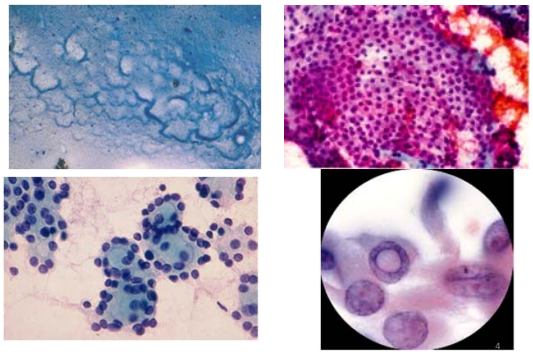
Navigating the Gray Zones of Thyroid Nodules: From Cytomorphology to Ancillary Testing Part 1

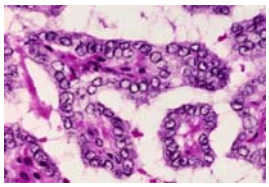
Patricia G. Tiscornia-Wasserman, MD
Professor of Pathology and Cell Biology
Director of Cytopathology

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

CYTOMORPHOLOGY



Orphan Annie Nuclei



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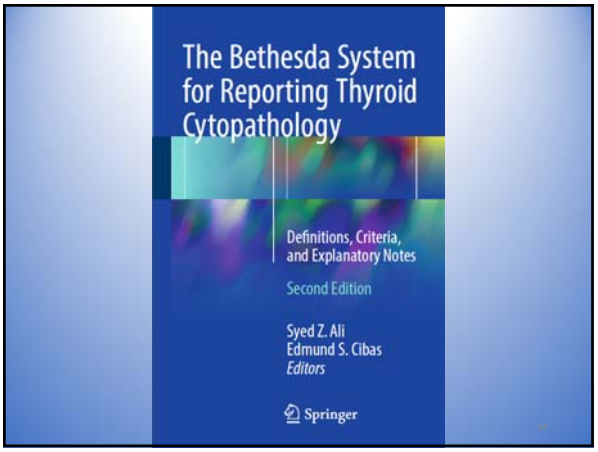

2017 Bethesda System for Reporting Thyroid Cytopathology

Diagnostic Category	ROM if NIFTP not cancer	ROM if NIFTP is cancer	Management
Nondiagnostic/unsatisfactory Cyst fluid only Acellular specimen Other: Obscuring factors	5–10%	5–10%	Repeat fine needle aspiration under ultrasound guidance
Benign Benign follicular nodule Chronic lymphocytic (Hashimoto) thyroiditis, in proper clinical setting Granulomatous (subacute) thyroiditis	0–3%	0–3%	Clinical and US follow-up until two negative
Atypia of undetermined significance/ follicular lesion of undetermined significance	6–18%	10–30%	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm/ suspicious for a follicular neoplasm (Specify if Hürthle cell type)	10–40%	25–40%	Molecular testing, lobectomy
Suspicious for malignancy	45–60%	50–75%	Lobectomy or near-total thyroidectomy
Malignant Papillary thyroid carcinoma Medullary thyroid carcinoma Poorly differentiated carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic malignancy Non-Hodgkin lymphoma Other	94–96%	97–99%	Lobectomy or near-total thyroidectomy

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Thyroid FNA - Specimen Adequacy

- **A minimum of 6-8 groups of benign follicular cells with 10 cells each**
- Atypical cells
  - adequate for evaluation
- Abundant colloid but few follicular cells
  - "Suggestive of colloid nodule"
- Macrophages and cyst contents only
  - "Cyst fluid only"
  - Recommend correlation with ultrasound findings
  - Optional disclaimer: "cystic carcinoma cannot be excluded" may be added

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Reasons for Inadequate Specimens

- Sclerotic lesions
  - Fibrous variant of Hashimoto's thyroiditis
  - Neoplasms with marked desmoplasia
- Thick, fibrous, sclerotic and calcified capsule
- Large lesions with cystic degeneration
- Necrotic lesions
  - Abscess, infarct, necrosis
- Vascular neoplasms
- Sampling error (needle not in lesion)
- Faulty technique (too much or too little suction)

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BC II – Colloid nodule

Exceptions to the adequacy "rule"

- Solid nodules with cytologic atypia
  - Presence of one or two small clusters of malignant or highly atypical cells should be reported as suspicious or malignant and not unsatisfactory or inadequate
  - A minimum number of follicular cells is not required
- Solid nodules with inflammation
  - HT, abscess, granulomatous thyroiditis
  - A minimum number of follicular cells is not required
- **Colloid nodules**
  - **A minimum number of follicular cells is not required if present within abundant thick colloid material (benign colloid nodule)**

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BC III – AUS/FLUS

- Accounts for 1-22% of thyroid FNAs
- Fair reproducibility
- Limit AUS category: **up to 10%** recommended
- Better QA indicator: **AUS:malignant ratio up to 3.0**
- Should be an interpretation of last resort
- Must be used judiciously

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BC III – AUS/FLUS

- Reserved for cases with lesser degree of atypia compared to BC IV (SFN) or BC V (SM)
- Atypia
  - Cytologic in nature
  - Architectural in nature
  - Combination of cytologic and architectural
- Lower ROM than other indeterminate categories
- Calculating ROM in AUS is challenging because only a minority of cases undergo excision
  - Estimating ROM based on surgical excisions overestimates the ROM due to selection bias
  - Resections only when clinical or US worrisome findings, or abnormal repeat aspiration, or abnormal molecular testing result

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BC III – AUS/FLUS Sub-Categories

1. **Prominent microfollicles**, but insufficient for SFN
2. **Predominance of Hurthle cells** in a paucicellular specimen
3. **Predominance of Hurthle cells** in a hypercellular specimen, but clinical history suggests MNG or HT
4. **Sample preparation artefact**: air-drying nuclear changes, crowded nuclei due to clotting
5. **Focal nuclear features of PTC** in an otherwise benign-appearing aspirate
6. **Cyst-lining cells with atypical features**, such as nuclear grooves, prominent nucleoli, nuclear pseudoinclusions, in an otherwise benign-appearing aspirate
7. **A minor population of cells with nuclear atypia**, enlargement or prominent nucleoli, in the setting of prior RAI or repair after cystic degeneration
8. **Atypical lymphoid infiltrate** but insufficient to call suspicious for malignancy; flow cytometry recommended
9. **Not otherwise categorized**

Cibas ES, Am J. Clin Path 2009; 132:658

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BC III – AUS/FLUS Subcategories

ARCHITECTURAL ATYPIA

- Predominantly microfollicles and/or crowded 3-dimensional groups in paucicellular specimen with scant colloid
  - Low risk pattern; however a poorly sampled SFN lesion could be made if more cellular
- Focally prominent microfollicles with minimal nuclear atypia in a moderately or hypercellular sample.
  - Proportion of microfollicles do not warrant a diagnosis of SFN

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BC III – AUS/FLUS Subcategories

CYTOLOGIC ATYPIA
Associated with PTC in 28-56% of cases
ROM 47%

- **Focal cytologic atypia**
  - Rare cells with nuclear enlargement, pale chromatin, irregular nuclear contours (?HT)
  - Rare or no pseudoinclusions
- **Extensive but mild cytologic atypia**
  - Milder nuclear atypia than described above
- **Atypical cyst-lining cells**
  - Should be recognized and called benign
  - If more atypia than usual -> AUS
  - They may show nuclear grooves, prominent nucleoli, elongated nuclei and cytoplasm, and/or rare intranuclear pseudoinclusions in an otherwise benign-appearing sample
- **Histiocytoid cells**
  - Larger than histiocytes, sometimes in clusters, rounder nuclei, higher N/C ratio, and glassier cytoplasm with larger, discrete vacuoles. Usually associated with PTC

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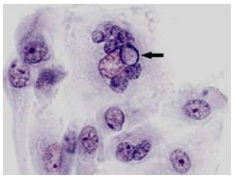
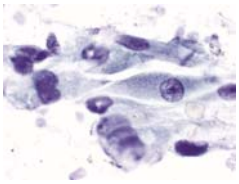
AUS/FLUS: Cell lining atypia

There are cyst-lining cells which may appear atypical due to the presence of nuclear grooves, prominent nucleoli, elongated nuclei and cytoplasm, and/or intranuclear cytoplasmic inclusions in an otherwise predominantly benign-appearing sample.





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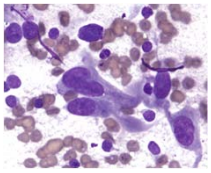
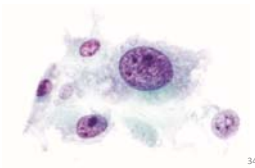
AUS/FLUS: Reactive/reparative changes

A minor population of follicular cells show nuclear enlargement, often accompanied by prominent nucleoli, e.g.,

- specimens from patients with history of radioactive iodine, carbimazole, or other pharmaceutical agents
- repair due to involutional changes such as cystic degeneration and or hemorrhage





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BC III – AUS/FLUS Subcategories

CYTOLOGIC AND ARCHITECTURAL ATYPIA

- Patterns can be combined and are not mutually exclusive
- This pattern is most common in non-invasive follicular thyroid neoplasms with papillary-like nuclear features or NIFTP

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BC III – AUS/FLUS

- Current ROM: 10-30%
- Previous ROM (2008): 5-15%
- Risks differ with type of atypia
- AUS based on nuclear atypia have a two fold higher ROM compared with AUS cases with architectural atypia
- Hurthle cell-type AUS has lower ROM than other patterns
- Introduction of NIFTP in 2016 has reduced the ROM for AUS

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BC III – AUS/FLUS

MANAGEMENT

- Conservative : repeat FNA or molecular testing
- Repeat FNA results in a more definitive interpretation in 70-90% of cases
- 10-30% will be repeat AUS
- If molecular studies are negative: ROM decreases to 5%
  - 50% of AUS have negative molecular results
  - Negative MS more frequent in AUS with architectural atypia
- **Surgery vs observation must be based on the constellation of cytologic, molecular, clinical, and imaging findings**

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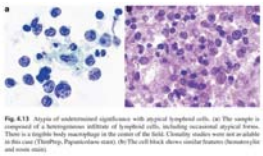
BC III – AUS/FLUS Subcategories

ATYPICAL LYMPHOID CELLS

- **Lymphoma cannot be ruled out**
  - Atypical lymphoid infiltrate with insufficient degree of atypia to interpret as SM
  - Extranodal marginal zone B-cell lymphoma may show prominent, polymorphous lymphoid component
  - Repeat aspirate for flow cytometry is recommended



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BC IV – Suspicious for follicular neoplasm

- Moderately or markedly cellular aspirates
- **Hallmark ->Significant architectural alterations**:
  - Cell crowding and overlapping
  - Microfollicles
    - Crowded, flat groups of <15 cells arranged in a circle, at least 2/3 complete
  - Trabeculae or ribbons of overlapping cells
  - Isolated cells
- Cytologic features:
  - Uniform, normal-size or enlarged follicular cells
  - Round nuclei, slight hyperchromatism
  - Mild nuclear atypia
  - Scant or absent colloid

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BC IV – Suspicious for follicular neoplasm

- Risk of neoplasia: 65-85%
- Risk of malignancy: 25-40%
- 27-68% are PTC
  - Cellular features of PTC not fully developed throughout the entire nodule
  - Discrepancies due to imperfect reproducibility of histologic diagnoses of follicular carcinoma and FVPTC
- Management:
  - Diagnostic surgical excision
  - Molecular testing to supplement risk assessment before surgery

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BC IV – Suspicious for follicular neoplasm

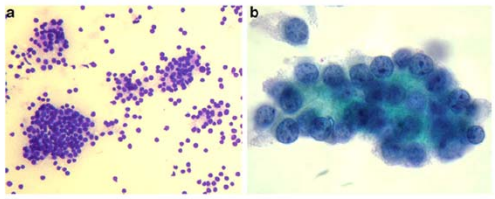

Fig. 5.4 Follicular neoplasm/suspicious for a follicular neoplasm. (**a**, **b**) Microfollicles demonstrate nuclear overlap. Some are loosely cohesive clusters, and there are dispersed, isolated cells (**a** smear, Diff-Quik stain; **b** ThinPrep, Papanicolaou stain).

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Cytopathologic Features of Follicular Carcinoma

- Syncytial fragments
- Marked crowding or overlapping nuclei
- Enlarged nuclei
- Coarse chromatin pattern
- Nucleoli always present
- Scanty or absent background colloid
- Inspissated colloid within lumina

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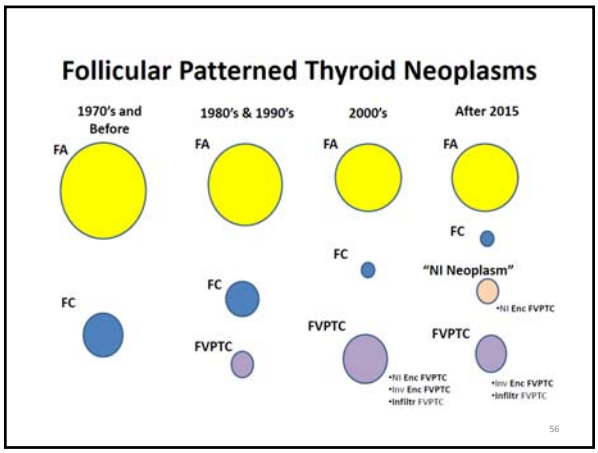

Need for reclassification

- Apparently indolent behavior of "**non-invasive follicular thyroid neoplasms with papillary-like nuclear features**" or **NIFTP**
  - 13 year follow up: all patients alive, without recurrences or any signs of disease
- NIFTP comprises 20-25% of all tumors previously classified as thyroid malignancies.
- NIFTP comprises 5% or less of thyroid FNAs currently classified as malignant.
- **Overdiagnosis**: intensified surveillance increases incidence of early cancers with indolent behavior.
- **Overtreatment** (i.e., total thyroidectomy, radioactive iodine)
- Reclassifying this tumor as something other than CARCINOMA
- Multidisciplinary expert group of endocrine pathologists met in March 2015 to formally propose reclassifying NI-FVPTC as a tumor or neoplasm rather than a carcinoma.
- This reclassification significantly alters the ROM for various diagnostic categories of TBS

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Is NIFTP truly indolent?

- Follow up data based on original landmark study
  - Incidence: ~20% of PTC
  - Morbidity and mortality rare
- New data (Parente DN et al. World J Surg 2017)
  - Incidence 2.1 %
  - "Malignant" behavior in ~6%

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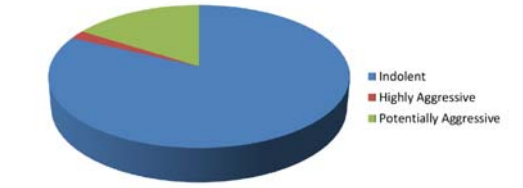
Thyroid Neoplasms: Clinico-pathologic Groups



Indolent
- Adenoma
- Non-invasive FVPTC
- Most Papillary MicroCa
- Majority of Stage I and II Ca

Potentially Aggressive
- Very few Stage I and II Ca
- Some Stage III and IV Ca
- Poorly Differentiated Ca
- Aggressive Variants of PTC

Highly Aggressive
- Undiff (Anaplastic) Ca

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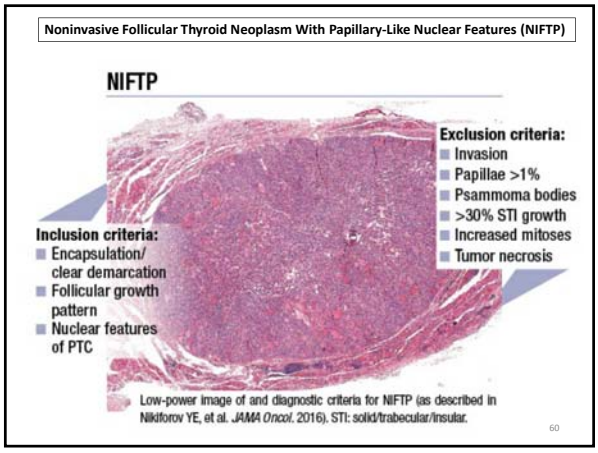

NIFTP criteria

- Samples are usually hypercellular, with syncytial-like fragments containing microfollicles ("rosettes").
- Dispersed microfollicular clusters, isolated neoplastic follicles, and some sheets with branched irregular contours may also be present.
- Some colloid may be present, typically dense-staining, thick, and sometimes within neoplastic follicles.
- In contrast to conventional PTC, the nuclear changes are often subtle.
- The following features are **usually absent or inconspicuous**: papillary and papillary-like fragments, multinucleated giant cells, INCIs, psammoma bodies, and marked cystic change.

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Cytologic features of NIFTP

- Definition: Cytologic features of PTC but a follicular architecture, lacking the papillae of classical PTC.
- Features indicative of **papillary growth**, presence of **psammomatous calcifications**, or numerous **pseudoinclusions** **preclude** the diagnosis of NIFTP.
  - 1% papillary growth will exclude the diagnosis of NIFTP.
- NIFTP is distinguished from FVPTC by the **lack of an infiltrative growth pattern, penetration of the tumor's capsule, and lymphovascular invasion.**
- **Even if cytologic features suggestive of an NIFTP can be recognized, definitive distinction from FVPTC cannot be made on cytologic material alone, and surgical resection is required.**

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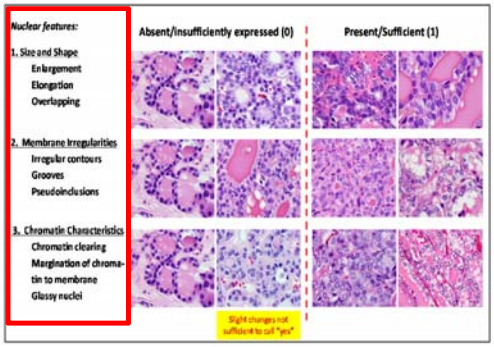

eFigure 4. Visual guide for scoring nuclear features using the three-point scoring scale.

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BC IV – Suspicious for follicular neoplasm

- If nuclear features of papillary carcinoma are ***not*** definitive or architectural features of classical papillary carcinoma are ***absent***, such aspirates raise ***concern for invasive follicular variant of papillary carcinoma or NIFTP.***
- Whether such aspirates are better classified as FN/SFN or "suspicious for malignancy, suspicious for papillary thyroid carcinoma" will be dictated by the quality and quantity of the cytologic changes.
- An explanatory note regarding concern for NIFTP/invasive follicular variant of papillary carcinoma is warranted

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ROM decrease with exclusion of NIFTP

- Greatest decrease in ROM observed for FNAB cases diagnosed as AUS/FLUS, FN/SFN, or SM (range, 13.6%-23.4%)
- Differences in ROM for all 3 indeterminate categories were statistically significant ($P < .05$).
- The **extent of the decrease** in the implied ROM is directly related to the rates at which NI-FVPTC is diagnosed in the corresponding **surgical pathology specimens**.
- NIFTP represents approximately 15% to 20% of all PTC cases, and the incidence of this PTC subtype appears to be increasing

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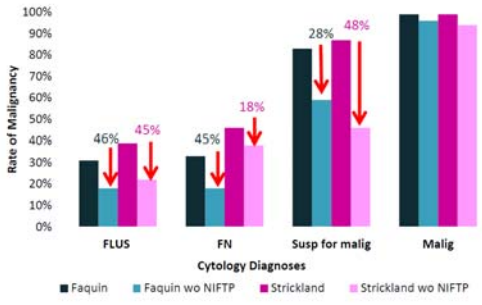
How does this affect rate of malignancy (ROM) for indeterminate cytology?



Faquin Cancer Cytopathol 2016;124:181; Strickland Thyroid 2015:9:987

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NIFTP: Pre-op challenges

- Why is NIFTP difficult to diagnose by cytology?
  - Cannot evaluate capsular invasion
  - Sampling: Sprinkling sign of diagnostic area
  - Architectural heterogeneity of NIFTP
    - Microfollicular, macrofollicular, cystic, fibrotic
    - Some FNA samples may appear "benign"
  - Overlap in nuclear features
    - FA, nodular hyperplasia, FC, invasive FVPTC
  - Cytologic interpretation: **BC IV, BC III**, BC V, BC II, BC VI
  - Inter-observer variability in Surgical Pathology

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BC IV – Suspicious for follicular neoplasm

- Cytologic-histologic correlation for the follicular-patterned thyroid nodules is hampered by the **imperfect reproducibility among histopathologists** in the diagnosis of nodular hyperplasia, follicular adenoma, follicular carcinoma, the follicular variant of papillary carcinoma, and the recently recognized noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

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Key implications for diagnosing NIFTP

- Must submit and evaluate the entire capsule
- Any cases suggestive of invasive growth should be excluded
- Nuclear atypia should be diffuse or multifocal
- Tumor should be predominantly follicular pattern and lack papillary architecture
- Oncocytic versions are not recognized
- Micro (<1 cm) versions are controversial

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Sample report for NIFTP

Example 2
SUSPICIOUS FOR MALIGNANCY.
Suspicious for papillary thyroid carcinoma; see Note.

Note: The overall cytomorphologic features are suggestive of a follicular variant of papillary carcinoma or its recently described indolent counterpart, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Definitive distinction between these entities is not possible on cytologic material.

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NIFTP: Management changes

- **ROM for BC III** had an average decrease from 5.2% to 13.6% → a molecular test with a high negative predictive value might be more appropriate.
- **ROM for BC V** had the greatest impact; decreased from 17.6 to 23.4%→ shift from total thyroidectomy to lobectomy and increased use of a molecular test with high positive predictive value.
- ROM represents a fundamental feature of TBSRTC that influences
  - Management decisions
  - Surgical intervention
  - Ancillary molecular testing

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NIFTP: Management changes

- NIFTP solves an essential thyroid pathology issue
  - Redefines this set of low-risk cancers as "neoplasms" not "carcinomas"
  - Management recommendations:
    - No completion thyroidectomy
    - No radioactive iodine

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BC IV – Suspicious for follicular neoplasm, Hurthle cell type

- Distinction necessary because follicular and Hurthle cell carcinomas are genetically different
- PAX8-PPARγ rearrangement present in 26-53% of follicular carcinomas but rarely in Hurthle cell carcinomas
- 16-25% of cases represent hyperplastic proliferations in NG or HT
- ROM: 10-40%

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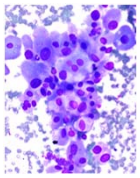
BC IV – Suspicious for follicular neoplasm, Hurthle cell type

- Moderately to markedly cellular aspirates
- Sample consists almost exclusively of Hurthle cells
- Crowded, syncytial arrangements
- Abundant finely granular cytoplasm
  - Representing mitochondrial content
- Enlarged, round nucleus
- Conspicuous nucleoli
- Small cells with high N/C ratio (small cell dysplasia)
- Large cells with at least 2X variability in nuclear size (large cell dysplasia)
- Scant or absent colloid
- Lack of lymphoid component
- Transgressing vessels



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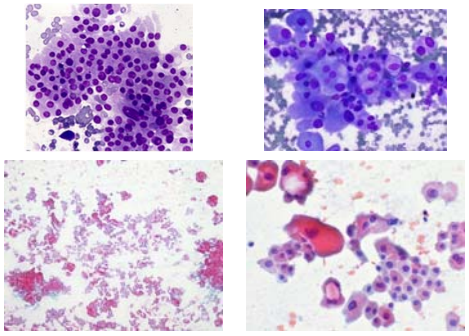
BC IV – Suspicious for follicular neoplasm, Hurthle cell type



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BC IV – Suspicious for follicular neoplasm, Hurthle cell type

Four general problematic scenarios:

1. Hypocellular specimen composed entirely of oncocytes -> AUS is acceptable
2. Cellular specimen composed entirely of oncocytes without atypia/dysplasia:
   - If admixed with abundant colloid -> Benign
   - If absent colloid ->
     - Acceptable to interpret as SFNHCT
     - Acceptable to interpret as benign with a disclaimer
       - "Although the predominance of oncocytes raises the possibility of a HCN, the absence of dysplasia suggests that it is benign."

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BC IV – Suspicious for follicular neoplasm, Hurthle cell type

3. Abnormal specimens with partial or minimal Hurthle cell differentiation
   - WHO guidelines: Follicular neoplasms that are comprised of >75% Hurthle cells are considered HC neoplasms.
   - If <75% HC -> SFN
4. Abnormal specimen with colloid
   - Predominant Hurthle cell population with dysplasia and watery colloid -> SFNHCT

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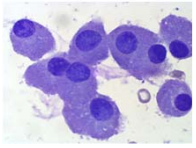
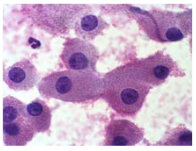
Conditions Associated with Hurthle Cell Changes

- Adenomatous goiter
- Hashimoto's thyroiditis
- Grave's disease
- Radiation changes
- Hurthle cell neoplasms





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Cytologic Features of Neoplastic and Non-Neoplastic Hurthle Cell Lesions

	Hurthle cell neoplasm	Adenomatous nodule with oncocytic features	Hashimoto thyroiditis
Hurthle cells	Abundant Hurthle cells: • Single cells • Macronucleoli	Oncocytic metaplasia: • Cohesive flat sheets • Indistinct nucleoli	Few Hurthle cells: • Small groups • Macronucleoli
Macrofollicles	Absent	Present	Few
Colloid	Absent	Watery colloid present	Scant to absent
Lymphocytes	Absent	Absent	Present

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BC IV – Suspicious for follicular neoplasm, Hurthle cell type

Differential diagnosis:

- Medullary carcinoma
- Granular cell tumor
  - Strongly reactive to S100 and negative for keratins
- Parathyroid adenoma/carcinoma
  - Only 20-30% of parathyroid lesions are recognized on FNAs
  - If clear cyst fluid, send for PTH chemical analysis

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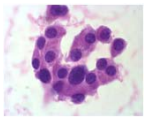
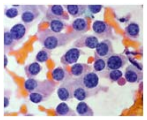
Hurthle Cell Neoplasm vs Medullary Carcinoma

- Hurthle Cell Neoplasm
  - Well defined cell borders
  - Granular or dense cytoplasm
  - Fine chromatin pattern
  - Inclusions rare
  - Scanty or absent colloid
  - Amyloid absent
  - Calcitonin negative



- Medullary Carcinoma
  - Poorly defined cell borders
  - Pale or fibrillary cytoplasm
  - Coarse chromatin pattern
  - Inclusions always present
  - Absent colloid
  - Amyloid present
  - Calcitonin positive



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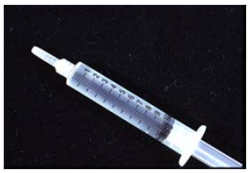
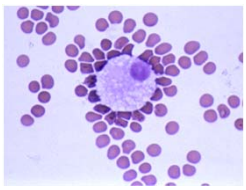
Parathyroid cyst

- Gross: Clear, watery fluid
- Smears hypocellular, and often called "unsatisfactory"
- Diagnostic test
  - PTH (C-terminal or mid-molecule) assay on cyst fluid





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BC V - Suspicious for Malignancy

- Definition: when cytomorphologic features raise strong suspicion but findings are not sufficient for conclusive diagnosis.
- Reasons for diagnosis of SFM:
  - Suboptimal sampling or poor cellular preservation
  - Unusual variants
  - Overlapping cytomorphologies
  - Reactive, involutional or metaplastic changes in LT

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BC V- Suspicious for malignancy

- Prevalence: 3% (range 1.0-6.3%) of thyroid FNAs
- ROM, when NIFTP considered indolent: 45-60%
  - Overall decrease pf ROM with NIFTP: 15-20%
- Usually cases suspicious but not entirely diagnostic of PTC
  - SFN or HCN are excluded from this category
  - Hyalinizing trabecular adenoma
    - Cytoplasmic staining for MIB-1 distinctive in this lesion
- Suspicious for MTC
  - Calcitonin, syn, chomo
- Suspicious for lymphoma
  - Repeat for flow, with ROSE preferred
- Suspicious for malignancy, NOS

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BC V - SFM criteria

Pattern A: Patchy nuclear changes

- Moderate to high cellularity
- Unremarkable follicular cells admixed with cells showing nuclear enlargement, pallor, grooves, membrane irregularity and/or molding
- Intranuclear pseudoinclusions (INCIs) few or absent
- Psammoma bodies and papillary architecture

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BC V - SFM criteria cont…

Pattern B: Incomplete nuclear changes

- Generalized mild-moderate nuclear enlargement and pallor
- Nuclear grooves evident and nuclear membrane irregularity and molding are minimal to absent
- INCIs few or absent and psammoma bodies papillary architecture is absent

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BC V - SFM criteria cont…

Pattern C: Sparsely cellular specimen

- Many features of PTC present by low cellularity

Pattern D: Cystic degeneration

- Hemosiderin-laden macrophages
- Scattered enlarged or pale nuclei and some nuclear grooves BUT INCIs few or absent and psammoma bodies or papillary architecture absent
- Occasional large atypical histiocytoid cells

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Histiocytoid cells, suspicious for PTC

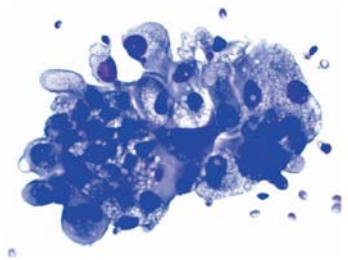

Fig. 7.4 Suspicious for papillary thyroid carcinoma. There is a loose sheet of histiocytoid cells with vacuolated cytoplasm, occasional small nucleoli, and small intranuclear pseudoinclusions (smear, Diff-Quik stain).

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PTC with histiocytoid cells

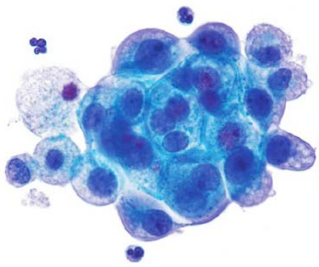

Fig. 8.19 Papillary thyroid carcinoma, cystic variant. Most of the cells in this image are neoplastic. They have abundant granular cytoplasm, hence the descriptor "histiocytoid." Classic nuclear features of papillary thyroid carcinoma are absent, but there is conspicuous nuclear enlargement (ThinPrep, Papanicolaou stain).

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Subcategories of SFM and etiologies

Suspicious for…

- PTC
- MTC
- Metastatic carcinoma
- Lymphoma
- Some NIFTPS = SFM or AUS/FLUS
- Hyalinizing trabecular tumors with many morphologic features of PTC

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BC VI: Malignant
Histologic subtypes of thyroid cancers

- PTC 70-80%
  - Tall cell variant (4% of PTCs)
  - FVPTC (18% of PTCs)
    - NIFTP
- Follicular carcinoma 6-10%
- Medullary carcinoma 3-4%
- Anaplastic carcinoma 1-2%
- Poorly diff carcinoma 0-7%
- Metastases
- Lymphoma

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BC VI – PTC

- Larger tissue fragments, papillary branching fronds, monolayered, syncytial
- Cuboidal, columnar, oval, polygonal, Hurtloid, squamoid, spindle cells
- Nucleus with granular, powdery dusty chromatin, slightly eccentric, linear chromatin ridges, intranuclear cytoplasmic inclusions
- Multiple micro- or macronucleoli
- Cytoplasm pale, foamy, vacuolated or dense

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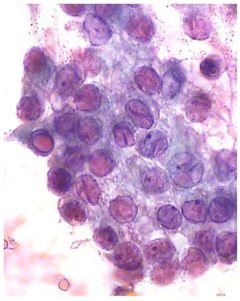
Papillary thyroid carcinoma

- Diagnosis is dependant on characteristic nuclear features:
  - hypochromasia
  - nuclear grooves
  - intranuclear pseudoinclusions
  - ovoid nucleus
  - micronucleolus



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Secondary cytomorphologic features of PTC

- Psammoma bodies
- Multinucleated foreign-body-type giant cells
  - Dense cytoplasm
  - Nuclei resemble those of carcinoma cells
  - Possibly derived from cancer cells
- Sticky colloid, in strands or blobs, dense staining (ropy colloid)
- Degenerative changes: histiocytes with or without hemosiderin
- Lymphocytic infiltrate

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PTC with histiocytoid cells

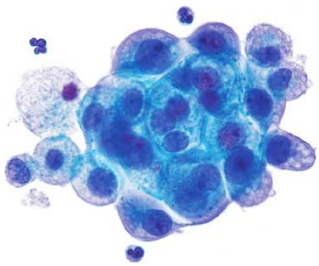

Fig. 8.19 Papillary thyroid carcinoma, cystic variant. Most of the cells in this image are neoplastic. They have abundant granular cytoplasm, hence the descriptor "histiocytoid." Classic nuclear features of papillary thyroid carcinoma are absent, but there is conspicuous nuclear enlargement (ThinPrep, Papanicolaou stain).

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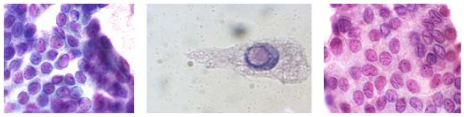
MINIMAL CRITERIA FOR PAPILLARY CARCINOMA

1. Syncytial arrangement of enlarged nuclei
2. Dusty, powdery chromatin pattern
3. Nuclear grooves
4. Nuclear pseudoinclusions
5. Multiple micro- and macronucleoli



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Papillary Tissue Fragments in Cytologic Samples

- Papillary carcinoma
- Papillary hyperplasia in nodular goiter
- Papillary change in follicular adenoma
- Hashimoto's thyroiditis

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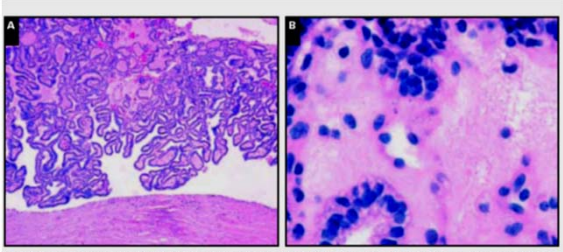

Image 5 A case of papillary hyperplastic nodule showing a well-formed papillary structure with complex growth pattern (**A**; H&E, ×20). **B**, High power showing lining cells with basally located, round nuclei lacking features of papillary carcinoma and edematous papillary core (H&E, ×100).

Baloch & Livolsi - Cytologic and Architectural Mimics of PTC - Am J Clin Pathol 2006;125(Suppl 1):S135-S144

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Differential Diagnosis

- Papillary hyperplasia
  - Peripheral nuclear palisading
  - Honeycomb pattern, well defined cell borders, cell polarity
  - Granular, uniformly distributed chromatin
  - Absent nuclear ridge
  - Micronucleoli +/-
  - Absent intranuclear inclusions
- Papillary carcinoma
  - Peripheral nuclear palisading
  - Syncytial clusters, crowded overlapped nuclei, altered polarity
  - Dusty chromatin
  - Present nuclear ridge
  - Multiple micro- &/or macronucleoli
  - Present intranuclear inclusions

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BC VI – Metastases to thyroid

- Mets to thyroid
- Incidence: 1-24% among cancer patients
- Most common sites
  - Lung
  - Kidney
  - Breast
  - Melanoma
- Thyroid may be involved by contiguous spread from esophageal or laryngeal cancers

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Metastases to thyroid

- **Breast**: Immunohistochemical stains for thyroid (e.g., thyroglobulin, TTF-1, calcitonin and PAX-8) and for breast antigens (e.g., estrogen and progesterone receptors, mammaglobin, and GATA-3) can be helpful for the separation of metastatic mammary carcinoma from benign and malignant neoplastic follicular/parafollicular cells.
- **Squamous cell carcinoma**: Immunohistochemistry for p40 can be helpful in identifying poorly differentiated squamous cell carcinomas. The distinction between a primary squamous carcinoma of the thyroid and a metastasis from a squamous cell carcinoma of the lung, however, is not possible based on cytomorphology or immunoprofile. Clinical history and imaging findings are indispensable for separating these two neoplasms.

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Metastases to thyroid

- Immunostaining for thyroid markers (e.g., thyroglobulin, TTF-1, PAX8, calcitonin) and RCC markers (e.g., RCC antigen, CA9, CD10) can aid in the differential diagnosis.
- Melanoma: Cells are usually immunoreactive for S-100 protein, melanA, SOX-10, and HMB45.
- Primary thyroid carcinomas with melanin pigment have been reported and are a histologic variant of medullary carcinoma of the thyroid. Immunocytochemistry can be helpful in this distinction: positivity for calcitonin favors a medullary thyroid carcinoma.

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