Advances in Cytology and Small Biopsies

Challenging Head and Neck Biopsies

Kristine Wong, MD

Department of Pathology, Brigham and Women's Hospital and Harvard Medical School

FNA/Core Biopsy of the Head and Neck

- Common biopsy sites include thyroid, salivary gland, and cervical lymph nodes
- Broad range of tumors that can have significant morphologic overlap
- Rare tumor types may be misdiagnosed as more common entities

Objective

Discuss unusual/challenging entities in the H&N and thyroid that can mimic common tumors or cause diagnostic confusion, focusing on the differential diagnosis of **squamoid/squamous lesions**

Squamoid/Squamous Lesions: Diagnostic Considerations

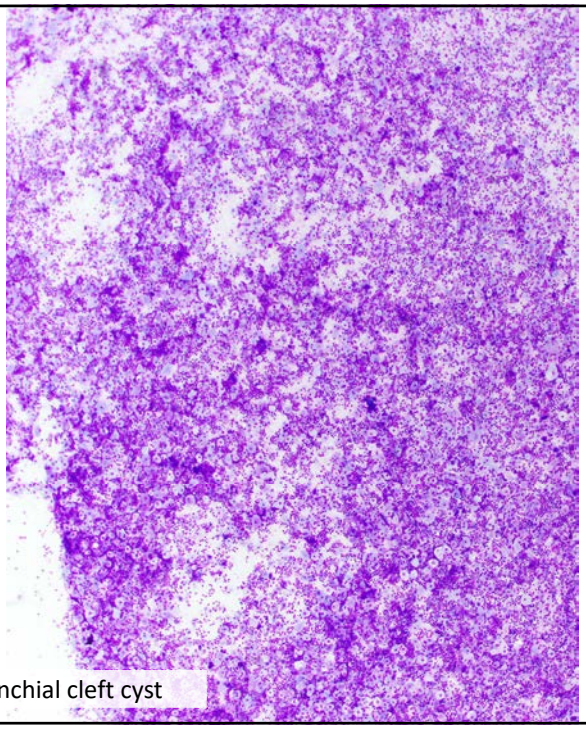
Thyroid	Neck/Salivary
Benign squamous/developmental cyst	Benign squamous/developmental cyst
Squamous metaplasia/morules (i.e. in PTC)	Myoepithelial-predominant neoplasms (+/- squamous metaplasia)
	Cutaneous tumors (epidermal/follicular)
Primary SCC (i.e. anaplastic carcinoma with squamous differentiation)	*"Primary" SCC*
Intrathyroidal thymic carcinoma	Salivary-type carcinomas (i.e. MEC, HCCC)
NUT carcinoma	NUT carcinoma
Extrathyroidal/metastatic SCC	Metastatic SCC

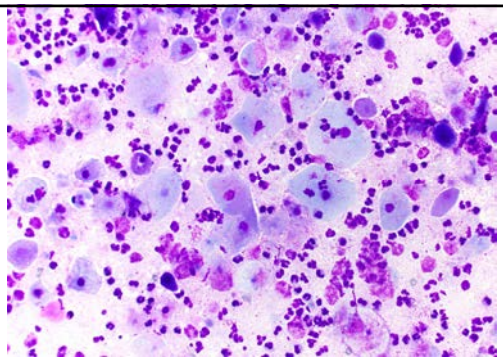
Benign squamous cysts

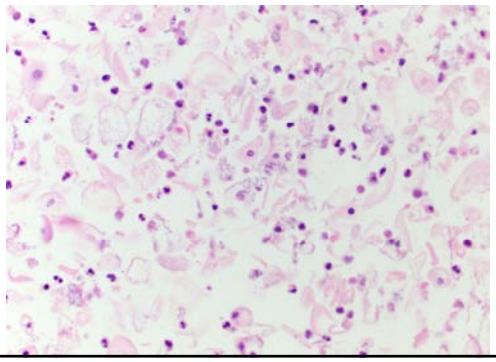
- Often the clinical/imaging features are most helpful in the differential, especially for developmental cysts in the neck
- Intrathyroidal benign squamous cysts can also rarely occur—while some may represent developmental rests/cysts (including thyroglossal duct cysts), others may be of unclear origin

Case 1

- 35F with a 2.5 cm cystic lateral neck mass



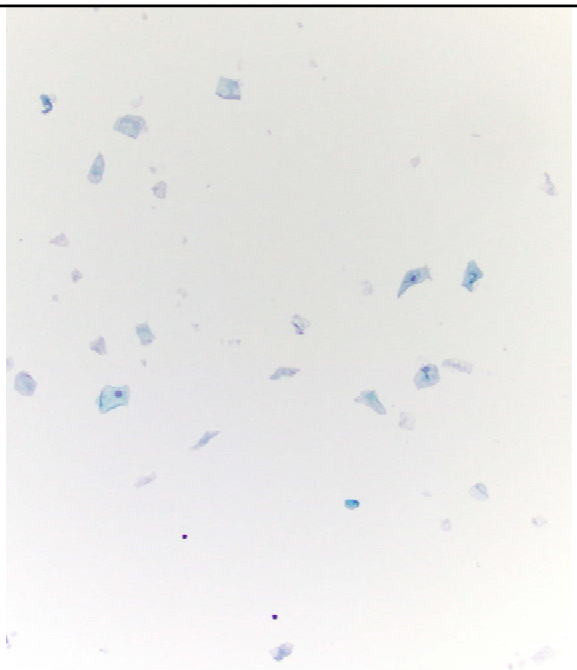


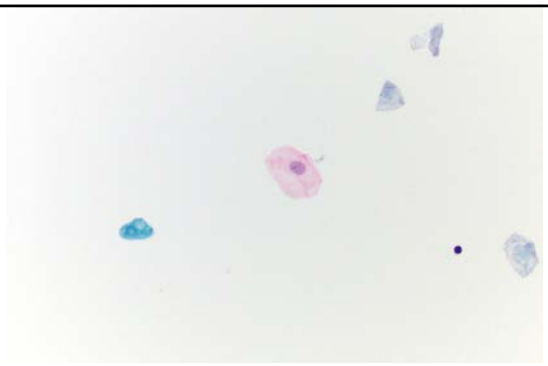


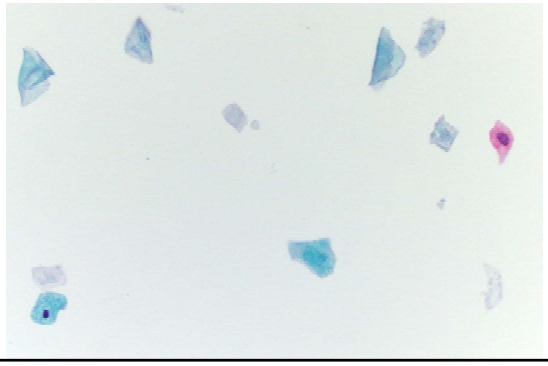
Branchial cleft cyst

Case 2

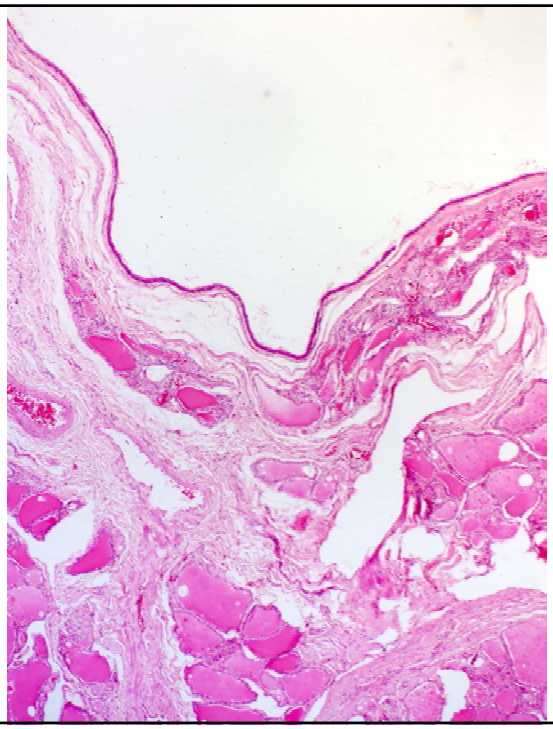
- 30F with a 1 cm cystic thyroid lesion

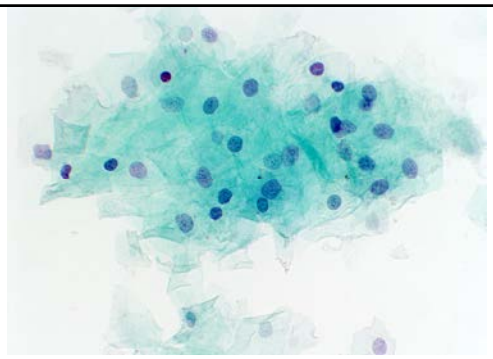


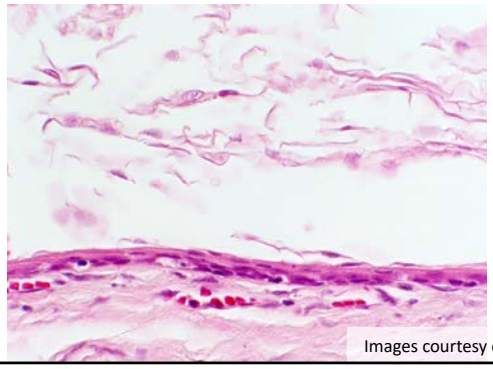




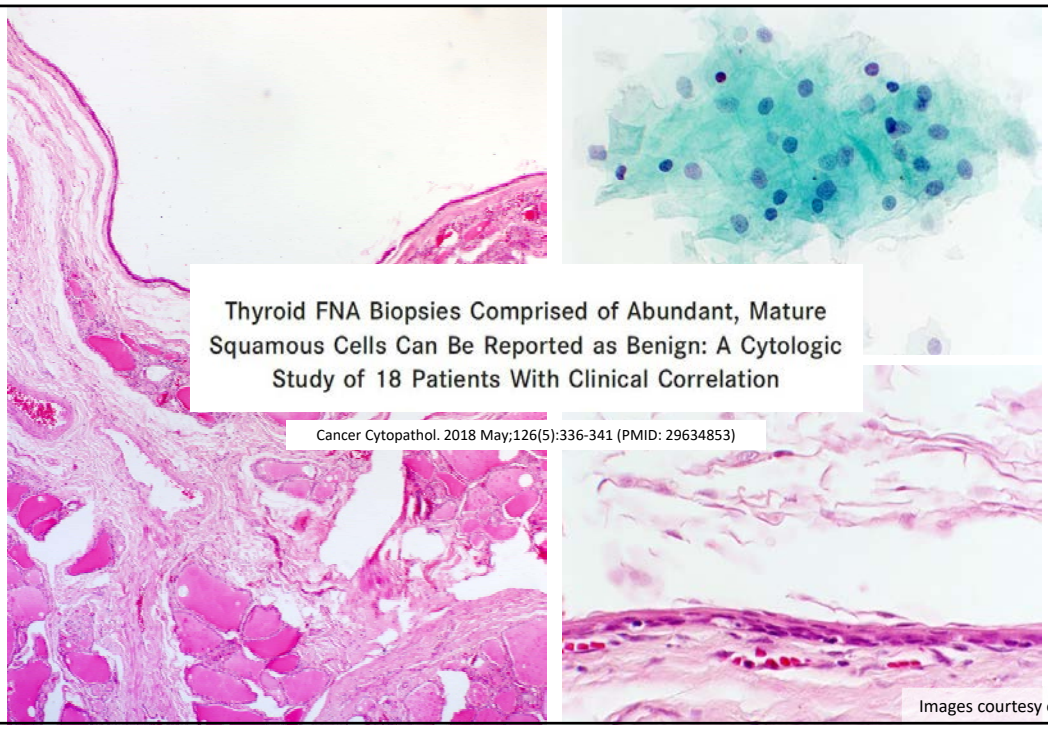
Benign/developmental thyroid cyst







Images courtesy of Dr. E. Cibas



Thyroid FNA Biopsies Comprised of Abundant, Mature Squamous Cells Can Be Reported as Benign: A Cytologic Study of 18 Patients With Clinical Correlation

Cancer Cytopathol. 2018 May;126(5):336-341 (PMID: 29634853)

Images courtesy of Dr. E. Cibas

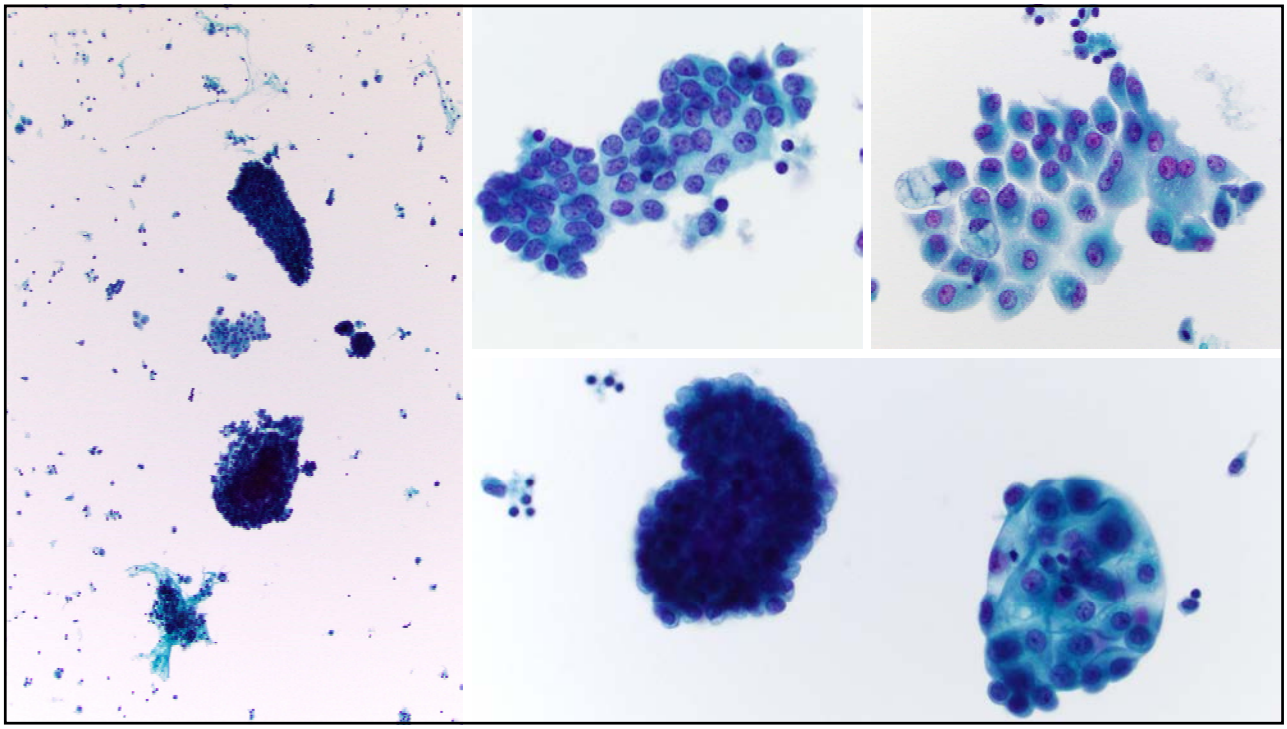
Squamous metaplasia in neoplasms

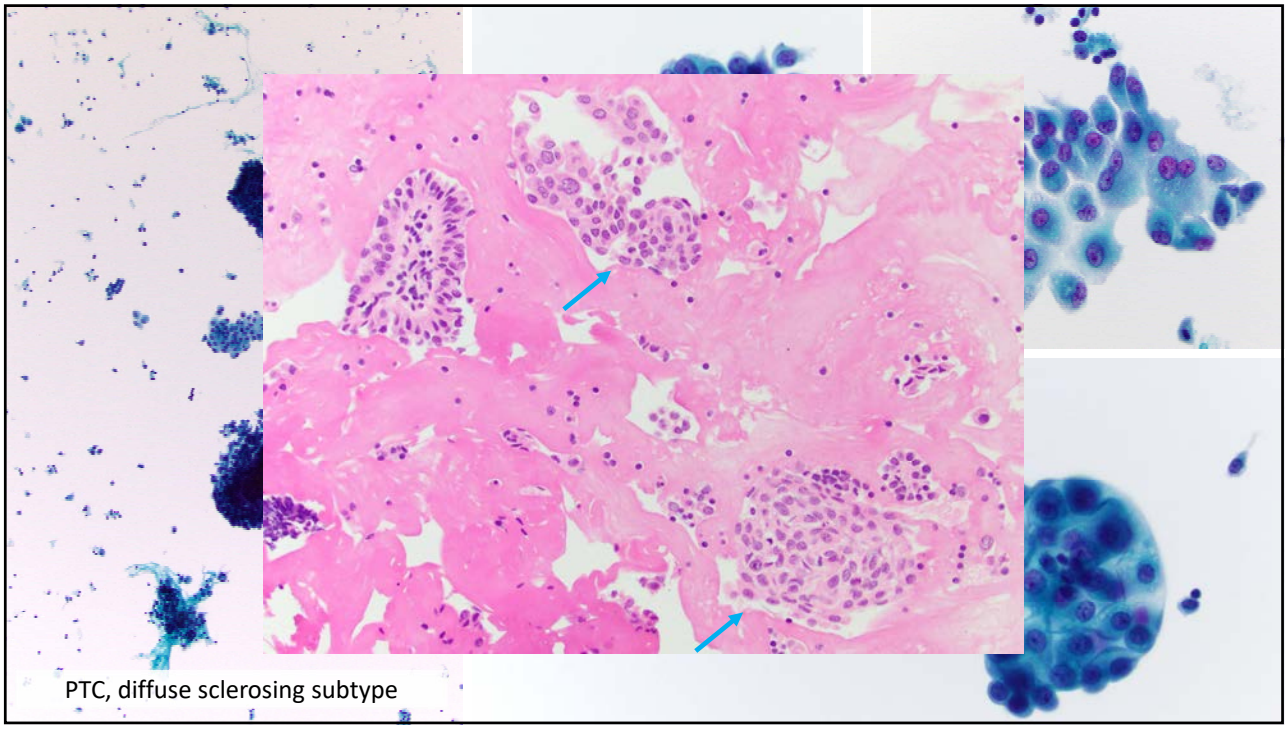
Squamous metaplasia in neoplasms

- In the thyroid, squamous metaplasia can be benign/reactive, i.e. in the setting of inflammation or prior biopsy, although this is often a focal or incidental finding
  - In neoplasms, squamous metaplasia or morules can be a more prominent finding and often seen in association with malignancies (especially PTC)

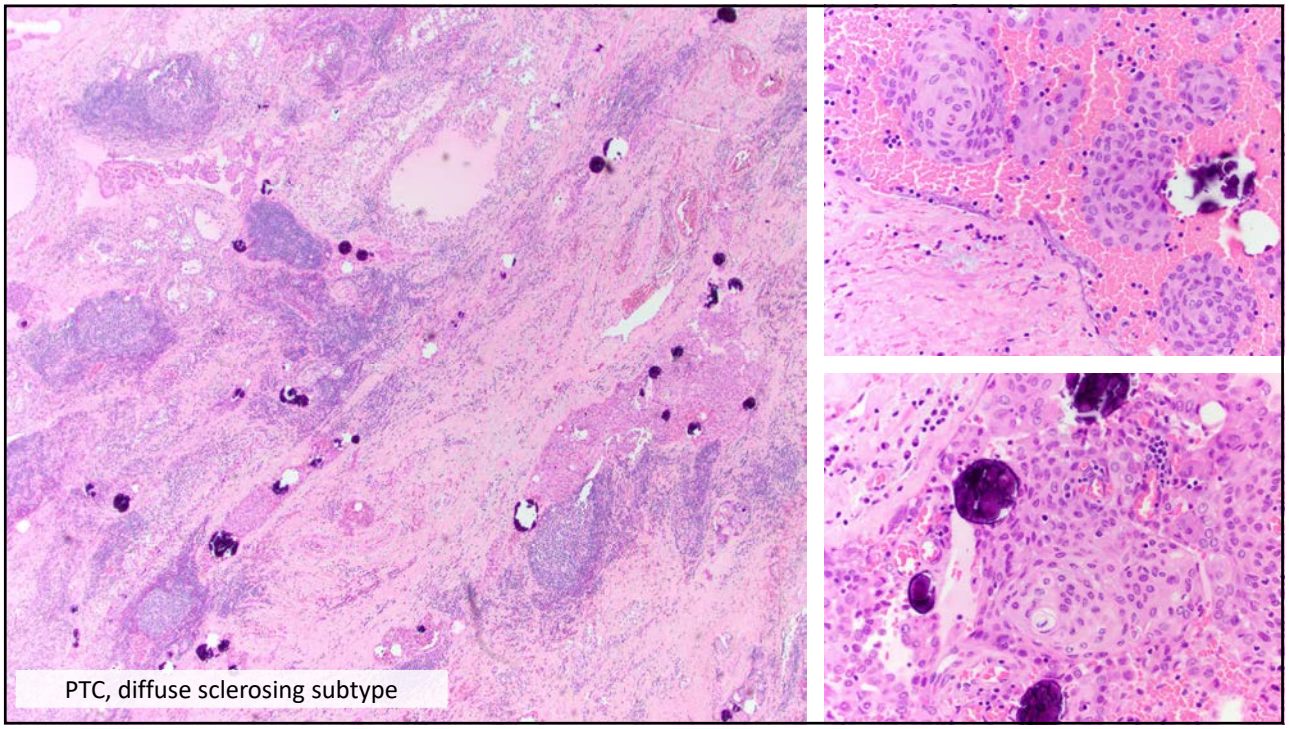
Case 3

- 15F with an enlarged, diffusely heterogeneous thyroid with microcalcifications



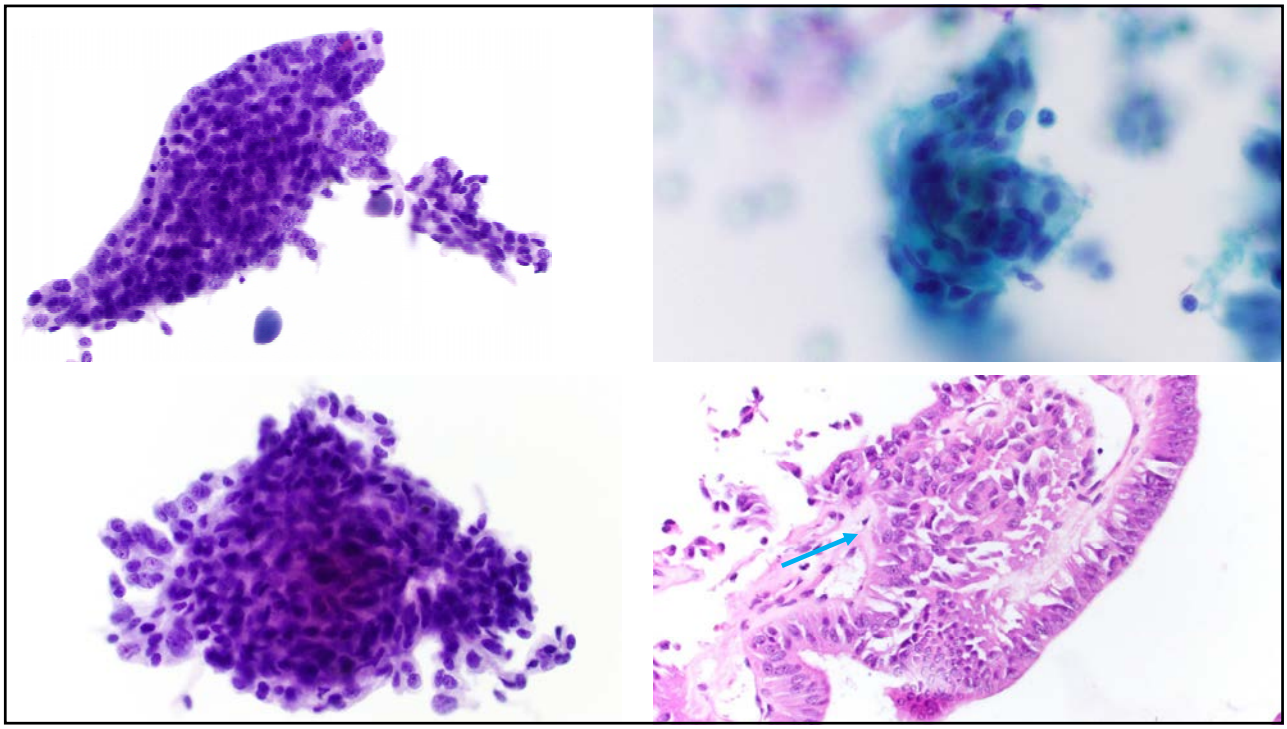


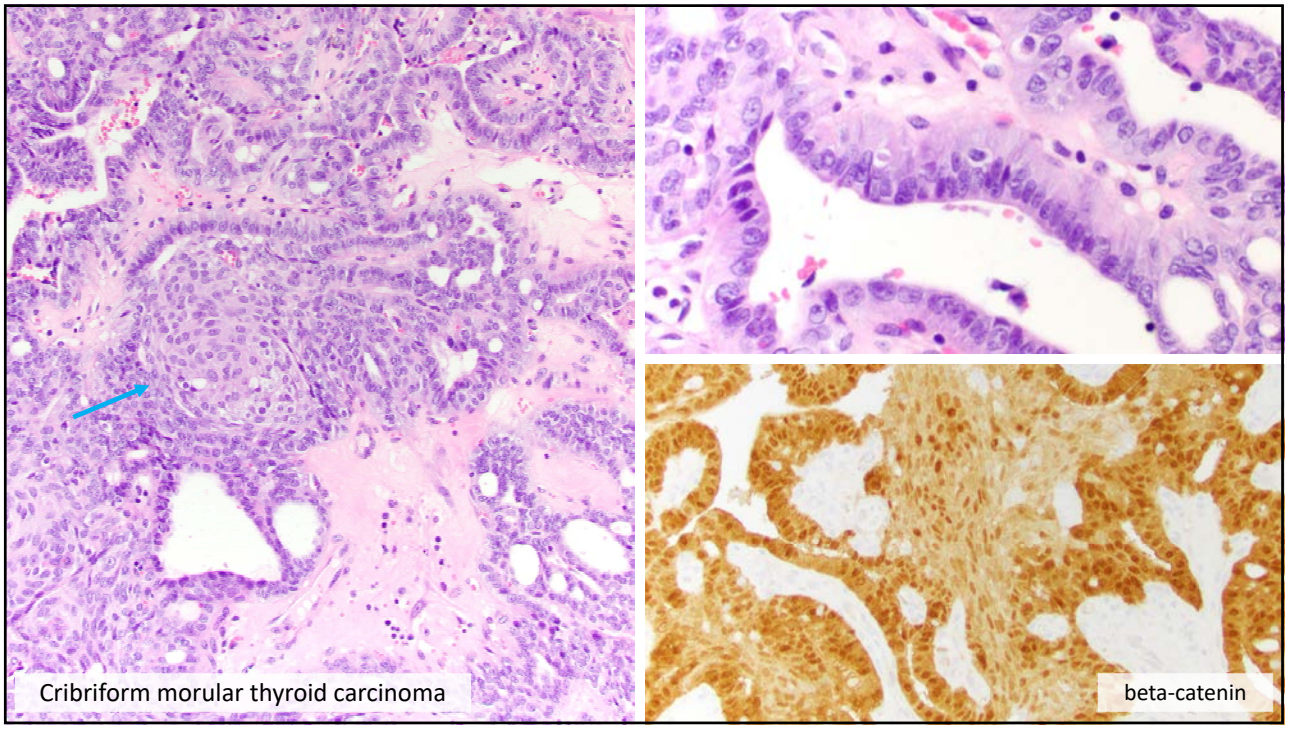
PTC, diffuse sclerosing subtype



Case 4

- 30F with multiple thyroid nodules




Cribriform morular thyroid carcinoma
beta-catenin

Cribriform morular thyroid carcinoma

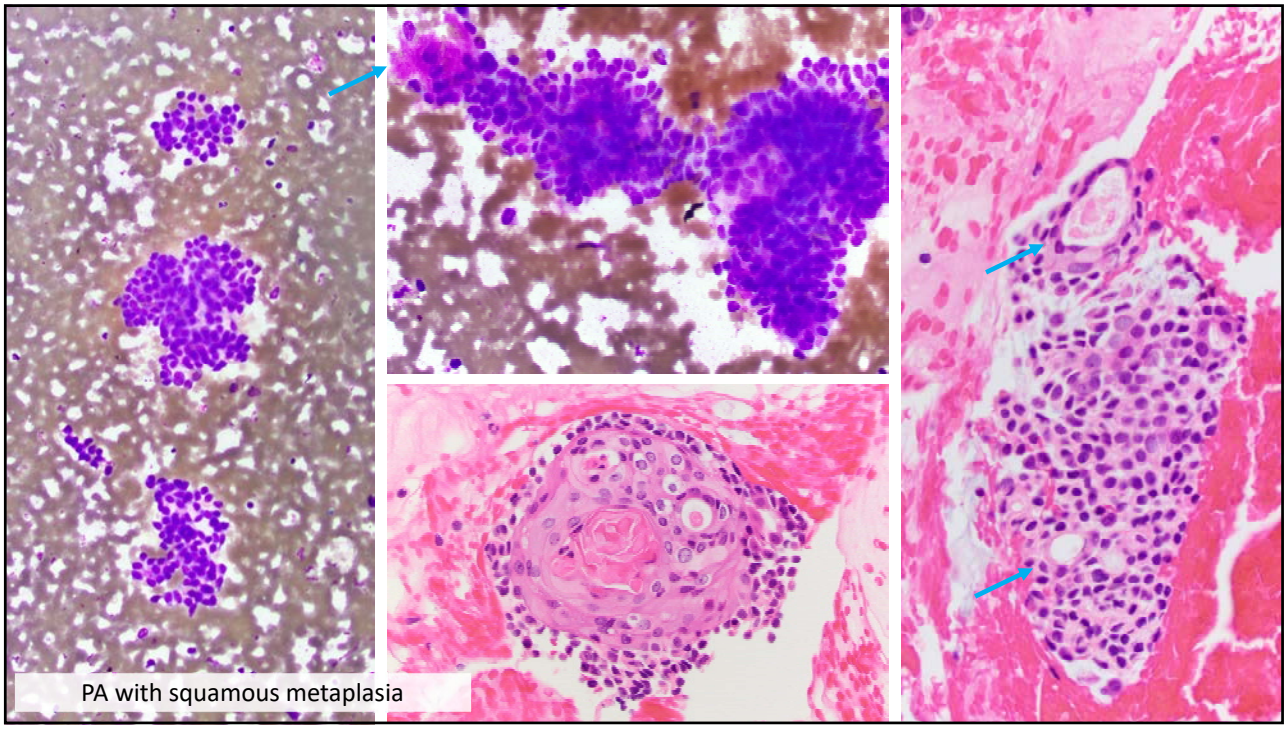
- Rare, F>>>M
- No longer considered a “variant” of PTC
- Characteristic morphologic features—variable nuclear atypia, but often without typical PTC-like nuclei
  - Morules appear squamoid but do not express p63/p40 by IHC
- Unclear histogenesis
  - Usually negative for PAX8, thyroglobulin
- Associated with germline (i.e. in FAP) and somatic mutations in *APC*
  - Diffuse nuclear/cytoplasmic beta-catenin expression

Squamous metaplasia in neoplasms

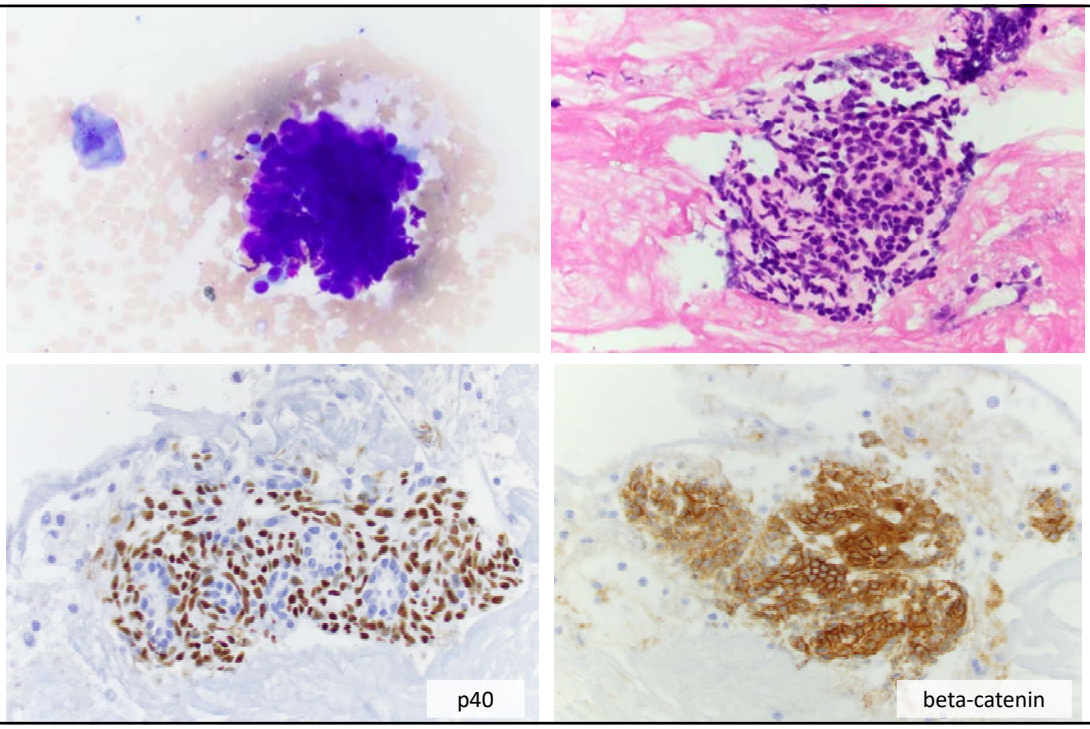
- In the thyroid, squamous metaplasia can be benign/reactive, i.e. in the setting of inflammation or prior biopsy, although this is often a focal or incidental finding
  - In neoplasms, squamous metaplasia or morules can be a more prominent finding and often seen in association with malignancies (especially PTC)
- In the salivary gland, squamous metaplasia is not uncommon in benign neoplasms such as pleomorphic adenoma and basal cell adenoma

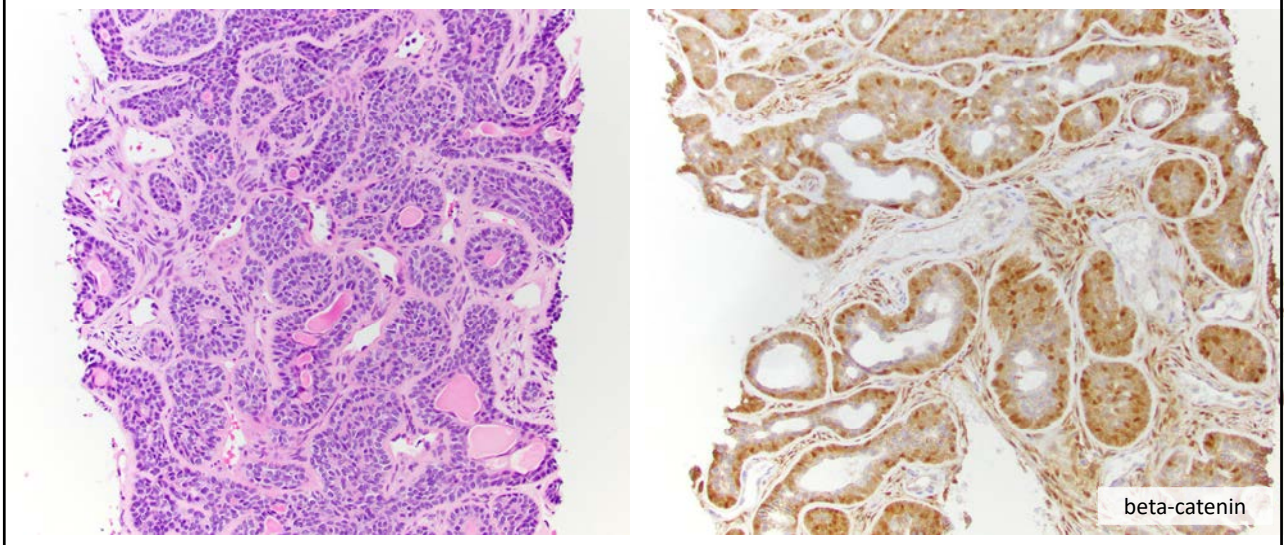
Case 5

- 50F with a well circumscribed 2 cm parotid nodule



PA with squamous metaplasia

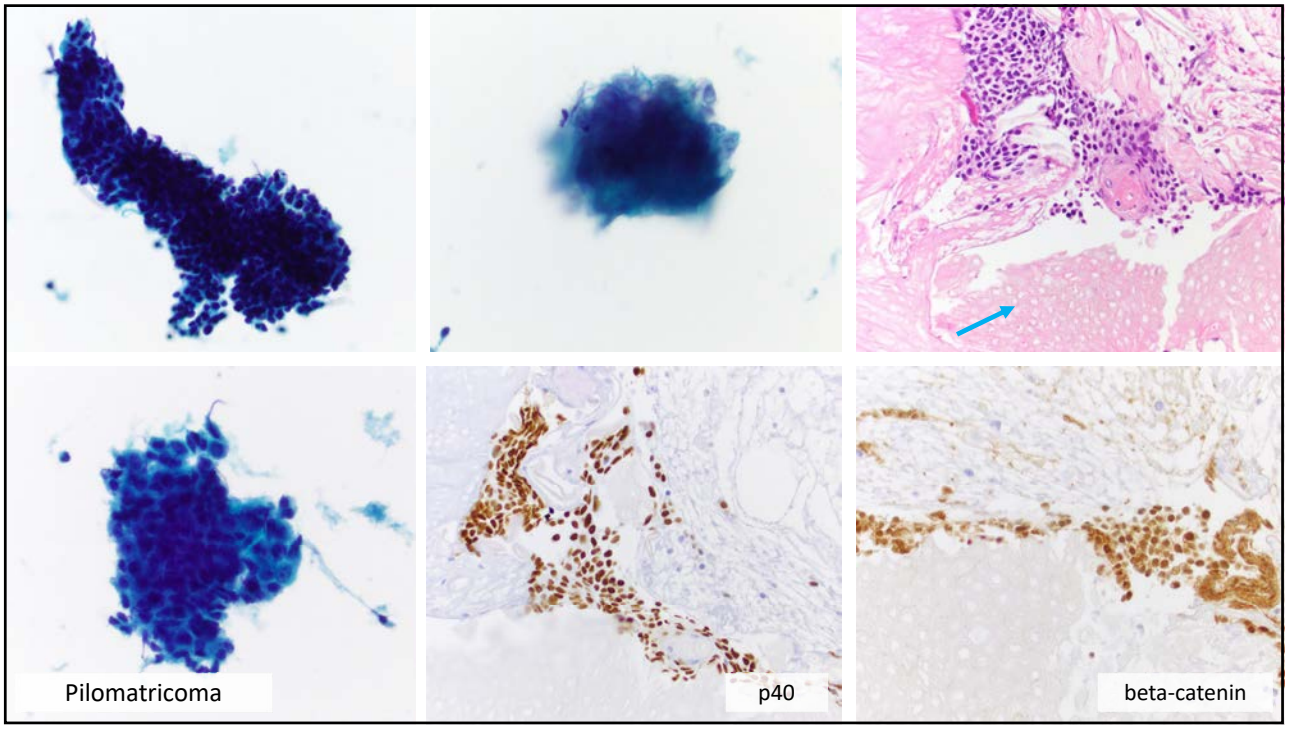


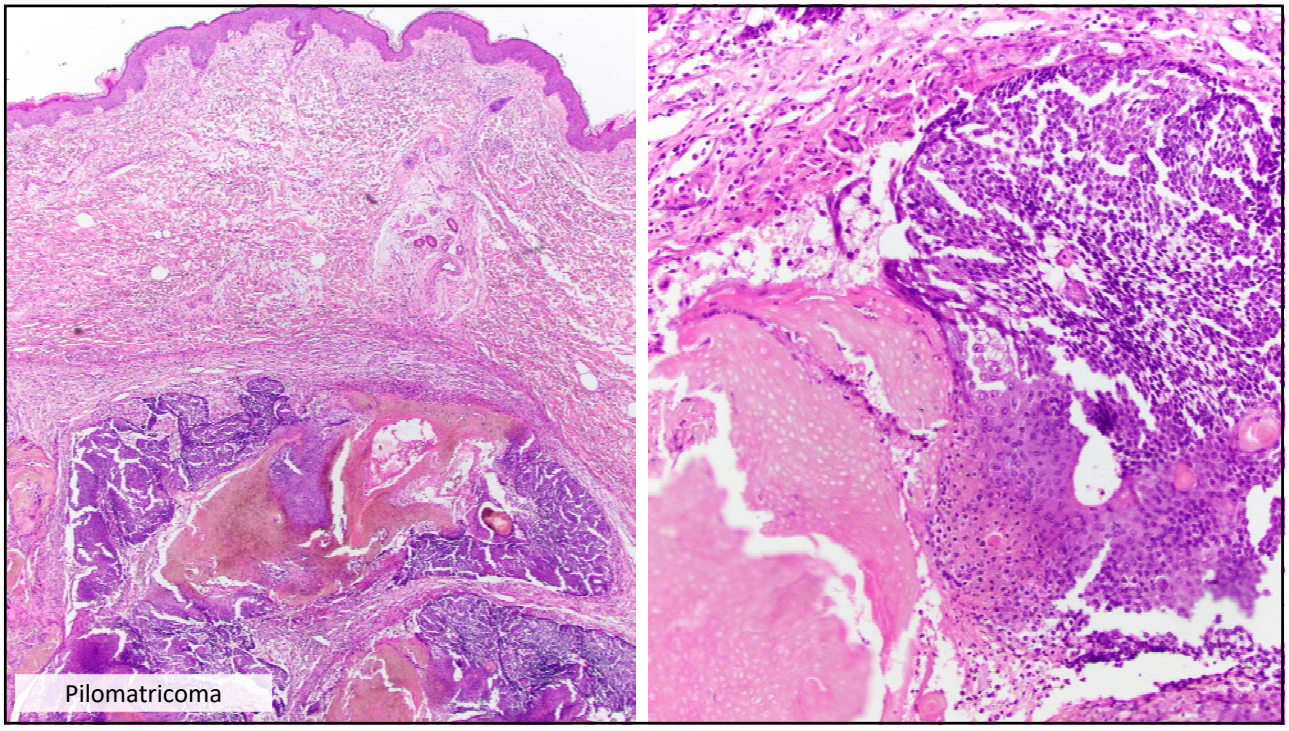


Basal cell adenoma

Case 6

- 50F with a well circumscribed 1 cm cheek/parotid nodule





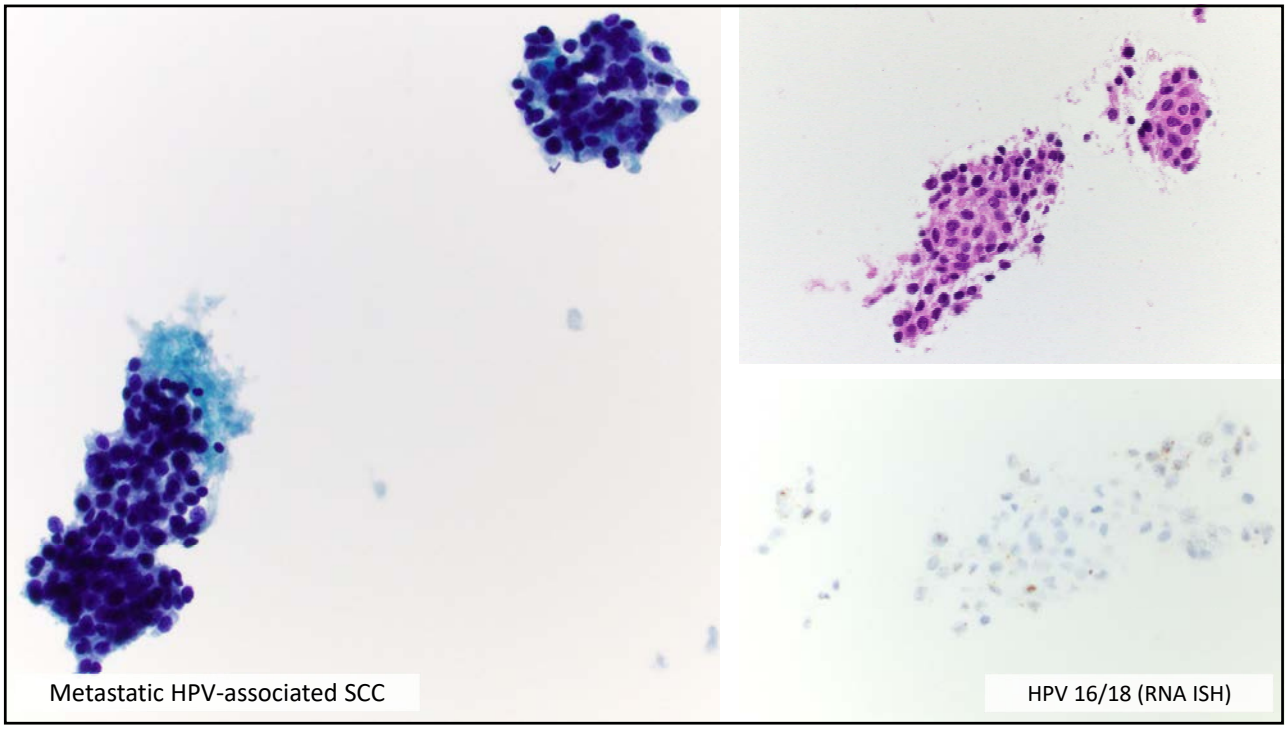
Squamous/squamoid malignancies

Squamous/squamoid malignancies

- In the neck/parotid/submandibular gland, metastasis should always be considered (may be from an unknown primary)
  - If a primary salivary carcinoma, entities that have a squamous immunophenotype include mucoepidermoid carcinoma and hyalinizing clear cell carcinoma (myoepithelial-predominant carcinomas can also enter the differential)
- In the thyroid, carcinomas with a squamous phenotype are rare and can also be primary or metastatic → clinical scenario may be especially helpful

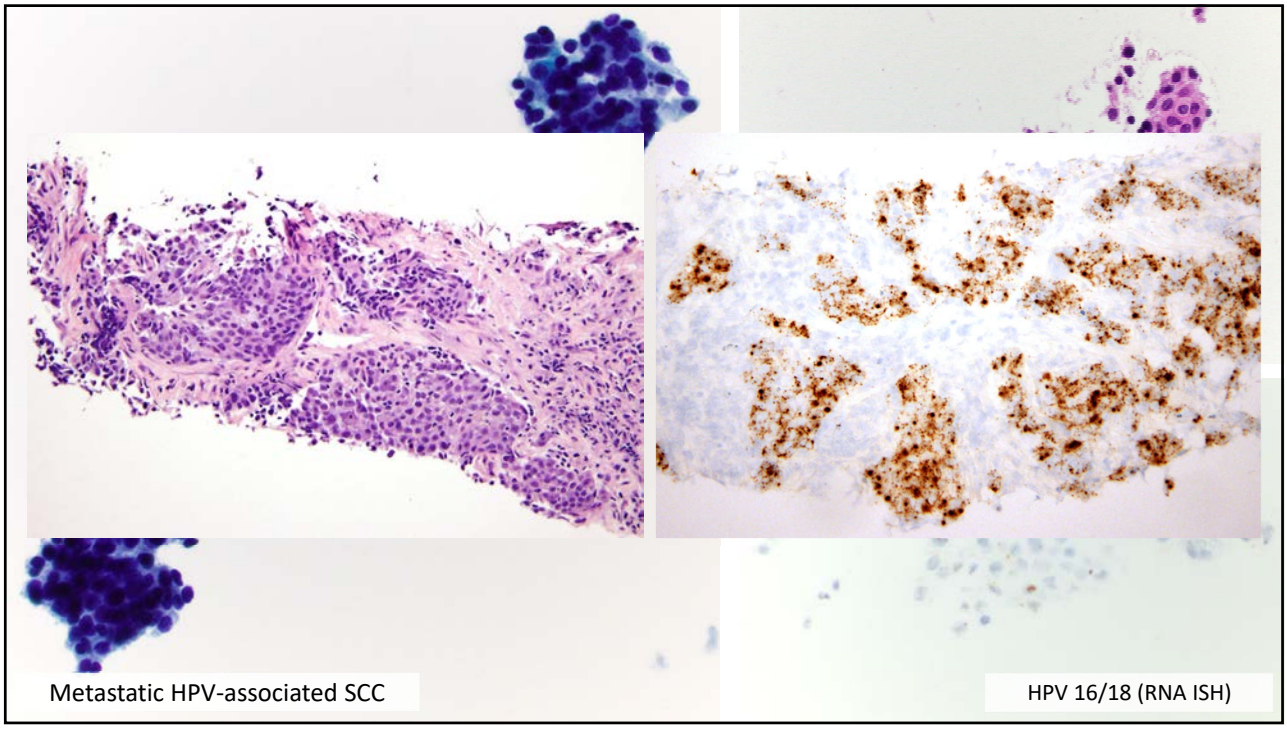
Case 7

- 60M with a 3 cm cystic lateral neck mass



Metastatic HPV-associated SCC

HPV 16/18 (RNA ISH)



Metastatic HPV-associated SCC

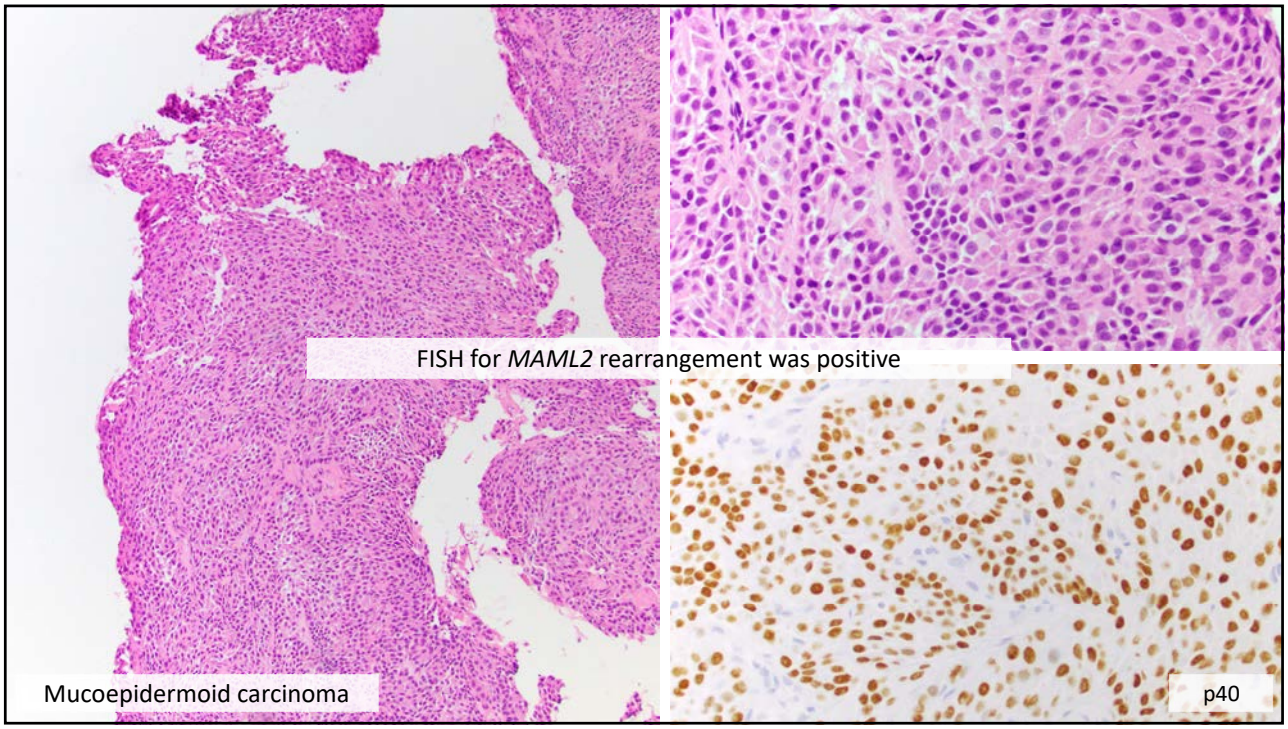
HPV 16/18 (RNA ISH)

Metastatic HNSCC

- Often from mucosal (i.e. oral cavity, oropharynx) or cutaneous sites
- If from oropharynx/nasopharynx, will often (but not always) have a non-keratinizing morphology
  - Should test for p16/HPV if oropharyngeal or unknown primary (may also want to perform EBER)
- Keratinizing SCC often from oral, laryngeal, and cutaneous primaries
- Should always consider metastatic SCC or a squamoid salivary-type carcinoma before "primary" SCC of salivary gland

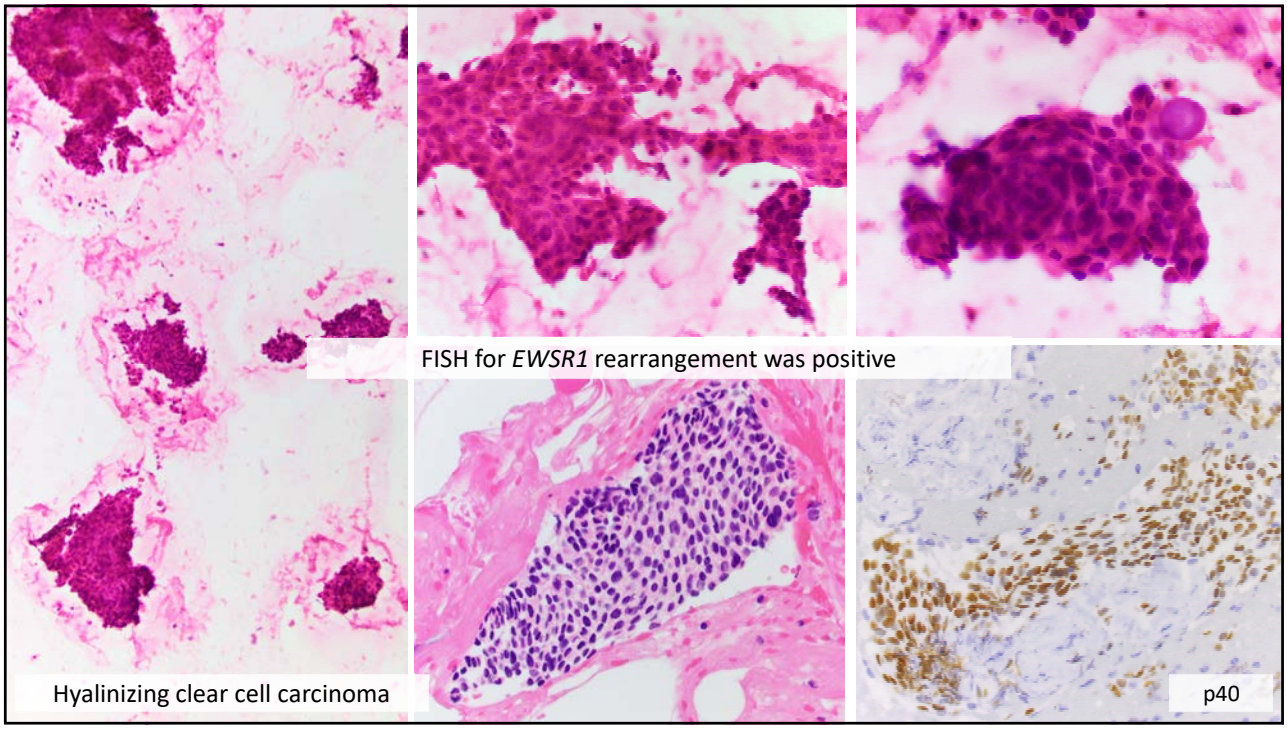
Case 8

- 50M with a 3 cm upper neck/submandibular mass



Mucoepidemoid carcinoma

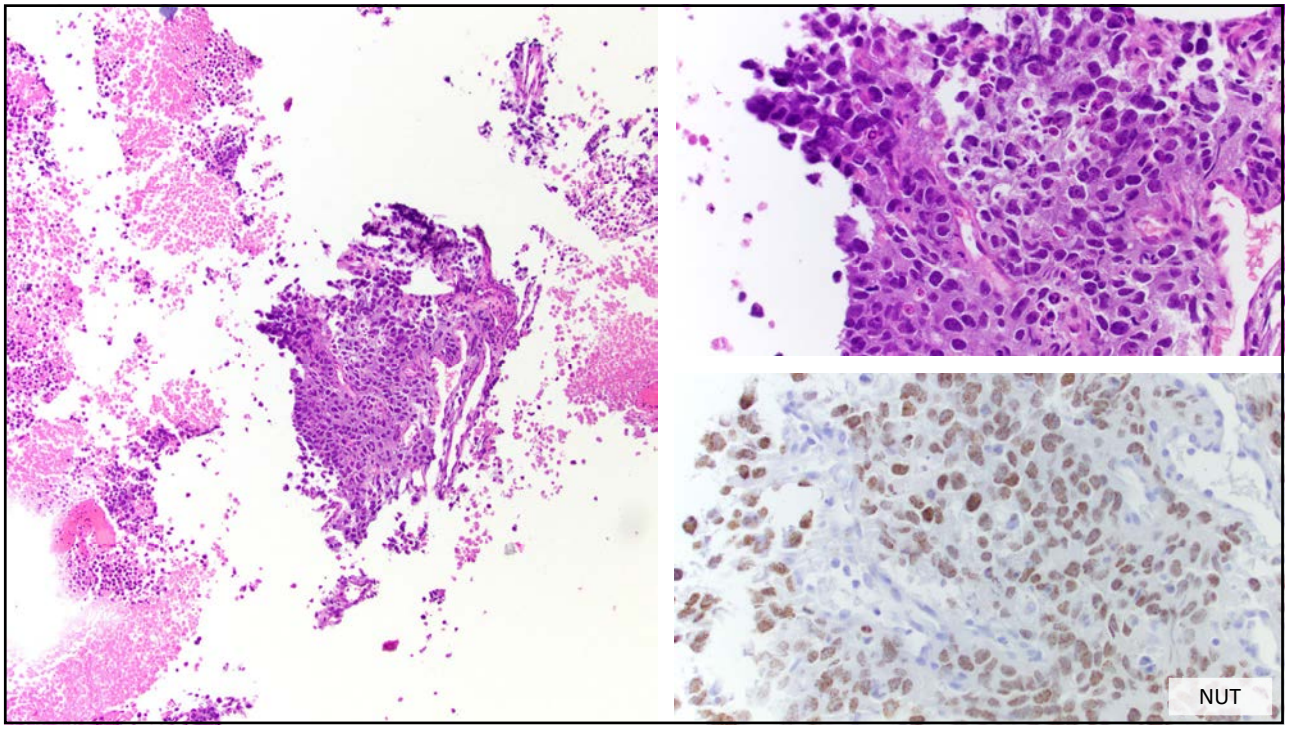
- Can be challenging to diagnose on FNA/core bx if mucinous component is not present and/or the tumor has predominantly solid/nested growth
- IHC may have limited utility (although can sometimes help to exclude other entities)
  - IHC in salivary neoplasms often has low specificity and can show highly variable staining even within a single tumor type (i.e. myoepithelial markers)
- May need to resort to molecular testing in challenging cases (i.e. FISH, sequencing/fusion panels) or defer to the resection
  - If considering a solid/nested primary salivary tumor with a squamous immunophenotype, the differential often also includes hyalinizing clear cell carcinoma (although most HCCC arise in minor salivary gland)

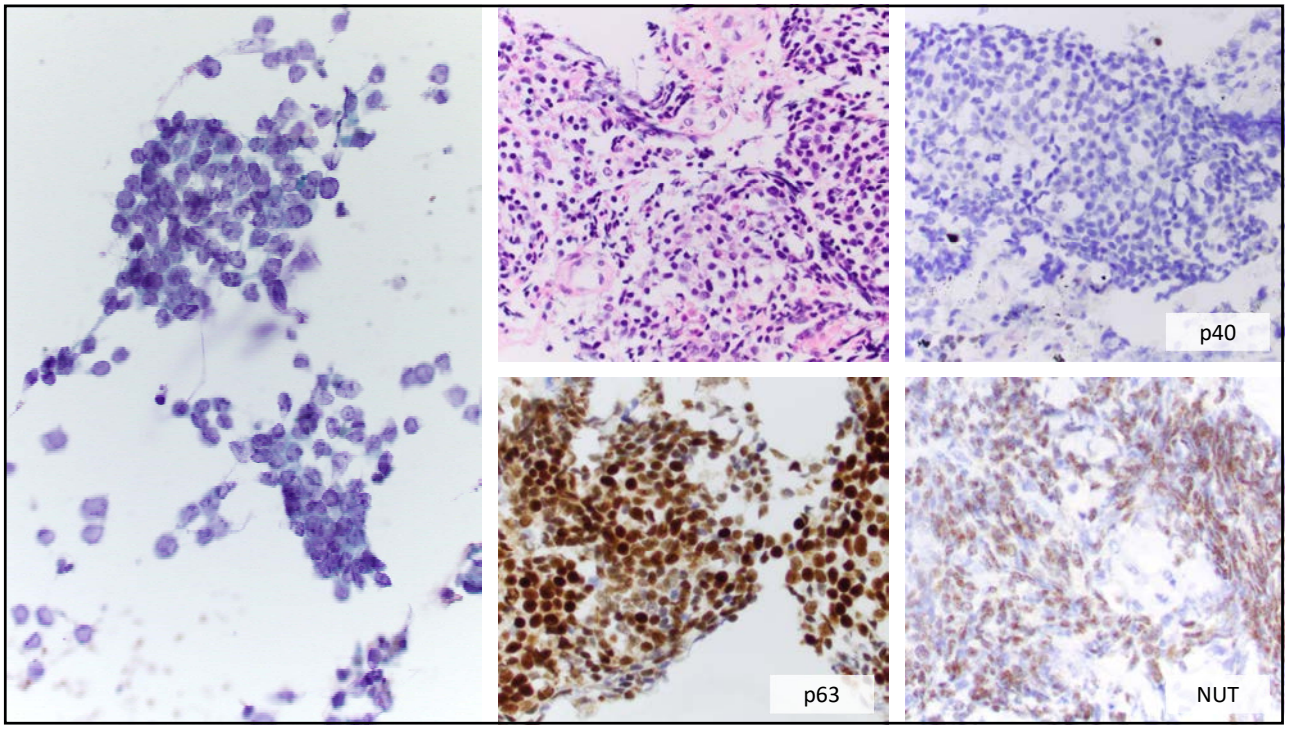


Other rare squamoid/squamous carcinomas

Case 9

- 30M with a 3 cm midline neck mass



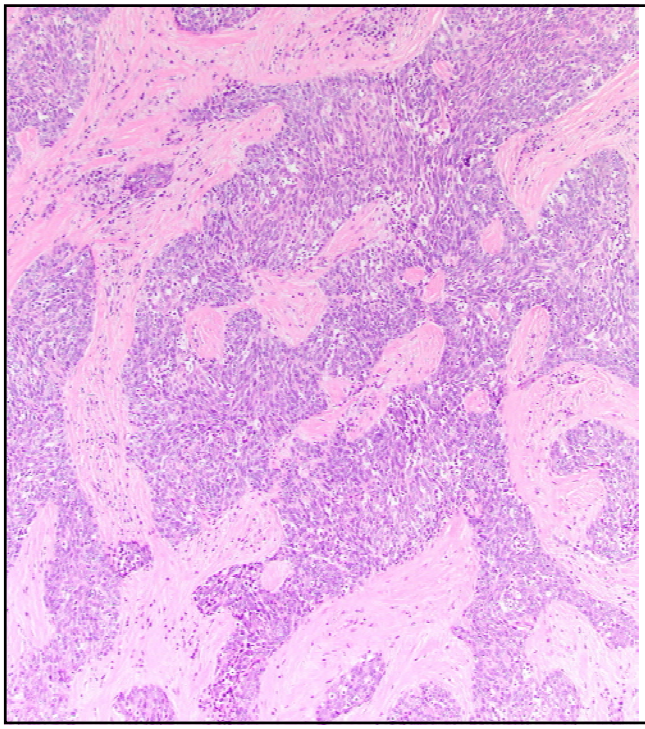


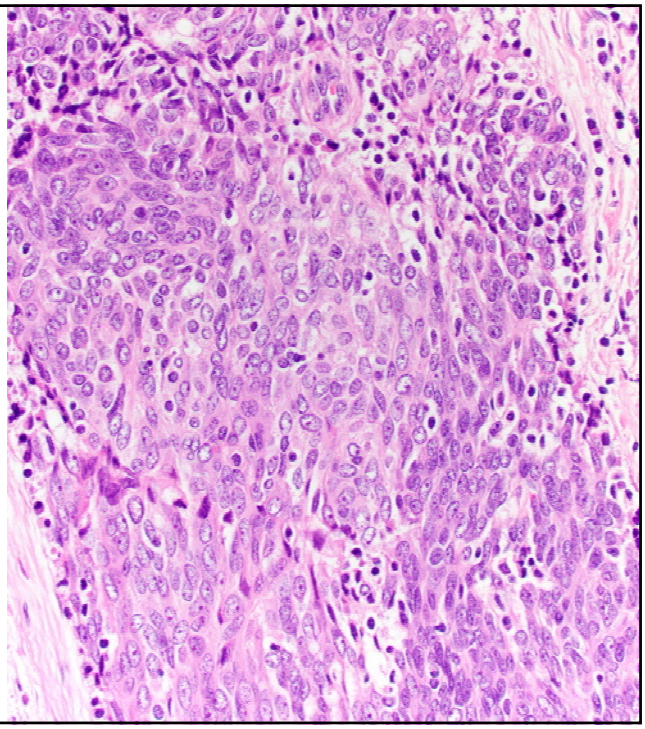
NUT carcinoma

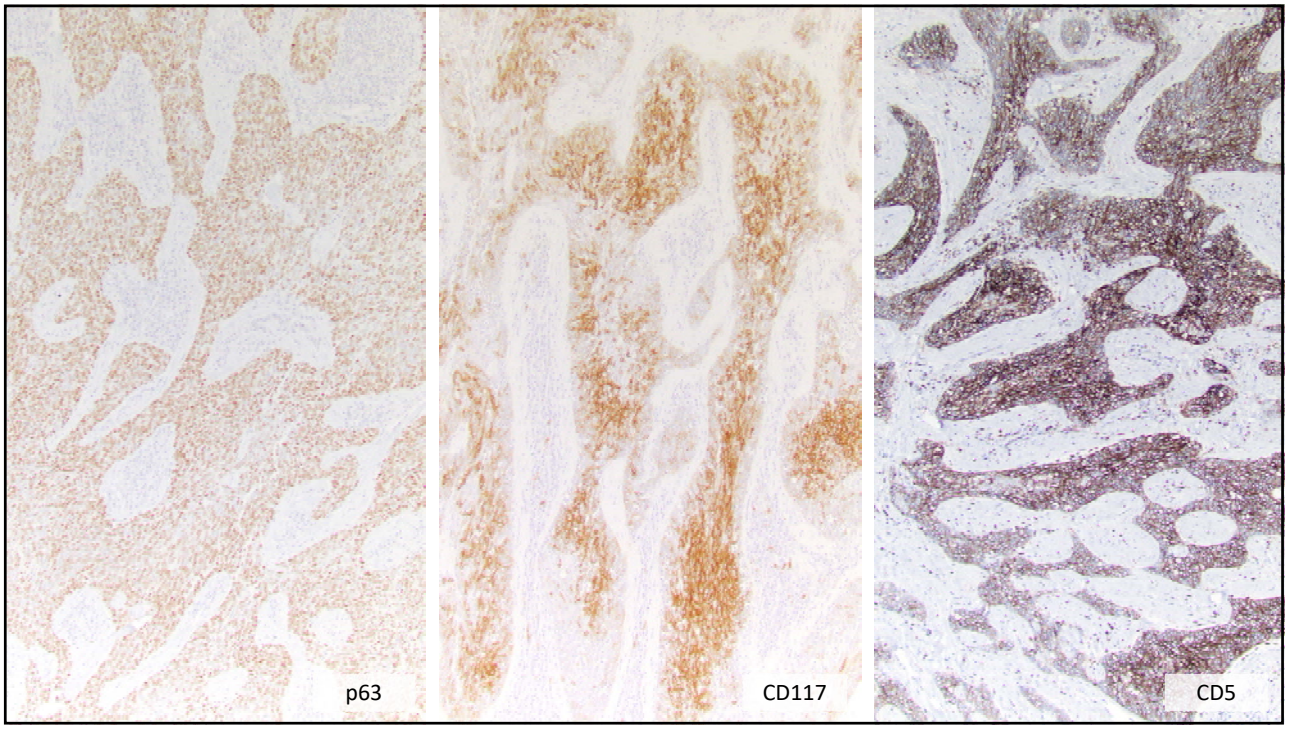
- Can occur at a wide range of sites in the H&N, including rarely in the thyroid
  - Characterized by *NUTM1* fusions (NUT IHC sensitive/specific, but performance can be affected by suboptimal fixation)
  - Data supports that NUT carcinoma is a subtype of SCC (PMID 39900969)
    - p63 is typically positive, but p40 can be negative
- Primary NUT carcinoma of the thyroid can mimic PDTC or other follicular-cell derived thyroid malignancies
  - May have an atypical morphology, including cribriform/fused follicular architecture (PMID 36040068)
  - Can express TTF-1 and PAX8 (especially if the tumor has an atypical morphology)

Case 10

- 60M with a 3.5 cm thyroid mass





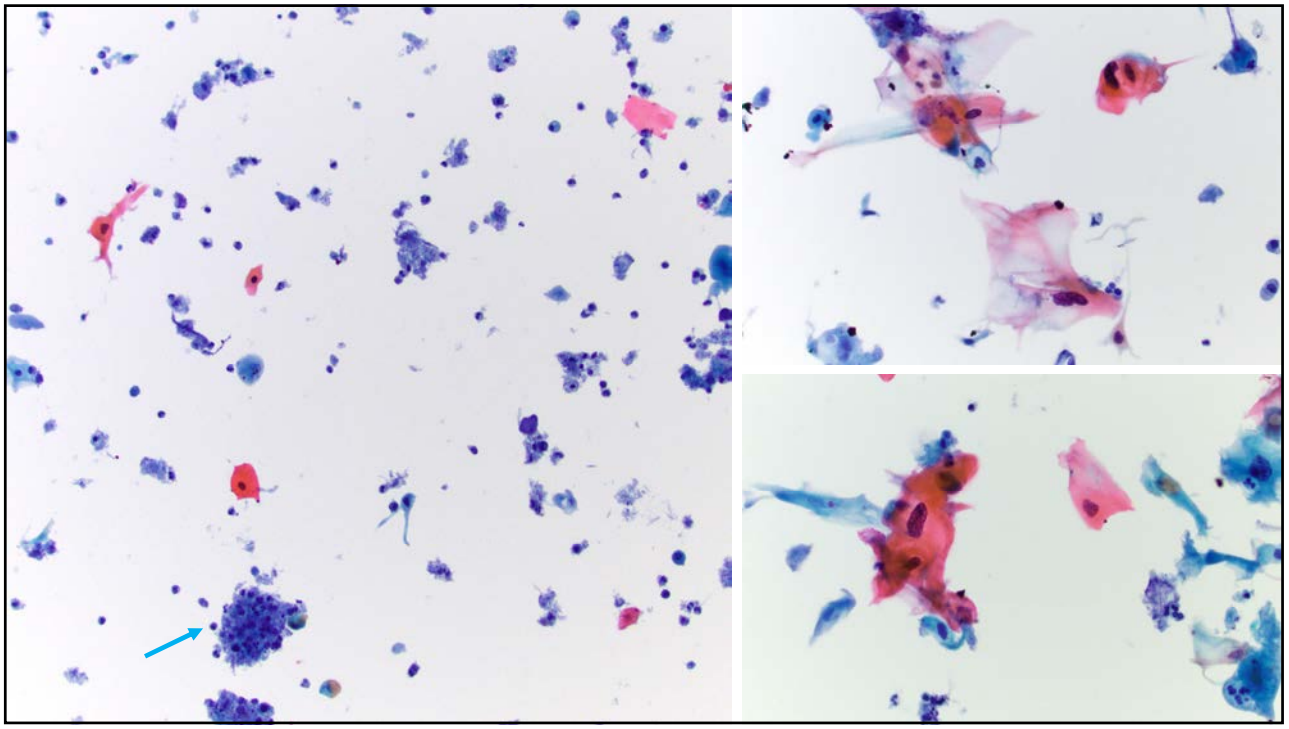


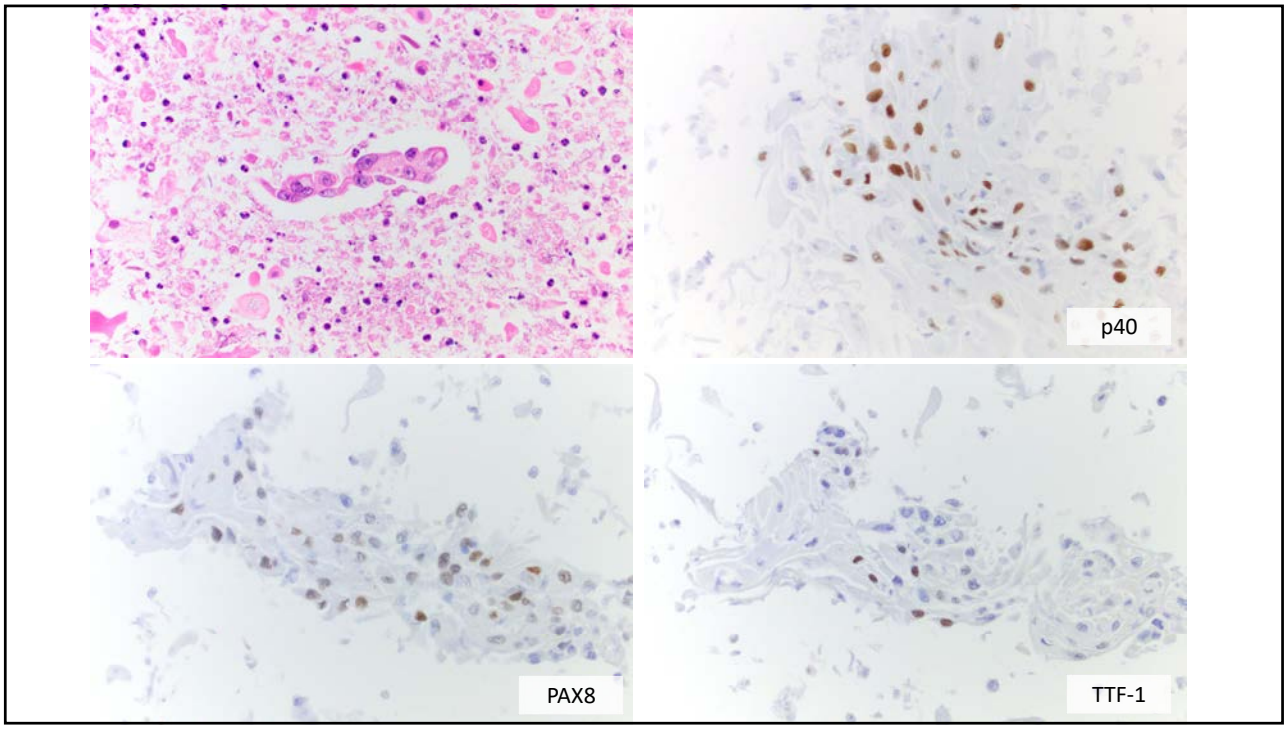
Intrathyroidal thymic carcinoma

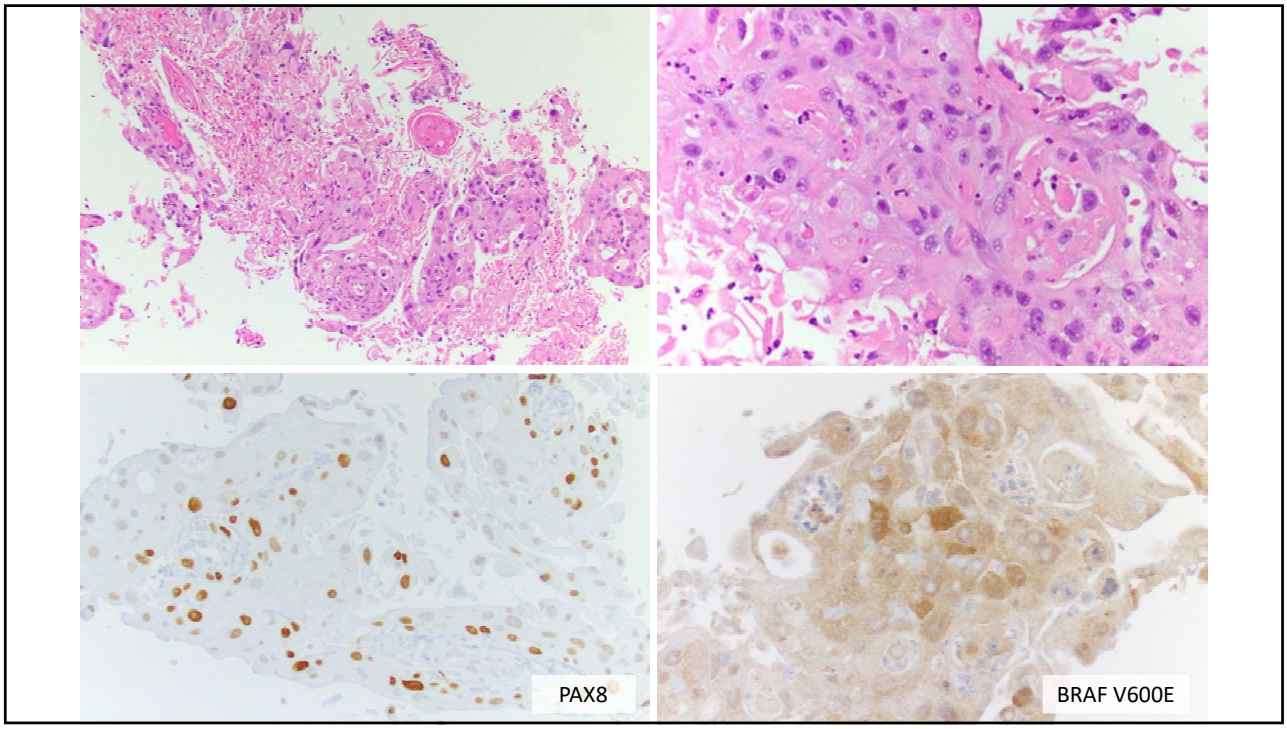
- Thought to arise from intra/perithyroidal thymic tissue or intrathyroidal developmental rests/remnants
- Morphology and immunophenotype similar to mediastinal thymic squamous carcinomas
  - Expression of squamous markers (p63/p40), polyclonal PAX8, CD117, CD5
- Other terminology (i.e. carcinoma showing thymic-like elements/CASTLE and lymphoepithelioma-like carcinoma) no longer recommended

Case 11

- 70M with a 5 cm thyroid mass and hoarseness




p40
PAX8
TTF-1

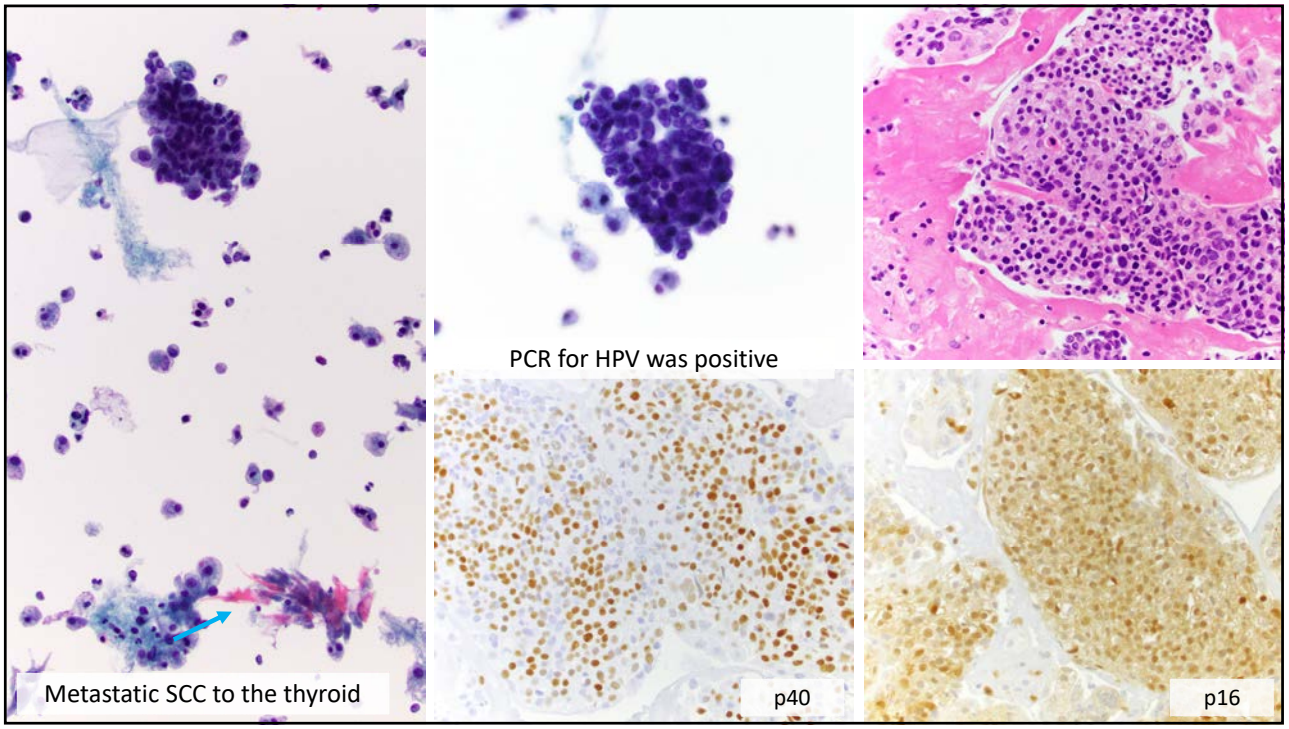

PAX8
BRAF V600E

Anaplastic thyroid carcinoma

- Can have a squamous phenotype (may be focal or extensive)
- Primary SCC of the thyroid considered to be a type of ATC
- Should exclude primary laryngeal SCC with invasion into the thyroid and metastases
  - Clinical history and imaging are key
  - Morphology can be helpful if there is a precursor/more differentiated component present (squamous ATC often arise from PTC), but this may be less obvious on biopsy
  - IHC may help if PAX8, TTF-1, and/or BRAF positive (if metastasis, other specific markers such as HPV ISH can be useful)
  - In challenging cases may need to rely on molecular testing results (at our institution, we also always confirm BRAF status with PCR)

Case 12

- 70F with a multiple enlarging thyroid nodules


Metastatic SCC to the thyroid
PCR for HPV was positive
p40
p16

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Primary SCC (i.e. anaplastic carcinoma with squamous differentiation)	*"Primary" SCC*
Intrathyroidal thymic carcinoma	Salivary-type carcinomas (i.e. MEC, HCCC)
NUT carcinoma	NUT carcinoma
Extrathyroidal/metastatic SCC	Metastatic SCC

Questions?