

Thyroid Cytopathology- Recent Advances and Update of The Bethesda System

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Bédard Lectureship
October 21, 2017



Dr. Yvan C. Bédard
1942-2006

CME Faculty Disclosure

- Dr. M. Auger has no affiliation with the manufacturer of any commercial product or provider of any commercial service discussed in this CME activity



Objectives: Upon completion of this lecture, participants will be able to:

- Discuss the key modifications of The Bethesda System for Reporting Thyroid Cytopathology 2018 (TBSRTC II)
- Describe the cytological features and their associated pitfalls of follicular neoplasms, noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) and invasive follicular variant of papillary thyroid carcinomas (FVPTC)
- Recognize the cytological features of papillary thyroid carcinoma and its variants
- List and discuss the most common molecular abnormalities encountered in thyroid neoplasms

Outline

- Key changes of TBSRTC II
 - AUS
 - NIFTP and implications for Risk of Malignancy (ROM) for each diagnostic category
 - PTC and variants
- Key highlights of 2015 American Thyroid Association (ATA) guidelines for management for adult patients with thyroid nodules and differentiated thyroid cancer
- Molecular aspects of thyroid neoplasms

The 2015 ATA Guidelines

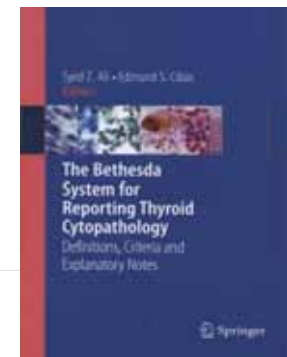
- An update from the 2009 version
- Endorse the use of TBSRTC
- Provide recommendations for the management of thyroid nodules
 - concept of low-risk vs high-risk disease, and
 - increased role of conservative management
 - through the application of molecular testing, clinico-radiologic risk stratification and a multidisciplinary team approach

2015 ATA Guidelines- Recommendations for FNA

- Aim to reduce unnecessary FNA for many nodules likely to be benign
- US interpretation should categorize each nodule as high, intermediate, low, or very low risk
- FNA, usually performed with US-guidance, is recommended
 - For high-risk US features nodules > 1 cm
 - For intermediate-risk US features nodules > 1 cm
 - For low-risk US features nodules 1.5 cm
 - For very low-risk US features nodules 2 cm
 - Purely cystic nodules not recommended

TBSRTC

- 2007: TBSRTC proposed at NCI Thyroid FNA state of the Art and Science conference in Bethesda
 - main aim
 - to address the inconsistent reporting terminologies used throughout the world
- 2010: 1st edition of atlas
 - Has found widespread international acceptance
 - Has contributed significantly to the management of thyroid nodules by
 - Increasing the quality and reproducibility of thyroid cytology reporting



1st edition, 2010

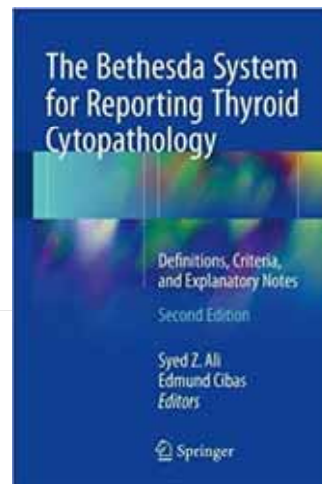
TBSRTC II (2nd edition: 2018)

- Since publication, considerable experience has been gained regarding its
 - Application to cytology practice
 - Clinical impact, and
 - Limitations
- TBSRTC II initiated by the creation, in conjunction with IAC, of an international panel to
 - Analyze the current worldwide impact of TBSTRC
 - Report on the current state of TBSRTC based on a review of published literature
 - Provide recommendations for a future update



TBSRTC II

- Publication
 - ebook: Sept 2017
 - Printed: Nov 2017
- Overall, only minor changes made
 - will be easy to adapt to
- Chapters expanded
 - Refined definitions and explanatory notes
 - More images for
 - Liquid-based cytology
 - Differential diagnoses



TBS classification in TBSRTC II

- No real change in main terminology
 - Although the use of only one term for each diagnostic category was favored by some, synonyms were kept as acceptable because already well established and accepted by clinicians and cytopathologists from the 1st edition
- However, best to use only one term for each category at a given institution
 - Main goal: clear communication between the various members of the health care team
- Some optional changes in sub-classification
 - AUS

TBSRTC II- Diagnostic Categories

- I. Non-diagnostic (or *Unsatisfactory*)
- II. Benign
- III. Atypia of Undetermined Significance (or *Follicular Lesion of Undetermined Significance*)
- IV. Follicular neoplasm (or *suspicious for follicular neoplasm*)
 - specify if Hürthle cell (oncocytic) type
- V. Suspicious for Malignancy
- VI. Malignant

TBSRTC II-

Implied Risk of Malignancy (ROM)

- Adjustments made based upon a selected group of studies that include large cohorts of cases or meta-analyses
- Changes relate mostly to
 - Depending on which denominator is used
 - All cases with clinical or surgical follow-up probably underestimating ROM
 - vs
 - Only cases with surgical follow-up introducing selection bias and overestimating ROM
 - Values listed in TBSRTC II are educated extrapolations based on above
 - Impact of NIFTP

DIAGNOSTIC CATEGORIES

ROM TBSRTC I

ROM TBSRTC II

I. Non-diagnostic
(or Unsatisfactory)

1-4%

5-10%

II. Benign

0-3%

0-3%

III. Atypia (or *Follicular Lesion*) of
Undetermined Significance (AUS)

5-15%

10-30%

IV. Follicular Neoplasm
(or *suspicious for follicular
neoplasm*)

15-30%

25-40%

-specify if oncocytic (Hürthle cell) type

V. Suspicious for Malignancy

60-75%

50-75%

VI. Malignant

97-99%

97-99%

Impact of NIFTP on TBSRTC II

- NIFTP: Formerly referred to as
 - “encapsulated/non-invasive follicular variant of papillary thyroid carcinoma”
 - A term replacing a subset of FVPTC which used to be classified as malignant but have indolent behavior
 - Should be considered “benign” and therefore should be excluded from ROM calculations
- The majority of NIFTP cases are sequestered within the indeterminate categories (AUS, FN, SM)
 - leading to a significant impact on the ROM (i.e. ↓ROM)

Can NIFTP be distinguished from classic papillary thyroid carcinoma and follicular adenoma by FNA?

Brandler TC, et al. Cancer Cytopathol 2017; 125:378-388

- Study included 56 NIFTP, 67 classic PTC and 30 follicular adenomas
- The pre-op cytologic DX of NIFTP
 - AUS 35%
 - FN 26.8%
 - SM 17.9%
 - Benign 10.7%
 - Malignant 7.1%

Impact of reclassifying NIFTP on the risk of malignancy in TBSRTC

Faquin WC, et al. Cancer Cytopathol 2016;124:181-7

- Multi-institutional study
 - N=6943 thyroid FNAs
- Conclusions: The impact of re-classifying NIFTP on the ROM and overall ROM (oROM) was most pronounced and statistically significant in the 3 indeterminate categories
 - AUS decreased by 5.2-13.6%
 - FN decreased by 9.9-15.1%
 - SM decreased by 17.6-23.4%

DIAGNOSTIC CATEGORIES	ROM TBSRTC II	ROM TBSRTC II (<i>excluding NIFTP</i>)
I. Non-diagnostic (or Unsatisfactory)	5-10%	No change
II. Benign	0-3%	No change
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	6-18%
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	10-40%
V. Suspicious for Malignancy	50-75%	45-60%
VI. Malignant	97-99%	94-96%

DIAGNOSTIC CATEGORIES	ROM TBSRTC II	Management
I. Non-diagnostic (or Unsatisfactory)	5-10%	Repeat FNA with US guidance
II. Benign	0-3%	Clinical and US Follow-up
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	Repeat FNA, molecular testing or lobectomy
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	Molecular testing, lobectomy
V. Suspicious for Malignancy	50-75%	Near-total thyroidectomy or lobectomy
VI. Malignant	97-99%	Near-total thyroidectomy or lobectomy

Adapted from TBSRTC II atlas, Table 1.2

I. Non-diagnostic (or unsatisfactory)

- FNA is diagnosed as such if it fails to meet the adequacy criteria
- Frequency: 3-34% depending on institution
- Should be sub-categorized as
 - Cyst fluid only
 - Virtually acellular
 - Other
 - obscuring blood
 - clotting artefact
 - air-drying artefact
 - other

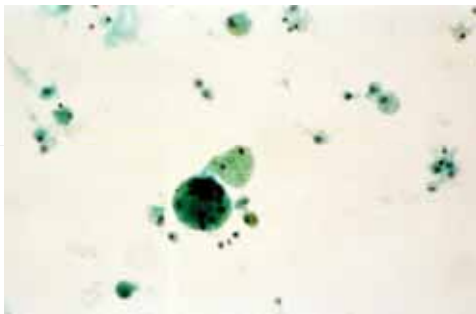
Adequate (satisfactory) sampling of solid and cystic lesions

- Criteria unchanged from TBSRTC 1
- A minimum of 6 groups of well-visualized follicular cells, with at least 10 cells per group, preferably on a single slide



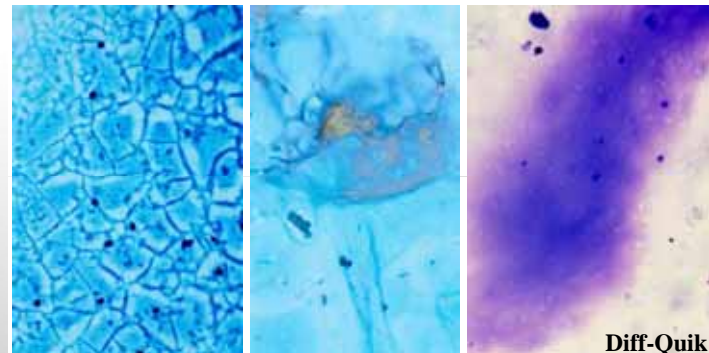
Non-Diagnostic: Cyst Fluid Only

- Cystic specimens containing macrophages only (or macrophages with <6 groups of follicular cells) should be diagnosed as
 - "Non-Diagnostic: "Cyst Fluid Only"



Exceptions to the Adequacy Requirements

- Unchanged from TBSRTC 1
- I. FNA containing abundant thick colloid (ie. slide full of colloid) and little else



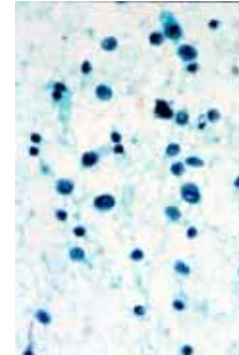
Diff-Quik

Why exception for FNA containing abundant colloid and little else?

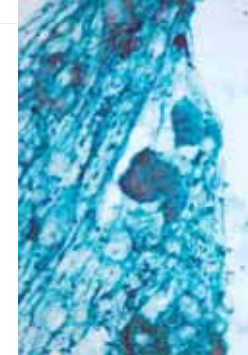
- Because such FNAs most likely represent colloid nodules and carry an insignificant risk of malignancy, they can be included in the benign category as being
 - “Benign Follicular Nodule: suggestive of colloid nodule”

Exceptions to the Adequacy Requirements

- II. Sample with inflammation:
 - lymphocytic/granulomatous or acute= Benign



Lymphocytic thyroiditis



Granulomatous thyroiditis

Exceptions to the Adequacy Requirements

- III. Any specimen with any atypical features, even if not meeting adequacy criteria, cannot be called Non-Diagnostic (ND) (or unsatisfactory)
 - should be placed in AUS category

DIAGNOSTIC CATEGORIES	ROM TBSRTC II	Management
I. Non-diagnostic (or Unsatisfactory)	5-10%	Repeat FNA with US guidance
II. Benign	0-3%	Clinical and US Follow-up
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	Repeat FNA, molecular testing or lobectomy
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	Molecular testing, lobectomy
V. Suspicious for Malignancy	50-75%	Near-total thyroidectomy or lobectomy
VI. Malignant	97-99%	Near-total thyroidectomy or lobectomy

Adapted from TBSRTC II atlas, Table 1.2

Non-Diagnostic and 2015 ATA Management Guidelines

- As before, FNA should be repeated (unless purely cystic) with US-guided FNA being strongly favored
 - and, if available, ROSE
- While originally recommended to wait >3 months to perform a repeat FNA, evidence support shorter intervals for repeating an FNA after a ND result
 - No real evidence of more atypical results if repeated <3 months

TBSRTC II-Benign

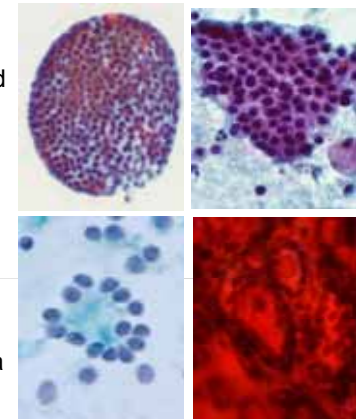
- Accounts for 60-70% of all thyroid FNAs
- No real changes from TBSRTC I
- Prefer to use “Benign” over “Negative for malignancy” or “Non-neoplastic”
- Continue to subtype
 - Benign follicular nodule (most common scenario)
 - Lymphocytic thyroiditis
 - Granulomatous thyroiditis
 - Other
 - IgG4 thyroiditis
 - Acute thyroiditis/abscess
 - Other

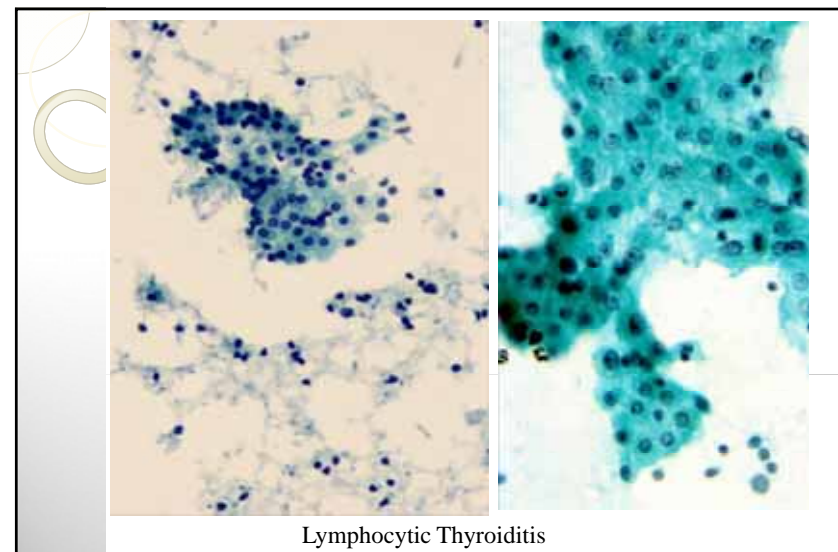
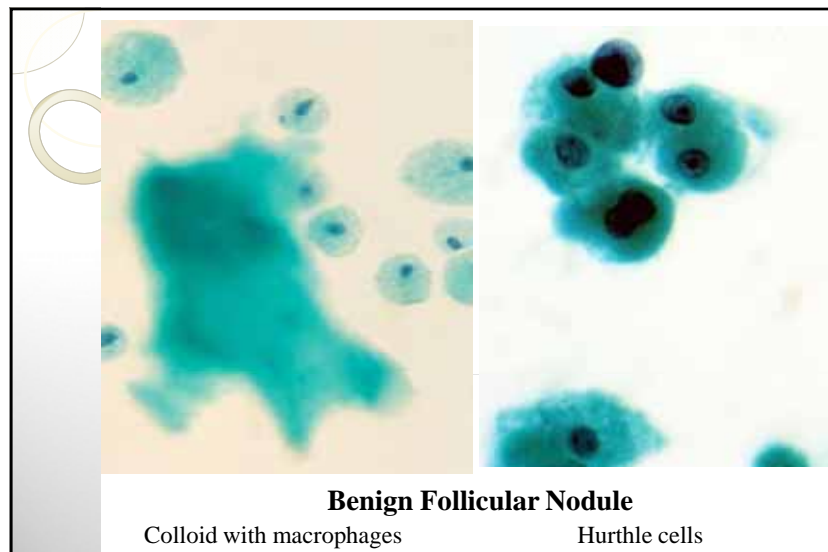
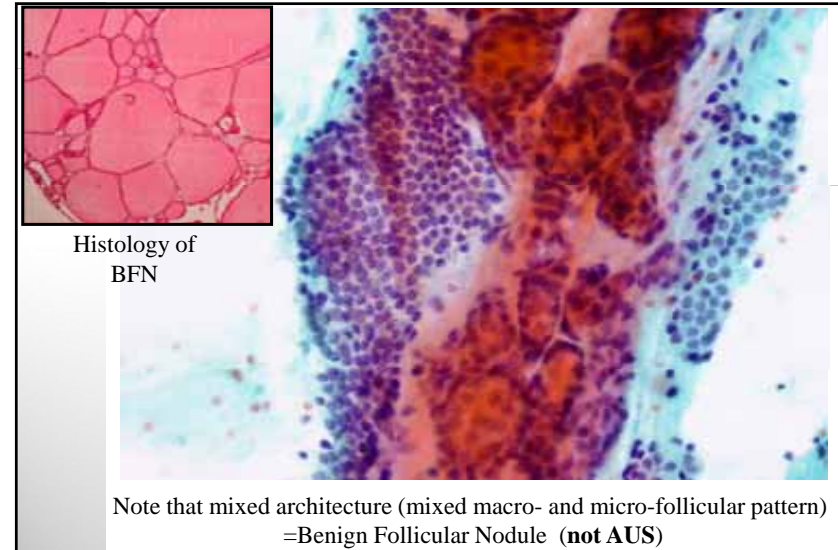
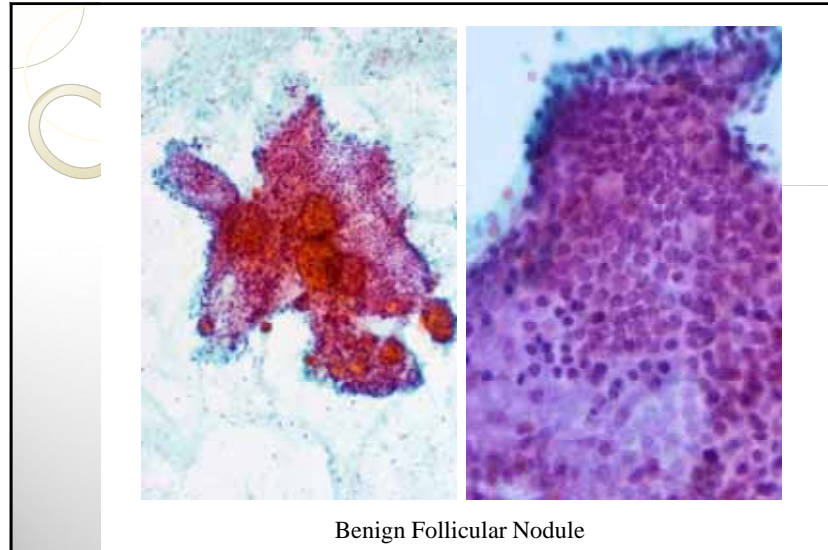
TBSRTC II-Benign Follicular Nodule

- Includes lesions that translate histologically as
 - Nodular hyperplasia in nodular goiter
 - Hyperplastic (adenomatoid) nodule
 - Colloid nodule
 - Nodules in Graves' disease
 - Follicular adenoma (uncommon):
 - macrofollicular (or normo-follicular) type
- Characterized cytologically by variable amounts of
 - Benign-appearing follicular cells
 - Mostly macrofollicles, but may contain some microfollicles
 - Colloid
 - Oncocytic (Hürthle) cells
 - Macrophages

Definitions

- Macrofollicles
 - larger than normal follicles; i.e. larger spheres composed of >15 follicular cells which are evenly spaced
 - When collapsed, are in flat honeycomb
- Microfollicles
 - 6 to 15 follicular cells arranged in a circular formation, occasionally with a central blob of colloid





DIAGNOSTIC CATEGORIES	ROM TBSRTC II	Management
I. Non-diagnostic (or Unsatisfactory)	5-10%	Repeat FNA with US guidance
II. Benign	0-3%	Clinical and US Follow-up
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	Repeat FNA, molecular testing or lobectomy
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	Molecular testing, lobectomy
V. Suspicious for Malignancy	50-75%	Near-total thyroidectomy or lobectomy
VI. Malignant	97-99%	Near-total thyroidectomy or lobectomy

Adapted from TBSRTC II atlas, Table 1.2

2015 ATA Management Recommendations for Benign FNAs

- Follow-up should be determined by risk stratification based on ultrasound (US) patterns
- Nodules with high suspicion US pattern
 - Repeat US and US-guided FNA within 12 months
- Nodules with low to intermediate suspicion US pattern
 - Repeat US at 12-24 months +/- FNA
 - or observation, depending on growth or US features
- Nodules with very low suspicion US pattern
 - Utility of surveillance US is limited
 - If US is repeated, it should be done >24 months

TBSRTC II-AUS/FLUS

- Should be reserved for specimens that contain cells with architectural and/or nuclear atypia that is insufficient for an interpretation of FN or SM or M
 - And the atypia is more marked than what can be ascribed confidently to "benign" changes
- Only one term, either AUS or FLUS, should be selected by a laboratory because they are synonymous
 - FLUS should not be used as a sub-classifier for AUS
 - Although the term "AUS" is preferred, FLUS is acceptable for the majority of cases in which the atypia is of follicular cell origin

TBSRTC II-AUS/FLUS

- Heterogeneous group with many scenarios
- Subclassification is encouraged
 - Particularly with respect to the presence or absence of nuclear (cytologic) atypia because
 - AUS with cytologic (nuclear) atypia have ROM 2X higher than AUS with architectural atypia
 - Hurthle cell atypia has a lower ROM than other AUS patterns
 - Enhance communication with other pathologists and clinicians, and
 - To facilitate further refinement of the category as new information becomes available and new entities (like NIFTP) are defined

TBSRTC II- AUS/FLUS Subclassification

- Different terms may be considered for AUS/FLUS subqualifiers
- Potential approach
 - To subclassify according to the most likely diagnosis
 - “Rule out papillary carcinoma”
 - “Rule out follicular neoplasm” or “Rule out Hurthle cell neoplasm”
 - This approach is not favoured because there is potential for confusion with the SUS, FN/SFN, or FNHCT/SFNHCT categories, with associated overtreatment
- Alternate favoured approach
 - To subclassify with descriptive language
 - eg. “cytologic atypia” rather than “rule out papillary carcinoma”
 - Such descriptive language is preferred due to its less provoking nature for clinicians and patients

TBSRTC II-AUS/FLUS

- 1. Cytologic atypia
 - a. Focal cytologic atypia
 - b. Extensive but mild cytologic atypia
 - c. Atypical cyst-lining cells
 - d. “Histiocytoid” cells
- 2. Architectural atypia
 - a. A scanty cellular specimen with rare clusters of follicular cells, almost entirely in microfollicles or crowded three dimensional groups and with scant colloid
 - b. Focally prominent microfollicles with minimal nuclear atypia
- 3. Cytologic and architectural atypia
- 4. Hürthle cell aspirates
- 5. Atypia, not otherwise specified (NOS)
- 6. Atypical lymphoid cells, rule out lymphoma

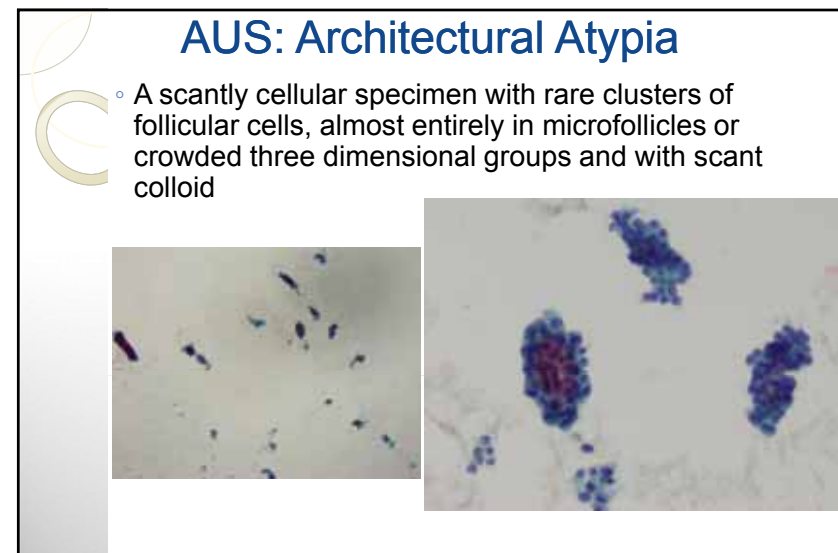
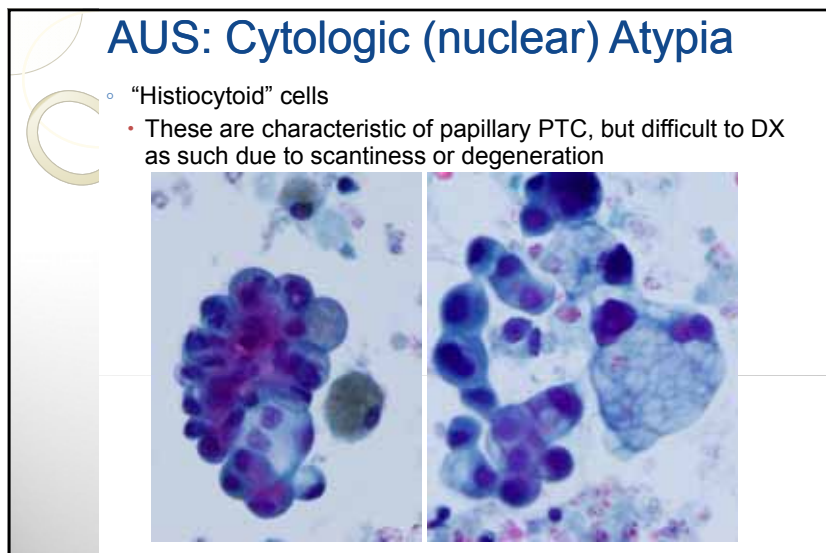
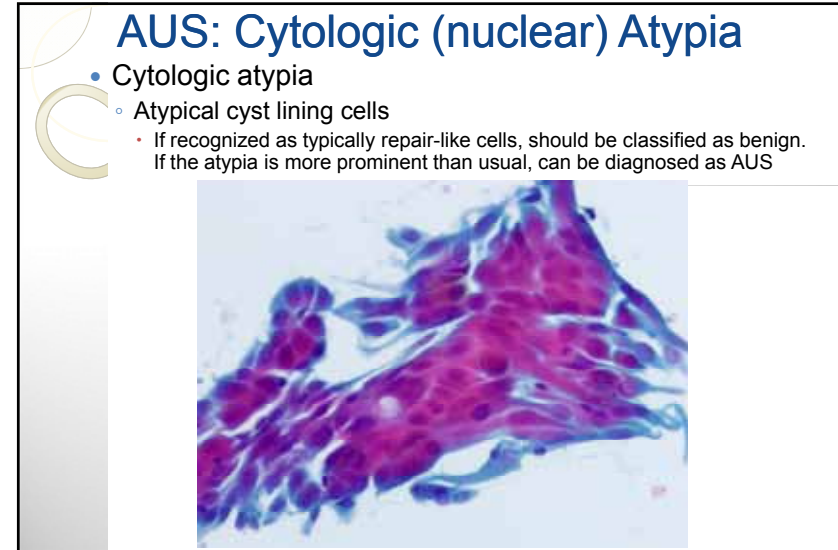
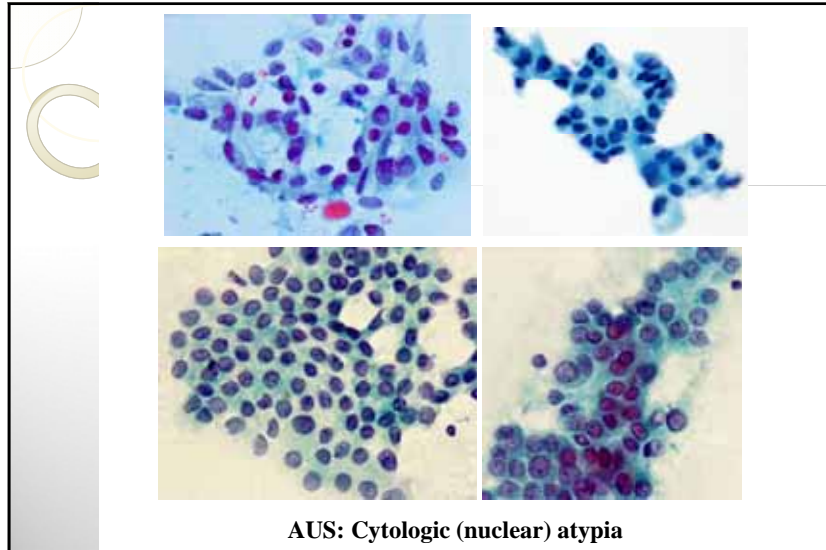
TBSRTC II-AUS/FLUS

Simplified approach to the many scenarios

- Cytologic (nuclear) atypia
 - Makes you think of “Cannot rule out PTC”
 - So usually when focal or subtle nuclear features of PTC
 - but insufficient to reach “suspicious for PTC”
- Architectural atypia
 - Makes you think of “Cannot rule out Follicular Neoplasm”
 - Microfollicles present diffusely in a scanty specimen
- Cytologic and architectural atypia
 - A mixture of above
- Hürthle cell aspirates
 - Makes you think of “Cannot rule out Hurthle cell Neoplasm”
 - Microfollicles present diffusely in a scanty specimen
 - Pure Hurthle cell population in a scanty specimen

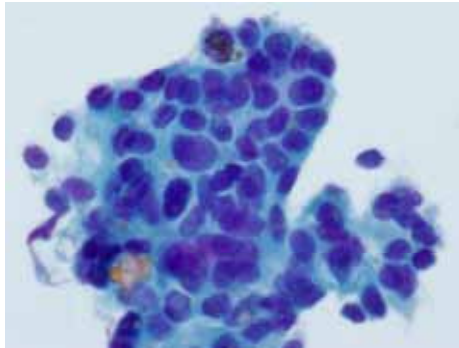
TBSRTC II-AUS/FLUS

- Cytologic (nuclear) atypia (a.k.a. Rule out PTC)
 - Focal cytologic atypia
 - Most of the FNA appears benign, but rare cells have nuclear enlargement, pale chromatin and irregular contours
 - Nuclear pseudoinclusions typically absent
 - eg. Lymphocytic thyroiditis
 - eg. Paucicellular but containing cells as above
 - Extensive but mild cytologic atypia
 - Many if not most cells have mildly enlarged nuclei with slightly pale chromatin and only limited nuclear contour irregularity
 - Nuclear pseudoinclusions typically absent

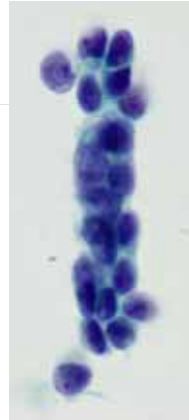


TBSRTC II-AUS/FLUS

3. Cytologic and architectural atypia



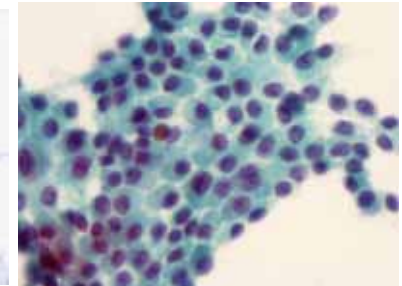
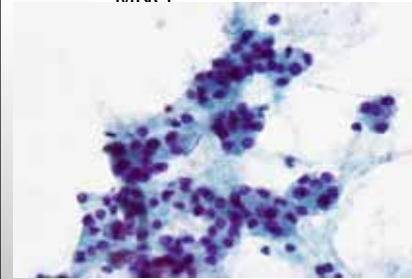
Note: The presence of both mild cytologic and architectural atypia may be more common with NIFTP, but this has not been firmly established



TBSRTC II-AUS/FLUS

Hürthle cell aspirates

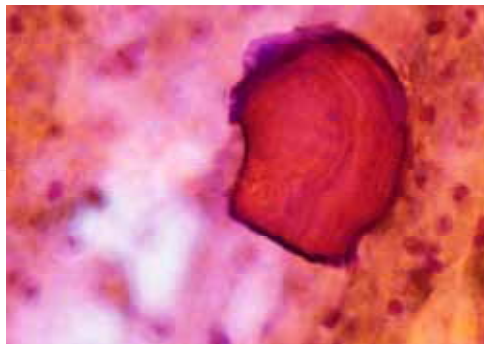
- A sparsely cellular aspirate comprised exclusively (or almost exclusively) of Hurthle cells with minimal atypia, or
- A moderately or markedly cellular sample composed exclusively of Hurthle cells, yet the clinical setting suggests a benign Hurthle cell nodule, such as in lymphocytic thyroiditis or MNG



TBSRTC II-AUS/FLUS

Atypia, not otherwise specified (NOS)

- A minor population of follicular cells shows nuclear enlargement, often with nucleoli, or
- Psammoma body in the absence of nuclear features of PTC



AUS

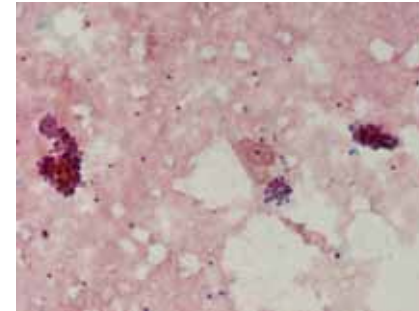
- Overall poor interobserver variability
 - Overlap with FN and ND categories depending on institutions
- AUS is an interpretation of last resort and should be used judiciously
- Should represent <10% of all thyroid FNAs
 - As compared to <7% in original TBSRTC

Tips to limit use of AUS

- Compromising factors such as sparse cellularity, air-drying artefact, obscuring blood do not warrant an AUS/FLUS Dx
 - such specimens should be called Non-Dx/unsatisfactory if adequacy criteria are not satisfied and there is no atypia
 - Only if atypia present= AUS
- Mixed architectural pattern (i.e. admixture of macro- and microfollicular pattern) should be called “Benign” rather than AUS
 - Unless microfollicles are present in a different slide from the ones with macrofollicles (or microfollicles are very prominent)
- The co-presence of follicular (non-Hurthle) cells and Hurthle cells in a same sample strongly favours “Benign” rather than AUS
- Make sure that you are not overcalling lymphocytic thyroiditis because it is often a cause of “false-positive DX”

Tips to limit use of AUS

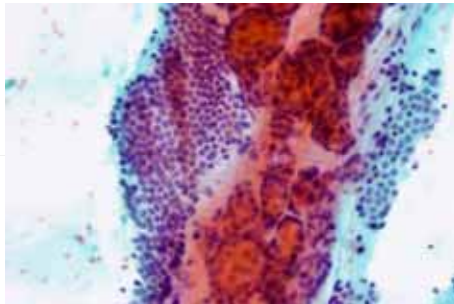
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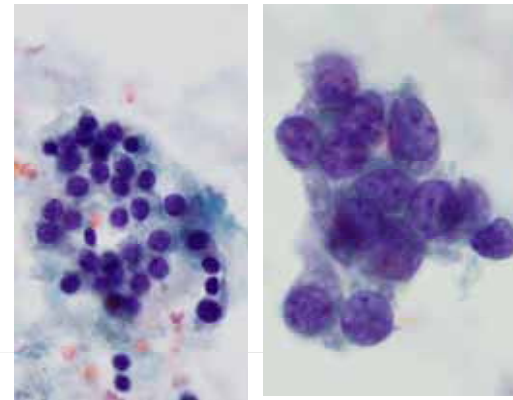
Suggested Dx=Non-Diagnostic

Tips to limit use of AUS

- Mixed architectural pattern (i.e. admixture of macro- and microfollicular pattern) should be called “Benign” rather than AUS
 - Unless microfollicles are present in a different slide from the ones with macrofollicles (or microfollicles are very prominent)



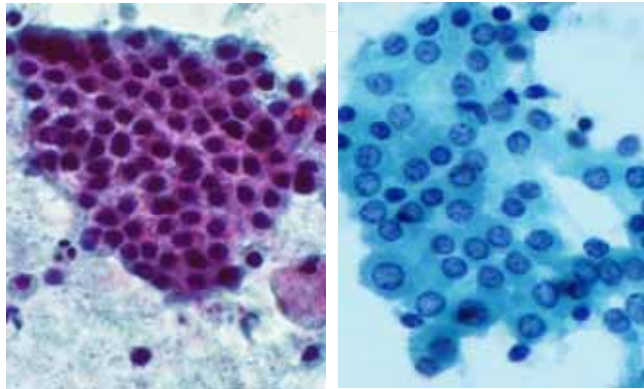
Dx= Benign Follicular Nodule



These fragments should not be considered microfollicles
 ◦ they are simply small flat sheets, so “give them the benefit of the doubt”, esp. when focal and with minimal overlapping

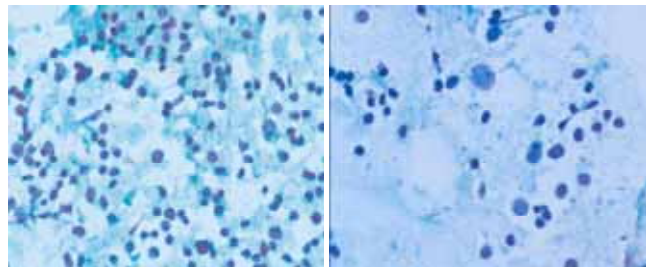
Tips to limit use of AUS

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Tips to limit use of AUS

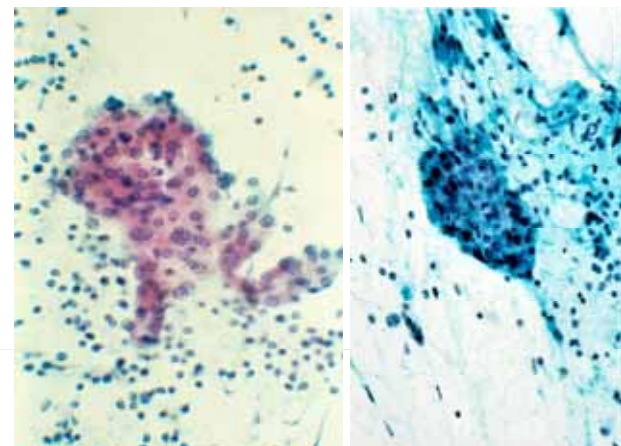
- Make sure that you are not overcalling lymphocytic thyroiditis (LT) because it is often a cause of "false-positive DX"
 - Look for polymorphous lymphoid population
 - Rule out lymphocytes from blood contamination
 - Rule out dyshesive follicular cells mimicking lymphocytes
 - If LT, adopt a higher threshold before considering AUS because known to often cause
 - "Hurthle cell atypia"
 - Nuclear clearing
 - Disorganization of cell groupings
 - Can show focal loss of honeycomb arrangement



Polymorphous lymphoid population in LT



Dyshesive follicular cells in hyperplastic follicular nodule



Left: Some Hurthle cell "atypia"; Right: Some loss of honeycomb
Dx for both: Benign, lymphocytic thyroiditis (not AUS)

DIAGNOSTIC CATEGORIES	ROM TBSRTC II	Management
I. Non-diagnostic (or Unsatisfactory)	5-10%	Repeat FNA with US guidance
II. Benign	0-3%	Clinical and US Follow-up
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	Repeat FNA, molecular testing or lobectomy
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	Molecular testing, lobectomy
V. Suspicious for Malignancy	50-75%	Near-total thyroidectomy or lobectomy
VI. Malignant	97-99%	Near-total thyroidectomy or lobectomy

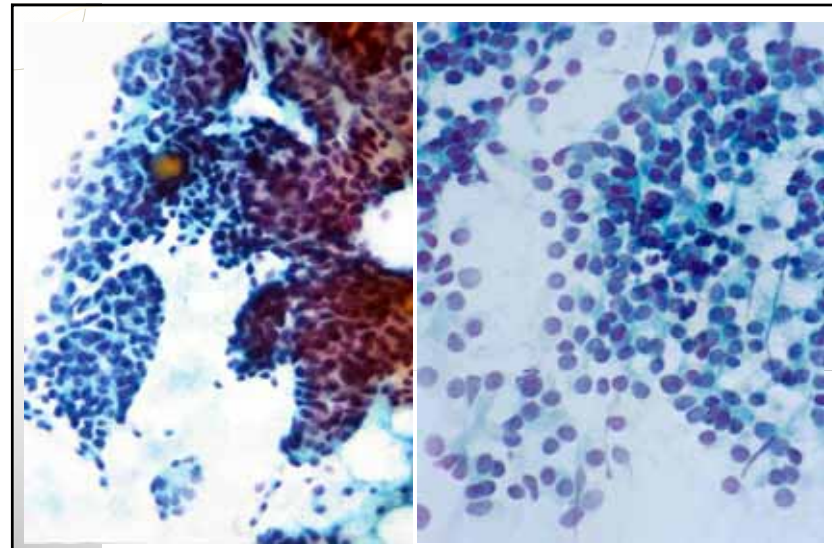
Adapted from TBSRTC II atlas, Table 1.2

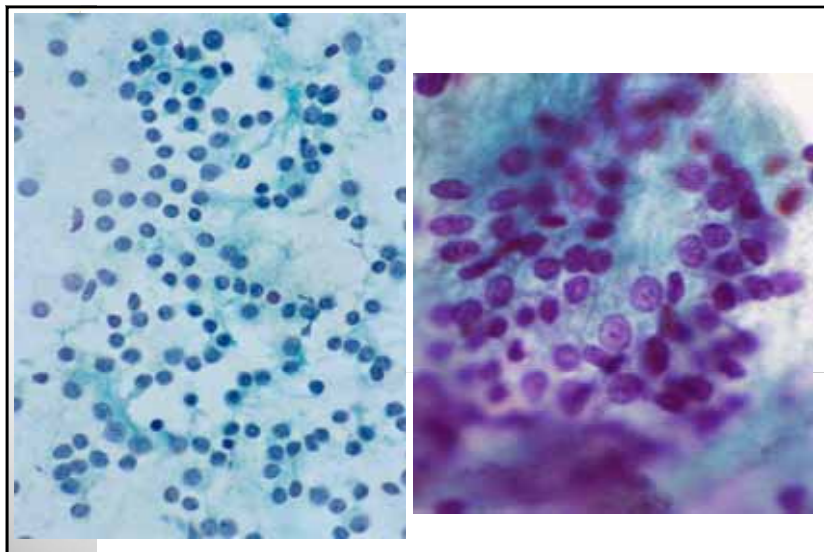
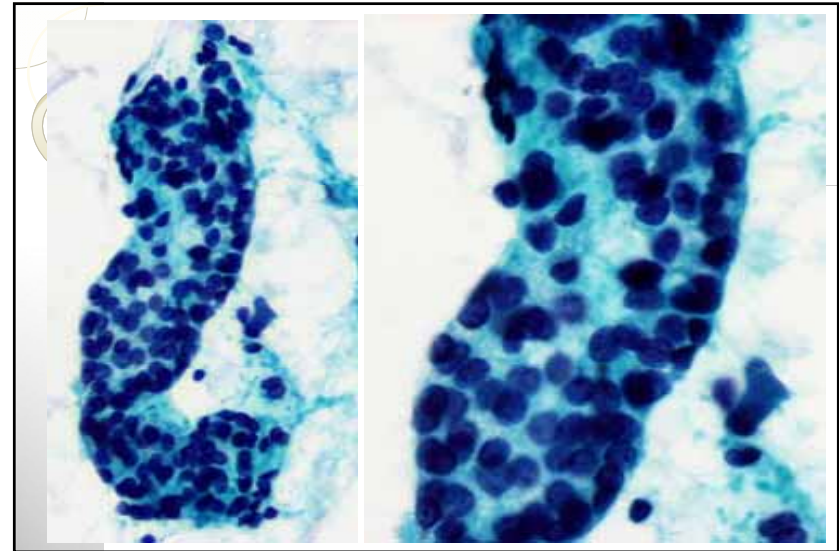
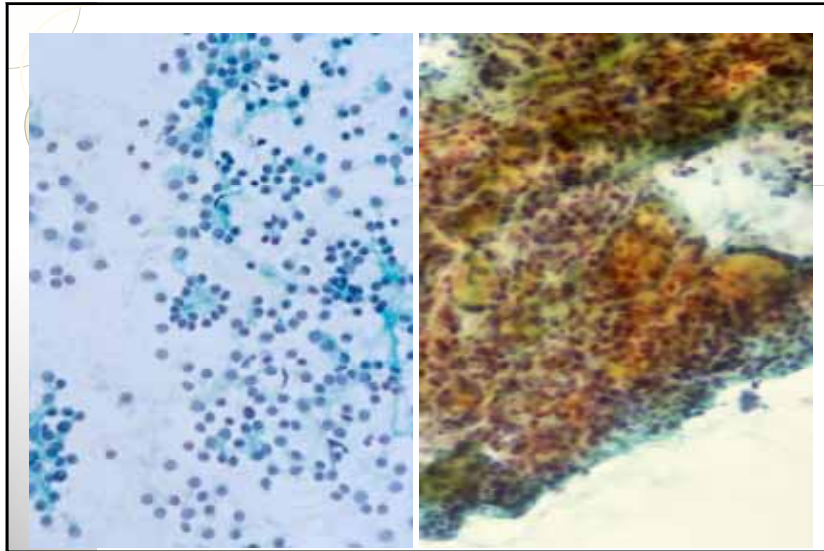
AUS Management and the 2015 ATA guideline

- For an initial AUS FNA, repeat FNA is endorsed as a suitable follow-up option
 - esp. useful when limited cellularity contributes to the initial AUS interpretation
- Because surgery is unnecessary for the majority of AUS, ATA endorses pre-operative molecular analysis to improve cancer risk assessment
 - Reflexive molecular testing is not mandated for all AUS
 - ATA does not endorse any single molecular test, acknowledging that different tests may prove beneficial in different clinical settings
- Surveillance or diagnostic surgical excision (ie. lobectomy) are also acceptable alternatives
 - after an initial AUS interpretation, or
 - when repeat FNA or molecular testing remain indeterminate

Follicular neoplasms-cytological criteria

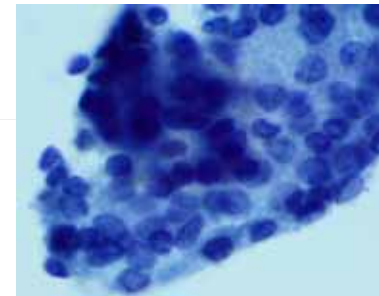
- Moderately or markedly cellular samples
- Significant alteration in follicular cell architecture, characterized
 - by cell crowding, microfollicles, and dispersed isolated cells
- Nuclei are usually round and slightly hyperchromatic, with inconspicuous nucleoli
- Some nuclear atypia may be seen, either enlarged, variably sized nuclei, and prominent nucleoli or enlarged nuclei with nuclear contour irregularity and mild and/or focal chromatin clearing
 - to account for NIFTP
- Colloid is scant or absent





Follicular neoplasms-cytological criteria

- Some nuclear atypia may be seen, either enlarged, variably sized nuclei, and prominent nucleoli or enlarged nuclei with nuclear contour irregularity and mild and/or focal chromatin clearing
 - to account for NIFTP



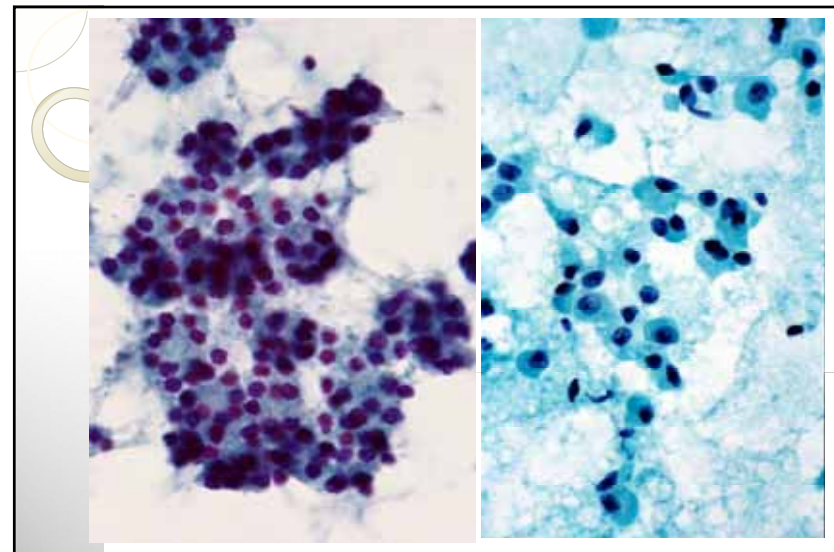
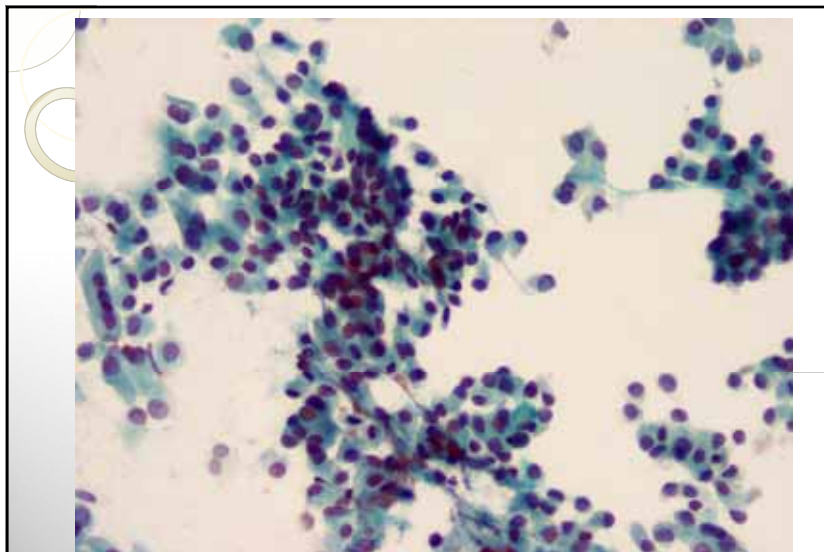
Optional note to reflect new reality of NIFTP

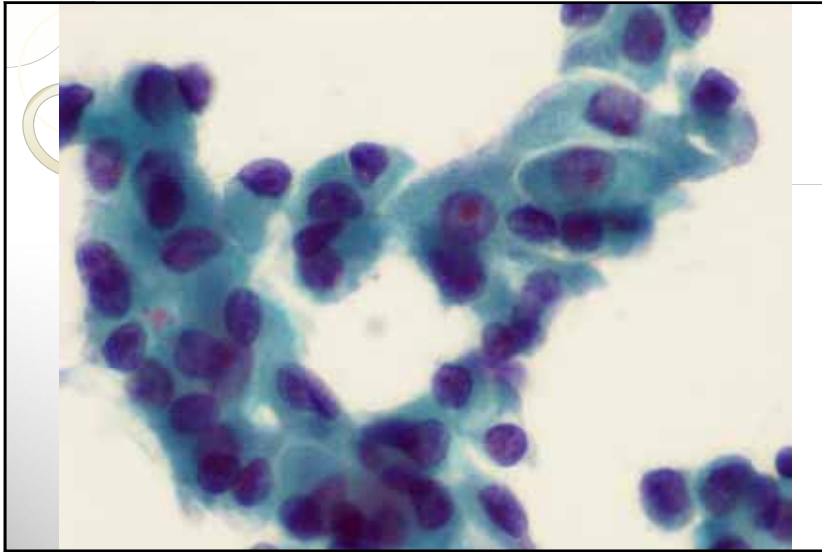
- For Follicular Neoplasm category
 - “The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and FVPTC, including its recently described indolent counterpart NIFTP”

Adapted from TBSRTC II, Table 1.3

Follicular neoplasms, Hürthle cell (oncocytic) type -cytological features

- Basically unchanged from TBSRTC 1
 - Moderately to markedly cellular specimens
 - Exclusively (or almost exclusively) composed of Hürthle
 - Typically with prominent nucleoli
 - Arranged as single cells and/or syncytial or microfollicular pattern and/or trabeculae





DIAGNOSTIC CATEGORIES	ROM TBSRTC II	Management
I. Non-diagnostic (or Unsatisfactory)	5-10%	Repeat FNA with US guidance
II. Benign	0-3%	Clinical and US Follow-up
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	Repeat FNA, molecular testing or lobectomy
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	Molecular testing, lobectomy
V. Suspicious for Malignancy	50-75%	Near-total thyroidectomy or lobectomy
VI. Malignant	97-99%	Near-total thyroidectomy or lobectomy

Adapted from TBSRTC II atlas, Table 1.2

FN and FNHCT Management and the 2015 ATA guidelines

- Diagnostic surgical excision (lobectomy) is the long-established standard of care for FN and FNHCT
- After consideration of clinical and US features, molecular testing may be used to supplement malignancy risk assessment data instead of proceeding directly to surgery

TBSRTC II-Suspicious for Malignancy (SM)

- To use when some cytomorphologic features (most often those of PTC) raise a strong suspicion of malignancy but the findings are not sufficient for a conclusive diagnosis
 - Specimens that are suspicious for a follicular or Hürthle cell neoplasm are excluded from this category
- The morphologic changes are of such a degree that a malignancy is considered more likely than not

TBSRTC II-Suspicious for Malignancy (SM)

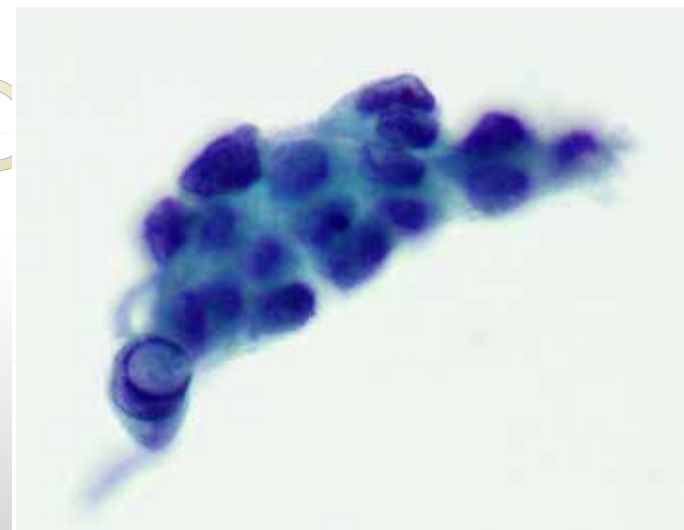
- Suspicious for PTC
- Suspicious for Medullary Thyroid carcinoma (MTC)
- Suspicious for lymphoma
- Suspicious for malignancy, NOS

TBSRTC II-When to Use Suspicious for PTC?

- Patterns listed in TBSRTC II
 - Pattern A: Patchy Nuclear Changes Pattern
 - Pattern B: Incomplete Nuclear Changes Pattern
 - Pattern C: Sparsely Cellular Specimen Pattern
 - Pattern D: Cystic Degeneration Pattern
- When fall short of the minimal criteria
 - Qualitatively, or
 - Quantitatively

TBSRTC II-AUS vs Suspicious PTC

- Distinction between AUS and suspicious for PTC is problematic
- AUS with cytologic (nuclear) atypia is associated with 28-56% PTC
 - If nuclear pseudoinclusions and/or psammoma bodies are present, the association is even higher, so best to Dx as "suspicious for PTC"



DIAGNOSTIC CATEGORIES	ROM TBSRTC II	Management
I. Non-diagnostic (or Unsatisfactory)	5-10%	Repeat FNA with US guidance
II. Benign	0-3%	Clinical and US Follow-up
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	Repeat FNA, molecular testing or lobectomy
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	Molecular testing, lobectomy
V. Suspicious for Malignancy	50-75%	Near-total thyroidectomy or lobectomy
VI. Malignant	97-99%	Near-total thyroidectomy or lobectomy

Adapted from TBSRTC II atlas, Table 1.2

SM Management and 2015 ATA Guidelines

- SM nodules should be managed like malignant ones
 - either lobectomy or near-total thyroidectomy
- Molecular testing rarely needed unless it alters the extent of surgical intervention
 - Total thyroidectomy is an option for patients with nodules that are cytologically SM, positive for known mutations specific for carcinoma (BRAF V600E, TERT-promoter, p53), sonographically suspicious, or of large size (>4 cm)
 - with the understanding that a subset of these may represent NIFTP on surgical excision

TBSRTC II-Malignant

- PTC
- Poorly differentiated carcinoma
 - Medullary thyroid carcinoma
 - Undifferentiated (anaplastic) carcinoma
 - Squamous cell carcinoma
 - Carcinoma with mixed features (specify)
- Metastatic malignancy
- Non-Hodgkin lymphoma
- Other

TBSRTC II-PTC

- Highlights certain differences in the cytological features of PTC in LBPs as compared to conventional cytologic preparations
- Several variants are better described and illustrated
- More detailed descriptions of the FVPTC as it relates to NIFTP
- Updated information pertaining to the clinical behavior, esp. in light of new molecular data, the new NIFTP terminology
- Hyalinizing trabecular tumor is now recognized as a mimic of PTC rather than as a variant of PTC

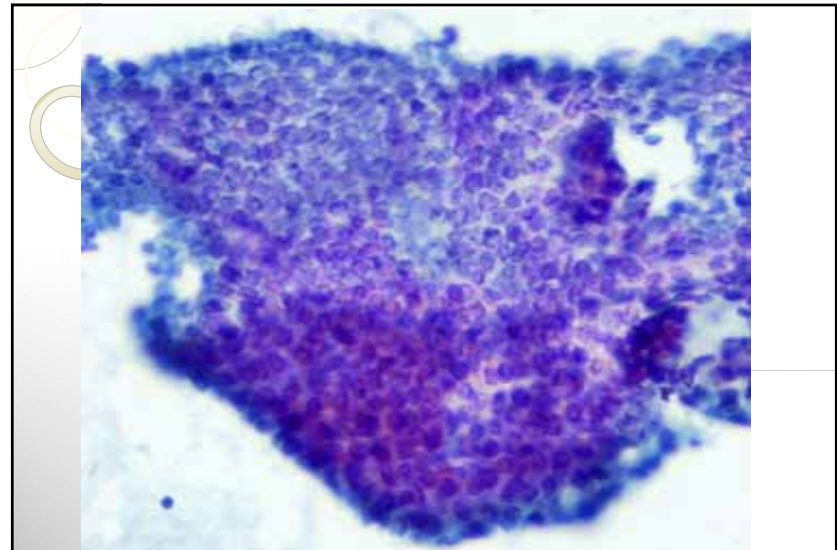
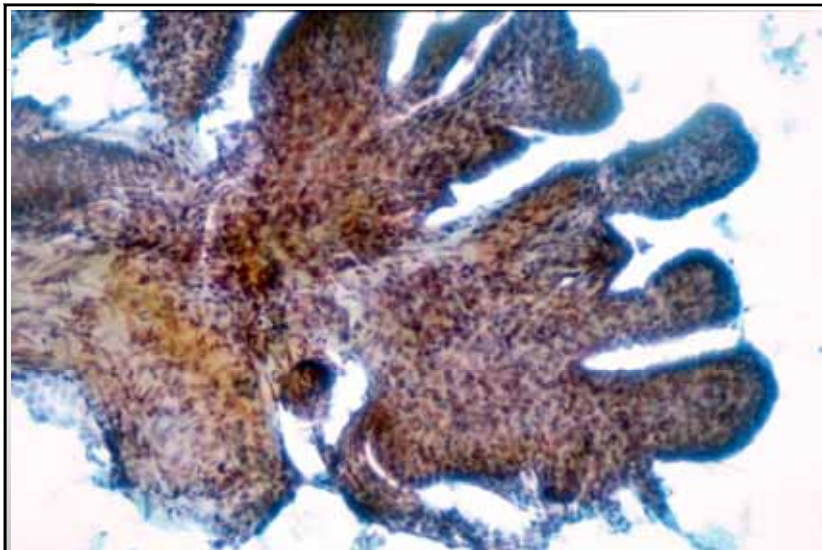
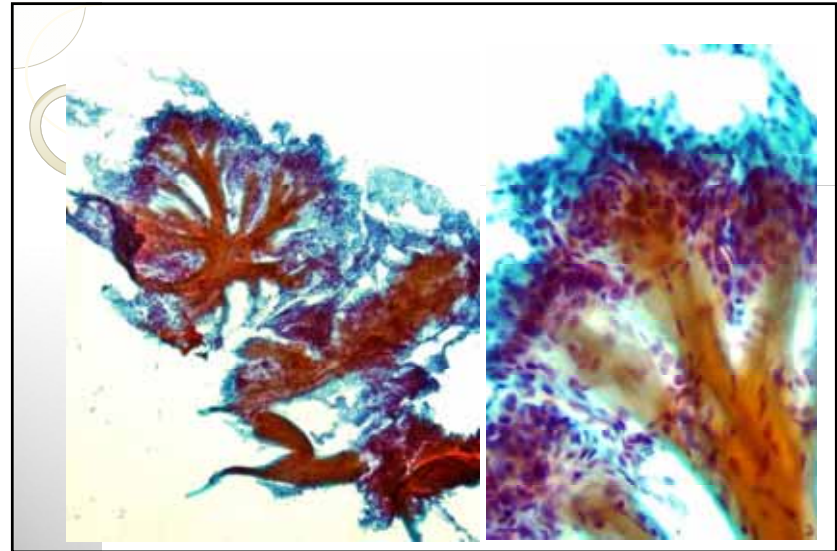
TBSRTC II-PTC Conventional type

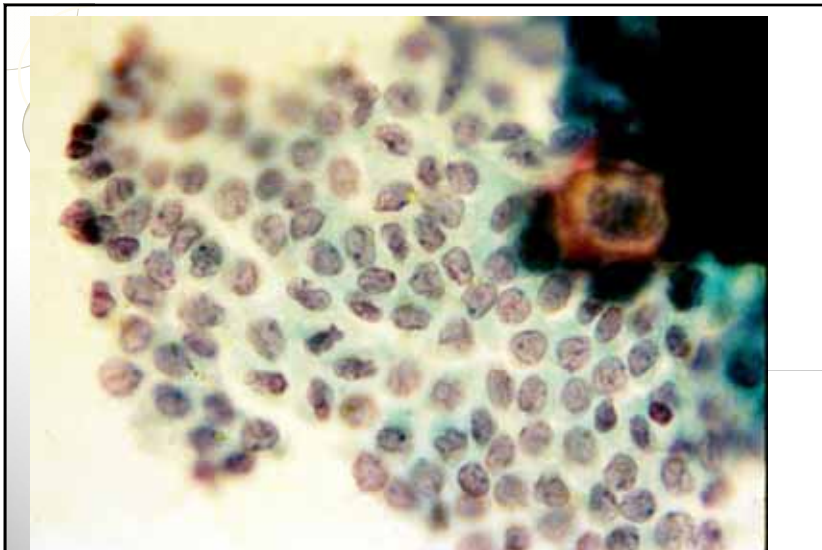
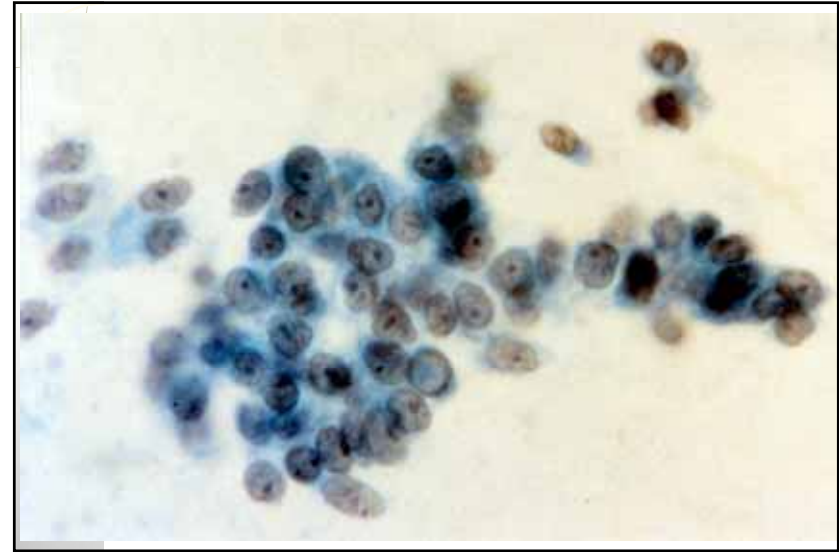
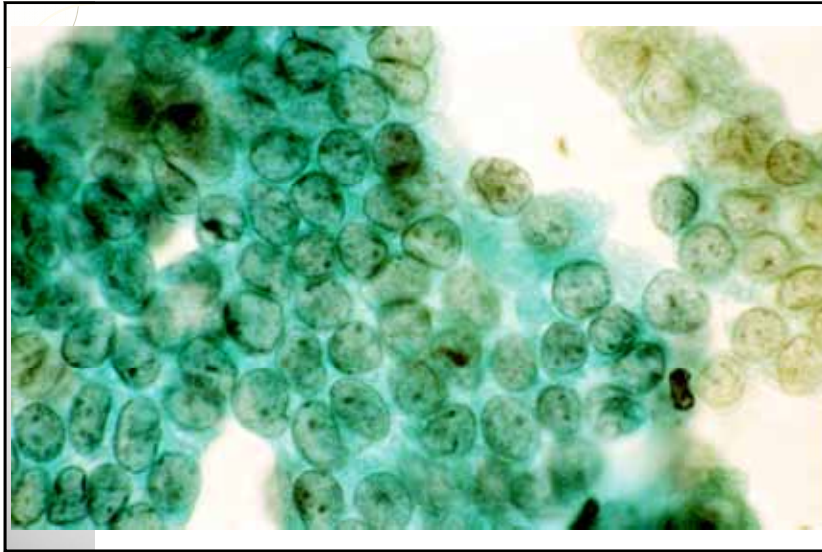
- **Definition**

- Malignant epithelial tumor derived from the thyroid follicular epithelium that displays papillary architecture and characteristic nuclear alterations

- **Criteria**

- Cells arranged in papillae and/or monolayers
 - Not in microfollicles
- Nuclear features as in original TBSRTC





PTC Variants

- A reliable definitive cytologic DX of classic PTCs is usually straightforward in FNA
- A significant proportion of PTCs exhibit variant architectural and/or cytologic features from those of conventional PTC
 - Some PTC variants have different genetics and biological behavior than classic PTC
- An awareness of the cytomorphologic spectrum of PTC variants helps prevent misdiagnosis
 - but it is not necessary to specify the subtype of PTC on an FNA specimen

PTC variants

- Follicular Variant (FVPTC) and NIFTP
- Tall Cell Variant (TCV)
- Columnar Cell Variant (CCV)
- Hobnail Variant (HV)
- Diffuse Sclerosing Variant (DSV)
- Solid Variant (SV)
- Oncocytic Variant (OV)
- Warthin-Like Variant (WLV)
- Macrofollicular Variant (MFV)
- Cystic PTC

Follicular variant PTC (FVPTC)

- Is the most common variant of PTC (~30%)
- Consists of a heterogeneous group of tumors with two major groups that differ morphologically, genetically and clinically
 - Invasive FVPTC
 - Non-invasive FVPTC (NIFVPTC=NIFTP)
 - Experts proposed name change in March 2015
 - NIFTP is no longer considered malignant but rather as a very low risk neoplasm that likely represents a preinvasive stage of FVPTC
 - for which a diagnostic and therapeutic lobectomy is still warranted

NIFTP vs IFVPTC

- NIFTP and IFVPTC are different prognostically and molecularly
- IFVPTC demonstrate more aggressive behavior
 - Lymph node metastases
 - Recurrences, and
 - BRAF mutations in 0-35% (average 15%)
- NIFTP (accounting for 50-70% of all FVPTCs) demonstrate virtually no metastatic progression or aggressive outcomes
 - Molecularly, NIFTPs are closer to the follicular adenoma/carcinoma group than the conventional PTC group

NIFTP

- At the molecular level, a very high association with other follicular-pattern neoplasms
 - Most common
 - RAS mutations
 - Others: *PAX8/PPARγ* translocations, *THADA* fusions, and *BRAF*^{K601E} mutations
- In contrast, *BRAF*^{V600E} mutations and *RET* (which are common in conventional PTC) are absent in NIFTP
 - Sequencing with large multigene panels may therefore assist in the detection of NIFTP
 - Some studies have shown the Afirma gene expression classifier test classifies NIFTP cases as "suspicious"

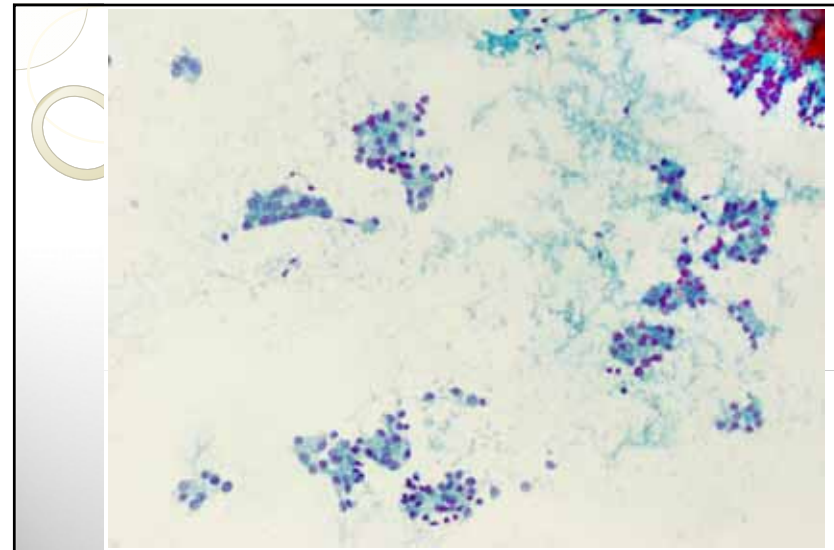
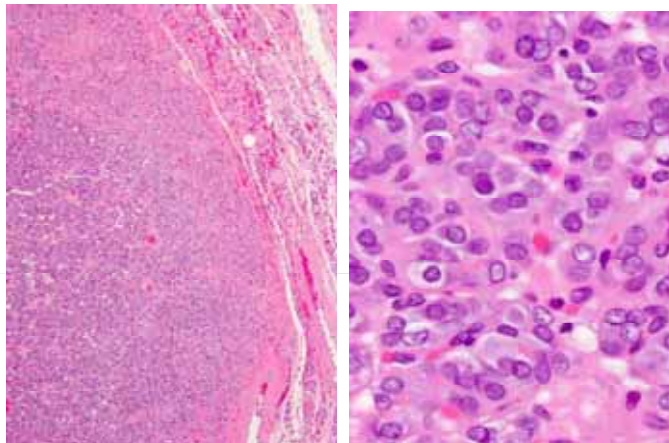
NIFTP

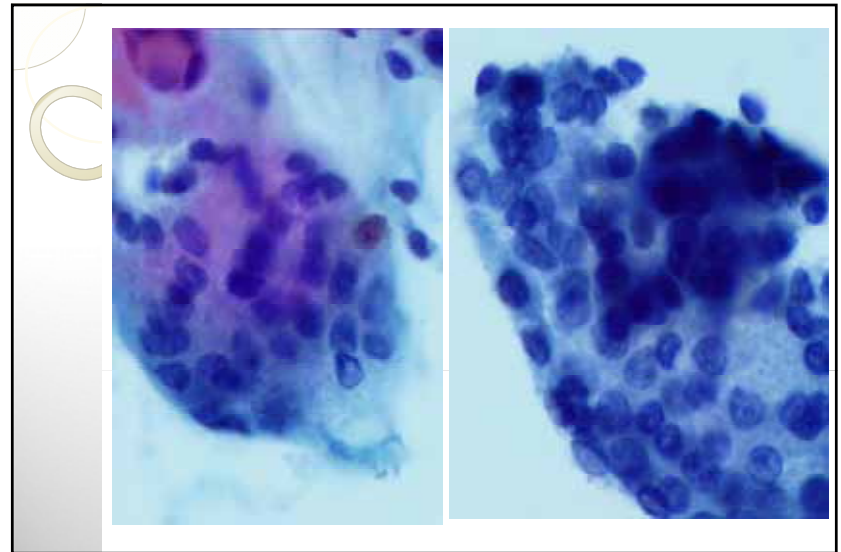
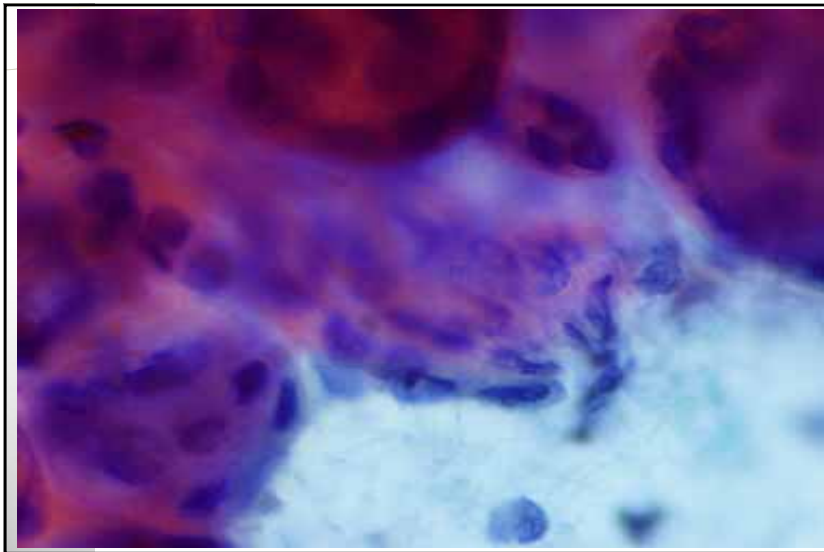
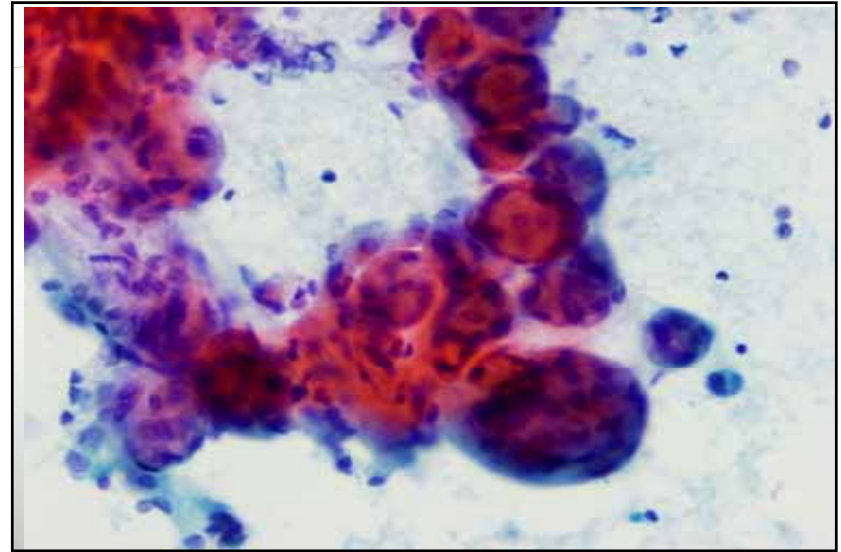
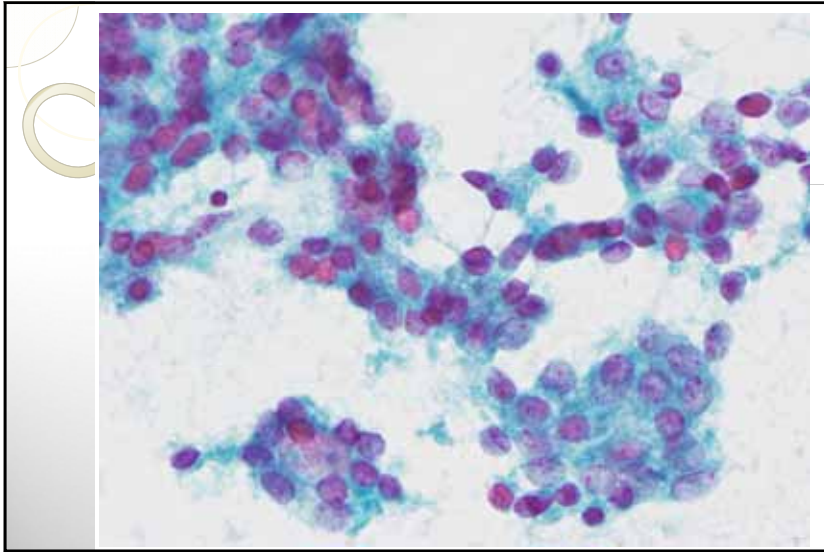
- Ultrasonography and molecular tests can also assist in risk stratification at the time of FNA diagnosis
- On US, most NIFTP are benign-appearing with round-to-oval, circumscribed nodules with a hypoechoic rim
 - However, a highly suspicious US appearance may be seen in some cases

NIFTP and FVPTC

- The degree to which the nuclear features are displayed in FVPTCs and NIFTP varies from case to case, with a wide quantitative and qualitative spectrum, and **overlap**
 - FVPTCs, usually invasive, usually have
 - prominent nuclear features of PTC
 - NIFTP, usually have
 - only mild nuclear enlargement and crowding, chromatin clearing and irregular nuclear membranes, and
 - papillae, nuclear grooves and pseudoinclusions are **rare or absent**
 - So often associated with more subtle nuclear features than invasive FVPTC and conventional PTC, but with more abnormalities than benign nodules including follicular adenoma

NIFTP





Cytologic Approach to PTC in view of NIFTP

- It is desirable to eliminate from the malignant category tumors likely to harbor a NIFTP
- Best to limit the Malignant category to conventional PTC and other variants of PTC
- Preliminary data suggest that a definitive Dx of PTC should be limited to cases that have, in addition to other characteristic features, at least one of the following
 - papillary architecture
 - psammoma bodies, or
 - nuclear pseudoinclusions

Cytologic Approach in view of NIFTP

- So a suspected PTC with an exclusively follicular architecture, especially one that lacks intranuclear cytoplasmic pseudoinclusions and psammoma bodies can be interpreted
 - as FN (if microfollicles are prominent and mild nuclear changes)
 - as SM (if microfollicles are prominent and marked nuclear changes)
- This approach leaves other subtypes of PTC in the malignant category but minimizes the contribution of FVPTC and NIFTP
- It is unlikely that NIFTPs can be completely eliminated from the malignant category
 - an educational note may be added in the report to reinforce this limitation

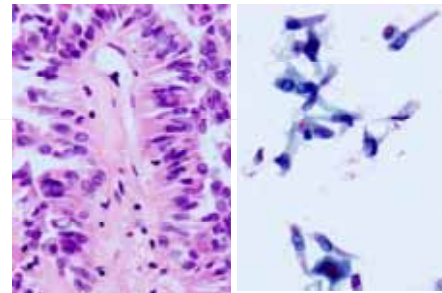
Optional notes to reflect new reality of NIFTP

- For Follicular Neoplasm category
 - "The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and FVPTC, including its recently described indolent counterpart NIFTP"
- For Suspicious for malignancy category
 - "The cytomorphic features are suspicious for FVPTC and its recently described indolent counterpart NIFTP"
- For Malignant category
 - "A small proportion of cases (3-4%) diagnosed as PTC may prove to be NIFTP on histopathologic examination"

Adapted from TBSRTC II, Table 1.3

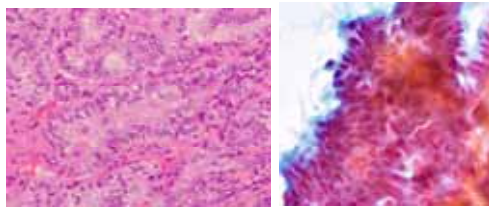
Tall Cell Variant, PTC (TCV)

- The most common aggressive variant of PTC (1-13%)
- Composed predominantly of elongated ("tall") tumor cells (height/width $\geq 3/1$) with
 - abundant dense oxyphilic granular cytoplasm
 - typical nuclear changes of PTC



Columnar Cell Variant, PTC

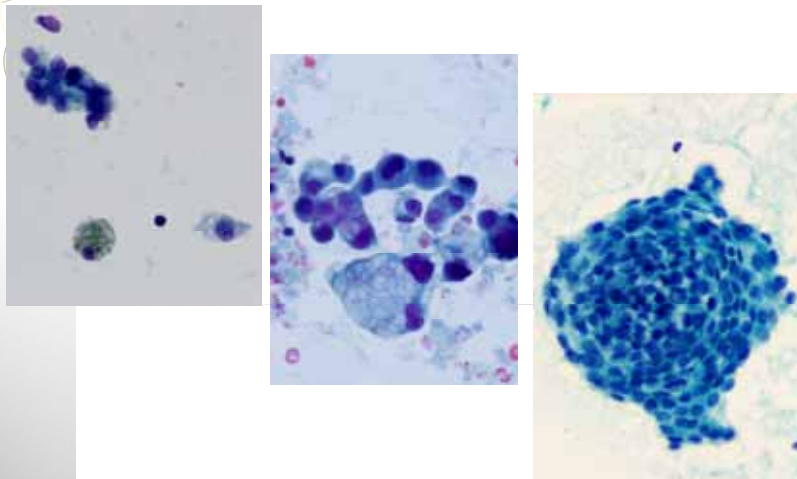
- One of the least common variants of PTC
- Occurs primarily in males
- Characterized by columnar cells with hyperchromatic, oval, and pseudostratified nuclei and supranuclear or subnuclear cytoplasmic vacuoles
 - reminiscent of colonic adenoma or secretory-type endometrium



Cystic Variant, PTC

- Although cystic changes occur much more commonly in non-neoplastic thyroid nodules, PTC is the most common malignant neoplasm of the thyroid to undergo cystic changes
- The amount of cystic change can vary
 - approximately 10% of PTCs are almost entirely cystic
- Cystic PTC is a possible cause for false-negative thyroid FNAs
 - main reason why a diagnosis of “cyst fluid only” should be classified as Non-Diagnostic according to TBSRTC (rate of malignancy: 3-6%)

Cystic Variant, PTC



Cystic Variant, PTC

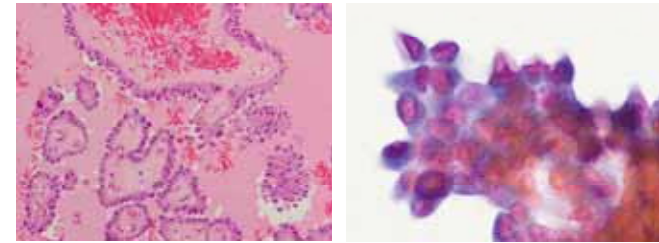
- The use of US allows precise guidance and adequate sampling of the solid mural nodules within the cyst
- Cytology
 - Neoplastic cells can be isolated, in clusters with a cartwheel or swirl pattern, or in papillary clusters
 - Nuclear grooves and pseudoinclusions are usually present
- The distinction between these neoplastic cells and histiocytes or benign epithelial cyst-lining cells that can undergo reactive nuclear changes can be very difficult
 - some cases are best diagnosed as SM (PTC) or AUS/FLUS

Hobnail Variant, PTC

- Rare variant associated with
 - frequent distant metastases (typically to lung), and
 - increased risk of tumor-related death in small series
- Characterized by loss of cellular polarity/cohesiveness with apically placed nuclei and bulging of the apical cell surface (hobnail features) in > 30% of neoplastic cells

Hobnail Variant, PTC

- Cytologically, the neoplastic cells show
 - loss of polarity and dyscohesiveness
 - But also either in papillary, micropapillary or discohesive cell clusters
 - Single cells with eccentric nuclei and tapering cytoplasm (“comet-like” or “tear drop-like” cells)

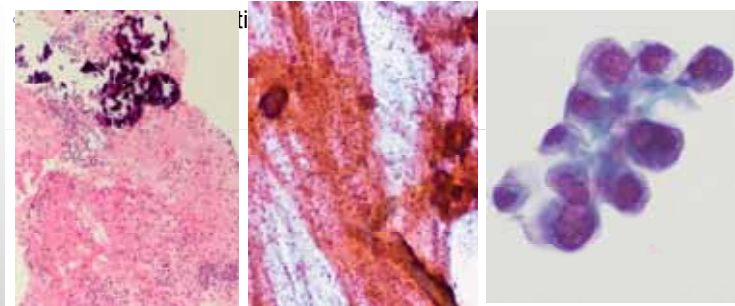


Diffuse Sclerosing Variant, PTC

- Uncommon variant (<6%) of PTC that typically occurs
 - in young individuals, especially women
 - presents as goiter without a dominant mass
 - can mimic Hashimoto thyroiditis and/or lymphoma
- Has a higher incidence of lymph node and lung metastases at presentation and a higher risk of persistent/recurrent disease
 - But cancer-related mortality appears to be similar to cPTC

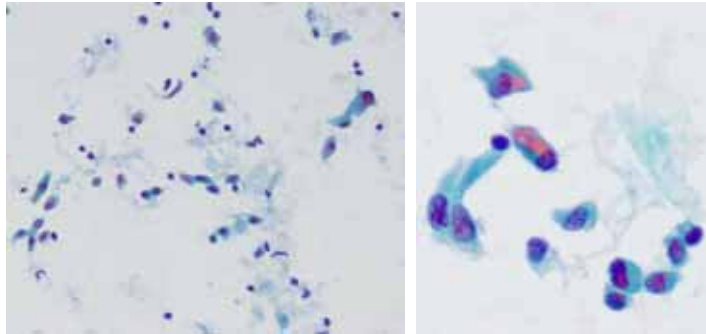
Diffuse Sclerosing Variant, PTC

- Cytology
 - 3D clusters of follicular cells
 - sometimes showing hobnail features or cytoplasmic vacuoles
 - Abundance of psammoma bodies

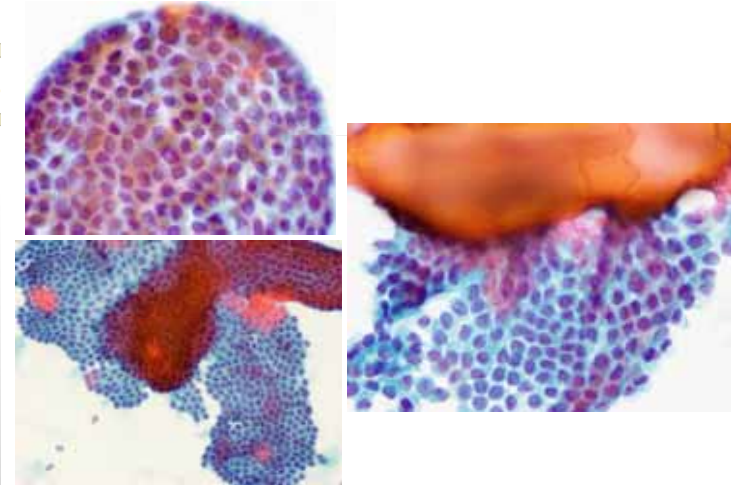


Oncocytic variant, PTC

- Composed predominantly of oncocytic cells with
 - variable architecture (follicular, papillary, solid) and
 - the nuclear changes characteristic of PTC



Macrofollicular Variant, PTC



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II. Benign	0-3%	Clinical and US Follow-up
III. Atypia (or Follicular Lesion) of Undetermined Significance (AUS)	10-30%	Repeat FNA, molecular testing or lobectomy
IV. Follicular Neoplasm (or suspicious for follicular neoplasm) -specify if oncocytic (Hürthle cell) type	25-40%	Molecular testing, lobectomy
V. Suspicious for Malignancy	50-75%	Near-total thyroidectomy or lobectomy
VI. Malignant	97-99%	Near-total thyroidectomy or lobectomy

Adapted from TBSRTC II atlas, Table 1.2

Molecular Aspects-I

- High percentages of PTC and FTC have genetic alterations
 - PTC
 - 40-50% BRAF v600E
 - 10-20% RET/PTC
 - 10-20% RAS
 - FTC
 - 40% RAS
 - 35% PAX8/PPAR γ
- Onenerk AM, et al. Cancer Cytopathol 2017;125(6 suppl):477-485 .Triaging of indeterminate thyroid FNA: What are the options for the practicing cytopathologist? Cancer Cytopathol 2017;125(6 suppl):477-485

Molecular Aspects-II

- PTC can be subclassified molecularly into 2 groups with fundamentally different epigenomic and proteomic profiles, and distinct clinical features
 - BRAF V600E-like phenotype
 - 80% tall cell variant PTC
 - 40-60% classic PTC
 - 10% FVPTC
 - 25% of I-FVPTC have this mutation and often show lymph node mets and recurrences
 - RAS-like phenotype
 - Most FVPTC

Triaging of indeterminate thyroid FNA: What are the options for the practicing cytopathologist?

Onenerk AM, et al. Cancer Cytopathol 2017;125(6 suppl):477-485

- Tests available
 - In-house
 - BRAF
 - RAS
 - RET/PTC
 - PPARγ/PAX8
 - 3 commercially available molecular testing panels
 - Afirma gene expression classifier (GEC)
 - High NPV
 - A "rule out" malignancy for AUS and FN categories
 - ThyroSeq v.2 and ThyGenX/ThyraMIR
 - High PPV
 - Can both "rule in" and "rule out" malignancy

Triaging of indeterminate thyroid FNA: What are the options for the practicing cytopathologist?

Onenerk AM, et al. Cancer Cytopathol 2017;125(6 suppl):477-485

- Which patients should be tested?
 - The option to use molecular testing usually applies to indeterminate thyroid nodules
 - esp. AUS or FN
- Nodules >1cm and patients >21 y.o.
- Not recommended for thyroid nodules >4 cm or for patients who have already planned surgery
- Reflex testing for all indeterminate thyroid nodules or molecular testing of cytologically benign and malignant FNAs is not recommended

Triaging of indeterminate thyroid FNA: What are the options for the practicing cytopathologist?

Onenerk AM, et al. Cancer Cytopathol 2017;125(6 suppl):477-485

- Unlike Afirma qualitative "benign" or "suspicious" results, ThyGenX and ThyroSeq provide information about the exact genetic alteration
 - so a mutation-specific/fusion-specific malignancy risk assessment would be possible
- In the presence of RAS and BRAF K601E mutations, which are present in a significant percentage of follicular adenomas and NIFTPs
 - hemithyroidectomy appears to be an acceptable option
- In the presence of BRAF V600E or TERT mutations, and possibly PAX8/PPARγ or RET/PTC alterations
 - total thyroidectomy would be acceptable

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Adapted from TBSRTC II atlas, Table 1.2

Conclusions

- TBSRTC II has been adjusted to reflect new evidence-based data since publication of the 1st edition, incorporating
 - NIFTP
 - More conservative approach to cytologic DX of PTC
 - Revised ROM
 - New American Thyroid Association (ATA) management guidelines for thyroid nodule and cancer
 - Other updates, in particular, molecular aspects

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