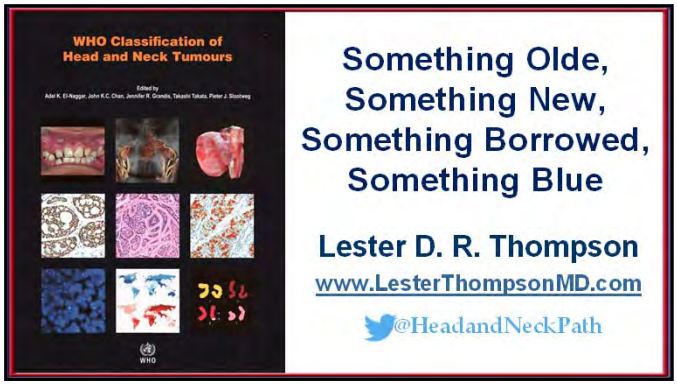
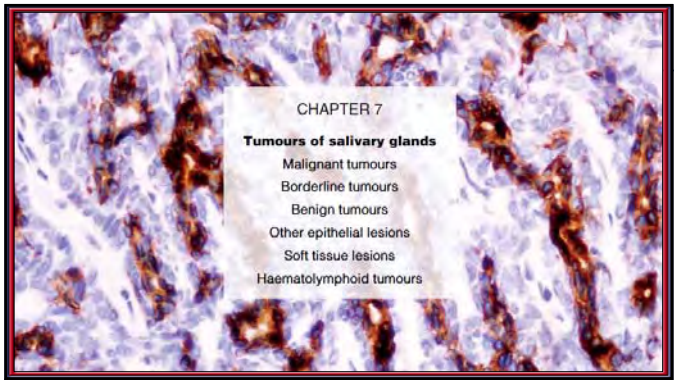



## General Considerations

- <1% of all tumors
- Most common in adults
- Fine needle aspiration first line screening test
- Little known about etiology
- Clinic stage is important
- Molecular techniques slow to catch on

## Salivary Gland Genetics

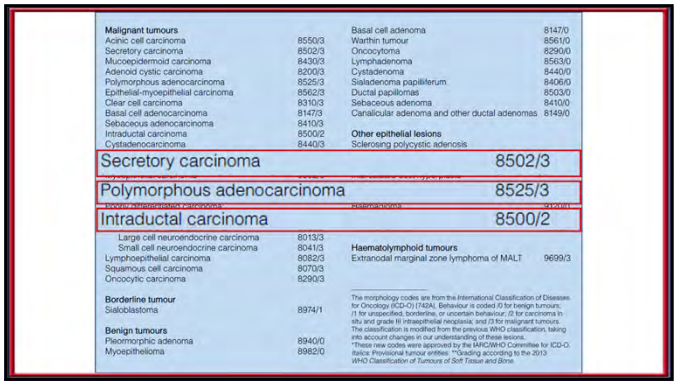
| Tumor | Gene | Frequency |
|---|---|---|
| Pleomorphic adenoma | *PLAG1* (8q12) (70%)<br>*HMGA2* (12q14-15) (20%) | Up to 90% |
| Basal cell adenoma | *CTNNB1* mutation | 70-80% |
| Mucoepidermoid carcinoma | *CRTC1-MAML2* (*CRTC3*) t(11;19)(q21;p13) | 80% (not grade associated) |
| Acinic cell carcinoma | t(4;9)(q13;q31) & *HTN3-MSANTD3* fusion | 80% and 10% |
| Adenoid cystic carcinoma | *MYB-NFIB* (*MYBL1*)<br>t(6;9)(q22-23;p23-24) | 60-70% |
| Polymorphous adenocarcinoma | *ARID1A-PRKD1* (*PRKD2*, *PRKD3*) or<br>*PRKD1* hotspot | 20-50% |
| Salivary duct carcinoma | *TP53*, *HRAS*, *PIK3CA*, *PTEN* mutations;<br>*ERBB2* amplification | 90% |
| Secretory carcinoma | *ETV6-NTRK3* (*RET*, *MET*)<br>t(12;15)(p13;q25) | >95% |
| Intraductal carcinoma | *NCOA4-RET* or *RET-TRIM27* | 50% |
| Clear cell carcinoma | *EWSR1-ATF1* (*CREM*) t(12;22)(q13;q12) | 90% |

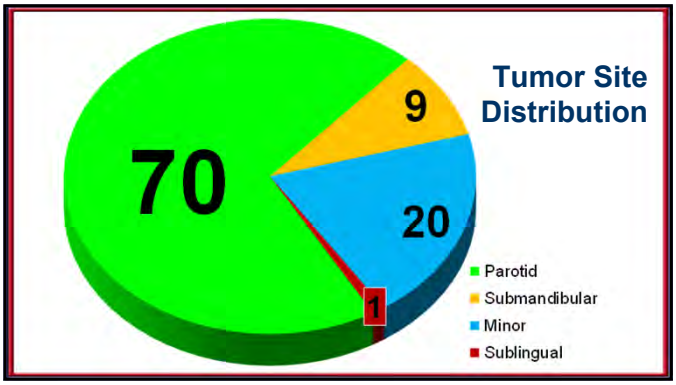



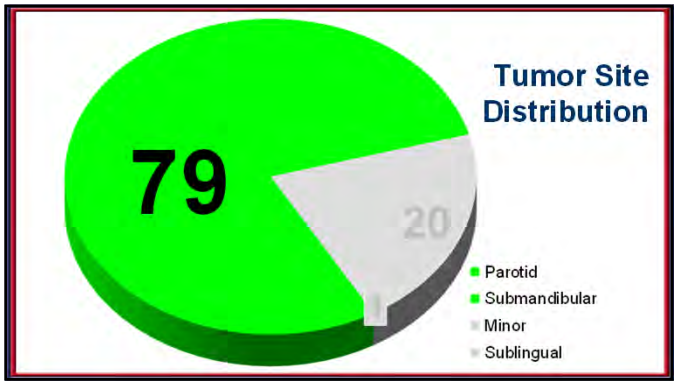

## Salivary Glands

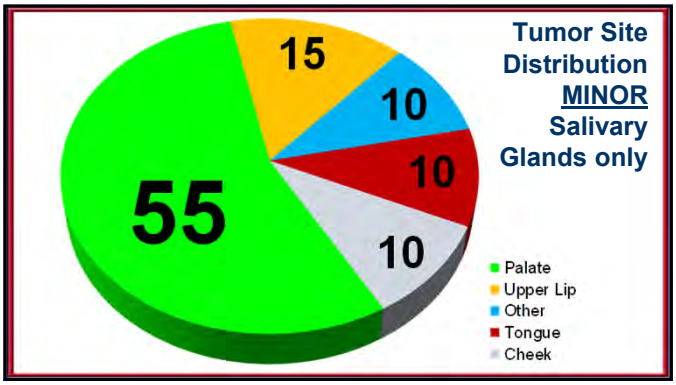
**2005 edition: 42 diagnoses**

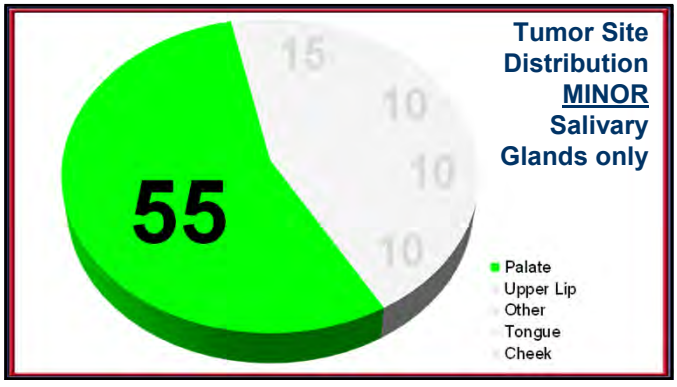
**2017 edition: 45 diagnoses**


Malignant tumours
Acinic cell carcinoma 8550/3
Secretory carcinoma 8502/3
Mucoepidermoid carcinoma 8430/3
Adenoid cystic carcinoma 8200/3
Polymorphous adenocarcinoma 8525/3
Epithelial-myoepithelial carcinoma 8562/3
Clear cell carcinoma 8310/3
Basal cell adenocarcinoma 8147/3
Sebaceous adenocarcinoma 8410/3
Intraductal carcinoma 8500/2
Cystadenocarcinoma 8440/3
Large cell neuroendocrine carcinoma 8013/3
Small cell neuroendocrine carcinoma 8041/3
Lymphoepithelial carcinoma 8082/3
Squamous cell carcinoma 8070/3
Oncocytic carcinoma 8290/3
Borderline tumour
Sialoblastoma 8974/1
Benign tumours
Pleomorphic adenoma 8940/0
Myoepithelioma 8982/0
Basal cell adenoma 8147/0
Warthin tumour 8561/0
Oncocytoma 8290/0
Lymphadenoma 8563/0
Cystadenoma 8440/0
Sialadenoma papilliferum 8406/0
Ductal papillomas 8503/0
Sebaceous adenoma 8410/0
Canalicular adenoma and other ductal adenomas 8149/0
Other epithelial lesions
Sclerosing polycystic adenosis
Secretory carcinoma 8502/3
Polymorphous adenocarcinoma 8525/3
Intraductal carcinoma 8500/2
Haematolymphoid tumours
Extranodal marginal zone lymphoma of MALT 9699/3


Tumor Site Distribution
70
9
20
1
Parotid
Submandibular
Minor
Sublingual


Tumor Site Distribution
79
20
1
Parotid
Submandibular
Minor
Sublingual


Tumor Site Distribution MINOR Salivary Glands only
55
15
10
10
10
Palate
Upper Lip
Other
Tongue
Cheek


Tumor Site Distribution MINOR Salivary Glands only
55
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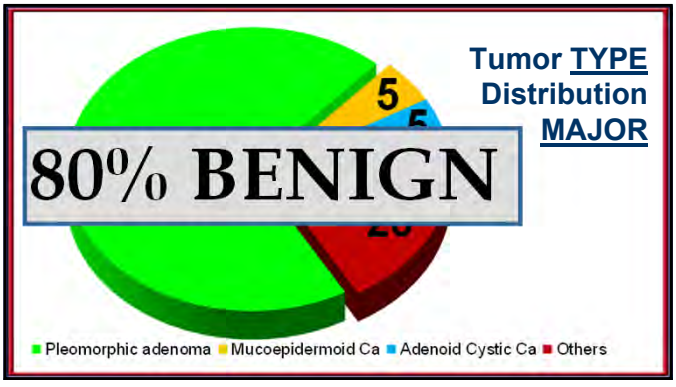
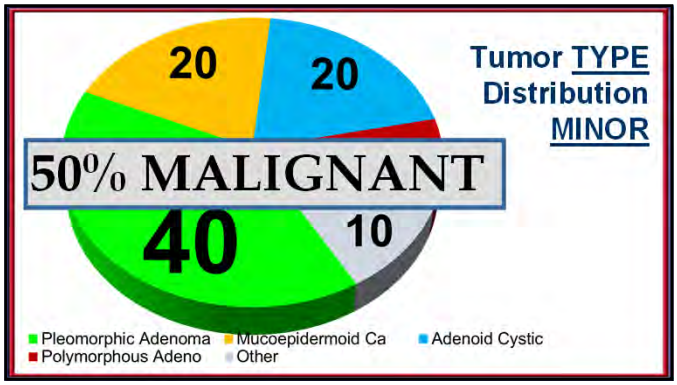
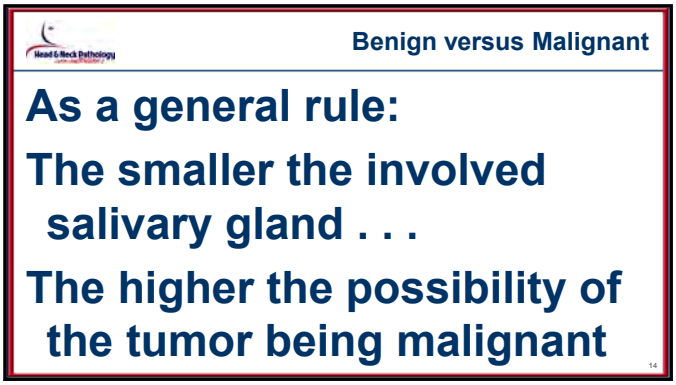
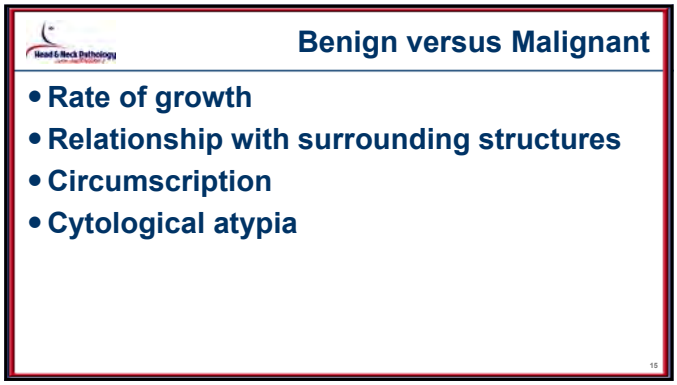
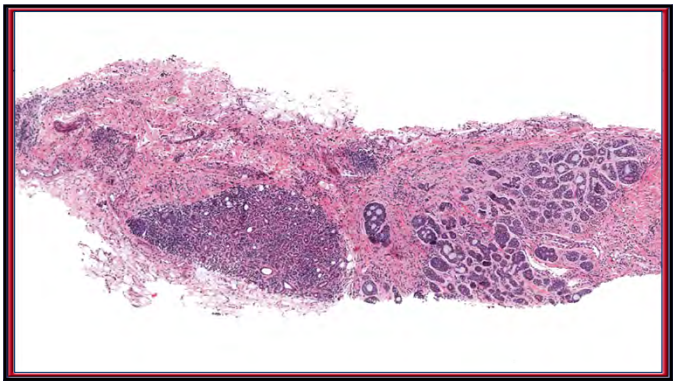
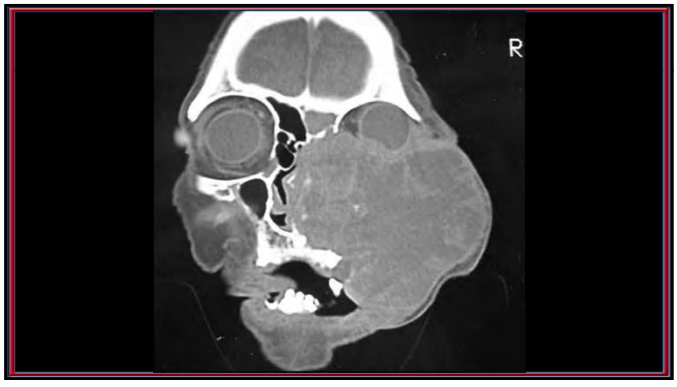

Tumor TYPE Distribution MAJOR
80% BENIGN
5
Pleomorphic adenoma
Mucoepidermoid Ca
Adenoid Cystic Ca
Others

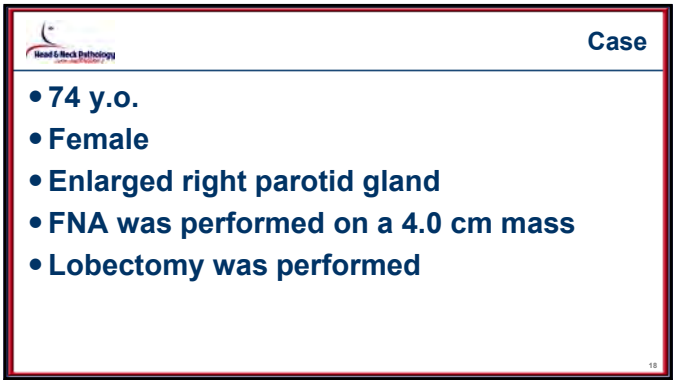

Tumor TYPE
Distribution
MINOR
20
20
50% MALIGNANT
40
10
Pleomorphic Adenoma
Mucoepidermoid Ca
Adenoid Cystic
Polymorphous Adeno
Other


Benign versus Malignant
As a general rule:
The smaller the involved salivary gland . . .
The higher the possibility of the tumor being malignant


Benign versus Malignant
• Rate of growth
• Relationship with surrounding structures
• Circumscription
• Cytological atypia




R


Case
• 74 y.o.
• Female
• Enlarged right parotid gland
• FNA was performed on a 4.0 cm mass
• Lobectomy was performed

## Acinic Cell Carcinoma

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

- Incidence
  - ~ 6% of salivary gland tumors (2nd to MEC)
  - ~ 10-12% of all malignant salivary gland tumors
- Sex: Female > Male (3:2)
- Age: Wide range
  - Mean: 5th decade
  - 2nd most common malignant salivary gland tumor in children (after MEC)
- Presentation: Slowly growing mass
  Vague pain – usually for years!


## Acinic cell carcinoma Site

- Parotid gland most common (95%)
  - Parotid is largest salivary gland, comprised nearly exclusively of serous type acini
- Minor salivary glands 2nd most common site (but doubt: may be SC, PAC-C)
  - Intraoral, buccal mucosa, upper lip, and palate specifically (5%)
- Most common bilateral salivary gland malignancy
  - Dwarfed by bilateral Warthin tumor and pleomorphic adenoma

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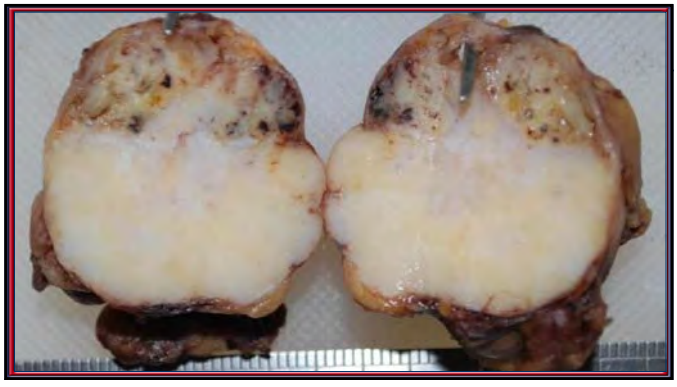
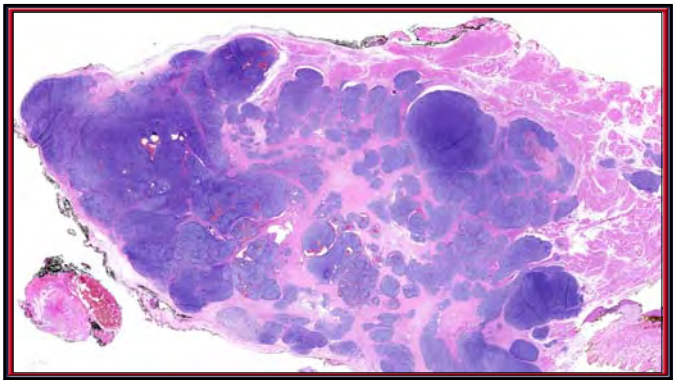
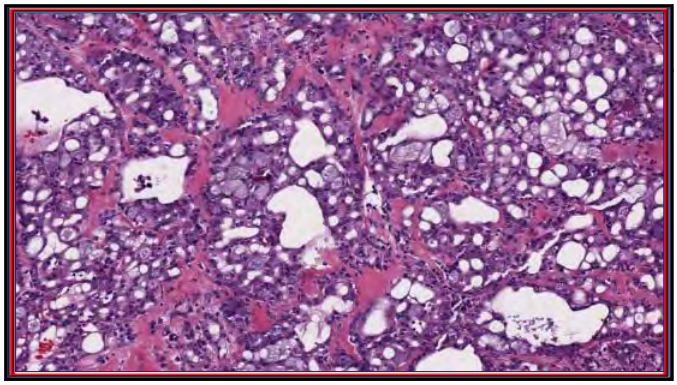
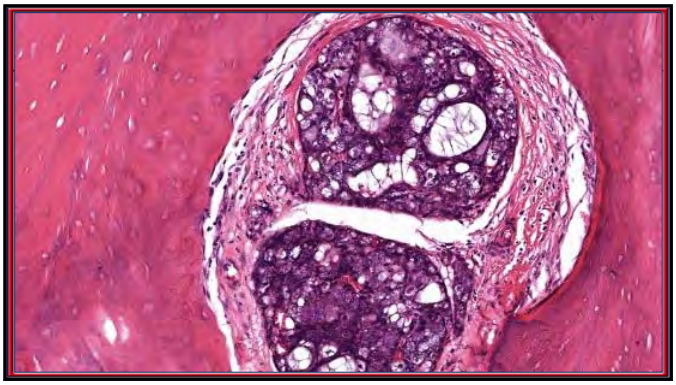




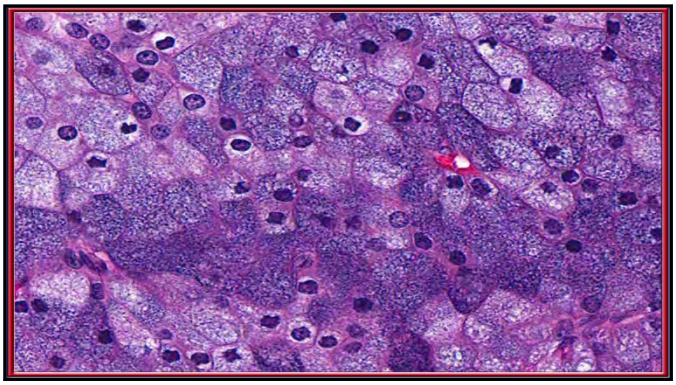


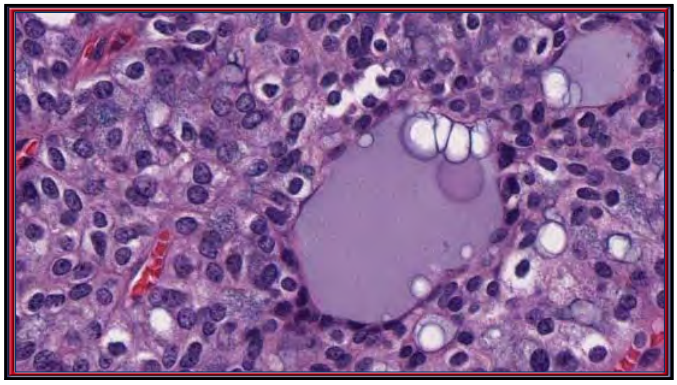


## Acinic cell carcinoma
## Cell types

- **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

27

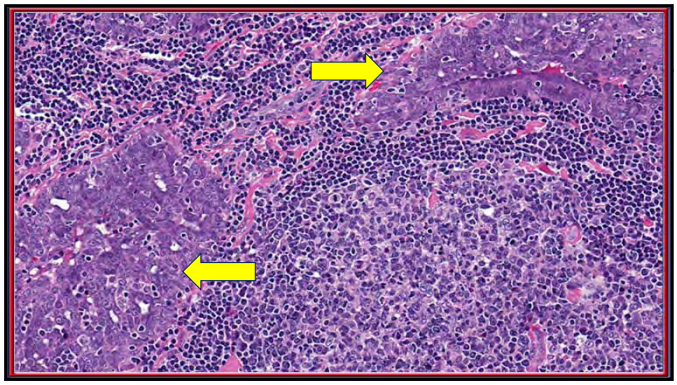




## Acinic cell carcinoma
## Histologic Findings

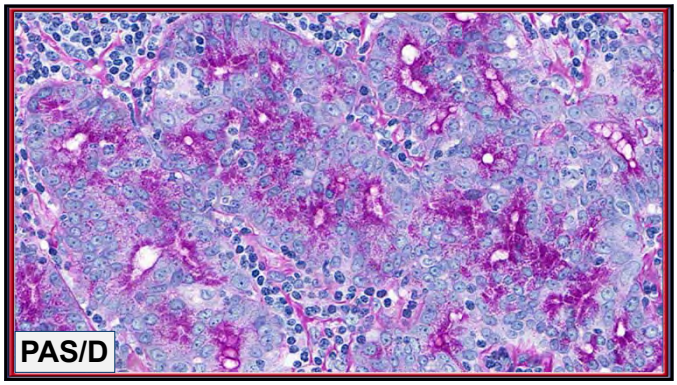
- **Lymphoid infiltrate, often with prominent germinal centers, may be seen**
  - "Tumor-associated lymphoid proliferation" (TALP)
  - May simulate a lymph node (not metastasis)
  - CAM5.2 is + in interfollicular dendritic cells in lymph node
- **Stromal fibrosis/desmoplasia is uncommon**

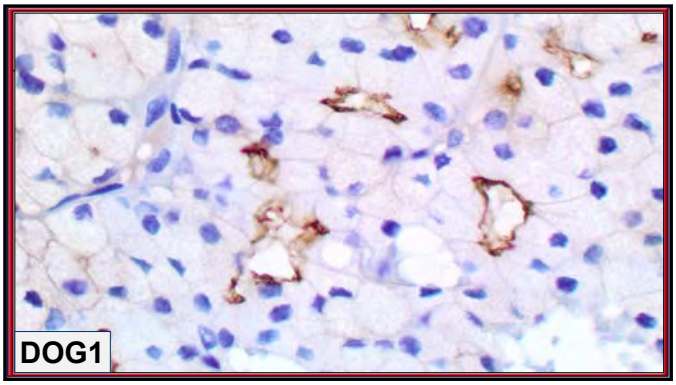
30

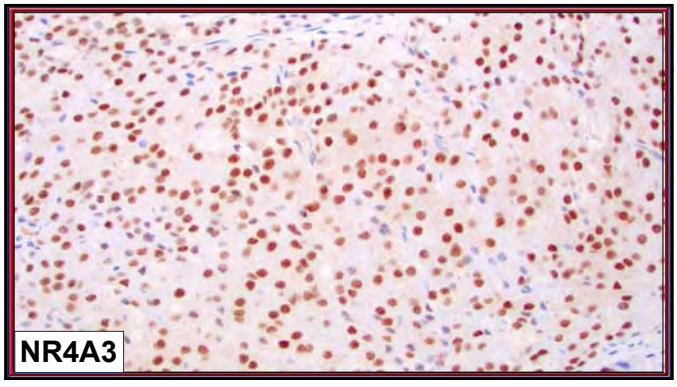


## Acinic cell carcinoma
## Special Studies

- PAS(+), diastase-resistant zymogen granules
  - Reaction can be patchy and limited
- Immunohistochemistry is nonspecific and unpredictable
  - Positive: DOG1, SOX10, NR4A3
  - Negative: S100 protein, mammaglobin
- *NR4A3* recurrent rearrangement (84%)
  - t(4;9)(q13;q31)
- *HTN3-MSANTD3* fusion defines a small subset




## Management and Prognosis

- Complete surgical excision
  - Incomplete excision portends poor prognosis
- Radiation only for incompletely excised tumors or advanced stage disease
- Generally, good prognosis
  - 5-year 80 – 90% (disease specific)
  - 10-year 65%
- Clinical stage more reliable than histologic grade or growth pattern in determining outcome
- Recurrences in ~ 35% of cases (within 5 years)

## High Grade Transformation

- High-grade transformation (*dedifferentiation*) into high-grade carcinoma (including small cell carcinoma) heralds poor prognosis
- Up to 15% of acinic cell carcinoma undergo high grade transformation
- Parotid gland only
- Age: Mean: 64 years
  ~ 20 years older than conventional
- Sex: Female > Male (3:2)

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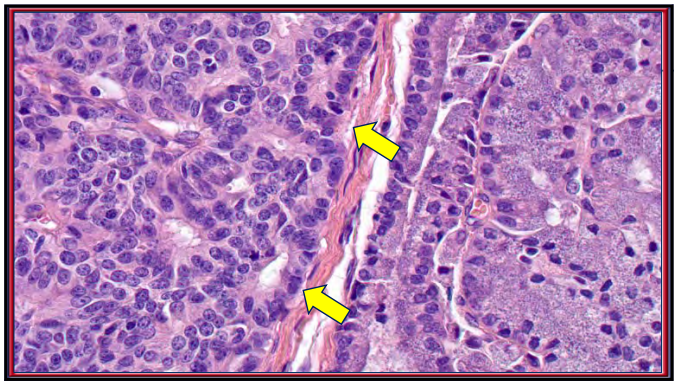
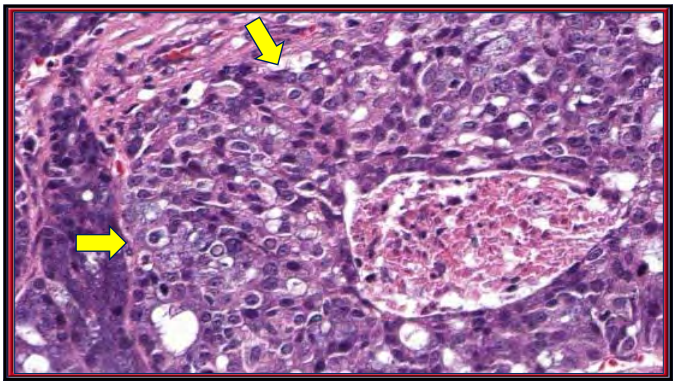
## High Grade Transformation

- Conventional low grade tumor is juxtaposed and/or blended with areas of high grade tumor
- Undifferentiated (small or large cell) carcinoma or poorly differentiated adenocarcinoma
  - Small or large cell neuroendocrine type
- Increased mitoses, including atypical forms
- Vascular and perineural invasion
- Central comedo-type of necrosis
- Anaplastic cells with large vesicular pleomorphic nuclei, prominent nucleoli and abundant cytoplasm

38





## Case

- 57 y.o.
- Female
- Presented with an enlarged parotid gland
- FNA was performed
- Superficial parotidectomy was performed

41

## Secretory Carcinoma

- Where did the tumor come from (2010, described by Skálová, et al.)?
  - Acinic cell carcinoma
    - ✓ 12% on re-review were SC
  - Adenocarcinoma, NOS
    - ✓ 38% on re-review were SC
  - Other ductal derived tumors
    - ✓ Mucoepidermoid carcinoma, cystadenocarcinoma

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## Secretory Carcinoma

*Secretory carcinoma is a generally low-grade salivary carcinoma characterized by morphologic resemblance to its mammary counterpart with an ETV6 associated gene fusion*

- Sites:
  - Salivary gland
  - Breast
  - Thyroid gland
  - Skin
  - Genitourinary tract

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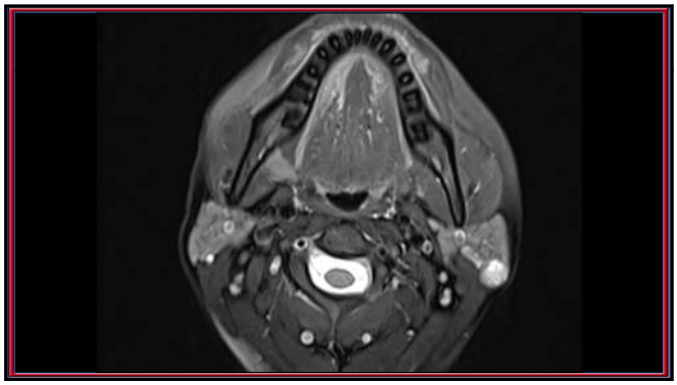
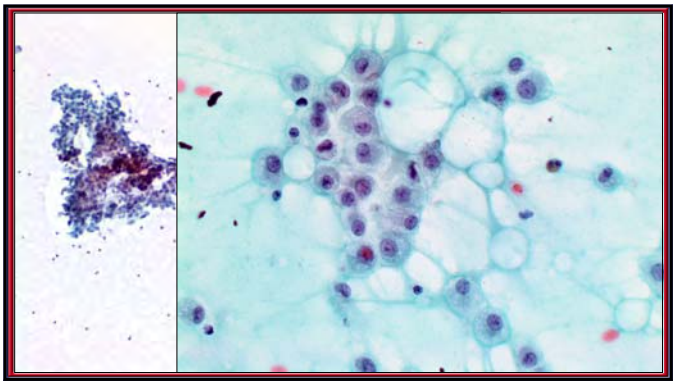
## Secretory Carcinoma

- Age: Middle aged
  - Mean: 47 years
  - Range: 7 – 88 years
- Sex: Male > Female (1.3:1)
- Site: Major salivary glands and oral cavity (88%) > > upper lip, retromolar trigone

44

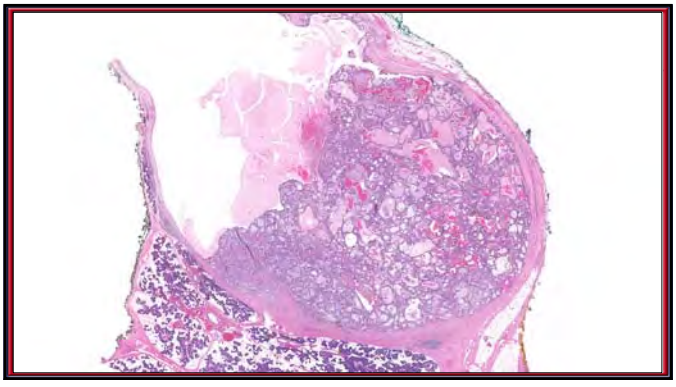


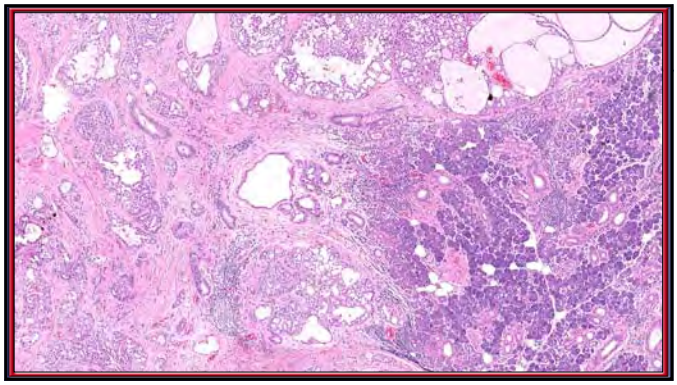


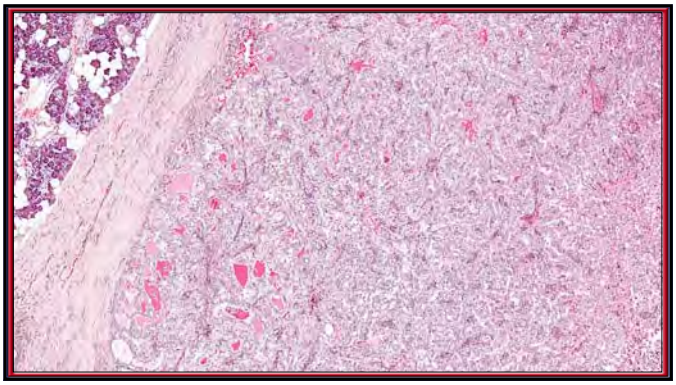
## Secretory Carcinoma

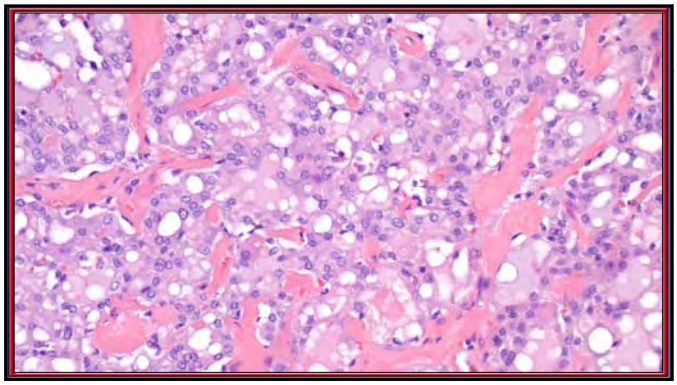
- Lobulated, pushing growth (no capsule generally)
- Invasive growth into parenchyma (40%)
  - Perineural invasion (20%)
- Microcystic to glandular appearance (45%)
- Papillary (30%); Solid or macrofollicular (20%)
- Oligocystic (<5%)
- Eosinophilic, homogenous or bubbly secretory (colloid-like) material in the lumen

47









Secretory Carcinoma
Histologic Features

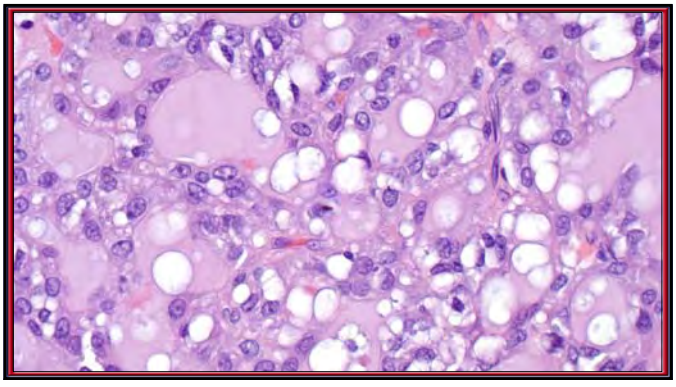
- Vesicular nuclei with finely granular chromatin but distinct centrally placed nucleoli
- Ample pale pink, granular or vacuolated cytoplasm
- Pleomorphism is limited
- Necrosis is absent
- Mitoses are rare

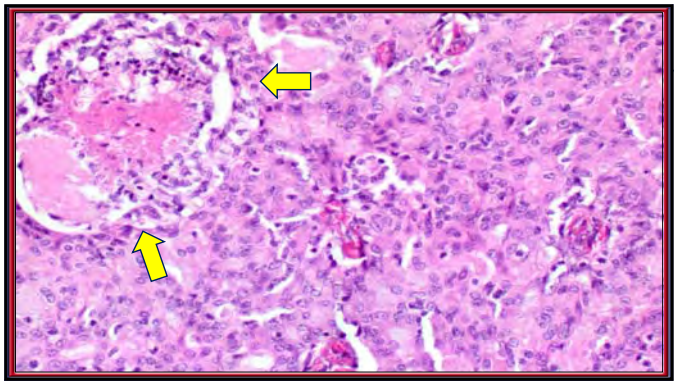
52

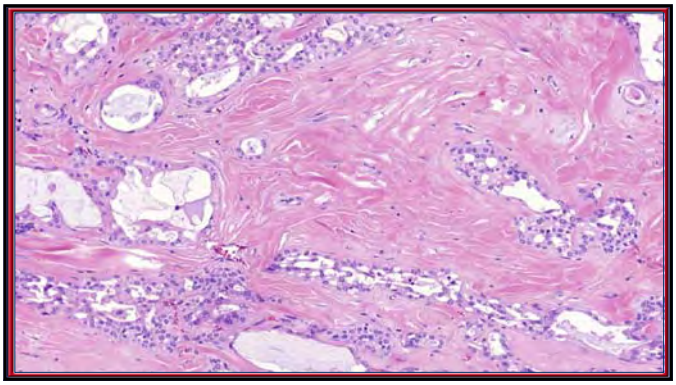
Secretory Carcinoma
Histologic Features

- Vesicular nuclei with finely granular chromatin but distinct centrally placed nucleoli
- Ample pale pink, granular or vacuolated cytoplasm
- Pleomorphism is limited: When present ➞ HGT
- Necrosis is absent: When present ➞ HGT
- Mitoses are rare: >3/2 mm$^2$ ➞ HGT

53

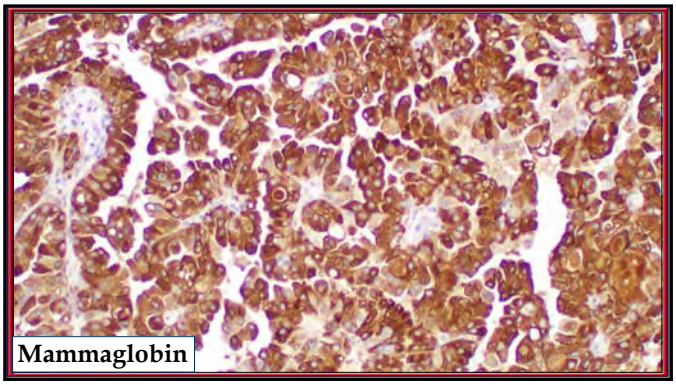


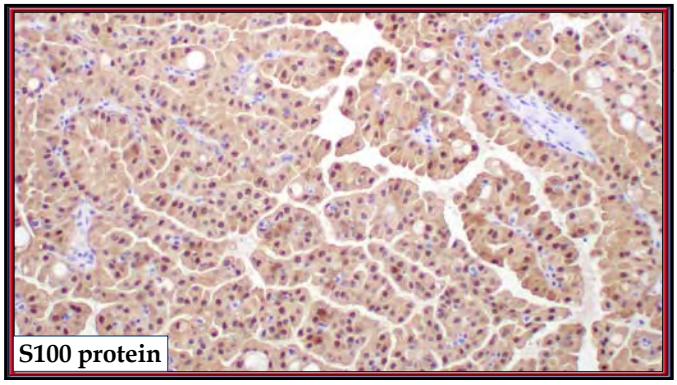


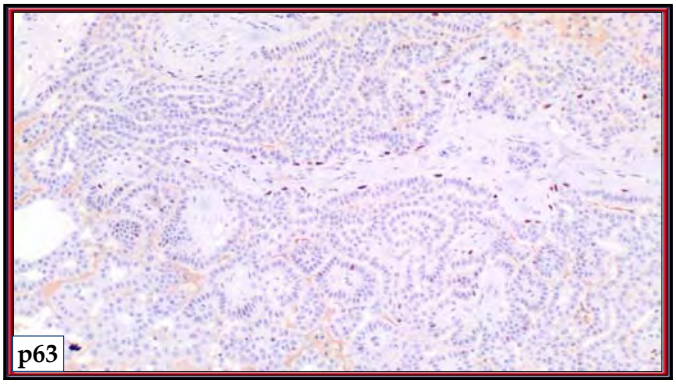


## Secretory Carcinoma Immunohistochemistry

| Antibody | Reactivity | Pattern | Comment |
|---|---|---|---|
| **Mammaglobin** | **Positive** | **Cell membrane & cytoplasm** | **Strong, diffuse** |
| **S100 protein** | **Positive** | **Nuclear & cytoplasmic** | **Strong, diffuse** |
| SOX10 | Positive | Nuclear | Strong, diffuse |
| GCDFP-15 | Positive | Cytoplasmic | Strong, but focal (secretory material) |
| STAT5 | Positive | Nuclear | Strong, diffuse |
| GATA3 | Positive | Nuclear | Strong, diffuse in most tumor cells |
| CK7 | Positive | Cytoplasmic | Strong, diffuse |
| CK-pan | Positive | Cytoplasmic | Strong, diffuse |
| Adipophilin | Positive | Cytoplasmic | Large lipid droplets |
| **p63** | **Negative** | | |
| **DOG1** | **Negative** | | **+ in Acinic cell carcinoma** |



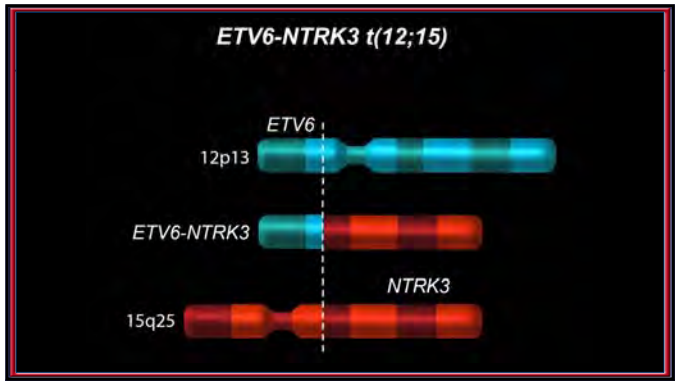



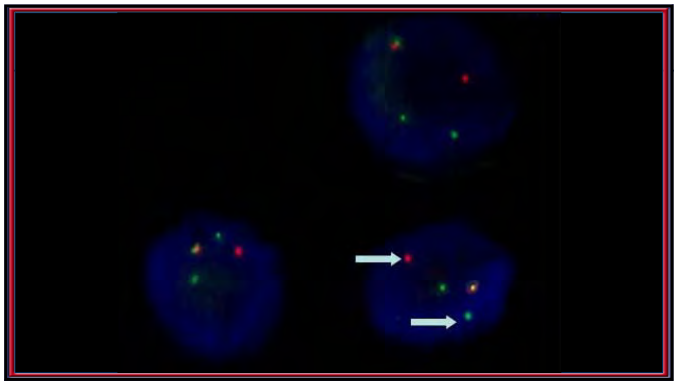



## Secretory Carcinoma: Molecular Findings

- *Definitional* specific recurrent balanced chromosomal translocation *ETV6-NTRK3* fusion transcript at t(12;15)(p13;q25)
  - Chimeric tyrosine kinase identical to secretory breast carcinoma (triple negative, basal phenotype), mesoblastic nephroma and infantile fibrosarcoma
- Rarely, *ETV6-RET*, *ETV6-MET*, *ETV6-MAML3*, *VIM-RET*, *MYB-SMR3B* may be detected
- Before targeted therapy (Larotrectnib, Entrectinib, Selpercatinib, Pralsetinib), must do NGS to confirm specific findings (*TRK* vs. *RET*)

61



## Secretory carcinoma Prognosis and Predictive Behavior

- Lymph node metastases in about 25%
- Local recurrence is about 20%
- Distant metastases in about 2%
- High grade transformation:
  - 5%; Male; 56 years; Solid, necrosis, >3/2 mm$^2$
- Disease free survival: 7.5 years
  - Only about 10% die with disease
- Clinical stage and high grade transformation are poor prognostic markers

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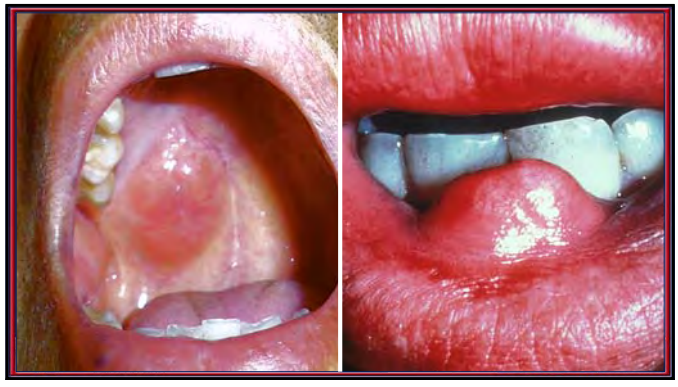
## Pleomorphic adenoma Clinical

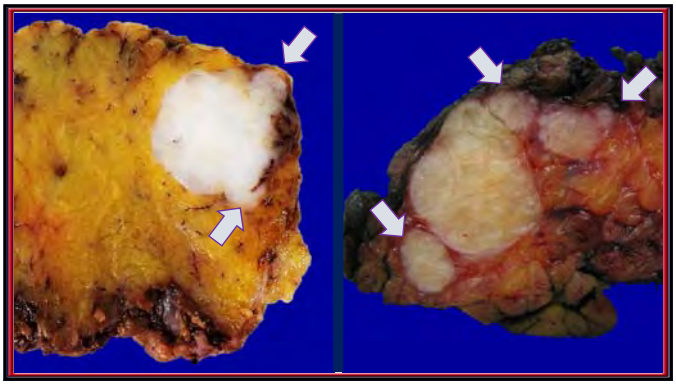
- The MOST common salivary gland neoplasm
  So, consider it every time
- Age: 30 – 60 years
- Sex: Equal
- Site: Parotid most common site (superficial > deep)
  Palate next most common
- Slow growing, painless, lobular mass
  - Can reach huge size

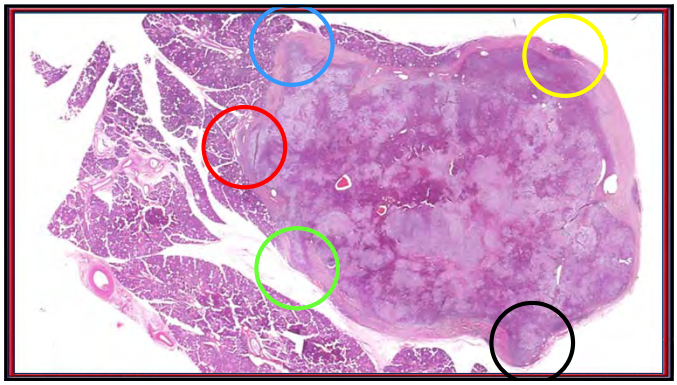
65



Pleomorphic Adenoma
Macroscopic

- Cirumscribed
- Tumor may be multinodular
- Tumor has "pseudopods" that bulge outwards

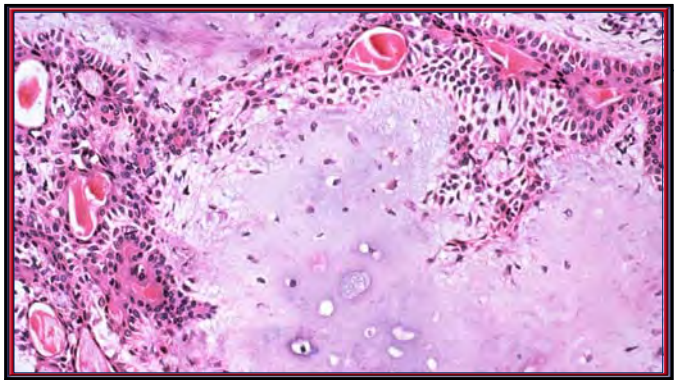


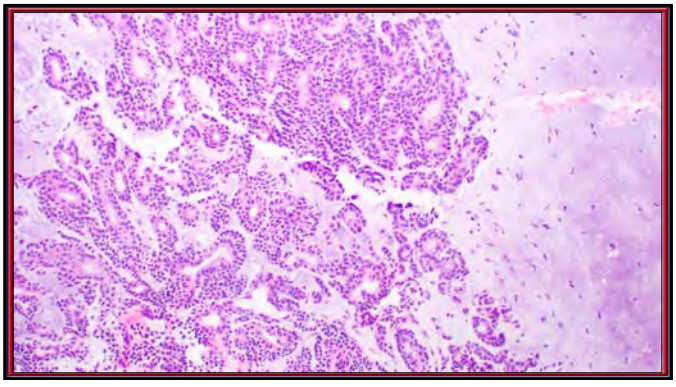


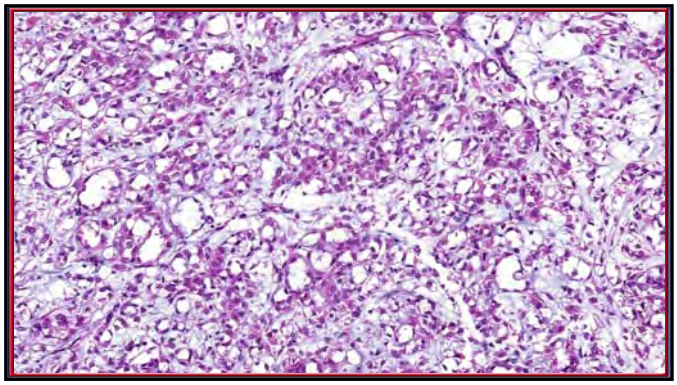
## Pleomorphic Adenoma

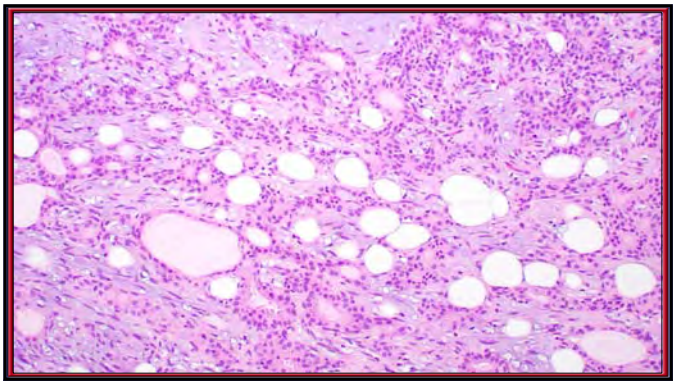
*Tumor is epithelial (ductal), basal, and myoepithelial with mesenchymal component (myxoid, chondroid, hyaline, osseous)*

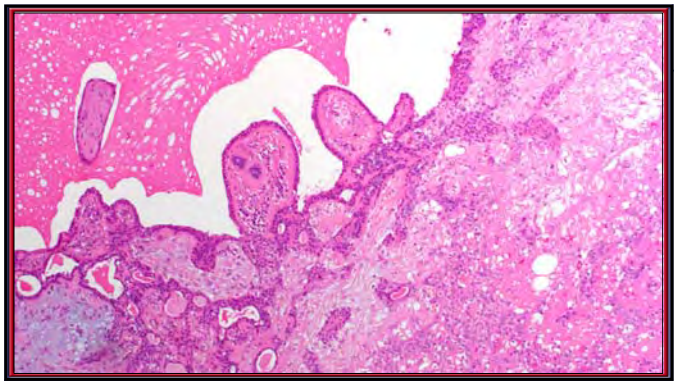
- Remarkably variable histology (pleomorphic)
  - Solid, tubular, trabecular, cystic
  - Cells literally "melt" into the chondromyxoid background stroma
  - Stroma may be heavily fibrotic/hyalinized
  - Spindled, epithelioid, *glandular*, & plasmacytoid cells
  - Squamous metaplasia is common

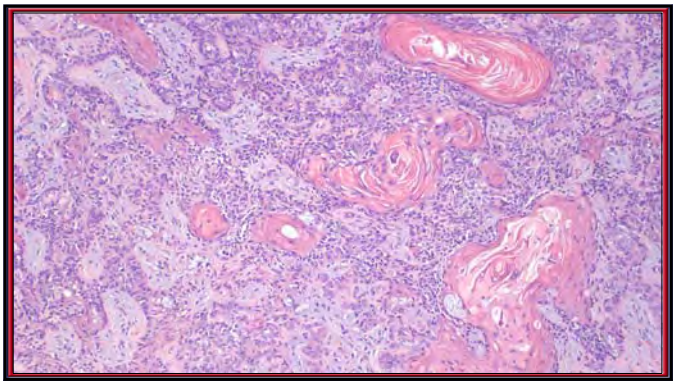


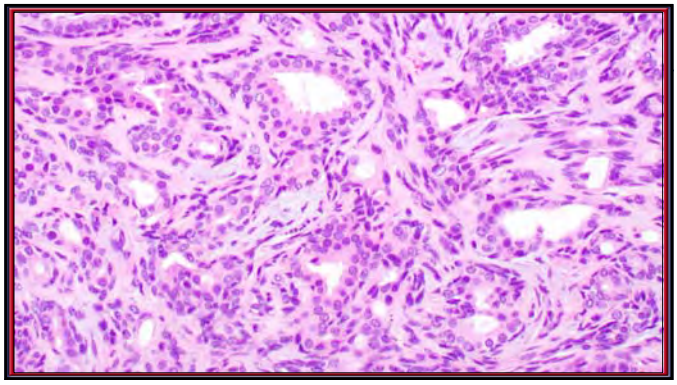


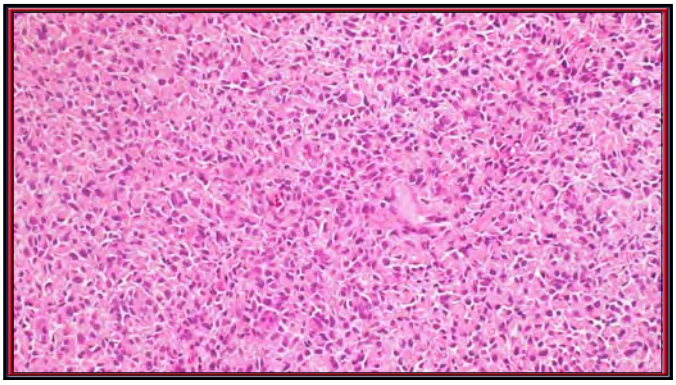


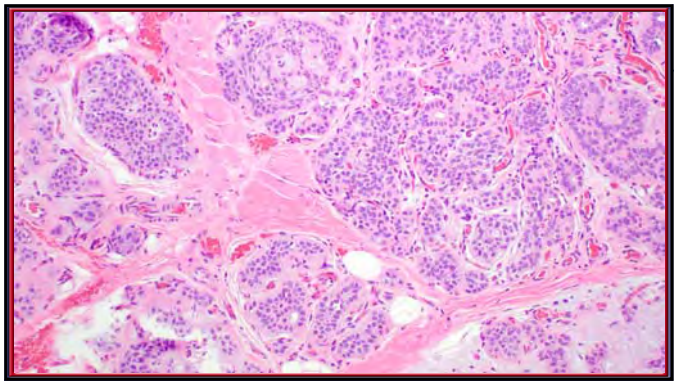


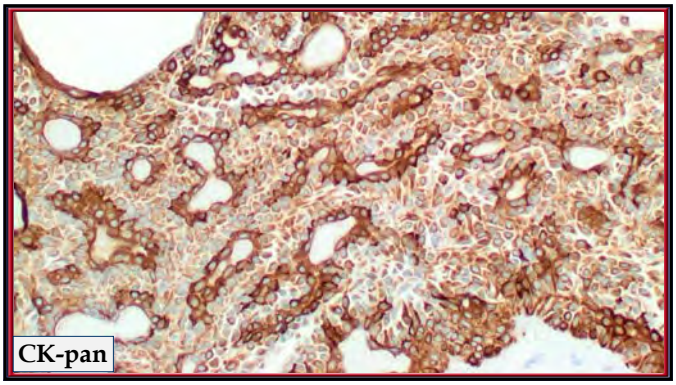


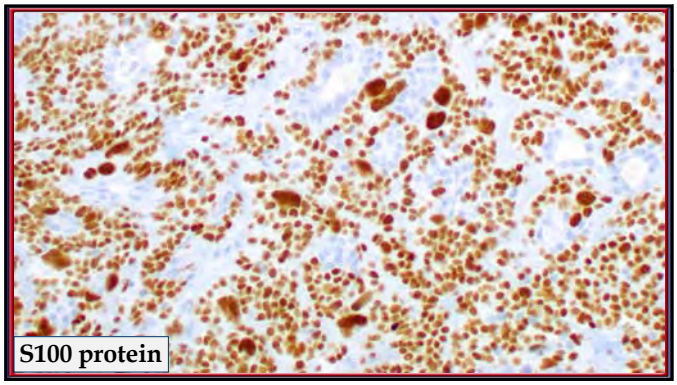


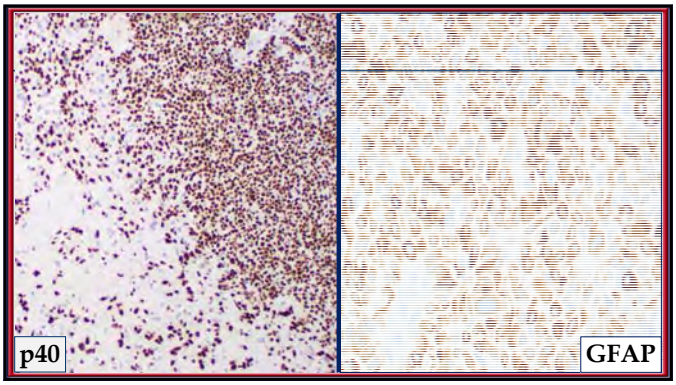








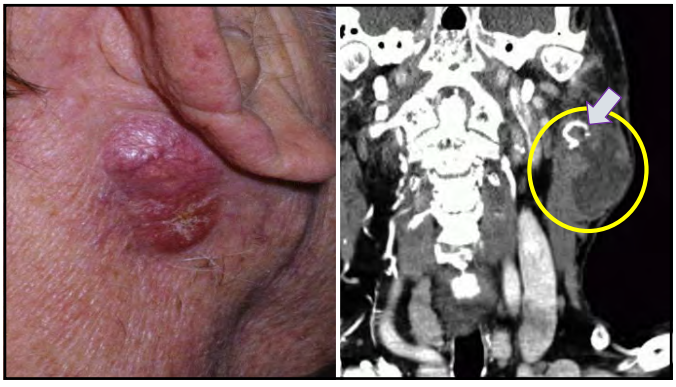



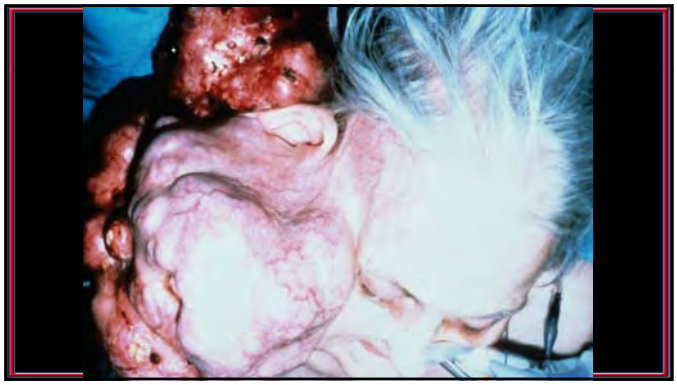

## Salivary Duct Carcinoma (SDC) Definition

*Aggressive malignant epithelial neoplasm histologically with apocrine appearance resembling high-grade apocrine breast carcinoma with strong, diffuse nuclear androgen receptor reactivity*

- Approximately 10% of malignancies
- Age: Older, with peak in 7th decade
- Sex: Male > Female (2 — 4:1)
- Site: Parotid gland >>> other sites (rare in minor glands)
- Presentation: Recent rapid growth

  Nerves: Facial nerve paresthesia, pain, paresis, paralysis



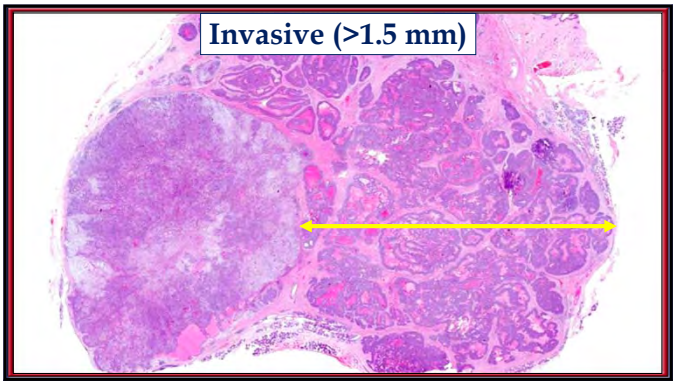


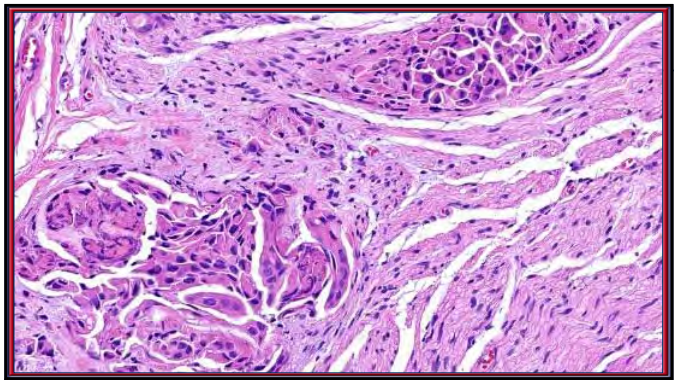
## Salivary Duct Carcinoma
## Pleomorphic Adenoma Origin

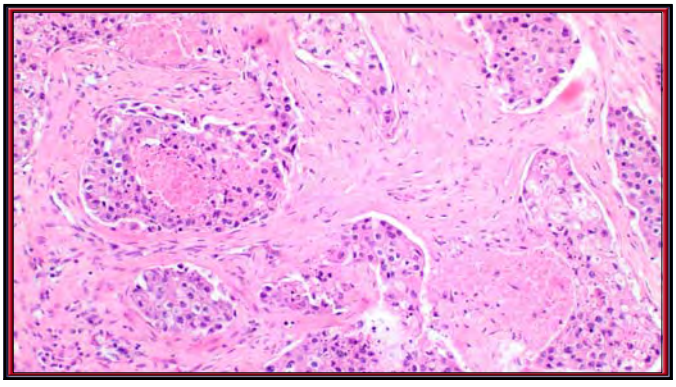
- Hyalinized/sclerotic nodule may be all that remains of pleomorphic adenoma
- Molecular evidence of pleomorphic adenoma
  - *PLAG1* (33%) or *HMGA2* (13%)
  - 15—60% will show molecular support without obvious histology support
- Activating mutations and amplifications of oncogenes: *PIK3CA*, *HRAS*, *ERBB2*, *BRAF*
- Inactivating mutations or deletions of tumor suppressors: *TP53*, *CDKN2A*, *PTEN*, *ATM*
- *ERBB2* (Her-2) amplification only in SDC ex PA (rare)

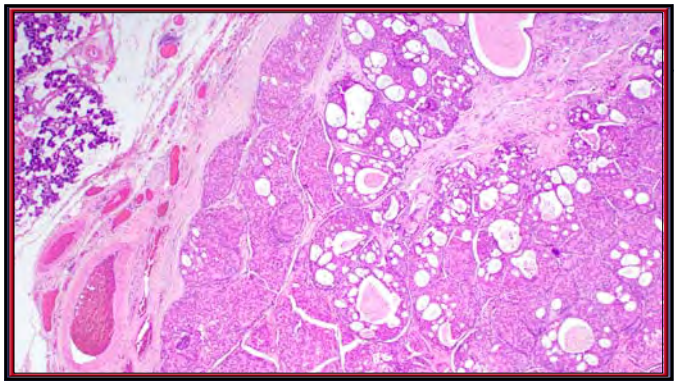
## Salivary Duct Carcinoma (SDC)
## Microscopic Features

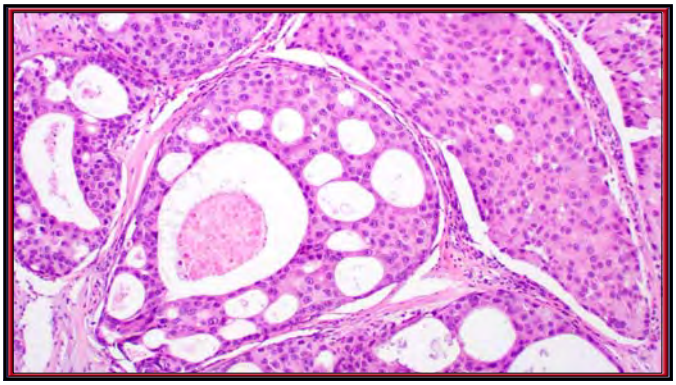
- Unencapsulated, poorly circumscribed, widely infiltrative
- Cysts with comedonecrosis
- Marked, dense, desmoplastic (hyalinized) fibrosis
- Concurrent/preexisting pleomorphic adenoma in ~80%
- Cells are arranged in papillary-cribriform to band-like solid patterns
  - "Roman bridge" architecture is classic
- Moderate to marked pleomorphism of apocrine cells
  - Large, prominent nucleoli and hyperchromatic chromatin
- High mitotic index

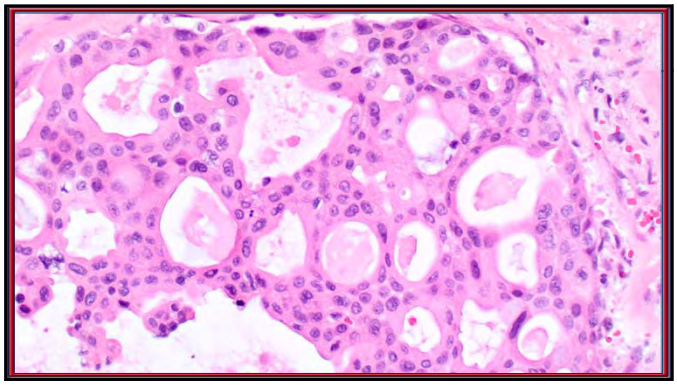


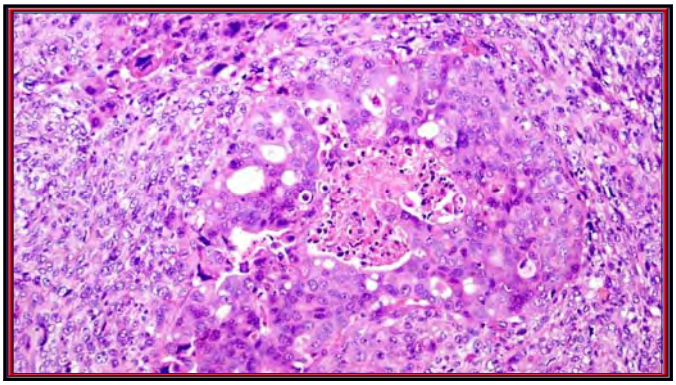







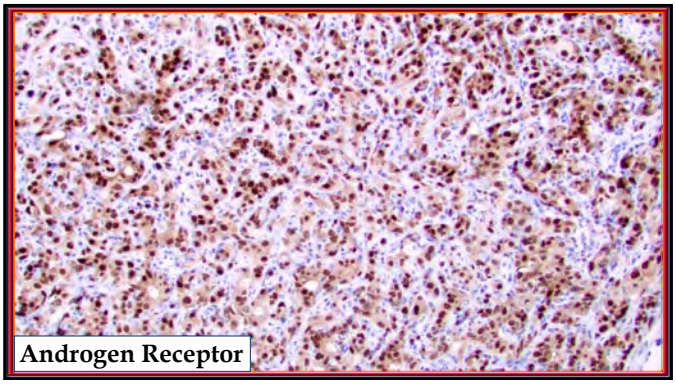


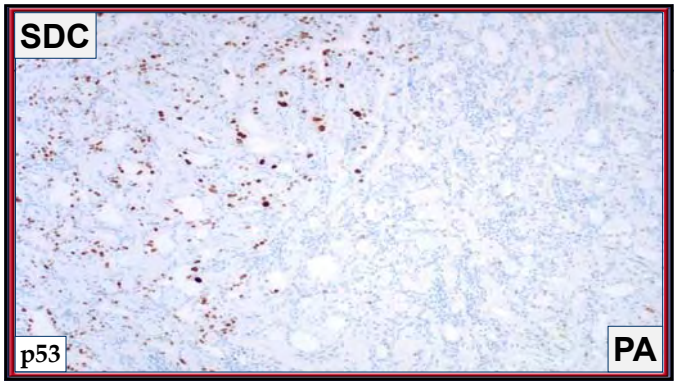




## Salivary Duct Carcinoma (SDC) Immunohistochemistry

- **Positive:**
  - Epithelial markers (including CK7)
  - **Androgen receptor**
  - HER-2/neu (40-50%)
  - GCDFP15
  - **p53**
  - EGFR
- Negative:
  - p63
  - CK5/6
  - GFAP






## Salivary Duct Carcinoma (SDC)
### Treatment and Outcome

- Aggressive multimodality therapy required
- Surgery (including lymph node dissection)
- Radiation
- Androgen deprivation therapy and chemotherapy
- Poor prognosis overall (< 35% 5-year survival)
  - Local recurrences in up to 50% (usually <5 years), often multiple
  - Lymph node metastases (up to 25%)
  - Distant metastases (up to 70%)
    - ✓ Lung, bone, liver, brain, skin

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## Salivary Duct Carcinoma (SDC)
### Prognosis

- Prognostically significant factors (in order)
  - Grade (high grade usually die from disease)
  - Stage (T2 or higher)
  - Extent of invasion (>1.5 mm poor prognosis)
  - Proportion of tumor that is carcinoma (>50%)
  - Large tumor size (>4 cm)
  - Proliferation index (Ki-67) (>50%)
  - Histologic subtype (undifferentiated is worst)
  - Margin status (positive increases recurrence)

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## Salivary Duct Carcinoma (SDC)
### Differential Diagnosis

- Intraductal carcinoma (replaces low grade cribriform cystadenocarcinoma/low grade salivary duct carcinoma):
  - Predominantly papillary, cystic tumor, with low-grade cytologic features, absent comedonecrosis and lacks infiltration
- Carcinomas with High Grade transformation
  - Oncocytic carcinoma (no apocrine; more granular cytoplasm), epithelial-myoepithelial carcinoma, myoepithelial carcinoma
- Mucoepidermoid Carcinoma, High Grade
  - Lacks prominent papillary or cribriform patterns, shows goblet cells, epidermoid and transitional cells
  - Positive: p63, CK5/6, p40; Negative: AR
- Metastatic Squamous cell Carcinoma
  - Prominent lymphoid reaction, squamous differentiation, keratinization, may have necrosis
  - Positive: p63, CK5/6, p40; Negative: AR

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## Mucoepidermoid Carcinoma
### Clinical

*A malignant epithelial neoplasm with variable components of mucous, epidermoid, and intermediate cells, with columnar, clear cell and oncocytic populations*

- Most common malignant salivary gland tumor
- Age: Wide range
- Sex: Female > Male (3:2)
- Site: Major (parotid): 45% Minor: 48%
- Presentation: Painless, firm, fixed, slow-growing mass

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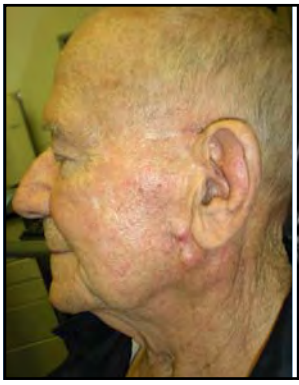
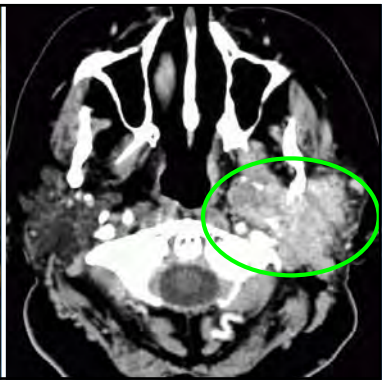
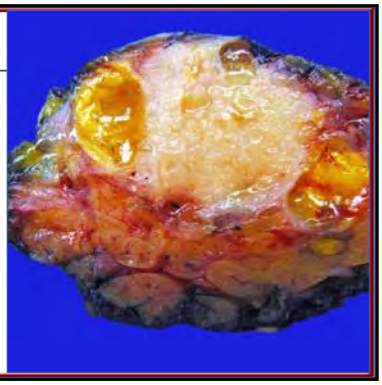


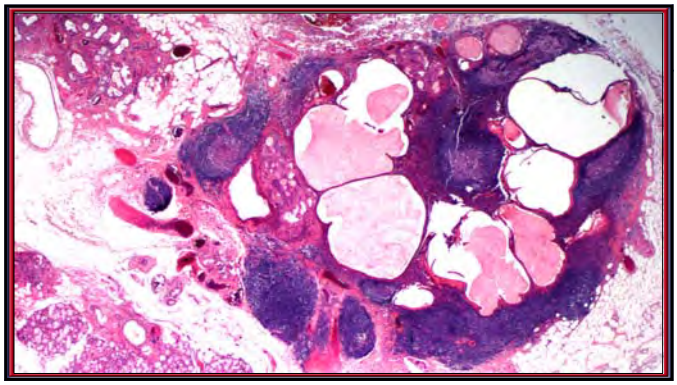


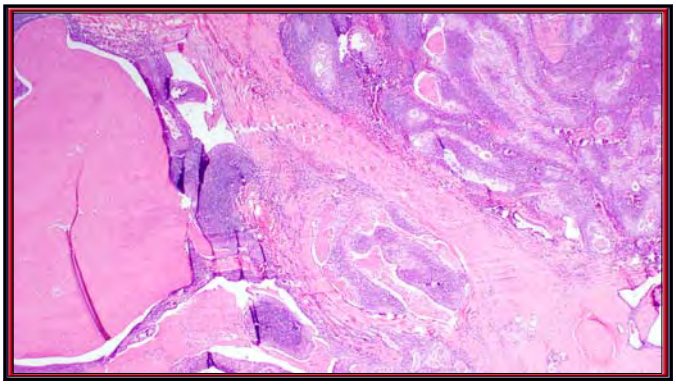
- Circumscribed, partially encapsulated, or poorly defined periphery
- Cut surface
  - Cystic, sometimes with blood
- Highly variable size
  - < 1 cm to large disfiguring masses

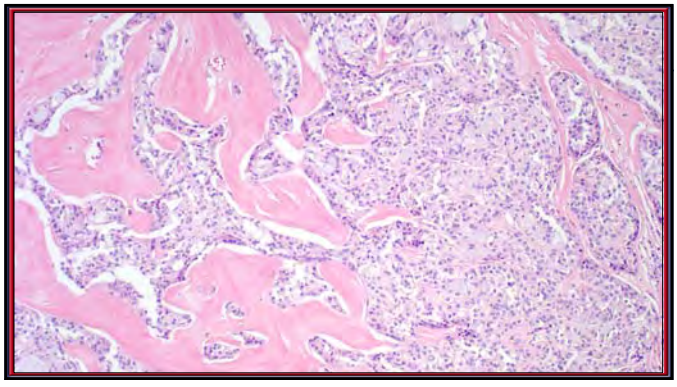


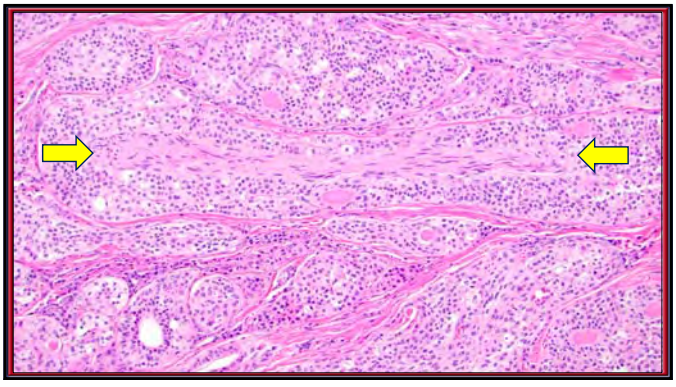
## Mucoepidermoid Carcinoma
### Histologic Features

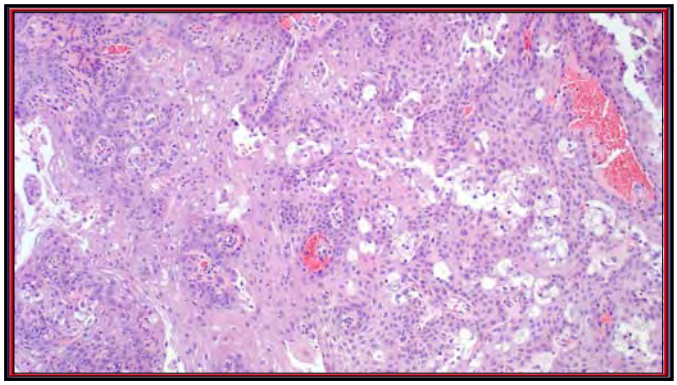
- Cystic spaces
  - Often filled with mucin, sometimes with papillary projections
- Dissecting fibrosis;
- Tumor Associated Lymphoid Proliferation (TALP)
- Perineural and vascular invasion may be seen
- Neoplasm consists of:
  - Epidermoid cells: nests polygonal cells, focal keratinization
  - Intermediate cells: large polygonal to small basal cells
  - Mucus cells: Intracytoplasmic mucin (goblet-cell); vacuolated or clear cytoplasm
- Necrosis, anaplasia, and mitoses variably present
- Spilled mucus: Incites inflammatory response

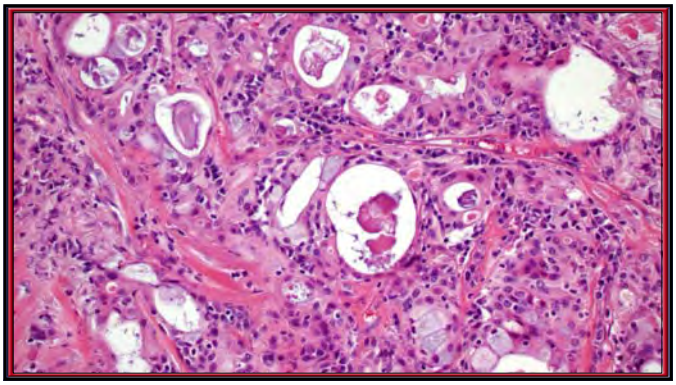


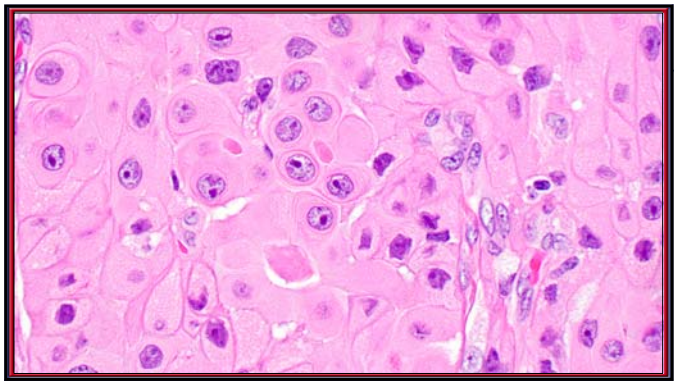


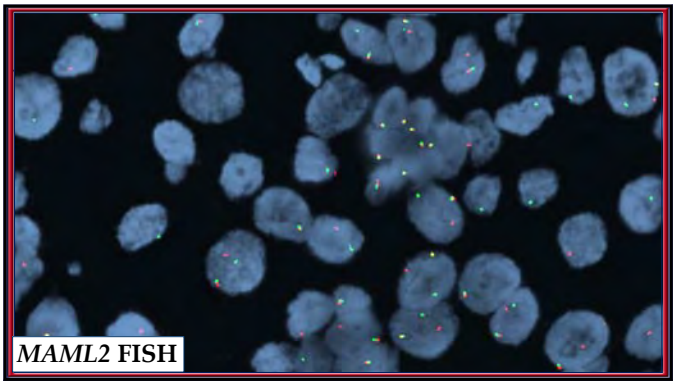








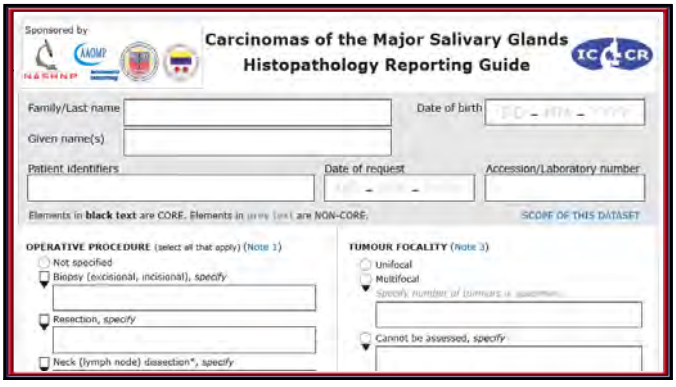


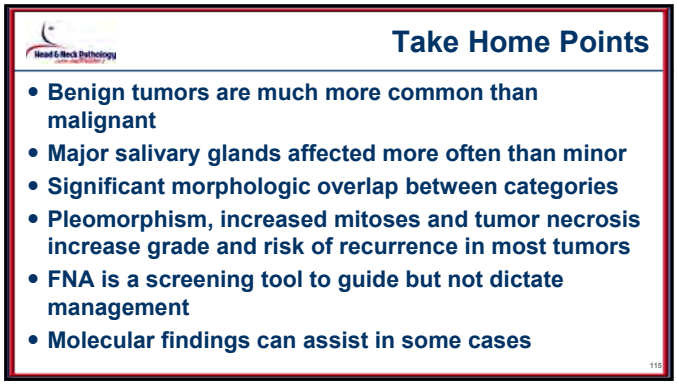



## Mucoepidermoid Carcinoma Grading

| Parameter | Point Value |
|---|---|
| Intracystic component < 20% | 2 |
| Neural invasion present | 2 |
| Necrosis present | 3 |
| 4 or more mitoses per 10 HPF | 3 |
| Anaplasia | 4 |

| Grade | Total point score |
|---|---|
| Low grade | 0-4 |
| Intermediate grade | 5-6 |
| High grade | 7 or more |




Head & Neck Pathology
Take Home Points
• Benign tumors are much more common than malignant
• Major salivary glands affected more often than minor
• Significant morphologic overlap between categories
• Pleomorphism, increased mitoses and tumor necrosis increase grade and risk of recurrence in most tumors
• FNA is a screening tool to guide but not dictate management
• Molecular findings can assist in some cases
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