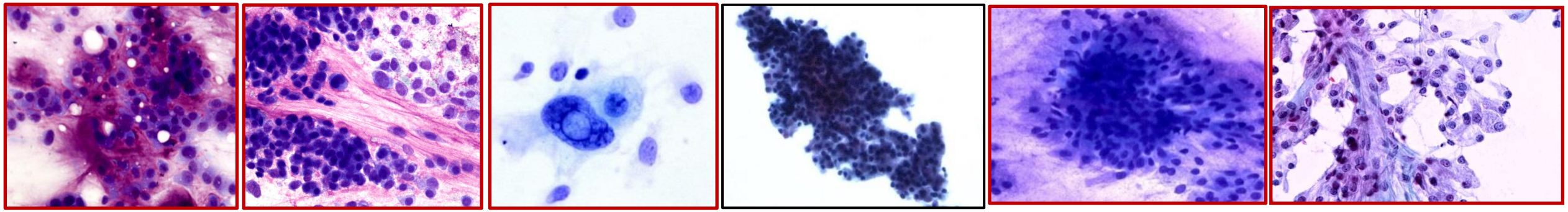

Salivary Gland Cytopathology

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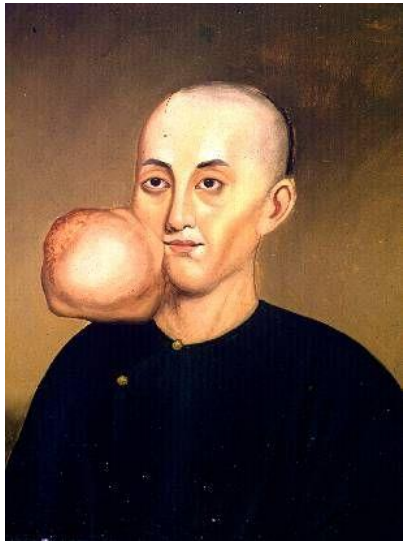
Salivary Gland Fine Needle Aspiration



Advantages of Salivary Gland FNA

1.Differentiation of inflammatory from neoplastic disease

1. Especially important in immunosuppressed

2.Culture for suspected infectious masses

3.Differentiation of benign from malignant disease

4.Differentiation of the specific tumor cell type

5.Determination of site of origin, primary vs. metastatic

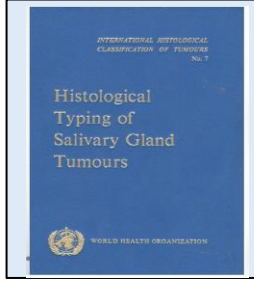
6.Squamous cell carcinoma diagnosis:

1. Squamous cell carcinoma can be accurately diagnosed, and treatment can be planned based on fine-needle aspiration (FNA) findings.
2. A highly cellular muco-epidermoid carcinoma may appear to be squamous cell carcinoma by fine-needle aspiration (FNA) cytology.
3. This difference is purely academic and does not change the treatment.

Complications of Salivary Gland FNA

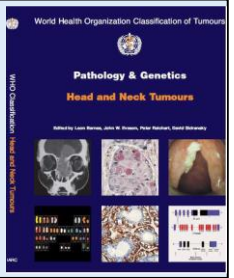
- **Needle track contamination by lesional cells**:
  - Rare complication despite thousands of fine-needle aspirations (FNAs) performed worldwide.
  - A positive correlation exists with number of passes and needle size.
- **Local hemorrhage**:
  - Major salivary glands are in close proximity to the great vessels of the head and neck, local hemorrhage due to piercing of these vessels is possible but very unlikely.
  - Hematoma formation can be prevented by applying firm pressure in the area of aspiration immediately after the procedure.
- **Infection**:
  - This risk is no greater than that of veni-puncture and is closely correlated with the patient's immune status.
  - Adherence to sterile techniques and cleaning the skin with alcohol minimizes this risk.
- *Warthin tumor (papillary cystadenoma lymphomatosum or adenolymphoma) has a high predisposition for parotitis from FNA due to a combination of cystic spaces surrounded by oncocytic cells and poor blood supply.*
- Syncope:
  - Some patients are prone to vasovagal reactions.
  - Perform aspiration while the patient is lying down or sitting.
- **Dissemination of the dislodged tumor cells through lymphatics and blood vessels**:
  - Risk is certainly lower in fine-needle aspiration (FNA) than in ***incisional biopsy***.

The Gold Standard



WHO Classification of Salivary Gland Tumors

Then & Now



1972 WHO Classification of Salivary Gland Tumors

HISTOLOGICAL TYPING
OF SALIVARY GLAND TUMOURS

I. EPITHELIAL TUMOURS

A. ADENOMAS
1. Pleomorphic adenoma (mixed tumour)
2. Monomorphic adenomas
   (*a*) Adenolymphoma
   (*b*) Oxyphilic adenoma
   (*c*) Other types

B. MUCOEPIDERMOID TUMOUR

C. ACINIC CELL TUMOUR

D. CARCINOMAS
1. Adenoid cystic carcinoma
2. Adenocarcinoma
3. Epidermoid carcinoma
4. Undifferentiated carcinoma
5. Carcinoma in pleomorphic adenoma (malignant mixed tumour)

II. NON-EPITHELIAL TUMOURS

III. UNCLASSIFIED TUMOURS

IV. ALLIED CONDITIONS

A. BENIGN LYMPHOEPITHELIAL LESION

B. SIALOSIS

C. ONCOCYTOSIS

2017 WHO Classification of Salivary Gland Tumors

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
Adenocarcinoma, NOS	8140/3
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Carcinoma ex pleomorphic adenoma	8941/3
Carcinosarcoma	8980/3
Poorly differentiated carcinoma:	
Neuroendocrine and non-neuroendocrine	
Uwndifferentiated carcinoma	8020/3
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	
Pleormorphic 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	
Nodular oncocytic hyperplasia	
Lymphoepithelial lesions	
Intercalated duct hyperplasia	
Soft tissue lesions	
Haemagioma	9120/0
Lipoma/sialolipoma	8850/0
Nodular fasciitis	8828/0
Haematolymphoid tumours	
Extranodal marginal zone lymphoma of MALT	9699/3

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.
Italics: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*.

Tumor type	Chromosomal region	Gene and mechanism
Pleomorphic adenoma	8q12	PLAG1 fusions/amplification
	12q13-15	HMGA2 fusions/amplification
Basal cell adenoma	3p22.1	CTNNB1 mutations
	16q12.1	CYLD mutations
	16p13.3	AXIN1 mutations
	5q22.2	APC mutations
Myoepithelioma, oncocytic subtype	8q12	PLAG1 fusions
Sialadenoma papilliferum	7q34	BRAF V600E mutations
Sclerosing polycystic adenoma	3q26.32 PIK3CA mutation high	
Mucoepidermoid carcinoma	t(11;19) (q21;p13)	CRTC1-MAML2
	t(11;15) (q21;q26)	CRTC3-MAML2
	9p21.3	CDKN2A deletion
Adenoid cystic carcinoma	6q22-23	MYB fusion/activation/amplification
	8q13	MYBL1 fusion/activation/amplification
	9q34.3	NOTCH mutations
Acinic cell carcinoma	9q31	NR4A3 fusion/activation
	19q31.1	MSANTD3 fusion/amplification
Secretory carcinoma	t(12;15) (p13;q25)	ETV6-NTRK3 fusion
	t(12;10) (p13;q11)	ETV6-RET fusion
	t(12;7) (p13;q31)	ETV6-MET fusion
	t(12;4) (p13;q31)	ETV6-MAML3 fusion
	t(10;10) (p13;q11)	VIM-RET fusion
Microsecretory adenocarcinoma	t(5q14.3) (18q11.2)	MEF2C-SS18 fusion
Polymorphous adenocarcinoma		
Classic subtype	14q12	PRKD1 mutations
Cribriform subtype	14q12	PRKD1 fusions
	19q13.2	PRKD2 fusions
	2p22.2	PRKD3 fusions

Tumor type	Chromosomal region	Gene and mechanism
Hyalinizing clear cell carcinoma	t(12;22) (q21;q12)	EWSR1-ATF1 fusions
		EWSR1-CREM fusions
Basal cell adenocarcinoma	16q12.1	CYLD mutations
Intraductal carcinoma		
Intercalated duct subtype	10q11.21	RET fusions
Apocrine subtype	3q26.32	PIK3CA mutations
	11p15.5	HRAS mutations
Salivary duct carcinoma	17q21.1	HER2 amplification
	8p11.23	FGFR1 amplification
	17p13.1	TP53 mutation
	3q26.32	PIK3CA mutation
	11p15.5	HRAS mutation
	Xq12	AR copy gain
	10q23.31	PTEN loss
	9p21.3	CDKN2A loss
Myoepithelial carcinoma	8q12	PLAG1 fusions
	t(12, 22) (q21;q12)	EWSR1 rearrangement
Epithelial-myoepithelial carcinoma	11p15.5	HRAS mutations
Mucinous adenocarcinoma	14q32.33	AKT1 E17K mutations
	17p13.1	TP53 mutations
Sclerosing microcystic adenocarcinoma	1p36.33	CDK11B mutation
Carcinoma ex pleomorphic adenoma	8q12	PLAG1 fusions/amplification
	12q13-15	HMGA2 fusions/amplification
	17p13.1	TP53 mutations
Sebaceous adenocarcinoma	2p21	MSH2 loss

Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands

Salivary Gland Tumors – Diagnostic Paradigm

Benign ⟷ **Malignant**

Invasion Absent, BUT Benign Tumors can show

- Multinodular and Irregular growth
- Lack of encapsulation
- Capsular violation
- Outpouching into surrounding normal parenchyma
- Vascular invasion?
- Fatty metaplasia within the tumor mimicking invasion into fat
- Invasion absent but still Malignant
  - Intraductal Carcinoma
  - Intracapsular Carcinoma

Benign Tumors (especially Pleomorphic Adenoma) can show / mimic Cytologic Features of Malignancy:

- Increased Cellularity
- Nuclear Pleomorphism
- Mitoses
- Infarction mistaken for Tumor Necrosis
- Post FNA tumor necrosis
- Atypical Architecture

Invasion Present

- Macroscopic
- Microscopic
  - Perineural
  - Into surrounding normal parenchyma
  - Angioinvasion

Cytologic Features of Malignancy

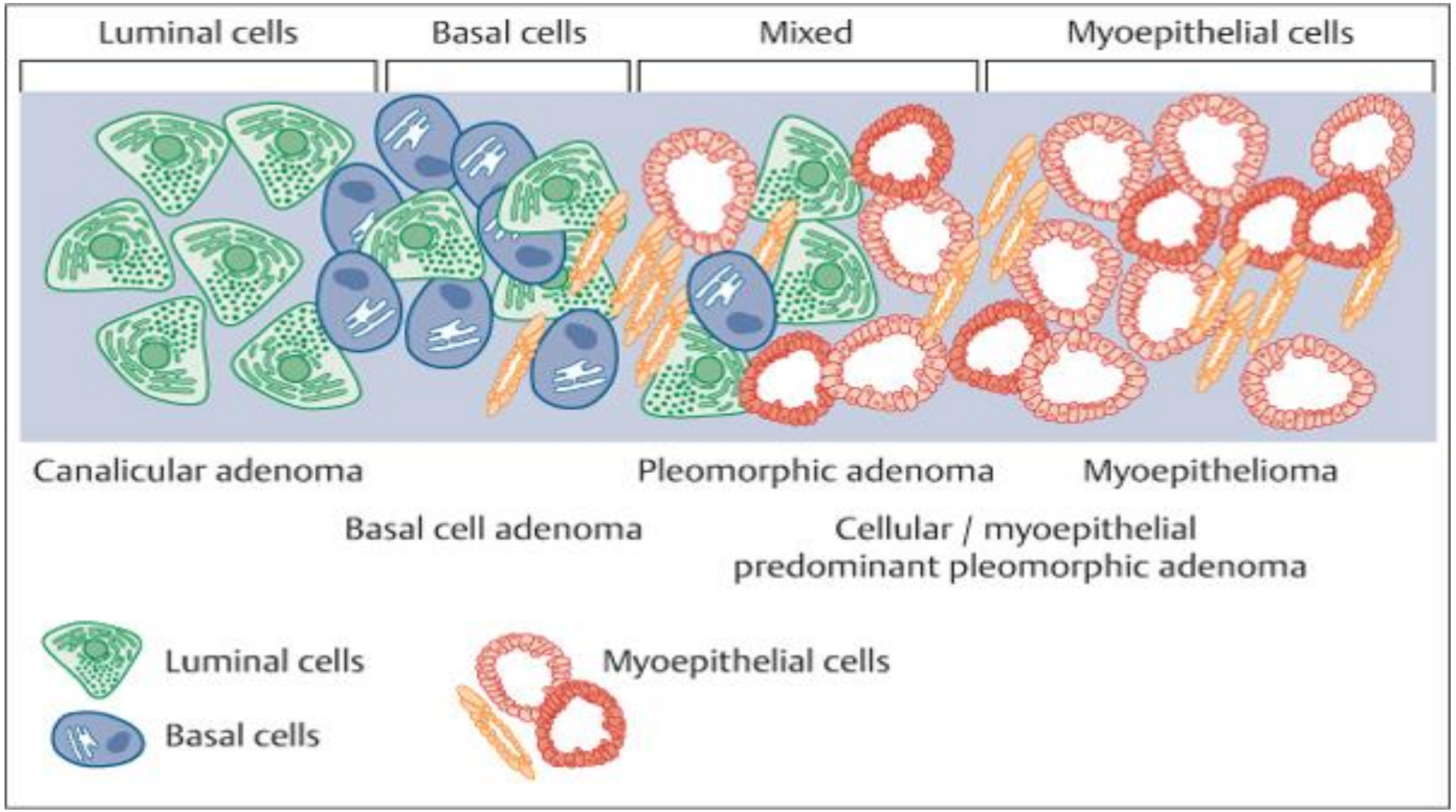
- Marked Nuclear Pleomorphism
- Atypical Mitoses
- Tumor Necrosis

But some Malignant Tumors May Not show Cytologic Features of Malignancy

- Monotonous basaloid cells and low grade nuclear cytology of "Adenoid Cystic Carcinoma"

Histogenesis of Salivary Gland Tumors

Reason for Morphologic Heterogeneity



Histogenesis of Salivary Gland Tumors
Reason for Morphologic Heterogeneity

Myoepithelial Cell Differentiation in in salivary gland tumors

Benign salivary gland tumors[1,2,4,5]			Malignant salivary gland tumors[1,2,4,5]		
No MCD	**Partial MCD**	**Predominant MCD**	**No MCD**	**Partial MCD**	**Predominant MCD**
Canalicular adenoma, Warthins tumor Oncocytoma, Sebaceous adenoma, Ductal papilloma	Basal cell adenoma	Pleomorphic adenoma, Myoepithelioma	Acinic cell carcinoma, Salivary duct carcinoma, Hyalinizing clear cell carcinoma, Squamous cell carcinoma, Oncocytic carcinoma	Basal cell adenocarcinoma, Polymorphous low-grade carcinoma, Mucoepidermoid carcinoma	Adenoid cystic carcinoma, Myoepithelial carcinoma, Epithelial-myoepithelial carcinoma, Myoepithelial carcinoma Ex-pleomorphic adenoma

MCD=Myoepithelial cell differentiation

Redder et al. Clin Can Invest J 2013;2:101-105

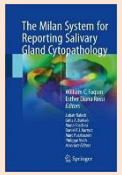
Immunohistochemistry

Cell	PanK	LMWK	HMWK	EMA	CEA	S100	p63	SMA	CAL	VIM	GFAP	DOG1
Ductal	+	+	−	+	+	−	−	−	−	−	−	-/+
Acinar	+	+	−	+	+	−	−	−	−	−	−	+
Myoepi	+	+	+	−	−	+	+	+	+	+	V+	−

Fine-Needle Aspiration of Salivary Gland lesions
Reality Check

What We Know or Can Accomplish in this Limited Cellularity Specimen in Light of

1. ***Ever Expanding List of Salivary Gland Lesions***
2. ***Tumor Cellular and Architectural Heterogeneity***
3. ***Mode of Biopsy, Manual vs. Ultrasound***
4. ***Reporting of Specific Entities vs. Main Diagnostic Categories***
5. ***Management Options***



The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC): implied risk of malignancy and recommended clinical management

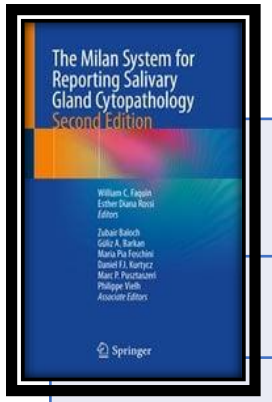
Diagnostic Category	% ROM (ROM range)	Management
Non-Diagnostic [c]	25 (0-67%)	Clinical and radiologic correlation/ repeat FNAC
Non-Neoplastic	10.2% (0-20%)	Clinical follow-up and radiologic correlation
Atypia of Undetermined Significance (AUS)	TBD	Repeat FNAC or surgery
Neoplasm		
i. Benign	3.4% (0-13%)	Surgery or clinical follow-up
ii. Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)[e]	37% (0-100%)	
Suspicious for Malignancy	57% (0-100%)	Surgery
Malignant	92% (57-100%)	Surgery

Post MSRSGC Literature, as of Today

Diagnostic Category	% ROM – *Ist ed* (ROM range)	% ROM Review in 51 studies (post MSRSGC)
Non-Diagnostic	25	15
Non-Neoplastic	10.2	11
Atypia of Undetermined Significance (AUS)	TBD	30
Neoplasm		
i. Benign	3.4	3
ii. Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)	37	26
Suspicious for Malignancy	57	83
Malignant	92	98

Non-neoplastic + Benign neoplasm as Benign/Negative
and
Suspicious for Malignancy and Malignant as positive

Sensitivity	94.04%	92.84% to 95.09%
Specificity	89.63%	87.54% to 91.47%
Positive Likelihood Ratio	9.07	7.54 to 10.91
Negative Likelihood Ratio	0.07	0.06 to 0.08
Positive Predictive Value (*)	94.35%	93.28% to 95.26%
Negative Predictive Value (*)	89.08%	87.15% to 90.76%
Accuracy (*)	92.49%	91.44% to 93.44%



The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) - 2nd edition

Diagnostic Category	% ROM[a]	Management
• I. Non-Diagnostic [c]	15%	Clinical and radiologic correlation/ repeat FNA
• II. Non-Neoplastic	11%	Clinical follow-up and radiologic correlation
• III. Atypia of Undetermined Significance (AUS)	30%	Repeat FNA or surgery
IV. Neoplasm		
• IVA. Neoplasm: Benign	<3%	Surgery or clinical follow-up
• IVB. Neoplasm: Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)[e]	35%	Surgery
V. Suspicious for Malignancy	83%	Surgery
VI. Malignant	98%	Surgery

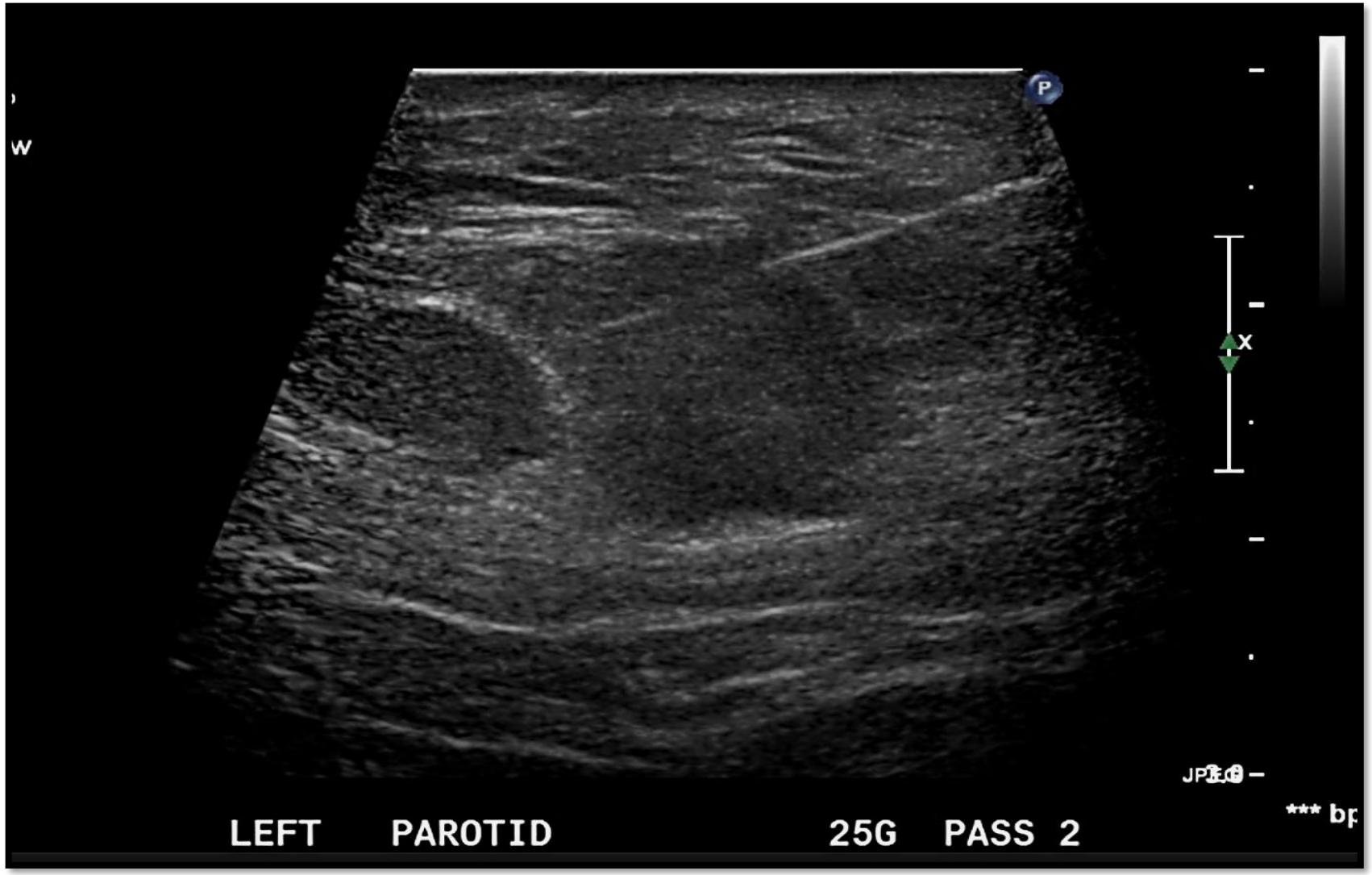
[a] *The following ranges for ROM for diagnostic categories have been cited in the literature published after publication of the 1st edition of MSRSGC: Non-diagnostic 0-50%, Non-neoplastic 0-100%, AUS 0-100%, Benign Neoplasm 0-50%, SUMP 0-100%, Suspicious for malignancy 50-100% and Malignant 80-100%. The test characteristics calculated by considering non-neoplastic and benign neoplasm diagnosis as true negative, and suspicious for malignancy as true positive outcomes on excision are as follows: sensitivity 86.71% (85.19%-88.14%), specificity 98.28% (97.92%-98.59%), positive likelihood ratio 50.42 (41.71-60.93), negative likelihood ratio 0.14 (0.12-0.15), positive predictive value 94.50% (93.43%-95.41%), negative predictive value 95.60% (95.11%-96.03%), and accuracy 95.34% (94.86%-95.79%),*

Case History

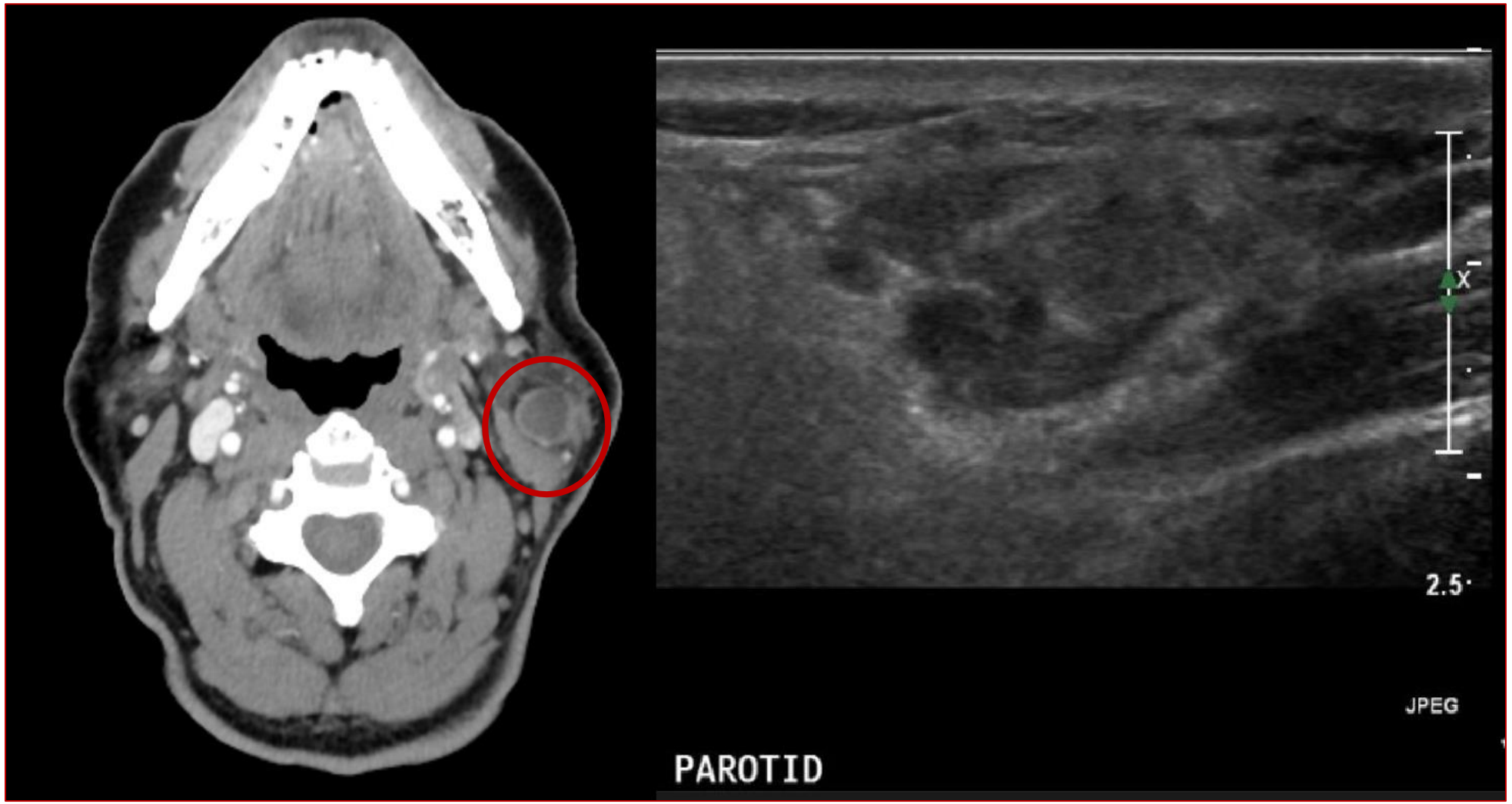
76 year-old genetic male with a history of left neck mass.

- Within the course of 3-4 months he has developed left neck mass- presented to local hospital ED- notes no changes since that time.
- Mild pain on palpation but denies chronic pain.
- No dysphagia, hoarseness, or dyspnea.
- No rhinitis or sinusitis symptoms.
- No fevers, chills, unexplained weight loss, or other symptoms.
- History of GERD and gets rare heartburn.

Ultrasound

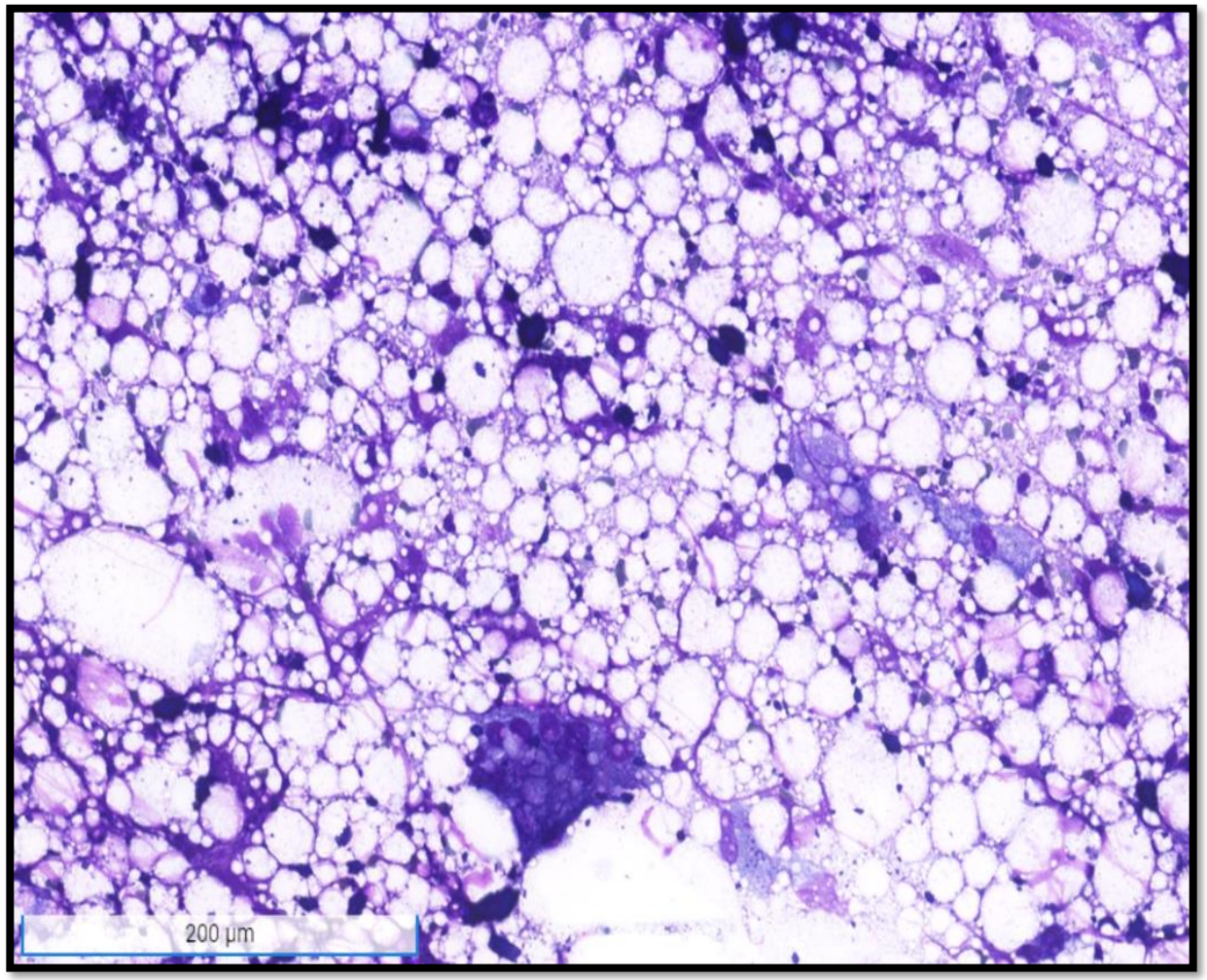


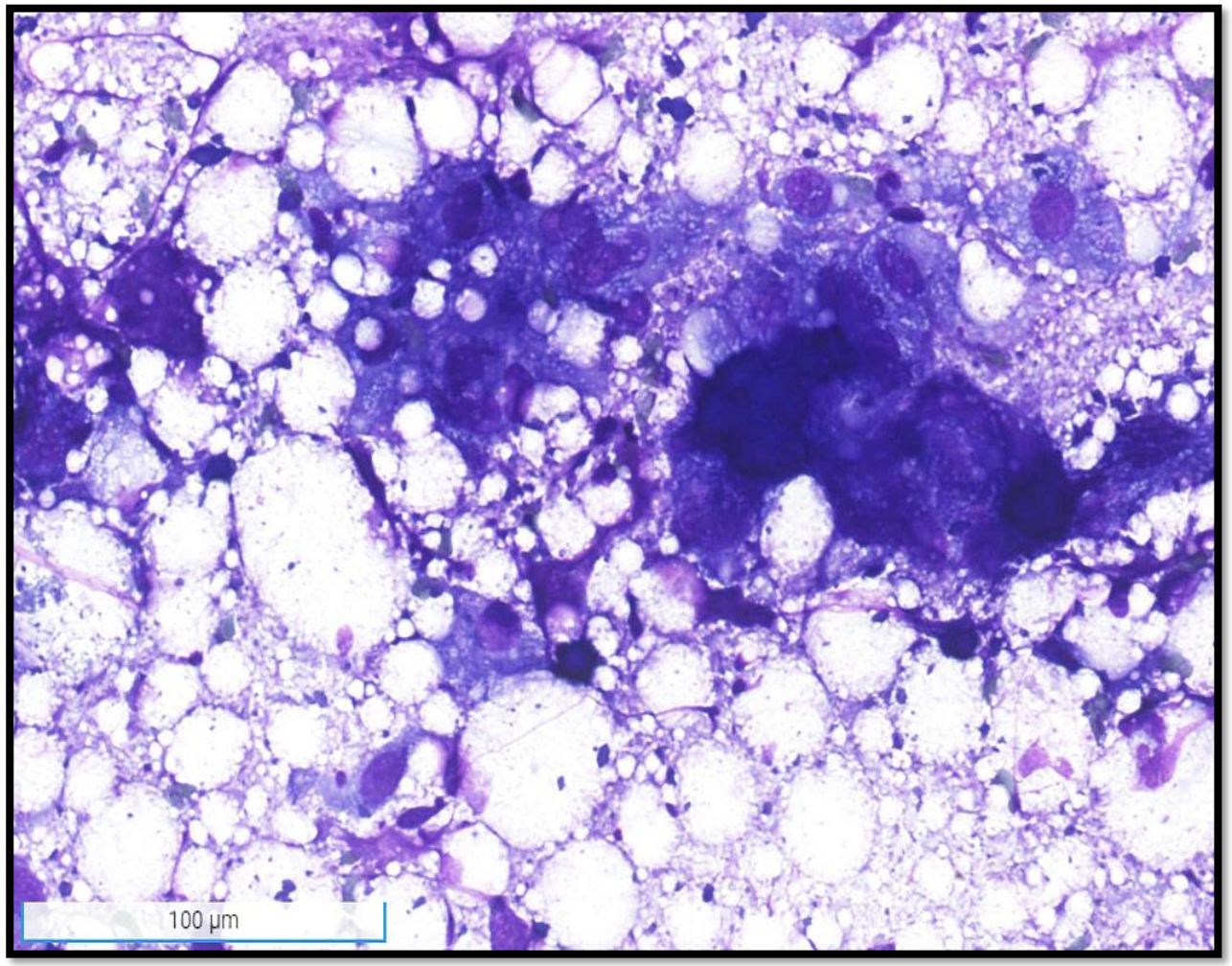
“Solid and Cystic Parotid Mass”



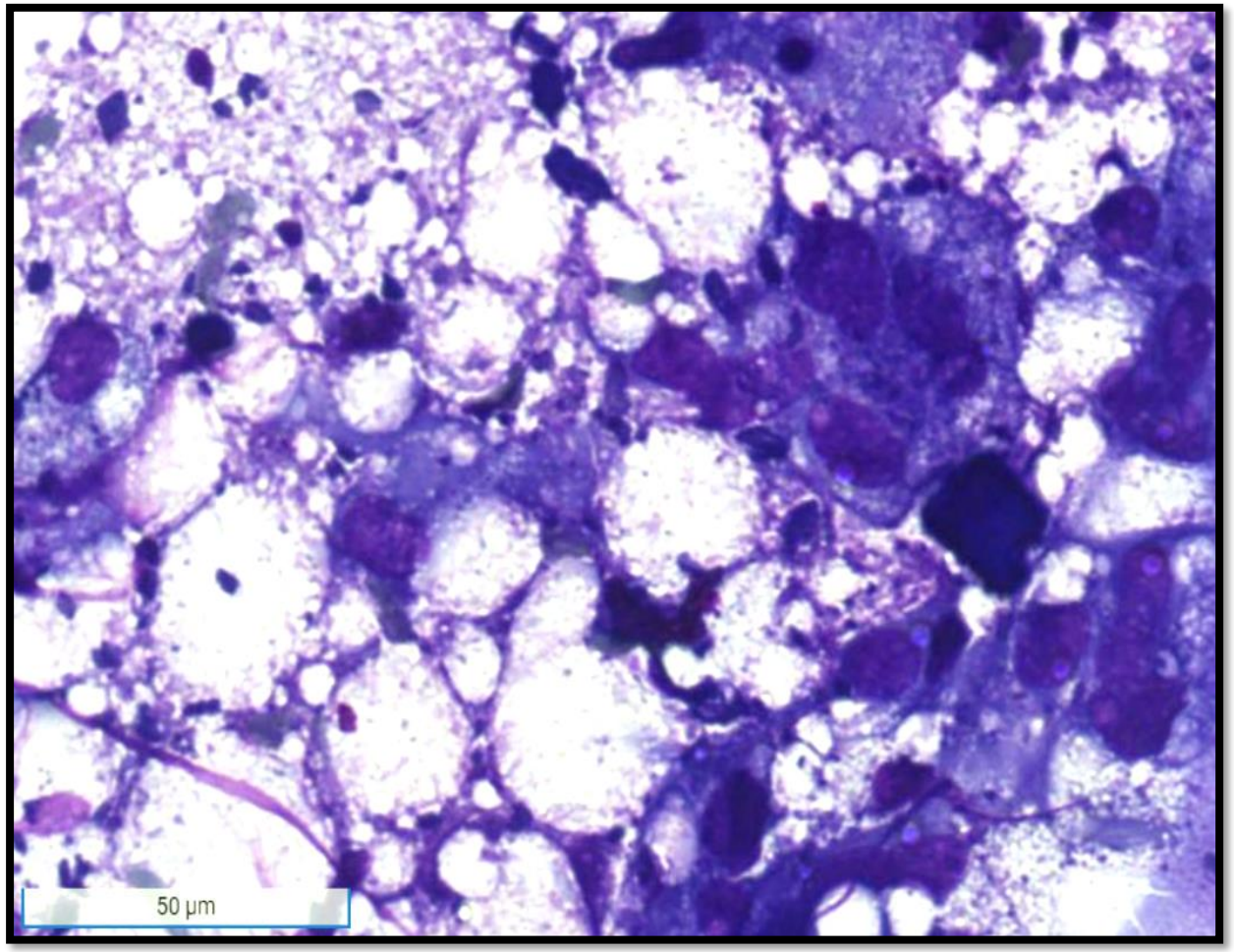
1.9 cm centrally necrotic mass arising from inferior left parotid gland

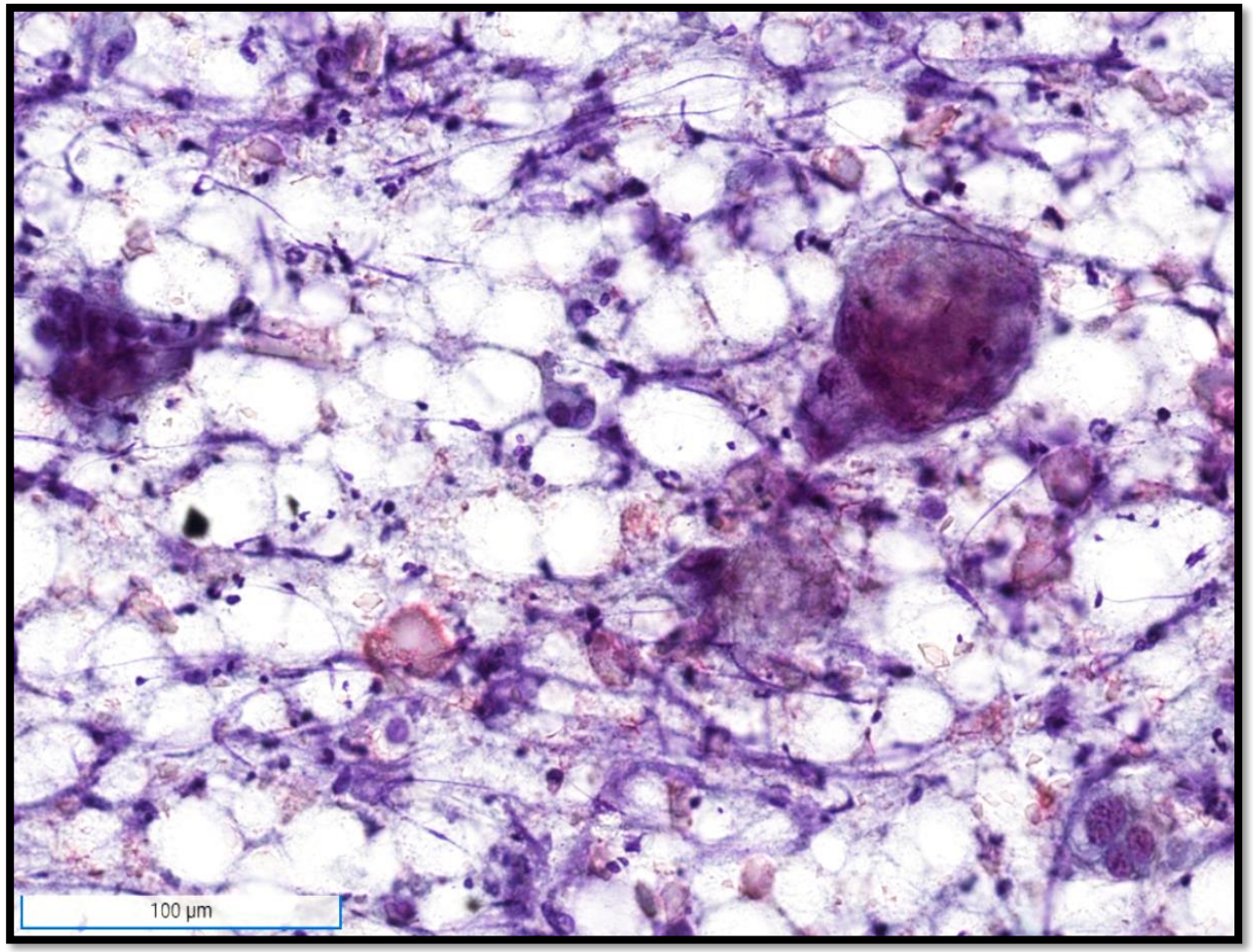
On-site Preparations





On-site Preparations





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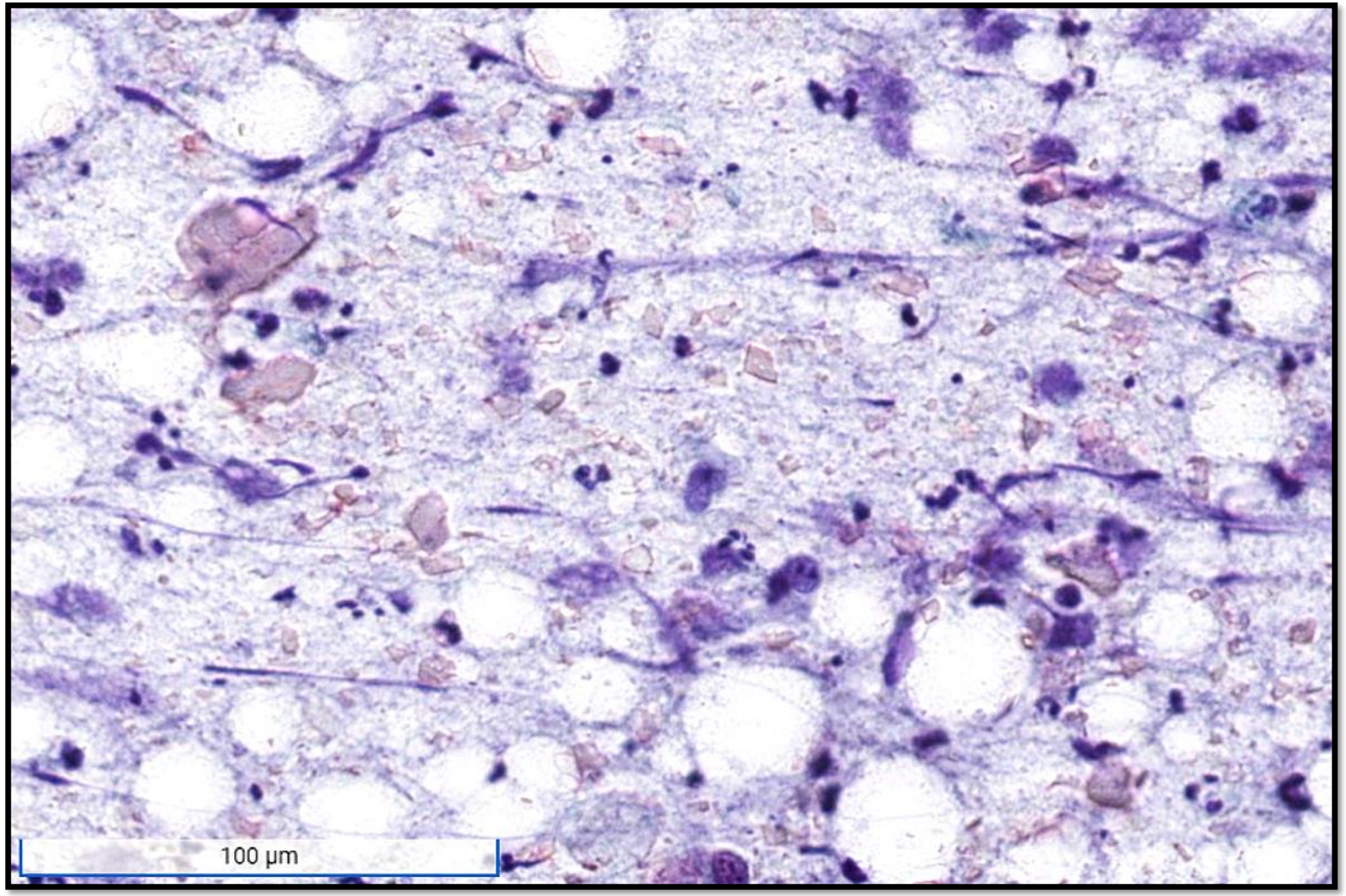
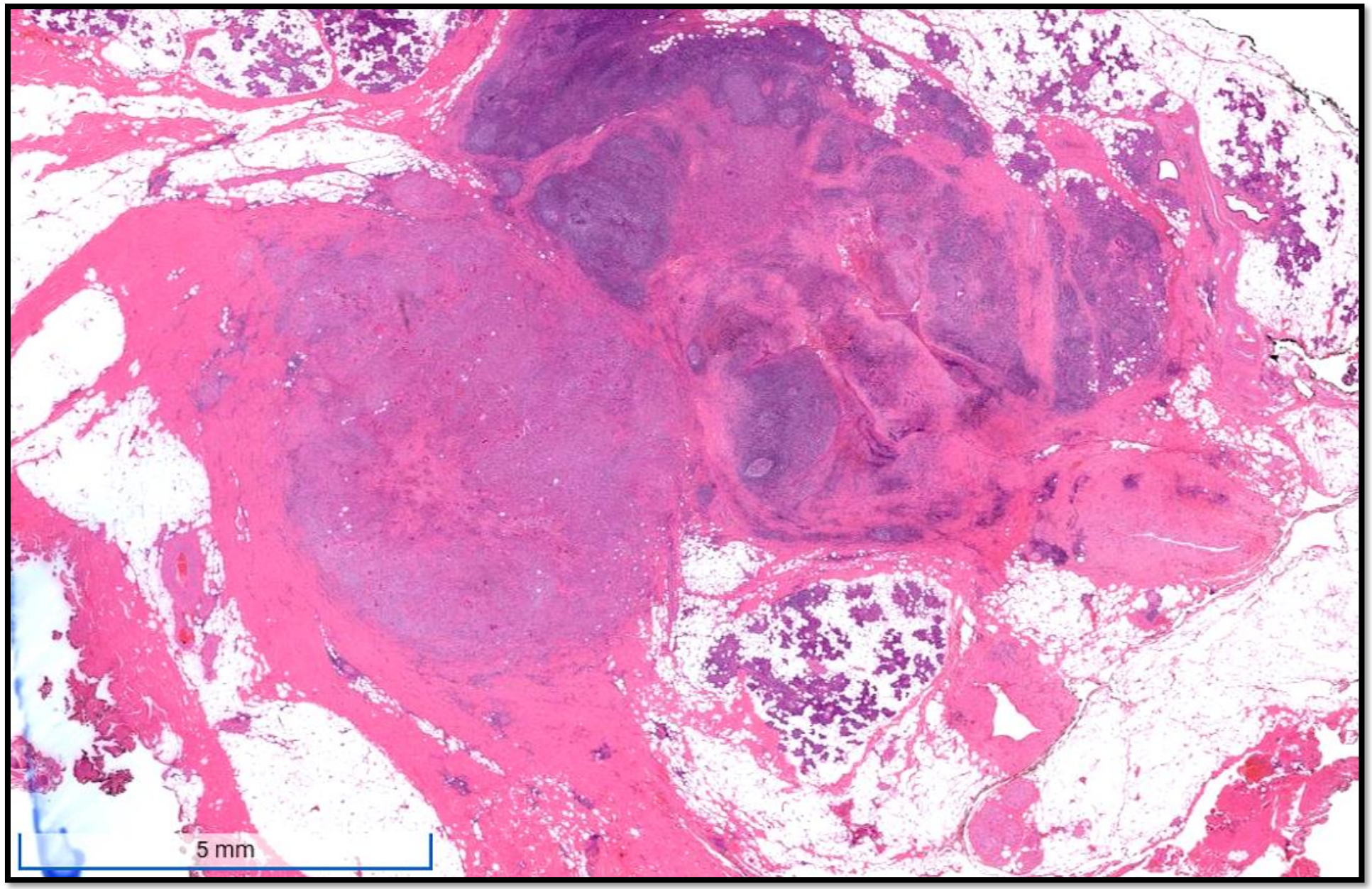
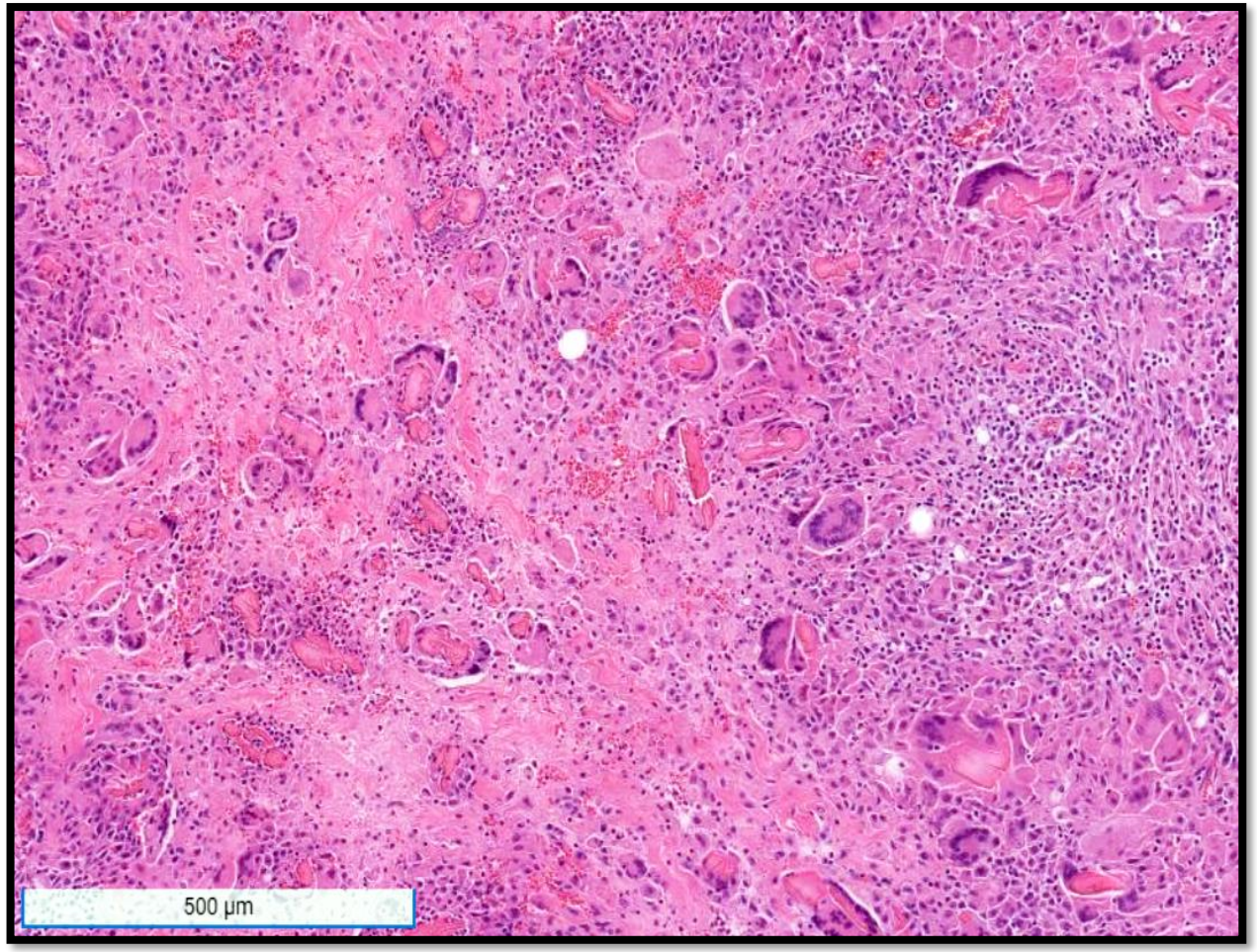
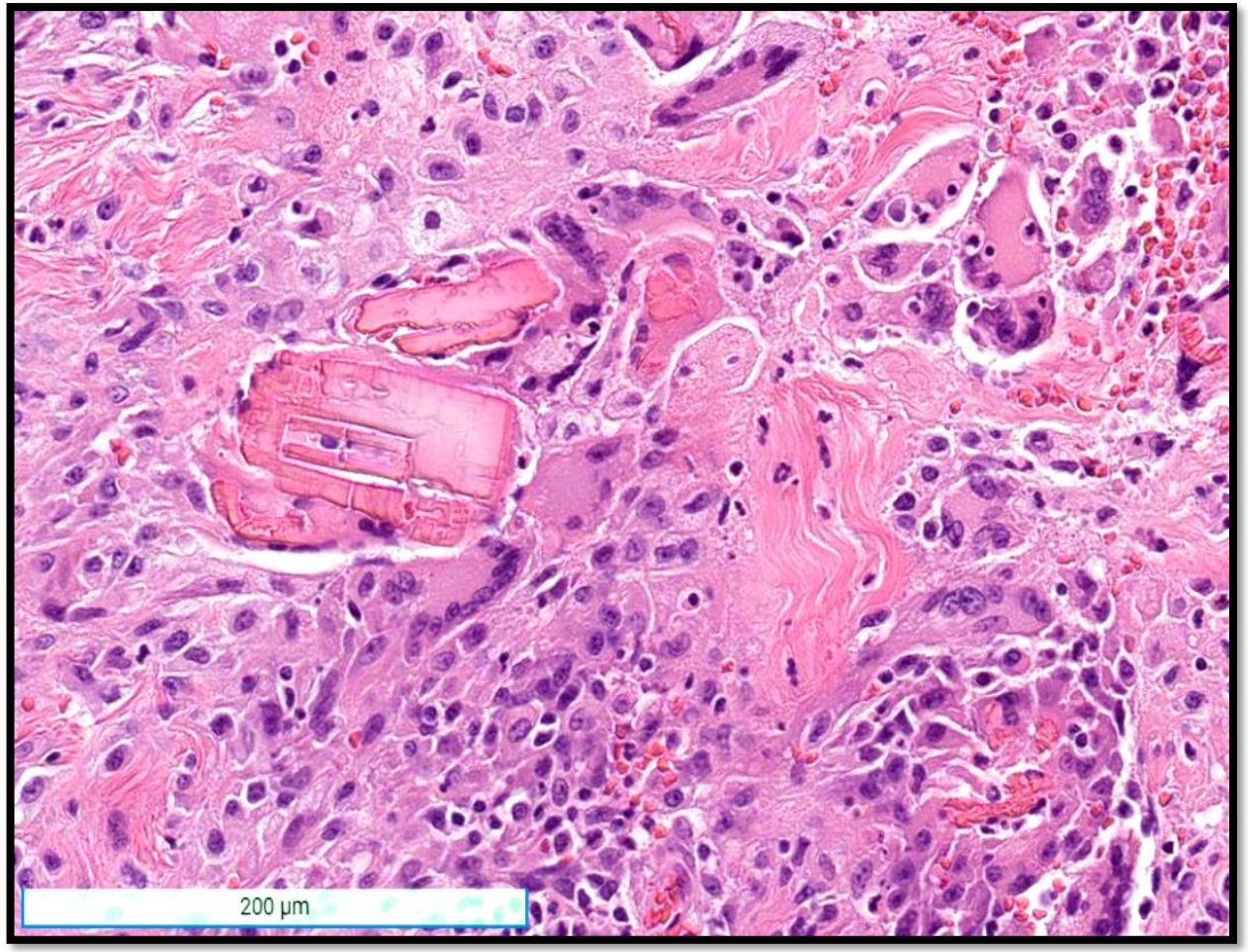


Surgical Follow-up



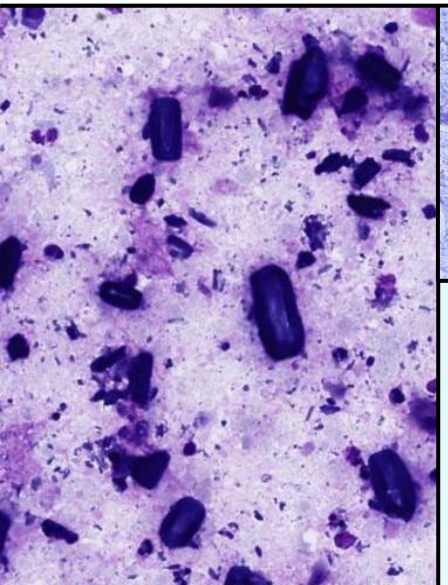
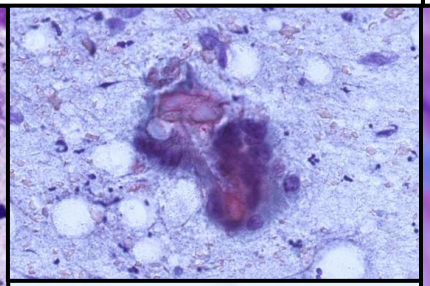
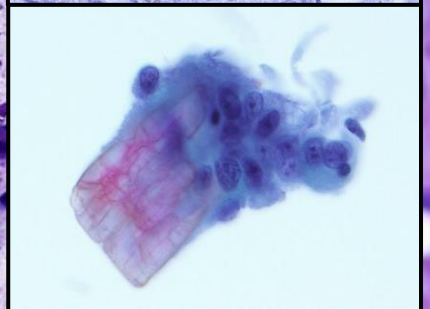
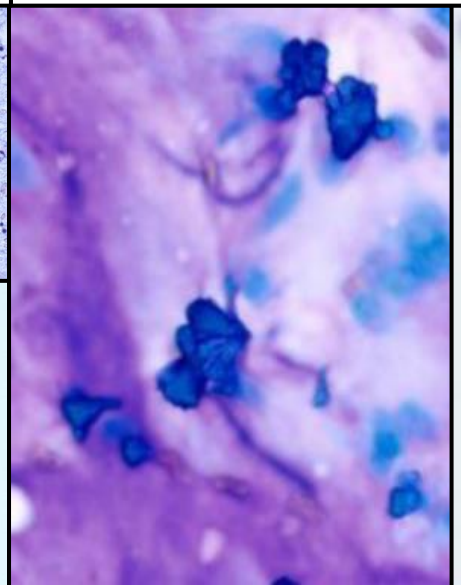
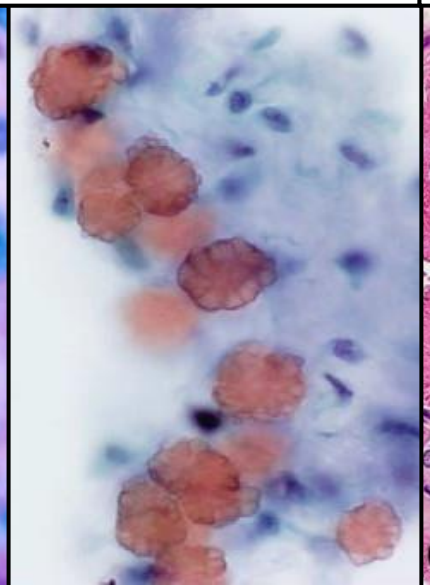
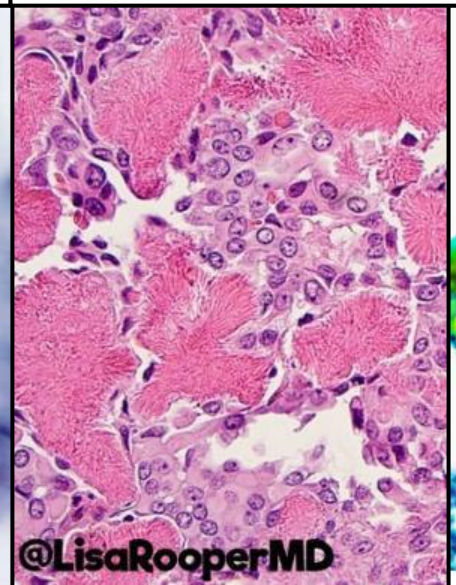
Surgical Follow-up

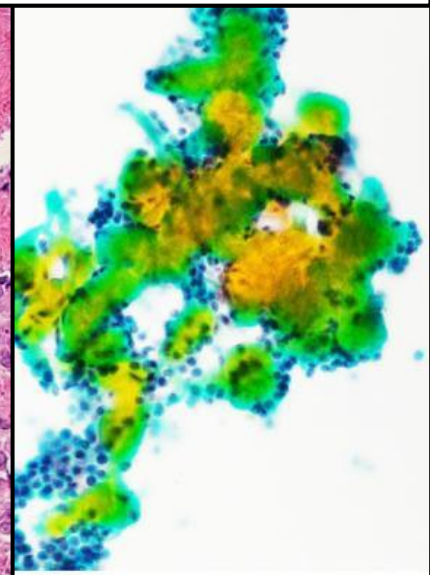




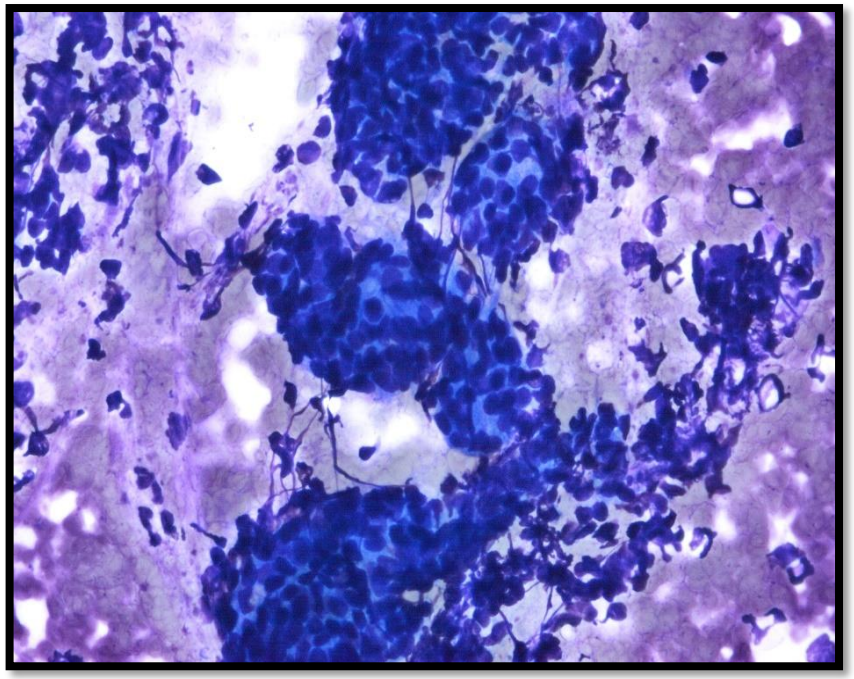
Salivary Gland Crystalloids

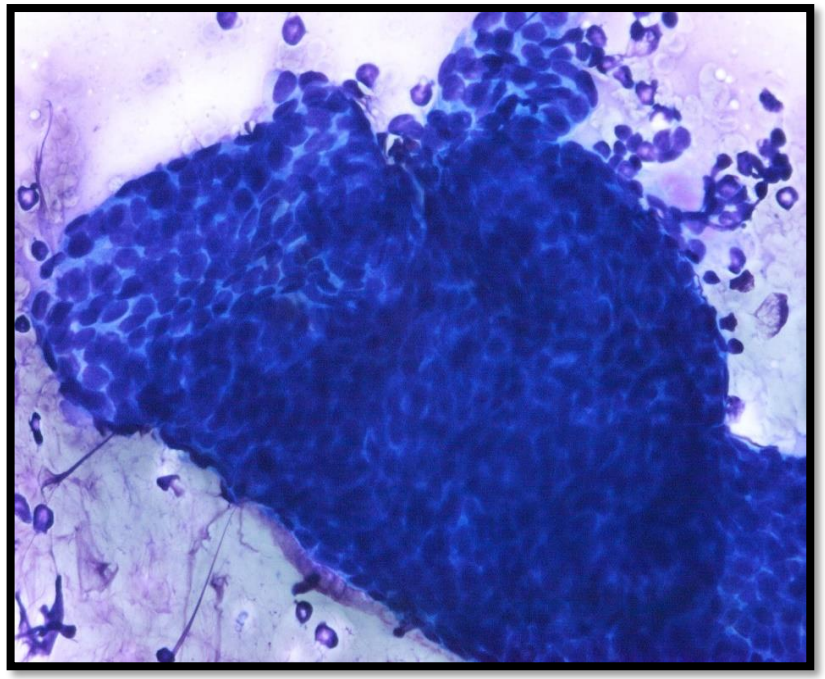
Amylase	Tyrosine	Collagenous
Produced by serous acinar cells (P>SM) Salivary stasis -> Saturation -> crystallization (sialolithiasis/sialadenitis, oncocytic/lymphoepithelial cysts, Warthin) So far only seen in benign conditions *Rhomboid/rectangular/linear – 5-200 µm* *Romanowsky - Deep Blue; Pap - OJ/Pink; H&E - Pink* *Refractile, non-polarizable*	Likely produced by stromal or neoplastic myoepithelial cells See mostly in Pas, but also malignant neoplasms (CA ex-PA, AdCC, polymorphous adeno, etc.) and rarely non-neoplastic cysts. *Floret/petal-like w/ rounded edges – 30-60 µm* *Romanowsky - Blue; Pap – Orange; H&E - Pink* *Refractile, non-polarizable*	Produced by neoplastic myoepithelial cells Seen in PAs (including cutaneous), myoepitheliomas, and myoepithelial carcinomas *Spherules composed of radially arranged needle-shaped collagen fibers – 30-50 µm* *Romanowsky - Red; Pap – yellow/green; H&E - Pink* *Non-refractile, birefringent*

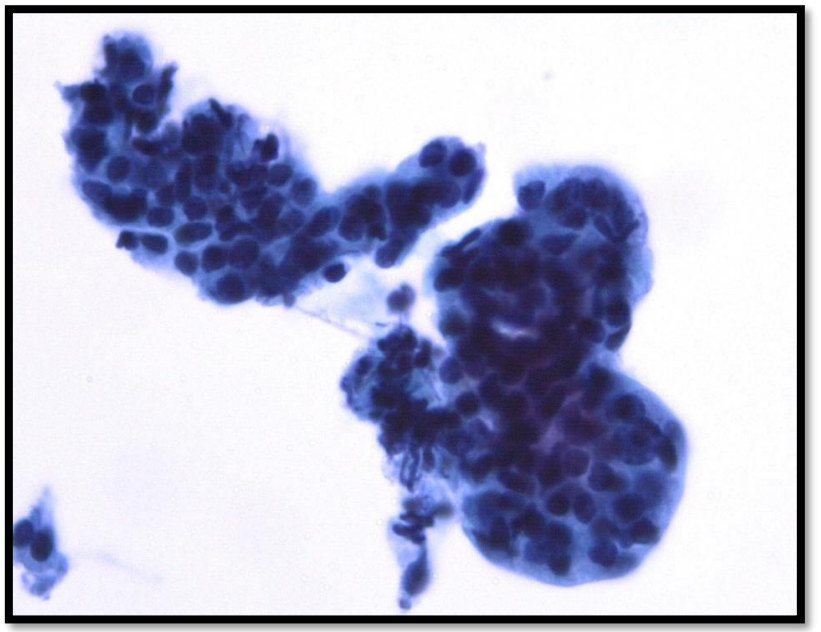







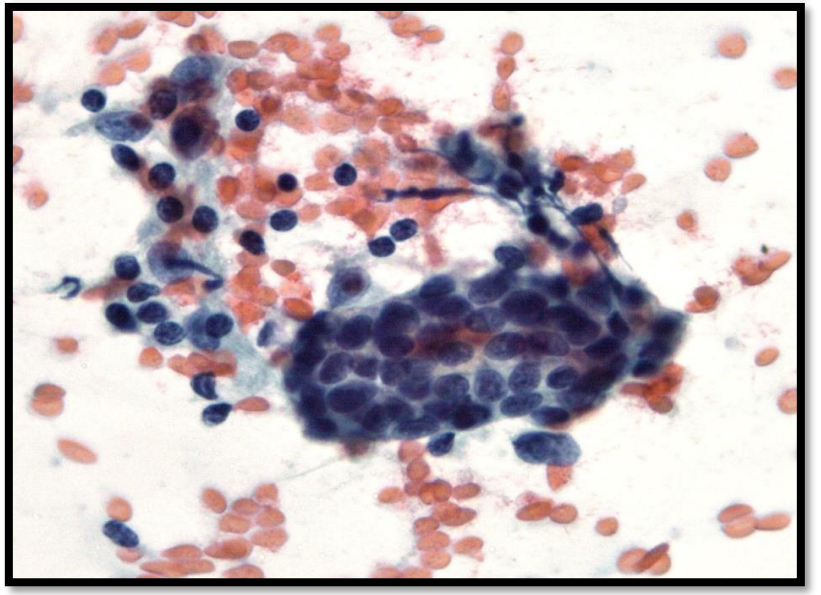


67-year-old man with 2.9 cm Submandibular Lymph Node





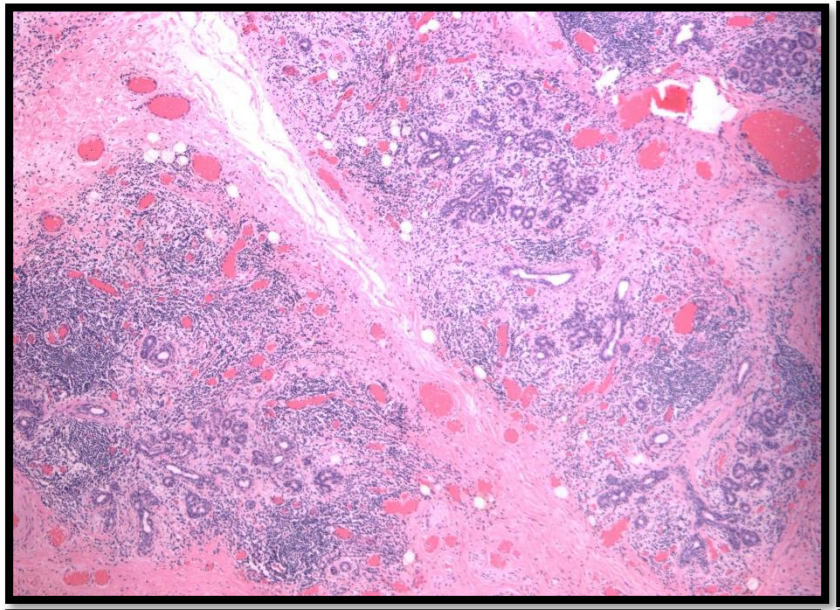
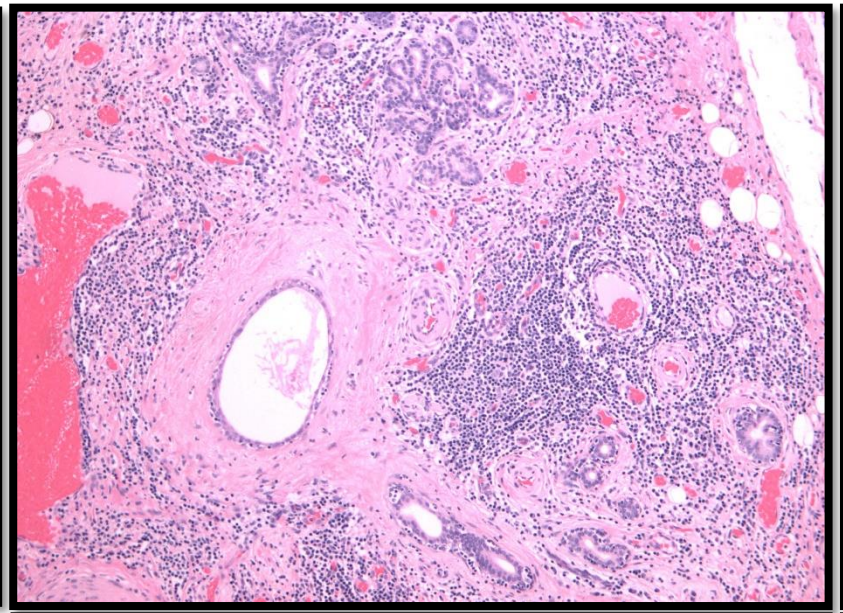
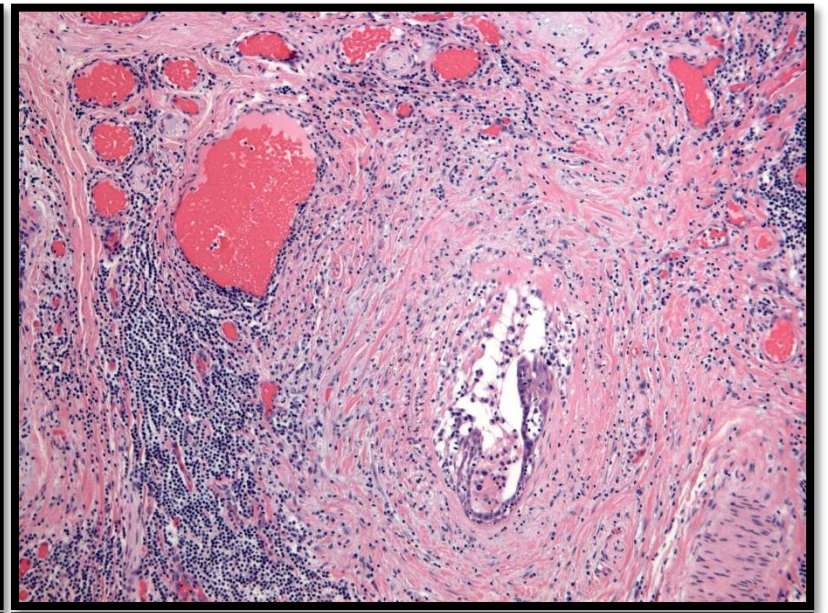
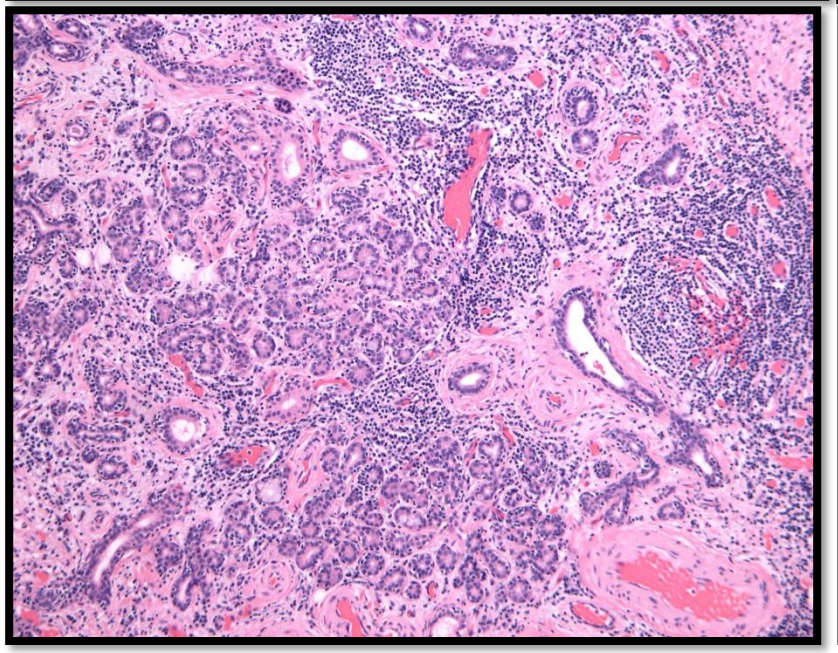
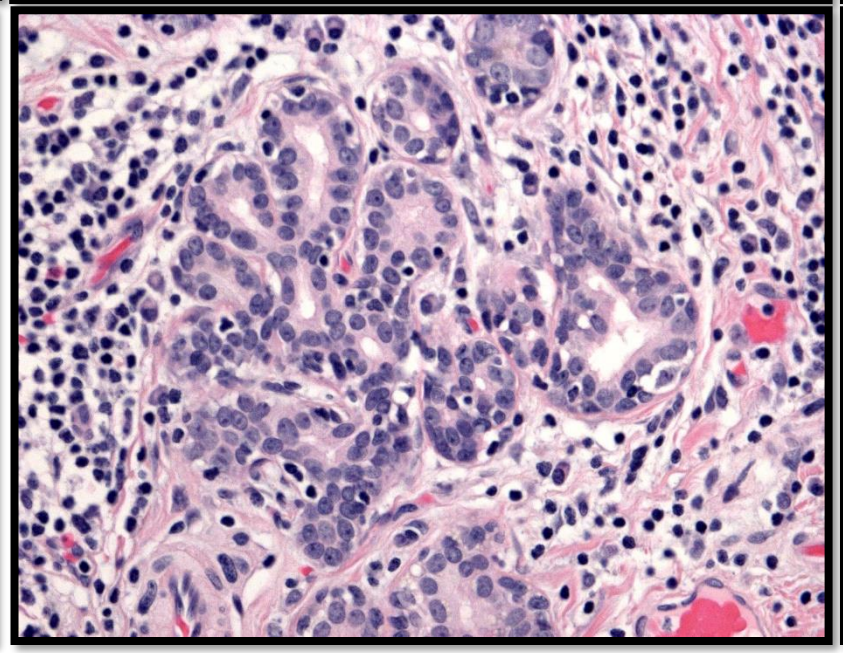
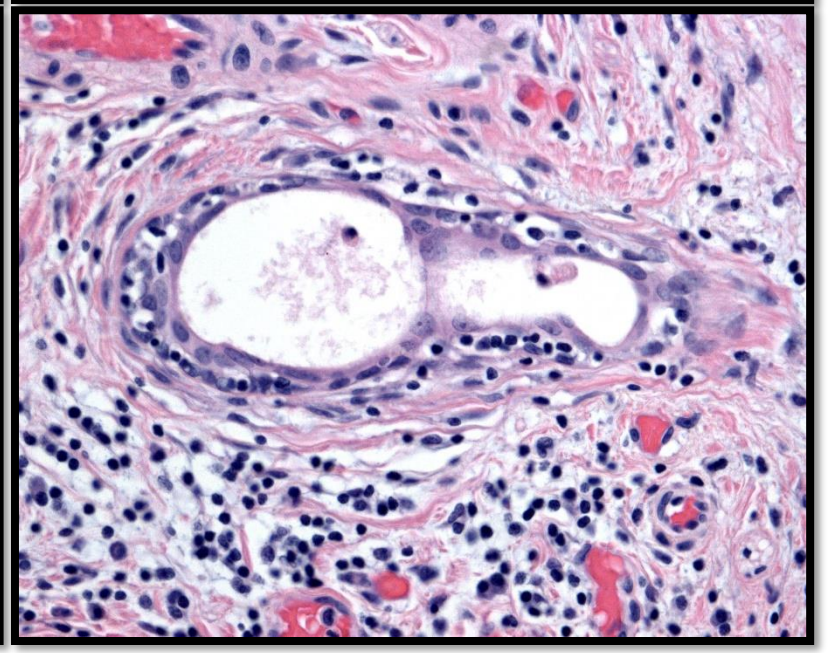




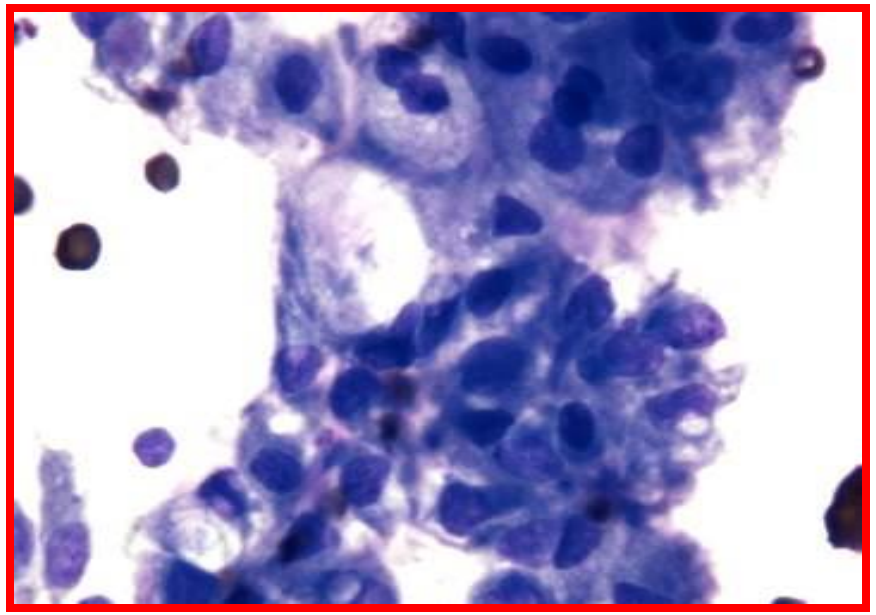
MSRSGC III – AUS

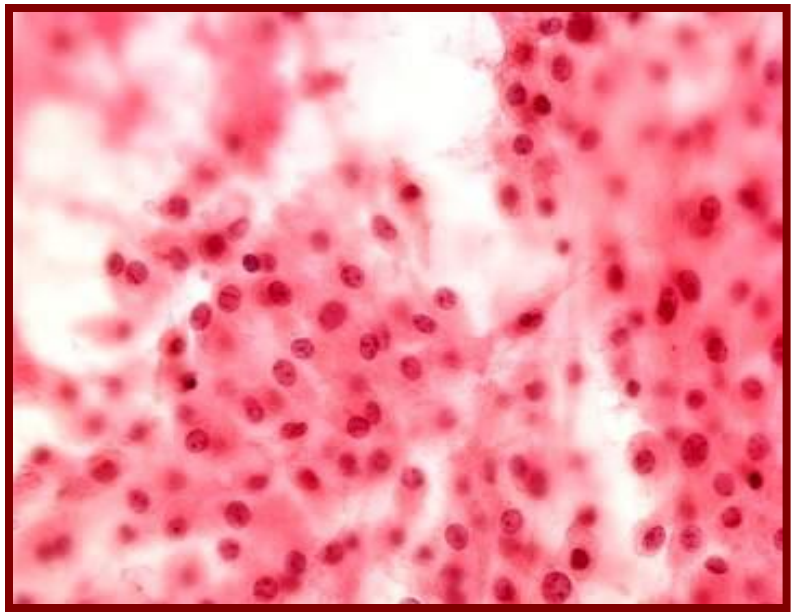
Groups of basaloid and epithelioid cells with mild nuclear atypia are present in a background of lymphocytes, see note.

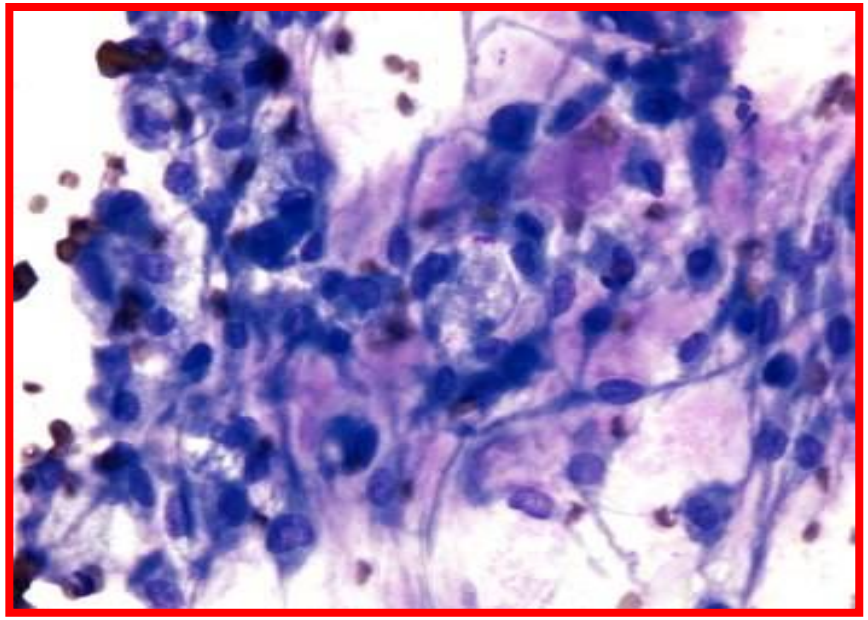
FNA Follow-up – Chronic Sialadenitis

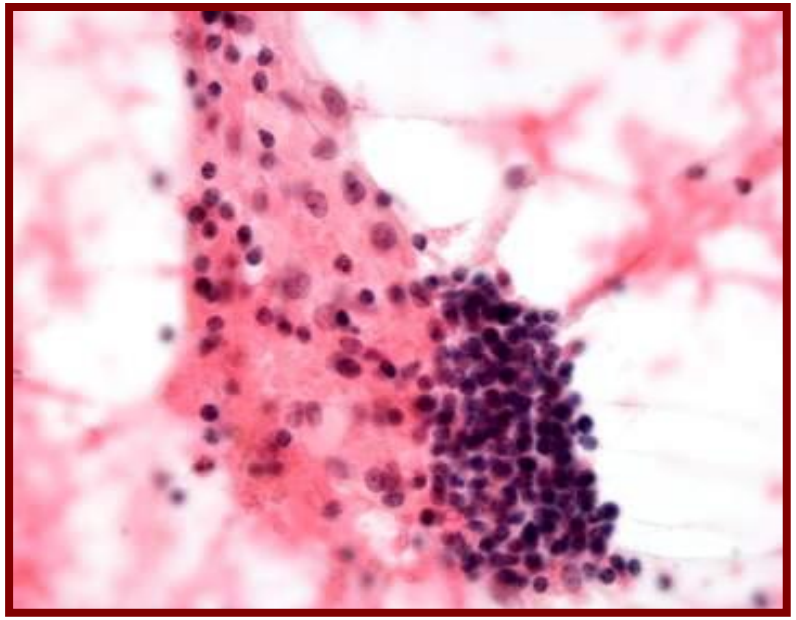







23 Year-old-man with Right Parotid Mass



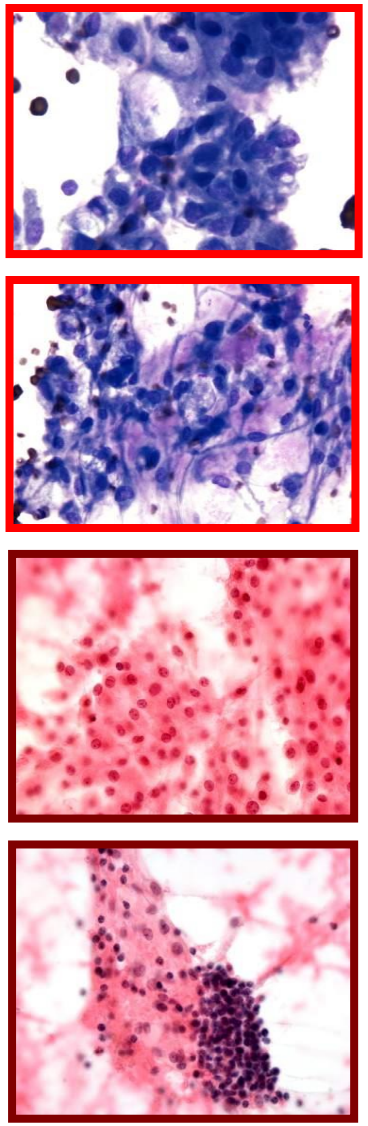


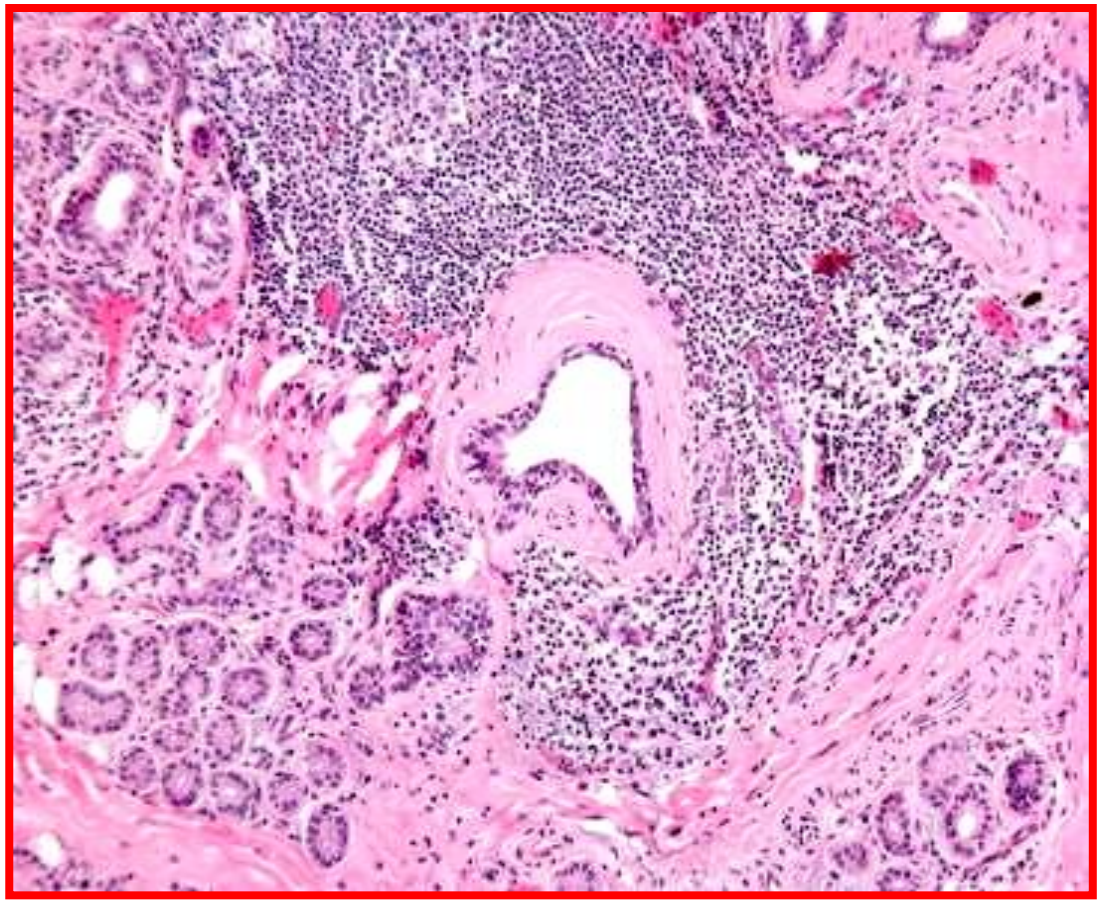


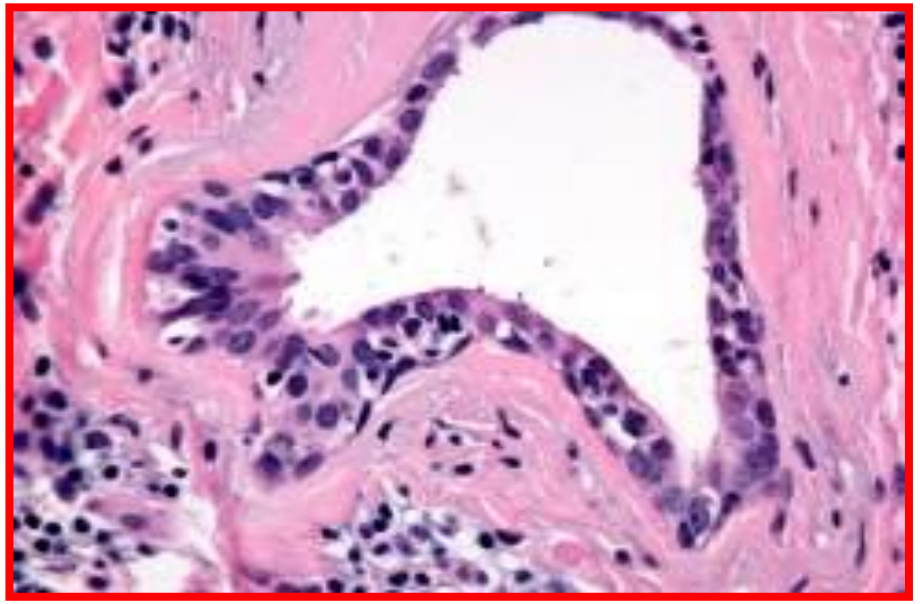


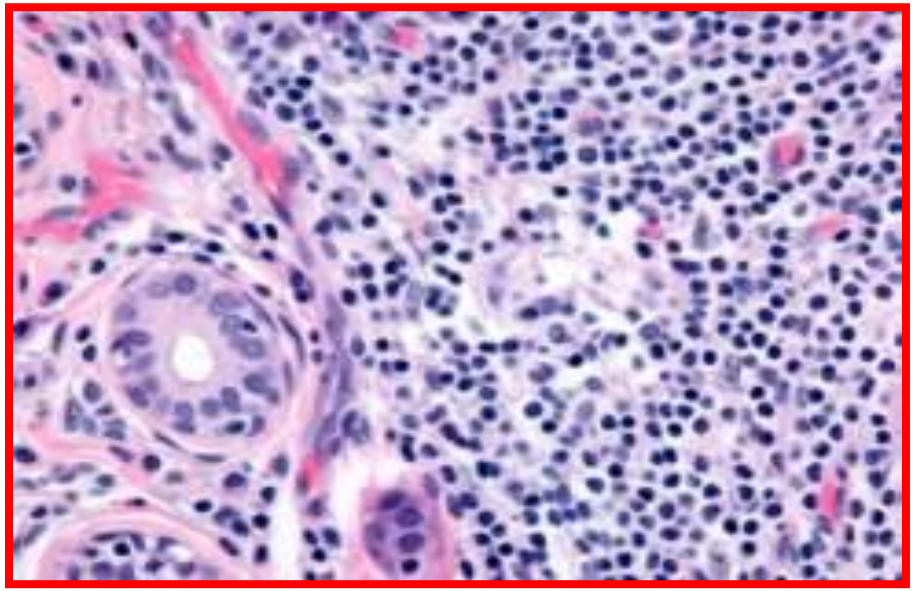
Atypical cells Suspicious for Mucoepidermoid Carcinoma – Mucicarmine stain positive on the smear

23 Year-old-man with Right Parotid Mass







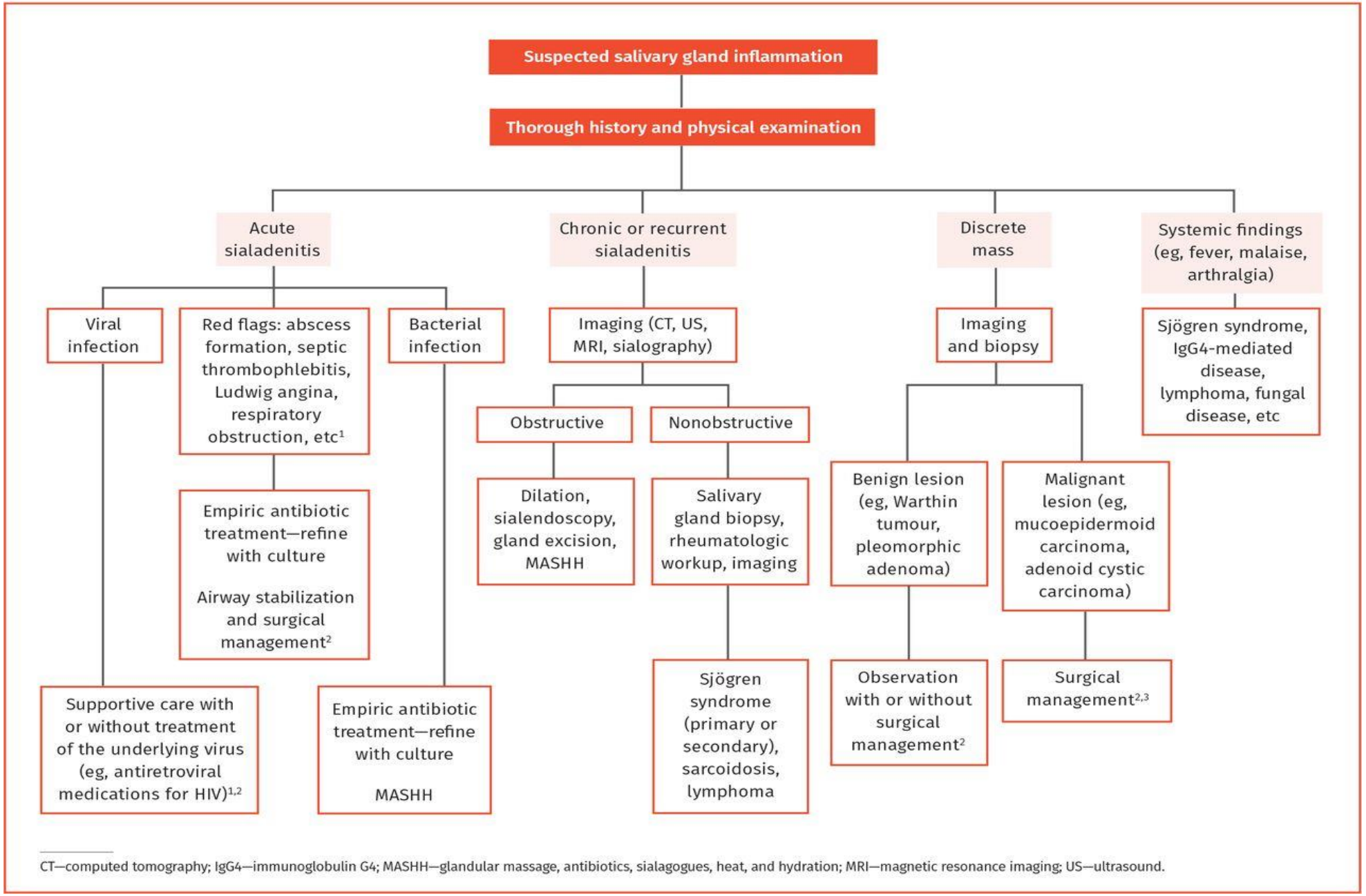


Surgical Pathology Diagnosis:
Chronic Sialadenitis

Battle of Non-Neoplastic vs. Atypical vs. Neoplasm

- **Inflammatory conditions leading to reactive / reparative atypia**
- **Cystic lesions**
- **Lesions with lymphocyte enriched infiltrate or associated lymphoid hyperplasia**

Figure 1. Algorithm for diagnosing and managing patients presenting with suspected salivary gland disorder



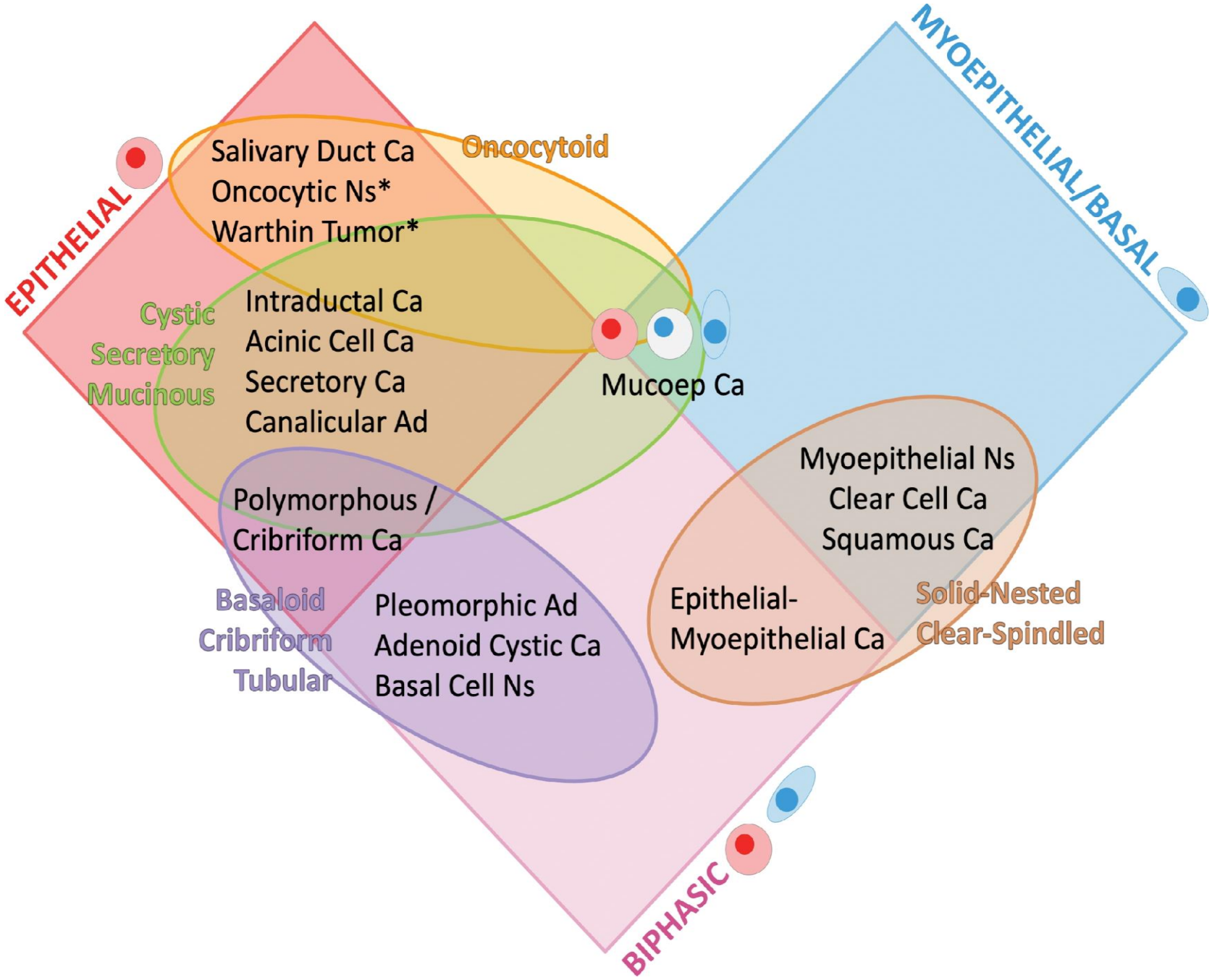
CT—computed tomography; IgG4—immunoglobulin G4; MASHH—glandular massage, antibiotics, sialagogues, heat, and hydration; MRI—magnetic resonance imaging; US—ultrasound.

Approach to sialadenitis
Jonah Moore, Matthew T.W. Simpson, Natasha Cohen, Jason A. Beyea and Timothy Phillips
Canadian Family Physician August 2023, 69 (8) 531-536; DOI: https://doi.org/10.46747/cfp.6908531

Inflammatory Disorders	
Acute sialadenitis •Viral: •Mumps •Coxsackie •Cytomegalovirus •Paramyxovirus •Bacterial: Staphylococcus aureus (acute suppurative parotitis)	**Chronic sialadenitis** ••Granulomatous: •TB •Cat scratch disease ••Actinomycosis ••Sarcoidosis ••HIV ••Abscess (parotid and submandibular) ••Recurrent subacute parotitis ••Radiation sialadenitis
Noninflammatory Enlargement	
Parotitis •Associated with alcohol cirrhosis •Diabetes mellitus •Bulimia •Malnutrition	
Obstructive Disorders	
Traumatic	•Mucocele •Ranula •Traumatic strictures of major ducts
Stones	**Mostly submandibular**
Impaction of foreign body into a duct	

- Sialolithiasis is the most common problem in the salivary gland.
- Dry mouth is associated with xerogenic medications, dehydration, exposure to radiation, and smoking.
- Infections are either bacterial or viral.
- Several systemic diseases can cause enlargement of salivary glands.

Salivary Gland Neoplasms



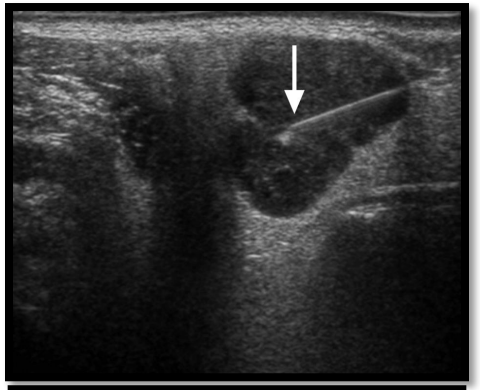
Practical immunohistochemistry in the classification of salivary gland neoplasms

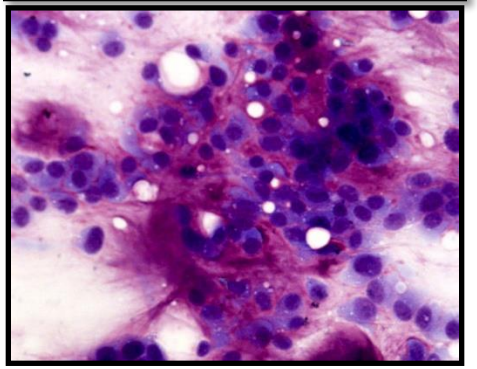
Kathleen E. Higgins and Nicole A. Cipriani

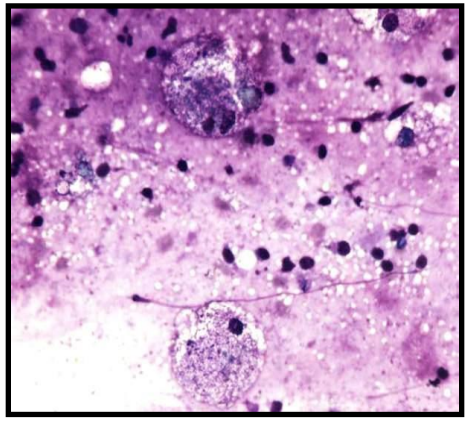
Seminars in Diagnostic Pathology, 2022-01-01, Volume 39, Issue 1, Pages 17-28

Salivary Gland Tumors: Pattern Recognition

- ***Architecture – cytology-radiology correlation***
  - Cystic (includes microcystic), solid, cribriform, papillary, acinar, tubular, trabecular
- ***Cell type***
  - Ductal cells, myoepithelial cell and variants
- ***Stroma and basement membrane type material***
  - Association with lesional cells
- ***Background***
  - Mucin, inflammatory cells, macrophages







Benign Mixed Tumor (BMT) / Pleomorphic Adenoma (PA)

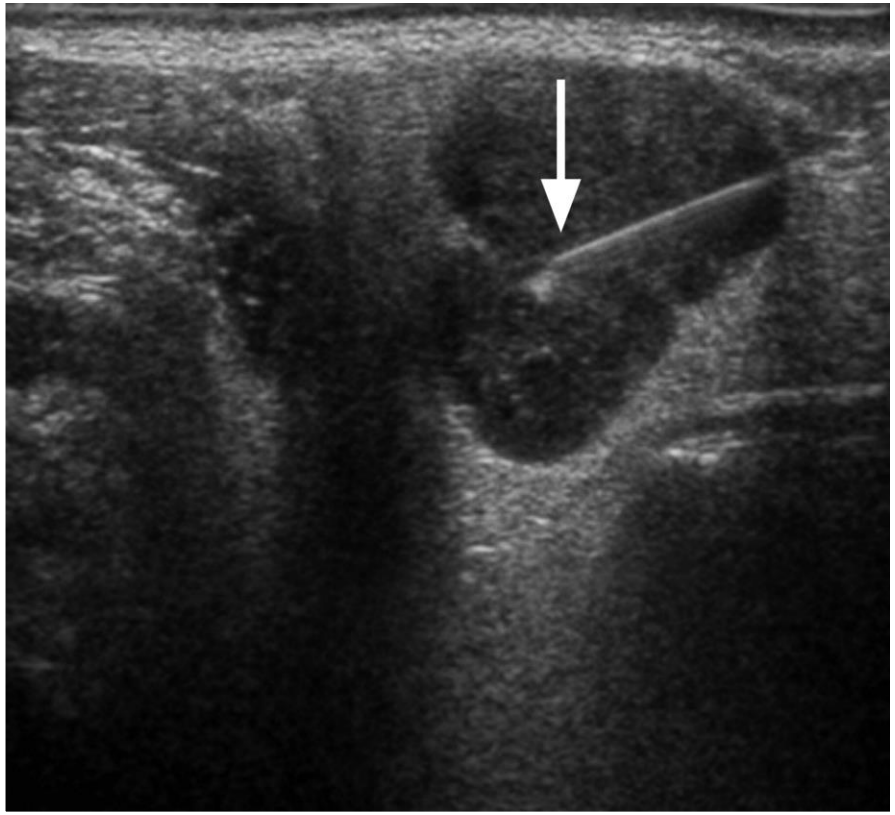
Clinical Features

- Most common tumor of salivary glands in children and adults
- Two-thirds of parotid tumors
- 50% of all salivary gland tumors
- PE: Circumscribed; firm; rubbery

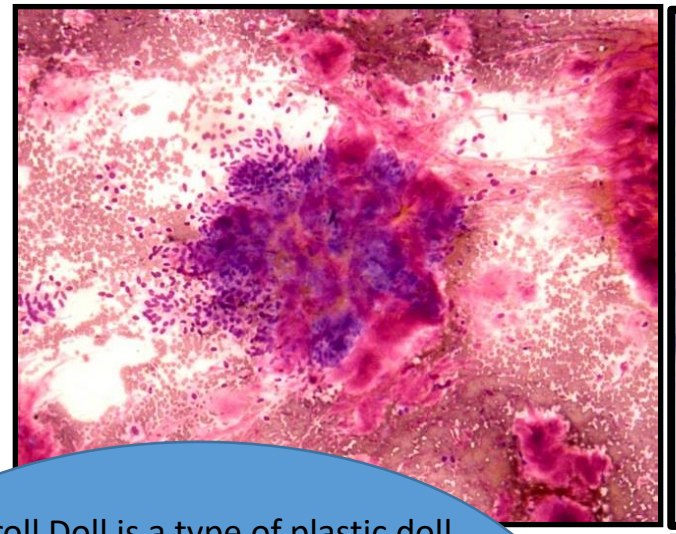
Cytomorphology

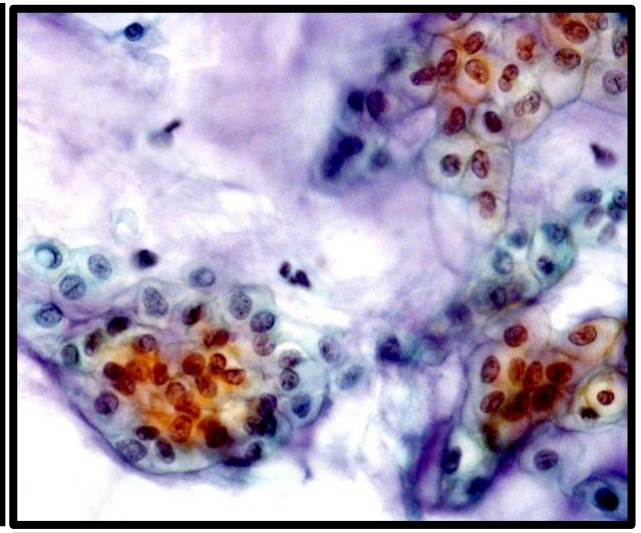
- Cells
  - ***Epithelial cells*** arranged in cohesive, honeycomb groups
  - ***Myoepithelial cells*** arranged singly or loosely arranged groups
  - ***Plasmacytoid, epithelioid, spindled or clear cells***
- Chondromyxoid matrix
  - ***Fibrillar with frayed edges***
  - ***Embedded myoepithelial cells***
  - ***Surrounding individual tumor cells***

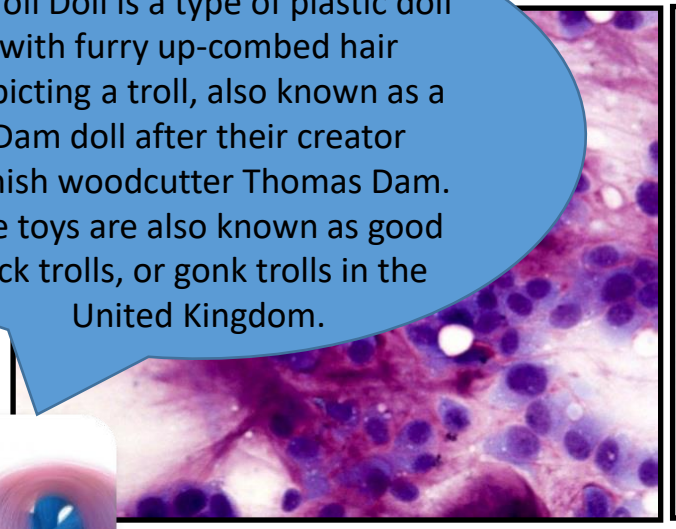
The Classic Case of BMT / PA

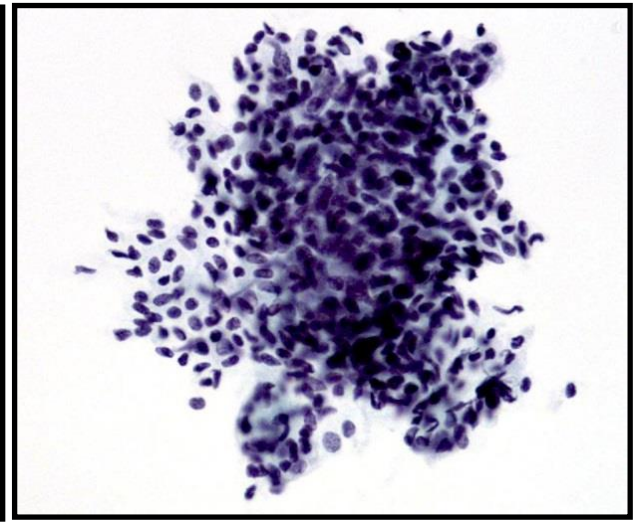


Sharma G et al. Radiology 2011;259:471-478 2011 by Radiological Society of North America



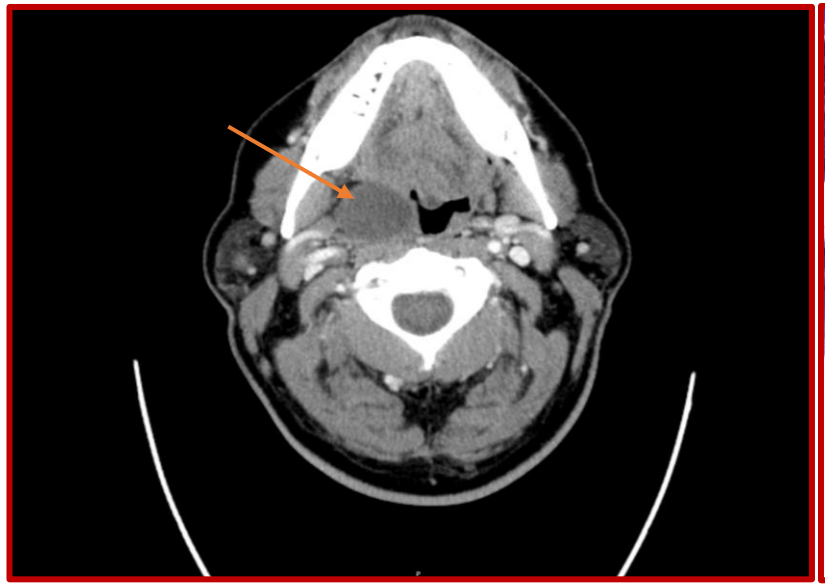


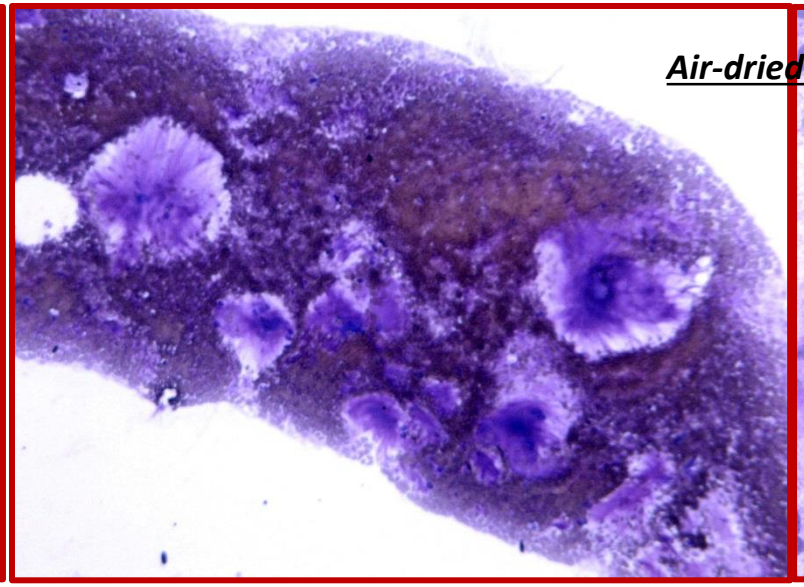


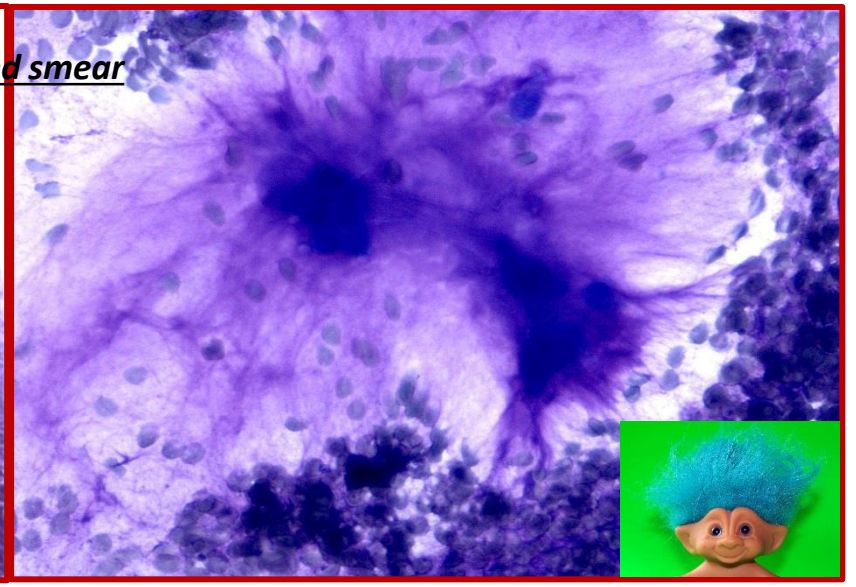


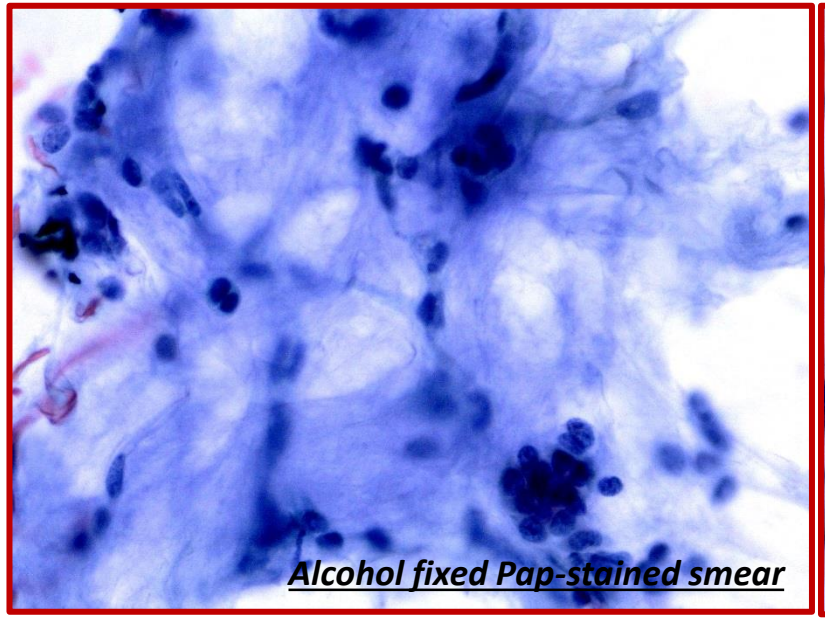
A Troll Doll is a type of plastic doll with furry up-combed hair depicting a troll, also known as a Dam doll after their creator Danish woodcutter Thomas Dam. The toys are also known as good luck trolls, or gonk trolls in the United Kingdom.

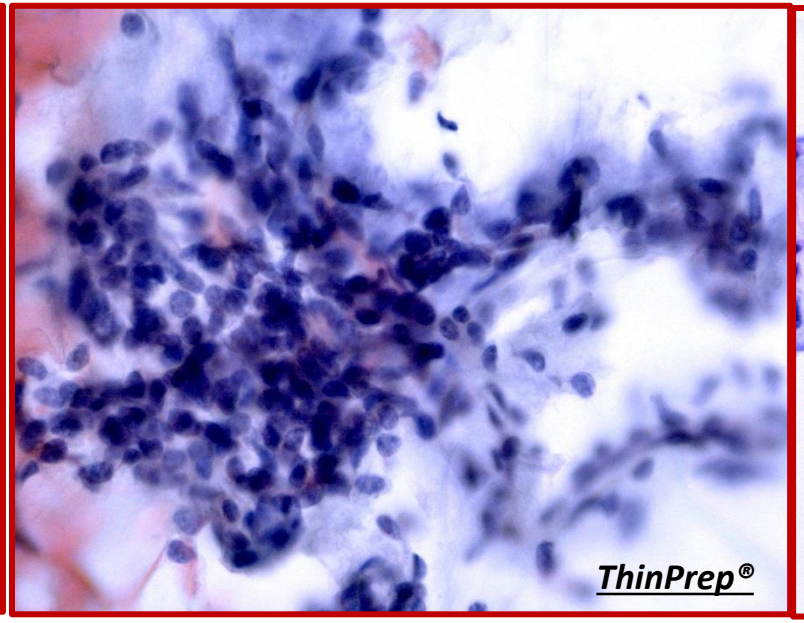
Parapharyngeal mass. Benign Mixed Tumor

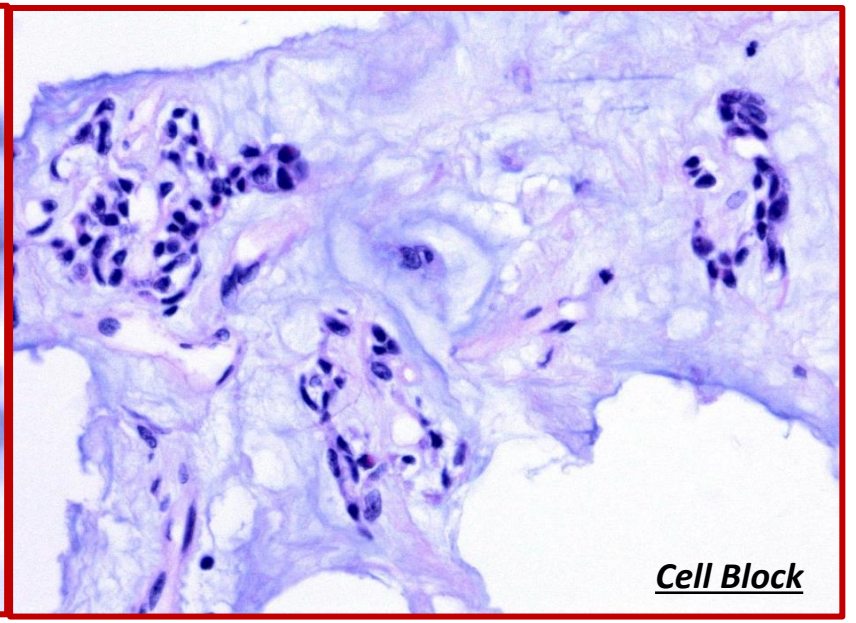




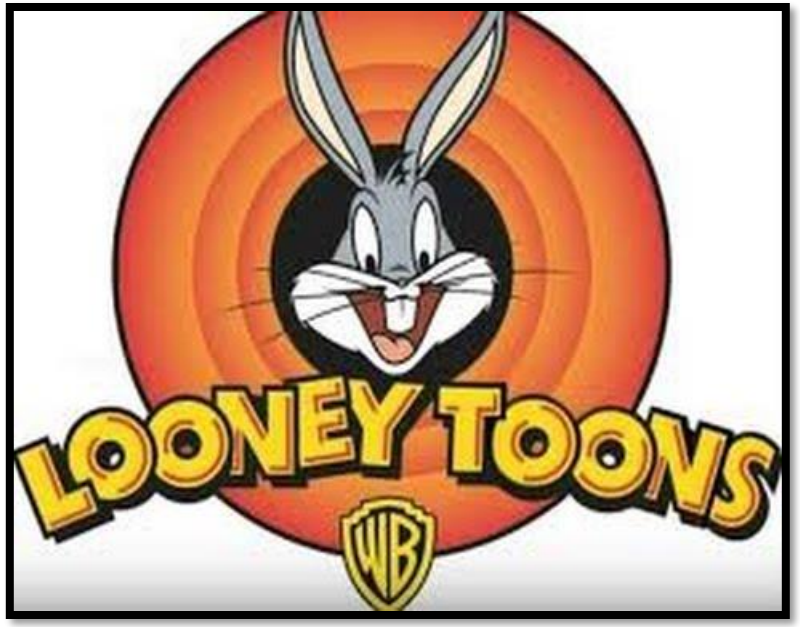






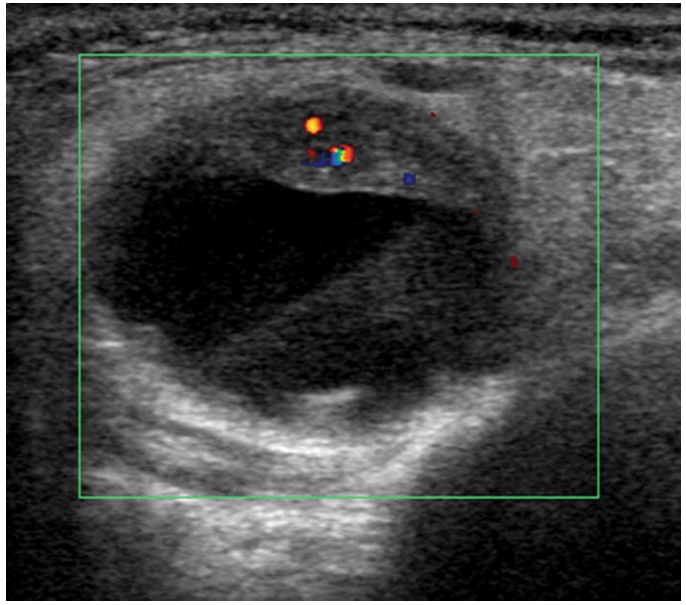


Not so Classic Cases

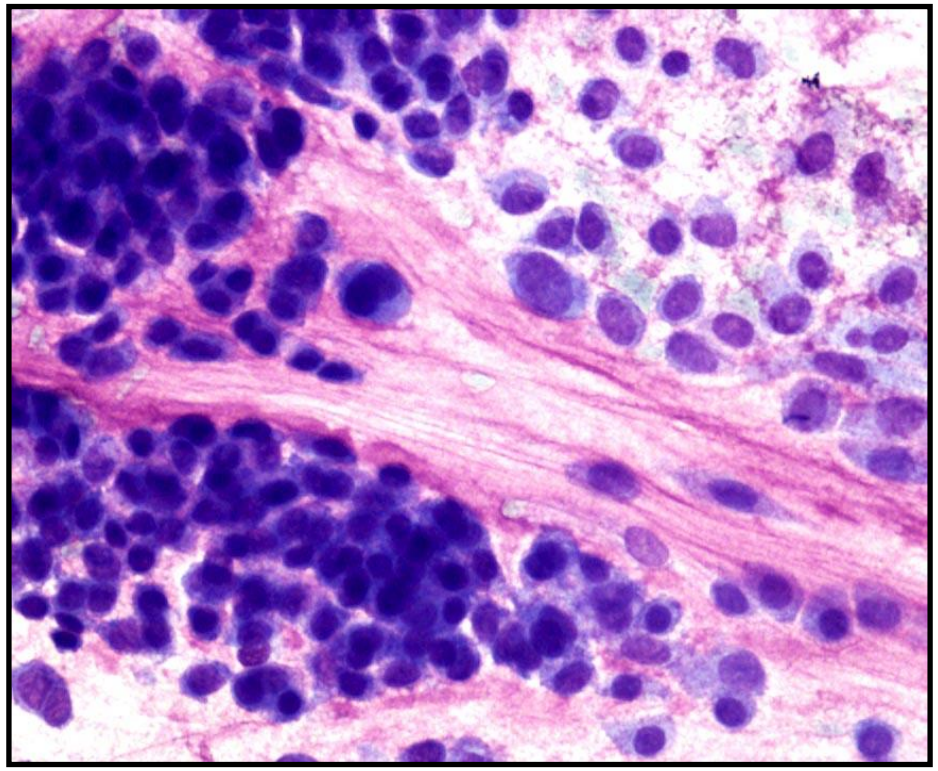


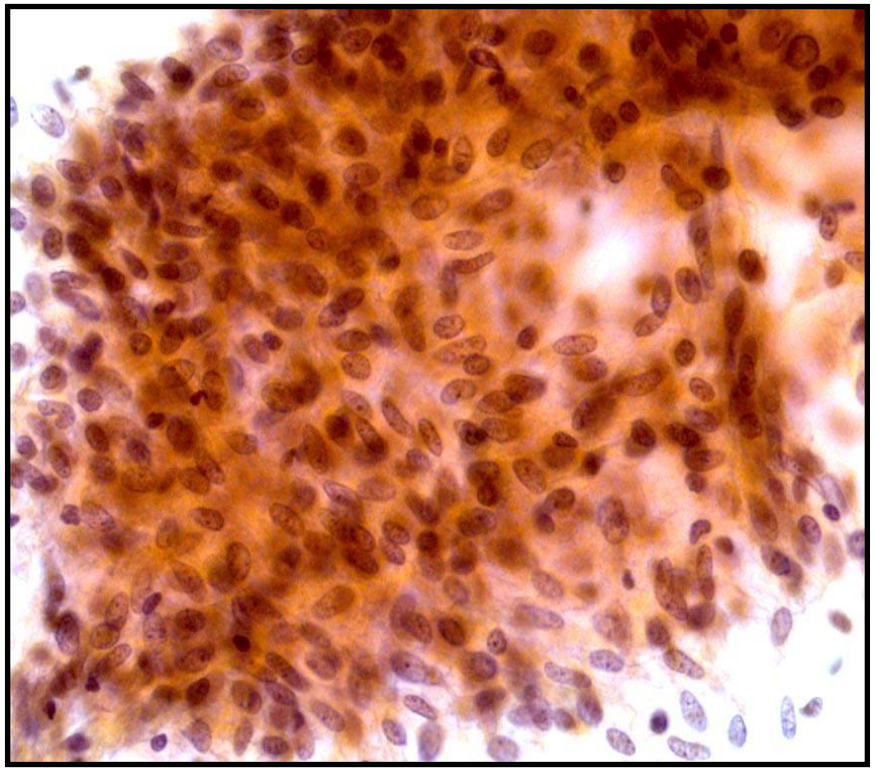
vs.

BMT w Cystic Change

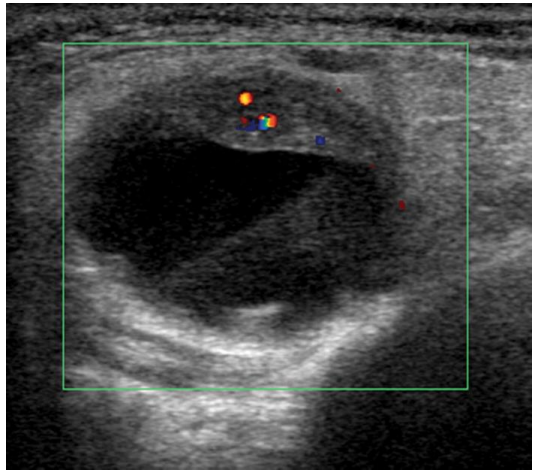


Sharma G et al. Radiology 2011;259:471-478

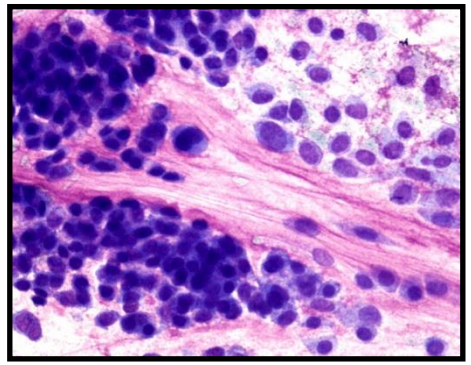


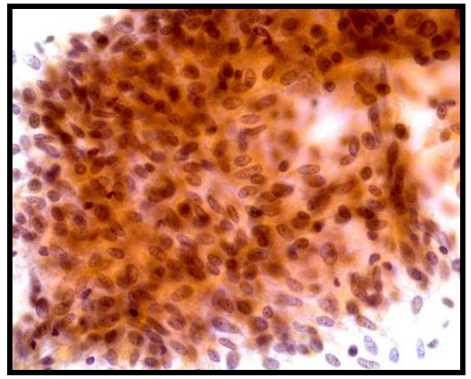


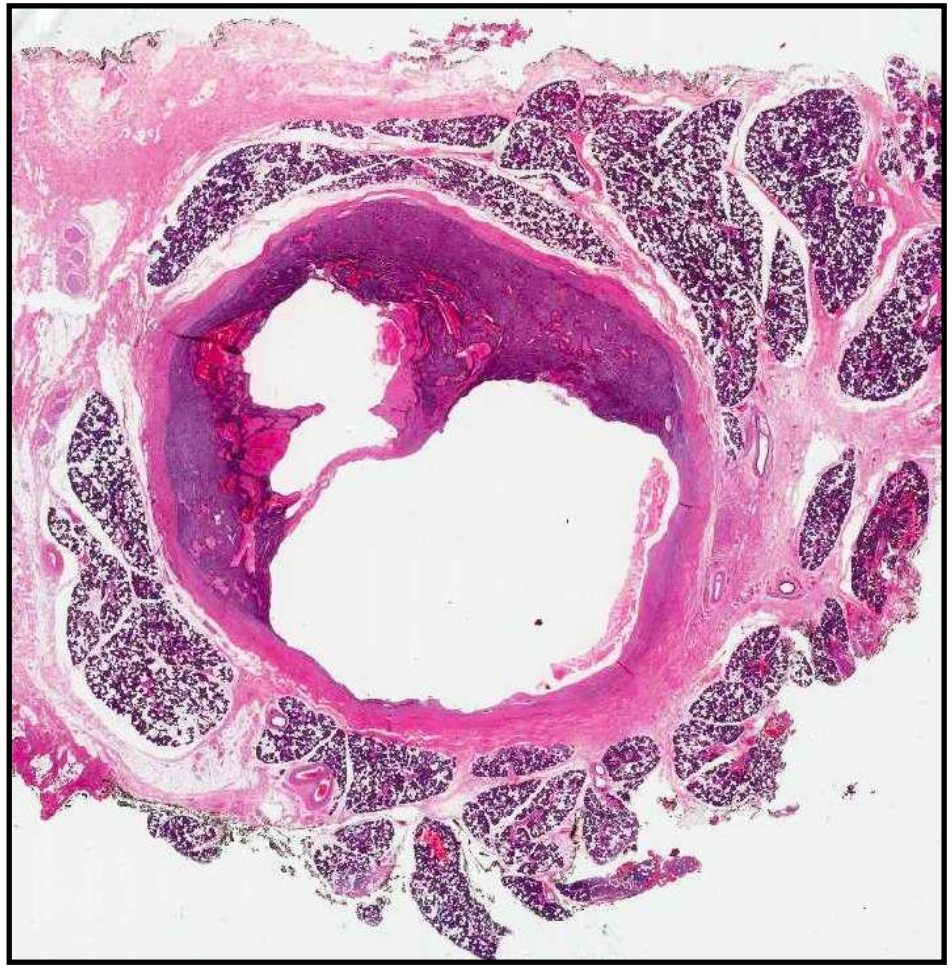
BMT w Cystic Change

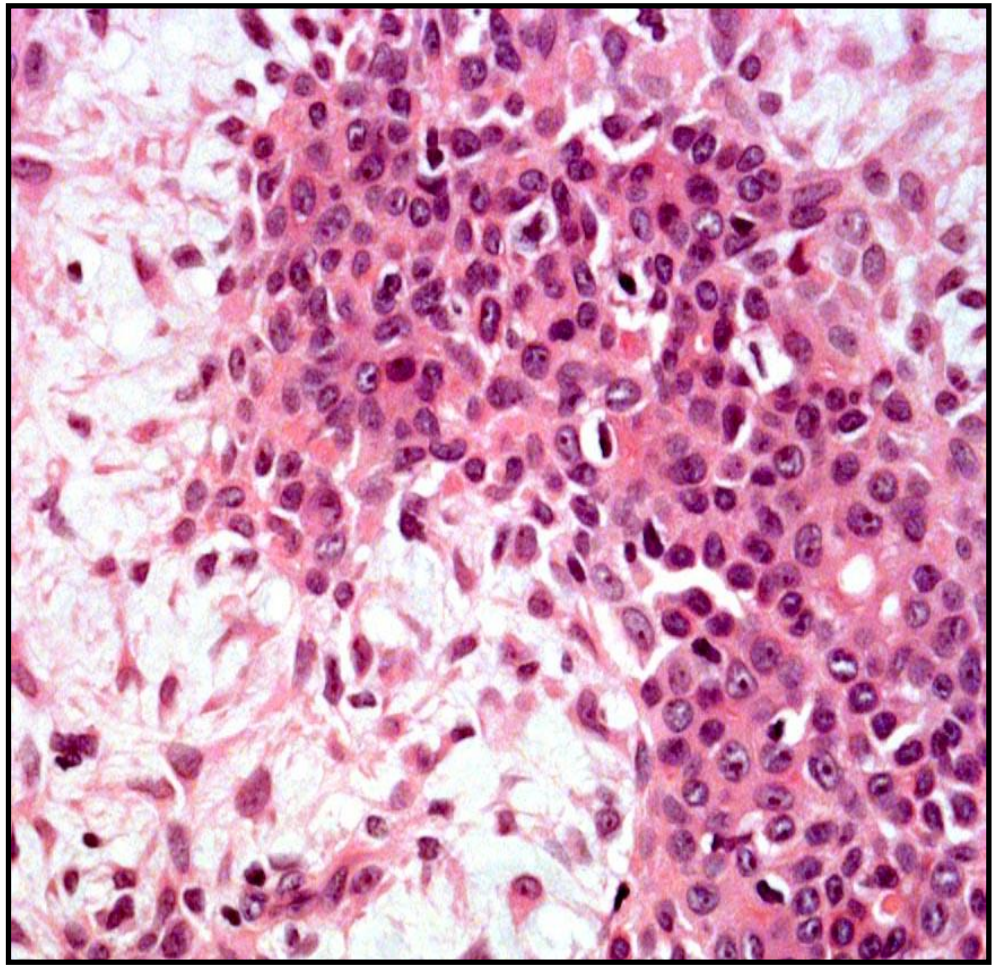


Sharma G et al. Radiology 2011;259:471-478

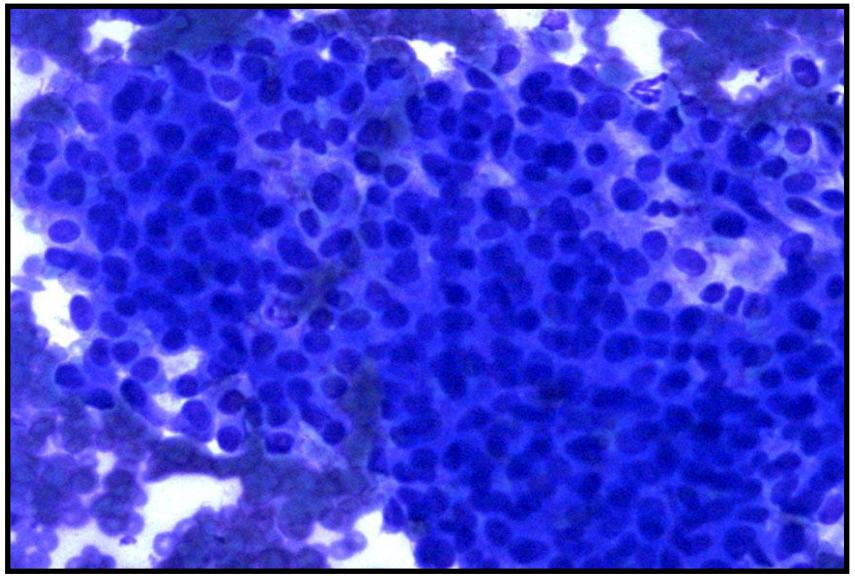


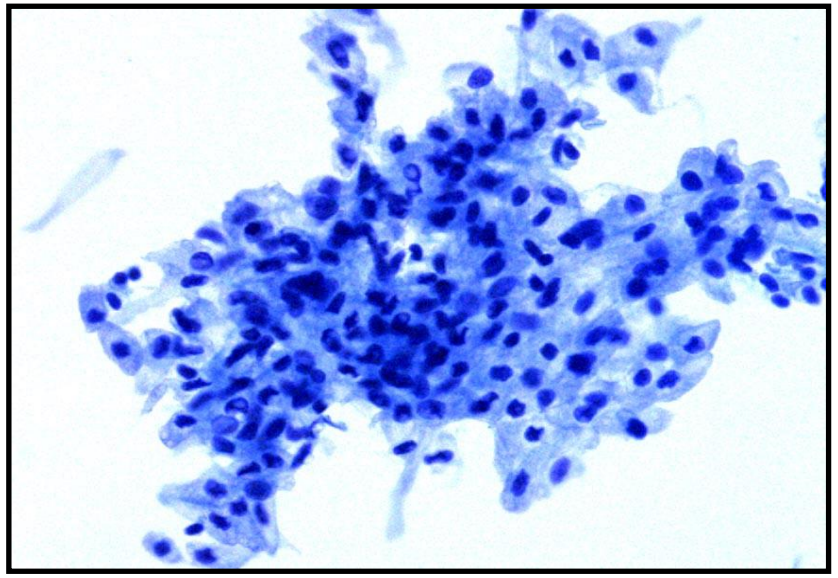


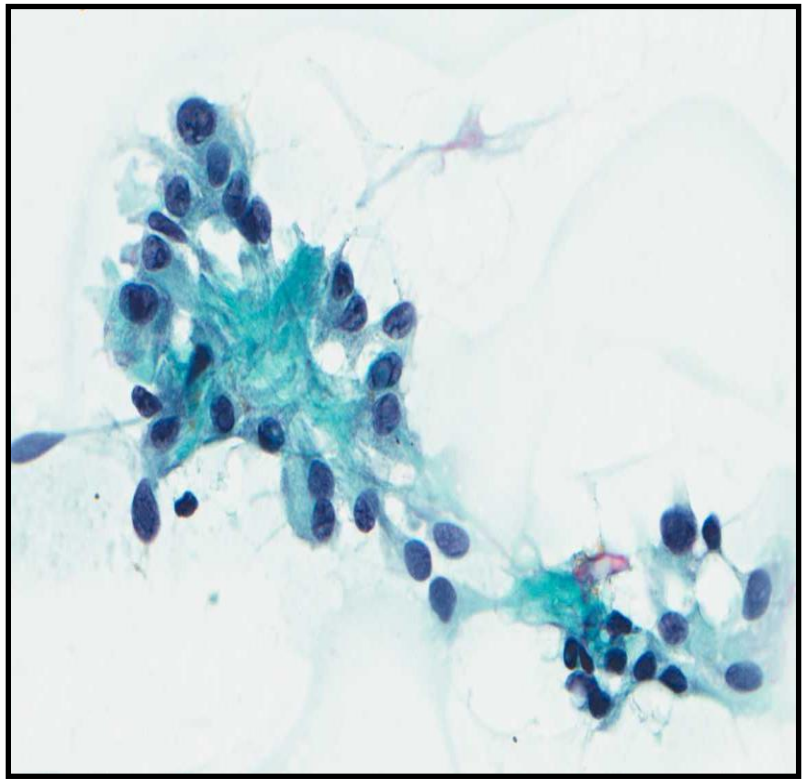


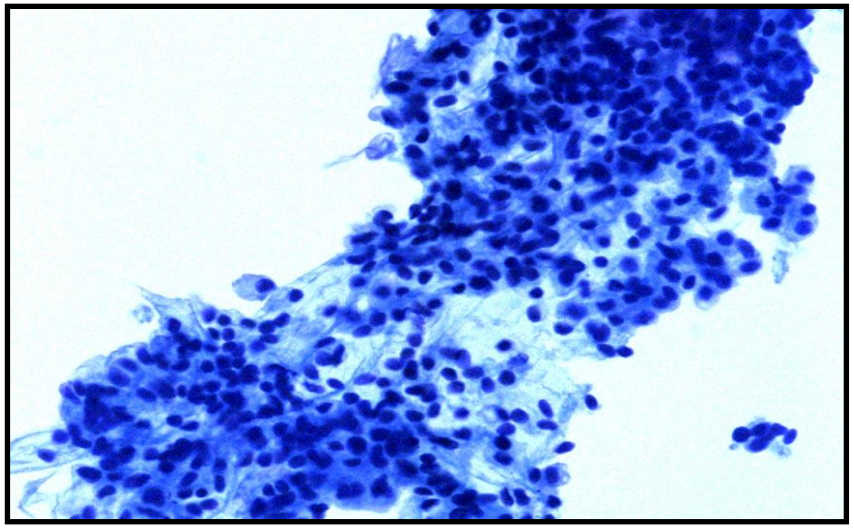


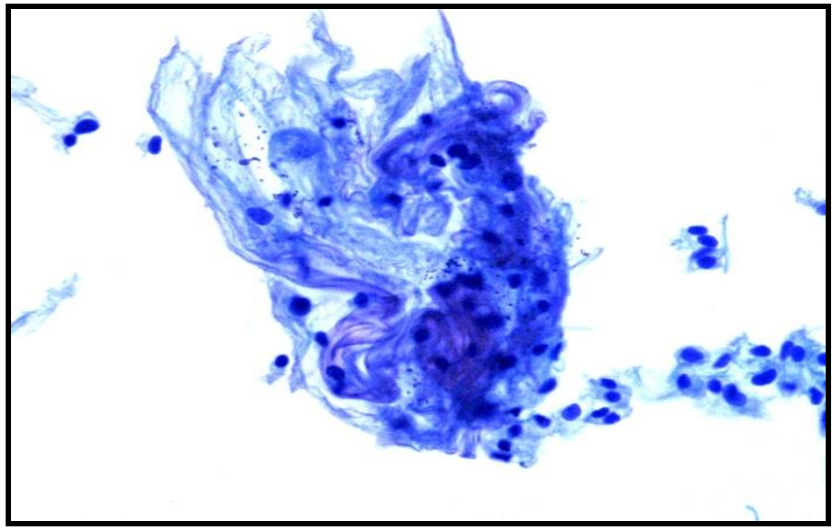
Cellular BMT with Increased Plasmacytoid Cells



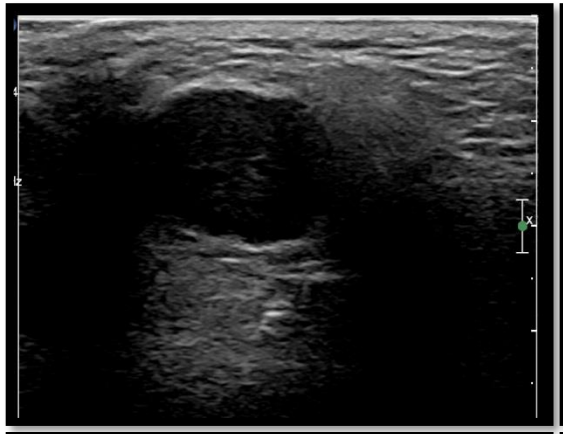
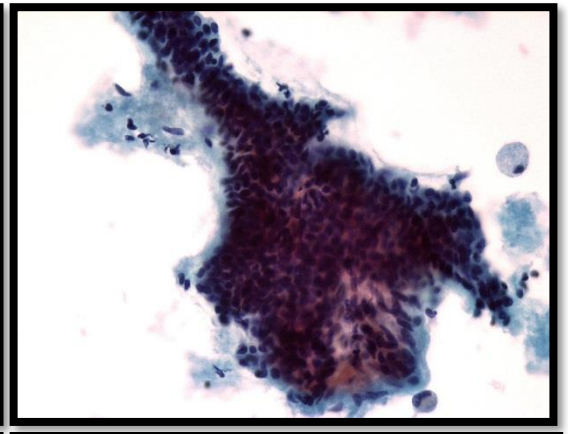
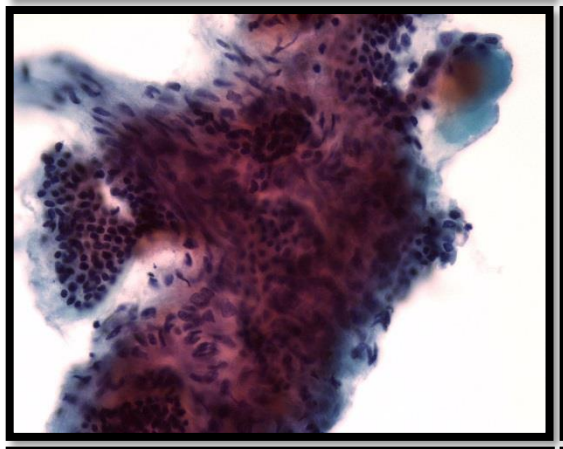
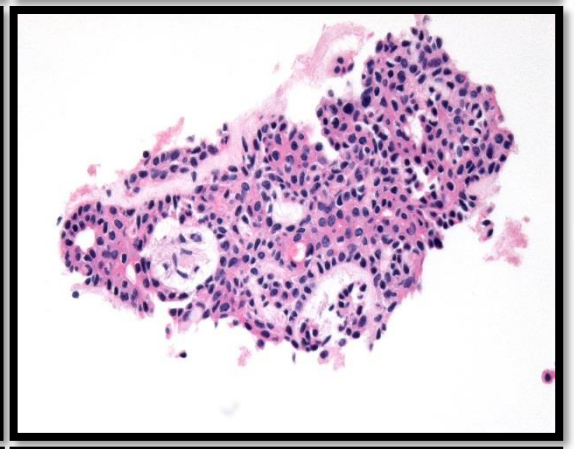
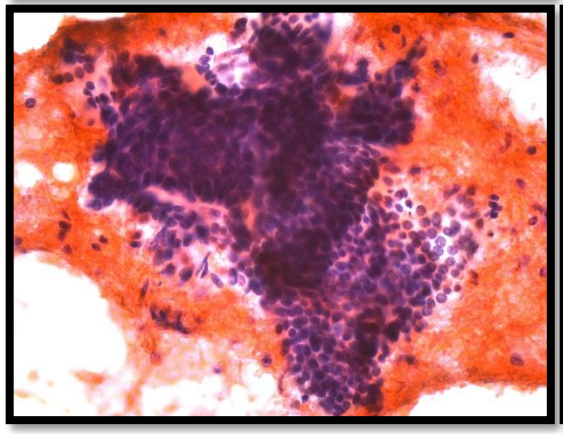
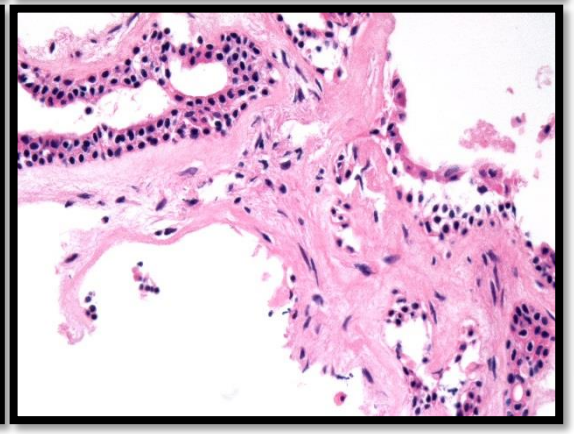
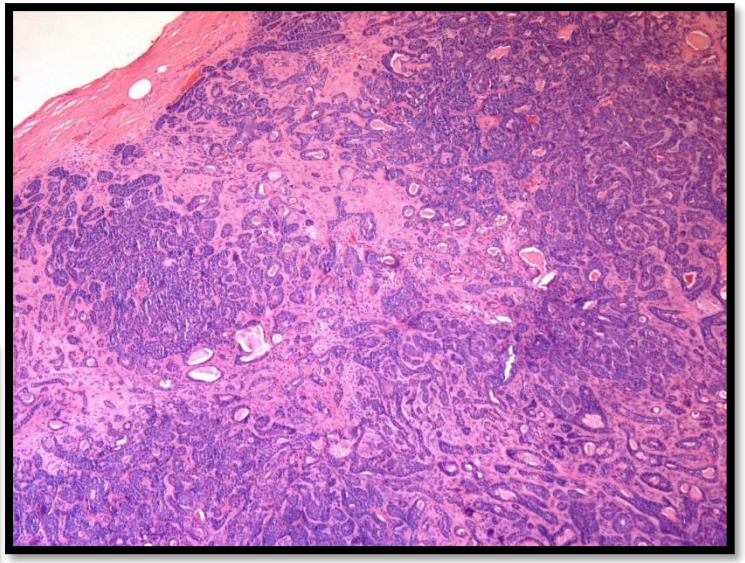
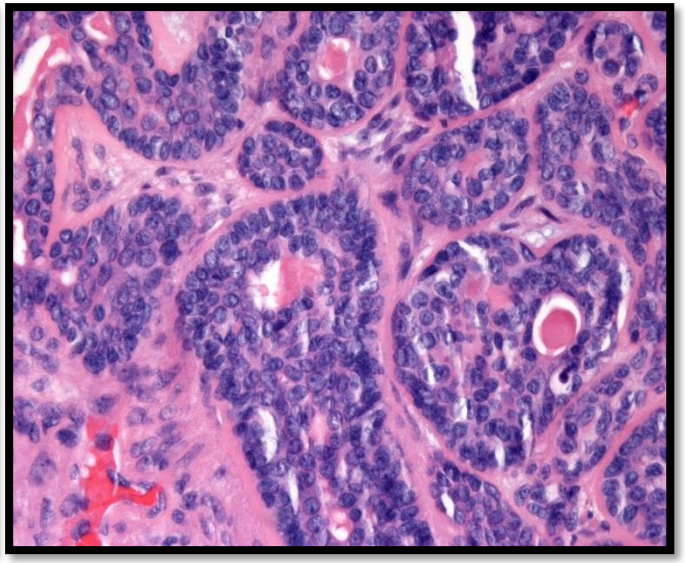
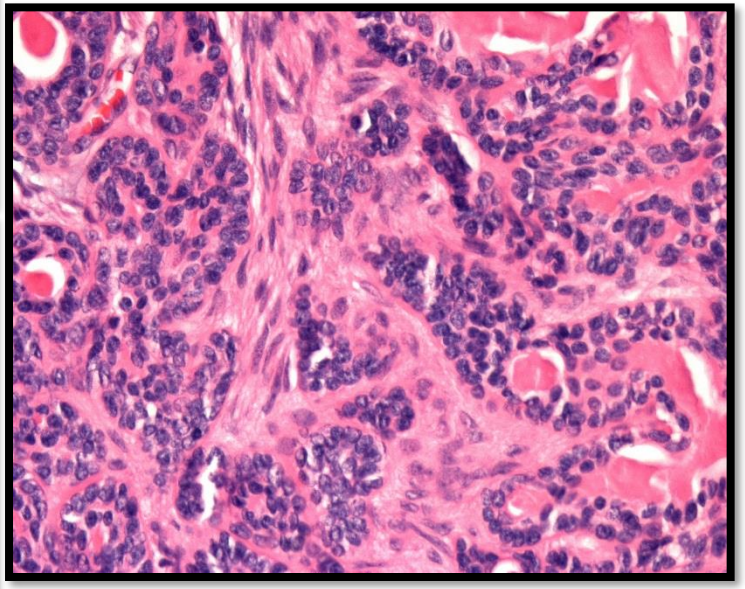
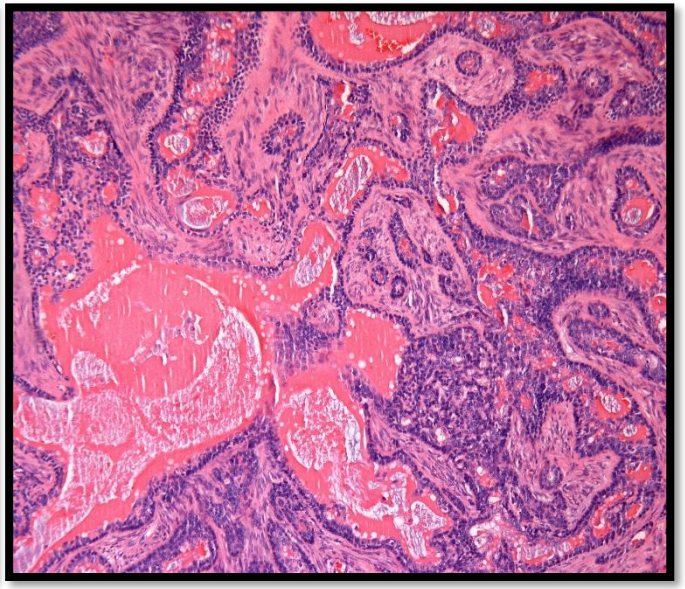




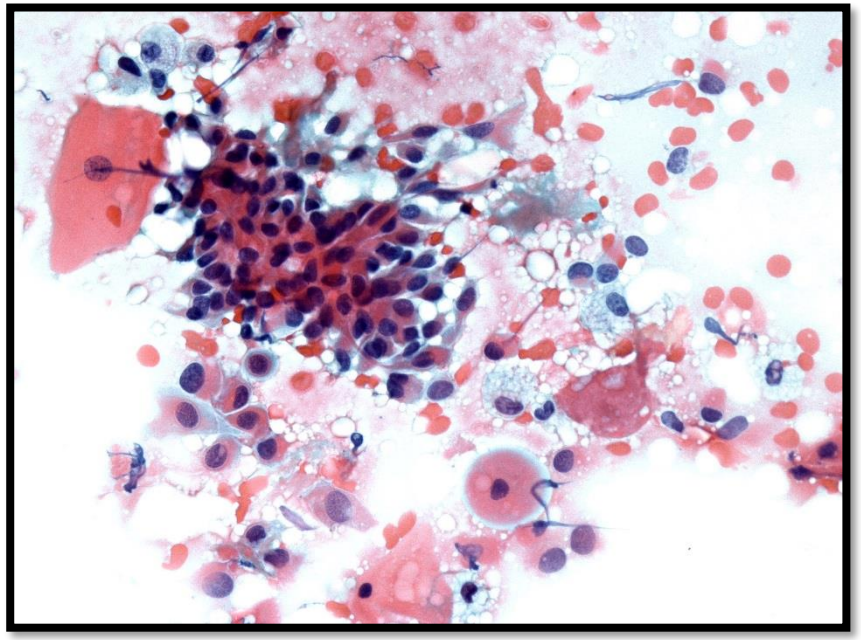


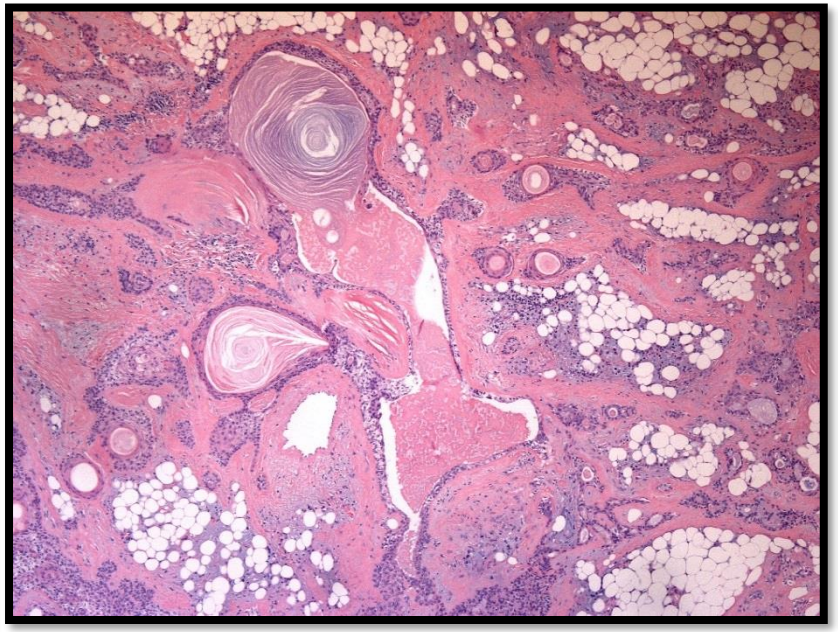


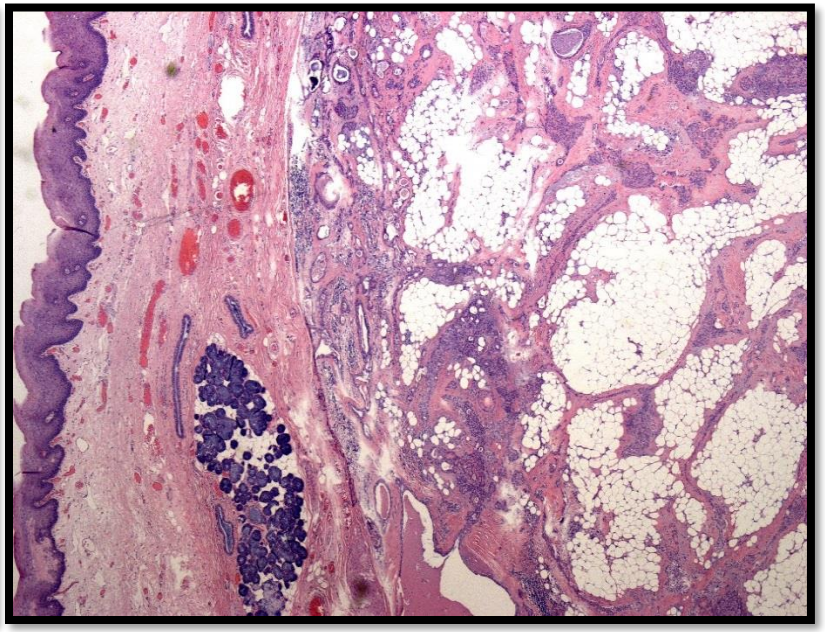
"SUMP" with a Differential Including Cellular BMT

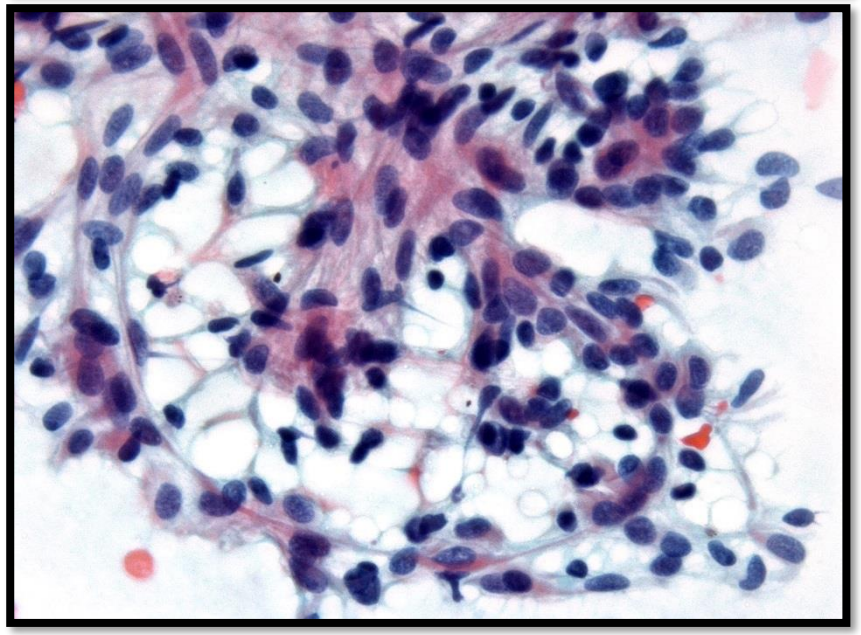











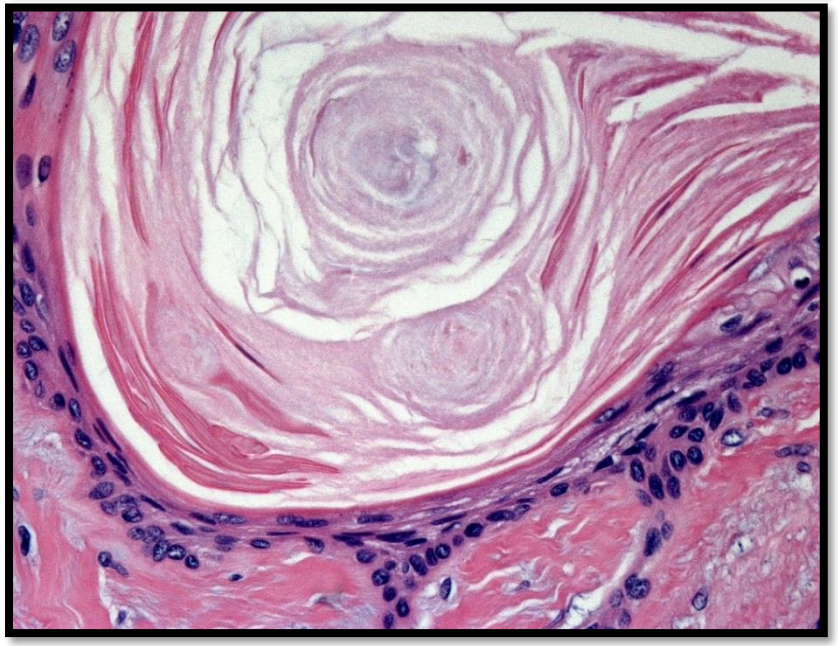
Pleomorphic Adenoma w Extensive Squamous & Lipomatous Metaplasia

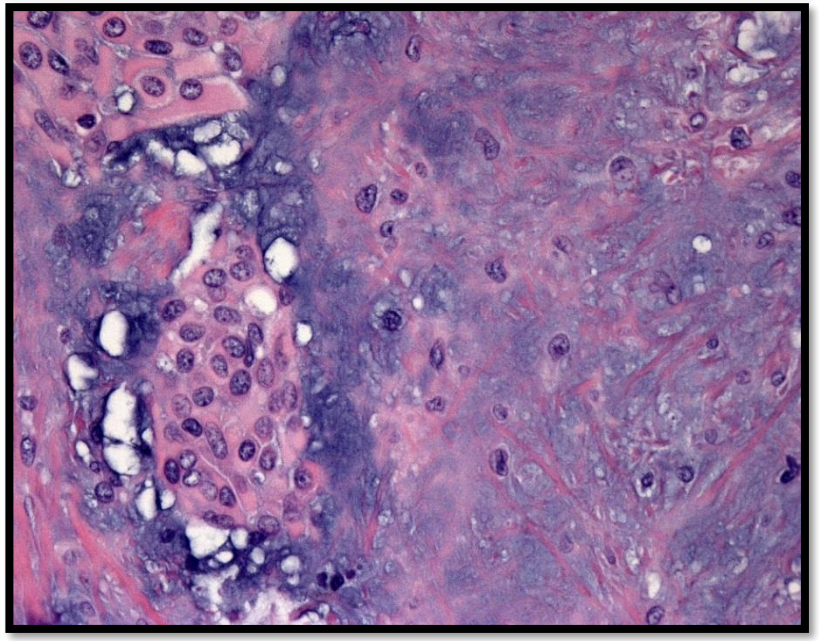




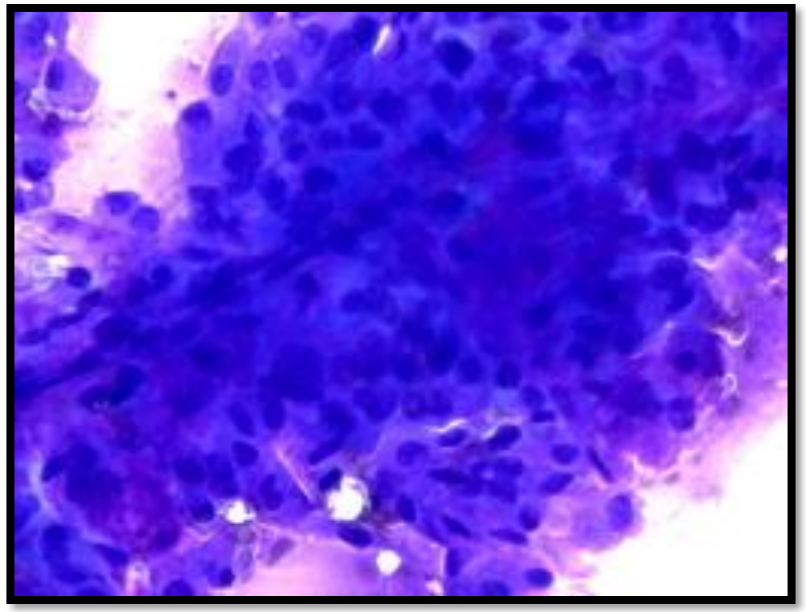


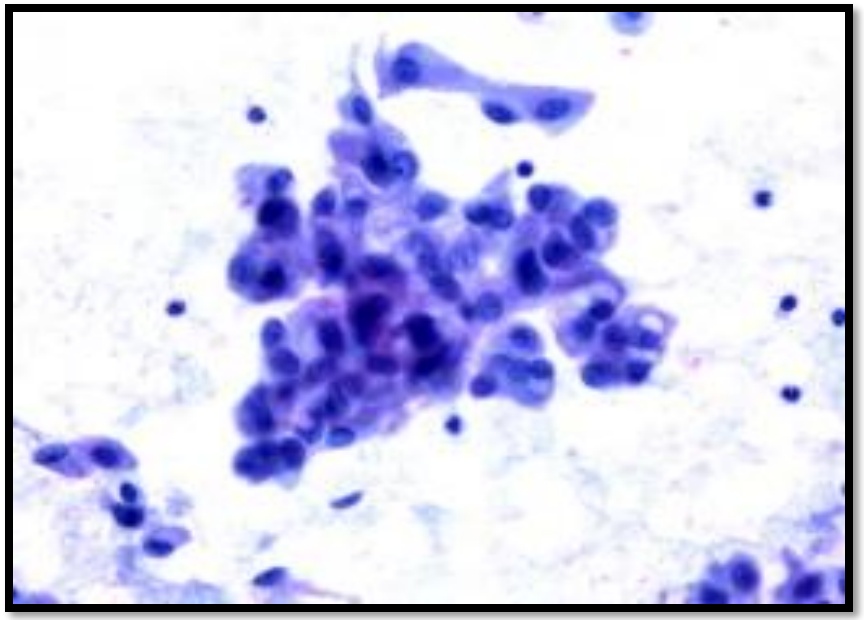


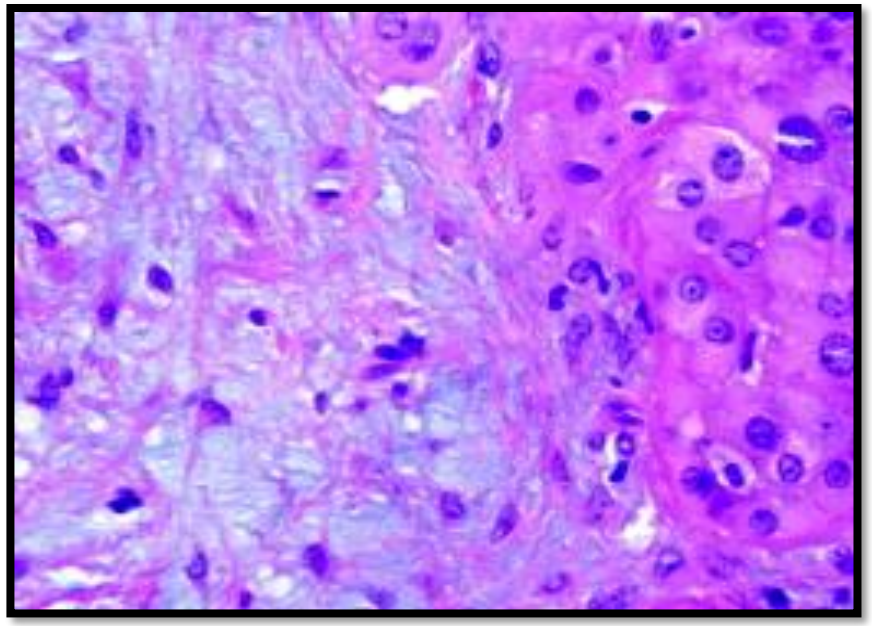


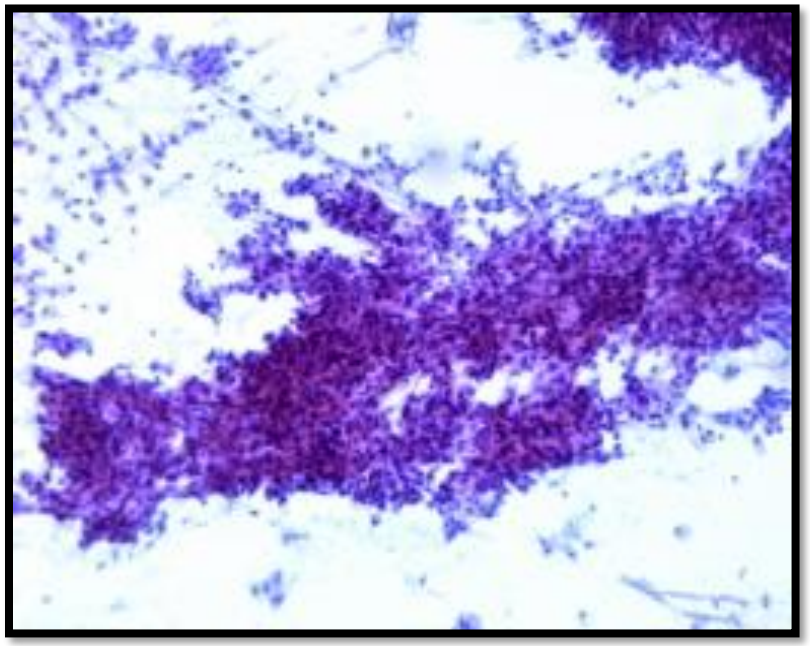


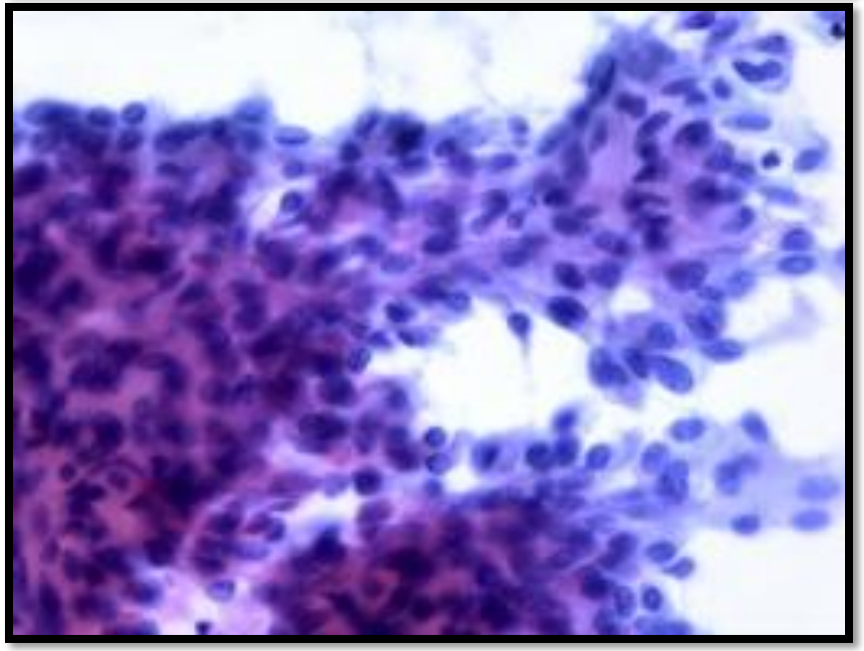
Oncocytic – Pleomorphic Adenoma

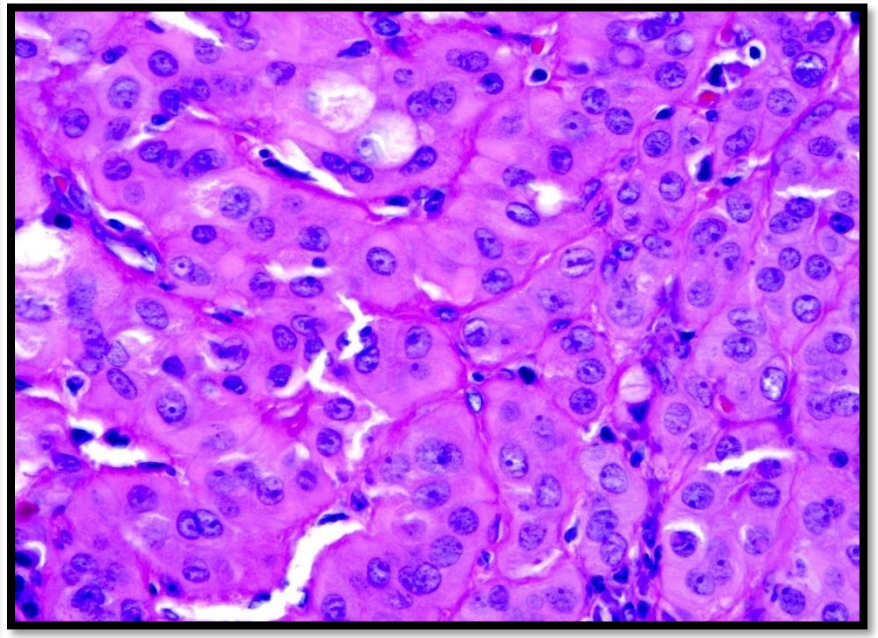






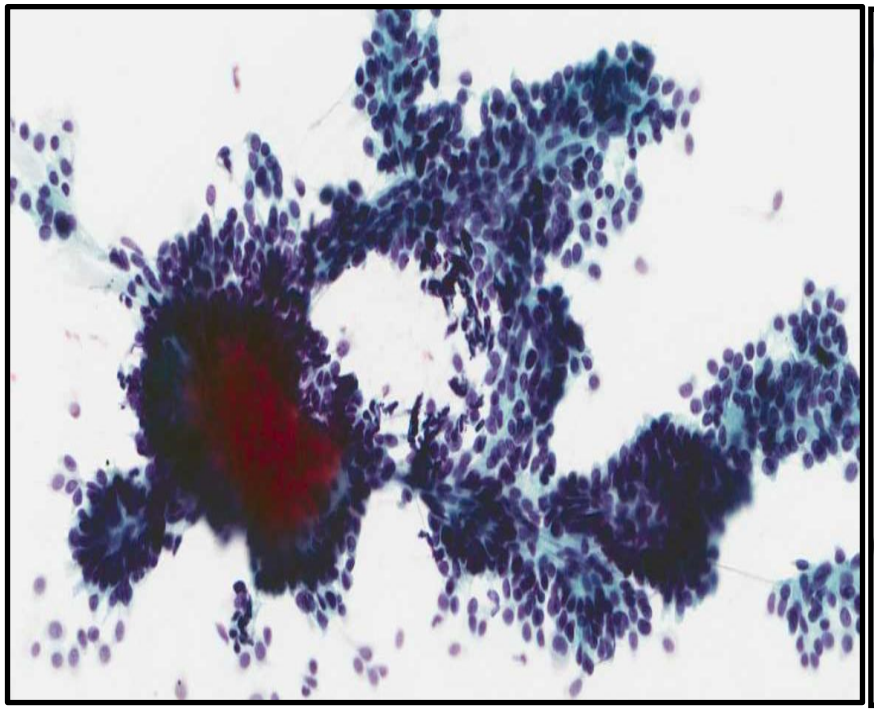


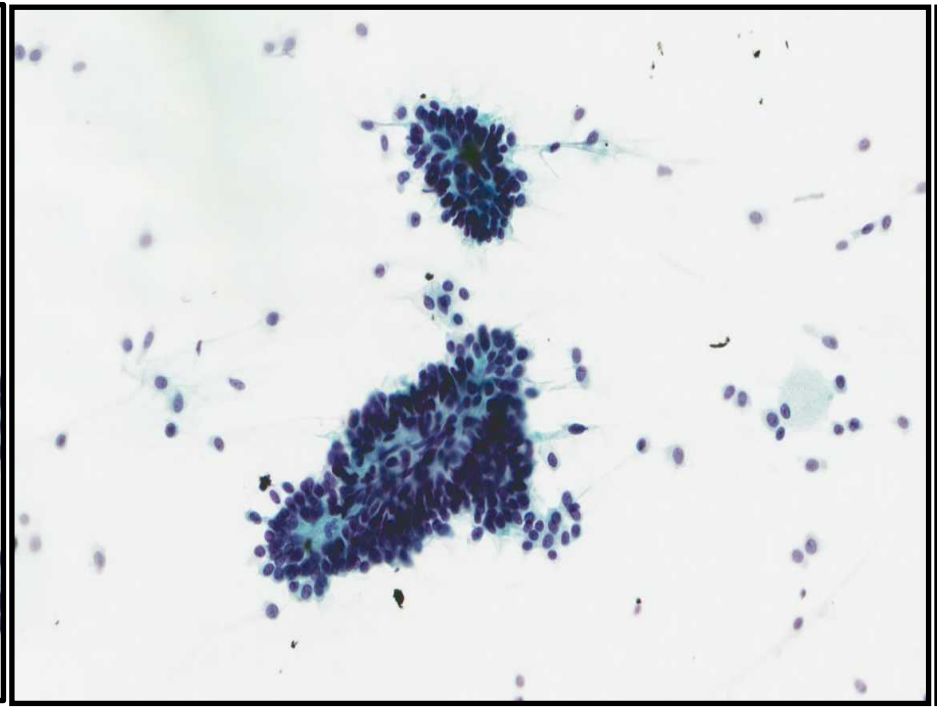


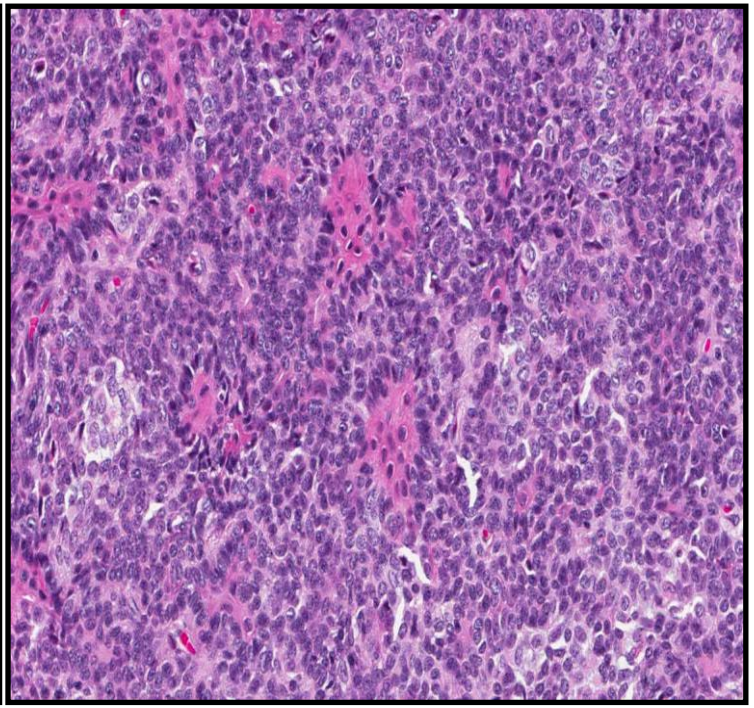


Pleomorphic Adenoma Mimicking Other Salivary Gland Tumors

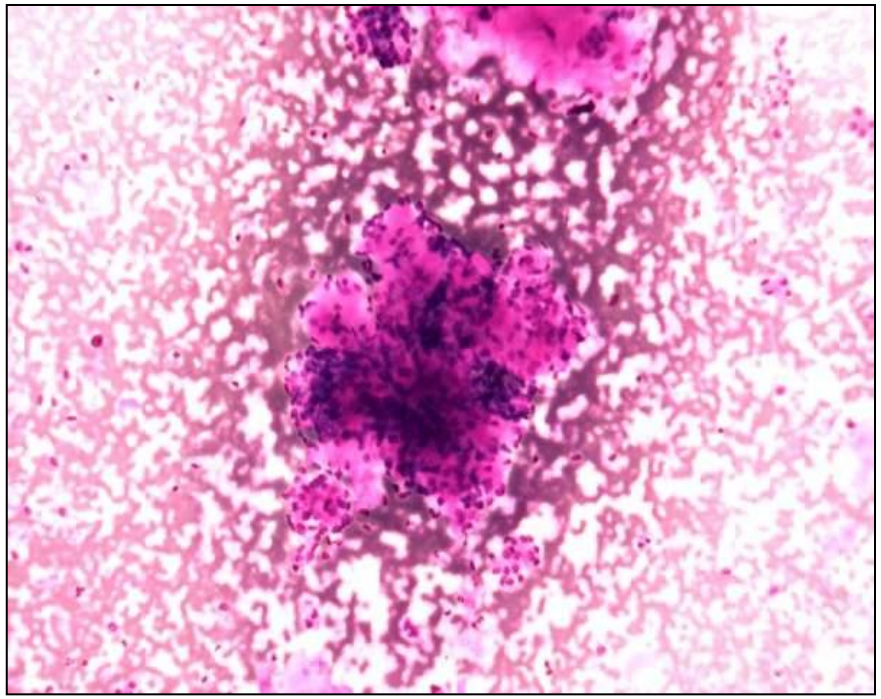
Cellular BMT with Stromal Cores Mimicking Basaloid Neoplasms

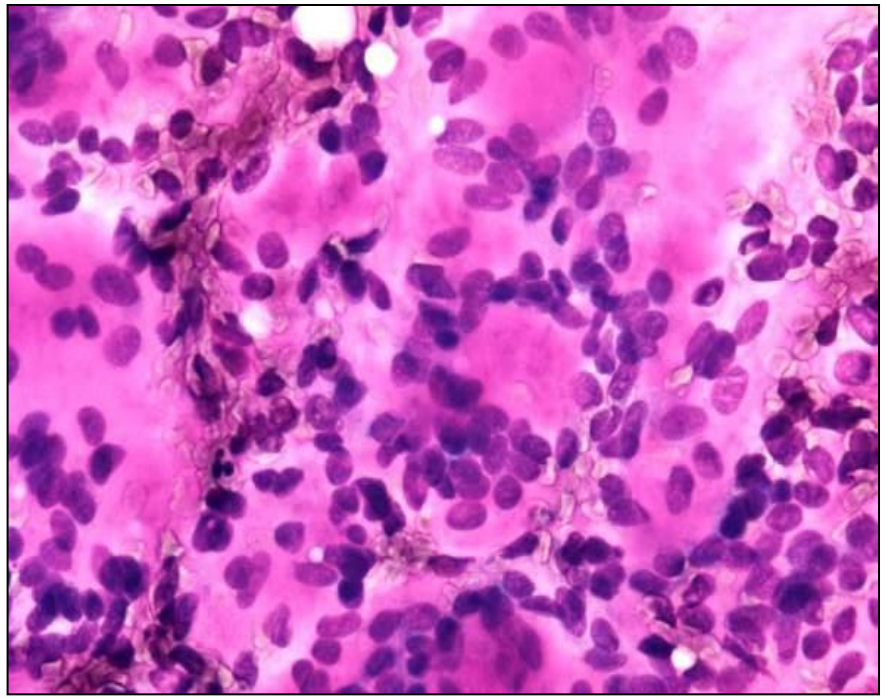


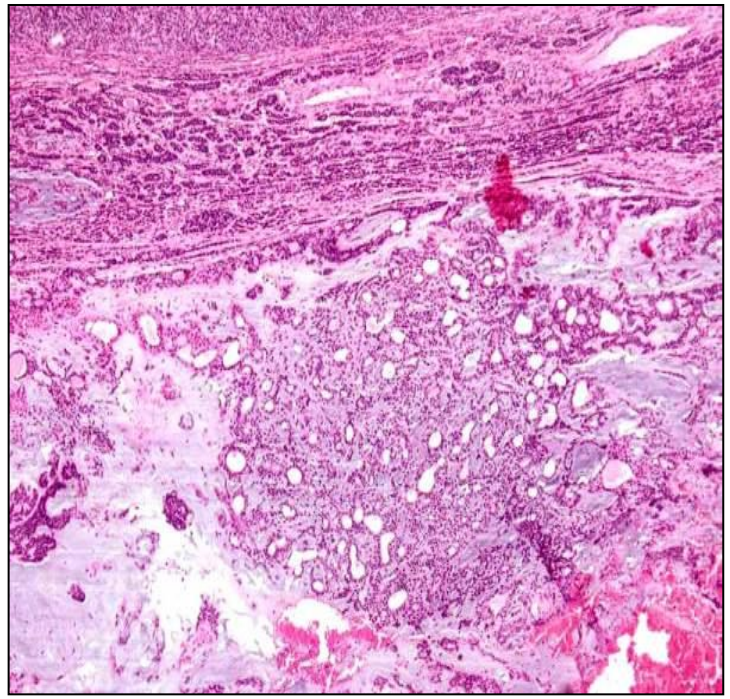




Cellular BMT with Stromal Arrangements Mimicking Adenoid Cystic Carcinoma







. Look for spindle shaped and/or plasmacytoid cells

. Classic features of Pleomorphic Adenoma will be evident in other areas of the slide

. Process the entire specimen

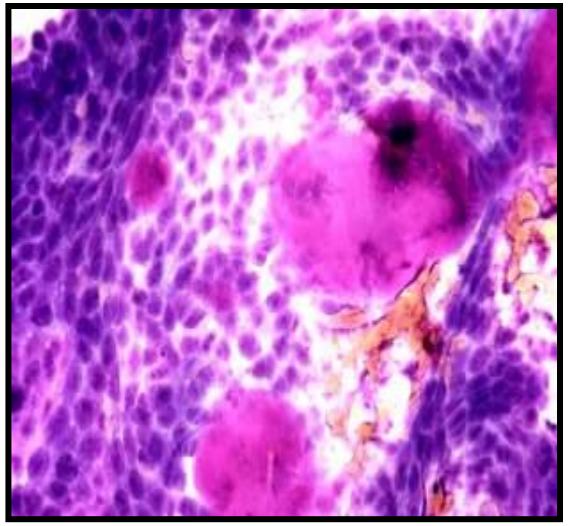
. Immunostains can be helpful – Cell block

Adenoid Cystic Carcinoma (ADCC)

- 3rd most common malignancy
- Higher frequency in submandibular gland
- Poor long-term survival

  Painful – due to invasion of the nerves

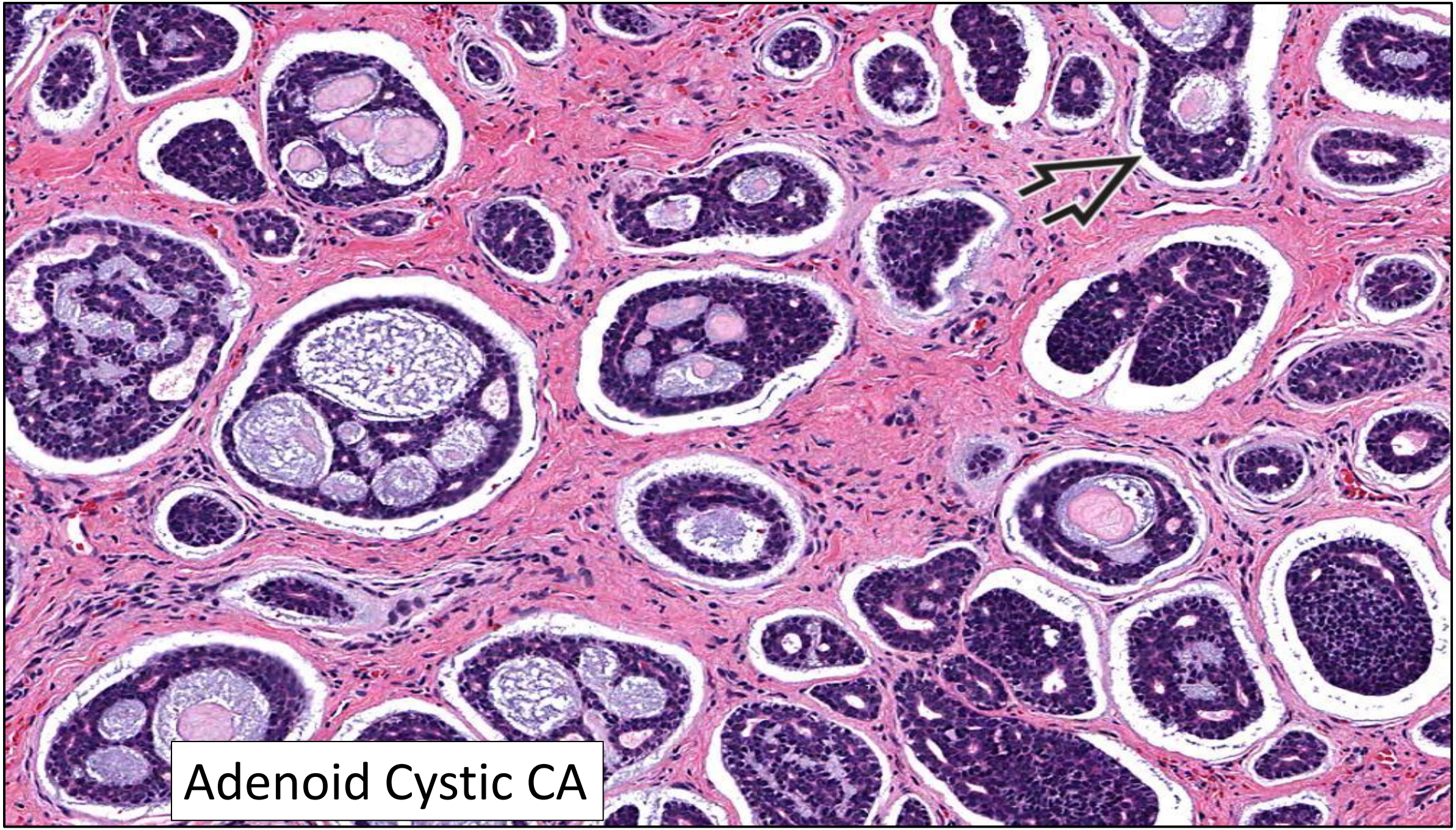
- Cytomorphology
  - Variably sized three dimensional ***Acellular Hyaline Matrix Globules*** surrounded by monotonous ***Basaloid Cells***
- ***Cellular atypia – not frequent***

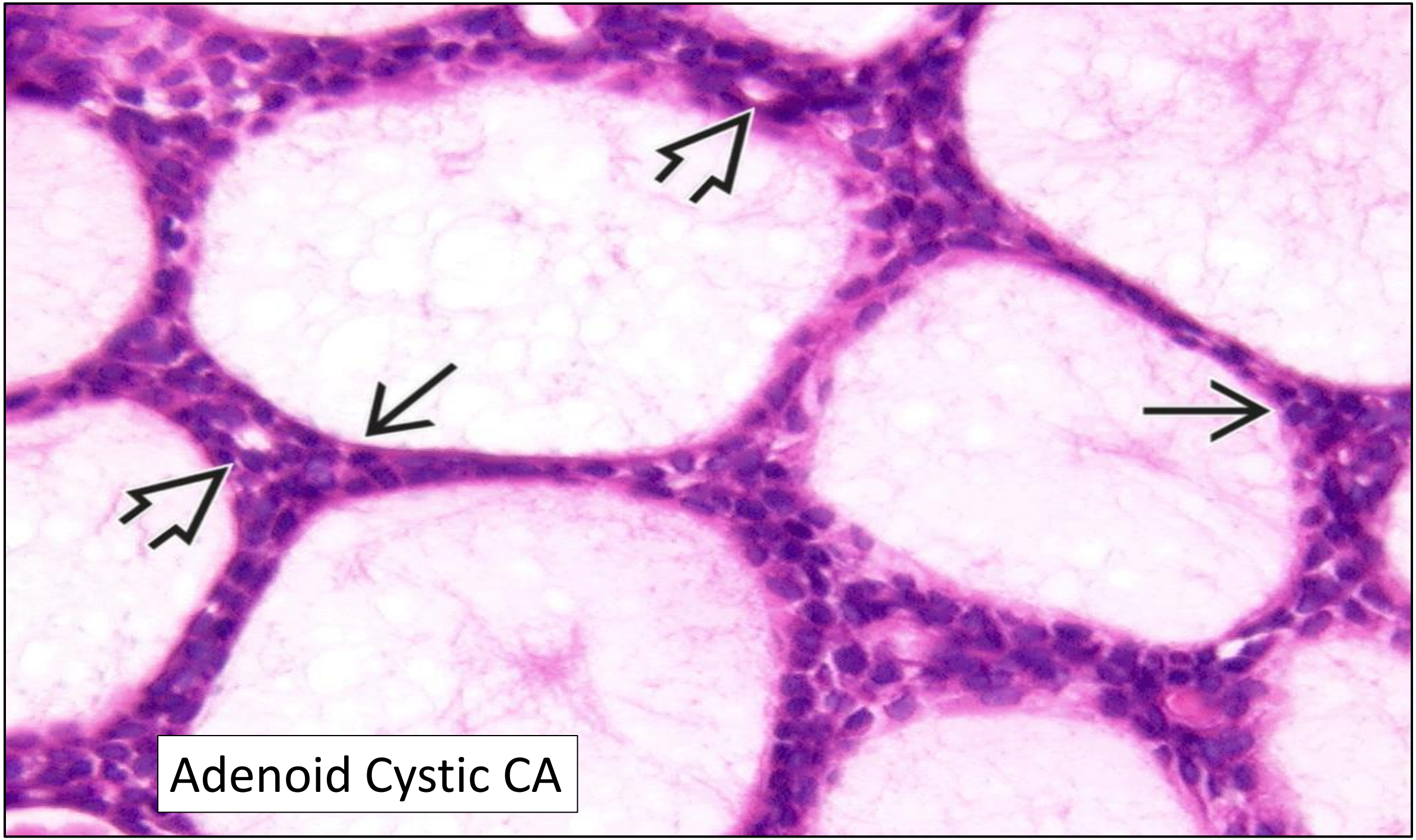


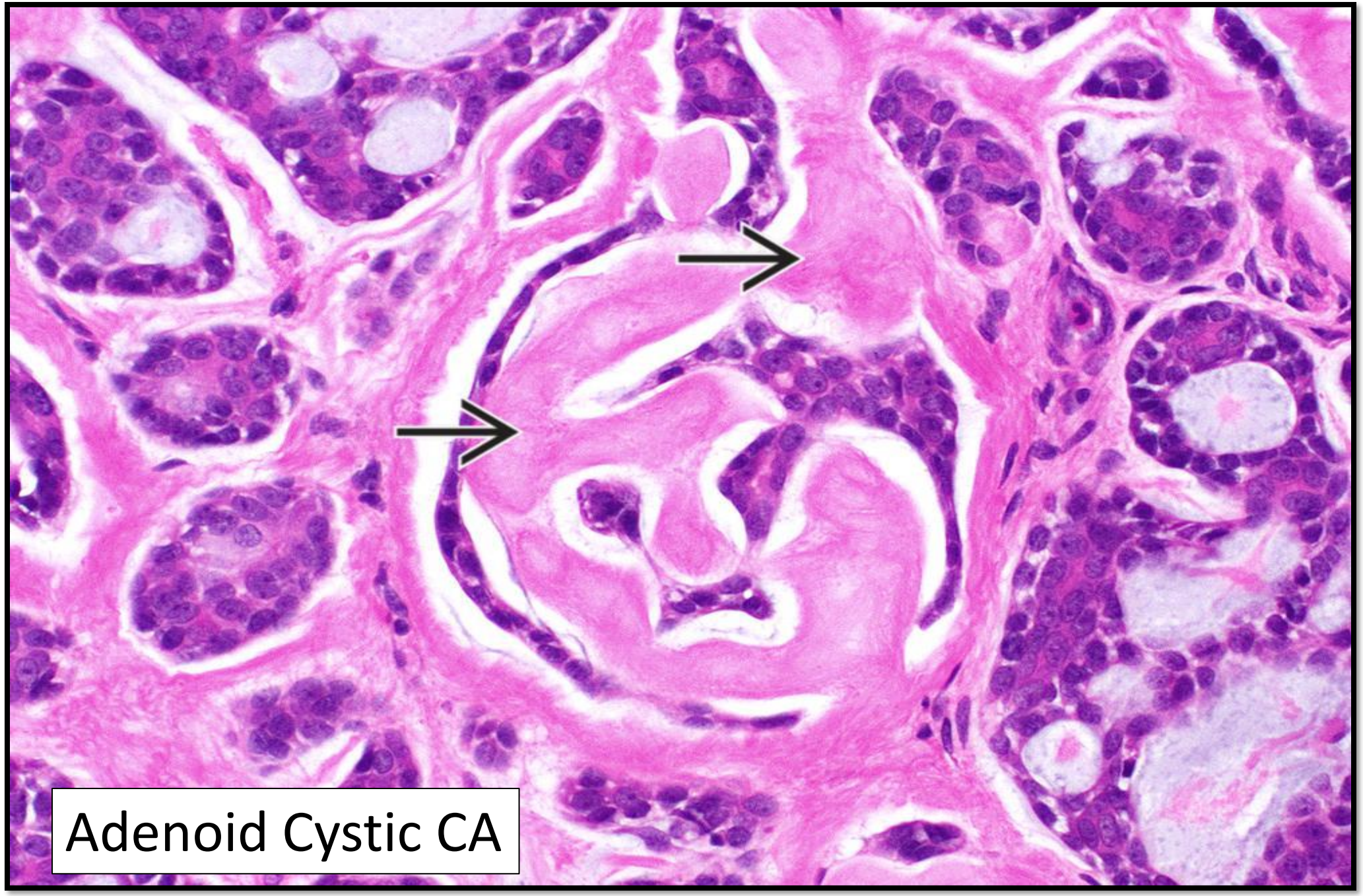
Adenoid Cystic Carcinoma

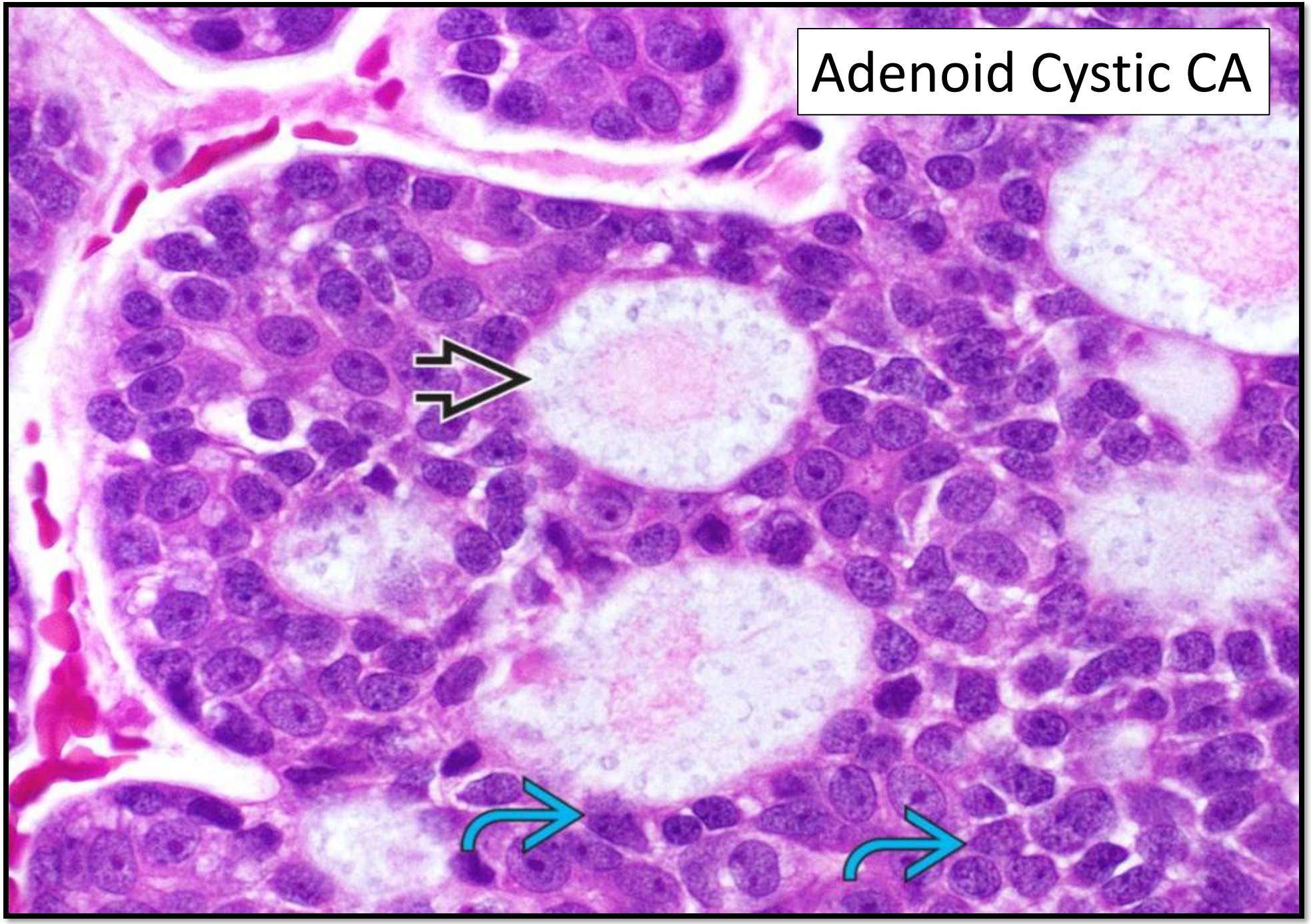
- Malignant; usually slow-growing; late-onset mets common
- All ages but most common in 4^{th}-6^{th} decades
- F>M
- Major and minor salivary glands
- Histology:
  - Cells small with limited cytoplasm; nuclei **oval to sharply-angulated**, coarse chromatin and small nucleoli
  - Architecture: Cribriform, tubular, solid (or combo)
  - **Perineural invasion** common
- Majority (80-90%) show **t(6;9) creating MYB-NFIB fusion**
- IHC: MYB+, CKIT+

*Greater solid component predicts poor prognosis

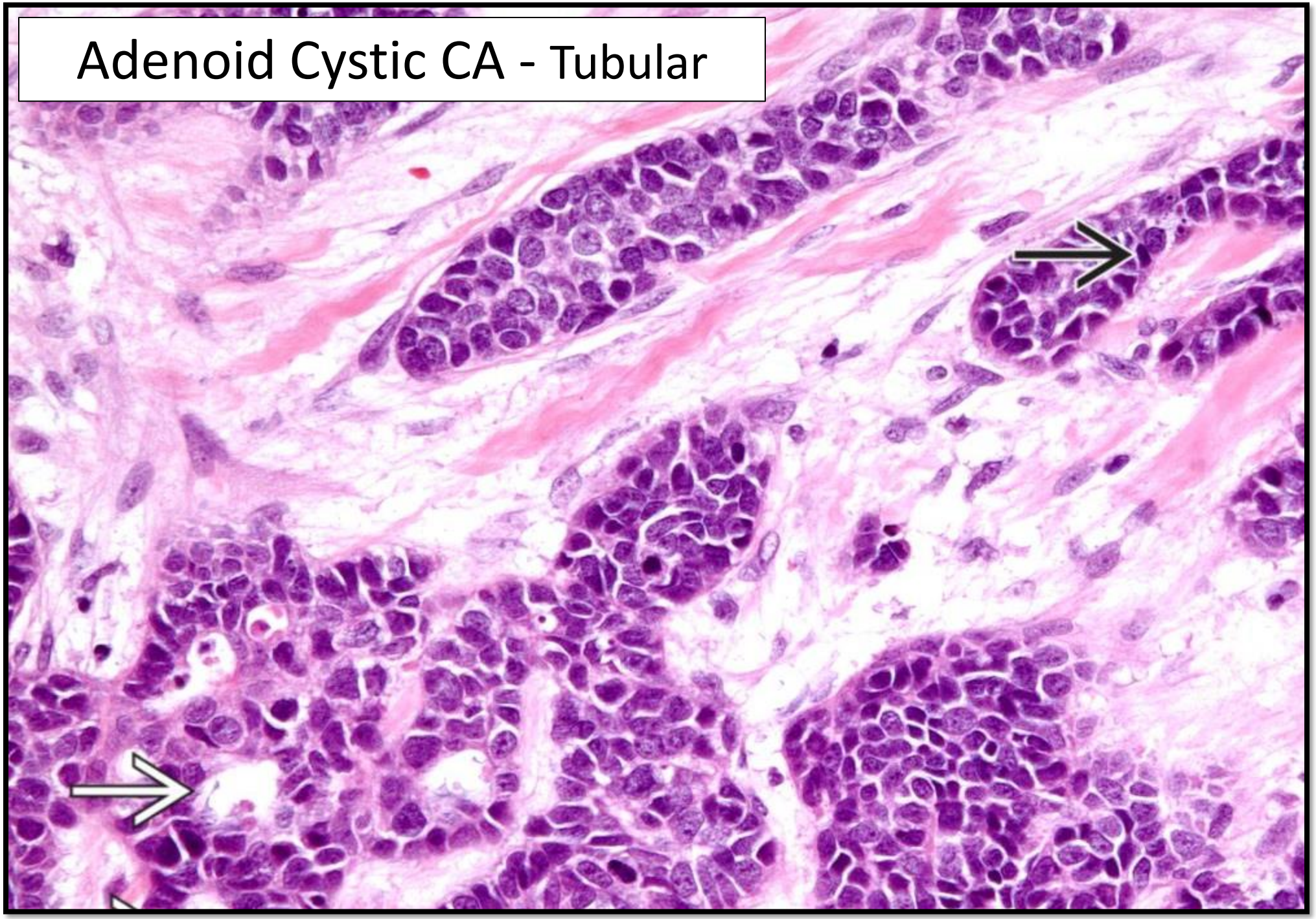

Adenoid Cystic CA


Adenoid Cystic CA

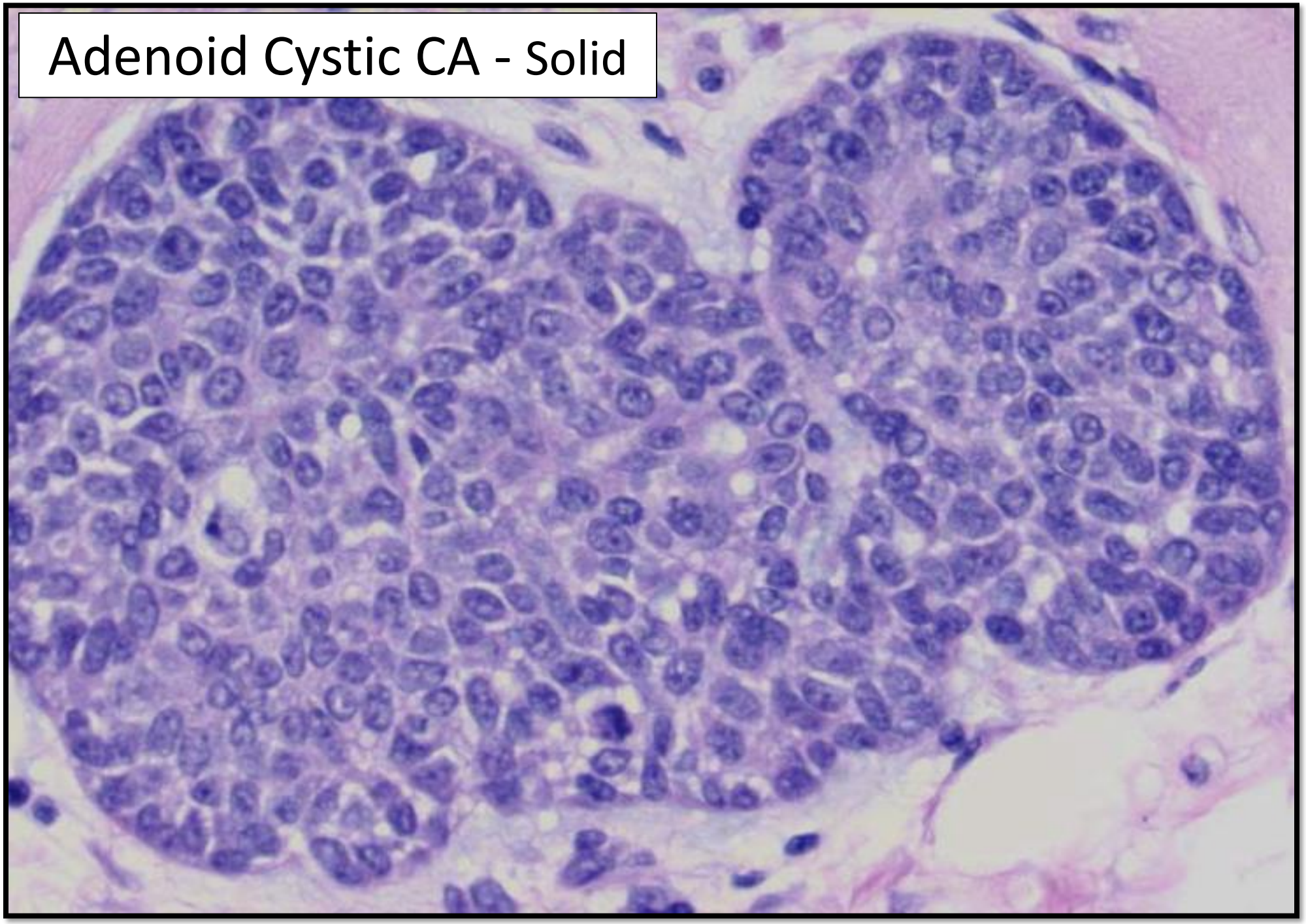

Adenoid Cystic CA


Adenoid Cystic CA

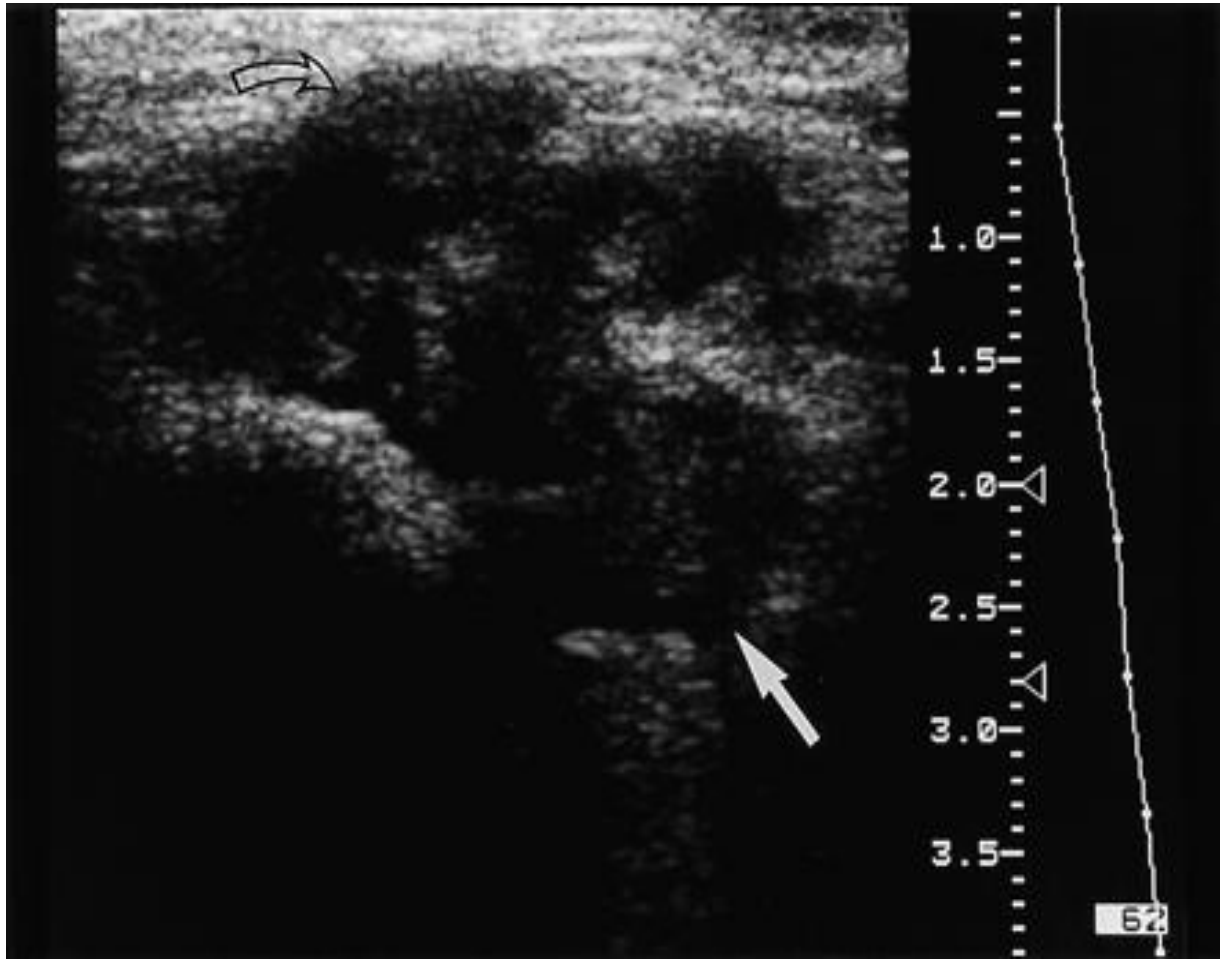
Adenoid Cystic CA - Tubular



Adenoid Cystic CA - Solid



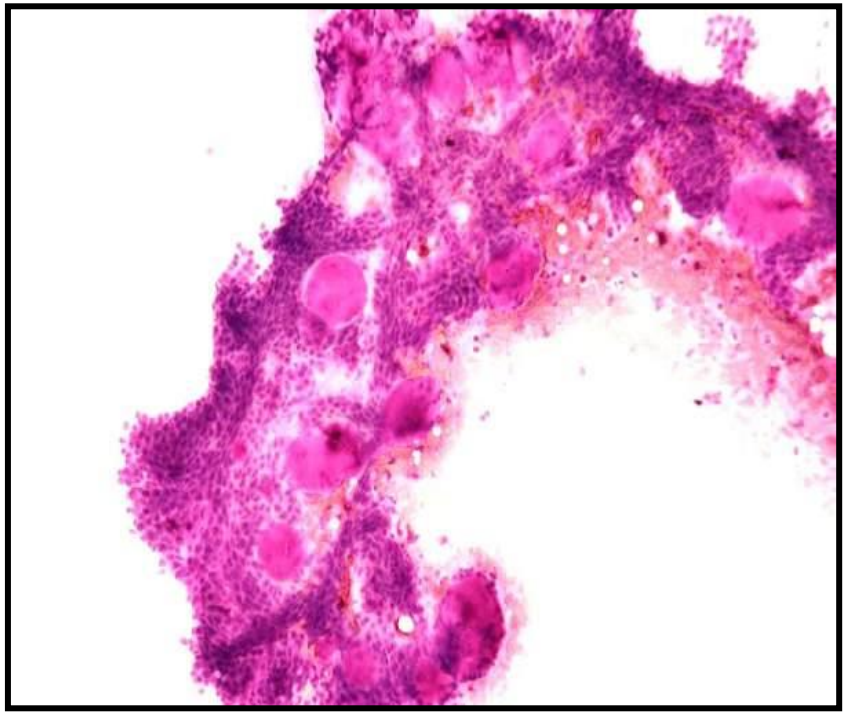
Ultrasound Features of Adenoid Cystic Carcinoma (ADCC)

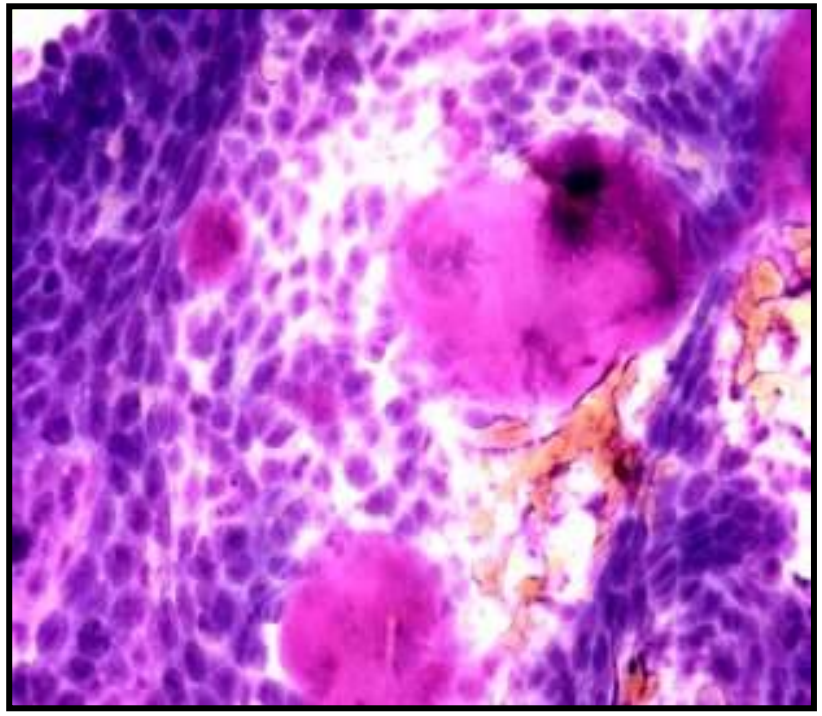


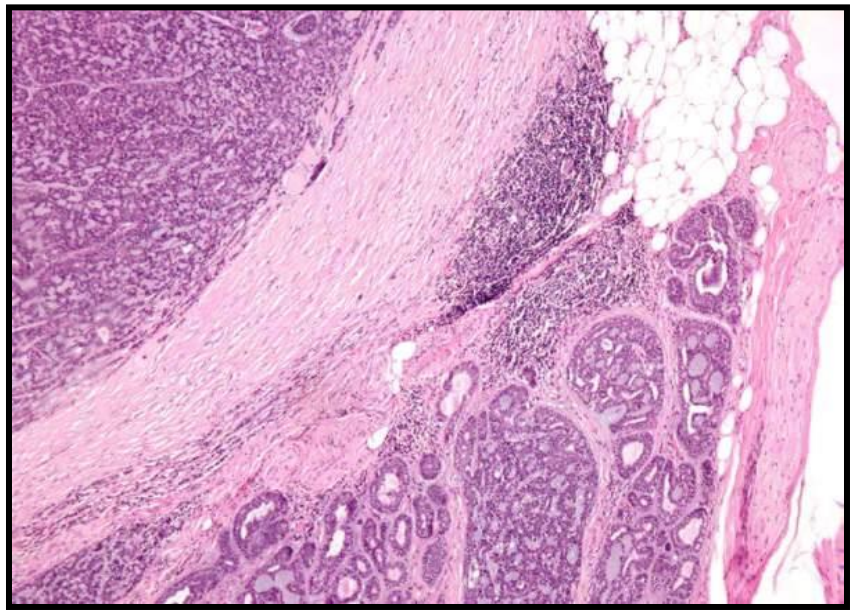
Hypoechoic tumor
Irregular margins
Infiltration / Extension
(into deep lobe of parotid gland)

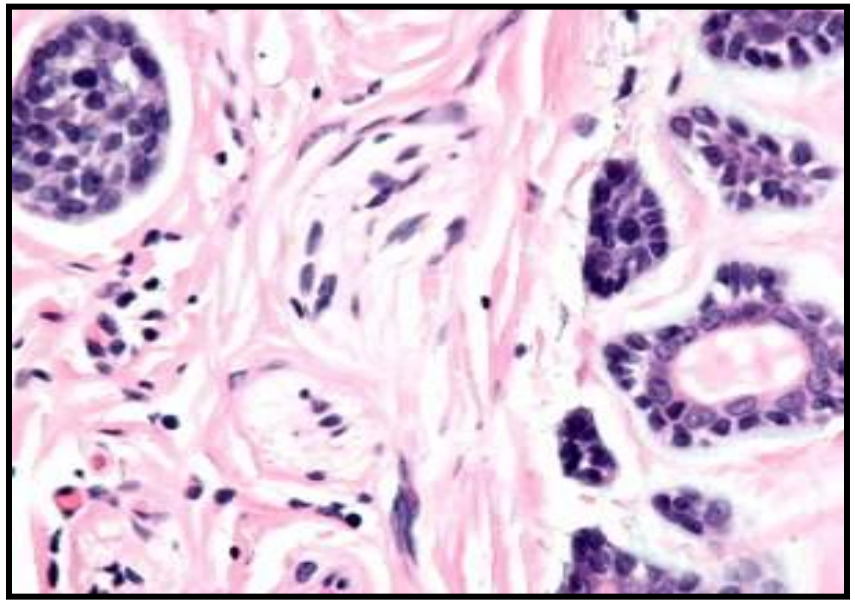
D C Howlett, Br J of Radiology 2003

ADCC – Classic Cytomorphology

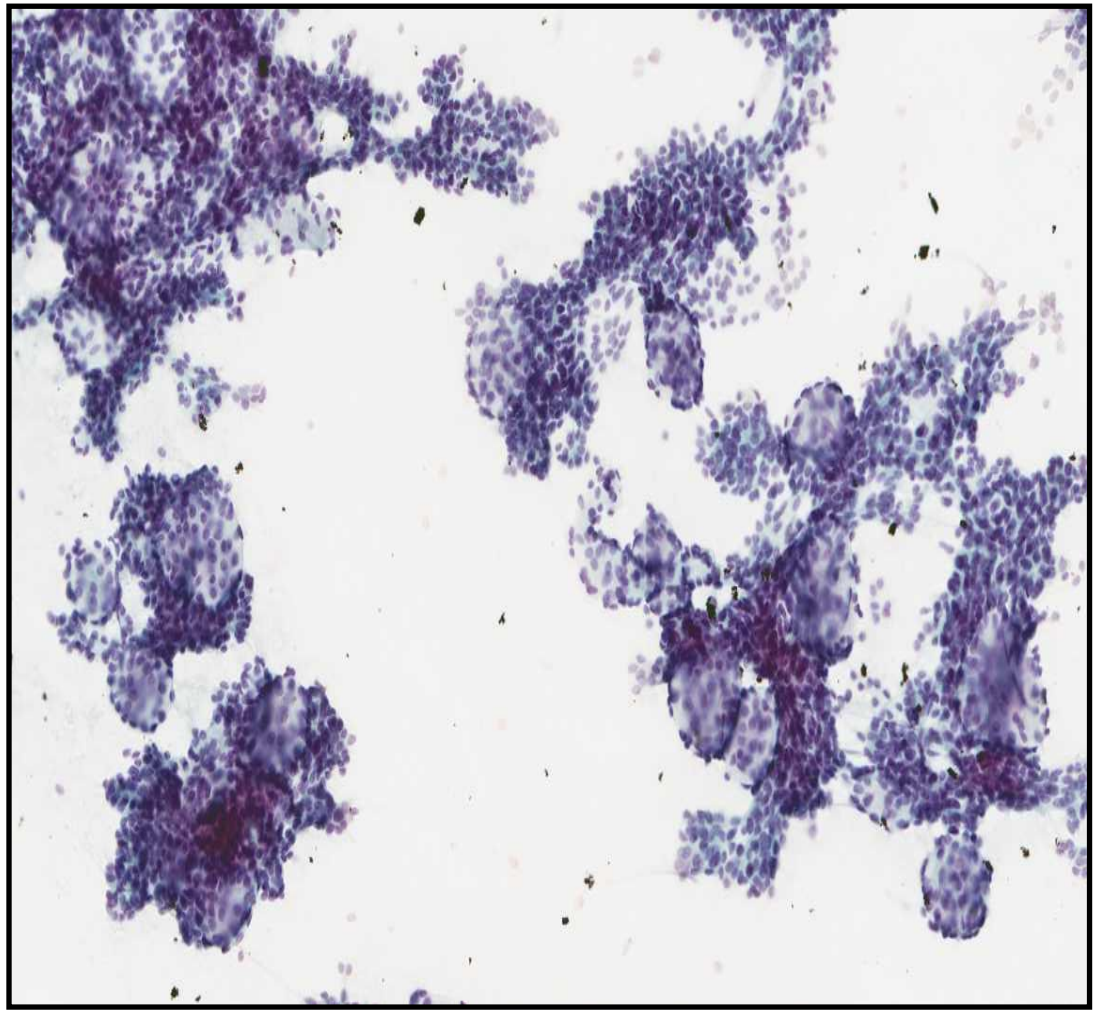


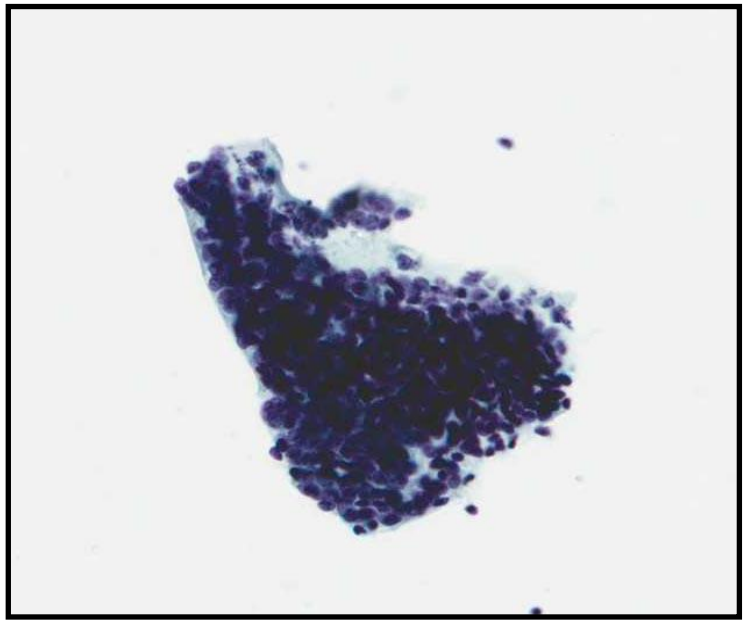






55-year-old man with history smoking and leukoplakia presented with a right sub-mandibular mass slowly enlarging for 5-years. Patient complains of fullness without pain or paresthesia.

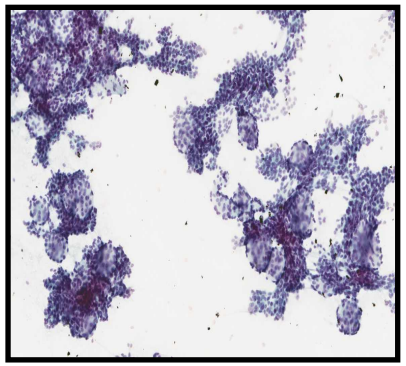


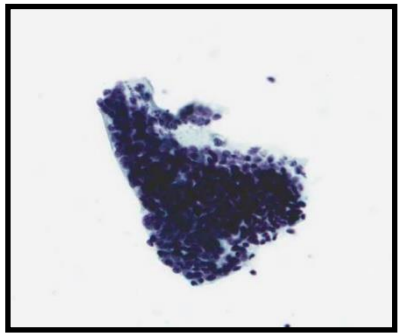


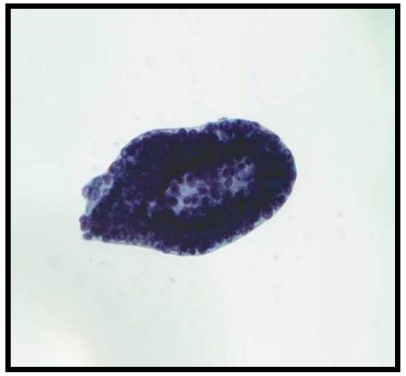
<u>ThinPrep Preparation Only</u>

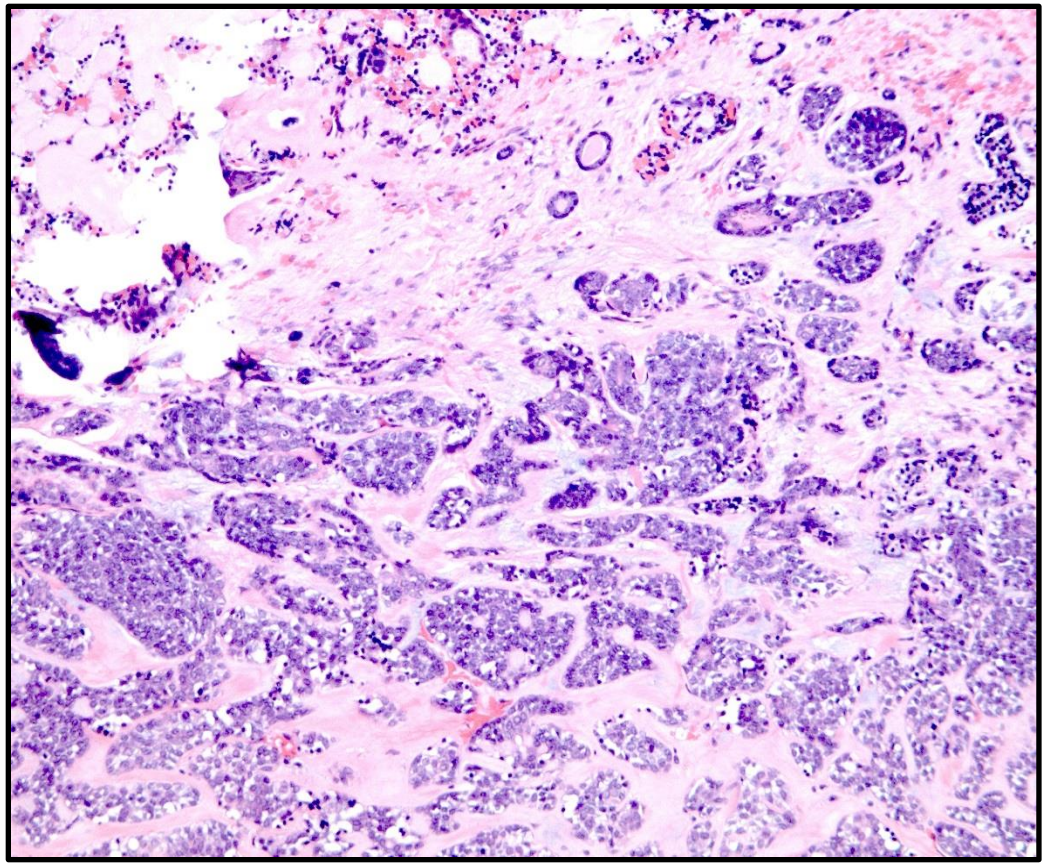
<u>Lightly staining Hyaline Globules</u>

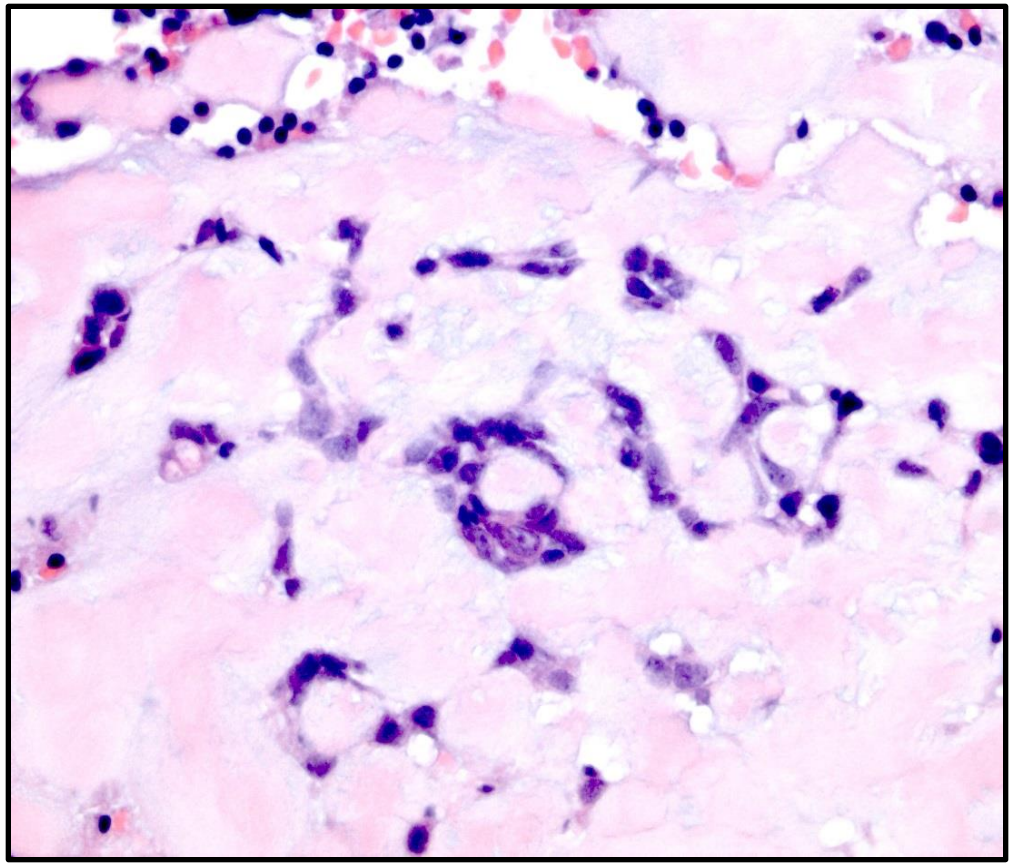
55-year-old man with history smoking and leukoplakia presented with a right sub-mandibular mass slowly enlarging for 5-years. Patient complains of fullness without pain or paresthesia.





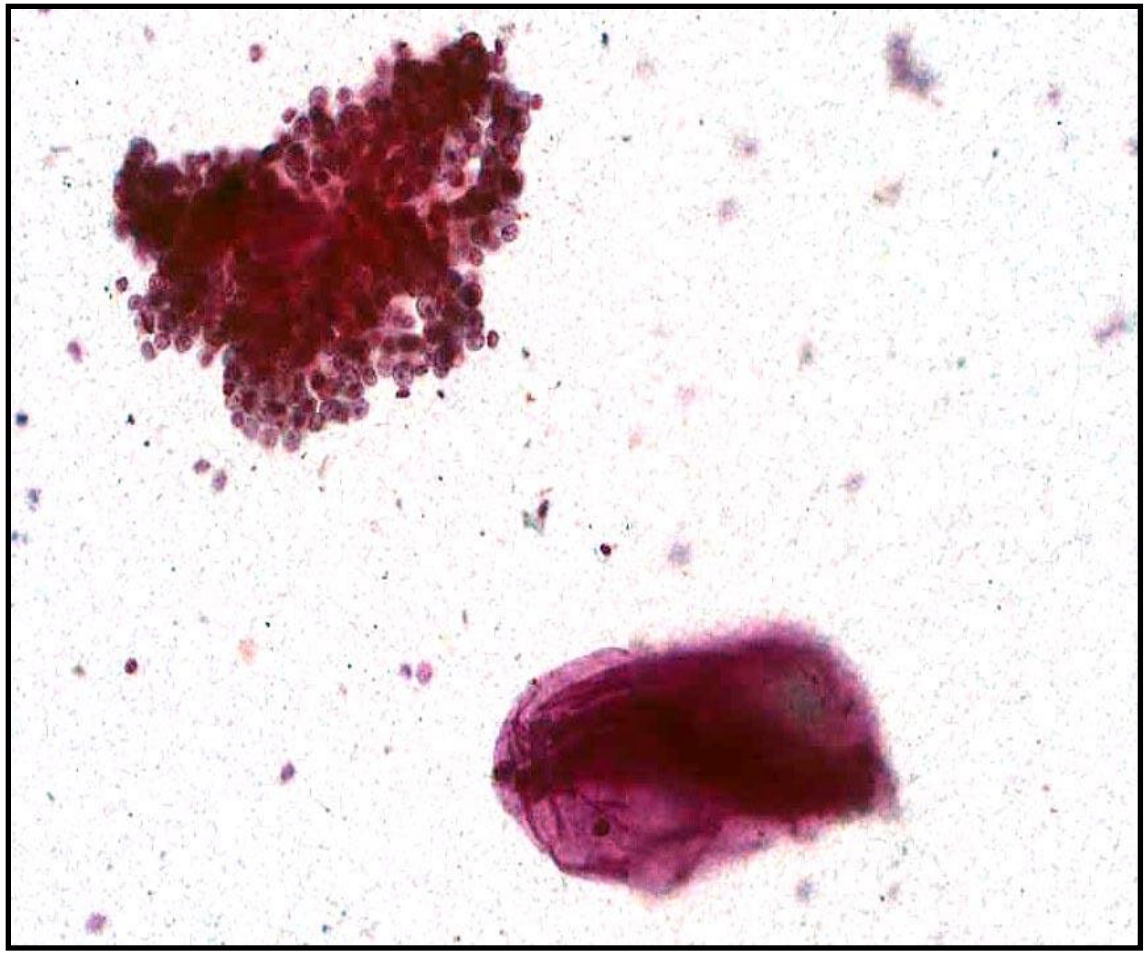


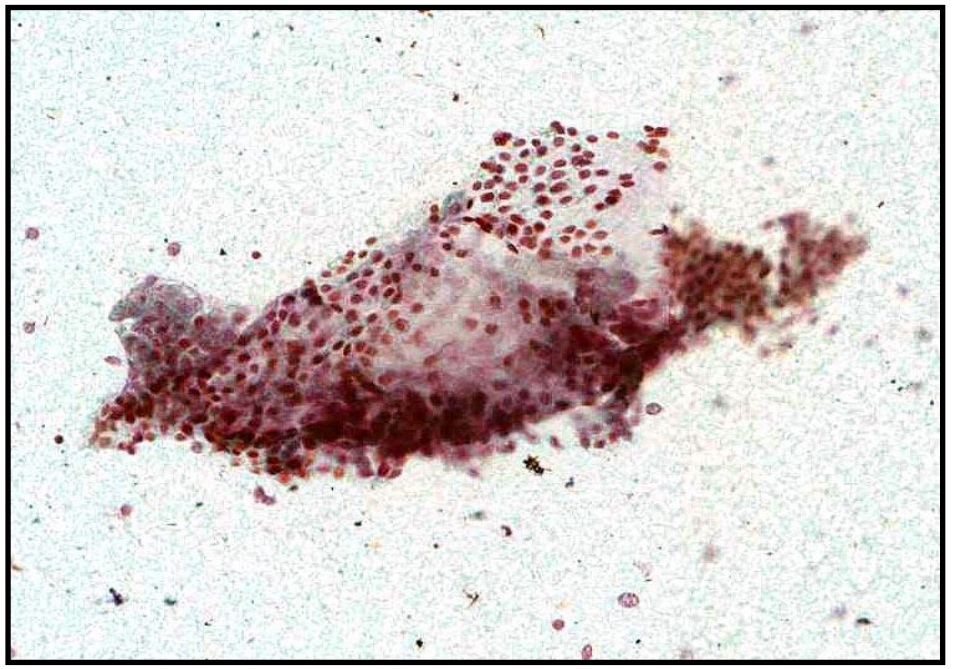


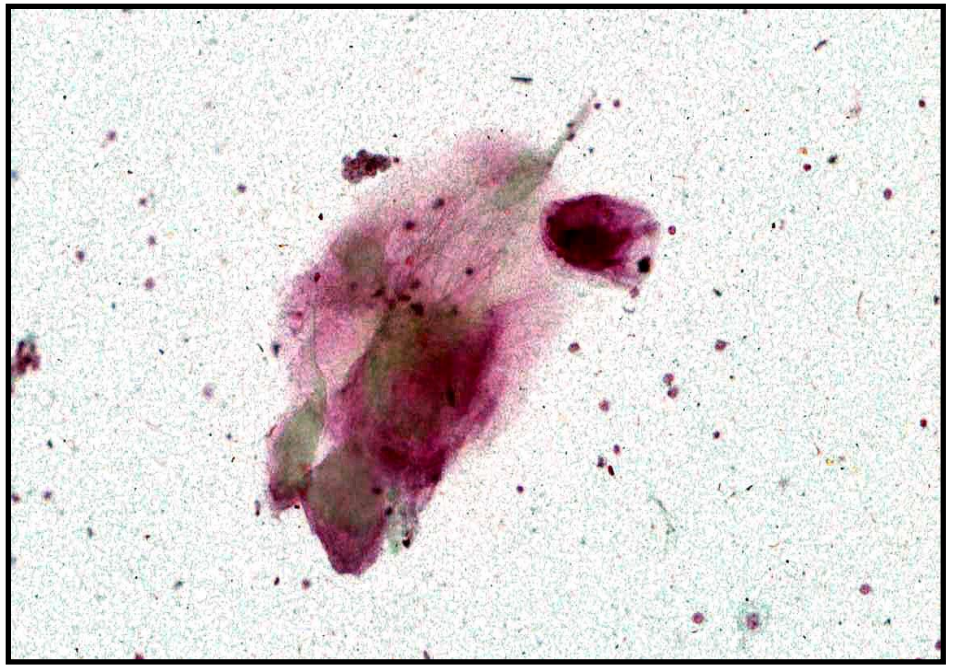


Adenoid Cystic Carcinoma

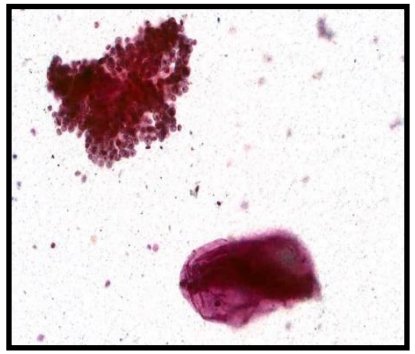
ADCCa – ThinPrep Specimen
Structure / shape of stroma
Stromal fragments devoid of cells

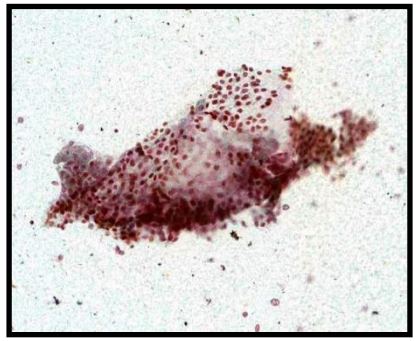


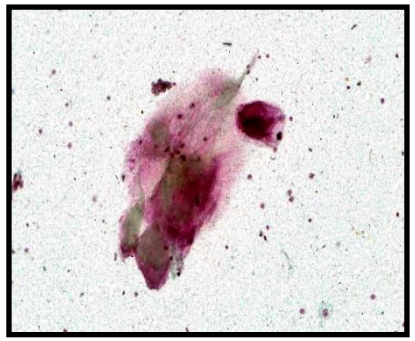


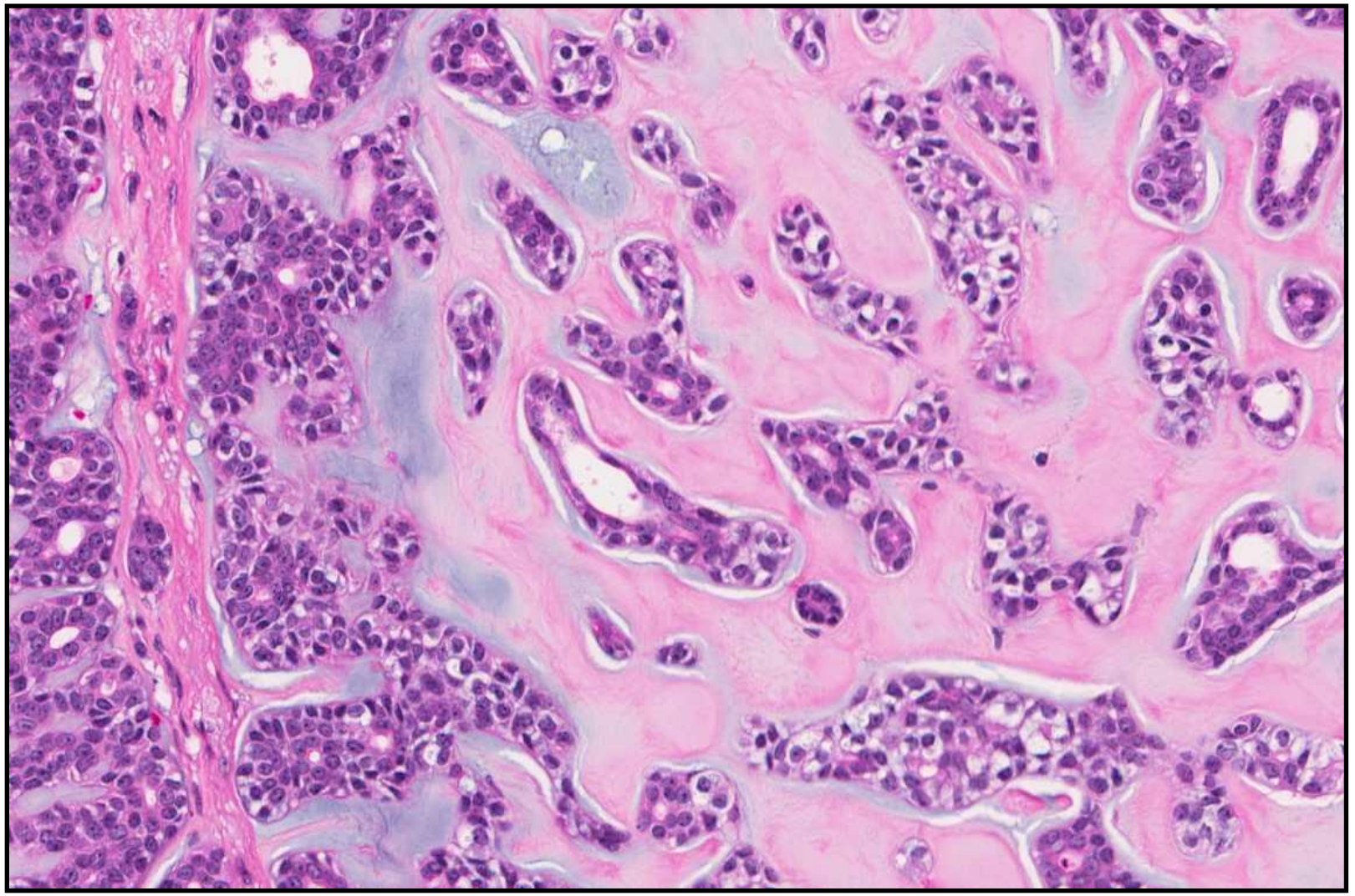


ADCCa – Thin-Prep Specimen. Structure / shape of Stroma fragments devoid of cells





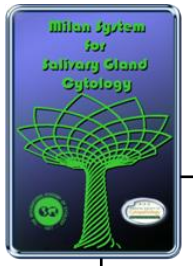




Summary
Diagnostic Scenarios – Basaloid Cells

- **Diagnosable as:**
  - Neoplasm-Benign: Pleomorphic Adenoma. Basal cell adenoma
  - Malignant: ADCCa

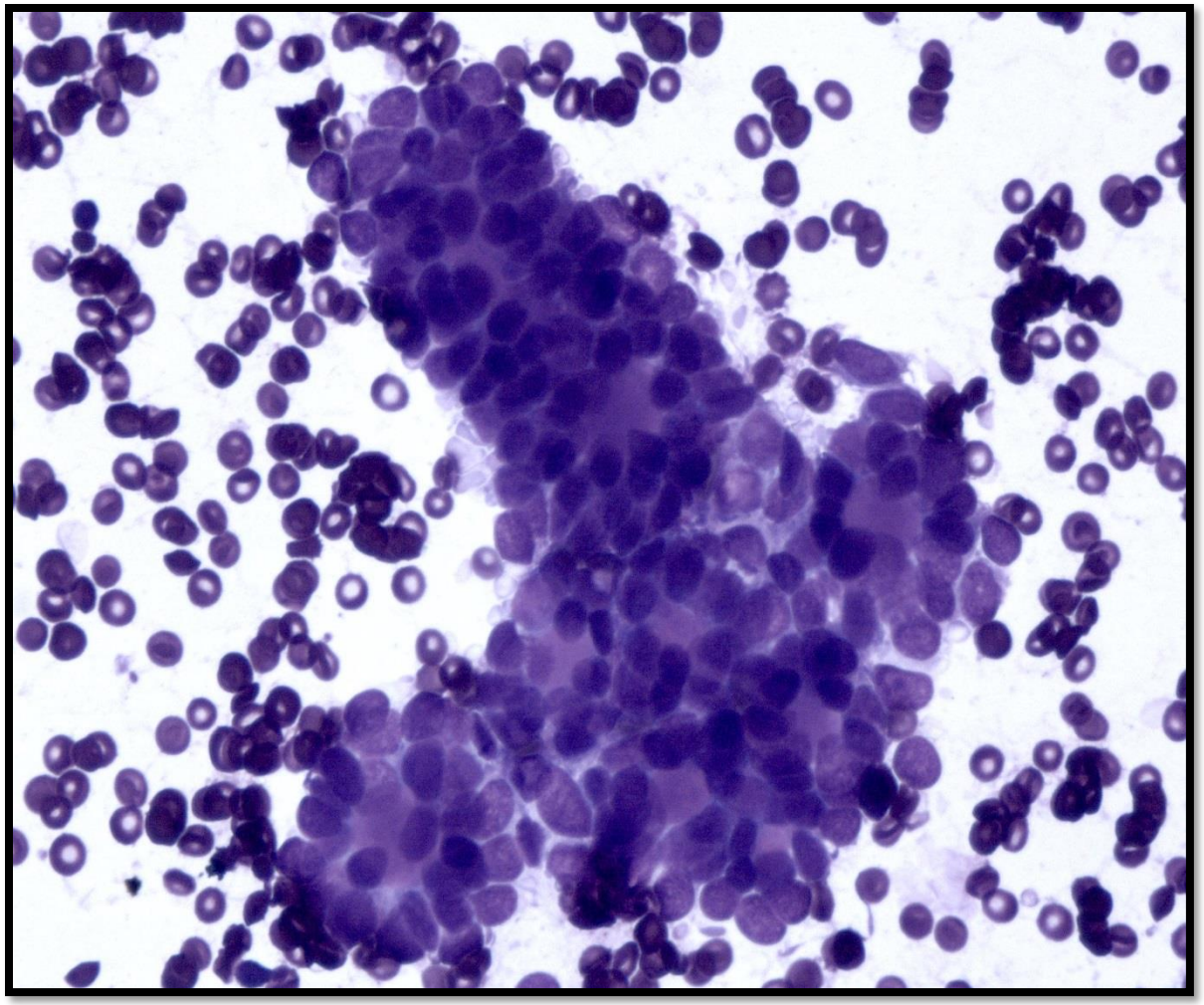
- **If morphology not typical:**
  - Salivary gland neoplasm of uncertain malignant potential
    - ***Basaloid features with differential***
    - Atypical nuclei

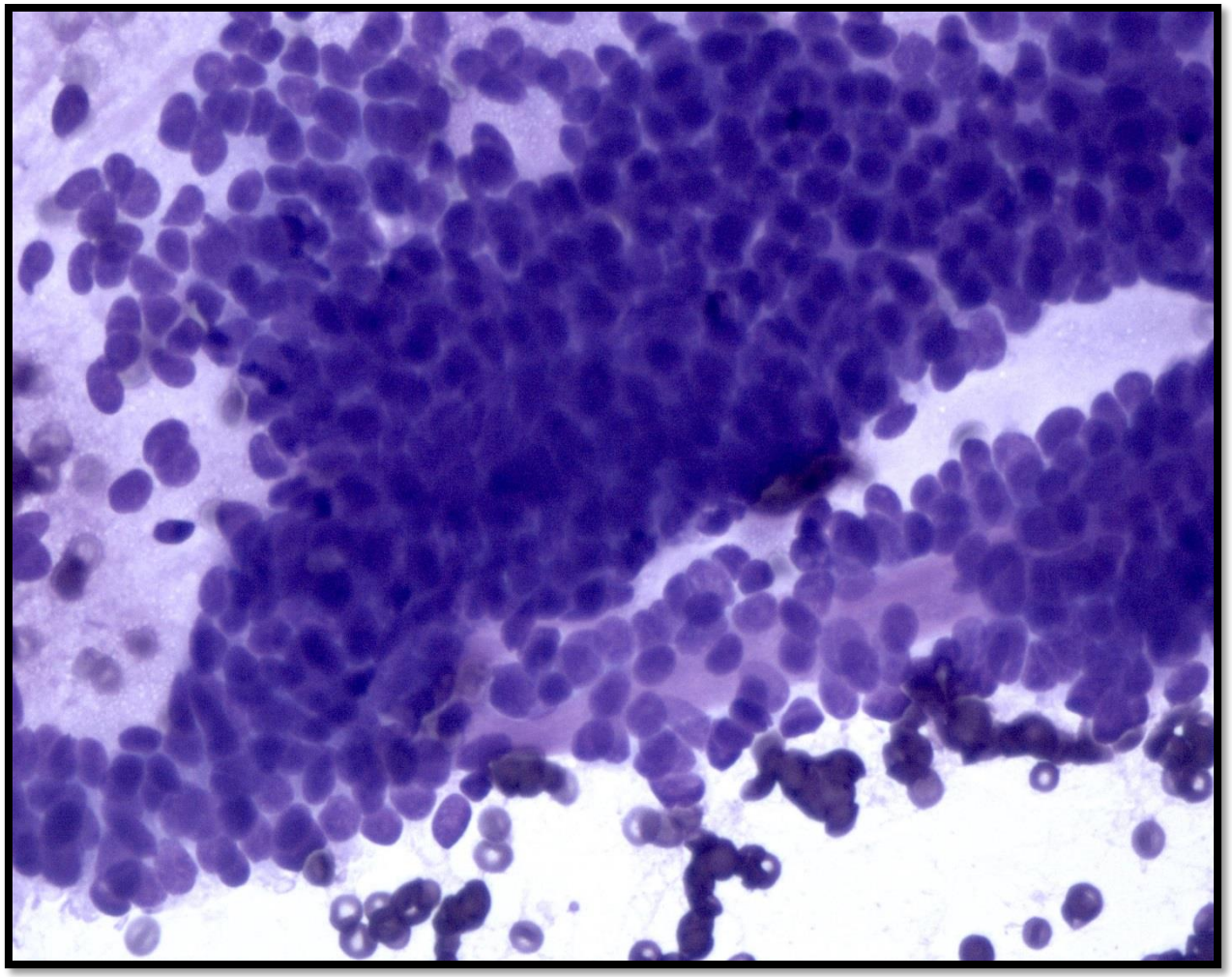


Differential Diagnosis of Tumors with Salivary Gland Neoplasm w Basaloid Features - Based On Amount & Type of Stroma

1. Fibrillary	Pleomorphic Adenoma Epithelial-myoepithelial carcinoma Basal cell adenoma / Adenocarcinoma
2. Hyalinized	Basal cell adenoma / Adenocarcinoma Adenoid cystic carcinoma Epithelial-myoepithelial carcinoma Polymorphous adenocarcinoma (location)
3. Mixed or Other Types (globular structures)	Adenoid cystic carcinoma Polymorphous adenocarcinoma
4. Scant to None	Pleomorphic adenoma Basal cell adenoma (usually canalicular type) Myoepithelioma Myoepthelial carcinoma

45-year-old woman underwent ultrasound guided FNA of a 2.0 cm solid and painless right parotid gland mass.





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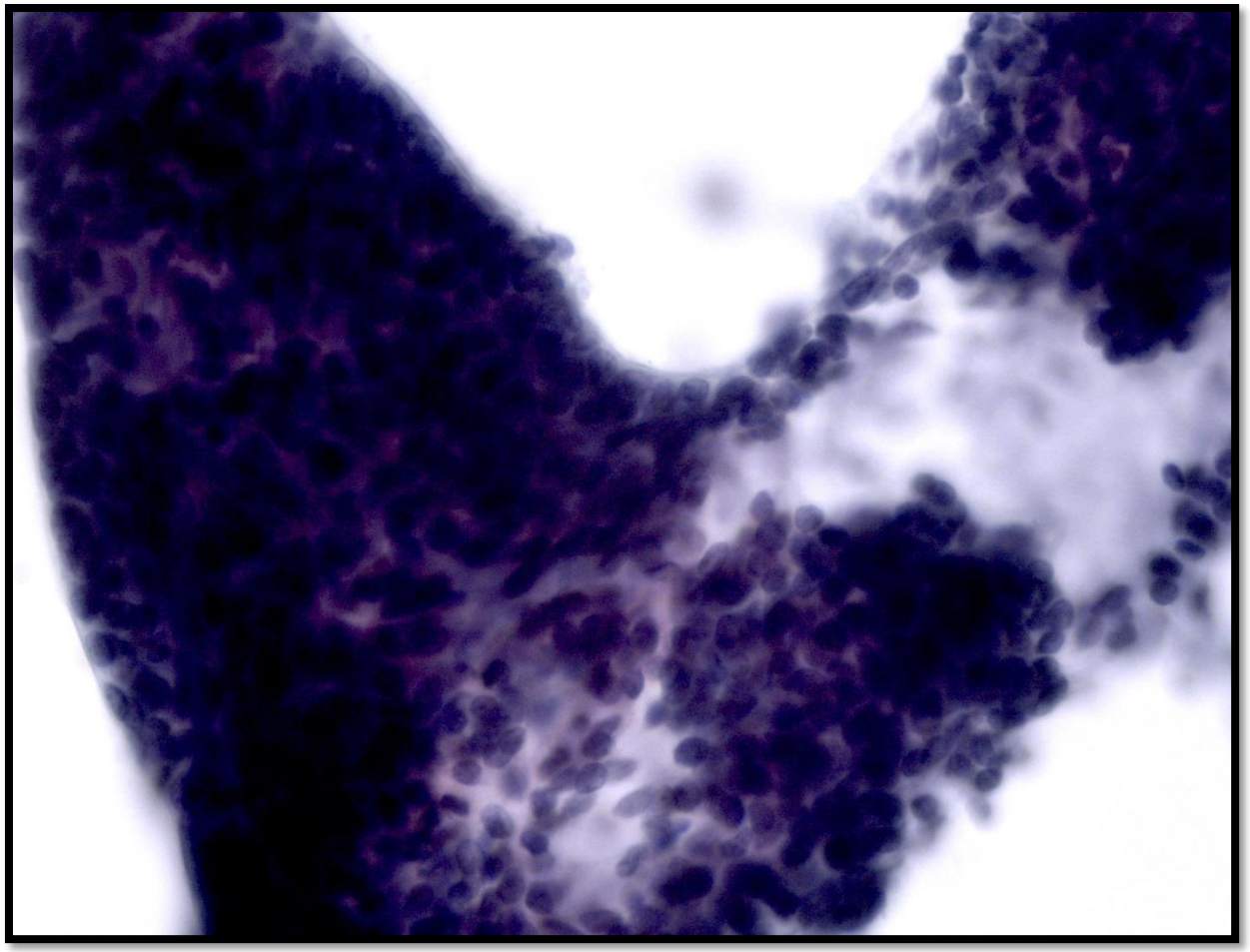
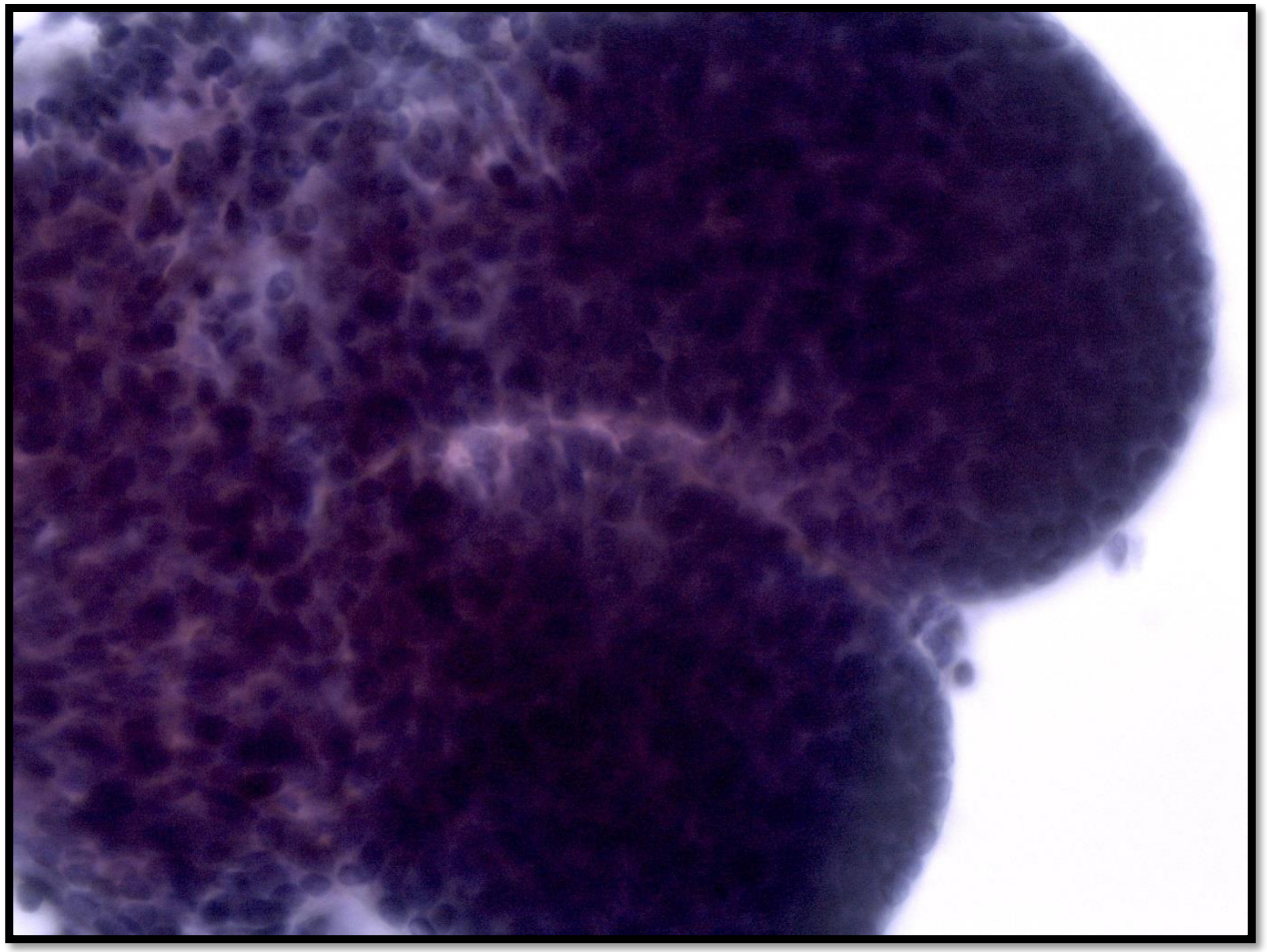




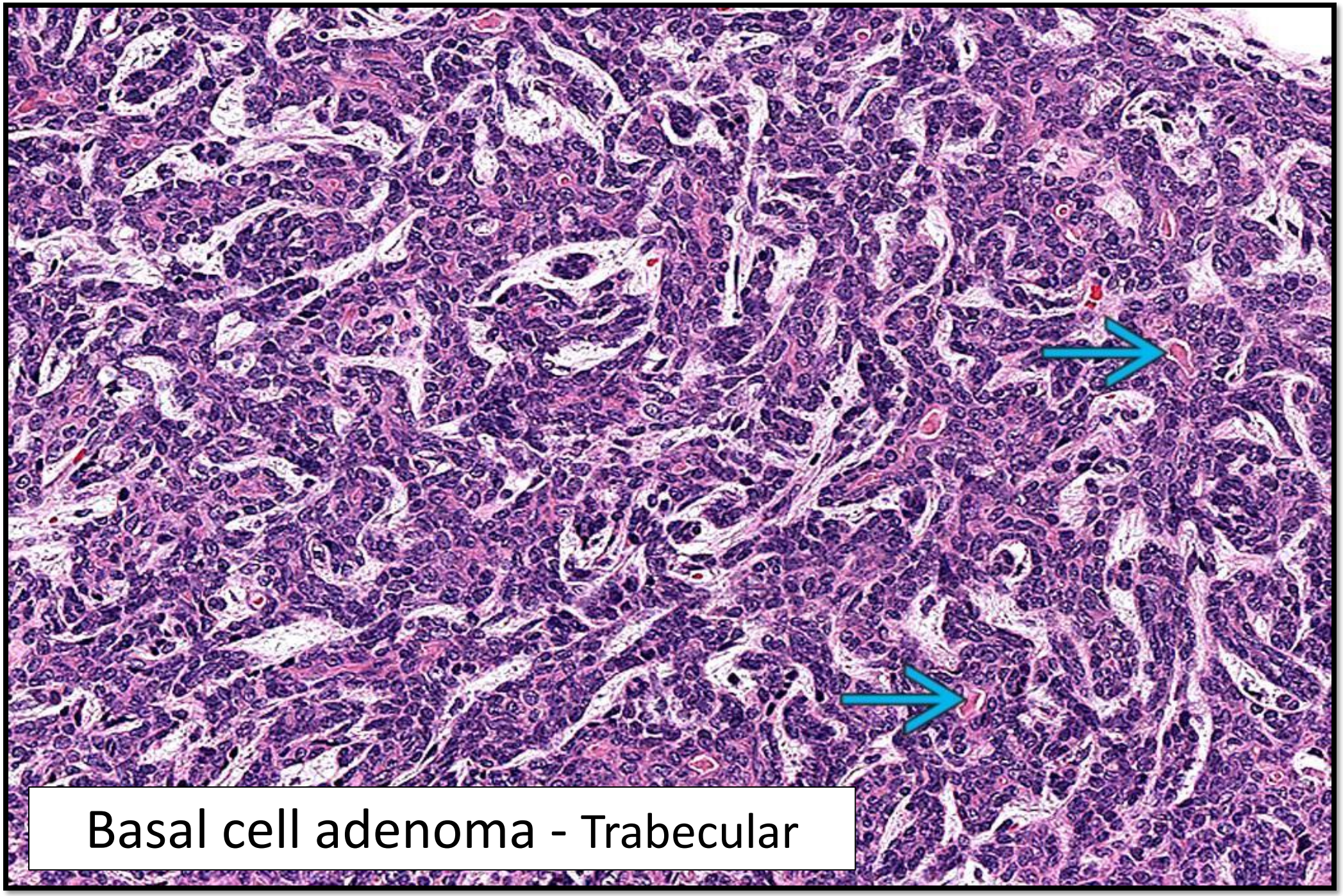
Basal cell adenoma

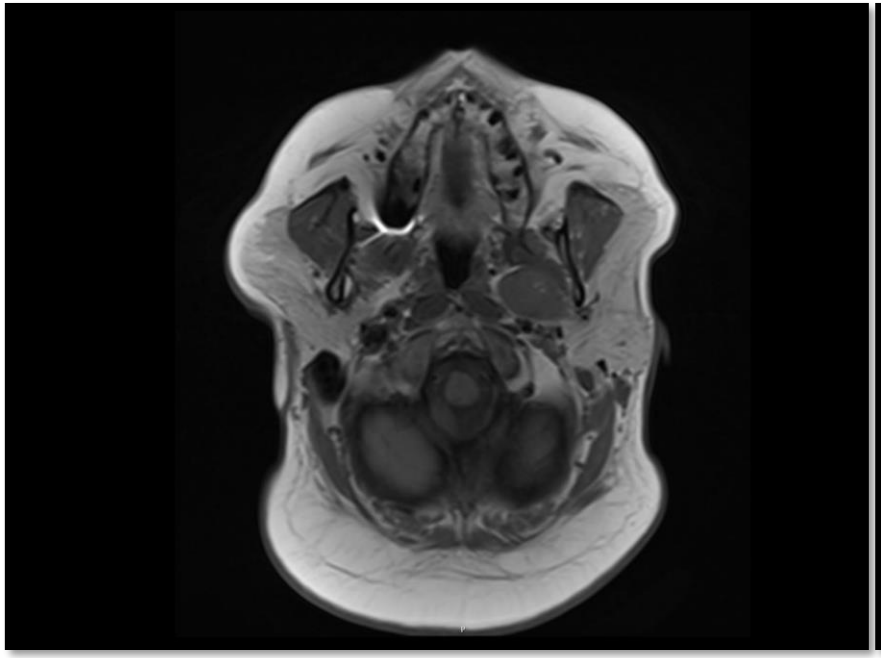
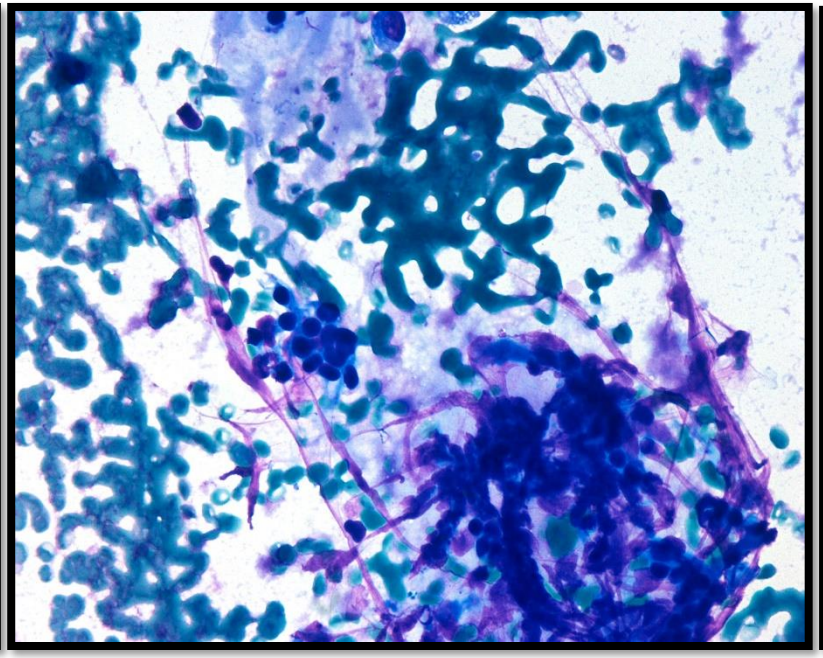
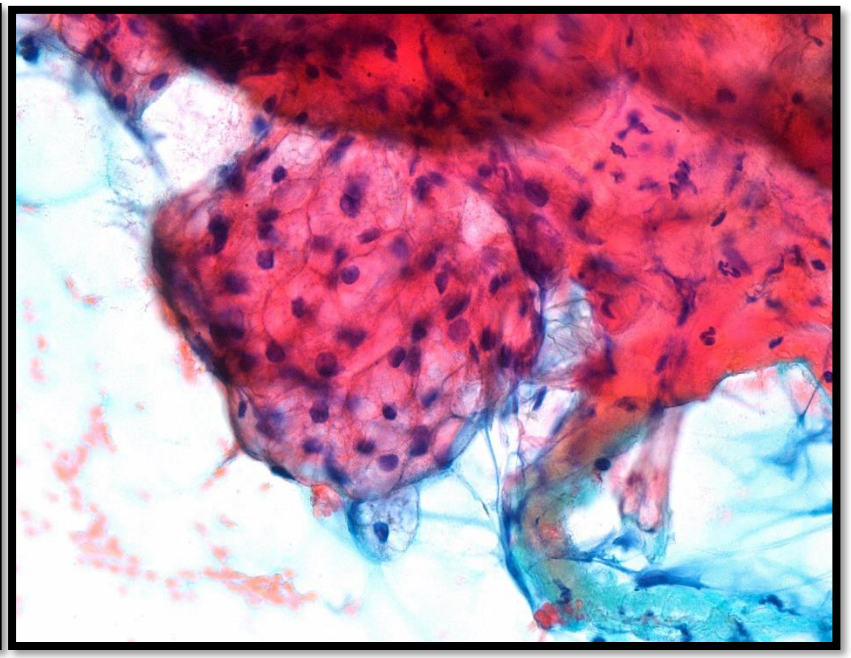
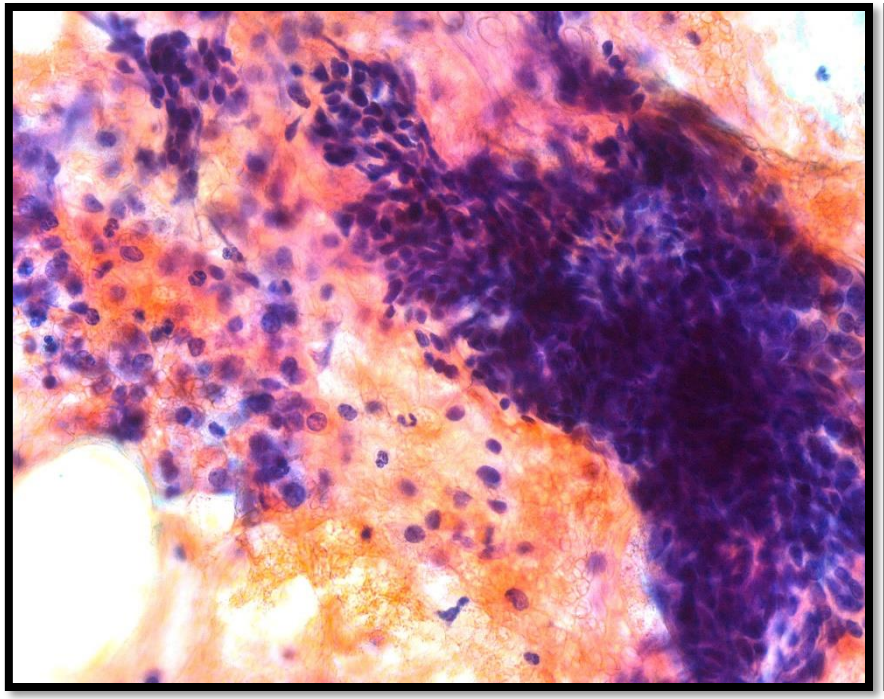
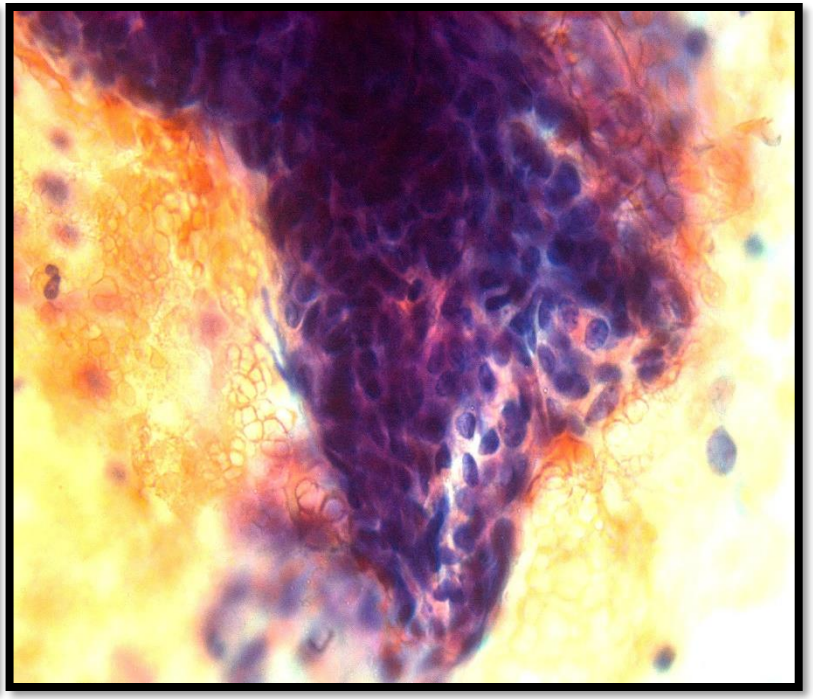
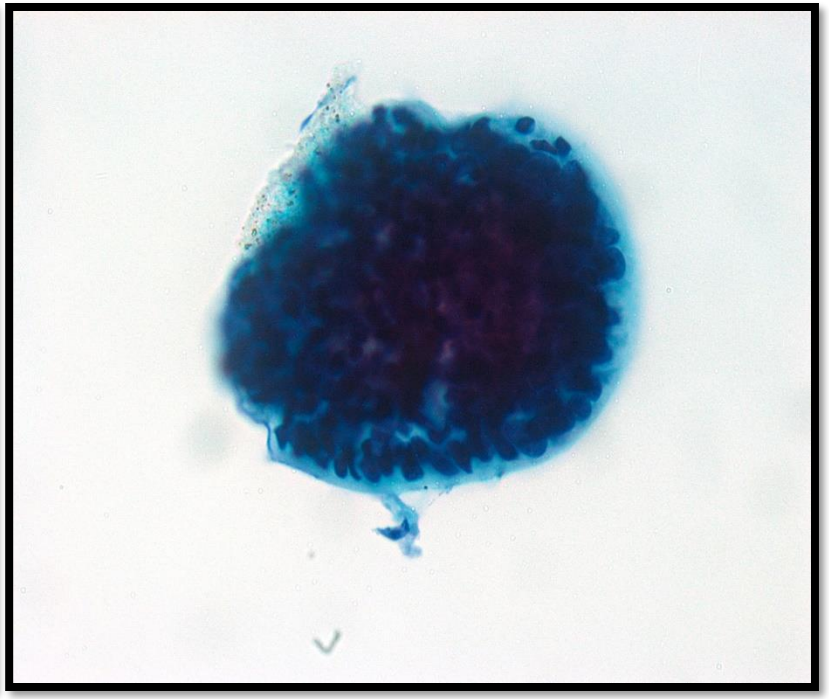
- Benign, slowly growing neoplasm
- Wide age range, F>M (2:1)
- Histology:
  - 2 types of basaloid cells, different parts of tumor nests:
    - Smaller cells at periphery: scant cytoplasm, dark basophilic nuclei
    - Larger cells in interior: more abundant cytoplasm, paler nuclei
  - Varied architectural patterns:
    - Solid: Basaloid nests of variable size
    - Trabecular: Plexiform nests of basal cells
    - Tubular: Small ductal lumens surrounded by bands of basal cells
    - Membranous: Islands of basaloid cells surrounded by hyaline material
- IHC:
  - Inner larger cells: Keratin +
  - Outer smaller cells: SMA, p63, calponin +, Beta-Catenin +

1. Tubular / Trabecular
   1. *CTNNB1 135S mutations*
   2. *B-catenin expression (82%)*
   3. *Highly specific (96%)*
2. *Membranous*
   1. *CYLD1 alterations (Brooke-Spiegler Syndrome*

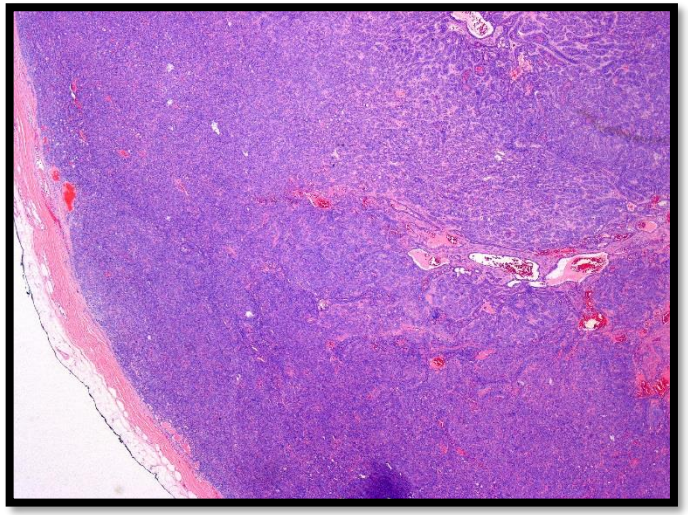

Basal cell adenoma - Tubular

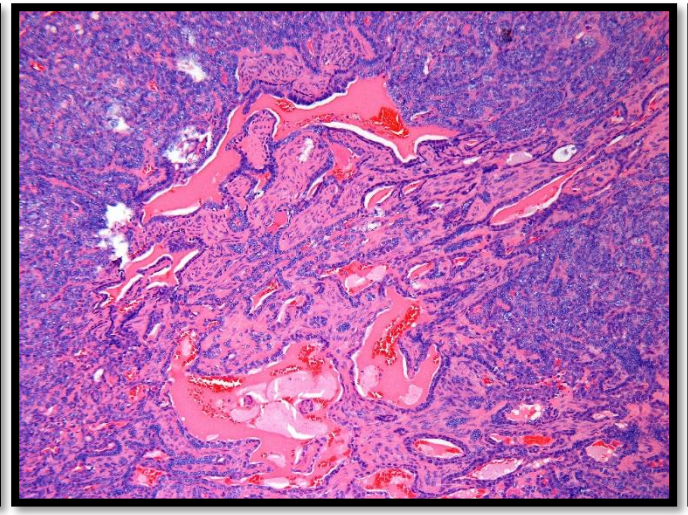

Basal cell adenoma - Tubular

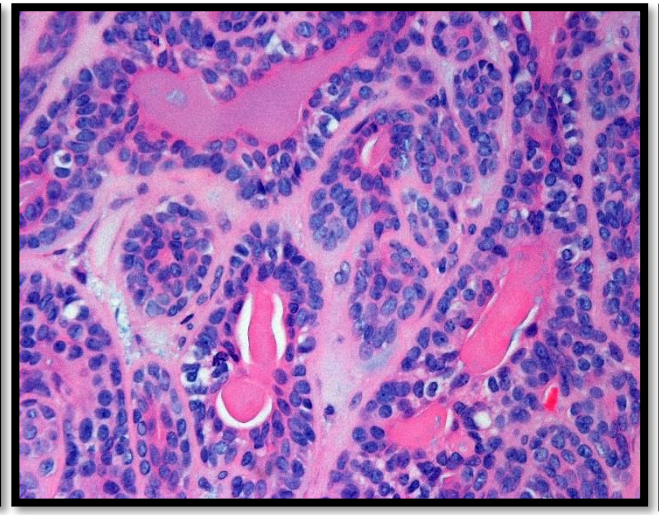

Basal cell adenoma - Trabecular

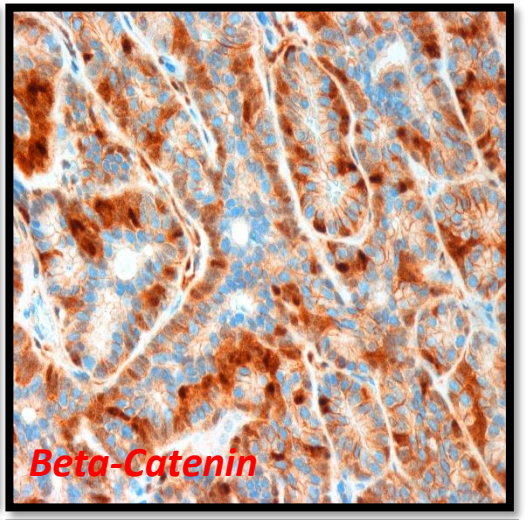







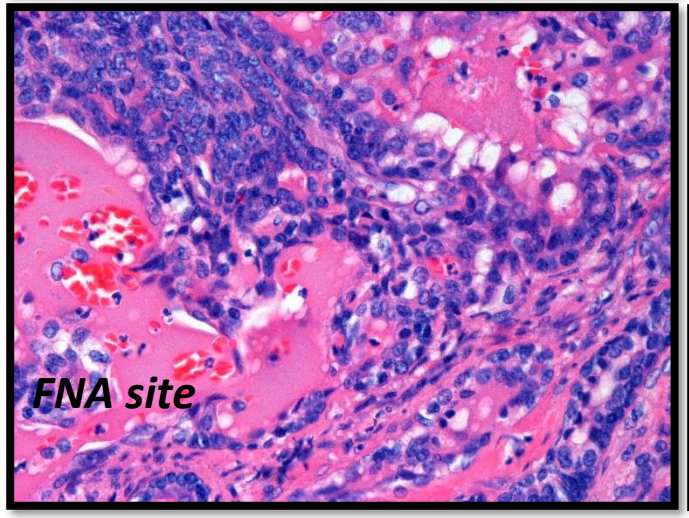
Follow-up, Basal Cell Adenoma

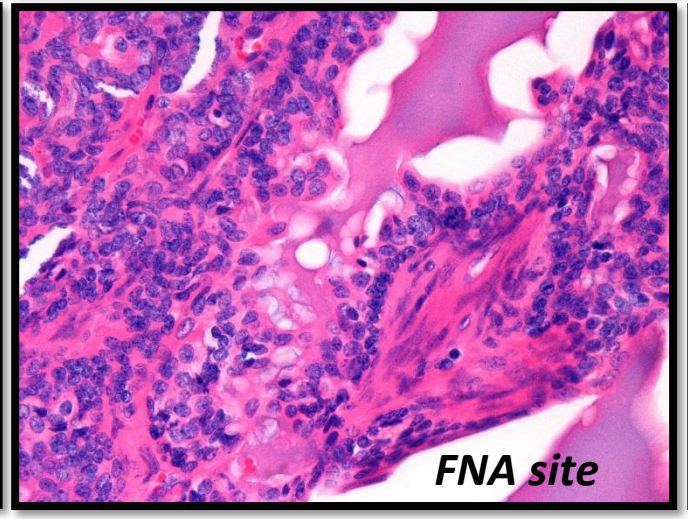


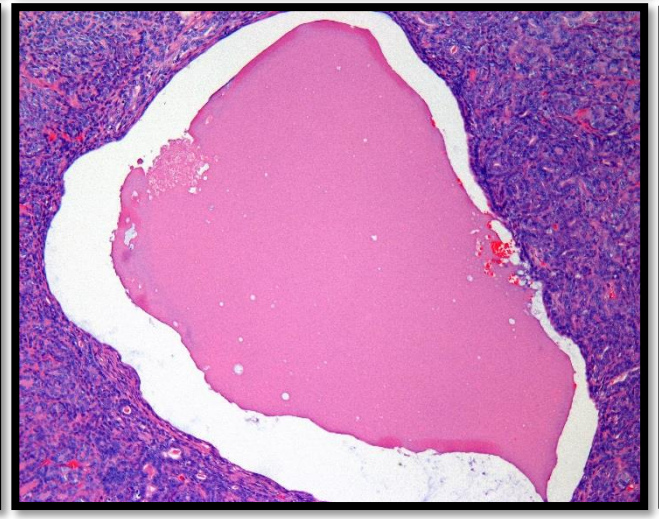


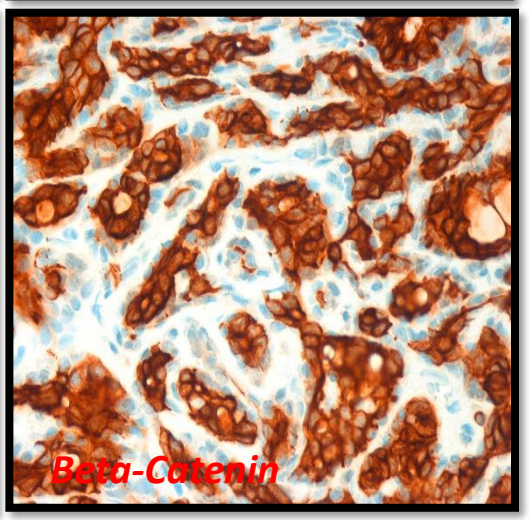










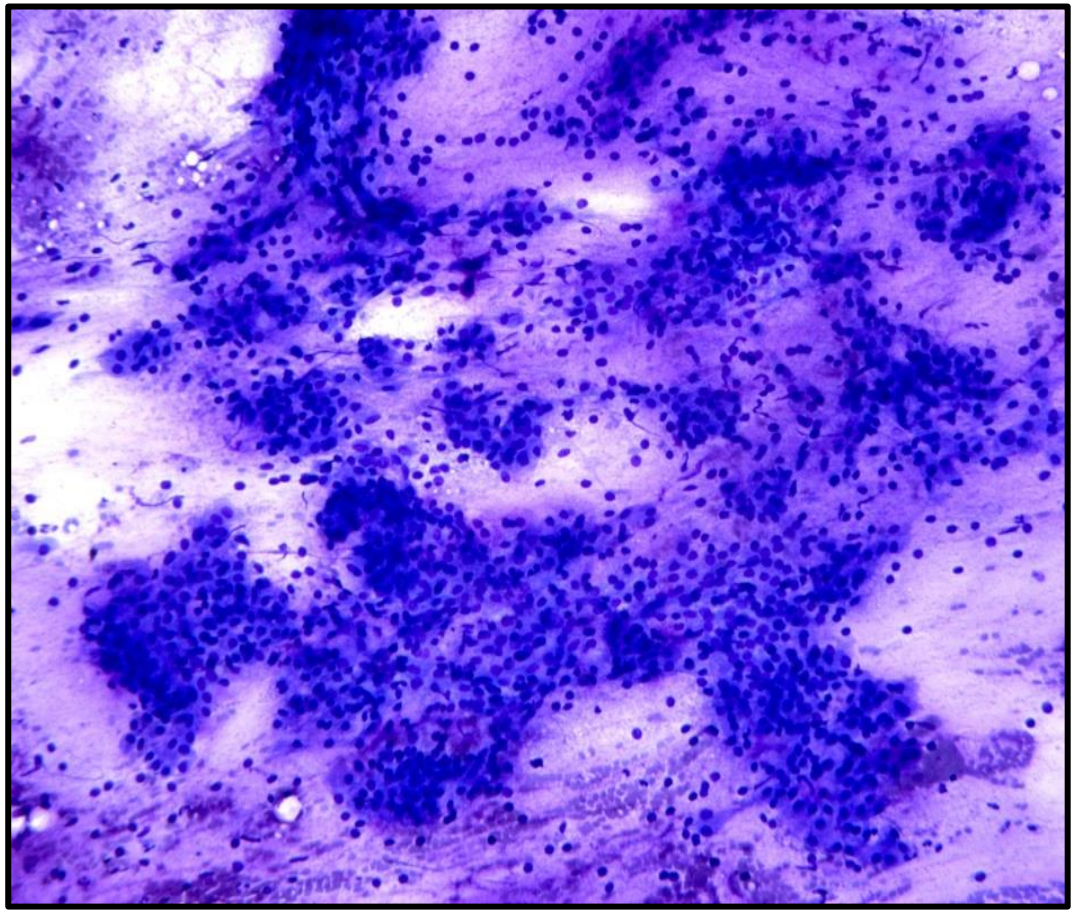


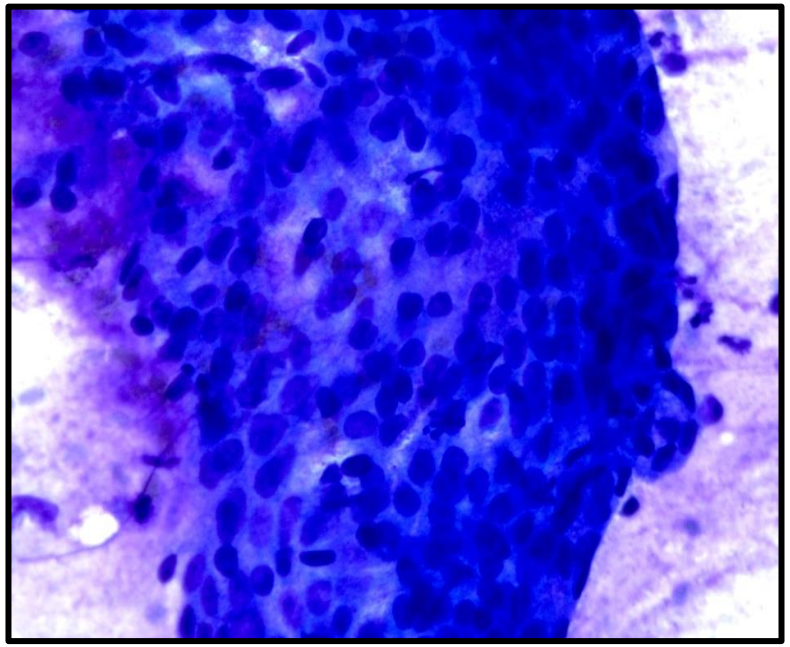
FNA – SUMP – neoplasm with clear cells and basaloid features, favor Basal cell adenoma.

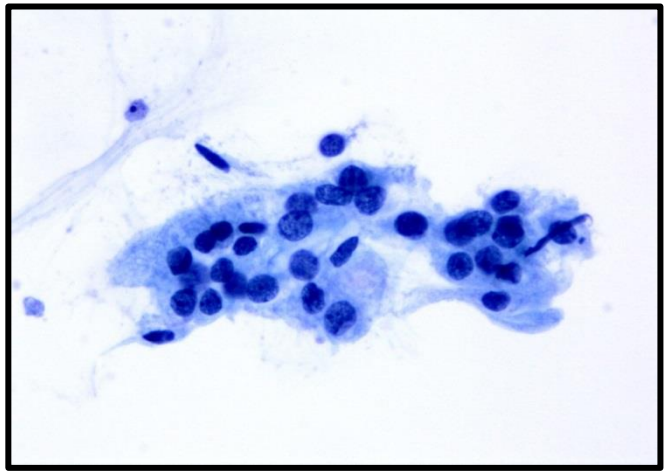
Lessons learned:

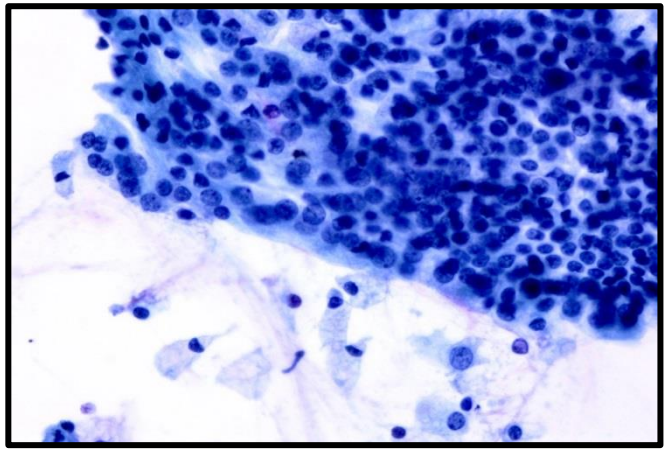
- ***Cystic areas within a benign tumor can be misleading on FNA – background debris, macrophages, clear or foam cells***
- ***FNA sample should be obtained from multiple regions within the same tumor***

26-year-old man with 2.8 cm ill-defined mass bridging superficial and deep lobes of parotid gland

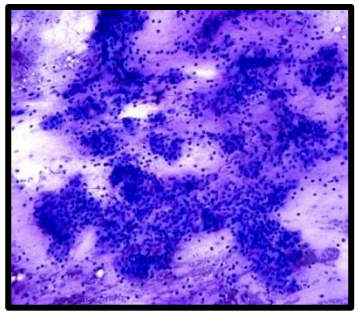


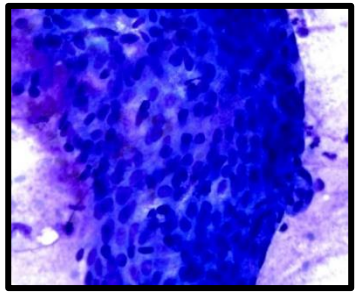


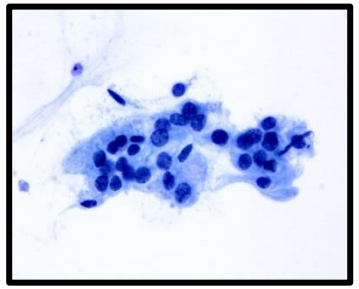


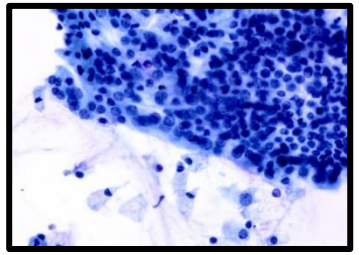


Malignant – Mucoepidermoid Carcinoma

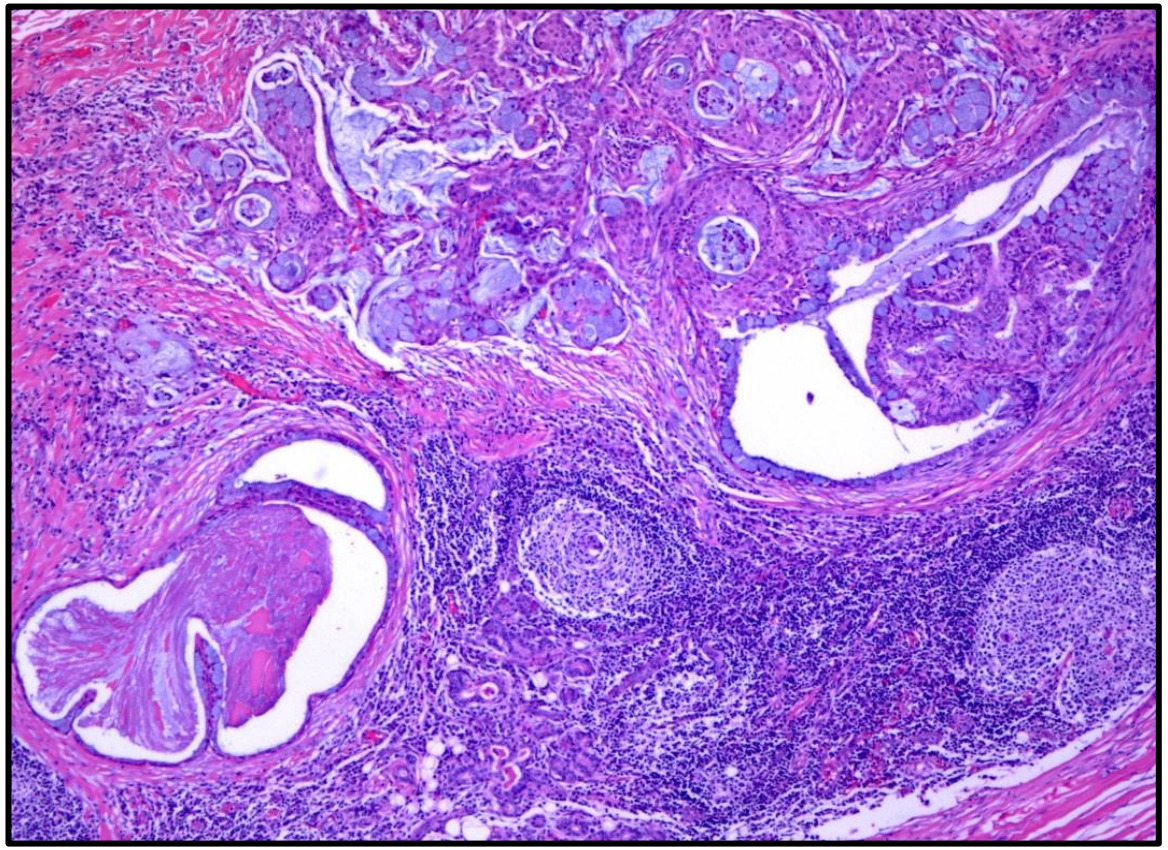


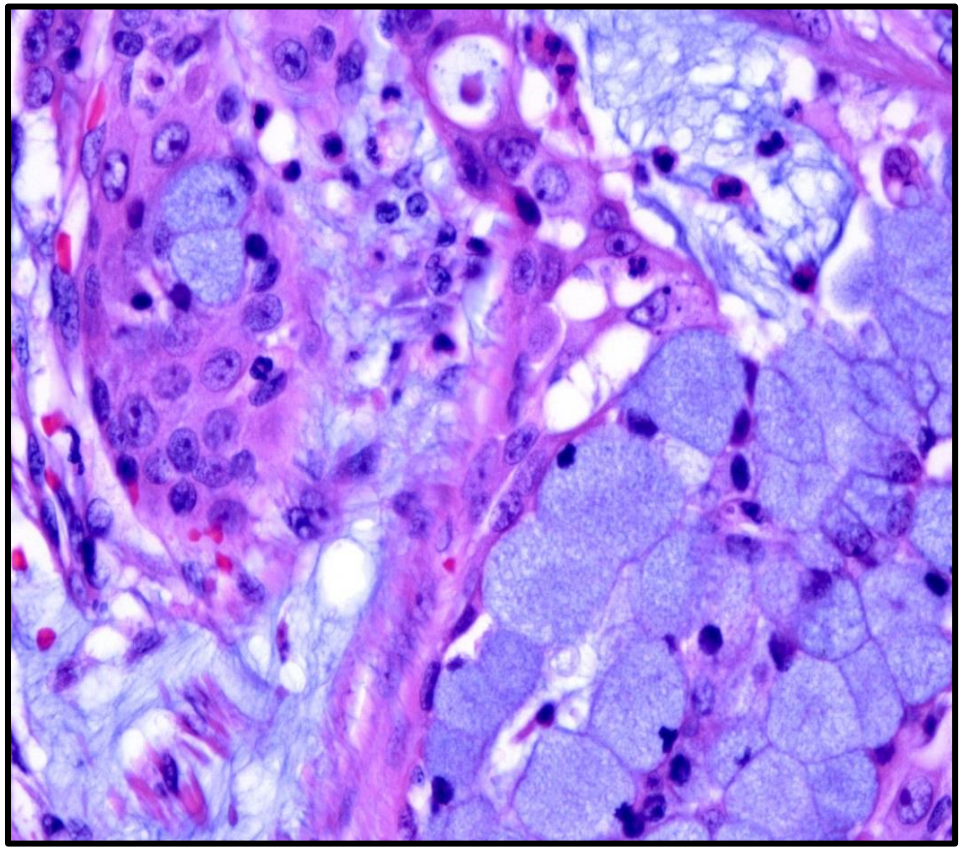






26-year-old man with 2.8 cm ill-defined mass bridging superficial and deep lobes of parotid gland

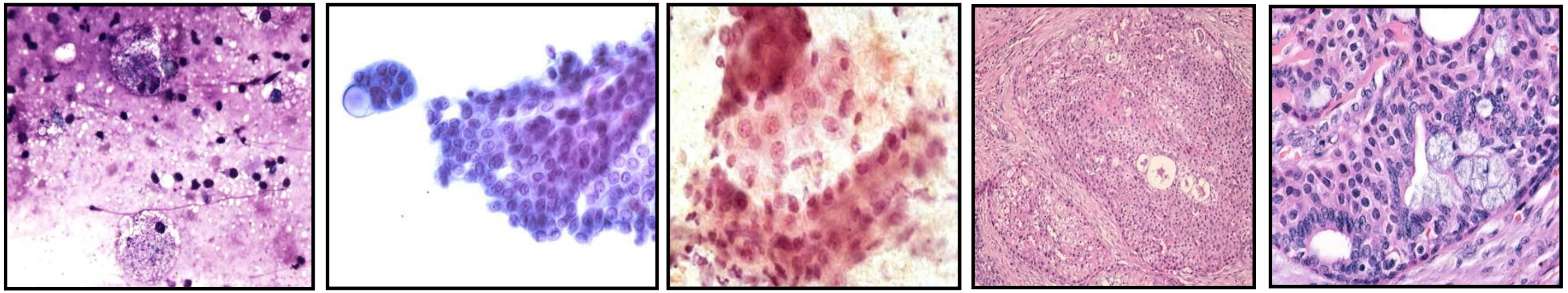




Malignant – Mucoepidermoid Carcinoma

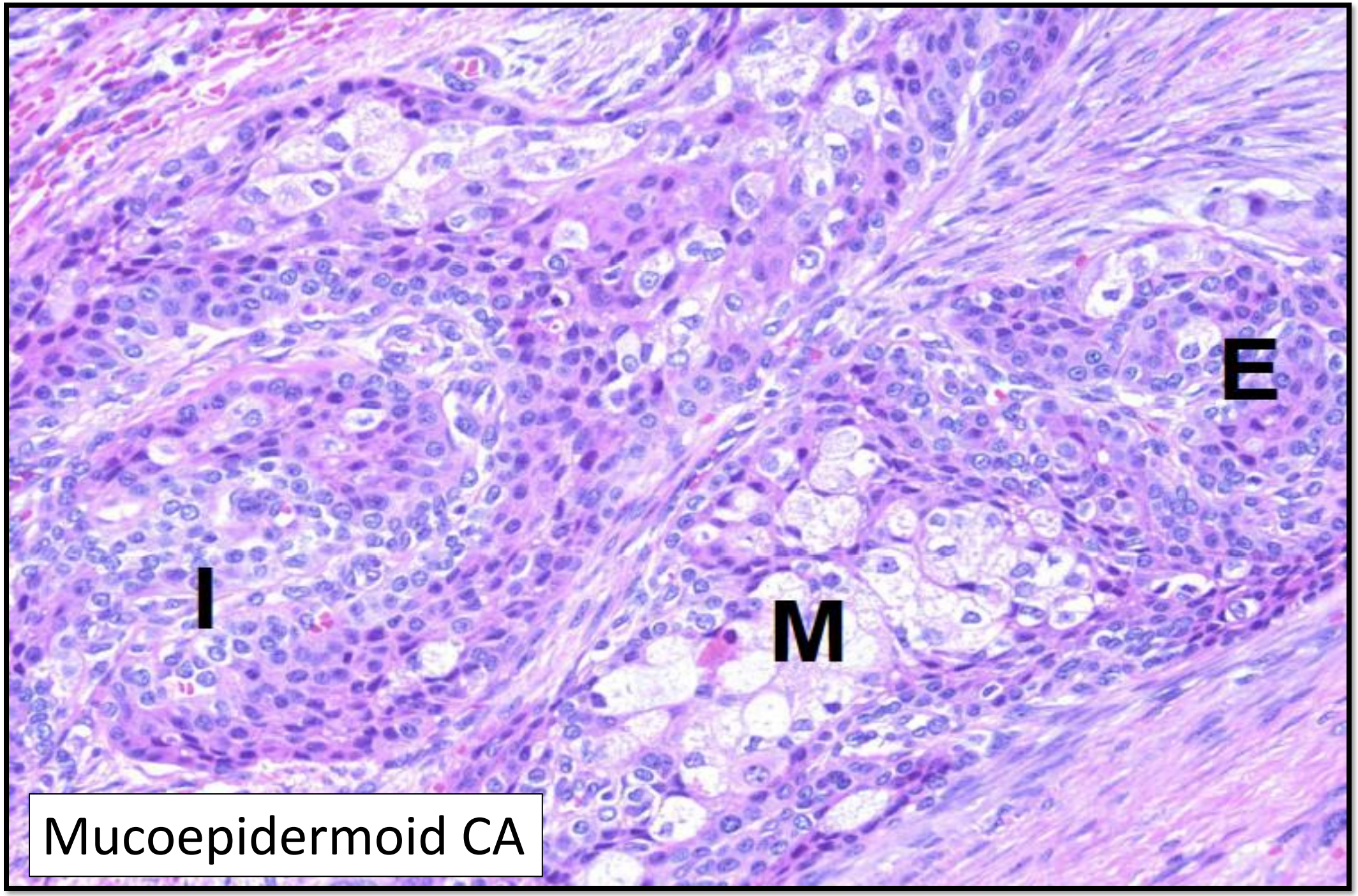
Mucoepidermoid Carcinoma - Classic Case

- **Background**
  - **Mucinous (low grade tumors), extracellular mucin, easily detected strings of mucin**
  - **Lymphocytes**
- **Cells**
  - **Clear / foamy macrophage type cells (mucous glandular cells)**
  - **Ductal appearing intermediate cells.**
  - **Glandular cells, singly or gland formation.**
  - **Squamous cells. Lymphocytes**



Mucoepidermoid Carcinoma

- Malignant; painless or tender, facial paralysis
- Most common malignant salivary gland tumor (16% of all salivary gland tumors)
- F>M
- Histology:
  - Three cell types: mucus / intermediate / epidermoid
  - Mucus pools common
- **t(11;19)(q21;p13): *CRTC1-MAML2* (55-65%)**
  - Associated with better prognosis
- Prognosis:
  - Low-grade tumors: 5% mets to nodes; 2.5% lethal
  - High-grade tumors: 55% mets to nodes; 80% lethal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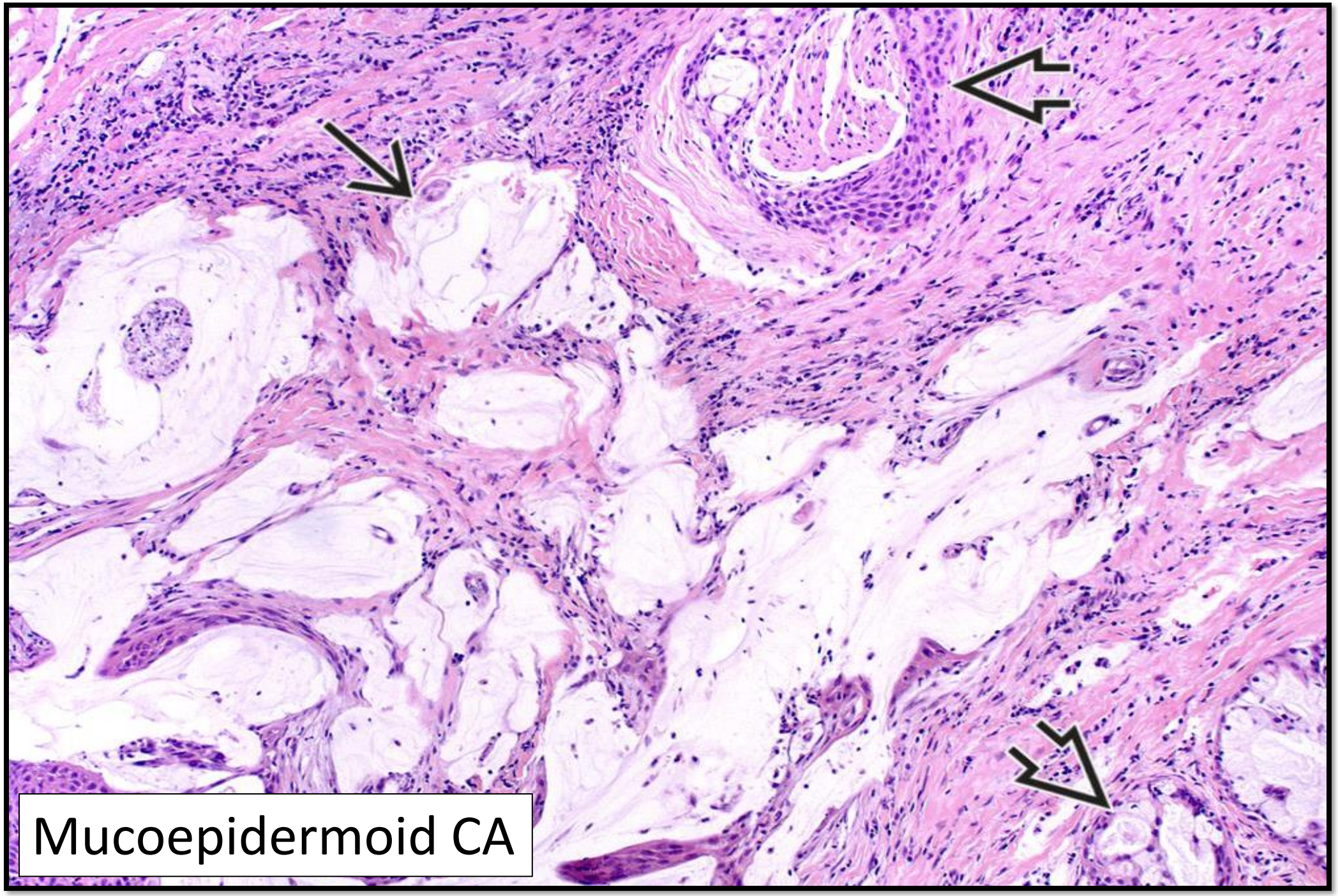
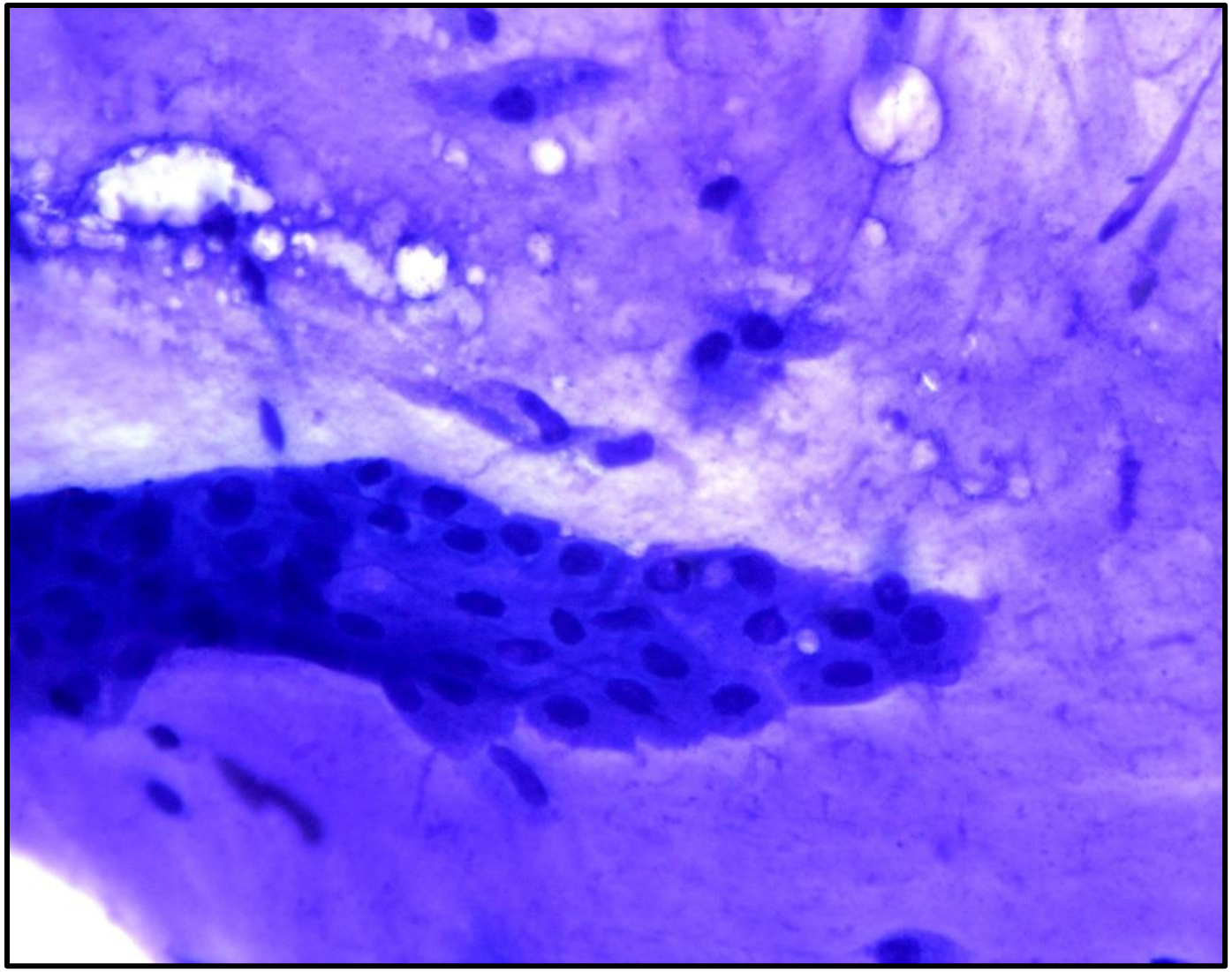
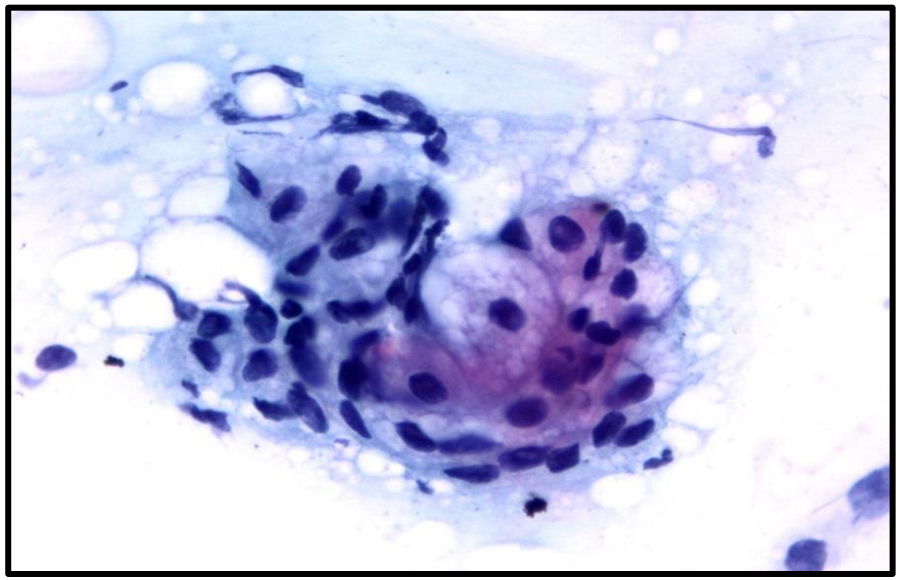
Mucoepidermoid CA

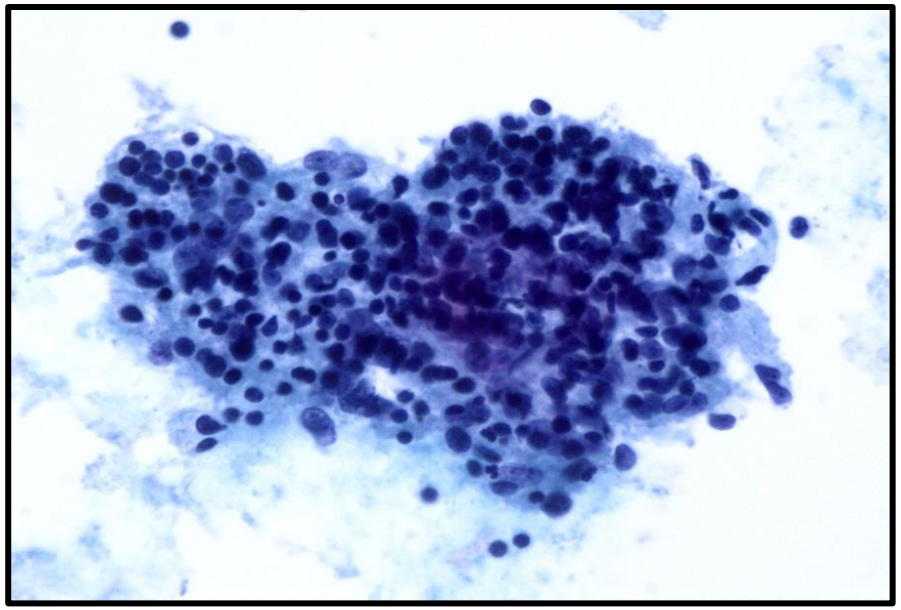

Mucoepidermoid CA

Mucoepidermoid Carcinoma – Not so Classic Cases

Low Cellularity Specimens

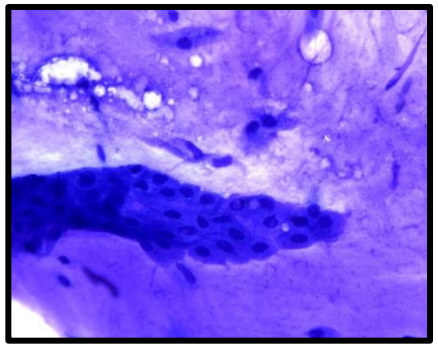


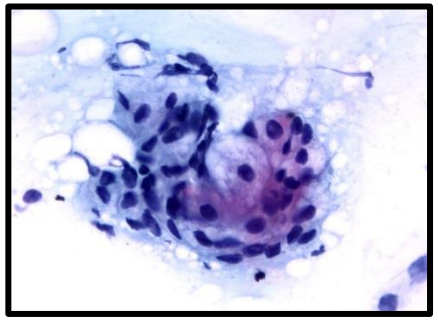


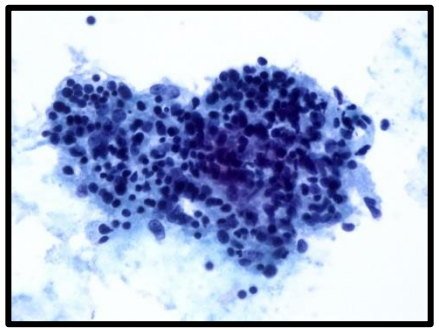


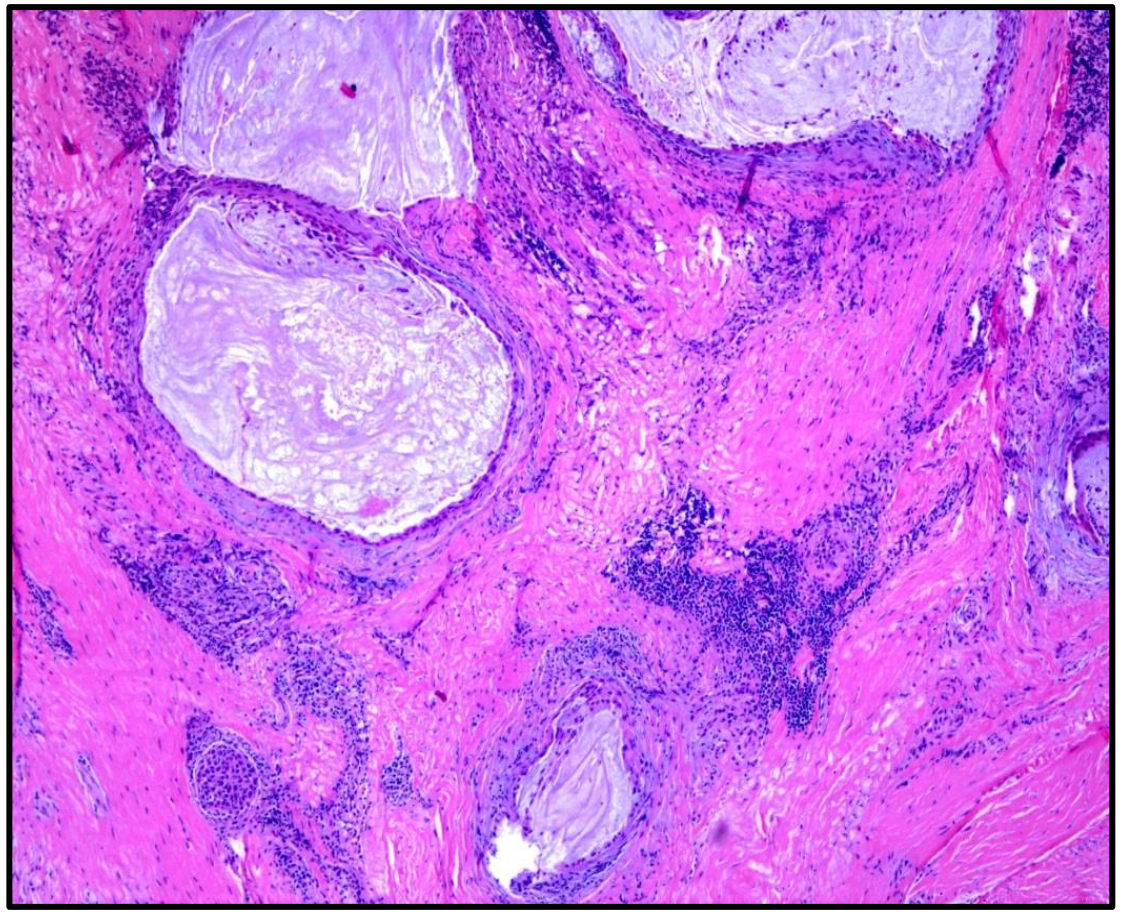
Mucoepidermoid Carcinoma – Not so Classic Cases

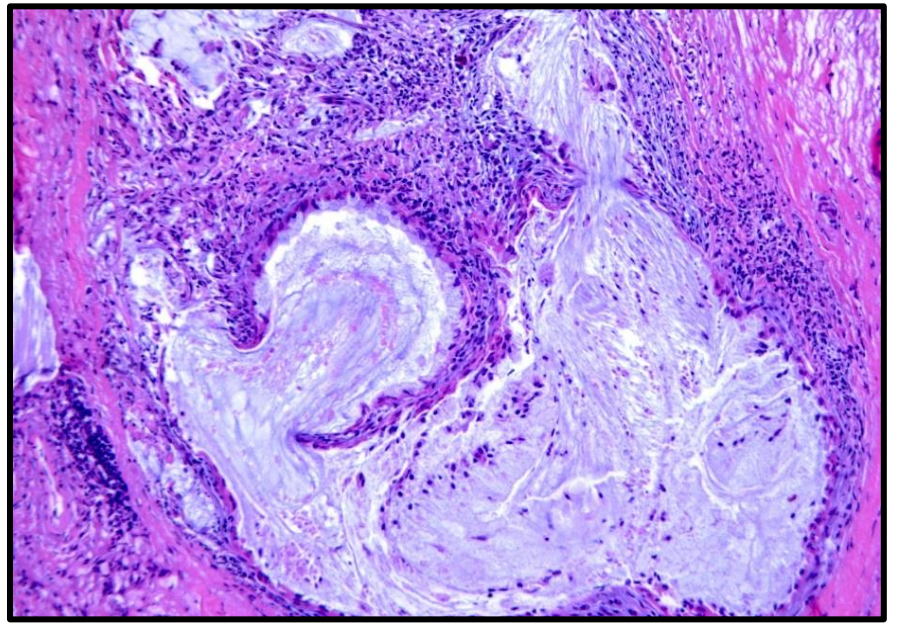
Low Cellularity Specimens

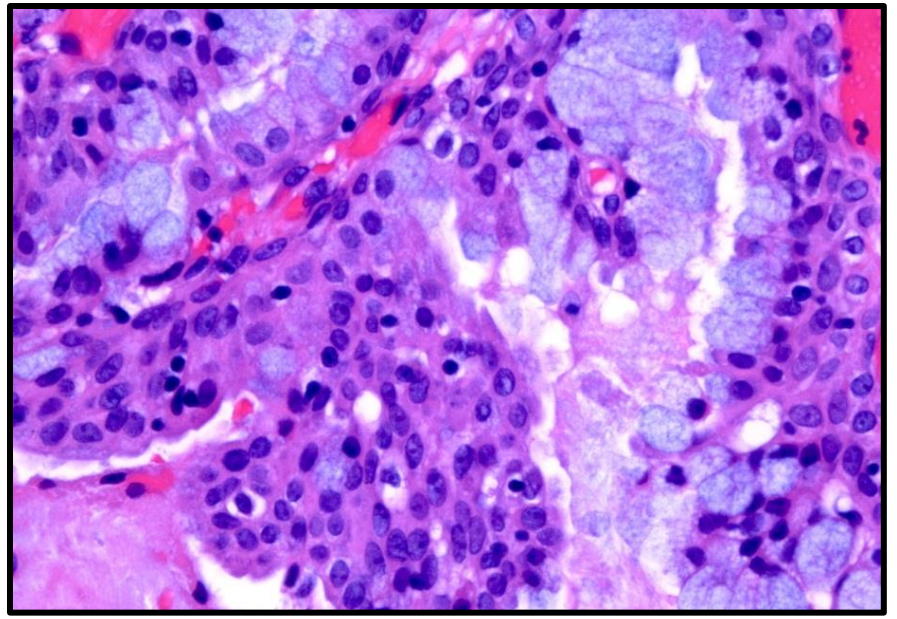








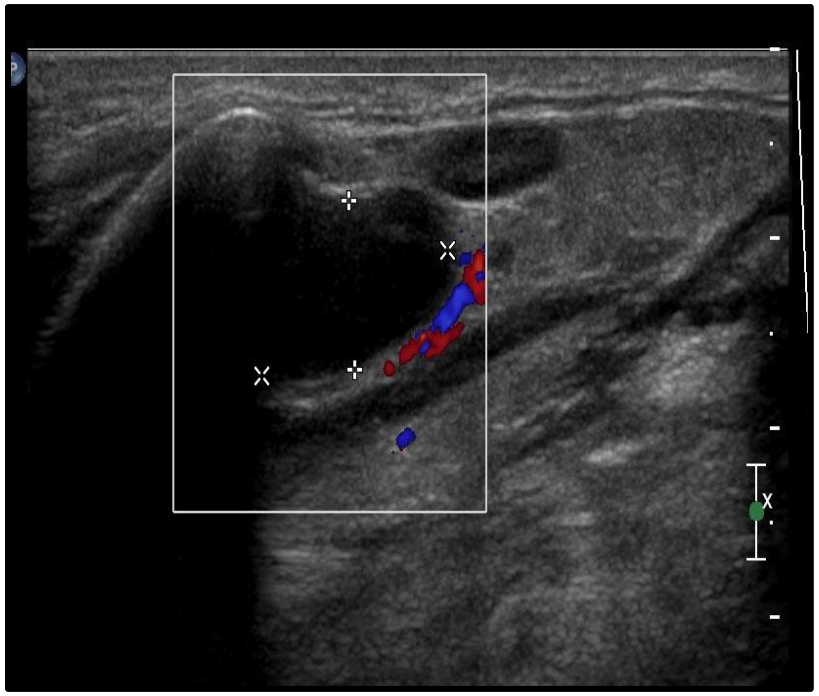


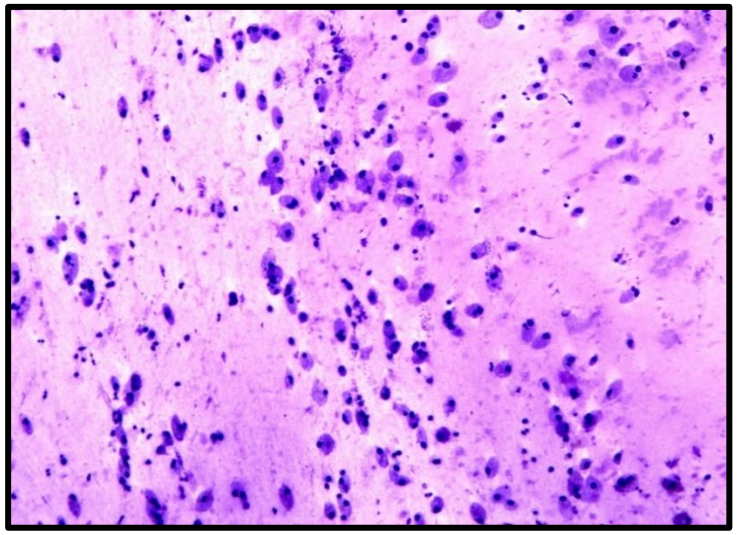


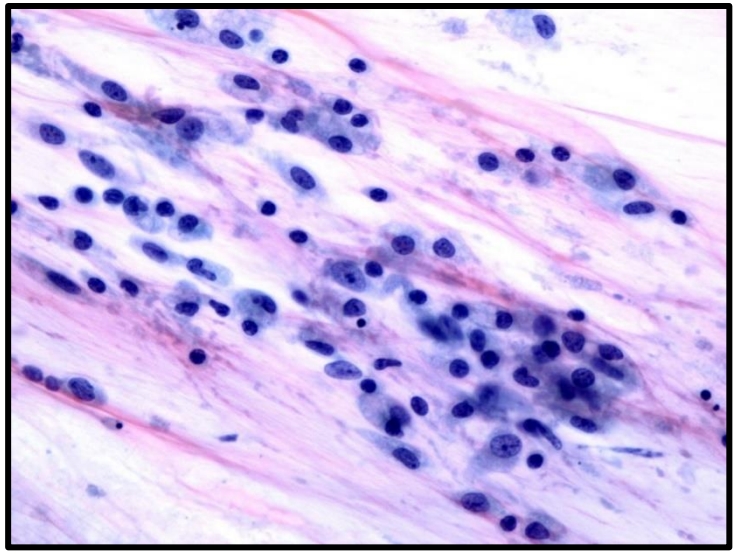
Low Grade Mucoepidermoid Carcinoma FNA Differential Diagnosis

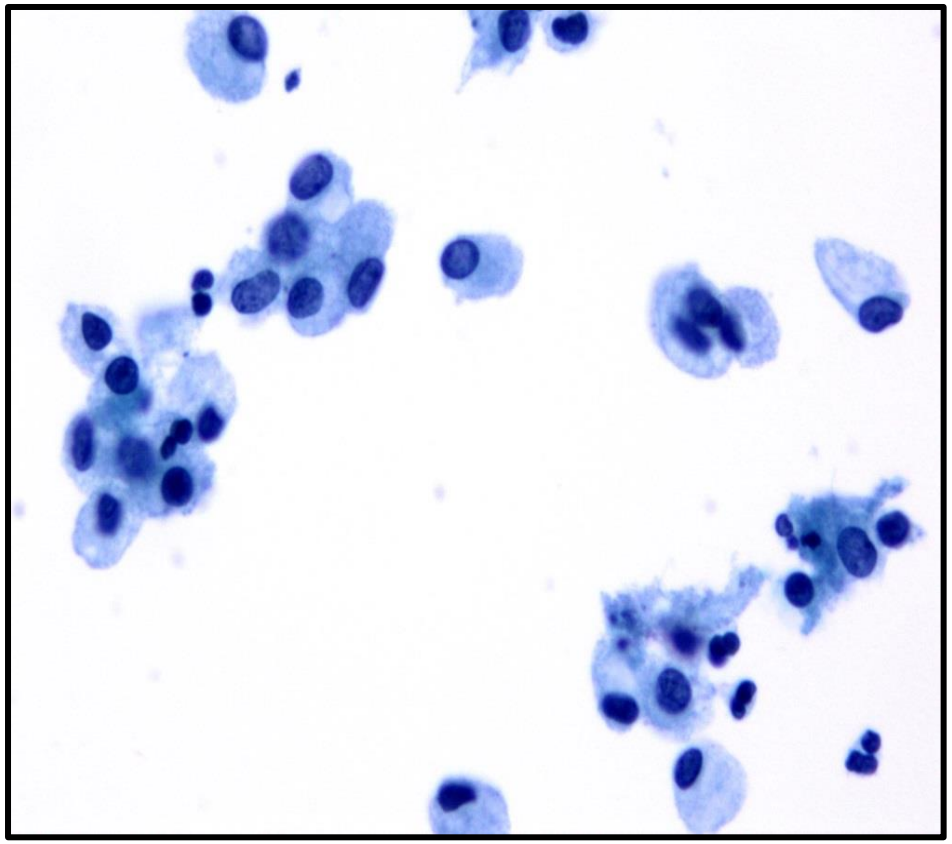
- **Benign tumors with focal mucinous or clear cell change**
  - **Pleomorphic adenoma**
- **Benign cysts**
- **Chronic sialadenitis with mucinous metaplasia**
- **Low grade salivary duct carcinoma**
- **Squamous cell carcinoma**
- **Acinic cell carcinoma**
- **Carcinoma with clear cell features**

45 year-old man with 2.5 cm submandibular/sub-mental space mass



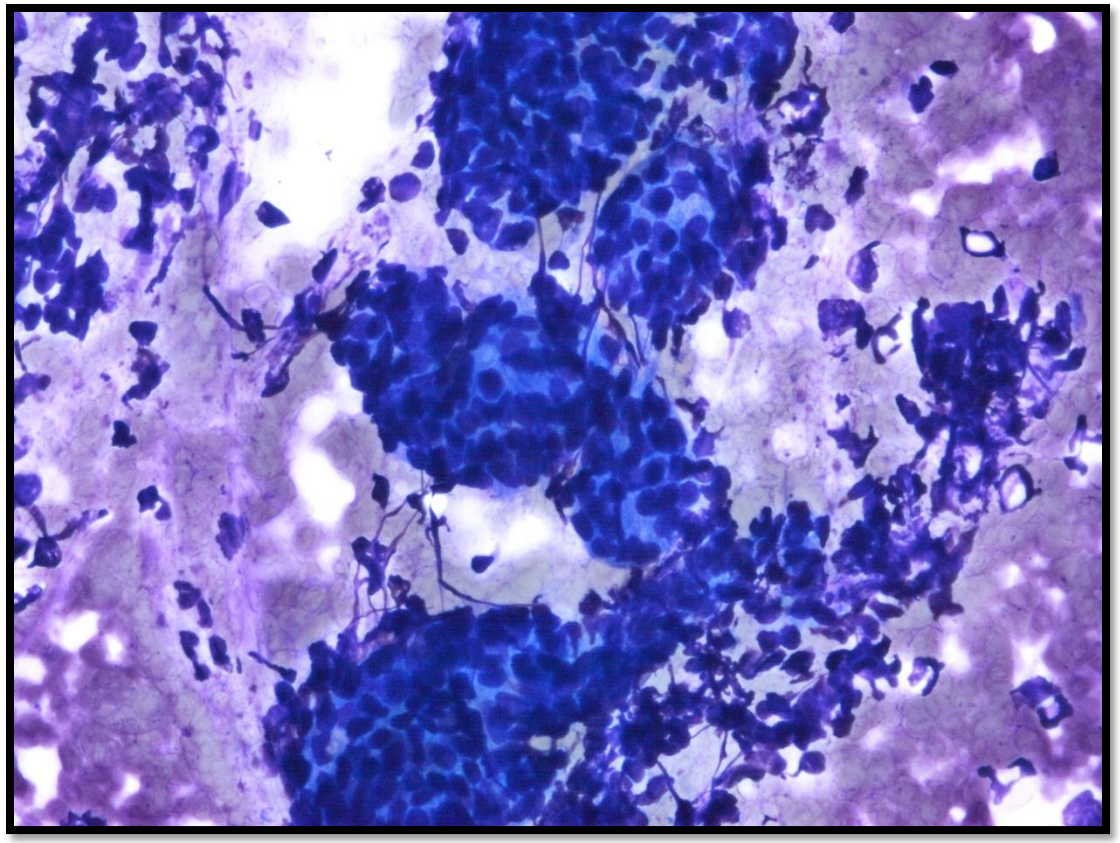


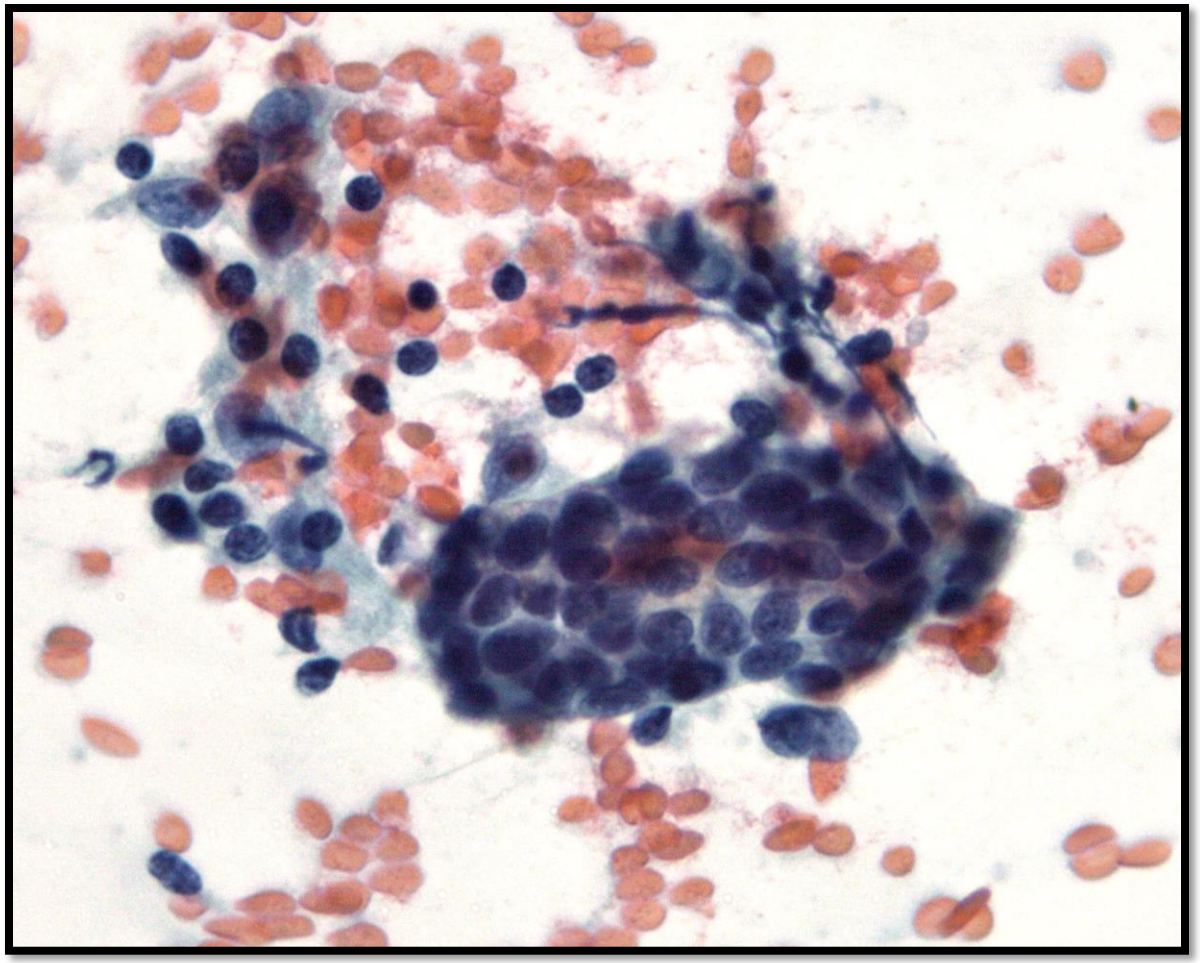




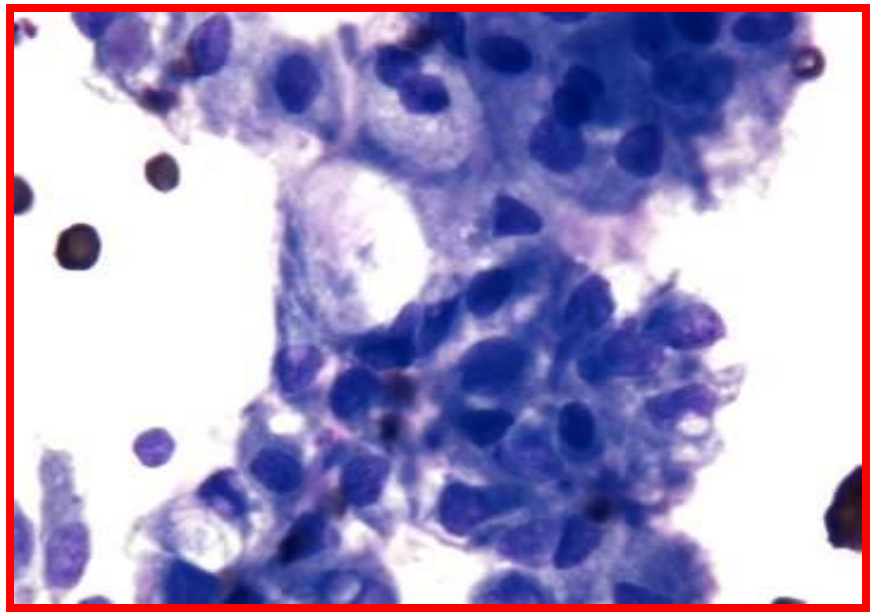
Chronic Sialadenitis

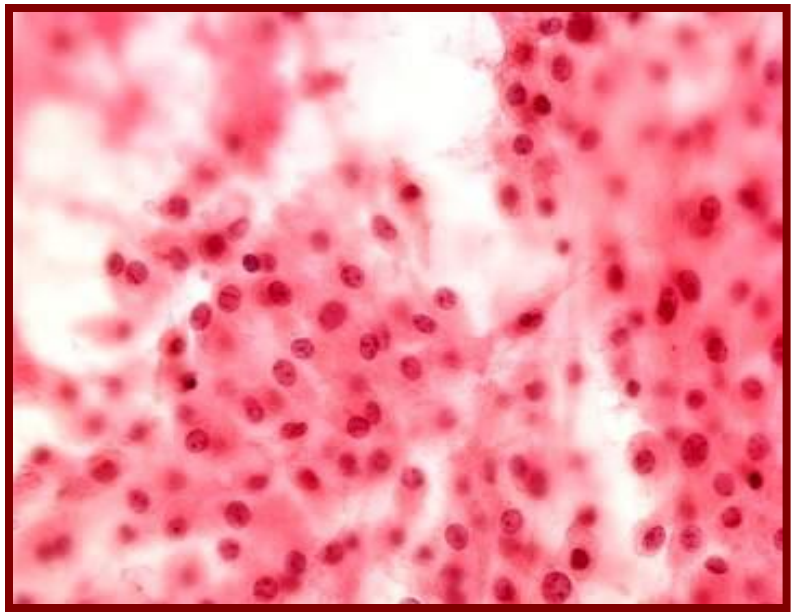
- Scant cellularity. Ductal epithelium (sheets & tubules). Paucity of acinar elements.
- Background debris & inflammation. Fragments of mesenchymal tissue.
- Squamous & mucinous Metaplasia. Cell atypia ?

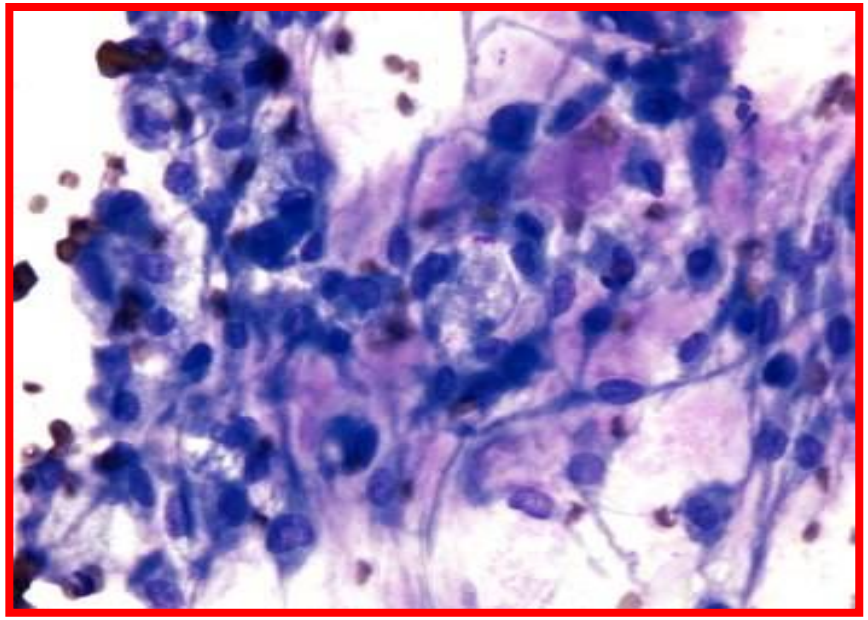


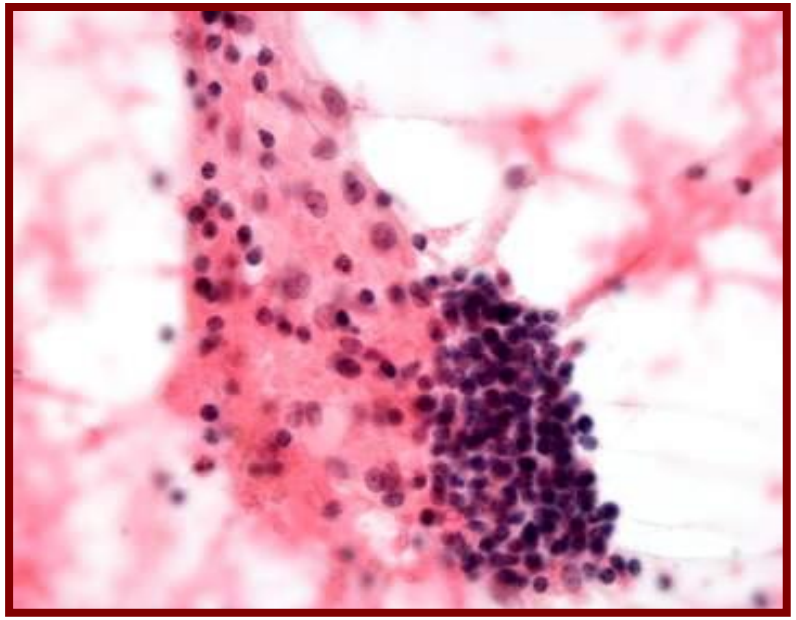


23 Year-old-man with Right Parotid Mass



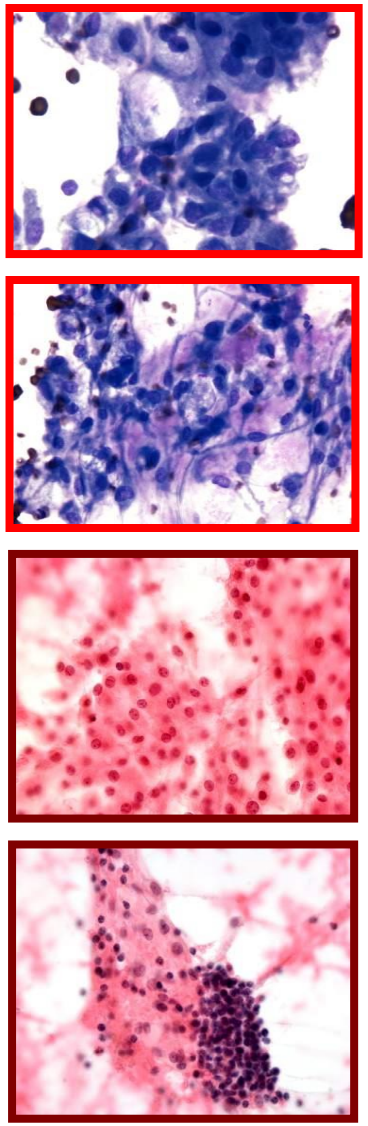


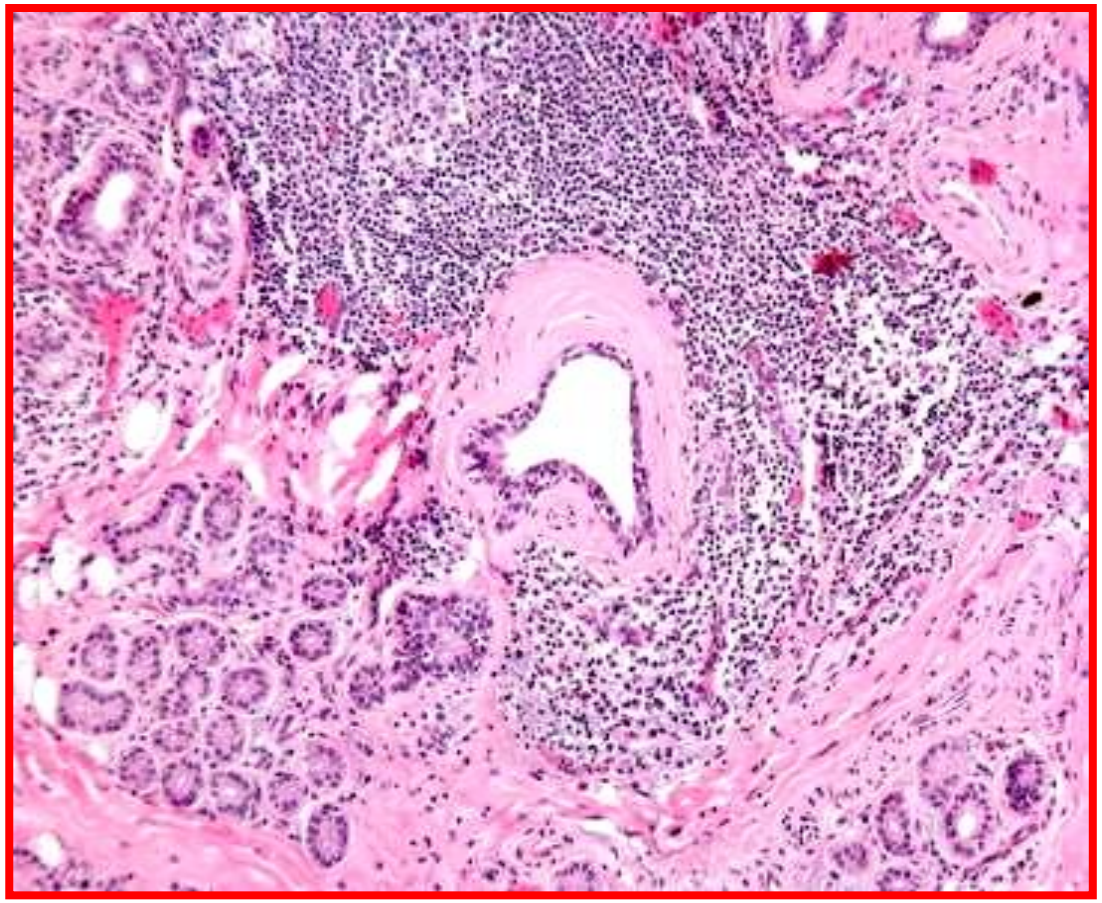


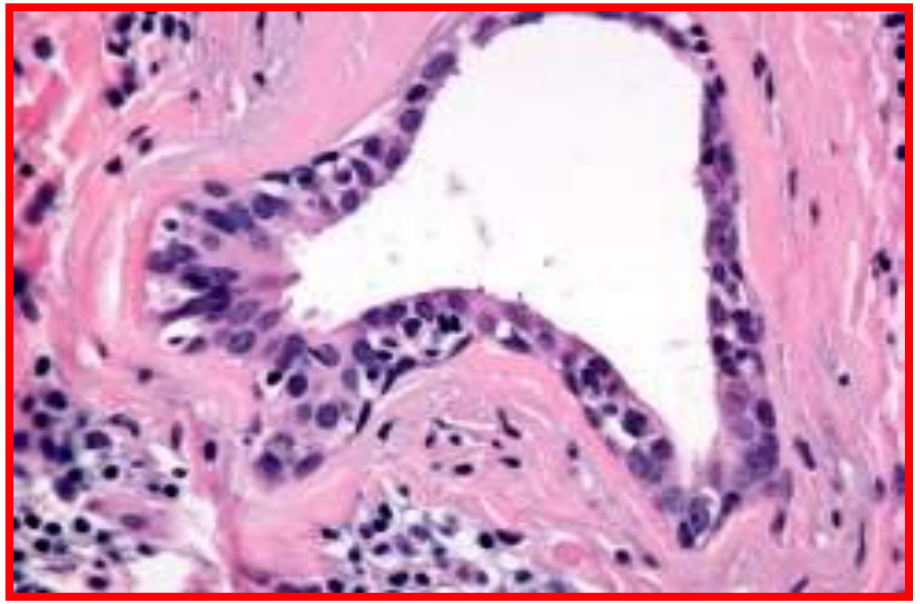


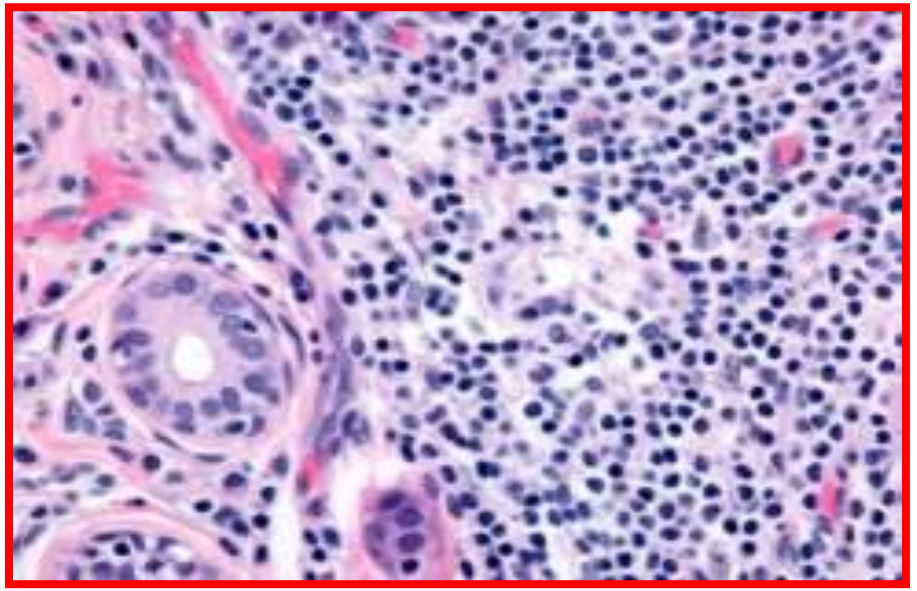
Atypical cells Suspicious for Mucoepidermoid Carcinoma – Mucicarmine stain positive on the smear

23 Year-old-man with Right Parotid Mass









Surgical Pathology Diagnosis:
Chronic Sialadenitis

Lymphocytes in Salivary Gland FNA Specimens

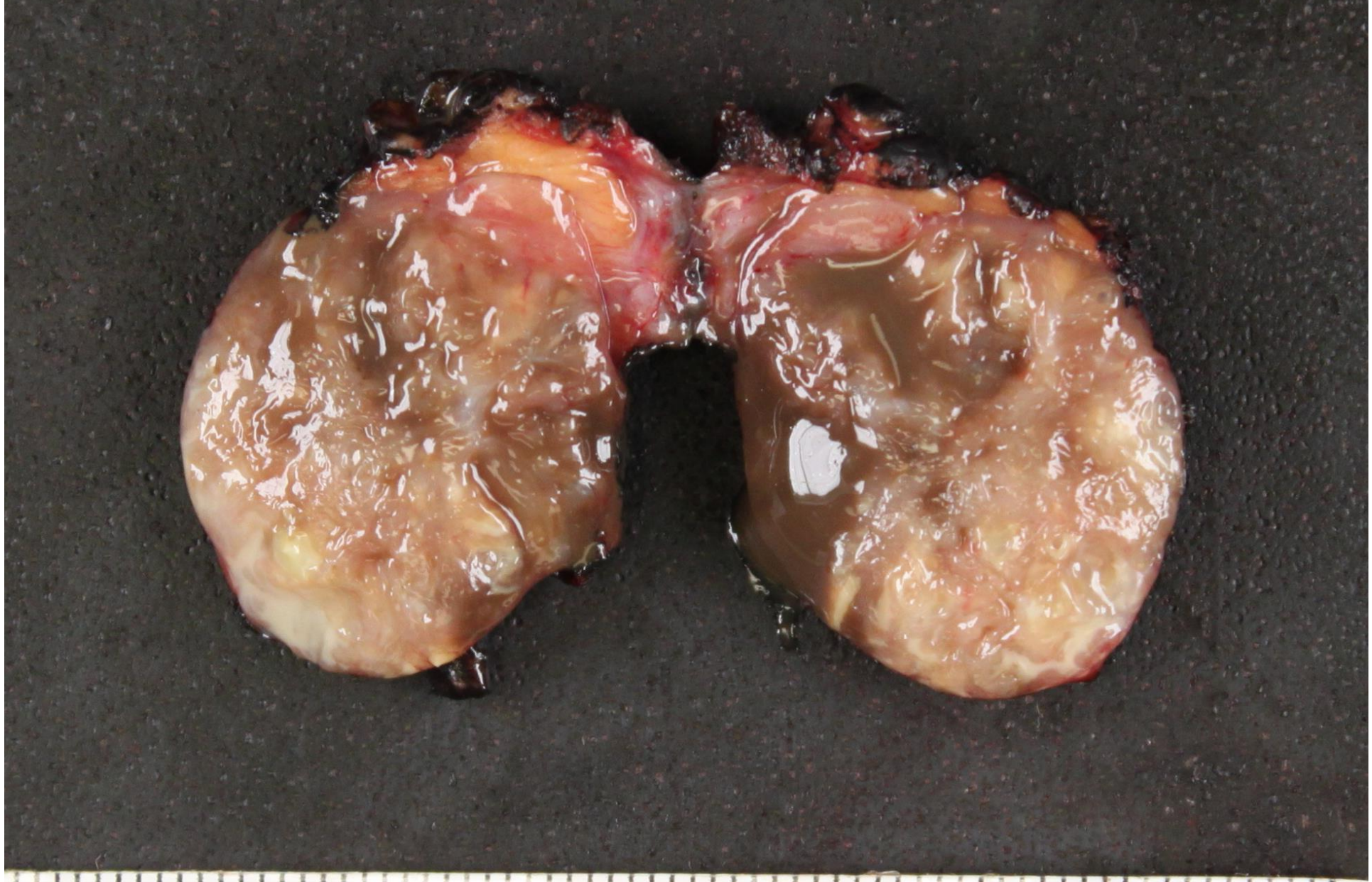
- Intraparotid LN
- Lymphoepithelial cyst
- Chronic Sialadenitis
- Warthin Tumor
- Acinic cell carcinoma
- **Mucoepidermoid Carcinoma**
- Lymphoma

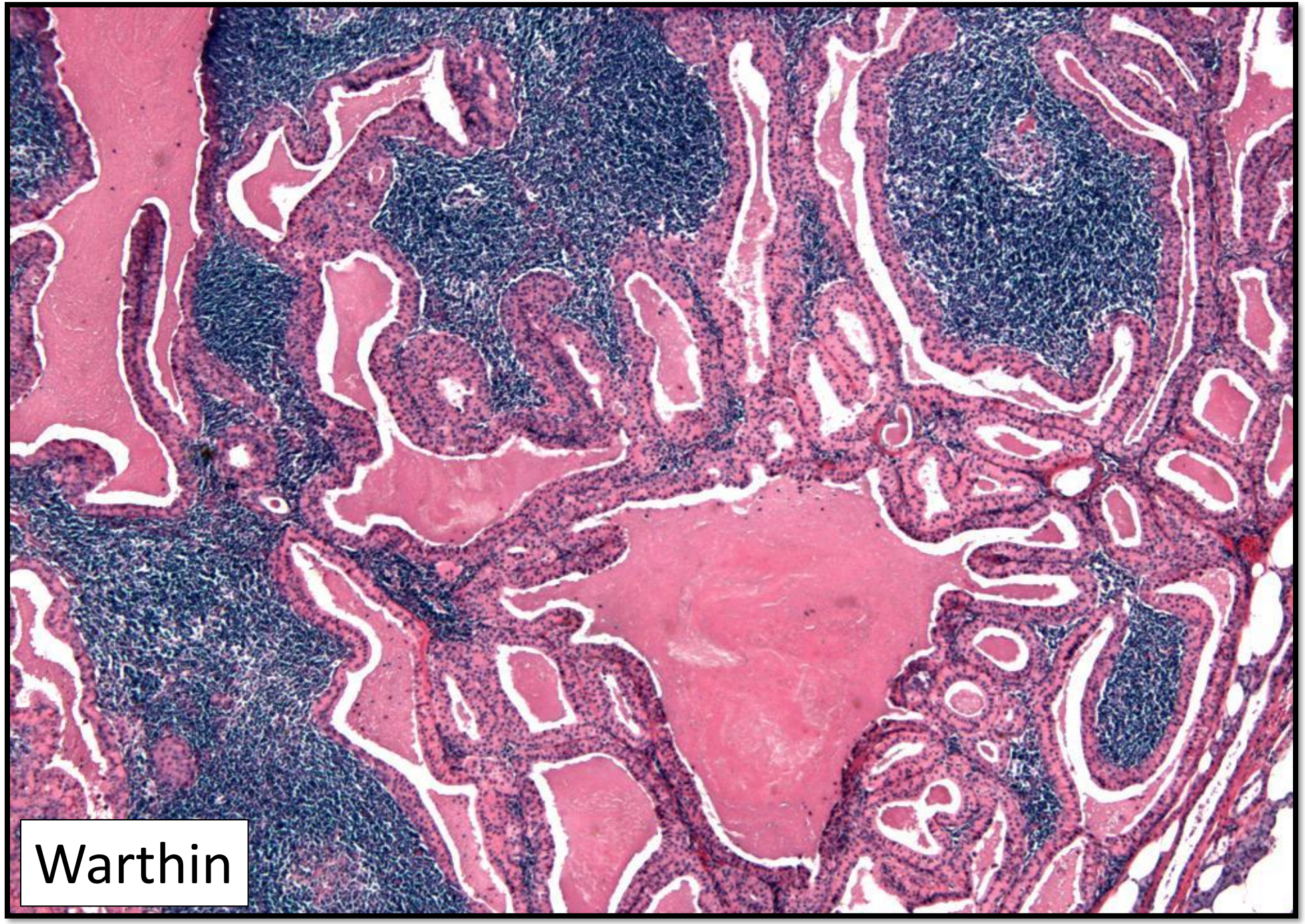
Warthin Tumor

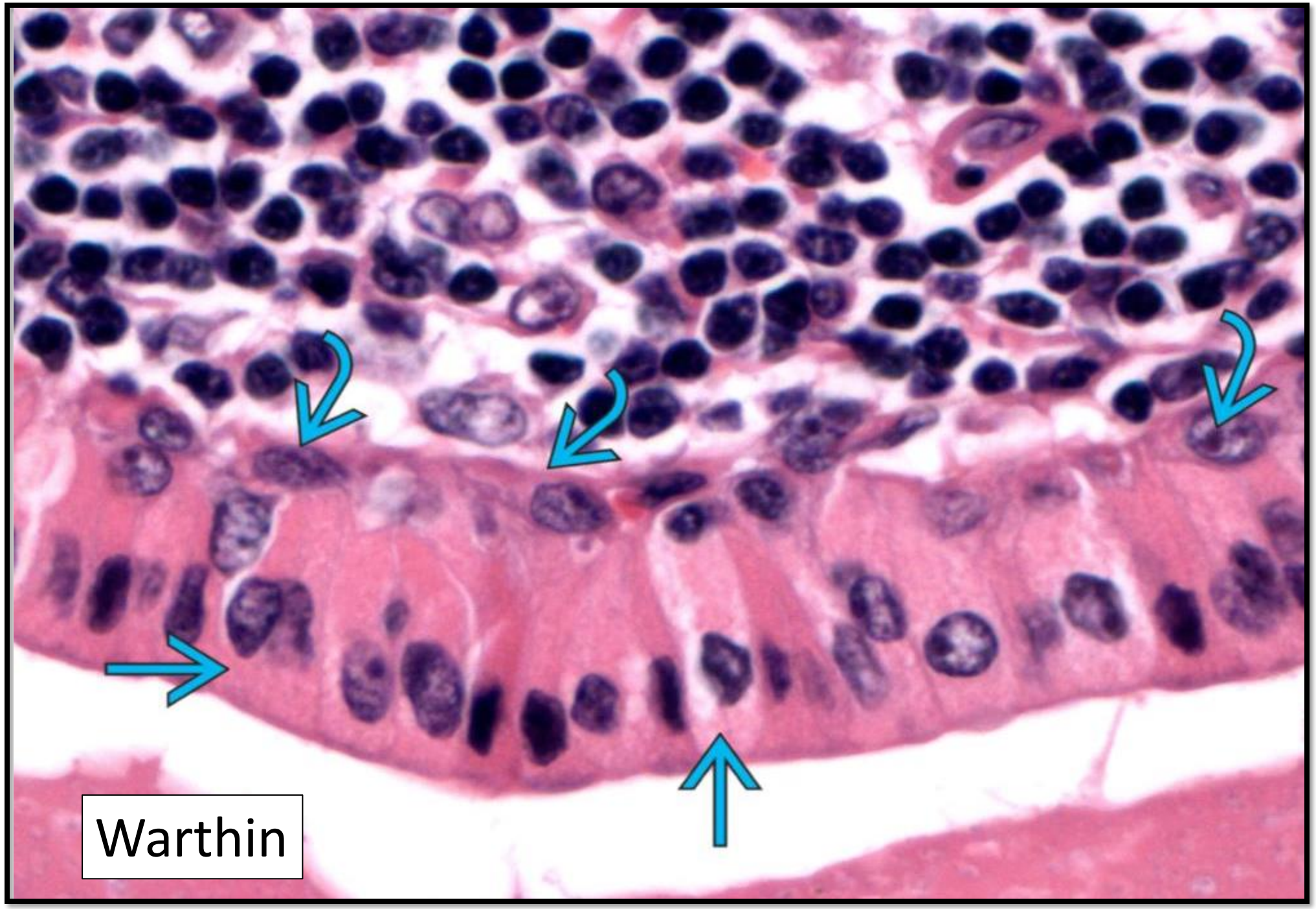
- **Primarily occurs within parotid gland**
  - Second most common salivary gland neoplasm – 5-10%
  - Believed to originate from salivary duct remnants entrapped within glandular lymphoid tissue
- **Clinical features:**
  - 50-79 year-old
  - Common in men
  - Bilateral
  - PET and TC-99 positive

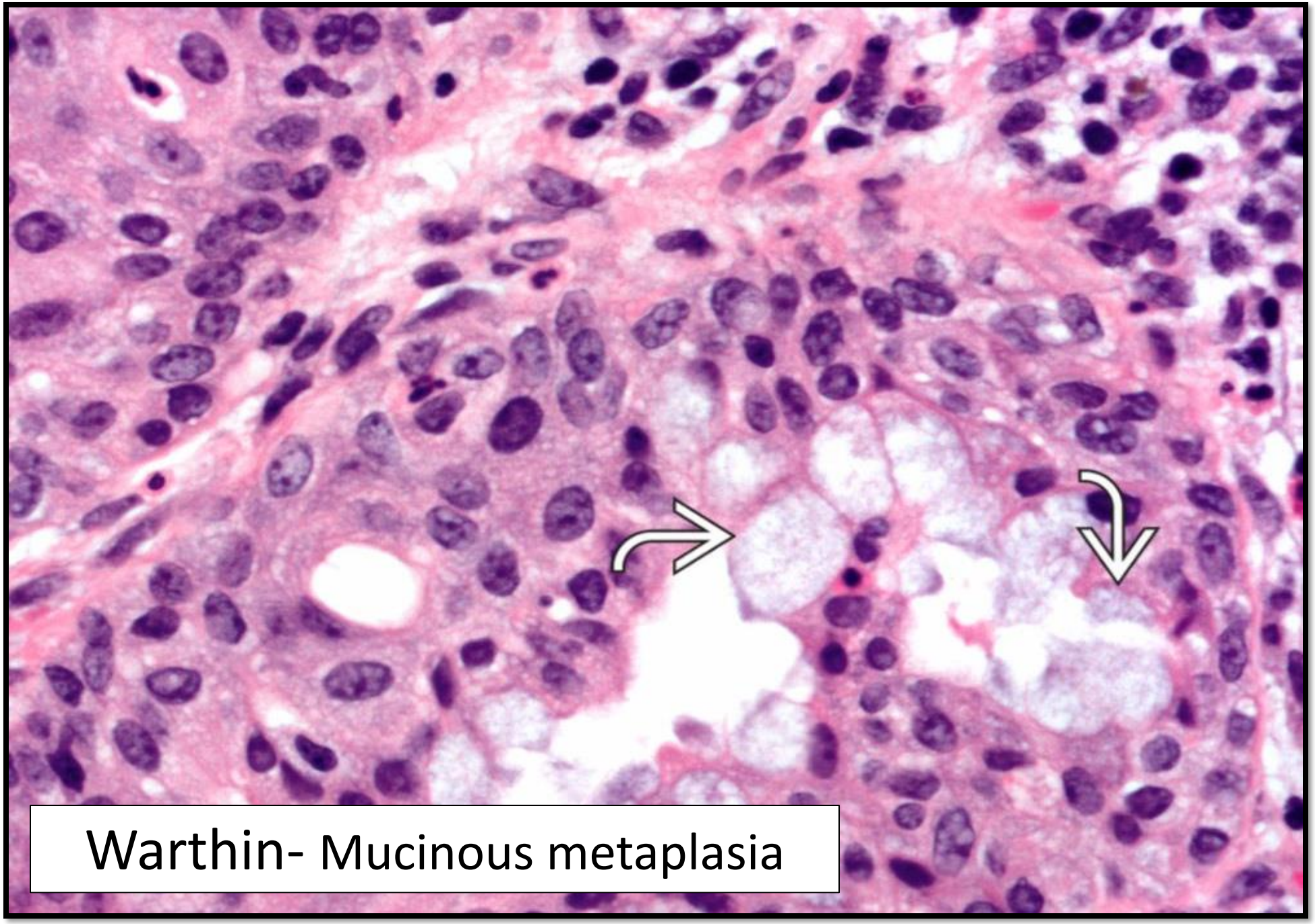
Cyto-morphology: Lymphocytes & Oncocytes

- Mixed population of lymphocytes in the background and intimately associated with oncocytic cells
- Background debris (grossly mobile oil consistency)
- Rarely Mucous cells (think of oncocytic mucoepidermoid carcinoma)


Warthin


Warthin

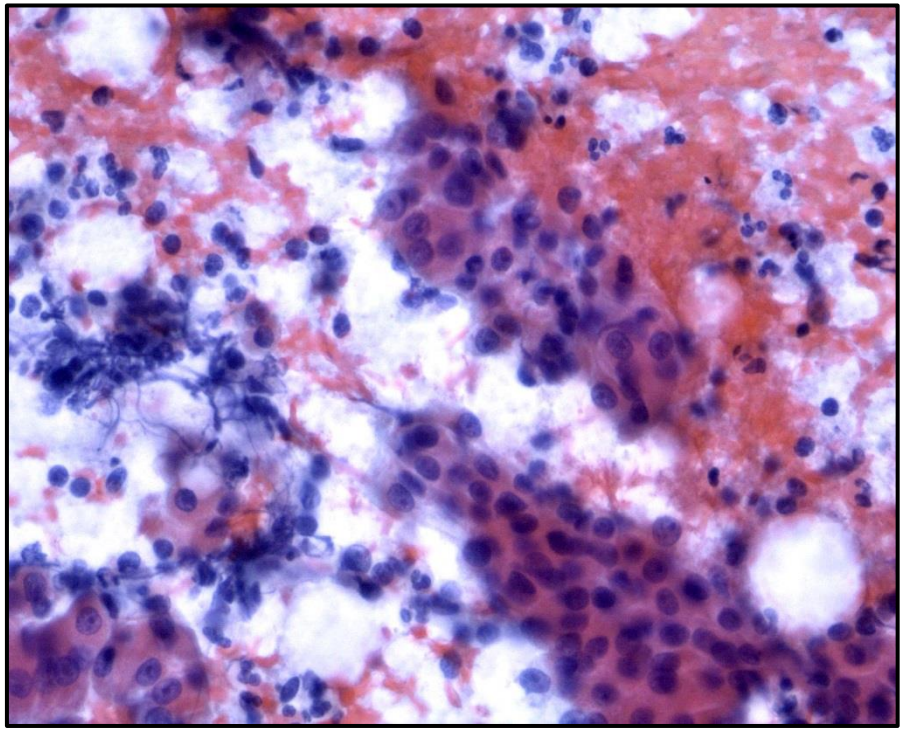

Warthin

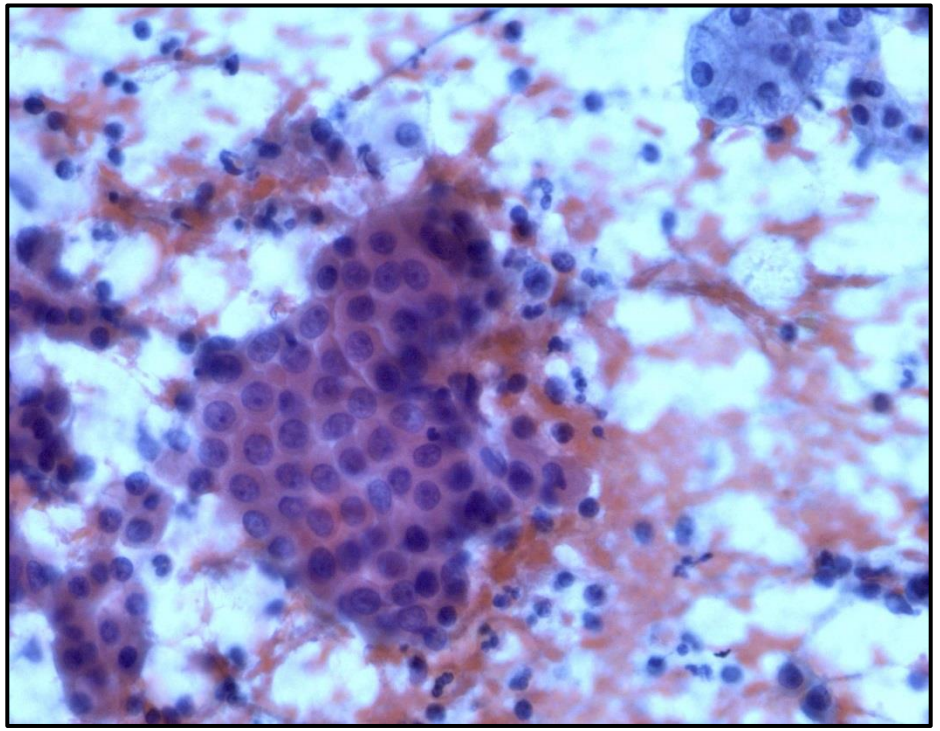

Warthin- Mucinous metaplasia

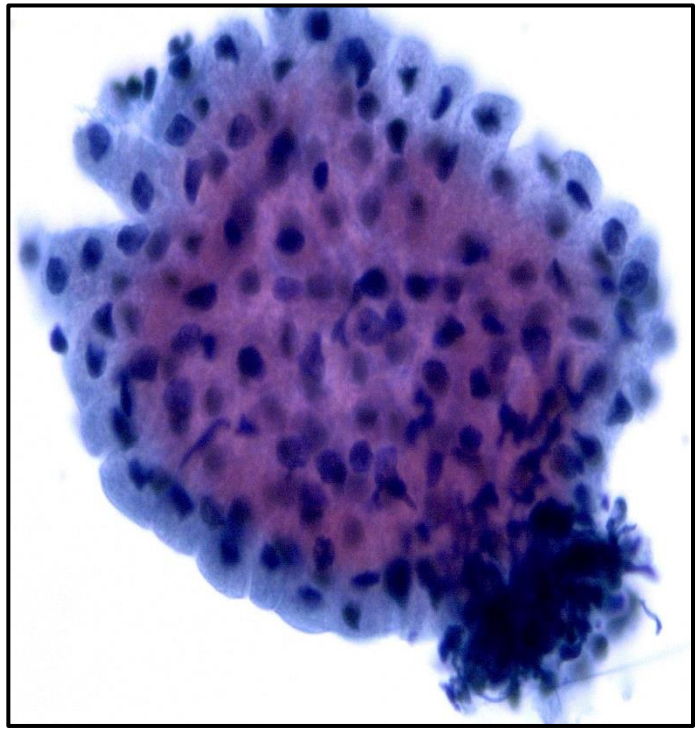
Warthin Tumor

Cyto-morphology: Lymphocytes & Oncocytes

- Mixed population of lymphocytes in the background and intimately associated with oncocytic cells
- Background debris (grossly mobile oil consistency)







Warthin Tumor

Cyto-morphology: Lymphocytes & Oncocytes

- **Mixed population of lymphocytes in the background and intimately associated with oncocytic cells**
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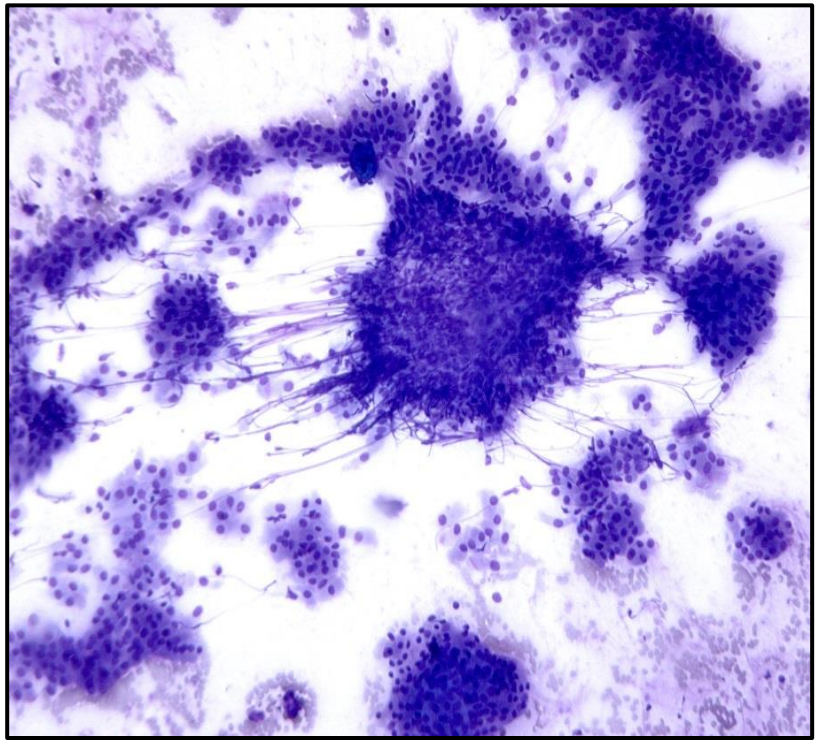
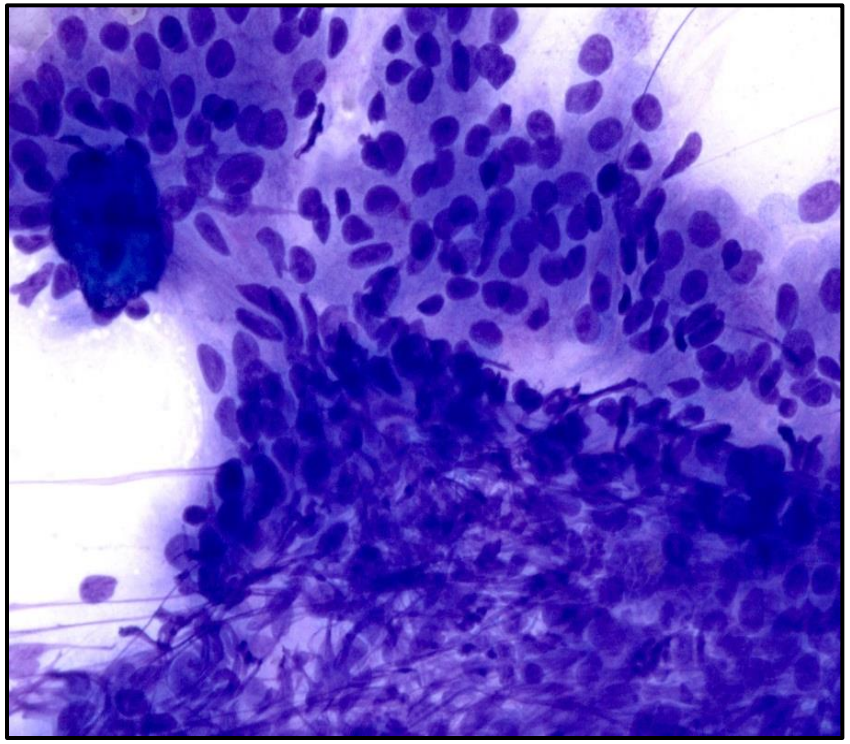
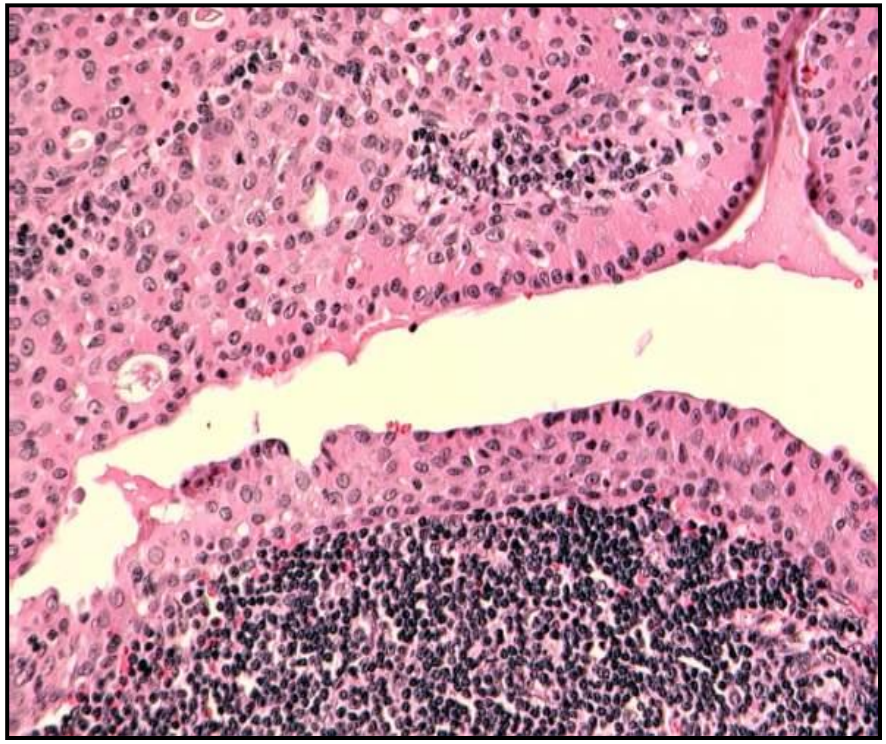
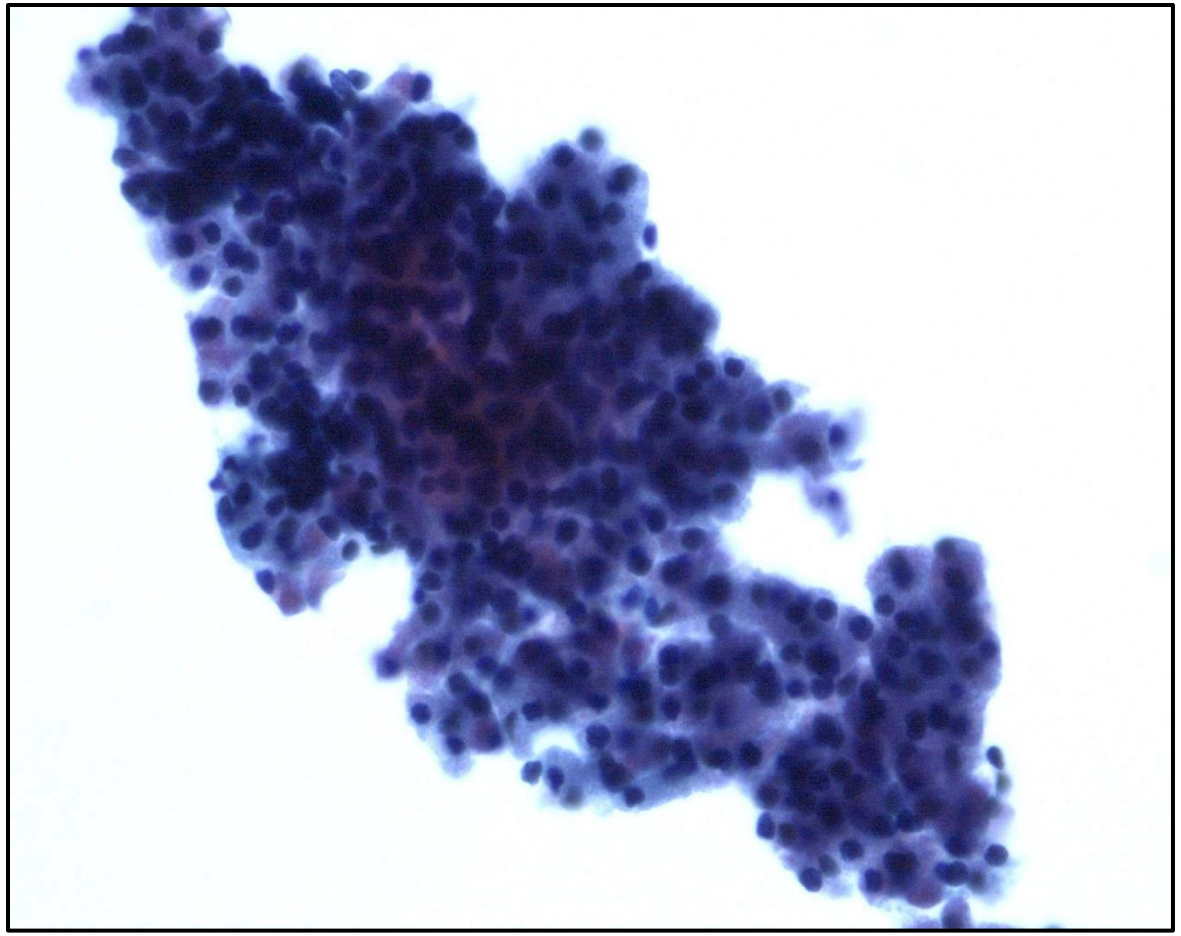
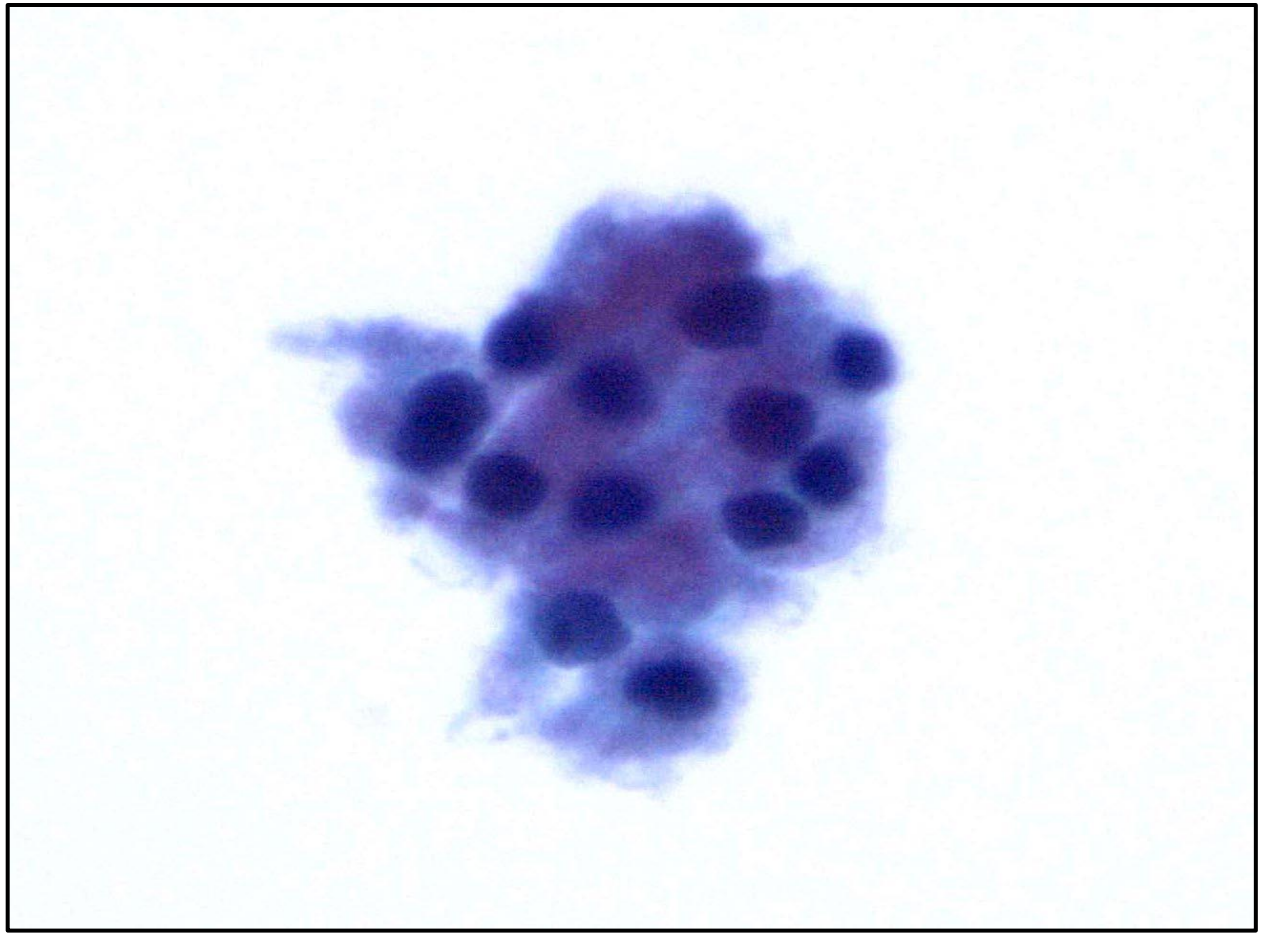






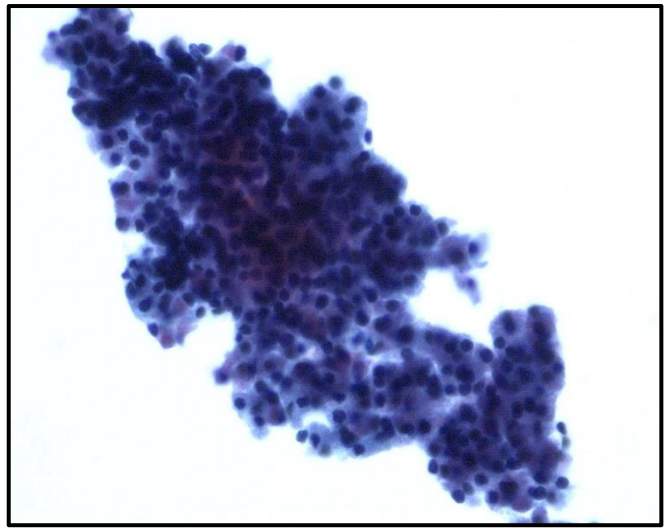
45-old-woman with 2.5 cm right parotid mass

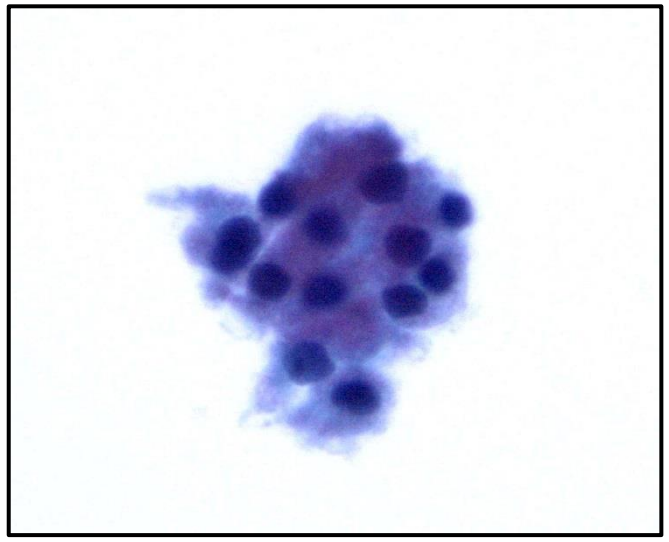


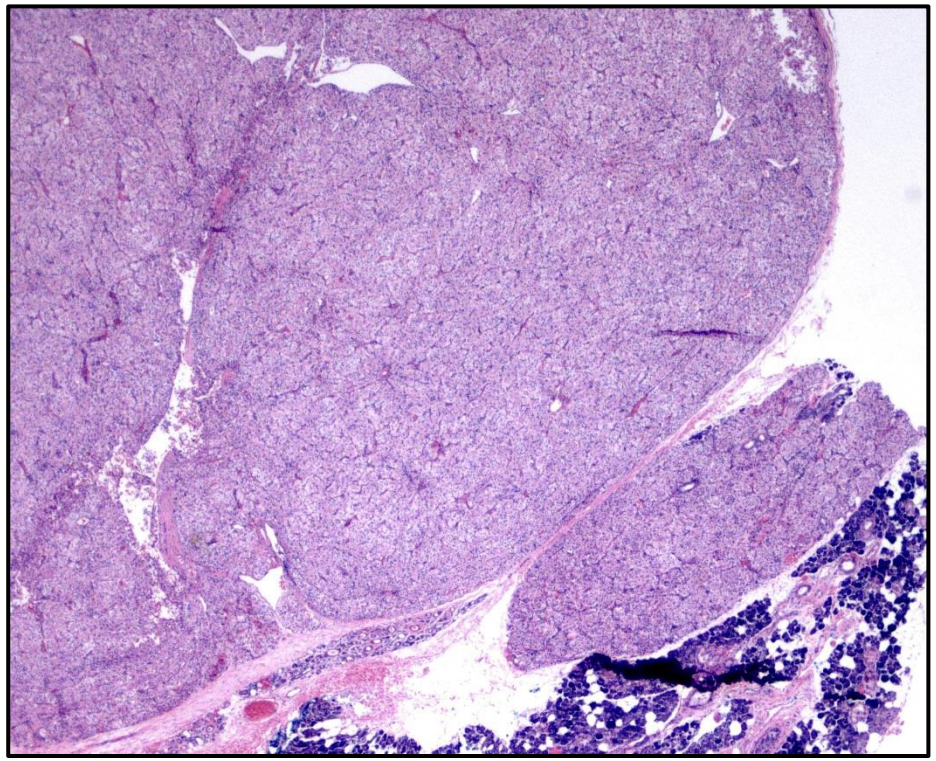


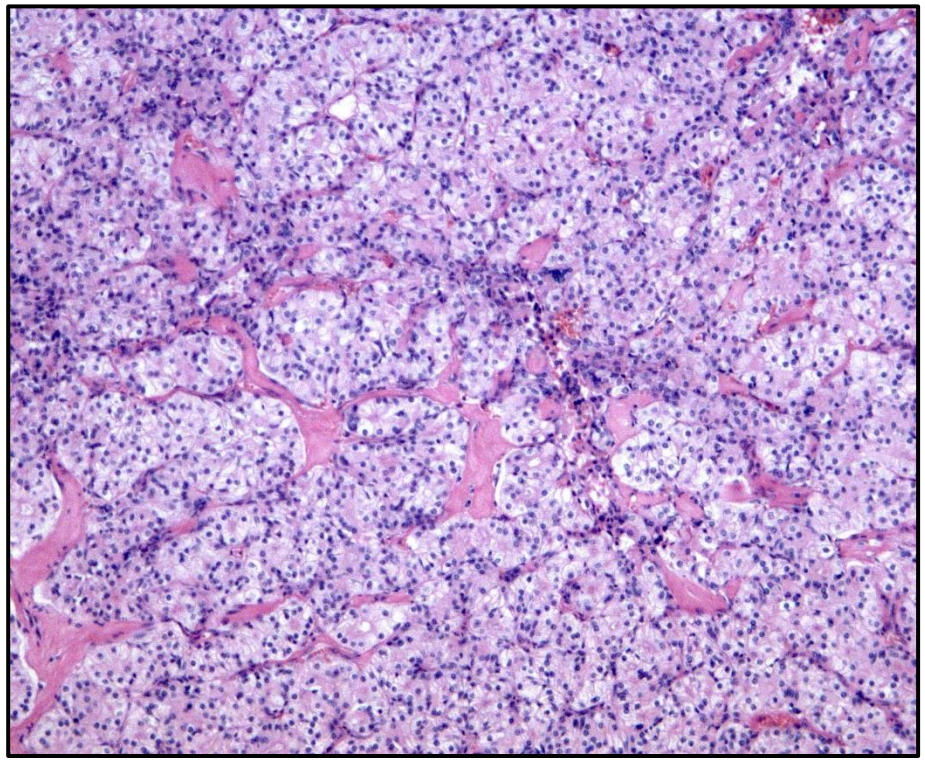
Oncocytic Neoplasm vs. Secretory Carcinoma

45-old-woman with 2.5 cm right parotid mass



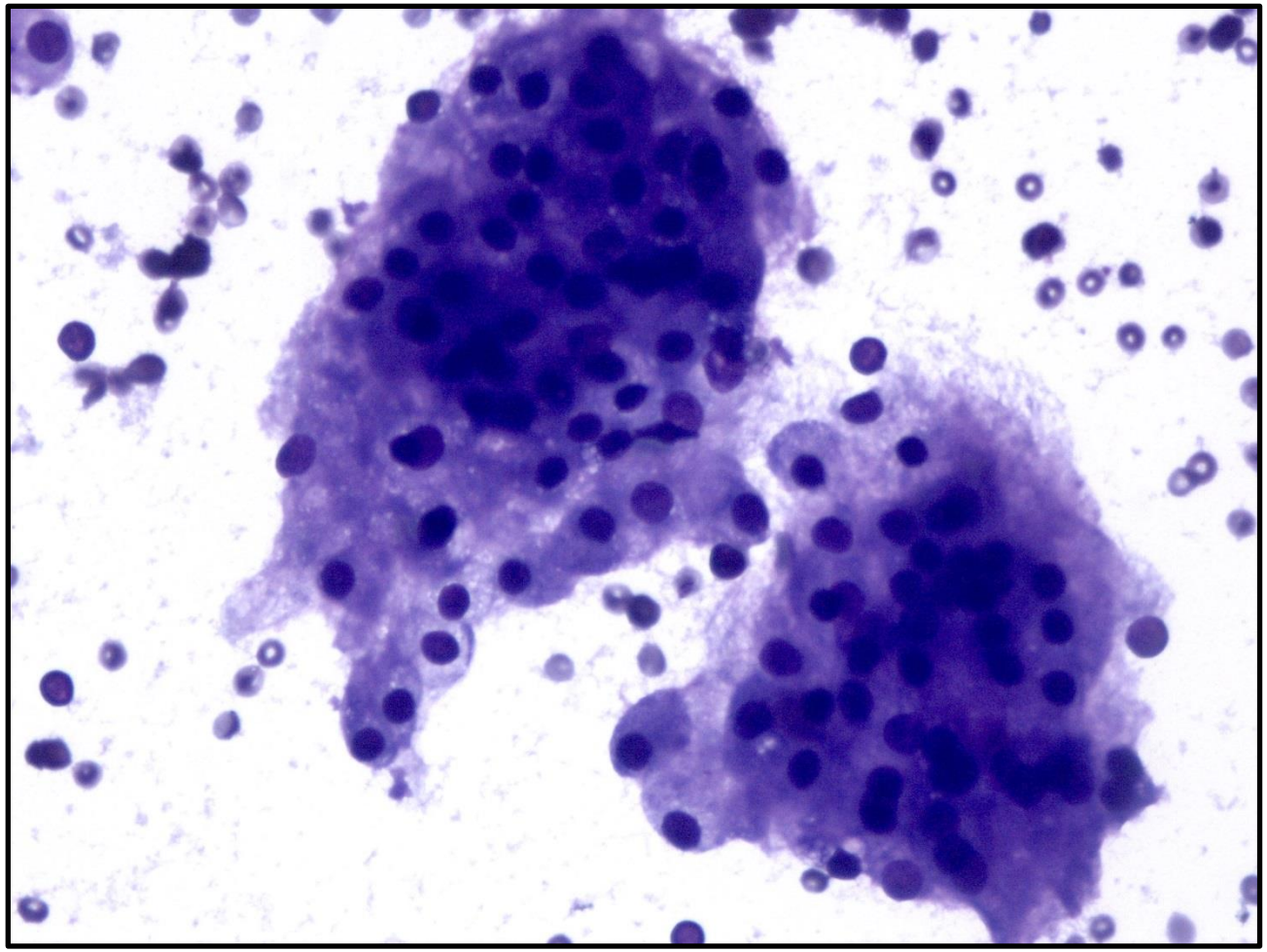


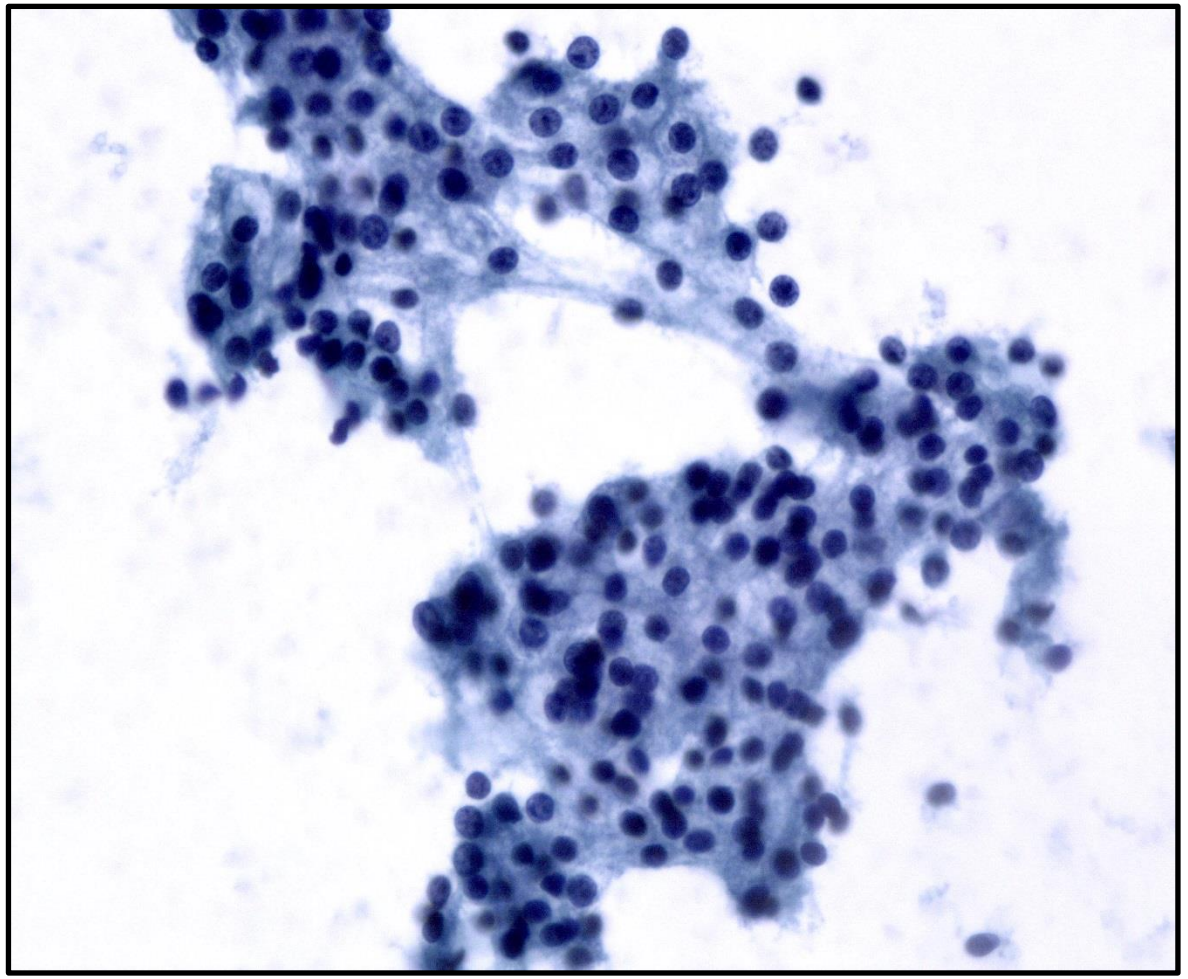




Oncocytoma

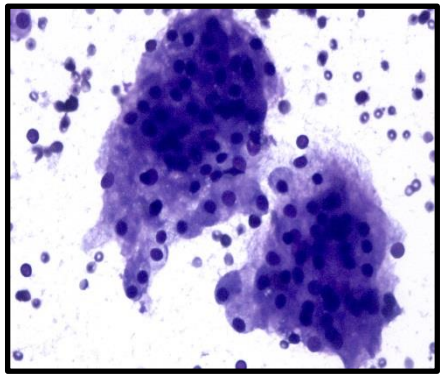
50 year old woman with a slow growing right parotid mass, present size 5.0 cm

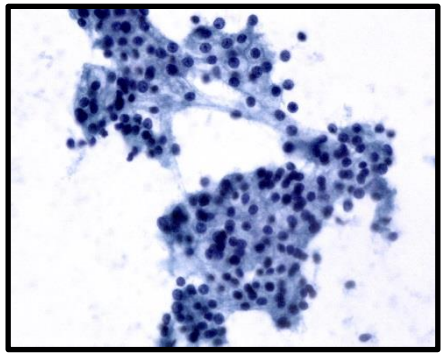


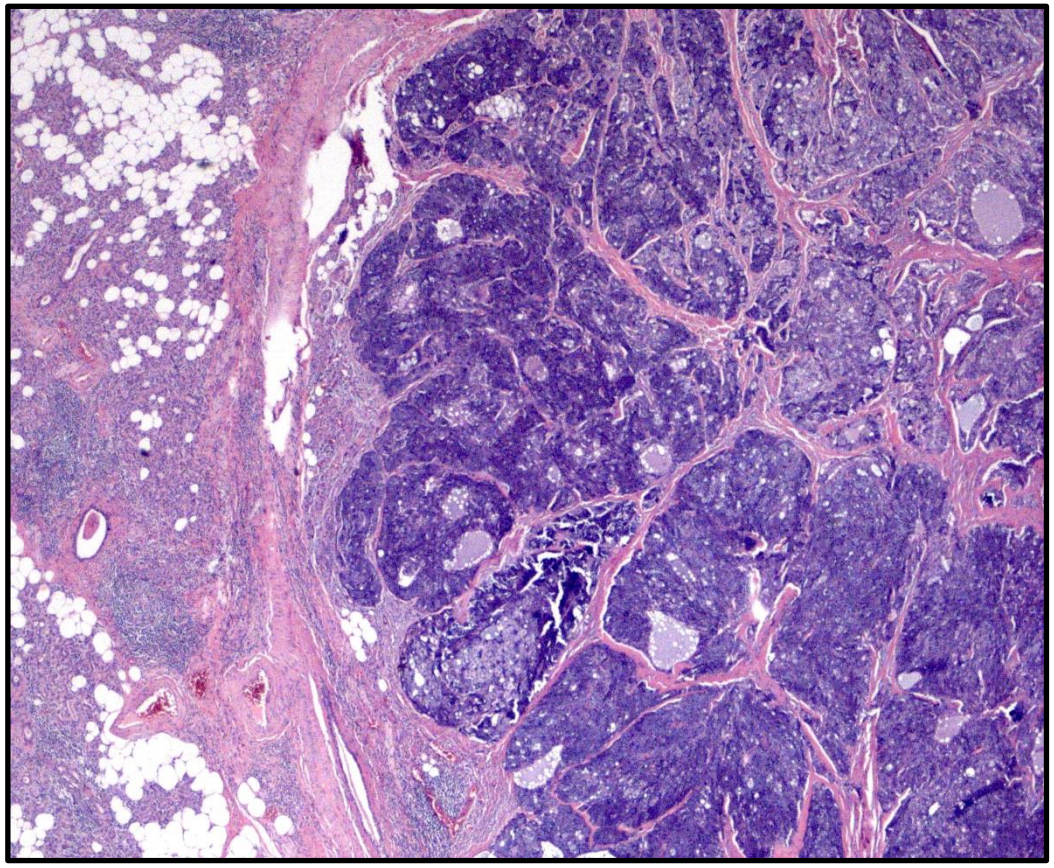


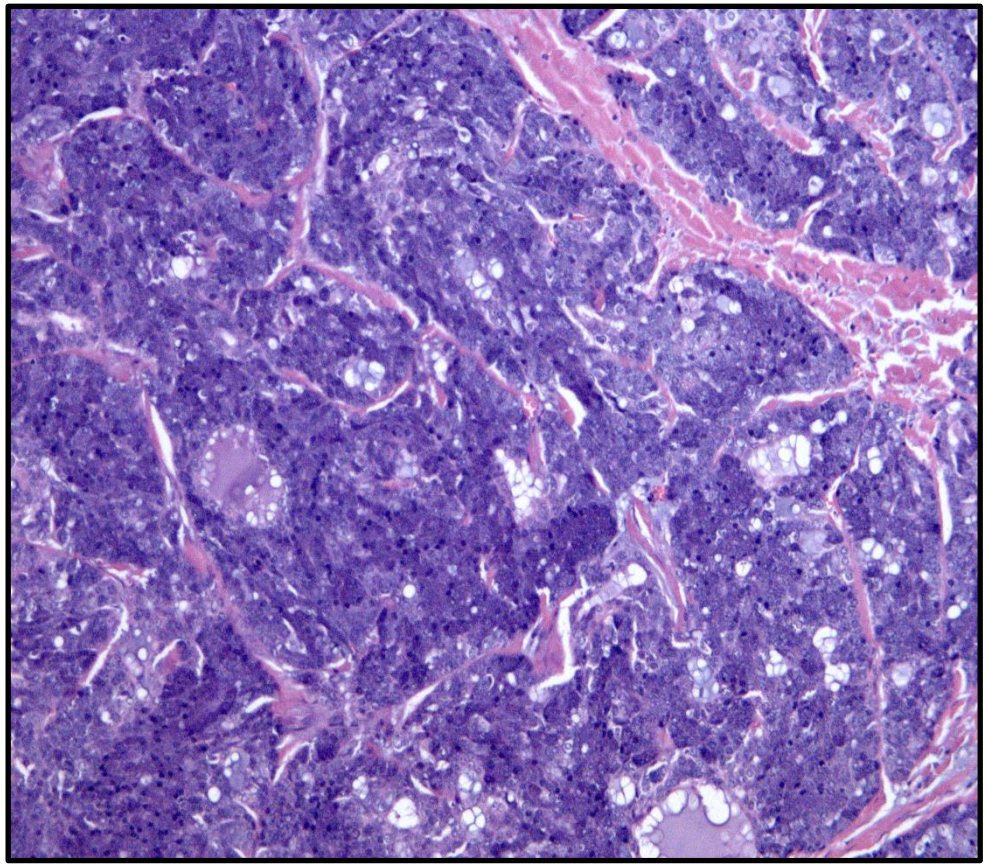
Malignant: Acinic Cell Carcinoma

50 year old woman with a slow growing right parotid mass, present size 5.0 cm





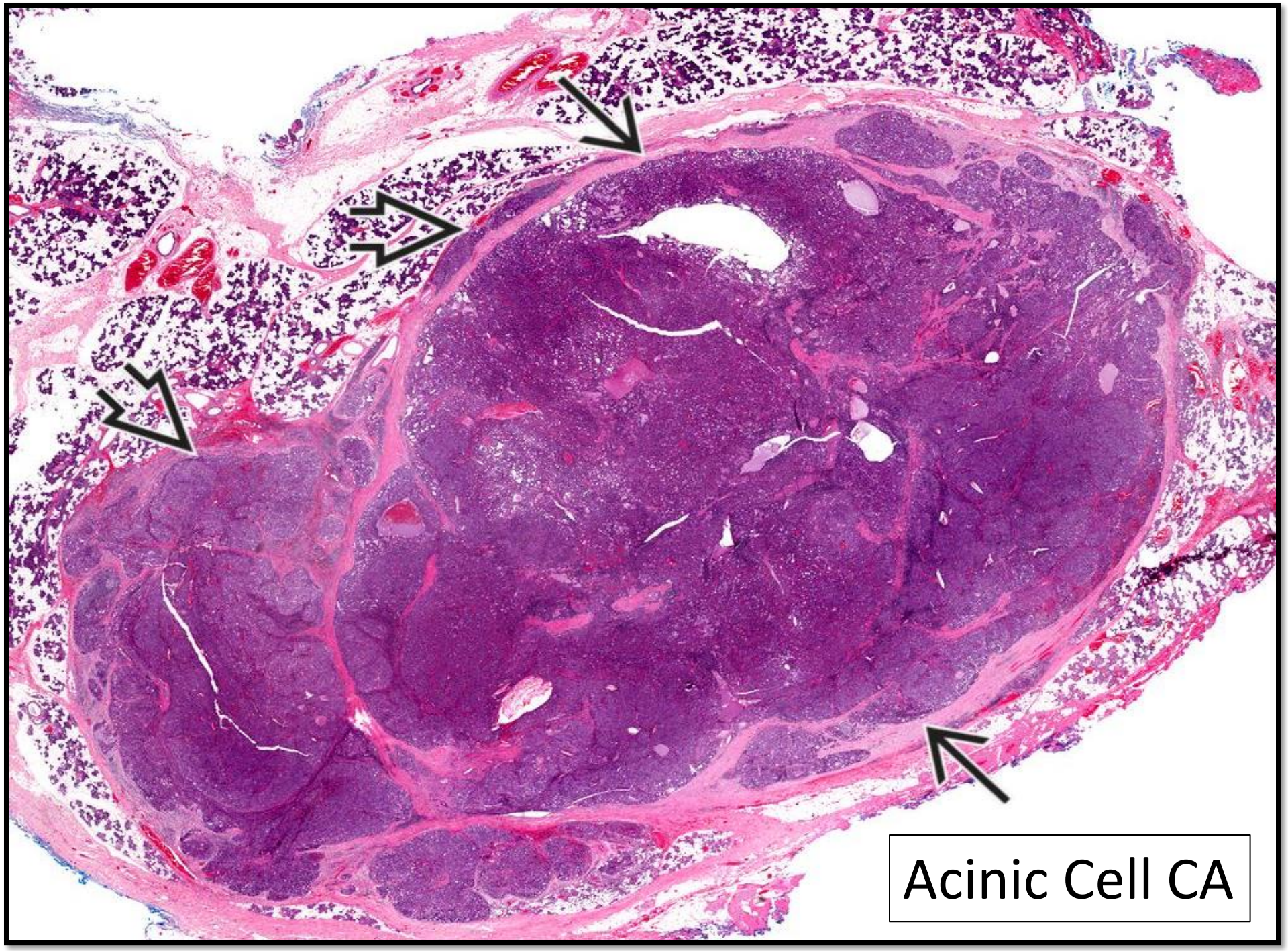


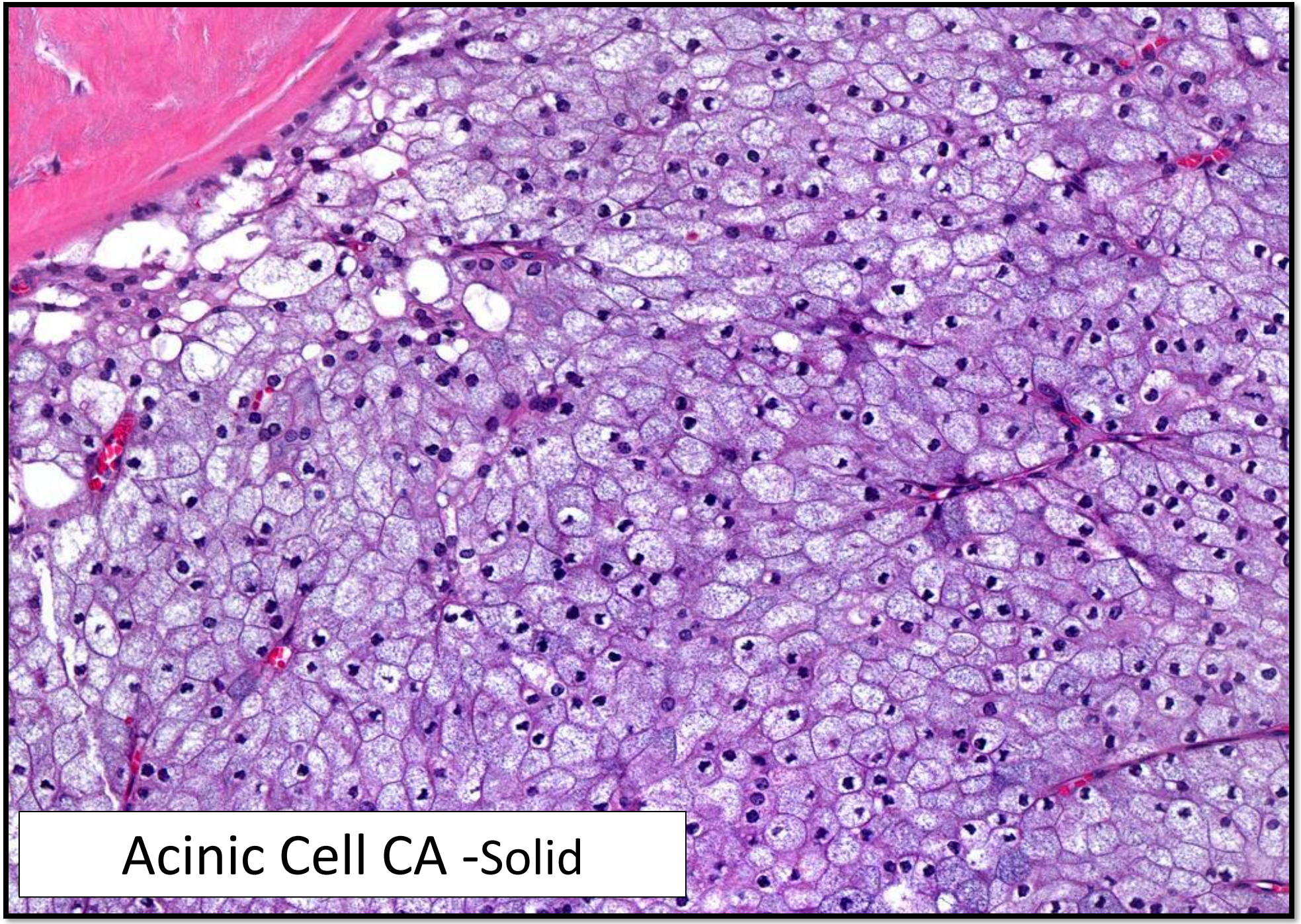


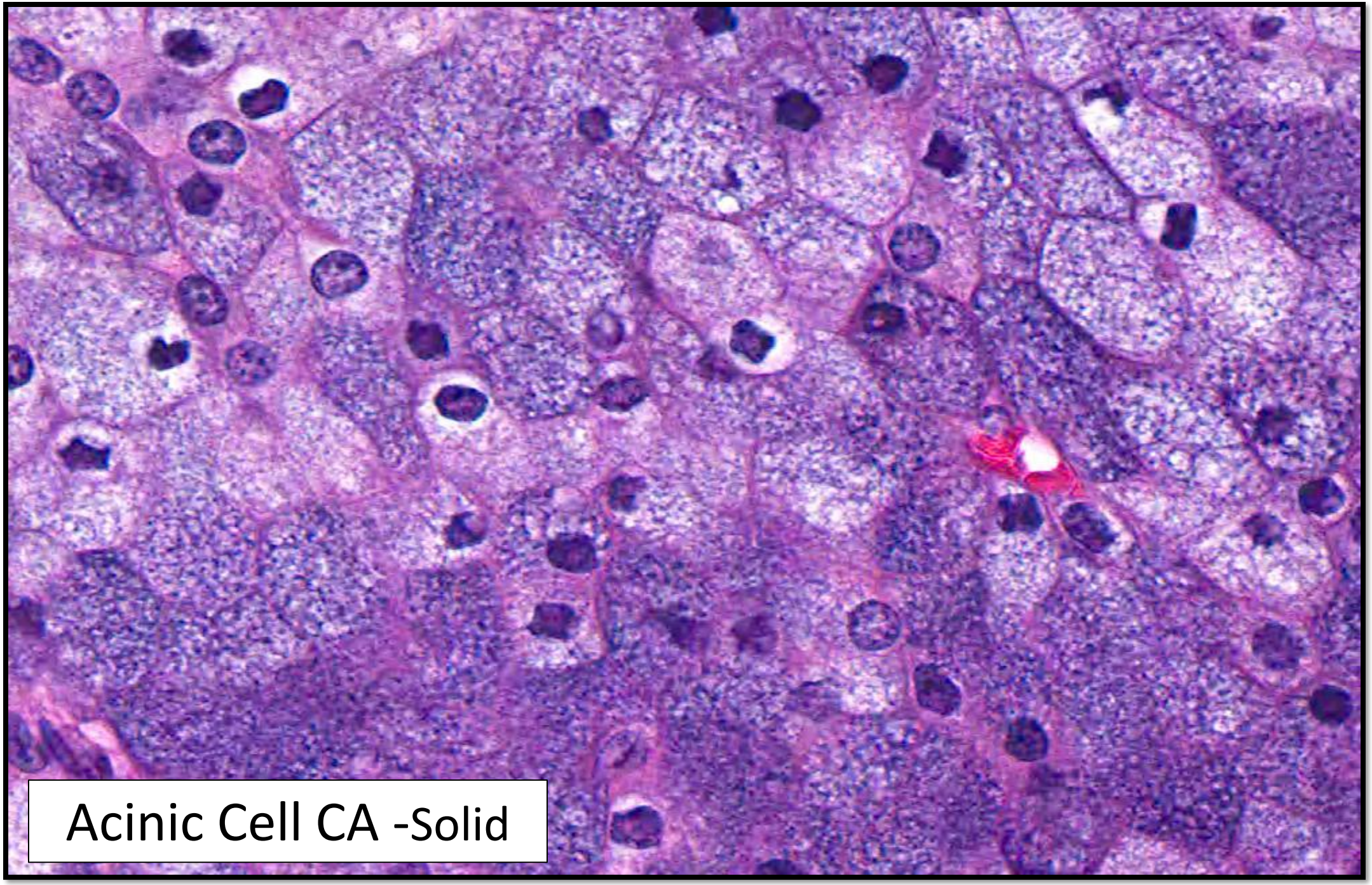
Malignant: Acinic Cell Carcinoma

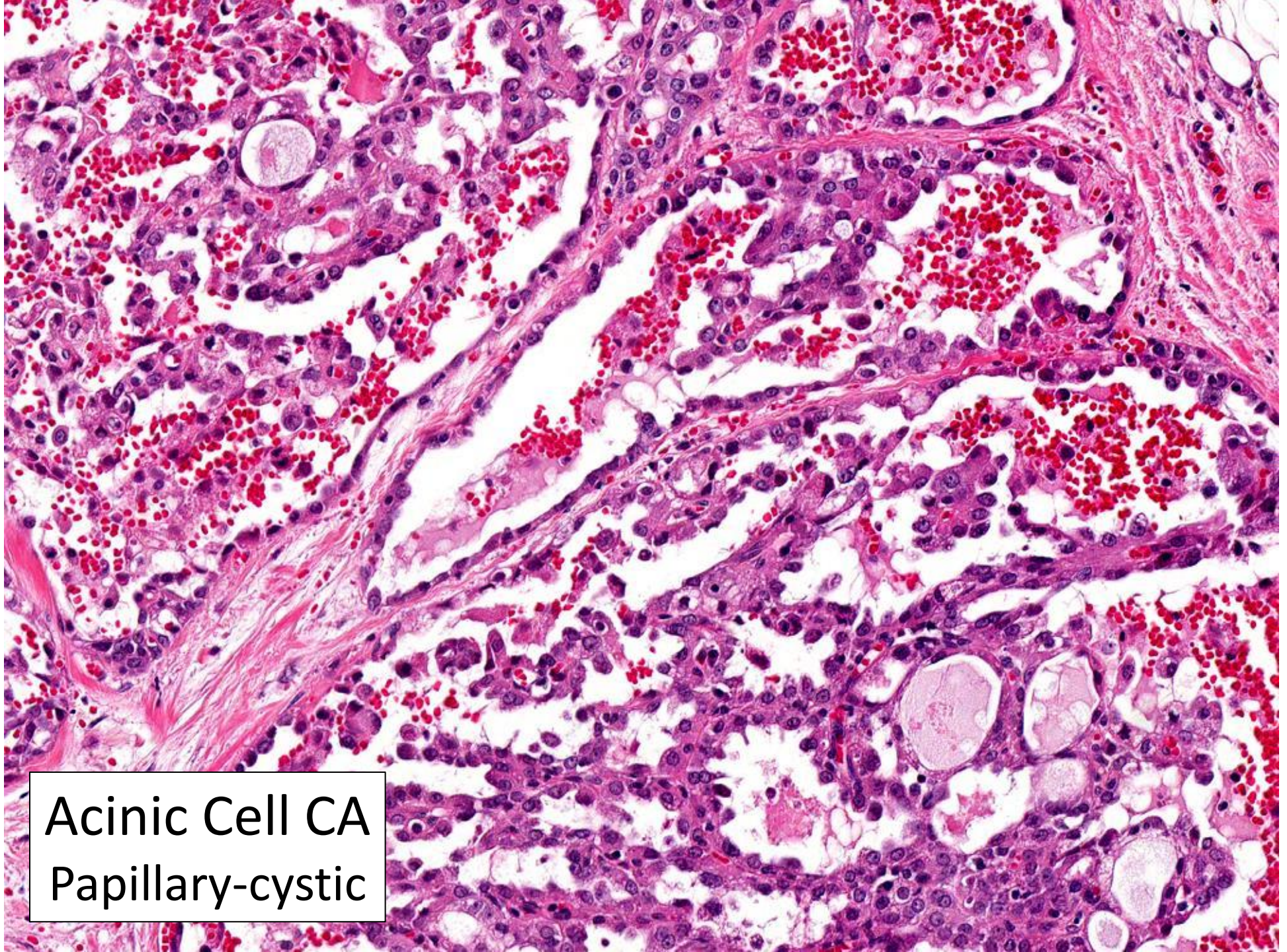
Acinic Cell Carcinoma

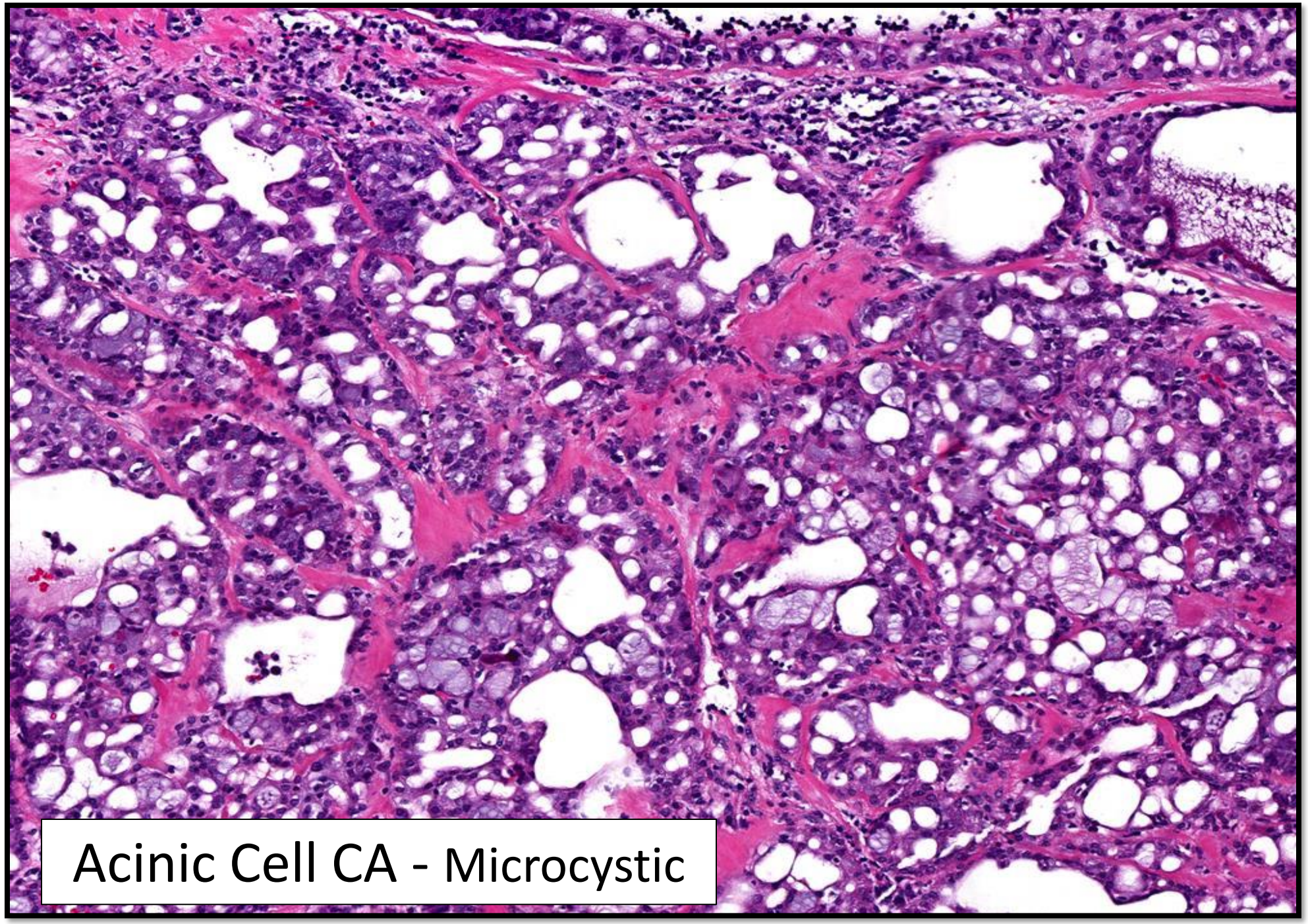
- Malignant but good prognosis with proper excision
- **Parotid (90%)** most commonly
- Wide age range (mean 40s)
- F>M (2:1)
- Roughly 10% of malignant tumors (2nd most common)
- Histology:
  - Different cell types: serous acinar, intercalated duct-type, vacuolated, nonspecific glandular, clear cells
  - Architecture: Solid/lobular, papillary-cystic, microcystic
- IHC: **PAS(D)+**; negative or only focal mucicarmine; DOG-1, SOX10+, NR4A3+

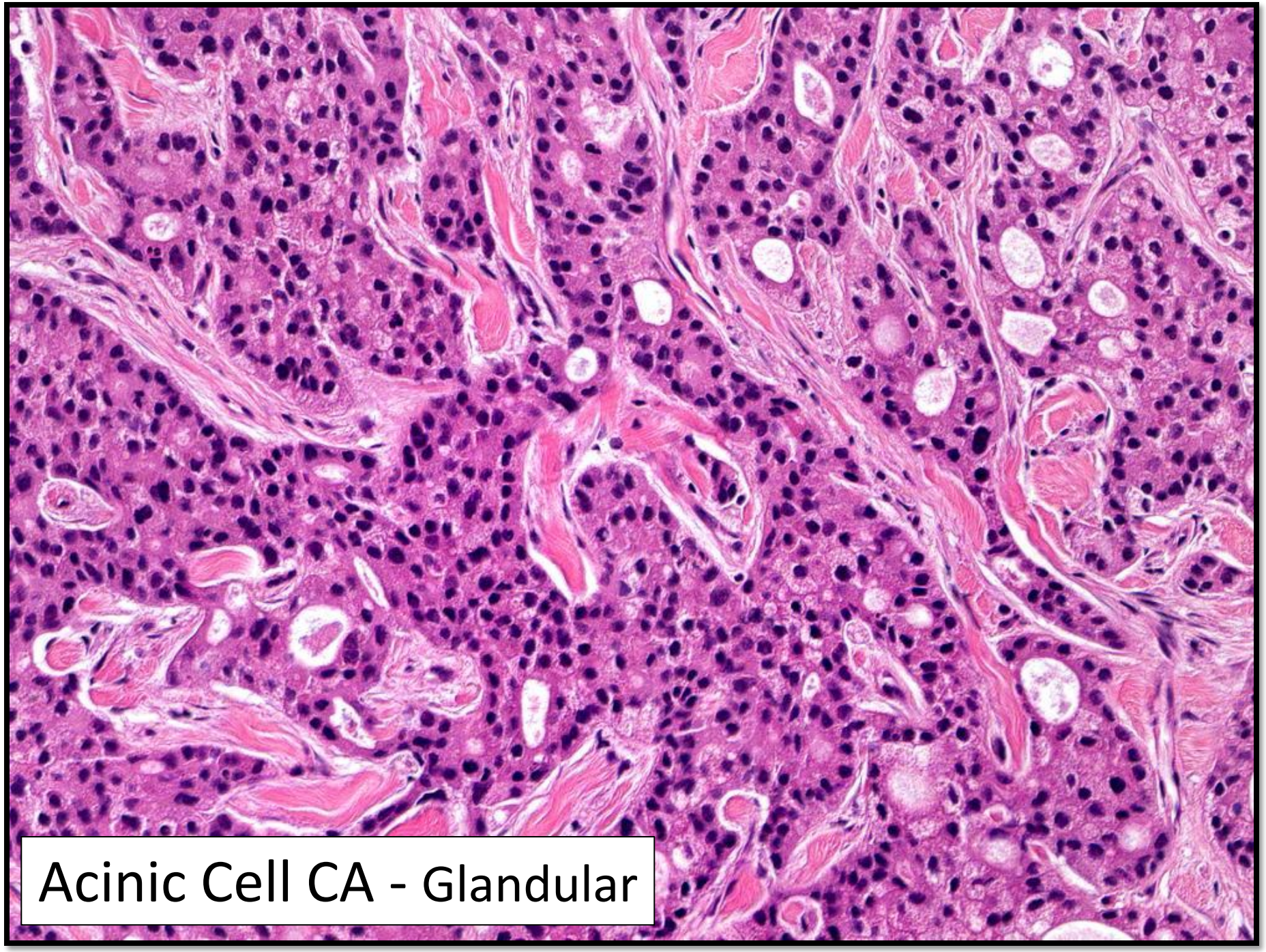

Acinic Cell CA


Acinic Cell CA -Solid

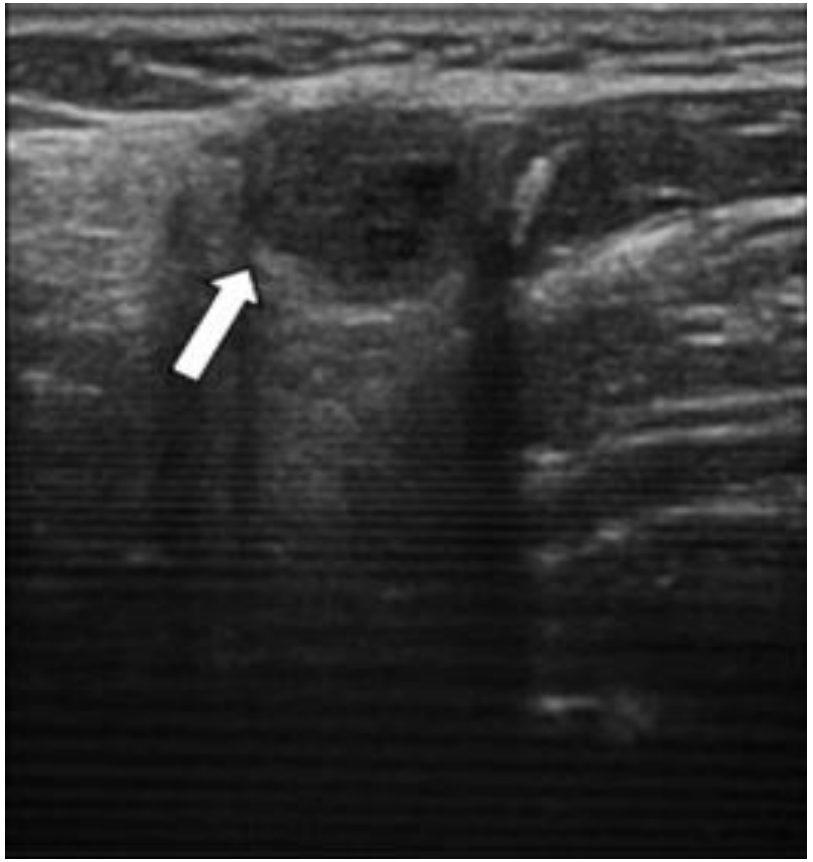

Acinic Cell CA -Solid


Acinic Cell CA
Papillary-cystic

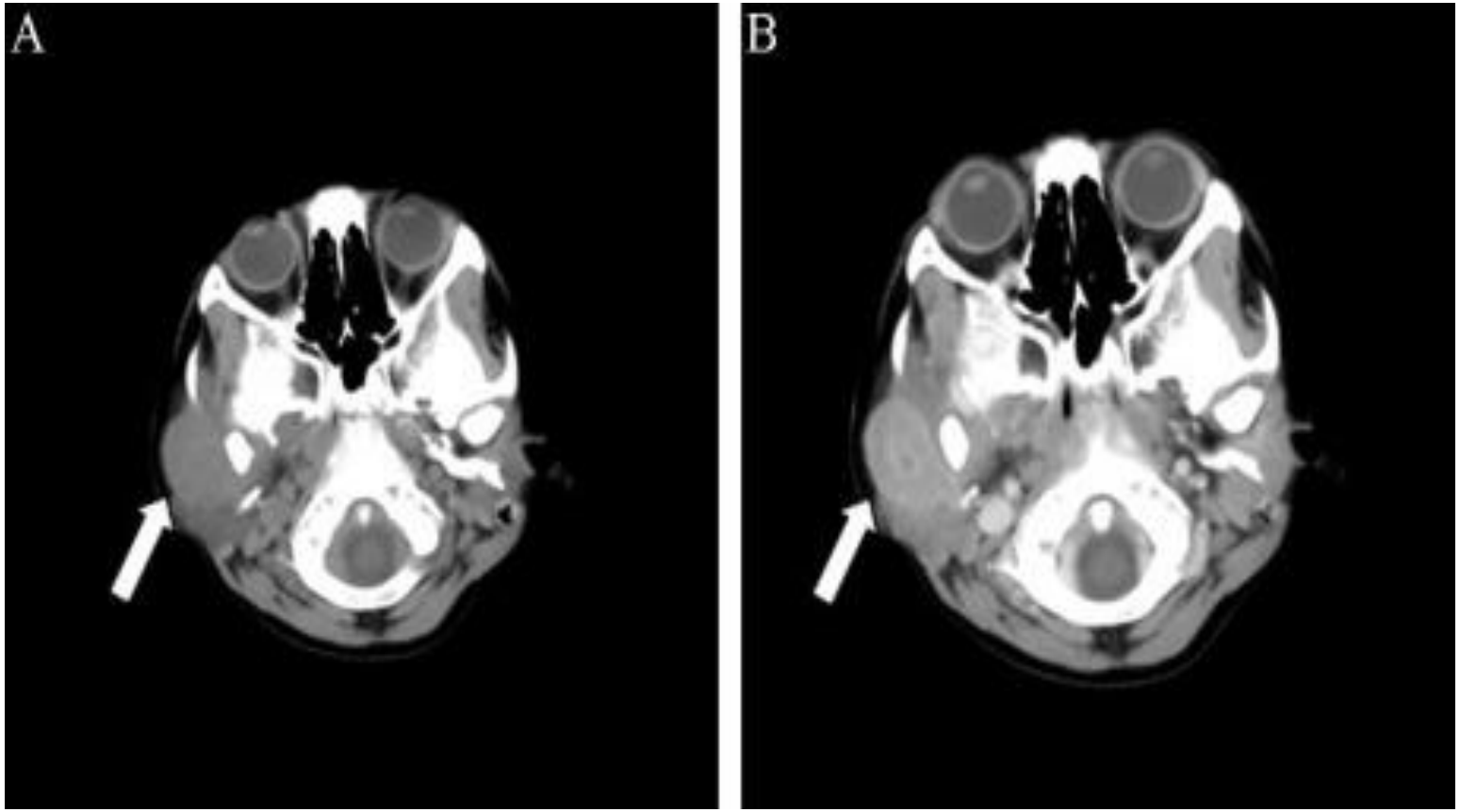

Acinic Cell CA - Microcystic


Acinic Cell CA - Glandular

Acinic Cell Carcinoma – Radiologic Features
Li et al. Eur J Radiol 2014;83:1152-1156



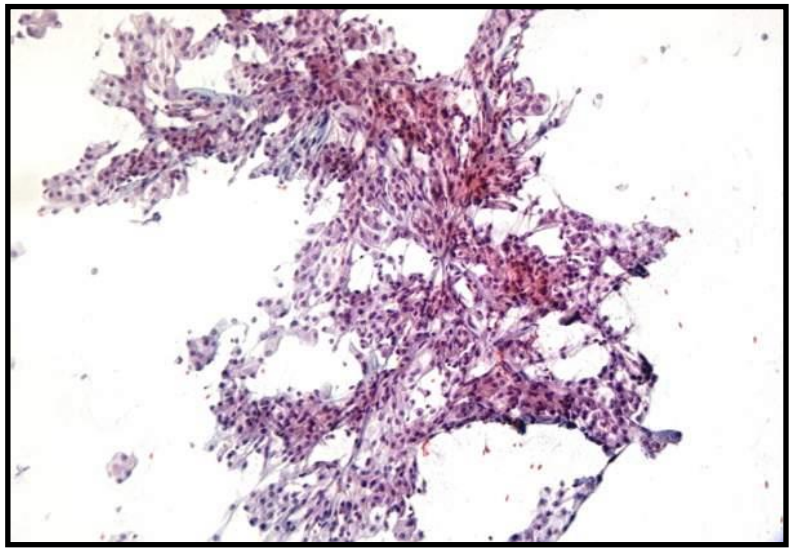
Irregular borders
Well-defined
Hypoechoic

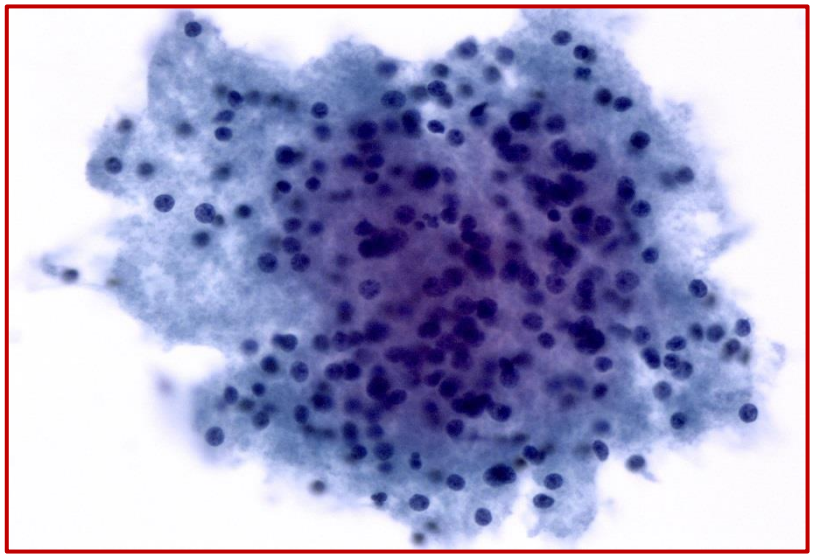


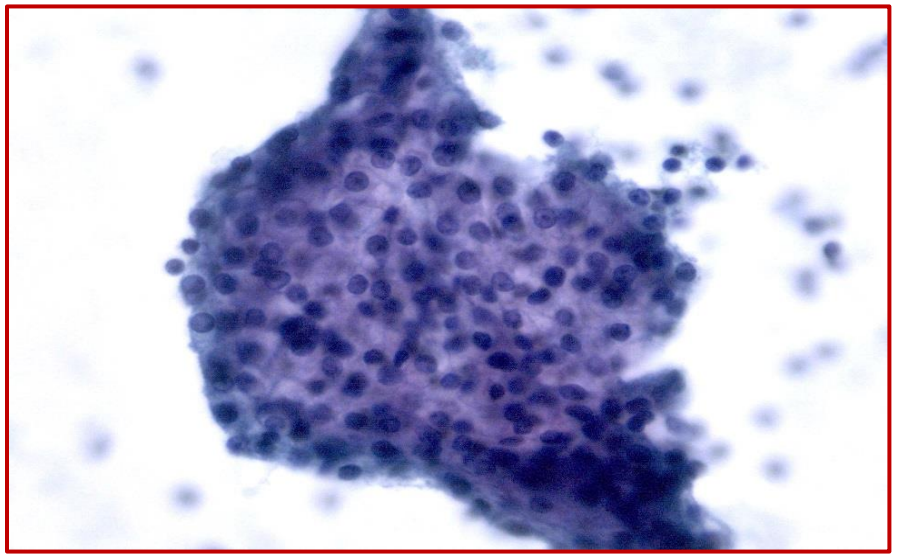
Plain CT: Regular defined homogeneous lesion
Contrast: Moderate homogeneous enhancement

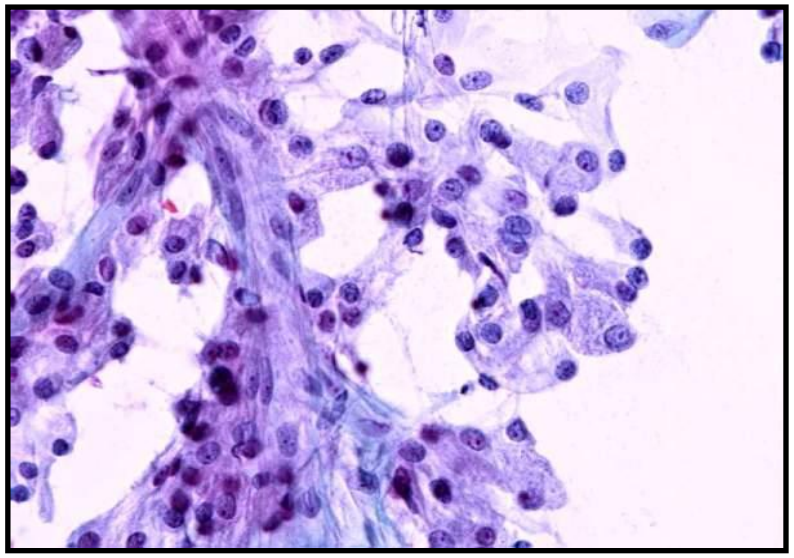
Acinic Cell Carcinoma – Cytomorphologic Features

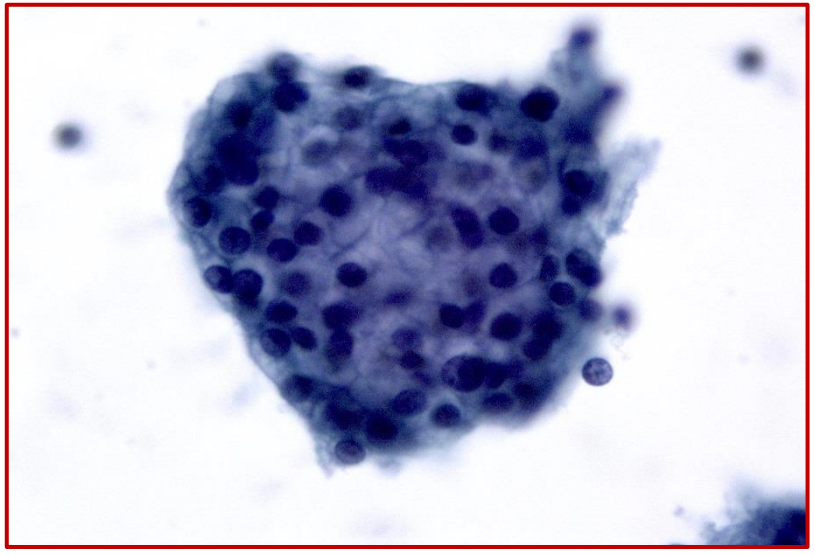
1. **Sheets of large cells with abundant foamy vacuolated and granular cytoplasm**
2. **Eccentrically placed nuclei with small, inconspicuous nucleoli, naked nuclei in the background (delicate cytoplasm)**
3. **Lymphocytes**

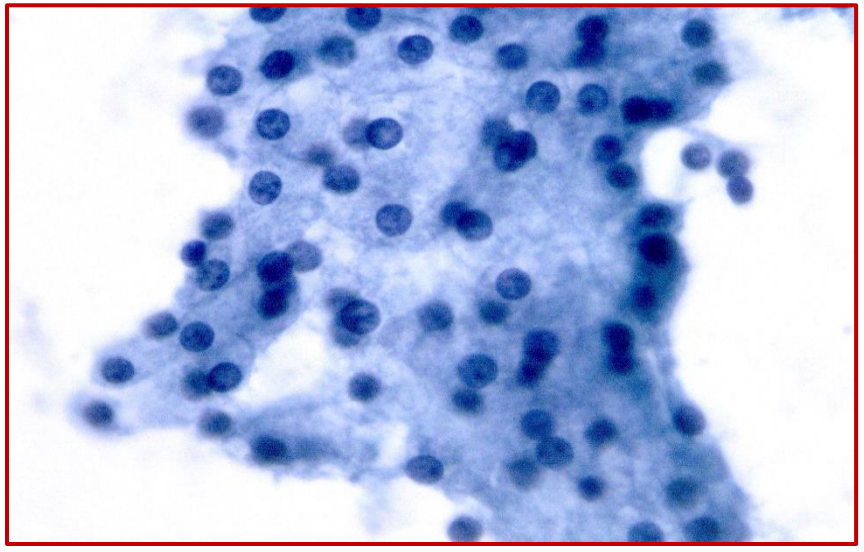






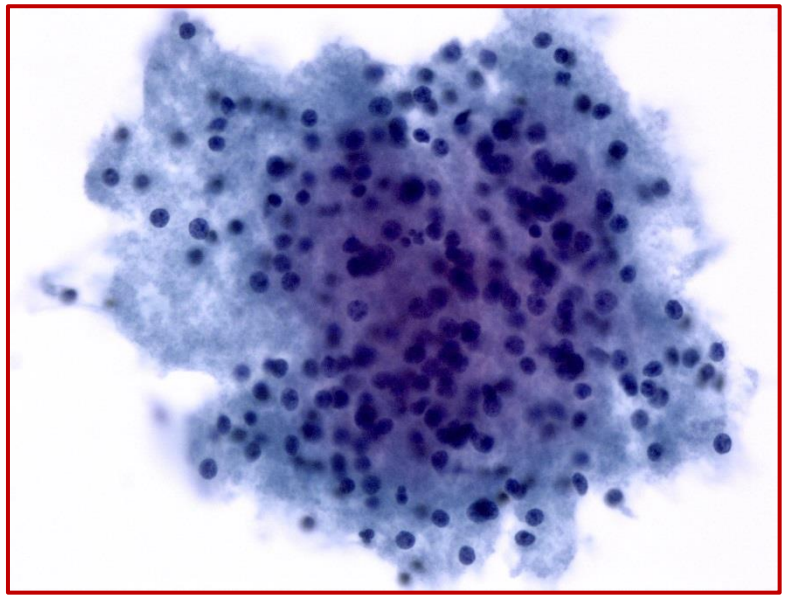


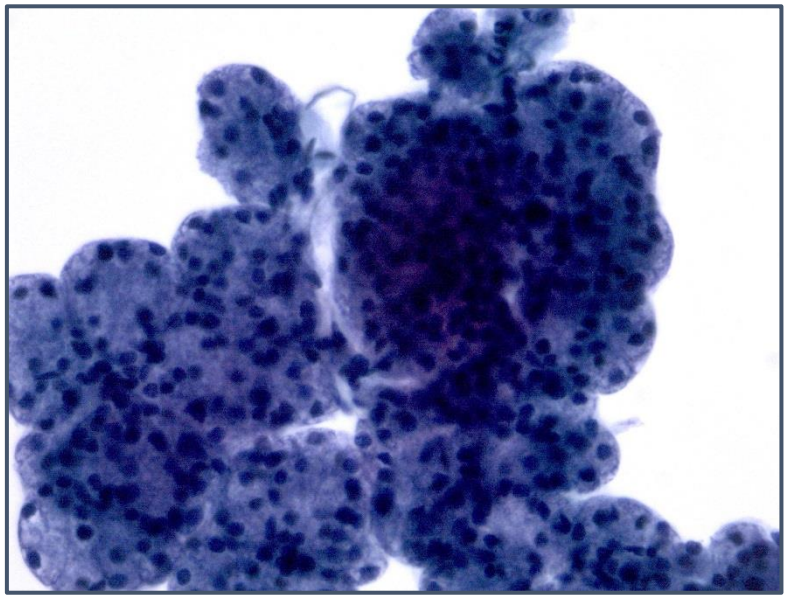


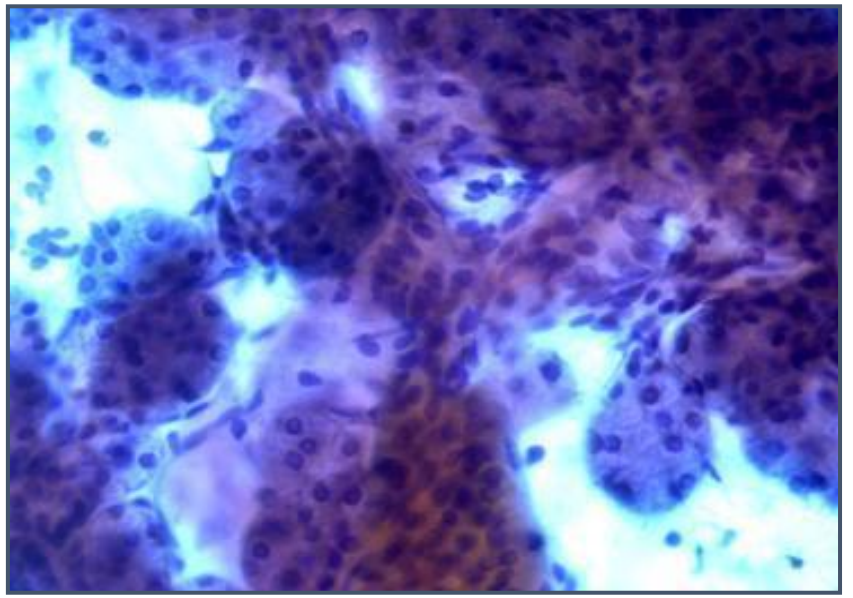


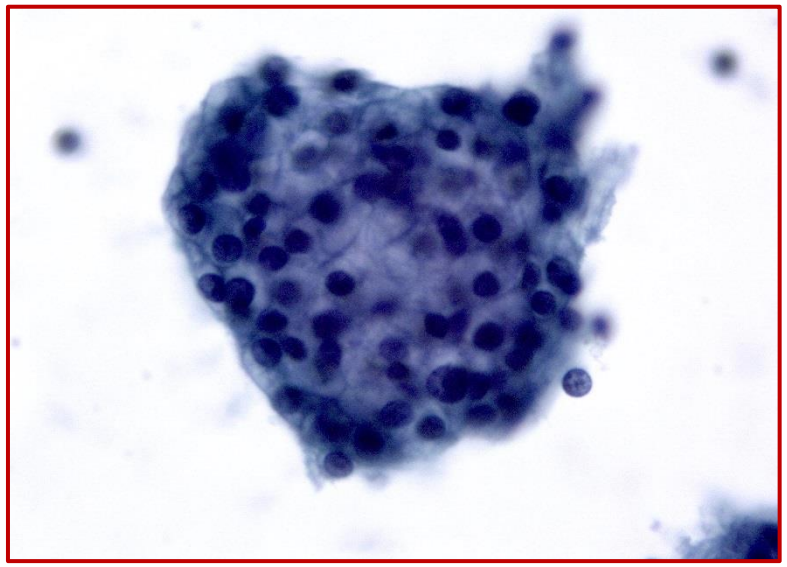
Acinic Cell Carcinoma –Differentiate from Benign Acinar Tissue (BAT)

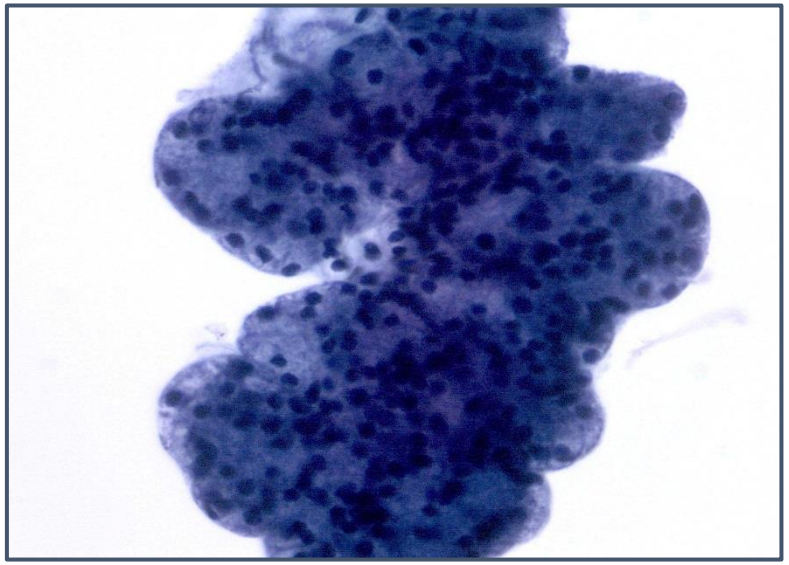
BAT – Low power "Rosette" pattern or "Clustered Ball-like" strructures

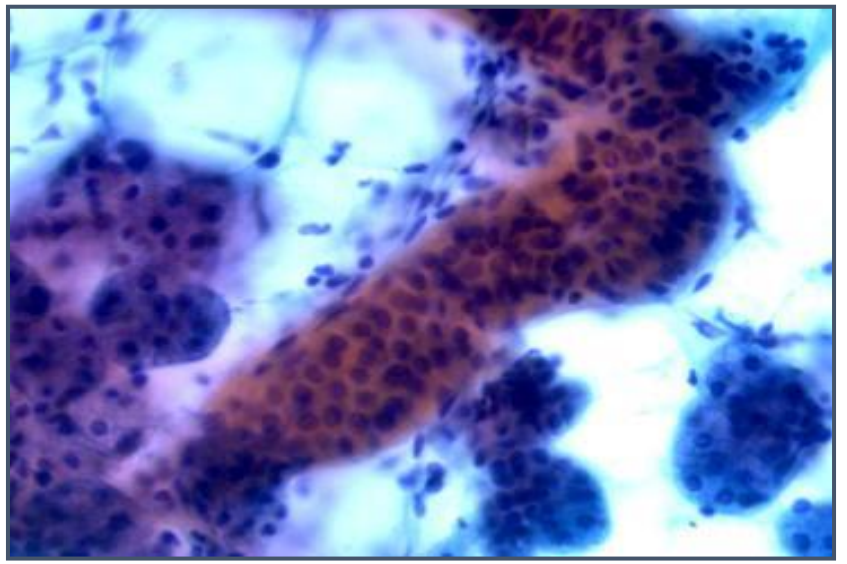




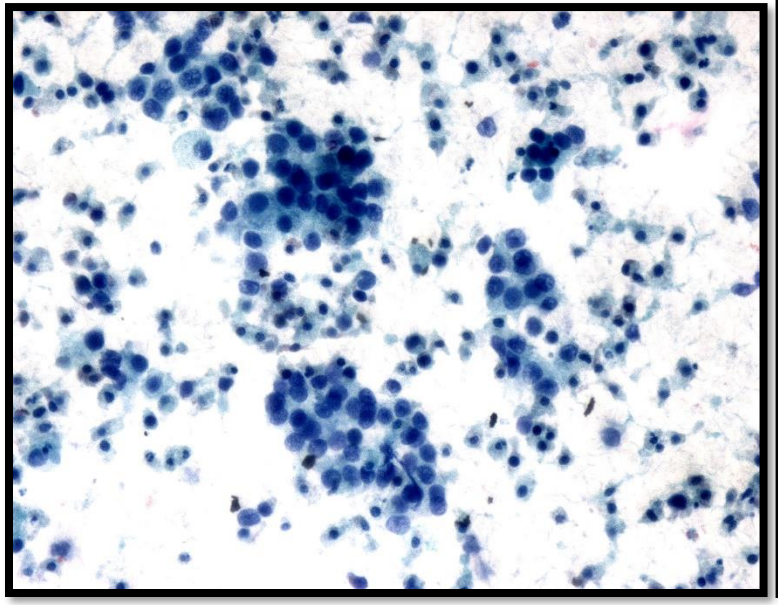
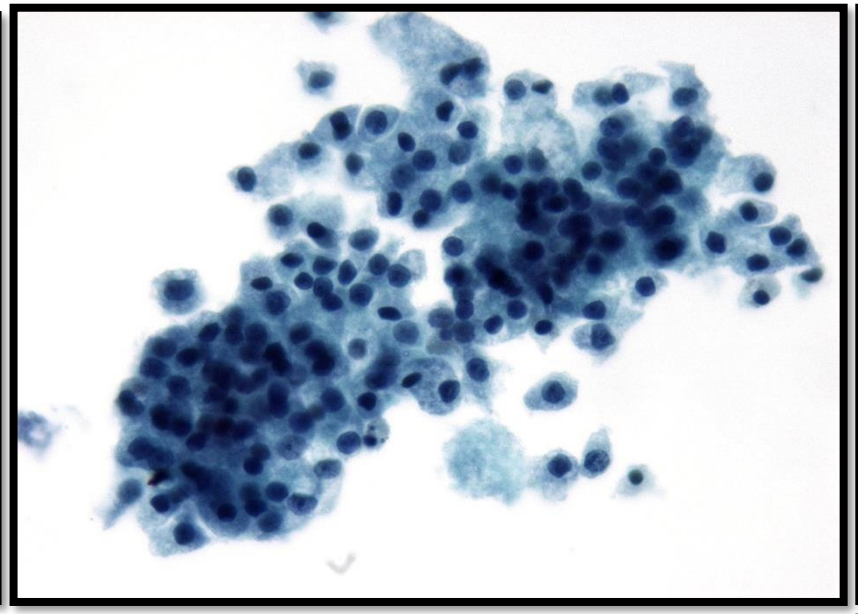
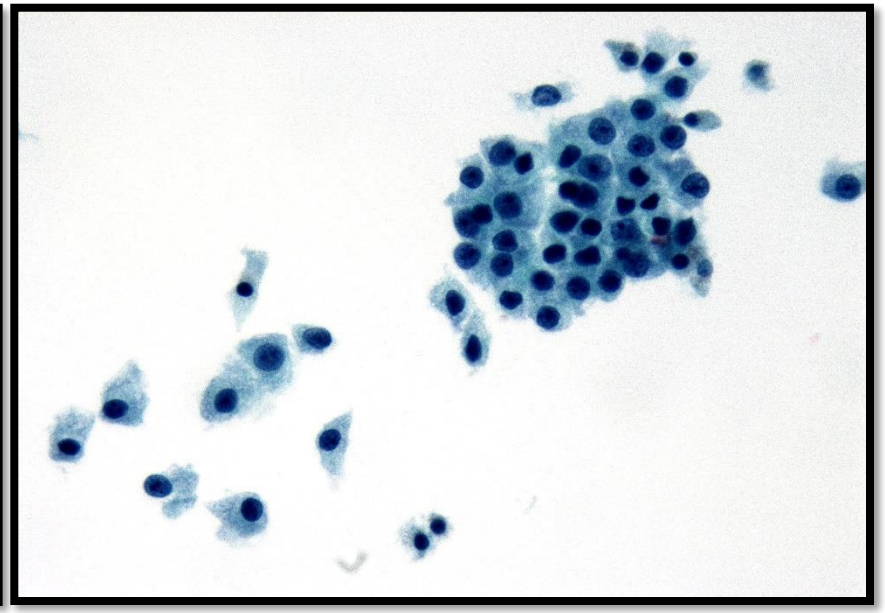
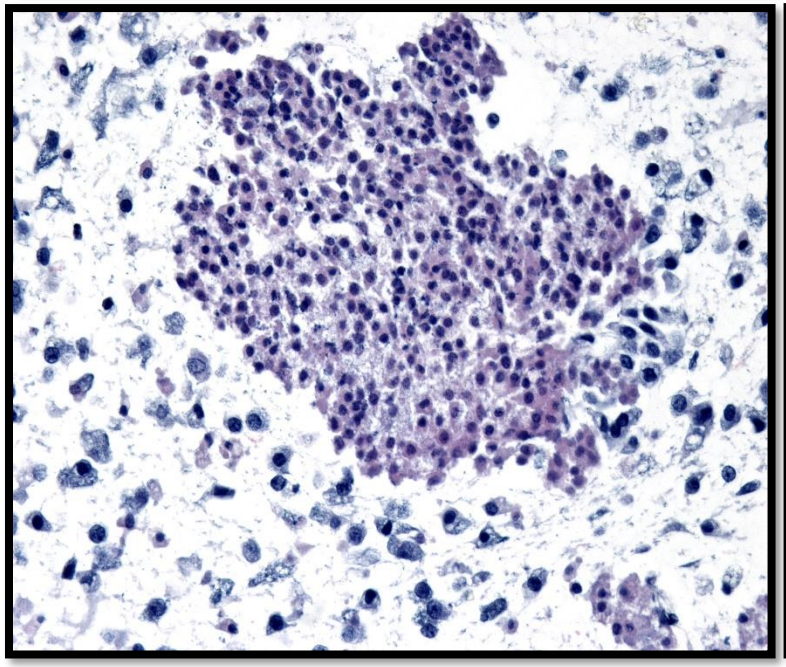
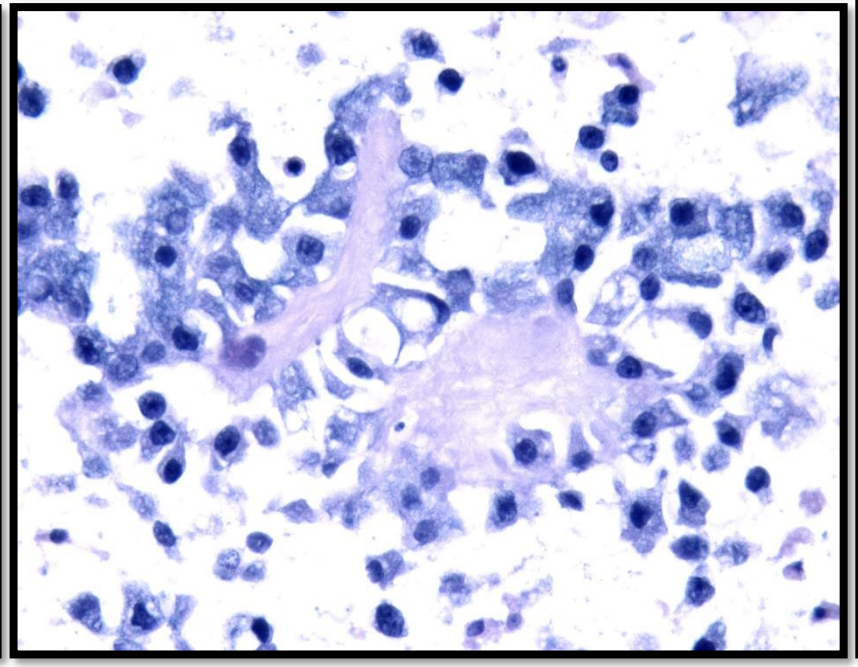
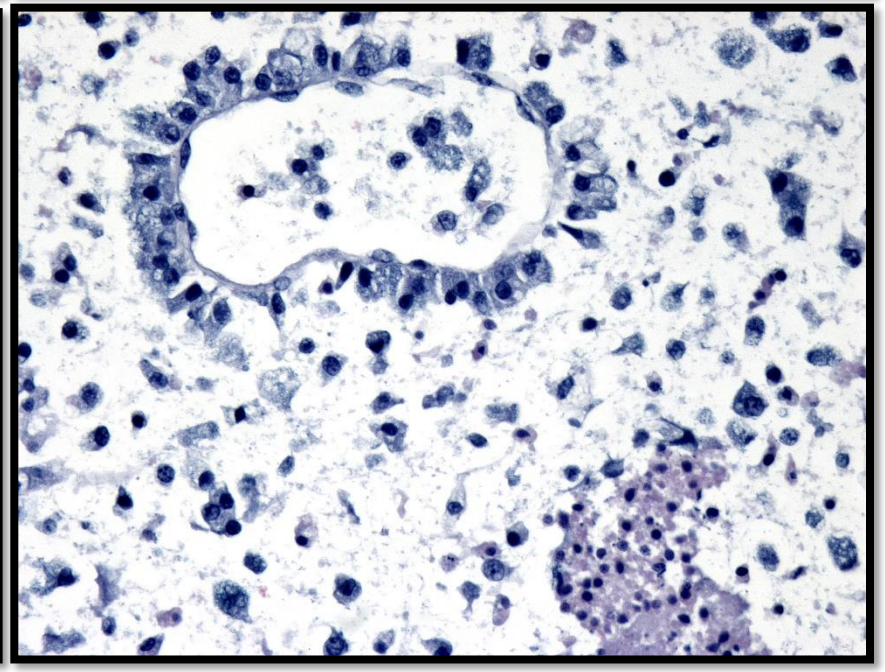






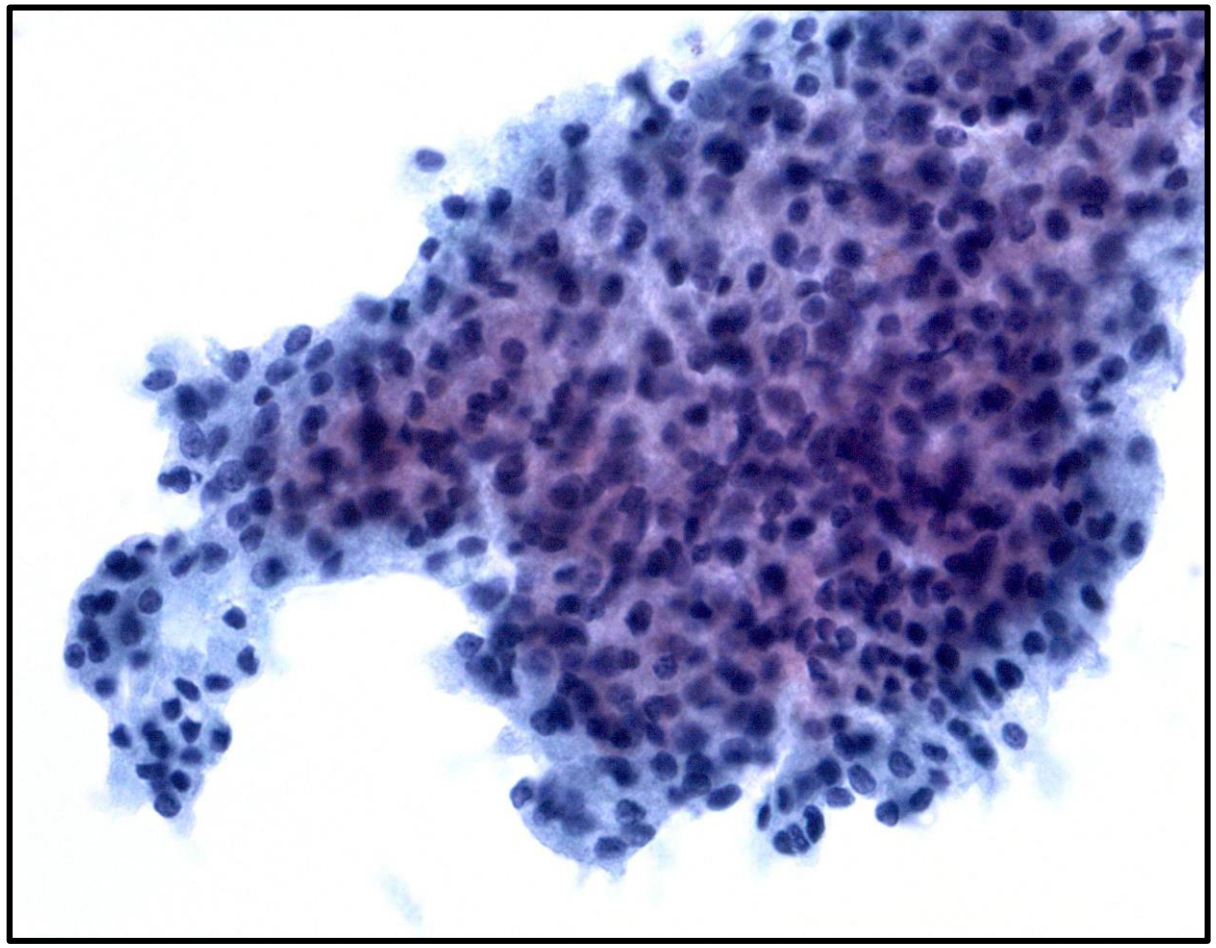


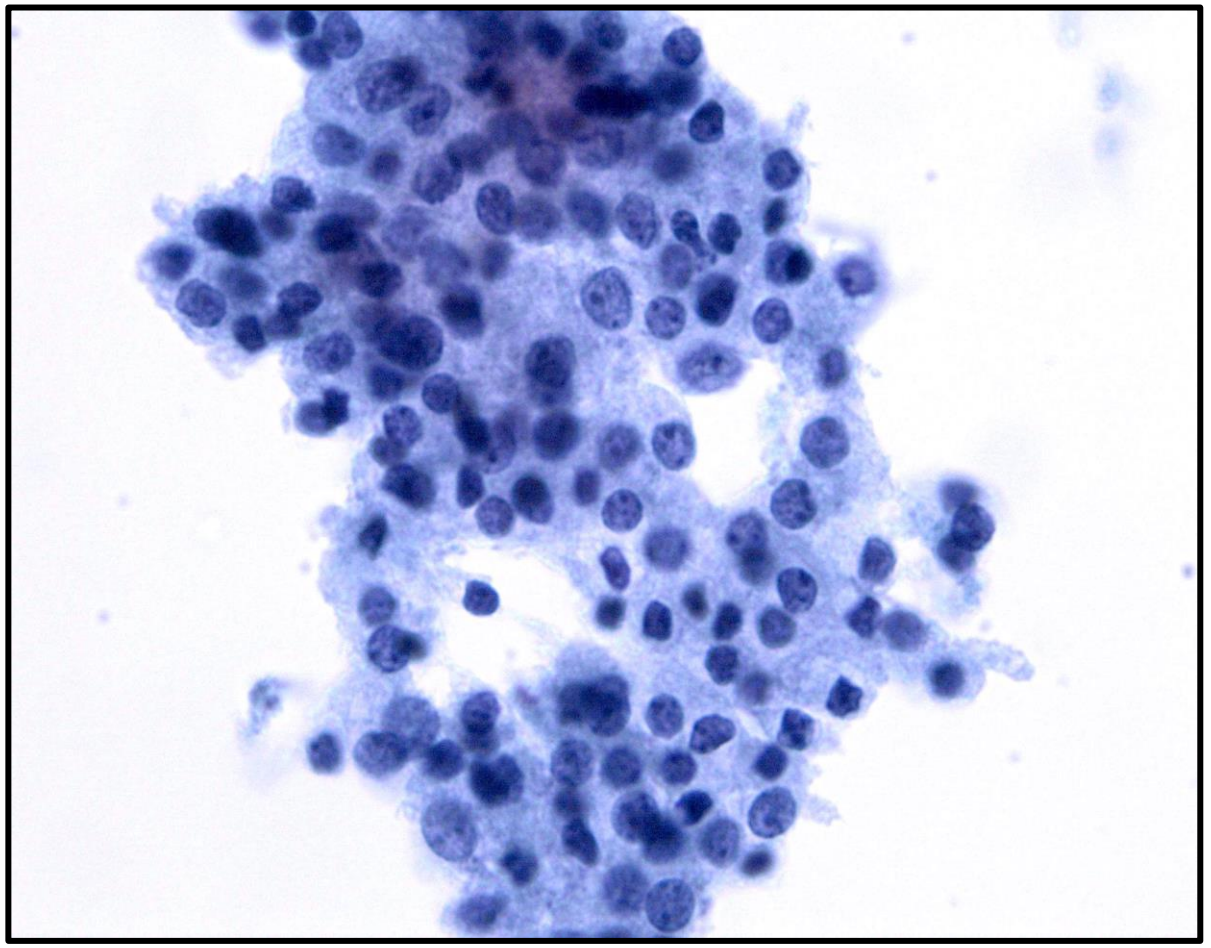
Acinic Cell Carcinoma – Cytomorphologic Features – Thin Prep & Cellblock

Another Case:

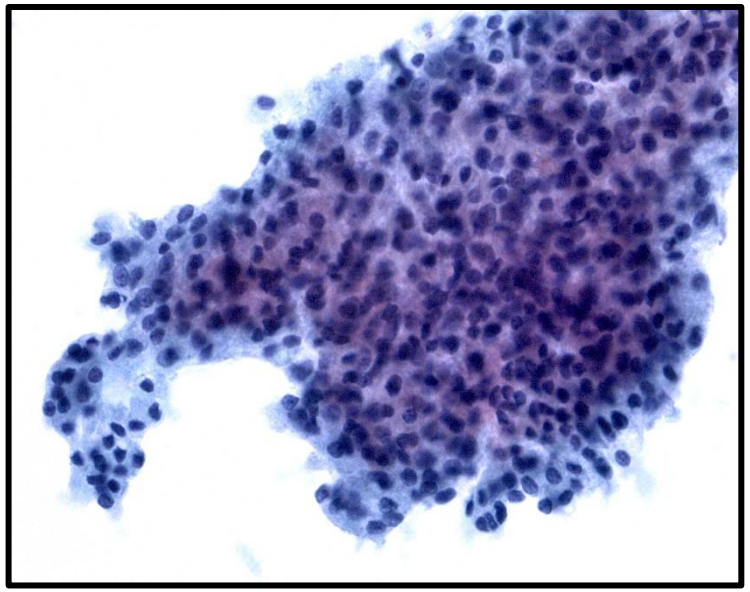
71-year old with <1.0 cm left submandibular gland mass

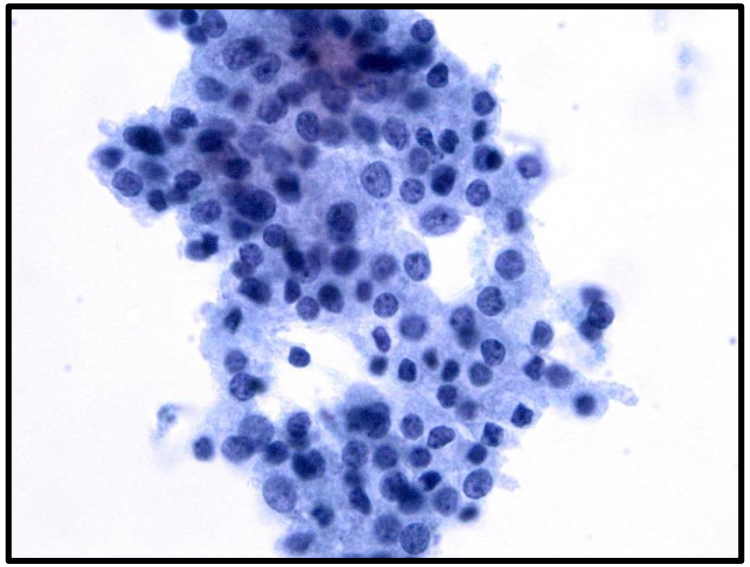


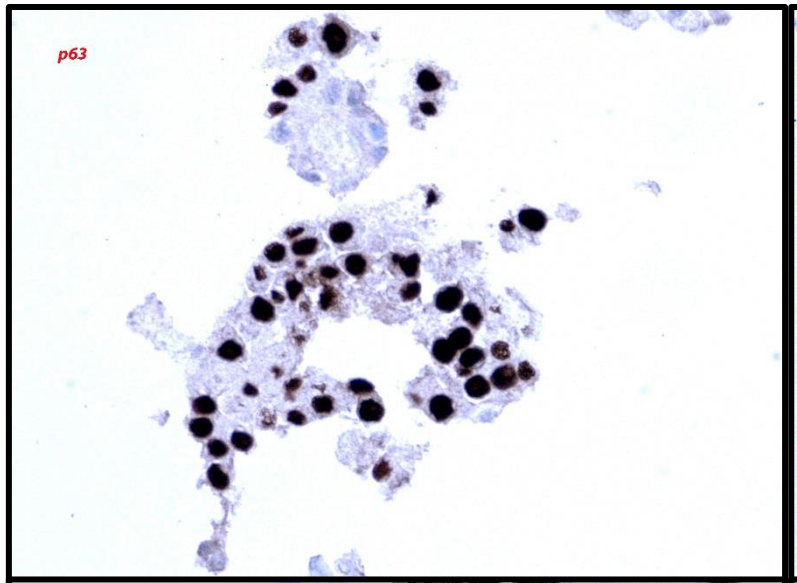


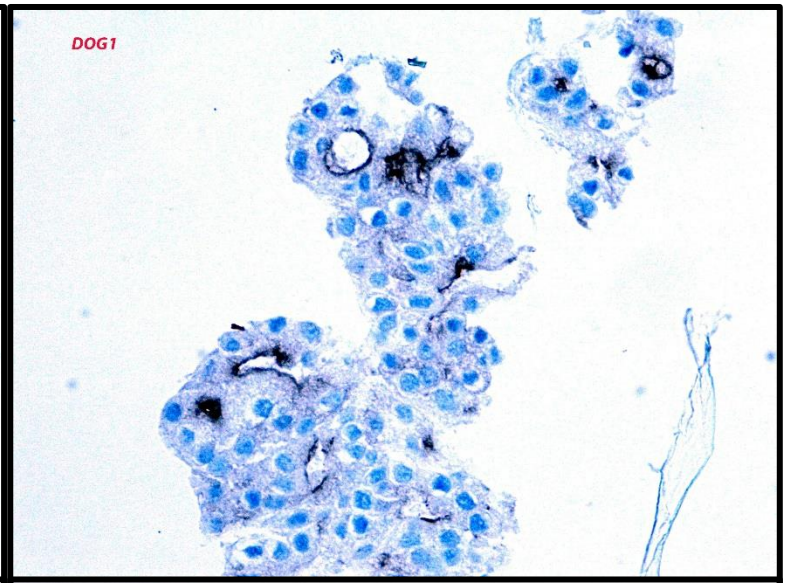
A Case of:

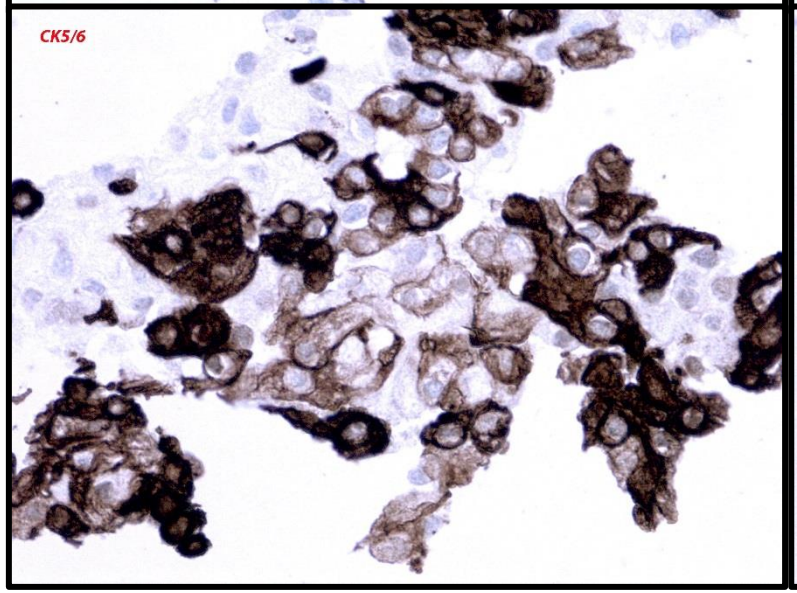
71-year old with <1.0 cm left submandibular gland mass

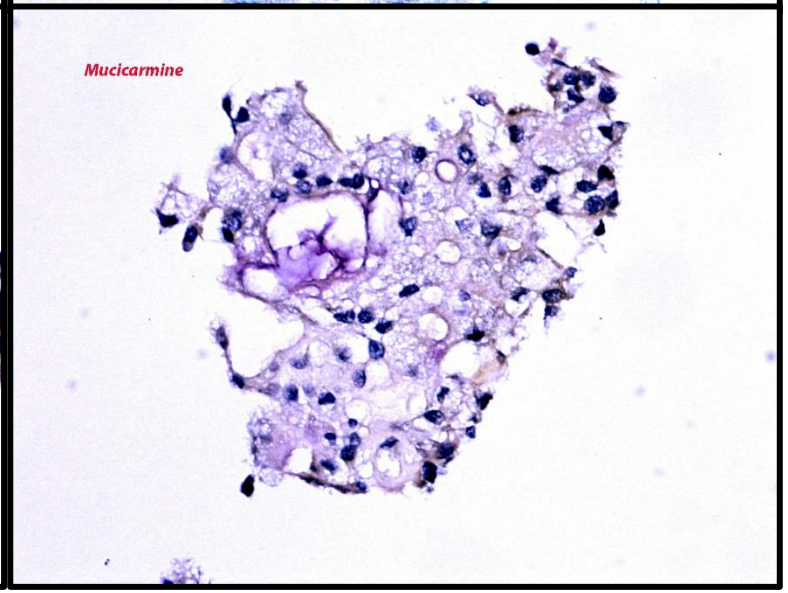






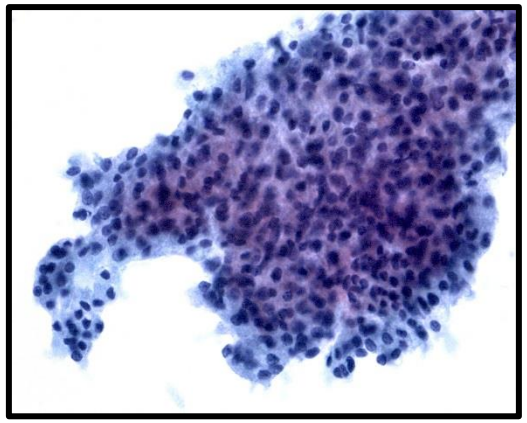


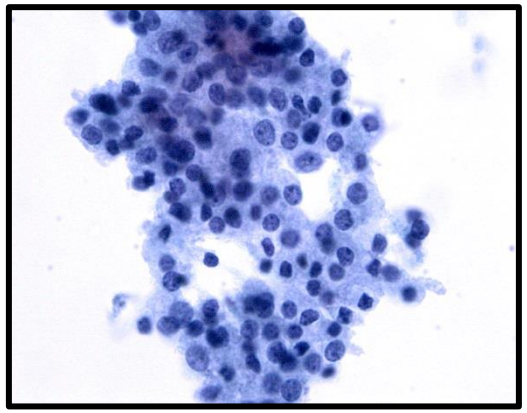


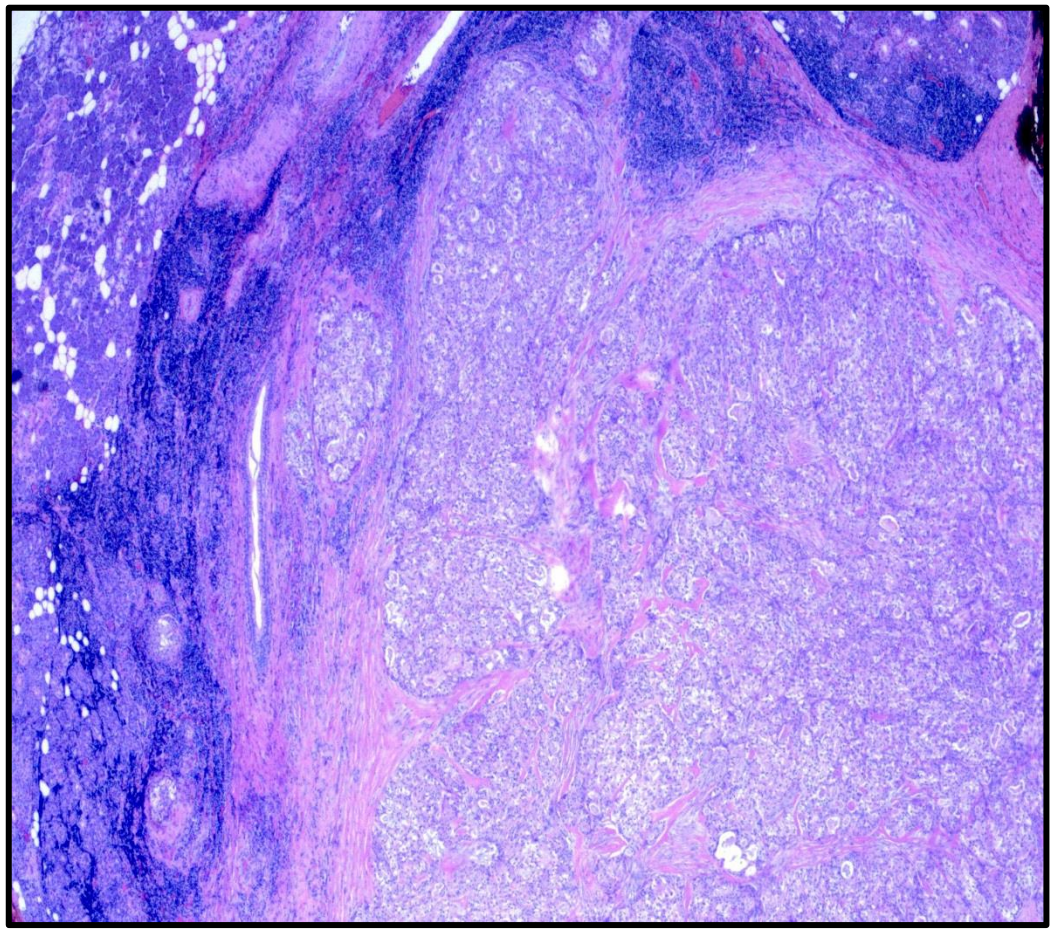


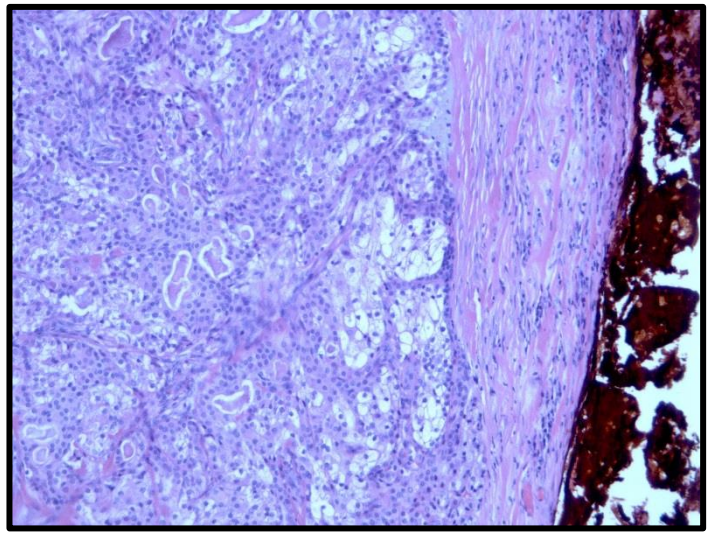
Recent Case:

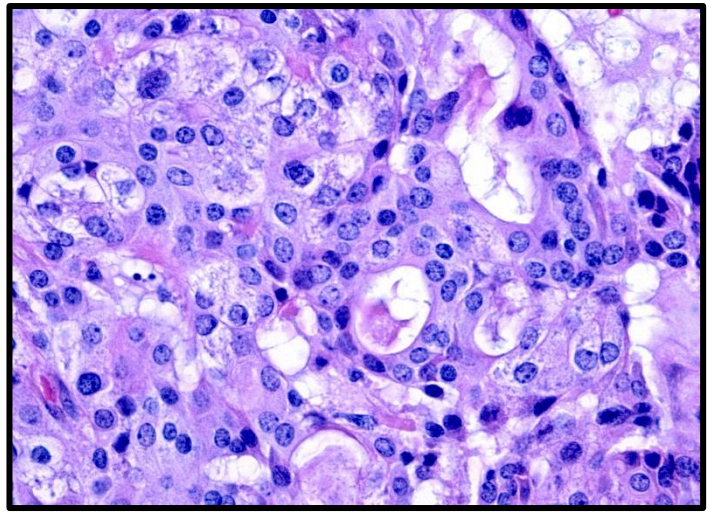
71-year old with <1.0 cm left submandibular gland mass





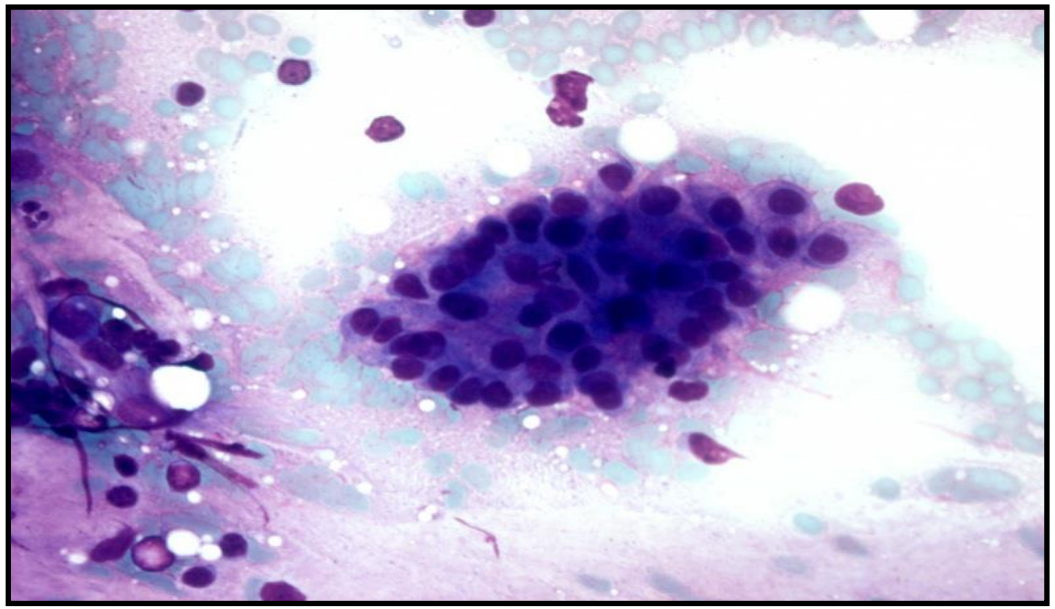


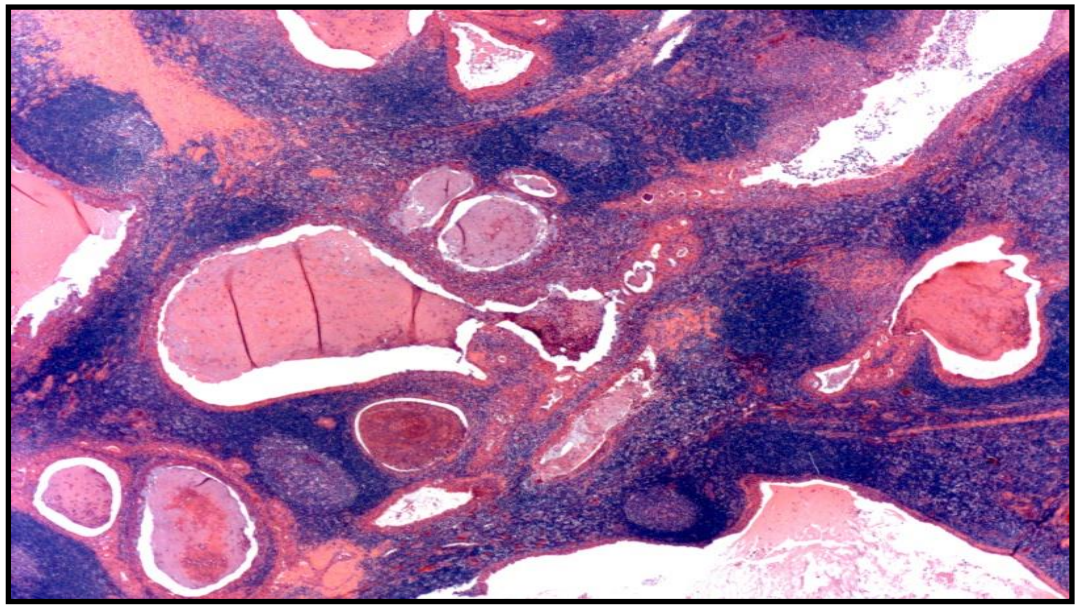


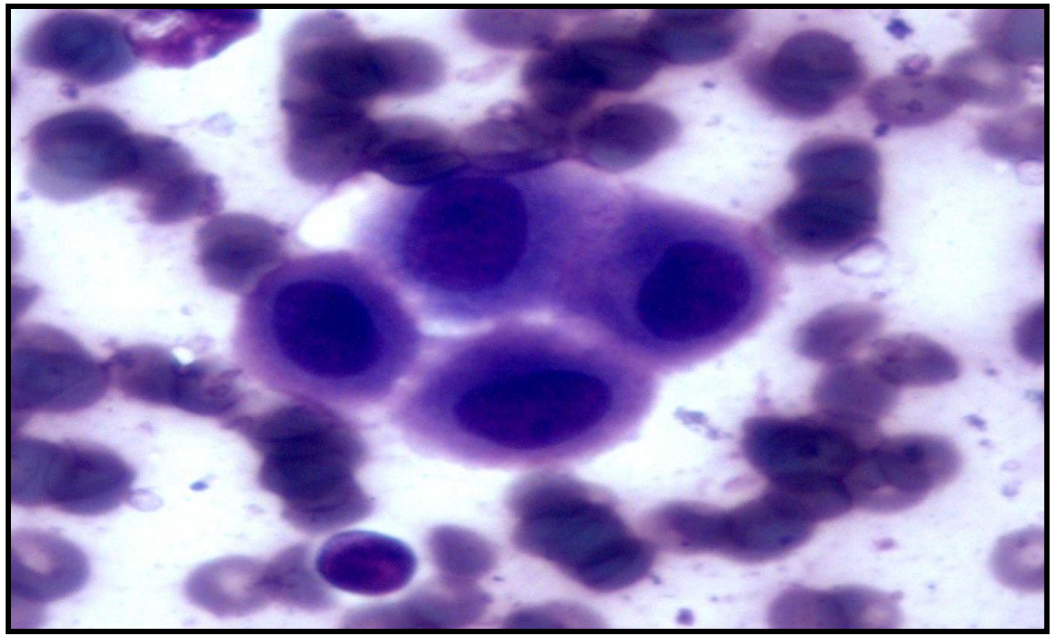


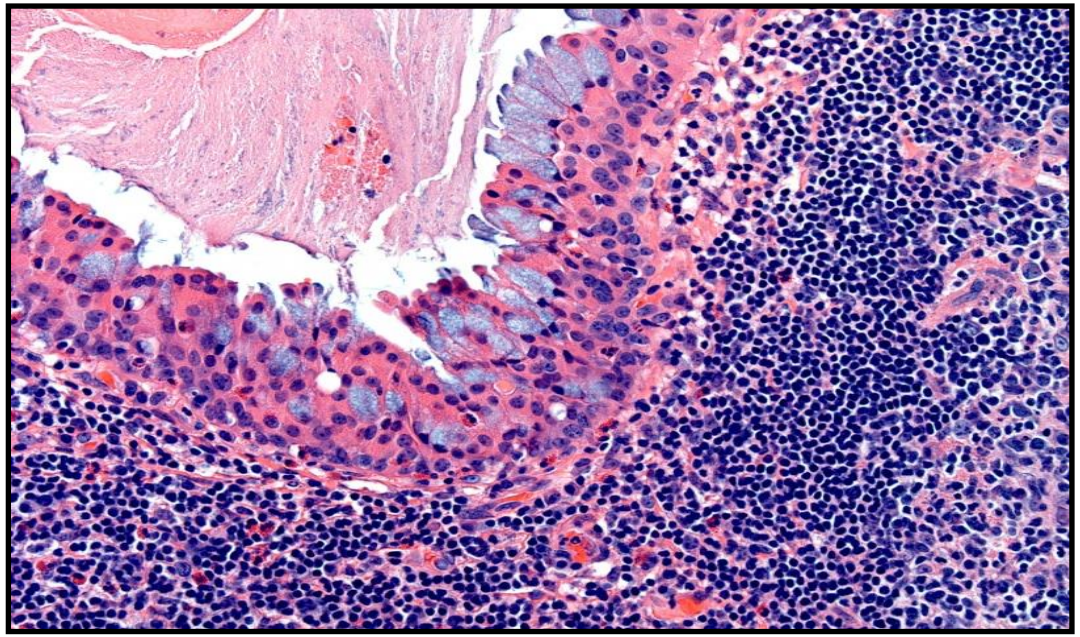
MAML2 FISH +ve, DOG-1 negative

Oncocytic Mucoepidermoid Carcinoma vs. Just Mucinous Cells in Warthin-Tumor

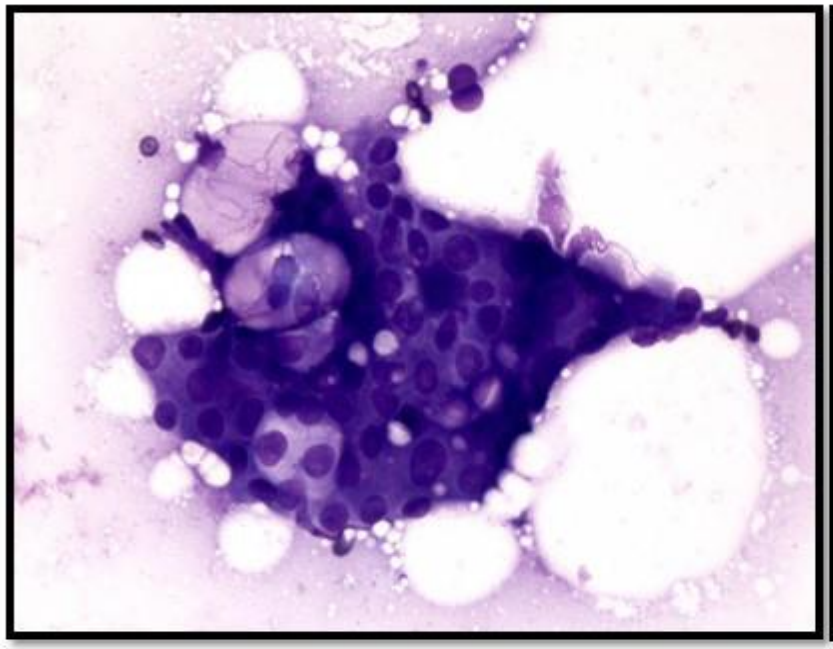
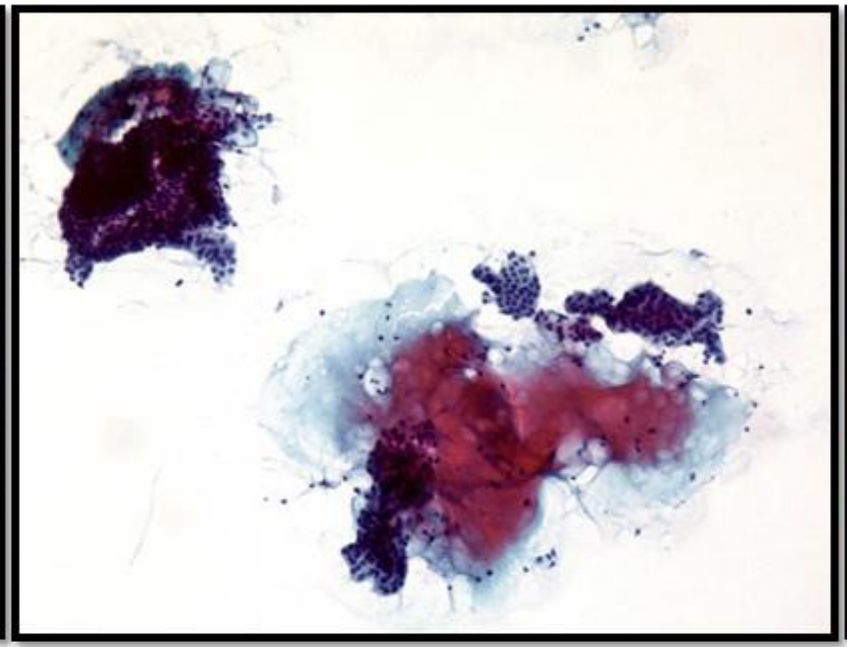
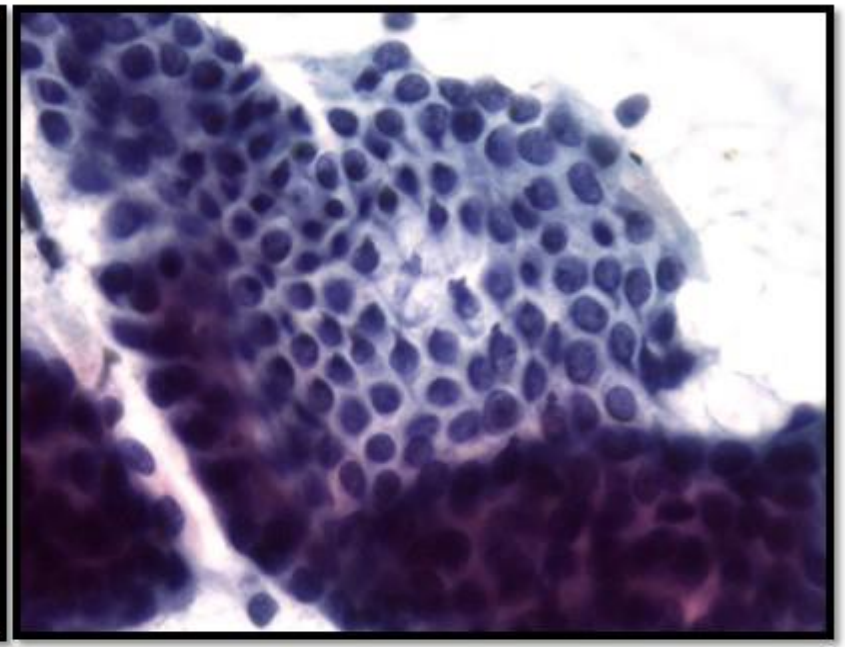
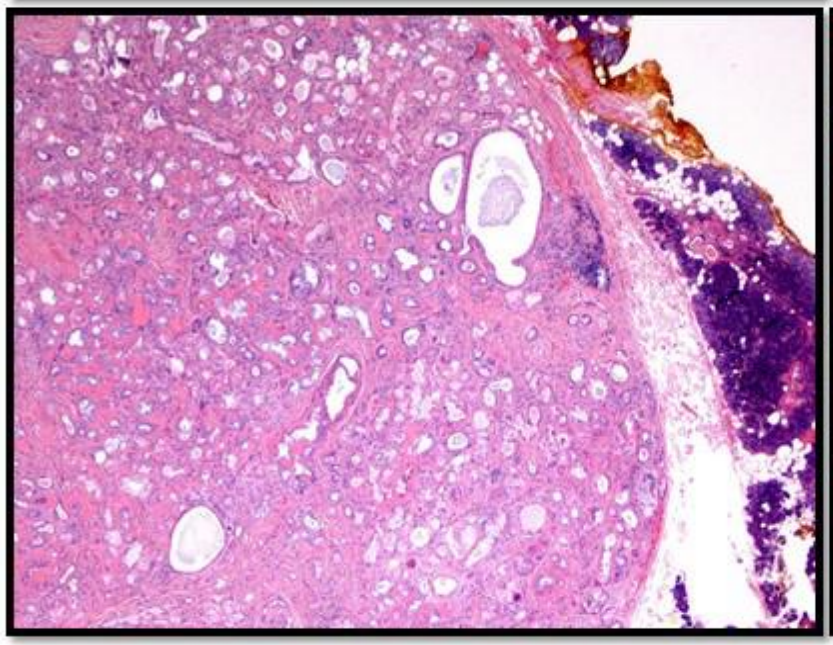
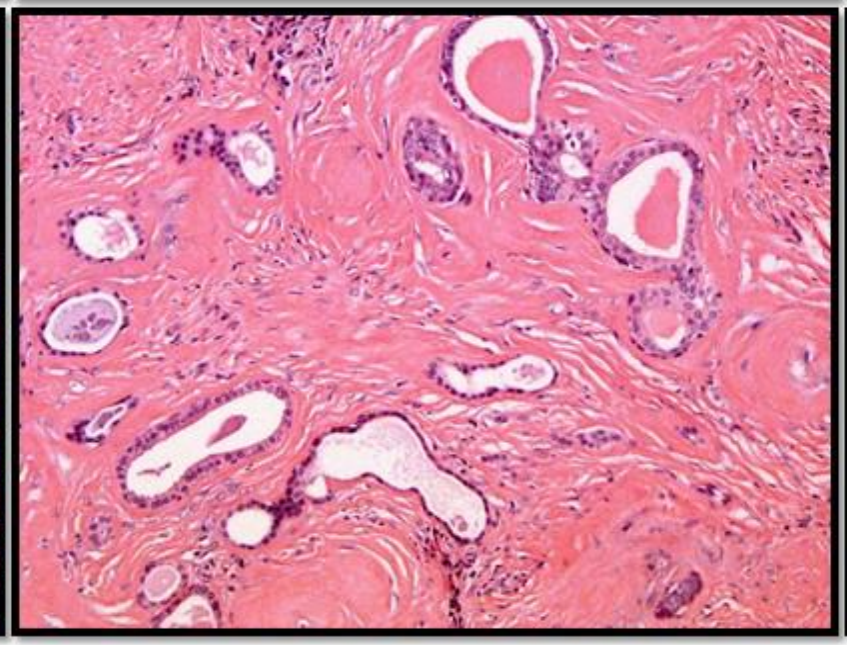
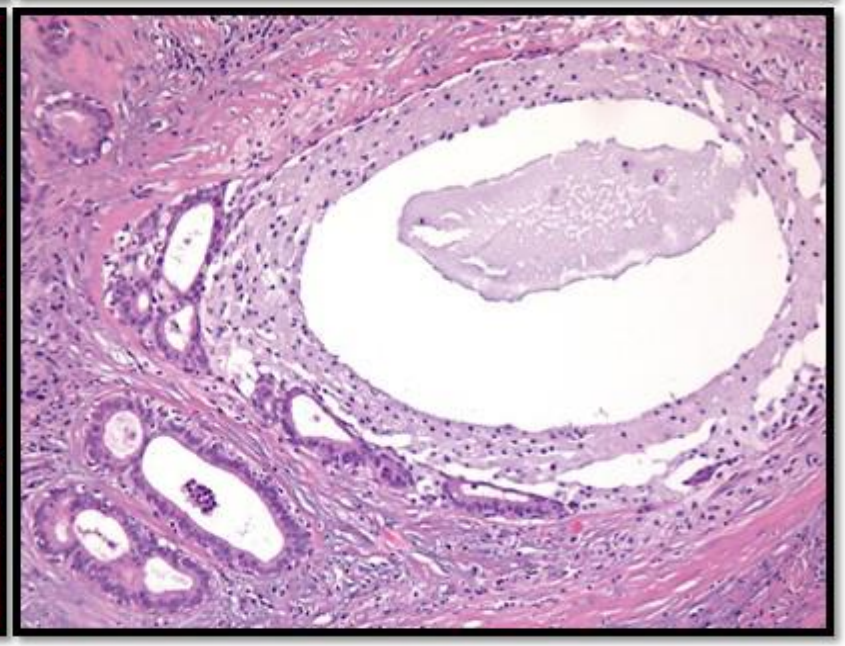




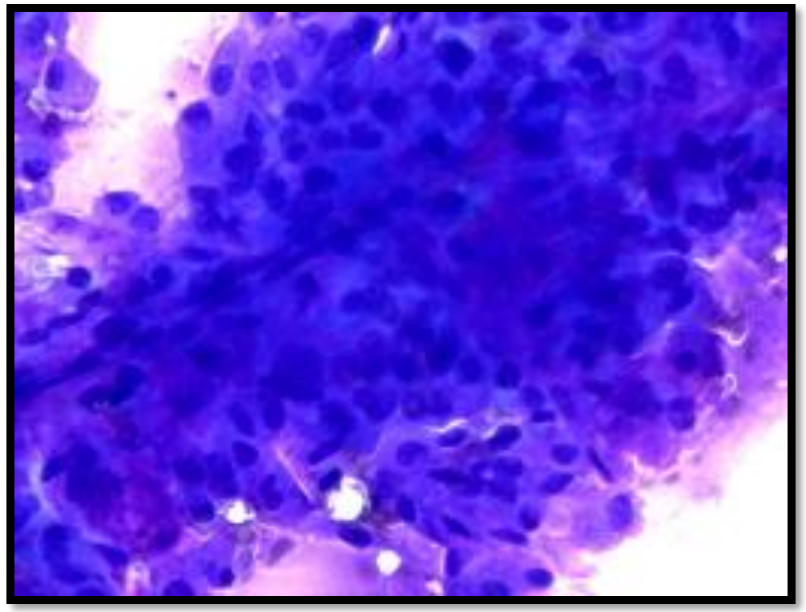
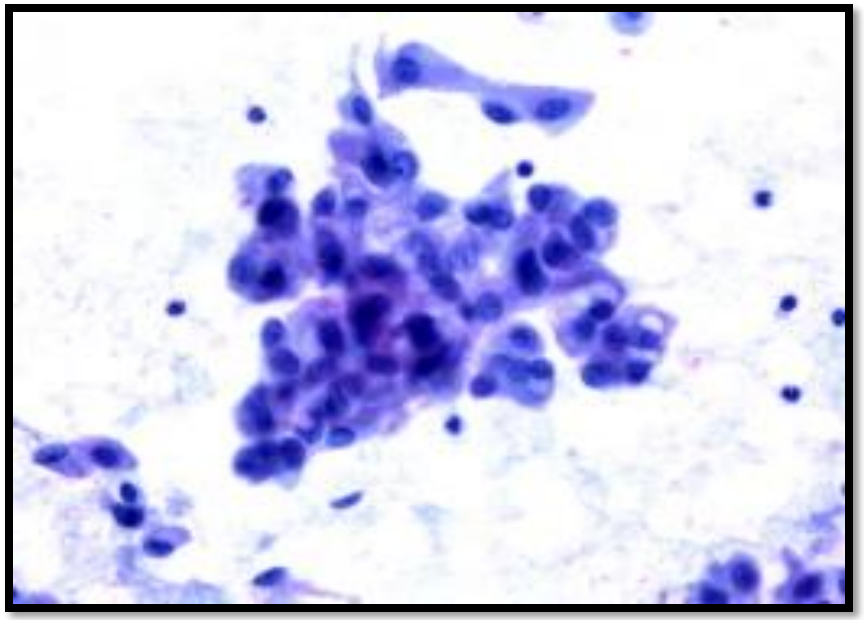
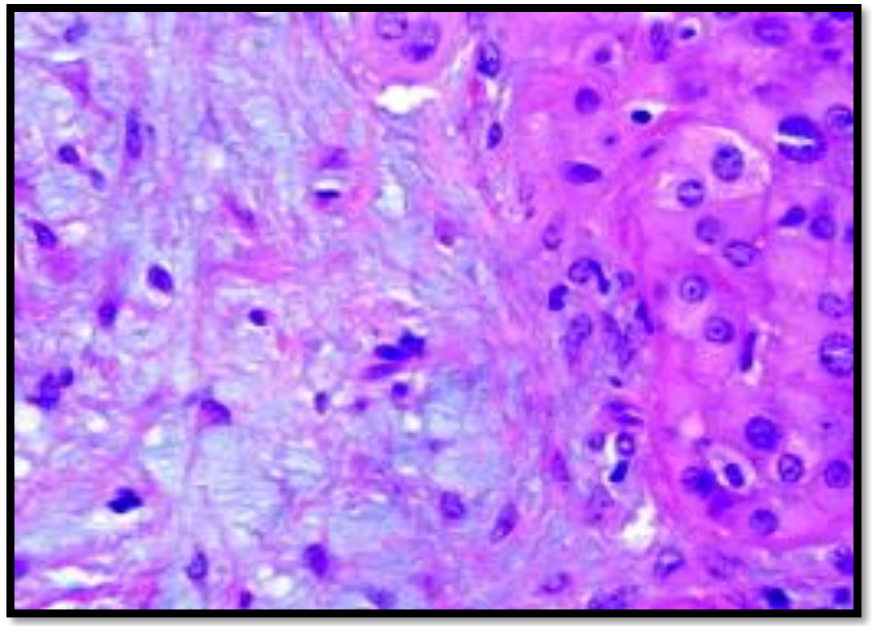
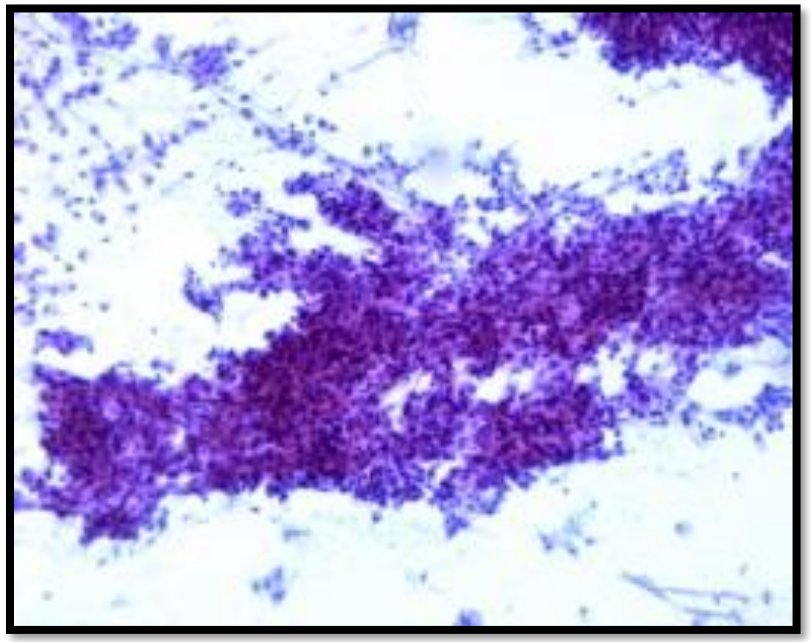
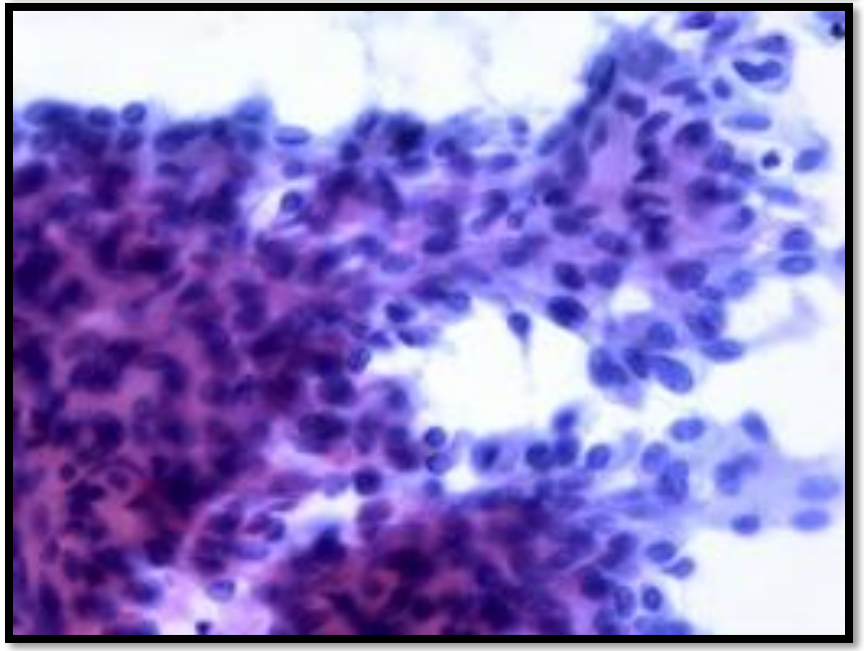
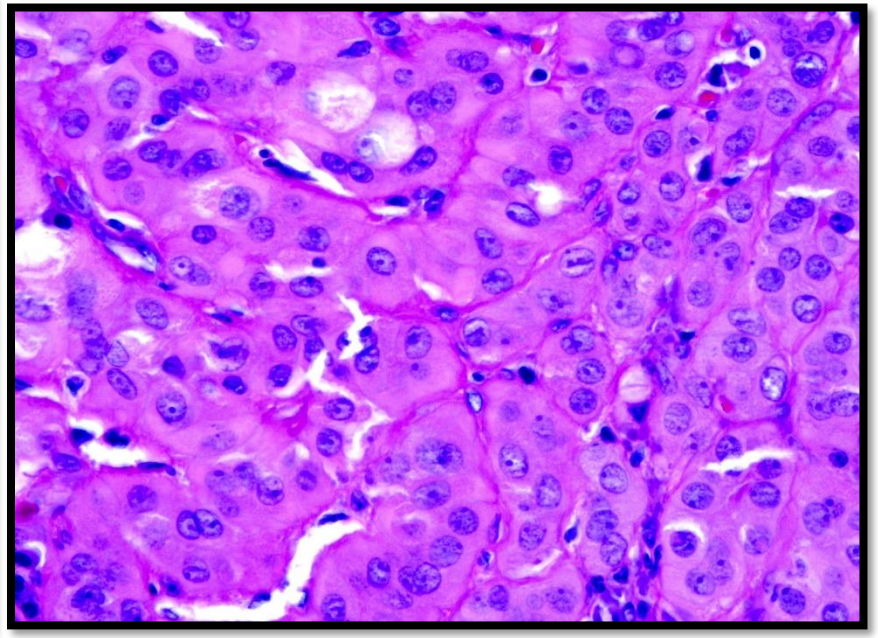




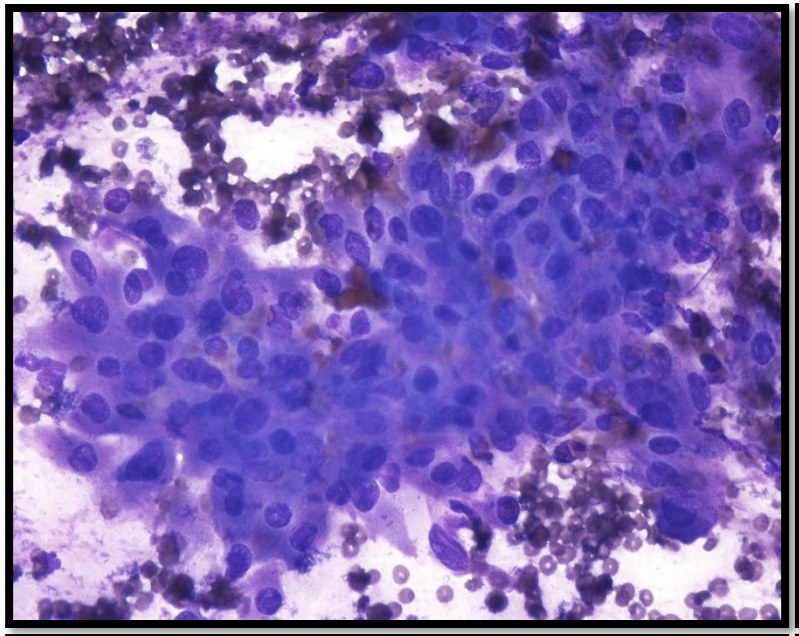
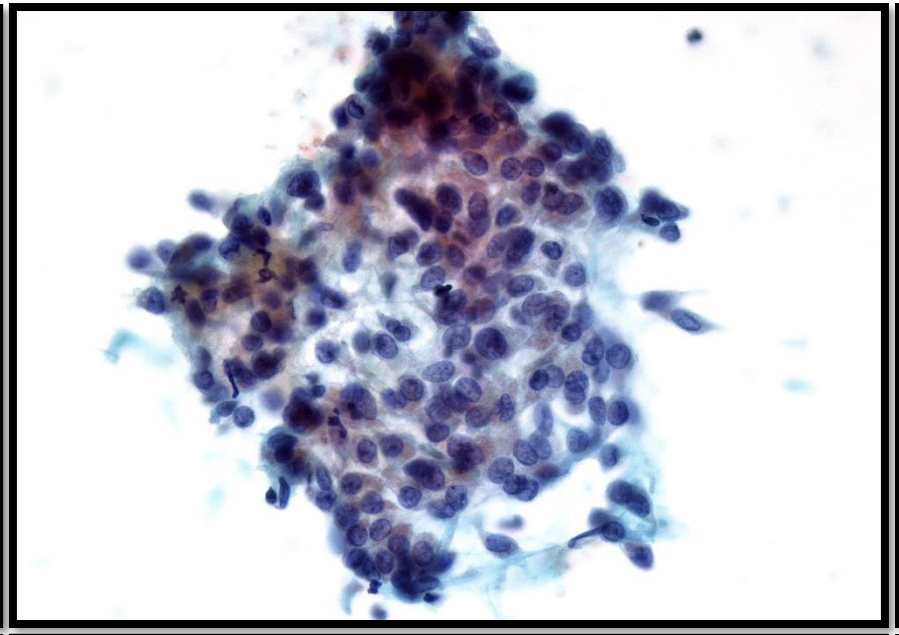
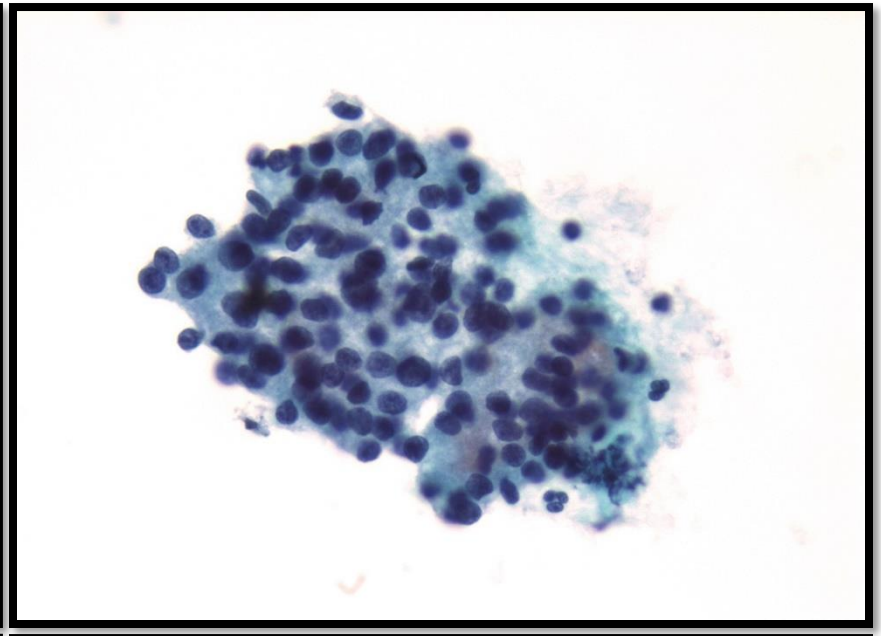
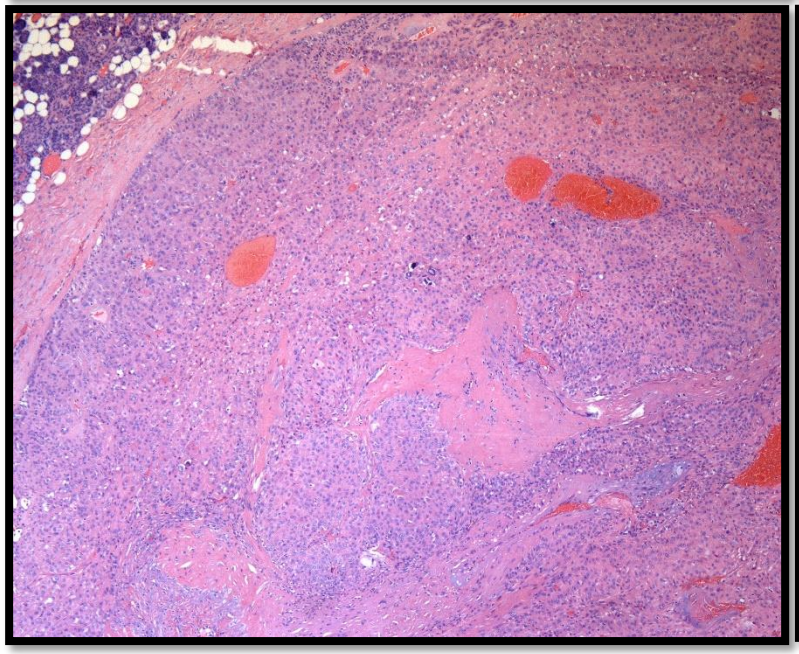
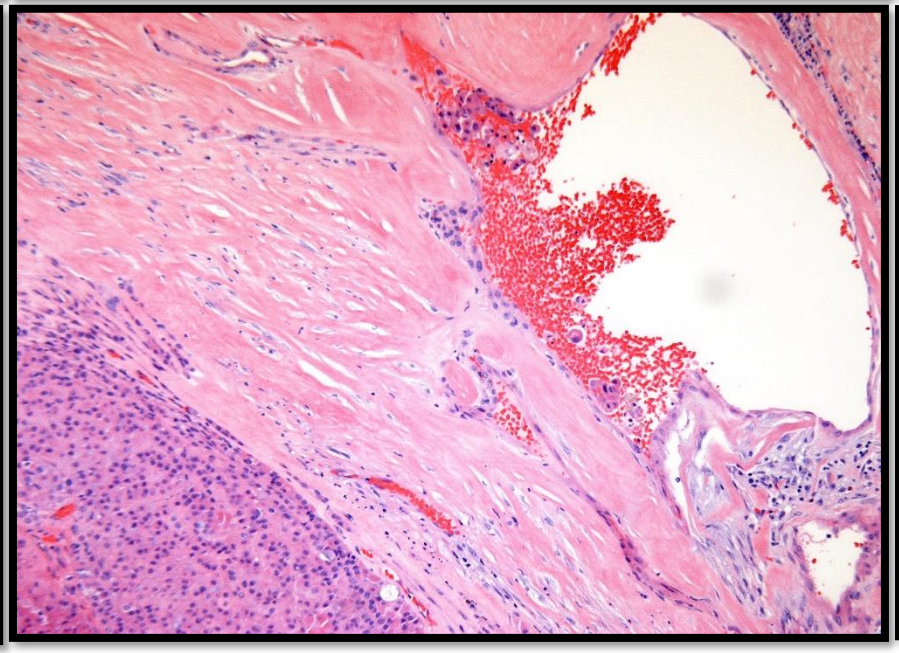
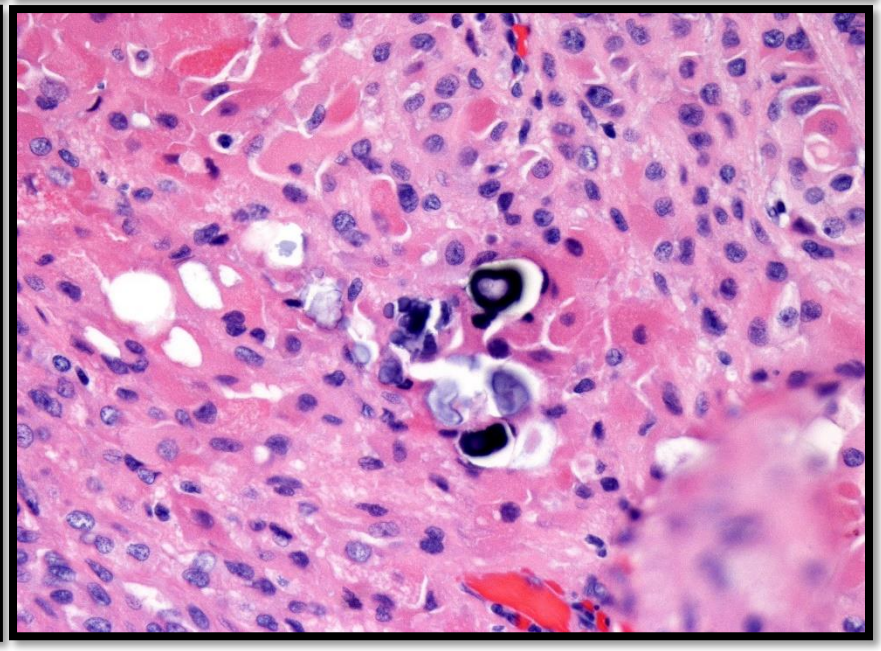
Sclerosing Polycystic Adenoma (Formerly Known as Sclerosing Polycystic Adenosis)

Oncocytic – Pleomorphic Adenoma

Another Oncocytic / Oncocytoid Neoplasm

Acinic Cell Carcinoma

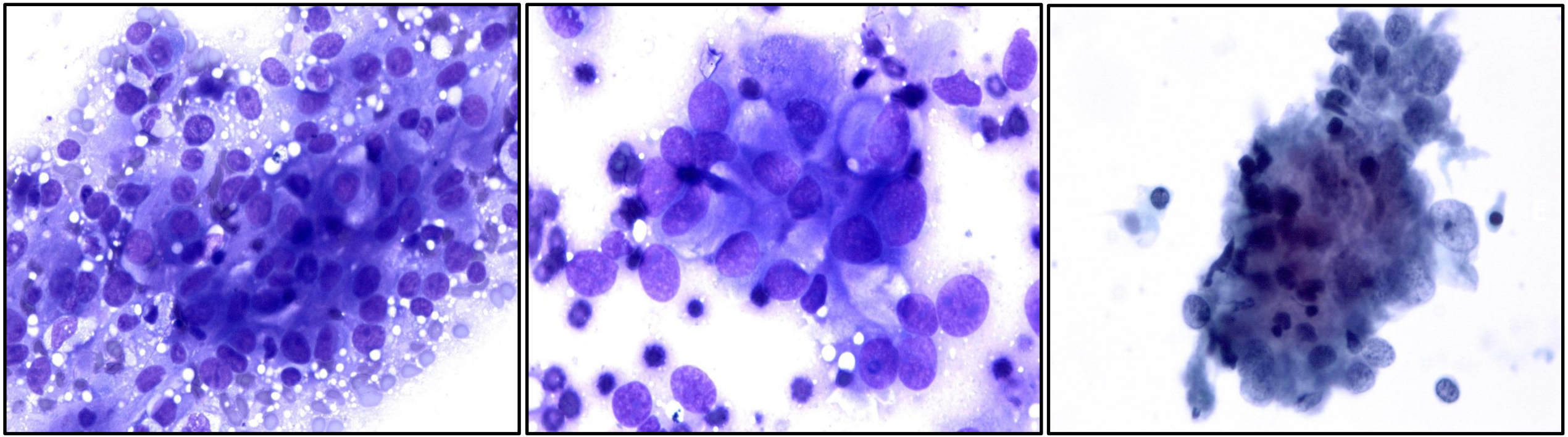
Differential Diagnosis

- ***Granular cytoplasm***
  - **Oncocytic / Oncocytoid Tumors**
  - **Secretory Carcinoma**

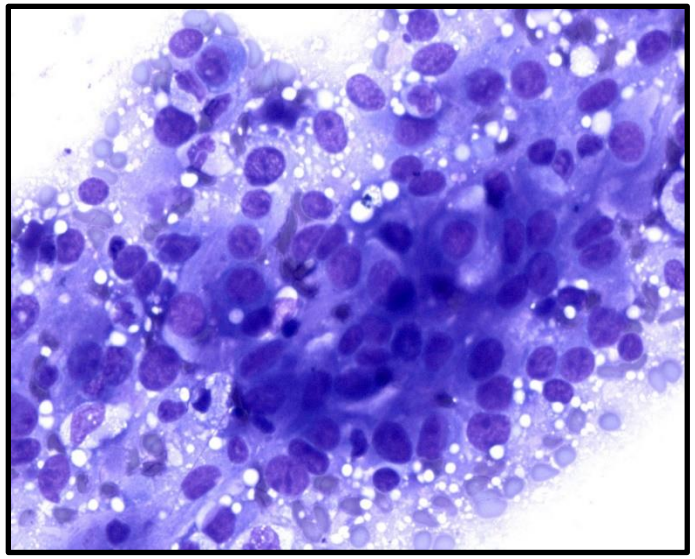
- ***Clear or vacuolated cytoplasm***
  - **Myoepithelial differentiation**
  - **Metastatic tumors**

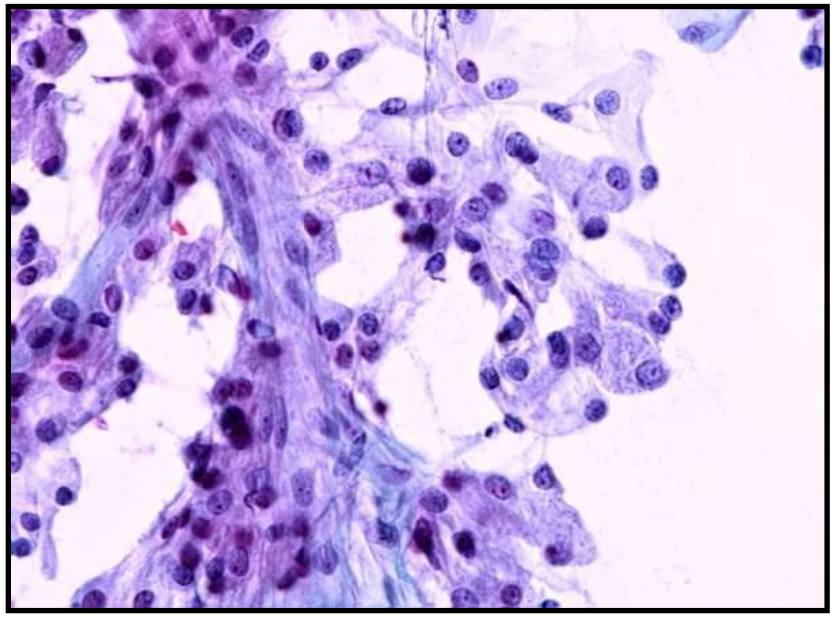
- ***Granular Cytoplasm + Lymphocytes***
  - ***Warthin Tumor***

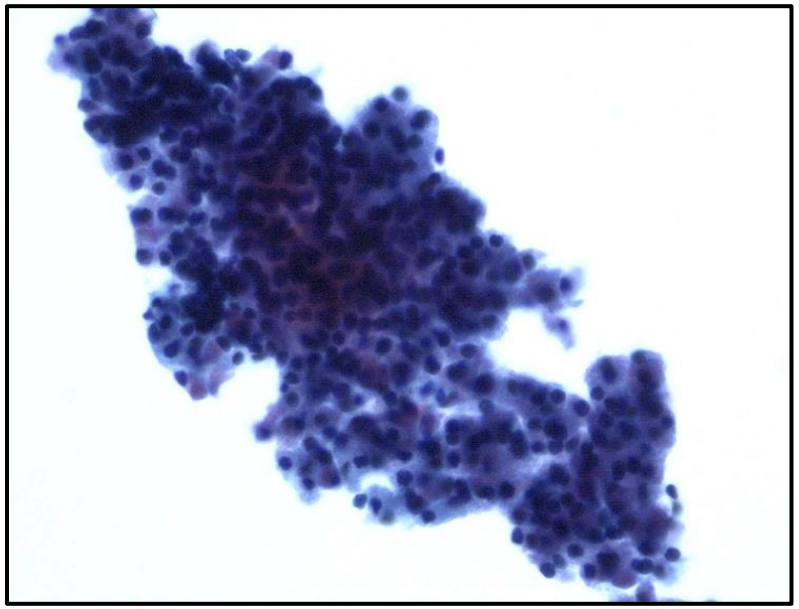
45-year-old man with right parotid gland mass

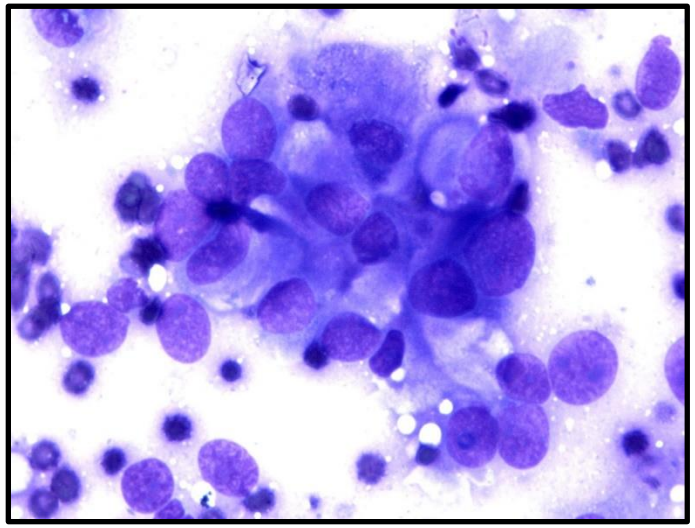


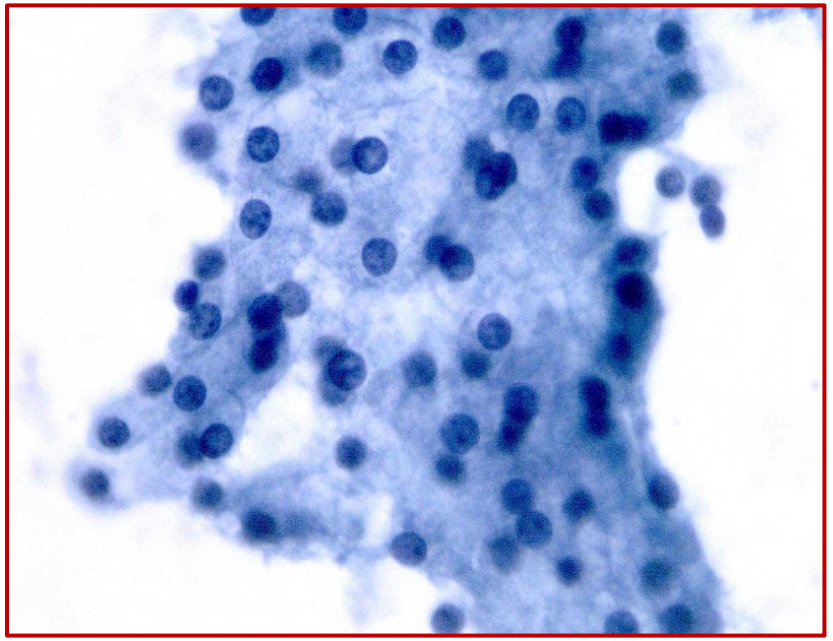
45-year-old man with right parotid gland mass

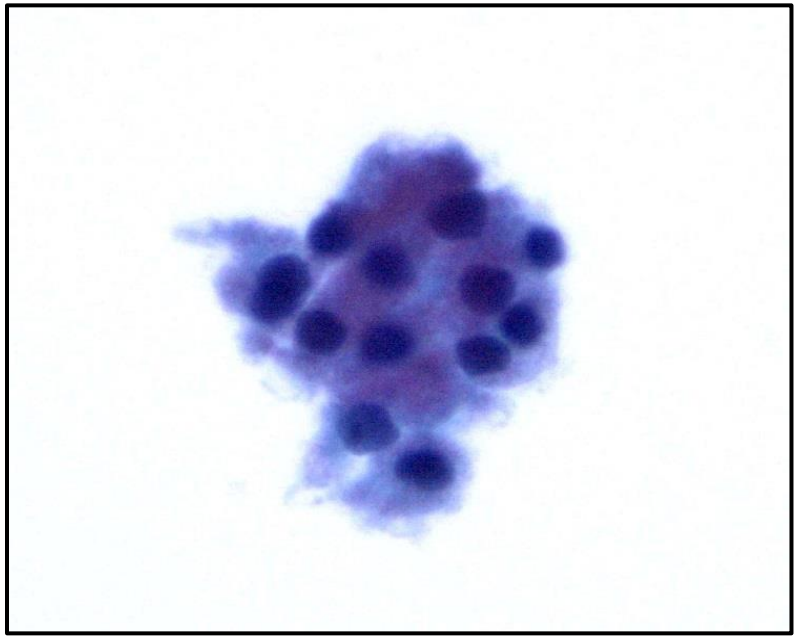




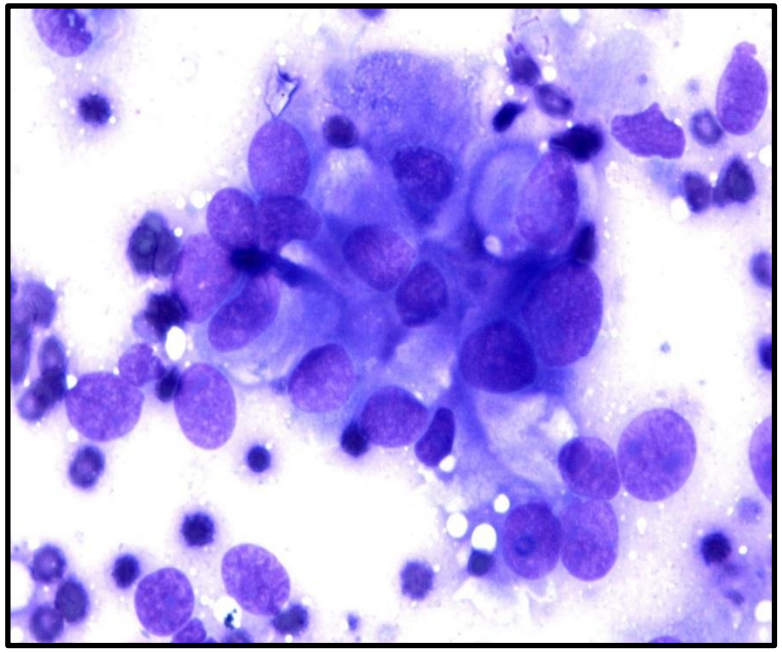


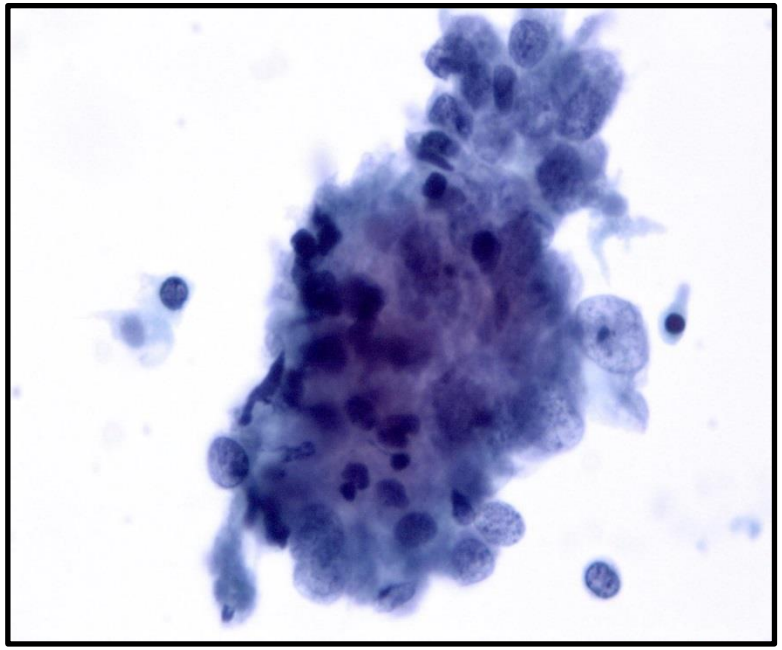


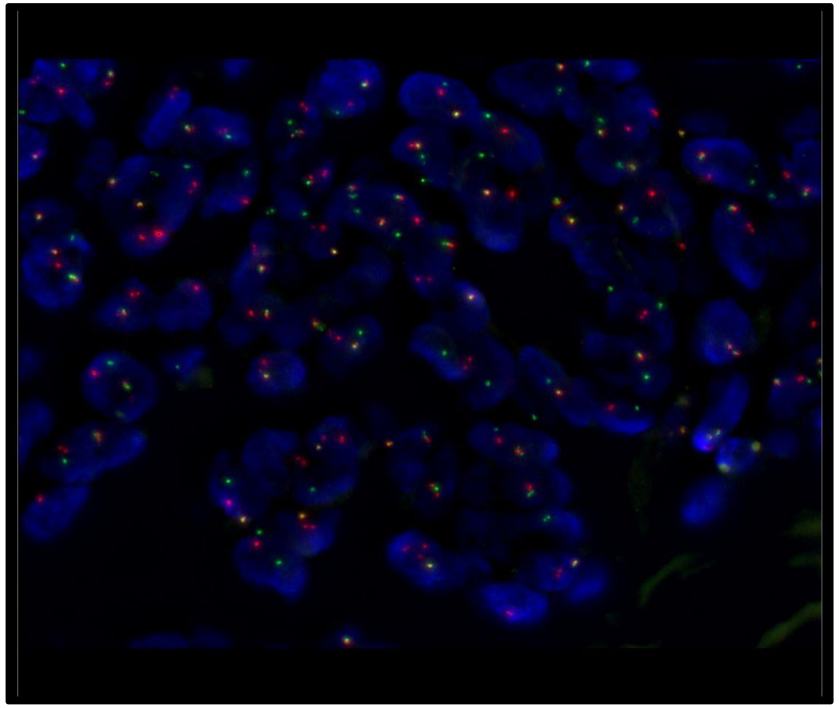


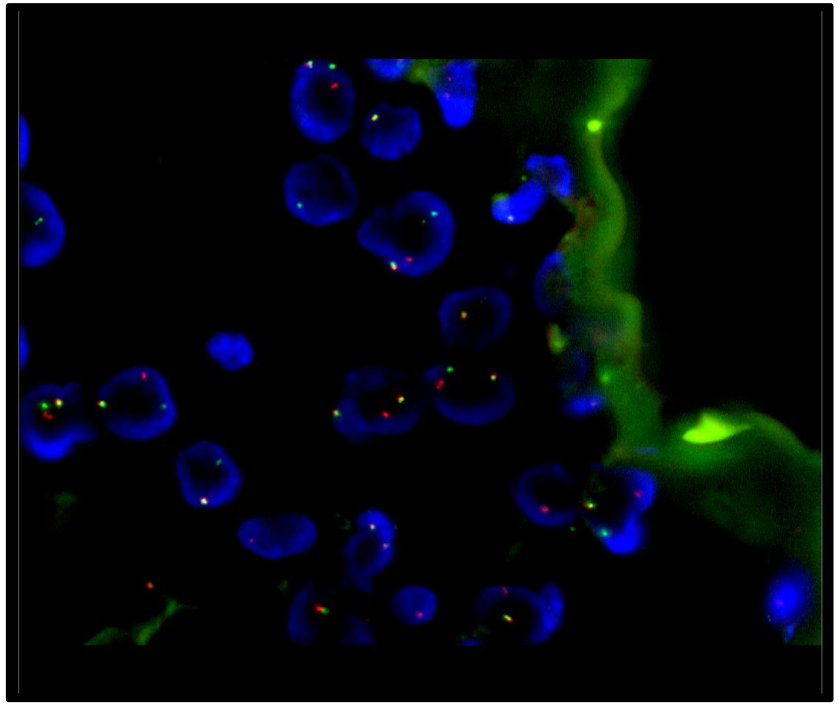


45-year-old man with right parotid gland mass





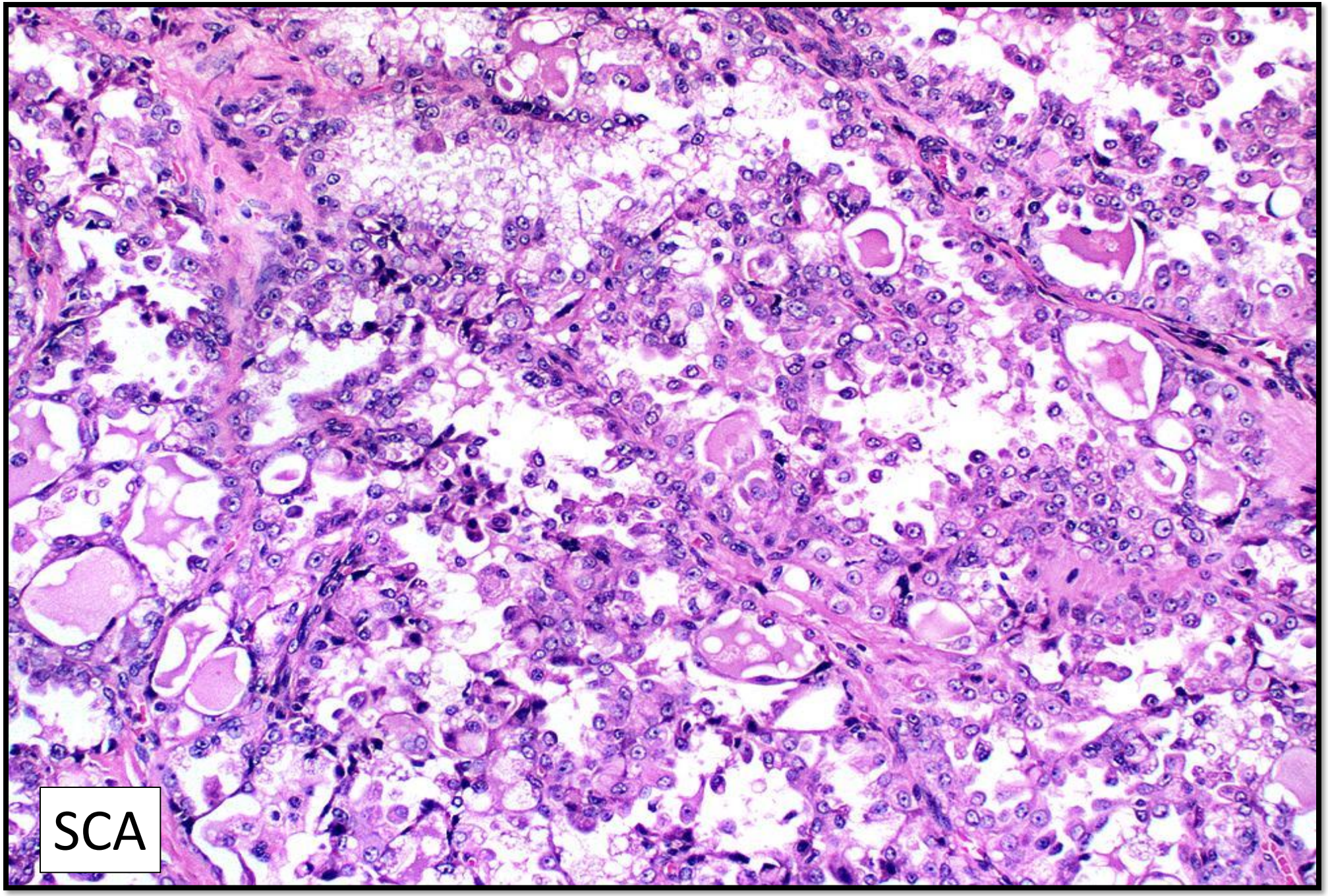


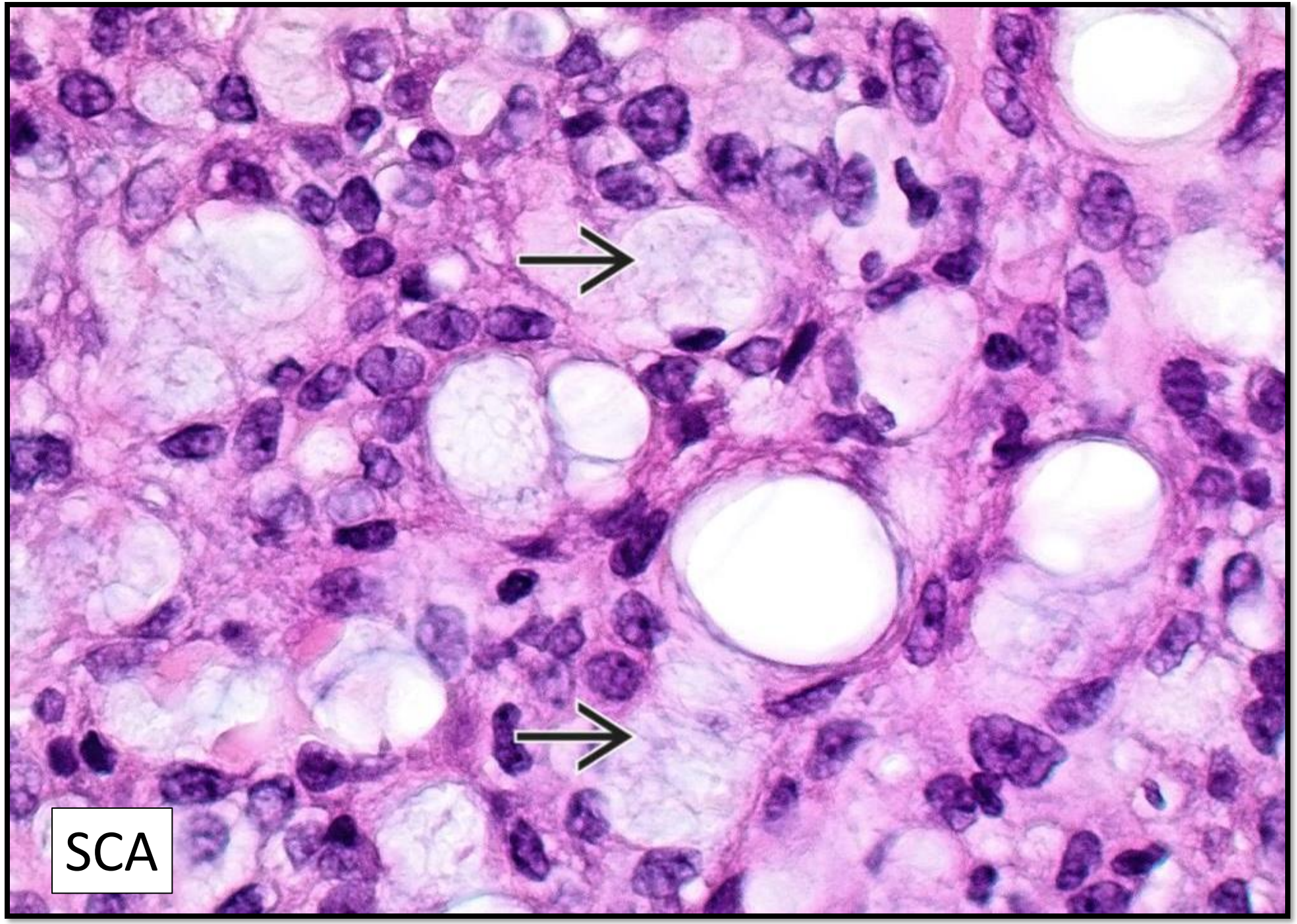


FISH - ETV6 Rearrangement

Secretory Carcinoma (Previously classified as MASC)

- Malignant but good prognosis with proper excision
- High Grade tumors have been reported
- Wide age range, equal gender distribution
- Parotid (60%) followed by minor salivary glands (~20%)
- Defined by **t(12;15)- *ETV6-NTRK3*** fusion
- Histology:
  - **Cells: Bland vesicular nuclei, abundant pale to pink granular cytoplasm, vacuolated/bubbly secretions**
  - Many architectural patterns (cystic, tubular, papillary)
  - **Colloid-like material**
- IHC:
  - Positive: **Mammoglobin**, CK7, S100, GATA3, GCDFP15, MUC1/4
  - Negative: p63, CK/56, DOG1, SMA, calponin, CK14


SCA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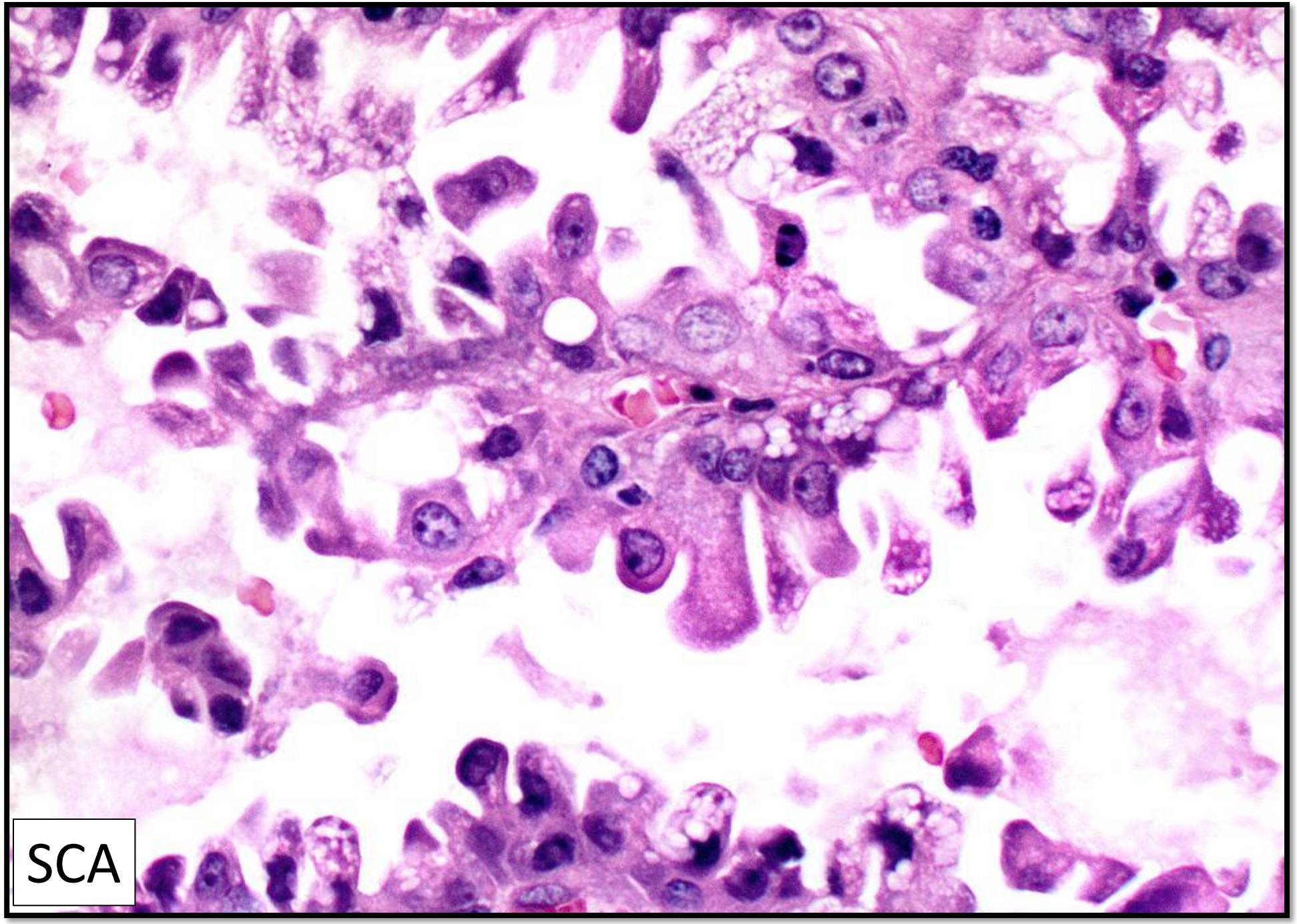

SCA


SCA

Ancillary Studies

Special Stains and Immunostains

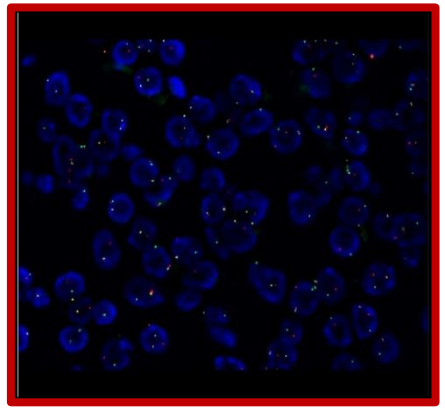
Molecular Targets

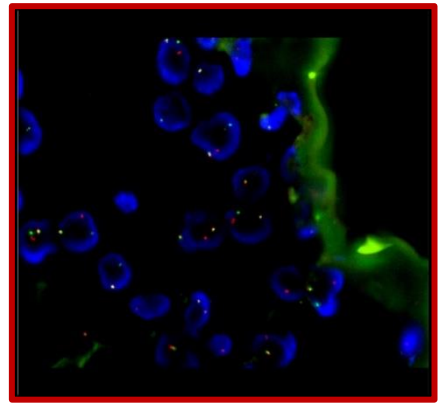
Ancillary Studies - Immunohistochemistry

	PanCK	p63 & p40	SOX10	S100	DOG1	Mammoglobin	Androgen Receptor	GATA3	CD117	PLAG1
Tumor Type										
Pleomorphic Adenoma	+	+	+	+	-	-	-	v	v	+
Basal Cell Adenoma/Adenoca	+	+	+	+	-	-	-	v	v	v
Mucoepidermoid Ca	+	+	+/-	-	-	-	-	v	v	-
Acinic Cell Ca	+	-	+	-	+	-	-	-	-	-
Secretory Ca (MASC)	+	-	+	+	-	+	-	+ (n)	-	-
Adenoid Cystic Ca	+	+	+	+	+	-	-	-	+ (luminal)	-
Oncocytoma	+	+	-	-	?	-	-	-	?	?

Caution should be applied when using these in cytology preparations - validation

Tumor	Alteration	% cases
Acinic cell carcinoma	*NR4A3* rearrangements *HTN3::MSANTD3* fusion	95% 5%
Adenoid cystic carcinoma	*MYB, MYBL1,* and/or *NFIB* fusions *MYB* activation/amplification	~80%
Basal cell adenoma/ Basal cell adenocarcinoma	*CTNNB1 or CYLD* mutation	40-80% (adenoma) 5-30% (carcinoma)
Clear cell carcinoma	*EWSR1::ATF1*, rare others	~80-90%
Epithelial-myoepithelial carcinoma	*PLAG1* or *HMGA2* fusions *HRAS* mutations	~50%
Intraductal carcinoma (intercalated duct, mixed, oncocytic)	*NCOA4::RET*, *TRIM27::RET*, *TRIM33::RET*, other fusions *BRAF* V600E mutation	~50%
Mucoepidermoid carcinoma	*MAML2* fusions	~70-80%
Mucinous adenocarcinoma	*AKT1* and *TP53* mutations	>90%
Pleomorphic adenoma and carcinoma ex-pleomorphic adenoma	*PLAG1* or *HMGA2* fusions	~60-90%
Polymorphous adenocarcinoma	*PRKD1, PRKD2* and *PRKD3* fusions or mutations	80-90%
Sialadenoma papilliferum	*BRAF* V600E mutations	80%
Salivary duct carcinoma (also apocrine intraductal carcinoma and sclerosing polycystic adenoma)	*TP53*, *HRAS*, *PIK3CA*, *PTEN* mutations *ERBB2* amplification *PLAG1* or *HMGA2* fusions, rare others	90-100%
Secretory carcinoma	*ETV6::NTRK3* *ETV6::RET, ETV6::MET,* others	100%





Tumour	Gene	Sequencing based molecular tests	PCR	Fish	Surrogate IHC markers
Mucopeidermoid carcinoma	CRTC1-MAML2 CRTC3-MAML2 EWSR1-POU5F1	(a) SalvGlandDx (b) NGS	(a) CRTC1-MAML2 (b) CRTC3-MAML2 Fusions by RT-PCR	MAML2 (Breakapart probes)	AREG
Adenoid cystic carcinoma	MYB-NFIB; MYBL1-NFIB	(a) Amplicon sequencing (b) SalvGlandDx (c) NGS	MYB-NFIB RTPCR	MYB and MYBL1 (Breakapart probes) MYB-NFIB (fusion probe)	MyB
Acinic cell carcinoma	SCPP-NR4A3 MSANTD3-HTN3	SalvGland Dx (b) NGS	SCPP-NR4A3 RT-PCR	NR4A3	NR4A3
Secretory carcinoma	ETV6-NTRK3 ETV6-RET ETV6-MET	SalvGlandDx (b) NGS	ETV6-NTRK3 Fusion by RT-PCR	ETV6 NTRK3 (Breakapart probes)	Pan-Trk
Polymporphous adenocarcinoma	PRKD1 E710D	(1) Sanger sequencing (2)SalvGlandDx (b) NGS	–	–	–
Cribriform adenocarcinoma of minor salivary gland	ARID1A-PRKD1, PRKD1-DDX3X, PRKD2 and PRKD3 fusions	SalvGlandDx (b) NGS	–	FISH	–
Clear cell carcinoma	EWSR1-ATF1 EWSR1-CREM Fusion	NGS SalvGlandDx	RT-PCR	EWSR1 ATF1 breakapart probes	–
Salivary duct carcinoma	AR gene alterations ERBB2 amplification TP53, PIK3CA, H-RAS, KIT, EGFR, BRAF, N-RAS, AKT1, FBXW7, ATM, NF1 mutations	Sequencing NGS	–	PLAG1 HMAG2	PLAG1 HMAG2 AR Her2
Pleomorphic adenoma, CAexPA	PLAG1 rearrangements (50–60%) HMAG2 rearrangements (10–20%)	(1) Amplicon sequencing (2) SalvGlandDx (b) NGS	RT PCR	PLAG1 HMAG2	PLAG1 HMAG2
Epithelial myoepithelial carcinoma	HRAS p.Q61R	(1) Hotspot mutation analysis by direct DNA sequencing (2) Amplicon sequencing (3) SalvGlandDx b) NGS	–	–	RAS Q61R
Basal cell adenoma	CTNNB1	(1) Hotspot mutation analysis by direct DNA sequencing (2) Amplicon sequencing (3) SalvGlandDx (b) NGS	PCR	–	β-Catenin, LEF-1
Basal cell adenoma	CYLD	(1) hotspot mutation analysis by direct DNA sequencing (2) NGS	PCR	–	CYLD LEF-1 But negative for β-Catenin
Intraductal carcinoma: intercalated duct type	NCOA4-RET	SalvGlandDx (b) NGS	–	–	–
Intraductal carcinoma: hybrid type	TRIM27-RET fusion	SalvGlandDx (b) NGS	–	–	–
Intraductal carcinoma: Apocrine type	PIK3CA HRAS	SalvGlandDx (b) NGS	–	–	–
Microsecretory adenocarcinoma	MEF2C-SS18 SS18-ZBTB7A	SalvGlandDx (b) NGS	–	SS18 breakapart probe	–
Sialadenoma papilliferum	BRAF V600E	(1) Amplicon sequencing (2) SalvGlandDx (b) NGS	–	–	–
Intraductal papillary mucinous neoplasm	AKT1 E17K	SalvGlandDx (b) NGS	–	–	

Summary

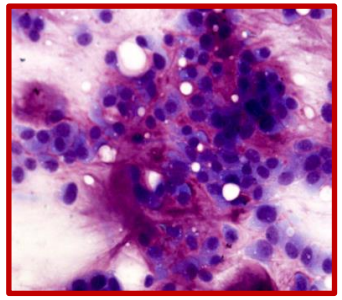
Diagnosing Salivary Gland Lesions on Fine-needle Aspiration Cytology

- Clinical History
- Radiologic features (if available)
- Architectural pattern
- Cellular elements & their distribution
  - Background
- Differential diagnosis
- If specific diagnosis cannot be provided – Grouping based on:
  - Cellular elements – everything counts (background, cell, stroma, other)
  - Differential

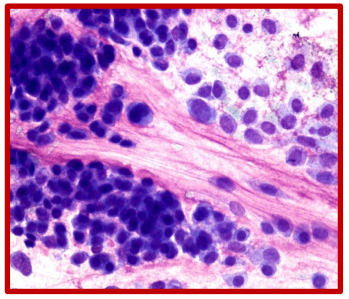
Fine Tuning – SUMP – Say What You See

Cytomorphologic Features*	Differential Diagnosis**
1. Cellular basaloid neoplasm with scant fibrillary matrix	• Cellular pleomorphic adenoma • Epithelial-myoepithelial carcinoma • Basal cell adenoma / adenocarcinoma • Carcinoma ex pleomorphic adenoma
1. Cellular basaloid neoplasm with hyaline stroma	• Basal cell adenoma / adenocarcinoma • Adenoid cystic carcinoma • Epithelial-myoepithelial carcinoma • Carcinoma ex pleomorphic adenoma
1. Cellular basaloid neoplasm with mixed/other matrix	• Adenoid cystic carcinoma • Polymorphous adenocarcinoma∞ • Cellular pleomorphic adenoma • Carcinoma ex pleomorphic adenoma
1. Cellular basaloid neoplasm with minimal to no matrix	• Cellular pleomorphic adenoma • Canalicular adenoma • Myoepithelioma • Myoepithelial carcinoma • Adenoid cystic carcinoma • Carcinoma ex pleomorphic adenoma

Cytomorphologic Features	Differential Diagnosis
Cellular oncocytic / oncocytoid neoplasm with	
1. Cystic background (histiocytes, proteinaceous debris, +/- inflammatory cells)	• Warthin Tumor* • Sclerosing polycystic adenoma • Cystadenoma, oncocytic • Acinic cell carcinoma • Mucoepidermoid carcinoma, oncocytic variant
1. Mucinous background	• Mucoepidermoid carcinoma, oncocytic variant • Rare case of Warthin tumor with focal mucinous metaplastic change∞
Granular (usually coarse) / Vacuolated cytoplasm	• Acinic cell carcinoma • Secretory carcinoma (MASC) • Metastatic renal cell carcinoma
1. Appreciable focal nuclear atypia€	• Salivary duct carcinoma • High grade mucoepidermoid carcinoma • Oncocytic carcinoma • High grade, oncocytic epithelial-myoepithelial carcinoma • Metastatic carcinoma



BMT/PA



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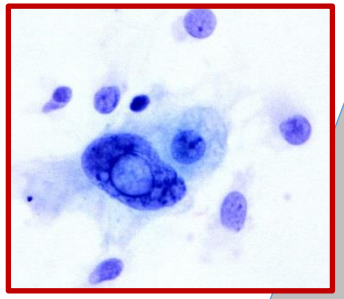

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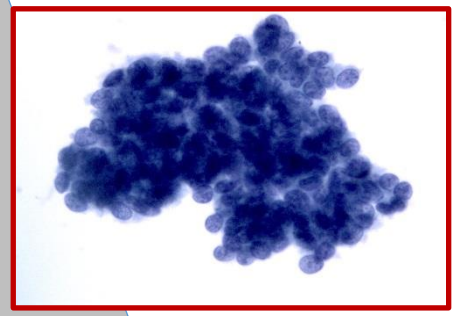
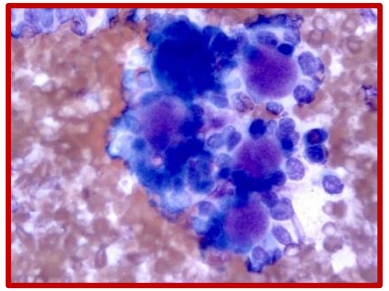
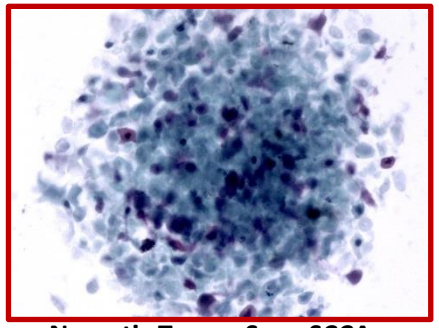


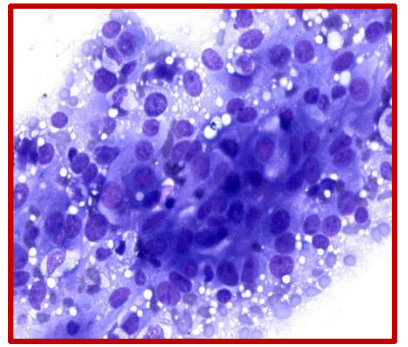
Basaloid Neoplasm



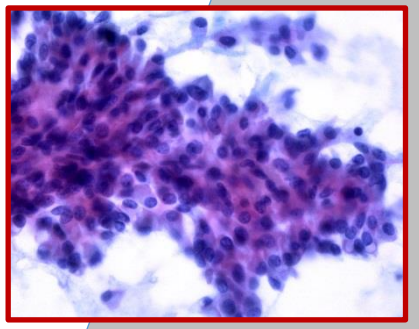
Adenoid Cystic Ca

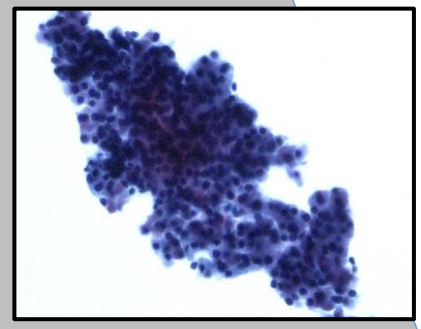


Necrotic Tumor Susp SCCA

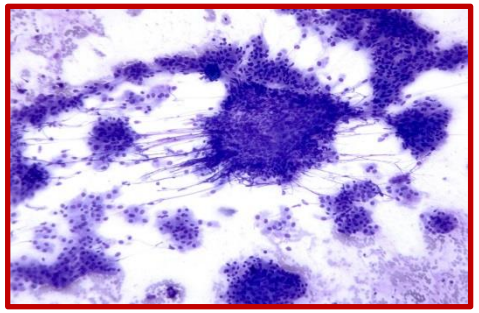


Secretory Carcinoma

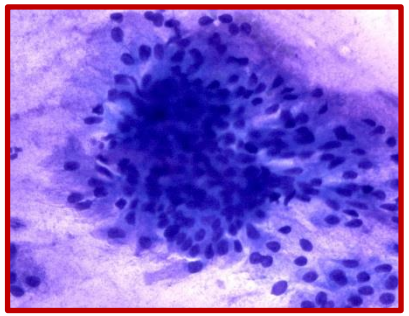




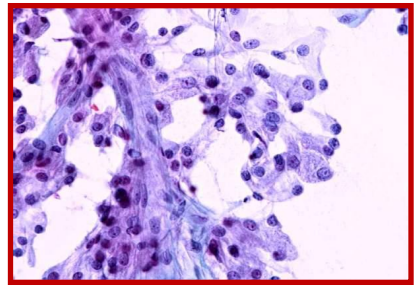
Oncocytic / Oncocytoid Neoplasm



Warthin T



Susp-MEC

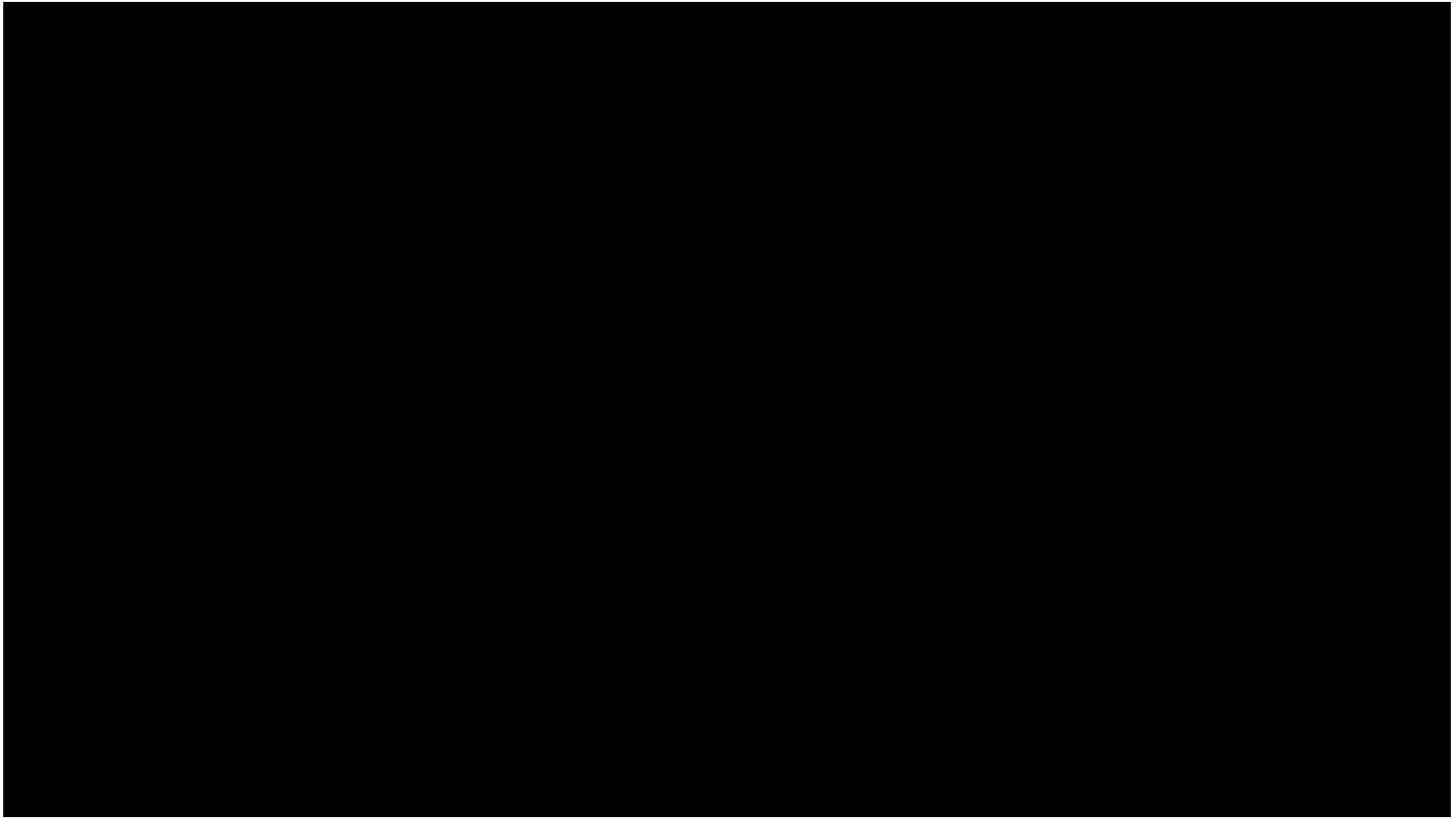


Acinic Cell Ca

Benign Neoplasm ***SUMP*** ***Suspicious-Malignancy*** ***Malignant***

Salivary Gland Fine Needle Aspiration Reporting – Milan System

Surgical Pathology Follow-up – Acinic Cell Carcinoma



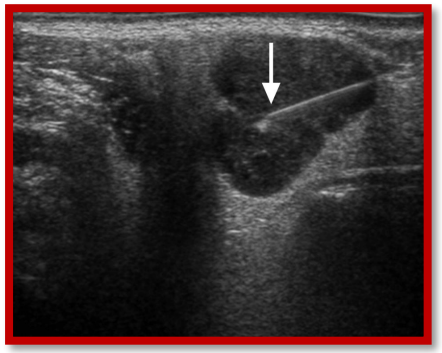
Personalized Approach to Salivary Gland Lesion Management

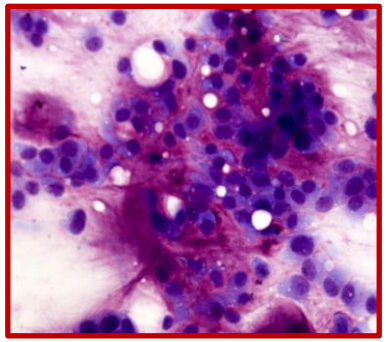
Clinical Presentation

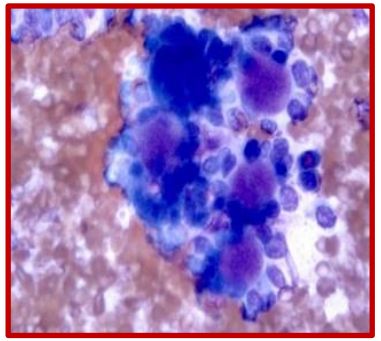
The ancillary studies can help guide clinicians in making management decisions for patients with Salivary gland lesions.

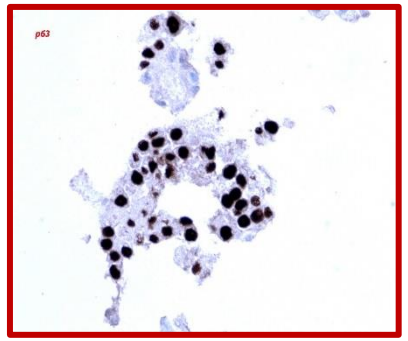
Further Management

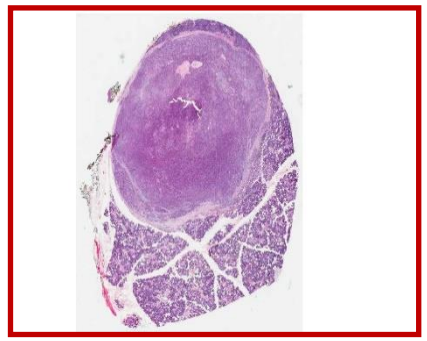
Histologic Follow-up

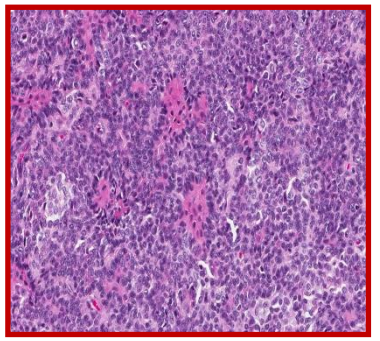


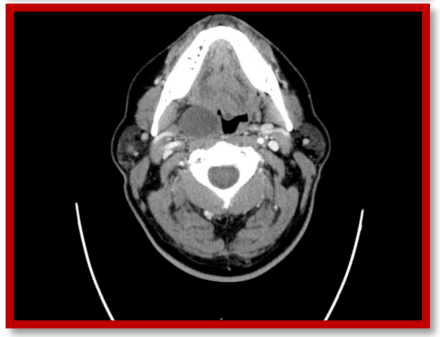


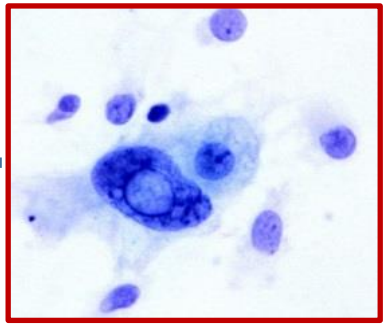


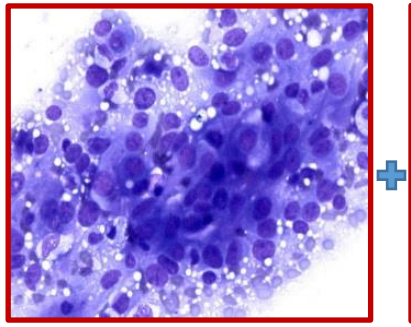


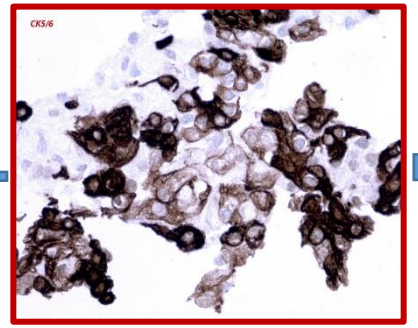


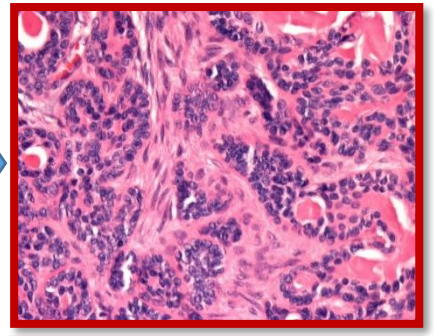


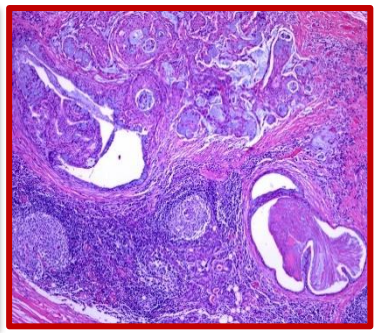


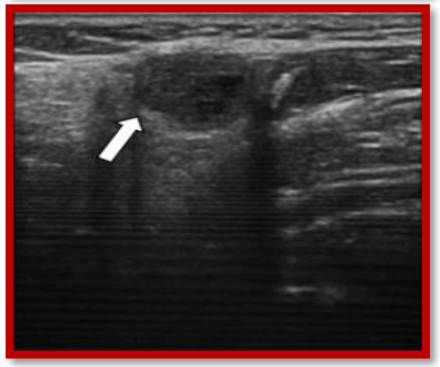


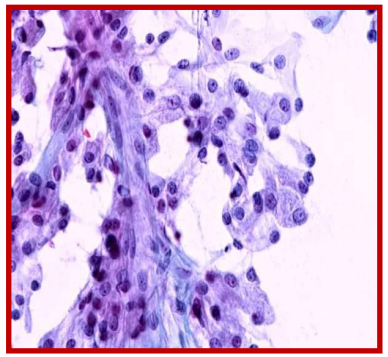


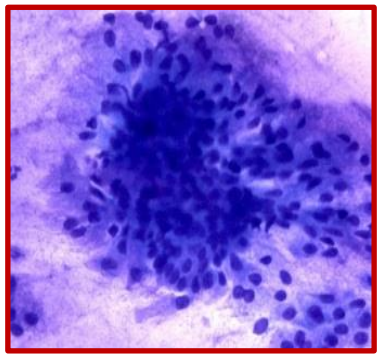


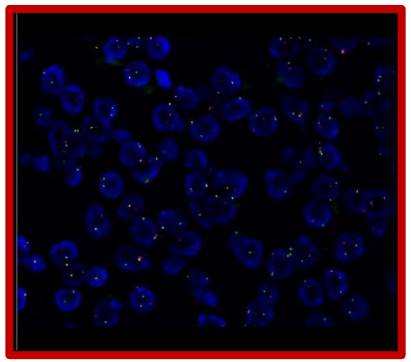


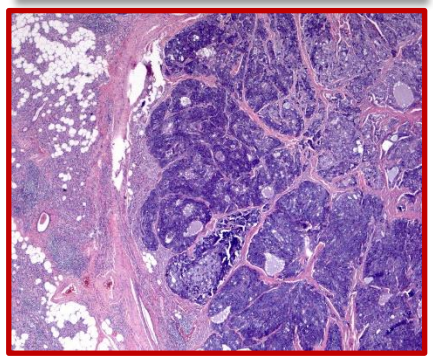


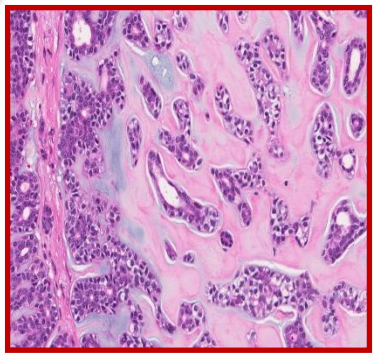












Milan System for Reporting Salivary Gland Cytopathology