NCI Thyroid FNA Conference

Subcommittee IV

Diagnostic Terminology / Morphologic Criteria

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Thyroid FNA Diagnostic Terminology

Classification Scheme

Classification Schemes

- Papanicolaou Society – 1997
- American Thyroid Association – 2006
- American Association of Clinical Endocrinologists (AACE) & Associazione Medici Endocrinologi (AME) - 2006

Papanicolaou Society of Cytopathology Task Force on Standards of Practice– 1997

5 Categories

- Inadequate / Unsatisfactory
- Benign
- Atypical Cells Present
- Suspicious for Malignancy
- Malignant

American Thyroid Association – 2006

4 Categories

- Inadequate
- Malignant
- Indeterminate
  - Suspect for neoplasia
  - Suspect for carcinoma
- Benign

American Association of Clinical Endocrinologists & Associazione Medici Endocrinologi - 2006

4 Categories

- Benign
- Malignant or Suspicious
- Follicular neoplasia
- Non-diagnostic or Ultrasound suspicious

Review
Four Category Schemes

Benign	*Benign*	*Benign (goiter)*	*Benign*	*Benign*
Indeterminate	*Indeterminate / suspicious*	*Inflammatory*	*Thyroiditis*	*Hurthle cell lesion / Neoplasm*
Suspicious	*Cancer*	*Neoplasm / Indeterminate*	*Indeterminate*	*Cellular follicular lesion*
Malignant	*Follicular neoplasm / adenoma*	*Malignant*	*Neoplasm / Malignant*	*Malignant*

Review
Five Category Schemes

Benign	*Benign*	*Benign*	*Benign – Adenomatoid nodule*	*Benign Tumor*
Indeterminate	*Neoplasm*	***Follicular Adenoma***	*Hashimoto's Thyroiditis*	*Thyroiditis*
Atypical	*Atypical*	*Adenoma – possible Ca*	*Follicular neoplasm*	*Hurthle cell tumor*
Suspicious	*Suspicious*	*Suspicious*	*Indeterminate*	*Suspicious for malignancy*
Malignant	*Malignant*	*Carcinoma*	*Carcinoma*	*Malignant*

Web Site Posts / Controversies

I have been using five categories since 1994

- **1:malignant (i.e. papillary ca, medullary ca)**
- **2: suspicious for malignancy**
  - **(i.e. FVPC, microcarcinomas, because I worry the tiny nodule may not be found by the resident who gross the specimen)**
- **3: most likely benign**
  - **but cannot entirely exclude malignancy (large microfollicular nodules)**
- **4: benign**
  - **but need monitor**
  - **(hyperplastic nodule, i.e. small microfollicular nodules, it will be a over treatment to have lobectomy for most likely benign small nodule); 5:benign, and forget about it (colloid nodule).**
  - The term "microfollicular nodule", to me, are limited to "exceedingly bloody aspirate containing microfollcles with normal nuclear features", and exclude microfollicles in a background of thin colloid, or microfollicles with nuclei worrisome for follicular variant of papillary carcinoma.
- 5: Unsatisfactory category to me means blood only, no colloid and no follicles.

About 15 years ago we got rid of the confusing "Inconclusive". category. **We have 4 / 5 categories.**

- **Negative**
- **Suspicious**
  - **further qualified in a descriptive diagnosis section of the report. i.e. Follicular neoplasm, or Papillary ca or Hurthle cell neoplasm etc**
- **Positive - malignant**
- **unsatisfactory and non diagnostic**
  - **This made life a lot easier for my clinicians as well as pathologists and radiologists.**

We have found the following categories to be useful at our institution

- 1. Unsatisfactory
- 2. Negative for malignancy
- 3. Other/ Indeterminate for neoplasm
  - (not indeterminate for malignancy). We repeat FNA in 6 months for these cases if it is the first FNA with this diagnosis
  - These are usually grey zone lesions- hyperplastic nodule versus follicular neoplasm or Hurthle cell nodules that need clinical work up or follow up for metaplasia versus neoplasia.
- 4. Neoplasm: follicular/ Hurthle neoplasm.
- 5. Suspicious for malignancy
  - usually Papillary ca, but also follicular neoplasm cannot rule out follicular variant of papillary carcinoma
- 6. Malignant

Web Site Posts / Controversies

1. Benign nodular goiter/colloid nodule
2. Benign cyst contents
3. Follicular neoplasm
4. Suspicious for follicular neoplasm
5. Papillary carcinoma
6. Suspicious for papillary carcinoma
7. Medullary carcinoma
8. Suspicious for neoplasm, N.O.S
9. Hashimoto's/lymphocytic thyroiditis
10. Insufficient for diagnosis
11. Benign thyroid cells/elements, but non-diagnostic
12. lymphoma/suspicious for lymphoma

Web Site Posts / Controversies

- 1 Non diagnostic
- 2 Colloid (or macrofollicular) nodule without atypia
- 3 Colloid (or macrofollicular) nodule with atypia
- 4 Microfollicular nodule without atypia
- 5 Microfollicular nodule with atypia
- 6 Mixed micro-macro follicular nodule without atypia
- 7 Mixed micro-macro follicular nodule with atypia
- 8 Hürthle cell nodule without atypia
- 9 Hürthle cell nodule with atypia
- 10 Thyroiditis
- 11 Suspicious for follicular carcinoma
- 12 Suspicious/ suggestive of papillary carcinoma
- 13 Suspicious/ suggestive of CMT
- 14 Suspicious/ suggestive of lymphoma or metastasis

I prefer a simpler rather than more complicated set of nomenclature

- Non-diagnostic
  - with an explanation for the reason, generally scant cellularity or cyst contents with no follicular cells.
- Negative: Broken down into separate categories
  - Benign Thyroid Nodule
  - Hashimoto's thyroiditis
- Suspicious: Broken down into the following separate categories
  - Suspicious for follicular neoplasm
  - Suspicious for Hürthle cell neoplasm
  - Suspicious for papillary carcinoma
  - Suspicious for other such as lymphoma, metastasis etc.
- Positive
  - Used when a definitive diagnosis of a specific malignant entity can be made.

I agree with the 6 tiered system

- 1. Non-diagnostic
- 2. Non-neoplastic
- 3. Cellular Follicular Lesion-defer (whatever this is called)
- 4. Suspicious for FN / HN (or whatever terminology is agreed upon)
- 5. Suspicious for Malignancy (mostly papillary ca)
- 6. Malignancy (mostly pap ca)

What most of us saying …

1. Benign
2. Don’t know – Follow & Repeat FNA
3. Suspicious - Surgery
    1. Neoplasm
    2. Carcinoma
4. Carcinoma
5. Non diagnostic / unsatisfactory

Committee Members

Almost all committee members except one support the tiered classification scheme

Website Responses
+
Committee Members

Proposal

6 Category System

Or

7 Category System

Proposed Scheme – Not done yet

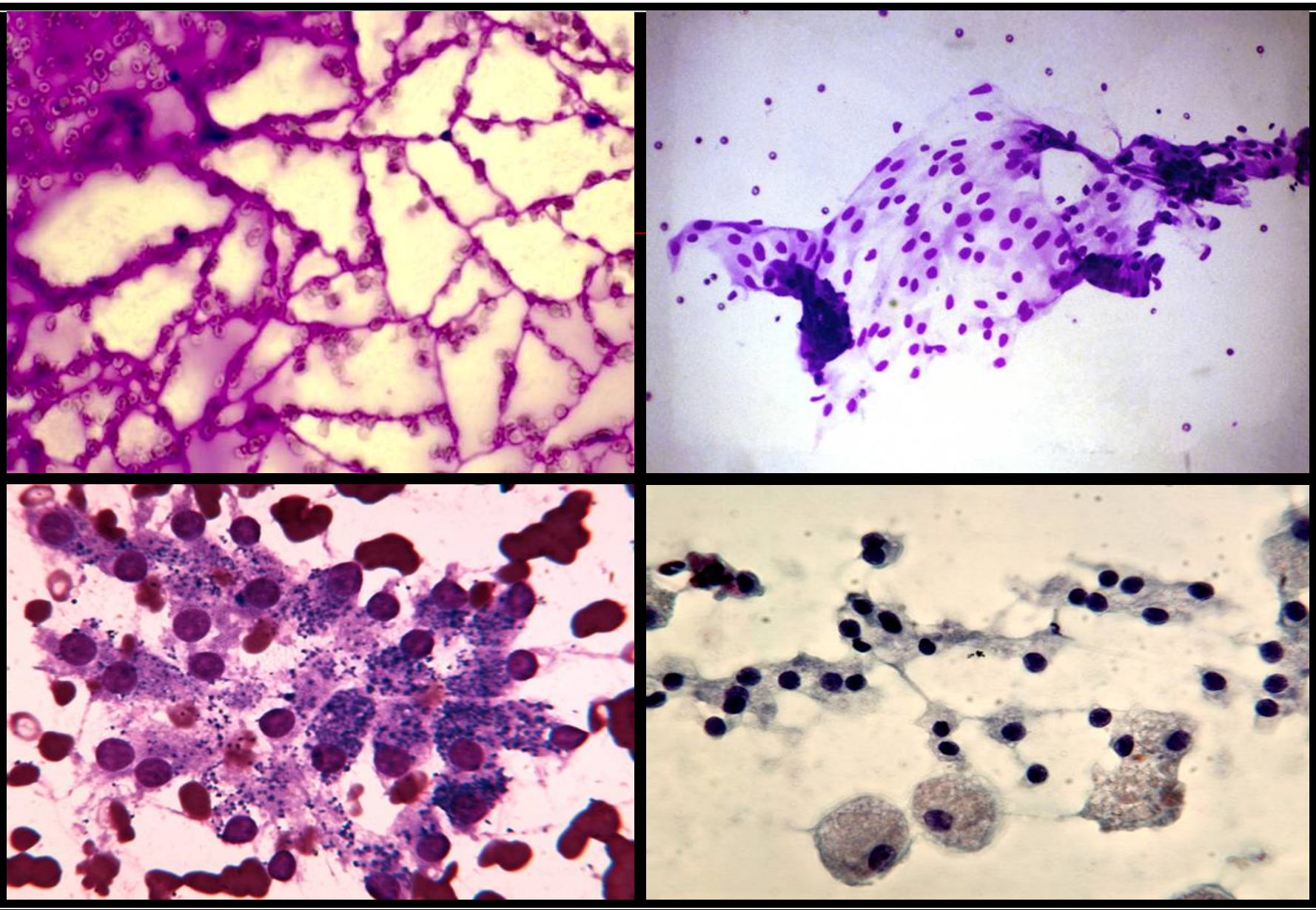
- Benign
- Follicular lesion of Undetermined Significance ? (term to be determined)
- Neoplasm
- Suspicious
- Malignant
- Non-Diagnostic

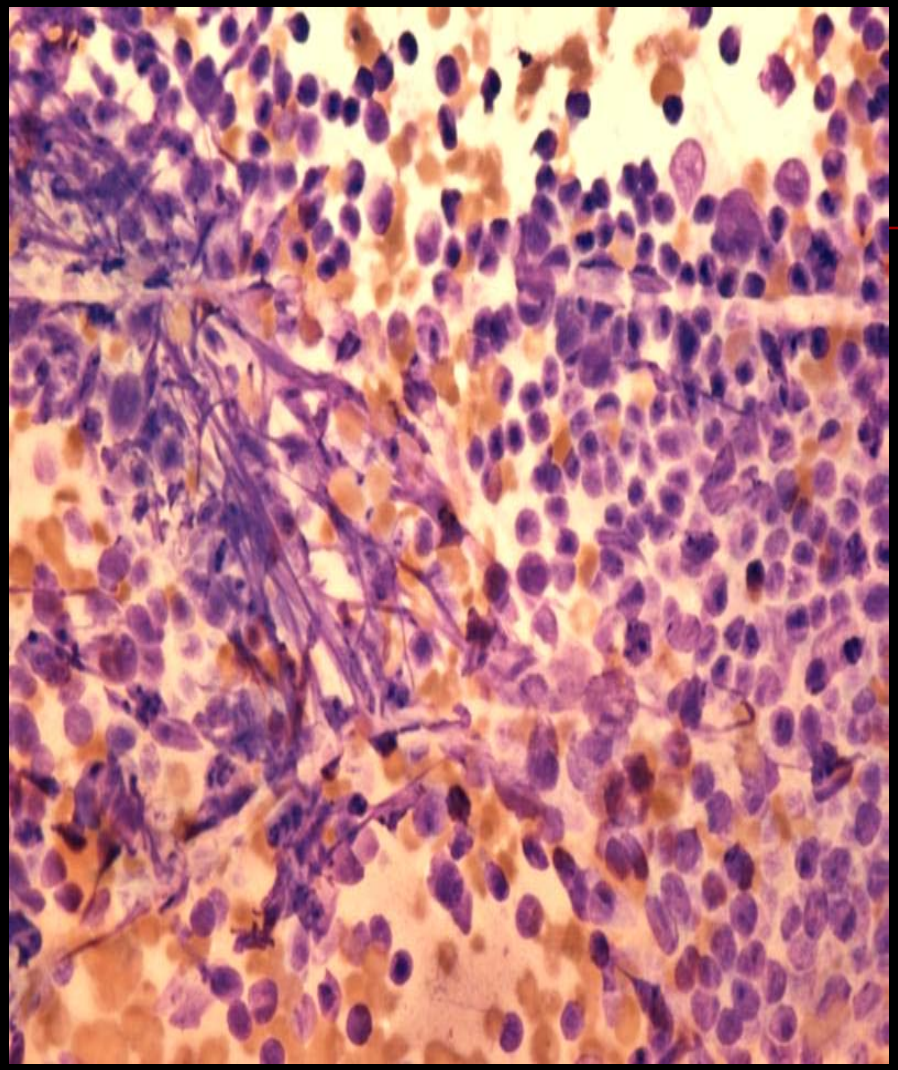
Diagnostic Terminology

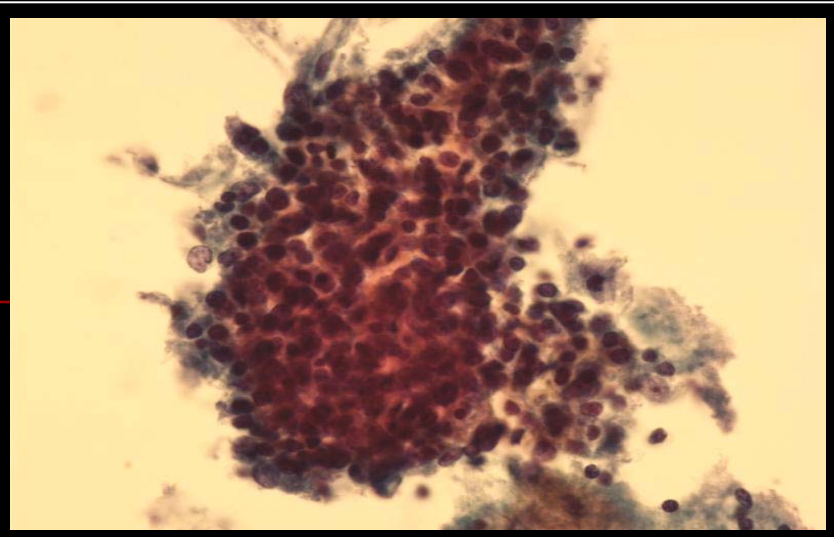
Benign / Non-neoplastic Lesions

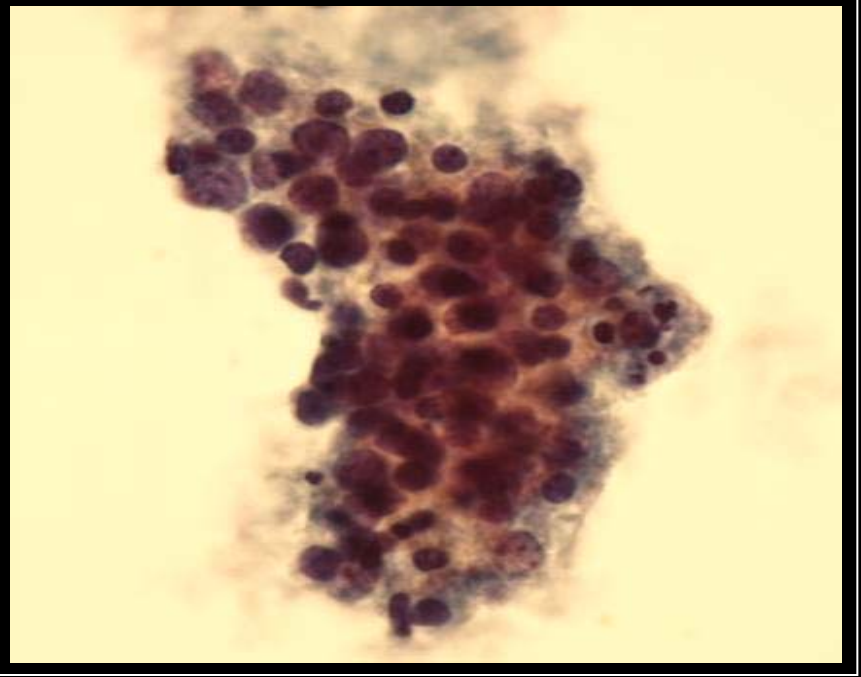
Benign

1. Very low risk of neoplasm
2. This category includes
    1. Nodular goiter
    2. Chronic lymphocytic thyroiditis
    3. Hyperplastic / Adenomatoid nodule
    4. Colloid nodule.
3. Patients with a benign nodule are followed by clinical and periodic radiologic examination and some patients may undergo repeat FNA due to increase in the size of nodule.









Probability-Based Reporting System (Wang HH Diagnostic Cytopathology 2005)

Category	Probability of malignancy (%)
Positive for papillary carcinoma, medullary carcinoma, or other specified malignancy	100
Suspicious for papillary carcinoma, medullary carcinoma, or other specified malignancy	>65
Indeterminate for malignancy, including indeterminate for papillary carcinoma, microfollicular neoplasm, and Hurthle cell neoplasm	10–30
Most probably benign follicular lesion, including mixed micro- and macrofollicular and macrofollicular lesion	5 or less
Negative for malignancy, consistent with thyroiditis	**~ 0**
Suboptimal cellularity but suggestive of (any of the above category)	To be determined
Nondiagnostic	

Literature Review

- Gharib and Goellner - 1993
  - 1750 nodules with histologic follow-up
    - False-negative 2%
    - False-positive 0.7%
    - Sensitivity 98%, Specificity 99%, Accuracy 98.5%
- Giuffrida – 1995
  - 827 Nodules with histologic follow-up
    - False-negative 1.7%
    - False-positive 2.2%
    - Sensitivity 98%, Specificity 98%, Accuracy 98%

AACE/AME Guidelines

	Mean (%)	Range (%)
Sensitivity	83	65-98
Specificity	92	72-100
Positive predictive value	75	50-96
False-negative rate	5	1-11
False-positive rate	5	0-7

Data from Gharib (1994), Castro and Gharib (2003), Gharib and Goellner (1995) Jeffrey and Miller (1996).

Literature Review

- Yassa et. al. (in press Cancer Cytopathol)
  - Ten-year experience evaluating over 2,500 patients with 3,589 thyroid nodules ≥ 1cm in diameter evaluated by Ultrasound Guided-FNA
  - Nodules with initial benign cytology showing substantial growth, persistent or worsening symptoms, or growth beyond 4cm were considered for repeat aspiration or resection
  - 192 patients (with 369 nodules), only six were found to have thyroid cancer despite a benign cytologic diagnosis.

Adapted from Yang et. al. Cancer Cytopathology 2007

Cytologic Diagnosis	*Total*	*Surgical Follow-up*	*Malignancy Rate*
Unsatisfactory	309	46 (14.9)	10.9%
Benign	2526	247 (9.8)	7.3%
Atypical Cellular Lesion	128	52 (40.6)	13.5%
Follicular Neoplasm	516	326 (63.1)	32.2%
Suspicious	122	105 (86.1)	64.7%
Malignant	348	276 (79.3)	98.6%

Question?

reporting
"risk of malignancy"
for each diagnostic category

Web Site Posts / Controversies

- I bet if you ask any clinician, they would love to be able to tell their patients that the risk of malignancy is X% when advising them regarding surgery, and really don't care at all about discussions of atypical versus suspicious, lesion versus neoplasm, etc.
- *This risk level would make it very easy to compare sign outs from different laboratories who chose to use different wording for the same idea/level of risk. And it would force cytologists to be explicitly clear about exactly what they mean, instead of writing very long winded diagnoses that can mean anything from benign to very worried.*

Web Site Posts / Controversies

- We do not include probabilities in our reports of thyroid FNA's. *However, we communicate to our thyroid FNA providers these probabilities either verbally or in writing.*
- We have a one-page thyroid FNA diagnostic scheme that explains our diagnostic categories, terminology and probabilities of malignancy associated with each category. We distribute this to all new thyroid FNA providers and anyone who requests it.
- The probabilities are based on the literature as well as the experiences of our own lab which are similar to (within the range in) the literature.

Web Site Posts / Controversies

- *False-positive rates* and *false-negative rates* can be put on the informed consent to allow the patients to refuse FNA if they expect total accuracy.
- I have had the privileged to meet and interact with over 6000 patients since 11/94 during on-site assessment, preparation, and immediate reporting.
- *It is much better to let them know before than after the biopsy.*

Web Site Posts / Controversies

- It is alright to list the false positive and negative rates of your lab., but to report there is a low but definite risk of cancer, in a nodule that is benign by all cytology criteria, will be read as ***not conclusive***
- As a referral consultant for 30+ years, I have seen too many patients told that the biopsy was not conclusive, ***when the pathologist wrote there is still a "low risk of cancer", on an obvious benign thyroid nodule***
- *It may be better to ---, but you have to live with extra surgeries on benign nodules with more complications in the heartland of our fair country.*

Web Site Posts / Controversies

- It seems unlikely that surgeons will rush to take out thyroids when their negative diagnosis are noted to have a risk of malignancy of less than 1%, which is about what it is in most good labs.
- *On the other hand, noting this clearly shows that the risk is not zero, which is what the lawyers like to assume.*

NCI Conference Attendee Comments:

- Which term to use instead of “Benign”
- “Benign” may also apply to neoplastic lesions
- Suggested terms
  - Negative for malignancy
  - Non-neoplastic

NCI Conference Attendee Comments:

- Majority agree including clinicians (endocrinologist and surgeons) the term “Benign” is preferable

Conclusions

- Reporting risk assessment according to the literature (or individual lab results)
  - Optional
  - Can be communicated verbally to the clinician

Thyroid FNA Diagnostic Terminology

The 2nd Category

Follicular lesion of Undetermined Significance ?

The Ultimate Head Scratch

Follicular lesion of Undetermined Significance ?

- Heterogeneous category
- Includes cases that do not exactly fit into either the Benign, Follicular Neoplasm, Suspicious or Malignant categories.

Follicular lesion of Undetermined Significance ?

- Features
  - Cellularity (still has some watery colloid and few macrophages)
  - Architecture (microfollicles)
  - Focal nuclear overlapping and Crowding / Atypia
  - Scant specimen with focal nuclear overlapping and Crowding / Atypia?
  - Cellular specimen with poor fixation and preservation

Terminology

- Indeterminate
- Suspicious for neoplasm
- Cellular follicular lesion
- Rule-out neoplasm
- Atypical follicular proliferation
- Cannot exclude neoplasm
- Cellular follicular nodule

Which term to use?

Literature Review

- Redman et al (Thyroid 2006)
  - Clinician % recommending surgery
    - Suspicious 96%
    - Indeterminate 58%
    - Atypical 37%

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Yassa et. al. (in press Cancer Cytopathol)

- Atypical cells of undetermined significance
  - 144
    - Resection **84** nodules
    - 20 malignant (24% of resected nodules, 3 cases <1.0 cm)
- Suspicious for follicular neoplasm
  - 328
    - Resection **268** nodules
    - 74(28% of resected nodules, 4 cases <1.0 cm)

Elsheikh TM, Singh S, Saad R, Sliverman JF. Fine Needle Aspiration of the Head and Neck. In Surgical Pathology of the Head and Neck, 3rd Edition, edited by Leon Barnes (In Press).

Assessment of Probability of Cancer Risk on follow-up Thyroidectomies

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

* *Cancer risk is compared to benign nonneoplastic diagnosis; R/O FN: Can not rule out follicular neoplasm*

Web Site Posts / Controversies

- For aspirates less than diagnostic of a neoplasm but cellular enough for some form of interpretation, *I recommend using a descriptive interpretation with macro, micro or mixed macro-microfollicular proliferation (rather than lesion) with or without colloid that may or may not represent a neoplasm.*

Web Site Posts / Controversies

- *The term that is currently proposed as a general heading--"indeterminate" -- is seriously flawed because it has been used by many labs to mean something entirely different, namely "follicular neoplasm"*

- If these laboratories are to adopt the terminology proposed here, too many would need to redefine "indeterminate" to mean something very different from they used to mean, with different clinical implications (repeat FNA vs. lobectomy). I fear for those laboratories and their patients.

Web Site Posts / Controversies

- *For laboratories that don't already use "indeterminate", adopting it will be awkward because the term is not self explanatory and has no application to other specimen types in cytology*

- *I recommend a descriptive term that is familiar to cytologists and defines the category through its words: "atypia of undetermined significance"? By including the phrase "...of undetermined significance"*

NCI Conference Attendee Comments

- Majority of the conference participants (especially the clinicians) agree that follicular patterned lesions should be divided into two categories:
  - *Follicular lesion (atypia) of undetermined significance – managed by repeat FNA*
  - ***Follicular or Hurthle cell neoplasm (suspicious for follicular or Hurthle cell neoplasm) - most likely to be managed by surgical excision***

Conclusions

- Follicular Lesion of Undetermined Significance or
  - Atypical lesion of undetermined significance
  - Cellular follicular lesion / proliferation – rule out follicular neoplasm
- A recommendation may be added to repeat FNA to procure additional specimen

Thyroid FNA Diagnostic Terminology

The 3rd Category

1. Follicular Lesion or Neoplasm

Follicular lesion
or
Follicular Neoplasm

The Term “Follicular Lesion”

- Ambiguous term
  - **>95% of thyroid lesions are follicular derived**
  - **What next after the “lesion” diagnosis?**
    - **Clinical follow-up**
    - **Repeat FNA**
    - **Surgery**

The Term “Follicular Neoplasm”

- **Surgical excision**
- **Some pathologist are afraid of using this term**
  - **Implies tumor**
    - **75% of hyperplastic/adenomatoid nodules are clonal proliferations**
  - **Litigation?**

Literature Review

- Schlinkert et al 1997 – 219 patients
  - 10% Follicular Carcinoma (FC)
- Poller et al 2000 – 156 patients
  - Carcinoma – 7 cases
  - 1 FC, 6 Papillary Ca (PTC)

Literature Review

- Barbaro et al 2001 – 79 patients
  - Malignant – 6 (7.6%)
  - 2 FC, 4 Follicular variant of PTC (FVPC)
- Baloch et al 2001 – 122 patients
  - Malignant – 37 (31%)
  - 11FC, 25 FVPC, 1 Medullary CA

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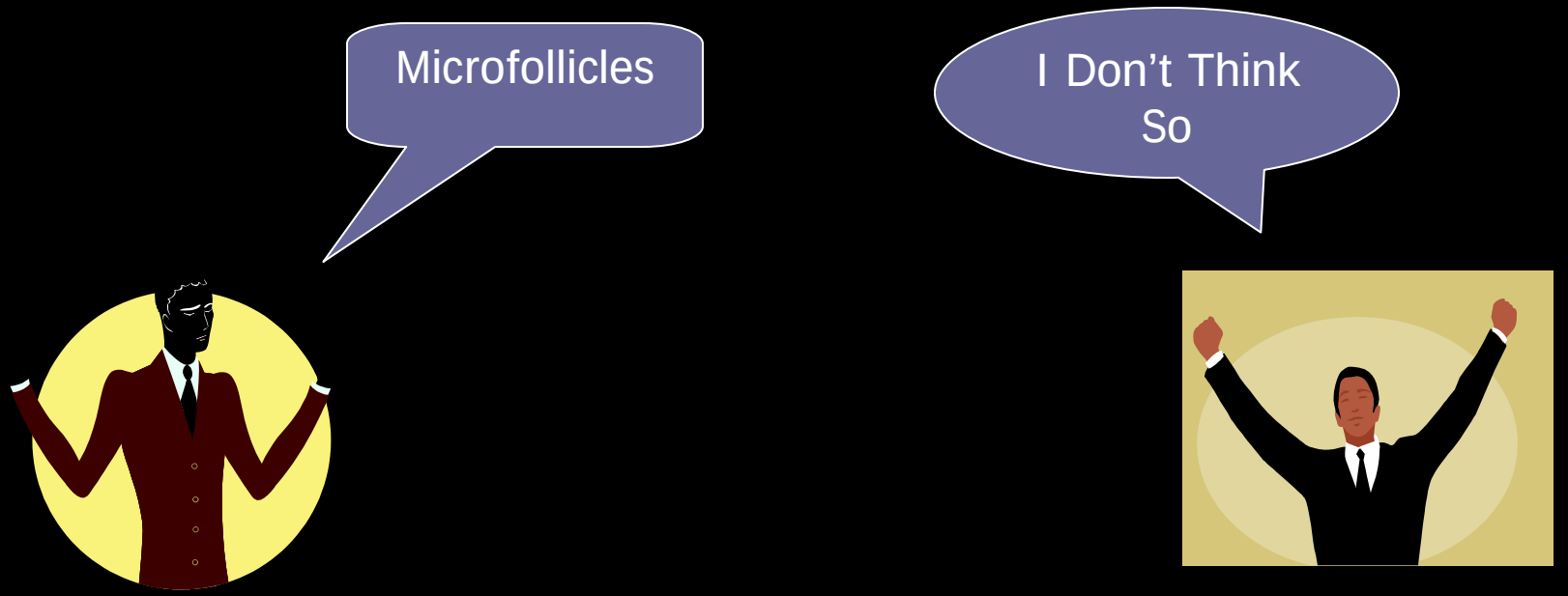
Microfollicles

- Define and measure the size of follicle



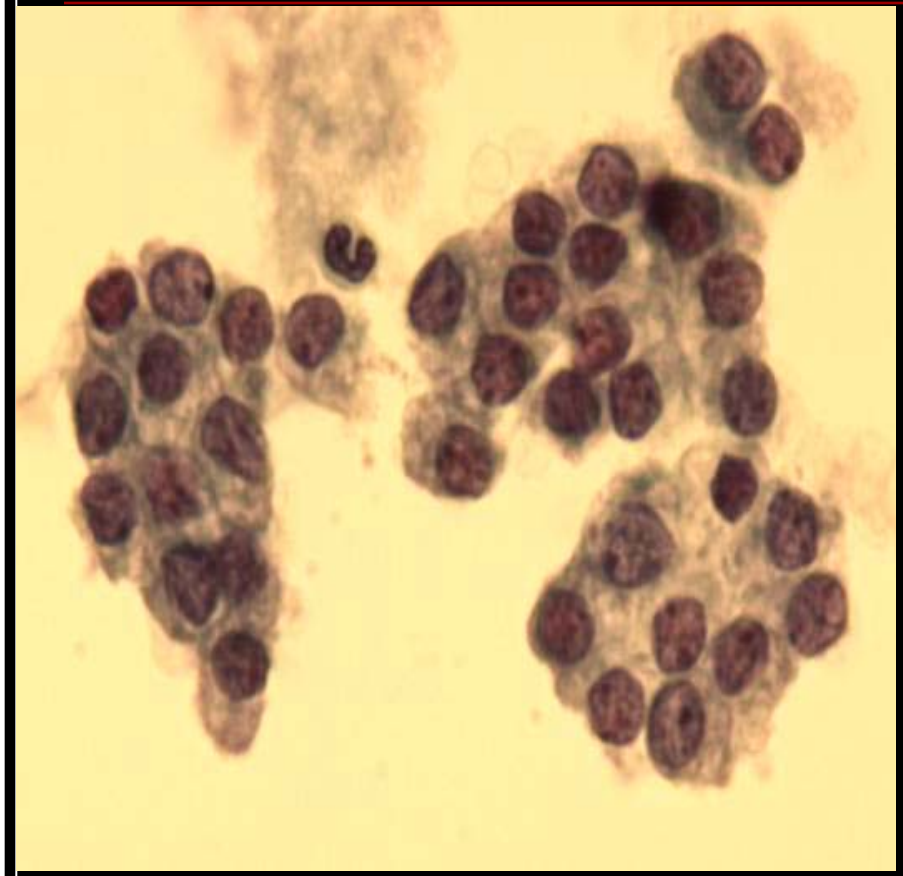
Microfollicles

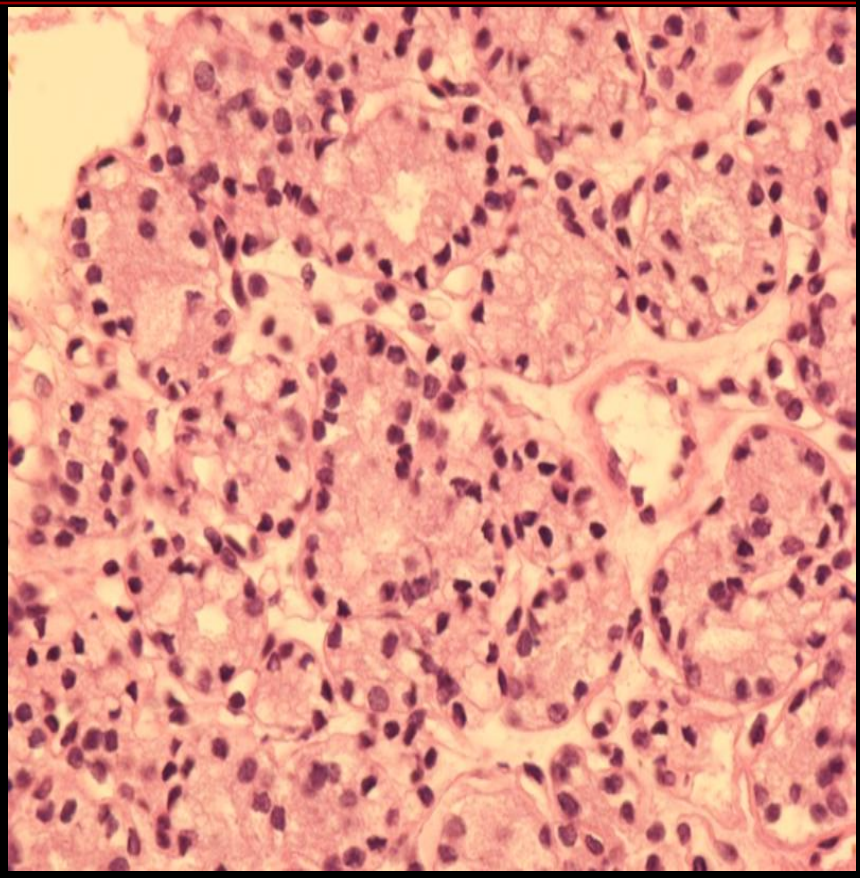
- **Inter-observer Agreement on Microfollicles**
  - **Renshaw AA et al. (Arch Pathol Lab Med 2006)**
  - **12 cytopathologists were shown 45 small groups of follicular cells**
    - **20 Microfollicles**
    - **7 Macrofollicles**
    - **18 Indeterminate**
  - **<15 cells arranged in circle that is at least two-thirds complete, should be classified as microfollicles.**

Microfollicles

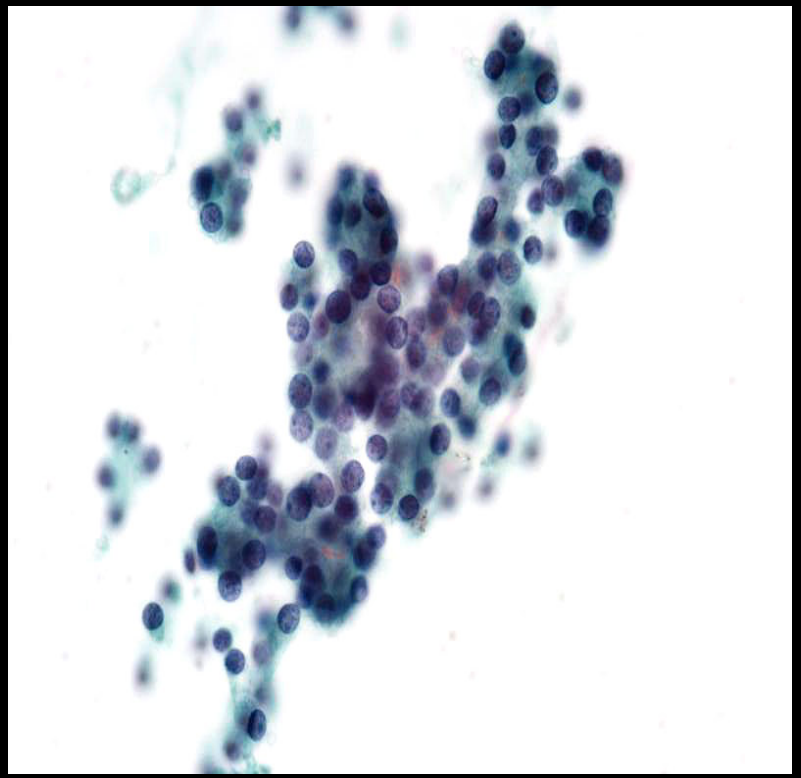
- Mowschenson PM et al (Surgery 1994)
- FNA of normal thyroid tissue may result in the misdiagnosis of micro-follicular lesions
  - 42 cases
    - 9 unremarkable
    - 18 microfollicular
    - 3 mixed macromicrofollicular
    - 1 Hurthle cell
    - 1 Papillary carcinoma

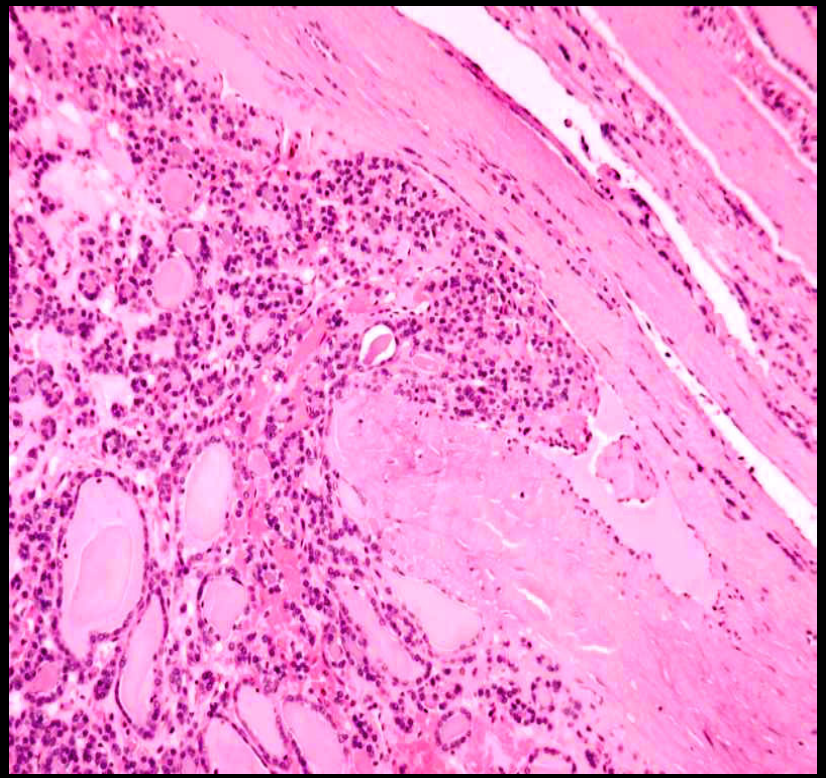
Diagnosis
Follicular Lesion / Neoplasm





Diagnosis
Follicular Lesion / Neoplasm





Diagnosis: Follicular Neoplasm

- **Helpful features**
  - **Cellular specimen**
  - **Less watery colloid**
    - **Dry smear**
  - **Monotonous cell population**
  - **Microfollicles**
  - **Nuclear overlapping and crowding**

Web Site Posts / Controversies

- We generally (I do not actually think we have a policy on this) would put macro-follicular nodules into the hyperplastic / colloid nodule category and use the term "follicular lesion" for those aspirates having enough microfollicles to require resection.
- I do not have a percentage for this. *Obviously, the more microfollicles, the more likely it will be neoplastic and the more likely it will be cancer.*
- It seems the committee will have to draw a line here. I fear an "indeterminate for indeterminate" category.

Web Site Posts / Controversies

- I do not believe that one should practice looking for attorneys over one's shoulder. The reactions of clinicians to a less specific diagnosis (e.g. lesion) is not uniform, and some patients with a tumor may be watched. This could be construed as litigious as well if the tumor is cancer.
- I do not see how calling something "lesion" is more accurate than "neoplasm."

Web Site Posts / Controversies

- **One way to resolve this terminology issue would be to use the phrase "SUSPICIOUS FOR A FOLLICULAR NEOPLASM", rather than flat-out "follicular neoplasm".**

Web Site Posts / Controversies

- **I don't agree with using the term "suspicious for neoplasm". the suspicious terminology should only be limited to cases suspicious for malignancy, which are associated with 60-70% risk of harboring cancer on follow-up surgery.**
- **As far as law suits, I do not know of a single lawsuit filed for an FNA diagnosis of "follicular neoplam"**

Web Site Posts / Controversies

- **I do not feel comfortable using the term follicular neoplasm.**
- I think our diagnoses should be as definitive and meaningful as possible and I think *we undermine the confidence of our clinicians when we provide a diagnosis that sounds definitive for neoplasia (i.e. follicular neoplasm*), but that ultimately has a fairly high incidence of being a non-neoplastic hyperplastic lesion.

Web Site Posts / Controversies

- I urge the committee to re-consider the wording of the proposed heading "Follicular-Patterned Neoplasm/Lesion". The word "lesion" is too vague and all-encompassing, and will be misinterpreted by many labs to permit including any nodule with follicular cells in any pattern. (The term does not describe any particular "pattern" for inclusion.) This category is clearly intended for the worrisome follicular patterns, and the wording of this heading should reflect this.

- One solution would be to eliminate "/Lesion" and call this heading "Follicular-Patterned Neoplasm".

Conclusions

- Follicular Neoplasm
  - Risk of malignancy (20-30%) can be communicated to the clinician
  - Other terms that can be used
    - Follicular patterned neoplasm
    - micro-follicular proliferation
    - suggestive of neoplasm
    - Follicular lesion
    - Suspicious for follicular neoplasm

Thyroid FNA Diagnostic Terminology

The 3rd Category

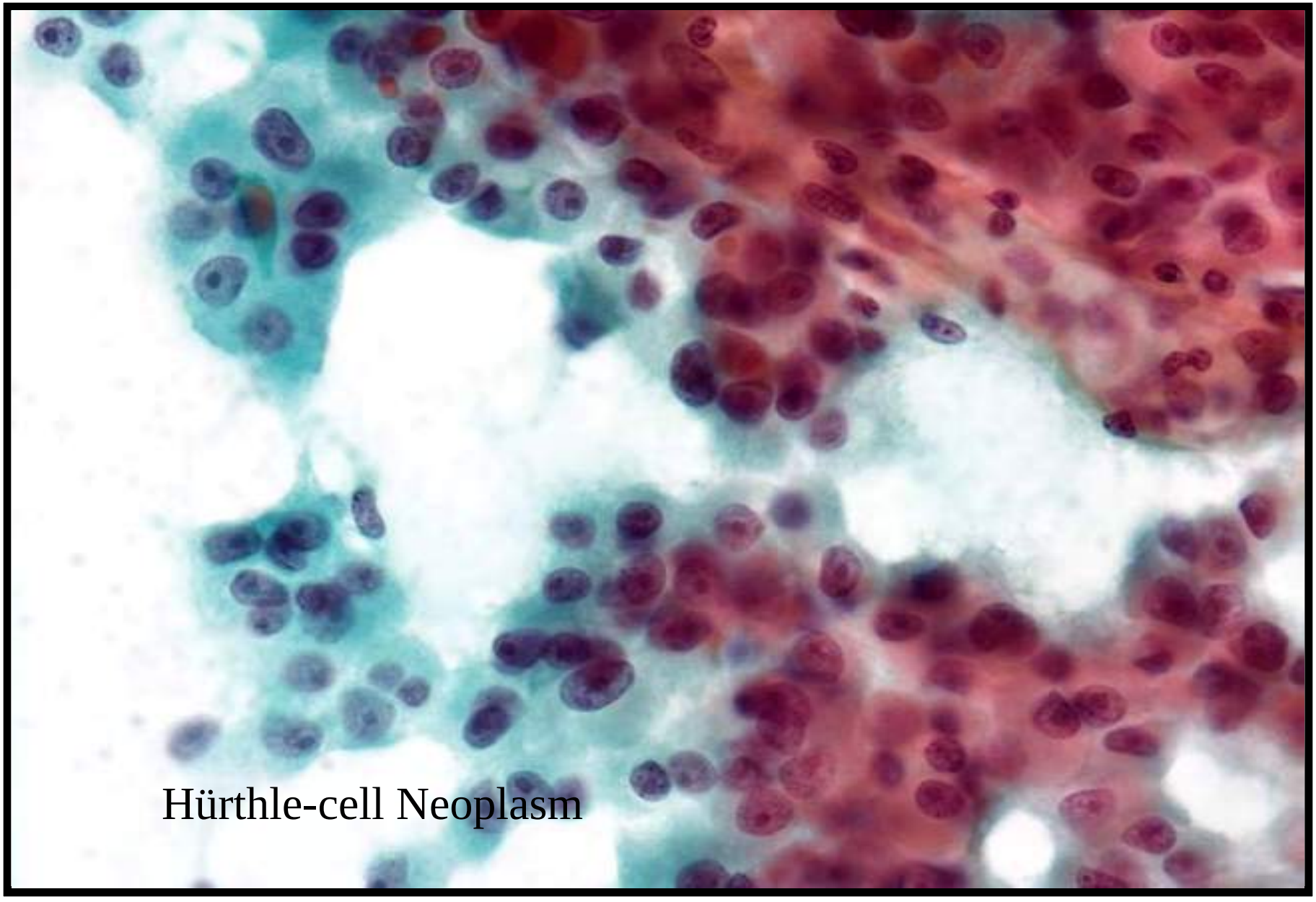
2. Hurthle cell Lesion or Neoplasm

Hurthle cell neoplasm

- Composed exclusively or mainly of Hurthle cells
- Higher prevalence of aggressive histologic and biologic features, since approximately 35% in major reported series fulfill criteria for malignancy
- Hurthle cell is a suspicious word in FNA report for some clinicians

Hurthle cell neoplasm

- Cytologic Features
  - Cellular Specimen containing Hurthle cells
  - Dispersed cells
  - Nuclear atypia
  - Bi-nucleation
  - Transgressing vessels
  - Follicular architecture or sheets


Hürthle-cell Neoplasm

Web Site Posts / Controversies

- Out in the real world of clinical medicine, one of the most abused DX of Thyroid FNA samples is Hurthle cells reported to be present in the biopsy sample. Can not R/O Hurthle cell tumor
- I see several cases a month with this as the reason for recommending surgery.

- the presence of Hashimoto's thyroiditis, or simple Goiter, and the repeat FNA confirms this by finding HC hyperplasia, in thyroiditis, or goiter. This is a major problem for clinicians when the pathologist call every single Hurthle cluster seen as possible tumor

Web Site Posts / Controversies

- Are we worried too much about the atypia issue, when the larger problem is too many surgeries on benign Hurthle cell changes in Hashimoto's, and goiter?

- Agree with you whole heartedly about the worrisome implication of "Hurthle cells present" to many clinicians, and sadly, to some of the pathologists who insist on mentioning them. I think we should only mention them when you have a monotonous cellular smear of Hurthle cells which are usually somewhat dyscohesive and have much less cytologic atypia than we see in thyroiditis or hyperplasia; they are usually more uniform in neoplasms. *They should be diagnosed as follicular neoplasm, Hurthle cell type, just like in surgical pathology.*

Web Site Posts / Controversies

- A well known university pathology department report on a lady with a thyroid nodule.

  Hurthle cells, giant cells, sheets of epithelial cells with iron pigment, colloid is present frequently. The pattern is consistent with a degenerating colloid nodule,
  BUT.....
- *A carcinoma can not be excluded. Consider re-aspiration, or surgical exploration. Can not exclude papillary thyroid carcinoma.*
- Why put Hurthle cell first in the report? It is a buzz word for possible cancer to some physicians.

NCI Conference Attendee Comments

- Majority of the conference participants (especially the clinicians) agree that follicular patterned lesions should be divided into two categories:
  - *Follicular lesion (atypia) of undetermined significance – managed by repeat FNA*
  - ***Follicular or Hurthle cell neoplasm (suspicious for follicular or Hurthle cell neoplasm) - most likely to be managed by surgical excision***

Conclusions

- Hurthle cell Neoplasm
  - Risk of malignancy (20-30%) can be communicated to the clinician
  - Other terms that can be used
    - Hurthle cell proliferation
    - suggestive of Hurthle cell neoplasm
    - Hurthle cell lesion – not preferred

Thyroid FNA Diagnostic Terminology

The 4th Category

Suspicious for Malignancy

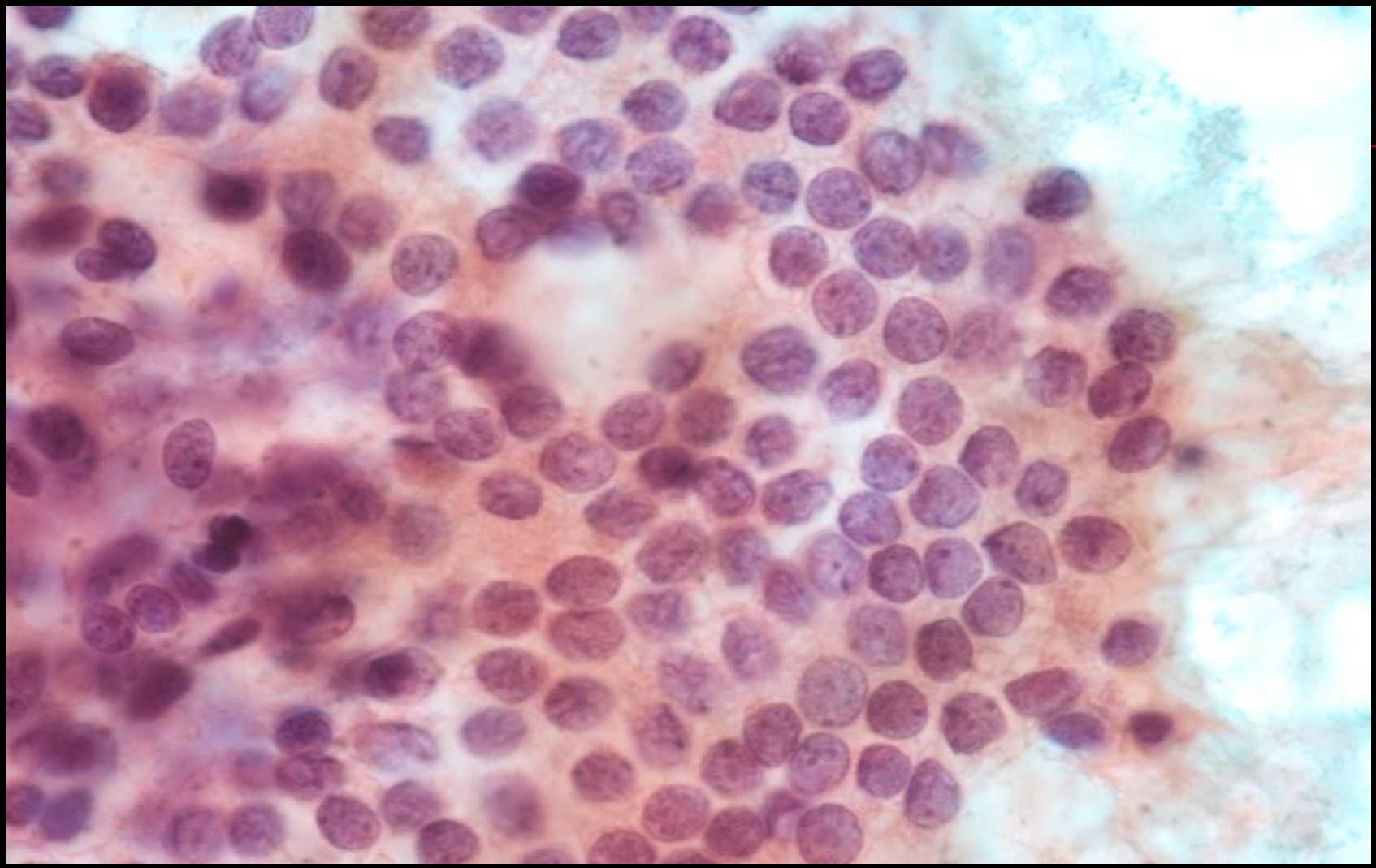
Suspicious for:

- Papillary carcinoma
- Medullary carcinoma
  - Serum calcitonin level
- Suspicious for lymphoma
  - May include recommendation to repeat FNA with flow cytometry.
- Suspicious for metastatic / secondary tumor of thyroid.

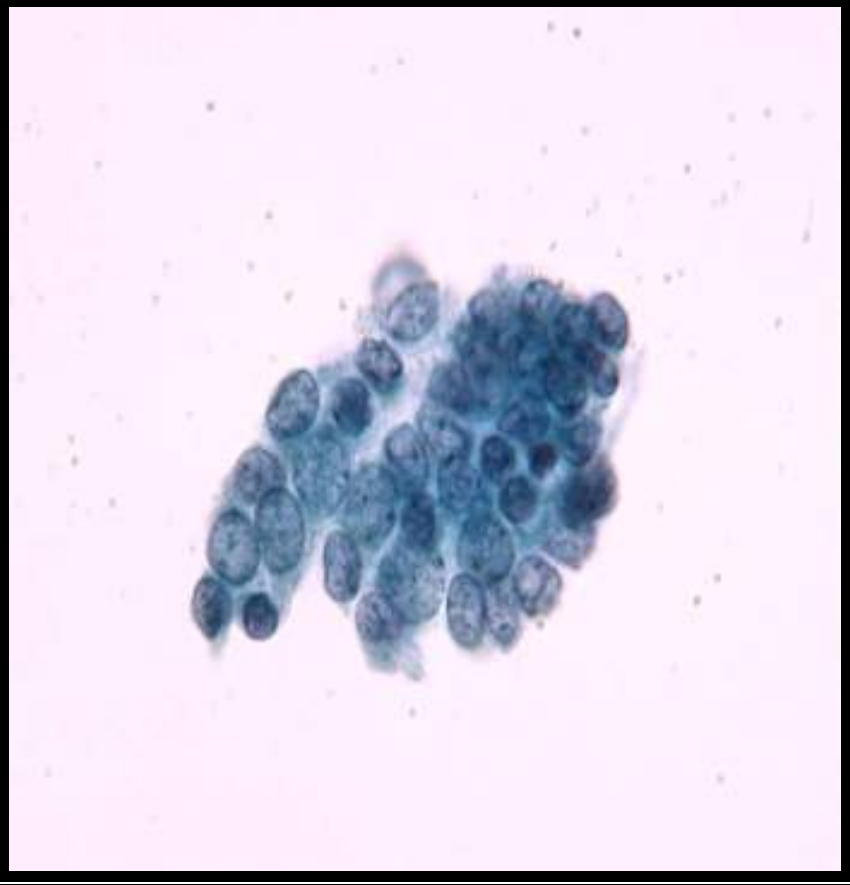
Focal Nuclear Atypia :suspicious for papillary thyroid carcinoma

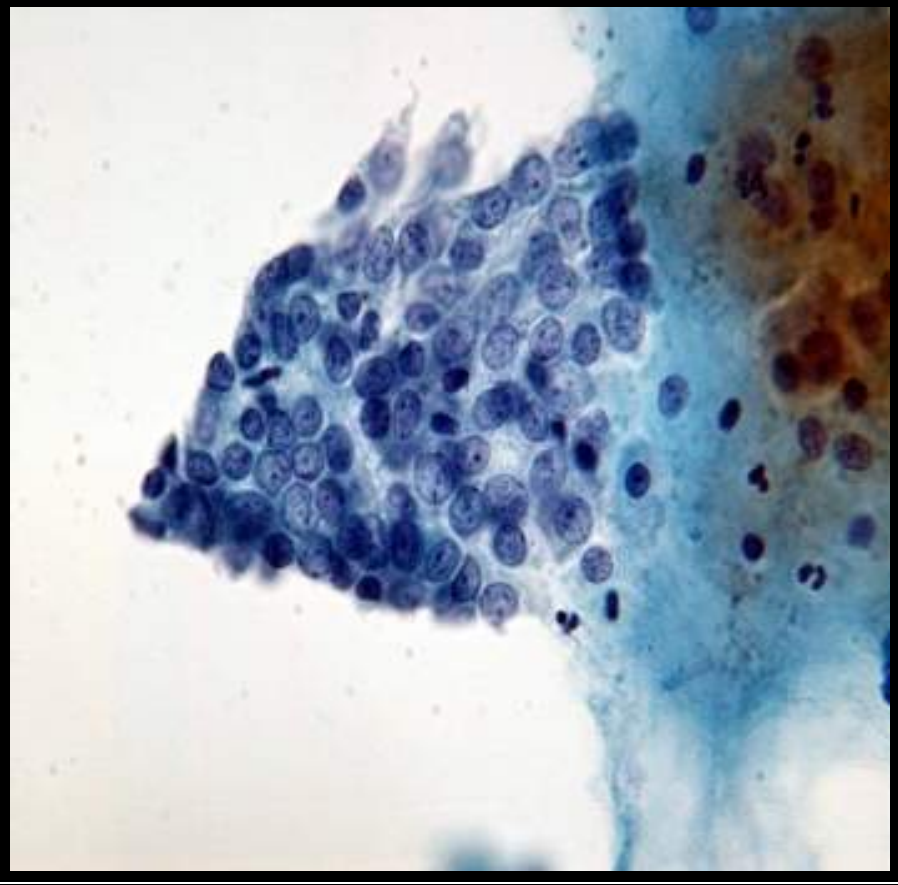
- Watery colloid intermixed with thick colloid
- Monolayer sheets, micro-follicles
- Focal nuclear features of papillary carcinoma
- 60-70% cases are malignant on histologic follow-up – majority follicular variant of papillary carcinoma

Follicular Neoplasm – Suspicious for FVPC



Suspicious of PTC





Probability-Based Reporting System (Wang HH Diagnostic Cytopathology 2005)

Category	Probability of malignancy (%)
Positive for papillary carcinoma, medullary carcinoma, or other specified malignancy	100
Suspicious for papillary carcinoma, medullary carcinoma, or other specified malignancy	**>65**
Indeterminate for malignancy, including indeterminate for papillary carcinoma, microfollicular neoplasm, and Hurthle cell neoplasm	10–30
Most probably benign follicular lesion, including mixed micro- and macrofollicular and macrofollicular lesion	5 or less
Negative for malignancy, consistent with thyroiditis	~ 0
Suboptimal cellularity but suggestive of (any of the above category)	To be determined
Nondiagnostic	

Adapted from Yang et. al. Cancer Cytopathology 2007

Cytologic Diagnosis	*Total*	*Surgical Follow-up*	*Malignancy Rate*
Unsatisfactory	309	46 (14.9)	10.9%
Benign	2526	247 (9.8)	7.3%
Atypical Cellular Lesion	128	52 (40.6)	13.5%
Follicular Neoplasm	516	326 (63.1)	32.2%
Suspicious	122	105 (86.1)	64.7%
Malignant	348	276 (79.3)	98.6%

Elsheikh TM, Singh S, Saad R, Sliverman JF. Fine Needle Aspiration of the Head and Neck. In Surgical Pathology of the Head and Neck, 3rd Edition, edited by Leon Barnes (In Press).

Assessment of Probability of Cancer Risk on followup Thyroidectomies

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

* *Cancer risk is compared to benign nonneoplastic diagnosis; R/O FN: Can not rule out follicular neoplasm*

Yassa et. al. (in press Cancer Cytopathol)

Cytologic Diagnosis	***Nodules Resected***	***Carcinoma***
Suspicious for Papillary Carcinoma 314 (9% of 3,589 nodules)	288	173 (60%) PC ≥ 1 cm - 149 PC < 1 cm - 22 Poorly diff - 1 MTC - 1

Follicular Neoplasm – Suspicious for Follicular Variant of PTC

Suspicious for FVPTC

(Logani et al Diag Cytopathol)

- 52 cases with surgical follow-up
- Malignant – 77%
  - 39 (75%) - papillary carcinoma
  - 12 (23%) – benign
  - 1 (2%) - insular carcinoma

Web Site Posts / Controversies

- ***I use the term suspicious when I believe the lesion is in all likelihood papillary carcinoma, but I am not entirely sure*** **- In other words I only diagnose pap ca when I am absolutely sure it is pap ca. Fortunately, it seems to be more common for aspirates to fall into the latter category.**

- ***I think the term "suspicious" is exceeding useful*****, however, as patients diagnosed definitively undergo (usually) complete thyroidectomy.**

Conclusions

- Suspicious for:
  - Papillary carcinoma
  - Medullary carcinoma
    - Serum calcitonin level
  - Suspicious for lymphoma
    - May include recommendation to repeat FNA with flow cytometry.
  - Suspicious for metastatic / secondary tumor of thyroid.

Thyroid FNA Diagnostic Terminology

The 5th Category

Malignant

Malignant

- Papillary carcinoma
  - Variants
- Medullary carcinoma
- Poorly differentiated carcinoma
- Anaplastic carcinoma
- Lymphoma
- Secondary Tumor
- Other

Medullary Carcinoma

- Medullary thyroid carcinoma originates from the C-cells of the thyroid.
- Interesting due to its clinical presentation, familial origin, and association with other neuroendocrine lesions and morphologic spectrum

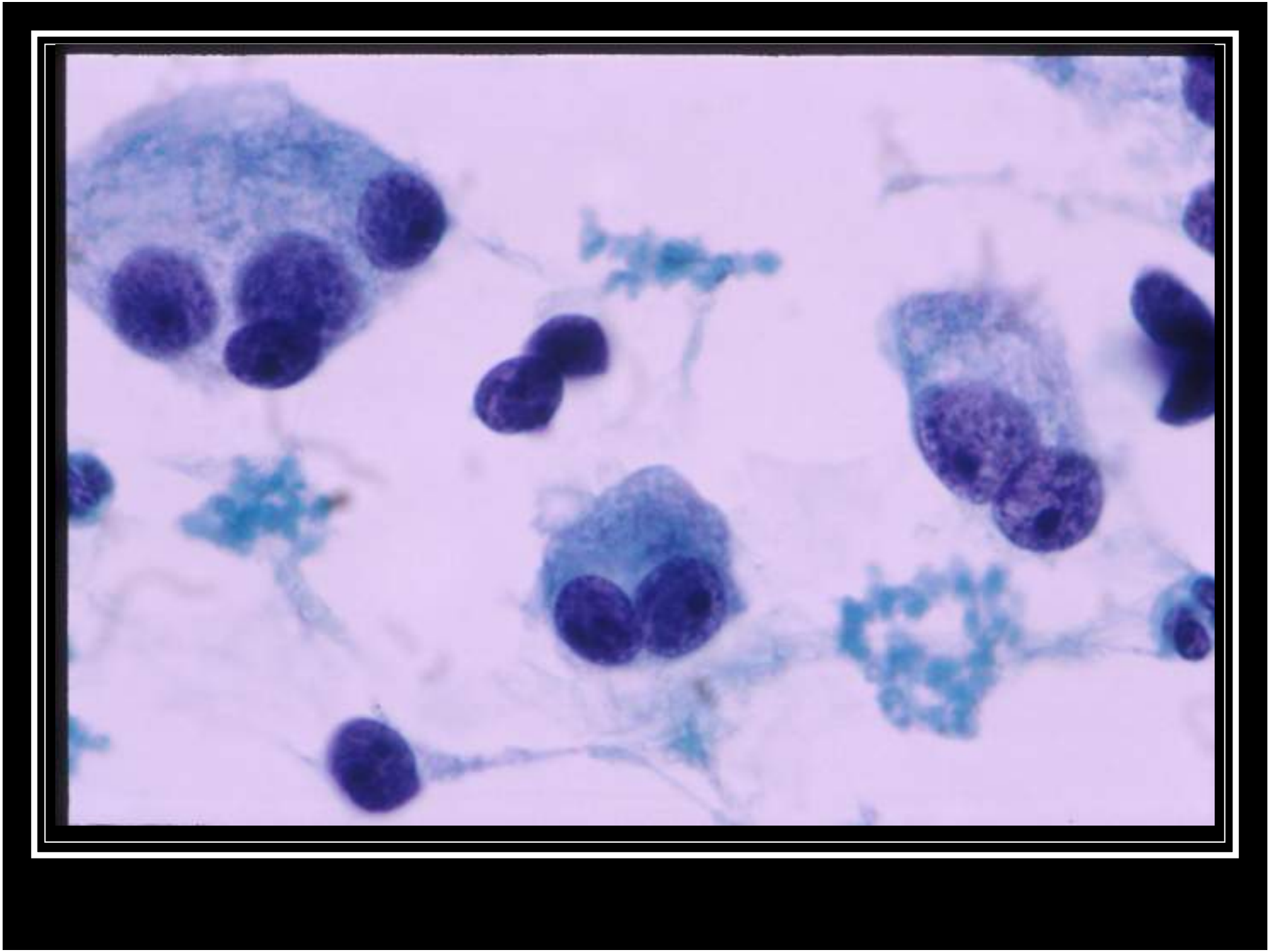
Cytologic Features

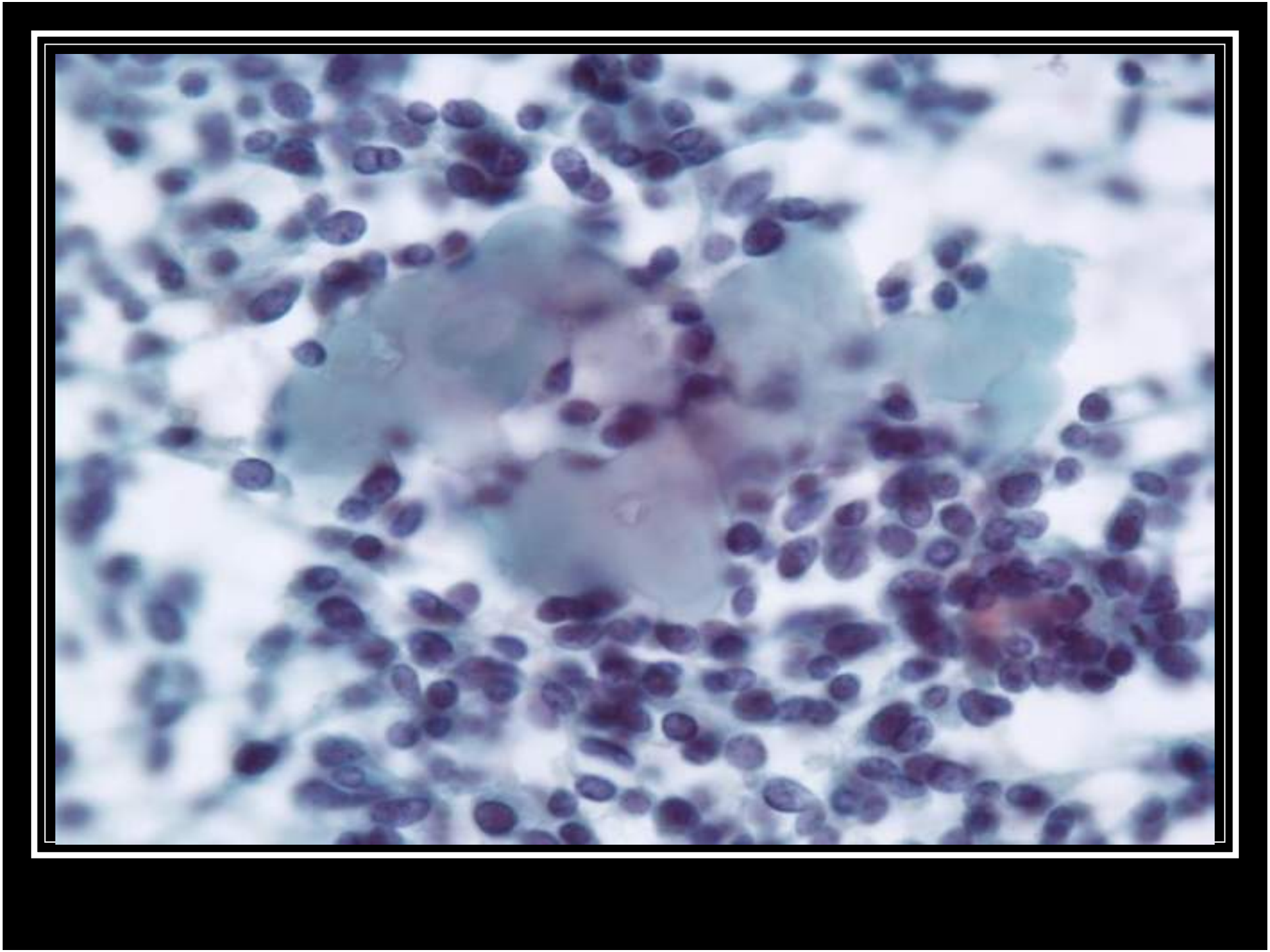
- Cellular specimen
  - Loose tissue fragments
  - Single cells
- Varied morphologic patterns
  - Round to oval cells
  - Spindle cells
- Amyloid
  - Acellular deposits (thick colloid)

Cytologic Features

Tumor cells:

- Abundant eosinophilic cytoplasm
  - Hürthle cell lesions
- Plasmacytoid tumor cells
- 20% of cells can show cytoplasmic granules in Romanowsky stained-preps
- Neuroendocrine chromatin pattern



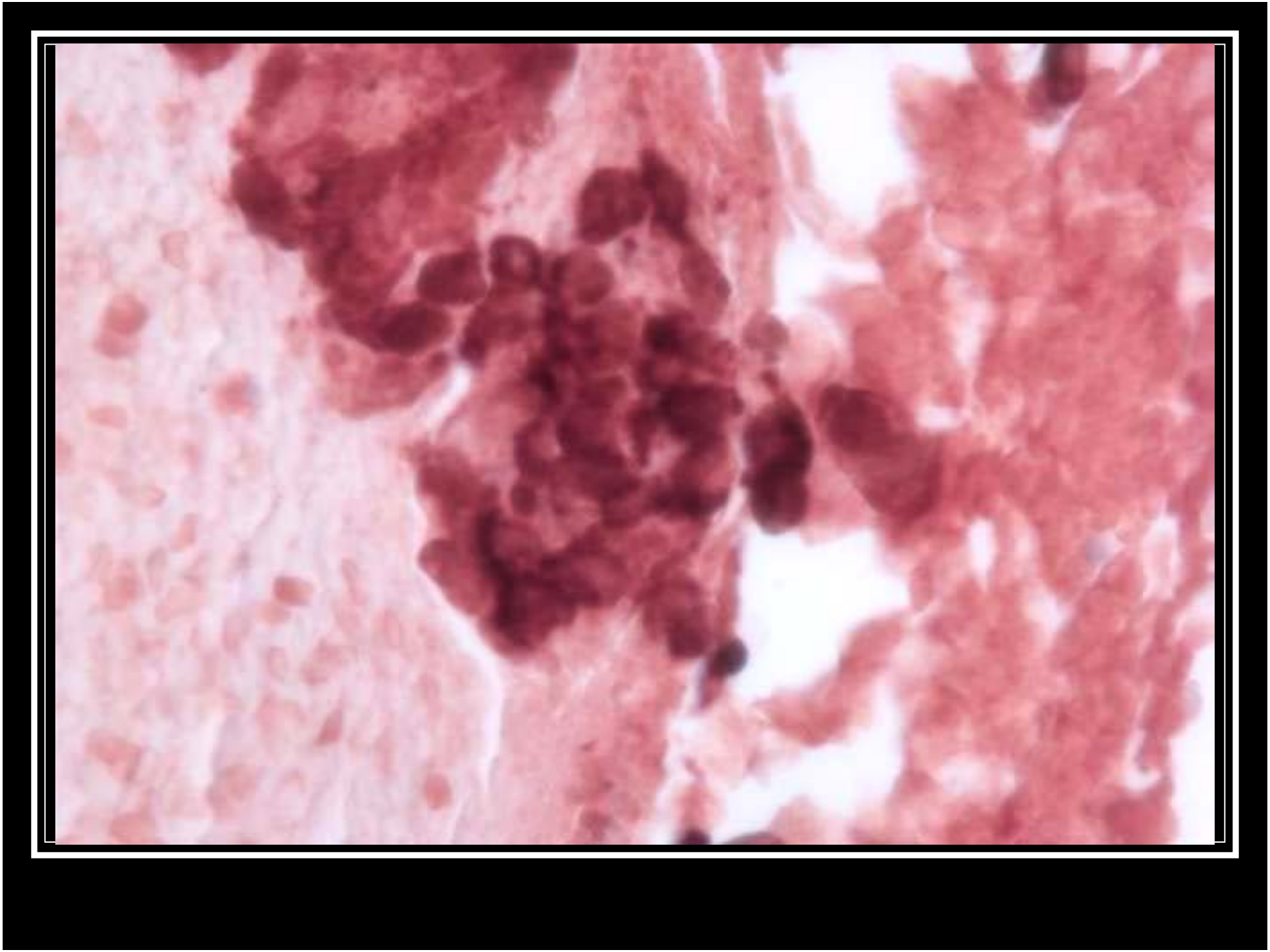


Differential Diagnosis of MTC in FNA Specimens

- Hürthle cell neoplasm
- Papillary carcinoma
- Hyalinizing Trabecular Neoplasm
- Anaplastic Carcinoma
- Metastatic neuroendocrine tumors
- Plasmacytoma

Differential Diagnosis of MTC in FNA Specimens

- Calcitonin immunostains
  - ?Hürthle-cells
    - Or
- Ask for serum Calcitonin levels



Thyroid FNA Diagnostic Terminology

The 6th Category

Non-diagnostic

Non-diagnostic. Specimen processed and examined, but unsatisfactory for evaluation due to:

- Inadequate specimen due to:
  - Few follicular cells and blood
    - aspirate from a solid nodule
  - No follicular cells
  - Poor fixation and preservation.
- A repeat FNA can be recommended.

Morphologic Criteria

- **Should the cases of cystic thyroid nodule which show only colloid and macrophages and rare or no follicular cells be diagnosed as colloid nodule or non-diagnostic?**

Web Site Posts / Controversies

- **I think a diagnosis of "Nonspecific cyst" should be made in cases with insufficient follicular cells for an adequate sample (whatever that is decided to be). This meaning and follow-up for this diagnosis will then have to be worked out.**
- Once sufficient numbers of follicular cells are present - without features of pap ca, these lesions can be diagnosed as "colloid nodule with cystic change" or whatever terminology is favored.

Web Site Posts / Controversies

- **I have been reporting "Colloid nodule" in this kind of aspirates, "unsatisfactory or non-diagnostic" will led to repeated aspirations wasting time and money and make patients anxious and eventual led to surgery.**

Web Site Posts / Controversies

- **We also routinely sign out cases with abundant colloid but very few cells as "negative - colloid nodule" rather than "non-diagnostic."**
- **If we started calling these colloid nodules "non-diagnostic", there would be a lot of unnecessary repeat aspirations.**

Non-diagnostic – Cystic lesion

- Cases that show abundant watery colloid and macrophages.
- No follicular cells
- Recommend clinical and radiologic follow-up.
- Do not include “No tumor seen” or “Negative for malignant cells”

Conclusions - 6 Tiered System

- Benign
- Indeterminate Follicular lesion
  - Atypical lesion of undetermined significance
  - Cellular follicular lesion / proliferation – rule out follicular neoplasm
  - A recommendation may be added to repeat FNA to procure additional specimen

Conclusions – 6 Tiered System

- Follicular / Hurthle cell Neoplasm
  - Suspicious for Follicular / Hurthle cell neoplasm
  - micro-follicular / Hurthle cell proliferation
  - suggestive of Follicular / Hurthle cell neoplasm
  - Follicular / Hurthle cell lesion
- Suspicious for Malignancy
- Malignant
- Non-Diagnostic

Suggested Classification Scheme

Suggested Categories	Alternate Term (s)*	Risk of Malignancy**
Benign		<1%
Indeterminate Follicular lesion	Atypia of Undetermined Significance R/O Neoplasm Atypical follicular lesion Cellular Follicular Lesion	5-10%
Neoplasm 1. Follicular Neoplasm 2. Hurthle cell Neoplasm	Suspicious for: 1. Follicular Neoplasm 2. Hurthle cell Neoplasm	20-30%
Suspicious for Malignancy		50-75%
Malignant		100%
Non-diagnostic	Unsatisfactory	

*These terms can be used instead of the suggested terms (based on website responses and NCI meeting attendees); ** Data collected from literature


There is hope