Clearing out the House: An approach to Clear Cell Salivary Gland Tumors

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General Considerations about Salivary Gland Tumors

- Represent about 0.00065% of all surgical pathology cases!
  - 8.5 tumors/100,000 patient years
- Most common in adults
- Fine needle aspiration first line screening test
- Little known about etiology
- Clinic stage is important
- Molecular techniques have caught up

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Tumor	Gene	Frequency
Pleomorphic adenoma	*PLAG1* (8q12) (70%) *HMGA2* (12q14-15) (20%)	Up to 90%
Mucoepidermoid carcinoma	*MAML2* rearrangement *(CRTC1/3)* *EWSR1::POU5F1 (minority)*	80% (not grade associated)
Adenoid cystic carcinoma	*MYB/MYBL1::NIFB* *EWSR1 (minority)*	80%
Secretory carcinoma	*ETV6::NTRK3 (RET, MET, MAML2)* *VIM::RET* (minority)	>90%

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Pleomorphic adenoma	*PLAG1* (8q12) (70%) *HMGA2* (12q14-15) (20%)	Up to 90%
Basal cell adenoma	*CTNNB1* mutation	70-80%
Mucoepidermoid carcinoma	*MAML2* rearrangement *(CRTC1/3)* *EWSR1::POU5F1 (minority)*	80% (not grade associated)
Acinic cell carcinoma	*NR4A3* rearrangement *HTN3::MSANTD3* fusion (minority)	80%
Adenoid cystic carcinoma	*MYB/MYBL1::NIFB* *EWSR1 (minority)*	80%
Polymorphous adenocarcinoma	*ARID1A::PRKD1/2/3* *PRKD1* hotspot	50%
Salivary duct carcinoma	*TP53, HRAS, PIK3CA, PTEN* mutations; *ERBB2* amplification	90%
Secretory carcinoma	*ETV6::NTRK3 (RET, MET, MAML2)* *VIM::RET* (minority)	>90%
Microsecretory adenocarcinoma	*MEF2C::SS18*	Definitional
Intraductal carcinoma	*NCOA4::RET, STRN::ALK, TUT1::ETV5, KIAA217::RET* *TRIM33::RET, NCOA4::RET, BRAF* p.V600E *HRAS, PIK3CA, TP53*	Pattern dependent
Hyalinizing clear cell carcinoma	*EWSR1::ATF1 (CREM)*	90%
Mucinous adenocarcinoma	*AKT1* E17K mutations; *TP53* mutations	Majority tested

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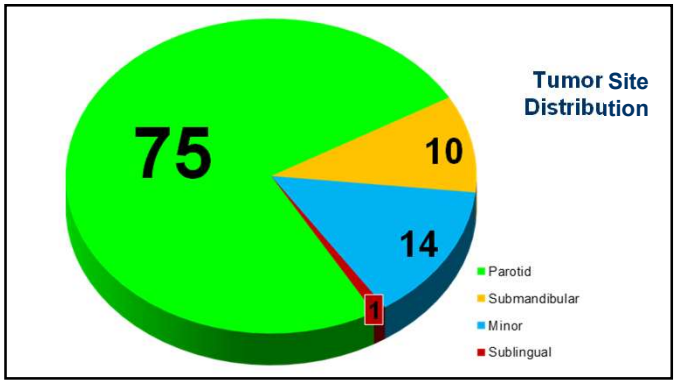

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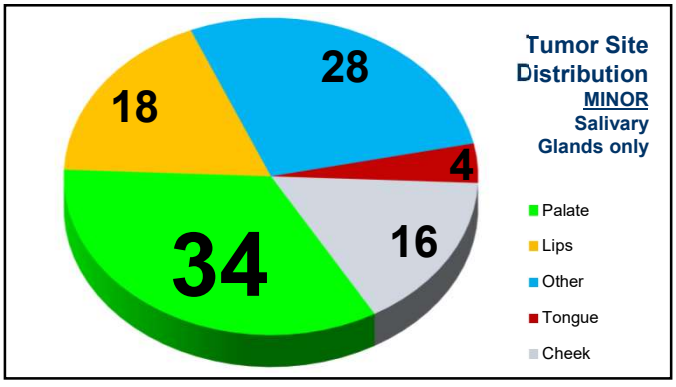

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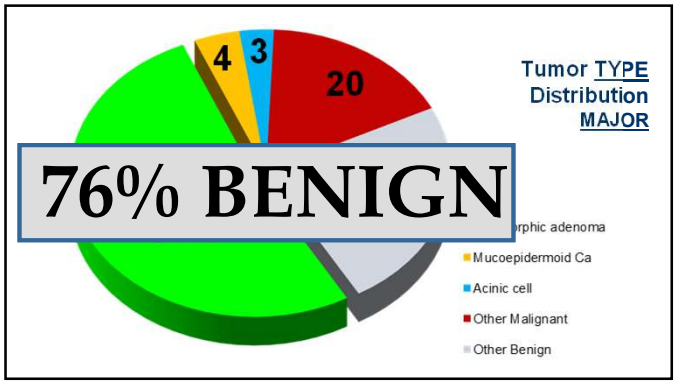

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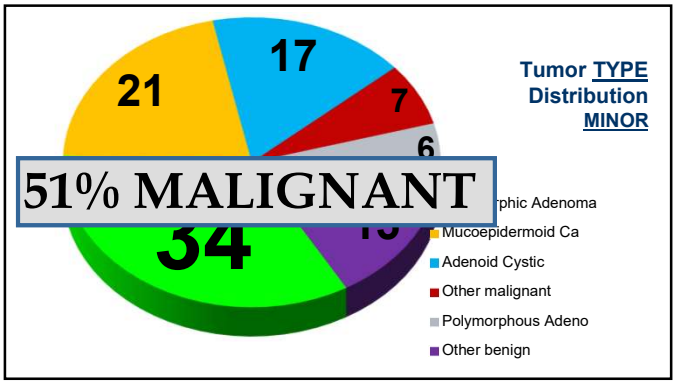

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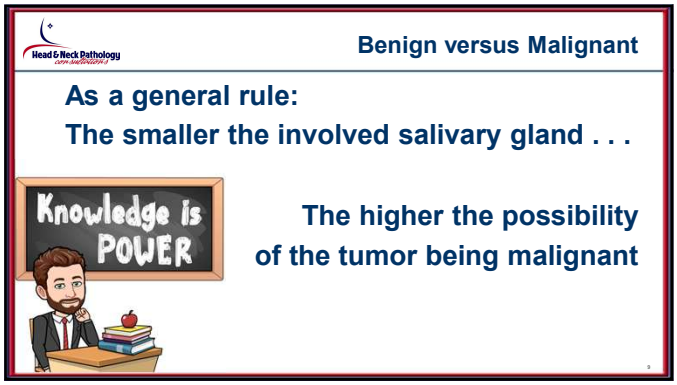

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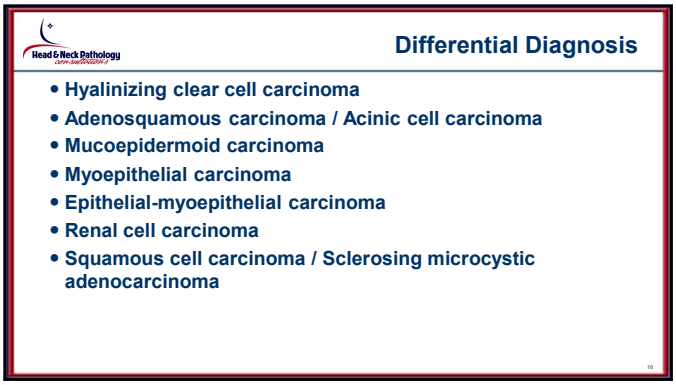

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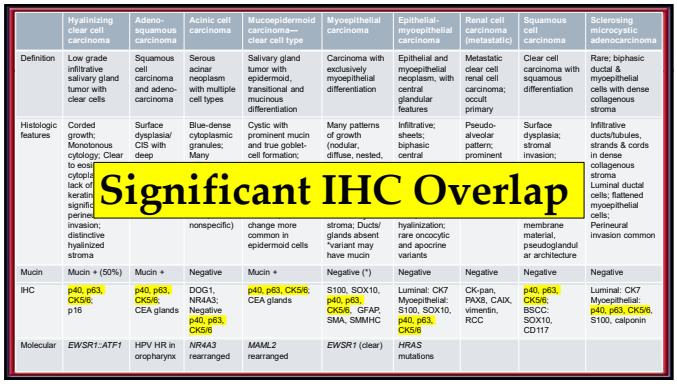

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Definition	Low grade infiltrative salivary gland tumor with clear cells	Squamous cell carcinoma and adeno-carcinoma	Serous acinar neoplasm with multiple cell types	Salivary gland tumor with epidermoid, transitional and mucinous differentiation	Carcinoma with exclusively myoepithelial differentiation	Epithelial and myoepithelial neoplasm, with central glandular features	Metastatic clear cell renal cell carcinoma; occult primary	Clear cell carcinoma with squamous differentiation	Rare; biphasic ductal & myoepithelial cells with dense collagenous stroma
Histologic features	Corded growth; Monotonous cytology; Clear to eosi cytopla lack of keratin signific perine invasion; distinctive hyalinized stroma	Surface dysplasia/ CIS with deep	Blue-dense cytoplasmic granules; Many nonspecific)	Cystic with prominent mucin and true goblet-cell formation; change more common in epidermoid cells	Many patterns of growth (nodular, diffuse, nested, stroma; Ducts/ glands absent *variant may have mucin	Infiltrative; sheets; biphasic central hyalinization; rare oncocytic and apocrine variants	Pseudo-alveolar pattern; prominent	Surface dysplasia; stromal invasion; membrane material, pseudoglandul ar architecture	Infiltrative ducts/tubules, strands & cords in dense collagenous stroma Luminal ductal cells; flattened myoepithelial cells; Perineural invasion common
Mucin	Mucin + (50%)	Mucin +	Negative	Mucin +	Negative (*)	Negative	Negative	Negative	Negative
IHC	p40, p63, CK5/6; p16	p40, p63, CK5/6; CEA glands	DOG1, NR4A3; Negative p40, p63, CK5/6	p40, p63, CK5/6; CEA glands	S100, SOX10, p40, p63, CK5/6, GFAP, SMA, SMMHC	Luminal: CK7 Myoepithelial: S100, SOX10, p40, p63, CK5/6	CK-pan, PAX8, CAIX, vimentin, RCC	p40, p63, CK5/6; BSCC: SOX10, CD117	Luminal: CK7 Myoepithelial: p40, p63, CK5/6, S100, calponin
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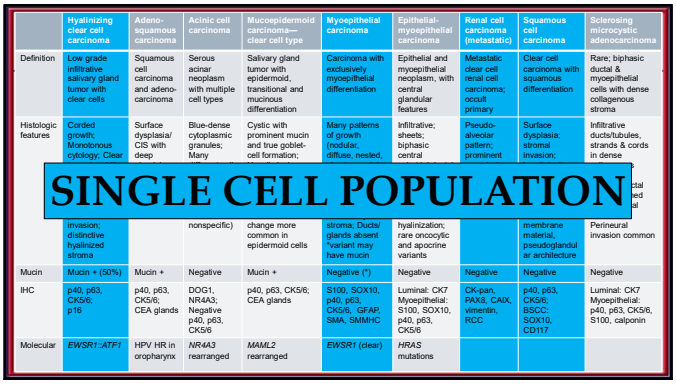

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DUAL CELL POPULATION

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Hyalinizing clear cell carcinoma: Clinical Features

A low-grade salivary gland carcinoma composed of clear and eosinophilic cells in a variably hyalinizing stroma usually with EWSR1 rearrangement

- Lacks features of other clear cell salivary gland tumors
- Sex: Females ~ Males
- Age: 6th decade; range 23-87 years
- Site: >80% minor salivary glands (palate, tongue)
- Symptoms: Slow growing submucosal swelling

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Hyalinizing clear cell carcinoma: Histologic Features

- Unencapsulated, infiltrating into adjacent tissues
- Frequent connection to surface epithelium, including pagetoid spread
- Sheets, cords, nests, or trabeculae of monotonous epithelial cells with variably clear to eosinophilic cytoplasm
  - Ducts and cysts may be present
  - Mucocytes and squamous differentiation is common
  - Prominent cell borders
- Perineural invasion usually prominent
- Densely hyalinized basement membrane-like to desmoplastic/fibrocellular stroma
- Necrosis, increased mitoses, and pleomorphism

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- Densely hyalinized basement membrane-like to desmoplastic/fibrocellular stroma
- Necrosis, increased mitoses, and pleomorphism → high grade transformation

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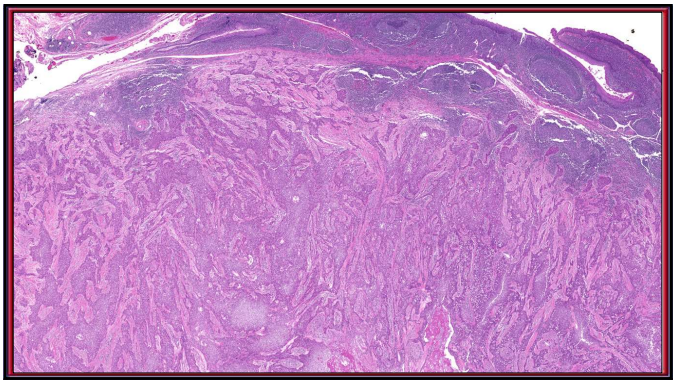

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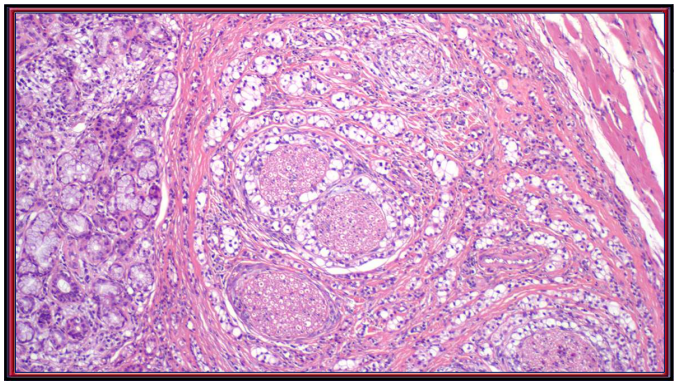

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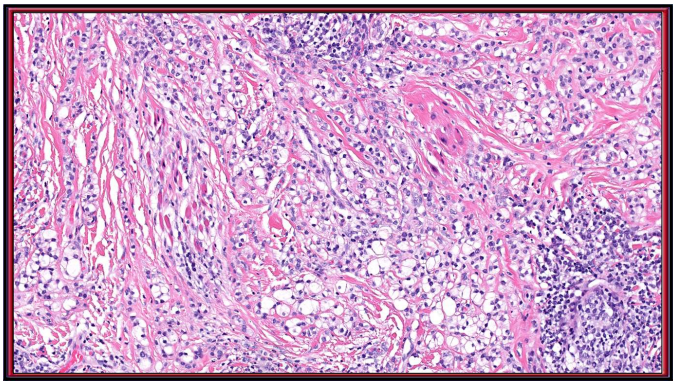

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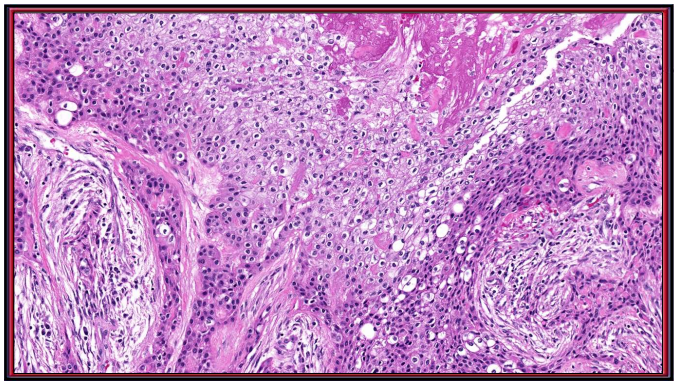

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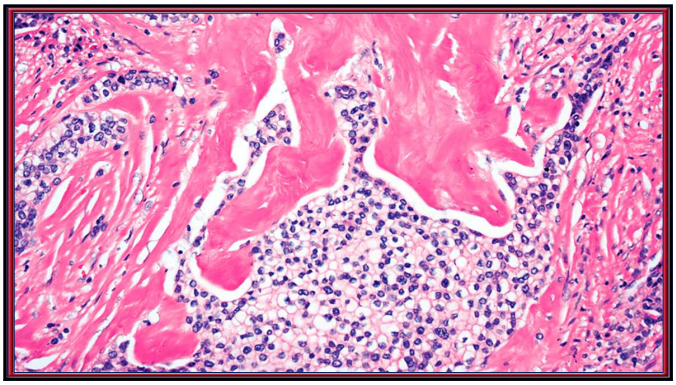

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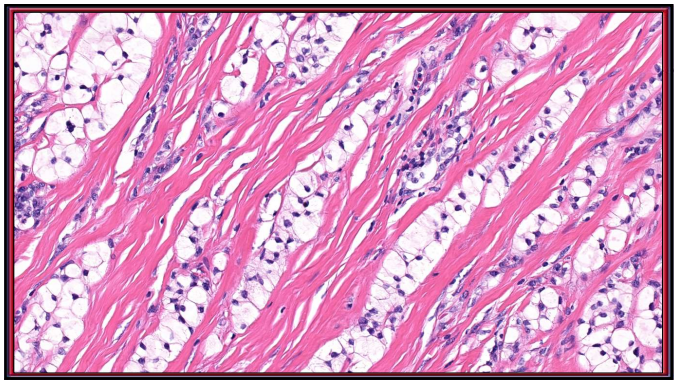

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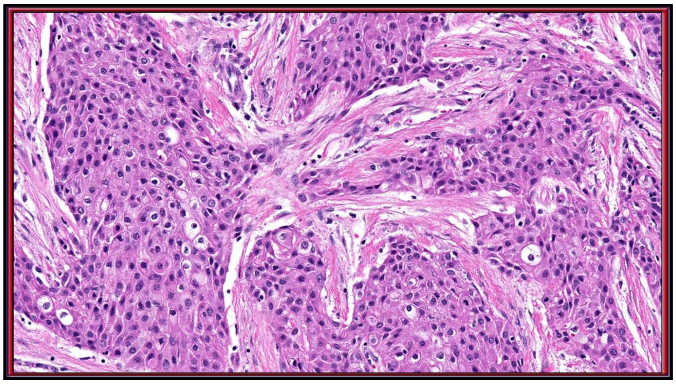

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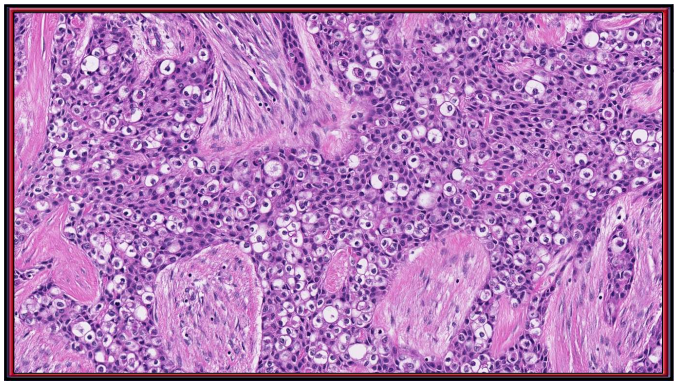

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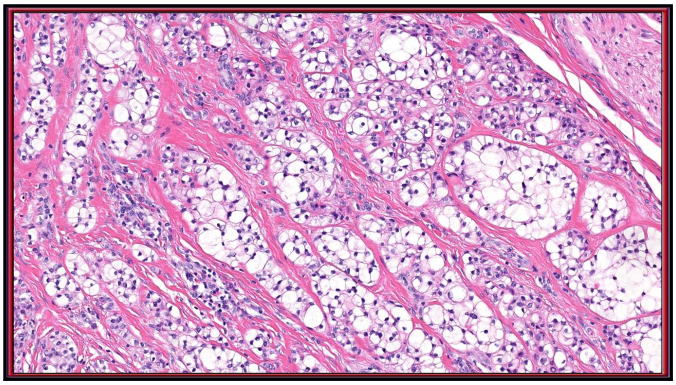

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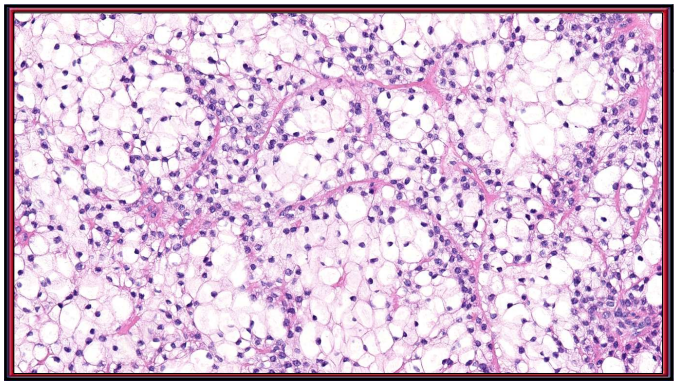

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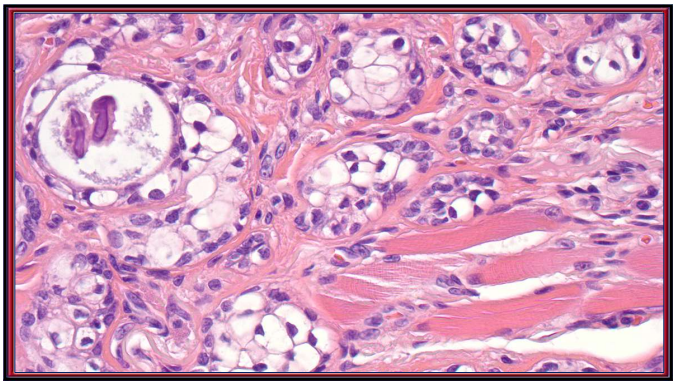

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Hyalinizing clear cell carcinoma: Special Studies

- Positive: PAS/diastase (glycogen)
  Mucicarmine (mucin)
- Positive: CK-pan, CAM5.2, EMA; CK7, CK14, CK19
  p63, p40, CK5/6; p16
- Negative: S100 protein, SMA, MSA, calponin,
  HR HPV RNA ISH
- Molecular: *EWSR1::ATF1* fusion (FISH)

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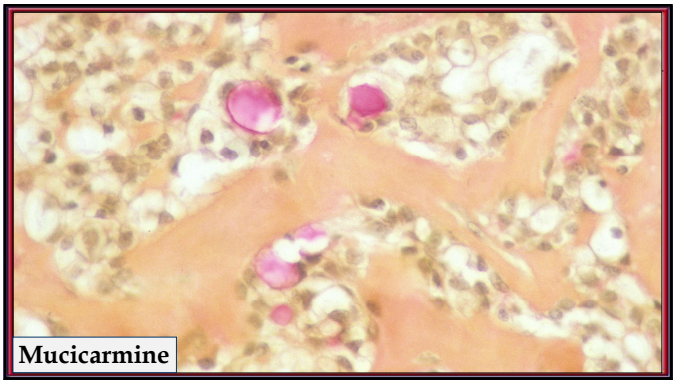

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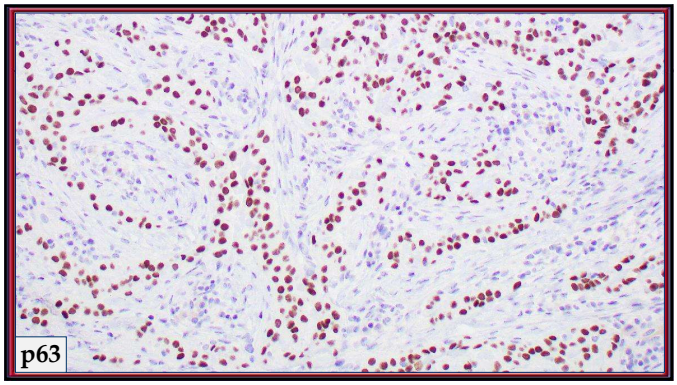

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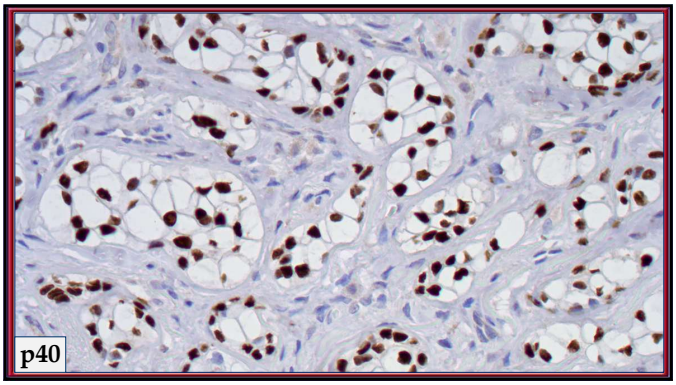

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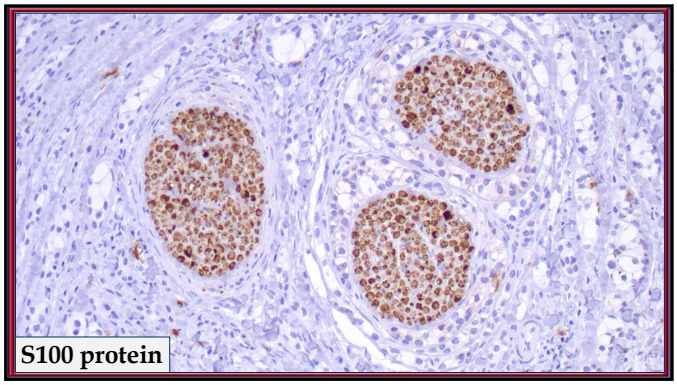

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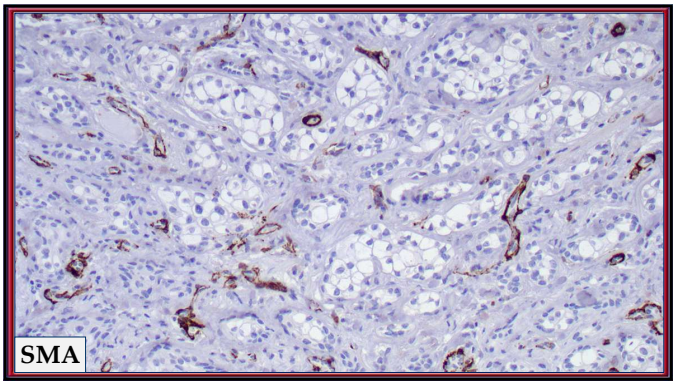

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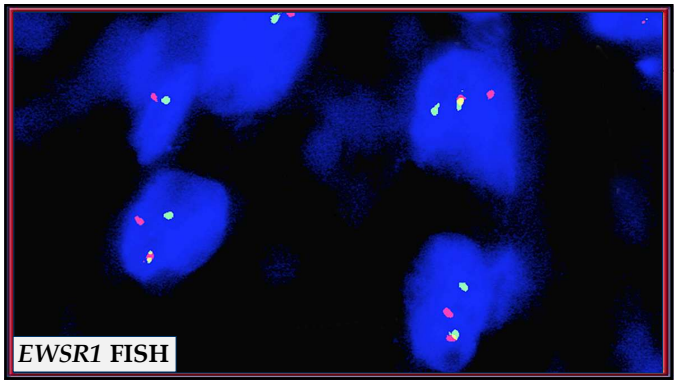

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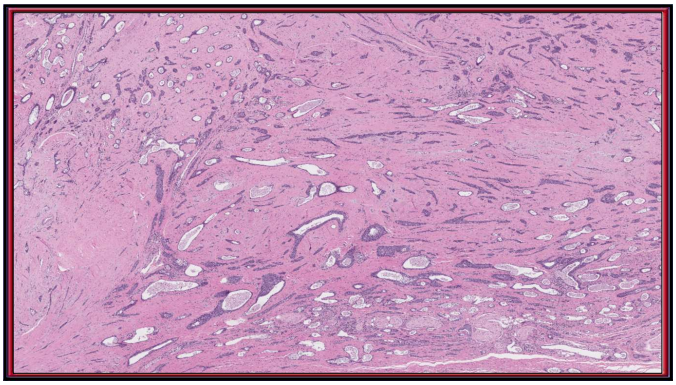
Sclerosing Microcystic Adenocarcinoma

Indolent biphasic ductal and myoepithelial carcinoma embedded in dense collagenous stroma

- Minor salivary glands (tongue)
- Infiltrative ducts/tubules, strands and cords in dense collagenous stroma
- Luminal lining ductal cells, surrounded by flattened myoepithelial cells
- Perineural invasion is common
- Positive (biphasic):
  - Luminal: CK7
  - Myoepithelial: p40, p63, CK5/6, S100 protein, calponin
- Indolent behavior without recurrence of metastasis

37



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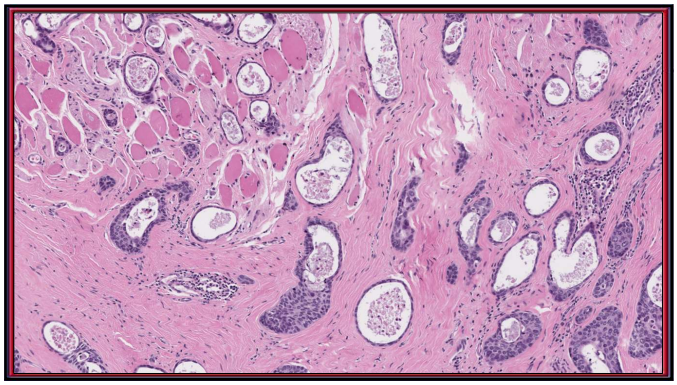

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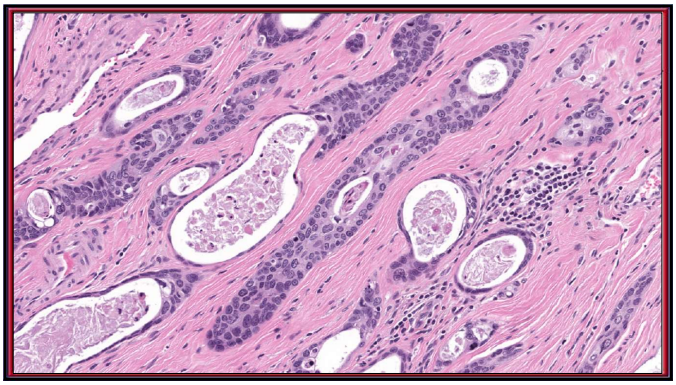

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	Hyalinizing clear cell carcinoma	Adeno-squamous carcinoma	Acinic cell carcinoma	Mucoepidermoid carcinoma—clear cell type	Myoepithelial carcinoma	Epithelial-myoepithelial carcinoma	Renal cell carcinoma (metastatic)	Squamous cell carcinoma	Sclerosing microcystic adenocarcinoma
Definition	Low grade infiltrative salivary gland tumor with clear cells	Squamous cell carcinoma and adeno-carcinoma	Serous acinar neoplasm with multiple cell types	Salivary gland tumor with epidermoid, transitional and mucinous differentiation	Carcinoma with exclusively myoepithelial differentiation	Epithelial and myoepithelial neoplasm, with central glandular features	Metastatic clear cell renal cell carcinoma; occult primary	Clear cell carcinoma with squamous differentiation	Rare; biphasic ductal & myoepithelial cells with dense collagenous stroma
Histologic features	Corded growth; Monotonous cytology; Clear to eosinophilic cytoplasm; lack of keratinization; significant perineural invasion; distinctive hyalinized stroma	Surface dysplasia/ CIS with deep glandular differentia-tion	Blue-dense cytoplasmic granules; Many different cell types (intercalated duct; glandular; clear; nonspecific)	Cystic with prominent mucin and true goblet-cell formation; Usually lacks significant overt keratinization; low grade tumors lack perineural invasion; clear cell change more common in epidermoid cells	Many patterns of growth (nodular, diffuse, nested, sheets, cords); plasmacytoid, epithelioid, spindled neoplastic cells mucoid/myxoid stroma; Ducts/ glands absent *variant may have mucin	Infiltrative; sheets; biphasic central cuboidal ductal epithelium, surrounded by cleared myoepithelial cells; lacks hyalinization; rare oncocytic and apocrine variants	Pseudo-alveolar pattern; prominent vascularity; clear cells; prominent cell borders; not biphasic; LVI	Surface dysplasia; stromal invasion; keratinization; pleomorphism; comedonecrosis; Basaloid type may have basement membrane material, pseudoglandular architecture	Infiltrative ducts/tubules, strands & cords in dense collagenous stroma Luminal ductal cells; flattened myoepithelial cells; Perineural invasion common
Mucin	Mucin + (50%)	Mucin +	Negative	Mucin +	Negative (*)	Negative	Negative	Negative	Negative
IHC	p40, p63, CK5/6; p16	p40, p63, CK5/6; CEA glands	DOG1, NR4A3; Negative p40, p63, CK5/6	p40, p63, CK5/6; CEA glands	S100, SOX10, p40, p63, CK5/6, GFAP, SMA, SMMHC	Luminal: CK7 Myoepithelial: S100, SOX10, p40, p63, CK5/6	CK-pan, PAX8, CAIX, vimentin, RCC	p40, p63, CK5/6; BSCC: SOX10, CD117	Luminal: CK7 Myoepithelial: p40, p63, CK5/6, S100, calponin
Molecular	*EWSR1::ATF1*	HPV HR in oropharynx	*NR4A3* rearranged	*MAML2* rearranged	*EWSR1* (clear)	*HRAS* mutations			

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Squamous cell carcinoma

Primary mucosal tumor with variable squamous differentiation

- Note: Metastatic SCC to major salivary gland lymph nodes is the most common malignancy identified in salivary glands
- Surface origin (mucosal sites); keratinization generally noted; degree of differentiation varies
- Tumor necrosis and high mitoses common
- Desmoplastic stromal reaction
- Positive (single population): CK-pan, p40, p63, CK5/6
- Prognosis based on many factors

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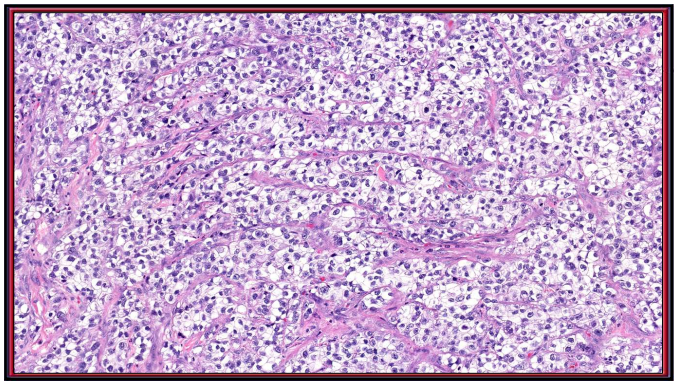

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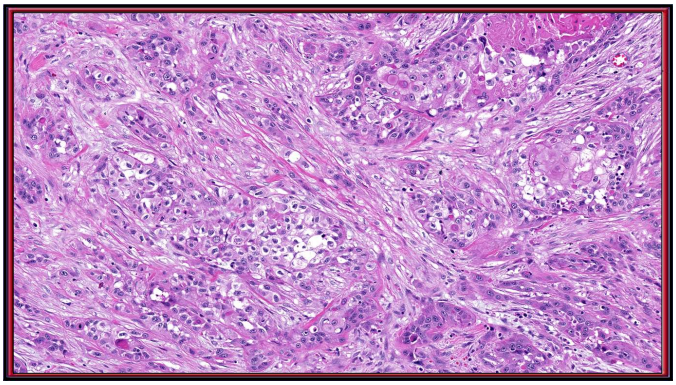

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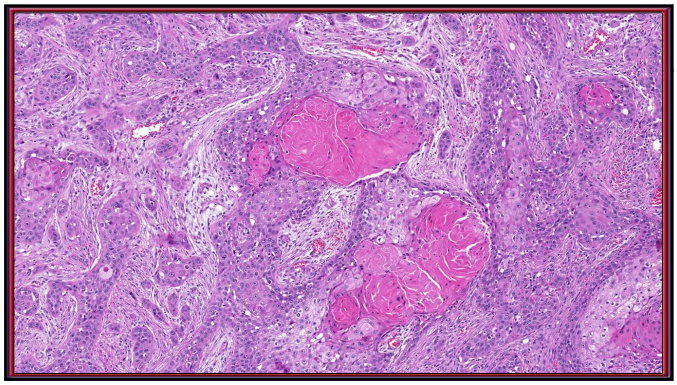

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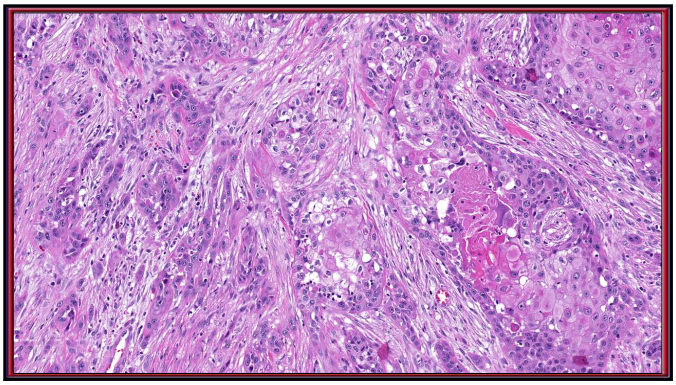

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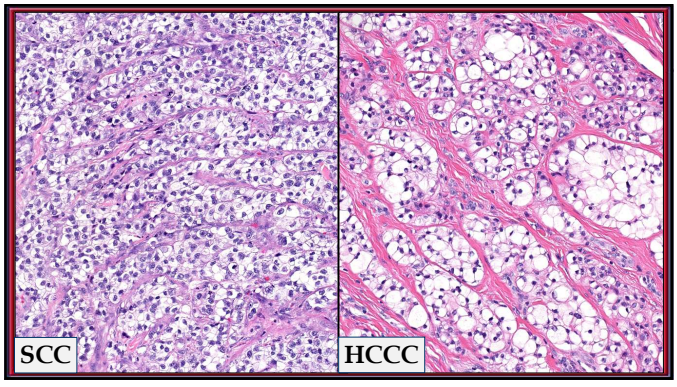

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	Hyalinizing clear cell carcinoma	Adeno-squamous carcinoma	Acinic cell carcinoma	Mucoepidermoid carcinoma—clear cell type	Myoepithelial carcinoma	Epithelial-myoepithelial carcinoma	Renal cell carcinoma (metastatic)	Squamous cell carcinoma	Sclerosing microcystic adenocarcinoma
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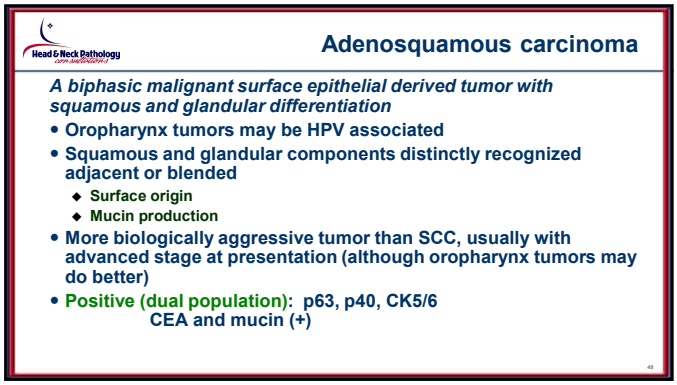

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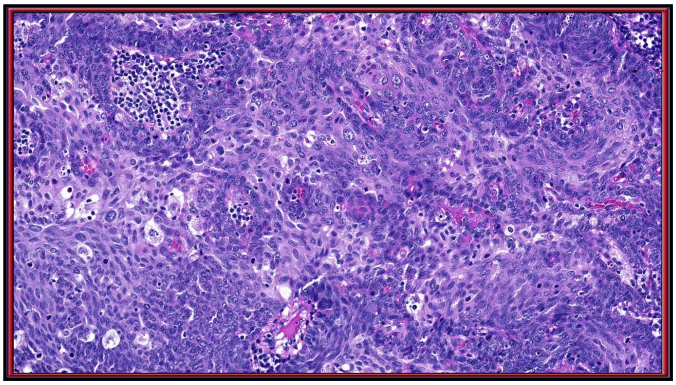

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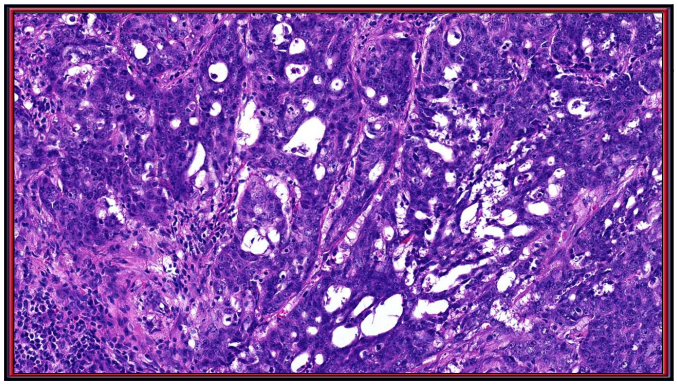

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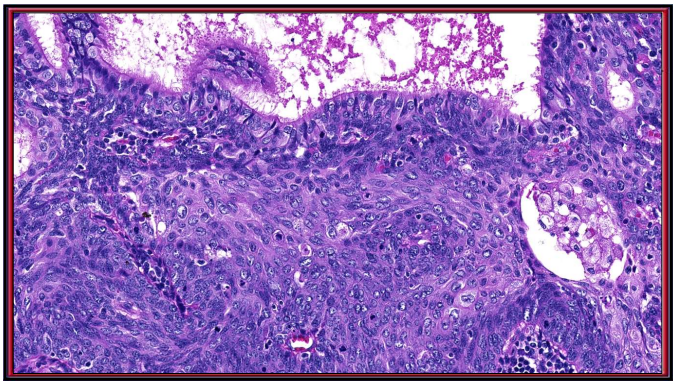

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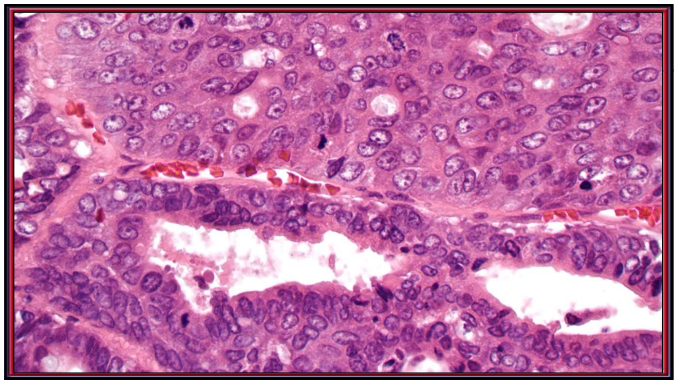

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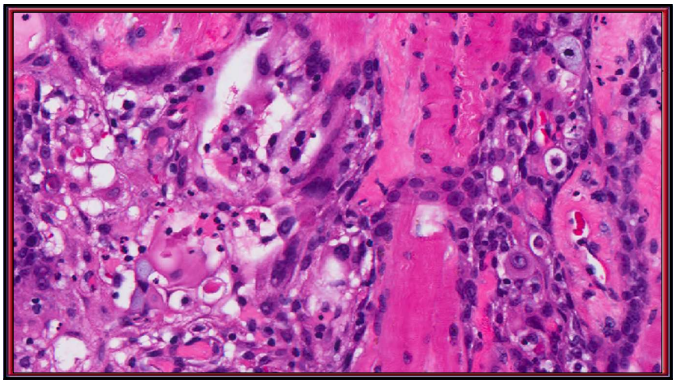

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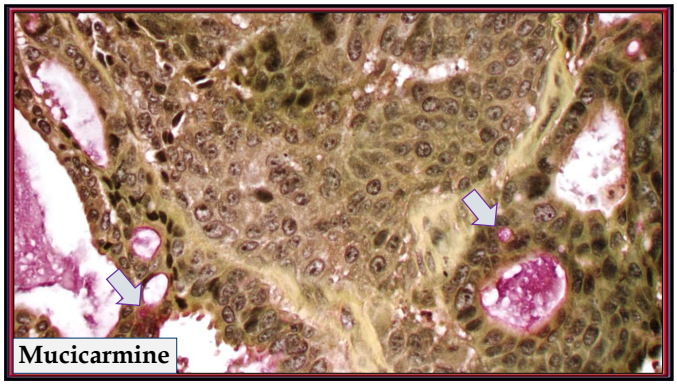

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Molecular	*EWSR1::ATF1*	HPV HR in oropharynx	*NR4A3* rearranged	*MAML2* rearranged	*EWSR1* (clear)	*HRAS* mutations			

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Head & Neck Pathology

Mucoepidermoid carcinoma

Malignant salivary gland carcinoma with mucous, intermediate and epidermoid cells forming cystic and solid growth, usually associated with MAML2 rearrangement

- Major and minor glands equally
- Solid and cystic
- Mucous (goblet-like cells), intermediate and squamoid cells
- Clear cells may predominate
- Sclerosis is common
- Positive (biphasic): p63, p40, CK5/6; CEA; mucicarmine
- *MAML2* rearrangements
- Outcome is grade and stage dependent

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Head & Neck Pathology

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- Clear cells may predominate
- Sclerosis is common
- Positive (biphasic): p63, p40, CK5/6; CEA; mucicarmine
- *MAML2* rearrangements—but *EWSR1::POU5F1* also reported
- Outcome is grade and stage dependent

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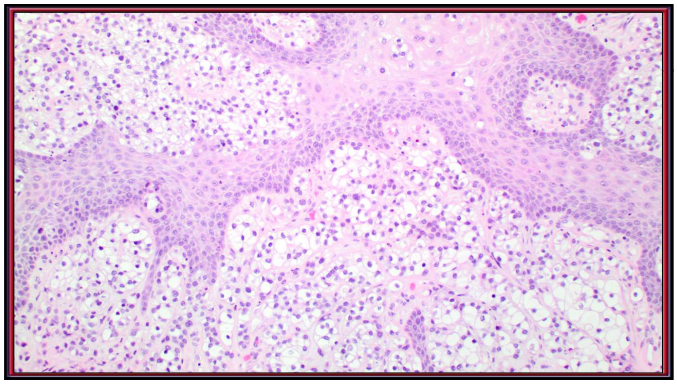

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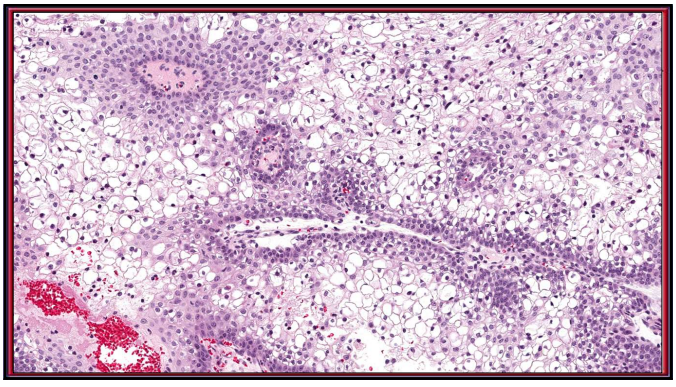

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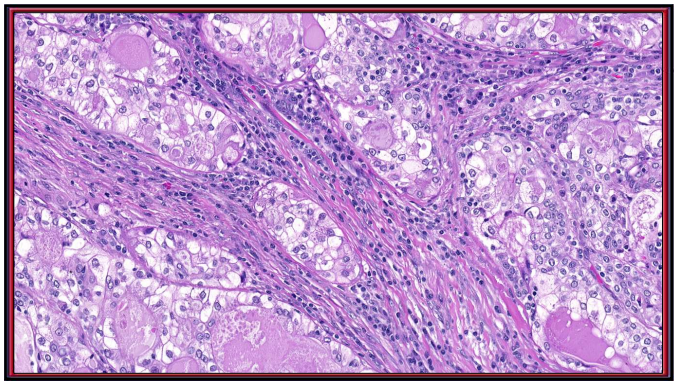

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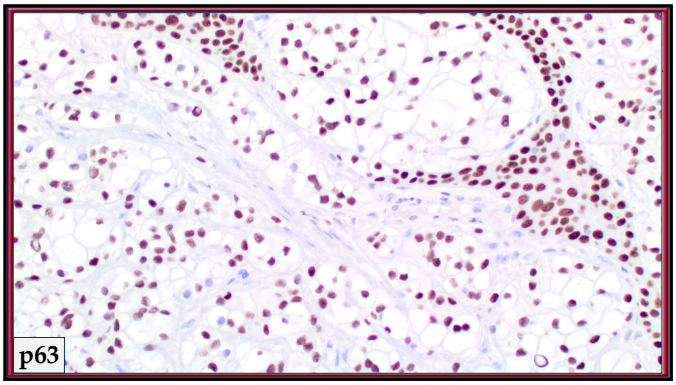

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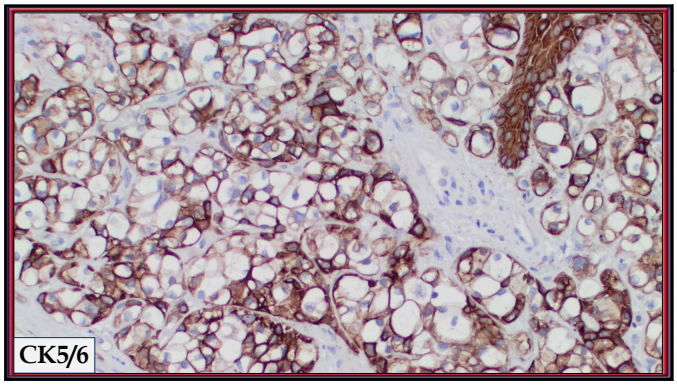

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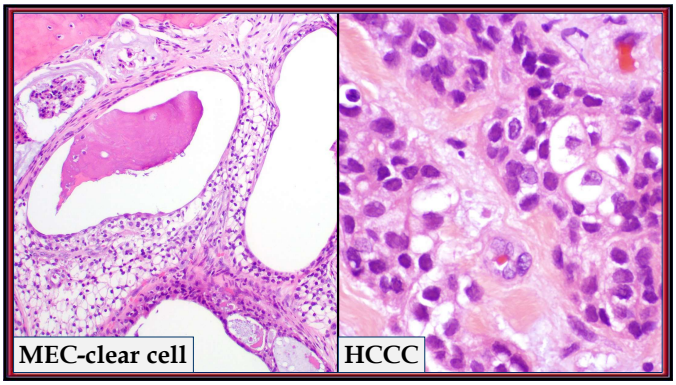

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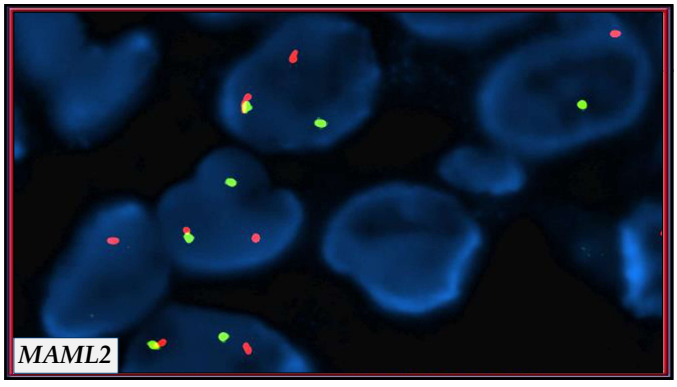

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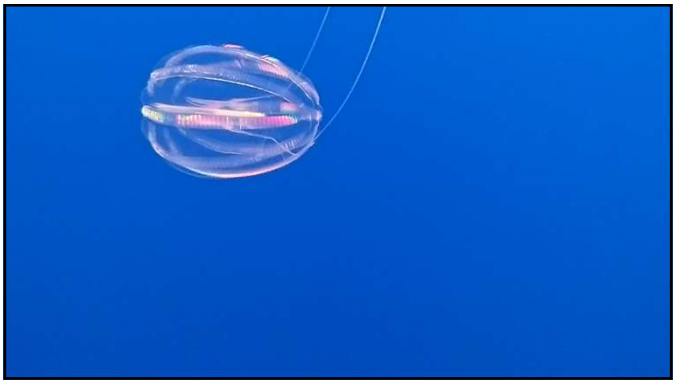

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Head & Neck Pathology

Myoepithelial carcinoma

A malignant salivary gland neoplasm exclusively of myoepithelial cells with invasive growth

- Palate > submandibular gland
- Often as carcinoma in Ca-Ex-PA; Relatively aggressive
- Diverse architecture: solid, trabecular, reticular
- Diverse morphologies: spindled, epithelioid, plasmacytoid, vacuolated, clear
- Stroma is myxoid, mucoid, hyalinized stroma
- Positive (single population): CK-pan, CK14, p40, p63, SOX10, S100 protein, GFAP, SMA, calponin
- Molecular: *EWSR1* rearrangements in clear tumors

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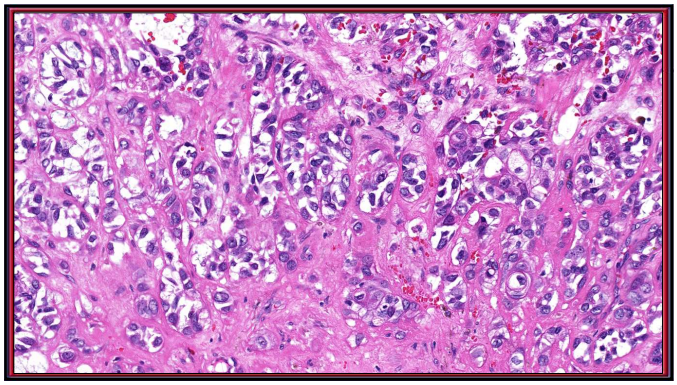

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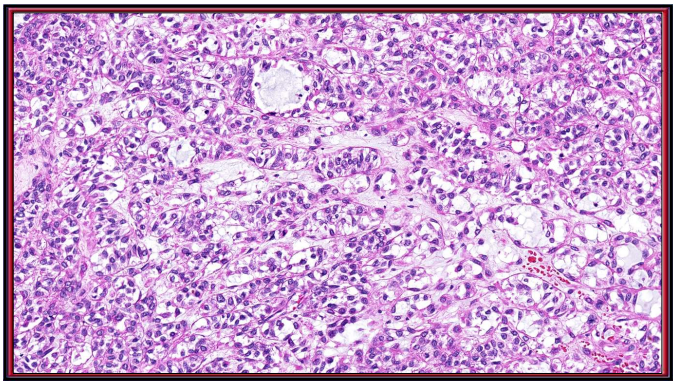

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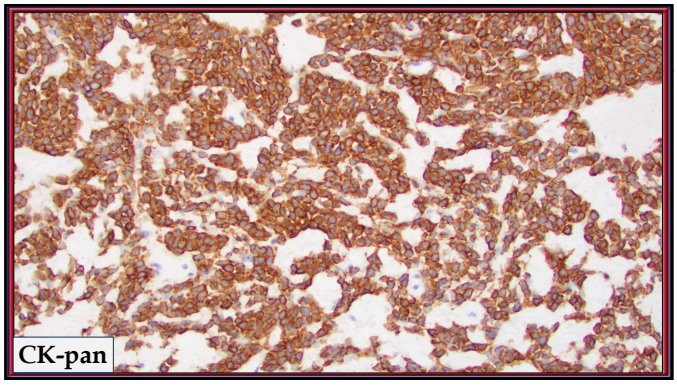

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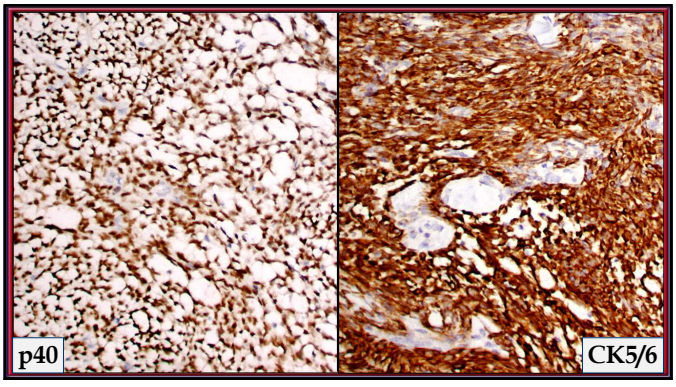

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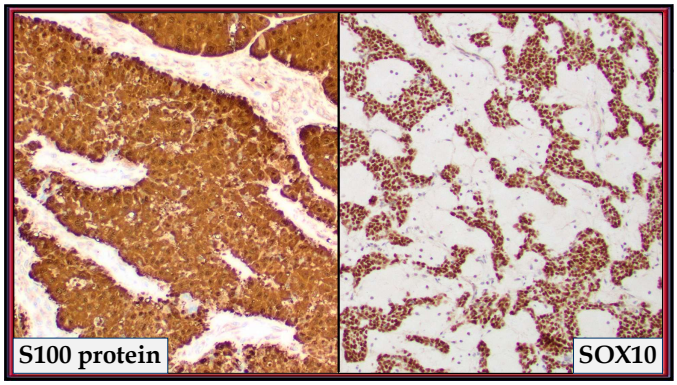

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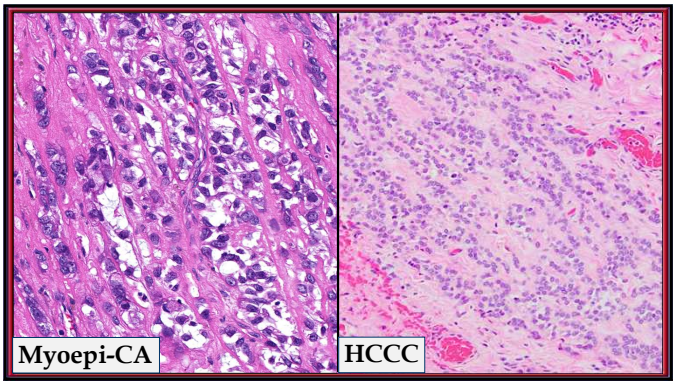

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Head & Neck Pathology

Epithelial-myoepithelial carcinoma

Salivary gland malignancy characterized by biphasic tubular structures with tightly coupled inner ductal and prominent outer myoepithelial cells

- **Major salivary gland most common**
  - **May represent carcinoma in Ca-Ex-PA**
- **Multinodular biphasic growth**
  - **Inner luminal ductal cells surrounded by**
  - **Outer (abluminal) cleared myoepithelial cells (single/multilayered)**
- **Positive (biphasic):**
  - **Luminal: CK7; RAS membranous**
  - **Abluminal: SMA, calponin, SOX10, p40, p63**
- **Molecular: Many have *HRAS* mutations (codon 61)**

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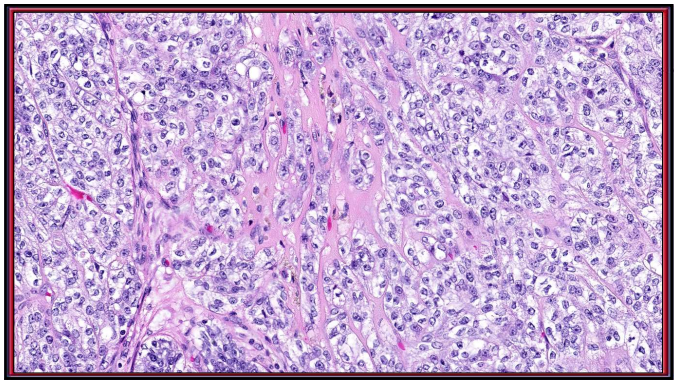

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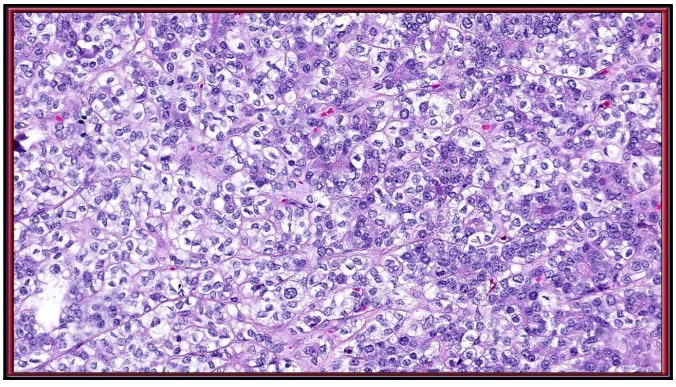

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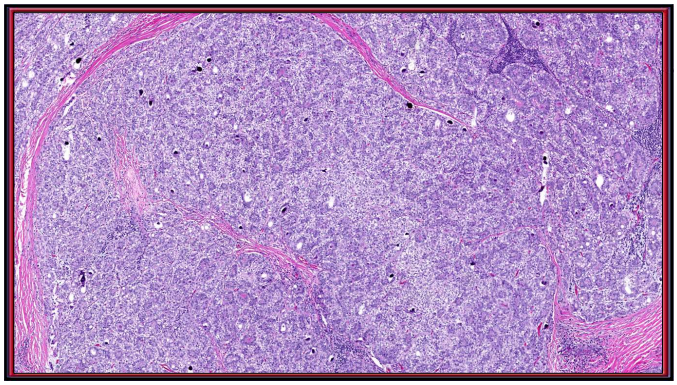

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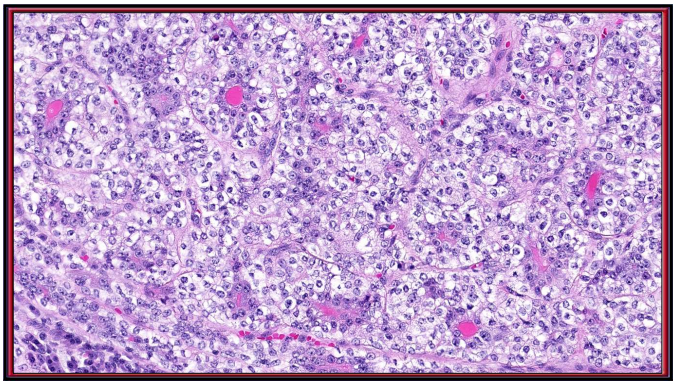

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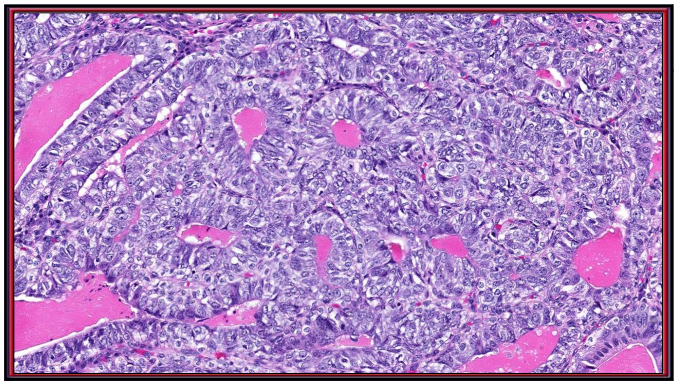

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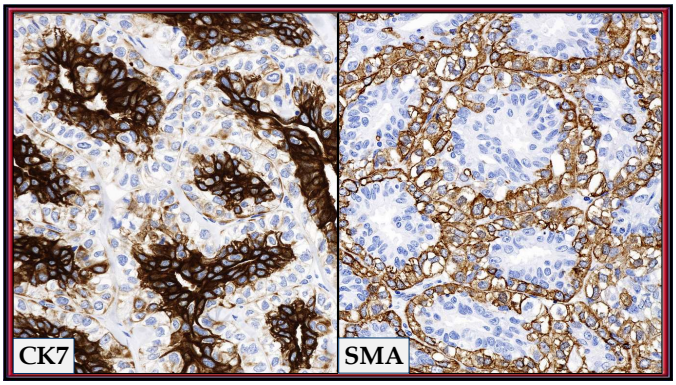

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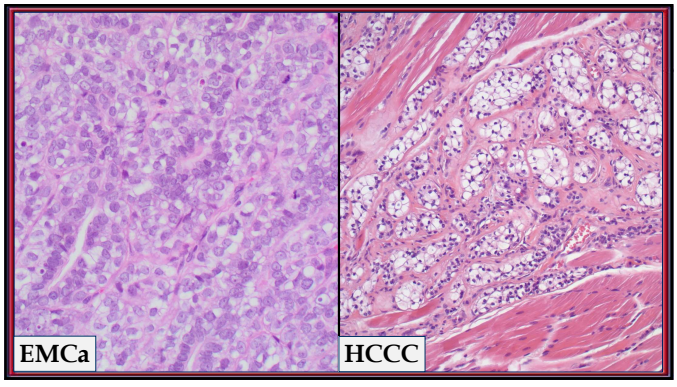

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Acinic Cell Carcinoma

Malignant epithelial salivary gland neoplasm demonstrating serous acinar cell differentiation with cytoplasmic zymogen secretory granules

- Incidence: Common malignant salivary gland neoplasm
- Sex: Female > Male (3:2)
- Site: Major >>>>> Minor salivary glands
- Specific pattern is the dominant or only finding
  - Solid, microcystic, papillary-cystic, follicular
  - However, combinations and spectrum are common

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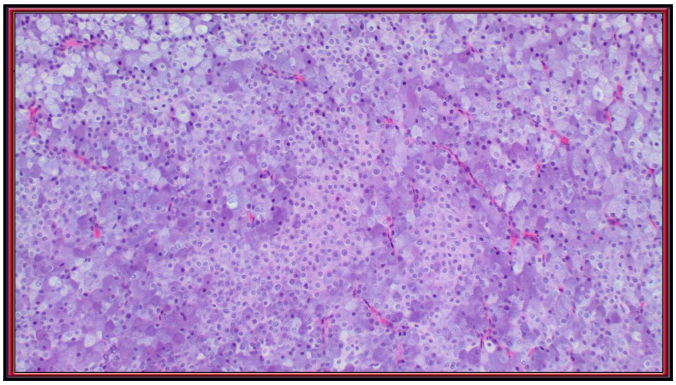

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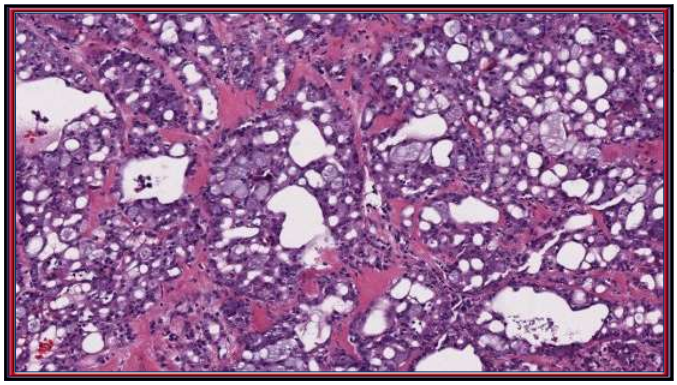

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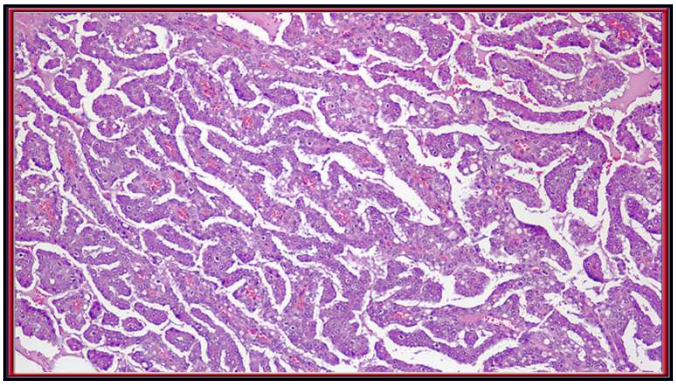

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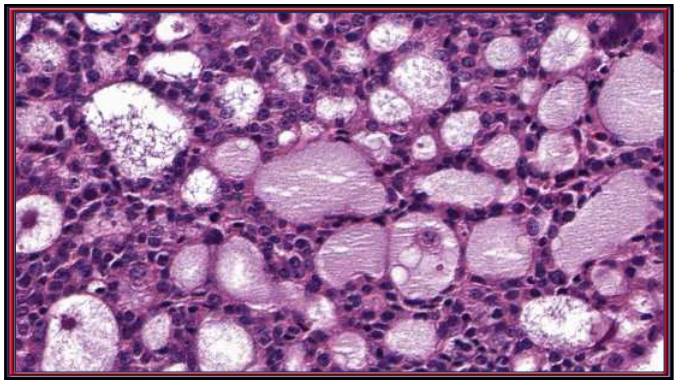

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Acinic cell carcinoma: Cell types

- Serous acinar cells: Large, polygonal cells with abundant lightly basophilic, granular cytoplasm
  - Strong resemblance to normal serous acini cells
  - Dense, gray to blue to purple, fine to coarse zymogen granules
- Intercalated duct type cells: Surround luminal spaces and tend to be smaller, eosinophilic to amphophilic cells with central nuclei
- Nonspecific glandular cells: Round to polygonal, often syncytial, and smaller than acinar cells
  - Amphophilic to eosinophilic cytoplasm without granules
- Clear cells have nonstaining cytoplasm with prominent cell borders (no glycogen)
- Vacuolated cells have clear, large cytoplasmic vacuoles
  - PAS and mucicarmine negative

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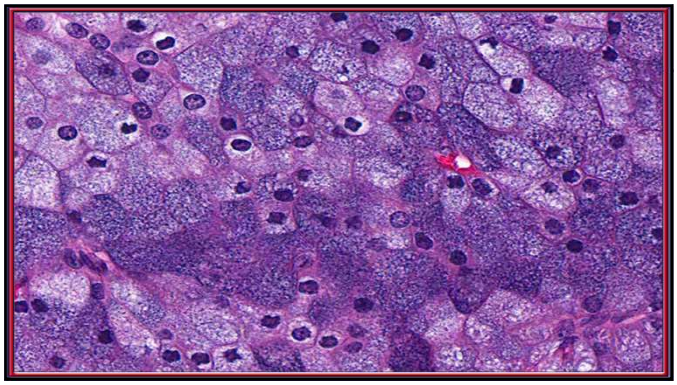

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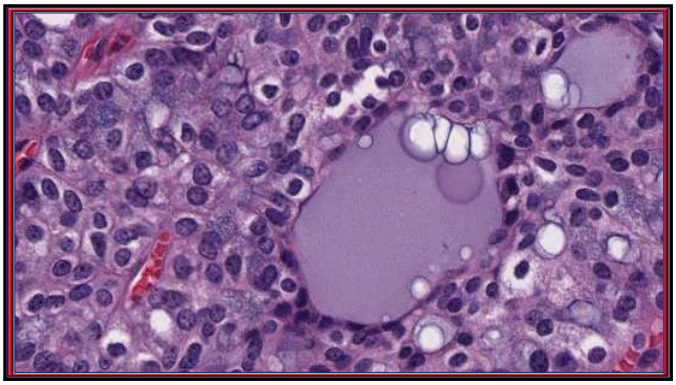

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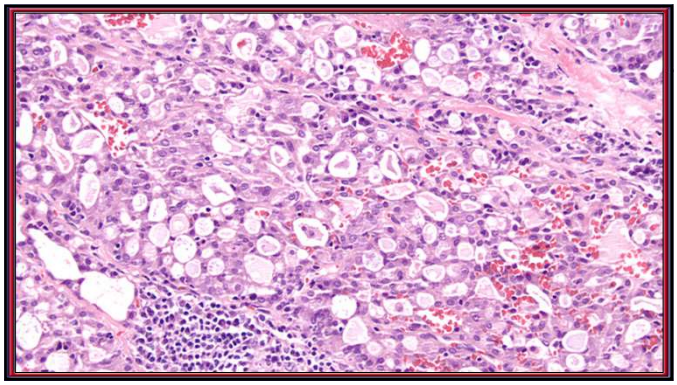

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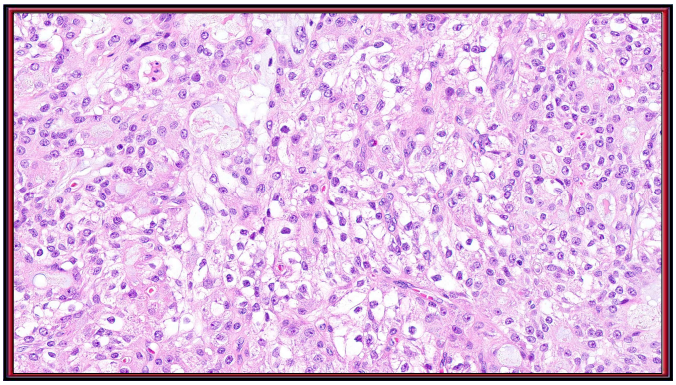

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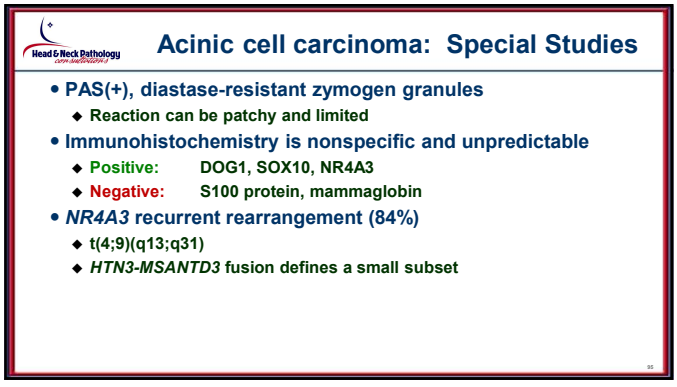

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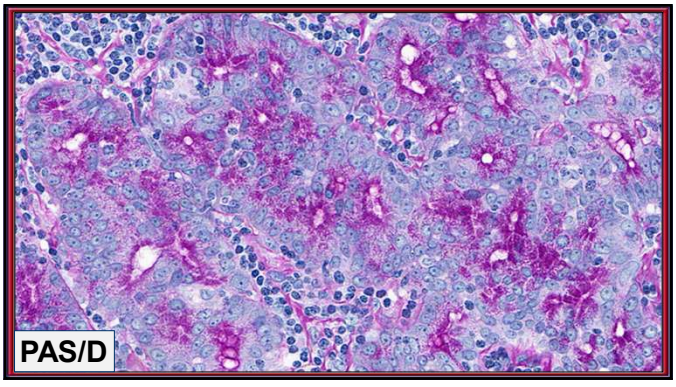

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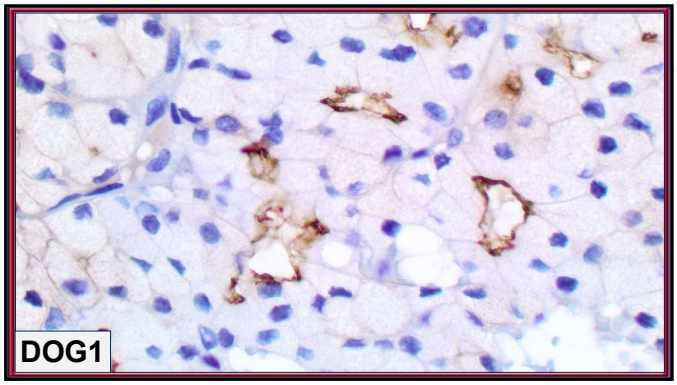

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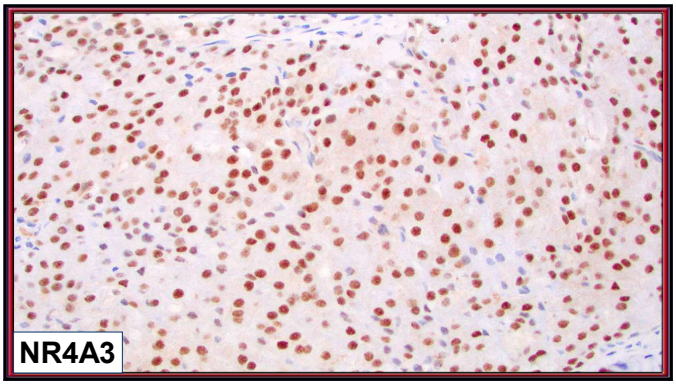

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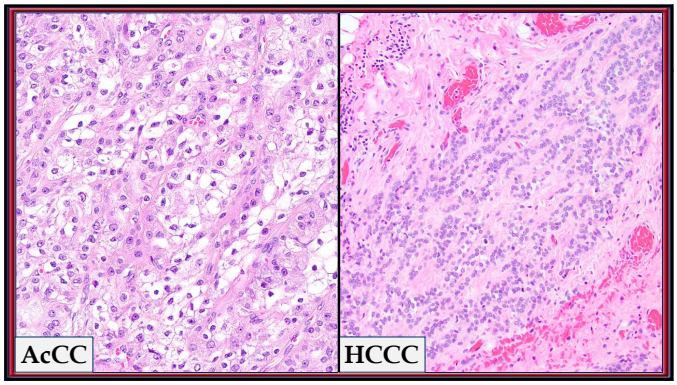

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Head & Neck Pathology

Renal cell carcinoma

Metastatic (secondary) tumor of head and neck sites via lymphovascular spread

- Often present as a mass lesion; may be occult primary
- Kidney clear cell carcinomas are a common tumor to metastasize to oral cavity and salivary glands
- Histology:
  - Alveolar pattern with extravasated erythrocytes
  - Cleared to eosinophilic cytoplasm
  - Prominent cell borders
- Positive (single population): CK-pan, PAX8, CAIX, CK7

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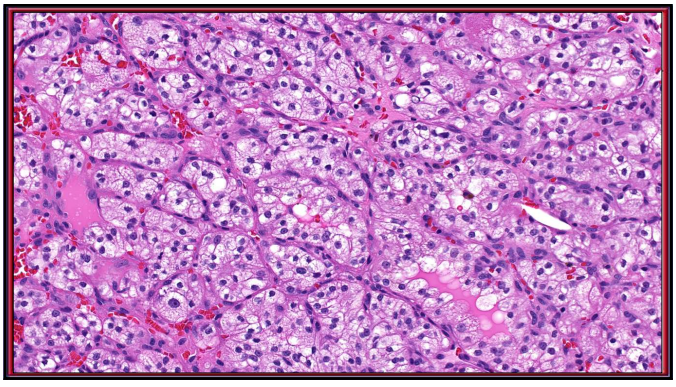

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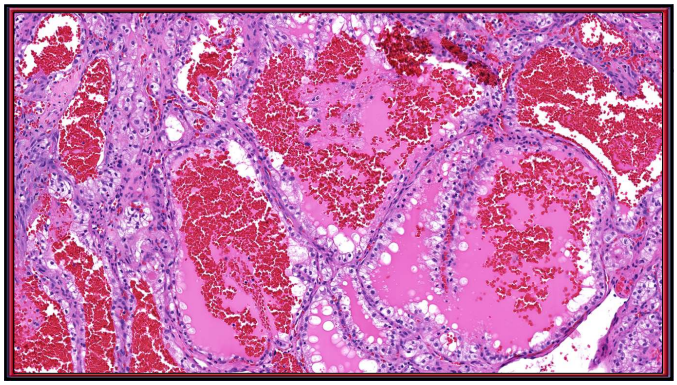

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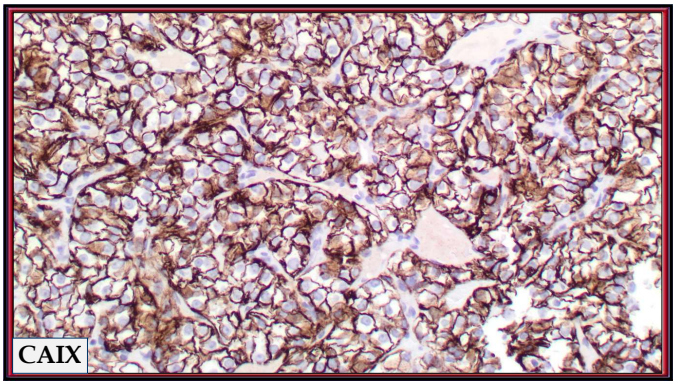

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Differential Diagnosis (Closing/Summary)

- Hyalinizing clear cell carcinoma
- Adenosquamous carcinoma / Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Myoepithelial carcinoma
- Epithelial-myoepithelial carcinoma
- Renal cell carcinoma
- Squamous cell carcinoma / Sclerosing microcystic adenocarcinoma

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