Papillary carcinoma and indolent follicular patterned tumors

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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
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Differentiated Thyroid Carcinoma

PTC nuclei

Papillae

Follicles

Encapsulation

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

- PTC nuclei
- Papillae
- Follicles
- Encapsulation

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

PTC nuclei

Papillae

Follicles

Encapsulation

Dominance of papillary carcinoma diagnosis (after the 1980s)
«Malignant» (invasive growth)

«Benign» (unless there is invasion)

PTC

PTC nuclei

Papillae

PTC-Cl
(Foll predominant)

PTC-FV
Infiltrative

PTC-FV
Encapsulated

FA/FC

Follicles

Encapsulation
Infiltrative PTC - Cl (Foll predeominant)

Encapsulated PTC - Cl

«Malignant» (invasive growth)

«Benign» (unless there is invasion)

BRAF\textsuperscript{V600E}-like

RAS-like

Infiltrative PTC (Foll predeominant)

PTC-FV

Encapsulated

RAS-like

 PT C-nuclei
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FA/FC

 «Benign»
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FA/FC

Infiltrative

PTC-

Cl

(Foll predeominant)

PTC-

FV

Encapsulated
+ «Malignant»
(invasive growth)

RAS-like

PTC-FV

Encapsulated

Invasion
No → NIFTP

Invasion?
→ WDT-UMP

Invasion
Yes → PTC-FV
with vascular or capsular invasion

FA/FC

Follicles

Encapsulation

No → NIFTP

WDT-UMP

Papillae

PTC nuclei

BRAF\textsuperscript{V600E}-like

«Benign»
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PTC-Cl

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PTC-FV

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Infiltrative PTC - Cl (Foll predeominant)

PTC - Cl

Encapsulated +

«Malignant» (invasive growth)

«Benign» (unless there is invasion)

FA/FC

BRAF\(^{V600E}\)-like

**Infiltrative PTC (Foll predeominant)**

- **FA/FC**
- **Benign** (unless there is invasion)
- **Benign** (invasive growth)

**Follicular adenoma**

**BRAF V600E-like**

**FA/FC**

- Invasion No
- Follicular adenoma

**Invasion Yes**

- Follicular carcinoma

**FT-UMP**

- Invasion ?
<table>
<thead>
<tr>
<th>Tumour classification</th>
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<tbody>
<tr>
<td>Follicular adenoma</td>
<td>Spindle epithelial tumour with thymus-like differentiation</td>
<td>Intra-thyroid thymic carcinoma</td>
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<tr>
<td>Hyalinizing trabecular tumour</td>
<td>Paraganglioma and mesenchymal/stromal tumours</td>
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</table>
Other encapsulated follicular-patterned thyroid tumors:
- Follicular tumor of uncertain malignant potential
- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features

Low risk neoplasms:
- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
- Thyroid tumors of uncertain malignant potential

Malignant neoplasms:
- Invasive encapsulated follicular variant papillary carcinoma
Follicular patterned tumor with PTC nuclear features is ~benign when not invasive

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


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

#### Box. Revised Diagnostic Criteria for NIFTP

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
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</table>
| • Encapsulation or clear demarcation<sup>a</sup>
  • Follicular growth pattern with:
    • No well-formed papillae
    • No psammoma bodies
    • <30% solid/trabecular/insular growth pattern
    • Nuclear score 2-3<sup>b</sup>
    • No vascular or capsular invasion<sup>c</sup>
    • No tumor necrosis or high mitotic activity<sup>d</sup> | • Lack of *BRAF V600E* mutation detected by molecular assays or immunohistochemistry
  • Lack of *BRAF V600E*-like mutations or other high-risk mutations (TERT, TPS3) |

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

<sup>a</sup> Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid parenchyma.

<sup>b</sup> 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.

<sup>c</sup> Requires microscopic examination of the entire tumor capsule interface.

<sup>d</sup> High mitotic activity, defined as 3 or more mitoses per 10 high-power fields (>400).

<sup>e</sup> Secondary criteria are helpful but not required for NIFTP diagnosis.
Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5\textsuperscript{TH} 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\textsuperscript{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

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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

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 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)
### 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


“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


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

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**Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5th edition**
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<p>| Table 2. Tumor Encapsulation and Its Influence on Prognosis and Metastatic Behavior |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Absent Capsule</th>
<th>Partial Capsule</th>
<th>Total Capsule</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive &amp; well</td>
<td>92 (42.0%)</td>
<td>106 (48.4%)</td>
<td>21 (9.6%)</td>
<td>P &lt; 0.05*</td>
</tr>
<tr>
<td>Alive with tumor</td>
<td>67 (72.8%)</td>
<td>86 (81.1%)</td>
<td>19 (90.5%)</td>
<td></td>
</tr>
<tr>
<td>Dead of tumor</td>
<td>19 (20.6%)</td>
<td>9 (8.5%)</td>
<td>2 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>Node metastases</td>
<td>19 (3.3%)</td>
<td>6 (5.7%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Lung metastases</td>
<td>52 (56.5%)</td>
<td>49 (46.2%)</td>
<td>8 (38%)</td>
<td>P &lt; 0.25*</td>
</tr>
<tr>
<td></td>
<td>13 (14.1%)</td>
<td>16 (15.1%)</td>
<td>0 (0%)</td>
<td></td>
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</tbody>
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* 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)

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- 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

PTC nuclei score 3
NIFTP exclusion criteria: nuclear alterations as a marker for classic PTC

PTC nuclei score 3

Area of papillary growth on additional sections
NIFTP exclusion criteria: nuclear alterations as a marker for classic PTC

PTC nuclei score 3

Encapsulated (well circumscribed) PTC, classic, with follicular predominant growth pattern

*BRAFV600E-like*

Area of papillary growth on additional sections
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NIFTP is still a histopathologic diagnosis!

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

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

#### Developmental abnormalities
- Thyroglossal duct cyst
- Other congenital thyroid abnormalities

#### Follicular cell-derived neoplasms

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
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<tbody>
<tr>
<td>Benign tumours</td>
<td></td>
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<tr>
<td>Thyroid follicular nodular disease</td>
<td></td>
</tr>
<tr>
<td>Follicular thyroid adenoma</td>
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<tr>
<td>Follicular thyroid adenoma with papillary architecture</td>
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<tr>
<td>Congenital adenoma of the thyroid</td>
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</table>

#### Low risk neoplasms
- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
- Thyroid tumours of uncertain malignant potential

#### Malignant neoplasms
- Malignant follicular thyroid tumour of thyroid

#### Invasive encapsulated follicular variant papillary carcinoma

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**Notes:**
- The microsurgical codes are from the World Health Organization (WHO) and the American Joint Committee on Cancer (AJCC). They reflect the latest understanding in the field and are subject to change as new data is released.
- These codes are based on the latest editions of the WHO and AJCC classification systems.
### Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5\textsuperscript{TH} 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
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Lessons learnt from follicular-patterned lesions: follicular variant papillary carcinoma and NIFTP in WHO 5th edition:

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

For a diagnosis of carcinoma the burden of proof is 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

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

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

Additional sections are important: three serial sections per block with foci suspicious for invasion
Tumors of uncertain malignant potential (UMP): rule out capsular invasion

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

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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
Oncocytic carcinoma with vascular (not capsular) invasion
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
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)

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)
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)
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 is 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


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


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


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

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
### 3. Thyroid gland

#### Benign tumours
- Thyroid follicular nodular disease
- Follicular thyroid adenoma
- Follicular thyroid adenoma with papillary architecture
- Congenital anomalies of the thyroid

#### Low risk neoplasms
- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
- Thyroid tumours of uncertain malignant potential

#### Malignant neoplasms
- Invasive encapsulated follicular variant papillary carcinoma
- Thyroid C-cell derived carcinoma
- Medullary thyroid carcinoma
- Mixed medullary and follicular-cell derived carcinomas
- Salivary gland-type carcinomas of the thyroid
- Mucopseudomucoid carcinoma of the thyroid
- Secretory carcinomas of salivary gland type
- Thyroid tumours of uncertain histogenesis
- Sclerosing mucopseudomucoid carcinoma
- Cribriform monar thyroid carcinoma
- Thymus carcinomas within the thyroid
- Thymus 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)
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«conventional papillary carcinomas»
| Classic papillary carcinoma | Tall cell variant papillary carcinoma |
Diffuse sclerosing PTC  |  Columnar cell PTC  |  Hobnail PTC
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• Sclerosis  
• Multicentric tumor foci |
| Tall cell | ≥ 30% tall cells | • Tightly packed follicles and papillae — AKA “tram track appearance.”  
• Tumor cell height at least 3x 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 lymphatic permeation, numerous psammoma bodies and associated chronic lymphocytic thyroiditis  
• Tumor cells arranged in solid nests and papillary formations with squamous metaplasia  
• Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis |
| Warthin-like | NA | • Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate  
• Well-developed papillae lined by oncocytic cells |
| Oncocytic | NA | • Monochrome nuclei, abundant pink cytoplasm  
• Tumor cells with clear cytoplasm and bland nuclei |

**Papillary carcinoma: subtypes and “Farewell to microcarcinoma” (WHO 5\textsuperscript{TH} edition)**

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- Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis  
- Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate  
- Well-developed papillae lined by oncocytic cells |

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


Figure 1. Histologic appearance and immunohistochemical features of PTC-TCV and cPTC. (A) PTC-TCV shows tall columnar cells with abundant eosinophilic cytoplasm and a monotonous appearance. (B) H&E staining shows the characteristic architecture of PTC-TCV. (C) Immunohistochemical staining for the pan-mitochondrial marker prohibitin shows high expression levels with strong, homogeneous granular staining in PTC-TCV. (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 (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).
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<tr>
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<td>Solid</td>
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<td>Warthin-like</td>
<td>NA</td>
<td>- Well-developed papillae lined by oncocytic cells</td>
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A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma


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 oedematosous. 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.

<table>
<thead>
<tr>
<th></th>
<th>‘Hobnail-like’ PTC (n = 20)</th>
<th>True hobnail PTC (n = 7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NED at last follow-up, n (%)</td>
<td>20 (100)</td>
<td>3 (43)</td>
<td>0.0020</td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>10.6</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Median follow-up (years)</td>
<td>11.3</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Residual/recurrent disease, n (%)</td>
<td>1 (5)†</td>
<td>4 (57)</td>
<td>0.0089</td>
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<tr>
<td>Local</td>
<td>1 (5)†</td>
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<td>0 (0)</td>
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<td>Died of disease, n (%)</td>
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<tr>
<td>Mean survival (years)</td>
<td>NA</td>
<td>1.3</td>
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<tr>
<td>Median survival (years)</td>
<td>NA</td>
<td>1.4</td>
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PTC, Papillary Thyroid carcinoma; NED, No evidence of disease; NA, Not available.
†From cohort 2.
*From cohort 2.

This patient had a local recurrence 2 years after thyroidectomy (disease-free survival of 6 years).
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| Oncocytic | NA | - Well-developed papillae lined by oncocytic cells |

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

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.
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.
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

Histologic features are distinctive, but not specific (found in tumors with other driver molecular alterations, e.g. BRAF p.V600E)
Gene fusion in thyroid tumors of follicular cells: RET (previously RET/PTC rearrangements)

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.

Figure 1. Representative scheme of RET and its fusion partners. (A) Representation of RET fusion protein partners. Arrows indicate the most frequent breakpoints 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
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

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; CP, 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
  - Uncommon 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)
Papillary carcinomas measuring $< 1.0$ 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 $\geq 5$ mm and distance of the edge of the tumor from the thyroid capsule = 0 mm

**Group B**, mPTC: size $\geq 5$ 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 analyses)
Papillary carcinomas measuring \( \leq 1.0 \text{ cm} \) arise at a median distance of \( 3.5 \text{ mm} \) below the surface of the thyroid gland with four distinct clusters:

**Group A**, mPTC: size \( \geq 5 \text{ mm} \) and distance of the edge of the tumor from the thyroid capsule = 0 mm

**Group B**, mPTC: size \( \geq 5 \text{ mm} \) 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 analyses)
Differentiated thyroid carcinoma 2013-2022

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<th>Millimeter</th>
<th>Standard deviation</th>
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<td>8.972</td>
</tr>
<tr>
<td>Median</td>
<td>12.00</td>
<td></td>
</tr>
<tr>
<td>25° percentile</td>
<td>7.000</td>
<td></td>
</tr>
<tr>
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</table>

Tumor size of differentiated thyroid carcinoma 2013-2022 per year (mm)

<table>
<thead>
<tr>
<th>Year</th>
<th>Average</th>
<th>Median</th>
<th>25° percentile</th>
<th>75° percentile</th>
</tr>
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<tbody>
<tr>
<td>2013</td>
<td>15.14</td>
<td>11.00</td>
<td>6.00</td>
<td>20.00</td>
</tr>
<tr>
<td>2014</td>
<td>14.90</td>
<td>10.00</td>
<td>6.00</td>
<td>18.00</td>
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<tr>
<td>2015</td>
<td>15.28</td>
<td>11.00</td>
<td>7.00</td>
<td>20.00</td>
</tr>
<tr>
<td>2016</td>
<td>16.77</td>
<td>11.00</td>
<td>7.00</td>
<td>20.00</td>
</tr>
<tr>
<td>2017</td>
<td>17.22</td>
<td>11.00</td>
<td>7.00</td>
<td>20.00</td>
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<tr>
<td>2018</td>
<td>16.00</td>
<td>12.00</td>
<td>7.00</td>
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<td>2019</td>
<td>15.94</td>
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<td>20.74</td>
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<tr>
<td>2021</td>
<td>17.45</td>
<td>12.00</td>
<td>8.00</td>
<td>22.75</td>
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<tr>
<td>2022</td>
<td>14.80</td>
<td>11.00</td>
<td>7.00</td>
<td>19.00</td>
</tr>
</tbody>
</table>

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

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 5\textsuperscript{TH} edition: “Farewell to microcarcinoma”

Renaming papillary microcarcinoma of the thyroid gland: the Porto proposal
Rosai J, LiVolisi VA, Sobrinho-Simoes M, Williams ED

- 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

Thyroid Papillary Microtumor: Validation of the (Updated) Porto Proposal Assessing Sex Hormone Receptor Expression and Mutational BRAF Gene Status
Aliyev E...Cameselle-Teijeiro JM

- 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

- “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
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


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 5\textsuperscript{TH} edition: Thyroid follicular nodular disease (FND)
## WHO 5TH edition: Thyroid follicular nodular disease (FND)

<table>
<thead>
<tr>
<th></th>
<th><strong>Multinodular hyperplasia</strong></th>
<th><strong>Encapsulated well-differentiated neoplasm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nodules</td>
<td>Multiple</td>
<td>Single</td>
</tr>
<tr>
<td>Lesional capsule</td>
<td>No (or poorly defined)</td>
<td>Yes (well defined)</td>
</tr>
<tr>
<td>Histology</td>
<td>Heterogeneous (No «clonal appearance»)</td>
<td>Homogeneous («Clonal» appearance)</td>
</tr>
</tbody>
</table>

*Images from Rosai J et al. Tumors of the thyroid and parathyroid glands. AFIP Atlas of Tumor Pathology. ARB Press, 2014*
### WHO 5TH edition: Thyroid follicular nodular disease (FND)

Table:

<table>
<thead>
<tr>
<th></th>
<th>Multinodular goiter</th>
<th>Encapsulated well-differentiated neoplasm*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of nodules</strong></td>
<td>Multiple</td>
<td>Single</td>
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<td><strong>Histology</strong></td>
<td>Heterogeneous (No «clonal appearance»)</td>
<td>Homogeneous («Clonal» appearance)</td>
</tr>
</tbody>
</table>

*«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
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")
DICER1 Syndrome

Table 1. DICER1-associated neoplasms.

<table>
<thead>
<tr>
<th>DICER1 Syndrome</th>
<th>Age &lt;10 years</th>
<th>Age 10-40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleuropulmonary blastoma (PPB) and PPB-like neoplasms</td>
<td>Nasal chondromesenchymal hamartoma</td>
<td>Nasal chondromesenchymal hamartoma</td>
</tr>
<tr>
<td>Pleuropulmonary blastoma, type I, II, III</td>
<td>Pleuropulmonary blastoma, type I, II, III</td>
<td></td>
</tr>
<tr>
<td>PPB-like Sertoli-Leydig cell tumor of lung</td>
<td>Ciliary body medulloepithelioma</td>
<td>Multinodular goiter</td>
</tr>
<tr>
<td>Pediatric cystic neoplasms and DICER1-sarcoma (anaplastic sarcoma of kidney)</td>
<td>Cystic nephroma</td>
<td>Cystic nephroma</td>
</tr>
<tr>
<td>Nasal chondromesenchymal hamartoma</td>
<td>Anaplastic sarcoma of the kidney</td>
<td>Anaplastic sarcoma of the kidney</td>
</tr>
<tr>
<td>Central nervous system sarcoma with rhabdomyosarcoma/PPB-like features</td>
<td>Differentiated thyroid cancer</td>
<td>Differentiated thyroid cancer</td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumor with and without heterologous features and type I PPB-like features</td>
<td>Ciliary body medulloepithelioma</td>
<td>Ciliary body medulloepithelioma</td>
</tr>
<tr>
<td>Peritoneal, ovarian and fallopian tube sarcoma with PPB-like features</td>
<td>pPB</td>
<td>pPB</td>
</tr>
<tr>
<td>DICER1-associated cystic hepatic neoplasm with type I PPB-like features</td>
<td>Wilms tumor</td>
<td>Wilms tumor</td>
</tr>
<tr>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Teratoid and primitive neuroepithelial neoplasms</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Cervical-thyroid teratoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Malignant teratoid neoplasm of sacrococcygeal region</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Ciliary body medulloepithelioma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Pituitary blastoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
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<td>Pineoblastoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
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<tr>
<td>Embryonal tumor with multilayered rosettes</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
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<tr>
<td>Thyroid</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
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<tr>
<td>Multinodular hyperplasia (goiter)</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Papillary thyroid carcinoma, invasive follicular variant</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
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<tr>
<td>Follicular carcinoma, pediatric type</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Poorly differentiated thyroid carcinoma, pediatric type</td>
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<td>Cervical embryonal rhabdomyosarcoma</td>
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<td>Intestine</td>
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<td>Hamartomatous polyp with juvenile polyp-like features</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
<td>Cervical embryonal rhabdomyosarcoma</td>
</tr>
</tbody>
</table>

- 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.
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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 [deKock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: Provenance, distribution, and associated phenotypes. Hum Mutat. 2019 Nov;40(11):1939-1953]

- Nasal chondromesenchymal hamartoma
- Multinodular goiter
- Sertoli-Leydig cell tumors
- Pleuropulmonary blastoma
-CHILD (cystic nephroma, differentiated thyroid cancer, hepatocellular carcinoma, lymphoma, fibrosarcoma, osteosarcoma, rhabdomyosarcoma)
- Pheochromocytoma
- Retinoblastoma
- Wilms tumor
- Hepatoblastoma
DICER1 Syndrome

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**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 the 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]

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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

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)

DICER1 Syndrome

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Family tree of **index case**

INDEX CASE
16 year old
Thyroidecctomy at age 15:
multiple adenomas with papillary architecture
*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)
Case 2: 50 year old woman with longstanding multinodular goiter
Thyroidectomy for multinodular goiter at age 50
PTEN IHC: loss of expression in follicular cells (endothelial cells: pos. control)

Thyroidectomy for multinodular goiter at age 50
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 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)

Figure 3. PTEN structure and germline mutation spectrum in PHTS. (A) PTEN germline mutation spectrum from 631 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, 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. Clin Genet. 2019 Feb;126(2):452-464)
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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 (IQ ≤ 75).
- Surveillance focused on early detection of breast, endometrial, thyroid, colorectal, renal, and skin cancer.

- 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
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. J Surg Pathol. 2010 Jun;18(3 Suppl):194S-200S]

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

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 et al. Thyroid pathologic findings in patients with Cowden disease. Ann Diagn Pathol. 1999 Dec;3(6):331-40]
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**WHO 5TH edition: subtypes of invasion in encapsulated carcinomas**

- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic 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)

**Invasion of the tumor capsule**

**Vascular invasion**

---

WHO 5\textsuperscript{TH} edition: subtypes of invasion in encapsulated carcinomas

- Subtypes of invasion in encapsulated carcinomas (Follicular carcinoma, encapsulated follicular variant papillary carcinoma, oncocytic 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)

Invasion of the tumor capsule

Vascular 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 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.
Molecular classification of follicular thyroid carcinoma based on TERT promoter mutations


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, oncocytic 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. Belleeannee, University of Bordeaux Medical Center