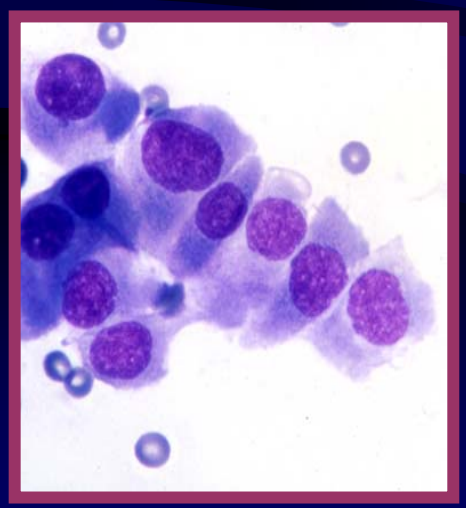
DIAGNOSTIC TERMINOLOGY AND CRITERIA FOR THE CYTOLOGIC DIAGNOSIS OF THYROID LESIONS



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Diagnostic Terminology and Criteria: Part I

- Chronic lymphocytic thyroiditis
- Primary lymphoma
- Papillary thyroid carcinoma
- Undifferentiated carcinoma
- Medullary carcinoma
- Secondary tumors

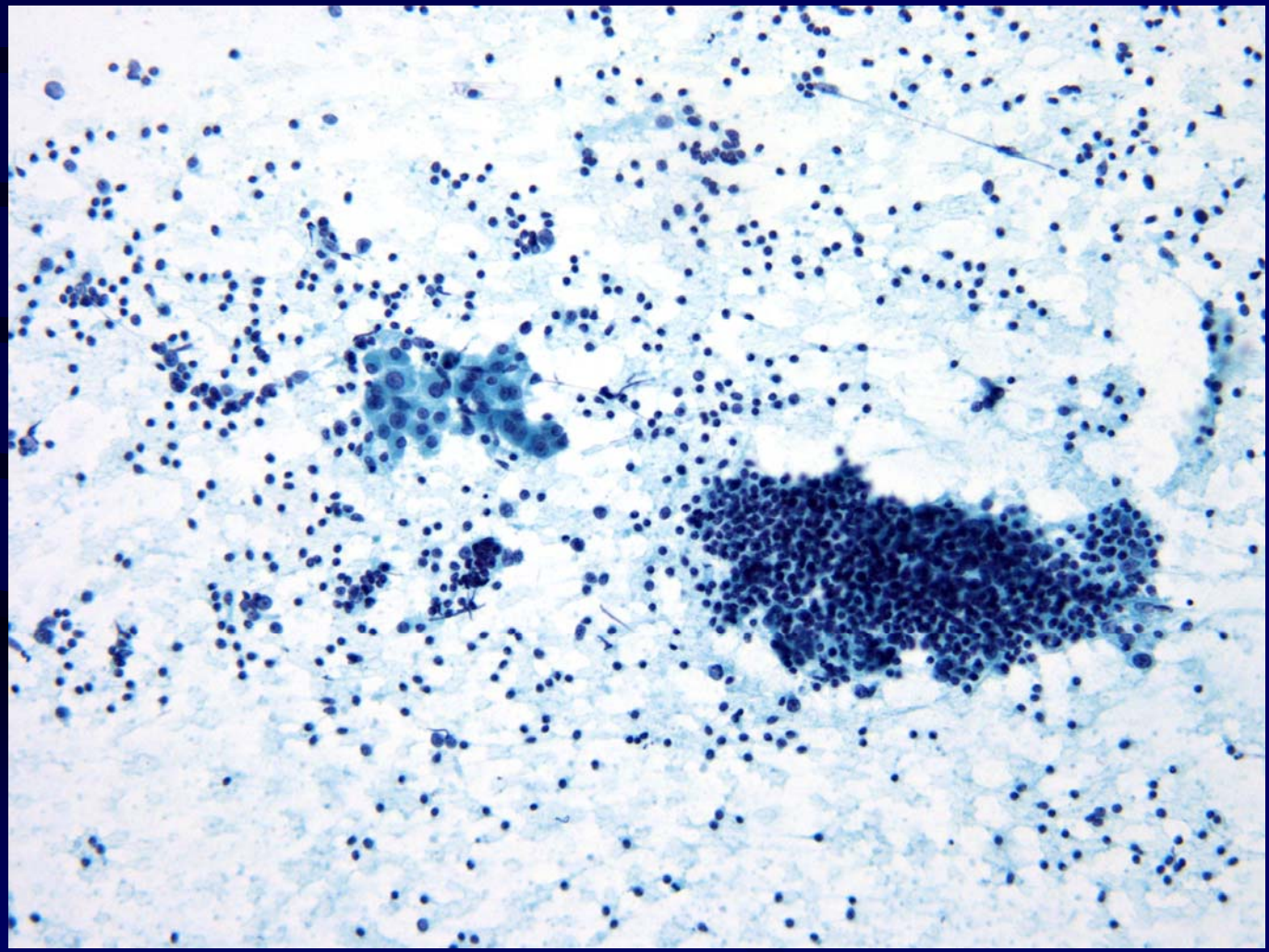
Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)

- First described in 1912
- Most common form of thyroiditis
- Most common cause of hypothyroidism in the U.S.
- >90% patients have autoantibodies to thyroid peroxidase and thyroglobulin

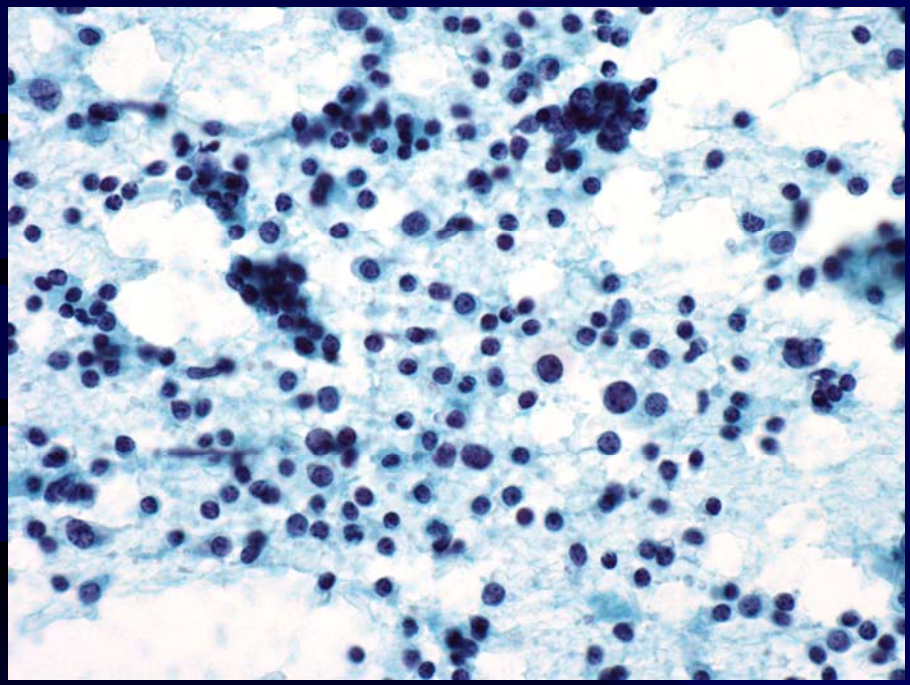
Chronic Lymphocytic Thyroiditis

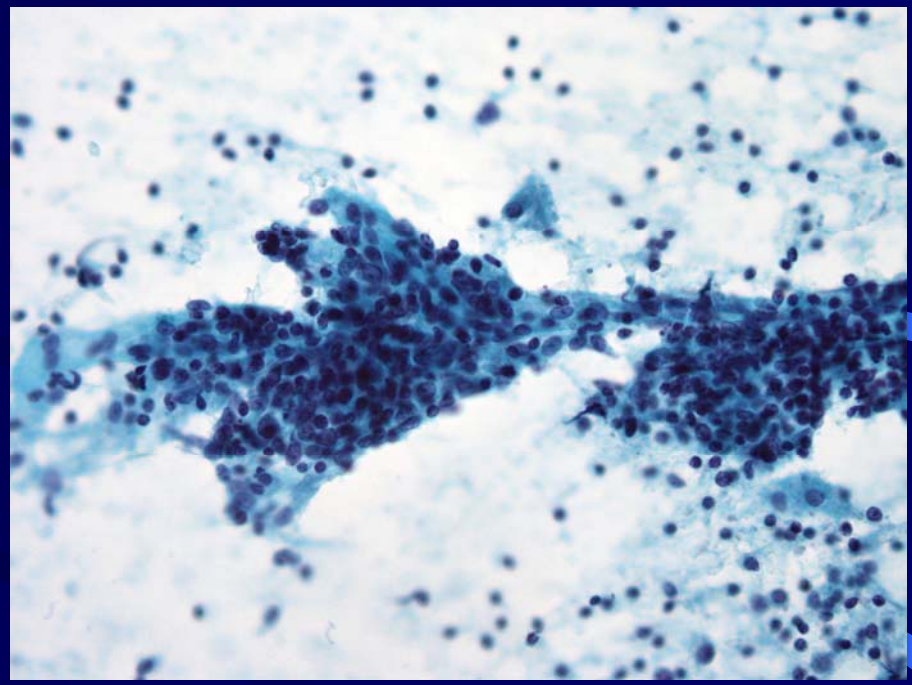
- **Cytologic Features:**
  - Mixed population of lymphocytes and plasma cells
  - Lymphohistiocytic aggregates
  - Cohesive groups of follicular cells with oncocytic features
  - Variable nuclear atypia

Chronic Lymphocytic Thyroiditis

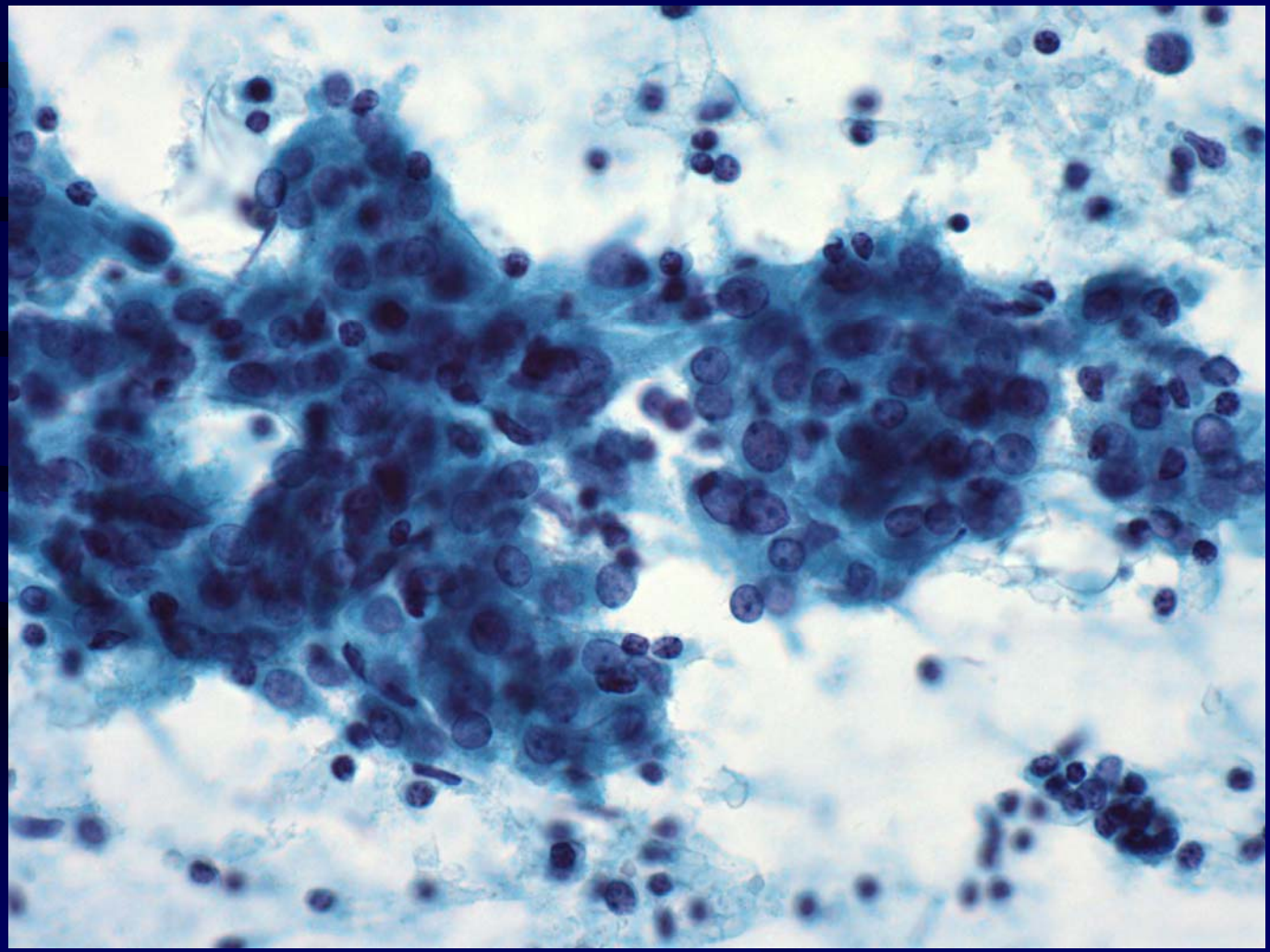


Chronic Lymphocytic Thyroiditis

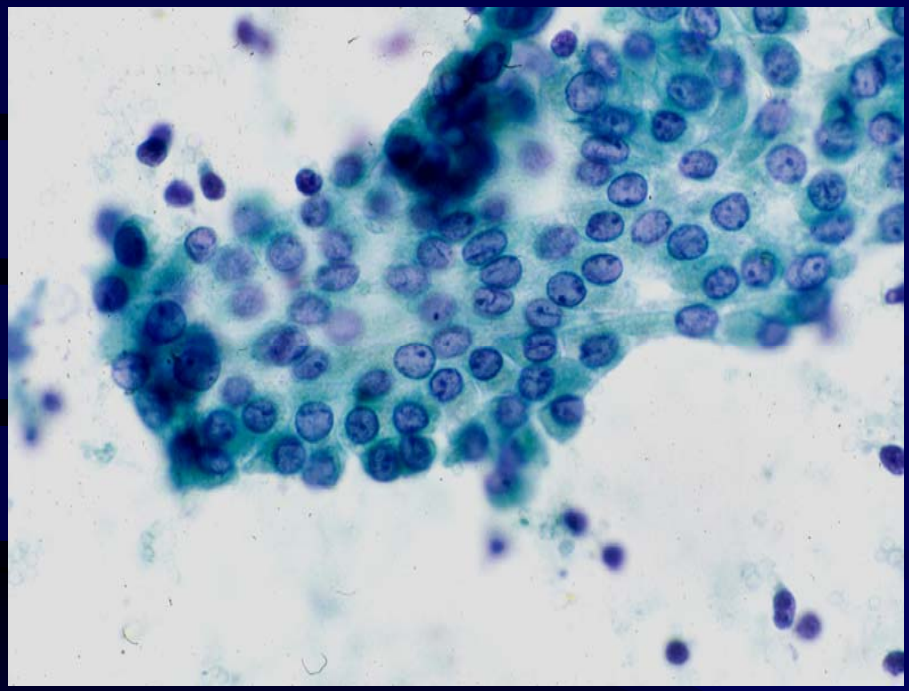


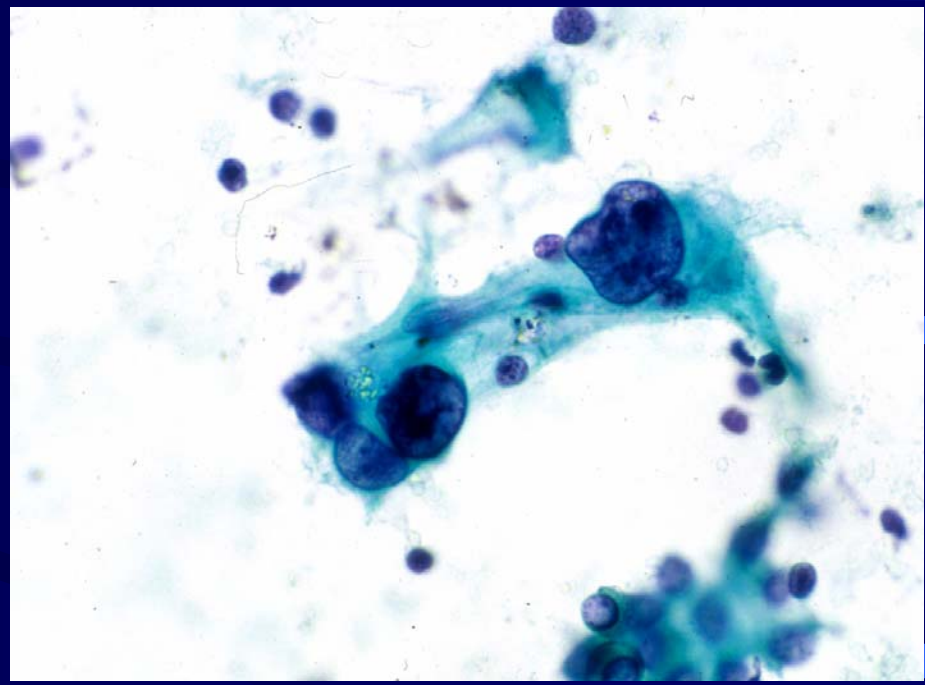


Chronic Lymphocytic Thyroiditis



Chronic Lymphocytic Thyroiditis





Chronic Lymphocytic Thyroiditis

- **Differential Diagnosis:**
  - **Papillary thyroid carcinoma**
  - **Hurthle cell neoplasm**
  - **Reactive lymph node**
  - **Primary lymphoma**

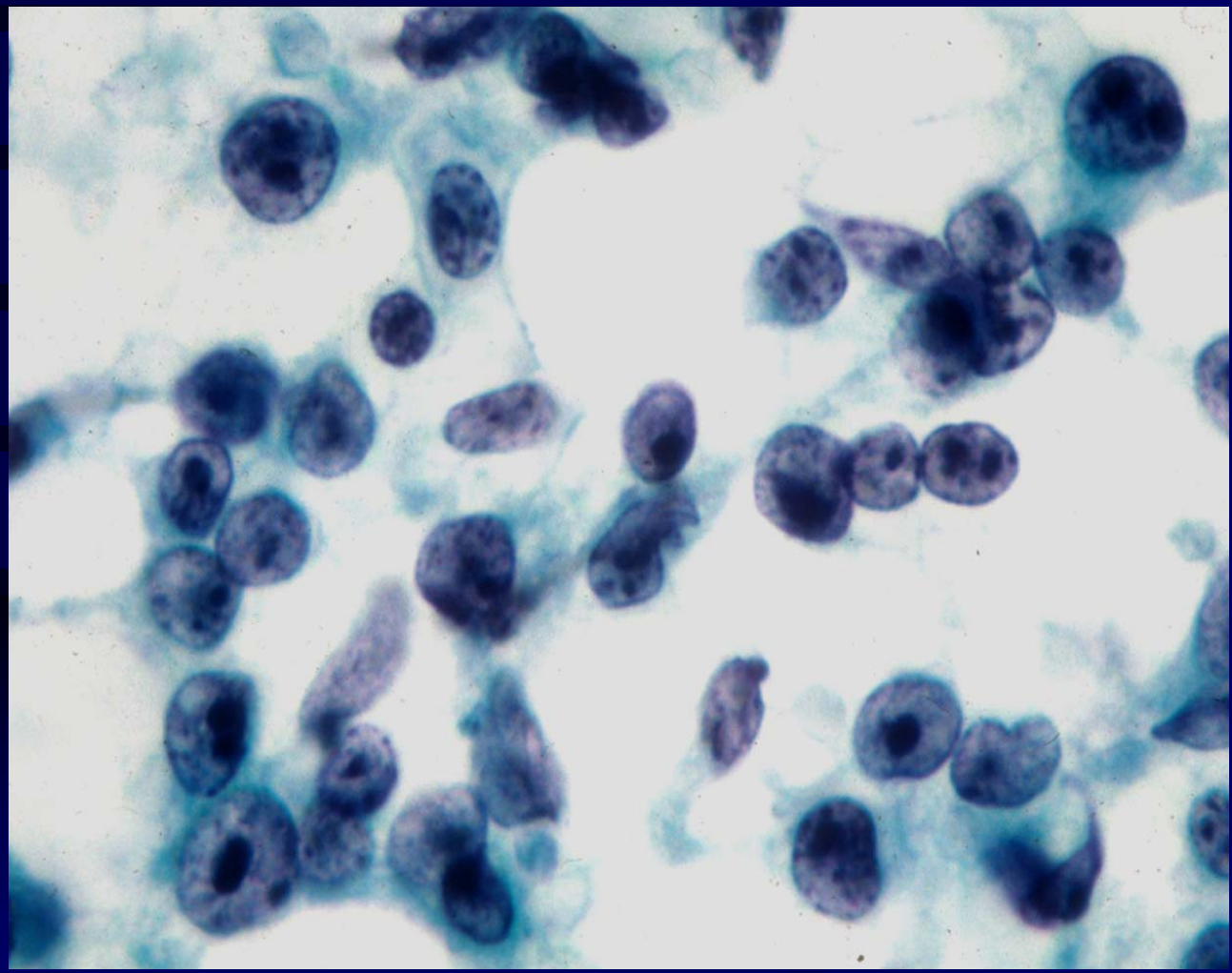
Primary Malignant Lymphoma Involving the Thyroid

- NHL accounts for <5% of primary thyroid neoplasms; 2.5% of extranodal lymphomas
- 70-100% arise in the setting of Hashimoto's thyroiditis (RR=40-80x)
- 20-30 years after onset of thyroiditis
- Approx. 50% present with a single dominant thyroid nodule

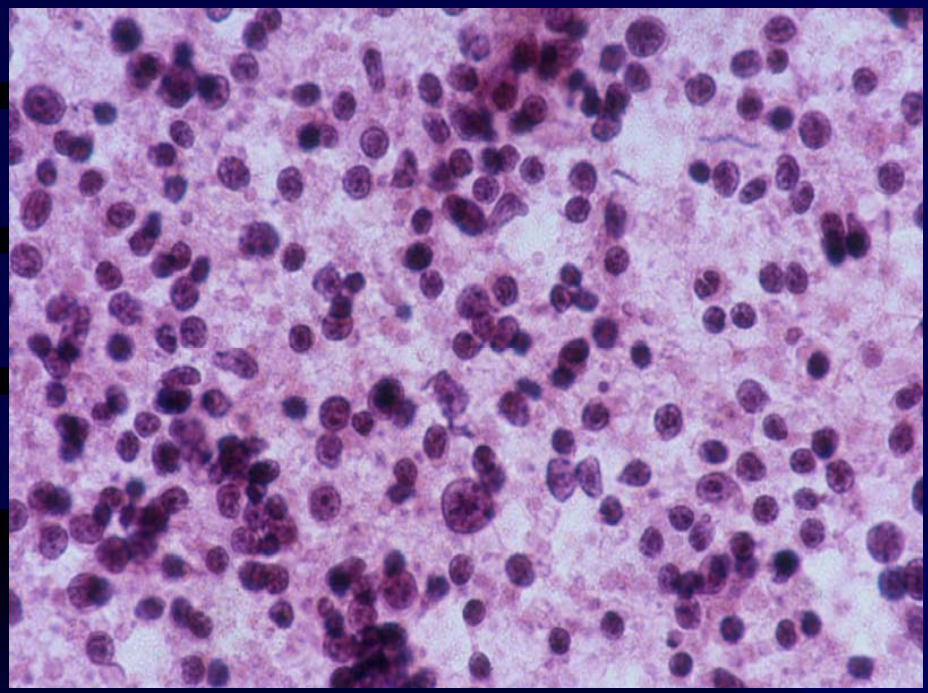
Primary Malignant Lymphoma Involving the Thyroid

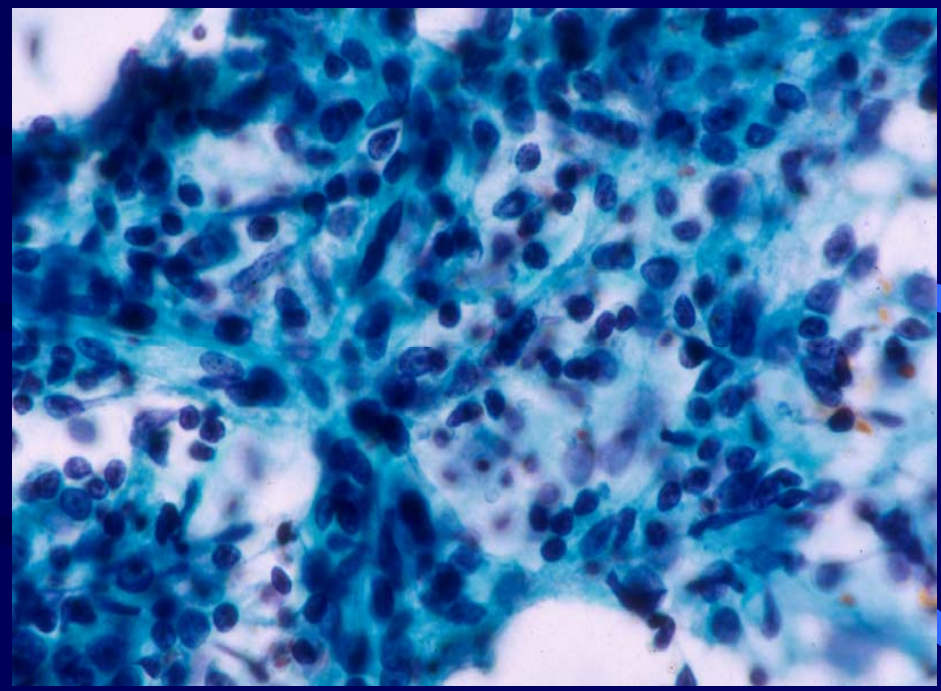
- **Derringer et al. (AFIP) (AJSP, 2000, 24:623-639) - 108 cases**
  - **28% MALT**
  - **33% DLBCL + MALT**
  - **38% DLBCL only**
  - **1% Follicle center lymphoma**
- **Hodgkin lymphoma, plasmactyoma, and T-cell lymphomas are very rare**

Primary Malignant Lymphoma Involving the Thyroid



Primary Malignant Lymphoma Involving the Thyroid





Marker studies such as flow cytometry are essential in the evaluation of aspirates where there is a suspicion of lymphoma.

PAPILLARY THYROID CARCINOMA

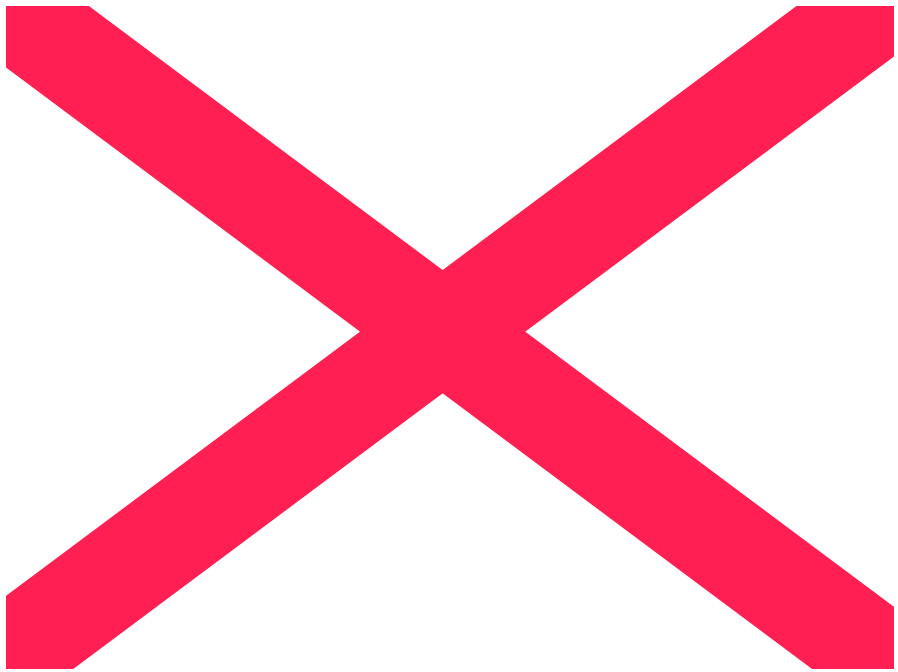
- Up to 80% of thyroid carcinomas
- Indolent (although certain variants are aggressive) - <6.5% mortality
- May show local invasion and LN mets
- Young to middle-aged women
- Prior radiation exposure

PAPILLARY THYROID CARCINOMA

- **FNA is highly accurate:**
  - >90% are diagnosed as positive or suspicious by FNA
  - In some studies, FNA is more accurate than frozen section
  - False negative rate is low:
    - Cystic papillary carcinomas
    - Follicular variant of papillary carcinoma
    - Admixture of benign thyroid tissue

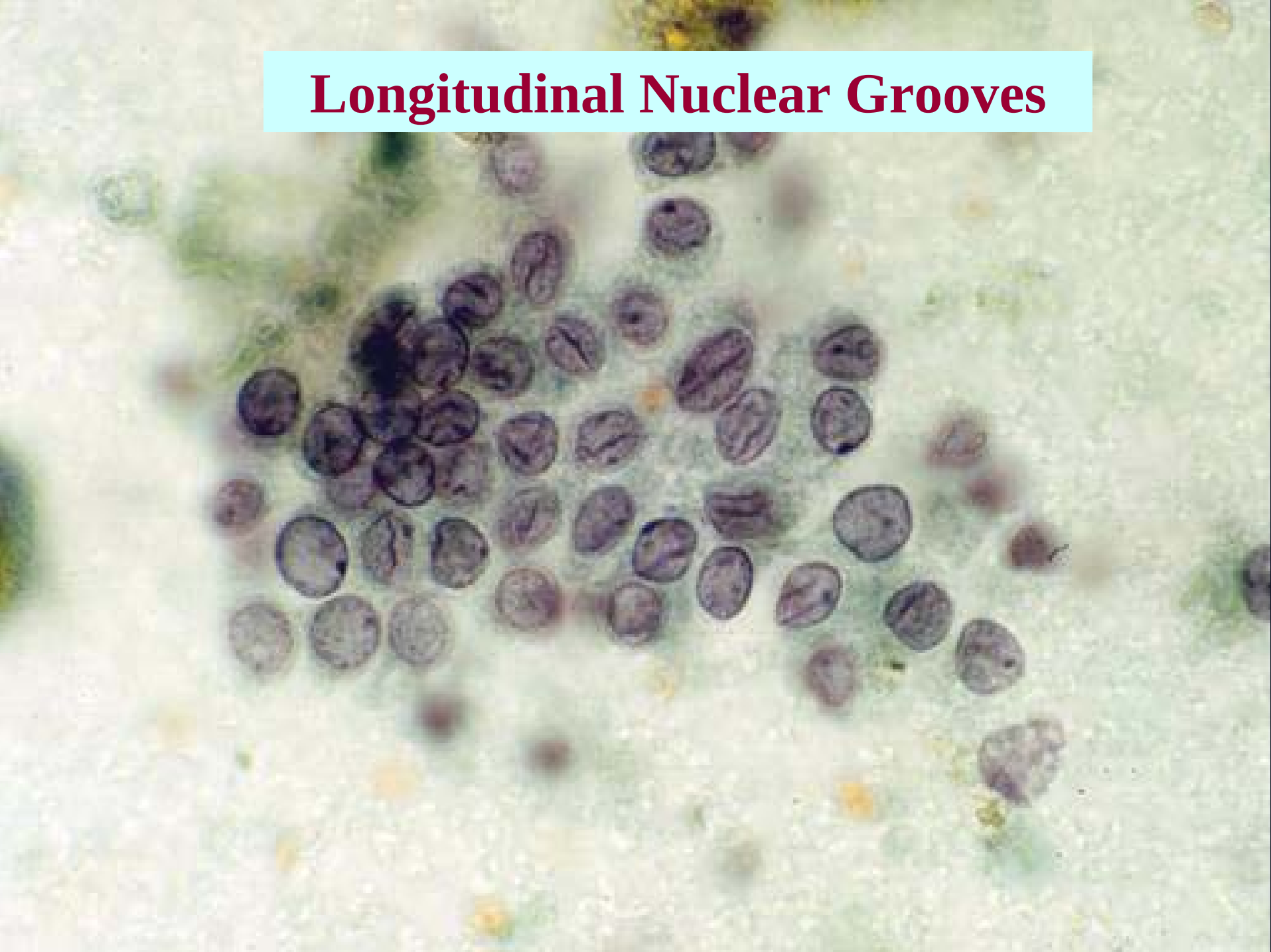
PAPILLARY THYROID CARCINOMA

- **Diagnostic Cytologic Features:**
  - **Enlarged, oval nucleus with eccentric nucleolus**
  - **Fine, pale chromatin**
  - **Longitudinal nuclear grooves**
  - **Intranuclear pseudoinclusions**

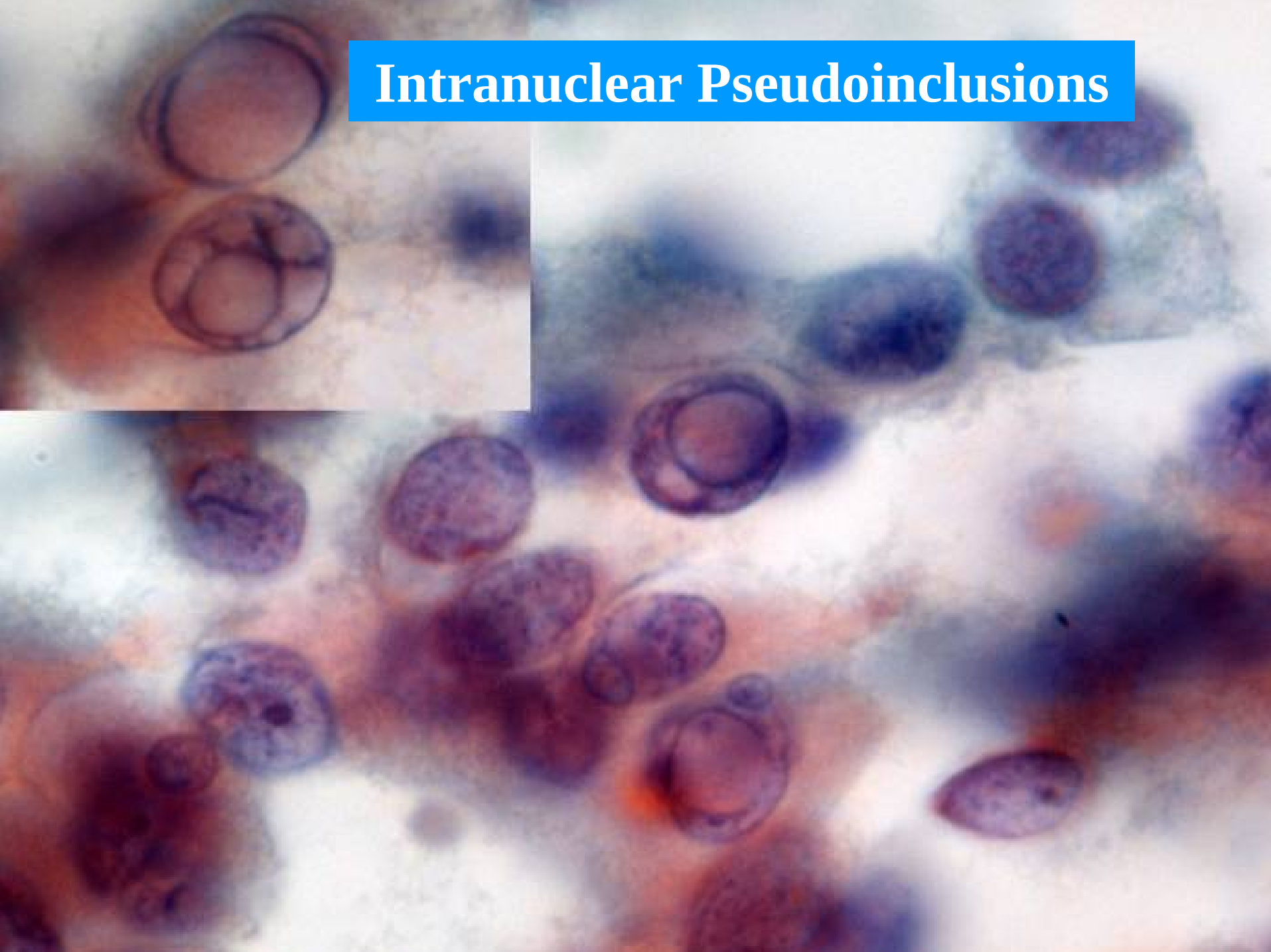


Enlarged oval nuclei with pale chromatin, and small eccentric nucleolus.

Longitudinal Nuclear Grooves



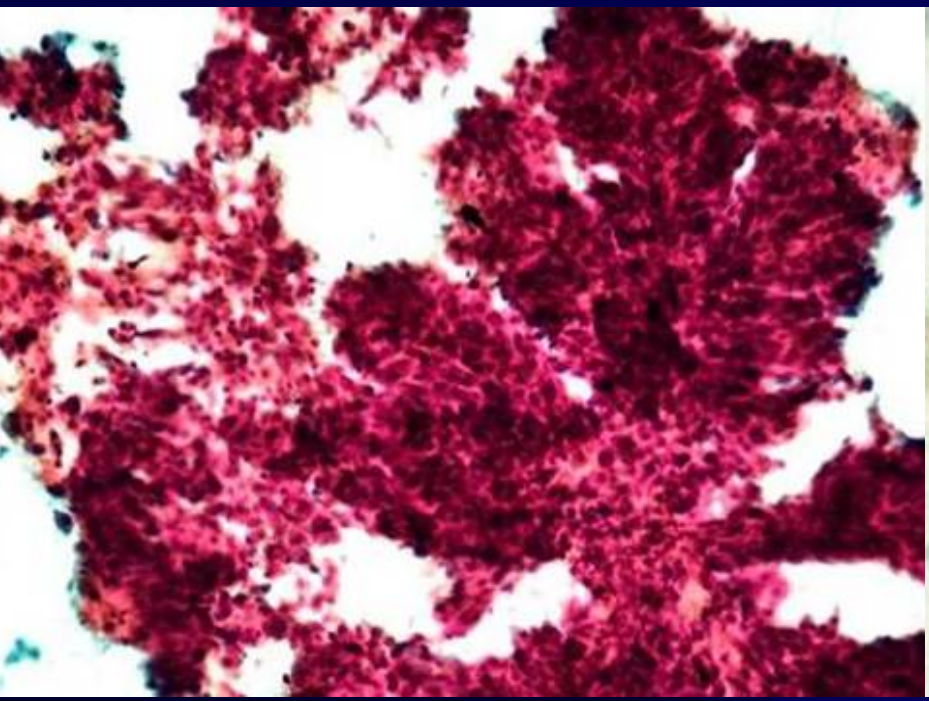
Intranuclear Pseudoinclusions

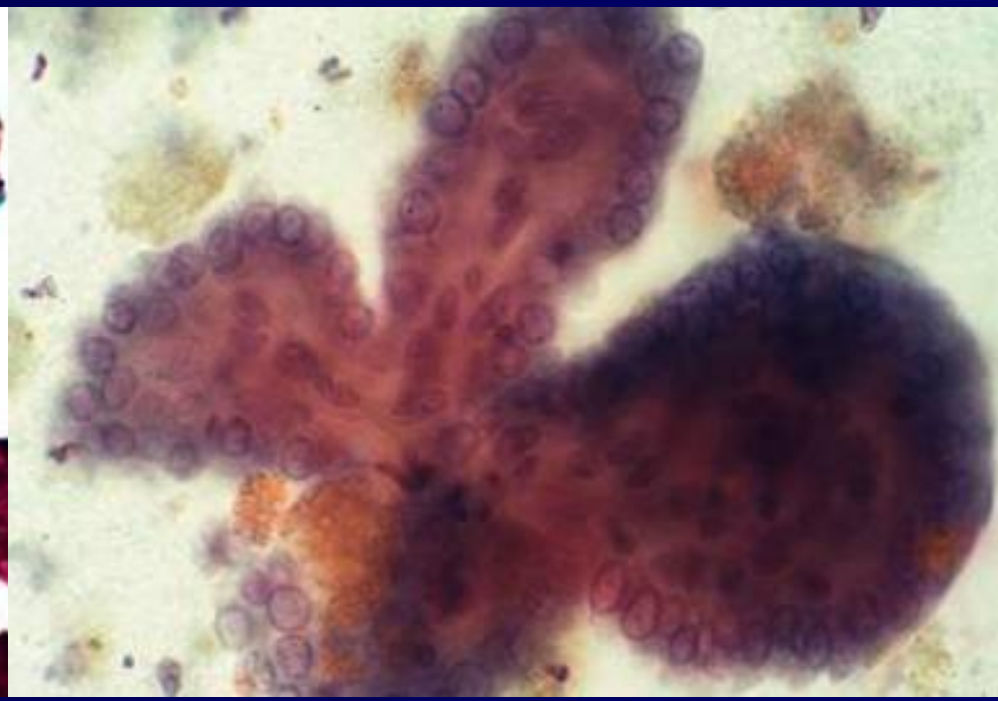


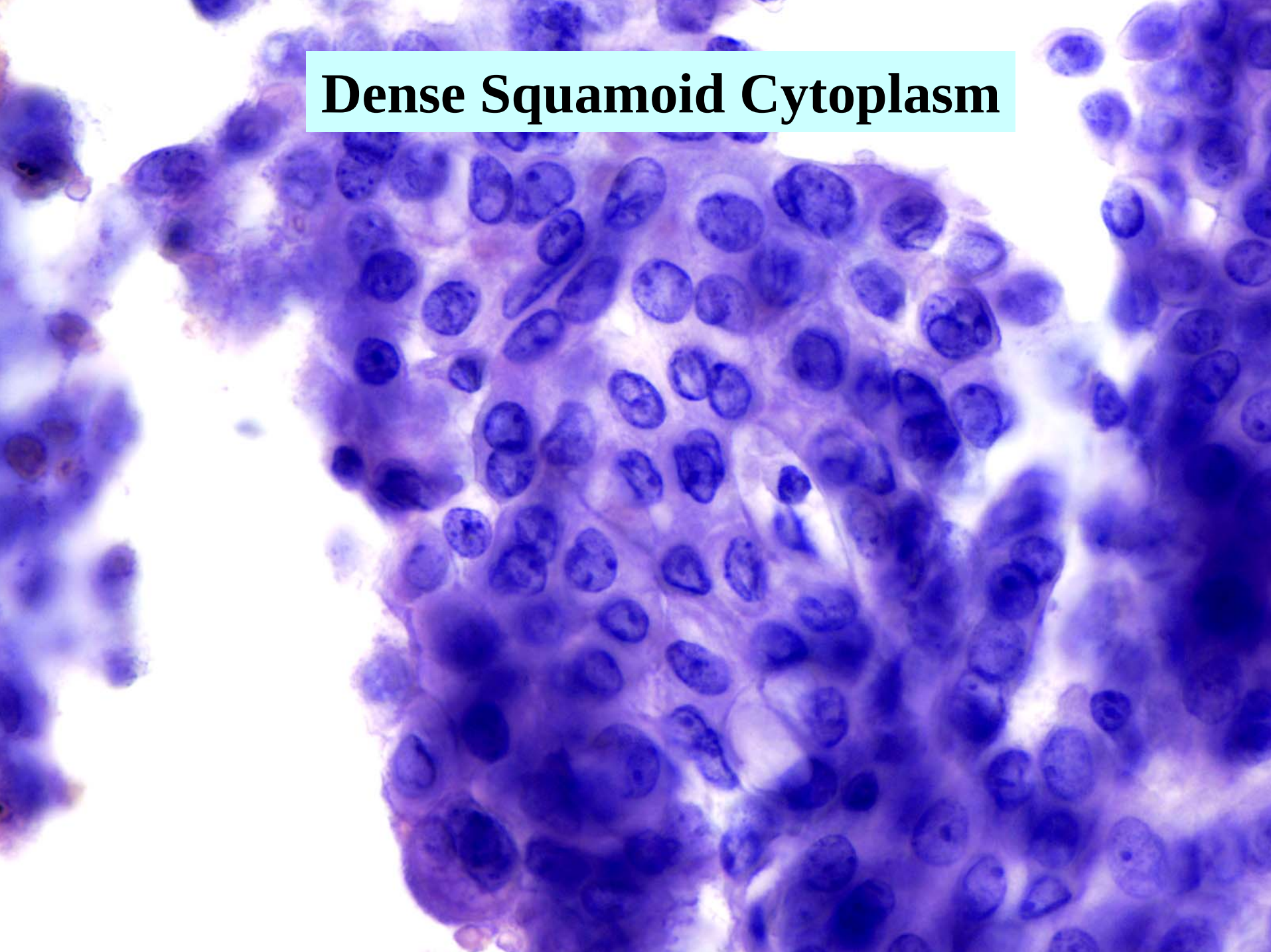
PAPILLARY THYROID CARCINOMA

- **Additional Cytologic Features:**
  - Papillary cytoarchitecture
  - Syncytial monolayers
  - Dense squamoid cytoplasm
  - "Bubble-gum" colloid
  - Psammoma bodies
  - Multinucleated giant cells

Papillary Cytoarchitecture

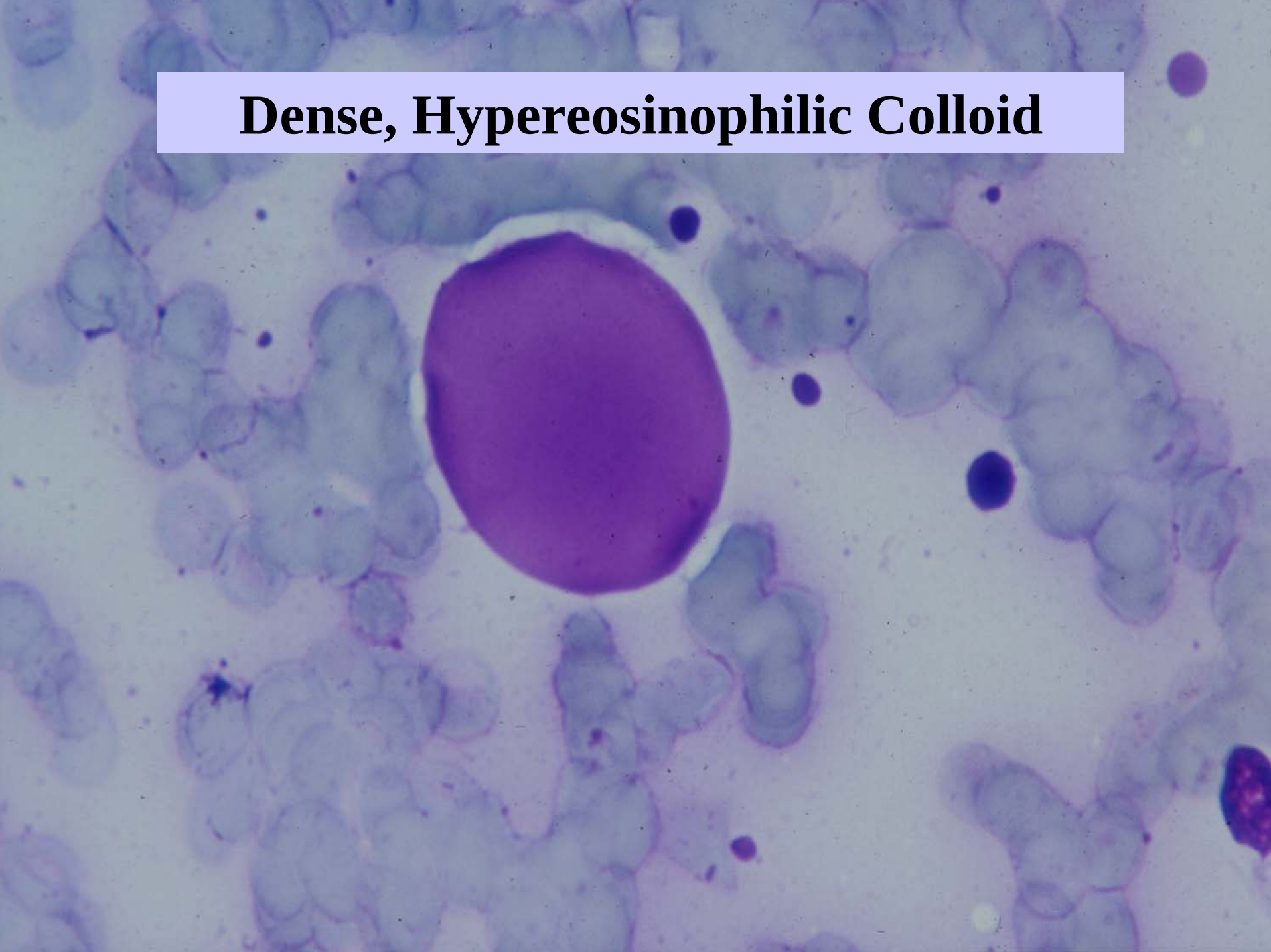




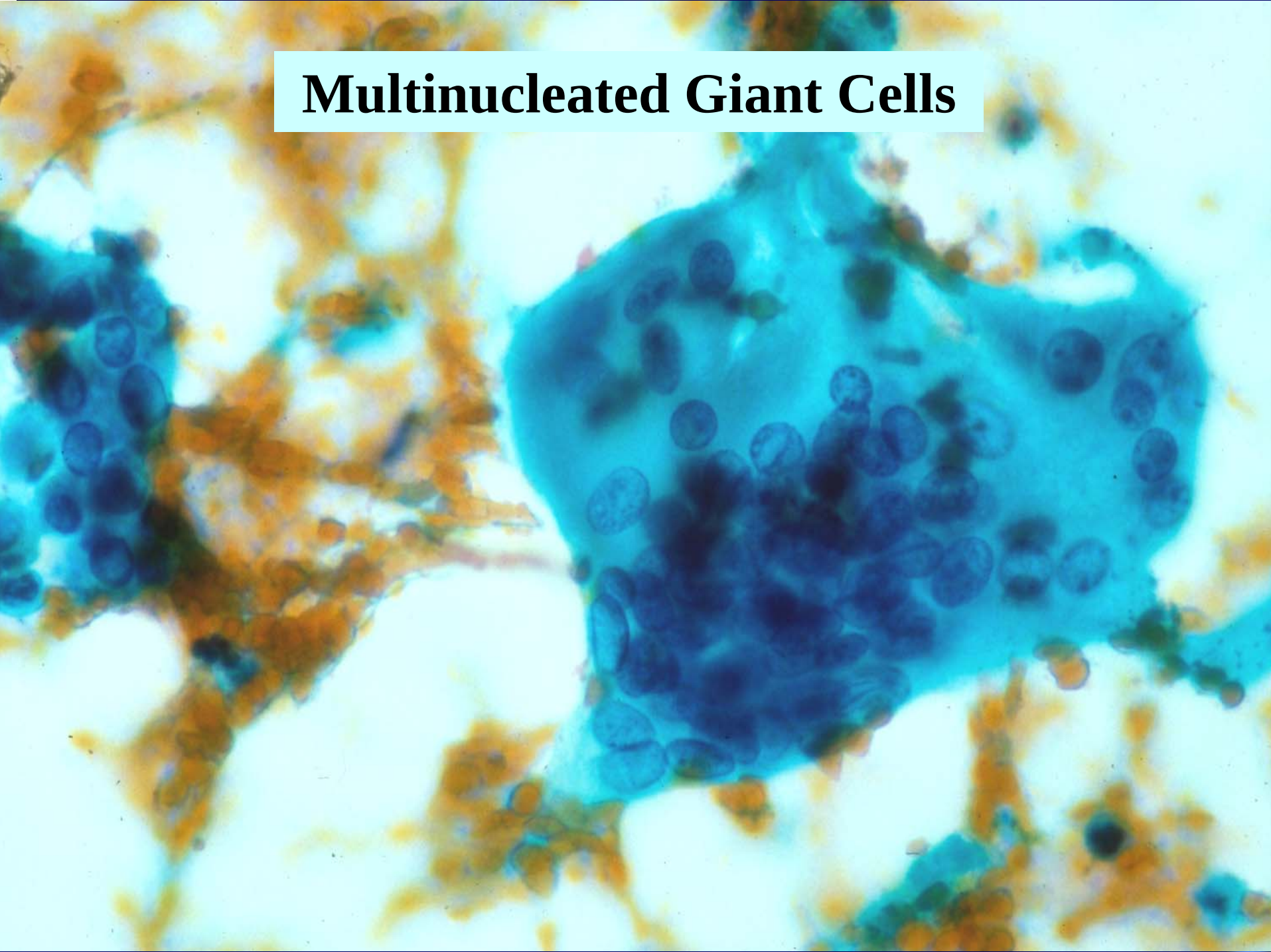

Dense Squamoid Cytoplasm

Psammoma Bodies

Dense, Hypereosinophilic Colloid



Multinucleated Giant Cells



PAPILLARY THYROID CARCINOMA

What are the most diagnostic features?

- **Kini et al. (1980):**
  - Syncytial-type fragments
  - Pale, enlarged nuclei
  - Multiple nucleoli
  - Intranuclear pseudoinclusions
  - Nuclear grooves
- **Miller et al. (1986) - stepwise regression analysis:**
  - Papillary structures without vessels
  - Intranuclear pseudoinclusions
  - Metaplastic cytoplasm
- **Basu et al. (1992):**
  - Extensive nuclear grooves
  - Dense squamoid cytoplasm
  - Papillary architecture

PAPILLARY THYROID CARCINOMA

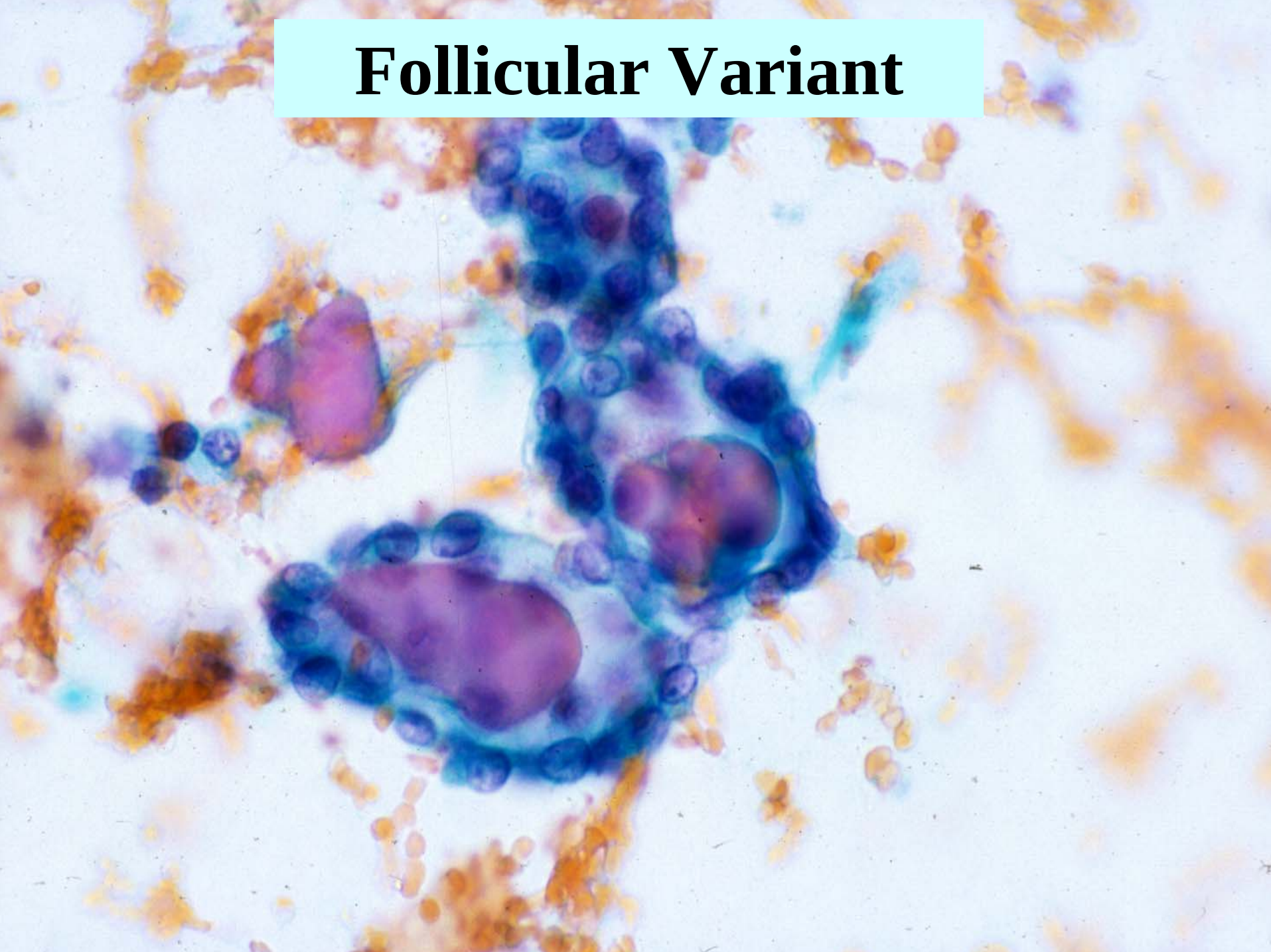
No single cytologic feature is diagnostic of papillary thyroid carcinoma!

Papillary Thyroid Carcinoma

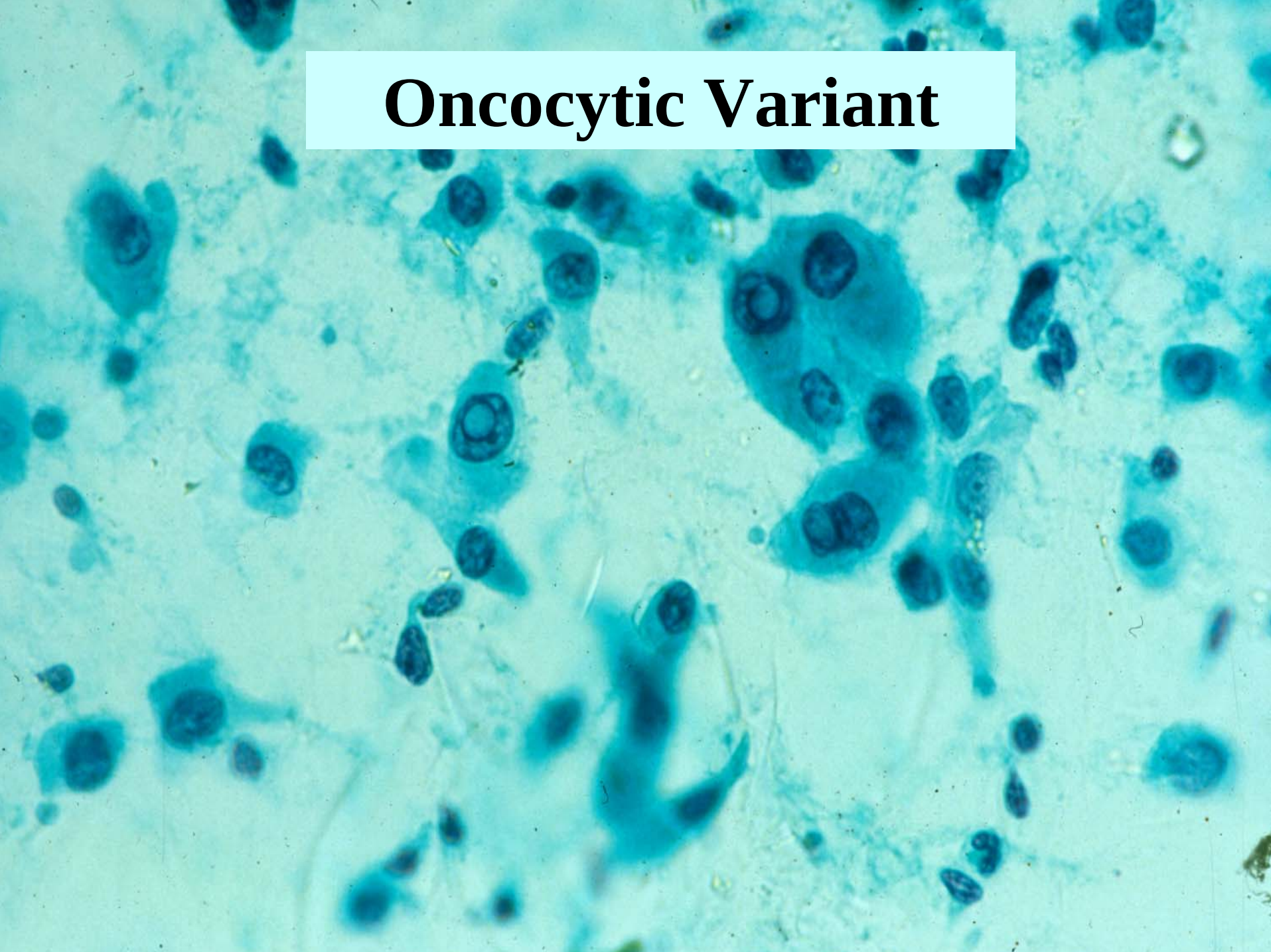
Variants:

- Follicular
- Diffuse sclerosing
- Warthin-like
- Solid
- Trabecular
- Cribriform-morular
- Oncocytic
- Tall cell
- Columnar cell

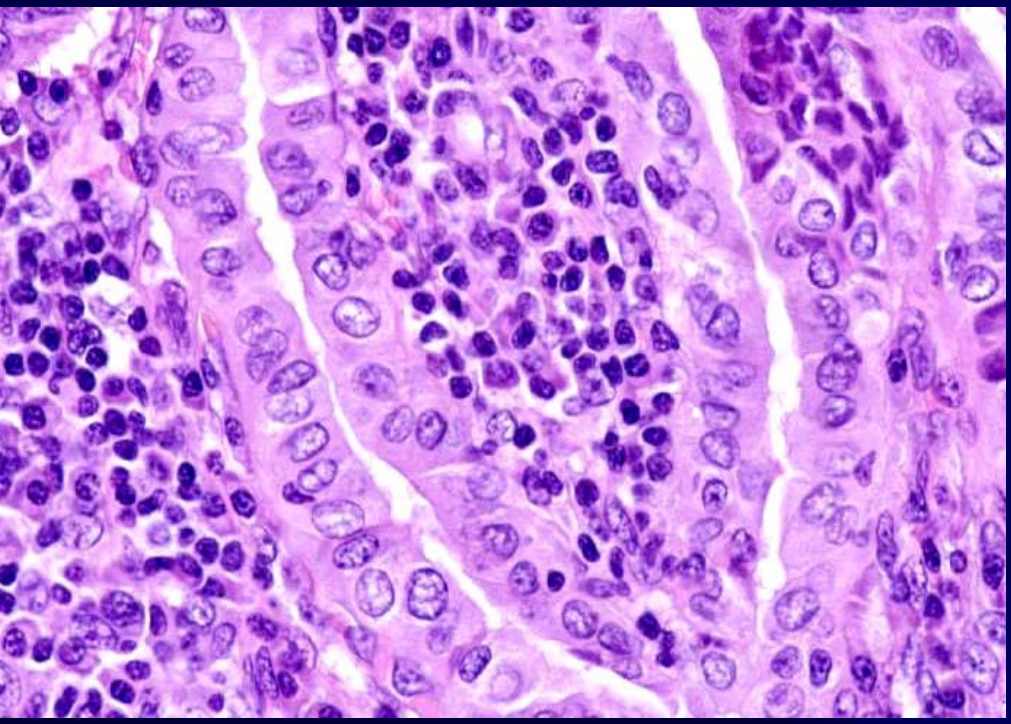
Follicular Variant

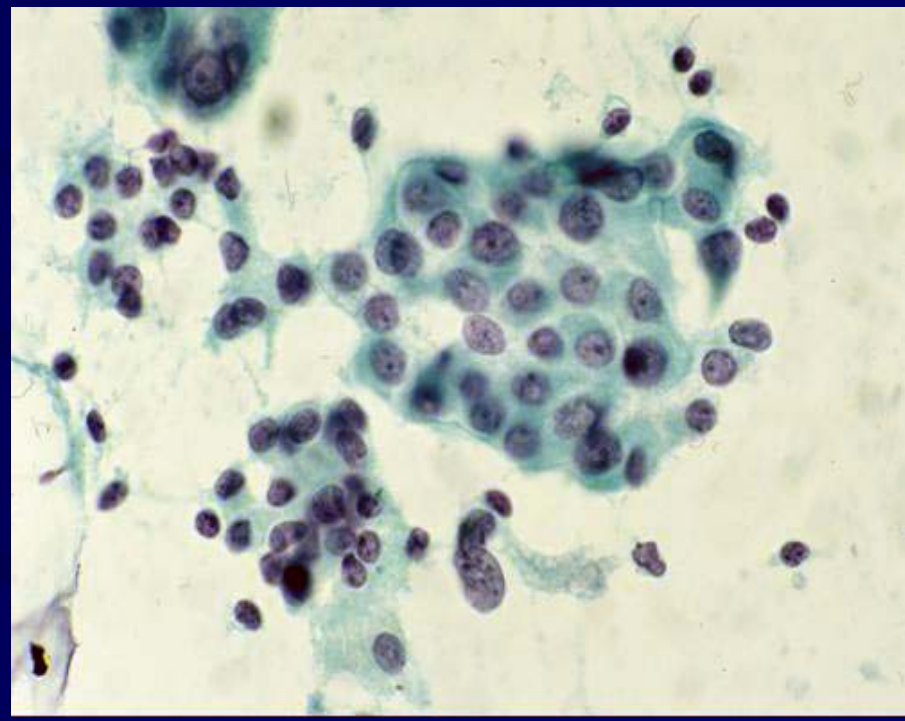


Oncocytic Variant

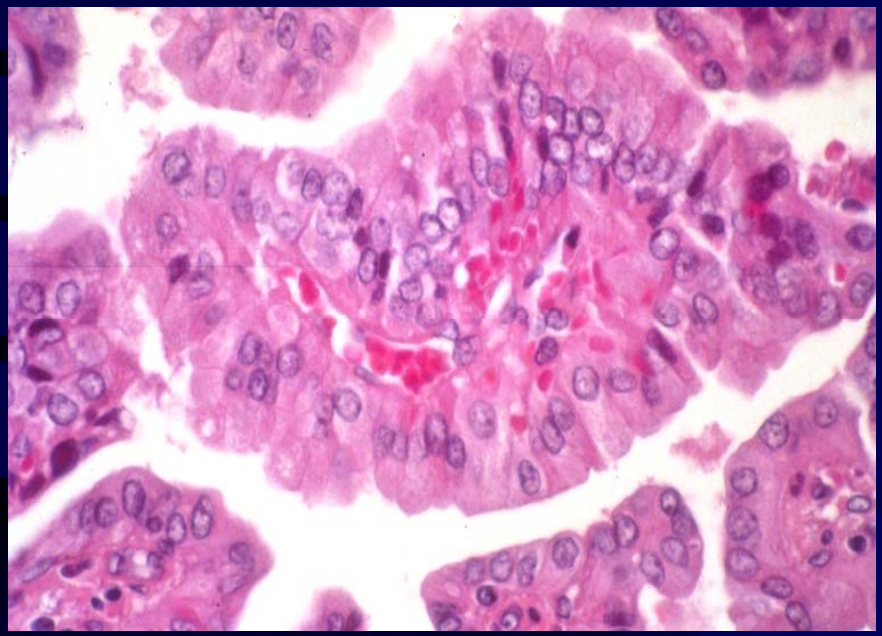


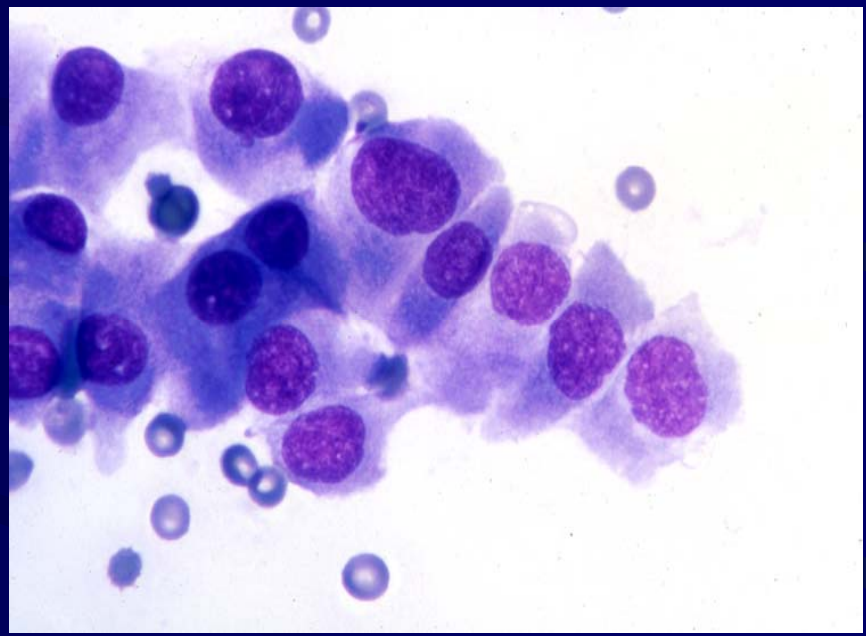
“Warthin-Like” Variant



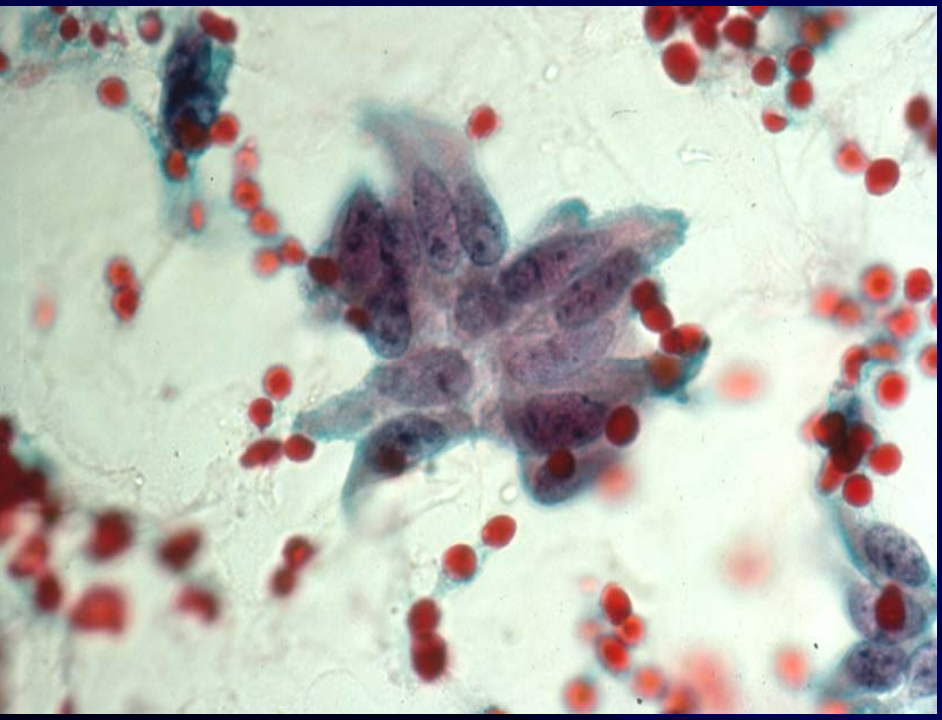


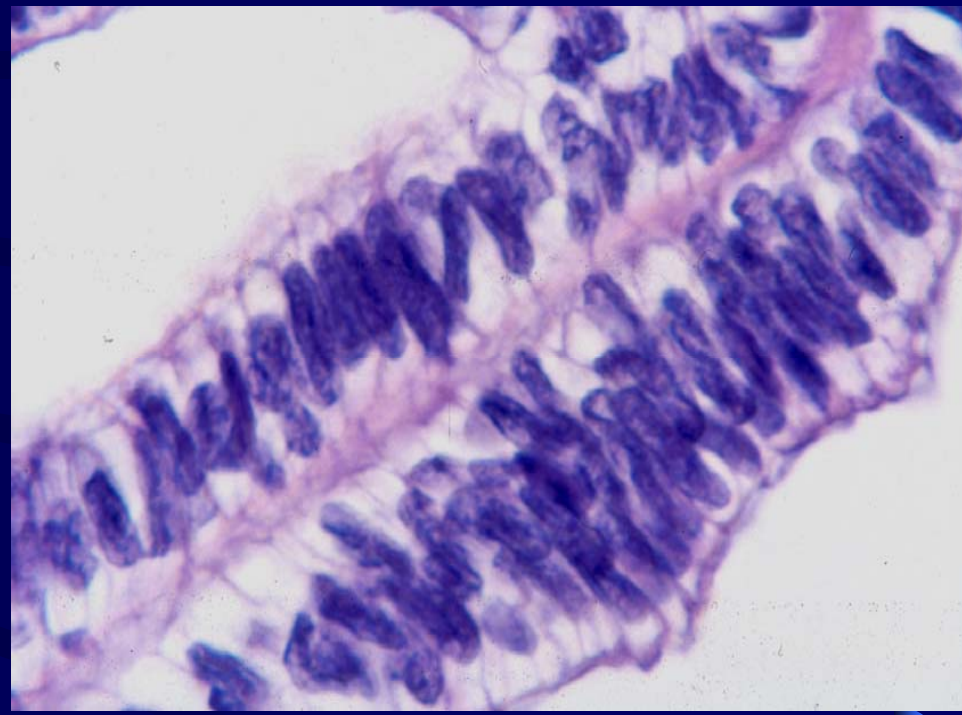
Tall Cell Variant





Columnar Cell Variant





Undifferentiated Thyroid Carcinoma

- AKA: Anaplastic carcinoma
- < 5% of all thyroid malignancies
- Rapidly fatal prognosis - local infiltration (mean survival = 6 months)
- Elderly patients (very rare before age 40)
- Clinical history:
  - » Rapid increase in size of a long-standing cold thyroid nodule in an elderly patient
  - » Up to 80% have a history of well or poorly differentiated thyroid carcinoma

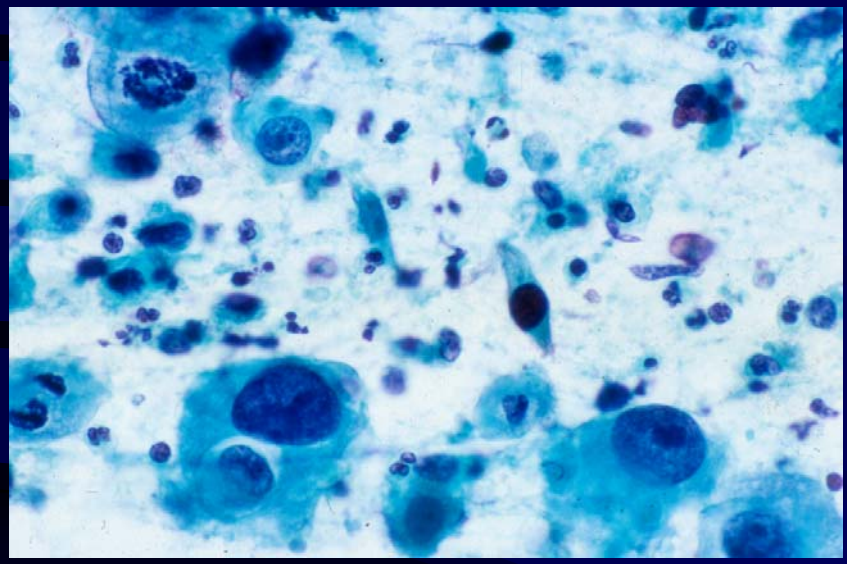
Undifferentiated Thyroid Carcinoma

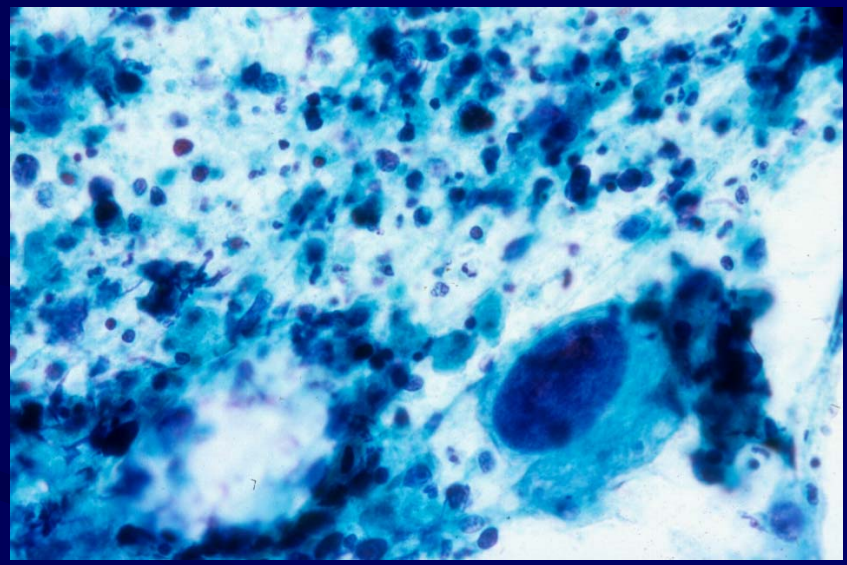
- **Diagnostic Cytologic Features:**
  - **Highly malignant and bizarre cells**
  - **High-grade nuclear features:**
    - **Marked pleomorphism**
    - **Dark clumped chromatin**
    - **Macronucleoli**
    - **Atypical mitoses**
  - **Tumor diathesis**

Undifferentiated Thyroid Carcinoma

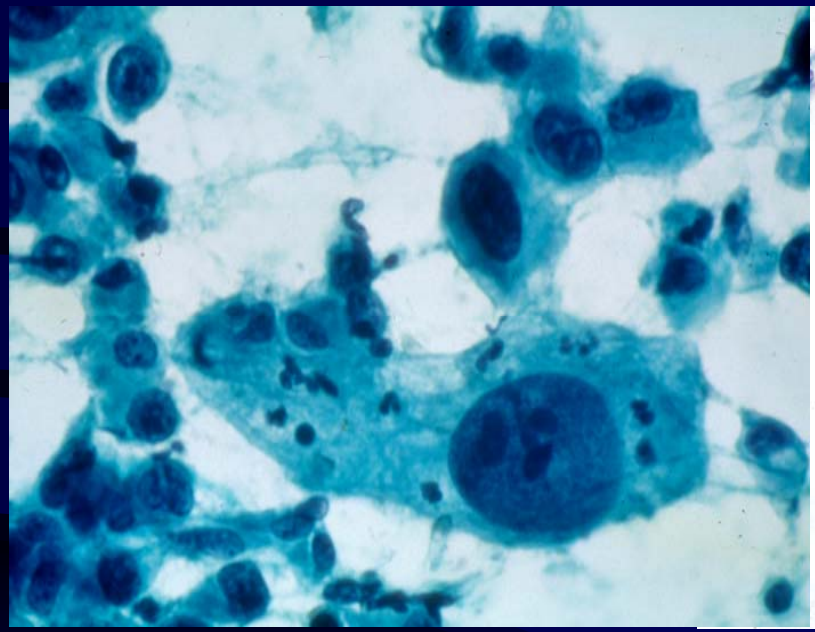
- Combination of three cellular patterns:
  - Spindle cell
  - Giant cell
  - Squamoid

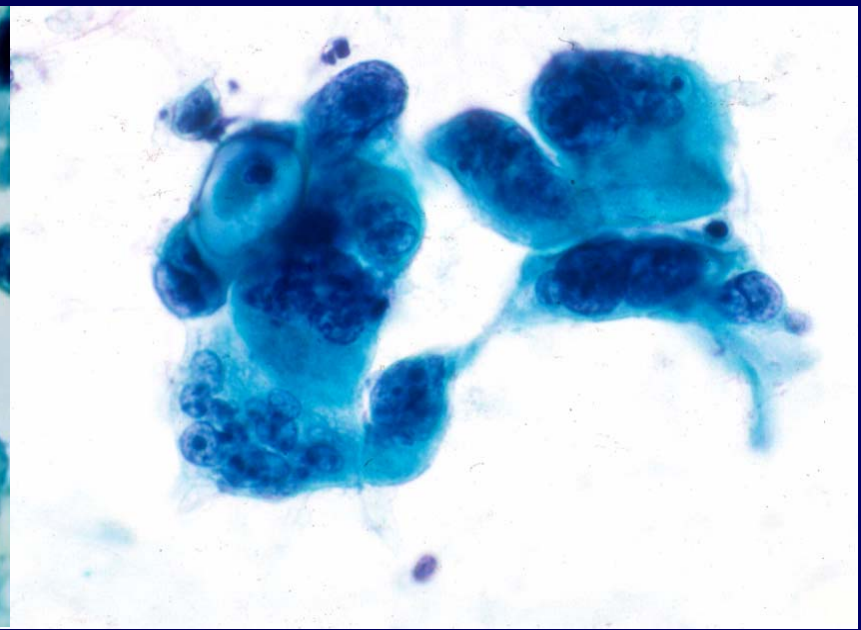
Undifferentiated Thyroid Carcinoma



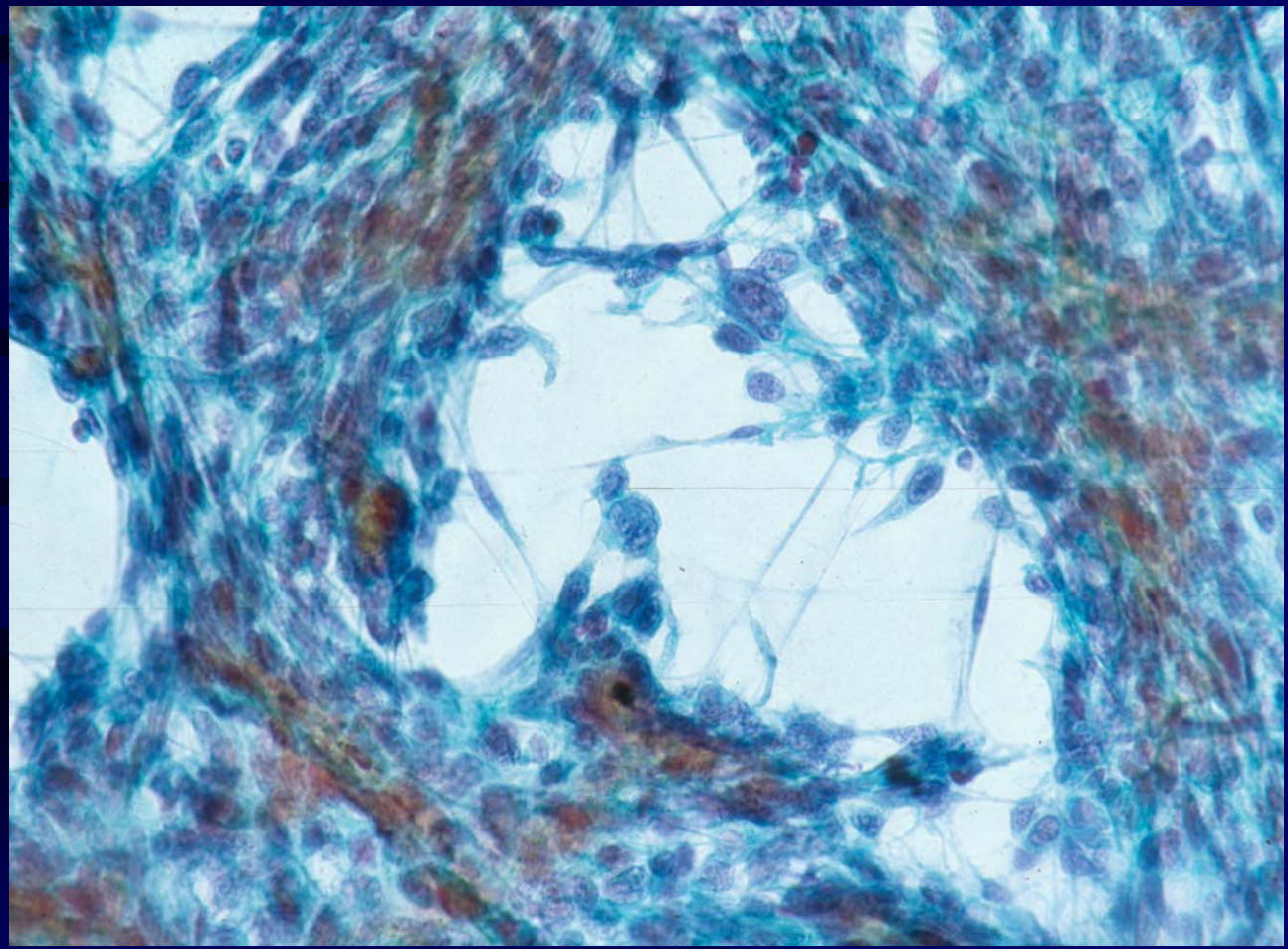


Undifferentiated Thyroid Carcinoma





Undifferentiated Thyroid Carcinoma



Undifferentiated Thyroid Carcinoma

How to distinguish from other thyroid and non-thyroid lesions:

- Immunocytochemistry:
  - LMW keratin +
  - Thyroglobulin +
  - TTF-1+
  - Calcitonin & CEA -
- EM:
  - Demonstrates epithelial features
- Clinical:
  - Radiologic evidence of thyroid origin
  - Clinical history of prior better differentiated thyroid carcinoma

Medullary Thyroid Carcinoma

- Neuroendocrine carcinoma arising from the C-cell of the thyroid gland
- 5% of all thyroid cancers
- Mean age = 50 years (sporadic cases), slightly more common in women
- 75-90% are sporadic
- 10-25% are inherited (e.g. MEN II syndrome)
- >70% develop LN metastasis
- FNA: approx. 75% accurate

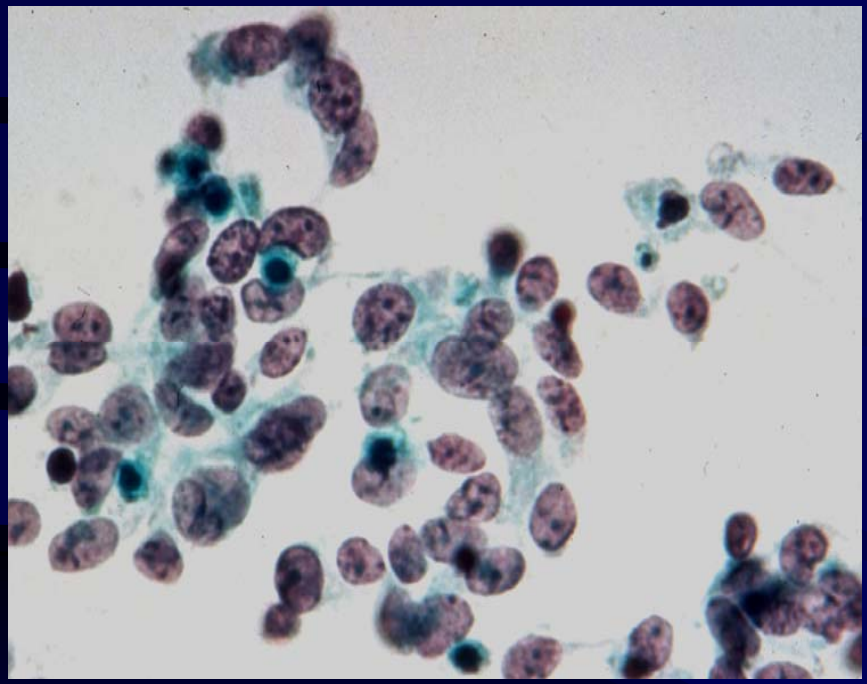
Medullary Thyroid Carcinoma

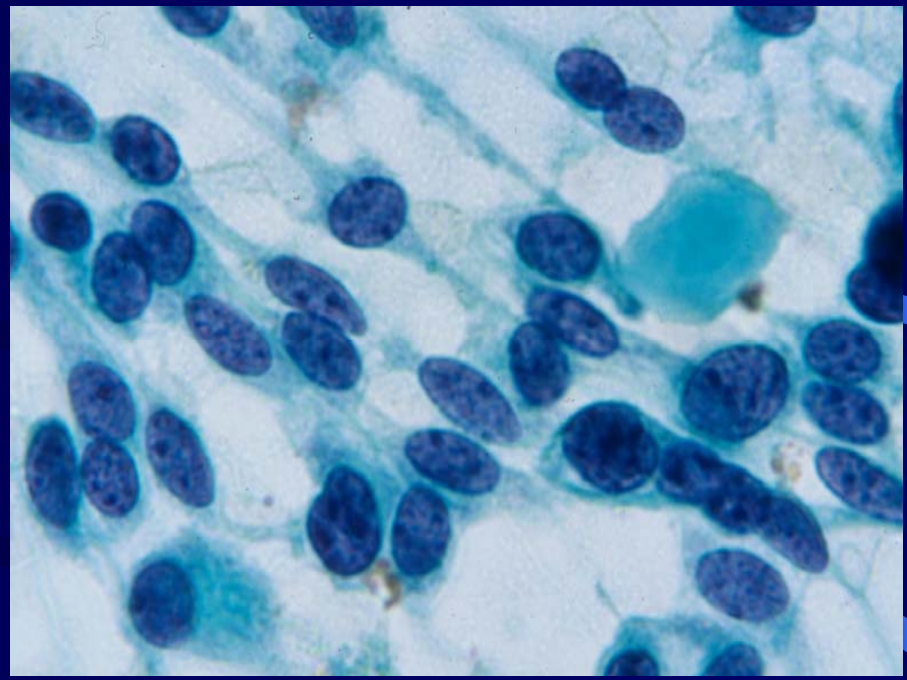
- **Cytologic Features:**
  - **Uniform, dispersed single cells:**
    - » **Plasmacytoid**
    - » **Spindled**
    - » **Polygonal**
  - **Granular "salt-and-pepper" chromatin**
  - **Background amyloid (approx. 80% of cases)**

Medullary Thyroid Carcinoma

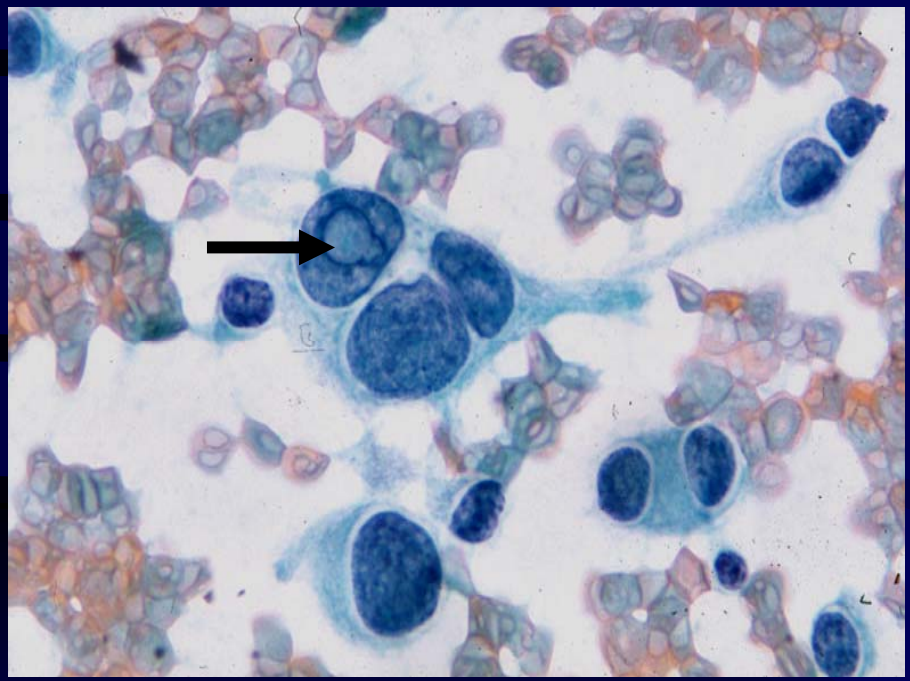
- **Additional Cytologic Features:**
  - **Eccentric nuclei are common**
  - **Multinucleation**
  - **Intranuclear pseudoinclusions**
  - **Predominantly indistinct nucleoli**
  - **Red cytoplasmic granules in Romanowsky stains**

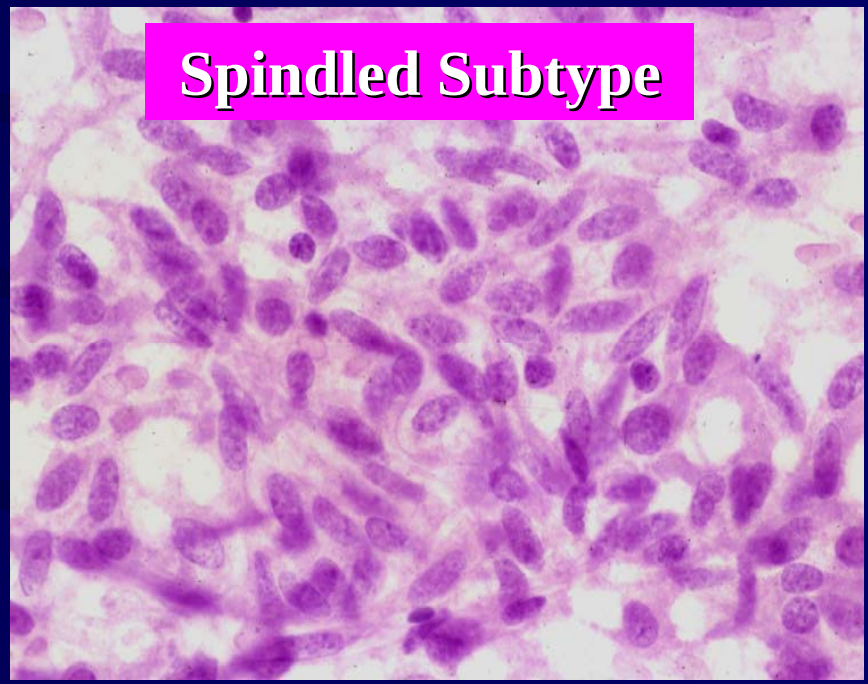
Medullary Thyroid Carcinoma



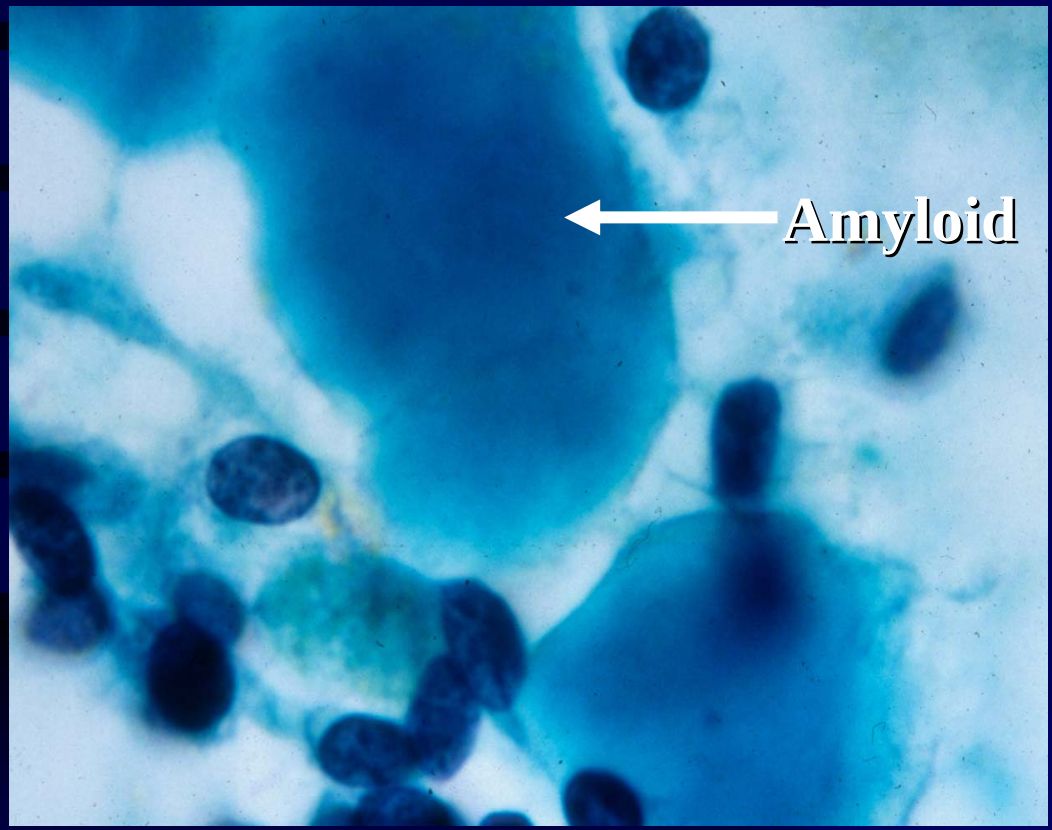


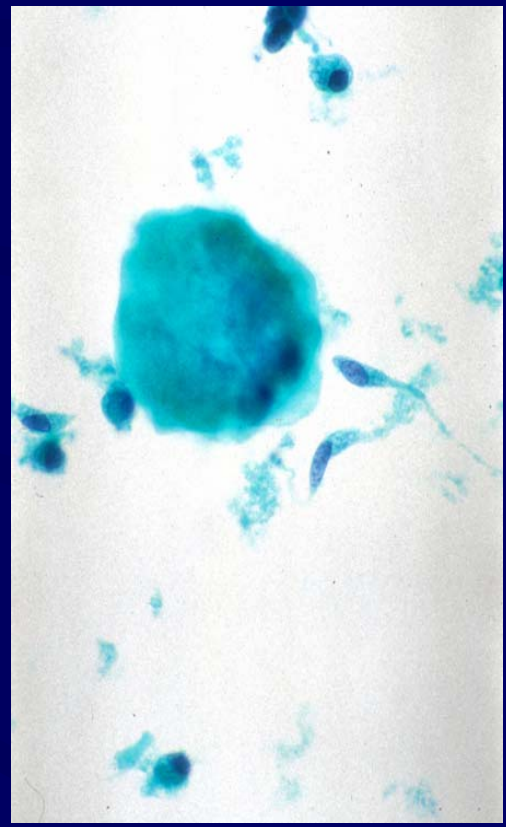
Medullary Thyroid Carcinoma





Medullary Thyroid Carcinoma



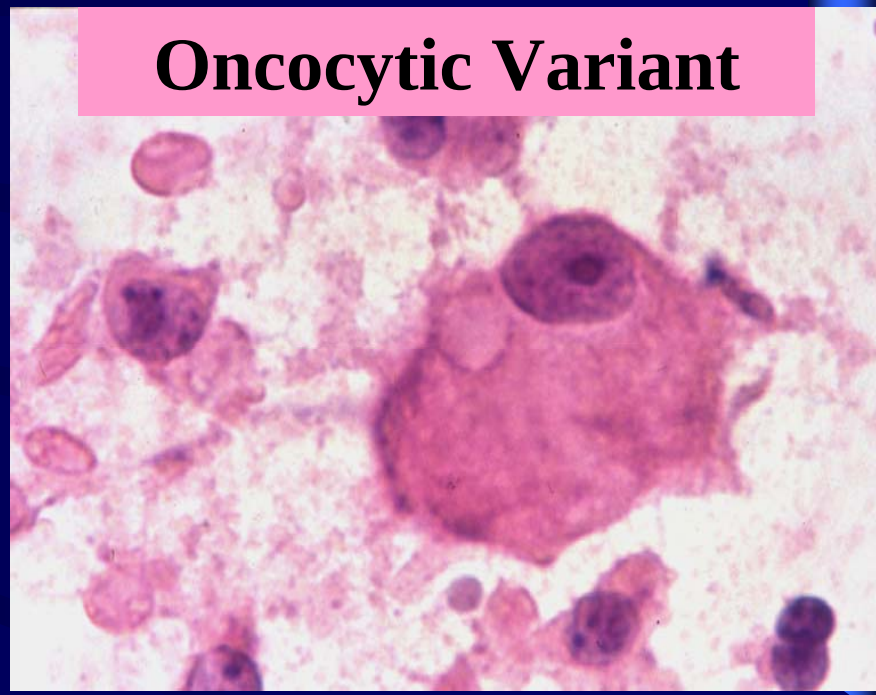


Medullary Thyroid Carcinoma

"Cytologically and histologically, MTC is a great mimicker!"

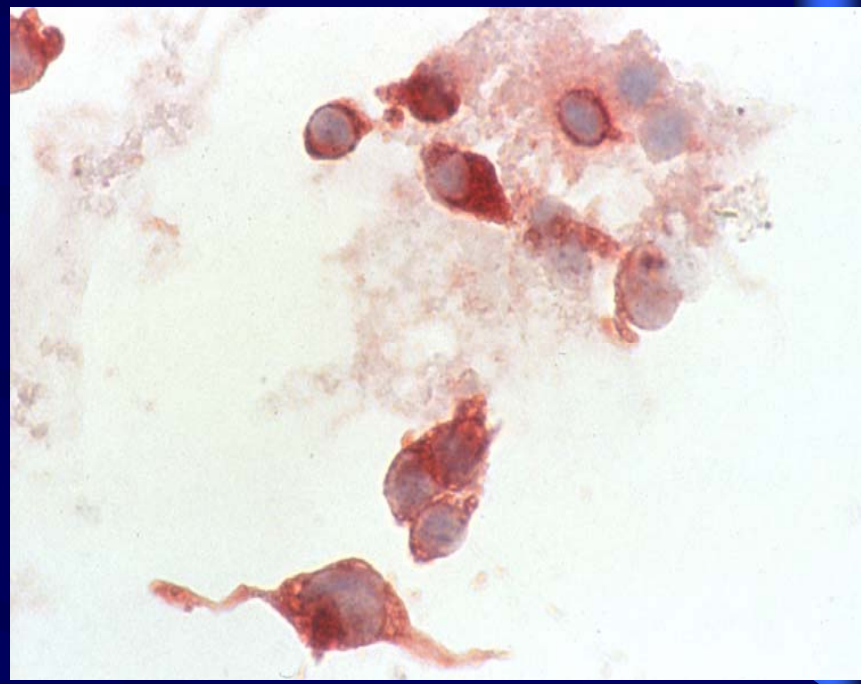
- **MTC Variants:**
  - Oncocytic
  - Spindle cell
  - Papillary
  - Melanin-producing
  - Clear cell
  - Small cell
  - Giant cell

Oncocytic Variant



Medullary Thyroid Carcinoma

- **Immunocytochemistry for calcitonin is recommended before making a definitive diagnosis.**



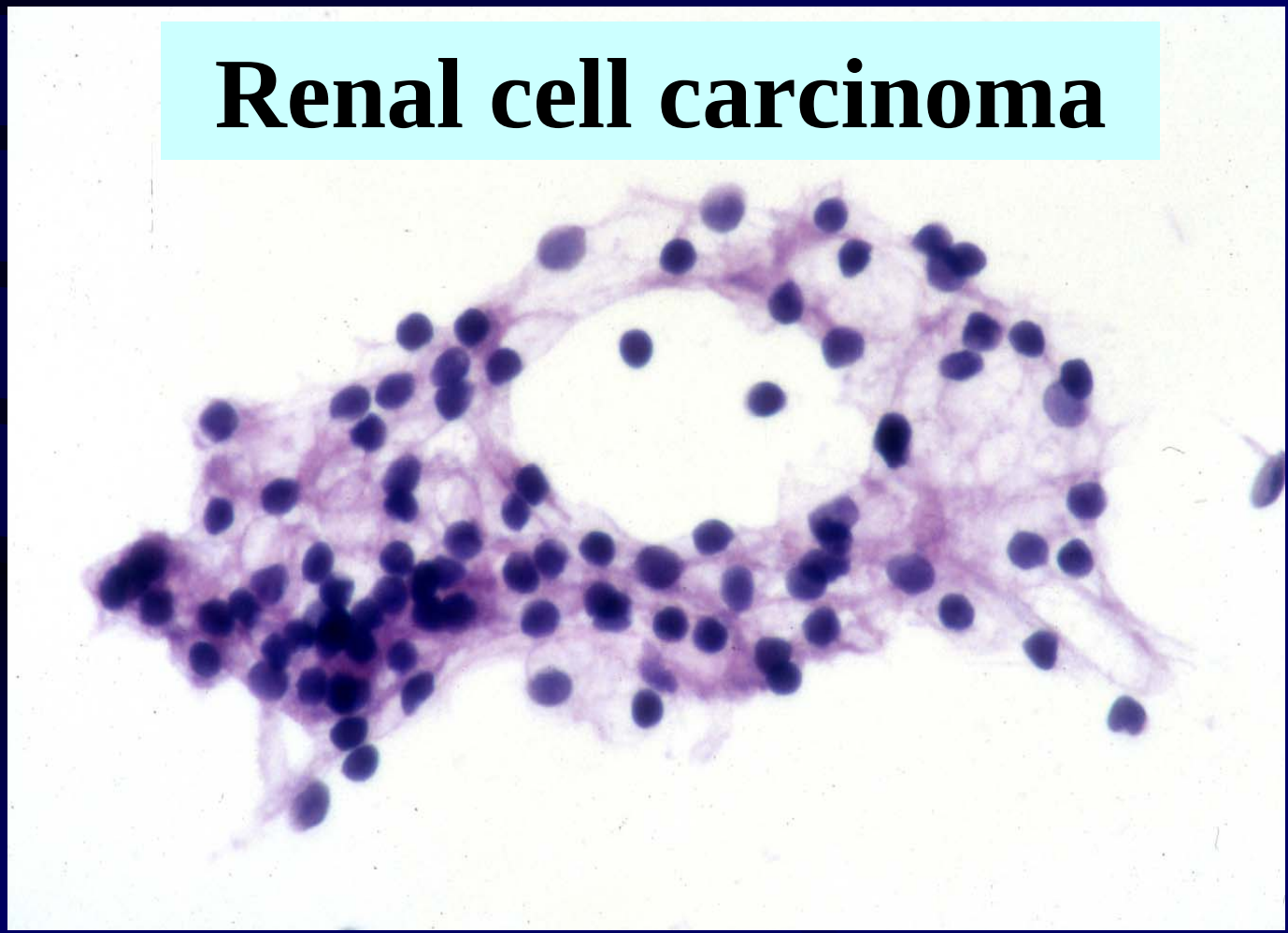
Secondary Tumors of the Thyroid

- Clinical history of a non-thyroid malignancy
  - Caveat: >25% of metastatic tumors to the thyroid do not have a prior history!
- Does not fit into the classic microscopic pattern of a thyroid primary
- Solitary (direct extension) or multiple nodules (distant mets) and tumor diathesis
- Neither mucin nor keratinization can be taken as evidence of an extrathyroidal origin
- Immunocytochemistry for thyroglobulin, TTF-1, and calcitonin

Secondary Tumors of the Thyroid

- Uncommon (0.1% of thyroid FNAs)
- Most frequent include:
  - Renal (among the most difficult to recognize)
  - Lung
  - Breast
  - Malignant melanoma
  - Colorectal
  - Malignant lymphoma
  - Head and neck squamous cell carcinoma

Secondary Tumors of the Thyroid



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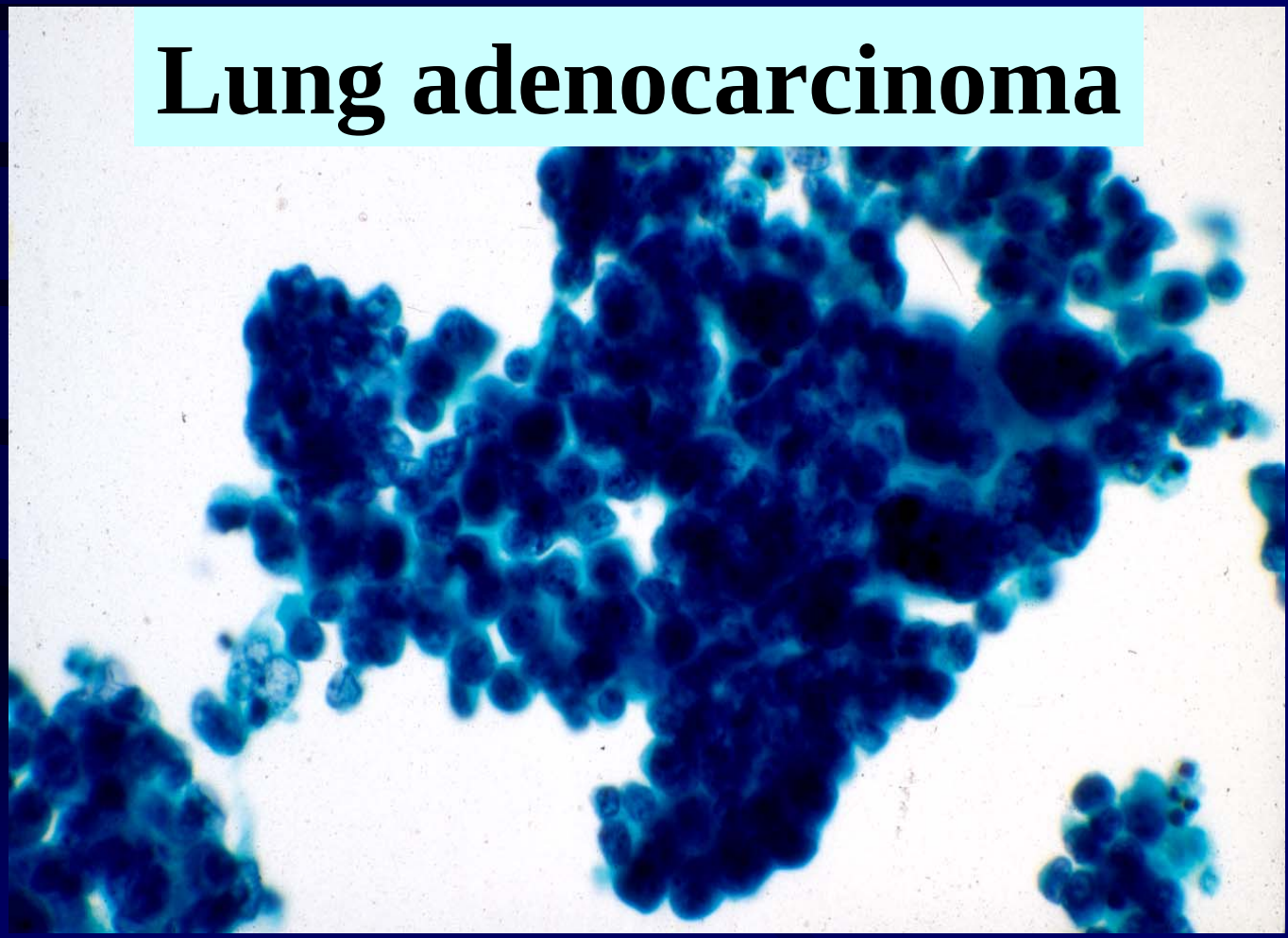
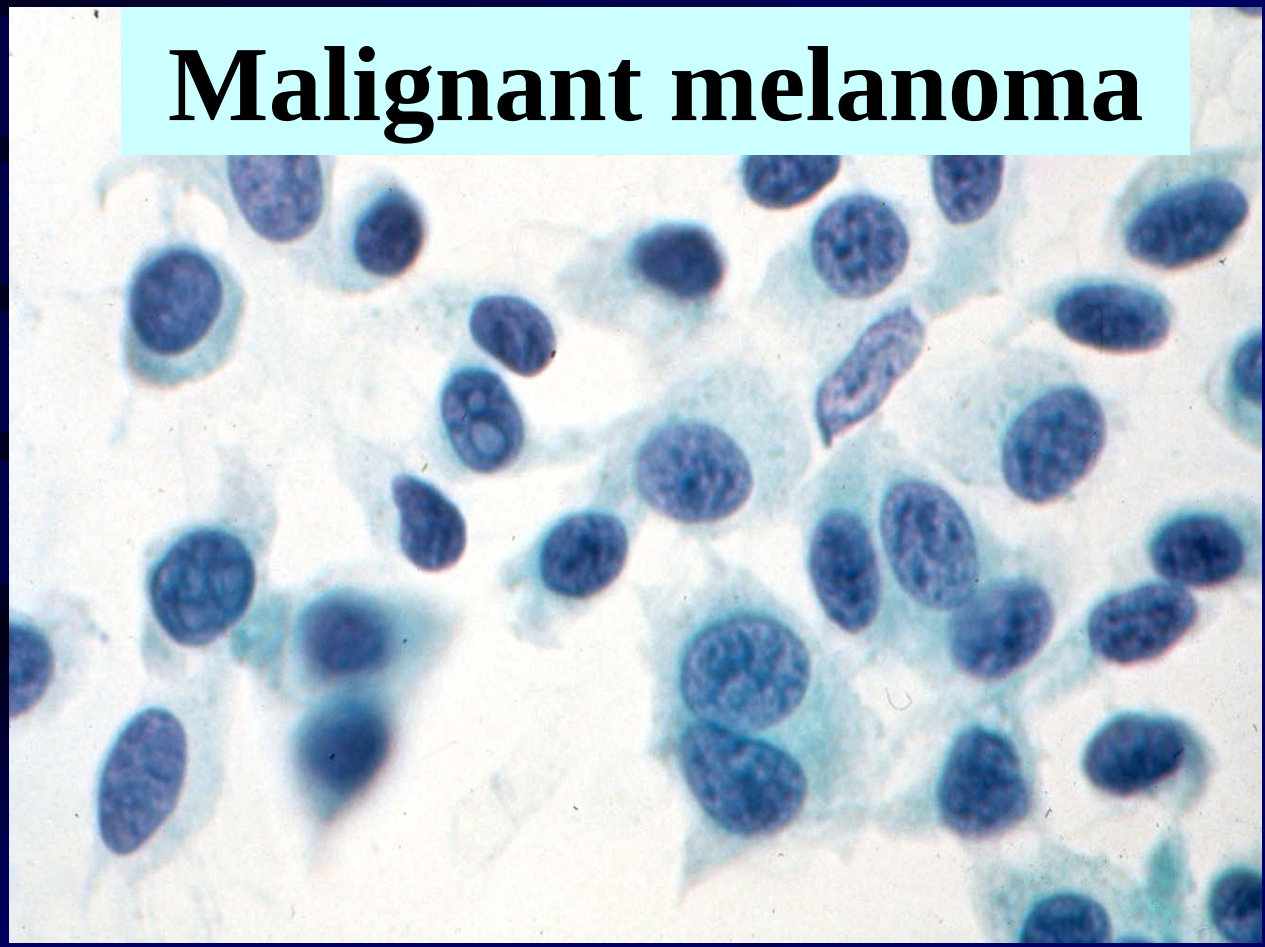
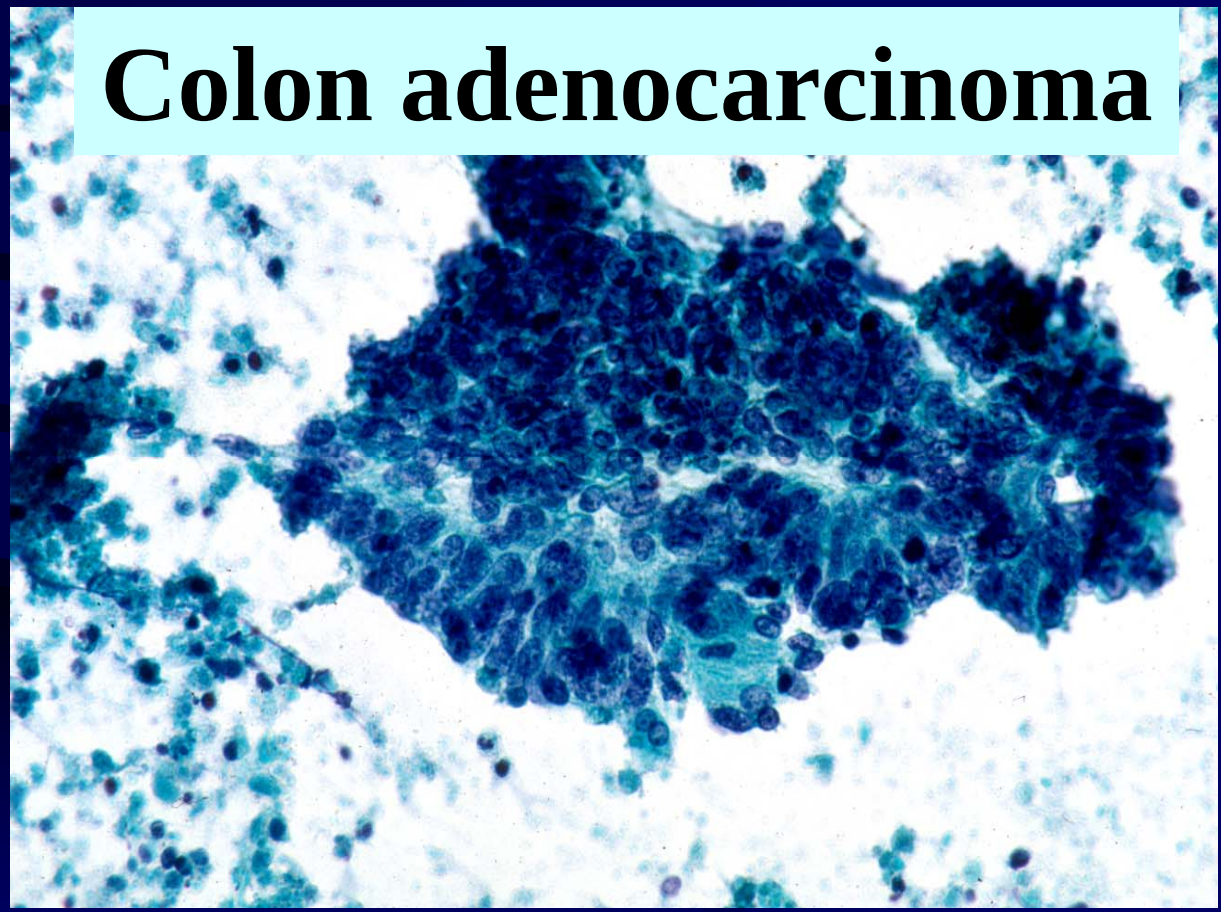


Secondary Tumors of the Thyroid



Secondary Tumors of the Thyroid



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Diagnostic Terminology and Criteria for the Cytologic Diagnosis of Thyroid Lesions - Part 1

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Part II: Follicular Lesions

Tarik ElSheikh, M.D.

Follicular Lesions of the Thyroid

Classification and Criteria

Tarik M. Elsheikh, MD
Director of Cytology
Pathologists Associated
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Diagnostic Terminology and Criteria

Committee members:

Zubair Baloch, MD, PhD

Tarik M. Elsheikh, MD

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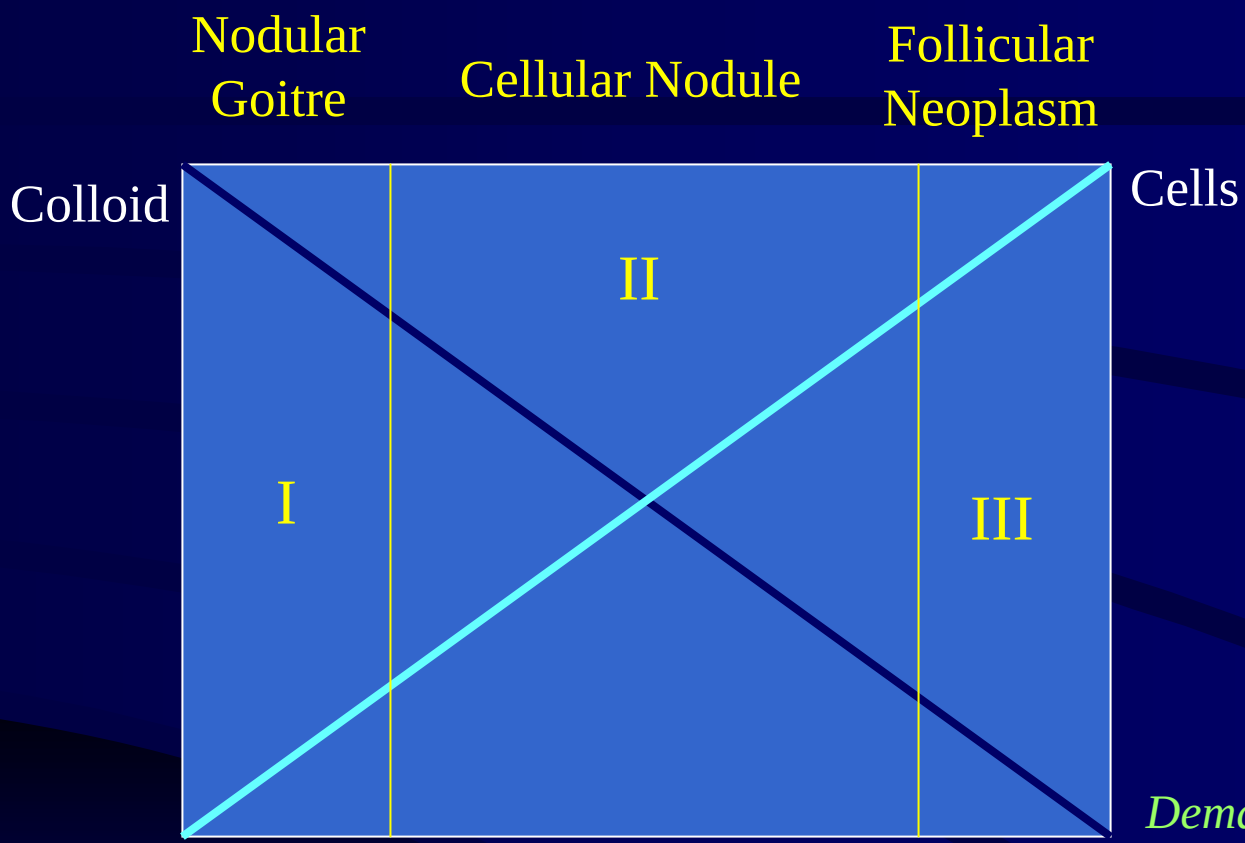
Sanjay Logani, MD

Differential Diagnosis of Follicular Lesions

- Hyperplastic/adenomatoid nodule
- Follicular Neoplasm
  - Follicular adenoma
  - Follicular carcinoma
- Follicular variant of Papillary carcinoma

Differential Diagnosis of Follicular Lesions



Demay. Art & Science of Cytopathology, 1996

- General principles:
  - Abundant colloid→ more likely benign
  - Marked cellularity→ more likely neoplastic

Inter-observer Variability

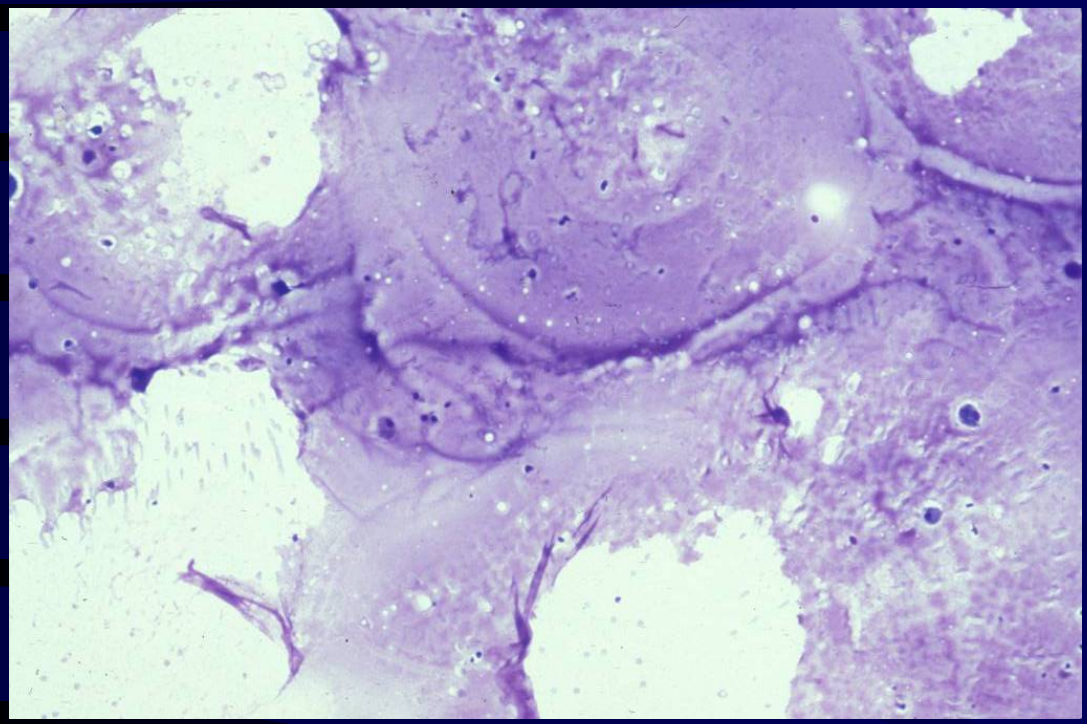
- Studies examined correlation in distinguishing FN from cellular hyperplastic nodule
- Areas of greatest debate and confusion
  - Criteria for diagnosis of FN
    - Proportion of microfollicles
    - Overall cellularity
    - Assessment of watery/thin colloid
  - Terminology
    - Two diagnostic categories (FL & FN) vs. one

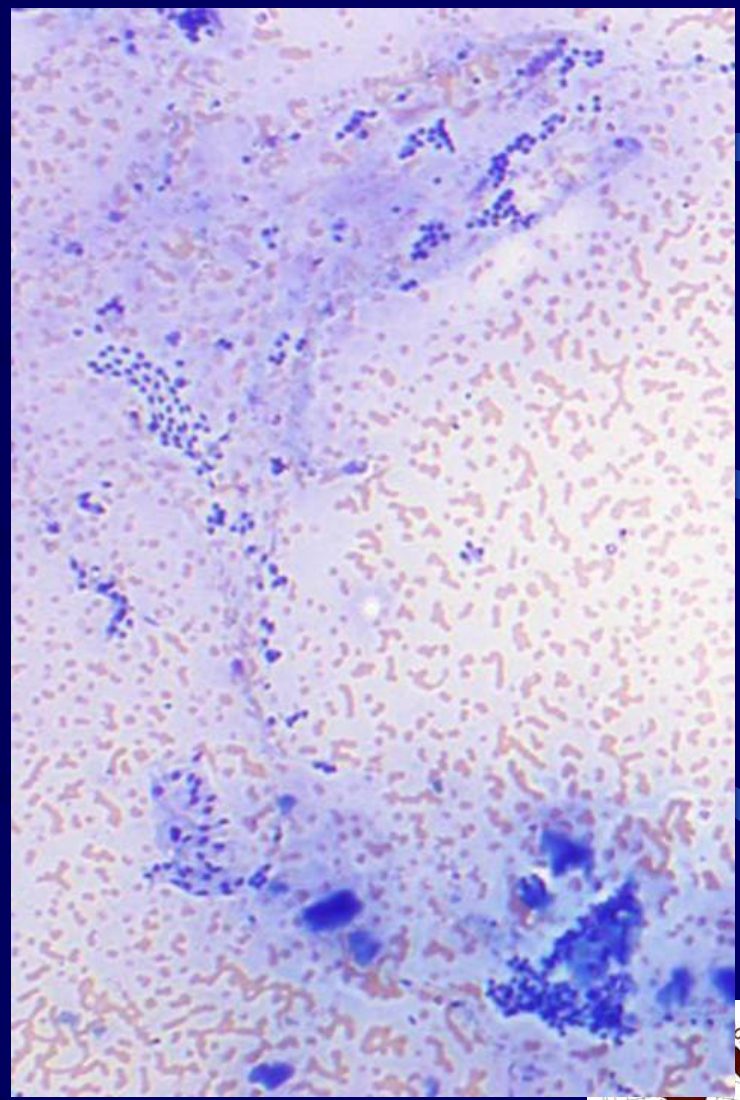
Yang 2003, Stelow 2005, Clay 2005

Follicular Lesions
Outline

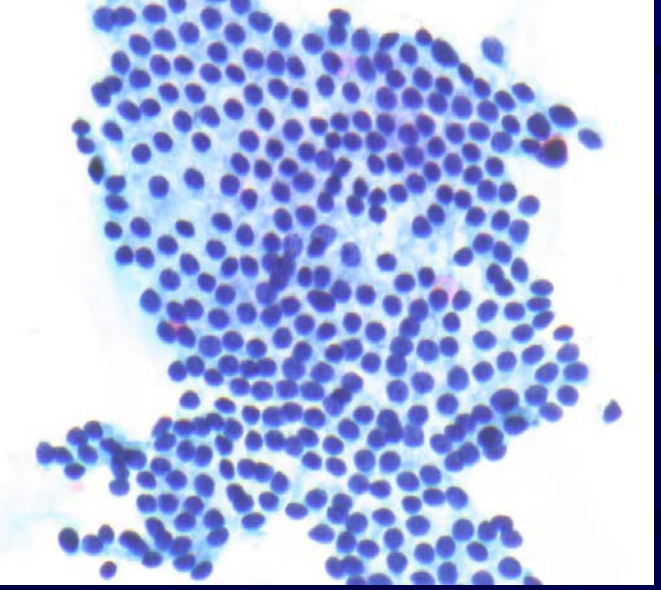
- Differential diagnosis
- Cytologic criteria
- Terminology
- Classification
- Clinical implications

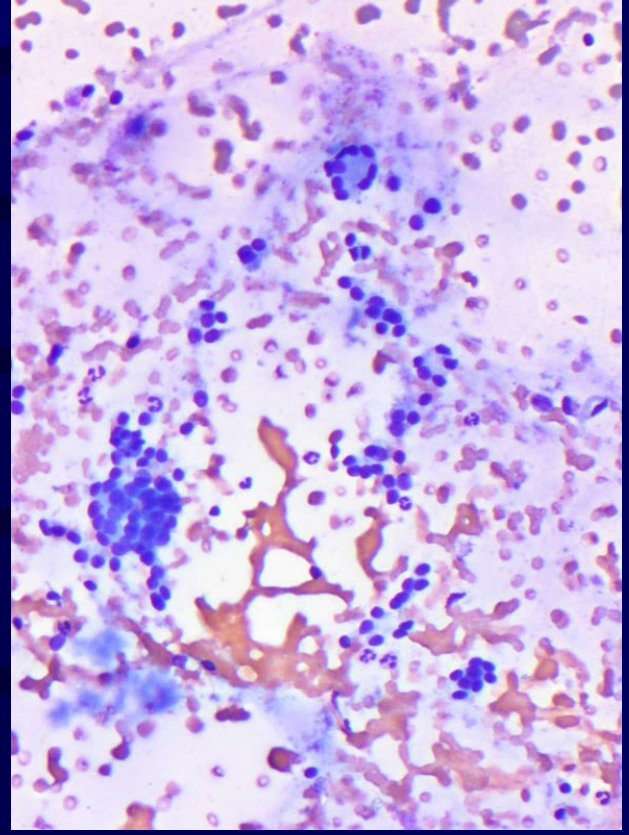
Hyperplastic / Adenomatoid Nodule

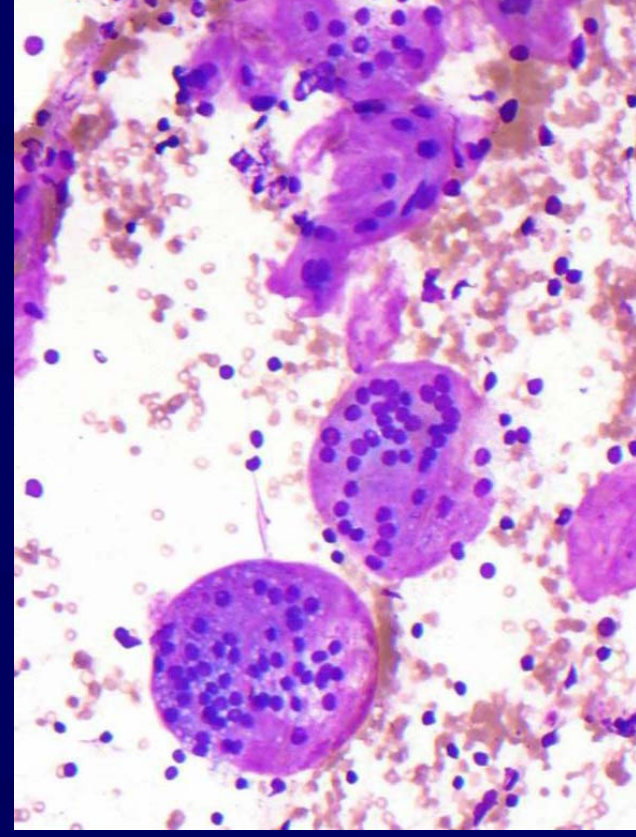




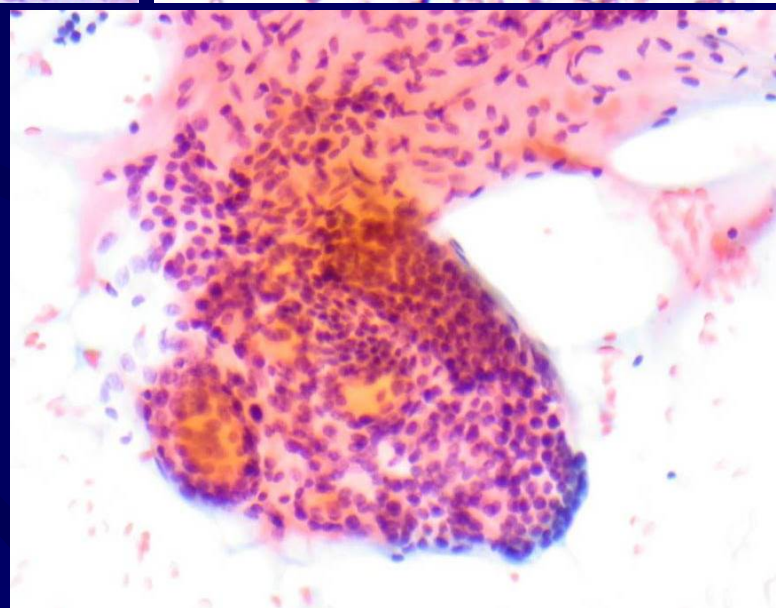
- Abundant colloid
- Variable cellularity
- Oncocytic metaplasia
- Degenerative changes

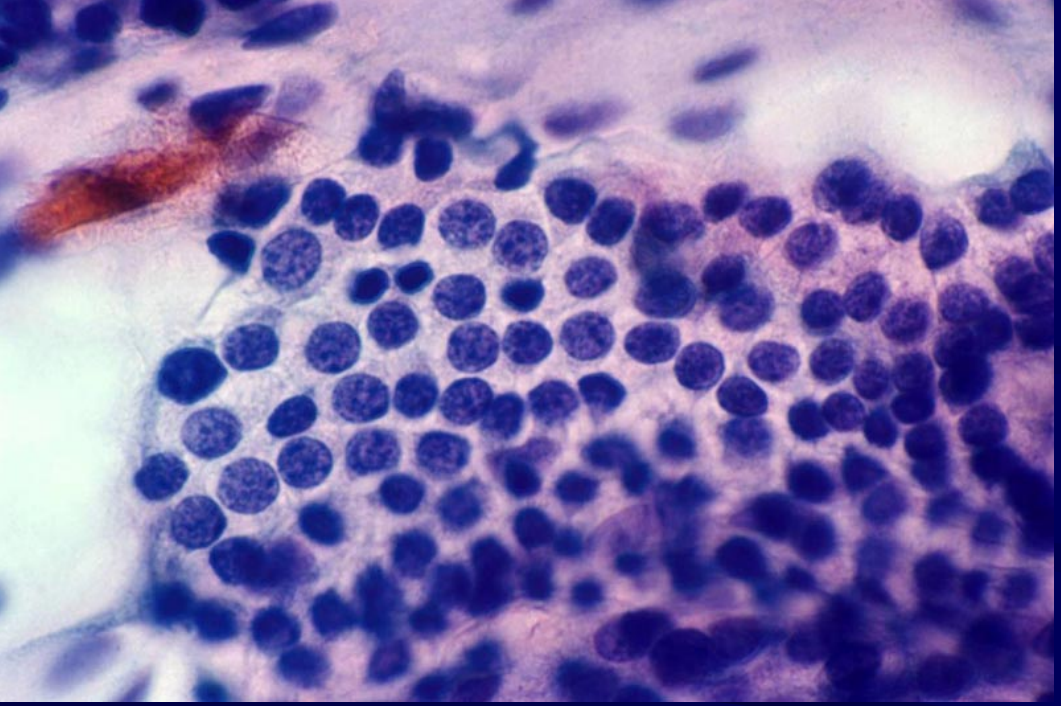


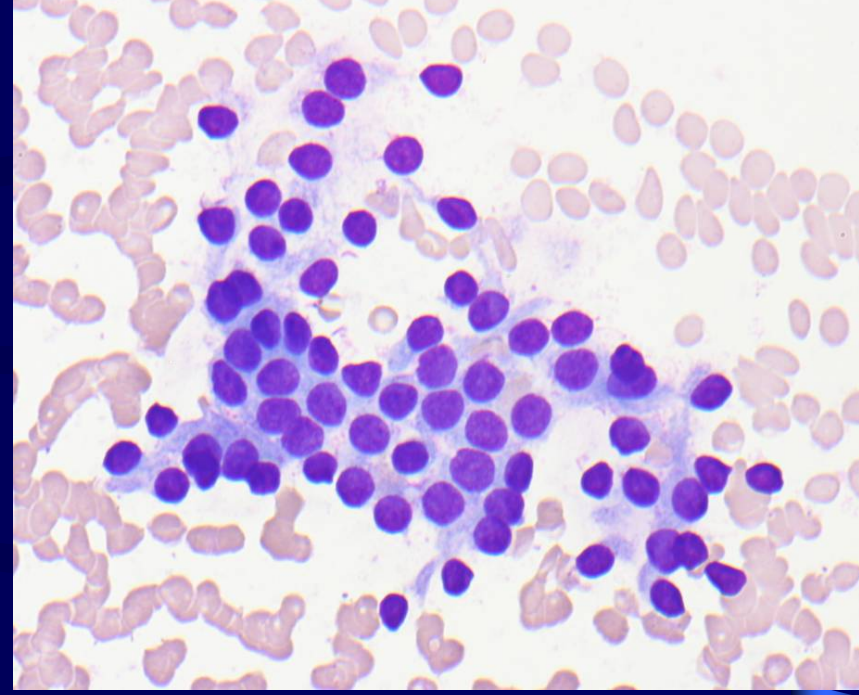




- Flat sheets- honeycomb
  - Few microfollicles accepted
  - Occasional balls and micro-tissue fragments

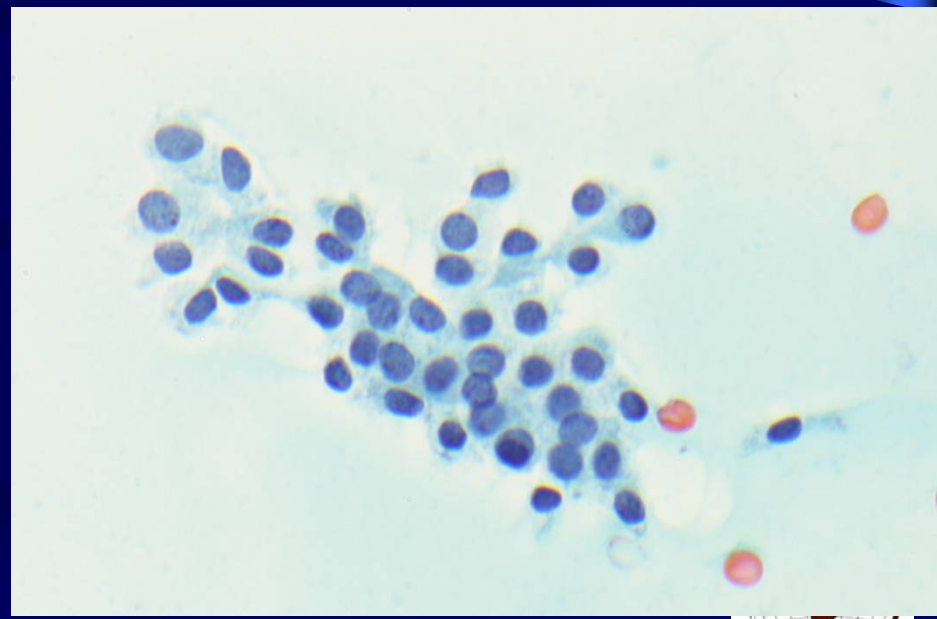


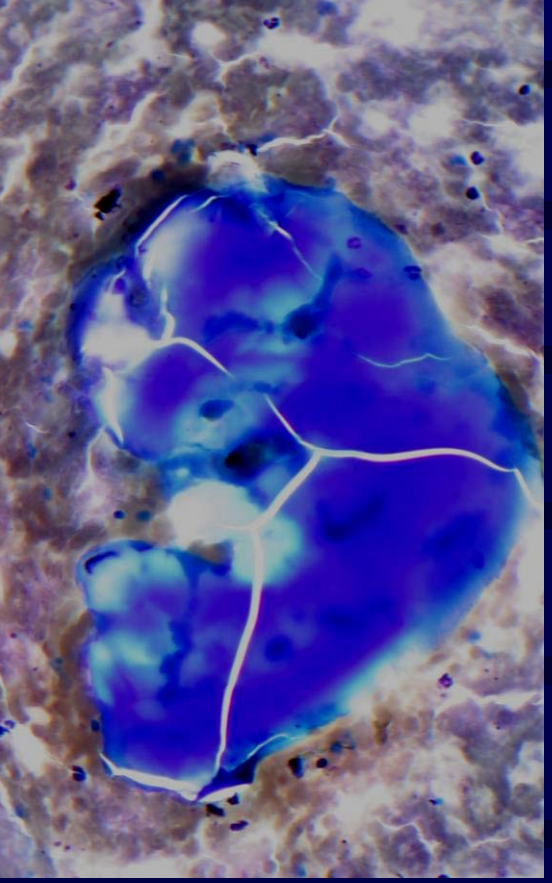


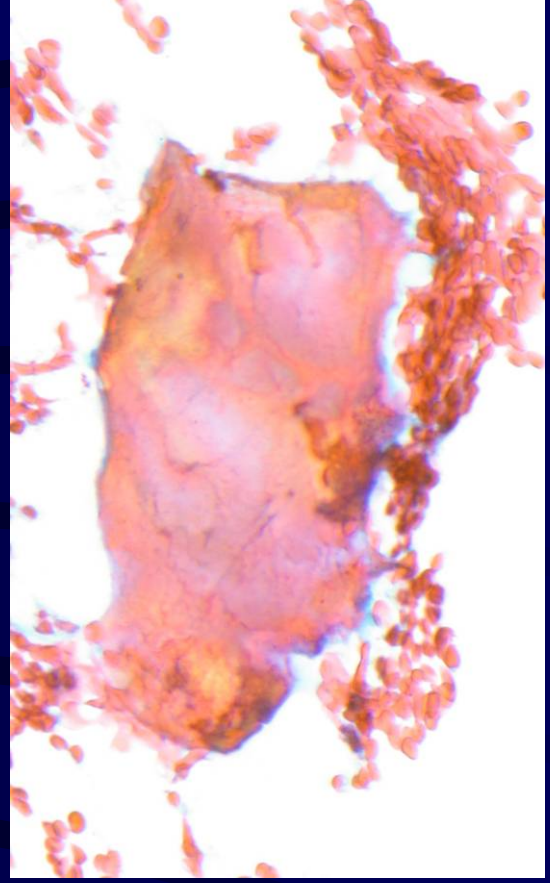


Hyperplastic Nodule

- Uniform nuclei:
  - Same size as RBC
  - Minimal nuclear overlapping
  - Finely granular chromatin
  - Rare nucleoli

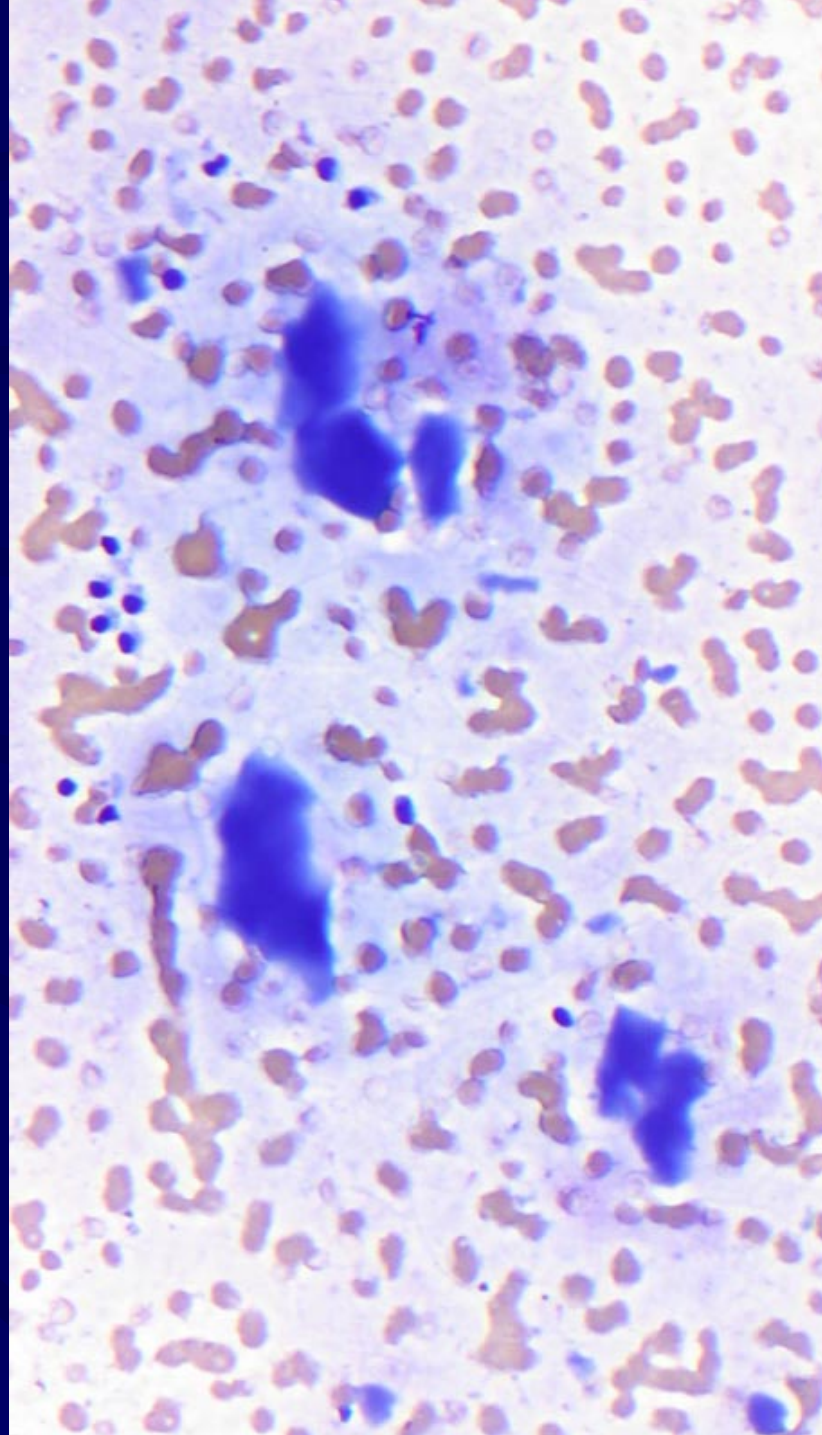


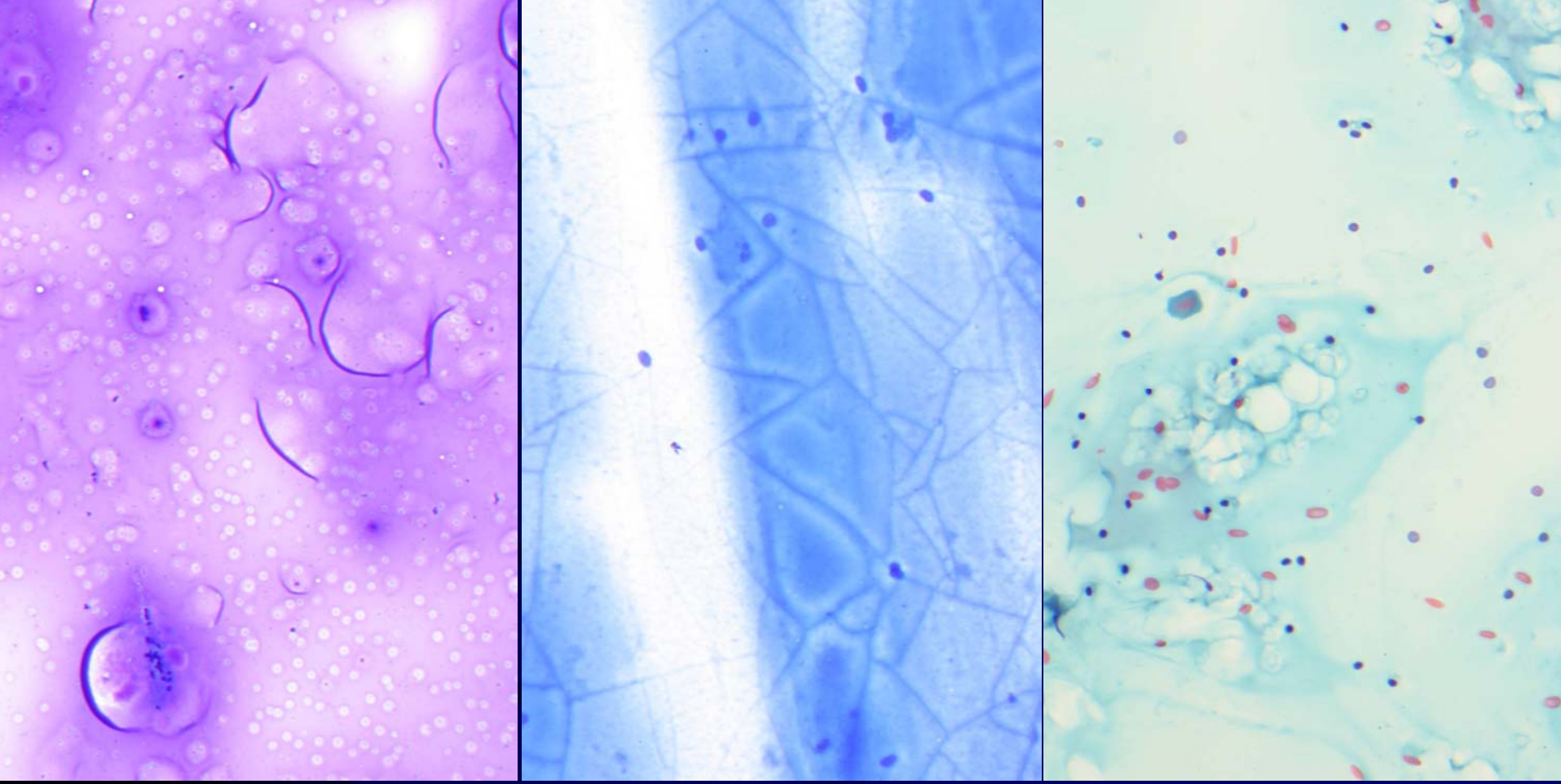




Dense colloid

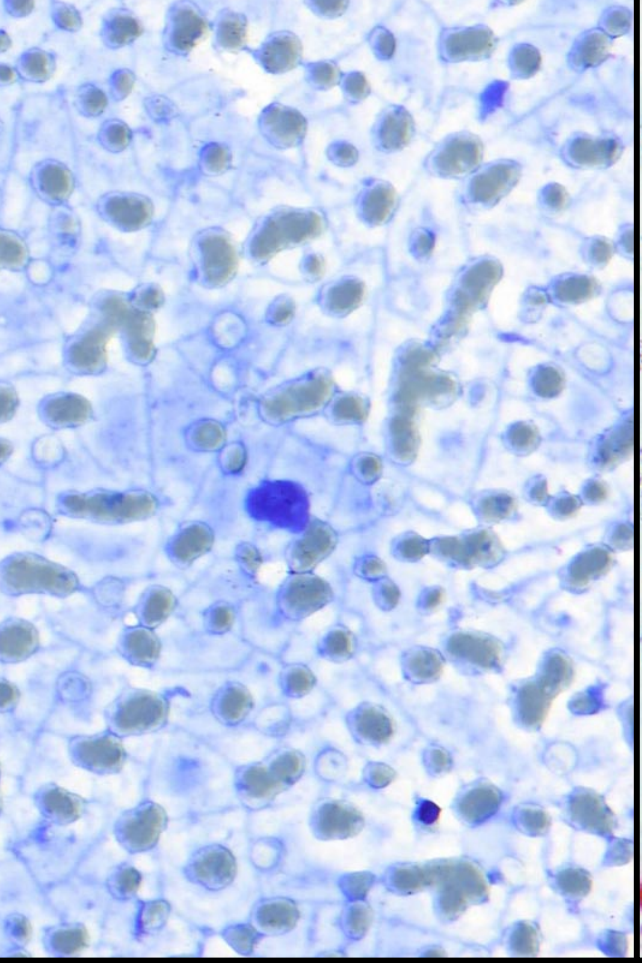
- Easy to recognize
- Dark blue-violet-magenta (DQ)
- Dark green-orange (Pap)

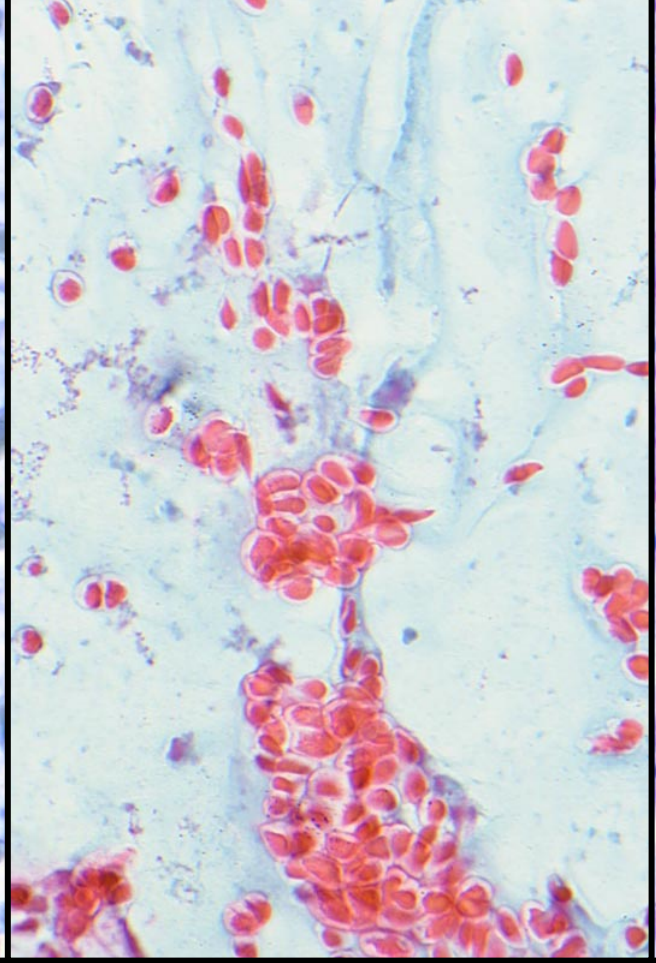


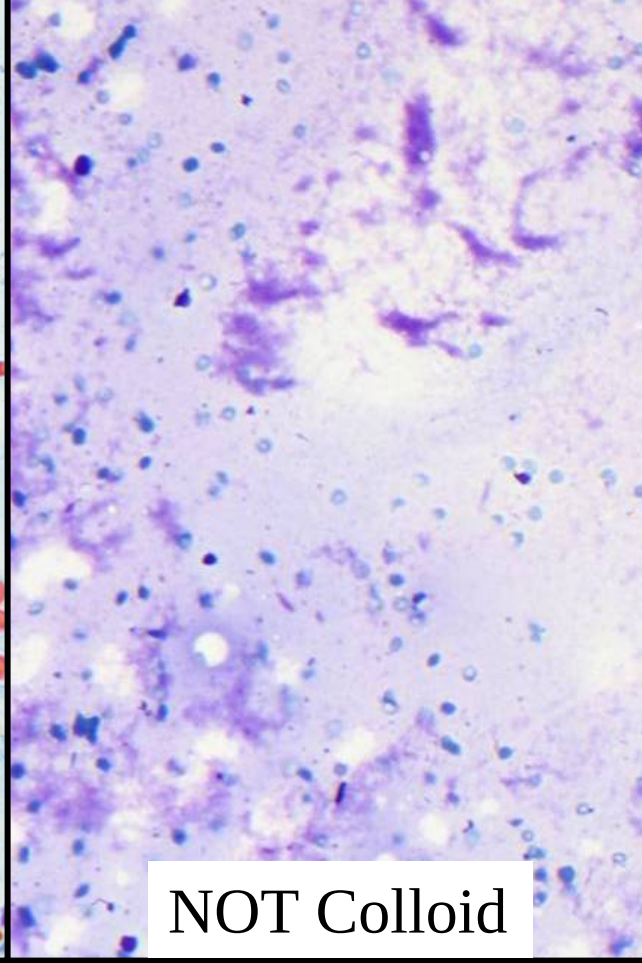


Watery/Thin Colloid

- Blue-violet (DQ), light green-orange (Pap)
- Cracks, folds, “thin-membrane”, “crazy pavement” appearance







NOT Colloid

Thin Colloid

- Difficult to recognize
- Easily confused with serum in bloody specimens
- May disappear completely on liquid-based preps

(Stelow 2005)

Papanicolaou Society of Cytopathology

Follicular Neoplasm

- Using specific cytologic criteria, Kini reported a 75% accuracy rate in DX of FC
  - Nuclear enlargement (3-4X) + architectural disarray *(Kini 1985)*
- Most other studies could not reproduce such accuracy
- Cytology can not distinguish between FA and FC. Need histologic confirmation

Cytologic Features Associated with Significant Cancer Risk

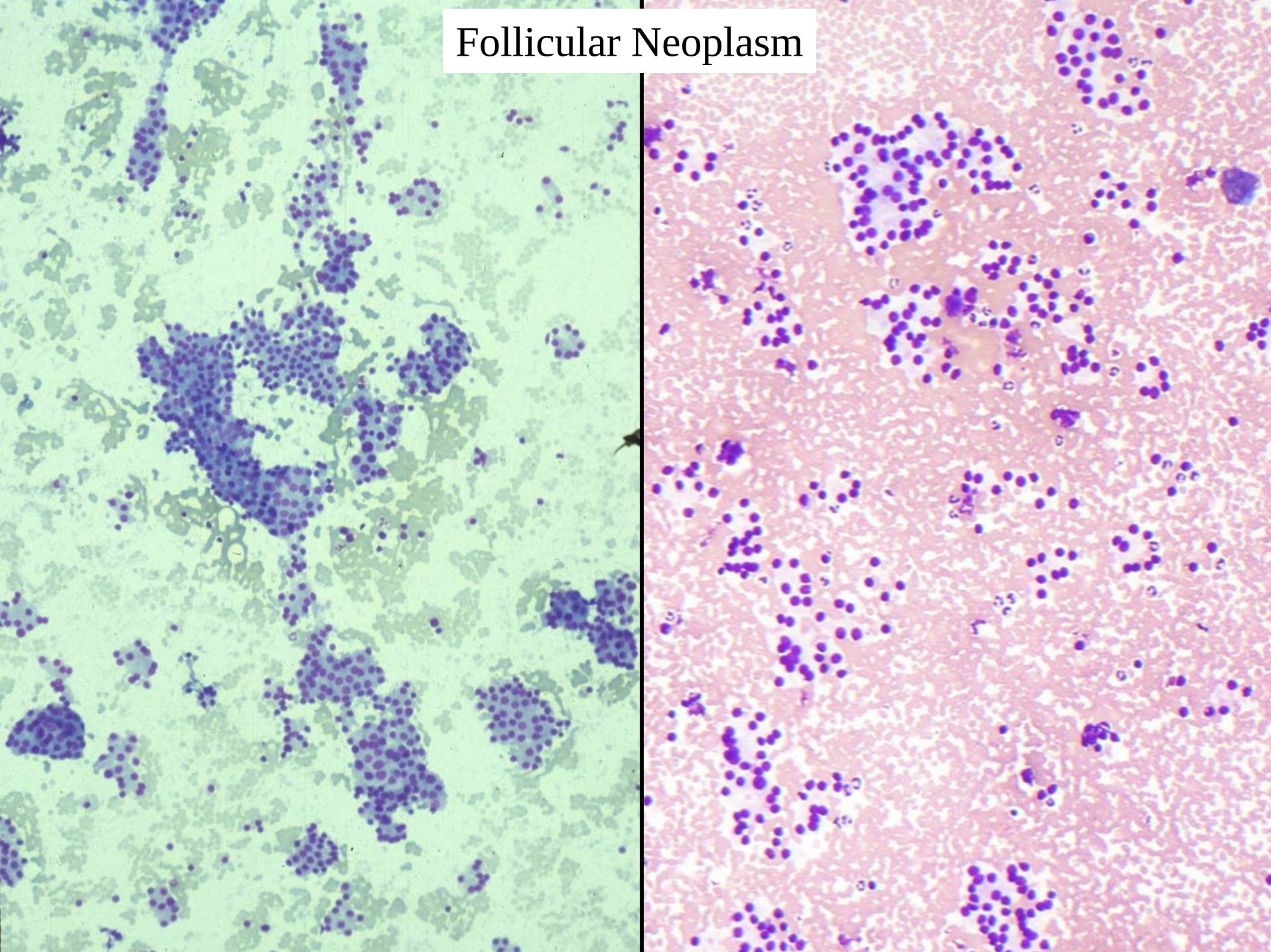
- Nuclear size > 2X RBC
- Nuclear atypia
  - Significant nuclear pleomorphism (high N/C, nuclear irregularity, variable size and shape)
- Nuclear overlap, significant
- Microfollicle structures, prominent (>75%)
- Cancer risk ranged from 40-60%
- Microfollicles + no atypia → low cancer risk (6%)
  Microfollicles + abundant colloid + absence of nuclear overlap → 0% cancer

Ersoz 2004, Kelman 2001, Yang 2003, Goldstein 2002, Barbaro 2001

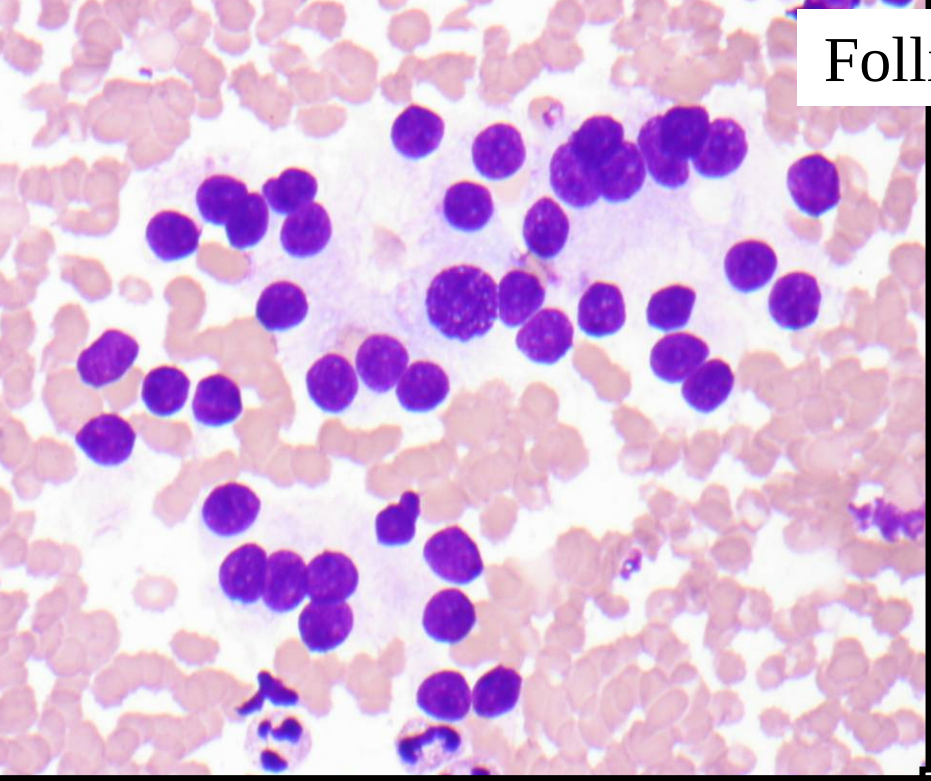
Follicular Neoplasm [2]
Cytologic Criteria

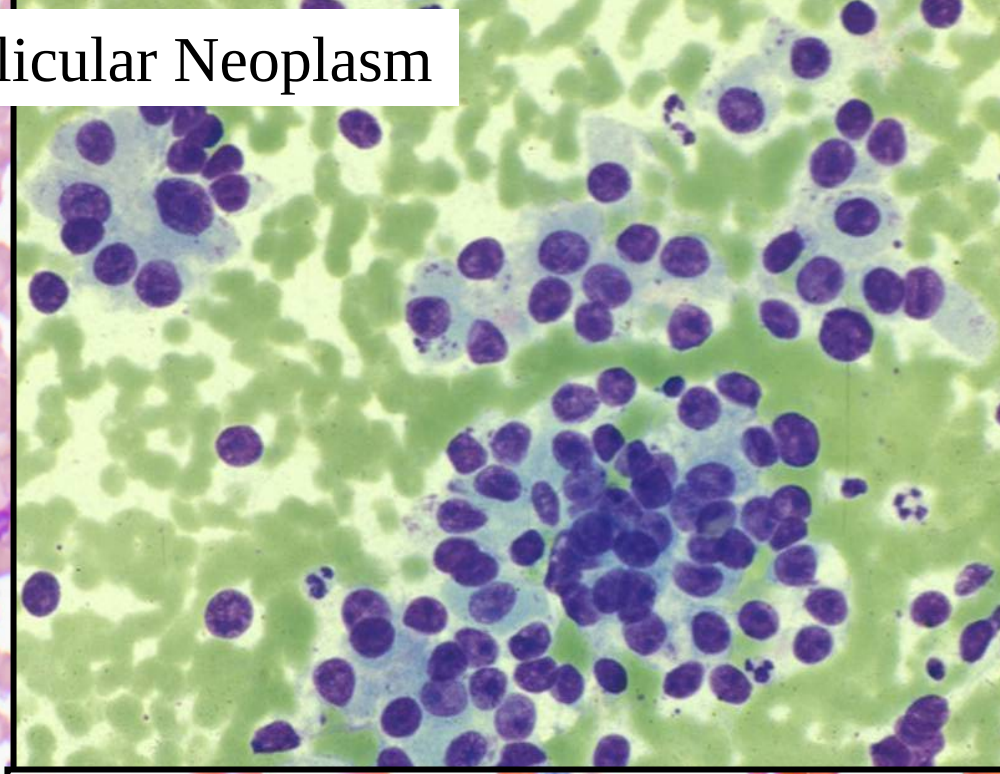
- High cellularity
- Scant colloid
- Prominent microfollicles and syncytial fragments (> 50-75% of cells)
- Nuclear overlapping and crowding
- Nuclear atypia ±
  - Uniform enlargement > 2X RBC
  - Coarse and clumped chromatin
  - Prominent nucleoli

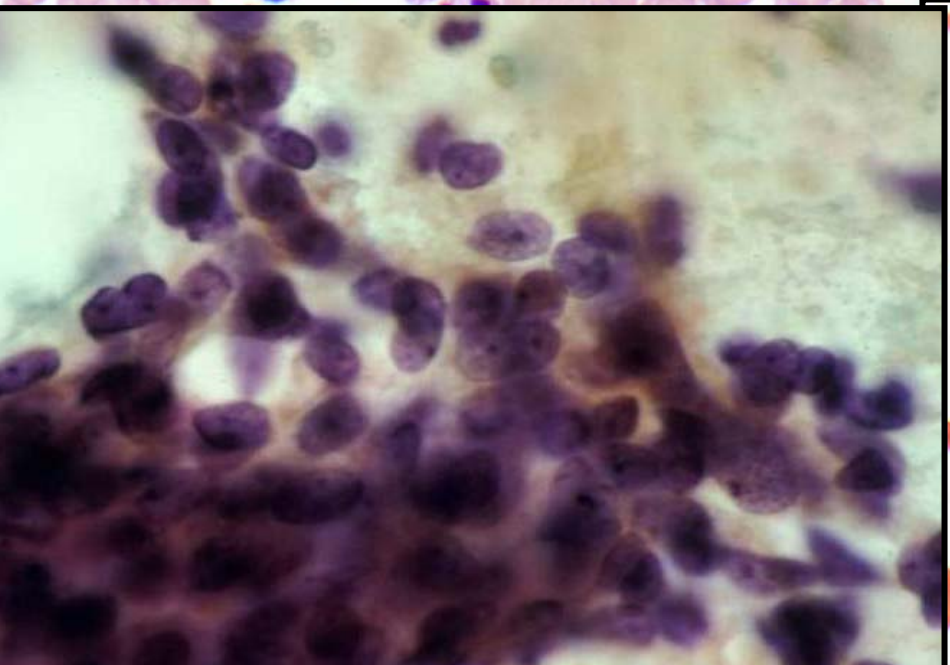
Follicular Neoplasm

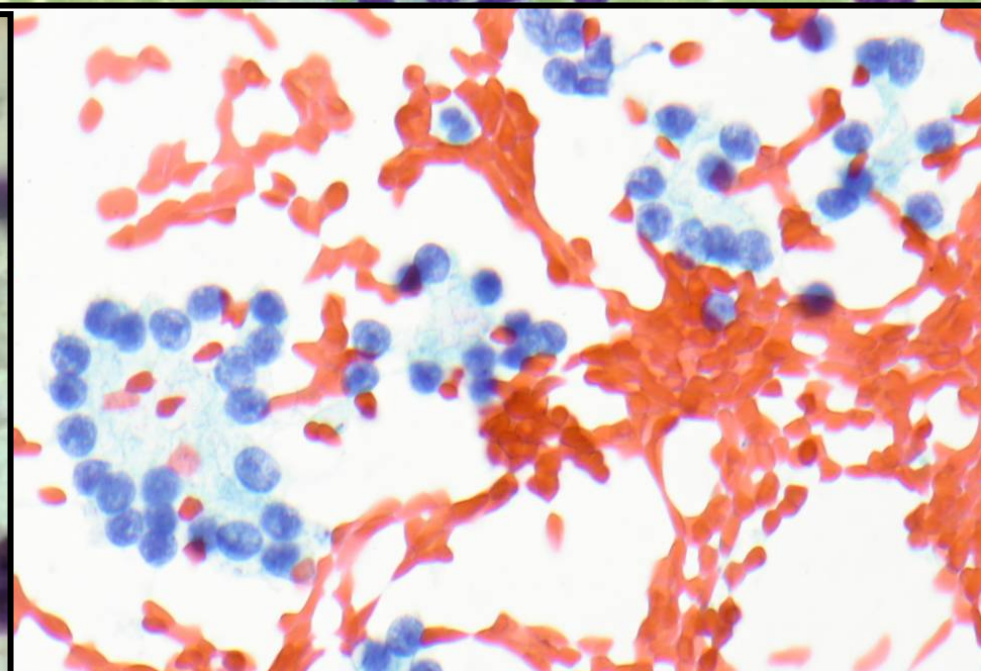


Follicular Neoplasm









Challenges in DX of Hyperplastic/Adenomatoid nodule

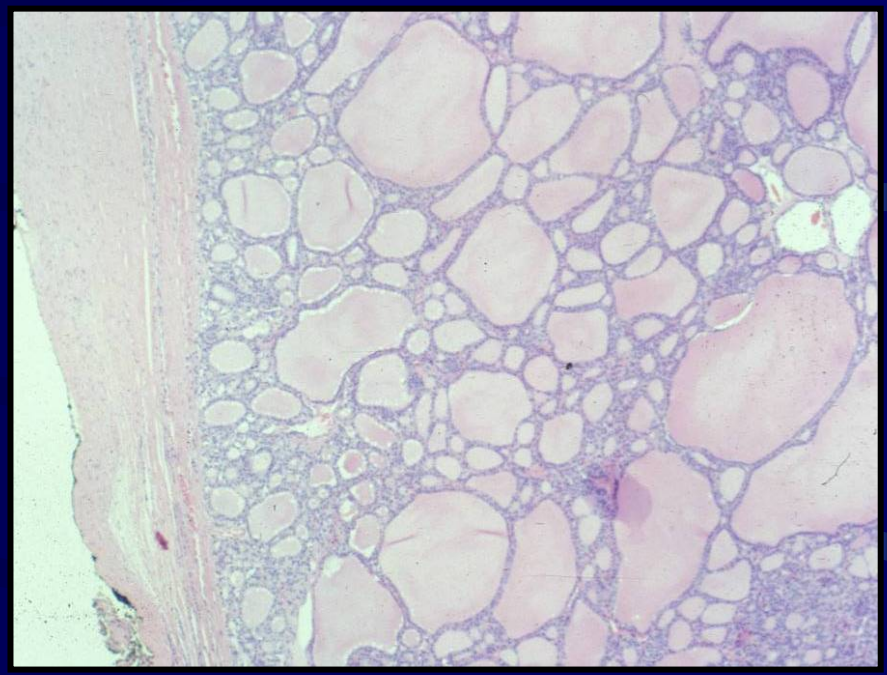
- Most difficult problem is distinguishing HN with little colloid from FN with some colloid
- Microfollicles may be focally seen in HN (5-10% of cases)
- High cellularity → up to 30% of HN
- Scant colloid→ 15-20% of HN
- Degenerative changes →up to 30% of neoplasms
- Should not make DX in absence of colloid

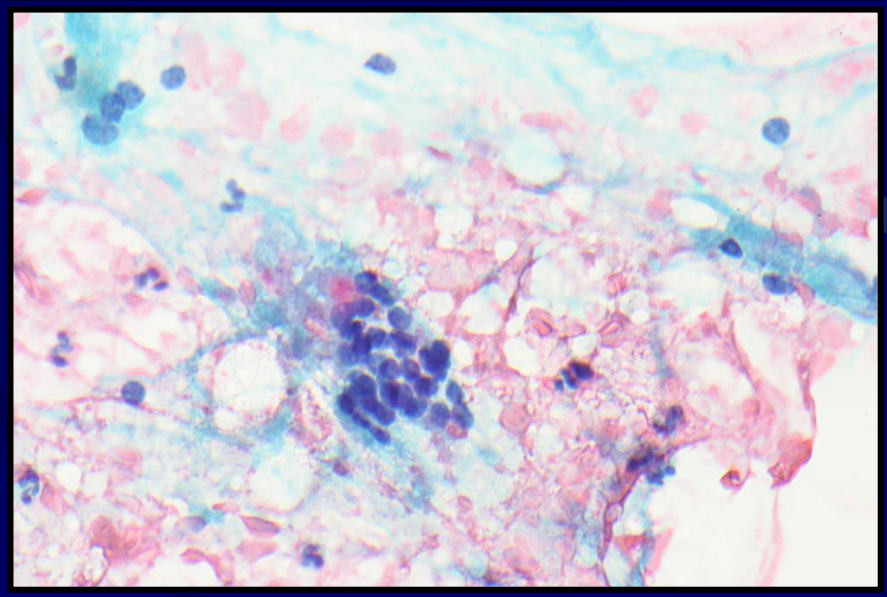
Basu 1992, Harach 1992, DeMay 1996, Geisinger 2004

Challenges in DX of Follicular Neoplasm

- Low cellularity due to:
  - Poor biopsy technique
  - Macrofollicular architecture
  - Highly vascular lesion. Clue: abundant blood with rare microfollicles

(Yang 2003, Lowhagen & Oertel)





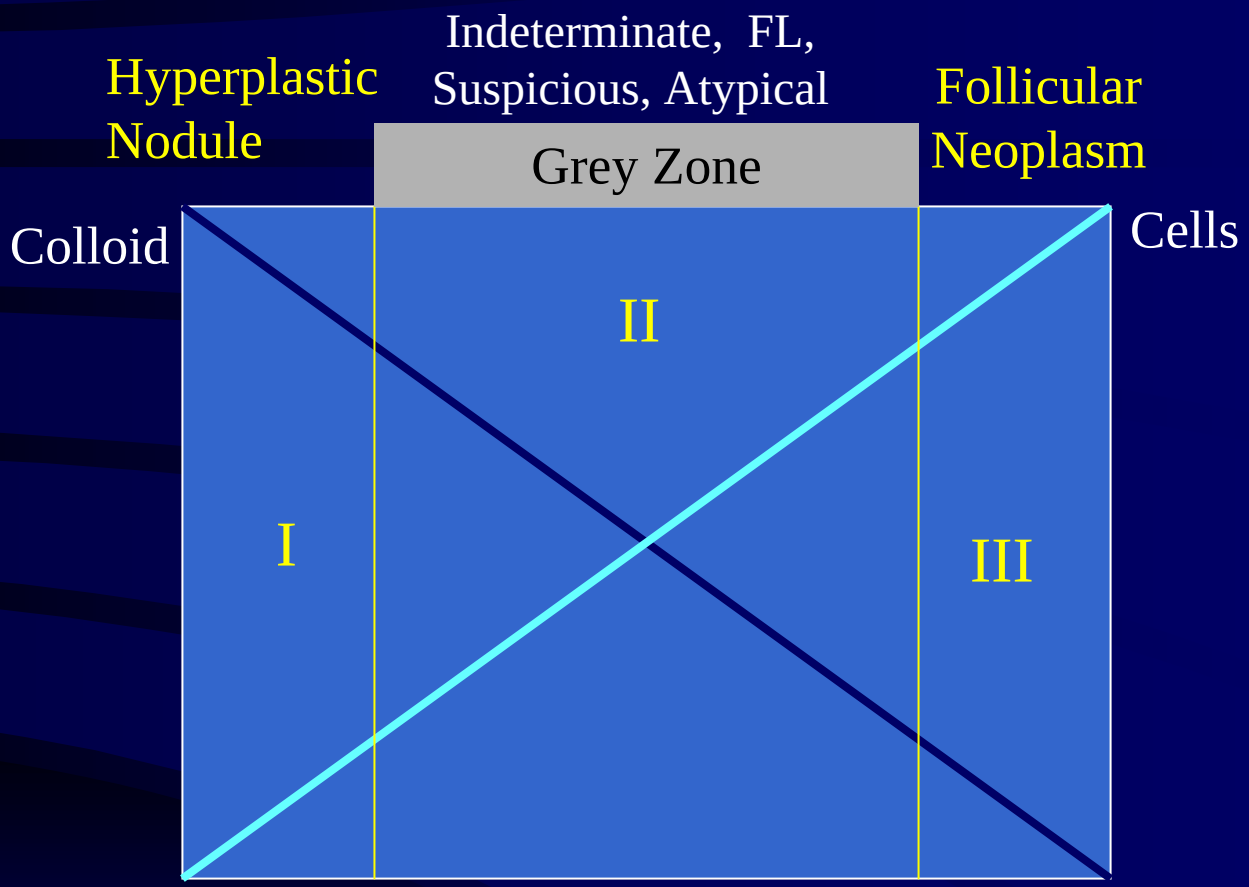
Diagnostic Categories

1. Unsatisfactory
2. Benign
3. Cellular lesion, can not rule out FN
4. Follicular Neoplasm
5. Suspicious for malignancy
6. Malignant.

PSC Approach to Grey Zone and Terminology

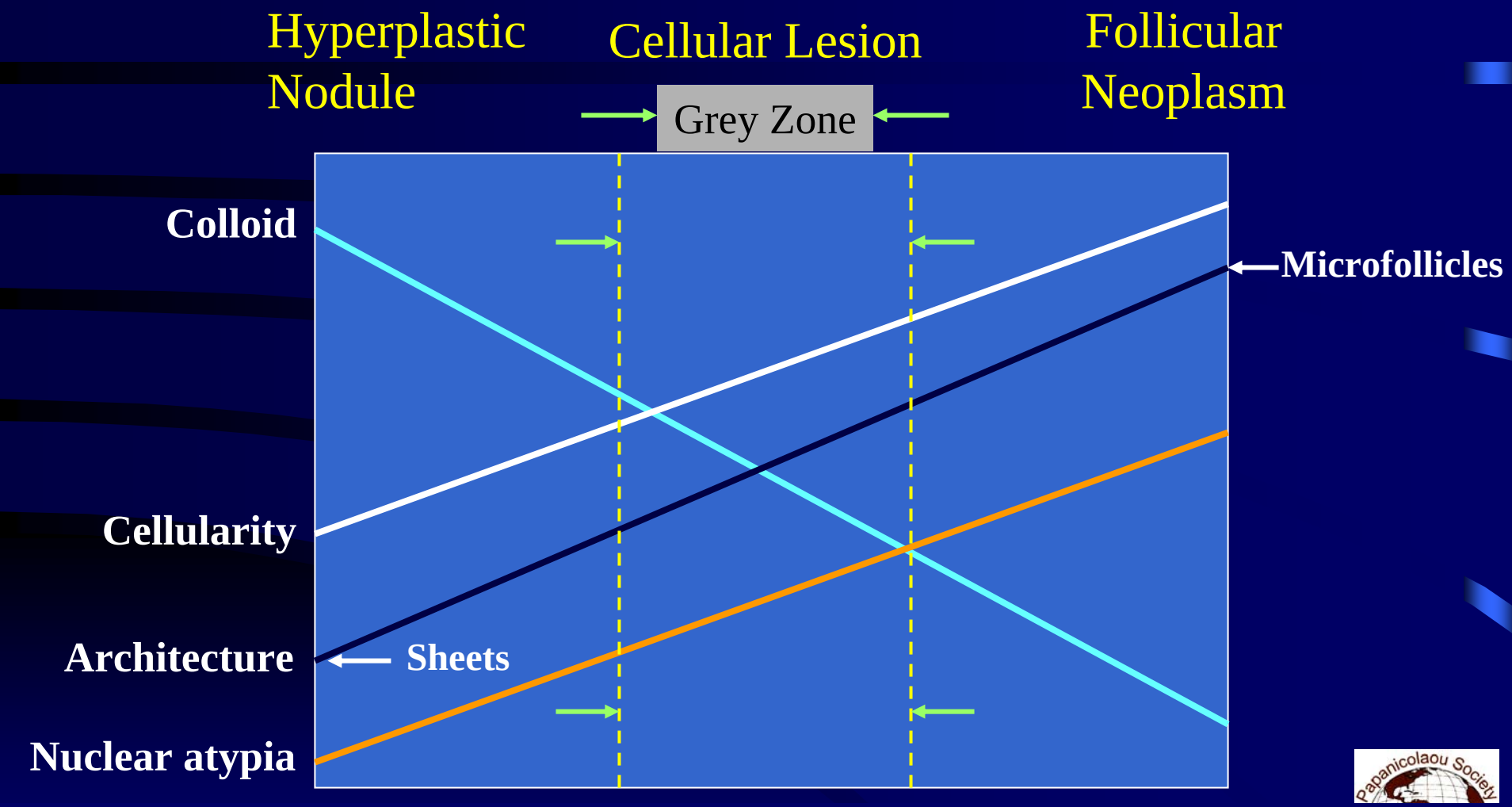
- "Follicular Lesion" & "Follicular Neoplasm" used interchangeably by some authors
  - We do not consider them synonymous
- "Indeterminate" cytologic category included FN, FL, Susp. for malignancy, Atypia NOS

Differential Diagnosis of Follicular Lesions [2]



- Overlapping cytologic features makes it difficult, at times, to separate between HN & FN
- Indeterminate category accounts for 5-42% of FNA DX's

Differential Diagnosis of Follicular Lesions [3]



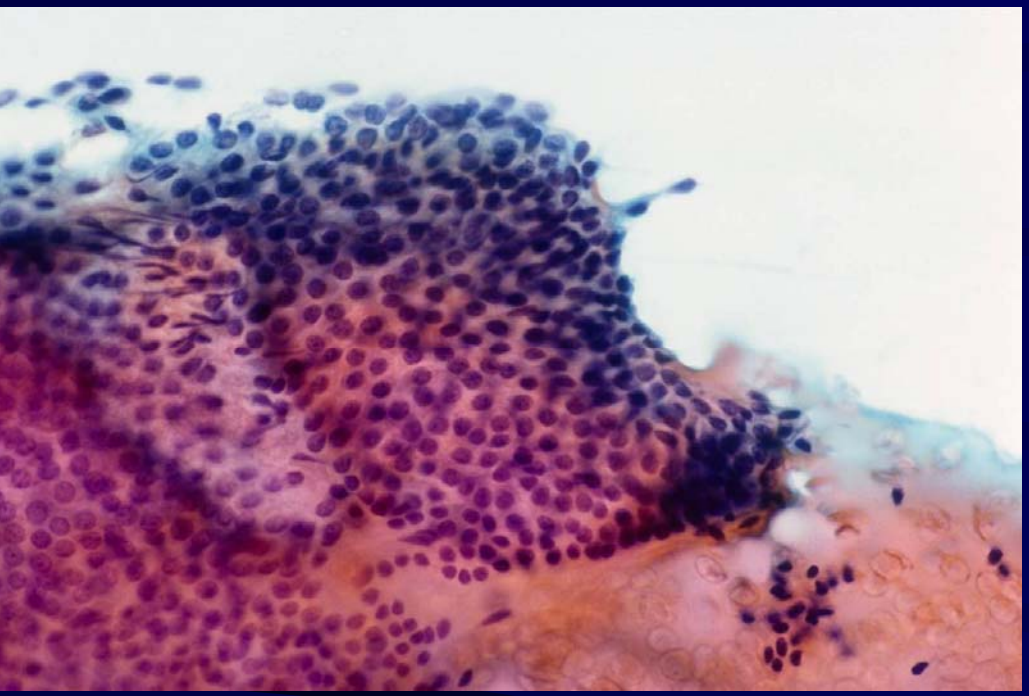
•Permissiveness in applying strict criteria to DX of FN→ significant reduction of malignancy rate on FU

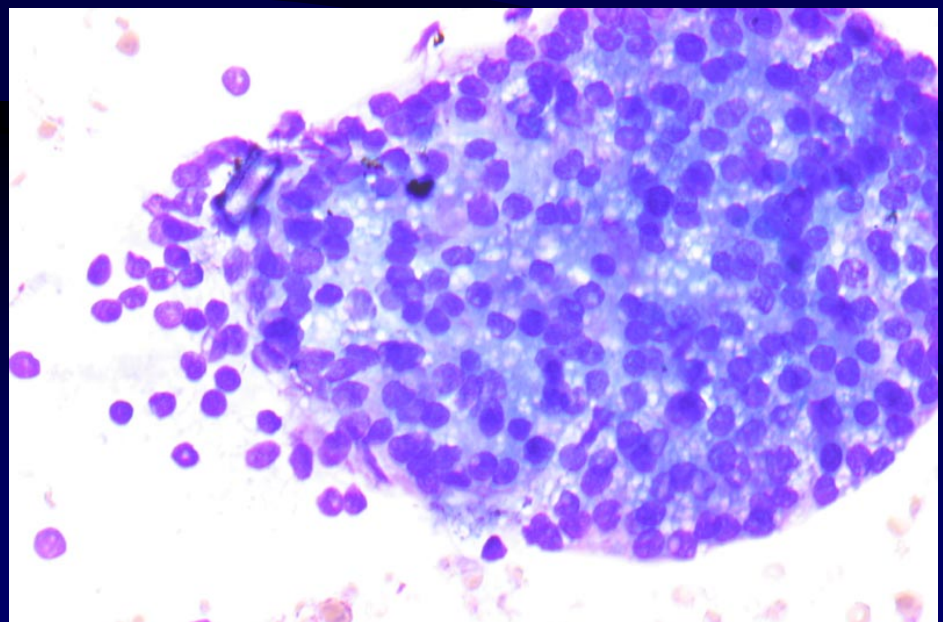
Cellular Lesion, can not rule out FN

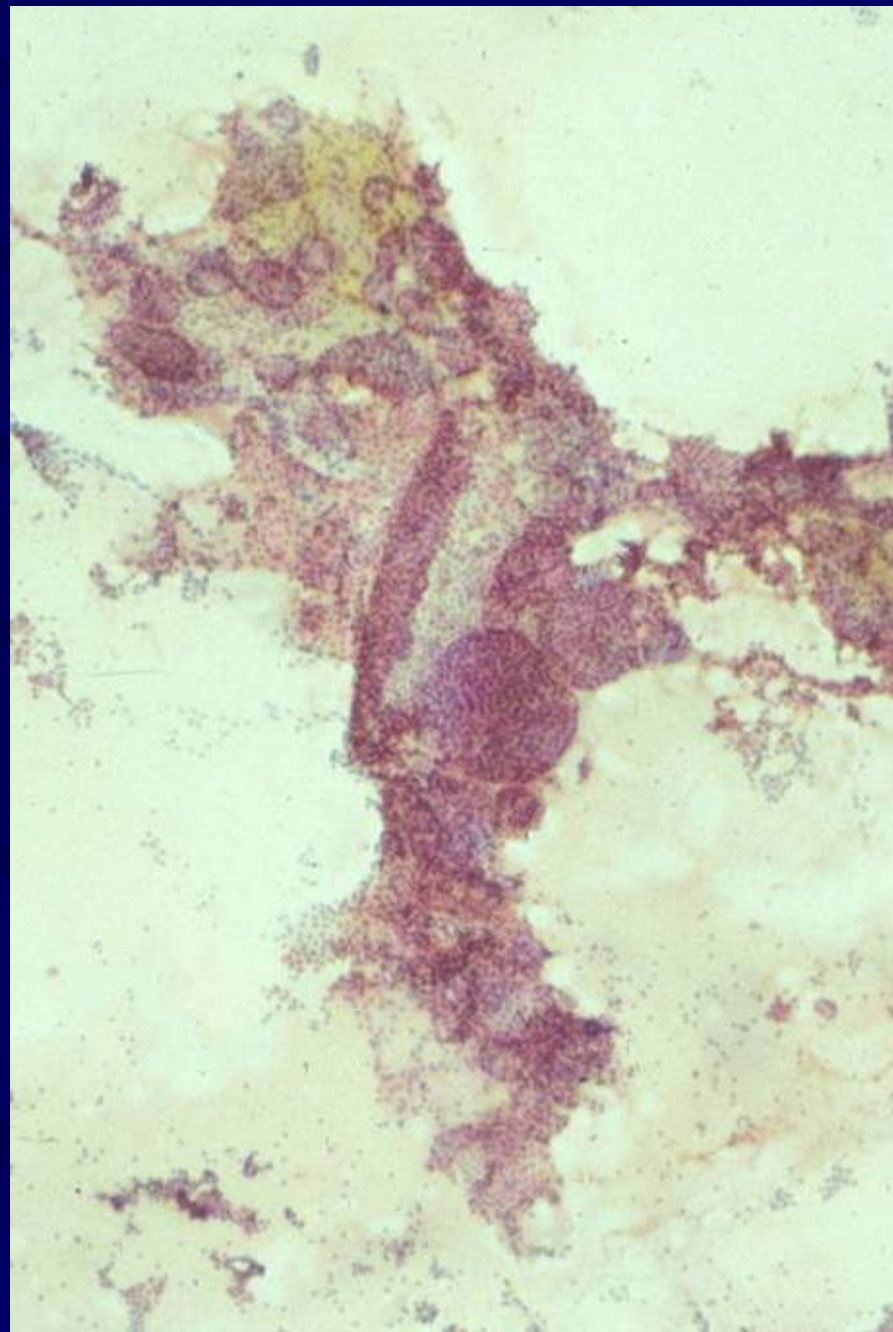
Cytologic Features

- Major differential diagnosis is HN vs. FN
- High cellularity, scant colloid
- Admixture of flat sheets and microfollicles/syncytial fragments
- Minimal nuclear overlapping and crowding
- Smears from different passes show a spectrum ranging from “benign” to “possible FN”
- Low cellularity, but microfollicles and prominent nuclear overlap (highly vascular lesions)

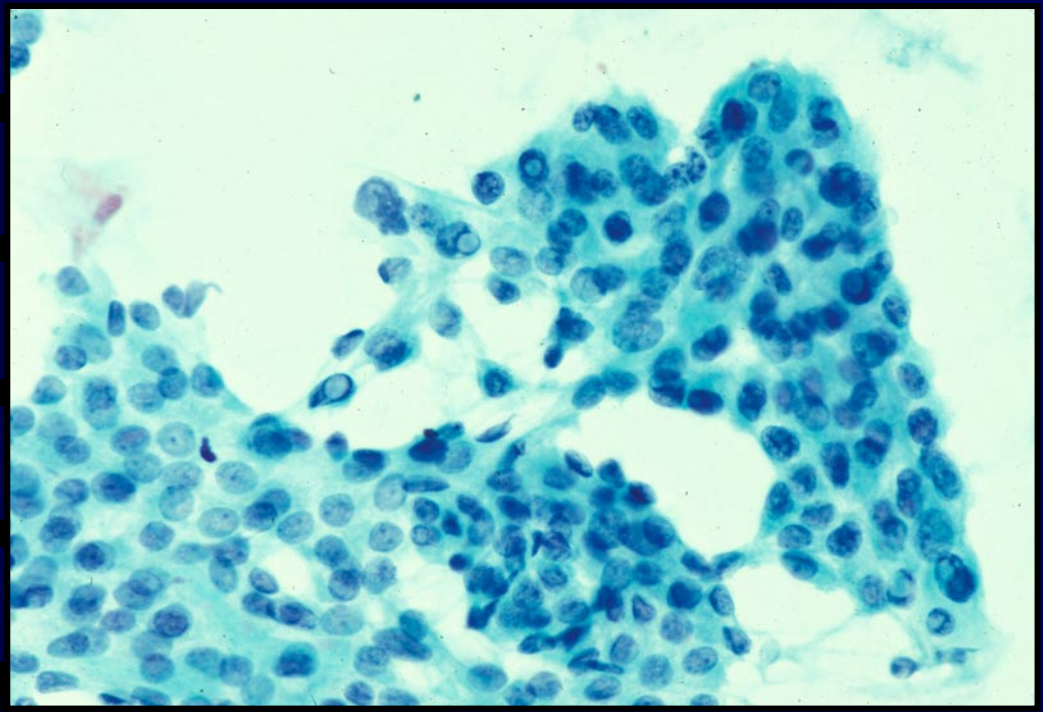
Cellular lesion, R/O FN

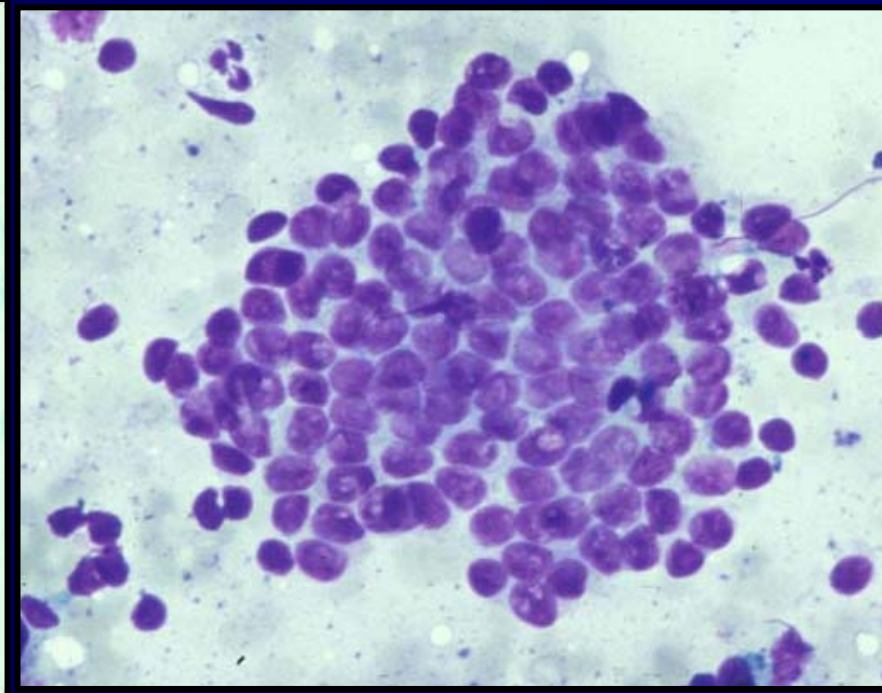




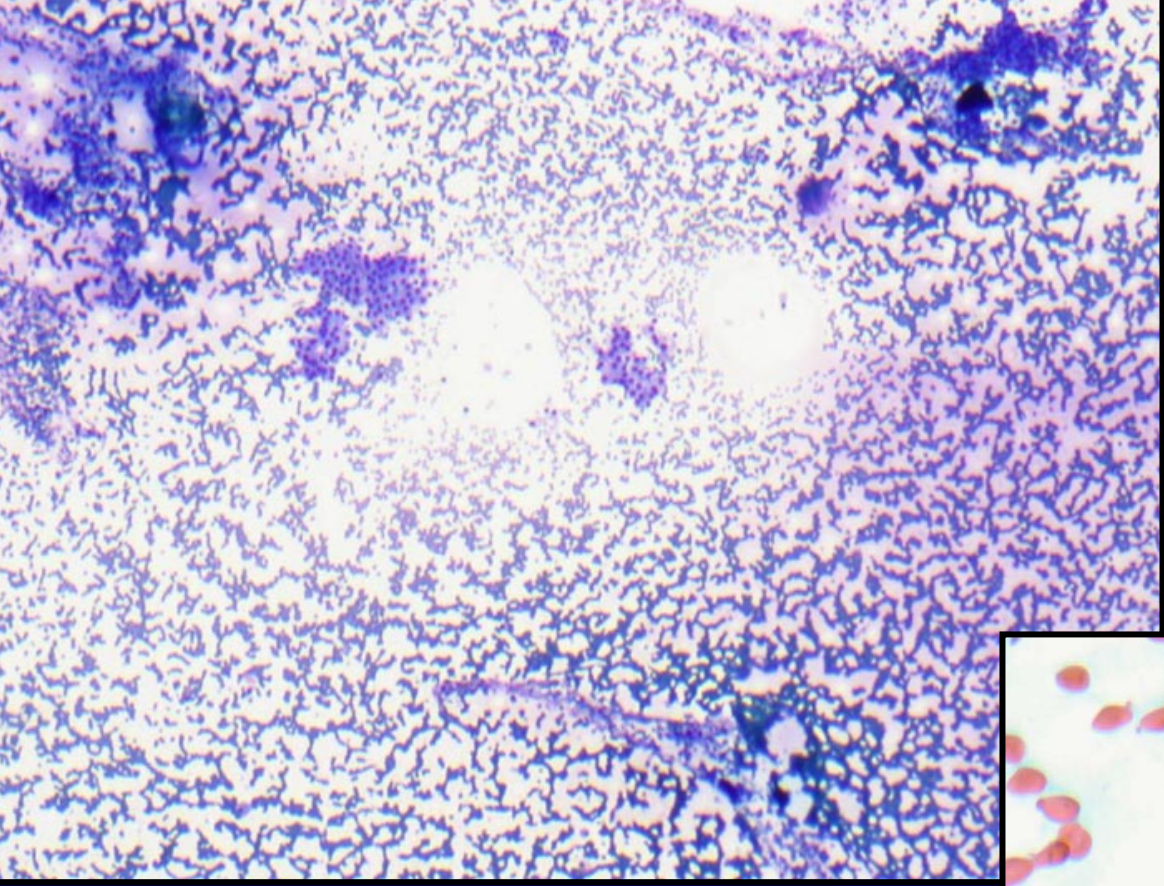


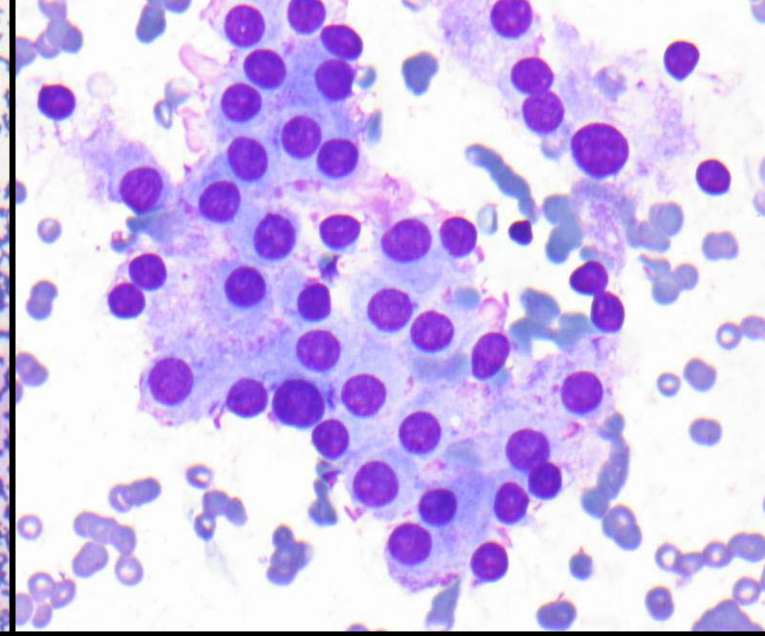
Follicular Variant of PTC

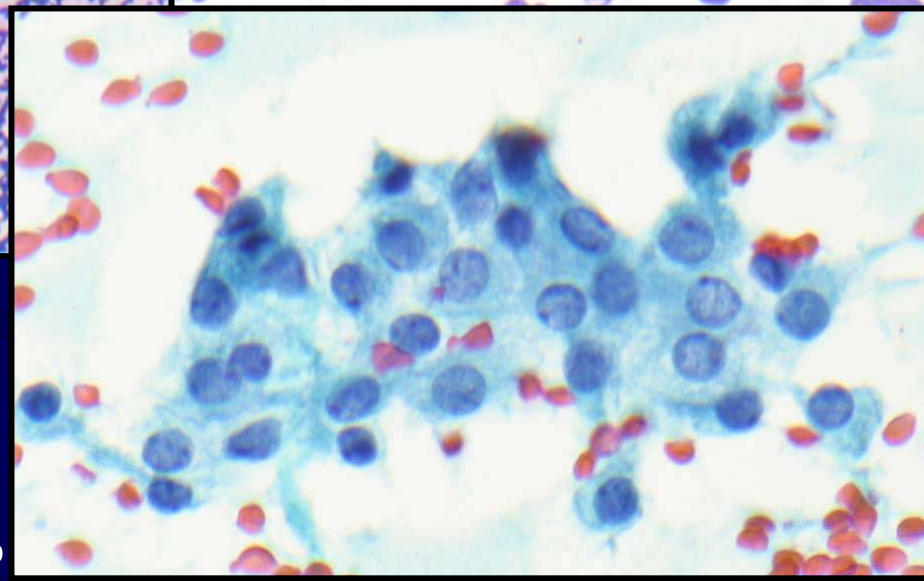




- Second to sampling error as most common cause of false negative diagnoses

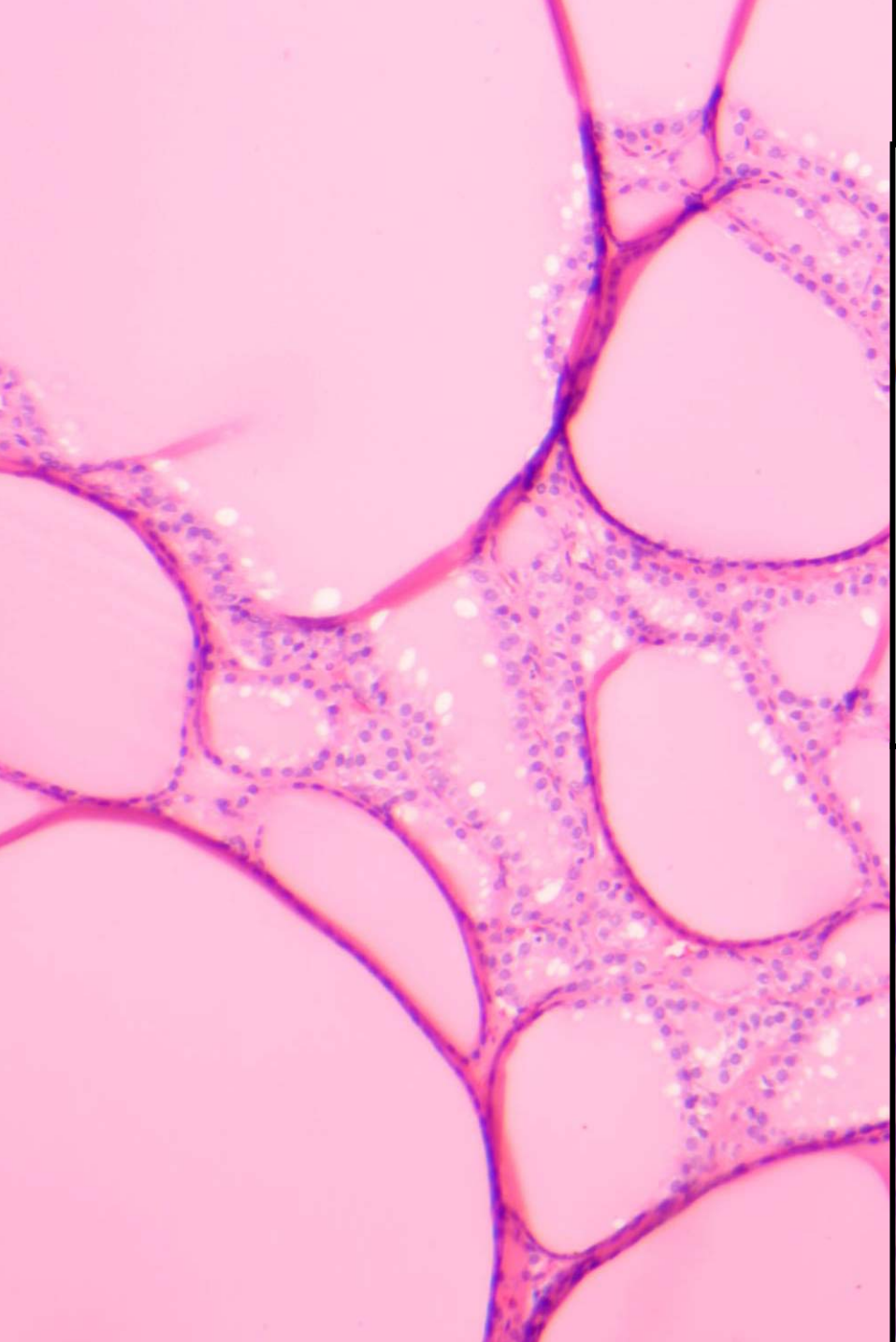


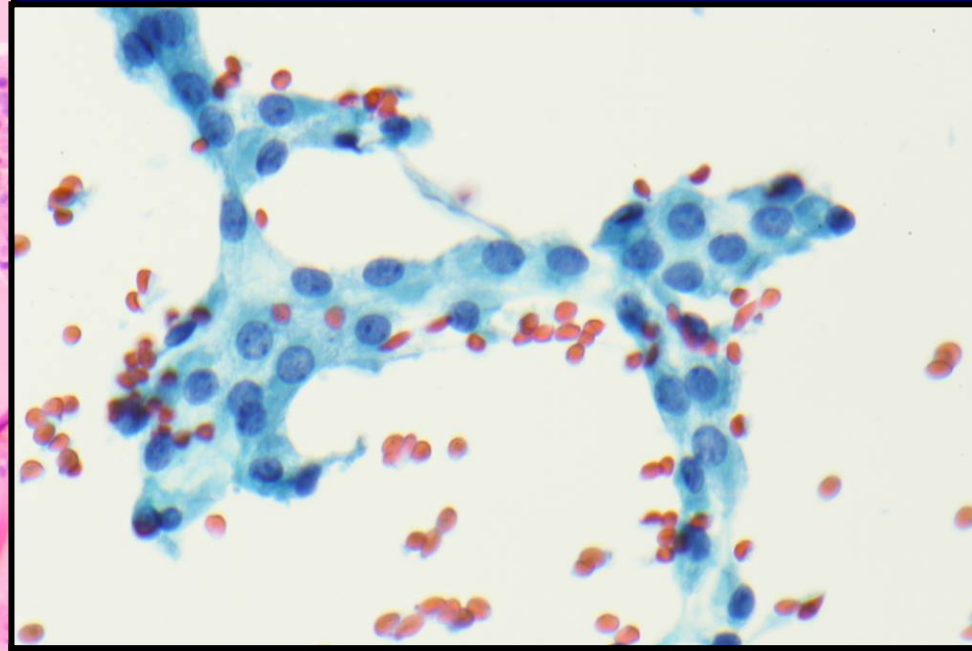


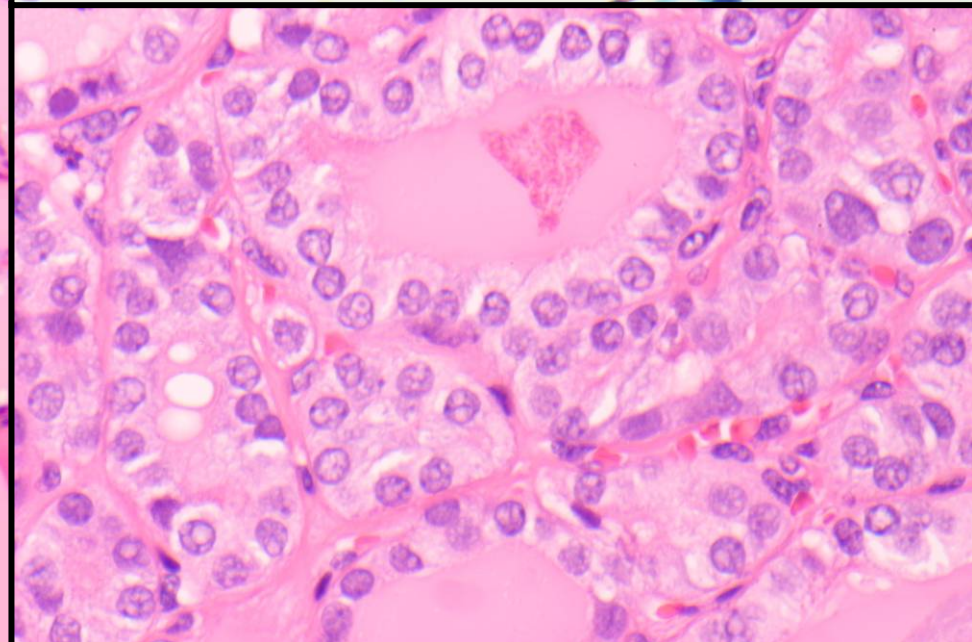


- FVPC may show abundant colloid and paucity of nuclear features of PTC→ misdiagnosed as benign or FN

FVPC, false negative







Suspicious for PTC

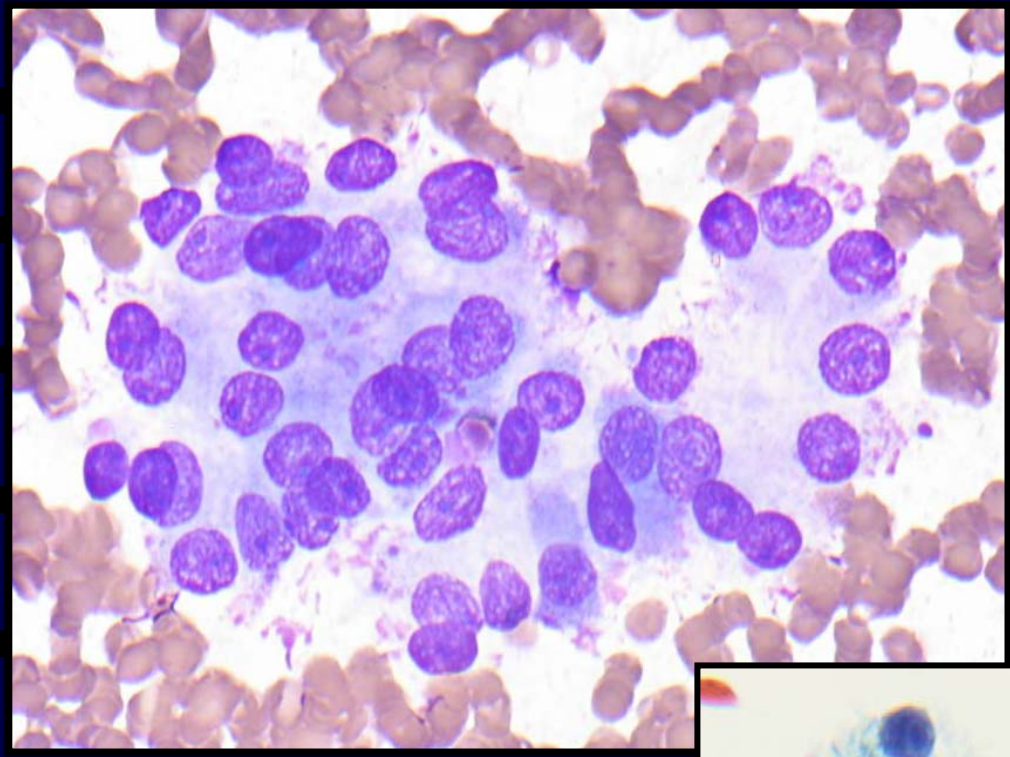
- 36/48 cases (75%)→ cancer on FU (26 PTC,10 FC)
  - 77% cancer rate *(Logani 2000)*
- Important not to include these cases with "indeterminate" or "FN" (10-30% cancer rate)
- Sensitive cytologic criteria for detecting FVPC
  - Flat syncytial sheets
  - Nuclear enlargement
  - Fine chromatin
  - Nuclear grooves

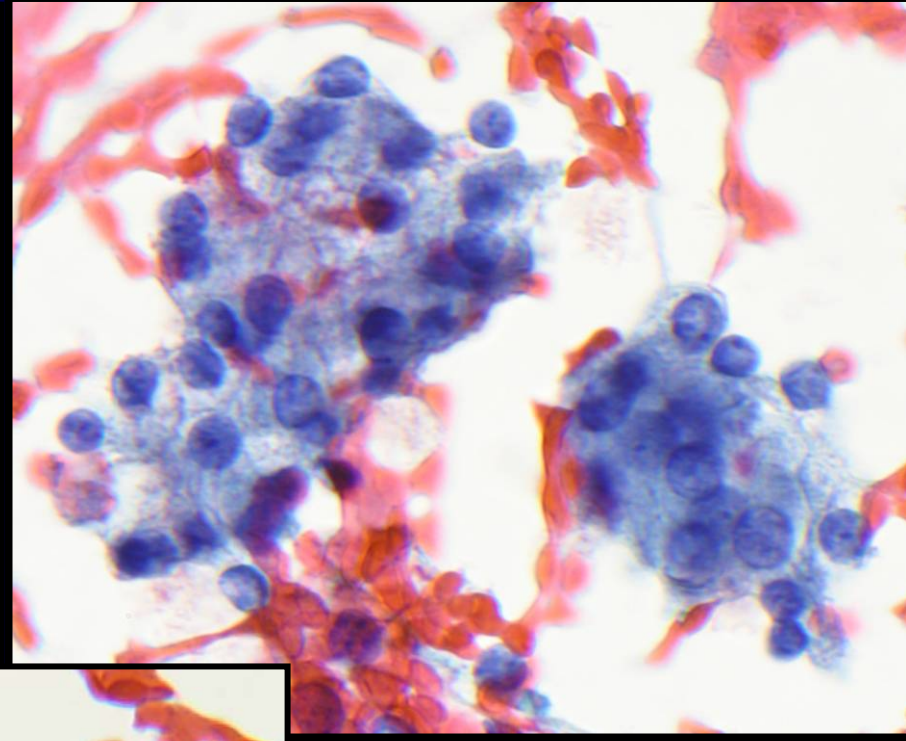
Most sensitive

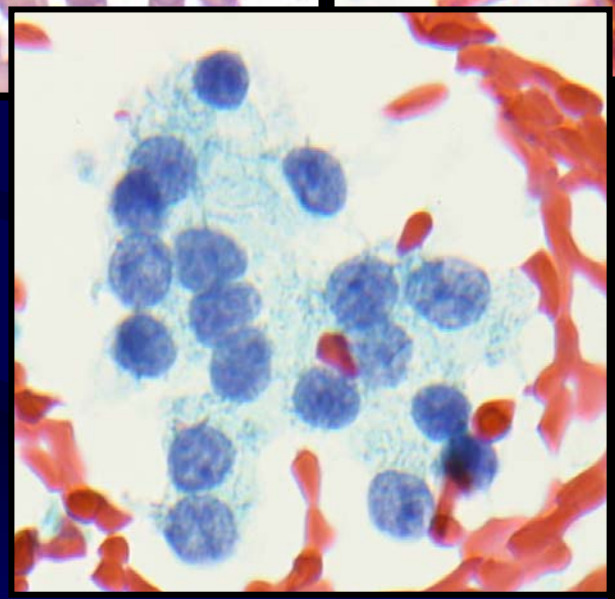
Most consistent

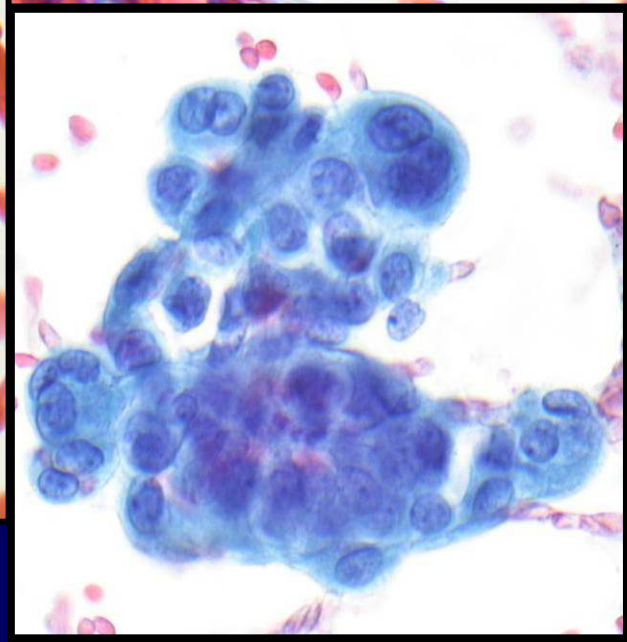
- < ½ FVPC showed intra-nuclear holes

(Wu 2003)









Susp. for PTC

- Focal nuclear grooves, enlargement and powdery chromatin

Diagnostic Categories

1. Unsatisfactory
2. Benign
3. Cellular lesion, can not rule out FN
4. Follicular Neoplasm
5. Suspicious for malignancy
6. Malignant.

Suspicious for Malignancy

- Cytologic features are suggestive of a specific malignancy, but a definitive DX can not be rendered
  - Suspicious for PTC
  - Malignant appearing cells, but limited cellularity
  - Atypical lymphoid population, i.e. in a background of Hashimoto's

Classification
Diagnostic Categories

1. Unsatisfactory
2. Benign
3. Cellular lesion, can not rule out FN
4. Follicular Neoplasm
5. Suspicious for malignancy
6. Malignant.

Clinical Implications

- Histologic follow up of FN
  - Neoplastic: 70-80%
  - Malignant: 12-87%
- Strict cytologic criteria:
  - FN →30% cancer
  - Cellular nodule, R/O FN→ 10% cancer
- FN & indeterminate (combined) → 20% cancer risk
- Most clinicians recommend excision for FN, and accept the fact that DX is probabilistic and may be benign on FU
- Cellular nodule→ F/U or repeat FNA

Baloch 2002, Greaves 2000, Sidawy 1997, Hamburger 1998, LaRosa 1991

Papanicolaou Society of Cytopathology

Assessment of Probability of finding Cancer on Thyroidectomies

- Examined 401 FNA's with F/U surgery

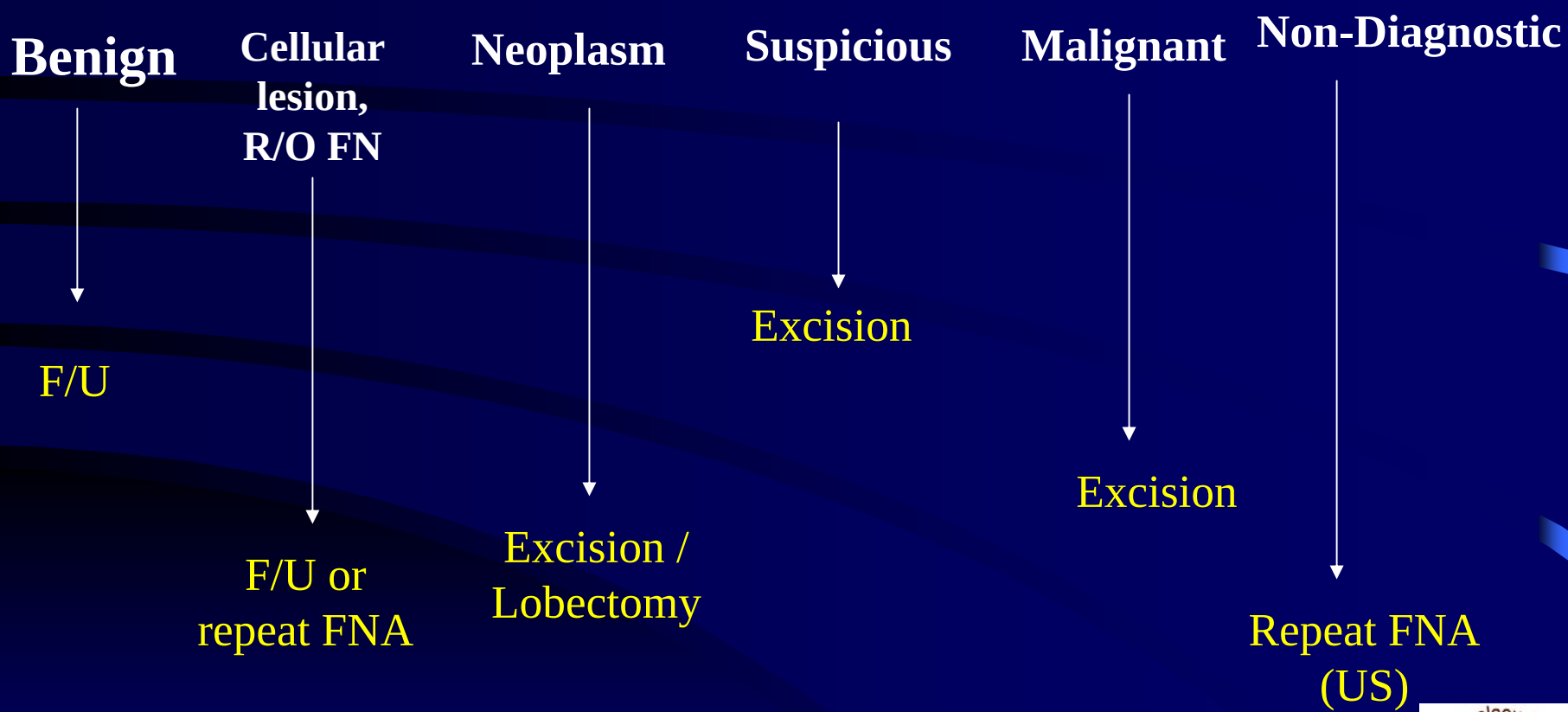
  (*Wu et al. Diagn Cytopathol. In Press)*

FNA Diagnosis	Cancer Rate	Cancer Risk*
Benign non-neoplastic	3 %	--
Cellular lesion, R/O FN	14 %	5 X
Follicular neoplasm	33 %	11 X
Suspicious	56 %	20 X
Malignant	100 %	
Inadequate/unsatisfactory	12 %	

**Cancer risk is compared to benign NN diagnosis*

- Providing this data to clinicians and patients may be useful in assessing management options

Thyroid FNA Diagnosis and Follow-up



Diagnostic Terminology and Reporting
USCAP Abstract # 307, Redman et al.

- Surveyed 133 clinicians (Endocrinologists, Surgeons, Thyroid specialists)
- Implications of FNA DX and management options
  - Non-diagnostic →98% repeat FNA
  - Suspicious →96% surgery
  - Indeterminate →58% repeat FNA, 32% surgery
  - Atypical →37% repeat FNA, 52% surgery
- "Indeterminate" was confused with ND in some cases. "Atypical" was too ambiguous and treated as "Susp." in many cases

Summary

- Thyroid FNA is primarily a screening tool, therefore a conclusive DX is not always required
- Pathologist's role: minimize # of indeterminate diagnoses without yielding an unacceptable false neg. and false pos. rates
- FNA can assign diagnostic probabilities that can help guide management in many cases

Summary [2]

- The use of the term “Atypical” or “Indeterminate” as a stand alone diagnosis is not recommended. Its meaning is not standardized and may be interpreted in different ways
- Close cooperation between pathologist and clinician is essential, so that terminology used in report and its clinical implications are clearly defined

Follicular Lesions of the Thyroid

Tarik M. Elsheikh, MD

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