NOVEDADES EN LA CLASIFICACIÓN DE LOS TUMORES TIROIDEOS

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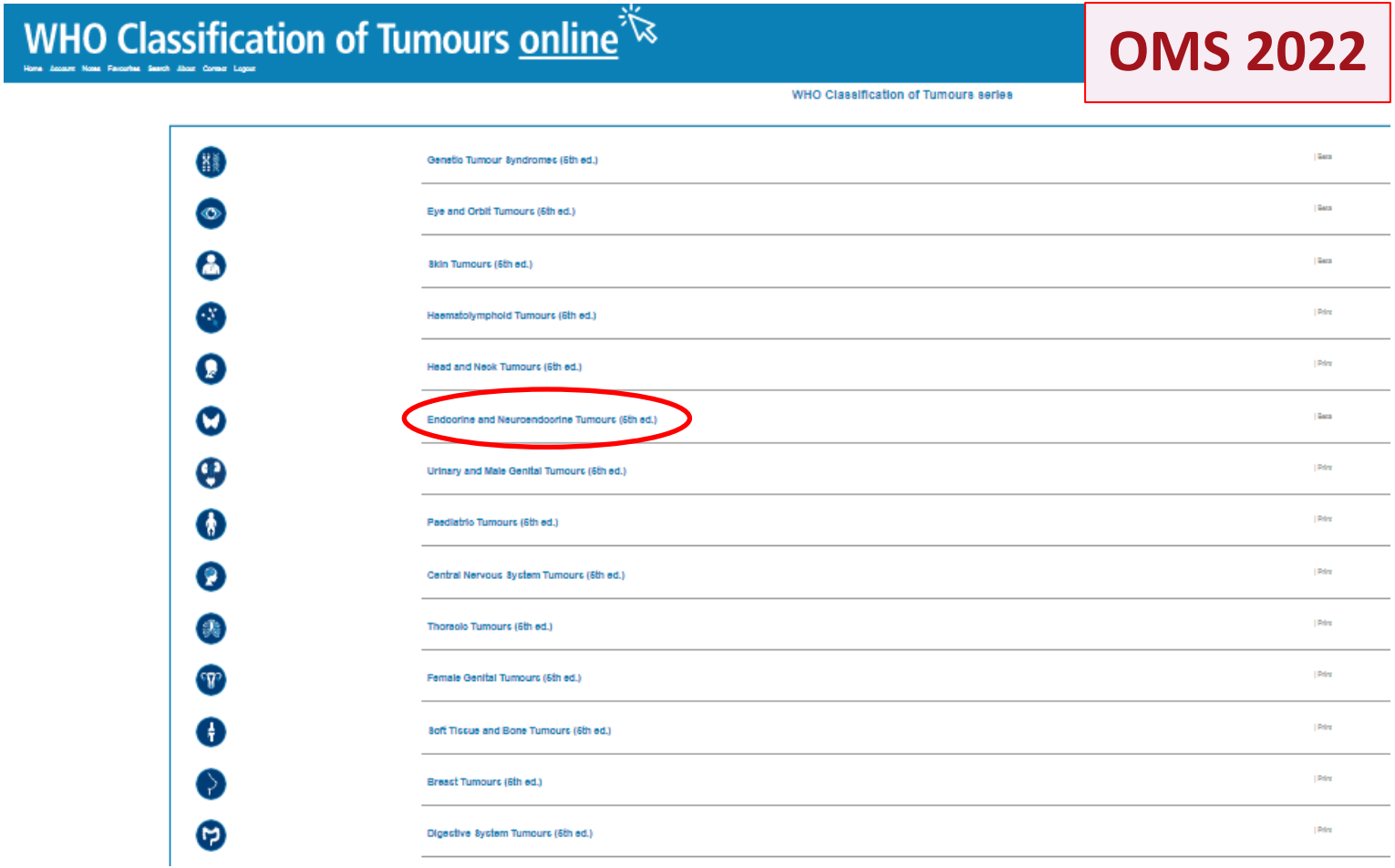
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Endocrine and Neuroendocrine Tumours (5th ed.)

1. Forewords and introductions

WHO Classification of Tumours: Editorial Board
How to cite this volume
Foreword with changes from the book, including corrigenda
ICD-O coding of Endocrine and neuroendocrine tumours
Introduction to Endocrine and Neuroendocrine tumours

2. Pituitary gland

3. Thyroid gland

4. Parathyroid glands

5. Adrenal gland

6. Tumours of the adrenal medulla and extra-adrenal paraganglia

7. Neuroendocrine pancreas

8. Neuroendocrine neoplasms, non-endocrine organs

9. Mesenchymal and stromal tumours

10. Haematolymphoid tumours

11. Germ cell tumours

12. Metastasis

13. Genetic tumour syndromes

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

Check for updates

Overview of the 2022 WHO Classification of Thyroid Neoplasms

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

Accepted: 27 January 2022 / Published online: 14 March 2022

¿CUÁLES SON LOS TITULARES...?

CAMBIOS CONCEPTUALES

CAMBIOS TERMINOLÓGICOS

CAMBIOS EN LOS CRITERIOS DIAGNÓSTICOS

CAMBIOS CONCEPTUALES

*La **estirpe celular**, **biología molecular,** características anatomopatológicas, y comportamiento biológico de los distintos tumores son los que guían su clasificación*

- Las neoplasias derivadas de la célula folicular se dividen en **benignas**, de **bajo riesgo** y **malignas**
- Las neoplasias malignas de célula folicular se estratifican según su perfil molecular (**BRAF like vs. RAS like**) y agresividad
- Se introduce el concepto "**alto grado**" (en carcinoma diferenciado de célula folicular y en carcinoma medular)
- Los tumores en tiroides de **tipos celulares no específicamente tiroideos** (mesenquimales, hematolinfoides, germinales, metástasis…) constituyen capítulos independientes
- Se incluyen las **anomalías del desarrollo tiroideo** (quiste tirogloso y disgenesias tiroideas)

CAMBIOS TERMINOLÓGICOS

- Se introduce el diagnóstico “**enfermedad folicular nodular benigna**” en el contexto clínico de bocio multinodular
- Se sustituye definitivamente el término célula de Hürthle por el de célula “**oncocítica”**
- Se sustituye el término “variante” por “**subtipo**” para los diferentes CPT
- El “**carcinoma cribiforme morular”** deja de ser un subtipo de CPT
- El “**microcarcinoma papilar”** deja de ser un subtipo de CPT
- El “**carcinoma escamoso”** primario tiroideo pasa a ser un carcinoma anaplásico

CAMBIOS EN LOS CRITERIOS DIAGNÓSTICOS

- Se *actualiza* el método de contaje del índice mitótico (**mitosis/mm^2**), que cobra mayor importancia como criterio diagnóstico
- Se *revisan* los criterios diagnósticos del **NIFTP**
- Se *revisan* los criterios diagnósticos del subtipo "**células altas**" del CPT
- Se *define* con mayor precisión el criterio de "**neoplasia oncocítica**" (>75% del total)
- Se *incluye* el **adenoma folicular de arquitectura papilar** como una nueva entidad
- Se *introduce* el **tiroblastoma** como una nueva entidad

WHO 2017 → TUMORES ***EN*** TIROIDES

ANARQUÍA EN LA CLASIFICACIÓN

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 International Classification of Diseases for Oncology (ICD-O) (898A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

*These new codes were approved by the IARC/WHO Committee for ICD-O.

WHO 2022 → TUMORES ***DE*** TIROIDES

TAXONOMÍA EN LA CLASIFICACIÓN

- **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

Developmental abnormalities
1. Thyroglossal duct cyst
2. Other congenital thyroid abnormalities

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

Thyroid C-cell–derived carcinoma
1. Medullary thyroid carcinoma

Mixed medullary and follicular cell–derived carcinomas

Salivary gland–type carcinomas of the thyroid
1. Mucoepidermoid carcinoma of the thyroid
2. Secretory carcinoma of salivary gland type

Thyroid tumors of uncertain histogenesis
1. Sclerosing mucoepidermoid carcinoma with eosinophilia
2. Cribriform morular thyroid carcinoma

Thymic tumors within the thyroid
1. Thymoma family
2. Spindle epithelial tumor with thymus-like elements
3. Thymic carcinoma family

Embryonal thyroid neoplasms
1. Thyroblastoma

NEOPLASIAS DERIVADAS DE LA CÉLULA FOLICULAR

NEOPLASIAS DERIVADAS DE LA CÉLULA PARAFOLICULAR

OTRAS ESTIRPES O ESTIRPES INCIERTAS

Follicular cell–derived neoplasms

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

Thyroid C-cell–derived carcinoma

1. Medullary thyroid carcinoma

Mixed medullary and follicular cell–derived carcinomas

Salivary gland–type carcinomas of the thyroid

1. Mucoepidermoid carcinoma of the thyroid
2. Secretory carcinoma of salivary gland type

Thyroid tumors of uncertain histogenesis

1. Sclerosing mucoepidermoid carcinoma with eosinophilia
2. Cribriform morular thyroid carcinoma

Thymic tumors within the thyroid

1. Thymoma family
2. Spindle epithelial tumor with thymus-like elements
3. Thymic carcinoma family

Embryonal thyroid neoplasms

1. Thyroblastoma

NEOPLASIAS BENIGNAS

NEOPLASIAS DE BAJO RIESGO

NEW

NEOPLASIAS MALIGNAS

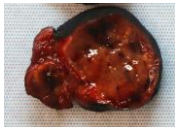
NEOPLASIAS DERIVADAS DE LA CÉLULA FOLICULAR

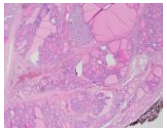
Follicular cell–derived neoplasms

1. Benign tumors
   a. Thyroid follicular nodular disease
   b. Follicular adenoma
   c. Follicular adenoma with papillary architecture
   d. Oncocytic adenoma of the thyroid

NEOPLASIAS BENIGNAS
Fenotipo *RAS like*

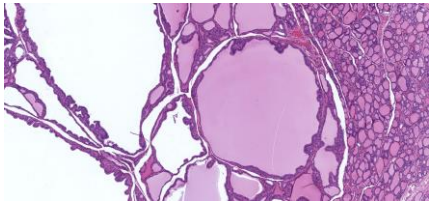
Desparecen los términos bocio multinodular, hiperplasia nodular, nódulo coloide, nódulo hiperplásico, nódulo adenomatoso, hiperplasia adenomatosa…





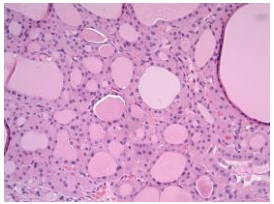
Mezcla de proliferaciones hiperplásicas y neoplásicas que se engloban en el término "**enfermedad nodular folicular**" NEW

"Adenoma folicular de arquitectura papilar" NEW



Arquitectura centrípeta característica, hipertiroidismo

"Adenoma oncocítico" NEW



>75% componente oncocítico

2. Low-risk neoplasms
   a. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
   b. Thyroid tumors of uncertain malignant potential
   c. Hyalinizing trabecular tumor

NEOPLASIAS DE BAJO RIESGO RAS LIKE (excepto TTH) NEW

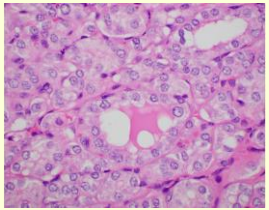
Tumores de estirpe folicular con clínica y morfología **intermedia** entre los benignos y los malignos

Extremadamente baja capacidad de metástasis

Agrupados en una única categoría NEW

NIFTP
Neoplasia folicular no invasiva con núcleos de tipo papilar

- < 1 % de papilas en ausencia de mutación BRAF V600E NEW
- Incluye lesiones > 2 mm NEW
- Incluye lesiones oncocíticas NEW

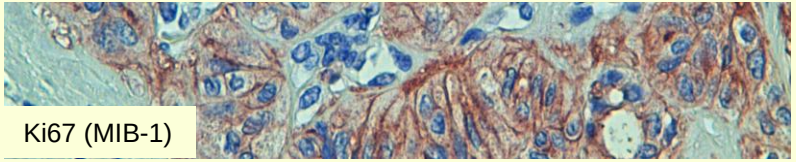


TUMORES DE POTENCIAL INCIERTO (FT-UMP y WDT-UMP)

- Invasión vascular y/o capsular cuestionable

TUMOR TRABECULAR HIALINIZANTE

- Se incorpora a la categoria de tumores inciertos NEW
- Reordenamiento de GLIS (específico)



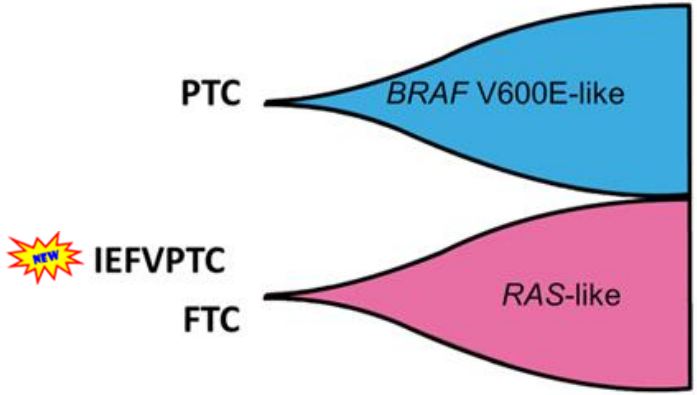
Ki67 (MIB-1)

3. Malignant neoplasms
   a. Follicular thyroid carcinoma
   b. Invasive encapsulated follicular variant papillary carcinoma
   c. Papillary thyroid carcinoma
   d. Oncocytic carcinoma of the thyroid
   e. Follicular-derived carcinomas, high-grade
      i. Differentiated high-grade thyroid carcinoma
      ii. Poorly differentiated thyroid carcinoma
   f. Anaplastic follicular cell–derived thyroid carcinoma

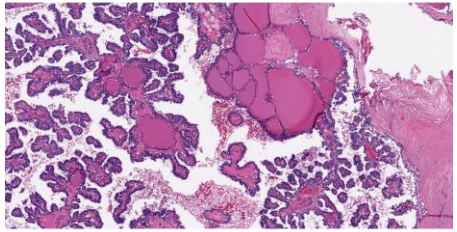
NEOPLASIAS MALIGNAS

El ***fenotipo molecular*** rige la clasificación de los tumores y correlaciona con la morfología
El **IEVFPTC** deja de ser un subtipo de CPT

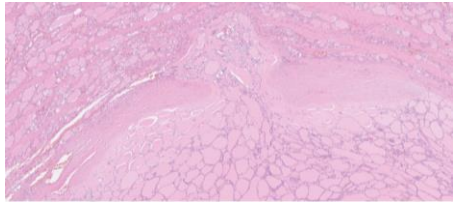
NEW



Atipia nuclear florida
Arquitectura no folicular
Patrón infiltrativo
Cápsula infrecuente
Cuerpos de psamoma



Escasa atipia nuclear
Arquitectura folicular
Patrón expansivo/invasivo
Cápsula frecuente
No cuerpos psamoma



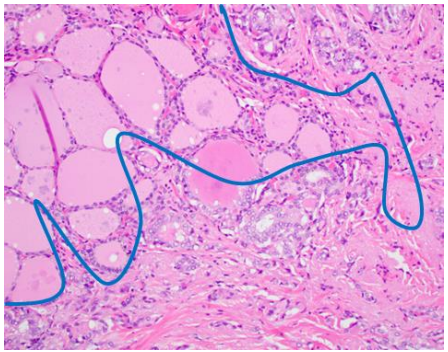
3. Malignant neoplasms
   a. Follicular thyroid carcinoma
   b. Invasive encapsulated follicular variant papillary carcinoma
   c. Papillary thyroid carcinoma **(VF)**
   d. Oncocytic carcinoma of the thyroid
   e. Follicular-derived carcinomas, high-grade
      i. Differentiated high-grade thyroid carcinoma
      ii. Poorly differentiated thyroid carcinoma
   f. Anaplastic follicular cell–derived thyroid carcinoma

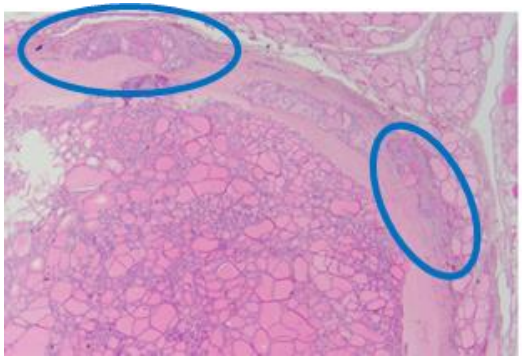
NEOPLASIAS MALIGNAS

CARCINOMA PAPILAR DE VARIANTE FOLICULAR (CPVF)

CPVF INFILTRATIVO ➡ BRAF LIKE

CPVF ENCAPSULADO INVASIVO ➡ RAS LIKE





3. Malignant neoplasms
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   c. Papillary thyroid carcinoma **(VF)**
   d. Oncocytic carcinoma of the thyroid
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      i. Differentiated high-grade thyroid carcinoma
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   f. Anaplastic follicular cell–derived thyroid carcinoma

NEOPLASIAS MALIGNAS

CARCINOMAS DIFERENCIADOS DE PATRÓN FOLICULAR

CARCINOMA FOLICULAR | CPVF | CARCINOMA ONCOCÍTICO

REPERCUSIÓN CLÍNICA

MÍNIMAMENTE INVASIVO → **BAJO RIESGO**

ANGIOINVASIVO / AMPLIAMENTE INVASIVO → **ALTO RIESGO**

3. Malignant neoplasms
   a. Follicular thyroid carcinoma
   b. Invasive encapsulated follicular variant papillary carcinoma
   c. Papillary thyroid carcinoma
   d. Oncocytic carcinoma of the thyroid
   e. Follicular-derived carcinomas, high-grade
      i. Differentiated high-grade thyroid carcinoma
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   f. Anaplastic follicular cell–derived thyroid carcinoma

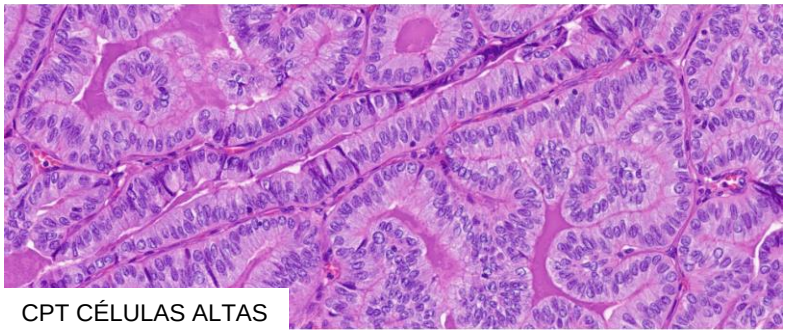
NEOPLASIAS MALIGNAS

Subtype(s)
Classic PTC
Encapsulated classic PTC
Infiltrative follicular PTC
Diffuse sclerosing PTC
Solid/trabecular PTC
Warthin-like PTC
Oncocytic PTC
Clear cell PTC
Spindle cell PTC
PTC with fibromatosis/fasciitis-like/desmoid-type stroma
Tall cell PTC
Hobnail PTC
Columnar cell PTC

RIESGO INTERMEDIO
DE RECURRENCIA (ATA)

El **microcarcinoma papilar** deja de ser un subtipo de CPT NEW

Criterios más estrictos para el **CPT de células altas** NEW
(células 3 veces más altas que anchas)



CPT CÉLULAS ALTAS

Los subtipos de CPT *BRAF*-like muestran un "sub-perfil" mutacional característico: el concepto de CORRELACIÓN FENOTIPO-GENOTIPO

PTC subtype	Proportion of subtype features	
Infiltrative follicular	≥90% neoplastic follicles	• *BRAF* V600E and K601E, *NRAS**, *CTNNB1**mutations • *RET* translocation, *NTRK* and *ALK* fusions
Tall cell	≥30% tall cells	• *BRAF* V600E, *TERT* promoter and *TP53* mutations
Columnar cell	NA	• *BRAF* V600E, *RAS**, *TERT* promoter*, and *TP53** • *BRAF* fusions, activating *BRAF* deletions, loss of *CDKN2A* and copy number alterations (recurrent gain of chromosome 1q)
Hobnail	≥30% hobnail cells	• *BRAF* V600E, *TP53*, *TERT* promoter, *PIK3CA* mutations • Rarely, *RET* rearrangements, moleular *CTNNB1*, *EGFR*, *ATK1*, *ATM*, *ARID2*, and *NOTCH1*
Solid	>50% solid trabecular growth	• *CCD6::RET* and *NCOA4::RET* rearrangements (later in radiation indiuced tumors), and *BRAF* V600E* • *ETV6::NTRK3* fusions
Diffuse sclerosing	100% diffuse unilateral or bilateral involvement, without dominant tumor mass	• *RET* rearrangements (especially *NCOA4::RET* in radiation induced cases), *BRAF* V600E mutations (20% of cases) and *ALK* rearrangements (10% of cases) • High frequency of *LOH* of 3p24, 9p21, 17q21, 21q22, and 22q13
Warthin-like	NA	• *BRAF* V600E mutation
Oncocytic***	NA	• *BRAF* V600E mutations • *GRIM-19* (germline mutations) and *RET* rearrangements*

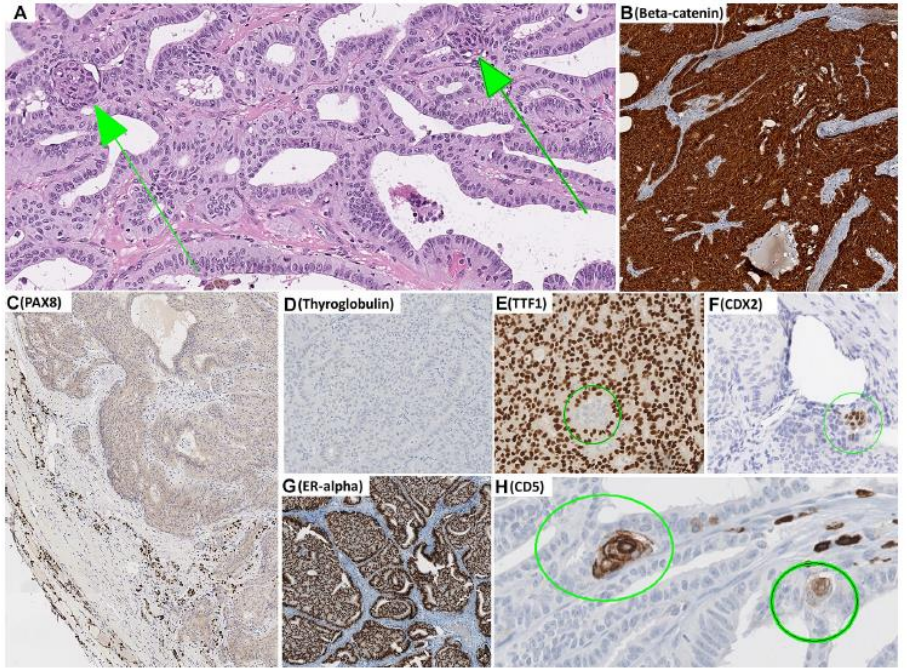
#FemVHambTu

Thyroid tumors of uncertain histogenesis

1. Sclerosing mucoepidermoid carcinoma with eosinophilia
2. Cribriform morular thyroid carcinoma

El **CARCINOMA CRIBIFORME MORULAR** DEJA DE SER UN CPT Y PARA PASAR A SER UN CARCINOMA DE HISTOGÉNESIS INCIERTA

Alteración de la via Wnt/beta-catenina
Perfil IHQ híbrido



3. Malignant neoplasms
   a. Follicular thyroid carcinoma
   b. Invasive encapsulated follicular variant papillary carcinoma
   c. Papillary thyroid carcinoma
   d. Oncocytic carcinoma of the thyroid
   e. Follicular-derived carcinomas, high-grade
      i. Differentiated high-grade thyroid carcinoma
      ii. Poorly differentiated thyroid carcinoma
   f. Anaplastic follicular cell–derived thyroid carcinoma

NEW

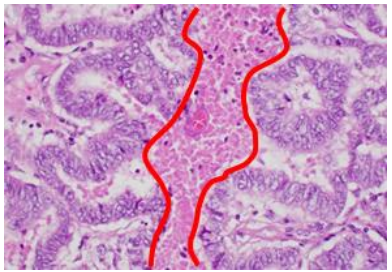
NEOPLASIAS MALIGNAS

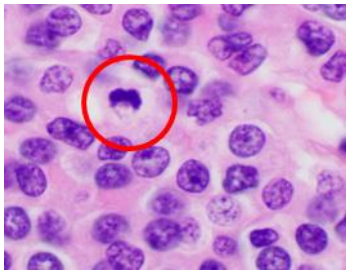
CARCINOMA DIFERENCIADO DE ALTO GRADO
BRAF like (la mayoría)

NEW

CUALQUIER CARCINOMA DIFERENCIADO (CPT >%) INVASIVO CON:

- NECROSIS y/o
- ≥ 5 MITOSIS / 2 mm^2 (10 campos de gran aumento)

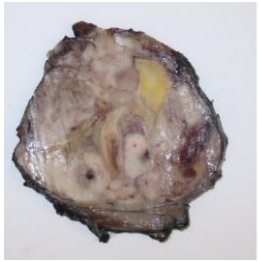


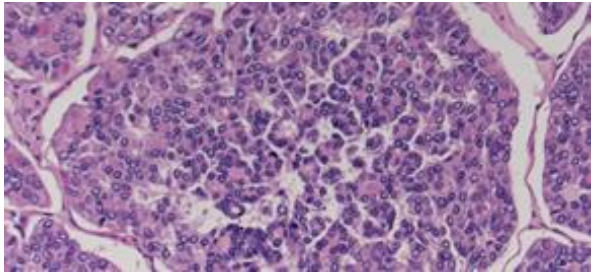


CARCINOMA POCO DIFERENCIADO
RAS like

CRITERIOS DE TORINO CLÁSICOS

- TUMOR INVASIVO DE PATRÓN SÓLIDO/INSUL AR/TRABECULAR
- NO NÚCLEOS DE CPT
- NÚCLEOS CONVOLUTOS Y/O ≥ 3 MITOSIS / 2 mm^2 Y/O NECROSIS





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NEW

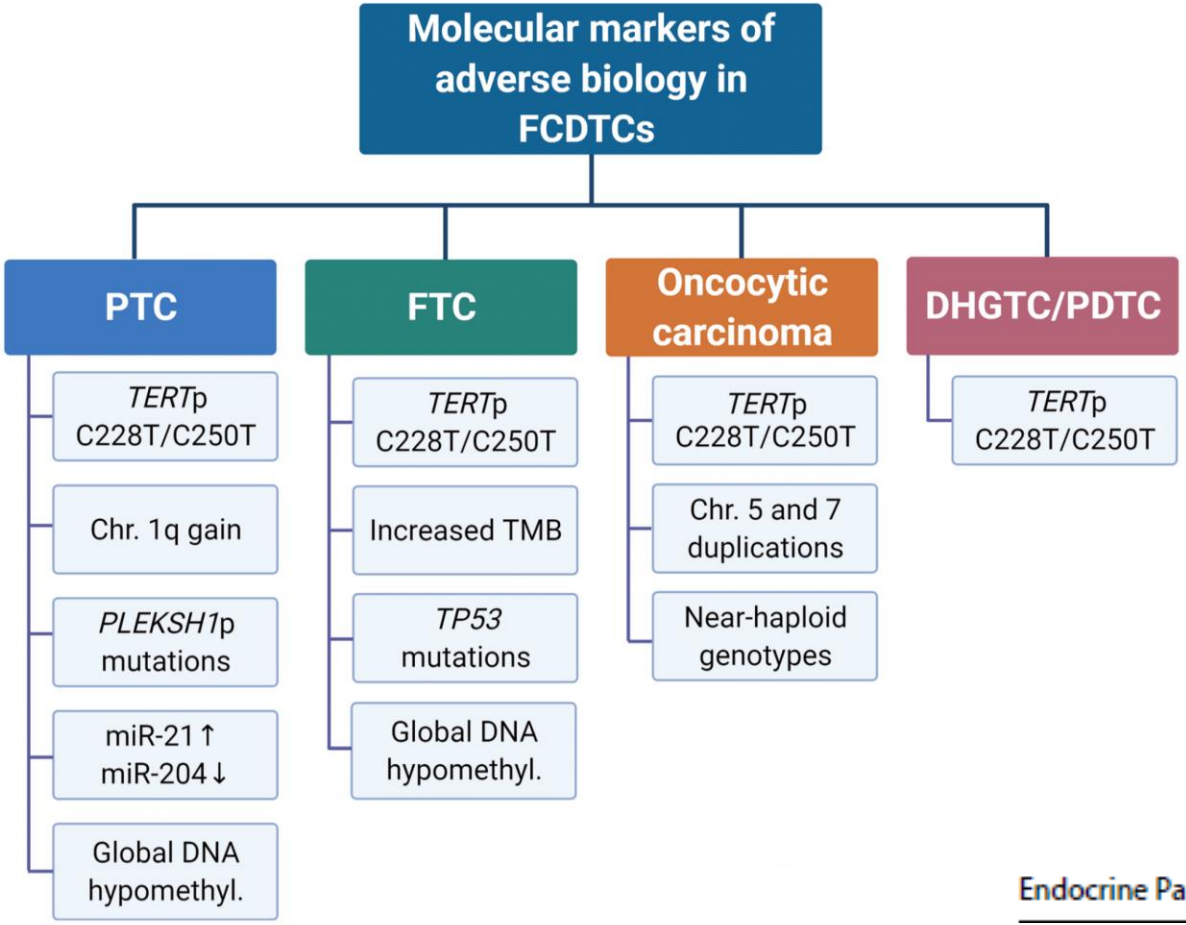
NEOPLASIAS MALIGNAS

Histotype	Differentiation (growth pattern)	Grade (mitotic activity, tumor necrosis)	Prognosis
PTC	Good (papillae, follicles)	Low	Excellent
FTC			
OCA			
NEW **DHGTC** (papillary, follicular, oncocytic)		High	Intermediate
PDTC	Poor (solid/trabecular/insular growth)		
ACA	Absent (undifferentiated growth)		Dismal

AMBOS **ALTO RIESGO,** SIN DIFERENCIAS

SUPERVIVENCIA 50% A LOS 10 AÑOS

50% SON **RESISTENTES** A TERAPIA CON **YODO** (CANDIDATOS A TERAPIA SISTÉMICA SEGÚN FIRMA MOLECULAR)



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NEOPLASIAS MALIGNAS

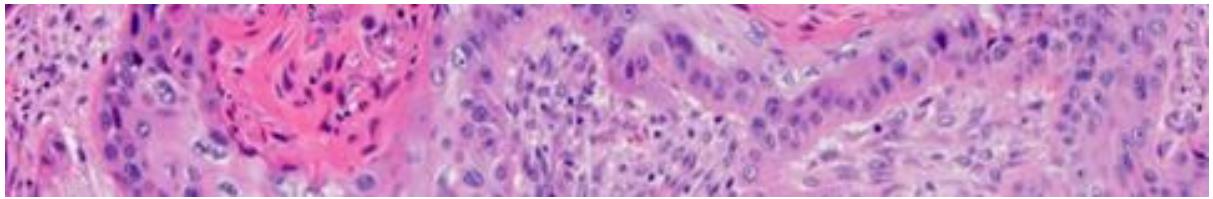
EL **CARCINOMA ESCAMOSO PRIMARIO DE TIROIDES** SE CONSIDERA UN CARCINOMA ANAPLÁSICO

↓

MUTACIÓN *BRAF* V600E O EXPRESIÓN DE PAX8/TTF1 QUE CONFIRMAN ESTIRPE FOLICULAR
COMPORTAMIENTO CLÍNICO SIMILAR

NEW

TESTAR LA MUTACIÓN *BRAF* V600E DE ENTRADA → TERAPIA DIRIGIDA (BRAF/MEK)



Thyroid C-cell–derived carcinoma

1. Medullary thyroid carcinoma

SE INTRODUCE LA **GRADACIÓN** DE LOS TUMORES

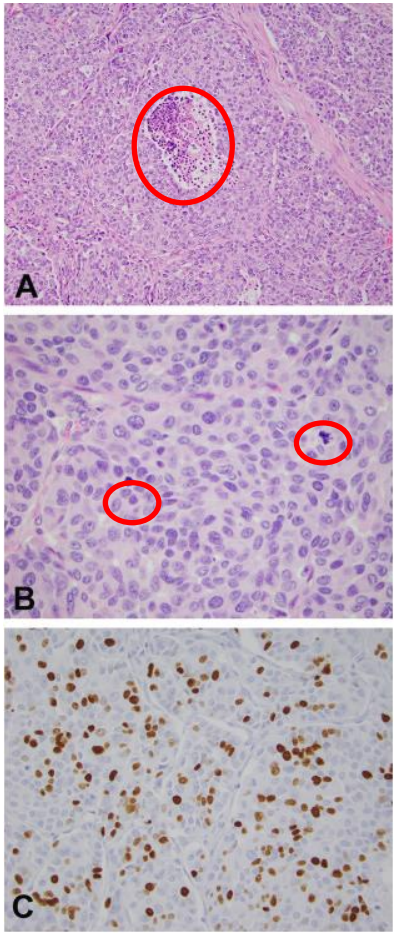
ALTO GRADO

NEW

NECROSIS
Y/O
≥ 5 MITOSIS / 2 mm ^{2}
Y/O
Ki67 ≥ 5%

INCLUIR ESTOS CRITERIOS *EN EL INFORME AP, SEA O NO UN CMT DE ALTO GRADO*

ALTO GRADO SUPONEN EL 25% APROX., INDEPENDIENTE DE MUTACIÓN *RET* O *RAS*
BUEN PREDICTOR DE EVOLUCIÓN ADVERSA



Mixed medullary and follicular cell–derived carcinomas
Salivary gland–type carcinomas of the thyroid
1. Mucoepidermoid carcinoma of the thyroid
2. Secretory carcinoma of salivary gland type

Thyroid tumors of uncertain histogenesis
1. Sclerosing mucoepidermoid carcinoma with eosinophilia
2. Cribriform morular thyroid carcinoma

Thymic tumors within the thyroid
1. Thymoma family
2. Spindle epithelial tumor with thymus-like elements
3. Thymic carcinoma family

Embryonal thyroid neoplasms
1. Thyroblastoma NEW

NEOPLASIAS RARAS

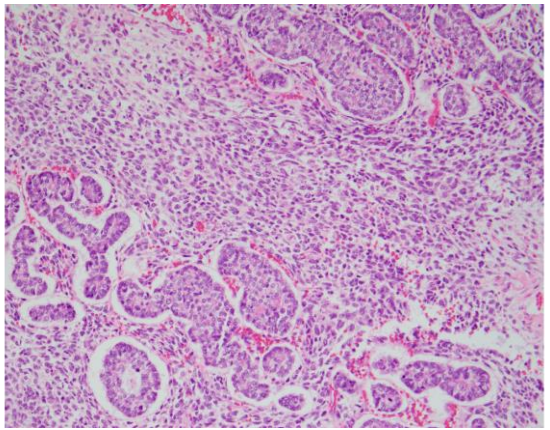
La **histogénesis** también rige la clasificación de los tumores infrecuentes

NEW

Aparece el **tiroblastoma** como una nueva entidad

Tumor embionario de alto grado
Mutaciones en *DICER1*

Células foliculares primitivas + células pequeñas + estroma mesenquimal



GRACIAS