What's New in the 5th Edition WHO Tumor Classification:
Endocrine & Neuroendocrine Tumors
and
Head & Neck Tumors
10 December, 2024

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Standing Editorial Board Member of World Health Organization Tumour Classification 5th Edition
Expert Board Member of WHO 5th Edition for Tumours of Head and Neck
Expert Board Member of WHO 5th Edition for Endocrine and Neuroendocrine Tumours

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Strategy

- Since 1956, the WHO has been responsible for the classification of tumours in all organs and systems.
- The WHO Blue Books provide a definitive evidence-based classification of all cancer types to enable diagnosis and research worldwide.
- The diagnosis of cancers underpins individual patient treatment, as well as research into all aspects of cancer causation, prevention, therapy, and education.
- **The WHO Blue Books are not just for pathologists…**

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The 5th Edition: What is Different

Better governance
- Editorial Board was formed in 2017 with standing and expert members to lead the classification, and to decide on entries, based on evidence
- Informed bibliometrics used to select editors and authors, removing selection bias
  - 2,500 authors have been involved in the 5th edition
- Links to other organisations: from coding, staging, genetics to implementation, among others

Quality and Standards
- One hierarchical classification using Linnean principles, managed in a database
- Greatly improved harmonization across the whole series
  - Neuroendocrine neoplasms, hematolymphoid, soft tissue, melanocytic, familial syndromes
- Improved image quality, linked references, standardized statistics, global epidemiology and mandated SI units (mitoses/2 mm^2)
- Multidisciplinary classification

Production
- The edition will be published within 5 years of the first volume appearing
- Website allows easier access to references, digitized whole slide images, and notes

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Endocrine & Neuroendocrine Tumours

29 Expert Editorial Board Members (5 for 4th ed.)

Sylvia L	Asa	Canada	Ozgur	Mete	Canada
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Alex	Lazar*	USA	Mary K.	Washington	USA
Holger	Moch	Germany			

*Standing Board members and content experts for this volume

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Overview

- 128 unique diagnostic entities
  - Subtypes (formerly called variants) included within the entity
- Instructions were quite meticulous and comprehensive
- Hierarchical classification (different from malignant 1st in 4th ed.)

Hamartomas/reactive tumor-like
▼
Benign tumors
▼
Uncertain or Borderline tumors
▼
Malignant tumors (low to high grade)

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Major changes

- Aggregated tumors affecting all anatomic sites into their own chapters to avoid redundancy/repetition/duplication
  - Neuroendocrine neoplasms in non-endocrine organs
  - Soft tissue lesions (mesenchymal and stroma tumors)
  - Hematolymphoid proliferations and neoplasms
  - Germ cell tumors
  - Metastases to endocrine organs
  - Genetic tumor syndromes (15 with endocrine organ lesions and/or tumor manifestations especially)

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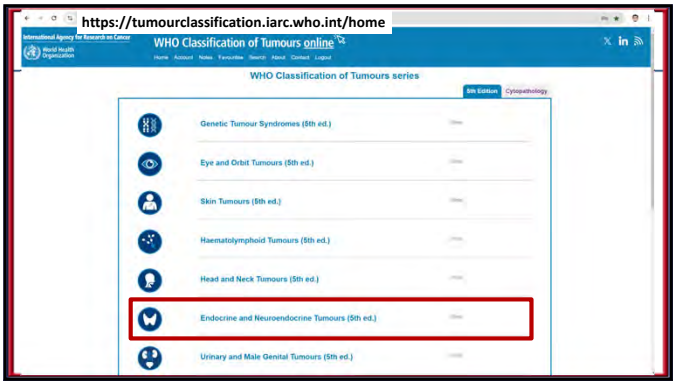

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BFF: Best Features Forever

- Virtual whole slide case for each diagnosis
- All references link to PubMed ID number
- Online version will have more images that were not published in the book

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Follicular cell-derived Neoplasms

Low-risk neoplasms

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
Thyroid tumours of uncertain malignant potential
Hyalinizing trabecular tumour

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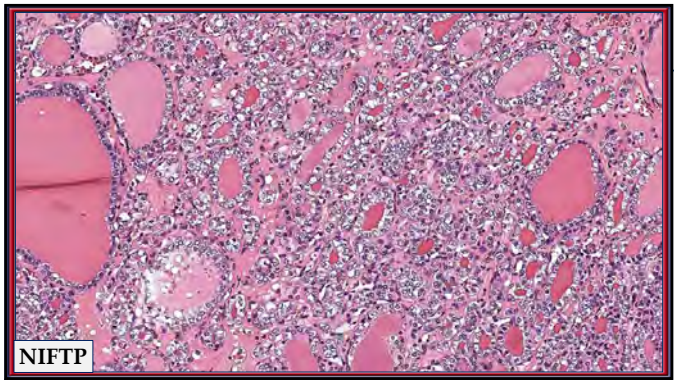

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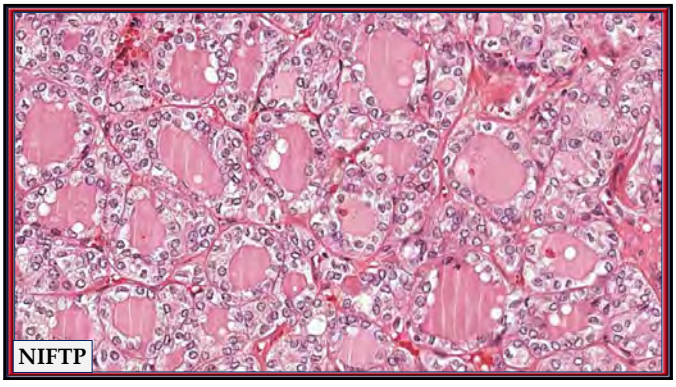

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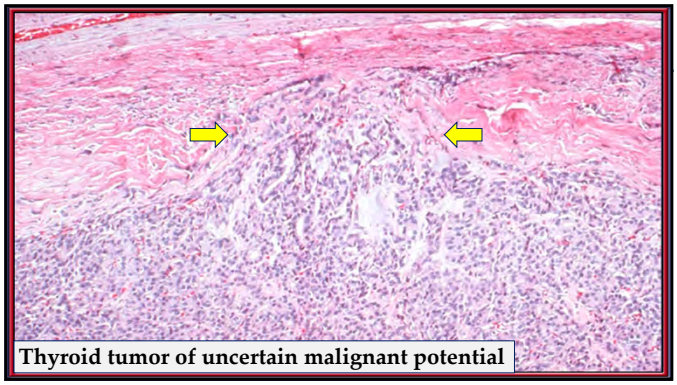

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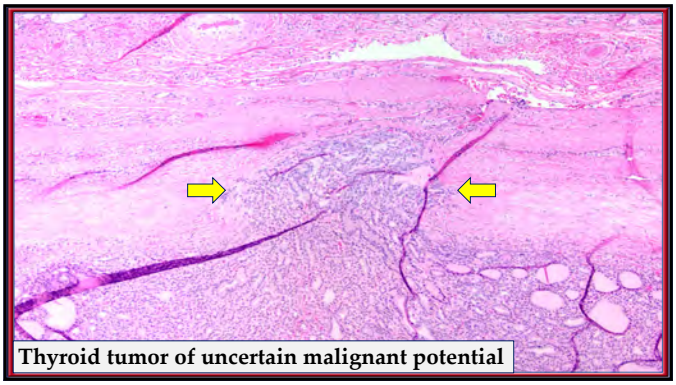

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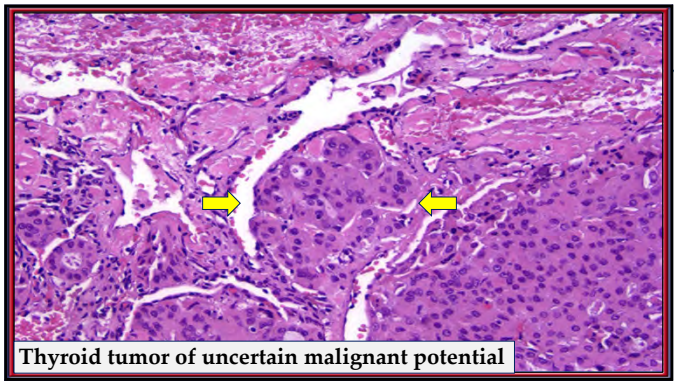

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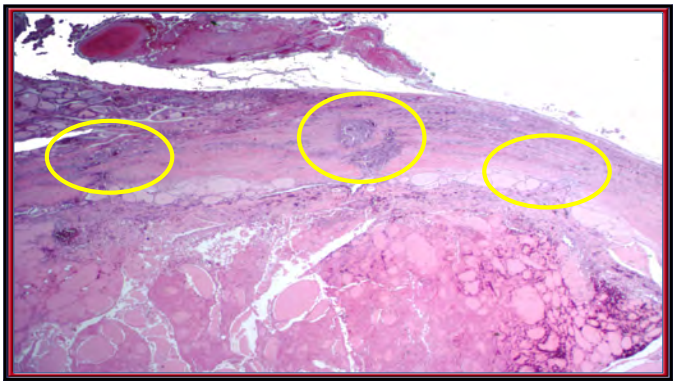

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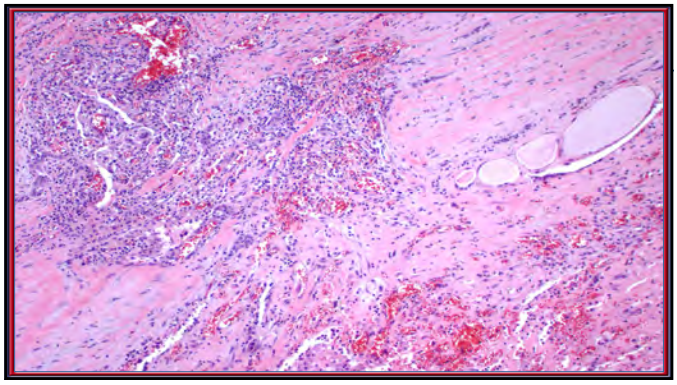

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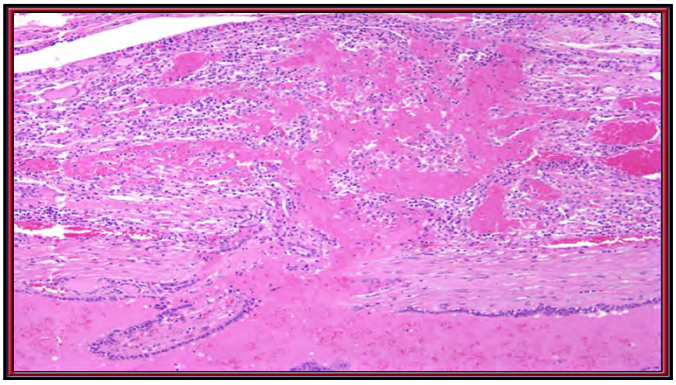

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Follicular cell-derived Neoplasms

Malignant neoplasms

- Follicular thyroid carcinoma
- Invasive encapsulated follicular variant of papillary thyroid carcinoma
- Papillary thyroid carcinoma
- Oncocytic carcinoma of the thyroid
- High-grade follicular cell-derived non-anaplastic thyroid carcinoma
- Anaplastic thyroid carcinoma

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Invasive Encapsulated Follicular Variant of Papillary carcinoma

Encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) is a malignant well-differentiated follicular cell-derived neoplasm that is encapsulated, has an exclusive or almost exclusive follicular architecture, nuclear features of papillary thyroid carcinoma (PTC), and invasive growth.

- Essential:
  - Capsular and/or vascular invasion
    - ✓ Encapsulated tumors with an exclusive or almost exclusive follicular architecture
    - ✓ Widely invasive FVPTC have grossly apparent invasive growth
  - Nuclear features of PTC

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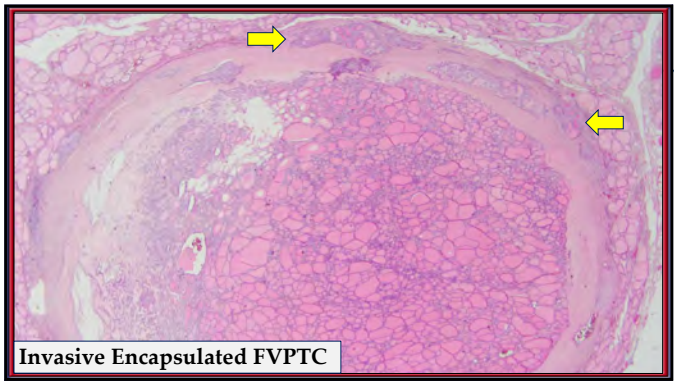

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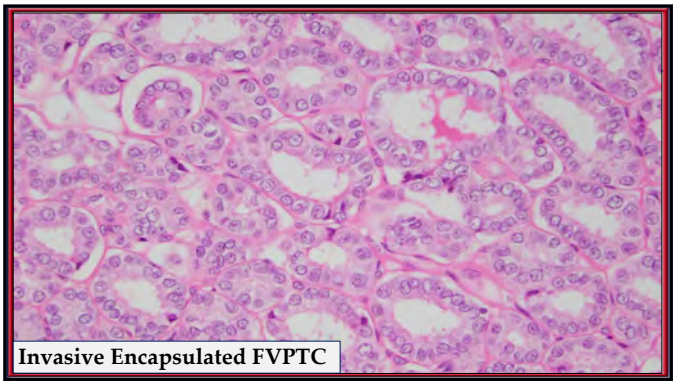

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Papillary thyroid carcinoma

Papillary thyroid carcinoma (PTC) is a 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.

- **Subtypes (variants)**
  - Classical PTC
  - Encapsulated classical PTC
  - Infiltrative follicular variant PTC
  - Diffuse sclerosing PTC
  - Solid/trabecular PTC
  - Warthin-like PTC
  - Oncocytic PTCs
  - Clear cell PTC
  - Spindle cell PTC
  - PTC with fibromatosis/fasciitis-like/desmoid-type stroma
  - Tall cell PTC
  - Hobnail PTC
  - Columnar cell
  - Cribriform morular variant
  - Microcarcinoma

23

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  - Tall cell PTC
  - Hobnail PTC
  - Columnar cell

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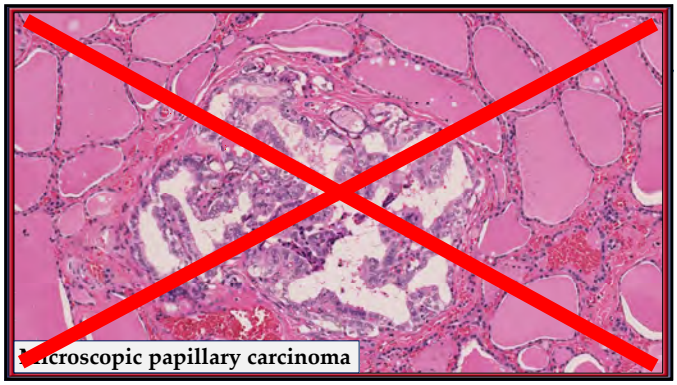

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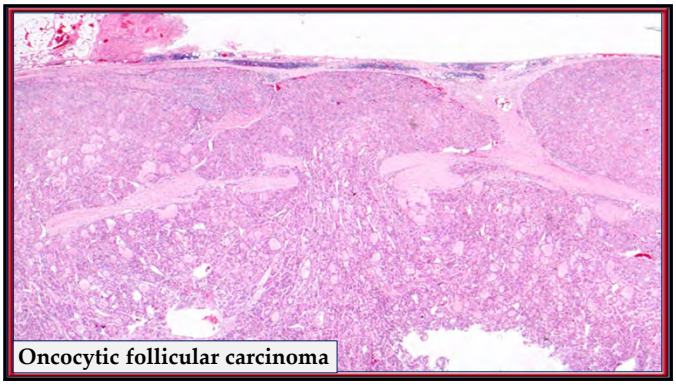

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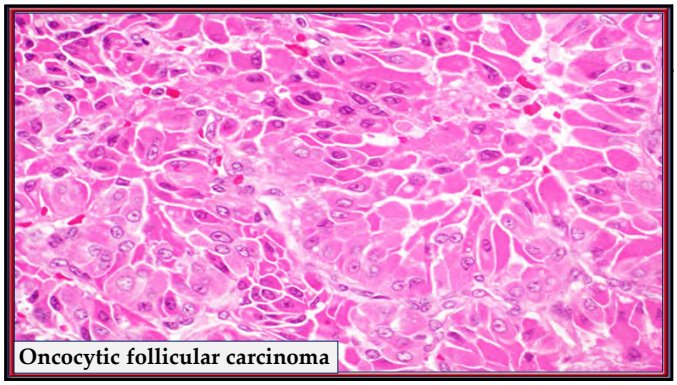

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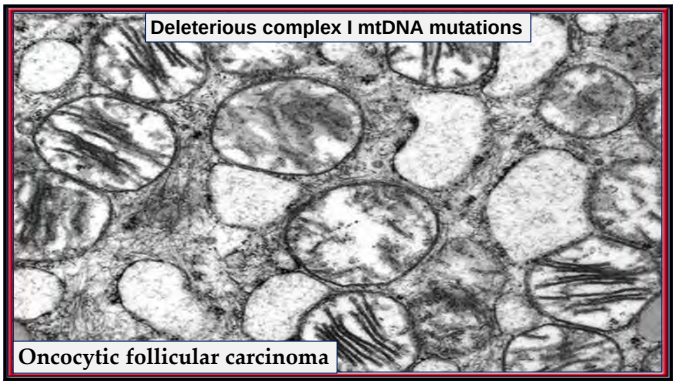

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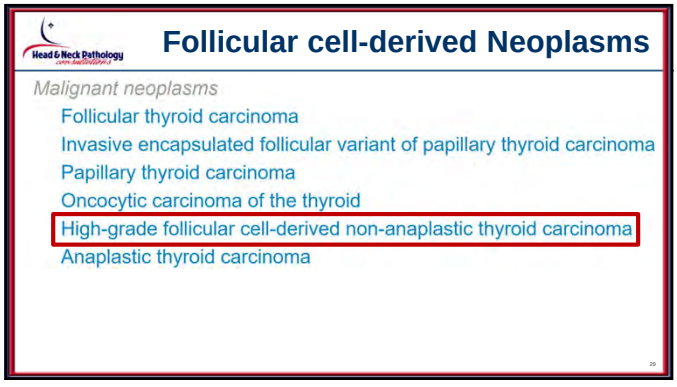

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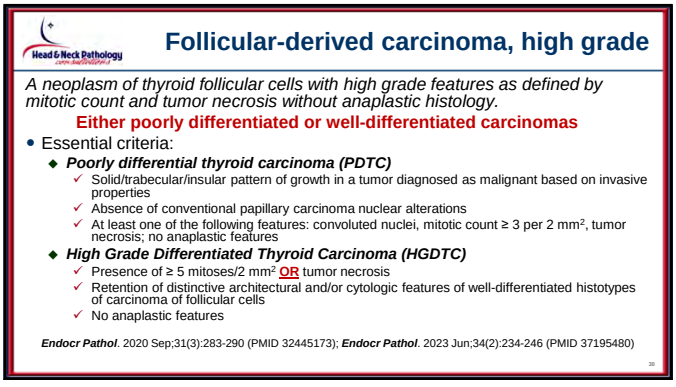

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Diagnostic criteria for high grade follicular cell derived thyroid carcinomas

Feature	Poorly differentiated thyroid carcinoma (Turin proposal)
Architectural pattern	Solid/trabecular/insular growth required
Nuclear features	**Absence** of nuclear features of papillary thyroid carcinoma (PTC) required
Necrosis, mitoses, and convoluted nuclei	At least **one** of the following three features: Mitotic count ≥3/2 mm² Tumor necrosis Convoluted nuclei
Anaplastic features	None

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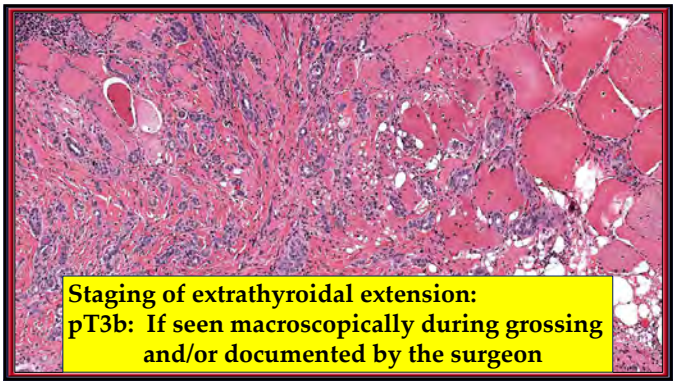

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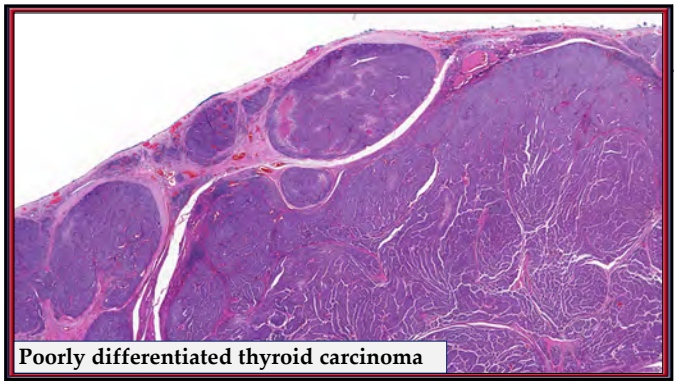

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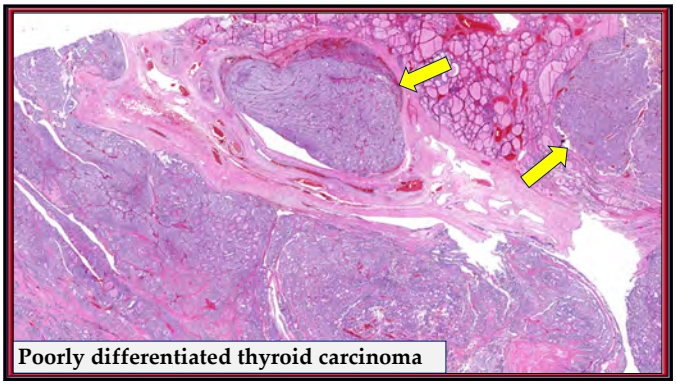

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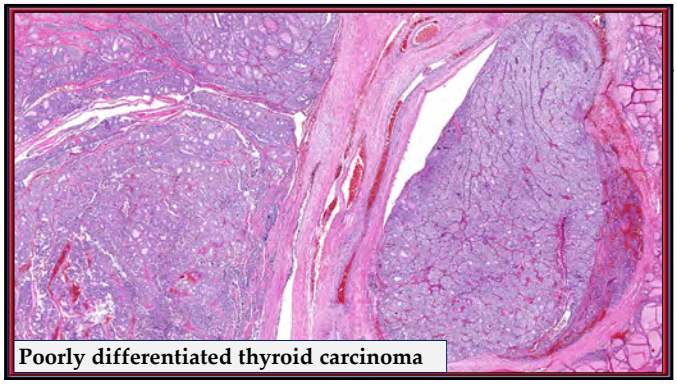

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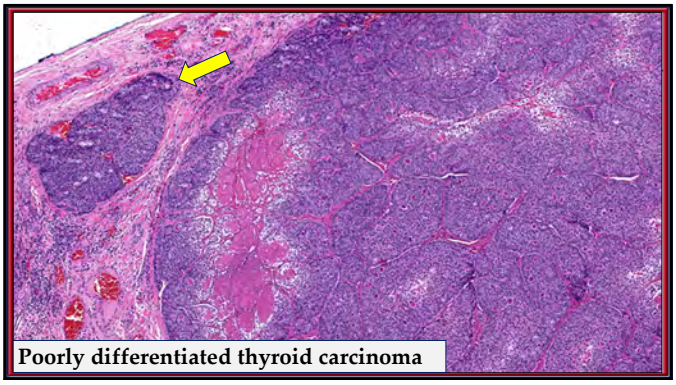

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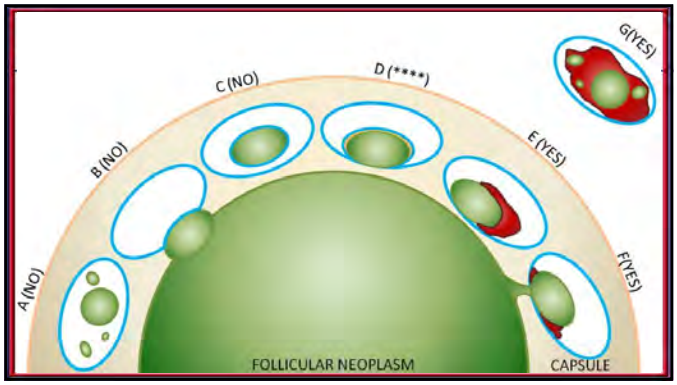

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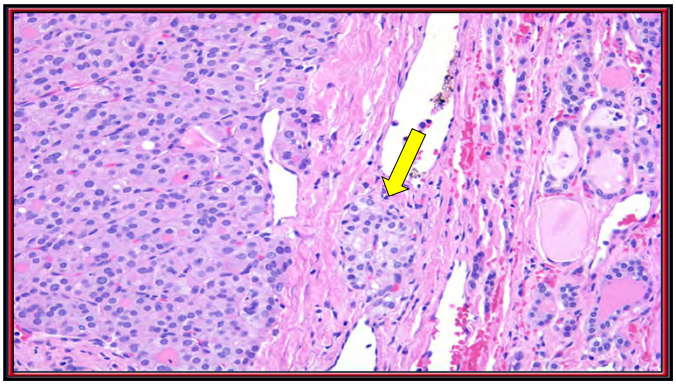

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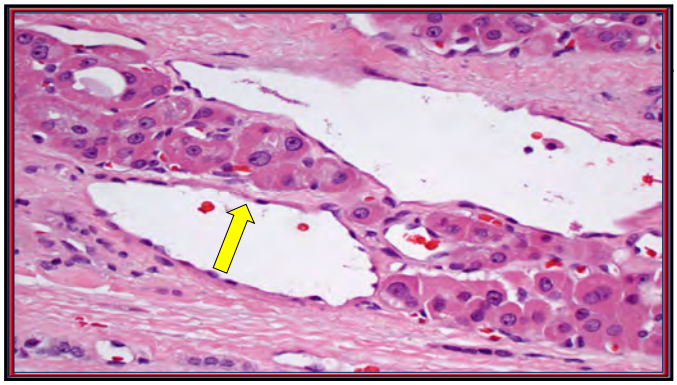

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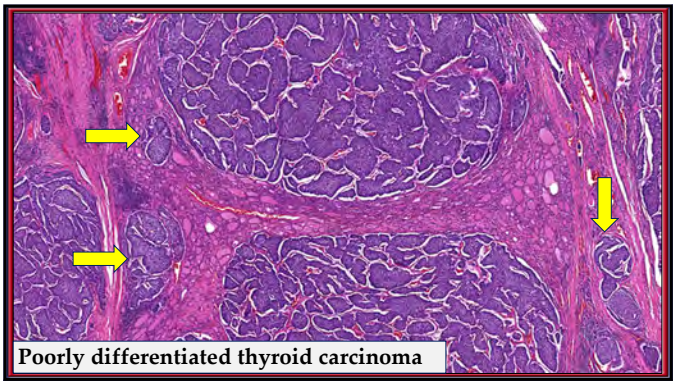

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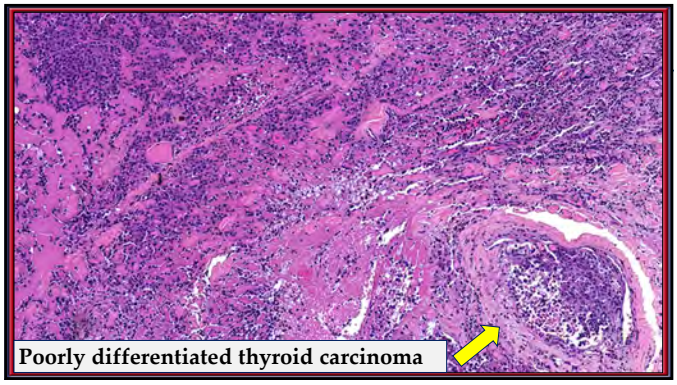

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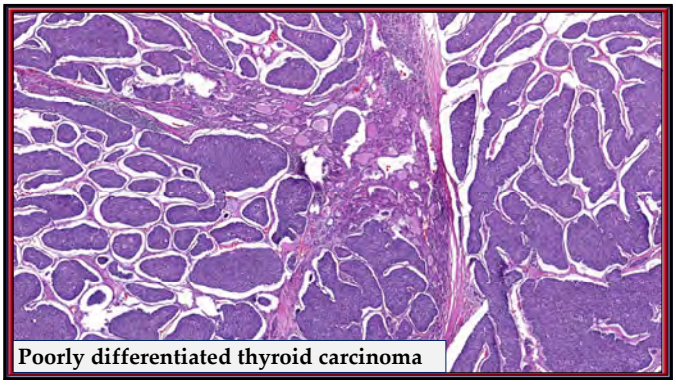

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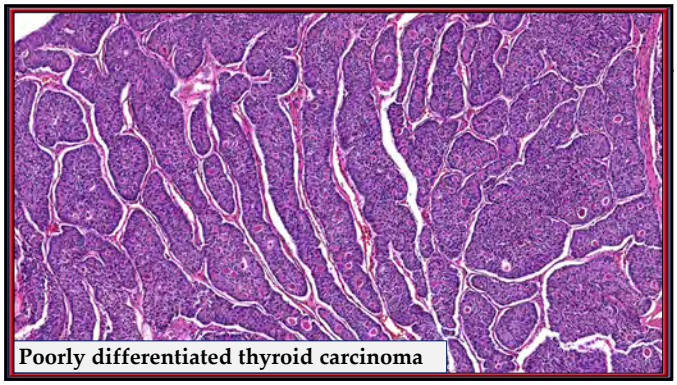
Poorly differentiated thyroid carcinoma

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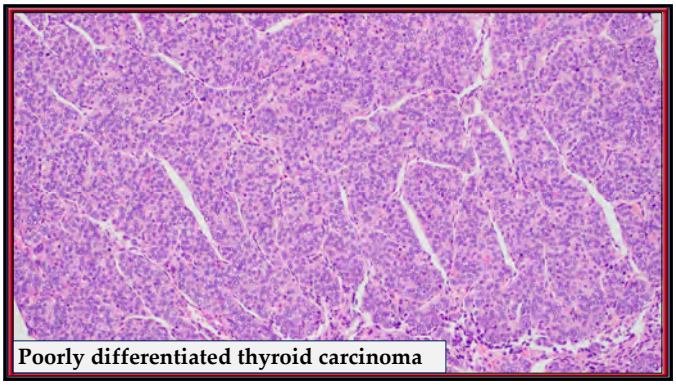
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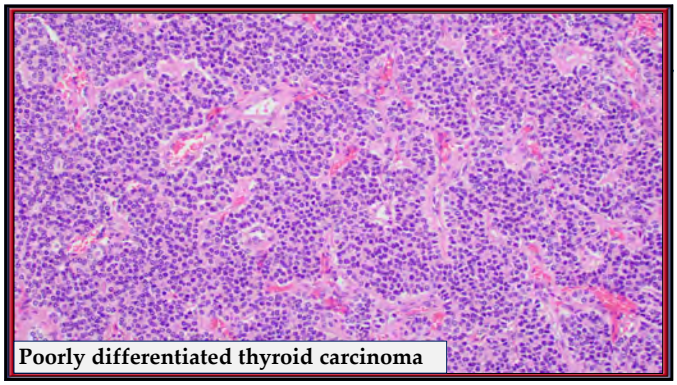
Poorly differentiated thyroid carcinoma

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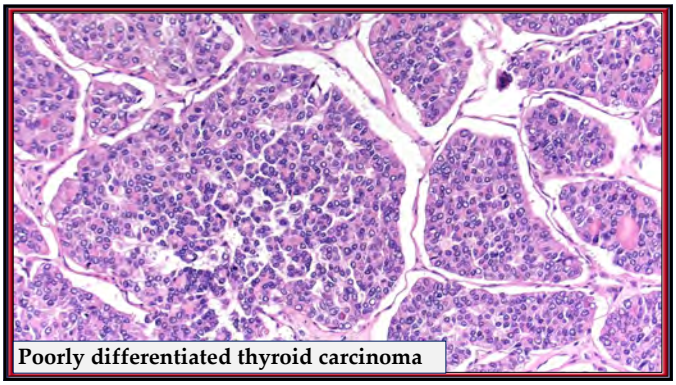
Poorly differentiated thyroid carcinoma

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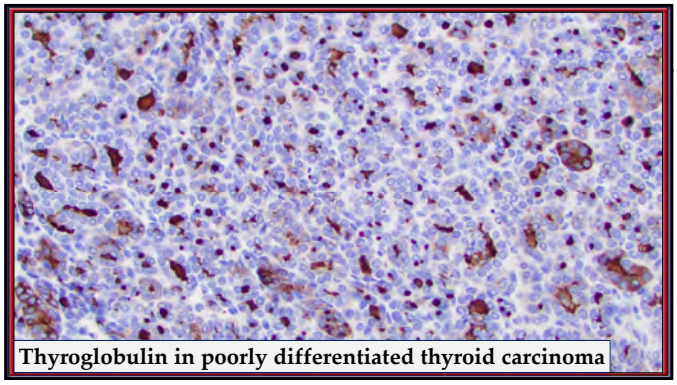
Thyroglobulin in poorly differentiated thyroid carcinoma

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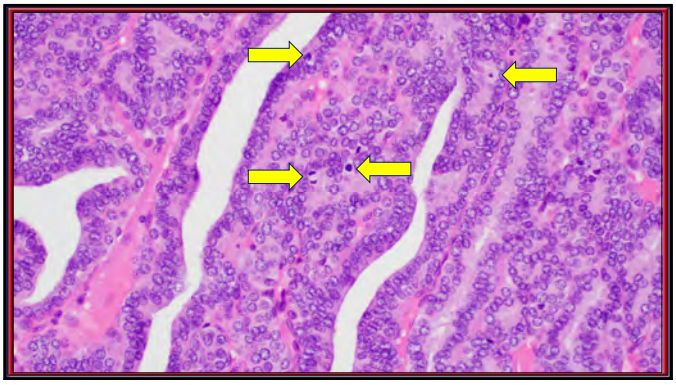

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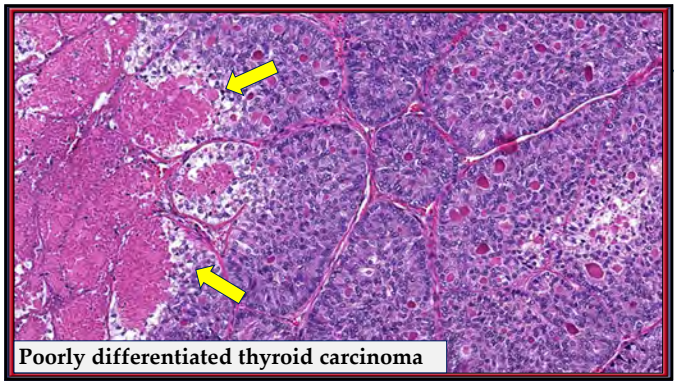

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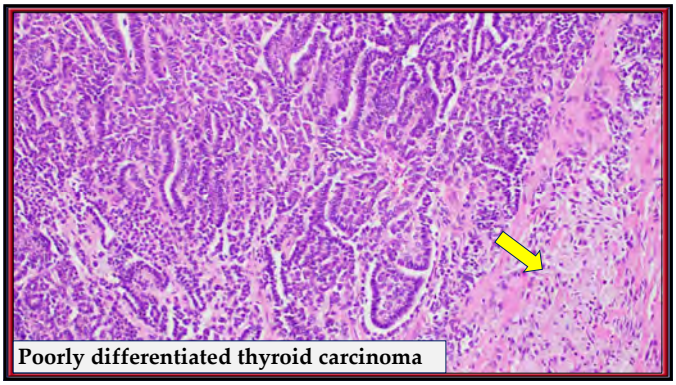

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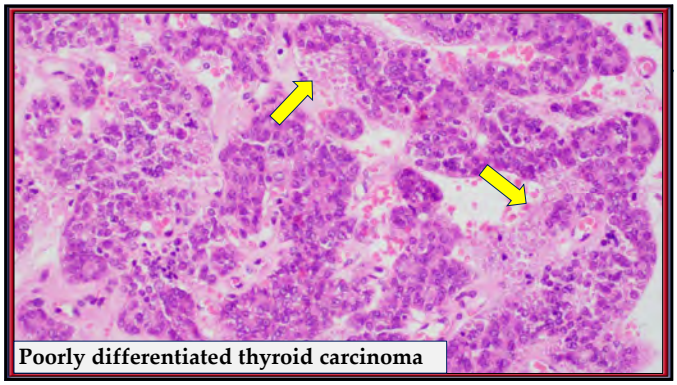

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Diagnostic criteria for high grade follicular cell derived thyroid carcinomas

Feature	Poorly differentiated thyroid carcinoma (Turin proposal)	High Grade Differentiated Thyroid carcinoma
Architectural pattern	Solid/trabecular/insular growth required	Papillary, follicular, solid
Nuclear features	**Absence** of nuclear features of papillary thyroid carcinoma (PTC) required	Any
Necrosis, mitoses, and convoluted nuclei	At least **one** of the following three features: Mitotic count ≥3/2 mm² Tumor necrosis Convoluted nuclei	At least **one** of two present: Mitotic count ≥5/2 mm² Tumor necrosis
Anaplastic features	None	None

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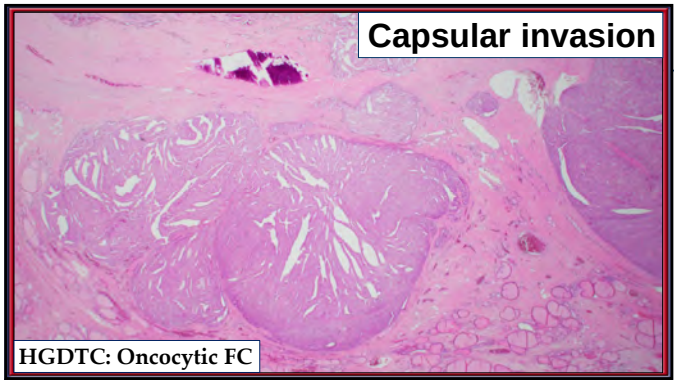

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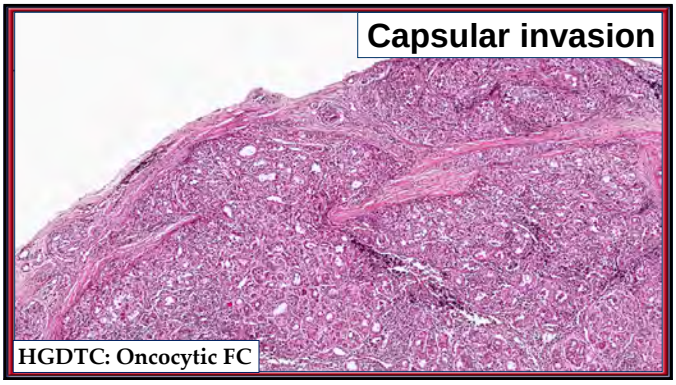

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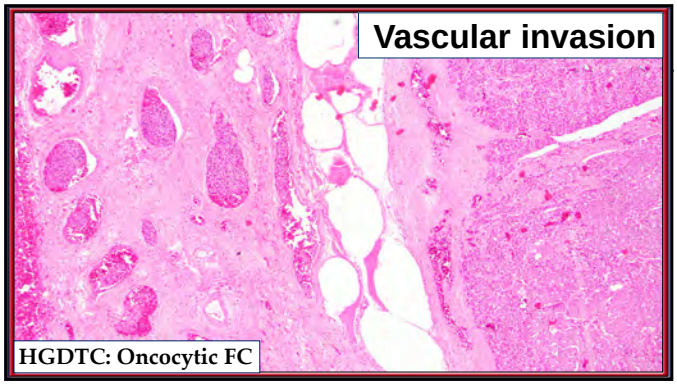

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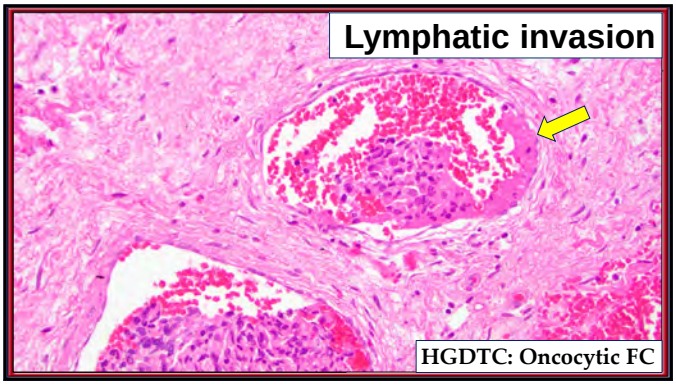

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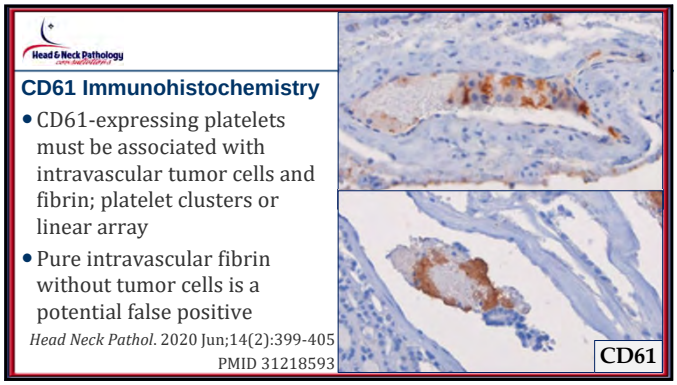

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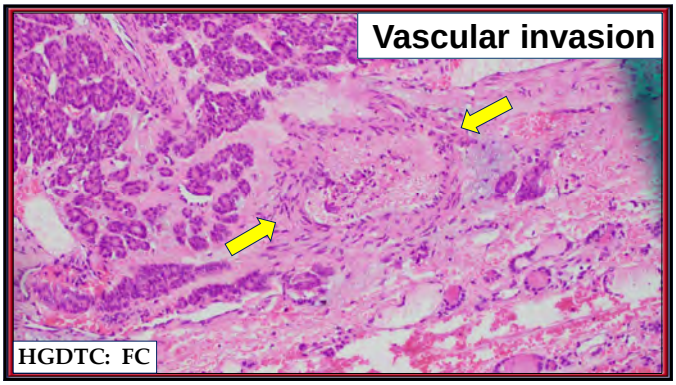

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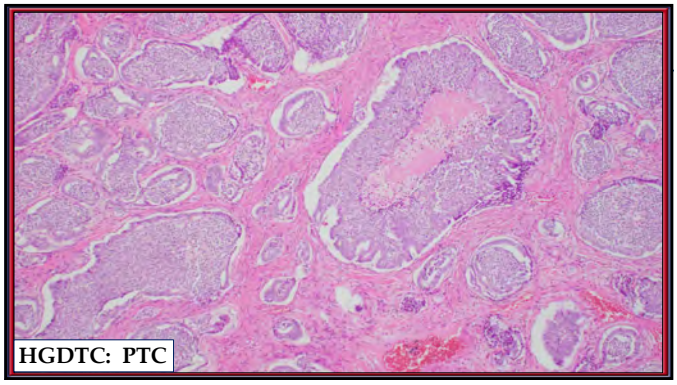

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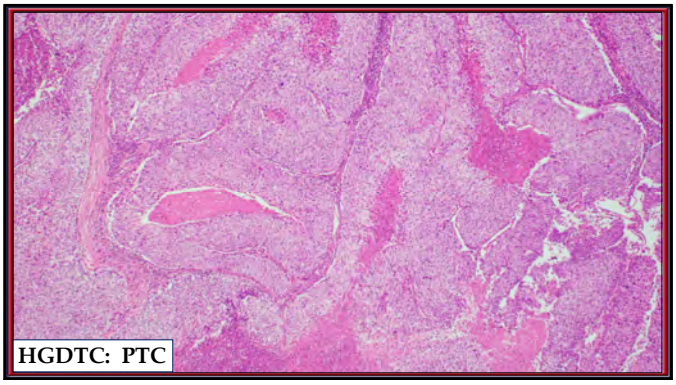

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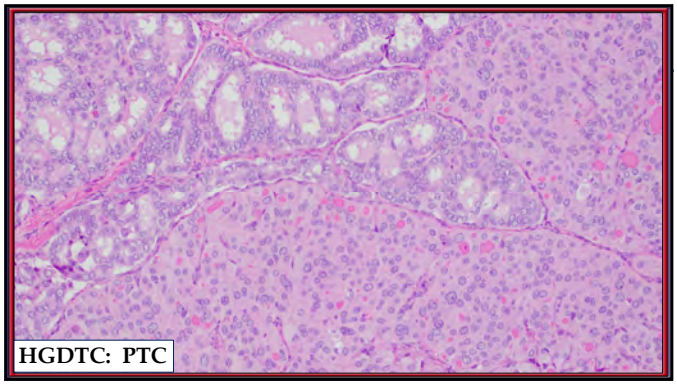

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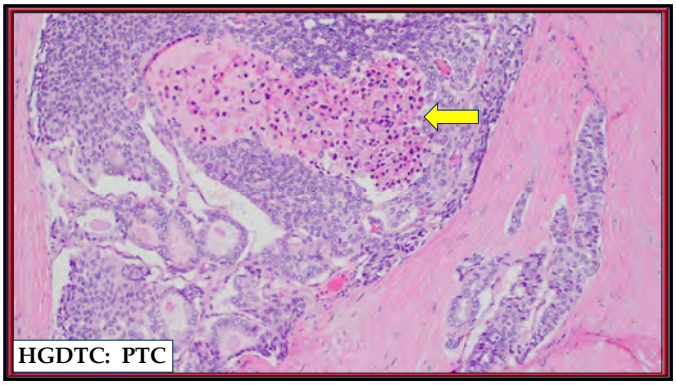

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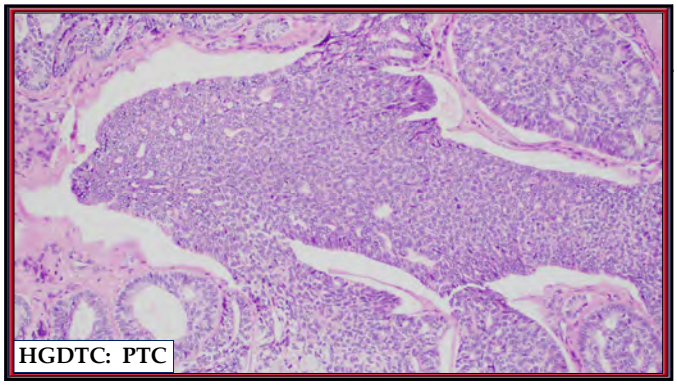

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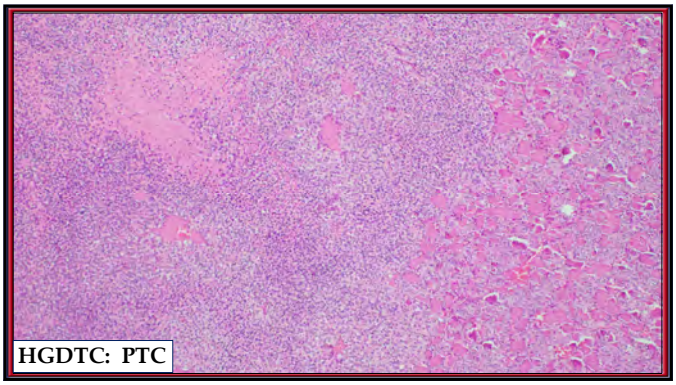

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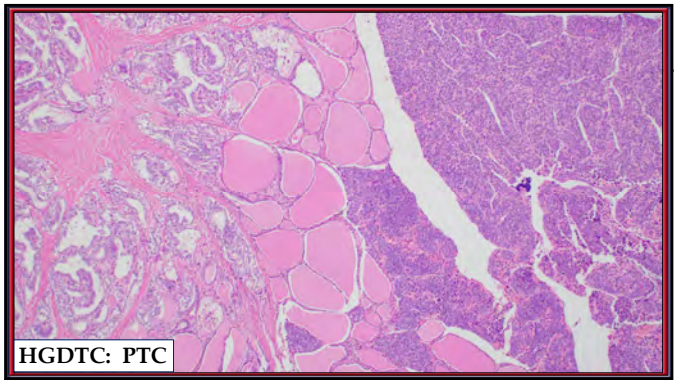

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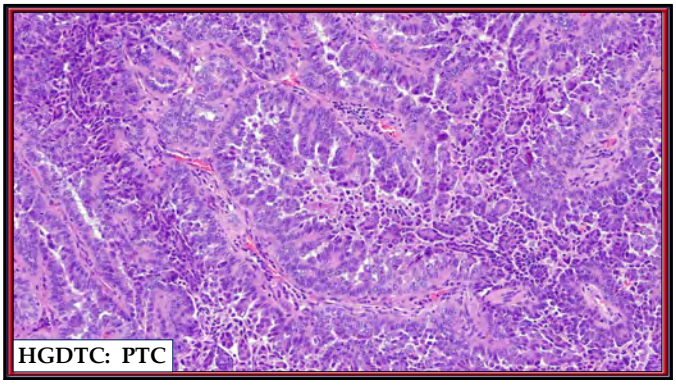

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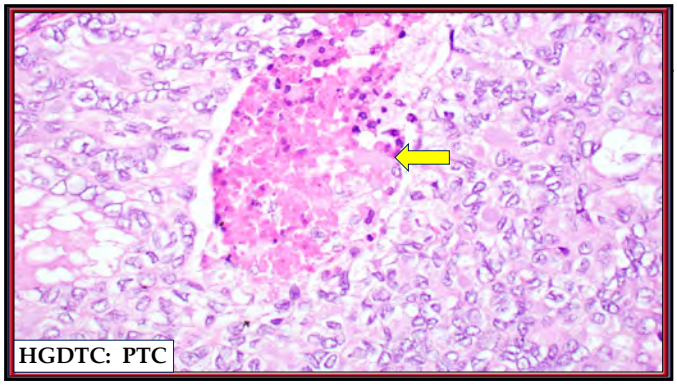

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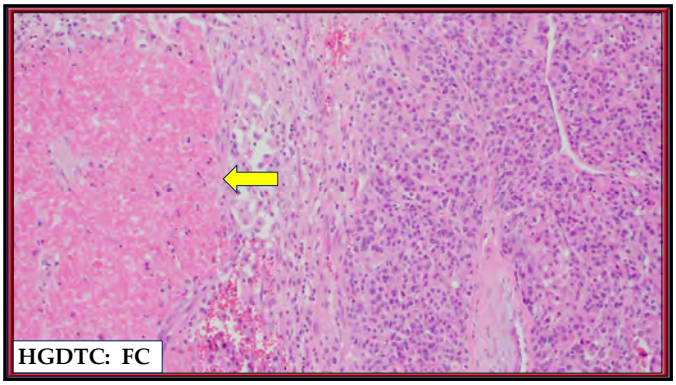

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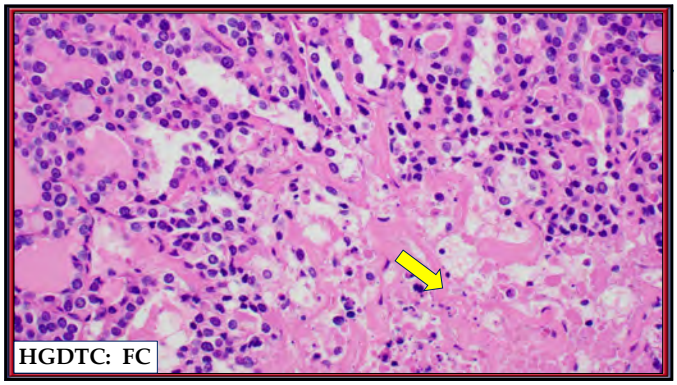

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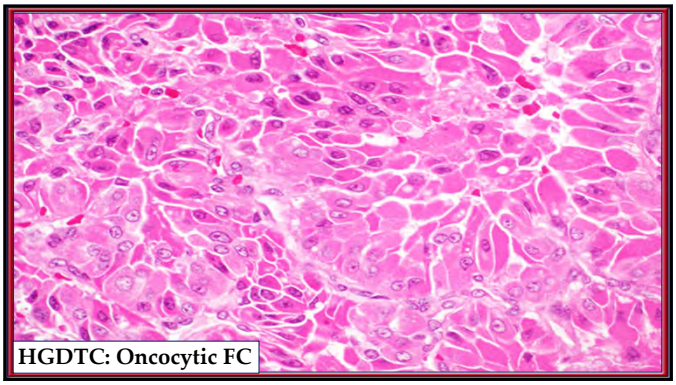

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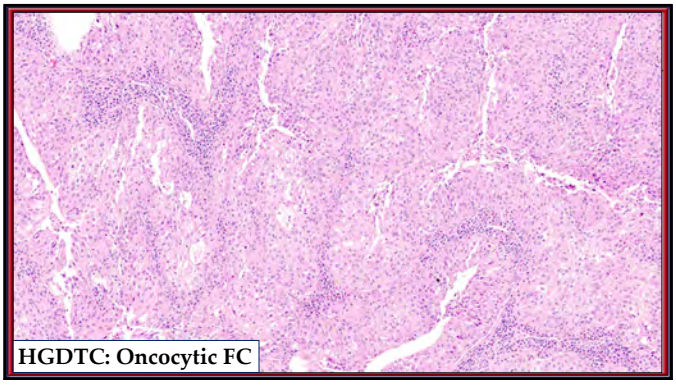

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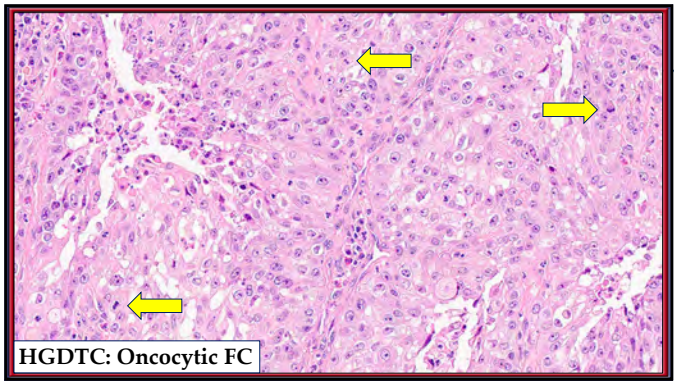

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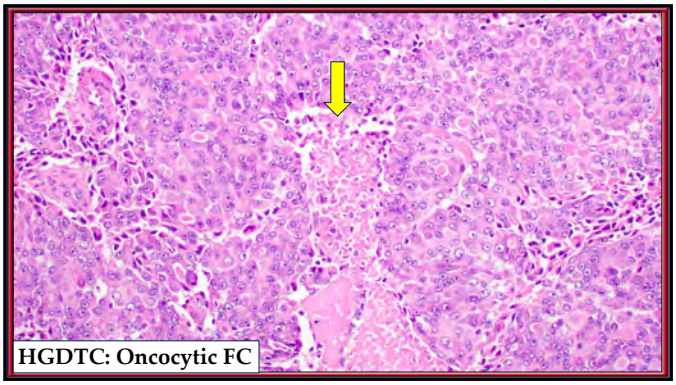

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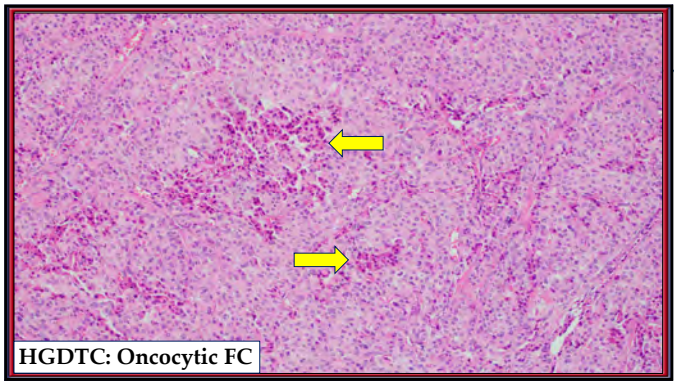

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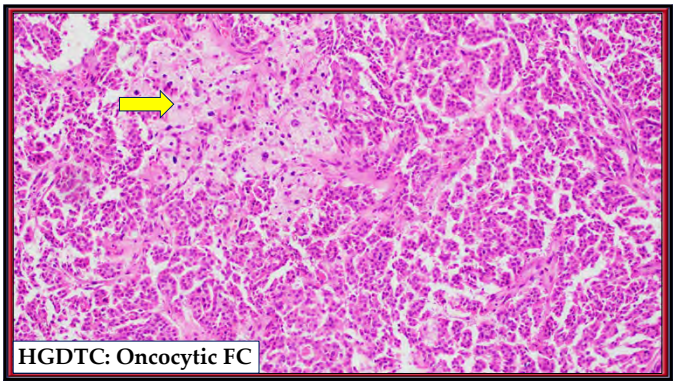

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Common molecular alterations in high-grade non anaplastic follicular cell-derived carcinoma

Subtype	*BRAF* V600E	*RAS*	*TERT*	*TP53*	*EIF1AX*	*PTEN*	*PIK3CA*
Poorly differentiated thyroid carcinoma (PDTC)	6%	44%	44%	15%	15%	6%	2%
High grade differentiated thyroid carcinoma (HGDTC)	81%	6%	39%	3%	3%	0%	3%

77

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79

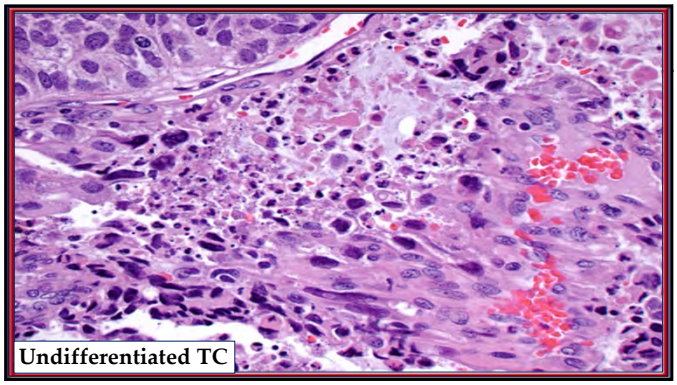
Follicular cell-derived Neoplasms

Malignant neoplasms

- Follicular thyroid carcinoma
- Invasive encapsulated follicular variant of papillary thyroid carcinoma
- Papillary thyroid carcinoma
- Oncocytic carcinoma of the thyroid
- High-grade follicular cell-derived non-anaplastic thyroid carcinoma
- Anaplastic thyroid carcinoma

Squamous cell carcinoma is now a subtype of anaplastic

80



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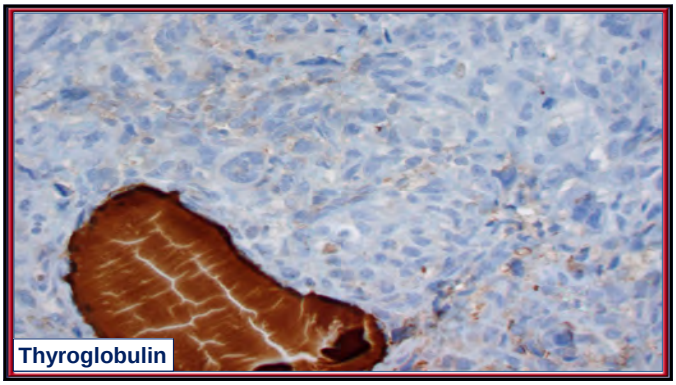

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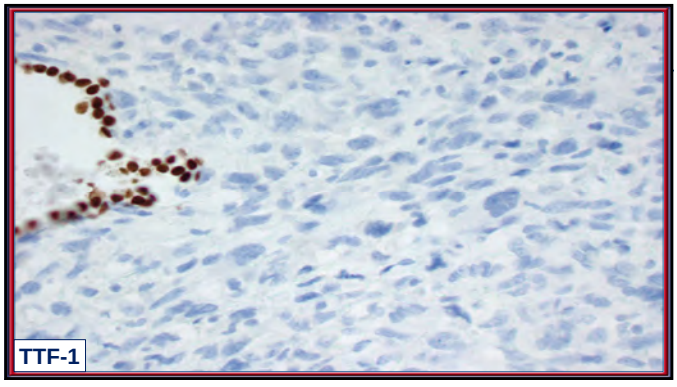

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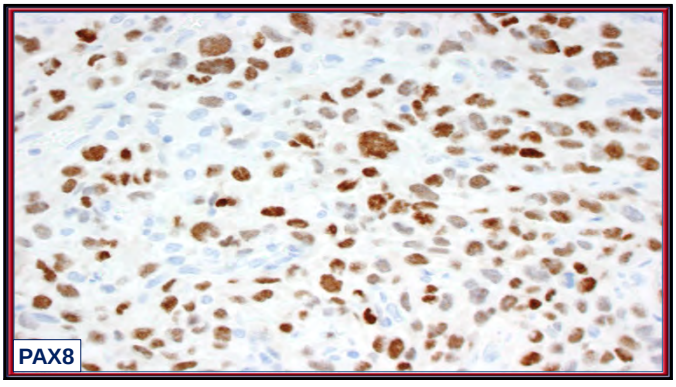


84

Embryonal tumors

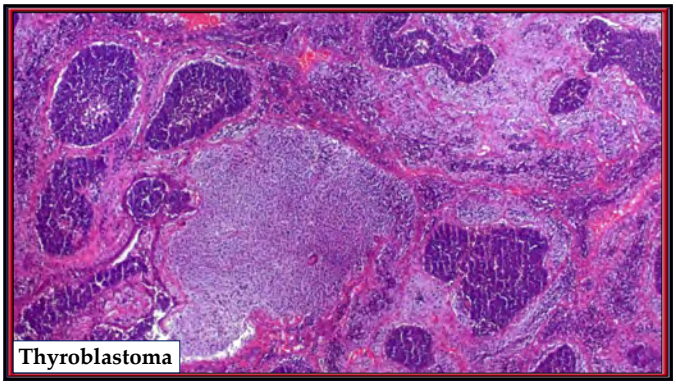
Embryonal thyroid neoplasms

Thyroblastoma

Thyroblastoma is an embryonal high-grade thyroid neoplasm composed of primitive thyroid-like follicular cells surrounded by a primitive small cell component and mesenchymal stroma with variable differentiation

- **Previously malignant thyroid teratoma**
- **Those tested have *DICER1* variants**

85



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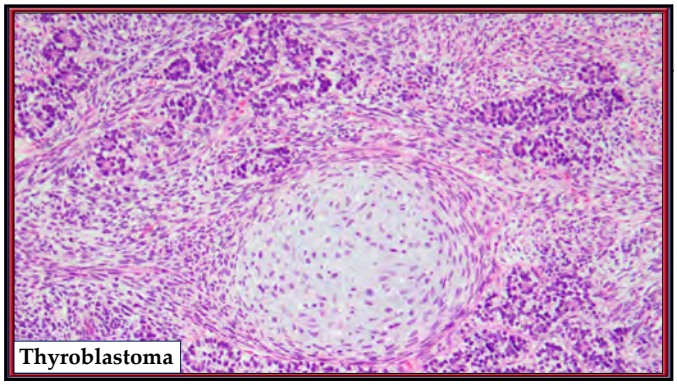

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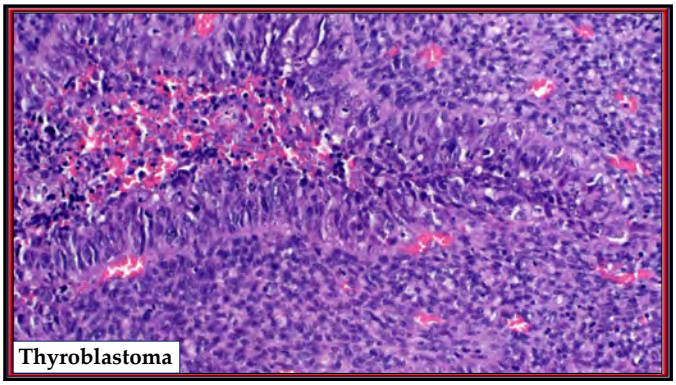

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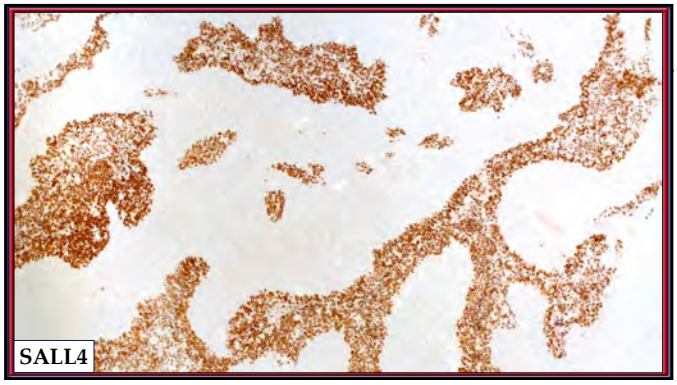

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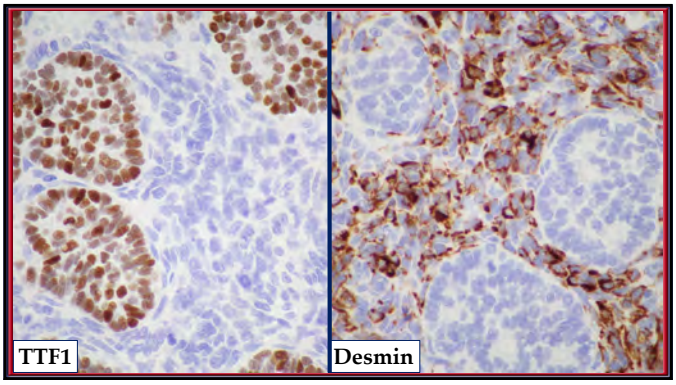

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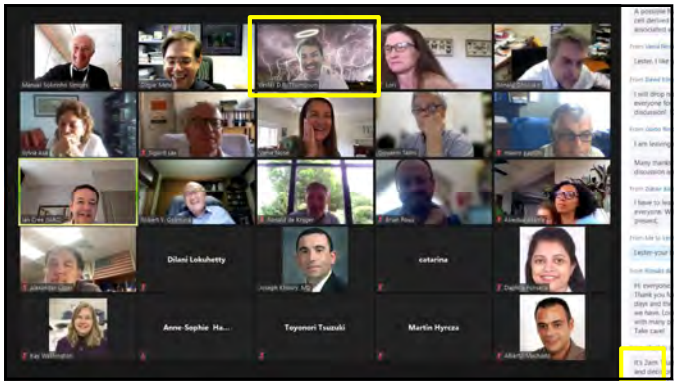

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Head and Neck Tumors Book Overview

- 253 unique diagnostic entities
  - Subtypes (formerly called variants) included within the entity
- 288 authors
- 35 countries represented
- Hierarchical classification (different from malignant 1st in 4th ed.)

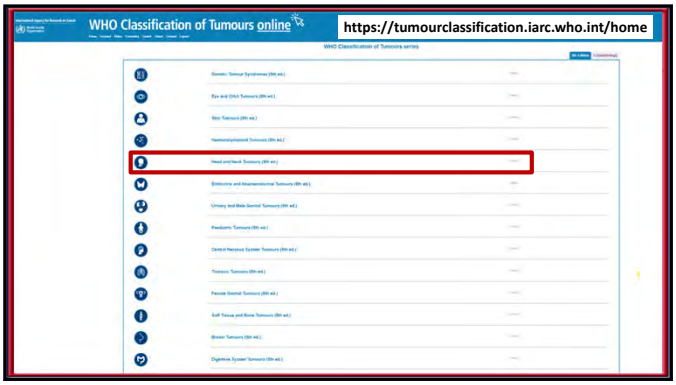
Hamartomas/reactive tumor-like
▼
Benign tumors
▼
Uncertain or Borderline tumors
▼
Malignant tumors (low to high grade)

92

Major changes

- Aggregated tumors affecting all anatomic sites into their own chapters to avoid redundancy/repetition/duplication
  - Salivary gland tumors (not repeated in each anatomic site)
  - Soft tissue lesions (some site specific exclusions)
  - Hematolymphoid proliferations and neoplasms
  - Melanocytic tumors
  - Metastases to the head and neck
  - Germ cell tumors
  - Bone tumors grouped with odontogenic & maxillofacial
  - Neuroendocrine tumors and paraganglioma
  - Genetic tumor syndromes (15 with head and neck manifestations)

93



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BFF: Best Features Forever

- Books hosted as interactive on-line books
  - Optimized for desktop and mobile devices for anytime, anywhere, on-demand access
  - Online version has more images than printed book
- Virtual whole slide case for each diagnosis
- All references link to PubMed ID number
- Tables open in new browser window

95

Neuroendocrine neoplasms and Paraganglioma	
2005 edition	14 diagnoses
2017 edition	11 diagnoses
2022 edition	7 diagnoses

12.1: Neuroendocrine neoplasms
12.1.1: Neuroendocrine tumours
12.1.1.1: Neuroendocrine tumour
12.1.1.3: Ectopic or invasive PitNET/adenoma
12.1.2: Neuroendocrine carcinoma
12.1.2.1: Small cell neuroendocrine carcinoma
12.1.2.2: Large cell neuroendocrine carcinoma
12.1.2.3: Merkel cell carcinoma
12.2: Paraganglion tumours
12.2.0.2: Head and neck paraganglioma

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Neuroendocrine Neoplasms & Paragangliomas

- New Entities
  - **One of the most significant changes in the book!!!**
  - ◆ Neuroendocrine tumor (NET)
    - ✓ Grades 1, 2, and 3
    - ✓ Site specific – but not yet defined in many locations
  - ◆ Neuroendocrine carcinoma (NEC)
    - ✓ Small cell neuroendocrine carcinoma
    - ✓ Large cell neuroendocrine carcinoma
    - ✓ Merkel cell carcinoma

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Neuroendocrine Tumor

Neuroendocrine tumours are well differentiated epithelial neuroendocrine neoplasms that arise in the upper aerodigestive tract and salivary glands

- Arise from the cells of the dispersed neuroendocrine system
- Functional imaging studies (^{68}Ga-DOTA PET/CT) that target somatostatin receptors located on the tumor cell membrane are particularly useful in localizing, staging and follow-up of these tumours
- Rarely, hormone excess syndromes

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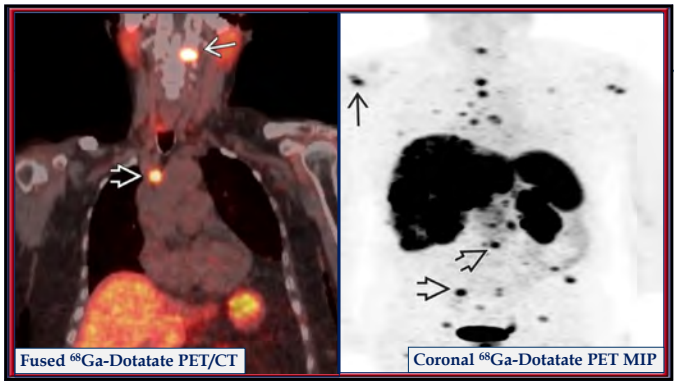

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Neuroendocrine Tumor

- Well differentiated epithelial neoplasms arranged in cords, trabecula or small nests
- Neuroendocrine cells with ample granular pale acidophilic cytoplasm and relatively monotonous nuclei
- Typical "salt-and-pepper" nuclear appearance
- Grade 1 NETs lack necrosis and have <2 mitoses/2 mm^2
- Grade 2 NETs exhibit necrosis and/or 2-10 mitoses/2 mm^2
- Grade 3 NETs exhibit necrosis and/or >10 mitoses/2 mm^2
- Optimal Ki67 proliferation index for distinction between grades remains to be defined
- Positive: CK-pan, CK7, CAM5.2 (at least one)
  synaptophysin, chromogranin-A; transcription factors: INSM1
  ± serotonin, calcitonin, m-CEA, TTF1
  Intact p53 and Rb (lost/aberrant in ScNEC)
- Ki67 should be used to avoid overdiagnosis

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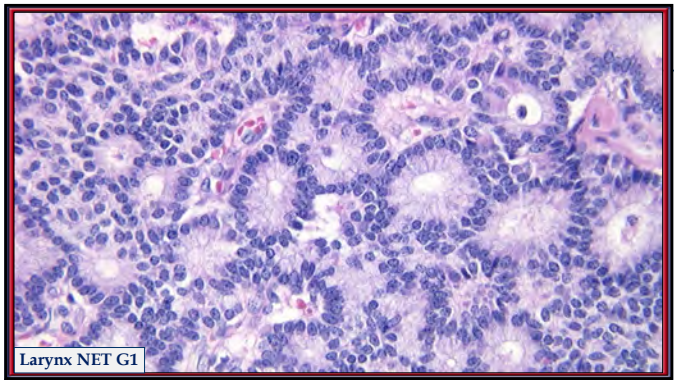

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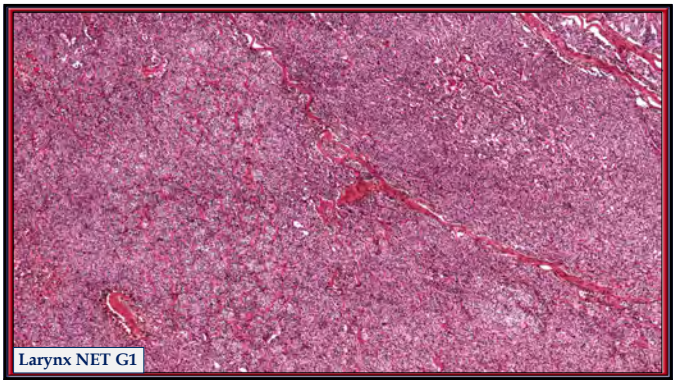

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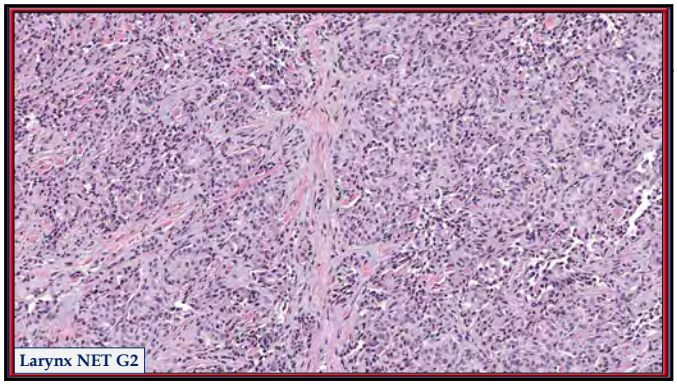

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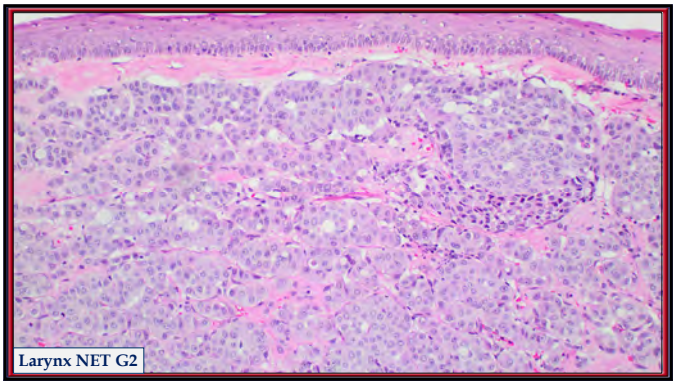

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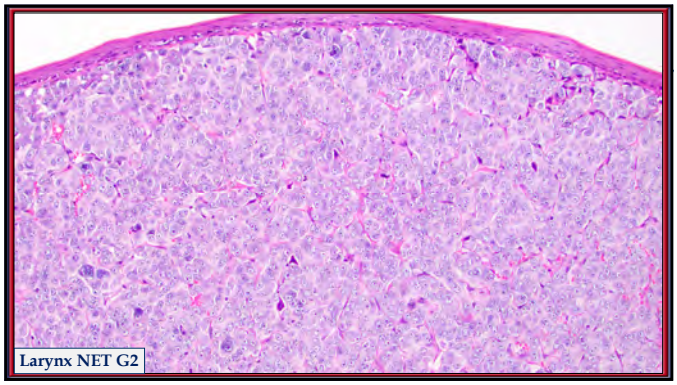

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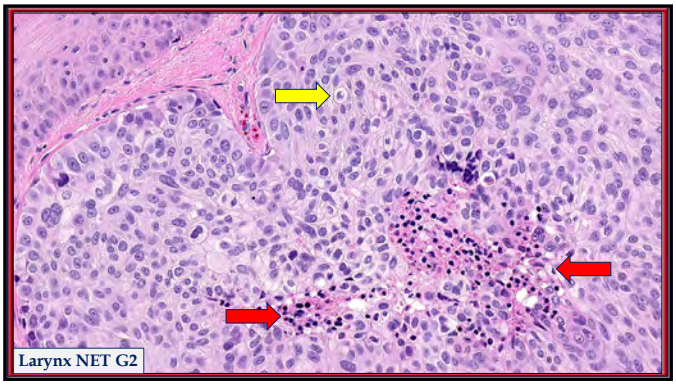

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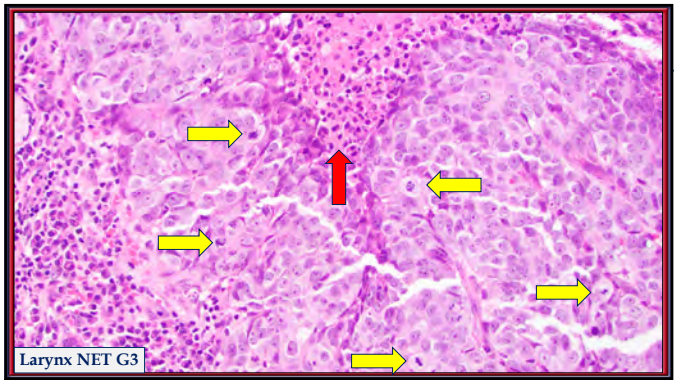

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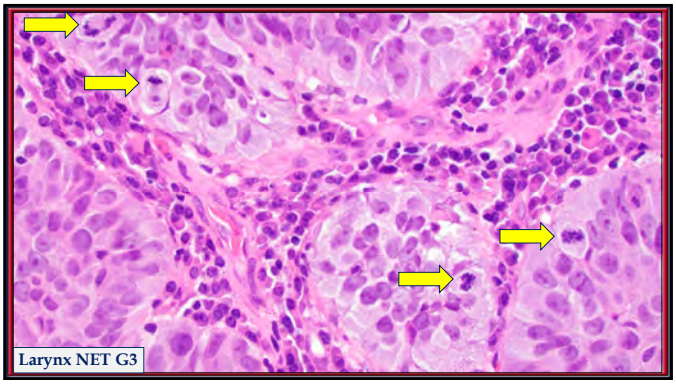

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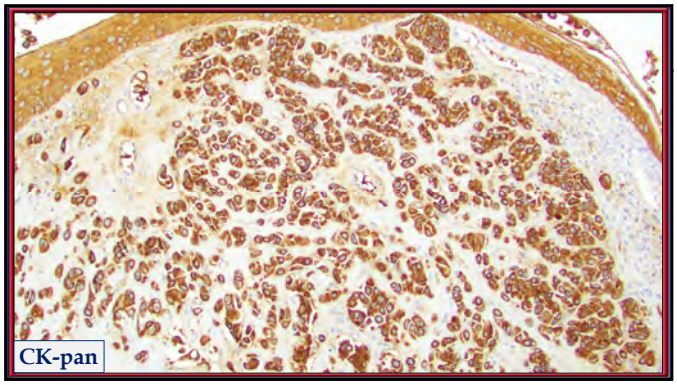

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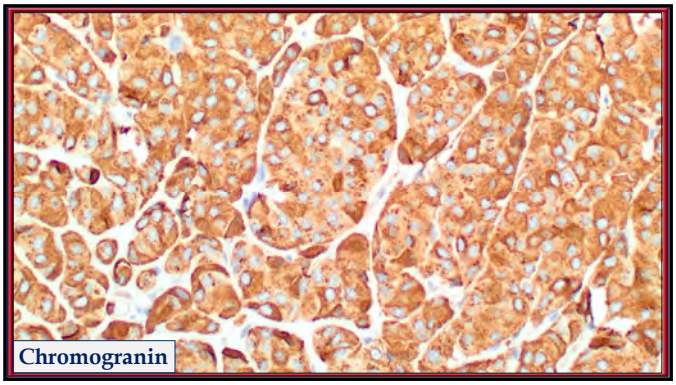

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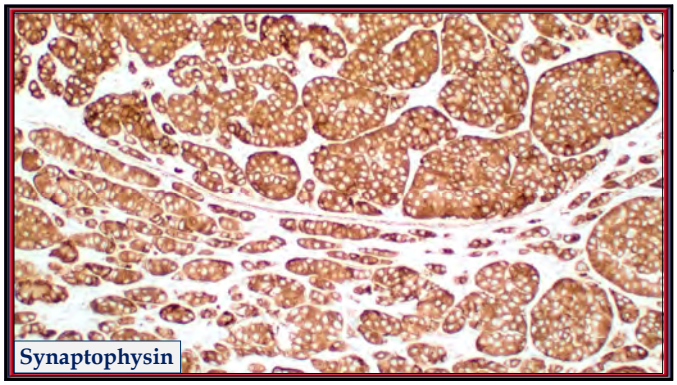

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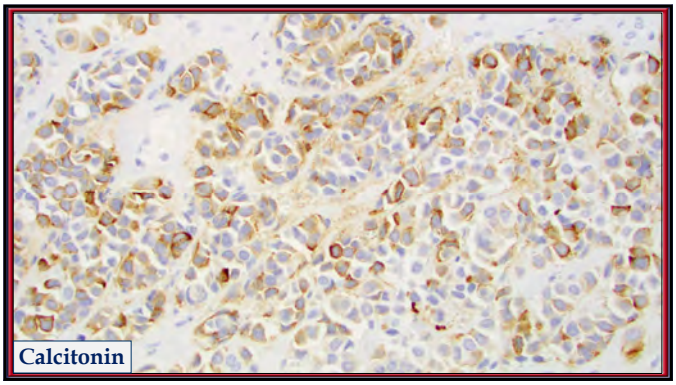

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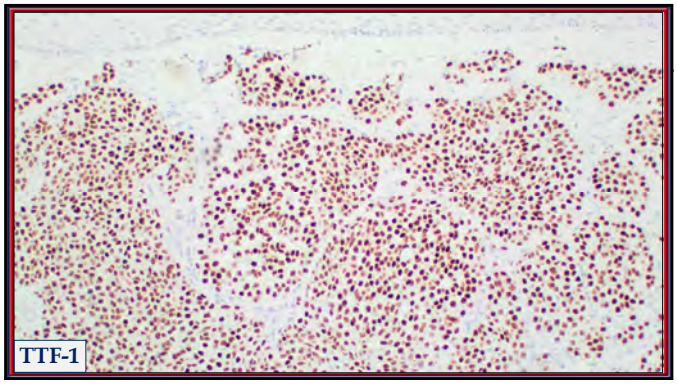

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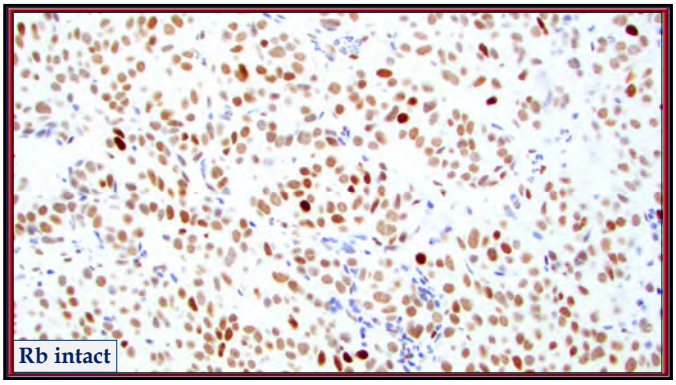

114

Small Cell Neuroendocrine Carcinoma

Small cell neuroendocrine carcinoma is a poorly differentiated (high-grade) neuroendocrine carcinoma composed of epithelial cells with scant cytoplasm, hyperchromatic nuclei, finely granular chromatin, inconspicuous nucleoli, high mitotic count, and frequent necrosis

- **Site:** Majority (60%) of H&N SCNEC arise in the larynx
  - 35% occur in sinonasal tract
- **Associations**
  - Laryngeal tumors strongly associated with tobacco use
  - Oropharyngeal tumors are positive for high-risk HPV (smoking also common)

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Small Cell Neuroendocrine Carcinoma

- **Histology:**
  - Neuroendocrine features must predominate histologically
  - Sheets and nests, with occasional trabeculae, peripheral palisading, or rosettes
  - Smaller than diameter of three lymphocytes
  - Scant cytoplasm and indistinct cellular borders
  - Large hyperchromatic nuclei, finely granular to stippled chromatin, and absent or inconspicuous nucleoli with frequent nuclear molding
  - Mitotic count is >10 mitoses/2 mm^2
  - Numerous apoptotic bodies and necrosis
  - Crush artifact with extravasated DNA coating blood vessels (Azzopardi phenomenon)
  - Site dependent combination with another tumor (usually SCC)

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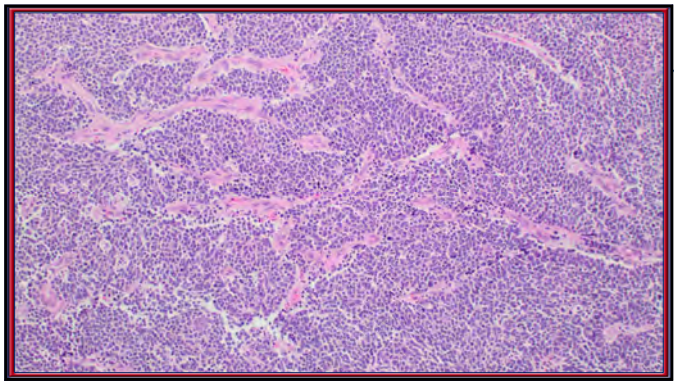

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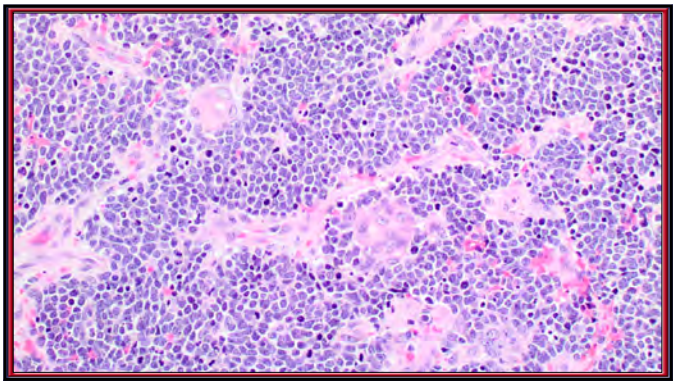

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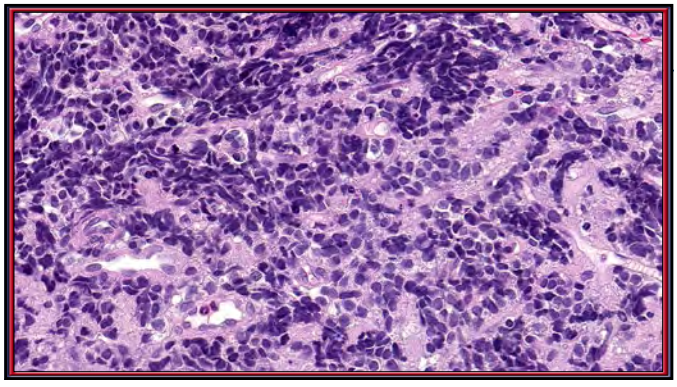

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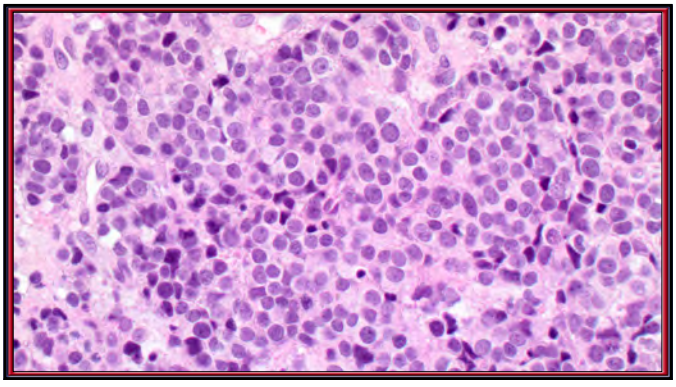

120

Small Cell Neuroendocrine Carcinoma

- Positive:
  - CK-pan, CAM5.2, EMA (perinuclear dot-like)
  - Synaptophysin, chromogranin-A (first generation); INSM1 (sensitive)
  - TTF1 may be positive
  - Abnormal p53 expression
  - Global Rb loss
  - p16 is often overexpressed regardless of HPV status
- Ki67 for grading of H&N SCNEC is not well-established
  - Index of >20% (usually >70%) seems appropriate

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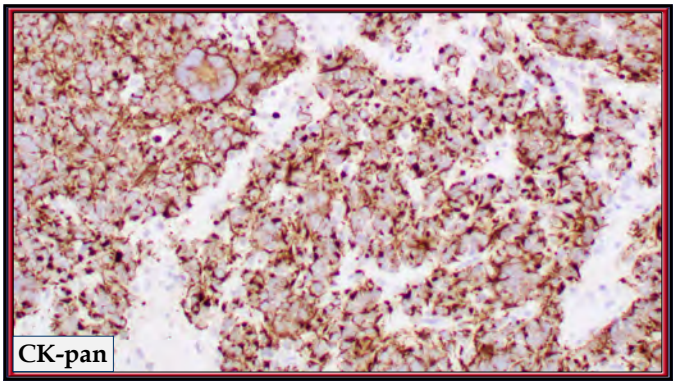

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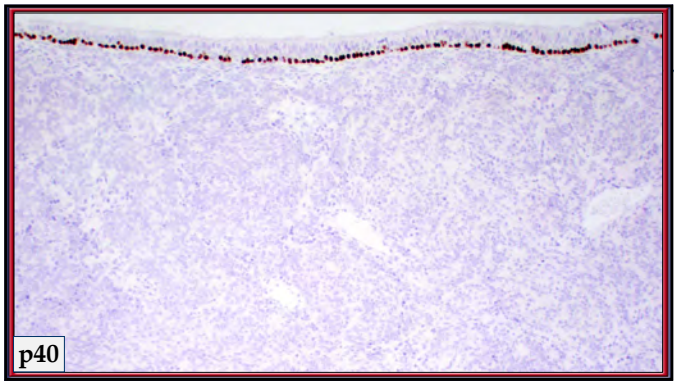

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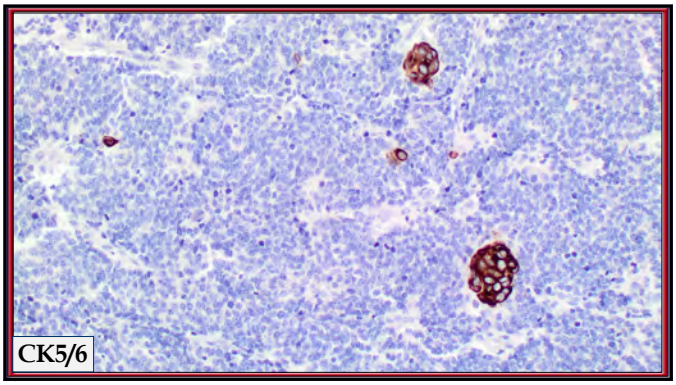

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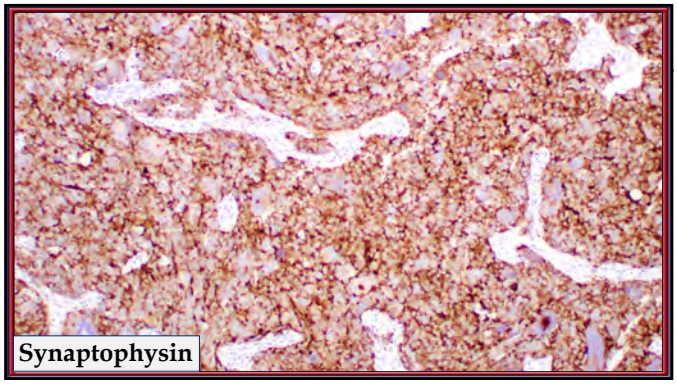

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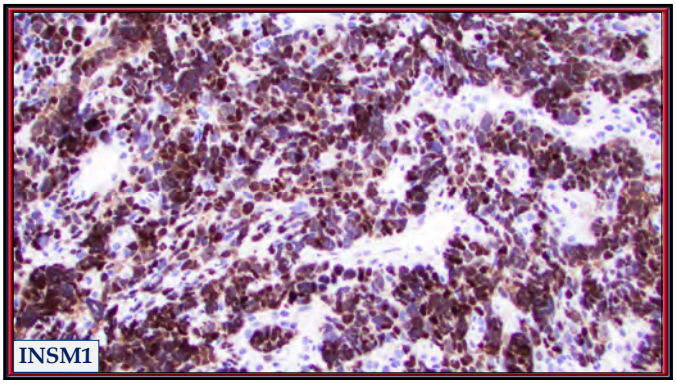

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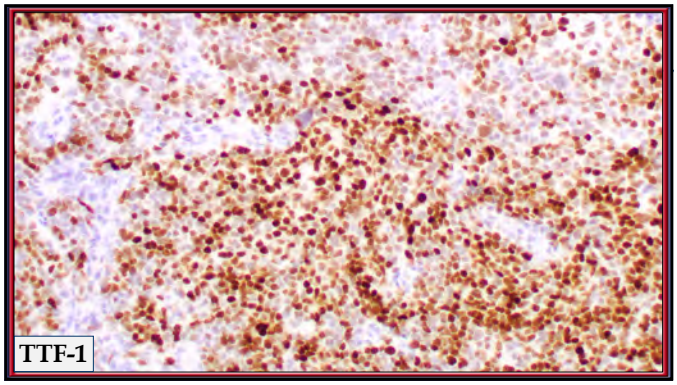

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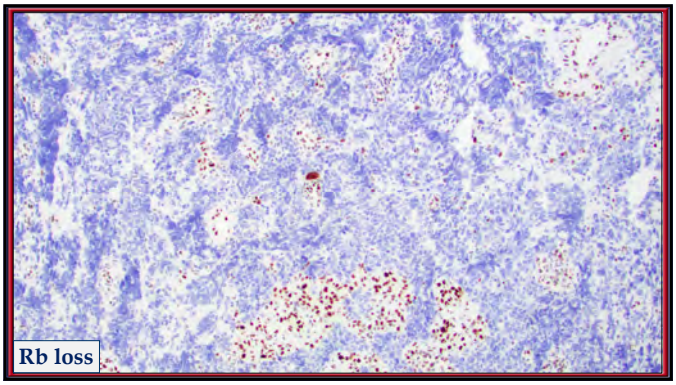

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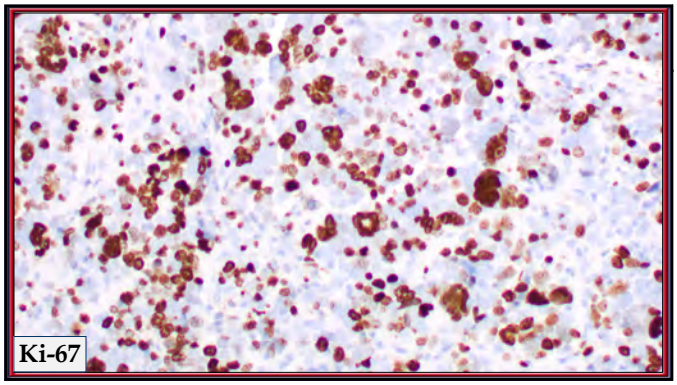

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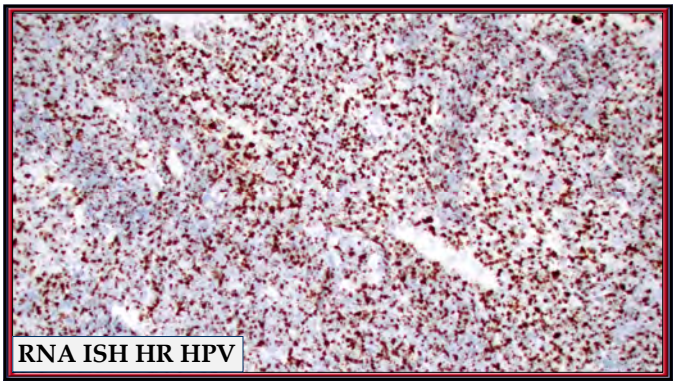

130

Immunohistochemistry Profile

	CK	p40	Syn	INI1	Des	CD99	S100	CD45	Other
Mucosal Melanoma	N	N	N	I	N	R	P	N	SOX10, HMB45, Melan-A
Rhabdomyosarcoma	S	N	S	I	P	R	R	N	Myogenin, MYOD1, SMA
Teratocarcinosarcoma	P	P	P	I	P	P	P	N	*SMARCA4* loss
SNUC	P	-/F	-/F	I	N	N	N	N	- CK5/6, p63; *IDH1/2* mut.
SMARCB1-Deficient Ca	P	±	±	L	N	N	N	N	+CD56
NUT carcinoma	P	P	N	I	N	N	N	N	+NUT; ±CD34
Lymphoid (NK-T and Plasmacytoma)	N	N	N	I	N	N	N	P	EBER; CD3; CD56, TIA-1, ±p63
Esthesioneuroblastoma (Olfactory Neuroblastoma)	R	N	P	I	R	N	P (S)	N	+Calretinin
Neuroendocrine Carcinoma	P (D)	N	P	I	N	N	N	N	+ TTF-1, INSM1, p16
Ewing Sarcoma or Adamantinoma-like ES	S	N/P	S	I	-/F	P	N	N	NKX2.2 strong; **ALES**: p40
PitNET	P	N	P	I	N	R	-/F	N	Prolactin; Pit1, SF1

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Large Cell Neuroendocrine Carcinoma

A poorly differentiated neuroendocrine carcinoma composed of cells with abundant eosinophilic cytoplasm, vesicular chromatin and prominent nucleoli

- Site: larynx, oropharynx, and sinonasal tract
- Loss of Rb and p53 overexpression
- In SNT, *IDH2* mutations may be seen
- *SMARCA4* loss defines SWI/SNF complex-deficient sinonasal carcinoma and would not be NEC

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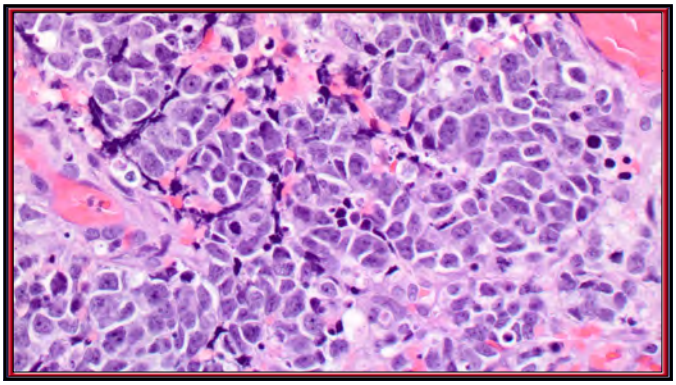
Large Cell Neuroendocrine Carcinoma

- Histology:
  - Nested, organoid, or trabecular growth
  - Frequent peripheral palisading, and rosette formation
  - Central, comedo-pattern necrosis.
  - Larger than the diameter of 3 lymphocytes and have abundant eosinophilic cytoplasm
  - Nuclei have coarse to speckled chromatin, often with a single prominent nucleolus
  - Mitotic rate: >10 mitoses/2 mm^2 (usually much higher)
- Positive:
  - Cytokeratin, CAM5.2
  - Synaptophysin, chromogranin-A (dot-like), INSM1
  - p53 overexpression
  - p16 (regardless of HPV status)
  - TTF1 in minority of cases
- Negative: Rb (global loss)
- Ki67 for grading is not well-established for ENT tumors
  - >20%, and often >50% common

133



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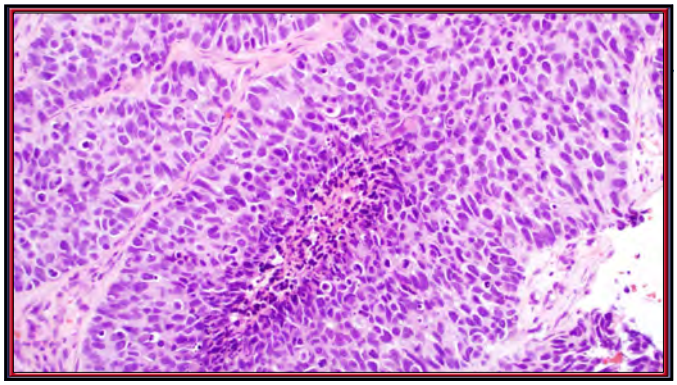

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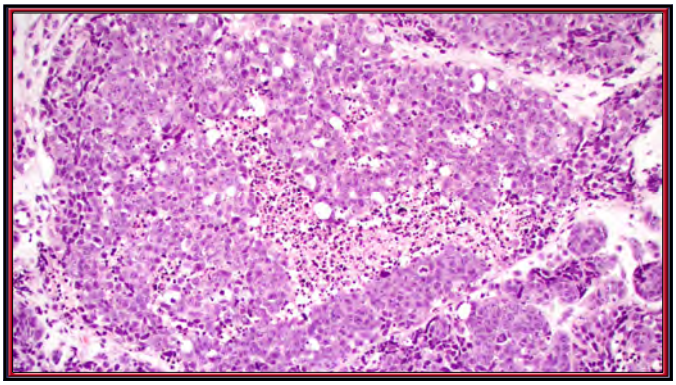

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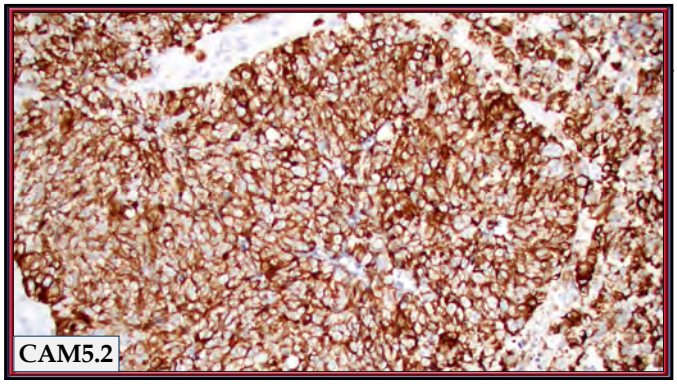

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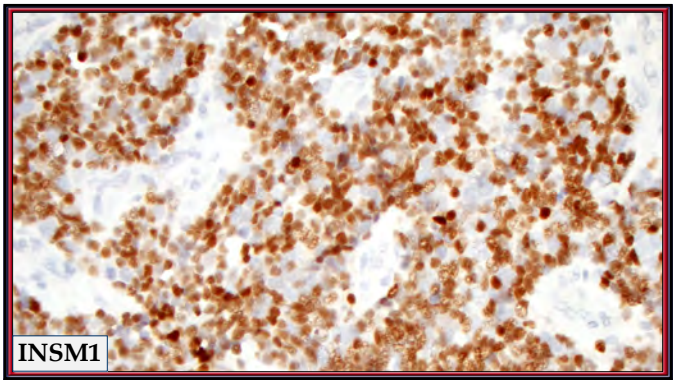

138

Sphenoid Sinus
Pituitary Neuroendocrine Tumor (PitNET)

Benign anterior pituitary gland neoplasm arising from remnants of Rathke pouch without involving the sella turcica

- Direct extension from intrasellar pituitary tumors in about 2% should be excluded

- Incidence: ~3% of sphenoid sinus tumors
- Age: Wide range: 2 – 84 years Mean: 54 years
- Sex: Female > Male (1.3:1)
- Symptoms: Obstruction, sinusitis, rhinorrhea, discharge, headache, pain, visual disturbances, endocrine syndrome

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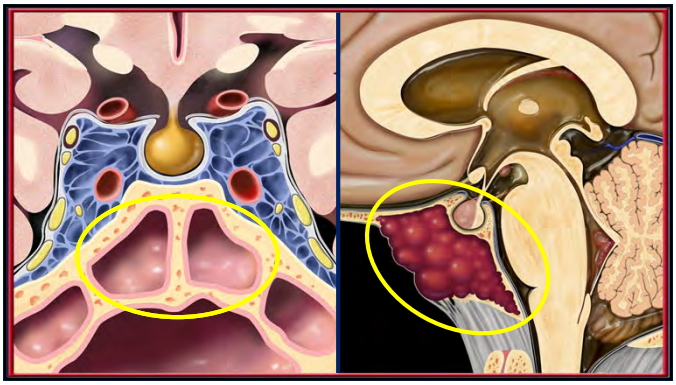

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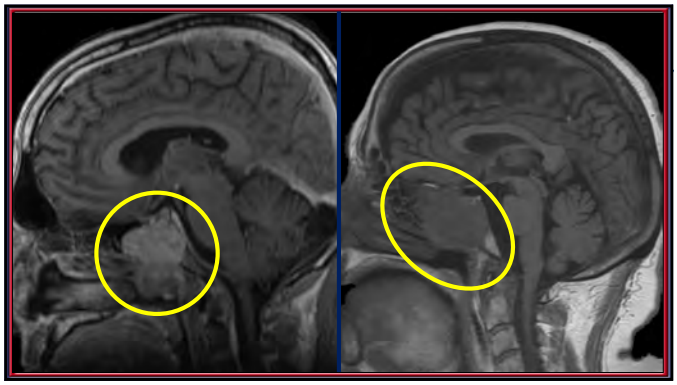

141

Pituitary Neuroendocrine Tumor (PitNET)
Pathology Findings

- Sphenoid sinus mass with bone erosion
- Size: Range: 0.5 to 8.0 cm (mean, 3 cm)
- Intact surface epithelium, unencapsulated tumor
- Many patterns
  - Solid, organoid, glandular, insular, festoons, ribbons, single file, rosettes—pseudorosettes, papillary, cystic
- Epithelial cells
  - Polygonal, plasmacytoid, cuboidal, spindled, round or oval nuclei with "salt-and-pepper," clumped chromatin, small nucleoli, intranuclear inclusions and variable cytoplasm
- Necrosis (up to 25% of cases); pleomorphism
- No perineural or lymphovascular invasion
- No atypical mitoses
- Surgery or medical therapy (such as: bromocriptine)

142

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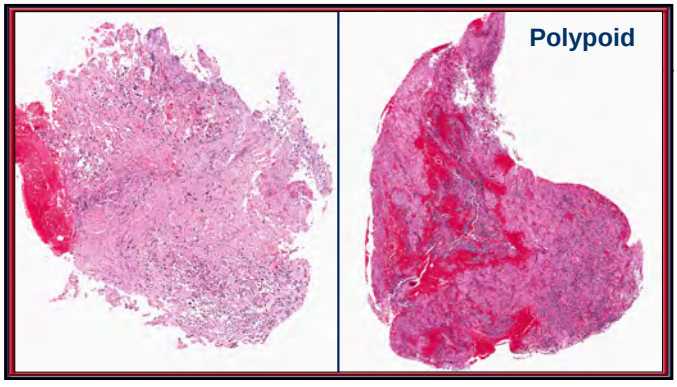

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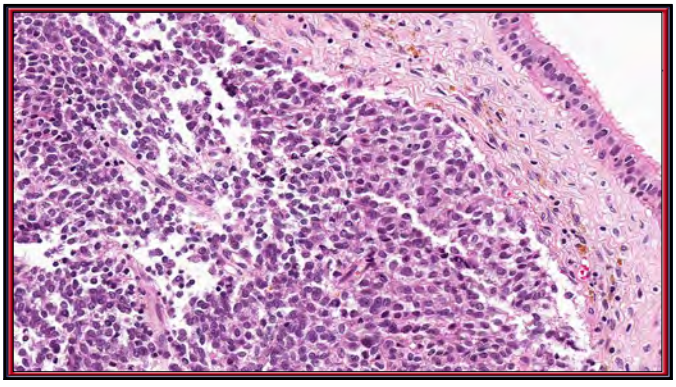

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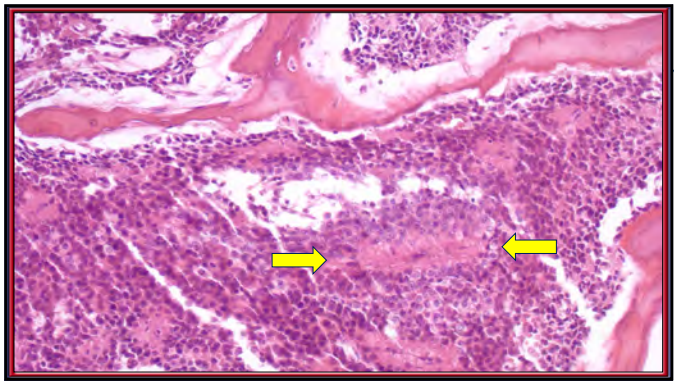

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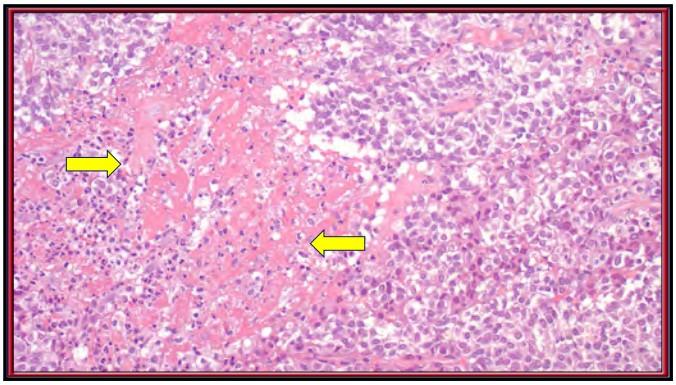

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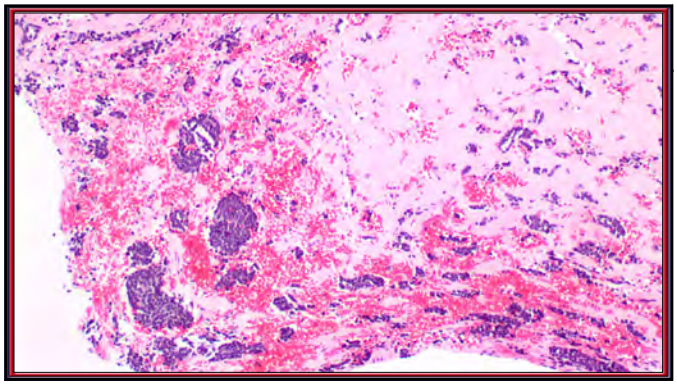

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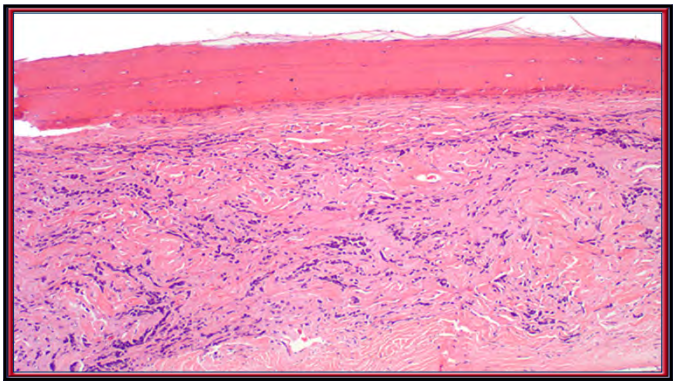

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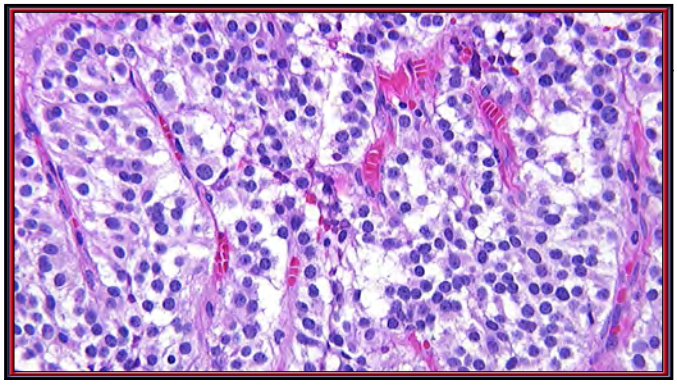

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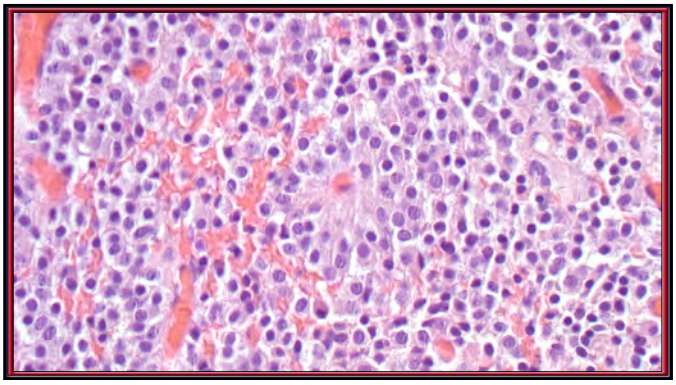

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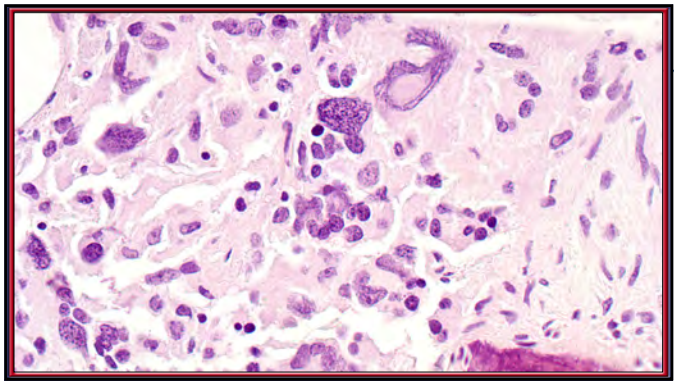

151

Immunohistochemistry Profile

	CK	p40	Syn	INI1	Des	CD99	S100	CD45	Other
Mucosal Melanoma	N	N	N	I	N	R	P	N	SOX10, HMB45, Melan-A
Rhabdomyosarcoma	S	N	S	I	P	R	R	N	Myogenin, MYOD1, SMA
Teratocarcinosarcoma	P	P	P	I	P	P	P	N	*SMARCA4* loss
SNUC	P	-/F	-/F	I	N	N	N	N	- CK5/6, p63; *IDH2* mut.
SMARCB1-Deficient Ca	P	±	±	L	N	N	N	N	+CD56
NUT carcinoma	P	P	N	I	N	N	N	N	+NUT; ±CD34
Lymphoid (NK-T and Plasmacytoma)	N	N	N	I	N	N	N	P	EBER; CD3; CD56, TIA-1, ±p63
Esthesioneuroblastoma (Olfactory Neuroblastoma)	R	N	P	I	R	N	P (S)	N	+Calretinin
Neuroendocrine Carcinoma	P (D)	-/F	P	I	N	N	N	N	+ TTF-1, INSM1, p16
Ewing Sarcoma or Adamantinoma-like ES	S	N/P	S	I	-/F	P	N	N	NKX2.2 strong; **ALES**: p40
PitNET	P	N	P	I	N	R	-/F	N	PIT1, SF1, TPIT; Prolactin

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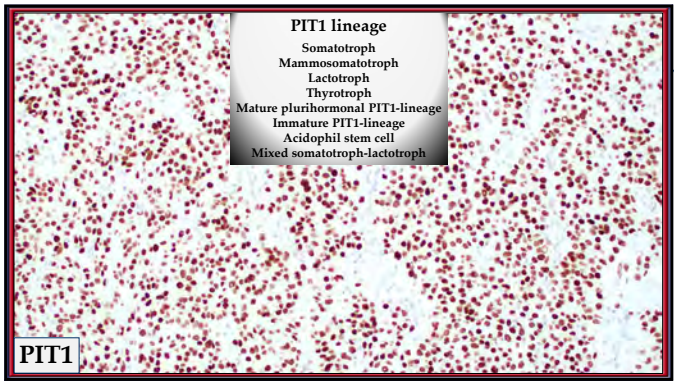

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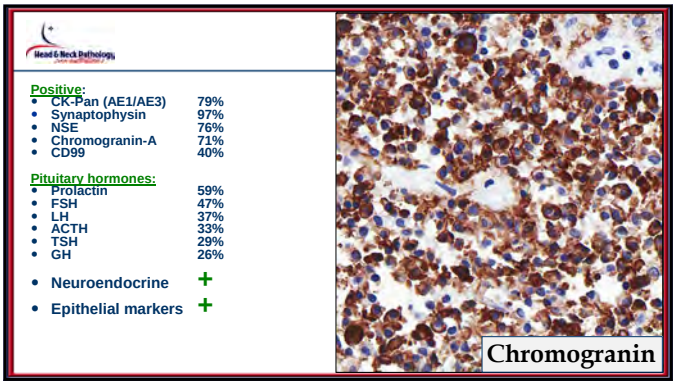

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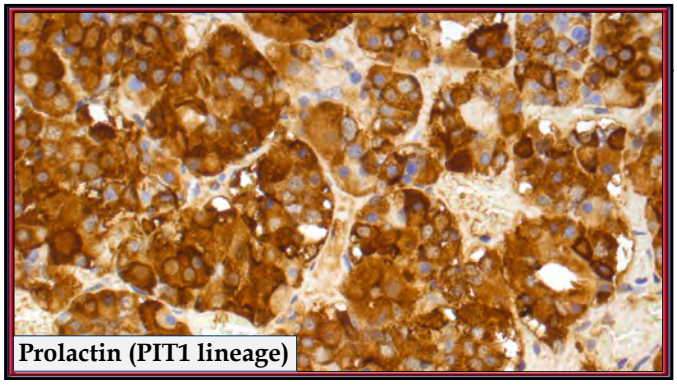

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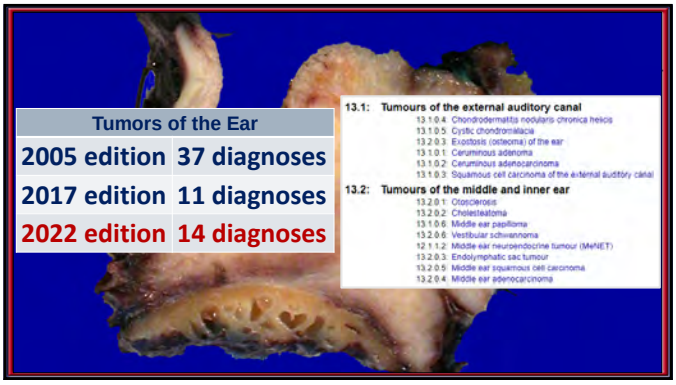

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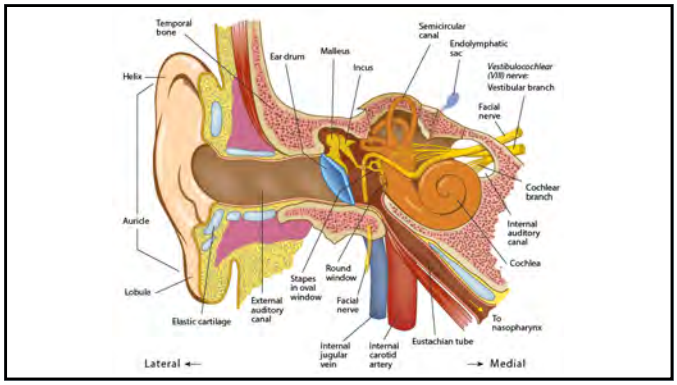

157

Middle Ear Neuroendocrine Tumor (MeNET)

Neoplasm arising from the middle ear mucosa with epithelial and neuroendocrine differentiation.

- Neuroendocrine Adenoma of the Middle Ear (NAME)
- Middle ear adenoma (MEA)
- Middle ear adenomatous tumor (MEAT)
- Middle ear adenoma with neuroendocrine differentiation (MEA-ND)
- Carcinoid tumor (CT)
- Amphicrine tumor (APT)
- Amphicrine adenoma of the middle ear (AAME)
- Adenoma of the middle ear (AME)
- Adenocarcinoid (AC)
- Adenomatoid tumor of middle ear (ATME)
- Adenomatous tumor of the middle ear (ATME)
- Neuroendocrine tumor of middle ear (NETME)
- Mixed epithelial neuroendocrine tumor of the middle ear (MENETME)

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Middle Ear Neuroendocrine Tumor (MeNET): Clinical

- Incidence: Rare (~3% of all ear neoplasms)
- Sex: Males = Females
- Age: Mean: 45 years (range: 13—80 years)
- Site: Any portion of middle ear, but often encases ossicles
  May extend into adjacent structures
- Symptoms: Unilateral conductive hearing loss,
  pressure, fullness, tinnitus, ear popping, mass,
  pain, facial nerve paralysis, dizziness, discharge
- Symptom duration: About 2 years (but up to 228 months!)
- Tan-pink soft tissue mass behind an intact tympanic membrane

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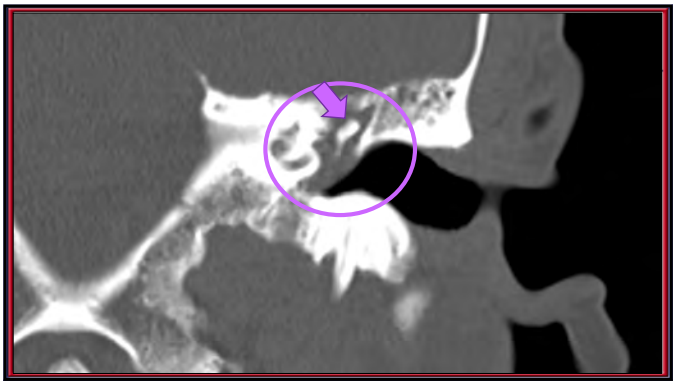

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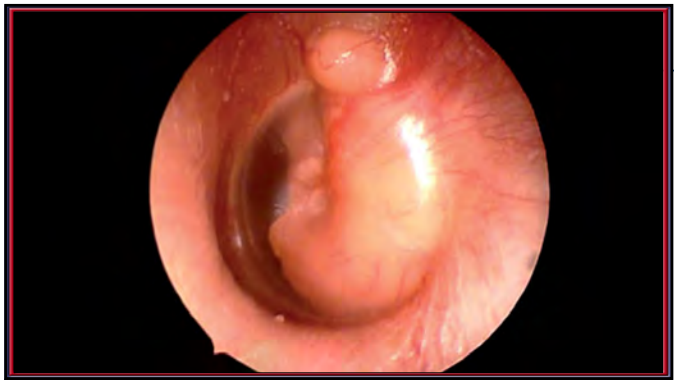

161

Middle Ear Neuroendocrine Tumor (MeNET): Clinical

- No serologic evidence of hormone production
  - ◆ No paraneoplastic syndromes (carcinoid syndrome)
  - ◆ May be due to very small size of the tumors
    - ✓ Large lung tumors are the ones that most frequently have carcinoid syndrome and have highest frequency of liver metastases
- Two exceptions: Flushing, palpitation, dizziness, diarrhea
  - ◆ But no relationship to symptoms and tumor removal
  - ◆ No biochemical analysis to support the clinical findings
    - ✓ Latif MA, et al J Layrngol Otol 1987;101:480-6
    - ✓ Azzoni C, et al, Virchows Arch 1995;426(4):411-8

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Middle Ear Neuroendocrine Tumor (MeNET): Histology

- Varied growth pattern of moderately cellular tumors
  - Nearly all tumors show more than one pattern
  - Glandular, trabecular, solid, organoid, cords, festoons, single cells
  - Duct-like structures with back to back configuration
  - Trabecular pattern shows stroma-epithelial clefting
- Positive: Keratins (AE1/AE3, Cam5.2) and neuroendocrine markers
  Synaptophysin, chromogranin, INSM1, islet-1 (ISL1), SATB2;
  Glucagon, pancreatic polypeptide, PYY, serotonin, SSTR2a
  May co-express CDX2 and GATA3
  Ki67 labelling index: majority low (<2%), but reported >20%
- NET G1, G2, and G3 seems appropriate

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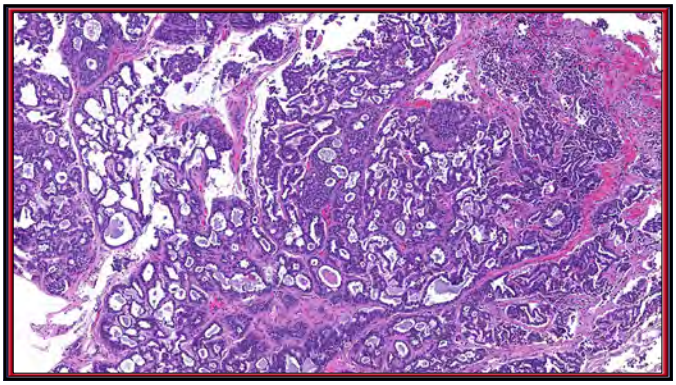

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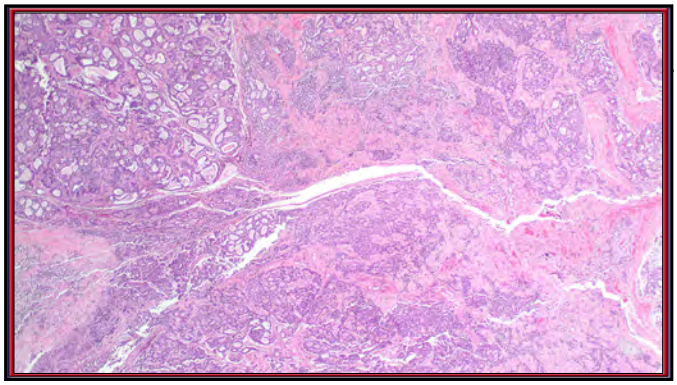

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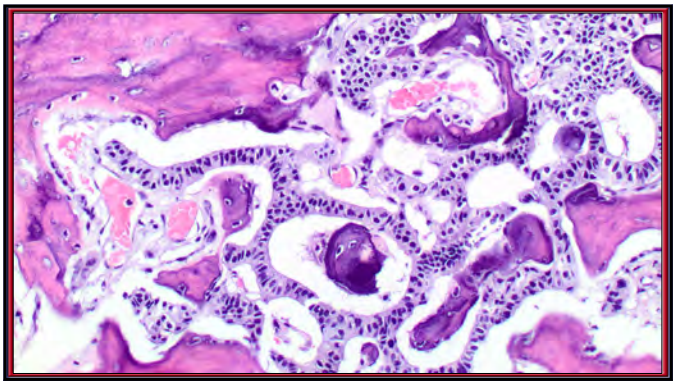

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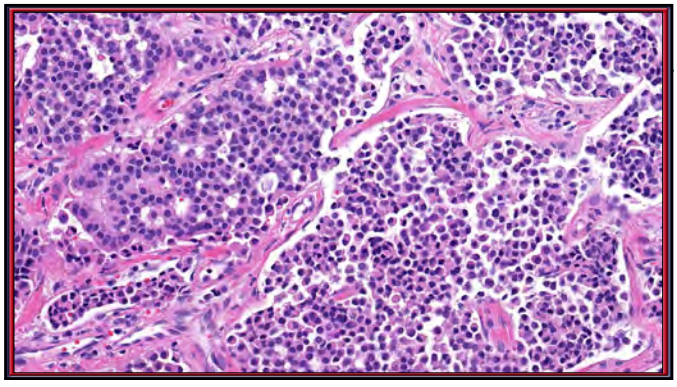

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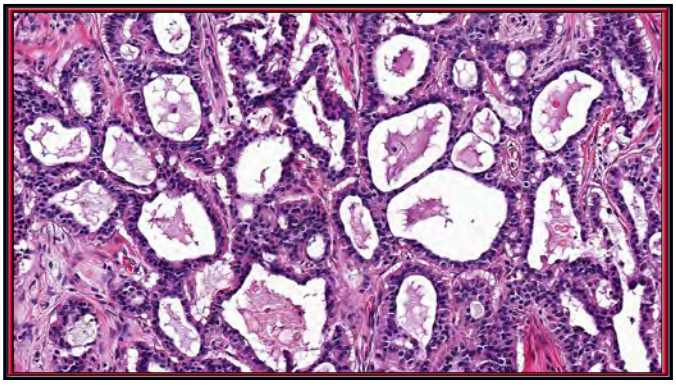

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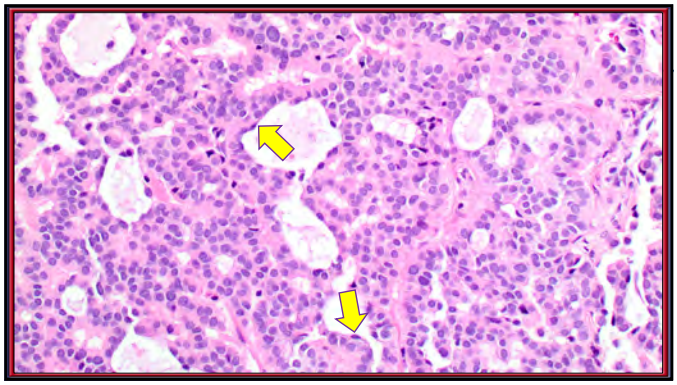

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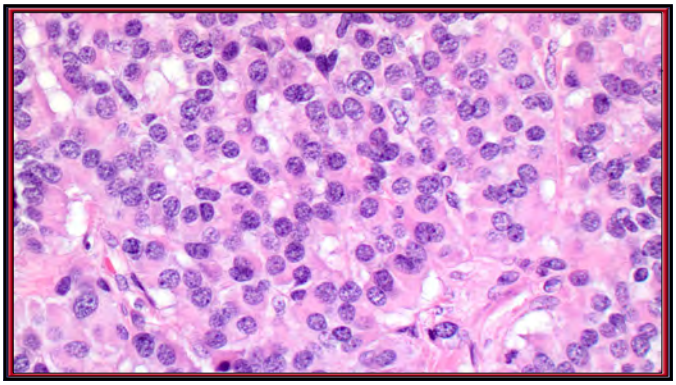

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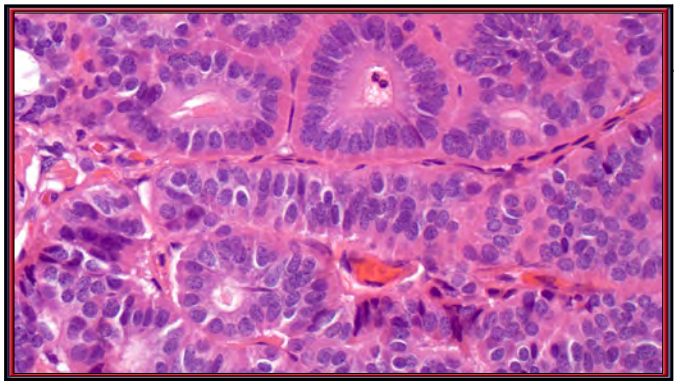

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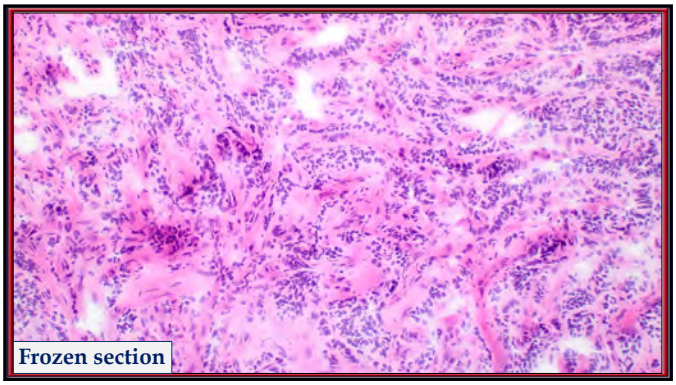

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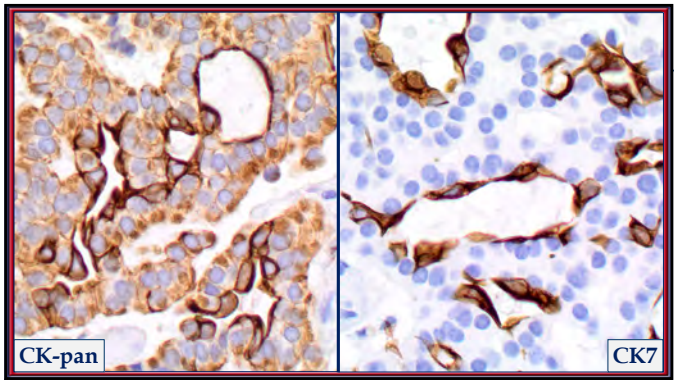

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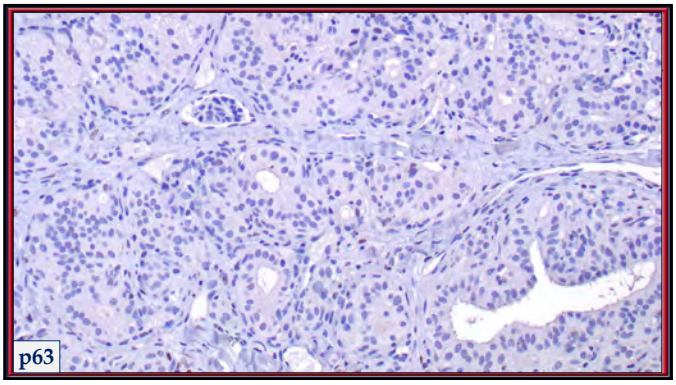

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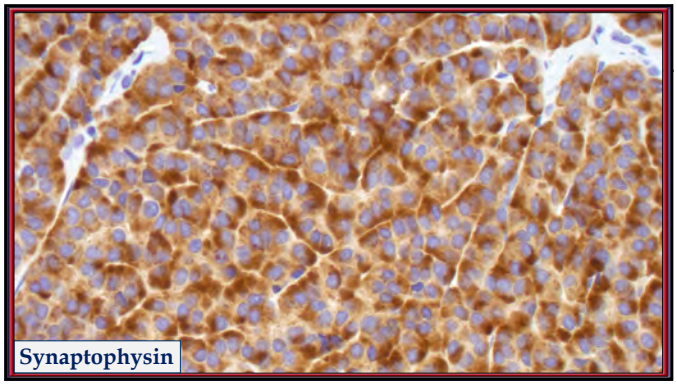

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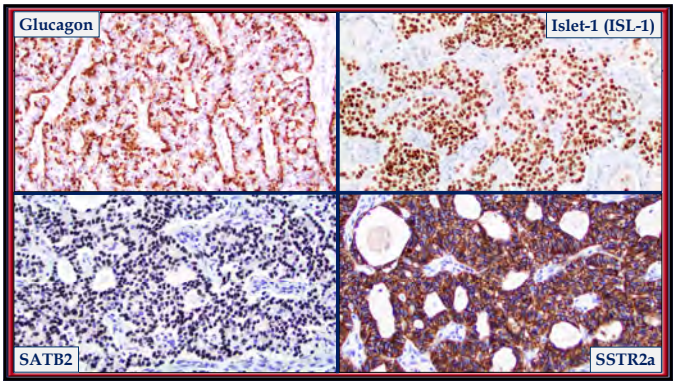

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Paragangliomas

Well differentiated non-epithelial neoplasms derived from paraganglion cells of the autonomic nervous system

- ^{68}Ga-DOTATATE PET/CT uses somatostatin receptor avidity
  - Can suggest response to somatostatin-based therapies and Peptide Receptor Radionuclide Therapy (PRRT)
- Commonly inherited: Germline mutations in *SDHD* (47%); *SDHB* (30%); *SDHC* (16%)
  - Rarely associated with mutations of *VHL*, *RET*, or *NF1*
- Histology:
  - Nested/zellballen pattern
  - Round, hyperchromatic nuclei with stippled chromatin
- Positive: Neuroendocrine markers, GATA-3, tyrosine hydroxylase, SSTR2a, dopamine β-hydroxylase; S100 protein/GFAP/SOX10 + sustentacular cells
- SDHB immunohistochemistry and/or relevant genetic evaluation to exclude hereditary risk

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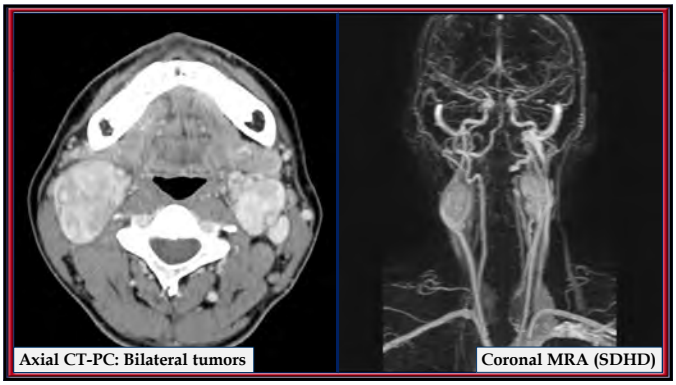

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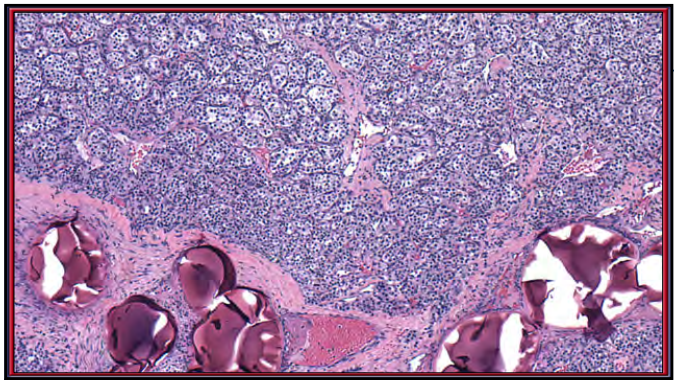

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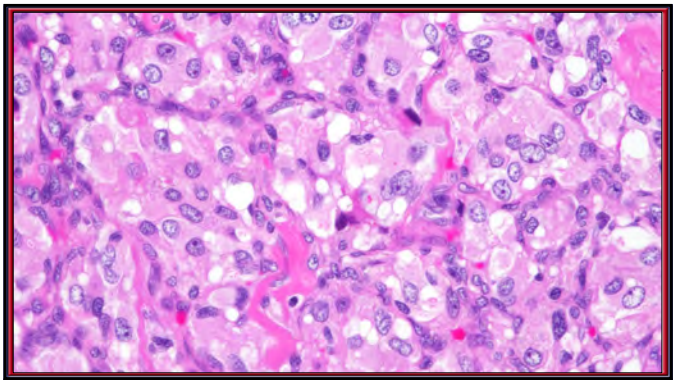

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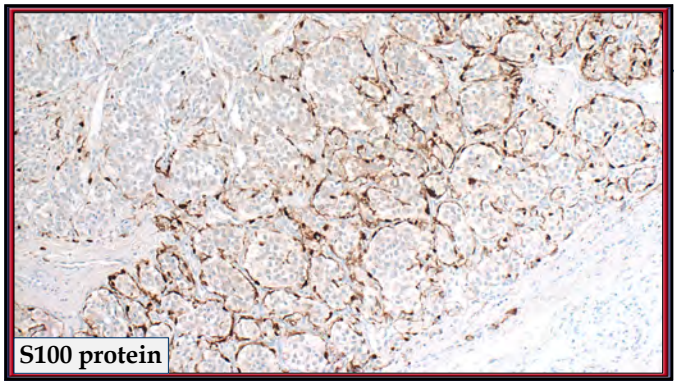

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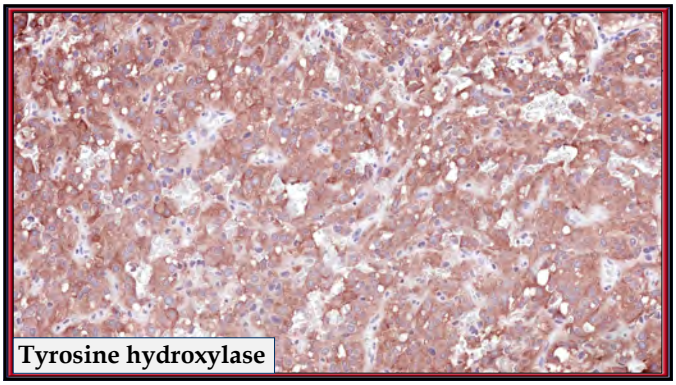

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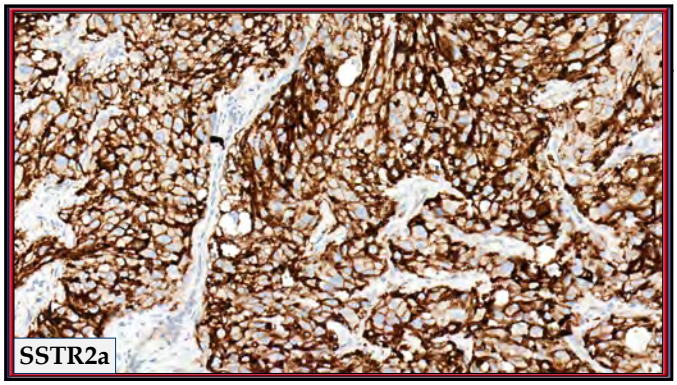

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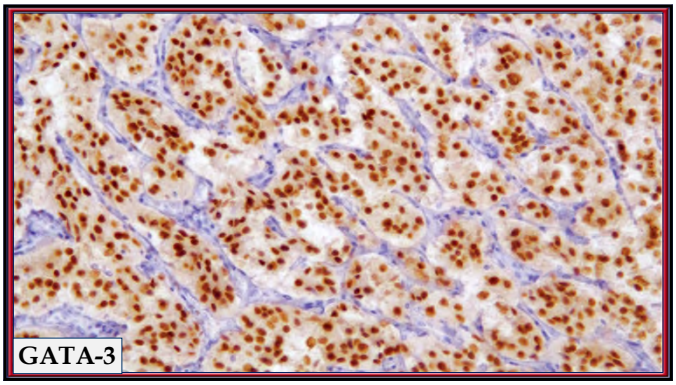

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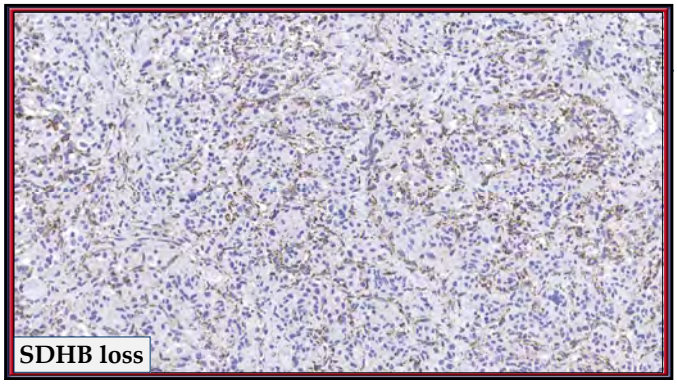

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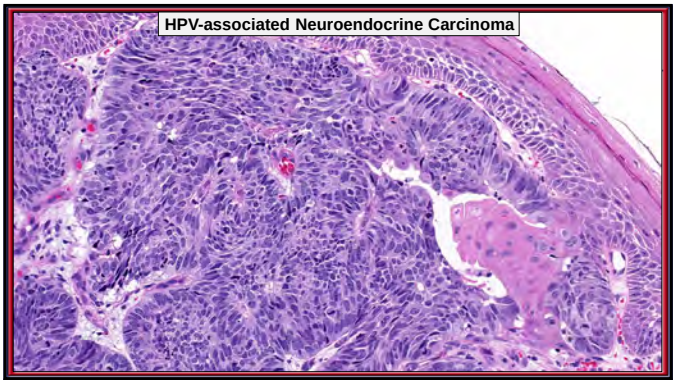

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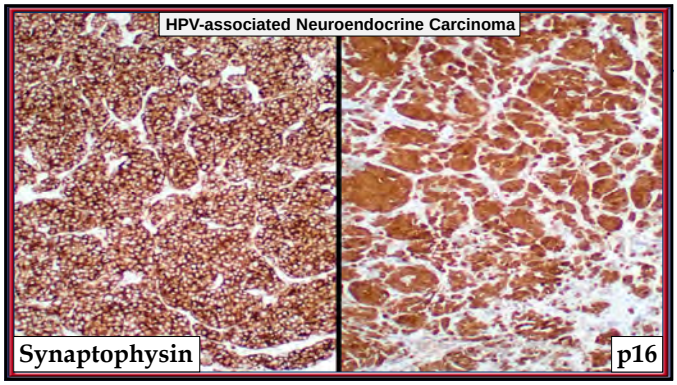

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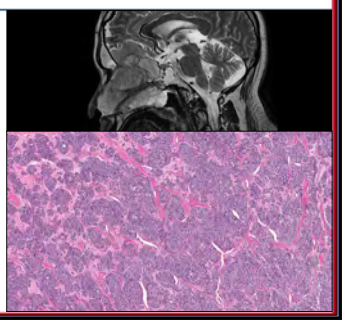
Olfactory Neuroblastoma

A malignant neuroectodermal neoplasm with neuroblastic differentiation, most often localized to the superior nasal cavity

- Age: Peak 5th – 6th decades
- Sex: Males > Females (1.2:1)
- Extends across the cribriform plate of ethmoid sinus
- Circumscribed lobules or nests of small, round, blue tumor in syncytial arrangement with neural processes
- Positive: Chromogranin, synaptophysin, INSM1;
  - Sustentacular: S100 protein, SOX10, GFAP



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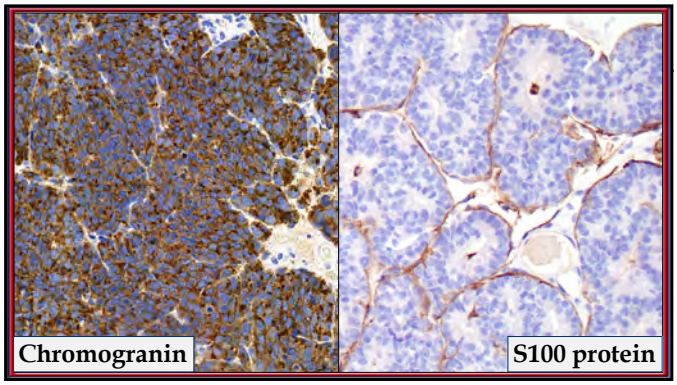

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Summary

- Look for tumor necrosis in all thyroid gland neoplasms
- Use new standardized terminology for all neuroendocrine neoplasms, including grade based on Ki-67/mitotic index
  - Neuroendocrine tumor (NET): G1, G2, G3
  - Neuroendocrine carcinoma: small cell carcinoma, large cell carcinoma, Merkel cell carcinoma and mixed epithelial-neuroendocrine carcinoma

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