



Memorial Sloan Kettering  
Cancer Center

# *Anaplastic Thyroid Carcinoma (ATC)*

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Memorial Sloan Kettering  
Cancer Center

# Basis of this lecture

- Dissecting Anaplastic Thyroid Carcinoma: A Comprehensive Clinical, Histologic, Immunophenotypic, and Molecular Study of 360 Cases

**Xu B**, Fuchs T, Dogan S, Landa I, Katabi N, Fagin JA, Tuttle RM, Sherman E, Gill AJ, Ghossein R. *Thyroid*. 2020 Oct;30(10):1505-1517



# Outline

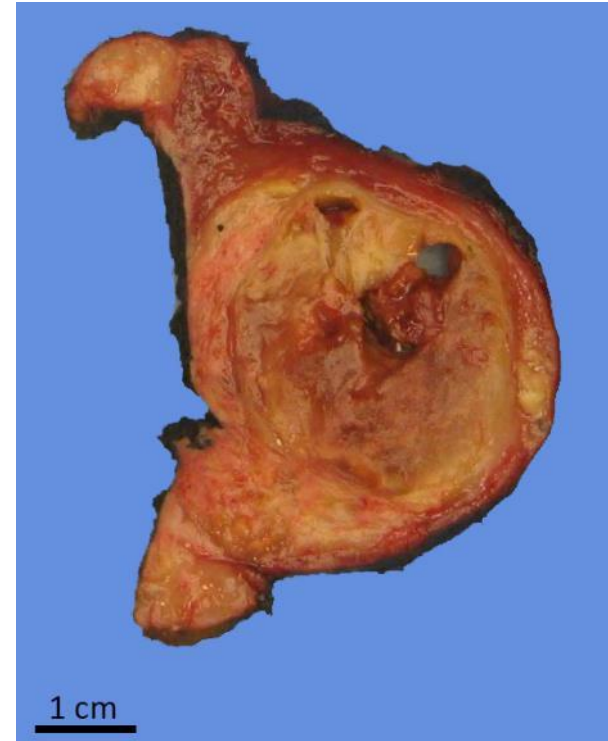
- The basics:
  - Clinical presentation
  - Pathologic features
  - Immunohistochemistry
  - Differential diagnosis
- Recent advances:
  - Prognostic and predictive biomarkers
  - Molecular profile
  - Targeted therapy

# Anaplastic thyroid carcinoma (ATC)

- WHO definition: a highly aggressive thyroid malignancy composed of **undifferentiated** follicular thyroid cells
- The Roles of pathologists:
  - Traditional: making the right diagnosis
  - New roles: providing prognostic and/or predictive information, including actionable molecular targets.

# The basics of ATC: clinical presentation

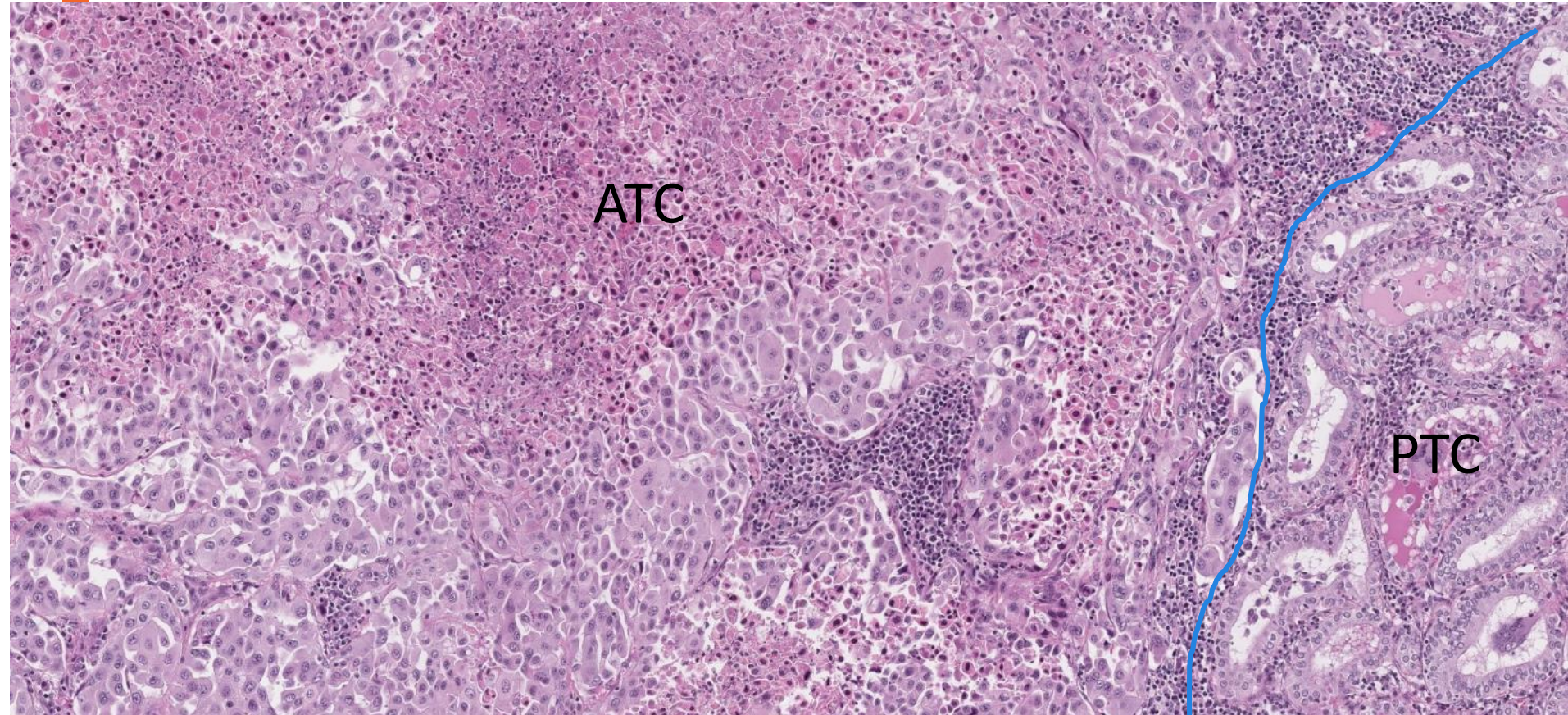
- Large rapidly-enlarging thyroid-based (necrotic) mass
- Affects patients in their 60-70s (median 68, range 29-99)
- Infrequent (<2%) in patients under 40 (including a few case reports in pediatric patients)
  - Other diagnostic possibility should be considered.
  - ATC diagnosis in pediatric patients is highly debatable
- Nearly always fatal: median survival: 3 months; 1-year survival 20%
  - Multimodality treatment in referral centers: median survival ~9 months; 1-year survival ~35%



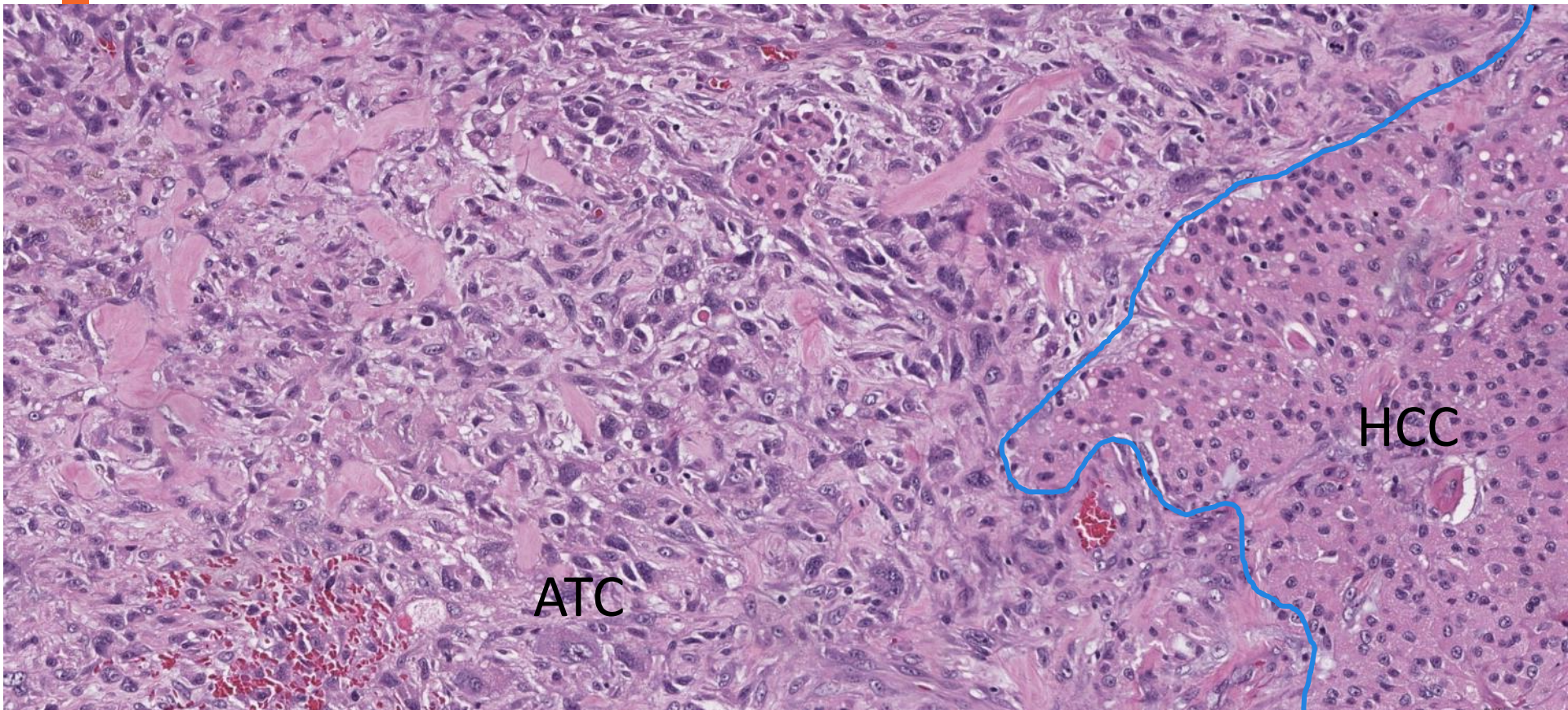
# The majority of ATC are associated with a differentiated thyroid carcinoma

- ~ 60% of ATC have either a history of previously resected or co-existing differentiated thyroid carcinoma (DTC) component :
  - Well-differentiated
    - Papillary thyroid carcinoma (PTC) most common (75%), in particular tall cell variant
    - Hurthle cell carcinoma (10%)
    - Follicular carcinoma (5%)
  - Poorly differentiated thyroid carcinoma (35%)

# ATC with adjacent PTC



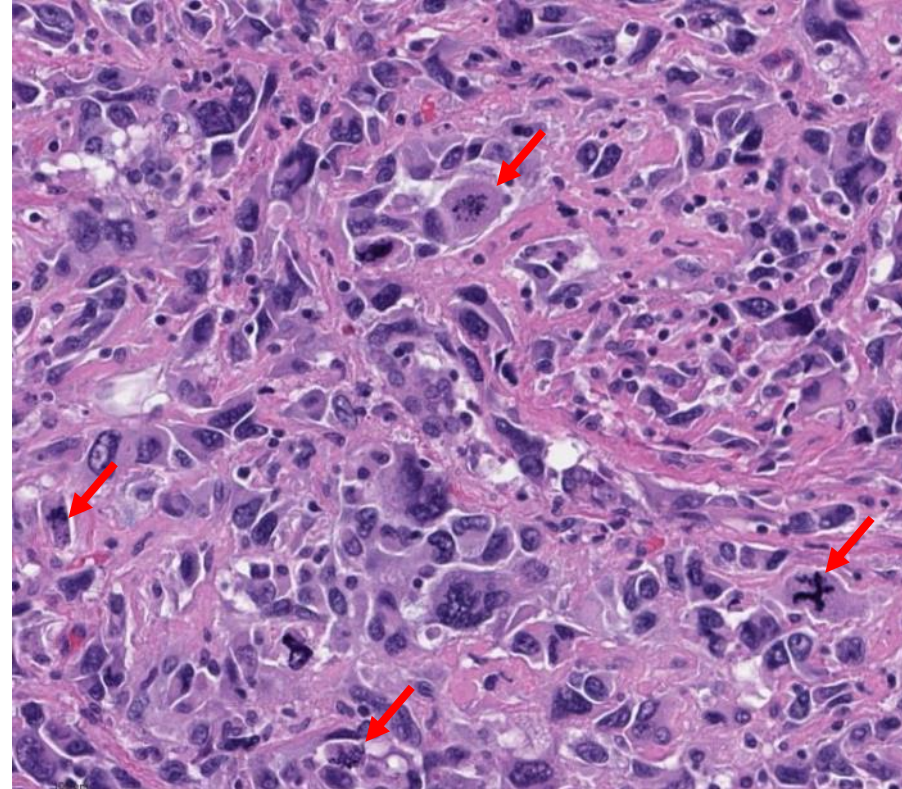
# ATC with adjacent Hurthle cell carcinoma (HCC)





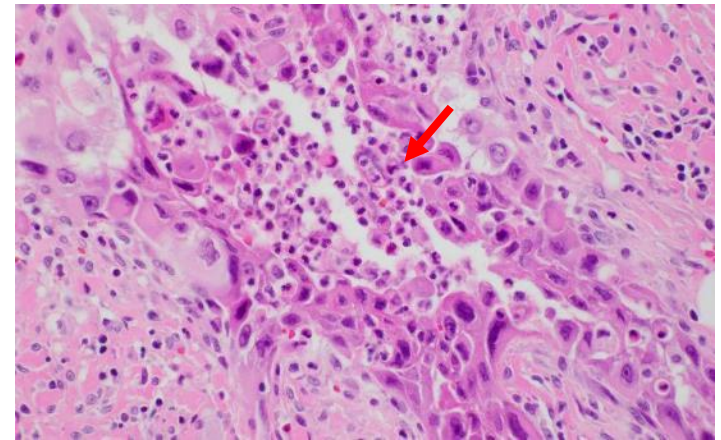
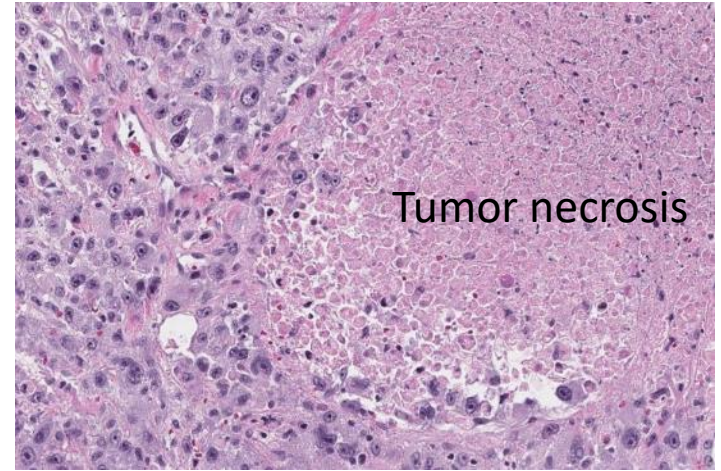
# The basics of ATC: typical histologic features

- Marked pleomorphism
- High mitotic index (>5/10 HPFs in 70%)
- Atypical mitosis (85%)
- **Caveat: mitotic rate can be low**
  - A mitotic index of  $\leq 5/10$  HPFs can be seen in 30% of ATC and 22% of resected ATC
  - In such cases, a diagnosis of ATC can be rendered based on:
    - Other histologic features: e.g. marked nuclear pleomorphism
    - Loss of immunohistochemical evidence of thyroid follicular differentiation



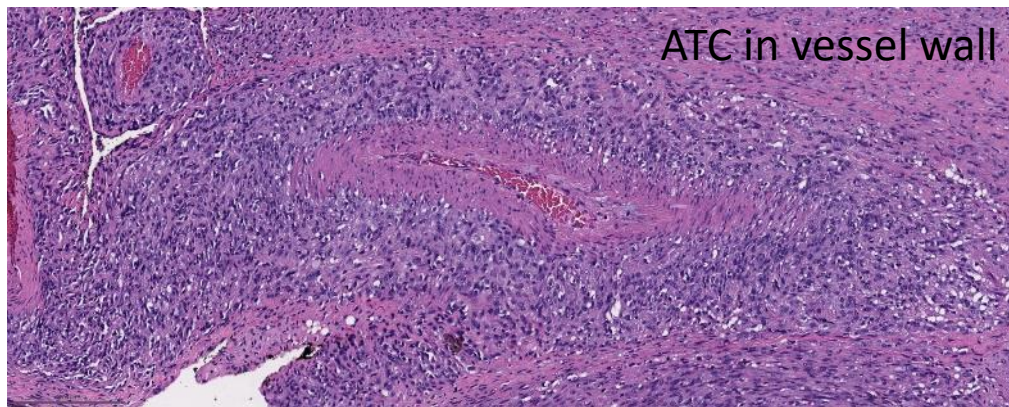
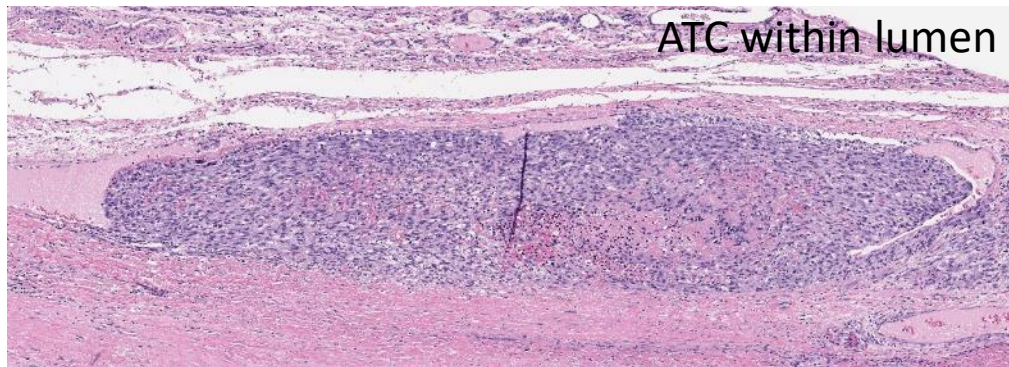
# The basics of ATC: typical histologic features

- Tumor necrosis (86%)
- Abundant inflammatory infiltrates (esp. neutrophils and macrophages, 71%)



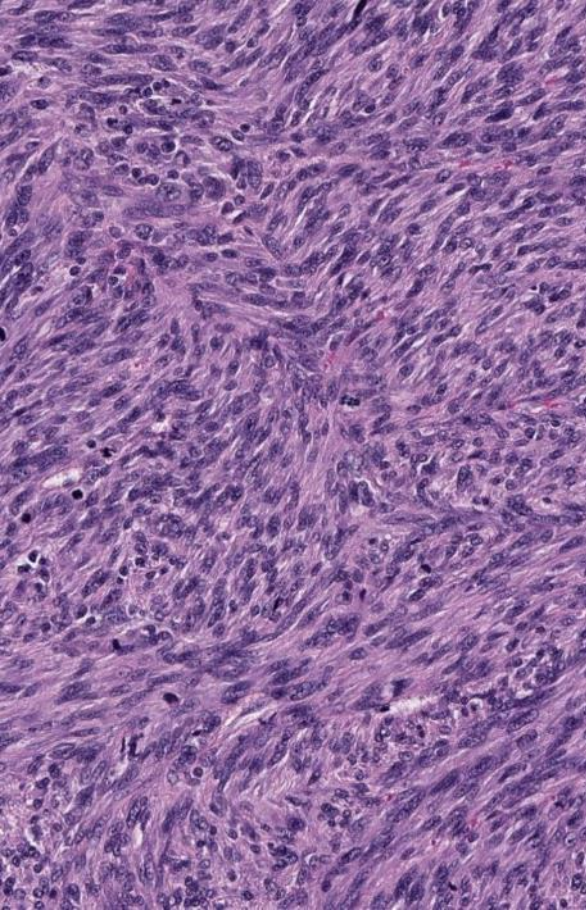
# The basics of ATC: typical histologic features

- Widely invasive, often with gross extrathyroidal extension (90%)
- Lymphovascular invasion (79%)
  - Including invasion of vessel wall

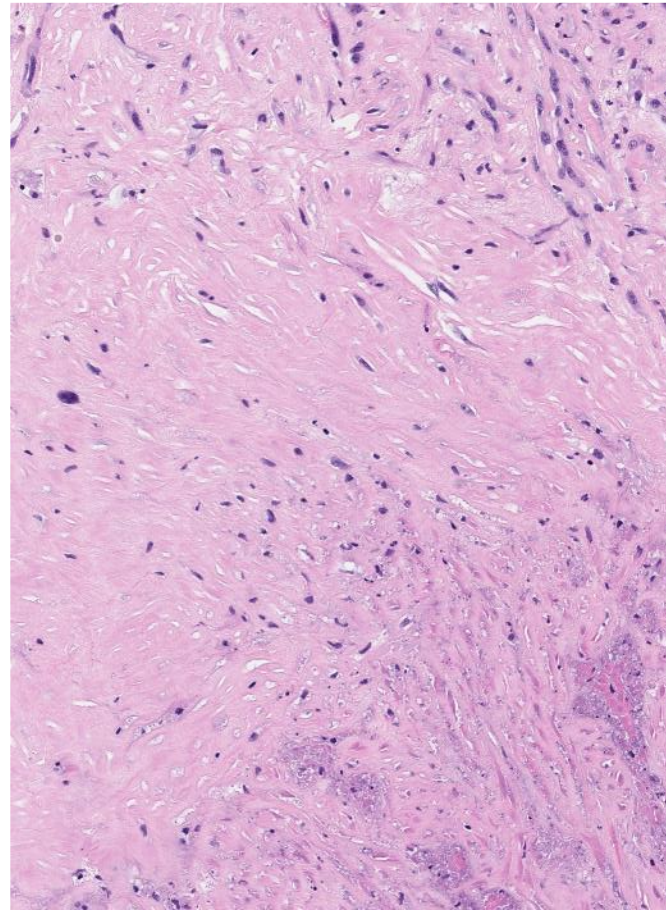


# ATC: cytologic features

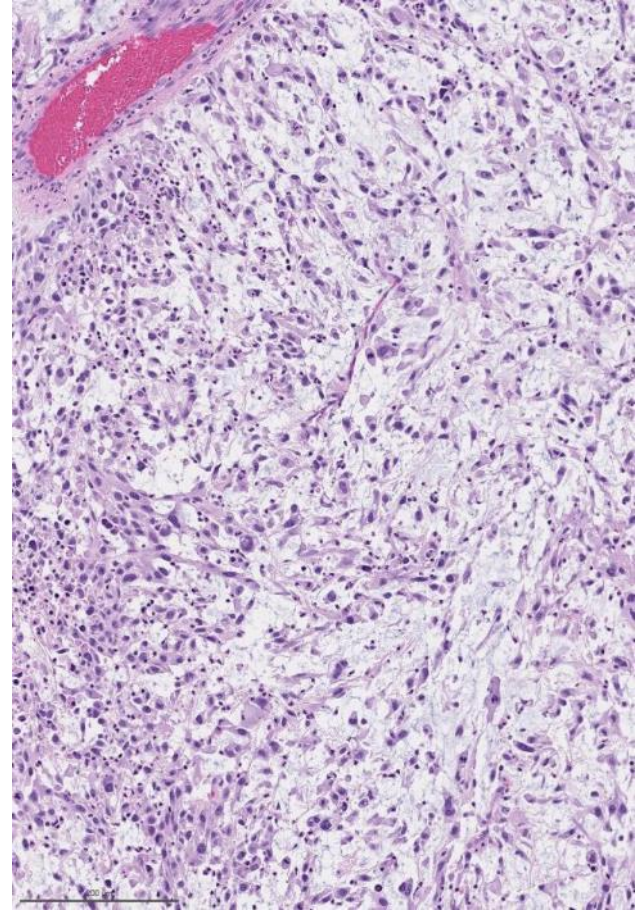
Spindle 26% (& cellular)



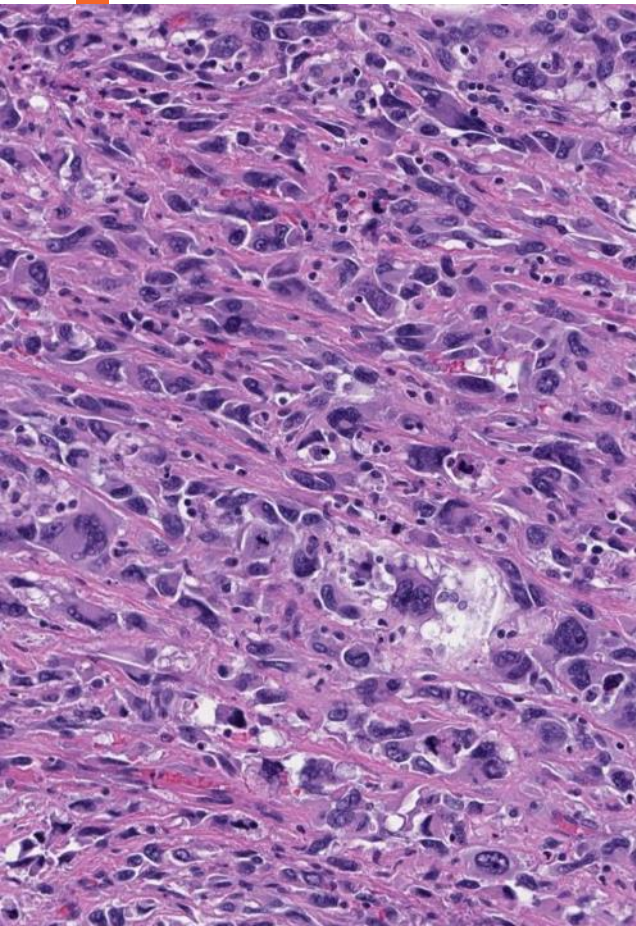
Spindle (& paucicellular)



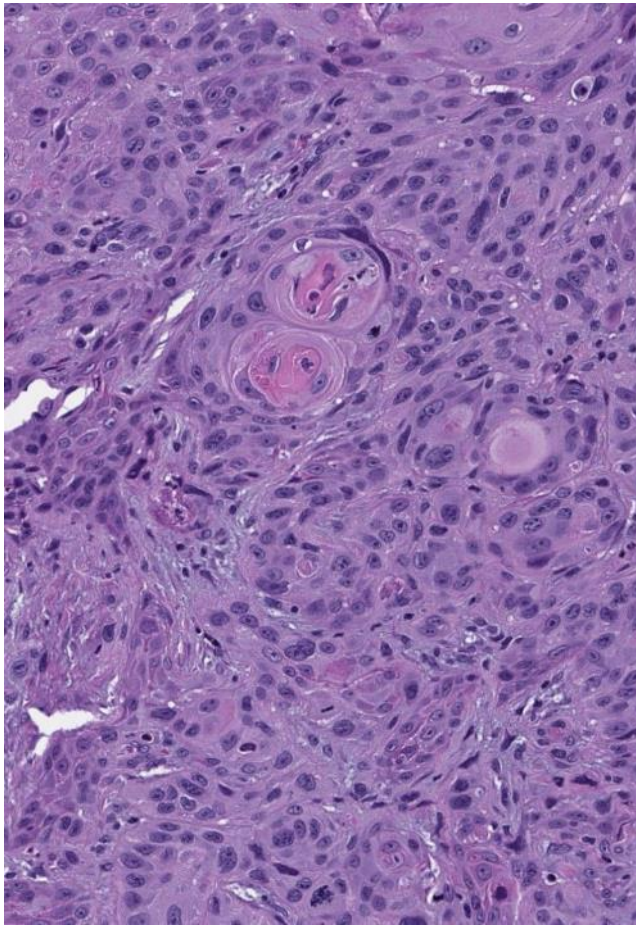
Spindle (with myxoid stroma)



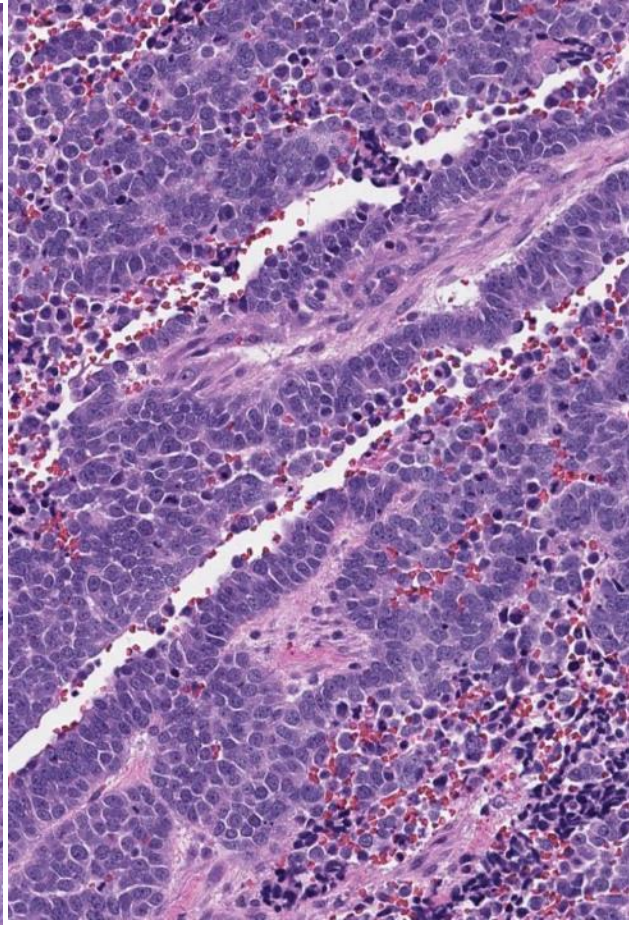
Pleomorphic (23%)



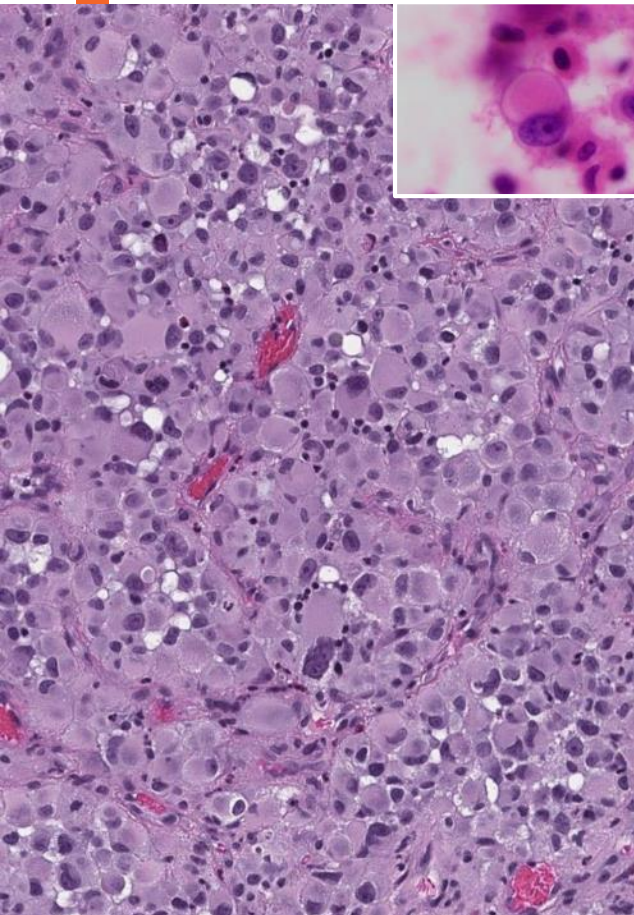
Squamous (21%)



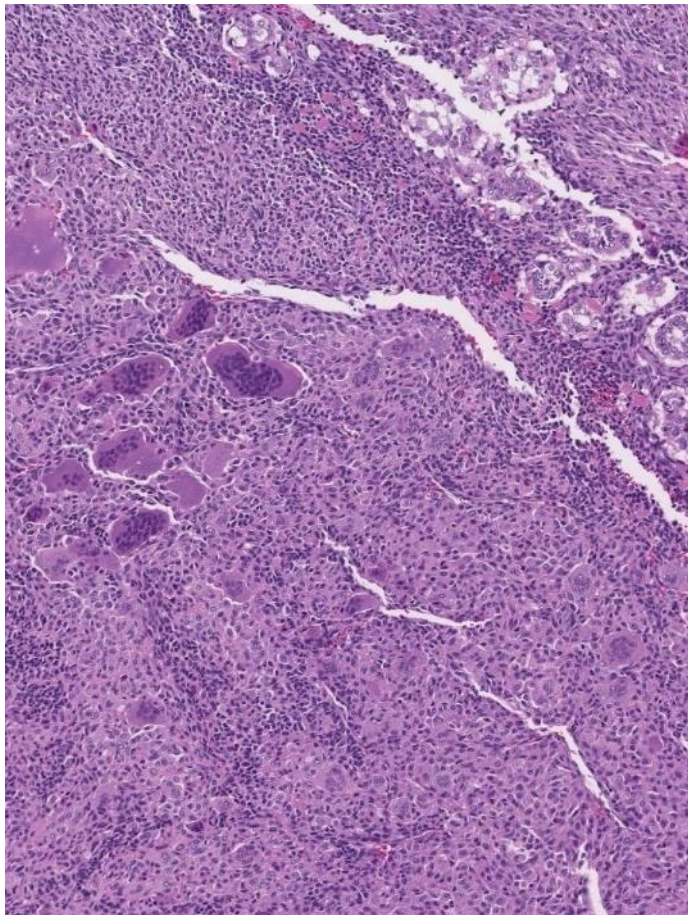
Epithelial/epithelioid (19%)



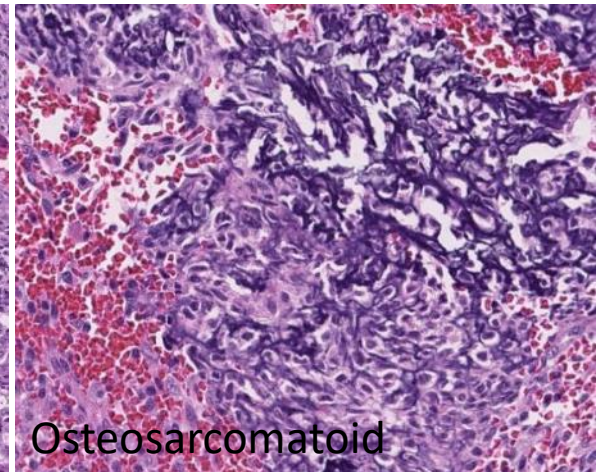
Rhabdoid (8%)



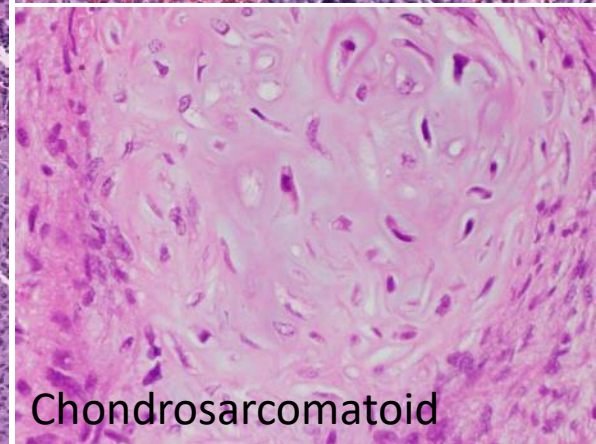
Osteoclast giant cell rich (3%)



Heterologous component (<1%)



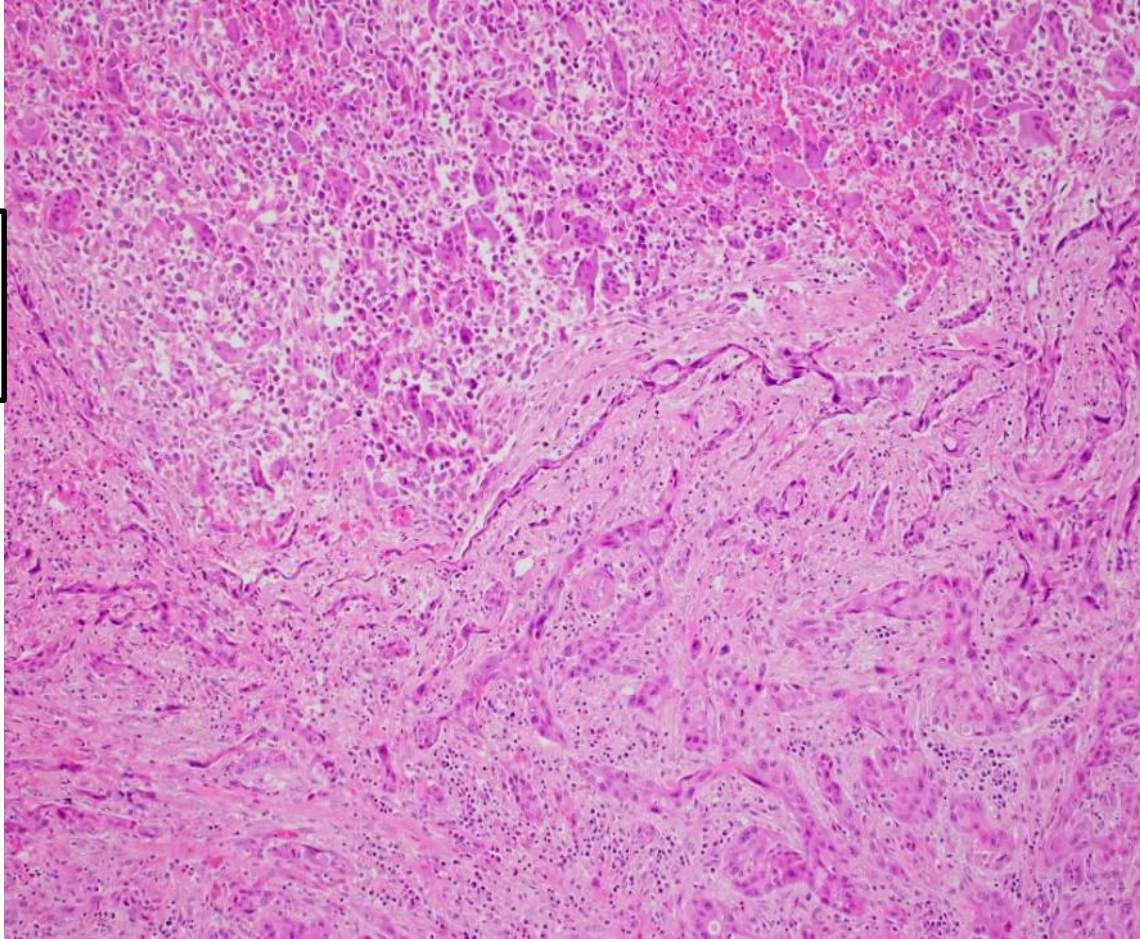
Osteosarcomatoid



Chondrosarcomatoid

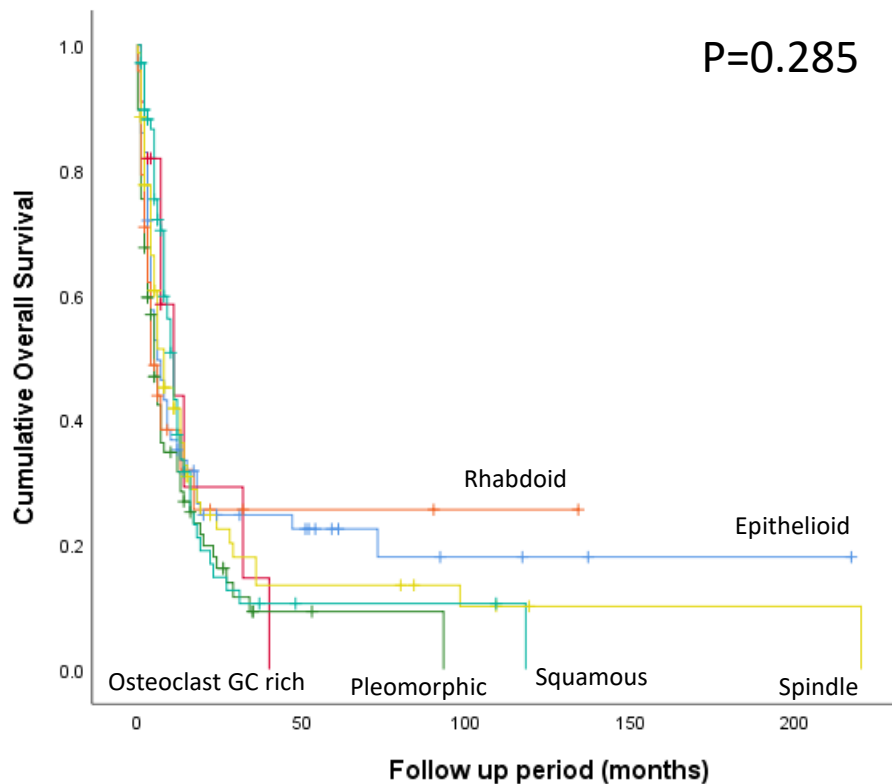
# Mixture of morphologic features within one ATC

Osteoclast  
giant cell rich  
area



Squamous area

# Cytoarchitectural features of ATC do not impact outcome



- Dominant cytologic features did not impact survival
- Paucicellular variant of ATC may have an improved survival: scanty evidence to draw any convincing conclusion.



# Immunoprofile of ATC



## Mutation proteins

Aberrant p53 60%

BRAF V600E 40%

(N)RAS Q61R 15%

## Differentiation

75% Any keratin

70% PAX8 polyclonal

54% PAX8 monoclonal

30% TTF-1

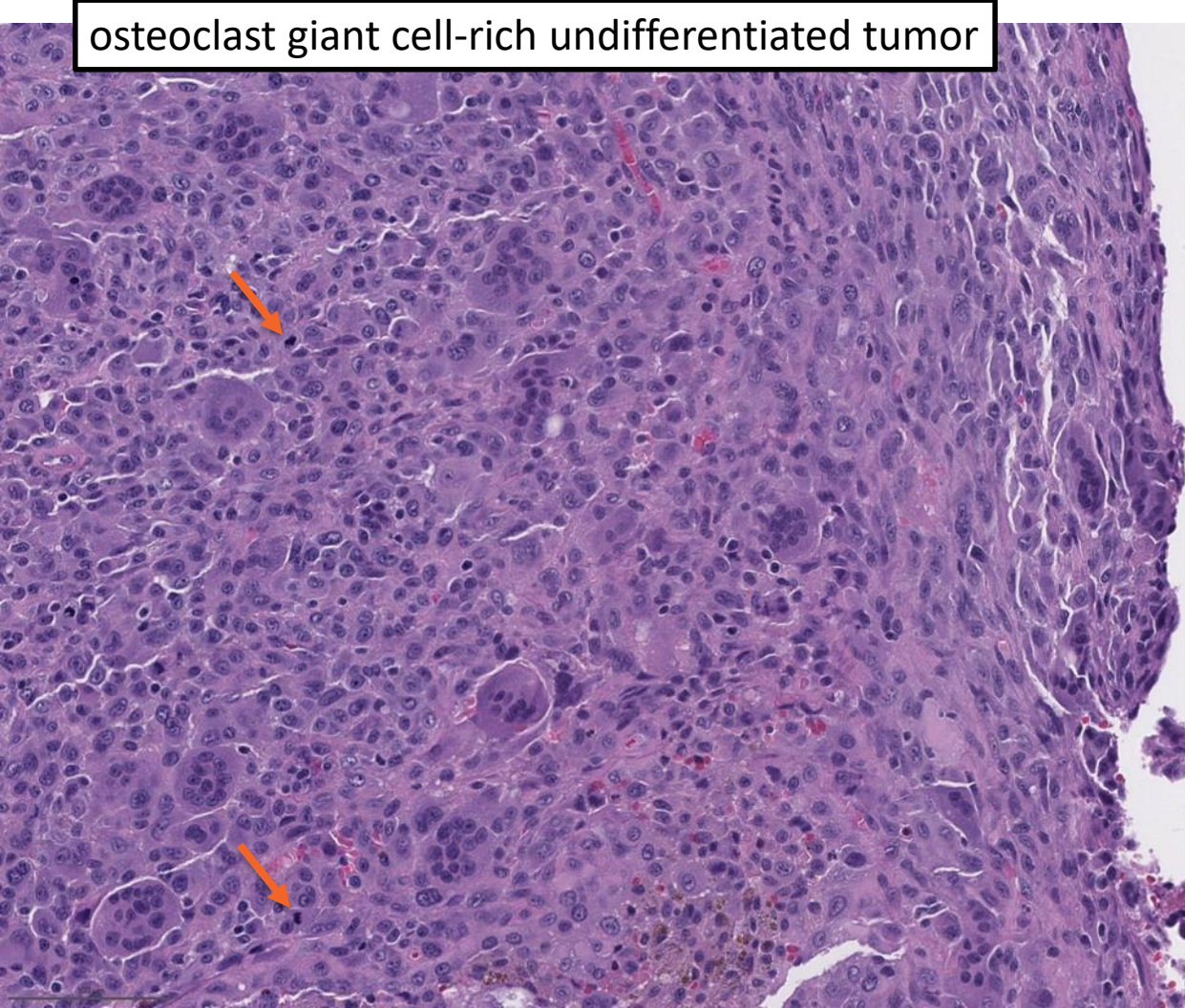
0-4% Thyroglobulin (TG)

68% CAM5.2  
67% AE1/3  
65% CK18  
55% CK5/6  
47% 34βE12

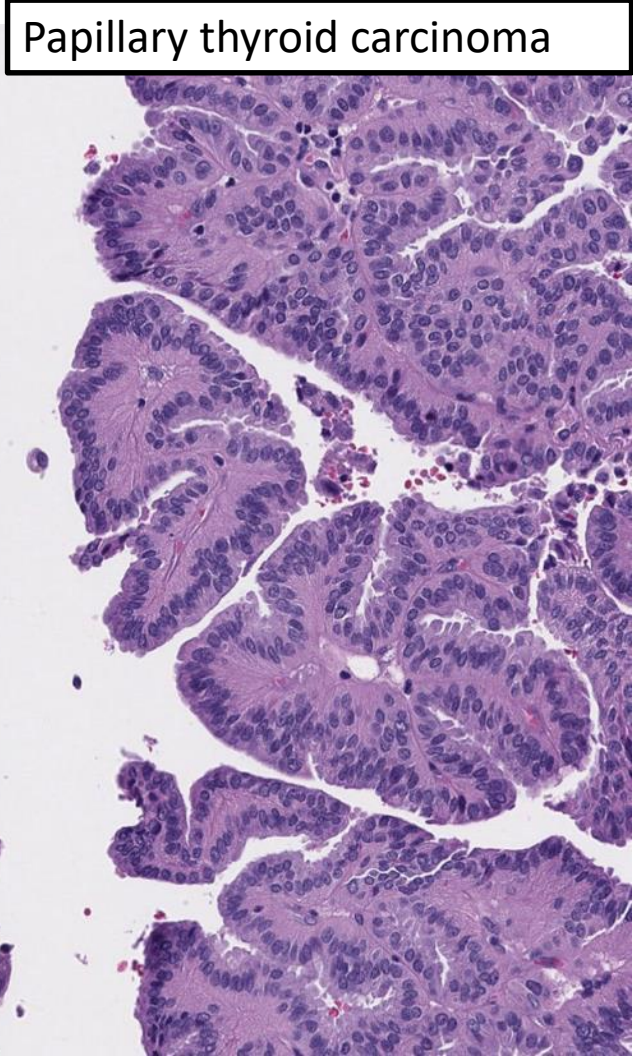
High Ki67: median 50% (range 10-100%)

- In practice: a combination of**
- **Keratins, TTF-1, TG, & PAX8**
  - **BRAF V600E/NRAS Q61R**
  - **± Ki67, p53**

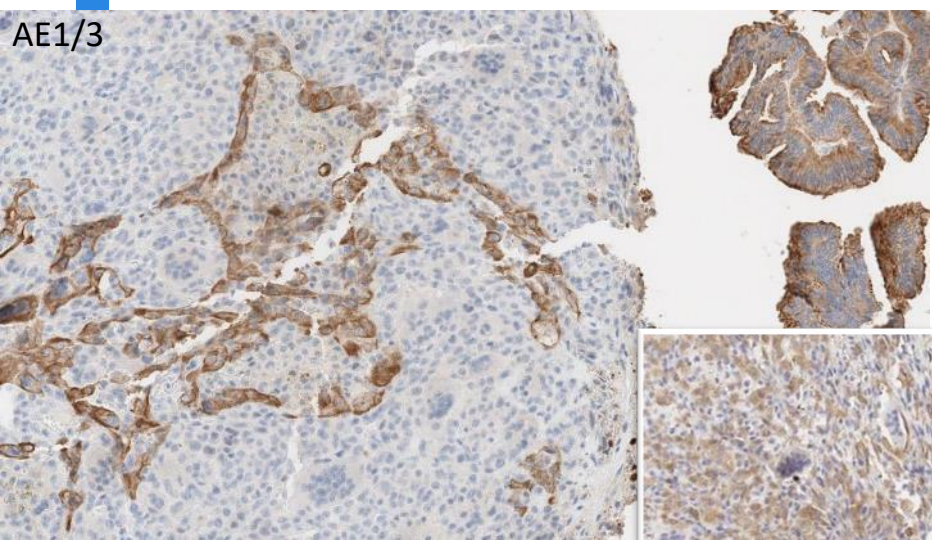
osteoclast giant cell-rich undifferentiated tumor



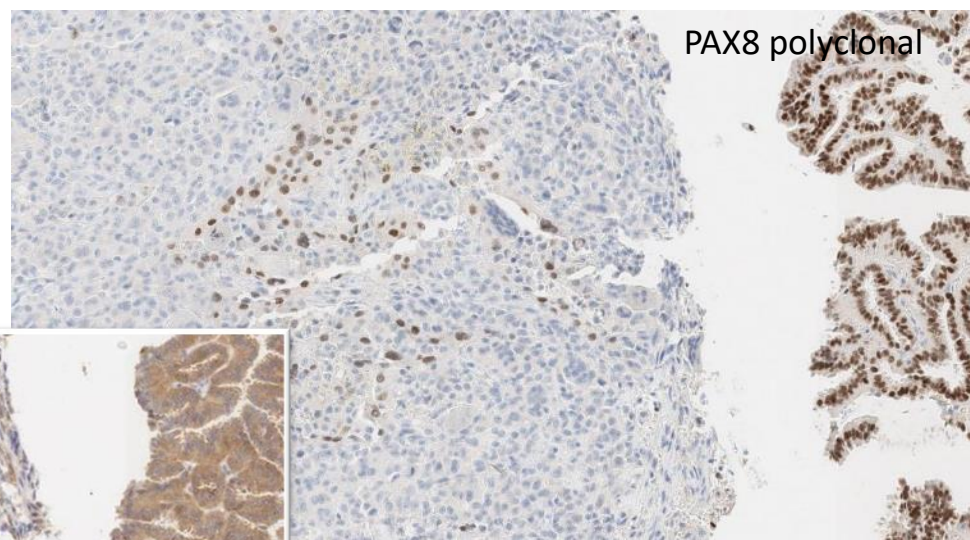
Papillary thyroid carcinoma



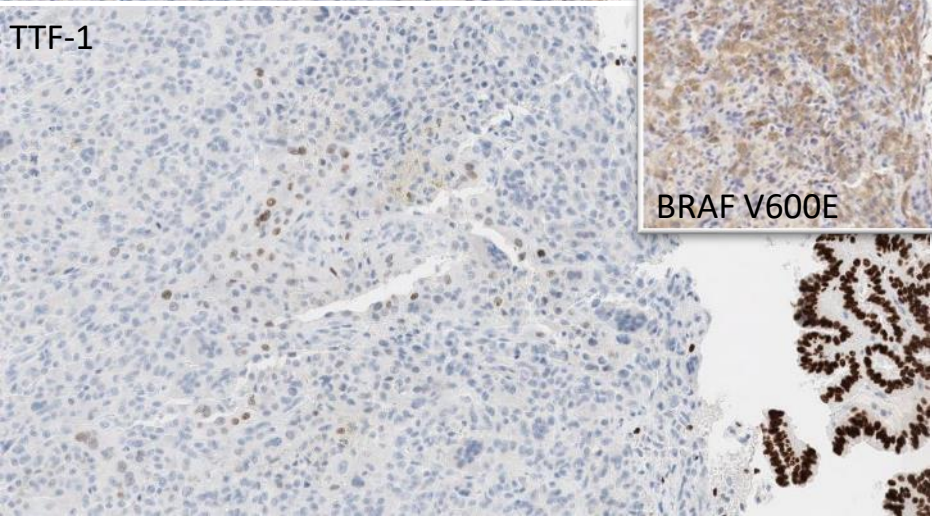
AE1/3



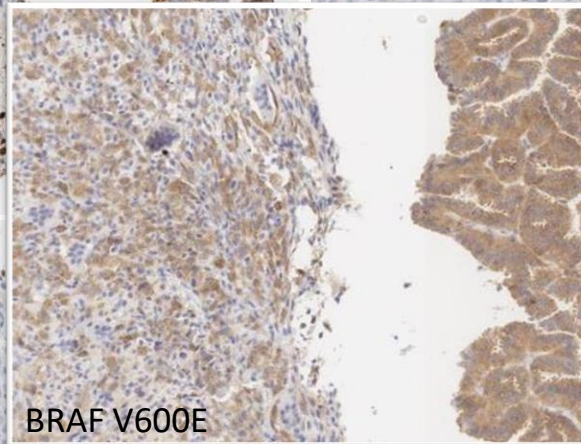
PAX8 polyclonal



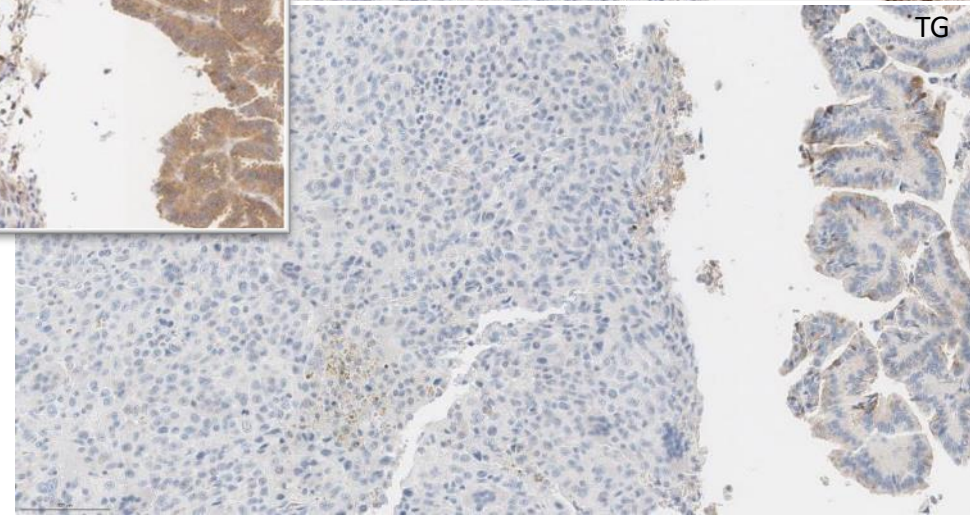
TTF-1



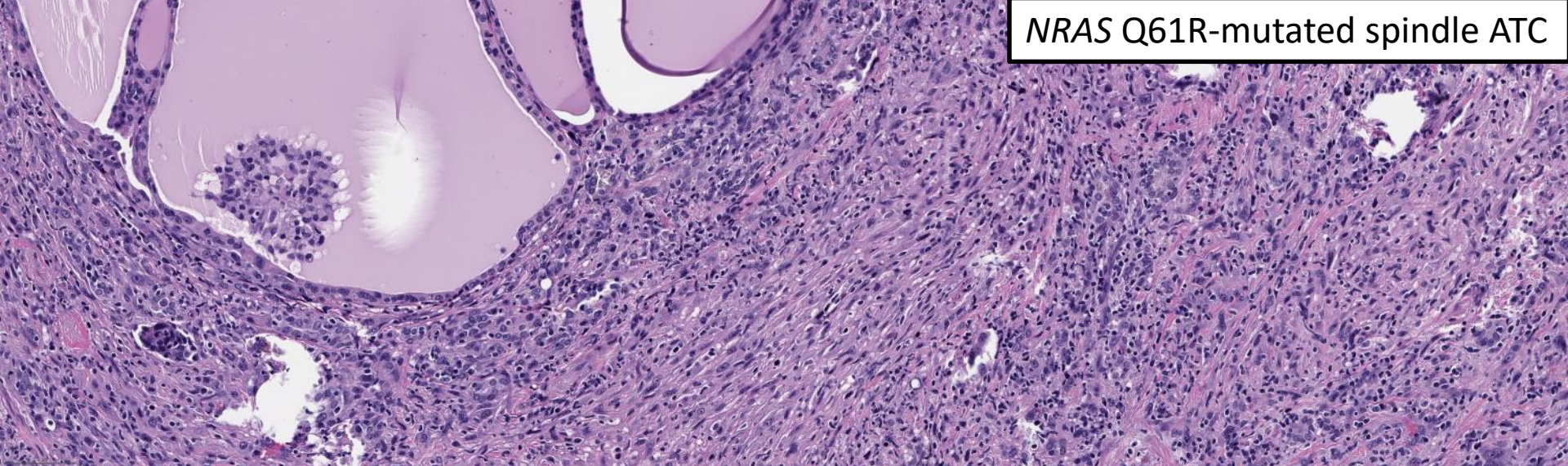
BRAF V600E



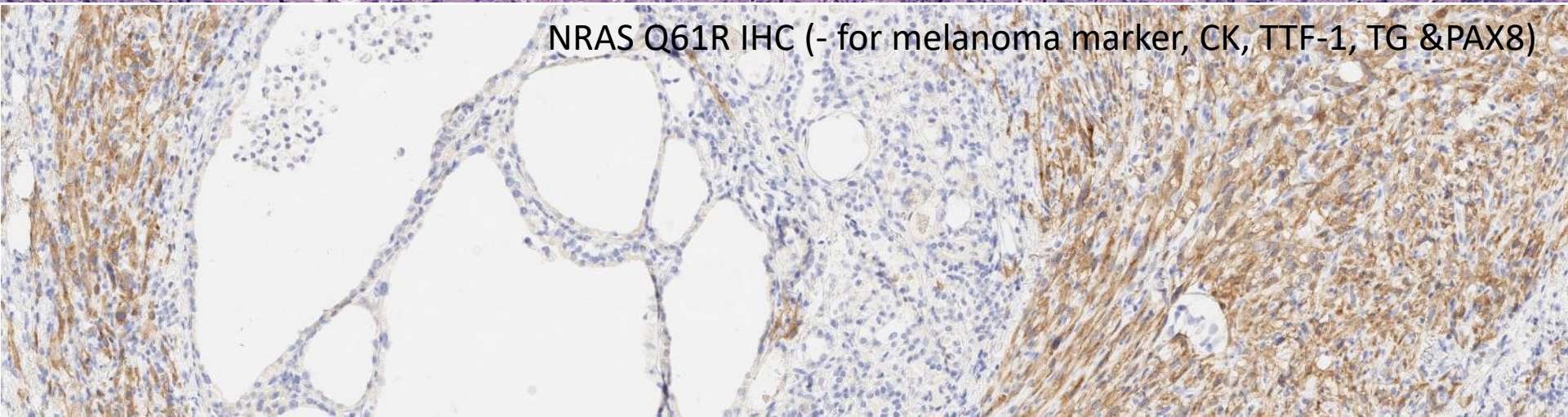
TG



*NRAS* Q61R-mutated spindle ATC

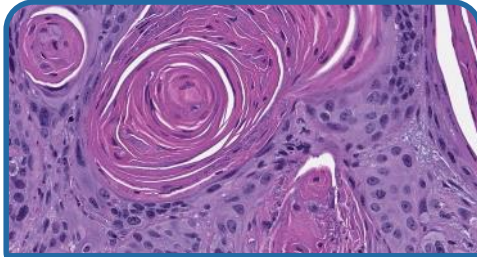


*NRAS* Q61R IHC (- for melanoma marker, CK, TTF-1, TG & PAX8)



# Differential diagnosis

## Squamous ATC



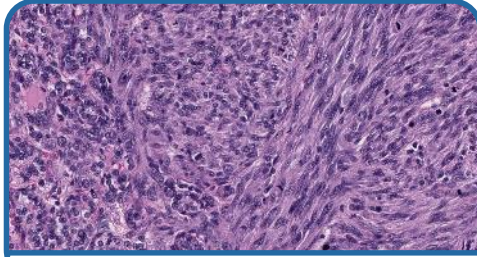
### Malignant:

**Squamous cell carcinoma**  
(extension from larynx)  
Mucoepidermoid carcinoma  
Sclerosing mucoepidermoid carcinoma with eosinophilia

### Benign:

**Squamous metaplasia**

## Spindle/pleomorphic ATC



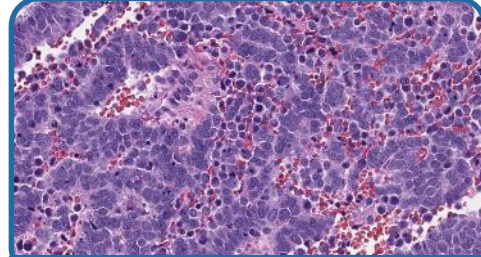
### Malignant:

Medullary thyroid carcinoma  
PTC Spindle variant  
Sarcoma (primary or met.)  
SETTLE

### Benign:

Post-FNA spindle cell nodule  
Endocrine atypia  
Adenoma with spindle cell metaplasia

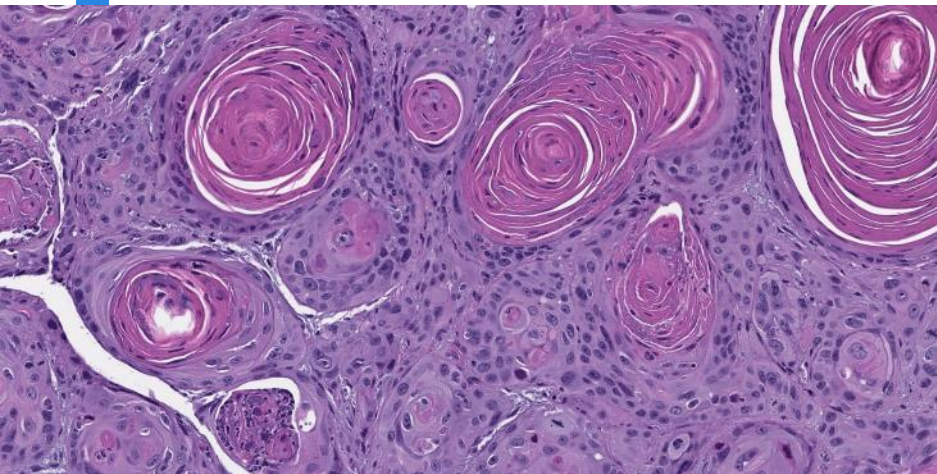
## Epithelial/epithelioid ATC



### Malignant:

Metastasis  
NUT carcinoma  
Adamantinoma-like Ewing Sarcoma  
Lymphoma

# Squamous ATC vs. laryngeal squamous cell carcinoma



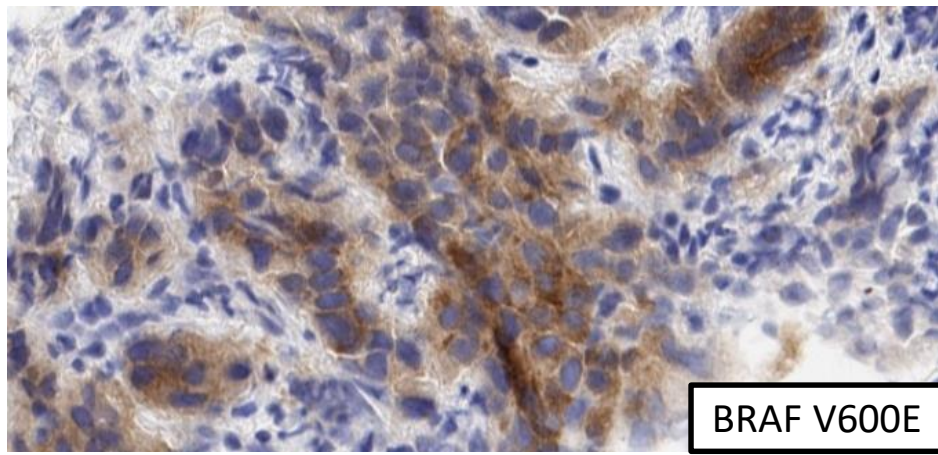
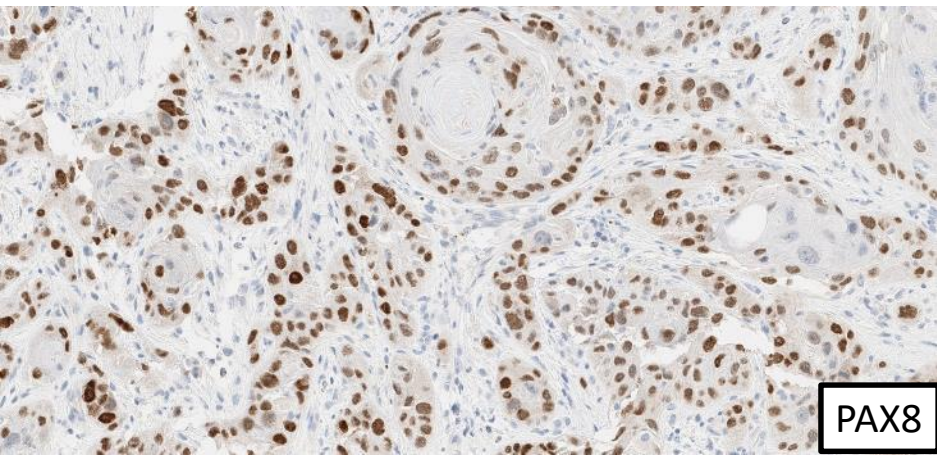
## Similarity:

- True keratinization & intercellular bridge
- Immunoexpression of squamous markers: p40, p63, HMWCK

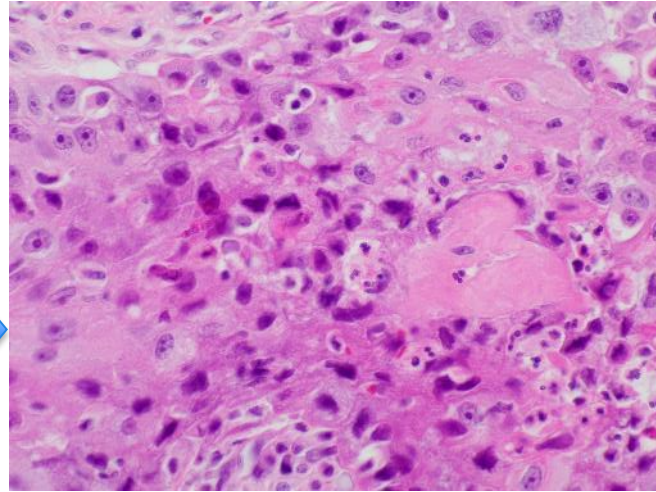
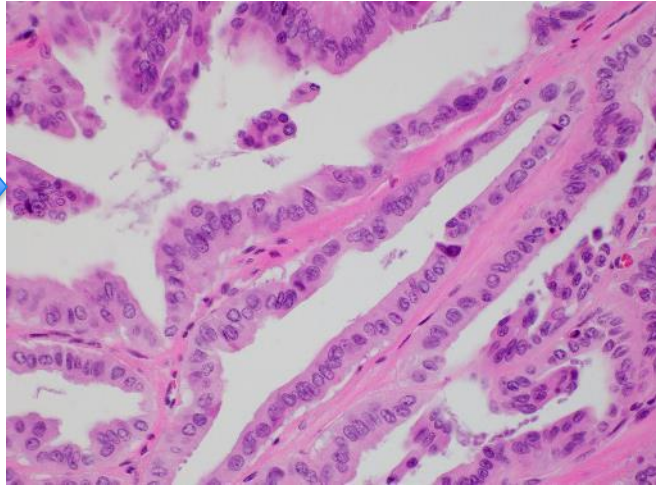
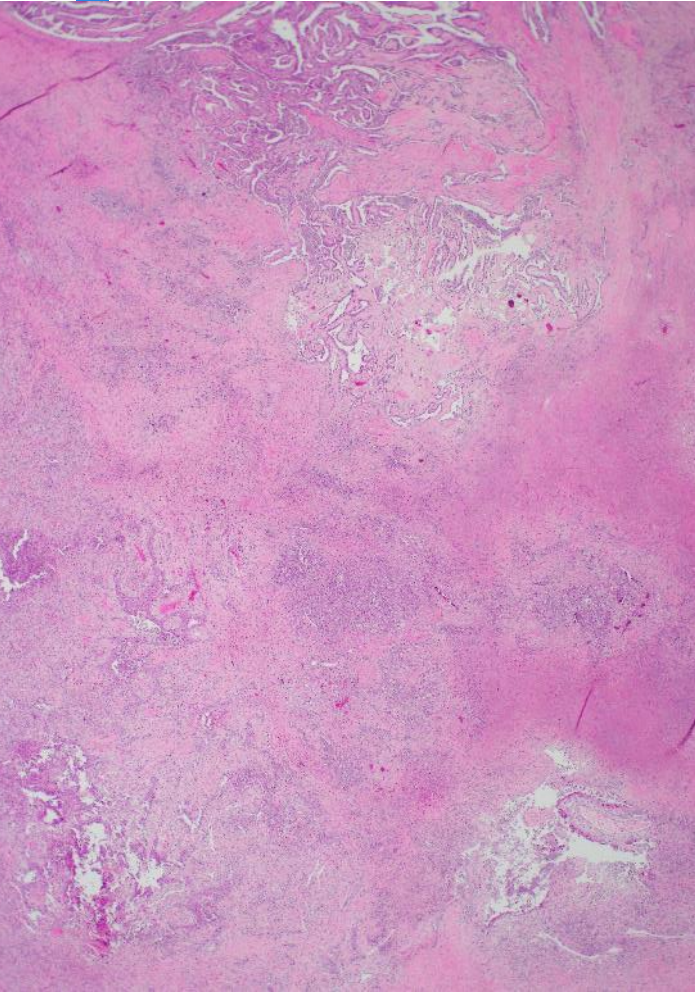
## Pathologic clues towards ATC:

- High frequency (91%) of PAX8 positivity
- High frequency (87.5%) of BRAF V600E mutation
- Differentiated thyroid carcinoma component/history (95%) in particular tall cell variant of PTC

Xu et al. 2020 Thyroid 30:1505-1517.



# Association between pure squamous ATC & PTC TCV



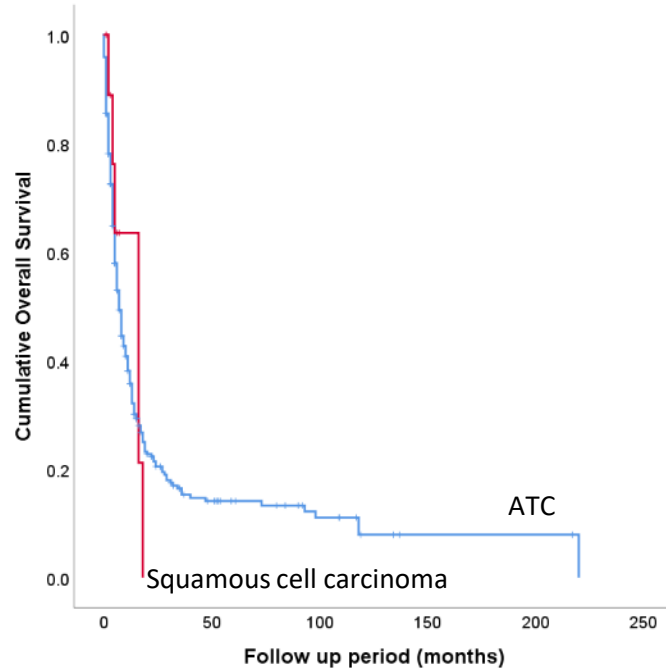
95% of pure squamous ATCs have a **history or coexisting PTC**

- 69% is tall cell variant

Bronner MP, LiVolsi VA. *Mod Pathol* 4:637, 1991

Xu et al. 2020 *Thyroid* 30:1505-1517.

# Thyroid squamous cell carcinoma: a subtype of ATC (WHO 2022)



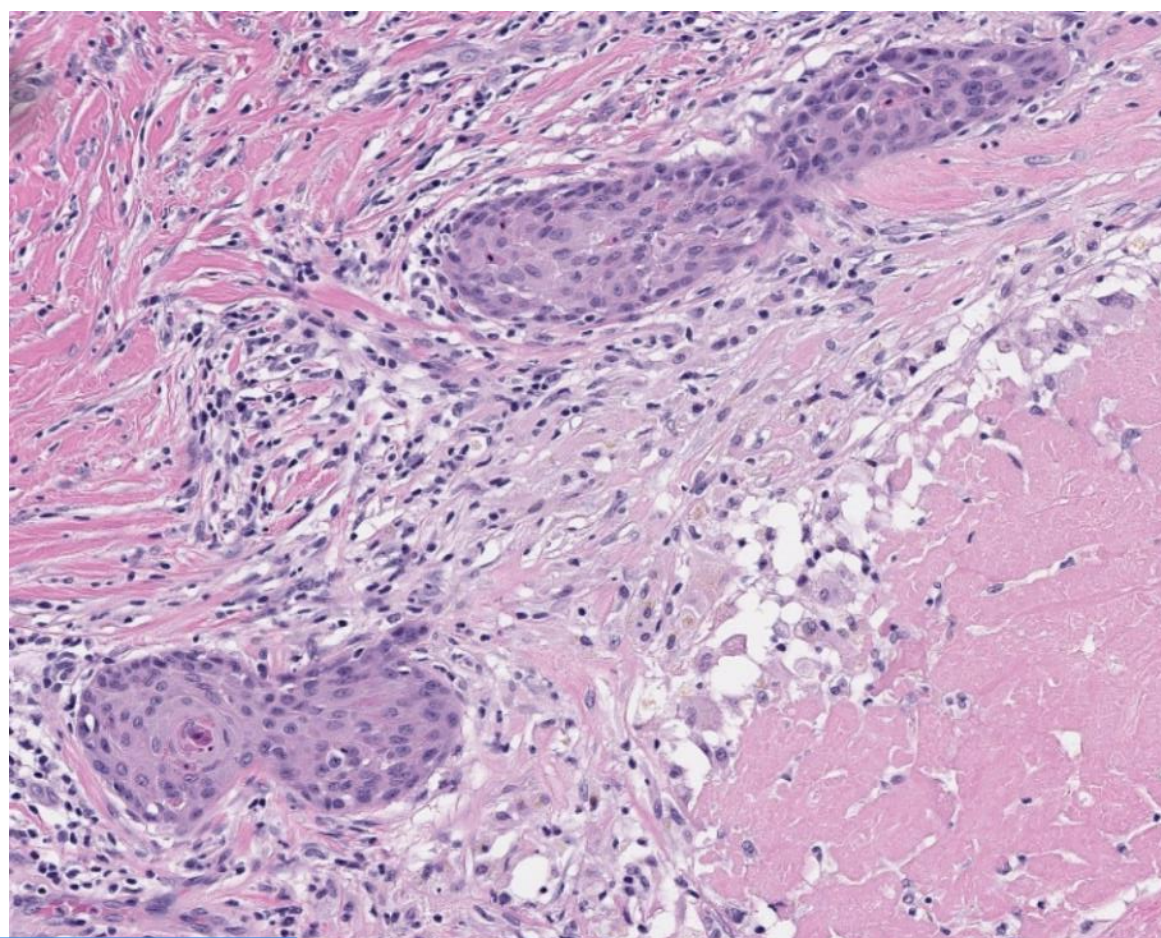
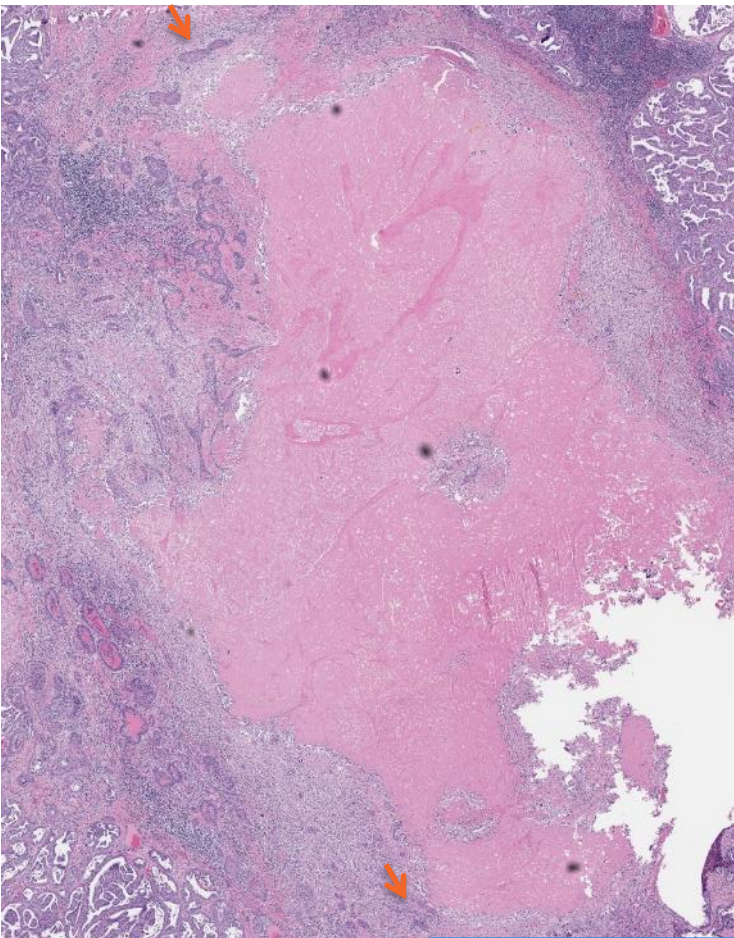
- Defined as a separate entity in WHO 2017:
  - Comprised entirely of tumor cells with squamous differentiation
  - No evidence of other type of thyroid carcinoma
- Similar molecular profile as other ATC
  - *BRAFV600E* 60%
- Similar outcome as other ATCs
  - Median overall survival 14 months (vs. 10 months)



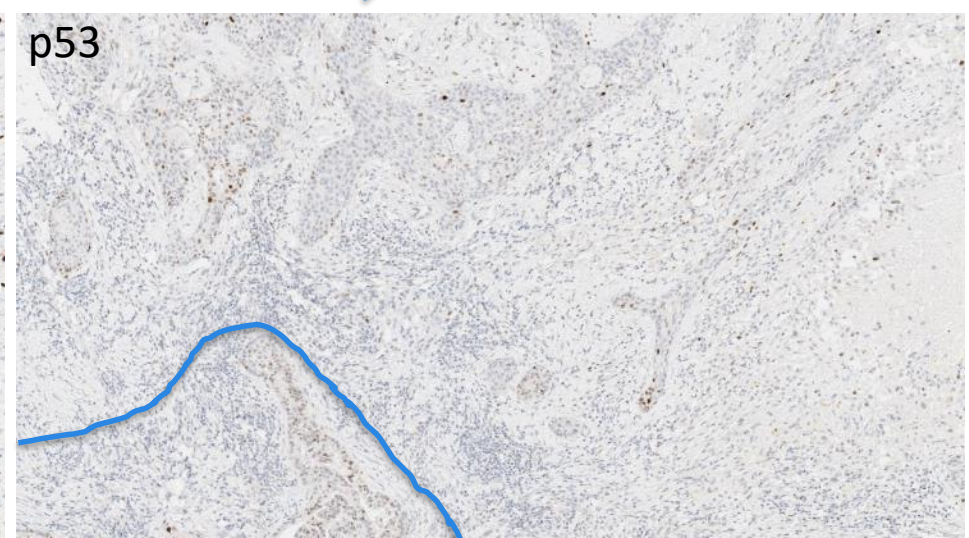
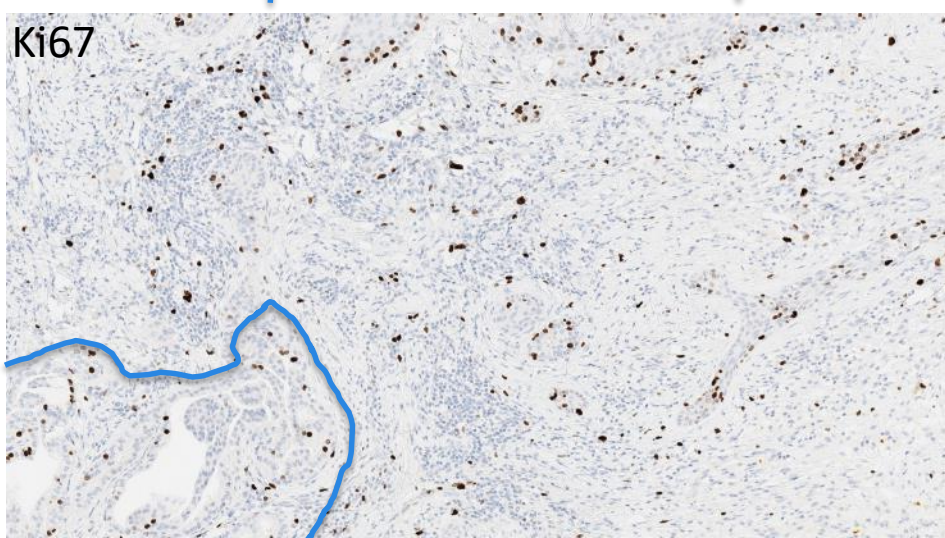
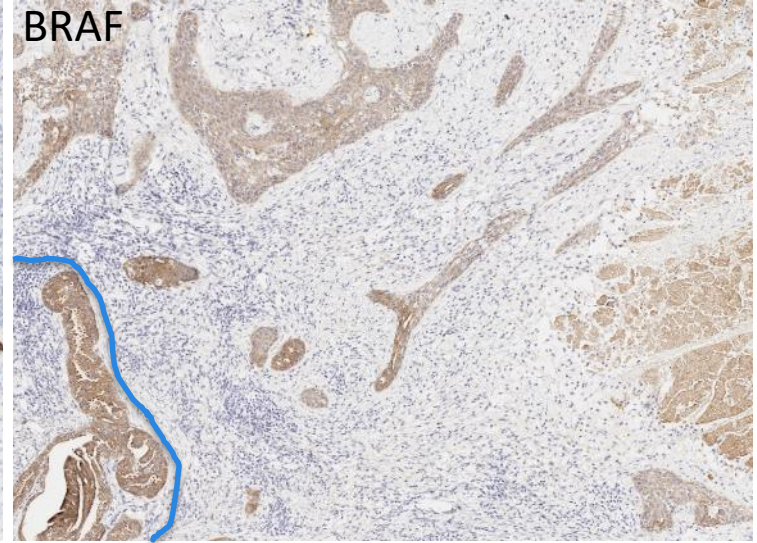
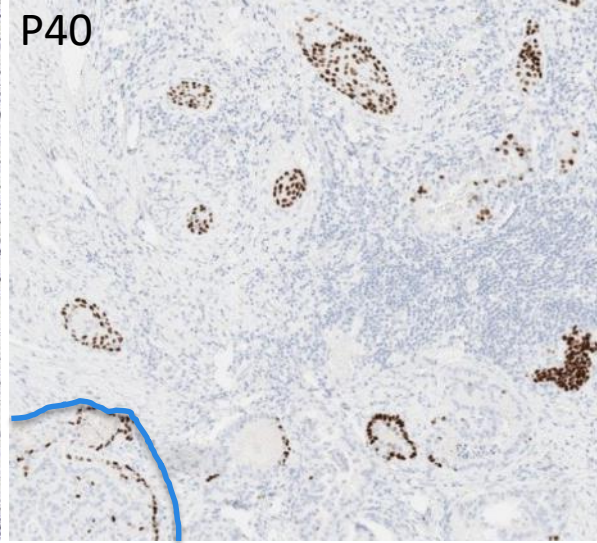
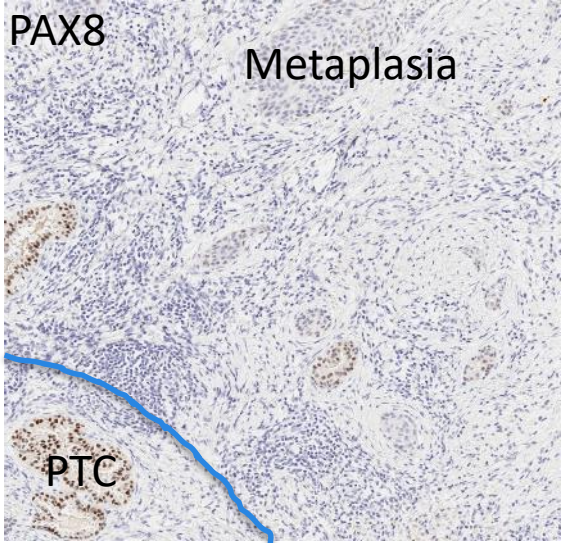
# Squamous ATC vs. squamous metaplasia

	Squamous metaplasia	Squamous ATC
<b>Similarity</b>	Keratin pearls, intercellular bridge (+) IHC: CK5/6, 34BE12, p63, p40, <b>PAX8</b> (-) IHC: TTF-1, thyroglobulin <b>Both can be BRAF V600E positive</b>	
<b>Difference</b> <ul style="list-style-type: none"><li>• Histology</li><li>• Mitosis</li><li>• Nuclear pleomorphism</li><li>• P53 IHC</li><li>• Ki67 compared with background lesion</li></ul>	Focal, adjacent to FNA cavity Absent Absent No abnormal expression Not elevated	Extensive Present w/ atypical form Present – marked Abnormal (60%) Elevated

Focal squamous area immediate adjacent to FNA cavity. Bland cytology, lack pleomorphism and mitotic activity



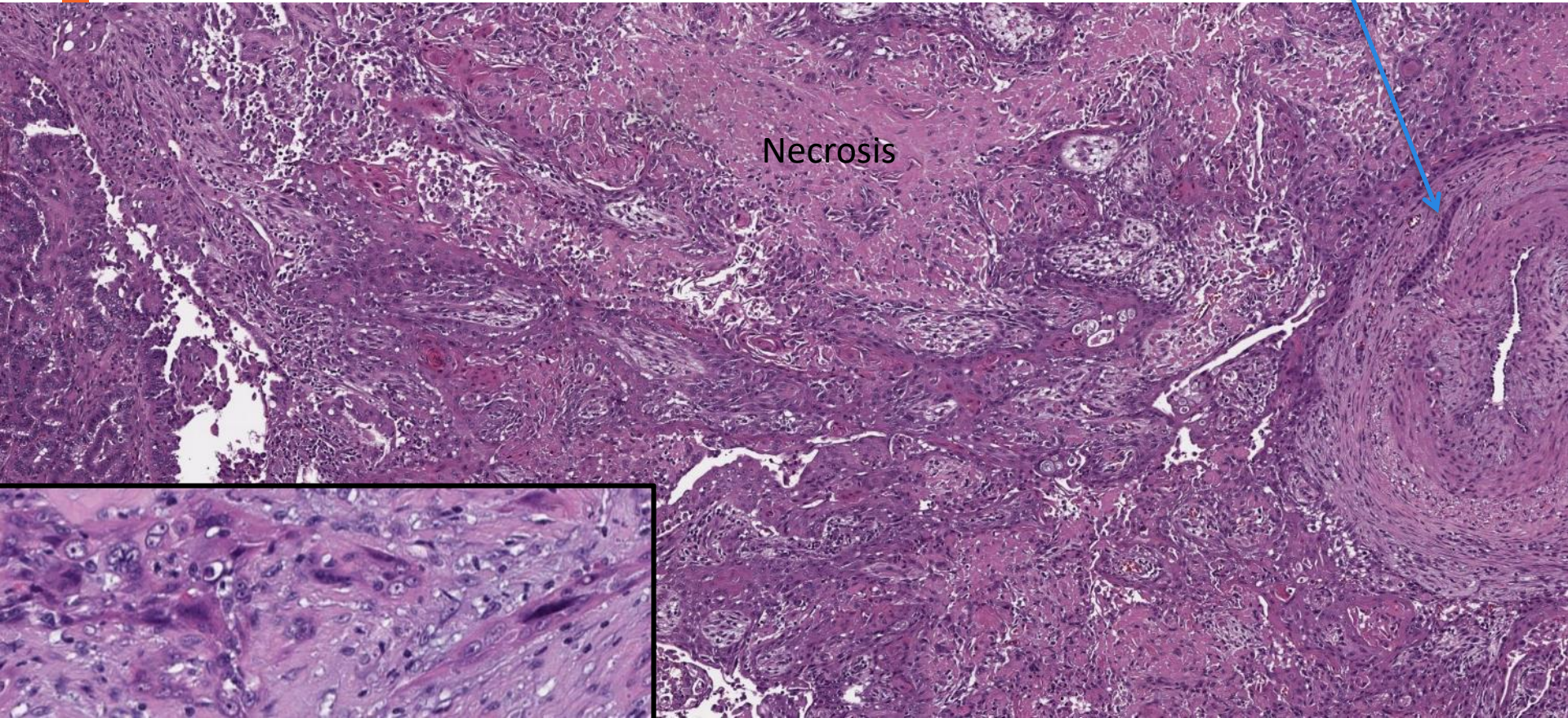
Squamous metaplasia



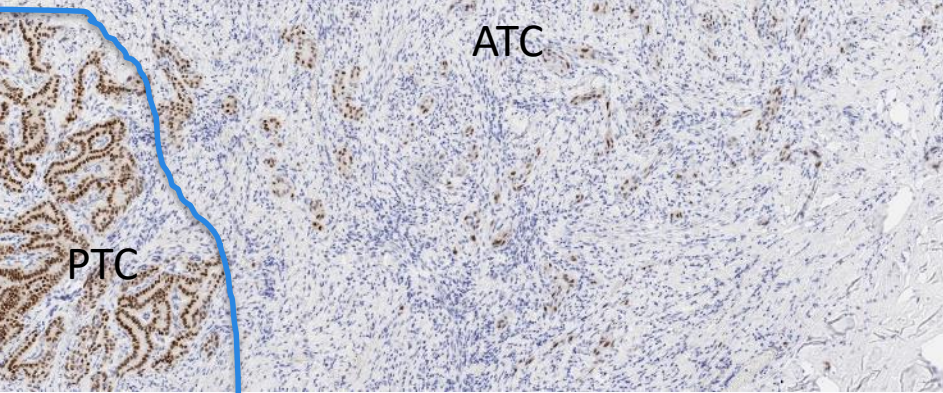
# Squamous ATC

Extensive squamous area  
Nuclear pleomorphism  
Necrosis, mitosis  
Absence of FNA changes

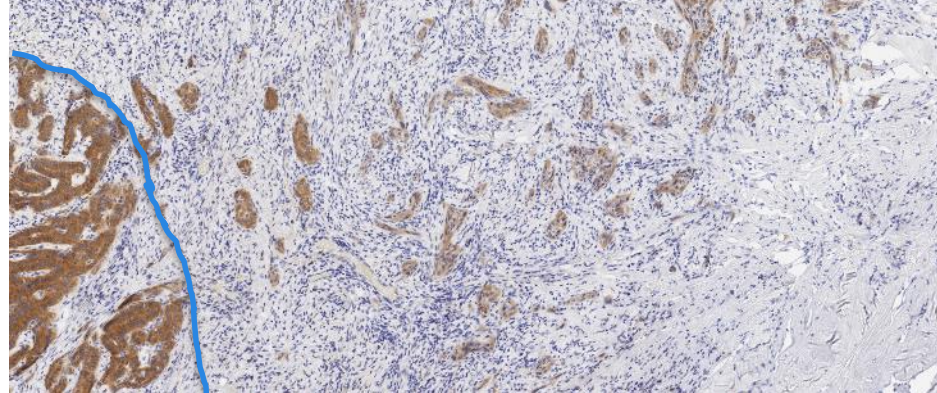
PNI or LVI



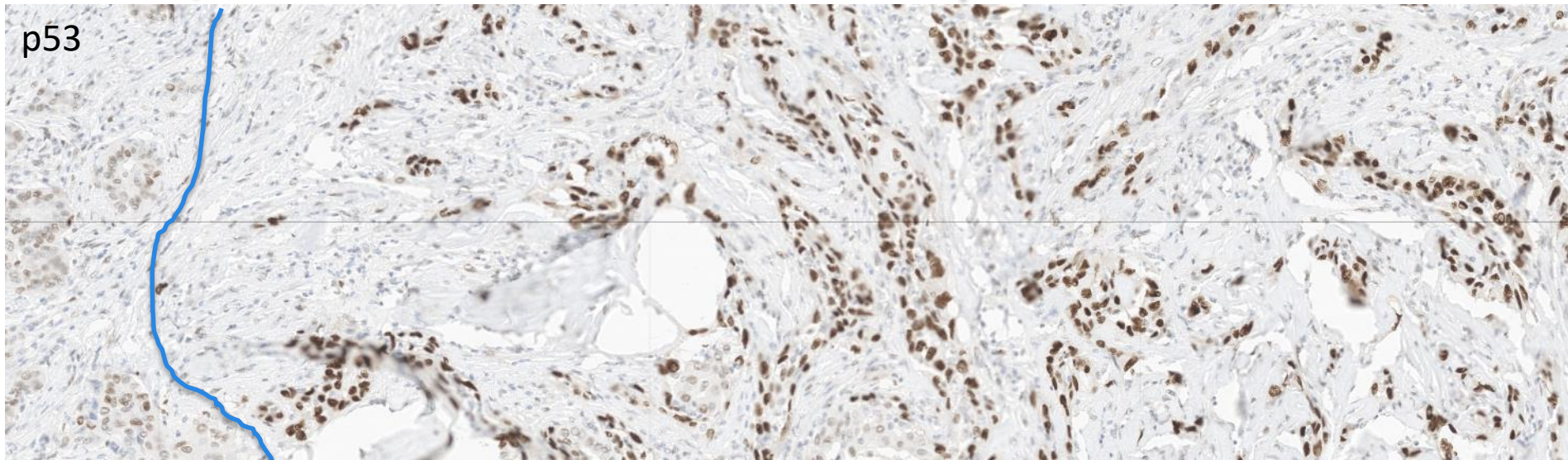
PAX8



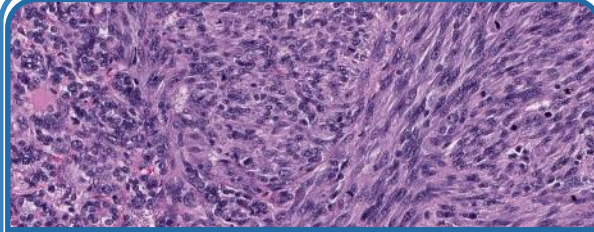
BRAF



p53



## Spindle/pleomorphic ATC



### **Malignant:**

Medullary thyroid carcinoma

PTC Spindle cell variant

Sarcoma (primary or met.)

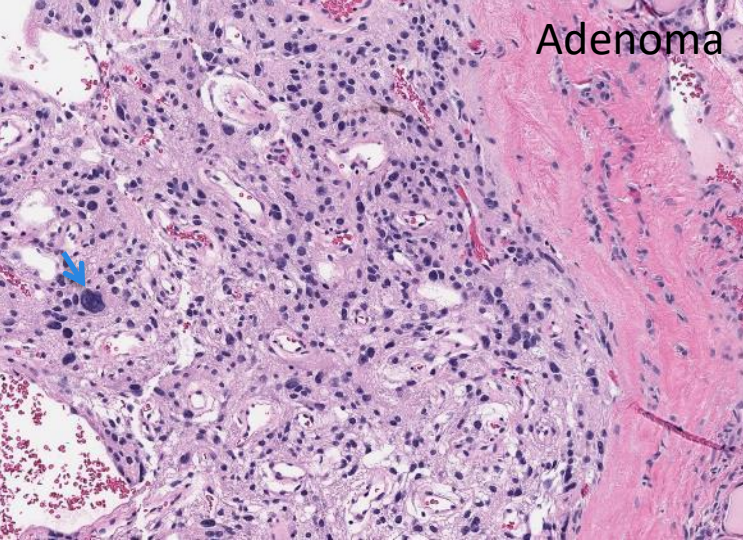
Spindle epithelial tumor with  
thymus-like differentiation

### **Benign:**

Endocrine atypia/RAI-related atypia

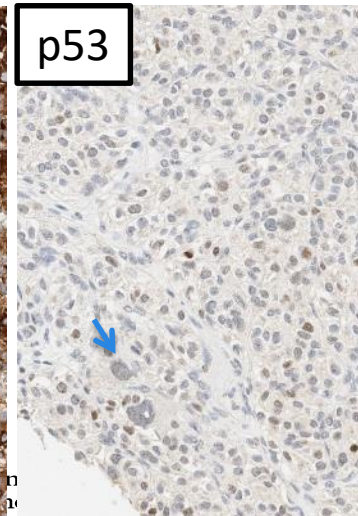
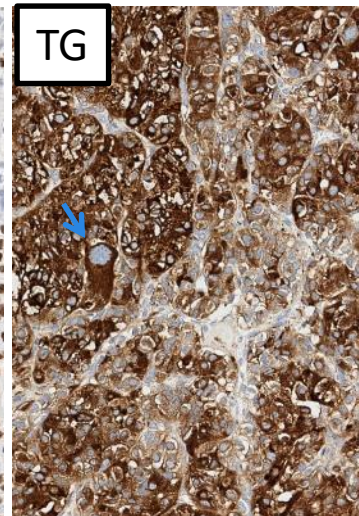
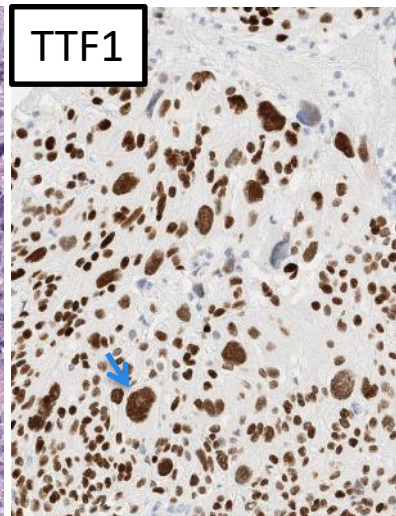
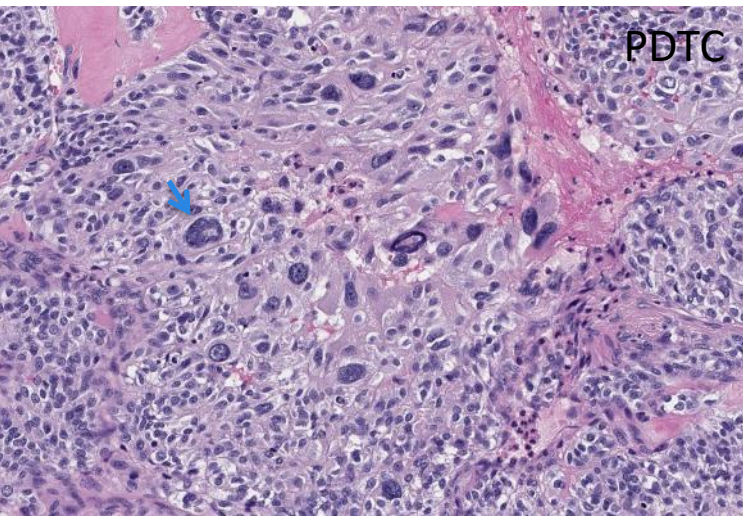
Post-FNA spindle cell nodule

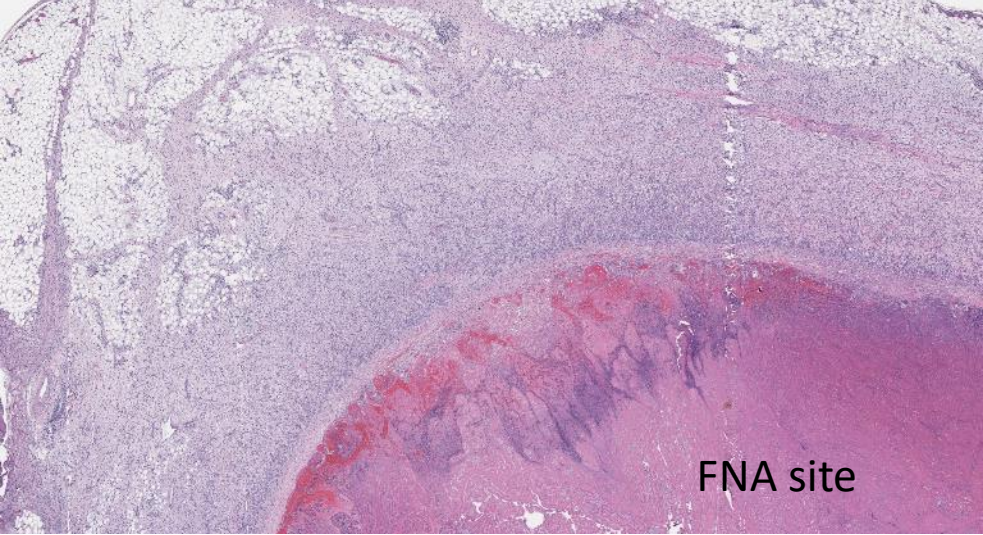
Follicular adenoma with spindle cell  
metaplasia



# Endocrine atypia

- Bizarre pleomorphic nuclei with smudgy chromatin
- Can be seen in benign or malignant lesions
- Lacks mitosis/necrosis
- Retains TTF-1 & thyroglobulin
- Lacks abnormal p53 expression



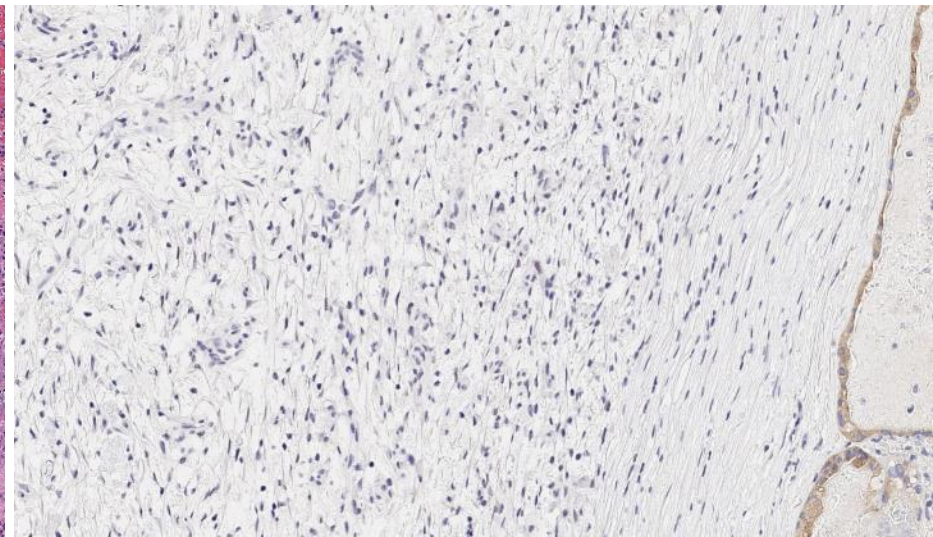
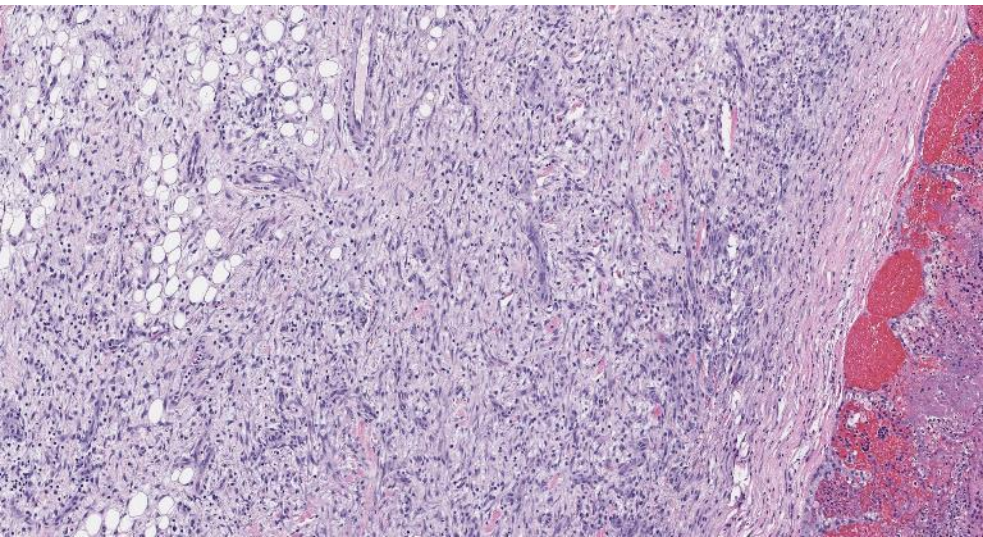


FNA site

## Post-FNA spindle cell nodule

- Spindle cell (myofibroblast) proliferation immediate adjacent to FNA site
- No pleomorphism, mitosis, or necrosis
- IHC shows myofibroblast differentiation and lack BRAF V600E mutation

Baloch ZW, Wu H, LiVolsi VA. AJCP 1999 111: 70-74

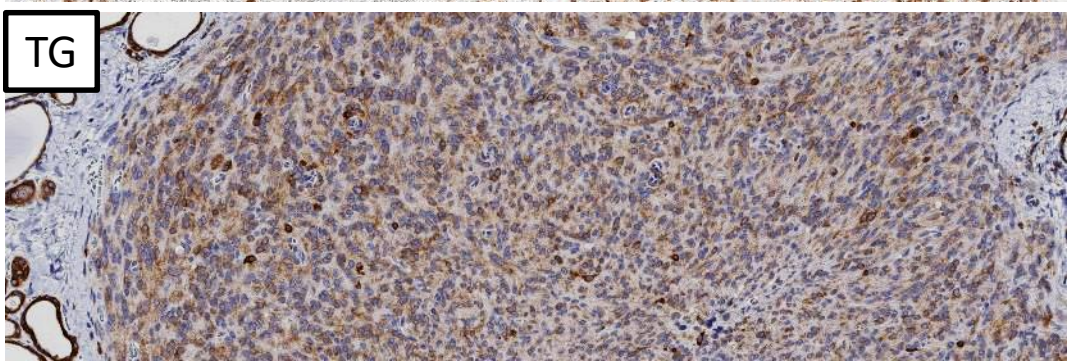
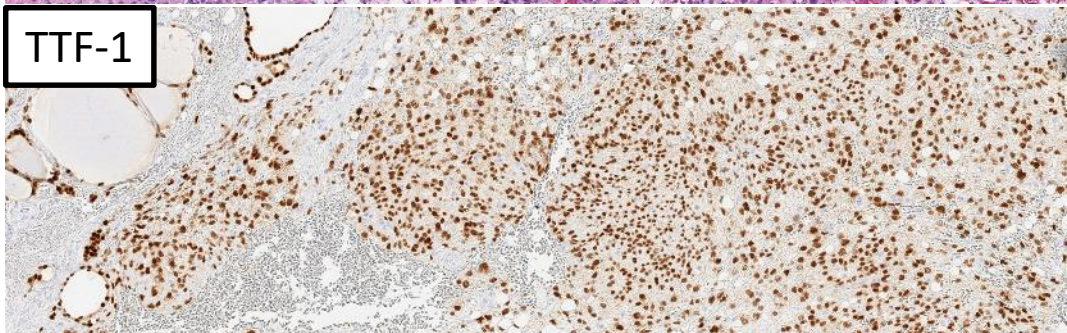
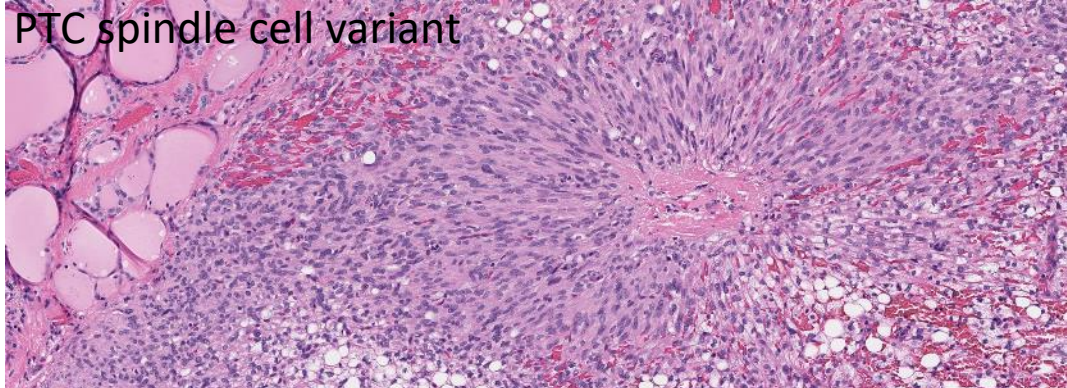




## PTC spindle cell variant

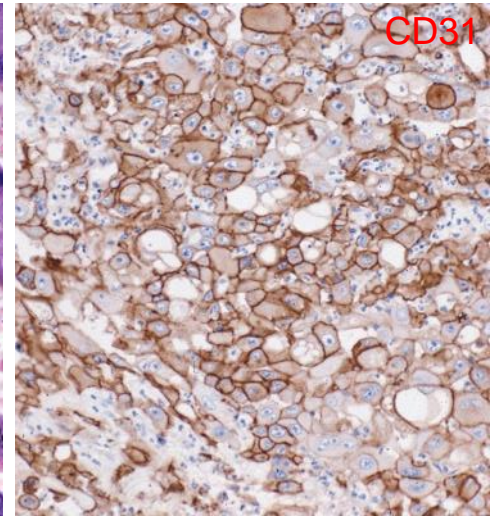
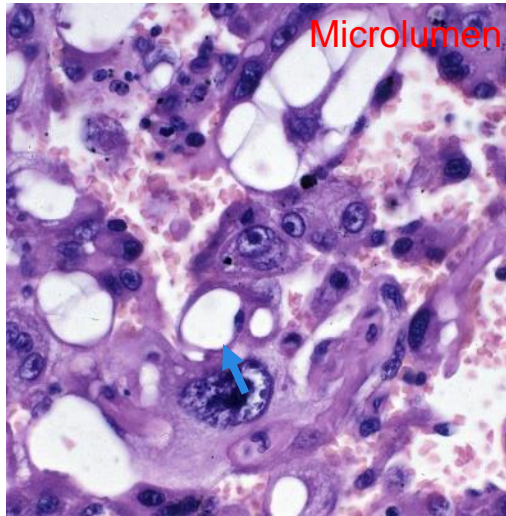
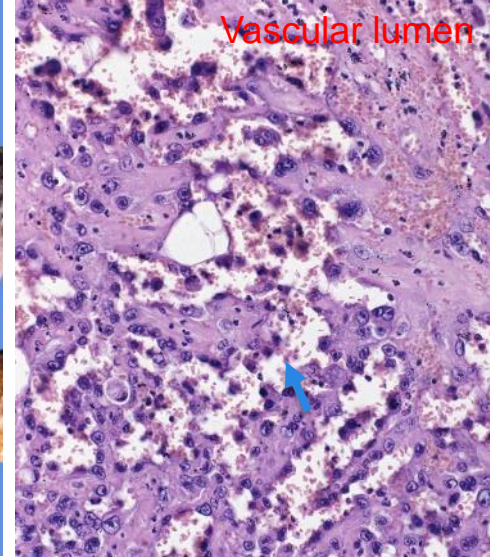
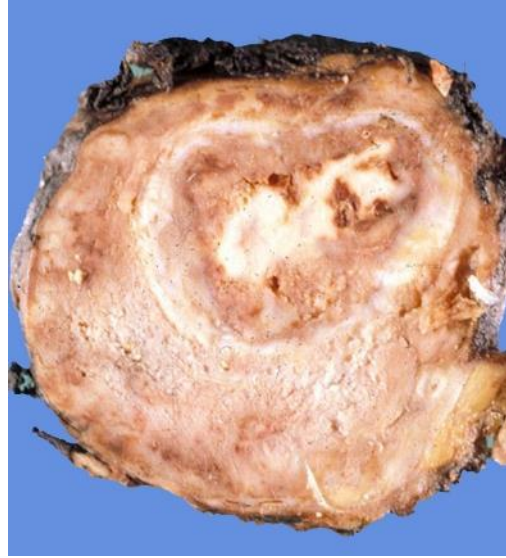
### Spindle cell metaplasia in follicular adenoma

- No pleomorphism, mitosis, or necrosis
- IHC: retain of thyroid follicular differentiation (TG+, TTF1+, PAX8+)



# Angiosarcoma of thyroid

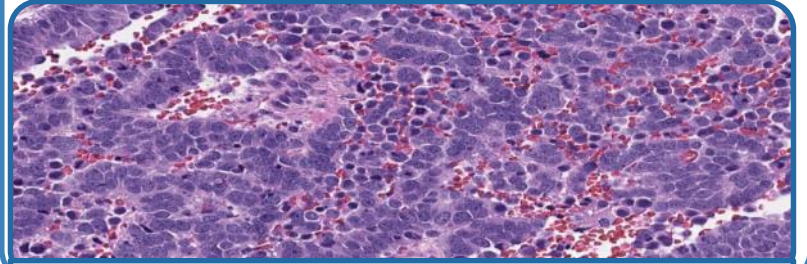
	Angiosarcoma	ATC
Similarity	Common in areas of endemic goiter elder patients Rapidly fatal May be cytokeratin positive TTF-1/TG negative	
Difference	Vascular lumen (+) CD31/ERG	(+) BRAF/RAS





Clinical history/suspicion and IHC work up are crucial for diagnosis.

### Epithelial/epithelioid ATC



**Malignant:**

Metastasis

Lymphoma

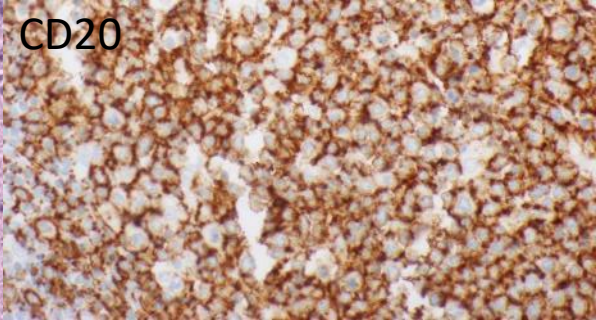
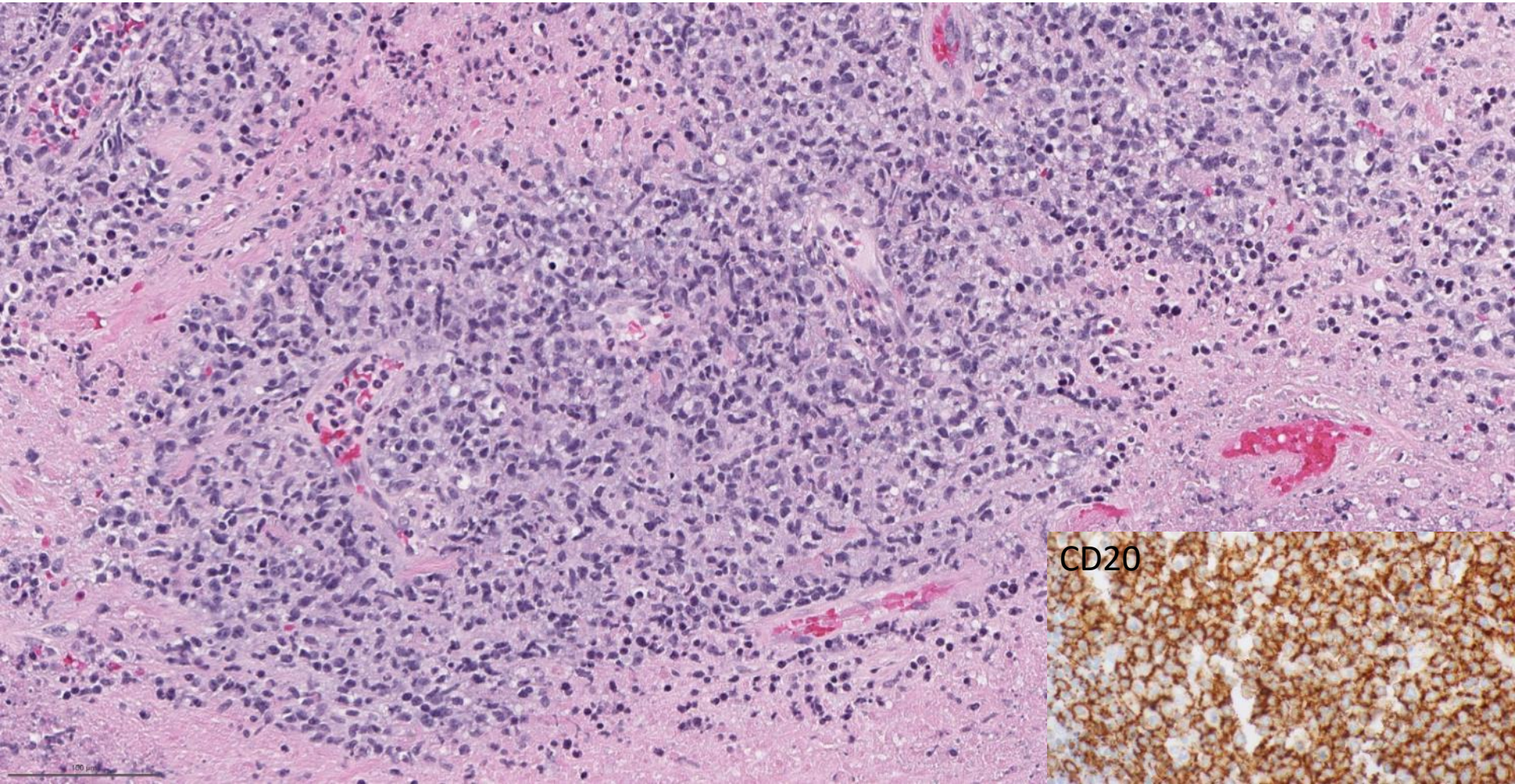
Adamantinoma-like Ewing

Sarcoma

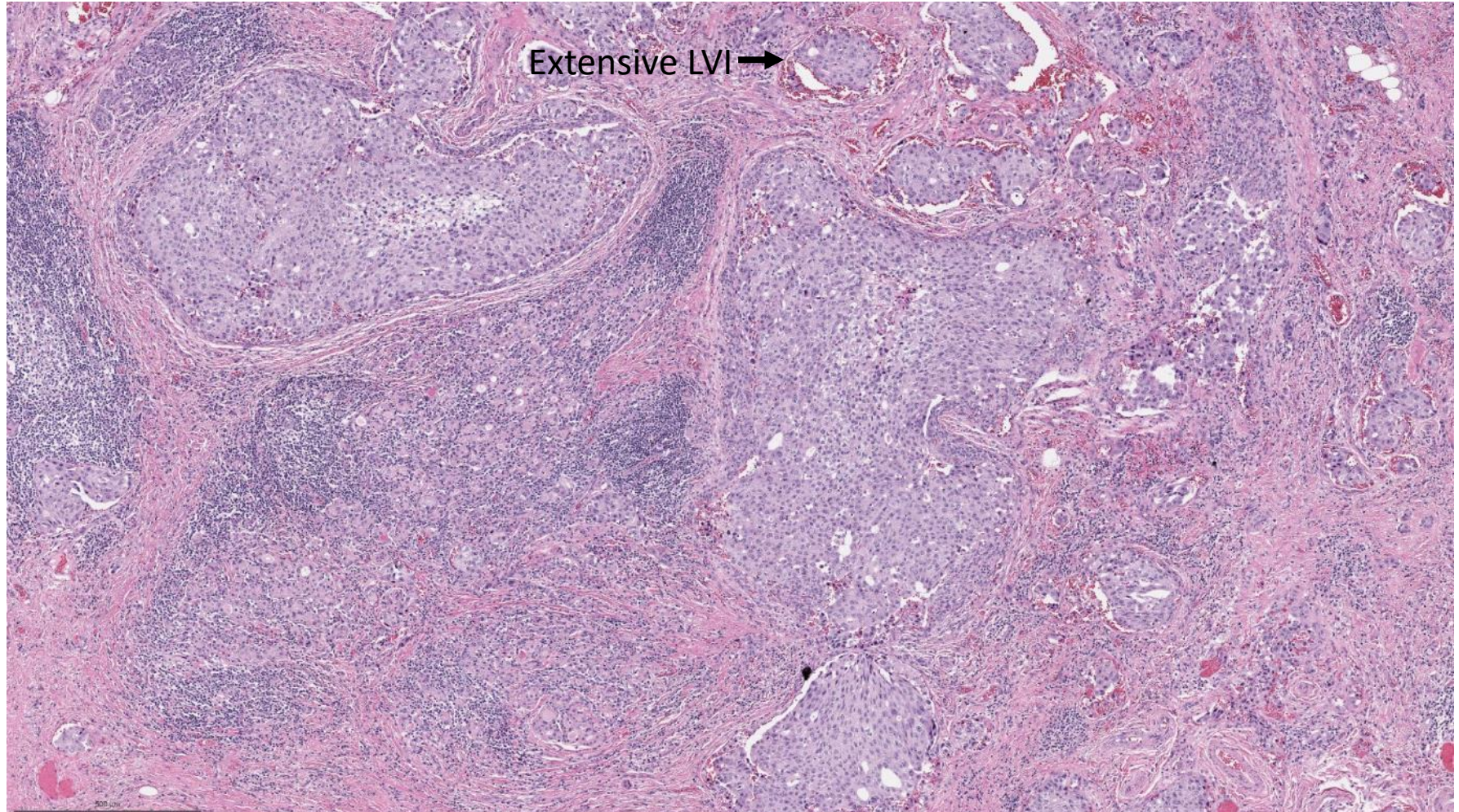
NUT carcinoma

59F, rapidly enlarging thyroid mass

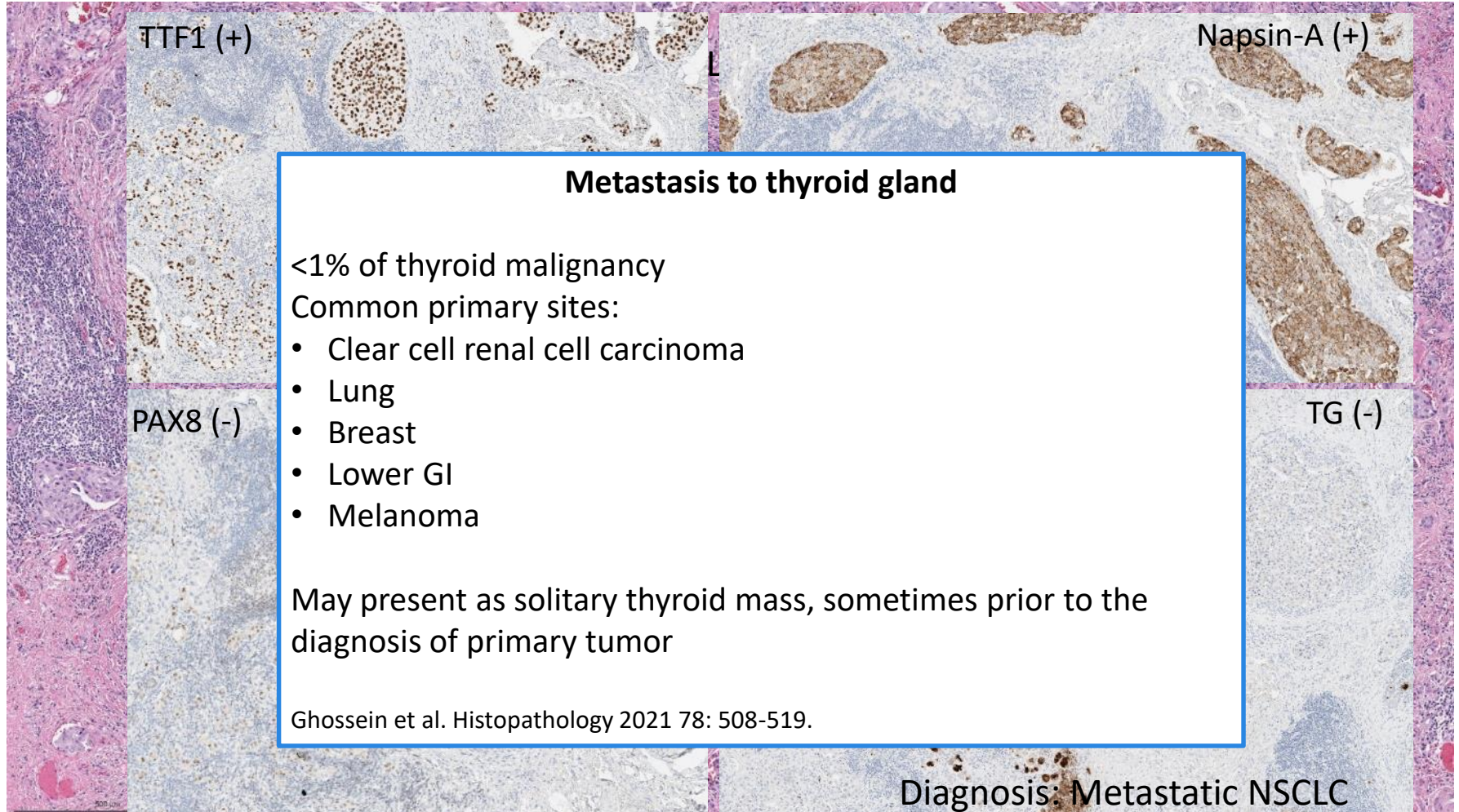
Diagnosis: DLBCL



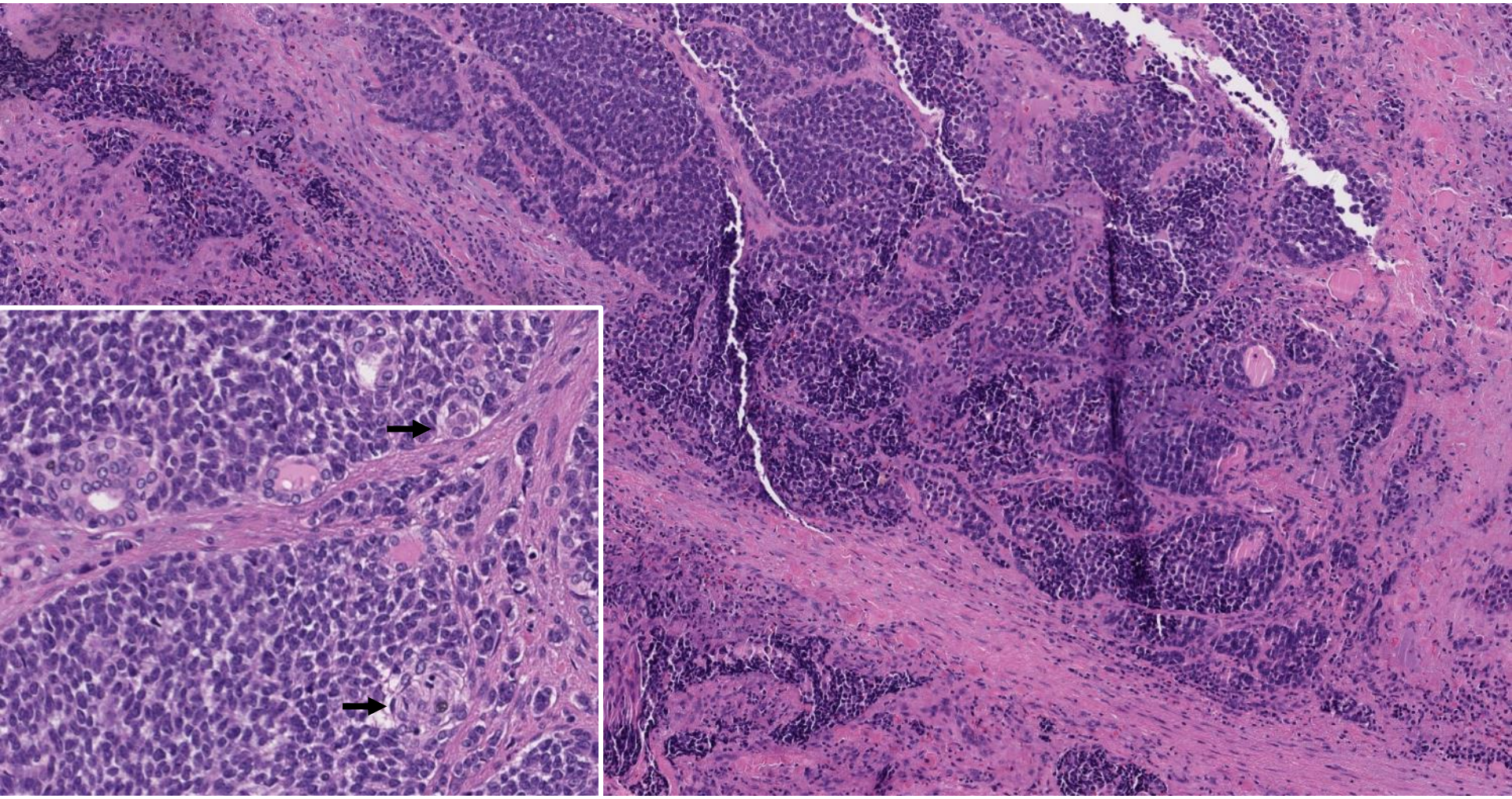
63M, diffuse thyroid enlargement & cervical/mediastinal lymphadenopathy

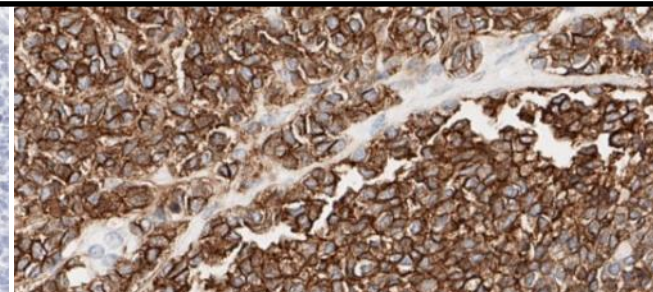
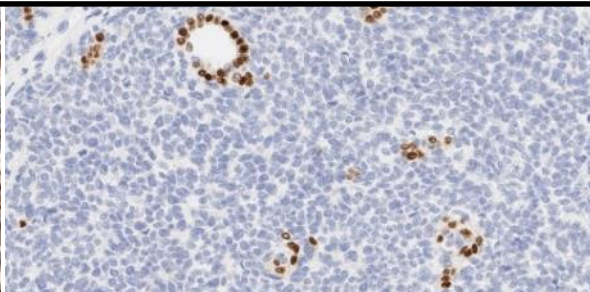
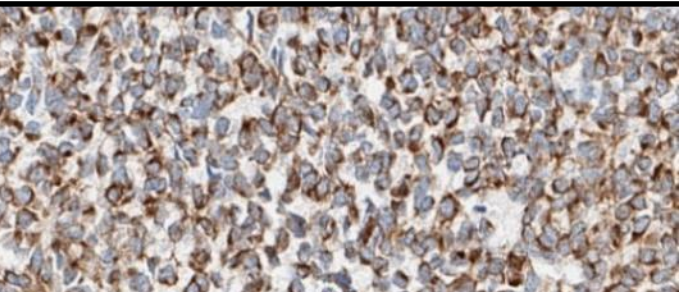


# 63M, diffuse thyroid enlargement & cervical/mediastinal lymphadenopathy



16-year-old, thyroid mass



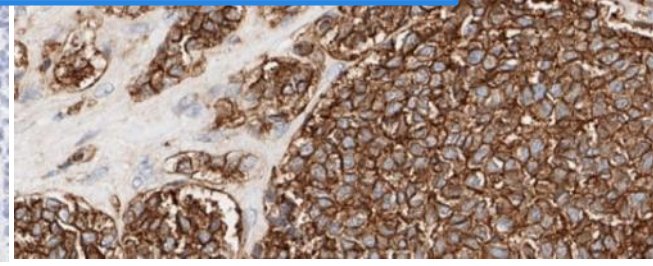
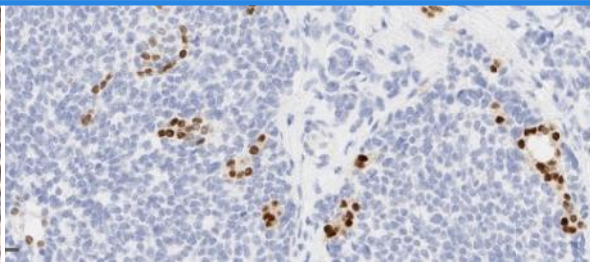
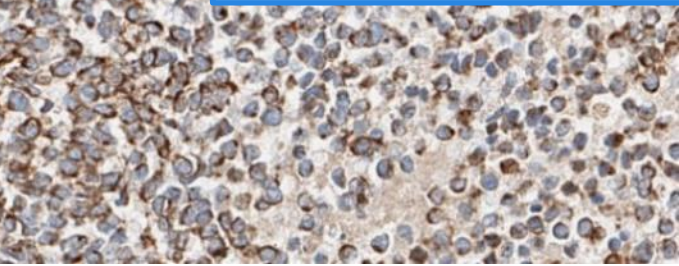


## FISH/NGS confirmed *EWSR1-FLI1* rearrangement

**Adamantinoma-like Ewing sarcoma** (Bishop et al. AJSP 2015 39: 1267-74)

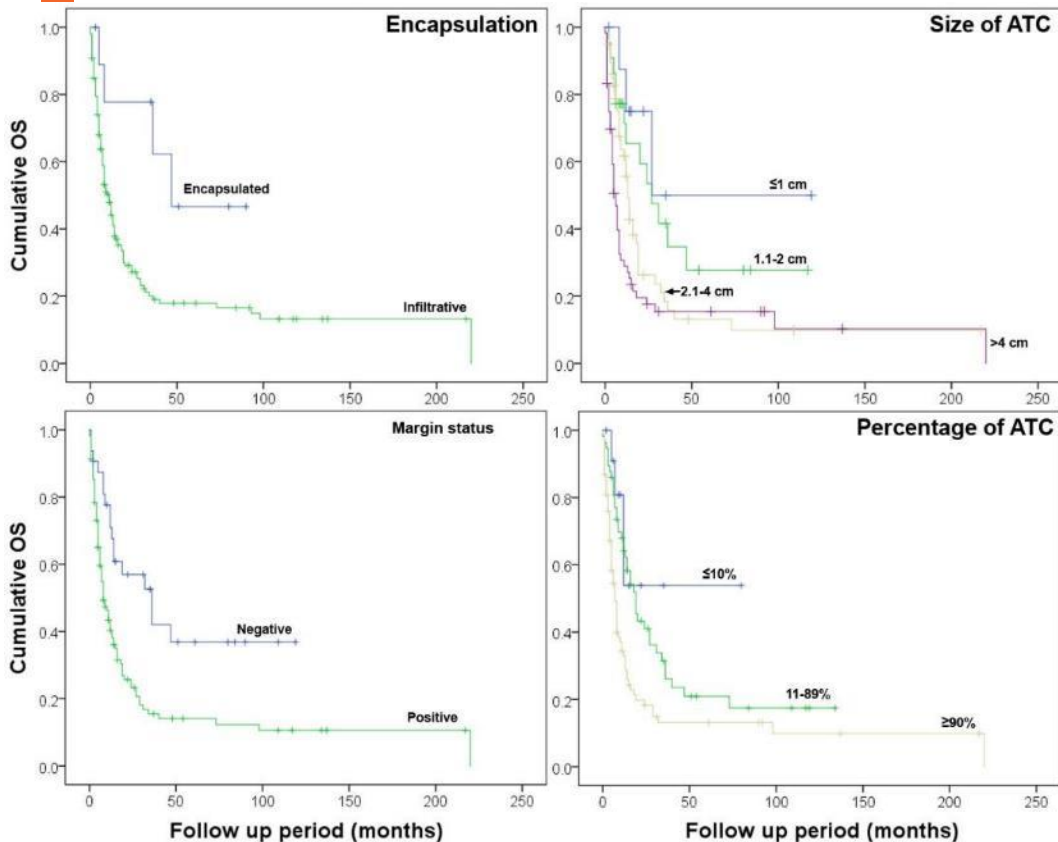
**Carcinoma of the thyroid with Ewing family tumor elements** (Oliveira et al. Virchows Arch. 2017 270: 517-25)

- Young patients (16-42 years)
- Positive IHC: NKX2.2, CD99, AE1/AE3, squamous markers (e.g. p40)
- Outcome better than traditional Ewing sarcoma





# It is prognostically prudent to report encapsulation, size and % of ATC in primary resected ATC



Pathologic factors that are associated with improved survival on univariate analysis

- Smaller size and percentage of ATC
- Encapsulation
- Negative pathologic (microscopic) margin

Independent prognostic factors are:

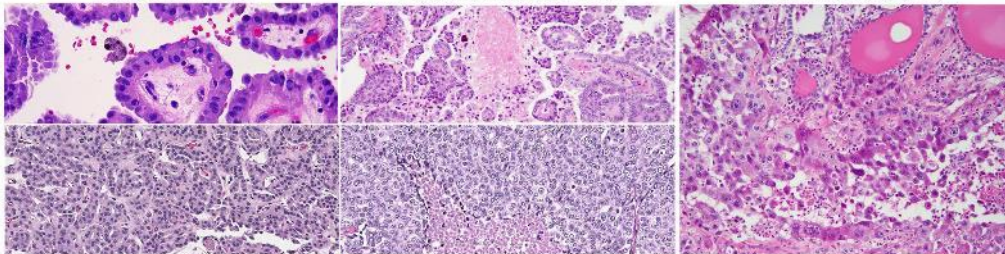
- Age at diagnosis,
- Resectability,
- Chemotherapy
- Gross residual disease in resected primary ATC

# New advances: Molecular profile of ATC

PTC classic type

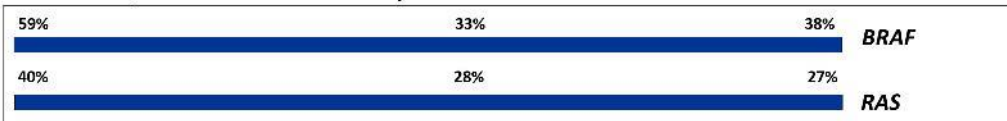
High grade carcinoma

Anaplastic carcinoma



FTC & PTC, follicular variant

Poorly differentiated carcinoma

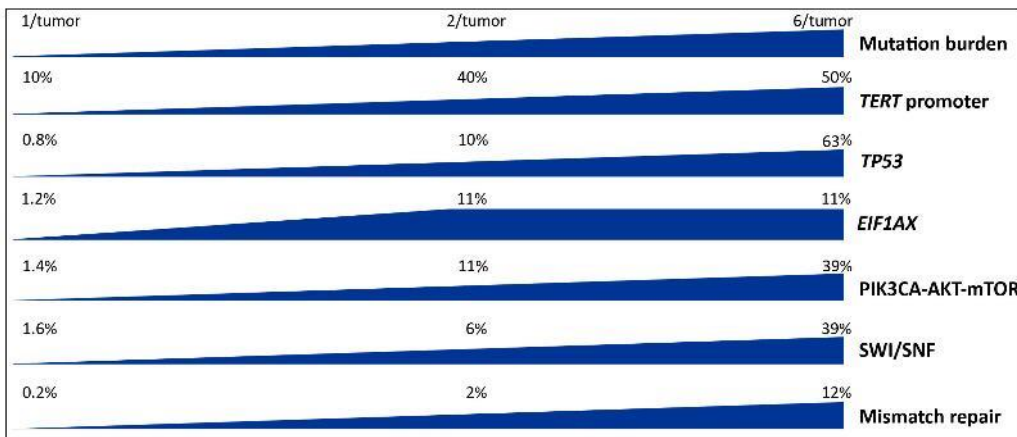


ATC has same driver mutations as differentiated thyroid carcinoma:

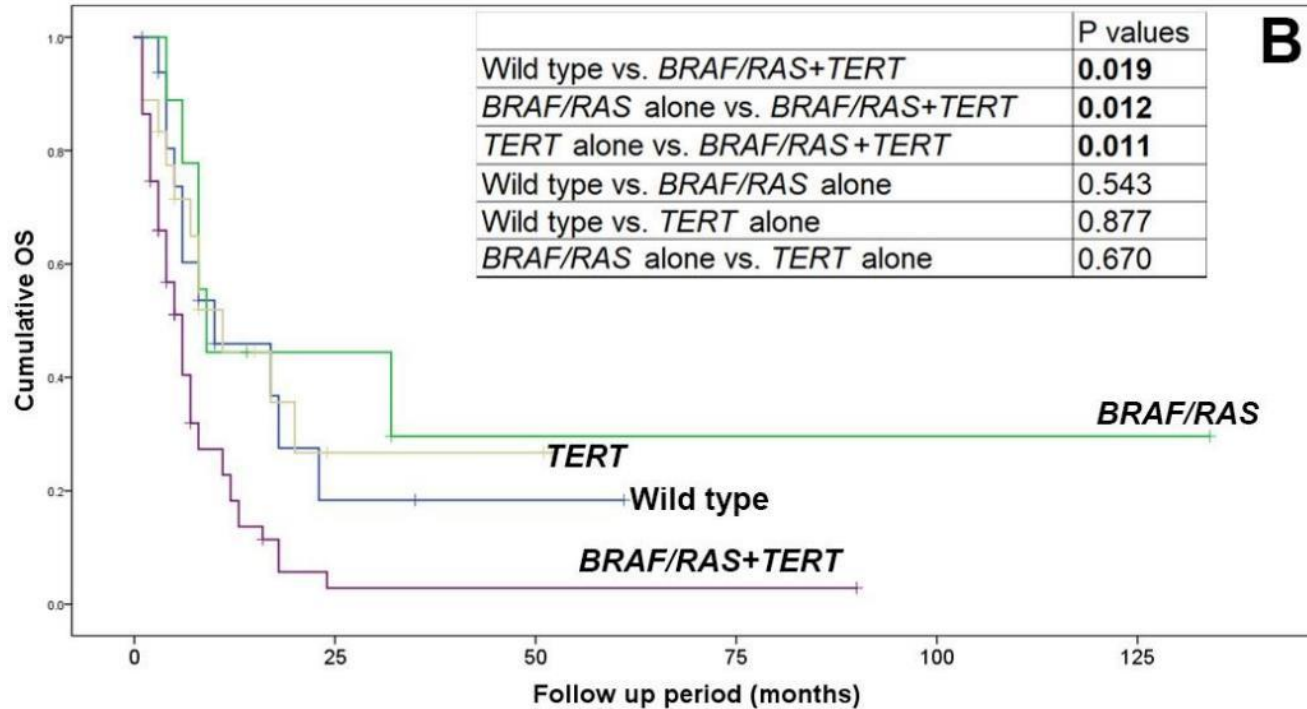
- *BRAF*, especially V600E: 38%
- *RAS*: 27%

ATC accumulates additional mutations:

- *TP53*: 63%
- *TERT* promoter mutation: 50%
- PI3K-AKT-mTOR 39%
  - *PIK3CA*: 13%
  - *PTEN*: 11%



# Double-mutated (*BRAF/RAS+TERT*) ATC is associated with worse outcome

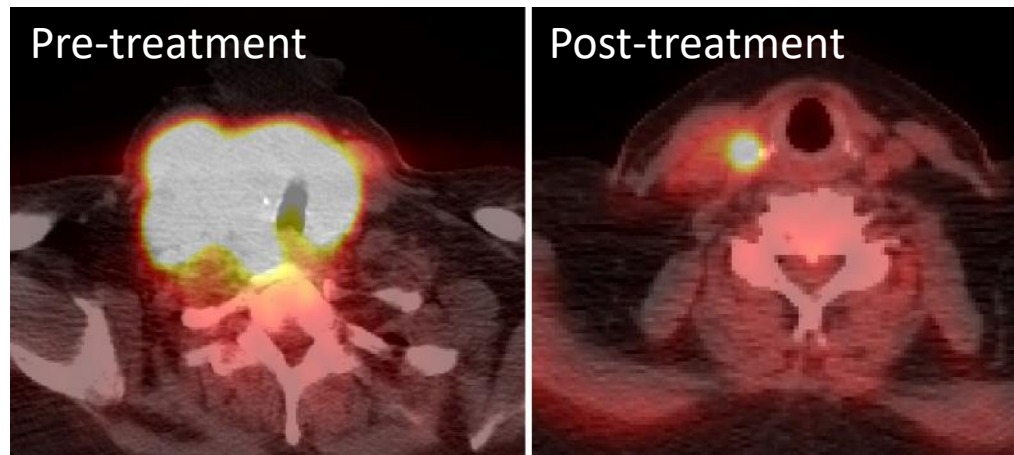
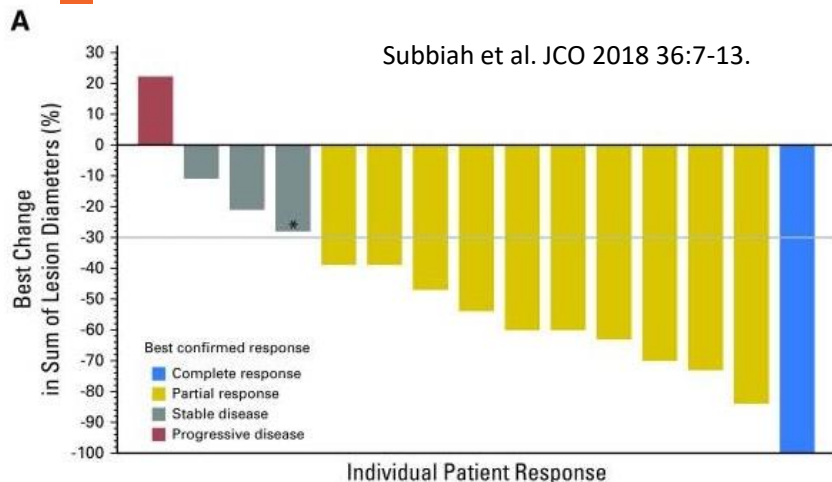




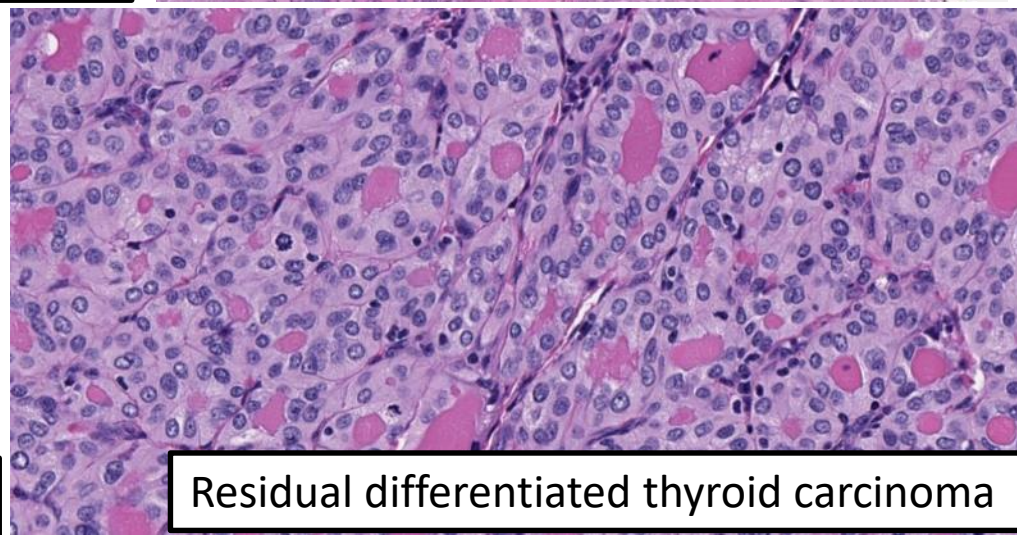
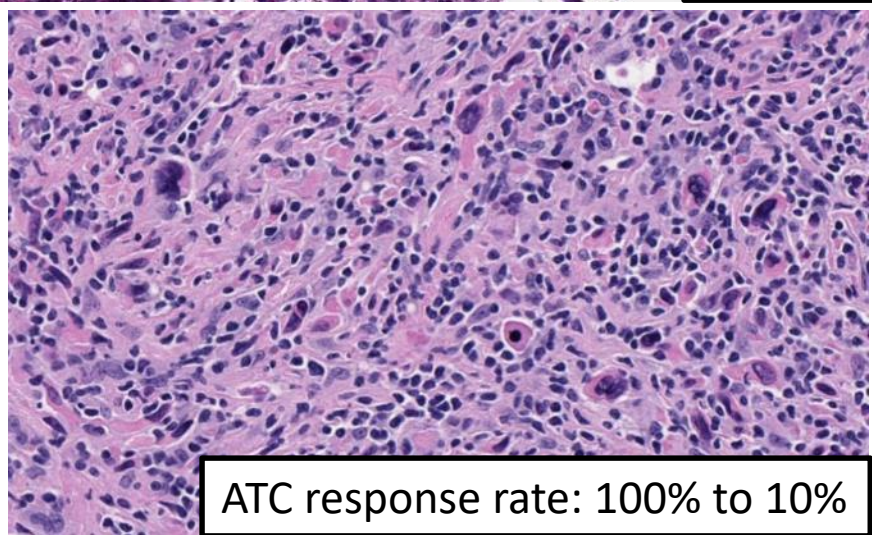
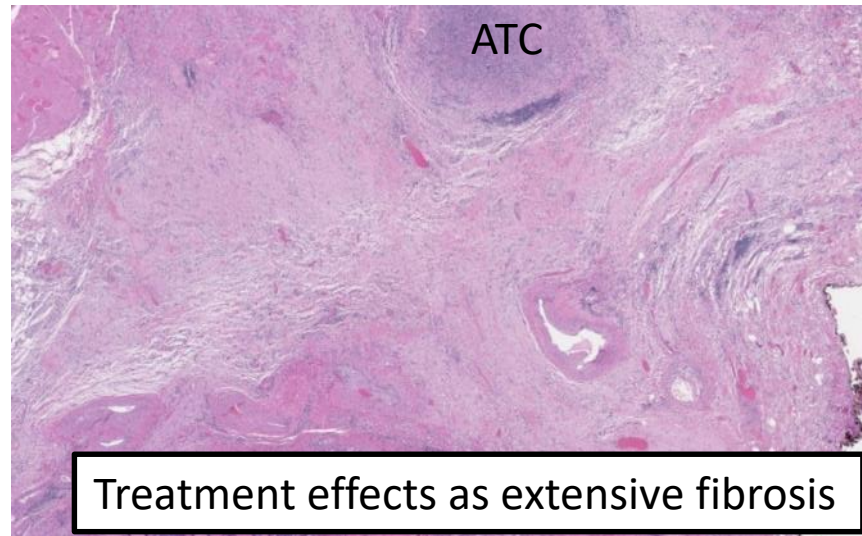
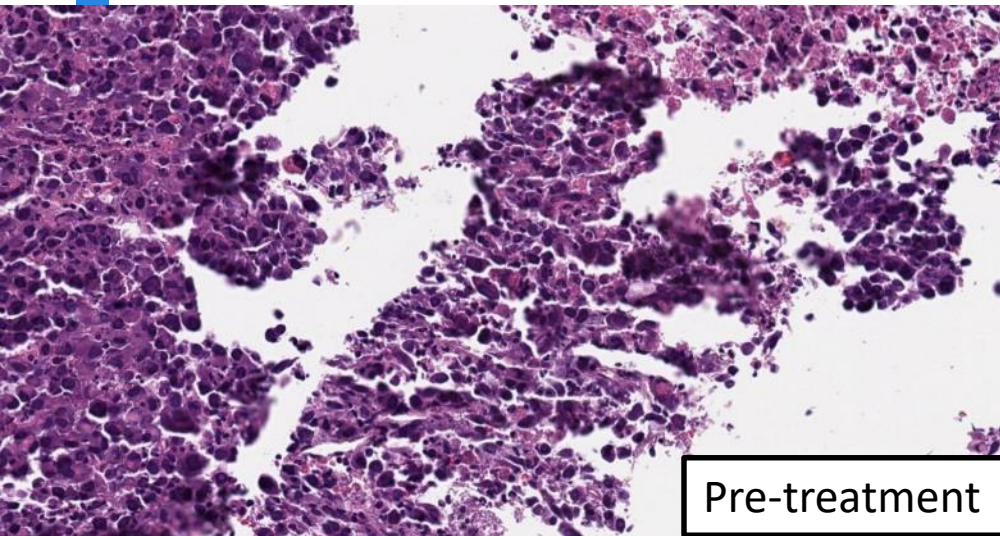
# Targeted therapies in ATC

- Multikinase inhibitors: sorafenib, pazopanib, imatinib, lenvatinib, sunitinib
- BRAF inhibitors: vemurafenib
- MEK inhibitors: trametinib
- PI<sub>3</sub>K/mTOR inhibitors: everolimus
- EGFR inhibitors: gefitinib
- VEGF inhibitors: axitinib

# Neoadjuvant Dabrafenib (BRAF inhibitor) and Trametinib (MEK inhibitor) in *BRAF* V600E-mutated ATC

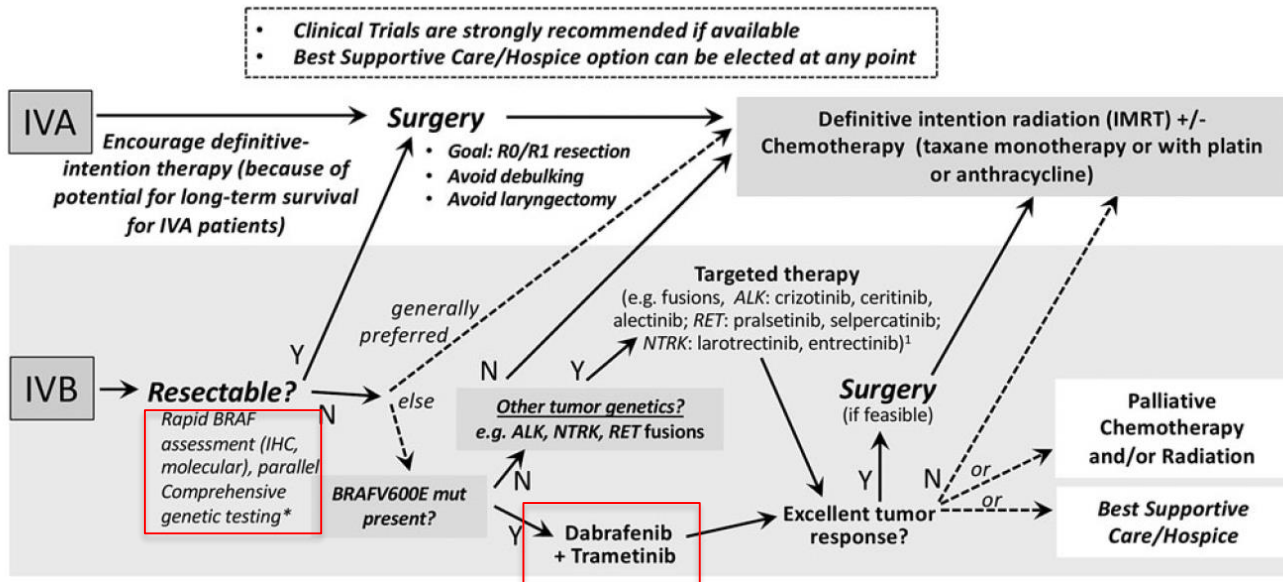


- Feasibility of complete surgical resection
- High pathologic response rate
- Durable locoregional control
- FDA approved and now a standard treatment for *BRAF* V600E-mutated ATC



# 2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

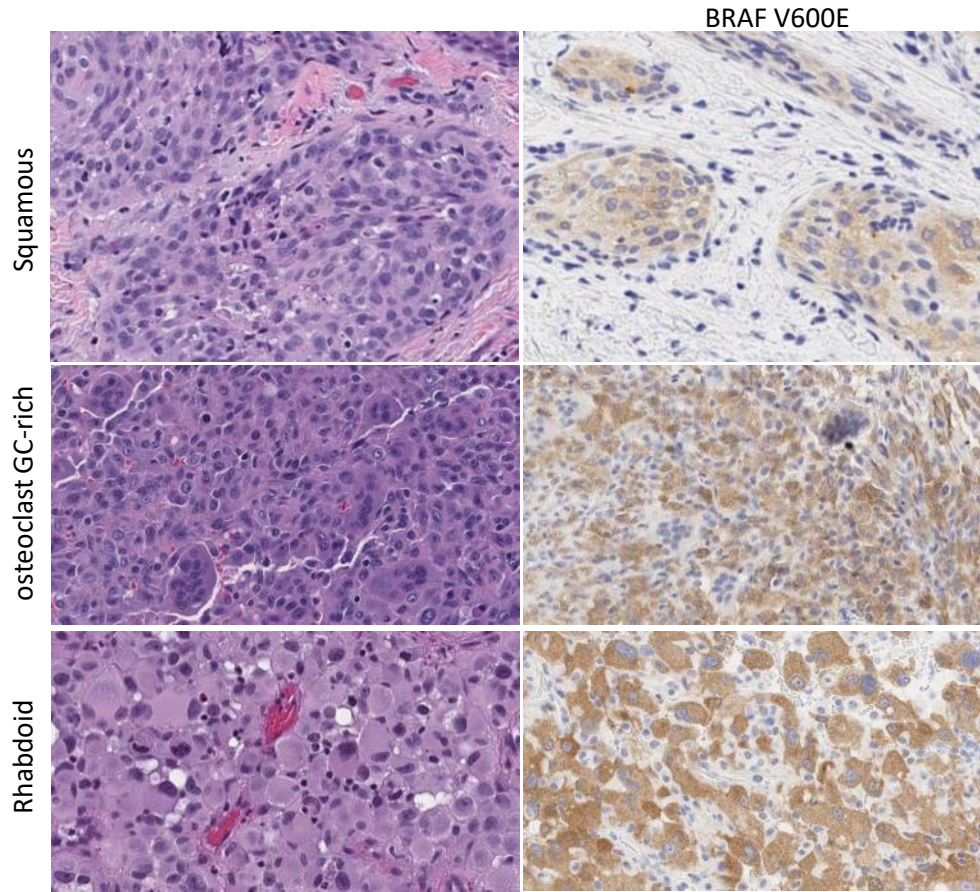
American Thyroid Association Anaplastic Thyroid  
Cancer Guidelines Task Force



# BRAF V600E IHC is a sensitive & specific screening tool for *BRAF* mutation in ATC

- Sensitivity: 95%
- Specificity: 100%

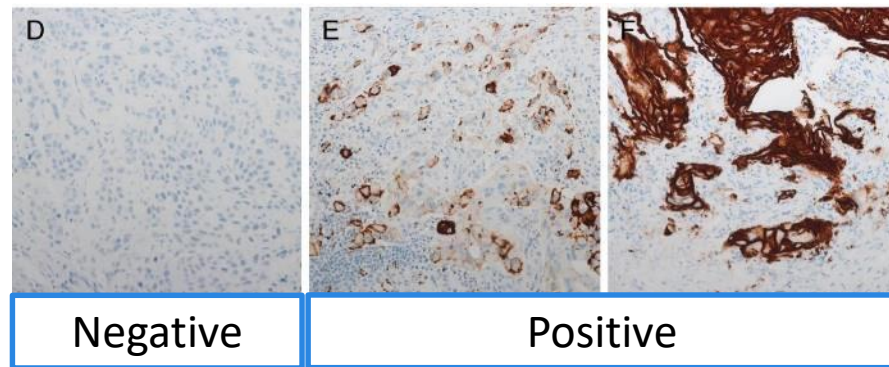
		<i>BRAF</i> V600E mutation	
		Positive	Negative
<i>BRAF</i> V600E IHC	Positive	18	0
	Negative	1	13





# Immune checkpoint inhibitors in ATC

- PD-L1 positivity in 22-28% ATC
- High PD-L1 tumor cell (TC) expression in *BRAF*-mutated ATC
- A trend towards worse PFS and OS in ATC with high PD-L1 expression (>33% tumor cells)
- Early results from multiple phase I and II studies on immune checkpoint inhibitors in ATC are **disappointing**



- **Currently, there is no guideline or criteria of PD-L1 in ATC.**
  - Perform per clinical requests only
  - Report combined positive score (CPS)

# Take home messages

- ATC can have various histologic features, but they are not prognostically significant
- It is important for pathologist to report encapsulation, margin, percentage and size of ATC in resected primary ATC
  - However, the only independent prognostic factors in ATC are age, resectability, gross residual disease and chemotherapy
- BRAF V600E immunostain is useful for:
  - Diagnosis & differential diagnosis
  - for rapid assessment of *BRAF* V600E mutation status for dabrafenib and trametinib treatment (a crucial and urgent step in ATC work up)

Thank you!

