What's (not so) New in the WHO in Head and Neck Pathology

American Registry of Pathology Fascicles in Partnership with Johns Hopkins Pathology

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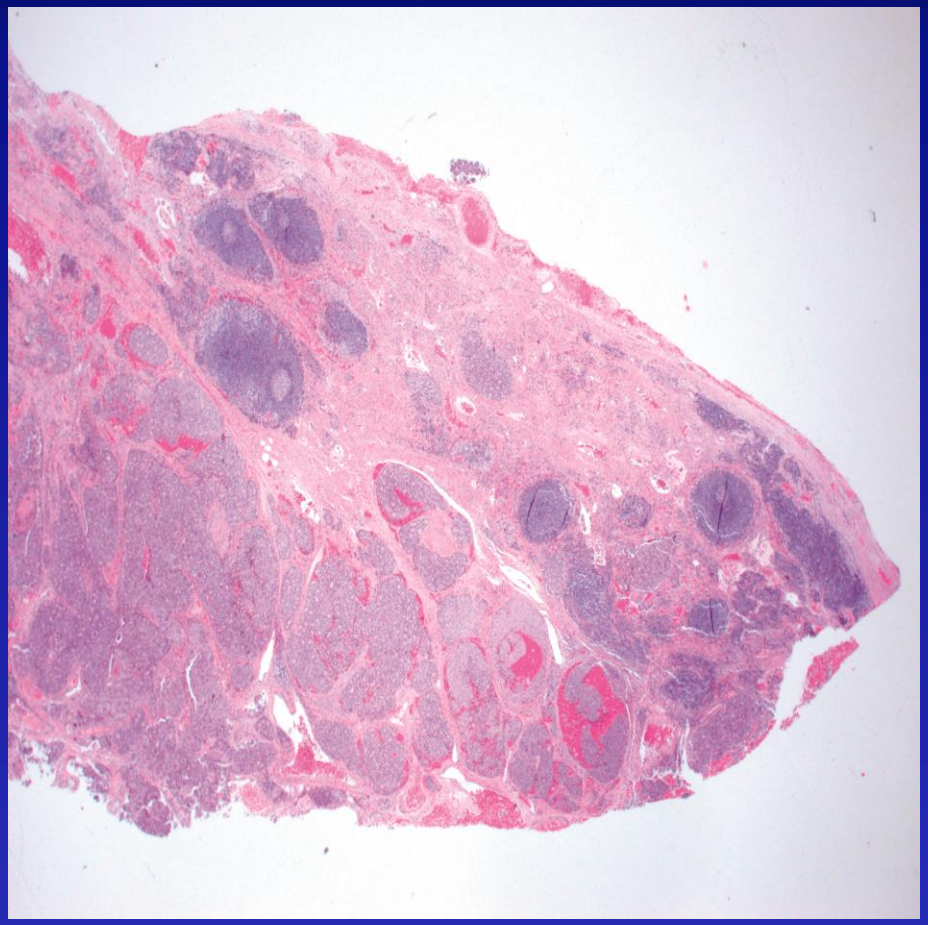
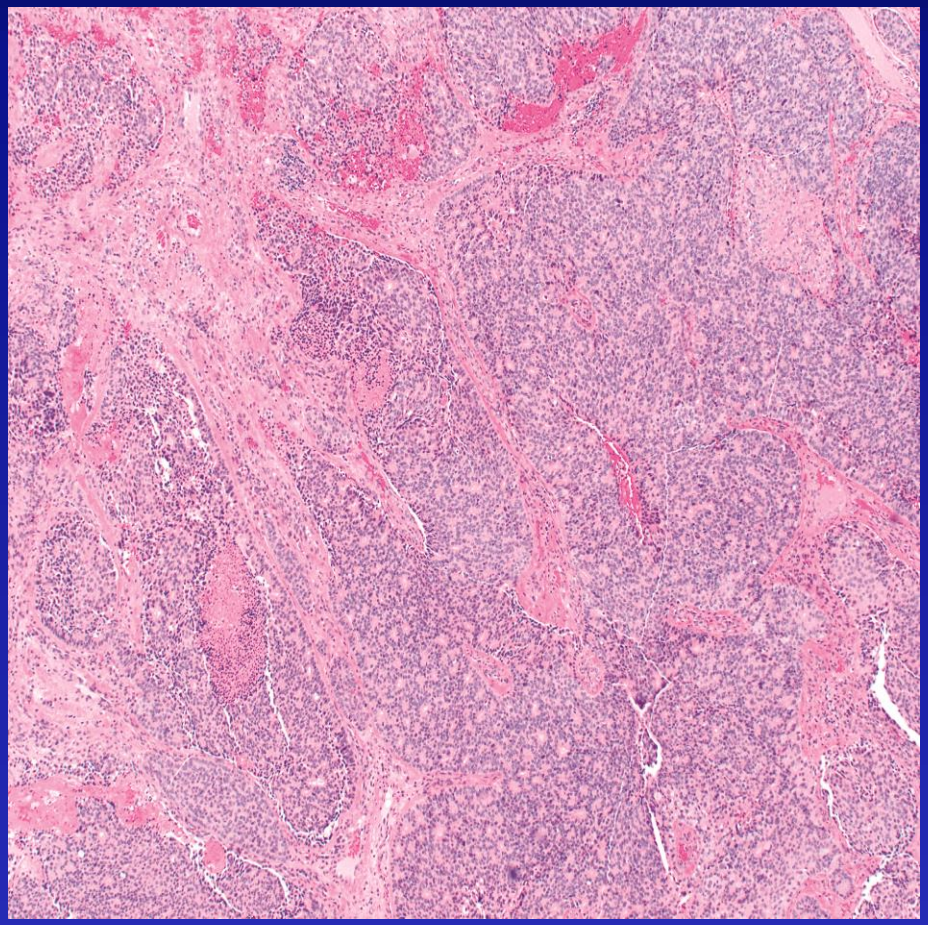
Case 1
History

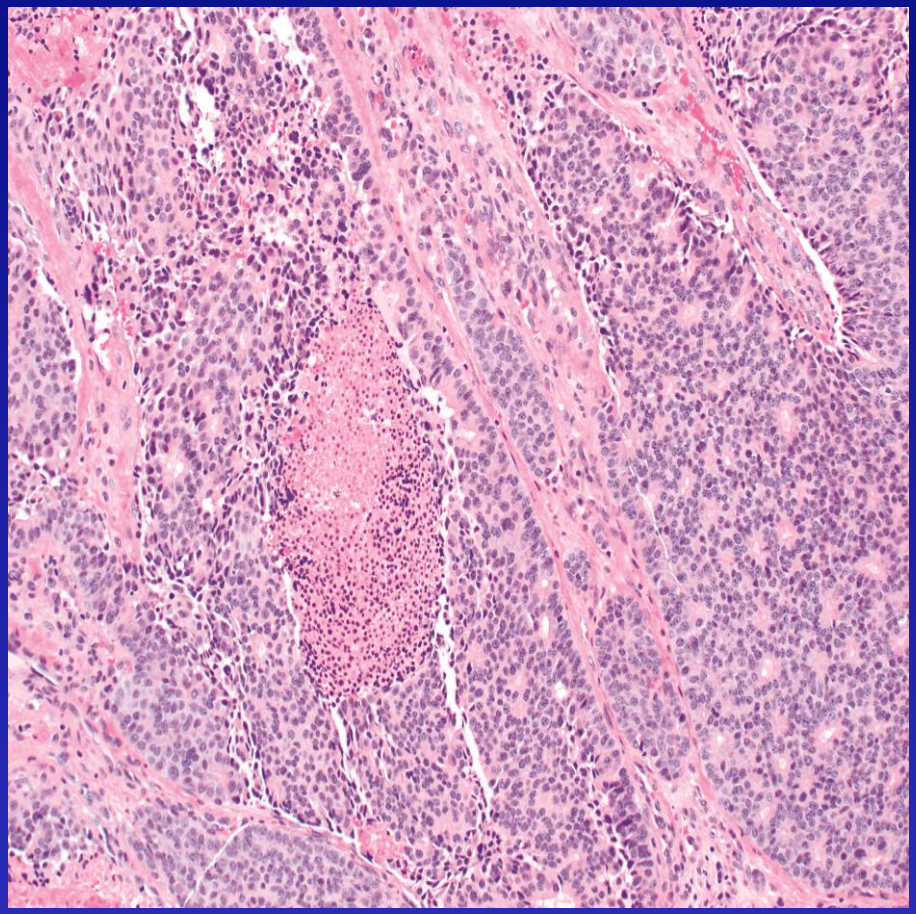
- 45 year old male presented with an enlarging left-sided neck mass at Level III (mid-jugular lymph node)
- The lymph node was excised

Level III Lymph Node

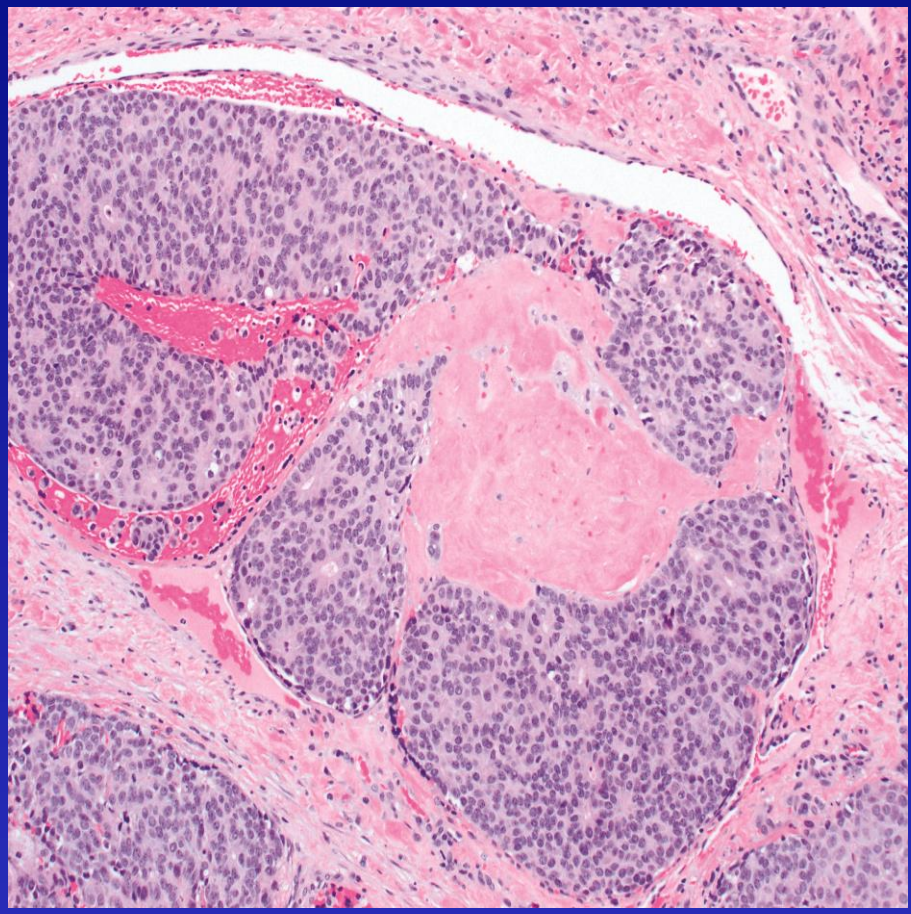




Level III Lymph Node

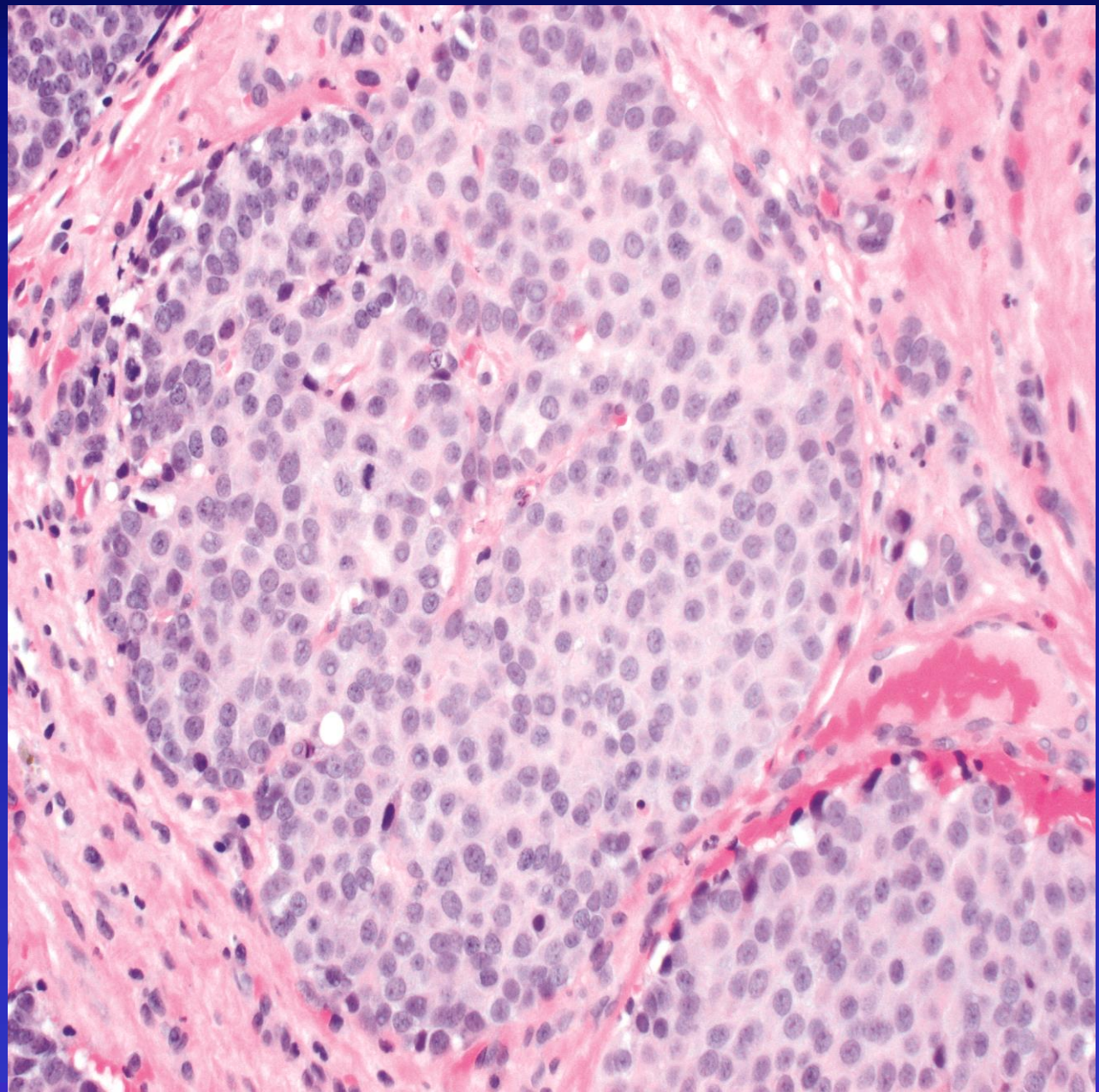


Necrosis

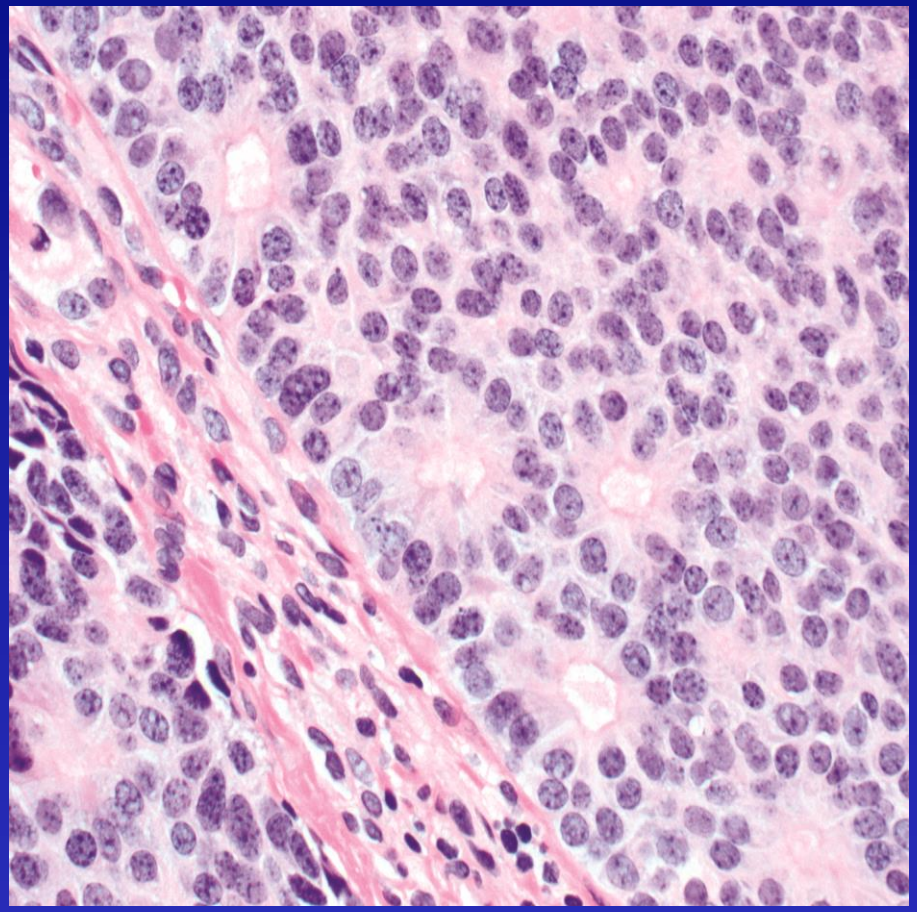


Amyloid-like stroma

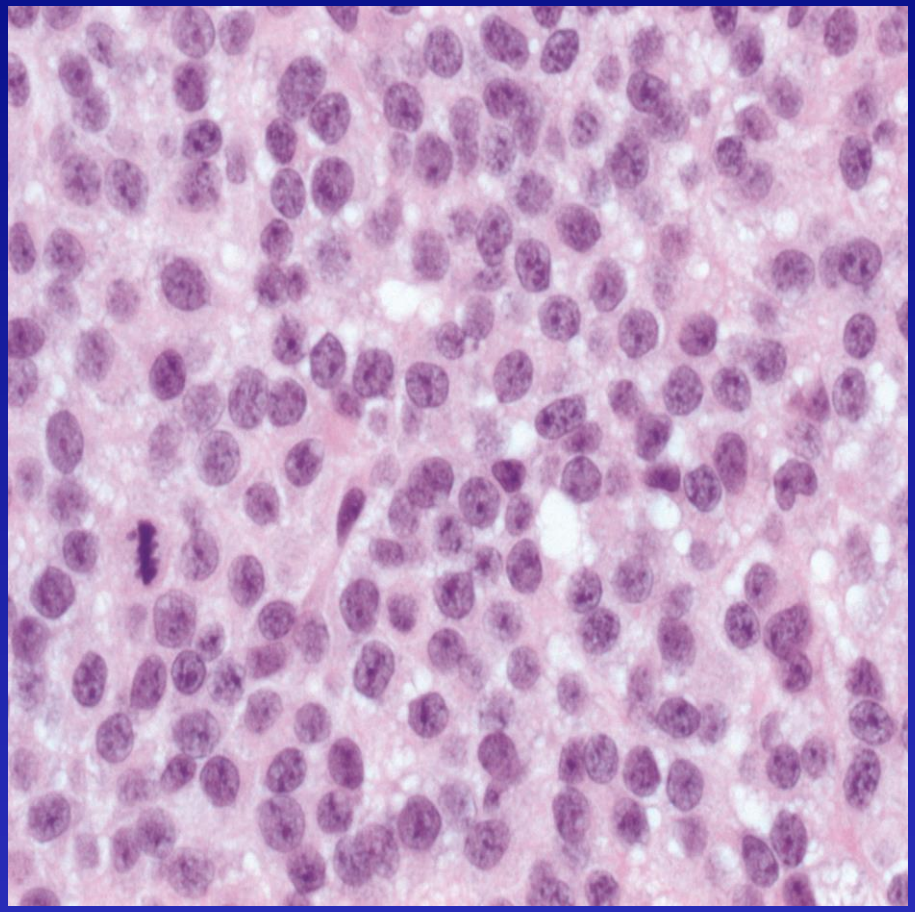
Level III Lymph Node



Level III Lymph Node

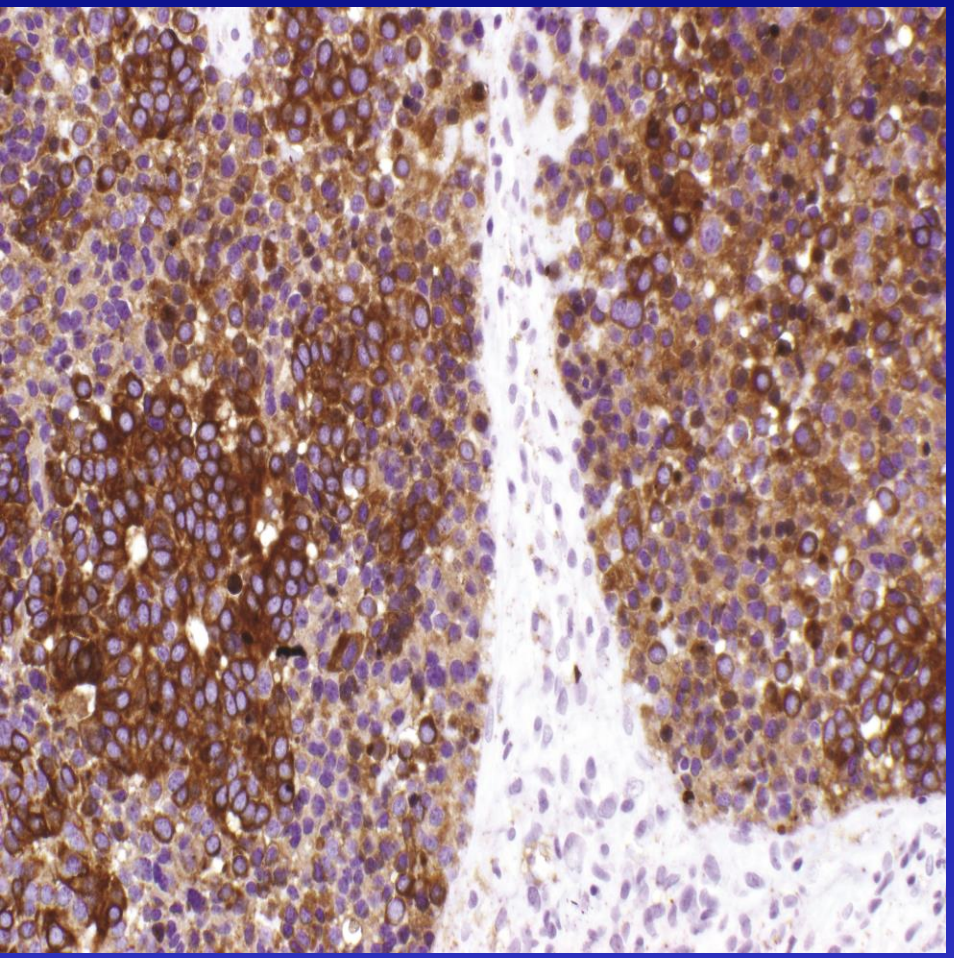


Rosettes

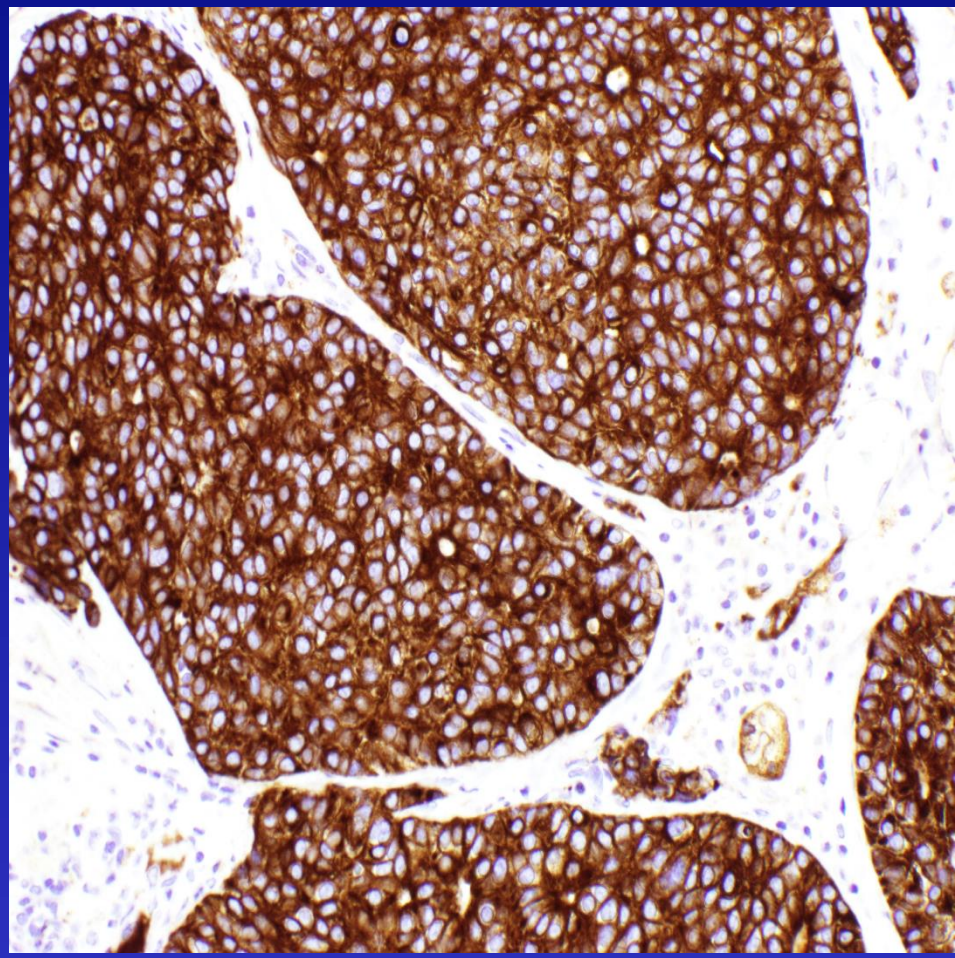


Mitosis; “salt & pepper” nuclear chromatin

Case 1

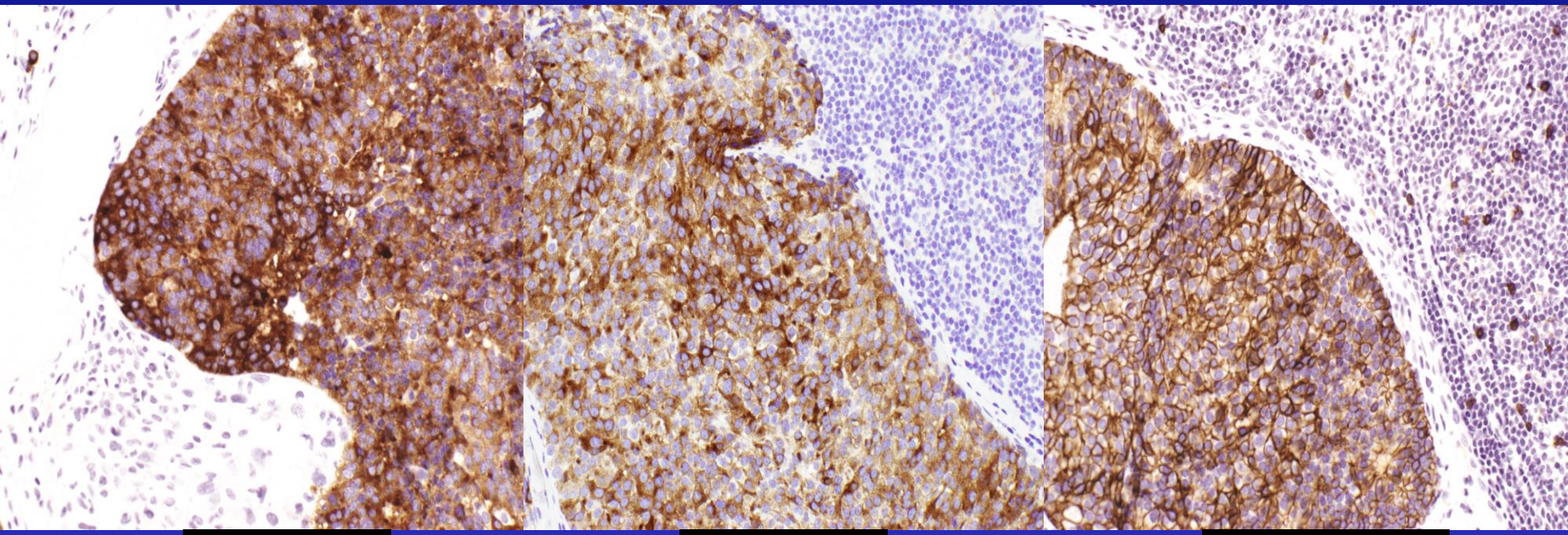


AE1/AE3



CAM5.2

Case 1

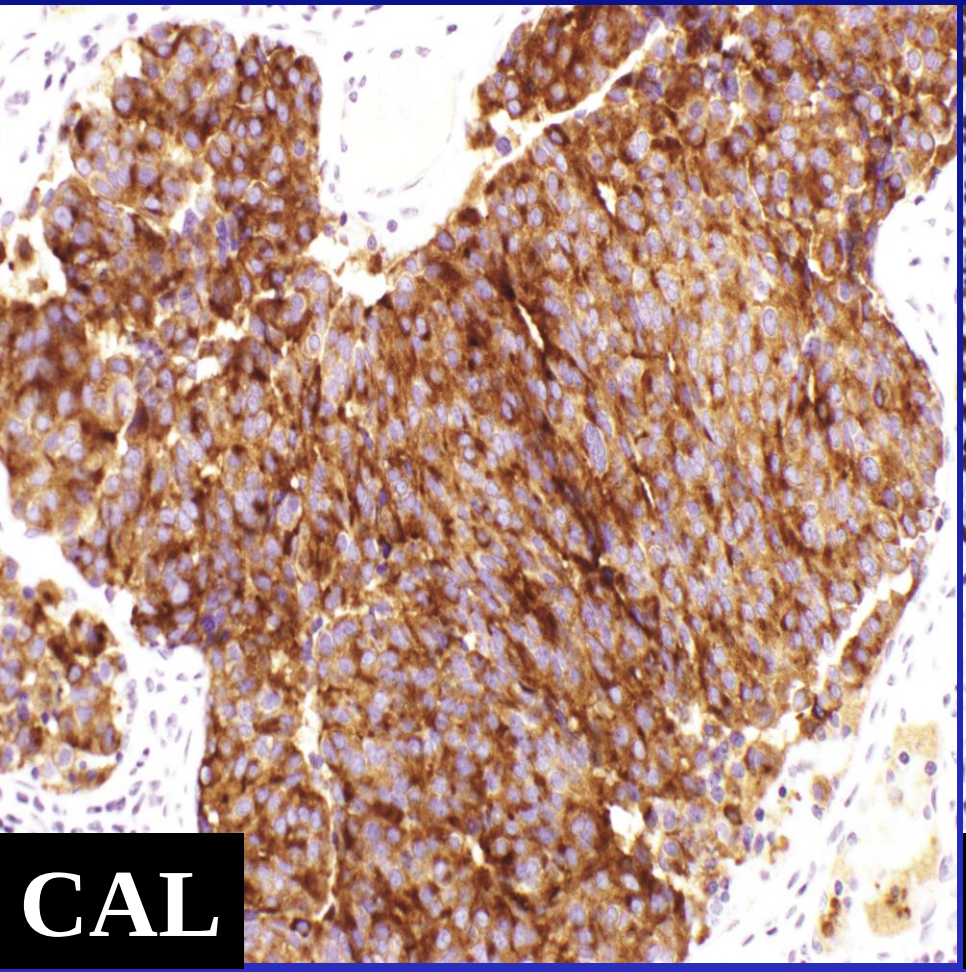


SYN

CHR

CD56

Case 1



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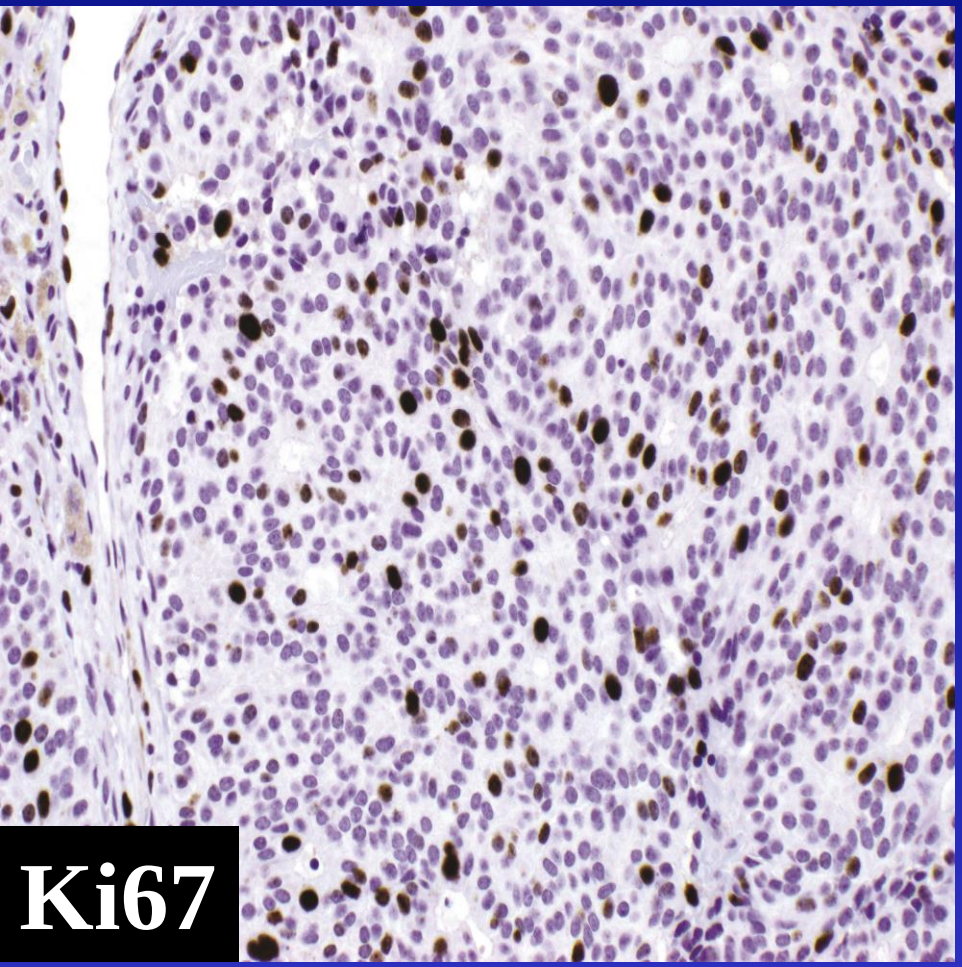
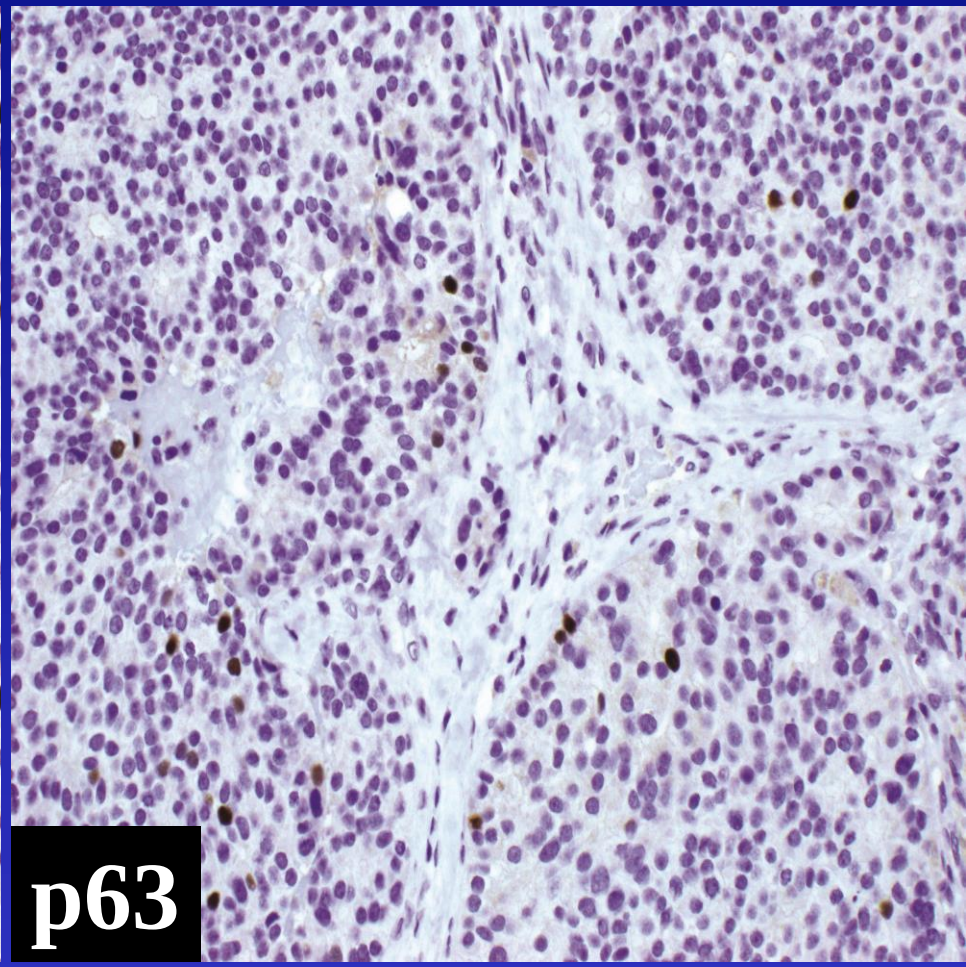


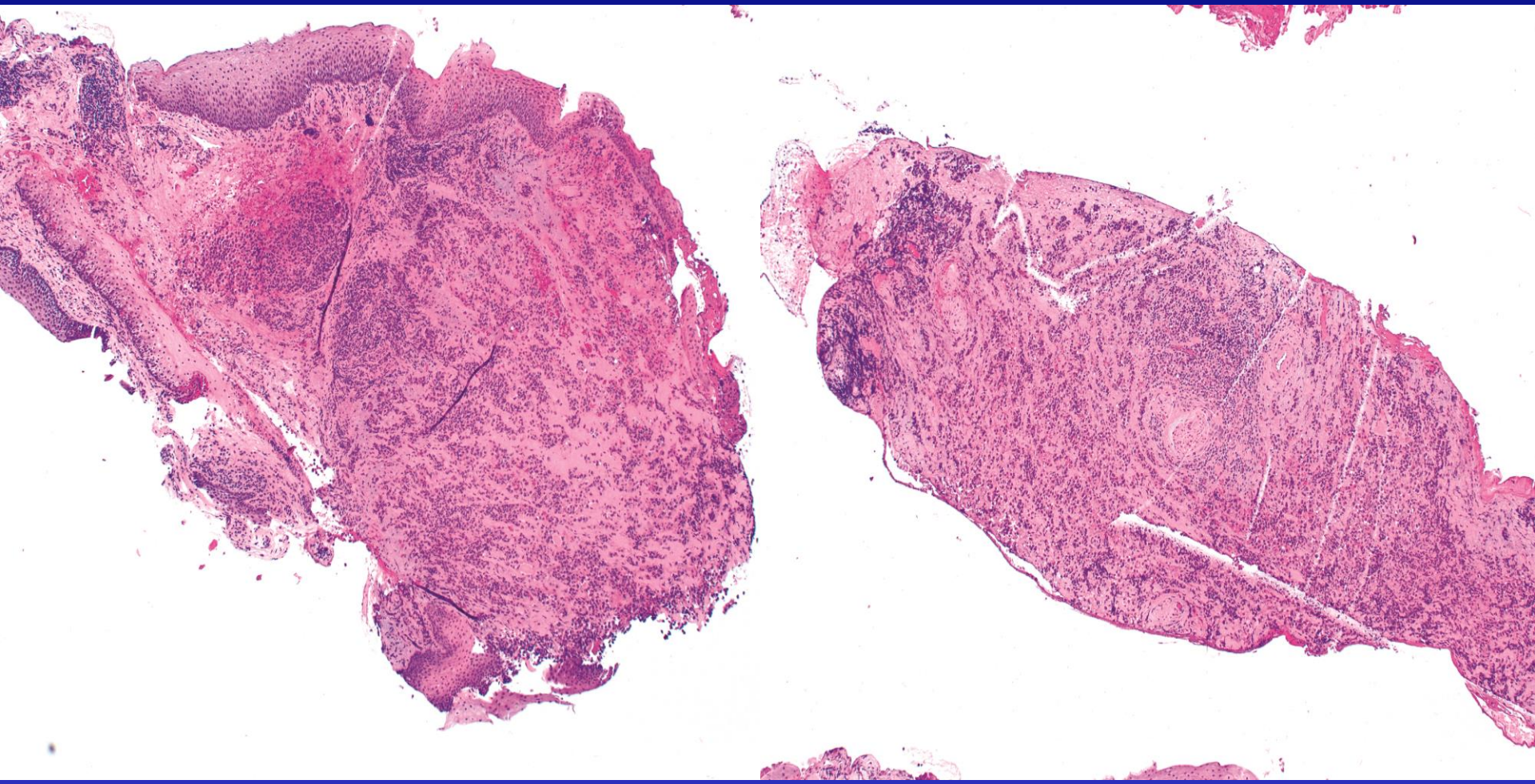


Case 1
Diagnosis?

Case 1
Diagnosis?

- Metastatic Neuroendocrine Malignant Neoplasm
- Presence of calcitonin staining suggests medullary thyroid carcinoma (MTC)
- MTC almost invariably associated with elevated serum calcitonin level
- Serum calcitonin within normal limits
- Where is the primary?
- Thyroid imaging negative for mass
- Endoscopic biopsies of UADT performed

Case 1
Biopsy of Supraglottic Larynx



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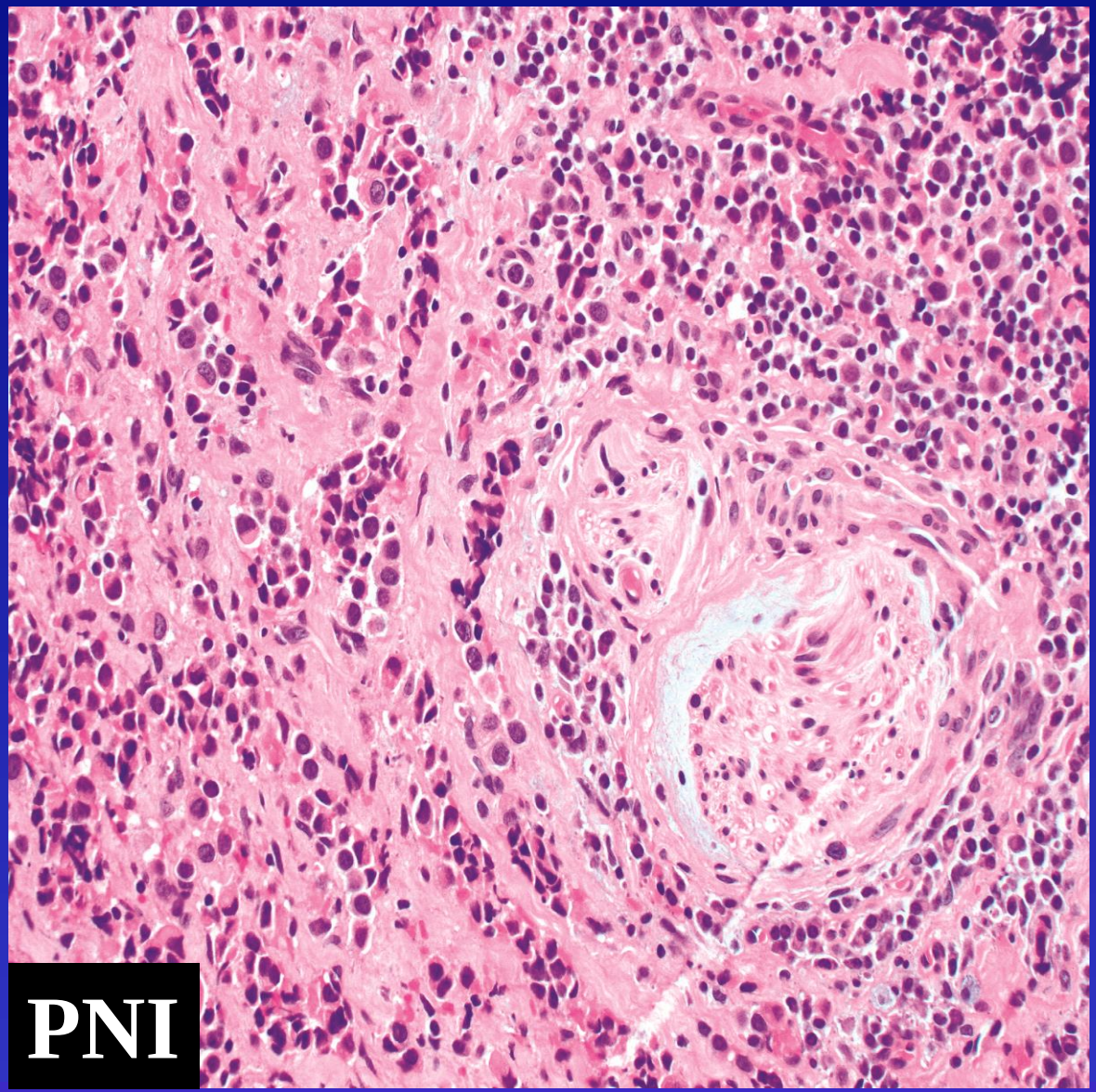

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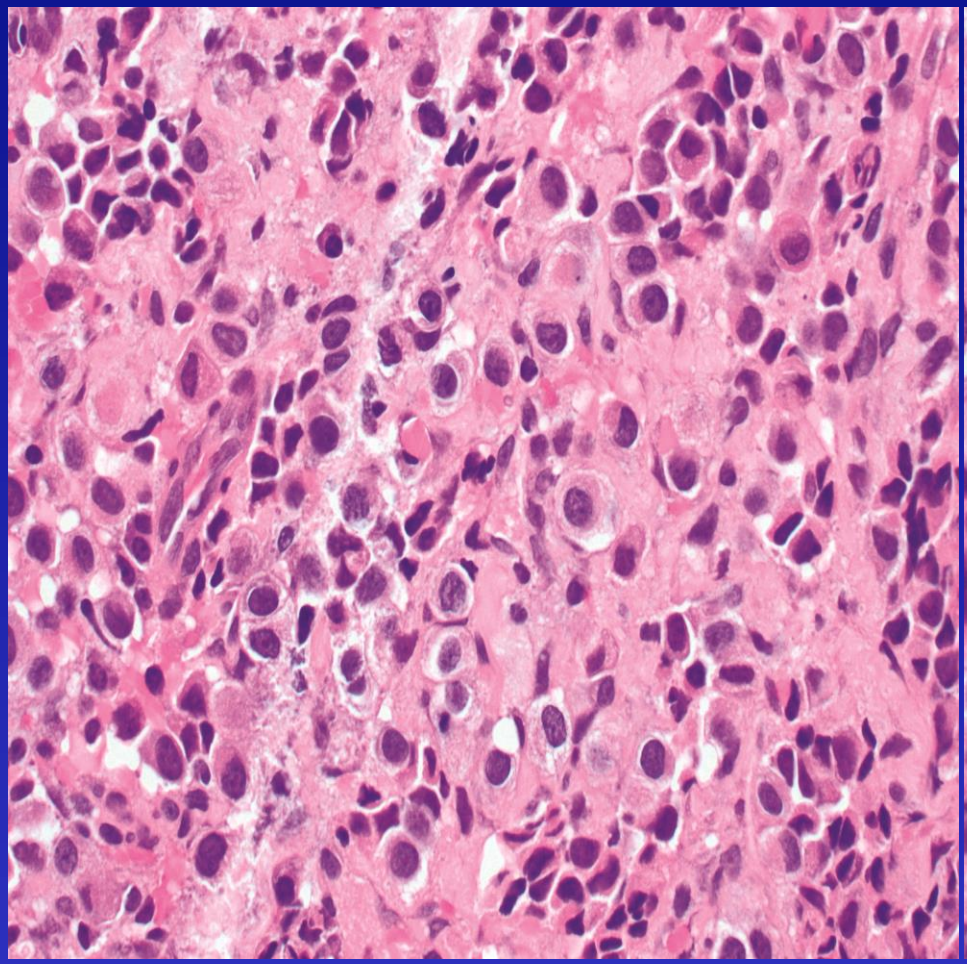
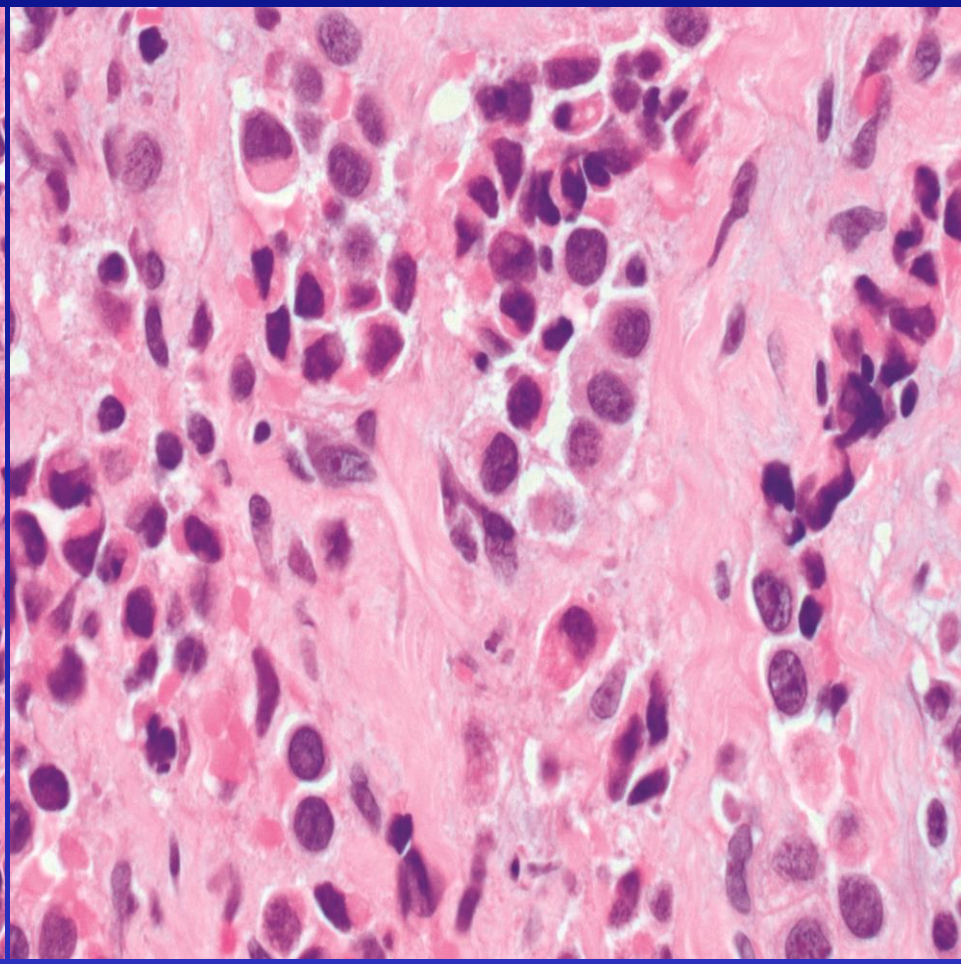
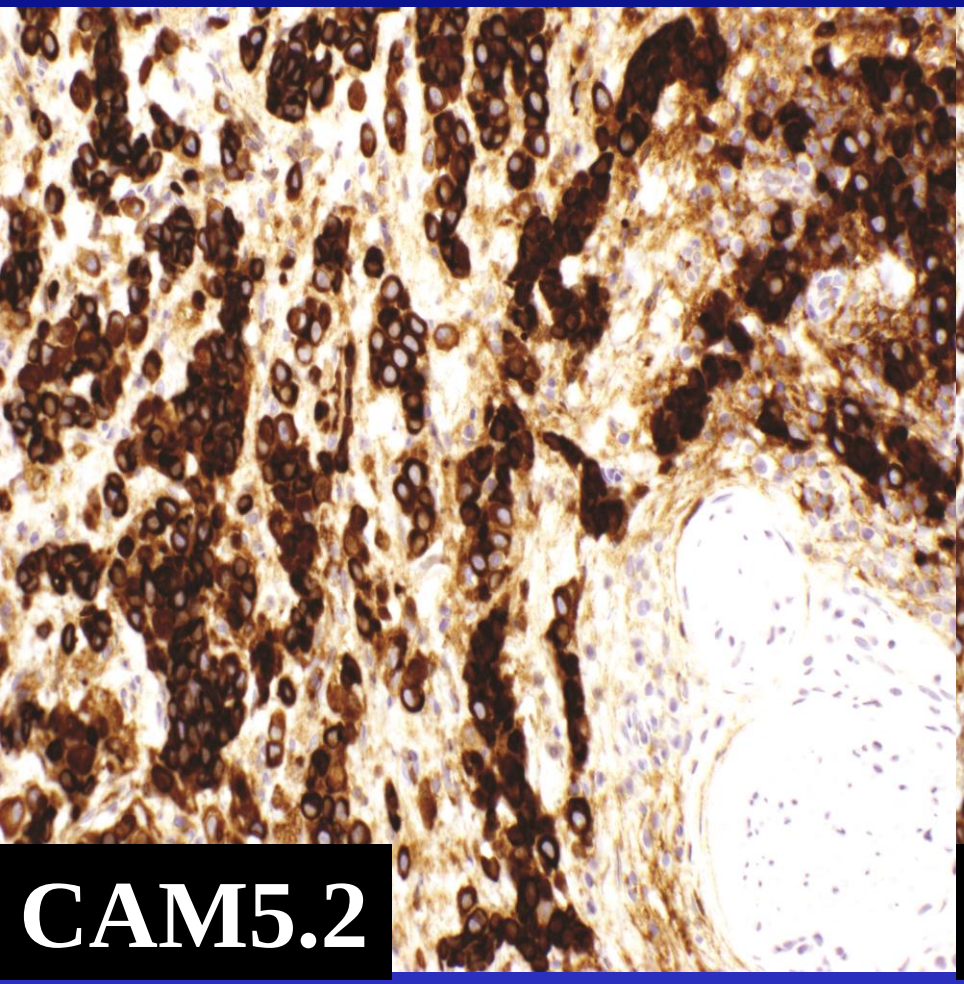
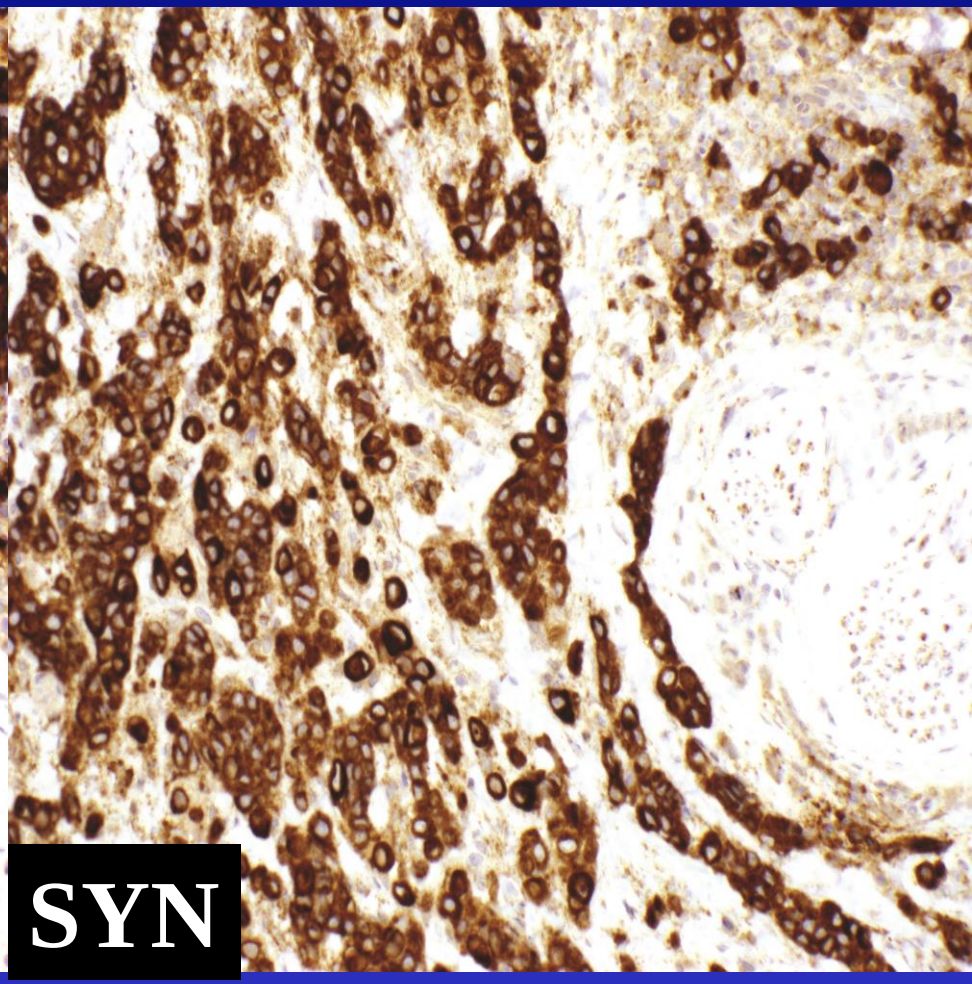




Case 1
Supraglottic Larynx - IHC





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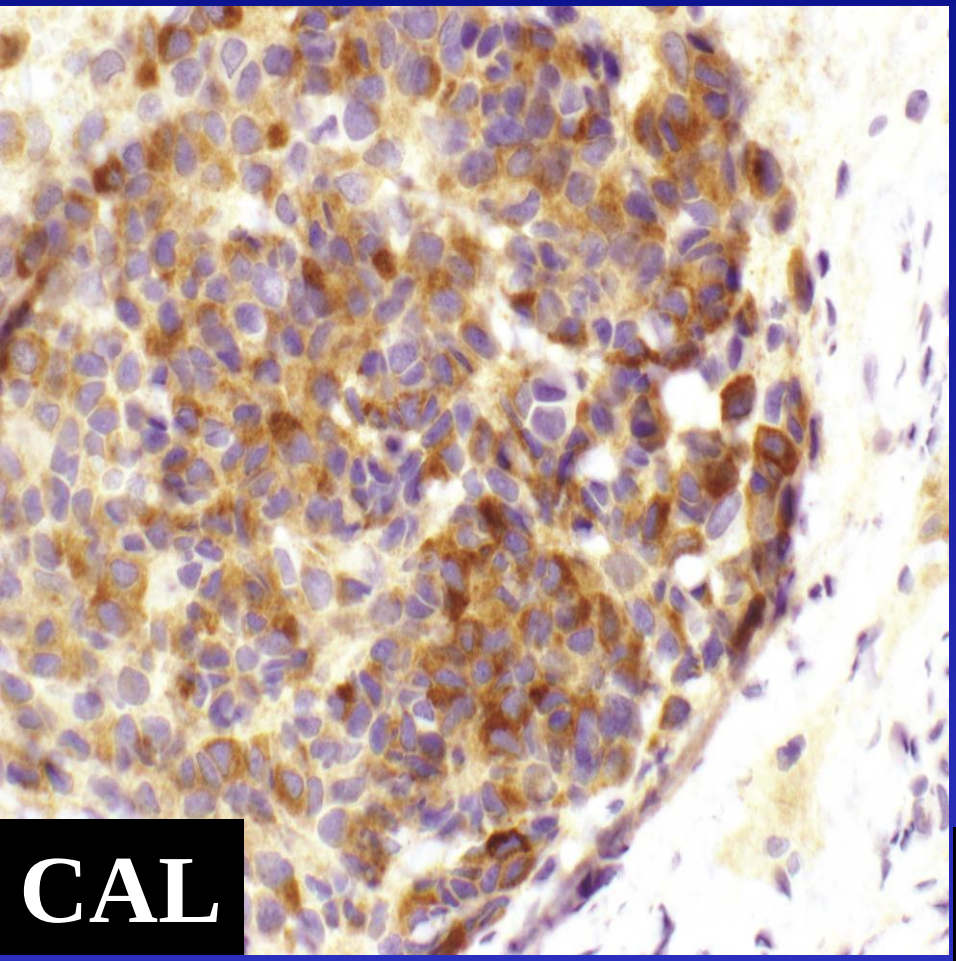

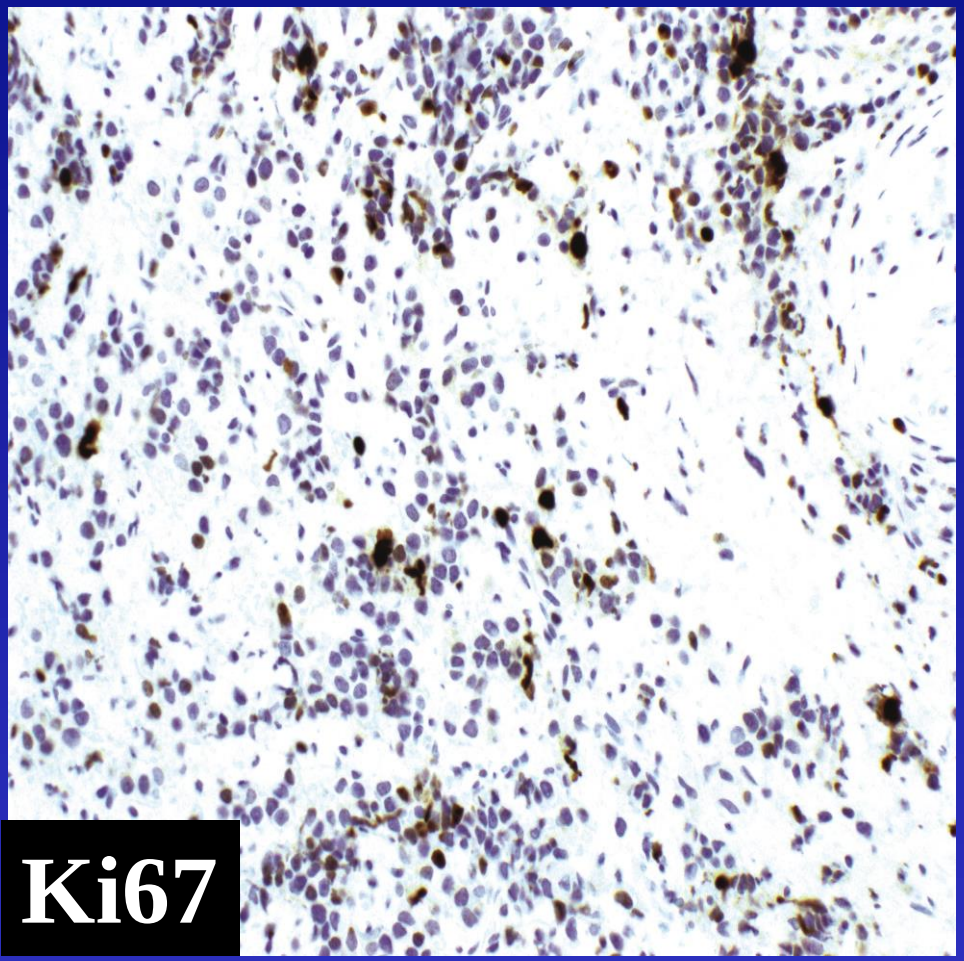

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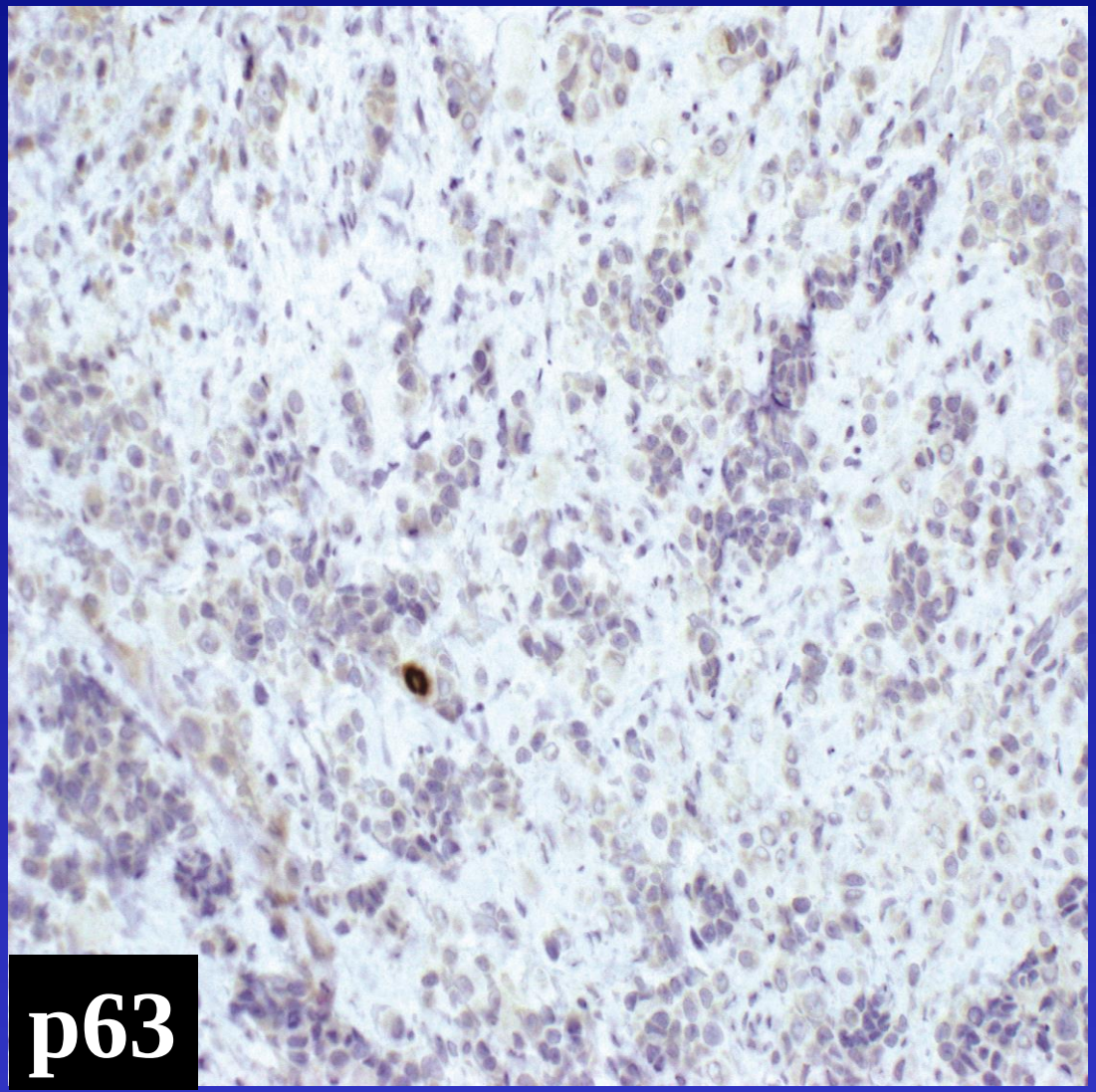


Case 1
Diagnosis

- **Metastatic moderately-differentiated neuroendocrine carcinoma (atypical carcinoid) of laryngeal (supraglottic) origin**

Neuroendocrine Carcinoma (NEC) Definition

- Heterogeneous group of malignant neoplasms with divergent differentiation along epithelial and neuroendocrine cell lines

NEC of the Head and Neck
2017 WHO Classification

- **Well-differentiated NEC (WDNEC) = Carcinoid Tumor**
- **Moderately-differentiated NEC (MDNEC) = Atypical Carcinoid**
- **Poorly-differentiated NEC = Small Cell Carcinoma (SmCC)**
- **Poorly-differentiated NEC = Large Cell Carcinoma (LCNEC)**

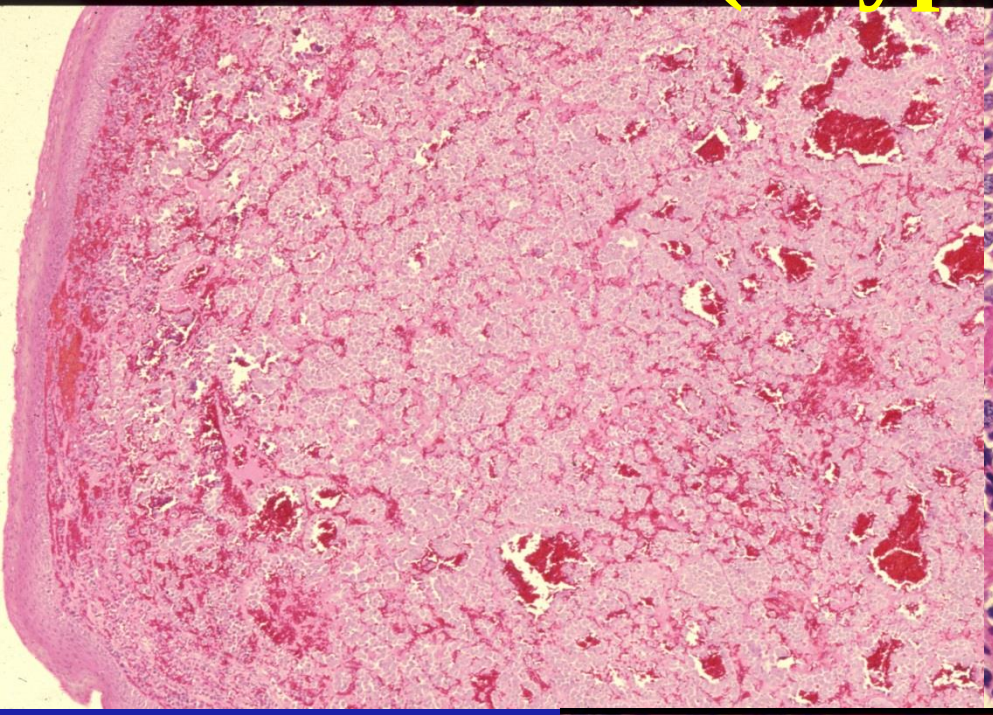
Head and Neck NECs

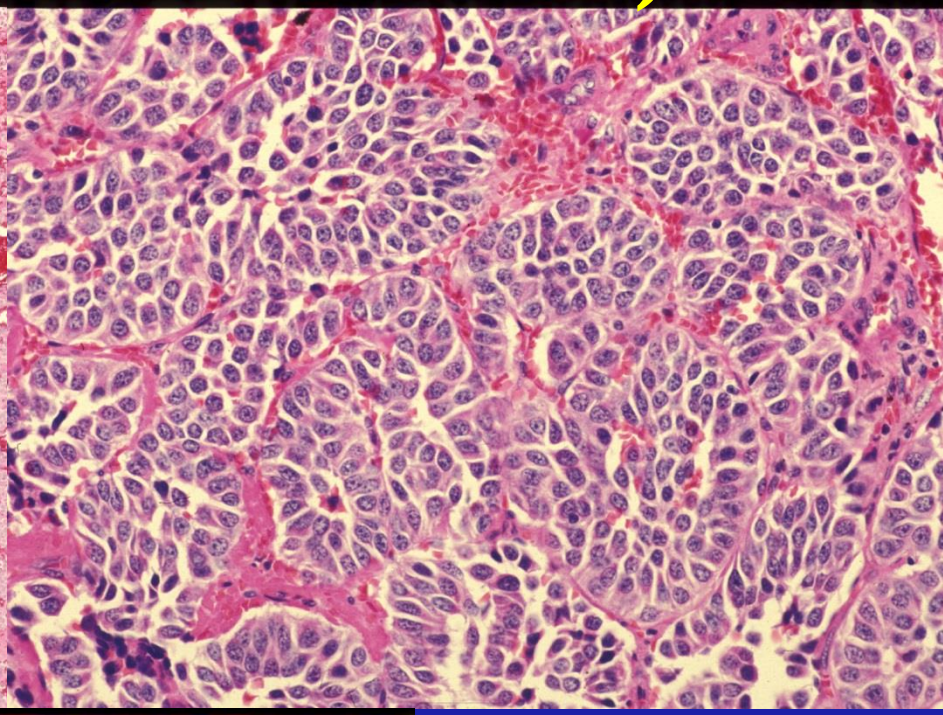
- Larynx most common site; less common sites include SNT, salivary gland, others
- M > F; generally occurs in the 6th-7th decades of life
- Larynx:
  - Supraglottic larynx overwhelmingly the most common site of occurrence
  - History of cigarette smoking > 60%
  - MDNEC >>> SmCC >> LCNEC >>> WDNEC
- SNT and Salivary Gland (Parotid):
  - SmCC >>> LCNEC >> MDNEC > WDNEC

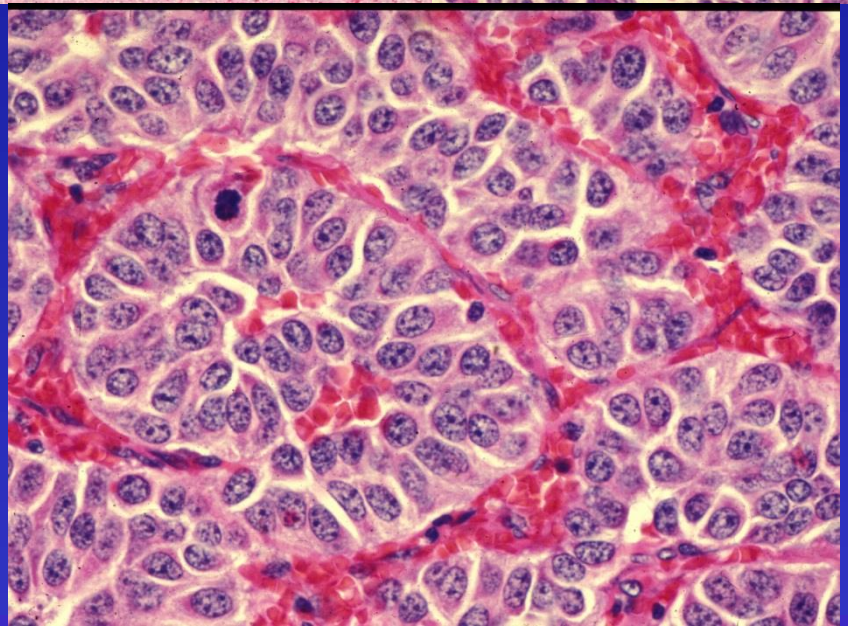
MDNEC (Atypical Carcinoid) Clinical Features

- M >> F; wide age range from the 4th - 9th decades
- Symptoms: hoarseness and dysphagia; rarely associated with paraneoplastic syndrome
- Site: Supraglottic larynx
- Stronger link with tobacco use
- May metastasize as an occult primary

MDNEC (Atypical Carcinoid)







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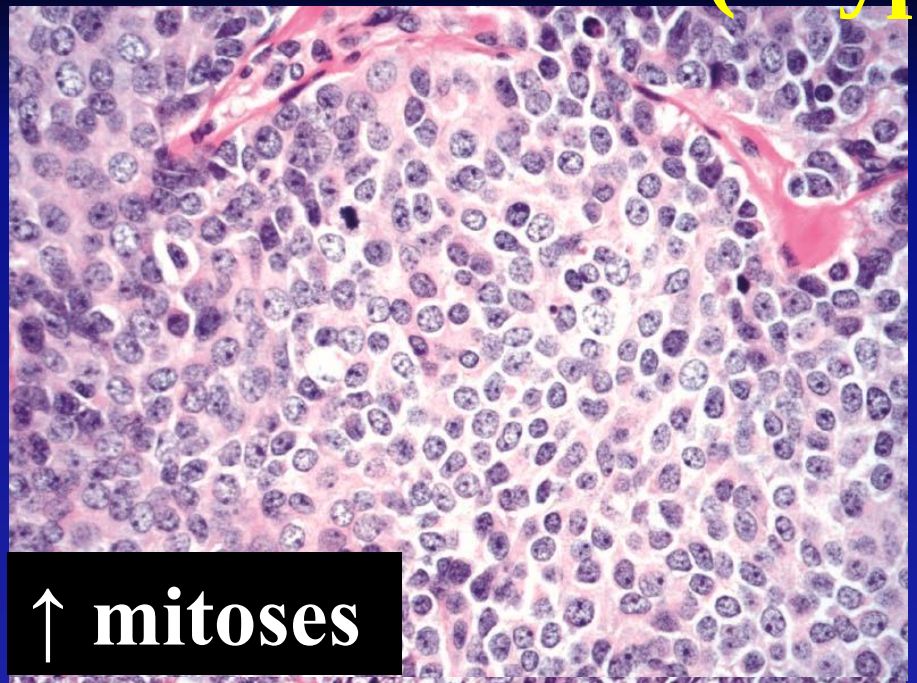

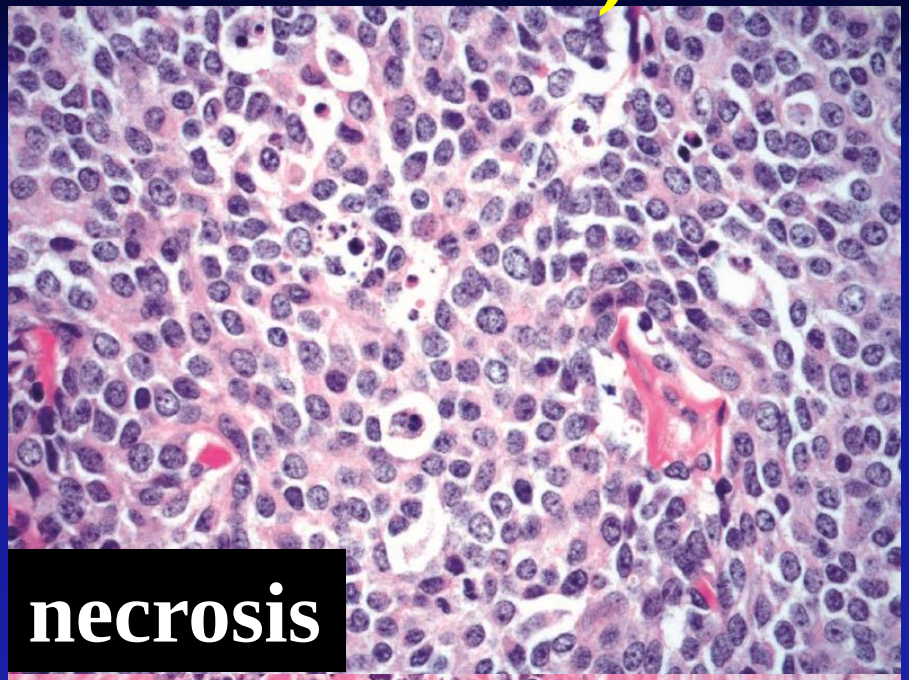

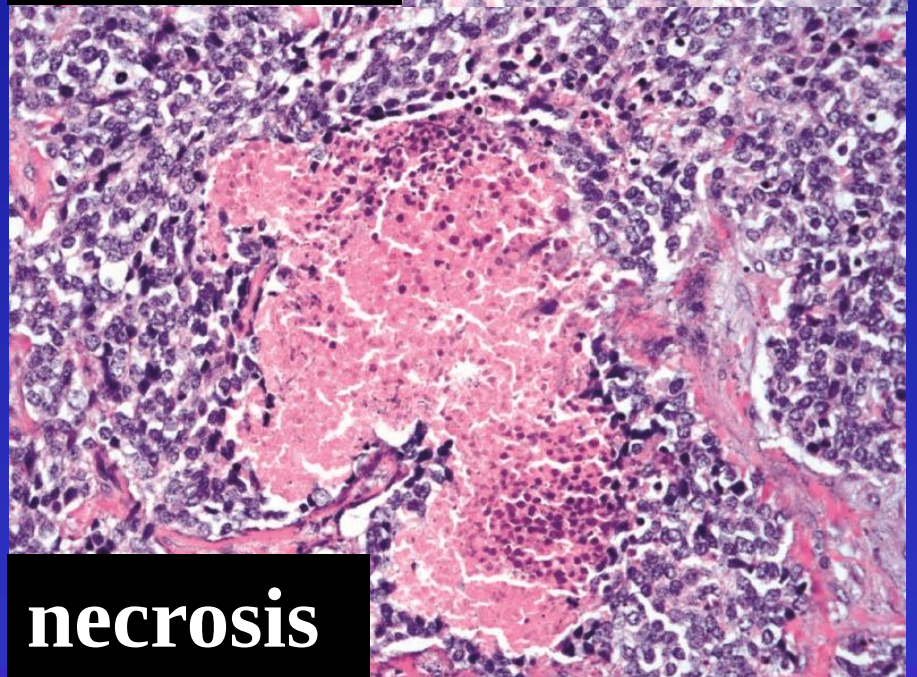

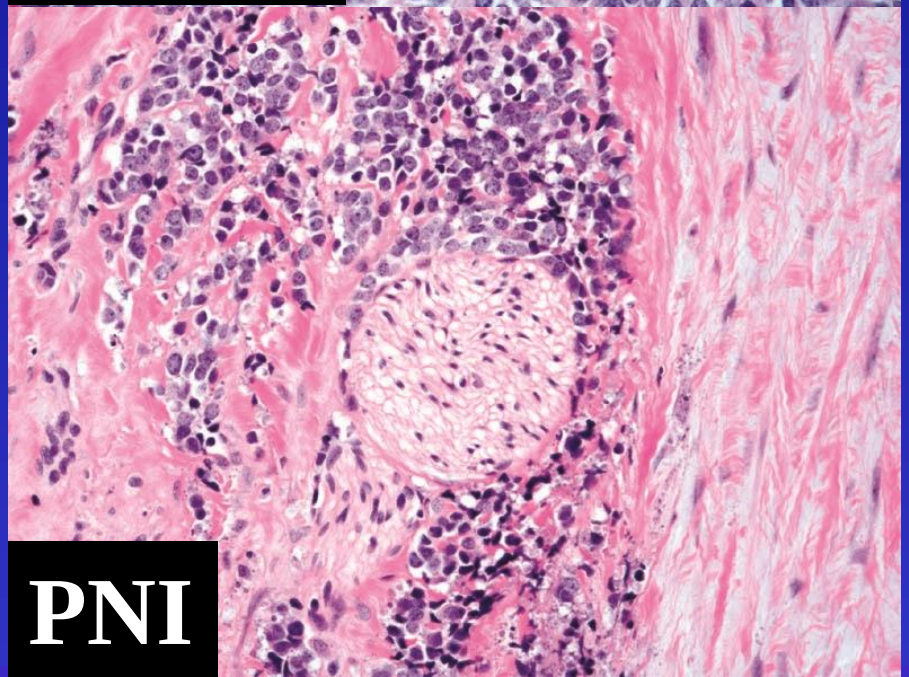

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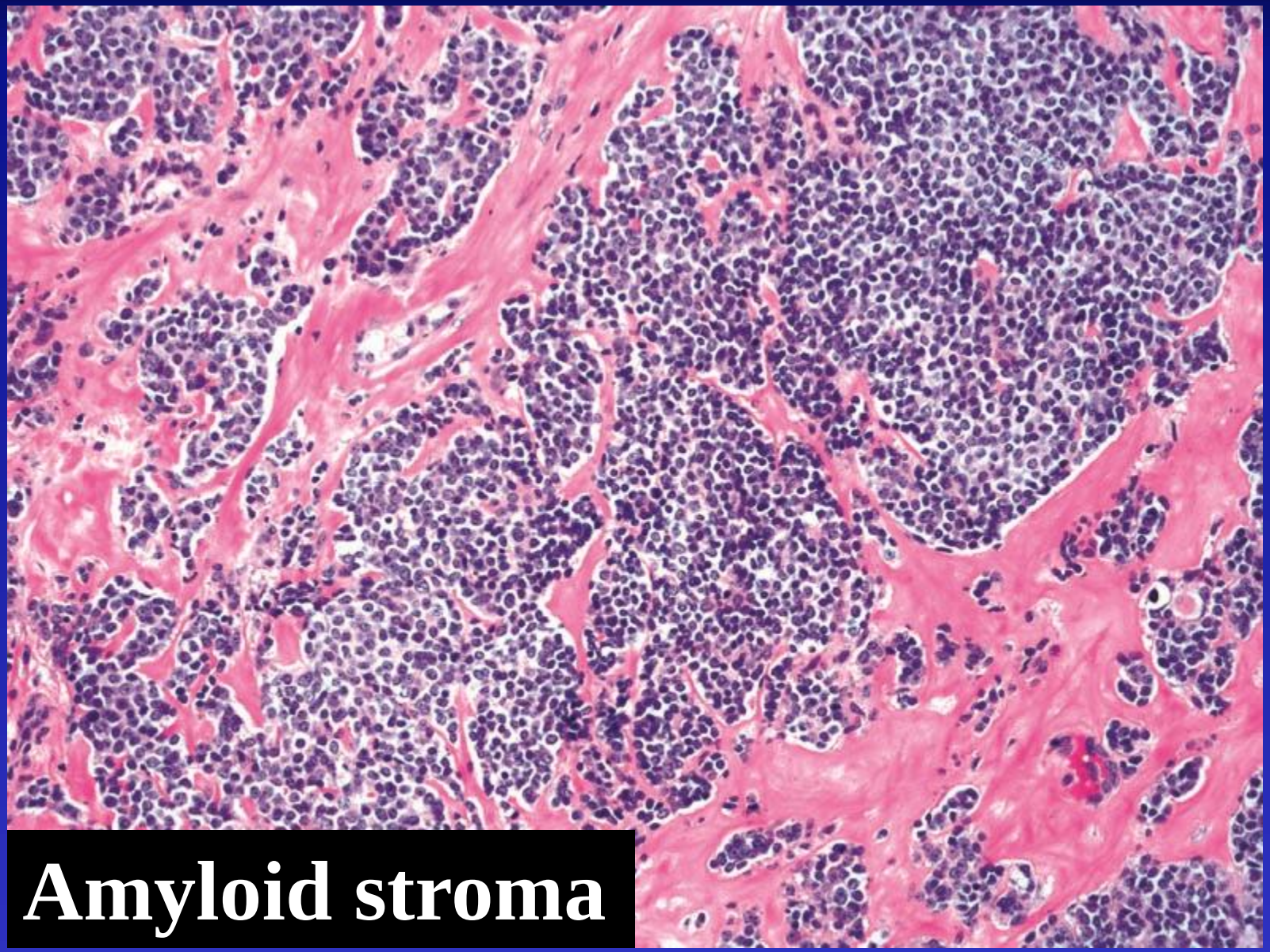

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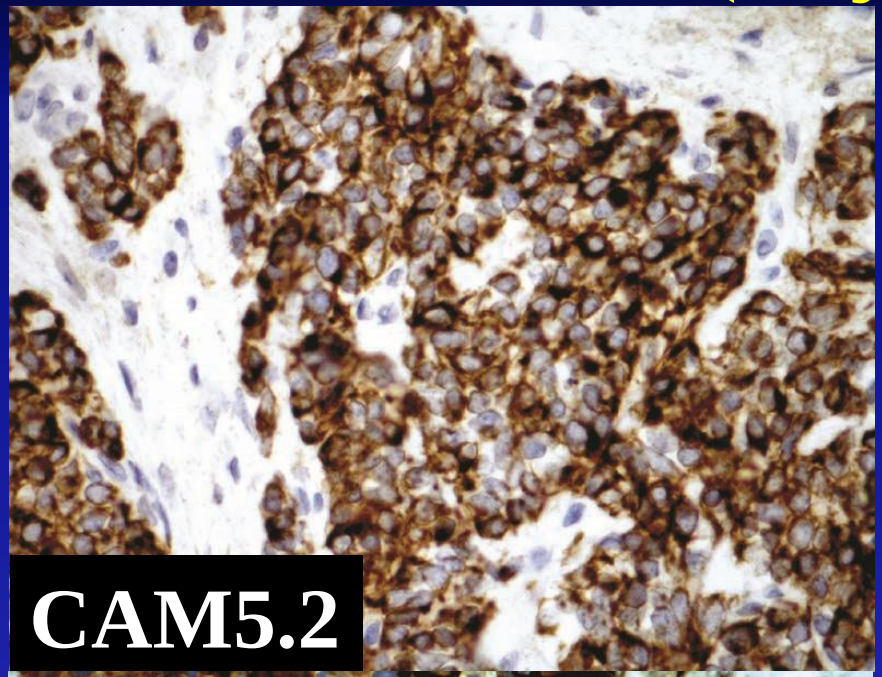
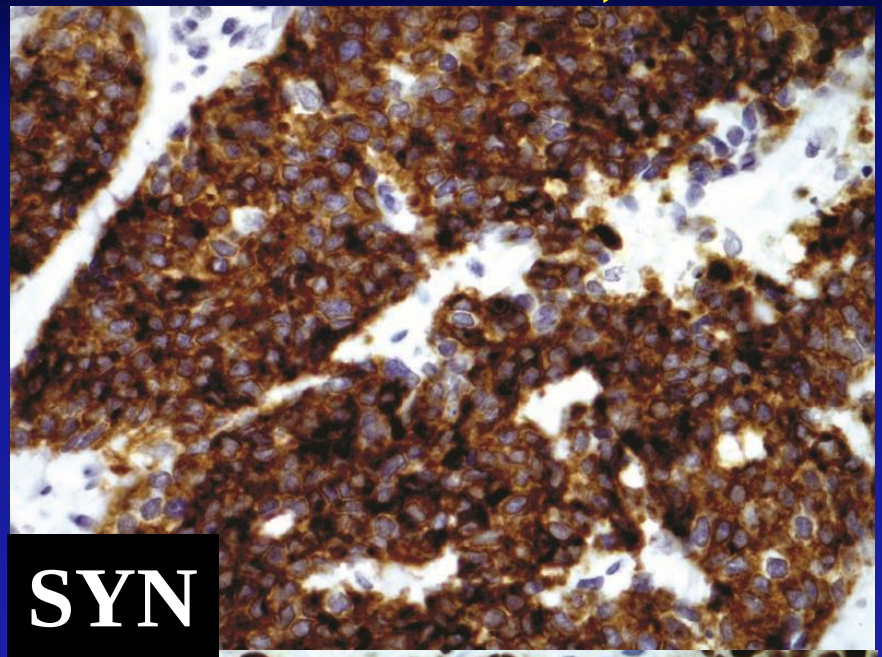
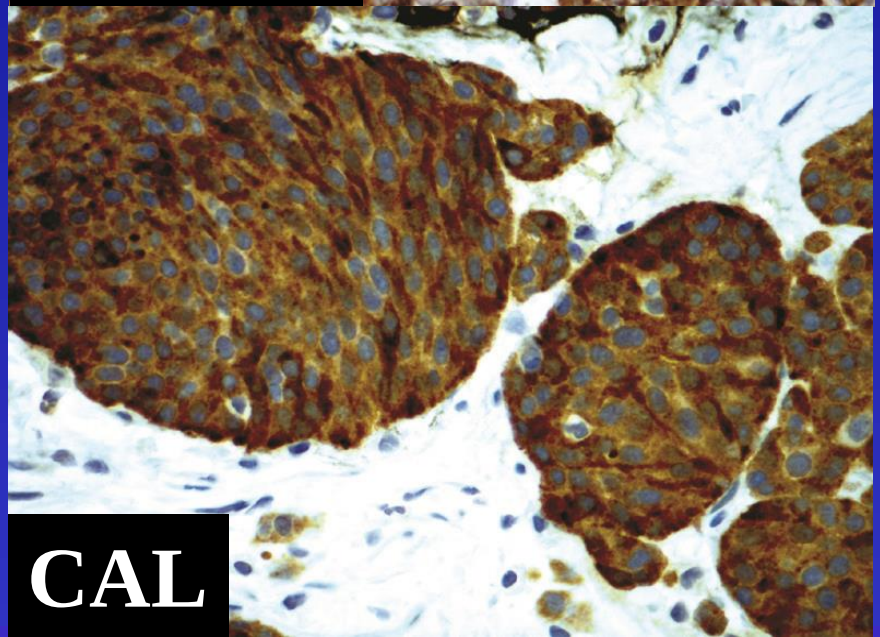
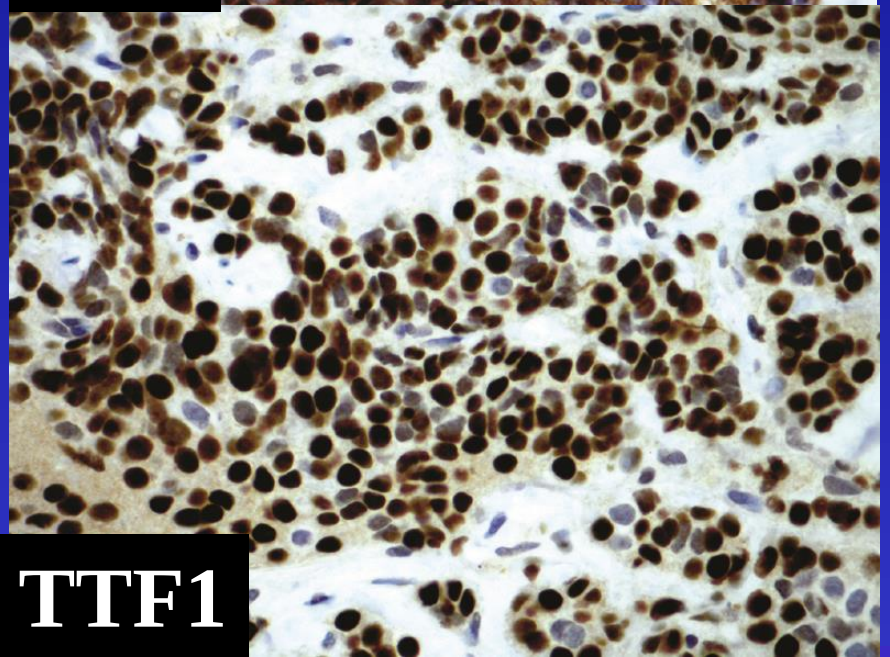








MDNEC (Atypical Carcinoid) Treatment and Prognosis

- Complete surgical excision
  - depending on site surgery may include partial or total laryngectomy
- High incidence of cervical lymph node metastasis warrants neck dissection even in clinically N0 necks:
  - nodal metastasis may be present at time of presentation or subsequently develop nodal metastasis
  - patients not undergoing surgical treatment of the neck reported to develop isolated regional recurrence in 30% of cases

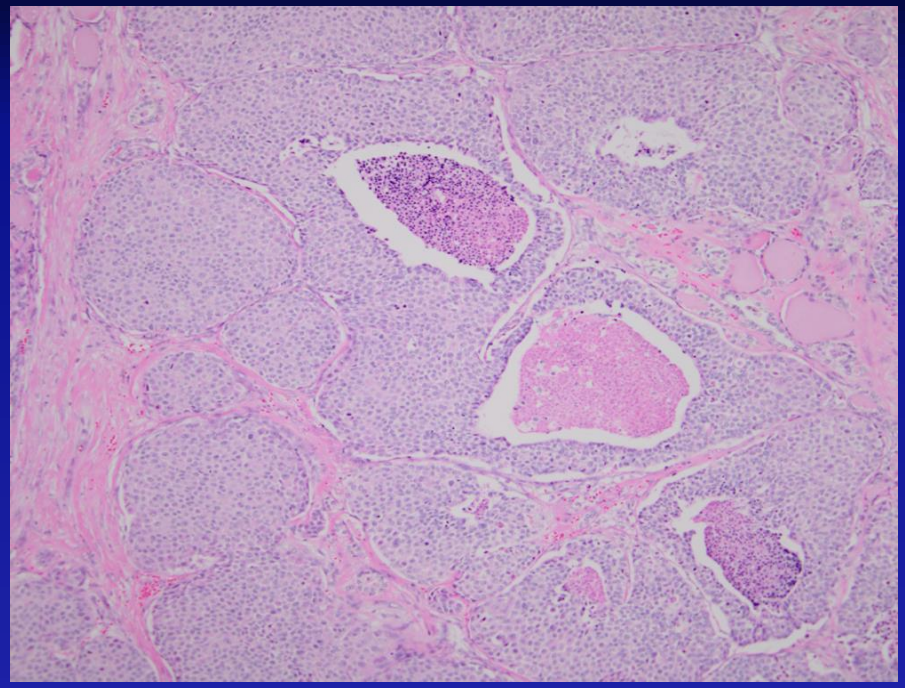
MDNEC (Atypical Carcinoid) Treatment and Prognosis

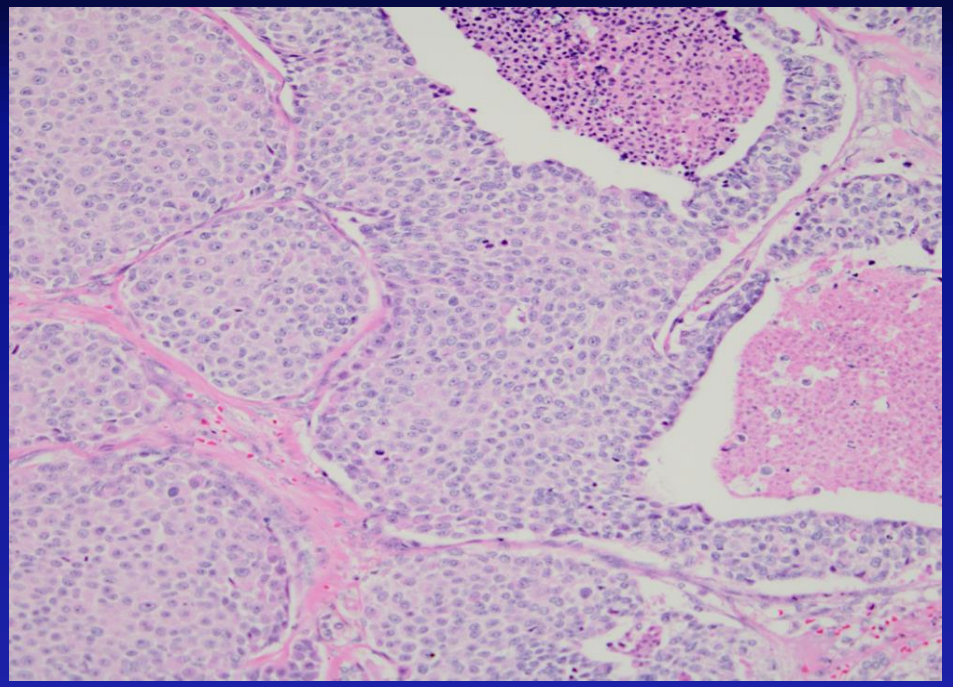
- Radiotherapy and chemotherapy not beneficial
- Overall survival rates include:
  - 5-year survival rate of 48%
  - 10-year survival rate of 30%
- Fully malignant tumor that often metastasis to:
  - cervical lymph nodes (43%)
  - lungs, bone, liver (44%)
  - skin and subcutaneous tissue (22%)
- Prognosis dependent on extent of disease at presentation
- Death results from metastatic disease

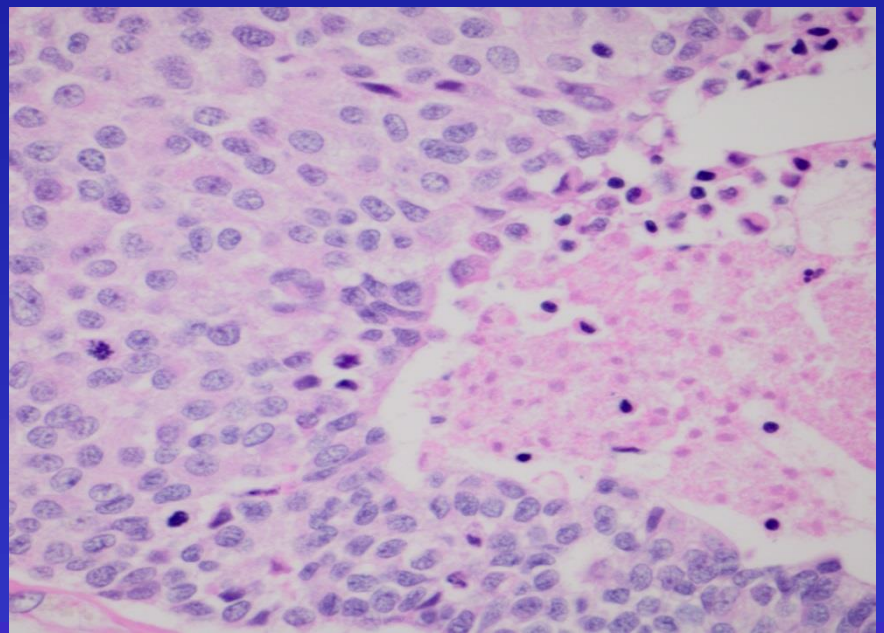
MDNEC (Atypical Carcinoid) Differential Diagnosis

- **Medullary Thyroid Carcinoma (MTC)**
- **Well-differentiated Neuroendocrine Carcinoma**
  - **Typical carcinoid**
- **Poorly-differentiated Neuroendocrine Carcinoma:**
  - **Small Cell Carcinoma**
  - **Large Cell NEC**

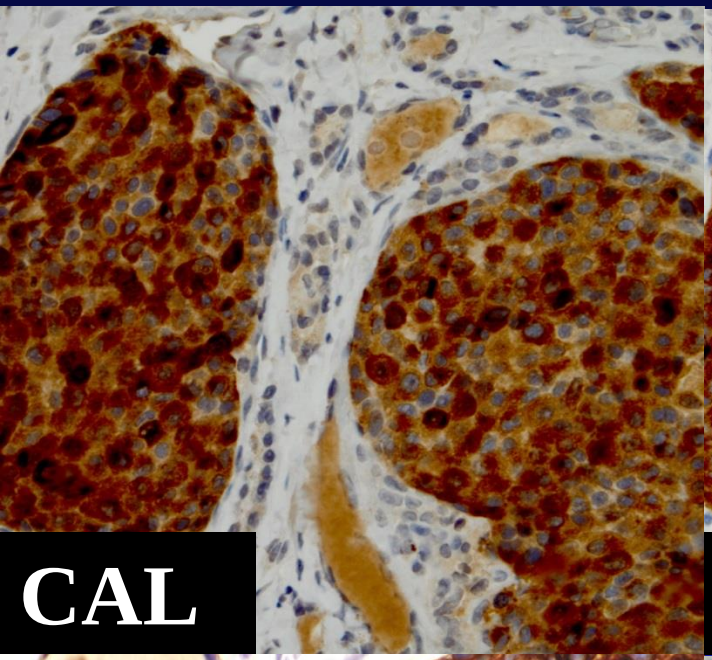
Medullary Thyroid Carcinoma (MTC)

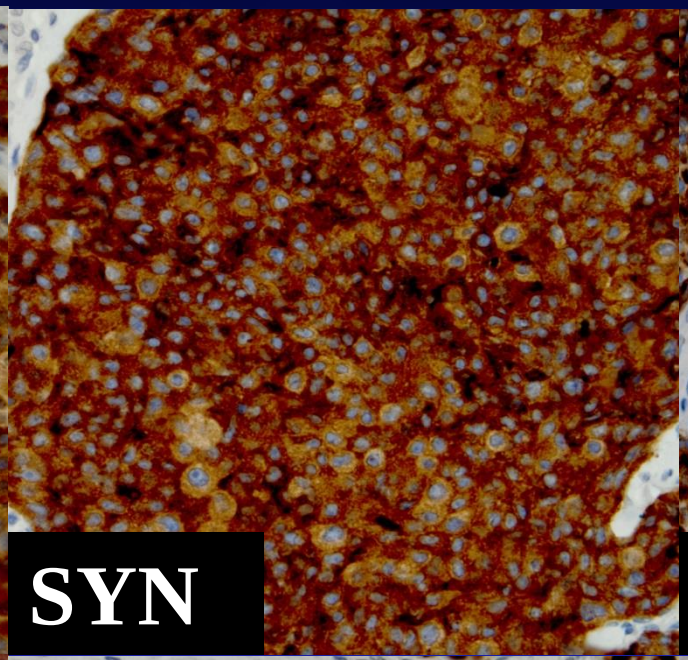


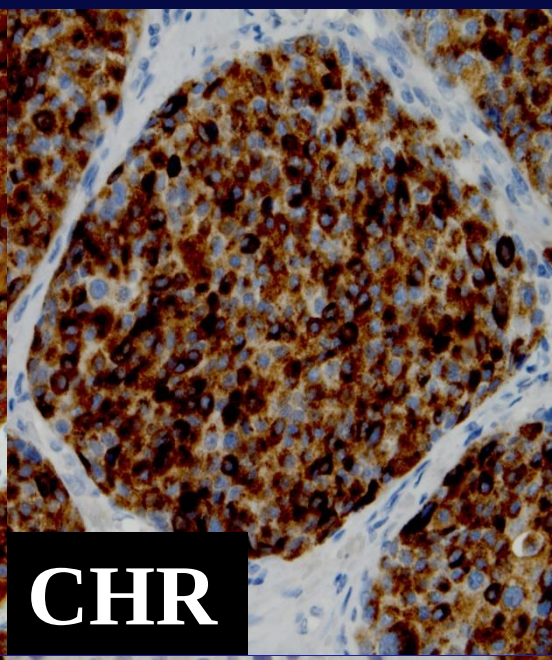


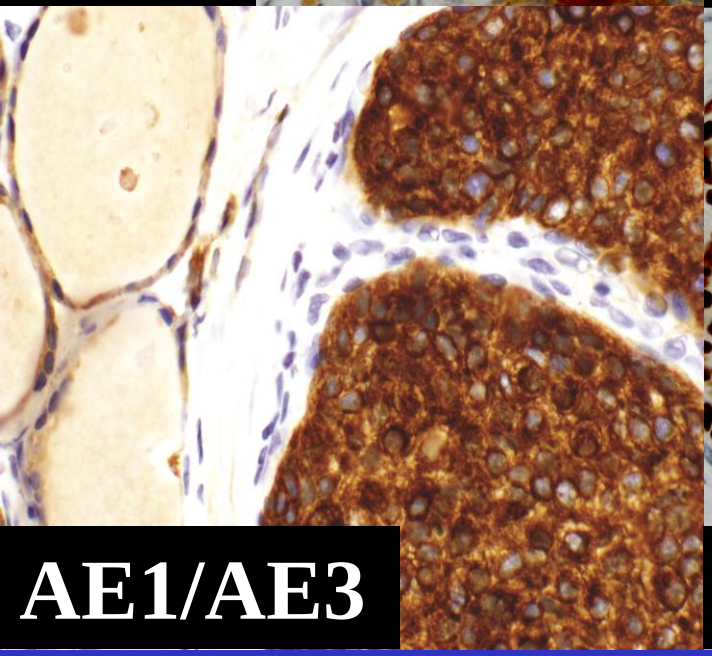


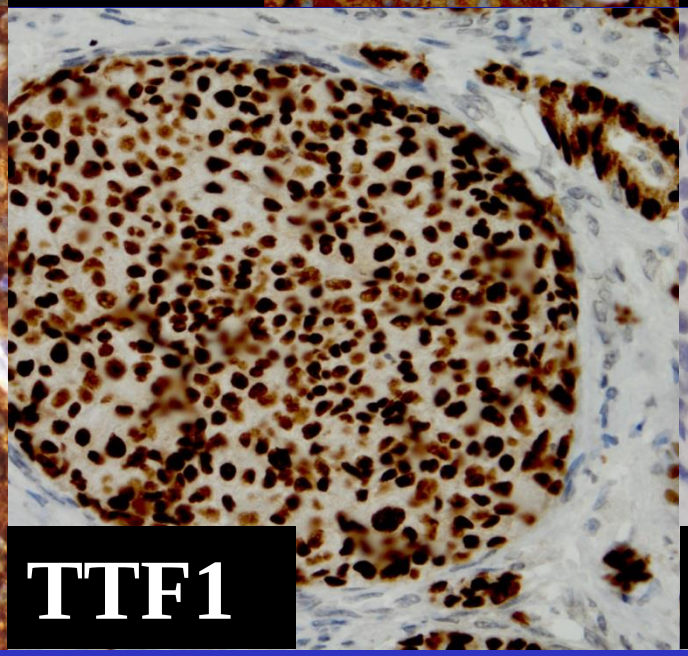
MTC - IHC

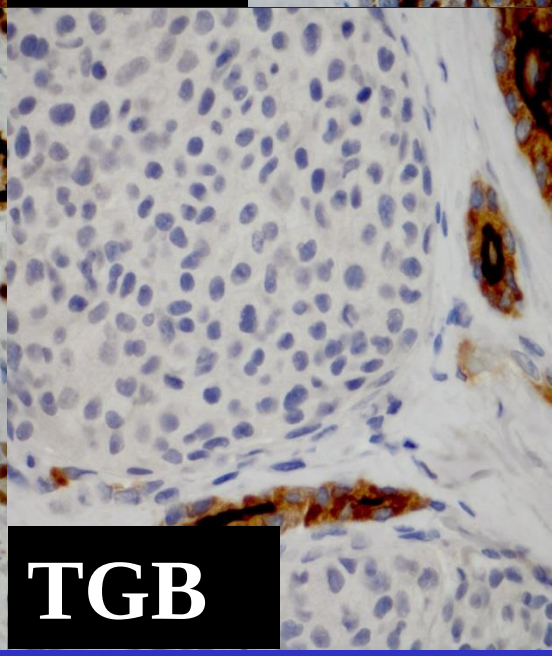












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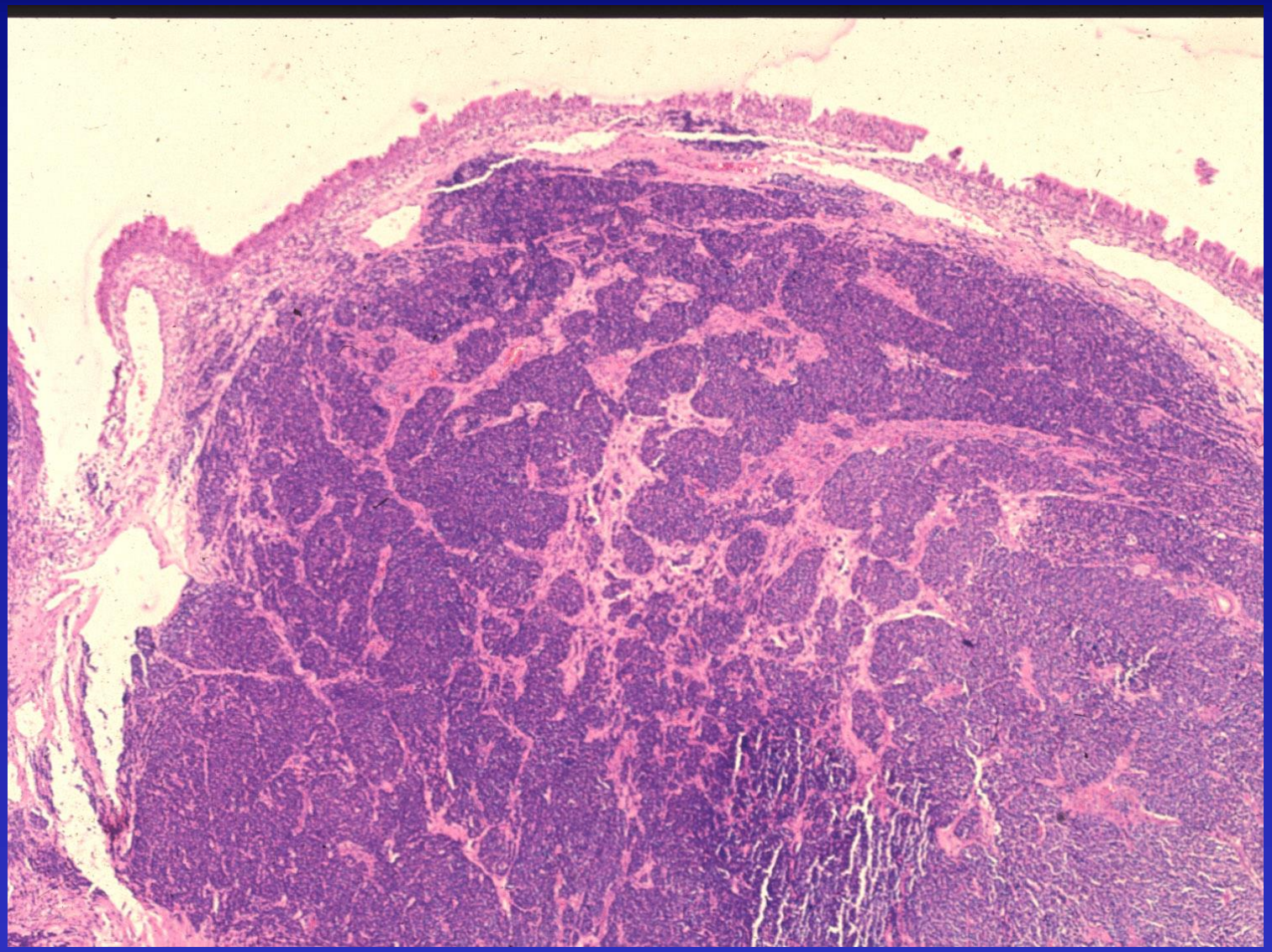
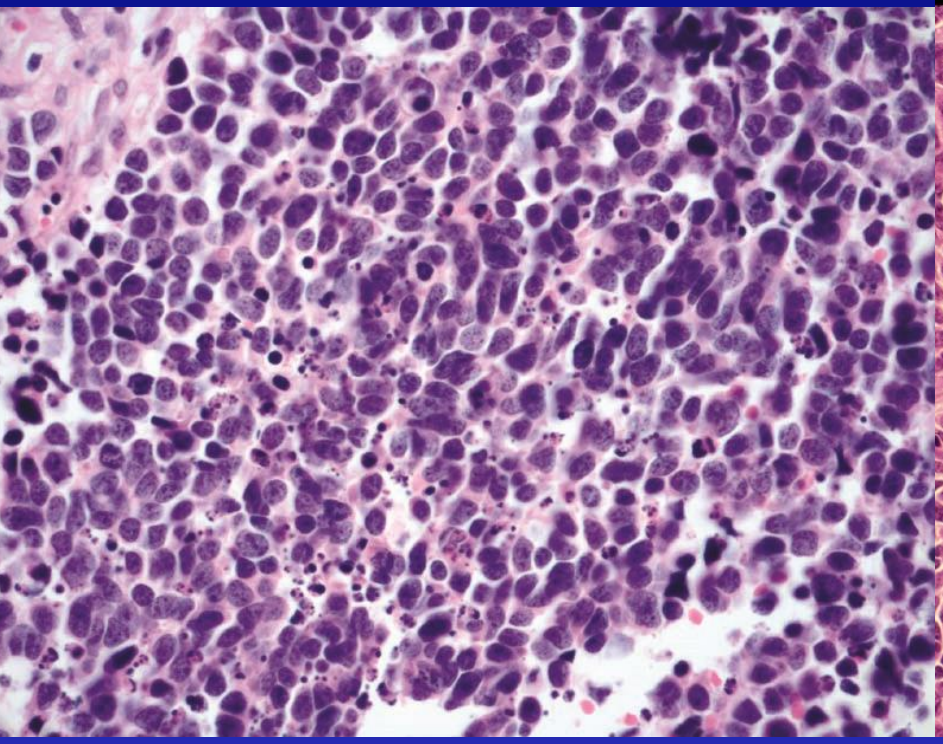
PDNEC - SmCC
Clinical Features

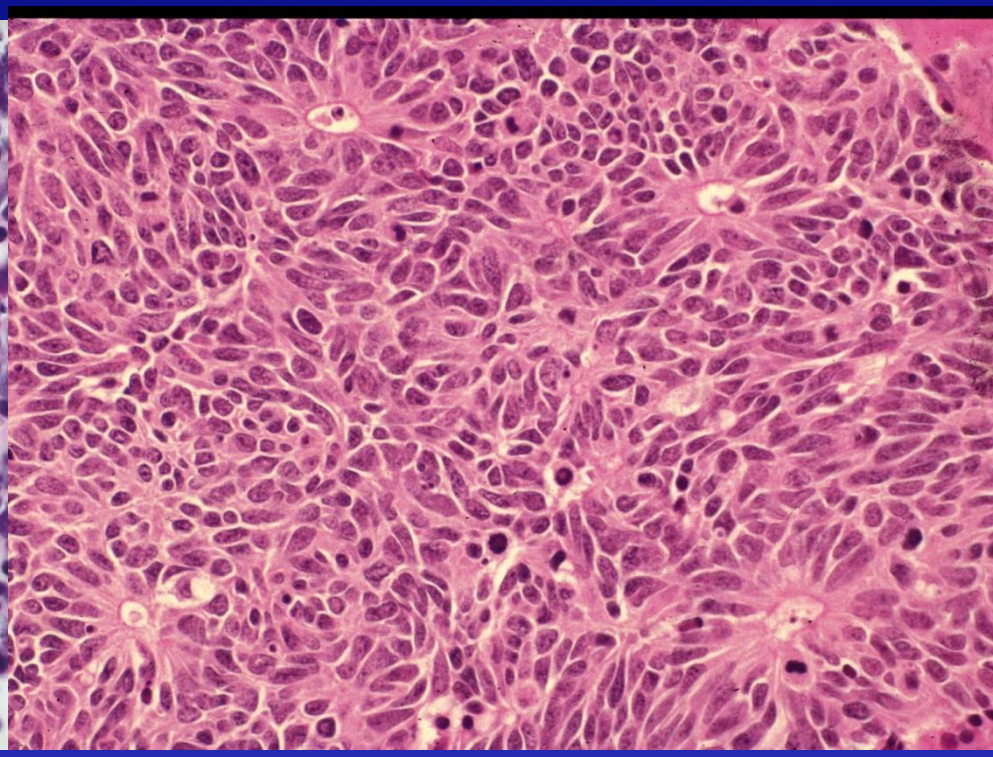
- May be identified in virtually all upper aerodigestive tract sites but primarily involve the larynx
- M >> F; most commonly occurs in the 6th to 7th decades of life
- Symptoms: hoarseness, voice changes, airway obstruction, and dysphagia; may be associated with a paraneoplastic syndrome
- Site: Supraglottic larynx
- Cigarette smoking, and possibly alcohol, appear to be causative risk factor

PDNEC - SmCC



PDNEC - SmCC





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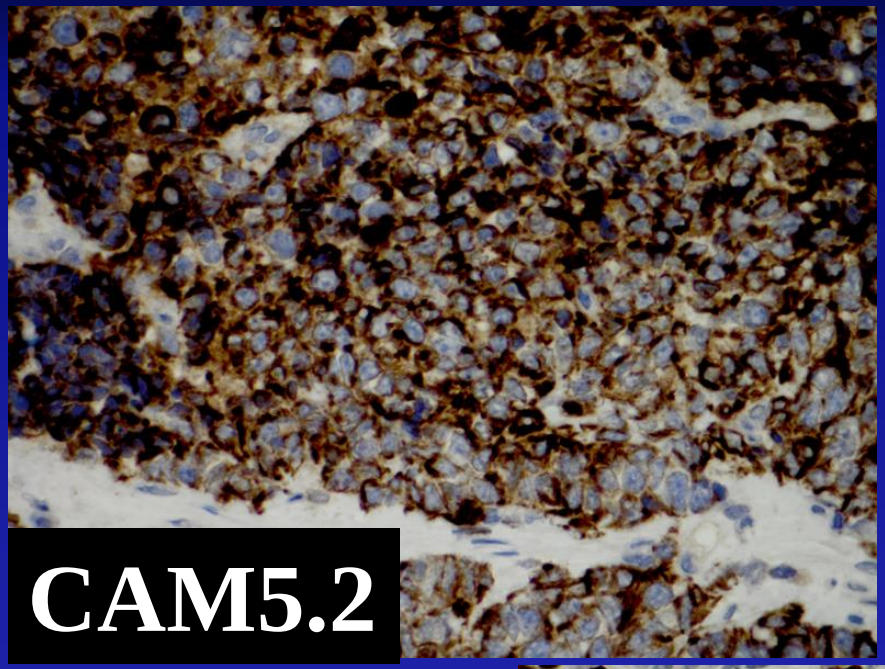
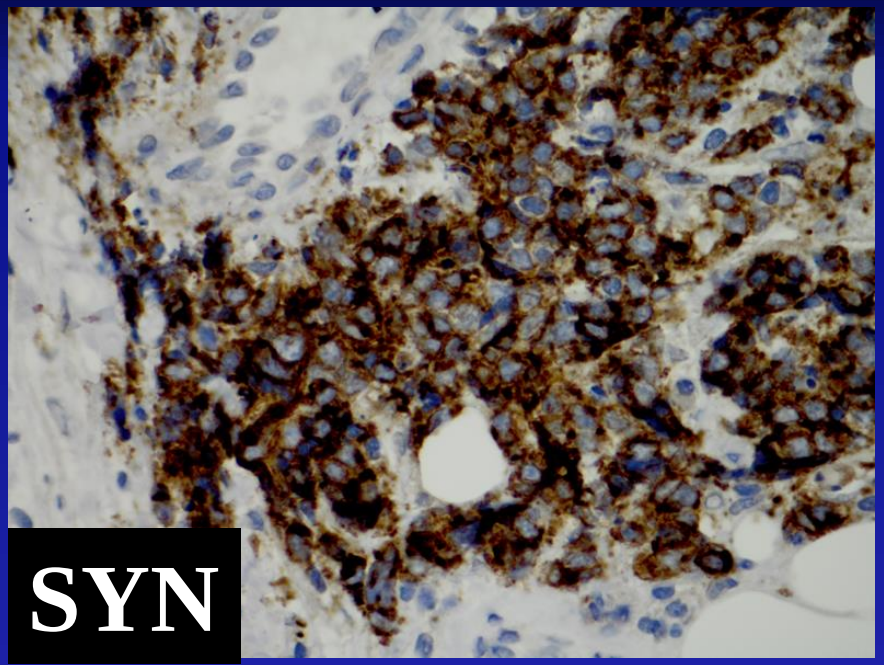
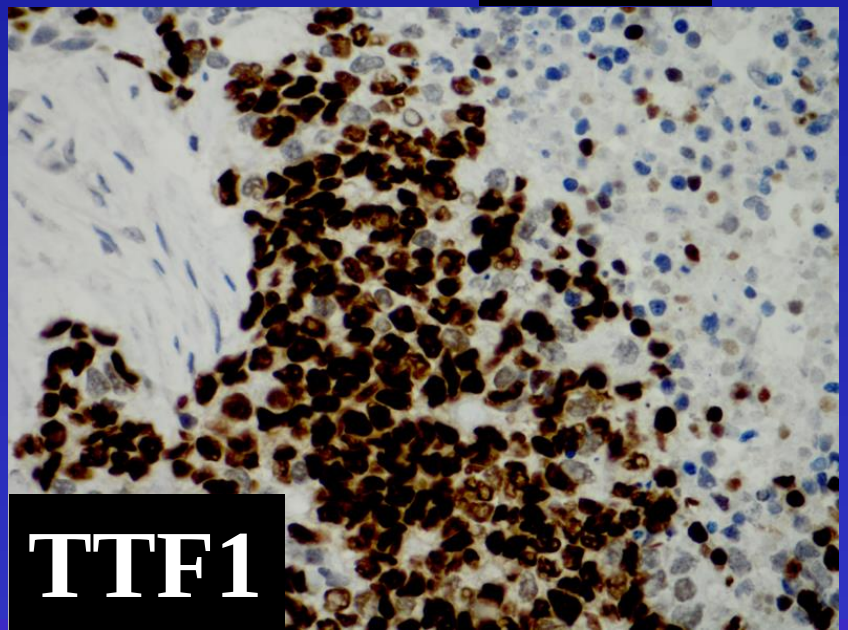






PDNEC - SmCC
Differential Diagnosis

- **Larynx:**
  - **MDNEC (Atypical carcinoid)**
  - **Basaloid squamous cell carcinoma (Non-HPV)**
- **Pharynx:**
  - **HPV-associated basaloid SCC**
  - **Mucosal malignant melanoma**
  - **Lymphoma**
  - **Rhabdomyosarcoma**
  - **Others**

PDNEC - SmCC
Differential Diagnosis

- **Sinonasal Tract**
  - **Olfactory neuroblastoma**
  - **Sinonasal undifferentiated carcinoma**
  - **NUT midline carcinoma**
  - **SMARCB1 (INI-1) deficient carcinoma**
  - **Mucosal malignant melanoma**
  - **NK/T cell lymphoma**
  - **Rhabdomyosarcoma**
  - **Others**

PDNEC - SmCC
Treatment and Prognosis

- **Preferred treatment for SmCC is systemic chemotherapy and therapeutic irradiation**
- **Highly malignant tumors commonly associated with metastatic disease: liver, lung, bone, lymph nodes, brain, pancreas**

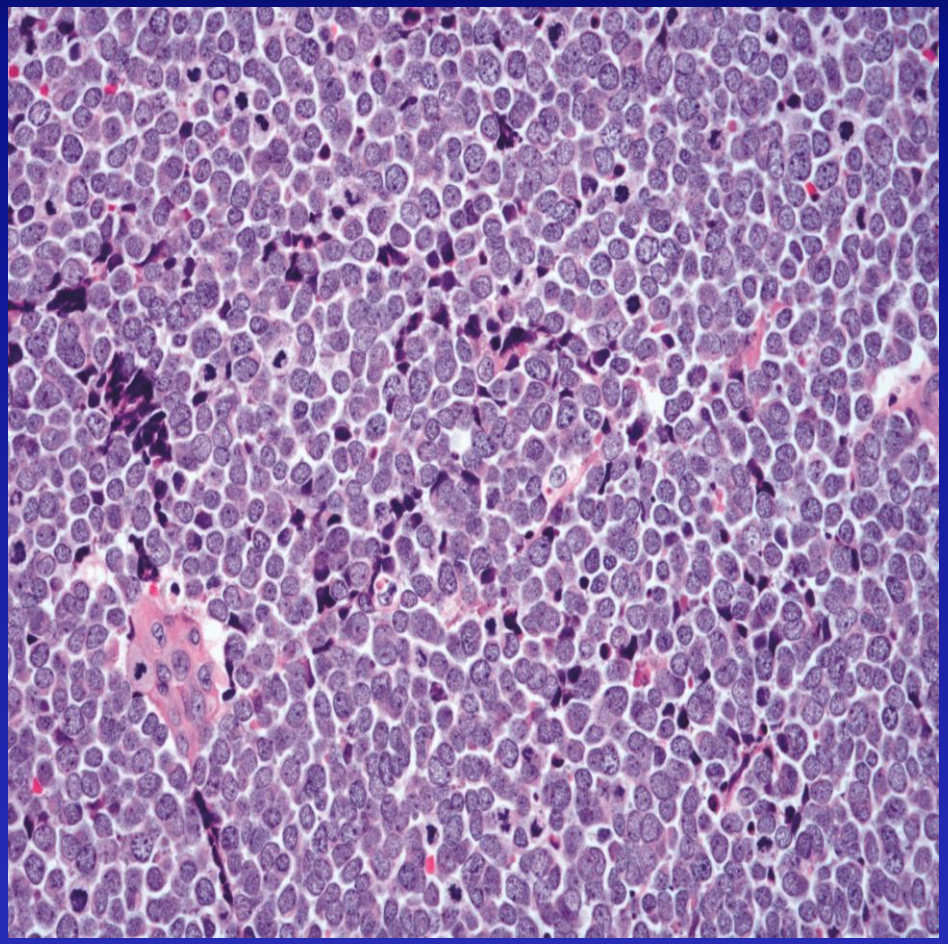
PDNEC - SmCC
Treatment and Prognosis

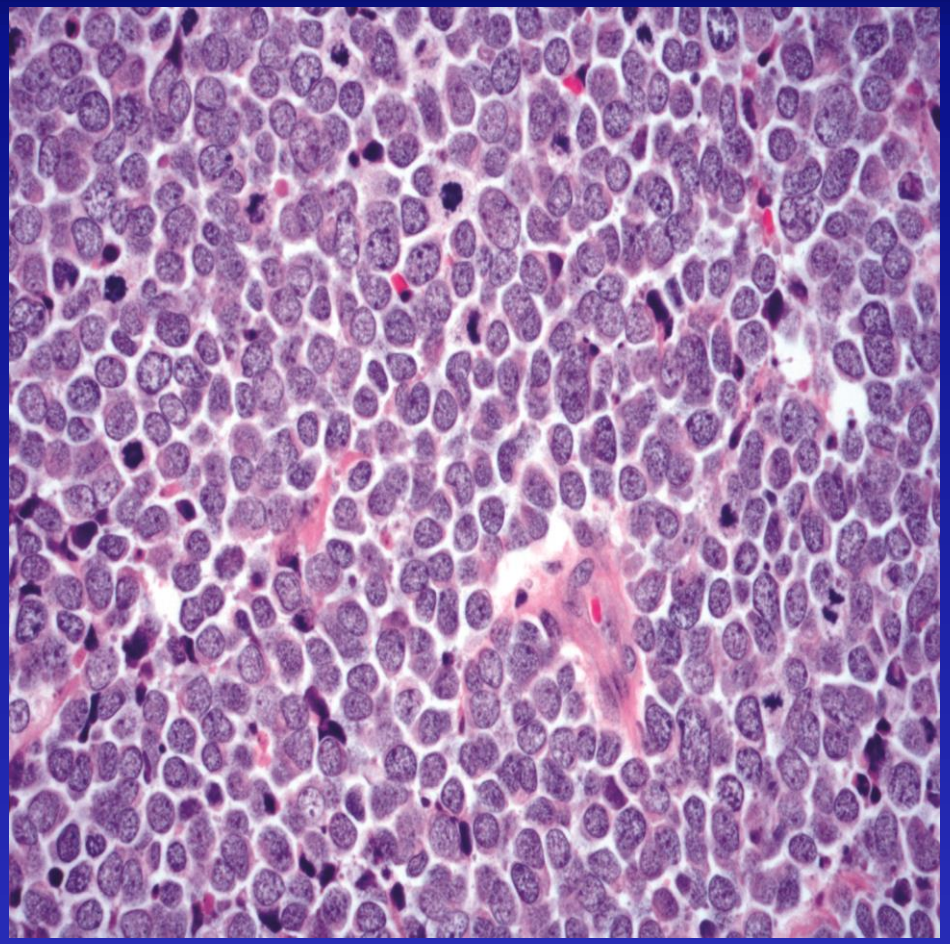
- **Laryngeal SmCC have a dismal prognosis:**
  - **> 70 percent died of disease with a mean survival time of 9.8 months**
  - **2-year survival : 16%**
  - **5-year survival: 2%**
- **Sinonasal tract SmCC:**
  - **all died within 2.5 years of diagnosis**

PDNEC - SmCC
Treatment and Prognosis

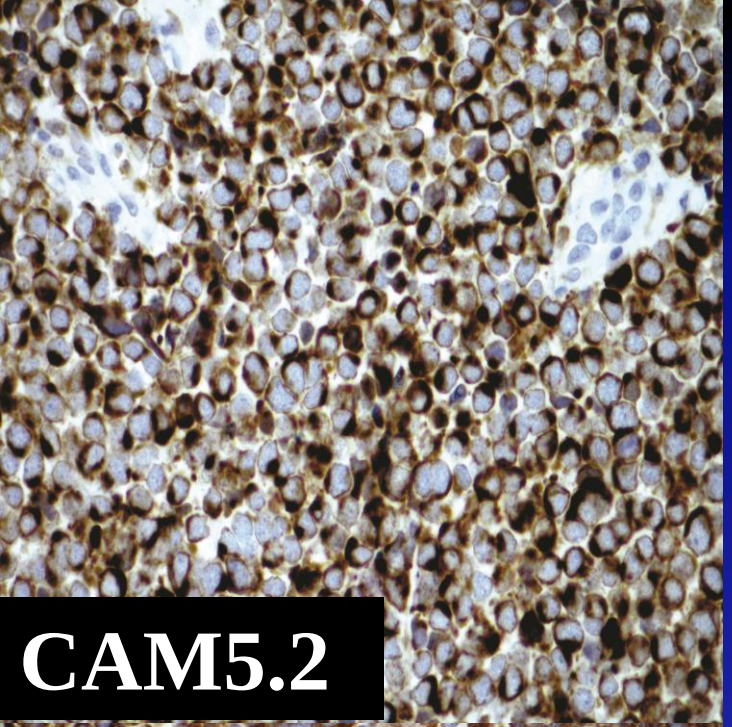
- SmCC of the salivary glands are considered to have a better overall prognosis:
  - Survival rates include:
    - 2-year of 70%
    - 5-year of 46%
  - represent Merkel cell carcinomas (CK20 positive; ± Merkel cell polyoma virus positive [MCPyV])

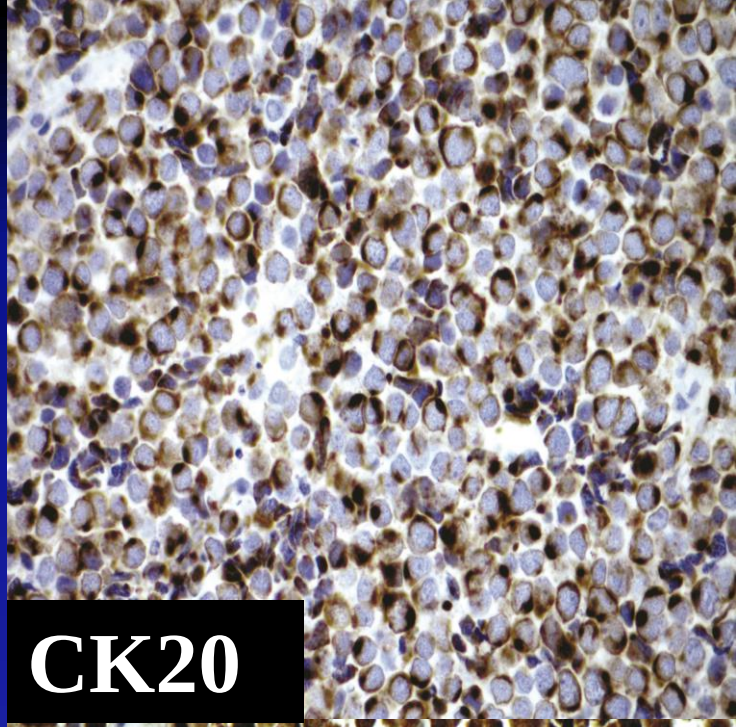
Merkel Cell Carcinoma (MCC)

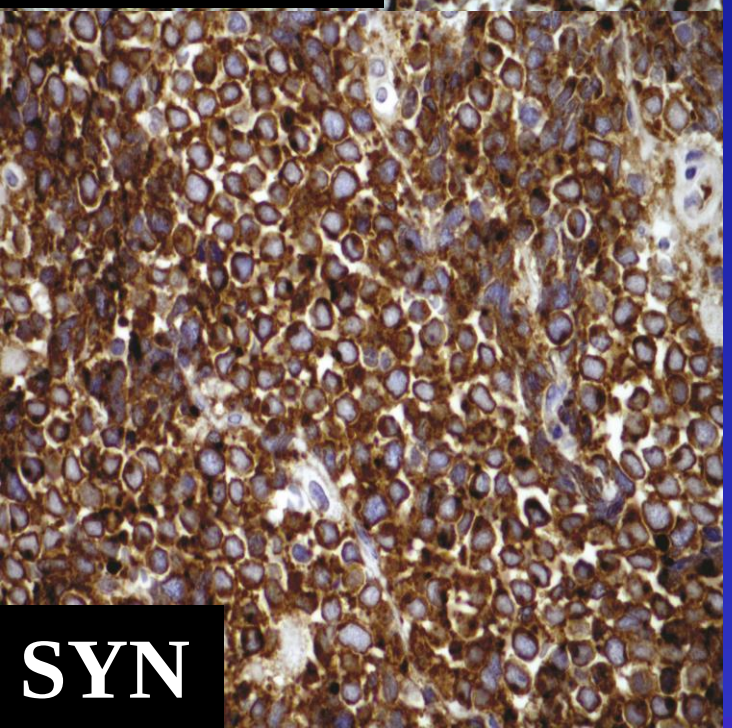


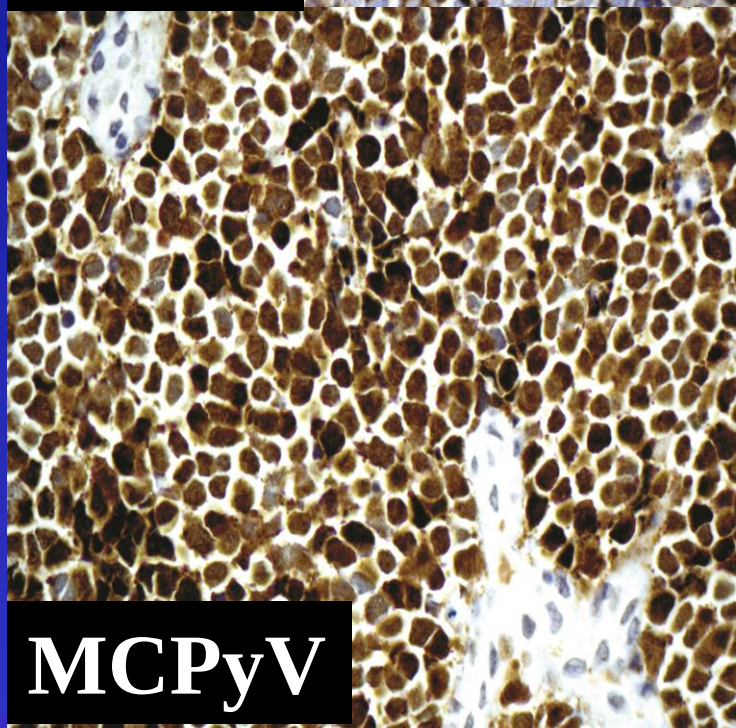


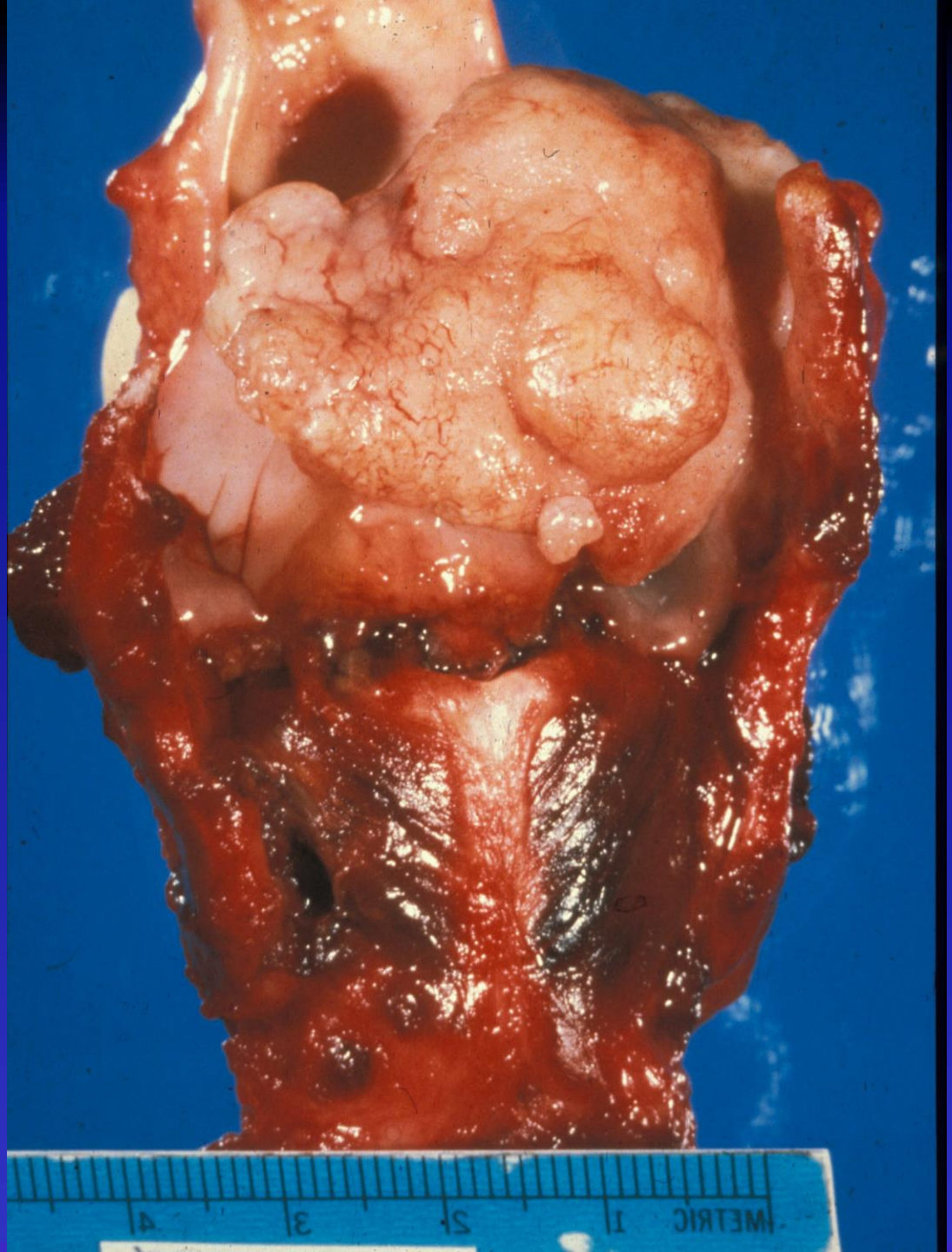
MCC



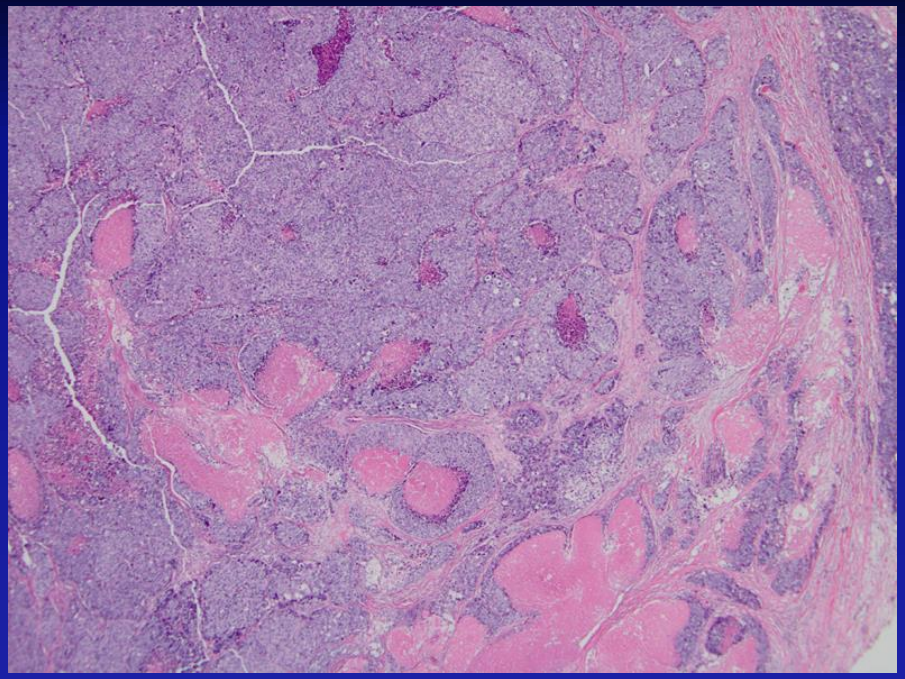


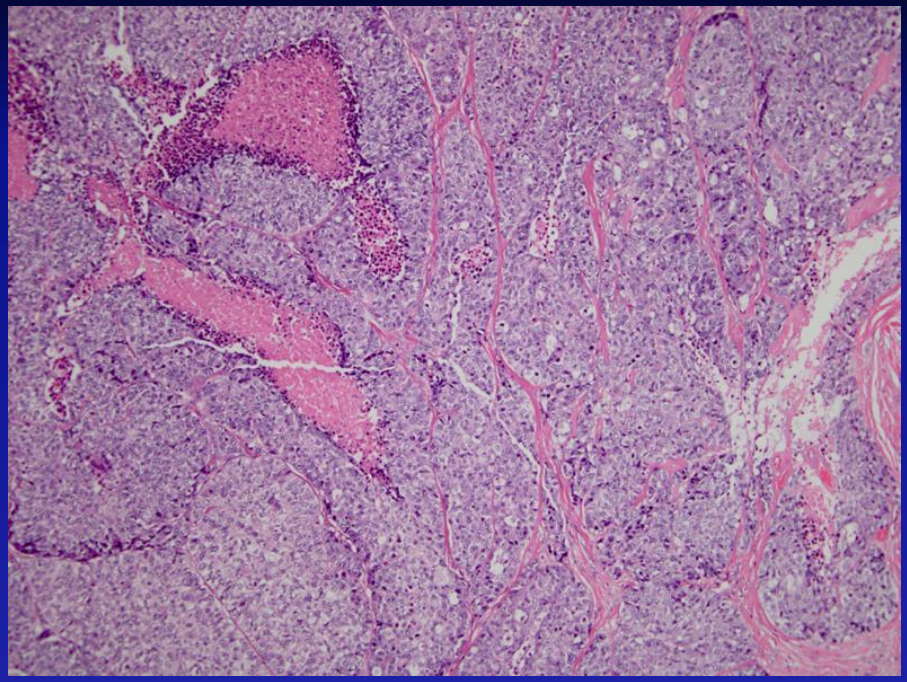


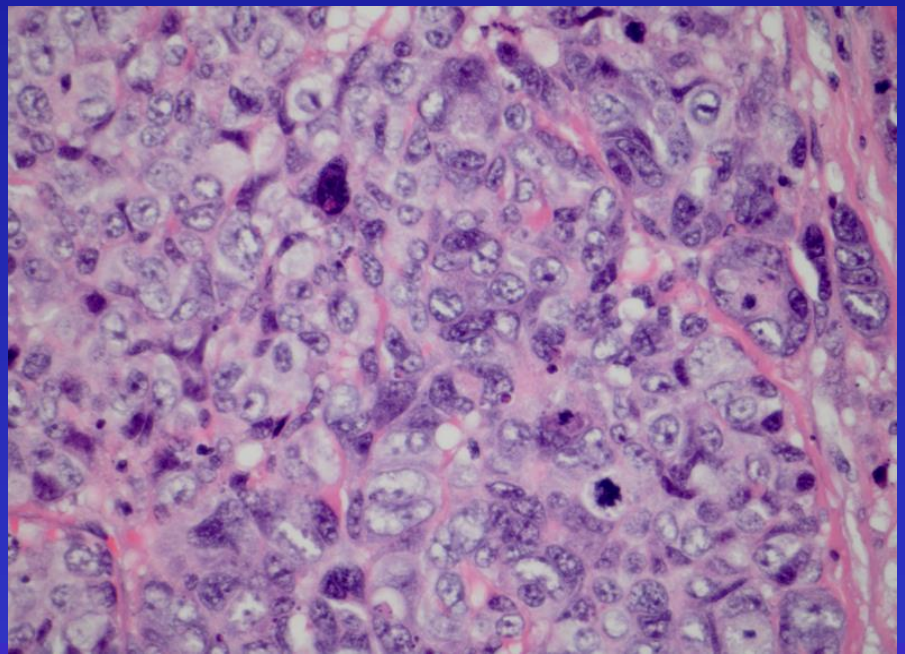


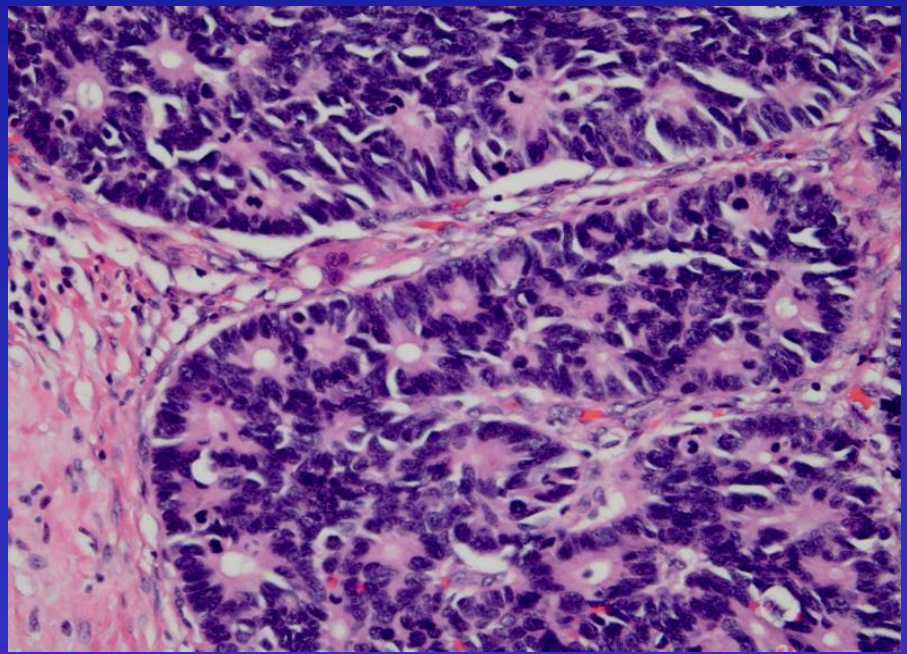

METRIC
1
2
3
4

PDNEC - LCNEC

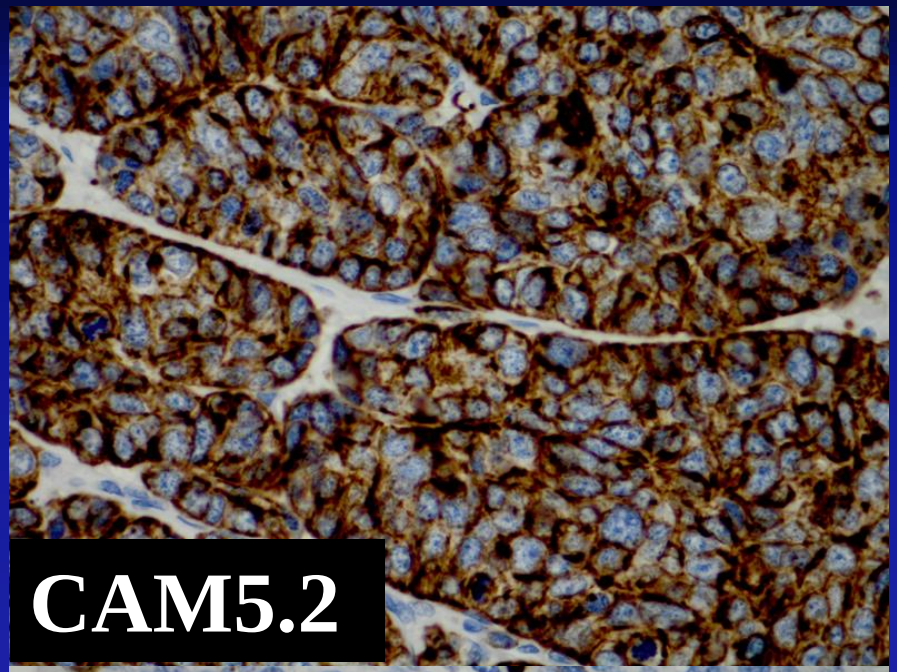


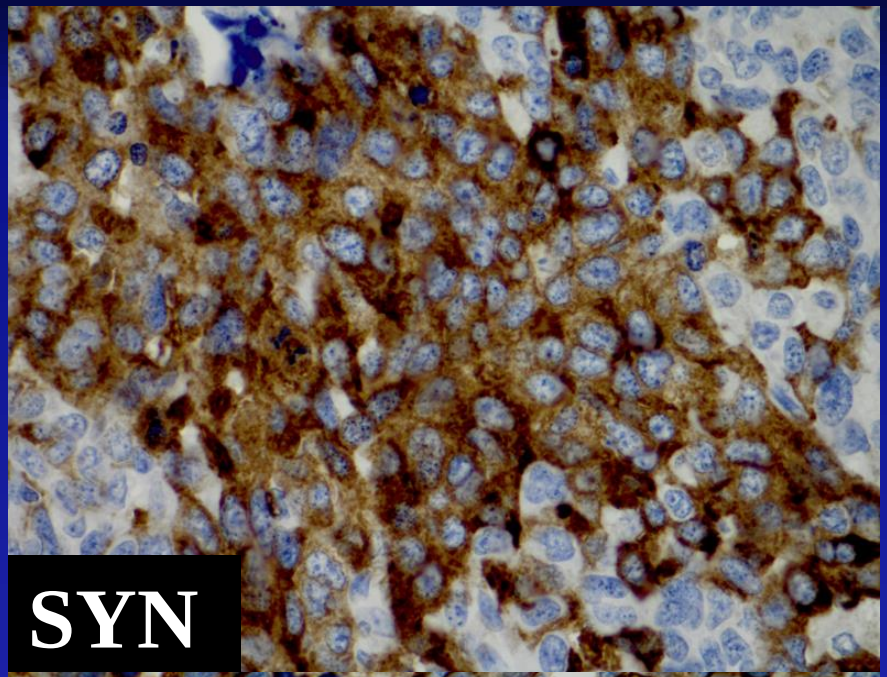


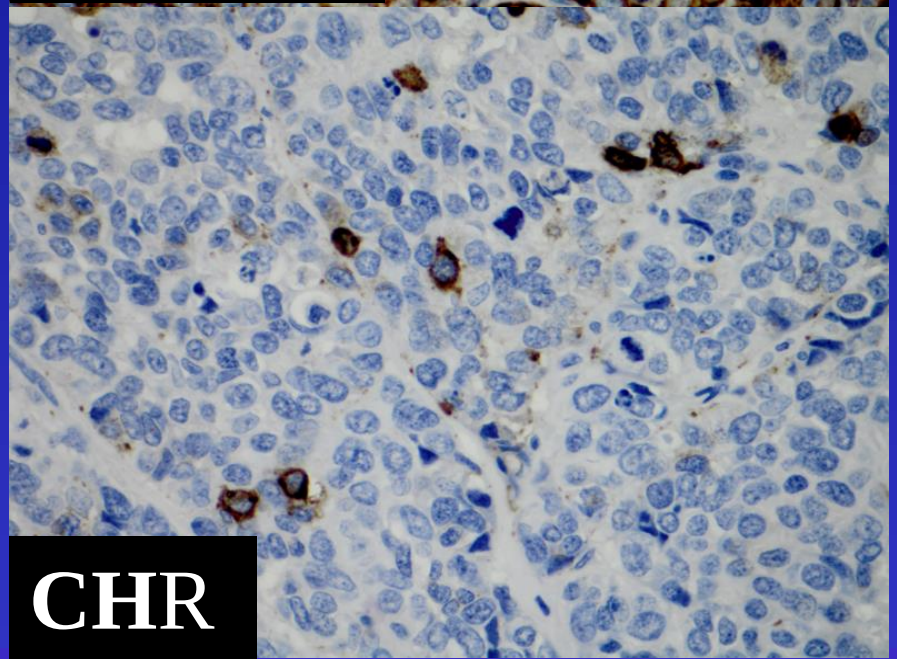


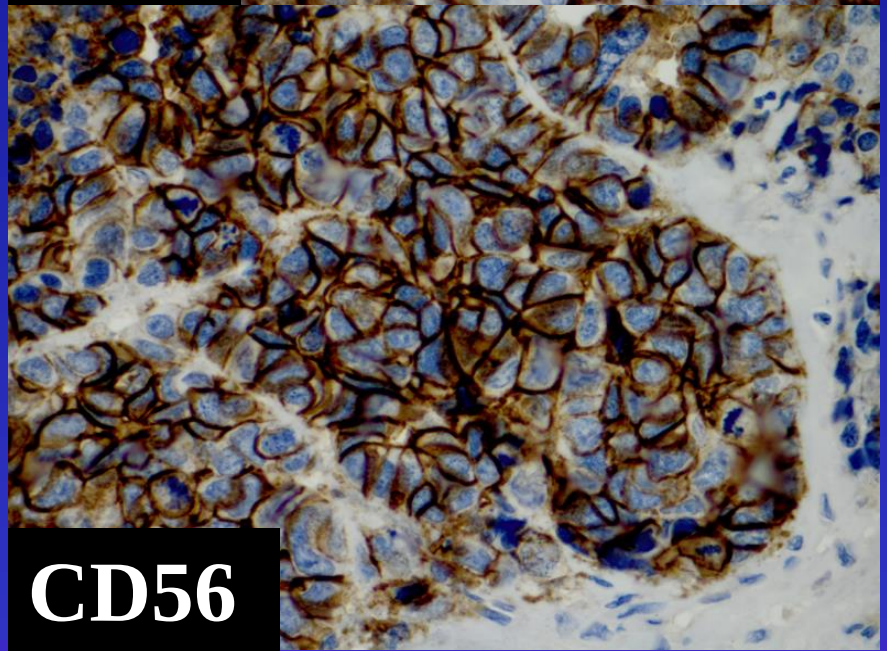


PDNEC - LCNEC - IHC









Criteria for (Laryngeal) LCNEC

Lewis J, et al. Head Neck Pathol 2010;4:198-207

Requisite criteria	Other typical features
Tumor cells with moderate to abundant cytoplasm	Nuclei with prominent nucleoli
Features of neuroendocrine differentiation (organoid nesting, trabecular growth, rosettes, and peripheral palisading)	Cellular pleomorphism
Mitotic activity > 10/10 hpf (2 mm^2)	Large areas of necrosis
Confirmation of neuroendocrine differentiation using immunohistochemical staining	

PDNEC - LCNEC
Treatment and Prognosis

- Chemoradiotherapy
- Many patients have disseminated disease at presentation obviating option of laryngectomy and neck dissection
- Commonly present with advanced stage (stages III and IV):
  - may be metastatic to cervical lymph nodes at presentation
  - may be metastatic to distant sites at presentation (e.g., liver)
- 5-year disease specific survival (DSS) of 15-21%

PDNEC - LCNEC
Differential Diagnosis

- **Moderately-Differentiated Neuroendocrine Carcinoma (Atypical Carcinoid):**
  - **Mitotic activity and proliferation rate**
- **Oropharyngeal HPV-associated SCC (nonkeratinizing type; basaloid squamous cell carcinoma):**
  - **p63 and CK5/6 positive**

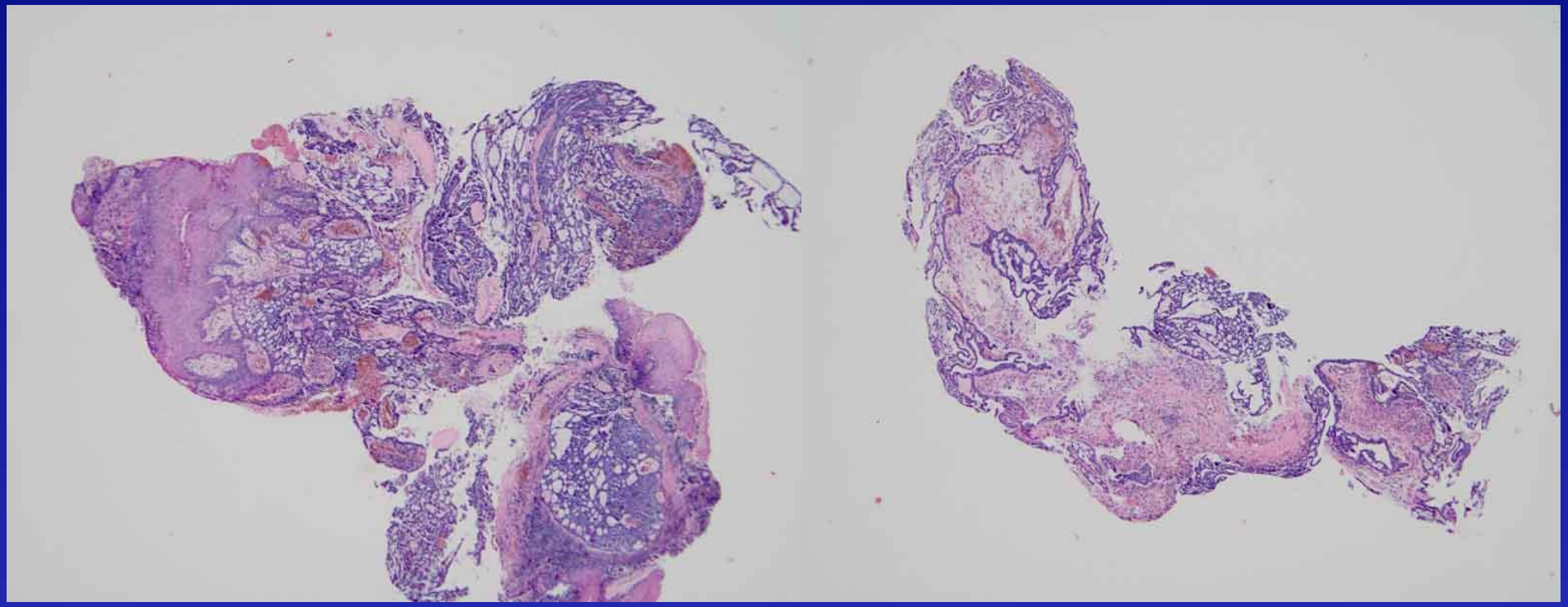
Case 1
Summary

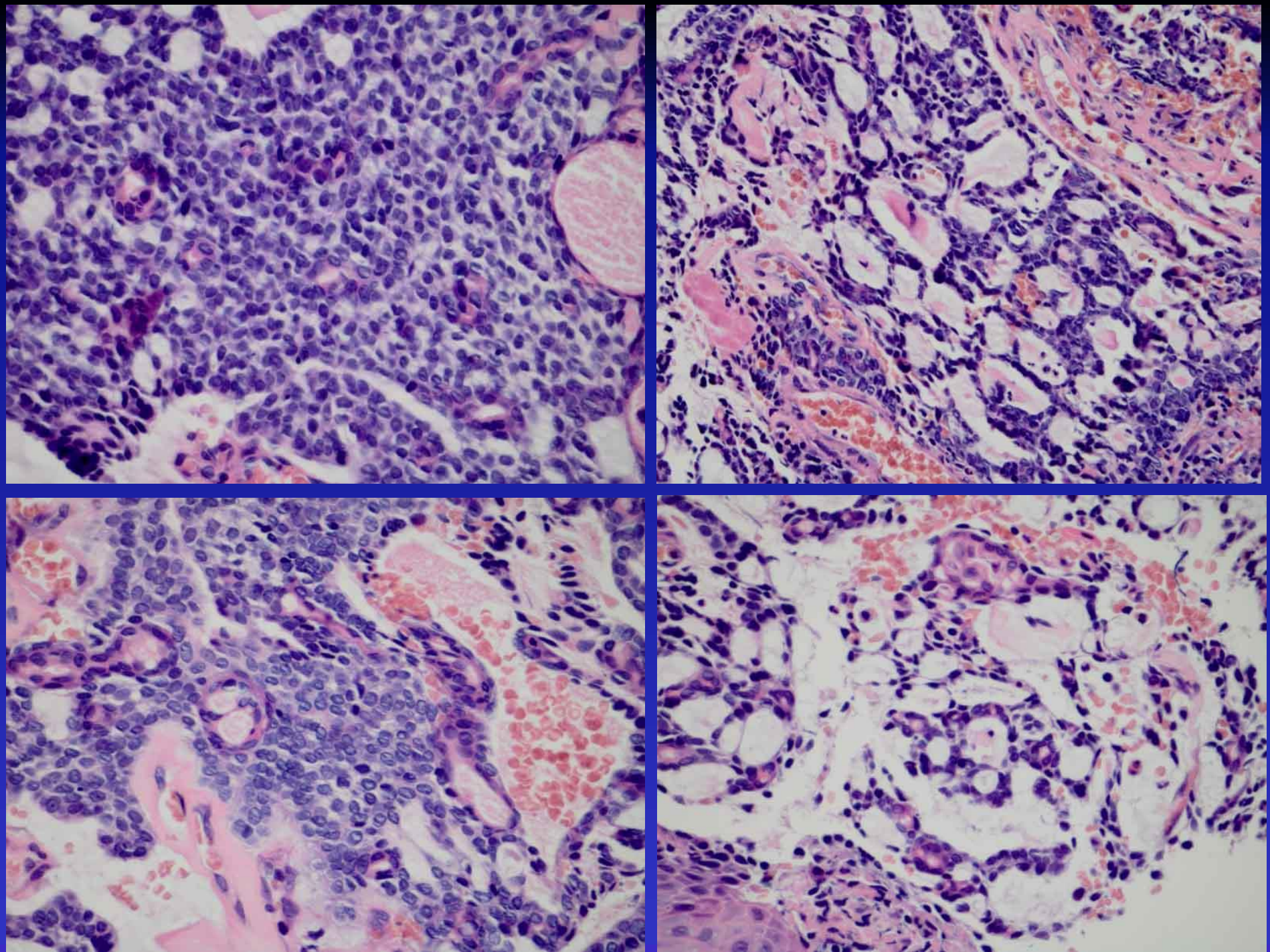
- **NECs, including MTC, MDNEC, PDNEC may metastasize to cervical neck nodes without primary**
- **MTC and MDNEC share overlapping histologic and IHC findings including calcitonin reactivity:**
  - **Differentiation usually achievable on basis of serum calcitonin (MTC+; MDNEC-) and/or imaging**
- **New WHO Classification of H&N PDNEC includes small cell and large cell types**
- **PDNEC may also metastasize without a known primary particularly of oropharyngeal origin:**
  - **May be HPV+ (not associated with more favorable prognosis)**

Case 2 – Clinical History

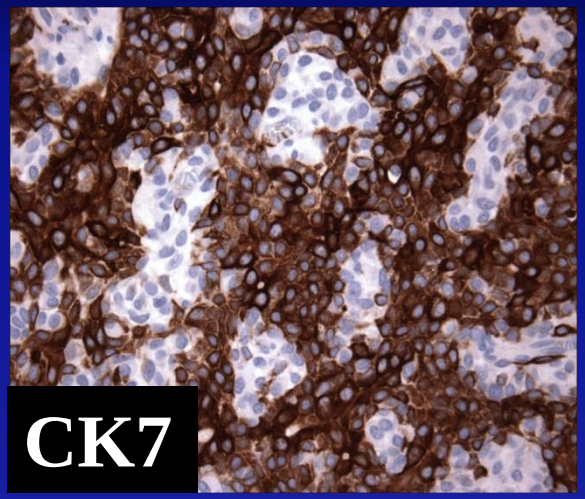
- 35 year old female presented with a palate mass at the junction of the hard and soft palate with associated tingling sensation but no pain. The mass measuring approximately 2.5cm in greatest dimension appeared as a bulge with intact overlying epithelium. The mass was biopsied.

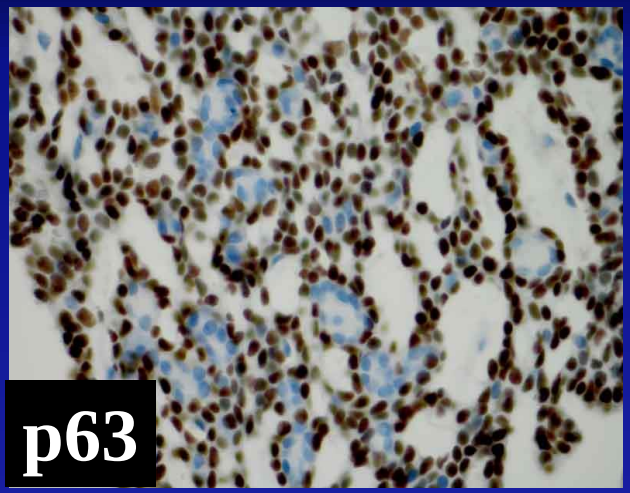
Case 2

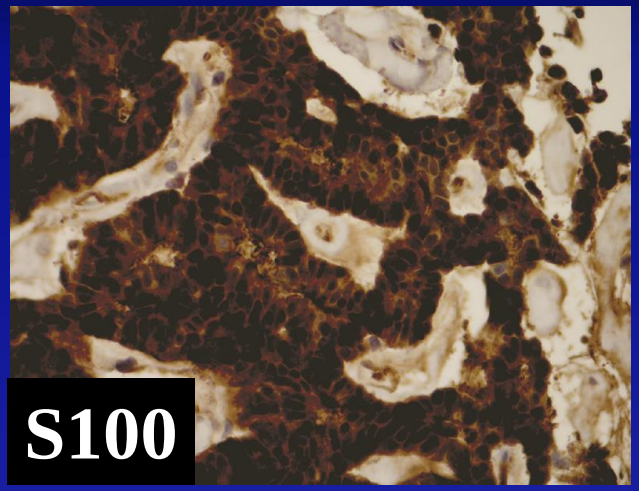


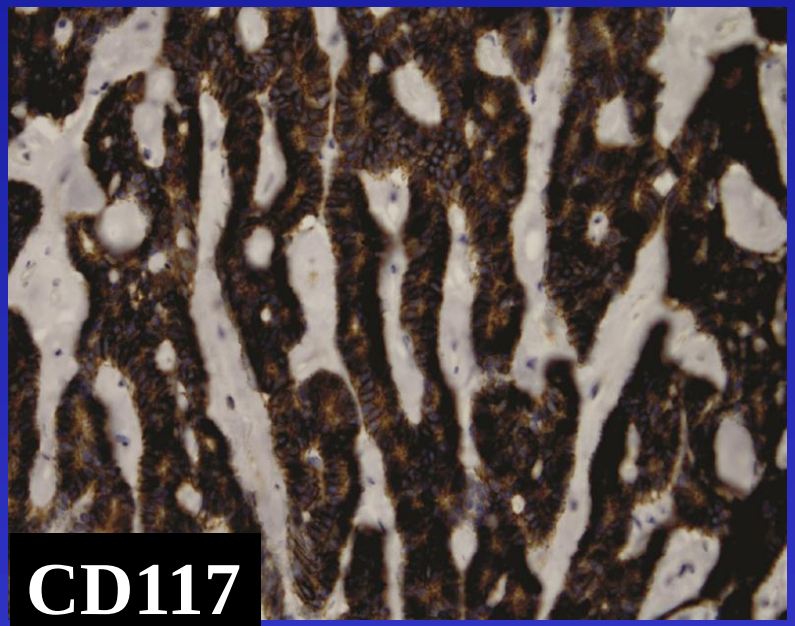


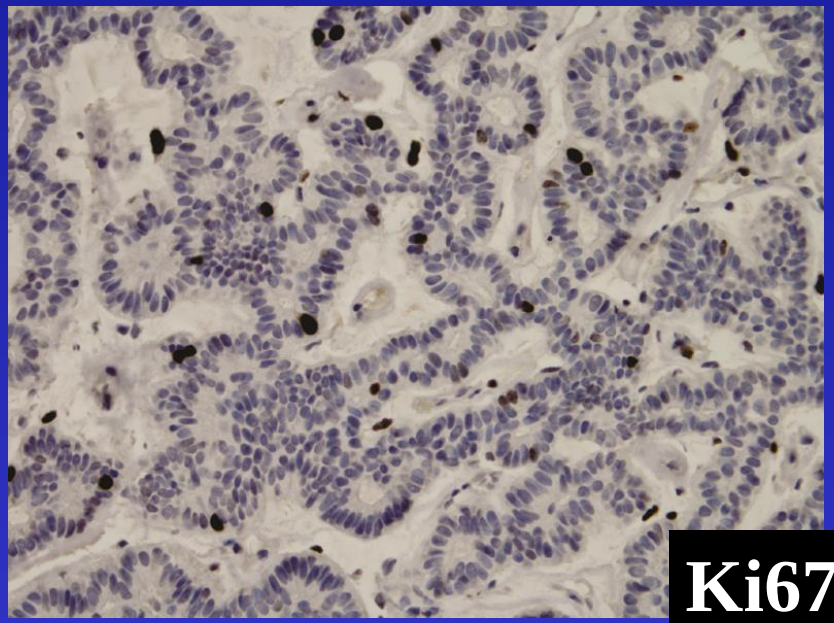
Case 2 – IHC











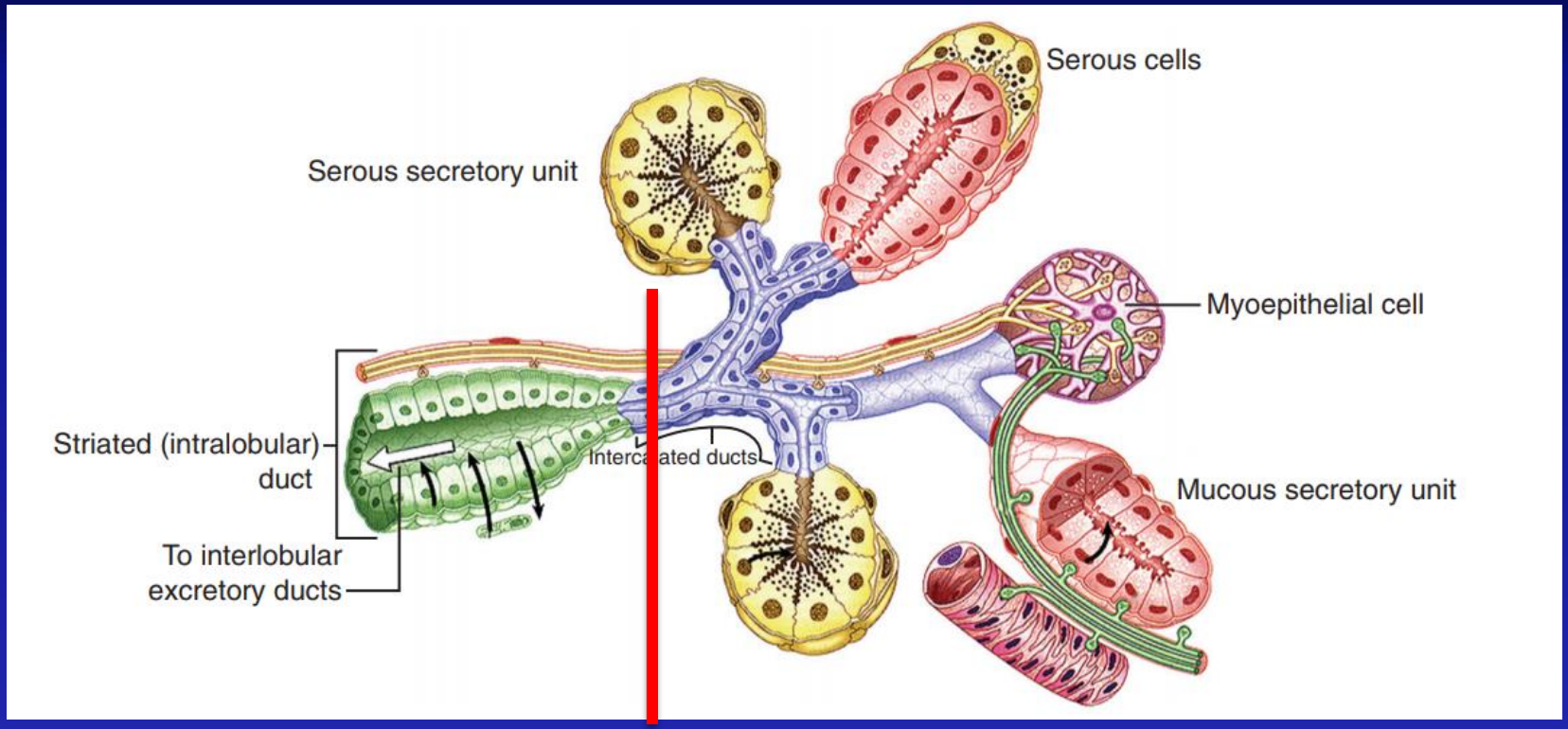
Case 2 – IHC reactivity

- Cytokeratins (AE1/AE3, CK7) +
- p63, S100 protein & vimentin +
- CD117 +
- p40, calponin, GFAP negative
- Mammaglobin, DOG1 negative
- Ki67 – low proliferation (<5%)

Case 2
Diagnosis ?

- Adenoid cystic carcinoma
- Basal cell adenoma
- Basal cell adenocarcinoma
- Cellular pleomorphic adenoma
- Polymorphous (low-grade) adenocarcinoma
- Minor salivary gland neoplasm, not further specified

Salivary Glands = Tubuloacinar Exocrine Gland



Ductal (Excretory & Striated) derived:

- Mucoepidermoid CA
- Salivary Duct CA
- Warthin tumor
- Oncocytoma
- Others

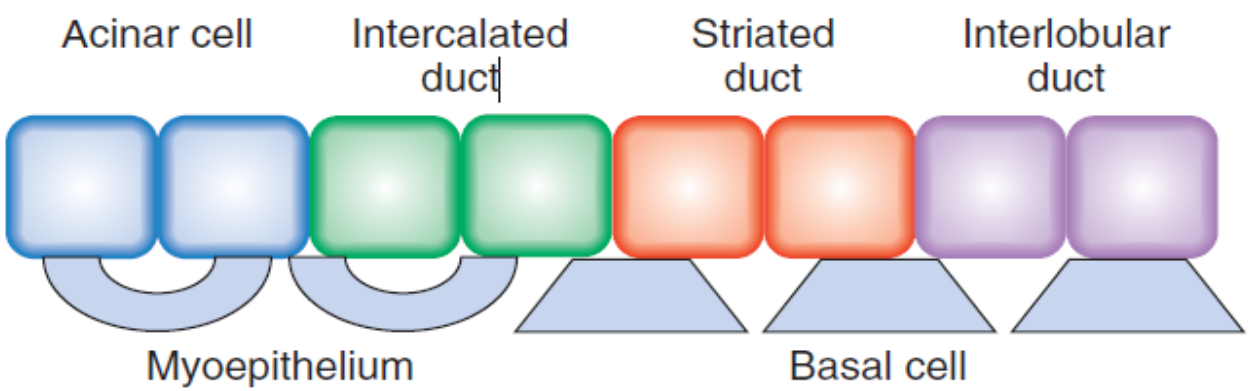
Epithelial & Myoepithelial or Acinar derived:

- Pleomorphic adenoma
- Monomorphic (Basal cell) adenoma
- Adenoid cystic CA; EMA; PLGA
- Acinic cell adenocarcinoma
- Others

IHC Reactivity

Amylase +
DOG1 +

Pan-cytokeratin +; High MW cytokeratin –; EMA +; CEA +
Vimentin –; p63 –; myoid markers –



Luminal cells →

Abluminal cells →

Pan-cytokeratin +; High MW cytokeratin +; EMA –; CEA –
Vimentin +; p63+

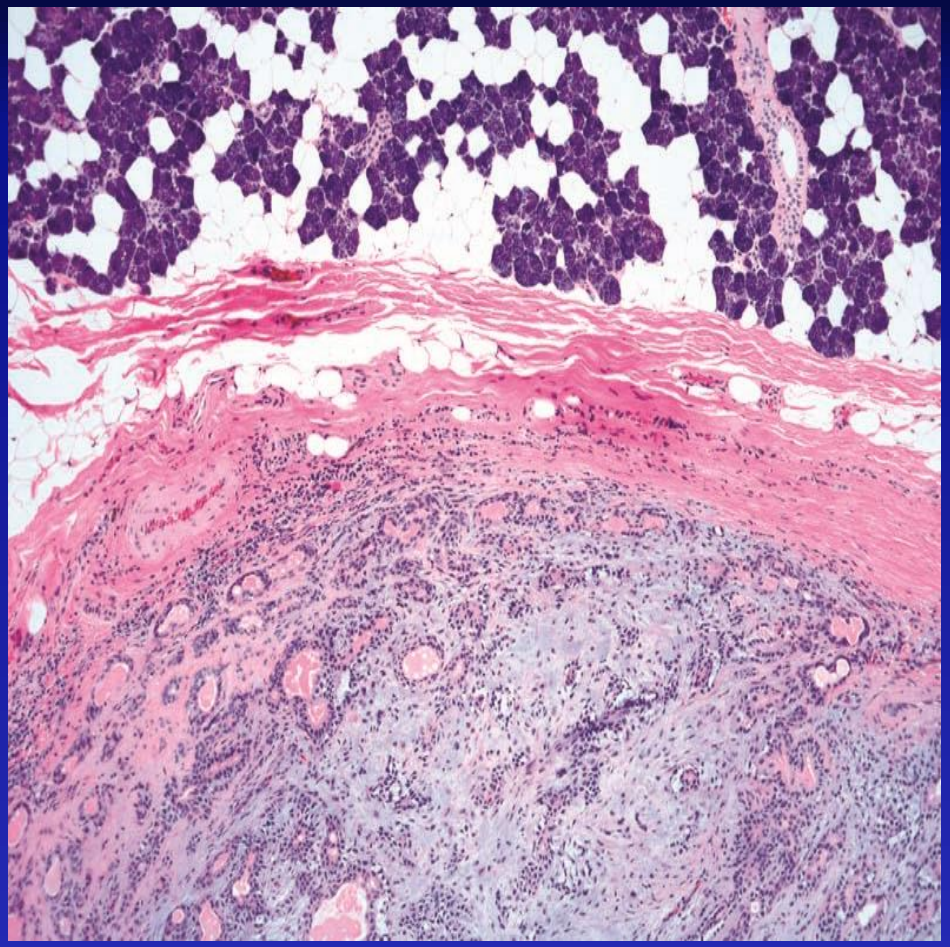
Myoid markers (actin, myosin, calponin) + S100 protein +/–; GFAP +/–

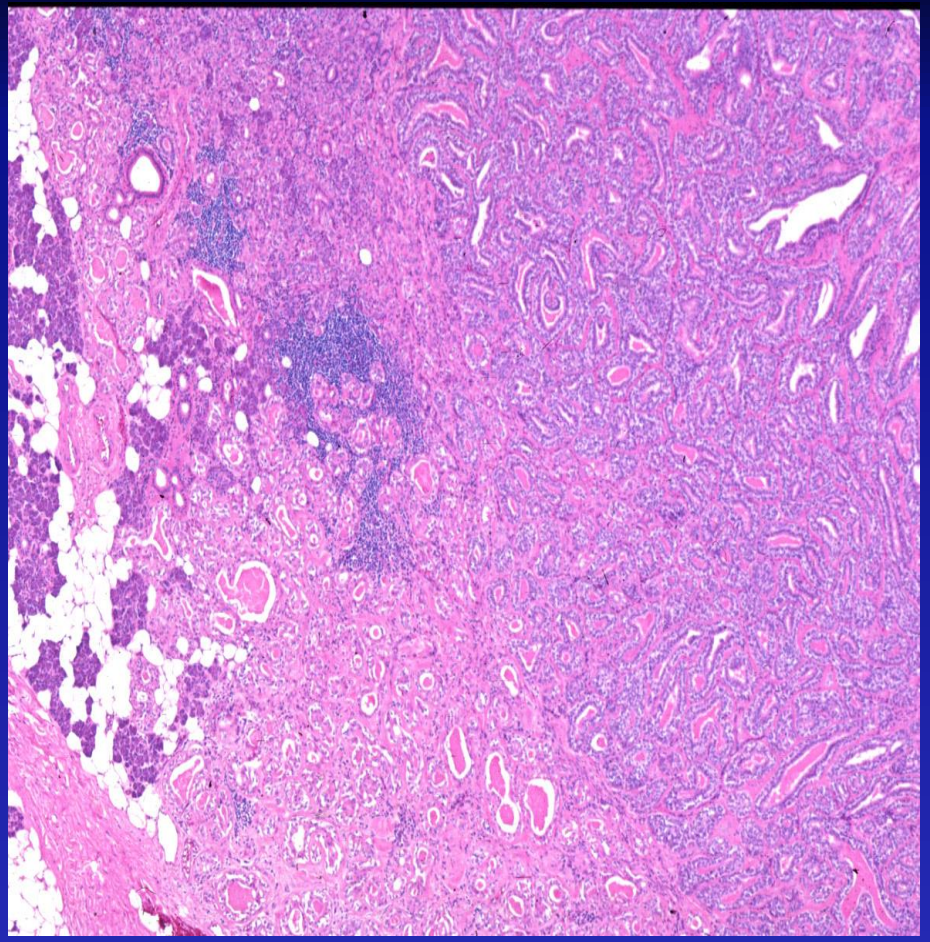
Myoid markers –
S100 protein –; GFAP –

SOX10

Major Salivary Gland Neoplasms

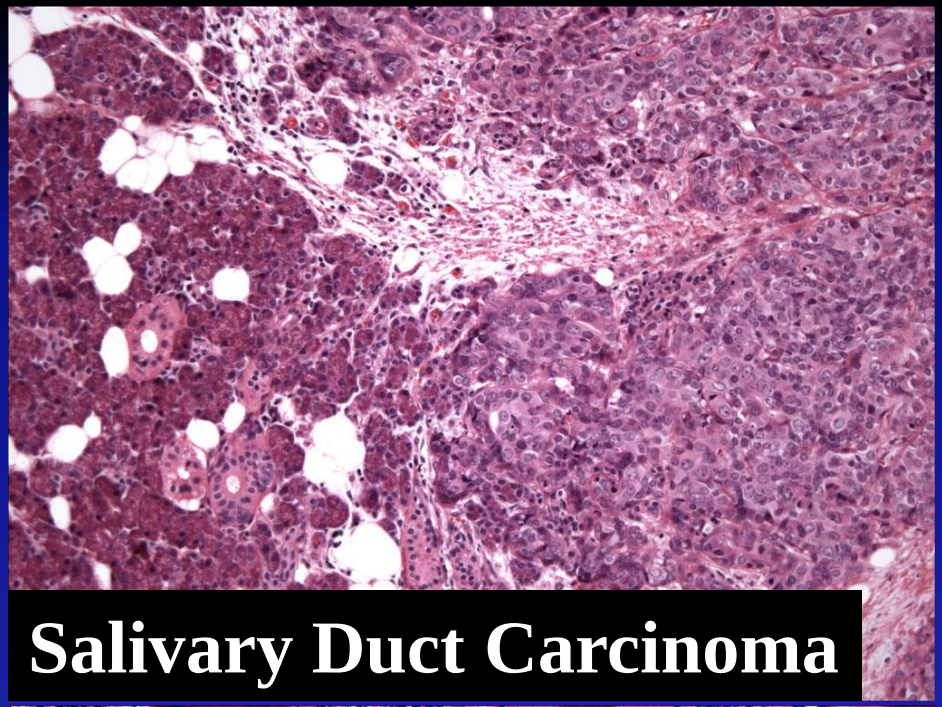
- **Encapsulation and circumscription:**
  - **All major gland neoplasms are encapsulated:**
    - **Benign → Noninvasive**
    - **Malignant → Invasive; exceptions include:**
      - **Mucoepidermoid carcinoma**
      - **Acinic cell adenocarcinoma**
      - **Adenoid cystic carcinoma**
      - **Mammary analogue secretory carcinoma**
      - **Epithelial-myoepithelial carcinoma**
      - **Noninvasive carcinoma ex pleomorphic adenoma**



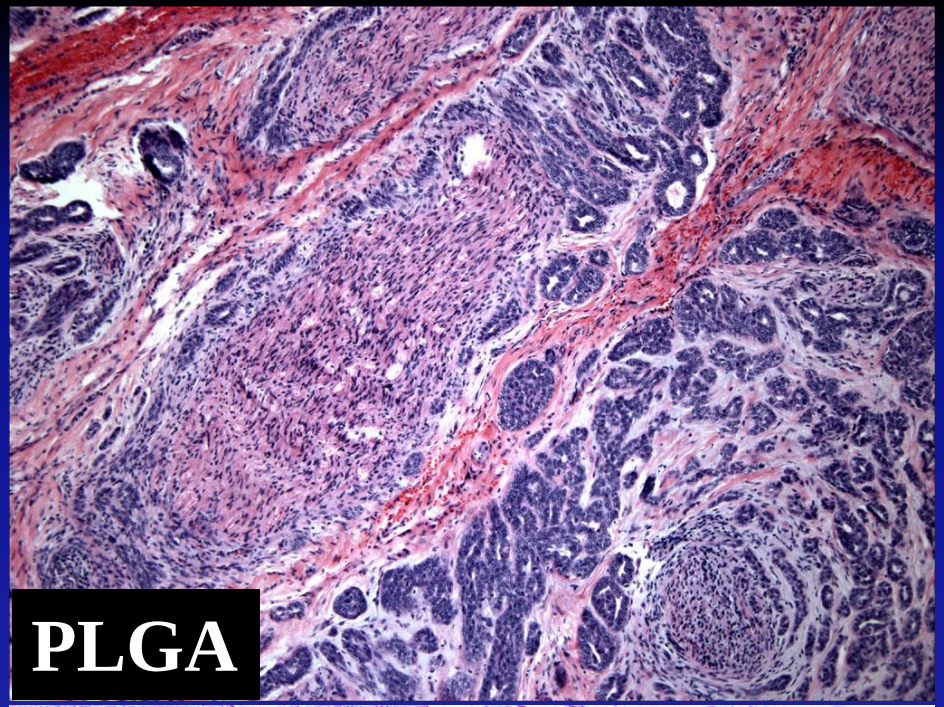


Pleomorphic Adenoma

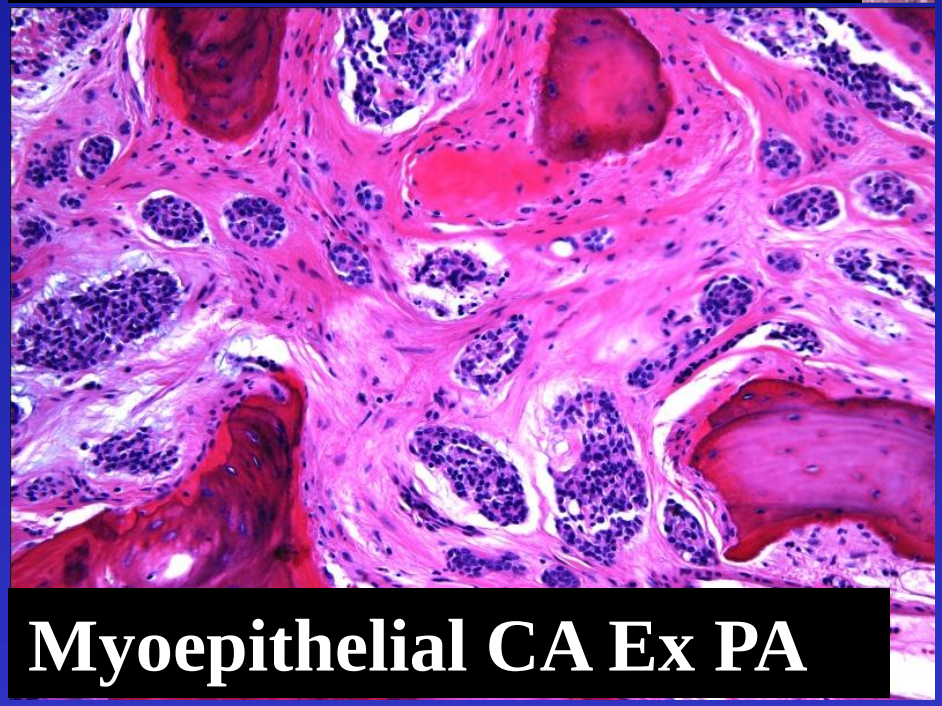
Epithelial-Myoepithelial Carcinoma



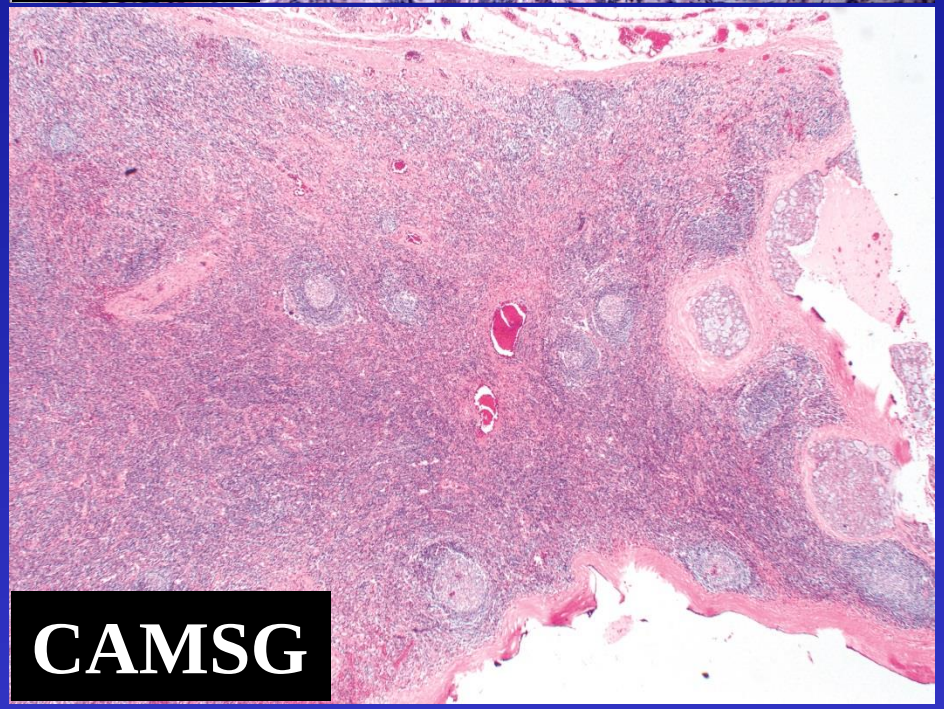
Salivary Duct Carcinoma



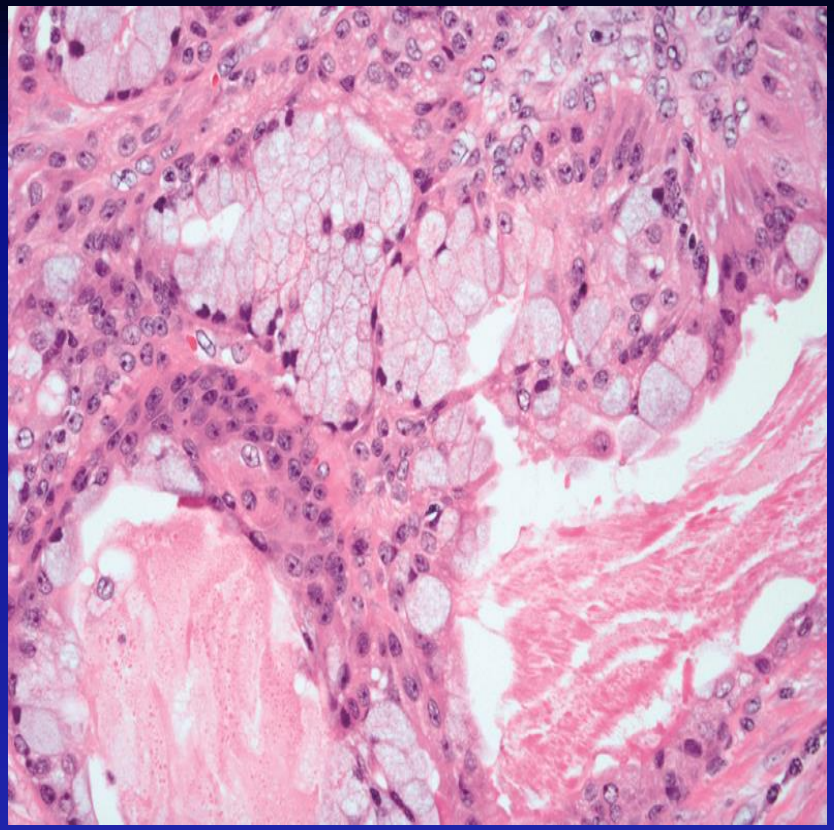
PLGA



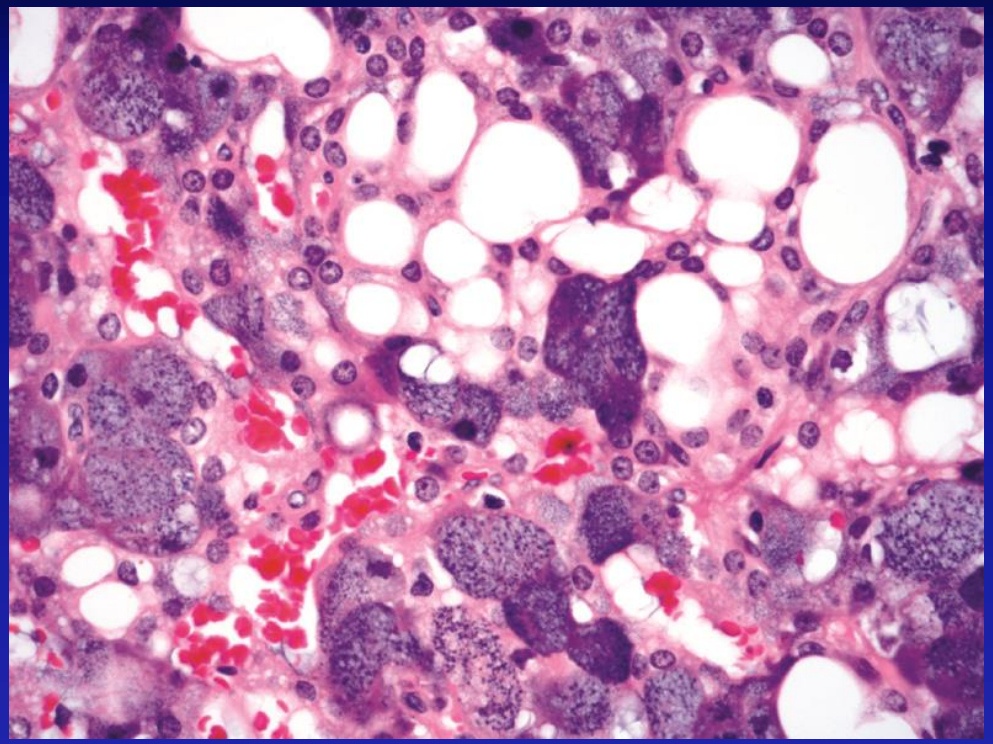
Myoepithelial CA Ex PA



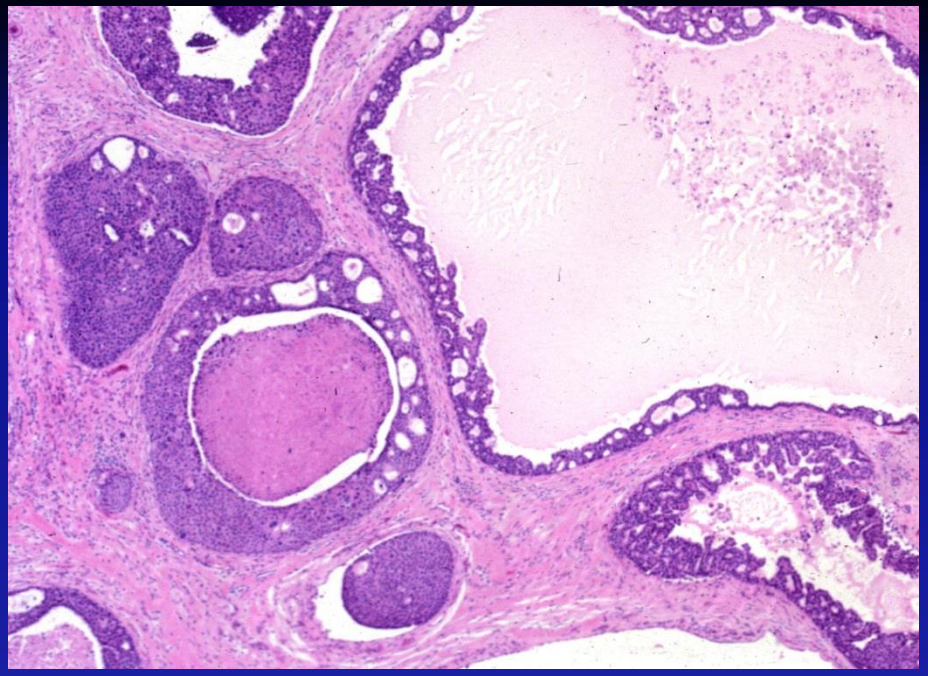
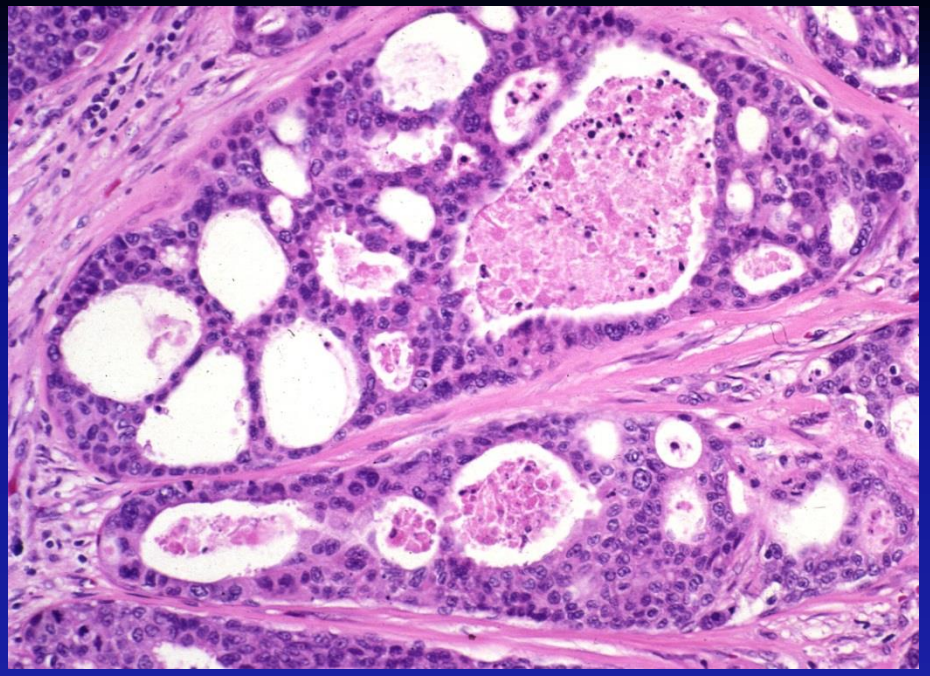
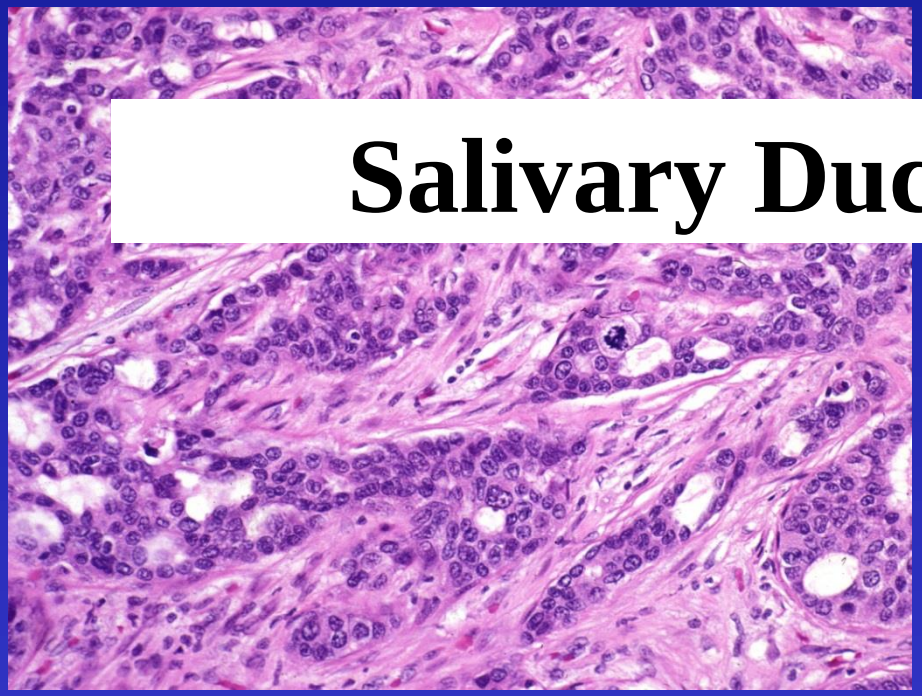
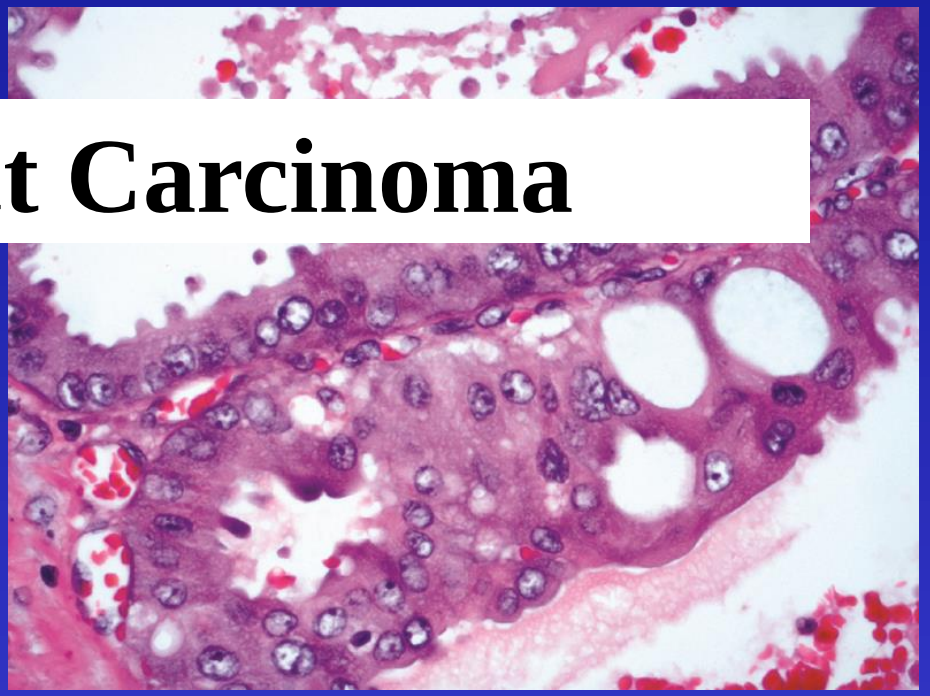
CAMSG



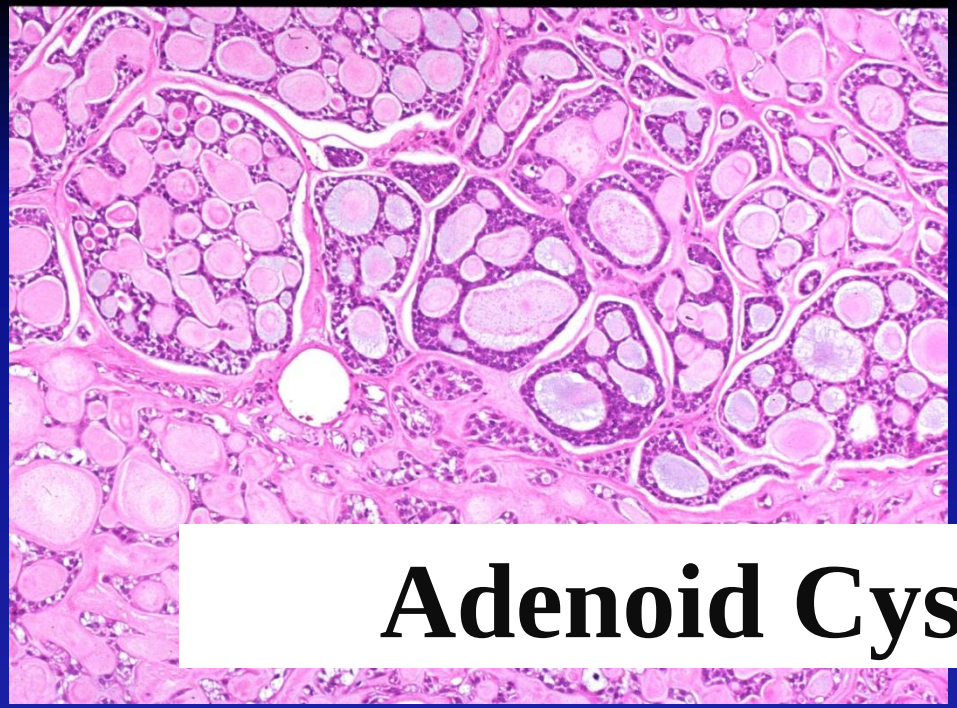
Mucoepidermoid Carcinoma

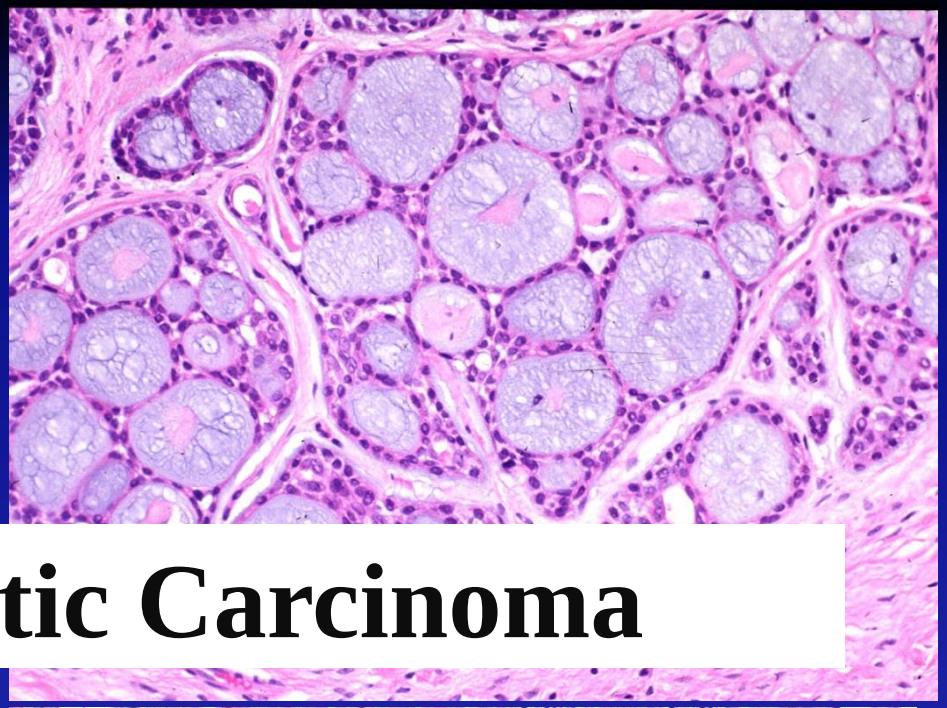


Acinic cell adenocarcinoma

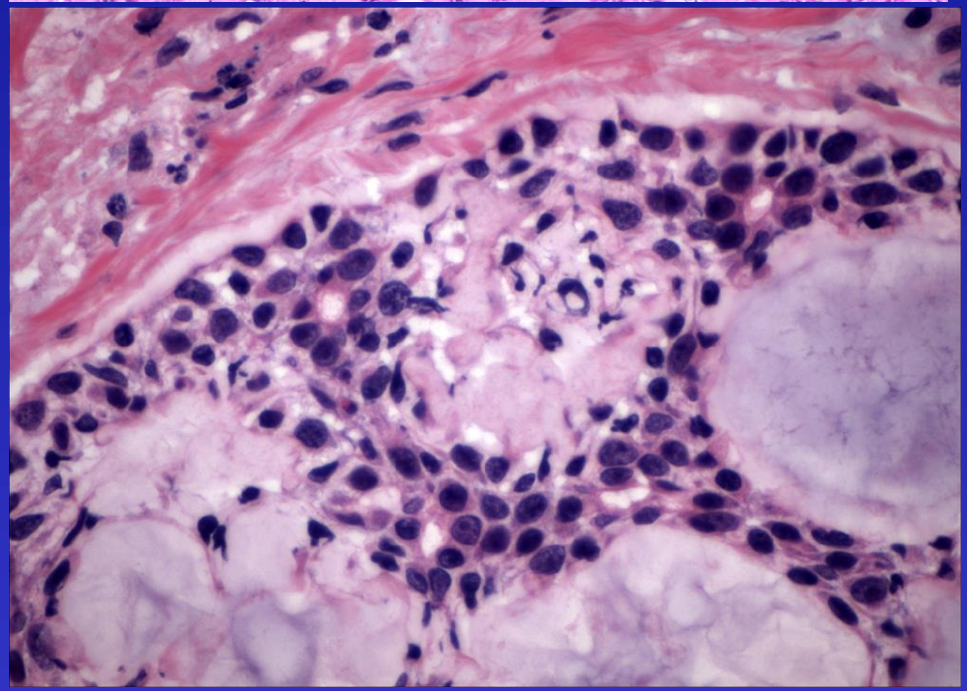





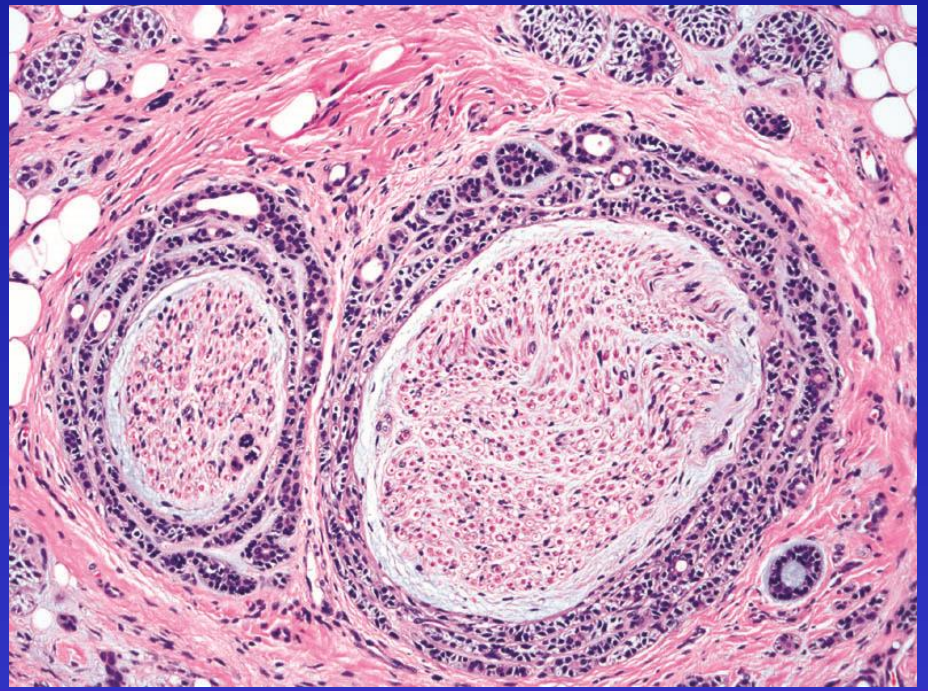
Salivary Duct Carcinoma

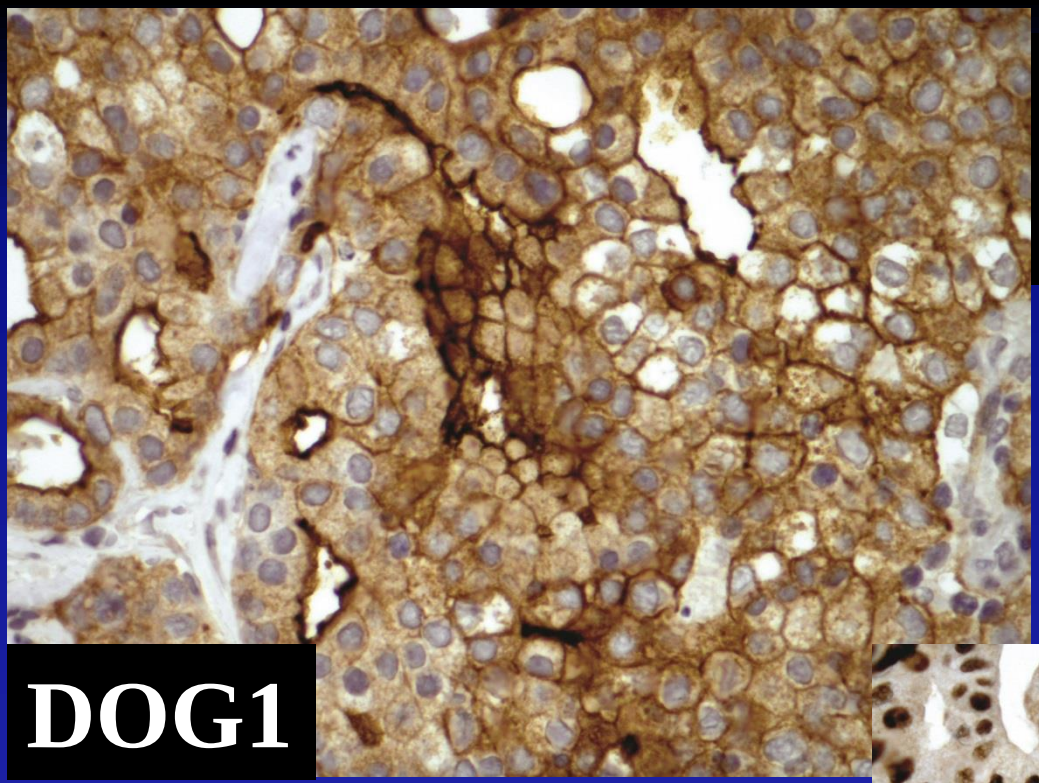




Adenoid Cystic Carcinoma



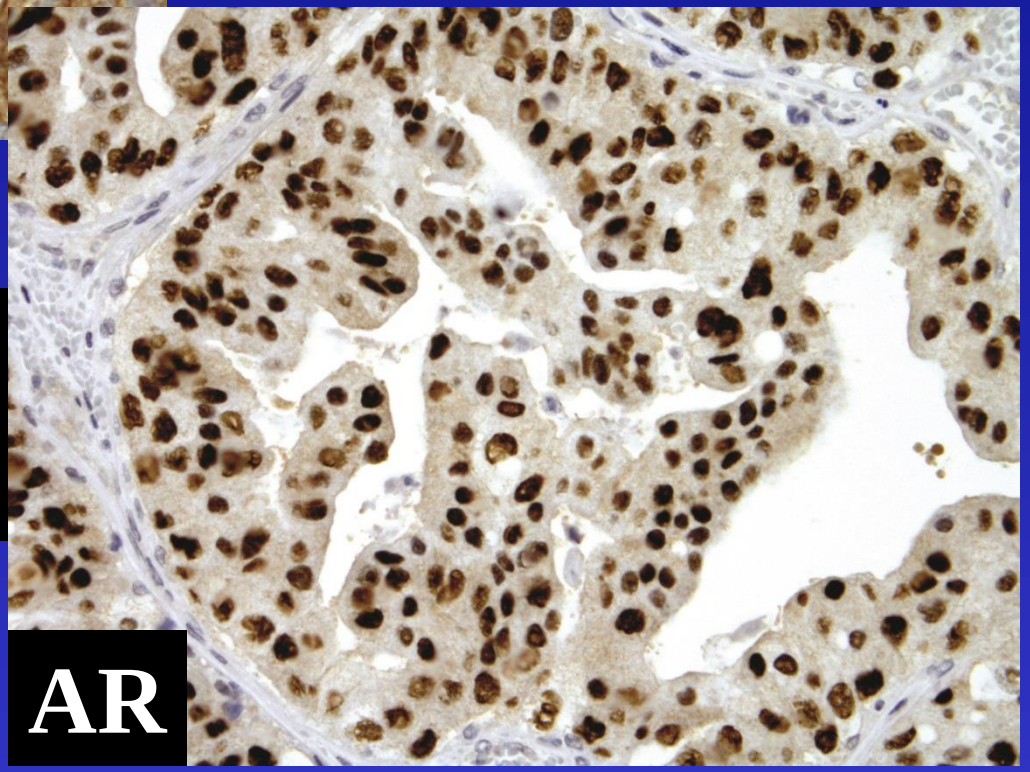




Acinic cell adenocarcinoma

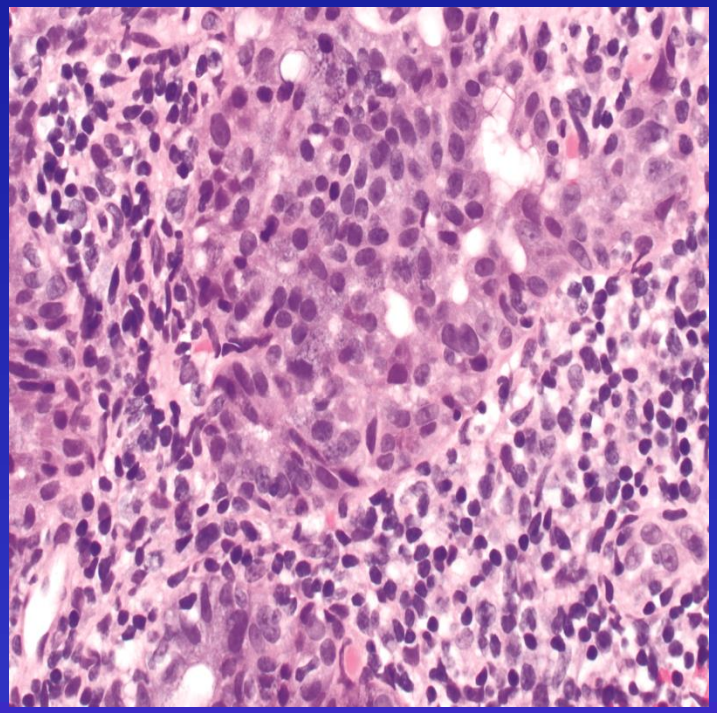
DOG1

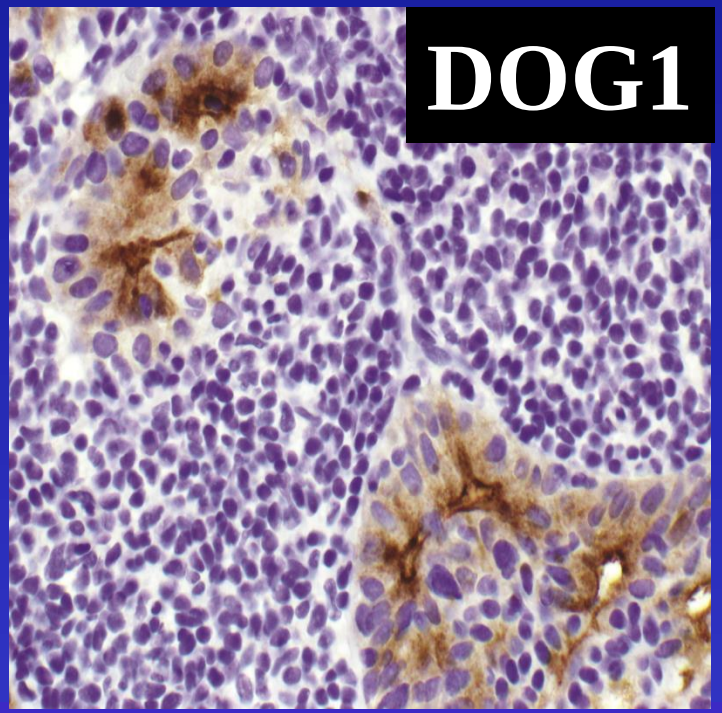
Salivary duct carcinoma

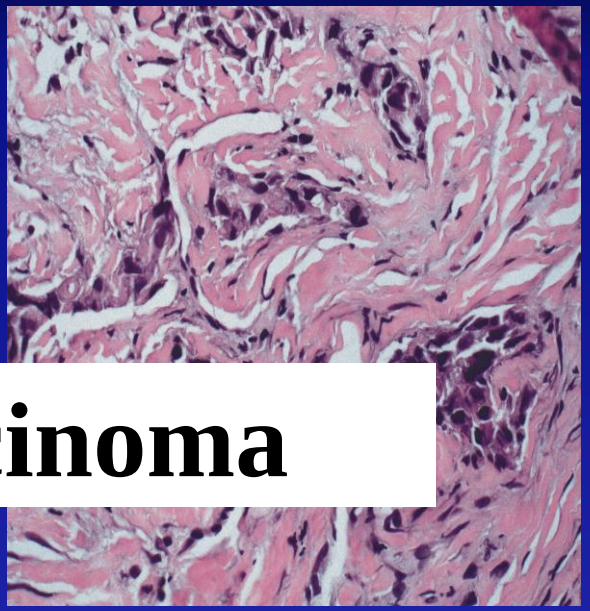


AR

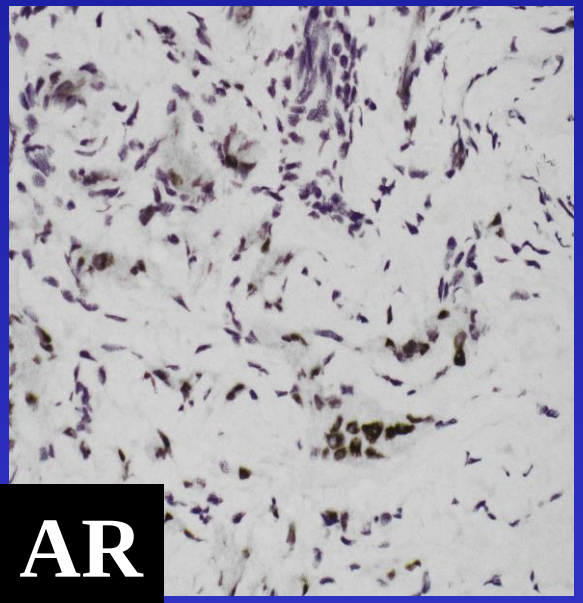
Acinic Cell Adenocarcinoma







c/w Salivary Duct Carcinoma



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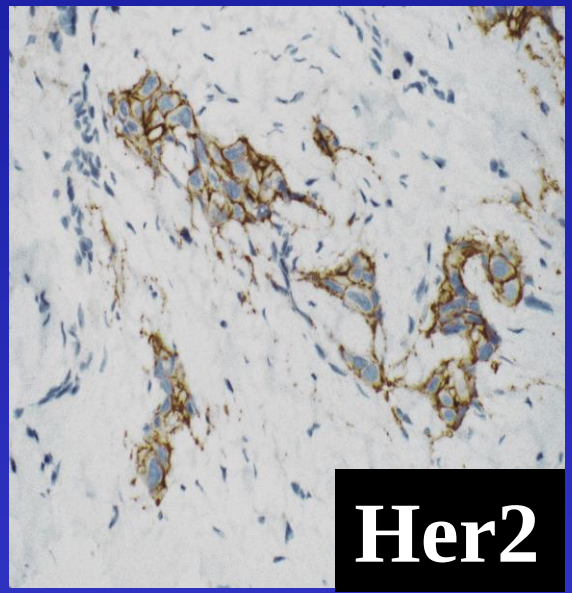
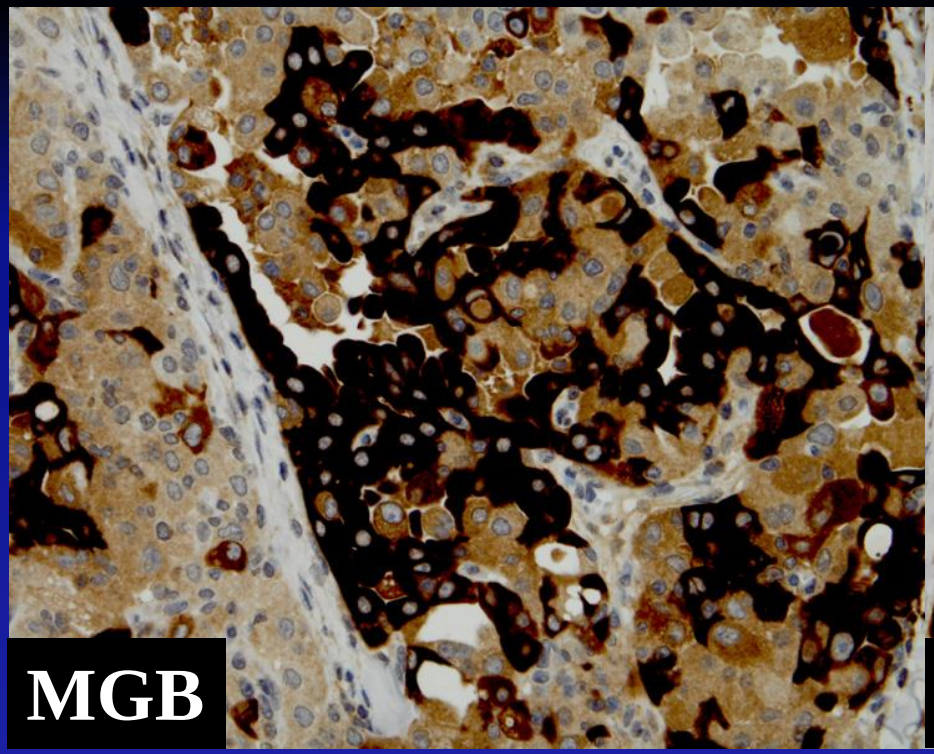
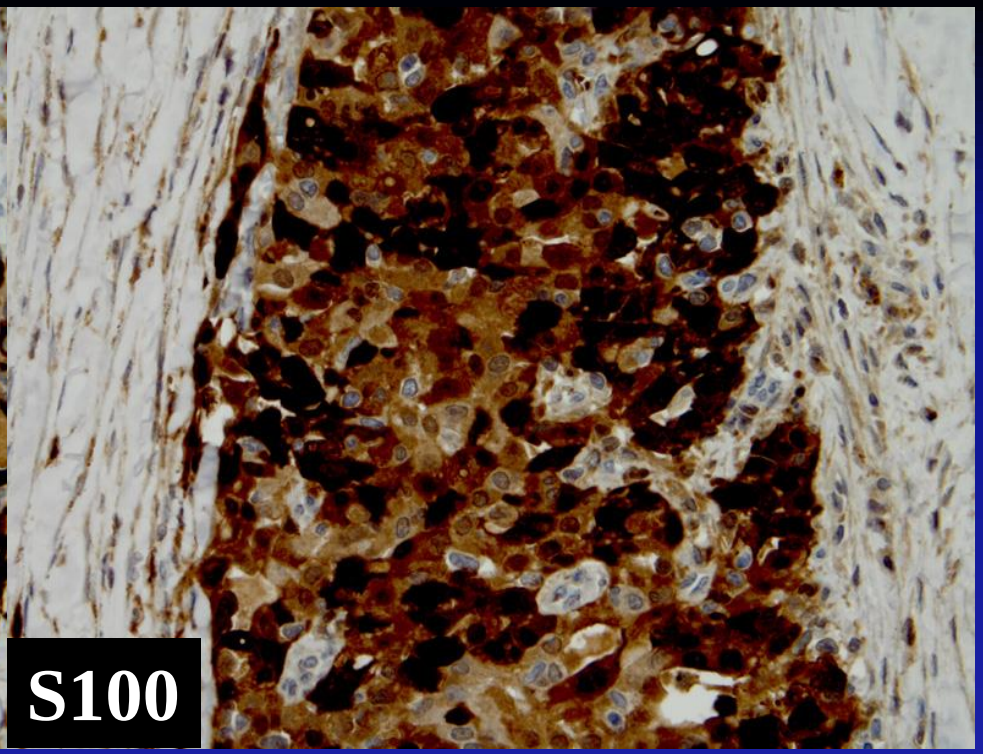


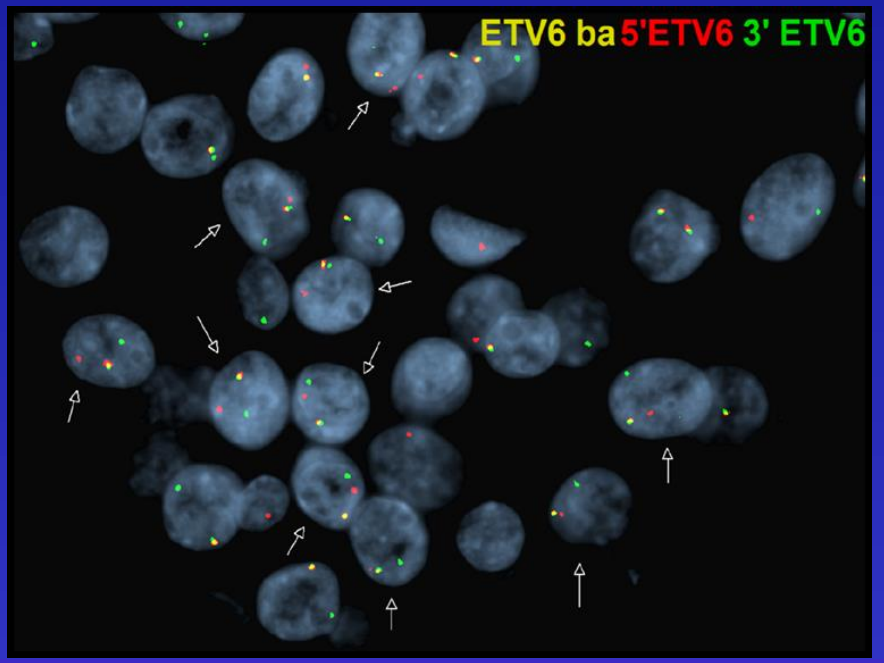
Her2





- **Recurrent t(12;15)(p13;q25) translocation - ETV6-NTRK3 gene fusion**

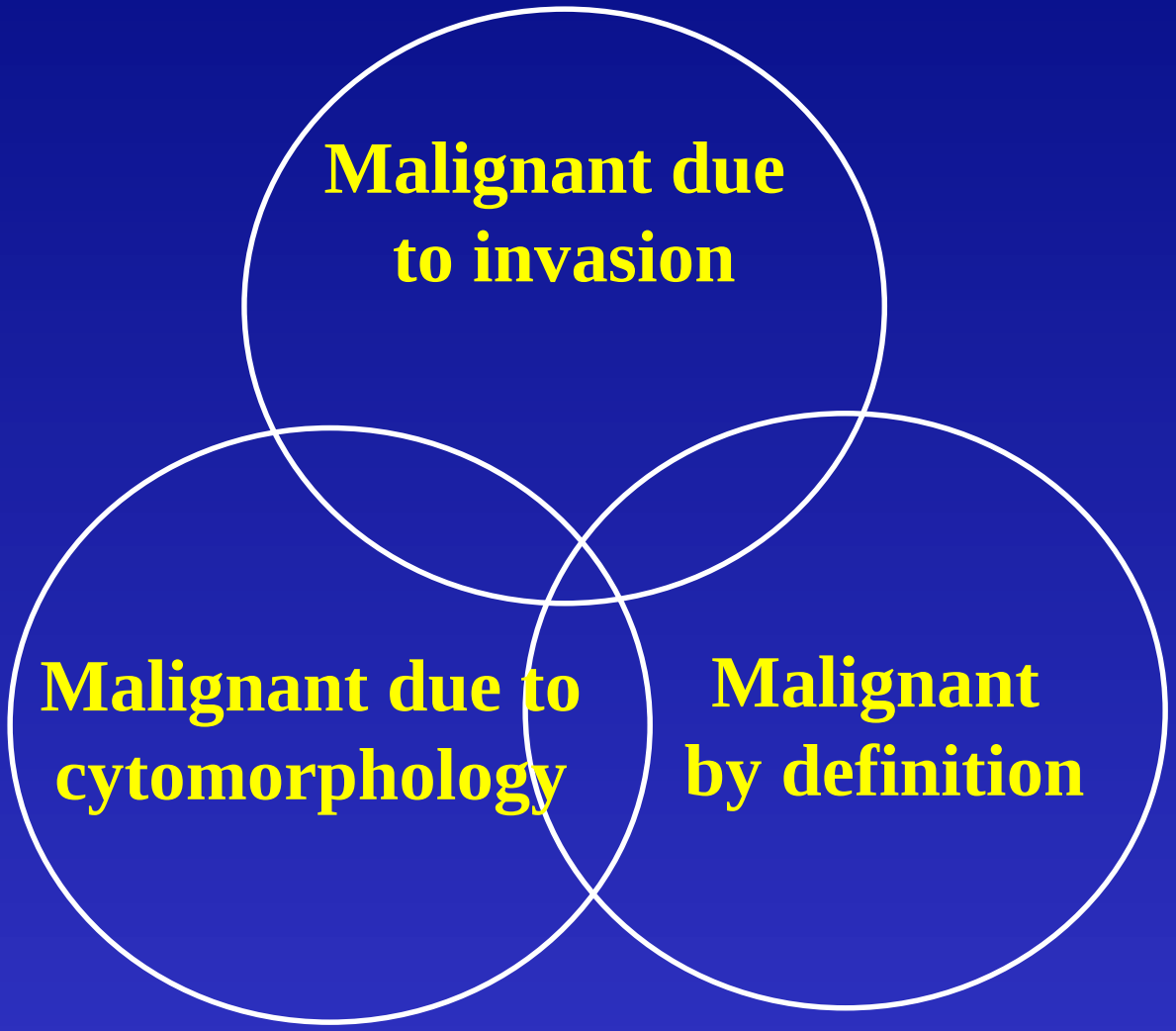
MASC



Chromosomal Translocation in Salivary Gland Neoplasms

Tumor Type	Gene Fusion
• Pleomorphic adenoma	• *PLAG1; HMGA2*
• Mucoepidermoid carcinoma	• *CRTC1-MAML2*
• Adenoid cystic carcinoma	• *MYB-NFIB*
• Mammary Analogue Secretory Carcinoma	• *ETV6-NTKR3*
• Hyalinizing clear cell carcinoma; clear cell myoepithelial carcinoma	• *EWSR1-ATF1*
• PLGA; CAMSG	• *PRKD* family
• Acinic cell adenocarcinoma	• *HTN3-MSANTD3*
• Intraductal carcinoma	• *NCOA4-RET*

Malignant Diagnostic Categories



Features of Benign & Malignant Minor Salivary Gland Neoplasms

- **Encapsulation and circumscription:**
  - **All minor gland neoplasms are unencapsulated**
    - **Specific tumor-type defined by cytomorphology +/- growth pattern**
    - **Presence or absence of invasion: neurotropism, LVI, salivary gland parenchyma, soft tissue, bone**

Shared Features between Benign and Low-Grade Malignant Salivary Gland Neoplasms

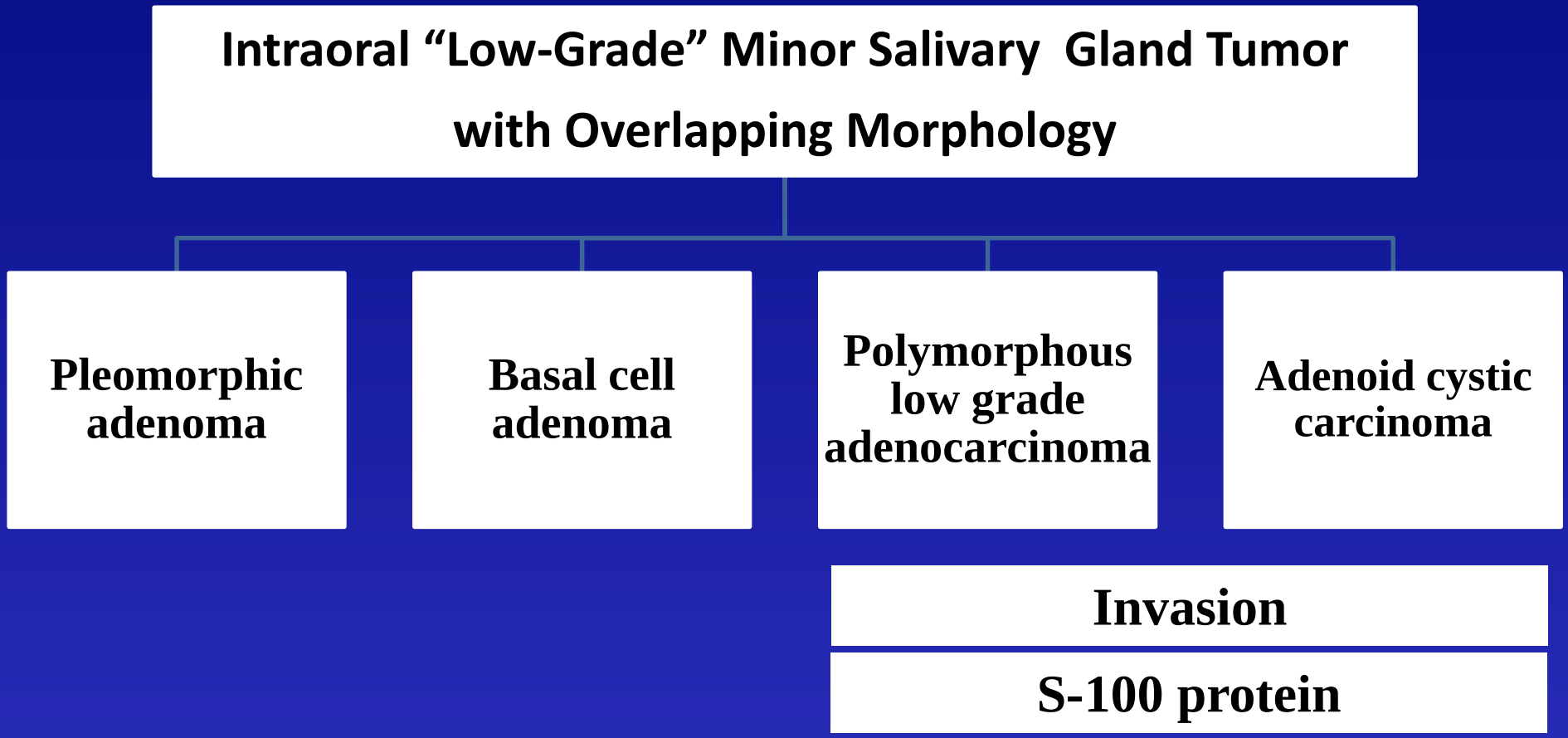
- **Growth patterns:**
  - **ALL salivary gland neoplasms are polymorphic**
- **Cytomorphology:**
  - **Isomorphic cell type(s) lacking significant nuclear pleomorphism, increased mitotic activity**
- **Dual cell composition:**
  - **Many neoplasms composed of epithelial & myoepithelial cells:**
    - **Light microscopy**
    - **IHC: cytokeratins, myoepithelial-related markers (p63, p40, calponin, S100 protein, others)**

Intraoral Minor Salivary Gland BX "Low-Grade" Neoplasms

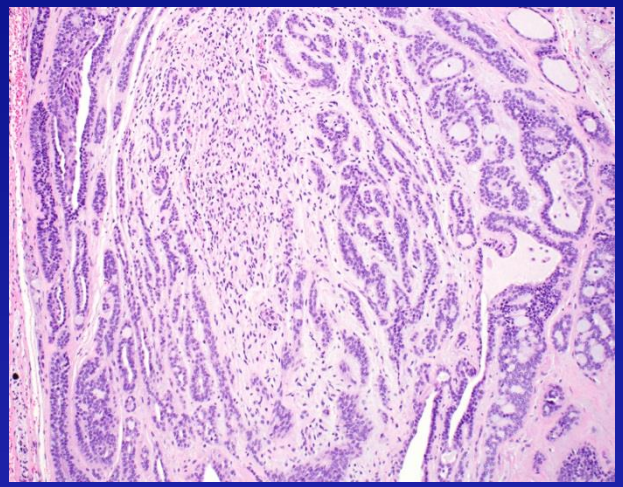
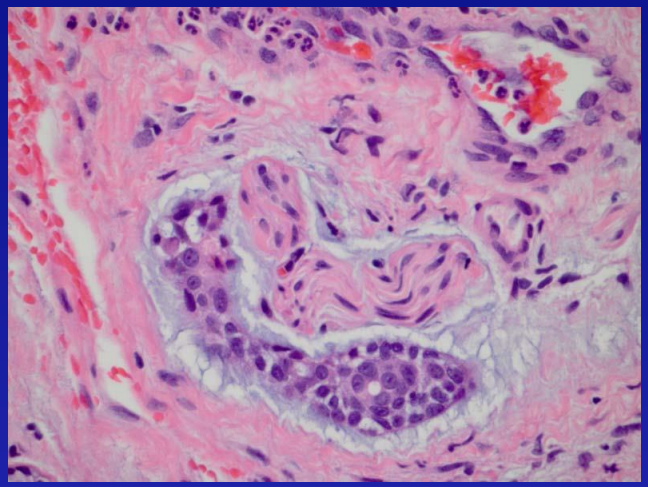
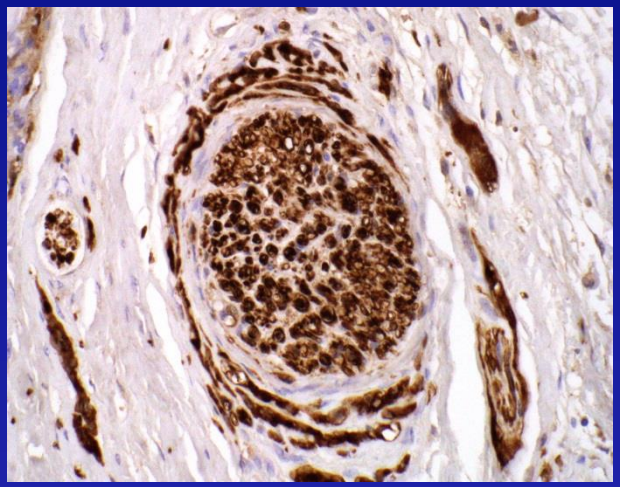
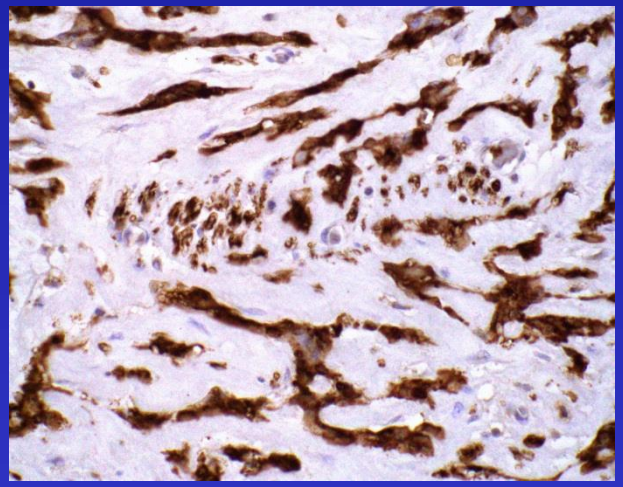
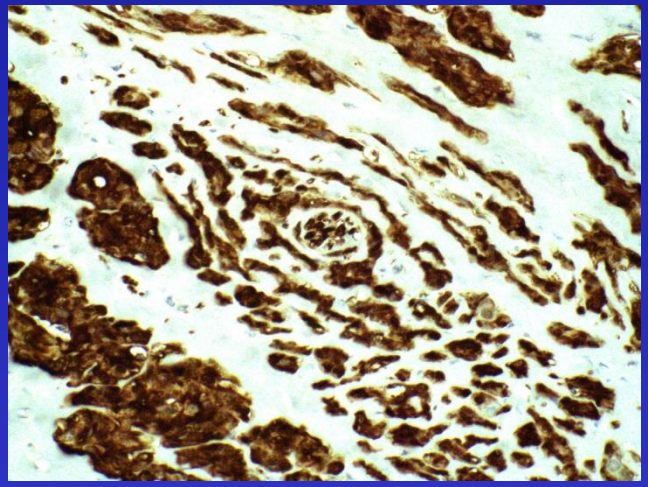
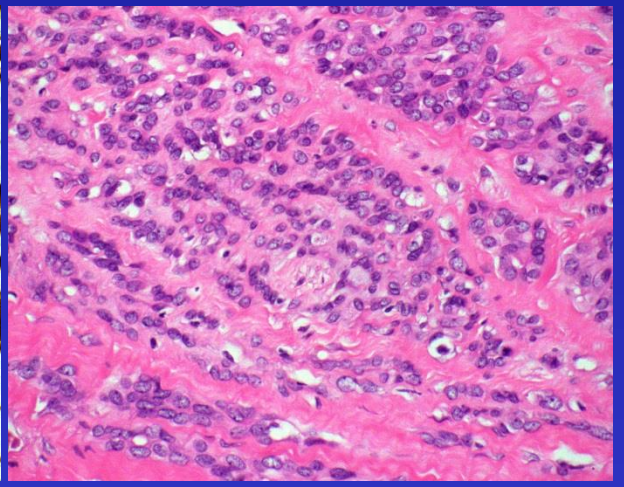
- In limited sampling especially those without surrounding tissue to evaluated for invasion, differentiation often cannot be achieved as these neoplasms share overlapping:
  - Growth patterns
  - Cytomorphology
  - Cell composition
  - Immunohistochemical reactivity

IHC in DDX of "Low-Grade" Salivary Gland Neoplasms

- Pairing p63 and p40 reported to assist in differentiating pleomorphic adenoma (PA) from polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (AdCC):
  - PA: p63+; p40+
  - Cellular PA: p63+; p40+ or p63- ; p40-
  - PLGA: p63+; p40-
  - AdCC: p63 +; p40+
- Proliferation indices (Ki67 or MIB1)
  - PA: <5%
  - PLGA: <5%
  - AdCC: increased up to 20%


Intraoral “Low-Grade” Minor Salivary Gland Tumor with Overlapping Morphology
Pleomorphic adenoma
Basal cell adenoma
Polymorphous low grade adenocarcinoma
Adenoid cystic carcinoma
Invasion
S-100 protein

PNI & S100 Protein

Salivary Gland Neoplasms
FNAB &/or Biopsy

- Excellent and efficient first line diagnostic modality in guiding management of salivary gland lesions/neoplasms
- Differentiate nonneoplastic from neoplastic salivary gland lesions
- Diagnose benign neoplasms (pleomorphic adenoma, Warthin tumor, others)
- Differentiate low- and high-grade carcinomas

Low- & Intermediate-Grade Salivary Gland Carcinomas Treatment

- **Wide local excision:**
  - **Tumor free-margins**
  - **Same treatment for benign salivary gland neoplasms**
- **Neck Dissection:**
  - **Not indicated unless there is clinical evidence of neck disease**
- **Postoperative Radiation**
  - **Not indicated**
  - **Exception for adenoid cystic carcinoma**

Low-Grade Salivary Gland Carcinomas That May Present with Neck Disease

- Any may be associated with nodal metastasis at presentation but more common in association with:
  - Cribriform Adenocarcinoma of Salivary Glands (CASG)
  - (Hyalinizing) Clear Cell Carcinoma
- May present with nodal disease usually with clinically apparent lesion (e.g., oral cavity, other)
- When diagnosing these cancers in particular recommend clinical evaluation for possible presence of neck disease

High-Grade Salivary Gland Carcinomas Treatment

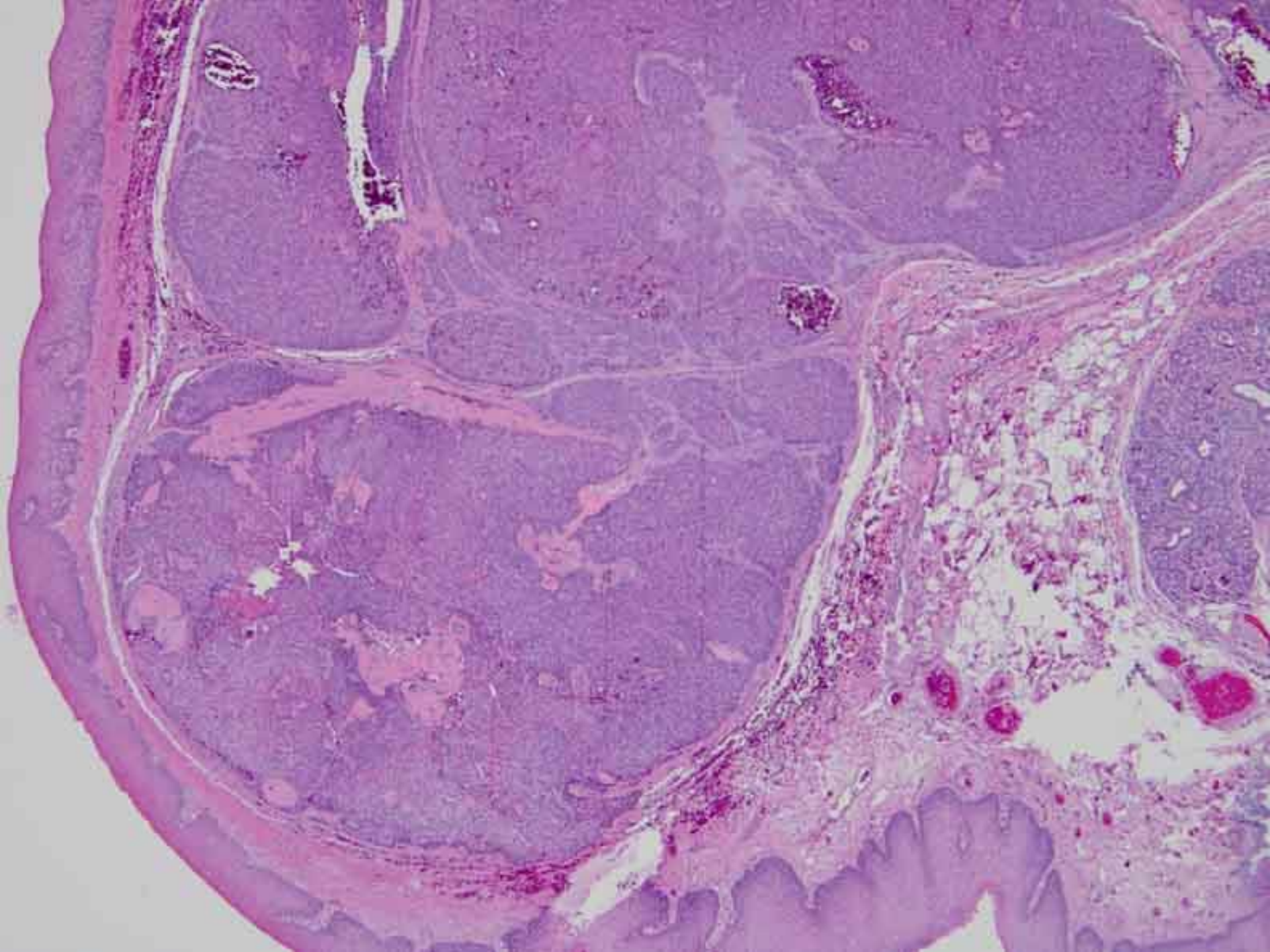
- Radical extirpation:
  - Wide block surgical excision:
    - May include facial nerve
    - Tumor free margins
- Neck Dissection:
  - Indicated even in cN0 neck
- Postoperative Radiation
  - Indicated

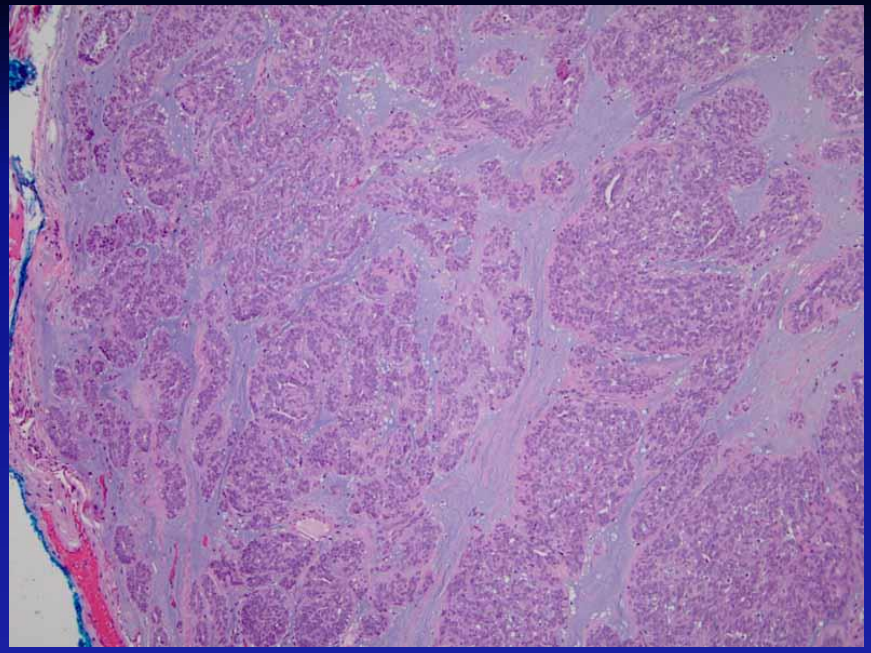
"Low-Grade" Salivary Gland Neoplasms FNAB &/or Biopsy

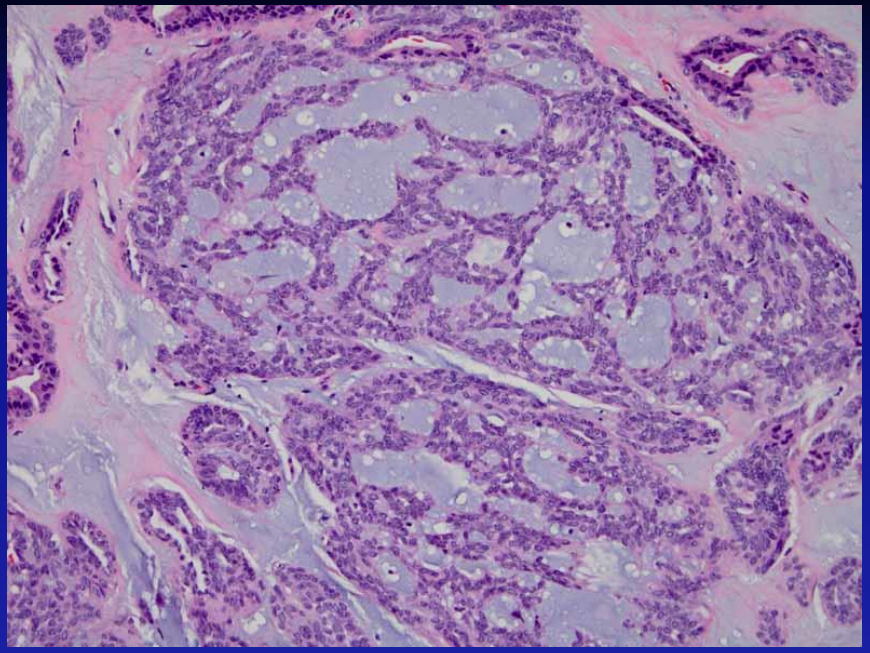
- Limitations of tissue may preclude a definitive diagnosis
- Presence of invasion diagnostic for carcinoma but may not allow for a specific diagnosis
- Absence of invasion does not exclude a diagnosis of carcinoma as evidence of invasion may be present in aspects of the neoplasm not sampled
- Use of "low-grade" likely engenders diagnostic consideration of a malignancy

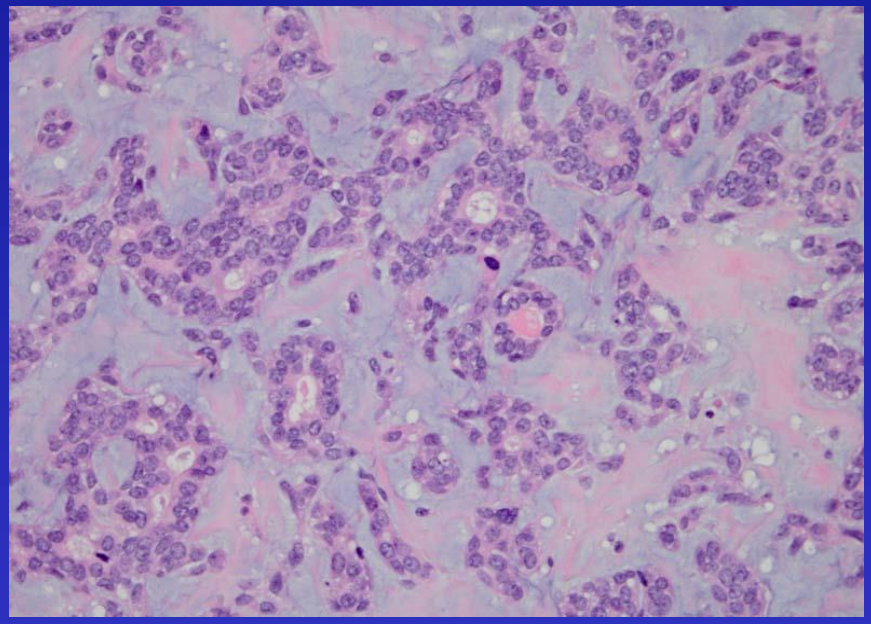
Diagnostic Terminology

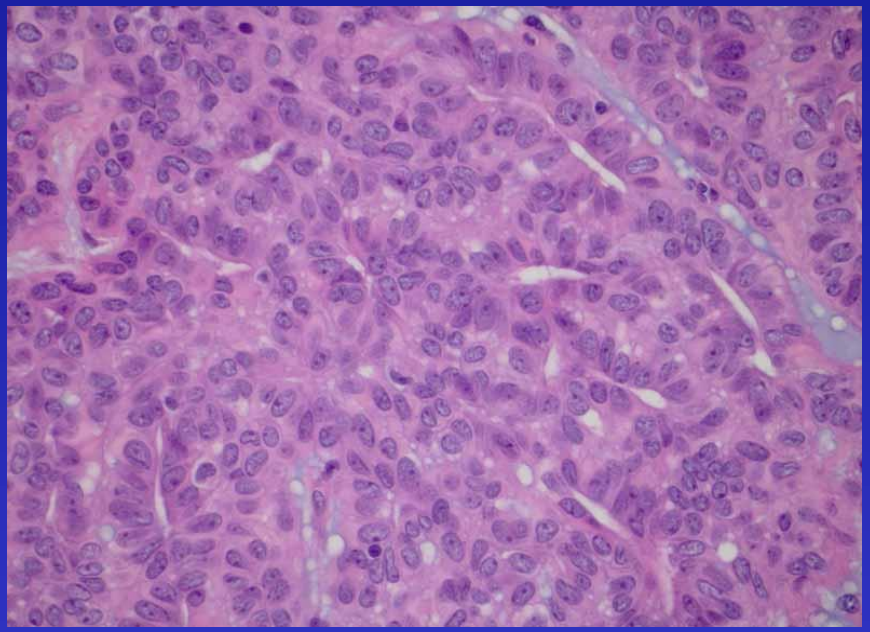
- Minor salivary gland neoplasm, not further specified
- Recommendation:
  - Additional sampling
  - Conservative but complete excision to include tumor free margins
  - Following complete excision a definitive diagnosis can be rendered

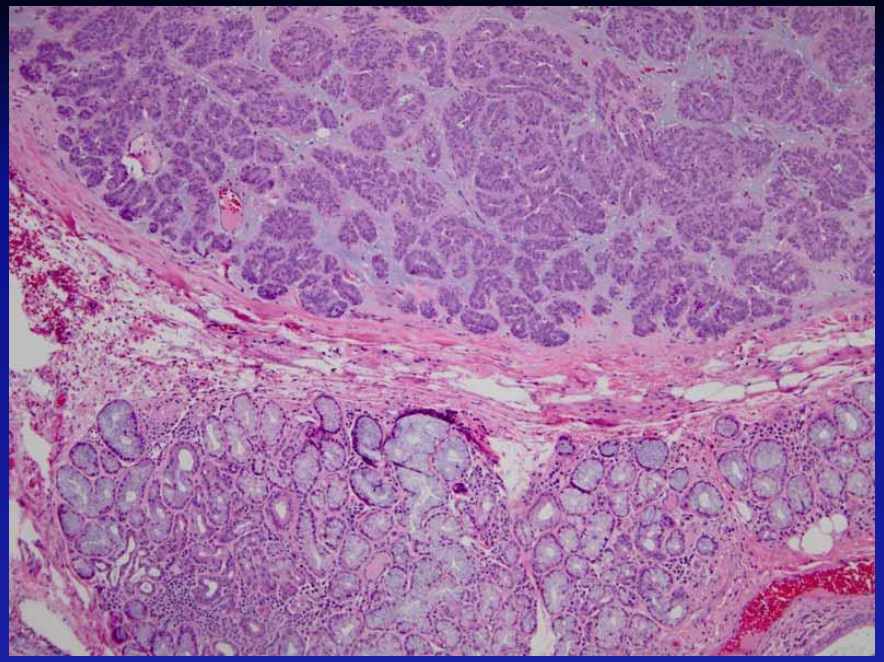


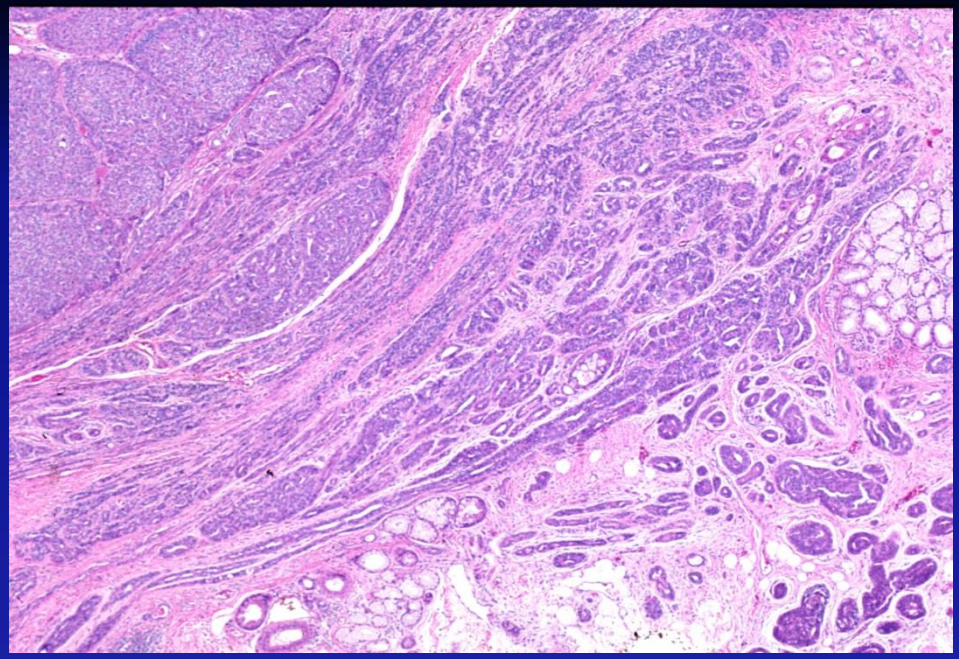


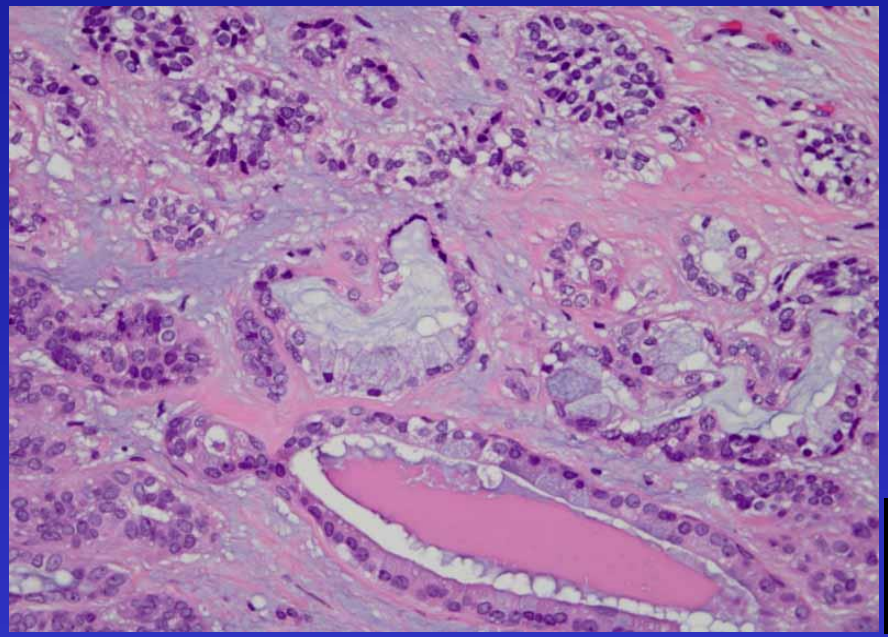


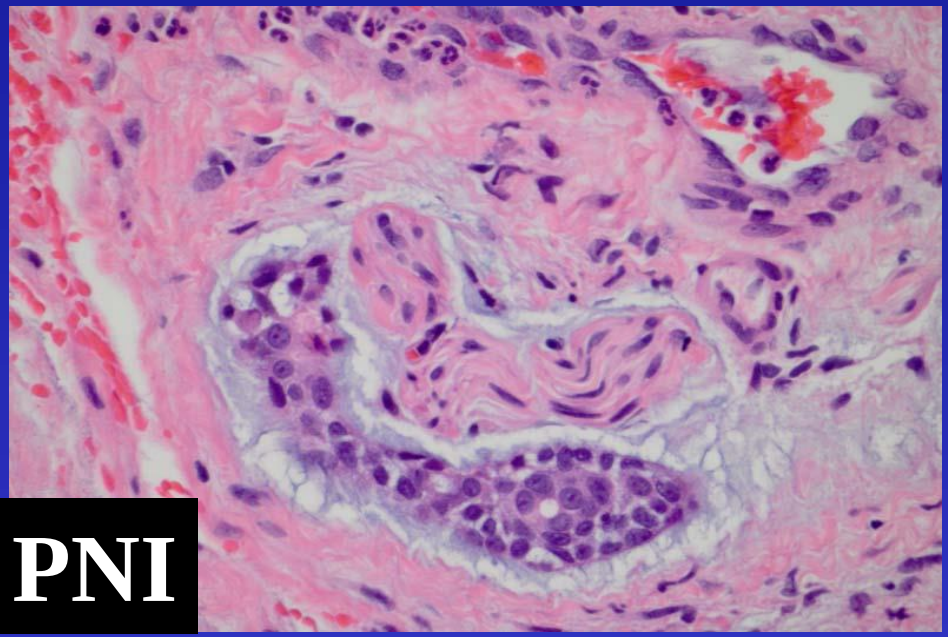










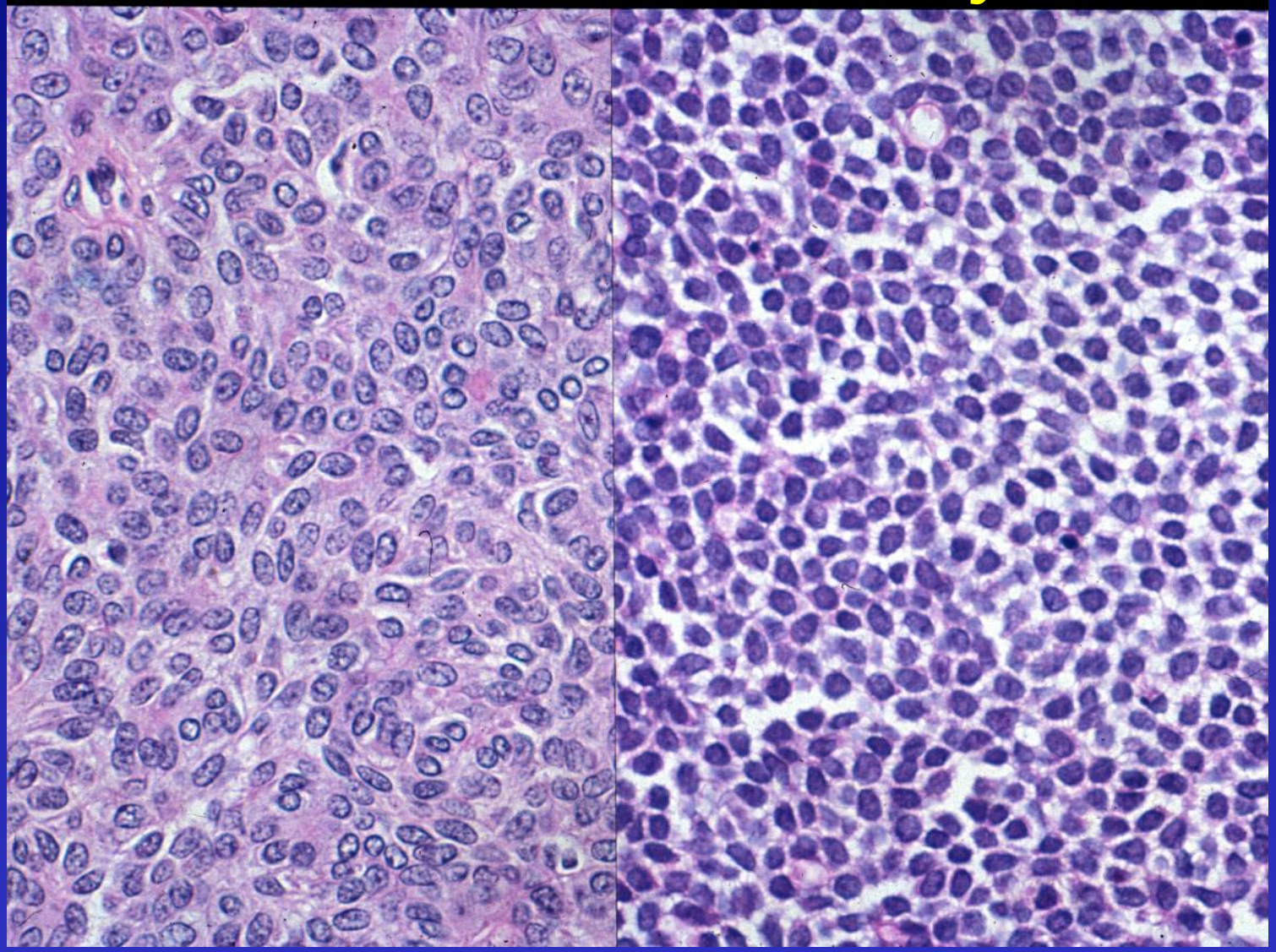


PNI

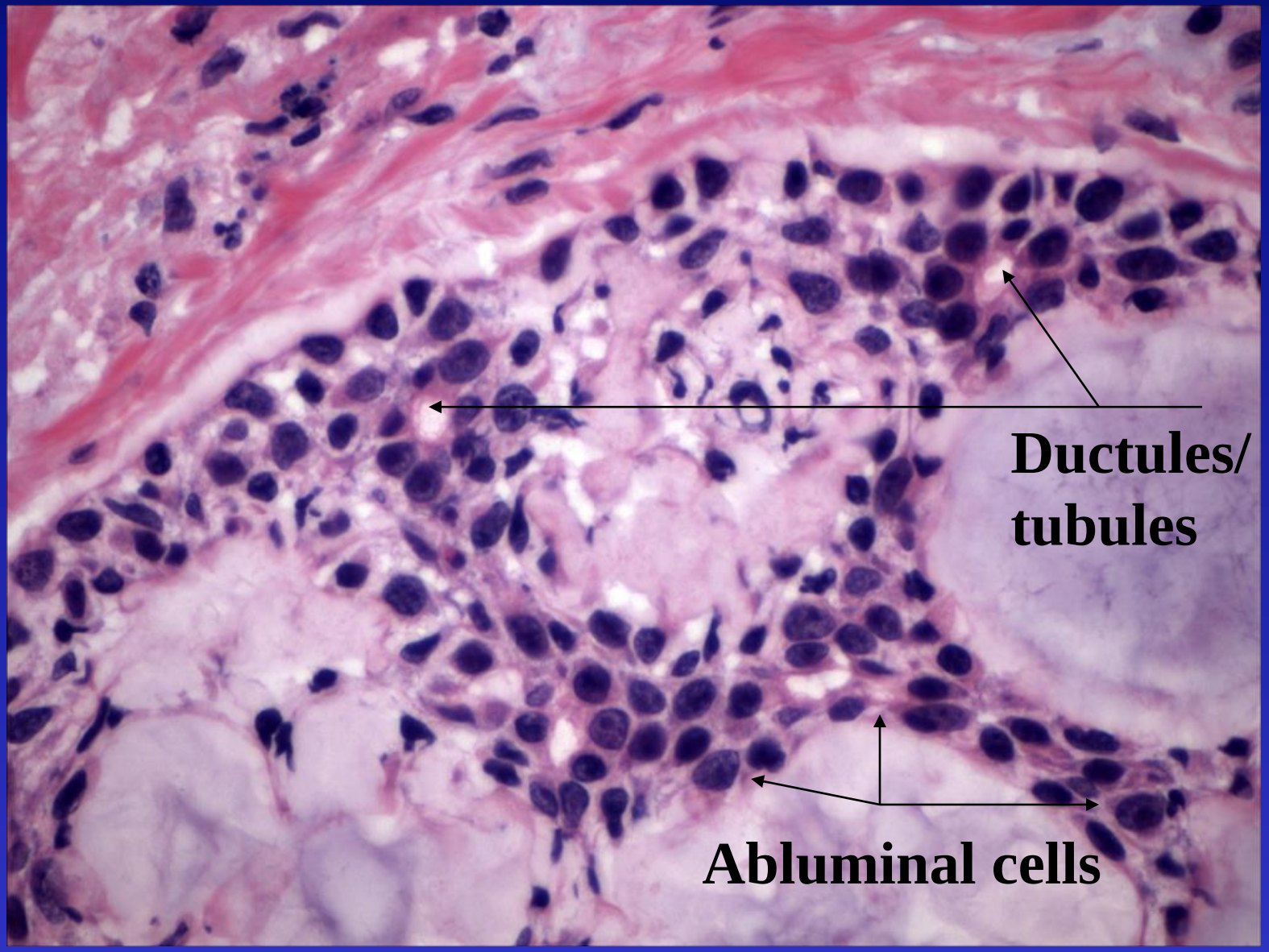
Case 2
Diagnosis

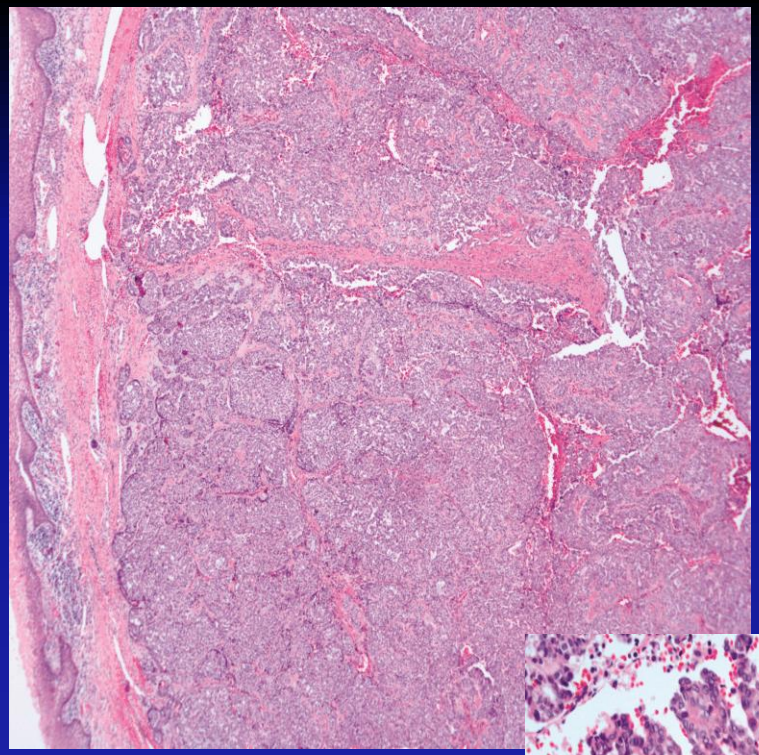
- **Polymorphous (low-grade) Adenocarcinoma of minor salivary glands**

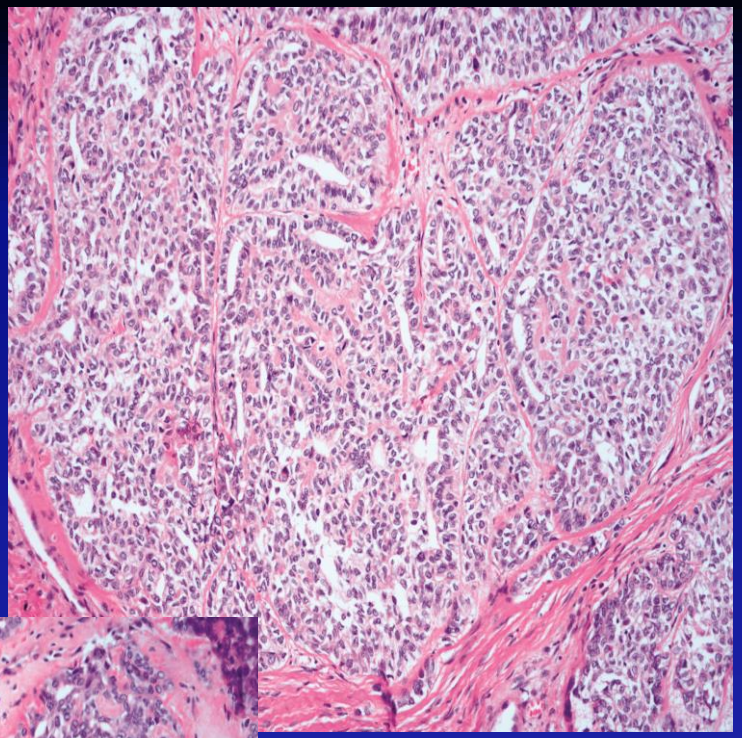
PLGA Adenoid Cystic Ca

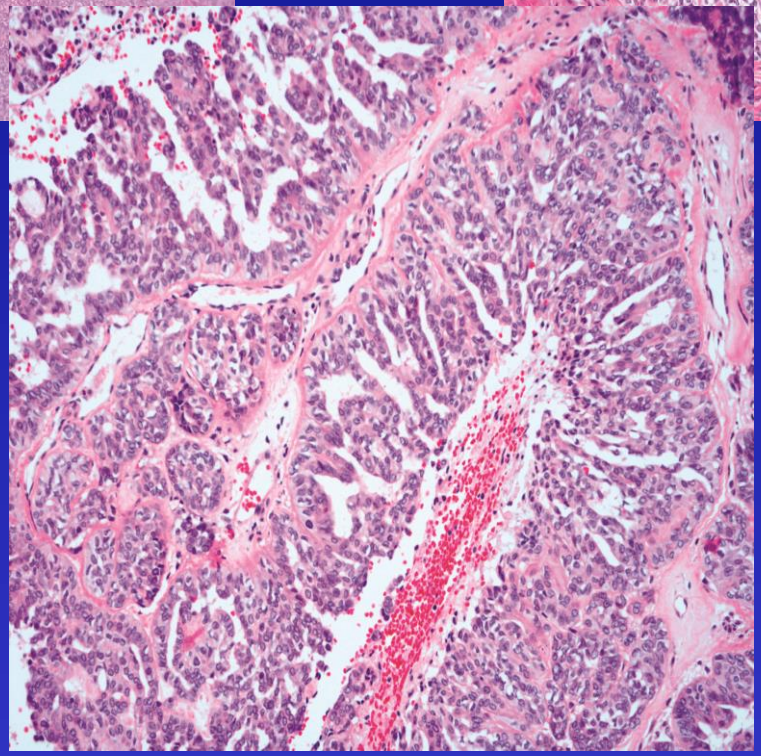


Adenoid Cystic Carcinoma



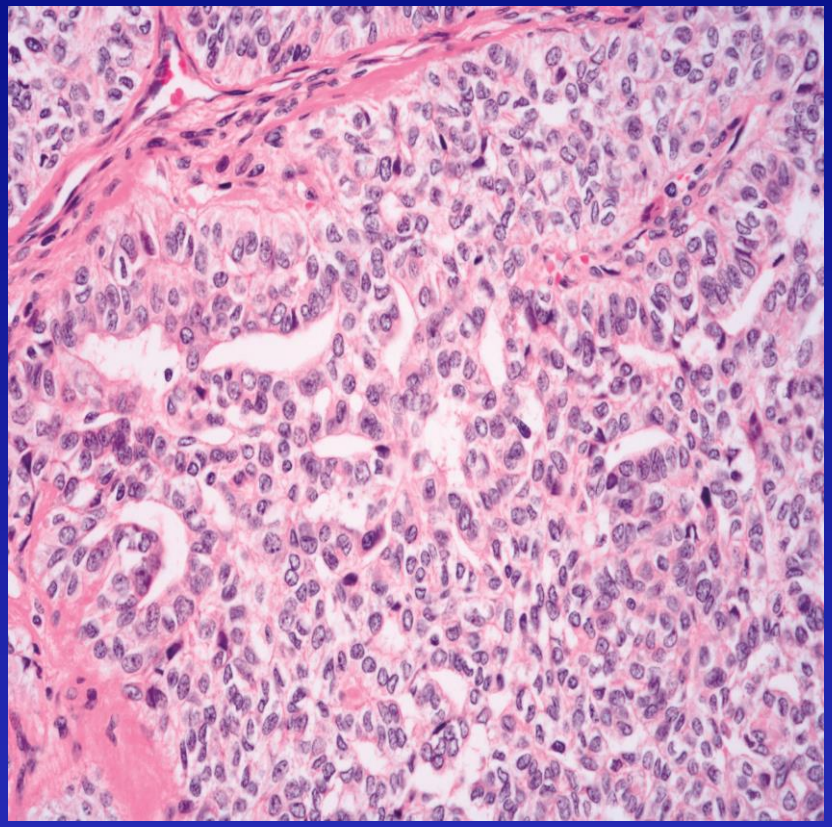


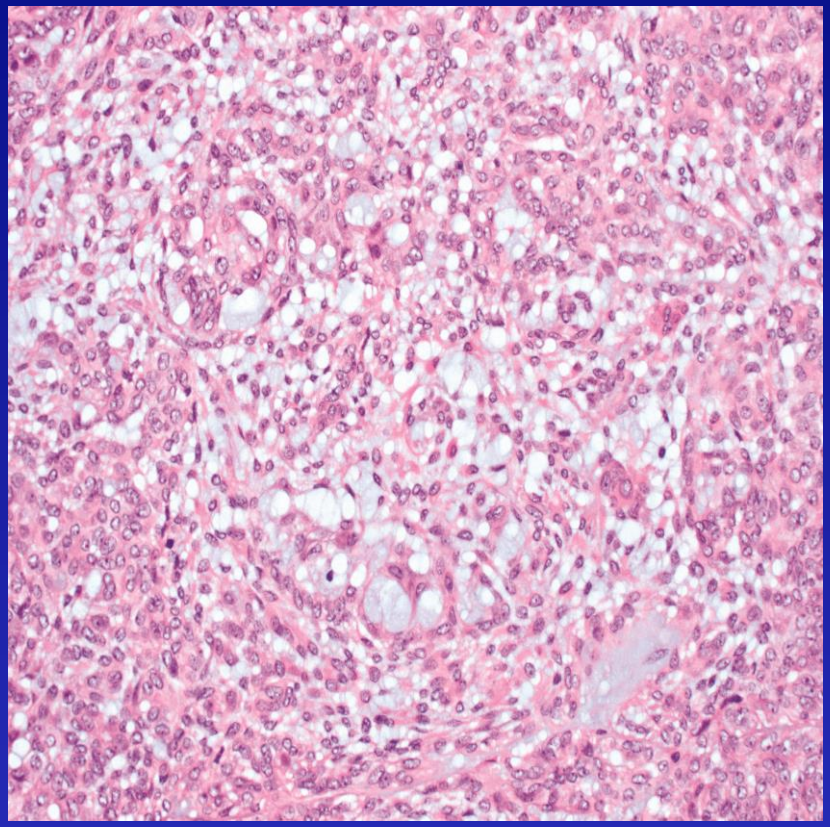




CASG

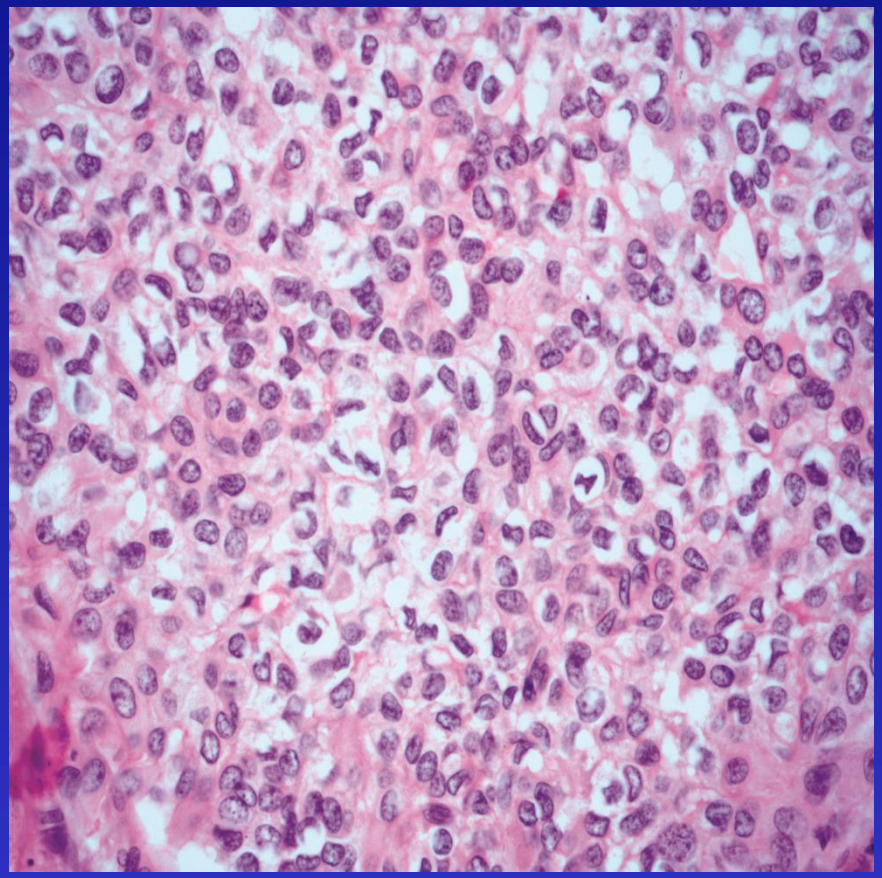
CASG



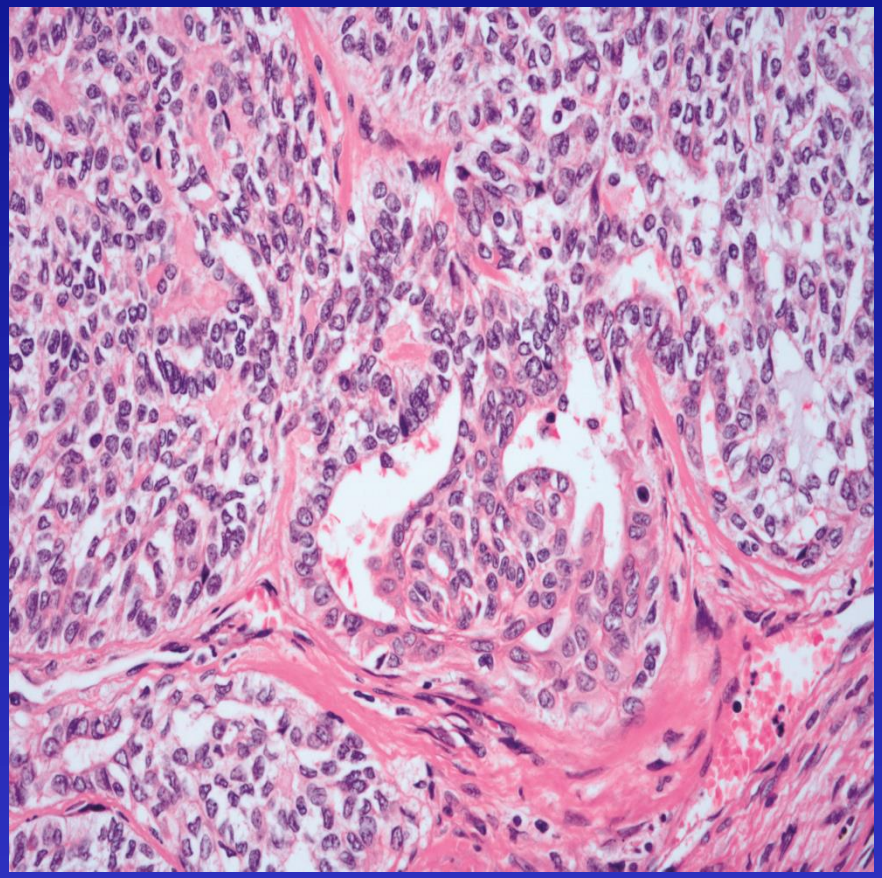


CAMSG

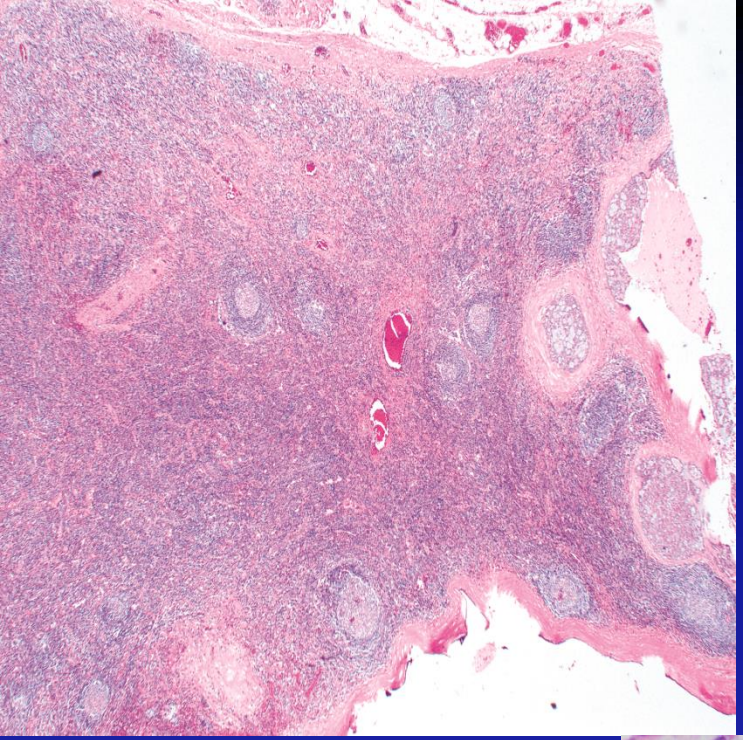
Nuclear features similar to PTC

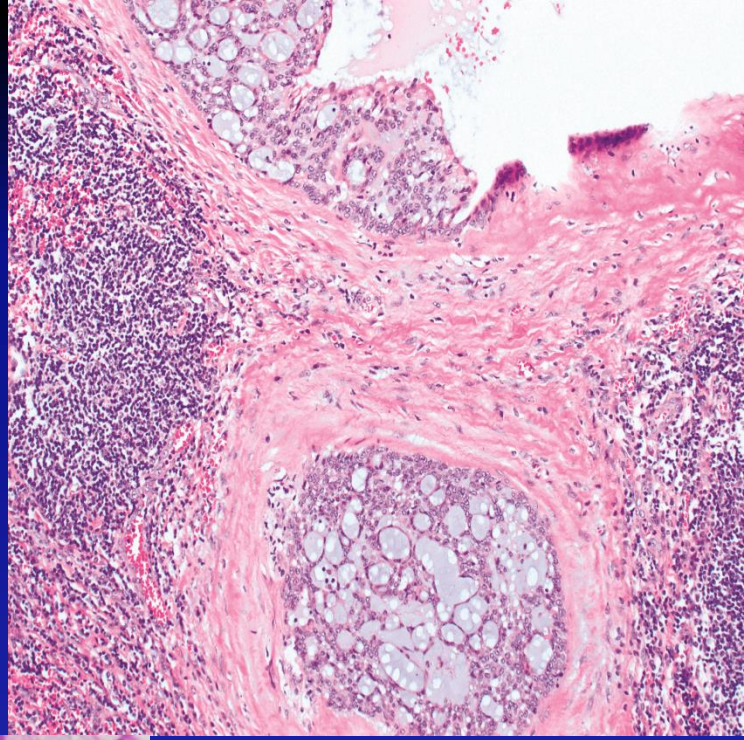


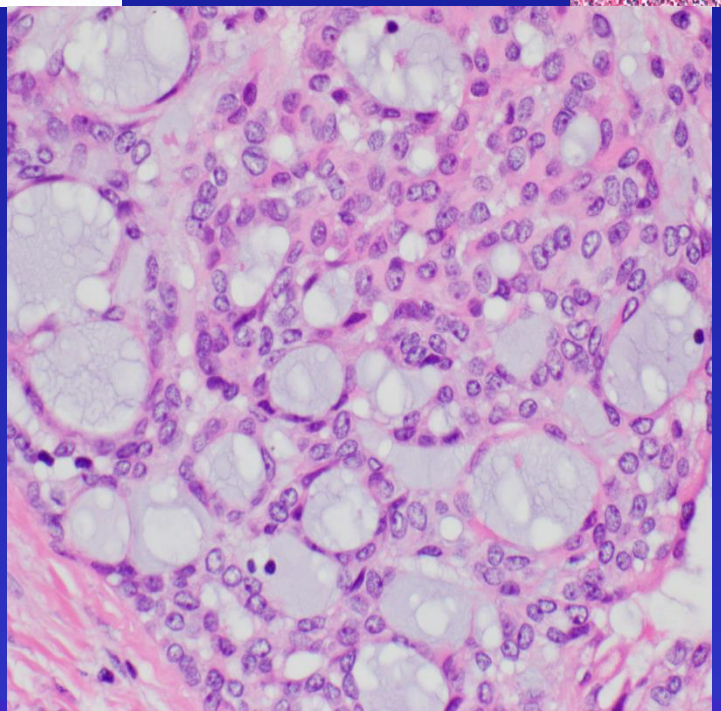
“Glomeruloid” body



CASG Nodal Metastasis







CASG
Genetic Profile

- Alterations in PRKD gene family
- Recurrent gene rearrangements in PRKD1, PRKD2, PRKD3
- Activating mutation of PRKD1 (p.Glu710ASP, Exon 15)
- PRKD1 and PRKD3 rearrangements found in clinically aggressive tumors

CASG
Treatment and Prognosis

- Complete surgical resection to include tumor-free margins is indicated
- Regional (cervical) lymph node metastasis:
  - High frequency (65%) at presentation
  - Should necessitate neck dissection as part of initial treatment protocol
- Highly favorable prognosis:
  - majority of patients alive without disease or alive with recurrent disease over extended periods
  - prognosis does not appear to be altered by presence of nodal metastasis

Salivary Gland Neoplasms Summary

- Salivary gland lesions are diverse with overlapping clinical and pathologic features
- Diagnosis and DDX:
  - Cytomorphologic criteria supplemented by IHC & molecular pathology
- "Minor salivary gland neoplasm, not further specified" - complete excision to include tumor free margins

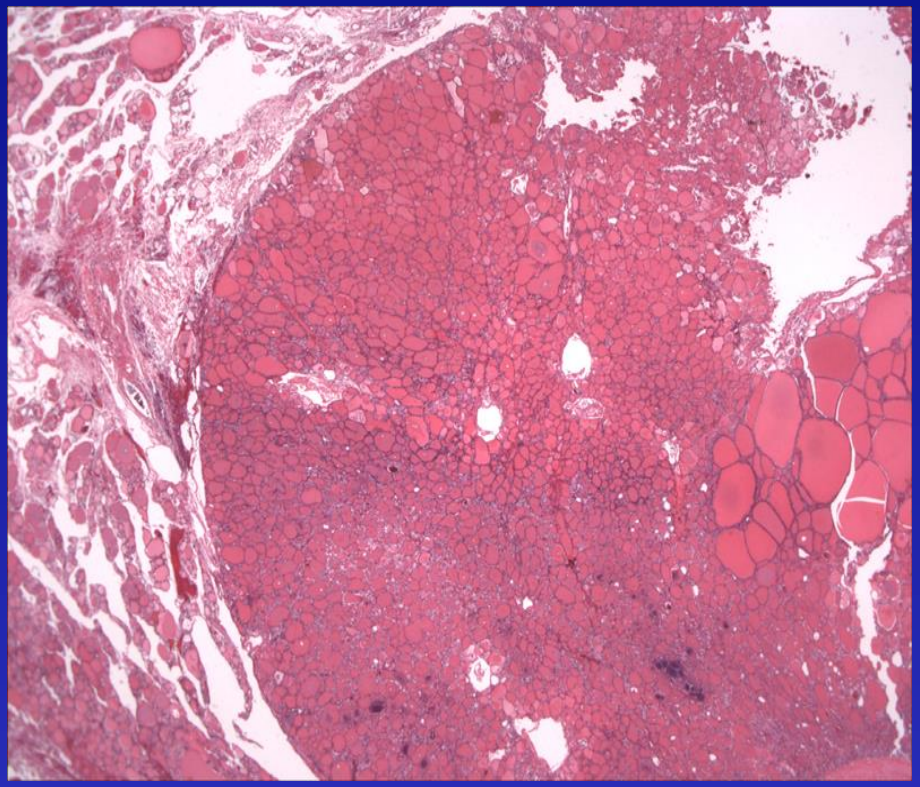
Salivary Gland Neoplasms Summary

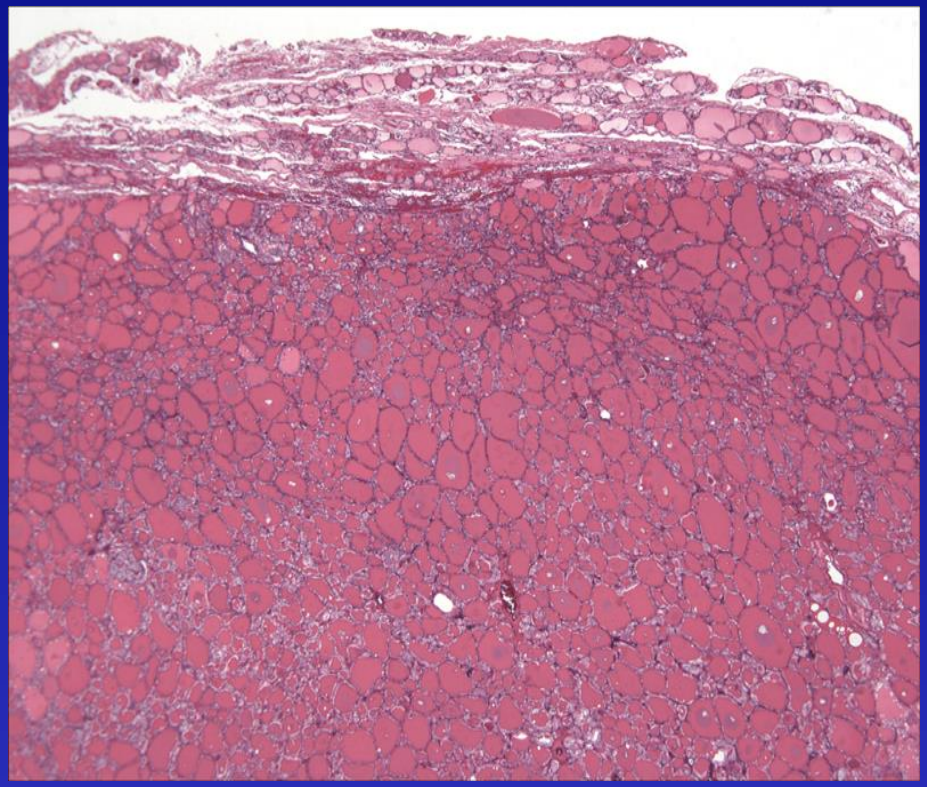
- **FNAB &/or Biopsy:**
  - **Excellent and efficient first line diagnostic modality in guiding management of salivary gland lesions/neoplasms**
  - **Differentiate nonneoplastic from neoplastic salivary gland lesions**
  - **Diagnose benign neoplasms (pleomorphic adenoma, Warthin tumor, others)**
  - **Differentiate low- and high-grade carcinomas**

Case 3 - Clinical History

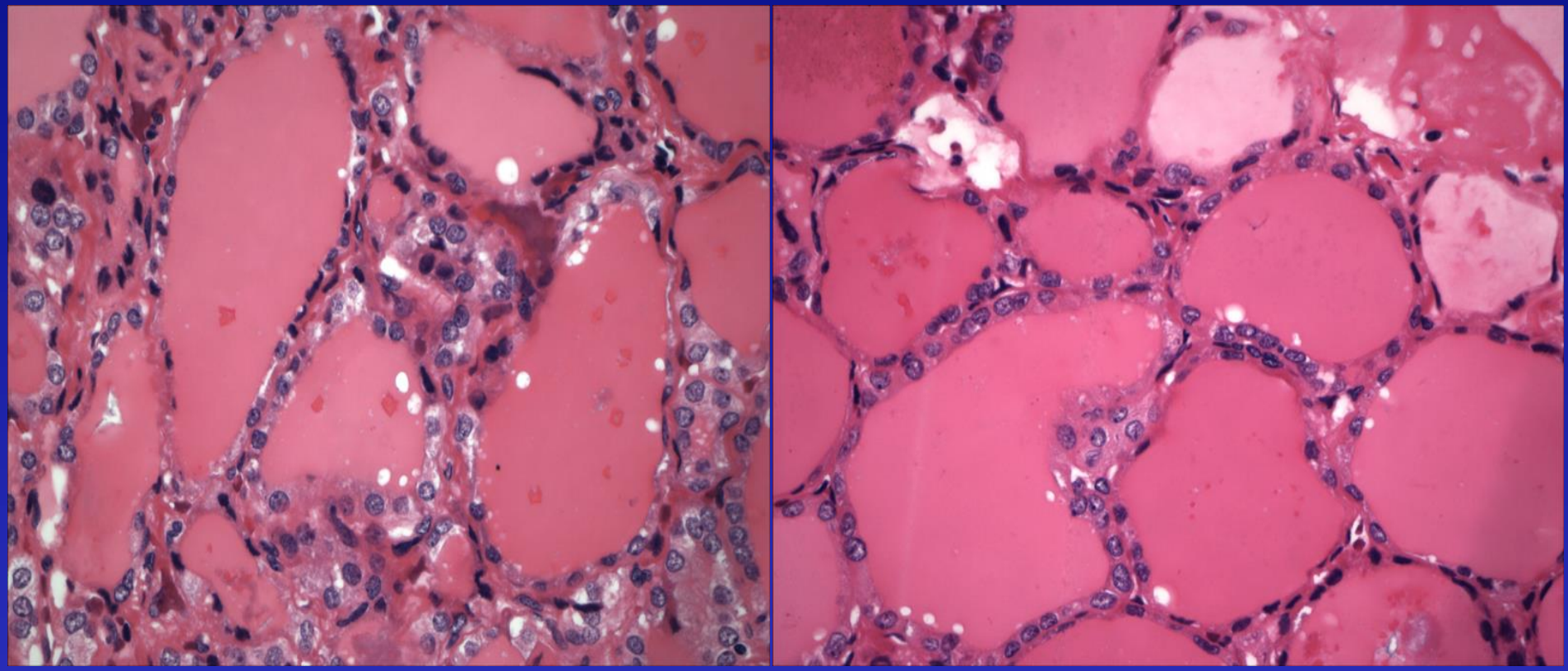
A 67 year old female presented with a right neck mass. Work-up revealed a "cold" nodule in the right lobe of the thyroid gland. A fine needle aspiration biopsy was performed with a diagnosis of suspicious for papillary thyroid carcinoma (Bethesda V) with the recommendation for surgical resection of the thyroid lobe with intraoperative evaluation. At the time of surgery, frozen section was performed with a diagnosis of "follicular epithelial lesion, defer to permanent section". A right thyroid lobectomy and isthmusectomy was performed. A well-circumscribed nodule measuring 2.1 cm in greatest dimension was identified in the right lobe of the thyroid gland

Case 3

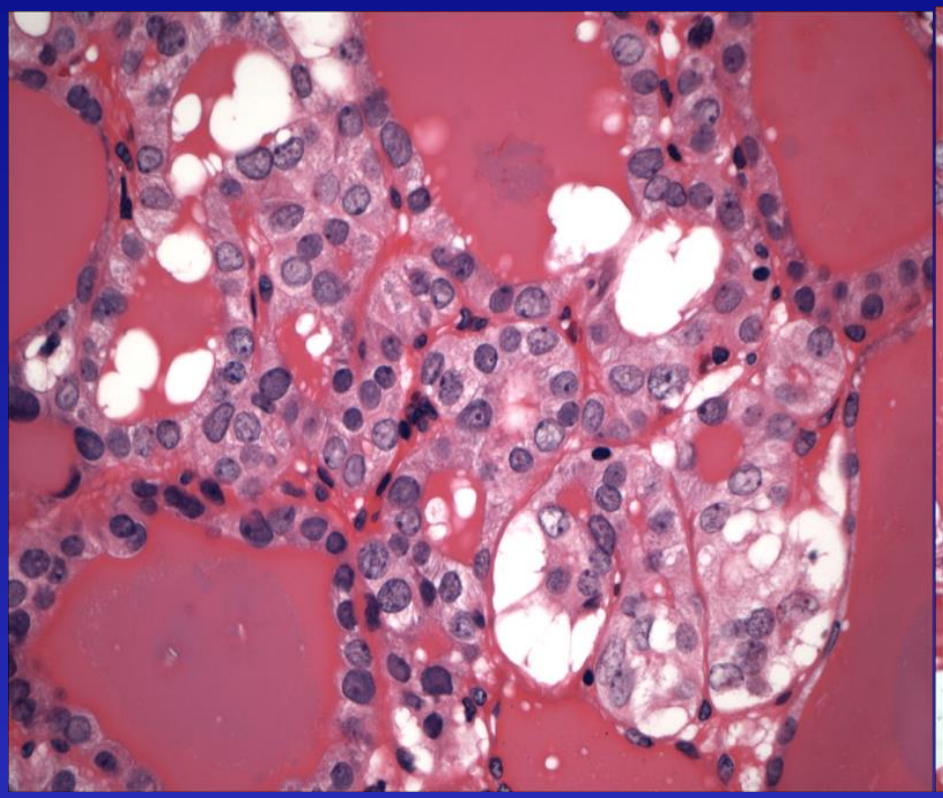


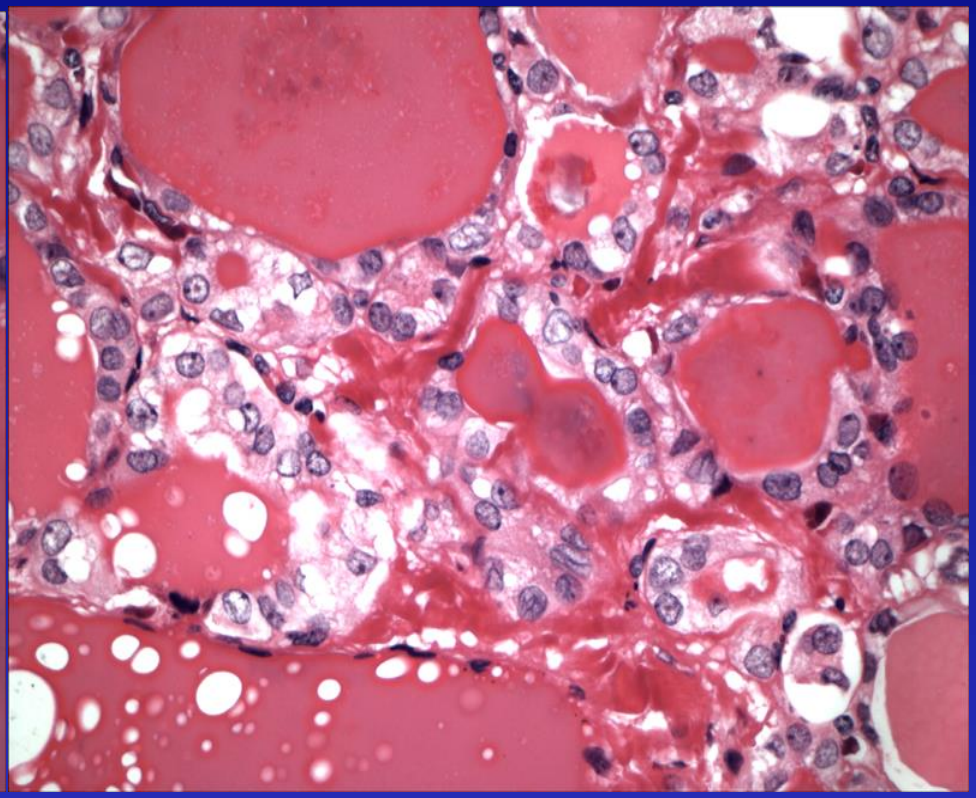


Case 3

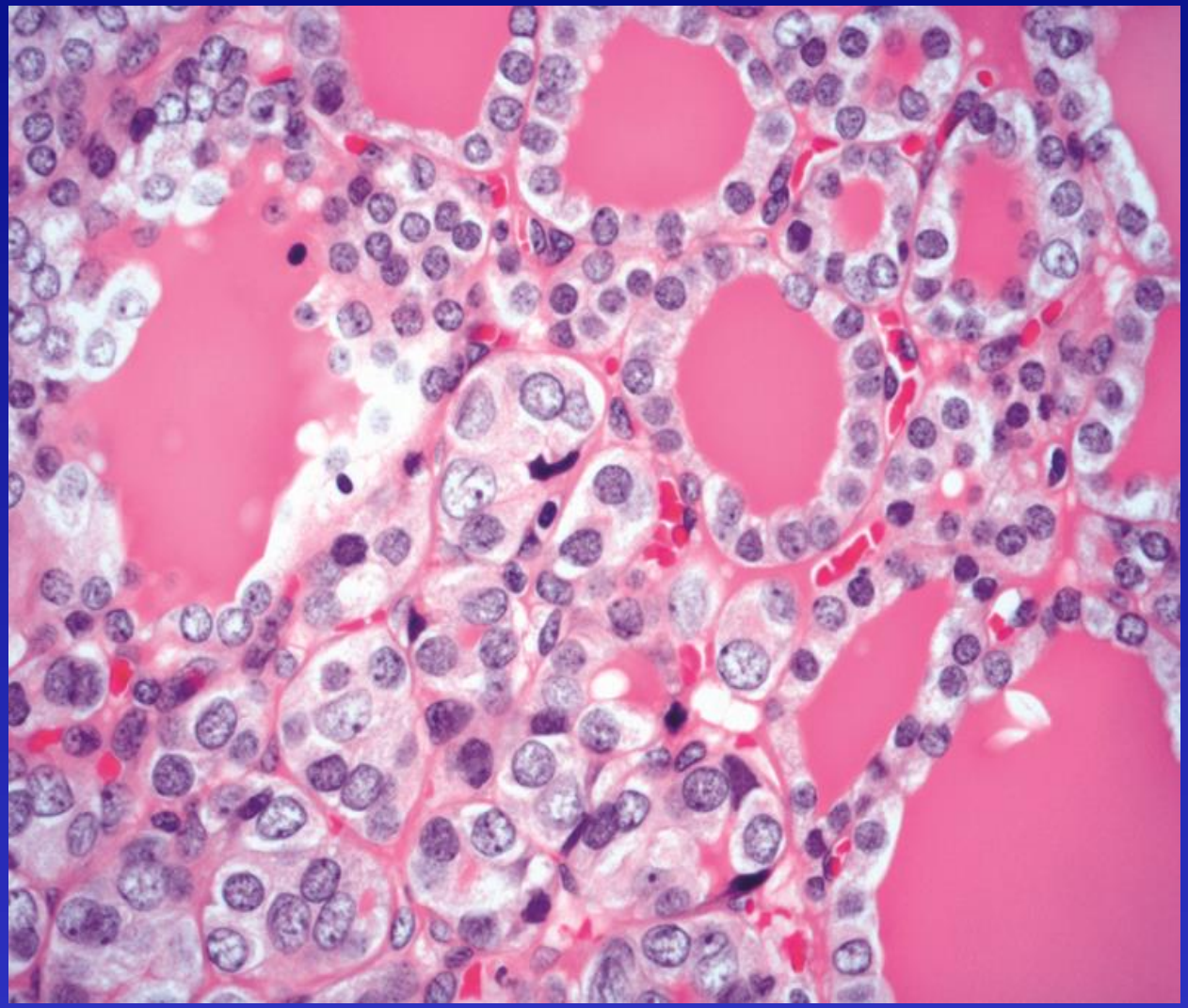


Case 3





Case 3



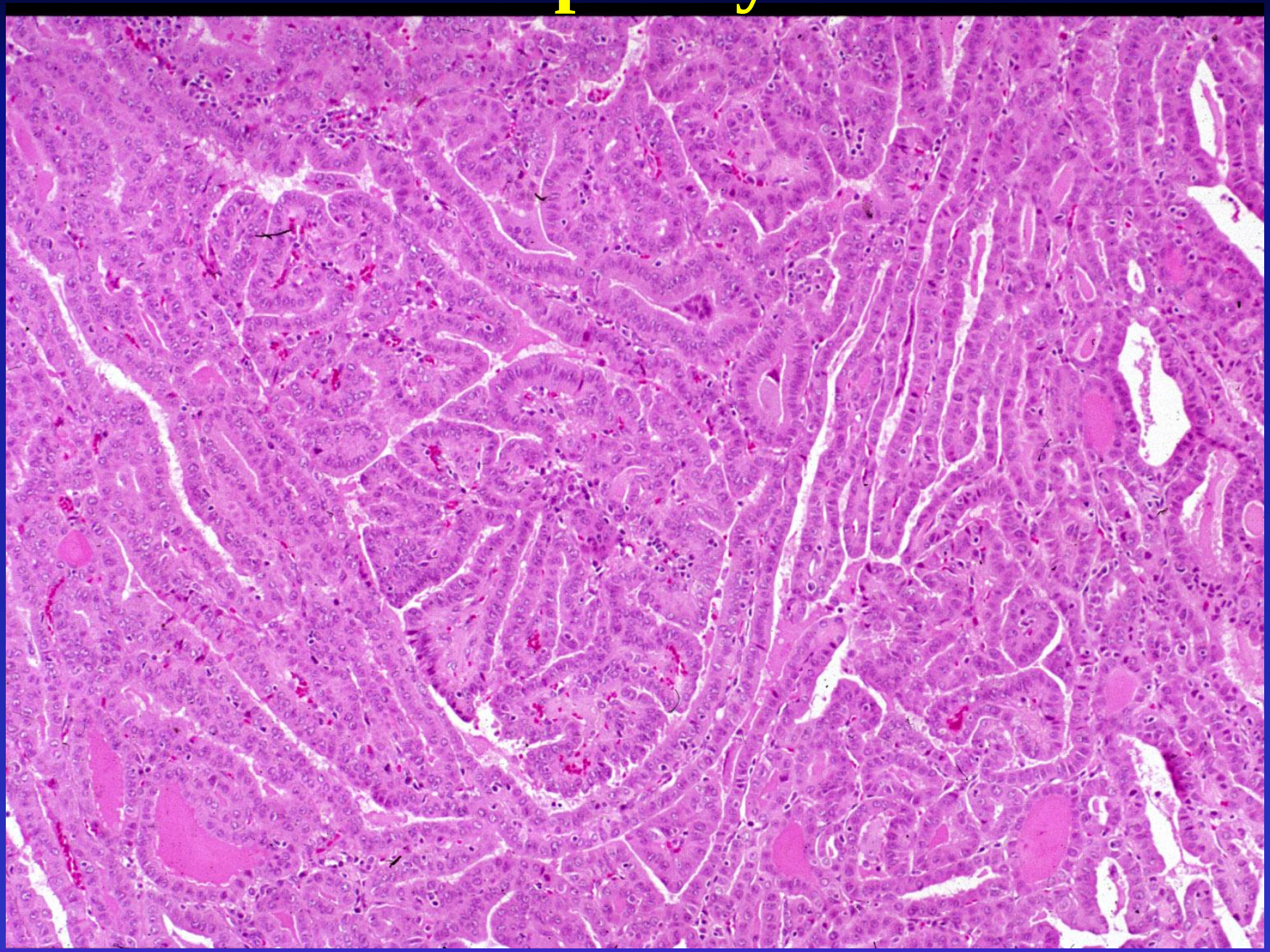
Case 3
Diagnosis ?

- Adenomatoid nodule
- Follicular adenoma
- Noninvasive follicular neoplasm with papillary-like features (NIFTP)
- Papillary thyroid carcinoma, classic variant
- Papillary thyroid carcinoma, follicular variant

Papillary Thyroid Carcinoma Definition

- **Malignant thyroid follicular epithelial cell neoplasm characterized by distinctive nuclear features**

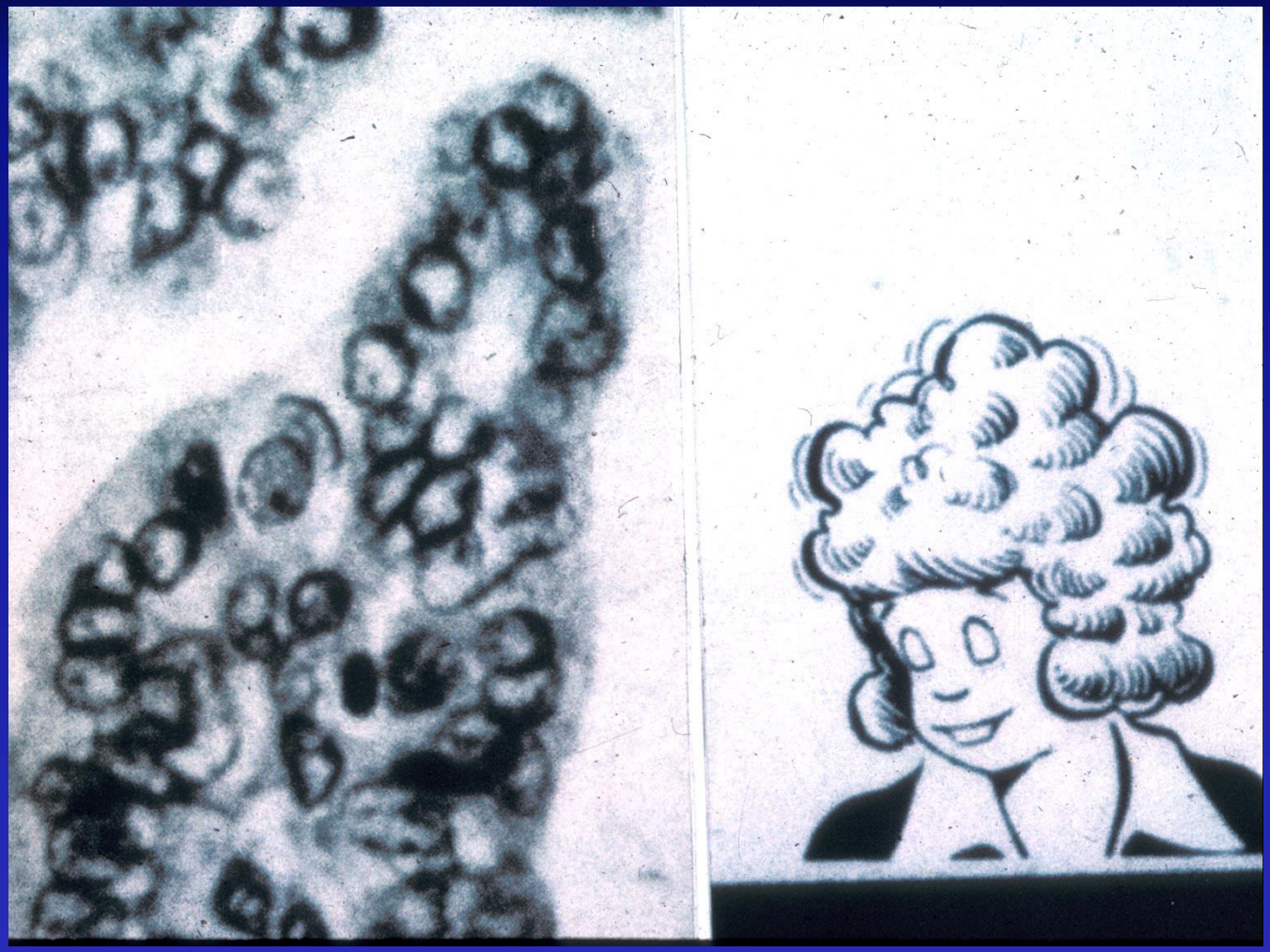
PTC – Papillary Growth



Papillary Thyroid Carcinoma
Pathologic Features

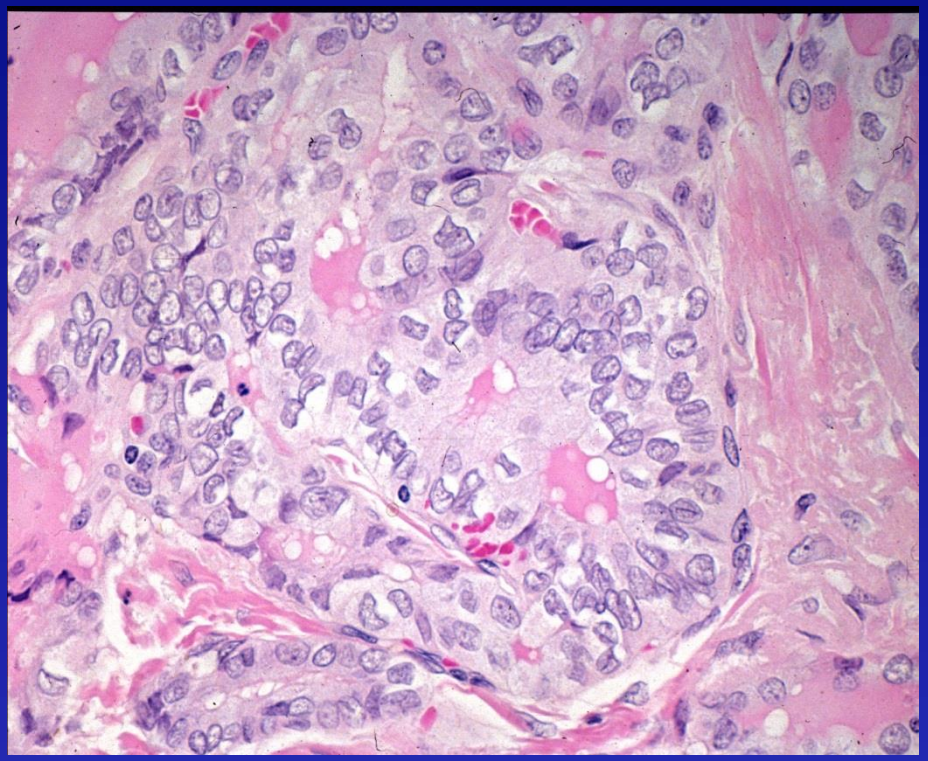
- **Cytopathologic (Nuclear) features:**
  - **Nuclear enlargement and/or elongation with irregularities in size and shape**
  - **Dispersed (very fine) to optically clear appearing chromatin**
  - **Crowding and overlapping**
  - **Nuclear grooves**
  - **Cytoplasmic invagination into nucleus (inclusions)**

PTC – “Orphan Annie” Nuclei

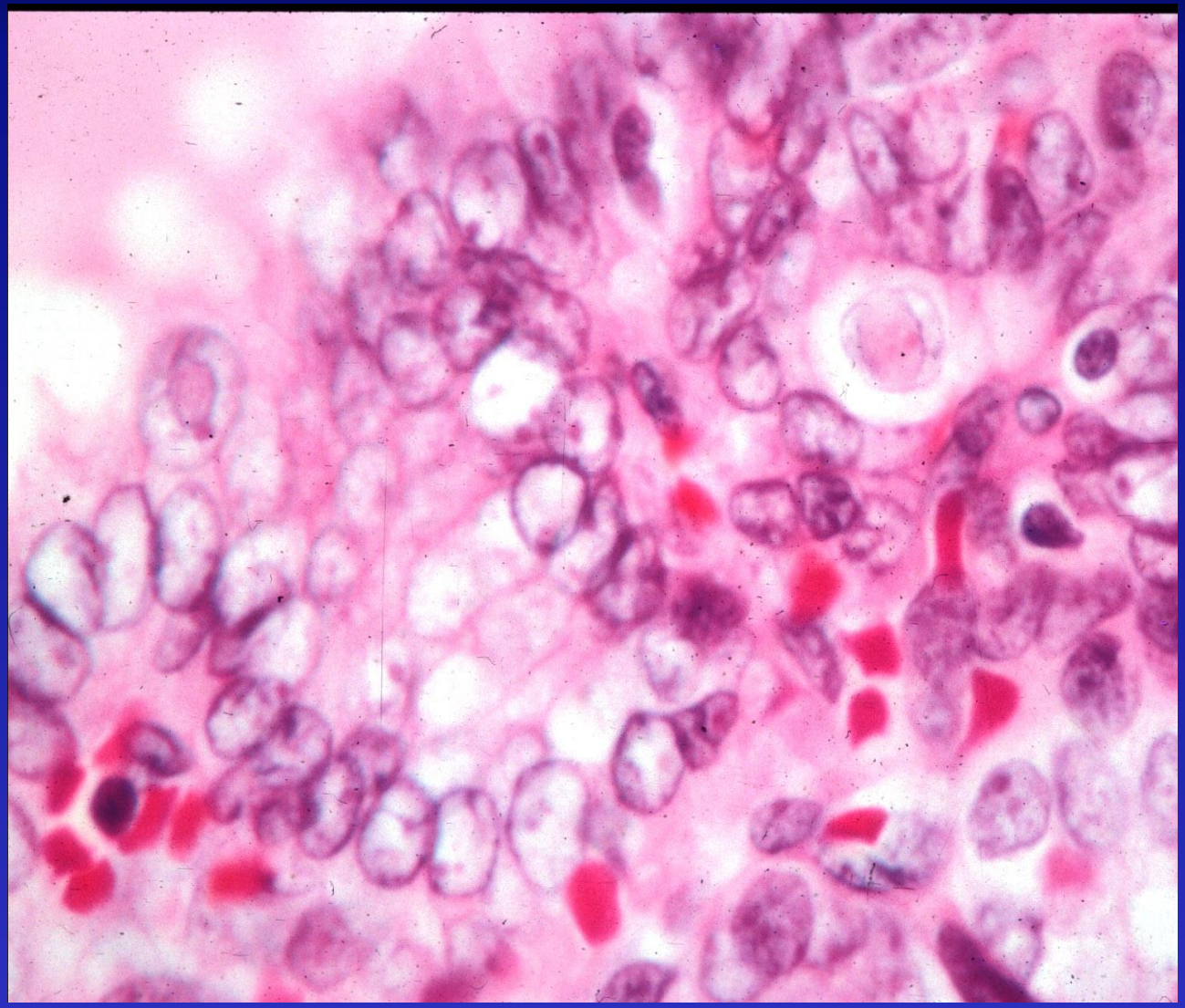


Hapke MR, Dehner LP. The optically clear nucleus. A reliable sign of papillary carcinoma of the thyroid? AJSP 1979;3:31-38.

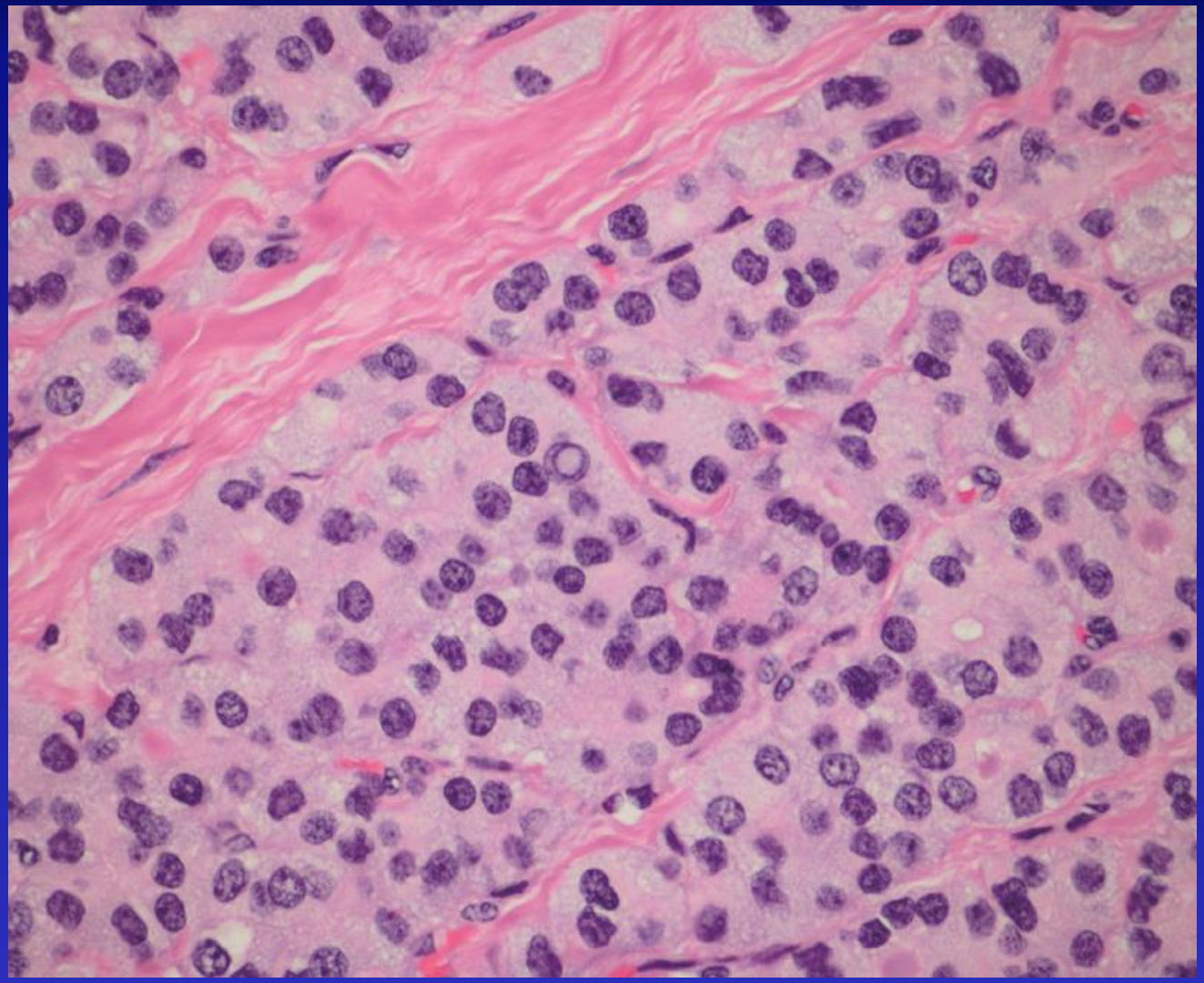
PTC – Diagnostic Nuclei



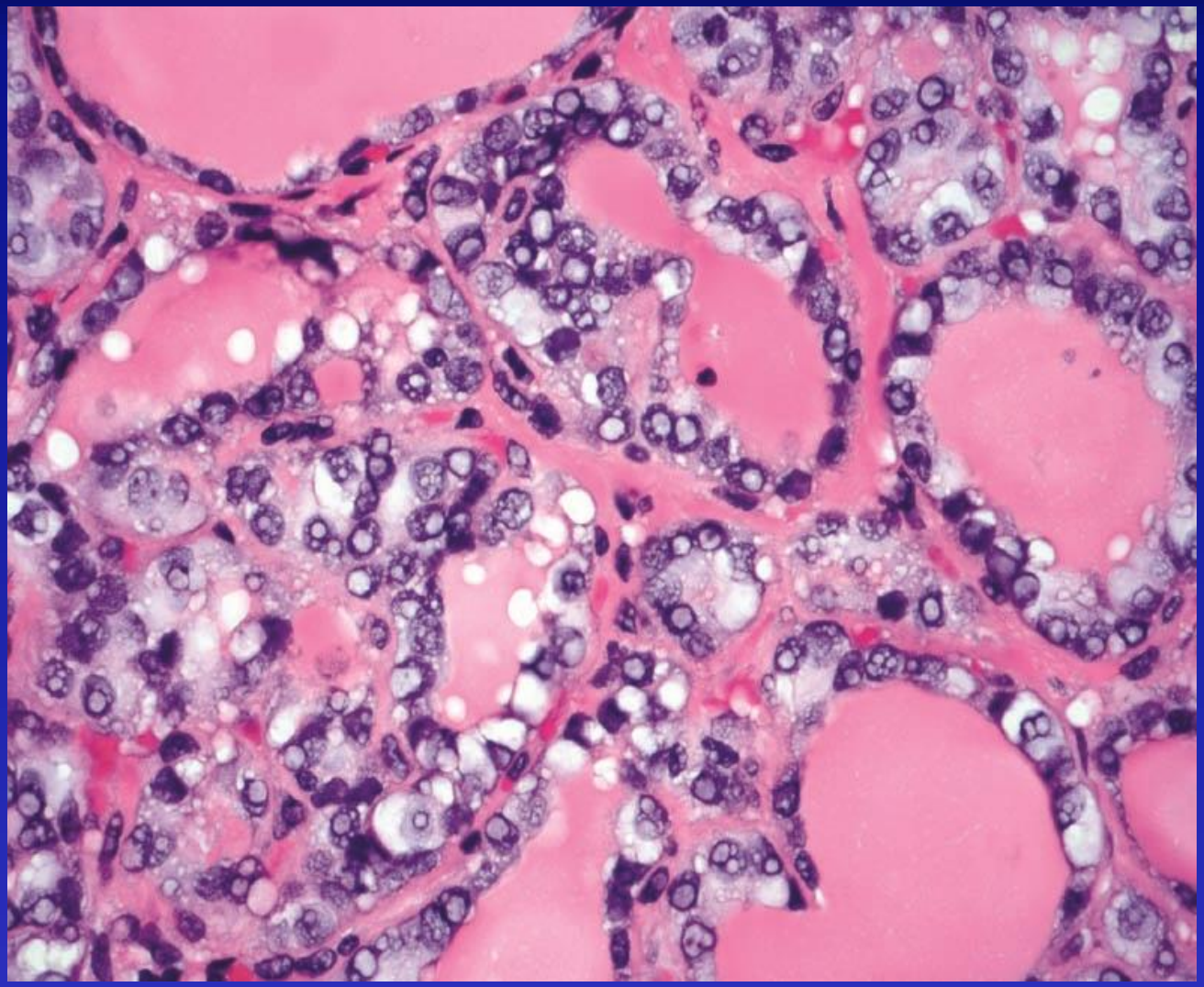
PTC – Nuclear Inclusions



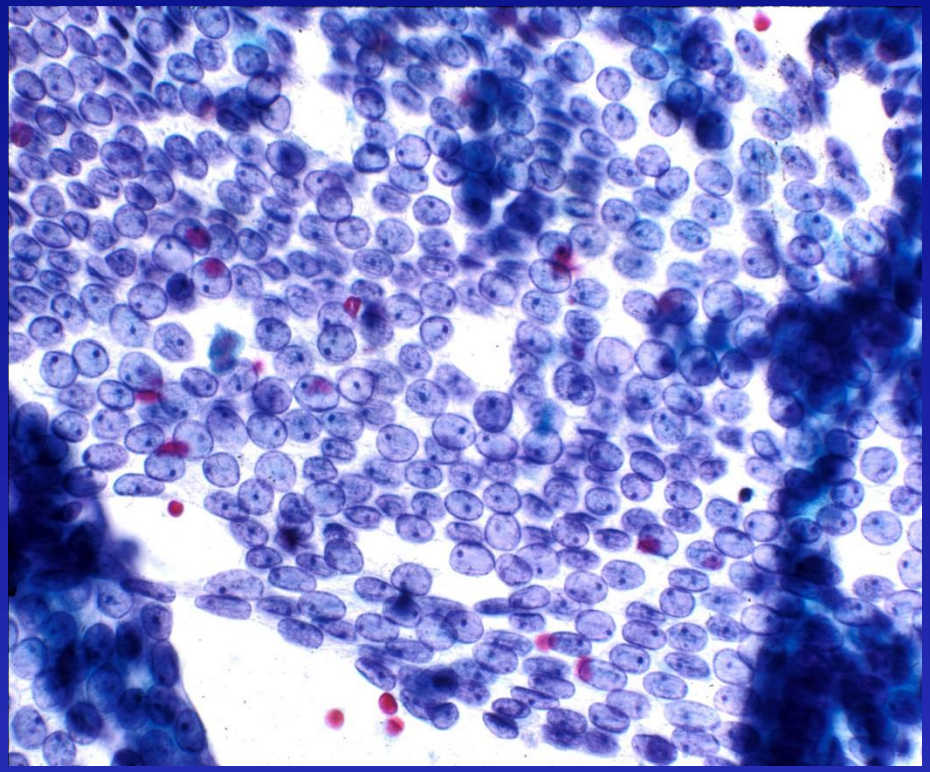
Inclusion in Follicular Adenoma

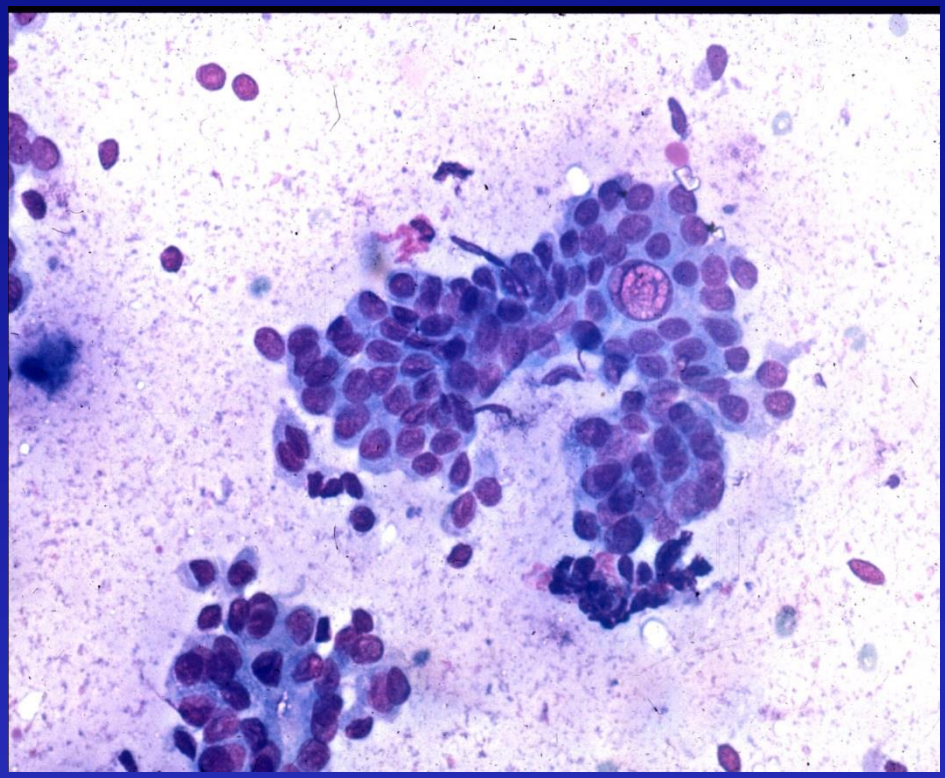


“Bubble artifact” ≠ Inclusions

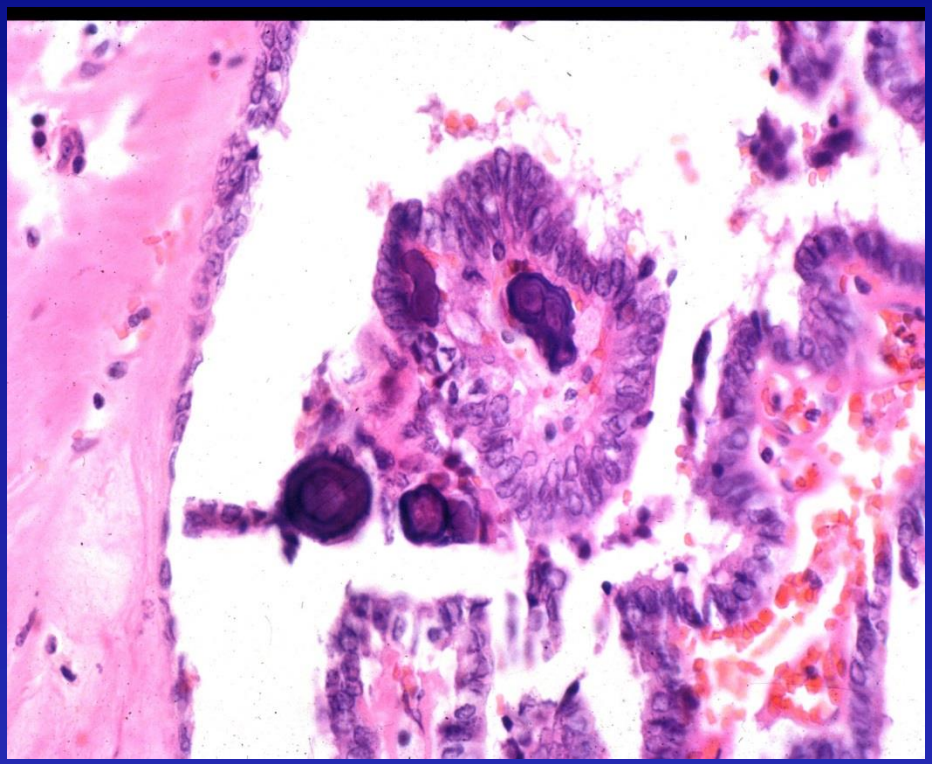


PTC can be diagnosed by FNAB

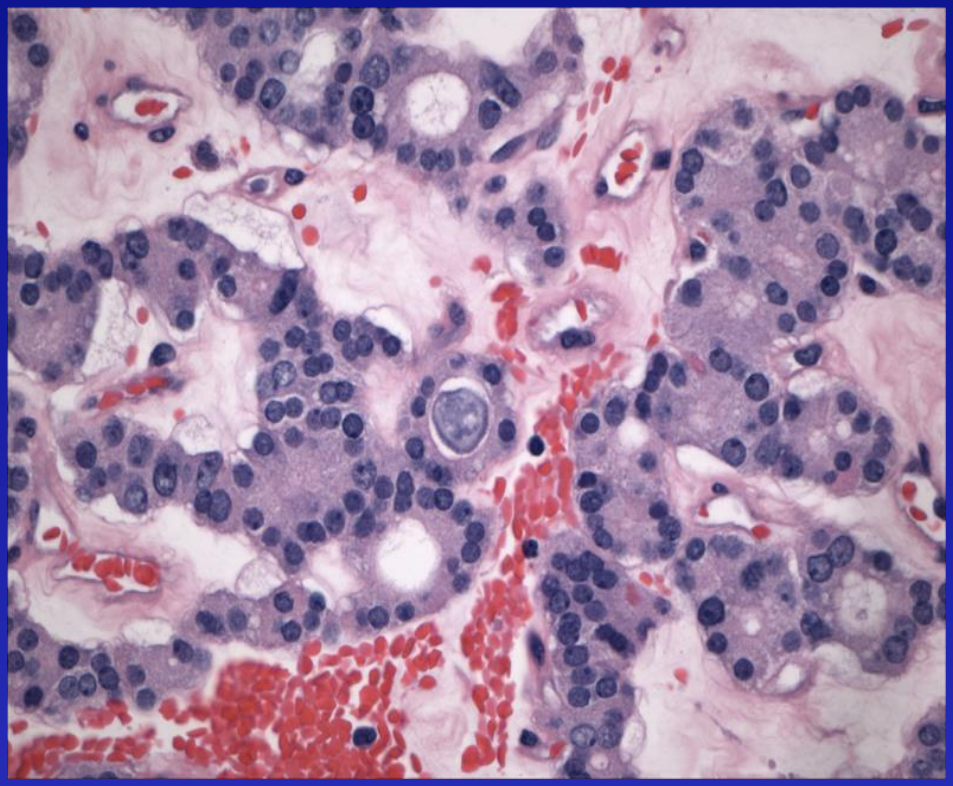


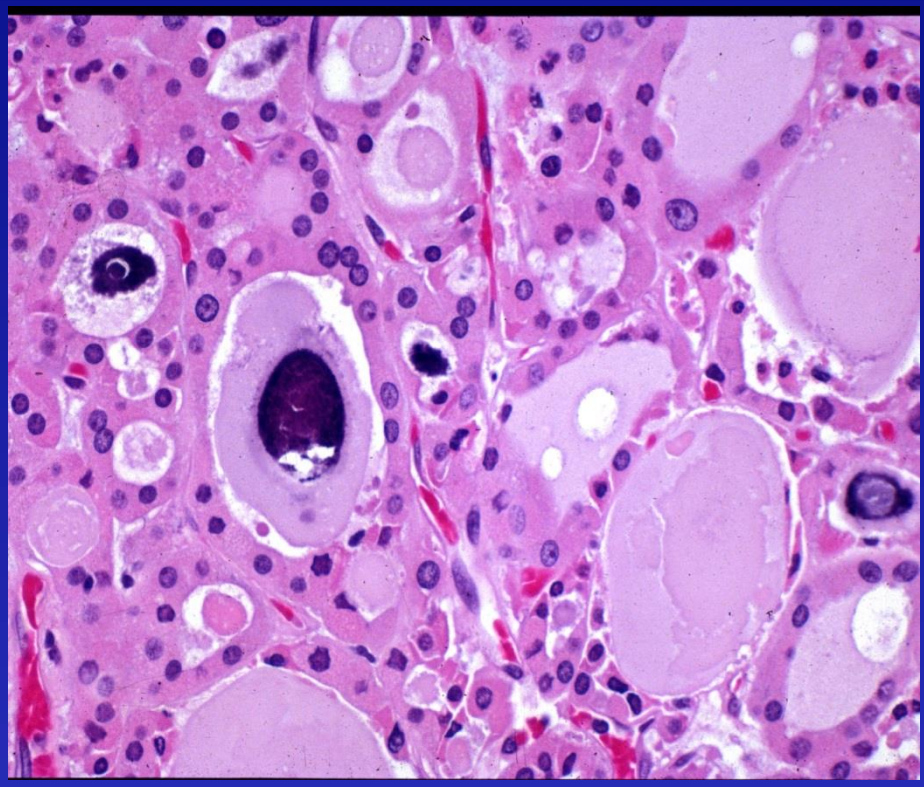


Psammoma Bodies



Calcified/inspissated colloid – not psammoma body





Papillary Thyroid Carcinoma Histologic Types/Variants

- Usual or conventional
- Papillary microcarcinoma
- Encapsulated
- Follicular
- Macrofollicular
- Oncocytic or oxyphilic
- Clear cell

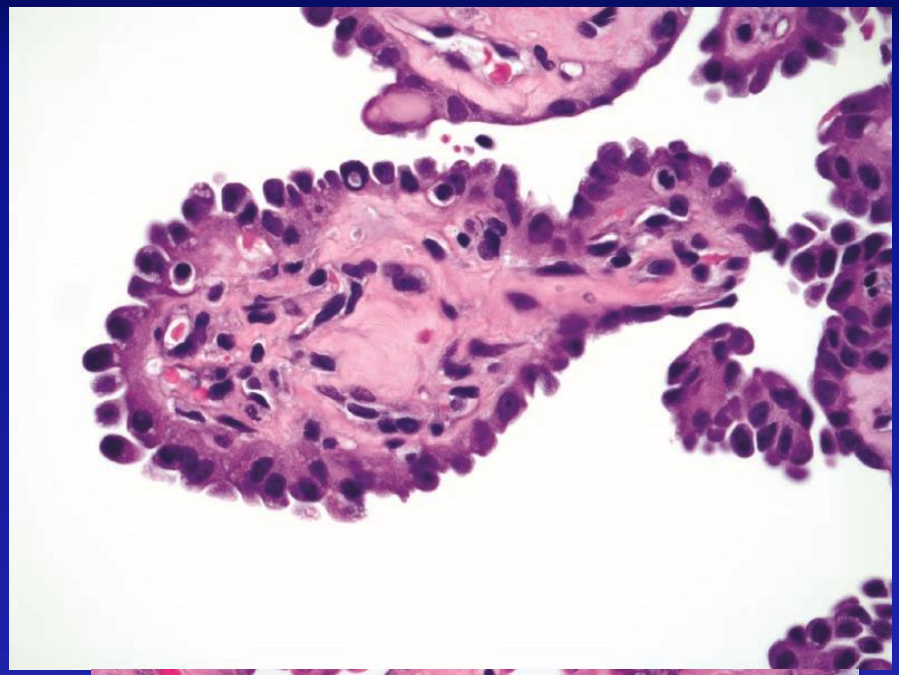
Papillary Thyroid Carcinoma Histologic Types/Variants Cont'd

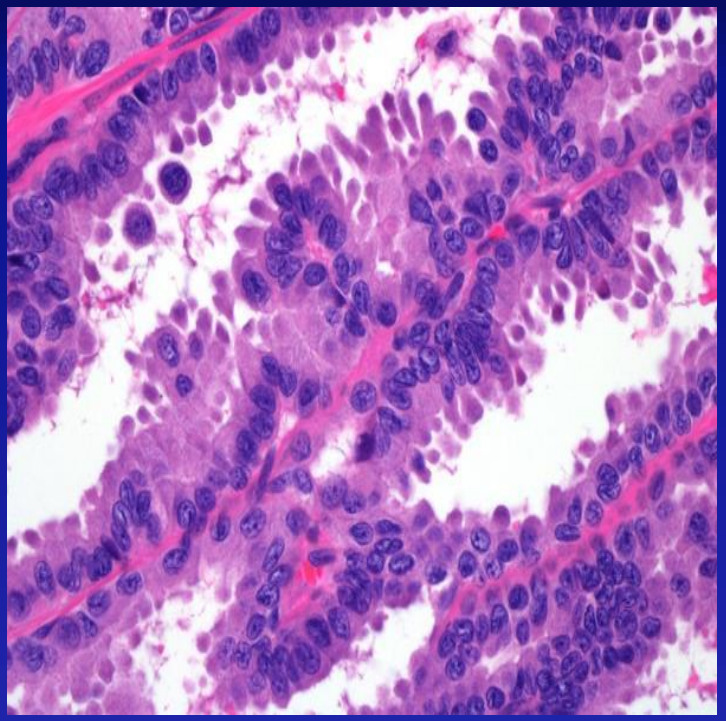
- Warthin tumor-like
- Diffuse (Multinodular) Follicular
- PTC with nodular fasciitis-like stroma
- PTC with spindle cell metaplasia
- PTC with lipomatous stroma

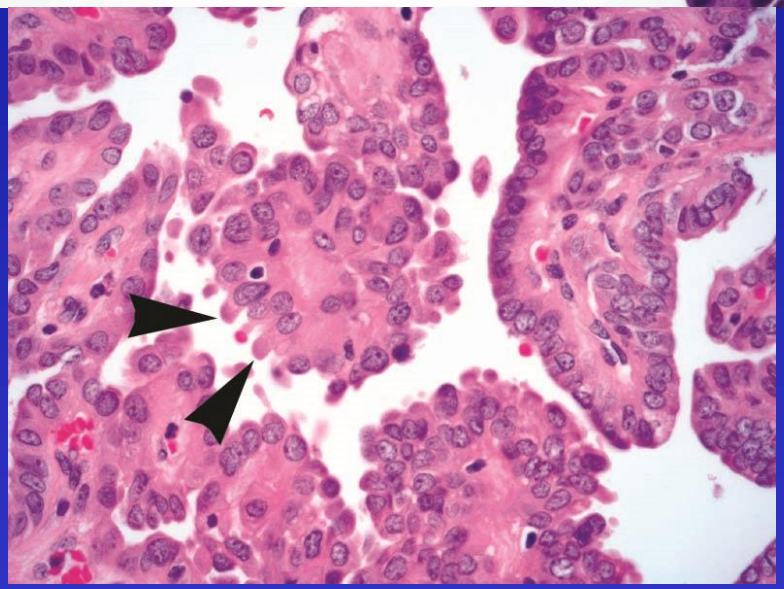
Papillary Thyroid Carcinoma Histologic Types/Variants Cont'd

- Solid and Radiation-Induced
- Cribriform-Morular
- "Hobnail" (AJSP 2010;34:44-52)
- Aggressive variants

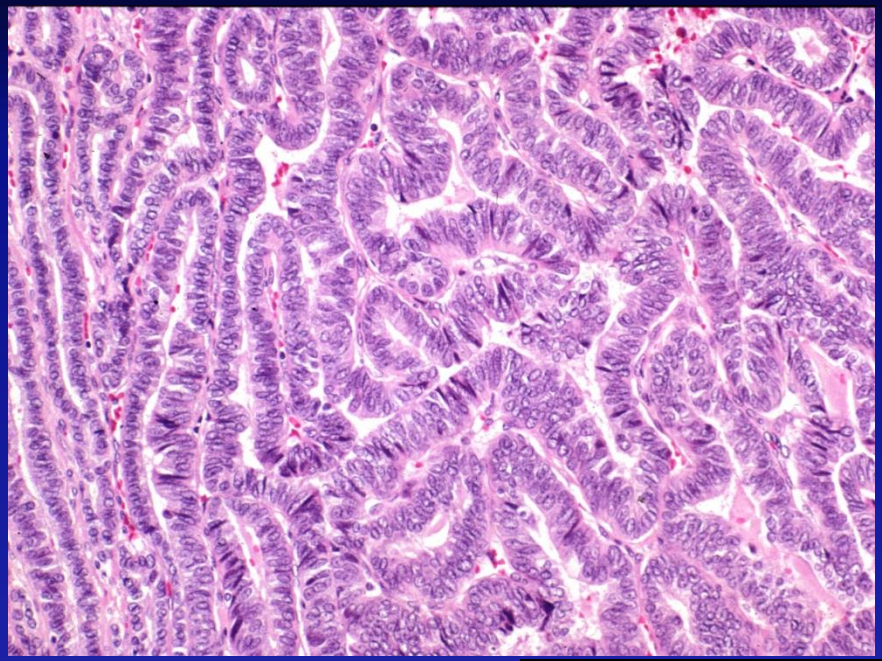
PTC, Hobnail Variant

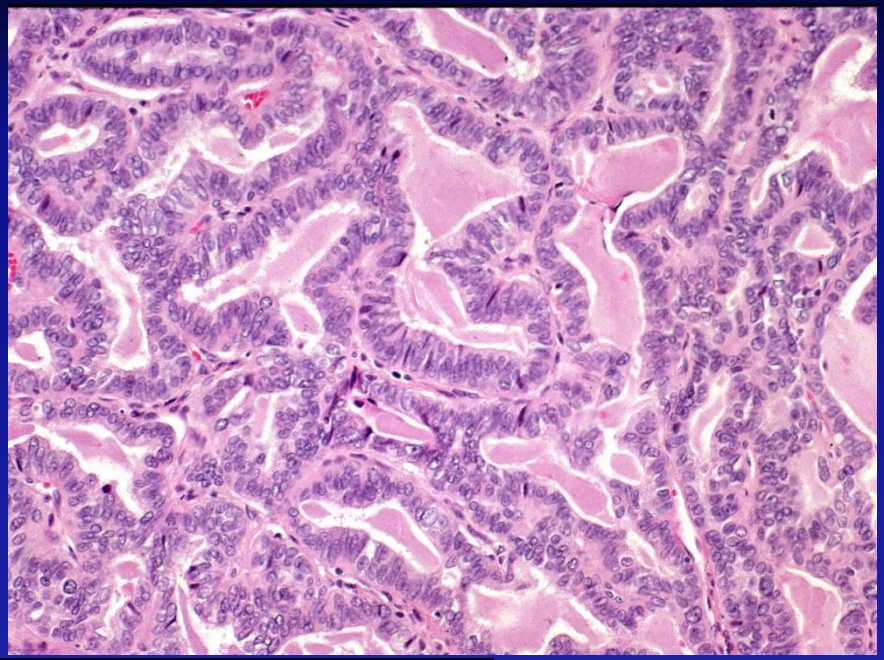


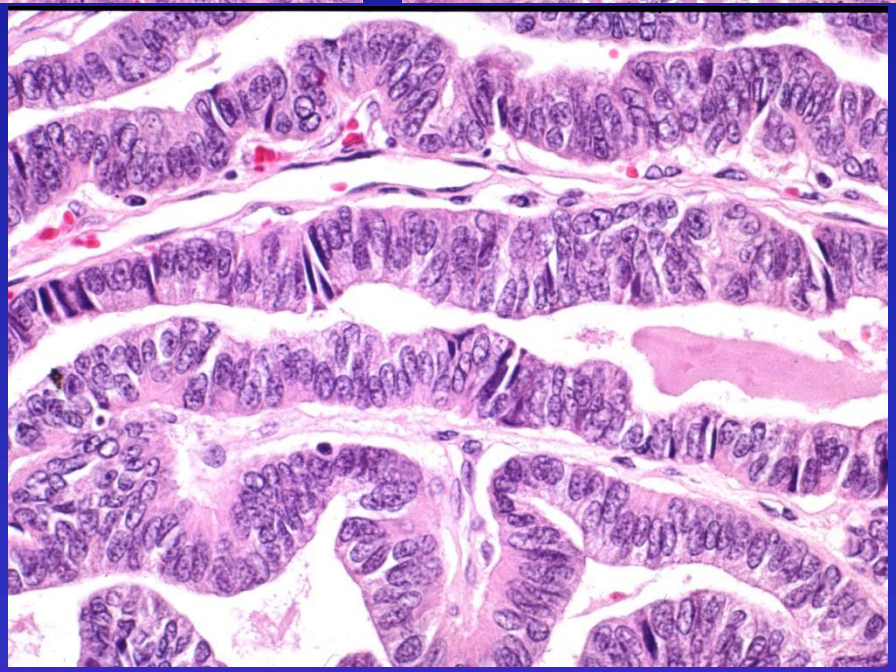




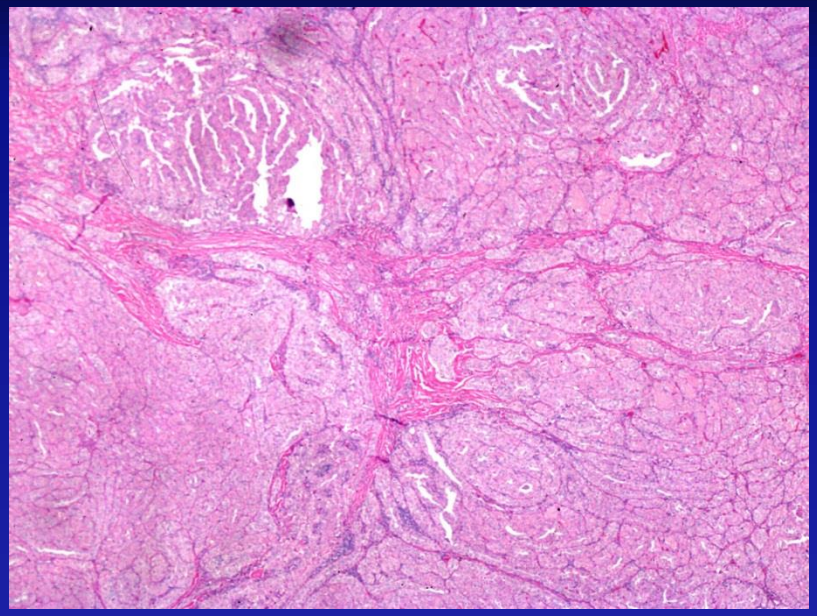
PTC, Columnar Cell Variant

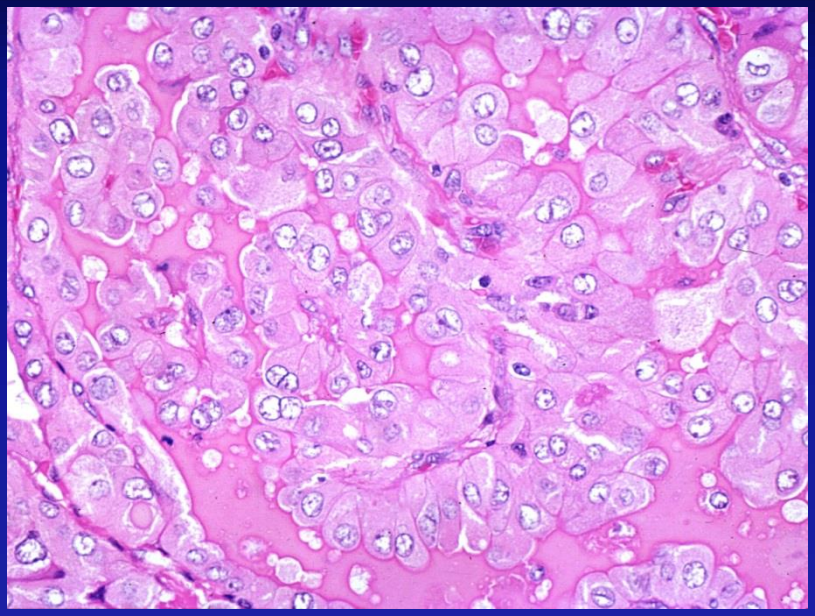


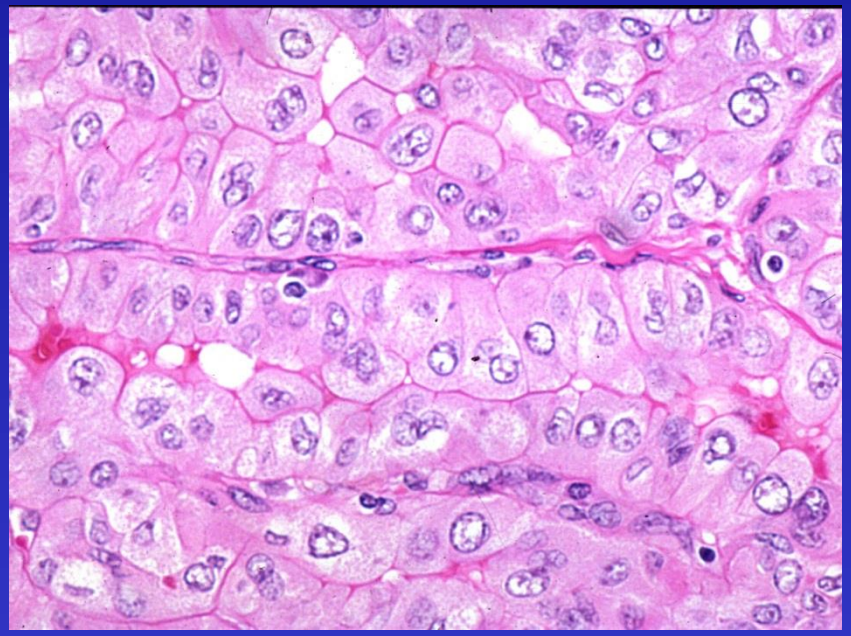




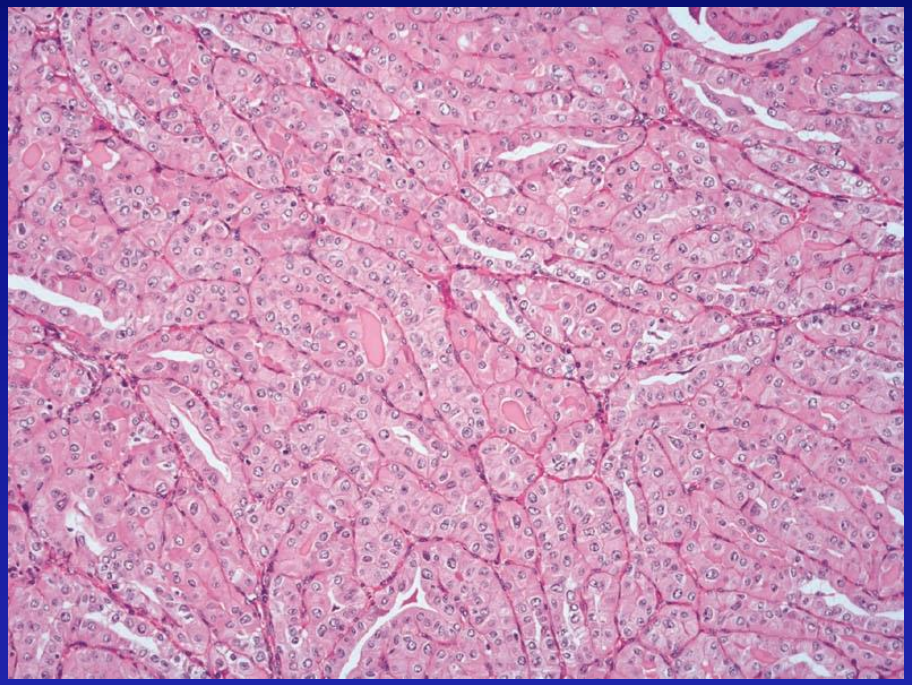
PTC, Tall Cell Variant

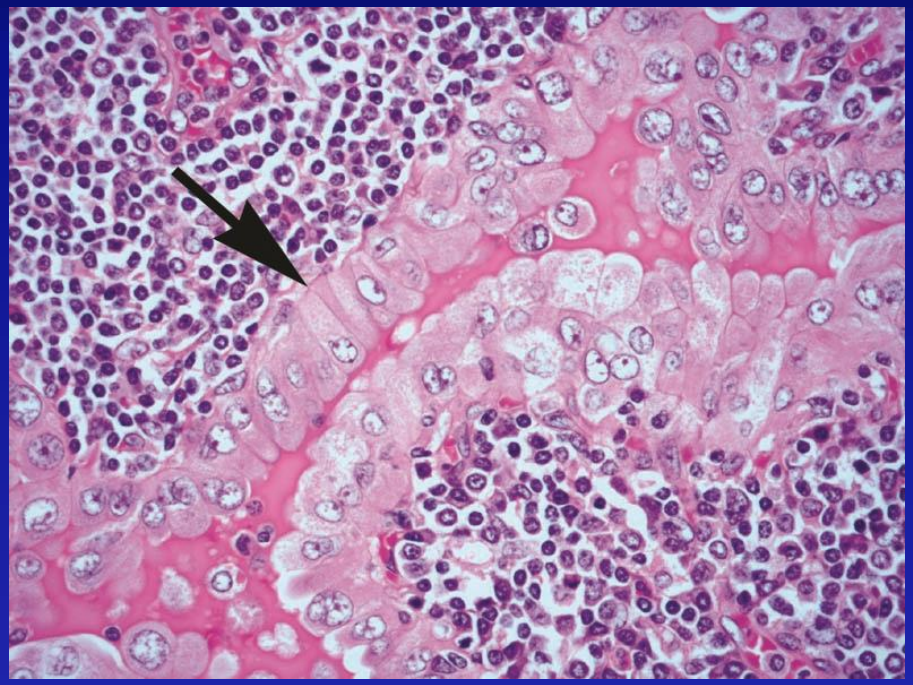






PTC, Tall Cell Variant





- **WHO 2017 criteria:**
  - **Cells 2-3x tall as wide**
  - **Abundant eosinophilic (oncocytic-like) cytoplasm**
  - **Typical nuclear features for PTC**
  - **Account for ≥30% of all tumor cells**

Follicular Variant of Papillary Thyroid Carcinoma (FVPTC)

- Subset of papillary carcinoma entirely composed of follicular growth lacking papillary architecture lined by cells having the nuclear features of PTC

FVPTC
Observer Variation*

- 10 reviewers; 87 tumors
- Concordant Diagnosis
- Most important criteria for diagnosis
- Less important criteria for diagnosis

* Lloyd et al: AJSP 2004;28:1336-40

Summary of Diagnoses

Reviewer	FVPTC	FA	FCA	Other
1	100	0	0	0
2	74.7	12.6	0	12.6
3	85.1	13.8	1.1	0
4	77	20.7	1.1	1.1
5	91.9	4.7	0	3.5
6	100	0	0	0
7	91.9	1.1	0	6.9
8	98.9	0	1.1	0
9	46.6	37.9	12.6	3.5
10	60.9	11.5	1.2	26.4

FVPTC
Observer Variation

- **Concordant diagnosis with a cumulative frequency of 39%**
- **Only 51% were diagnosed as follicular variant by all pathologists**
- **Metastatic disease in 24.1% affirming need to differentiate follicular variant of PTC from benign thyroid lesions**

FVPTC
Observer Variation*

- 6 reviewers; 15 cases
- Interobserver and intraobserver variation
- Nuclear features of TPC not well developed or only focally developed

* Elsheikh TM, et al: AJCP 2008;130:736-744

FVPTC
Observer Variation

- Unanimous agreement FVPTC in 13% (2 cases)
- Majority agreement on benign and malignant diagnoses in 27% (4 cases)
- Majority agreement on malignant diagnosis in 53% (8 cases)
- Intraobserver agreement ranged 17-100%
- Lack of agreement on minimal criteria needed to diagnose FVPTC

FVPTC
Issues

- Isolated or limited foci of PTC in an otherwise nondescript follicular lesion:
  - Is there a percentage of the lesion below which not PTC but beyond which it is PTC?
  - Does IHC assist in the diagnosis and DDX?
  - What diagnostic term(s) should be used if not PTC?
  - How to treat?

Encapsulated/Circumscribed Follicular Neoplasms

- Equivocal nuclear features but definitely invasive diagnose as carcinoma
- In such circumstances specific designation type of carcinoma is academic as treatment is similar
- For a neoplasm with invasive growth but equivocal cytomorphologic features:
    - carcinoma, favor FVPTC
    - carcinoma, favor follicular carcinoma
    - well-differentiated carcinoma, NOS

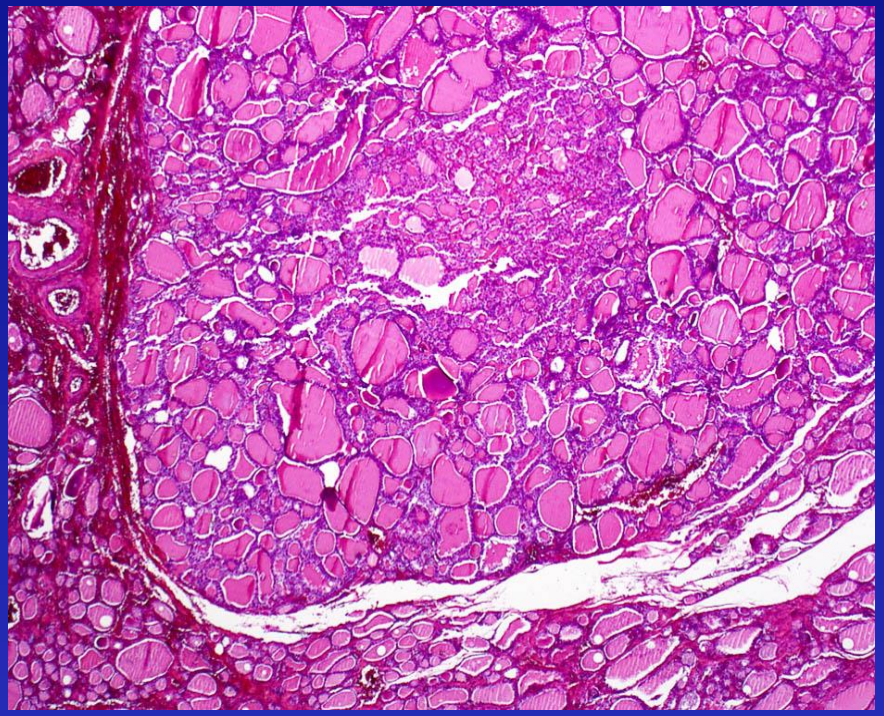
Encapsulated/Circumscribed Follicular Neoplasms Issues

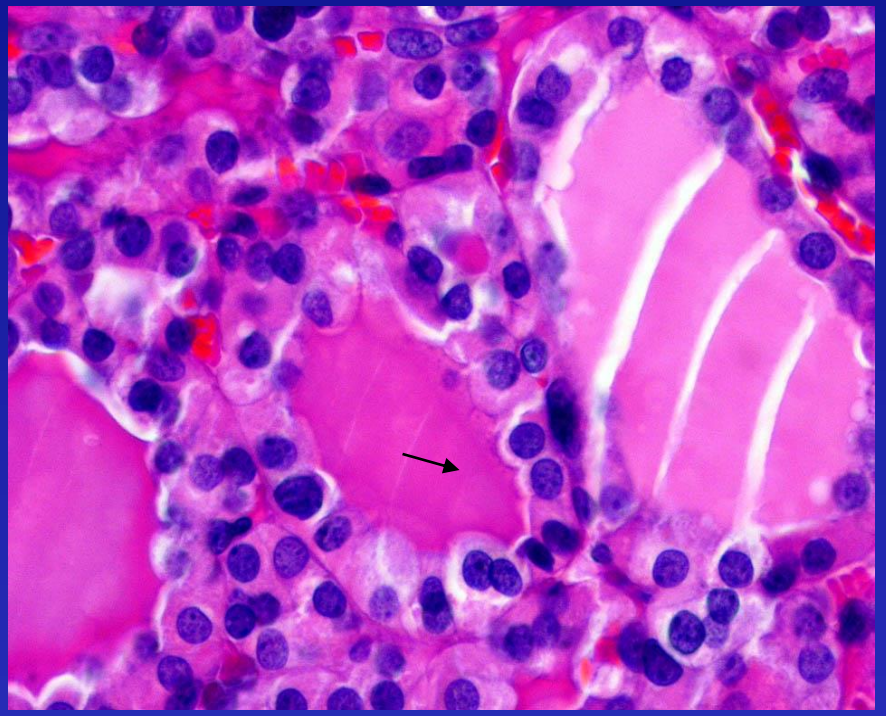
- Isolated or limited foci of PTC in an otherwise nondescript follicular lesion:
  - is there a percentage of the lesion below which not PTC but beyond which is PTC?
    - varying thresholds
    - there are no set criteria defining a minimum percentage that equates to a diagnosis of PTC

Encapsulated/Circumscribed Follicular Neoplasms Does IHC Help?

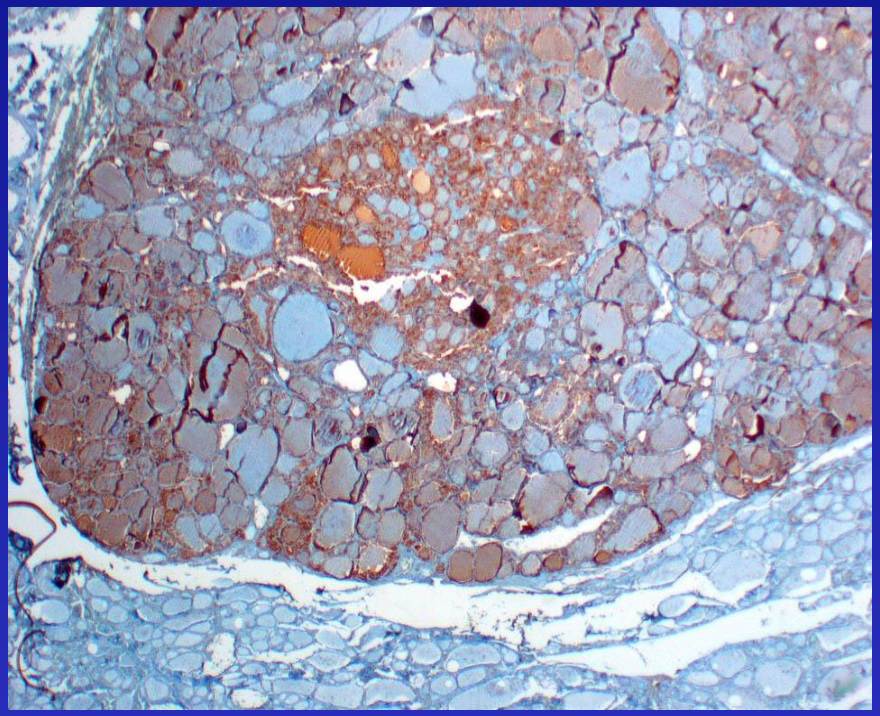
- Thyroglobulin, TTF-1, cytokeratin positive
- Calcitonin, neuroendocrine markers negative
- Markers purportedly valuable in diagnosis and DDX:
  - HBME1, CK19, galectin-3:
    - not specific
    - staining can be patchy and weak even in PTC
    - may be positive in normal follicles, nonneoplastic thyroid lesions and benign lesions/neoplasms

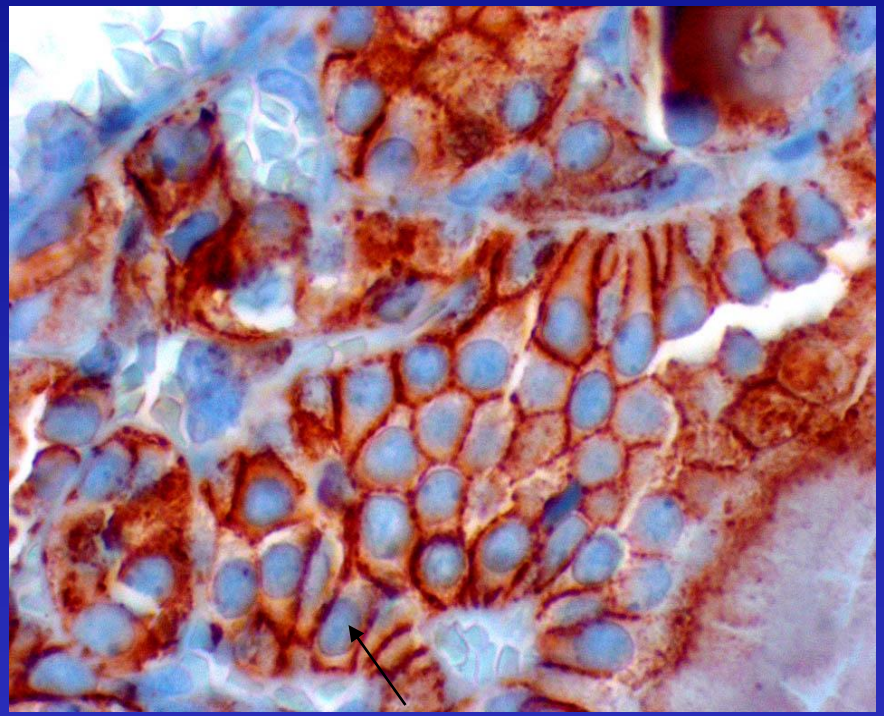
Adenomatoid Nodule





Adenomatoid Nodule
False positive HBME-1 Staining





Papillary Thyroid Carcinoma

- **Does IHC assist in the diagnosis?**
  - **at present there are no IHC markers that can reliably differentiate PTC from other follicular lesions (e.g., adenoma, carcinoma, adenomatoid nodules)**

Isolated foci of PTC in an otherwise nondescript follicular lesion

- What diagnostic term should be used if is PTC?
  - Follicular variant of PTC (FVPTC)
- Treatment:
  - Total thyroidectomy and postoperative radioactive iodine

Isolated foci of PTC in an otherwise nondescript follicular lesion

- What diagnostic term(s) should be used if not PTC?
  - Follicular adenoma (atypical)
  - FT-UMP
  - WDT-UMP
- Treatment:
  - Subtotal thyroidectomy

Isolated foci of PTC in an otherwise nondescript follicular lesion

- What diagnostic term should be used if you are unsure of the diagnosis?
  - tendency to overdiagnose FVPTC
  - err on the side of benignancy (follicular adenoma or atypical follicular adenoma)
  - Treat conservatively

Frequency of various molecular alterations in papillary carcinoma and follicular neoplasms

	Follicular adenoma or carcinoma (%)	Conventional papillary carcinoma (%)	Follicular variant of papillary carcinoma (%)
RET/PTC translocation	0	26–28	3
BRAF mutation	0	53–75 (V600E)	0–7 (K601E)
RAS mutation	18–53	0	25–47
PAX8/PPARγ translocation	Follicular adenoma: 4–33 Follicular carcinoma: 45–63	0	38

FVPTC
Molecular Biology

- **Molecular profile much closer to follicular adenoma and follicular carcinoma than to classical papillary carcinoma**

Biologic Behavior of FVPTC

- Liu J, et al. Cancer. 2006;107:1255-64:
  - No recurrence, lymph node metastasis
- Rivera M, et al. Mod Pathol 2010;23:1191-200:
  - Encapsulated/noninvasive tumors extremely low recurrence rate
  - Metastatic nodal pattern:
    - Noninvasive similar to follicular adenoma
    - Infiltrative similar to classical PTC

Molecular Classification of PTC

- Giordano T, et al. Integrated genomic characterization of papillary thyroid carcinoma - Cancer Genome Atlas Research Network. Cell 2014;159:676-690
- Noninvasive: among RAS-like tumors rather than BRAF V600E-like tumors
- Invasive: among BRAF V600E-like tumors rather than RAS-like tumors

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

JAMA Oncology April 2016

Reclassification Noninvasive FVPTC

- **Recent recommendation to replace use of noninvasive FVPTC with "Noninvasive Follicular Thyroid Neoplasm with Papillary-like Features (NIFTP)" reflecting:**
  - **subjectivity among pathologists in diagnosis of FVPTC**
  - ***RAS*-like molecular profile**
  - **extremely indolent biology not warranting the designation as "cancer"**

NIFTP
Inclusion Criteria

- Encapsulated or circumscribed
- Follicular pattern growth (<1% “true” papillae)
- No psammoma bodies
- Nuclear score 2-3
- < 30% solid, trabecular, insular growth
- No cellular features of other variants of PTC
- No tumor necrosis or high mitotic activity (≥ 3/10HPF)
- No invasion (vascular or capsular): entire tumor-capsule or tumor-parenchymal interface must be submitted

NIFTP
Nuclear Score

- Enlargement, crowding/overlapping
- Elongation
- Irregular contours
- Grooves
- Chromatin clearing
- Inclusions

- 3-point scoring scheme with each class of nuclear features assigned score of 0 or 1 yielding a range of scores from 0-3

NIFTP

- Reclassification as a close entity to the follicular adenoma/carcinoma group:

  - Treatment by lobectomy alone even in the presence of adverse demographic prognostic factors (e.g., > 45 yrs, > 4 cm)

  - Countless number of patients with non-invasive follicular variant spared unnecessary therapy with associated morbidity, financial costs and the psychological impact of “cancer” diagnosis

NIFTP

- **Since NIFTP initially reported:**

  - Several patients with locoregional nodal (micro)metastasis reported in primary tumors meeting proposed diagnostic criteria for NIFTP

- **Re-evaluation of criteria for NIFTP:**

  - No well formed papillae

  - Presence of diffuse nuclear features of PTC → examination of entire tumor (not just the tumor-to-capsule/parenchymal interface)

    - NIFTPs typically show moderate expression of diagnostic nuclear features of PTC

  - Presence of BRAF V600E or other BRAF-like mutations (RET/PTC fusions) or high-risk mutations (TERT; TP53) → search for exclusionary features (e.g., true papillae; invasion)

NIFTP – **Revised Diagnostic** Criteria

- **Primary:**
  - **Encapsulation of clear demarcation**
  - **Follicular growth pattern**
  - **Nuclear score 2-3**
  - **No vascular or capsular invasion**
  - **No tumor necrosis or high mitotic activity (≥3/10hpf)**
- **Secondary (helpful but not required for diagnosis of NIFTP):**
  - **Lack of *BRAF* V600E mutation detected by molecular assays or immunohistochemistry**
  - **Lack of BRAF V600E-like mutations or other high risk mutations (*TERT*, *TP53*)**

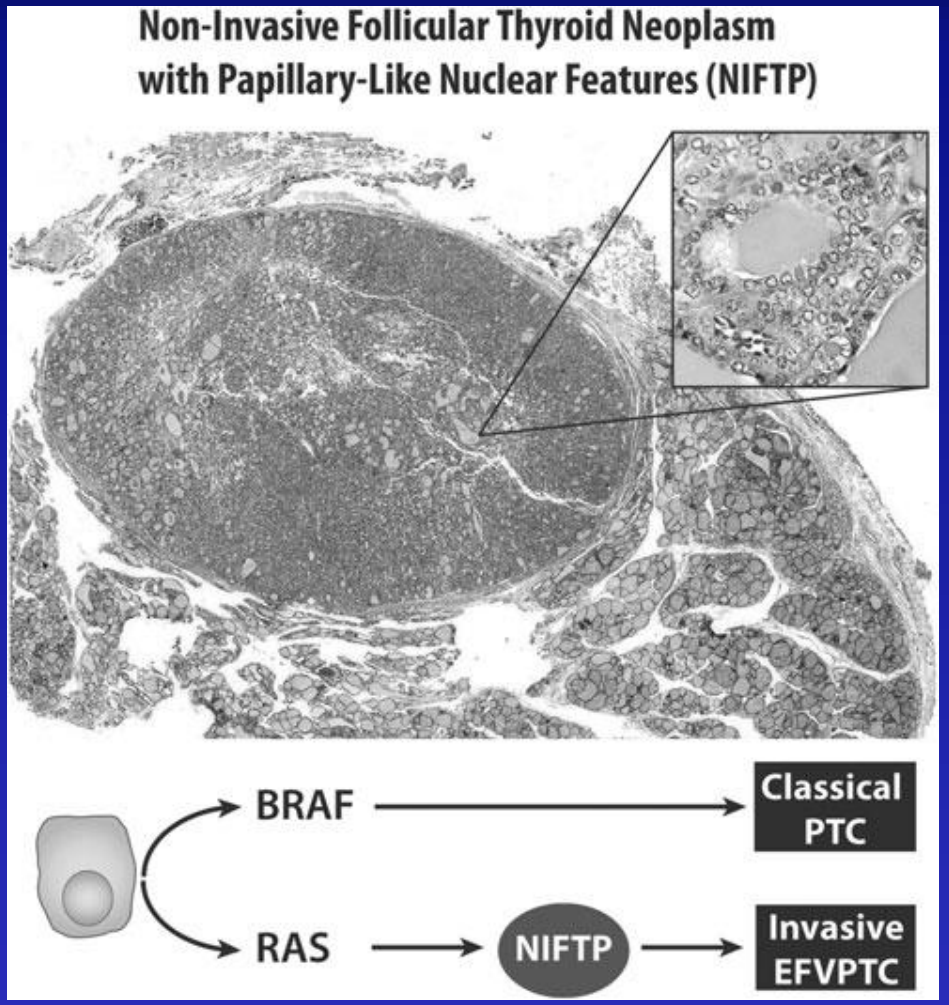
Nikiforov YE, Baloch ZW, Hodak SP, Giordano TJ, Seethala RR, Wenig BM. JAMA Oncology. 2018 June 14 (Epub ahead of print).

Pre-invasive Stage of Invasive FVPTC

Figure 2. Putative Scheme of Thyroid Carcinogenesis

Growth Pattern	Nuclear Features of PTC	Main Oncogene		
Papillary	Yes	*BRAF*	Papillary microcarcinoma	Classic PTC
Follicular	Yes	*RAS*	NIFTP	Invasive EFVPTC
Follicular	No	*RAS*	Follicular adenoma	Follicular thyroid carcinoma

EFVPTC indicates encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.



Hodak S, et al. Thyroid 2016;26:869-71

2017 CAP Protocol - Histologic Type
Papillary Thyroid Carcinoma

- ___ Papillary carcinoma, classic (usual, conventional)
- ___ Papillary carcinoma, follicular variant, encapsulated/well demarcated, with tumor capsular invasion
- ___ Papillary carcinoma, follicular variant, encapsulated/well demarcated, noninvasive#
- ___ Papillary carcinoma, follicular variant, infiltrative
- ___ Papillary carcinoma, tall cell variant
- ___ Papillary carcinoma, cribriform-morular variant
- ___ Papillary carcinoma, diffuse sclerosing variant
- ___ Papillary carcinoma, other variant (specify):
- ___ Papillary carcinoma

#A subset of noninvasive tumors can now be reclassified as NIFTP.

+Noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP)##

This category is not overtly malignant; reporting is optional and only size, laterality, and margin status are reported

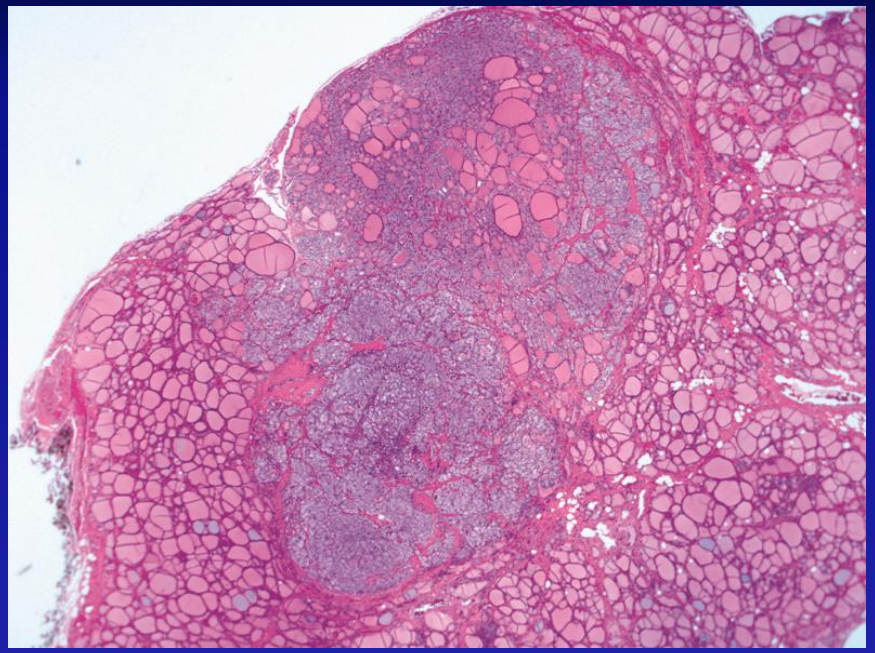
NIFTP

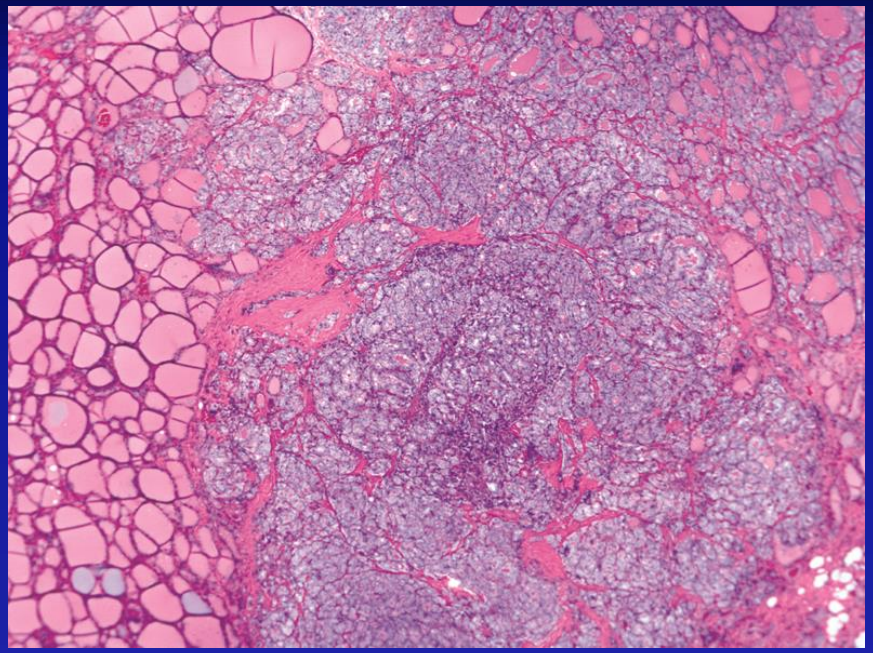
- Encapsulated, circumscribed (nonencapsulated)
- Low % intralesional sclerosis
- No psammoma bodies
- No ETE
- *RAS* mutation, *PAX8/PPARγ* translocation
- Low to no incidence of metastasis
- If invasive → Invasive FVPTC → behavior that of FTC

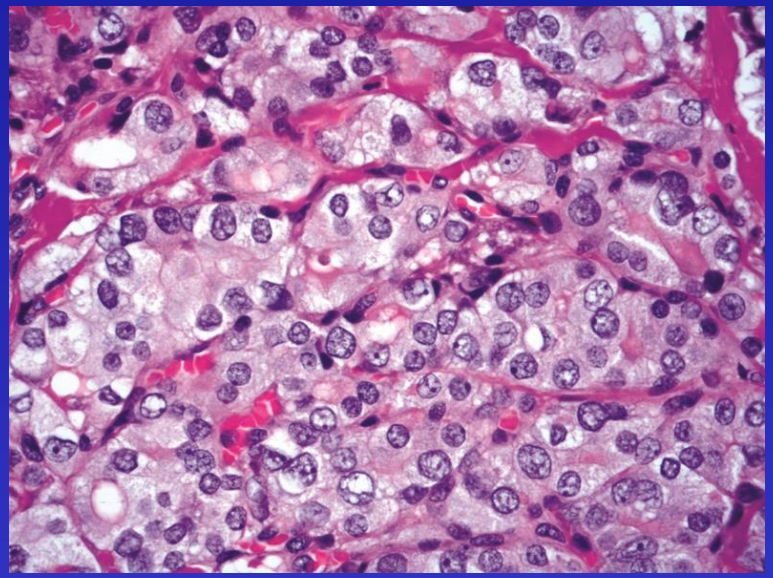
Invasive FVPTC

- Usually nonencapsulated
- ↑ % marked intralesional sclerosis
- Psammoma bodies may be present
- ↑ % ETE
- *BRAF* mutation, *RET/PTC* translocation
- Increased incidence of metastasis (nodal)

Invasive FVPTC



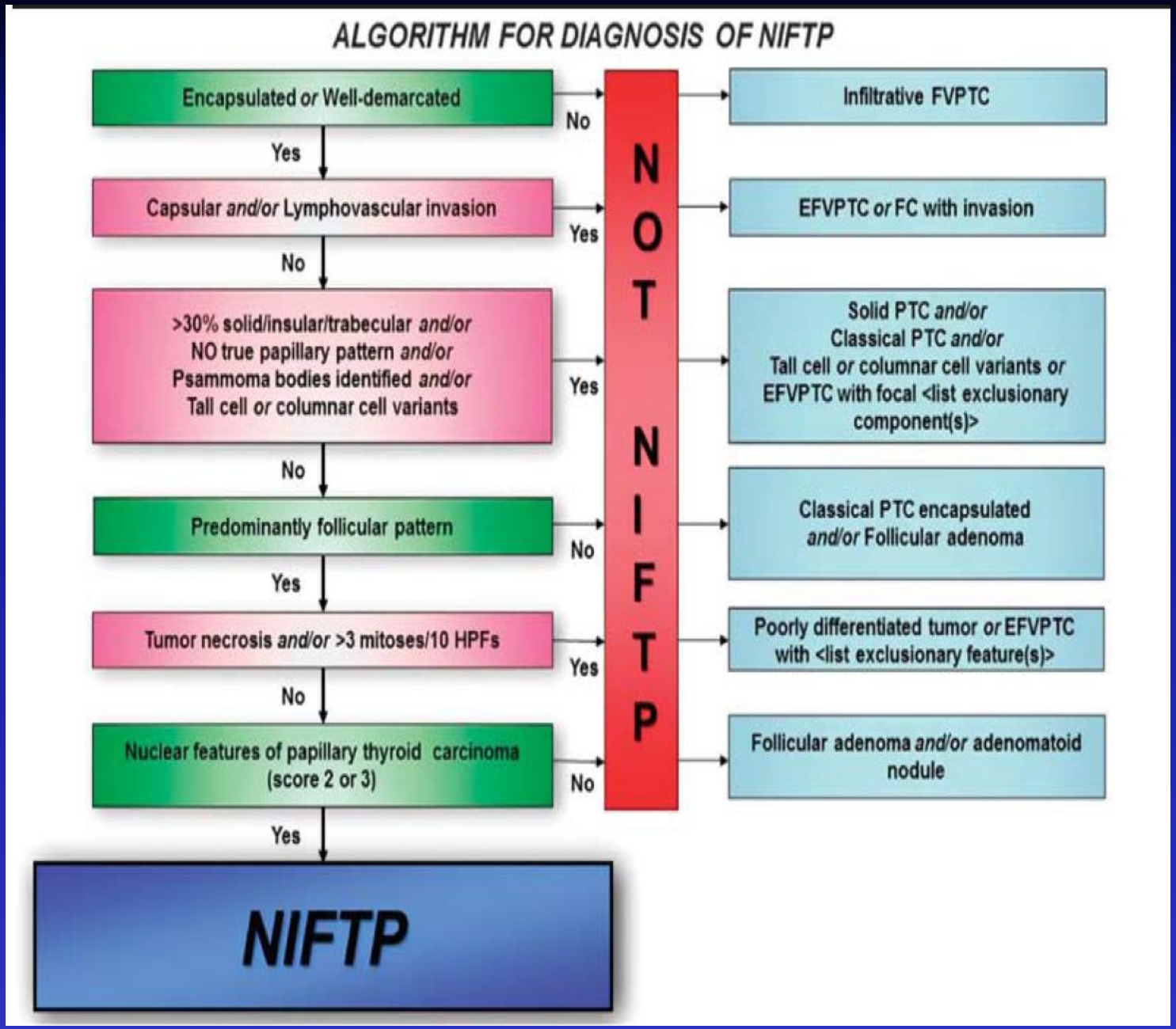




Follow-up Data for Noninvasive and Invasive FVPTC

Table. Summary of Follow-up Information for Patients in the Study Groups

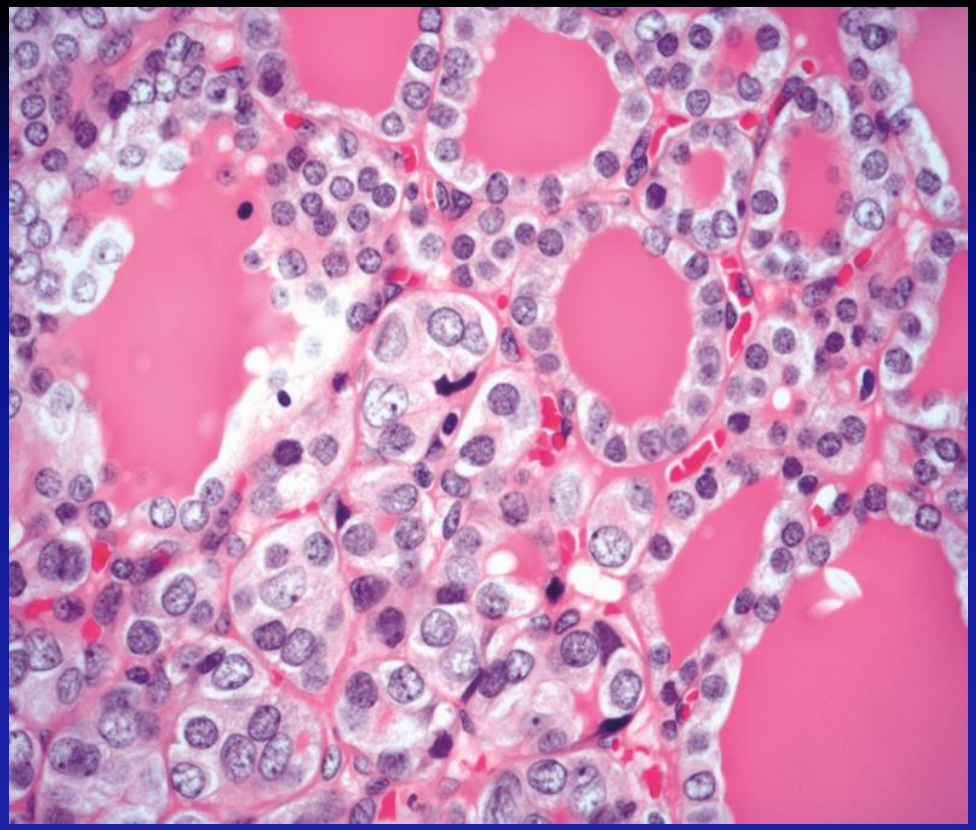
Characteristic	Group 1 (Noninvasive EFVPTC) (n = 109)	Group 2 (Invasive EFVPTC) (n = 101)
Age, mean (range), y	45.9 (21-81)	42.8 (8-78)
Sex, No. (%)		
Female	91 (83)	71 (70)
Male	18 (17)	30 (30)
Tumor size, mean (range), cm	3.1 (1.1-9.0)	2.5 (0.6-5.5)
Extent of surgery		
Lobectomy	67	15
Total thyroidectomy	42	86
Follow-up, y		
Mean (range)	14.4 (10-26)	5.6 (1-18)
Median	13.0	3.5
Adverse events during follow-up, No. (%)	0	12 (12)



Seethala RR et al. Mod Pathol 2018;31:39-55

NIFTP
Other Findings

- Multifocal lesions
- Subcentimeter lesions
- Lesions with oncocytic cytoplasm (Hürthle cells)



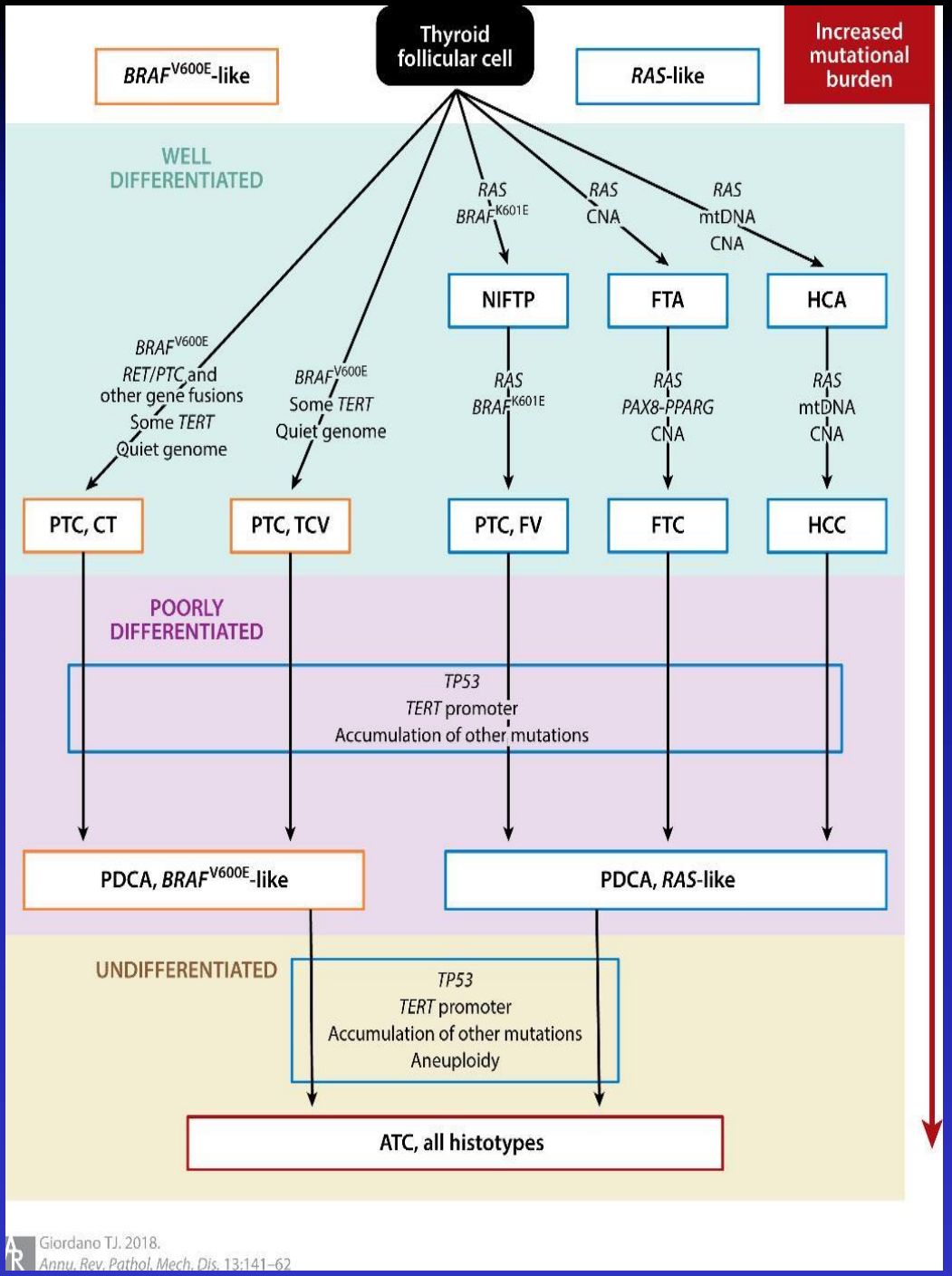
- **NIFTP or not? If not what diagnosis?**
- **Narrowing definition = NIFTP**
- **If not NIFTP = Follicular adenoma**
- **NIFTP not meant to be a waste basket diagnosis**

Case 3
Diagnosis ?

- Adenomatoid nodule
- Follicular adenoma
- Noninvasive follicular neoplasm with papillary-like features (NIFTP)
- Papillary thyroid carcinoma, classic variant
- Papillary thyroid carcinoma, follicular variant

Emerging view of thyroid cancer pathogenesis

Giordano TJ. Annu Rev Pathol 2018;13:141-62



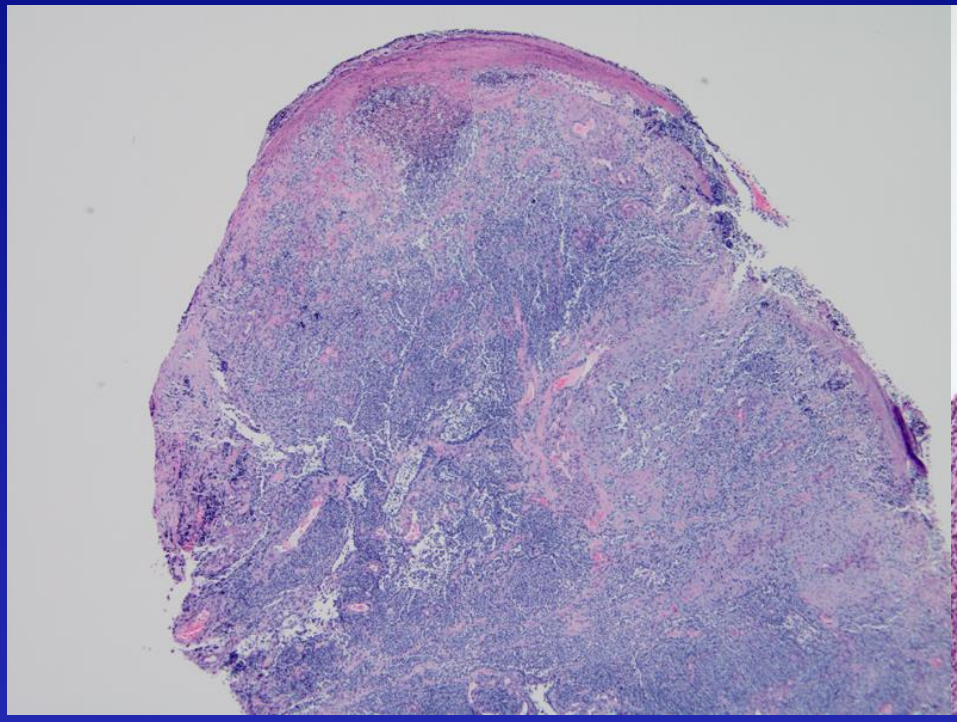
Case 3 Summary

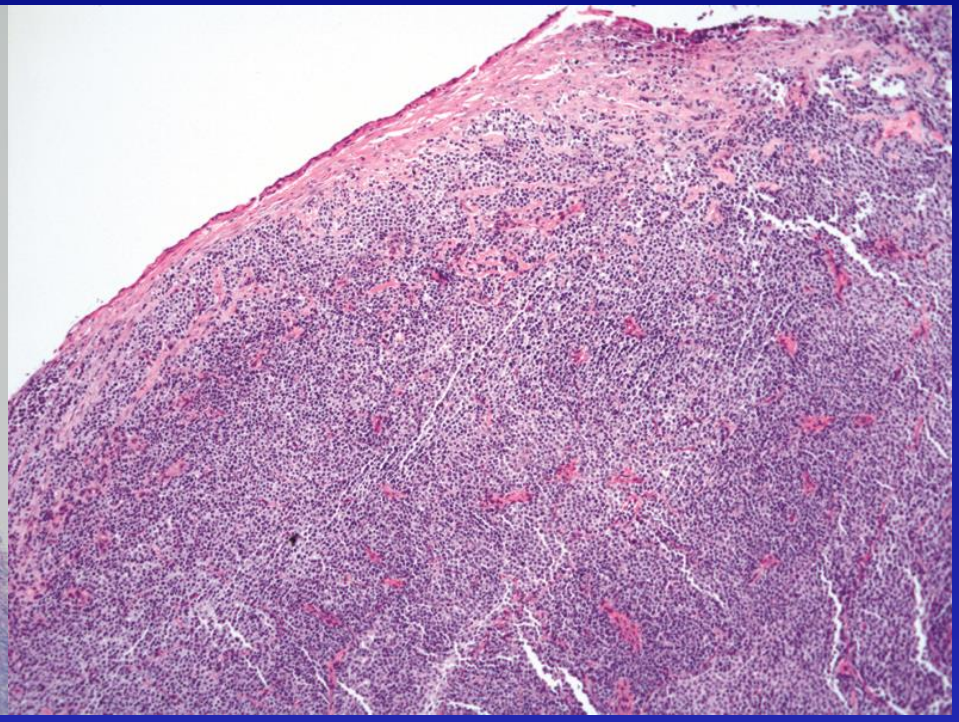
- Diagnosis of PTC based on constellation of histologic criteria coupled by IHC and molecular genetics:
  - Despite established criteria interpretation can be contentious and subjective
  - Beware of potential pitfalls
- Specific types have distinct pathology but not necessarily distinct clinical features
- Histology (e.g., cell type, growth patterns) does not necessarily portend specific biology behavior
- Prognosis & treatment predicated on many parameters
- NIFTP replaces NI-FVPTC but still evolving category
- Molecular findings playing greater role in diagnosis of follicular neoplasms

Case 4

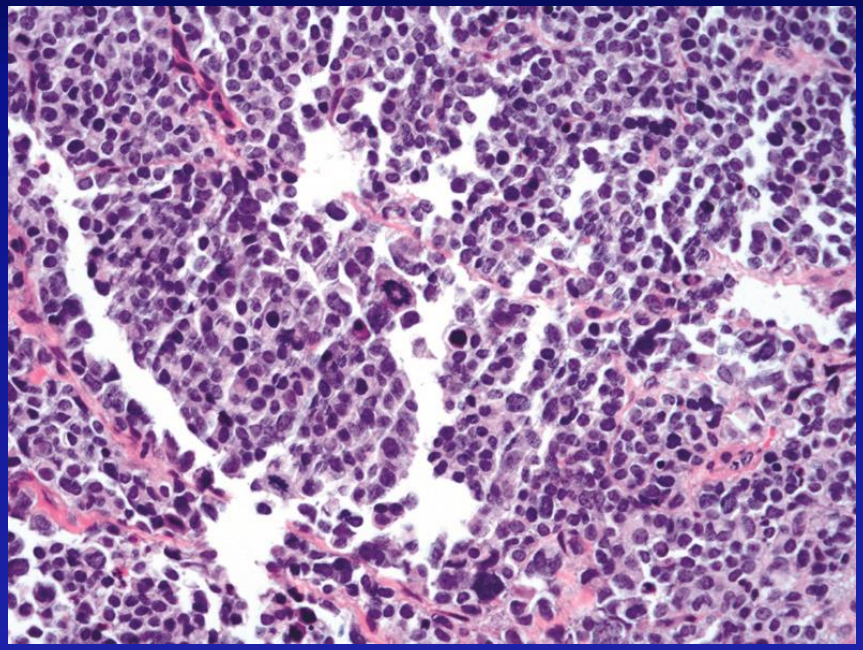
A 68 year old man presented with unilateral nasal obstruction unresponsive to antibiotic therapy. Clinical evaluation identified a polypoid left maxillary sinus mass. A biopsy was performed.

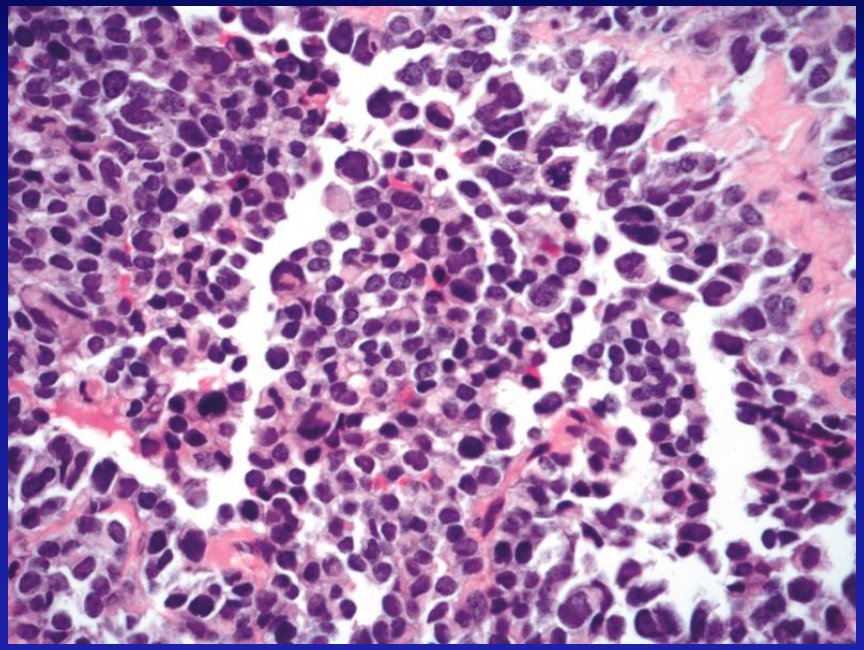
Case 4

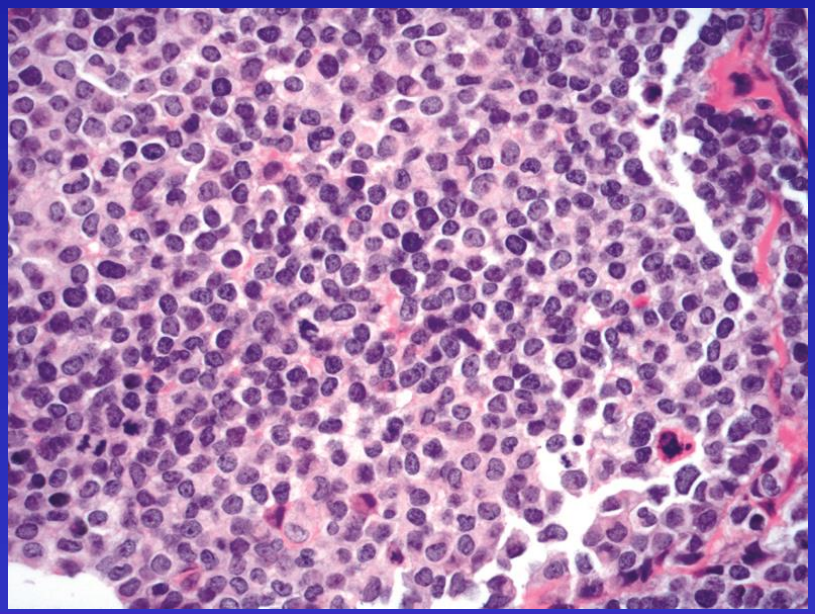




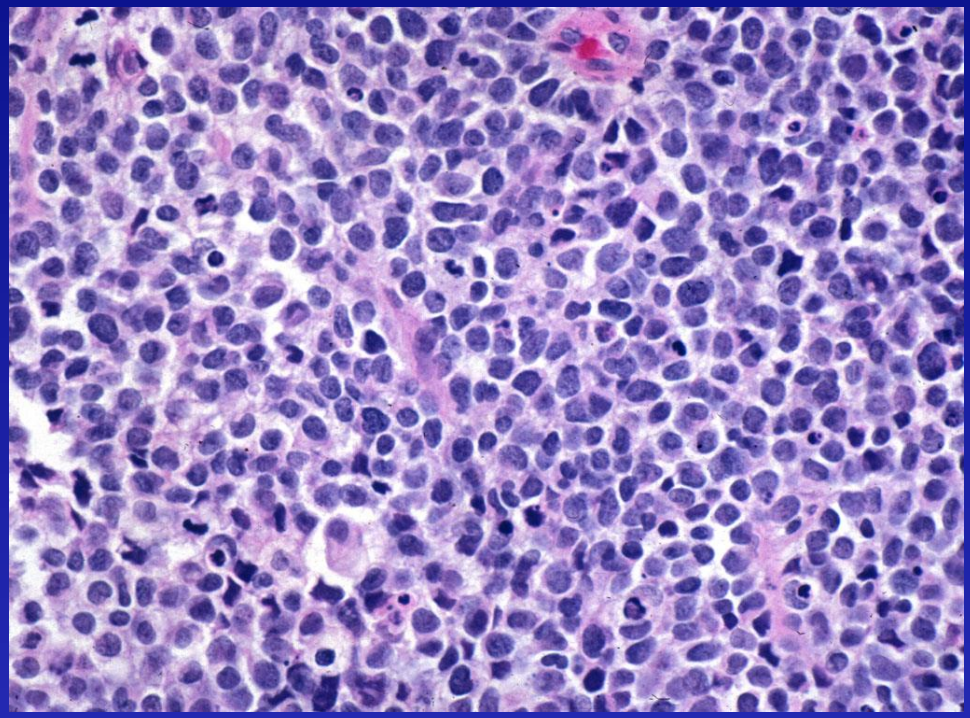
Case 4

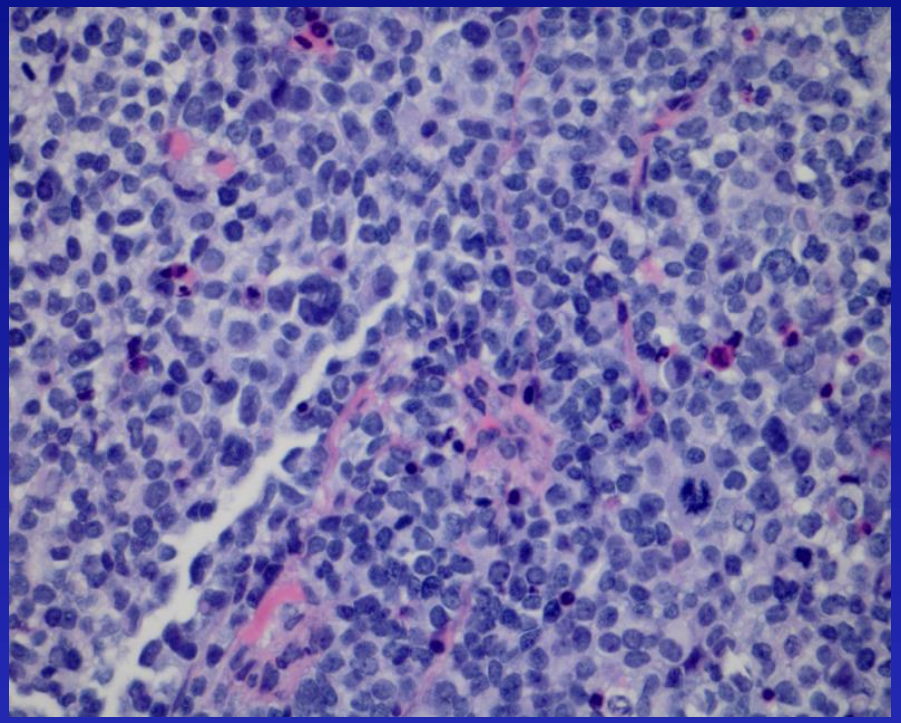






Case 4



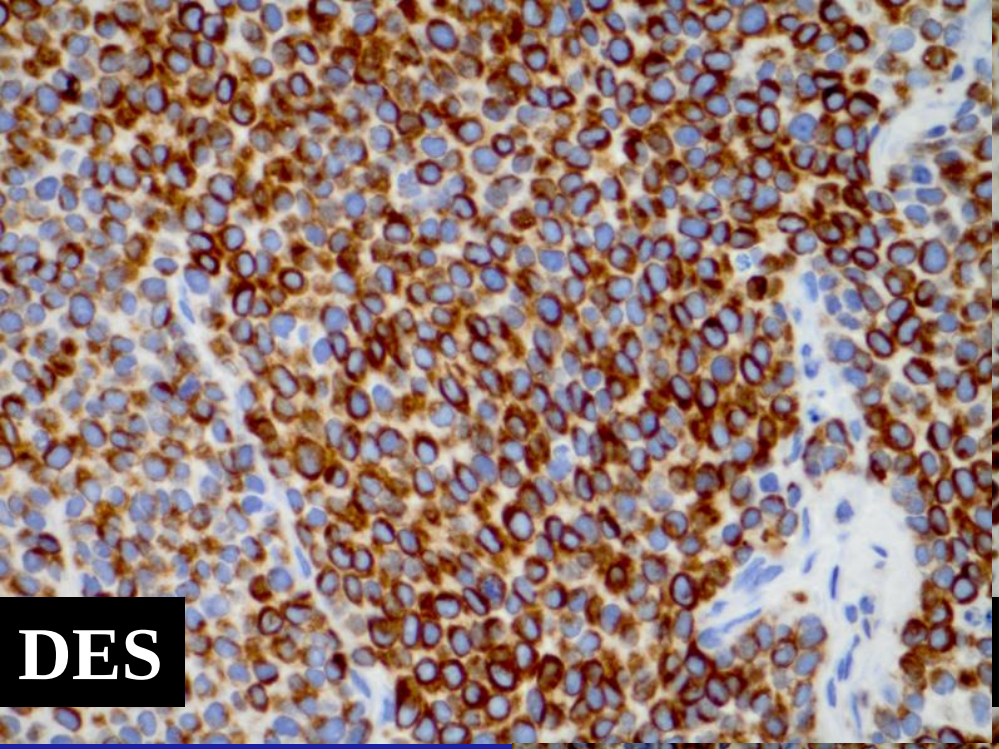


Case 4
Diagnosis ?

- Basaloid squamous cell carcinoma
- Ewing sarcoma
- Mucosal malignant melanoma
- Nasal type NK/T cell lymphoma
- Poorly-differentiated neuroendocrine carcinoma, small cell type
- Rhabdomyosarcoma, alveolar type

SNT Undifferentiated Malignant Neoplasms

- Squamous Cell Carcinoma
- Sinonasal Undifferentiated Carcinoma (SNUC)
- NUT Midline Carcinoma*
- SMARCB1 (INI-1)-Deficient Carcinoma*
- HPV-associated multiphenotypic sinonasal carcinoma (formerly HPV-associated carcinoma with adenoid cystic-like features*)
- Olfactory Neuroblastoma
- Mucosal Malignant Melanoma
- Neuroendocrine Carcinomas
- Malignant Lymphoma (NK/T cell Lymphoma)
- Rhabdomyosarcoma
- Ewing Sarcoma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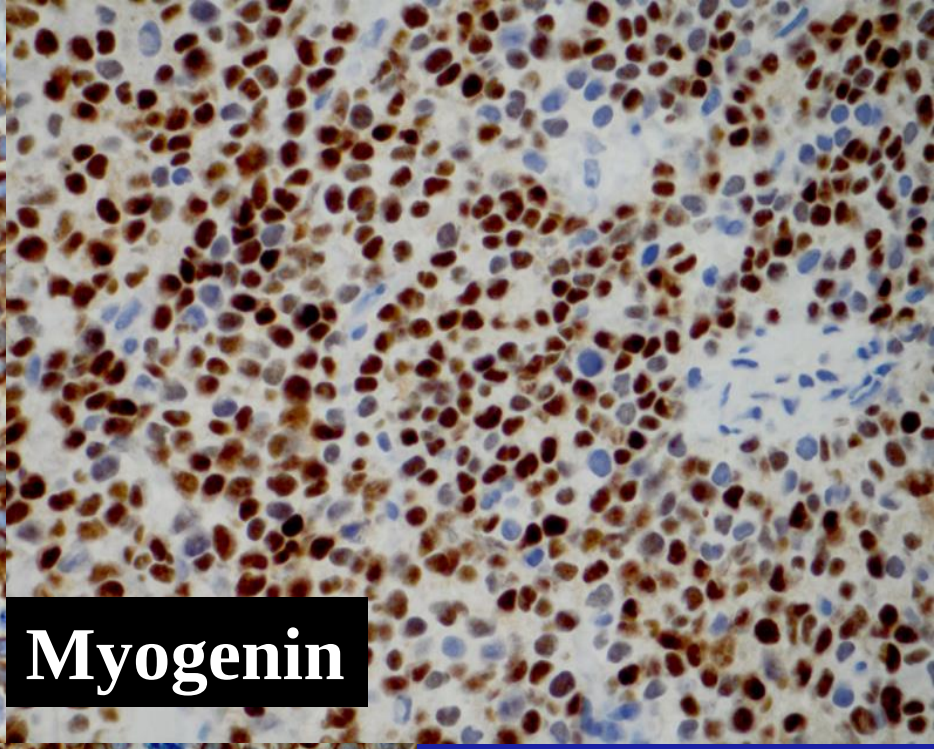
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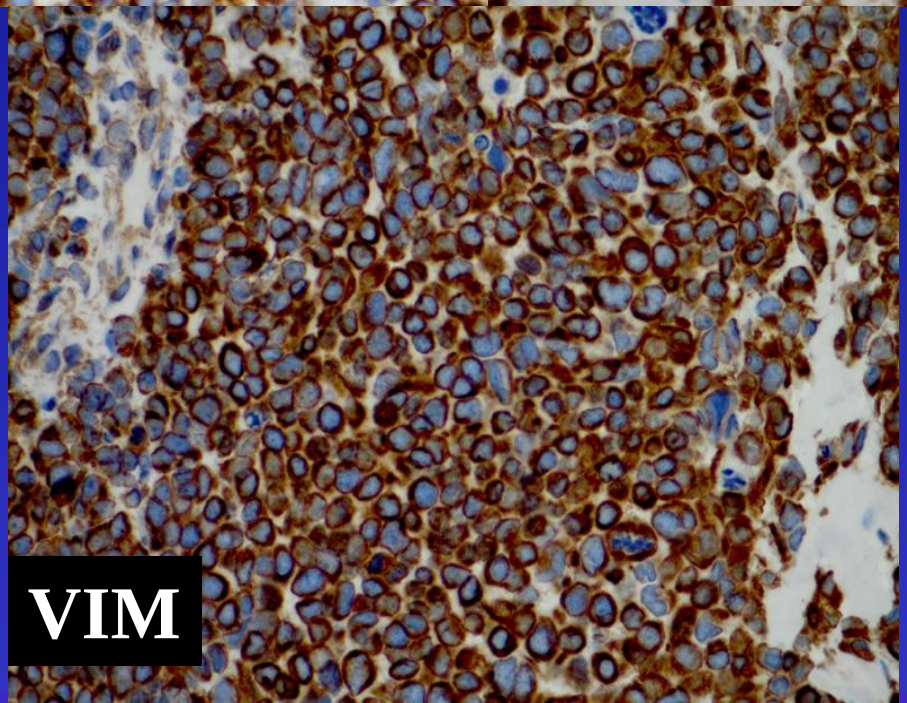
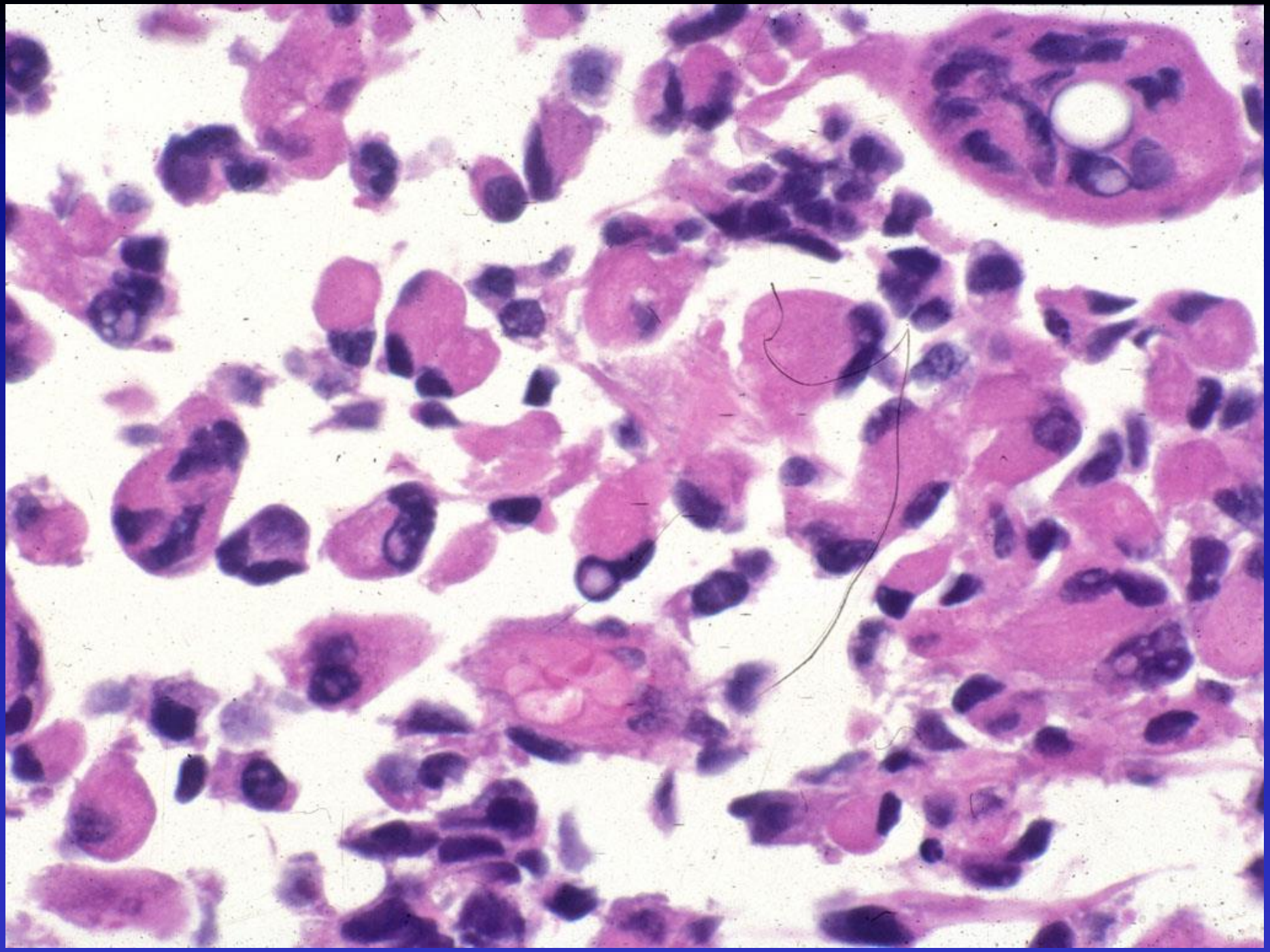

VIM

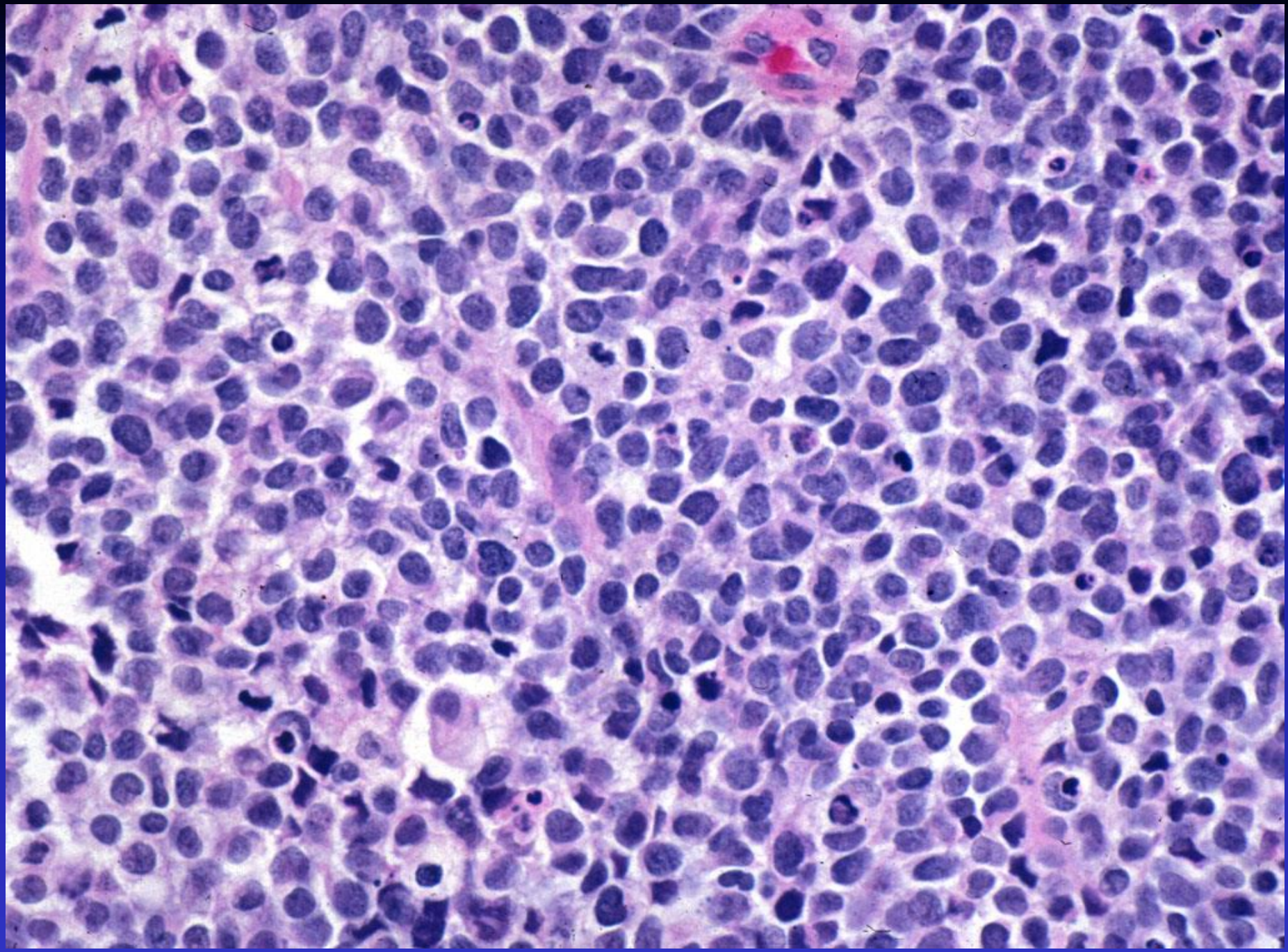
Case 4
Diagnosis

- **Alveolar rhabdomyosarcoma, solid type**

Rhabdomyosarcoma (RMS) Definition

- Malignant mesenchymal neoplasm of skeletal muscle cells (rhabdomyoblasts)



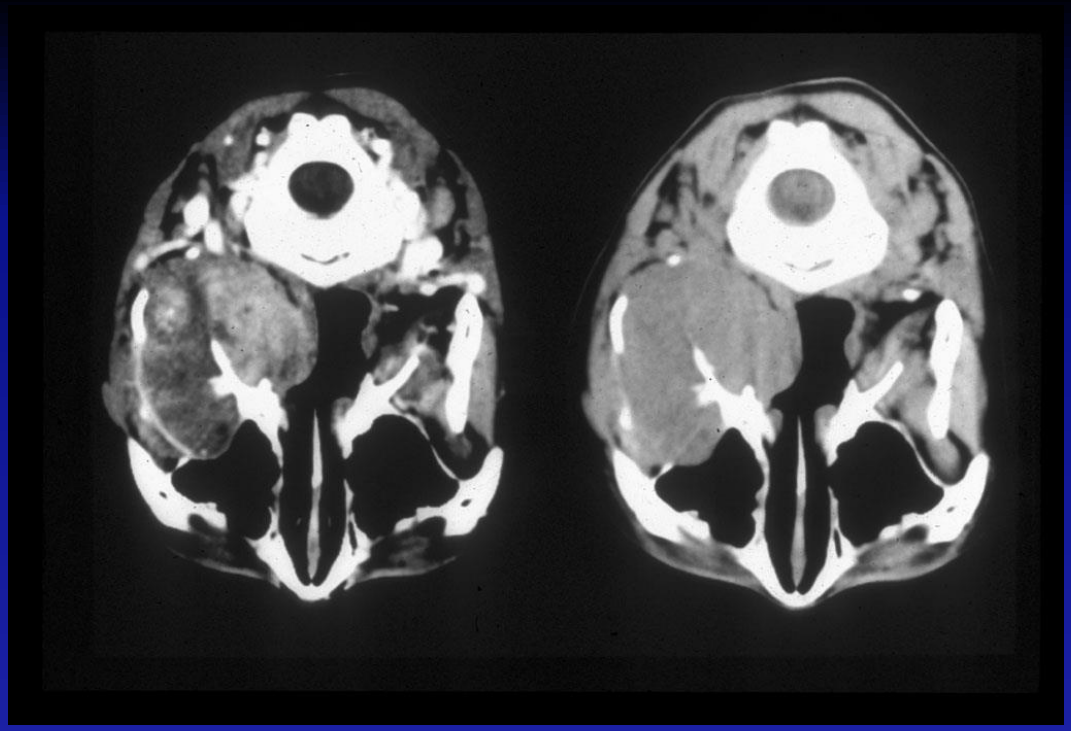


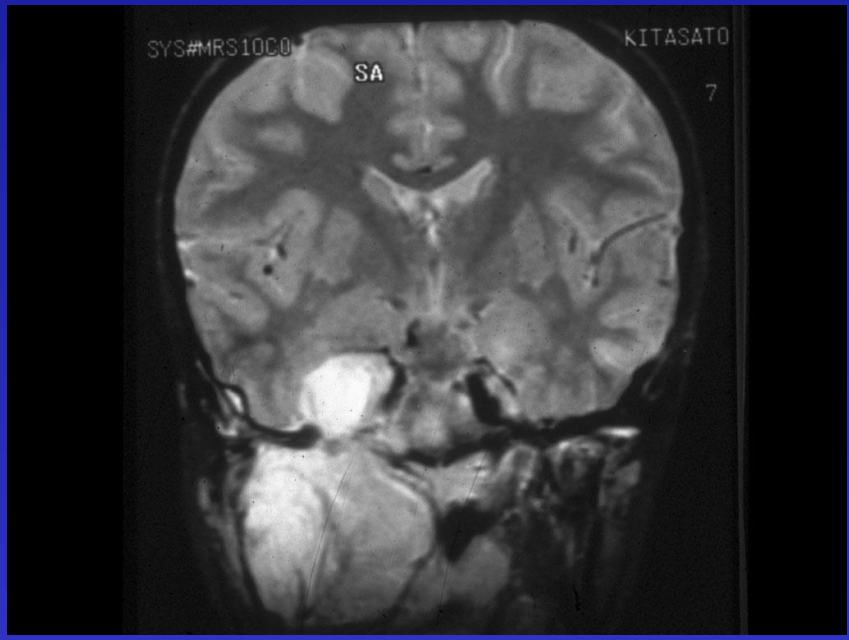
Head & Neck RMS
General Considerations

- Most common sarcoma of the H&N:
  - All ages: represents up to 50% of H&N sarcomas;
  - Pediatric RMS: represents up to 75% of H&N sarcomas
- Sites:
  - orbit > nasopharynx > ME/mastoid > SNT
- Symptoms dependent on site of occurrence

Sinonasal Tract RMS
Clinical Findings

- M=F; 1st and 2nd decades of life but occurs in adults
- Symptoms: nasal obstruction, rhinorrhea, epistaxis, sinusitis, pain, otalgia, headache, proptosis, visual disturbances, cranial nerve deficits
- Polypoid appearing mass that clinically may simulate the appearance of a nasal polyp (25% of RMS in the SNT are botryoid type)
- No known etiologic factors

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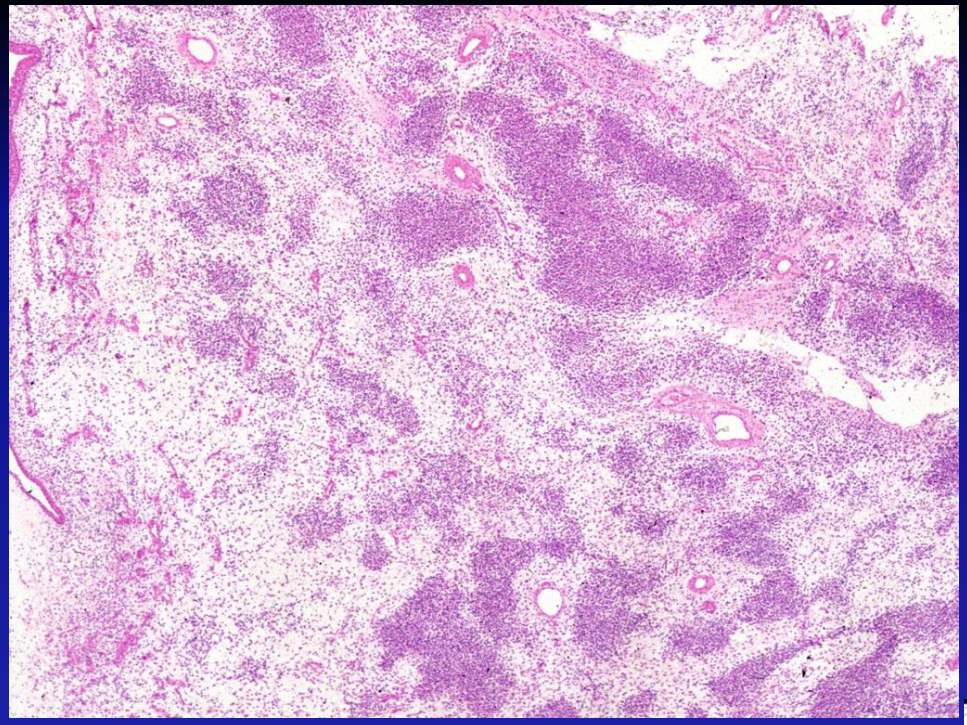
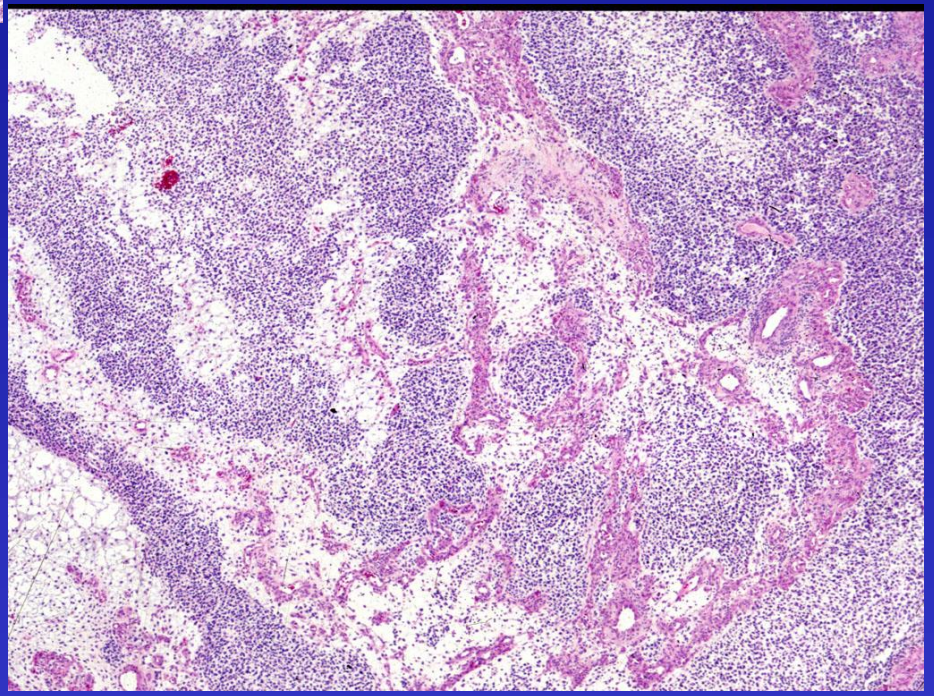
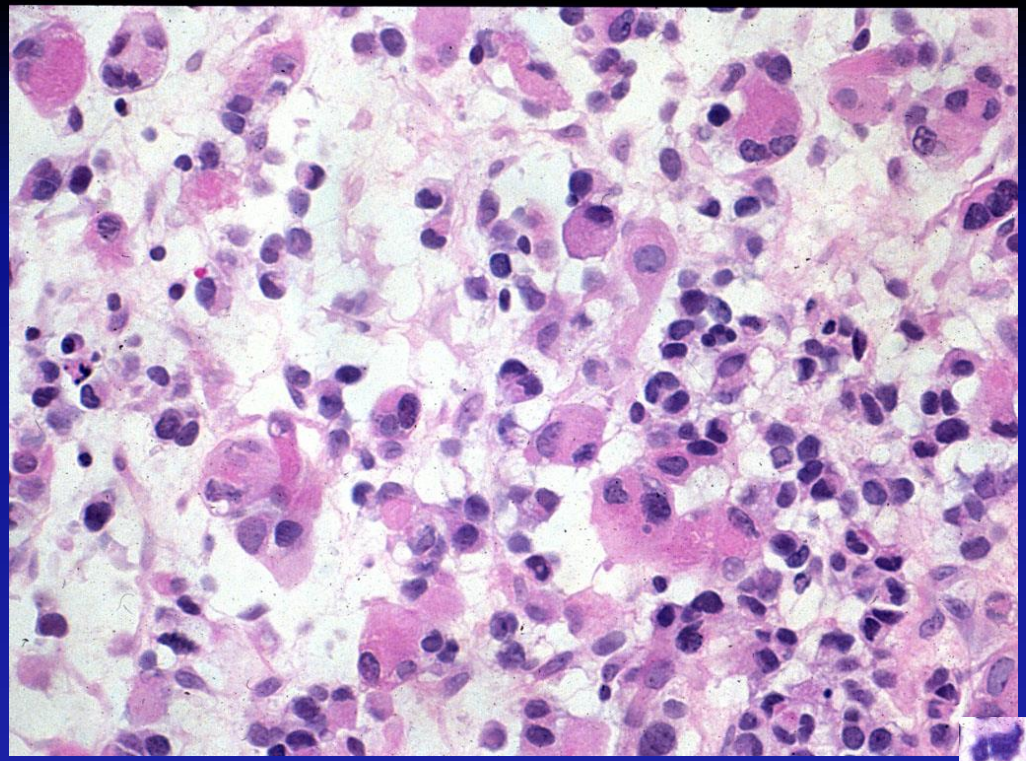
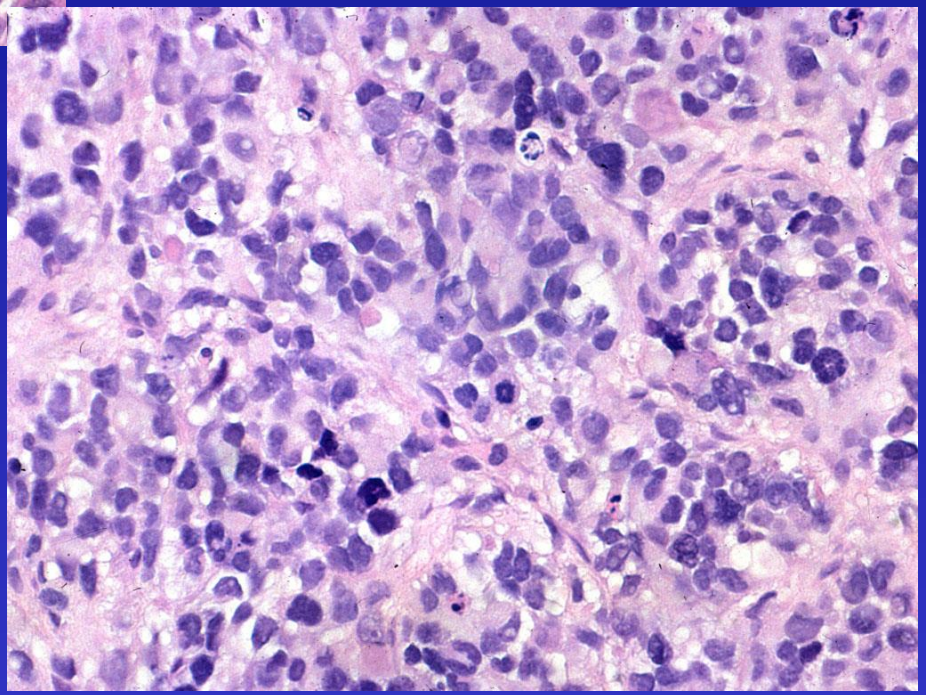
Rhabdomyosarcoma (RMS) Histologic Types

- Embryonal:
  - most common type (80-85%)
  - Botryoid type
  - spindle cell type
- Alveolar:
  - 10-15%
  - more frequent in adult population
- Pleomorphic RMS







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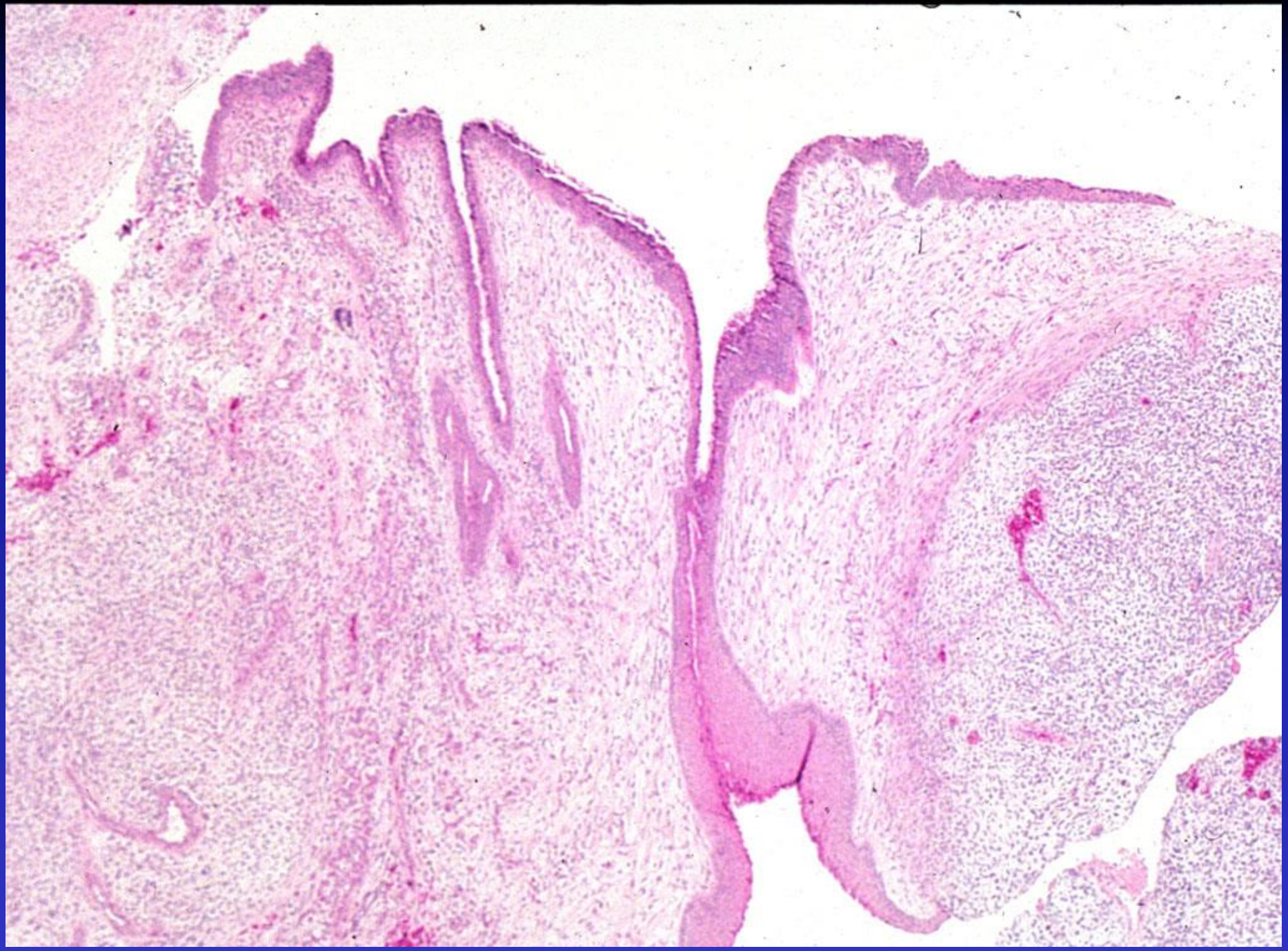

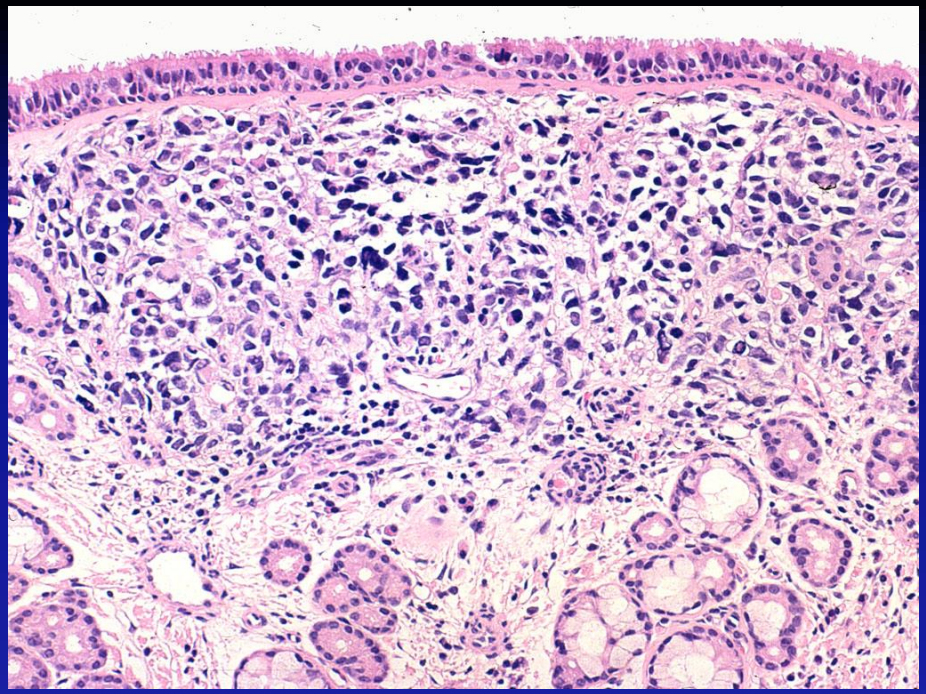

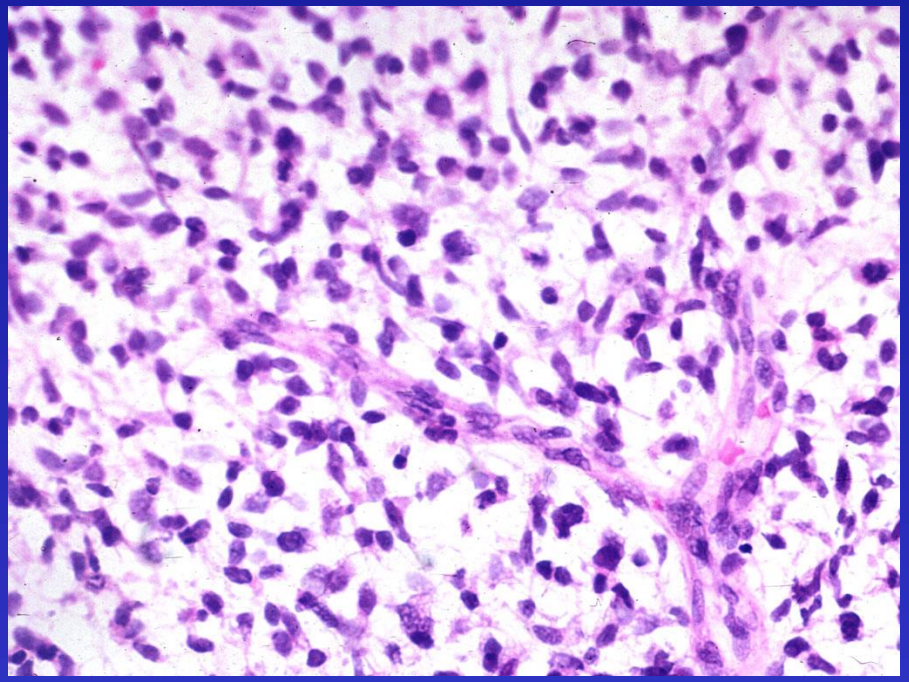

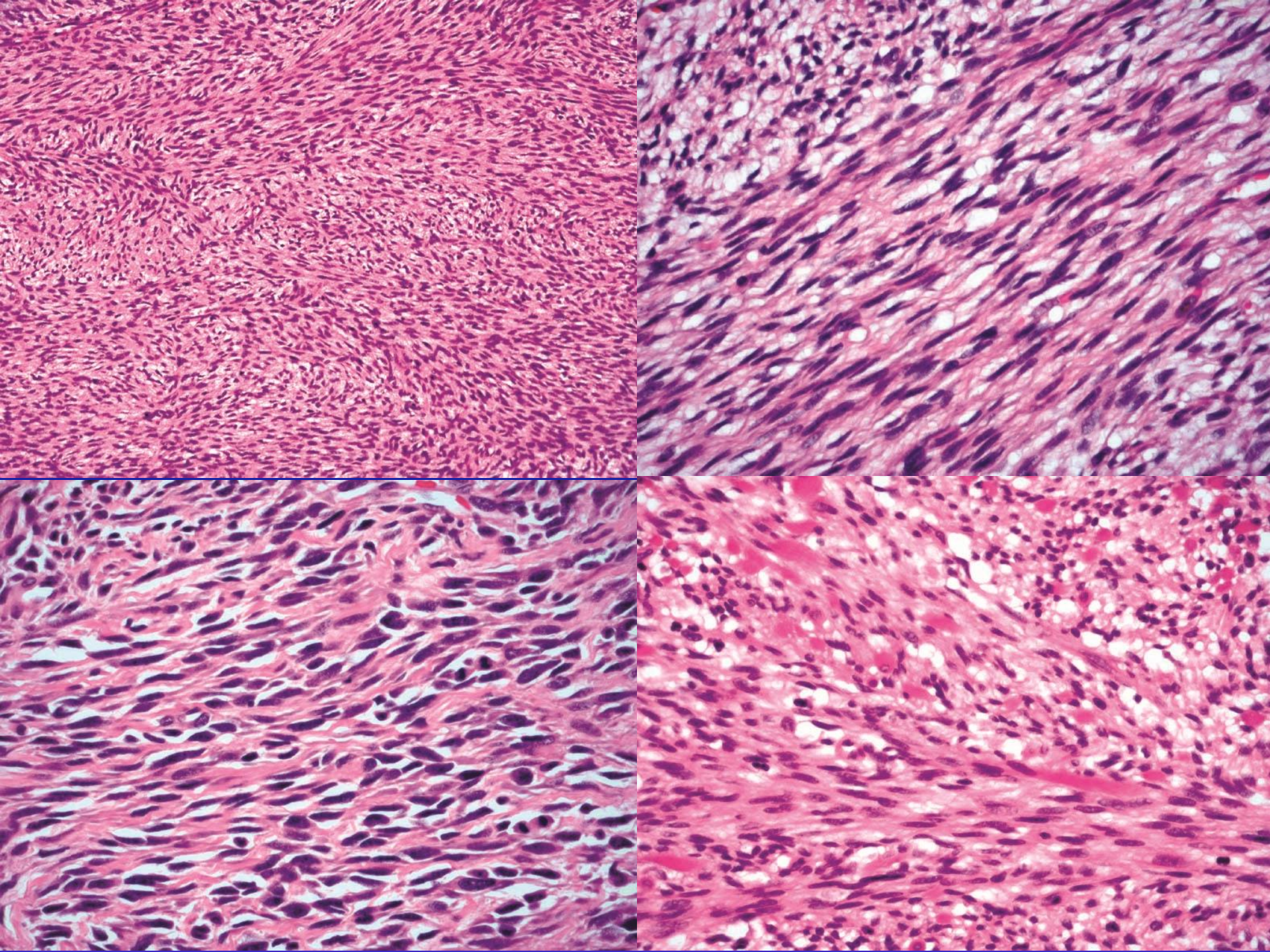

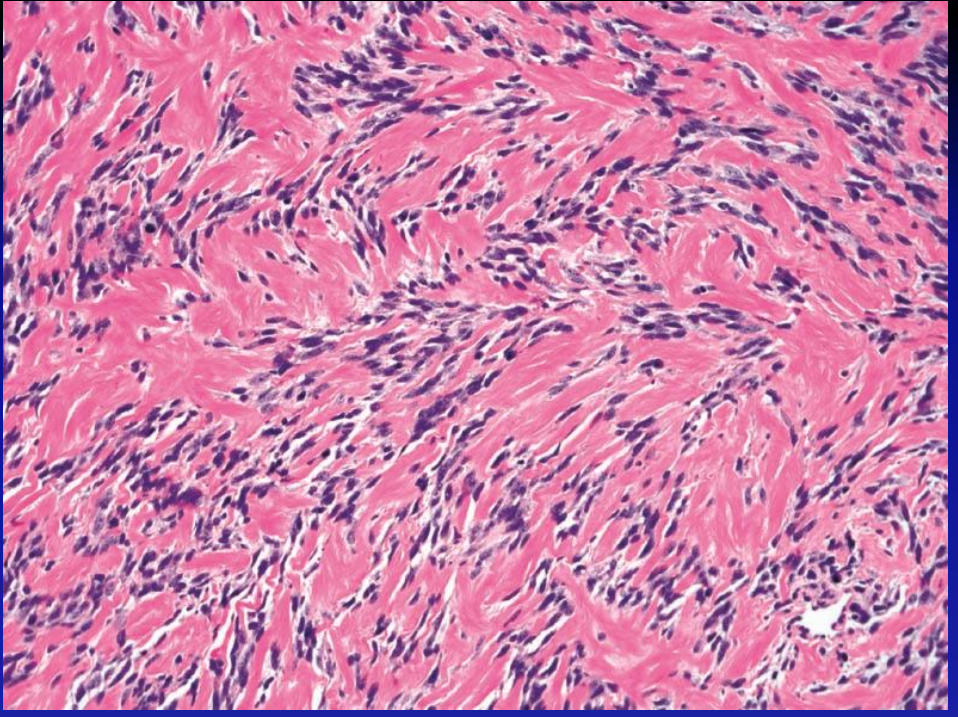

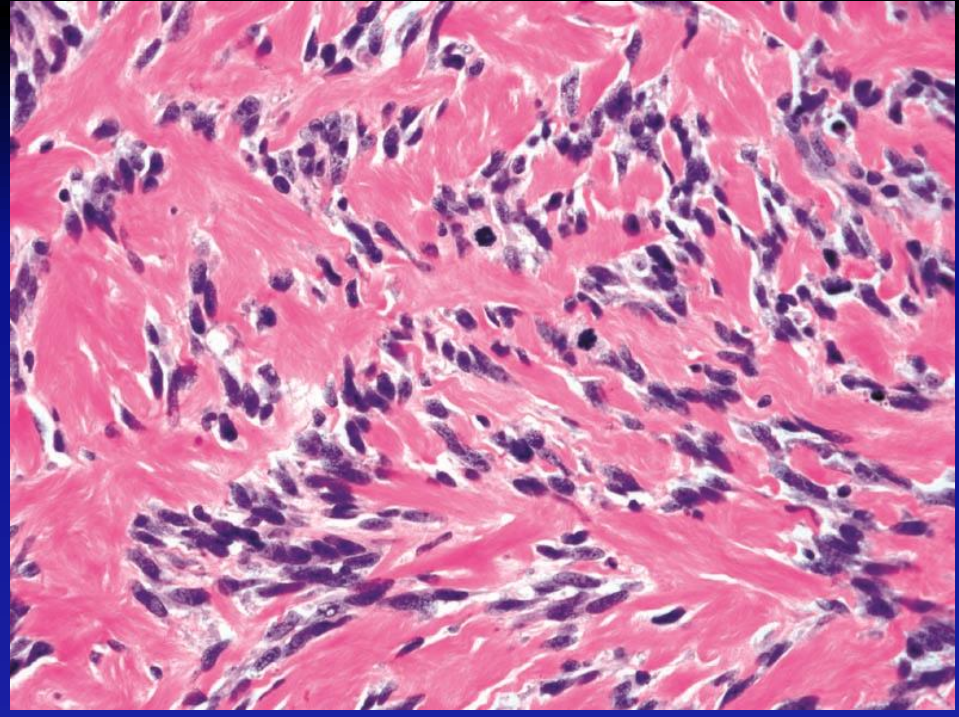

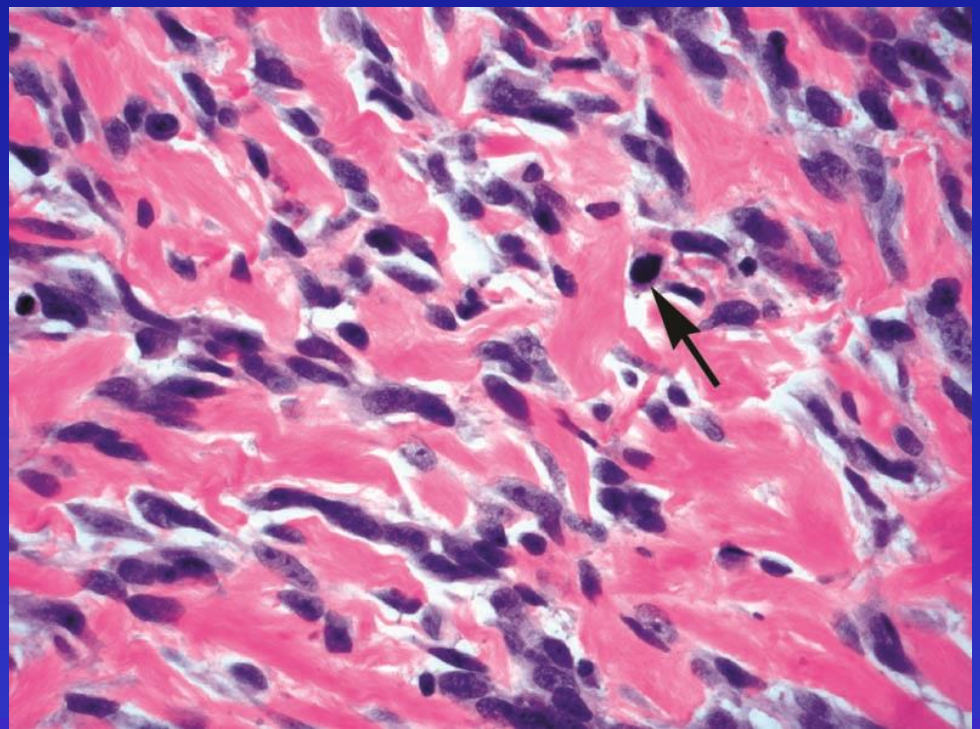

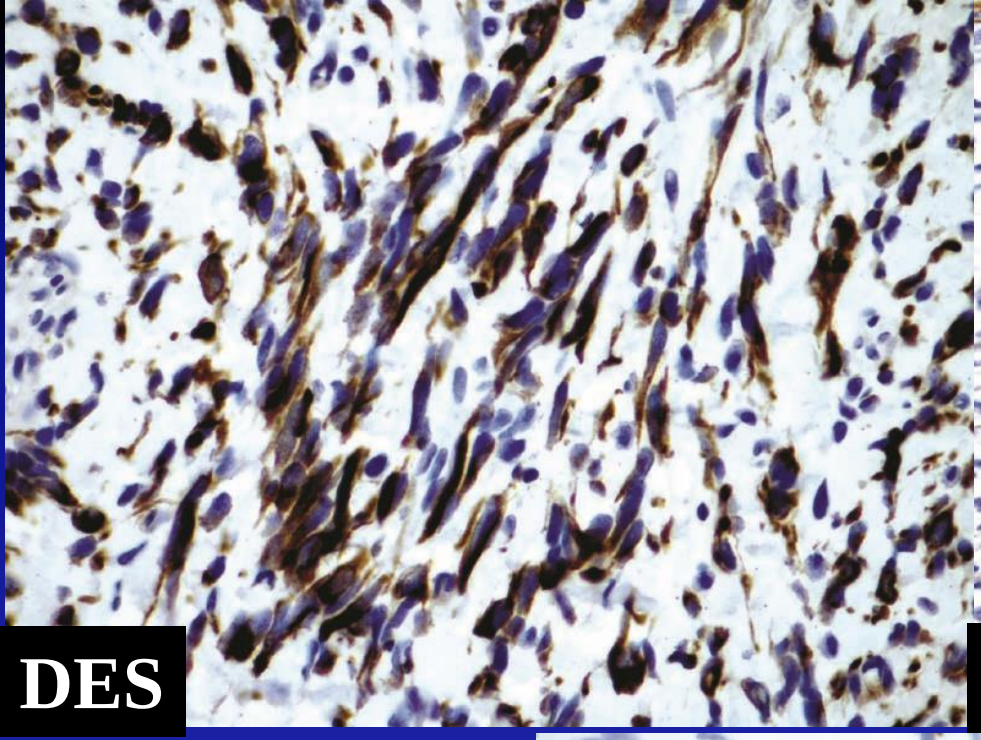
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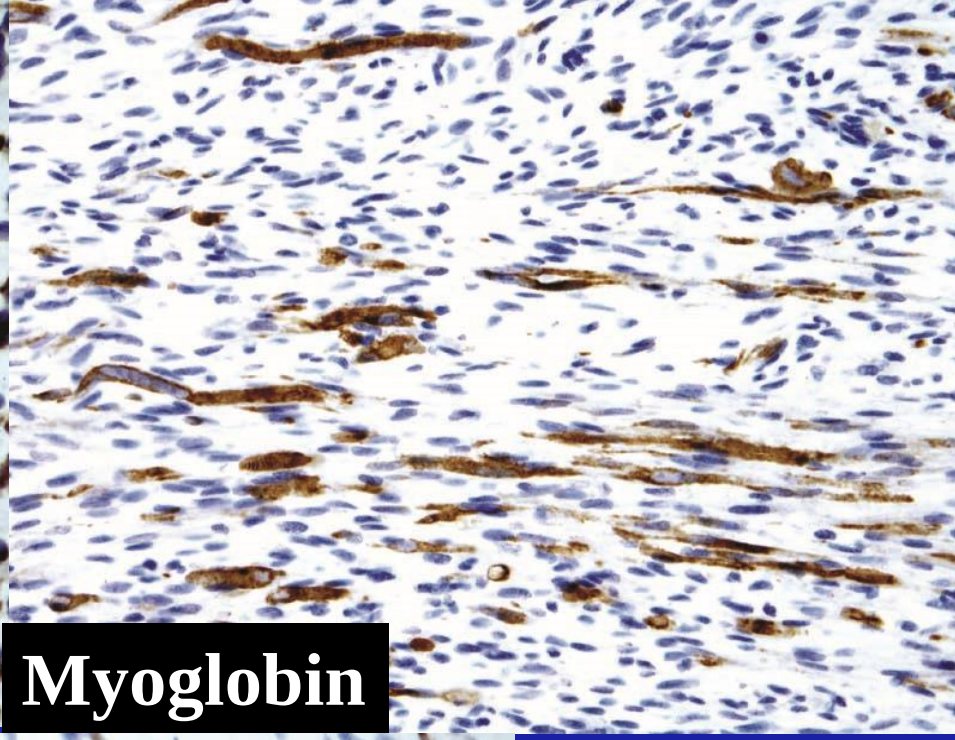
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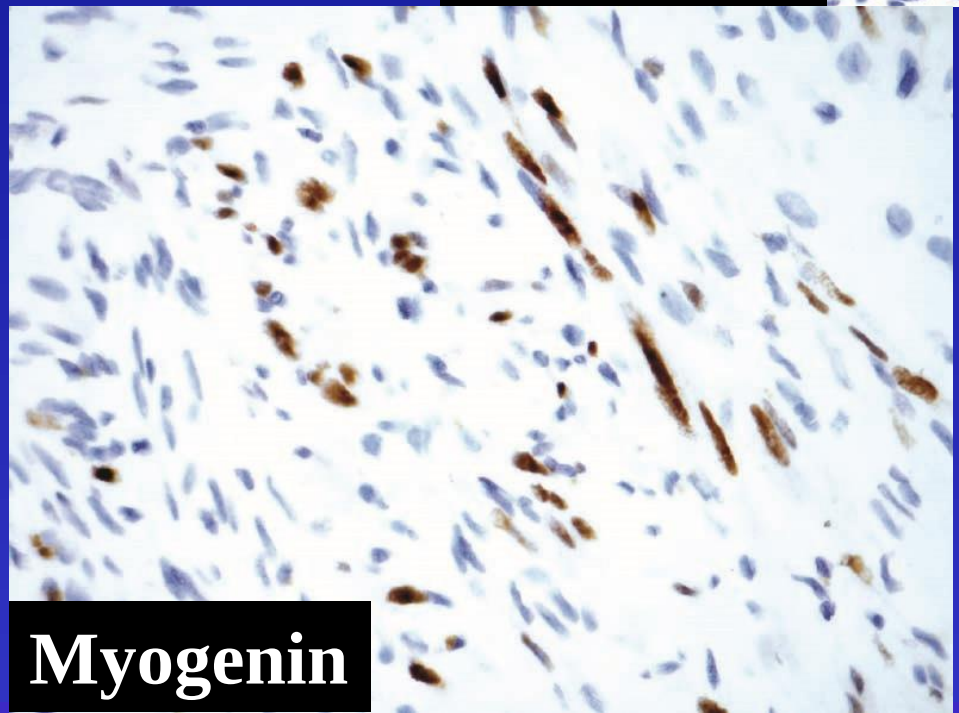
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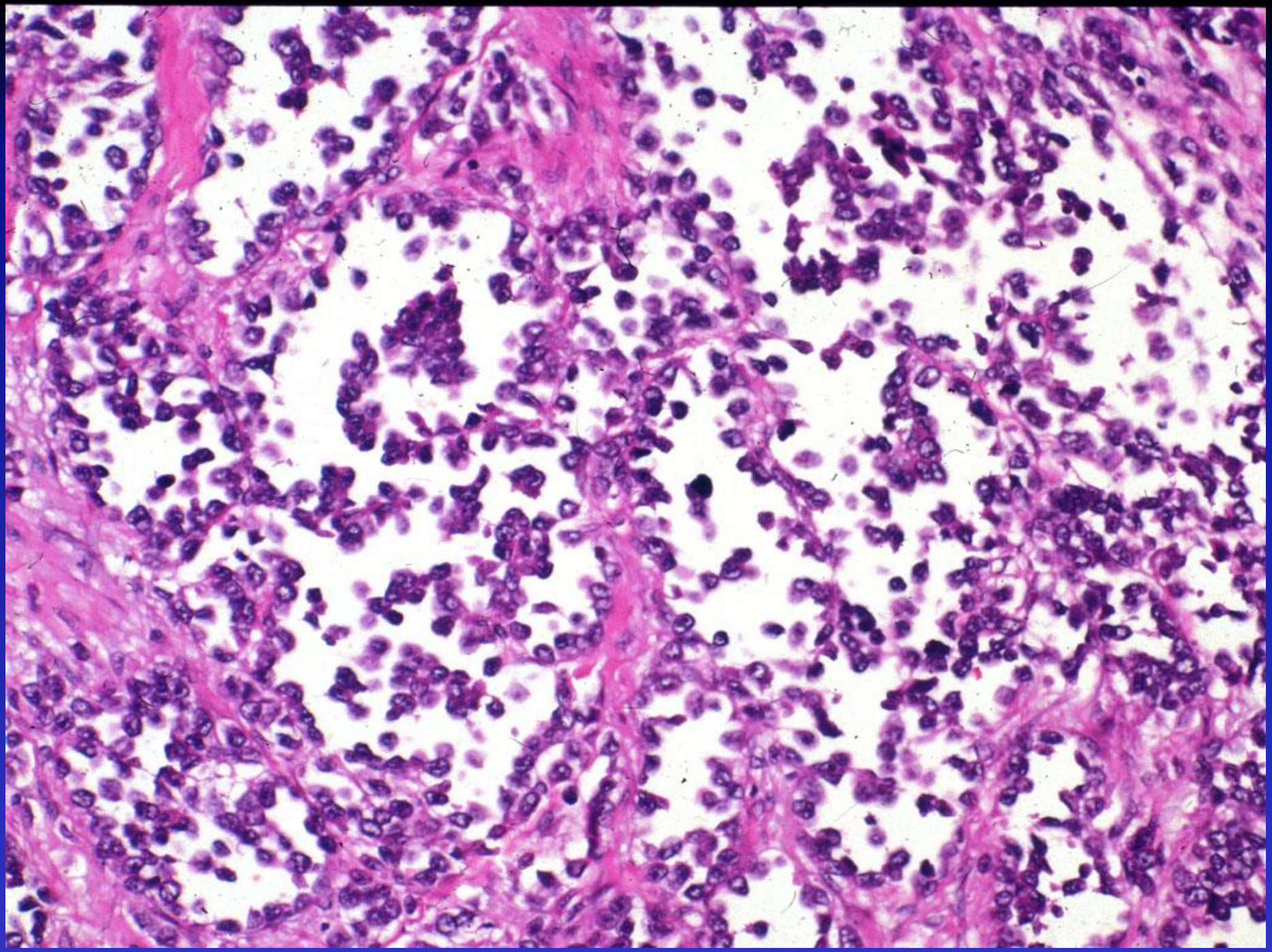
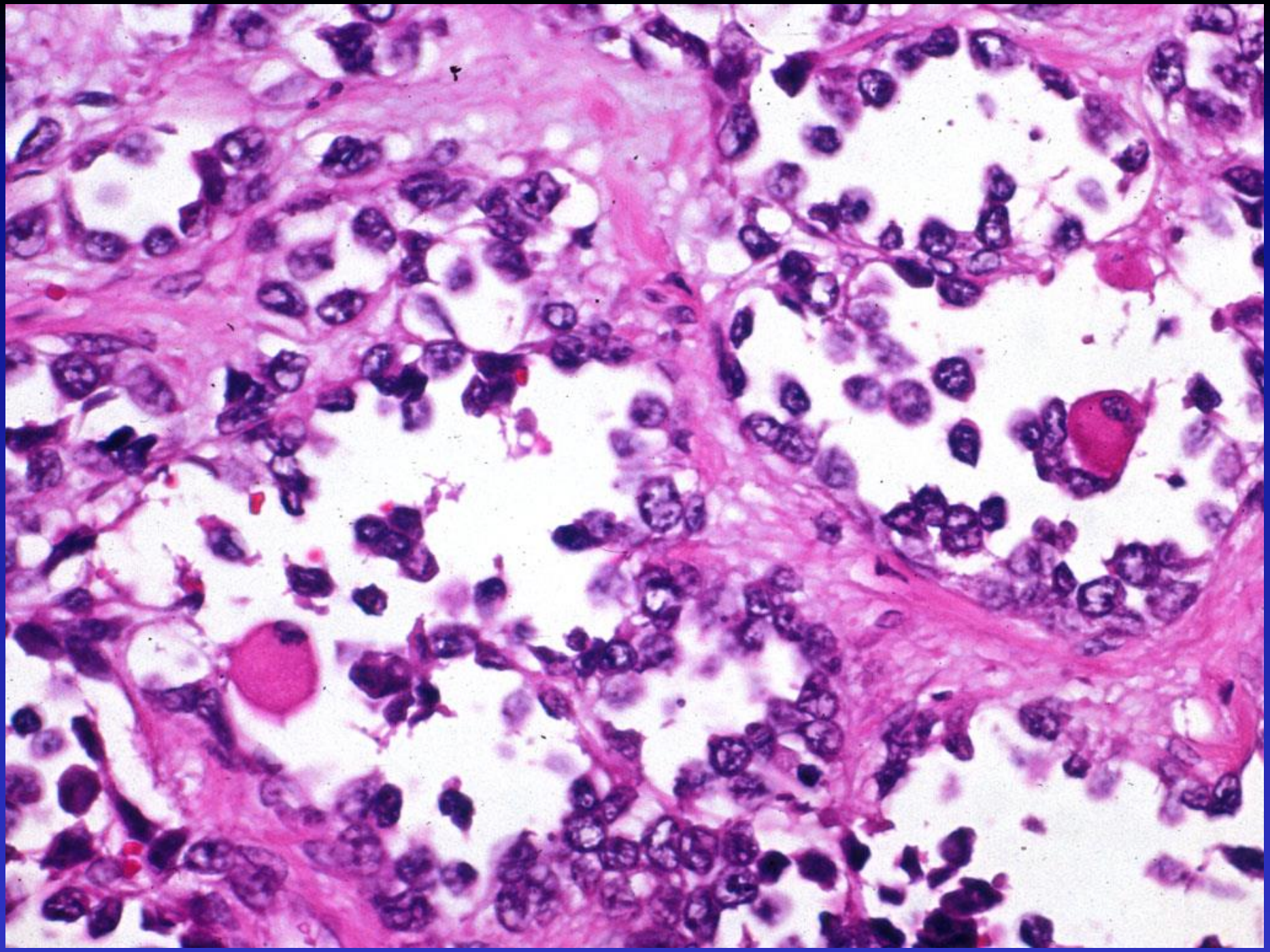
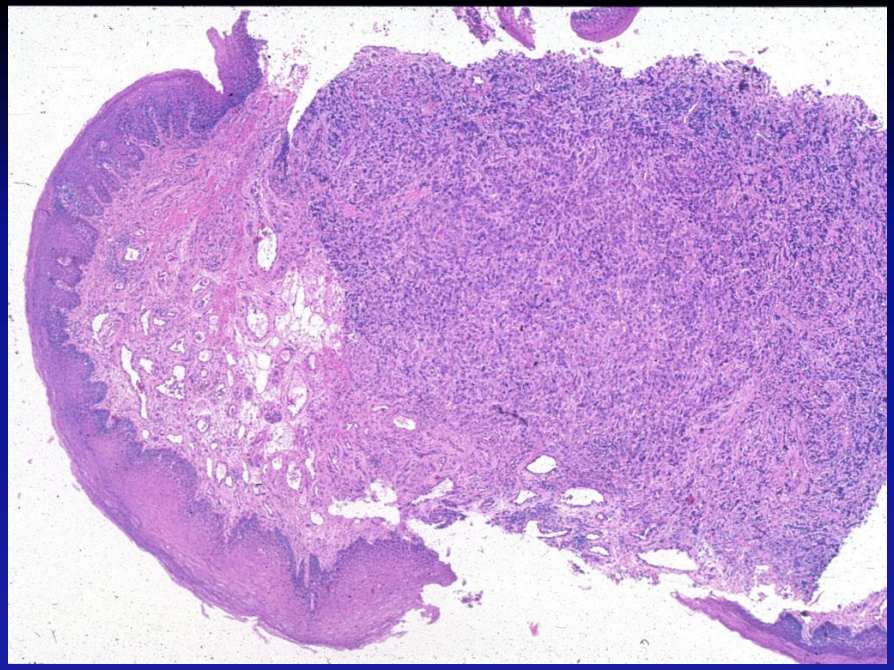
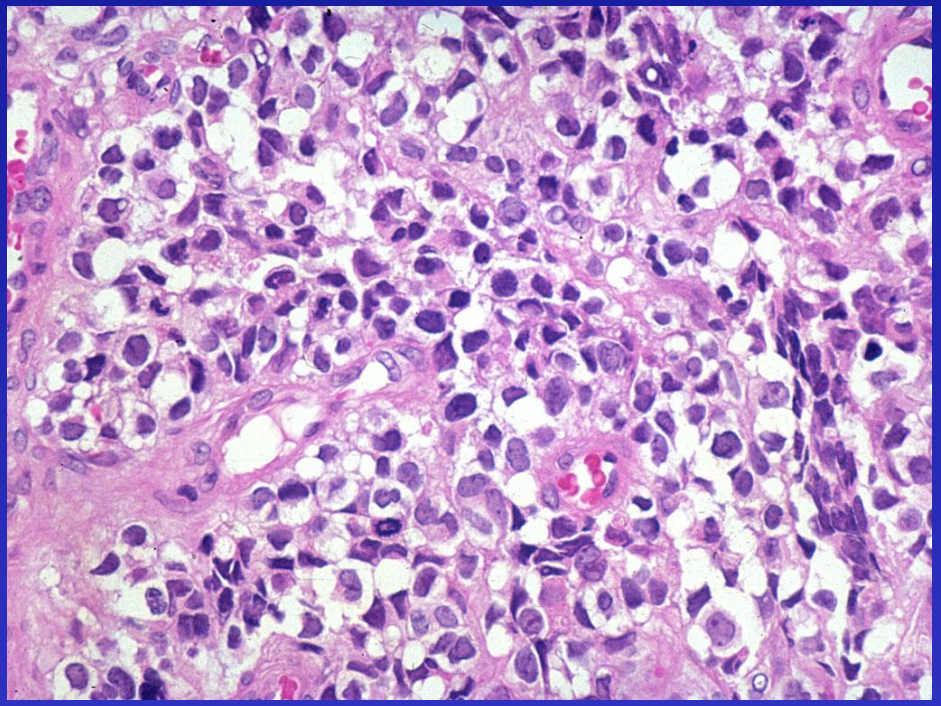
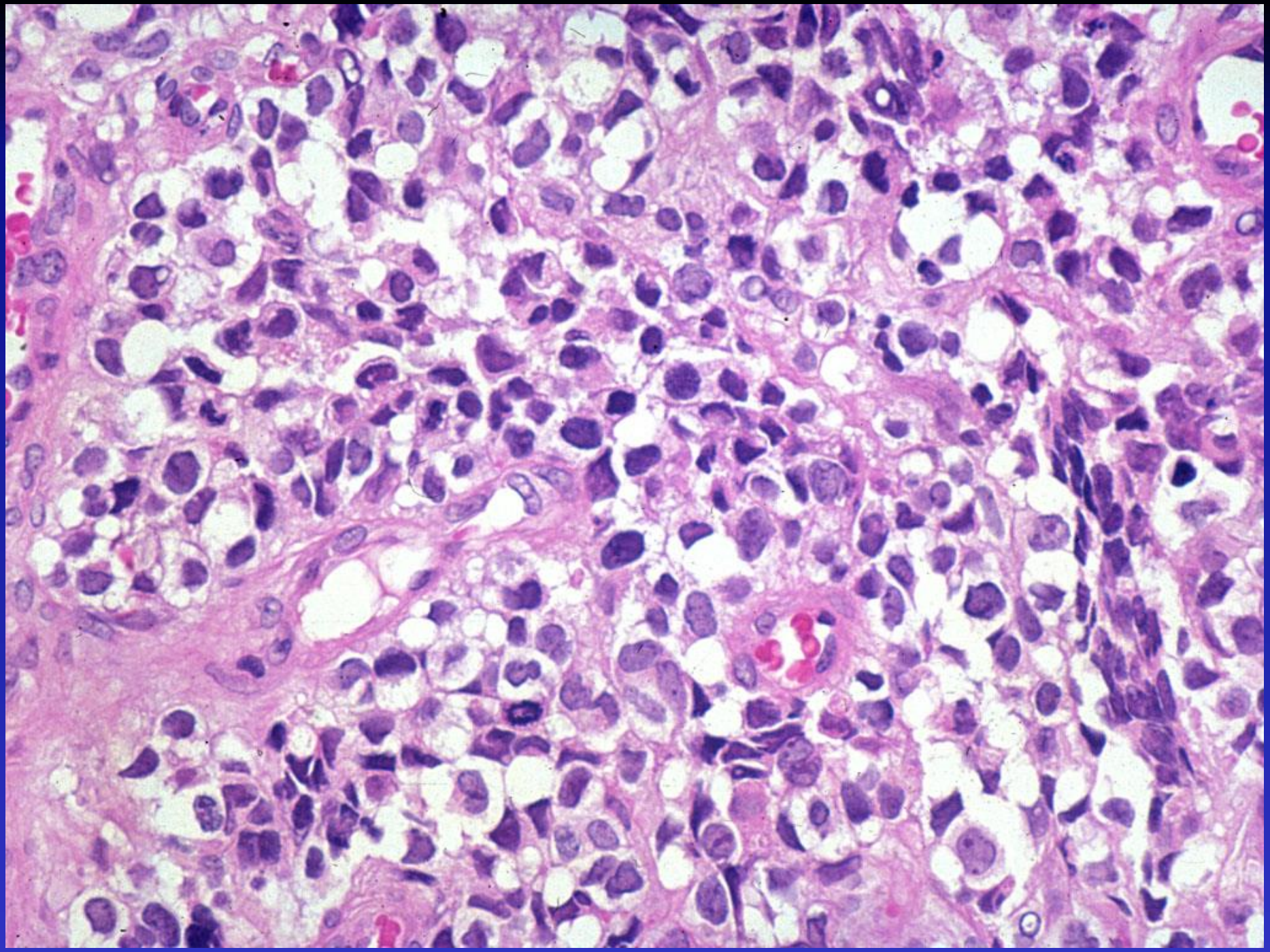
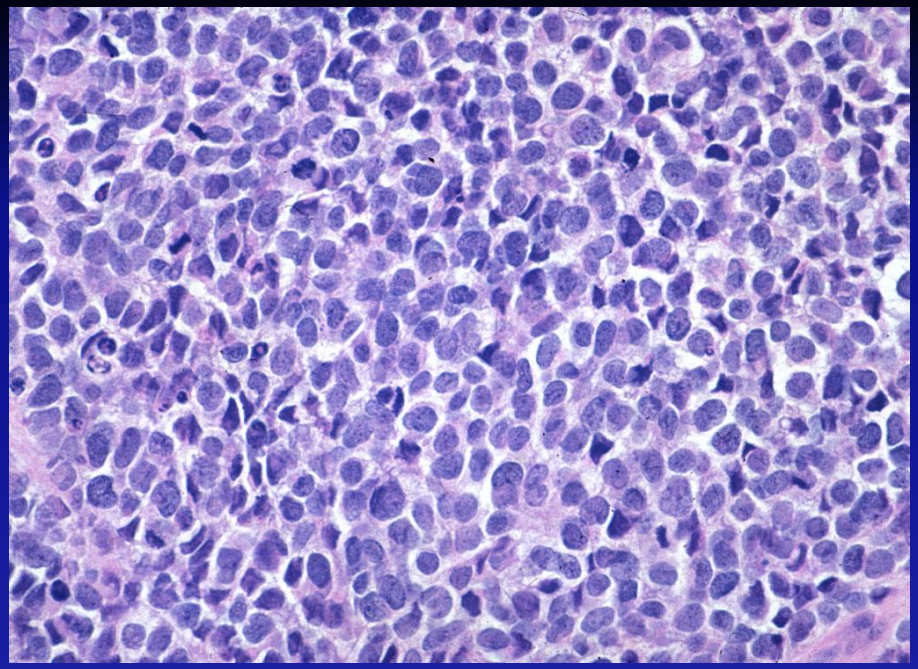


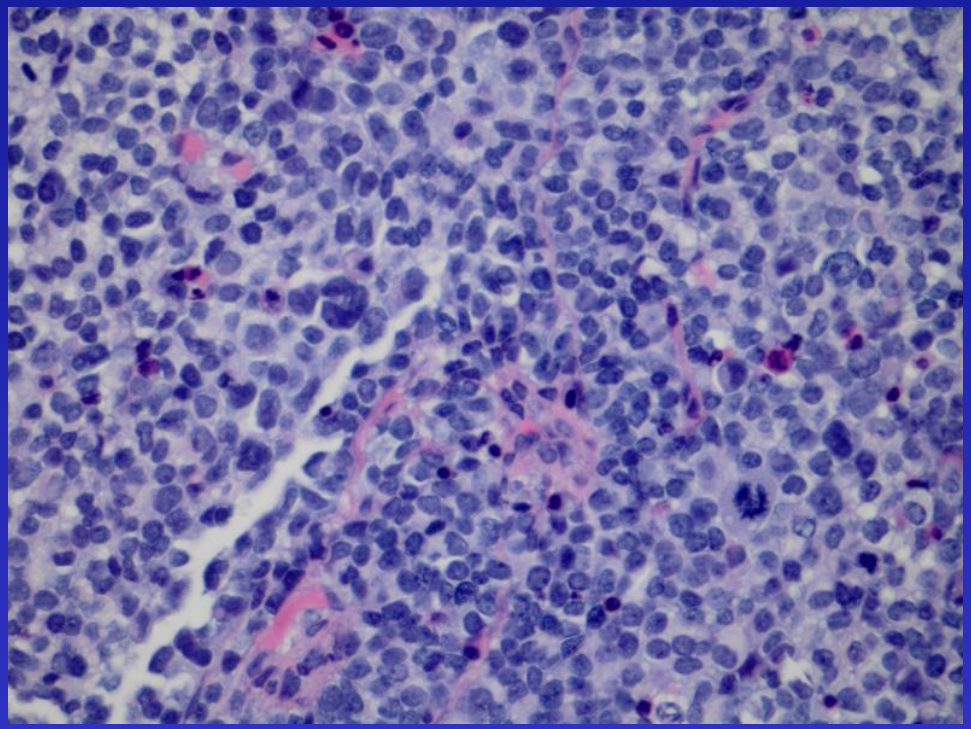












RMS
Special Stains

- **Histochemistry:**
  - **diastase-sensitive, PAS-positive (glycogen)**
- **IHC:**
  - **Myogenic markers: desmin, HHF35, myogenin (myf-4), myoglobin**
  - **Vimentin**

Genetic Abnormalities

- **Alveolar RMS:**
  - **t(2;13)(q36;q14) translocation – 60% of cases:**
    - **results in a *PAX3-FOXO1A* fusion gene on chromosome 13 and a *FOXO1A-PAX3* fusion gene on chromosome 2**
    - ***PAX3-FOXO1A* fusion appears to be more sensitive and specific than *FOXO1A-PAX3* in detecting RMS**

Genetic Abnormalities

- **Alveolar RMS:**
  - **t(1;13)(p36;q14) translocation – 20% of cases; juxtaposes *PAX7* gene on 1p36 with *FOXO1A* gene on 13q14;**
  - **approximately 80% have *PAX3-FOXO1A* fusion or *PAX7-FOXO1A* fusion**
  - **approximately 20% lack either of these fusions**

Biphenotypic Sinonasal Sarcoma

- **Low-grade spindle cell sarcoma with distinctive histological, IHC and molecular features:**
  - **Recurrent *PAX3-MAML3* gene fusion; subset harbor *PAX3-FOX01* & *PAX3-NCOA1* same as alveolar RMS**
- **Low-grade sinonasal sarcoma with neural and myogenic features**
- **Intimate association with epithelial proliferation (glands invaginating from surface)**

SNUC
Definition

- **An undifferentiated carcinoma of the sinonasal tract without glandular or squamous features and not otherwise classifiable (WHO 2017)**

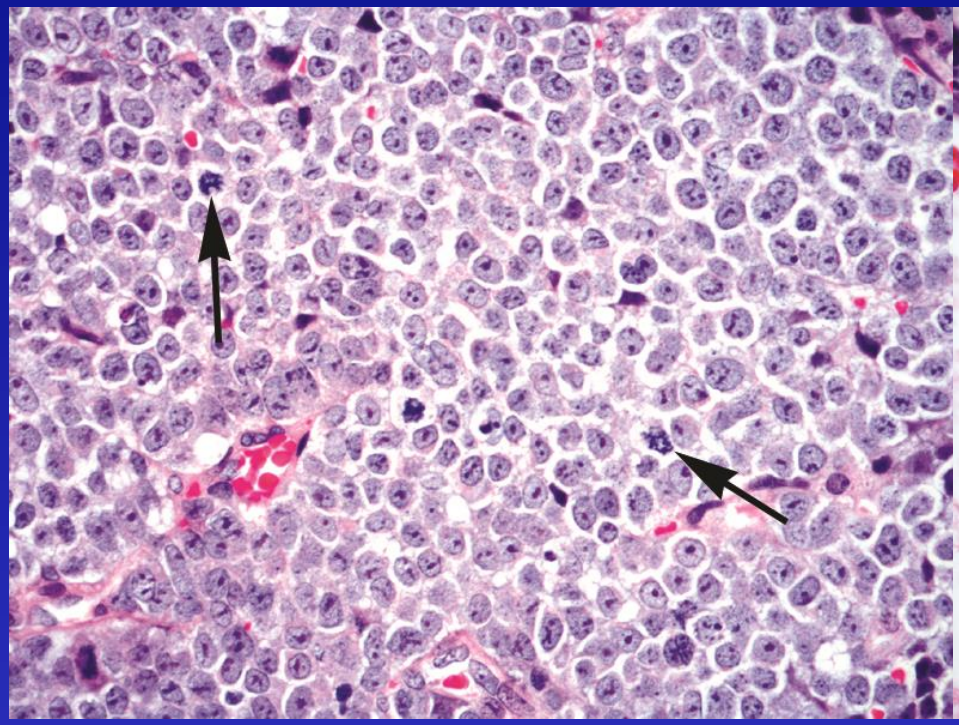
SNUC
Clinical Findings

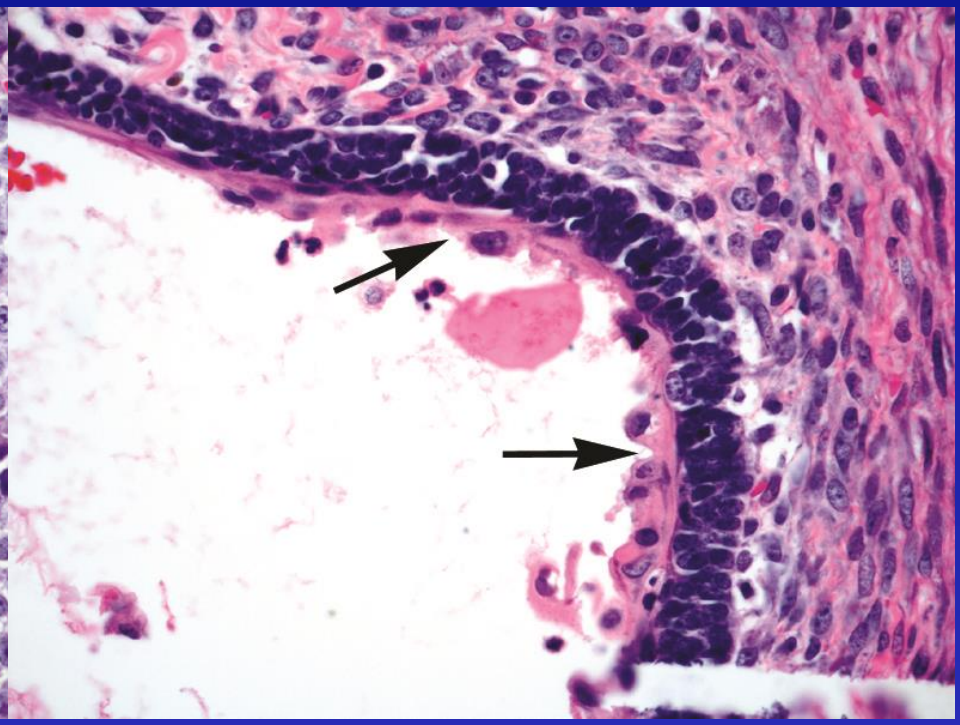
- Uncommon
- Male predominance (2-3:1)
- Broad age range (3^{rd}-9^{th} decades); median age at presentation 6th decade
- Presents as large mass involving multiple sites with extensive invasive growth
- Multiple symptoms: nasal obstruction, epistaxis, proptosis, cranial nerve palsies, visual disturbances, pain, other
- <u>Symptoms are usually of short duration (weeks to months)</u>

NUT Carcinoma

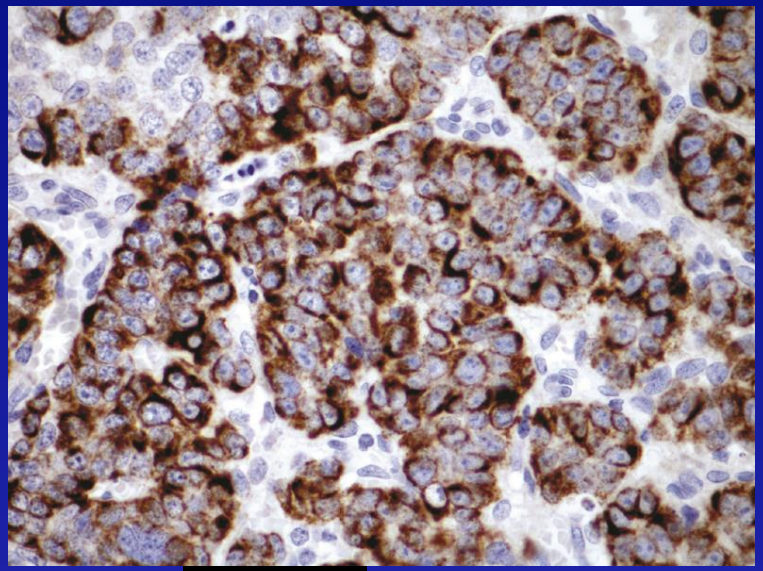
- **Poorly-differentiated carcinoma often with squamous differentiation defined by the presence of Nuclear protein in Testis (NUT) gene (*NUTM1*) rearrangement**
- **Vastly under-recognized and under-diagnosed**
- **Diagnosis should be considered in any non-smoking patient with poorly-differentiated squamous cell carcinoma**

NUT Carcinoma





NUT Carcinoma



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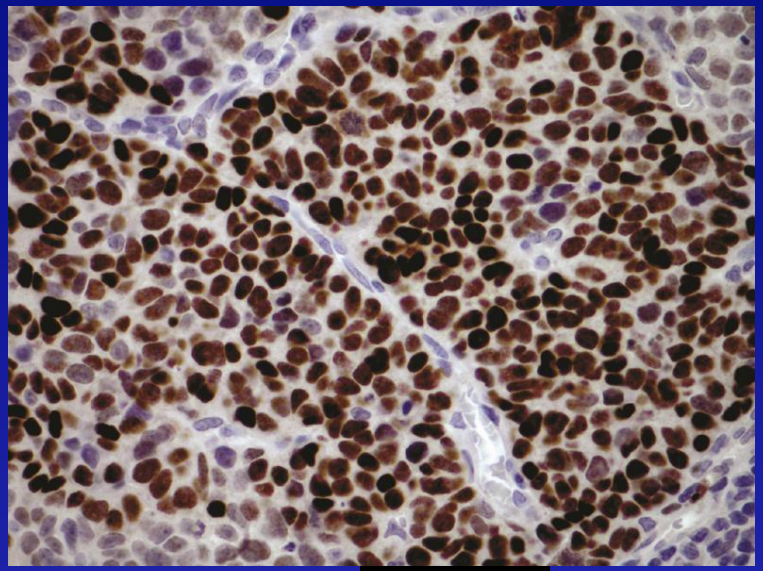

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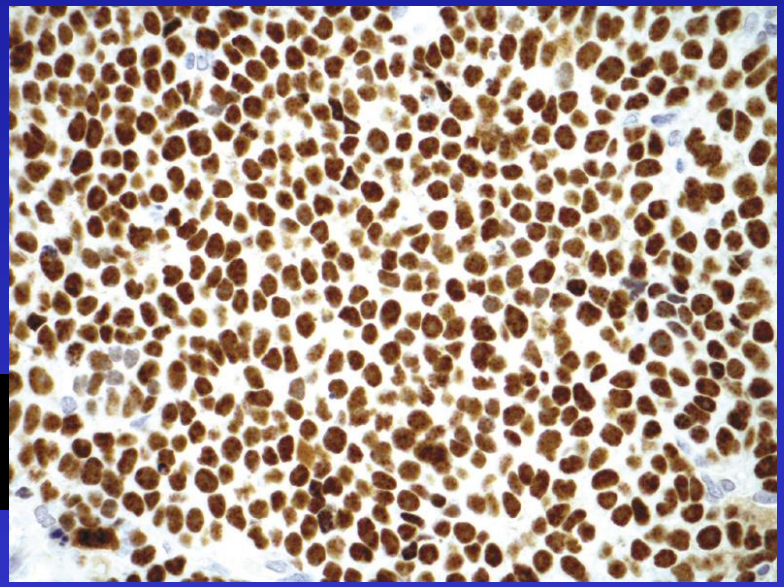


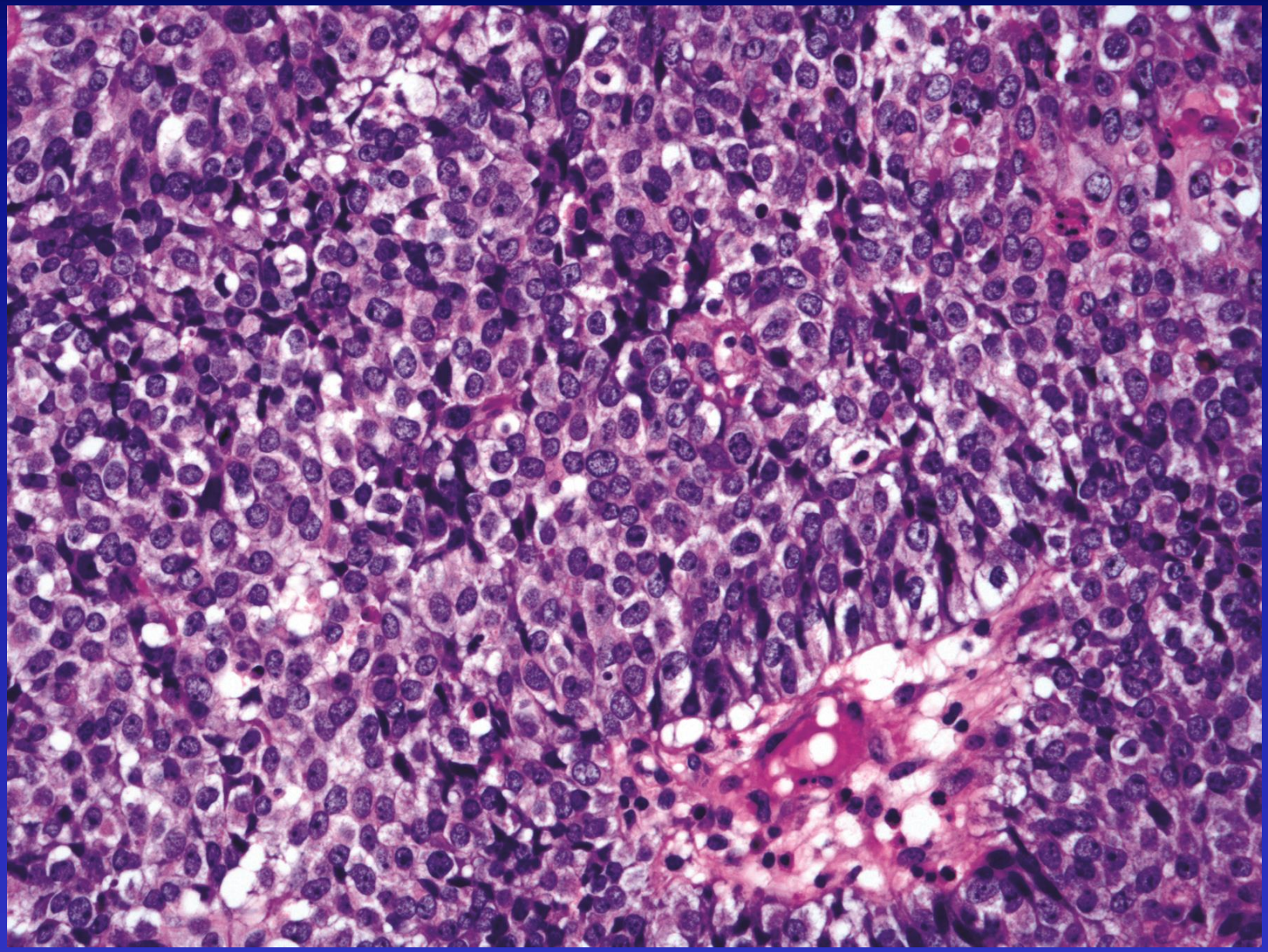
NUT

SMARCB1 (INI-1) Deficient Carcinoma - SNT* Definition

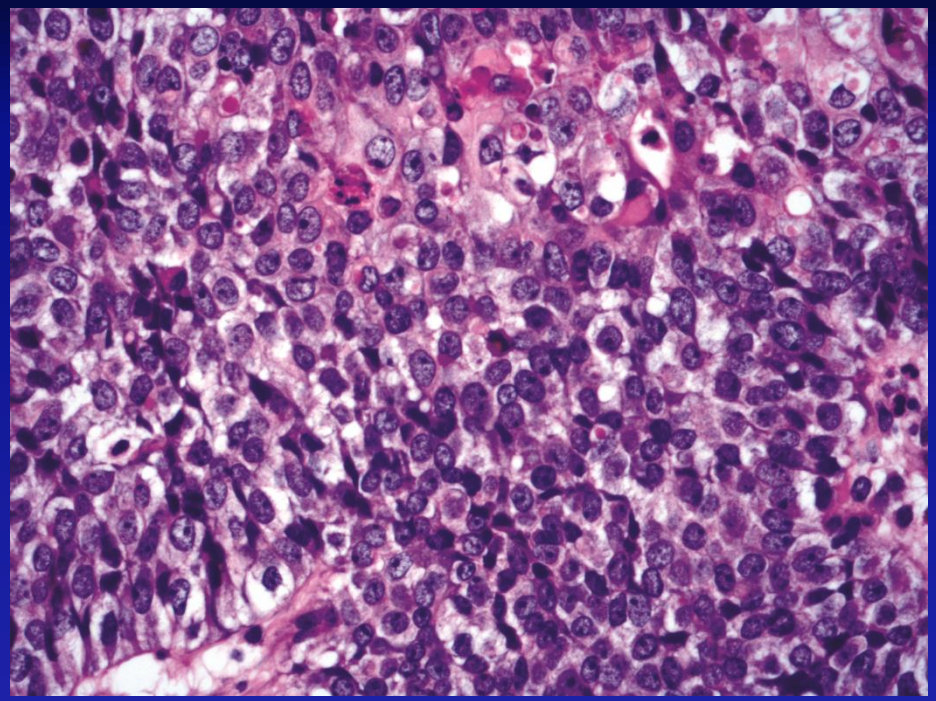
- Rare carcinoma characterized by:
  - basaloid and rhabdoid cells
  - loss of IHC expression of SMARCB1 (INI1)
  - SMARCB1 deletions by FISH
  - do not harbor HPV or NUT-1 alterations
  - Apparent aggressive clinical course including increased incidence of tumor-related mortality

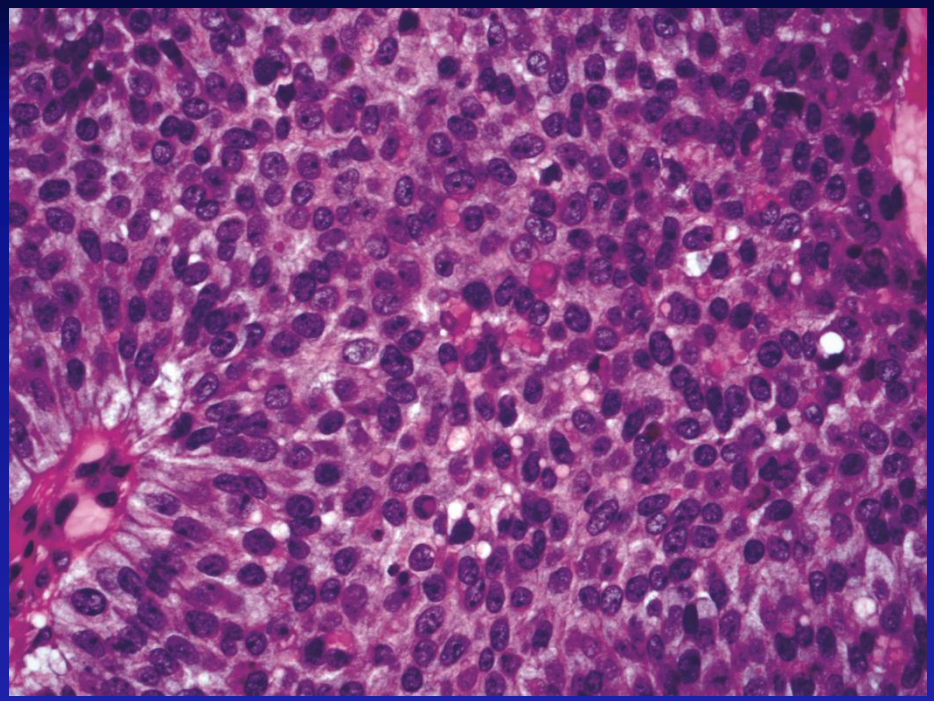
*Agaimy A, et al. Am J Surg Pathol 2014;38:1274-81
*Bishop J, et al. Am J Surg Pathol 2014;38:1282-89

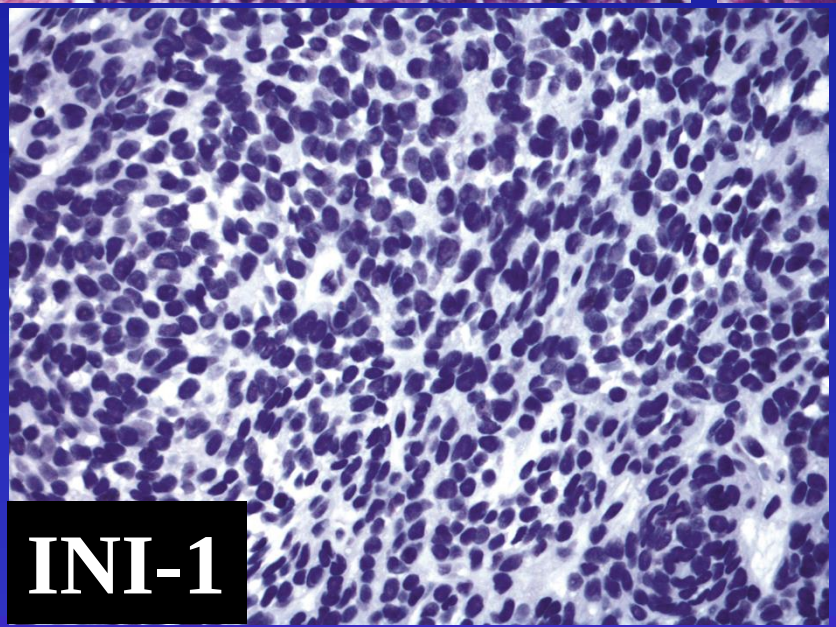
SMARCB1 (INI-1) Deficient Carcinoma



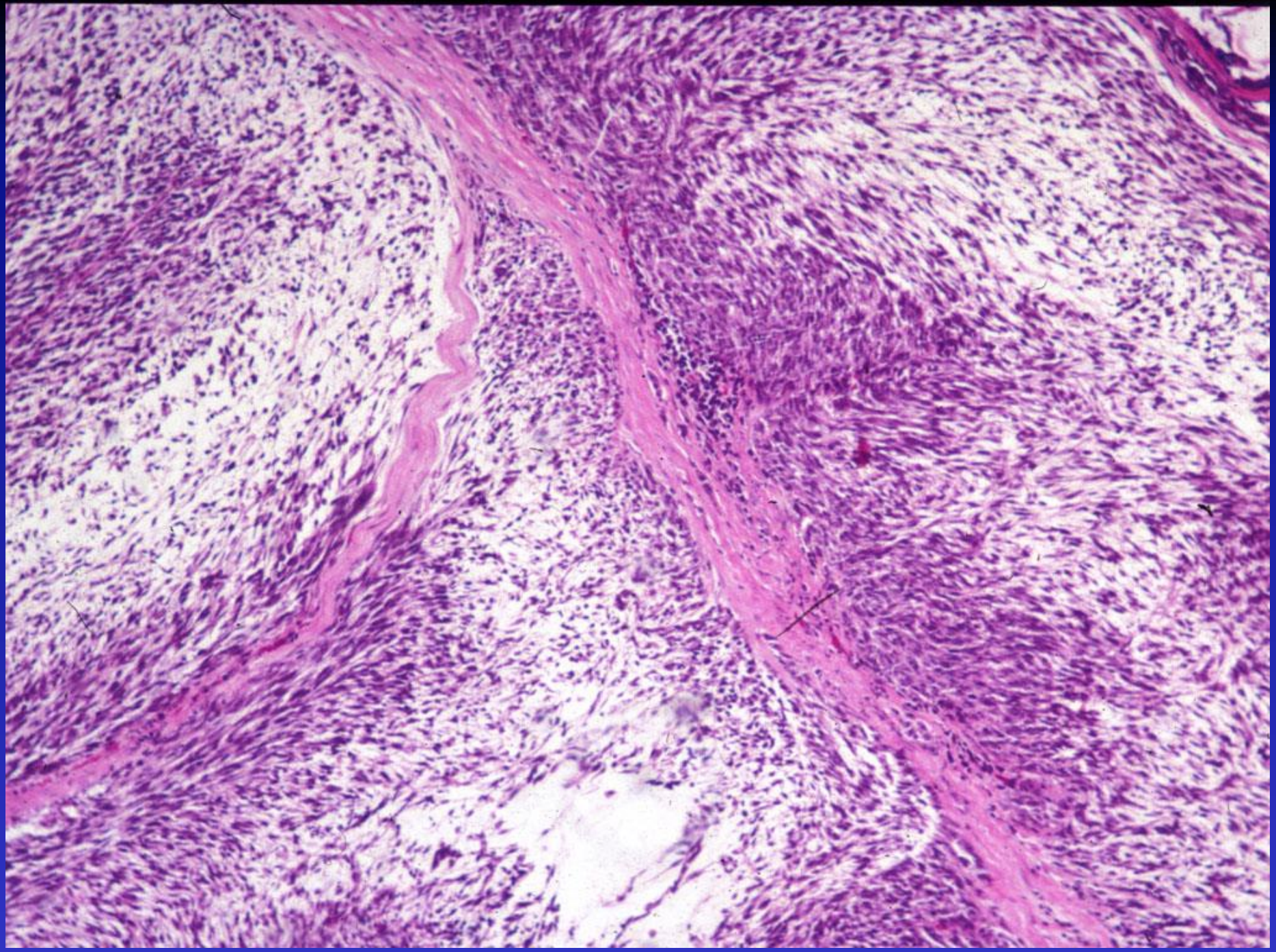
SMARCB1 (INI-1) Deficient Carcinoma



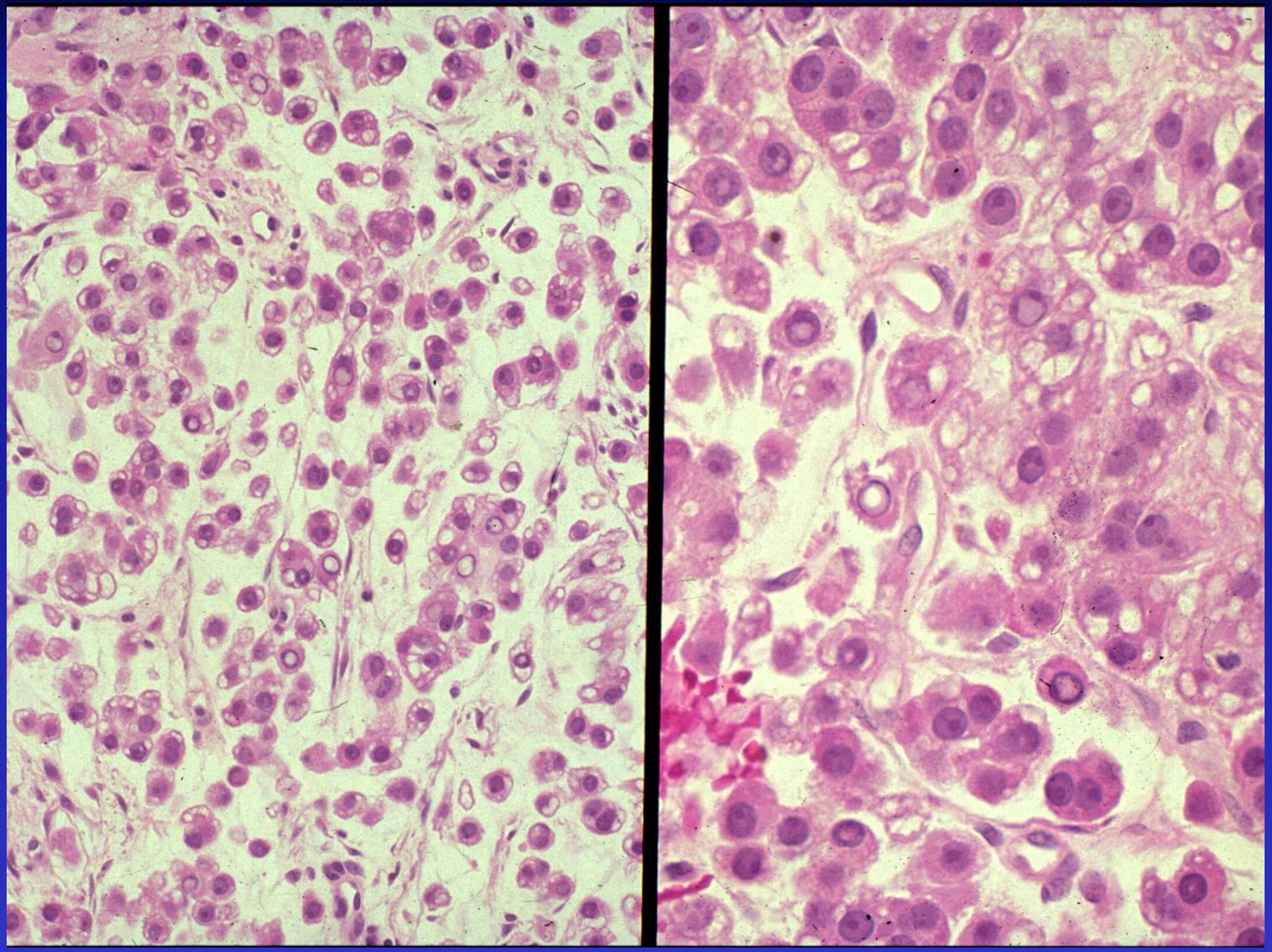


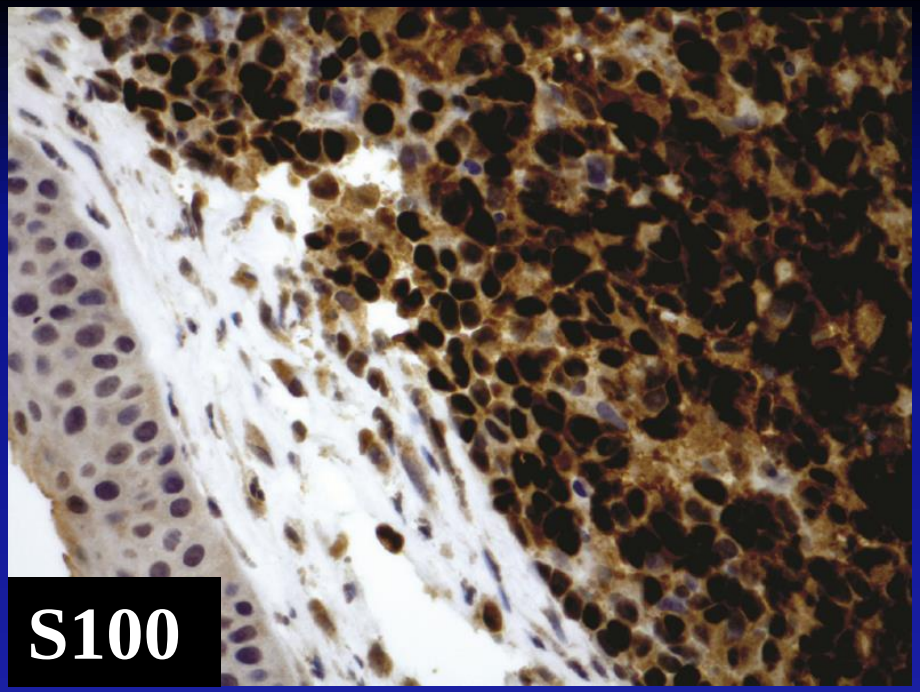


Rhabdoid &/or Plasmacytoid Cells



Signet Ring Appearing Cells

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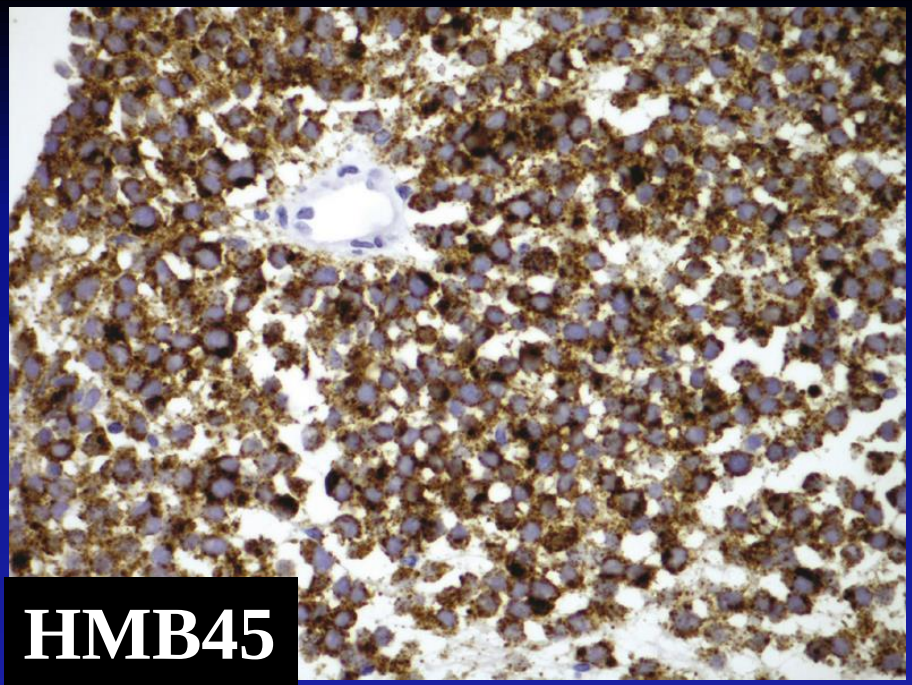
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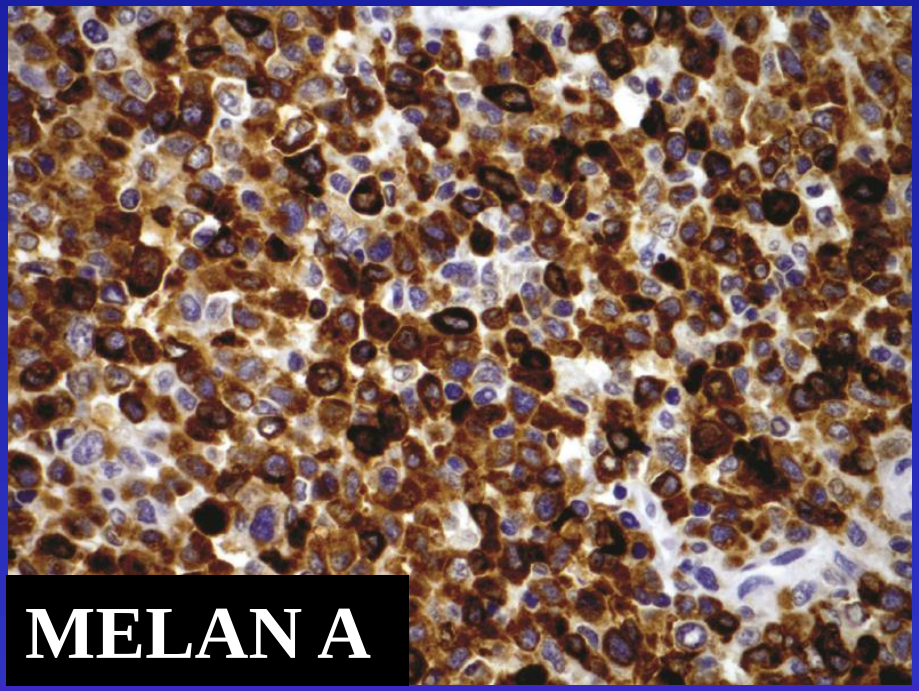
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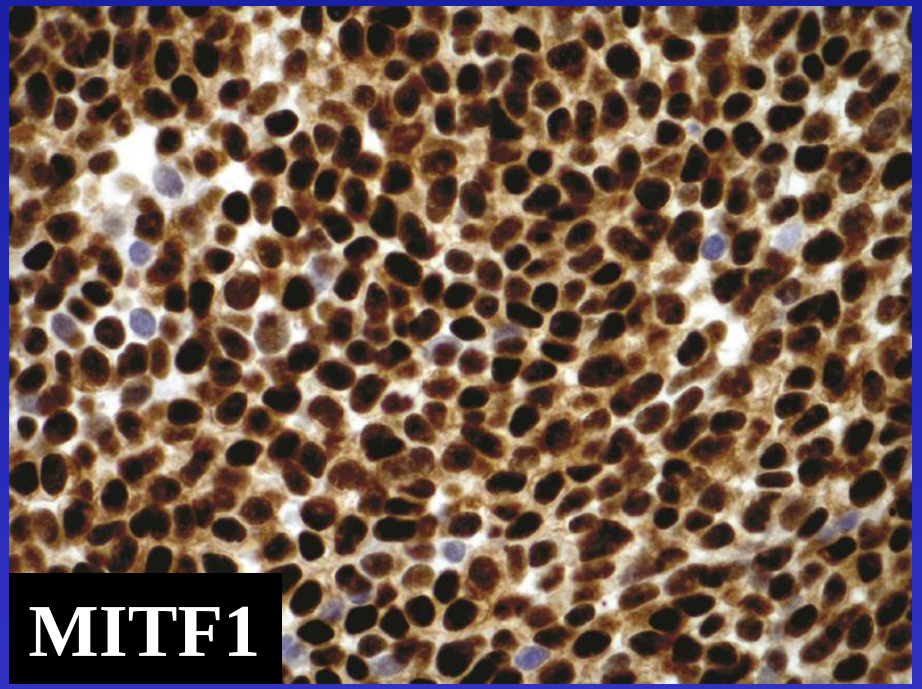
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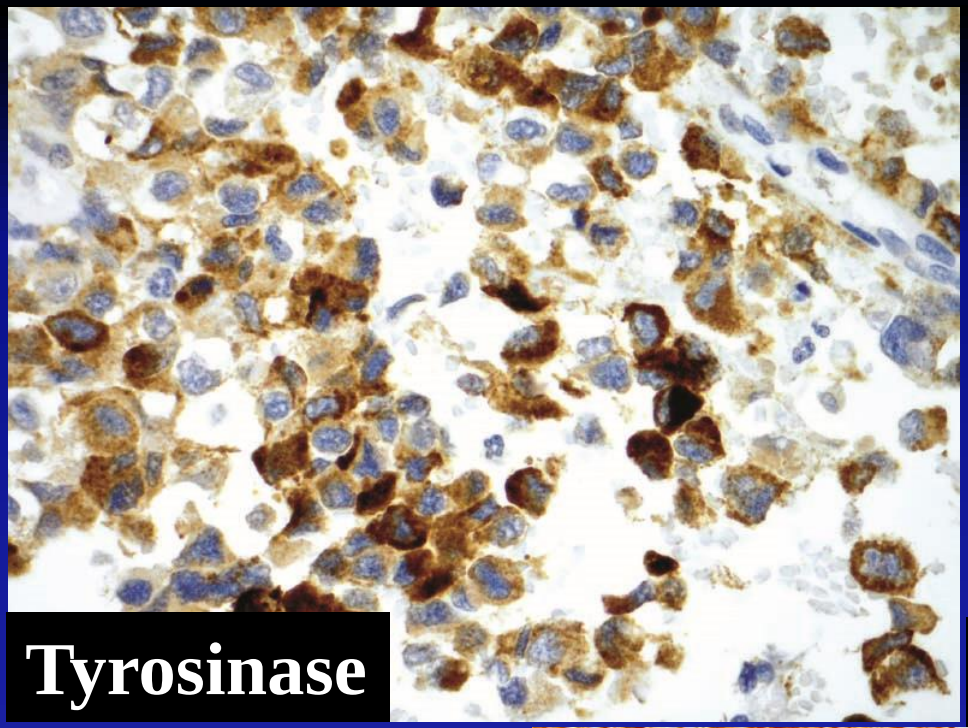
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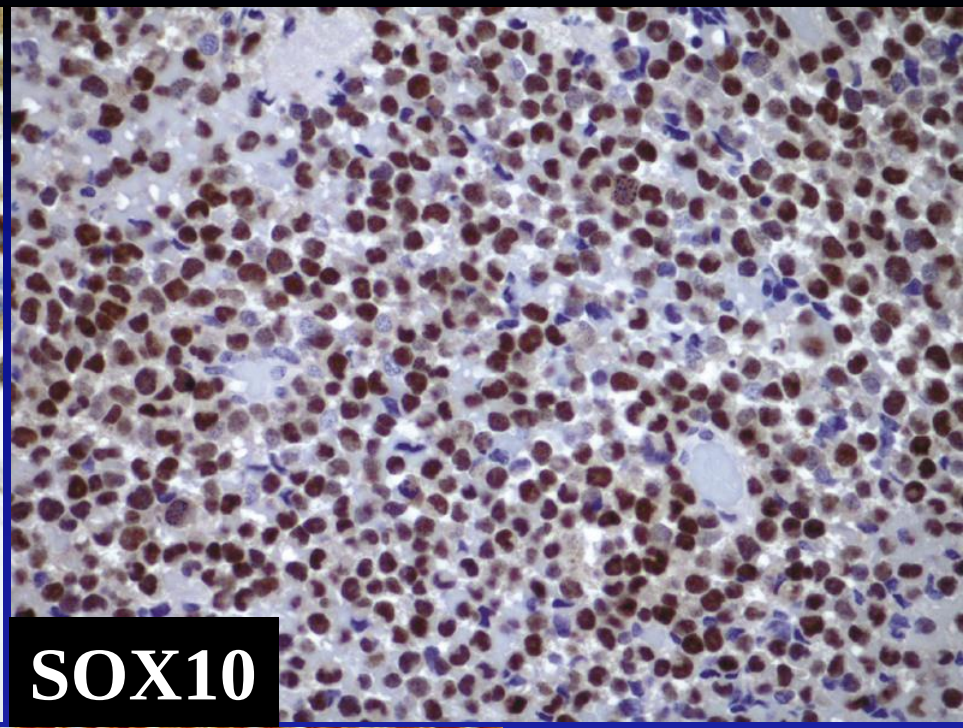
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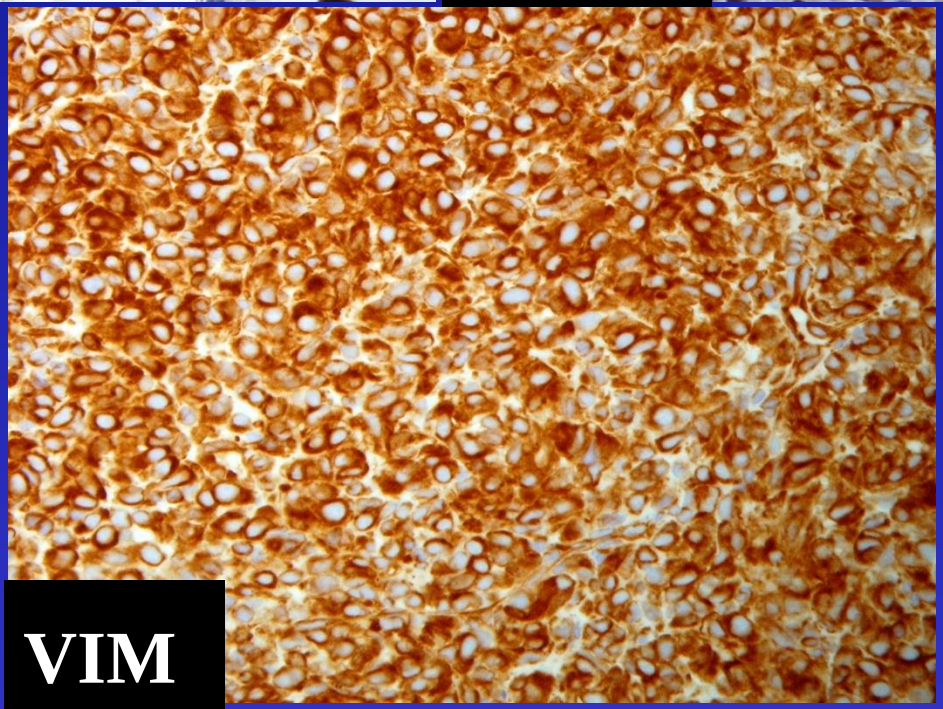
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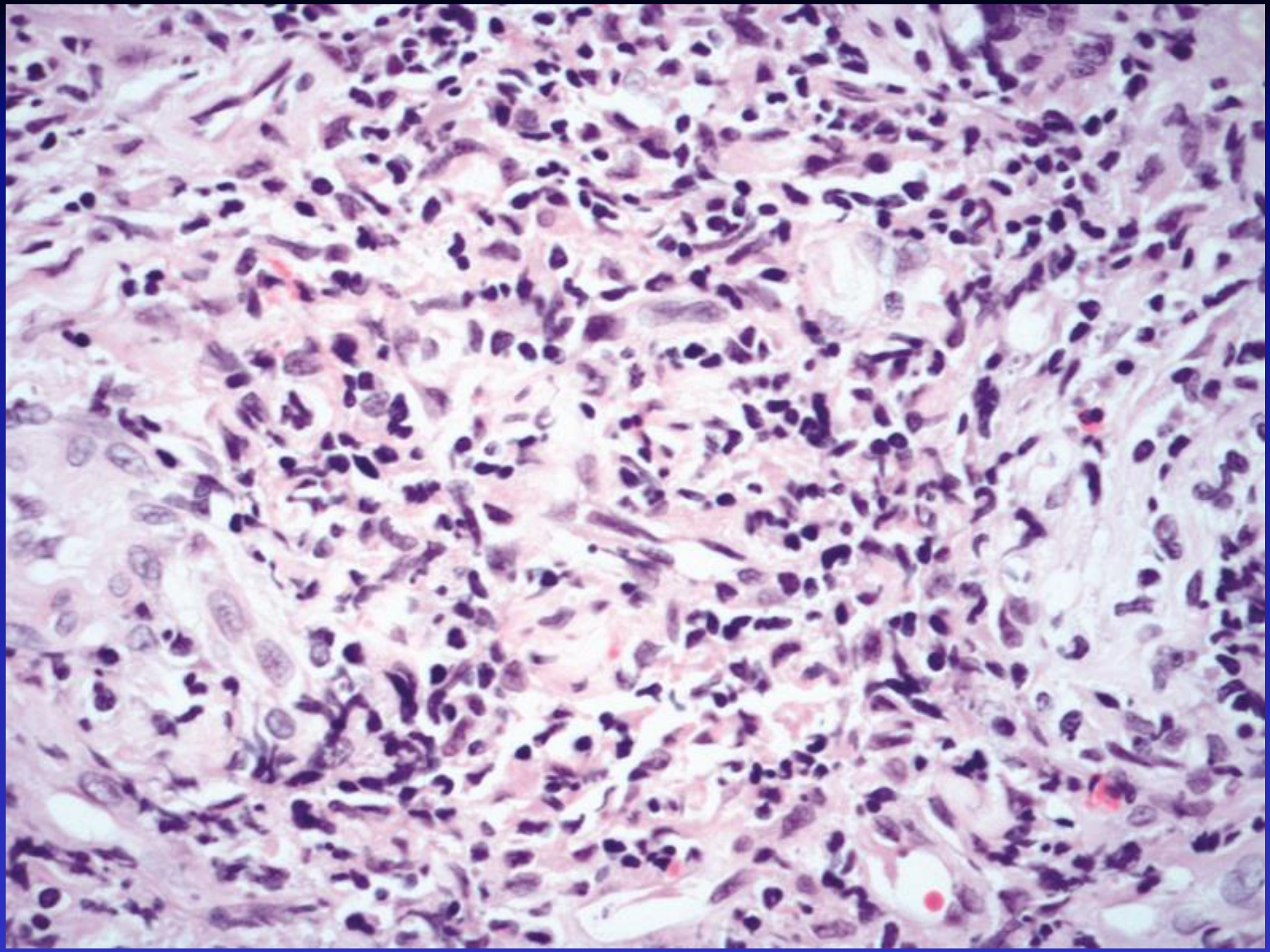
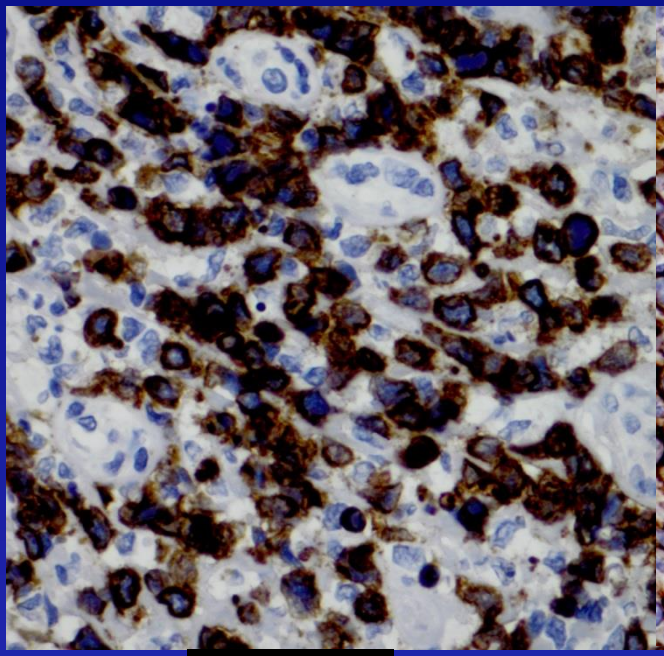


NK/T Cell Lymphoma



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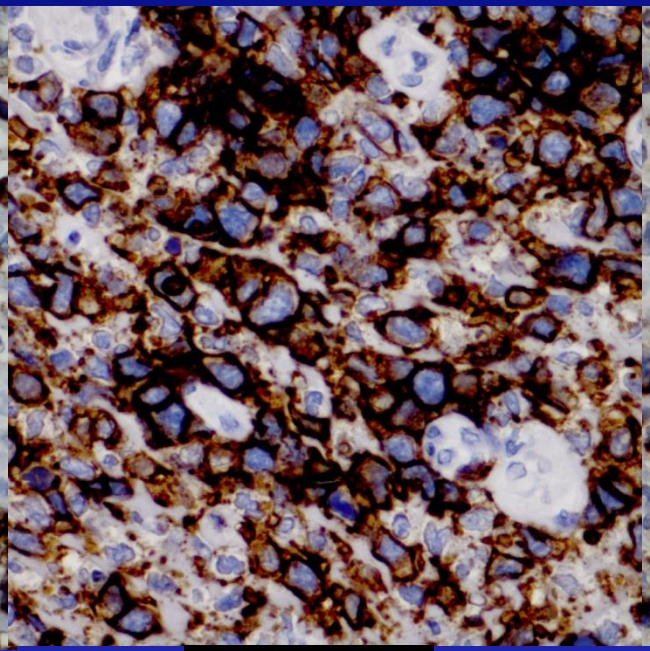

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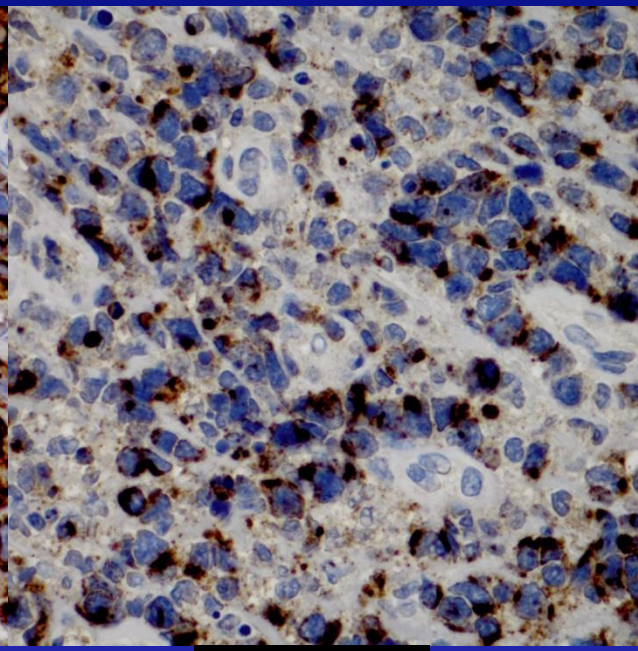

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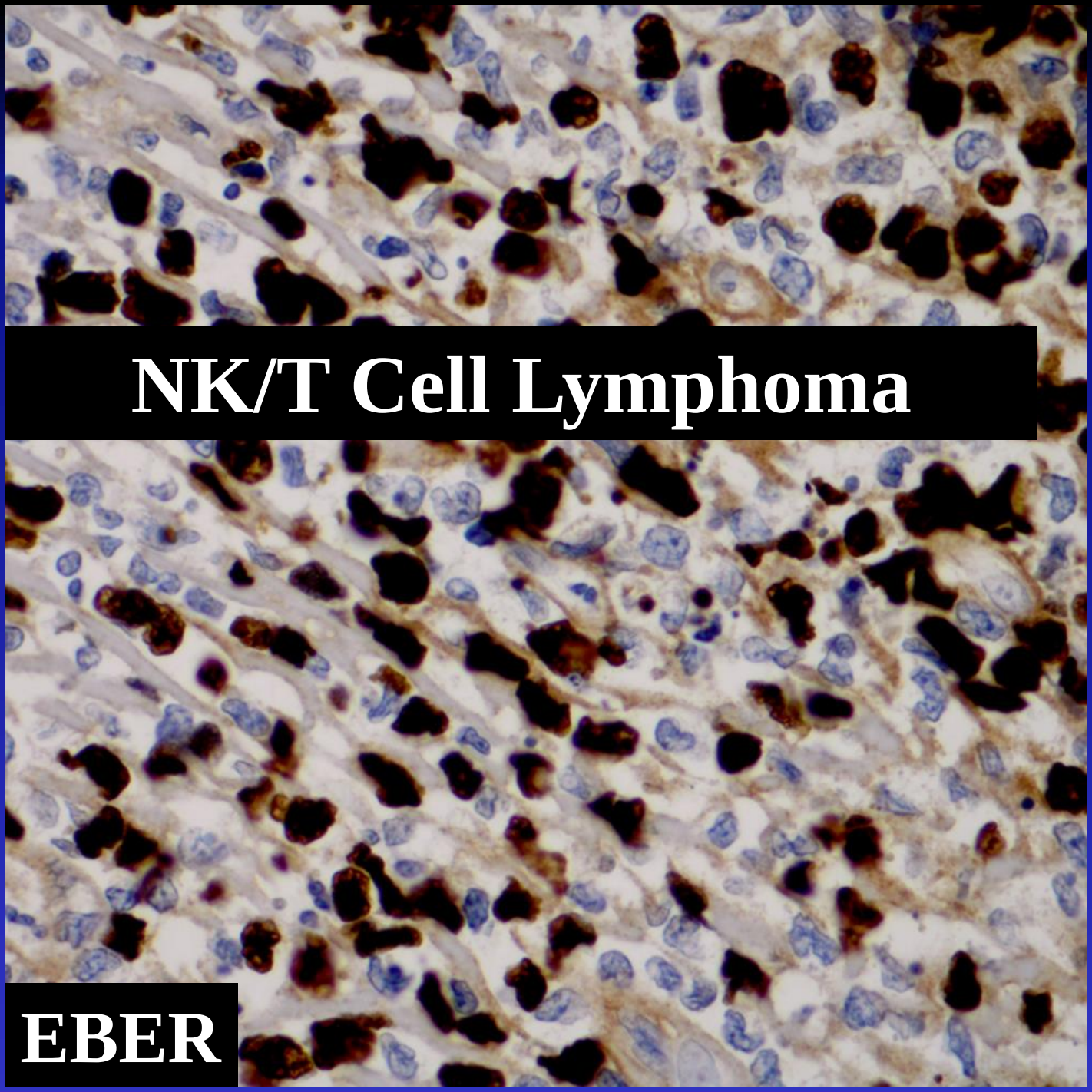
NK/T Cell Lymphoma
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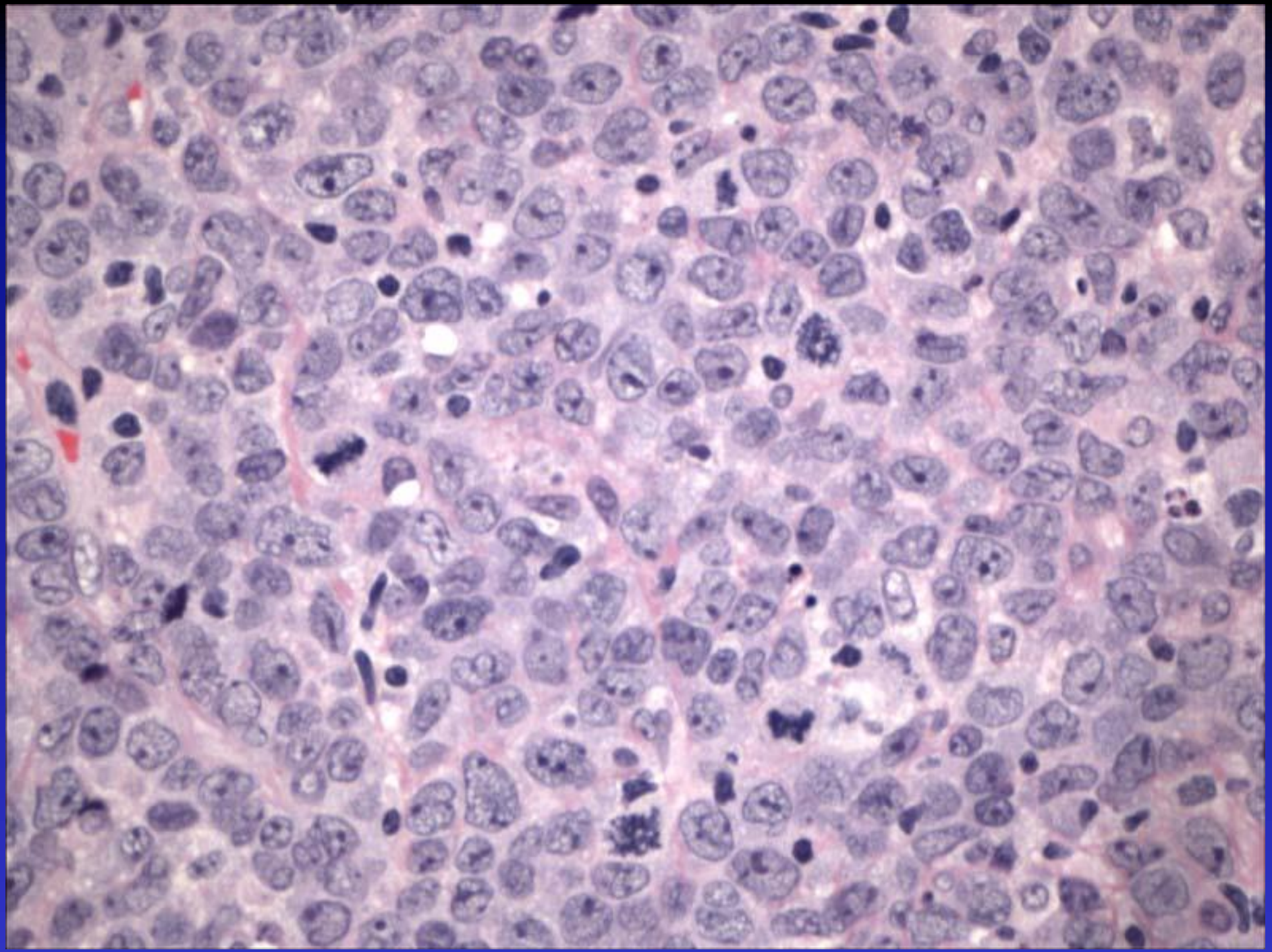

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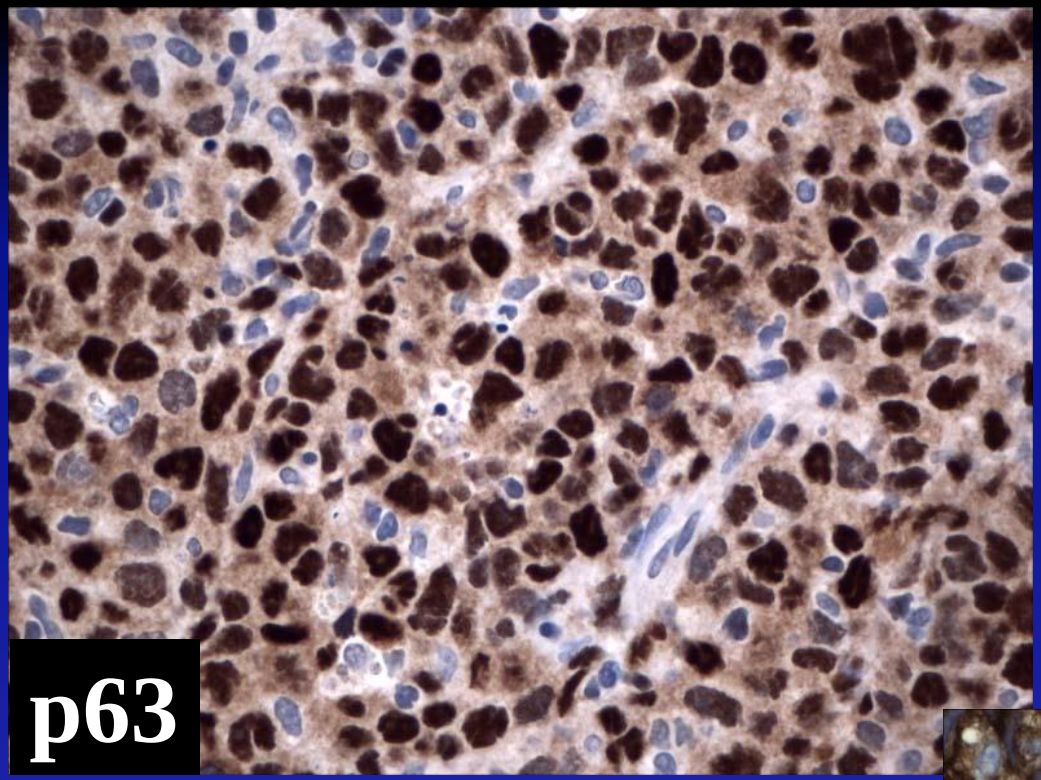

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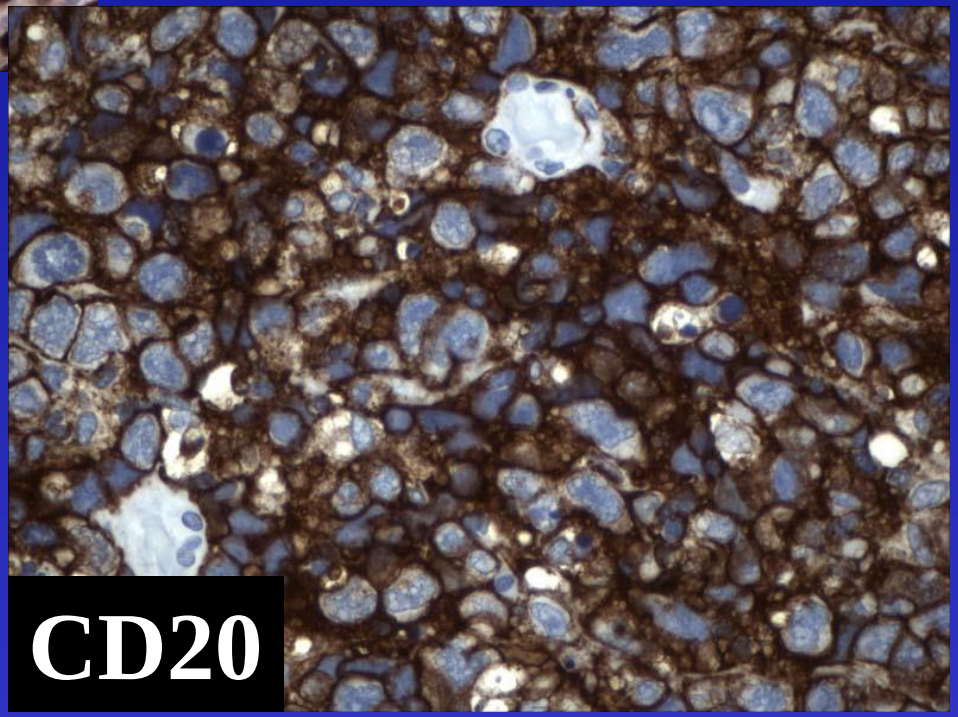

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Summary Case 4

- SCC is the most common malignant neoplasm
- SNT is host to neoplasms of varied histogenesis
- Many of these “other” neoplasms are undifferentiated and share overlapping clinical and histopathologic features
- Differentiation may require IHC and molecular analysis
- Therapy and prognosis may vary per tumor type

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Thank you

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