Thyroid Cytomorphology
Basic Concepts and Application in Everyday Practice

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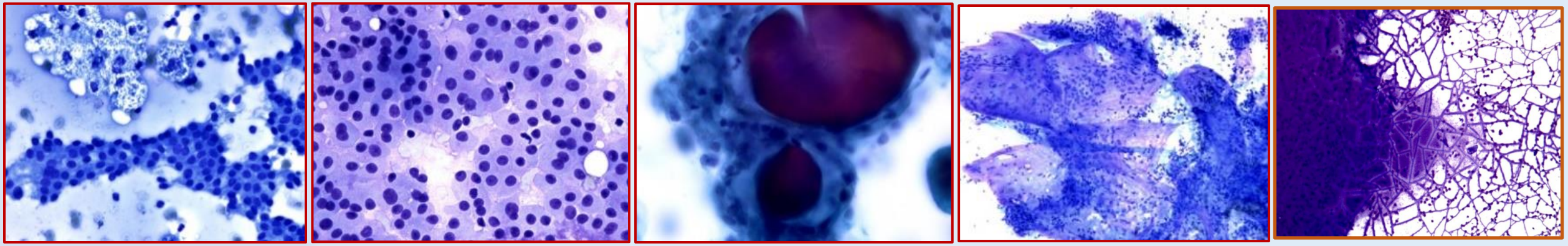


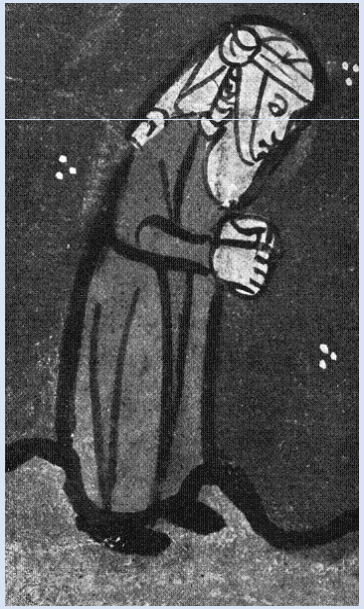
Conflict of Interest

- None to Report

Discussion Points

- Thyroid nodules
- Thyroid cytology
  - Patterned approach with correlation to surgical pathology.
  - Thyroid FNA Classification Scheme
  - Cytomorphology of common thyroid lesions – based on various cytologic preparations

Thyroid Gland Enlargement Through Ages



Thyroid Nodules *Are Common in Adults*

- Clinically apparent nodules affect 4-7% of US population
- By Ultrasound up to 60% of US population has one or more nodules
- More common in women and up to 95% are benign –

Pediatric Thyroid Nodule

Palpable thyroid nodules are less common in children than adults

- **Sonographic or pathological abnormalities are common**
  - **0.2–5% of children, 13% of adolescents**
- Thyroid cystic lesions occur in 57% of children
- **In adults, 7–15% of all thyroid nodules are malignant but the risk in children is higher -22–26%**
- History, ultrasound features, and FNA cytology are used to identify nodules at risk for malignancy.

Pediatric Thyroid Nodule

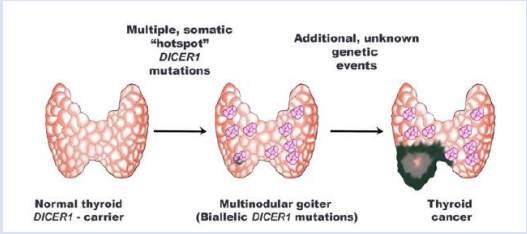
Risk Factors

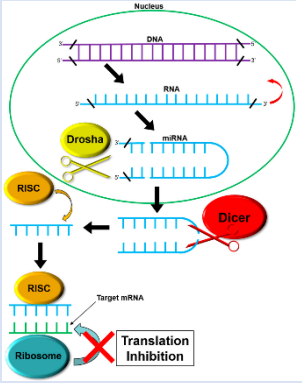
- **Family history of thyroid nodules or thyroid cancer**
  - 2.5-fold higher for children with a family history of benign thyroid disease
  - Four-fold higher for children with a family history of thyroid cancer
- **Iodine deficiency**
- **Radiation exposure**
  - Thyroid nodules develop in cancer survivors who:
    - Received radiation therapy at about 2% annually and ***reach a peak after 15–25 years***
    - A five-fold greater risk in patients with a history of neuroblastoma suggests the potential for genetic predisposition

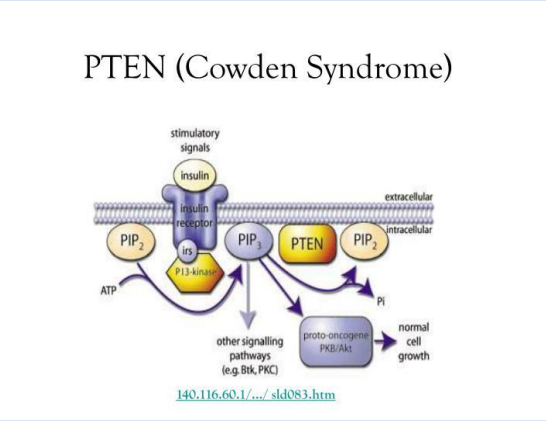
Pediatric Thyroid Nodule

Risk Factors

- **Thyroid disease**
  - Autoimmune Thyroiditis
- **Elevated serum thyrotropin (TSH)**
  - Thyroid nodules and serum thyrotropin(TSH) in the upper tertile may be at increased risk for DTC
- ***Genetic syndromes***
  - **Familial adenomatous polyposis**
  - Carney complex
  - **Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (Cowden's disease)**
  - Beckwith–Wiedemann Syndrome
  - Familial paraganglioma syndromes
  - Li–Fraumeni Syndrome
  - McCune-Albright syndrome
  - Werner syndrome/progeria
  - Peutz–Jeghers syndrome
  - **DICER1 syndrome**







Differential Diagnosis of Thyroid Nodules

- MALIGNANT (5-10%)
  - Papillary Ca(75%), Follicular Ca (15%), Medullary Ca(5%), Lymphoma, Poorly Differentiated & Analplastic Ca, Mets to thyroid (kidney)
- BENIGN (90%-95%)
  - Colloid or adenomatous nodules, Follicular adenomas, Chronic lymphocytic thyroiditis
- Developmental abnormalities
  - Unilateral lobe agenesis, thyroglossal duct cyst

Thyroid Nodule Management in the Era of Pre-Operative Risk Assessment

Everything ***Matters***

Clinical Features + Lab values + Ultrasound

+

Cytomorphology

+

Molecular Profiling

+

Management Strategy

History
Radiation
Family History
Symptoms
Thyroid Disease
Disorders of function
Structural abnormalities
Physical Exam
Initial
Serial
Laboratory determinations
TSH levels
Calcitonin levels
Imaging:
Ultrasound
Standard B mode imaging
Elastography
Contrast Enhanced Ultrasound
Artificial Intelligence
Computer Aided Diagnosis
Radiomics

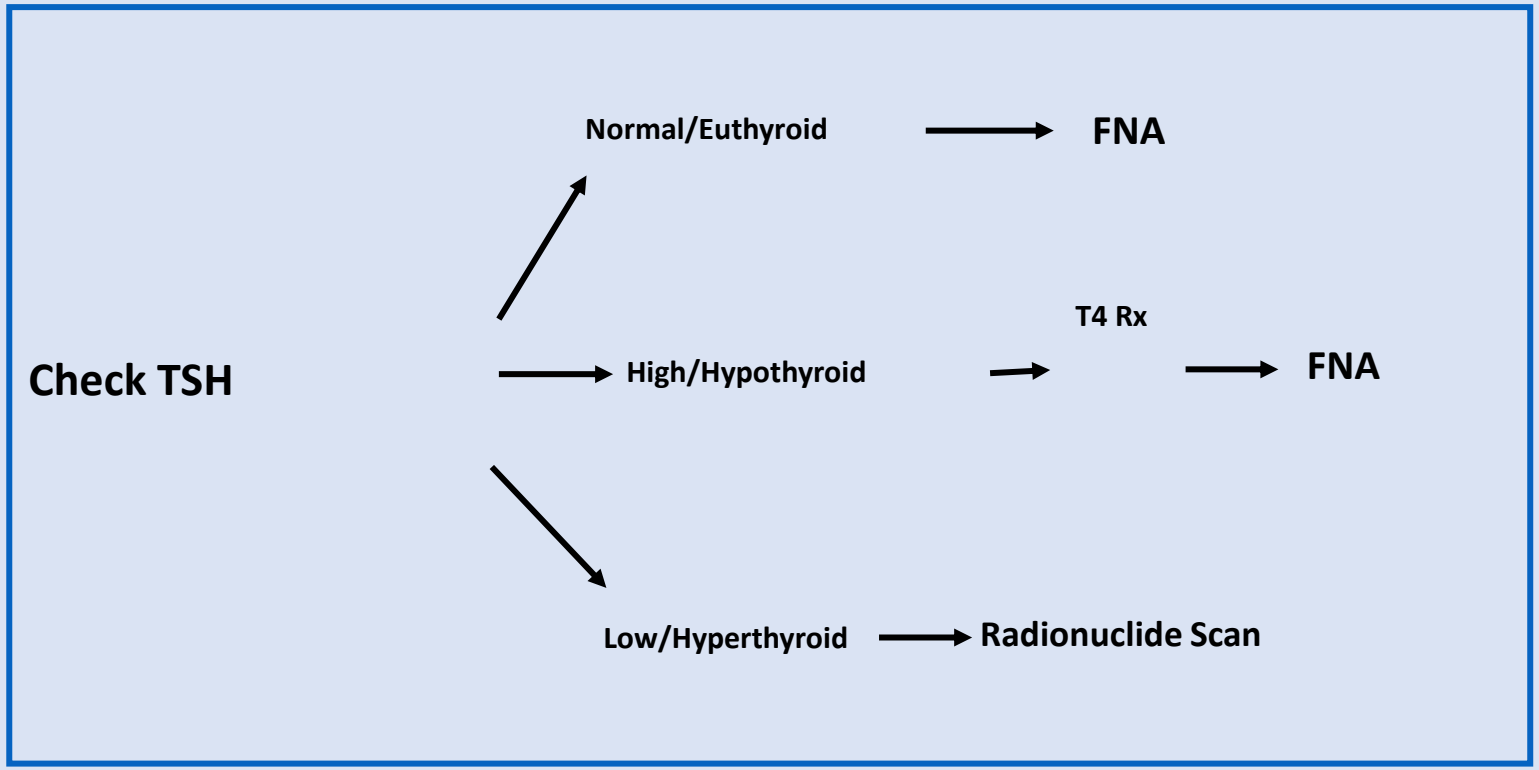
Nuclear medicine
Radioactive Iodine
PET (FDG)
Clinical Practice Guidelines (CPGs)
Risk Score Stratification Tools (Clinical Calculators)
Computer Interactive Guidelines
Fine Needle Aspiration
Molecular Marker/Diagnostics (mostly USA)
DNA (Mutations)
Messenger RNA
micro– RNA
Immunocytochemistry
Principal
Emerging

Garber JR, Frasoldati A, Patkar V and Papini E (2023) Editorial: Thyroid nodule evaluation: current, evolving, and emerging tools. Front. Endocrinol. 14:1276323.doi: 10.3389/fendo.2023.1276323

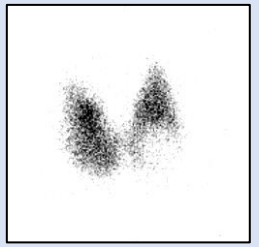
Thyroid Nodule Management in the Era of Pre-Operative Risk Assessment

Features Suggesting Increased Risk of Malignant Potential

History of head and neck irradiation
• Family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or papillary thyroid carcinoma
• Age < 14 or > 70 years
• Male sex
• Growth of the nodule
• Firm or hard nodule consistency
• Cervical adenopathy
• Fixed nodule
• Persistent dysphonia, dysphagia, or dyspnea

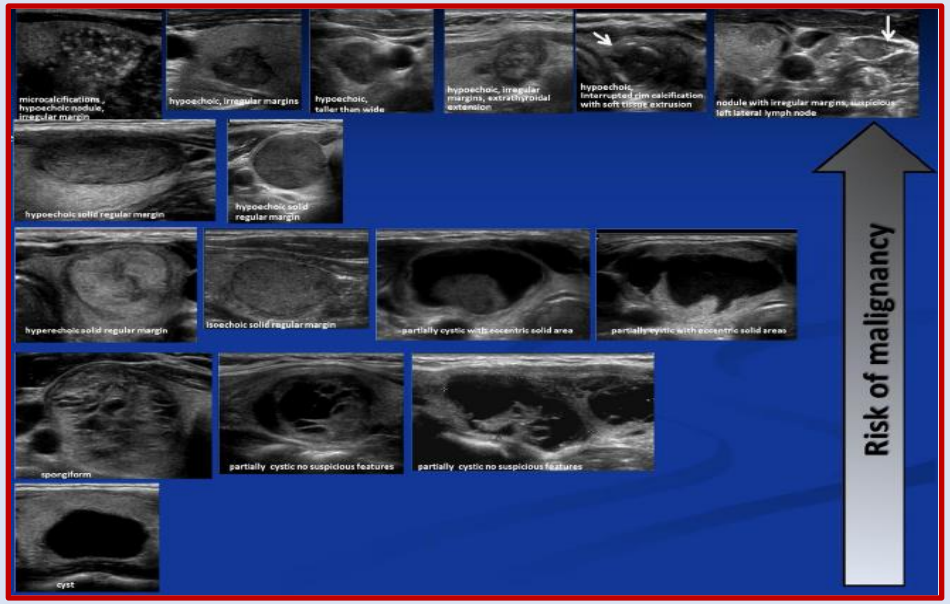


To Exclude the Possibility of Hyper-functioning Nodule ***AKA Hot Nodule***
Thyroid Carcinoma are rarely functioning or "Hot"

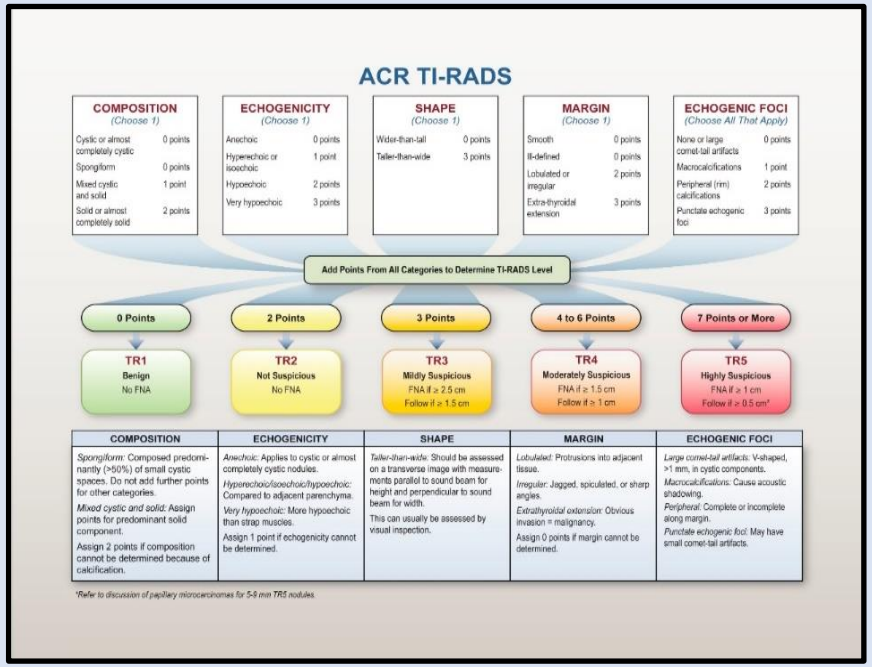


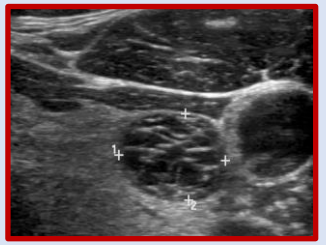
95% of nodules are hypofunctioning "AKA Cold"

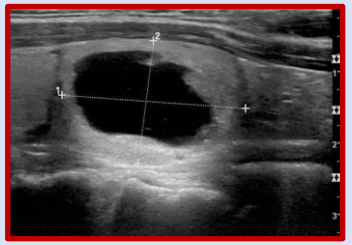
Thyroid Ultrasound Risk Assessment

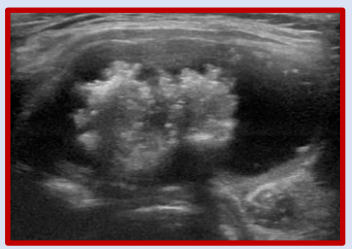


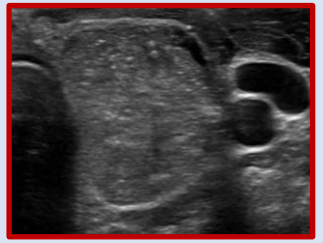
American Thyroid Association Nodule & Cancer Guidelines



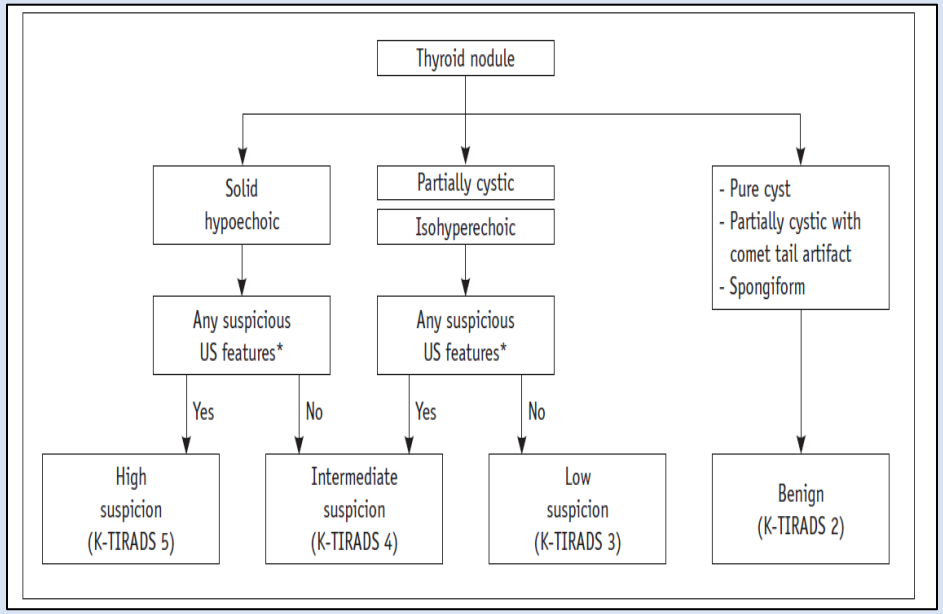








Tessler F, et al. Thyroid Imaging Reporting and Data System (TI-RADS): A User's Guide. RSNA 2018:287 (1)



Korean Society for Thyroid Radiology

Table 3
US Classification Levels 1, 2, and 3

US risk category	Corresponding US feature(s)	Numerical score
US 1 (low): 0-2	**Benign or low-risk US features**	
One or more of the corresponding low-risk features are present, and none of the intermediate or high-risk features are present	Nodule composition on US is spongiform (uniformly microcystic throughout)	0
	Nodule margin on US is either smooth, ill-defined, or cannot be determined	0
	Nodule shape on US is oval or round	0
	Nodule is cystic **and** anechoic	0
	Either solid or mixed **and** marked hyperechoic nodule (described as white knight) is often seen in a gland with clear features of Hashimoto thyroiditis	0
	Comet-tail echogenic foci and its variants are present on US	0
	Either solid or mixed **and** hyperechoic nodule	1
	Either solid or mixed **and** isoechoic nodule **and** size <20 mm **and** none of the US 2/3 features, such as microcalcifications, intranodular macrocalcifications, peripheral rim calcifications, echogenic foci difficult to characterize, spiculated or irregular margin, or extrathyroidal extension	2
	Mixed solid cystic nodule that has reverberating artifacts, which is a low-risk feature compared with an eccentric mural component (excluded from scoring)	No score
	Peripheral vascularity (excluded from scoring)	No score
	Mixed solid cystic nodule has a solid concentric/spongiform-like component (excluded from scoring)	No score
US 2 (intermediate): 3-4	**Intermediate-risk US features**	
One or more of the corresponding intermediate-risk features are present, and none of the high-risk features are present	Nodule margin on US is irregular with protrusion into adjacent thyroid tissue	1
	Echogenic foci, including either intranodular macrocalcifications or foci that are difficult to characterize, or peripheral rim calcifications, including either interrupted rim calcification or uninterrupted rim calcifications	1
	Nodule composition on US is either solid or mixed **and** the echogenicity of the solid part is either slightly hypoechoic or hypoechoic	3
	Either solid or mixed nodule **and** isoechoic **and** either size >20 mm or at least one more US 2 feature, such as an irregular margin or intranodular macrocalcifications or foci that are difficult to characterize or peripheral rim calcifications **and** none of the US 3 characteristics, such as microcalcifications, extrathyroidal extension, or spiculated margins	3
	Mixed solid cystic nodule has a solid eccentric mural component (excluded from scoring)	No score
	Solid or mixed nodule with solid part showing intranodular vascularity (excluded from scoring)	No score
	Mixed solid cystic nodule has indeterminate hyperechoic spots, which increase the risk of malignancy (excluded from scoring)	No score
US 3 (high): ≥5	**High-risk US features**	
One or more of the corresponding high-risk features are present	Nodule margin on US is spiculated or has sharp angles	5
	Nodule echogenicity on US is profoundly hypoechoic	5
	Microcalcifications are present within the nodule	5
	Nodule shape on US is taller-than-wide	5
	Solid **and** hypoechoic **and** either intranodular macrocalcifications or nonspecific echogenic foci or peripheral rim calcifications present (excluded from scoring)	No score
	Extrathyroidal extension is noted on the US (excluded from scoring)	No score

Abbreviation: US = ultrasound.
The sum of points does not denote absolute risk. The categorization of characteristics and all of the *possible* combinations of these characteristics under US 1, 2, and 3, unambiguously establish whether a nodule falls within the low, intermediate or high risk for being malignant.

AACE

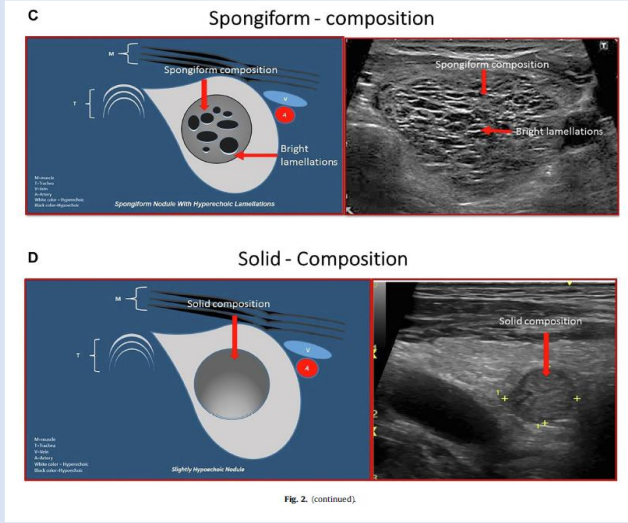


Fig. 2. (continued).

Characteristics of major ultrasound risk stratification systems

RSS	***Classification format***	***Number of categories***	***Categories and estimated RoM***
2021 AACE/ACE-AME tool/ TNAPP	Electronic algorithmic tool that uses history, labs, and combinations of US features	Clinical 2; US features 3	US1 – 1% US2 – 5-15% US3 – 50-90%
2015 ATA	Pattern recognition	5	Benign - <1% Very low - <3% Low - 5–10% Intermediate - 10–20% High - 70–90%
2017 ACR-TIRADS	Point-based system	5	TR1 - <2% TR2 - <2% TR3 - <5% TR4 - 5–20% TR5 - >20%
2017 EU-TIRADS	Algorithmic (combinations of US features)	5	TR1 – None TR2 – 0% TR3 - 2-4% TR4 - 6-17% TR5 - 26-87%
2016 K-TIRADS	Algorithmic (combinations of US features)	5	K-TIRADS 1 – None K-TIRADS 2 – < 3% K-TIRADS 3 – 3-15% K-TIRADS 4 – 15-50% K-TIRADS 5 - > 60%
2020 C-TIRADS	Point-based system	6	C-TR 1 – None C-TR 2 – 0% C-TR 3 – <2% C-TR 4 A– 2-10% C-TR 4 B– 10-50% C-TR 4 C– 50-90% C-TR 5 – >90% C-TR 6 – Proven malignancy

AACE/ACE/AME, American Association of Clinical Endocrinology, American College of Endocrinology, Associazione Medici Endocrinologi; TNAPP, The Thyroid Nodule App; ACR TI-RADS, American College of Radiology Thyroid Imaging Reporting and Data System; ATA, American Thyroid Association; EU-TIRADS, European Thyroid Association Thyroid Imaging Reporting and Data System; K-TIRADS, Korean Society of Thyroid Radiology/Korean Thyroid Association Thyroid Imaging Reporting and Data System; RSS, risk stratification system; RoM, risk of malignancy.

Majety P (2023) Thyroid nodules: need for a universal risk stratification system.Front. Endocrinol. 14:1209631. doi: 10.3389/fendo.2023.1209631

Majety P, Garber JR. Ultrasound scoring systems, clinical risk calculators, and emerging tools. In: Handbook of thyroid and neck ultrasonography: an illustrated case compendium with clinical and pathologic correlation. (Cham, Germany: Springer International Publishing) (2023). p. 25–52. doi: 10.1007/978-3-031-18448-2_2

Why is there a need for radiologists to characterize thyroid nodules and make follow up recommendations?

- Thyroid nodules are incredibly common, and most are detected by imaging exams
  - Incidental thyroid nodules (ITN)
- Most are detected in asymptomatic patients often undergoing imaging for another reason
- *Clinicians want guidance as to what is the appropriate management when detected in low risk patients*

Thyroid Nodules

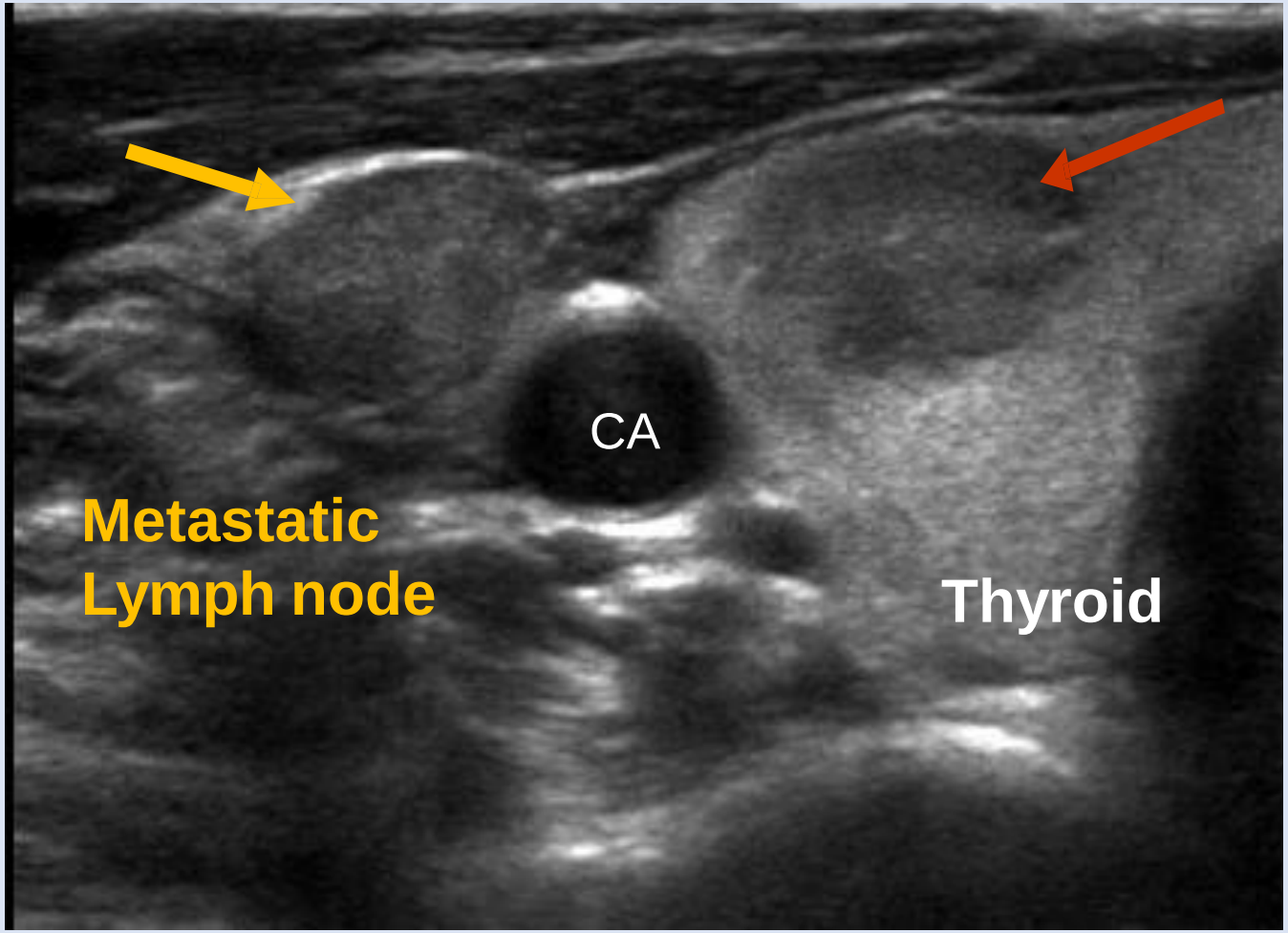
- Sonography is best imaging test to assess features that help predict the likelihood of malignancy
  - Recommended for ITN ≥ 1.5 cm in pts over 35 yo*
- Sonography can predict a benign nodule appearance
  - Entirely cystic nodule
  - Spongiform nodules
- Some nodules cannot be differentiated by appearance
  - Follicular adenoma vs Follicular histology cancers overlap in appearance on sonography

*ACR Incidental Thyroid Findings Committee
Hoang JK et al., J Am Coll Radiol 2015;12:143-150

Imaging Features Associated with Malignancy

- Local invasion- the lesion extends beyond the thyroid capsule into the adjacent soft tissue

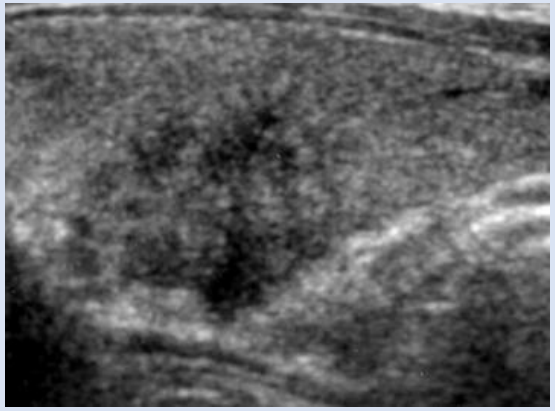
- Lymphadenopathy- identification of cervical Lymph nodes that have features of metastatic thyroid cancer
  - Cystic areas
  - Rounded Shape
  - Calcifications



Sonographic Features Associated with Thyroid Malignancy

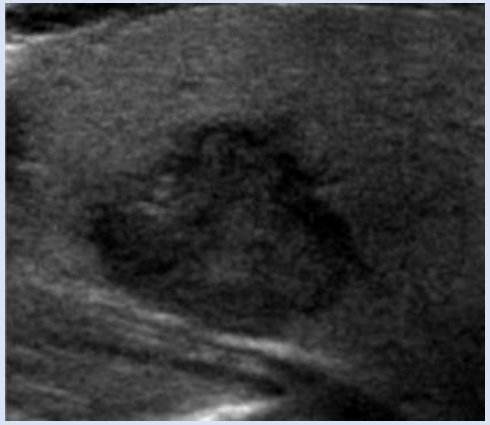
- All solid consistency
- Hypoechogenicity (how dark the nodule appears)
- Infiltrating and lobulated nodule margins
- Taller- than -wide shape
- Large and coarse calcifications
- True microcalcifications
  - Representing psammoma bodies seen in PTC
  - These appear as tiny bright dots or punctate echogenic foci (PEF)
  - Concerning on solid and hypoechoic nodules

Margins Associated with Malignancy

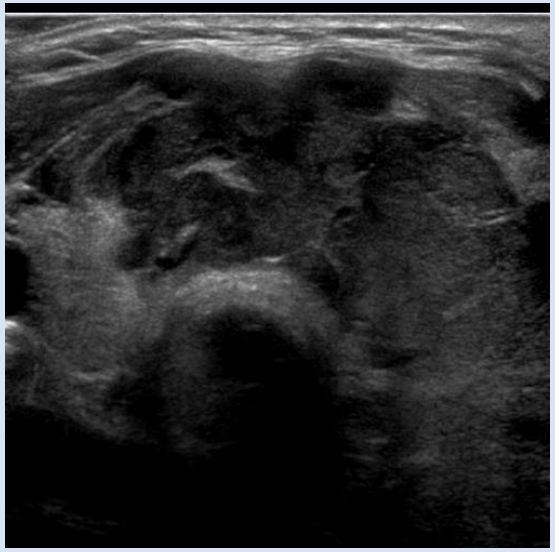


Papillary cancer

Spiculated

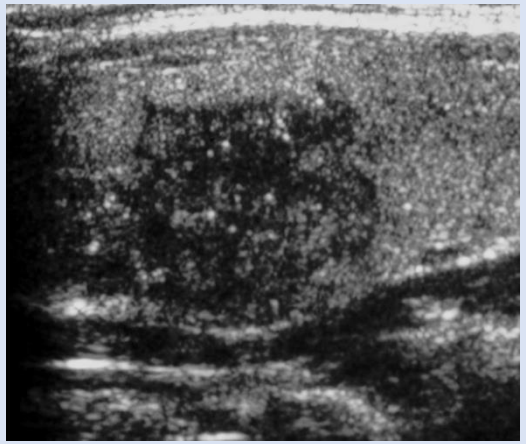


Papillary cancer



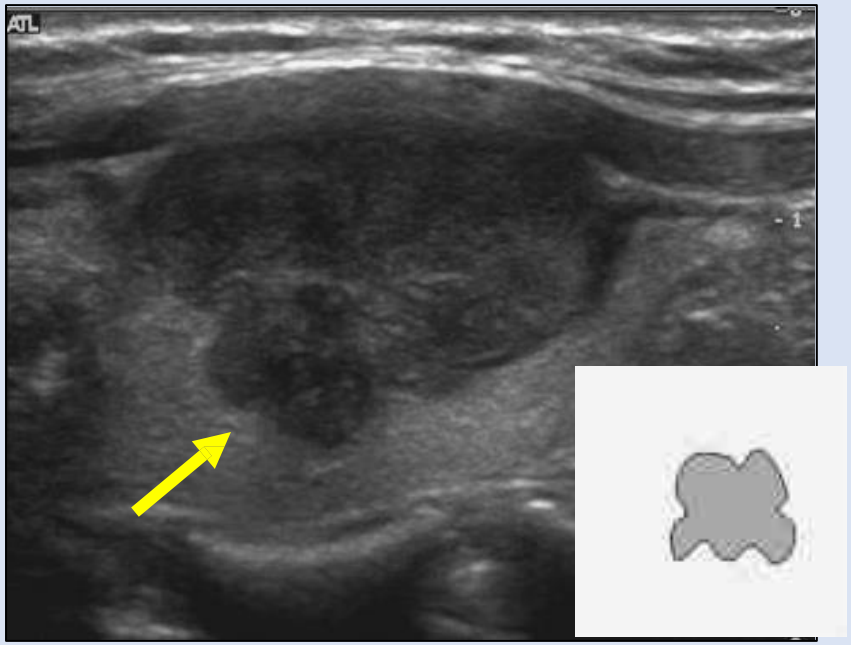
Anaplastic cancer

Jagged/Irregular

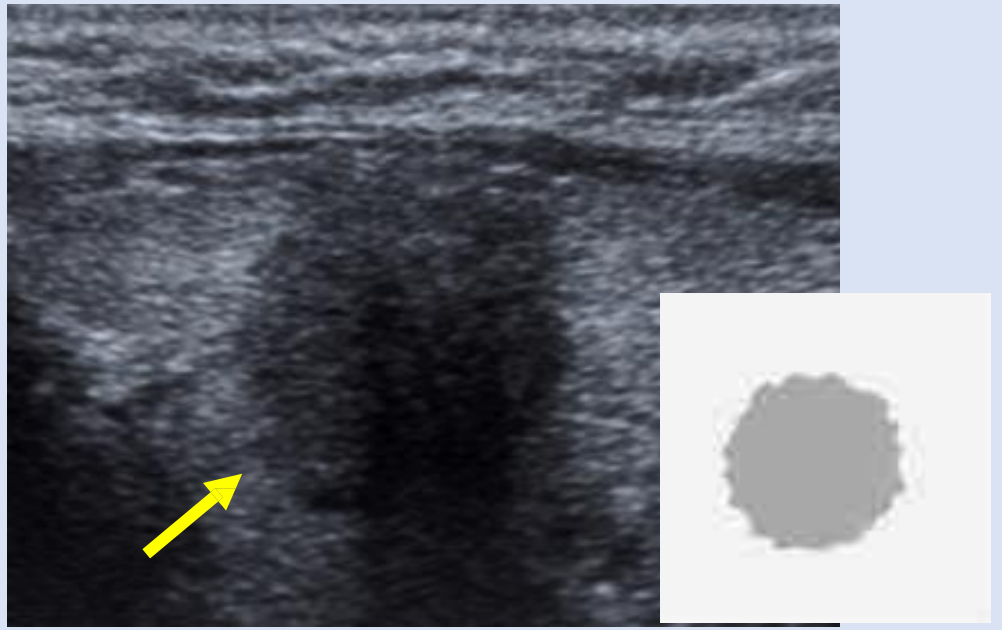


Papillary cancer

Margins Associated with Malignancy



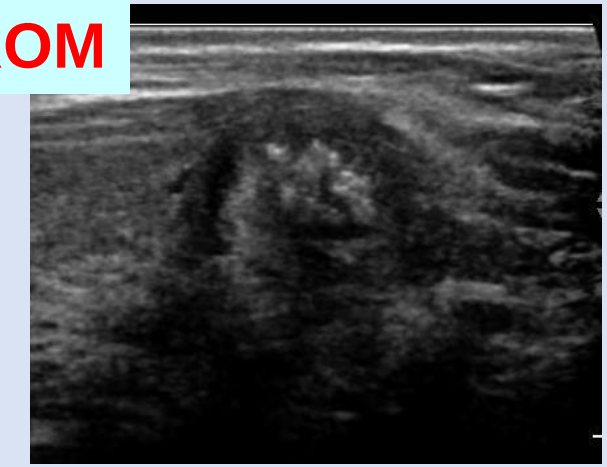
Macro-lobulated



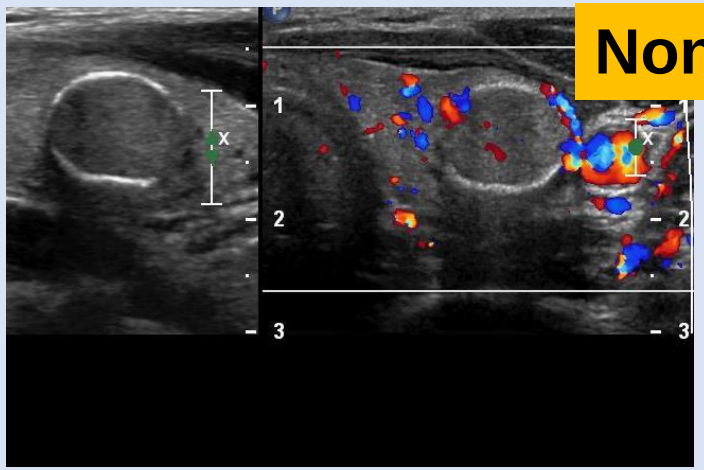
Micro-lobulated

Types of Macrocalcifications

High ROM



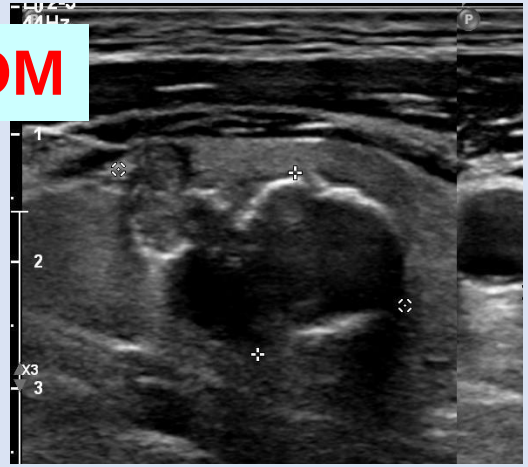
Central, large and dystrophic/coarse



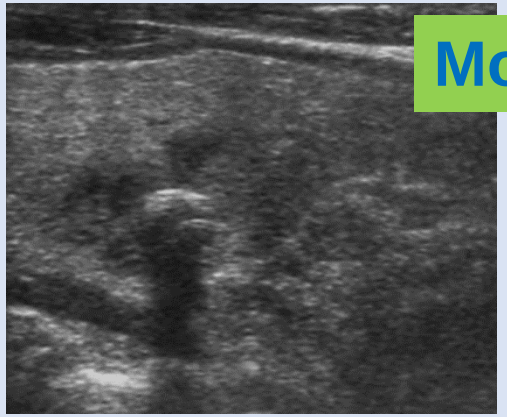
Non-specific

Peripheral complete or “eggshell”

High ROM



Peripheral & interrupted

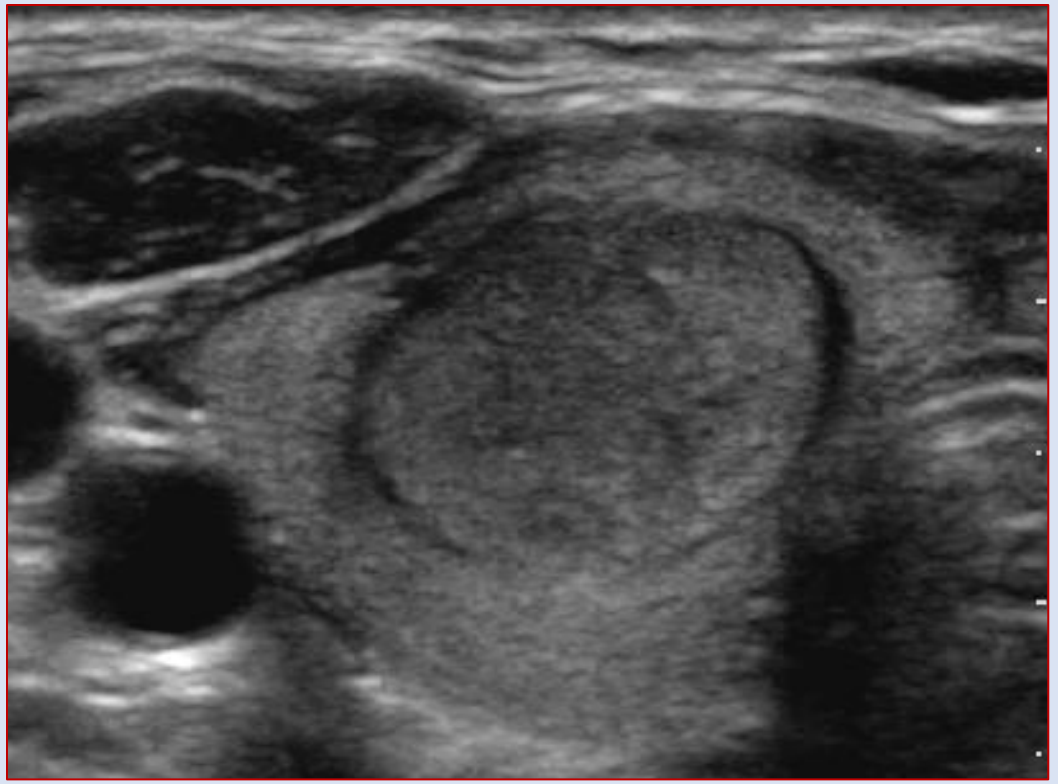


Most benign

Central and linear

20 to 30% of Thyroid Cancers are solid and isoechoic or hyperechoic

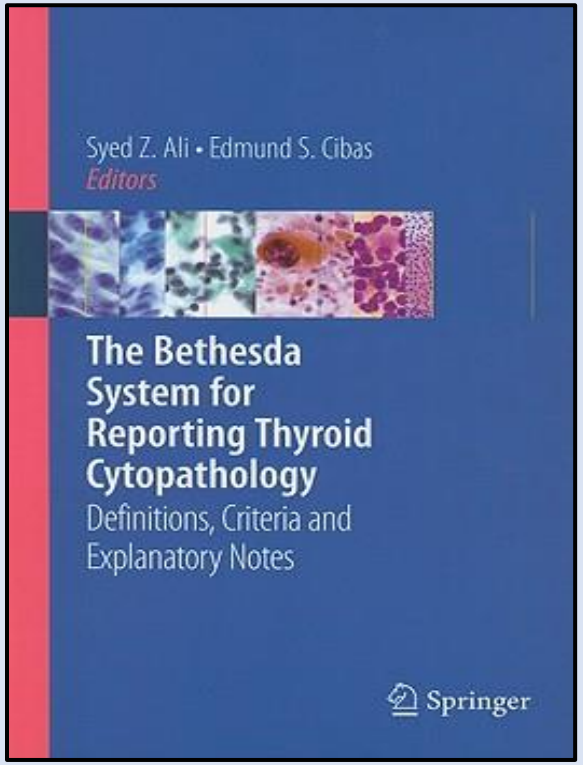
Follicular variant papillary thyroid cancer

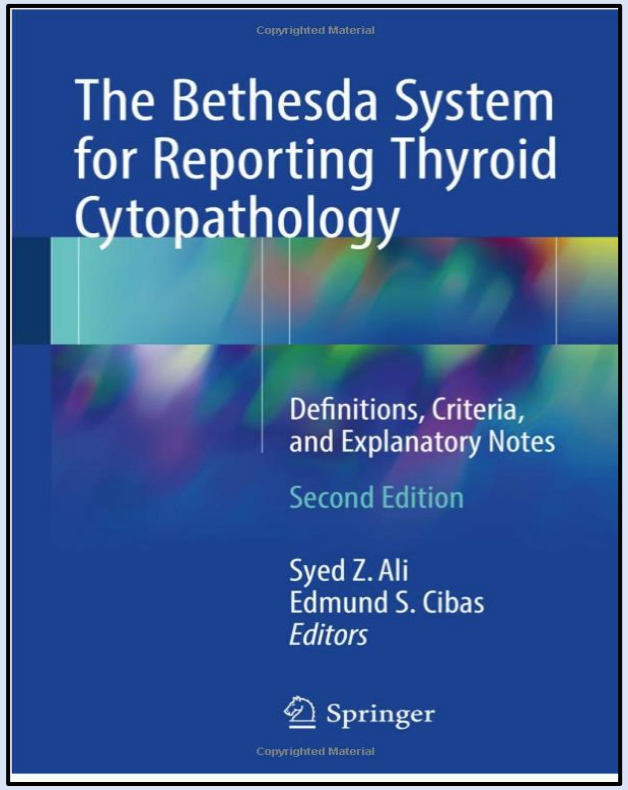


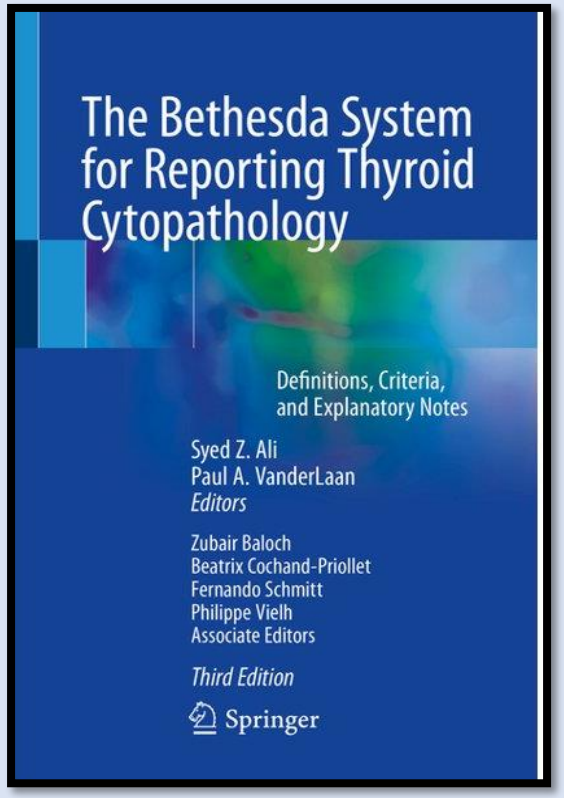
Pure Follicular Thyroid Cancer

Diagnosing & Interpreting FNA Specimens of Thyroid Nodules

- ***Reporting Framework / Scheme***



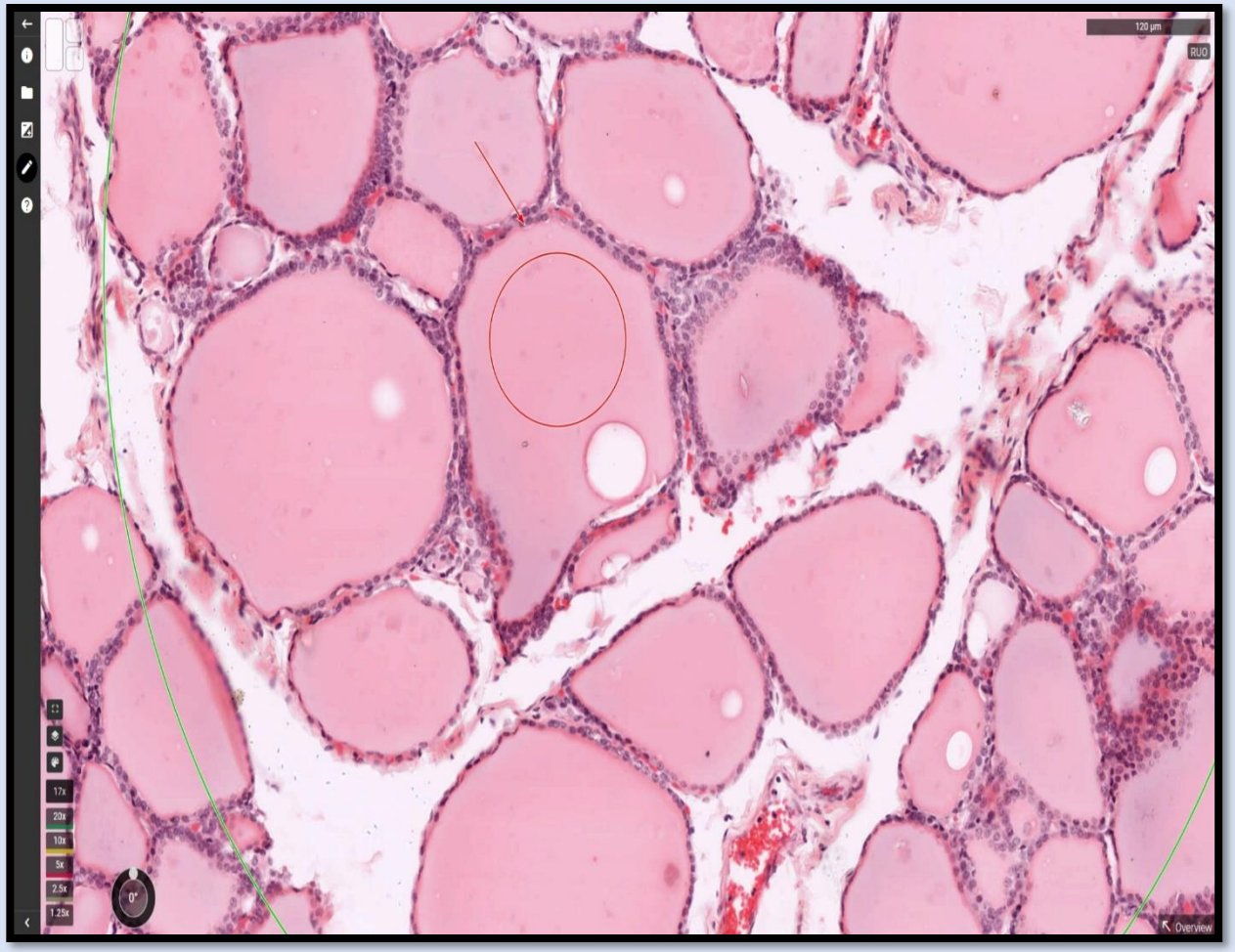




Basic Concepts in Thyroid Cytology

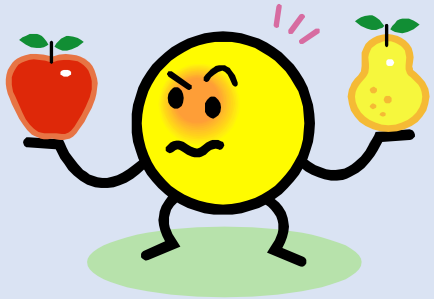
1. Architecture
2. Cellular Features

Normal Thyroid - Histology

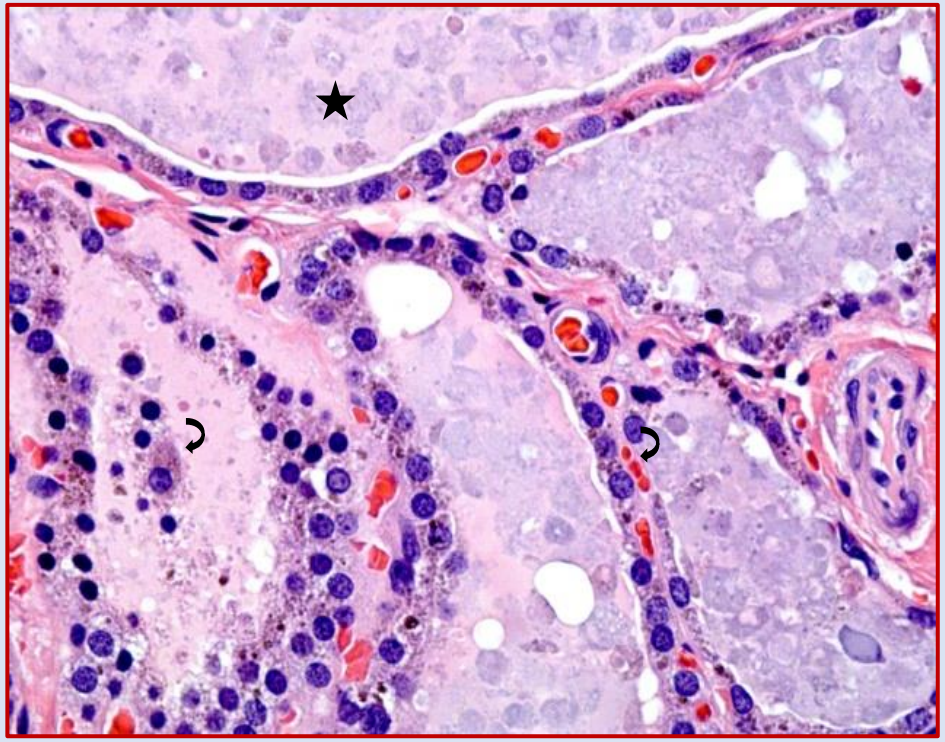


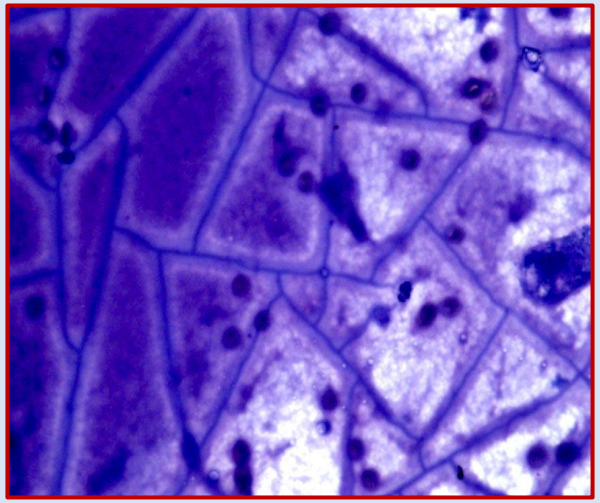
Let’s Correlate

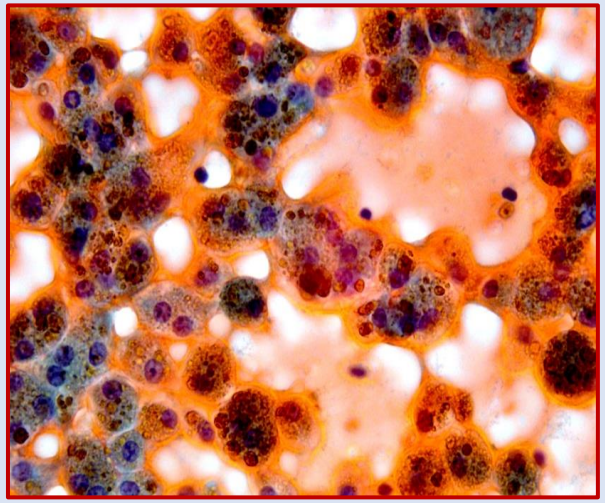
Thyroid Histology vs. Cytology

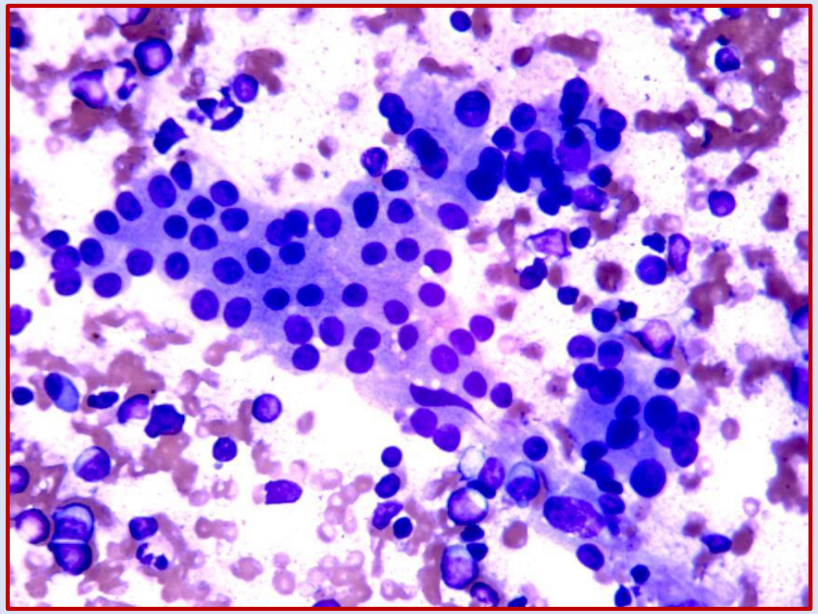


Colloid, Follicular cells & Macrophages/Histiocytes

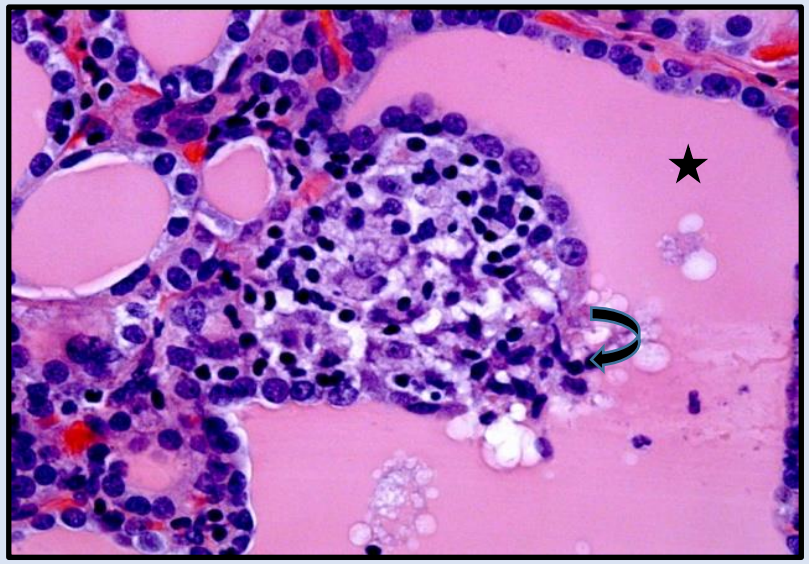


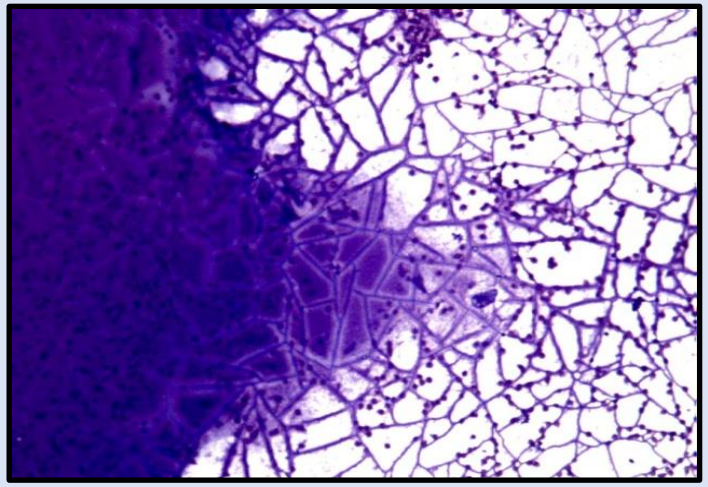


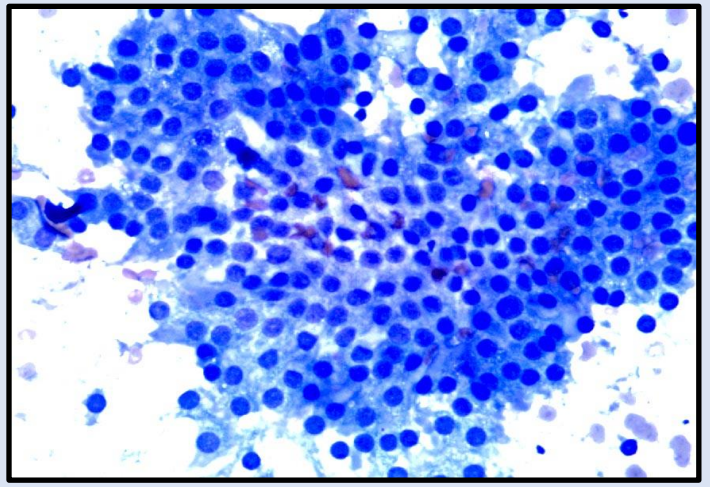


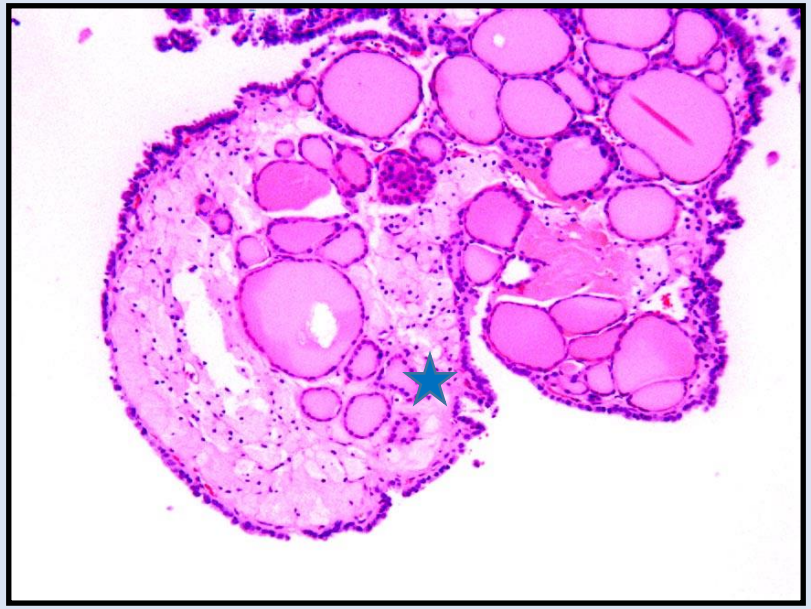


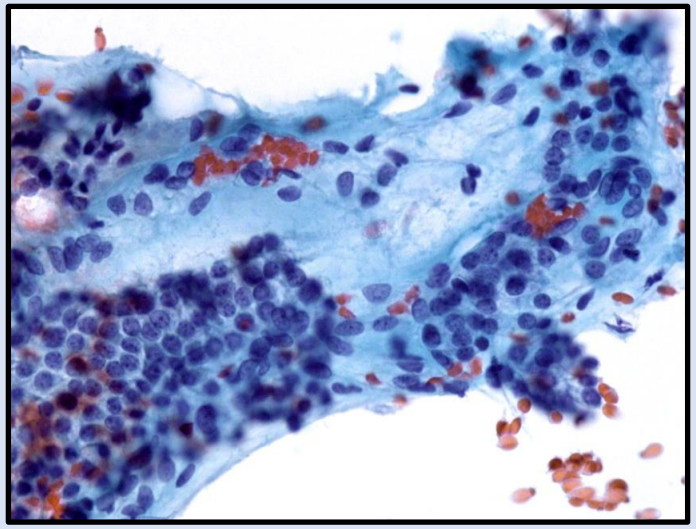
Follicles, Papillary Formation & Colloid

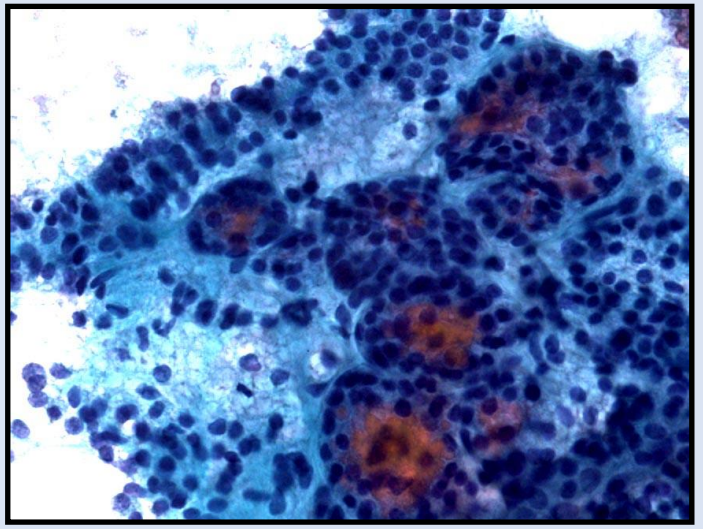




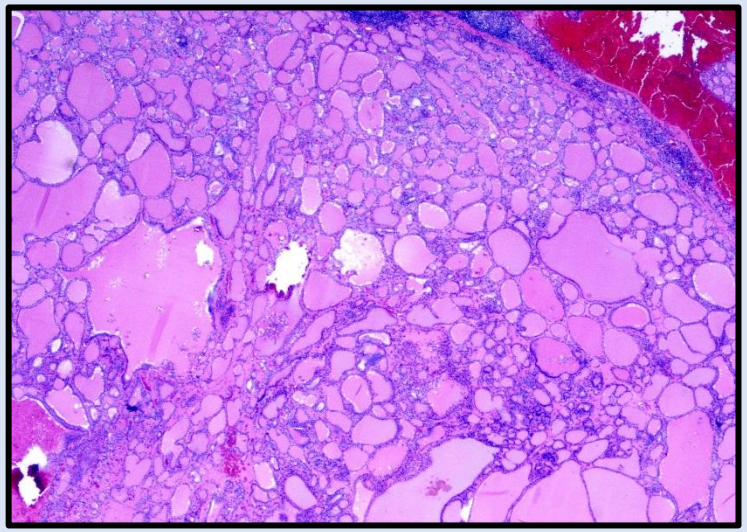


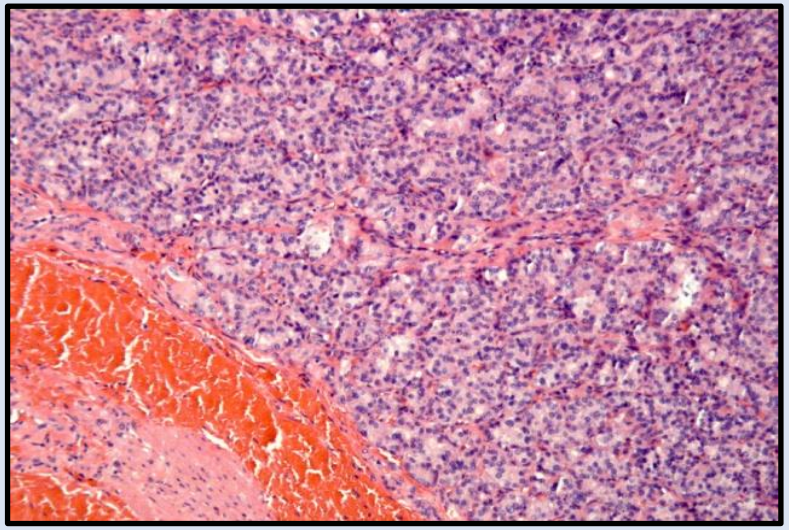


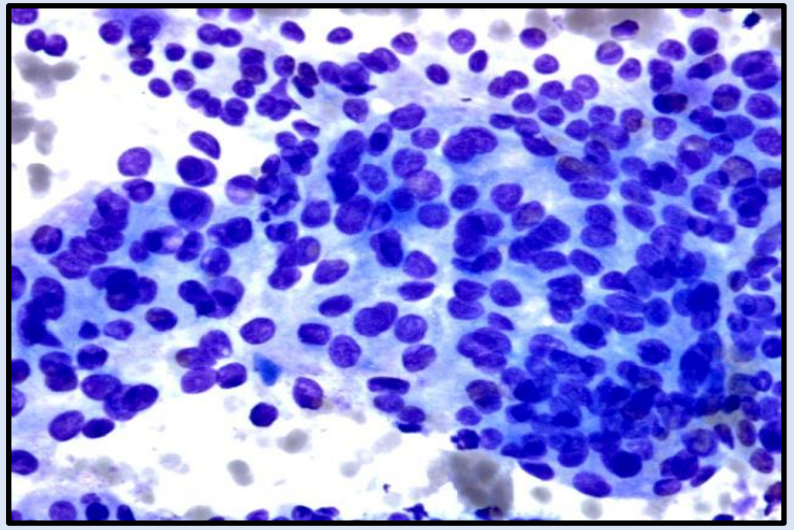


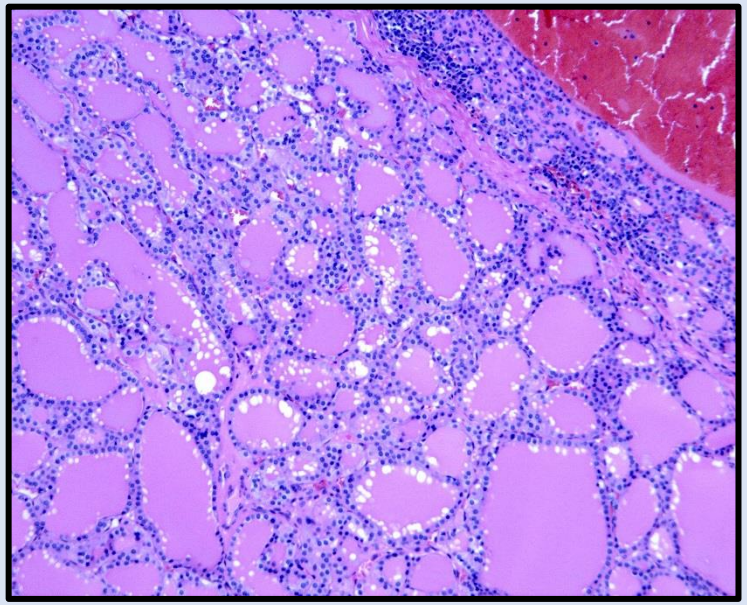


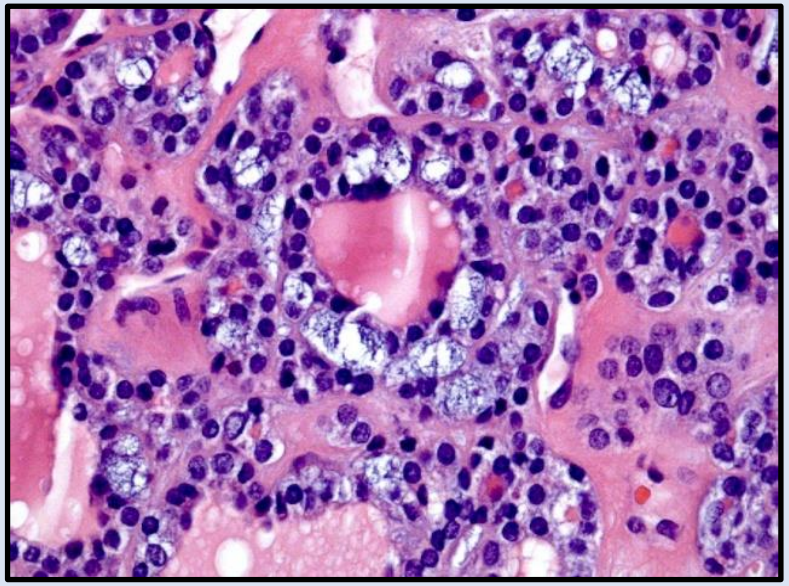
Microfollicles

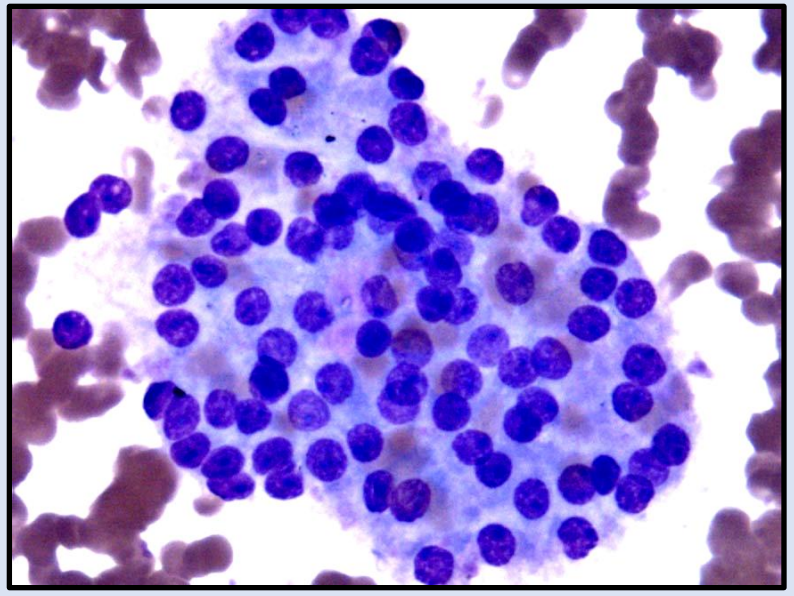




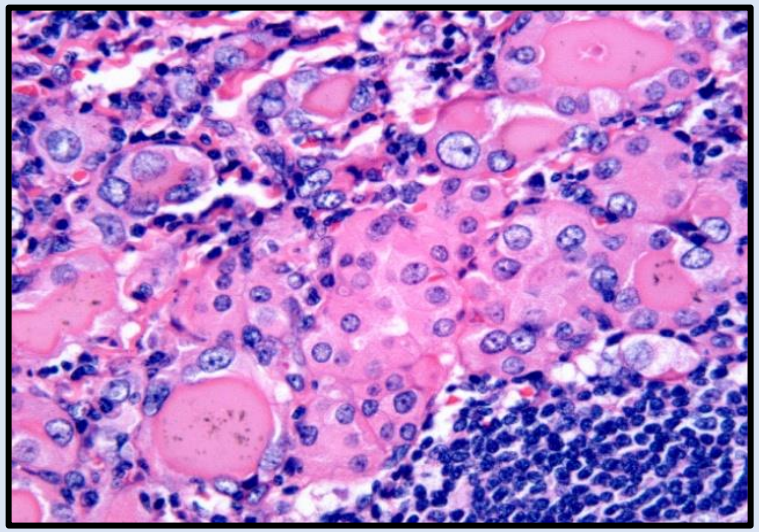
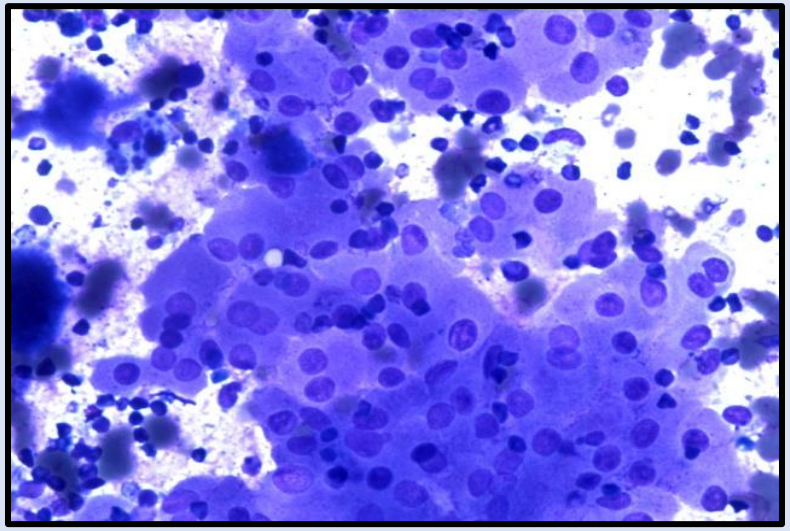
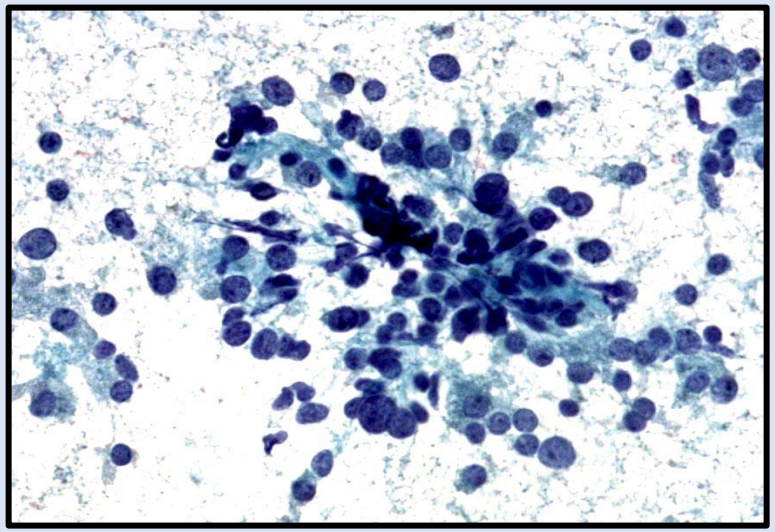
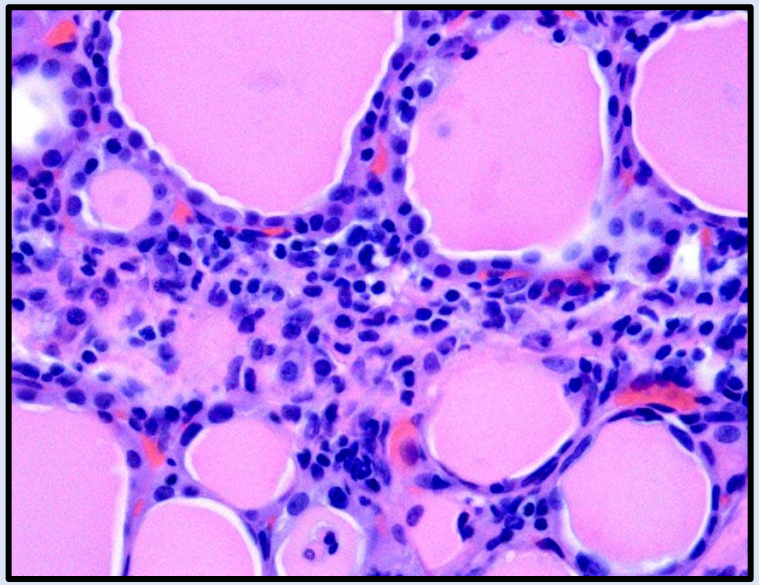
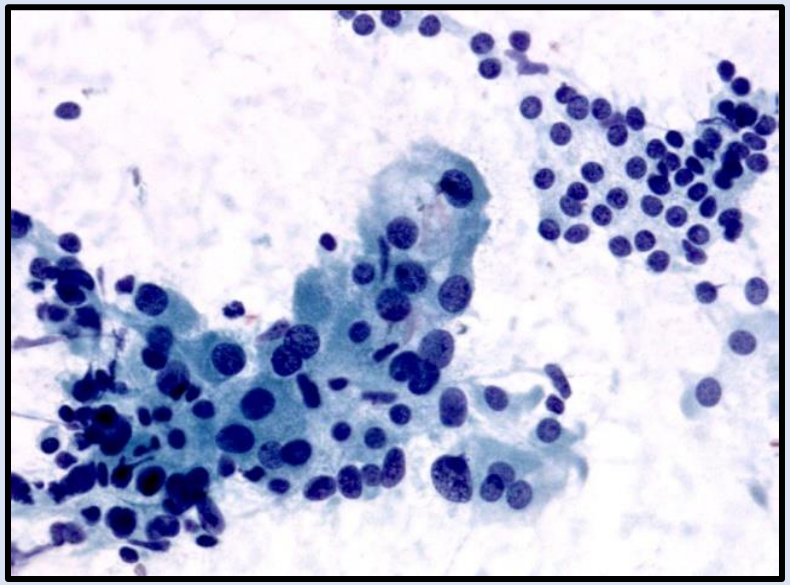
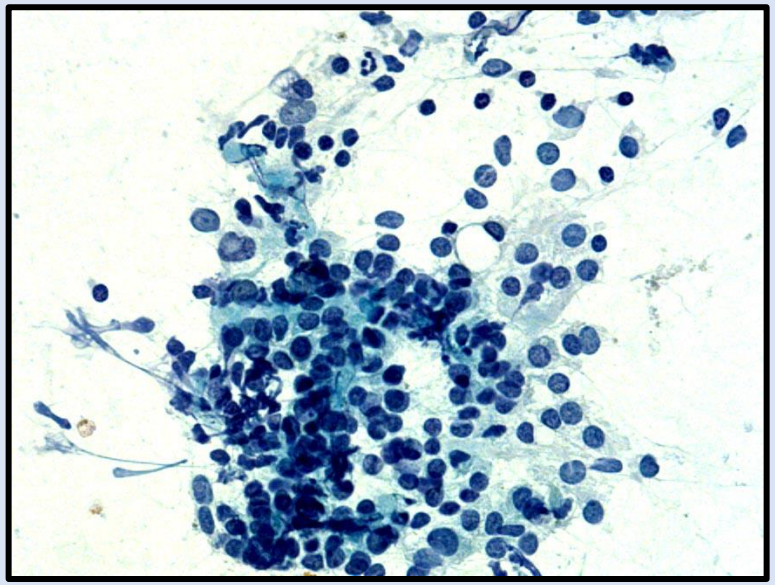






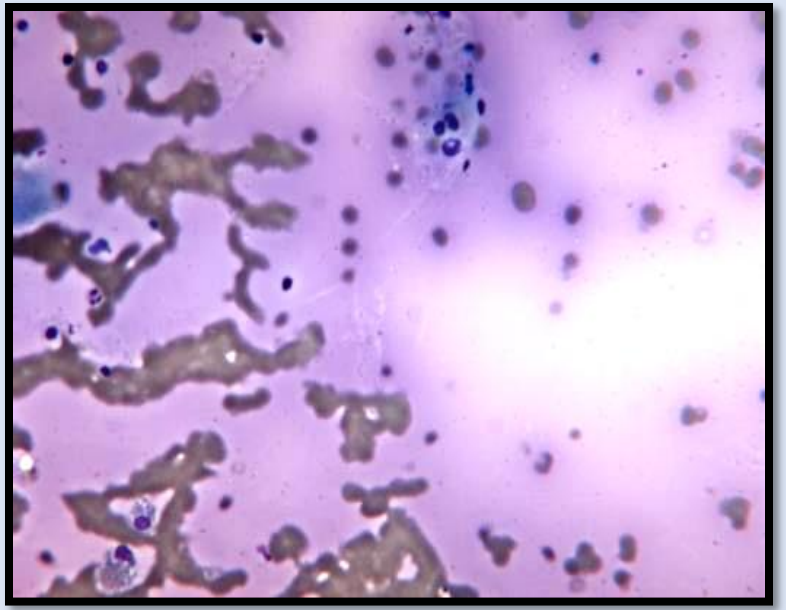


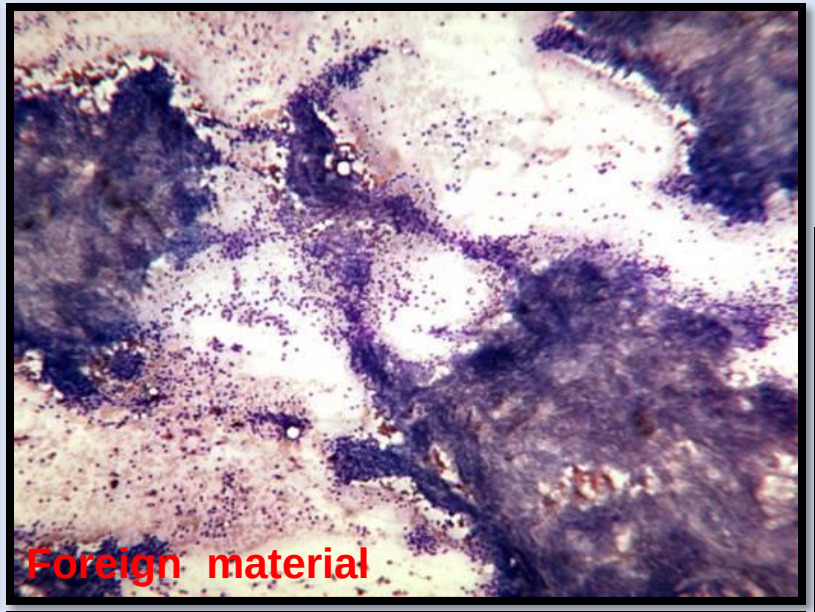
Oncocytic cells and Lymphocytes

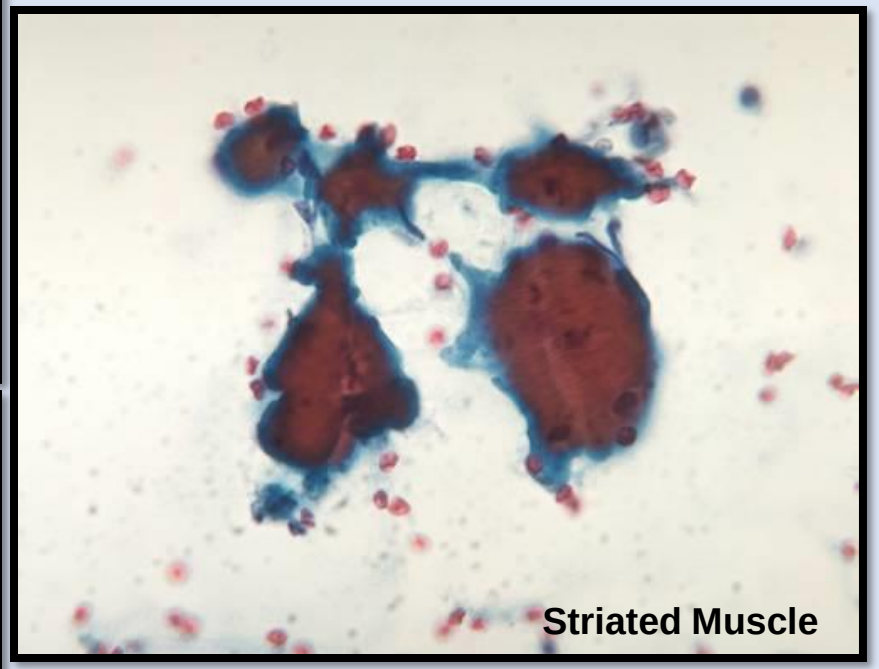







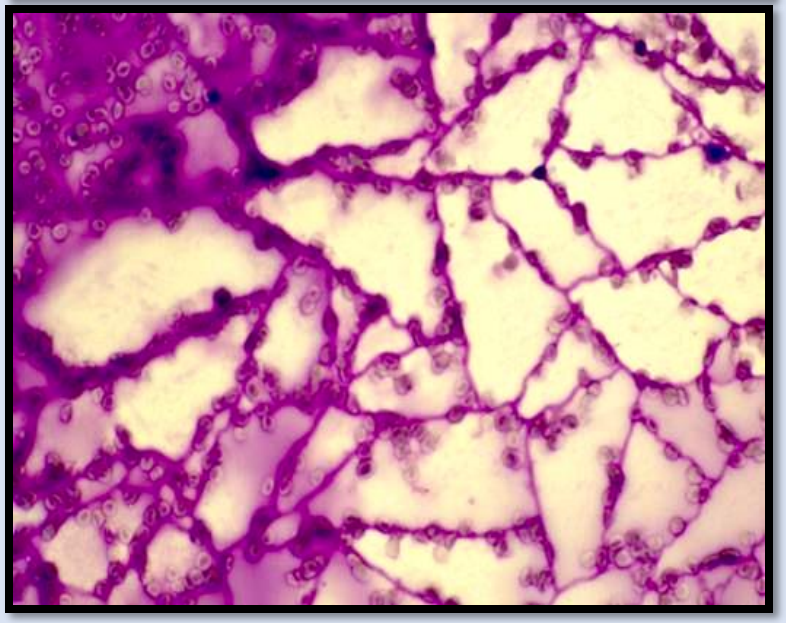
Thyroid Lesions Encountered in Everyday Practice of Cytopathology

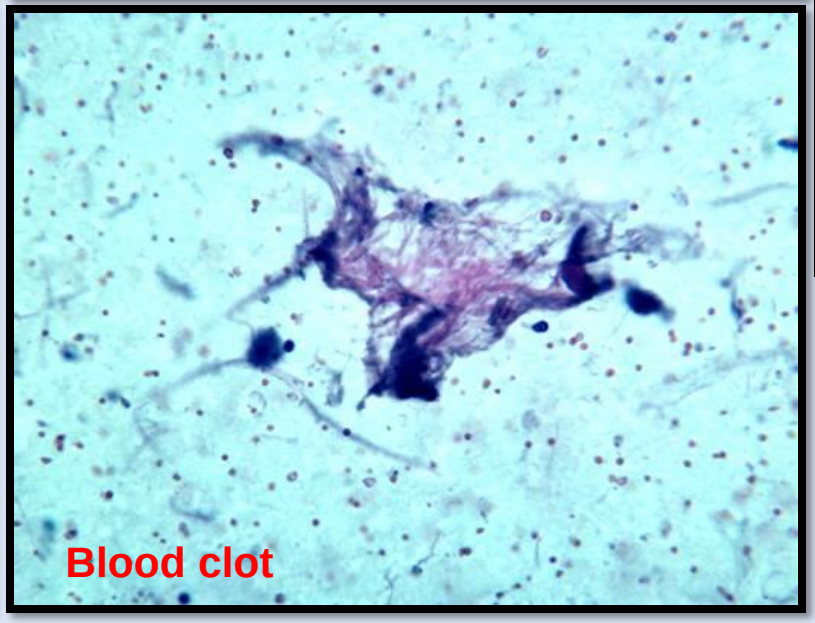
Colloid: Thyroid FNA



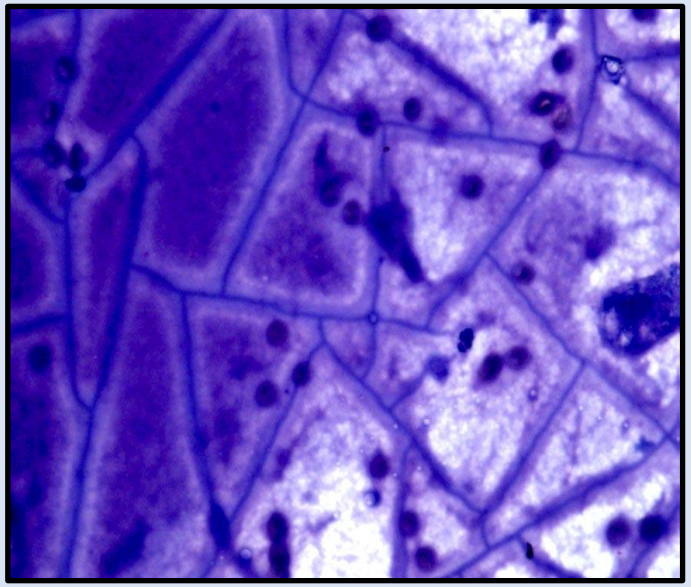


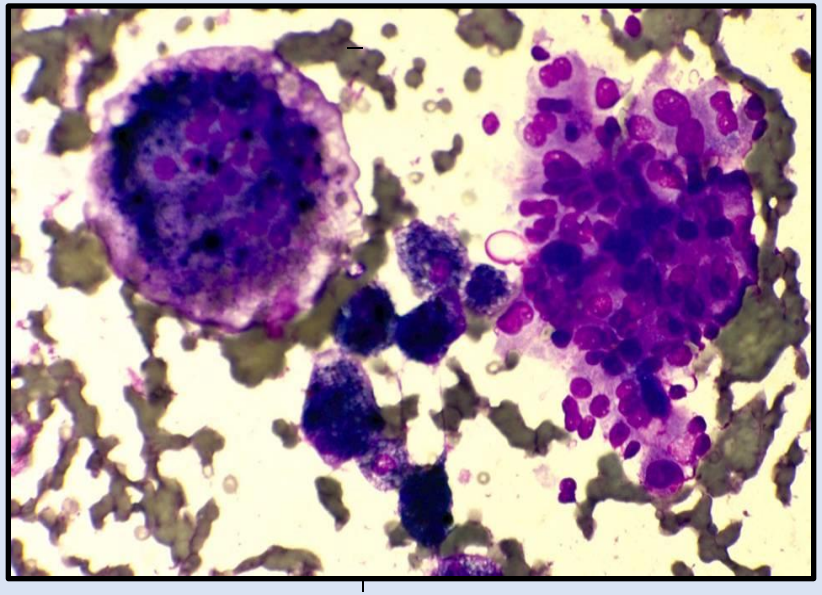


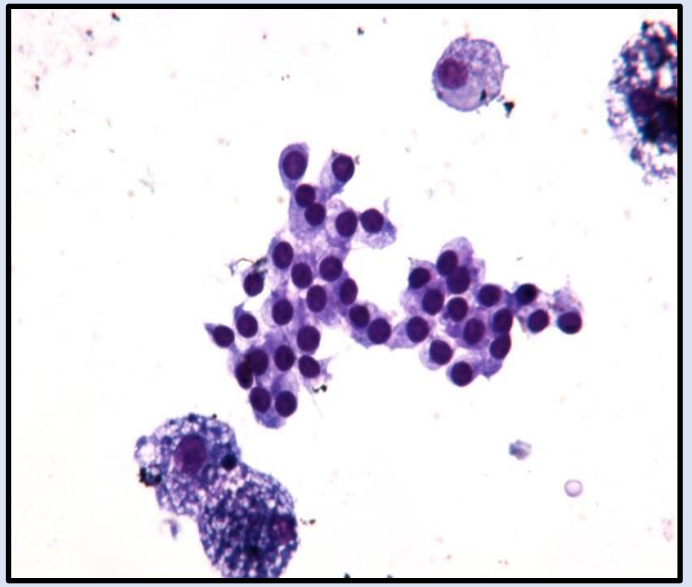


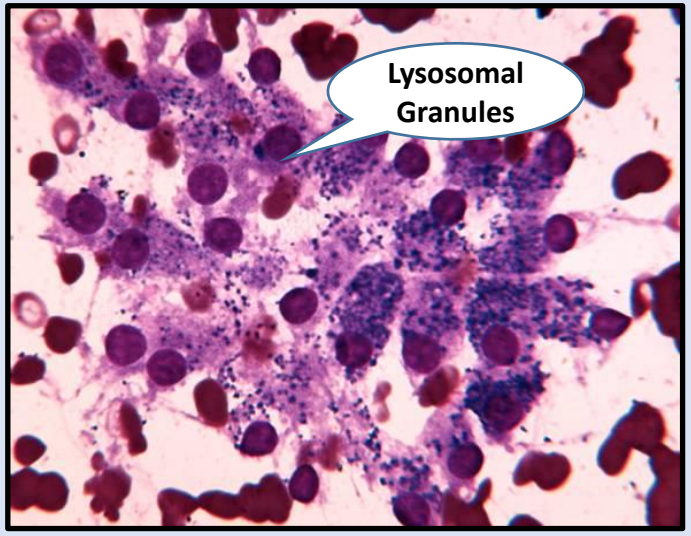


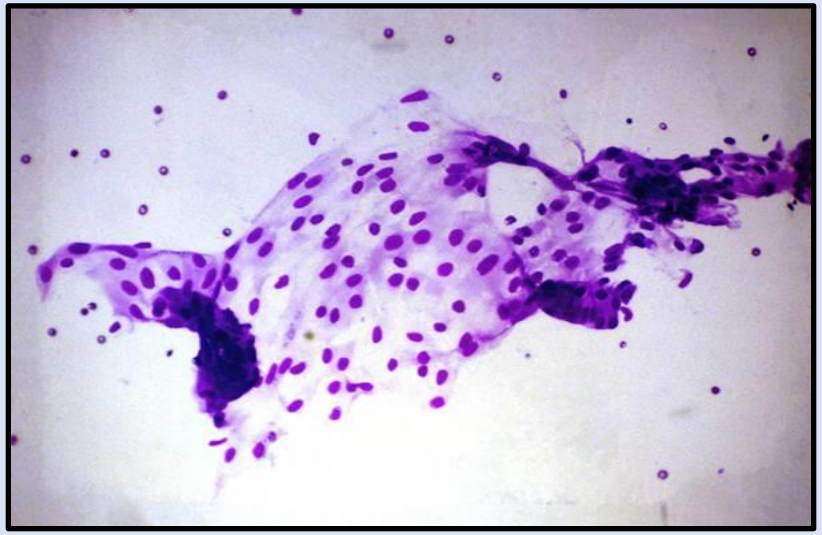
Cytomorphology of Adenomatous Nodule

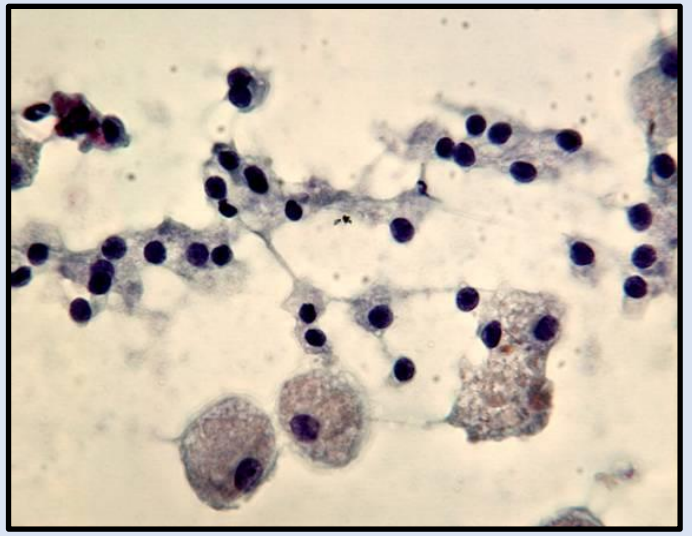






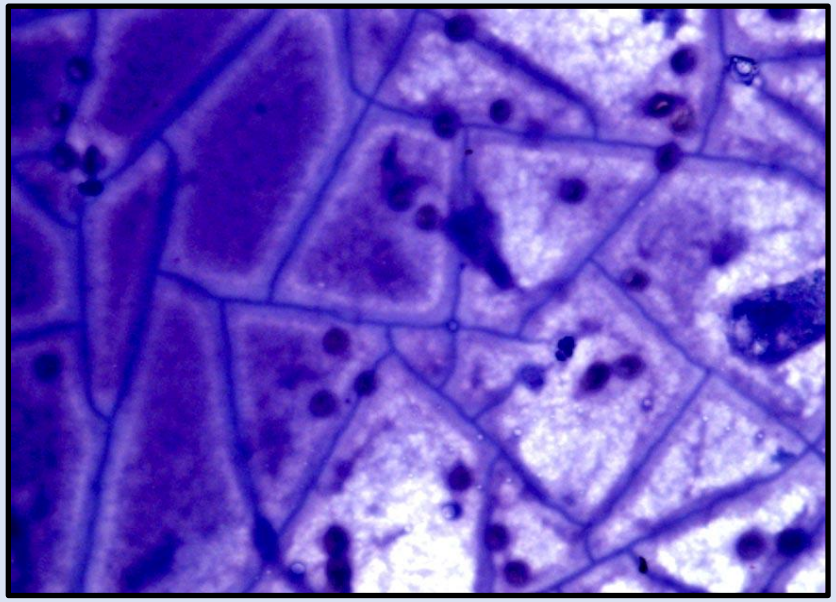


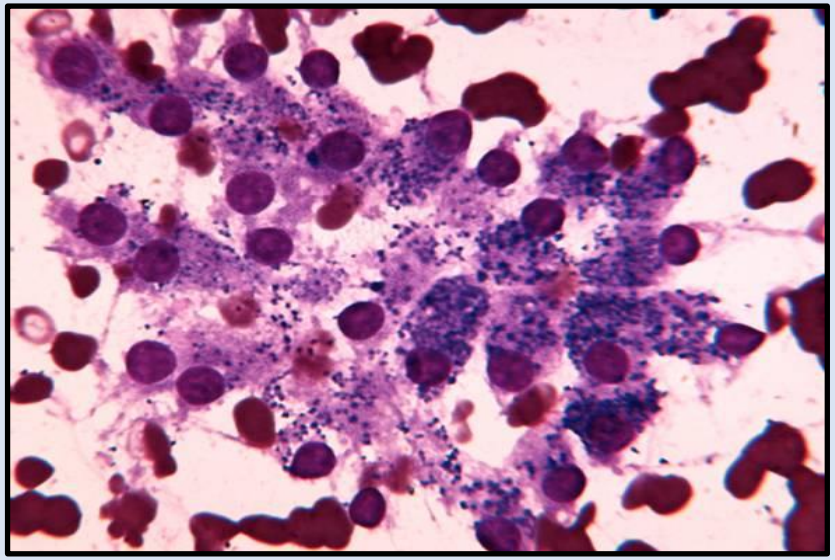




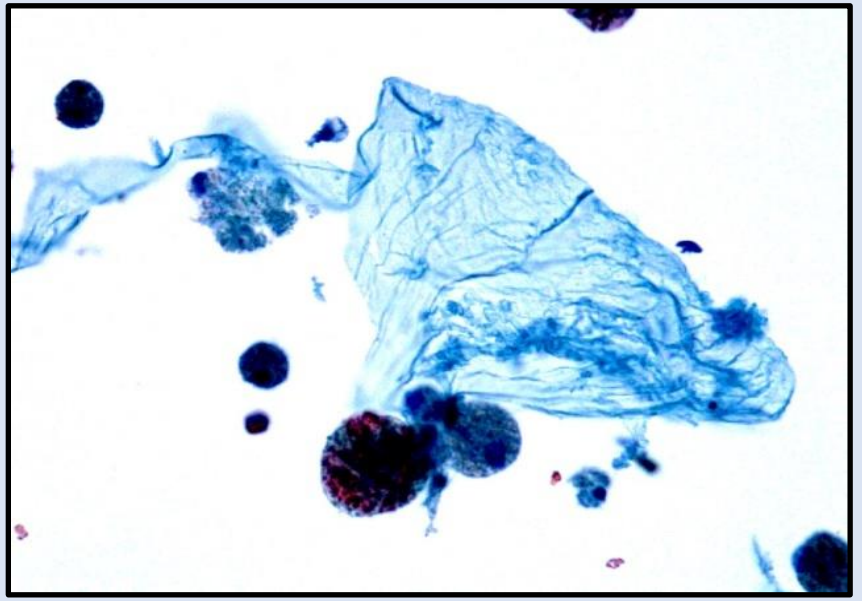
Cytomorphology: Hyperplastic Nodule

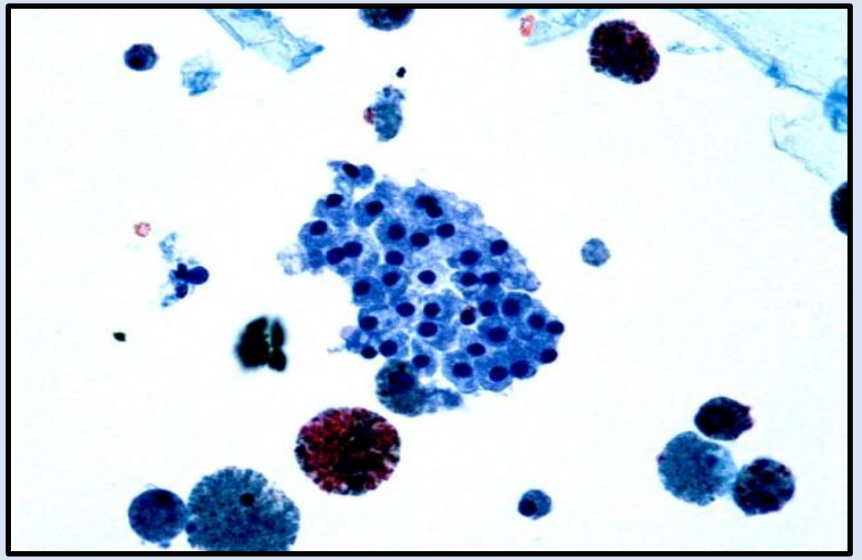
Conventional - Smear Preparations





ThinPrep®

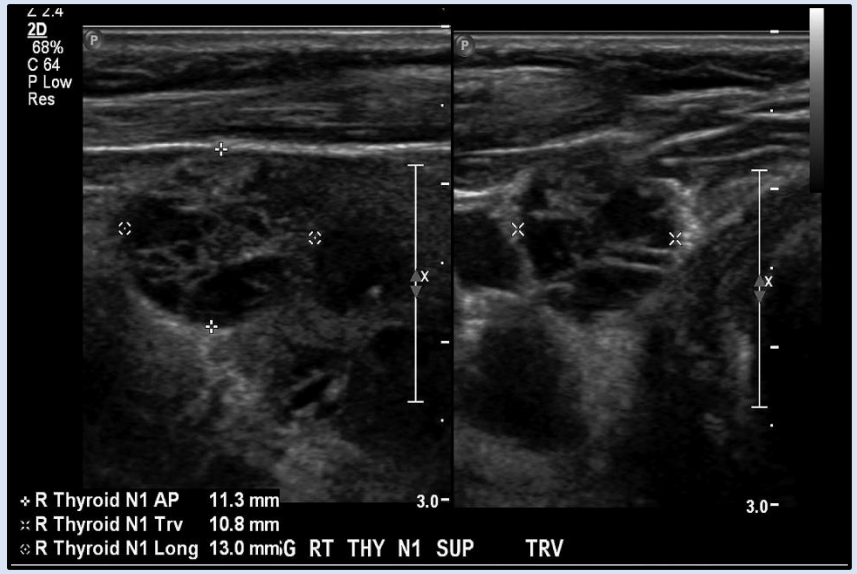


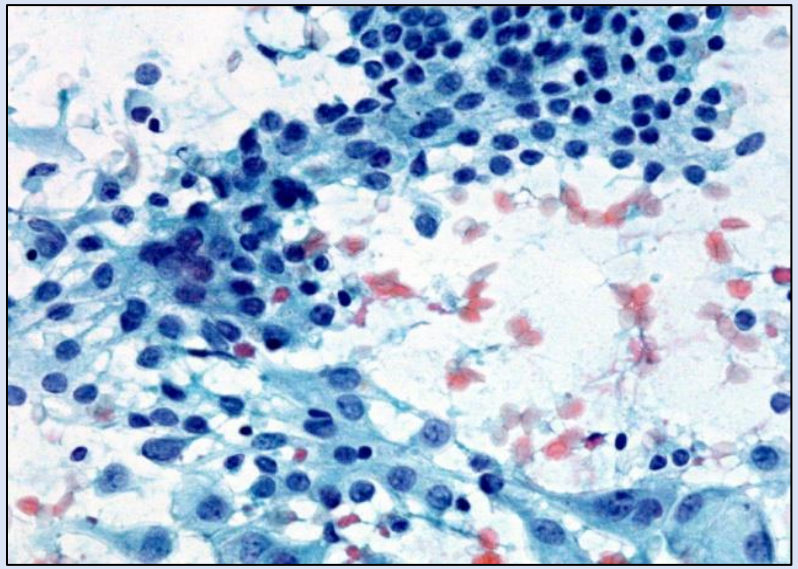


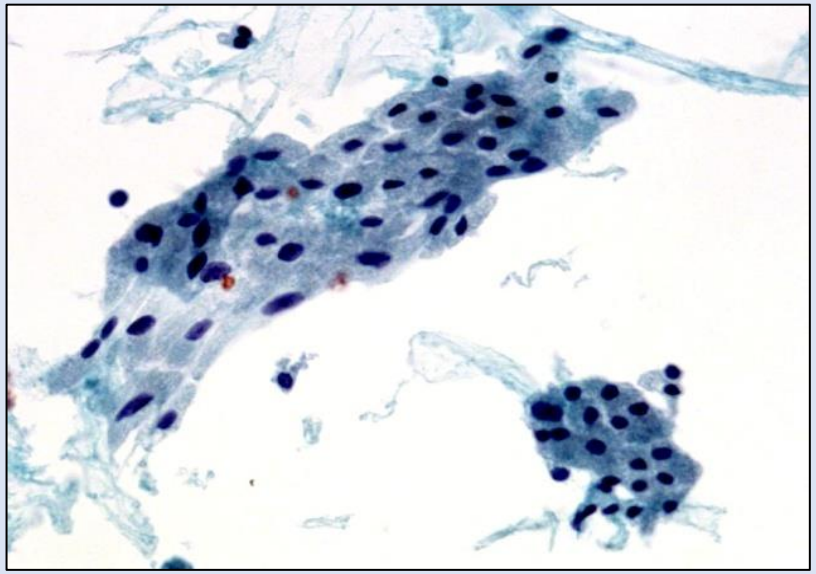
Adenomatous Nodule

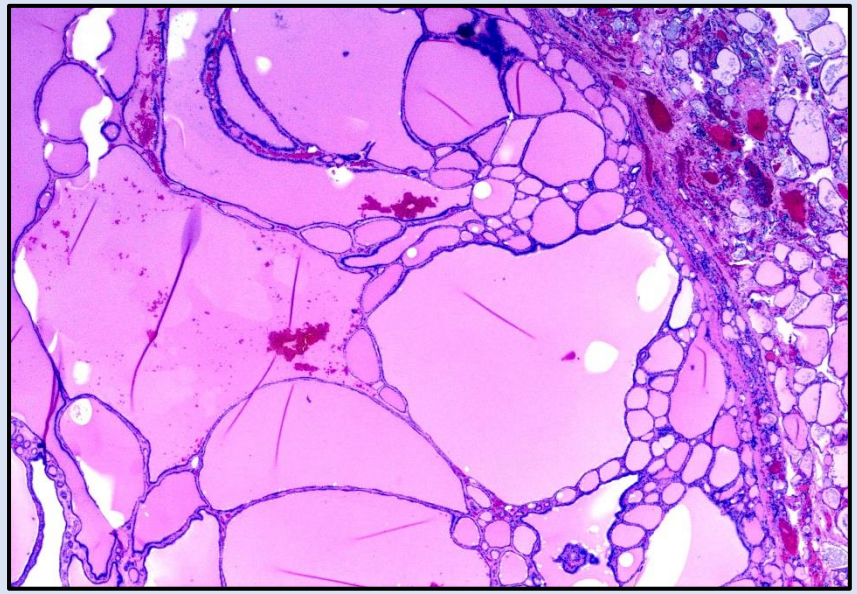
Colloid: Generally abundant . **Follicular cells** Variable morphology **.Oncocytes, Macrophages**

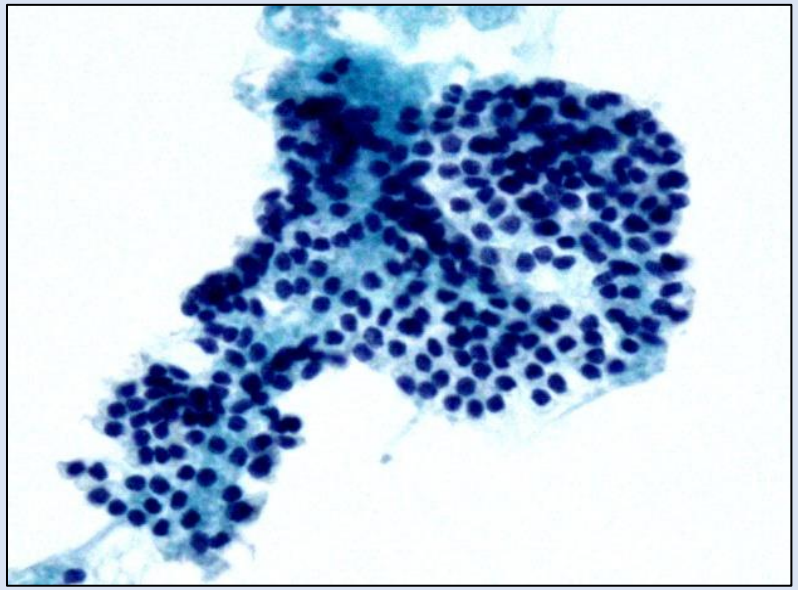
Degeneration/regeneration: Calcification, stromal proliferation, mitoses

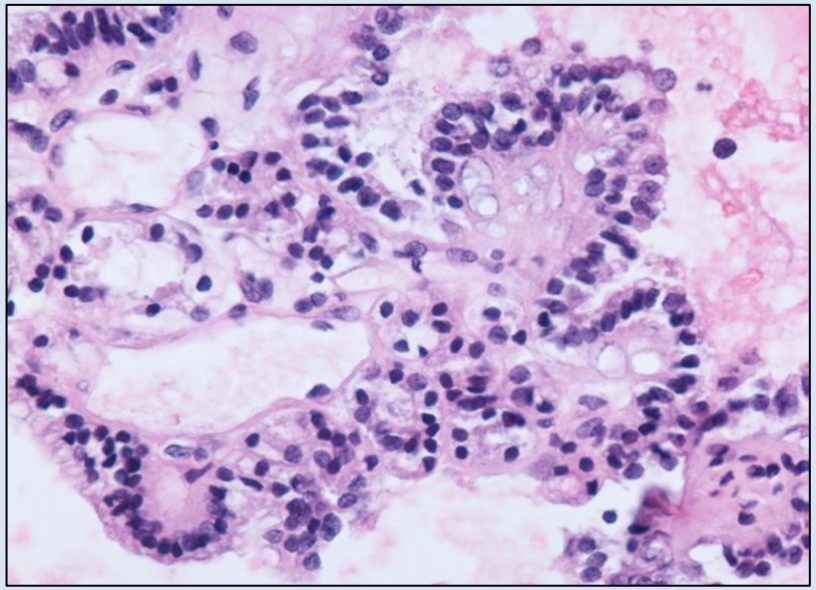




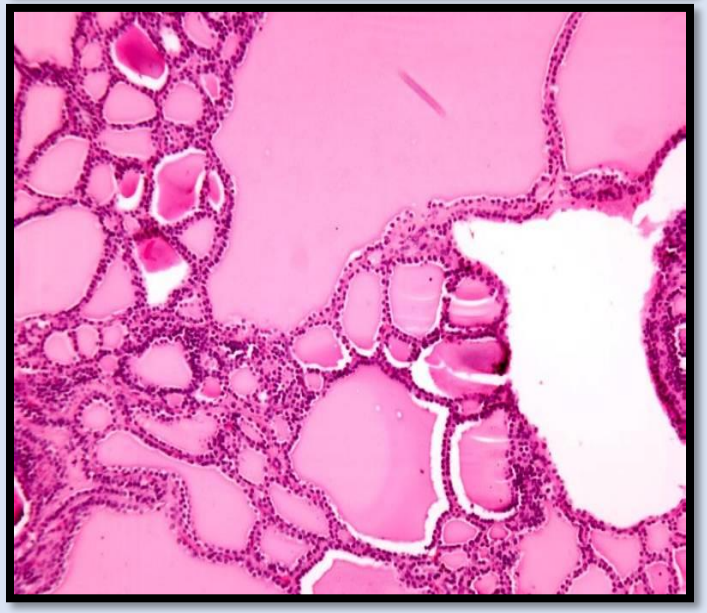


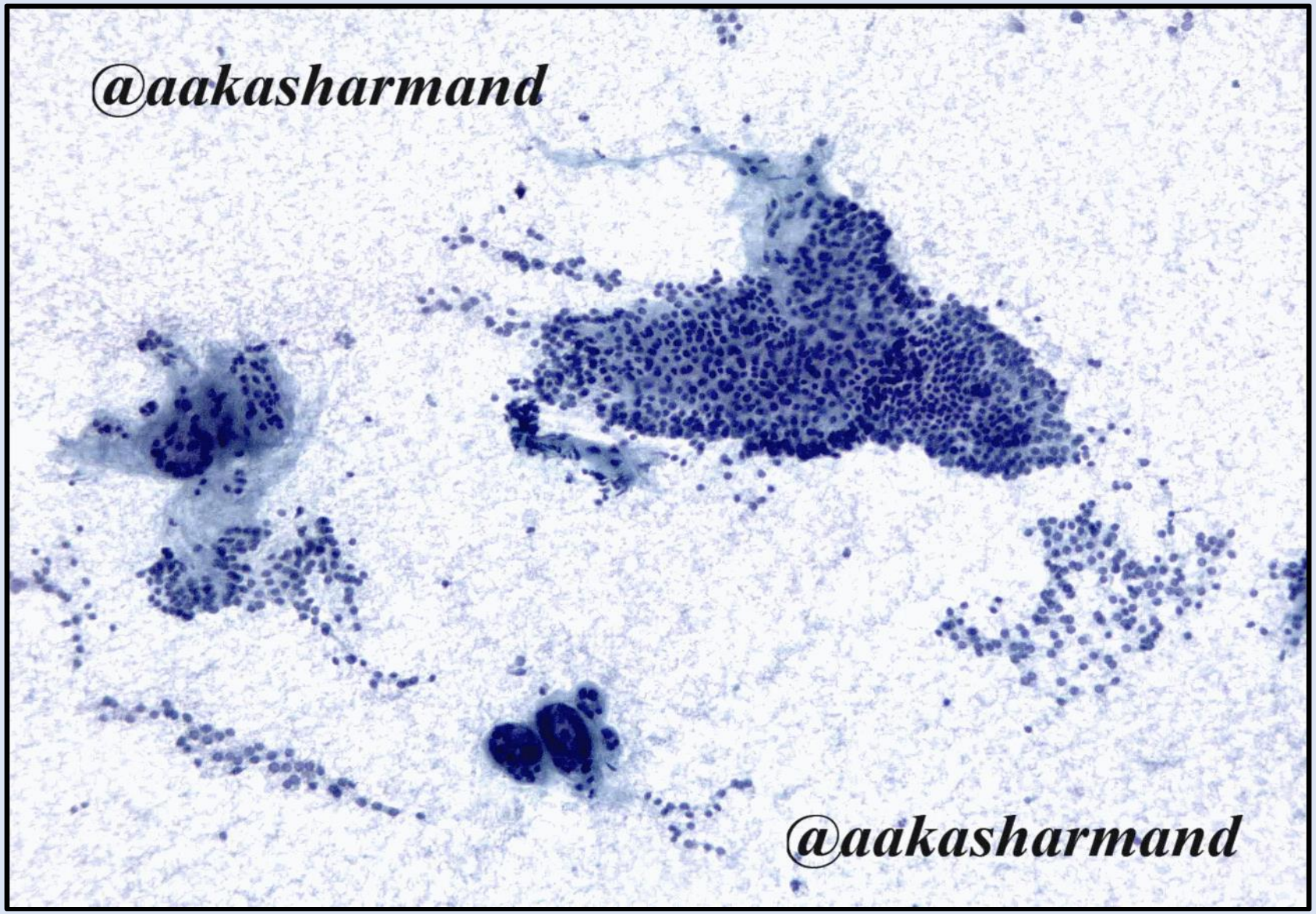






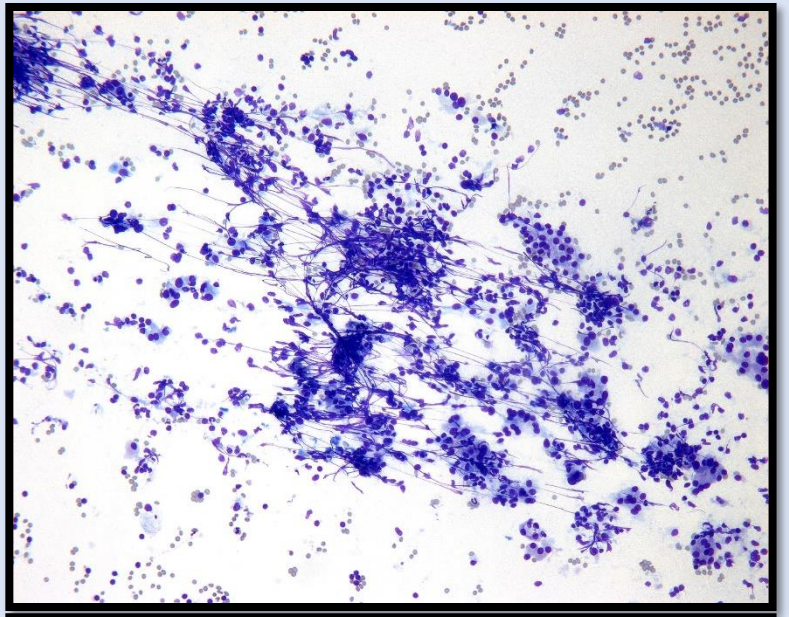
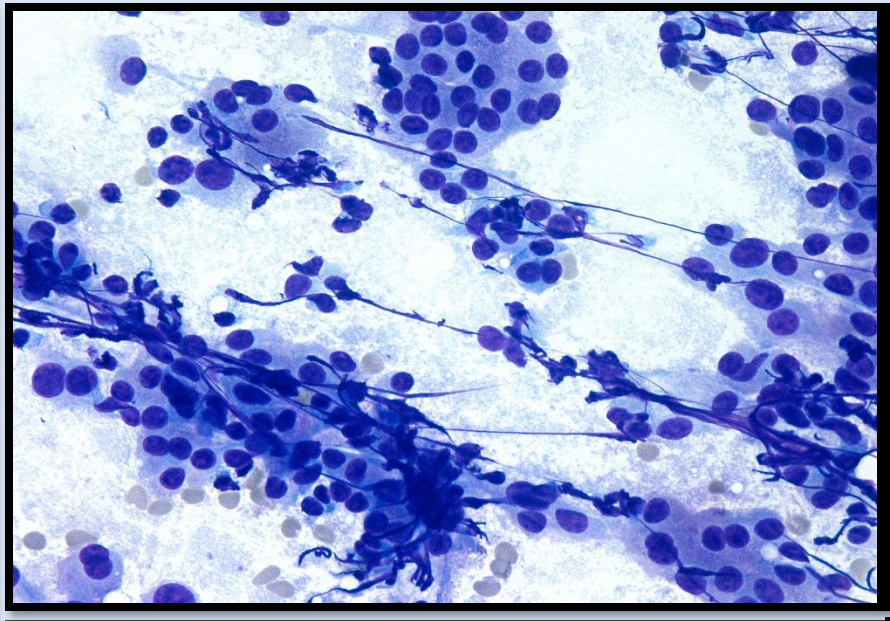
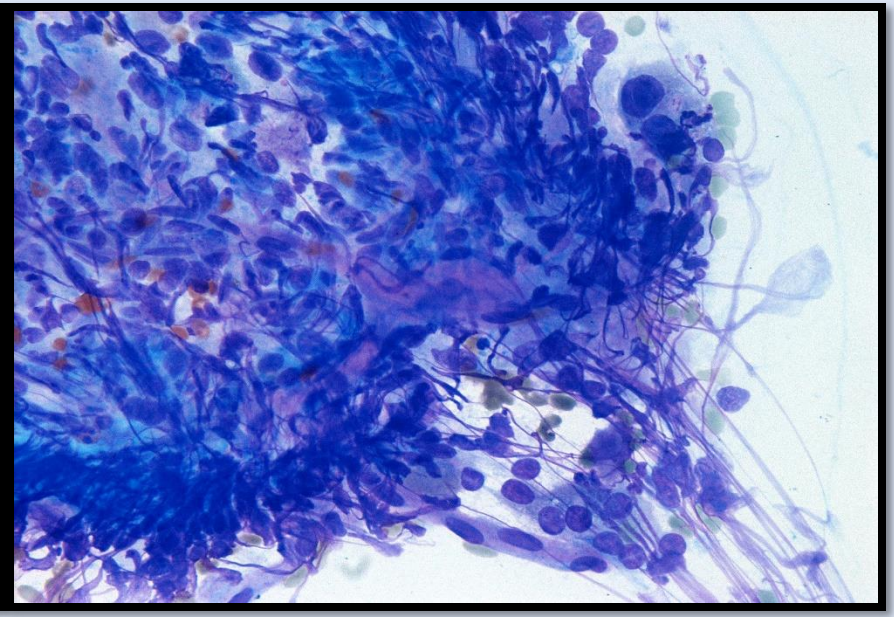
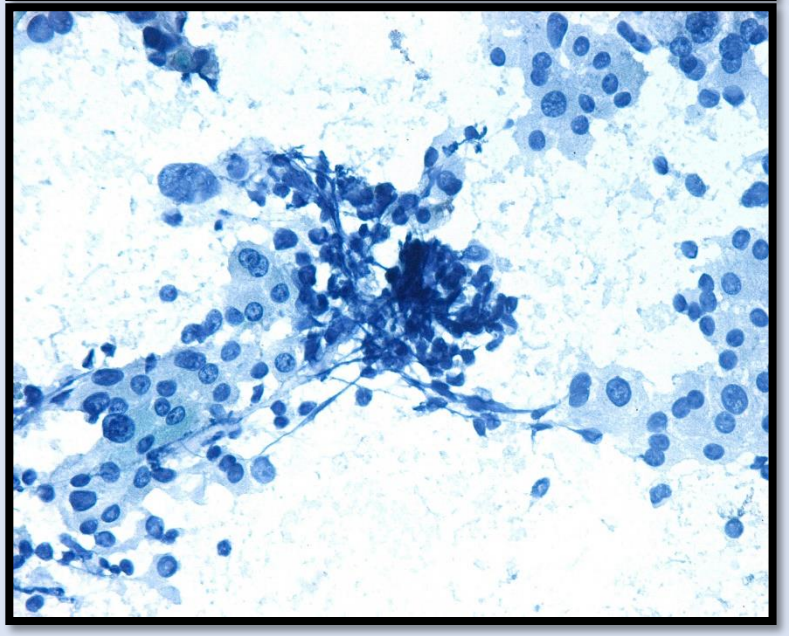
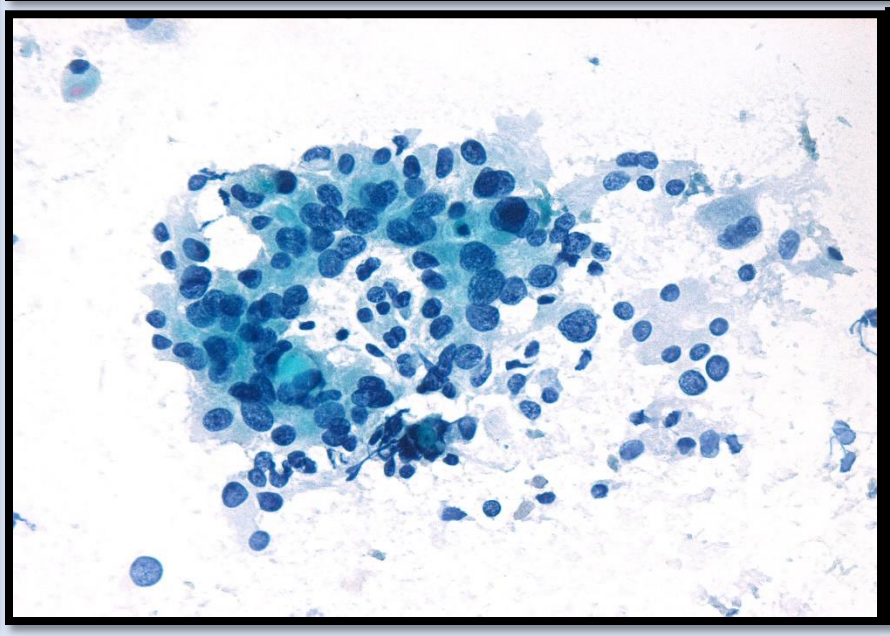
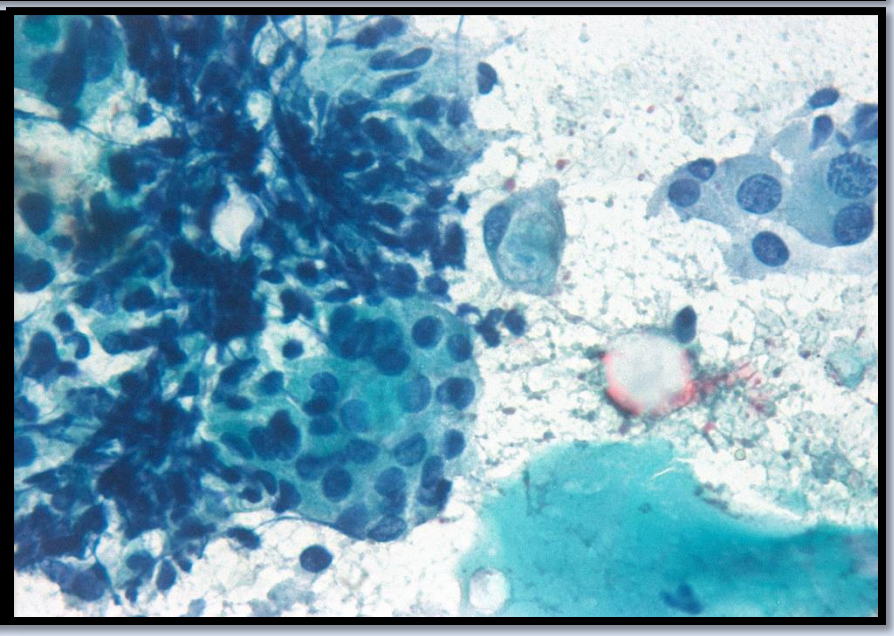
Hyperplastic Nodule - Heterogeneous Morphology





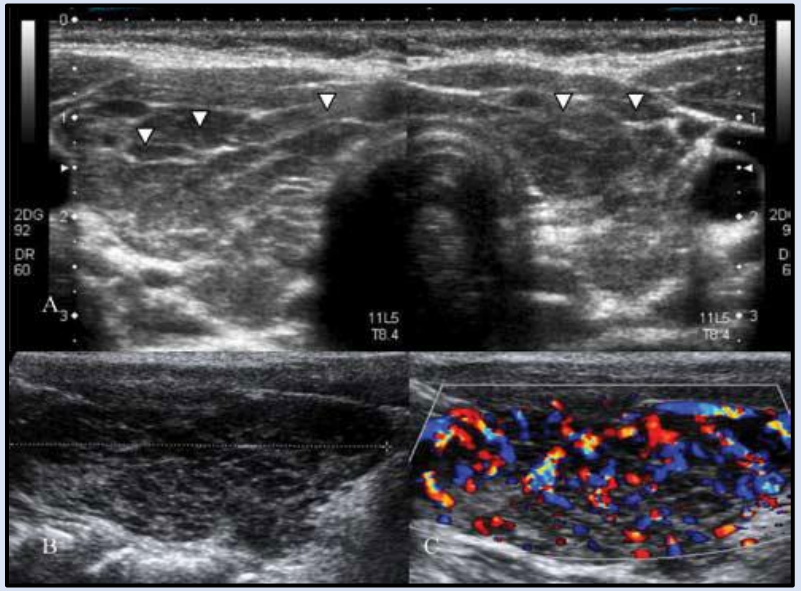
Chronic Lymphocytic Thyroiditis

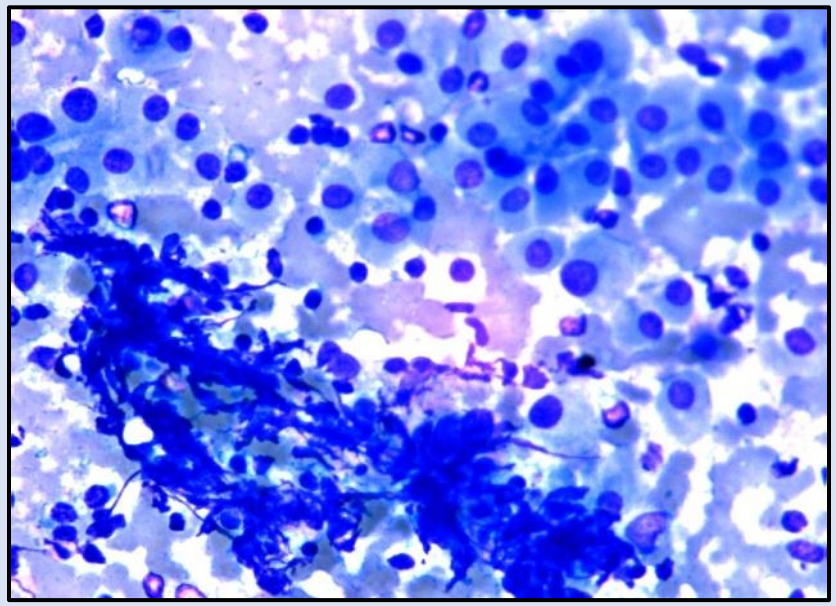
Oncocytes + Lymphocytes. Lymphocytes In the background & infiltrating the cell groups

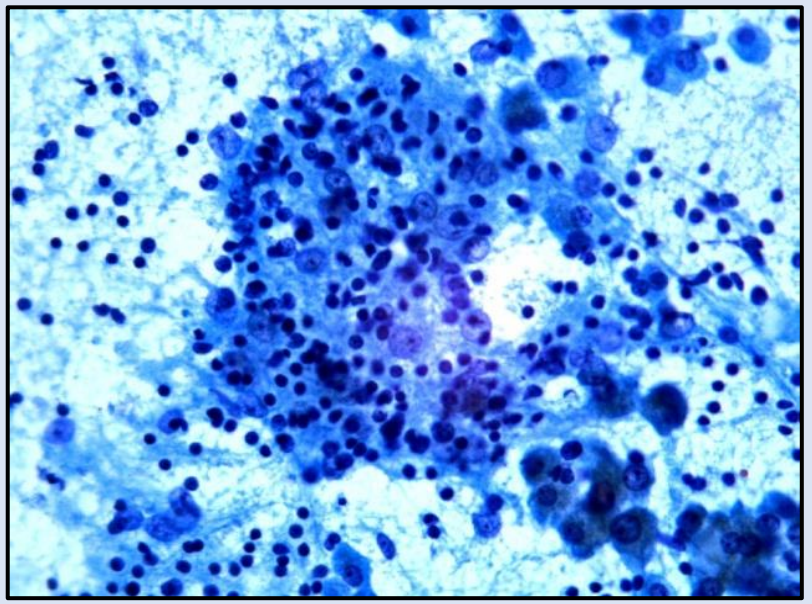







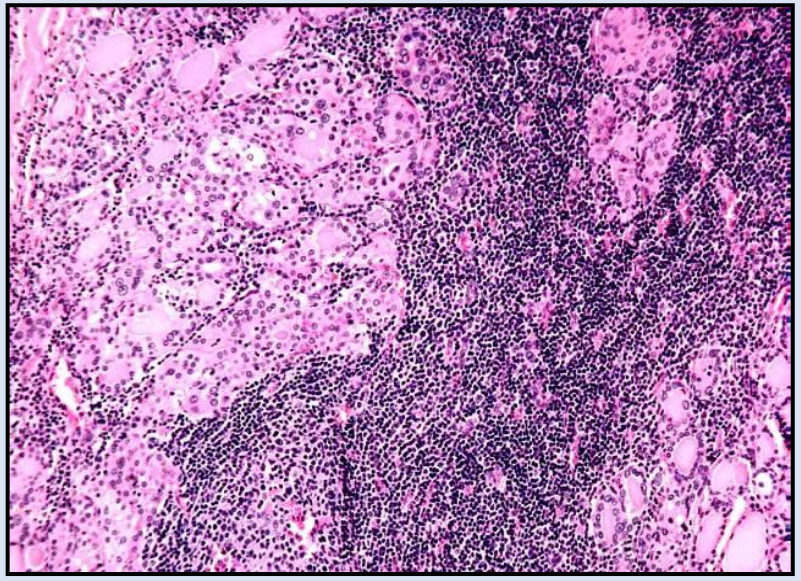
Chronic Lymphocytic Thyroiditis

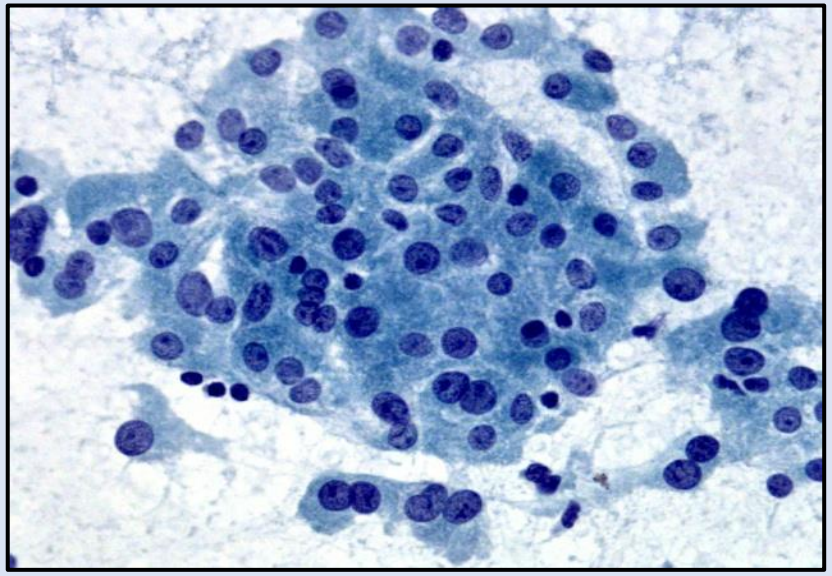
Oncocytes + Lymphocytes: In the background & infiltrating the cell groups

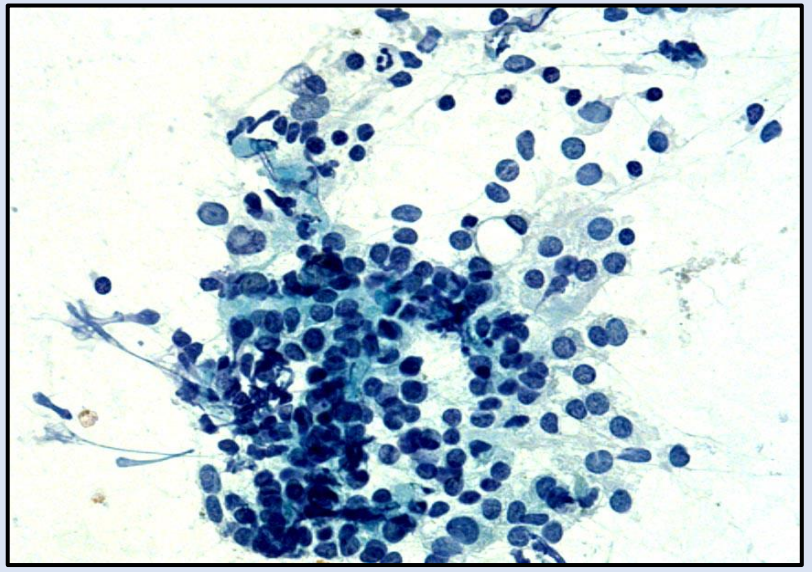








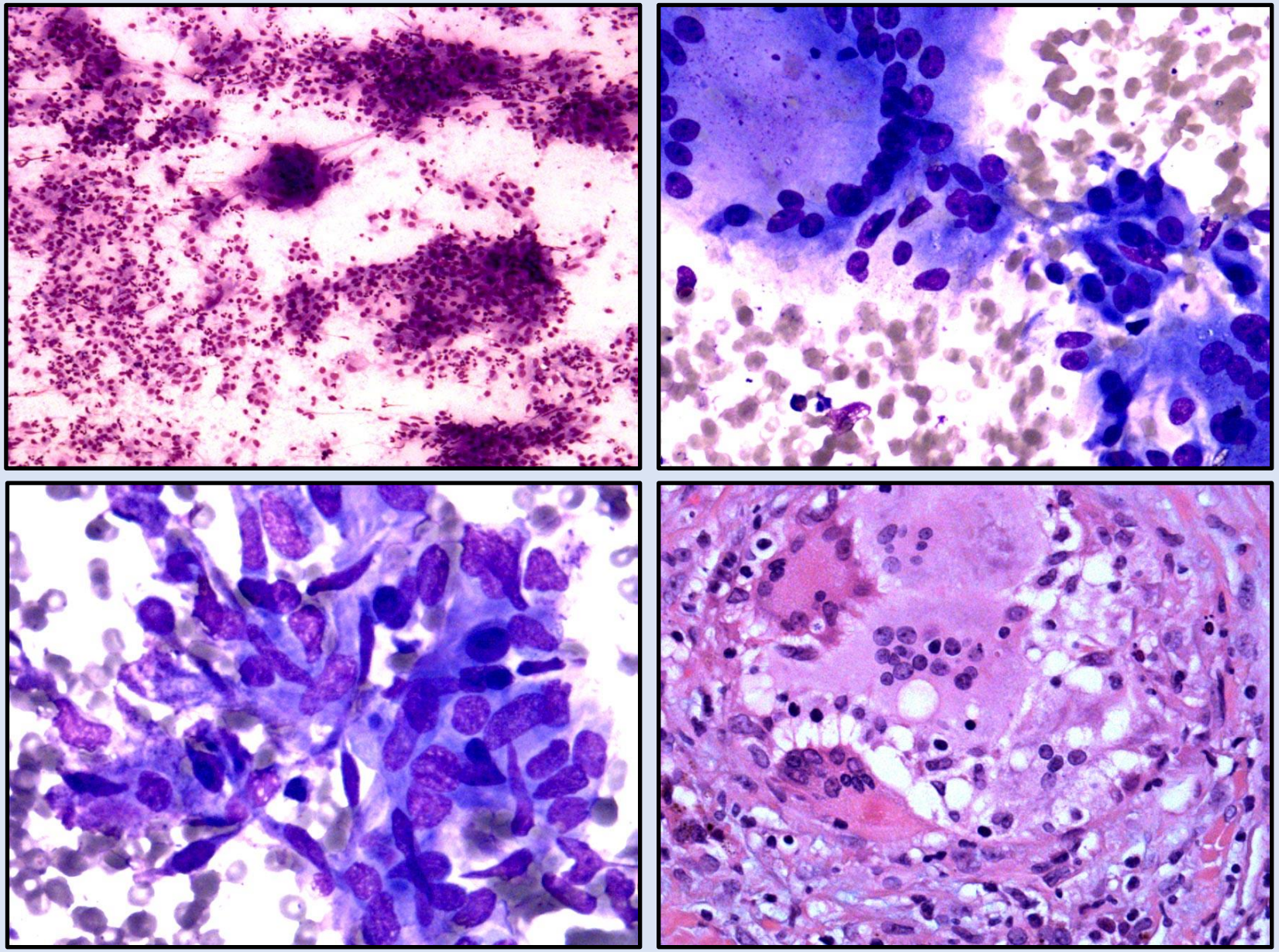




Subacute Thyroiditis (GranulomatousThyroiidtis)

- **Most Relevant is history**
  - **Painful enlargement of thyroid, usually bilateral**

- **Cytologic Findings**
  - Plump transformed follicular cells
  - Epitheloid granulomas
  - Multinucleated giant cells (97.2%)
  - Follicular cells with intra-vacuolar granules (77.7%)
  - Mature lymphocytes (100%)
  - Macrophages (100%)
  - Neutrophils (88.8%)
  - Oncocytic cells
  - Fire-flare follicular cells

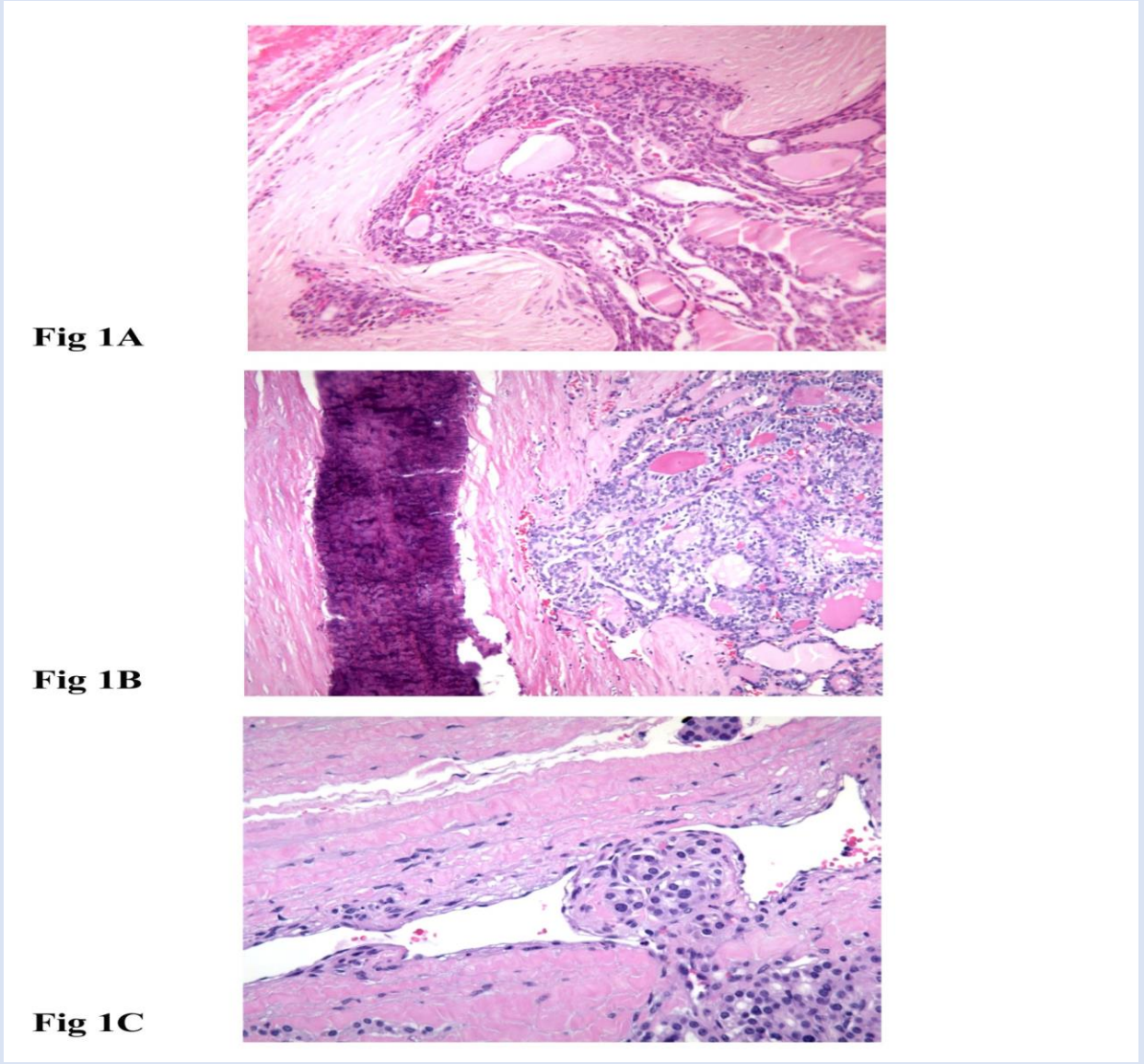


Follicular Patterned Lesions/Neoplasms of The Thyroid Gland

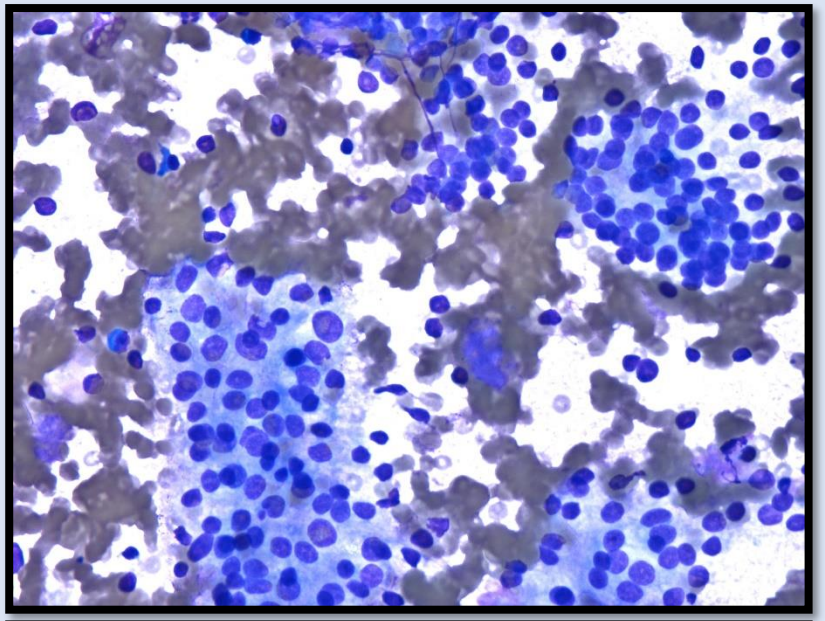
- **Adenomatous Nodule (Follicular Nodular Disease)**
- **Follicular Adenoma**
- **Follicular Lesion of Uncertain Malignant Potential**
- **Non-invasive Follicular Tumor with Papillary Like Nuclear Features (NIFTP)**
- **Follicular Thyroid Carcinoma**
- **Follicular Variant of Papillary Thyroid Carcinoma**

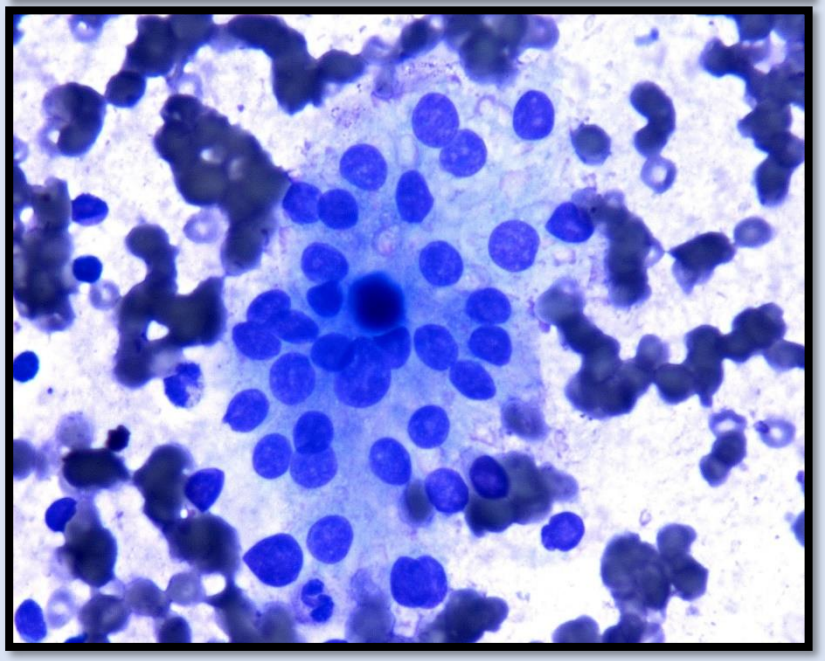
Follicular Patterned Lesions/Neoplasms of the Thyroid Gland

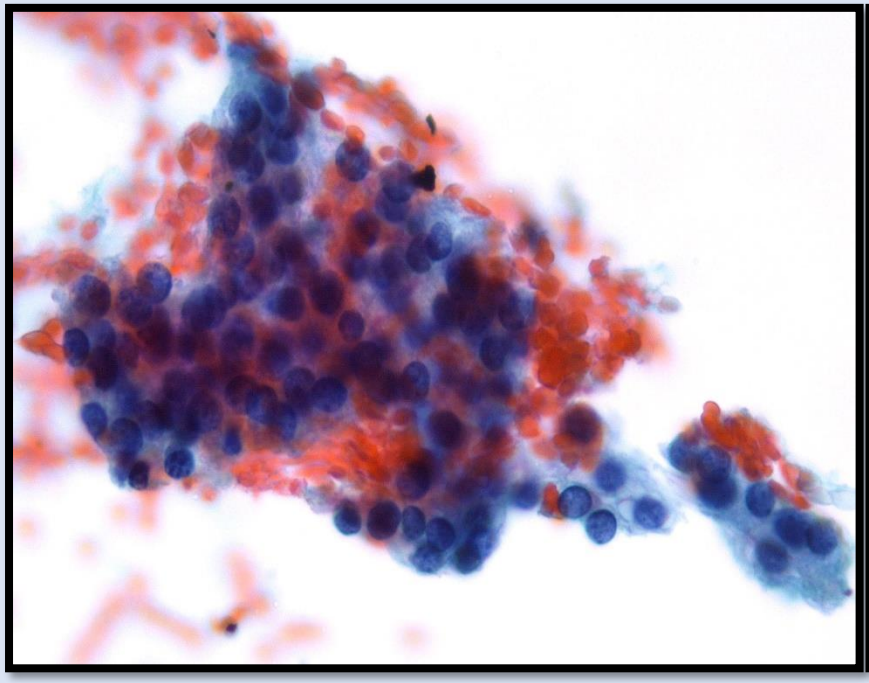
- Cytology – Reality Check
  - Cannot differentiate between follicular adenoma and carcinoma
  - Most are diagnosed as “Follicular Lesion / Neoplasm”
  - Up to 80% of cases diagnosed as such are benign on histologic examination (hyperplastic nodule or adenoma)
  - Approximately half of malignant cases are **NIFTP**

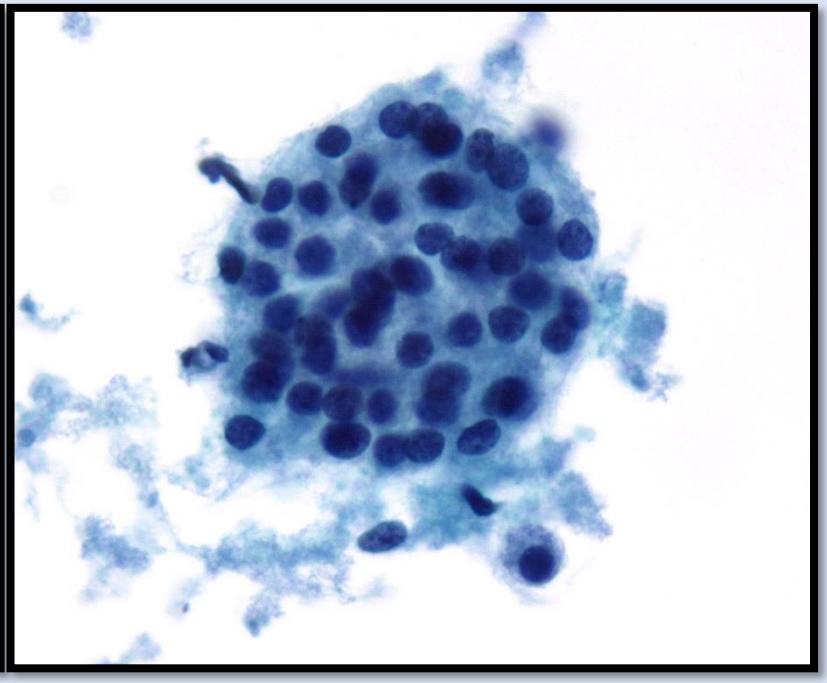


Cellular Follicular Patterned Lesion – AUS vs. Follicular Neoplasm

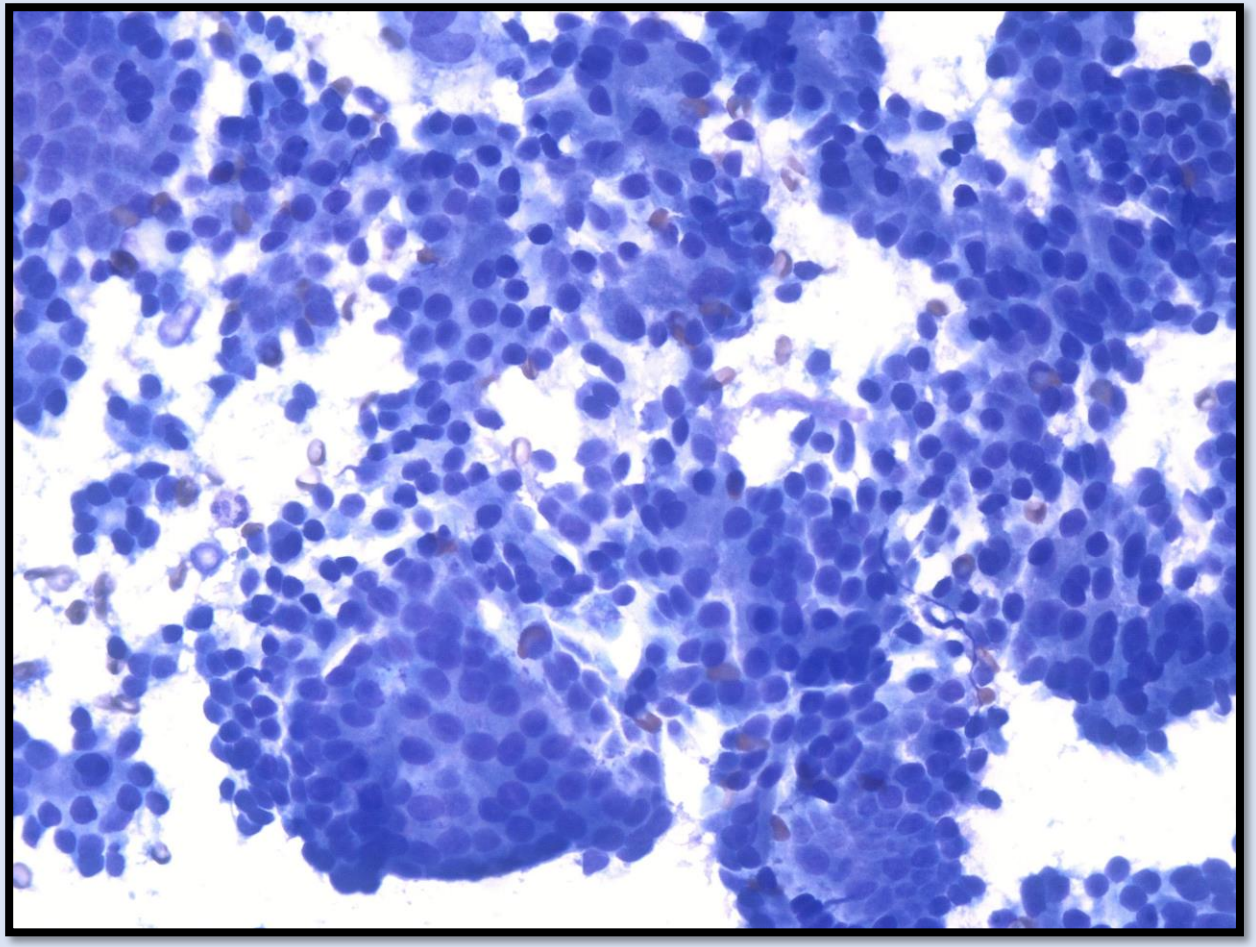


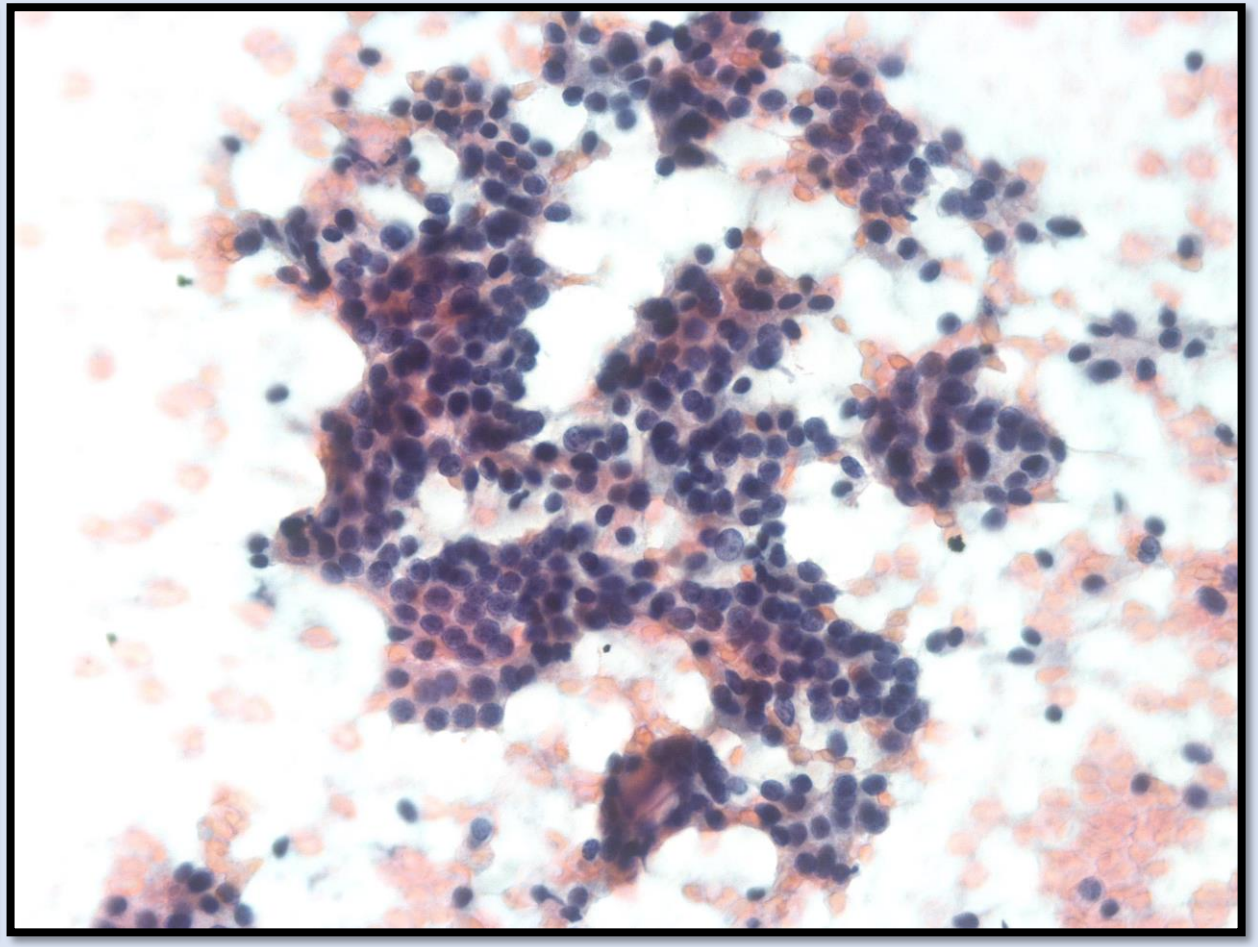




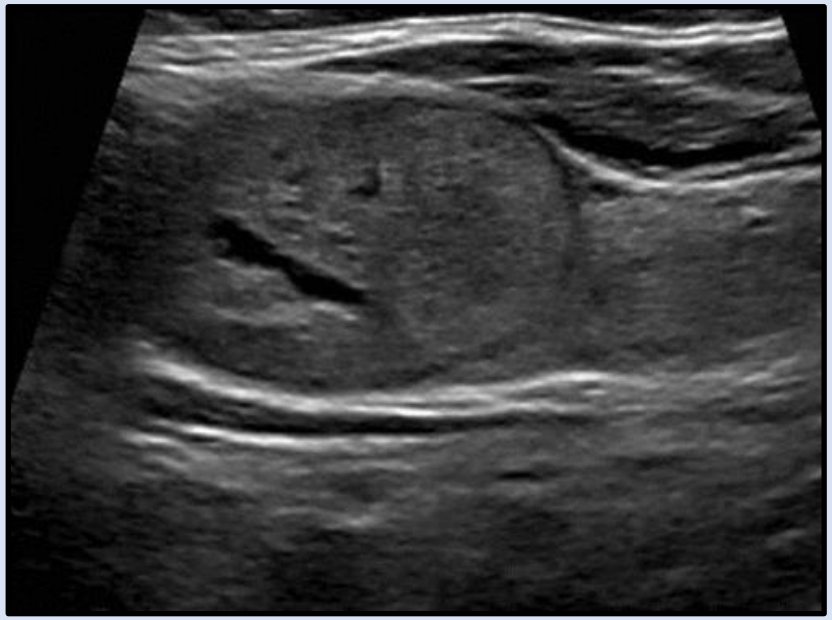


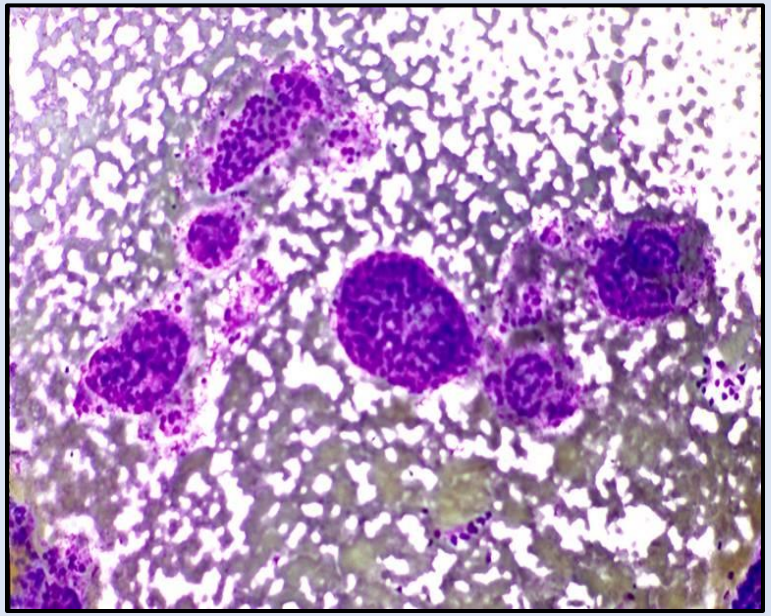
Cellular Follicular Patterned Lesion – Follicular Neoplasm

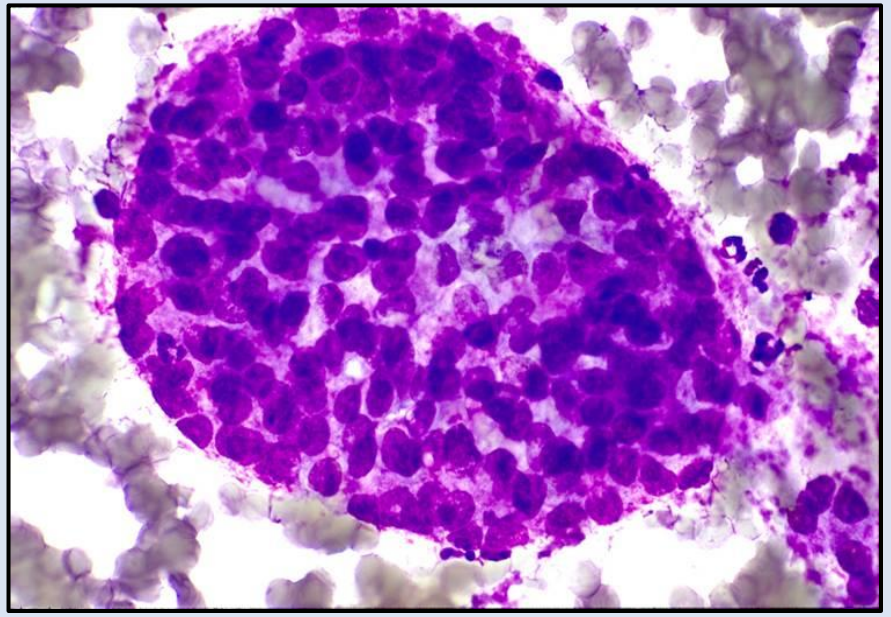


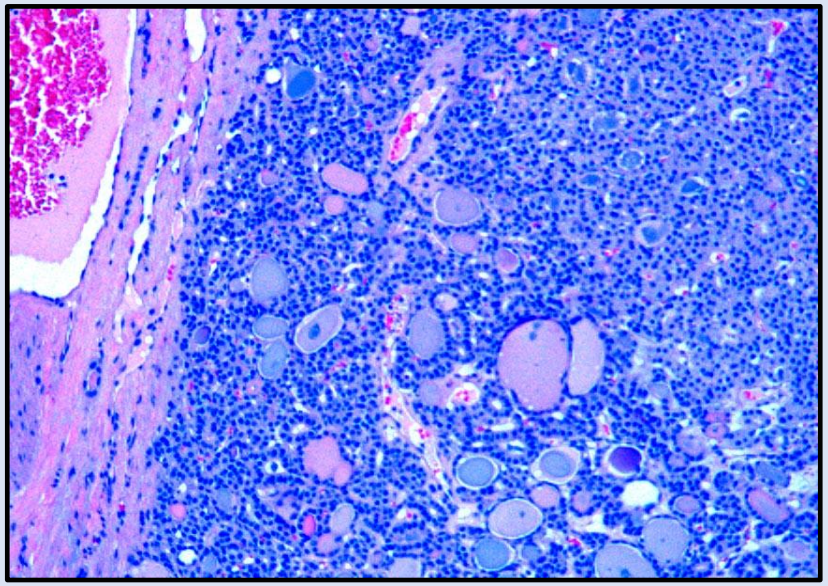


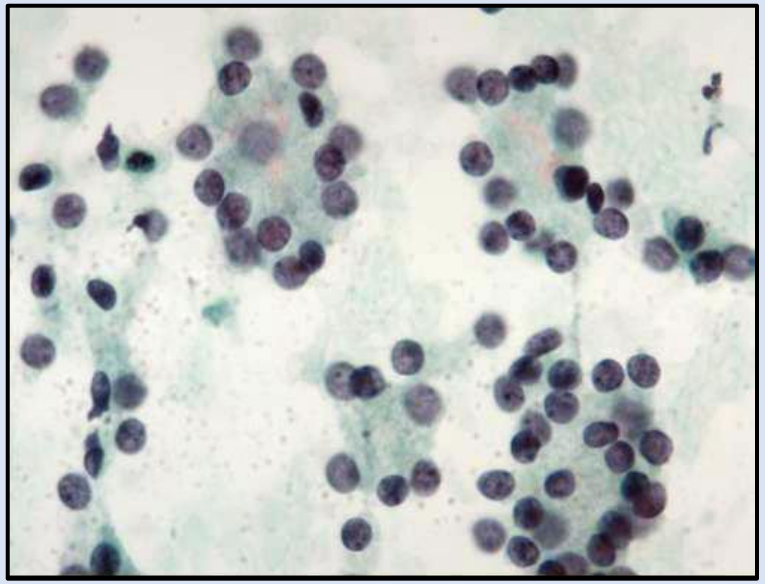
Follicular Neoplasm

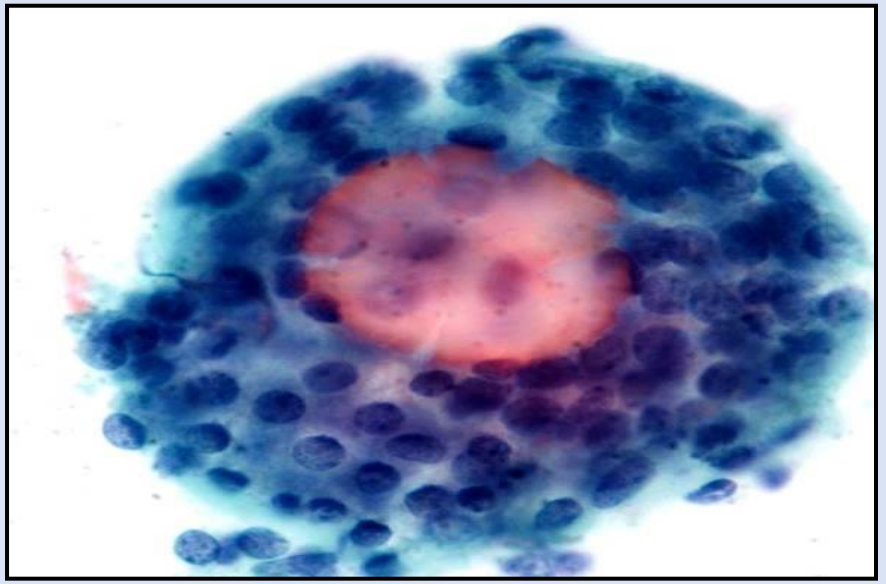






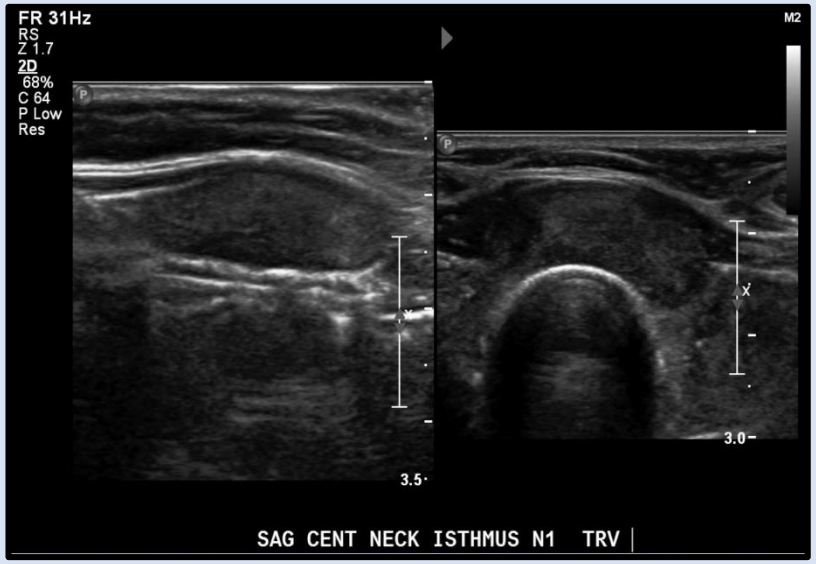


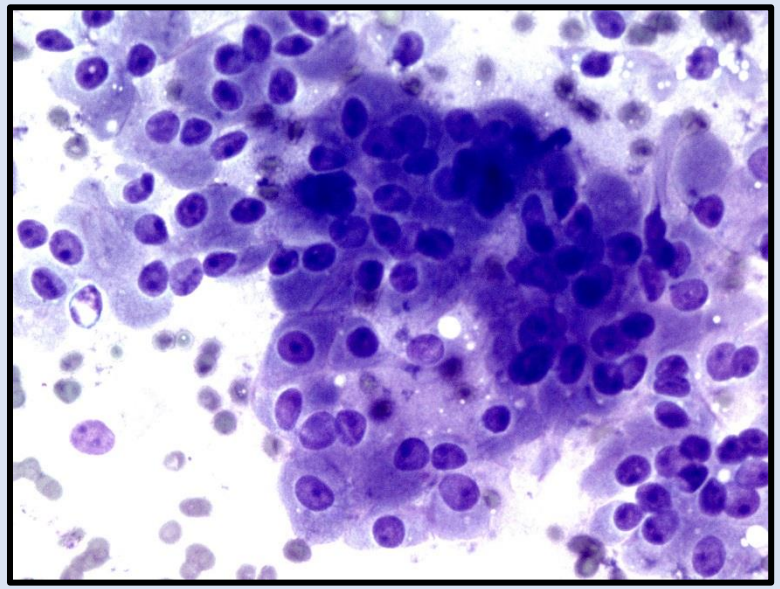


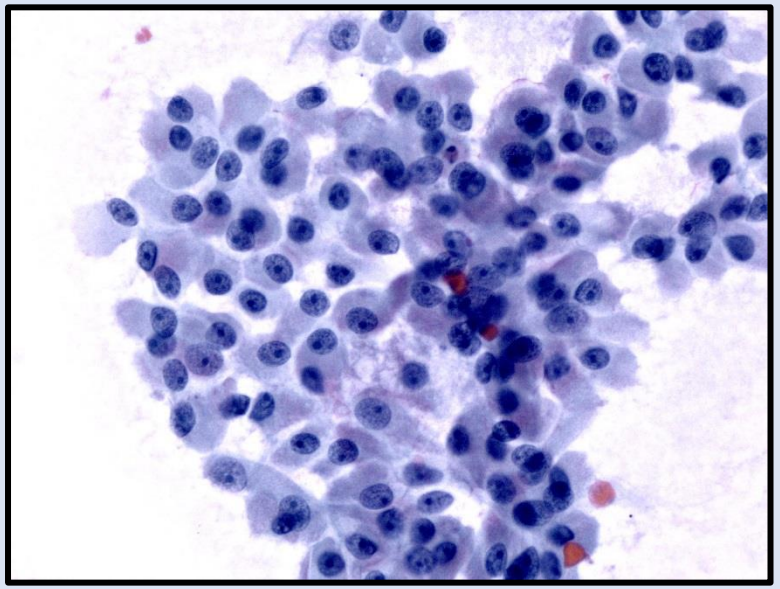


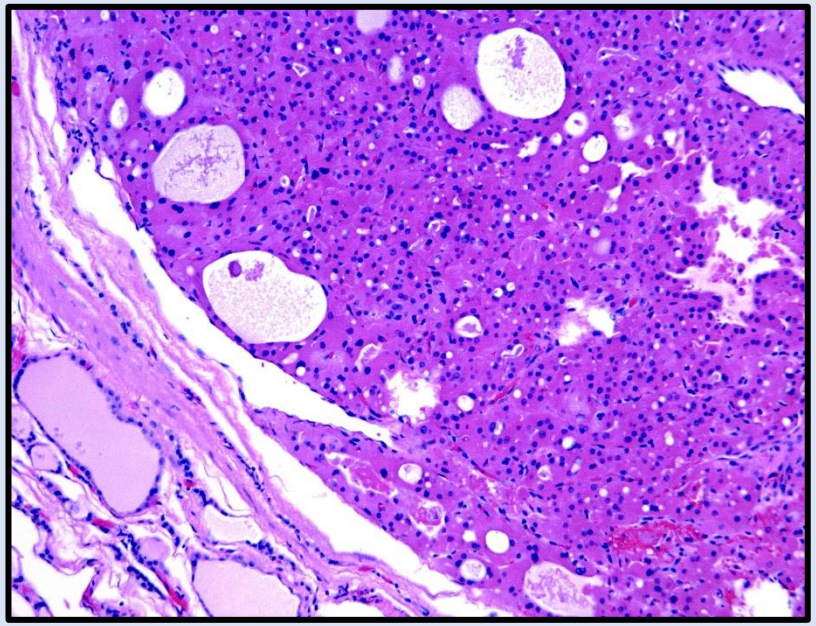
Follicular Neoplasm-Oncocytic (Hurthle Cell)

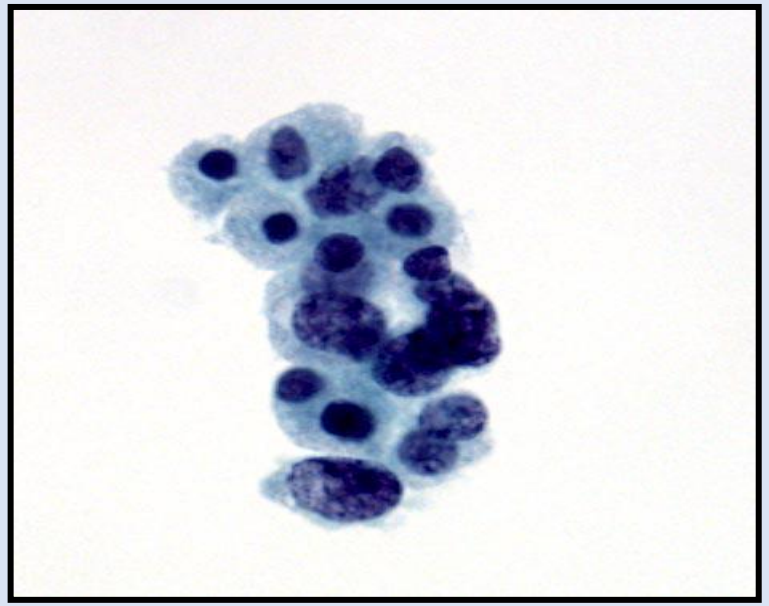
Cellular specimen. *Monotonous population of oncocytic follicular cells. Singly scattered cells. Transgressing vessels. Can have enlarged nuclei with prominent nucleoli.*

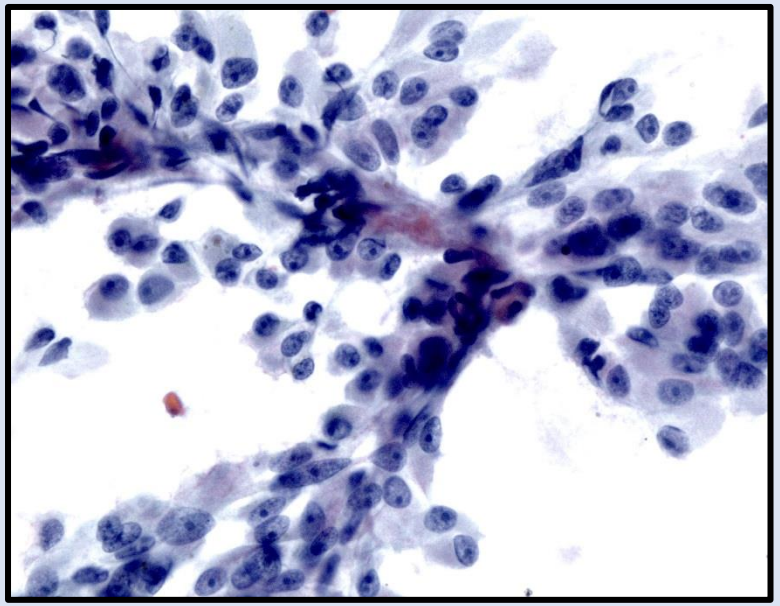












Suspicious for Malignancy

Diagnosis Suspicious for (Papillary Thyroid Carcinoma)

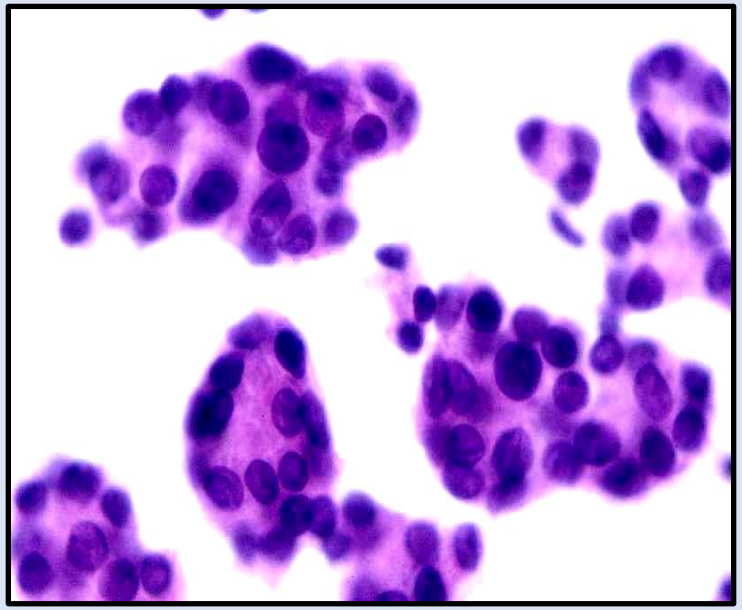
Focal nuclear features of papillary carcinoma

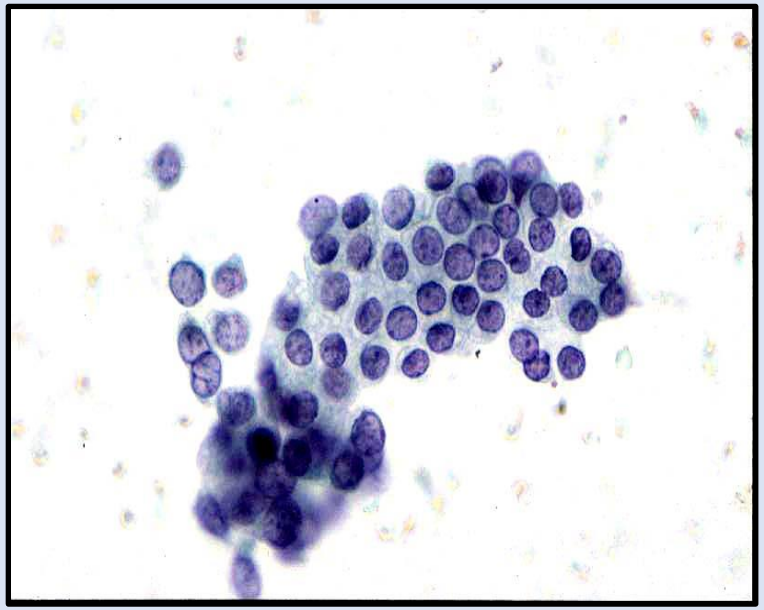
1. Diagnosis suspicious for papillary carcinoma
2. Up to 60-75% cases are malignant on histologic follow-up.
3. Most of the PTC cases are follicular variant of PTC, now **>50%**
   NIFTP

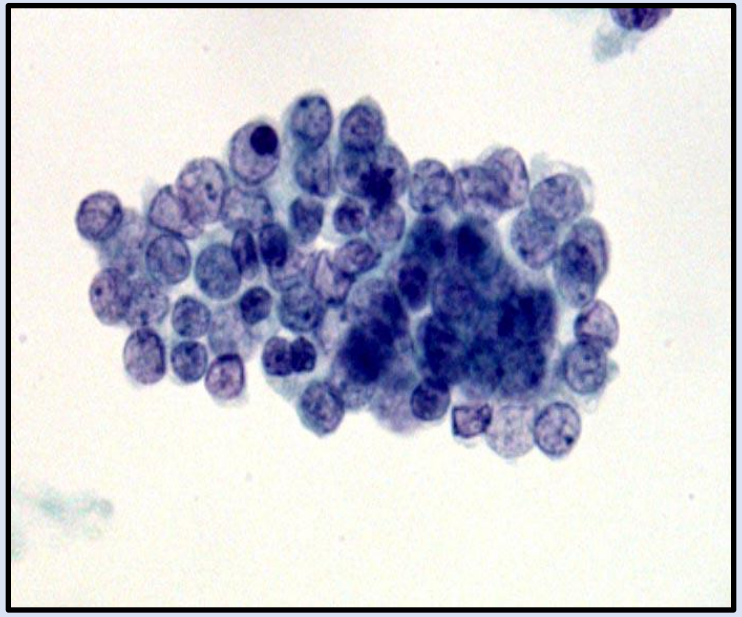
Suspicious for Papillary Thyroid Carcinoma Cytology

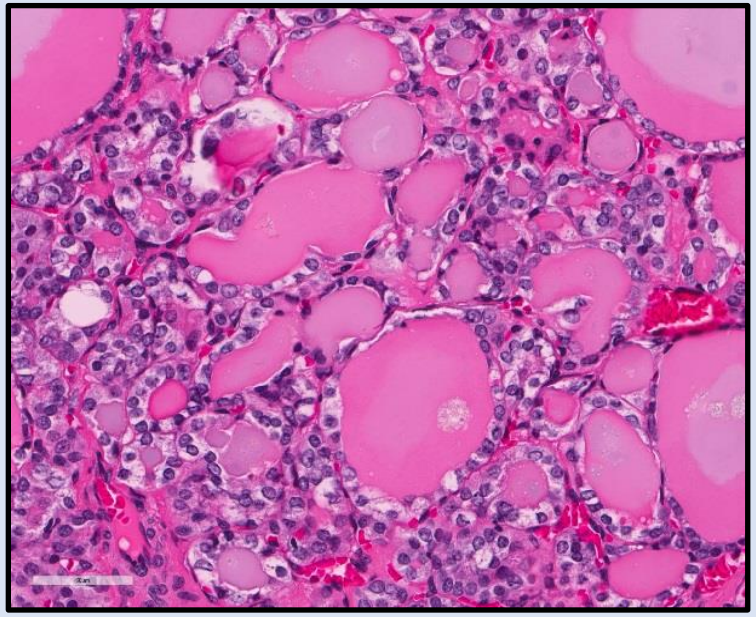
- ***Cytologic Features***

- Colloid (thick & watery)
- Monolayer sheets and follicle formation
- Paucity of nuclear features of Pap ca
  - Elongated nuclei
  - chromatin clearing and nuclear membrane thickening
  - Nuclear grooves and rare to no inclusions
- Macrophages

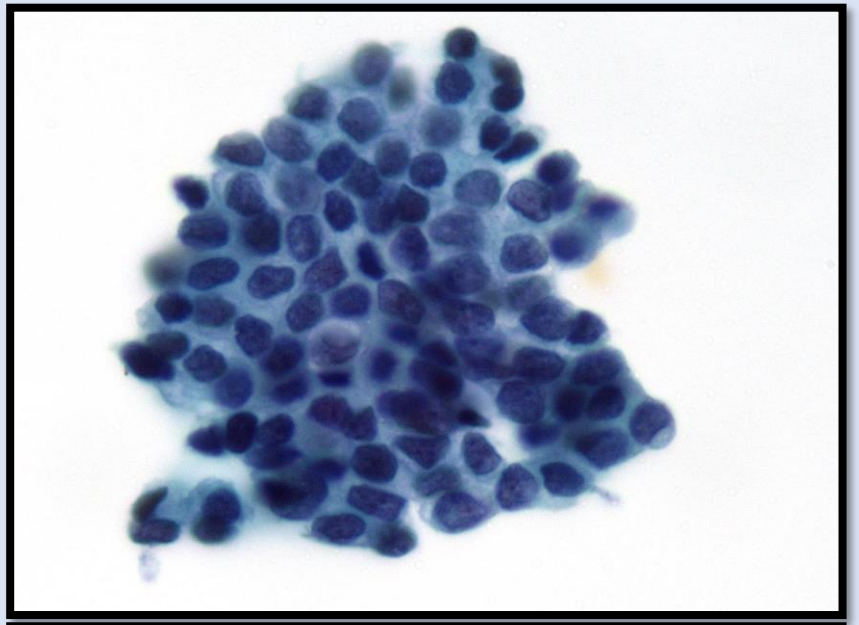


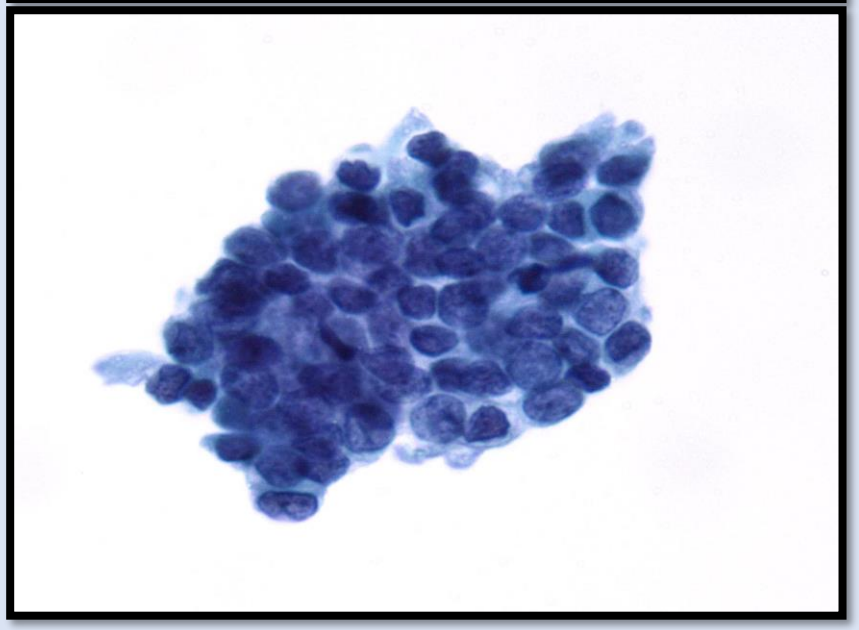


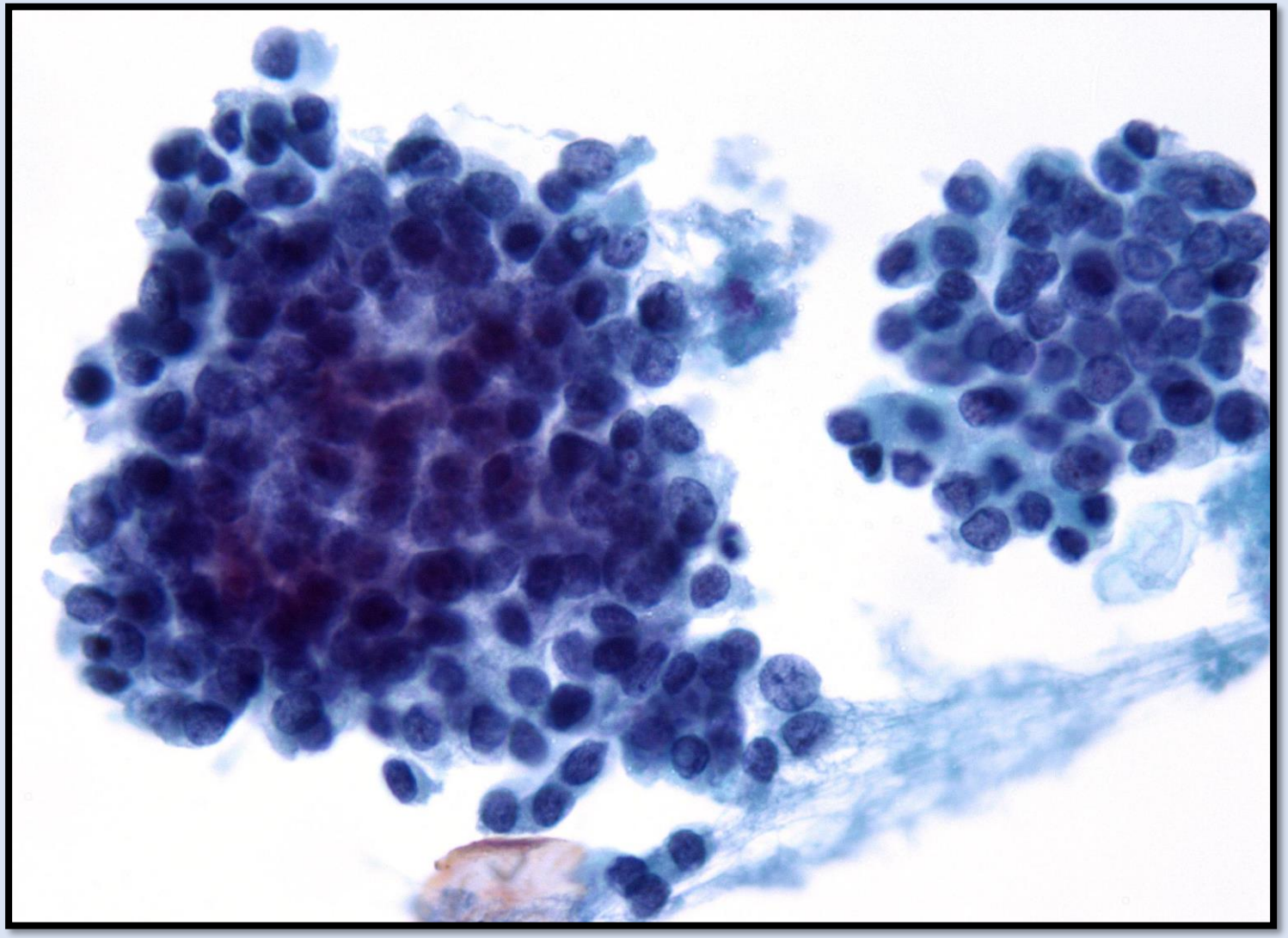




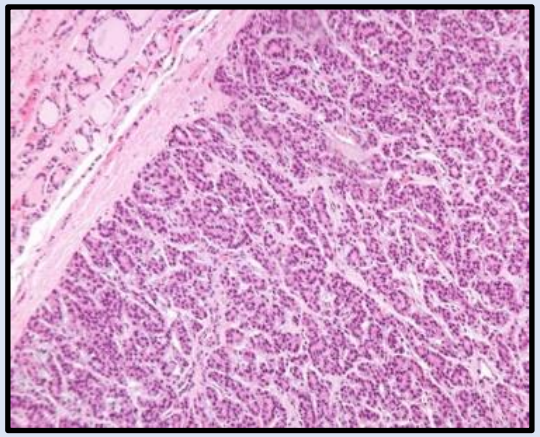
Suspicious for Papillary Thyroid Carcinoma





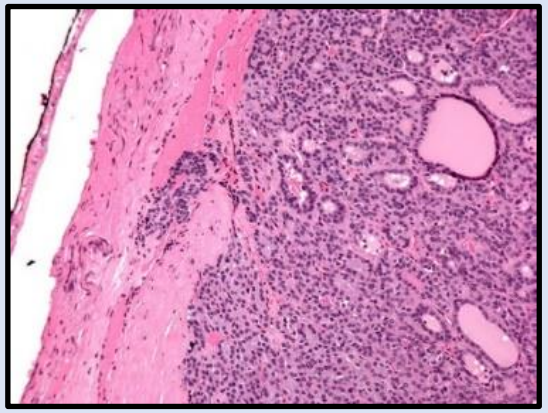


Reclassifying Encapsulated / Well-Demarcated Follicular Patterned Lesions - 2016



Follicular Adenoma

Non-Invasive



Follicular Carcinoma

Invasive (Tumor Capsule & Vascular Invasion)

Nuclear Features of PTC Absent

Nuclear Features of PTC Present

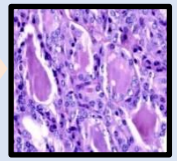
NIFTP

Well Demarcated

Solid and cystic

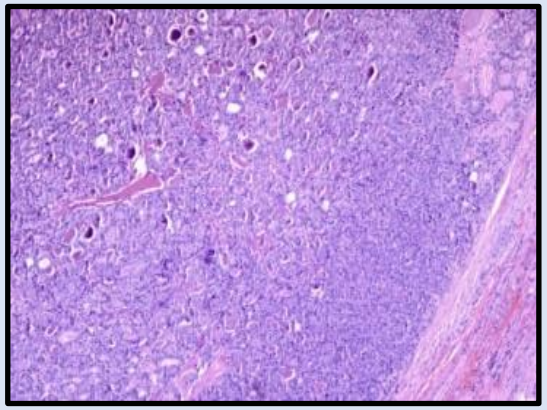
Usually mixed follicular growth pattern

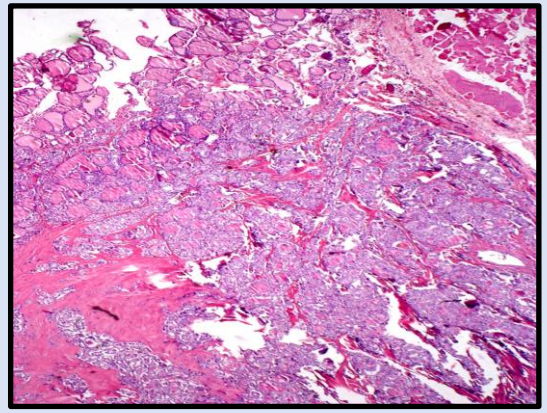
Isolated papillae comprising <1% of tumor mass



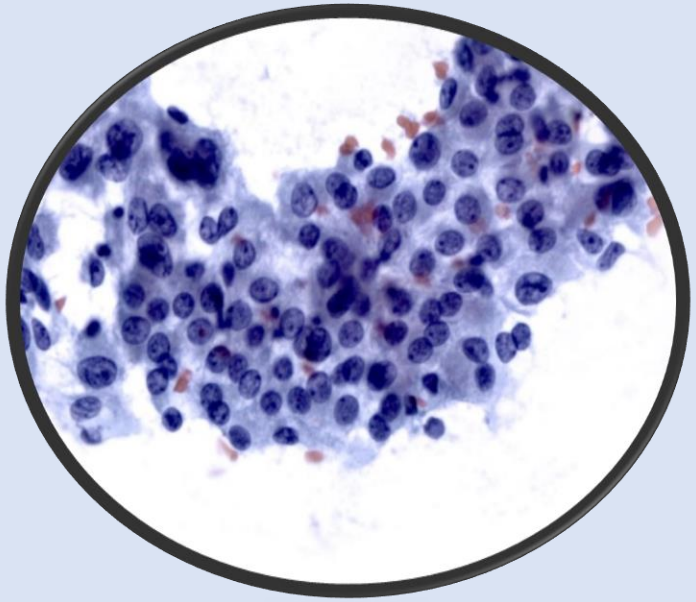
FVPTC

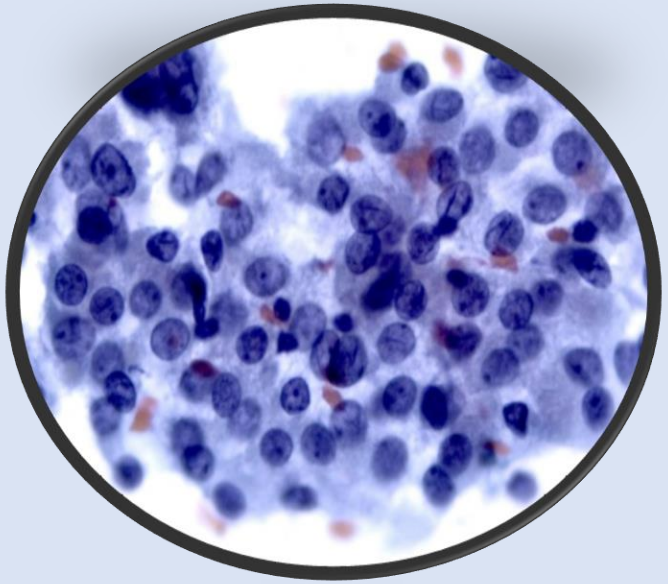
Invasive (Tumor Capsule & Vascular Invasion)

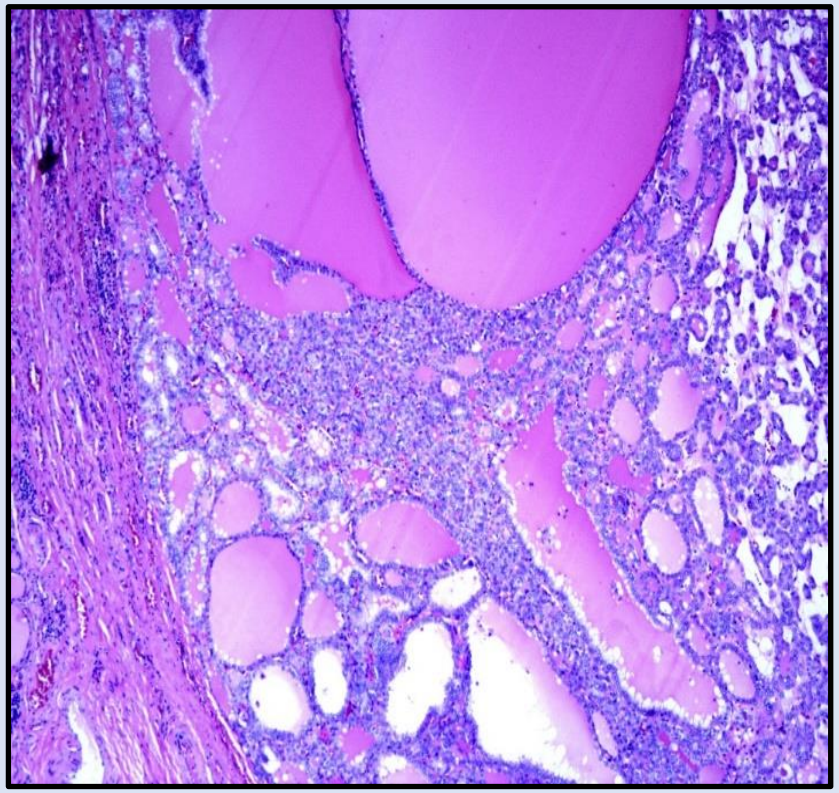


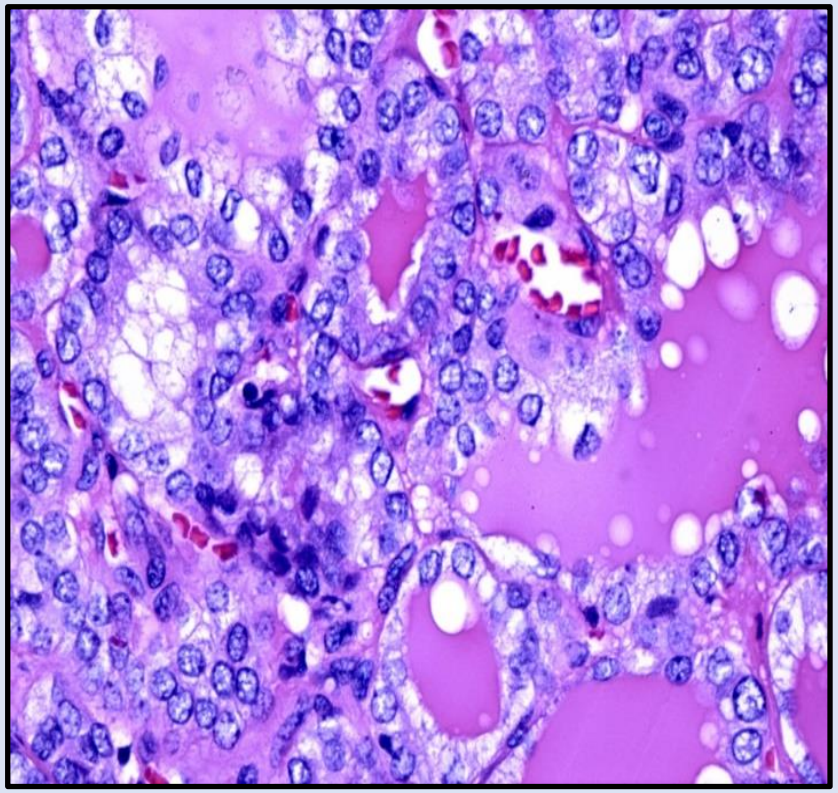


59-year-old hypothyroid woman, FNA of a 1.9 cm, isoechoic/hypoechoic thyroid nodule – Intermediate Suspicion on US









Follow-up NIFTP

Malignant

Papillary Thyroid Carcinoma

Medullary Thyroid Carcinoma

Anaplastic Thyroid Carcinoma

Secondary Tumors / Metastasis

Papillary Thyroid Carcinoma (PTC)
Salient Features

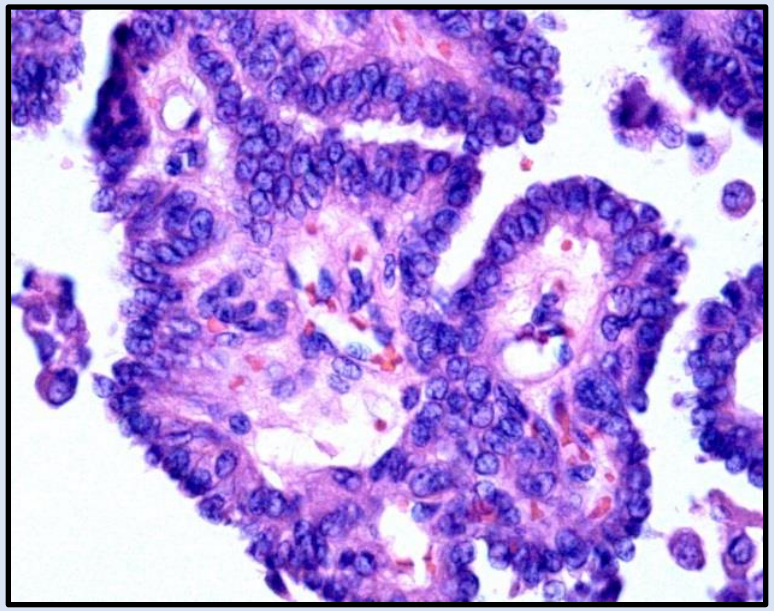
Nuclear features –Major Diagnostic Criteria

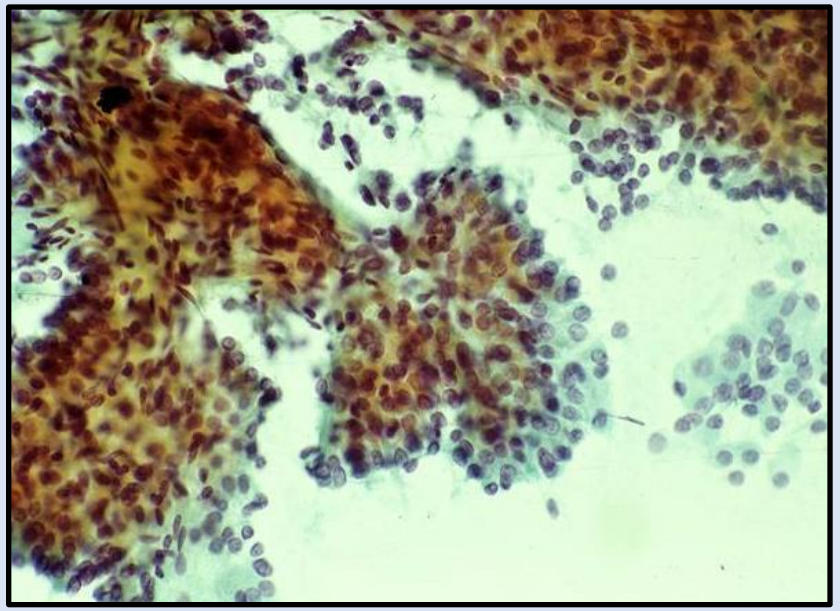
- Elongation, intranuclear grooves, chromatin clearing
- Cytoplasmic invagination and inclusions
- Small peripheral nucleoli

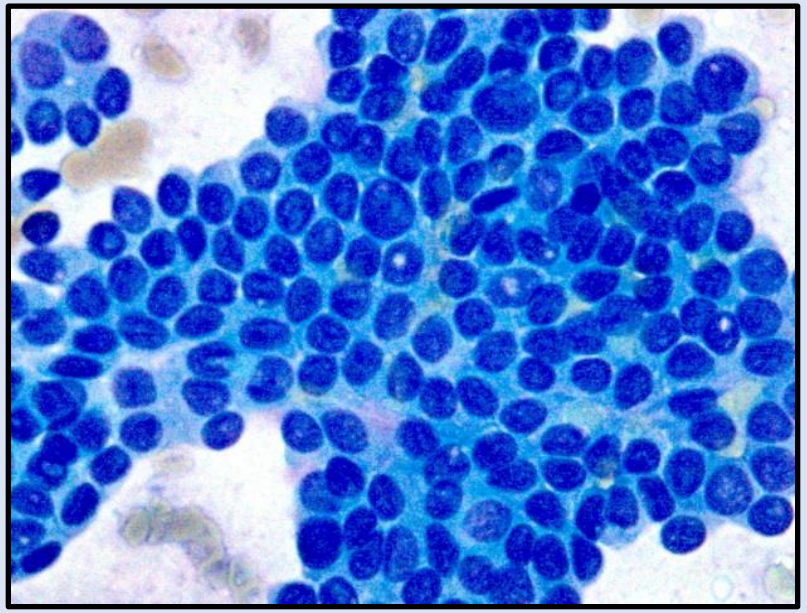
Additional Features:

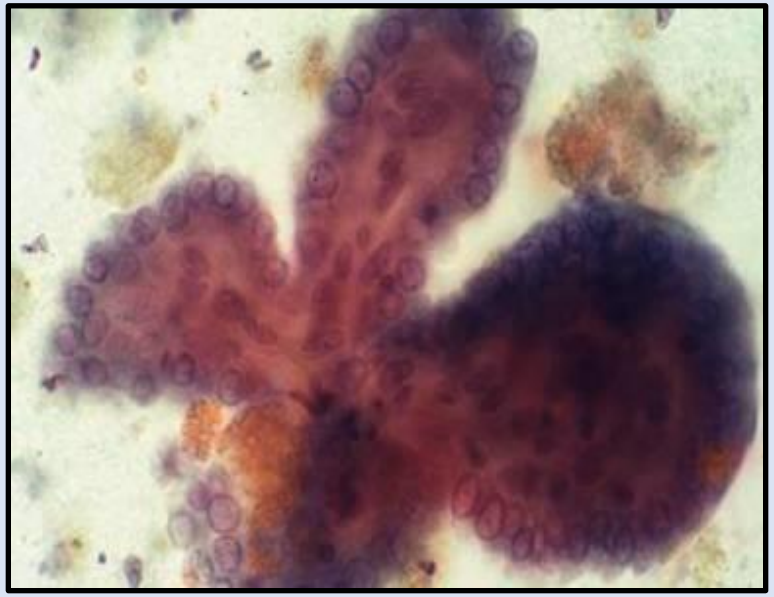
- *Variable thick colloid*
- *Psammoma bodies*
- *Tissue fragments common*
- *Histiocytoid /squamoid / mesothelial type cells*
- *Variable # of macrophages*

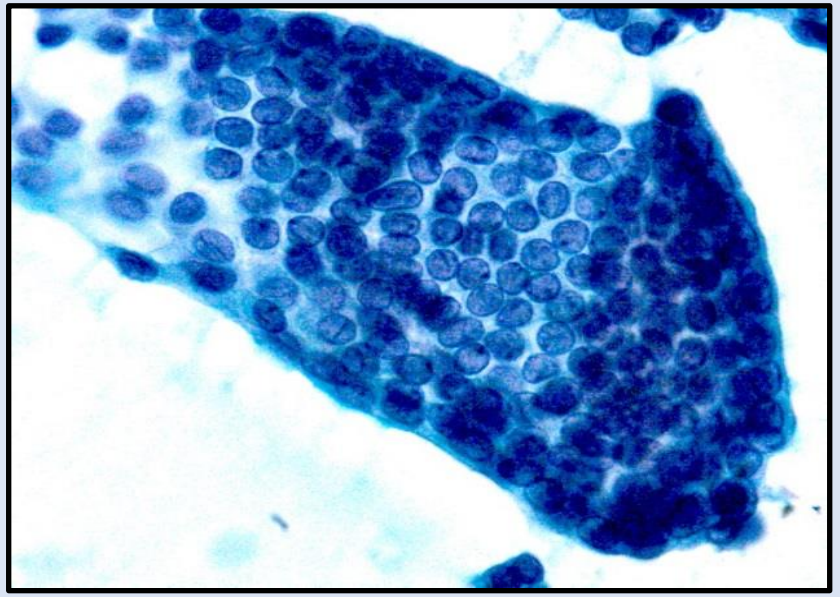
Papillary Thyroid Carcinoma: Cytomorphology

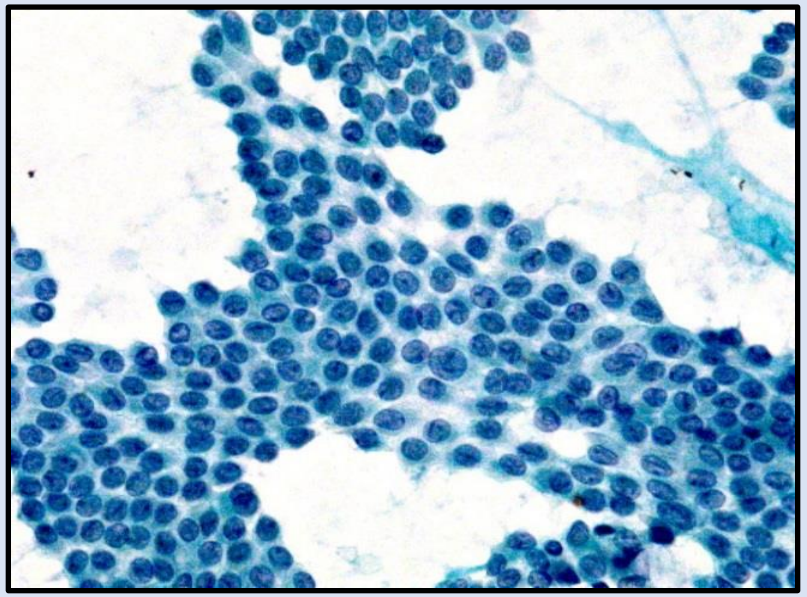




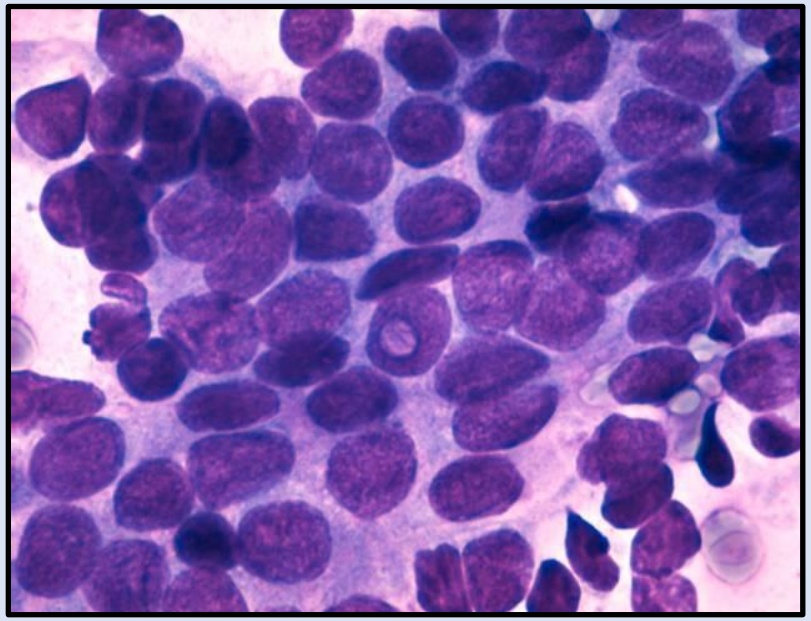
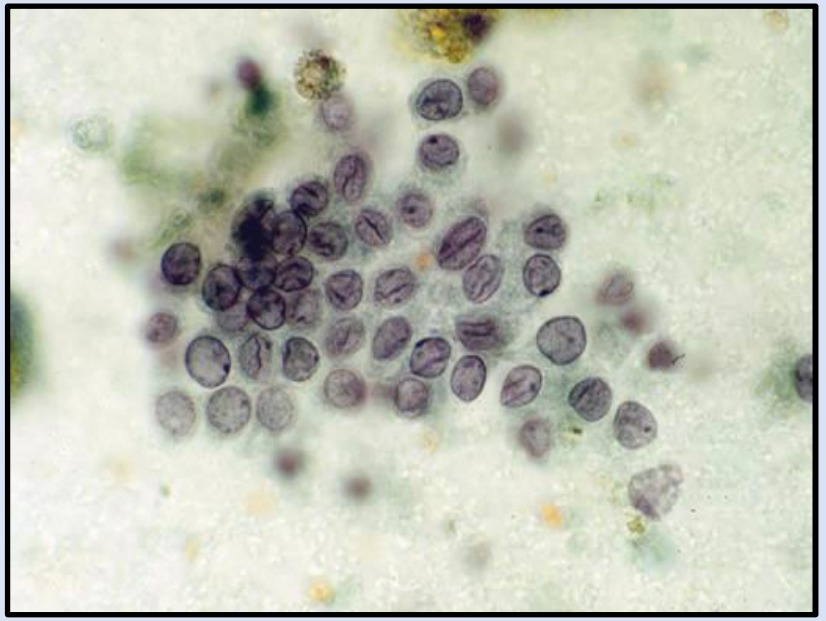
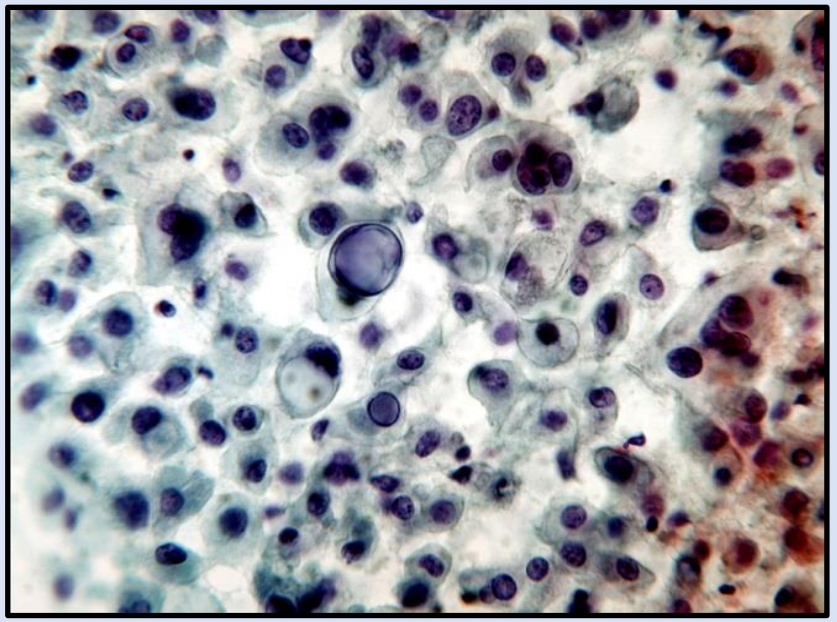
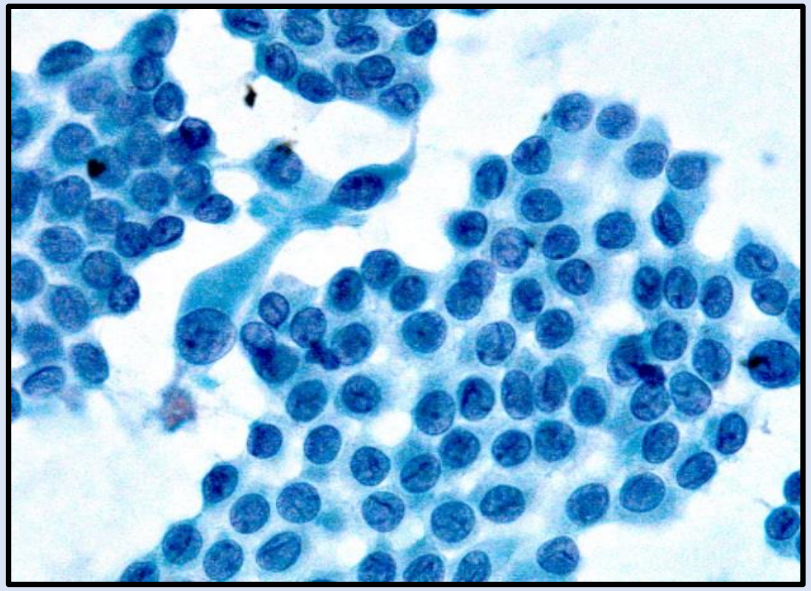
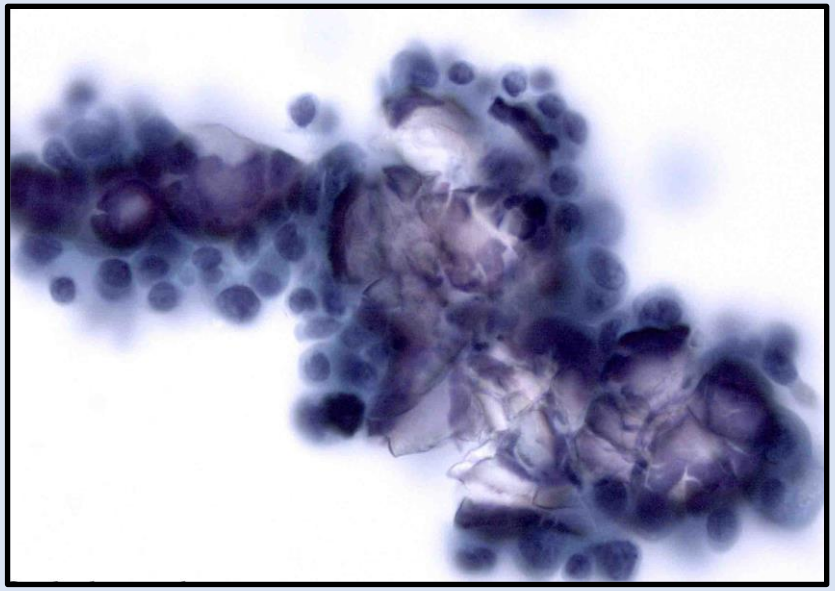
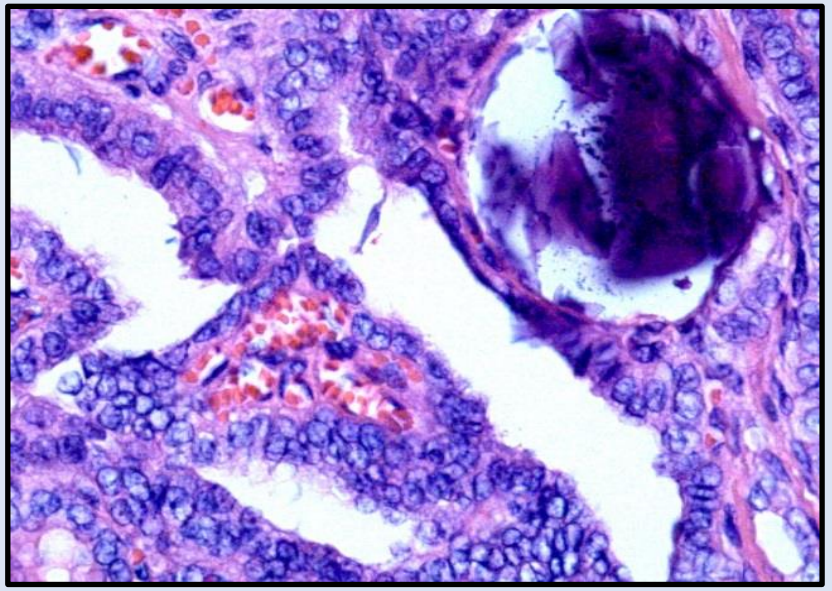




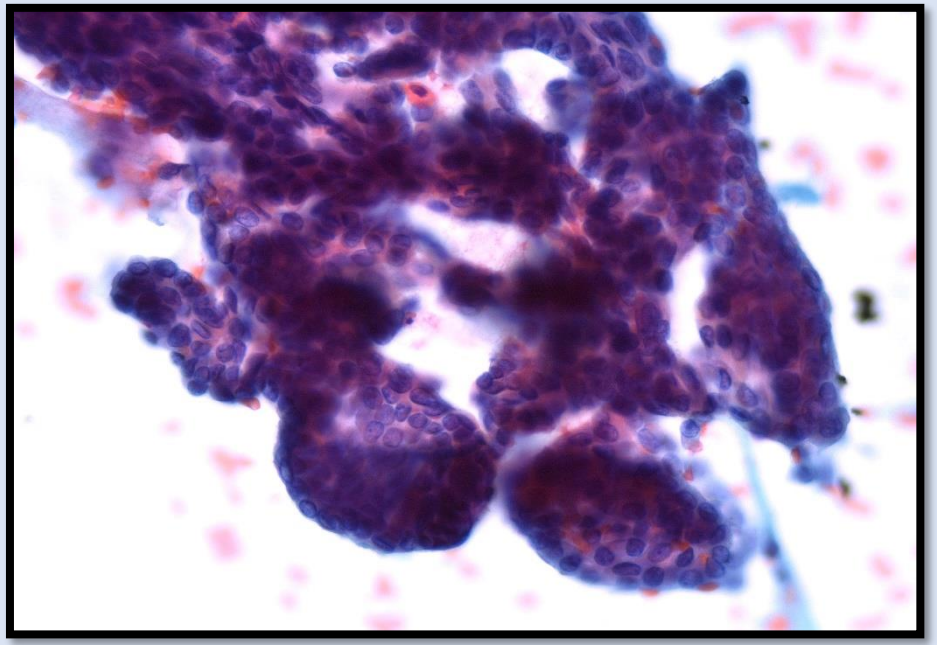


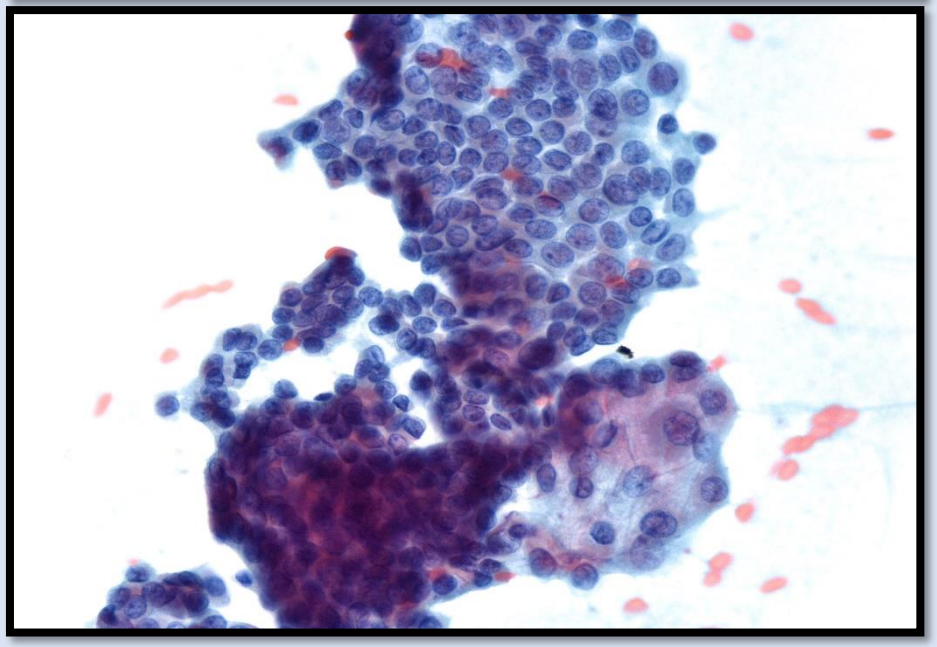


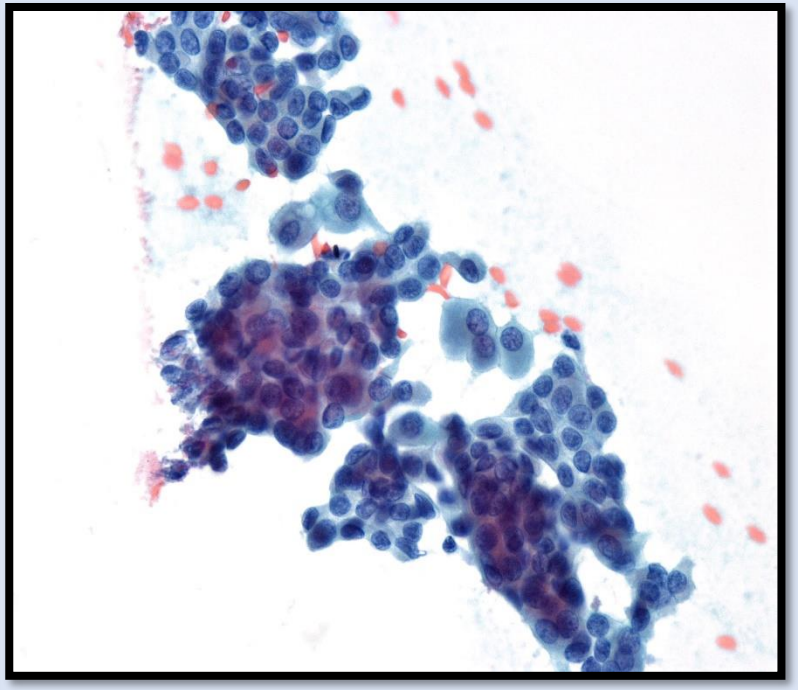
Papillary Thyroid Carcinoma

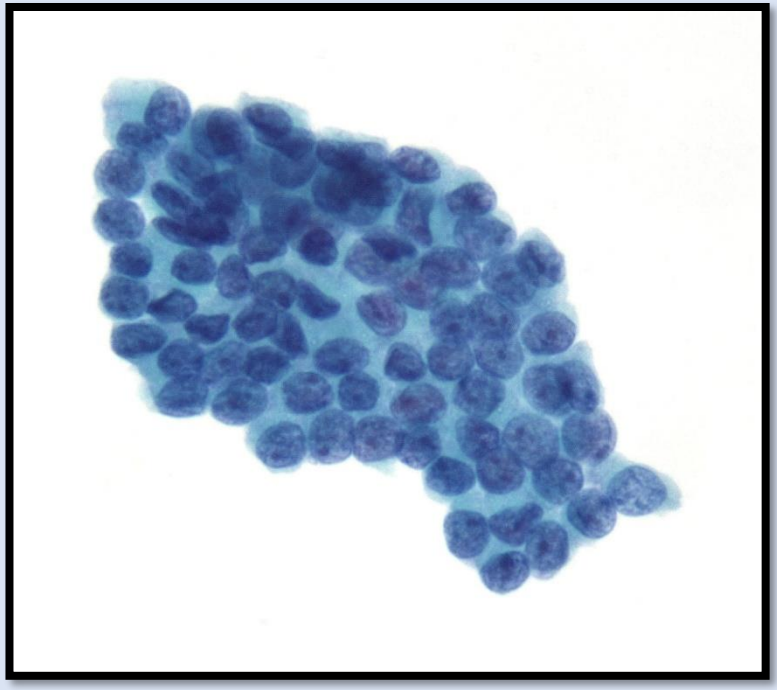







Papillary Thyroid Carcinoma



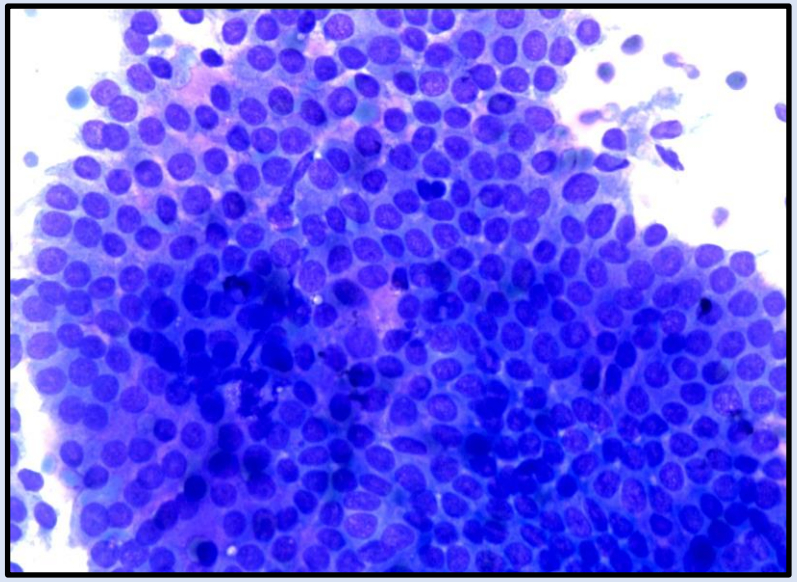


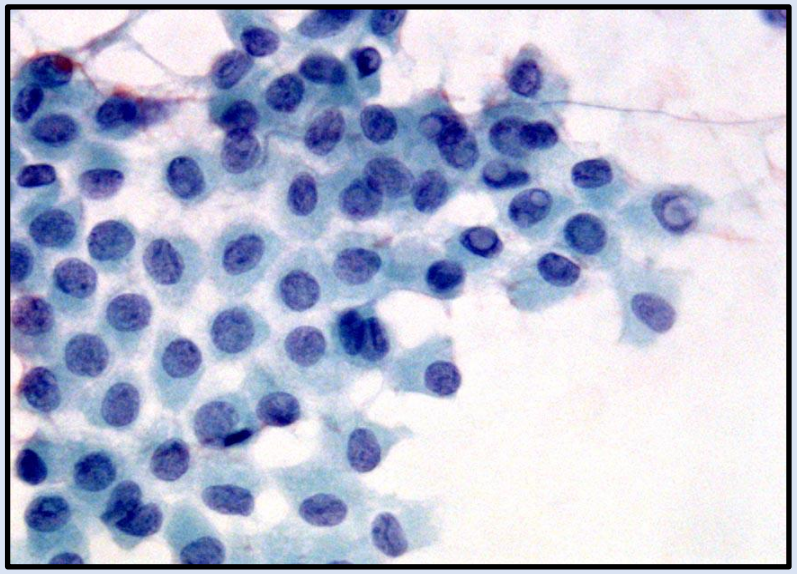




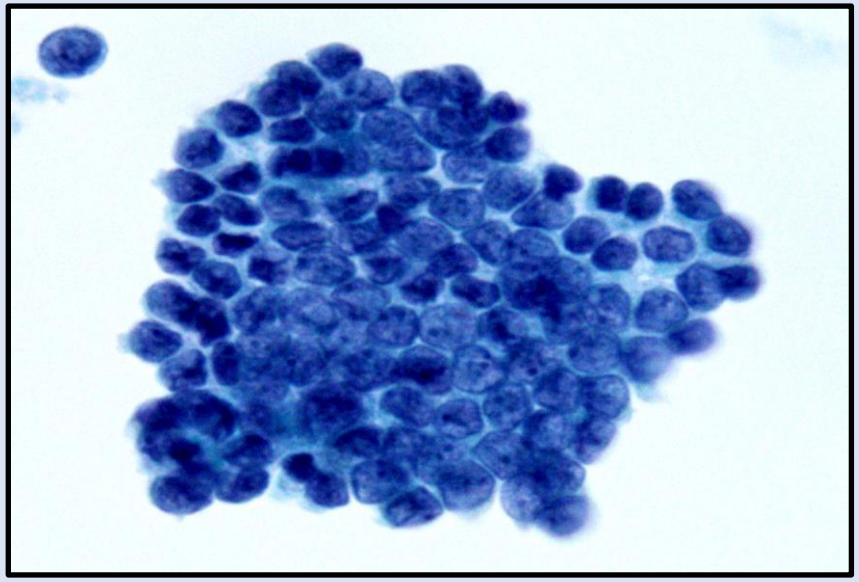
PTC – Cytomorphology. Smear Preparations vs. ThinPrep®

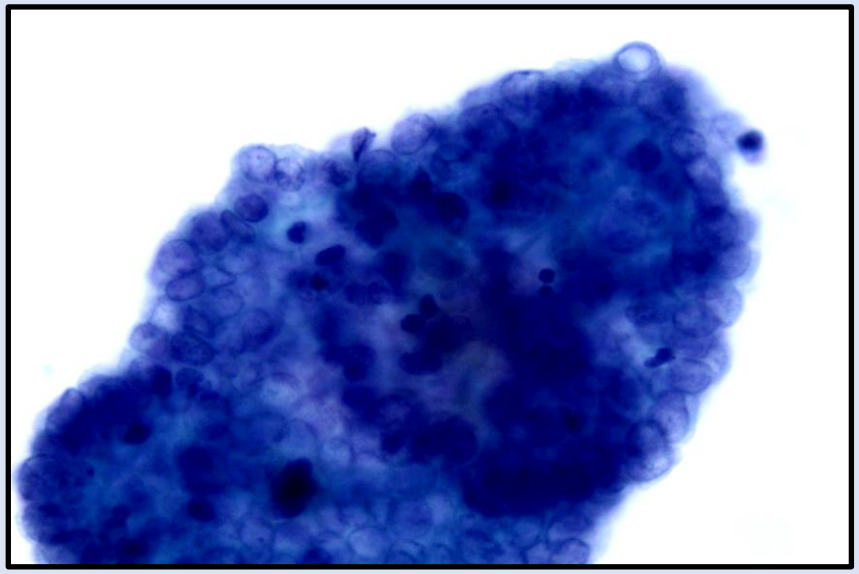
Conv - Smear Preparations



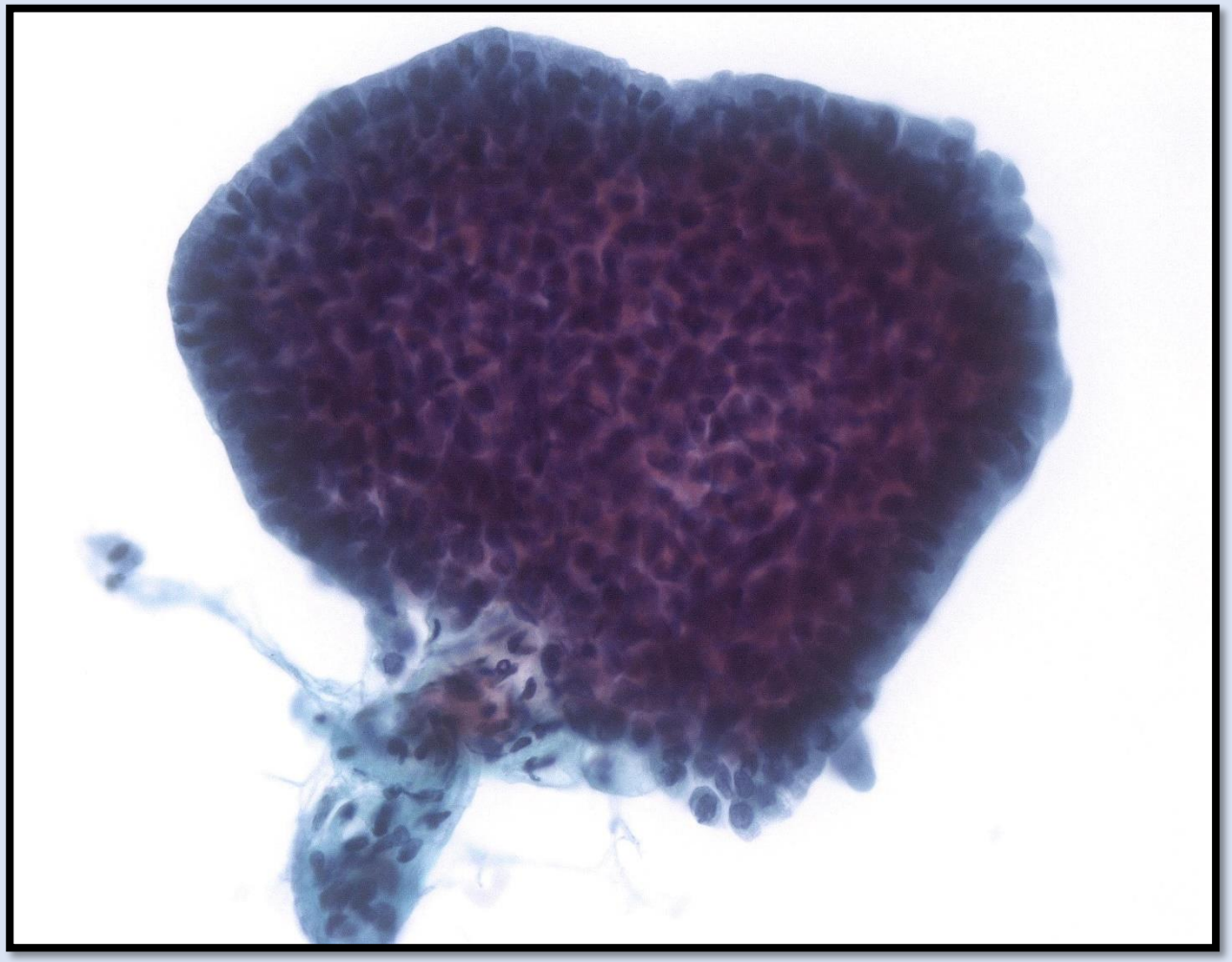


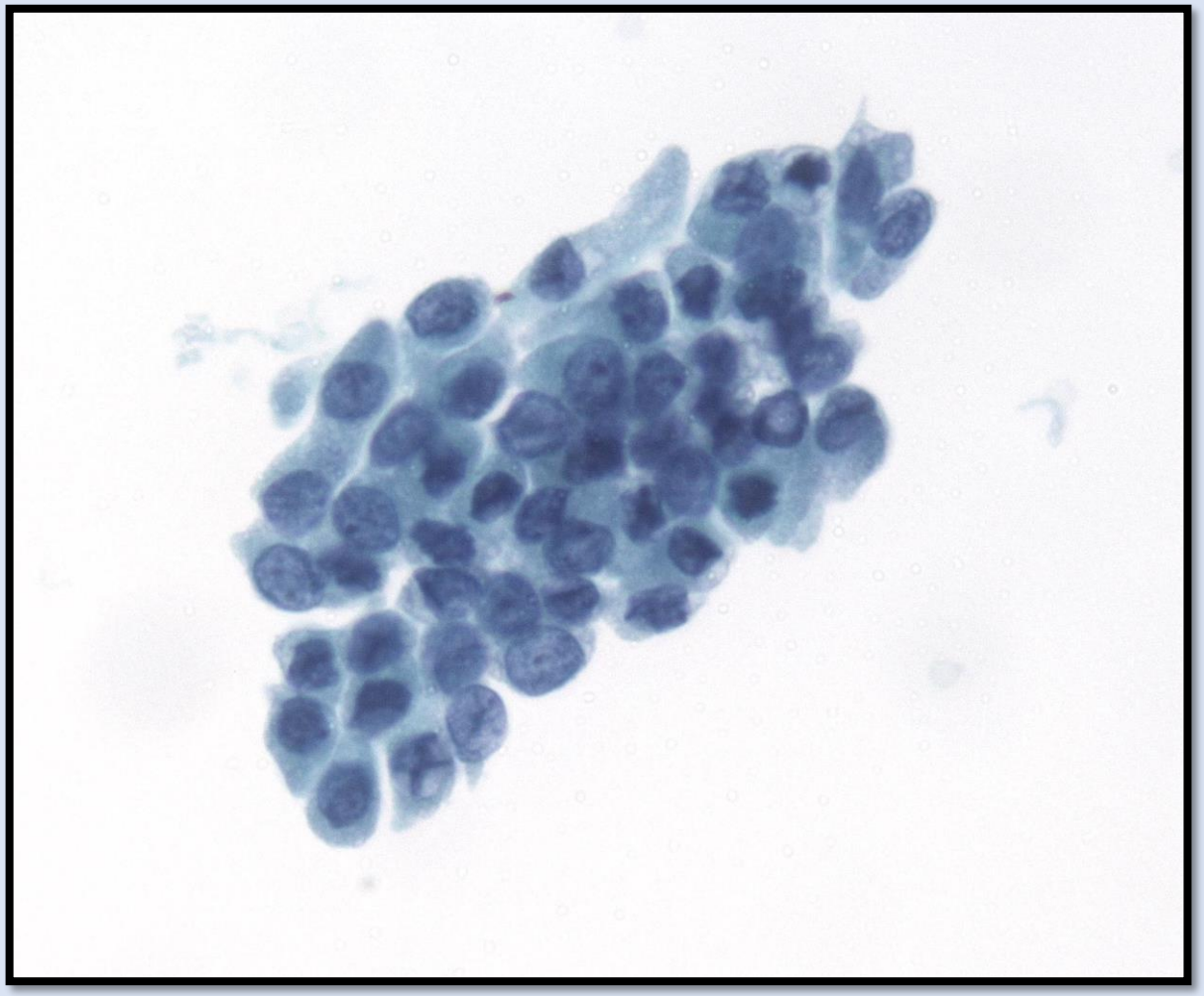
ThinPrep®





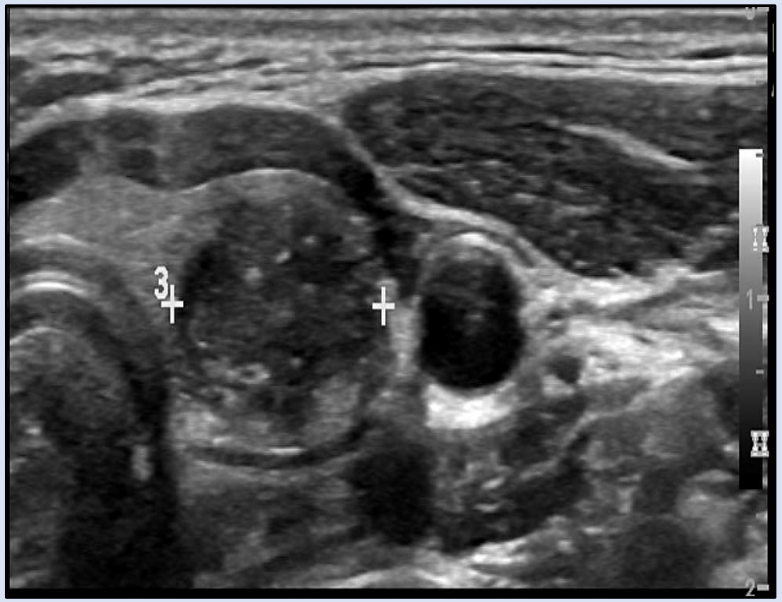
Papillary Thyroid Carcinoma

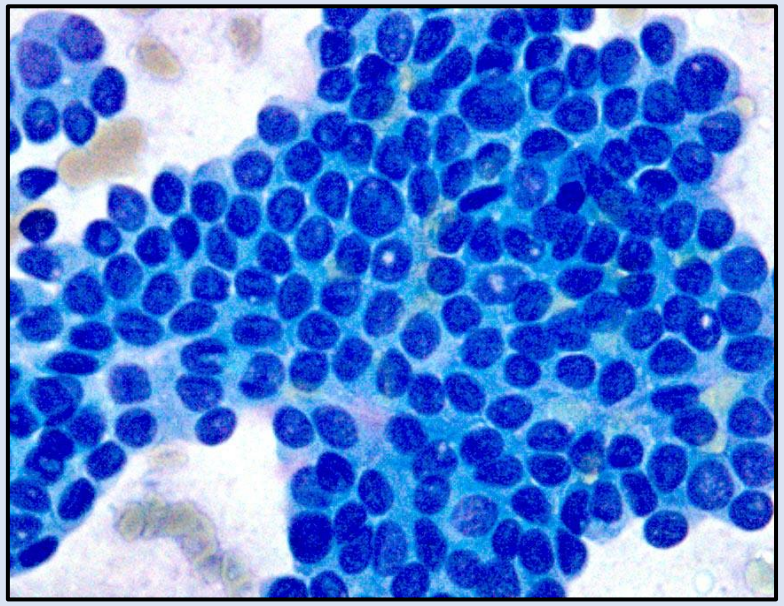


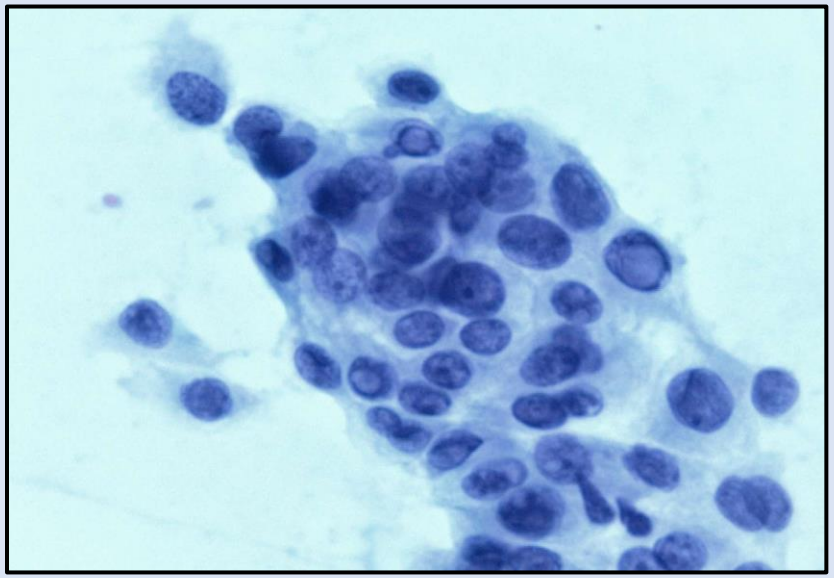


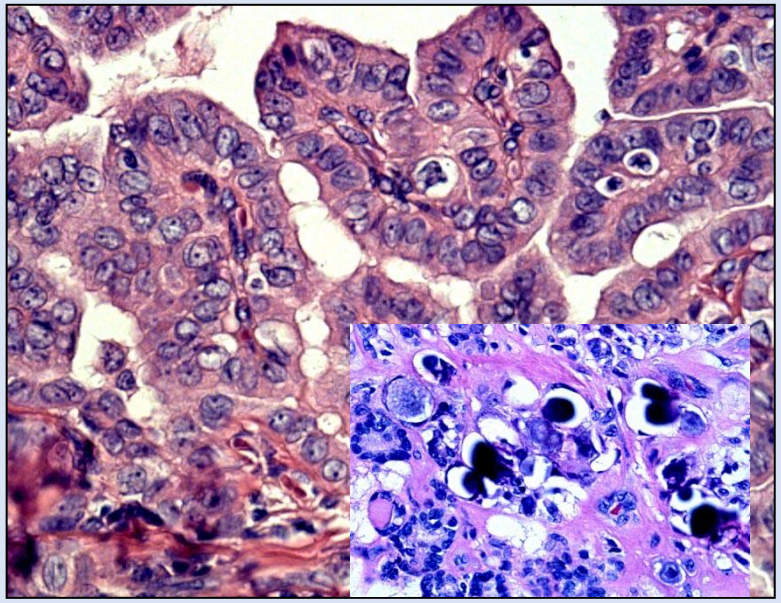
Papillary Thyroid Carcinoma. Nuclear features – Major Diagnostic Features

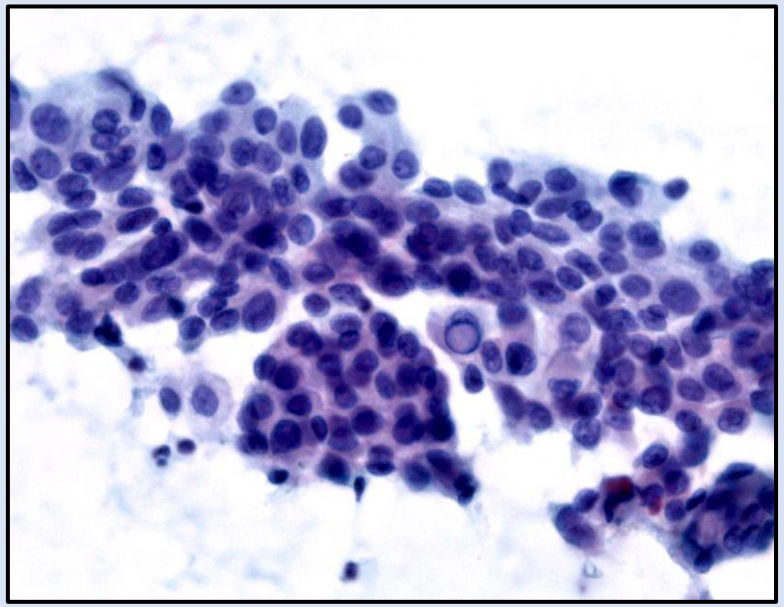
Elongation, chromatin clearing, Nuclear membrane irregularities Intranuclear grooves, Inclusions
Small peripheral nucleoli

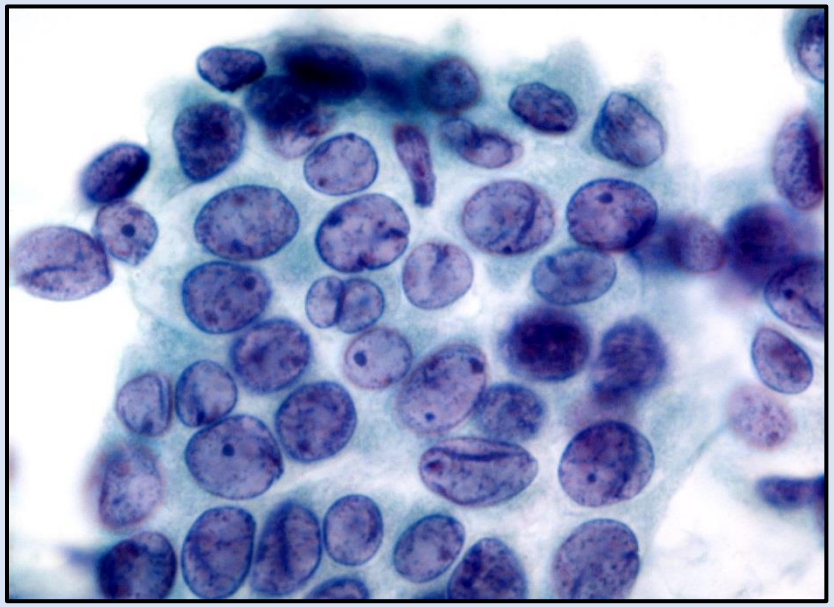




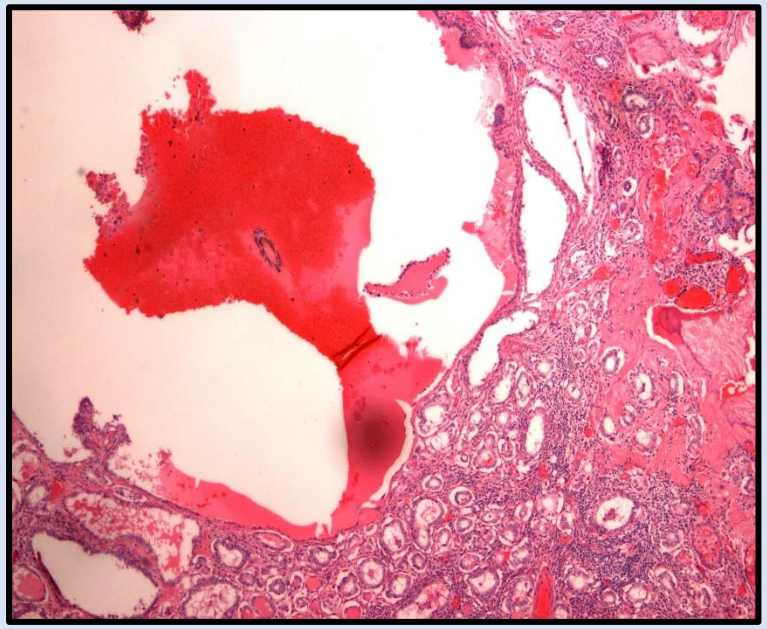
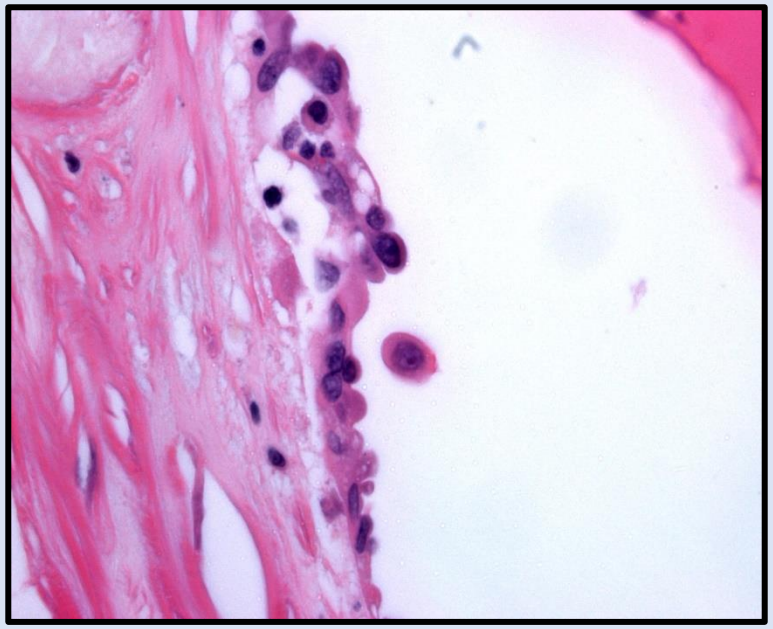
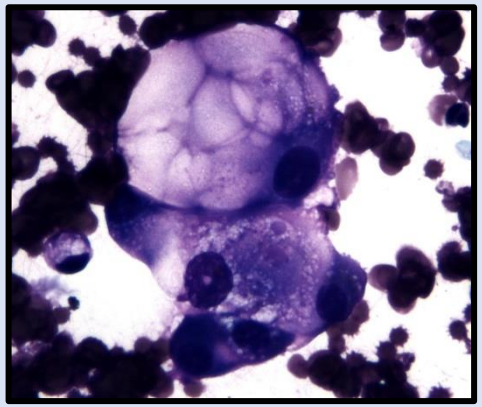
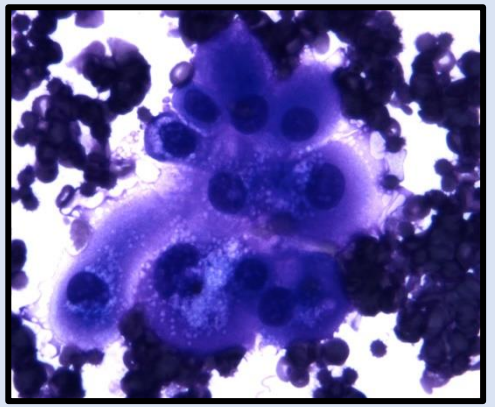
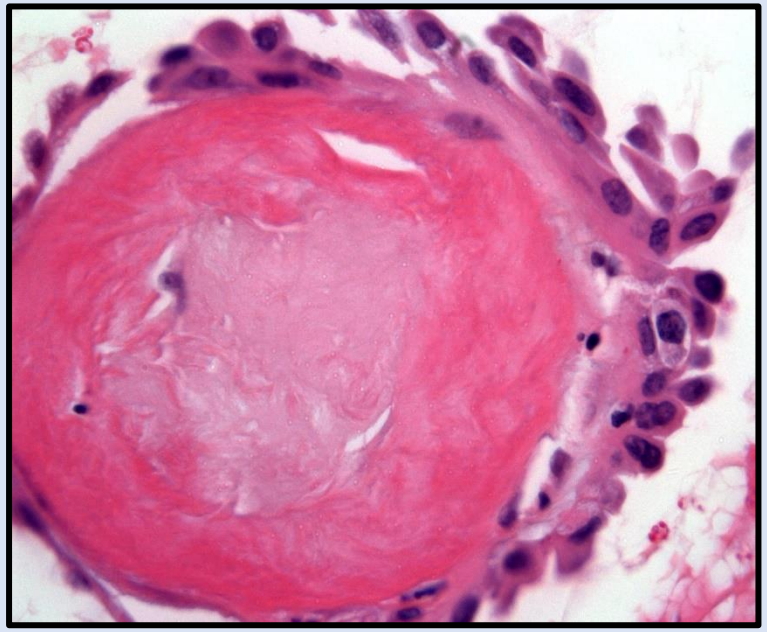
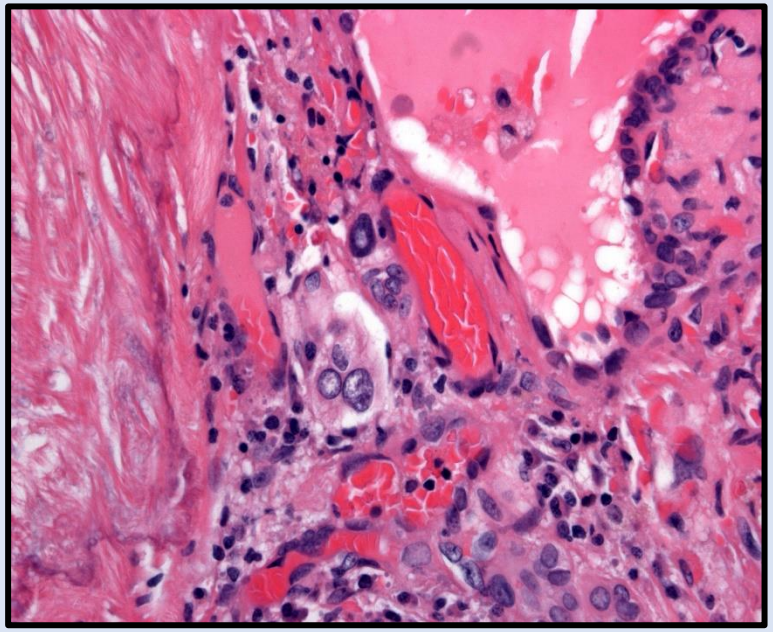
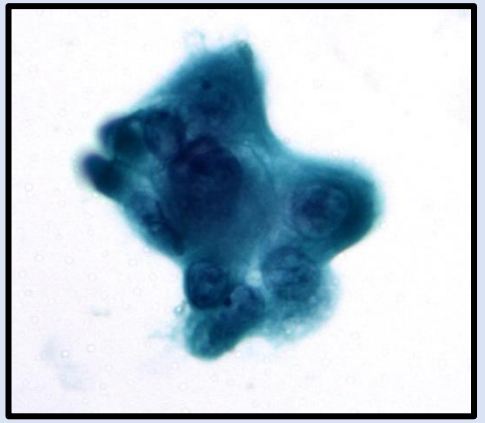
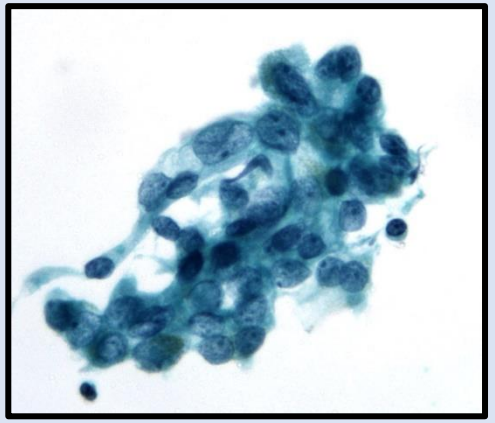
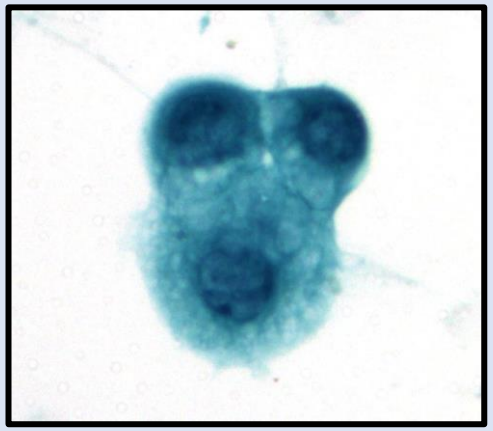
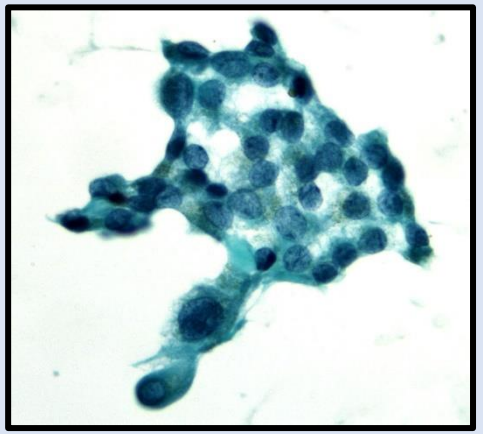




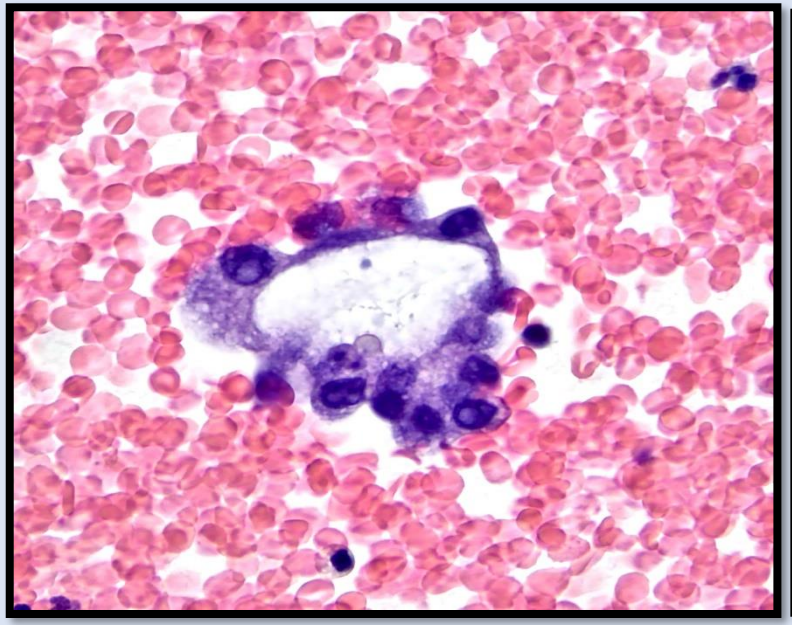


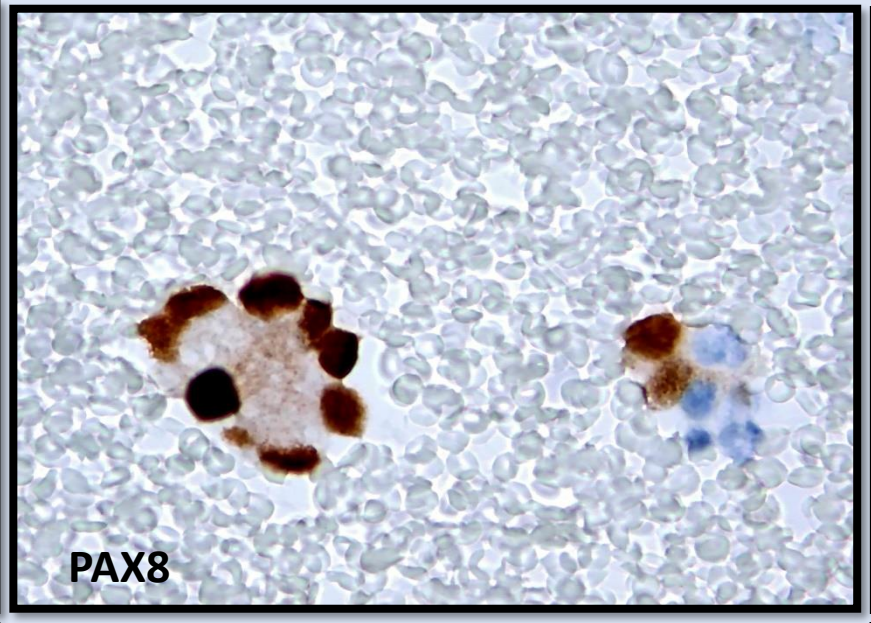


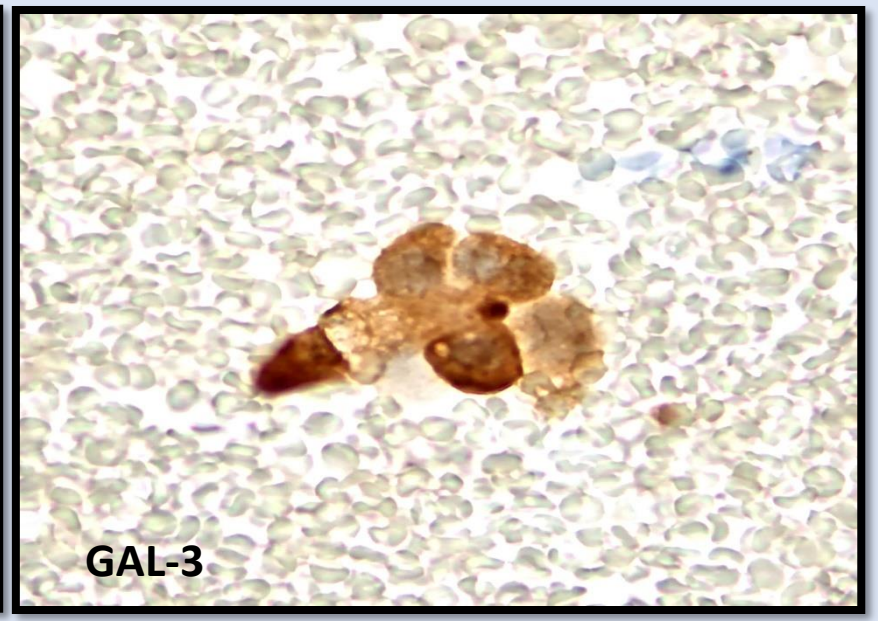
Challenging Aspirates of Cystic PTC

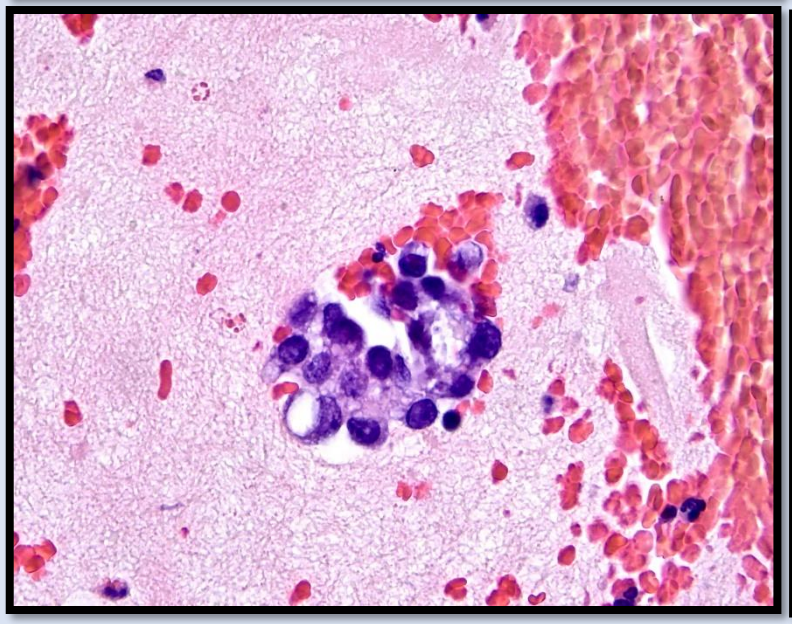











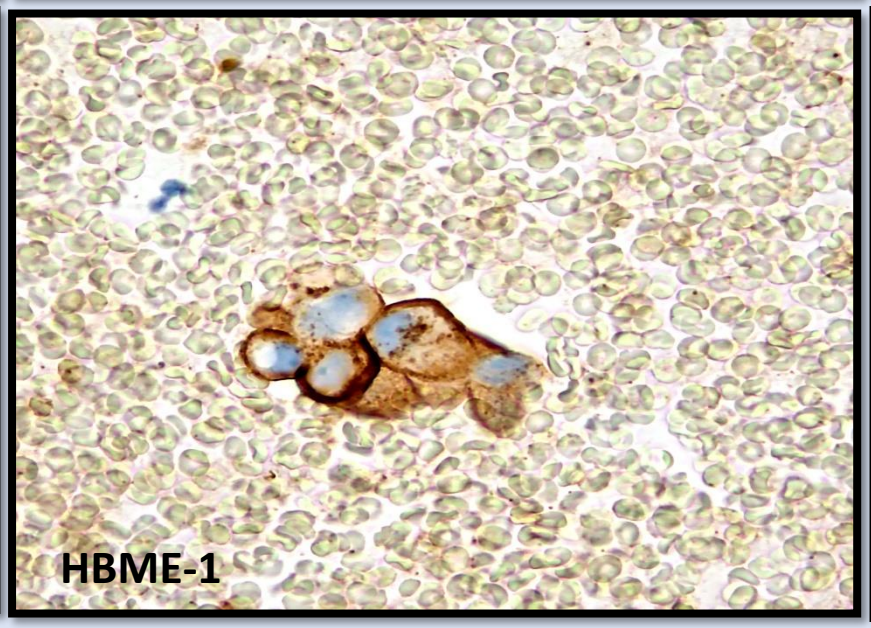
PTC – Immunohistochemistry

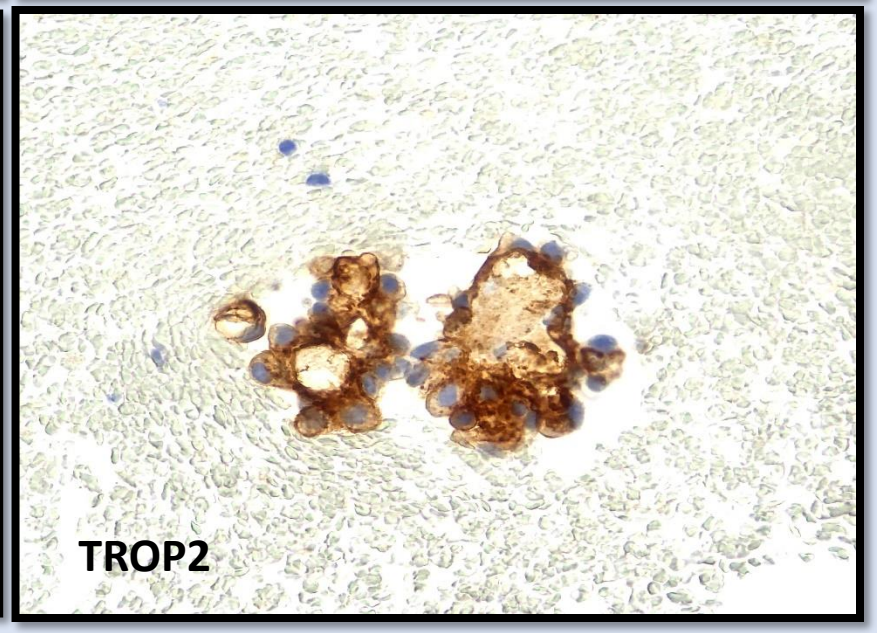








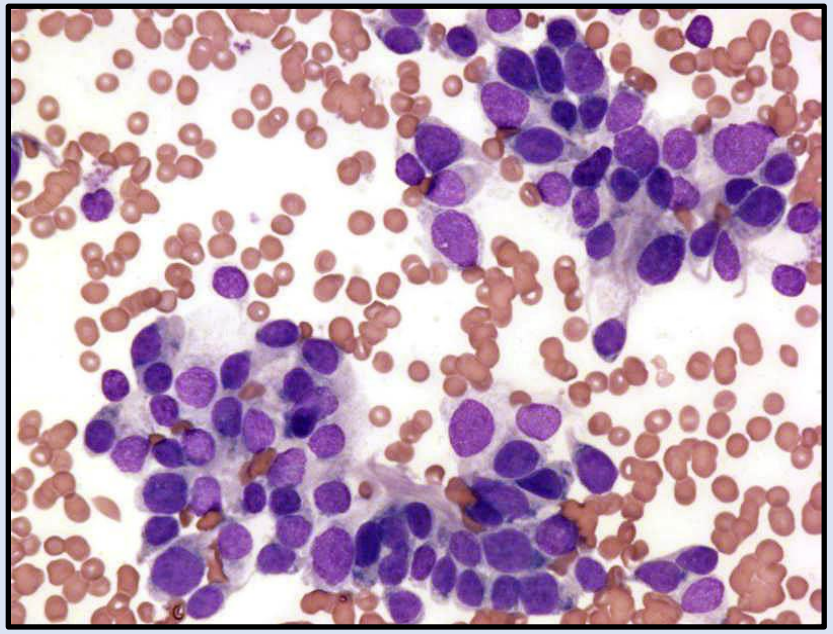


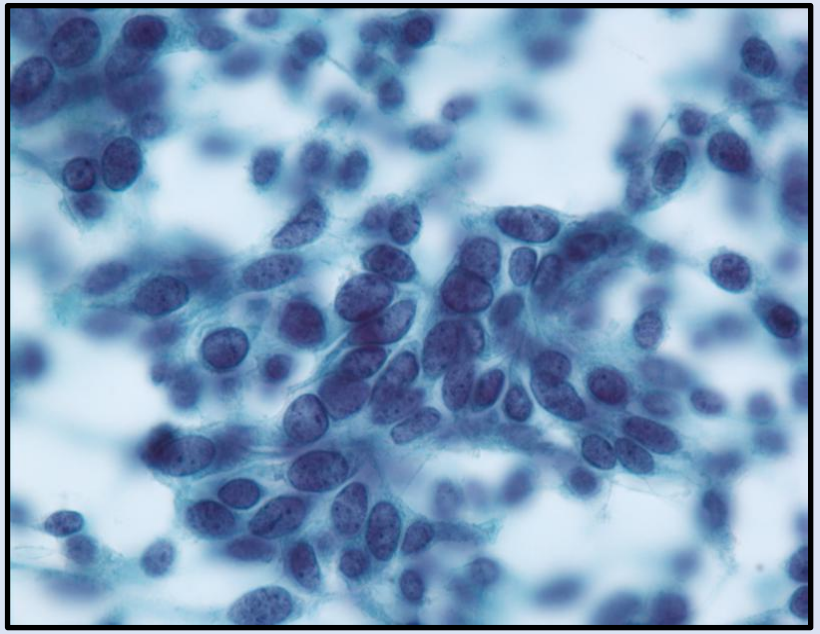


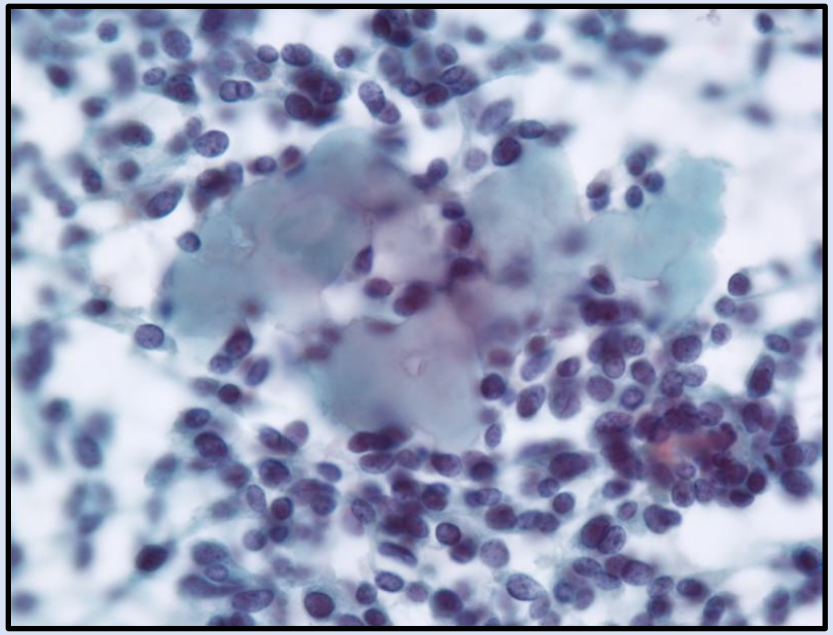
Medullary Thyroid Carcinoma

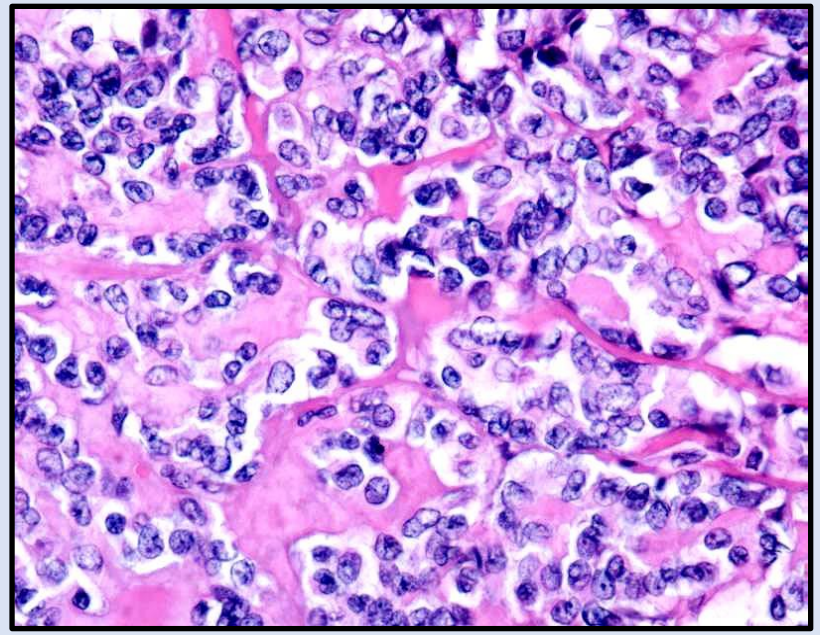
Medullary Thyroid Carcinoma - Cytologic Features

- **Cellular specimen:** Loose tissue fragments. Single cells
- **Heterogeneous Morphology:** Round to oval cells. Spindle cells
- **Amyloid:** Acellular deposits (thick colloid)





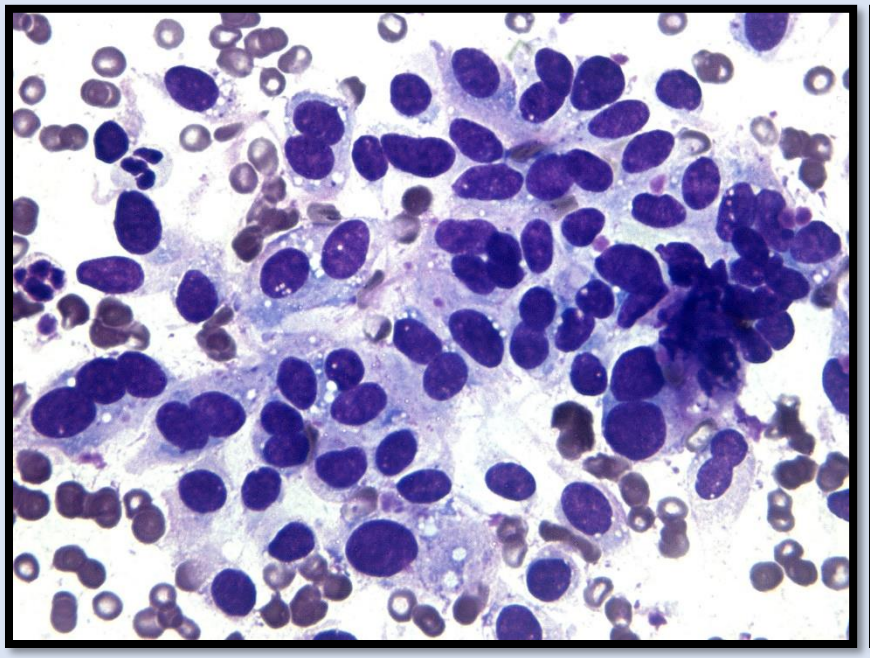


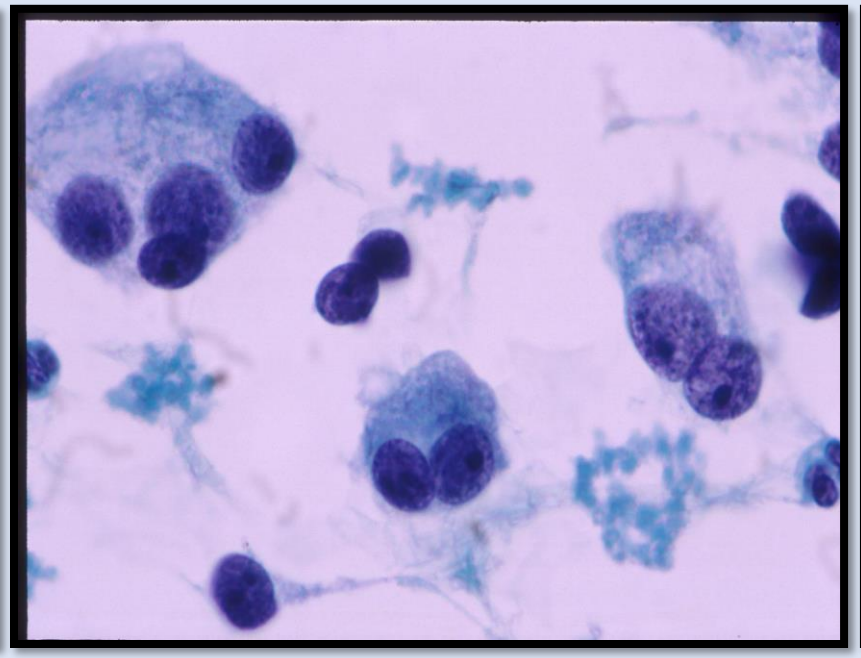


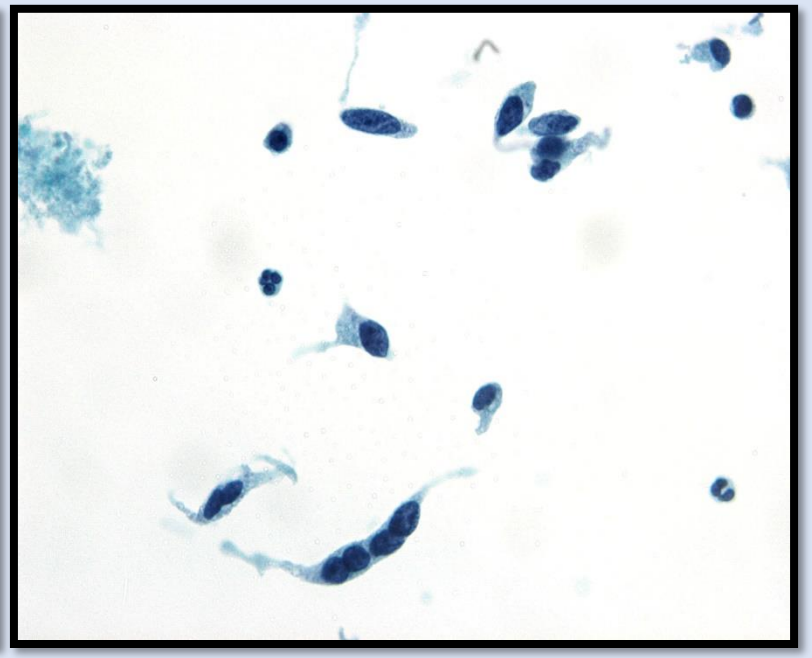
Medullary Thyroid Carcinoma - Cytologic Features

Tumor cells with:

- **Abundant eosinophilic cytoplasm. Plasmacytoid tumor cells. Neuroendocrine chromatin pattern**
- **20% of cells can show cytoplasmic granules in Romanowsky stained-preps**

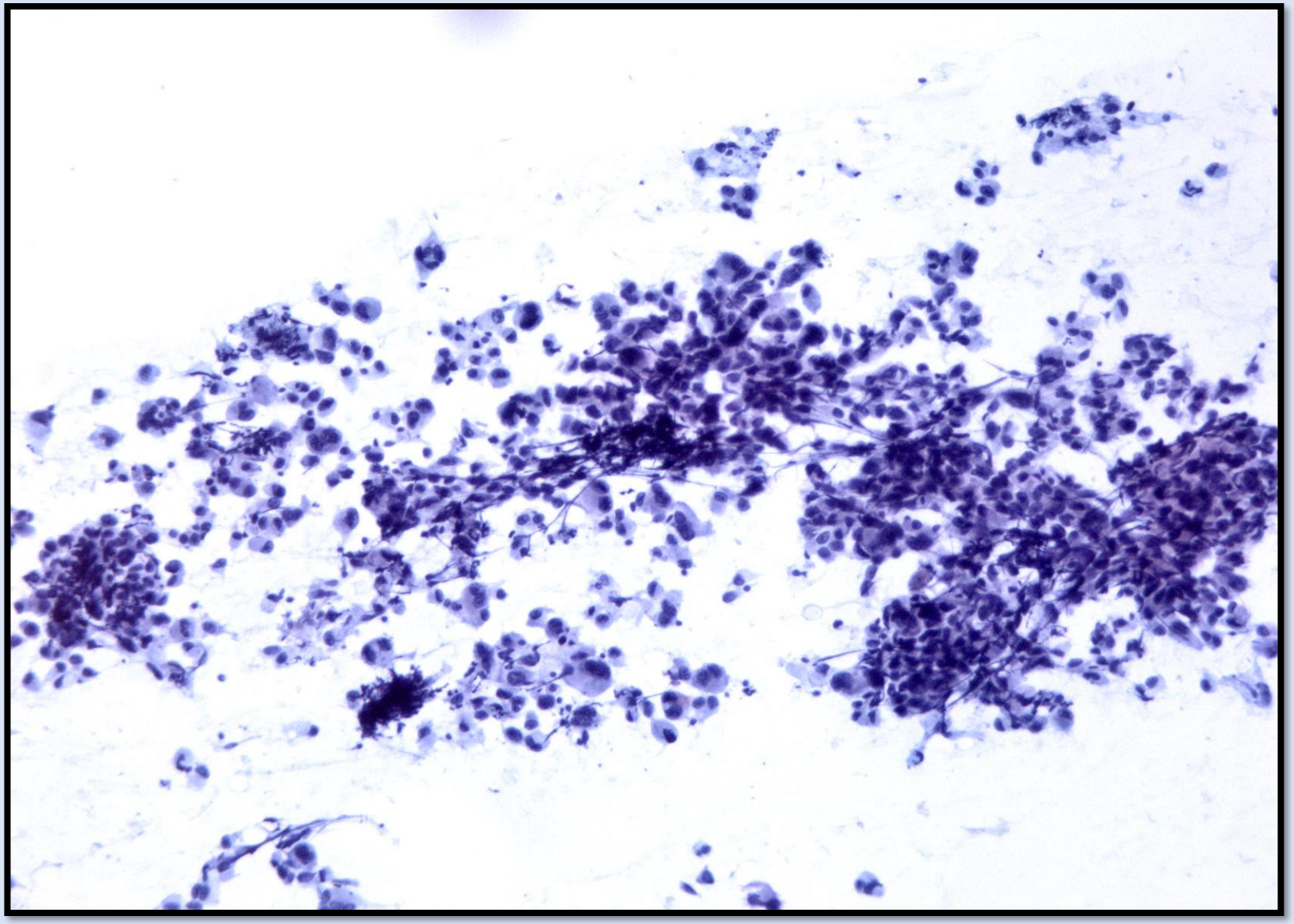


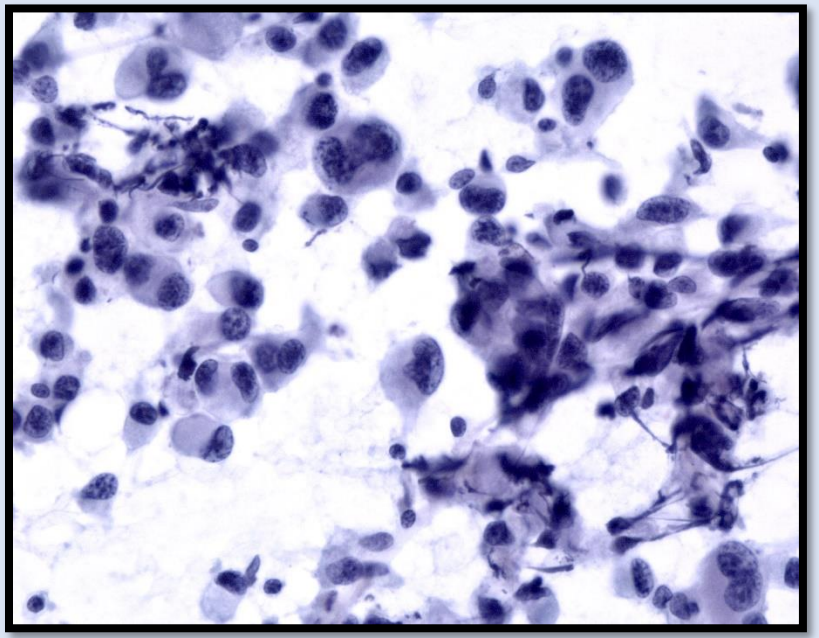


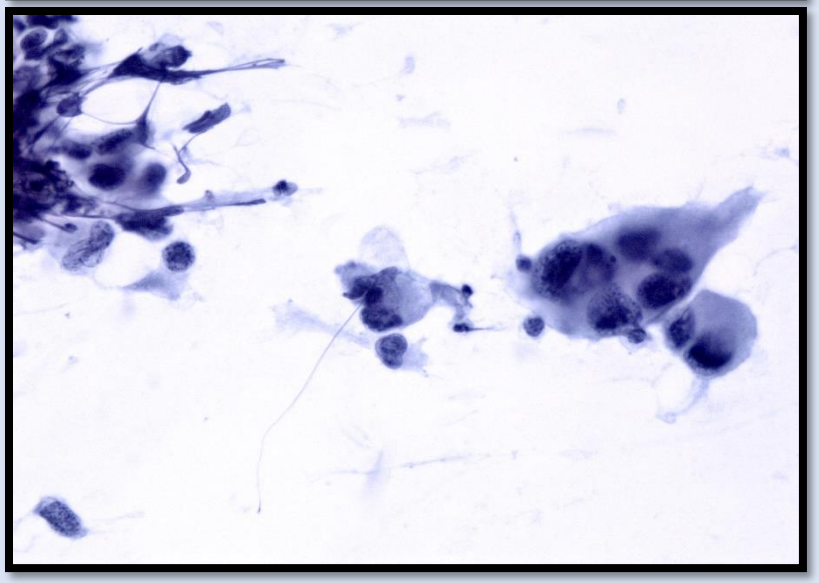


Anaplastic Thyroid Carcinoma

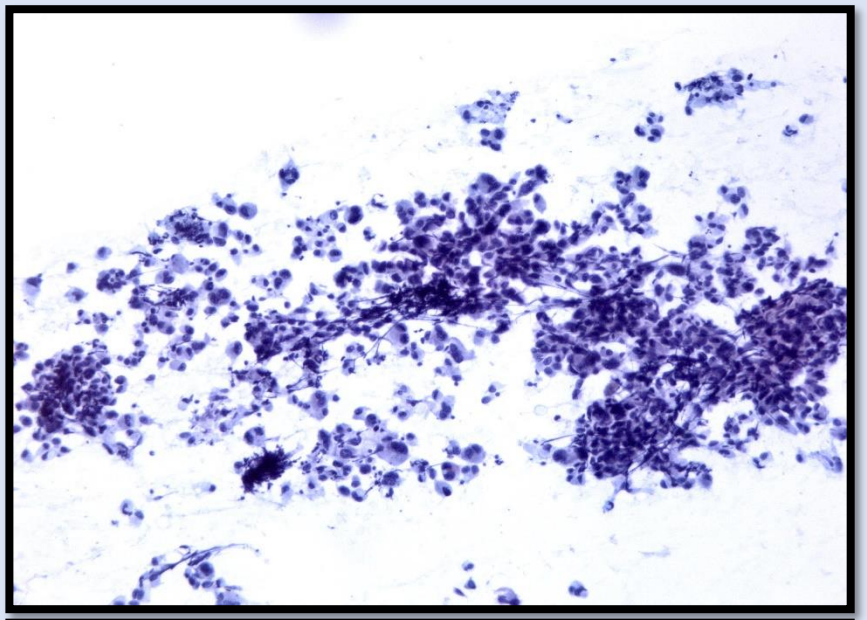
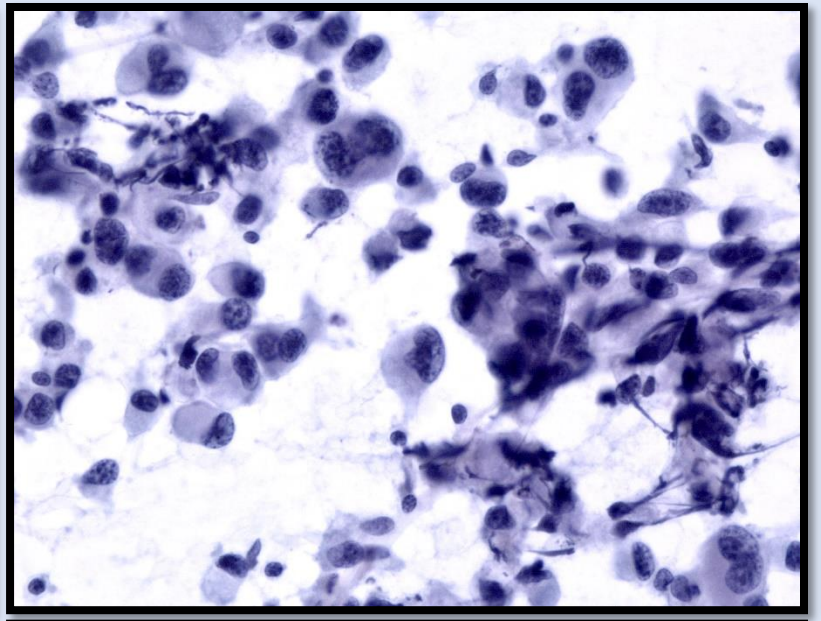
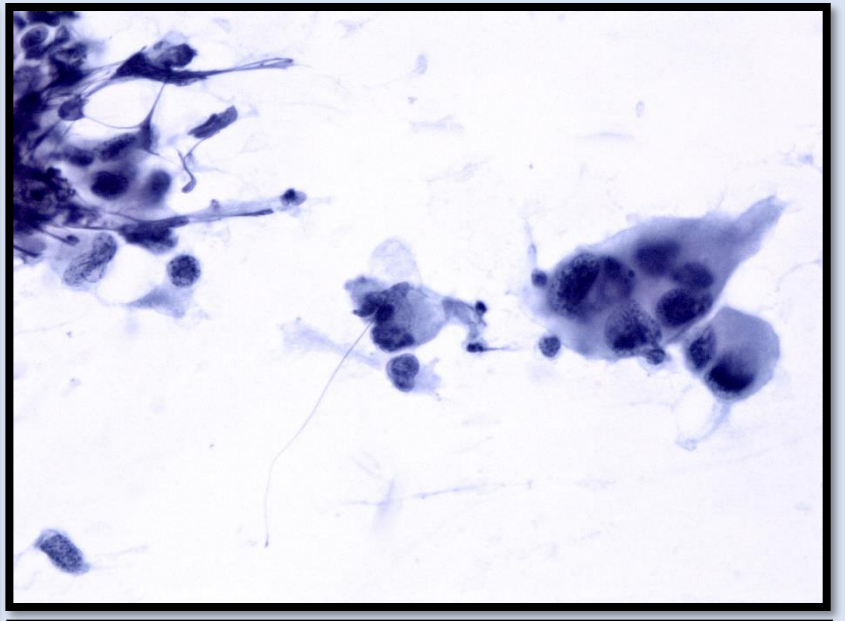
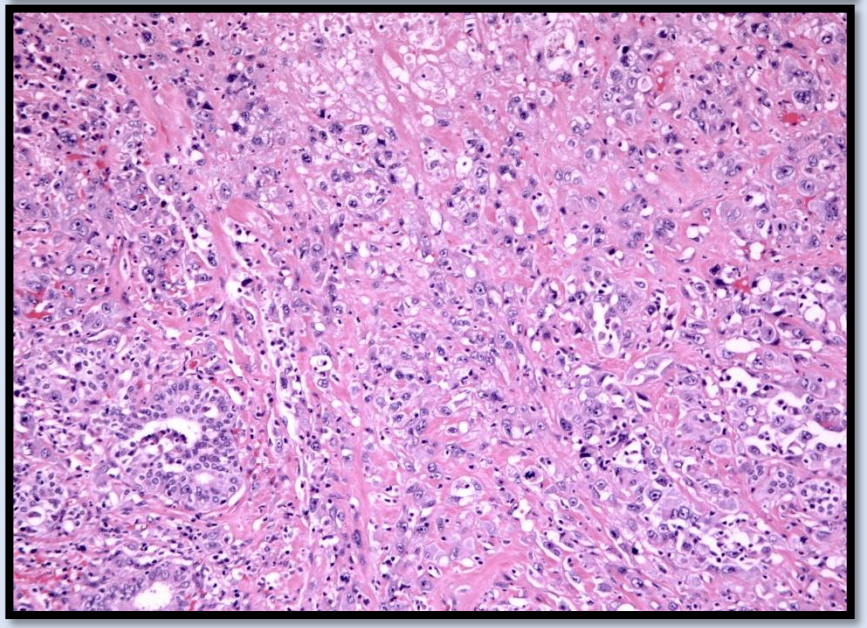
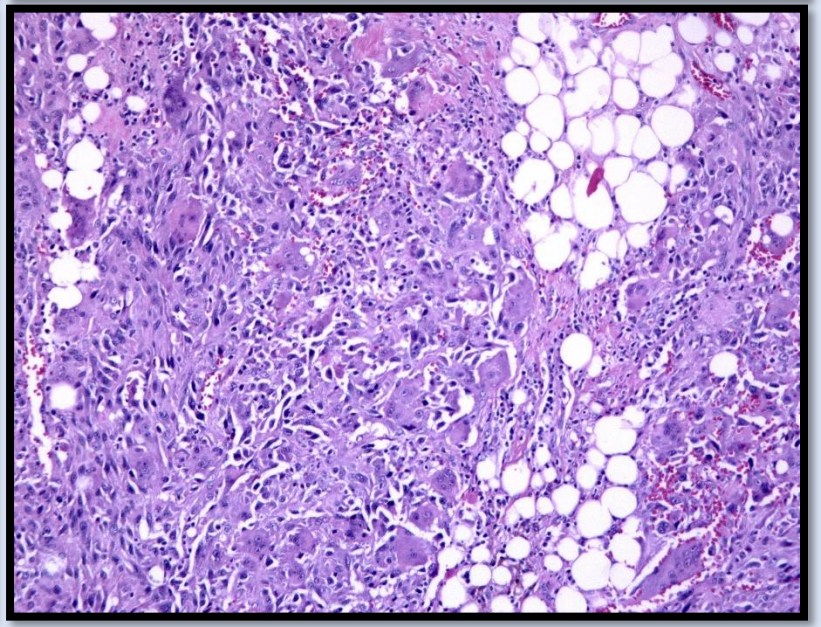
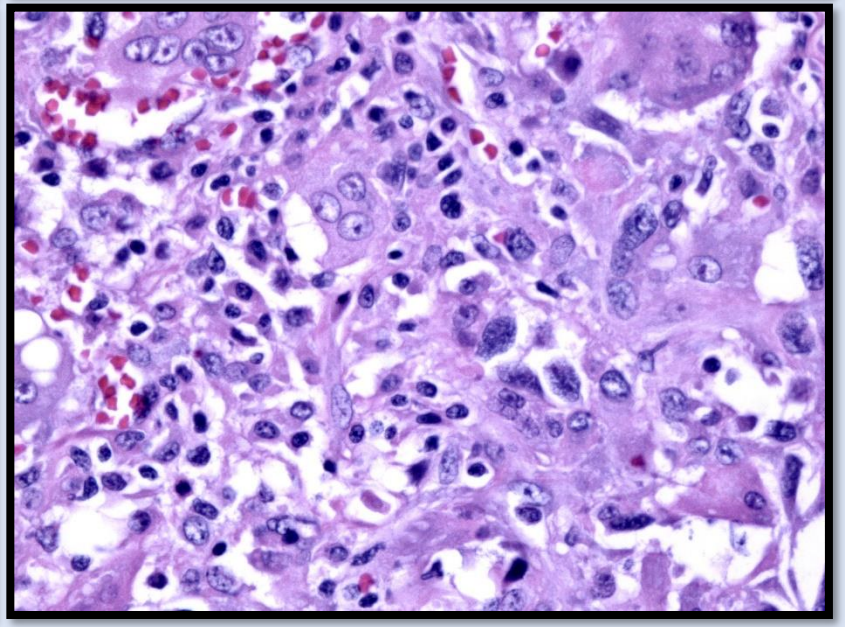
Variable Cellularity. Easily diagnosable as “Malignant Neoplasm”. Variably sized and shaped cells. Tumor necrosis. Squamous Differentiation. Infiltration by neutrophils







Variable Cellularity. Easily diagnosable as “Malignant Neoplasm”. Variably sized and shaped cells. Tumor necrosis. Squamous Differentiation. Infiltration by neutrophils

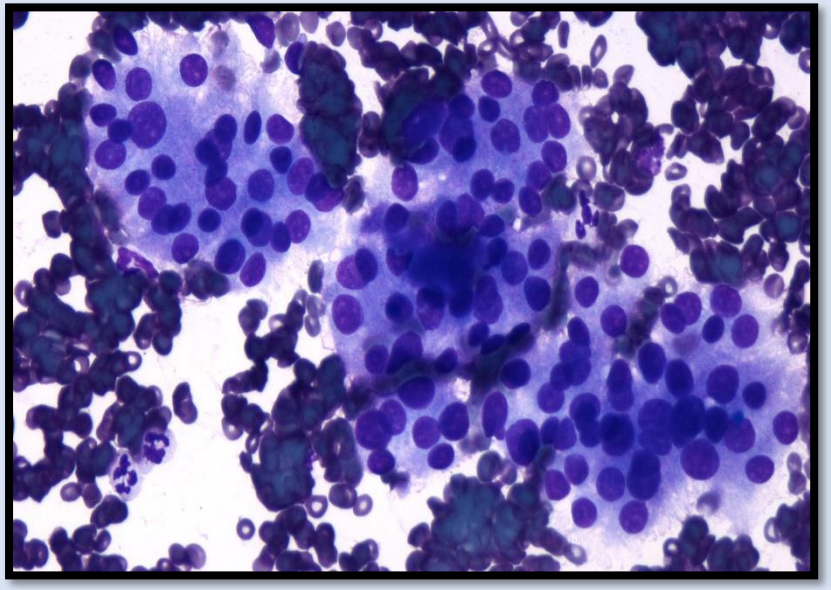
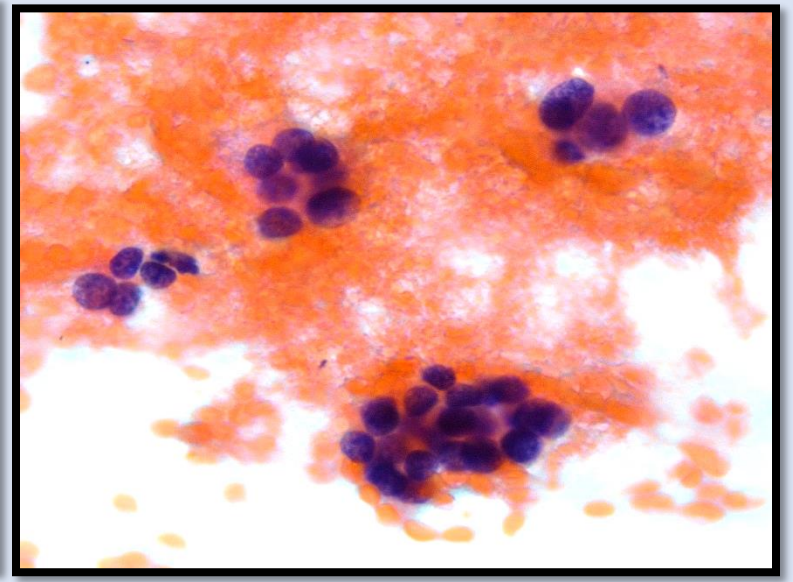
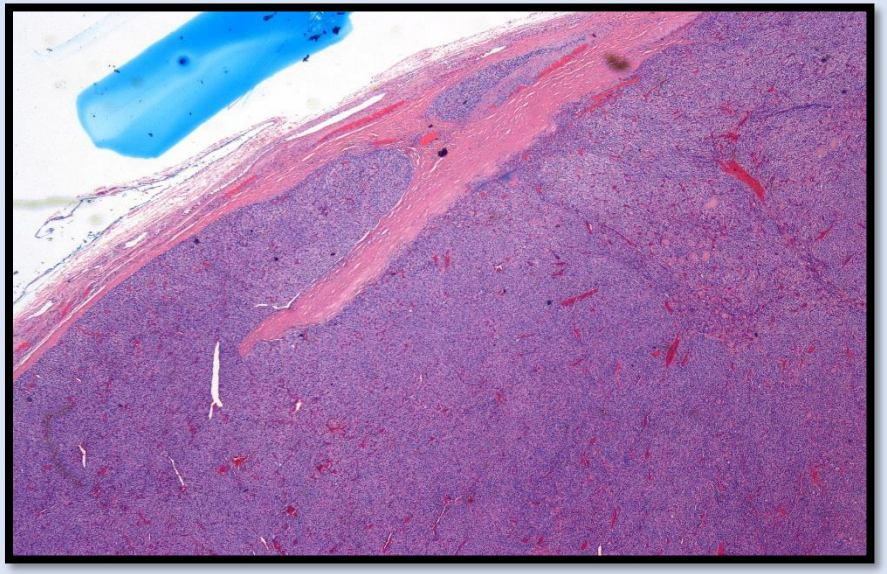
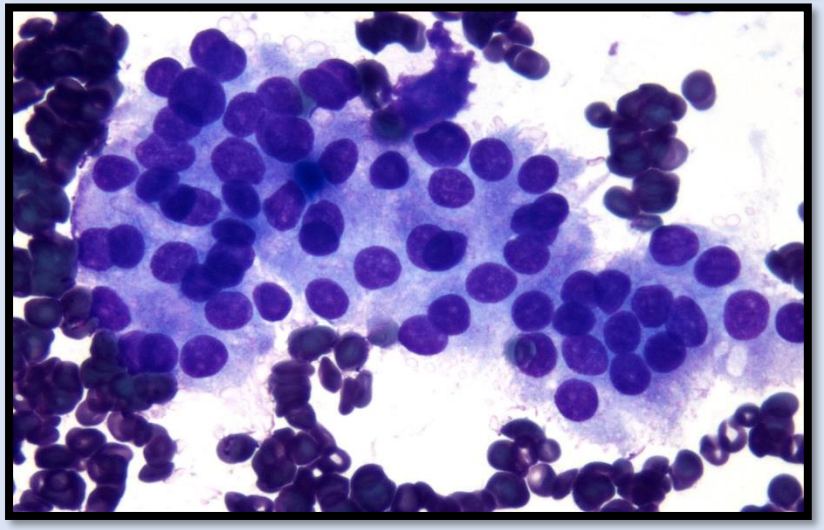
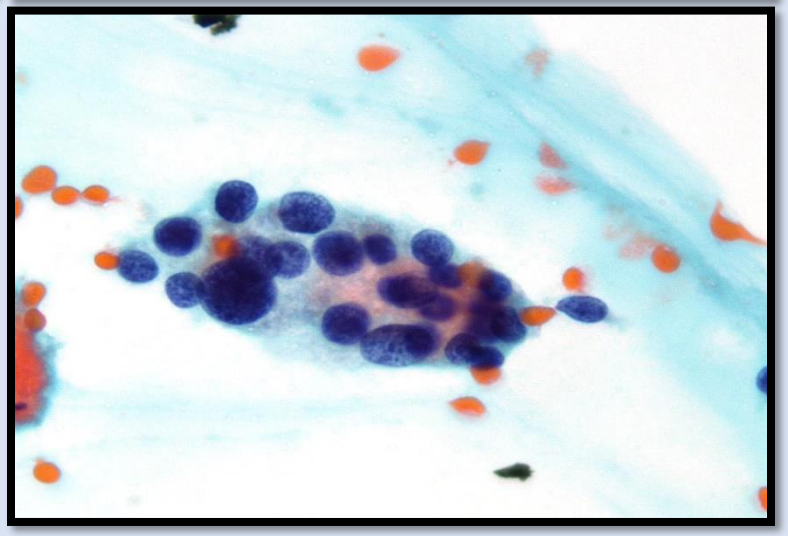
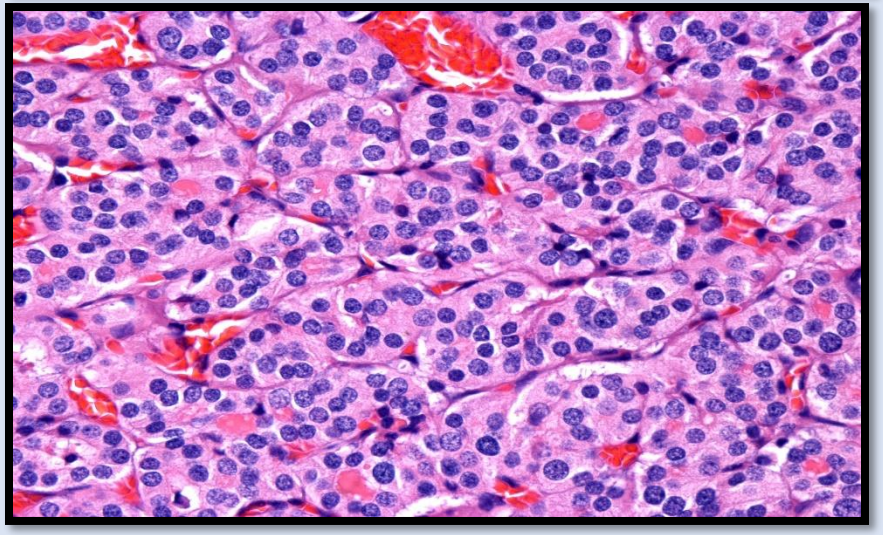
Poorly Differentiated Thyroid Carcinoma (PDTCA)

WHO 5th edition

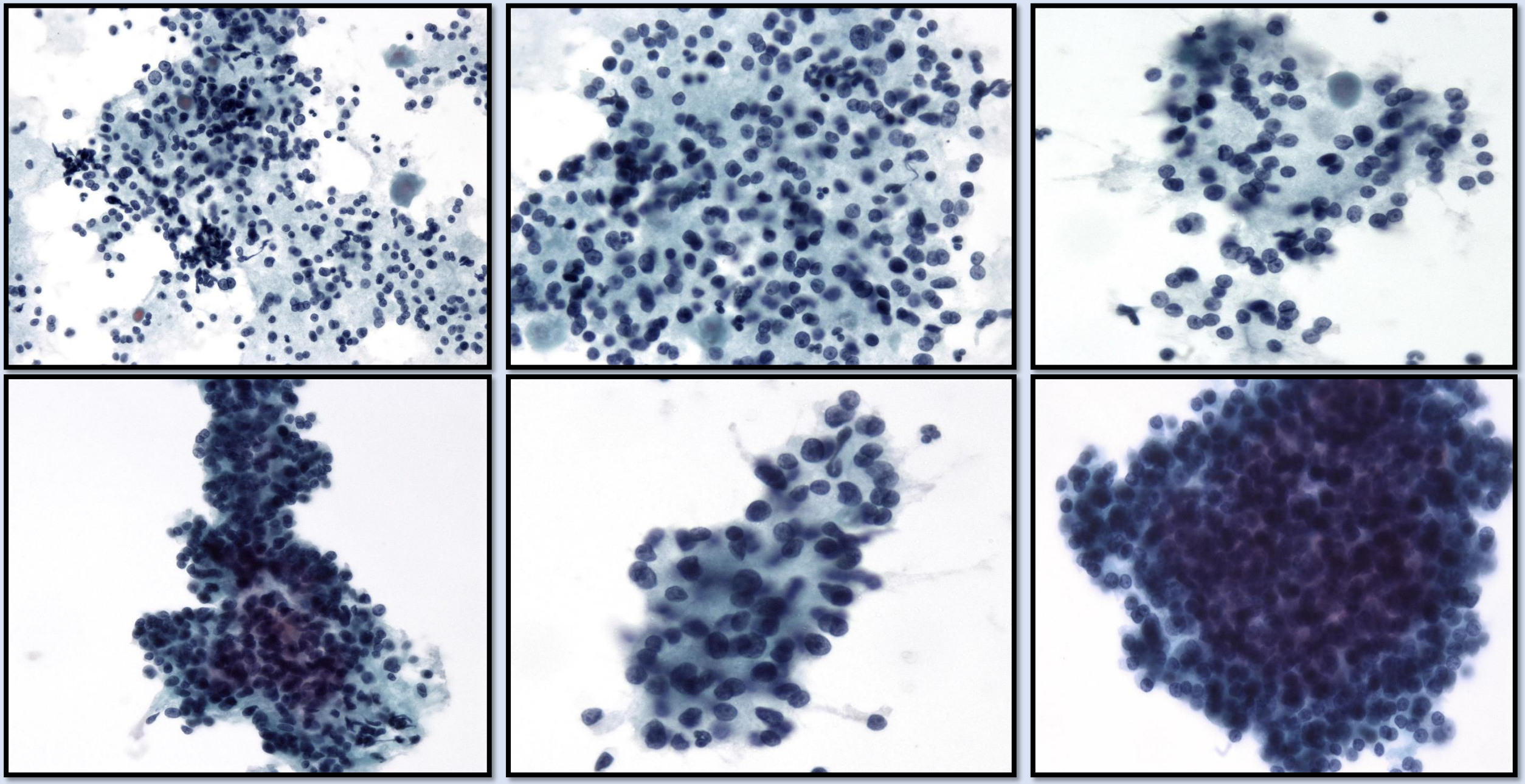
High-Grade Thyroid Carcinoma

- *Well-Differentiated High Grade Thyroid Carcinoma*
- *Poorly Differentiated Thyroid Carcinoma*

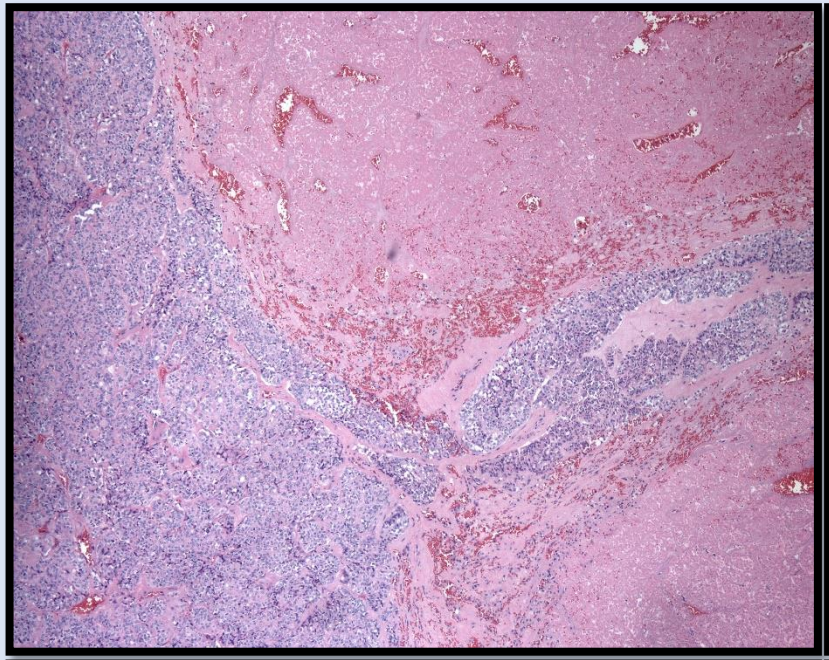
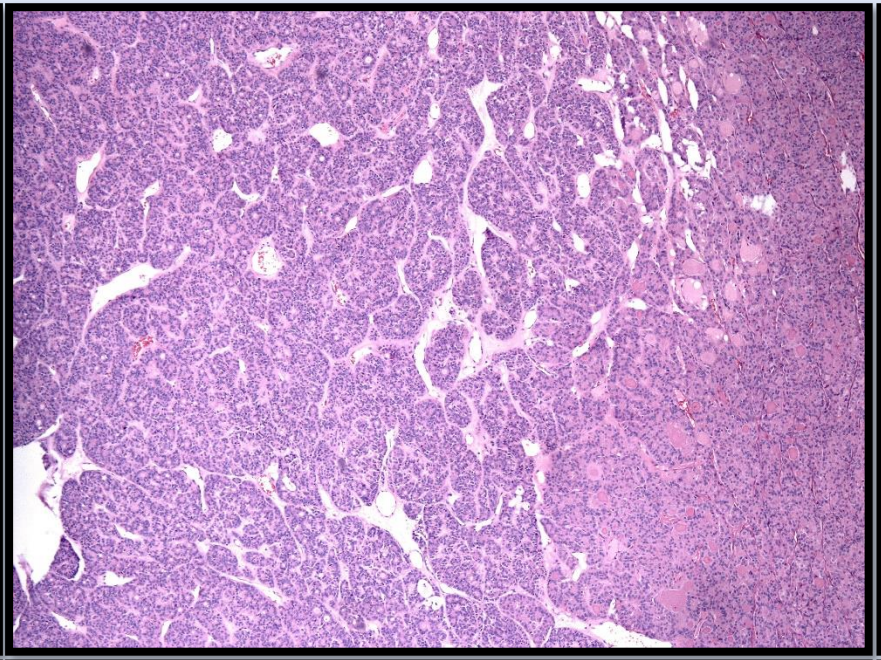
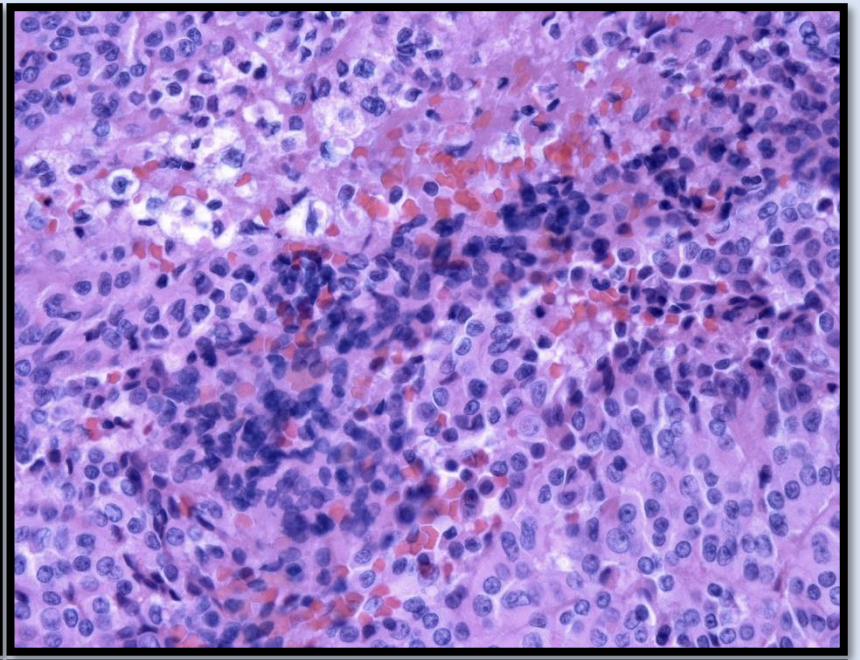
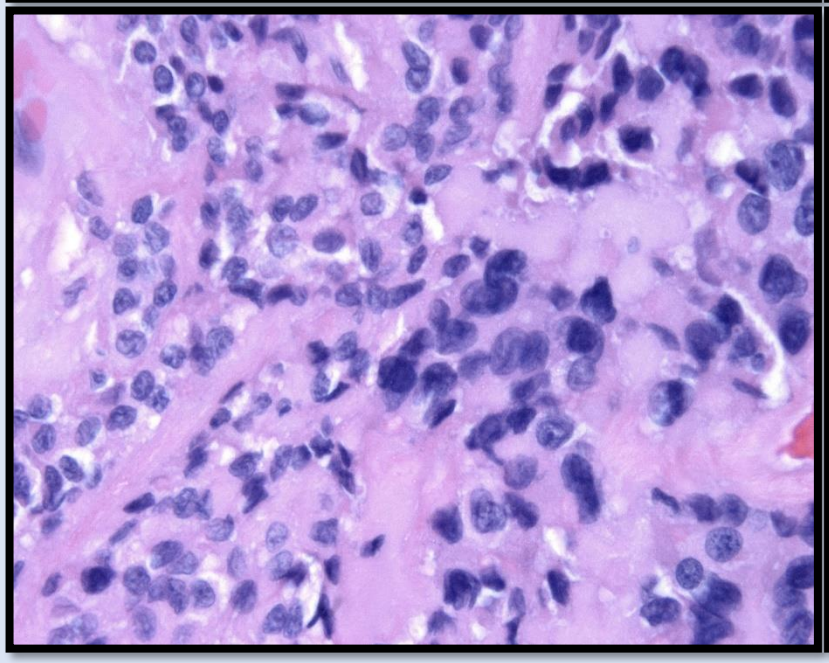
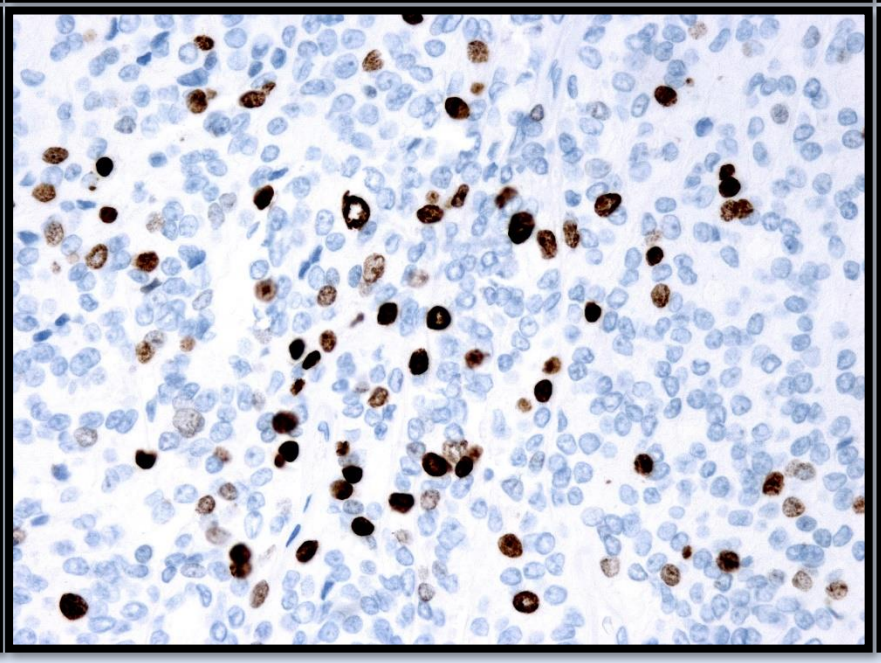
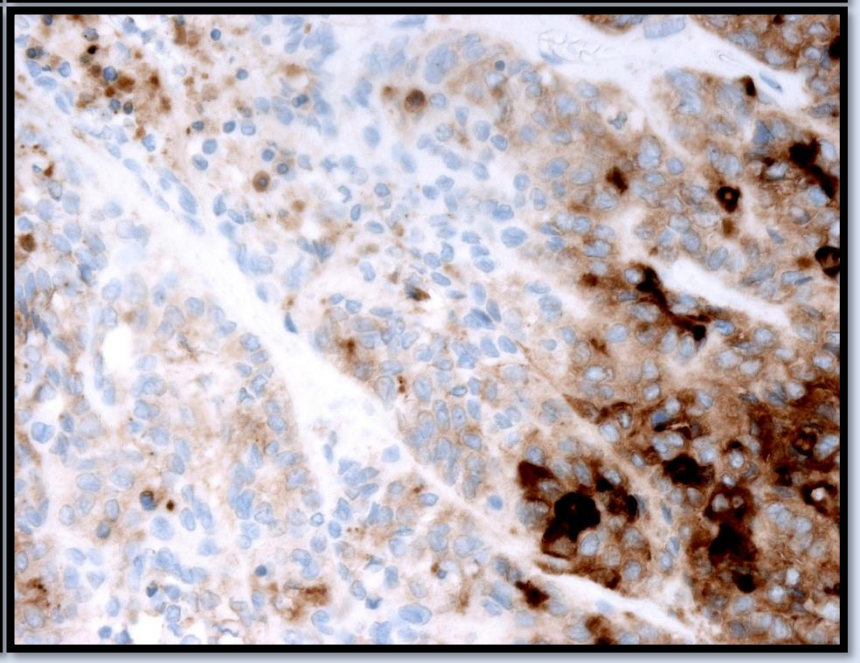
PDTCA: Cellular specimens. Monotonous cell population. Anisonucleosis, rare. Evenly dispersed nuclear chromatin. *Most diagnosed as follicular neoplasm.*

PDTCA: Cellular specimens. Monotonous cell population. Anisonucleosis, rare. Evenly dispersed nuclear chromatin.



PDTCA: Histologic Follow-up

What Else?

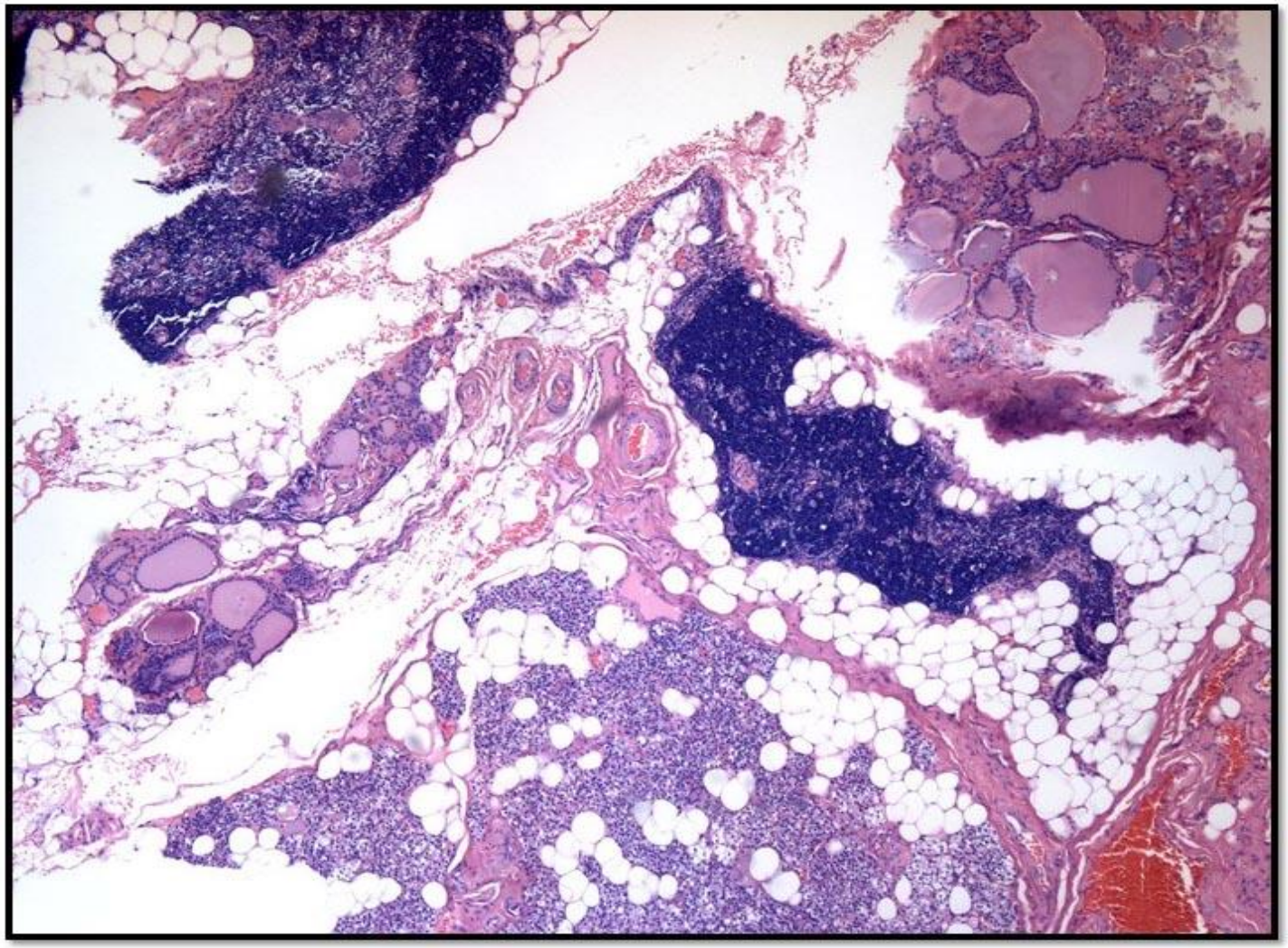
Things to Remember and be Reminded of…

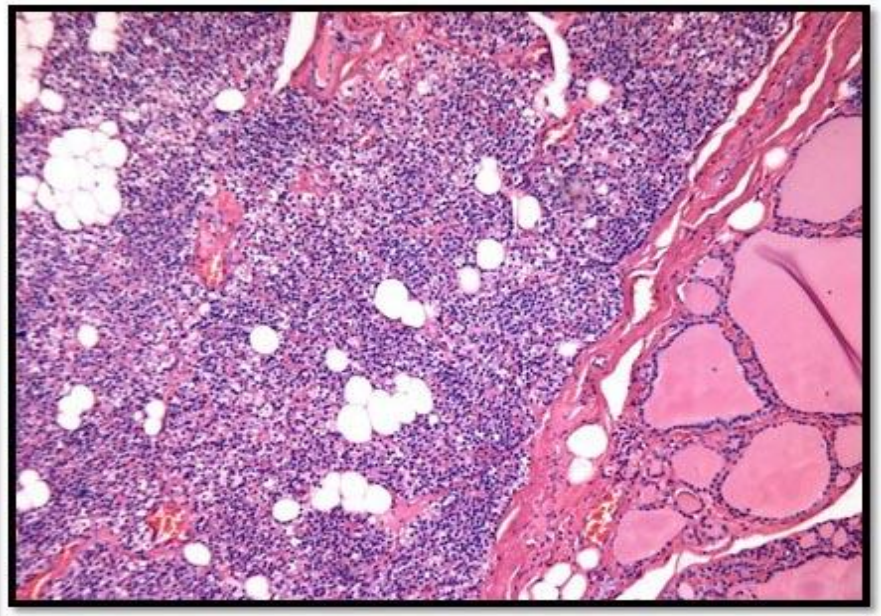
Nodules measuring 1.0 cm or less

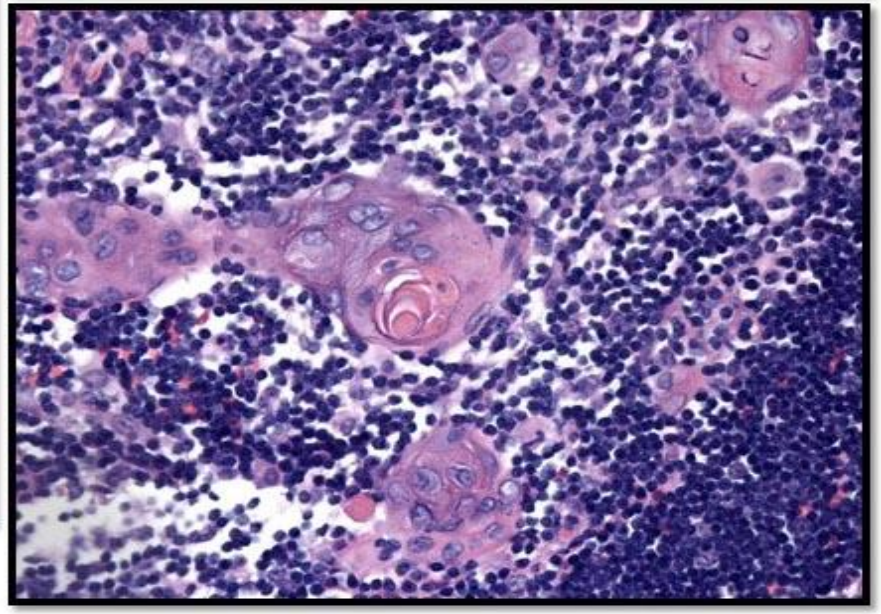
- Most are PTC (classic or follicular variant)
- Rarely Medullary microcarcinoma
- 1.0 cm or less Follicular Carcinoma – non-existent
- Rare cases of Hürthle cell / Oncocytic follicular carcinoma measuring ≤ 1.0 cm have been reported
- ***Think of "Intrathyroidal Parathyroid Lesions"***

Think long & hard before rendering a diagnosis of "Follicular Neoplasm" on a ≤ 1.0 cm nodule with microfollicles.

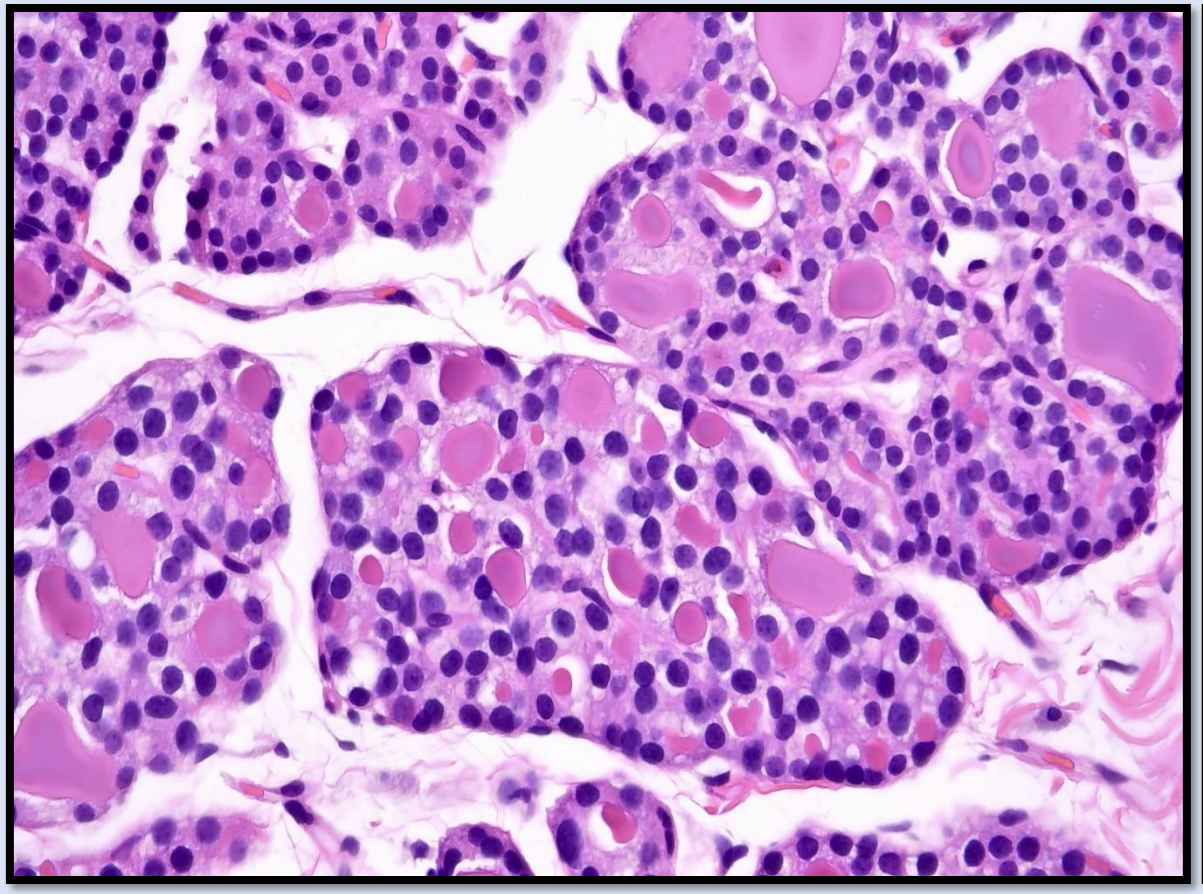
Ectopic Tissues

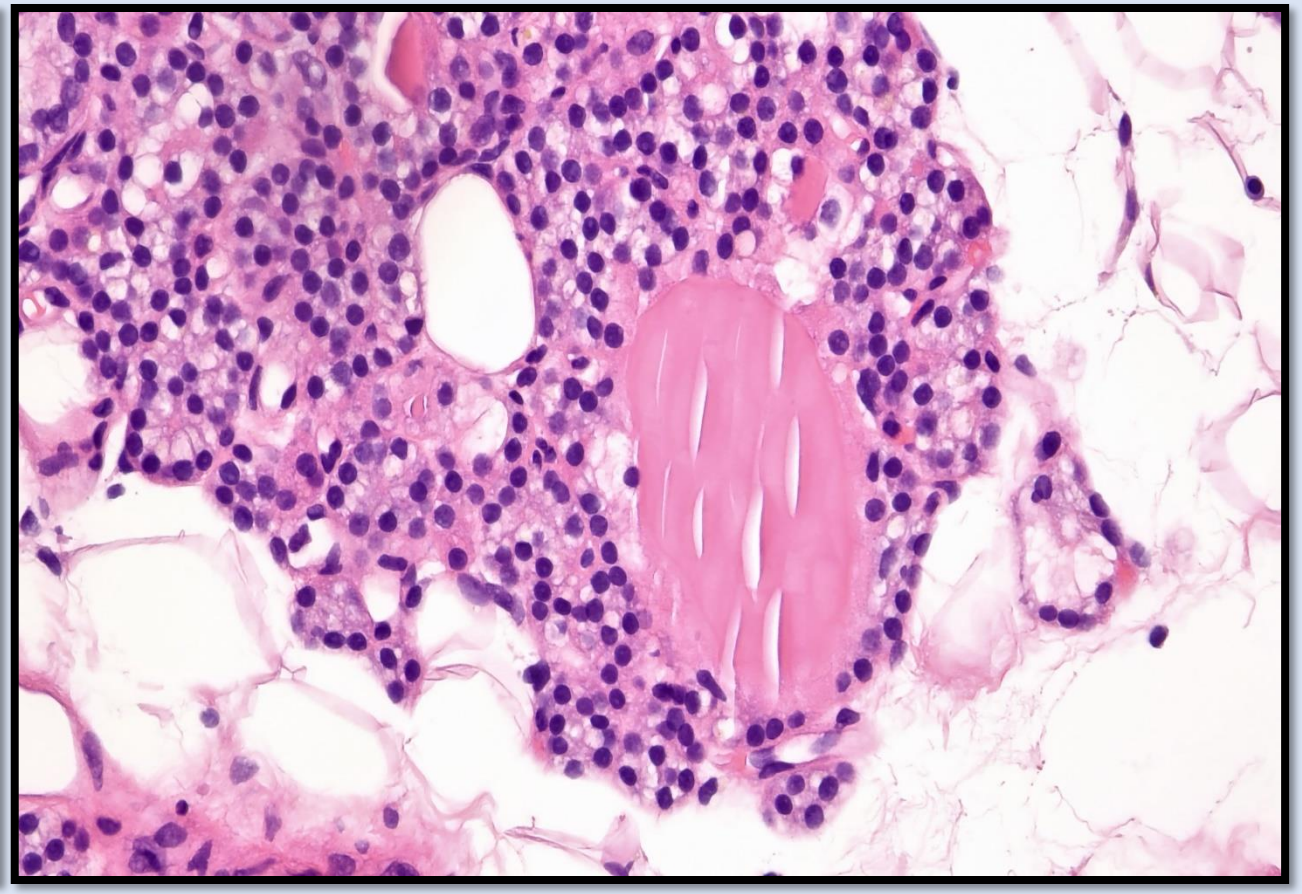






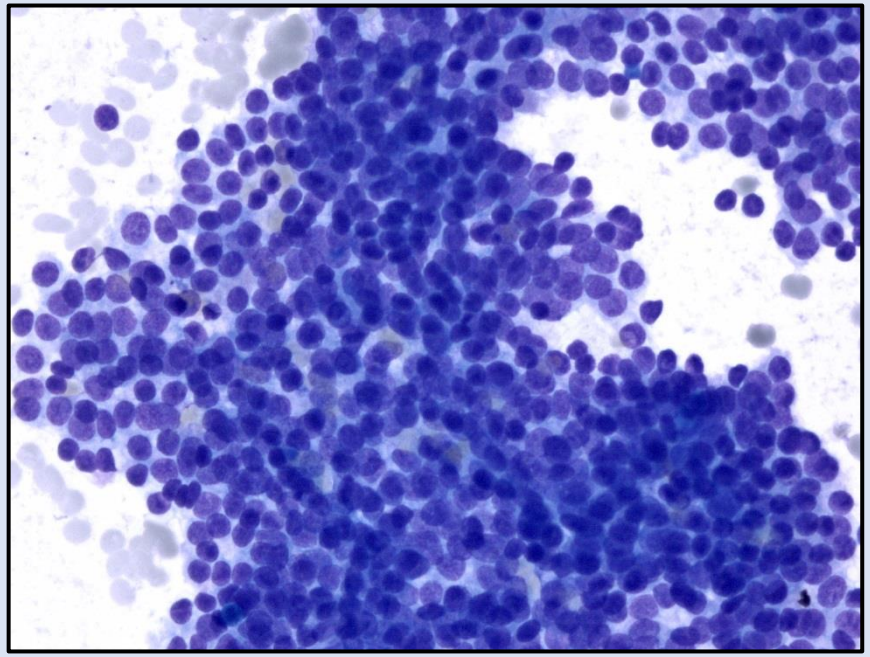
Parathyroid Acini Mimicking Thyroid Follicles

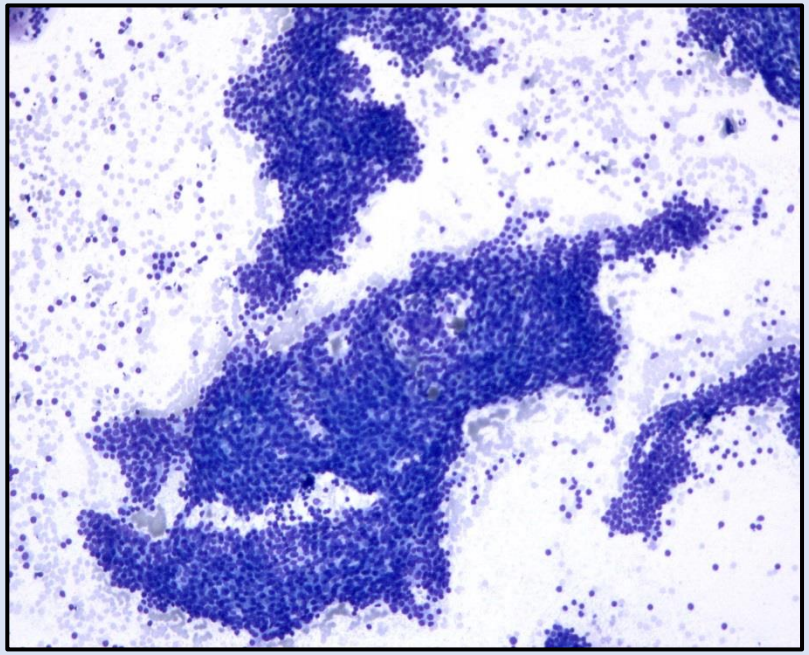


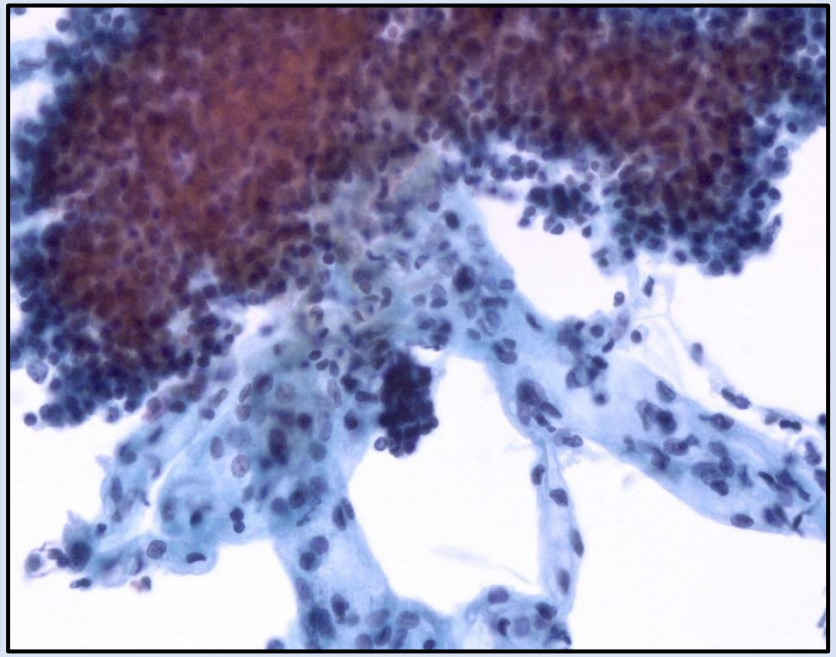


Intrathyroidal Parathyroid

Think long & hard before rendering a diagnosis of "Follicular Neoplasm" on a ≤ 1.0 cm nodule with microfollicles.

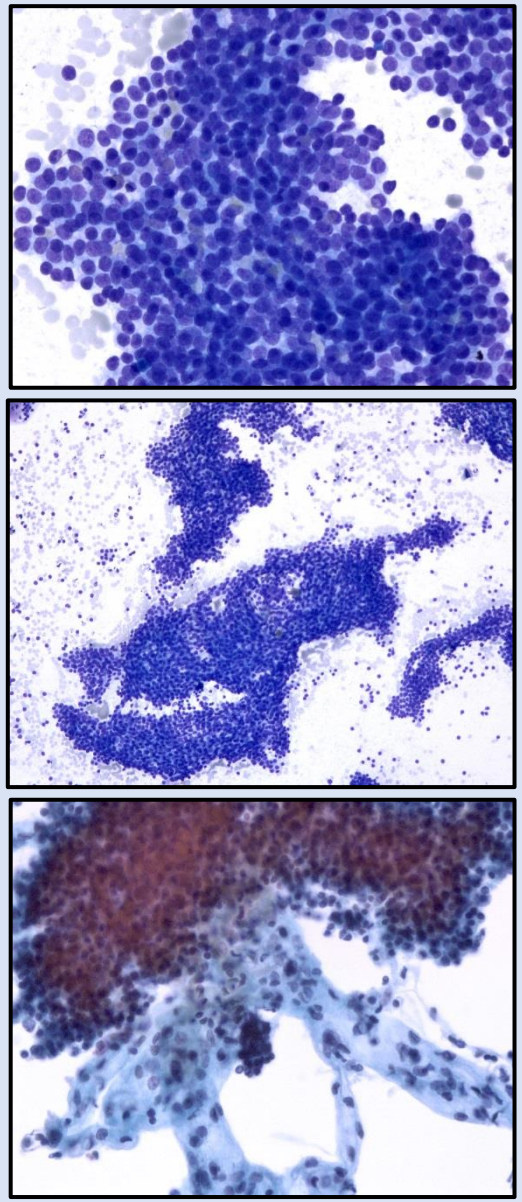


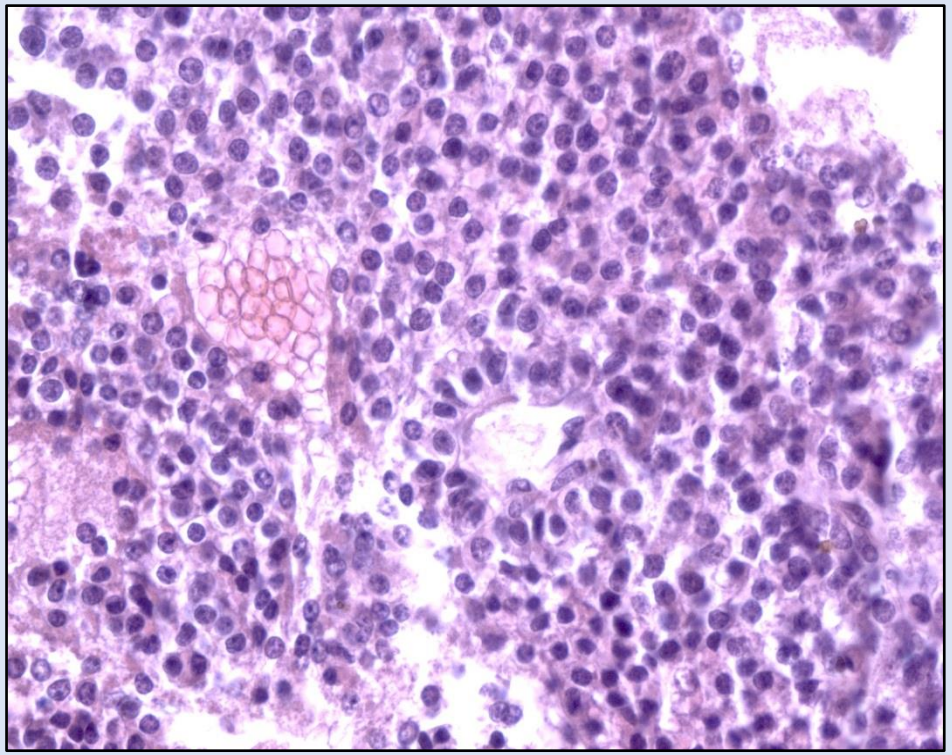


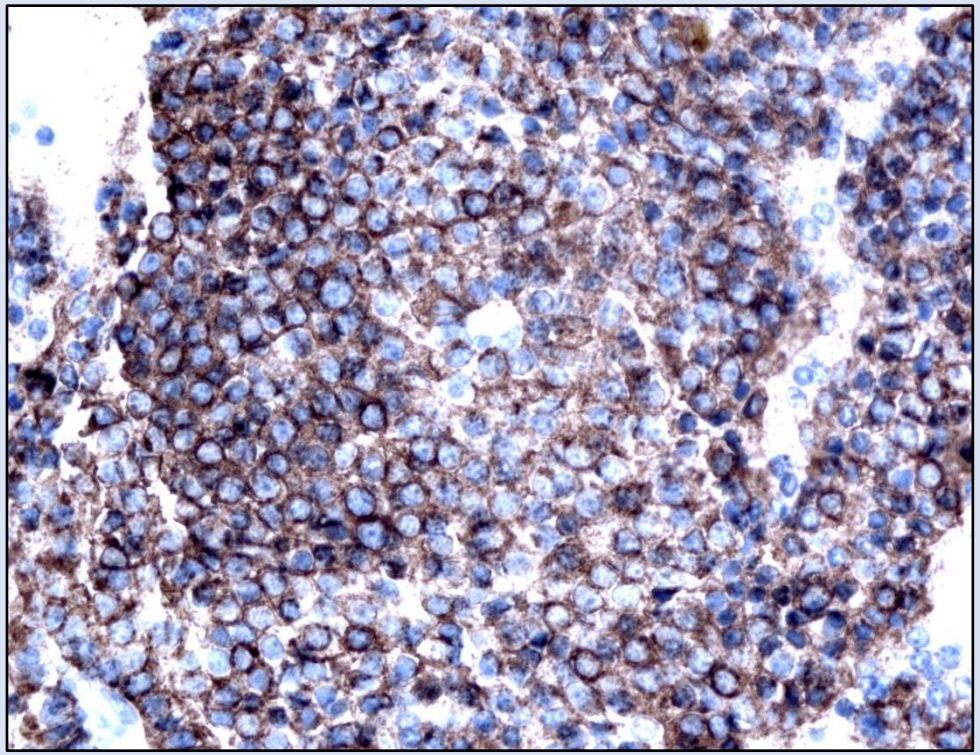


Papillary Formation can be seen in Parathyroid FNA Specimens

Intrathyroidal Parathyroid FNA

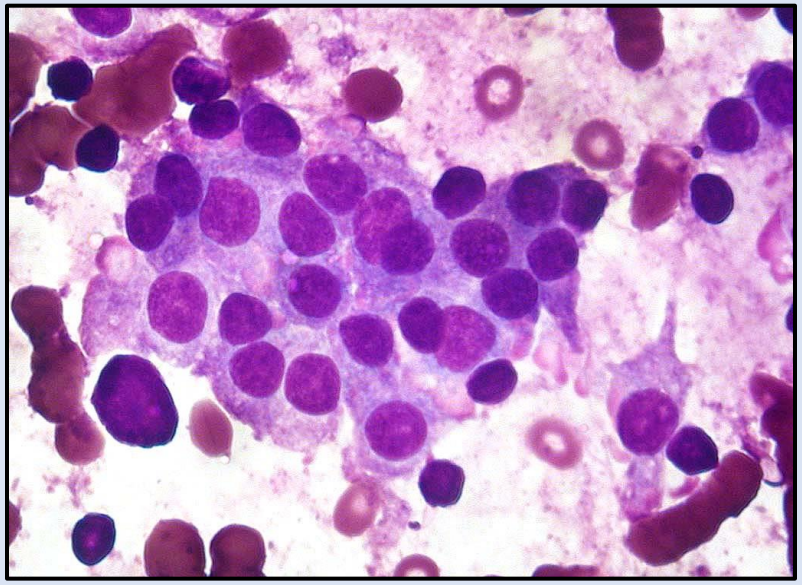


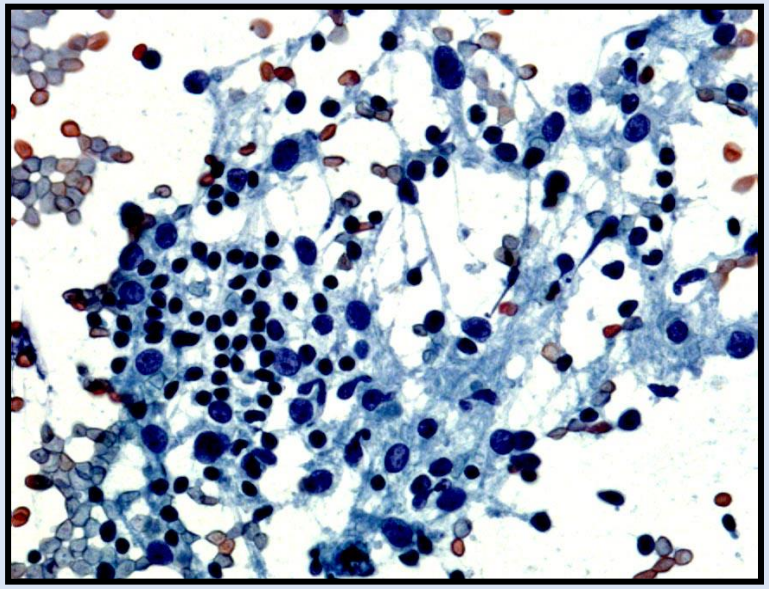


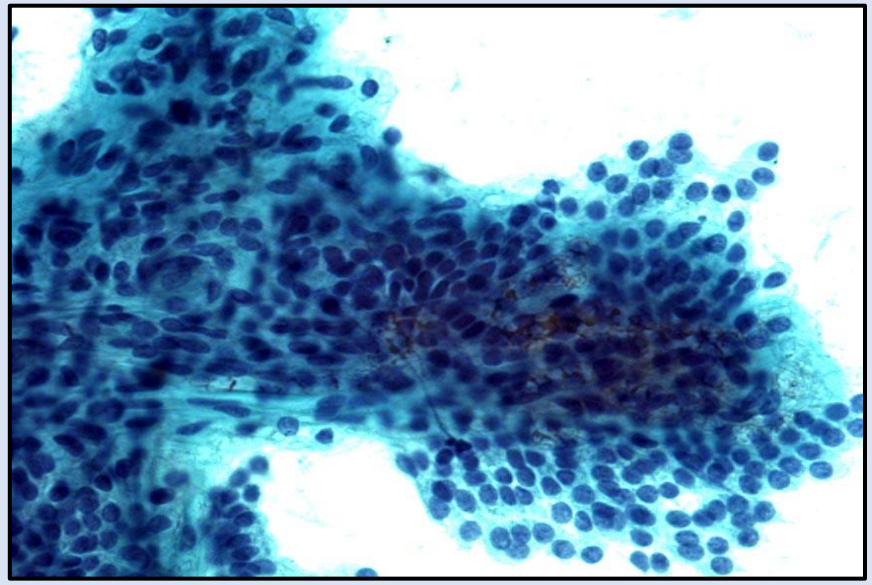


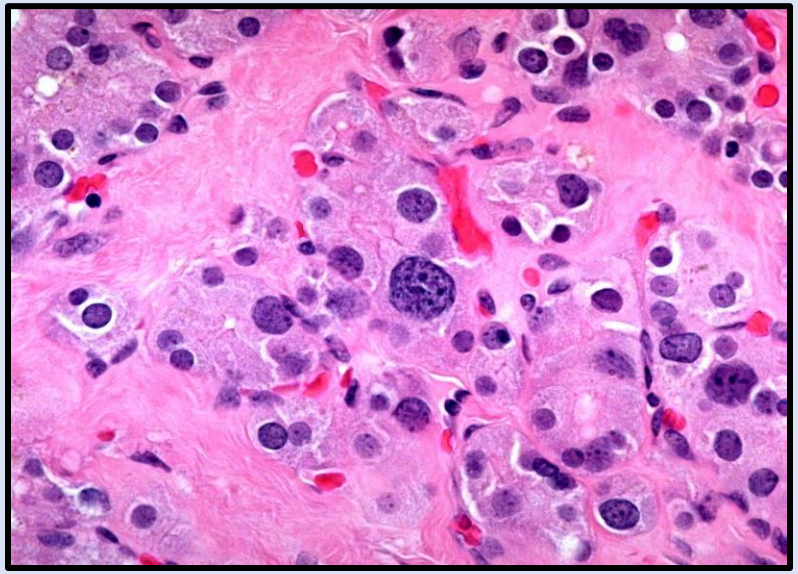
PTH Levels on portion of aspirate or
Immunostain for PTH on Cell Block
(other stains GATA3, Chromogranin or TTF-1)

Nuclear & Architectural Atypia Can be Encountered In Benign Lesions Of Thyroid Gland

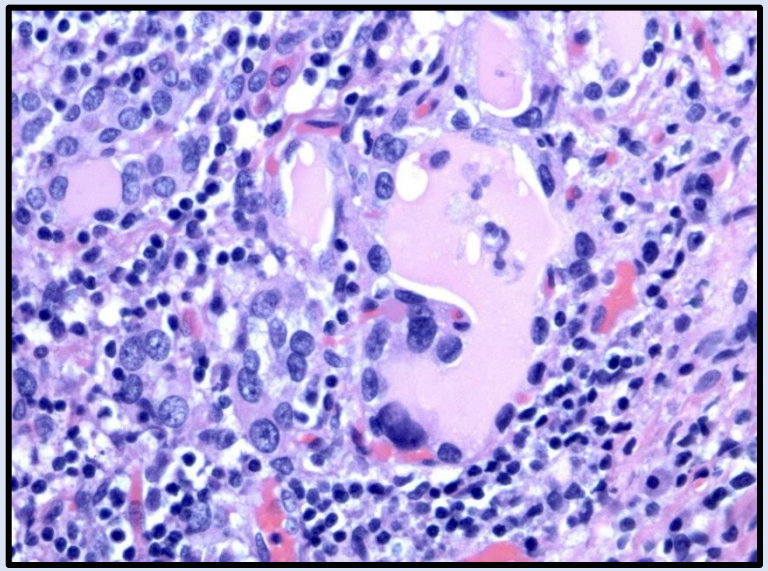




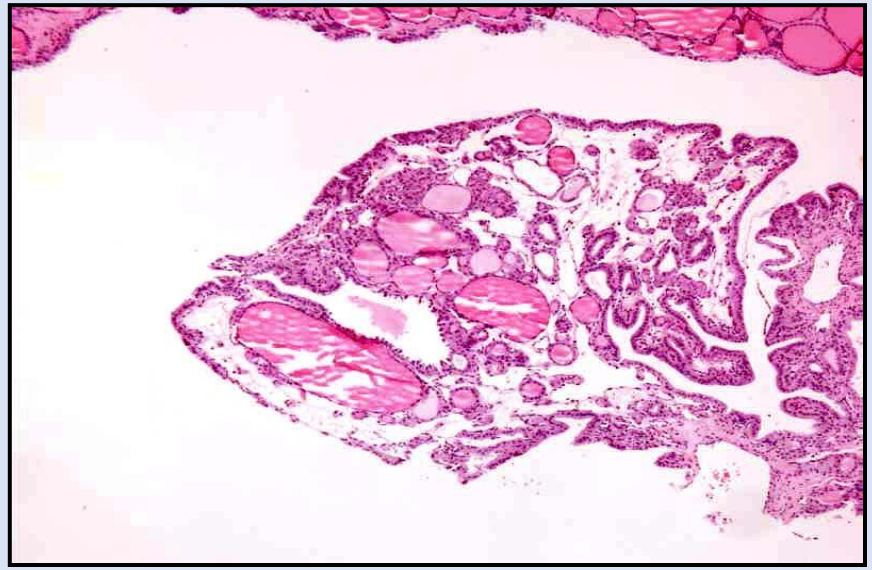




Graves' Disease



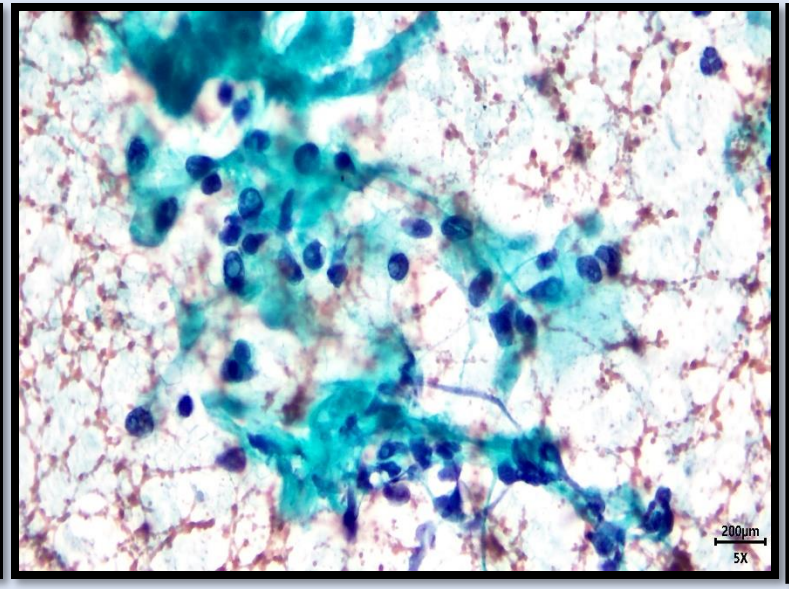
Chronic Lymphocytic Thyroiditis

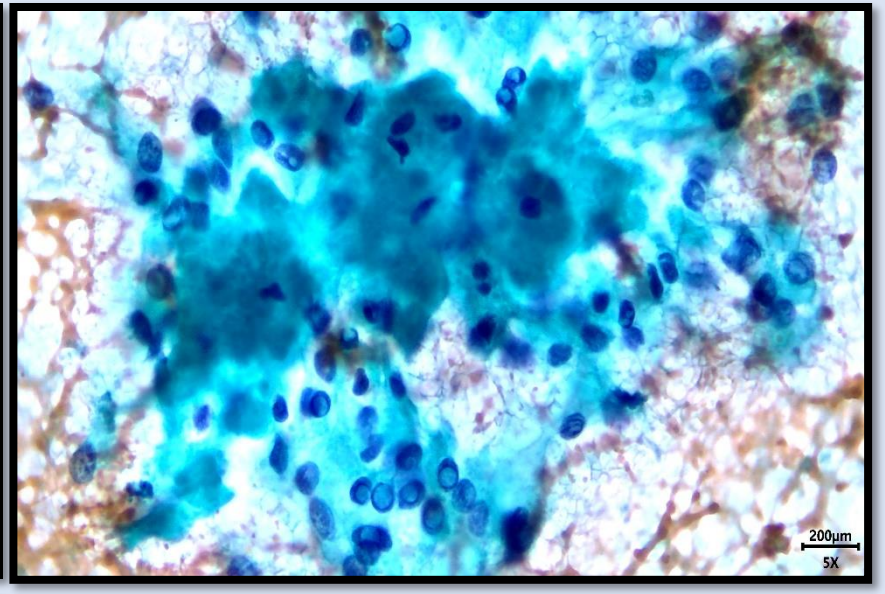


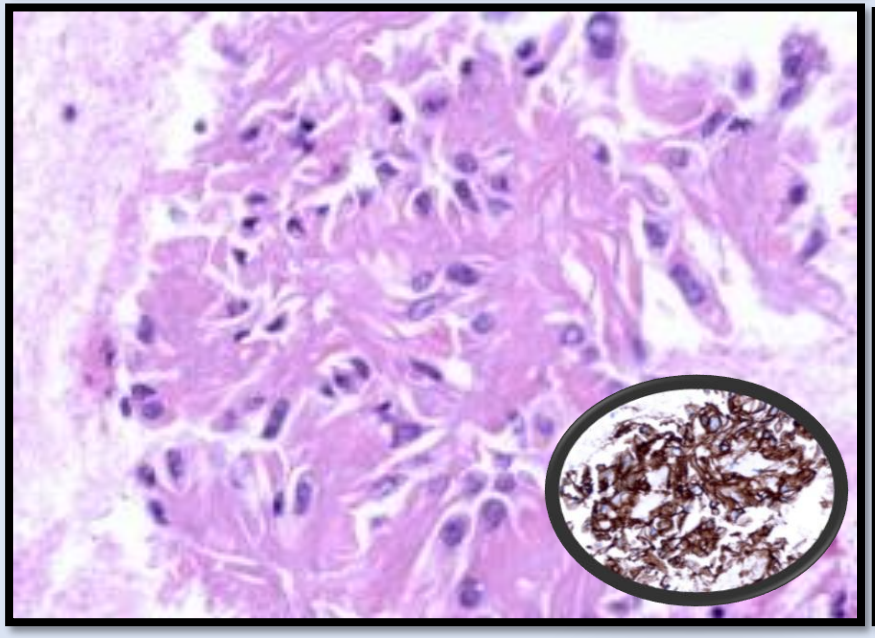
Papillary Adenomatous Nodule / Papillary Adenoma

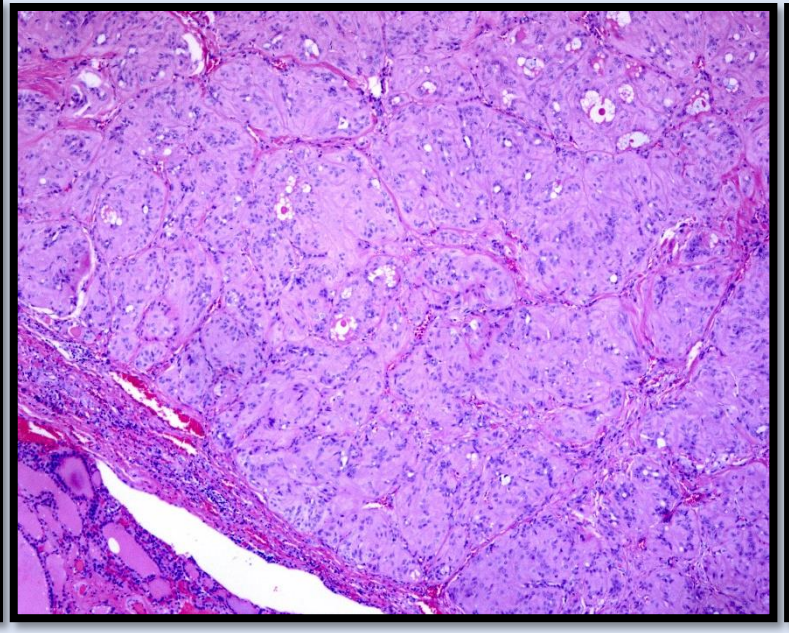
Mimics of Malignant Neoplasms – Hyalinizing Trabecular Tumor

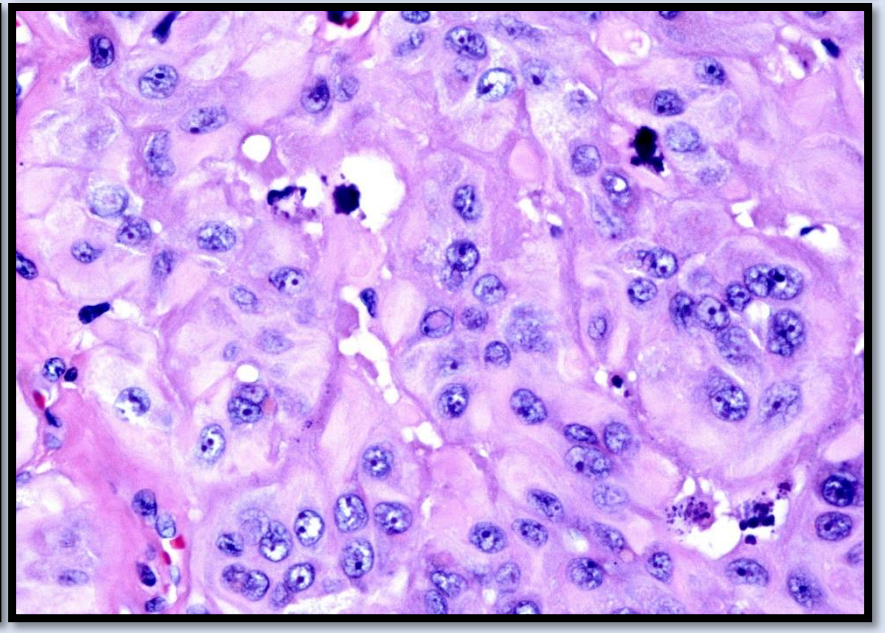
MIB1 IHC , GLIS - rearrangements



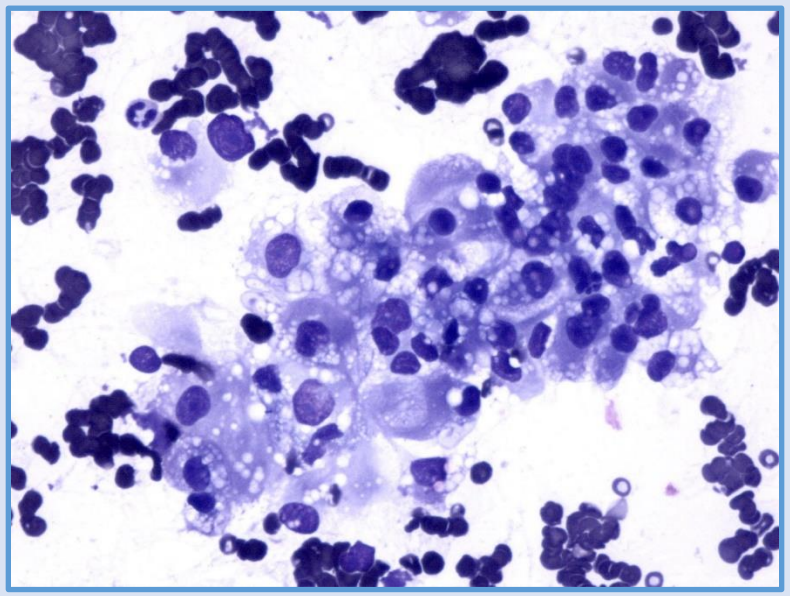


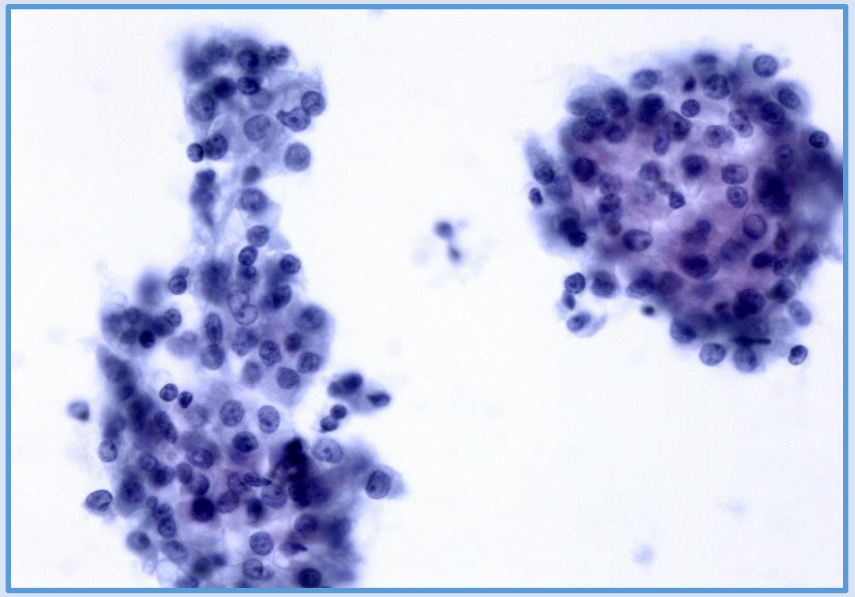


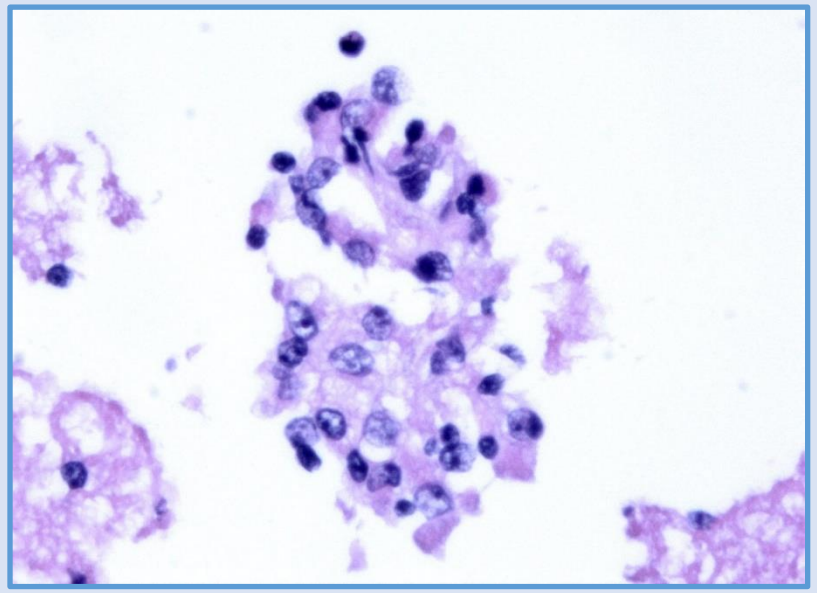


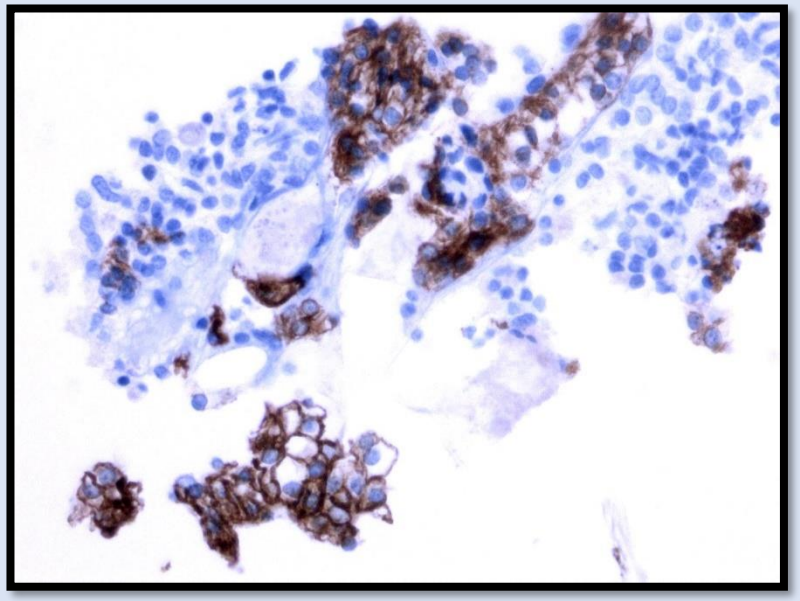


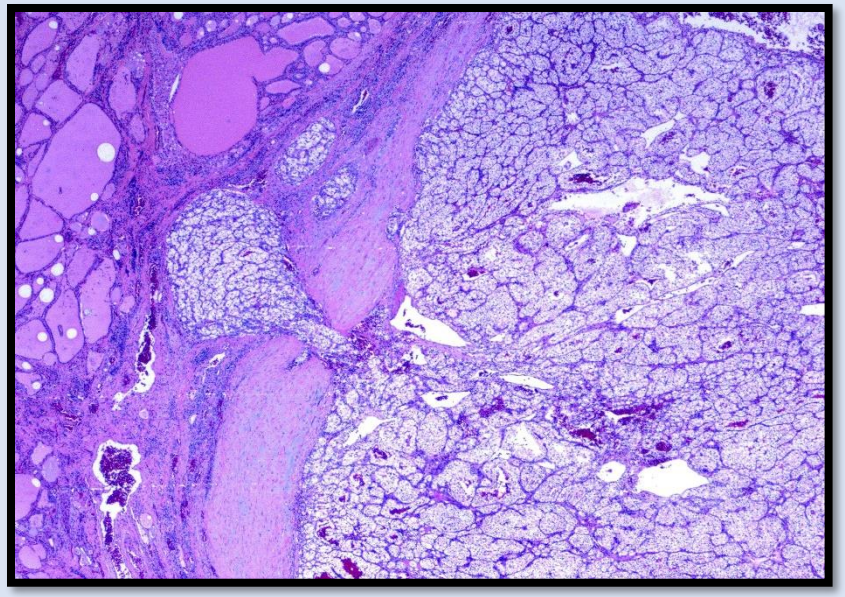
Clear Cells – Thinking of Metastatic Renal Cell

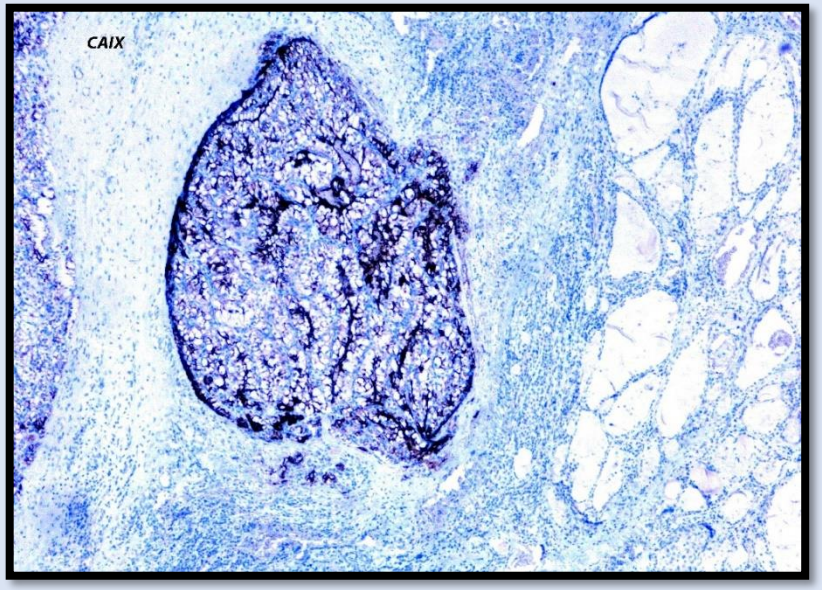




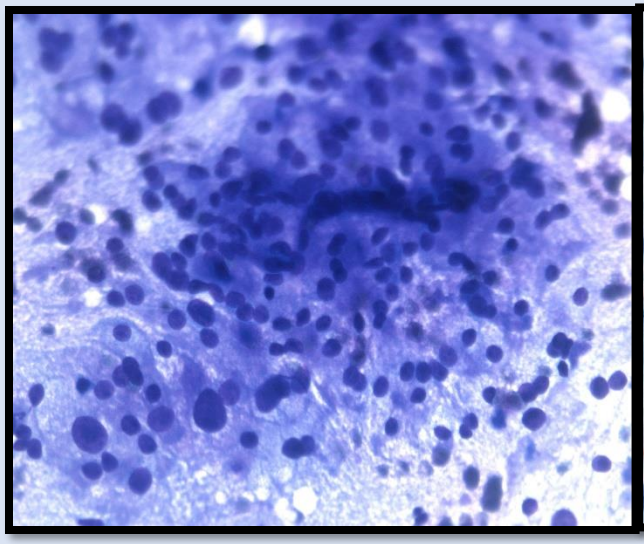


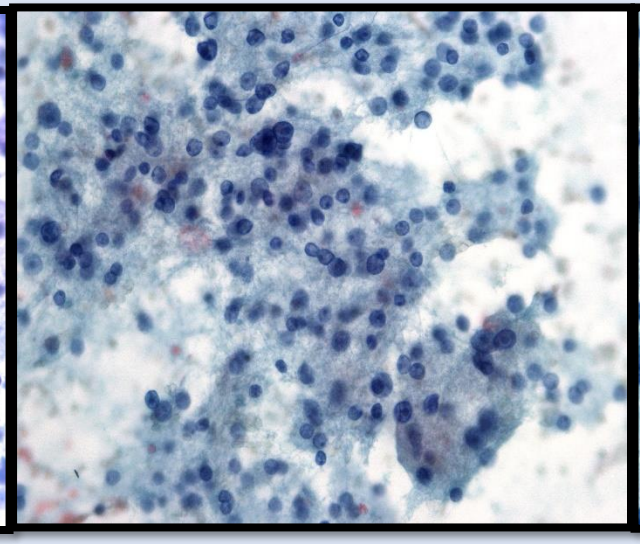


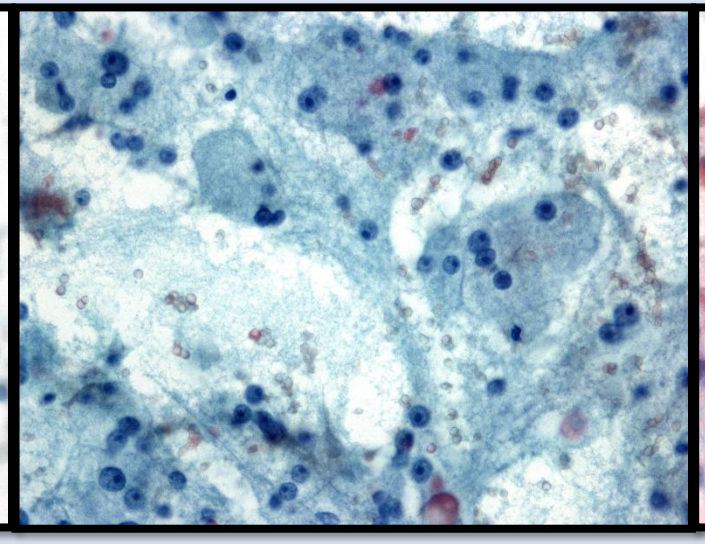


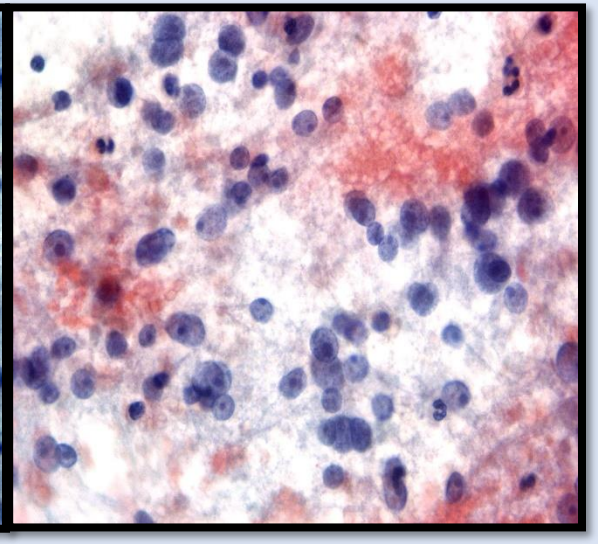


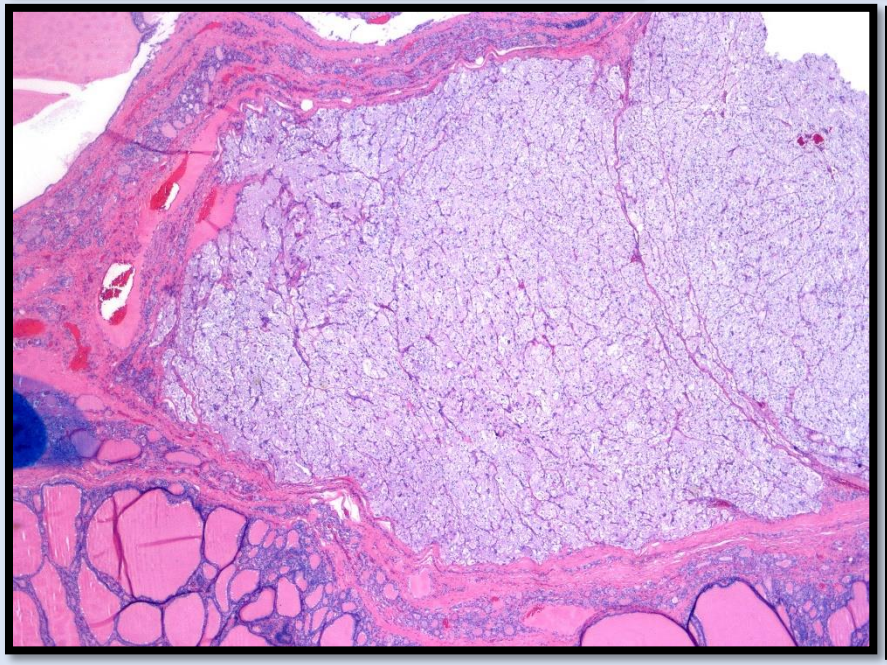
Clear Cell - Follicular Cell– Derived Neoplasm

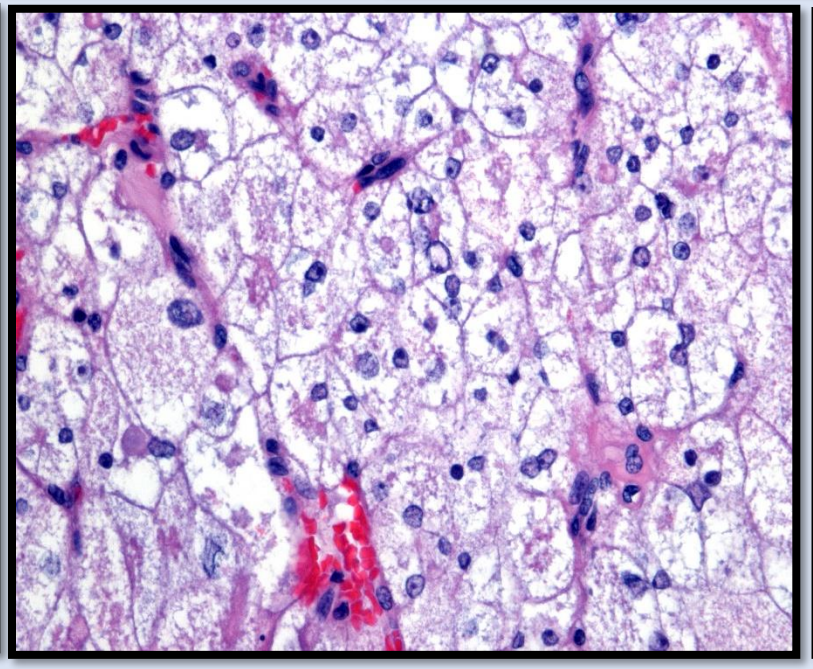




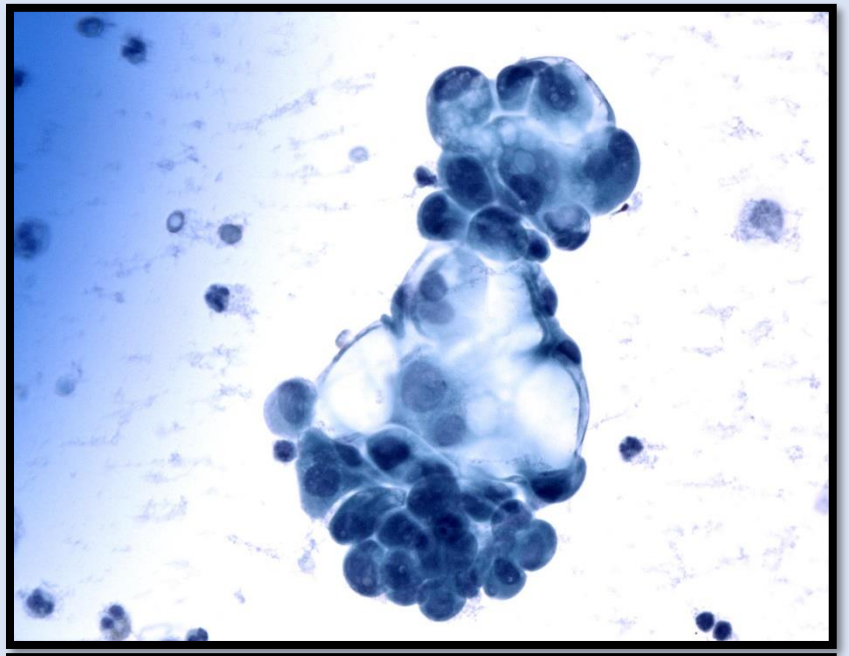


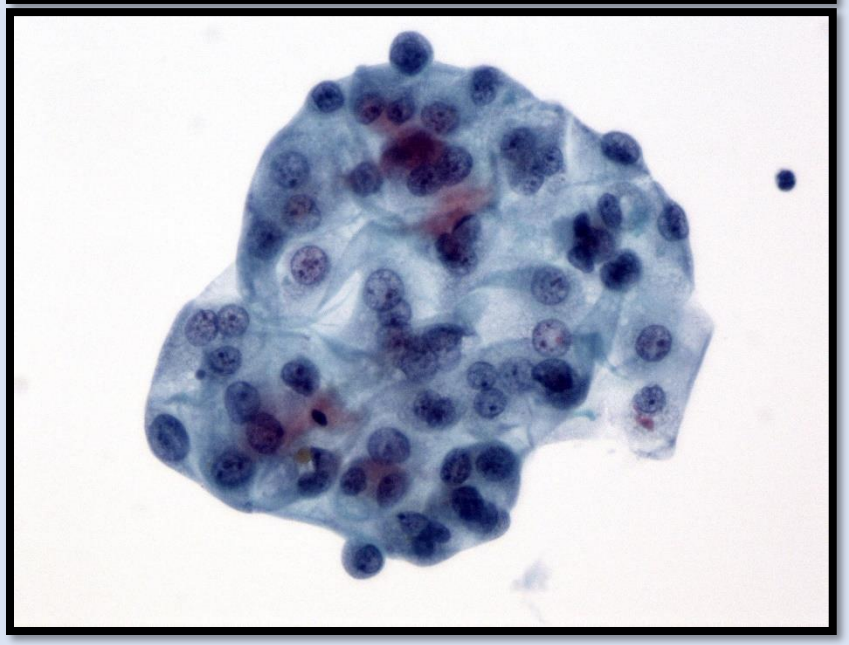


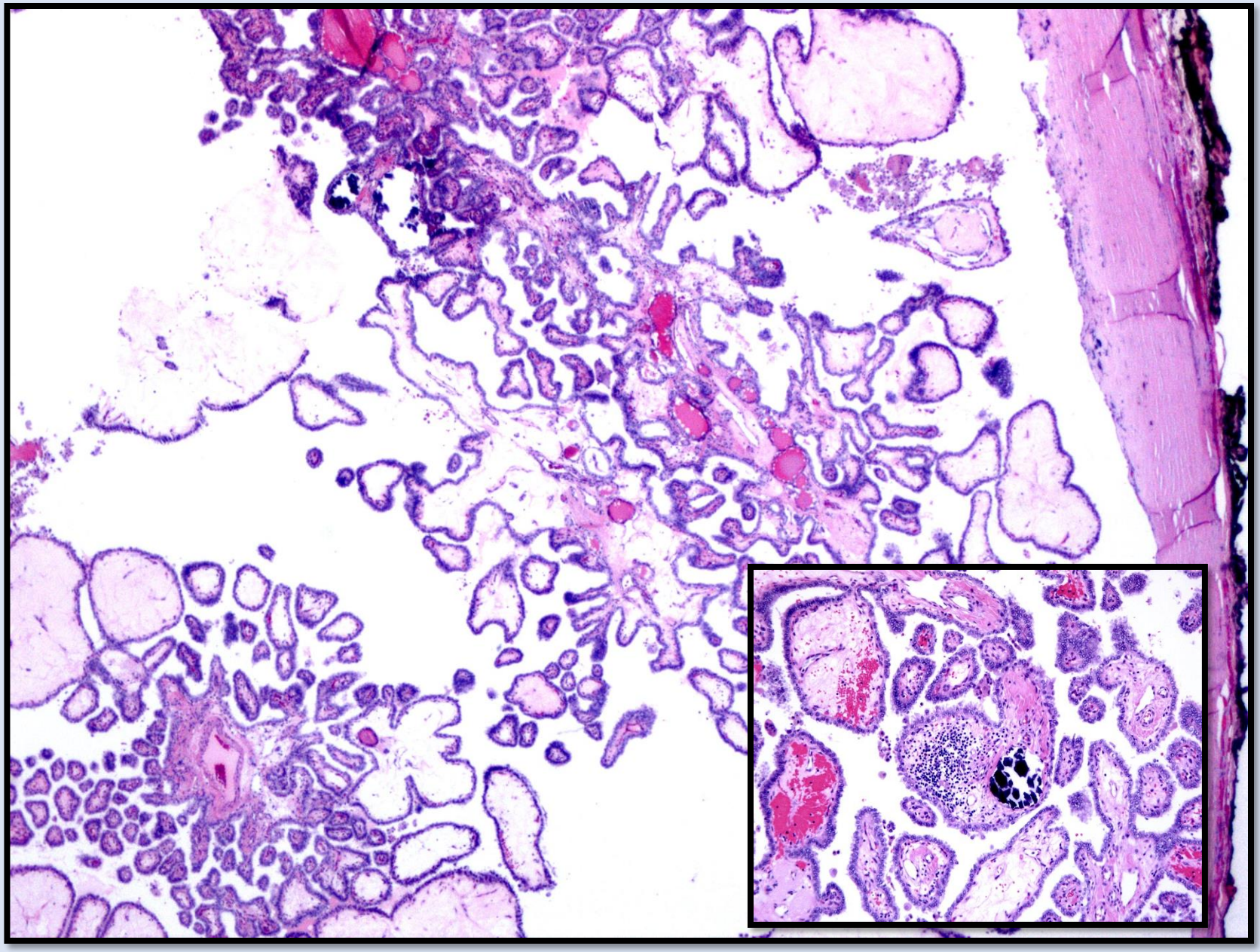




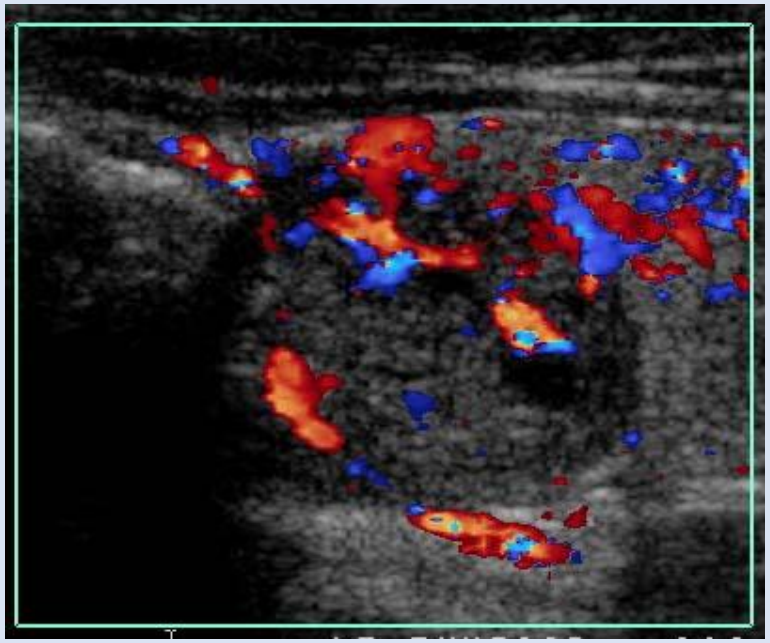
Clear Cell Follicular Cell Derived - Neoplasm – Cystic PTC

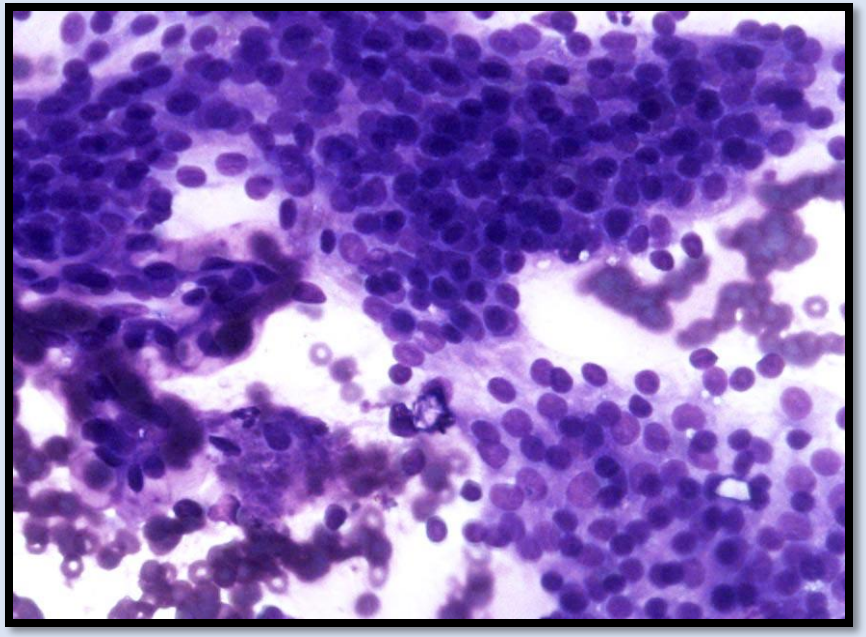


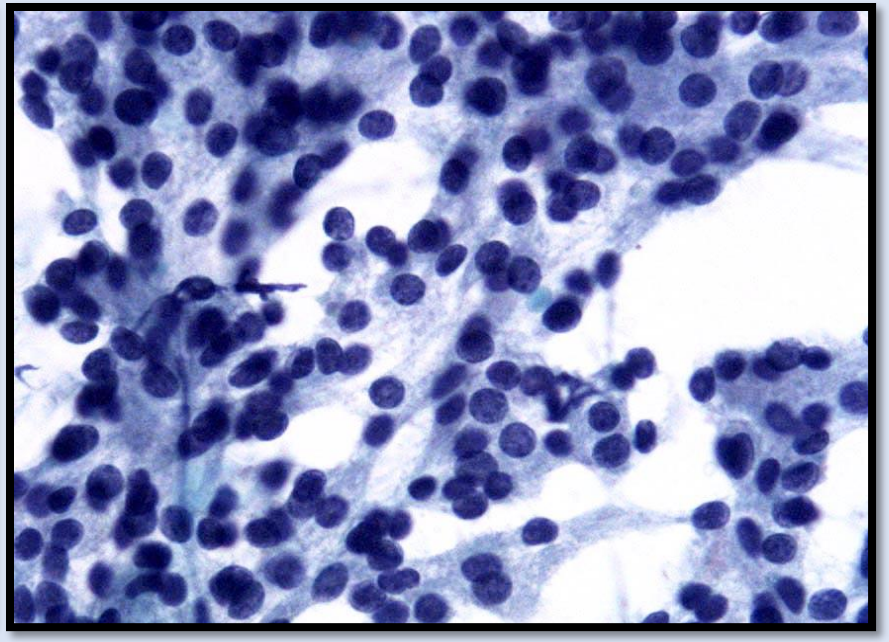


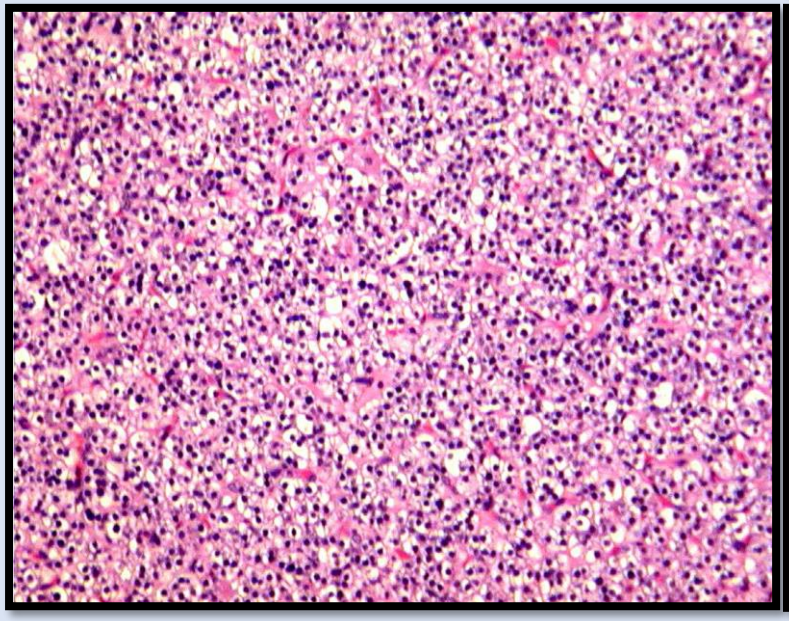


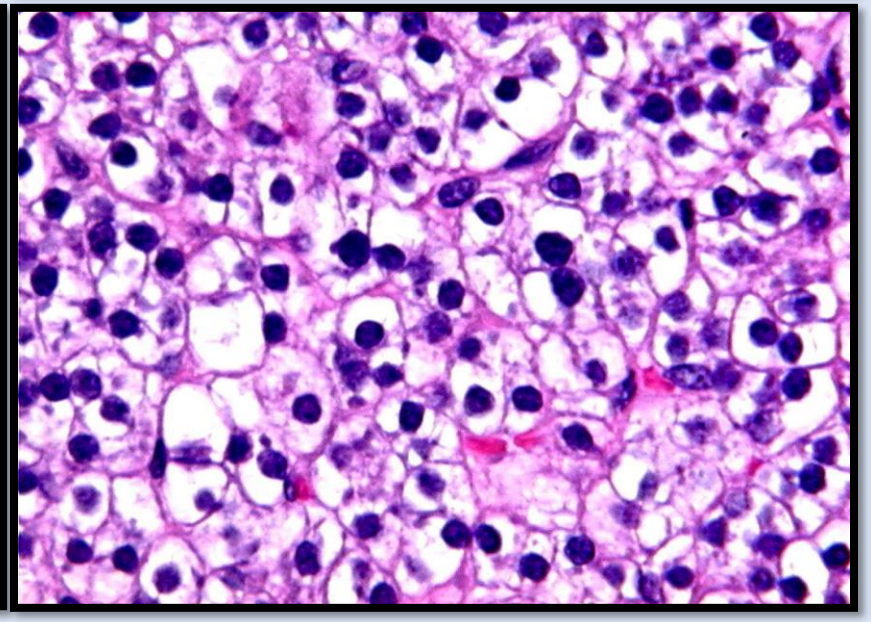
Clear Cell Non-Follicular Cell Derived – Neoplasms

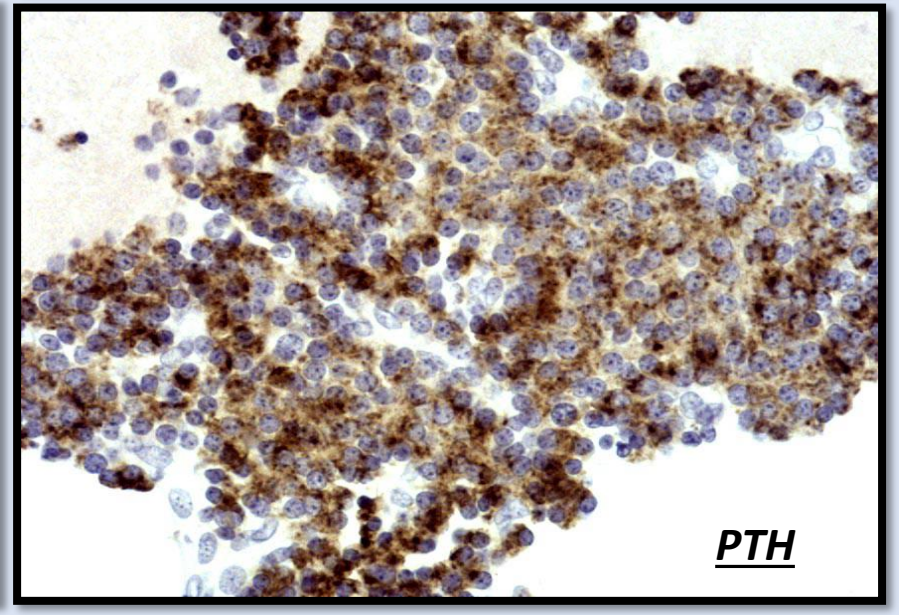


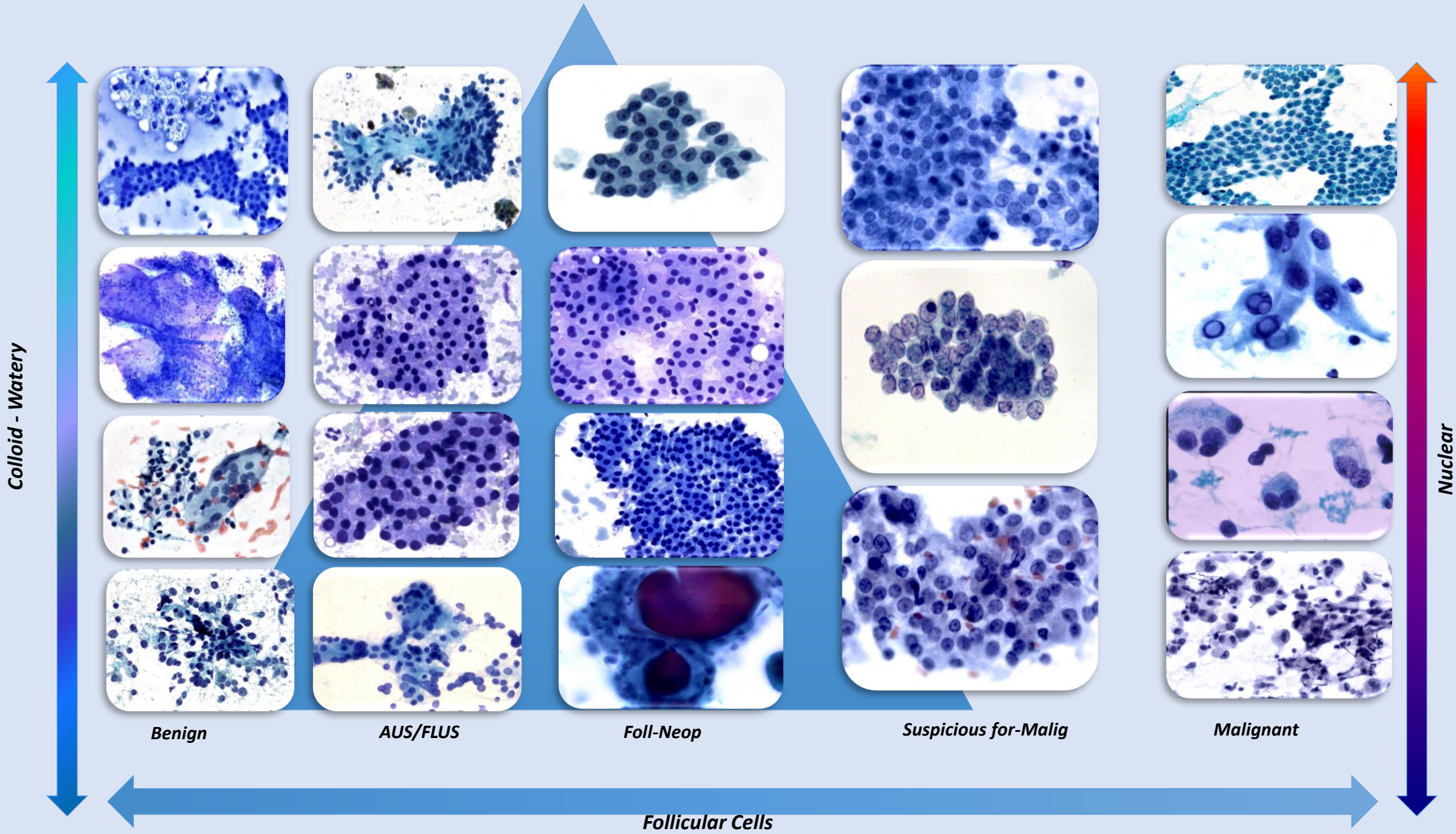











Colloid - Watery
Nuclear Atypia
Benign
AUS/FLUS
Foll-Neop
Suspicious for-Malig
Malignant
Follicular Cells

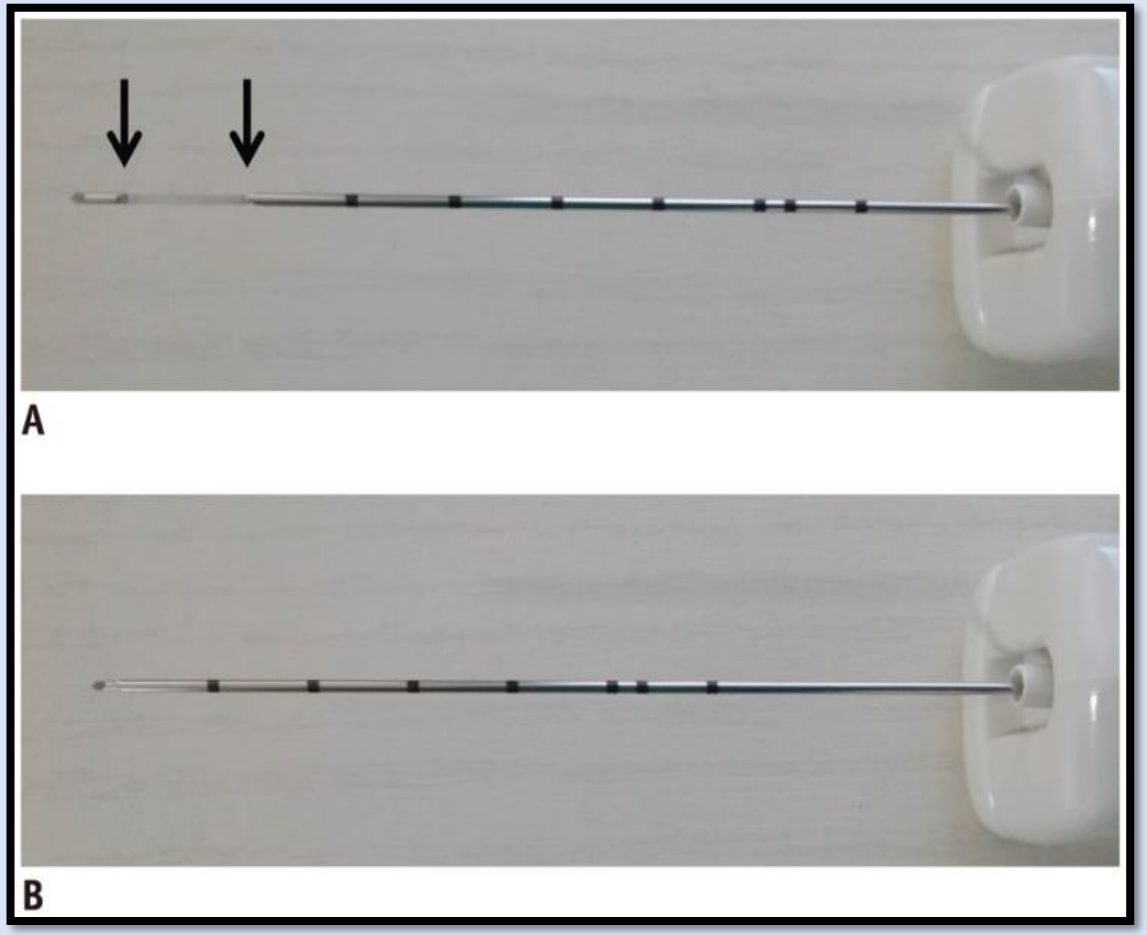
Thyroid Nodule Biopsy ---

Volume 15 | Issue 1 | January 2022
Clinical Thyroidology® for the Public
AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Thyroid biopsy is usually done with a thin needle (fine needle biopsy) and is a well-tolerated procedure with minimal to no complications and can be done in the office. ***However, up to 10% of thyroid fine needle biopsies will not have enough cells for a diagnosis.***

An alternative method to evaluate thyroid nodules is a Core Needle Biopsy (CNB).
This procedure uses a large needle and requires an experienced operator with specific training.
CNB also has a higher risk of complications than a fine needle biopsy, including injuries to the trachea and carotid artery.

2017 & 2019 Practice guidelines for thyroid core needle biopsy: a report of the Clinical Practice Guidelines Development Committee of the Korean Thyroid Association



Core needle device. **A.** Stylet and specimen notch (arrows). **B.** Cutting cannula.

Korean J Radiol. 2017 Jan-Feb;18(1):217-237.
https://doi.org/10.3348/kjr.2017.18.1.217

Consensus Statement and Recommendations from the Korean Society of Thyroid Radiology

Indication of CNB

1. CNB could be alternative to FNA in evaluation of thyroid nodules in selected cases.

Device and procedure of CNB

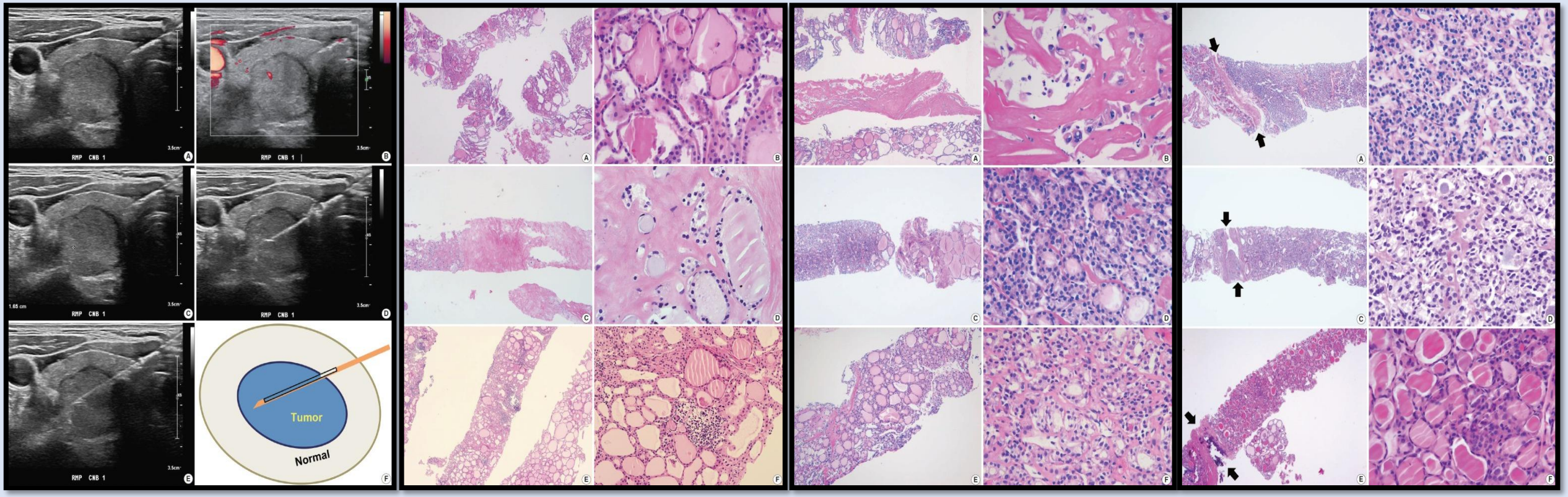
1. Modern CNB devices, **particularly 18–21-gauge, spring-activated, core needles, are recommended for procedure.**
2. **Patients with bleeding tendency**, such as those taking anticoagulation medications or with disorders affecting coagulation cascade, **should be thoroughly evaluated and any problems corrected before CNB**.
3. CNB should be performed by experienced operators under ultrasound guidance.
4. Manual compression of biopsy site should be performed immediately after procedure for 20–30 min.

2017 & 2019 Practice guidelines for thyroid core needle biopsy: a report of the Clinical Practice Guidelines Development Committee of the Korean Thyroid Association: Diagnostic Categories

I. Nondiagnostic or unsatisfactory	
	Non-tumor adjacent thyroid tissue only
	Extrathyroid tissue only (e.g., skeletal muscle, mature adipose tissue)
	Acellular specimen (e.g., acellular fibrotic tissue, acellular hyalinized tissue, cystic fluid only)
	Blood clot only
	Other
II. Benign lesion	
	Benign follicular nodule
	Hashimoto's thyroiditis
	Subacute granulomatous thyroiditis
	Nonthyroidal lesion (e.g., parathyroid lesions, benign neurogenic tumors, benign lymph node)
	Other
III. Indeterminate lesion	
	IIIa. Indeterminate follicular lesion with nuclear atypia
	IIIb. Indeterminate follicular lesion with architectural atypia
	IIIc. Indeterminate follicular lesion with nuclear and architectural atypia
	IIId. Indeterminate follicular lesion with Hürthle cell changes
	IIIe. Indeterminate lesion, not otherwise specified
IV. Follicular neoplasm	
	IVa. Follicular neoplasm, conventional type
	IVb. Follicular neoplasm with nuclear atypia
	IVc. Hürthle cell neoplasm
	IVd. Follicular neoplasm, not otherwise specified
V. Suspicious for malignancy	
	Suspicious for papillary thyroid carcinoma, medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, metastatic carcinoma, lymphoma, etc.
VI. Malignant	
	Papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, medullary thyroid carcinoma, lymphoma, metastatic carcinoma, etc

Thyroid Core Biopsy – Not an Uncommon Practice in Asia

Na DG, Baek JH, Jung SL, et al. *Korean J Radiol.* 2017;18:217–37Core needle biopsy of the thyroid: 2016 consensus statement and recommendations from Korean Society of Thyroid Radiology. .



<u>Jung CK et al.</u> **J Pathol Trans Med 2020 Jan; 54(1): 64–86. 2019 Practice guidelines for thyroid core needle biopsy: a report of the Clinical Practice Guidelines Development Committee of the Korean Thyroid Association. and Clinical Practice Guidelines Development Committee of the Korean Thyroid Association**

Jung Ck. J Pathol Transl Med 2023 Jul;57(4):208-216. Reevaluating diagnostic categories and associated malignancy risks in thyroid core needle biopsy

Ahn, S-H, Usage and Diagnostic Yield of Fine-Needle Aspiration Cytology and Core Needle Biopsy in Thyroid Nodules: A Systematic Review and Meta-Analysis of Literature Published by Korean Authors. Clin Exp Otolorhino, 2021

Table 1. Number of papers on FNA or CNB in thyroid diseases published by authors from Korea

Index	Institute	FNA	CNB
1	Ajou University	2	0
2	Asan Medical Center	18	29
3	Busan Paik Hospital	17	0
4	Catholic University	10	3
5	Chung-Ang University	1	1
6	Chungbuk National University	1	0
7	Chungnam National University	4	0
8	Dong-A University	1	0
9	Ewha Womans University	1	0
10	Gacheon University	1	1
11	Yonsei University Gangnam Severance Hospital	7	0
12	Gangneung Asan Hospital	2	2
13	Gyeongsang National University	2	0
14	Hallym University	1	0
15	Human Medical Imaging	5	3
16	Inha University	2	0
17	Inje University	1	0
18	Kangbuk Samsung Hospital	1	0
19	Konkuk University	7	0
20	Korea University	7	0
21	Kyungpook National University	2	1
22	Myongji Hospital	1	0
23	National Cancer Center	2	0
24	Pusan National University	3	0
25	Samsung Medical Center	20	4
26	Seoul National University Boramae Hospital	2	0
27	Seoul National University Bundang Hospital	6	4
28	Seoul National University Hospital	8	2
29	Yonsei University Severance Hospital	65	4
30	Soonchunhyang University	1	0
31	Ulsan University Hospital	1	0
32	Yeouido St. Mary's Hospital	1	0
Total		204	54

FNA, fine-needle aspiration; CNB, core needle biopsy.

- **CNB led to a significantly lower proportion of non-diagnostic results** than fine-needle aspiration (FNA).
- The **frequency of** atypia of undetermined significance/follicular lesion of undetermined significance **(AUS/FLUS) did not decrease** as a result of performing CNB in nodules with initial AUS/FLUS results, while **it increased in consecutive cases**.
- A subcategory analysis of AUS/FLUS showed that the increased frequency of AUS/FLUS findings on CNB was due to **more frequent diagnoses of architectural atypia and follicular neoplasm, which resulted in a higher frequency of inconclusive findings in consecutive cases compared to FNA.**
- Hospitals favoring CNB had a **higher proportion of AUS/FLUS diagnoses.**
- Although the complication rate did not differ significantly between CNB and FNA, **serious complications of CNB did occur**.

Core Biopsy - Complications

Case Cohort of 6,168 patients with 6,687 thyroid nodules.

- The complication rate after US-guided CNB for thyroid lesions was **0.81% (50 / 6,169 pts)**.
- The rate of major complications was **0.06% (4 / 6,169).**
- Vascular injury was the most common complication (47/6,169; 0.76 %).
- None of the patients experienced permanent problems resulting from complications.

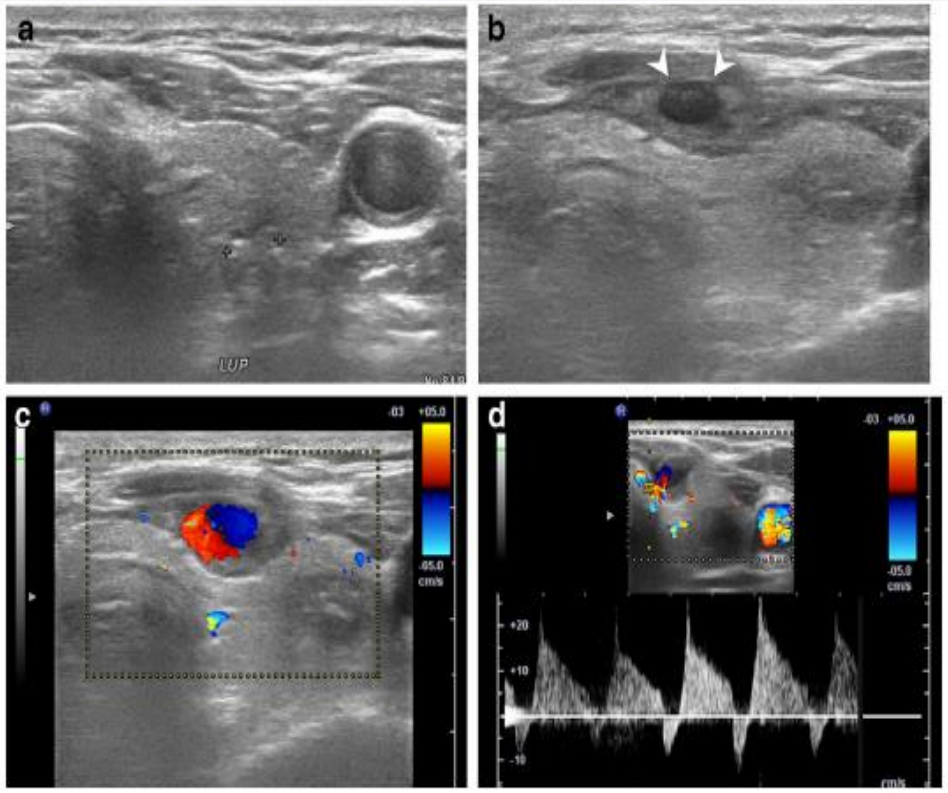
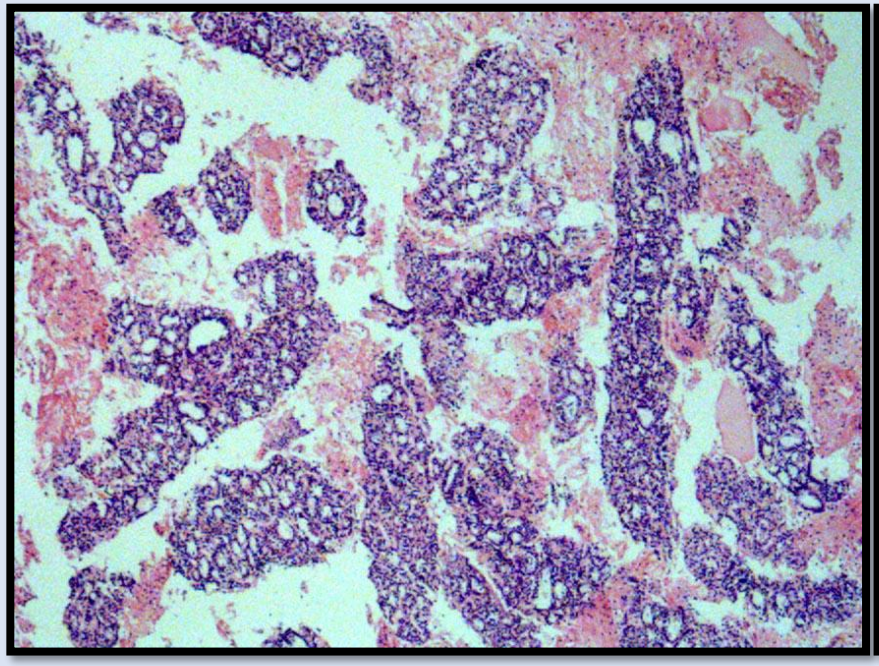
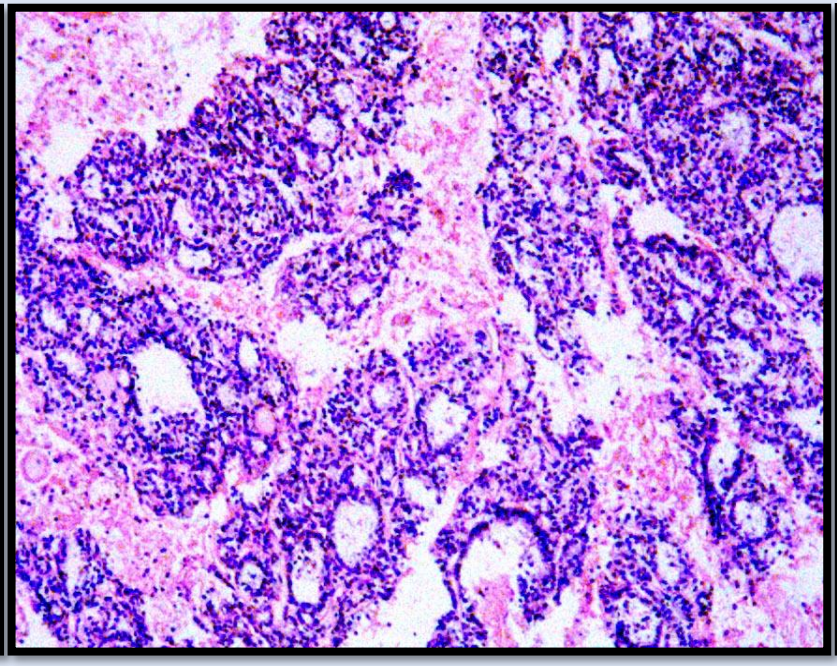
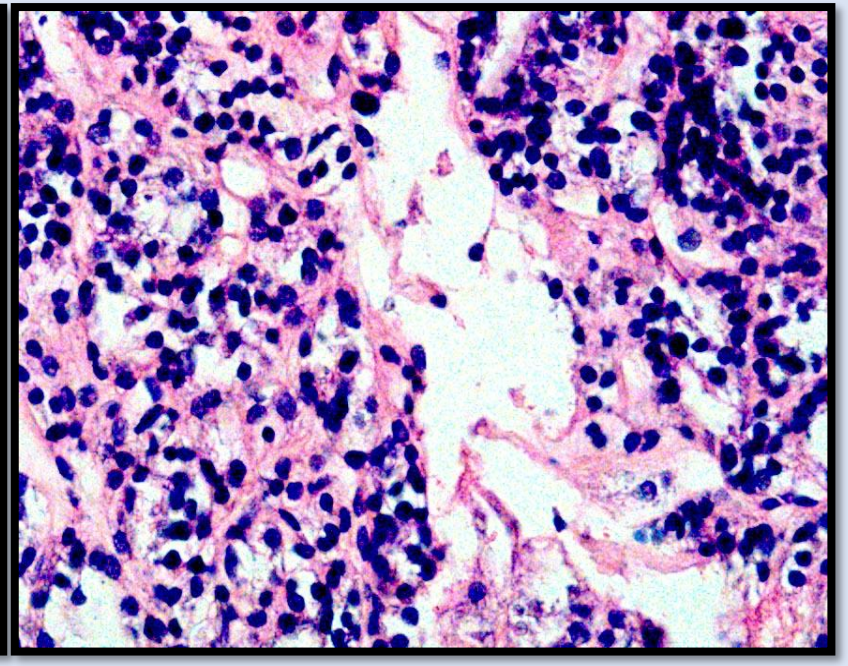


Fig. 2 A 60-year-old woman with pseudoaneurysm after CNB. **a** Transverse US scan shows a left thyroid nodule in a posterior location. **b–d** US scan reveals a pulsatile cystic mass (*arrowheads*) with a typical swirling motion connecting to the superior thyroidal artery after CNB

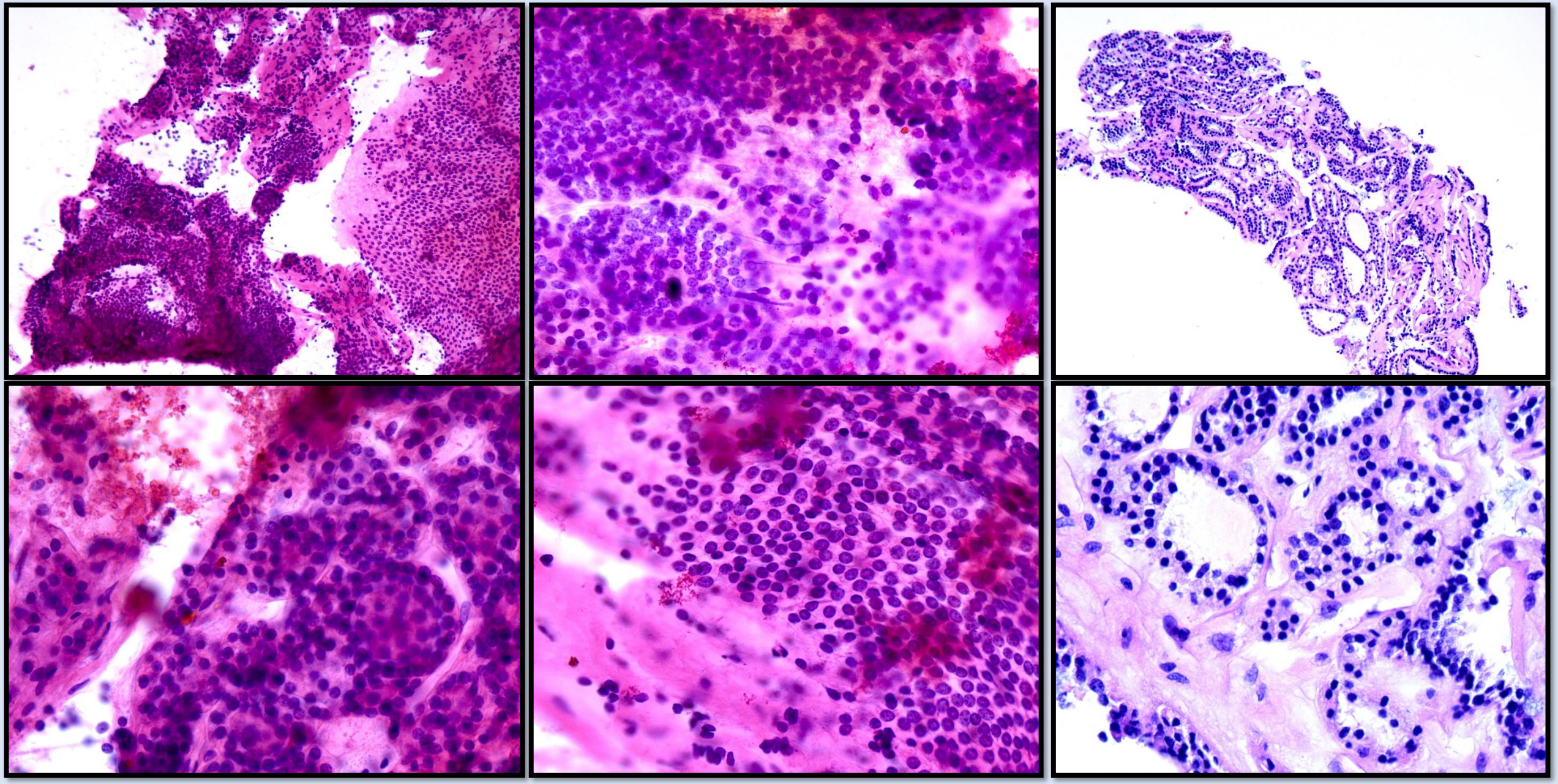
Ha EJ et al. Eur Radiol 2017. Complications following US-guided core-needle biopsy for thyroid lesions: a retrospective study of 6,169 consecutive patients with 6,687 thyroid nodules

Benign vs. Indeterminate Lesions

Follicular Patterned Lesions. CNB – Not so helpful

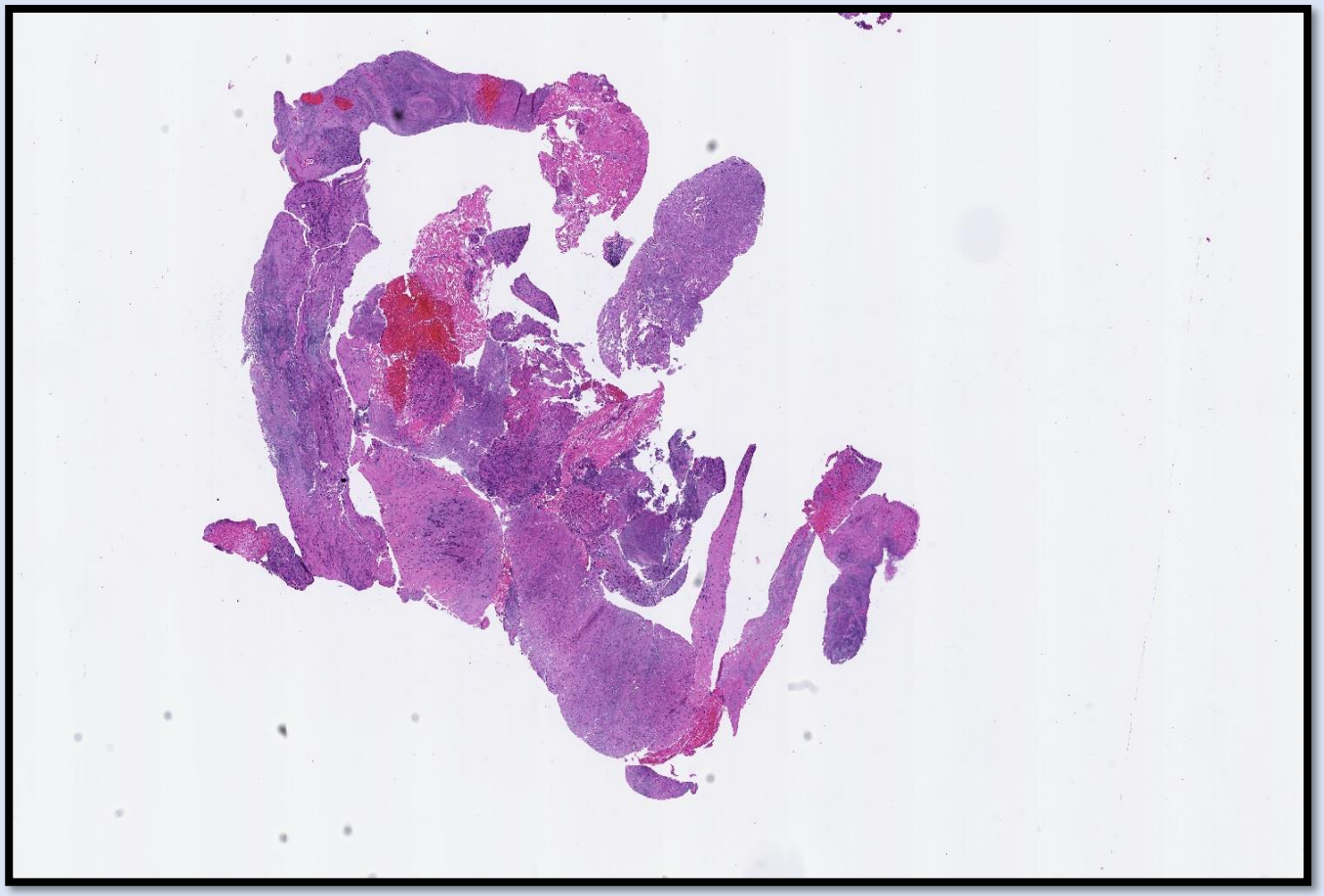




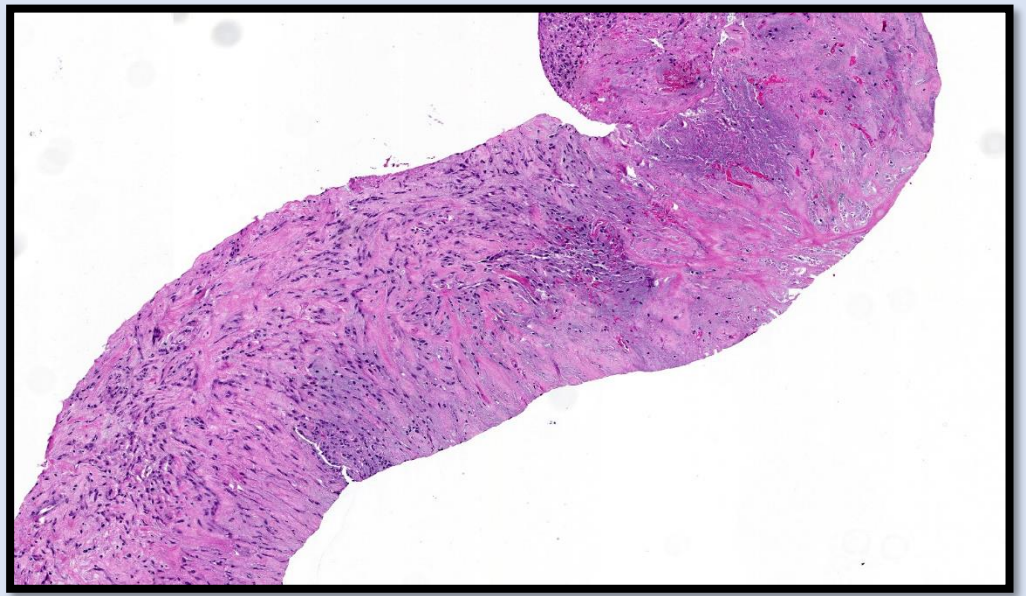
FNA – AUS, CNB - Benign

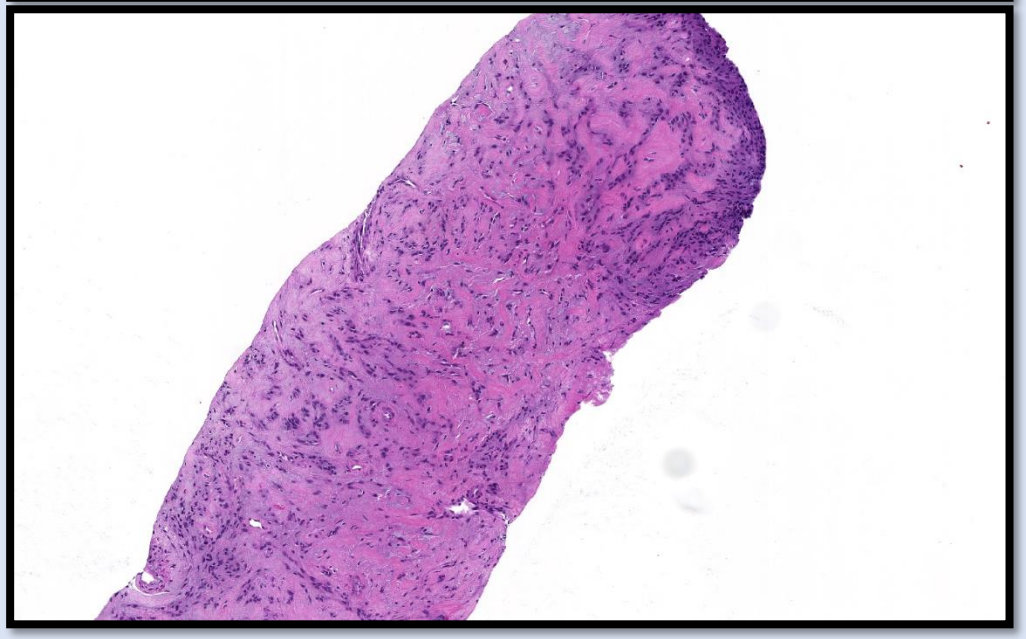


Confirming Diagnosis

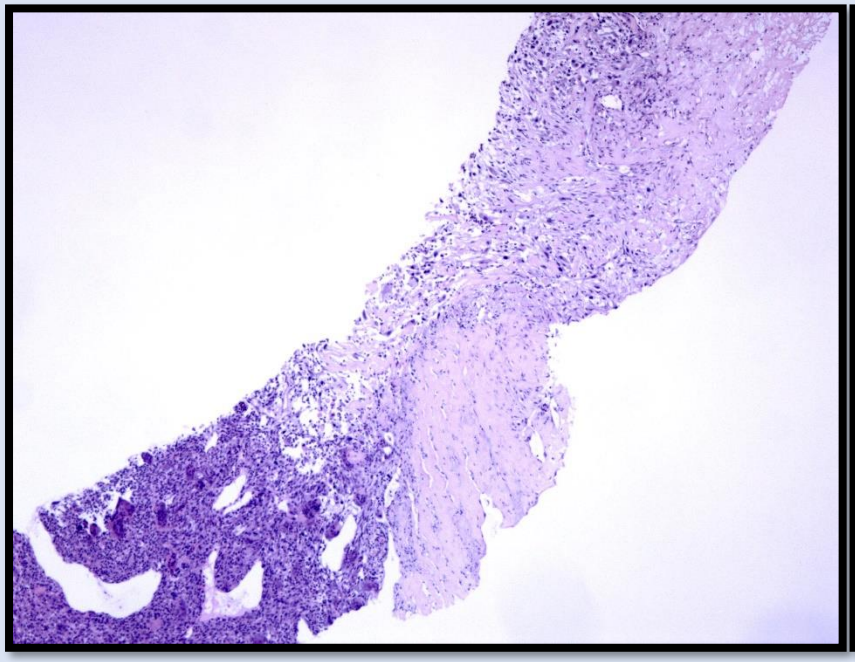
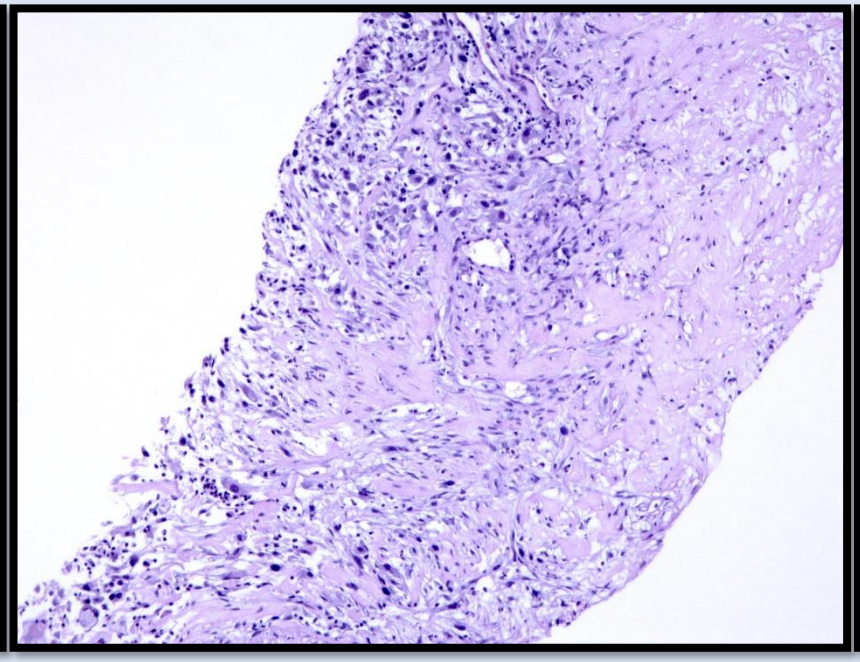
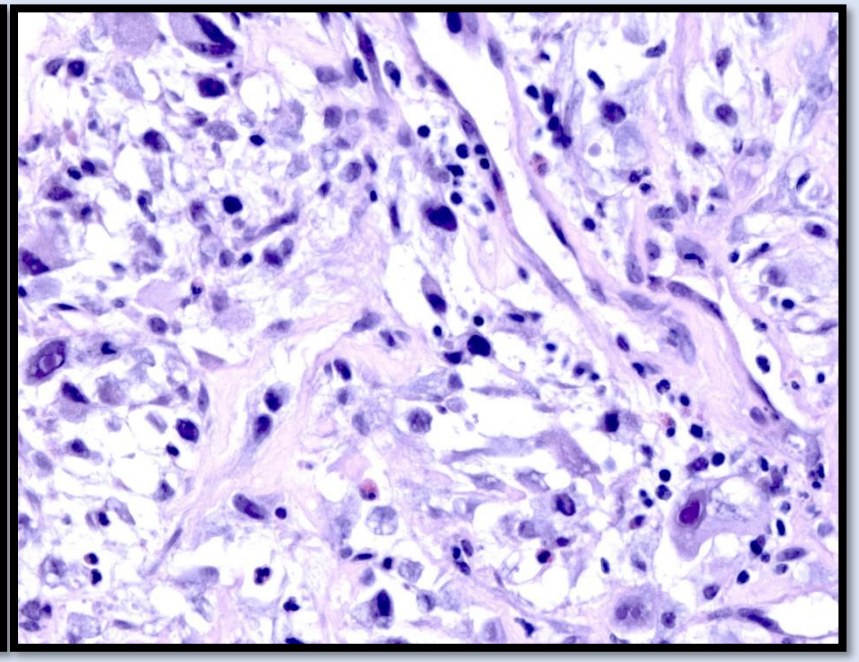
FNA x2: Non-Diagnostic. CNB – Anaplastic Ca, Paucicellular subtype



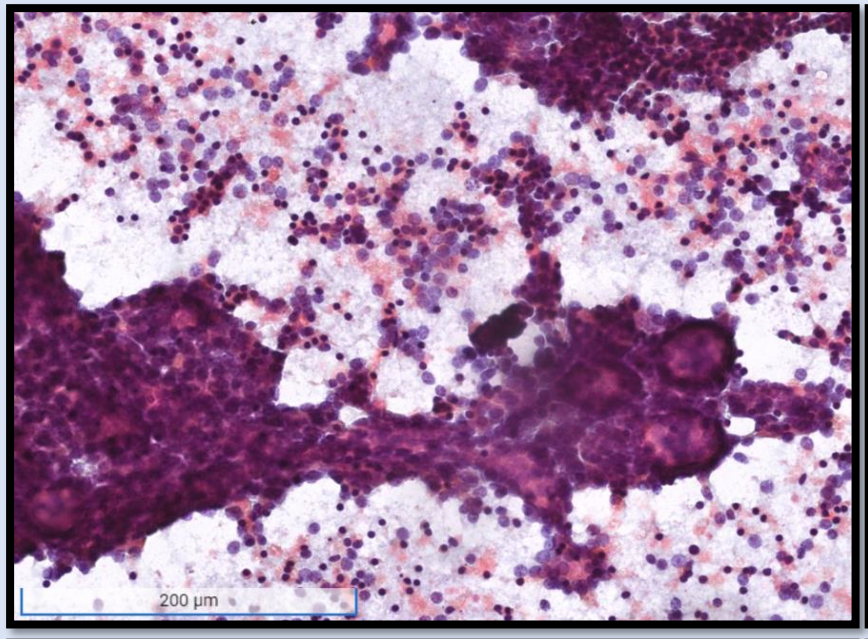


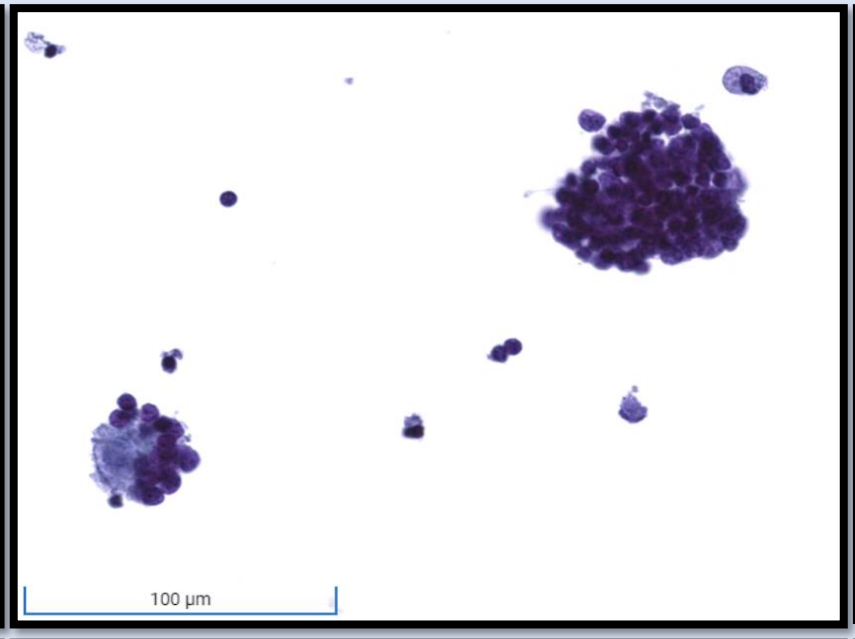


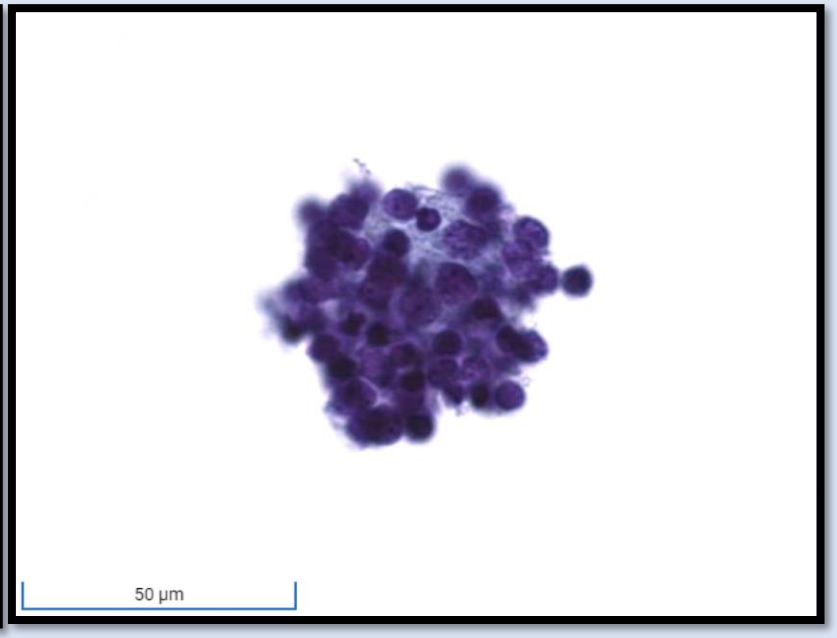
FNA x2: Non-Diagnostic. CNB – Anaplastic Ca, Paucicellular subtype

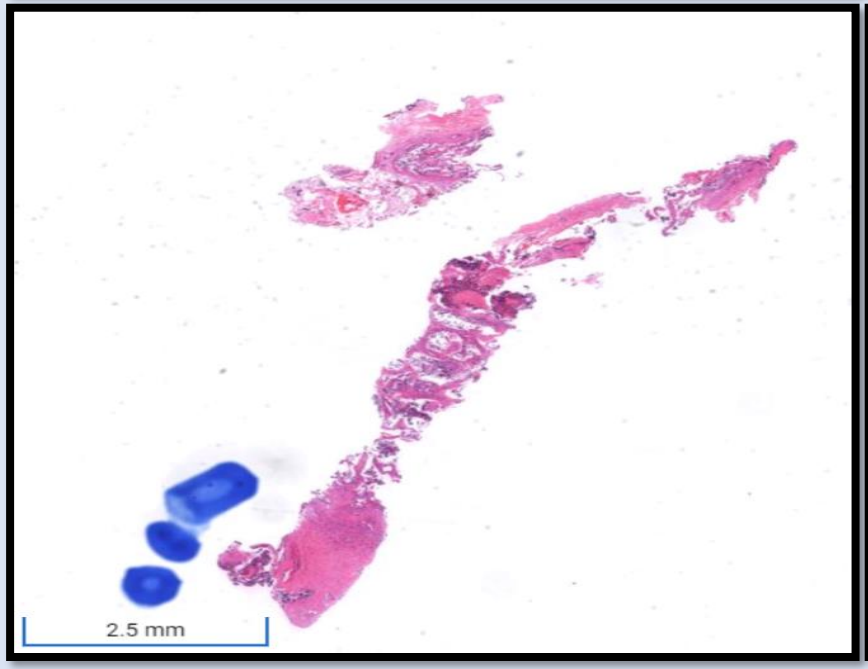




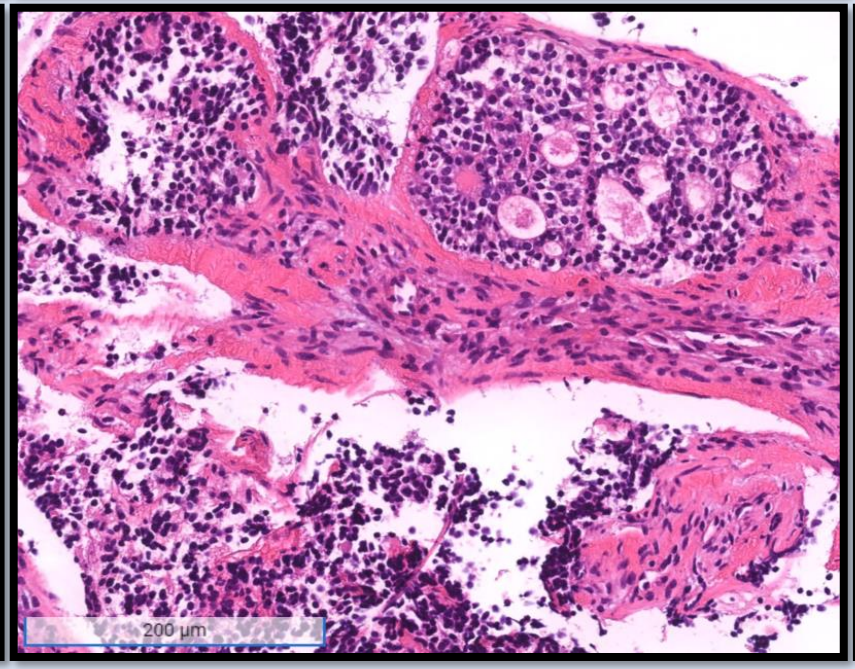
FNA Dx – Follicular Neoplasm, CNB – Poorly Differentiated Carcinoma

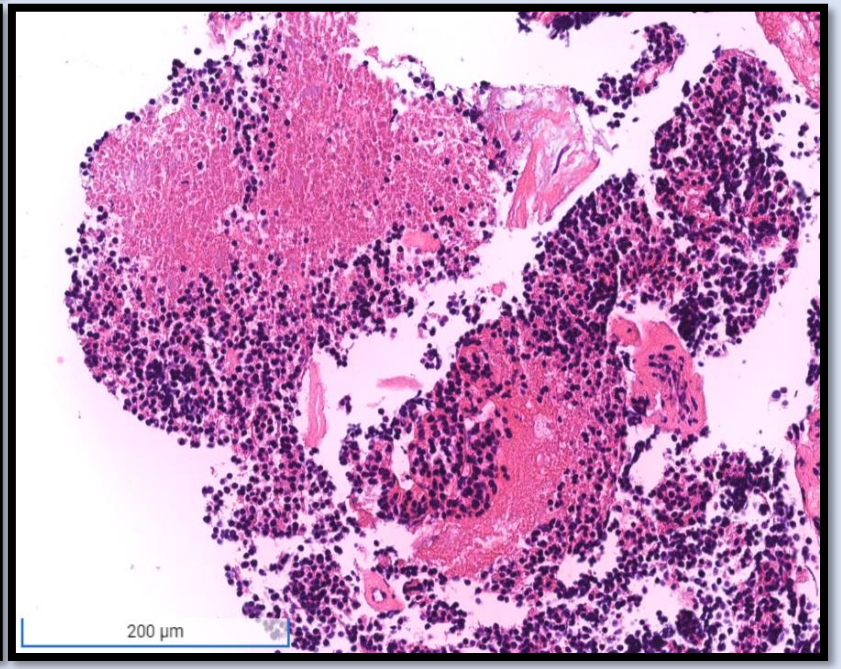




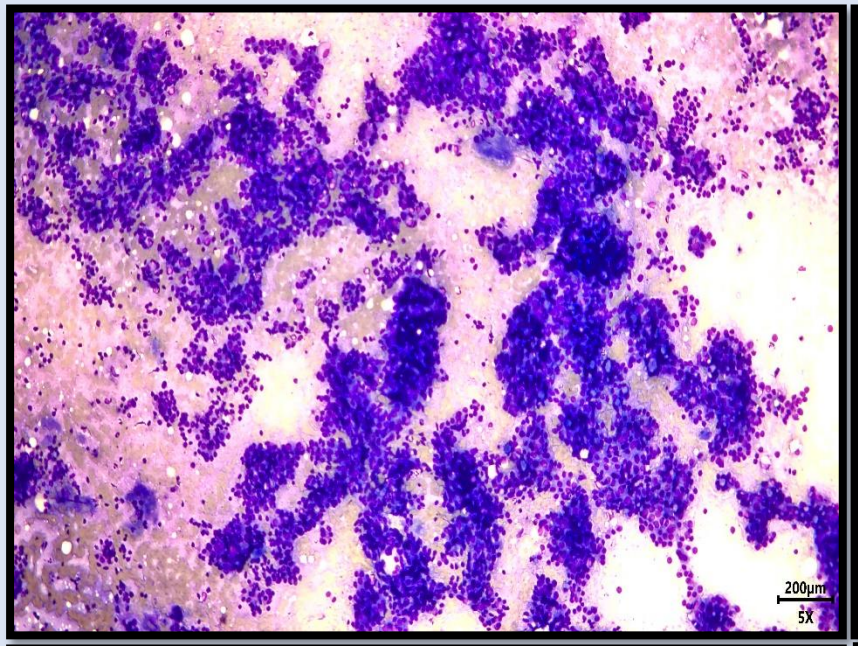


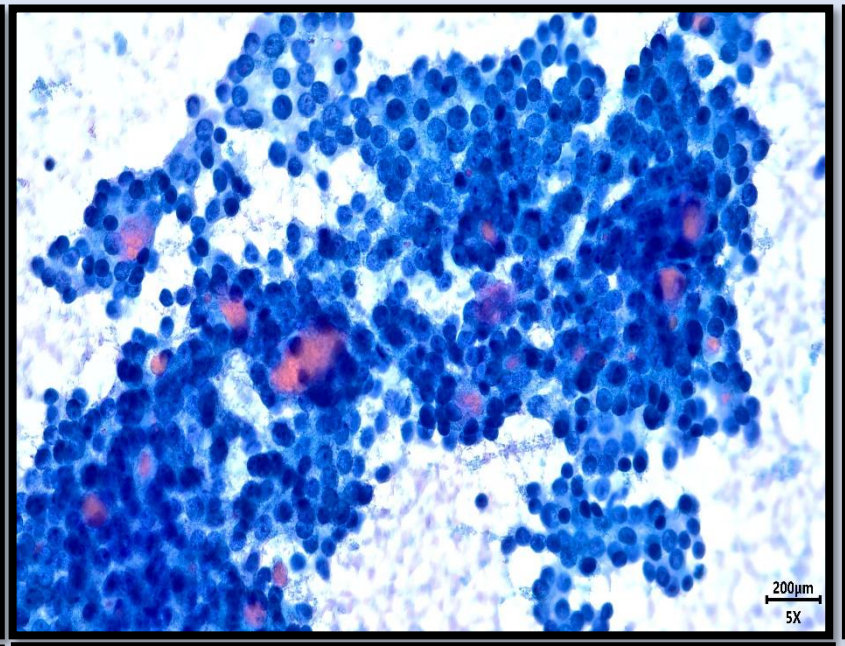


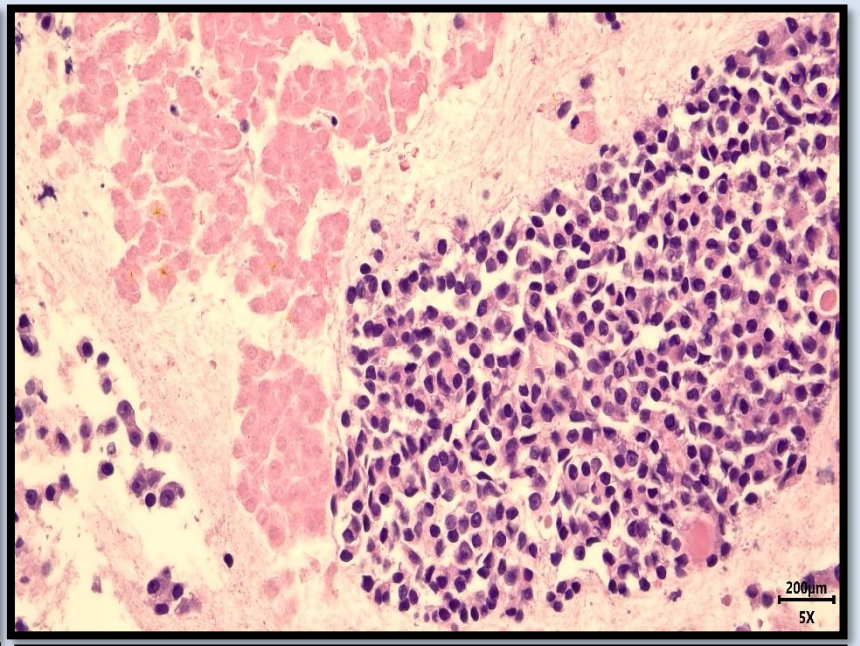


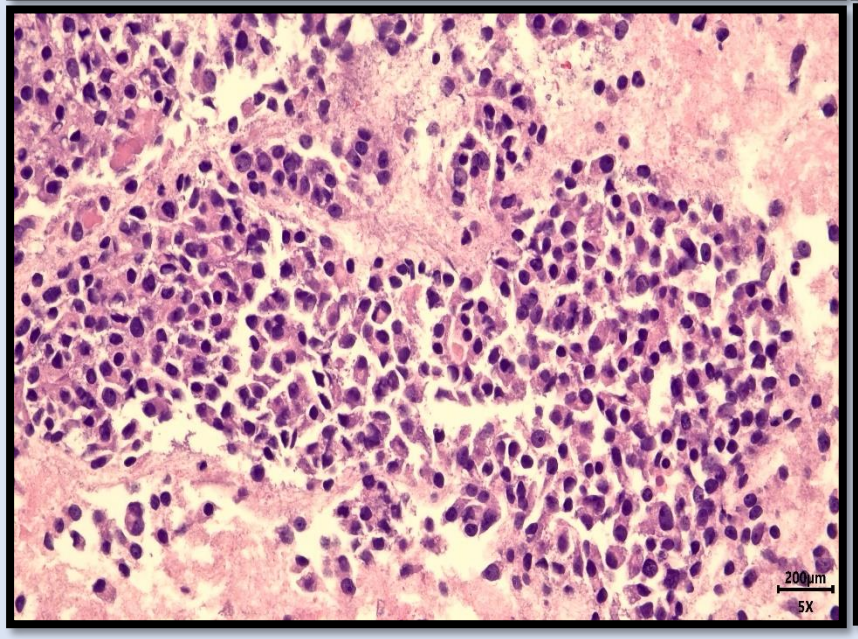


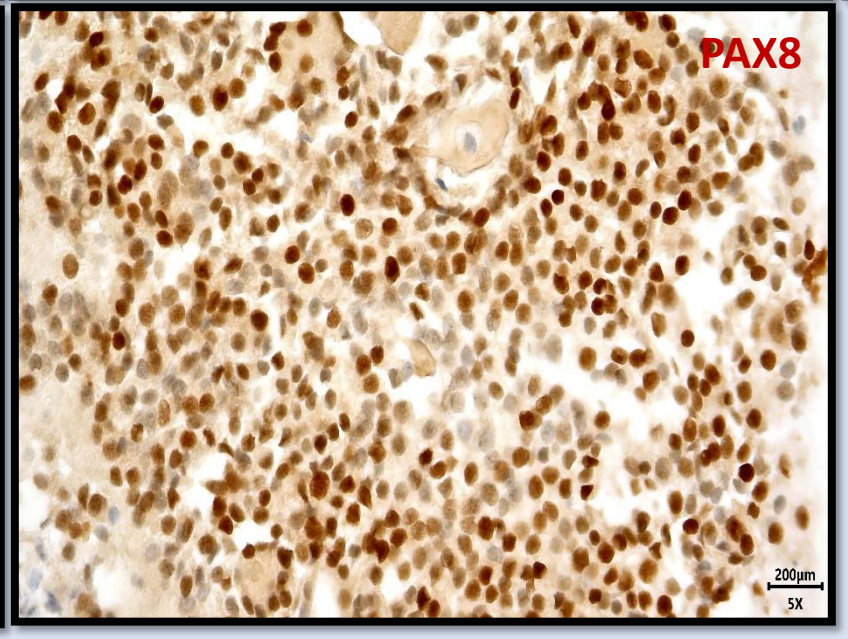
Multiple Passes Leading to Generous Cell Block – An Alternative to CNB

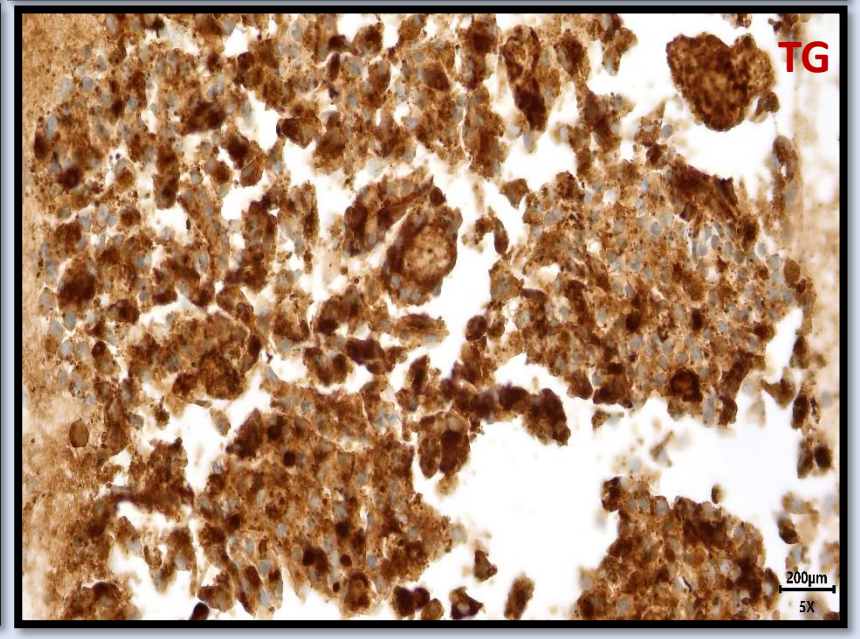




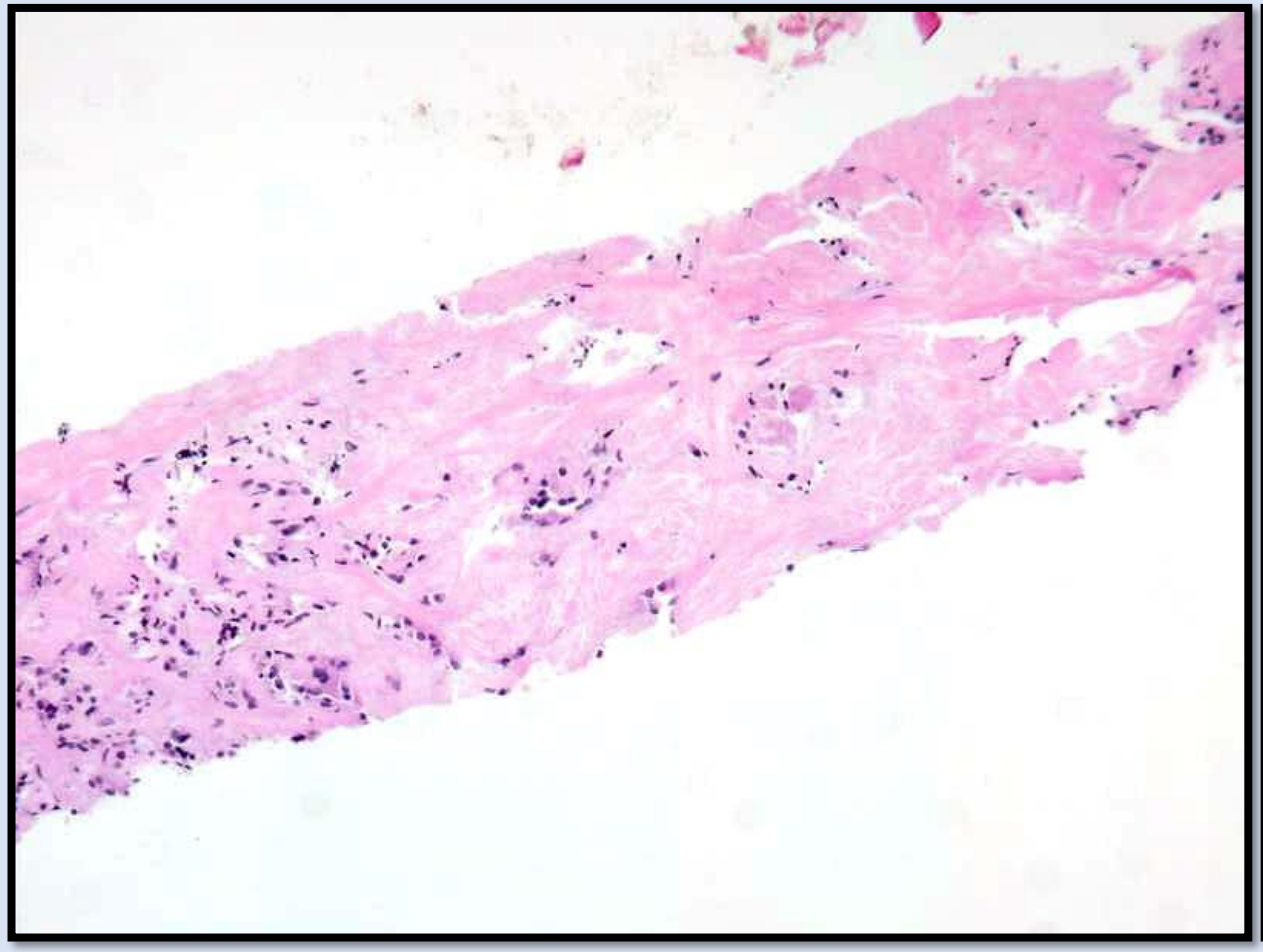


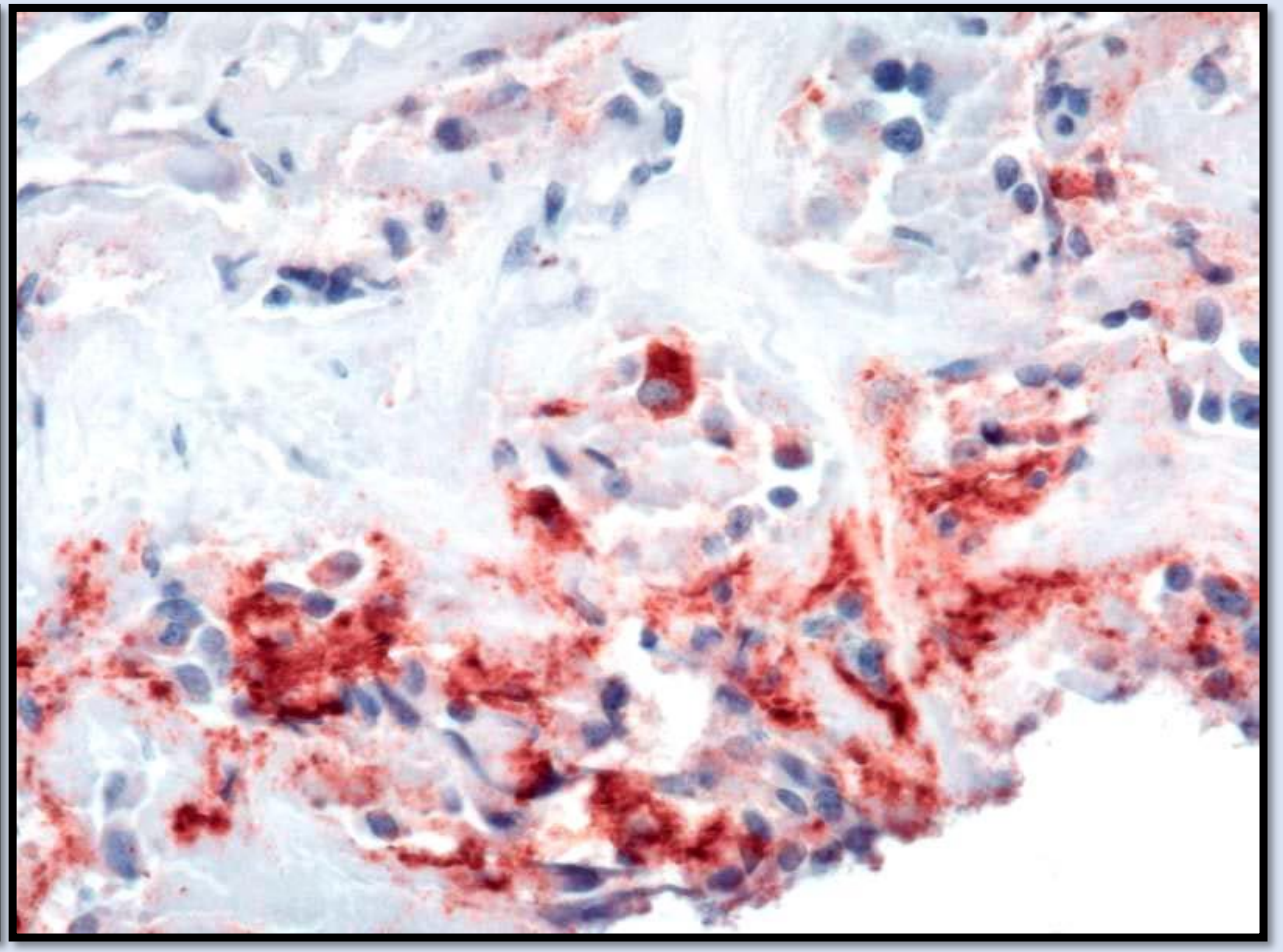






FNA x2: Non-Diagnostic. CNB – Medullary Thyroid Carcinoma

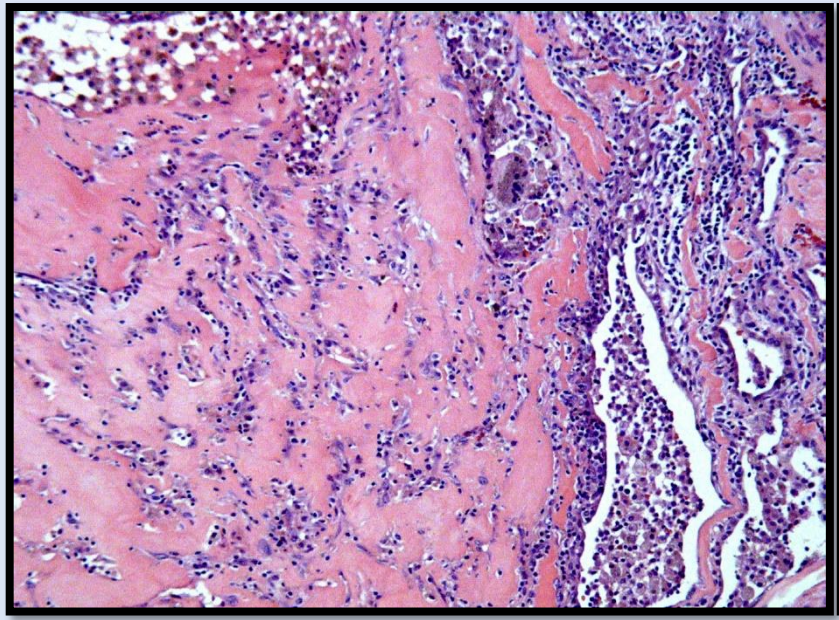
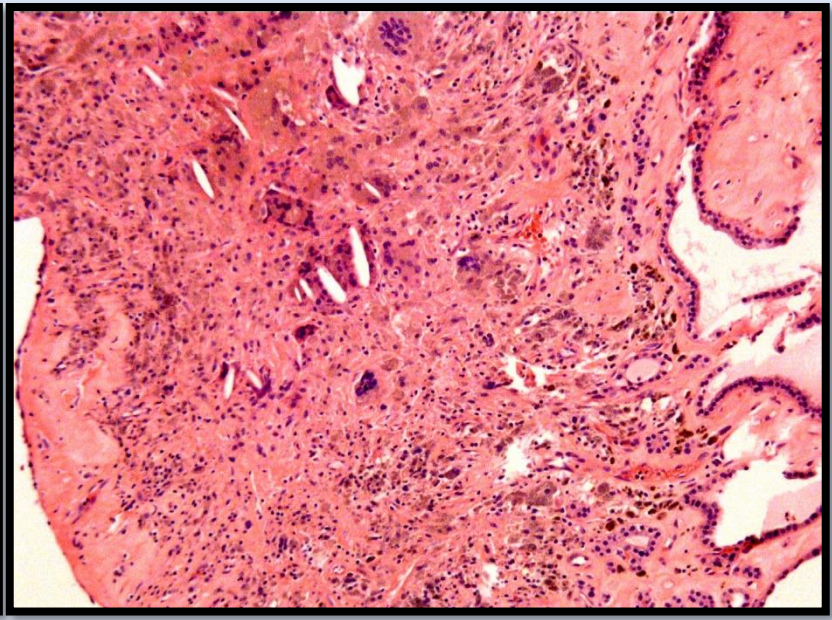
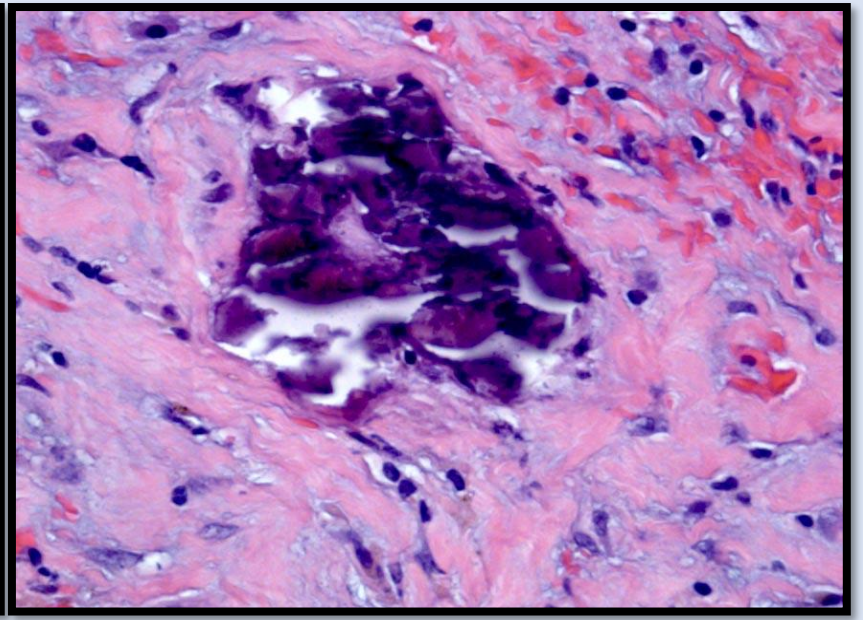
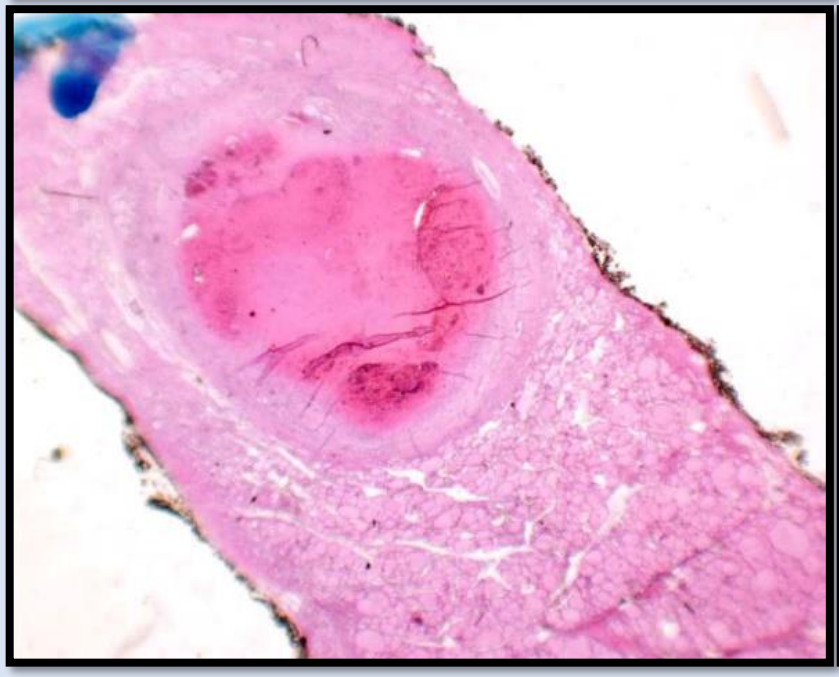
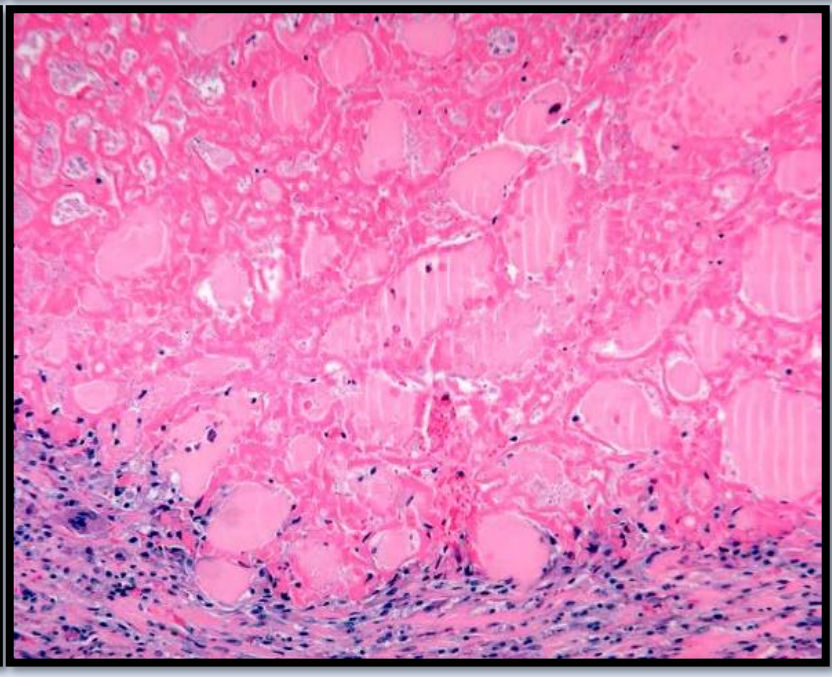
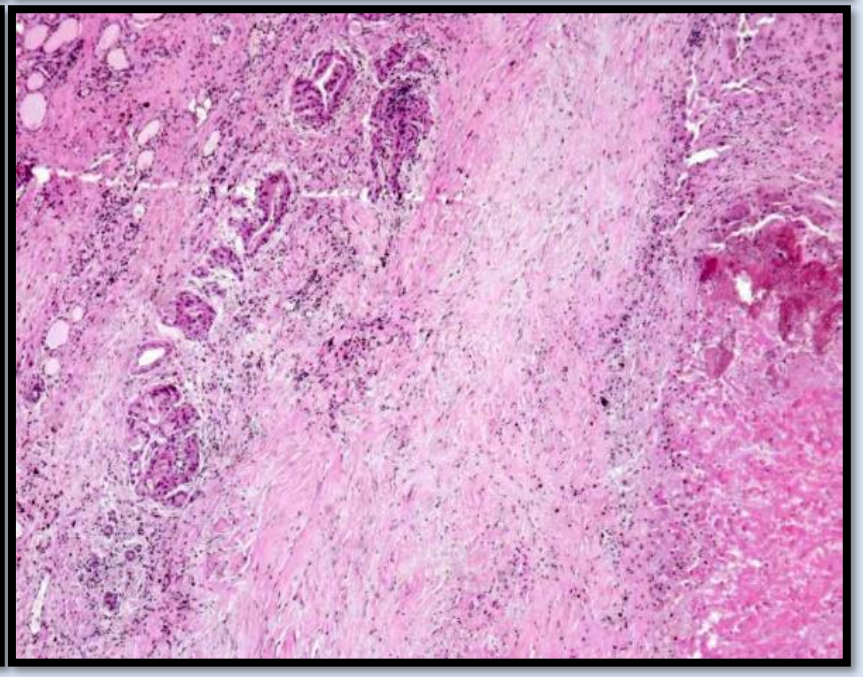




The Aftermath of CNB
Post CNB Histologic Alterations

Vector stock.com

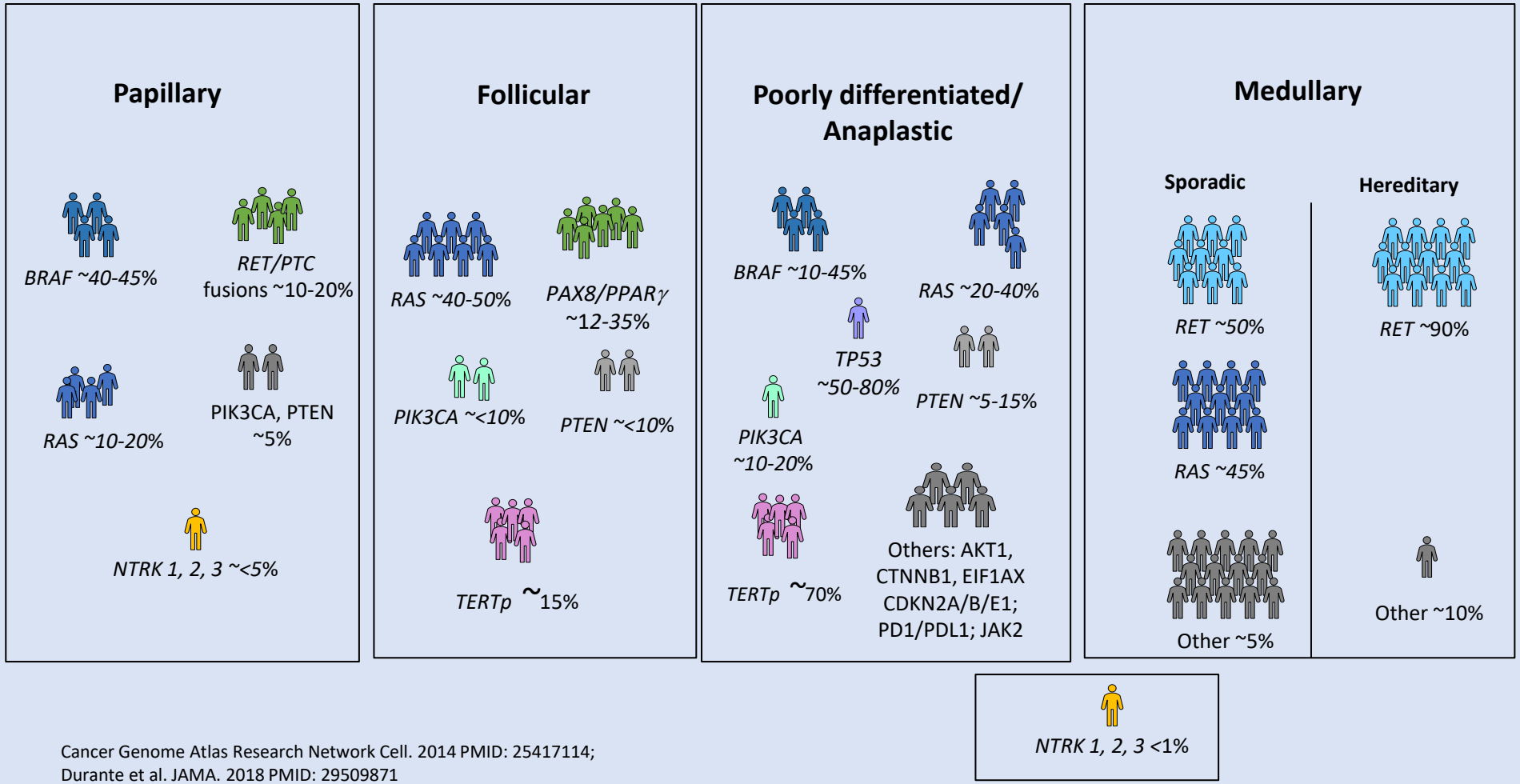
Post CNB Alterations

Conclusions

- Training to perform CNB
- Radiologic guidance
- The CNB can be considered in nodules with highly suspicious features especially prior non-diagnostic FNA.
  - Suspected diagnosis of Anaplastic Thyroid Carcinoma or Thyroid Lymphoma in a rapidly enlarging thyroid mass
- CNB has the potential to increase the % diagnosis of architectural atypia or follicular neoplasm.
- The literature on CNB ---?

Subtype-specific oncogenic drivers in thyroid cancer



Cancer Genome Atlas Research Network Cell. 2014 PMID: 25417114;
Durante et al. JAMA. 2018 PMID: 29509871

FDA approved molecularly targeted therapies in thyroid cancer

Dabrafenib (BRAF inhibitor) & Trametinib (MEK inhibitor)	Larotrectinib (Selective TRK inhibitor)	Entrectinib (multi-kinase inhibitor NTRK1/2/3, ROS1, & ALK)	Selpercatinib (Selective RET kinase inhibitor)	Pralsetinib (Tyrosine Kinase Inhibitor)
• 18 years old • locally advanced, unresectable or metastatic solid tumors • BRAFV600E mutant-positive	• 1 month old • locally advanced or metastatic solid tumors • Tumor agnostic • NTRK fusion-positive	• 18 years old • locally advanced or metastatic solid tumors • penetrate blood-brain barrier • Tumor agnostic • NTRK fusion-positive	• 12 years old • RET-driven advanced or metastatic cancer • RET mutant-positive Medullary Thyroid Cancer • RET fusion-positive radioactive iodine-refractory thyroid cancers	• 12 years old • RET-driven advanced or metastatic cancer • RET mutant-positive Medullary Thyroid Cancer • RET fusion-positive radioactive iodine-refractory thyroid cancers

Patel J, Klopper J and Cottrill EE (2023) Molecular diagnostics in the evaluation of thyroid nodules: Current use and prospective opportunities. Front. Endocrinol. 14:1101410. doi: 10.3389/fendo.2023.1101410

Nishino, Bellevicine and Baloch. Molecular Tests for Risk-Stratifying Cytologically Indeterminate Thyroid Nodules: An Overview of Commercially Available Testing Platforms in the United States. J Mol Pathol. 2021.

Table 2. Comparison of testing methodology, biomarkers, and quality control measures for the three commercially available thyroid molecular testing platforms in the United States.

	ThyroSeq v3	ThyGeNEXT and ThyraMIR	Afirma GSC and Xpression Atlas
Test methodology	NGS for DNA and RNA	NGS for DNA and RNA; qRT-PCR for microRNA	NGS for RNA
SNV, insertions, deletions, and gene fusions	12,135 variants in 112 genes; 120+ fusions	42 variants in 10 genes; 38 gene fusions	905 variants and 235 gene fusions from 593 genes
Gene expression analysis	19 genes	4 genes	10,196 genes (1115 for the GSC classifier algorithm)
MicroRNA expression analysis	None	10 microRNAs	None
Copy-number alterations	10 chromosomal regions	None	Loss-of-heterozygosity analysis
QC for follicular cell content	Yes	Yes	Yes
Recognition of parathyroid	Yes	Yes	Yes
Recognition of MTC	Yes	Yes	Yes

Abbreviations: GSC, gene sequencing classifier; NGS, next-generation sequencing; qRT-PCR, quantitative real-time polymerase chain reaction; SNV, single nucleotide variant; QC, quality control; MTC, medullary thyroid carcinoma.

Patel J, Klopper J and Cottrill EE (2023) Molecular diagnostics in the evaluation of thyroid nodules: Current use and prospective opportunities. Front. Endocrinol. 14:1101410. doi: 10.3389/fendo.2023.1101410

Meta-analysis data of Afirma GSC and Thyroseq v3.

	Afirma GSC®	***Afirma GSC®***	***Thyroseq v3®***
Meta-analysis			
# Included Studies	7 studies	7 studies	6 studies
Sample Size	807	472	530
Specificity	43%	53%	50%
Sensitivity	94.3%	96%	95%
NPV	90%	96%	92%
PPV	63.1%	63%	70%

Vuong HG, Nguyen TPX, Hassell LA, Jung CK. Diagnostic performances of theafirma gene sequencing classifier in comparison with the gene expression classifier: A meta-analysis. Cancer Cytopathol (2021) 129:182–9. doi: 10.1002/cncy.22332

Lee E, Terhaar S, McDaniel L, Gorelik D, Gerhard E, Chen C, et al. Diagnostic performance of the second-generation molecular tests in the assessment of indeterminate thyroid nodules: A systematic review and meta-analysis. Am J Otolaryngol (2022) 43:103394. doi: 10.1016/j.amjoto.2022.103394

Vargas-Salas S, Martinez JR, Urra S, Dominguez JM, Mena N, Uslar T, et al. Genetic testing for indeterminate thyroid cytology: Review and meta-analysis. Endocrine-related Cancer (2018) 25:R163–77. doi: 10.1530/ERC-17-0405

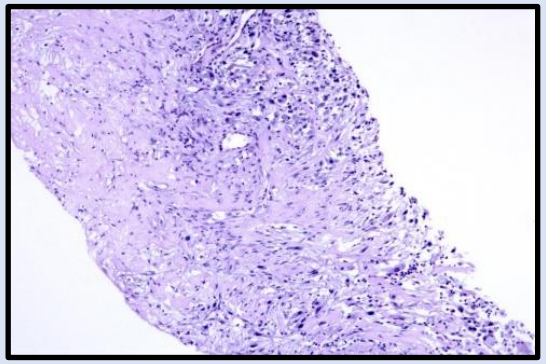
Silaghi CA, Lozovanu V, Georgescu CE, Georgescu RD, Susman S, Nasui BA, et al. Thyroseq v3, afirma GSC, and microRNA panels versus previous molecular testsin the preoperative diagnosis of indeterminate thyroid nodules: A systematic review and meta-analysis. Front Endocrinol (2021) 12:649522. doi: 10.3389/fendo.2021.649522

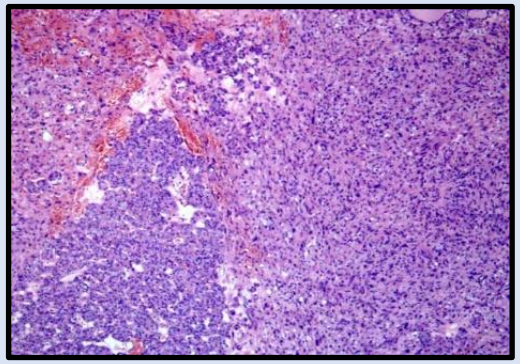
Risk Based Assessment: *we can all work together*

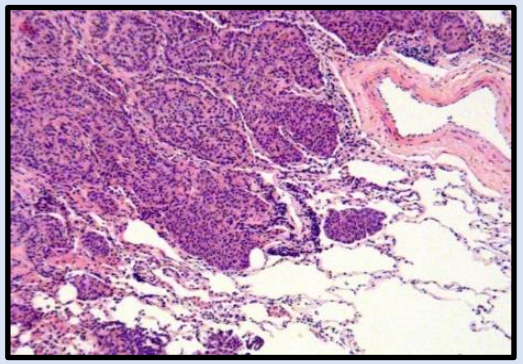
High Risk

Gross extrathyroidal extension, incomplete tumor resection, distant metastases or lymph node >3 cm

BRAF, TERT, p53 , copy number alterations, Fusions



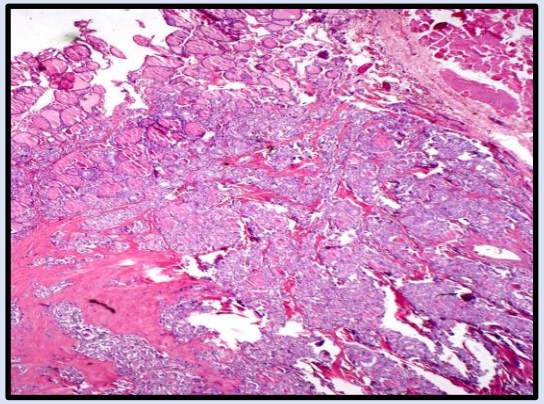


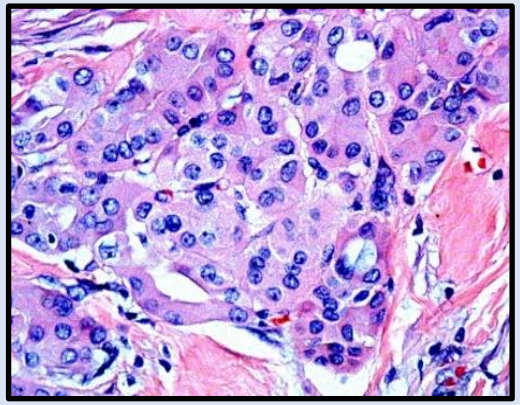


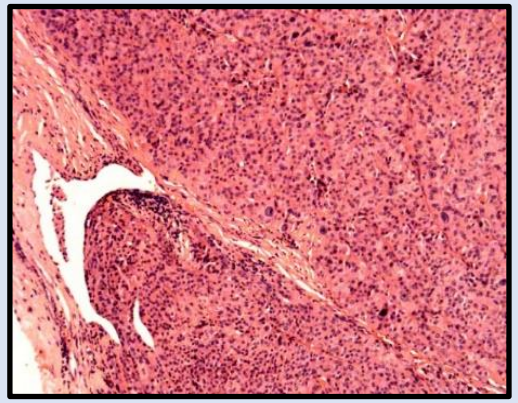
Intermediate Risk

Aggressive histology , minor extra-thyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)

BRAF, RAS (KRAS in Hurthle cell lesions), TERT, Fusions, Copy number alterations.





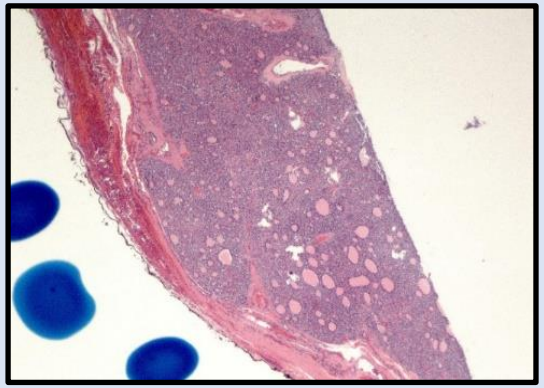


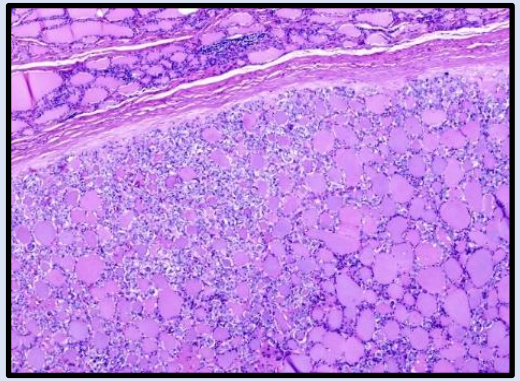
Low Risk

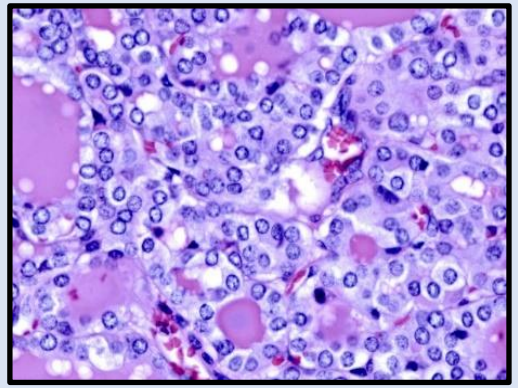
Intrathyroidal DTC

≤ 5 LN micrometastases (< 0.2 cm)

***Ras** mutations (**Nras, Hras, Kras**) & few w **BRAF** (V600e, K601), Fusions*







WHO Classification of Thyroid Neoplasms, 5th ed

Developmental Abnormalities

1. Thyroglossal duct cyst
2. Other congenital thyroid abnormalities

Follicular Derived Neoplasms

1. Benign Tumors
    a. Thyroid follicular nodular disease*
    b. Follicular adenoma
    c. Follicular adenoma with papillary architecture*
    d. Oncocytic adenoma of the thyroid*
2. Low Risk Neoplasms
    a. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
    b. Thyroid tumors of uncertain malignant potential
    c. Hyalinizing trabecular tumor
3. Malignant Neoplasms
    a. Follicular thyroid carcinoma
    b. Invasive encapsulated follicular variant papillary carcinoma*
    c. Papillary thyroid carcinoma
    d. Oncocytic carcinoma of the thyroid*
    e. Follicular-derived carcinomas, high-grade*
        i. Differentiated high-grade thyroid carcinoma
        ii. Poorly differentiated thyroid carcinoma
    f. Anaplastic follicular cell derived thyroid carcinoma

Thyroid C-cell Derived Carcinoma

1. Medullary thyroid carcinoma

Mixed Medullary and Follicular-cell Derived Carcinomas

Salivary Gland-type Carcinomas of the Thyroid*

1. Mucoepidermoid carcinoma of the thyroid
2. Secretory carcinoma of salivary gland type

Thyroid tumors of uncertain histogenesis*

1. Sclerosing mucoepidermoid carcinoma with eosinophilia
2. Cribriform morular thyroid carcinoma

Thymic Tumors Within the Thyroid

1. Thymoma family
2. Spindle epithelial tumour with thymus-like elements
3. Thymic carcinoma family

Embryonal Thyroid Neoplasms

1. Thyroblastoma

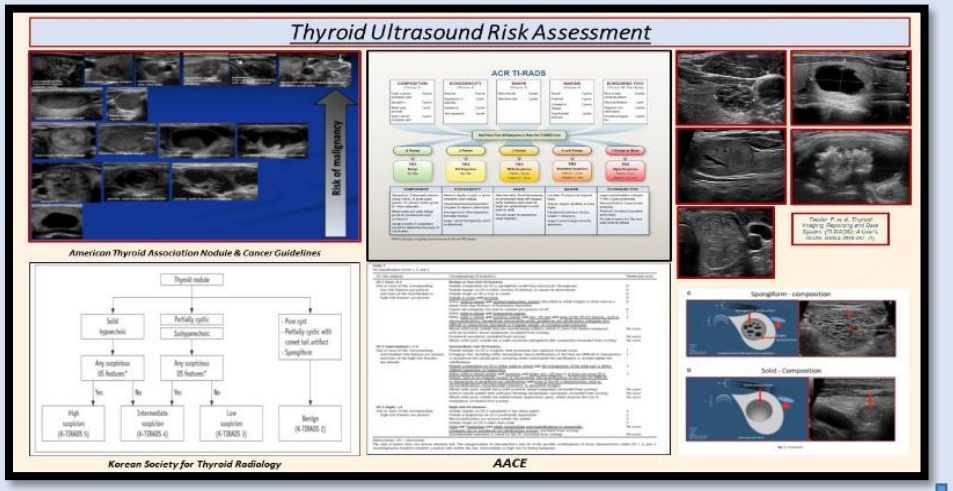
*Macerola, E.; Poma, A.M.;Vignali, P.; Basolo, A.; Ugolini, C.;Torregrossa, L.; Santini, F.; Basolo, F.Molecular Genetics of Follicular-Derived Thyroid Cancer. Cancers **2021**, 13, 1139.*

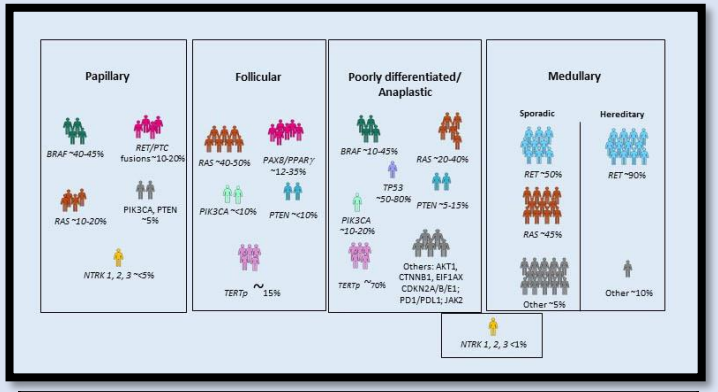
Gene	Advanced PTC			Advanced FTC		
	n° Mutant/n° Total	Frequency Range	Pooled Frequency	n° Mutant/n° Total	Frequency Range	Pooled Frequency
BRAF	583/894	45–71%	65%	6/136 [1]	0–8%	4%
RAS[2]	68/890	1–23%	8%	83/136	8–90%	61%
EIF1AX	3/62	0–10%	5%	5/88	0–40%	6%
PIK3CA	36/669	3–6%	5%	2/100	0–3%	2%
PTEN	10/669	0–2%	1%	9/100	0–14%	9%
TERT	314/651	13–62%	48%	68/103	50–82%	66%
TP53	64/669	3–13%	10%	9/100	0–12%	9%
RET **fusion**	37/558	3–7%	7%	0/89	0%	0%
PPARG **fusion**	0/59	0%	0%	0/89	0%	0%
ALK **fusion**	3/527	<1–2%	1%	0/89	0%	0%
NTRK **fusion**	8/527	1–5%	2%	0/89	0%	0%
BRAF **fusion**	14/527	0–3%	3%	0/89	0%	0%

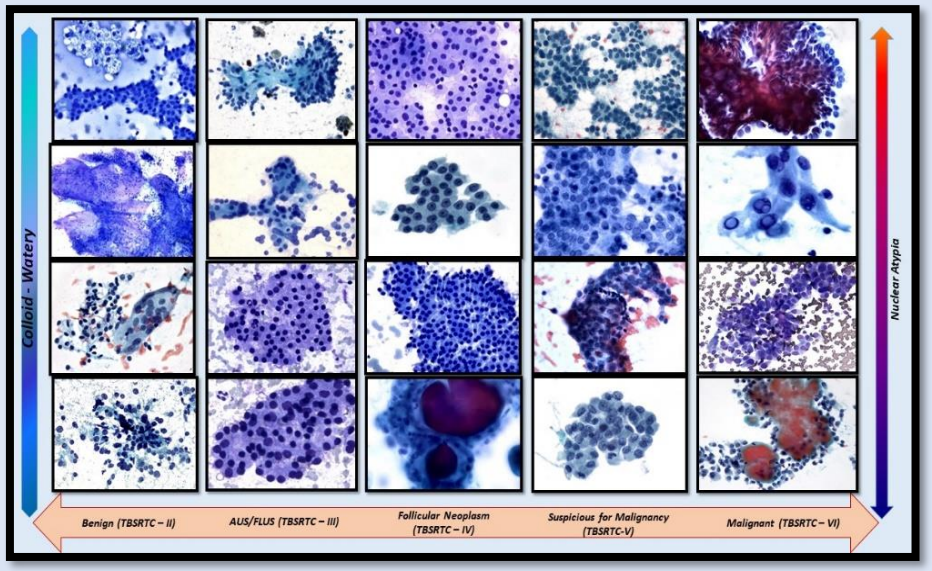
Gene	PDTC			ATC		
	n° Mutant/n° Total	Frequency Range	Pooled Frequency	n° Mutant/n° Total	Frequency Range	Pooled Frequency
BRAF	57/220	15–33%	26%	166/395	20–56%	42%
RAS	48/220	9–39%	22%	100/395	20–33%	25%
EIF1AX	11/125	5–11%	9%	22/181	8–14%	12%
PIK3CA	15/220	2–20%	7%	65/395	9–44%	16%
PTEN	6/220	4–33%	3%	45/395	11–20%	11%
TERT	43/125	22–40%	34%	242/355	56–75%	68%
TP53	45/220	8–67%	20%	244/395	25–80%	62%
RET **fusion**	11/125	6–15%	9%	5/355	0–2%	1%
PPARG **fusion**	4/125	2–4%	3%	0/159	0%	0%
ALK **fusion**	4/125	2–4%	3%	0/355	0%	0%
NTRK **fusion**	1/41	0–2%	2%	5/322	1–4%	2%

Personalized Approach to Thyroid Nodule Management

Clinical Presentation





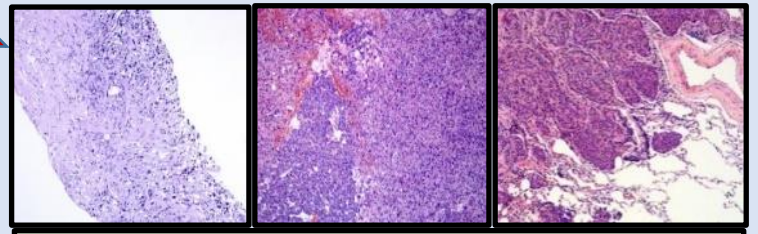


Molecular Tests

- *Afirma-GSC*
- *ThyroSeq v3*
- *ThyGenX/ThyraMIR*
- *RosettaGX Reveal*
- *Quest Molecular Test*
- *Home Brewed Tests*

The specific gene alterations can help guide clinicians in making management decisions for patients with thyroid nodules.

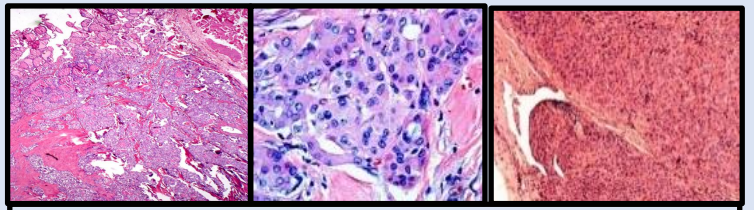
Risk of Recurrence



High Risk

Gross extrathyroidal extension, incomplete tumor resection, distant metastases or lymph node >3 cm

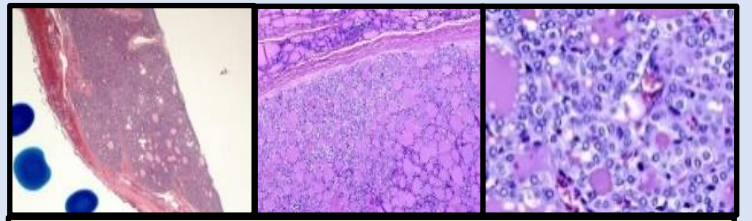
BRAF, TERT, p53 , copy number alterations , fusion (RET, NTRK).



Intermediate Risk

Aggressive histology , minor extra-thyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)

BRAF, RAS (KRAS in Hurthle cell lesions), TERT, p53, PIK3CA, Copy number alterations, fusions (RET, NTRK, PAX8::PPARγ).



Low Risk

Intrathyroidal DTC , ≤ 5 LN micrometastases (< 0.2 cm)

Ras** mutations (**Nras, Hras, Kras**) & few w **BRAF** (V600e, K601), PTEN, DICER1, THADA fusions, **PAX8::PPARγ