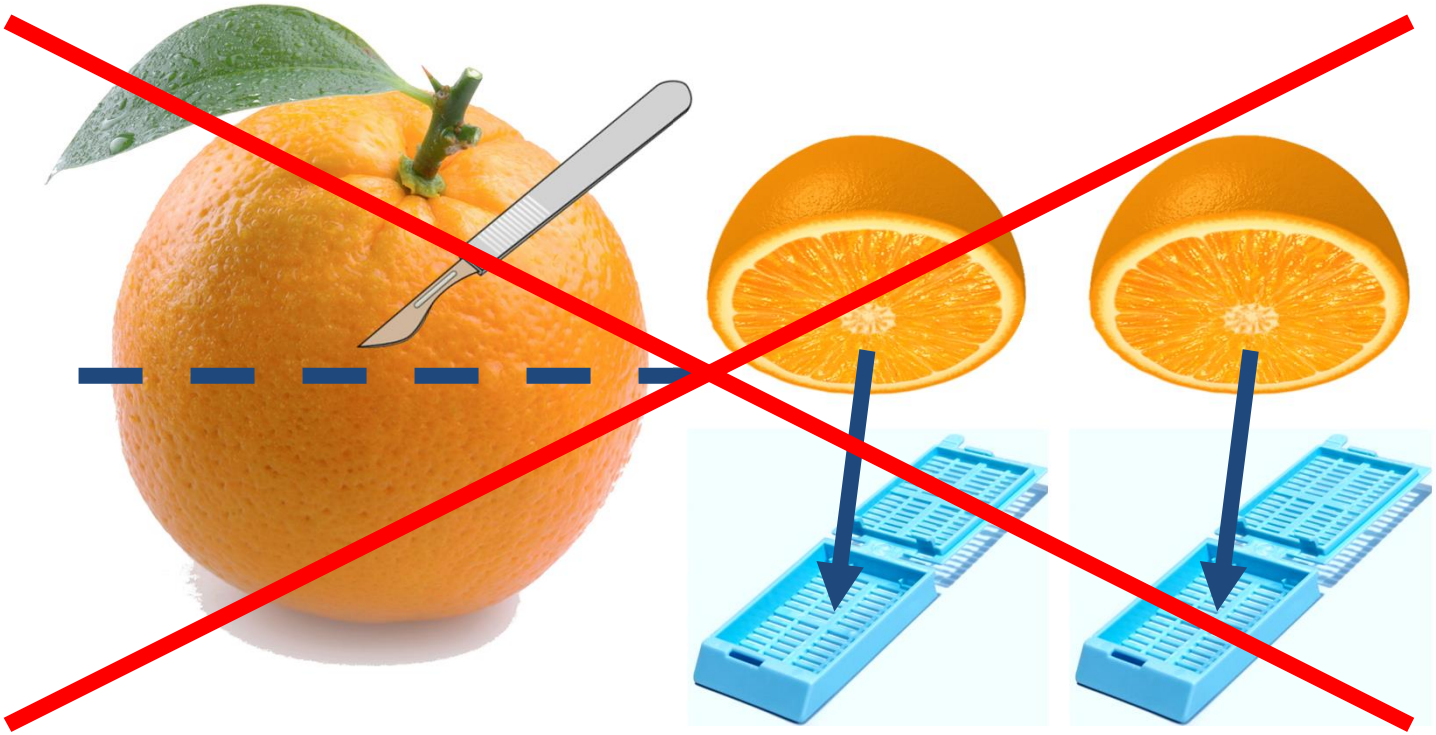
Tumors of uncertain malignant potential (UMP): proper sampling to rule out invasion

Never cut a thyroid nodule in large sections and squeeze them in a few cassettes: the nodule is embedded in toto, but the tumor interface with the surrounding parenchyma can never be properly examined microscopically, unless the paraffin is melted, the sections are properly recut and reprocessed….



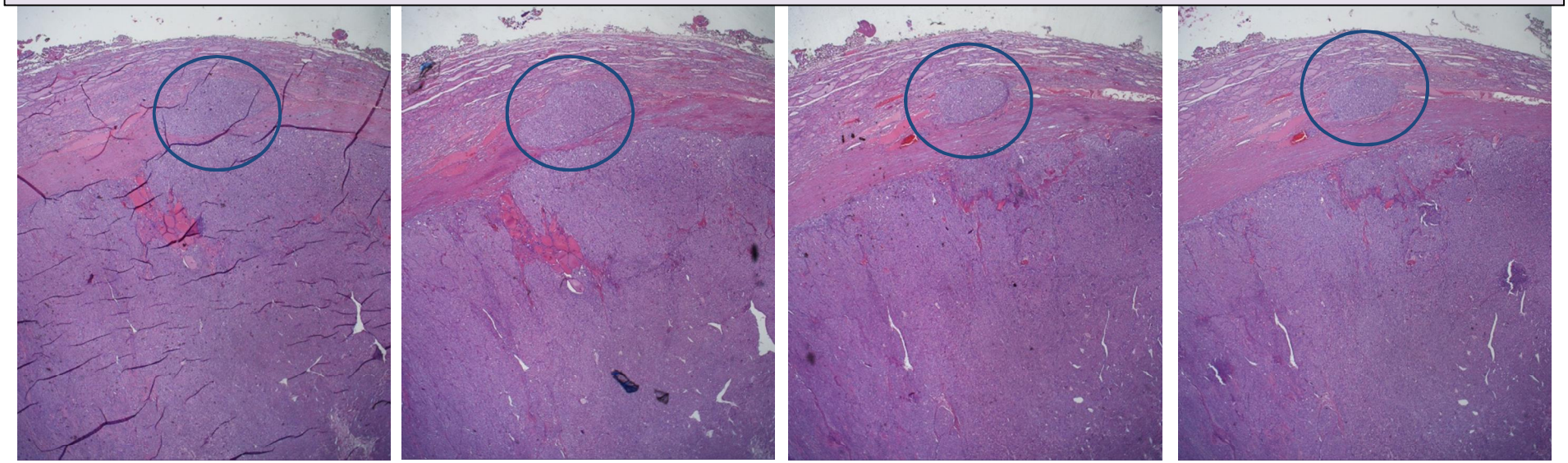
Tumors of uncertain malignant potential (UMP): proper sampling to rule out invasion

Never cut a thyroid nodule in large sections and squeeze them in a few cassettes: the nodule is embedded in toto, but the tumor interface with the surrounding parenchyma can never be properly examined microscopically, unless the paraffin is melted, the sections are properly recut and reprocessed….



Tumors of uncertain malignant potential (UMP): rule out capsular invasion

➢Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**

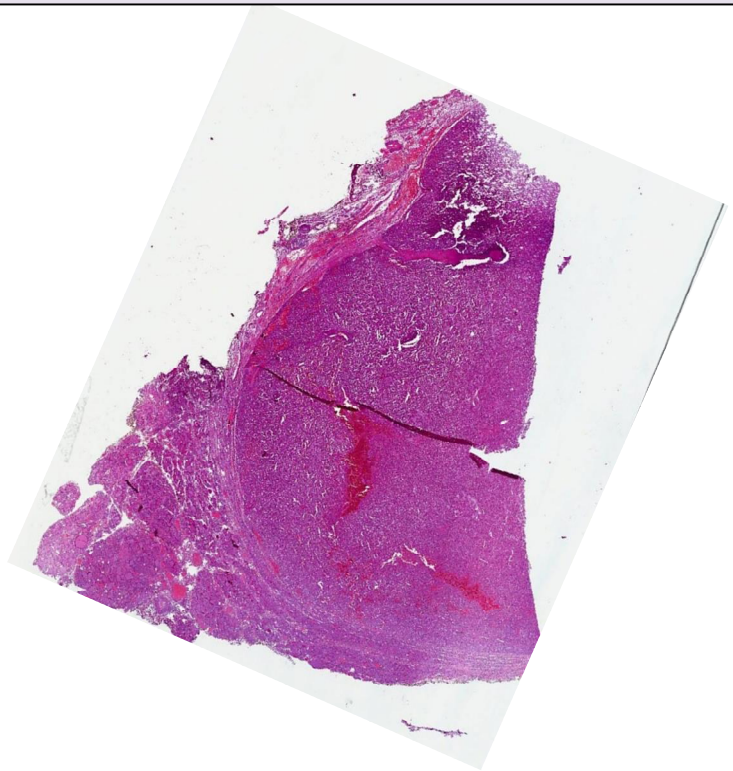


FT-UMP (Capsular invasion) → **Follicular carcinoma with capsular invasion**

Additional sections are important: three serial sections per block with foci suspicious for invasion

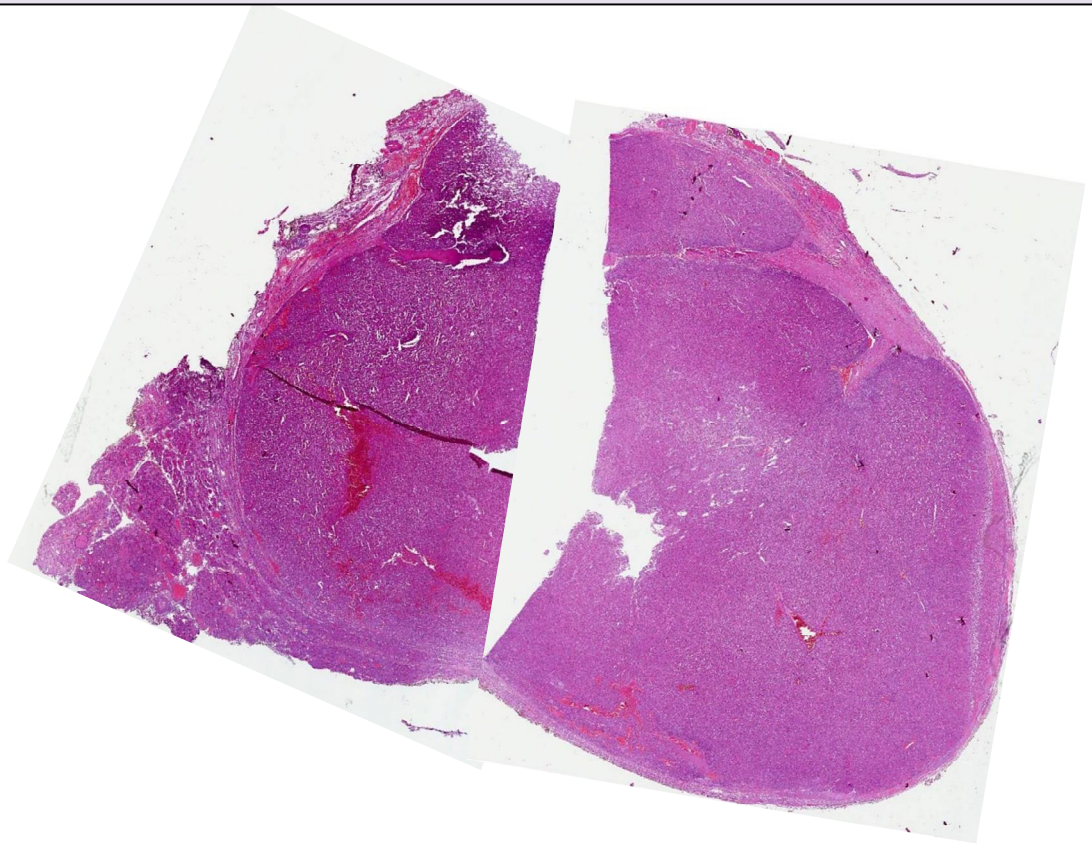
Tumors of uncertain malignant potential (UMP): rule out capsular invasion

- Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**



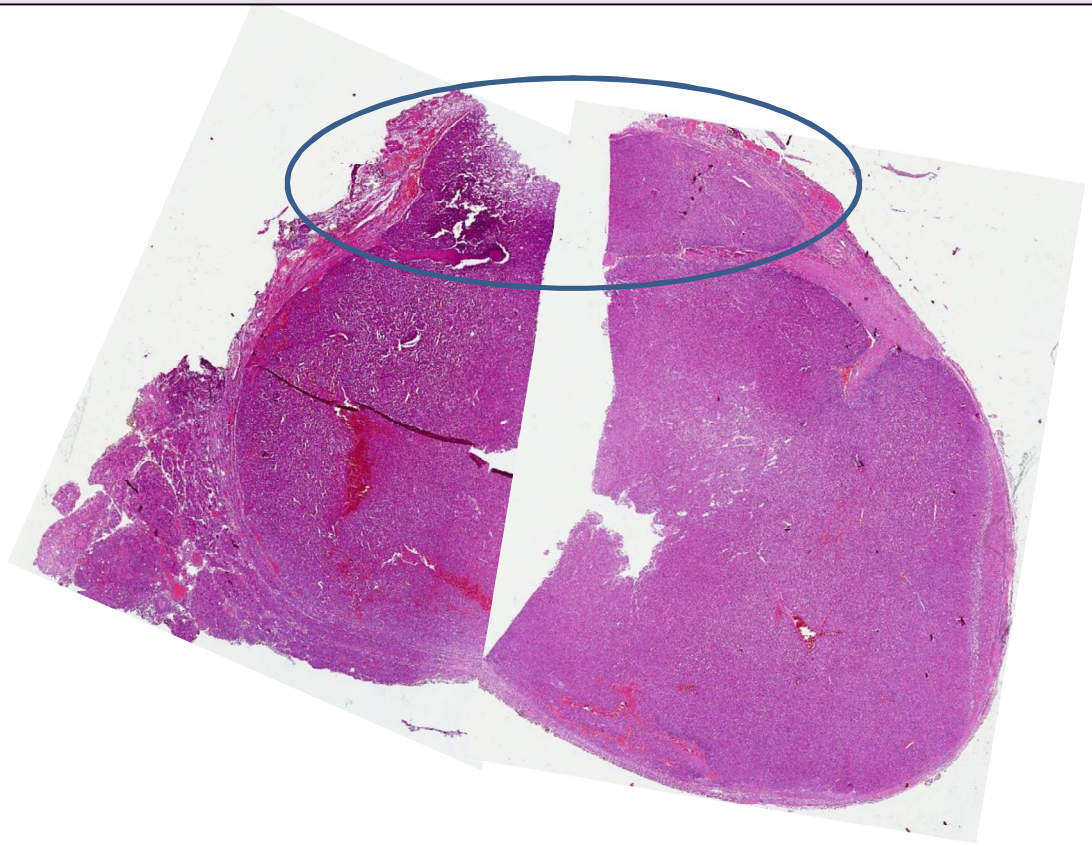
Tumors of uncertain malignant potential (UMP): rule out capsular invasion

- Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**



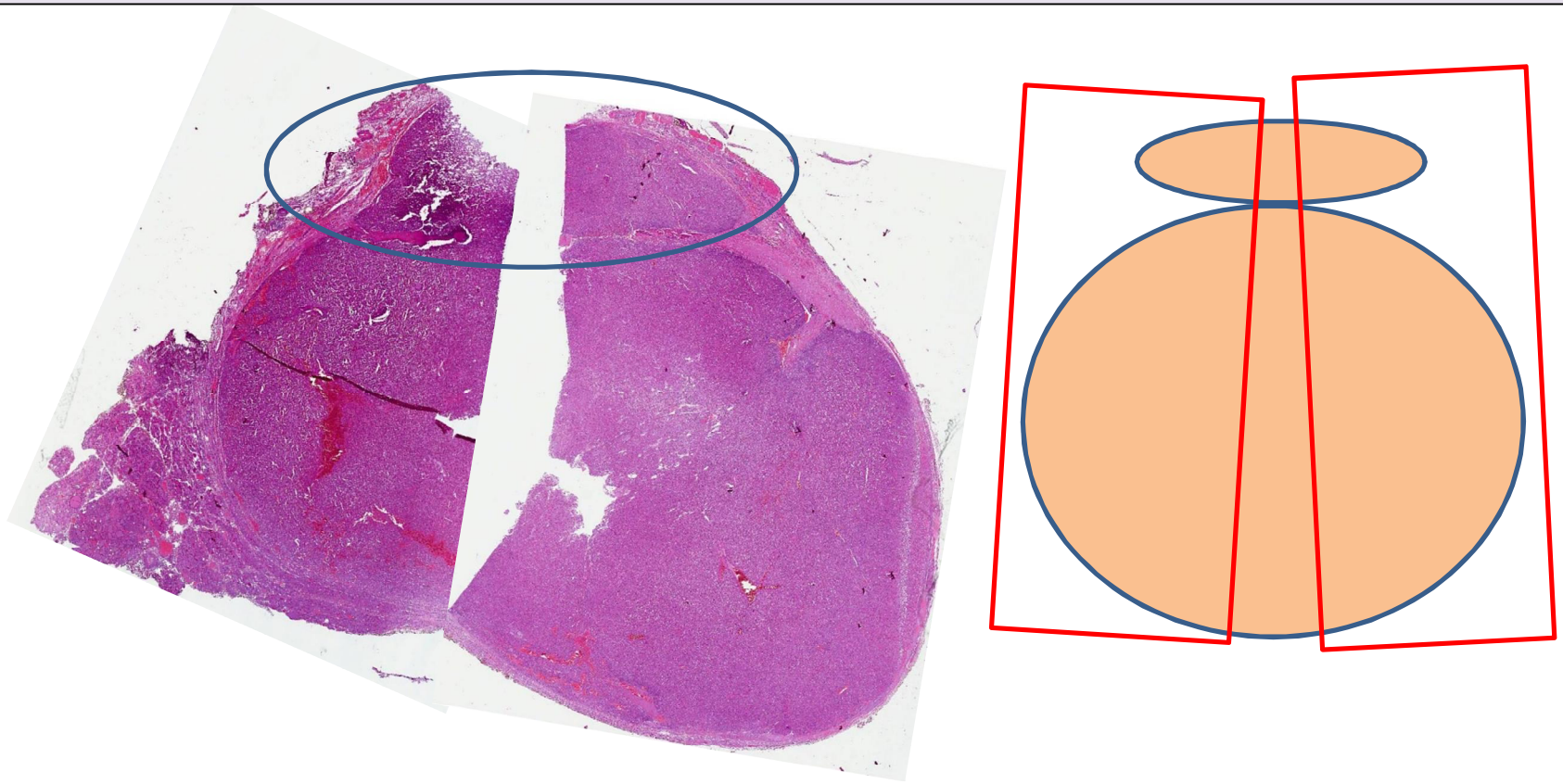
Tumors of uncertain malignant potential (UMP): rule out capsular invasion

- Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**



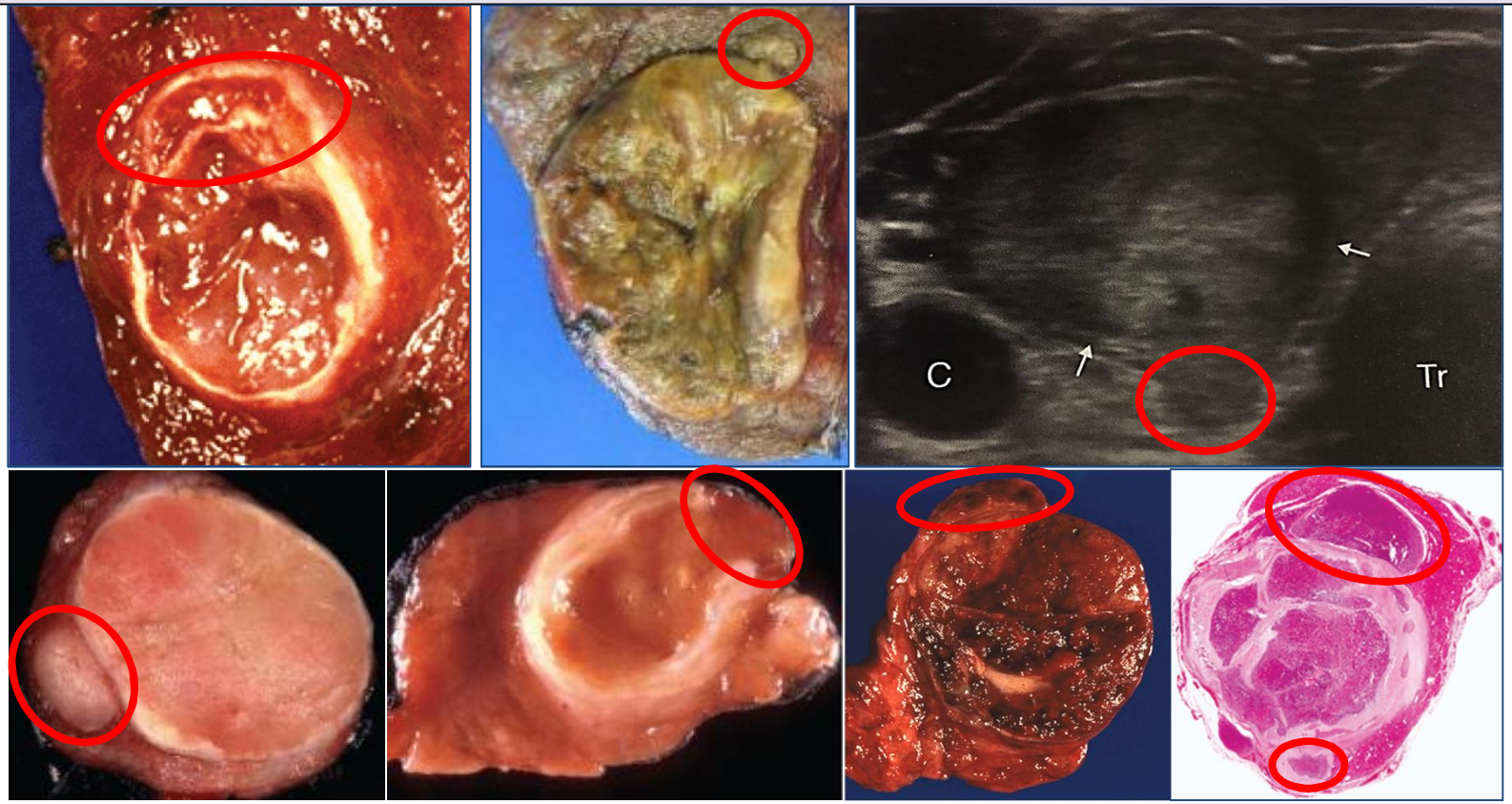
Tumors of uncertain malignant potential (UMP): rule out capsular invasion

- Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**

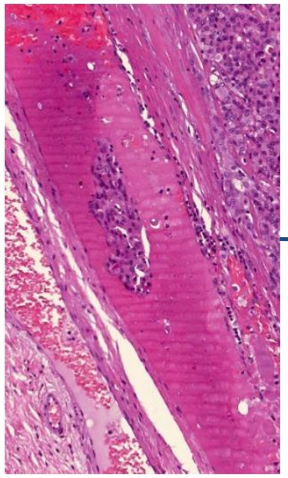


Tumors of uncertain malignant potential (UMP): rule out capsular invasion

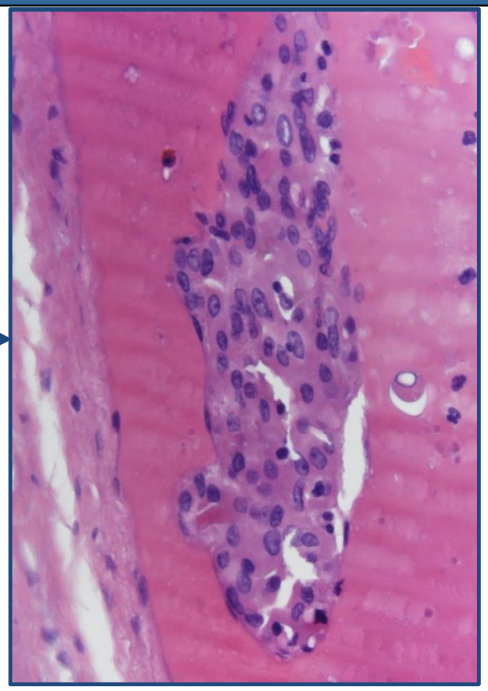
➢Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**

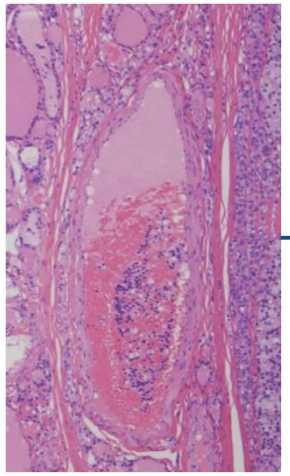


Tumors of uncertain malignant potential (UMP): rule out vascular invasion

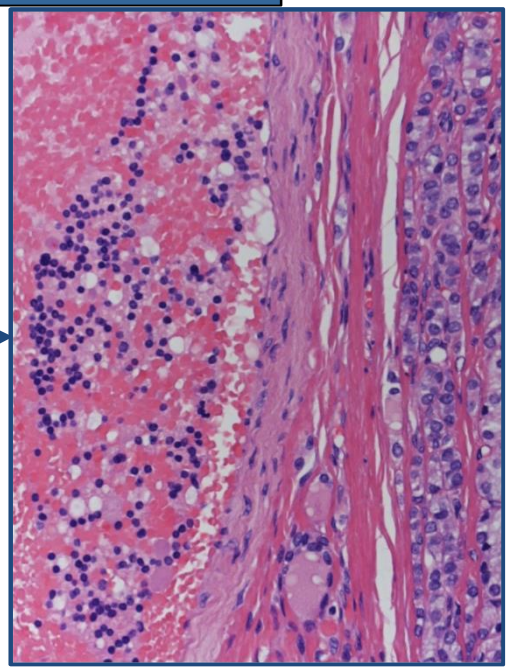


Vascular invasion: YES





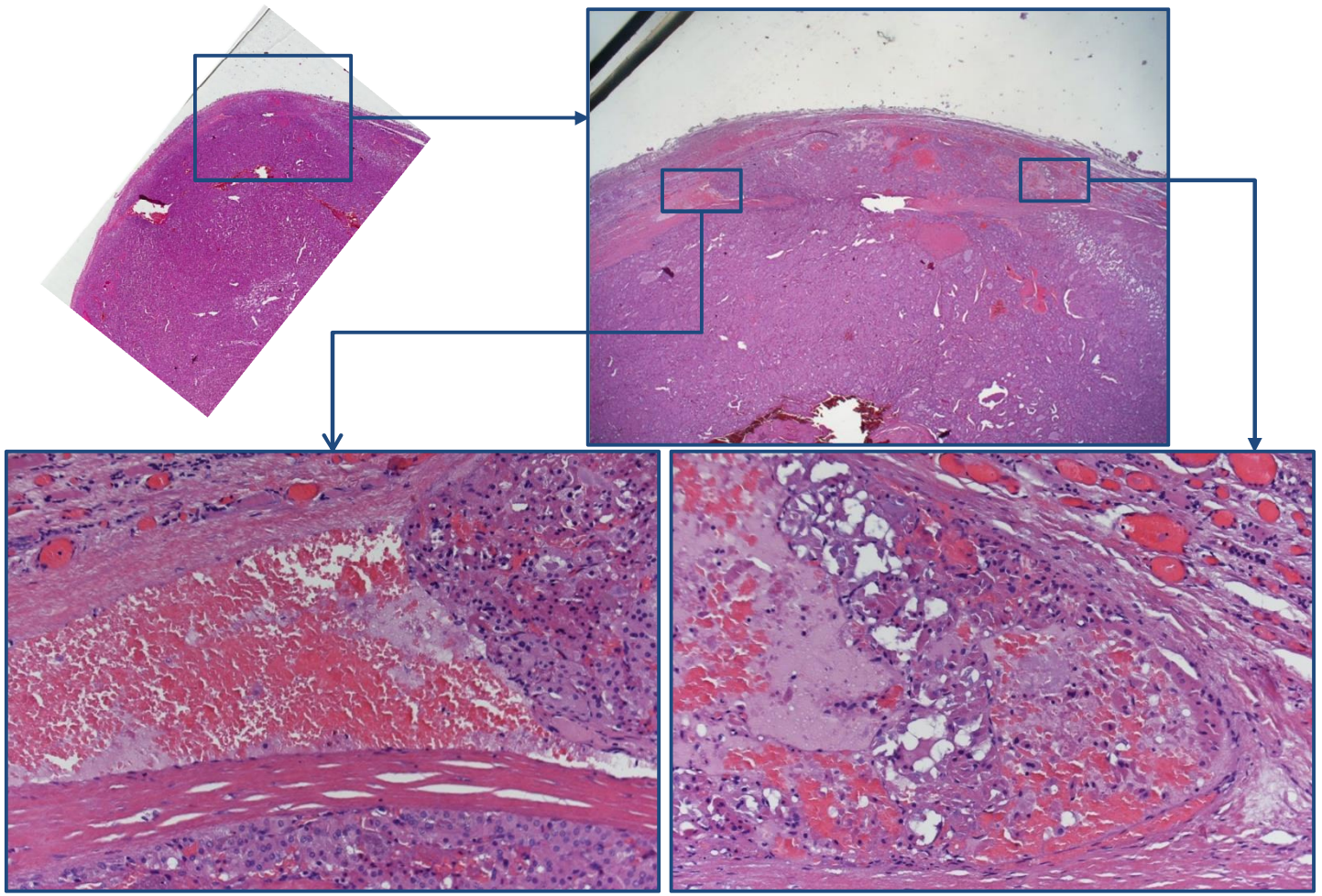
Vascular invasion: NO



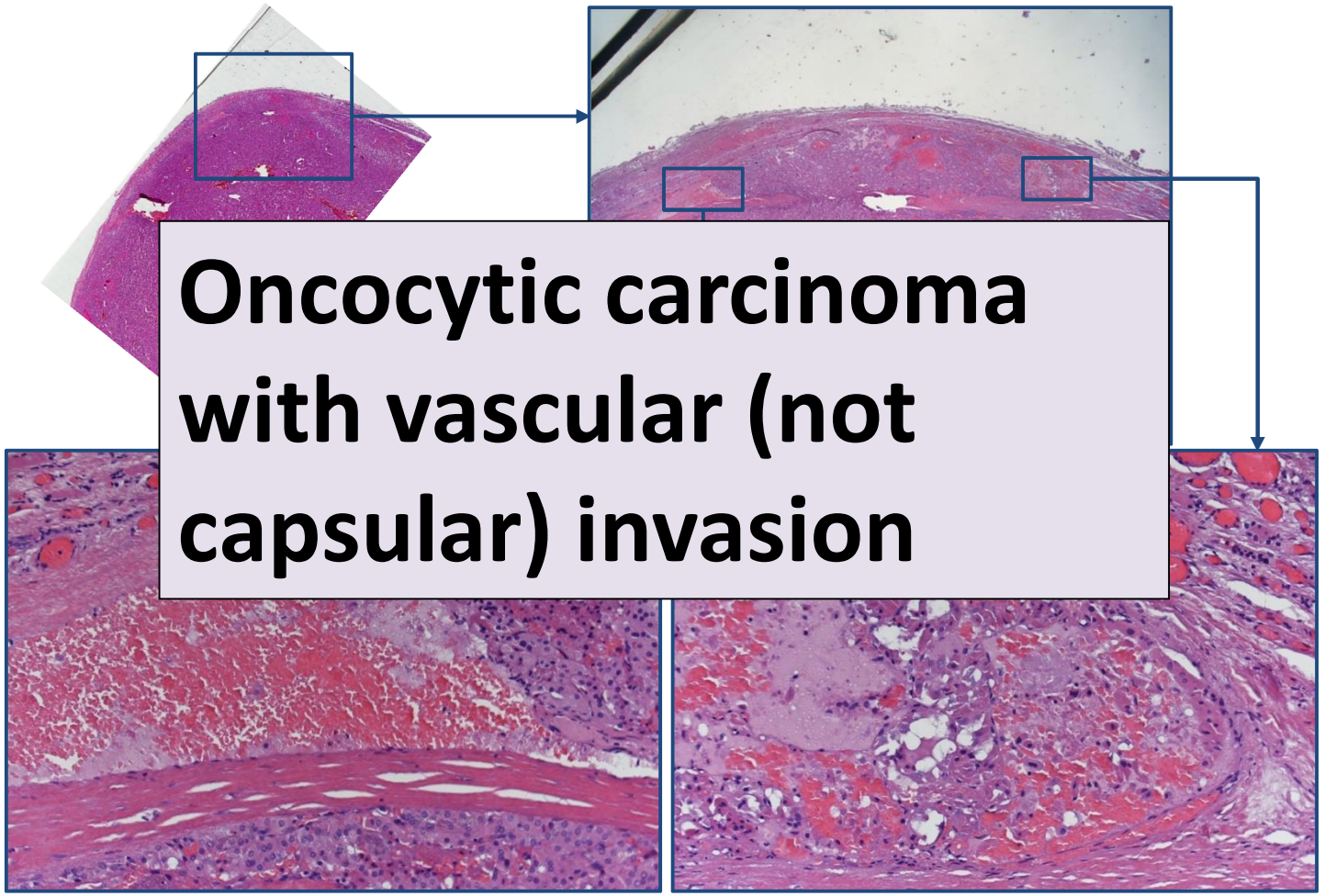
Requirements for a diagnosis of vascular invasion:

- Space lined by **endothelium** (i.e. a blood or lymphatic vessel)
- Cells in the vessel **must look like the cells inside the tumor**
- Cells in the vessel need to show **evidence that they have been "residing" in the vessel**: cell clusters projecting (in a "polypoid" fashion) or floating in the lumen must be covered by endothelium and/or show associated thrombus

Capsular vs. vascular invasion: it is important



Capsular vs. vascular invasion: it is important



Oncocytic carcinoma with vascular (not capsular) invasion

Tumors of uncertain malignant potential (UMP)

➢Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**

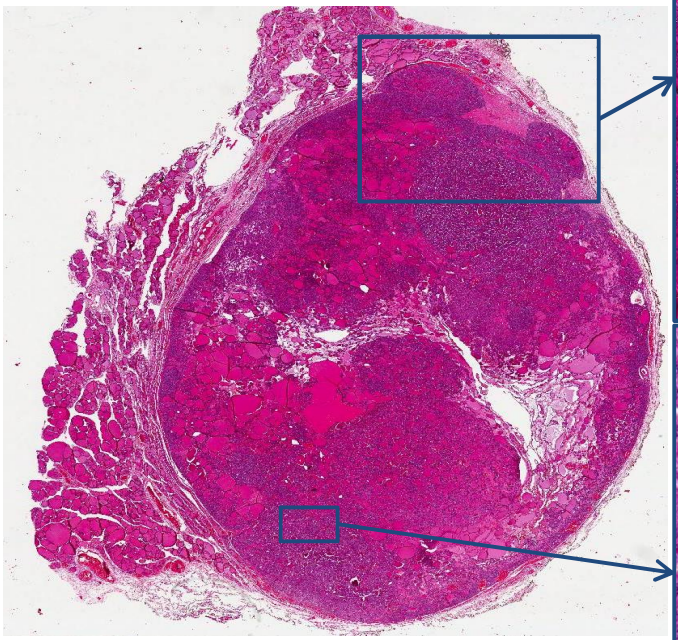
Questionable capsular invasion:

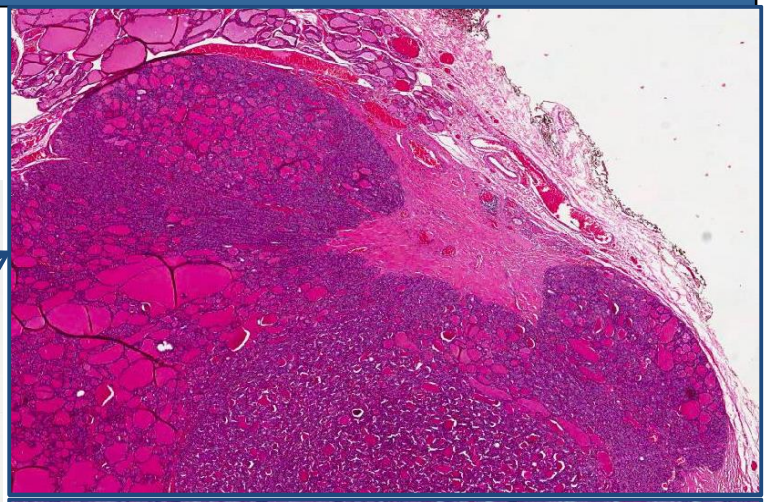
Invasion into but not completely through the capsule, as nests or as mushroom growths embedded in the fibrous capsular tissue

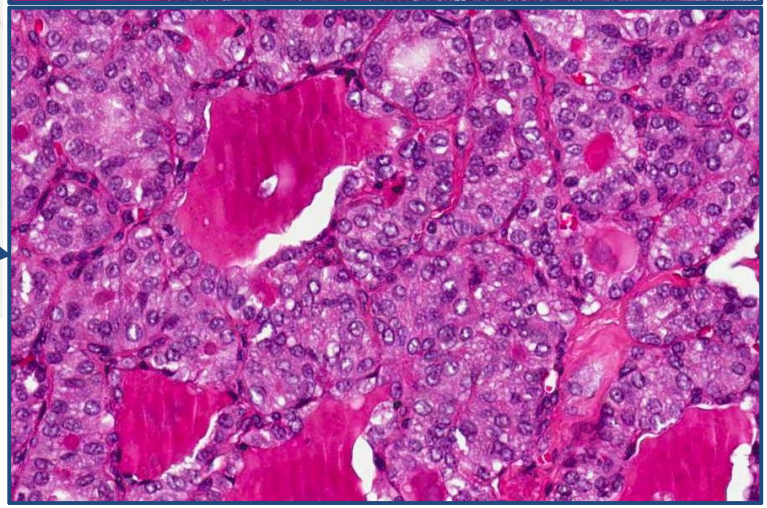
✓Particular concern: nodules with a thick capsule

Tumors of uncertain malignant potential (UMP)

WDT-UMP
(Capsular invasion)



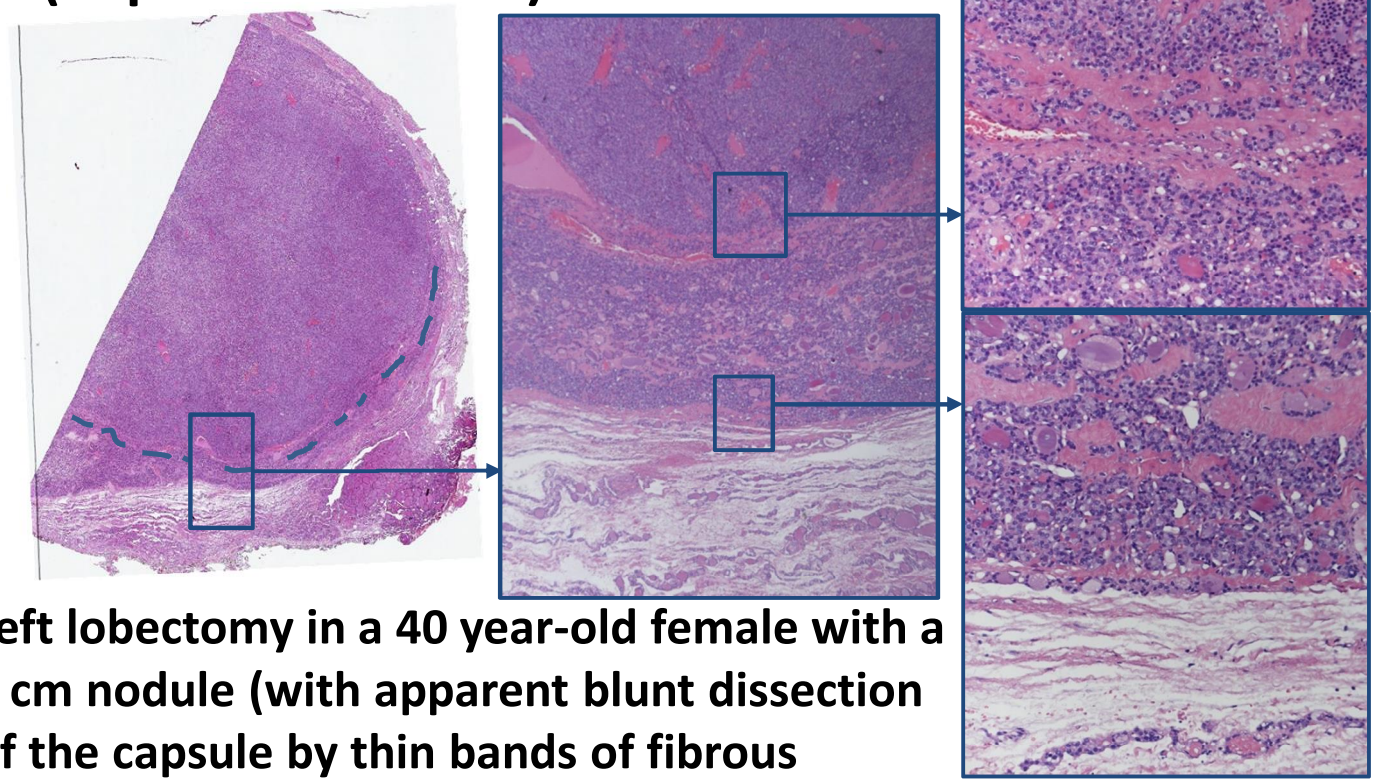




Thyroidectomy in a 44 year-old male with a 2.3 cm nodule in the left lobe

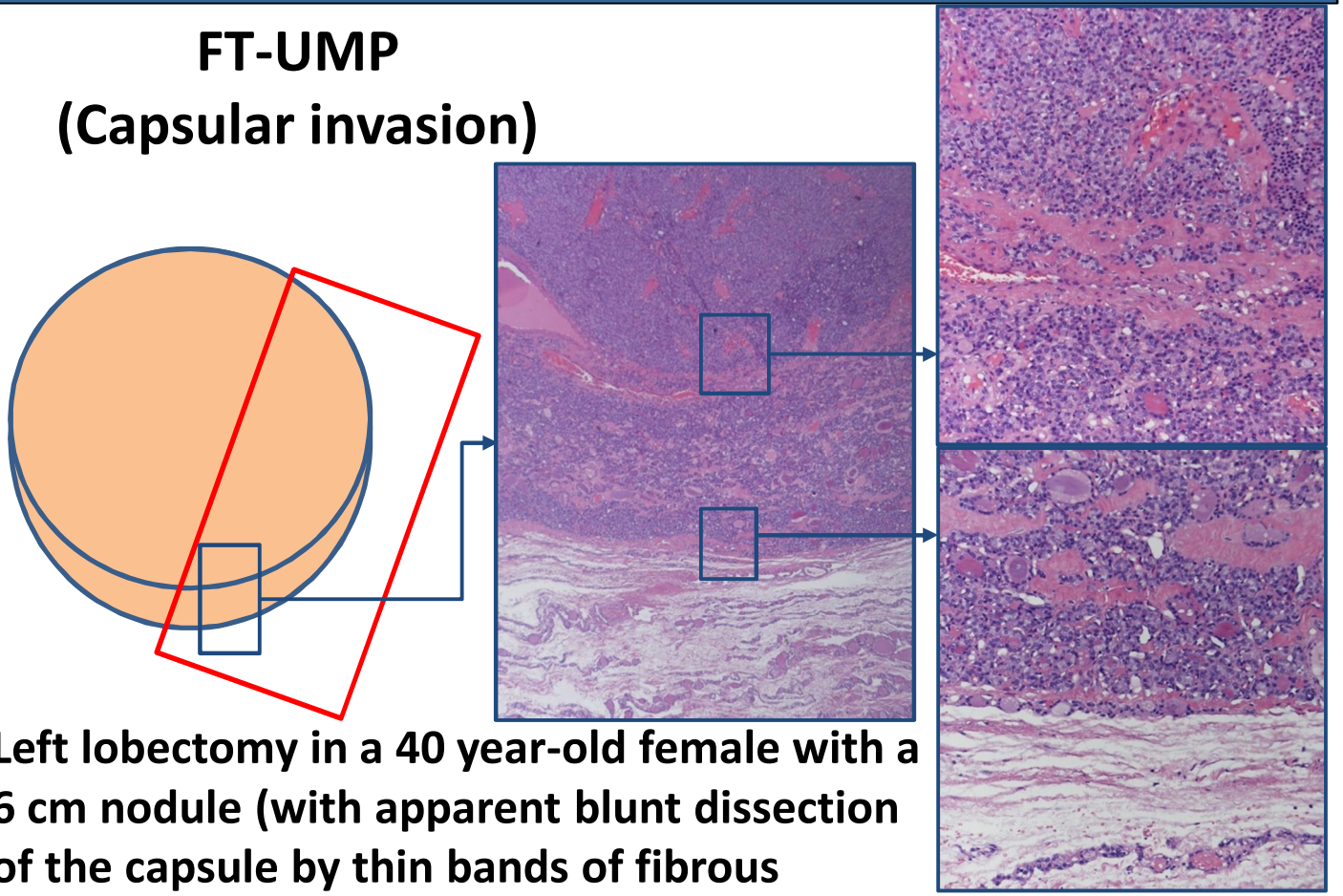
Tumors of uncertain malignant potential (UMP)

FT-UMP
(Capsular invasion)



Left lobectomy in a 40 year-old female with a 6 cm nodule (with apparent blunt dissection of the capsule by thin bands of fibrous tissue)

FT-UMP
(Capsular invasion)



Left lobectomy in a 40 year-old female with a 6 cm nodule (with apparent blunt dissection of the capsule by thin bands of fibrous tissue)

Tumors of uncertain malignant potential (UMP)

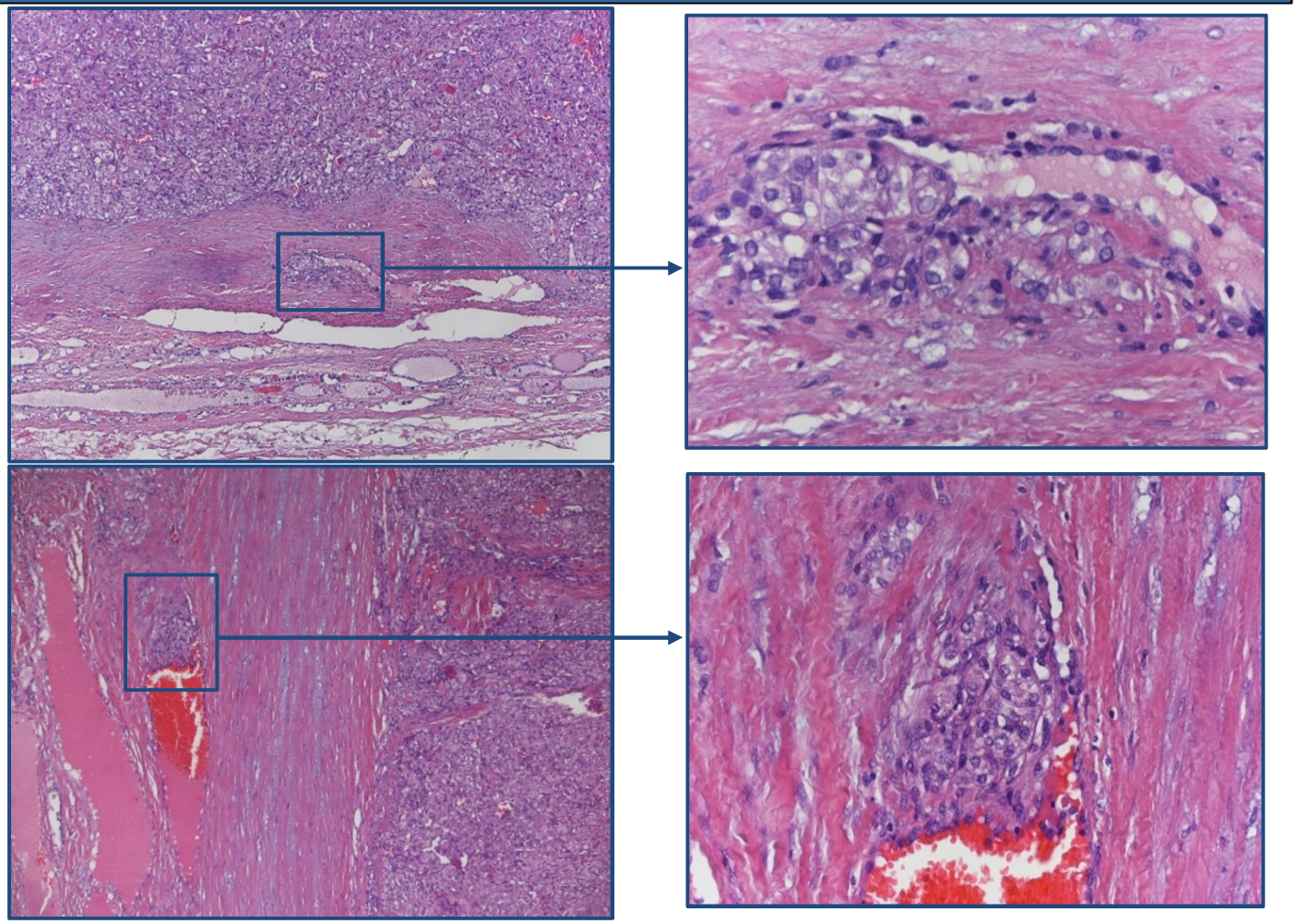
- Tumor capsule or vascular invasion is questionable/equivocal after **thorough sampling and careful examination**

Questionable vascular invasion:

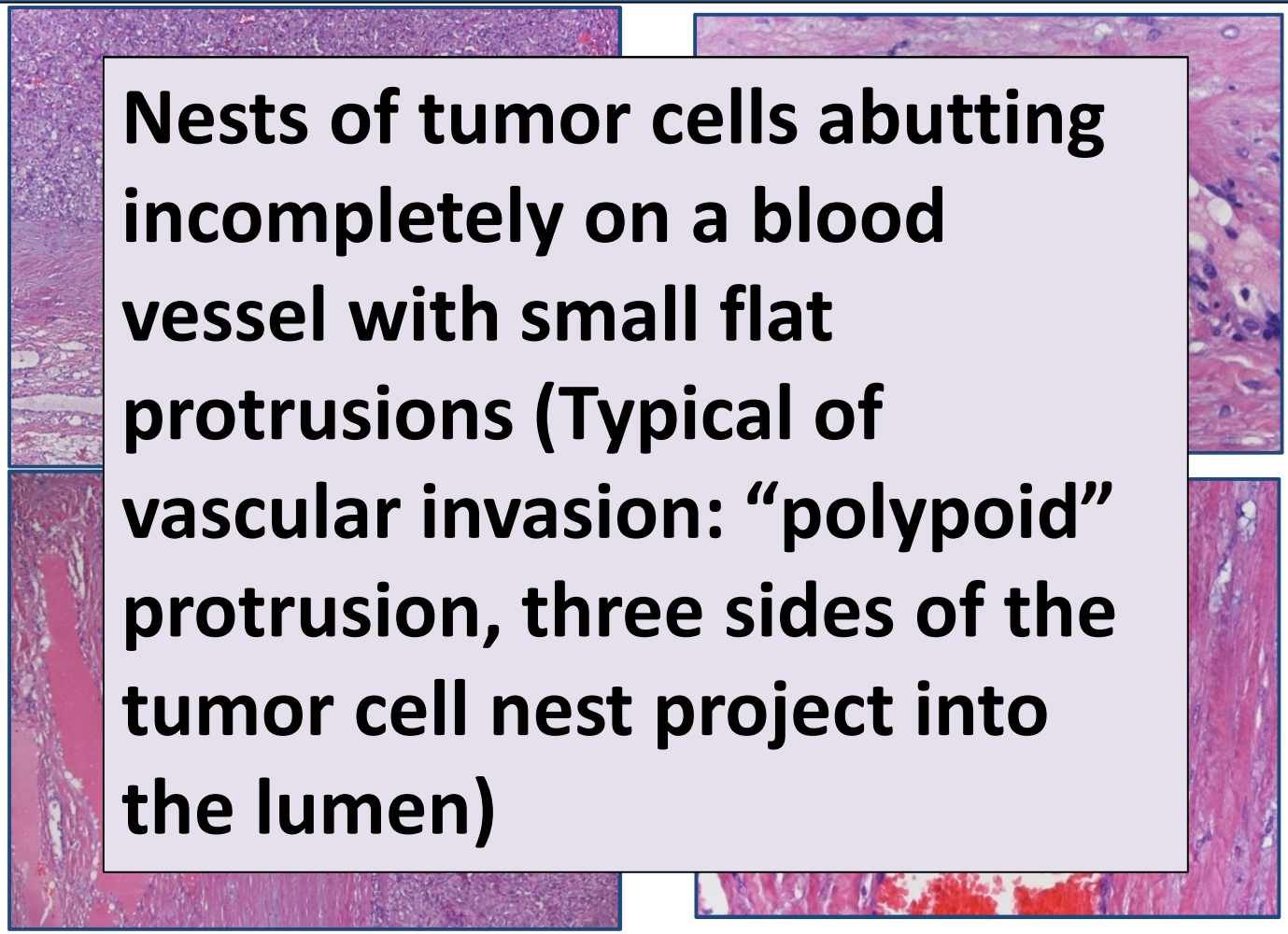
- Tumor cell nests in the fibrous capsule are intermixed with vascular endothelium
- Tumor cell nests incompletely abut on a blood vessel with small flat protrusions (Typical of vascular invasion: polypoid protrusion, three sides of the tumor cell nest project into the lumen)
- Smooth-contoured tumor cell nests located inside a vascular space lacking evident endothelial covering and thrombus

✓Particular concern: early vascular invasion versus co-localization of the tumor nest and the blood vessel (Follicular-patterned nodules are highly vascularized and there can be vascular hyperplasia in/around the tumor capsule)

Tumors of uncertain malignant potential (UMP)



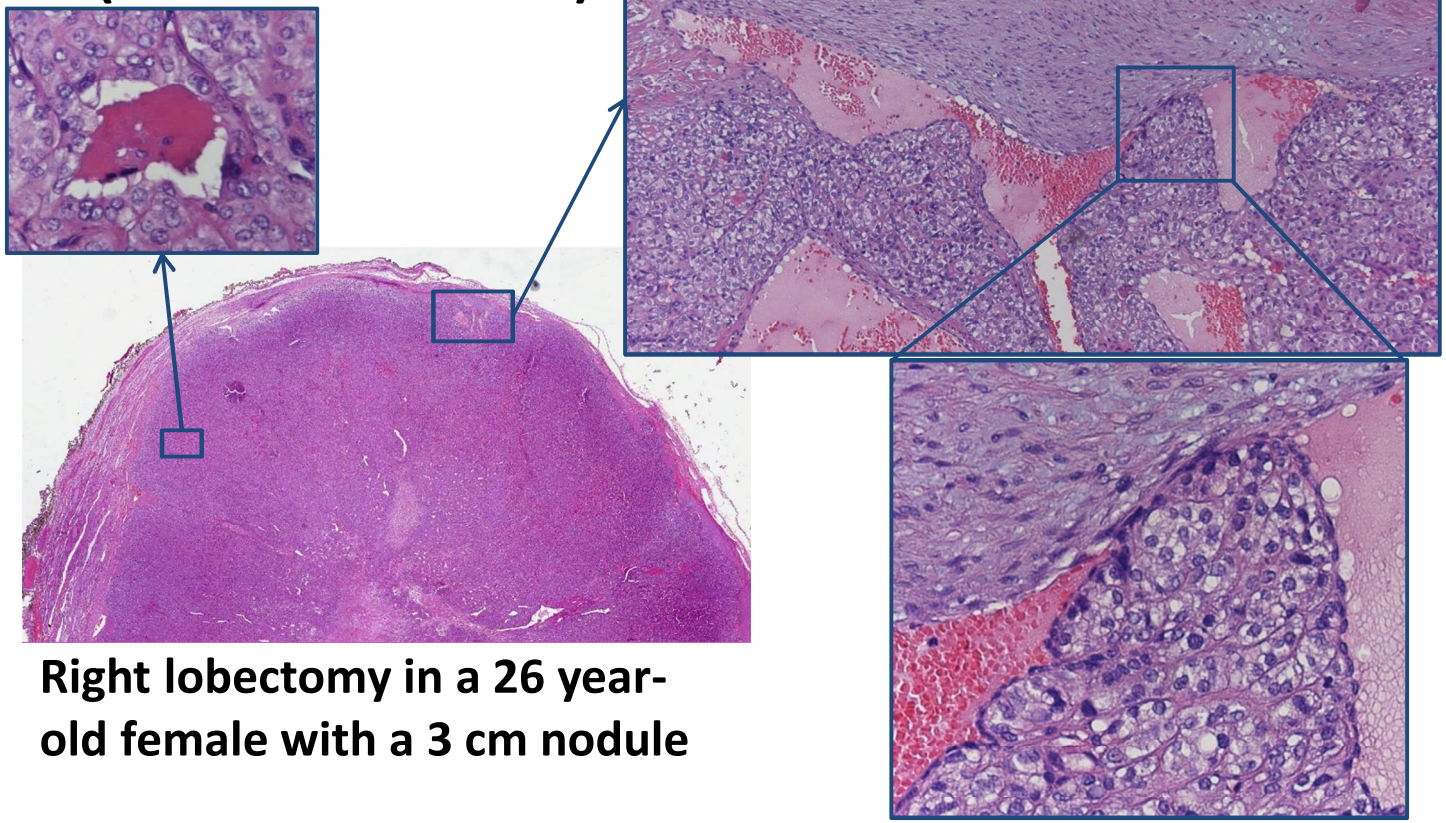
Tumors of uncertain malignant potential (UMP)



Nests of tumor cells abutting incompletely on a blood vessel with small flat protrusions (Typical of vascular invasion: “polypoid” protrusion, three sides of the tumor cell nest project into the lumen)

Tumors of uncertain malignant potential (UMP)

WDT-UMP
(Vascular invasion)



Right lobectomy in a 26 year-old female with a 3 cm nodule

Prognosis of Tumors of Uncertain Malignant Potential (FT-UMP and WDT-UMP)

➢**Specific data on the long term outcome of tumors of uncertain malignant potential (FT-UMP and WDT-UMP) are limited but the risk for the patient id very low**

Tumor of uncertain malignant potential, does not mean a malignant tumor of uncertain potential

Identification of borderline thyroid tumors by gene expression array analysis

Arora N, Scognamiglio T, Lubitz CC, Moo TA, Kato MA, Zhu B, Zarnegar R, Chen YT, Fahey TJ 3rd

Cancer. 2009 Dec 1;115(23):5421-31. doi: 10.1002/cncr.24616. PubMed PMID: 19658182

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

Piana S, Frasoldati A, Di Felice E, Gardini G, Tallini G, Rosai J

Am J Surg Pathol. 2010 Jun;34(6):868-72. doi: 10.1097/PAS.0b013e3181dbee07. PubMed PMID: 20463572

Follicular thyroid carcinoma

Sobrinho-Simões M, Eloy C, Magalhães J, Lobo C, Amaro T

Mod Pathol. 2011 Apr;24 Suppl 2:S10-8. doi: 10.1038/modpathol.2010.133

Encapsulated follicular thyroid tumor with equivocal nuclear changes, so-called well-differentiated tumor of uncertain malignant potential: a morphological, immunohistochemical, and molecular appraisal

Liu Z, Zhou G, Nakamura M, Koike E, Li Y, Ozaki T, Mori I, Taniguchi E, Kakudo K

Cancer Sci. 2011 Jan;102(1):288-94. doi: 10.1111/j.1349-7006.2010.01769.x

Several studies have not reported nodal or distant metastases, tumor recurrence, or tumor related deaths

Prognosis of Tumors of Uncertain Malignant Potential (FT-UMP and WDT-UMP)

➢**Overall risk for the patient (recurrence after complete excision, nodal or distant metastases, death): estimated < 1%**

Classification of thyroid follicular cell tumors: with special reference to borderline lesions
Kakudo K, Bai Y, Liu Z, Li Y, Ito Y, Ozaki T
Endocr J. 2012;59(1):1-12.

In one retrospective study of **2978 cases originally diagnosed as benign** thyroid nodule/tumor, **five cases** were found to later develop distant metastases: among these, **two would qualify for FT-UMP** - one with questionable vascular invasion, and one with questionable invasion of the thyroid parenchyma (< 0.1% metastatic potential)

Recommendation: follow up (similar to NIFTP). After simple lobectomy patients can now be reliably followed for potential recurrence by high resolution neck ultrasound and ultrasensitive thyroglobulin serum assays

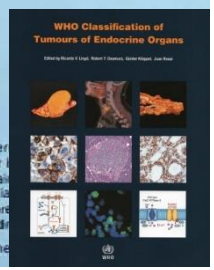
Topics

- Overview of current classification and lessons learnt from follicular-patterned lesions: Follicular variant papillary carcinoma, Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Tumors of uncertain malignant potential (UMP)
- Papillary carcinoma: subtypes and “Farewell to microcarcinoma”
- Thyroid follicular nodular disease
- Follicular thyroid adenoma with papillary architecture
- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic carcinoma): Minimally invasive (capsular invasion only); encapsulated angioinvasive; widely invasive

Follicular adenoma	8330/0
Hyalinizing trabecular tumour	8336/1*
Other encapsulated follicular-patterned thyroid tumours	
Follicular tumour of uncertain malignant potential	8335/1*
Well-differentiated tumour of uncertain malignant potential	8348/1*
Non-invasive follicular thyroid neoplasm with papillary-like nuclear features	8349/1*
Papillary thyroid carcinoma (PTC)	
Papillary carcinoma	8260/3
Follicular variant of PTC	8340/3
Encapsulated variant of PTC	8343/3
Papillary microcarcinoma	8341/3
Columnar cell variant of PTC	8344/3
Oncocytic variant of PTC	8342/3
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 tumours	
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
Mixed medullary and follicular thyroid carcinoma	8346/3
Mucoepidermoid carcinoma	8430/3
Sclerosing mucoepidermoid carcinoma with eosinophilia	8430/3
Mucinous carcinoma	8480/3
Ectopic thymoma	8580/3
Spindle epithelial tumour with thymus-like differentiation	8588/3
Intrathyroid thymic carcinoma	8589/3
Paraganglioma and mesenchymal/stromal tumours	
Paraganglioma	8693/3
Peripheral nerve sheath tumours (PNSTs)	
Schwannoma	9560/0
Malignant PNST	9540/3
Benign vascular tumours	
Haemangioma	9120/0
Cavernous haemangioma	9121/0
Lymphangioma	9170/0
Angiosarcoma	9120/3
Smooth muscle tumours	
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Solitary fibrous tumour	8815/1
Haematolymphoid tumours	
Langerhans cell histiocytosis	9751/3
Rosai-Dorfman disease	
Follicular dendritic cell sarcoma	9758/3
Primary thyroid lymphoma	
Germ cell tumours	
Benign teratoma (grade 0 or 1)	9080/0
Immature teratoma (grade 2)	9080/1
Malignant teratoma (grade 3)	9080/3
Secondary tumours	

The morphology codes are from the Inter
for Oncology (ICD-O) (8936A). Behaviour
/1 for unspecified, borderline, or uncerta
situ and grade III intraepithelial neoplas
The classification is modified from the pr
into account changes in our understandi

*These new codes were approved by the



tumourclassification.iarc.who.int/chapters/53

3. Thyroid gland

- Introduction
- **Developmental abnormalities**
  - Thyroglossal duct cyst
  - Other congenital thyroid abnormalities
- **Follicular cell-derived neoplasms**
  - *Benign tumours*
    - Thyroid follicular nodular disease
    - Follicular thyroid adenoma
    - Follicular thyroid adenoma with papillary architecture
    - Oncocytic adenoma of the thyroid
  - *Low risk neoplasms*
    - Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
    - Thyroid tumours of uncertain malignant potential
    - Hyalinizing trabecular tumour of thyroid
  - *Malignant neoplasms*
    - Follicular thyroid carcinoma
    - Invasive encapsulated follicular variant papillary carcinoma
    - Papillary thyroid carcinoma
    - Oncocytic carcinoma of the thyroid
    - Follicular-derived carcinomas, high-grade
    - Anaplastic follicular cell derived thyroid carcinoma
- **Thyroid C-cell derived carcinoma**
  - Medullary thyroid carcinoma
- **Mixed medullary and follicular-cell derived carcinomas**
  - Mixed medullary and follicular cell-derived thyroid carcinoma
- **Salivary gland-type carcinomas of the thyroid**
  - Mucoepidermoid carcinoma of the thyroid
  - Secretory carcinoma of salivary gland type
- **Thyroid tumours of uncertain histogenesis**
  - Sclerosing mucoepidermoid carcinoma with eosinophilia
  - Cribriform morular thyroid carcinoma
- **Thymic tumours within the thyroid**
  - Thymoma family
  - Spindle epithelial tumour with thymus-like elements
  - Thymic carcinoma family
- **Embryonal thyroid neoplasms**
  - Thyroblastoma

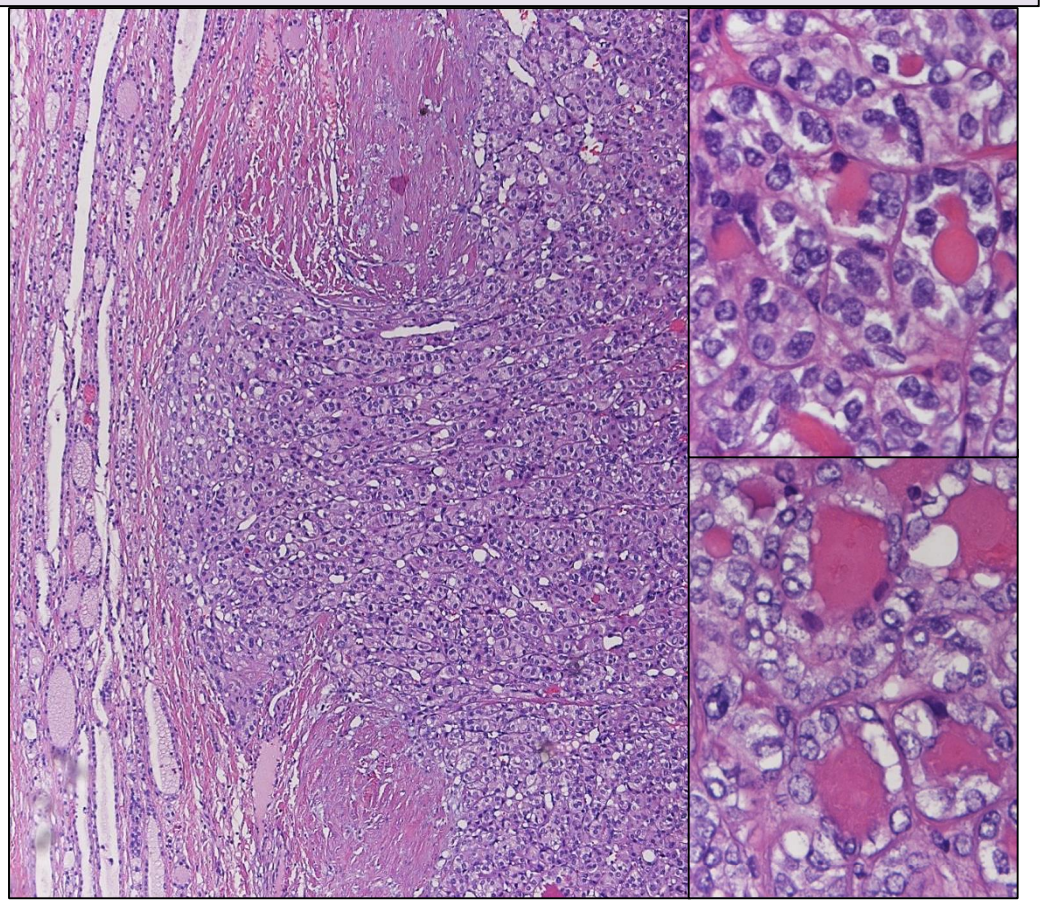
Papillary carcinoma: subtypes and "Farewell to microcarcinoma" (WHO 5TH edition)

Papillary thyroid carcinoma: malignant tumor of follicular cell derivation characterized by distinct nuclear features. PTC diagnosis requires either papillary or solid/trabecular architecture, or invasive growth in follicular-patterned tumors

Papillary carcinoma Subtypes (n=13)

- Classic
- Infiltrative follicular variant
- Tall cell
- Columnar cell
- Hobnail cell
- Solid/trabecular
- Diffuse sclerosing
- Warthin-like
- Oncocytic
- Encapsulated classic
- Clear cell
- Spindle cell
- With fibromatosis/fasciitis-like/desmoid-type stroma

✓ **Invasive encapsulated follicular variant papillary carcinoma as a distinct tumor type (not a papillary carcinoma subtype anymore)**



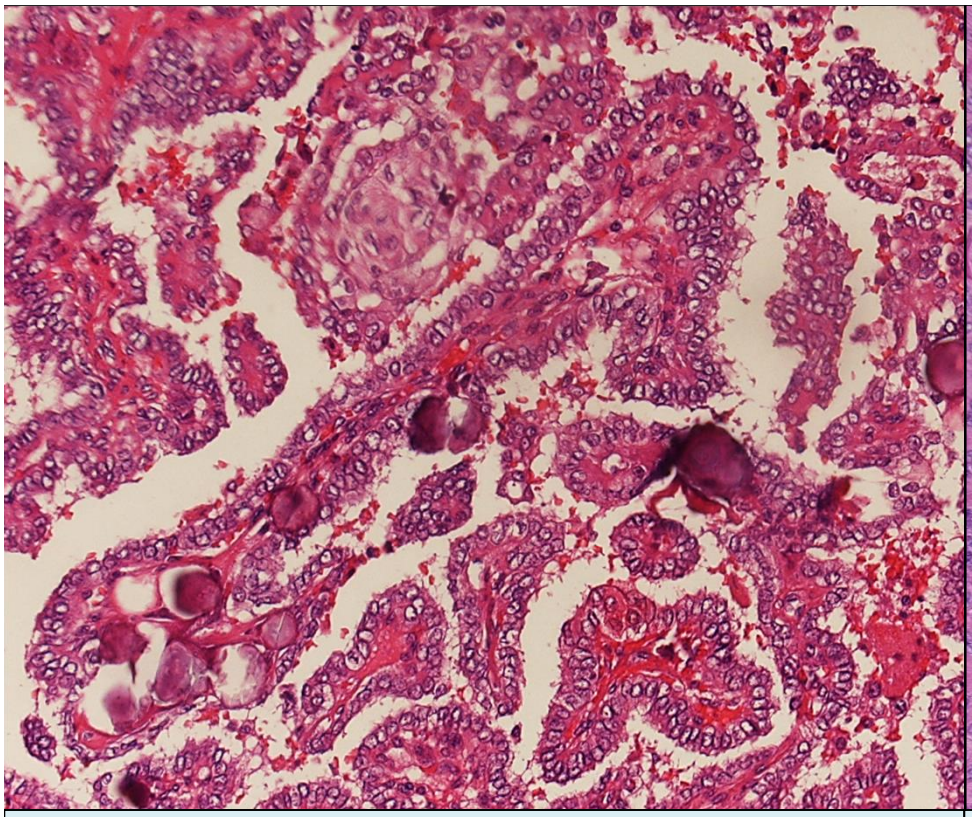
Papillary carcinoma: subtypes and “Farewell to microcarcinoma” (WHO 5TH edition)

Papillary thyroid carcinoma: malignant tumor of follicular cell derivation characterized by distinct nuclear features. PTC diagnosis requires either papillary or solid/trabecular architecture, or invasive growth in follicular-patterned tumors

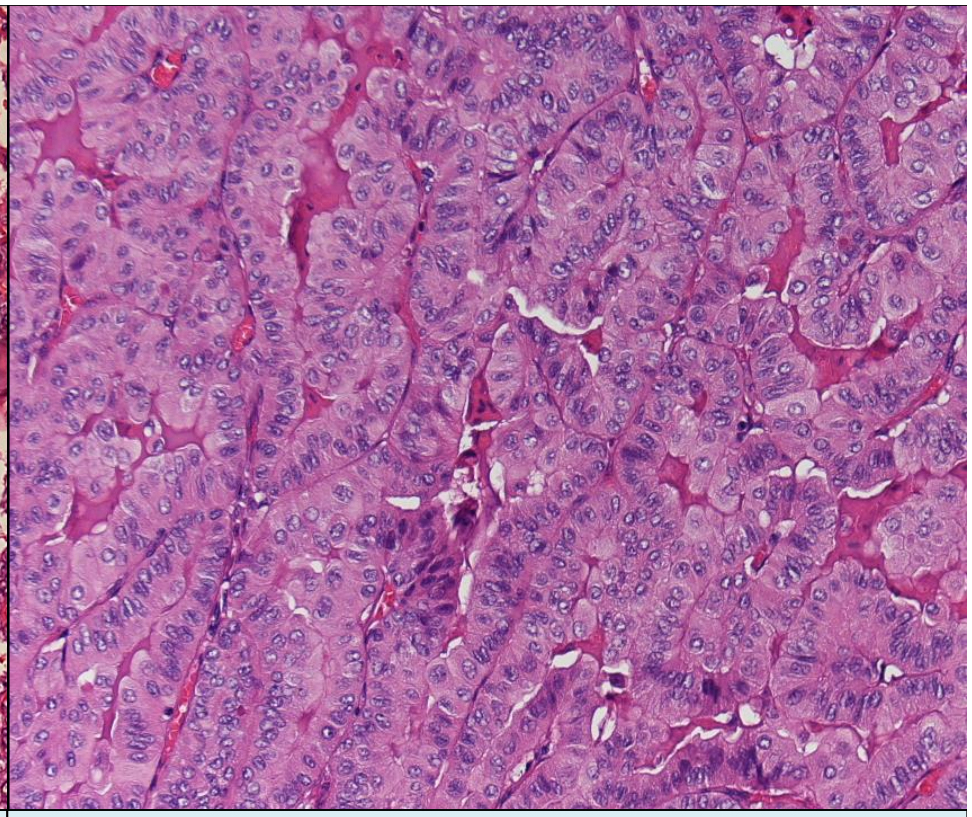
Papillary carcinoma Subtypes (n=13)

- Classic
- Infiltrative follicular variant
- Tall cell
- Columnar cell
- Hobnail cell
- Solid/trabecular
- Diffuse sclerosing
- Warthin-like
- Oncocytic
- Encapsulated classic
- Clear cell
- Spindle cell
- With fibromatosis/fasciitis-like/desmoid-type stroma

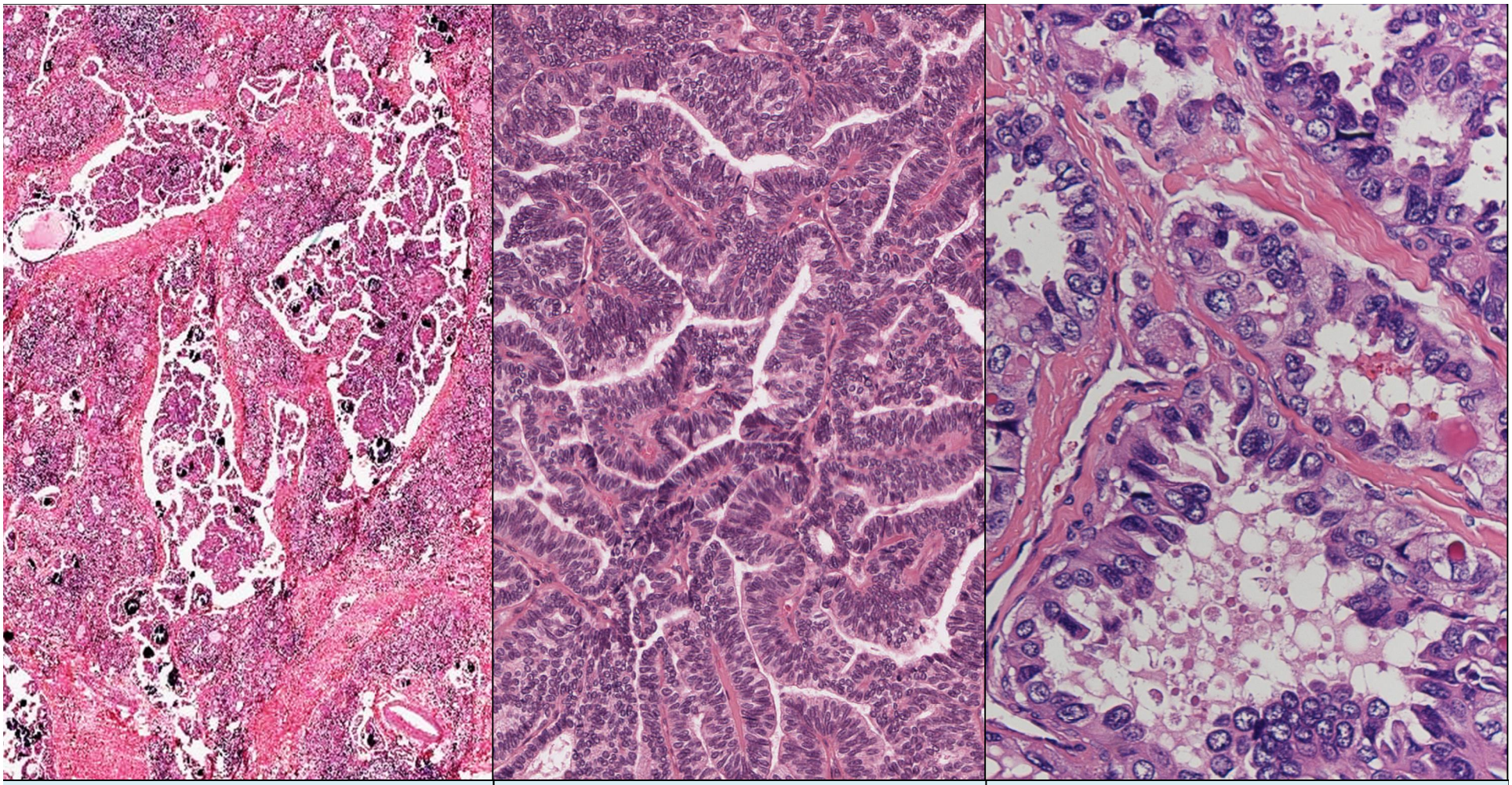
«conventional papillary carcinomas»



Classic papillary carcinoma



Tall cell variant papillary carcinoma



Diffuse sclerosing PTC	Columnar cell PTC	Hobnail PTC

Papillary carcinoma: subtypes and "Farewell to microcarcinoma" (WHO 5TH edition)

Papillary thyroid carcinoma: malignant tumor of follicular cell derivation characterized by distinct nuclear features. PTC diagnosis requires either papillary or solid/trabecular architecture, or invasive growth in follicular-patterned tumors

Papillary carcinoma Subtypes (n=13)

- Classic
- Infiltrative follicular
- Tall cell
- Columnar cell
- Hobnail cell
- Solid/trabecular
- Diffuse sclerosing
- Warthin-like
- Oncocytic
- Encapsulated classic
- Clear cell
- Spindle cell
- With fibromatosis/fasciitis-like/desmoid-type stroma

PTC subtype	Proportion of subtype features	Key histopathologic features
Infiltrative follicular	≥90% neoplastic follicles	• Infiltrative growth • Sclerosis • Multicentric tumor foci
Tall cell	≥30% tall cells	• Tightly packed follicles and papillae — AKA "tram track appearance." • Tumor cell height at least 3×the width • Eosinophilic cytoplasm with distinct cytoplasmic border • Easily identifiable nuclear features of PTC
Columnar cell	NA	• Papillary growth admixed with follicles • Columnar cells with pale to eosinophilic cytoplasm and prominent pseudostratification • Subnuclear vacuoles
Hobnail	≥30% hobnail cells	• Complex papillary or micropapillary growth pattern, rare presence of follicular architecture • Tumor cells with enlarged nuclei, bulging from the apical surface
Solid	>50% solid trabecular growth	• Solid, trabecular or nested growth pattern with intervening thin and delicate fibrovascular bands, rarely foci of dense sclerosis • Lack of tumor necrosis (including single cell necrosis) and high mitotic rate
Diffuse sclerosing	100% diffuse unilateral or bilateral involvement, without dominant tumor mass	• Dense sclerosis, extensive lympahtic permeation, numerous psammoma bodies and ssociated chronic lymphocytic thyroiditis • Tumor cells arranged in solid nests and papillary formations with squamous metaplasia
Warthin-like	NA	• Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis • Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate
Oncocytic	NA	• Well-developed papillae lined by oncocytic cells

Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022 Mar;33(1):27-63

Papillary carcinoma: subtypes and "Farewell to microcarcinoma" (WHO 5TH edition)

Papillary thyroid carcinoma: malignant tumor of follicular cell derivation characterized by distinct nuclear features. PTC diagnosis requires either papillary or solid/trabecular architecture, or invasive growth in follicular-patterned tumors

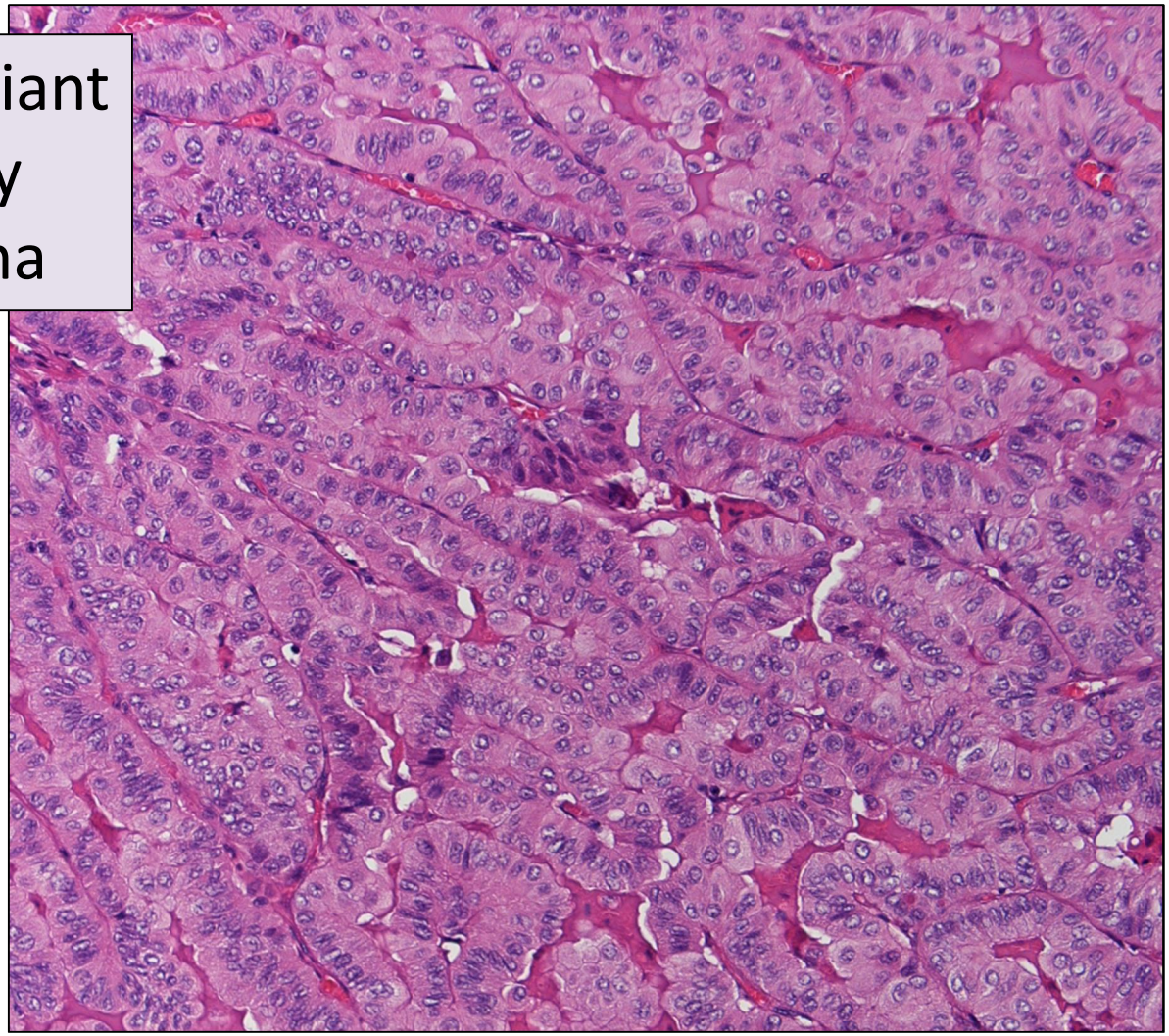
Papillary carcinoma Subtypes (n=13)

- Classic
- Infiltrative follicular
- **Tall cell**
- Columnar cell
- Hobnail cell
- Solid/trabecular
- Diffuse sclerosing
- Warthin-like
- Oncocytic
- Encapsulated classic
- Clear cell
- Spindle cell
- With fibromatosis/fasciitis-like/desmoid-type stroma

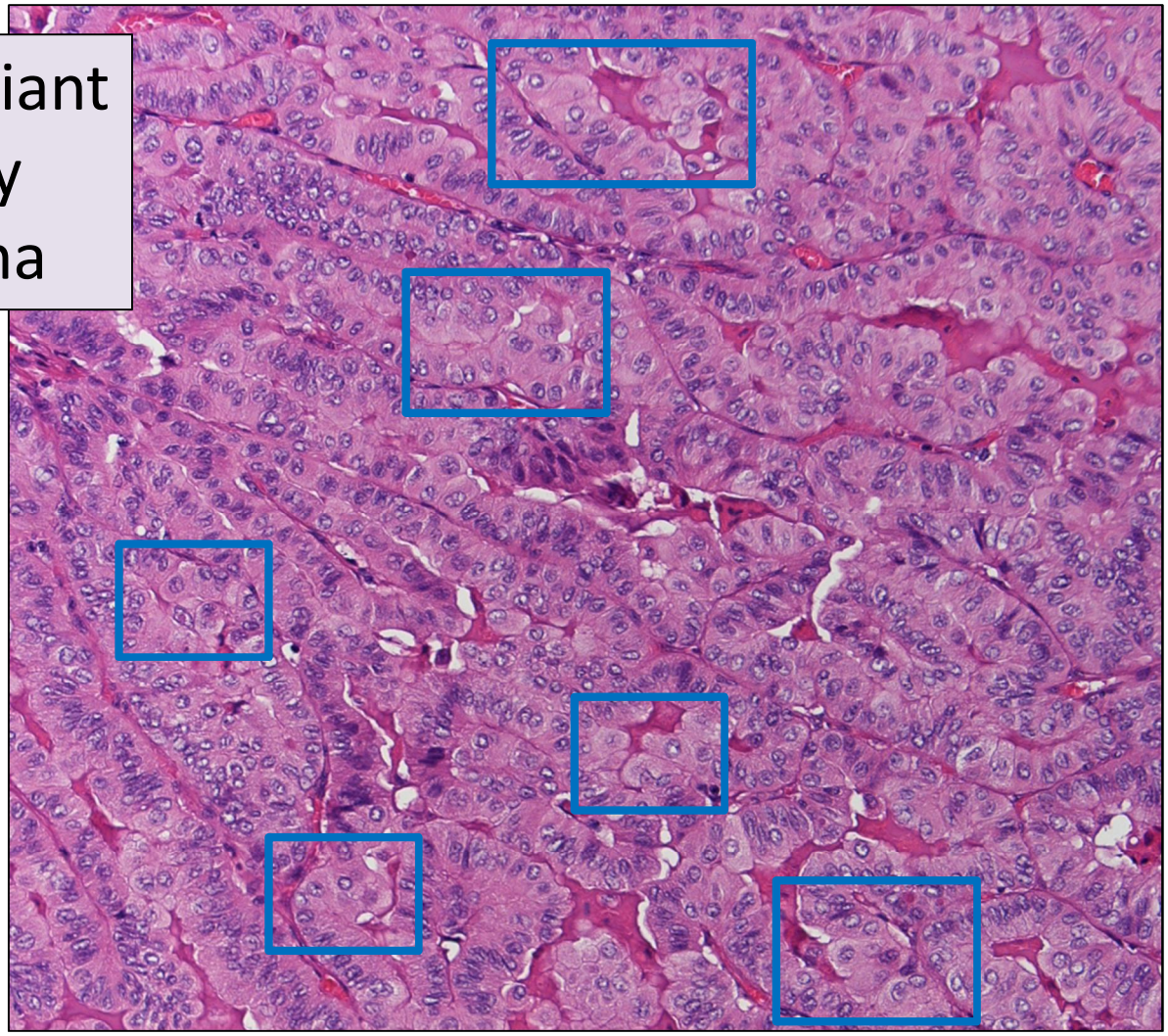
PTC subtype	Proportion of subtype features	Key histopathologic features
Infiltrative follicular	≥90% neoplastic follicles	• Infiltrative growth • Sclerosis • Multicentric tumor foci
Tall cell	≥30% tall cells	• Tightly packed follicles and papillae — AKA "tram track appearance." • Tumor cell height at least 3× the width • Eosinophilic cytoplasm with distinct cytoplasmic border • Easily identifiable nuclear features of PTC
Columnar cell	NA	• Papillary growth admixed with follicles • Columnar cells with pale to eosinophilic cytoplasm and prominent pseudostratification • Subnuclear vacuoles
Hobnail	≥30% hobnail cells	• Complex papillary or micropapillary growth pattern, rare presence of follicular architecture • Tumor cells with enlarged nuclei, bulging from the apical surface
Solid	>50% solid trabecular growth	• Solid, trabecular or nested growth pattern with intervening thin and delicate fibrovascular bands, rarely foci of dense sclerosis • Lack of tumor necrosis (including single cell necrosis) and high mitotic rate
Diffuse sclerosing	100% diffuse unilateral or bilateral involvement, without dominant tumor mass	• Dense sclerosis, extensive lympahtic permeation, numerous psammoma bodies and ssociated chronic lymphocytic thyroiditis • Tumor cells arranged in solid nests and papillary formations with squamous metaplasia
Warthin-like	NA	• Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis • Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate
Oncocytic	NA	• Well-developed papillae lined by oncocytic cells

Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022 Mar;33(1):27-63

Tall cell variant papillary carcinoma



Tall cell variant papillary carcinoma



Many cells are «Plump» rather than tall, and look oncocytic…

Papillary thyroid carcinoma tall cell variant shares accumulation of mitochondria, mitochondrial DNA mutations, and loss of oxidative phosphorylation complex I integrity with oncocytic tumors

Tsybrovskyy O, De Luise M, de Biase D, Caporali L, Fiorini C, Gasparre G, Carelli V, Hackl D, Imamovic L, Haim S, Sobrinho-Simões M, Tallini G

J Pathol Clin Res. 2022 Mar;8(2):155-168

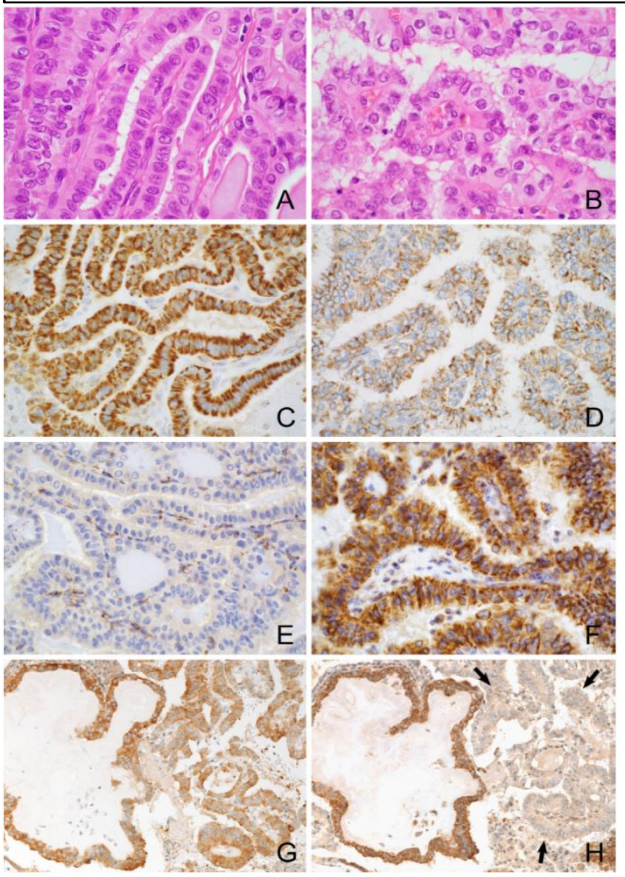
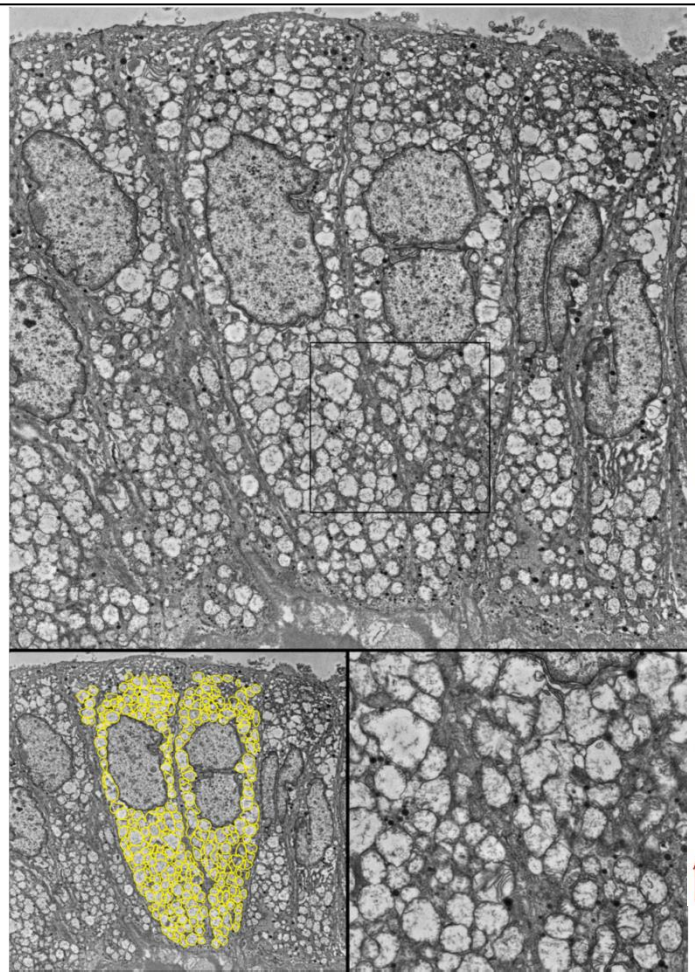
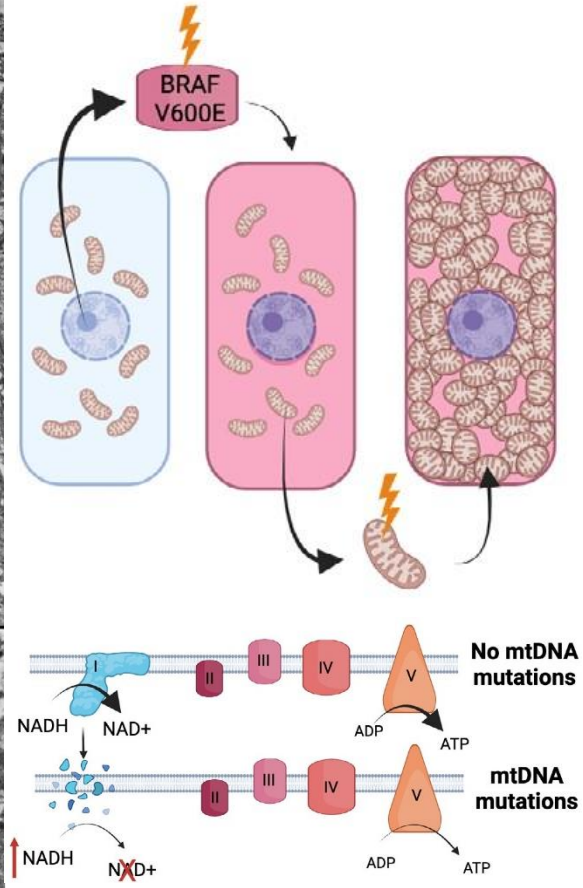


Figure 1. Histologic appearance and immunohistochemical features of PTC-TCV and cPTC. PTC-TCV (A) and classic papillary carcinoma cPTC (B), H&E staining. IHC for the pan-mitochondrial marker prohibitin shows high expression levels with strong, homogenous granular staining in PTC-TCV (C), but low levels of granular staining in cPTC (D). Expression of complex I NDUFS4 subunit is lost in the tumor cells of PTC-TCV, whereas it is preserved in endothelial cells that act as internal positive control (E); NDUFS4 expression is preserved in cPTC (F). The BRAF V600E mutated protein is expressed in the majority of tumor cells (IHC; BRAF V600E specific antibody, clone VE1) (G), while NDUFS4 loss is restricted to the tall cell subpopulation of the tumor (H, arrows), consistent with the hypothesis that papillary carcinomas first acquire BRAF V600E and then the mtDNA alterations that cause the tall cell phenotype (case T14)





Papillary carcinoma: subtypes and "Farewell to microcarcinoma" (WHO 5TH edition)

Papillary thyroid carcinoma: malignant tumor of follicular cell derivation characterized by distinct nuclear features. PTC diagnosis requires either papillary or solid/trabecular architecture, or invasive growth in follicular-patterned tumors

Papillary carcinoma Subtypes (n=13)

- Classic
- Infiltrative follicular
- Tall cell
- Columnar cell
- **Hobnail cell**
- Solid/trabecular
- Diffuse sclerosing
- Warthin-like
- Oncocytic
- Encapsulated classic
- Clear cell
- Spindle cell
- With fibromatosis/fasciitis-like/desmoid-type stroma

PTC subtype	Proportion of subtype features	Key histopathologic features
Infiltrative follicular	≥90% neoplastic follicles	• Infiltrative growth • Sclerosis • Multicentric tumor foci
Tall cell	≥30% tall cells	• Tightly packed follicles and papillae — AKA "tram track appearance." • Tumor cell height at least 3×the width • Eosinophilic cytoplasm with distinct cytoplasmic border • Easily identifiable nuclear features of PTC
Columnar cell	NA	• Papillary growth admixed with follicles • Columnar cells with pale to eosinophilic cytoplasm and prominent pseudostratification • Subnuclear vacuoles
Hobnail	≥30% hobnail cells	• Complex papillary or micropapillary growth pattern, rare presence of follicular architecture • Tumor cells with enlarged nuclei, bulging from the apical surface
Solid	>50% solid trabecular growth	• Solid, trabecular or nested growth pattern with intervening thin and delicate fibrovascular bands, rarely foci of dense sclerosis • Lack of tumor necrosis (including single cell necrosis) and high mitotic rate
Diffuse sclerosing	100% diffuse unilateral or bilateral involvement, without dominant tumor mass	• Dense sclerosis, extensive lympahtic permeation, numerous psammoma bodies and ssociated chronic lymphocytic thyroiditis • Tumor cells arranged in solid nests and papillary formations with squamous metaplasia
Warthin-like	NA	• Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis • Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate
Oncocytic	NA	• Well-developed papillae lined by oncocytic cells

Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022 Mar;33(1):27-63

A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma

Wong KS, Chen TY, Higgins SE, Howitt BE, Lorch JH, Alexander EK, Marquesee E, Cho NL, Nehs MA, Doherty GM, Barletta JA

Histopathology. 2020 Apr;76(5):707-713. doi: 10.1111/his.14042. Epub 2020 Apr 13. PMID: 31811787

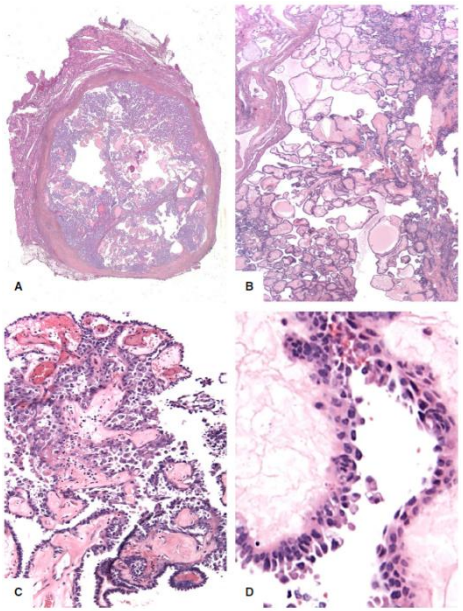


Figure 1. A–D, Examples of classic papillary thyroid carcinoma with 'hobnail-like' morphology. Many tumours were at least partially encapsulated and showed cystic change, and all tumours in this group were grossly confined to the thyroid. The papillae were thick, hyalinised and variably oedematous. Hobnailing and nuclear pseudo-stratification warranting characterisation as 'hobnail-like' can be appreciated at higher power

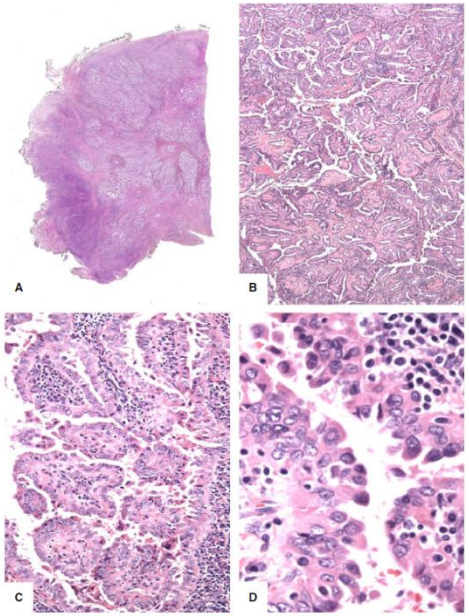


Figure 2. A–D, Examples of true hobnail variant of papillary thyroid carcinoma. These were large, invasive tumours with a complex papillary architecture and loss of cell polarity with nuclei jutting out from the apical surface, nuclear pseudostratification, cellular discohesion, increased nuclear atypia and increased mitotic activity

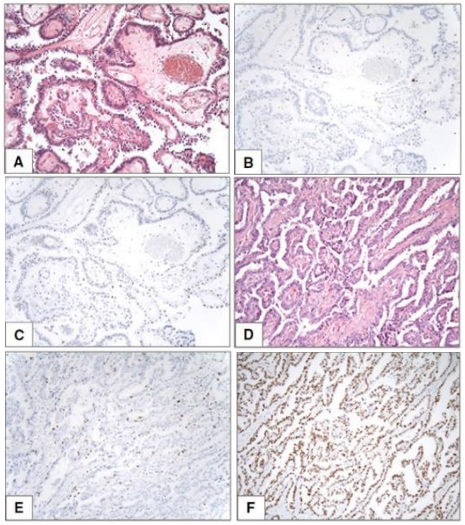


Figure 3. Examples of Ki67 (B, E) and p53 staining (C, F) in 'hobnail-like' classic papillary thyroid carcinoma (PTC) (A–C) and true hobnail variant of PTC (D–F). All 'hobnail-like' tumours demonstrated a Ki67 proliferative index of <5% and wild-type p53 expression. In contrast, the Ki67 was elevated (≥5%) in the majority of true hobnail variant. One hobnail variant demonstrated p53 overexpression

	'Hobnail-like' PTC* (n = 20)	True hobnail PTC (n = 7)	P-value
NED at last follow-up, n (%)	20 (100)	3 (43)	0.0020
Mean follow-up (years)	10.6	1.9	
Median follow-up (years)	11.3	1.9	
Residual/recurrent disease, n (%)	1 (5)†	4 (57)	0.0089
Local	1 (5)†	4 (57)	
Distant	0 (0)	3 (43)	
Died of disease, n (%)	0 (0)	3 (43)	0.012
Mean survival (years)	NA	1.3	
Median survival (years)	NA	1.4	

PTC, Papillary thyroid carcinoma; NED, No evidence of disease; NA, Not available.
*From cohort 2.
†This patient had a local recurrence 2 years after thyroidectomy (disease-free survival of 6 years).

A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma

Wong KS, Chen TY, Higgins SE, Howitt BE, Lorch JH, Alexander EK, Marqusee E, Cho NL, Nehs MA, Doherty GM, Barletta JA

Histopathology. 2020 Apr;76(5):707-713. doi: 10.1111/his.14042. Epub 2020 Apr 13. PMID: 31811787

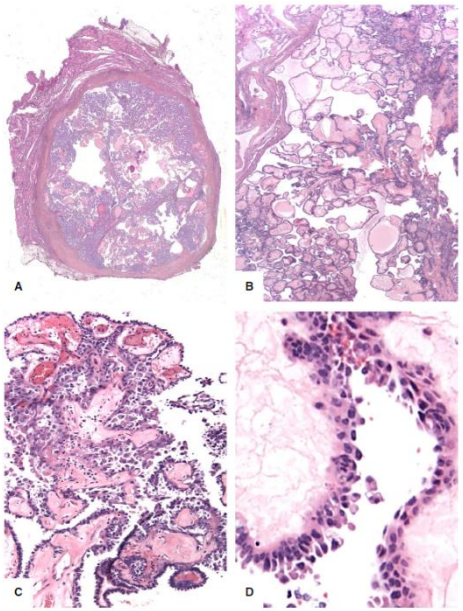


Figure 1. A–D, Examples of **classic papillary thyroid carcinoma** with **'hobnail-like'** morphology. Many tumours were at least **partially encapsulated and showed cystic change**, and all tumours in this group were **grossly confined to the thyroid**. The papillae were thick, hyalinised and variably oedematous. **Hobnailing and nuclear pseudo-stratification** warranting characterisation as 'hobnail-like' can be appreciated **at higher power**

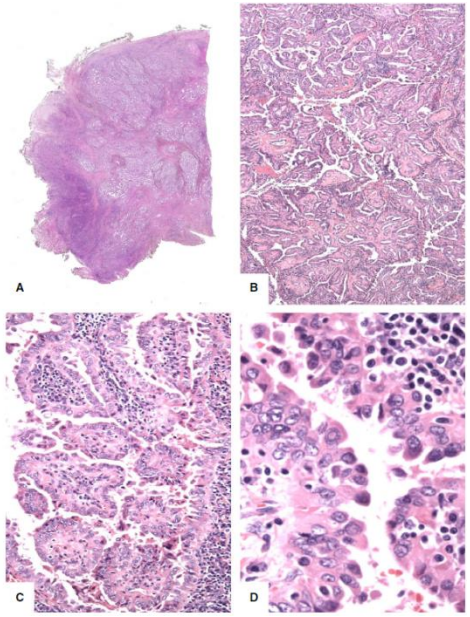


Figure 2. A–D, Examples **of true hobnail variant of papillary thyroid carcinoma**. These were **large, invasive tumours** with a complex papillary architecture and **loss of cell polarity with nuclei jutting out from the apical surface, nuclear pseudostratification, cellular discohesion, increased nuclear atypia and increased mitotic activity**

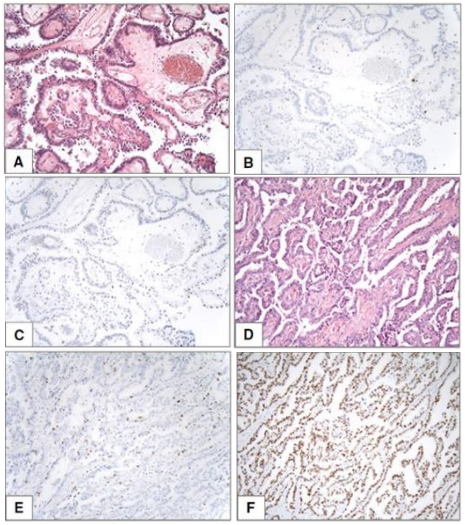


Figure 3. Examples of Ki67 (B, E) and p53 staining (C, F) in 'hobnail-like' classic papillary thyroid carcinoma (PTC) (A–C) and true hobnail variant of PTC (D–F). All 'hobnail-like' tumours demonstrated a Ki67 proliferative index of <5% and wild-type p53 expression. In contrast, **the Ki67 was elevated (≥5%) in the majority of true hobnail variant**. One hobnail variant demonstrated **p53 overexpression**

	'Hobnail-like' PTC* (n = 20)	True hobnail PTC (n = 7)	P-value
NED at last follow-up, n (%)	20 (100)	3 (43)	0.0020
Mean follow-up (years)	10.6	1.9	
Median follow-up (years)	11.3	1.9	
Residual/recurrent disease, n (%)	1 (5)†	4 (57)	0.0089
Local	1 (5)†	4 (57)	
Distant	0 (0)	3 (43)	
Died of disease, n (%)	0 (0)	3 (43)	0.012
Mean survival (years)	NA	1.3	
Median survival (years)	NA	1.4	

PTC, Papillary thyroid carcinoma; NED, No evidence of disease; NA, Not available.
*From cohort 2.
†This patient had a local recurrence 2 years after thyroidectomy (disease-free survival of 6 years).

Papillary carcinoma: subtypes and "Farewell to microcarcinoma" (WHO 5TH edition)

Papillary thyroid carcinoma: malignant tumor of follicular cell derivation characterized by distinct nuclear features. PTC diagnosis requires either papillary or solid/trabecular architecture, or invasive growth in follicular-patterned tumors

Papillary carcinoma Subtypes (n=13)

- Classic
- Infiltrative follicular
- Tall cell
- Columnar cell
- Hobnail cell
- **Solid/trabecular**
- Diffuse sclerosing
- Warthin-like
- Oncocytic
- Encapsulated classic
- Clear cell
- Spindle cell
- With fibromatosis/fasciitis-like/desmoid-type stroma

PTC subtype	Proportion of subtype features	Key histopathologic features
Infiltrative follicular	≥90% neoplastic follicles	• Infiltrative growth • Sclerosis • Multicentric tumor foci
Tall cell	≥30% tall cells	• Tightly packed follicles and papillae — AKA "tram track appearance." • Tumor cell height at least 3×the width • Eosinophilic cytoplasm with distinct cytoplasmic border • Easily identifiable nuclear features of PTC
Columnar cell	NA	• Papillary growth admixed with follicles • Columnar cells with pale to eosinophilic cytoplasm and prominent pseudostratification • Subnuclear vacuoles
Hobnail	≥30% hobnail cells	• Complex papillary or micropapillary growth pattern, rare presence of follicular architecture • Tumor cells with enlarged nuclei, bulging from the apical surface
Solid	>50% solid trabecular growth	• Solid, trabecular or nested growth pattern with intervening thin and delicate fibrovascular bands, rarely foci of dense sclerosis • Lack of tumor necrosis (including single cell necrosis) and high mitotic rate
Diffuse sclerosing	100% diffuse unilateral or bilateral involvement, without dominant tumor mass	• Dense sclerosis, extensive lympahtic permeation, numerous psammoma bodies and ssociated chronic lymphocytic thyroiditis • Tumor cells arranged in solid nests and papillary formations with squamous metaplasia
Warthin-like	NA	• Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis • Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate
Oncocytic	NA	• Well-developed papillae lined by oncocytic cells

Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022 Mar;33(1):27-63

Solid trabecular papillary carcinoma and tyrosine kinase gene fusion papillary carcinomas

Pattern of radiation-induced RET and NTRK1 rearrangements in 191 post-chernobyl papillary thyroid carcinomas: biological, phenotypic, and clinical implications

Rabes HM, Demidchik EP, Sidorow JD, Lengfelder E, Beimfohr C, Hoelzel D, Klugbauer S

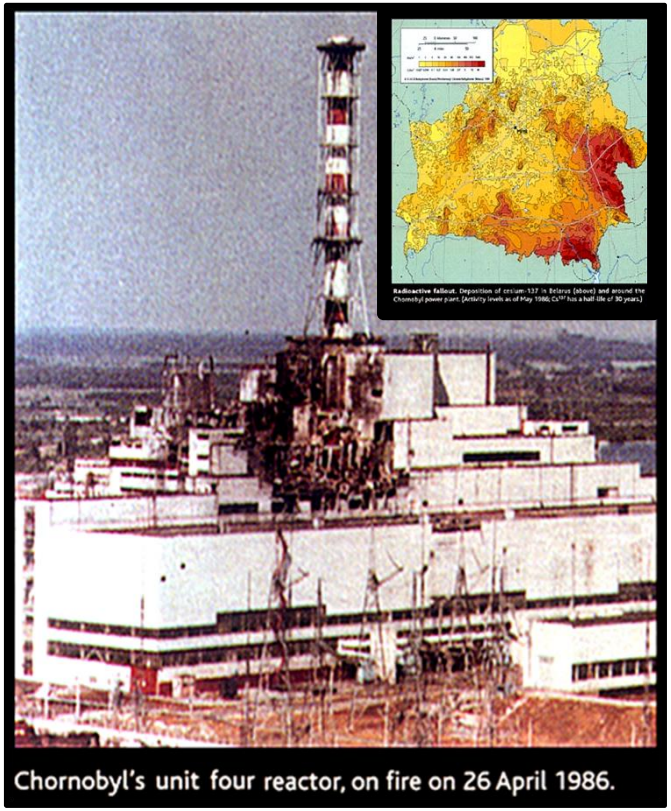
Clin Cancer Res. 2000 Mar;6(3):1093-103

Table 7 Histologic variants of 191 PTCs of children as a function of the type of gene rearrangement

Variant	Total number	Rearrangement positive		Rearrangement negative		PTC1		PTC3		PTC5, 6,7,X		*NTRK1*	
		n[a]	%	*n*[a]	%	*n*[b]	%[c]	*n*[b]	%[c]	*n*[b]	%[c]	*n*[b]	%[c]
Typical papillary	59	30	50.0	29	49.9	22	73.3	3	10.0	2	6.7	2	6.7
Follicular	71	29	40.9	42	59.1	16	55.2	7	24.1	3	10.3	3	10.3
Solid	42	30	71.4	12	28.6	2	6.7	25	83.3	2	6.7	1	3.3
Mixed	12	6	50.0	6	50.0	4	66.7	2	33.3	0		0	
Diffuse sclerosing	6	4	66.7	2	32.3	4	100.0	0		0		0	

[a] $P < 0.05$.
[b] $P < 0.001$.
[c] Percentages from total number of rearrangement-positive PTCs in each histological variant group.

Historically, solid/trabecular papillary carcinoma has been the first subtype to be specifically associated with tyrosine kinase gene fusion: NCOA4-RET (RET/PTC3) fusion solid/trabecular aggressive papillary carcinomas represented the majority of cases that developed with short latency, in children, in areas of greatest radioactive contamination after the Chernobyl nuclear reactor accident of 26 April 1986



Goldman M. Chernobyl radiation dose. Science. 1987 Aug 7;237(4815):575. PubMed PMID: 3603040

Solid trabecular papillary carcinoma and tyrosine kinase gene fusion papillary carcinomas

Pattern of radiation-induced RET and NTRK1 rearrangements in 191 post-chernobyl papillary thyroid carcinomas: biological, phenotypic, and clinical implications

Rabes HM, Demidchik EP, Sidorow JD, Lengfelder E, Beimfohr C, Hoelzel D, Klugbauer S

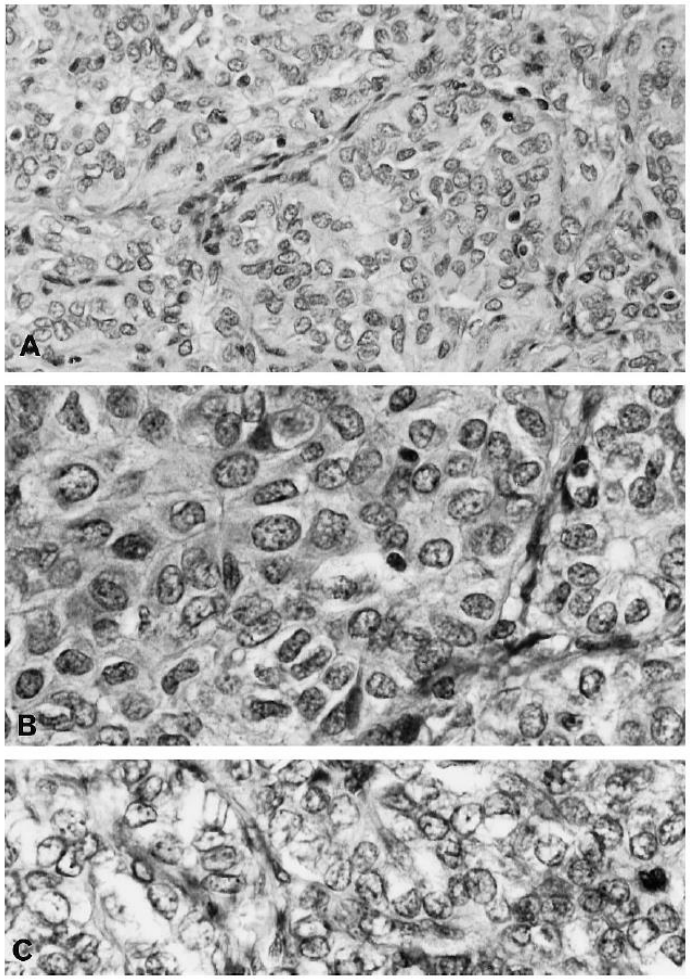
Clin Cancer Res. 2000 Mar;6(3):1093-103

Table 7 Histologic variants of 191 PTCs of children as a function of the type of gene rearrangement

Variant	Total number	Rearrangement positive		Rearrangement negative		PTC1		PTC3		PTC5, 6,7,X		*NTRK1*	
		n^a	%	n^a	%	n^b	%^{c}	n^b	%^{c}	n^b	%^{c}	n^b	%^{c}
Typical papillary	59	30	50.0	29	49.9	22	73.3	3	10.0	2	6.7	2	6.7
Follicular	71	29	40.9	42	59.1	16	55.2	7	24.1	3	10.3	3	10.3
Solid	42	30	71.4	12	28.6	2	6.7	25	83.3	2	6.7	1	3.3
Mixed	12	6	50.0	6	50.0	4	66.7	2	33.3	0		0	
Diffuse sclerosing	6	4	66.7	2	32.3	4	100.0	0		0		0	

[a] $P < 0.05$.
[b] $P < 0.001$.
[c] Percentages from total number of rearrangement-positive PTCs in each histological variant group.

Historically, solid/trabecular papillary carcinoma has been the first subtype to be specifically associated with tyrosine kinase gene fusion: NCOA4-RET (RET/PTC3) fusion solid/trabecular aggressive papillary carcinomas represented the majority of cases that developed with short latency, in children, in areas of greatest radioactive contamination after the Chernobyl nuclear reactor accident of 26 April 1986



Solid trabecular papillary carcinoma and tyrosine kinase gene fusion papillary carcinomas

NTRK fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States
Prasad ML, Vyas M, Horne MJ, Virk RK, Morotti R, Liu Z, Tallini G, Nikiforova MN, Christison-Lagay ER, Udelsman R, Dinauer CA, Nikiforov YE
Cancer. 2016 Apr 1;122(7):1097-107. doi: 10.1002/cncr.29887

RET, NTRK, ALK, BRAF, and MET Fusions in a Large Cohort of Pediatric Papillary Thyroid Carcinomas
Pekova B, Sykorova V, Dvorakova S, Vaclavikova E, Moravcova J, Katra R, Astl J, Vlcek P, Kodetova D, Vcelak J, Bendlova B
Thyroid. 2020 Dec;30(12):1771-1780

Clinicopathologic features of kinase fusion-related thyroid carcinomas: an integrative analysis with molecular characterization
Chu YH, Wirth LJ, Farahani AA, Nosé V, Faquin WC, Dias-Santagata D, Sadow PM
Mod Pathol. 2020 Dec;33(12):2458-2472

We now know that many papillary carcinoma subtypes carry tyrosine kinase gene fusions in addition to solid/trabecular PTC : classical (the most common among non radiation-associated tumors), diffuse sclerosing, infiltrative follicular, tall cell PTC

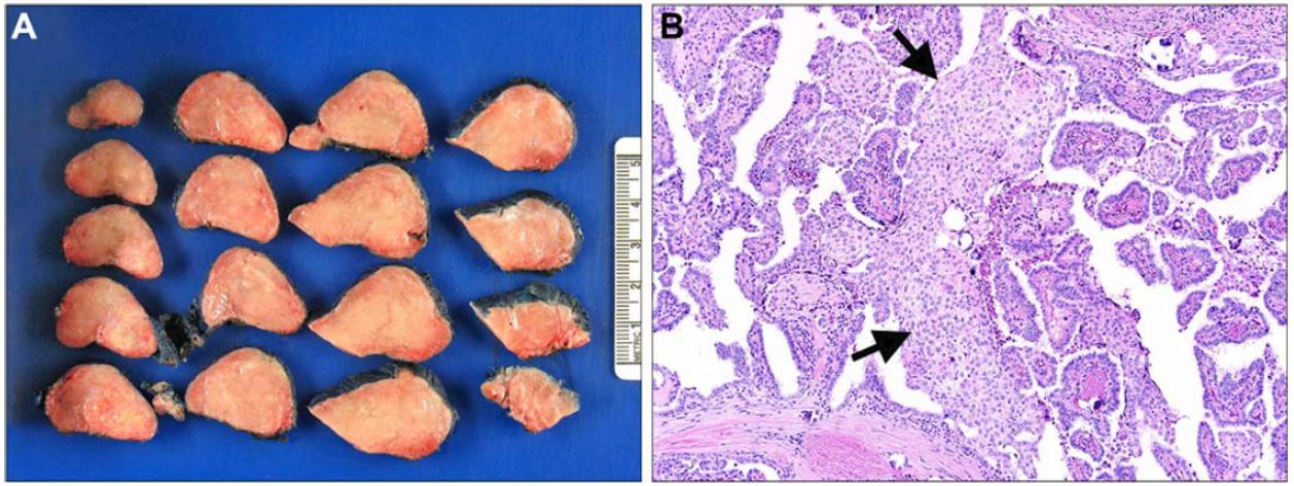
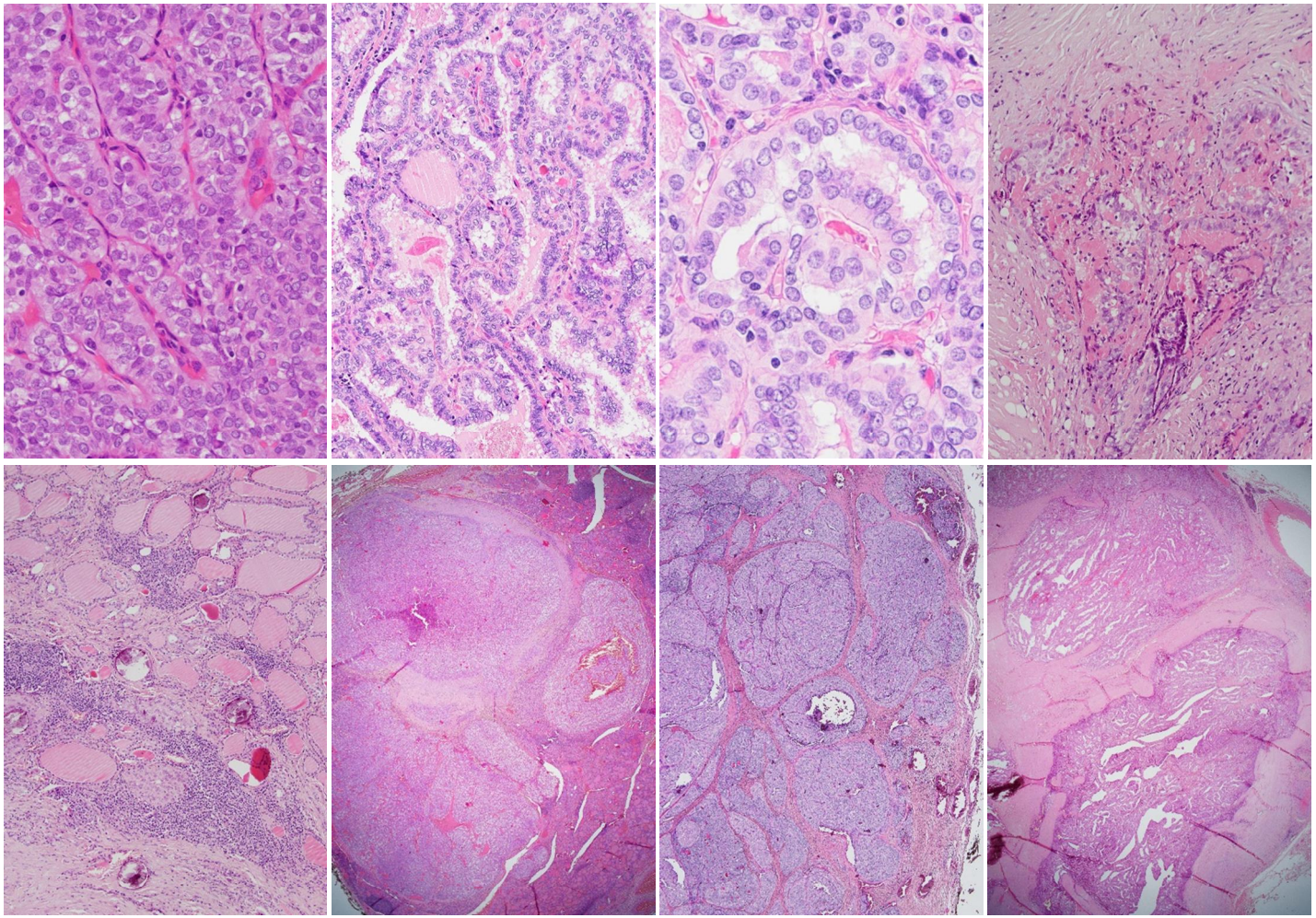
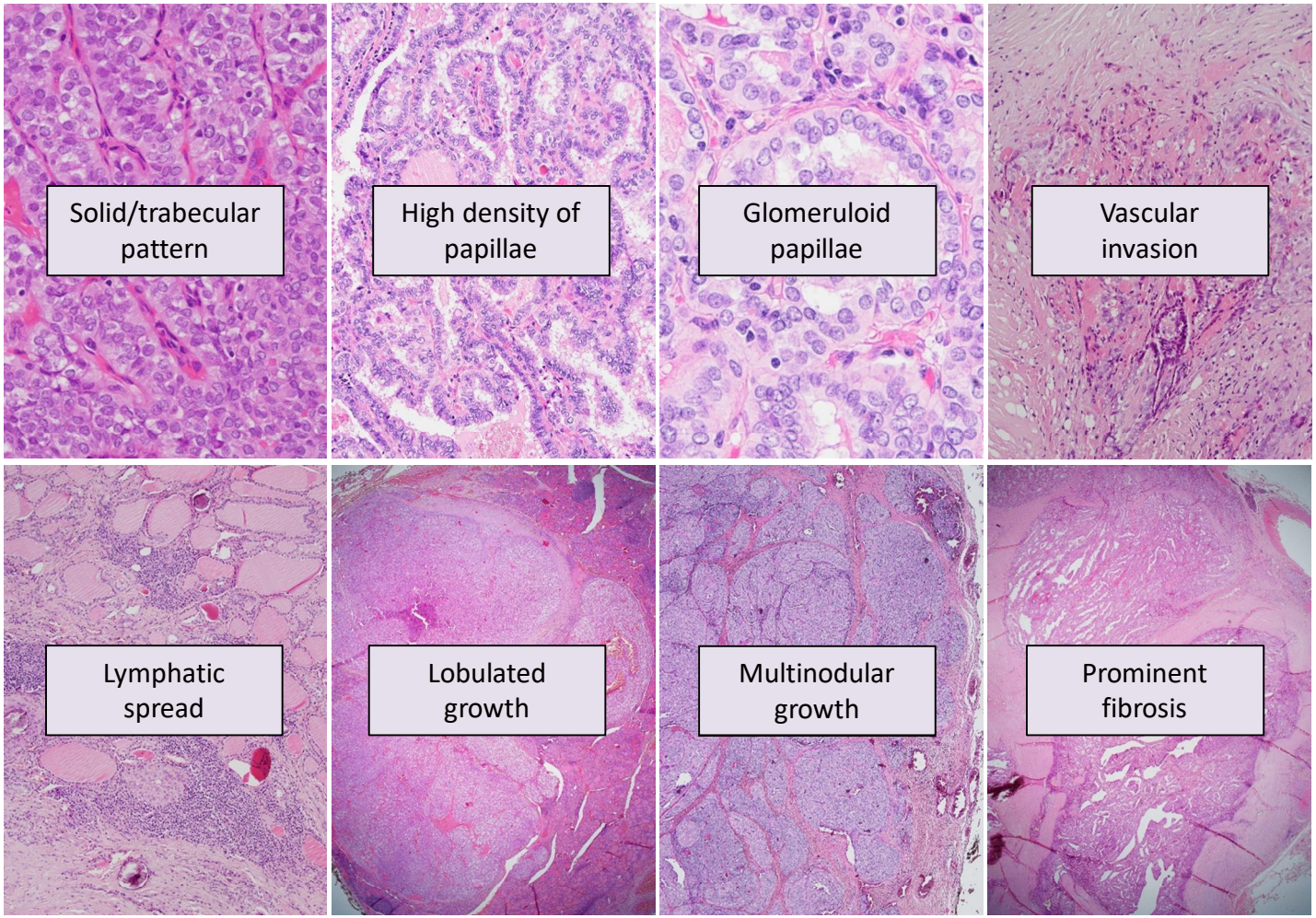


Figure 2. Photomicrographs reveal papillary thyroid carcinoma (PTC) with the ret proto-oncogene (RET)/PTC1 fusion oncogene and the B-Raf proto-oncogene, serine/threonine kinase (BRAF) valine-to-glutamic acid mutation at position 600 (BRAFV600E). (A,B) In a diffuse sclerosing variant of PTC with the RET/PTC1 fusion oncogene (patient 8), the tumor (A) diffusely infiltrates the entire lobe of the thyroid without forming a distinct nodule and (B) has papillary architecture with squamoid areas (arrows; original magnification X100)[Prasad ML, et al. NTRK fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States. Cancer. 2016 Apr 1;122(7):1097-107]

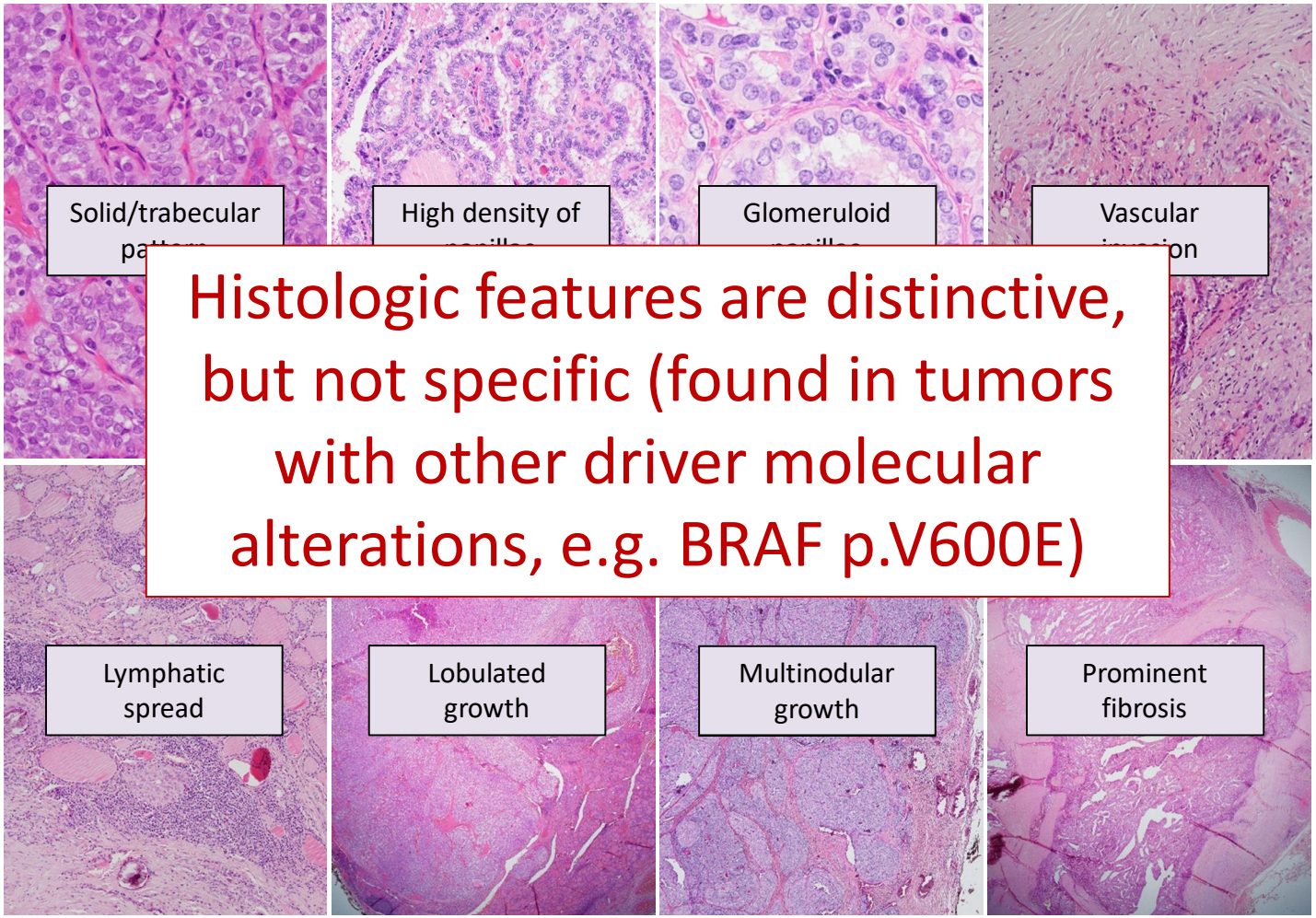
Solid trabecular papillary carcinoma and tyrosine kinase gene fusion papillary carcinomas



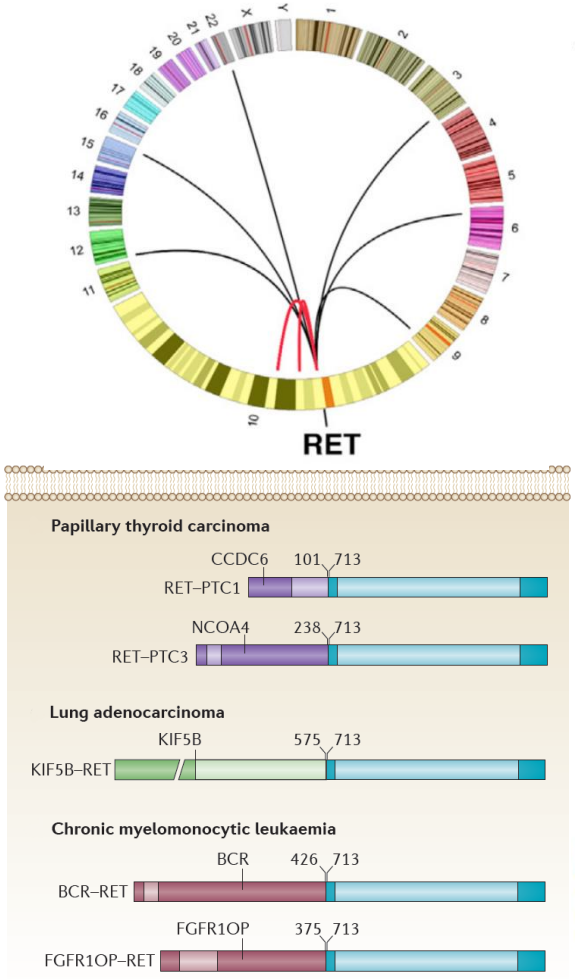
Solid trabecular papillary carcinoma and tyrosine kinase gene fusion papillary carcinomas



Solid trabecular papillary carcinoma and fusion gene papillary carcinomas



Gene fusion in thyroid tumors of follicular cells: RET (previously RET/PTC rearrangements)



Mulligan. Nat Rev Cancer. 2014;14:173-186. doi: 10.1038/nrc3680

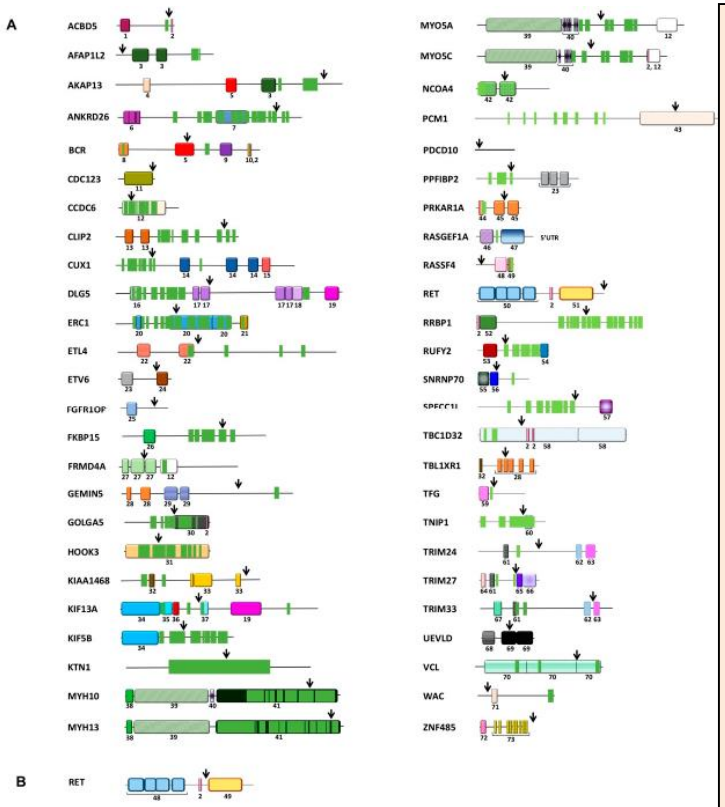


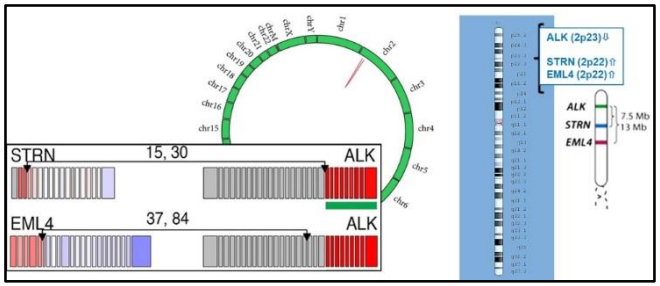
Figure 1. Representative scheme of RET and its fusion partners. (**A**) Representation of RET fusion protein partners. Arrows indicate the most frequent breakpoint sites in partner proteins. The number under each protein domain refers to the protein domain legend (Table 1). Coiled-coil domains are very numerous and, therefore, are represented as light green boxes without number. (**B**) Representation of the RET protein. Arrow indicates the most frequent breakpoint site in RET.

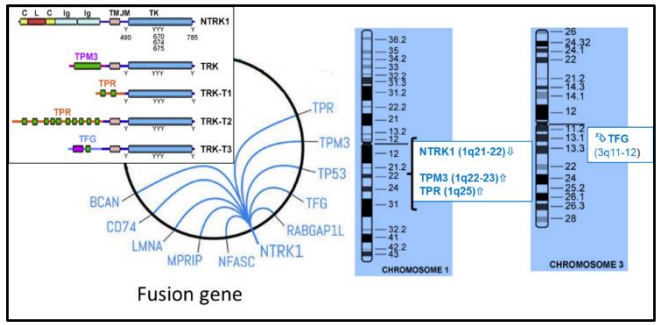
Santoro M et al.2020 Apr 15;11(4):424

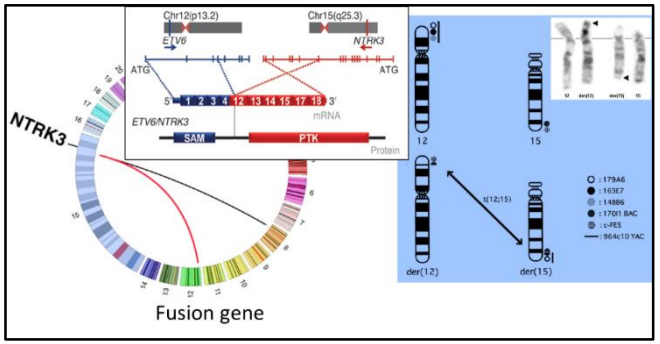
Chimeric gene with a chimeric protein that contains the RET kinase at the carboxyl terminus

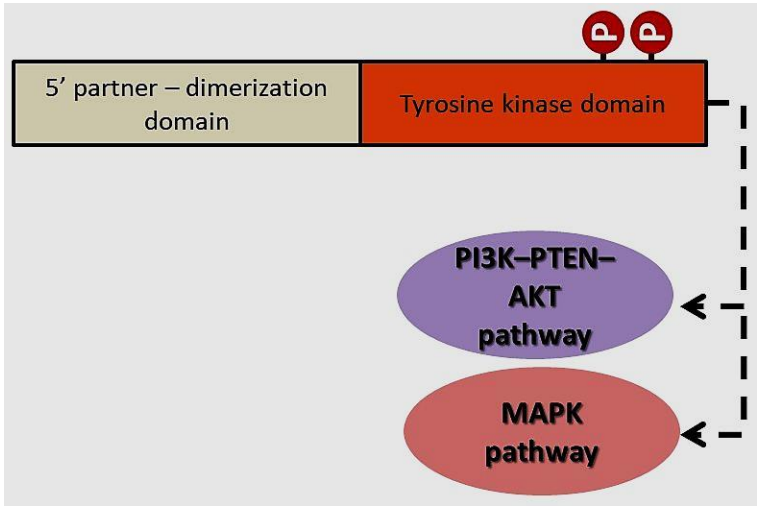
- balanced translocations involving the 3.0kb intron 11 of RET, before the RET-TK domain
- fusion of RET-TK with the 5'-end of activating heterologous genes that are ubiquitously expressed and therefore drive RET-TK expression in thyroid follicular cells that normally express little or no RET
- RET fused genes have dimerization domains (e.g. coiled-coil domains) that allow constitutive RET activation
- RET transmembrane domain is lost and RET-TK is redistributed from the membrane to the cytoplasm
- aberrant fusion proteins can phosphorylate substrates previously not accessible to RET-TK
- RET rearrangements in thyroid tumors involve at least 17 different genes: CCDC6-RET (RET/PTC1), NCOA4-RET (RET/PTC3), PRKAR1A-RET (RET/PTC2) etc.

Gene fusion in thyroid tumors of follicular cells: NTRK1 (previously TRK rearrangements), NTRK3, ALK









- **ALK/EML4; ALK/STRN**
- **NTRK1/TPM3; NTRK1/TPR; NTRK1/TFG**
- **NTRK3/ETV6**

Tyrosine kinase gene fusion papillary carcinomas

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

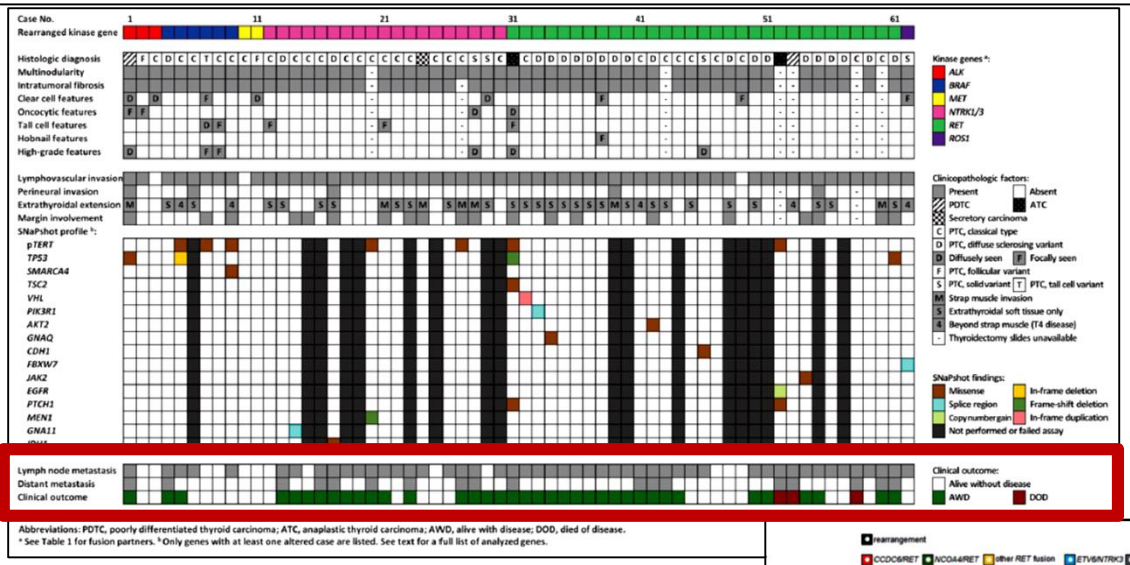
Chu YH, Wirth LJ, Farahani AA, Nosé V, Faquin WC, Dias-Santagata D, Sadow PM

Mod Pathol. 2020 Dec;33(12):2458-2472

RET, NTRK, ALK, BRAF, and MET Fusions in a Large Cohort of Pediatric Papillary Thyroid Carcinomas

Pekova B, Sykorova V, Dvorakova S, Vaclavikova E, Moravcova J, Katra R, Astl J, Vlcek P, Kodetova D, Vcelak J, Bendlova B

Thyroid. 2020 Dec;30(12):1771-1780



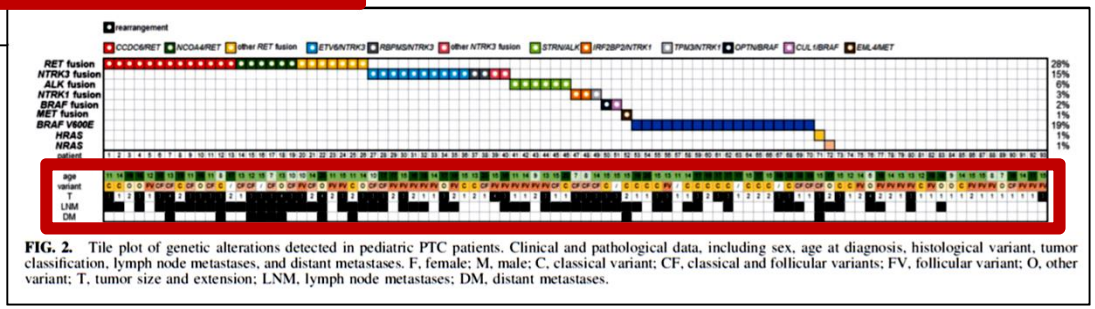


FIG. 2. Tile plot of genetic alterations detected in pediatric PTC patients. Clinical and pathological data, including sex, age at diagnosis, histological variant, tumor classification, lymph node metastases, and distant metastases. F, female; M, male; C, classical variant; CF, classical and follicular variants; FV, follicular variant; O, other variant; T, tumor size and extension; LNM, lymph node metastases; DM, distant metastases.

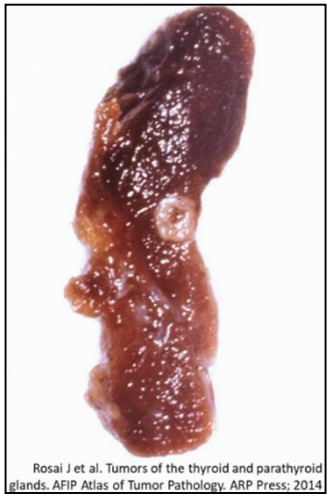
Tyrosine kinase gene fusion papillary carcinomas

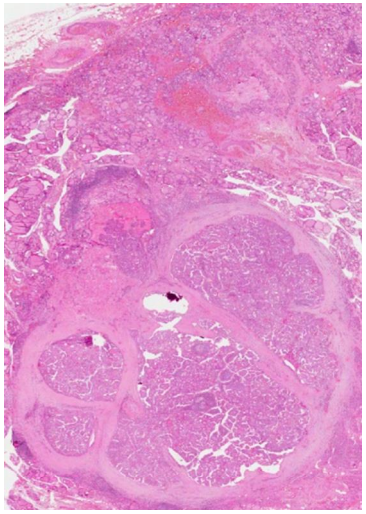
- Pediatric patients
- Radiation exposure
  - ✓Uncommmon in non radiation-exposed adult patients
- Frequent: TNM stage T3 to T4 disease, extrathyroidal extension, lymph node involvement; distant metastases at presentation: ~15% (pediatric patients), ~5% (non radiation-exposed adult patients)
  - ✓Advanced disease at presentation with early metastasis
- Diverse papillary carcinoma histology with: **multinodular/lobulated growth, prominent intratumoral fibrosis (confluent or arborizing), lymphovascular invasion evident histologically, common solid/trabecular or papillary patterns (papillae are highly dense and glomeruloid)**

➢ Thyroid carcinomas harbor actionable kinase fusions in up to 10–15% of cases (including aggressive high grade histotypes, e.g. poorly- and undifferentiated carcinomas)

Papillary carcinoma: subtypes and “Farewell to microcarcinoma” (WHO 5TH edition)

- Papillary carcinomas measuring < or = 1.0 cm have been called with various names (non encapsulated sclerosing tumors of the thyroid, occult sclerosing carcinoma) and since 1960 papillary microcarcinoma [Hazard, J.B. Small papillary carcinoma of the thyroid. A study with special reference to so-called nonencapsulated sclerosing tumor. Lab. Investig. 1960, 9, 86–97].
- Most papillary carcinomas are currently 1-2 cm and these small tumors are the main culprits of the so-called thyroid cancer “epidemic” (widespread use of ultrasound and thyroid FNA)
- **“Not all microcarcinomas are created equal”**
  - Very indolent tumors (10-15% of thyroid glands surgically removed for various reasons, in up to 35.6% of autopsy thyroids) [Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. Cancer. 1985 Aug 1;56(3):531-8]
  - Small papillary carcinomas on their way to become > 1 cm, with the potential to progress with the potential to progress; as they are low stage, the large majority have an excellent prognosis, but ~25% of cases are at risk of persistent/recurrent disease, rare cases have even been fatal (progression to high grade carcinoma in metastatic lymph nodes)


Rosai J et al. Tumors of the thyroid and parathyroid glands. AFIP Atlas of Tumor Pathology. ARP Press; 2014



WHO 5TH edition: “Farewell to microcarcinoma”

Does the Site of Origin of the Microcarcinoma with Respect to the Thyroid Surface Matter? A Multicenter Pathologic and Clinical Study for Risk Stratification

Tallini G…Durante C

Cancers (Basel). 2020 Jan 19;12(1):246. doi: 10.3390/cancers12010246

Papillary carcinomas measuring < or = 1.0 cm arise at a median distance of **3.5 mm below the surface of the thyroid gland** with four distinct clusters

Group A, mPTC: size ≥ 5 mm and distance of the edge of the tumor from the thyroid capsule = 0 mm

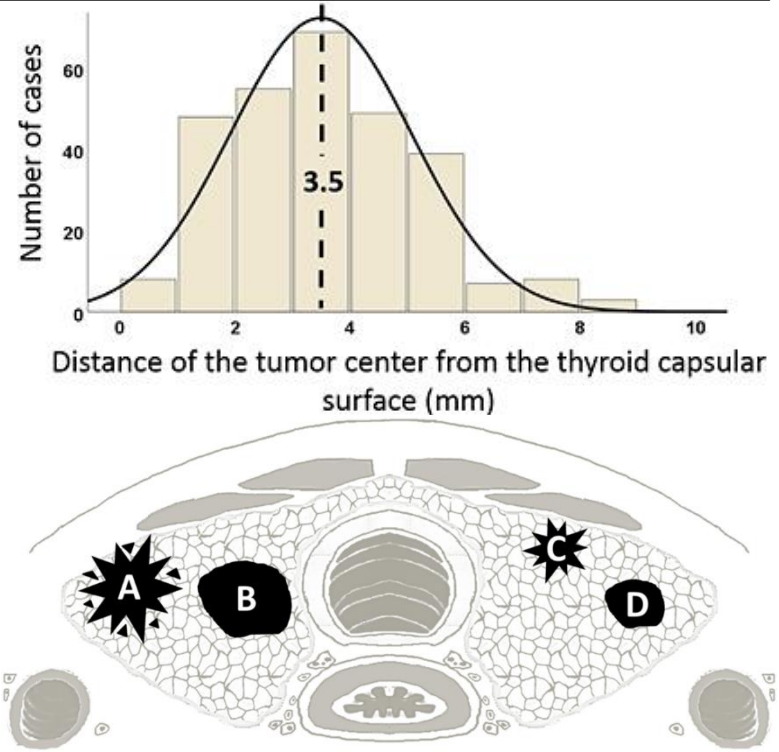
Group B, mPTC: size ≥ 5 mm and distance of the edge of the tumor from the thyroid capsule > 0 mm

Group C, mPTC: size < 5 mm and distance of the edge of the tumor from the thyroid capsule = 0 mm

Group D, mPTC: size < 5 mm and distance of the edge of the tumor from the thyroid capsule > 0 mm.

Group A: most threatening features, group D: most indolent ones

Group A tumors are characterized by **tall cell histotype, BRAF V600E mutation, tumor fibrosis, aggressive growth with invasive features, vascular invasion, lymph node metastases, intermediate (as opposed to low) ATA risk** (Multivariate analysys)



WHO 5TH edition: “Farewell to microcarcinoma”

Does the Site of Origin of the Microcarcinoma with Respect to the Thyroid Surface Matter? A Multicenter Pathologic and Clinical Study for Risk Stratification

Tallini G…Durante C

Cancers (Basel). 2020 Jan 19;12(1):246. doi: 10.3390/cancers12010246

Papillary carcinomas measuring < or = 1.0 cm arise at a median distance of **3.5 mm below the surface of the thyroid gland** with four distinct clusters

Group A, mPTC: size ≥ 5 mm and distance of the edge of the tumor from the thyroid capsule = 0 mm

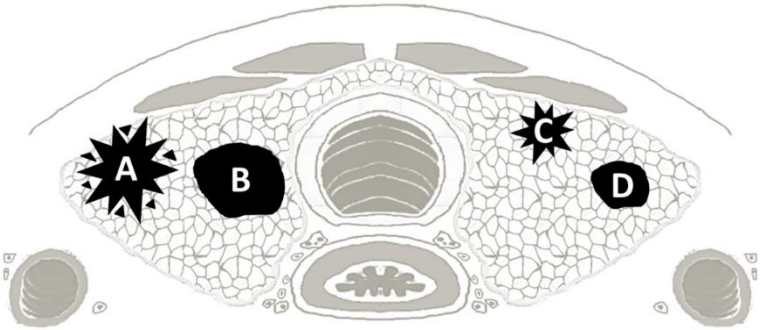
Group B, mPTC: size ≥ 5 mm and distance of the edge of the tumor from the thyroid capsule > 0 mm

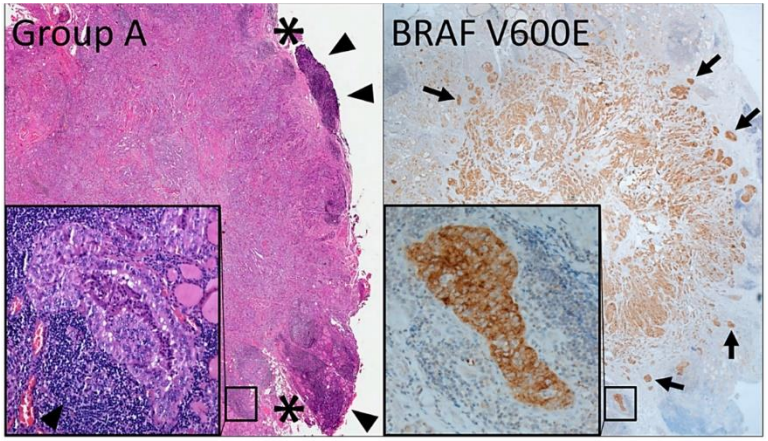
Group C, mPTC: size < 5 mm and distance of the edge of the tumor from the thyroid capsule = 0 mm

Group D, mPTC: size < 5 mm and distance of the edge of the tumor from the thyroid capsule > 0 mm.

Group A: most threatening features, group D: most indolent ones

Group A tumors are characterized by **tall cell histotype, BRAF V600E mutation, tumor fibrosis, aggressive growth with invasive features, vascular invasion, lymph node metastases, intermediate (as opposed to low) ATA risk** (Multivariate analysys)





Papillary carcinoma: subtypes and “Farewell to microcarcinoma” (WHO 5TH edition)

Differentiated thyroid carcinoma 2013-2022				
			Millimeter	Standard deviation
Tumor size	Average		25.36	8.972
	Median		**12.00**	
	25° percentile		7.000	
	75° percentile		20.000	

Tumor size of differentiated thyroid carcinoma 2013-2022 per year (mm)				
Year	Average	Median	25° percentile	75° percentile
2013	15.14	11.00	6.00	20.00
2014	14.90	10.00	6.00	18.00
2015	15.28	11.00	7.00	20.00
2016	16.77	11.00	7.00	20.00
2017	17.22	11.00	7.00	20.00
2018	16.00	12.00	7.00	21.00
2019	15.94	12.00	7.00	20.00
2020	20.74	12.00	8.00	21.00
2021	17.45	12.00	8.00	22.75
2022	14.80	11.00	7.00	19.00

ITCO includes 51 thyroid cancer centers in Italy with data on nearly 12000 patients diagnosed with thyroid carcinoma. Each case record contains information on patient demographics and biometrics, circumstances of the diagnosis, surgical and radioactive iodine treatment, as well as the results of periodic follow-up examination. Sensitive data are encrypted and the database is managed anonymously. The Observatory provides no guidance or restrictions in terms of patient management to the participating centers, since the database is designed to provide a picture of real-world practices.

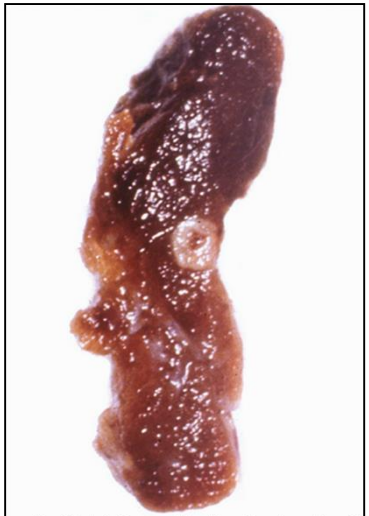
WHO 5TH edition: "Farewell to microcarcinoma"

Renaming papillary microcarcinoma of the thyroid gland: the Porto proposal

Rosai J, LiVolsi VA, Sobrinho-Simoes M, Williams ED

Int J Surg Pathol. 2003 Oct;11(4):249-51. doi: 10.1177/106689690301100401

- Patient age > 19 aa
- Single focus, or sum of all foci ≤1 cm
- No aggressive features: thyroid capsule infiltration, vascular invasion, tall cell features
- Incidental finding
- Whole thyroid resected and examined microscopically
- No lymph node metastases present or suspected



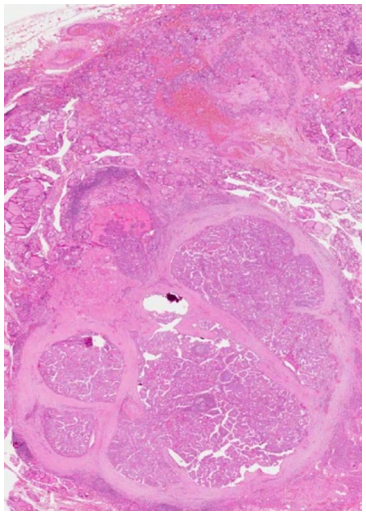
Rosai J et al. Tumors of the thyroid and parathyroid glands. AFIP Atlas of Tumor Pathology. ARP Press; 2014

Thyroid Papillary Microtumor: Validation of the (Updated) Porto Proposal Assessing Sex Hormone Receptor Expression and Mutational BRAF Gene Status

Aliyev E…Cameselle-Teijeiro JM

Am J Surg Pathol. 2020 Sep;44(9):1161-1172. doi: 10.1097/PAS.0000000000001522

- Patient age > 19 aa
- Single focus, or sum of all foci ≤1 cm
- No aggressive features: extrathyroidal extension, vascular invasion, tall cell/hobnail cell features



WHO 5TH edition: "Farewell to microcarcinoma"

Renaming papillary microcarcinoma of the thyroid gland: the Porto proposal

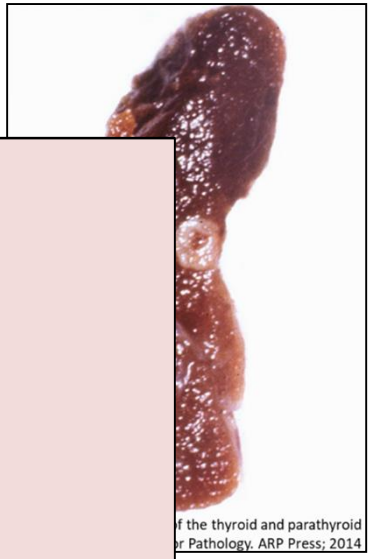
- Patient a
- Single fo
- No aggre features
- Incident
- Whole t
- No lymp

Thyroid Pa Receptor E

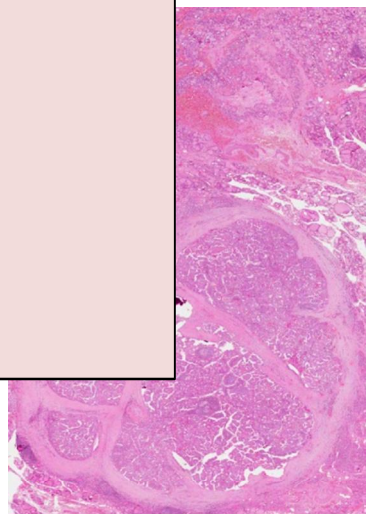
- Patient a
- Single focus, or sum of all foci ≤1 cm
- No aggressive features: extrathyroidal extension, vascular invasion, tall cell/hobnail cell features

- "Microcarcinoma" should not be considered a distinct papillary carcinoma subtype
- Tumors can not be subtyped based on size
- Papillary carcinomas measuring < or = 1.0 cm should be subtyped like those > 1cm
- Not enough evidence for the «Papillary microtumor» proposal

✓If the tumor is very small (< or = 2-3 mm) can be difficult to apply subtype criteria used for larger tumors



f the thyroid and parathyroid
r Pathology. ARP Press; 2014



Topics

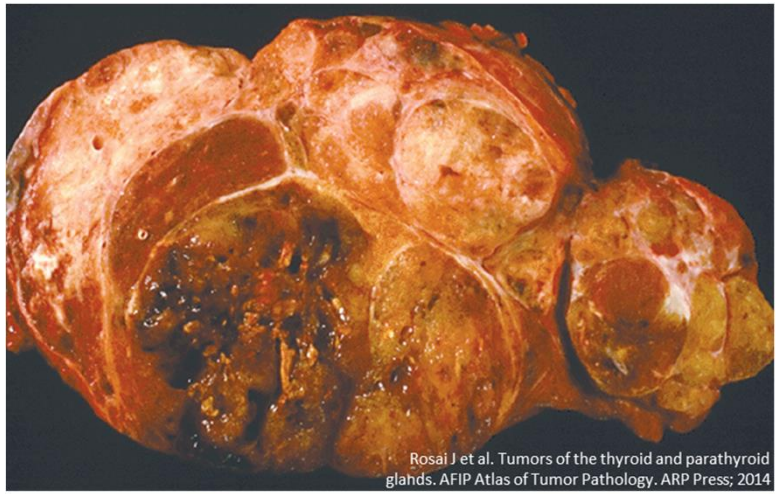
- Overview of current classification and lessons learnt from follicular-patterned lesions: Follicular variant papillary carcinoma, Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Tumors of uncertain malignant potential (UMP)
- Papillary carcinoma: subtypes and “Farewell to microcarcinoma”
- Thyroid follicular nodular disease
- Follicular thyroid adenoma with papillary architecture
- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic carcinoma): Minimally invasive (capsular invasion only); encapsulated angioinvasive; widely invasive

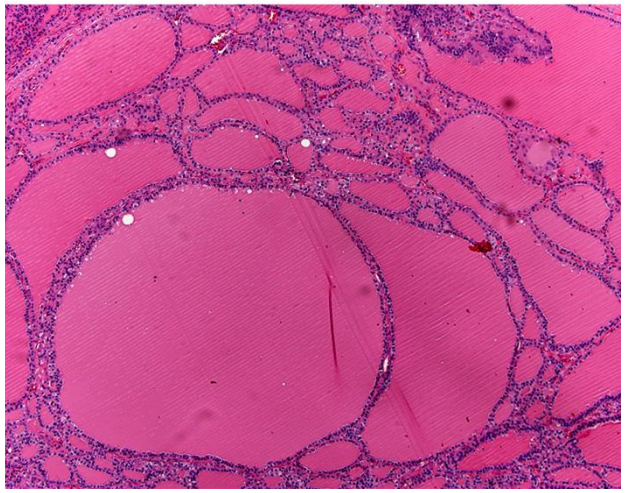
WHO 5TH edition: Thyroid follicular nodular disease (FND)

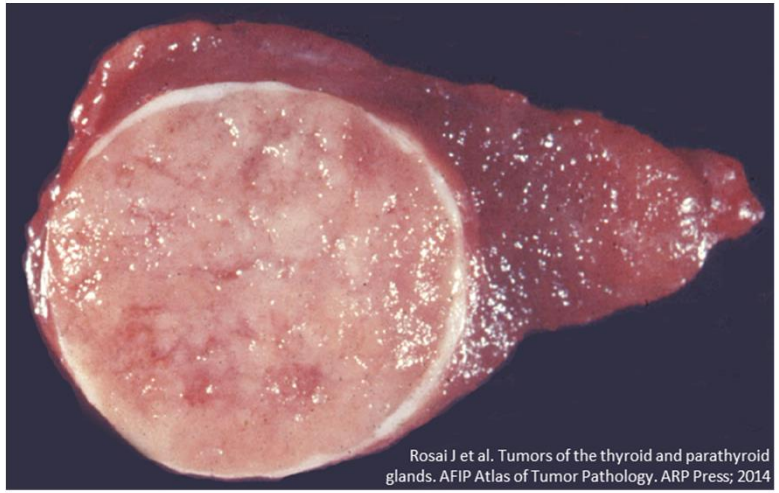
- "Multinodular goiter" or "Multinodular hyperplasia" have traditionally been used for pathology diagnosis
  - ✓Terms are inappropriate: many lesions (thyroiditis, hyperplasia, neoplasms) can give rise to clinically enlarged multinodular thyroid gland
  - ✓Sometimes impossible to tell apart follicular adenoma from hyperplastic nodule
- Studies have shown that nodules in goiter can be clonal (True neoplasms?)
  - Somatic alterations in SPOP, ZNF148 and EZH1 in around 25% of goiter nodules [Ye L et al. The genetic landscape of benign thyroid nodules revealed by whole exome and transcriptome sequencing. Nat Commun. 2017 Jun 5;8:15533. doi: 10.1038/ncomms15533]
  - Familial and early-onset FND can be associated with DICER1 syndrome
  - Alterations of thyroid hormone pathway genes e.g. TG, TPO, sodium-iodide symporter NIS, dual oxidase (DUOX2), XB130, TSHR are likely candidates in the pathogenesis of FND

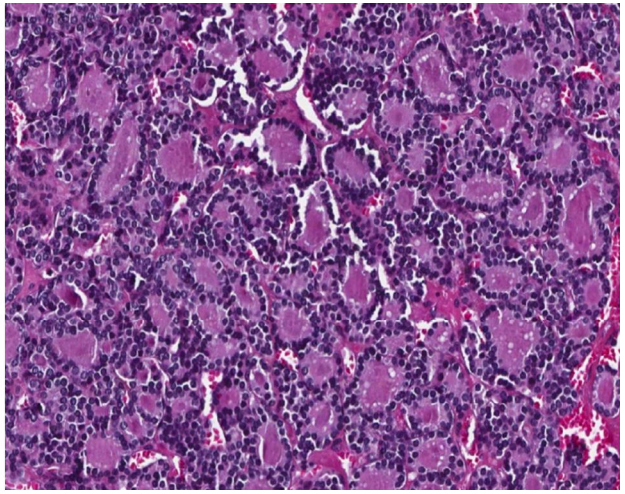
➢ **Since we can not tell hyperplasia from neoplasia "FND" is a better non-committal term**

WHO 5TH edition: Thyroid follicular nodular disease (FND)

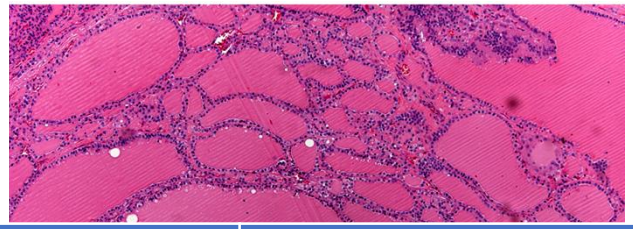




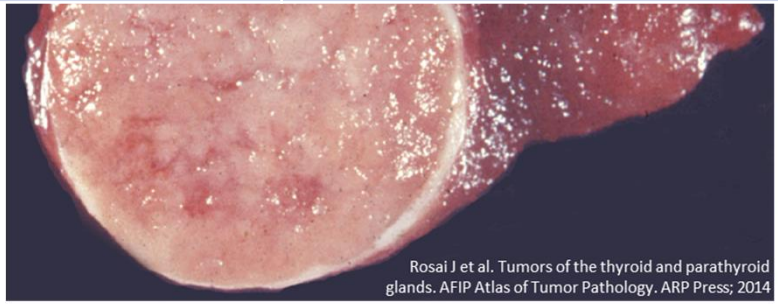


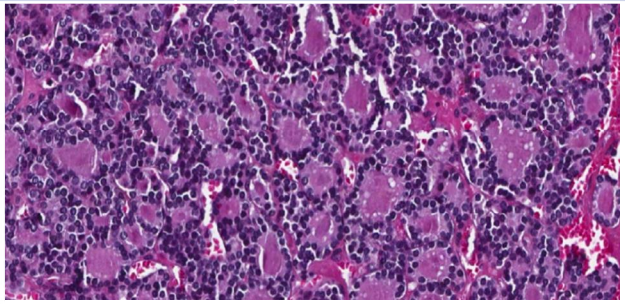


WHO 5TH edition: Thyroid follicular nodular disease (FND)

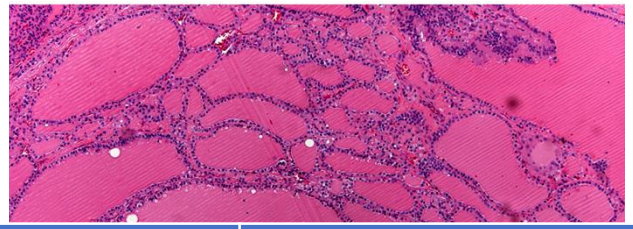


	Multinodular hyperplasia	Encapsulated well-differentiated neoplasm
Number of nodules	Multiple	Single
Lesional capsule	No (or poorly defined)	Yes (well defined)
Histology	Heterogeneous (No «clonal appearance»)	Homogeneous («Clonal» appearance)

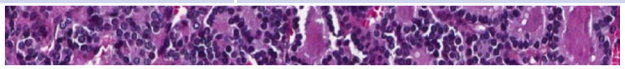




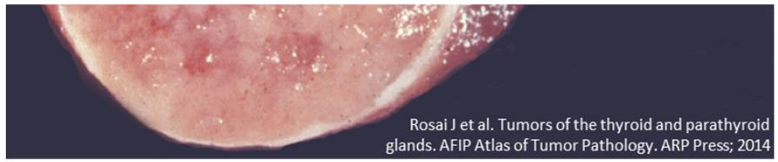
WHO 5TH edition: Thyroid follicular nodular disease (FND)

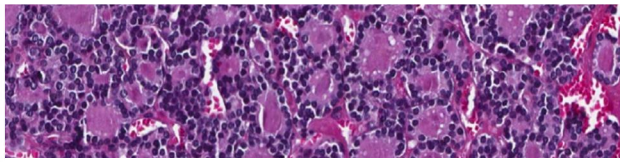


	Multinodular goiter	Encapsulated well-differentiated neoplasm*
Number of nodules	Multiple	Single
Lesional capsule	No (or poorly defined)	Yes (well defined)
Histology	Heterogeneous (No «clonal appearance»)	Homogeneous («Clonal» appearance)



*«Encapsulated well-differentiated neoplasms»: must meet at least two of the criteria in the table





Topics

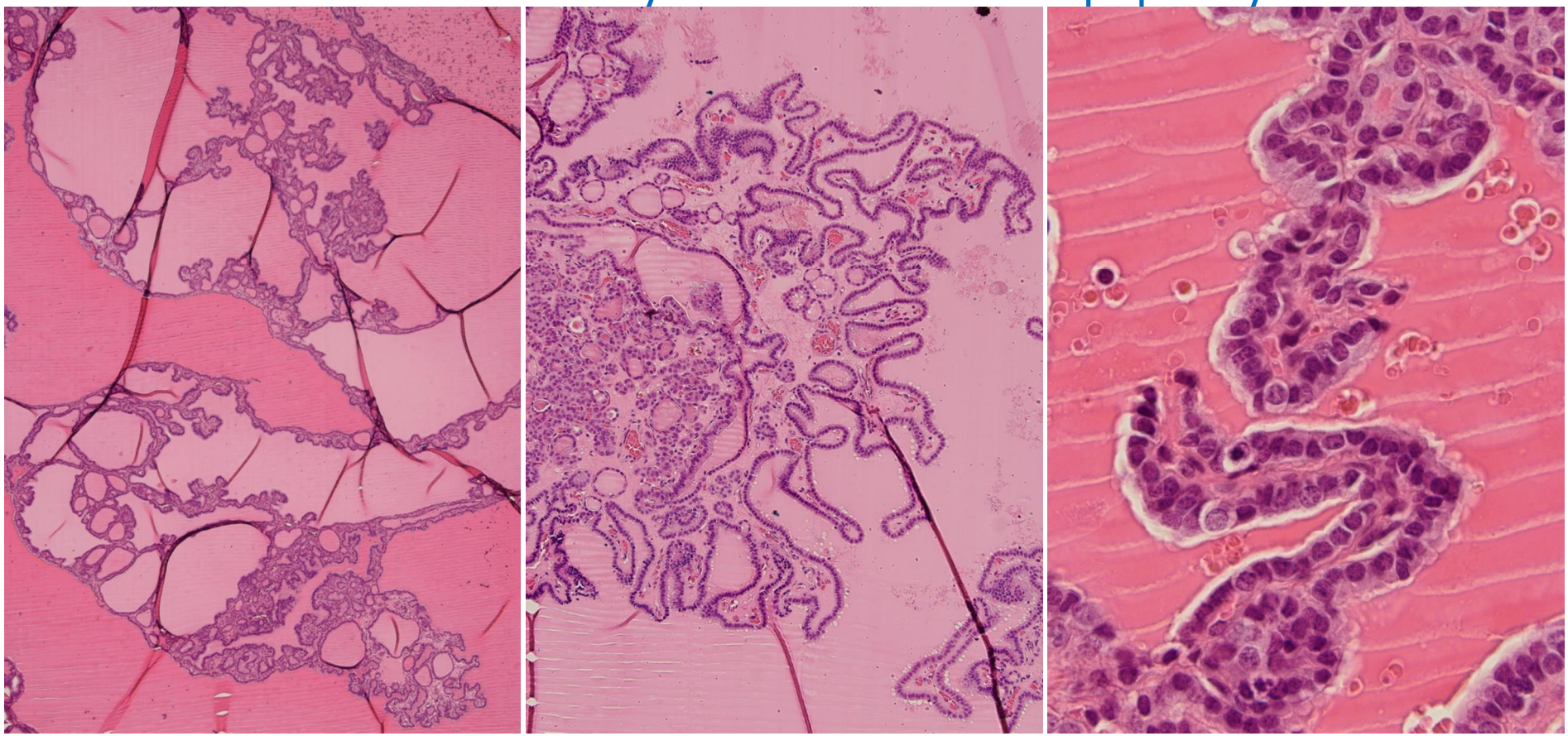
- Overview of current classification and lessons learnt from follicular-patterned lesions: Follicular variant papillary carcinoma, Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Tumors of uncertain malignant potential (UMP)
- Papillary carcinoma: subtypes and “Farewell to microcarcinoma”
- Thyroid follicular nodular disease
- Follicular thyroid adenoma with papillary architecture
- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic carcinoma): Minimally invasive (capsular invasion only); encapsulated angioinvasive; widely invasive

WHO 5TH edition: Follicular thyroid adenoma with papillary architecture

Benign non-invasive encapsulated follicular-cell-derived neoplasm characterized by distinctive papillary architecture, without nuclear features of papillary carcinoma

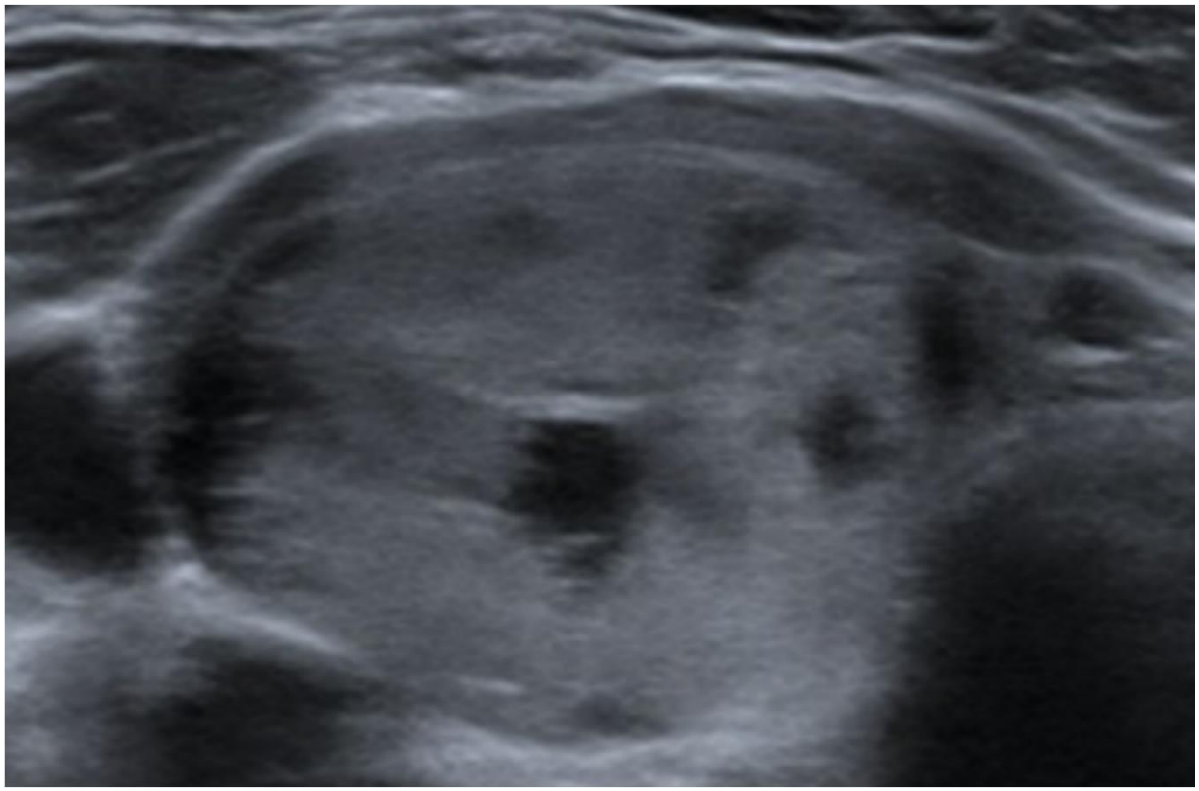
- Genetic alterations that stimulate thyroid hormone synthesis and secretion as well as follicular cell proliferation due to increased cyclic AMP signaling [Trülzsch B et al. Detection of thyroid-stimulating hormone receptor and Gs-alpha mutations: in 75 toxic thyroid nodules by denaturing gradient gel electrophoresis. J Mol Med (Berl). 2001;78(12):684-91] [Calebiro D et al. Recurrent EZH1 mutations are a second hit in autonomous thyroid adenomas. J Clin Invest. 2016 Sep 1;126(9):3383-8]
  - Activating *TSHR* mutations (up to 70%)
  - *GNAS* mutations (<5%)
  - *EZH1* mutation in combination with a *TSHR* or a *GNAS* mutation (up to 30%)
- Association with genetic syndromes: McCune-Albright (germline mosaic *GNAS* mutation), Carney complex (germline loss-of-function mutation in *PRKAR1A*), DICER1 syndrome (*DICER1* germline loss-of-function mutation)

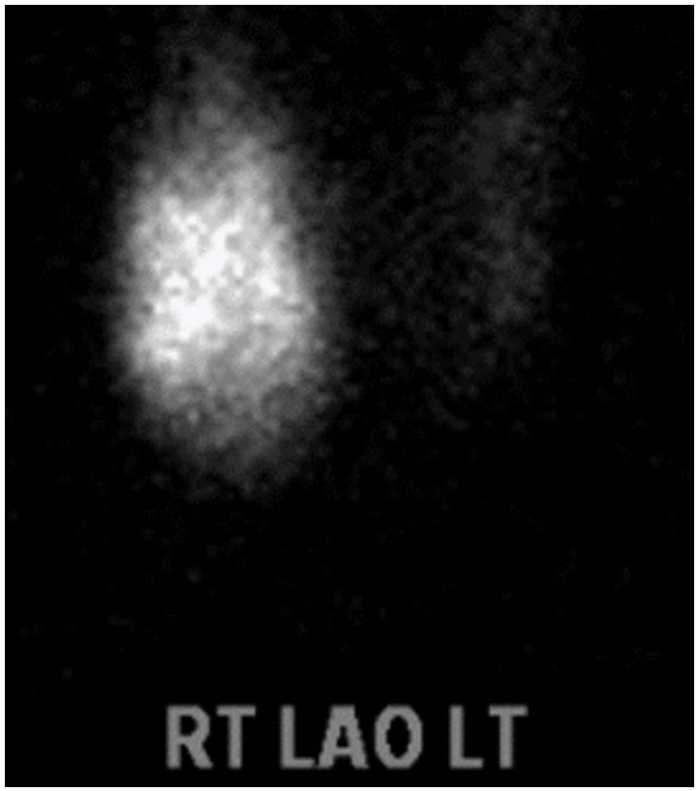
WHO 5TH edition: Follicular thyroid adenoma with papillary architecture



Mixture of follicular and papillary architecture: large follicles with intrafollicular papillary architecture (complex papillary infoldings of the lining epithelium, with broad papillae showing an organized “centripetal” orientation and edematous cores with embedded follicles)

WHO 5TH edition: Follicular thyroid adenoma with papillary architecture

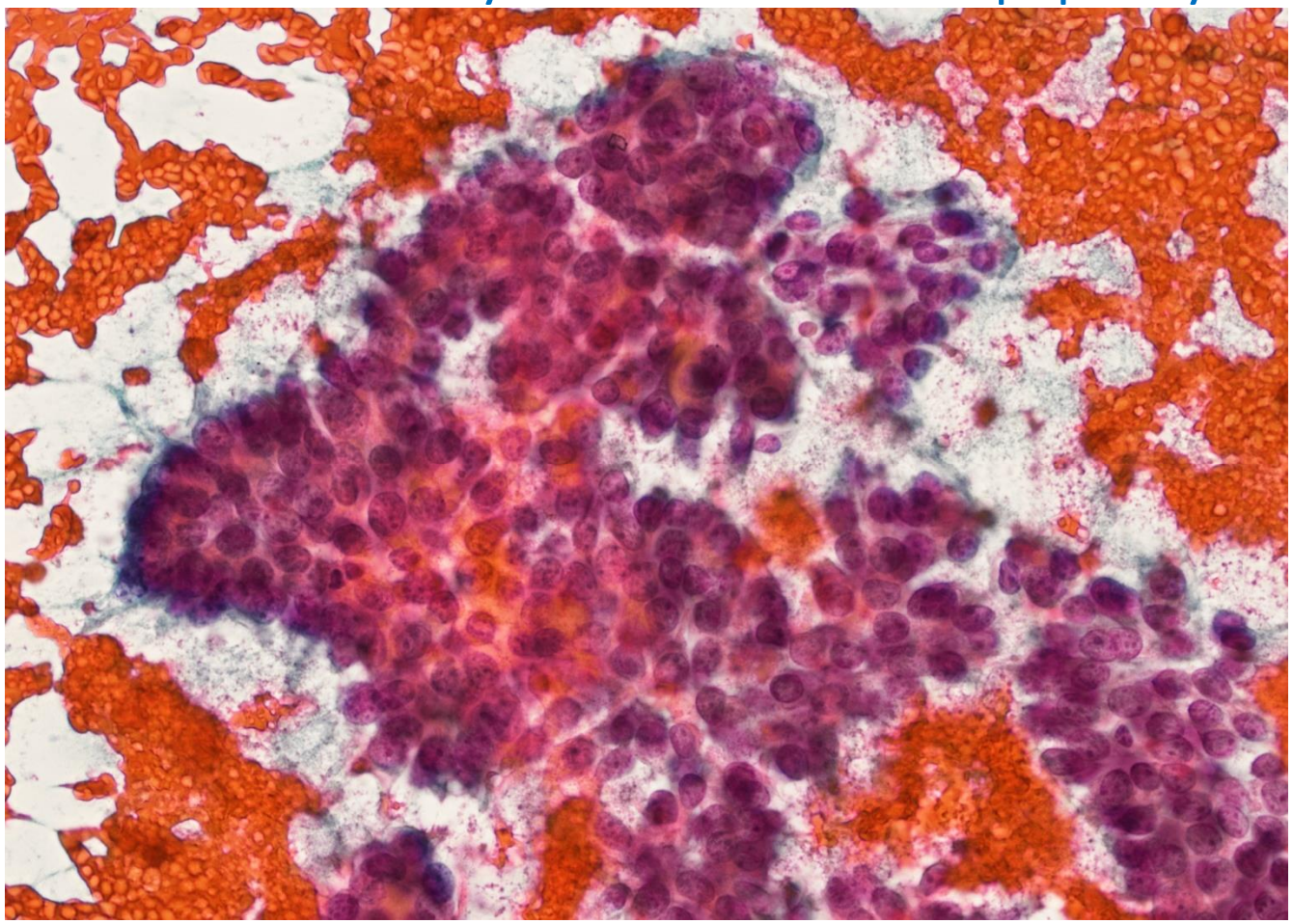




Cystic component is common, frequent clinical or subclinical hyperthyroidism, hyperfunction on radionuclide scan

Courtesy of Dr. Barletta, https://tumourclassification.iarc.who.int

WHO 5TH edition: Follicular thyroid adenoma with papillary architecture



Challenging fine-needle aspiration specimens: previous slide preoperative FNA was diagnosed as Bethesda V

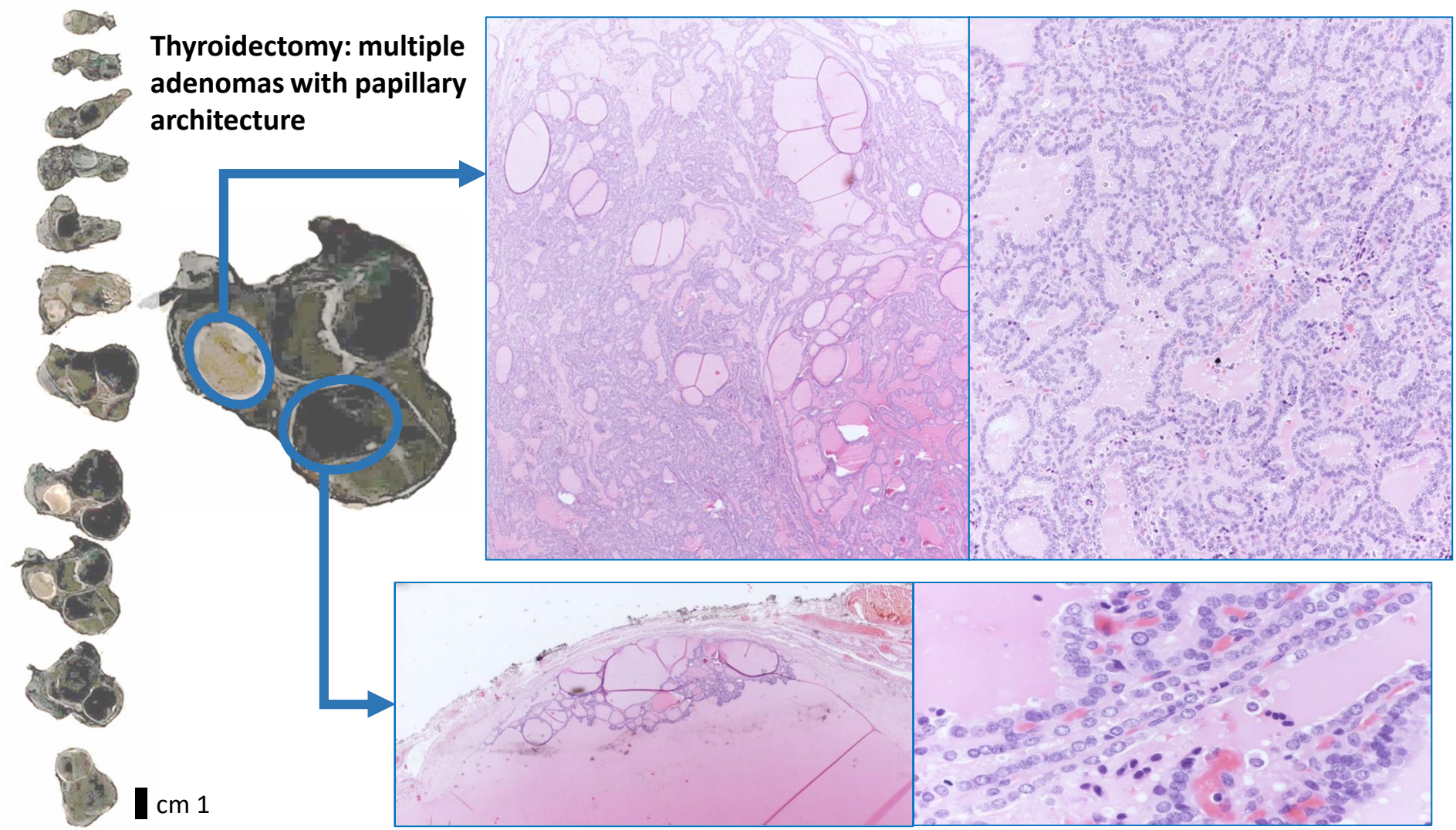
Thyroid follicular nodular disease and follicular thyroid adenoma with papillary architecture may be the first manifestation of genetic cancer syndromes…

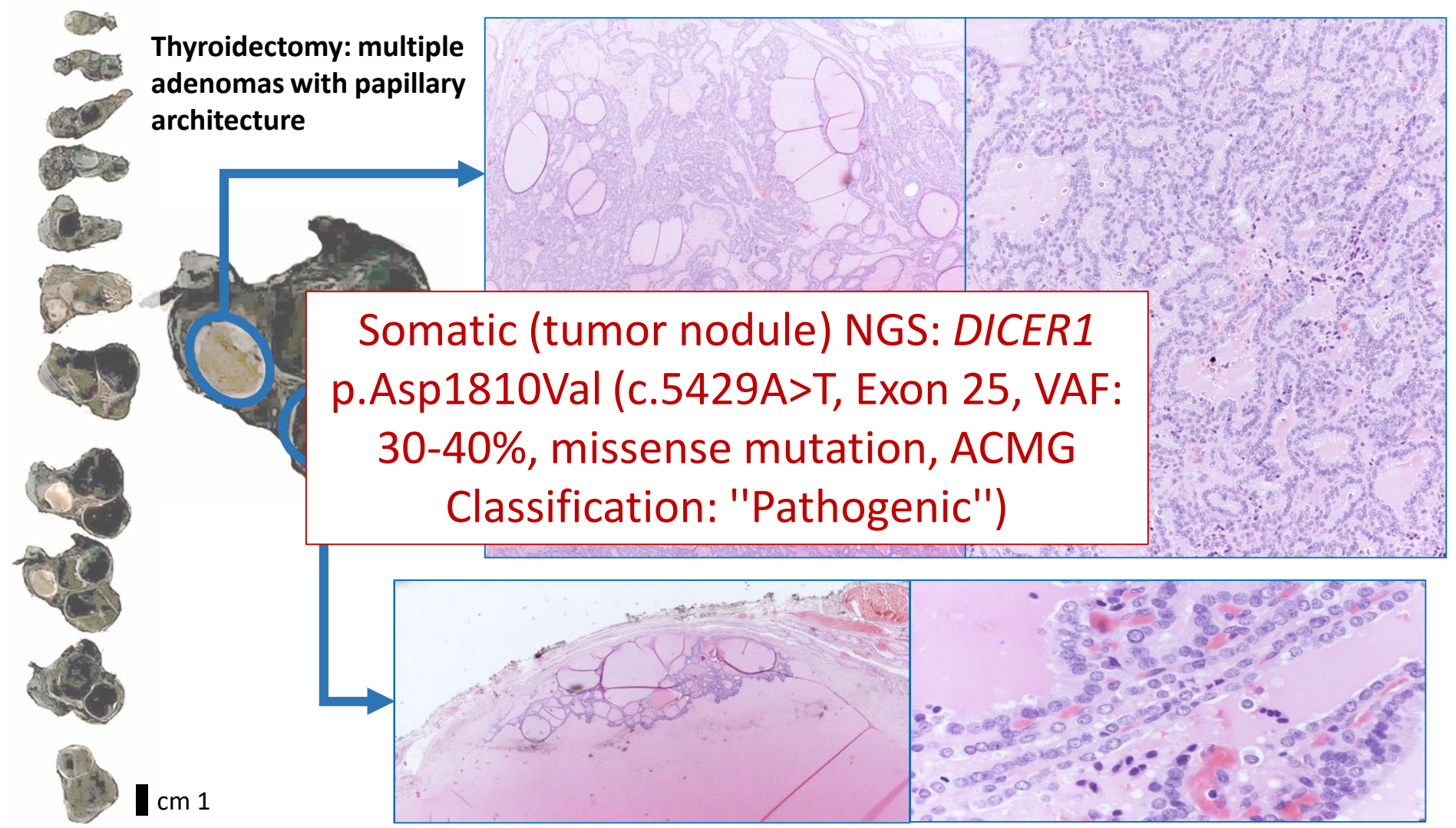
- *Two clinical examples from routine practice*

➢ *Case 1:*

15 year old young male with symptomatic multinodular goiter

Thyroidectomy: multiple adenomas with papillary architecture

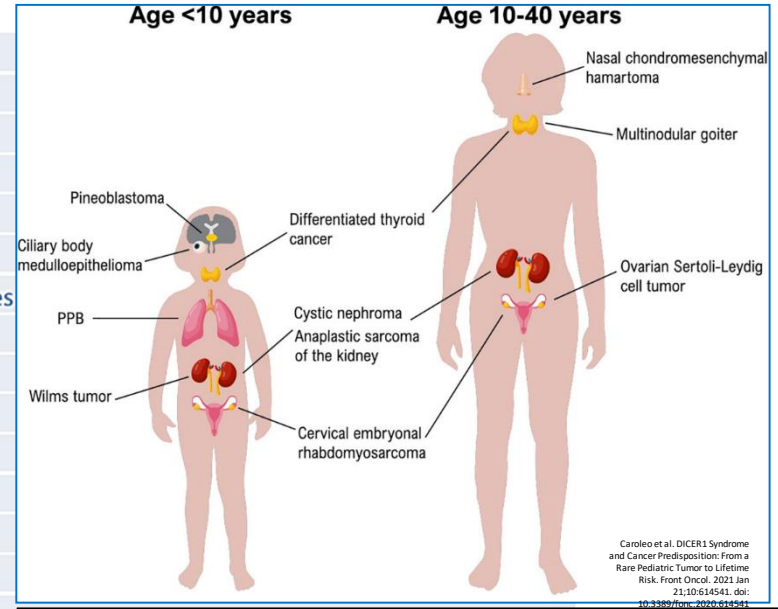



Thyroidectomy: multiple adenomas with papillary architecture
Somatic (tumor nodule) NGS: *DICER1* p.Asp1810Val (c.5429A>T, Exon 25, VAF: 30-40%, missense mutation, ACMG Classification: "Pathogenic")
cm 1

DICER1 Syndrome

Table 1. *DICER1*-associated neoplasms.

Pleuropulmonary blastoma (PPB) and PPB-like neoplasms
Pleuropulmonary blastoma, type I, IR, II, III
PPB-like Sertoli-Leydig cell tumor of lung
Pediatric cystic neoplasms and *DICER1*-sarcoma (anaplastic sarcoma of kidney)
Nasal chondromesenchymal hamartoma
Central nervous system sarcoma with rhabdomyosarcoma/PPB III-like features
Sertoli-Leydig cell tumor with and without heterologous features and type I PPB-like features
Peritoneal, ovarian and fallopian tube sarcoma with PPB-like features
DICER1-associated cystic hepatic neoplasm with type I PPB-like features
Cervical embryonal rhabdomyosarcoma
Teratoid and primitive neuroepithelial neoplasms
Cervical-thyroid teratoma
Malignant teratoid neoplasm of sacrococcygeal region
Ciliary body medulloepithelioma
Pituitary blastoma
Pineoblastoma
Embryonal tumor with multilayered rosettes
Thyroid
Multinodular hyperplasia (goiter)
Papillary thyroid carcinoma, invasive follicular variant
Follicular carcinoma, pediatric type
Poorly differentiated thyroid carcinoma, pediatric type
Intestine
Hamartomatous polyp with juvenile polyp-like features

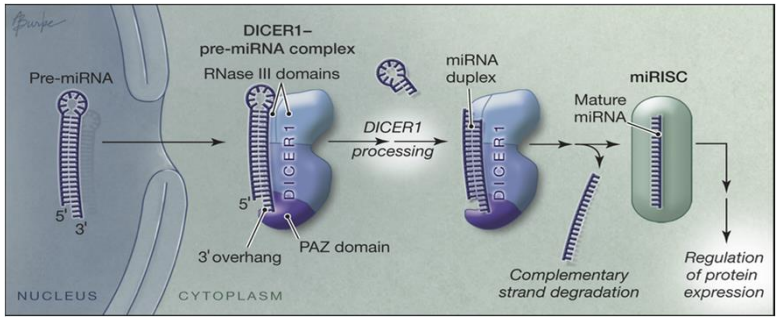


Caroleo et al. DICER1 Syndrome and Cancer Predisposition: From a Rare Pediatric Tumor to Lifetime Risk. Front Oncol. 2021 Jan 21;10:614541. doi: 10.3389/fonc.2020.614541

- DICER1 syndrome (OMIM 606241, 601200) is an autosomal dominant familial tumor predisposition disorder with heterozygous *DICER1* germline mutation
- *DICER1* on chromosome 14q32.13 encodes an RNA endonuclease (Dicer) involved in the post-transcriptional gene expression of over 30% of protein-coding genes by modulating microRNAs
- Reduced penetrance, which likely decreases the rate of familial cases; in cases with pleuropulmonary blastoma, ~80% of *DICER1* germline pathogenic variants are inherited by a parent, ~ 20% are *de novo*

González IA, Stewart DR, Schultz KAP, Field AP, Hill DA, Dehner LP. DICER1 tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma. Mod Pathol. 2022 Jan;35(1):4-22

DICER1 Syndrome



Schematic Diagram of the Role of DICER1 in MicroRNA Processing. The PAZ domain of DICER1 plays an important role in microRNA (miRNA) processing by functioning as a molecular ruler to ensure pre-miRNAs are cut to the correct length. Other proteins, such as PASHA and DROSHA, and cofactors involved in miRNA processing are not shown. miRISC indicates miRNA-induced silencing complex [Rio Frio T et al. DICER1 mutations in familial multinodular goiter with and without ovarian Sertoli-Leydig cell tumors. JAMA. 2011 Jan 5;305(1):68-77]

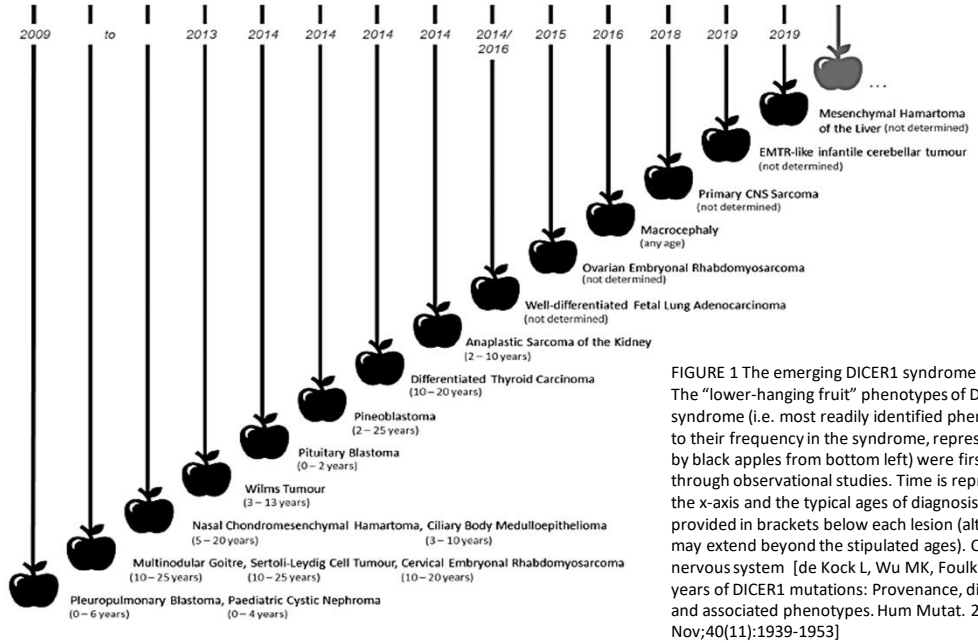
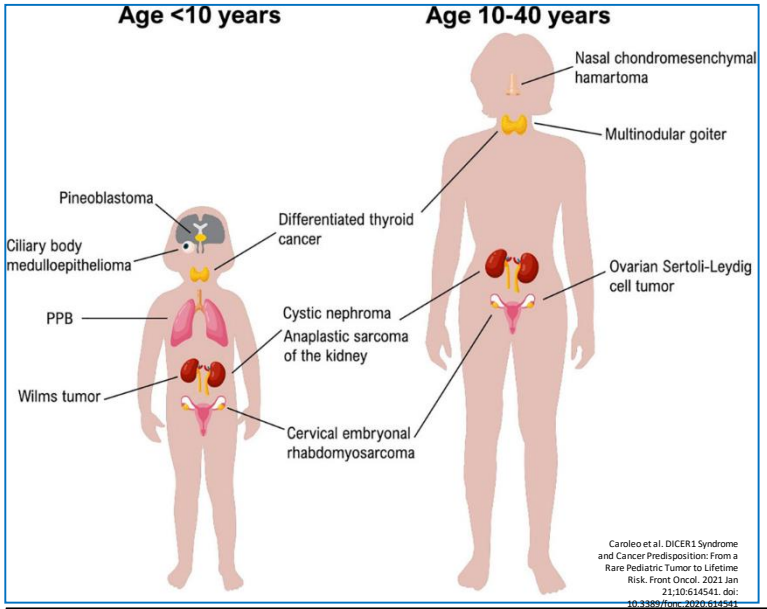
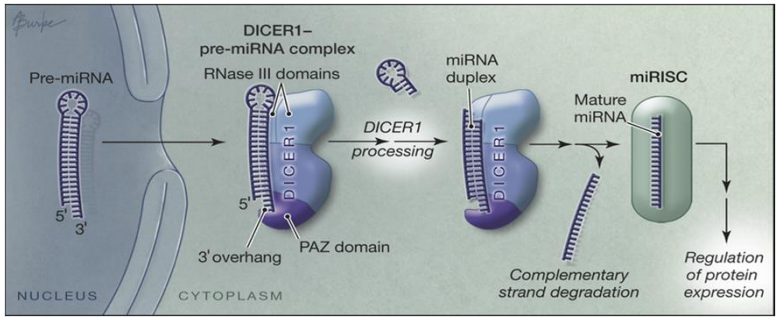


FIGURE 1 The emerging DICER1 syndrome phenotype. The "lower-hanging fruit" phenotypes of DICER1 syndrome (i.e. most readily identified phenotypes due to their frequency in the syndrome, represented here by black apples from bottom left) were first noted through observational studies. Time is represented on the x-axis and the typical ages of diagnosis are provided in brackets below each lesion (although risk may extend beyond the stipulated ages). CNS, central nervous system [de Kock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: Provenance, distribution, and associated phenotypes. Hum Mutat. 2019 Nov;40(11):1939-1953]



- DICER1 syndrome (OMIM 606241, 601200) is an autosomal dominant familial tumor predisposition disorder with heterozygous *DICER1* germline mutation
- *DICER1* on chromosome 14q32.13 encodes an RNA endonuclease (Dicer) involved in the post-transcriptional gene expression of over 30% of protein-coding genes by modulating microRNAs
- Reduced penetrance, which likely decreases the rate of familial cases; in cases with pleuropulmonary blastoma, ~80% of *DICER1* germline pathogenic variants are inherited by a parent, ~ 20% are *de novo*

DICER1 Syndrome



Schematic Diagram of the Role of DICER1 in MicroRNA Processing. The PAZ domain of DICER1 plays an important role in microRNA (miRNA) processing by functioning as a molecular ruler to ensure pre-miRNAs are cut to the correct length. Other proteins, such as PASHA and DROSHA, and cofactors involved in miRNA processing are not shown. miRISC indicates miRNA-induced silencing complex [Rio Frio T et al. DICER1 mutations in familial multinodular goiter with and without ovarian Sertoli-Leydig cell tumors. JAMA. 2011 Jan 5;305(1):68-77]

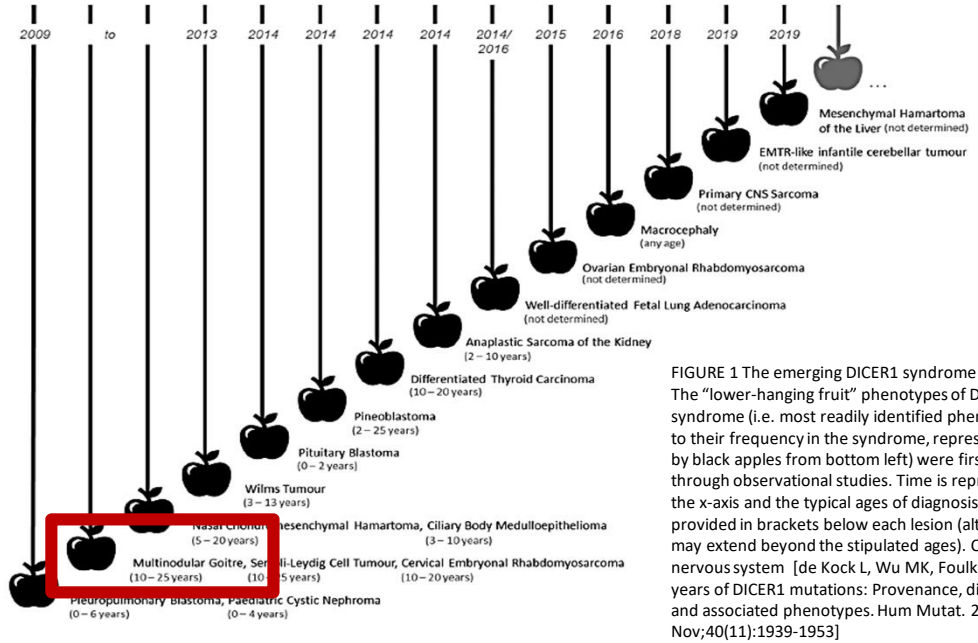
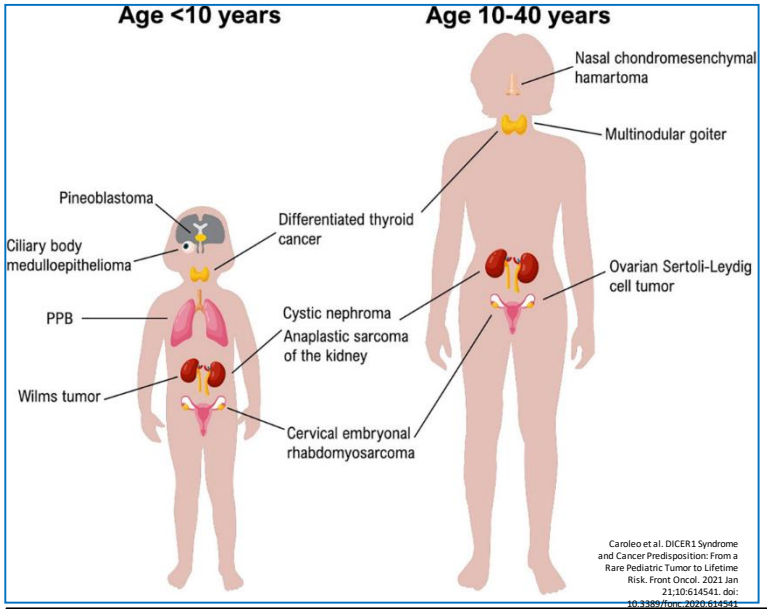


FIGURE 1 The emerging DICER1 syndrome phenotype. The "lower-hanging fruit" phenotypes of DICER1 syndrome (i.e. most readily identified phenotypes due to their frequency in the syndrome, represented here by black apples from bottom left) were first noted through observational studies. Time is represented on the x-axis and the typical ages of diagnosis are provided in brackets below each lesion (although risk may extend beyond the stipulated ages). CNS, central nervous system [de Kock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: Provenance, distribution, and associated phenotypes. Hum Mutat. 2019 Nov;40(11):1939-1953]



- DICER1 syndrome (OMIM 606241, 601200) is an autosomal dominant familial tumor predisposition disorder with heterozygous *DICER1* germline mutation
- *DICER1* on chromosome 14q32.13 encodes an RNA endonuclease (Dicer) involved in the post-transcriptional gene expression of over 30% of protein-coding genes by modulating microRNAs
- Reduced penetrance, which likely decreases the rate of familial cases; in cases with pleuropulmonary blastoma, ~80% of *DICER1* germline pathogenic variants are inherited by a parent, ~ 20% are *de novo*

DICER1 Syndrome

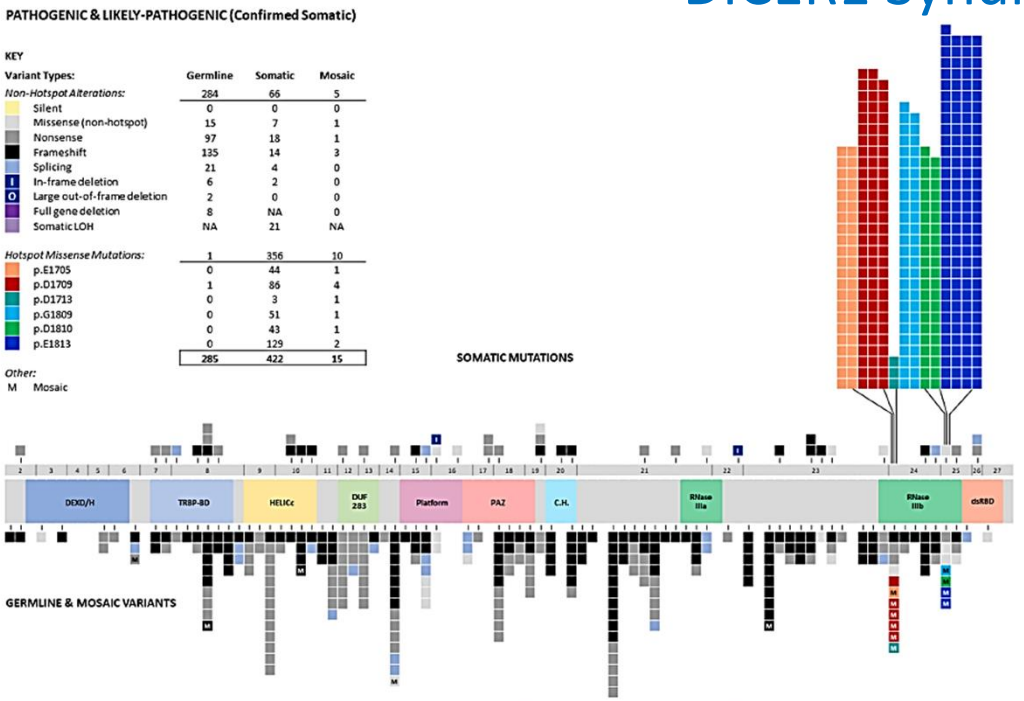
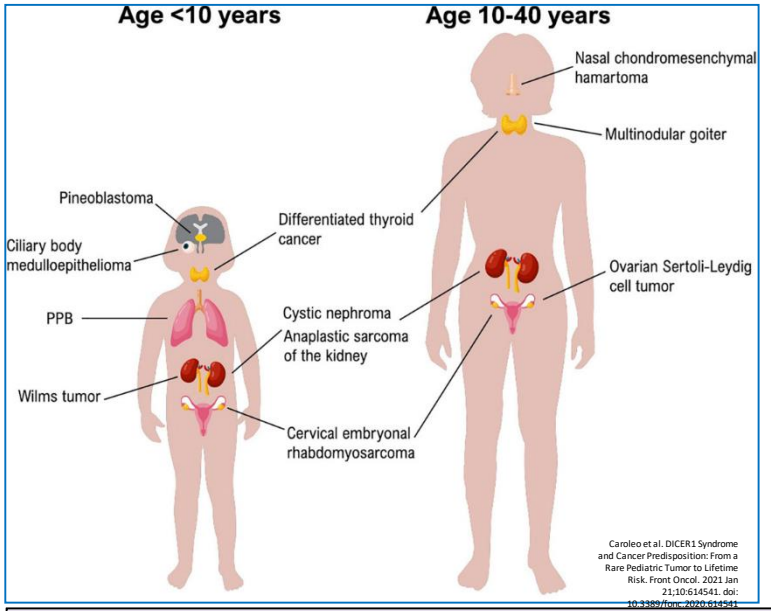


FIGURE 4 Pathogenic and likely pathogenic DICER1 alterations published before January 31st, 2019. Only unique-per-family (UPF) germline variants and confirmed-somatic mutations considered pathogenic or likely pathogenic have been plotted along the length of the unfolded DICER1 protein (n = 722). The 422 confirmed somatic events are plotted above the protein, except for the 21 confirmed-somatic LOH events that are shown at the bottom of the figure. LOH, loss of heterozygosity; NA, not applicable [de Kock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: Provenance, distribution, and associated phenotypes. Hum Mutat. 2019 Nov;40(11):1939-1953]



- DICER1 syndrome (OMIM 606241, 601200) is an autosomal dominant familial tumor predisposition disorder with heterozygous *DICER1* germline mutation
- *DICER1* on chromosome 14q32.13 encodes an RNA endonuclease (Dicer) involved in the post-transcriptional gene expression of over 30% of protein-coding genes by modulating microRNAs
- Reduced penetrance, which likely decreases the rate of familial cases; in cases with pleuropulmonary blastoma, ~80% of *DICER1* germline pathogenic variants are inherited by a parent, ~ 20% are *de novo*

DICER1 Syndrome

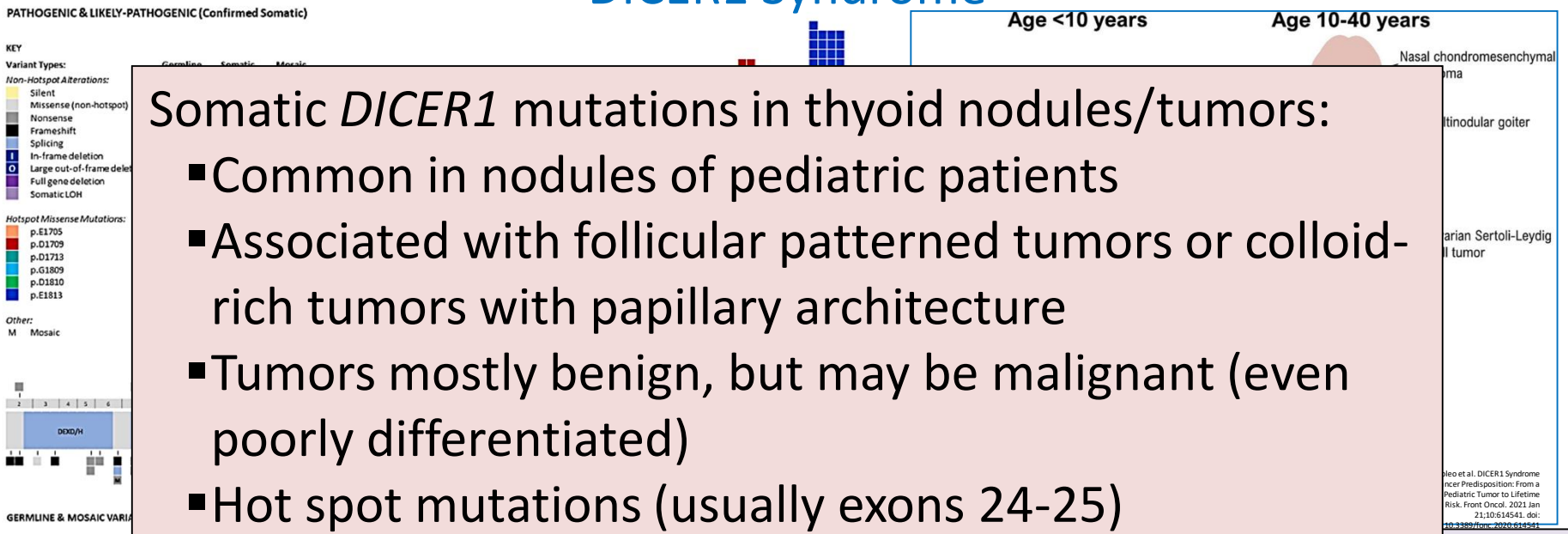


FIGURE 4 Pat
31st, 2019. O
mutations co
of the unfold
above the pr
bottom of the figure. LOH, loss of heterozygosity; NA, not applicable [de Kock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: Provenance, distribution, and associated phenotypes. Hum Mutat. 2019 Nov;40(11):1939-1953]

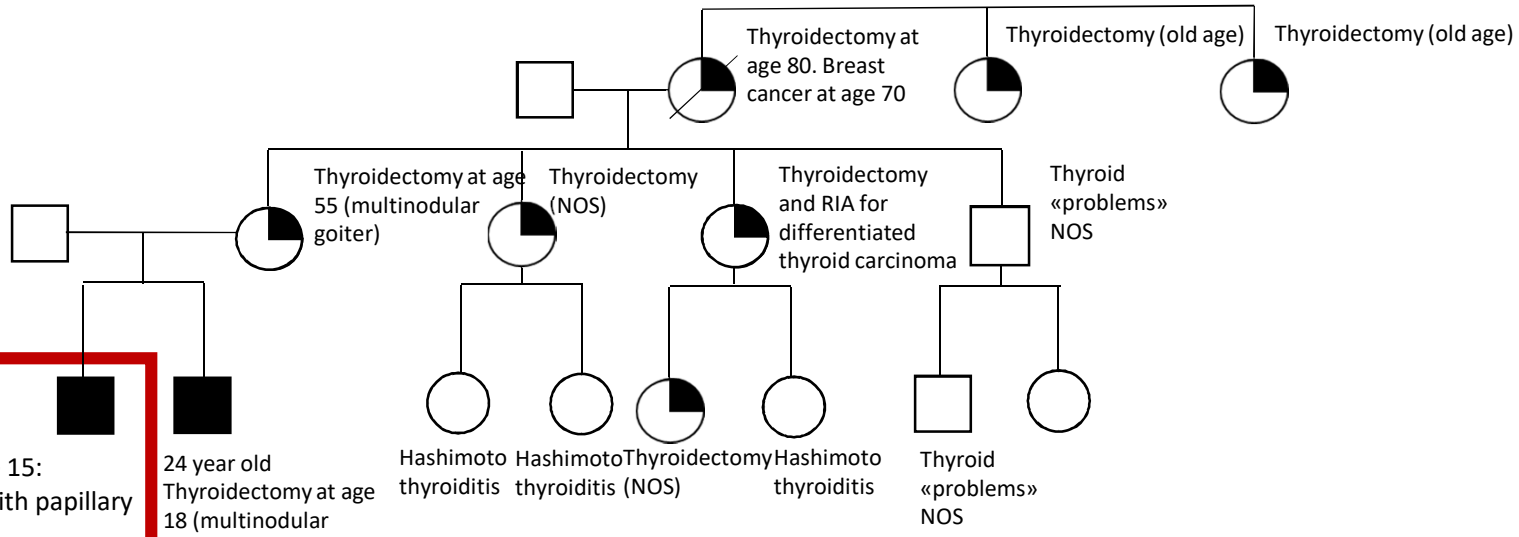
Somatic *DICER1* mutations in thyroid nodules/tumors:

- Common in nodules of pediatric patients
- Associated with follicular patterned tumors or colloid-rich tumors with papillary architecture
- Tumors mostly benign, but may be malignant (even poorly differentiated)
- Hot spot mutations (usually exons 24-25)
- Hot spot mutations may represent second hit in patients with germline *DICER1* mutations, need to evaluate *DICER1* germline (no hot spots)

tosomal
th

endonuclease
pression of
icroRNAs
e of familial
cases; in cases with pleuropulmonary blastoma, ~80% of *DICER1* germline pathogenic variants are inherited by a parent, ~ 20% are *de novo*

Family tree of **index case**



INDEX CASE
16 year old
Thyroidectomy at age 15: multiple adenomas with papillary architeture

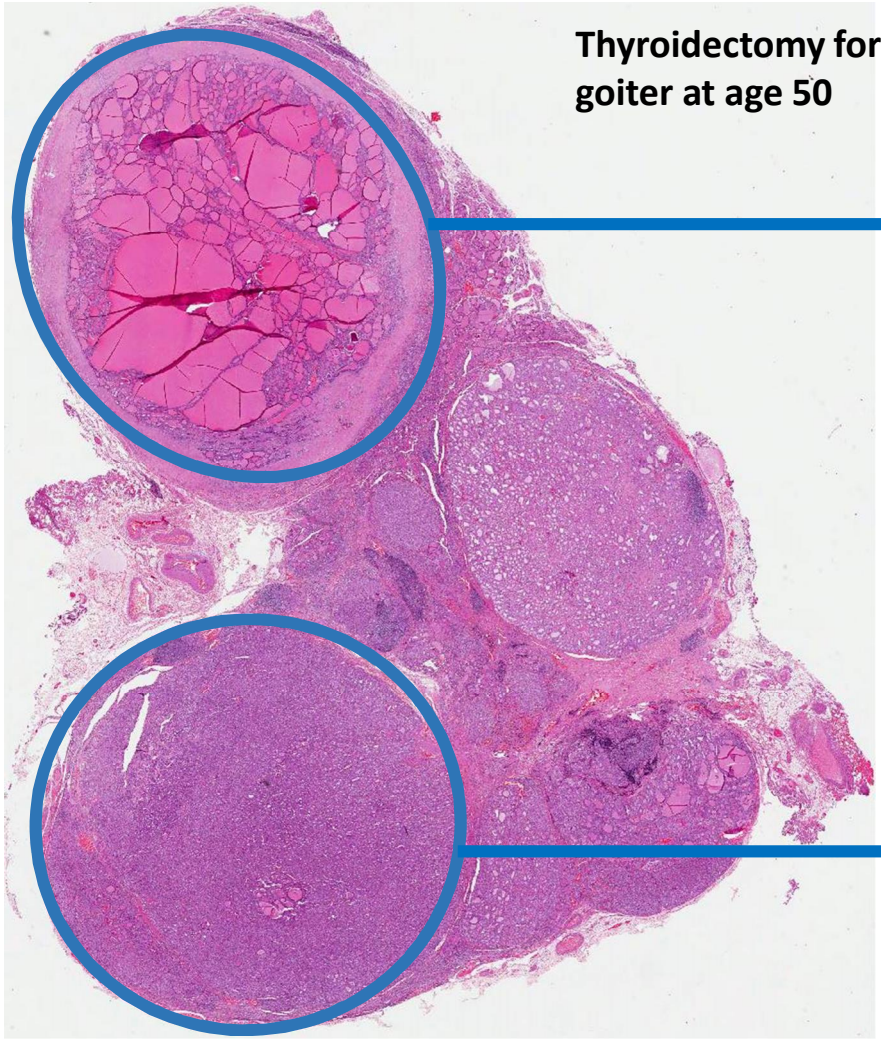
- *Somatic (tumor nodule) NGS: p.Asp1810Val (c.5429A>T, Exon 25, VAF: 37%, missense mutation, ACMG Classification: ''Pathogenic'')*
- *Germline DICER1 variant: p.Gly823Val (c.2468G>T, Exon 16, missense mutation)*

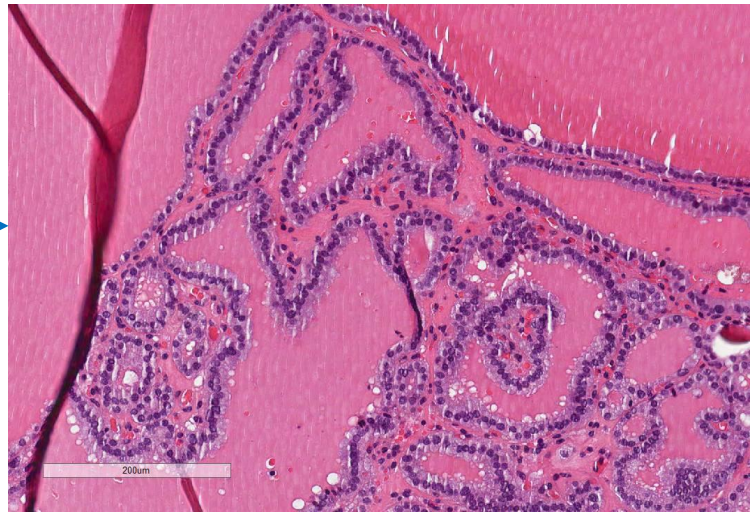
24 year old
Thyroidectomy at age 18 (multinodular goiter)
Germline DICER1 variant: p.Gly823Val (c.2468G>T, Exon 16, missense mutation)

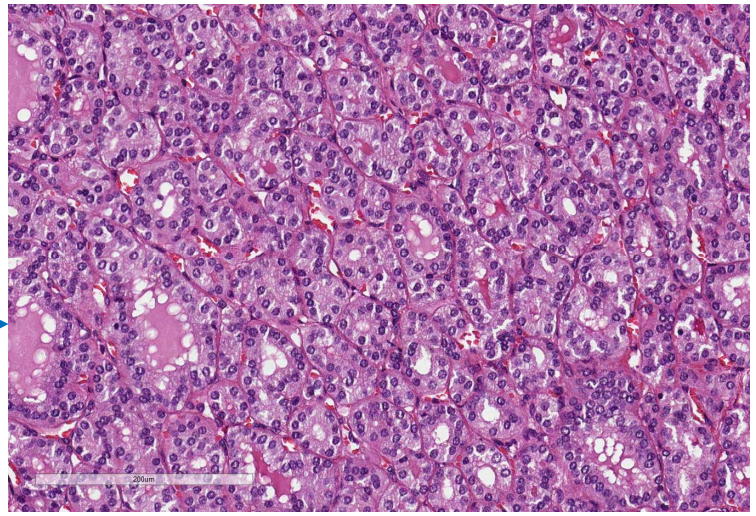
➢ *Case 2:*

50 year old woman with longstanding multinodular goiter

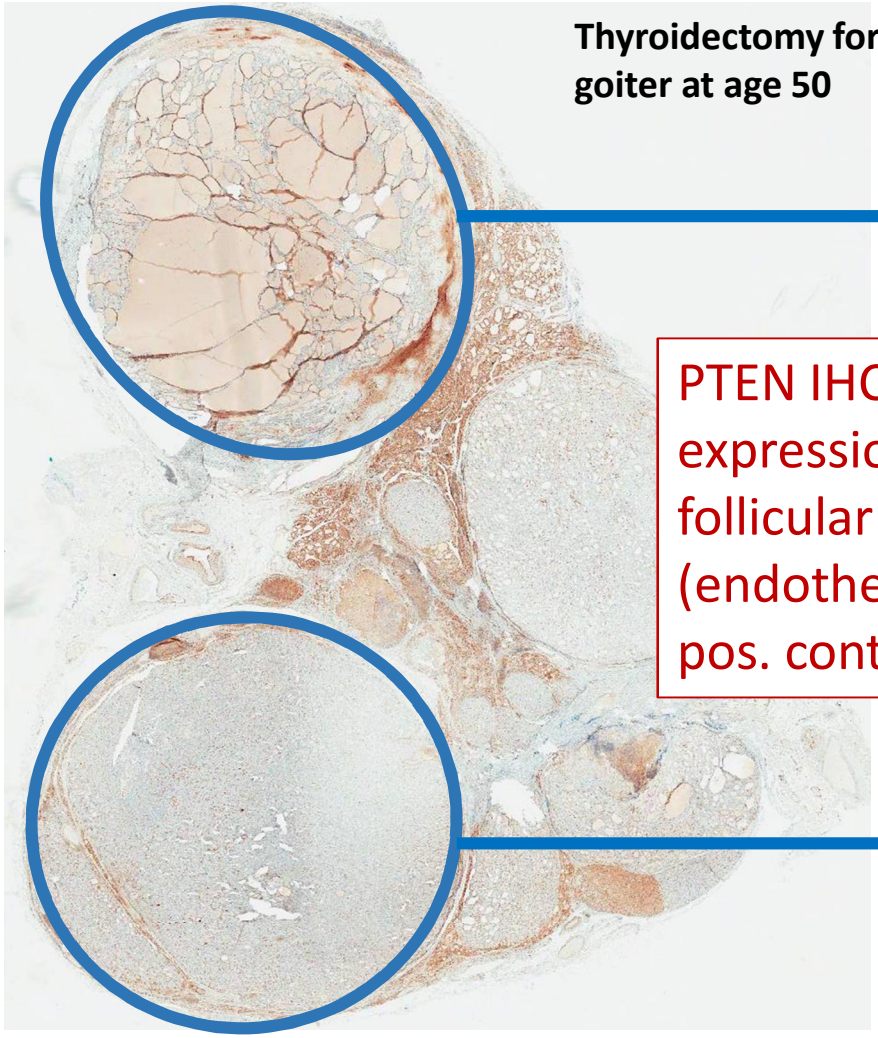
Thyroidectomy for multinodular goiter at age 50



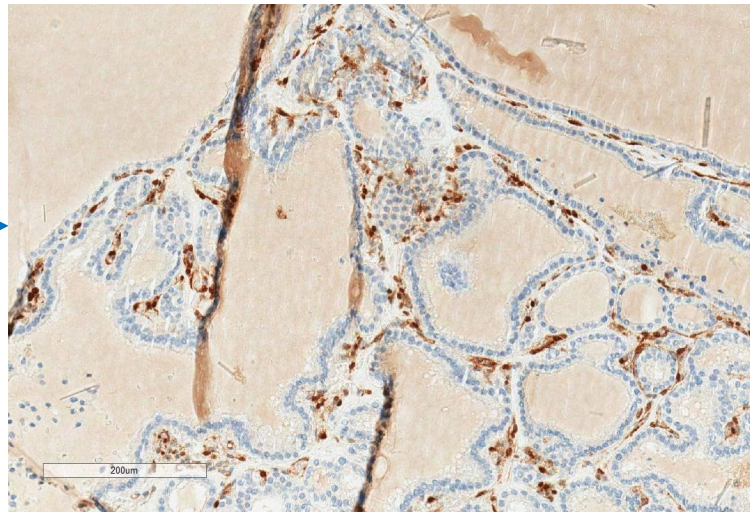


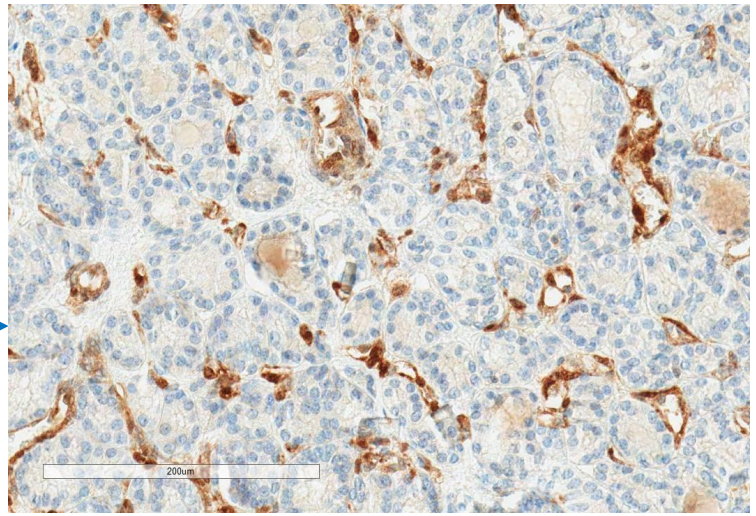


Thyroidectomy for multinodular goiter at age 50



PTEN IHC: loss of expression in follicular cells (endothelial cells: pos. control)





Cowden syndrome/PHTS

Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS)

- Germline pathogenic PTEN mutations cause PHTS: benign and malignant tumors, neurodevelopmental disorders (autism spectrum disorder), the prototypical form of which is **Cowden syndrome** (so named after the Cowden family, in which it was initially discovered)
- Cowden syndrome (a.k.a Cowden disease, multiple hamartoma syndrome; OMIM 158350); autosomal dominant condition characterized by hamartomas as well as increased lifetime risk of breast, thyroid, uterine, and other cancers; incidence ~1:200,000 - often underdiagnosed due to variability in disease presentation; PTEN mutations in up to 85% of Cowden's patients
  - ✓ Major criteria include: breast cancer, endometrial cancer, **thyroid cancer (follicular)**, mucocutaneous lesions (trichilemmomas, acral keratoses, neuromas, oral papillomas) gastrointestinal hamartomas
  - ✓ Minor criteria include: colon cancer, renal cell carcinoma, **multinodular goiter**, autism spectrum disorder, intellectual disability (i.e., iq ≤ 75)
- Surveillance focused on early detection of breast, endometrial, thyroid, colorectal, renal, and skin cancer

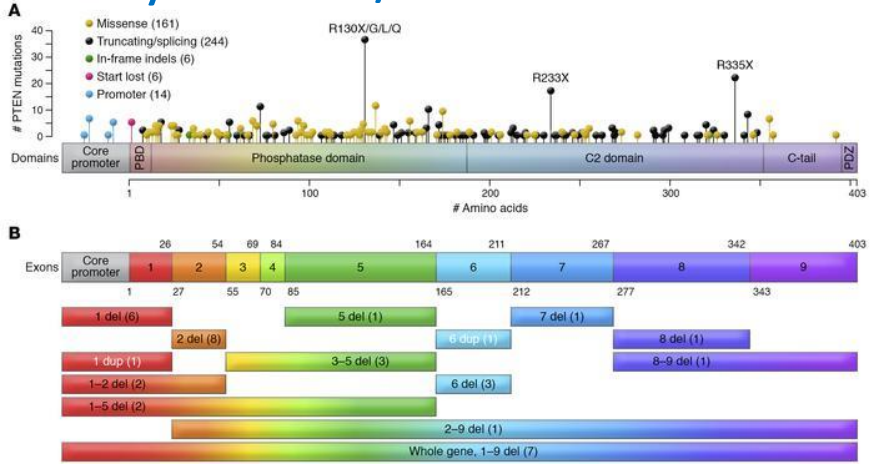


Figure 3. PTEN structure and germline mutation spectrum in PHTS. (A) PTEN germline mutation spectrum from 431 PHTS patients. PTEN is canonically a 403–amino acid protein. Different types of mutations are depicted in the lollipop plot overlaying the PTEN protein structure. The frequency of mutations correlates with the heights of the vertical lines representing each lollipop. PTEN comprises a PIP2-binding domain (PBD), a phosphatase domain, a C2 domain, and a C-terminal tail including a PDZ-binding domain. The active site is included within amino acid residues 123 and 130. (B) PTEN consists of 9 exons that encode the 403–amino acid protein. The exons are overlaid to match the protein domains in A. Intronic regions are not represented. The colored bars represent large deletions (abbreviated as del) and duplications (abbreviated as dup) annotated by affected exon numbers and the number of affected patients in parentheses [Yehia L, Ngeow J, Eng C. PTEN-opathies: from biological insights to evidence-based precision medicine. J Clin Invest. 2019 Feb 1;129(2):452-464]

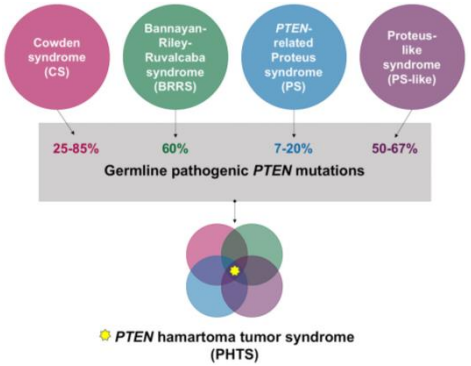
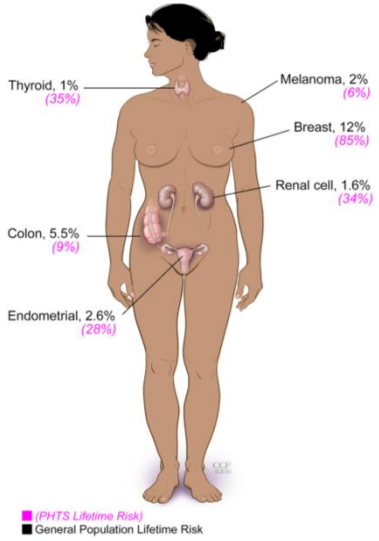


Figure 1. PTEN hamartoma tumor syndrome clinical spectrum. Subsets of patients with Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, and Proteus and Proteus-like syndrome represent a spectrum of heritable conditions associated with germline mutations in the PTEN tumor suppressor gene. Regardless of clinical phenotype, such individuals with germline PTEN mutations have PTEN hamartoma tumor syndrome [Yehia L, Eng C. 65 YEARS OF THE DOUBLE HELIX: One gene, many endocrine and metabolic syndromes: PTEN-opathies and precision medicine. Endocr Relat Cancer. 2018 Aug;25(8):T121-T140]



Cowden syndrome/PHTS

Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS)

- Germline pathogenic PTEN mutations cause PHTS: benign and malignant tumors, neurodevelopmental disorders (autism spectrum disorder), the prototypical form of which is **Cowden syndrome** (so named after the Cowden family, in which it was initially dis
- Cowden sy hamartom dominant well as inc uterine, ar often unde presentati Cowden's
  - ✓ Major cri cancer, th lesions (t neuroma hamartor
  - ✓ Minor cri carcinom disorder,
- Surveillanc endometri cancer

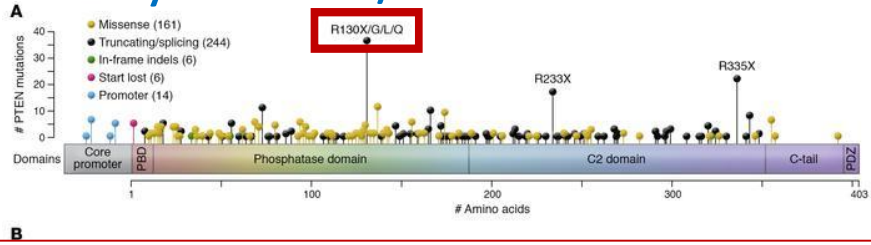


Figure 3. PTEN structure and germline mutation spectrum in PHTS. (A) PTEN germline mutation spectrum from 431 PHTS patients. PTEN is canonically a 403–amino acid protein. Different types of mutations are depicted in the lollipop plot overlaying the PTEN protein structure. The frequency of mutations correlates with the heights of the vertical lines
PTEN comprises a PIP2-
hosphatase domain, a C2
ail including a PDZ-binding
ncluded within amino acid
TEN consists of 9 exons that
d protein. The exons are
ein domains in A. Intronic
d. The colored bars
abbreviated as del) and
s dup) annotated by affected
mber of affected patients in
ow J, Eng C. PTEN-opathies:
evidence-based precision
19 Feb 1;129(2):452-464]

- Germline PTEN R130*, loss of function mutation, ACMG Classification: ''Pathogenic“
- PTEN IHC loss, likely epigenetic inactivation (sensitive and specific for Cowden/PHTS)

- Right mastectomy at age 35: 2.4 cm Ductal carcinoma G2, ER/PR+, Ki67 30%, HER2-, sLN-; DCIS, LCIS
- Left mastectomy at age 45: 1.4 cm Ductal carcinoma, G3, ER/PR+, Ki67 20%, HER2-, sLN-; DCIS

➢ Genetic counseling: Cowden syndrome

oma, 2% (6%)
st, 12% (85%)
ell, 1.6% (34%)

Aug;25(8):T121-T140]

(PHTS Lifetime Risk)
General Population Lifetime Risk

Thyroid nodules in young patients with clinically evident multinodular goiter

- Numerous adenomatous nodules (millimetric-centimetric) +/- papillary architecture, bilaterally
- Young age

...The findings of multiple thyroid nodules is not unusual, particularly in older people, but these nodules are usually heterogeneous hyperplastic nodules combining different patterns of growth with colloidals nodules, regressive changes and focal lymphocytic infiltration...[Cameselle-Teijeiro J. The pathologist's role in familial nonmedullary thyroid tumors. Int J Surg Pathol. 2010 Jun;18(3 Suppl):194S-200S]

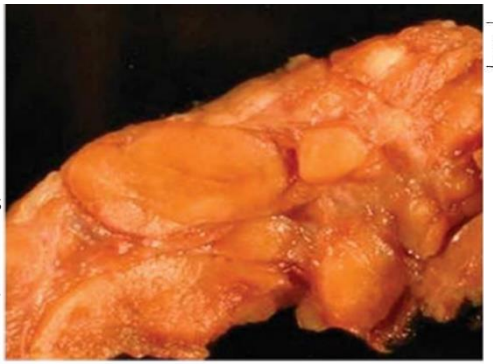


Figure 8 Gross pathologic features of multiple adenomatou nodules in a young patient with *PTEN*-hamartoma tumo syndrome.

Table 2. Histologic Findings in Thyroid Glands From 11 Patients With Cowden Disease

Case No.	Sex/ Age (yr)	No. of Blocks	Follicular Adenoma and Adenomatous Nodule: Clinically Significant	Size (cm)	<1 cm (adenoma)	Cellular Foci	Other Findings
1	F/40	6	Follicular adenoma	2.3	29 NOS (5)	12	Focal thyroiditis
			Follicular adenoma	1.6			Bone marrow
			Adenomatous nodule	1.4			
2	F/20	3	Adenomatous nodule	2.2	9 NOS (1)	8	
			Adenomatous nodule	1.5			
			Adenomatous nodule	1.5			
3	F/20	5	Follicular adenoma	2.2	10 NOS 1 Clear cell (1)* 1 Oxyphil cell	8	Focal thyroiditis
4	M/37	4	Hyalinising trabecular adenoma-like	2.5	4 NOS (2) 1 Oxyphil cell (1)	4	Focal thyroiditis
			Oxyphil cell adenoma	1.7			
5	M/20	17	Follicular adenoma*	3.0		NA	NA
			Follicular carcinoma				
			Adenomatous nodule				
			Follicular adenoma*	1.5			
6	F/13	14	Follicular adenoma	1.8	24 NOS (3)	18	Colloid nodule
			Adenomatous nodule	1.5	1 NOS*		
			Adenomatous nodule	1.4	1 Clear cell (1)		
			Follicular adenoma	1.3			
			Follicular adenoma	1.3			
			Adenomatous nodule	1.2			
7	F/32	20	Follicular adenoma*	1.5	10 NOS (1)	13	Focal thyroiditis
			Adenomatous nodule	1.2	3 Oxyphil cell (1)		Papillary microcarcinoma
							Thymic tissue
8	M/28		Follicular adenoma in a multinodular goiter?†				
	39	5	Follicular carcinoma*	3.1	NA	NA	NA
9	M/9	8	Follicular adenoma*	3.0	9 NOS (6) 1 Adenolipoma	4	
	27	1	Follicular neoplasm*	1.6	4 NOS	1	Colloid cyst Thyroglossal cyst?†
10	F/43	4	Follicular adenoma	2.2	20 NOS (3)	3	Focal thyroiditis
			Follicular adenoma	1.3			
			Adenomatous nodule	1.3			
11	M/29	5	Follicular adenoma*	3.0	12 NOS (5)	16 1*	Focal thyroiditis C-cell hyperplasia

Abbreviations: NOS, not otherwise specified; NA, not applicable.
*Features of tumor progression.
†Histology not available.

Harach HR et al. Thyroid pathologic findings in patients with Cowden disease. Ann Diagn Pathol. 1999 Dec;3(6):331-40

Hereditary condition likely
- Cowden syndrome
  → do IHC
- DICER1 syndrome
  → need to sequence hot spots in the nodules

...The istologic findings of a multiple adenomatous goiter and/or multiple follicular adenomas, particularly in children and young adults, should alert to the possibility if an inherited trait ... [Harach HR, Soubeyran I, Brown A, Bonneau D, Longy M. Thyroid pathologic findings in patients with Cowden disease. Ann Diagn Pathol. 1999 Dec;3(6):331-40]

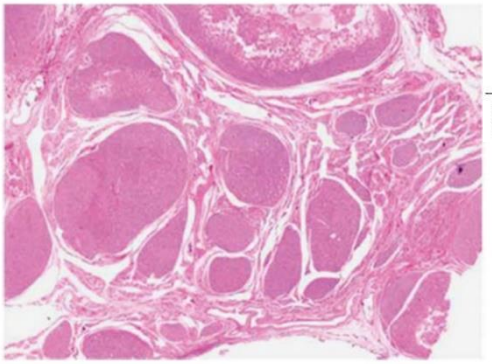


Figure 9 Histopathology of a thyroid with multiple adenomatous nodules in a young patient with *PTEN*-hamartoma tumor syndrome.

Nosé V. Familial thyroid cancer: a review. Mod Pathol. 2011 Apr;24 Suppl 2:S19-33

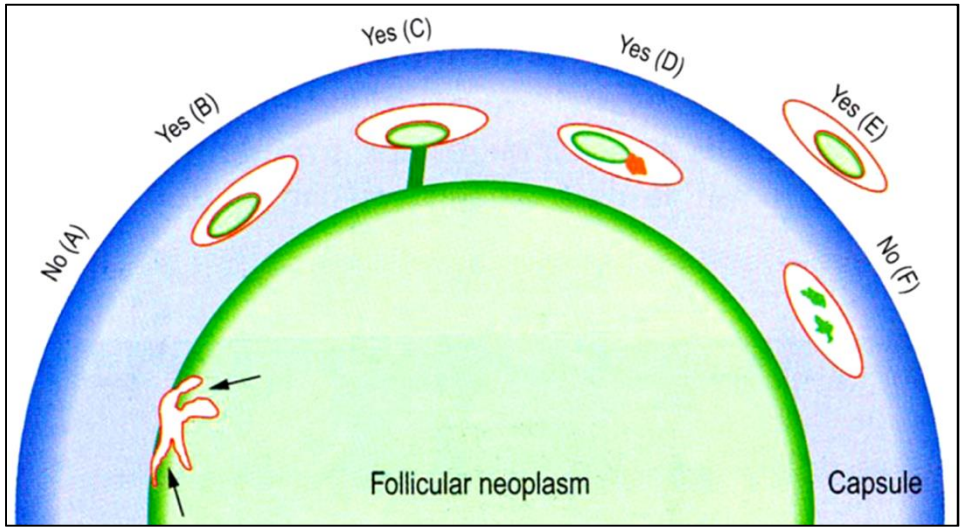
Topics

- Overview of current classification and lessons learnt from follicular-patterned lesions: Follicular variant papillary carcinoma, Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Tumors of uncertain malignant potential (UMP)
- Papillary carcinoma: subtypes and “Farewell to microcarcinoma”
- Thyroid follicular nodular disease
- Follicular thyroid adenoma with papillary architecture
- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic carcinoma): Minimally invasive (capsular invasion only); encapsulated angioinvasive; widely invasive

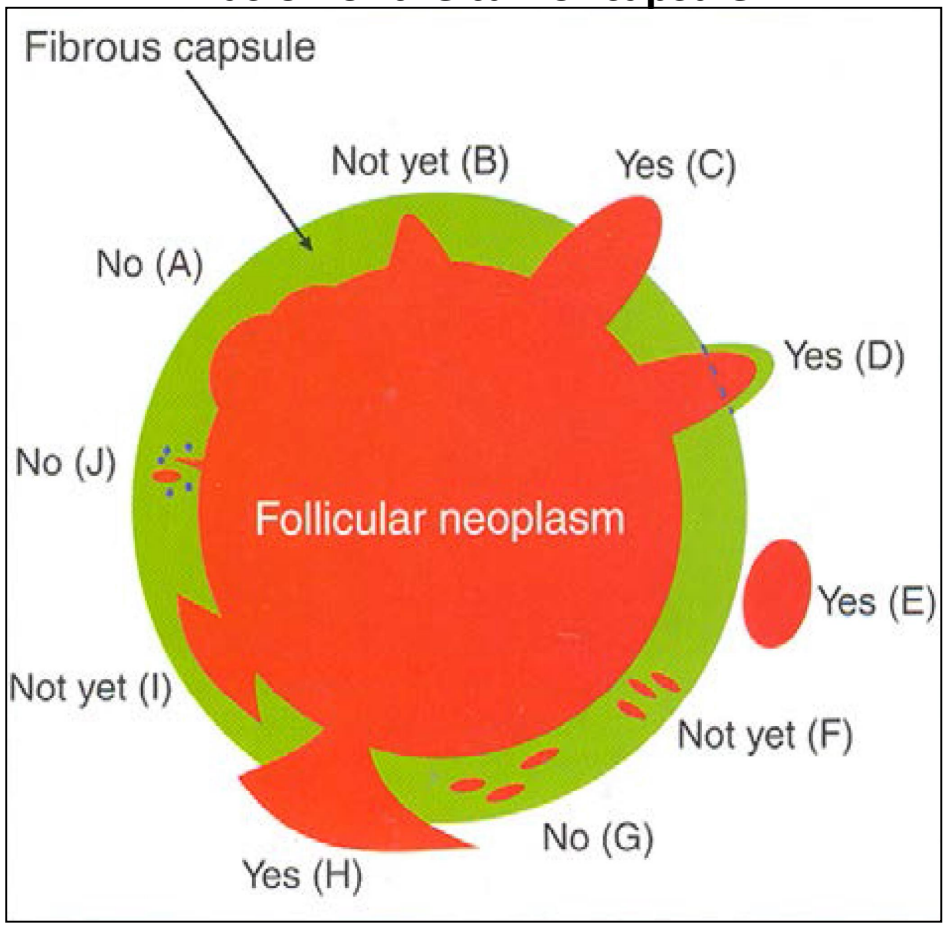
WHO 5TH edition: subtypes of invasion in encapsulated carcinomas

- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncoytic carcinoma):
  - Minimally invasive (capsular invasion only)
  - Encapsulated angioinvasive
    - Limited angioinvasion, into 1-3 vessels
    - Extensive angioinvasion, into 4 or more vessels
  - Widely invasive (simulate multinodular goiter)

Vascular invasion



Invasion of the tumor capsule

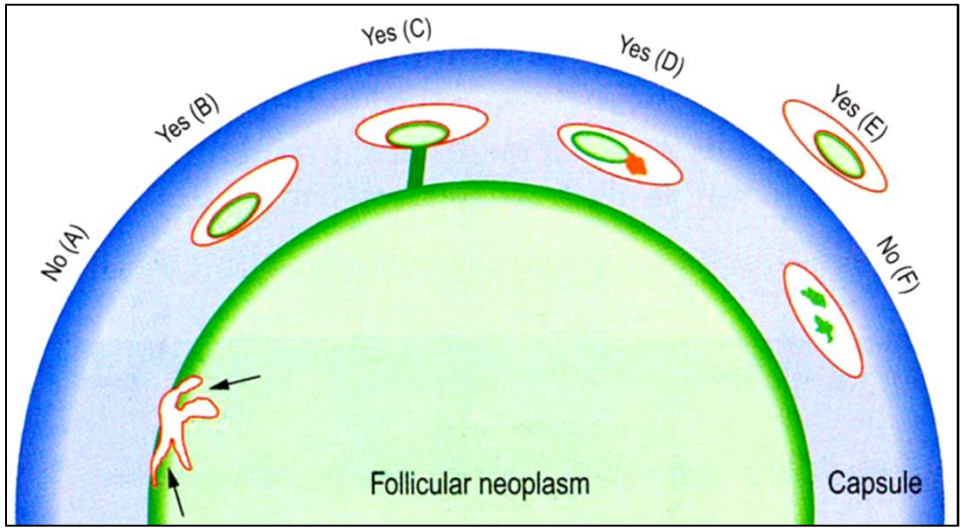


Chan JKC; Chapter 18 Tumors of the thyroid and parathyroid glands. Diagnostic Histopathology of Tumors. 3rd ed. Fletcher CDM, editor, 2007. p. 997–1078 (without College of American Pathologists modifications to criteria for vascular invasion 2014 to 2019)

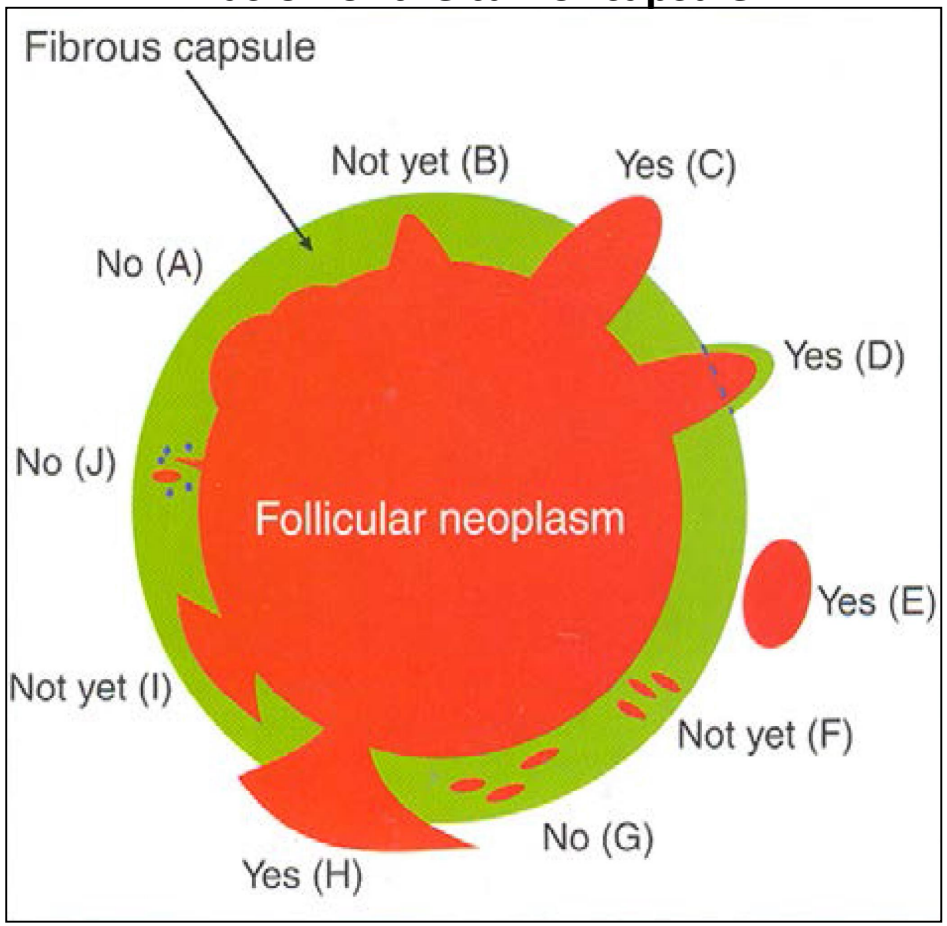
WHO 5TH edition: subtypes of invasion in encapsulated carcinomas

- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncoytic carcinoma):
  - Minimally invasive (capsular invasion only)
  - Encapsulated angioinvasive
    - Limited angioinvasion, into 1-3 vessels
    - Extensive angioinvasion, into 4 or more vessels
  - Widely invasive (simulate multinodular goiter)

Vascular invasion

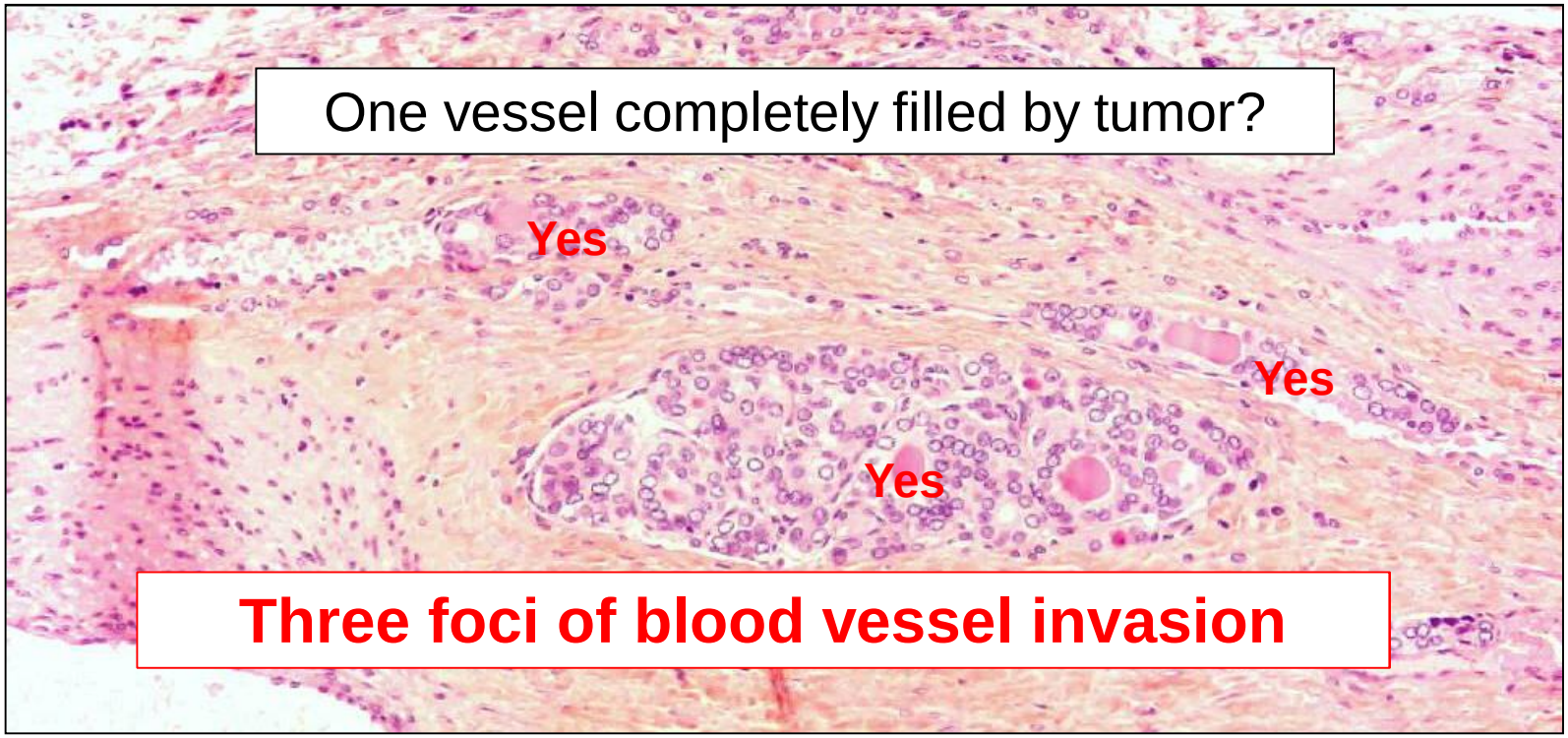


Invasion of the tumor capsule



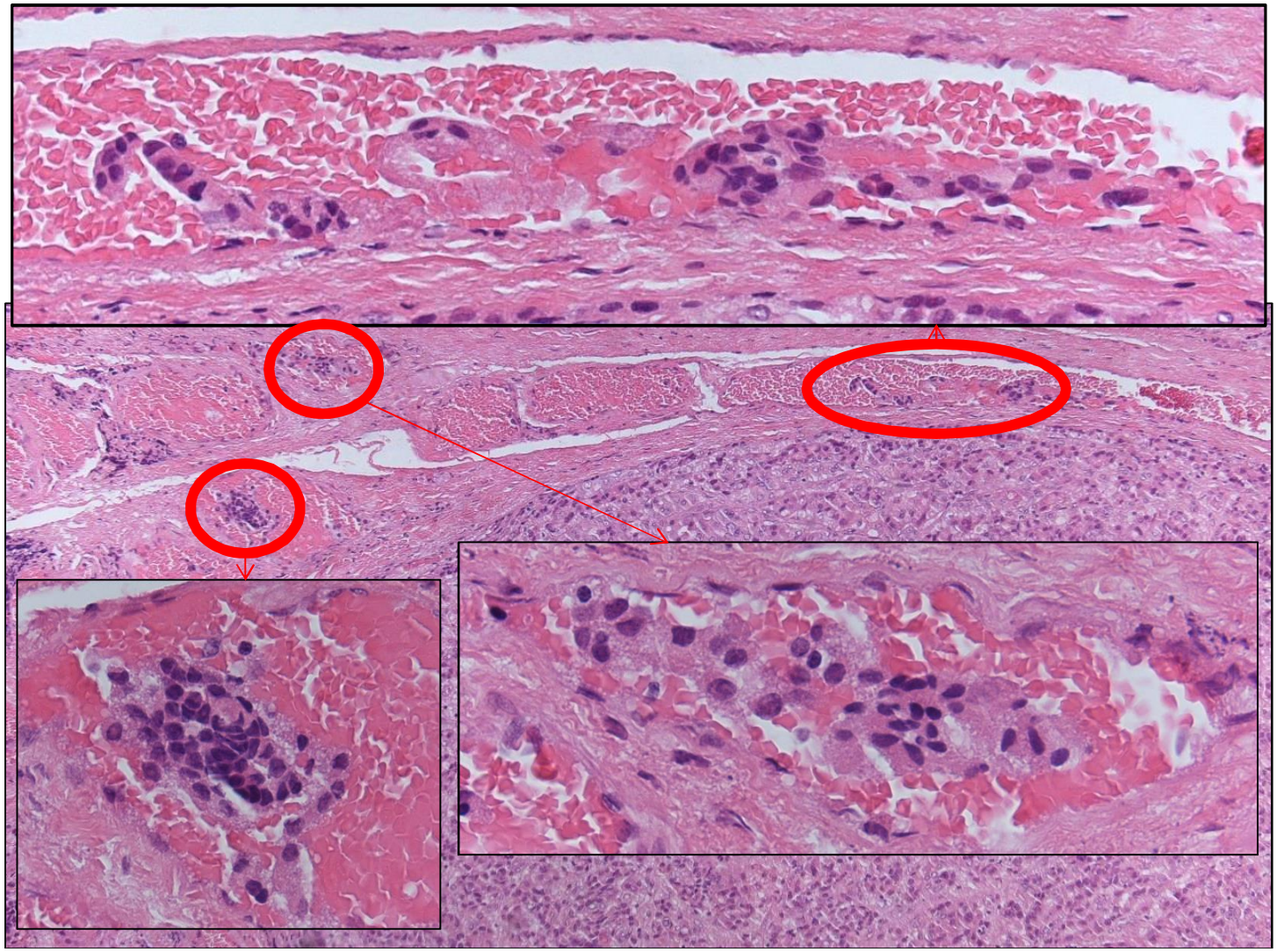
Chan JKC; Chapter 18 Tumors of the thyroid and parathyroid glands. Diagnostic Histopathology of Tumors. 3rd ed. Fletcher CDM, editor, 2007. p. 997–1078 (without College of American Pathologists modifications to criteria for vascular invasion 2014 to 2019)

Angioinvasion: blood vessel invasion

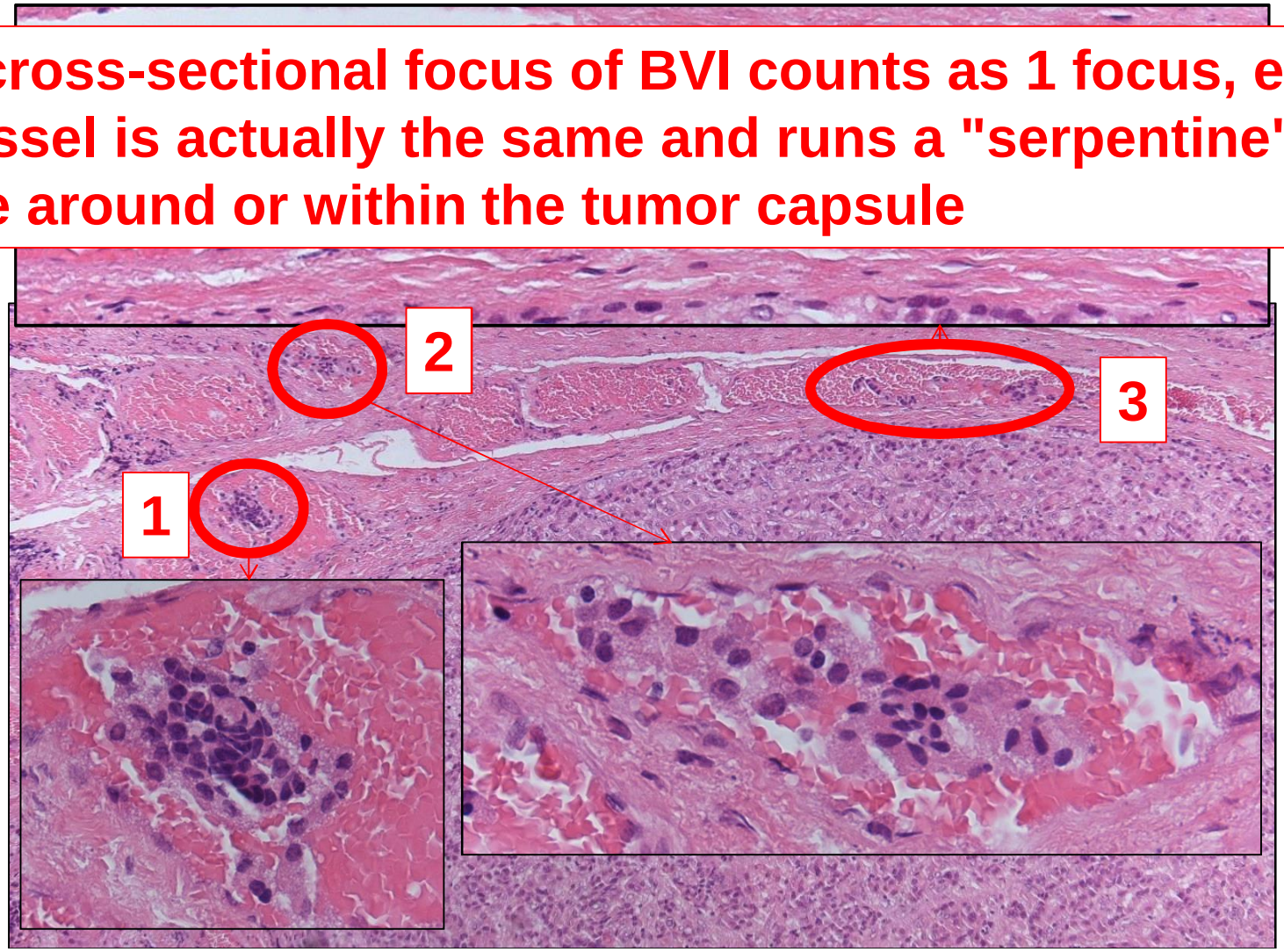


May seem strange, but it is the rule*:
Each cross-sectional focus of BVI counts as 1 focus, even if the vessel is actually the same and runs a "serpentine" course around or within the tumor capsule

Studies that validated prognostic value of blood vessel invasion followed this ruleé***



Each cross-sectional focus of BVI counts as 1 focus, even if the vessel is actually the same and runs a "serpentine" course around or within the tumor capsule



Molecular classification of follicular thyroid carcinoma based on TERT promoter mutations

Park H, Shin HC, Yang H, Heo J, Ki CS, Kim HS, Kim JH, Hahn SY, Chung YJ, Kim SW, Chung JH, Oh YL, Kim TH

Mod Pathol. 2021 Sep 8. doi: 10.1038/s41379-021-00907-6. PMID: 34497362

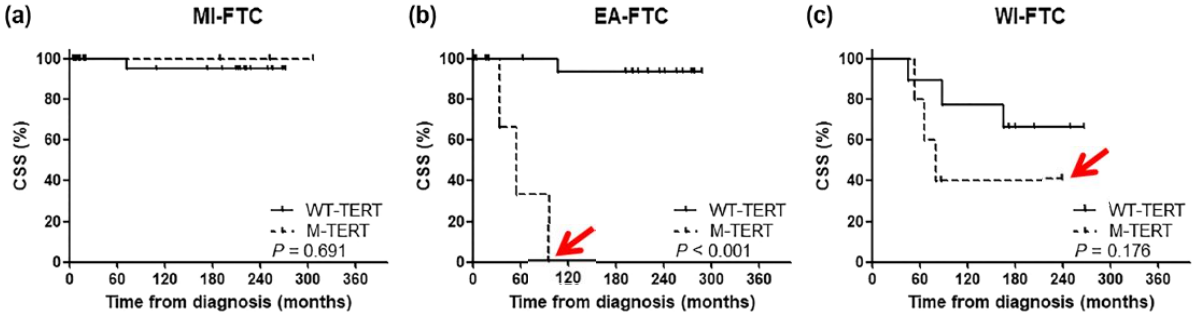


Fig. 1 **Cancer-specific survival** according to the presence of **TERT promoter mutations** in each WHO 2017 group. a Minimally invasive (i.e. capsular invasion-only) follicular thyroid carcinoma (MI-FTC), b Encapsulated angioinvasive follicular thyroid carcinoma (EA-FTC), and c Widely invasive follicular thyroid carcinoma (WI-FTC).

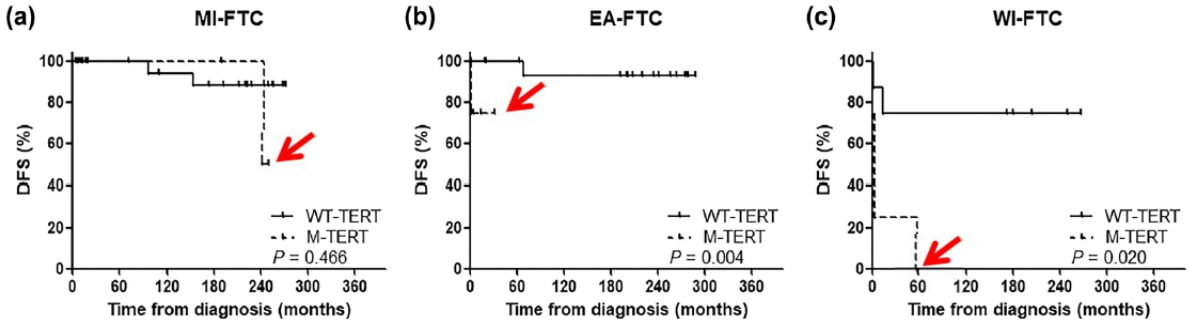


Fig. 2 **Disease-free survival** according to the presence of **TERT promoter mutations** in each WHO 2017 group. a Minimally invasive (i.e. capsular invasion-only) follicular thyroid carcinoma (MI-FTC), b Encapsulated angioinvasive follicular thyroid carcinoma (EA-FTC), and c Widely invasive follicular thyroid carcinoma (WI-FTC).

Molecular identification of TERT promoter mutation is better predictor of survival than the histologic identification of vascular invasion

WHO 5TH edition: subtypes of invasion in encapsulated carcinomas

- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncoytic carcinoma):
  - Minimally invasive (capsular invasion only)
  - Encapsulated angioinvasive
    - Limited angioinvasion, into 1-3 vessels
    - Extensive angioinvasion, into 4 or more vessels
  - **Widely invasive (simulate multinodular goiter)**

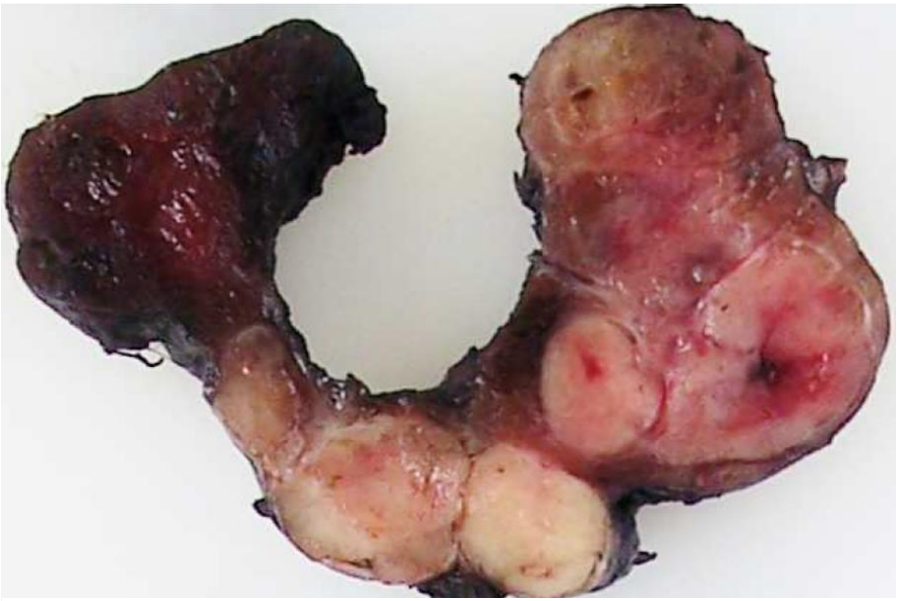
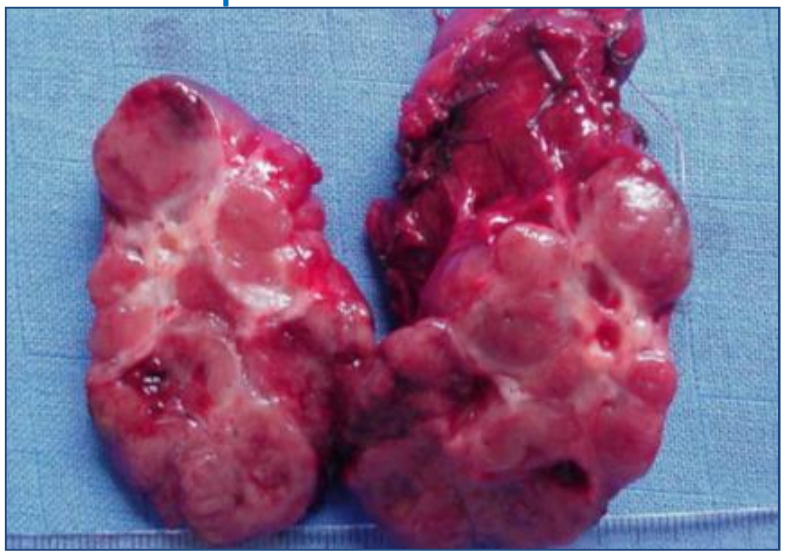


Fig. 2.50. World health organization (WHO) classification of tumours of endocrine organs WHO 5TH edition, 2017



Courtesy of Dr. G. Belleannee, University of Bordeaux Medical Center