Closer to Extinction of NOS: WHO Head and Neck Tumours Classification 5th Edition Update

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Disclosures

The faculty, committee members, and staff who are in position to control the content of this activity are required to disclose to learners any relevant financial relationship(s) of the individual or spouse/partner that have occurred within the last 12 months with any commercial interest(s) whose products or services are related to the CME content.

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Elsevier; Wolters Kluwer; ARP Press; Springer.

Compliance disclosure:
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

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Giving the correct names to cancers, we are ready for the mission to defeat them.

—Carl Linnaeus, *Philosophia Botanica*, 1751

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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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Sponsored by NASHNP AAOMP

Carcinomas of the Major Salivary Glands
Histopathology Reporting Guide
https://www.iccr-cancer.org/

ICCR

Family/Last name | Date of birth DD – MM – YYYY
Given name(s)
Patient identifiers | Date of request DD – MM – YYYY | Accession/Laboratory number

Elements in **black text** are CORE. Elements in grey text are NON-CORE. SCOPE OF THIS DATASET

OPERATIVE PROCEDURE (select all that apply) (Note 1)
- Not specified
- Biopsy (excisional, incisional), *specify*
- Resection, *specify*
- Neck (lymph node) dissection*, *specify*

TUMOUR FOCALITY (Note 3)
- Unifocal
- Multifocal
  - *Specify number of tumours in specimen*
- Cannot be assessed, *specify*

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Head and Neck Tumours

19 Expert Editorial Board Members (5 for 4th edition)

Justin A.	Bishop	USA	Elizabeth	Loney	UK
John	Chan	China	Ravi	Mehrotra	India
Nina	Gale	Slovenia	Ozgur	Mete	Canada
Anthony	Gill*	Australia	Susan	Muller	USA
Tim	Helliwell	UK	Vania	Nosé	USA
Martin	Hyrcza	Canada	Edward W.	Odell	UK
Joseph D.	Khoury*	USA	Alena	Skálová	Czech Republic
Alex	Lazar*	USA	Lester D. R.	Thompson*	USA
James S.	Lewis	USA	Tilak	Tilakaratne	Malaysia
			Bruce	Wenig	USA

*AG, JK, AL, & LT Standing Board members

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Overview

- 253 unique diagnostic entities
  - Subtypes (formerly called variants) included within the entity
- 288 authors
- 35 countries represented
- 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
  - 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)

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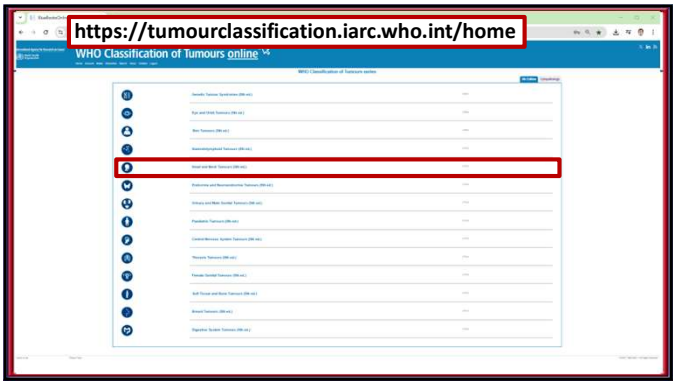

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BFF: Best Features Forever

- 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#
- Tables open in new browser window

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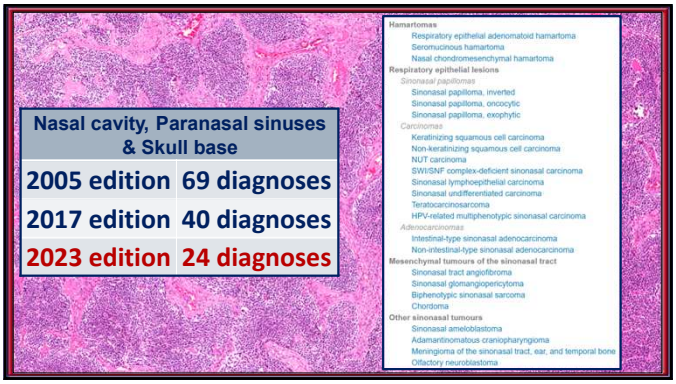

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Nasal Cavity, Paranasal Sinuses & Skull Base

- New entities (although emerging in 4th edition):
  - *SWI/SNF* complex-deficient sinonasal carcinomas
  - HPV-related multiphenotypic sinonasal carcinoma
- Emerging entities:
  - *IDH2* hotspot mutations: may develop into a separate entity (provisionally include in sinonasal undifferentiated carcinoma)
  - *DEK*::*AFF2* carcinoma (provisionally included in nonkeratinizing squamous cell carcinoma)
- Updated:
  - Teratocarcinosarcoma: recurrent inactivation of *SMARCA4* and activating mutations in *CTNNB1*
  - Sinonasal adenocarcinoma non-intestinal type: *CTNNB1* mutations and some fusions (*ETV6*::*NTRK3*) identified

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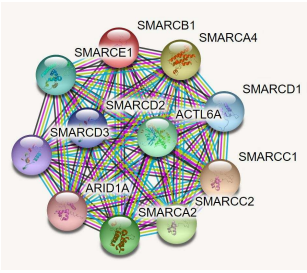
SWI/SNF complex-deficient carcinomas

SWI/SNF complex-deficient sinonasal carcinomas are poorly to undifferentiated epithelial malignancies defined by loss of one SWI/SNF complex subunit (either SMARCB1 [INI1] or SMARCA4 [BRG1]) without histologic features allowing classification into another specific entity

- *SMARCB1* (22q11.2) is most common (rare adenocarcinoma); rare *SMARCA4*-deficient carcinoma
  - SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
- Usually sole genetic driver based on specific SWI/SNF complex gene inactivation
- Biallelic inactivation of *SMARCB1* (most often)
  - Similar region to *EWSR1*: FISH may give false positive
- Age: range 19 — 89 years
  - Peak in 6th decade; *SMARCA4*: median 44 years
- Sex: slight male predominance
- Paranasal sinuses (especially ethmoid) and nasal cavity, often with orbital extension
- Present with high stage, obstruction, pain, eye symptoms
- Outcome: >50% died of disease (mean, 15 months)



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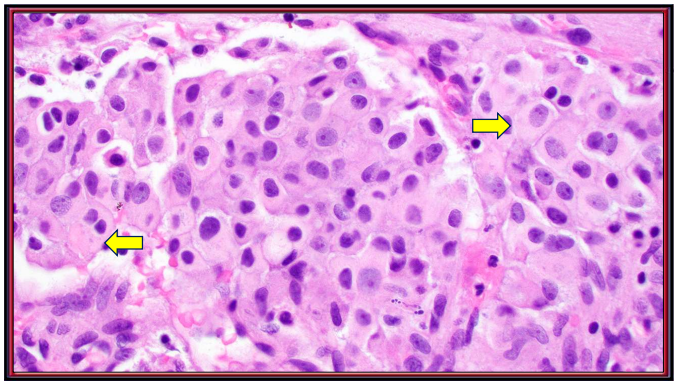

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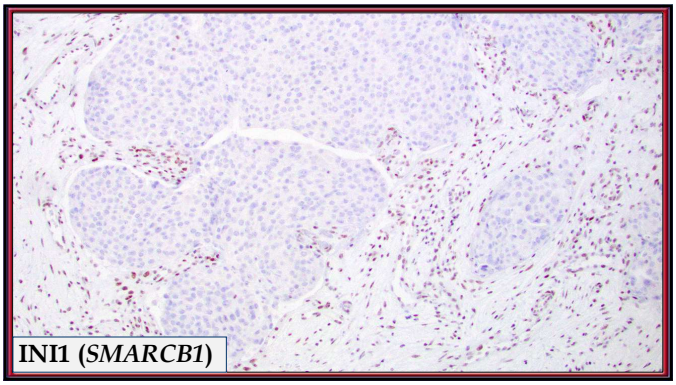

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Teratocarcinosarcoma

Complex malignant sinonasal neoplasm with immature and malignant endodermal, mesodermal, and neuroepithelial elements resembling immature teratoma

- No germ cell tumor (embryonal carcinoma, choriocarcinoma, seminoma)
- Rare
- Age: Mean: 54.5 years
- Sex: Male > > female (7:1)
- Sites: High in nasal cavity (72%)
  - Frequently involves more than 1 paranasal sinus
- Heterogeneous neoplasm with intermingled features of carcinoma, sarcoma, and immature neuroepithelial elements
- Shows loss of *SMARCA4* (BRG1)
- Multimodality therapy has mixed outcome, with high recurrence:
  - 60% dead in <3 years 40% respond, mean survival 6 years

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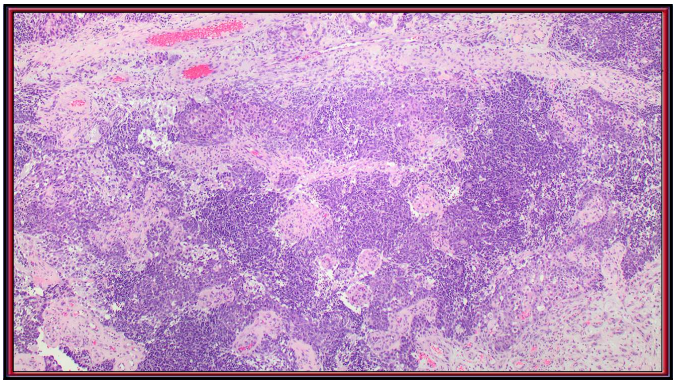

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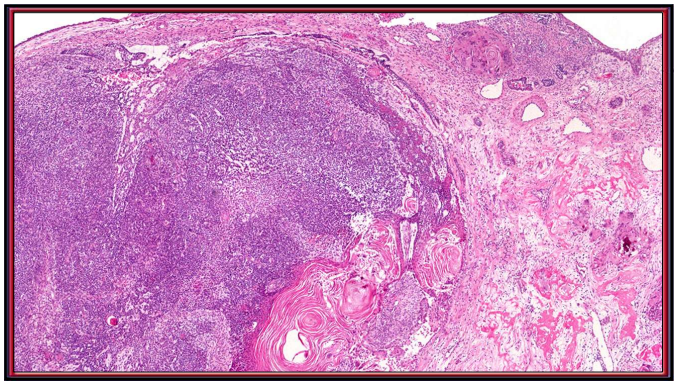

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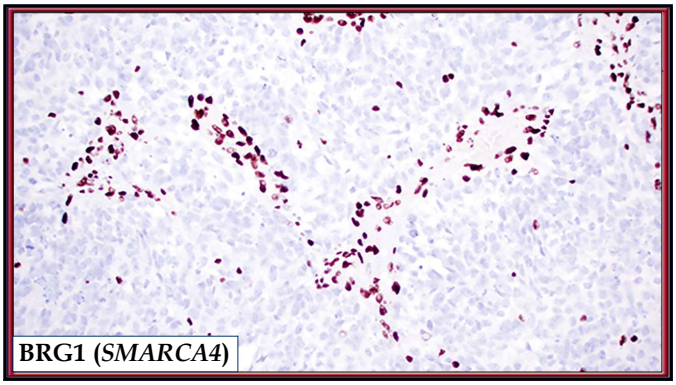

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Sinonasal Undifferentiated Carcinoma

Undifferentiated carcinoma of the sinonasal tract without glandular or squamous features and not otherwise classifiable

DIAGNOSIS OF EXCLUSION

- **Rare** 3-5% of sinonasal carcinomas
- **Age:** Older patients (mean 50-60 years)
- **Sex:** Males > Females
- **Presentation:** Rapid growth; high frequency of metastatic disease
- **Site:** Multiple sites, extensively infiltrative

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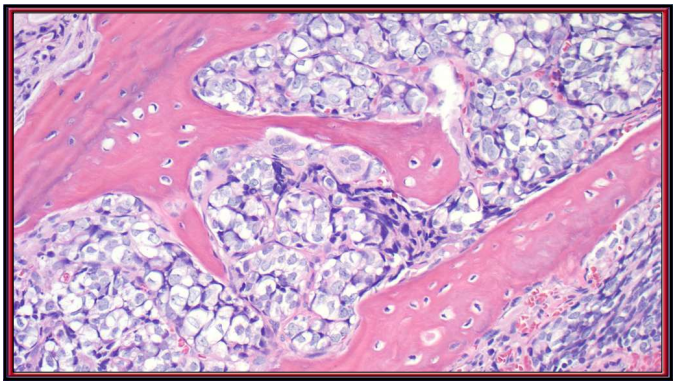

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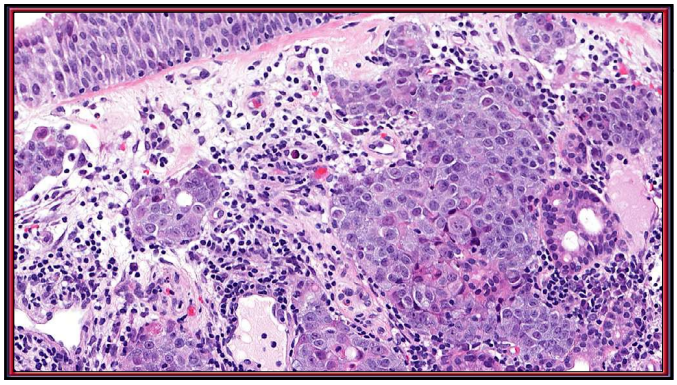

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Immunohistochemistry Profile

	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, EBER; **+IDH**
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, CD56, INSM1, p16
Ewing Sarcoma or Adamantinoma-like ES	S	N/P	S	I	-/F	P	N	N	NKX2.2 strong; **ALES**: p40
Pituitary Neuroendocrine Tumor	P	N	P	I	N	R	-/F	N	Prolactin; Pit1, SF1, TPit

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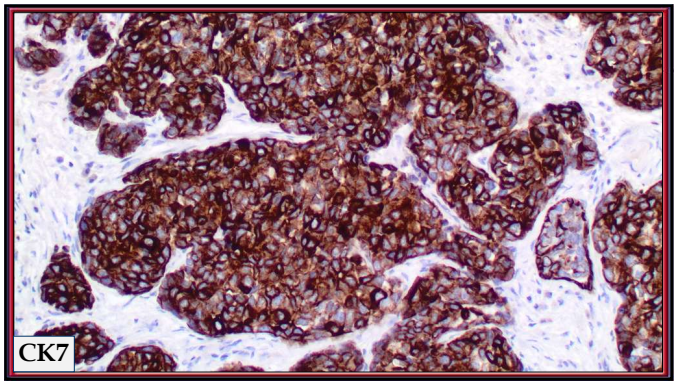

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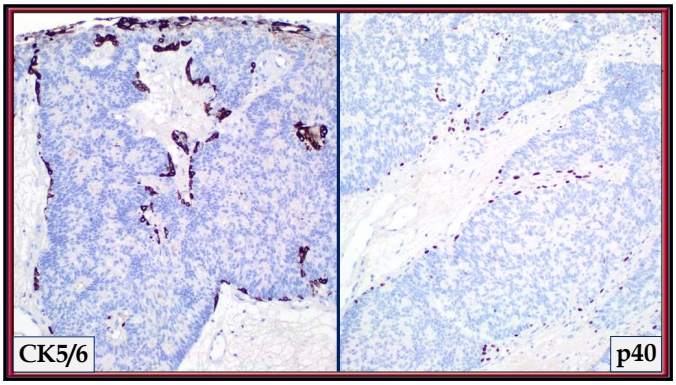

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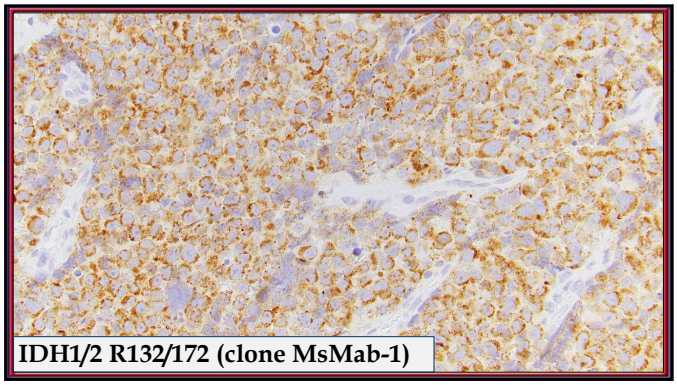

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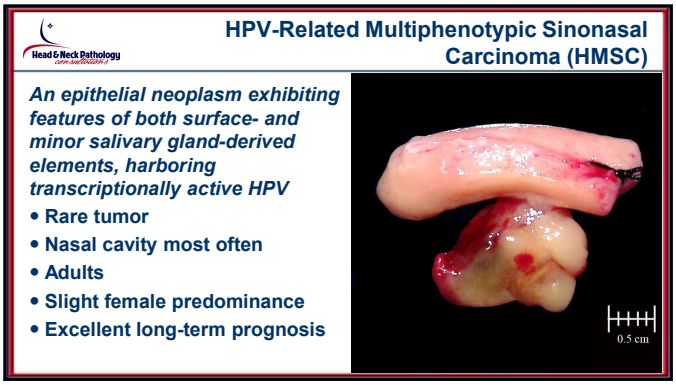

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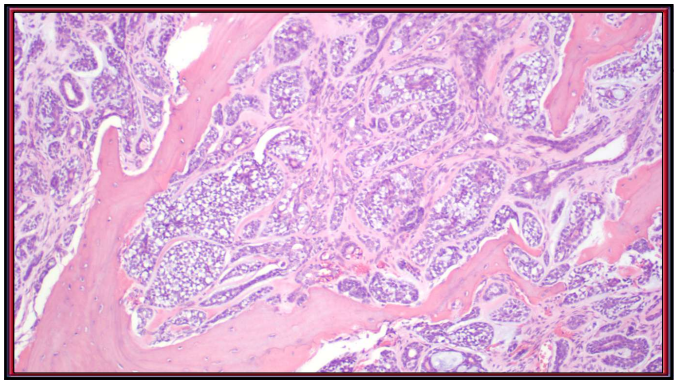

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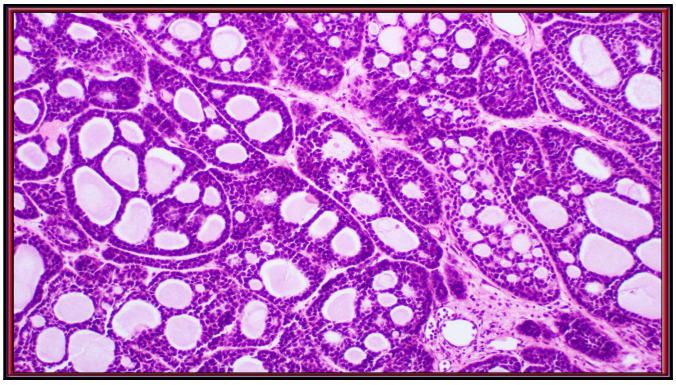

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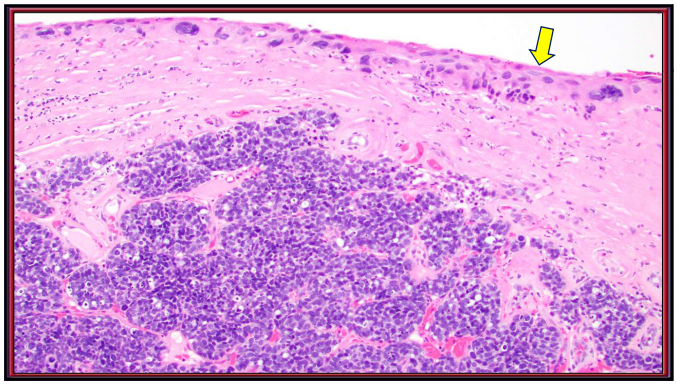

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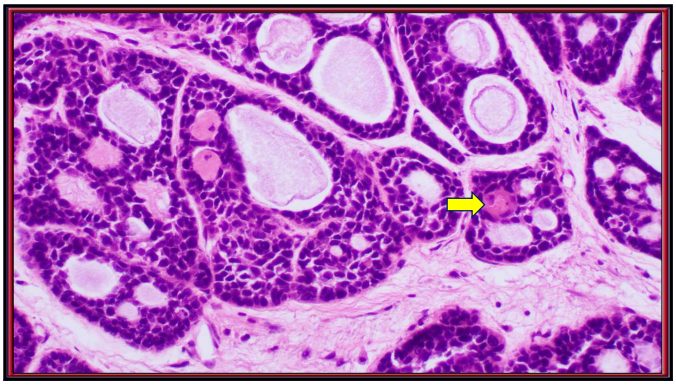

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HPV-Related Multiphenotypic Sinonasal Carcinoma (HMSC)

Immunohistochemistry

- Myoepithelial: p40, p63, SMA, calponin
- Ducts: CD117
- Both: S100 protein, SOX10
- MYB immunohistochemistry/RNA ISH positive, but there are no *MYB* rearrangements
- Strong diffuse p16; but must do HR-HPV RNA ISH (to include HPV33)

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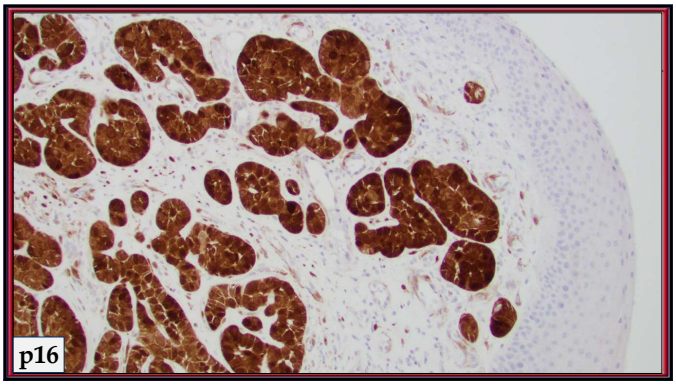

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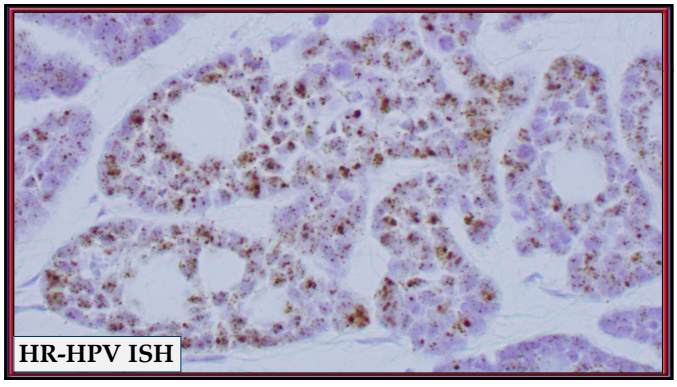

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DEK::*AFF2* Carcinoma

- Emerging category
- Often complex exophytic and endophytic growth
- Anastomosing lobules composed of monotonous tumor cells with transitional appearance
- Intraepithelial dyscohesion and tumor-infiltrating lymphocytes or neutrophils are unique and plentiful
- Requires *DEK*::*AFF2* fusion by RNA sequencing or *DEK* break-apart FISH or immunohistochemistry (recently developed to AFF2 C-terminus: nuclear +)

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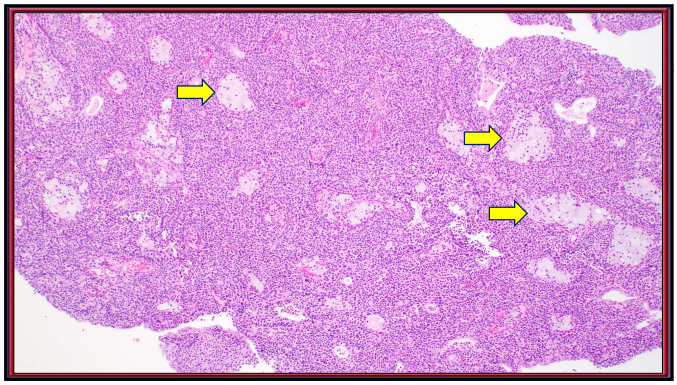

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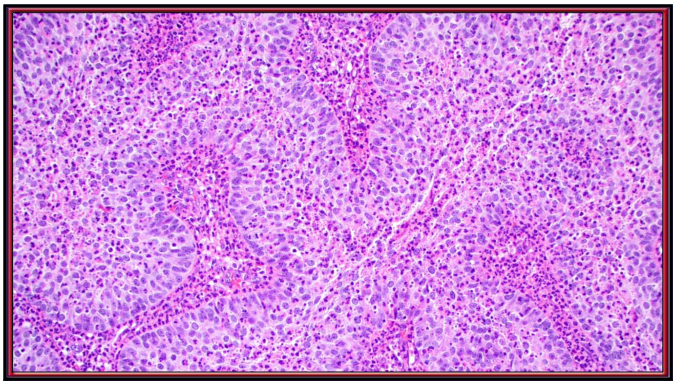

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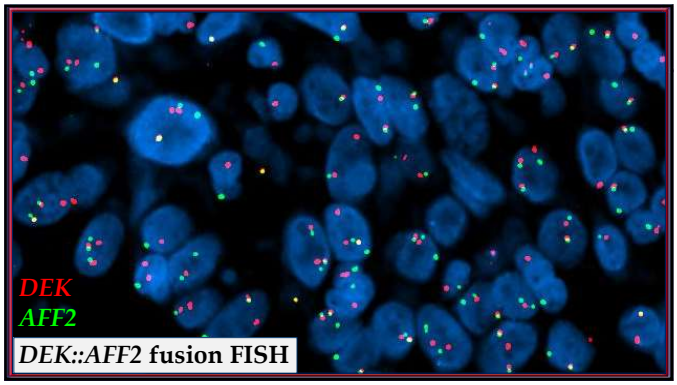

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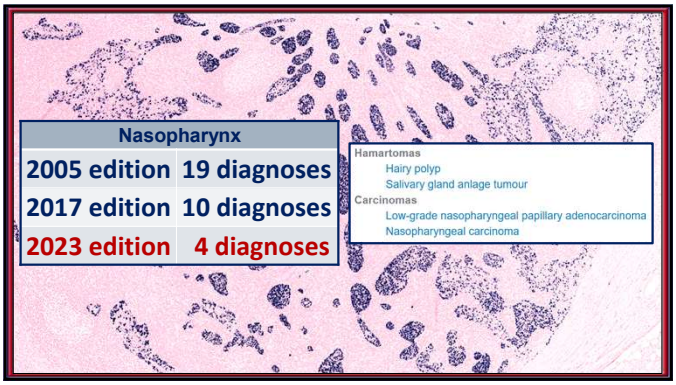

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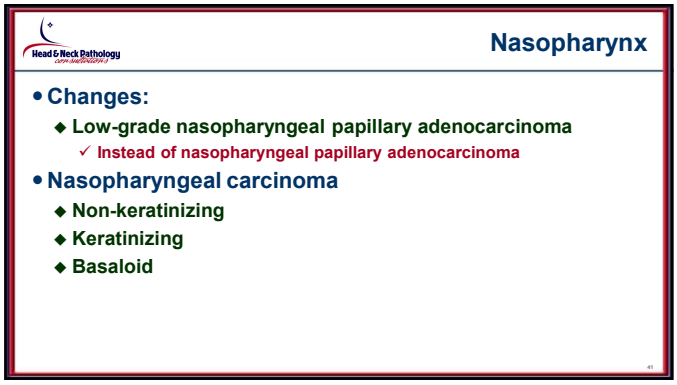

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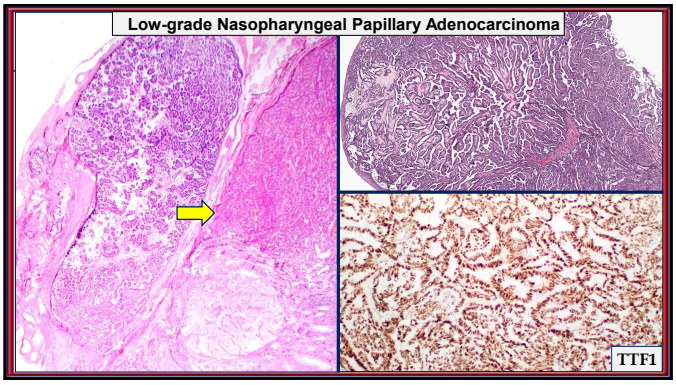

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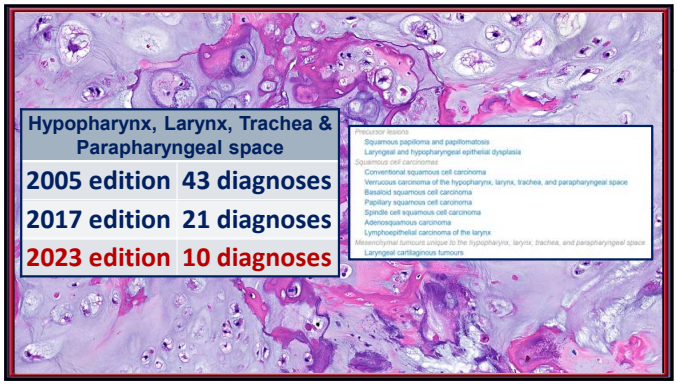

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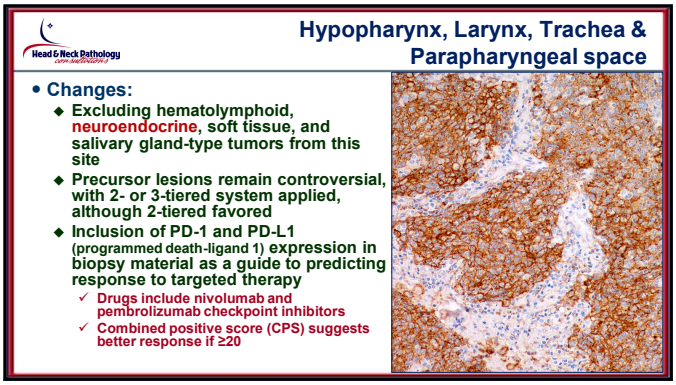

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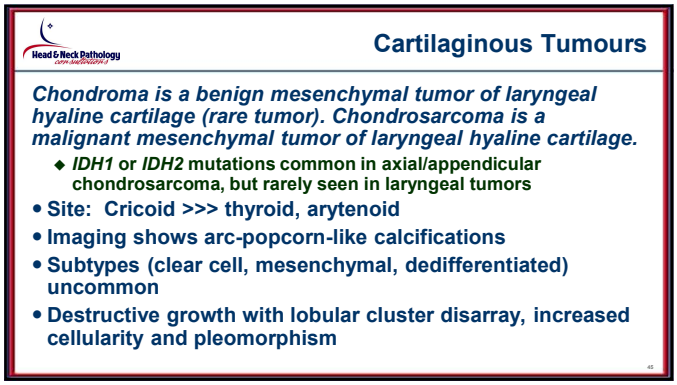

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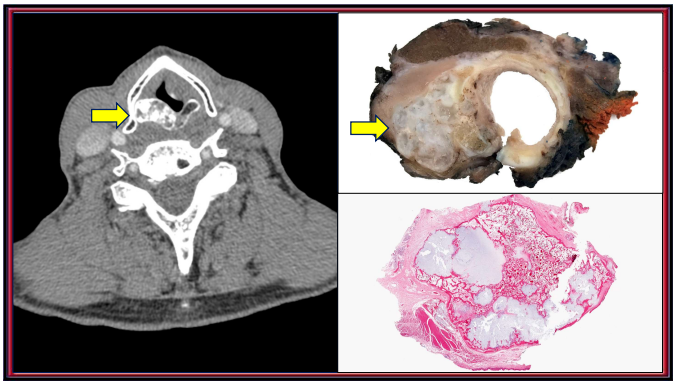

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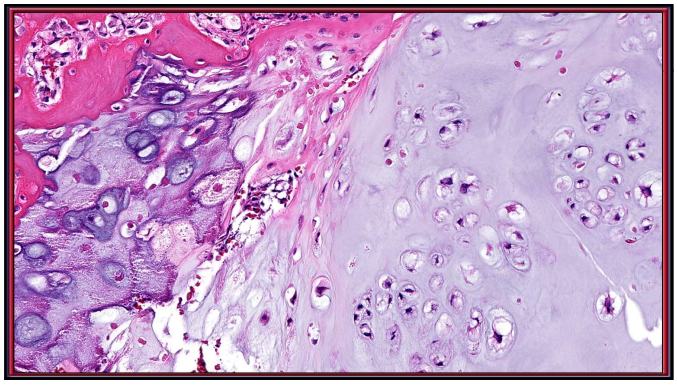

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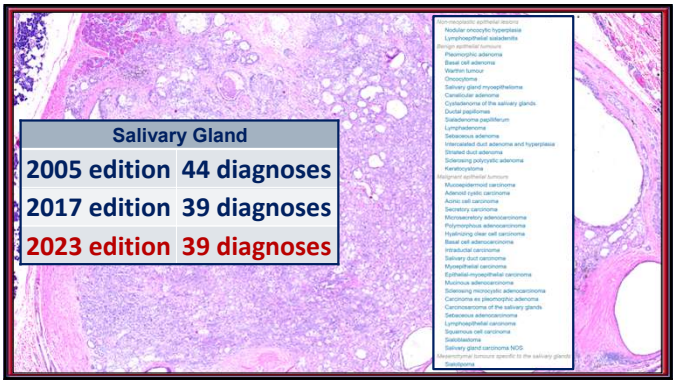

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Salivary Glands

- New Entities
  - Sclerosing polycystic adenoma
  - Keratocystoma
  - Intercalated duct adenoma
  - Striated duct adenoma
  - Microsecretory adenocarcinoma
  - Sclerosing microcystic adenocarcinoma
  - Mucinous adenocarcinoma
- Emerging or Submerging entities
  - Mucinous adenocarcinoma and Intraductal papillary mucinous neoplasm
  - Intraductal carcinoma when invasion is present
  - Poorly differentiated carcinoma
  - Oncocytic carcinoma is viewed to be classified by molecular findings into something specific
  - Carcinosarcoma: probably is epithelial-mesenchymal transition

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Salivary Glands

- Molecular data added to definitions when tumor type-specific rearrangements are recognized
  - Mucoepidermoid carcinoma — *CRTC1/3::MAML2*
  - Adenoid cystic carcinoma — *MYB/L1::NFIB*
  - Secretory carcinoma — *ETV6::NTRK3*
  - Polymorphous adenocarcinoma — *ARID1A::PRKD1/2/3* or *PRKD1*
  - Hyalinizing clear cell carcinoma — *EWSR1::ATF1*
  - Mucinous adenocarcinoma — *AKT1* p.E17K
  - Microsecretory adenocarcinoma — *MEF2C::SS18*
- Cytologic findings added to most entities
- Histologic grading (high grade transformation rather than de-differentiation) included for appropriate entities

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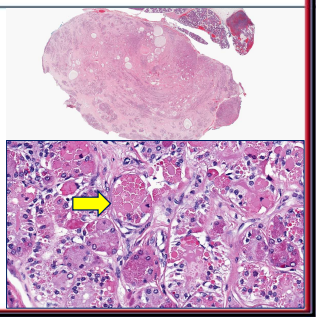
Sclerosing Polycystic Adenoma

SPA includes fibrosis, cystic alterations, apocrine metaplasia, and proliferations of ducts, acini composed of the cells with abundant eosinophilic cytoplasmic granules, and myoepithelial cells in variable proportions

- Mutations in *PTEN* (ductal component) confirmed neoplastic nature



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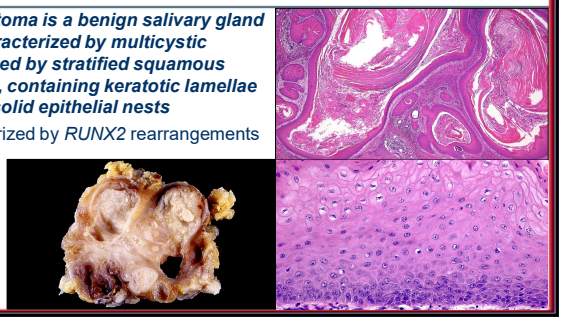
Keratocystoma

Keratocystoma is a benign salivary gland tumor characterized by multicystic spaces, lined by stratified squamous epithelium, containing keratotic lamellae and focal solid epithelial nests

- Characterized by *RUNX2* rearrangements



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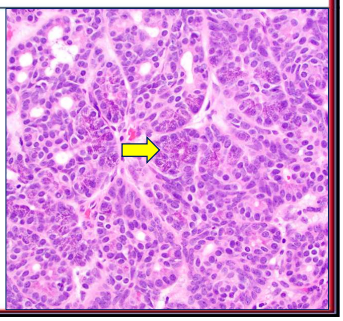
Intercalated Duct Adenoma

Intercalated duct adenoma-hyperplasia are benign salivary ductal proliferations resembling bi-layered (epithelial and myoepithelial) intercalated ducts

- 85% in the parotid gland
- A nodular to multinodular, proliferation of cuboidal ductal cells with attenuated myoepithelial cells, sometimes containing acinic cells
- Adenomas: when well circumscribed or encapsulated (*HRAS*)
- Hyperplasia: when blending with adjacent acini (*CTNNB1*)
- *CTNNB1* and *HRAS* pathogenic variants



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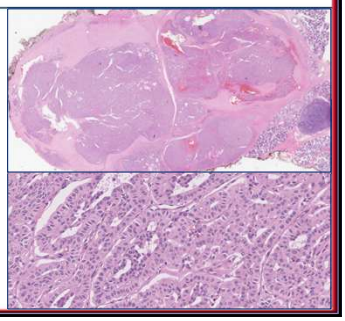
Striated Duct Adenoma

A benign salivary gland tumour composed of ducts resembling normal striated ducts lined by a single layer of luminal cells with minimal intervening stroma.

- Rare, adults (range 47-78 years) with a slight female predominance
- Well-circumscribed, encapsulated, small, closely spaced ducts with minimal intervening stroma, with ducts lined by a single layer of columnar cells with eosinophilic cytoplasm; vascularized stroma

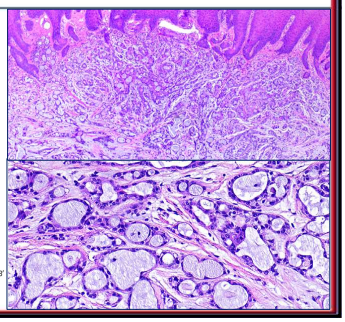


54

Microsecretory Adenocarcinoma

Microsecretory adenocarcinoma is a low-grade malignancy with an intercalated duct-like phenotype and MEF2C::SS18 fusion (5q14.3 and 18q11.2)

- Nearly all minor salivary glands
- **Positive:** SOX10, S100, p63

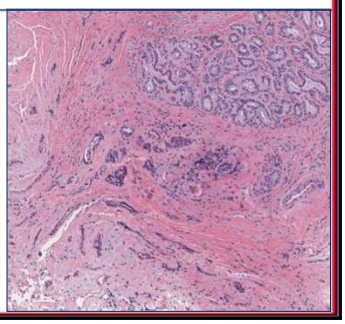


55

Sclerosing Microcystic Carcinoma

An indolent infiltrative salivary carcinoma composed of a biphasic population of ductal and myoepithelial cells embedded in a dense collagenous stroma, similar to microcystic adnexal carcinoma

- Site: Intraoral minor salivary glands
- Sex: Females > Males
- Age: Mean, 56 years



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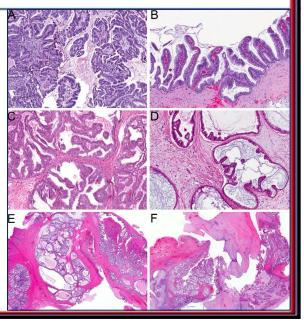
Mucinous Adenocarcinoma

Primary salivary carcinoma that displays prominent intracellular and/or extracellular mucin, lacks diagnostic features of other tumour types, and is usually associated with AKT1 alterations

- 8th decade; M = F
- Minor salivary glands most often
- Abundant intracellular and/or extracellular mucin production in multiple forms, including goblet cell-like vacuoles, apical caps, foveolar-type cytoplasmic droplets, or stromal pools
- Variable papillary, colloid, or signet ring architecture, with 40% displaying mixed patterns



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Oral Cavity	
2005 edition	58 diagnoses
2017 edition	26 diagnoses
2023 edition	16 diagnoses

Non-neoplastic lesions
- Necrotizing sialometaplasia
- Multifocal epithelial hyperplasia
- Oral melanoacanthoma

Epithelial tumours
- Papillomas
  - Squamous papilloma
- Oral potentially malignant disorders and oral epithelial dysplasia
  - Oral potentially malignant disorders
  - Proliferative verrucous leukoplakia
  - Submucous fibrosis
  - Oral epithelial dysplasia
  - HPV-associated oral epithelial dysplasia
- Squamous cell carcinomas
  - Oral squamous cell carcinoma
  - Verrucous carcinoma of the oral cavity and mobile tongue
  - Carcinoma cuniculatum

Tumours of uncertain histogenesis
- Congenital granular cell epulis
- Granular cell tumour
- Ectomesenchymal chondromyxoid tumour
- Melanotic neuroectodermal tumour of infancy

58

Oral Cavity and Mobile Tongue

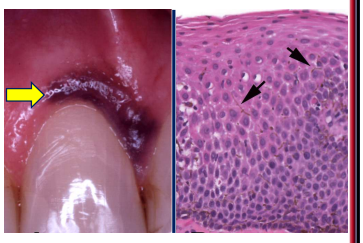
- **New Entities:**
  - Non-neoplastic lesions
    - ✓ Necrotizing sialometaplasia
    - ✓ Multifocal epithelial hyperplasia (Heck disease): moved from papilloma
    - ✓ Oral melanoacanthoma
- **Changes**
  - Oral potentially malignant disorders
  - Oral epithelial dysplasia: more architectural and cytologic features
  - Submucous fibrosis
  - HPV-associated dysplasia
  - Verrucous carcinoma
  - Carcinoma cuniculatum
- **Significant update**
  - Ectomesenchymal chondromyxoid tumor: *RREB1*::*MRTFB* gene fusion

59

Oral Melanoacanthoma

Oral melanoacanthoma is a non-neoplastic process, characterized by a dual proliferation of epidermal and melanocytic cells with a characteristic clinical profile of rapid initial growth but indolent behavior

- Dendritic melanocyte proliferation high in the epithelium
- Spongiosis
- Absence of atypia and invasion of melanocytic nests
- Epithelial acanthosis
- Melanin deposition at basal layer



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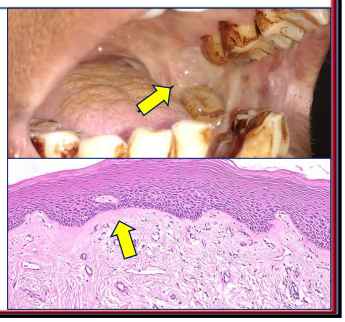
Submucous Fibrosis

Oral submucous fibrosis (OSF) is a chronic, insidious disease characterized by progressive fibrosis of submucosal tissues of the oral cavity and the oropharynx with a risk of transformation to SCC

- Early stage changes minimal with slightly increased vascularity, inflammatory infiltrate, and increased fibrillar collagen
- Later the collagen becomes homogeneous, starting superficially with juxta-epithelial hyalinization
- Advanced stage show loss of vascularity, hyalinization of collagen, and fibrous connective tissue



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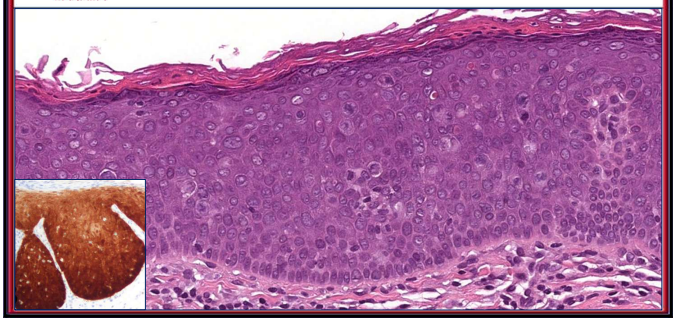
HPV-associated Dysplasia



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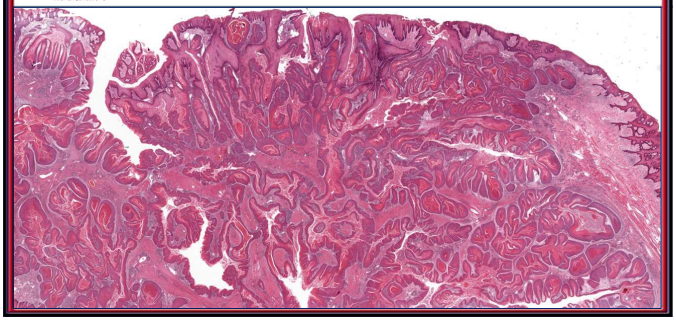
Carcinoma Cuniculatum



63

Oropharynx (base of tongue, tonsils & adenoids)	
2005 edition	Not included
2017 edition	11 diagnoses
2023 edition	3 diagnoses

Benign oropharyngeal lesions
- Hamartomatous polyps

Epithelial tumours
- *Squamous cell carcinoma*
  - Squamous cell carcinoma, HPV-associated
  - Squamous cell carcinoma, HPV-independent

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Oropharynx

- New Entities:
  - Hamartomatous polyps (lymphangiomatous polyps)
- Updated Entities
  - HPV-associated squamous cell carcinoma
    - ✓ No carcinoma in situ
    - ✓ All subtypes of SCC recognized
    - ✓ ≥70% block-like nuclear and cytoplasmic p16+ reaction
    - ✓ Neuroendocrine carcinoma separately reported
      - May be HPV-independent
  - HPV-independent squamous cell carcinoma

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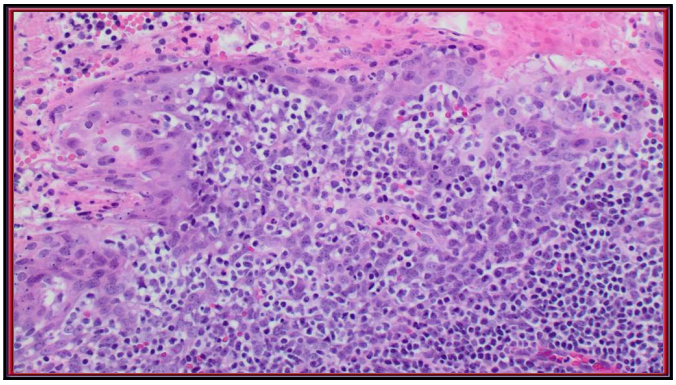

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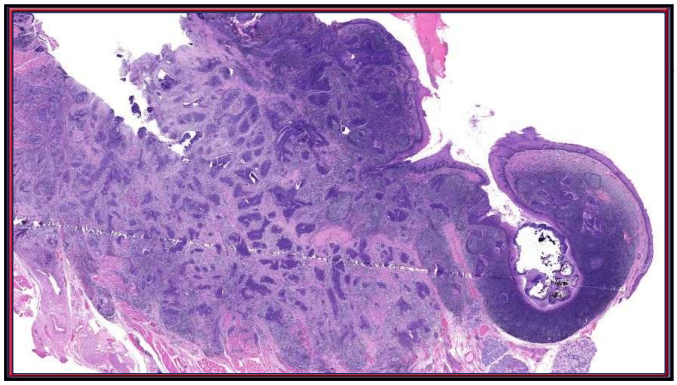

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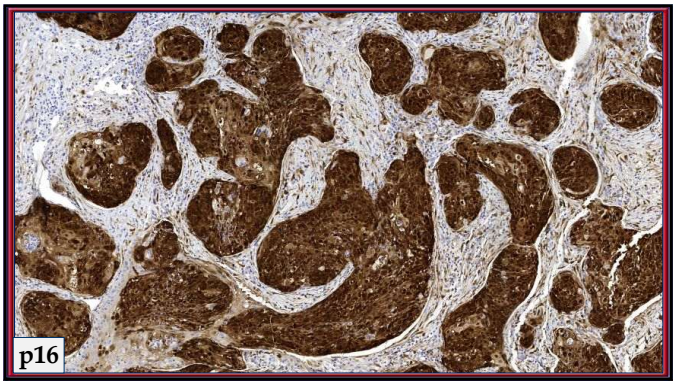

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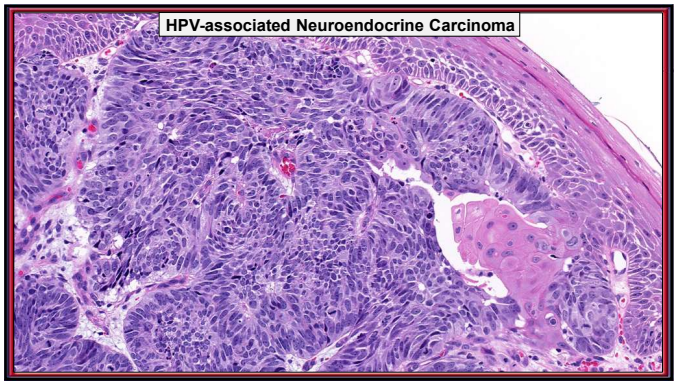

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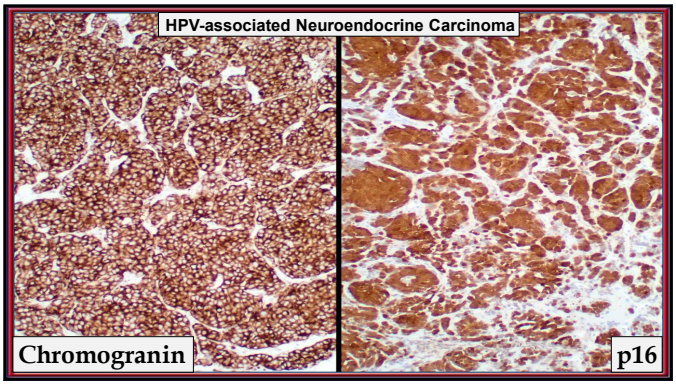

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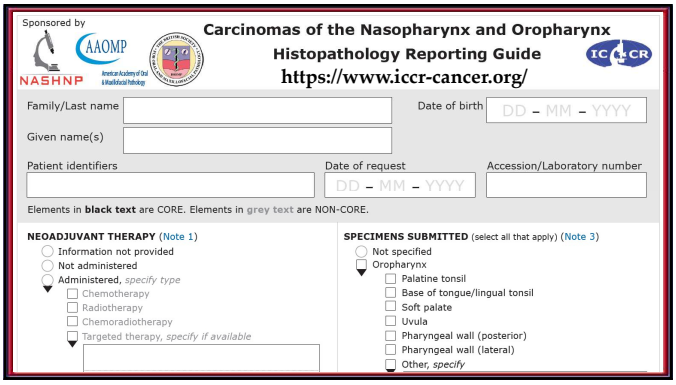

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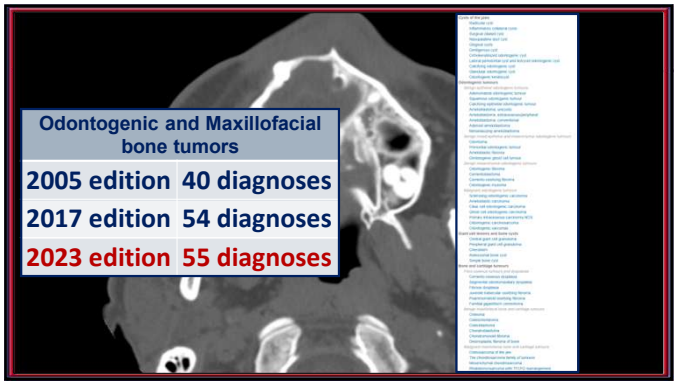

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Odontogenic & Maxillofacial Bone Tumors

- **New Entities:**
  - Odontogenic cysts: Surgical ciliated cyst
  - Benign epithelial odontogenic tumors: Adenoid ameloblastoma
  - Fibro-osseous tumors & dysplasias: Segmental odontomaxillary dysplasia; ossifying fibroma separated into juvenile trabecular and psammomatoid, with cemento-ossifying fibroma move to benign mesenchymal odontogenic tumors
  - Malignant jaw tumors: *TFCP2*-rearranged rhabdomyosarcoma
- **Moved:**
  - Melanotic neuroectodermal tumor of infancy, osteoid osteoma, and solitary plasmacytoma
- **Significant reorganization**
  - Cysts of the jaw: odontogenic cysts of inflammatory origin and odontogenic & non-odontogenic developmental cysts combined
  - Odontogenic carcinomas each given a separate section
  - Osteosarcomas (grouped) and chondrosarcoma family (grouped)
  - Re-ordered within categories with goal of "benign to malignant"

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Benign Odontogenic Tumors Distribution

	Radiolucent	Mixed Radiolucent-Radio-opaque	Radio-opaque
1st – 2nd decades	POF (sinus; max) AF (mand-post) UAM (1st peak; mand-post) OdM (mand-post)	AOT (max-ant)	Cementoblastoma (mand-post) Odontoma (cx-mand-post; cd-max-ant
3rd – 4th decades	SOT (max-an, mand-post) UAM (2nd peak; mand-post) MetAM (mand) COsF (mand-post) AdAM (no predilection)	OdF (max-ant; mand-post) CEOT (mand-post)	
5th – 6th decades	AM (mand-post)	DGCT (mand/max-post)	

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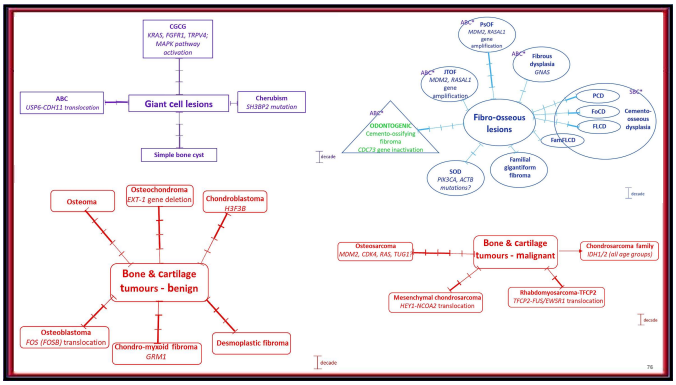

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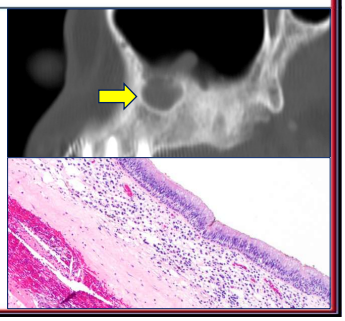
Surgical Ciliated Cyst

Surgical ciliated cyst is a benign cyst caused by the traumatic implantation (usually surgical) of respiratory epithelium in the gnathic bones

- Radiographs show a well-demarcated unilocular radiolucency of the jaws
- Cyst is lined by pseudostratified ciliated columnar (respiratory-type) epithelium
- Areas of squamous metaplasia or simple cuboidal cells may be seen
- Mucous (goblet) cells are common



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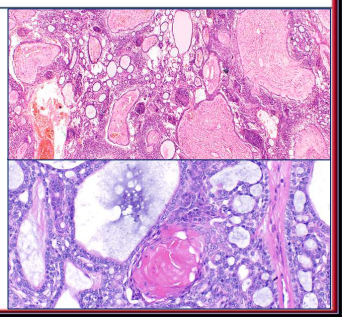
Adenoid Ameloblastoma

Adenoid ameloblastoma is an epithelial odontogenic neoplasm characterized by cribriform architecture and duct-like structures. Dentinoid is often present

- Partly cribriform arrangement of basal ameloblast-like cells demonstrating reversed nuclear polarity
- Minor component of suprabasal stellate reticulum-like epithelium
- Basal cells may be multi-layered with transition to a round or ovoid morphology
- Duct-like structures formed by cuboidal to columnar cells, some of which contain mucin
- Focal whorled cellular condensations reminiscent of morules
- Two-thirds of cases contain varying amounts of dentinoid
- Show *BRAF* pathogenic variants



78

TFCP2-rearranged Rhabdomyosarcoma

Rhabdomyosarcoma with TFCP2 rearrangement is a high grade rhabdomyosarcoma characterized by fusion of TFCP2 to EWSR1 or FUS

- Age: Majority in young patients
- Site: Most *TFCP2*-RMS arise in bone, specifically craniofacial bones: mandible > maxilla > skull bones
- Usually biphasic with spindle cell and epithelioid areas in solid sheets or fascicles with scant accompanying stroma
  - May be purely epithelioid, spindle or round cell
- Tumour nuclei are monotonous and large with conspicuous nucleoli
- High mitotic activity and tumor necrosis
- Positive: AE1/E3, desmin, MYOD1, myogenin, ALK
  Sometimes p63, CK7, SATB2, p53, CD30, CD4, S100

Histopathology. 2021 Sep;79(3):347-357 (PMID: 33382123); Mod Pathol. 2020 Mar;33(3):404-419 (PMID: 31383960); Head Neck Pathol. 2022 Mar 21 (PMID: 35307771)

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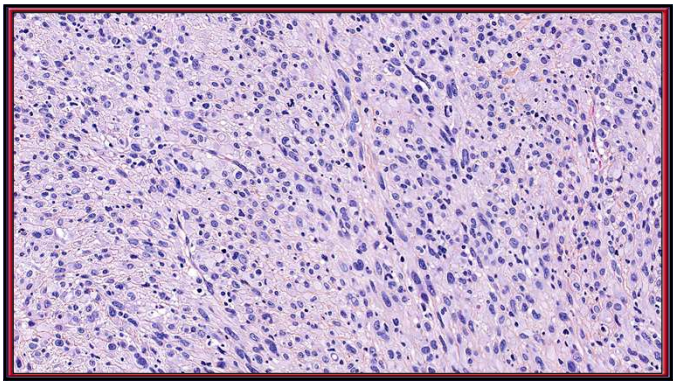

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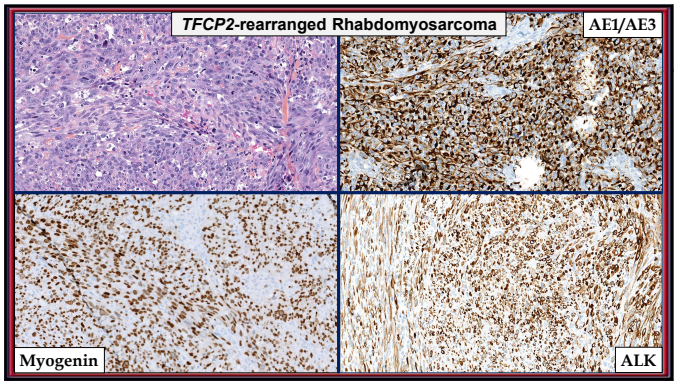

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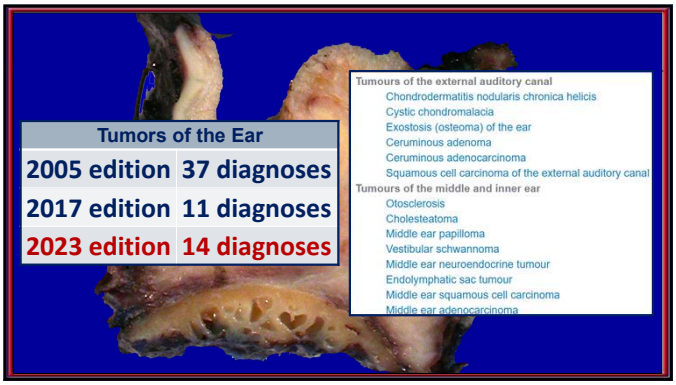


82

Tumors of the Ear

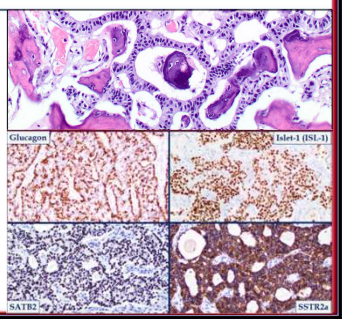
- New Entities (well not really: in 3rd but not in 4th edition)
  - Chondrodermatitis nodularis chronica helicis
  - Cystic chondromalacia
  - Osteoma
  - Middle ear papilloma
    - ✓ *MKRN1*::*BRAF* fusion identified in sinonasal-papilloma-like tumor
  - Middle ear squamous cell carcinoma includes emerging entity of *DEK*::*AFF2* fusion carcinoma
- Renamed
  - Middle ear neuroendocrine tumor (MeNET) from middle ear adenoma (kept in ear for this edition)
  - Middle ear adenocarcinoma from middle ear aggressive papillary tumor

83

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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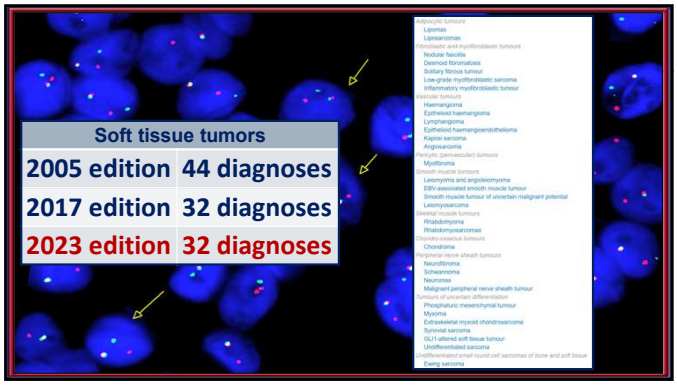

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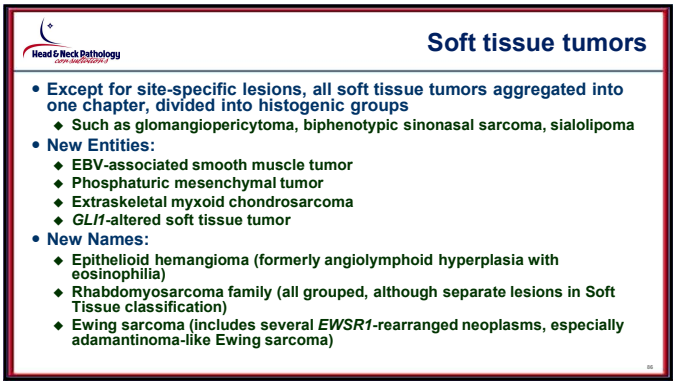

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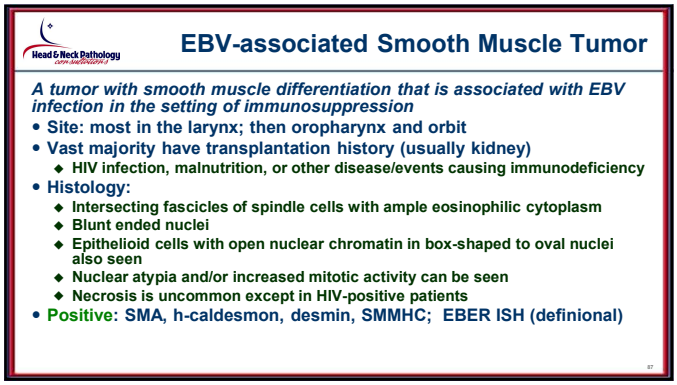

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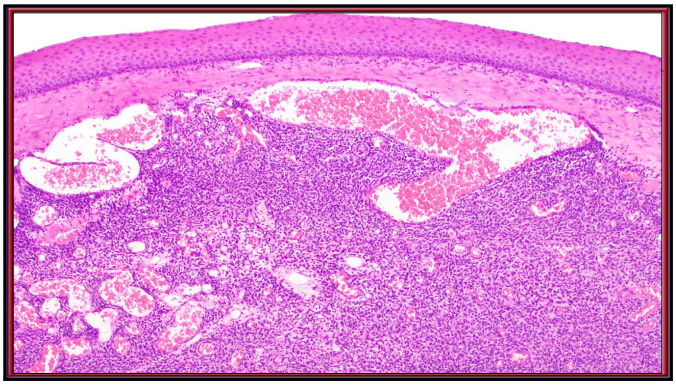

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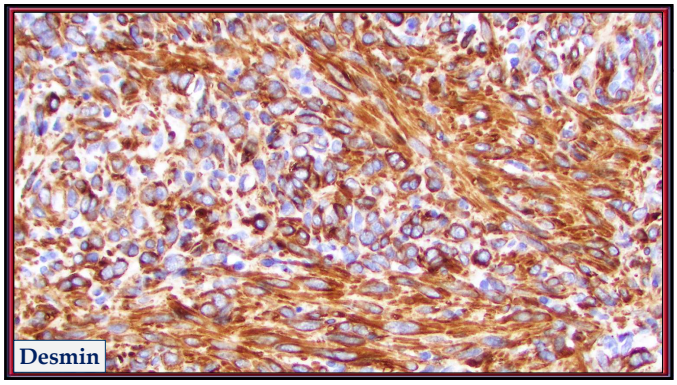

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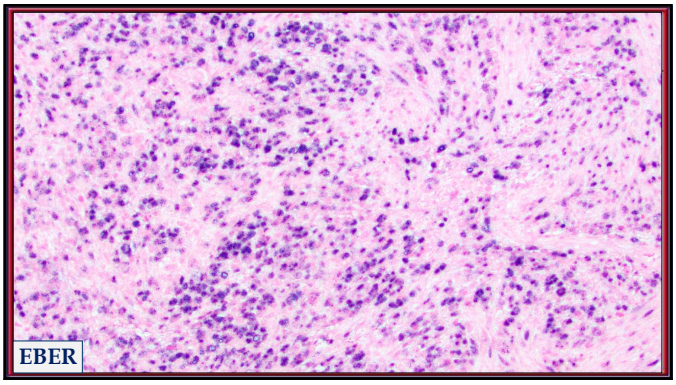

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Phosphaturic Mesenchymal Tumor

Distinctive neoplasms that cause tumor-induced osteomalacia, usually through production of fibroblast growth factor-23 (FGF23)

- Must have clinical evidence of phosphate wasting and/or osteomalacia
  - Should be reversed by complete removal of the tumor
  - FGF23 elevated levels in the serum in many cases
- Site: Head and neck region is the second most common site
  - About 50% affect the paranasal sinuses
- Histology:
  - Bland, ovoid, spindle to stellate cells embedded in a richly vascularized stroma
  - Pathognomonic basophilic, smudgy matrix with 'grungy' or 'flocculent' calcification
  - May contain adipose tissue and are more myoid with prominent thick-walled blood vessels
  - Head and neck cases show minimal/absent calcified matrix
- Positive: ERG, D2-40, SATB2, SSTR2A, FGF23, NSE, CD56

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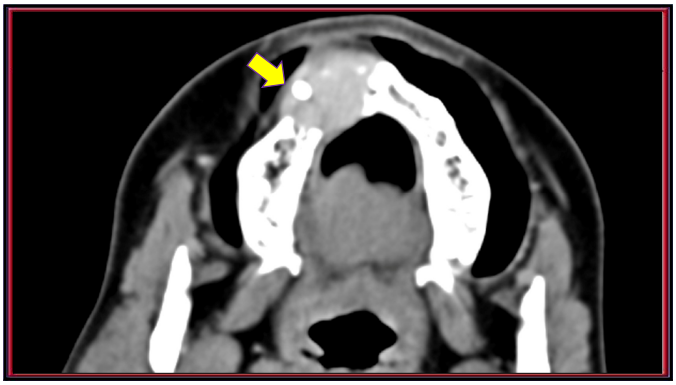

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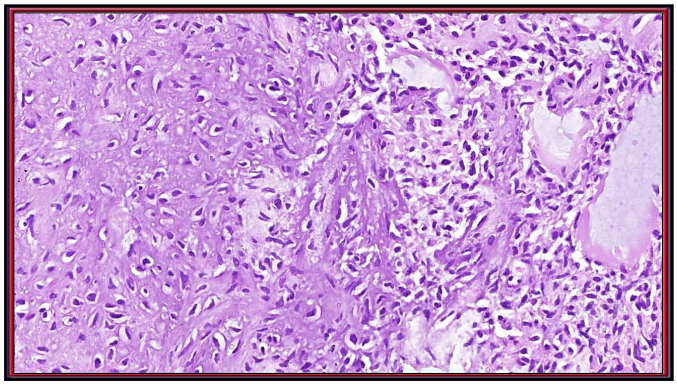

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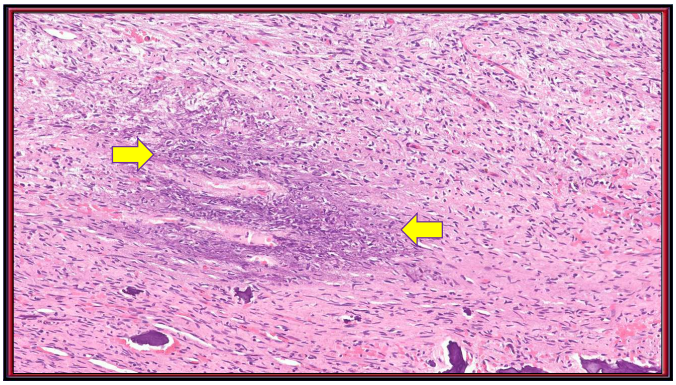

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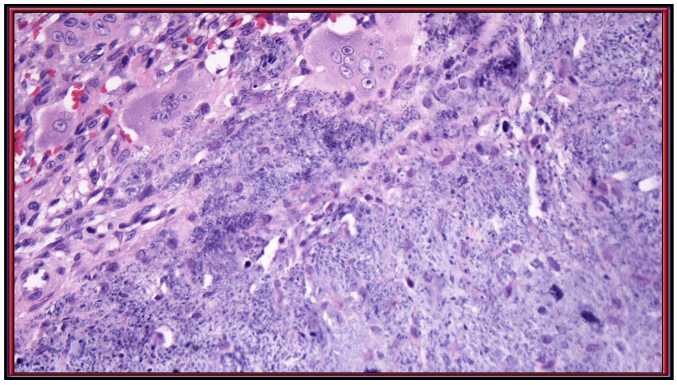

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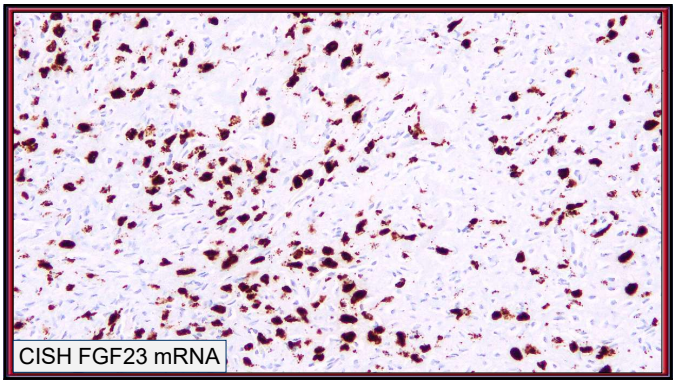

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GLI1-altered Soft Tissue Tumor

A mesenchymal neoplasm of uncertain histogenesis characterized by an epithelioid morphology and GLI1 alterations

- Gene fusions seen in 2/3 with remaining cases showing amplification, sometimes with co-amplification of neighboring genes
- Site: ~40% occur in the head and neck (tongue most commonly)
- Histology:
  - Protrusion into vascular spaces is common
  - Wide spectrum of architectural and cytologic findings
  - Arranged in nests and sheets, fascicles, pseudorosettes, cords and/or reticular pattern
  - Small-medium cells that range from epithelioid to ovoid to spindled, with variable eosinophilic to clear cytoplasm
  - Monomorphic round to ovoid nuclei, with pin-point nucleoli
  - Limited mitotic activity
  - A prominent capillary-sized vasculature is often present
  - Stroma may be myxoid or hyalinized

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GLI1-altered Soft Tissue Tumor

- Variable and patchy, focal immunohistochemistry
  - Smooth muscle actin, S100 protein, CD10, CD56, CD99, EMA, p16
  - Usually negative: SOX10, HMB45, GFAP, CD34, p63, chromogranin, synaptophysin
  - May have overexpression of CDK4, MDM2 and STAT6 (especially in GLI1-amplified tumors)
- FISH for *DDIT3* surrogate for *GLI1*; *GLI1* FISH for rearrangement not amplification

(Head Neck Pathol. 2022 Dec;16(4):1146-1156 PMID 35933574)

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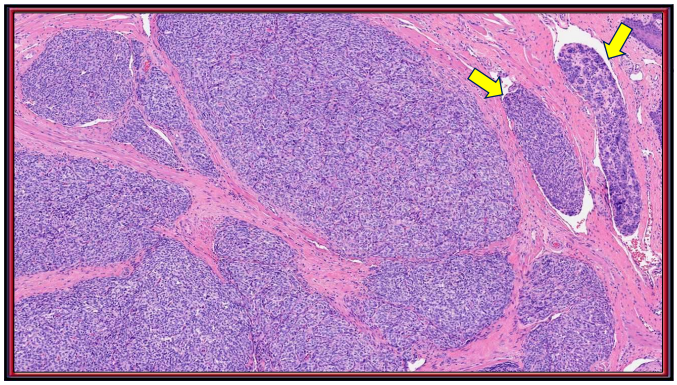

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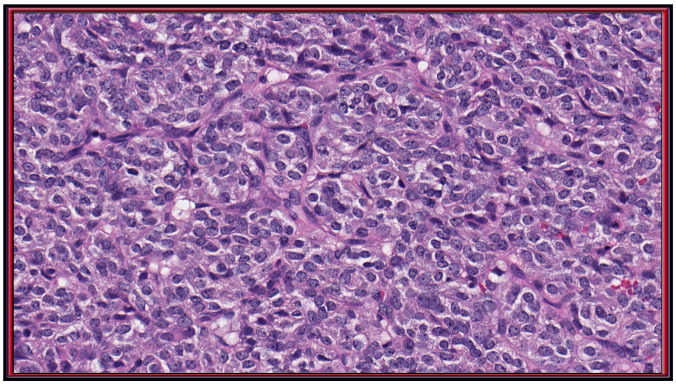

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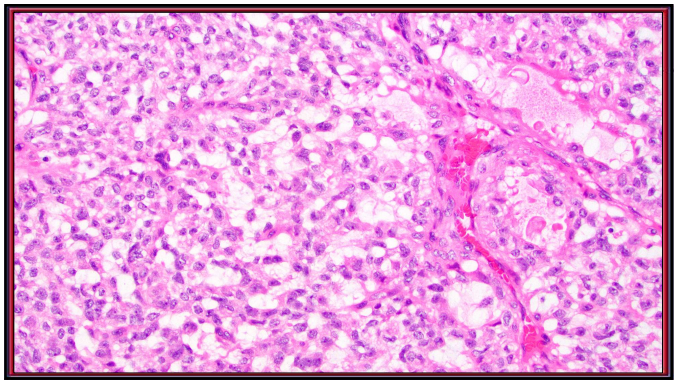

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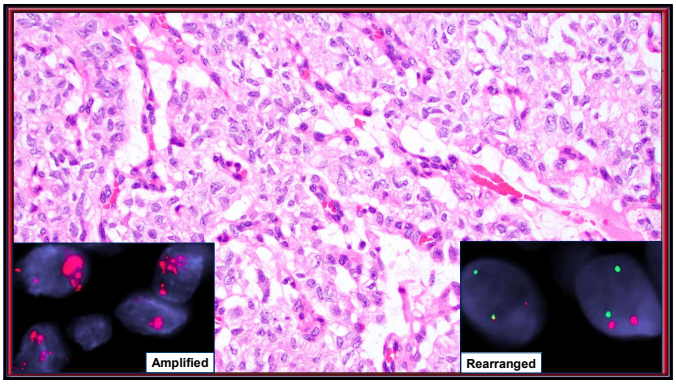

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Adamantinoma-like Ewing Sarcoma

A primitive small round cell sarcoma defined by fusions involving members of the FET and ETS gene families

- Age: 85% in first 4 decades of life
- Sex: Slight male predominance
- Site: adamantinoma-like subtype usually head and neck: salivary glands, thyroid gland, and sinonasal tract
- Histology: Lobulated architecture, peripheral palisading, and myxoid to hyalinized stroma; squamous differentiation focally present (but not in every case)
- Positive: CD99 (M), NKX2.2, FLI1, ERG, CK-pan, p40/p63
- Variable: chromogranin, synaptophysin

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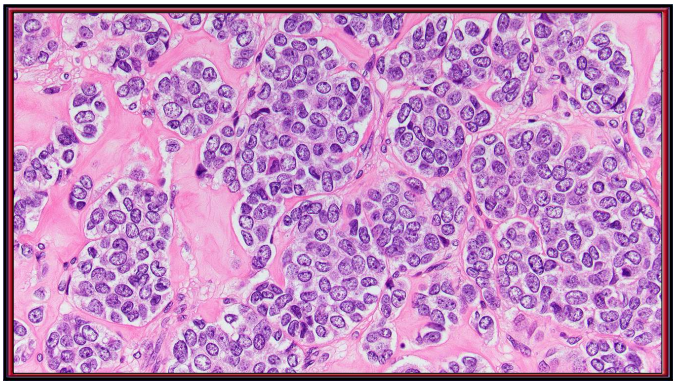

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Immunohistochemistry Profile

	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	
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
Pituitary neuroendocrine tumor	P	N	P	I	N	R	-/F	N	Prolactin; Pit1, SF1

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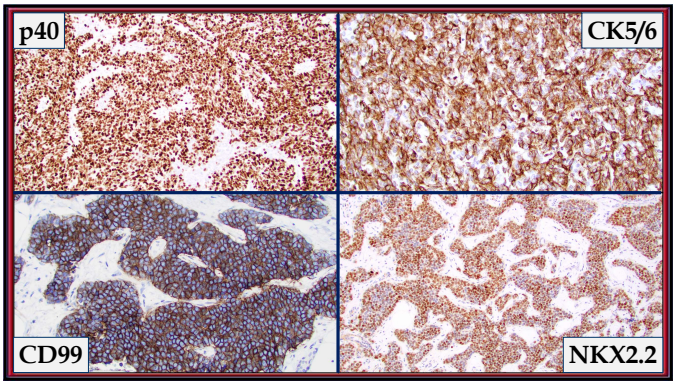

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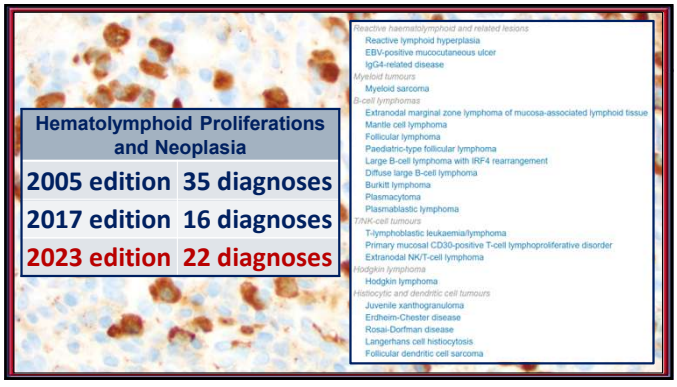

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Hematolymphoid Proliferations and Neoplasia

- Except for site-specific lesions, all hematolymphoid proliferations and neoplasms aggregated into one chapter, divided into groups
- New Entities:
  - EBV+ mucocutaneous ulcer
  - IgG_4-related disease
  - Large B-cell lymphoma with *IRF4* rearrangement
  - Juvenile xanthogranuloma
  - Erdheim Chester disease

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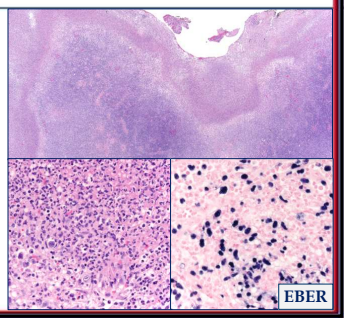
EBV+ Mucocutaneous Ulcer

A self-limiting lymphoproliferative disorder with a polymorphous lymphoid infiltrate including Hodgkin-like cells that typically involves mucosal and cutaneous sites in immunocompromised patients

- Immunosuppressed patients
  - Elderly, autoimmune, iatrogenic, HIV, and posttransplant settings
- Histology:
  - Well-circumscribed ulcers
  - At the base is a polymorphous infiltrate ranging from small to large lymphoid cells, variable numbers of immunoblasts, plasma cells, and Hodgkin-like cells
  - Vascular destruction, thrombosis and necrosis is often prominent
  - Overlying epithelium may show PEH
- Positive: mixed CD20 & CD3; EBER; CD30; rare CD15



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IgG_4-related Disease

A systemic, immune-mediated and mass-forming lesion characterized by IgG_4+ cell-rich lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and typically elevated serum IgG_4

- Site: Orbit; submandibular salivary gland
- Serum IgG_4 is elevated in the majority of cases
- Histology:
  - Obliterative phlebitis
  - Storiform fibrosis
  - Lymphoplasmacytic infiltrate with increased IgG_4+ cells (>400/mm^2)
    - ✓ IgG_4+/IgG+ ratio >40%
- Exclusion of known entities
  - ANCA-associated vasculitis, rheumatoid arthritis, multicentric Castleman disease, Rosai-Dorfman disease, inflammatory myofibroblastic tumor, chronic infection
- Clinically compatible features
  - IgG_4–related disease in other body sites, elevated serum IgG_4 and response to steroids and/or rituximab

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Table of Criteria for IgG_4-related Disease

Affected Sites	Nomenclature (obsolete terminology)	IgG_4+ Cell Count	Salient Clinical Features
Orbit, including lacrimal glands	IgG_4-related ophthalmic disease IgG_4-related orbital inflammation IgG_4-related orbital myositis (Pseudotumor; idiopathic fibroinflammatory disease)	>400/mm^2	• Unilateral or bilateral painless orbital swelling, proptosis and diplopia, rarely eye pain and visual impairment • Contrast-enhancing soft tissue mass • Preferentially affecting lateral rectus muscle • Bilateral infraorbital nerve involvement on imaging is pathognomonic of IgG_4-related ophthalmic disease
Salivary glands	IgG_4-related sialadenitis (Küttner tumor, chronic sclerosing sialadenitis)	>400/mm^2	• Unilateral or bilateral painless swelling most commonly involving submandibular gland • Occasionally simultaneous bilateral lacrimal, parotid and submandibular gland involvement (Mikulicz disease) • Xerostomia is usually mild and responds well to steroids • Sialography normal

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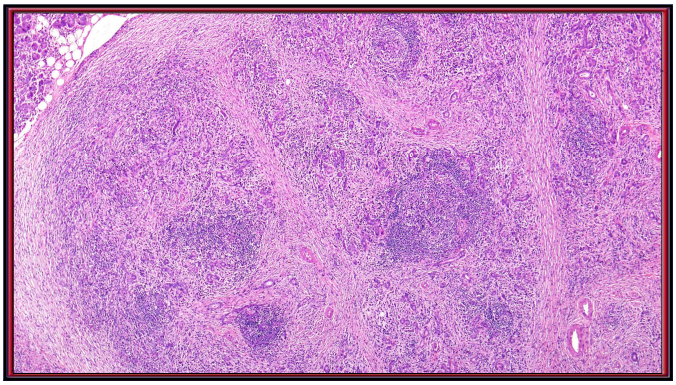

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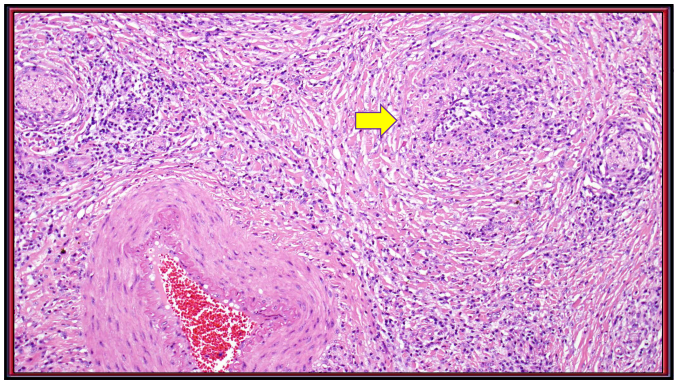

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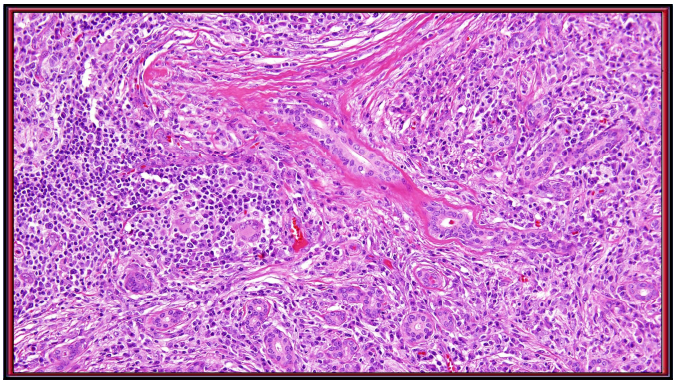

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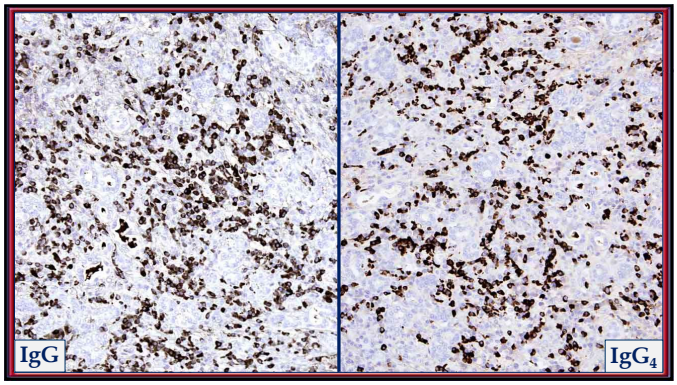

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Head & Neck Pathology

Erdheim Chester disease

A systemic histiocytic neoplasm characterized by multi-organ proliferation of mature histiocytes in a background of fibrosis

- Site: Xanthelasma-like lesions around the eyes, face, and neck
- Sex: Male predominance
- Sclerosis of facial sinuses (imaging studies)
- Underlying clonal hematopoiesis or overt myeloid neoplasms (mostly CMML) may be seen
- Histology:
  - Collections of histiocytes with bland cytologic features
  - Foamy and/or eosinophilic cytoplasm
- Positive: CD163, CD68, CD14, FXIIIa, CD4
- Negative: CD1a, CD207

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Head & Neck Pathology

Common sites of Erdheim-Chester Disease

Site	Presentation
Bones (80-95%)	Bilateral symmetric long bone involvement at the metadiaphysis
Retroperitoneum (55-65%)	Perinephric infiltration ("hairy kidneys")
Vasculature (50-80%)	Periaortic infiltration of entire thoracoabdominal aorta "coated aorta"
Heart (40-70%)	Right atrial pseudotumor; valvular infiltration; pericardial infiltration and effusion
Endocrine system (40-70%)	Diabetes insipidus; anterior pituitary dysfunction; testicular insufficiency; adrenal infiltration
Nervous system (40%)	Brainstem/cerebellum masses; cerebral white matter enhancement; dural and pituitary stalk thickening
Respiratory tract (30-55%)	Mediastinal infiltration; pleural, septal, and maxillary sinus thickening
Orbits (30%)	Orbital masses
Skin (25-30%)	Xanthelasma-like lesions around eyes, face, neck, and inguinal folds

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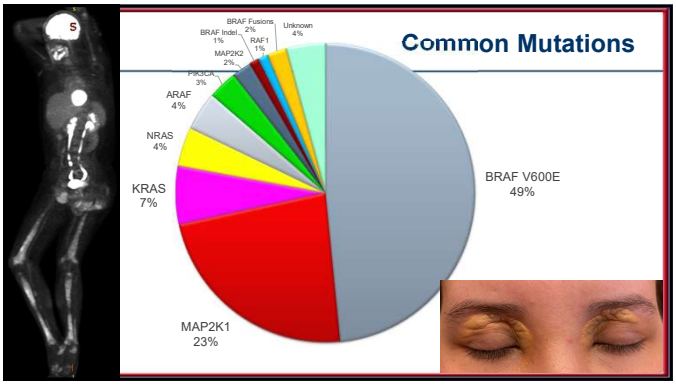

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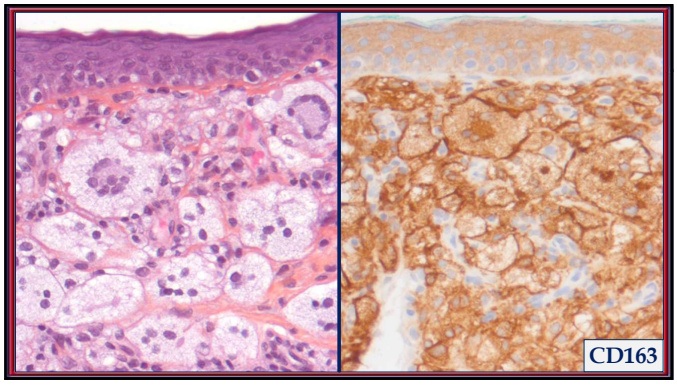

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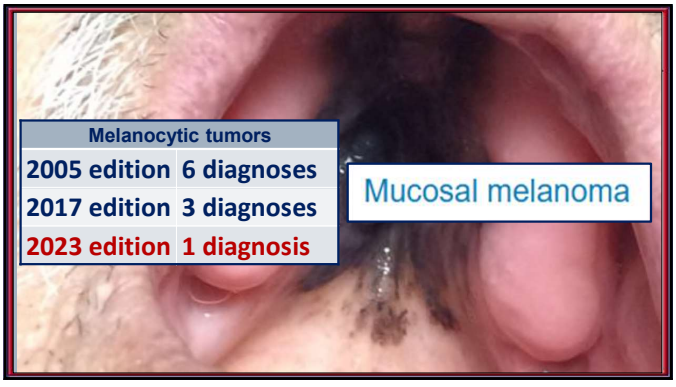

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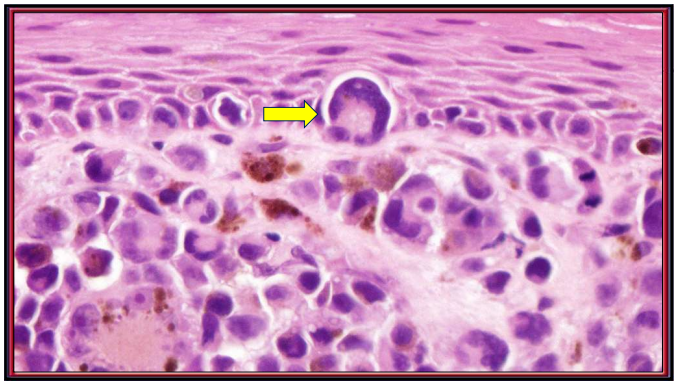

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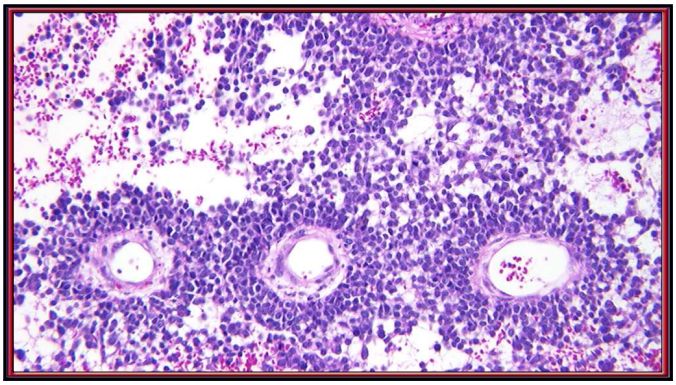

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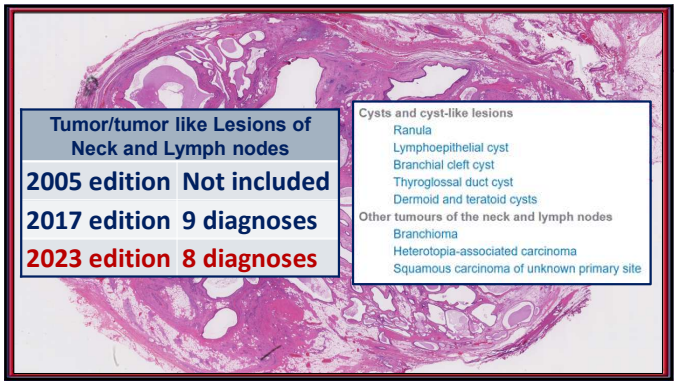

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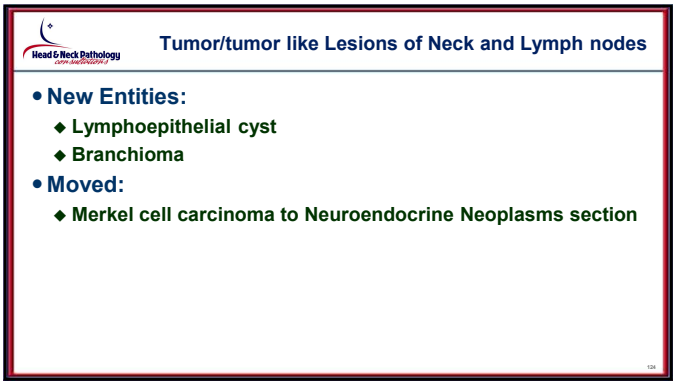

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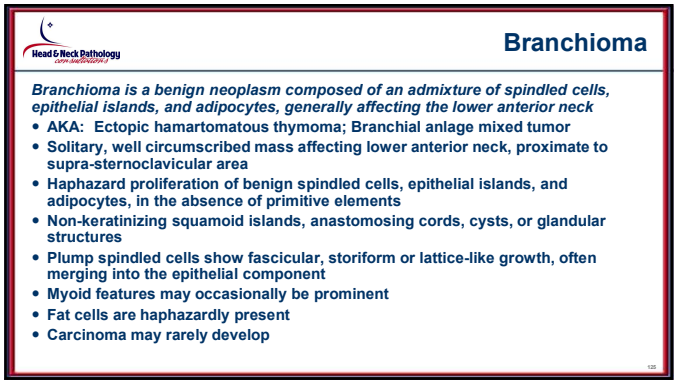

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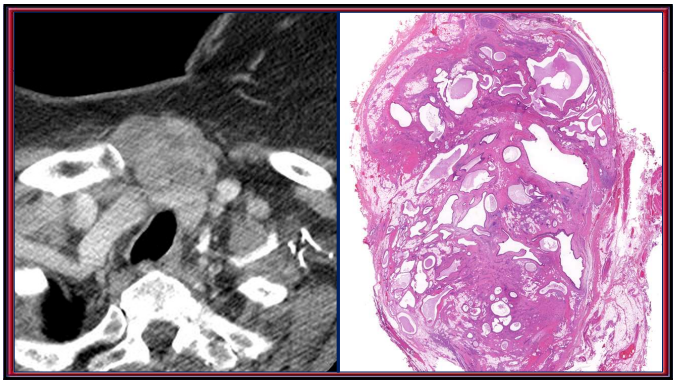

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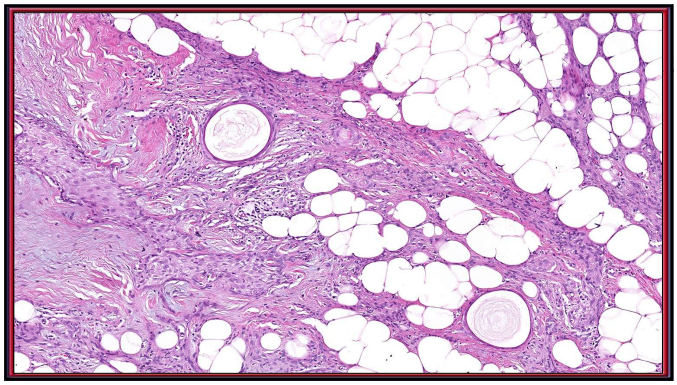

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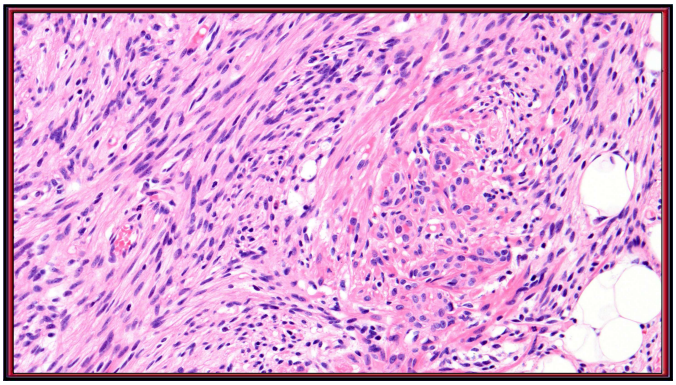

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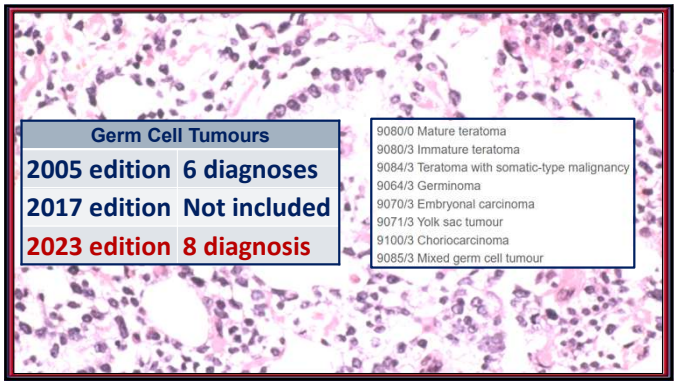

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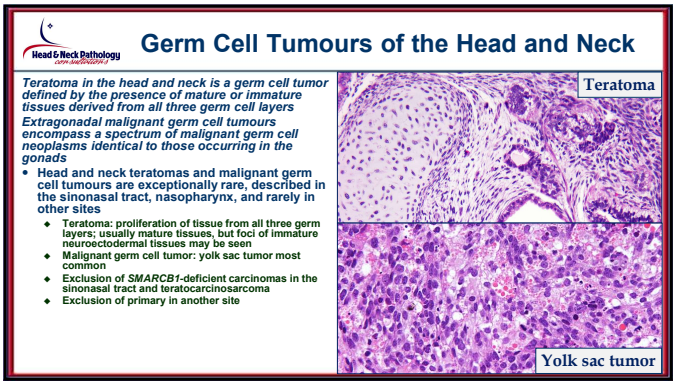

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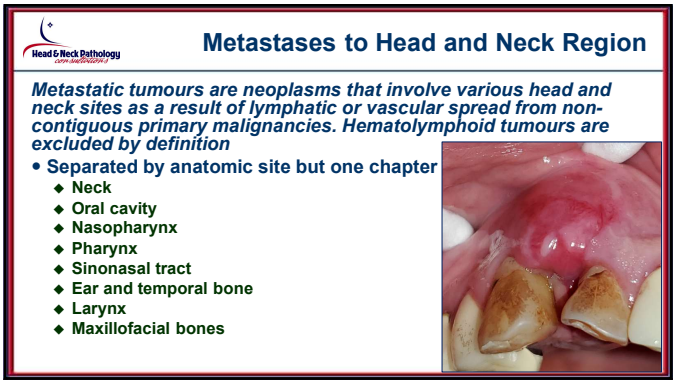

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Metastases to Head and Neck

Anatomic Location	Most Common Metastatic Malignancies	Relevant Immunohistochemical Markers
Neck and lymph nodes	Squamous cell carcinoma (mucosa and skin of head and neck)	Squamous carcinoma: pan-keratin, p40, p63, p16, CK5/6.
	Papillary thyroid carcinoma	Thyroid: PAX-8, TTF-1, thyroglobulin
	Salivary gland carcinoma	Salivary gland: pan-keratin, DOG-1, androgen receptor, CD117, mammaglobin, p40, p63, SOX-10, calponin, smooth muscle actin, β-catenin, GATA-3, NR4A3, and GFAP
Oral cavity	Lung	Lung: pan-keratin, p40, p63, CK5/6, TTF-1, claudin-4, synaptophysin, chromogranin, INSM-1
	Breast	Breast: GATA-3, ER, PR, TRPS1, mammaglobin
	Renal cell carcinomas	Renal: pan-keratin, PAX-8, CA IX, CK7
	Cutaneous squamous cell carcinoma	Cutaneous squamous: pan-keratin, p40, p63, CK5/6
	Melanoma	Melanoma: S-100 protein, SOX-10, HMB-45, MiTF, Melan-A
	Sarcomas (angiosarcoma, liposarcoma)	Sarcoma: pan-keratin, CD34, SS18, DDIT3, MDM2, MUC4, CD31, ERG, SMARCB-1, desmin, smooth muscle actin, myogenin, MyoD1, S-100, NKX2.2, and CD99
Maxillo-facial bones	Breast (most common)	Breast: GATA-3, ER, PR, TRPS1, mammaglobin
	Renal cell	Renal: PAX-8, CA IX, CK7
	Prostate carcinoma	Prostate: NKX3.1, PSA, PSAP
Major salivary glands	Cutaneous squamous cell carcinoma (head/neck)	Squamous carcinoma: pan-keratin, p40, p63, CK5/6
	Melanoma	Melanoma: S-100 protein, SOX-10, HMB-45, MiTF, Melan-A
	Merkel cell carcinoma	Merkel cell: pan-keratin, CK20, SATB2, synaptophysin, chromogranin, INSM-1
	Breast carcinoma	Breast: GATA-3, ER, PR, TRPS1, mammaglobin
	Lung carcinoma	Lung: pan-keratin, p40, p63, CK5/6, TTF-1, claudin-4

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Metastases to Head and Neck

Anatomic Location	Most Common Metastatic Malignancies	Relevant Immunohistochemical Markers
Pharynx (naso-, hypo- and oropharynx)	Lung	Lung: pan-keratin, p40, p63, CK5/6, TTF-1, synaptophysin, chromogranin, INSM-1
	GI tract	GI: pan-keratin, CK20, CDX2, SATB2
	Renal	Renal: pan-keratin, PAX-8, CAIX, CK7
	Breast	Breast: GATA-3, ER, PR, TRPS1, mammaglobin
	Skin SCC	Skin: pan-keratin, p40, p63, CK5/6; CK20 (Merkel cell)
	Melanoma	Melanoma: S-100 protein, SOX-10, HMB-45, MiTF, Melan-A, PRAME
Nasal cavity & paranasal sinuses	Renal cell carcinoma	Renal: pan-keratin, PAX-8, CAIX, CK7
	Breast carcinoma	Breast: GATA-3, ER, PR, TRPS1, mammaglobin
	Lung carcinoma	Lung: pan-keratin, p40, p63, CK5/6, TTF-1, synaptophysin, chromogranin, INSM-1
Ear and temporal bone	Breast, Female genital tract	Breast/Müllerian tract: GATA-3, ER, PR, TRPS1, mammaglobin, PAX-8, WT-1, p16
	Lung and prostate carcinoma (male)	Lung: pan-keratin, p40, p63, CK5/6, TTF-1, synaptophysin, chromogranin, INSM-1, NKX3.1, PSA
	Renal cell carcinoma	Renal: pan-keratin, PAX-8, CAIX, CK7
	Melanoma	Melanoma: S-100 protein, SOX-10, HMB-45, MiTF, Melan-A
Larynx, trachea, para-pharyngeal	Lung	Lung: pan-keratin, p40, p63, CK5/6, TTF-1, synaptophysin, chromogranin, INSM-1
	Breast	Breast: GATA-3, ER, PR, TRPS1, mammaglobin
	Renal cell carcinoma	Renal: pan-keratin, PAX-8, CAIX, CK7
	Melanoma	Melanoma: S-100 protein, SOX-10, HMB-45, MiTF, Melan-A

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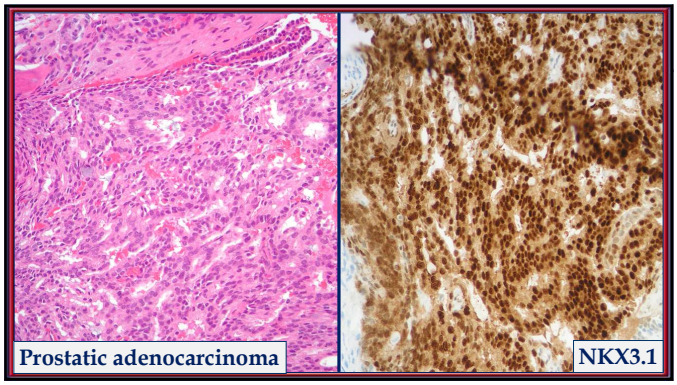

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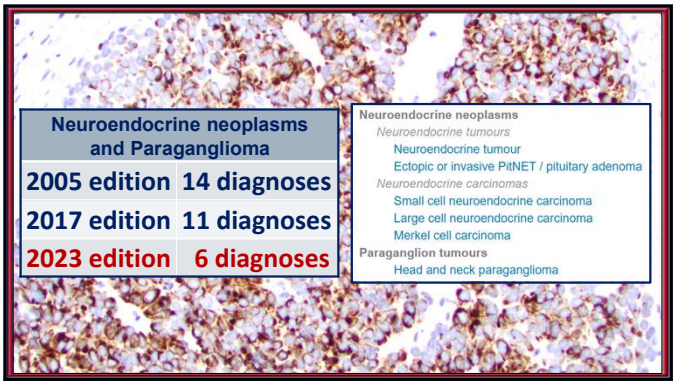

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Neuroendocrine Neoplasms & Paragangliomas

- **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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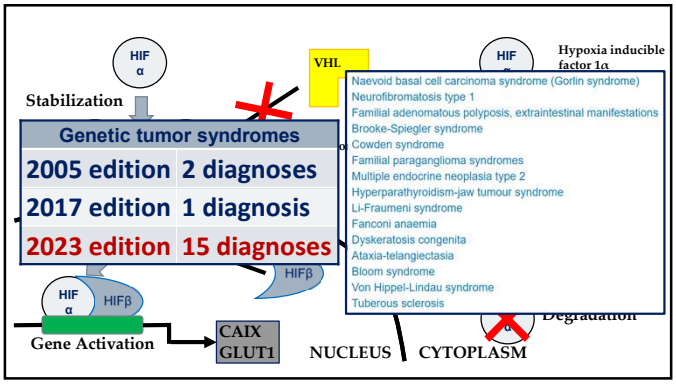

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Genetic Tumor Syndromes

- Familial-heritable tumor syndromes with tumors or lesions in the head and neck especially
  - Establish associated findings and disorders
  - Recommendations for monitoring
  - Recommendations for treating
- 15 syndromes presented
  - Careful family history documentation
  - DNA sequencing aids classification
  - Sporadic tumors are less likely and syndrome association increases

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Overall terminology

- *Syndrome name* is an autosomal dominant/recessive tumour syndrome caused by constitutional pathogenic variants affecting *gene name* located on *gene site* and characterized by these major defining features: *features*.
  - Naevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant tumour syndrome caused by constitutional pathogenetic variants of *PTCH1* and/or *SUFU*, and very rarely *GPCR1*, associated with developmental disorders and predisposition to benign and malignant tumors.
- MIM number standardized throughout
  - 109400 Basal cell nevus syndrome 1; BCNS1
- Incidence: 1 per 100,000 population
  - 0.6 100,000 population in Australia

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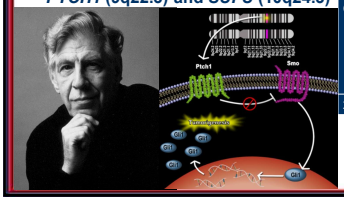
Nevoid Basal Cell Carcinoma Syndrome

- Described in 1894, but recognized as a distinct entity in 1959
- Autosomal dominant
- Sonic hedgehog pathway, including *PTCH1* (9q22.3) and *SUFU* (10q24.3)



Major Criteria	• Basal cell carcinomas before 20 years • Odontogenic keratocysts before 20 years • Palmar/plantar pitting • Falx calcification • Medulloblastoma • 1st degree relative with syndrome
Minor Criteria	• Rib abnormalities • Other skeletal abnormalities • Cleft lip/palate, • Macrocephaly • Ovarian or cardiac fibromas • Lymphomesenteric cysts • Ocular abnormalities
2 Major and 1 Minor or 1 Major and 3 Minor	

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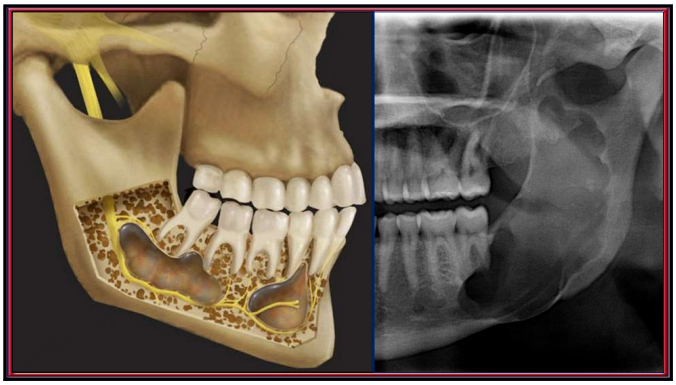

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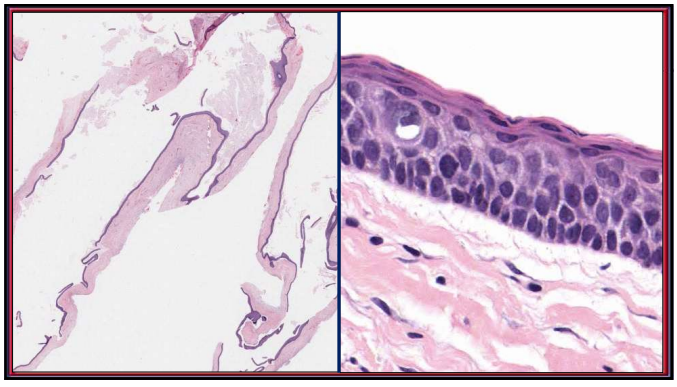

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