Thyroid Cytopathology –
Bethesda and Beyond

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Thyroid Cytology– Basic Facts

- Thyroid nodules are common - any thyroid disease can present as a nodule - most are predominantly benign
- Inability to distinguish malignant from benign thyroid nodule with non-invasive techniques
- FNA has proven to be the single most accurate diagnostic test for patients with thyroid nodules → for appropriately triaging of patients with malignant nodules for surgery (ATA Guidelines 2009, 2015)
  - 50% decrease in thyroid surgeries, doubling of % of thyroid cancer detected at surgery – 21% to 41% (Gharib, 1993)
- The rate of thyroid FNA has markedly increased "epidemic"
- At Johns Hopkins - septupled in the last 10 years

Thyroid FNA Terminology

- Succinct, unambiguous, clinically relevant → clarity of communication
- Endorsed by all in the multidisciplinary team
- Probabilistic approach
- Robust and reproducible morphologic criteria → exchange of data across institutions
- Well-defined clinical management algorithms

TBSRTC – Diagnostic Categories

- Nondiagnostic or Unsatisfactory*
- Benign
- Atypia of Undetermined Significance (AUS) or FLUS*
- Suspicious for a Follicular Neoplasm or FN*
- Suspicious for Malignancy
- Malignant

What Bethesda Really Said!

"The Busy World of Thyroid Terminologies"

Bethesda (NCI) 2007	UK (BTA/RCPath) (2007) 2009	Italian (SIAPEC-IAP) (2007) 2014
ND	Thy 1, Thy 1c	TIR1, TIR1C
Benign	Thy2	TIR2
AUS/FLUS	Thy3a	TIR3A (LRIL)
SFN/FN	Thy3f	TIR3B (HRIL)
SFM	Thy4	TIR4
Malignant	Thy5	TIR5

TBSRTC - Probabilistic Approach and Relationship to Clinical Algorithms

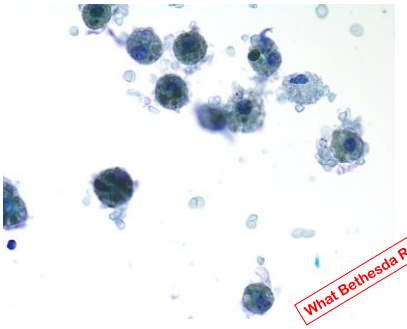
	ROM (%)	Management
Nondiagnostic	1-4	Repeat FNA with US
Benign	0.5-5.5	Follow-up
AUS/FLUS	~5-10 (15-32)	Repeat FNA
Suspicious for a FN/FN	15-30	Lobectomy
Suspicious for Malig	60-77	Lobectomy or total thyroidectomy
Malignant	96-99	Total thyroidectomy

Nondiagnostic
PPV 1-4%

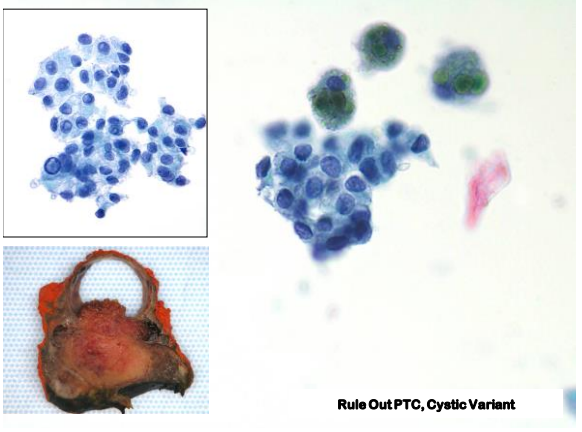
- Incidence: 2-20% (<10%)
- Specimen processed and examined
- Adequacy criterion
  - At least 6 groups, each with at least 10 benign-appearing, well-visualized follicular cells
- Exceptions
  - Chronic lymphocytic thyroiditis
  - Abundant colloid
  - Any atypia
- **Reaspirate at 3mo with US**

What Bethesda Really Said!

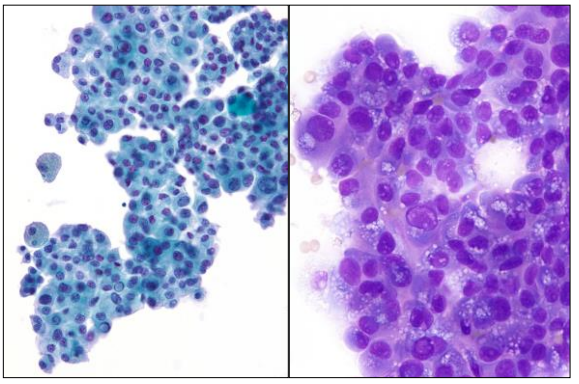
Macrophages - Cyst Fluid Only
"The CFO Dilemma"



What Bethesda Really Said!



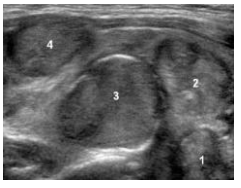
Rule Out PTC, Cystic Variant

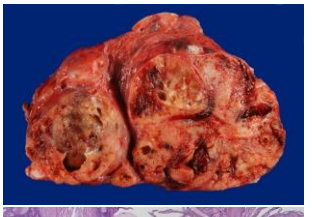


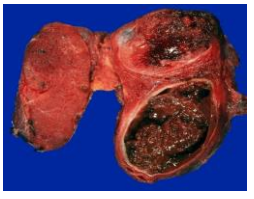
"Hypervacuolization"

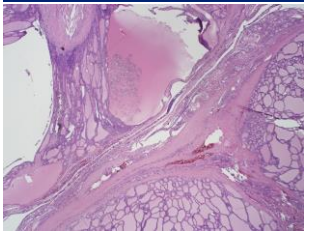
Benign
PPV 0.5%-5.5%

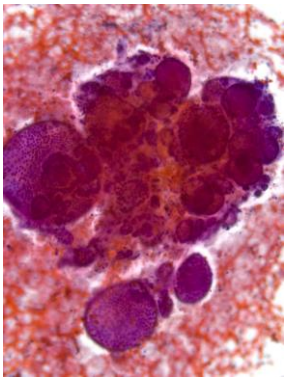
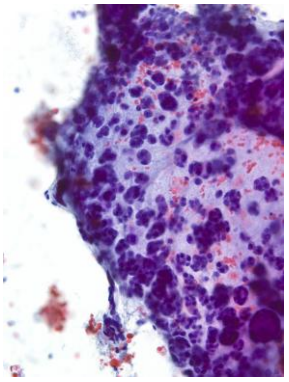
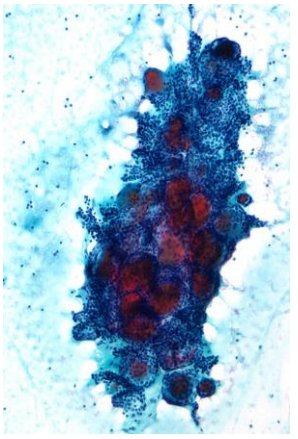
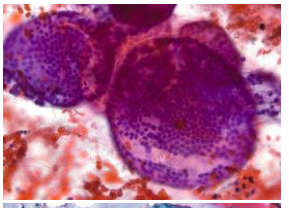
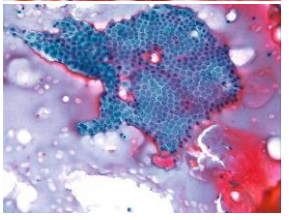
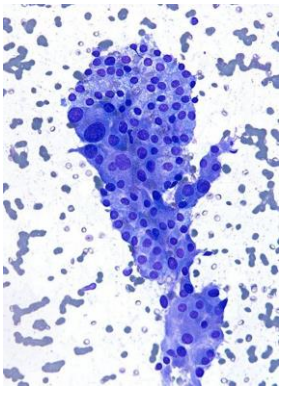
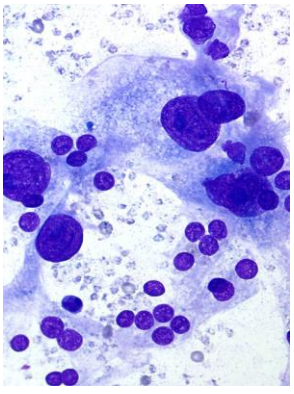
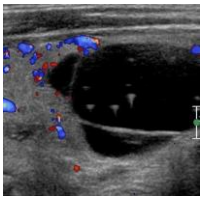
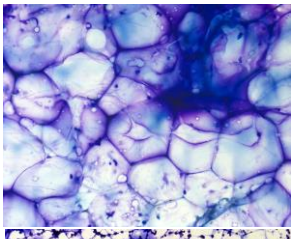
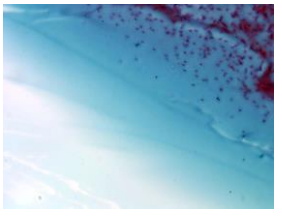
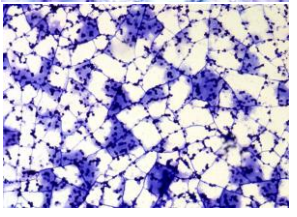
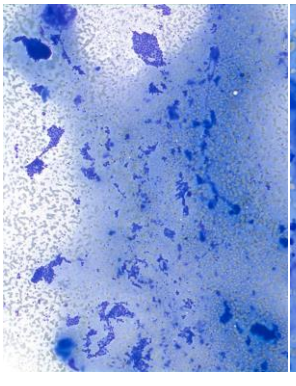
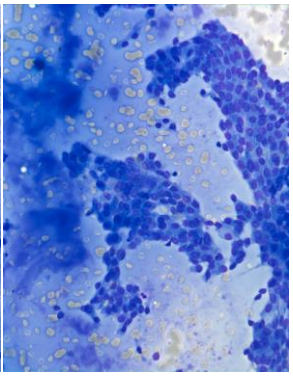
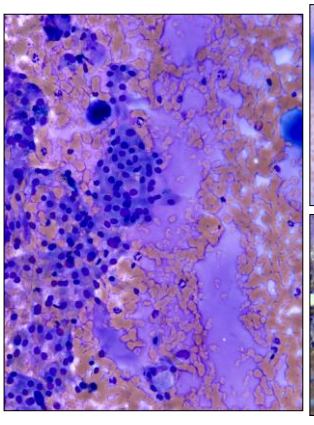
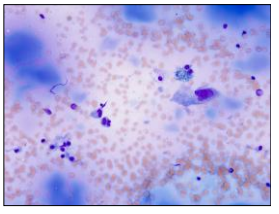
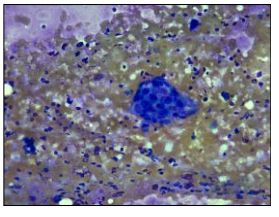
- Incidence: 60-65%
- This category includes
  - Hyperplastic / Adenomatoid nodule
  - Colloid nodule
  - Chronic lymphocytic thyroiditis
  - Graves' Disease
- F/U by clinical and possibly US examination

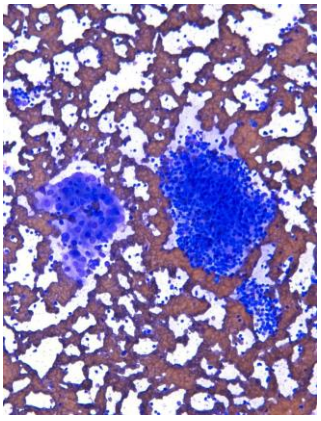


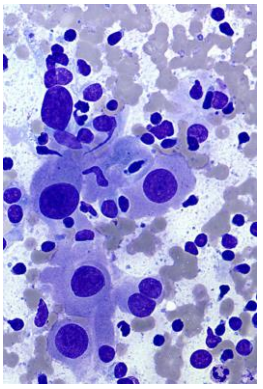


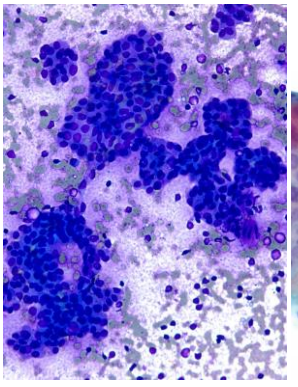


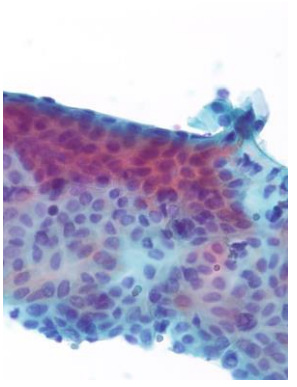


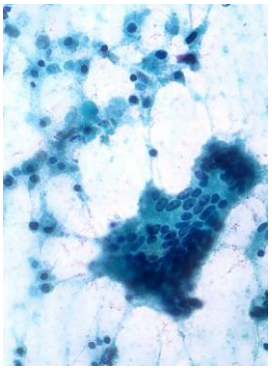



















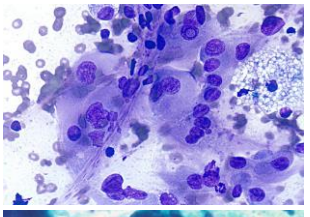


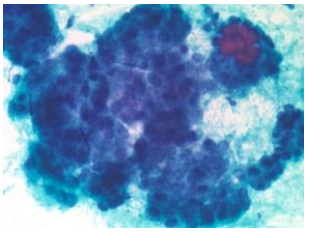


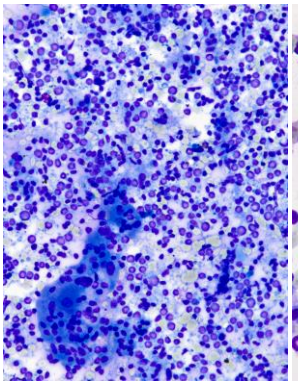


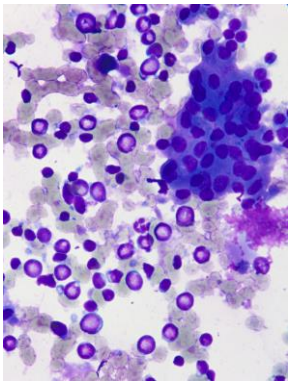


"The Leading Pitfall"





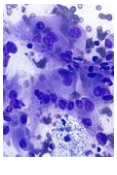


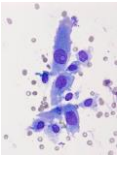


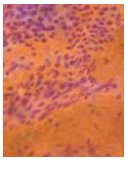
AUS/FLUS -
Birth Of An Entity

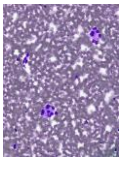
Benign

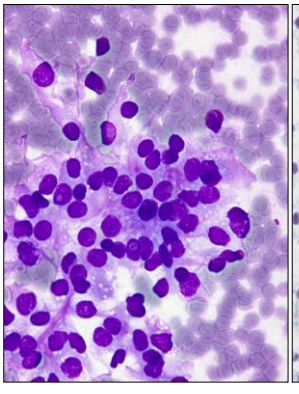
SFN or SFM

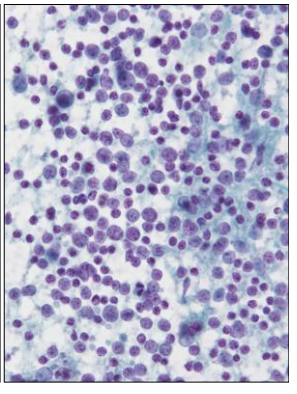












Atypia of Undetermined Significance (AUS)

PPV 15-32% (5-10%)

- The "Indeterminate" or "I don't know" Dx
- Do not fit easily into Benign or Suspicious categories
- 8 specific qualifying morphologic scenarios
- Recommended management: repeat FNA
- Surgery considered for "repeat AUS cases"

What Bethesda Really Said!

AUS– Important Facts

- A single diagnosis carries a low risk
- Avoid overuse of this category (useful benchmark 7-10%)
- Impact of new molecular tests
- Post-AUS diagnosis
  - 50% - benign
  - 50% - more significant lesion (follicular neoplasm and above) or a repeat AUS

AUS– Hopkins Experience

(n=3,956, 26-month)

- Rate 9.8% (AUS:M – 3.2)
- AUS – Nuclear, Follicular, Other
- Risk of Malignancy – 32%
  - AUS – N 48%
  - AUS – F 27%
  - AUS – O 12%

(Olson et al. Acta Cytol, 2012)

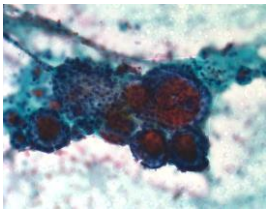
Suspicious for a Follicular Neoplasm or Follicular Neoplasm

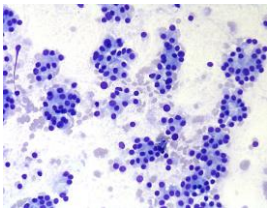
PPV 15-30%

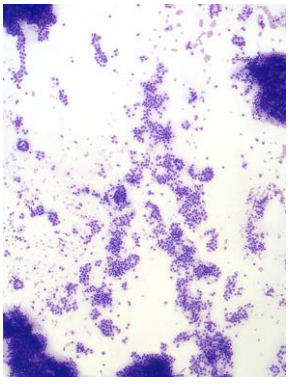
- Incidence: 7-18%
- Significant architectural atypia -
  - a predominance of microfollicles and/or trabecula
- Raising the possibility of follicular carcinoma
- Distinction between follicular adenoma and CA
- Surgery (usually lobectomy) is needed for definitive diagnosis

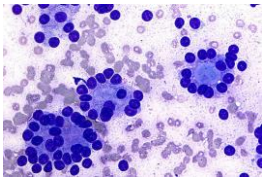
What Bethesda Really Said!

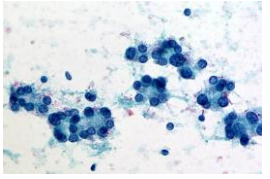
Macrofollicles Vs. Microfollicles

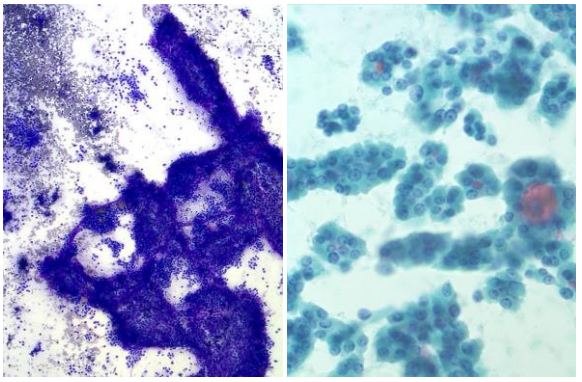


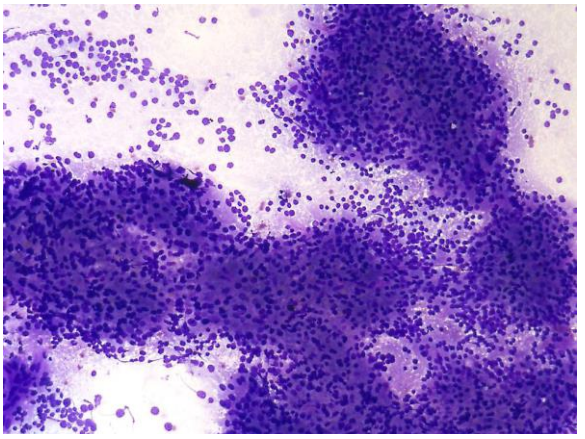


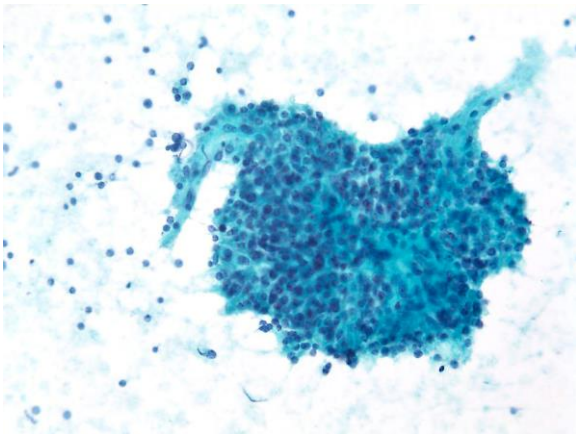


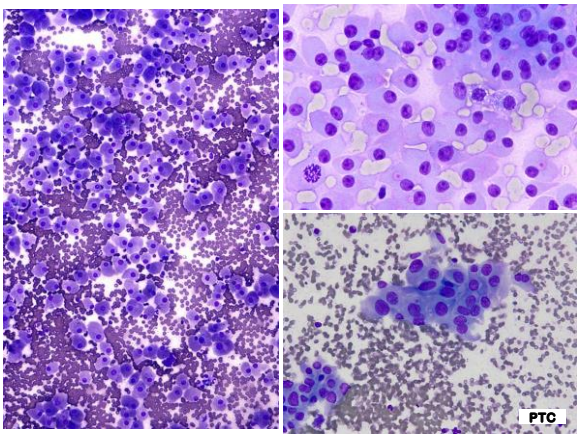


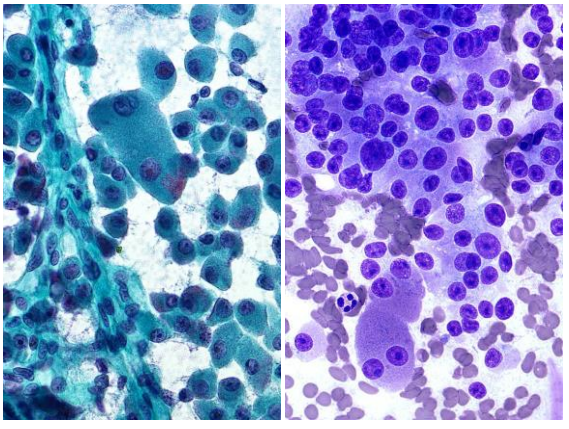


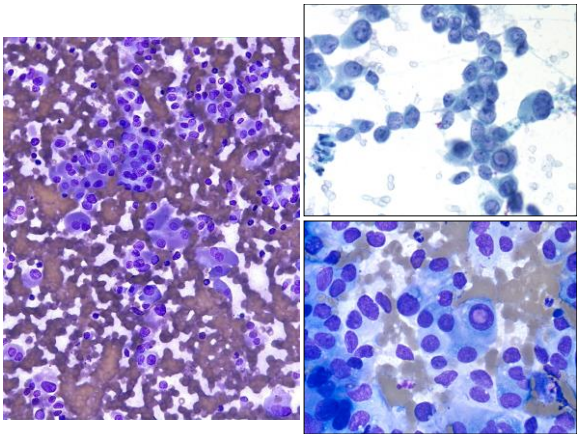







PTC





"Indeterminate" Thyroid Nodule

Commercial Molecular Diagnostic Tests
"Mutational Panels"

- Increase pre-operative diagnostic accuracy
- FNA specimens excellent source for molecular testing
- Very expensive
  - Diagnoses malignancy (PPV)
    - miRInform – Asuragen® ($ 2250)
  - Exclude malignancy (NPV)
    - Afirma GEC – Veracyte® ($ 3350 – 4,800)

"Indeterminate" Thyroid Nodule

Commercial Molecular Diagnostic Tests
"Mutational Panels"

The "Rule Out" Test

- **Afirma®**
  - Analyze expression of 142 genes – multidimensional algorithm
  - Results – Benign (53%) or Suspicious (38%)
  - NPV -94%, PPV- ~50%
  - Cost effectiveness (avoid surgery in ~43% of indeterminates)

"Indeterminate" Thyroid Nodule

Commercial Molecular Diagnostic Tests
"Mutational Panels"

The "Rule In" Test

- **miRInform®**
  - 7 molecular markers, DNA and RNA based
  - Analyze 17 mutations and translocations
  - 4-gene classifier (BRAF, RET/PTC, PAX8/PPARg and RAS)
  - PPV- 87%. NPV-72%
  - ? Cost effectiveness (decrease in completion thyroidectomies)

"Indeterminate" Thyroid Nodule

Commercial Molecular Diagnostic Tests
NexGen Sequencing Panel

The "Rule In+Rule Out" Test

- **ThyroSeq® (V 2.0)**
  - Next generation sequencing panel
  - Simultaneous sequencing and detection in >1000 hotspots of 14 thyroid cancer-related genes and for 42 types of gene fusions
  - Diagnosis and prognosis
  - NPV-96%, PPV-83%
  - Specificity-93%, Sensitivity-90%
  - Cost - $ 3,700

What's the final word?

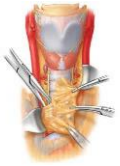
1. AUS/FLUS should get a repeat FNA
2. Decision for DNR-Surgery can be selectively made based on patient's risk factors and subcategory of the AUS/FLUS
3. In centers with provision of GEC test, there is a definite value in DNR-GEC test
4. GEC followed by GMP in GEC-suspicious cases is a new and expensive concept and requires validation

BRAF Analysis

- Most common mutation in PTC
- Most specific marker for PTC (PPV 99%)
- Low sensitivity (51%)
  - Even lower in PTC-FV (24%)
- Associations
  - Older age
  - Aggressive Phenotype
    - LN mets
    - Distant mets
    - Higher TNM stage
    - Recurrent and persistent disease

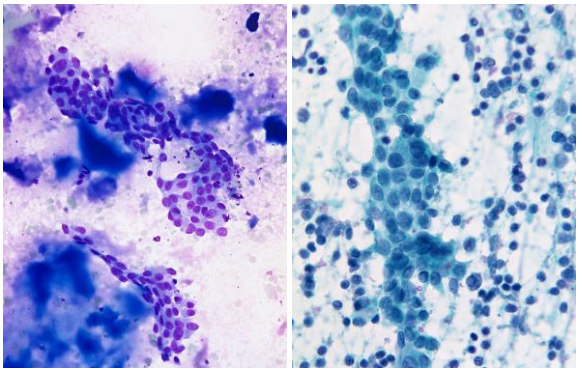
Suspicious for PTC or PTC Role of BRAF Analysis

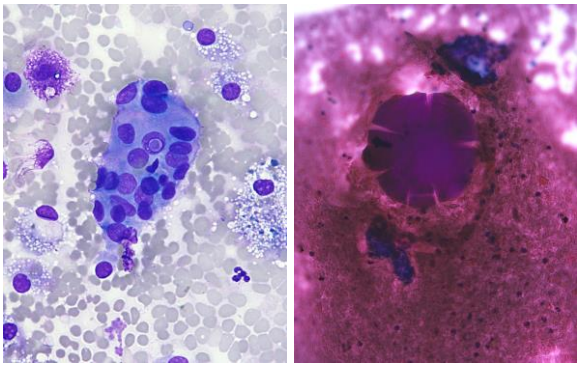
? Central Neck (Level VI) Dissection
(Post-op Complications)

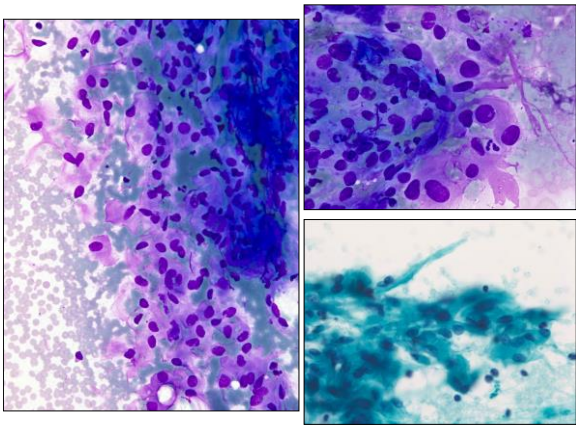


Suspicious for Malignancy
PPV 60-65% (up to 77%)

- Suspicious for Papillary Carcinoma
- Suspicious for Medullary Carcinoma
  - Serum calcitonin level
- Suspicious for Malignant Lymphoma
  - Recommendation to repeat FNA with flow cytometry
- Suspicious for Metastatic Cancer

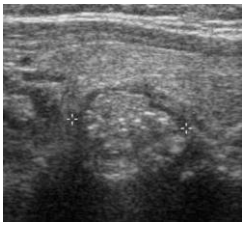


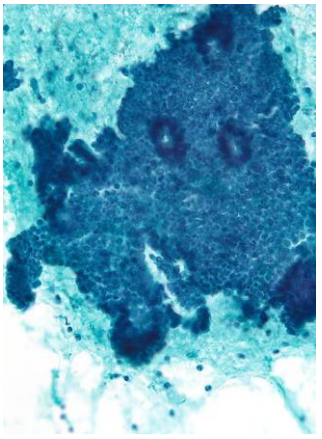


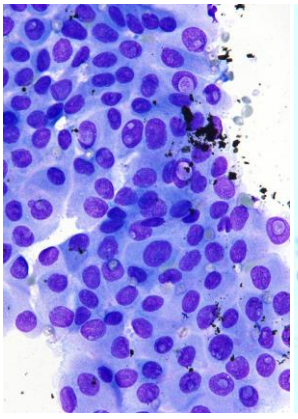


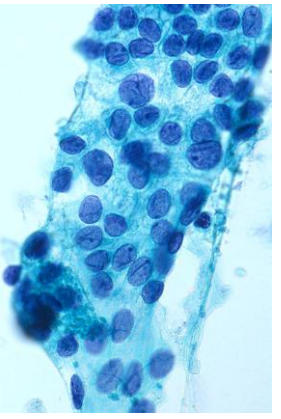
Malignant
PPV 96-99%

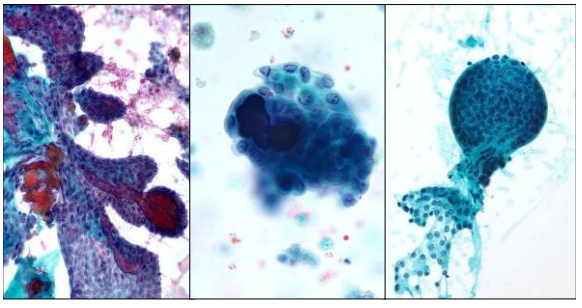
- Papillary carcinoma
  - Variants
- Medullary carcinoma
- Poorly differentiated carcinoma
- Anaplastic carcinoma
- Lymphoma
- Metastatic cancers
- Other

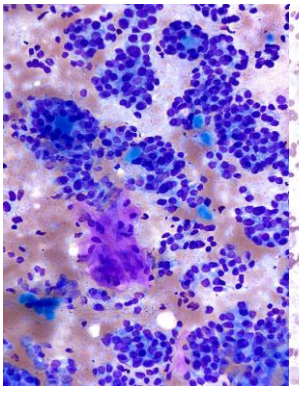


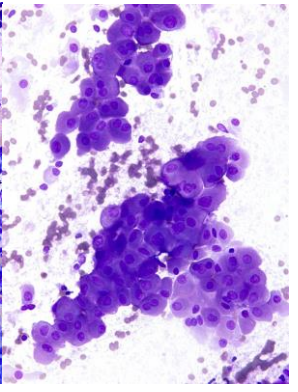


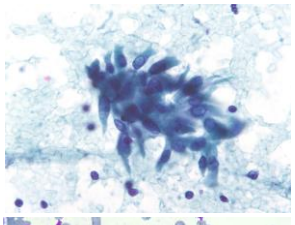


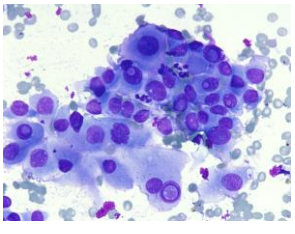


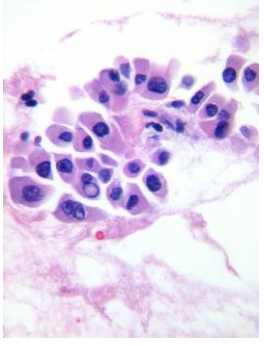


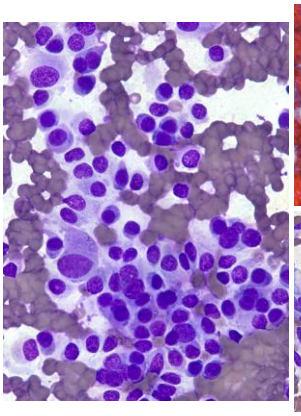


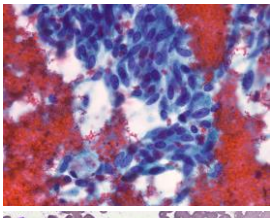


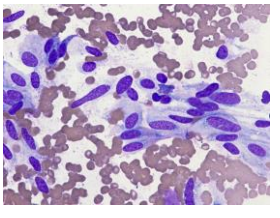


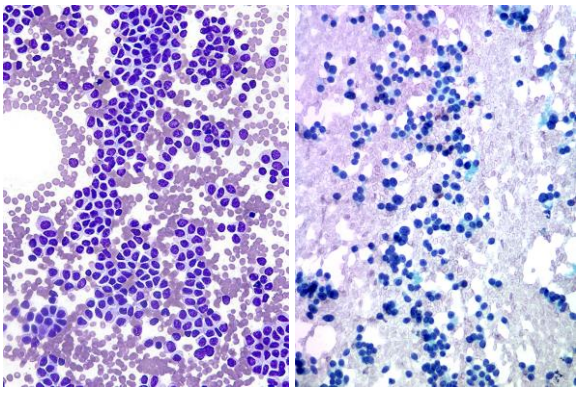


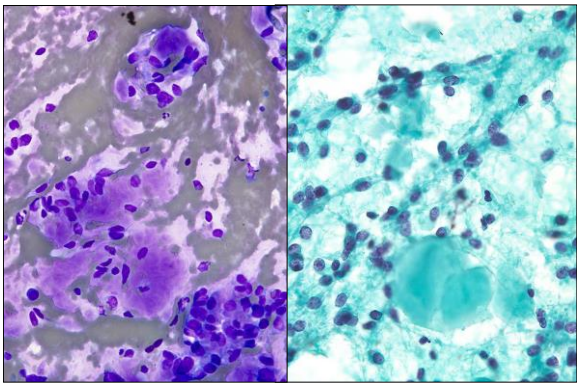


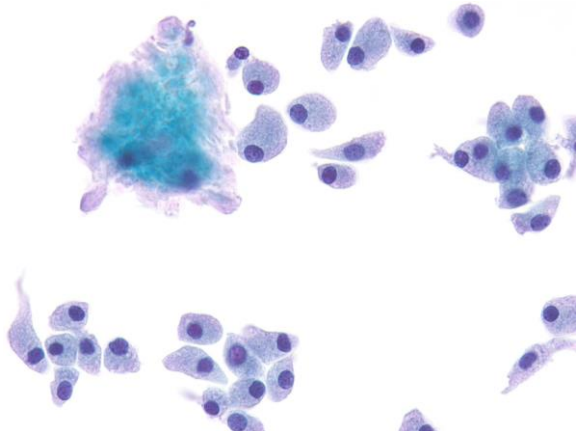


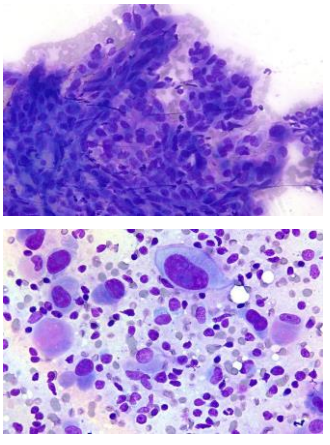


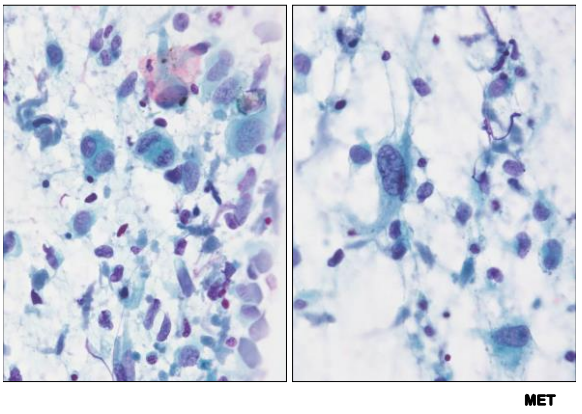












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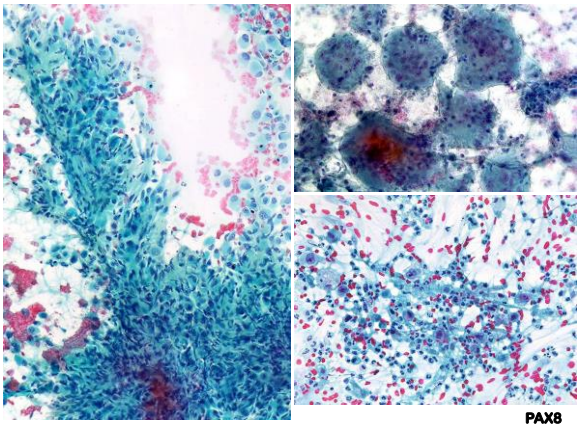

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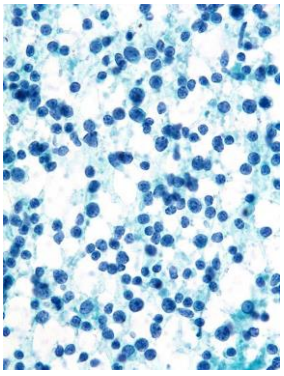

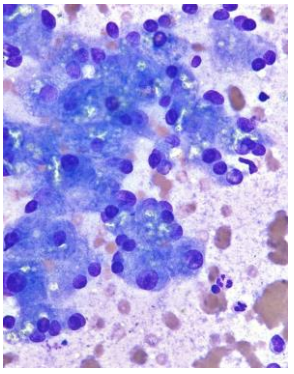

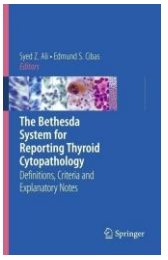

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April 5, 2016