Salivary Gland Tumors, Histology, Molecular and Beyond-Part I

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Diagnostic approach

Salivary gland neoplasm

1- Malignant vs Benign

- Invasive borders=Malignancy

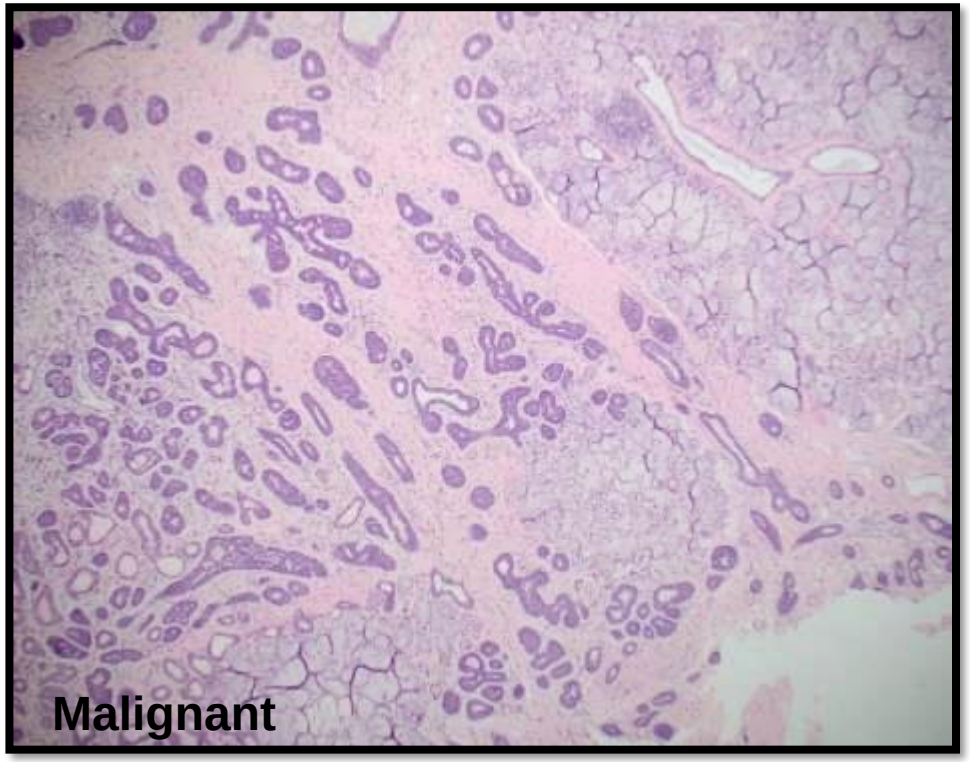
(except for nodular oncocytosis and pleomorphic adenoma)

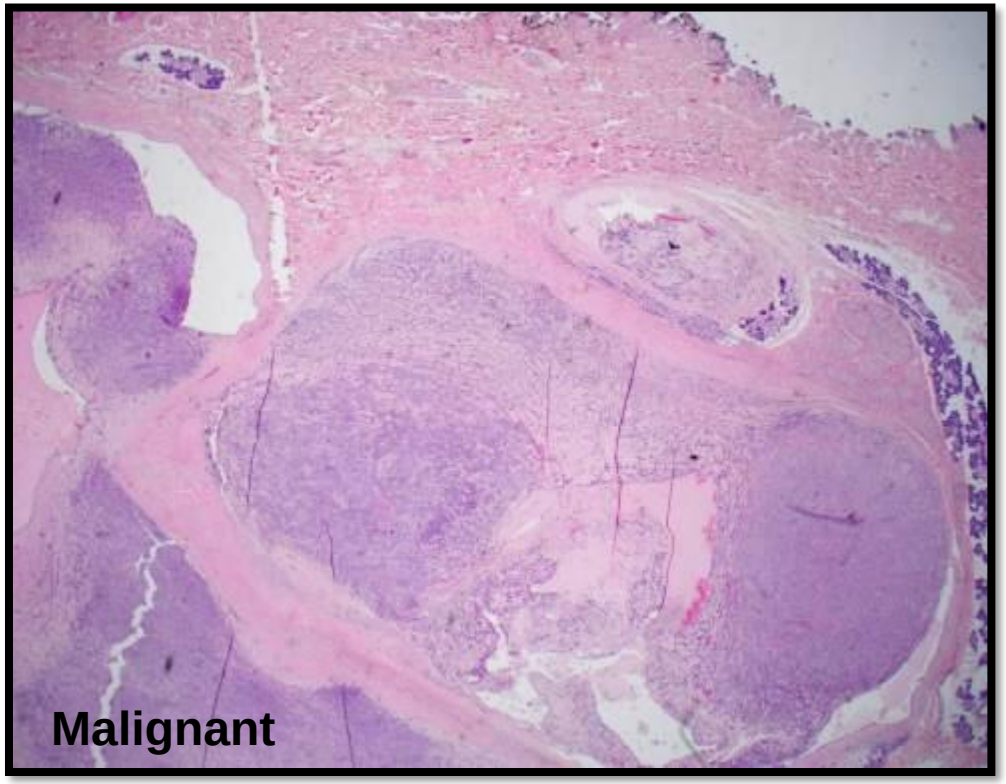
- Well circumscribed borders=Benign

(except for intracapsular CA ex PA)

2- Malignant:Grading

- Low grade
- High grade





3-Cellular composition

- Cell types:
  - Ductal, myoepithelial, oncocytic, squamous cells, glandular/mucinous cells, acinar cells (zymogen)
- One cell type
- Biphasic
  - Two cell types: ductal-myoepithelial

Benign

- **Two cell types (ductal and myoepithelial)**
- Pleomorphic adenoma
- Basal cell adenoma
- Intercalated duct adenoma
- **One cell type**
- Myoepithelioma
- Canalicular adenoma
- **Oncocytic**
- Warthin 's tumor
- Oncocytoma

Malignant

- **One cell type**
- Ductal:
  - Salivary duct carcinoma
  - Secretory carcinoma
- Myoepithelial/modified myoepithelial:
  - Myoepithelial carcinoma
  - Polymorphous adenocarcinoma
- **Biphasic** (ductal & myoepithelial)
  - Adenoid cystic carcinoma
  - Epithelial myoepithelial carcinoma
  - Basal cell adenocarcinoma
  - Intraductal carcinoma

- **Acinic cell carcinoma**

- **Tumor with squamous phenotype**
  - Mucoepidermoid carcinoma (squamous and glandular)
  - Hyalinizing clear cell carcinoma

4-Architecture

- Growth patterns: Cribriform, tubular, single files, papillary, microcystsic, solid
- Predominant growth pattern

5- Stroma

- Myxoid, chondromyxoid, chondroid, hyalinized, desmoplastic

6-Differential Diagnosis

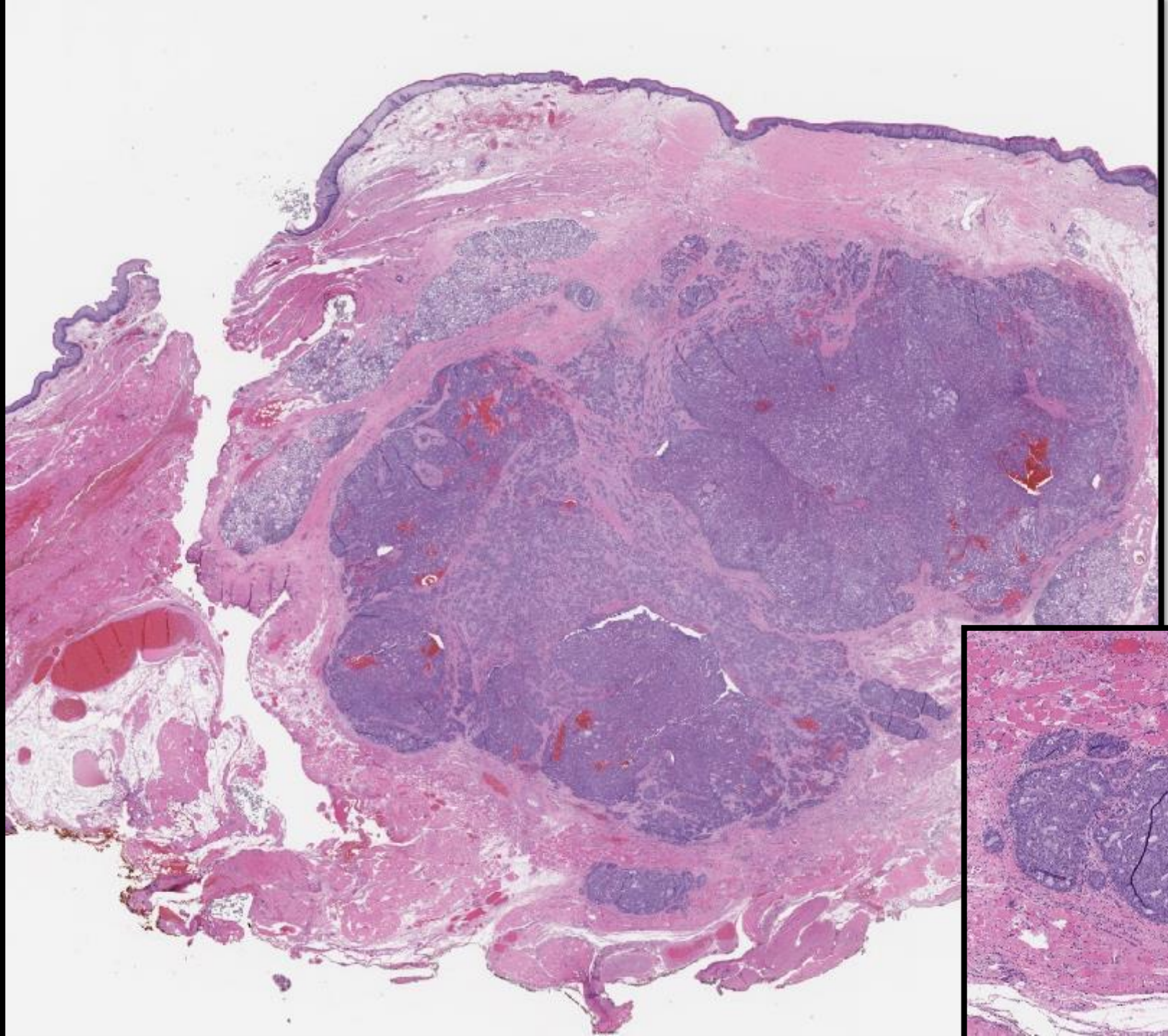
7-Immunohistochemistry

- Ductal: Cam5.2, CK7, EMA, CD117
- Myoepithelial: Calponin, SMA, myosin, S100, SOX10, GFAP
- Myoepithelial/basal/squamous: P63, P40, CK5/6
- S100: Positive: Myoepithelial carcinoma, secretory carcinoma, polymorphous adenocarcinoma. Negative: Salivary duct carcinoma, mucoepidermoid carcinoma, hyalinizing clear cell carcinoma
- SOX10: Can be positive in mucoepidermoid carcinoma & acinic cell ca
- DOG1, NR4A3 (NOR1): Acinic cell carcinoma
- AR: Salivary duct carcinoma
- Ki-67: High value supports malignancy

- IHC panel
- Highlights tumor architecture and cellular composition
- Highlights biphasic patterns
- Specific panels for certain entities
- Negative staining can rule out entities

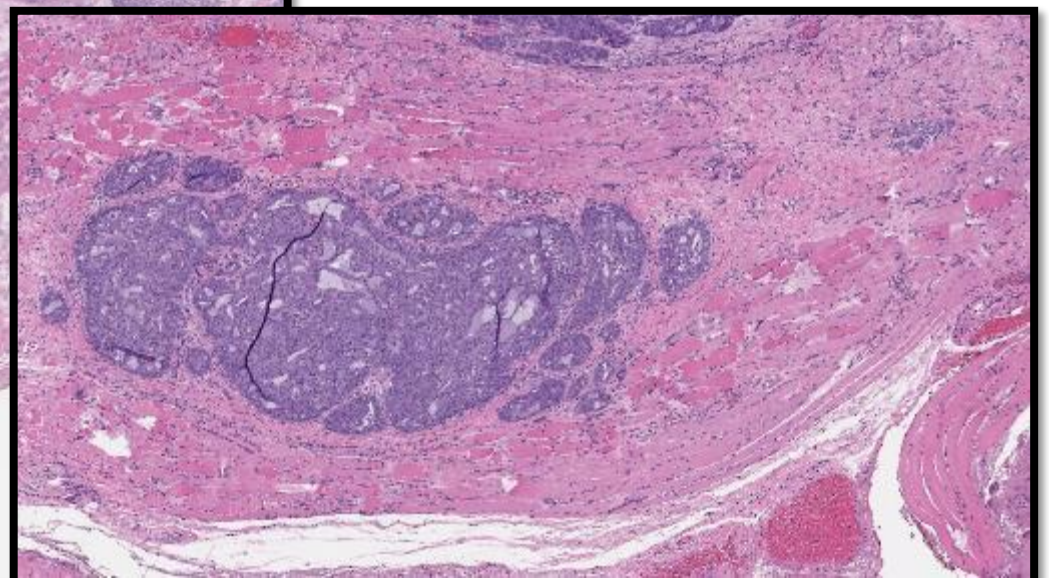
8-Molecular features

Tumor	Chromosome	Molecular Alterations
Pleomorphic adenoma Carcinoma ex PA	8q12 12q13-15	PLAG1 fusion HMGA2 fusion
Basal cell adenoma membranous variant	16q12.1	CYLD LOH/mutation
Basal cell adenoma and Basal cell adenocarcinoma, tubulotrabecullar variant	3p22	CTTNB1 mutation
Mucoepidermoid carcinoma	t(11;19) t(11;15)	CRTC1-MAML2 CRTC3-MAML2
Adenoid cystic carcinoma	6q22-23 including t(6;9) MYB-NFIB 8q13 translocation 9q34	MYB fusion MYBL1 fusion NOTCH1 mutation
Secretory carcinoma	t(12;15)	ETV6-NTRK3 ETV6-X
Clear cell carcinoma	t(12;22)	EWSR1-ATF1
Acinic cell carcinoma	t(4;9), t(9;12), t(8;9),t(2;4)	NR4A3, NR4A2
Epithelial-myoepithelial carcinoma	11p15	HRAS mutation
Polymorphous adenocarcinoma and cribriform adenocarcinoma of salivary gland	14q12 PRKD1 9q13 PRKD2 2p21 PRKD3	PRKD1 mutation PRKD1, PRKD2, PRKD3 rearrangement
Salivary duct carcinoma	17q21.1 Xq12 3q26	ERBB2 amplification AR copy gain PIK3CA mutation
Intraductal carcinoma	10q11.2 12p12.1 and 3q26	RET fusion KRAS or PIK3CA mutation
Microcystic adenocarcinoma	t(5q14.3) (18q11.2	*MEF2C-SS18* fusion

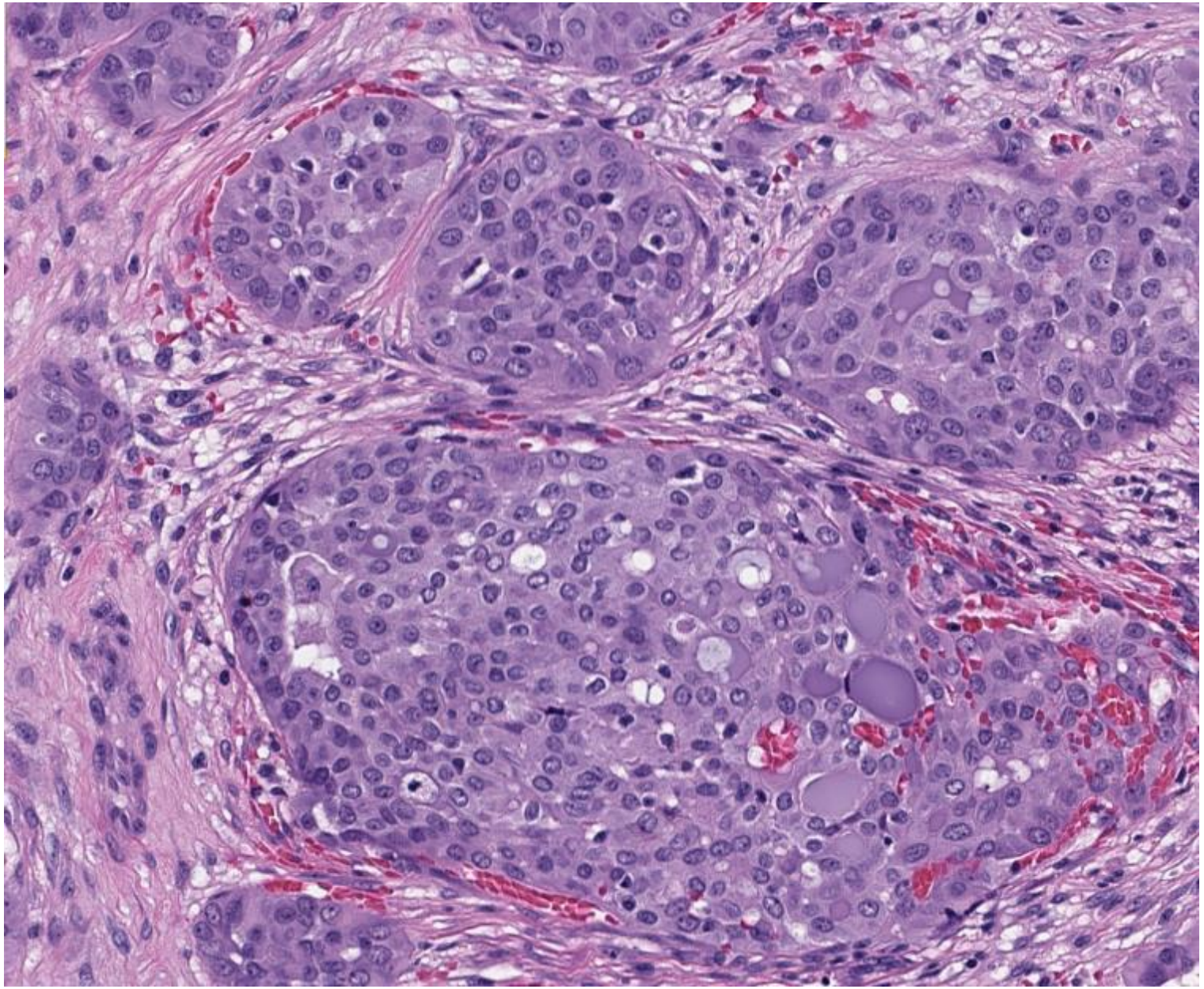


Palate mass

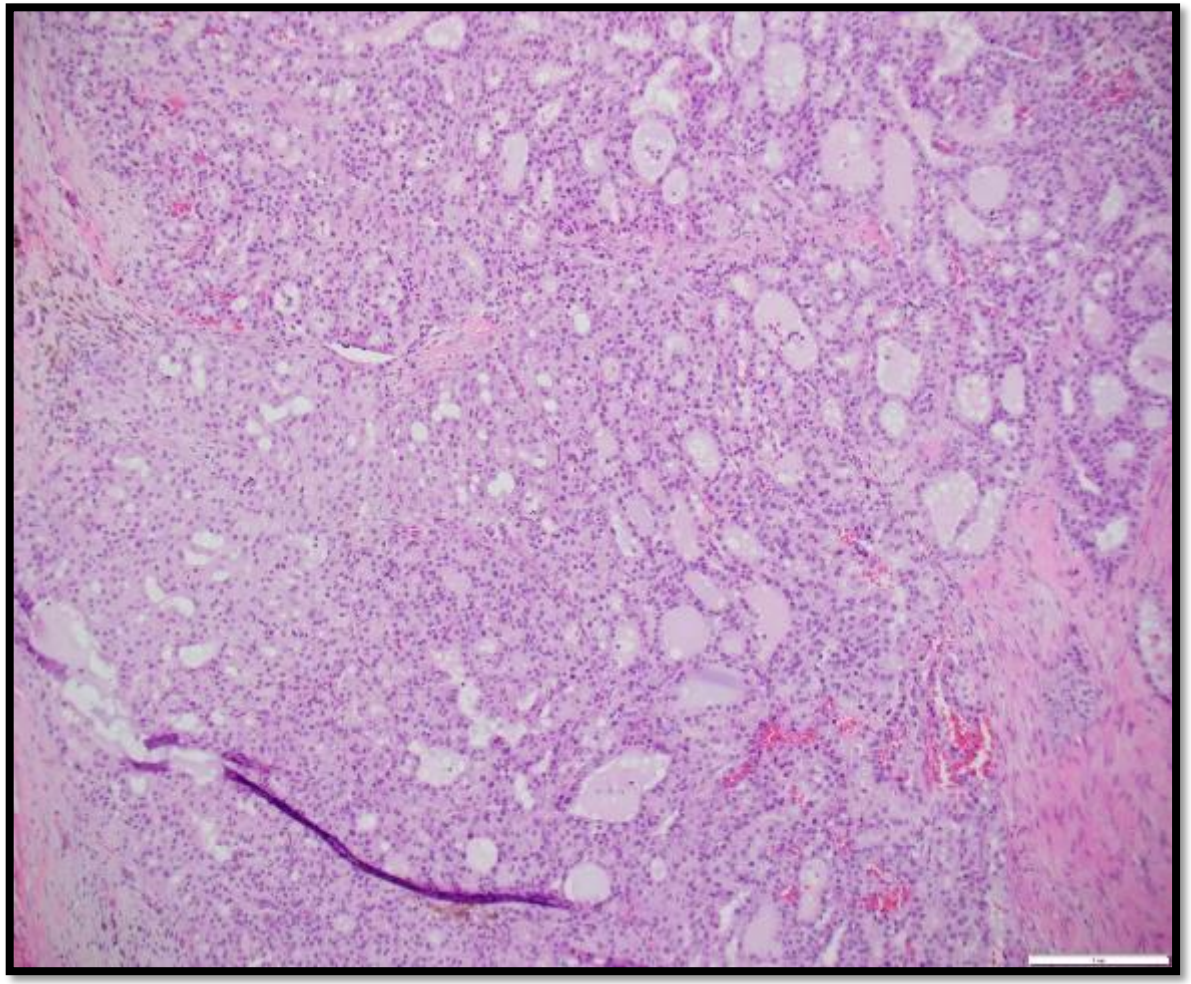
- Malignant

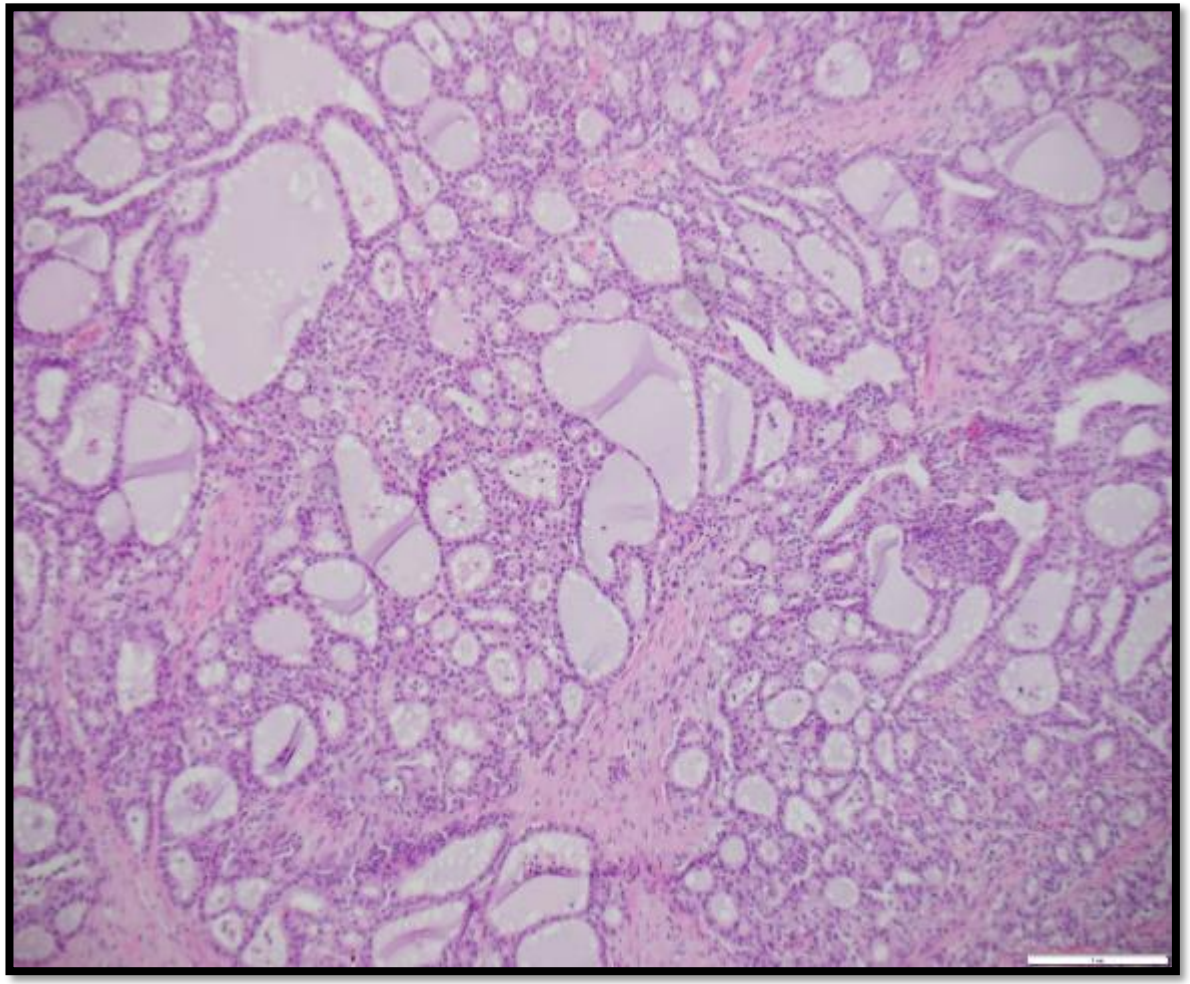


Cytomorphology Cellular composition

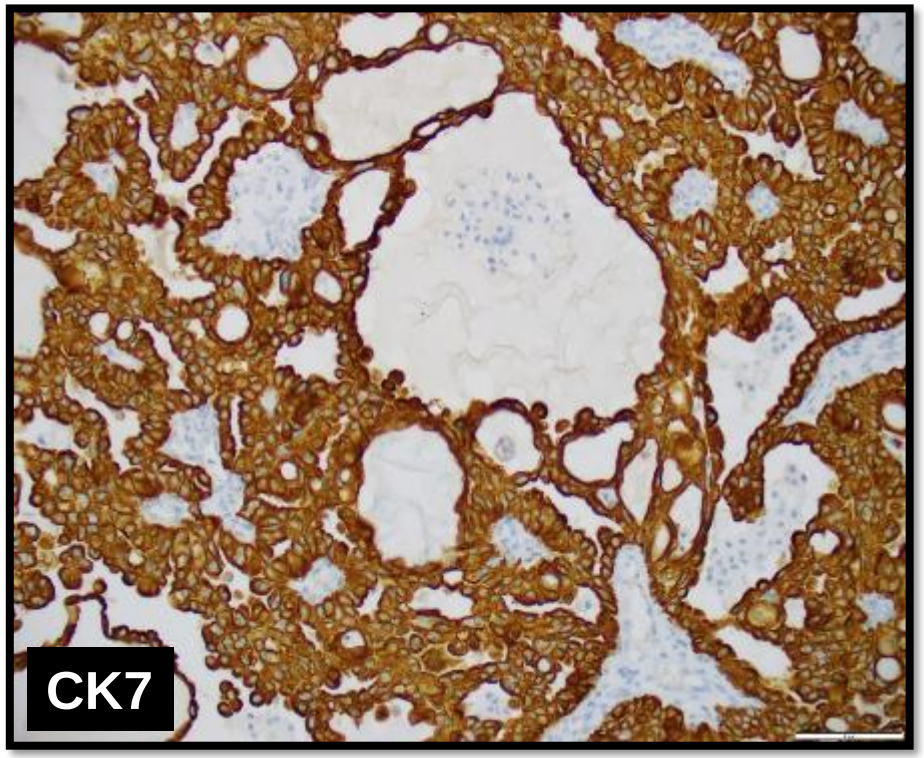


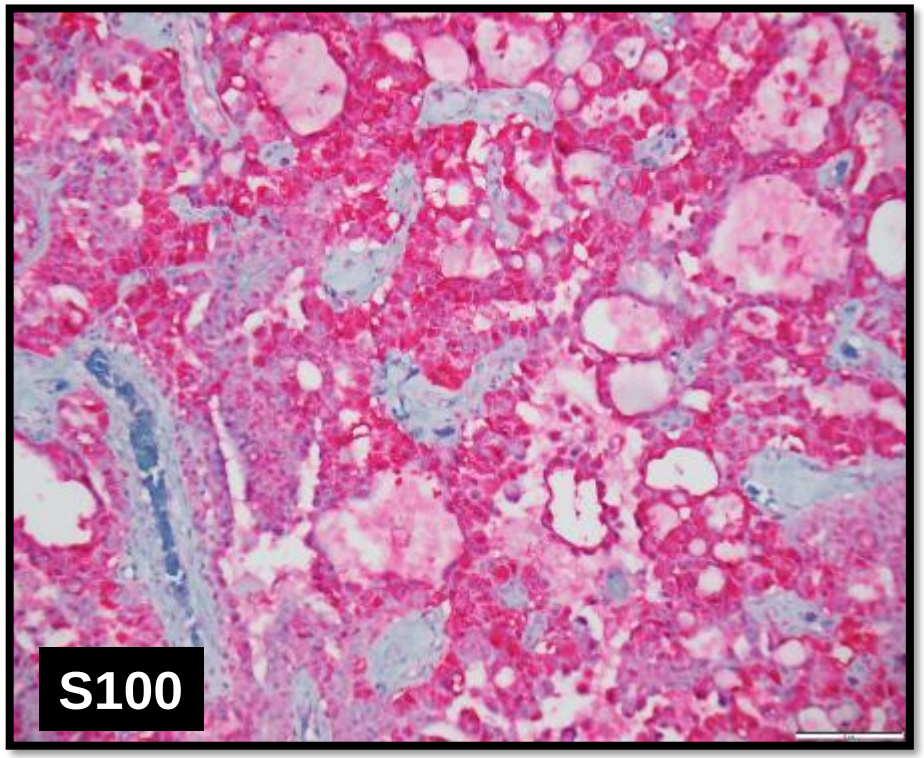
Architecture/stroma





Immunohistochemistry





- **<u>Negative</u>:**
  - P63, p40, calponin, SMA, AR

- **<u>Positive</u>**
  - BRST-2 (focal)
  - Mammaglobin
  - DOG1 (focal)

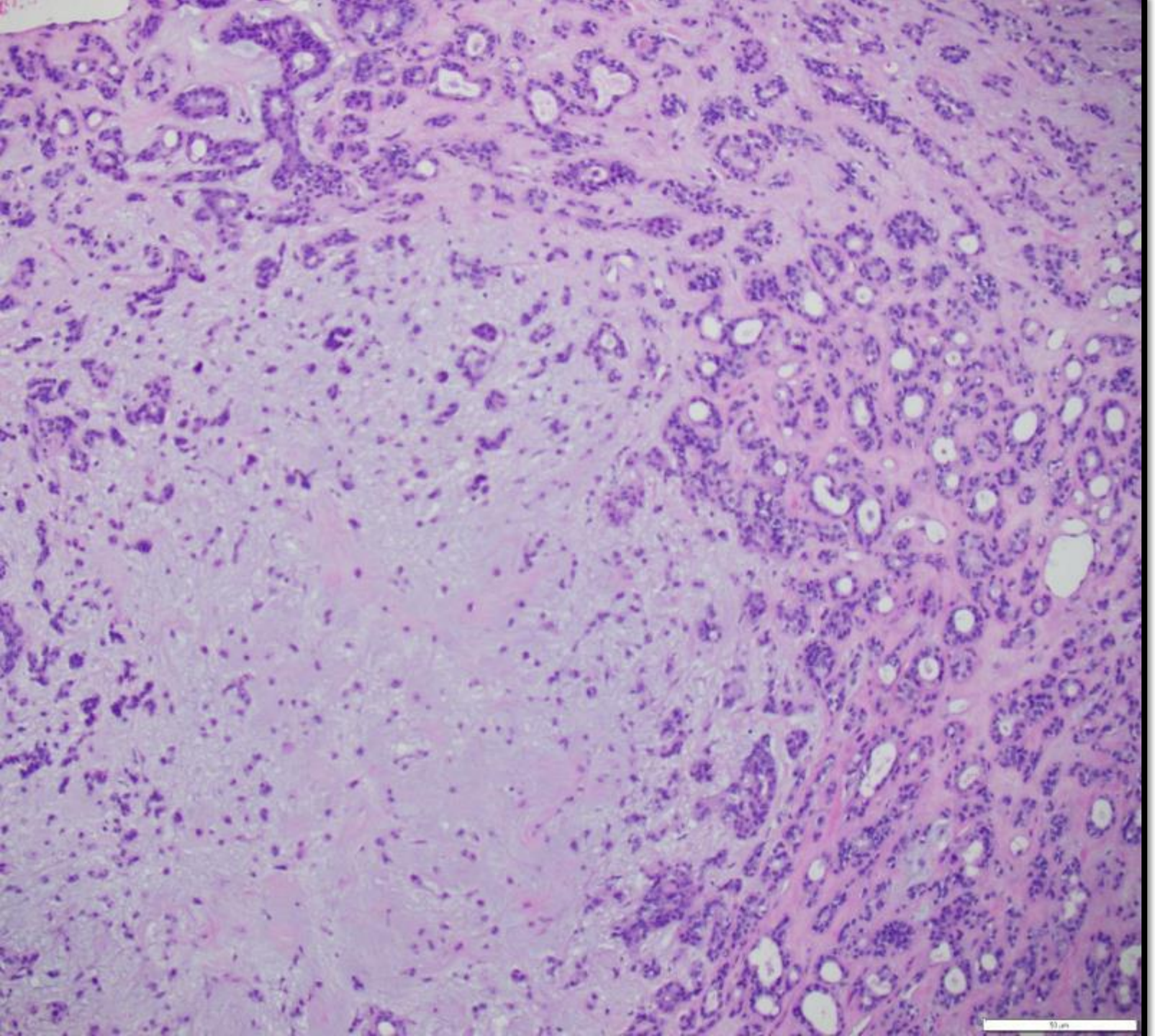
FISH- *ETV6::NTRK3*

Secretory Carcinoma

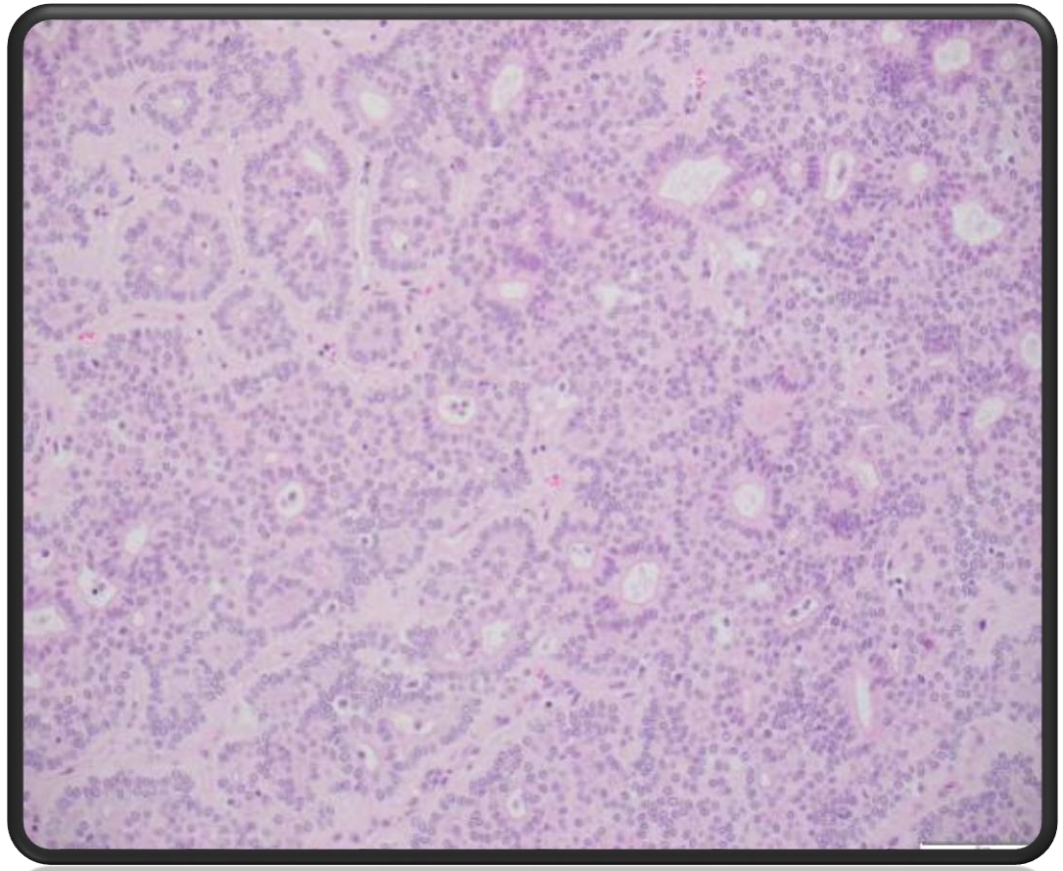
Salivary gland biopsy

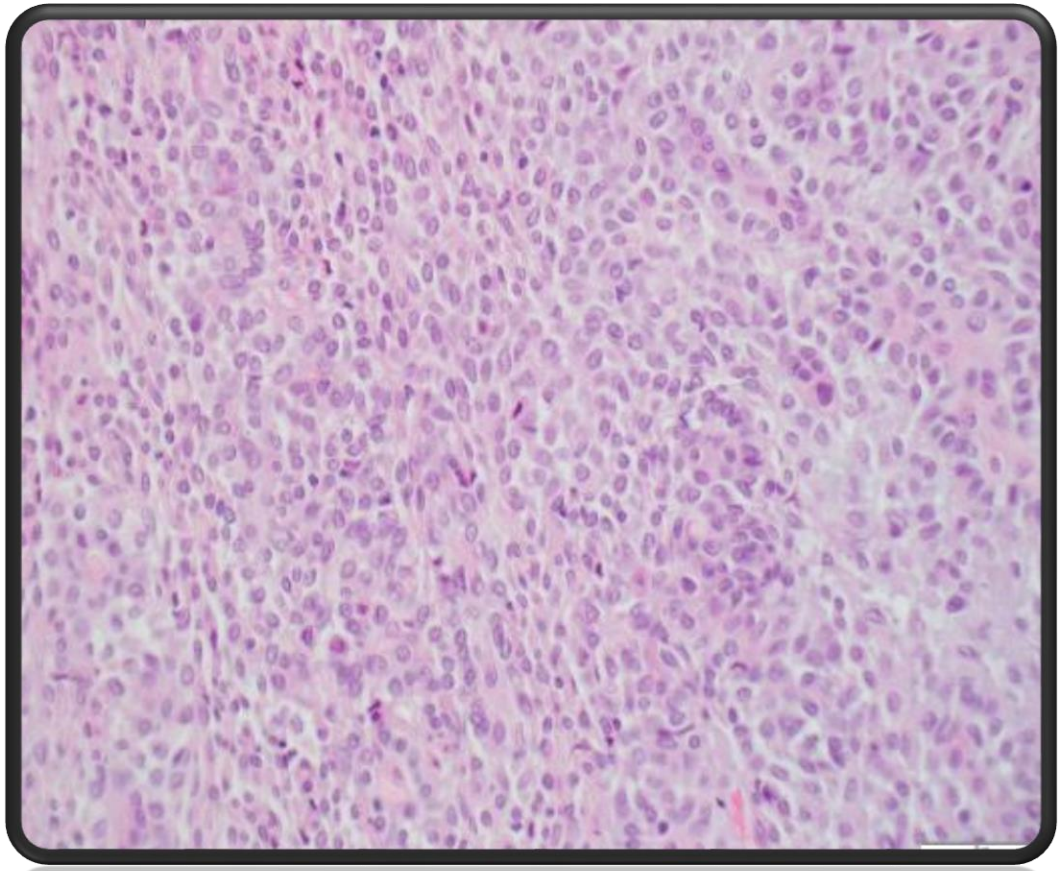
- Limitations
  - Small samples
  - The borders cannot be assessed
  - Cannot tell benign from low grade malignancy

- Typical histology of a specific entity



Typical
Pleomorphic adenoma

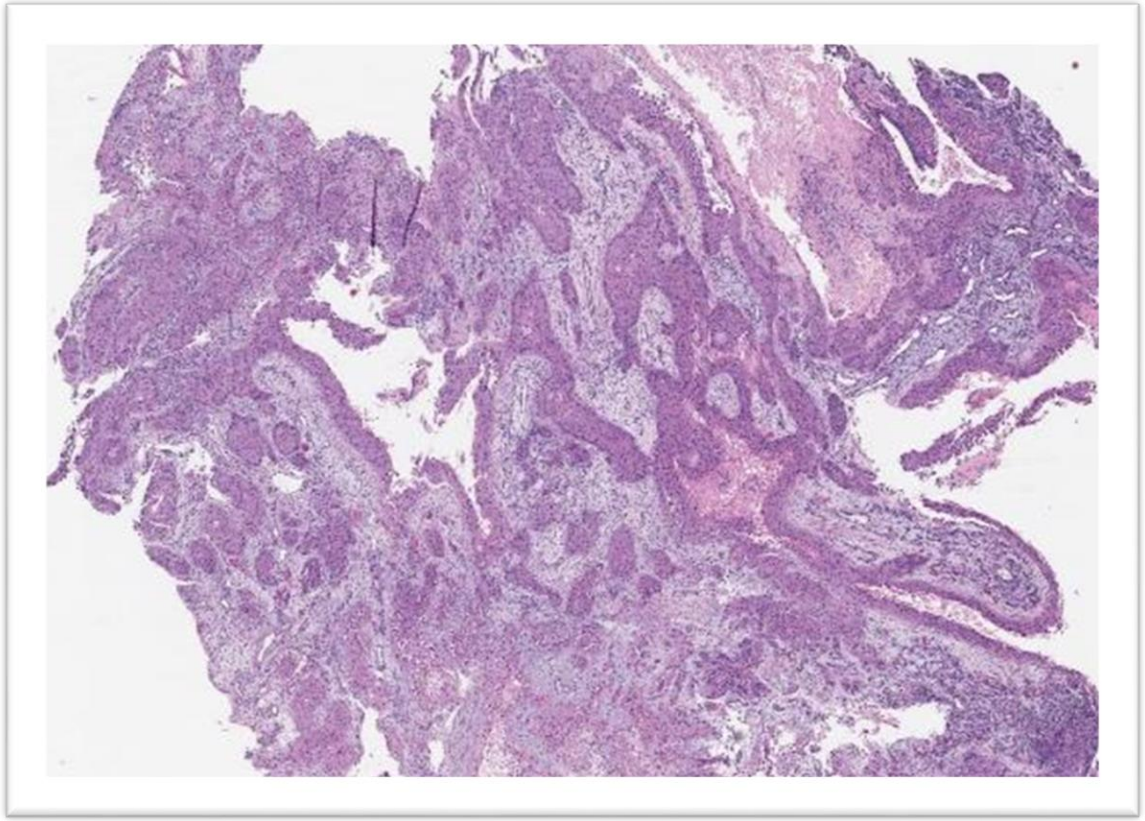


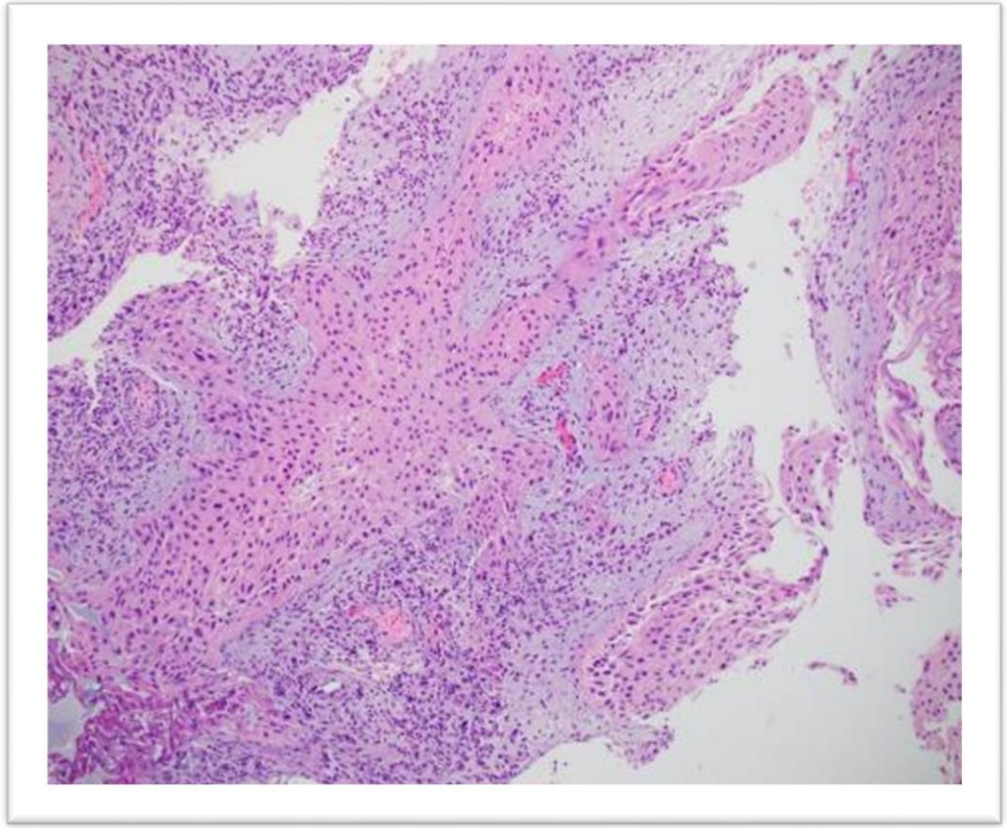


Salivary gland biopsy

- Malignant
  - Infiltration (sometimes)
  - High grade cytology

- Cellular composition/cell types and architecture/stroma
- Broad differential diagnosis
- IHC panel
- Molecular testing

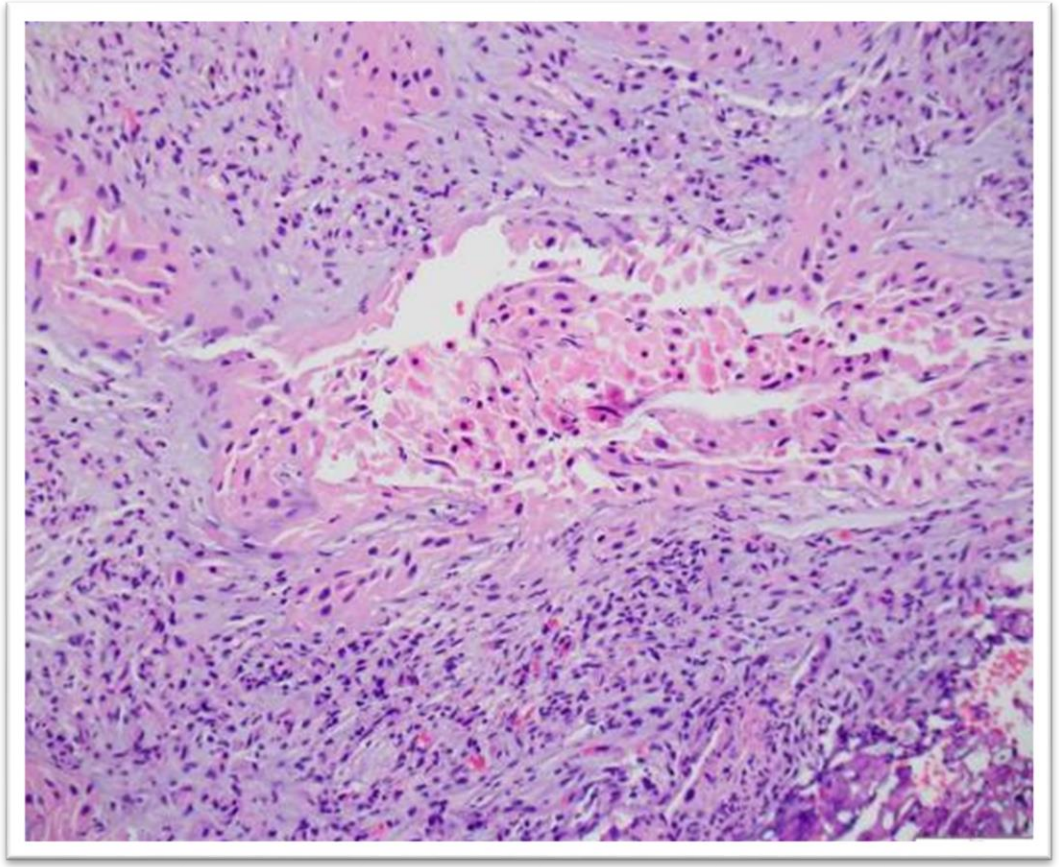




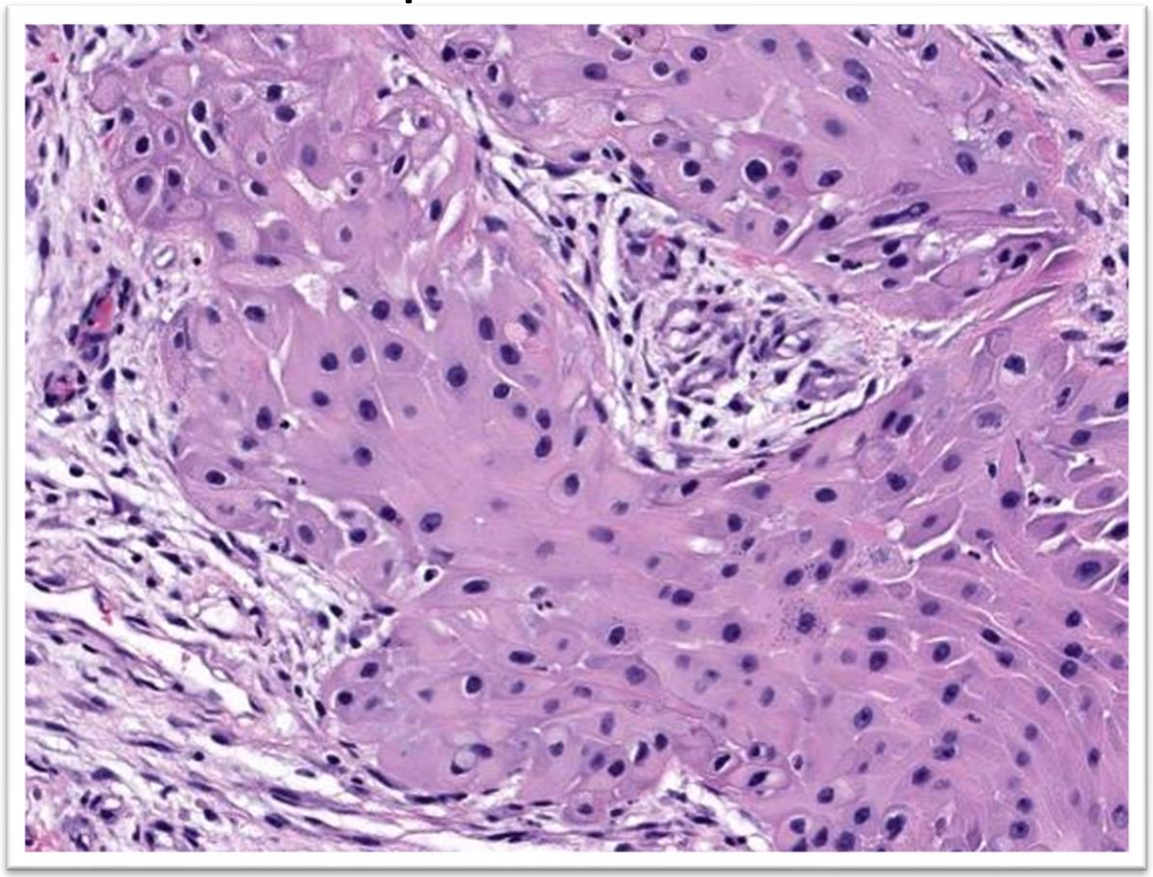
34 YO male
Biopsy from the oropharynx

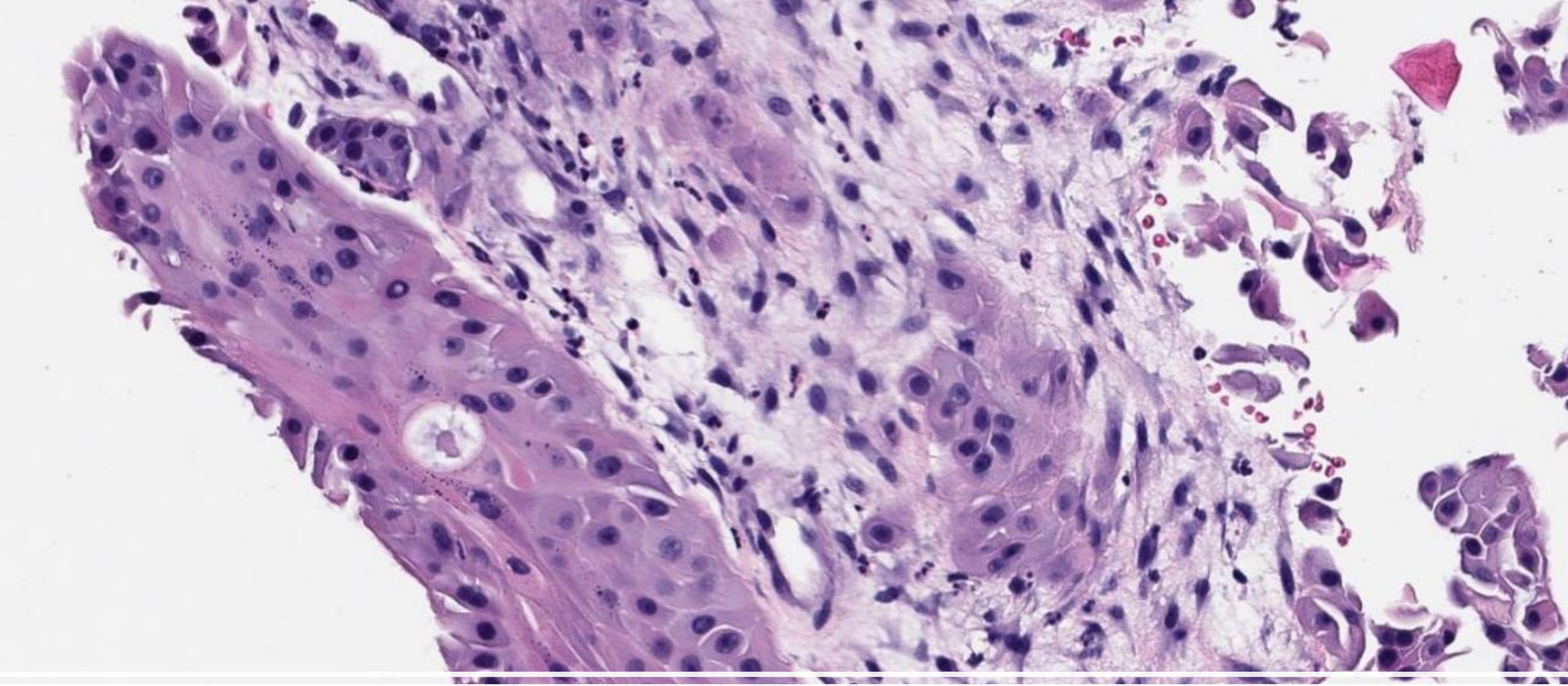
Infiltrative=Malignan

Keratinization



Squamous cells





Focal mucin

Differential Diagnosis

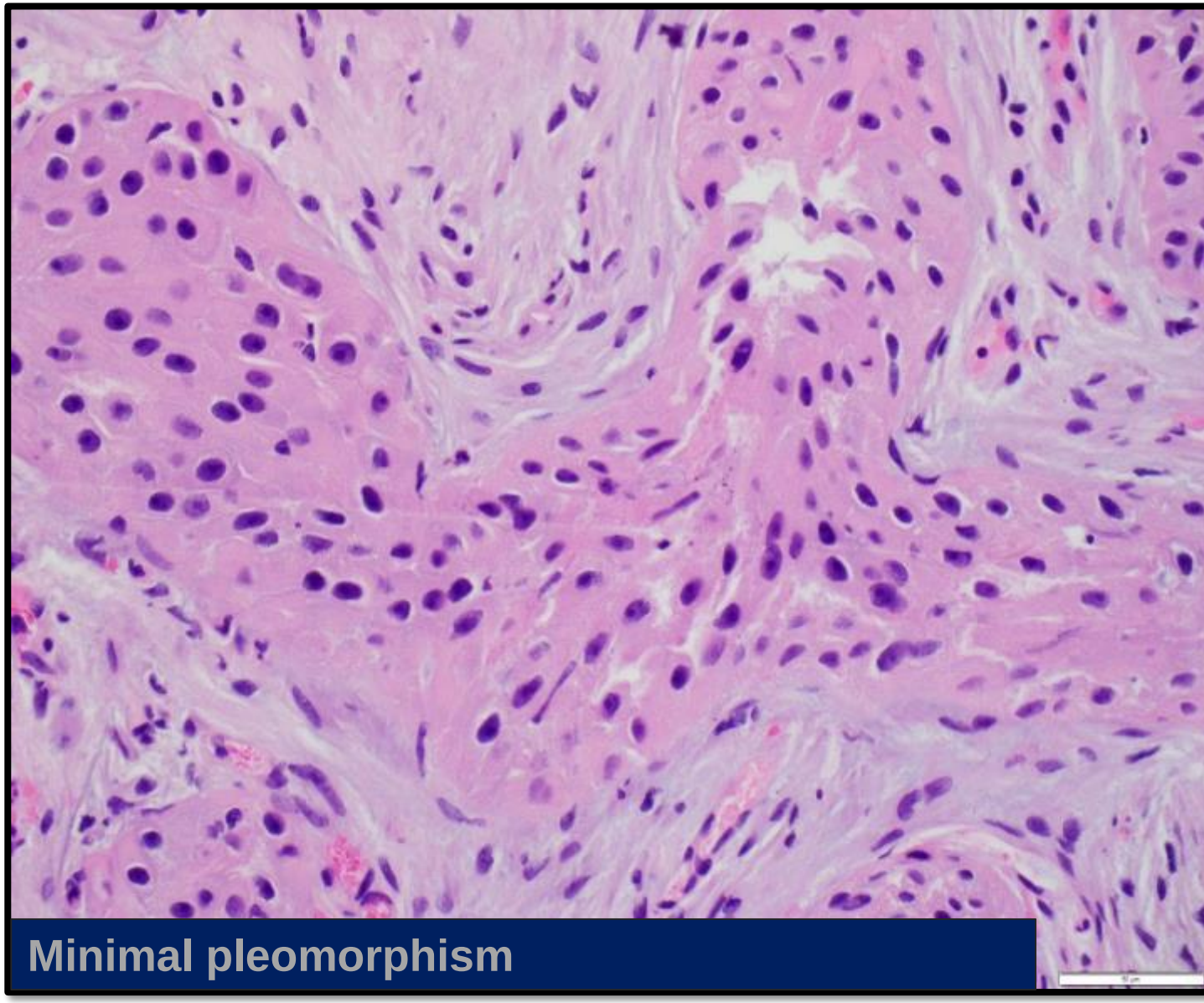
- Squamous cell carcinoma
- Adenosquamous carcinoma
- Hyalinizing clear cell carcinoma
- Mucoepidermoid carcinoma

- **IHC**
  - Positive for p63/CK5/6
  - Negative for p16, S100 and myoepithelial stains

FISH:

MAML2 rearrangements

Mucoepidermoid carcinoma

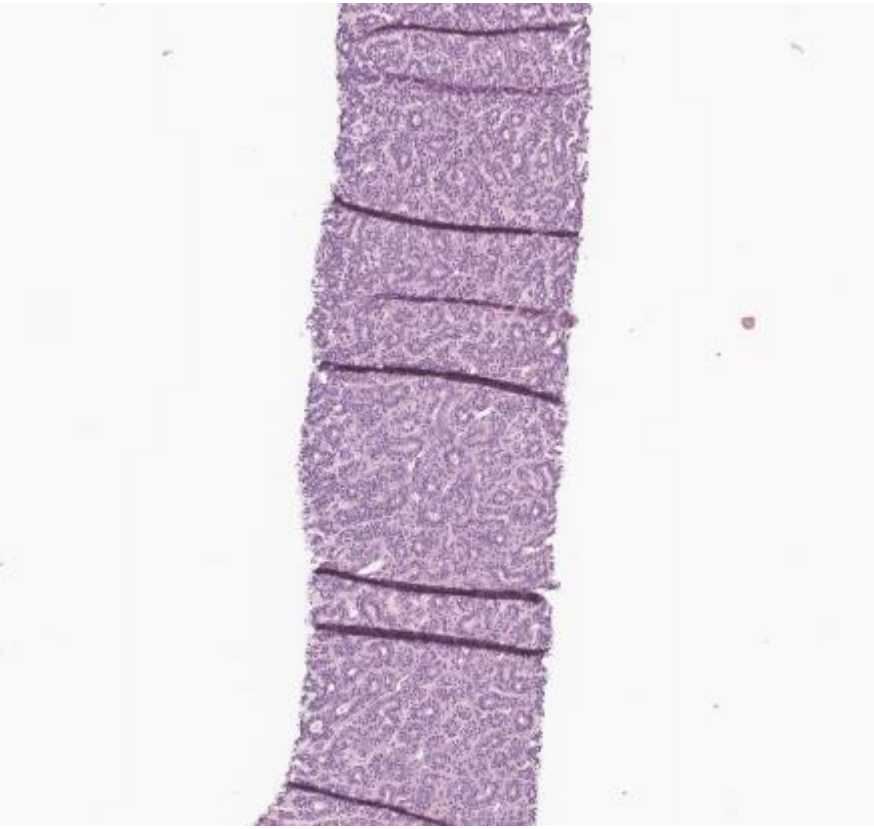


Salivary gland biopsy
No definite diagnosis

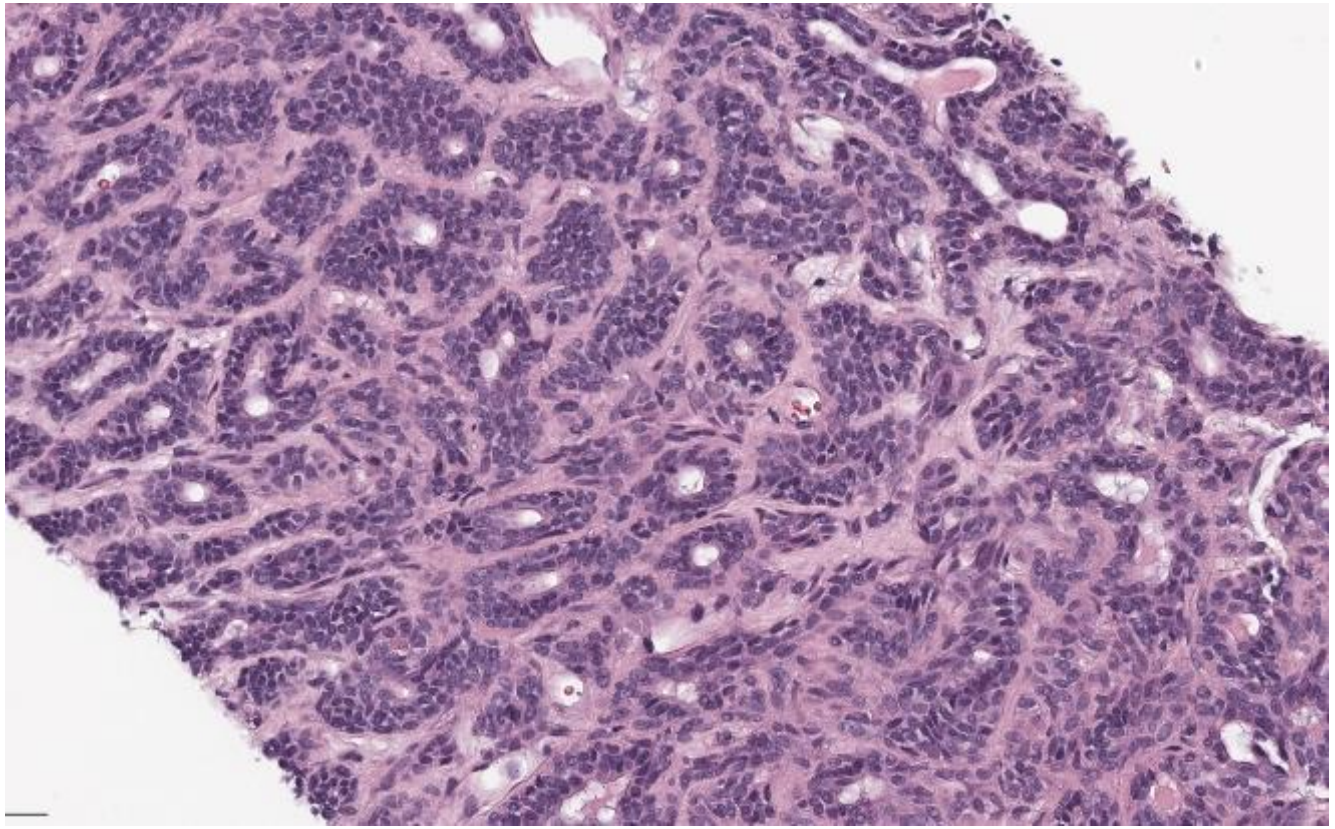
- 1-HG carcinoma
- 2-Low grade salivary gland neoplasm (Benign/pleomorphic adenoma and low-grade carcinomas)

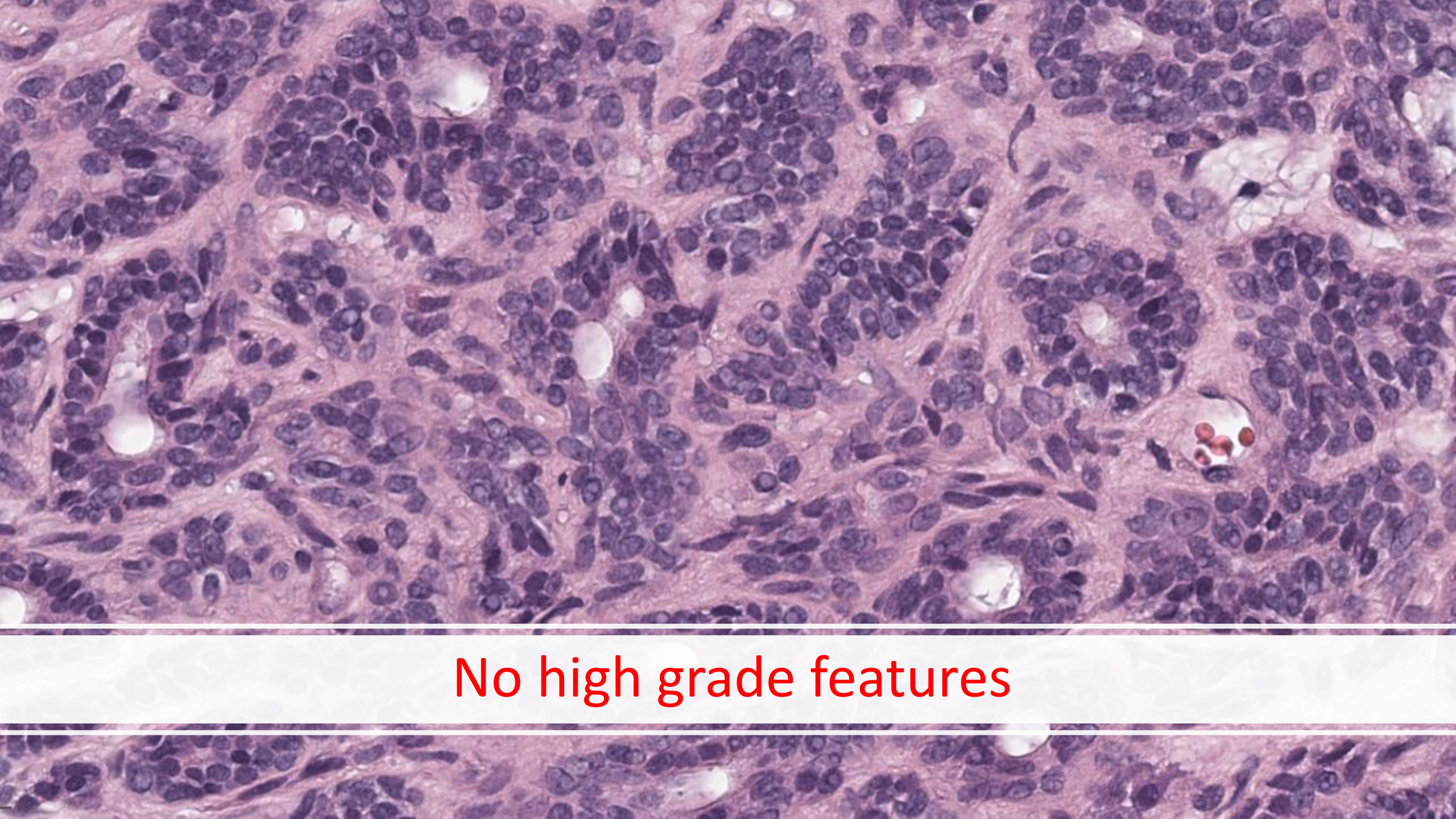
- Differential diagnosis

Neck biopsy



Ductal and myoepithelial cells

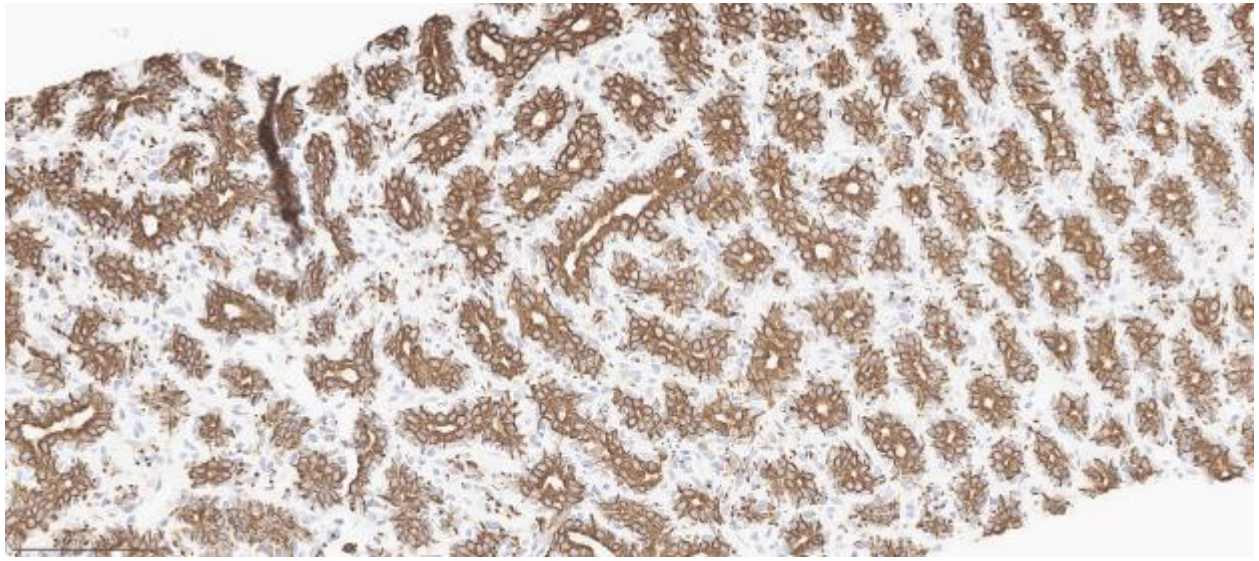




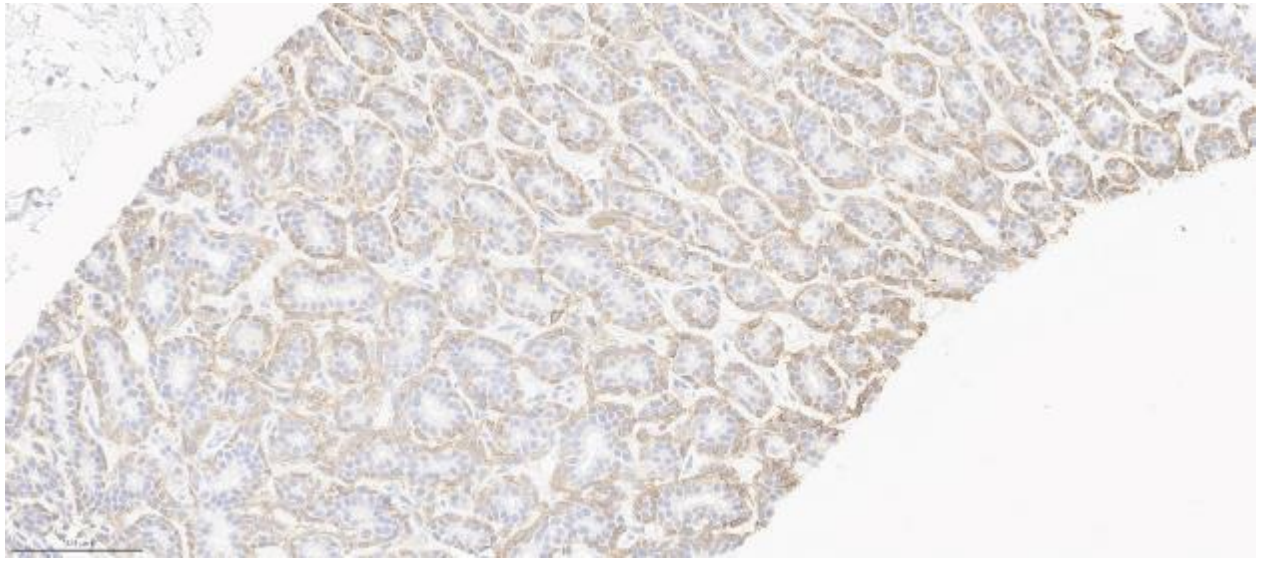
No high grade features

Immunohistochemistry

CK7



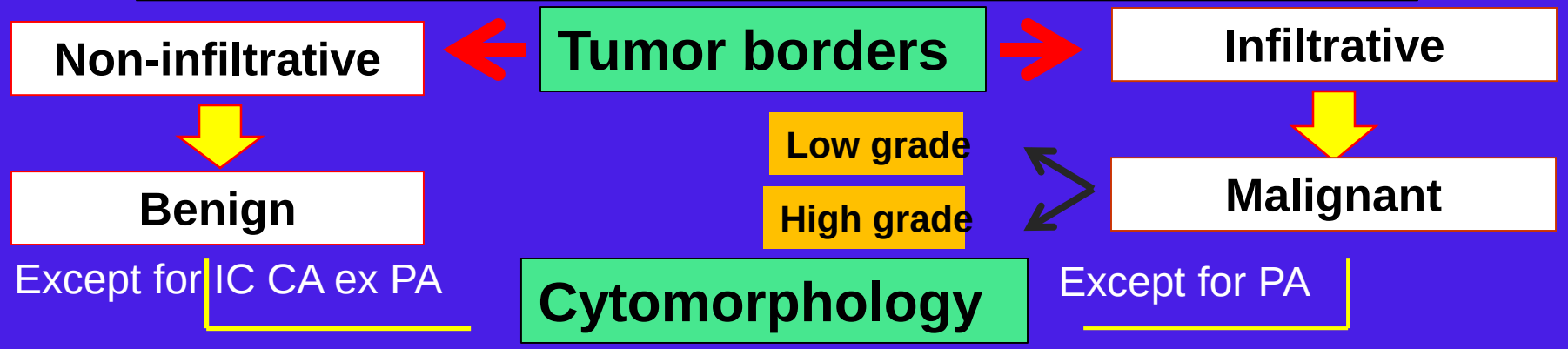
Calponin



Low grade salivary gland neoplasm with ductal and myoepithelial features

D.D: Pleomorphic adenoma, basal cell adenoma, basal cell adenocarcinoma, and epithelial myoepithelial carcinoma

Salivary gland neoplasm



Two cell types (ductal and myoepithelial)
Pleomorphic adenoma
Basal cell adenoma
Intercalated duct adenoma

One cell type
Canalicular adenoma
Myoepithelioma

Oncocytic
Warthin 's tumor
Oncocytoma

Two cell types (ductal and myoepithelial)
Adenoid cystic carcinoma
Epithelial myoepithelial carcinoma
Basal cell adenocarcinoma

One cell type

Ductal:
Salivary duct carcinoma
Secretory carcinoma

Myoep/modified myoep:
Myoepithelial carcinoma
Polymorphous adenoca

Acinic cell carcinoma

Tumor with squamous phenotype
Mucoepidermoid carcinoma
Hyalinizing clear cell carcinoma

Pleomorphic adenoma

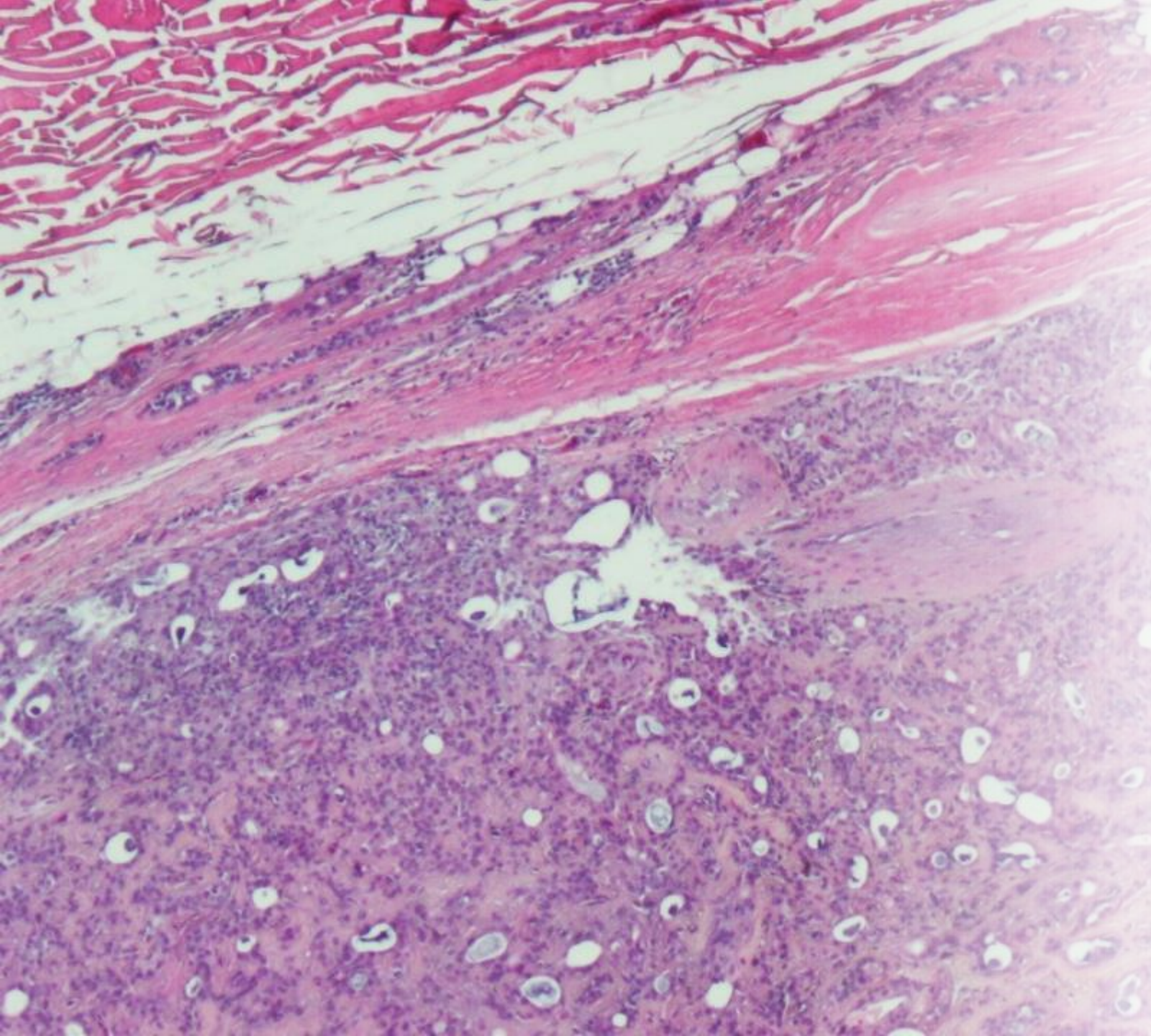
Myoepithelial carcinoma

Carcinoma ex pleomorphic adenoma

Salivary duct carcinoma

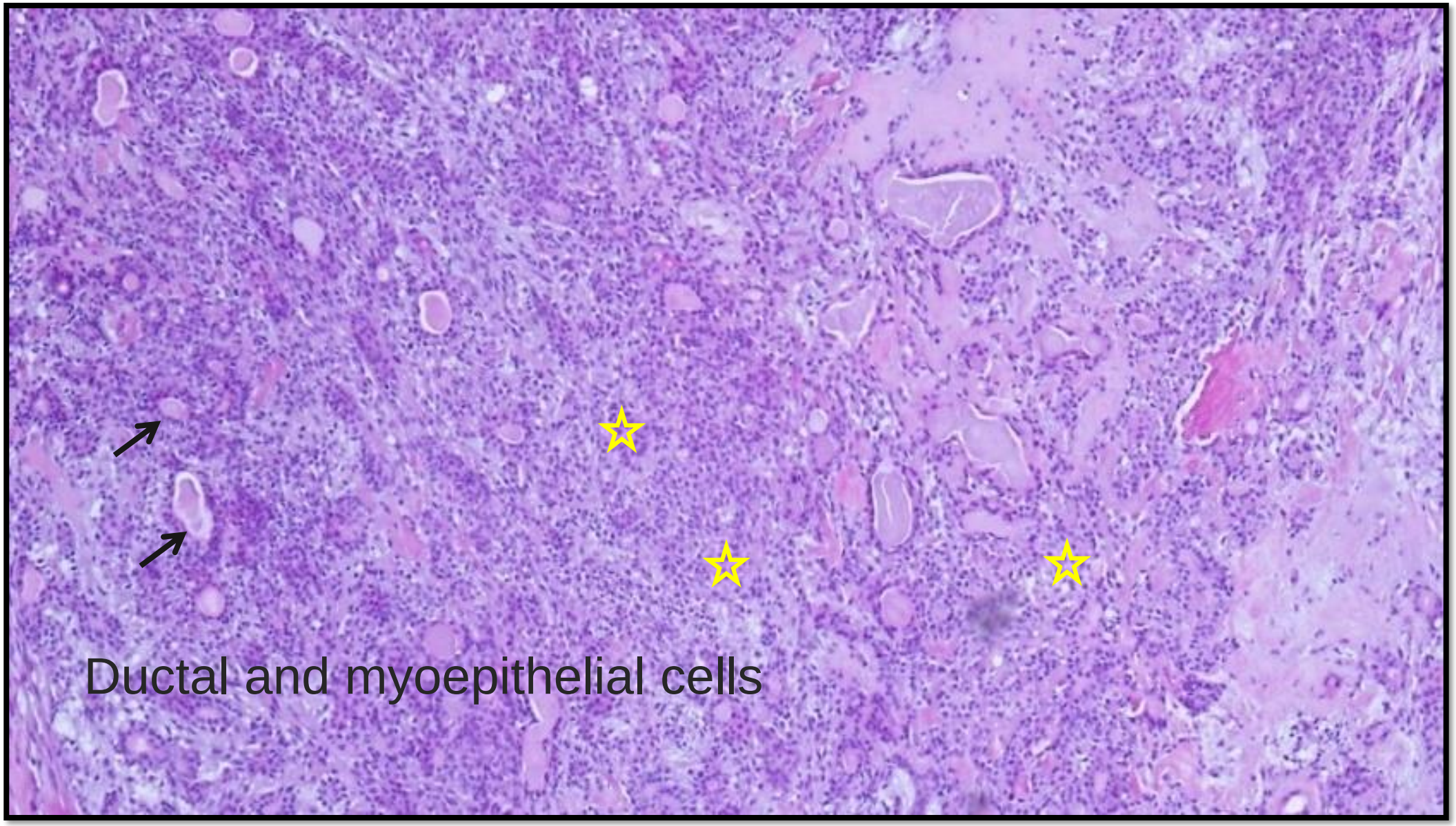
Pleomorphic adenoma (PA)

- Most common salivary gland tumor
- Parotid 80%, submandibular 10%, minor salivary gland 10%
- Slow growing mass, usually solitary
- Exposure to radiation increases the incidence

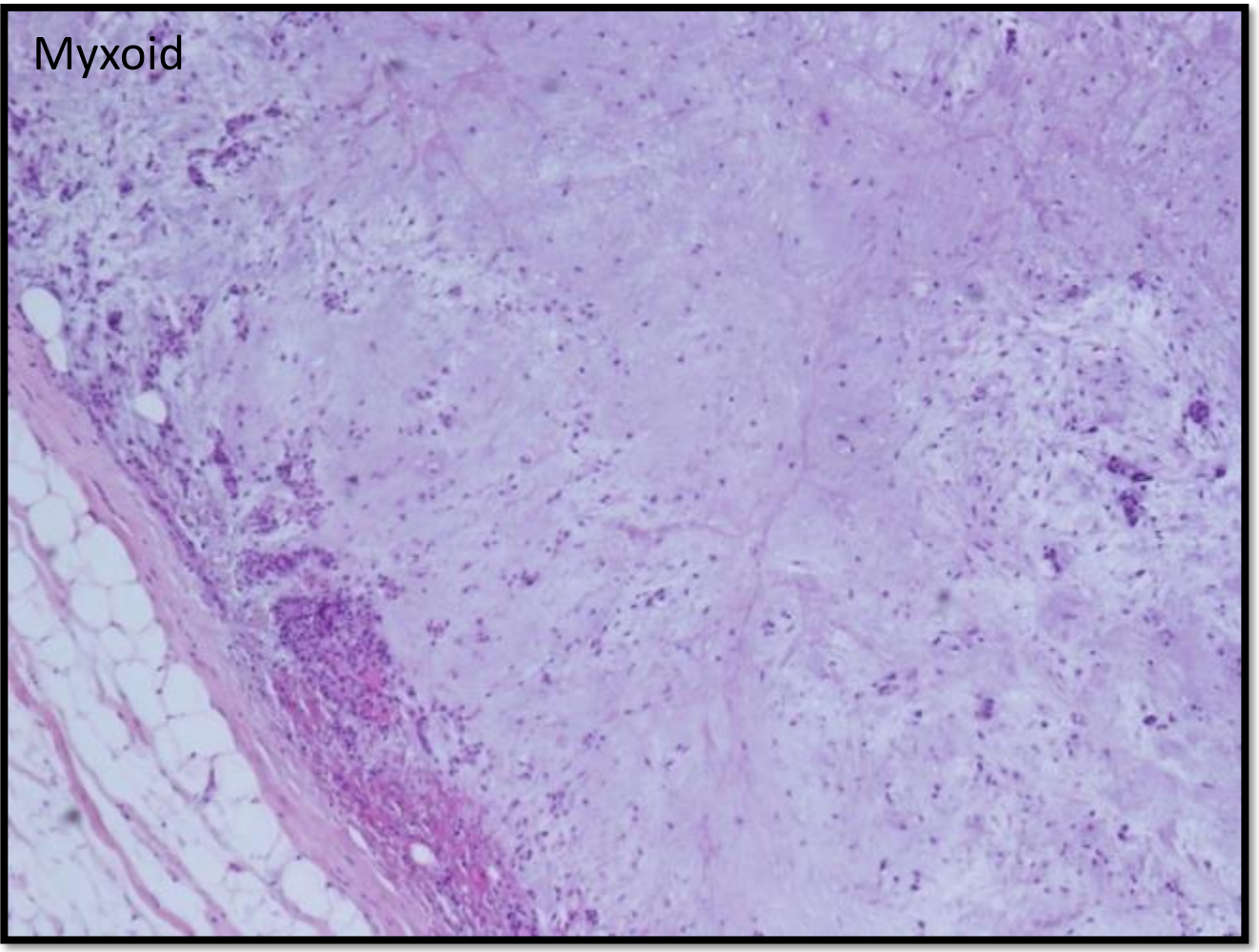


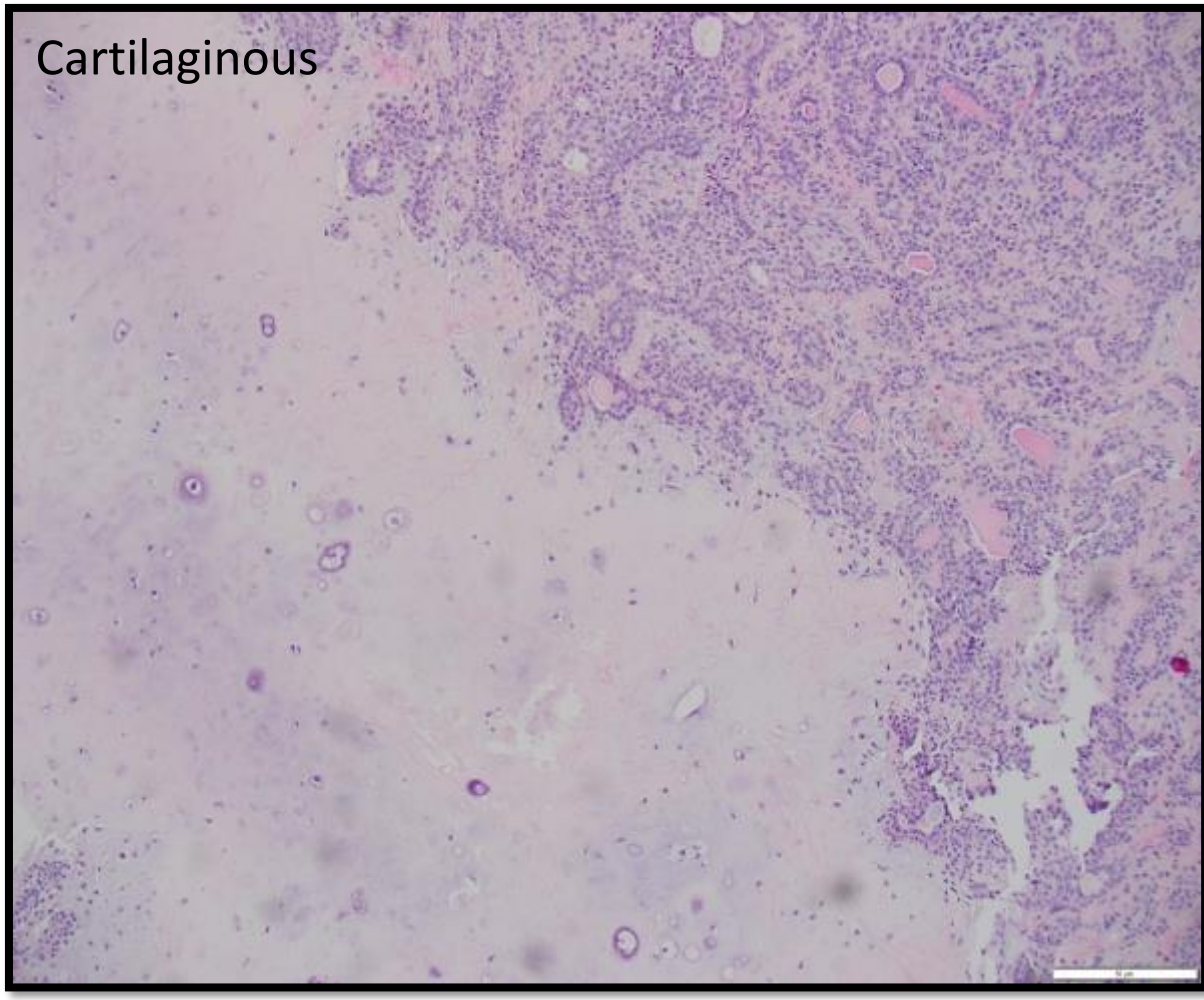
PA-Histology

- Encapsulated with variable encapsulation
- Composed of 3 elements:
  - Epithelial/ductal cells
  - Myoepithelial cells
  - Mesenchymal or stromal

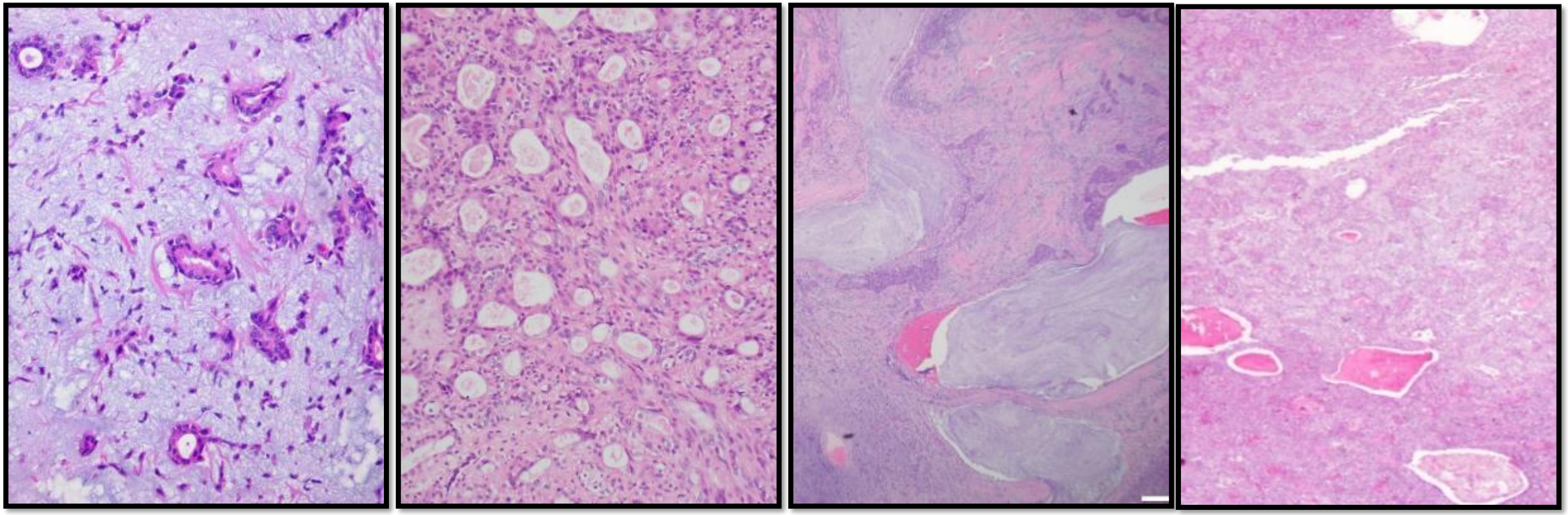

Ductal and myoepithelial cells

PA-Stroma



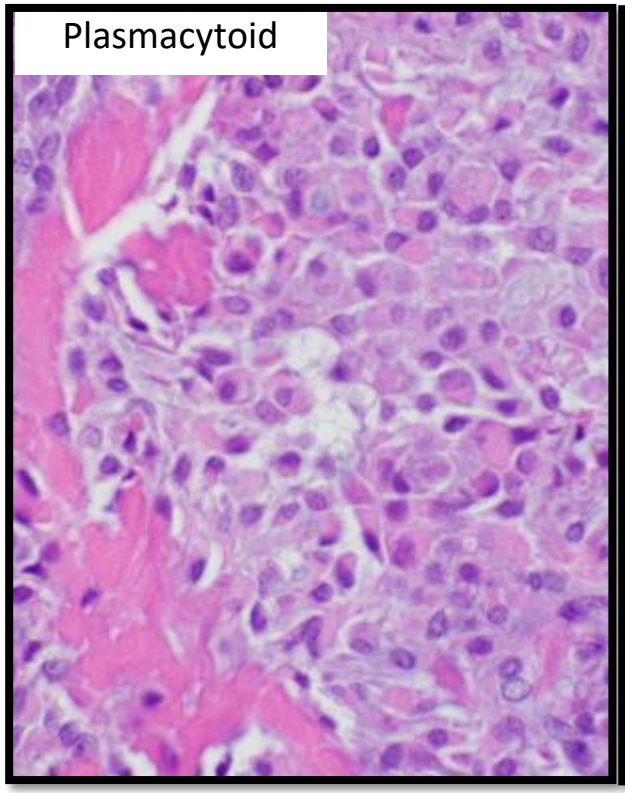


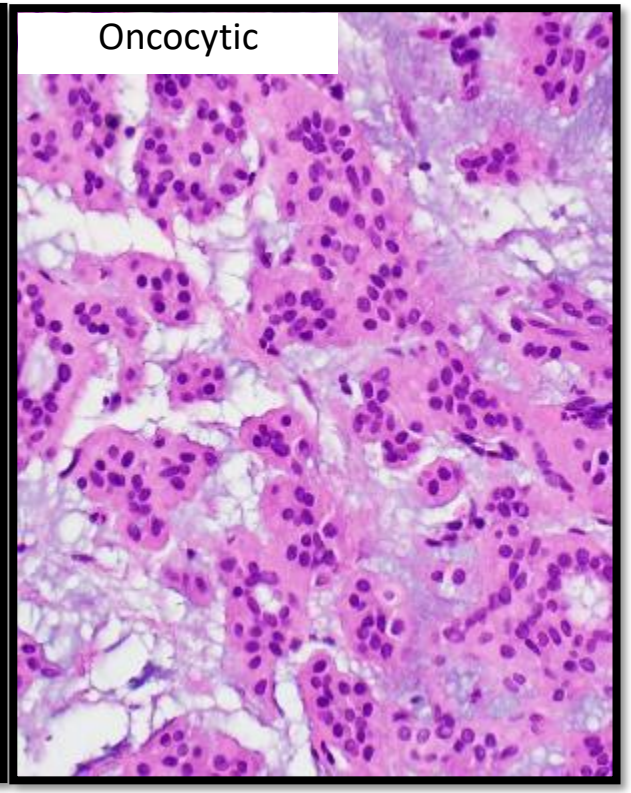
PA-Architectural pleomorphism

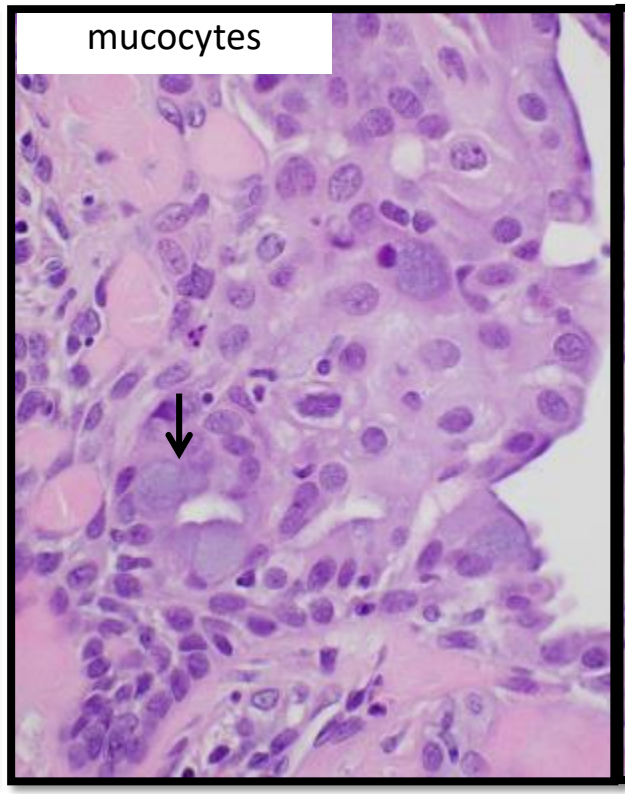


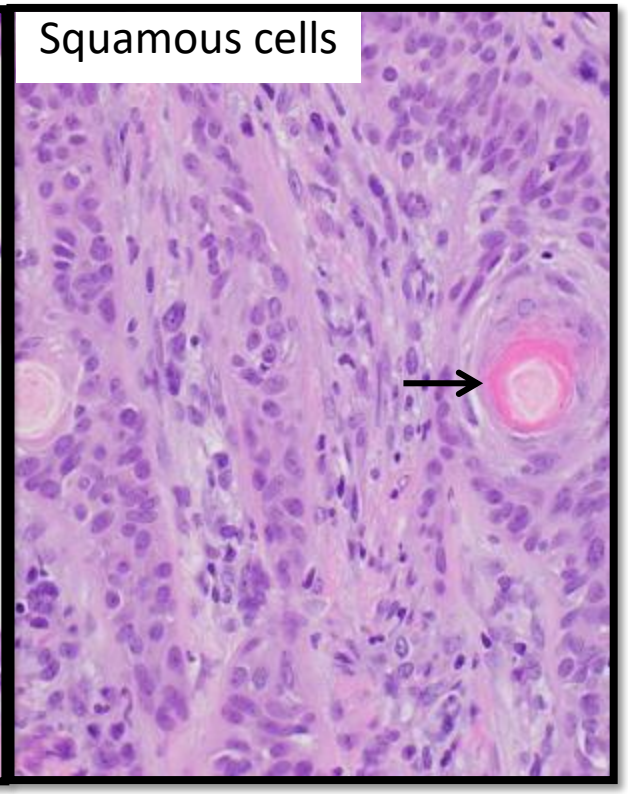
PA-Mixed type of cells

- Squamous cells with keratin, mucocytes, adipocytes, acinar cells, oncocytes

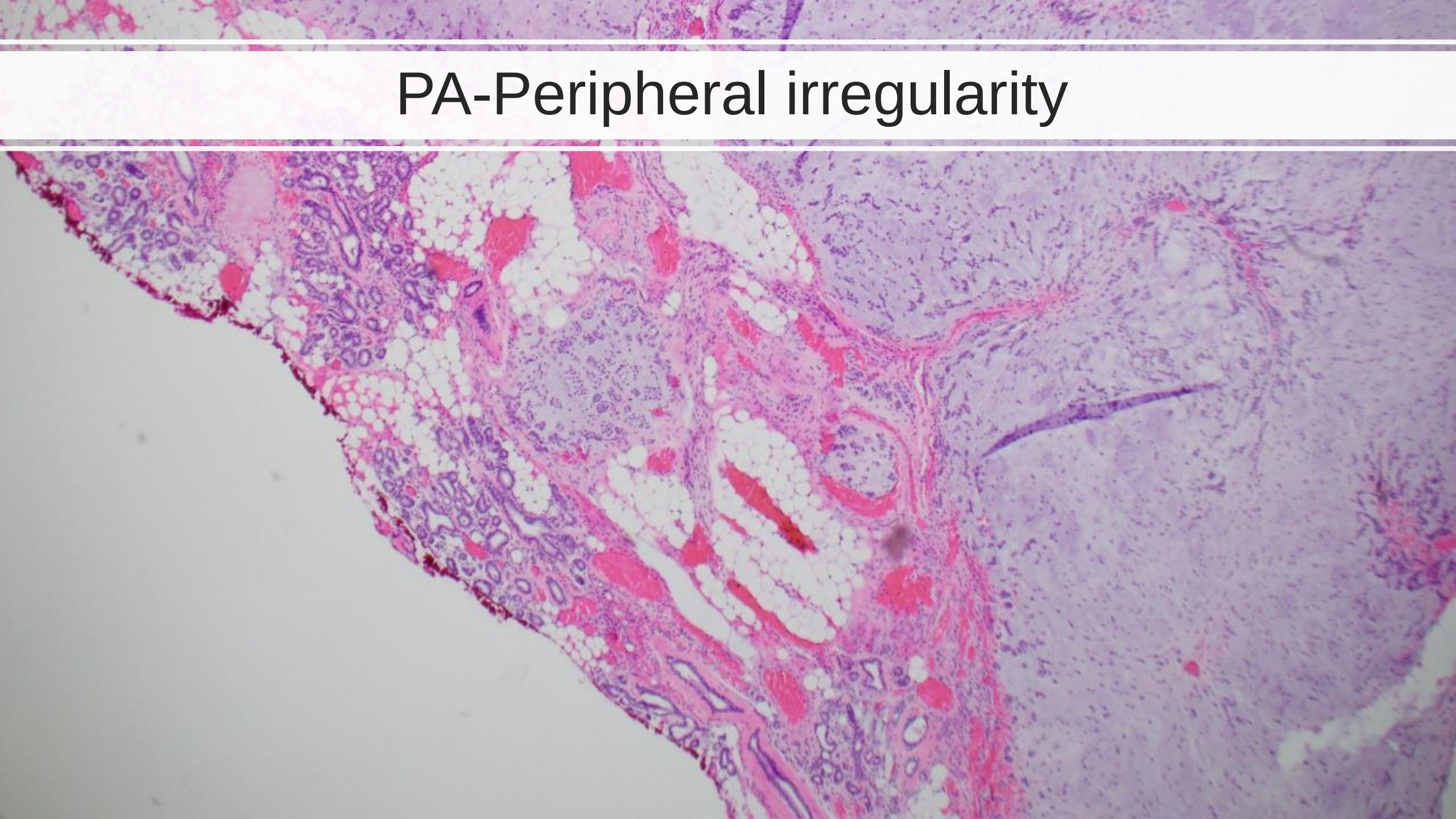






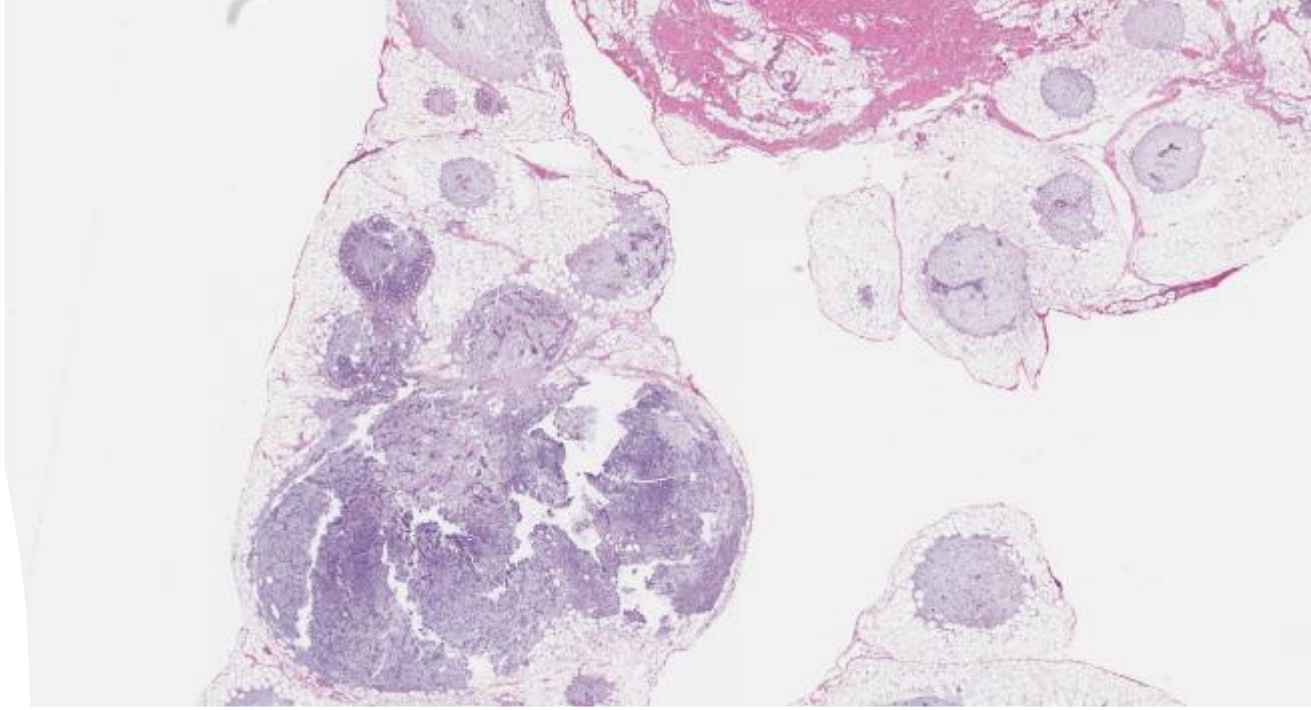


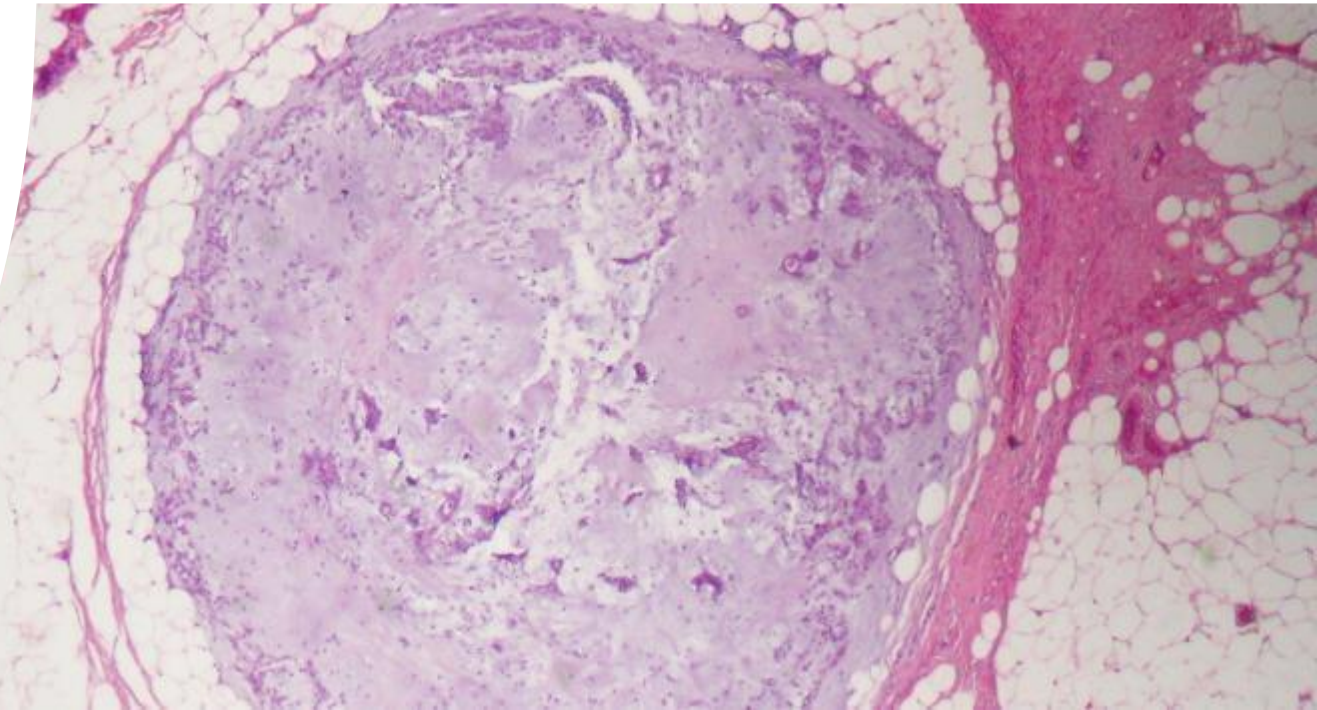
PA-Peripheral irregularity

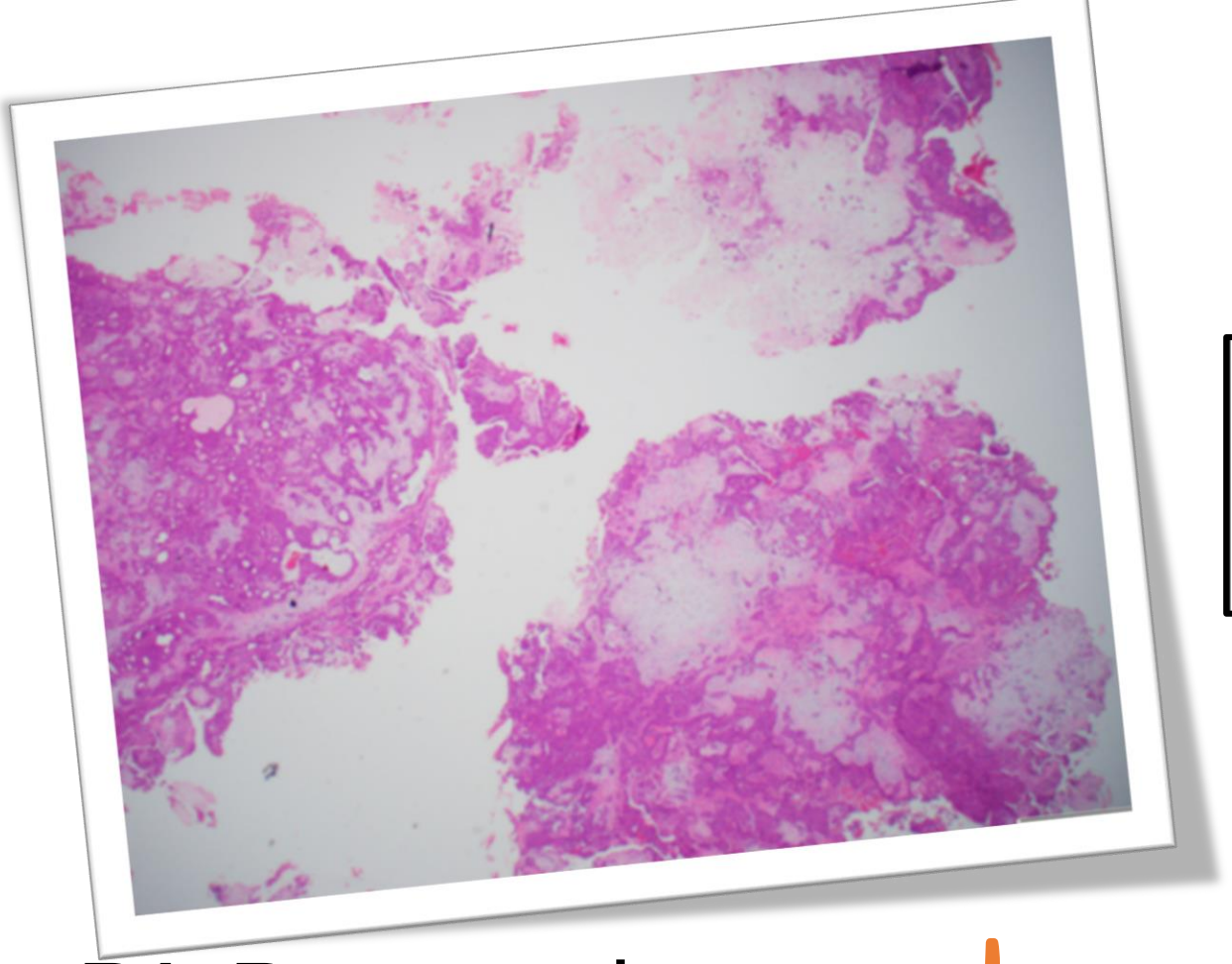


Recurrent PA

- Recurrence rate 3.4%
- Malignant transformation <1%







Clinicopathologic Characteristics and Prognostic Factors of Primary and Recurrent Pleomorphic Adenoma

A Single Institution Retrospective Study of 705 Cases

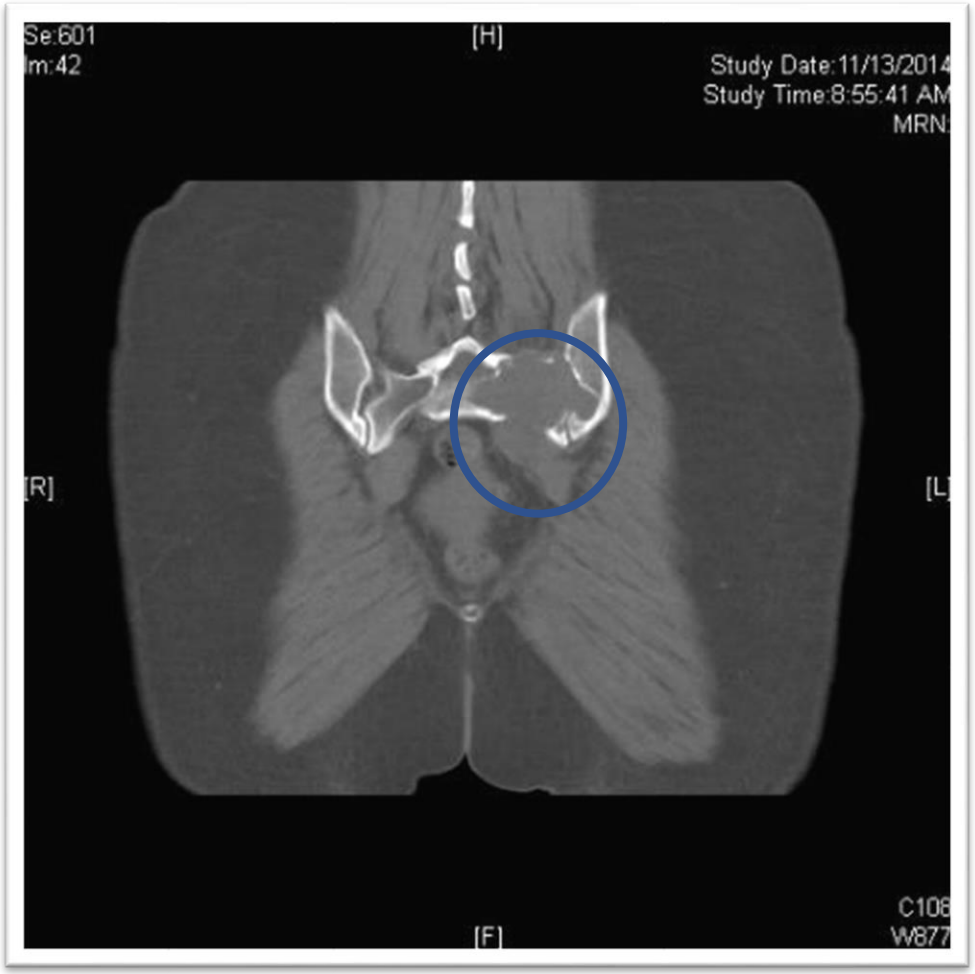
Bayan Alzumaili, MD, Bin Xu, MD, PhD,† Maelle Saliba, MD,‡ Abderhman Abuhashem, AB,§ Ian Ganly, MD,‖ Ronald Ghossein, MD,† and Nora Katabi, MD†*

PA-Prognostic factors

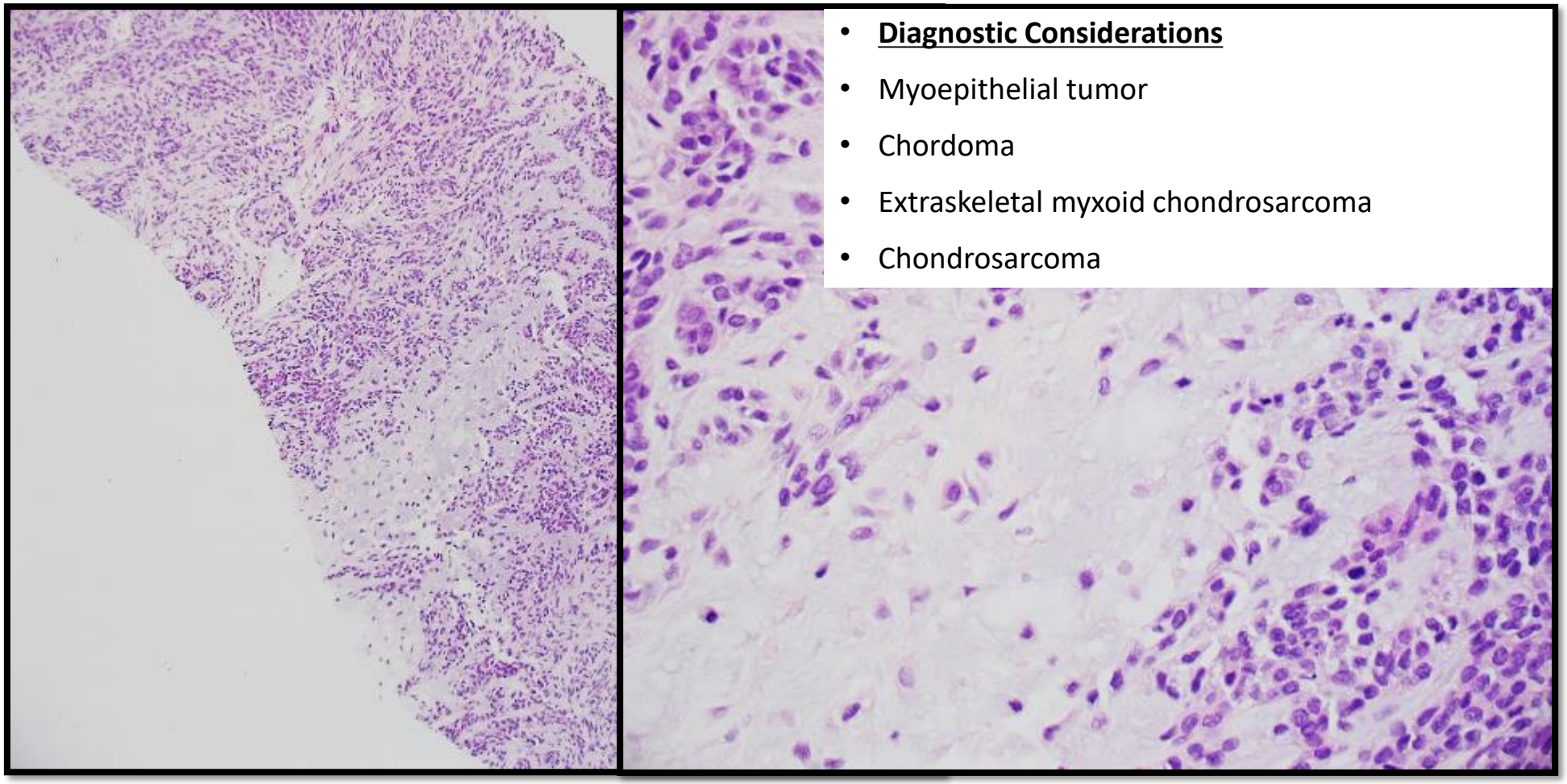
- Young age
- High mitotic activity
- Specimen integrity

Clinical case

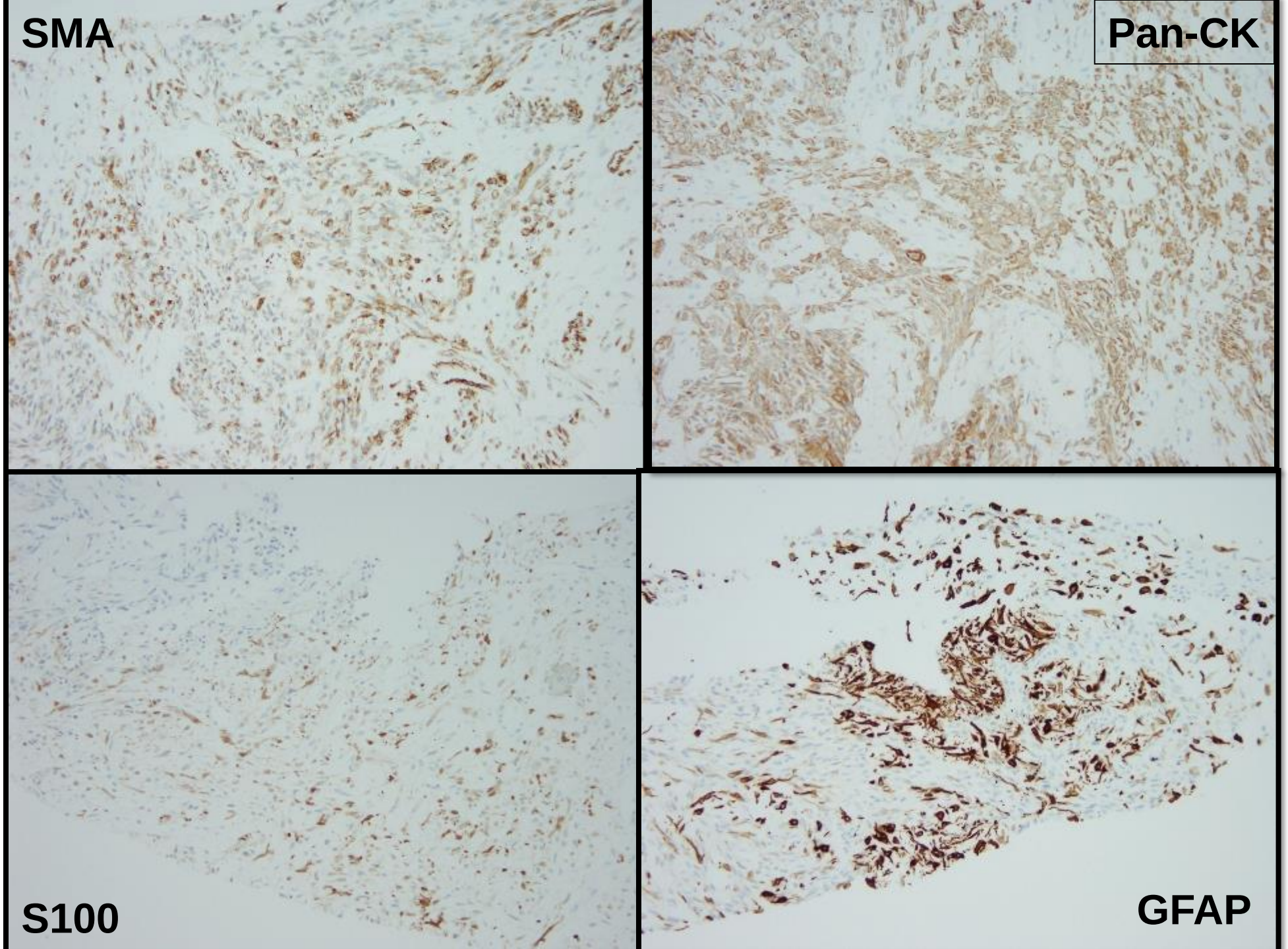
- 46-year-old who presented with lower back pain
- Seen by a physician who requested an MRI
- Referred to MSK
- Image-guided biopsy



Biopsy from sacrum



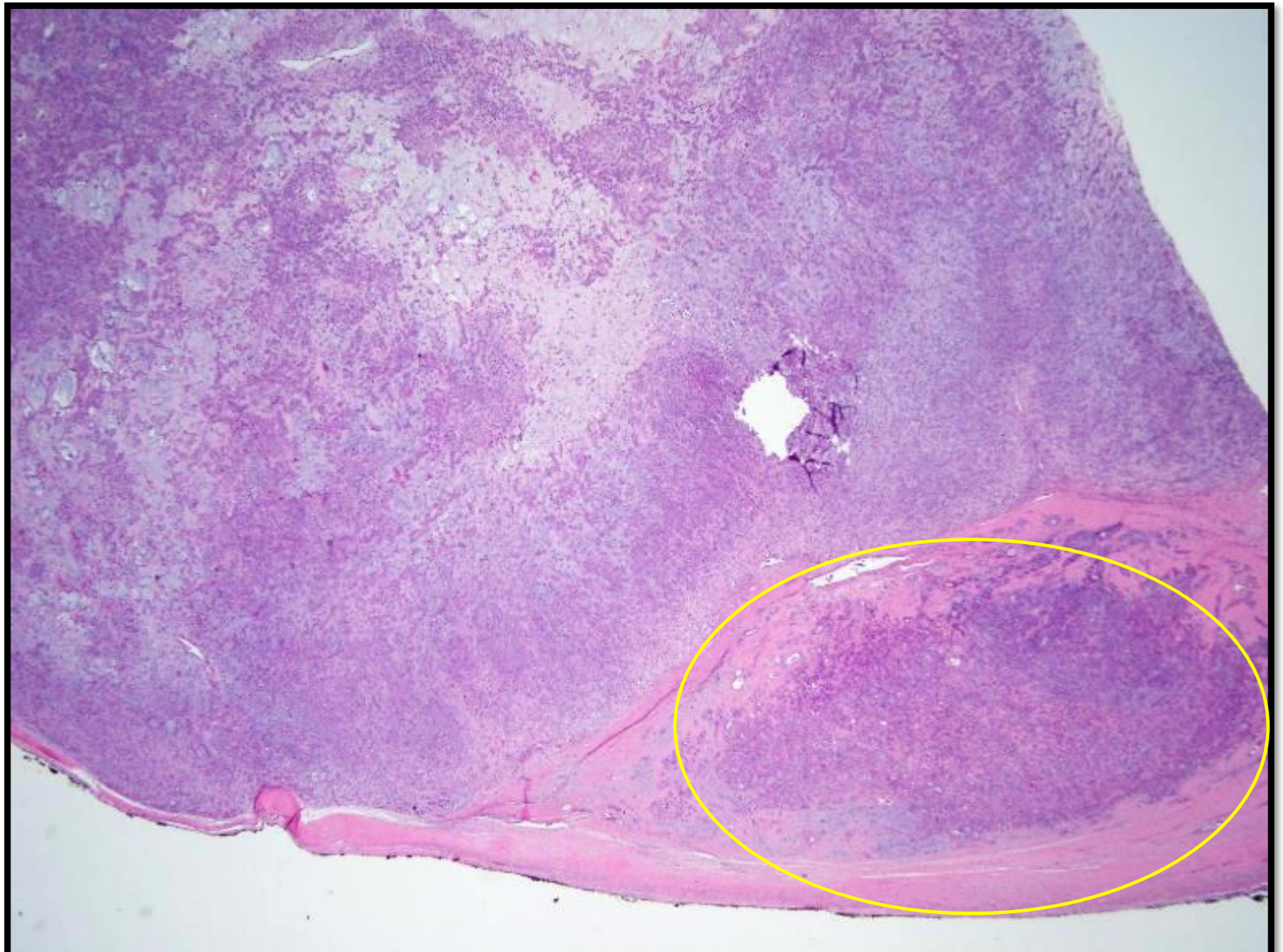
- **<u>Diagnostic Considerations</u>**
- Myoepithelial tumor
- Chordoma
- Extraskeletal myxoid chondrosarcoma
- Chondrosarcoma


SMA
Pan-CK
S100
GFAP

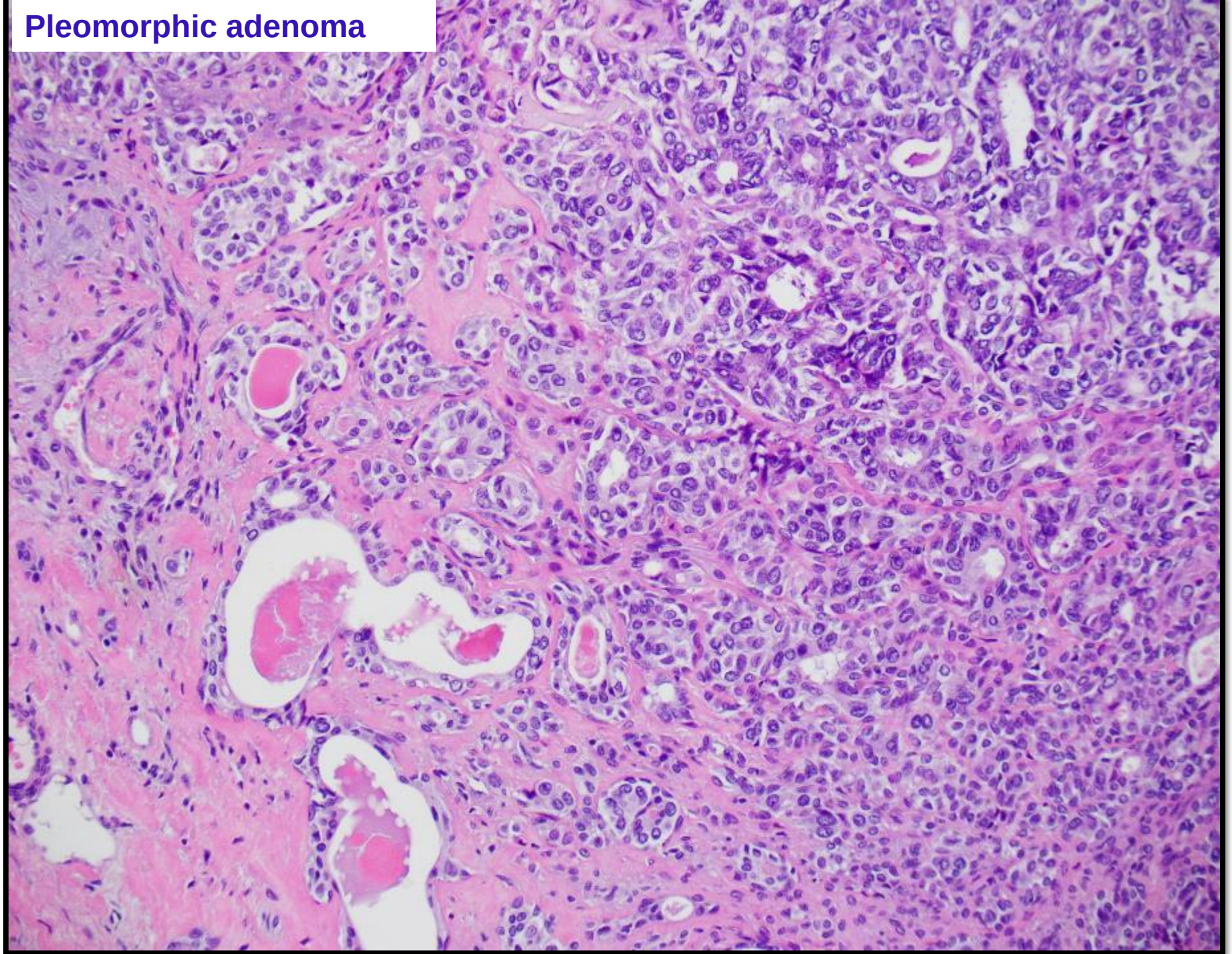
Diagnosis

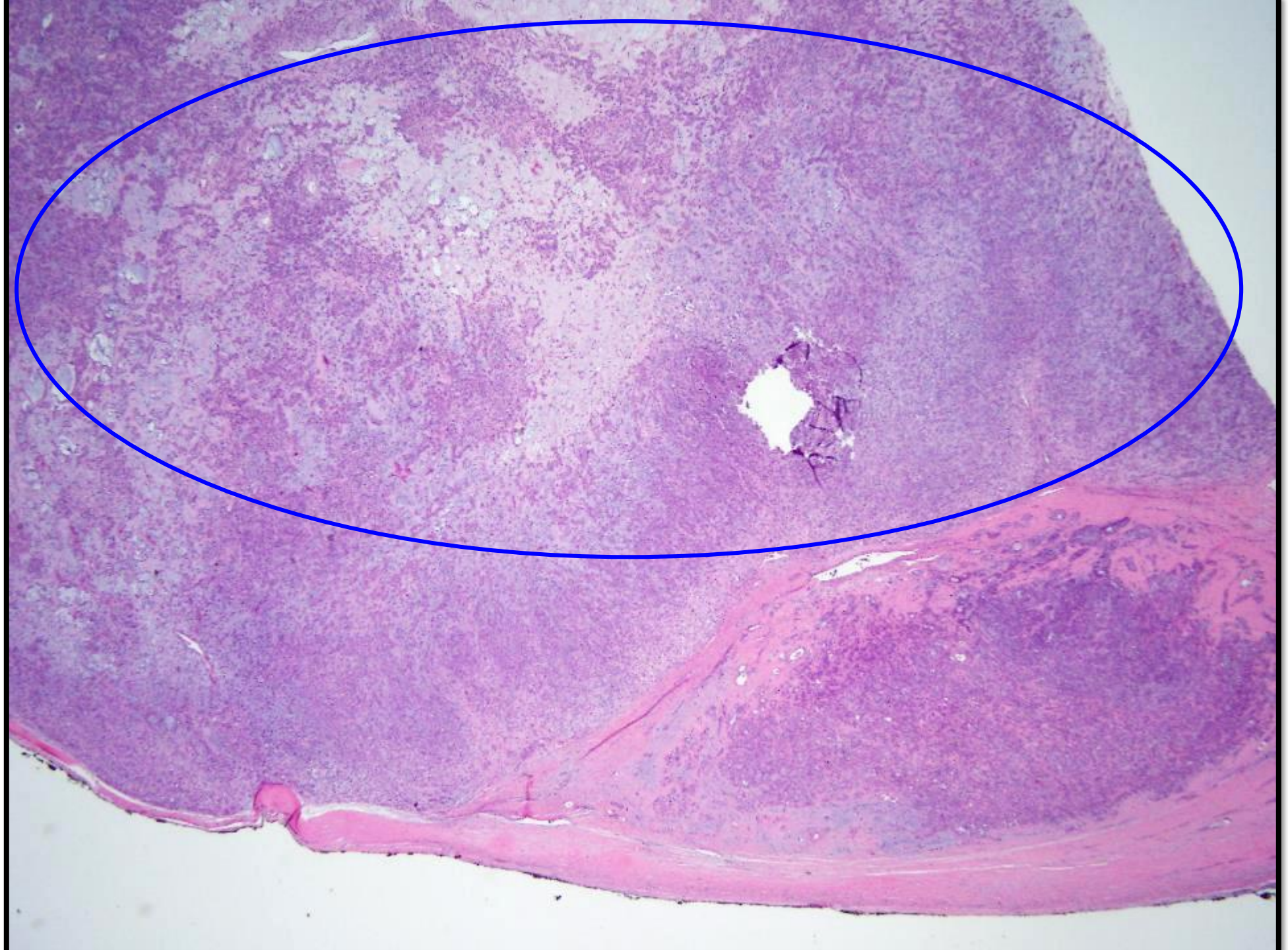
Spindle and epithelioid neoplasm with myxoid features, favor a myoepithelial neoplasm

Three years ago, patient had removal of a parapharyngeal “pleomorphic adenoma”

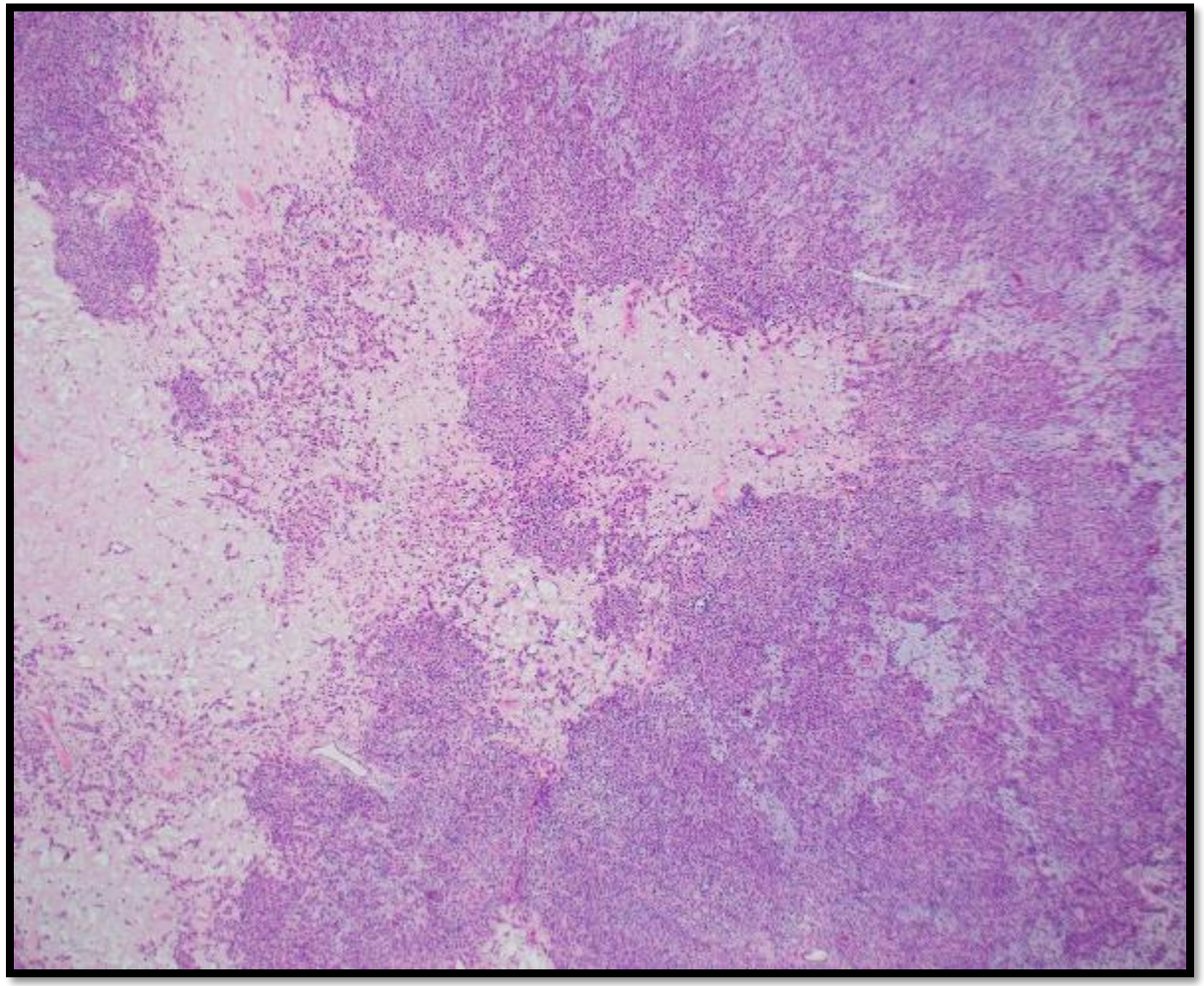


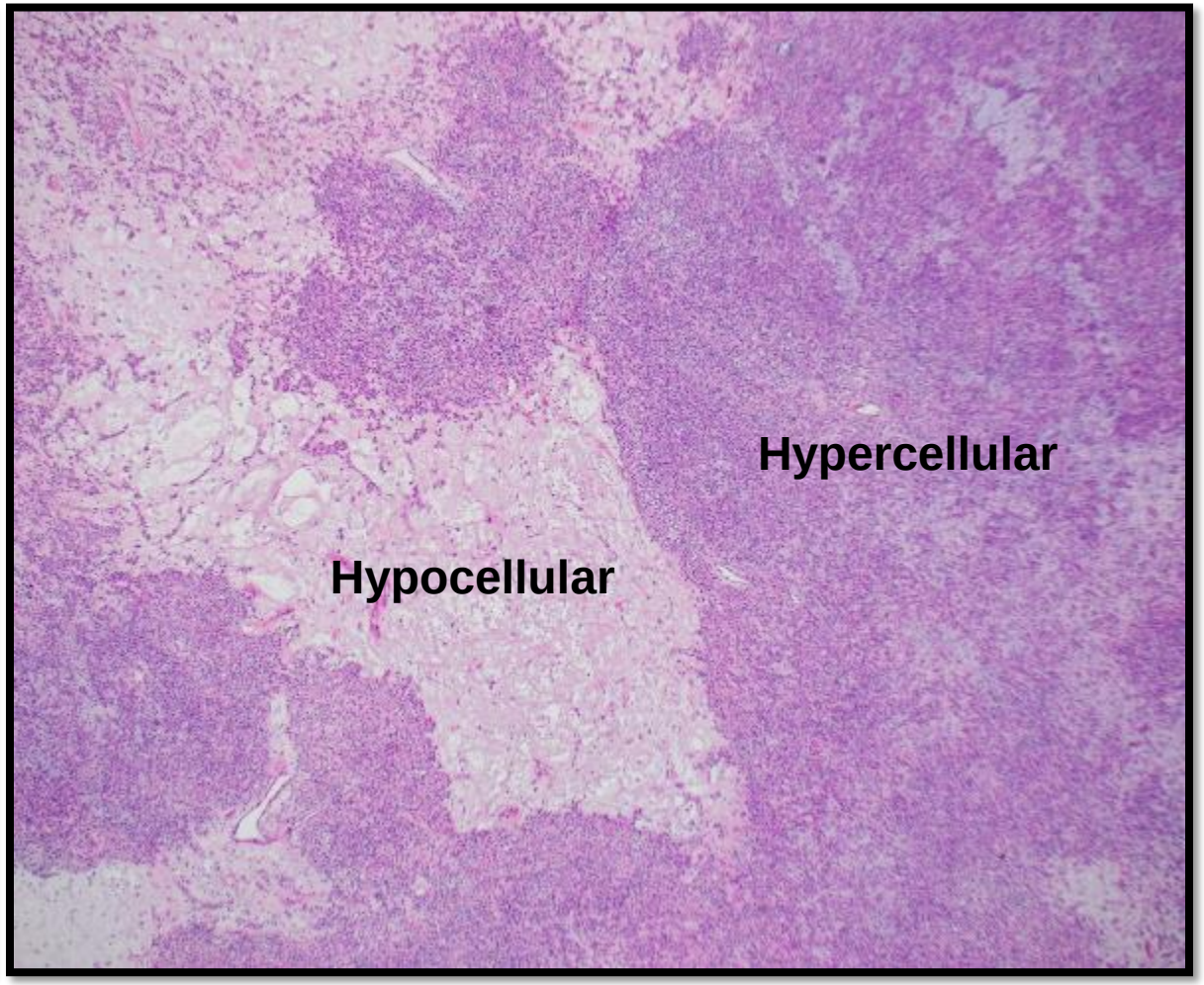
Pleomorphic adenoma



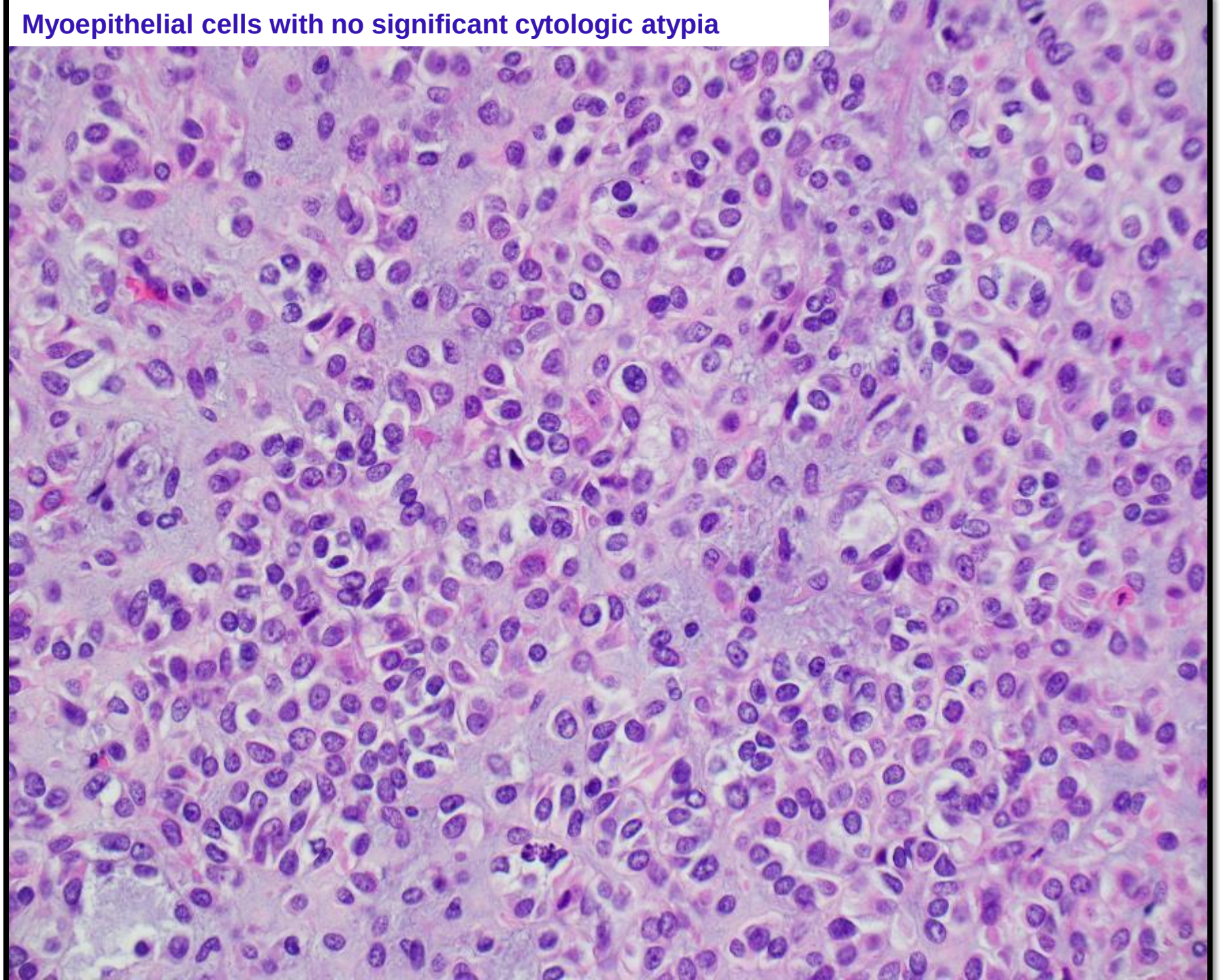


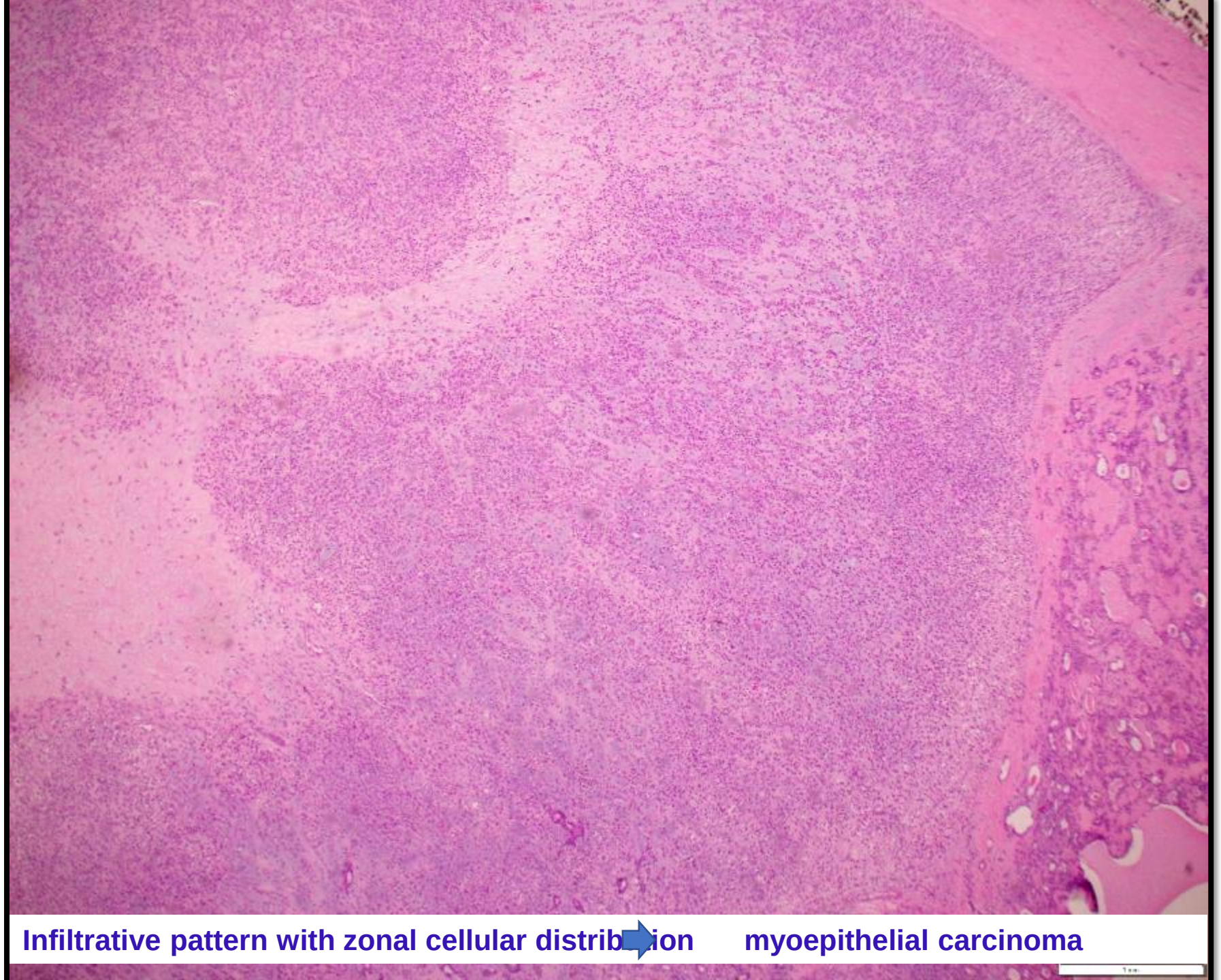
Proliferations of myoepithelial cells with nodular and expansile pattern





Myoepithelial cells with no significant cytologic atypia





Infiltrative pattern with zonal cellular distribution → myoepithelial carcinoma

Myoepithelial carcinoma ex pleomorphic adenoma

with metastasis to bone

Myoepithelial carcinoma

Histologically challenging entity that is difficult to recognize

Can closely mimic pleomorphic adenoma

Misinterpreted Myoepithelial Carcinoma of Salivary Gland A Challenging and Potentially Significant Pitfall

Bin Xu, Wadad Mneimneh, Dianne E Torrence, Kevin Higgins, David Klimstra, Ronald Ghossein, Nora Katabi

American Journal of Surgical Pathology, Februrary 15 2019

- 21 histologically challenging myoepithelial carcinomas:
  - 16 CA ex PA (most are intracapsular and minimally invasive)
  - 5 de novo myoepithelial carcinomas
- 18 cases (86%) had an initial diagnosis of benign

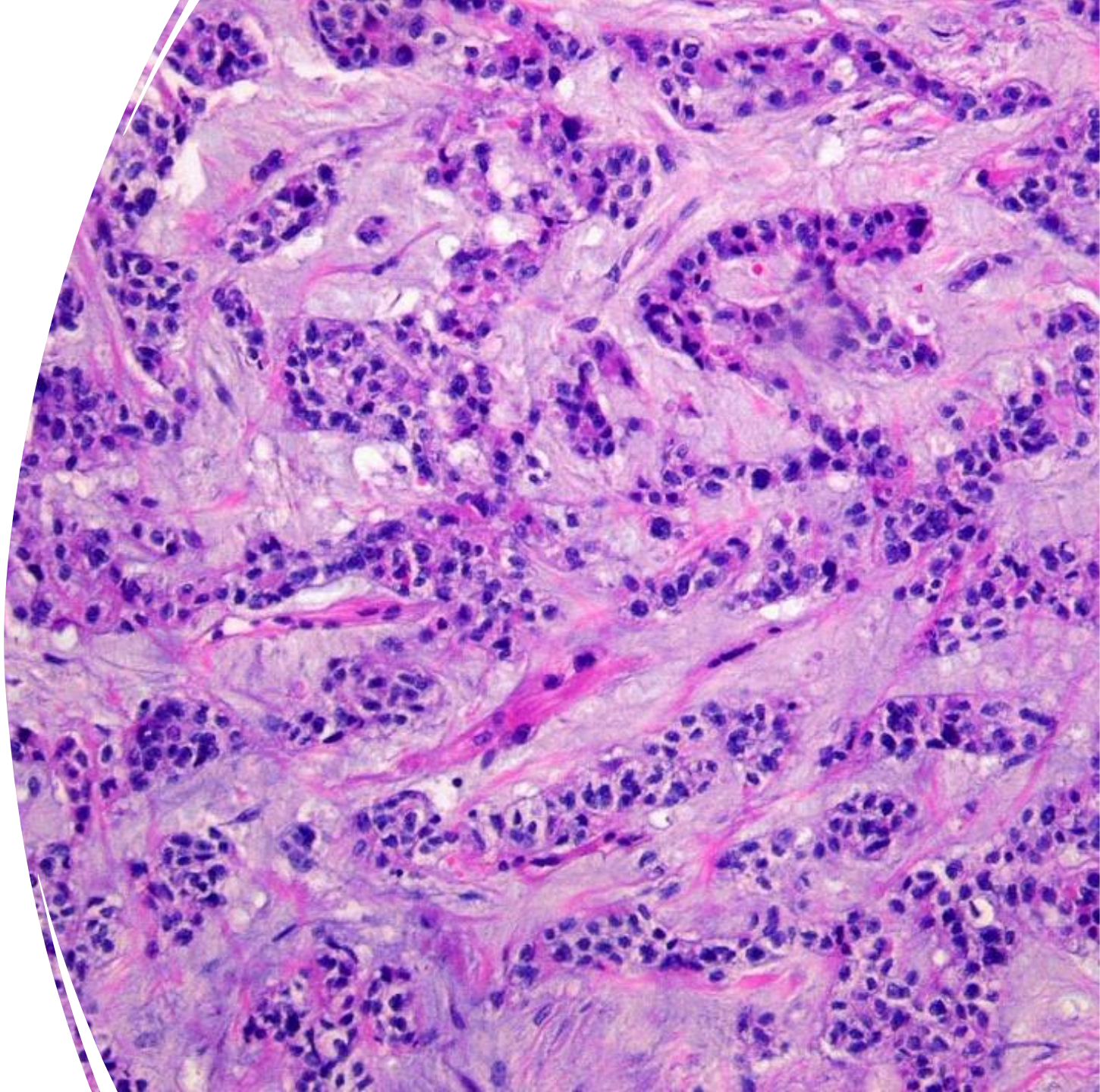
- 16 patients with FU: 14 (87.5%) progressed
  - 10 with local recurrences and 5 with distant metastases: lung, bone and skin
  - 2 patients died, one had an initial diagnosis of PA

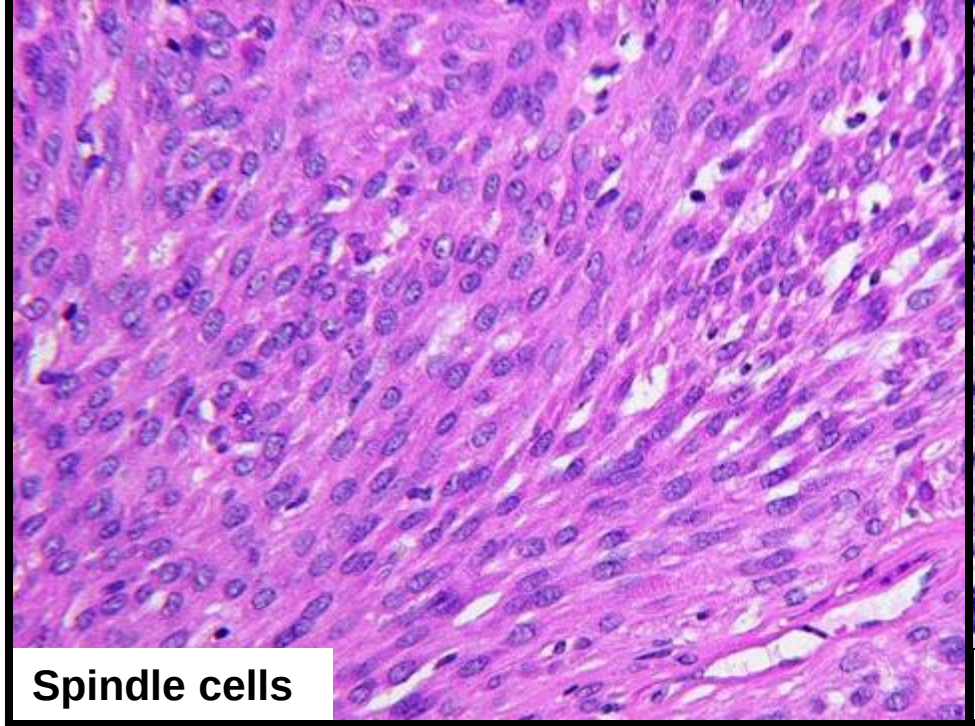
Myoepithelial carcinoma

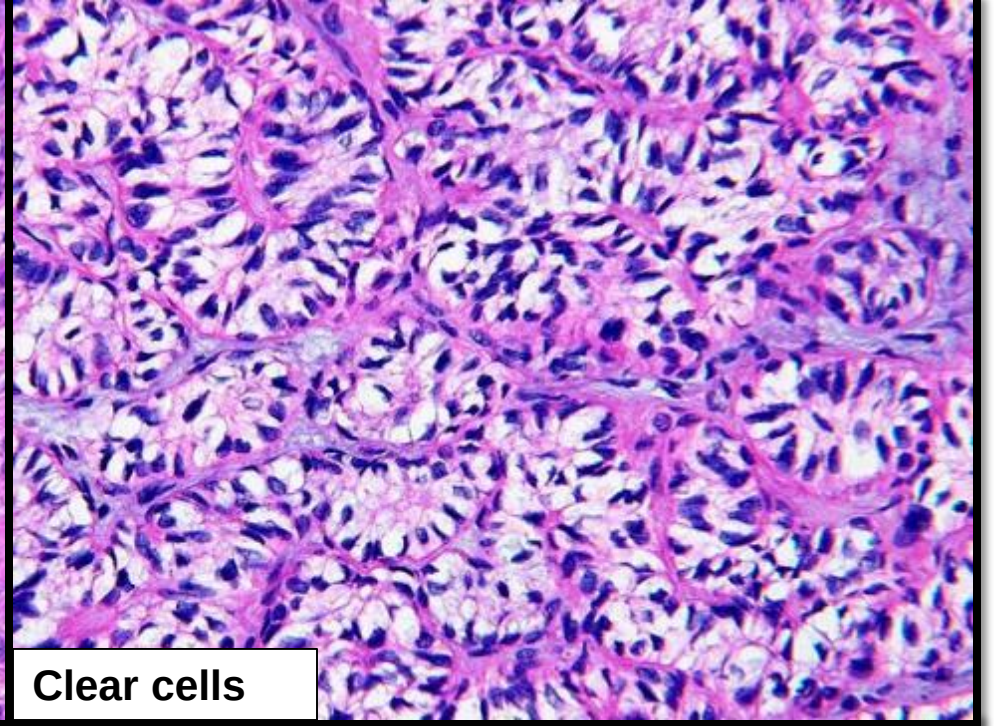
- <2% of all salivary gland carcinomas
- Under recognized entity
- De novo or CA ex PA
- Second most common histology of CA ex PA
- Parotid 75%
- Diverse clinical behavior

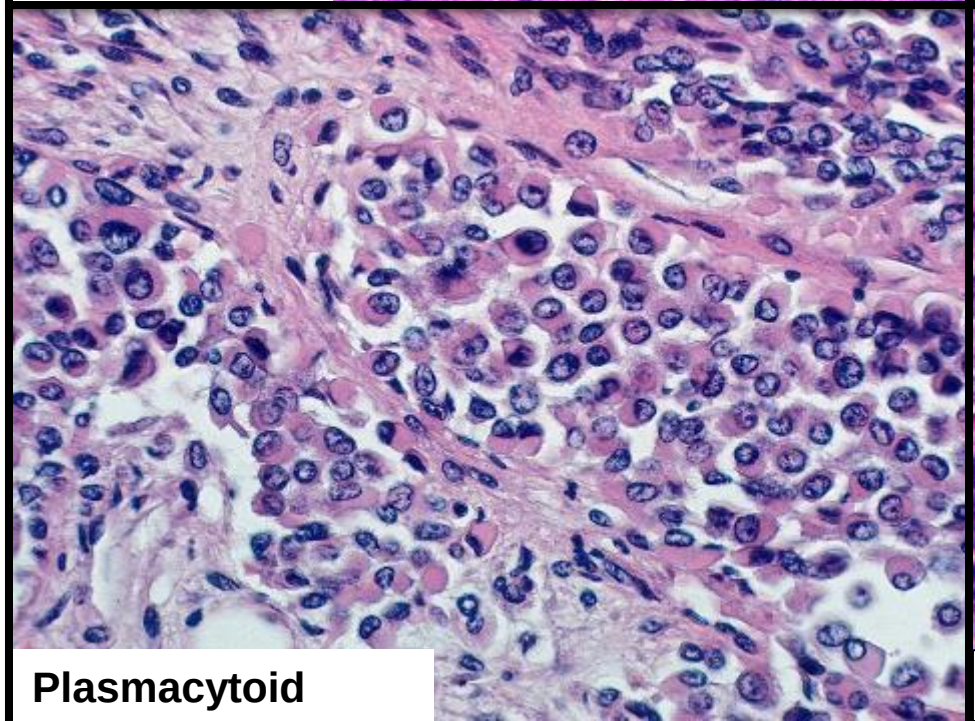
Myoepithelial carcinoma- Histology

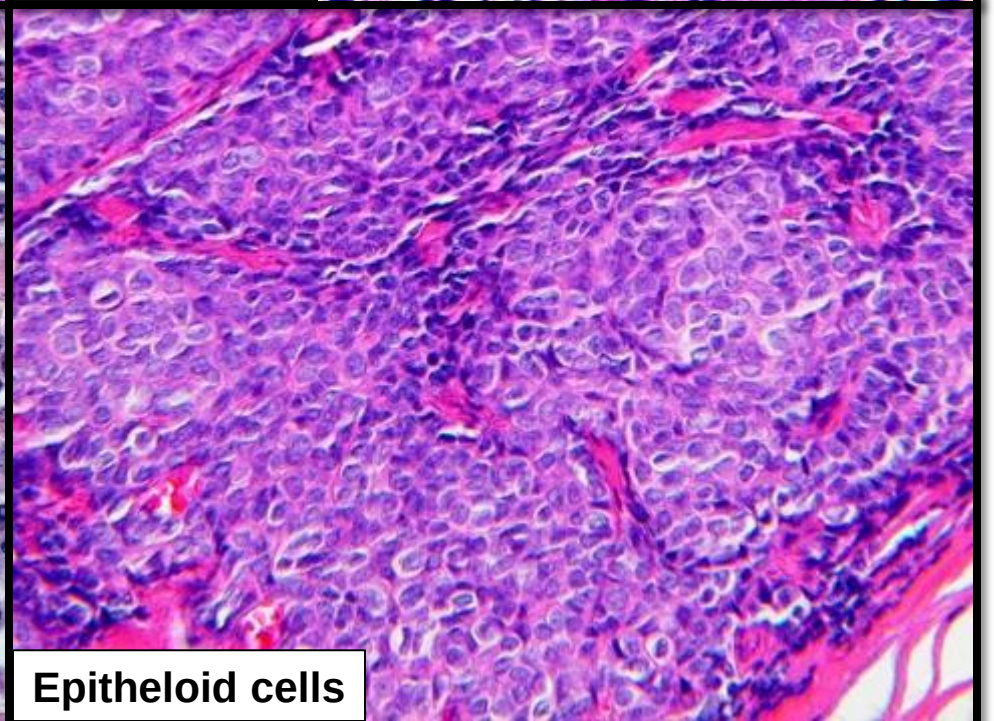
- Composed almost exclusively of myoepithelial cells
- Variety of cells types
- Variety of architectural patterns



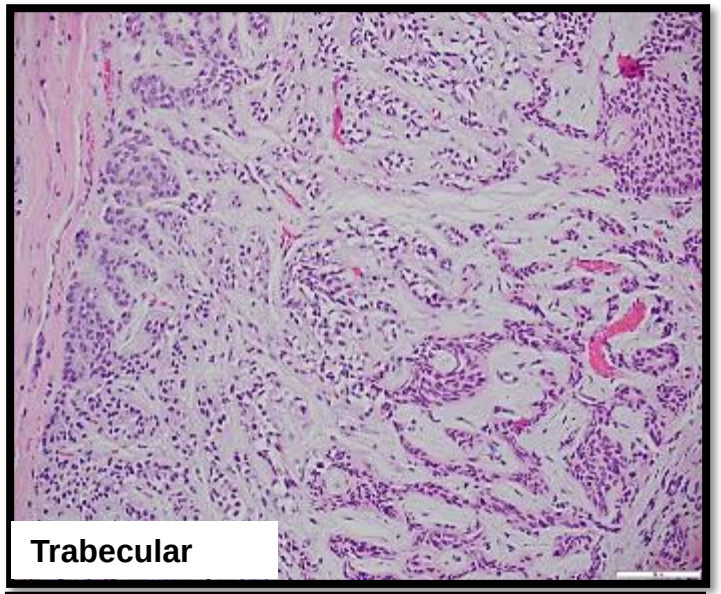

Spindle cells

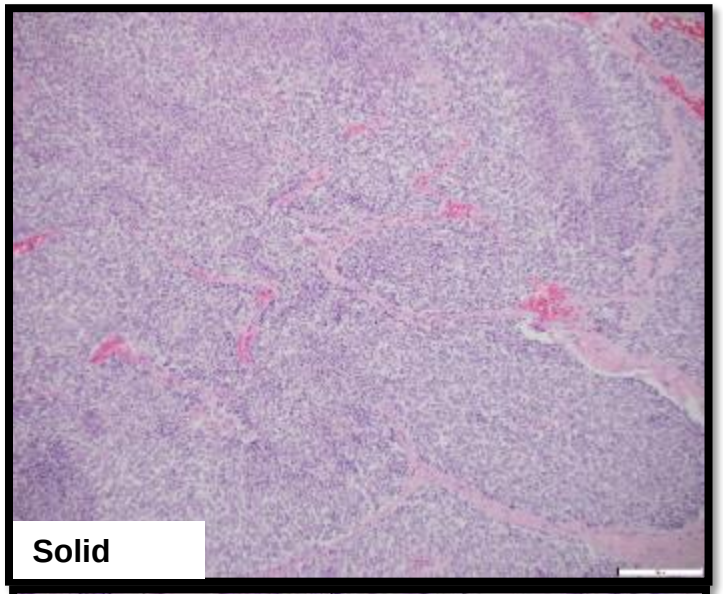

Clear cells

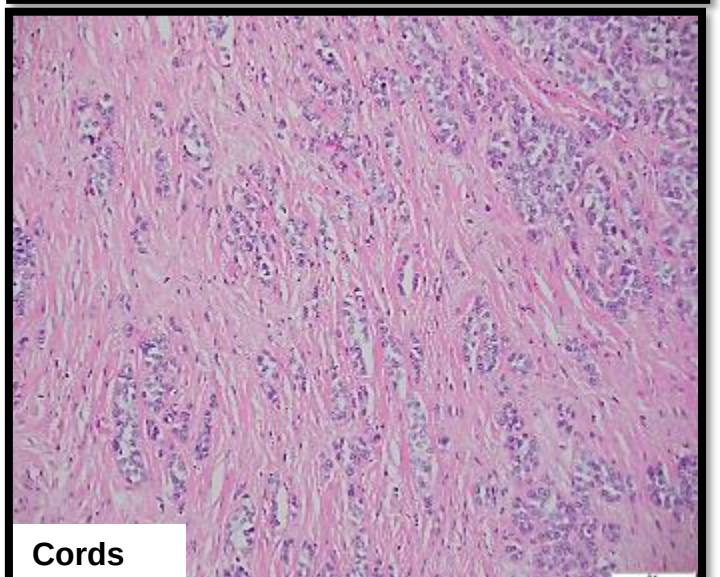

Plasmacytoid

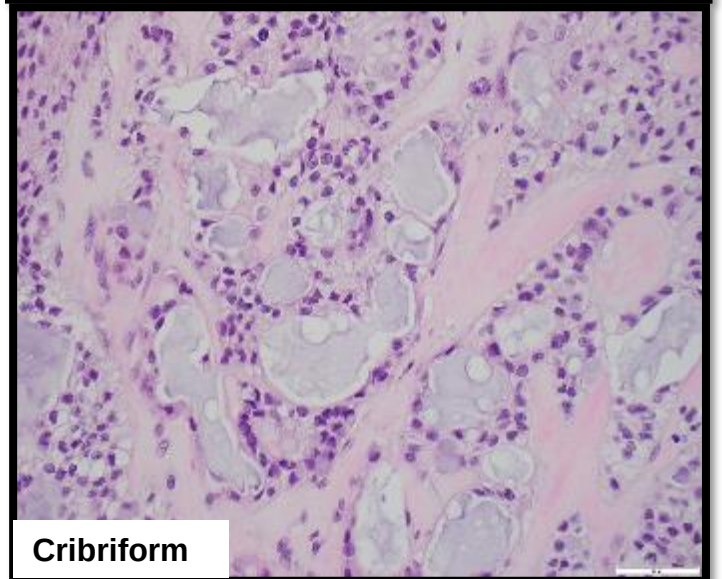

Epitheloid cells

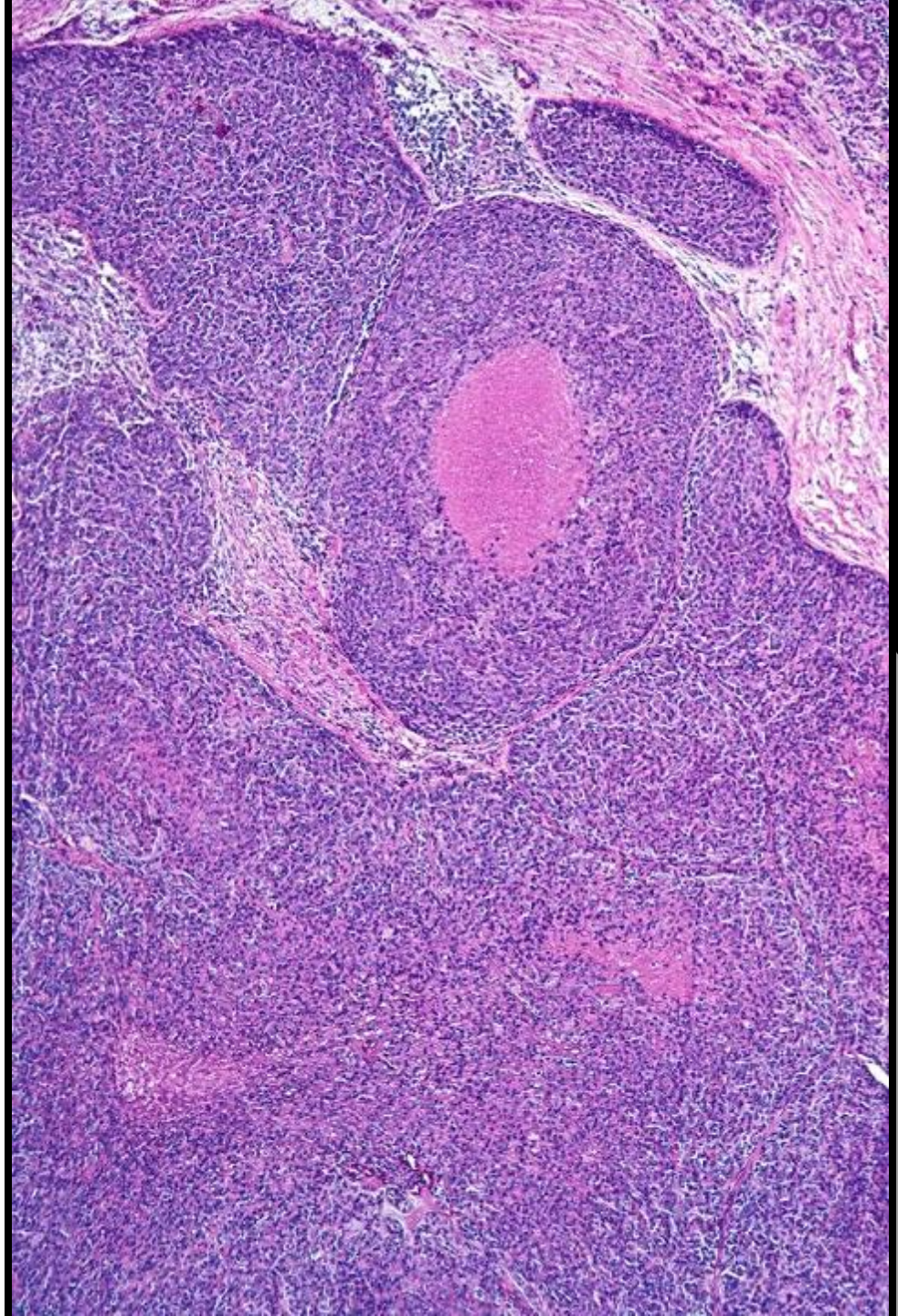
Architectural patterns

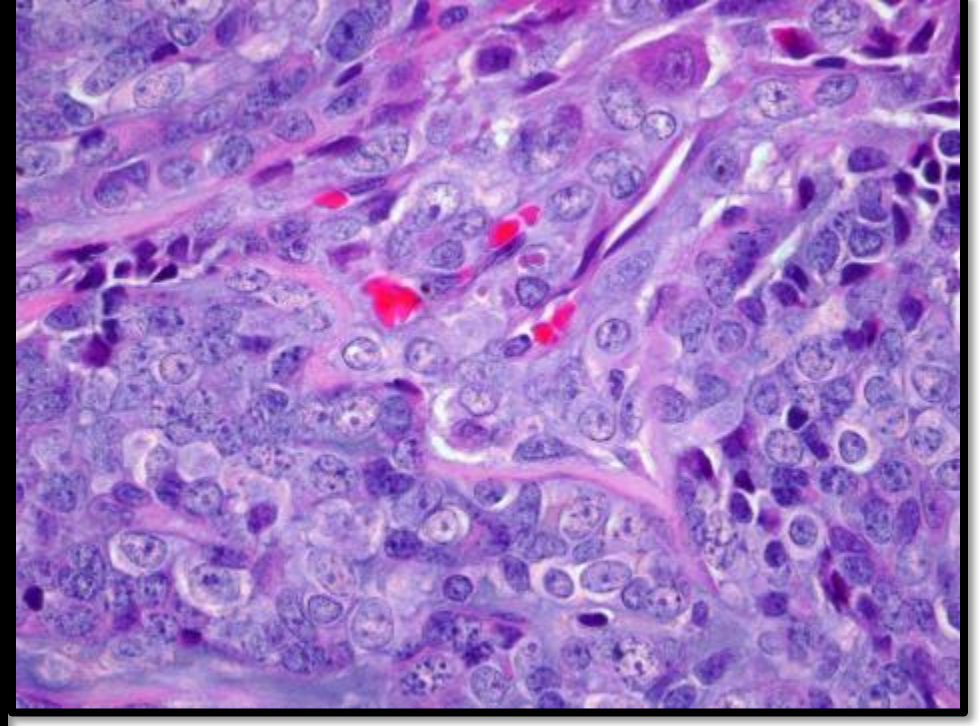

Trabecular


Solid


Cords


Cribriform





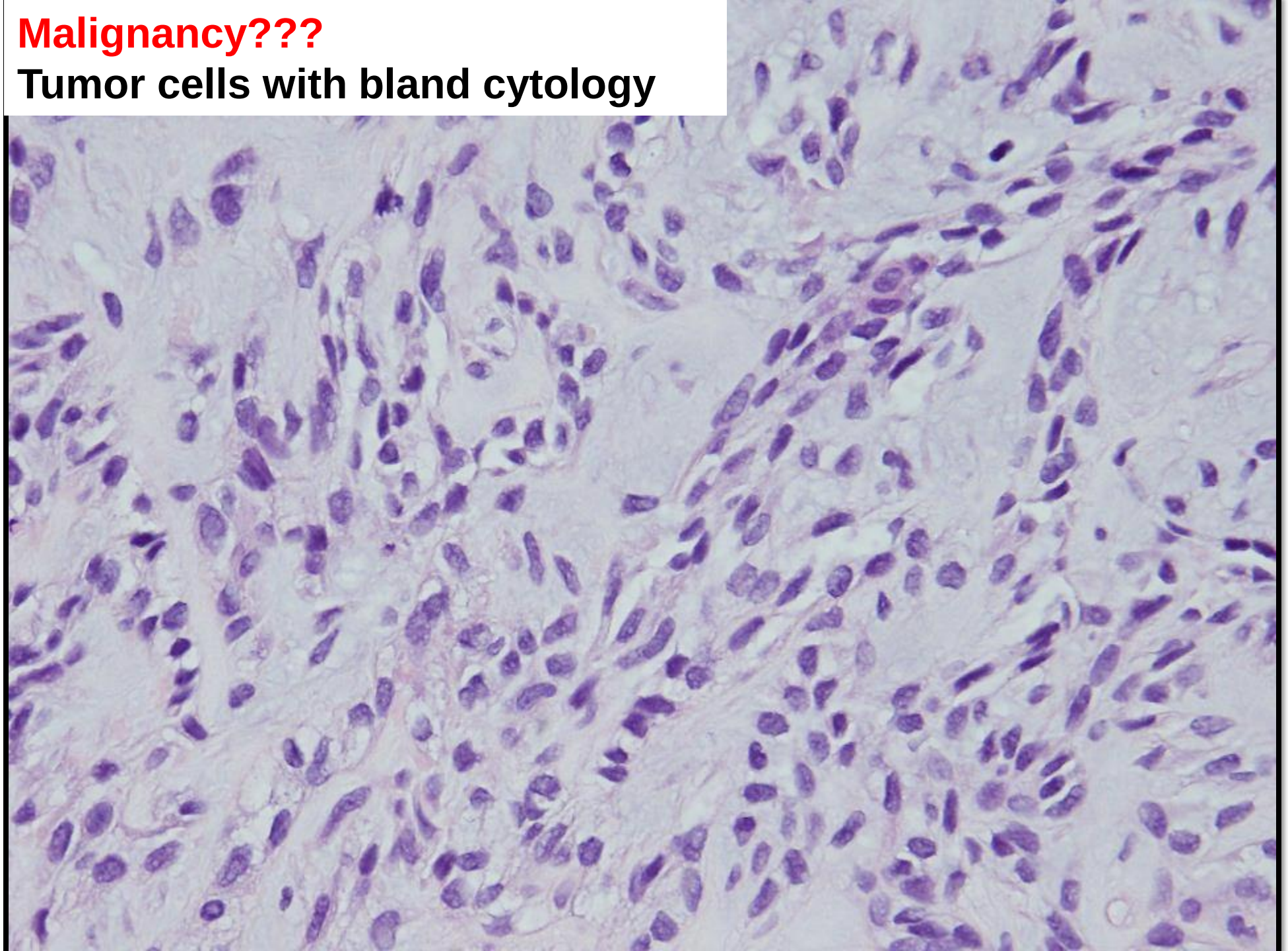
Malignancy →

High grade features

- Mitotic activity
- Necrosis
- Cytologic atypia

Malignancy???

Tumor cells with bland cytology

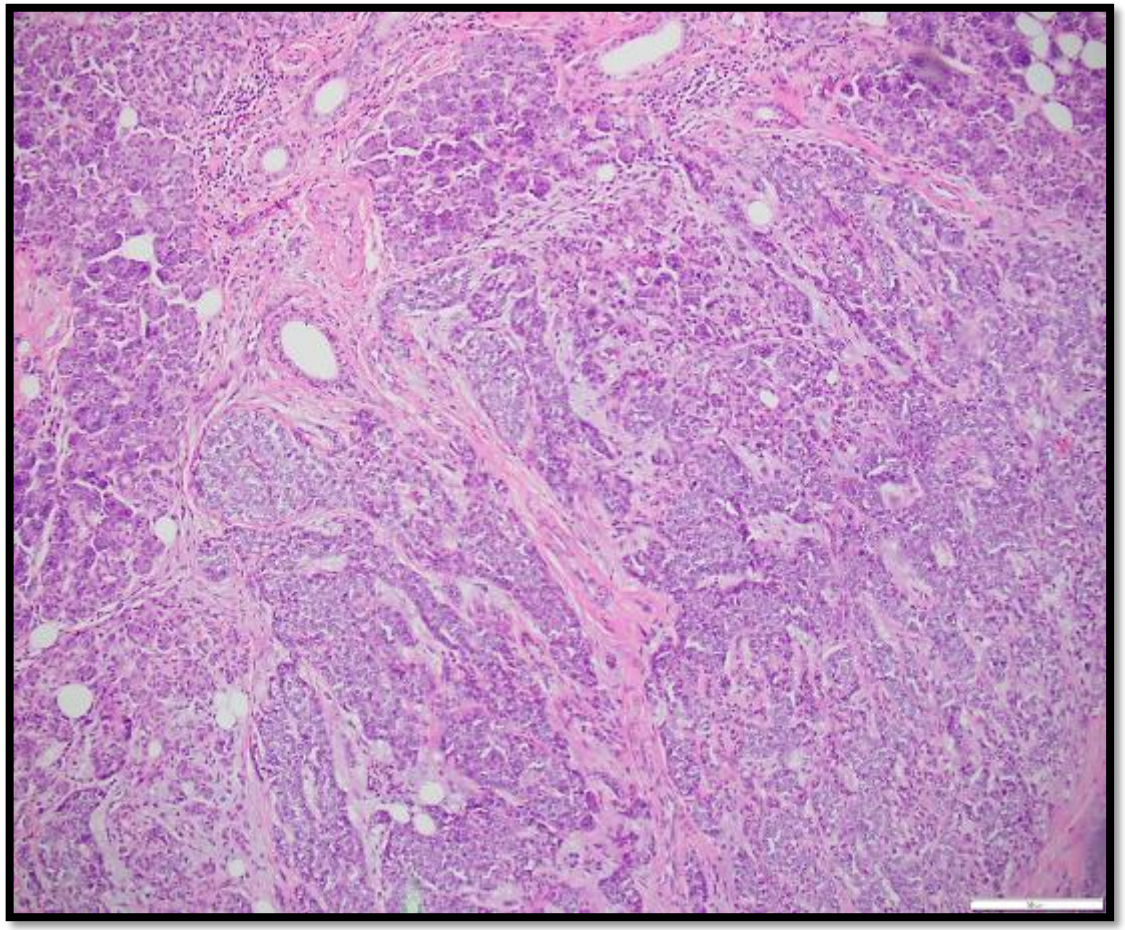


Malignancy=Invasion

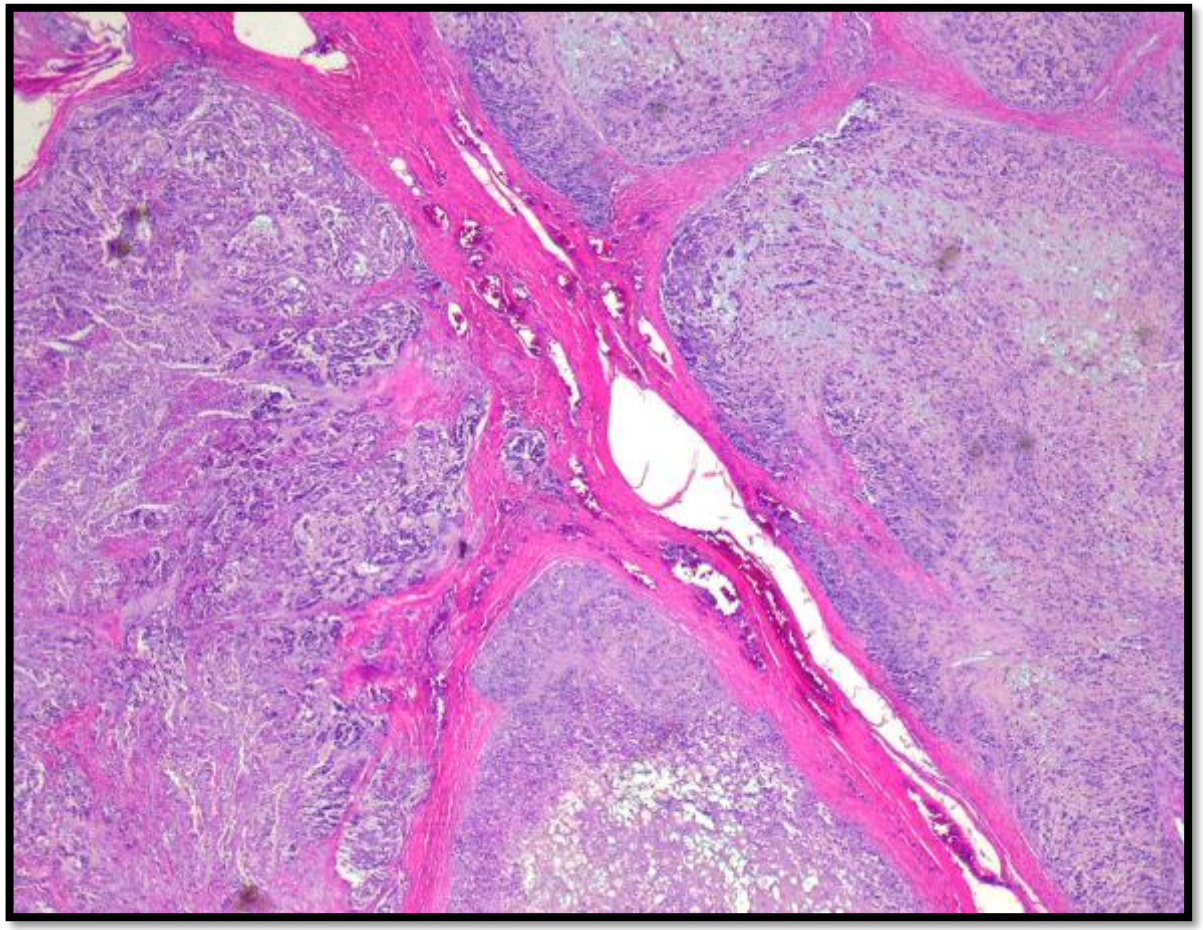
Tumor invasive pattern

Invasive patterns

Infiltrative



Nodular



Misinterpreted Myoepithelial Carcinoma of Salivary Gland
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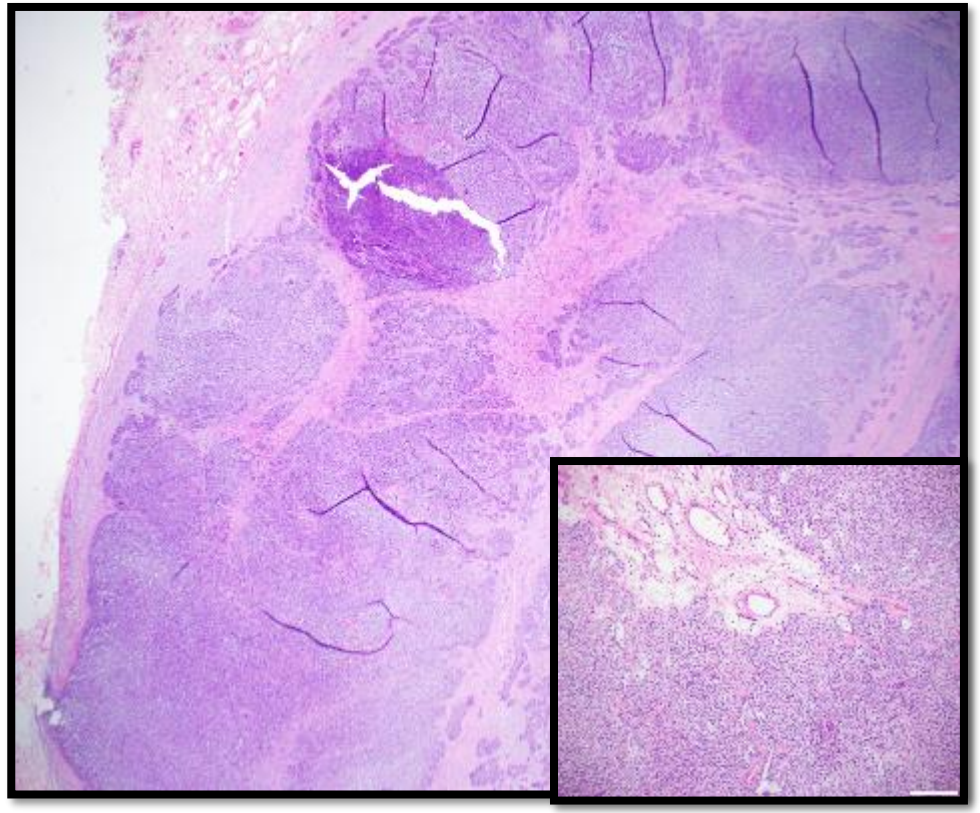
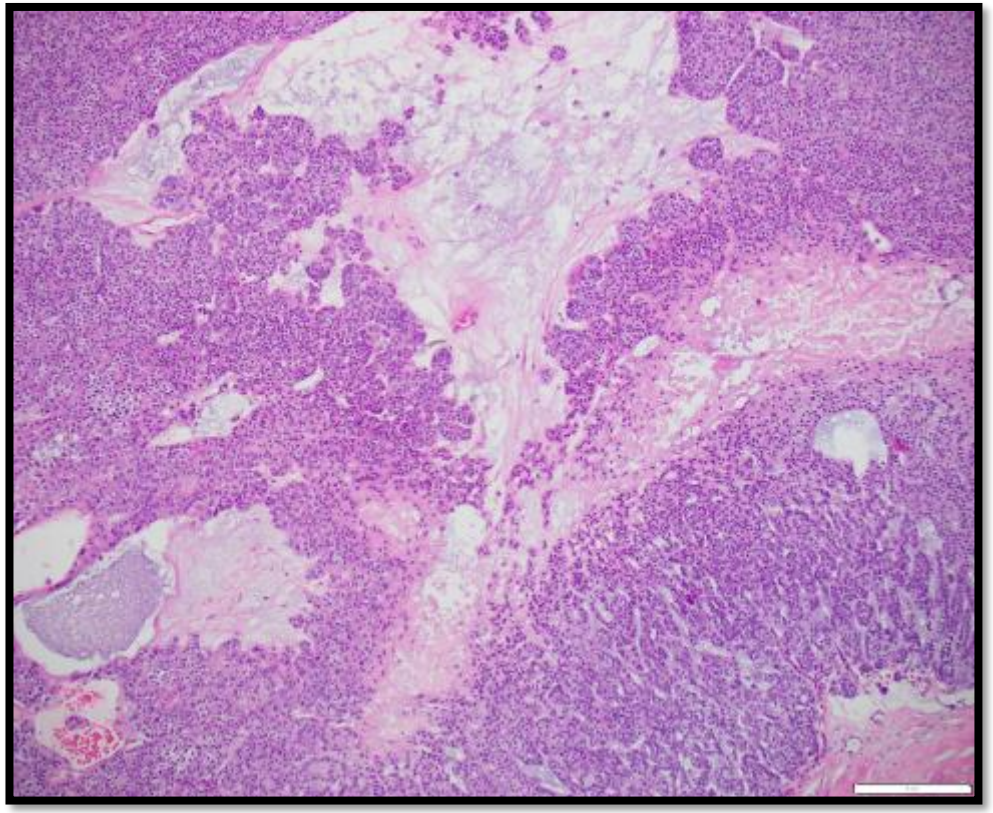
American Journal of Surgical Pathology, Februrary 15 2019

Histologic features that are helpful to recognize malignancy

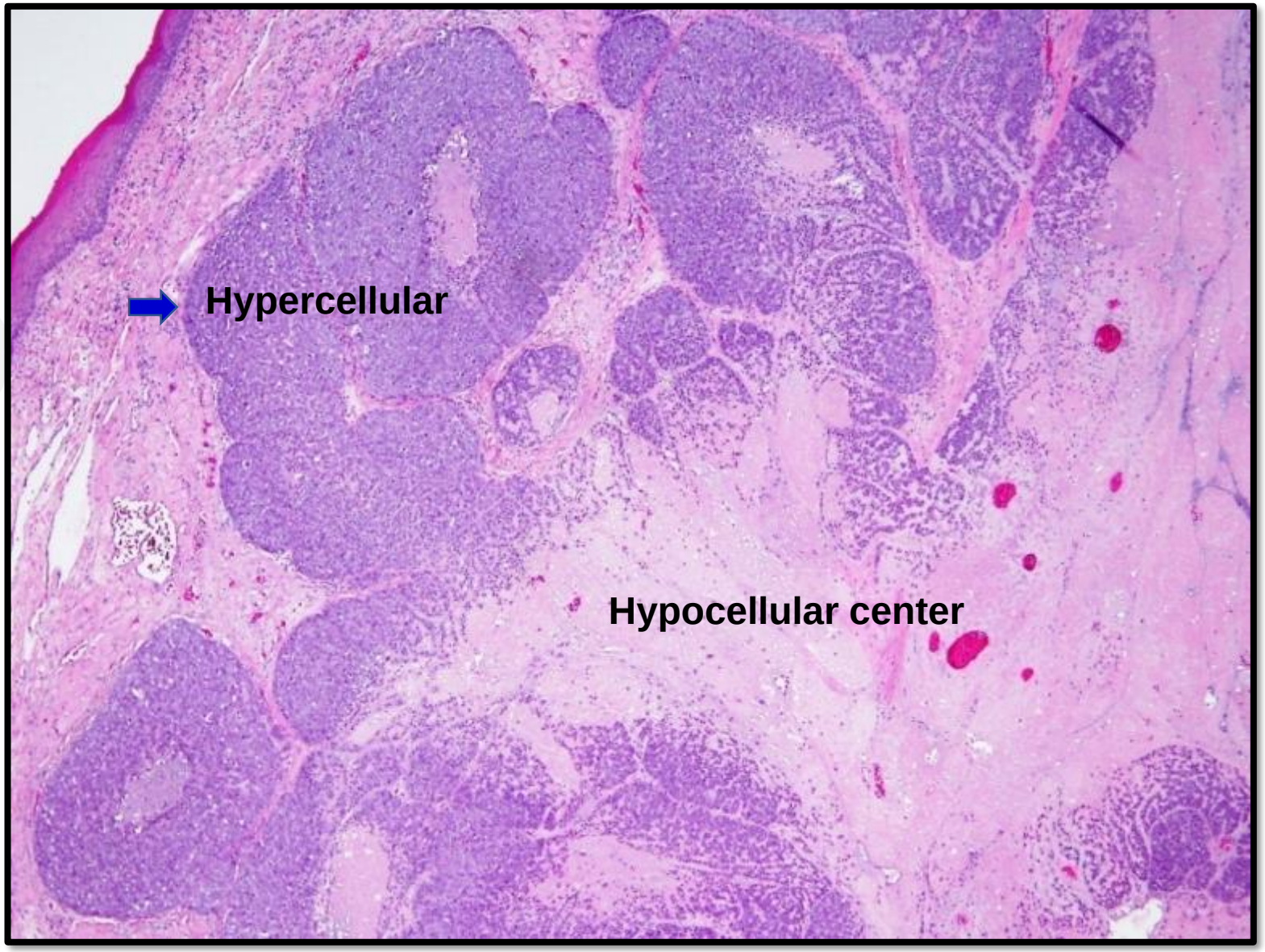
1- Uniformly cellular lobulated myoepithelial proliferation with pushing nodular pattern



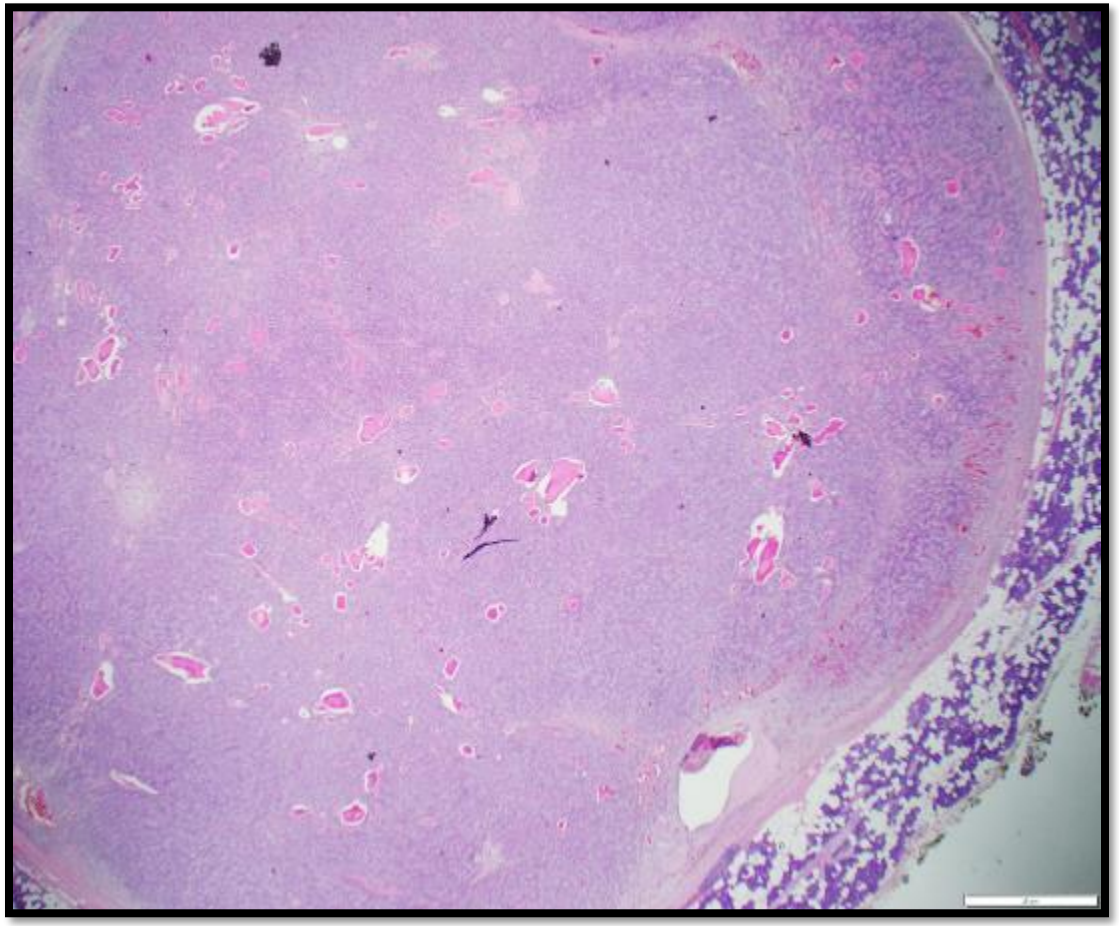
2- Alternating hypocellular and hypercellular zonal cellular distribution

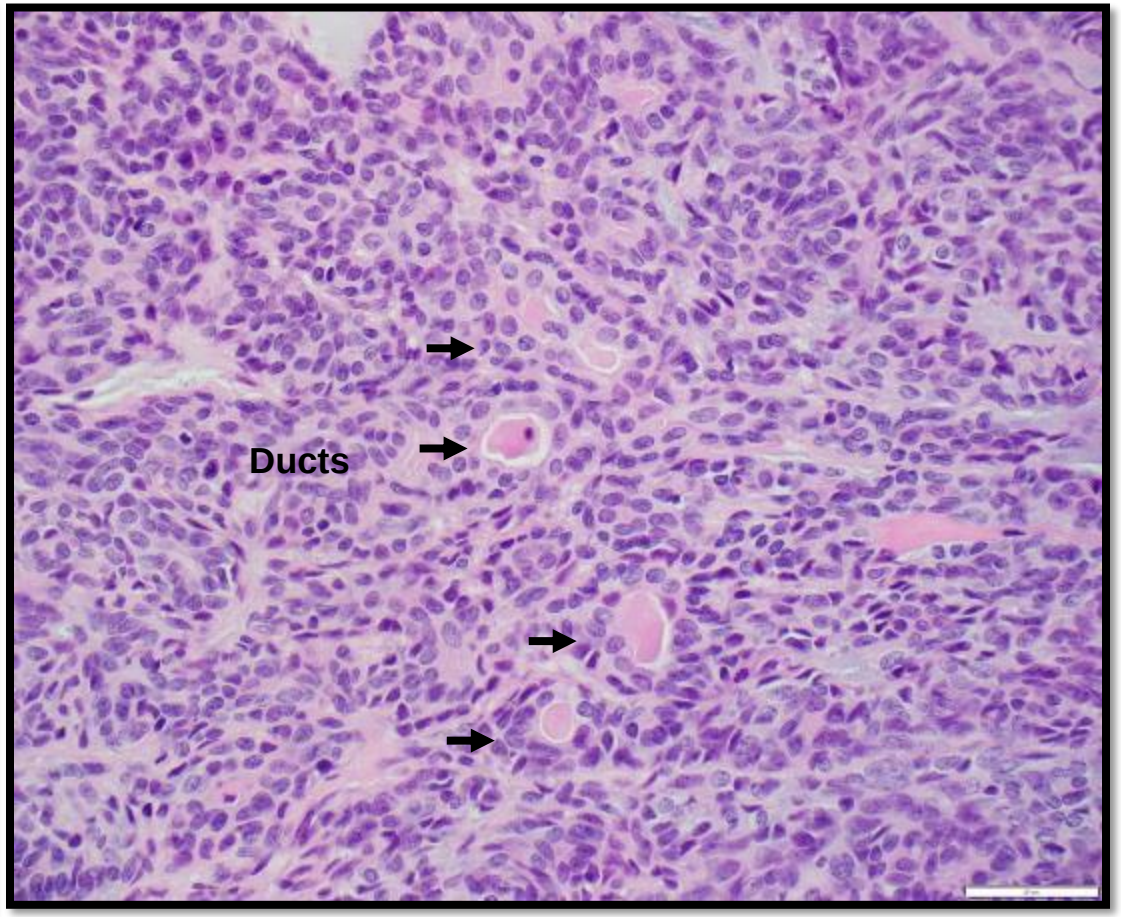


Multinodular with lobulated borders

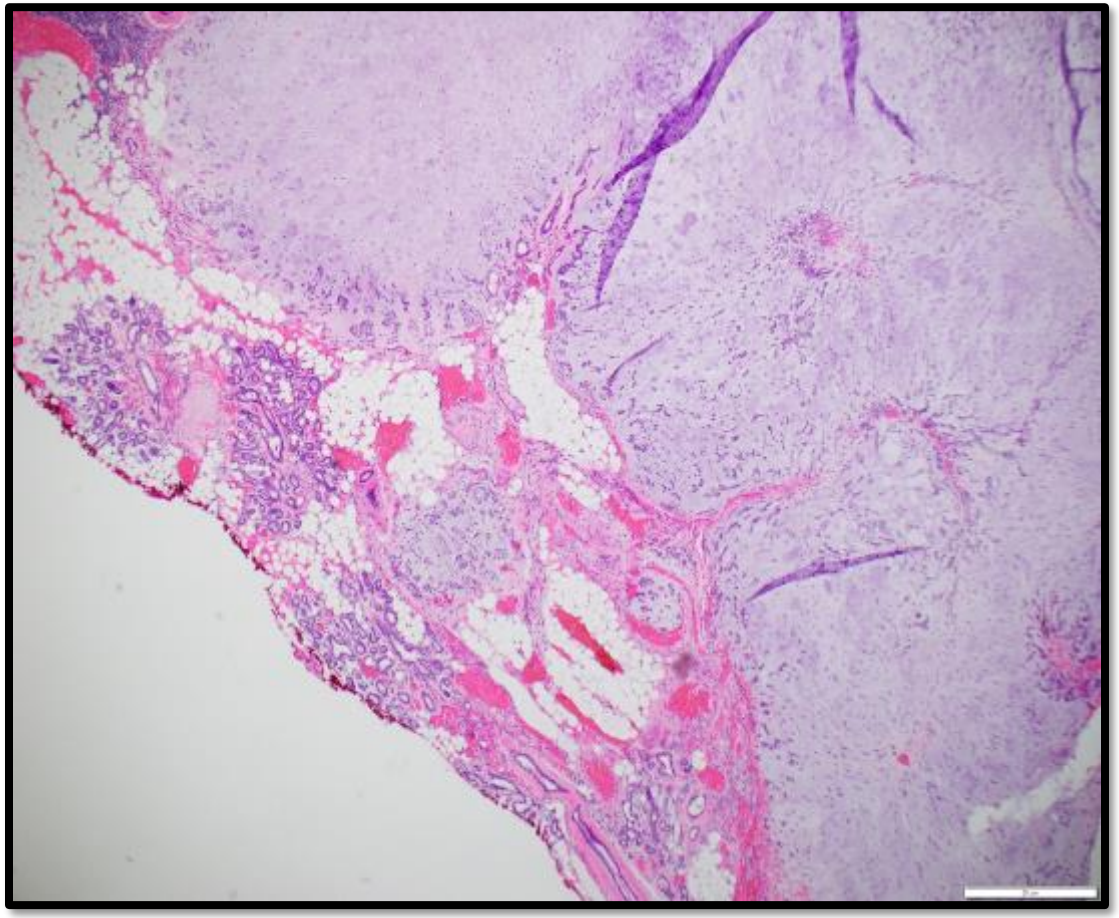


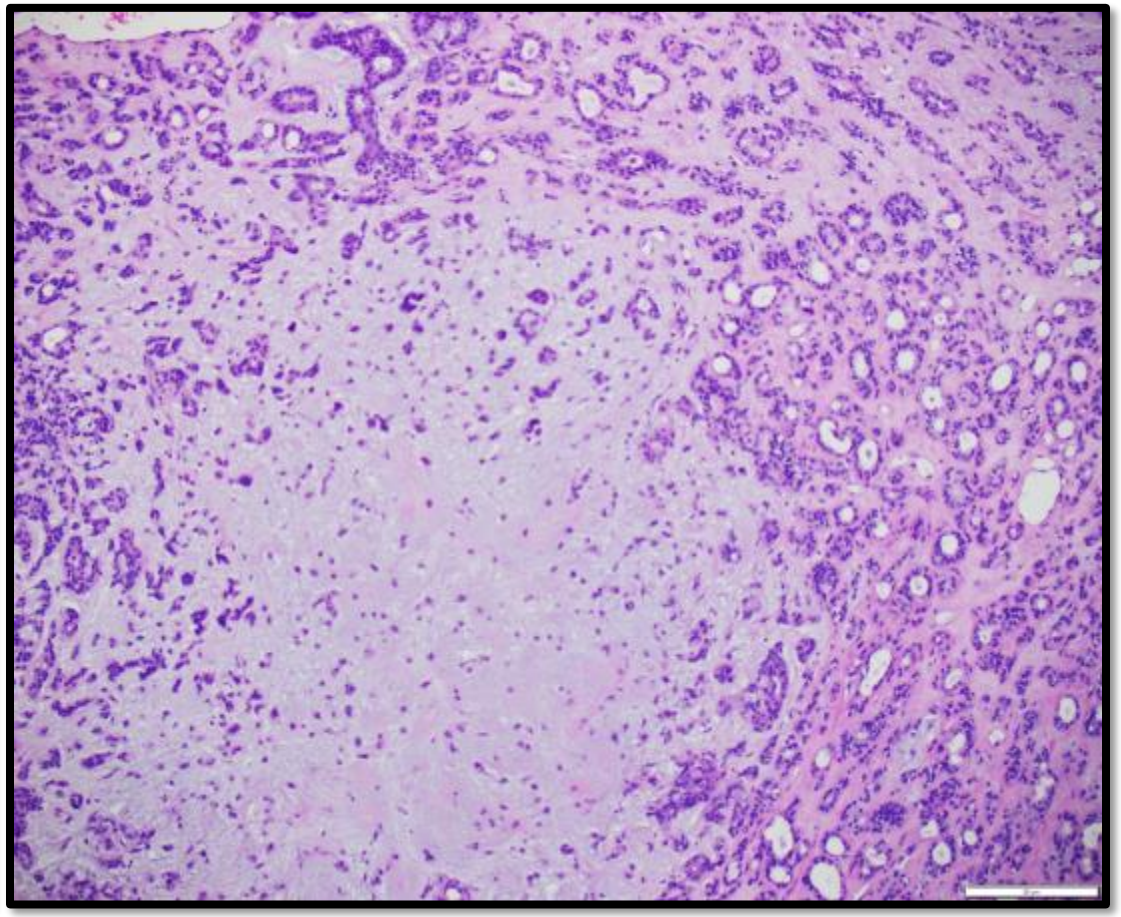
Cellular pleomorphic adenoma





Pleomorphic adenoma





Prognostic Factors in Myoepithelial Carcinoma of Salivary Glands: A Clinicopathologic Study of 48 Cases

Kong M, Drill EN, Morris L, Klimstra D, Gonen M, Ghossein R, Katabi N
American Journal of Surgical Pathology 2015

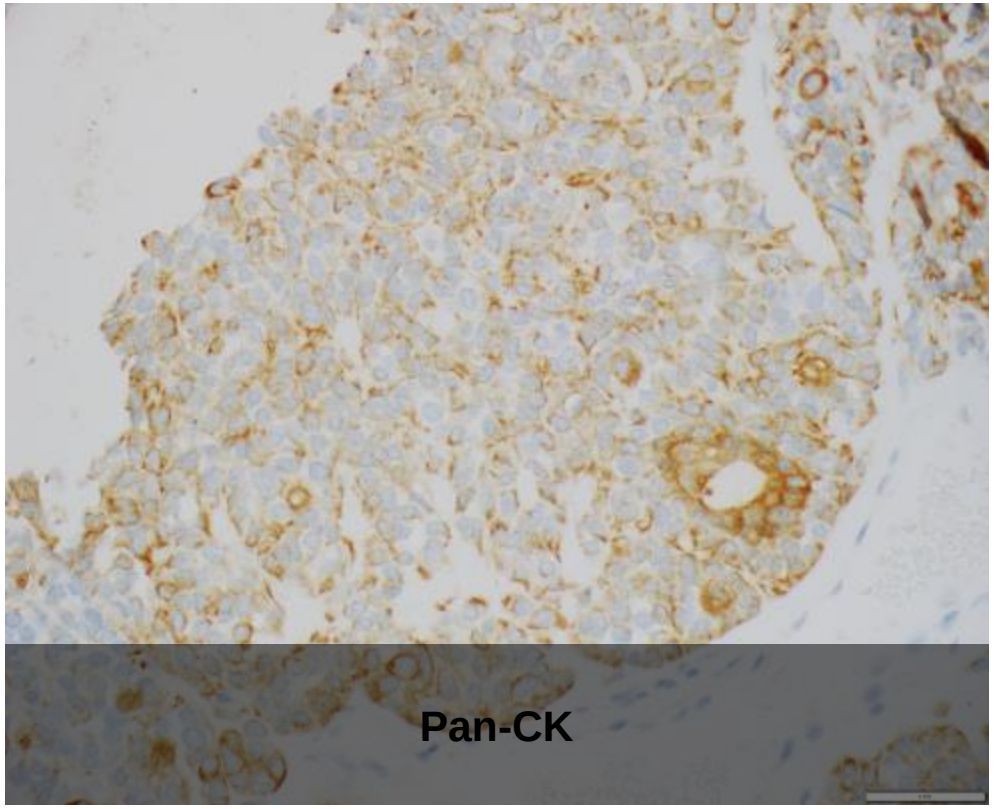
- 48 (22 de novo and 26 CA ex PA) (FU: 44 months)
  - 10% had LN metastasis
  - 20% had local recurrences
  - 27% had distant metastases (most common lung)

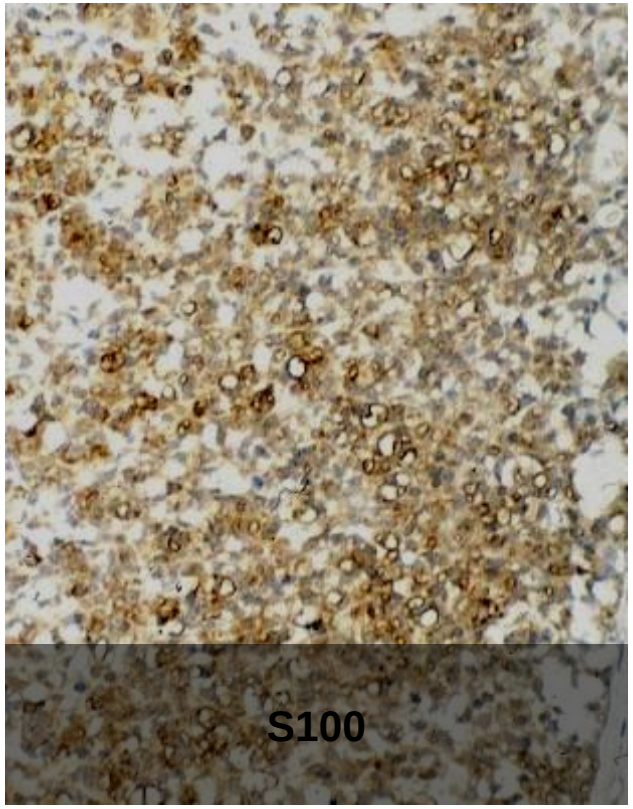
- Myoepithelial carcinoma is a relatively aggressive tumor that is associated with a high rate of distant metastasis

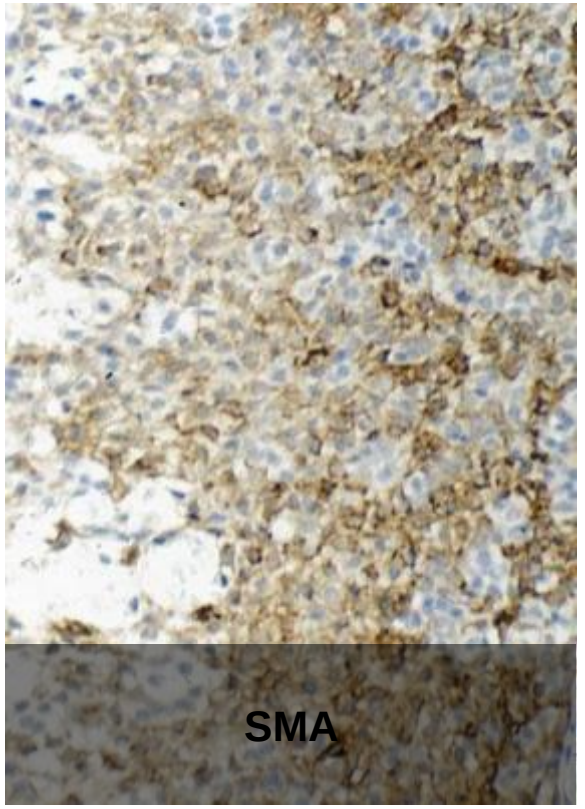
- The presence of CA ex PA, necrosis, and vascular invasion correlated significantly with DFS
- Necrosis should be used to identify high grade myoepithelial carcinoma

Myoepithelial carcinoma-IHC

A keratin and at least a myoepithelial marker



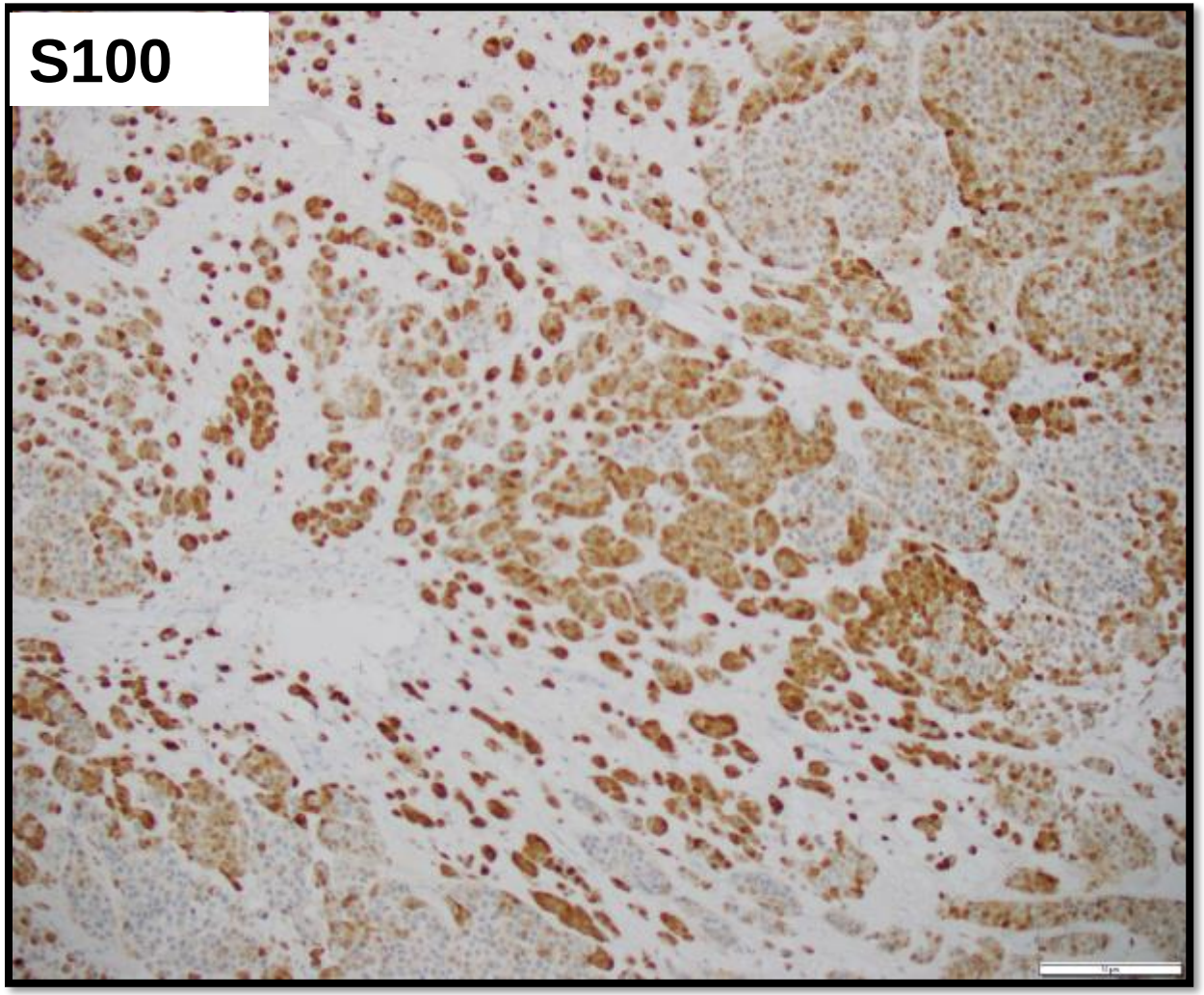




Myoepithelial carcinoma
Panel of Immunohistochemistry

- Keratin (100%)
- S100 (89%)
- Calponin (76%)
- P63 (87.5%)
- SMA (64%)

Kong et al, AJSP, 2015



Molecular features

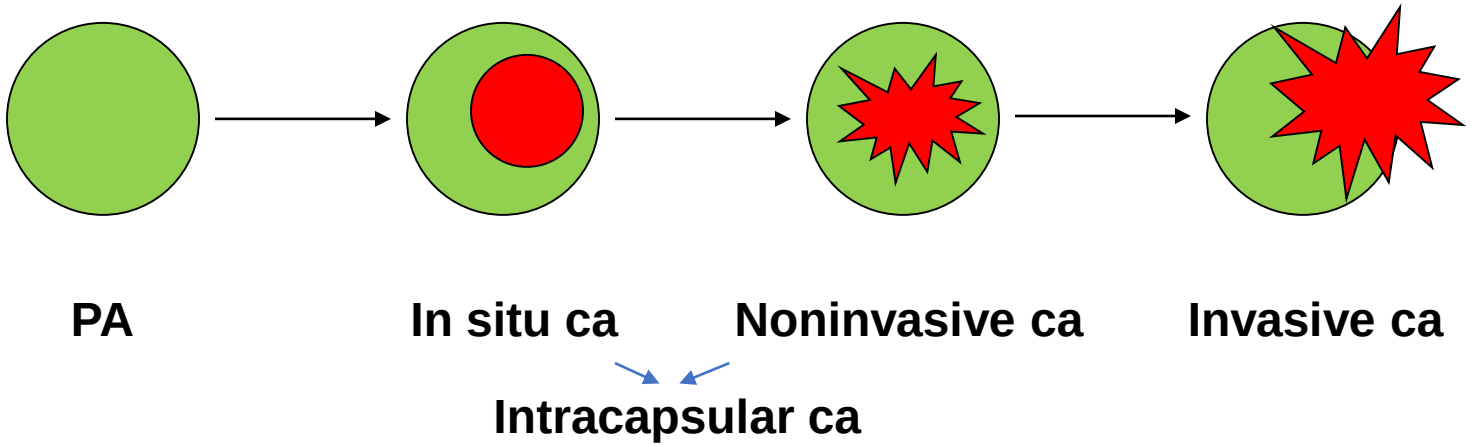
- 53% *PLAG1* translocations
- *HMGA2* translocations
- *EWSR1-ATF1* fusion gene
- High number of CNAs more common in myoepithelial CA ex PA and associated with poor survival

Carcinoma ex Pleomorphic Adenoma (CA ex PA)

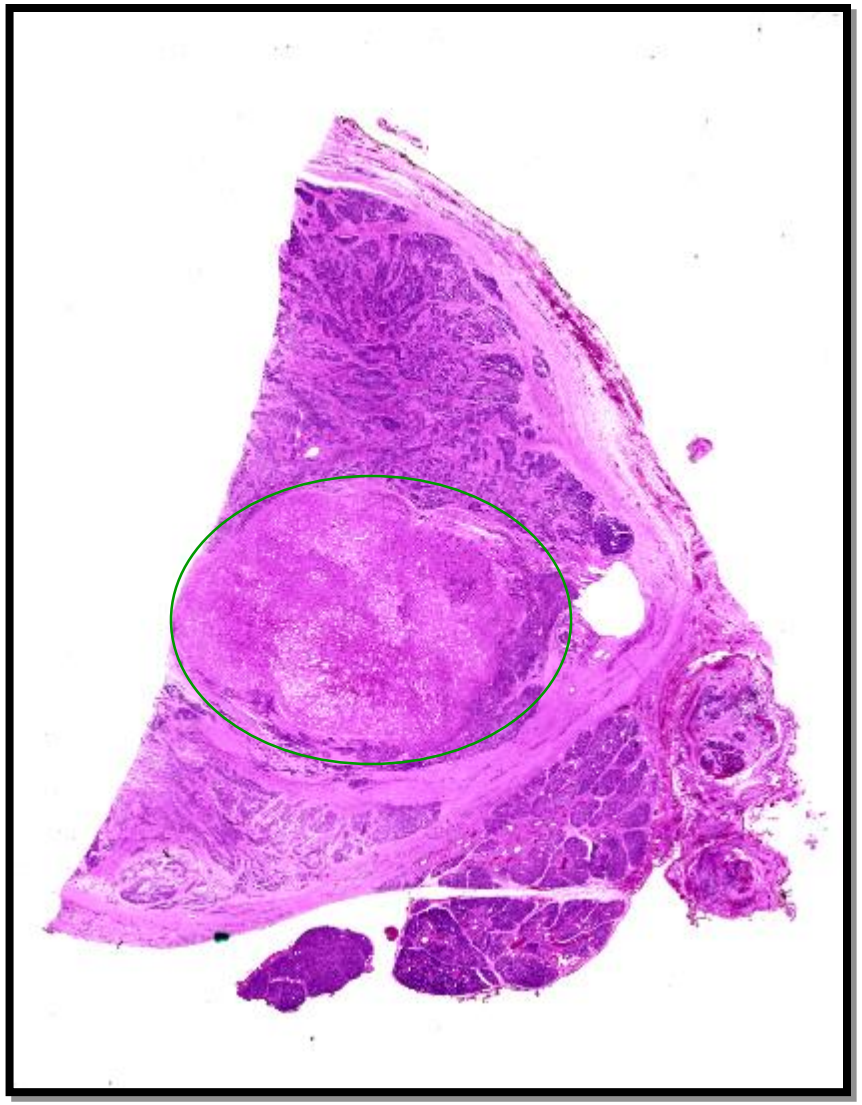
Carcinoma ex pleomorphic adenoma (CA ex PA)

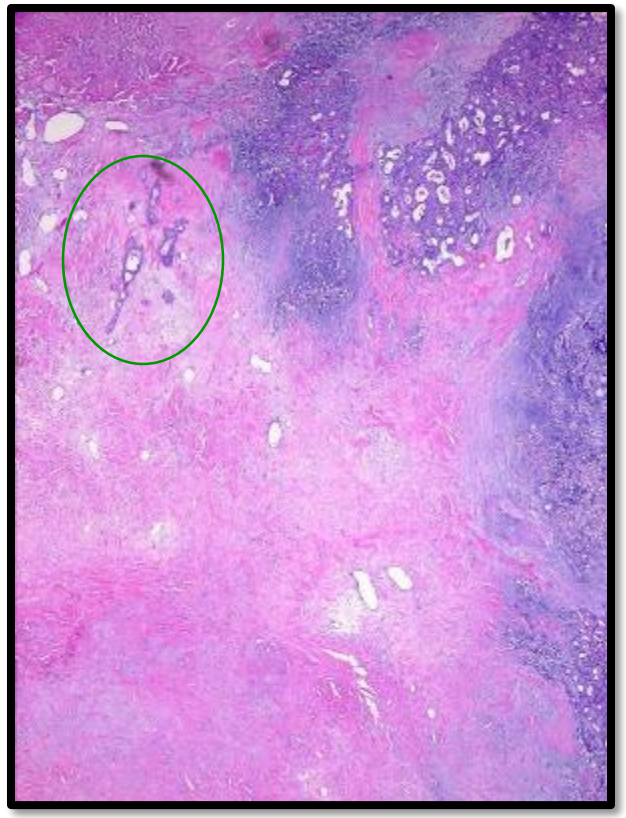
- Carcinoma that arises in association with a pleomorphic adenoma (PA)
- Long standing mass with recent rapid growth
- 12% of salivary gland malignancies
- 6.2% of PA
- Most common = parotid
- 12% recurrent PA
- Patients are 60-70 years old

CA ex PA
Histologically



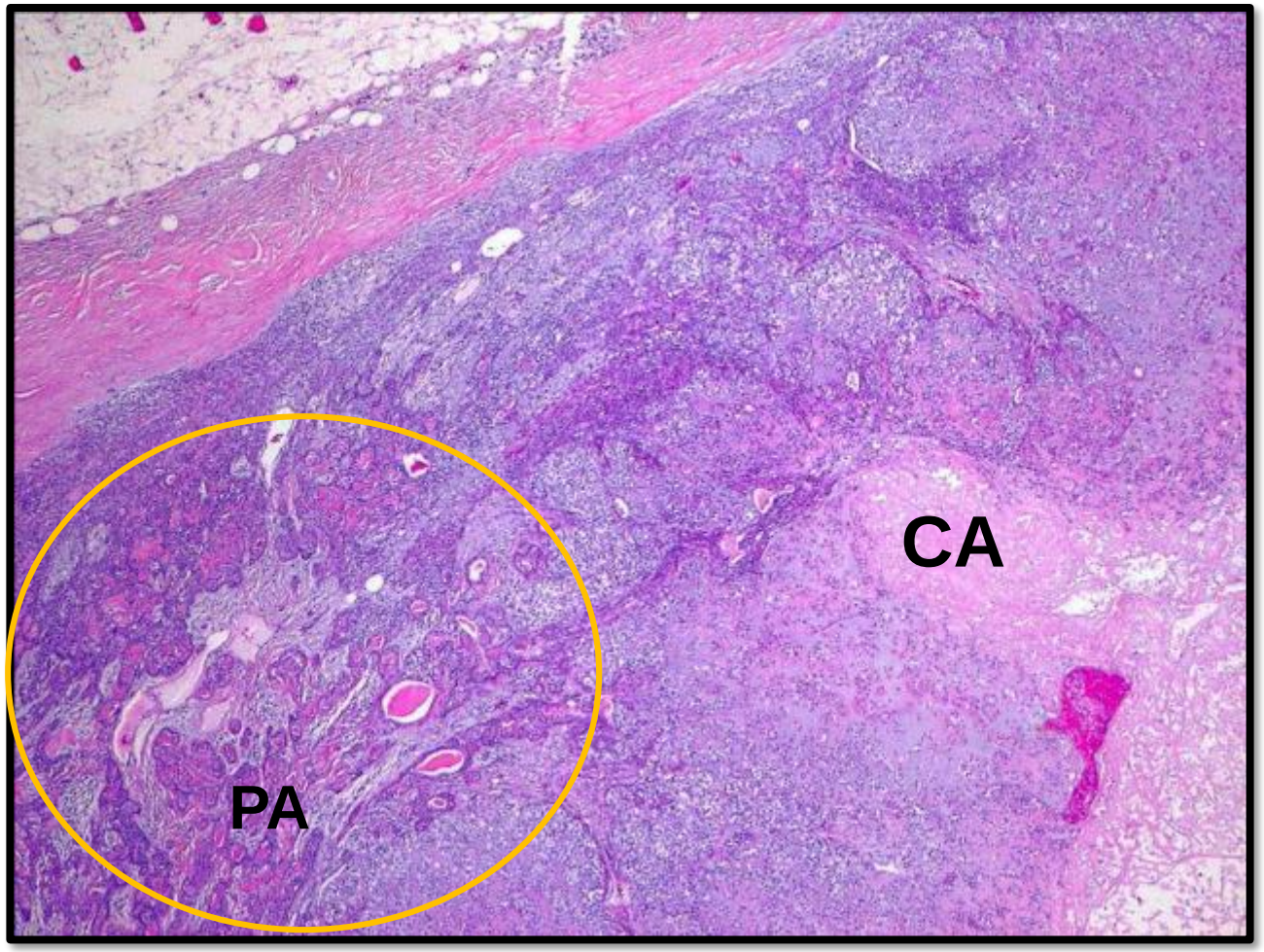
PA component





Hyalinized sclerotic central area
with benign ducts

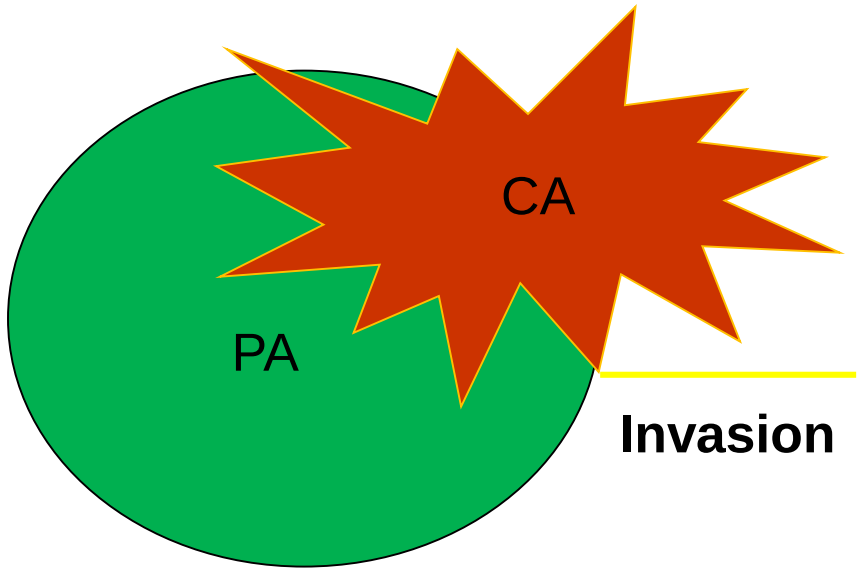
PA component



PA component is intermixed with carcinoma component

CA ex PA-Prognosis

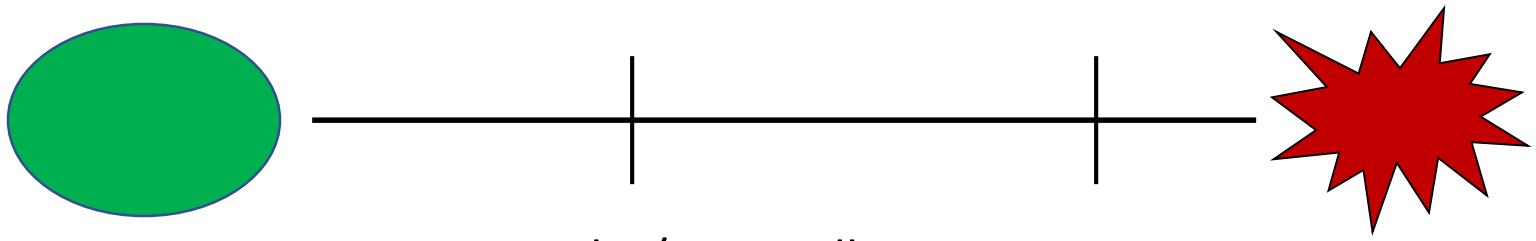
- Extent of invasion of carcinoma beyond PA capsule
- Histologic type of carcinoma



CA ex PA-Extent of invasion

- **Intracapsular**=malignant cytology with no extension beyond tumor capsule
- **Minimally invasive** (<4-6 mm)
- **Invasive**

Benign **Malignant**



Intracapsular/Minimally invasive CA ex PA

Excellent prognosis

Metastases are exceptional

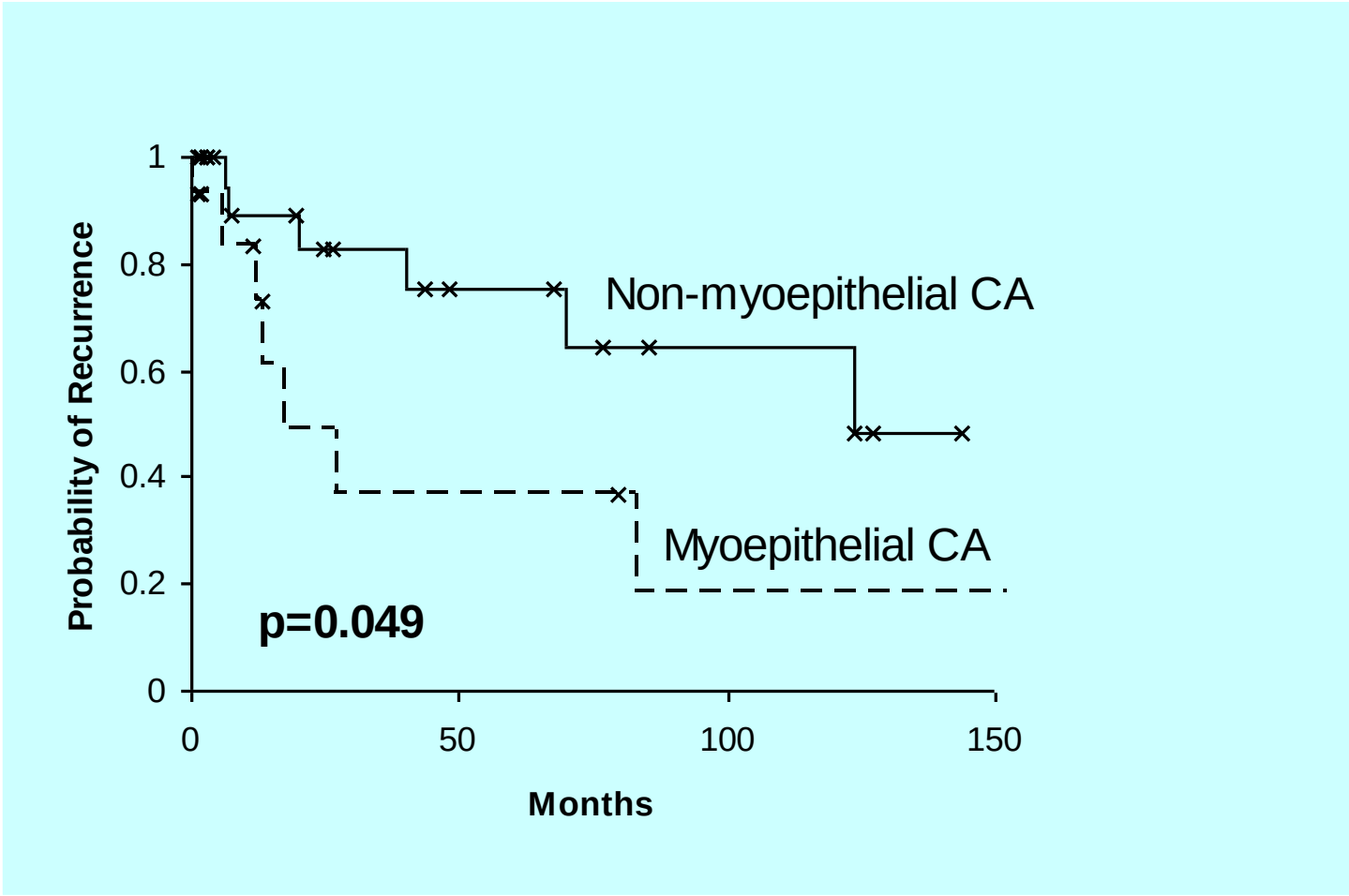
Invasive CA ex PA

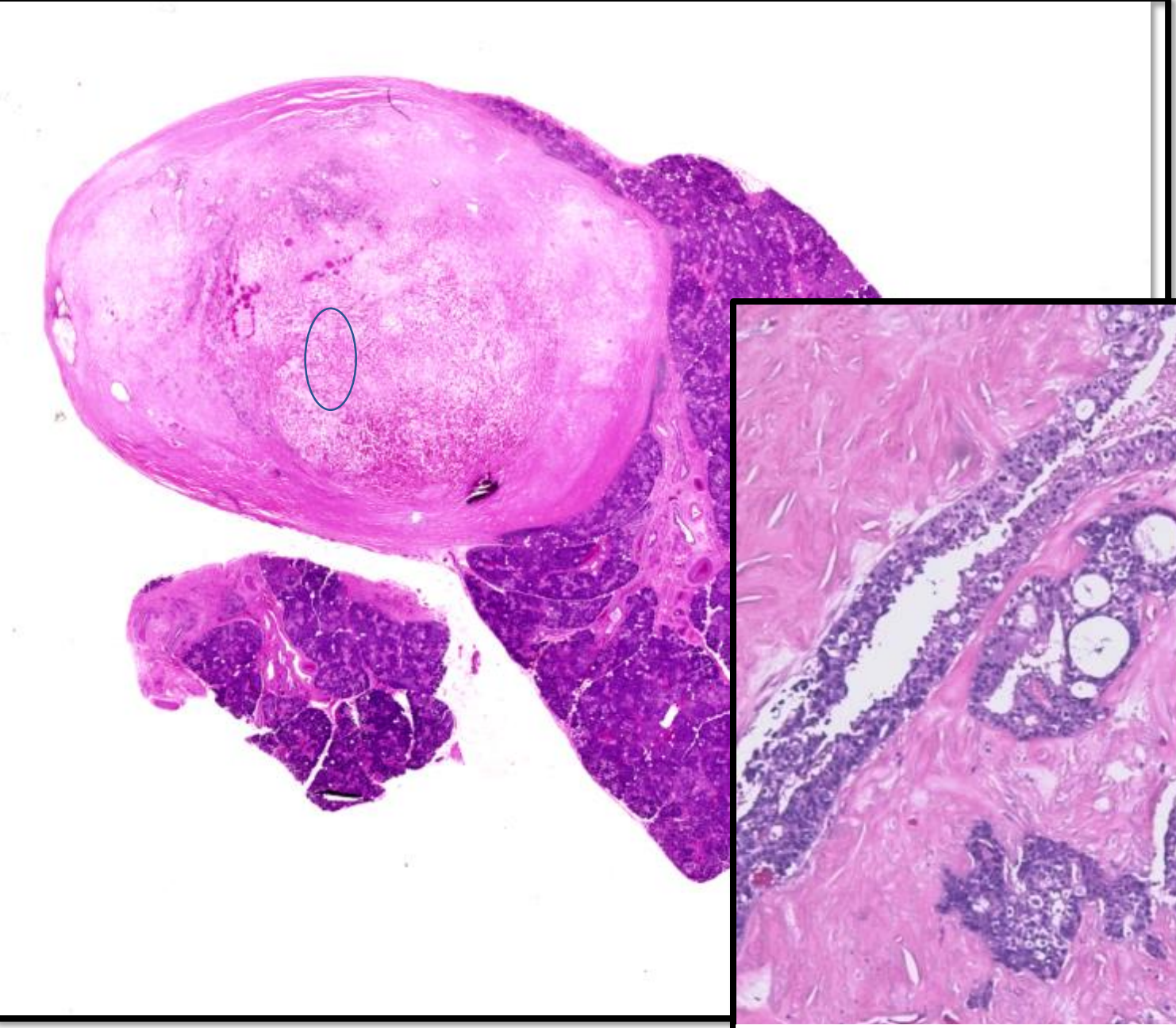
Poor prognosis
23-50% recurrences
5-year survival 25-65%

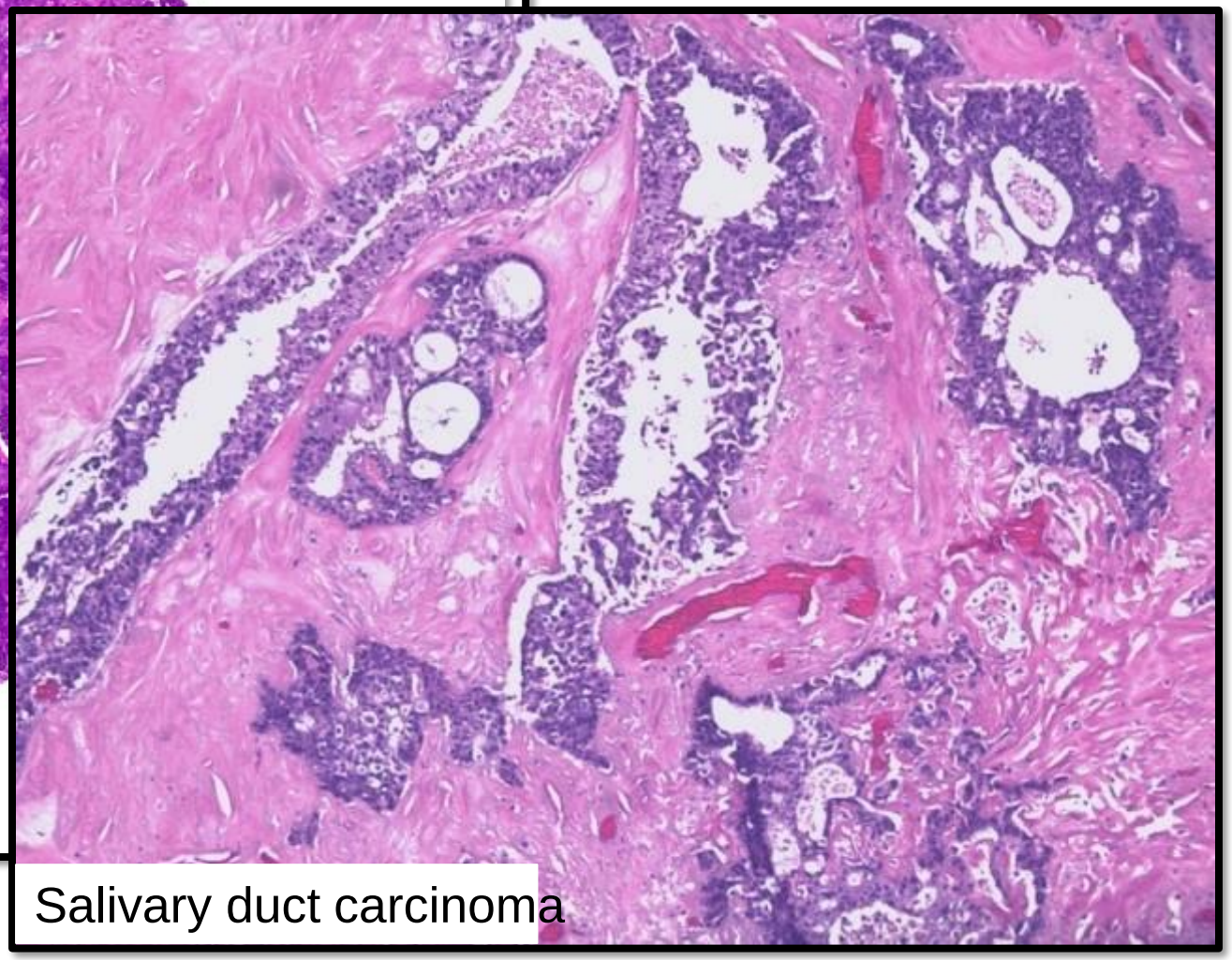
Up to 70% metastases

Myoepithelial carcinoma ex PA

Significant risk of distant & local recurrence even when it is intracapsular or minimally invasive!

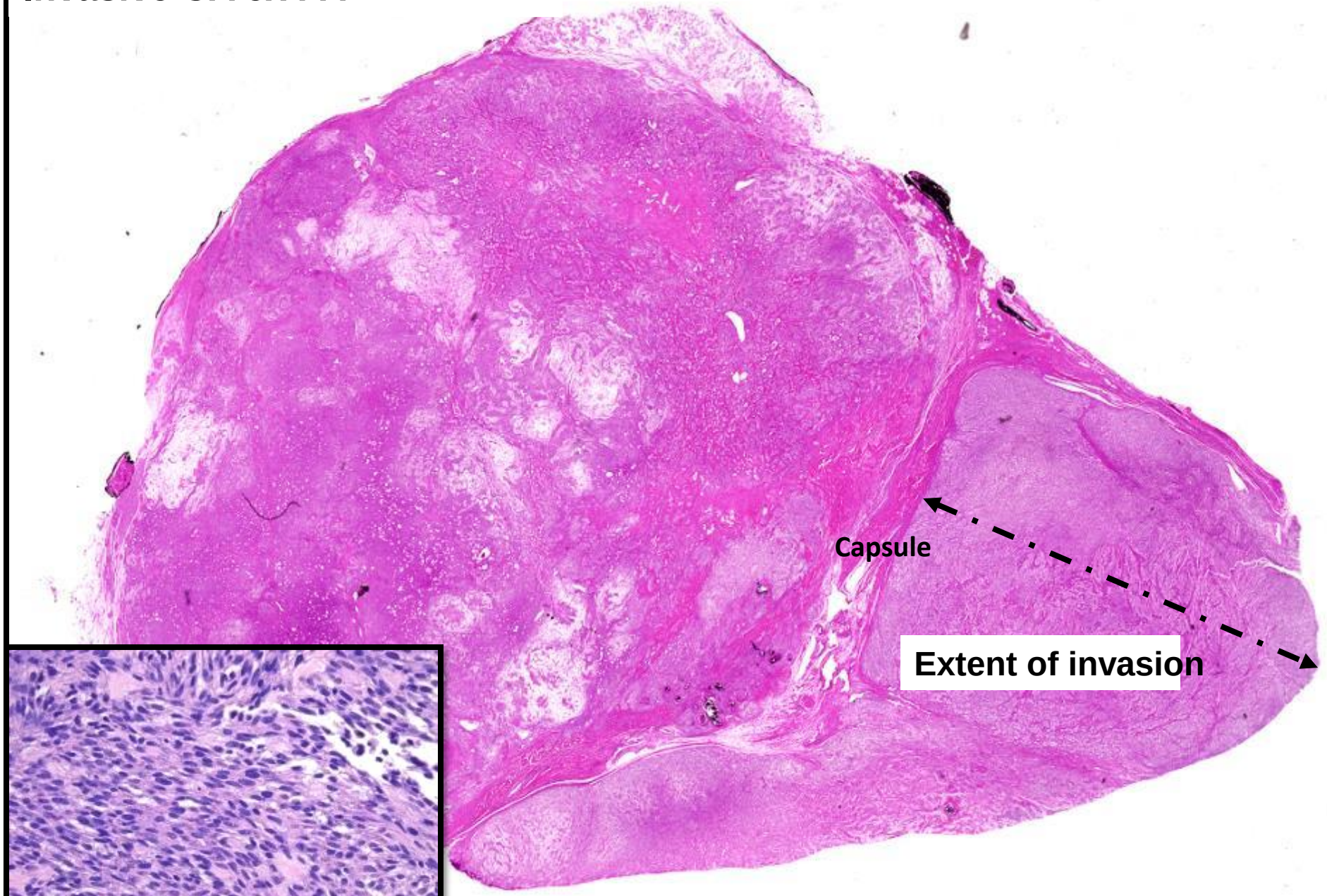






Salivary duct carcinoma

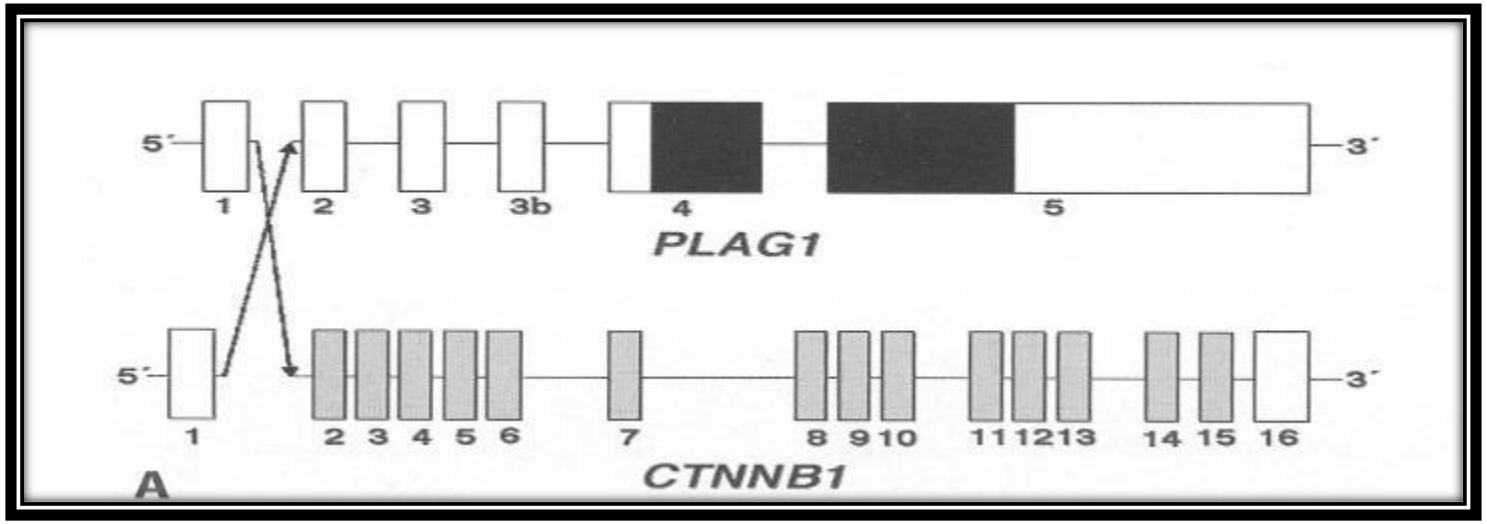
Invasive CA ex PA



Myoepithelial carcinoma

Molecular features

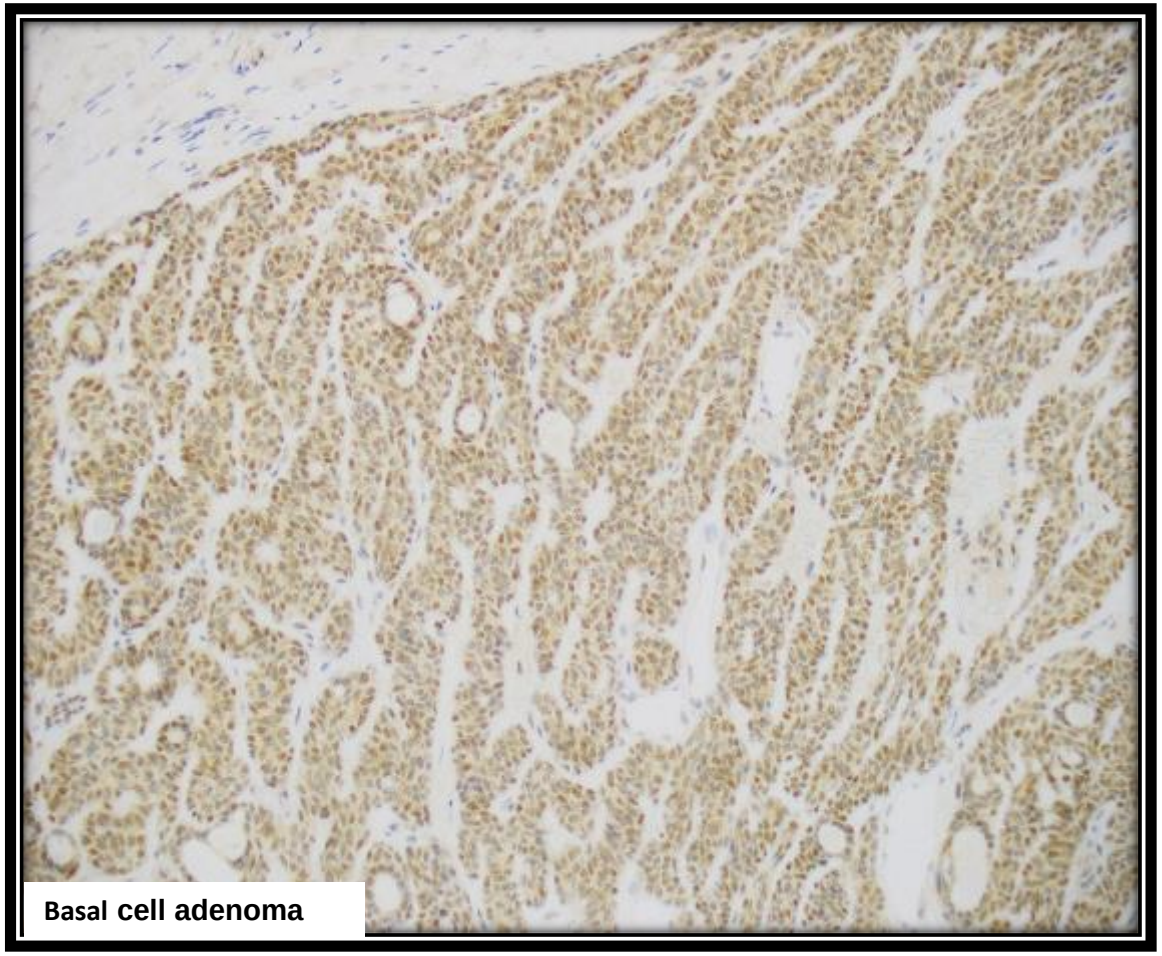
- <u>CA ex PA</u>
  - Rearrangements of *PLAG1* (Pleomorphic Adenoma Gene1) on 8q12 are the most gene in PA and CA ex-PA
  - Rearrangements of *HMGA2* on 12q14-15 is less frequent



PLAG1 immunohistochemical stain

- High sensitivity in PA
- Less sensitive in myoepithelial CA ex PA
  - De novo myoepithelial carcinoma negative for FISH but positive for PLAG1IHC

- Positive in other salivary gland tumors: polymorphous adenocarcinoma, basal cell adenoma/adenocarcinoma and adenoid cystic carcinoma



Katabi et al. Histopathology 2018

Avadhani et al. Acta Cytol 2016

De Brito et al. Virchow Arch 2016

CA ex PA-Histologic subtypes

- Salivary duct carcinoma
- Myoepithelial carcinoma
- Epithelial myoepithelial carcinoma
- Adenocarcinoma NOS
- Carcinosarcoma

Salivary duct carcinoma (SDC)

50% de novo

50% CA ex PA

- Most common histologic type of CA ex PA

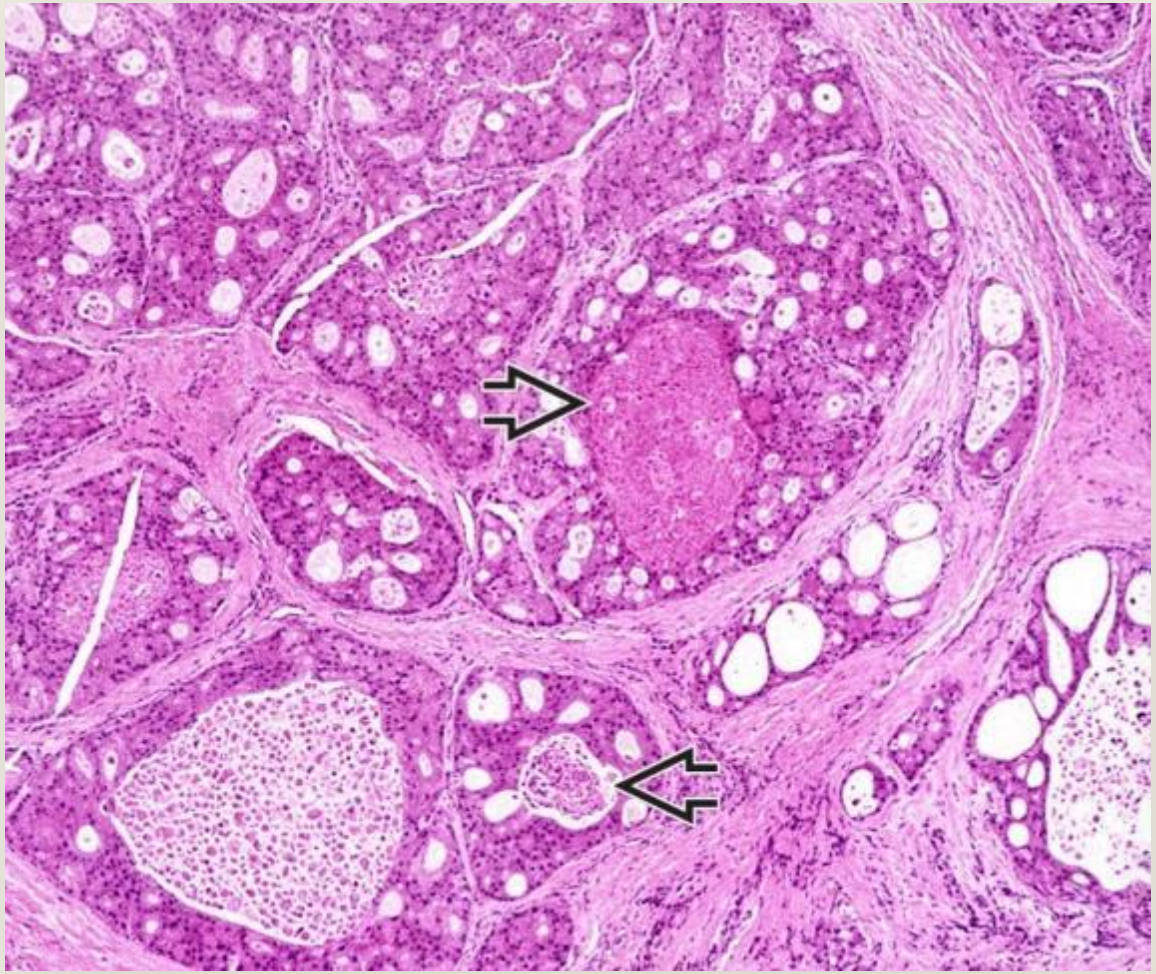
Salivary duct carcinoma

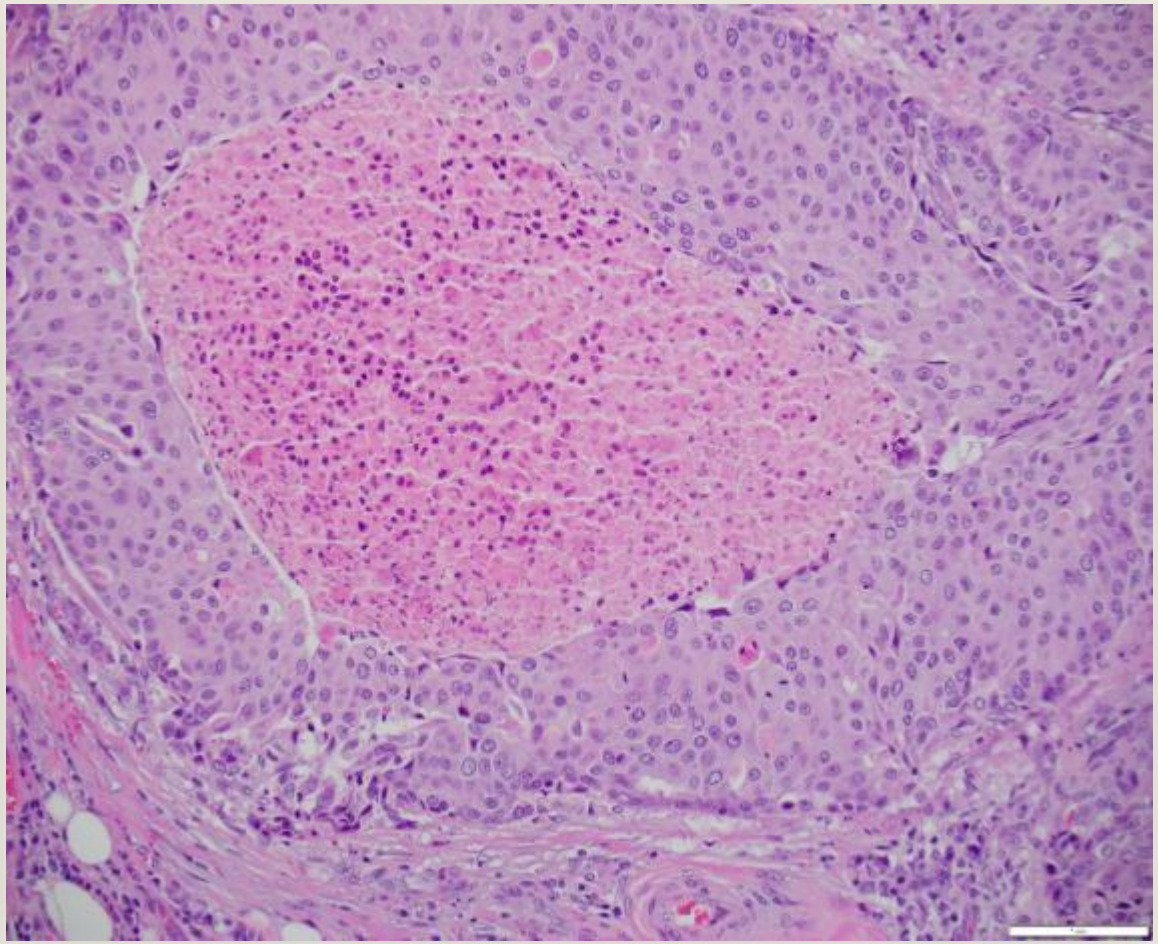
- 10% of salivary malignancies
- Male/female: 4/1
- Patients are older than 50 years
- Parotid most common site
- Aggressive, stage III or IV, PNI: 60%, LVI: 31%, positive lymph nodes: 59%, 33% local recurrence and 46% distant metastasis
- 55-65% death within 5 years

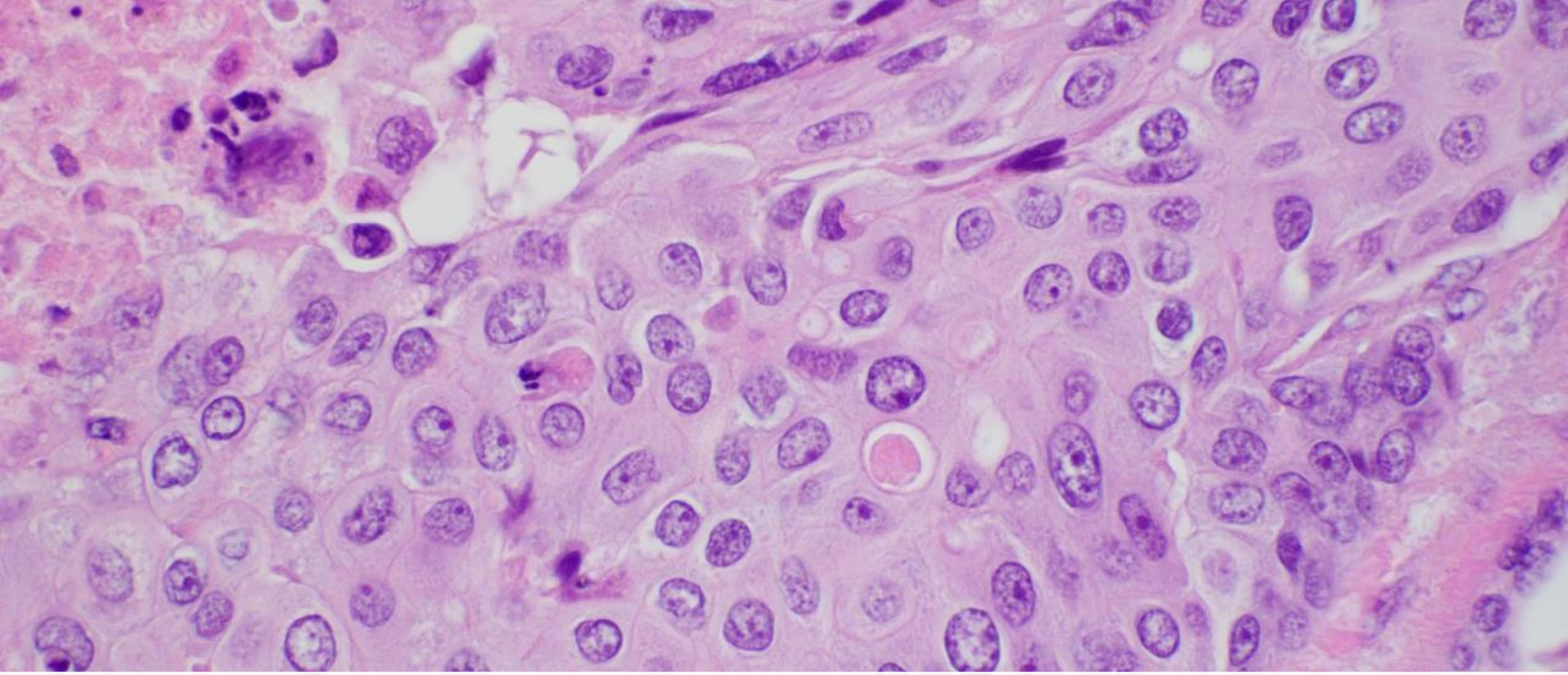
SDC-Histology

- High grade
- Resembles mammary carcinoma
- Ductal differentiation with apocrine features
- Squamous features, sarcomatoid, micropapillary mucin rich, oncocytic

SDC-Histology



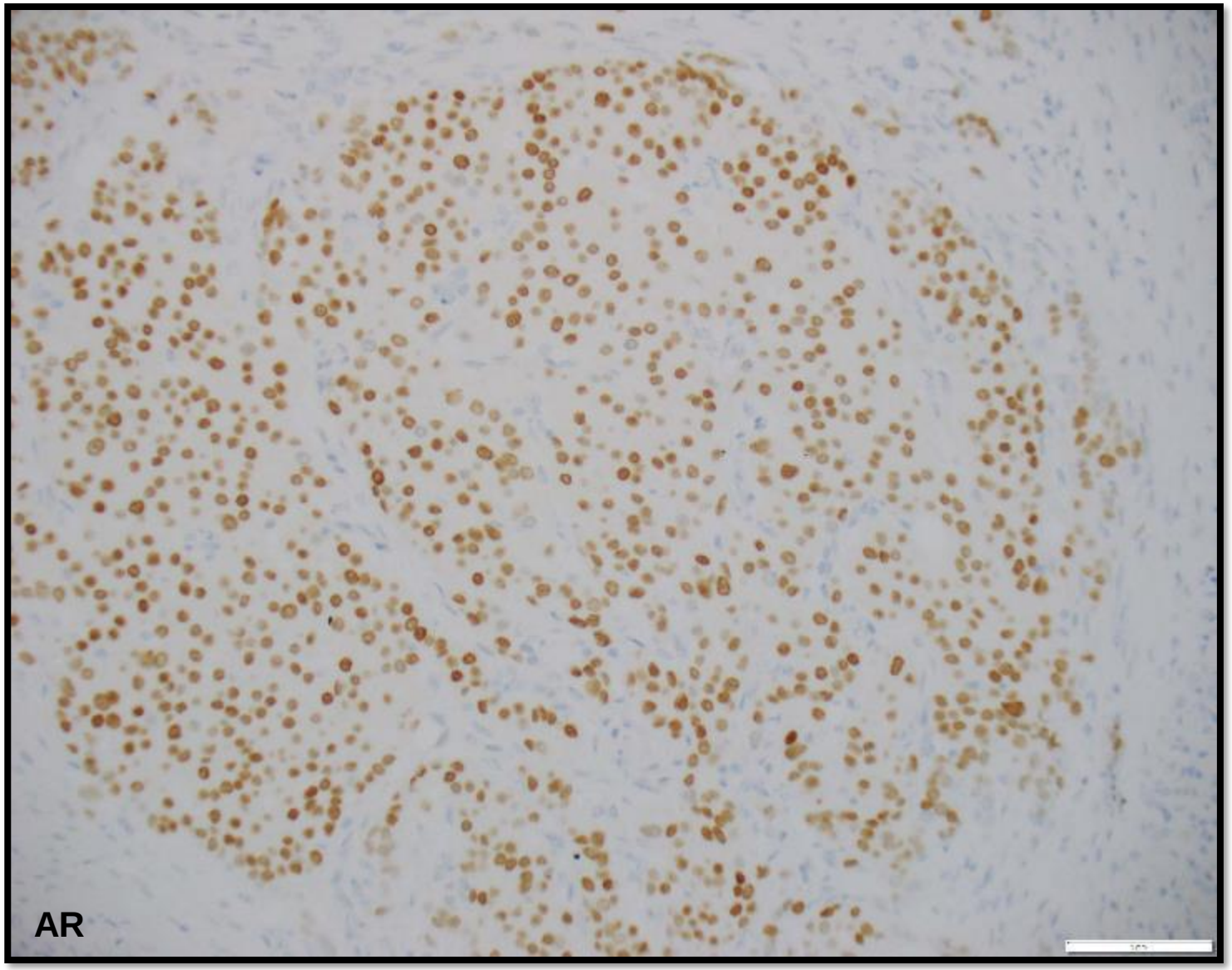




SDC-Apocrine features

SDC-IHC

- Positive:
  - CK7, GATA3, AR (>90%), Her2 (3+, 30%)
- Negative:
  - S100, SOX10, ER, PR, P63/P40



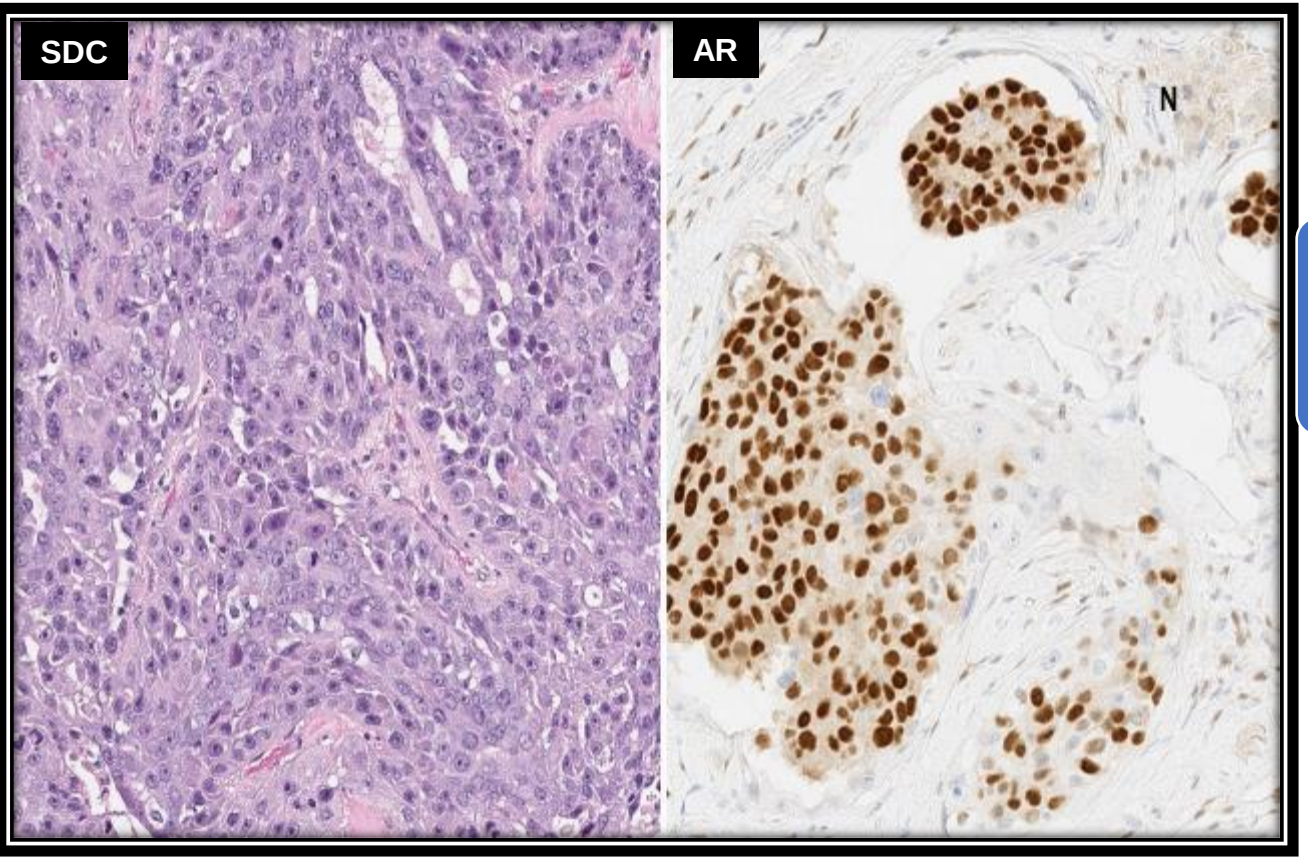
SDC-Molecular features

- AR copy number gain and splice variants
- TP53 mutation 55%
- HRAS mutations 23%
- PIK3CA mutations 23%
- ERBB2 (HER2) amplifications 35%
- PTEN deletion and BRAF mutations
- *PLAG1* and *HMGA2* rearrangement when it is CA ex PA

SDC-Differential diagnosis

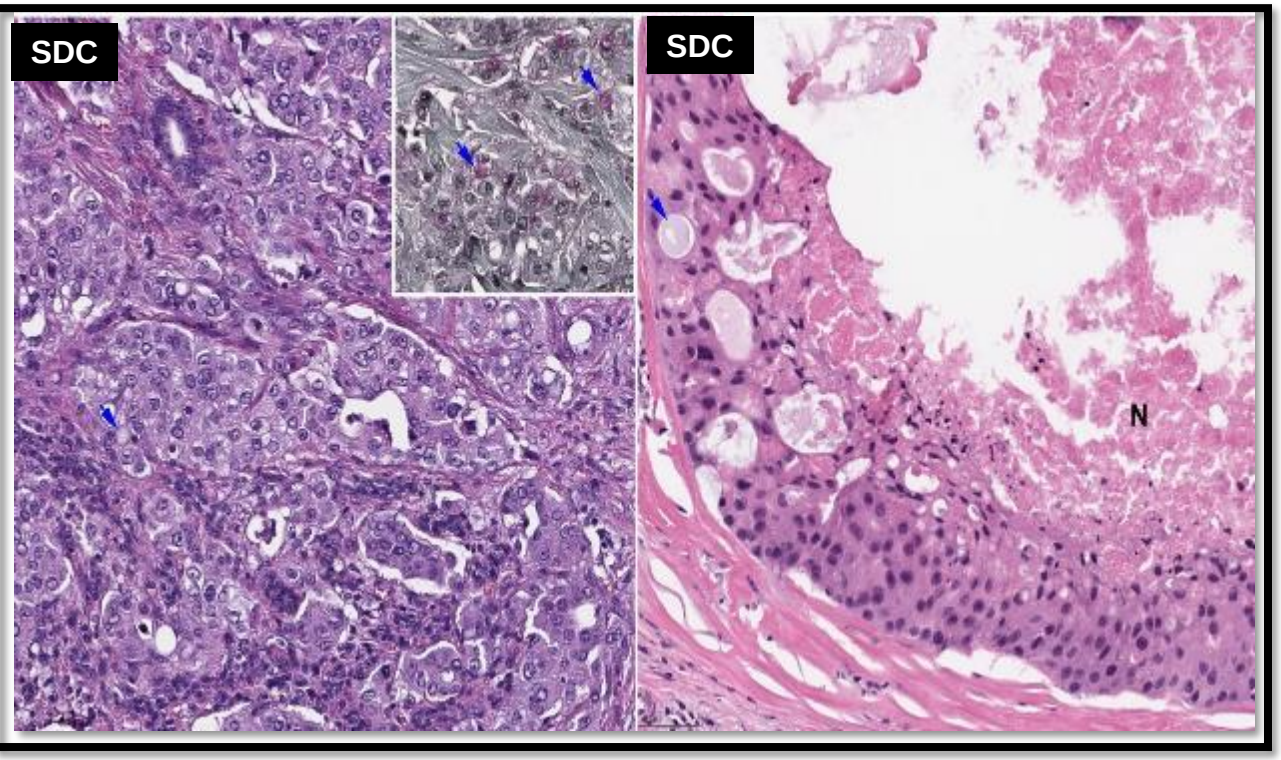
- Apocrine carcinoma of skin adnexa/breast
- Squamous cell carcinoma
- Mucoepidermoid carcinoma
- Oncocytic carcinoma
- Salivary carcinoma NOS

SDC versus squamous cell carcinoma



- Apocrine features
- Positive AR IHC
- Negative staining for squamous markers

SDC versus HG mucoepidermoid carcinoma



- Absence of typical LG mucoepidermoid ca
- Positive AR IHC
- Negative staining for squamous markers

Thanks!