# NIFTP and the Updated Bethesda System for Thyroid FNA

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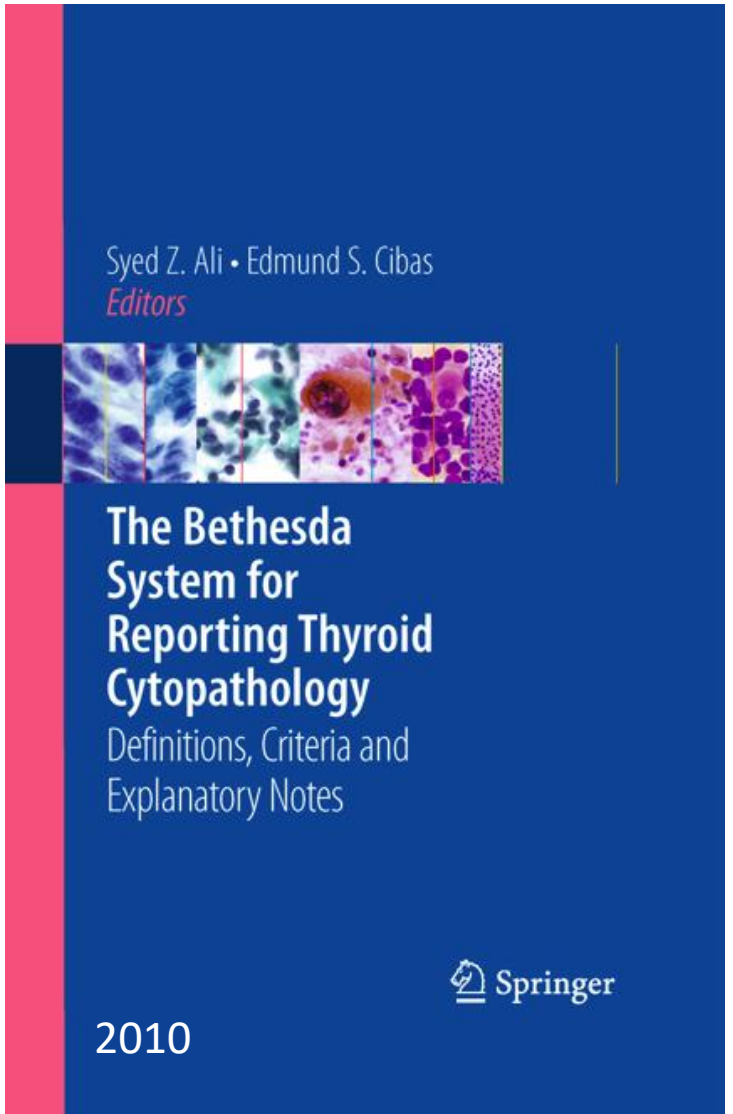
# Aims

- Provide an overview of NIFTP and its impact on thyroid FNA
- Highlight updates to the 2nd edition of TBSRTC

# The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

- Rationale for uniform terminology:
  - clarity of communication
  - exchange of information across institutions
- Widespread acceptance in U.S. and elsewhere
- Translated into Spanish, Turkish, Japanese, and Chinese
- Endorsed by 2015 American Thyroid Association guidelines



# What has changed?

- Experience with TBSRTC
- Advent of molecular testing
- Recognition of problem of overdiagnosis
- 2015 ATA Guidelines
- NIFTP

# Yokohama group

- 2016: Symposium to consider modifications
  - International Cytology Congress (Yokohama, Japan)

Commentary

ACTA CYTOLOGICA

Acta Cytologica 2016;60:399–405
DOI: 10.1159/000451020

Published online: October 21, 2016

## The Bethesda System for Reporting Thyroid Cytopathology: Proposed Modifications and Updates for the Second Edition from an International Panel

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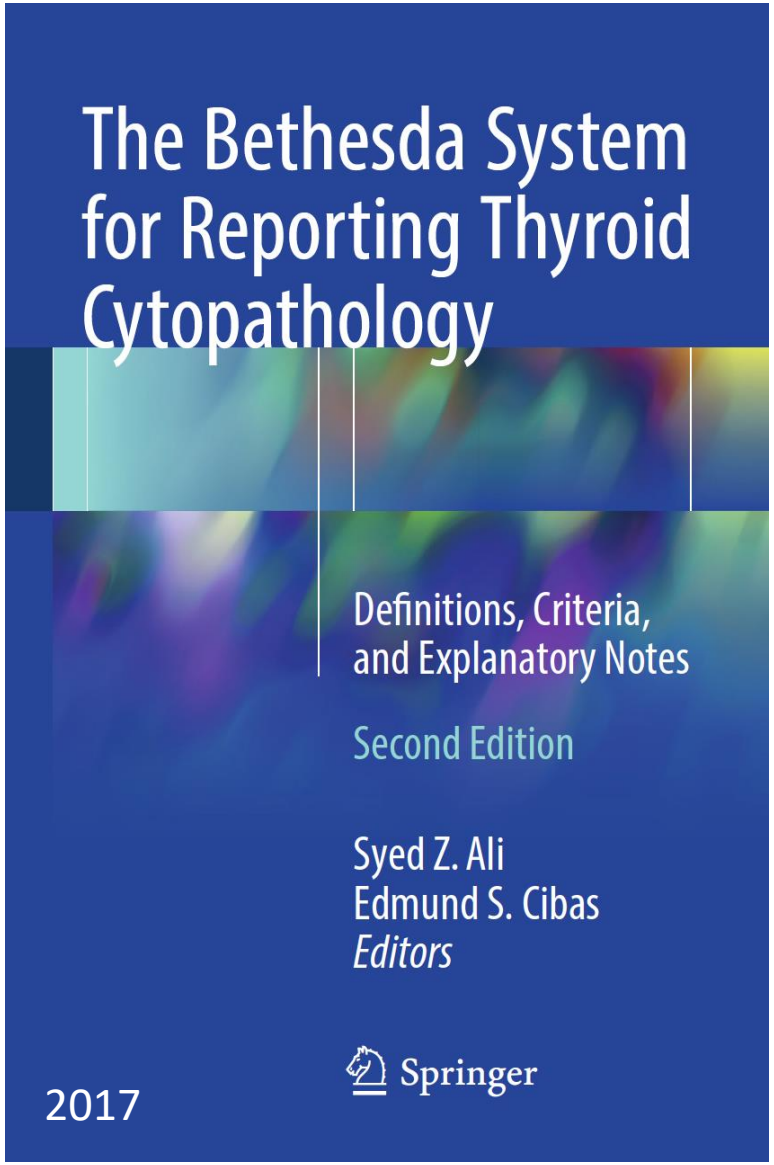
# The Bethesda System Atlas, 2nd edition

- Based on the Yokohama recommendations
- Publication: October 28, 2017



# TBSRTC v1 overview

| Diagnostic Category | Risk of Malignancy | Usual Management |
|---|---|---|
| I. ND/UNSAT | 1-4% | Repeat FNA |
| II. Benign | 0-3% | Clinical follow-up |
| III. AUS/FLUS | 5-15% | Repeat FNA |
| IV. FN/SFN | 15-30% | Lobectomy |
| V. Suspicious for Malignancy | 60-75% | N-T Thyroidectomy or Lobectomy |
| VI. Malignant | 97-99% | N-T Thyroidectomy |

Adapted from Ali and Cibas, *TBSRTC*, 2010

# TBSRTC ROM v1 to v2

| Diagnostic Category | V1 Risk of Malignancy | V2 Risk of Malignancy |
|---|---|---|
| I. ND/UNSAT | 1-4% | 5-10% |
| II. Benign | 0-3% | 0-3% |
| III. AUS/FLUS | 5-15% | ~10-30% |
| IV. FN/SFN | 15-30% | 25-40% |
| V. Suspicious for Malignancy | 60-75% | 50-75% |
| VI. Malignant | 97-99% | 97-99% |

Adapted from Ali and Cibas, *TBSRTC*, 2010 and 2017

# TBSRTC Management v1 to v2

| Diagnostic Category | V1 Usual Management | V2 Usual Management |
|---|---|---|
| I. ND/UNSAT | Repeat FNA | Repeat FNA with US |
| II. Benign | Clinical follow-up | Clinical & US follow-up |
| III. AUS/FLUS | Repeat FNA | Repeat FNA, molecular testing or lobectomy |
| IV. FN/SFN | Lobectomy | Molecular testing, Lobectomy |
| V. Suspicious for Malignancy | N-T Thyroidectomy or Lobectomy | N-T Thyroidectomy or Lobectomy |
| VI. Malignant | N-T Thyroidectomy | N-T Thyroidectomy or Lobectomy |

Adapted from Ali and Cibas, *TBSRTC*

# TBSRTC v2 overview

| Diagnostic Category | Risk of Malignancy | Usual Management |
|---|---|---|
| I. ND/UNSAT | 5-10% | Repeat FNA with US |
| II. Benign | 0-3% | Clinical & US follow-up |
| III. AUS/FLUS | ~10-30% | Repeat FNA, molecular testing or lobectomy |
| IV. FN/SFN | 25-40% | Molecular testing, Lobectomy |
| V. Suspicious for Malignancy | 50-75% | N-T Thyroidectomy or Lobectomy |
| VI. Malignant | 97-99% | N-T Thyroidectomy or Lobectomy |

Adapted from Ali and Cibas, *TBSRTC*

# AUS/FLUS

- ROM differs according to nature of atypia

| Diagnostic category | Average ROM* (%) |
|---|---|
| Cytologic atypia | 47 |
| Architectural atypia | 22 |
| Hürthle cell aspirate | 5 |

*Resected cases only

Adapted from Nishino and Wang *Cancer Cytopathol* (2014)

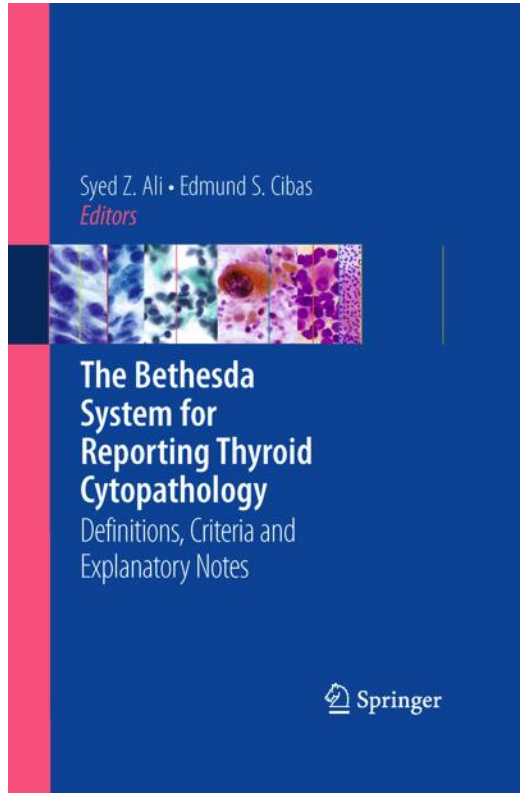
- Subclassification recommended

# AUS/FLUS

- Descriptive terms favored
  - Cytologic atypia (rather than “r/o PTC”)
  - Architectural atypia (rather than “r/o FN”)
- AUS and FLUS are synonymous
  - Lab should use AUS ***or*** FLUS
  - Should not use AUS ***and*** FLUS as subclassifiers

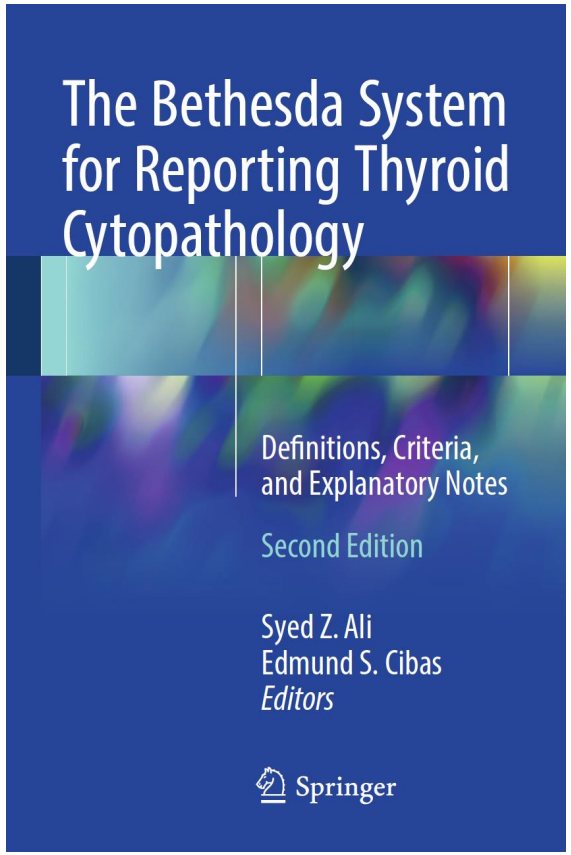
# AUS/FLUS Scenarios v1

1. Atypia hindered by preparation artifact
2. Hürthle cells only, in a patient with
   - Hashimoto's
   - Multinodular goiter
3. Hürthle cells only, but sparsely cellular
4. Focal architectural features of FOL
5. Focal cytologic features of PTC
6. Atypical cyst lining cells
7. Focal marked nuclear atypia
8. Atypical lymphoid infiltrate
9. Not otherwise specified



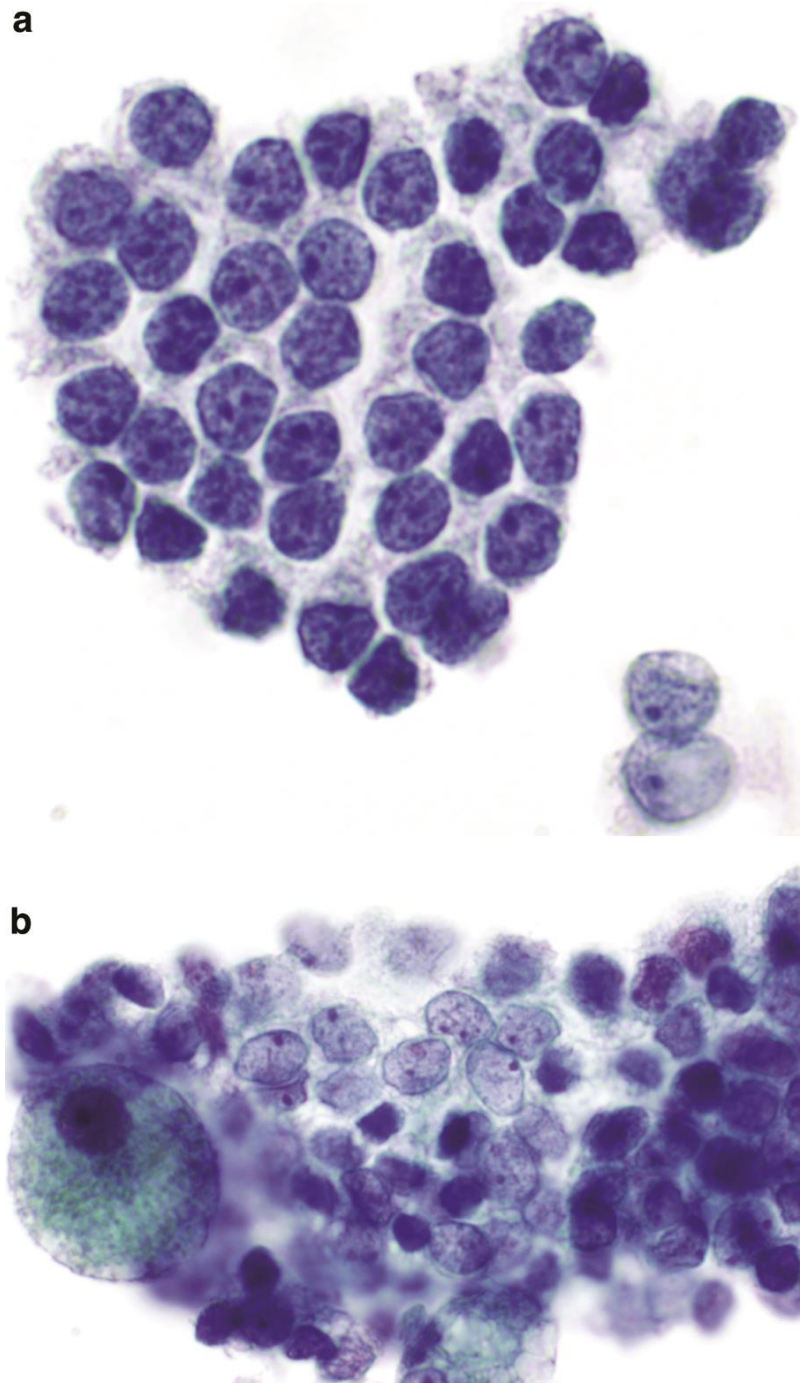
# AUS/FLUS Scenarios v2

1. Cytologic atypia
2. Architectural atypia
3. Cytologic and architectural atypia
4. Hürthle cell aspirates
5. Atypia, NOS
6. Atypical lymphoid cells, r/o lymphoma



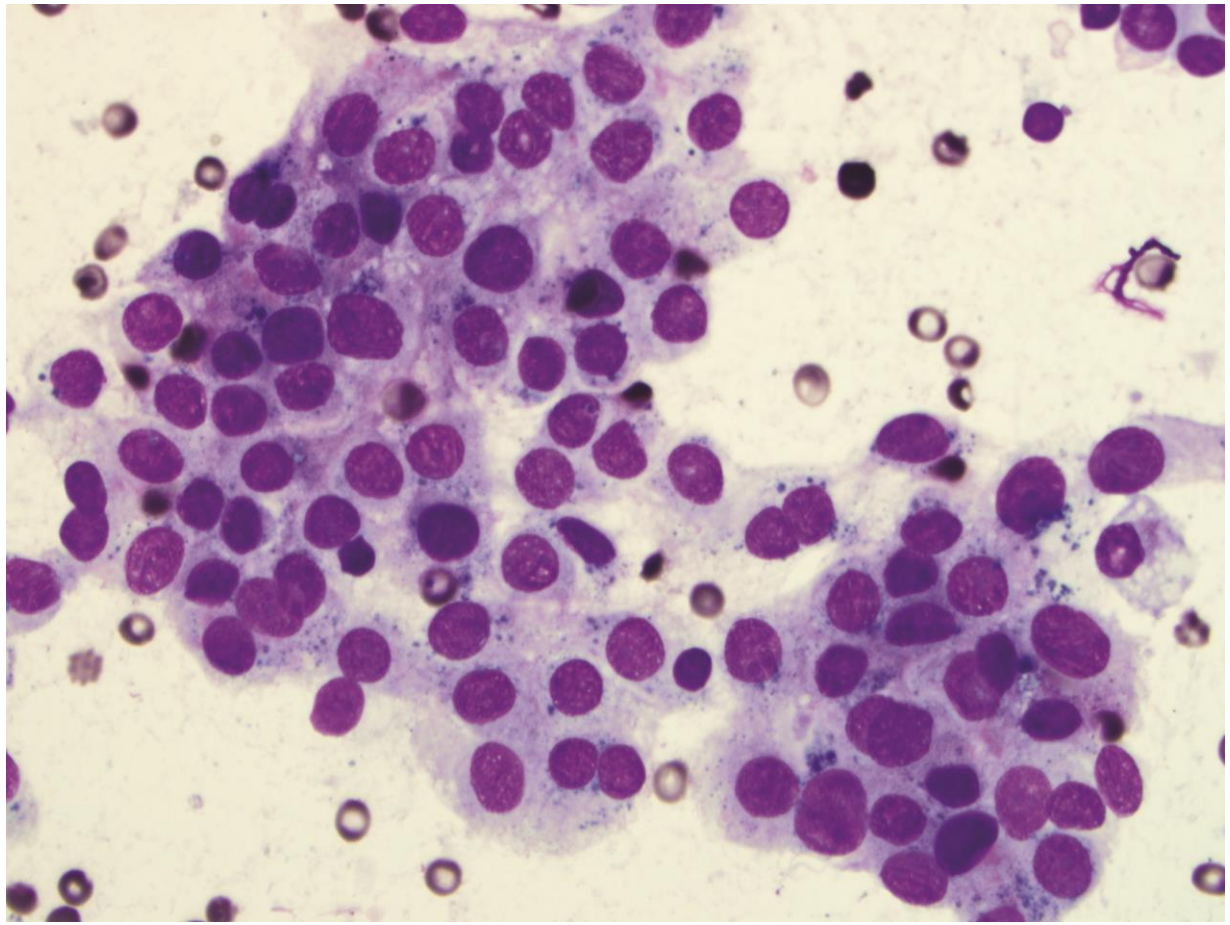
# Cytologic atypia

- Focal cytologic atypia



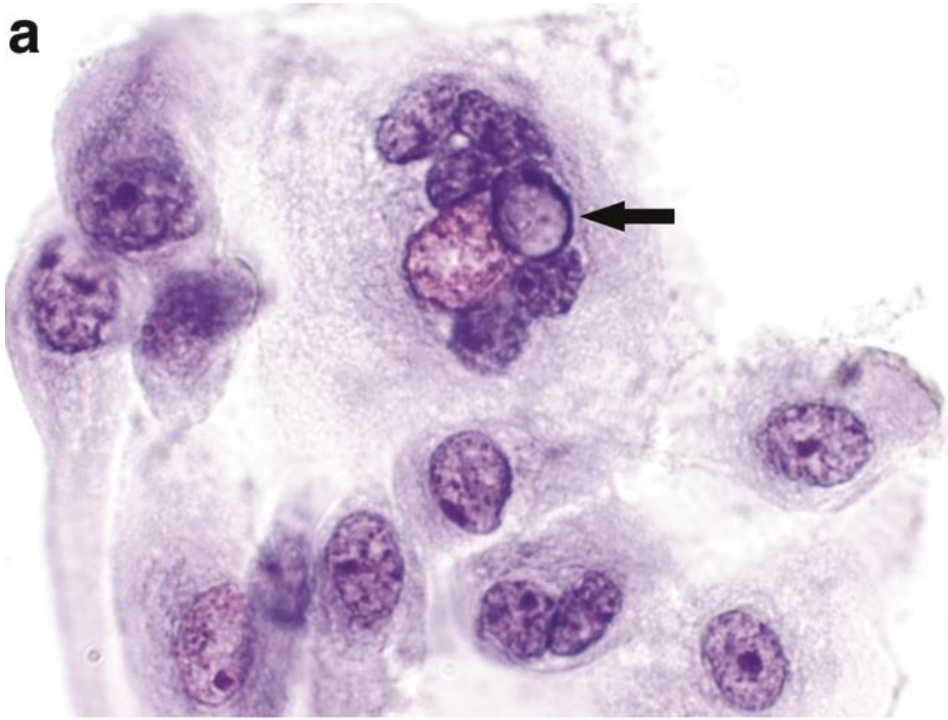
# Cytologic atypia

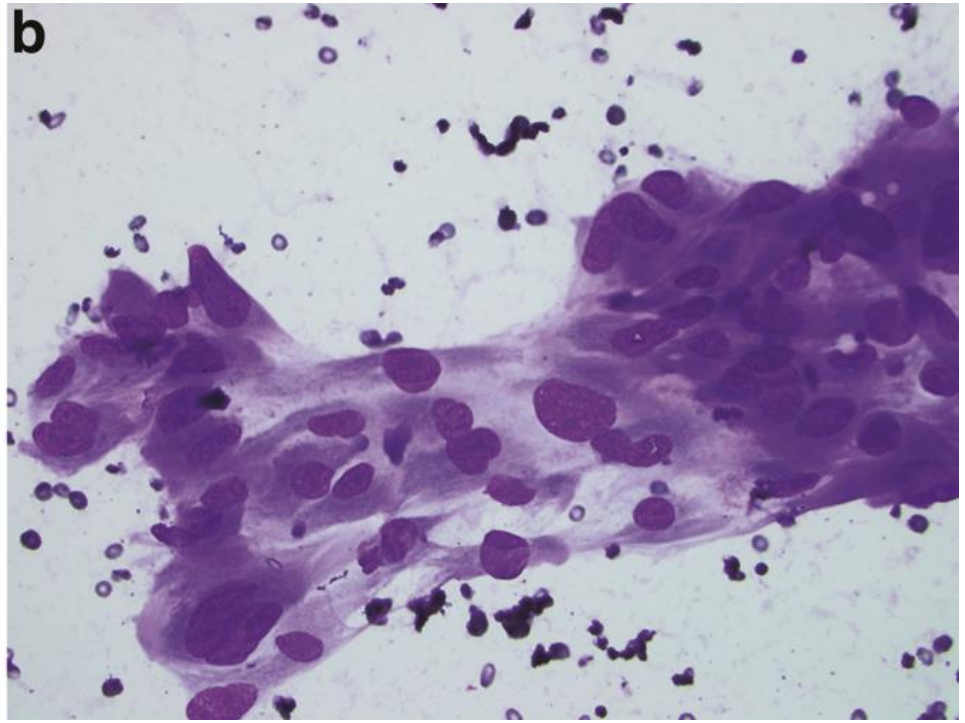
- Focal cytologic atypia
- Extensive but mild cytologic atypia



# Cytologic atypia

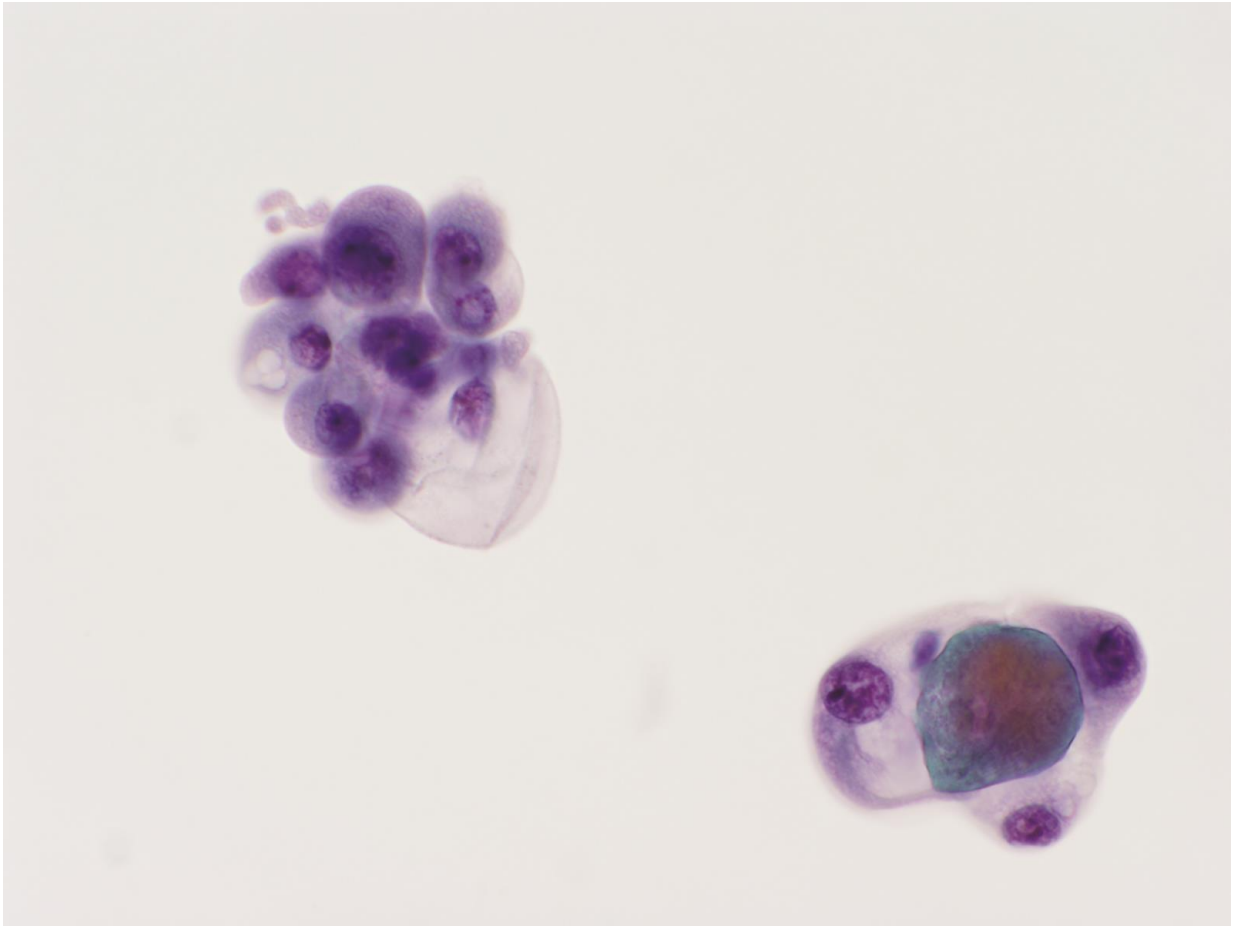
- Focal cytologic atypia
- Extensive but mild cytologic atypia
- Atypical cyst lining cells



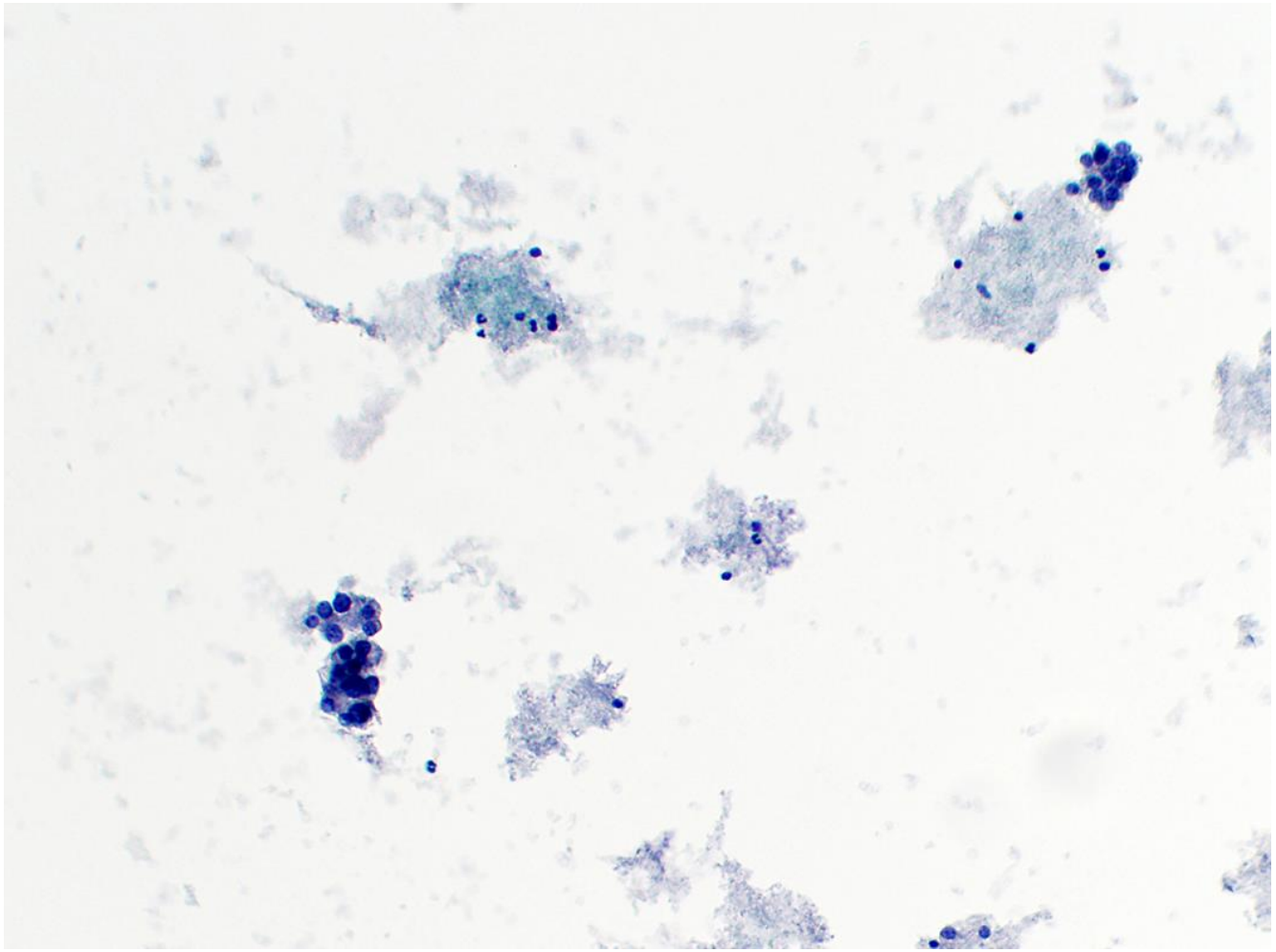
# Cytologic atypia

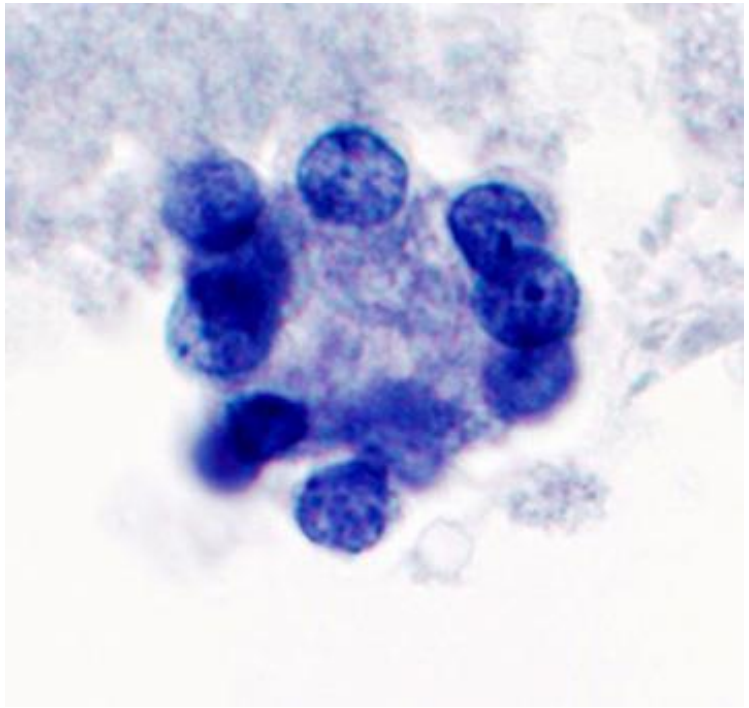
- Focal cytologic atypia
- Extensive but mild cytologic atypia
- Atypical cyst lining cells
- “Histiocytoid” cells



# Architectural atypia

- Sparsely cellular

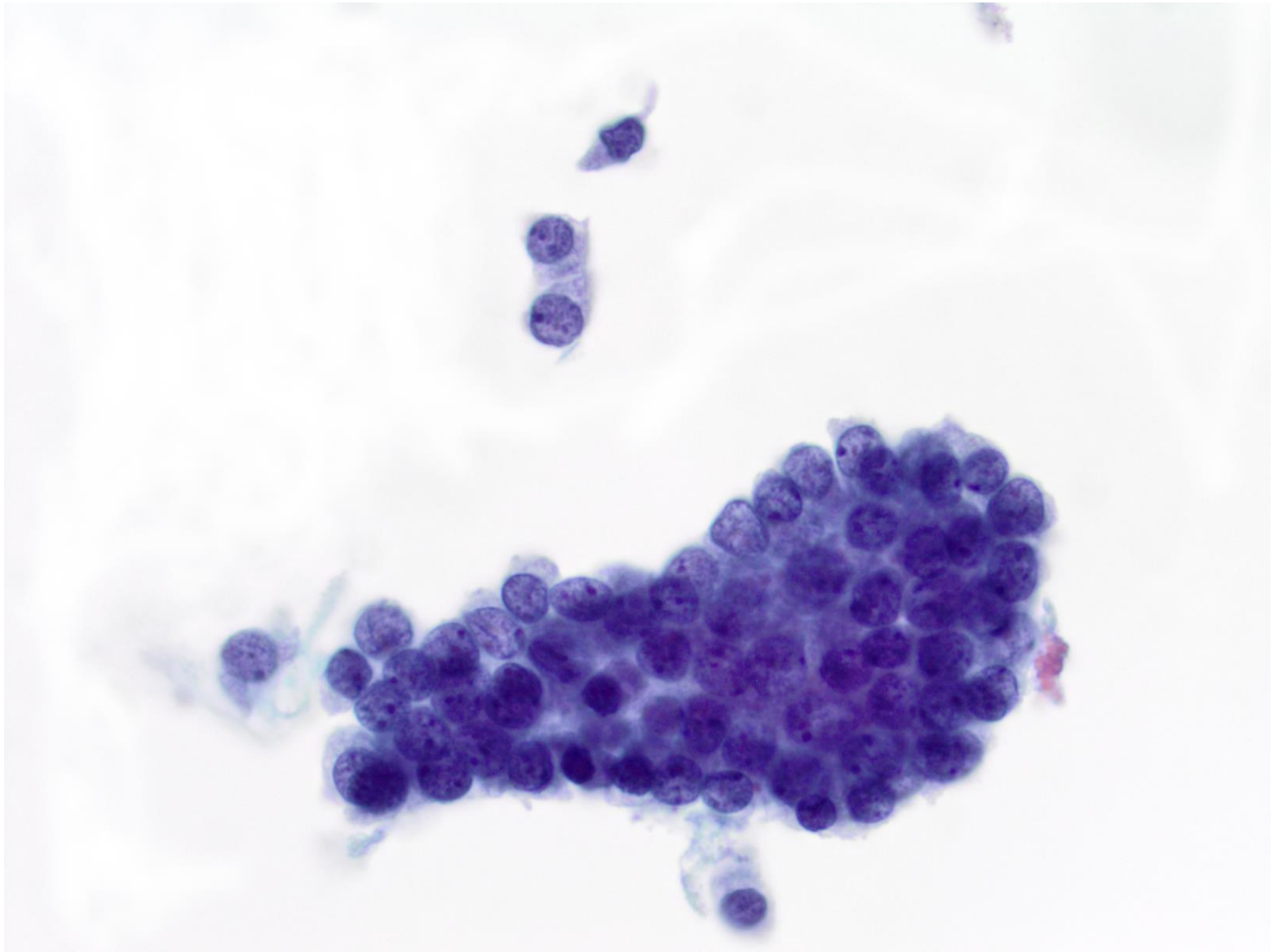




# Architectural atypia

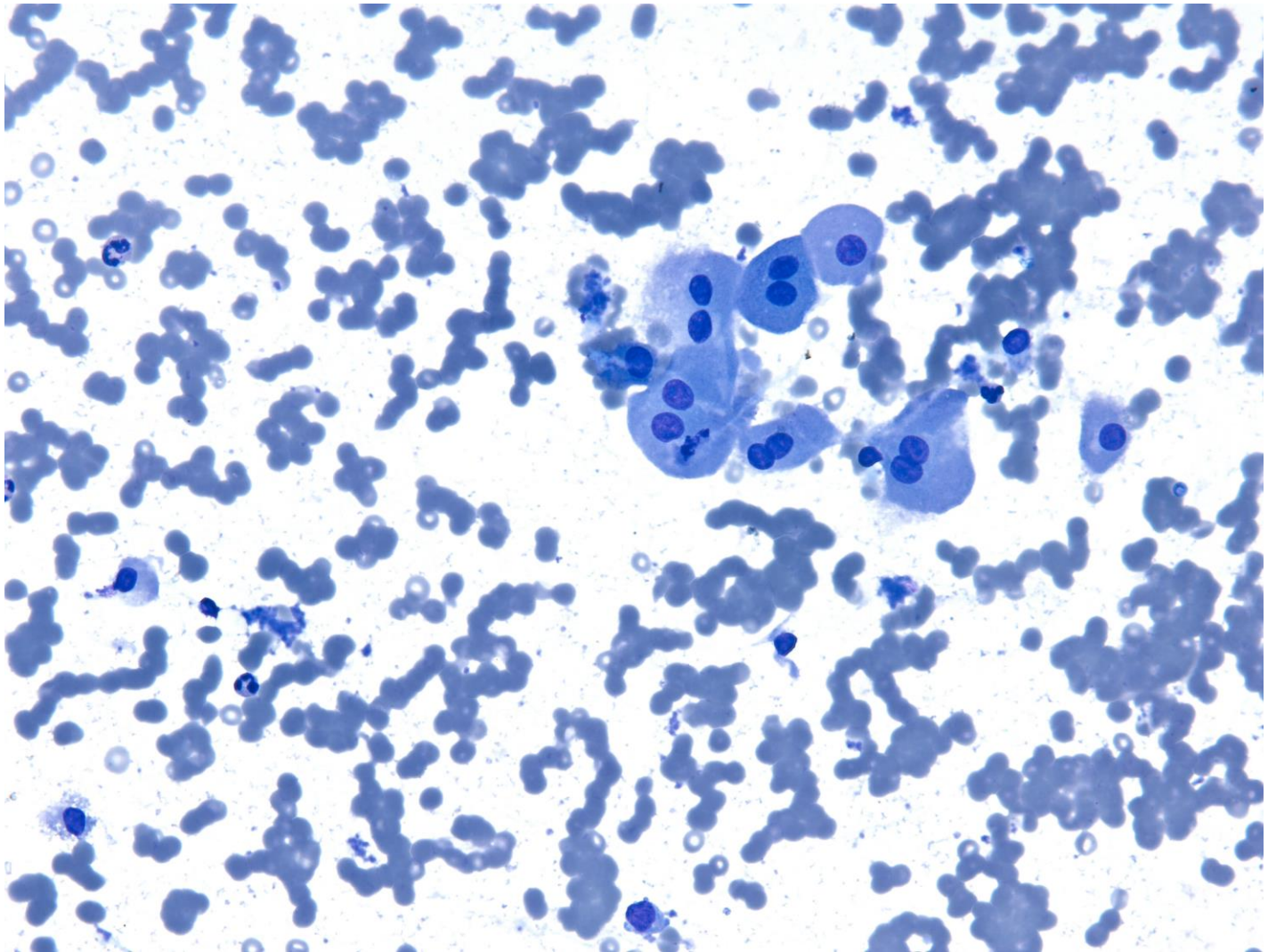
- Sparsely cellular
- Focally prominent microfollicles
  - NOT merely mixed pattern

# Cytologic and architectural atypia



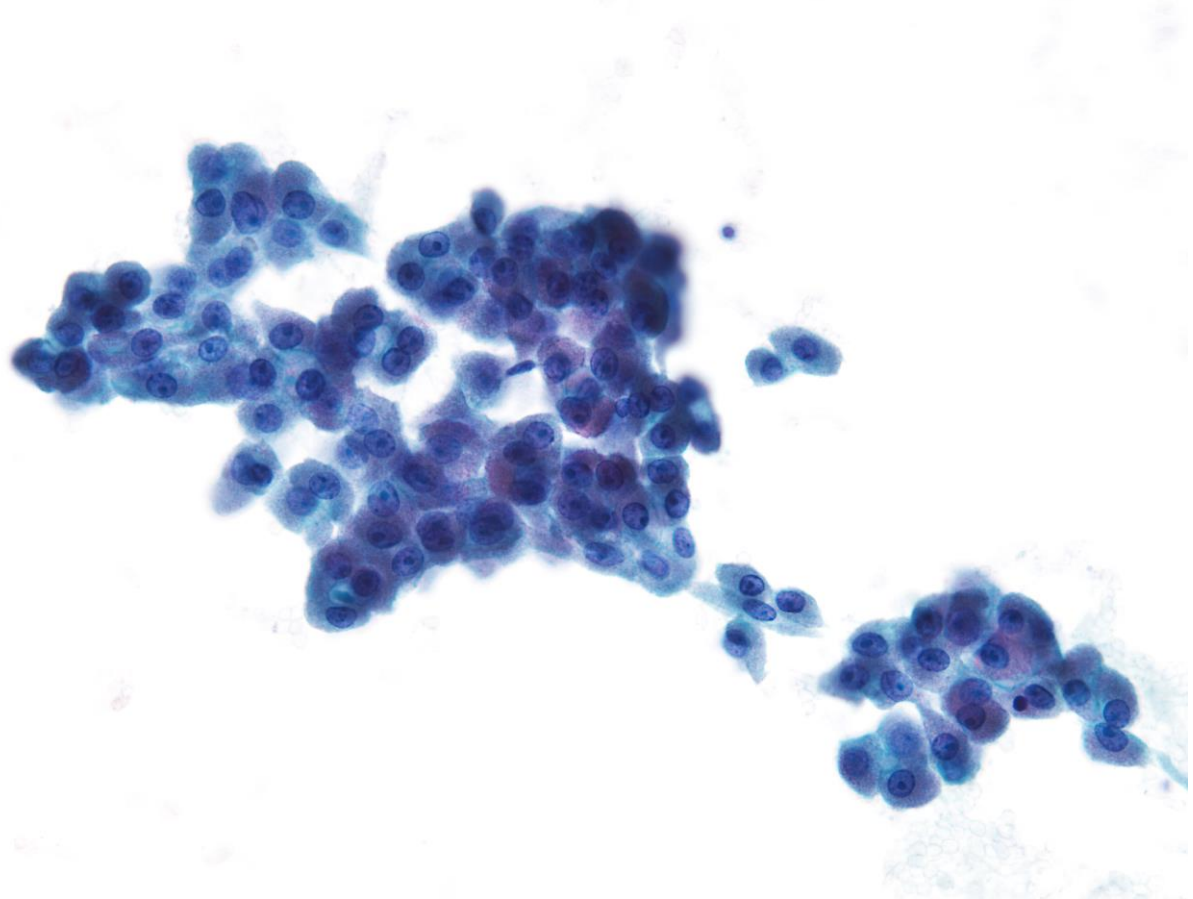
# Hürthle cell aspirates

- Sparsely cellular with minimal colloid



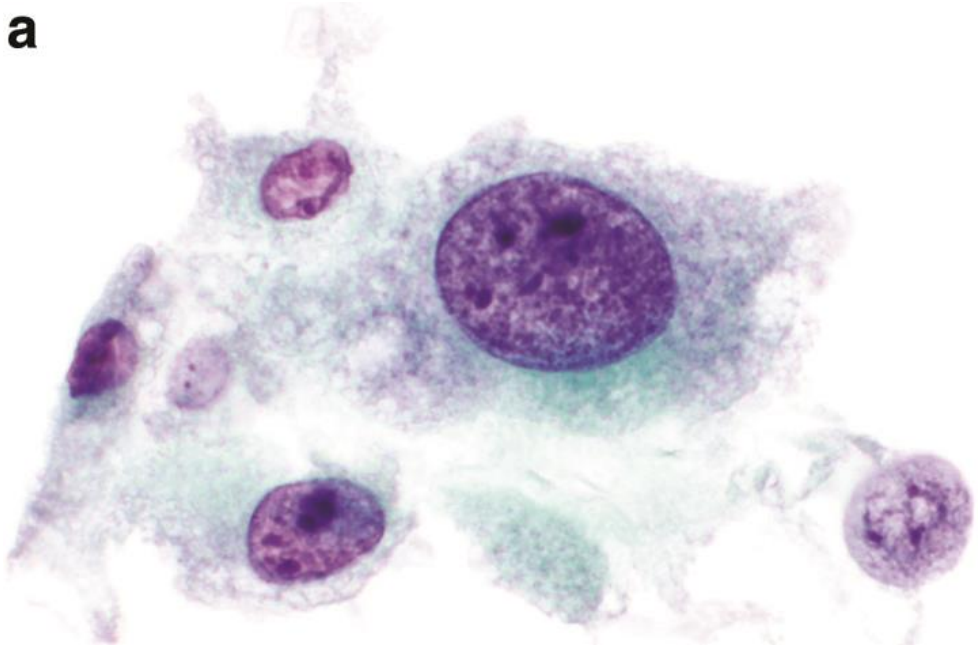
# Hürthle cell aspirates

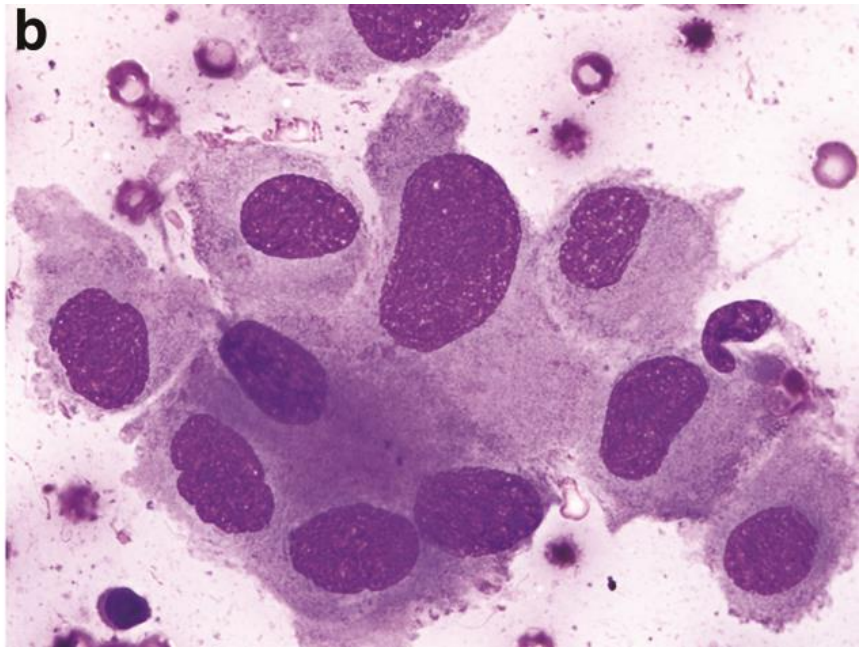
- Sparsely cellular with minimal colloid
- Cellular but clinical setting suggests a benign aspirate
  - Hash
  - MNG



# Atypia, NOS

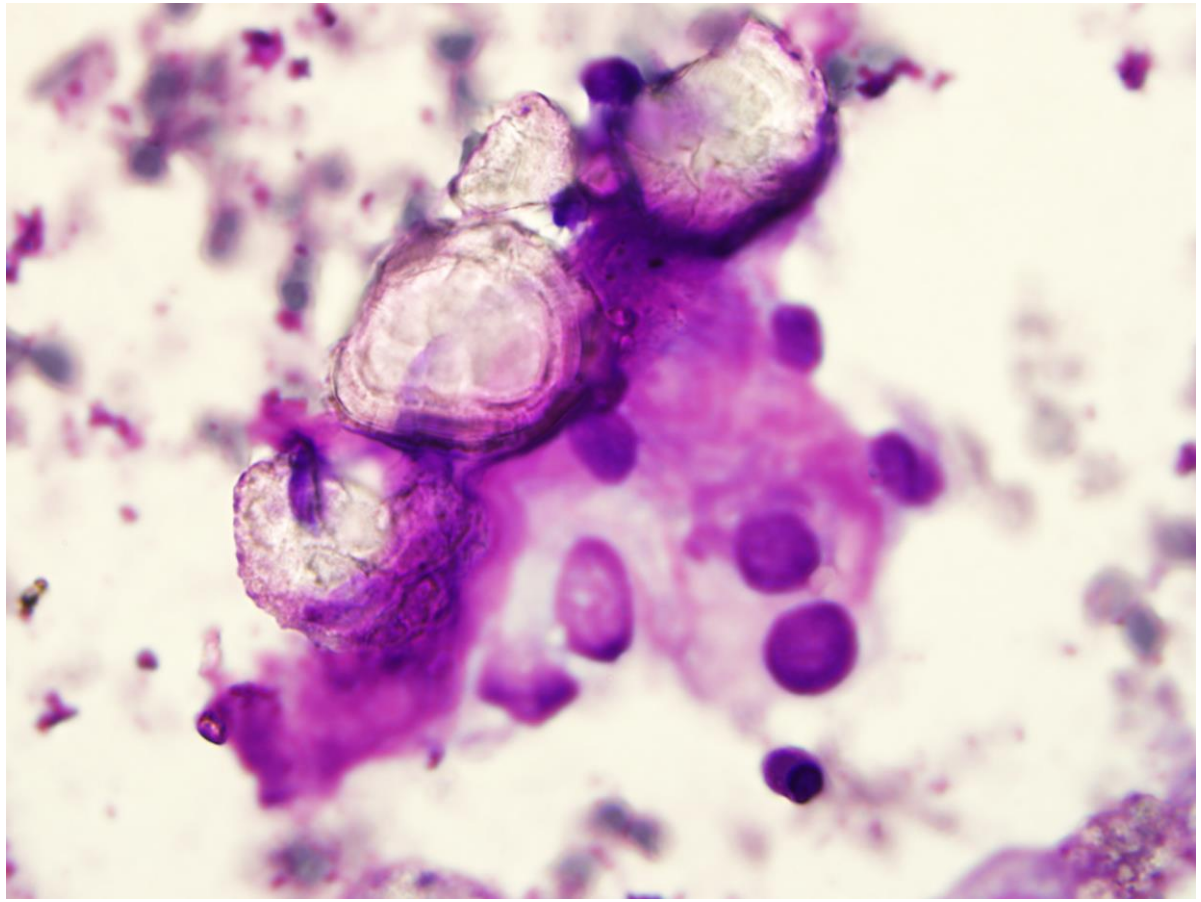
- Minor population with nuclear enlargement +/- nucleoli



# Atypia, NOS

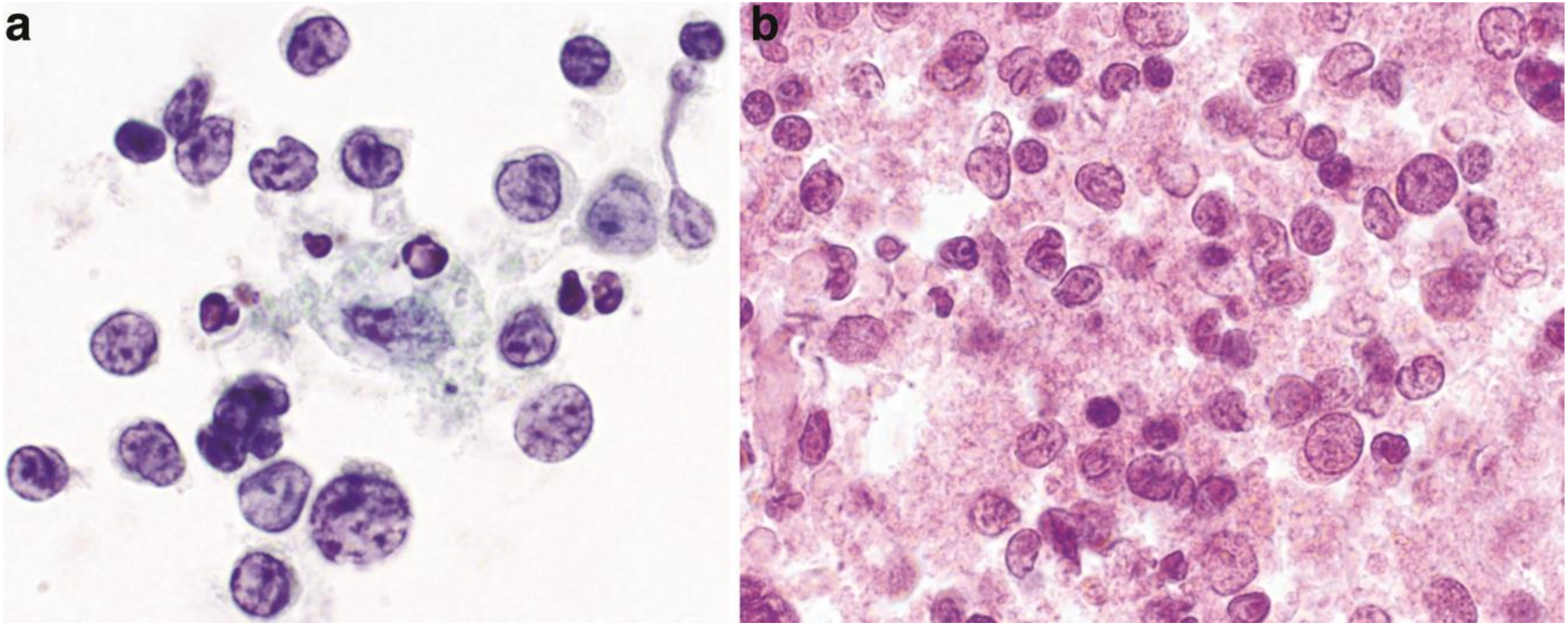
- Minor population with nuclear enlargement +/- nucleoli
- Psammoma bodies without nuclear features of PTC



# Atypia, NOS

- Minor population with nuclear enlargement +/- nucleoli
- Isolated psammoma bodies
- Not otherwise described

# Atypical lymphoid cells, r/o lymphoma

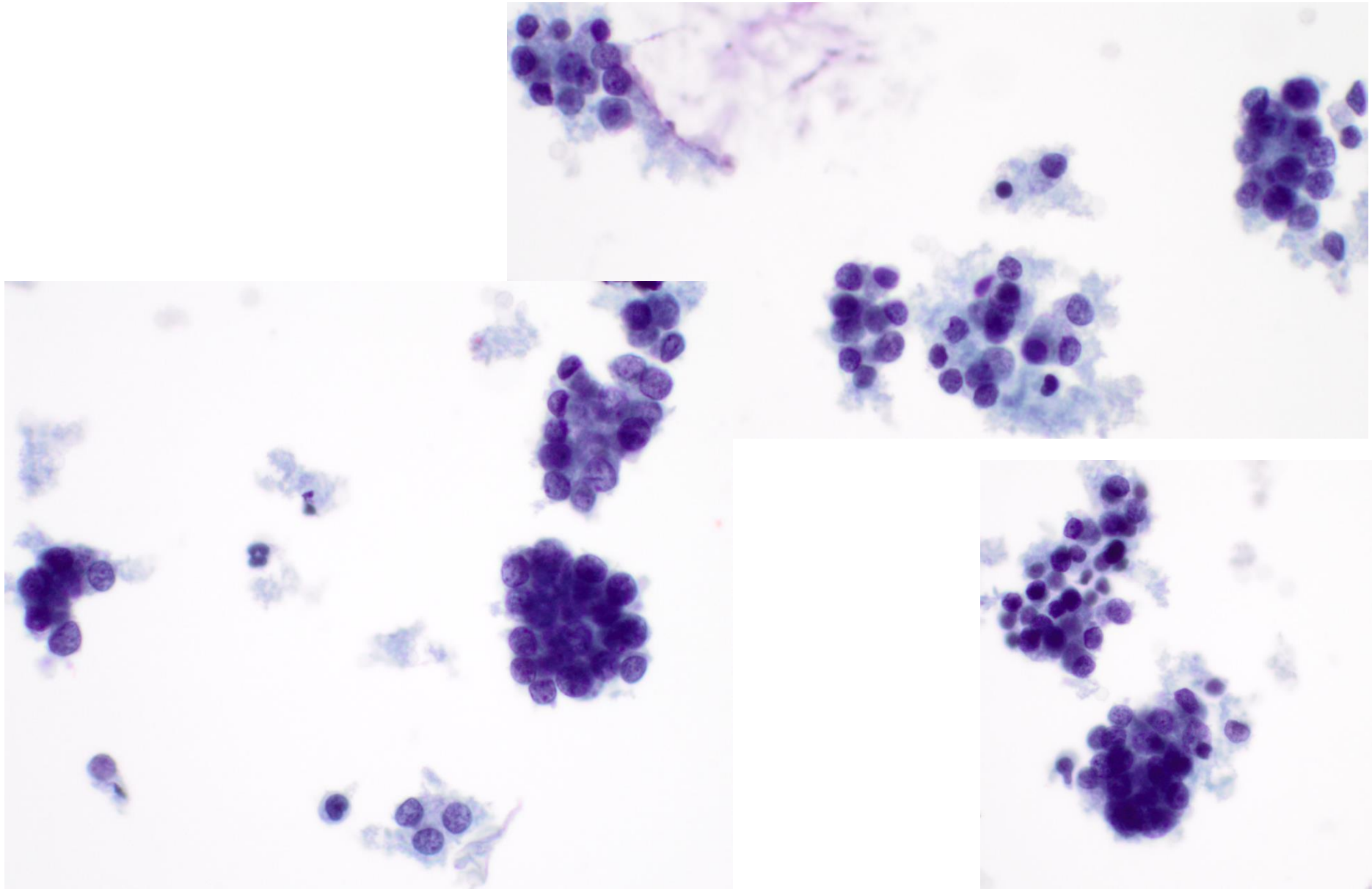


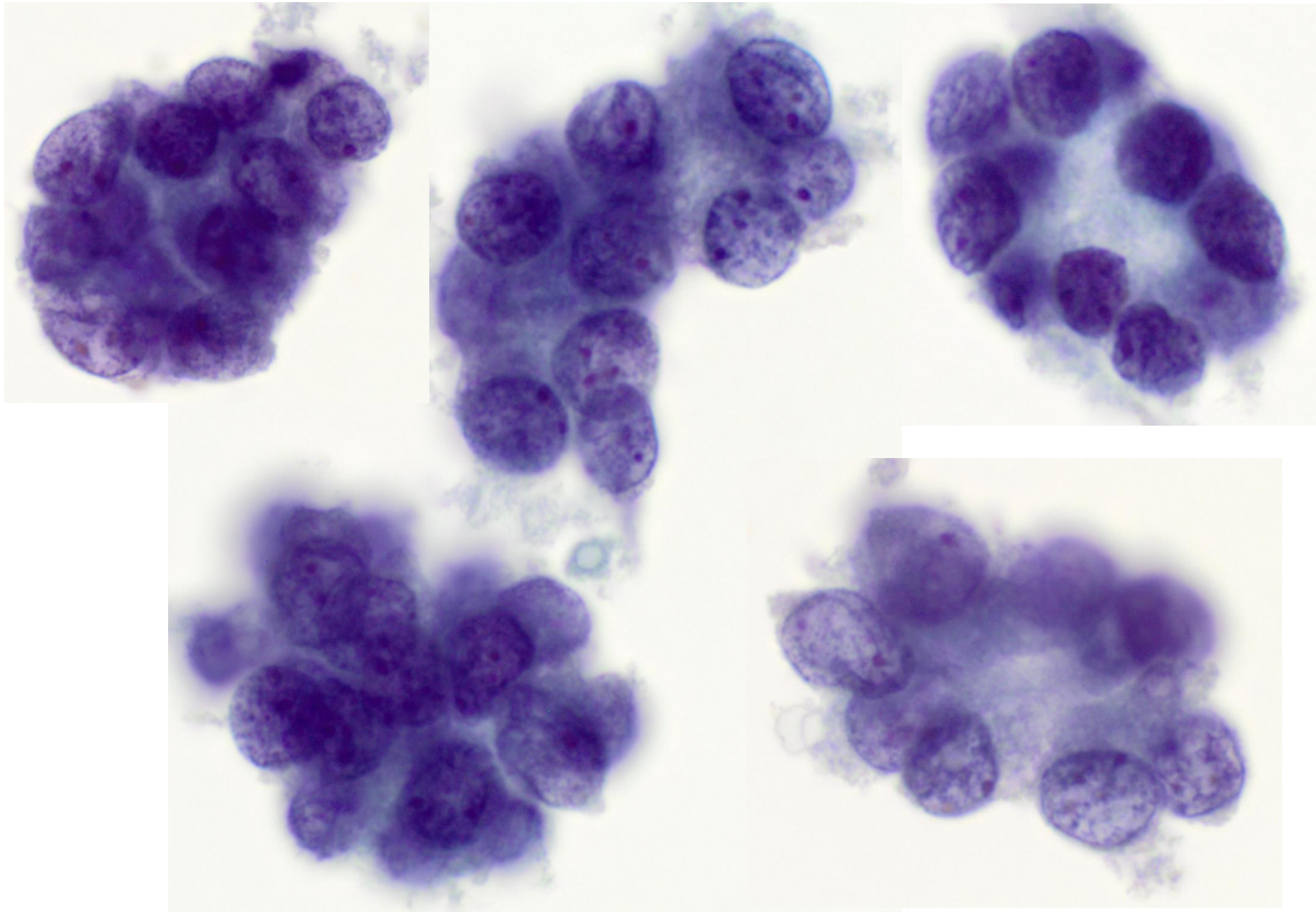
# AUS/FLUS use

- Diagnosis of last resort
- TBSRTC V1 upper limit proposed as 7%
- TBSRTC V2 upper limit proposed as 10%

# NIFTP

# A 37 year old man with a 2.2 cm solitary left thyroid mass





# Diagnosis?

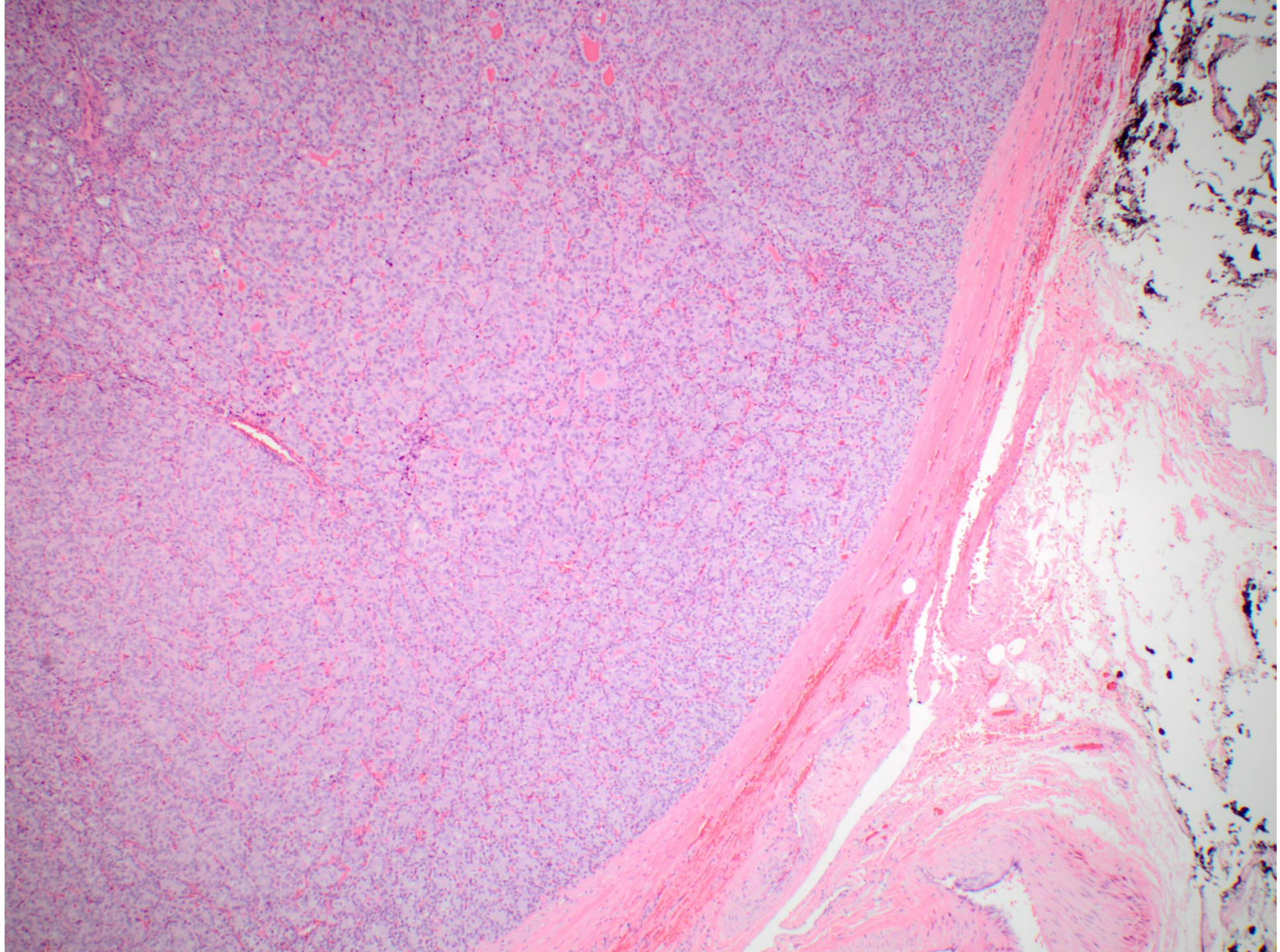
Suspicious for a follicular neoplasm?

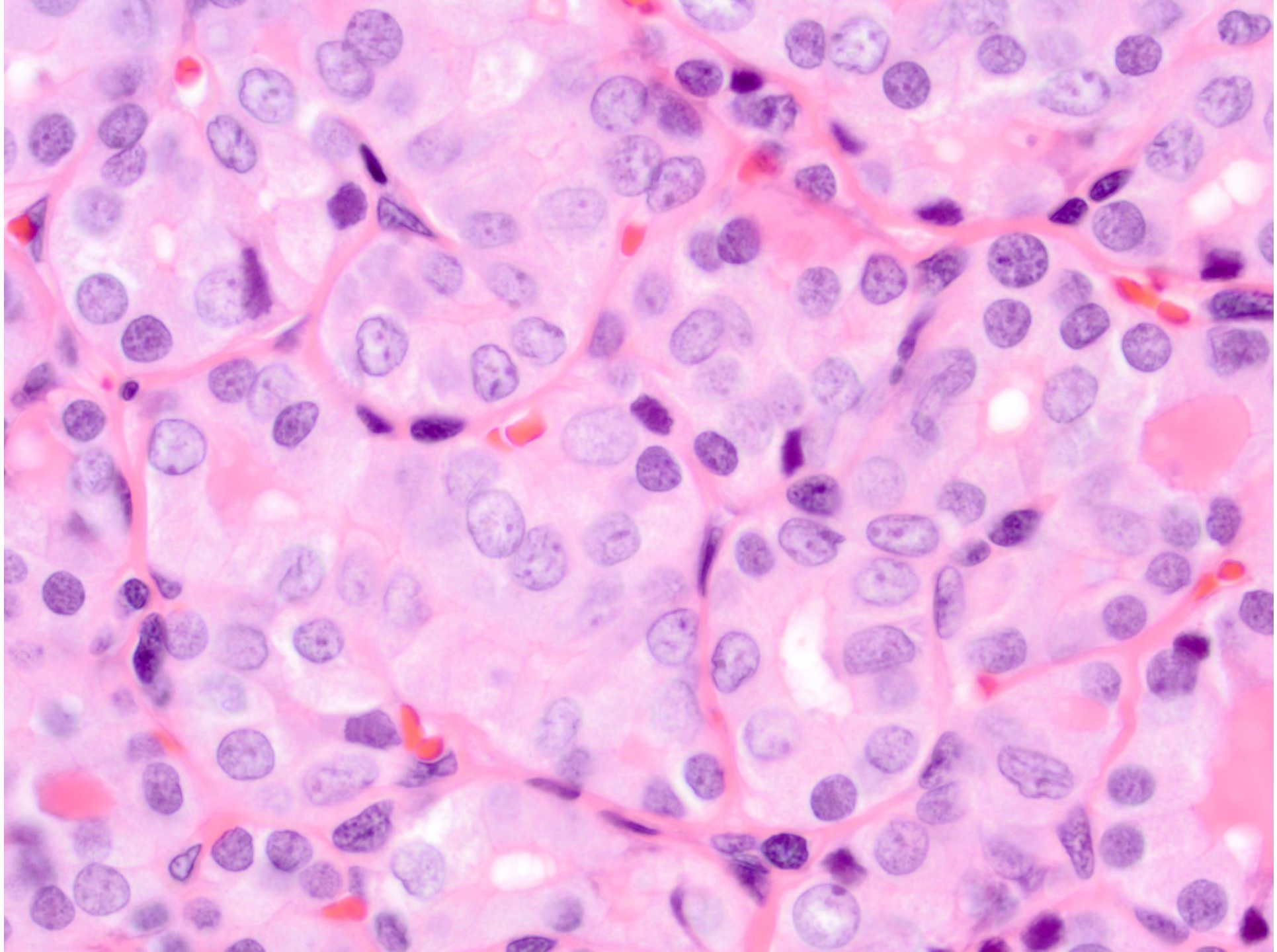
OR

Suspicious for malignancy?

# Cytologic Diagnosis

Suspicious for a follicular neoplasm
(FVPTC cannot be ruled out)

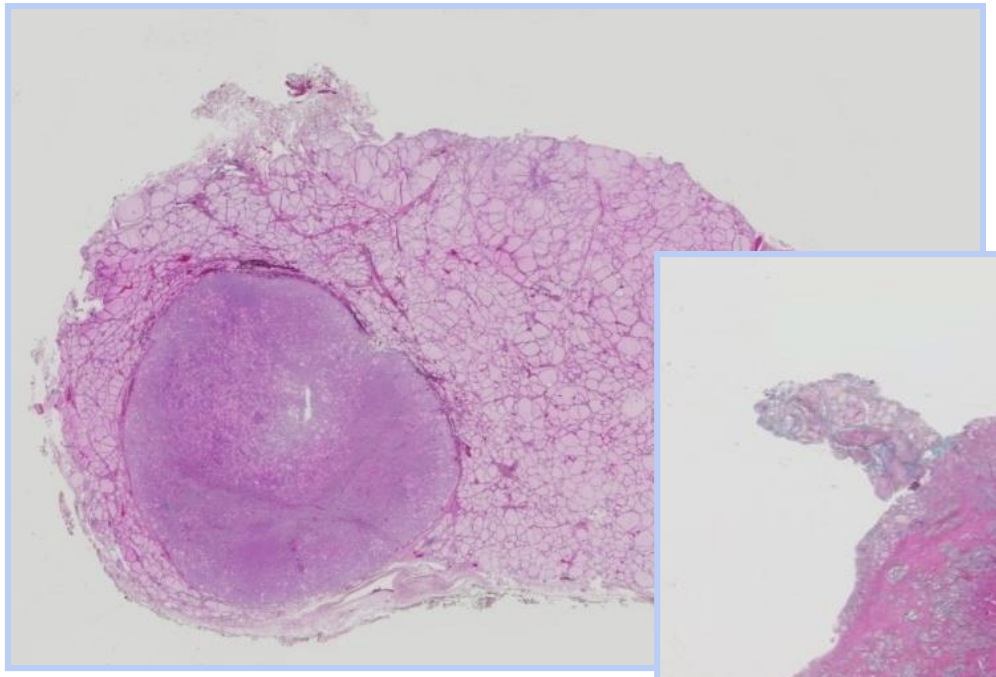




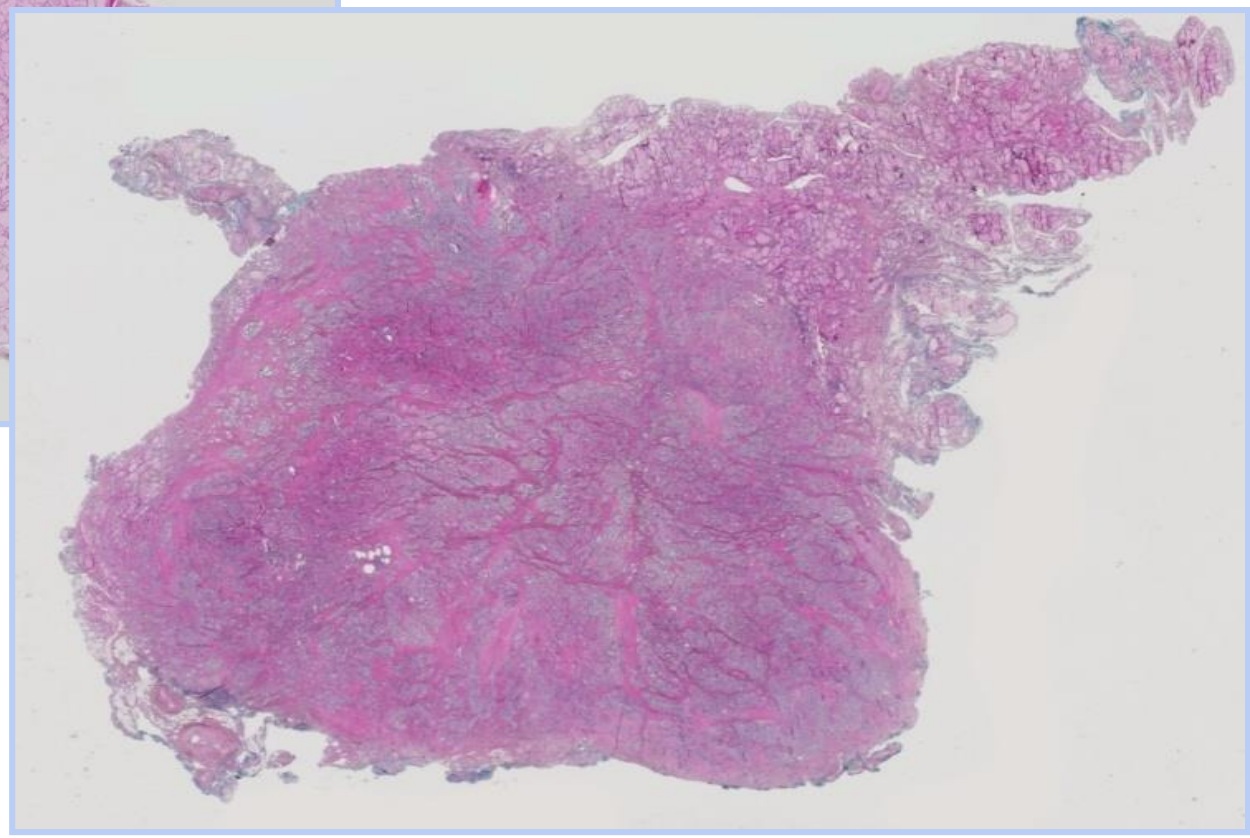
# Histologic Diagnosis

Encapsulated follicular variant of papillary thyroid carcinoma

# Follicular Variant of PTC



Encapsulated



Infiltrative

# Follicular Variant of PTC

**Encapsulated**

- 80%
- Essentially no met potential
- Behave like FA/FC
- *RAS (36%)* and *PAX8/PPARG (4%)* mutations, no *BRAF* V600E

**Infiltrative**

- 20%
- LN mets
- Behave like classical PTC
- *BRAF* (26%) and *RET/PTC* (10%) mutations, fewer *RAS (10%)*

# Endocrine Pathology Society Working Group Re-Examination of Encapsulated FVPTC

- Led by Dr. Yuri Nikiforov
- 25 endocrine pathologists from 7 countries
  - 1 cytopathologist (Dr. Zubair Baloch)
- 2 endocrinologists
- 1 endocrine surgeon
- 1 psychiatrist/ethicist
- 1 thyroid cancer survivor
- 8 teleconferences, 1.5 day meeting

# Follow-up of Encapsulated FVPTC

- Literature review
- >200 tumors with long term follow-up (>10 yr)
  - 1 metastases (primary had only limited sampling)
  - 1 local recurrence (tumor had a positive surgical margin)

# Terminology Proposal

- **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)**
  - Papillary nuclear features
  - No invasion
    - Capsule must be adequately sampled
  - <1% papillary architecture [essentially none]
    - No psammoma bodies
  - <30% solid
  - No high grade features
    - Mitoses <3/10 hpf
    - Necrosis
  - Treatment
    - Typically no further treatment after excision of nodule

Nikiforov et al *JAMA Oncol* (2016)

# Revised NIFTP Criteria

- May further limit false positive cytologic diagnoses
- May encourage complete sampling and molecular testing of MALIGNANT aspirates thought to be NIFTP on surgical pathology
- May encourage more molecular testing of follicular patterned lesions, particularly in SUS category

Nikiforov et al *JAMA Oncol* (2018)

**Primary**

- Encapsulation or clear demarcation[a]
- Follicular growth pattern with:
  - No well-formed papillae
  - No psammoma bodies
  - <30% solid/trabecular/insular growth pattern
- Nuclear score 2-3[b]
- No vascular or capsular invasion[c]
- No tumor necrosis or high mitotic activity[d]

**Secondary[e]**

- Lack of *BRAF* V600E mutation detected by molecular assays or immunohistochemistry
- Lack of *BRAF* V600E-like mutations or other high-risk mutations (TERT, TP53)

Abbreviation: NIFTP, noninvasive follicular thyroid neoplasm with papillarylike nuclear features.

[a] Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid parenchyma.

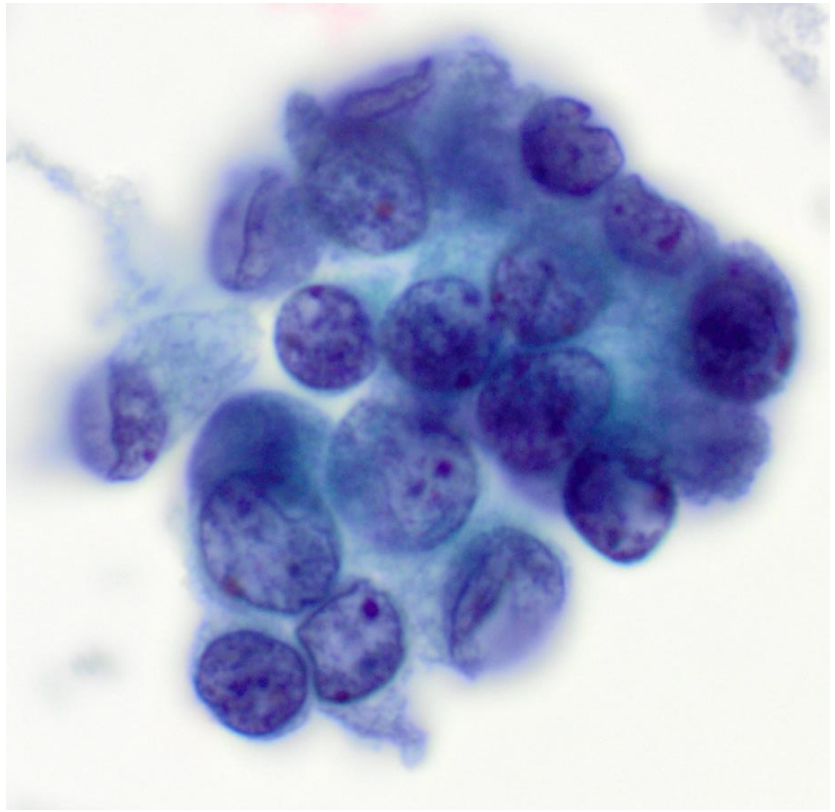
[b] Typically nuclear score 2 (moderately expressed nuclear features of papillary thyroid carcinoma). In tumors with florid nuclear features of papillary thyroid carcinoma (nuclear score 3), the entire tumor should be examined to exclude the presence of papillae. Molecular testing for *BRAF* V600E and other mutations or immunohistochemistry for *BRAF* V600E is advisable but not required for tumors with nuclear score 3.

[c] Requires microscopic examination of the entire tumor capsule interface.

[d] High mitotic activity, defined as 3 or more mitoses per 10 high-power fields (×400).

[e] Secondary criteria are helpful but not required for NIFTP diagnosis.

- How does NIFTP fit in TBSRTC?
- How does NIFTP affect ROM?
- How does NIFTP affect management?



# How are encapsulated FVPTC/NIFTP lesions classified on cytology?

| Cytologic diagnosis | % total N=72 | % total N=96 |
|---|---|---|
| ND | 4 | - |
| Benign | 13 | - |
| AUS/FLUS | 18 | 15 |
| FN/SFN | 10 | 56 |
| SUS | 49 | 27 |
| Malignant | 7 | 2 |

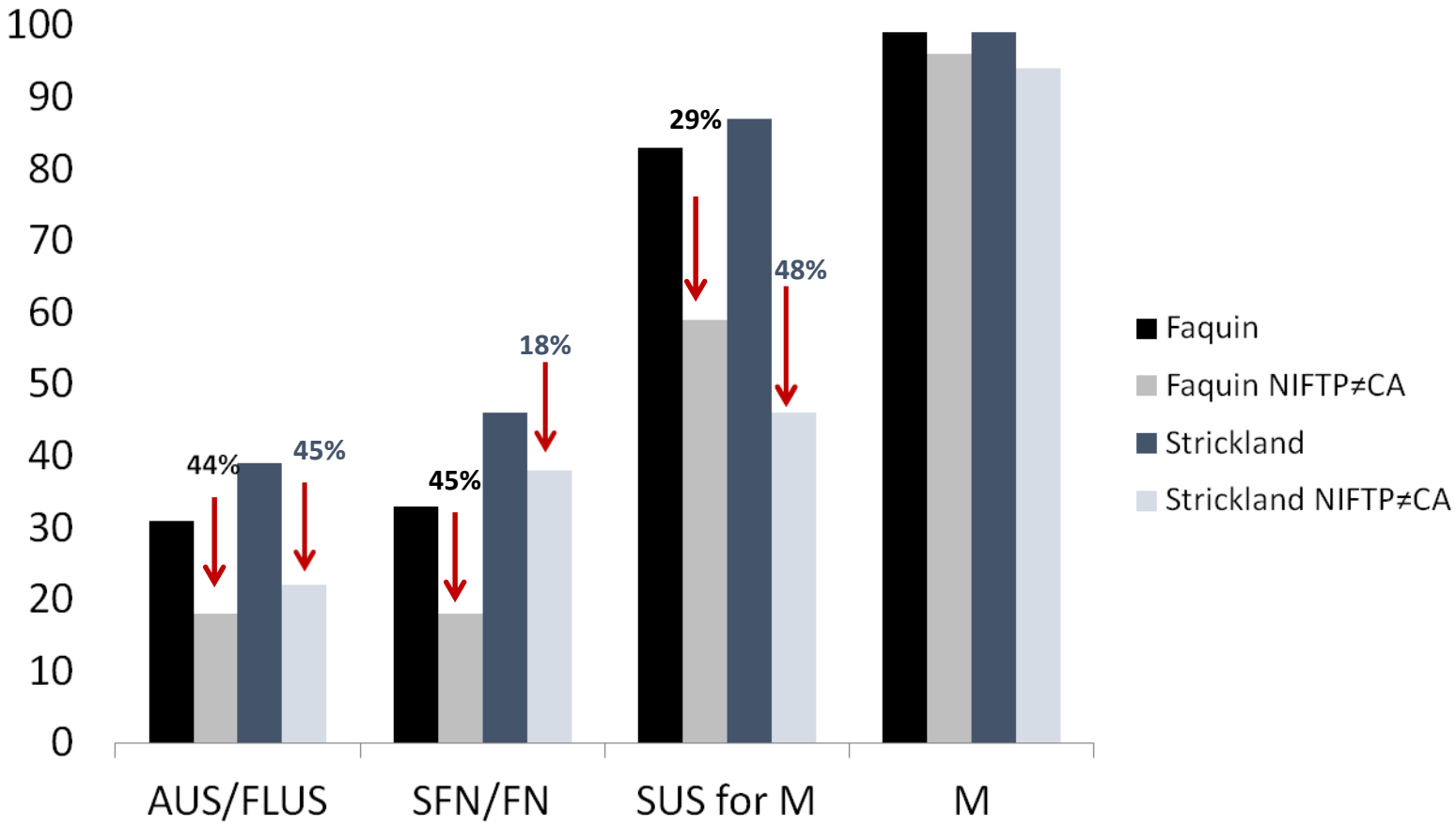
Howitt et al *Am J Clin Pathol* (2015)

Maletta et al *Human Pathol* (2016)

# Take Home Point #1

NIFTP is usually a “gray zone” diagnosis on FNA

# How does NIFTP affect risk of malignancy?

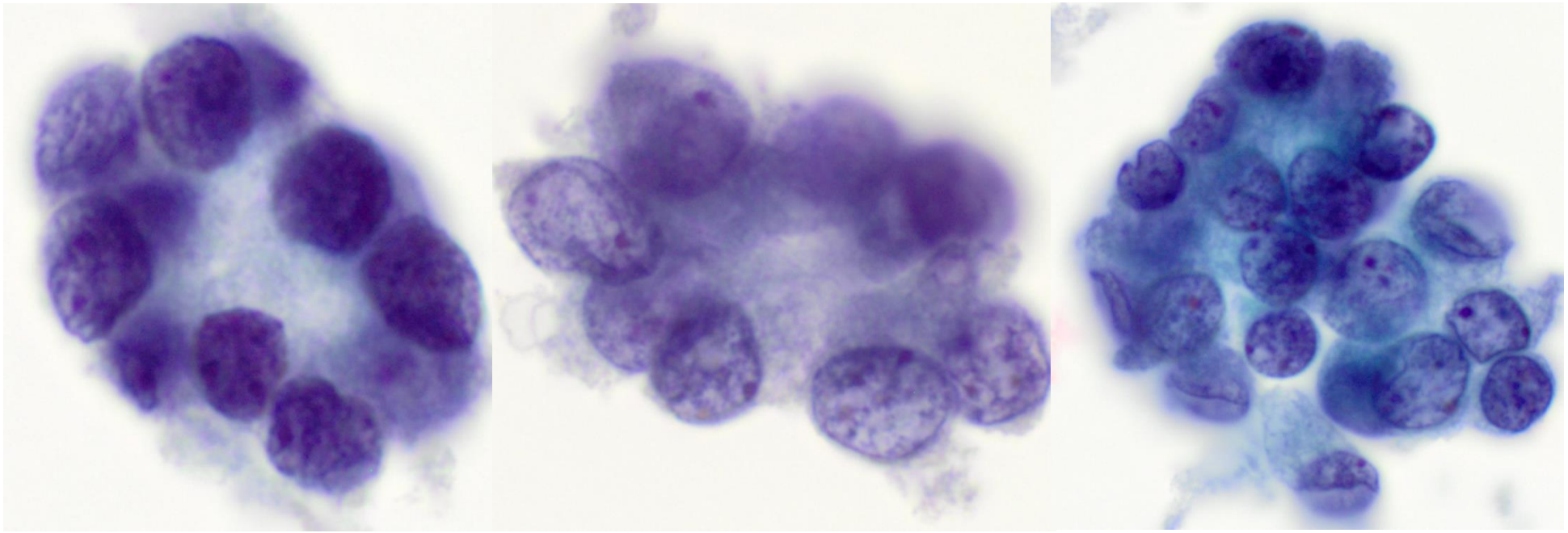



Faquin et al *Cancer Cytopathol* (2016)

Strickland et al *Thyroid* (2015)

# AUS, SFN or SUS for PTC?

Architecture



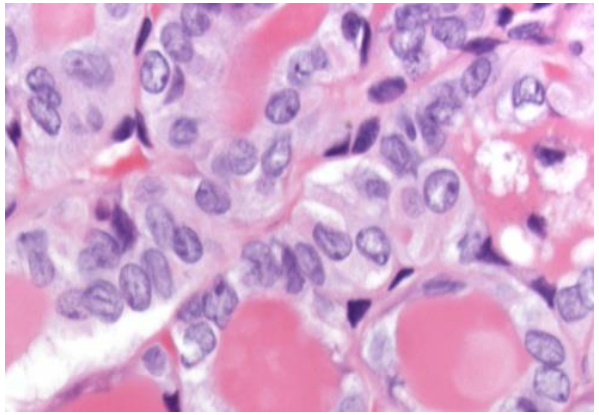
Cytology

# Nuclear Score

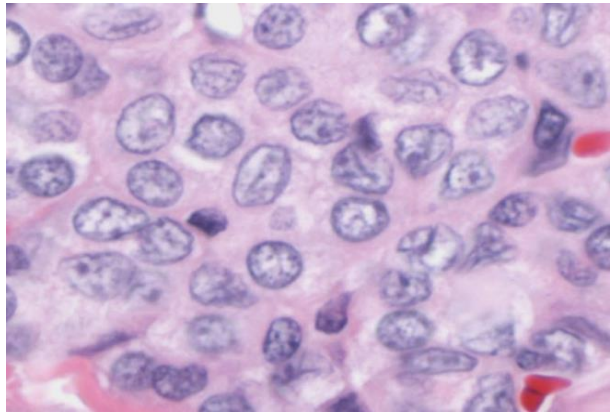
<u>Can get a total of 3 points:</u>

A score of 0 or 1= benign

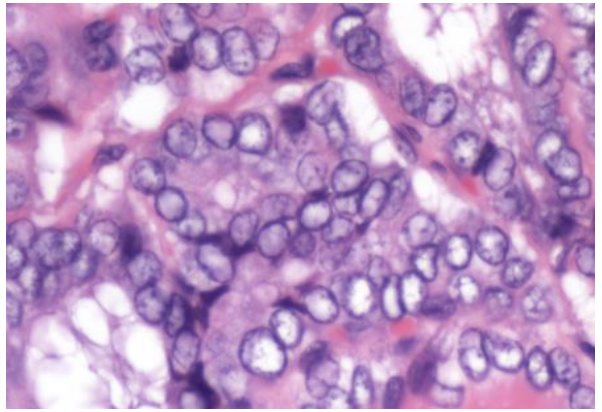
A score of 2 or 3=NIFTP (given correct growth pattern/architecture)



Nuclear enlargement, crowding, elongation→ 1 point



Nuclear membrane irregularities→ 1 point



Chromatin characteristics → 1 point

Courtesy of Dr. J. Barletta, Brigham and Women's Hospital, Boston

# NIFTP vs benign nodules

- Nuclear features distinguish NIFTP from benign nodules
  - Nuclear enlargement
  - Chromatin clearing
  - Nuclear contour irregularities

| | Nuclear score (no. of cases) | Categorization according to Bethesda System | | | |
|---|---|---|---|---|---|
| | | III [a] | IV [b] | V [c] | VI [d] |
| NIFTPs (n = 96) | Score 0-1 (22) | 12 | 9 | 1 | 0 |
| | Score 2-3 (74) | 2 | 45 | 25 | 2 |
| Benign follicular lesions (n = 37) | Score 0-1 (35) | 16 | 19 | 0 | 0 |
| | Score 2-3 (2) | 1 | 1 | 0 | 0 |

Maletta et al *Human Pathol* (2016)

# Cytological, Molecular, and Clinical Features of Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features Versus Invasive Forms of Follicular Variant of Papillary Thyroid Carcinoma

Liena Zhao, MD, PhD; Dora Dias-Santagata, PhD; Peter M. Sadow, MD, PhD; and William C. Faquin, MD, PhD

*Cancer Cytopathol* (2017)

| | NIFTP | IFVPTC |
|---|---|---|
| Molecular | Mostly RAS | RAS≈BRAF |
| Bethesda classification | Mostly AUS and SFN | Mostly SUS and M |

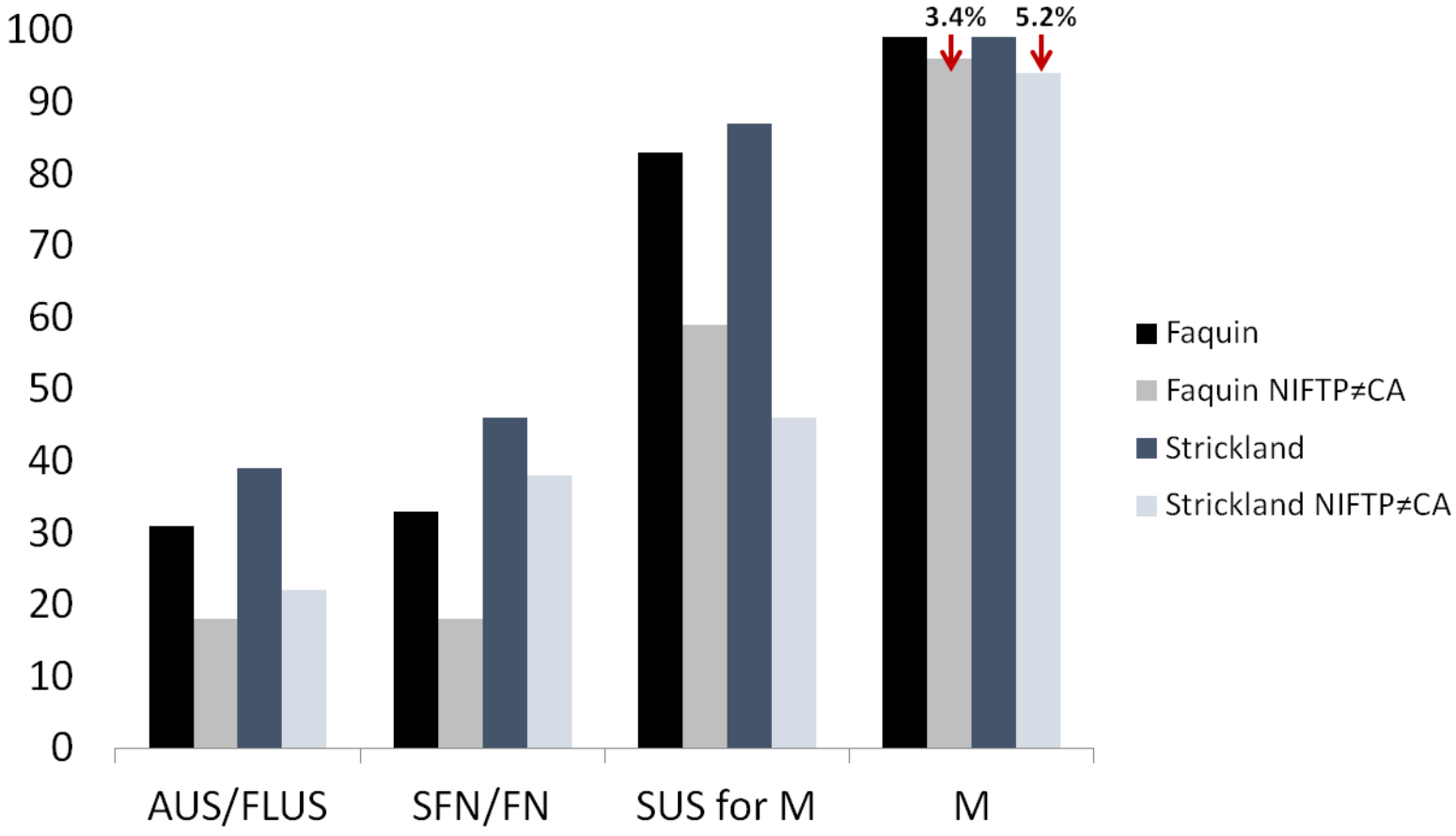
"Despite differences in the cytological classification and molecular profiles between NIFTP and IFVPTC, **the degree of overlap makes it unlikely that most cases of NIFTP and IFVPTC can be accurately distinguished with FNAB**"

And…cannot distinguish between infiltrative FVPTC and encapsulated FVPTC with invasion

# Take Home Point #2

NIFTP cannot be reliably distinguished from other follicular-patterned lesions by cytology alone

# How does NIFTP affect risk of malignancy?




- Faquin et al *Cancer Cytopathol* (2016)
- Strickland et al *Thyroid* (2015)

# Cytology of NIFTP vs classical PTC

| | Classical (%), n=28 | NIFTP (%), n=11 | P value |
|---|---|---|---|
| Suspicious on FNA | 6 (21) | 11 (100) | <0.0001 |
| Malignant on FNA | 22 (79) | 0 | |
| Microfollicle predominant | 1 (4) | 6 (55) | 0.0009 |
| Sheet predominant | 27 (96) | 4 (36) | 0.0002 |
| Papillae | 14 (50) | 0 | 0.0030 |
| Pseudoinclusions | 22 (79) | 0 | <0.0001 |

NIFTP: + SUS, Microfollicular; -Papillae, Pseudoinclusions

Classical PTC: + M, Sheet-like, Papillae, Pseudoinclusions

Howitt, Chang, et al *Am J Clin Pathol* (2015)

# Prospective study

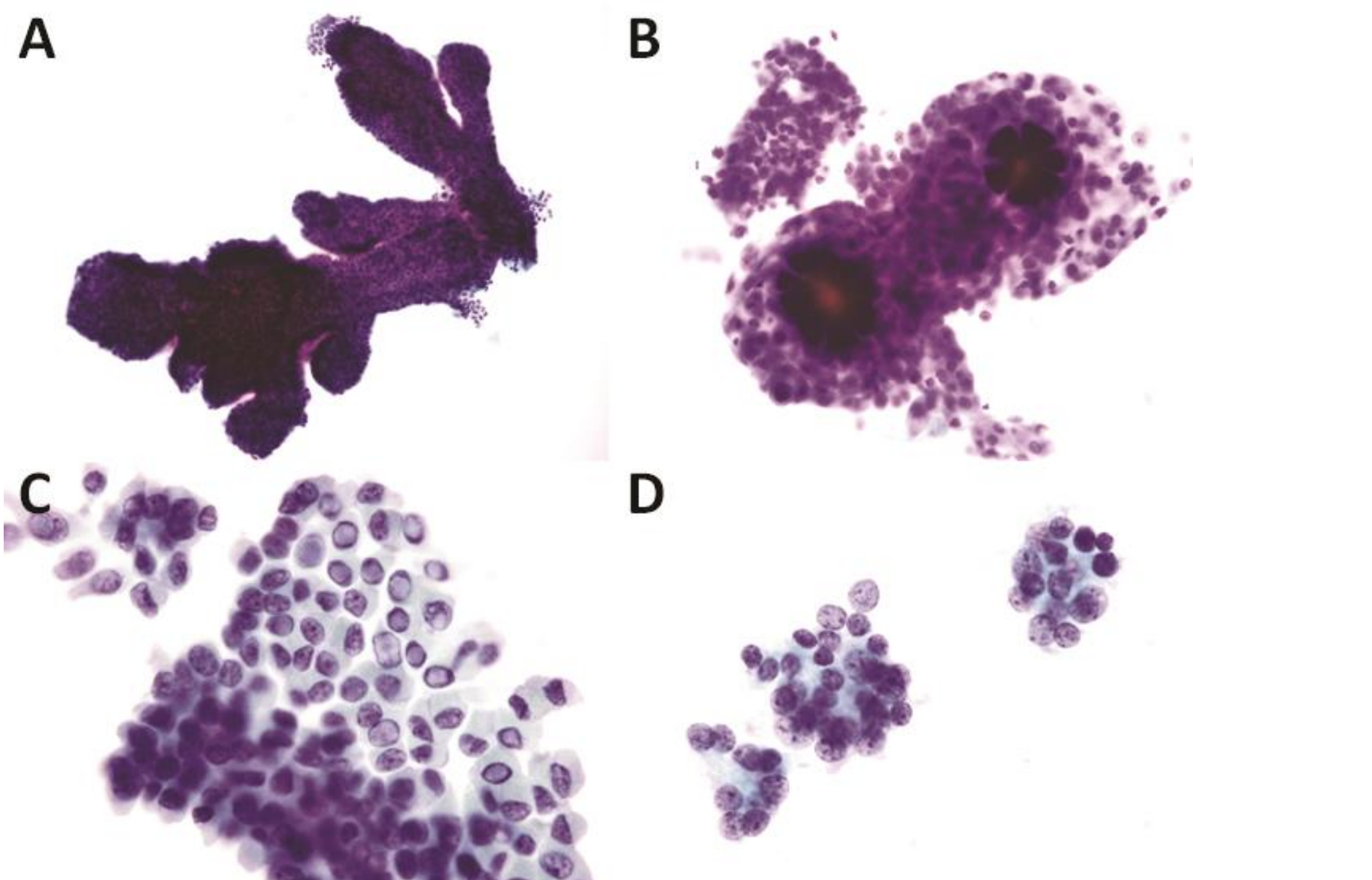
## Preoperative Cytologic Diagnosis of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: A Prospective Analysis

Kyle C. Strickland,[1] Marina Vivero,[1] Vickie Y. Jo,[1] Alarice Lowe,[1] Monica Hollowell,[1] Xiaohua Qian,[1] Tad Wieczorek,[1] Christopher A. French,[1] Lisa A. Teot,[1] Peter M. Sadow,[2] Erik K. Alexander,[3] Edmund S. Cibas,[1] Justine A. Barletta,[1,*] and Jeffrey F. Krane[1,*]

THYROID
Volume 26, Number X, 2016

Thyroid FNAs were evaluated from June 1, 2015 to January 15, 2016. All members of the cytology department participated in this study.

Each completed a questionnaire for nodules with a diagnosis of MALIGNANT or SUSPICIOUS at the time of initial evaluation (before the date of surgery).


A
B
C
D

# Prospective questionnaire

Morphologic Characteristics

Papillae – Present or Absent
Pseudoinclusions – Present or Absent
If present, frequent (3 or more) or rare (1-2)
Psammomatous Calcifications – Present or Absent
Microfollicle Predominance – Present or Absent

Cytopathologist's Assessment of PTC Type

Classic/Tall Cell – based on the presence of papillae, pseudoinclusions, or psammomatous calcifications

FVPTC/NIFTP – Based on microfollicle predominance without papillae, pseudoinclusions or psammomatous calcifications.

Indeterminate – Based on sheet predominance without papillae, pseudoinclusions or psammomatous calcifications.

# NIFTP can be distinguished from classical PTC

Excluding 7 indeterminate cases (12% of cohort).

| Cytologist Favored: | Surgical Pathology | #/total | % |
|---|---|---|---|
| Classical PTC | Classical PTC | 38/40 | 95% |
| FVPTC/NIFTP | Follicular-patterned tumor | 8/9 | 89% |
| Overall Agreement | | 46/49 | 94% |

Only 1/39 (2.6%) MALIGNANT cases favored to be classical PTC proved to be NIFTP.

Strickland et al *Thyroid* (2016)

# Take Home Point #3

Classical PTC features distinguish most from NIFTP

## Coming to Terms With NIFTP: A Provisional Approach for Cytologists

Jeffrey F. Krane, MD, PhD[1]; Erik K. Alexander, MD[2]; Edmund S. Cibas, MD[1]; and Justine A. Barletta, MD[1]

*Cancer Cytopathol* (2016)

- Minimize the classification of potential NIFTP cases as Malignant by limiting use to cases with features of classical PTC (true papillae, psammoma bodies, frequent nuclear pseudoinclusions)

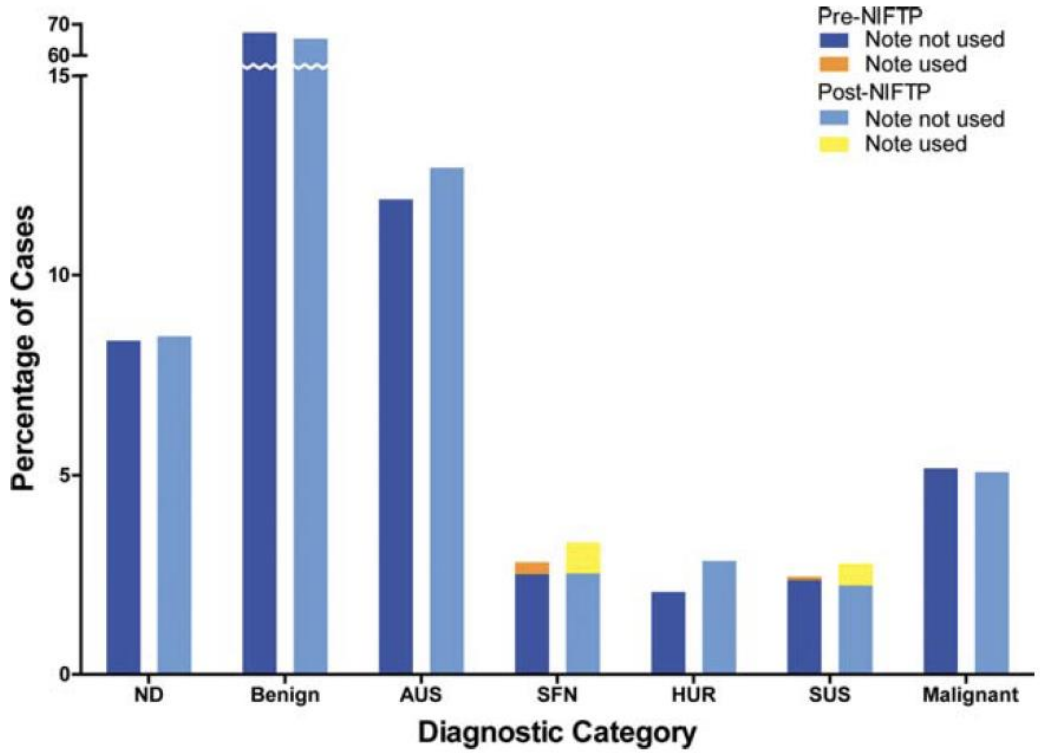
- Use descriptive notes to suggest NIFTP for indeterminate aspirates (esp. SUS) to encourage more conservative clinical management

# A Modified Reporting Approach for Thyroid FNA in the NIFTP Era: A 1-Year Institutional Experience

Jeffrey K. Mito, MD, PhD[1]; Erik K. Alexander, MD[2]; Trevor E. Angell, MD[2]; Justine A. Barletta, MD[1]; Matthew A. Nehs, MD[3]; Edmund S. Cibas, MD [1]; and Jeffrey F. Krane, MD, PhD [1]

*Cancer Cytopathol* (2017)

- Compared laboratory data (N=1300) for 1 year period after introducing policy to control time period



# Prospective NIFTP recognition

- NIFTP was rarely suspected: 17/1300 (1.3%)
- Prospectively suspected NIFTP often wrong
  - Only 6/12 (50%) confirmed
- Most NIFTP not suspected prospectively
  - Only 6/29 (21%) NIFTP suspected prospectively
- NIFTP note had desired effect on surgical management
  - –SUS with note more likely to have lobectomy
  - –5/7 (71%) vs 3/16 (19%) [P=0.02]

Mito et al *Cancer Cytopathol* (2017)

# Take Home Point #4

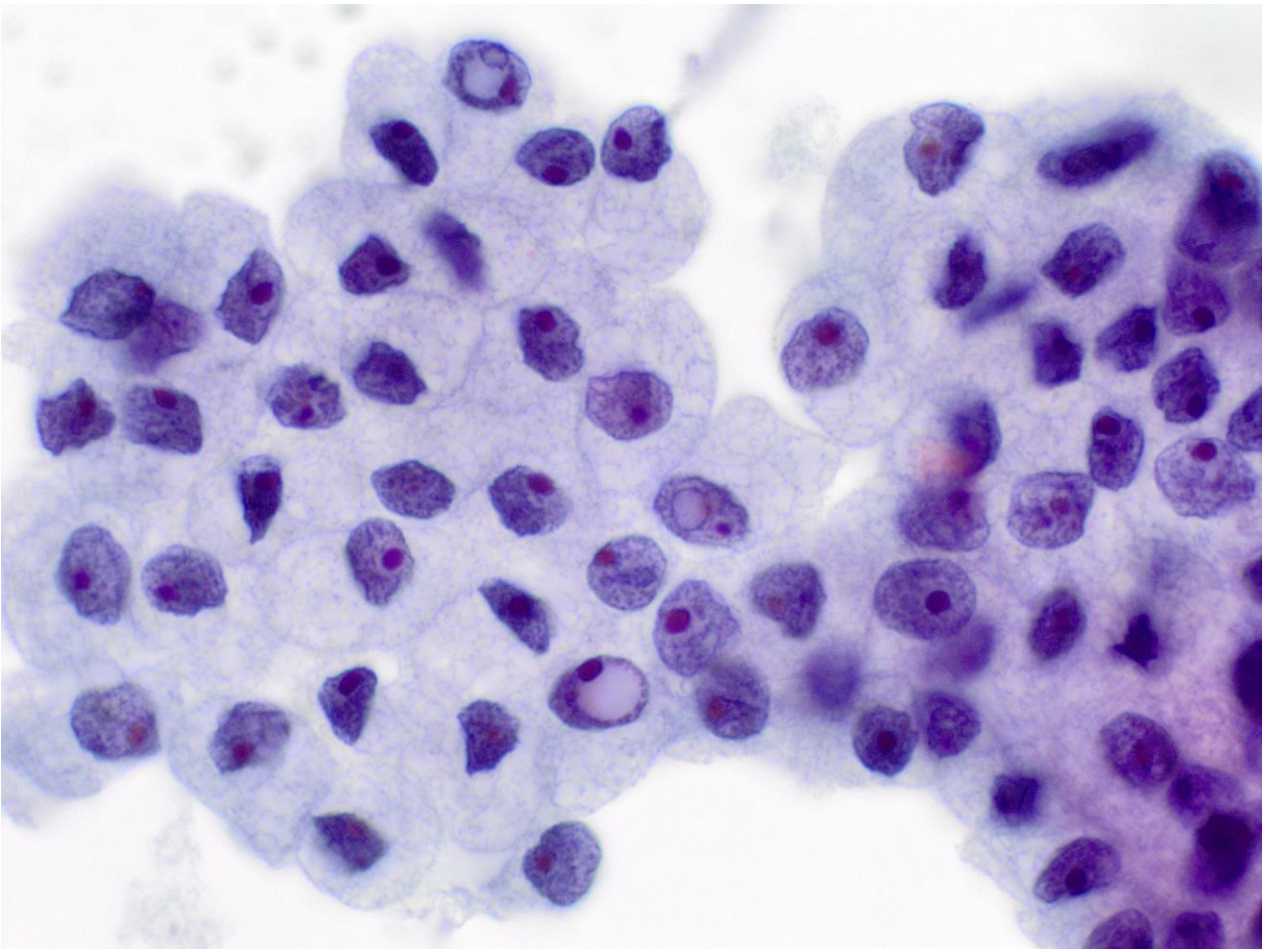
Despite our concerns, NIFTP is relatively uncommon on FNA

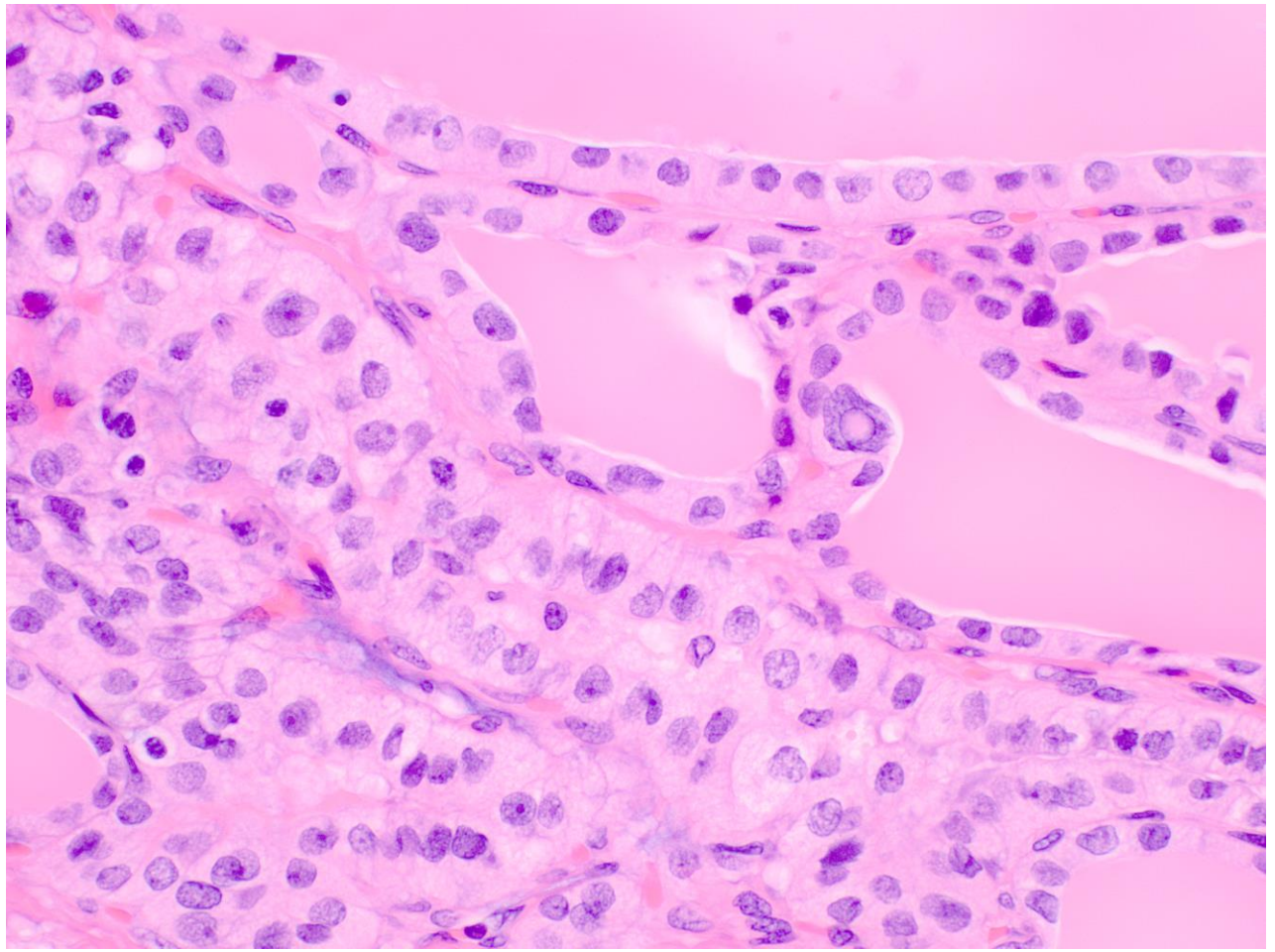
# Take Home Point #5

Descriptive notes help promote conservative surgical management

# NIFTP and Malignant category

- 4/60 (6.7%) before, 1/42 (2.4%) after





Mito et al *Cancer Cytopathol* (2017)

# Bethesda System for Reporting Thyroid Cytopathology?

# Impact of NIFTP on TBSRTC v2

- ROM
- Descriptive notes
- Altered criteria for SFN/FN and Malignant categories

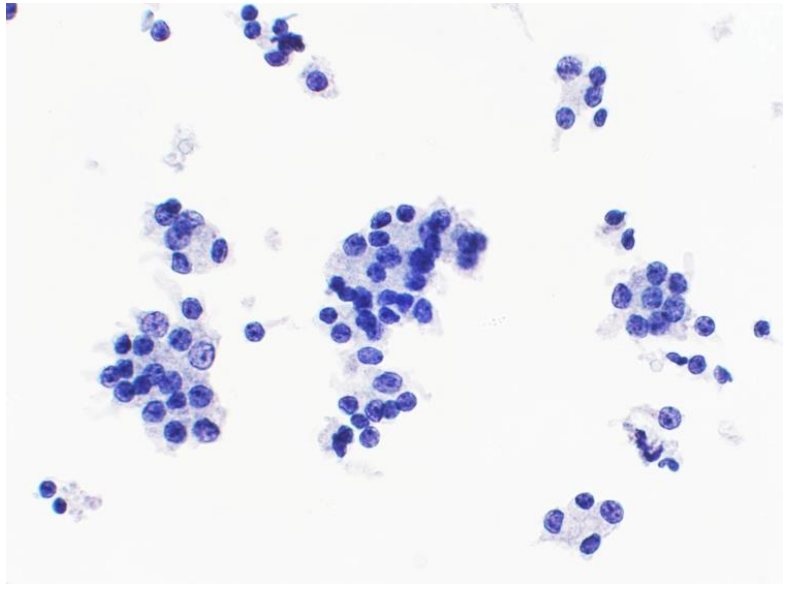
# The revised Bethesda System

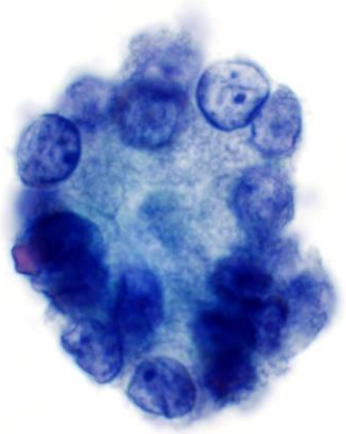
| Diagnostic Category | Risk of Malignancy (%) | Risk of Malignancy if NIFTP ≠ CA (%) |
|---|---|---|
| I. ND/UNSAT | 5-10 | no change |
| II. Benign | 0-3 | no change |
| | | |
| III. AUS/FLUS | ~10-30 | 6-18 |
| IV. FN/SFN | 25-40 | 10-40 |
| V. Suspicious for Malignancy | 50-75 | 45-60 |
| VI. Malignant | 97-99 | 94-96 |

Adapted from Ali and Cibas, *TBSRTC*, 2017

# Suspicious for a Follicular Neoplasm
## *What's New with the 2nd Edition?*

1. ***Definition:*** ***"…***Follicular-patterned cases with mild nuclear changes (increased nuclear size, nuclear contour irregularity, and/or chromatin clearing) can be classified as FN/SFN so long as true papillae and intranuclear pseudoinclusions are absent; a note that some nuclear features raise the possibility of a FVPTC or NIFTP can be included"





# NIFTP descriptive notes

## *What's New with the 2nd Edition?*

### *FN/SFN*

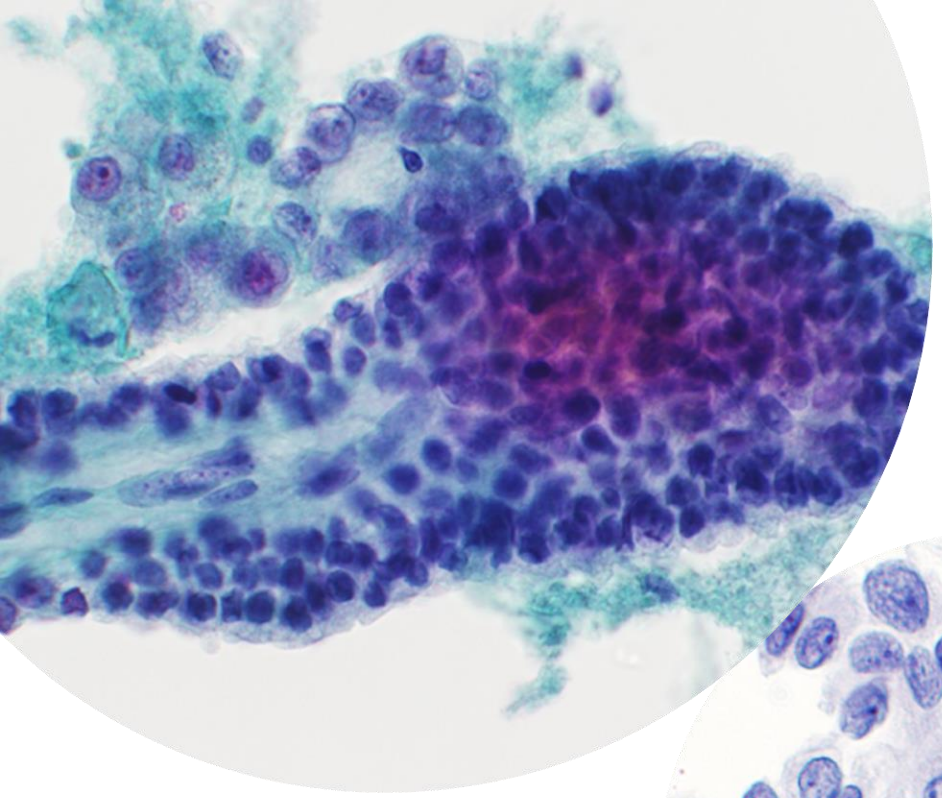
NOTE: The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma, including its recently described indolent counterpart NIFTP.

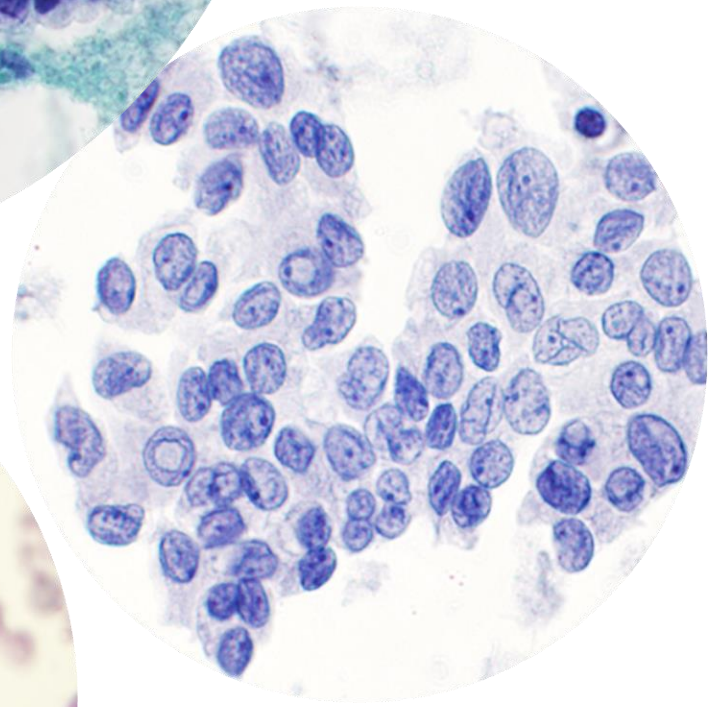
### *SUS*

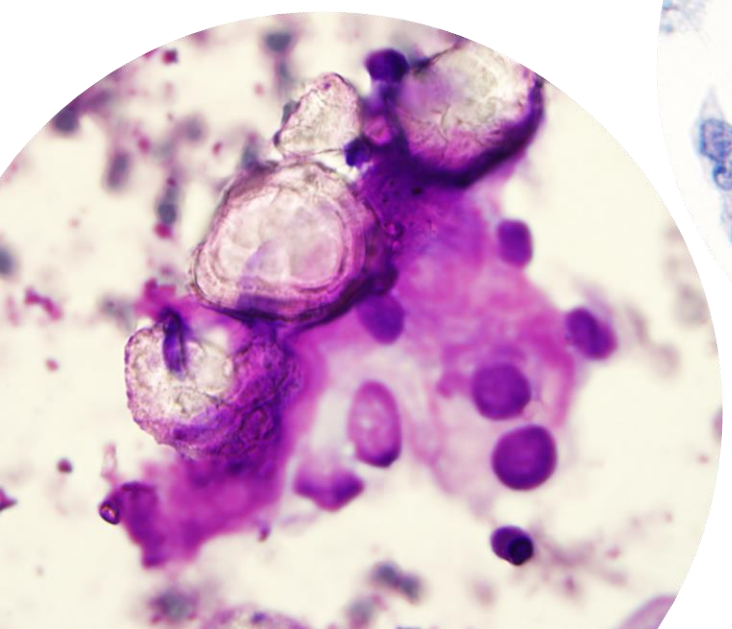
NOTE: The cytomorphologic features are suspicious for a follicular variant of papillary thyroid carcinoma or its recently described indolent counterpart NIFTP.

### *MALIGNANT*

NOTE: A small proportion of cases (~3-4%) diagnosed as malignant and compatible with papillary thyroid carcinoma may prove to be NIFTP on histopathologic examination.







# Malignant
## *What's New with the 2nd Edition?*

- To avoid false-positives due to NIFTP, limit use to cases with features of classic PTC (true papillae, psammoma bodies, frequent nuclear pseudoinclusions).

# Conclusions

- The updated Bethesda system has incremental rather than radical changes
- Main changes in TBSRTC are:
  - Altered ROM
  - Altered management
  - Refinements for AUS/FLUS
  - Refined diagnostic criteria for FN/SFN and Malignant to accommodate NIFTP
  - NIFTP notes

# Conclusions

- NIFTP is challenging on cytology, but belongs in the “gray zone”
- NIFTP cannot be reliably distinguished from other follicular patterned lesions
- Classical PTC features distinguish most from NIFTP
- Not possible to recognize NIFTP definitively prospectively
  - Worth trying to identify potential NIFTP in order to encourage conservative surgical management

# Acknowledgements


- Thanks to Drs. Justine Barletta and Edmund Cibas, BWH