2010-2011

HANDOUT

Order Out of Chaos: The Bethesda System for Thyroid Cytopathology

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Edmund S. Cibas, M.D. does not have any affiliations or financial interests in any of the corporate organizations involved with products to which her presentation may refer in this program.

Cytoteleconference
April 2010 - March 2011 Series

Order Out of Chaos: The Bethesda System for Reporting Thyroid Cytopathology

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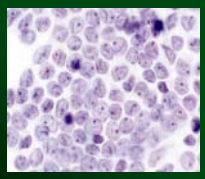

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OBJECTIVES

- To explain the rationale for the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)
- To describe the process by which consensus was reached on TBSRTC
- To explain the criteria for each of the six categories of TBSRTC, with illustrative examples
- To provide references for further reading on TBSRTC

Introduction

FNA is the single most useful test for thyroid nodules.

FNA saves countless patients unnecessary thyroid surgery while appropriately triaging patients with malignant nodules for surgery.

Prior to the routine use of thyroid FNA, only 14% of surgically resected thyroid nodules were malignant. (Hamberger et al., 1982)

With current thyroid FNA practice, >50% of resected nodules are malignant. (Yassa et al., 2007)

Terminology for Reporting Thyroid FNA: **Before Bethesda**

No standard reporting system

Many different approaches:

- multiplicity of **category names**, *vs.*
- **narrative reports** without categories, *vs.*
- **surgical pathology** terminology

NCI Thyroid FNA State of the Science Conference

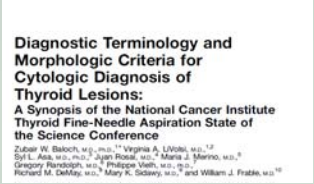
Bethesda, Maryland
October 22-23, 2007

Organized by Dr. Andrea Abati

NCI Thyroid FNA State of the Science Conference: Timeline

October 2006- April 2007	Terminology Committee drafted "Review and Conclusions" document
April – December, 2007	3 on-line discussion periods: http://thyroidfna.cancer.gov
October 22 and 23, 2007	Live meeting in Bethesda, MD (over 150 participants)
June, 2008	Final document published in **Diagnostic Cytopathology** and **Cytojournal**
December, 2009	Atlas published

Diagnostic Terminology and Morphologic Criteria


Diagnostic Terminology and Morphologic Criteria for Cytologic Diagnosis of Thyroid Lesions:
A Synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference

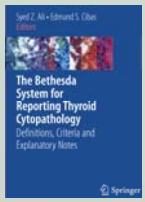
- Proposal for a category-based terminology system
- Terminology linked to management guidelines

Baloch ZW et al. **Diagn Cytopathol** 2008; 36: 425-437

The Bethesda Atlas Project

Led by Syed Ali, chair of the Online Atlas Committee
Online atlas: Papanicolaou Society web site
Paperback **print atlas**
- Over **40 contributing authors**
- Definitions, criteria, explanatory notes, sample reports
- 174 pages; 200 color images
- $39.95
- in print: December 2009

Summary articles
Am J Clin Pathol 2009: 132: 658-65.
Thyroid 2009; 2009: 19: 1159-65.



The Bethesda System for Reporting Thyroid Cytopathology: 6 Diagnostic Categories

I. NONDIAGNOSTIC or UNSATISFACTORY

II. BENIGN

III. ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM
- specify if Hürthle cell (oncocytic) type

V. SUSPICIOUS FOR MALIGNANCY

VI. MALIGNANT

The Bethesda System for Reporting Thyroid Cytopathology

I. NONDIAGNOSTIC or UNSATISFACTORY
- Cyst fluid only
- Virtually acellular specimen
- Other (obscuring blood, clotting artifact, etc.)

II. BENIGN
- Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
- Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
- Consistent with granulomatous (subacute) thyroiditis
- Other

III. ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM
- specify if Hürthle cell (oncocytic) type

V. SUSPICIOUS FOR MALIGNANCY
- Suspicious for papillary carcinoma
- Suspicious for medullary carcinoma
- Suspicious for metastatic carcinoma
- Suspicious for lymphoma
- Other

VI. MALIGNANT
- Papillary thyroid carcinoma
- Poorly differentiated carcinoma
- Medullary thyroid carcinoma
- Undifferentiated (anaplastic) carcinoma
- Squamous cell carcinoma
- Carcinoma with mixed features (specify)
- Metastatic carcinoma
- Non-Hodgkin lymphoma
- Other

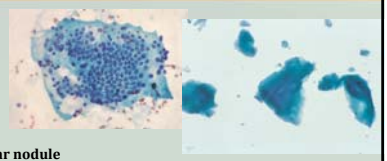
The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

- Each report begins with a general diagnostic category
- 6 general categories
- Some categories have a choice of two names; a consensus was not reached at the NCI conference on a single name for these categories
- Each category has an implied cancer risk (ranging from 0-3% for the **Benign** category to virtually 100% for the **Malignant** category) that links it to a clinical management guideline.

TBRTC: Relationship to Clinical Algorithms

Category	Risk of Malignancy (%)	Usual Management
Nondiagnostic *or* Unsatisfactory	1-4	Repeat FNA with U/S
Benign	<1-3	Follow
Atypia (*or* Follicular Lesion) of Undetermined Significance	~5-15	Repeat FNA
Follicular Neoplasm, *or* Sus. for a Follicular Neoplasm	20-30	Lobectomy
Suspicious for Malignancy (usually papillary CA)	60-75	Lobectomy or total thyroidectomy
Malignant	97-99	Total thyroidectomy

Benign

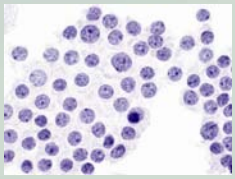


70% of thyroid FNAs
This category includes

- **Benign follicular nodule**
  - colloid nodule, adenomatoid nodule (i.e., NG)
  - follicular adenoma (macrofollicular)
- **Chronic lymphocytic (Hashimoto) thyroiditis**
- **Other** (subacute thyroiditis, amyloid goiter, etc.)

Estimated false-negative rate: <1 to 3%.
Patients with a benign nodule are followed by periodic clinical ± US examination.

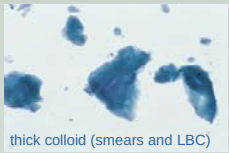
BENIGN: Benign follicular nodule

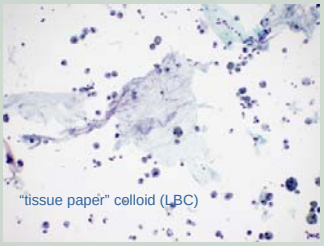


Criteria

- sparsely to moderately cellular
- abundant colloid
- benign follicular cells
  - benign cytology (nuclear features of papillary CA absent)
  - benign architecture (predominantly macrofollicle fragments)

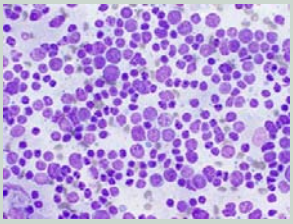
BENIGN:
Benign follicular nodule

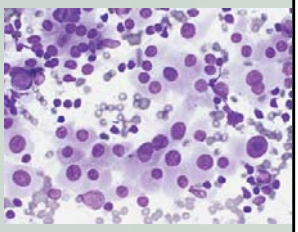

thick colloid (smears and LBC)


"tissue paper" colloid (LBC)

watery colloid (smears)

BENIGN:
c/w lymphocytic (Hashimoto's) thyroiditis





NONDIAGNOSTIC *or* UNSATISFACTORY

10-30% of thyroid FNAs

Adequacy criterion:

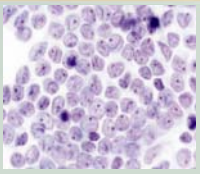
- At least 6 groups, each with at least 10 benign-appearing, well-visualized follicular cells

"Cyst fluid (macrophages) only" cases included as a subset

Exceptions:

- Thyroiditis (=Benign)
- Abundant colloid (=Benign)
- Any atypia

MALIGNANT

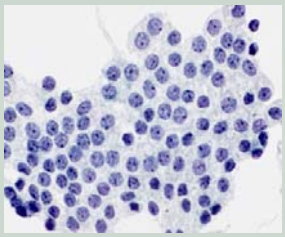


3-7% of thyroid FNAs

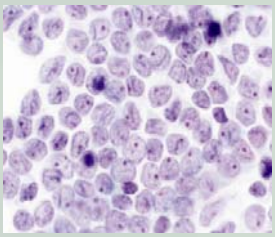
Includes

- Papillary carcinoma
- Medullary carcinoma
- Poorly differentiated carcinoma
- Undifferentiated (anaplastic) carcinoma
- Lymphoma
- Metastatic tumors
- Other

MALIGNANT: Papillary thyroid carcinoma

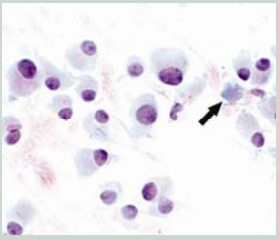


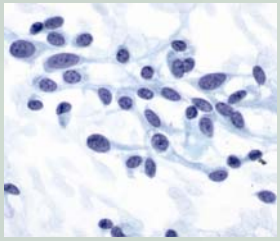
Benign thyroid nodule



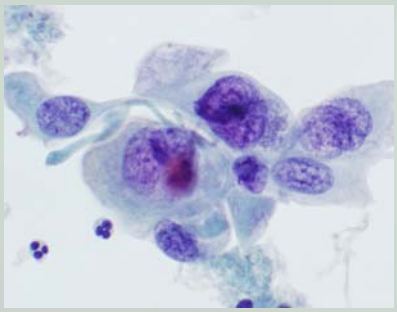
Papillary CA

MALIGNANT: Medullary thyroid carcinoma

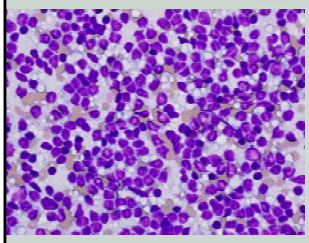




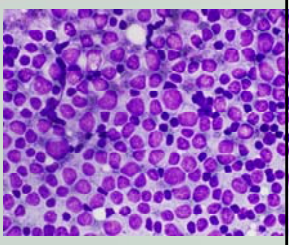
MALIGNANT:
Anaplastic carcinoma



MALIGNANT:
Non-Hodgkin Lymphoma

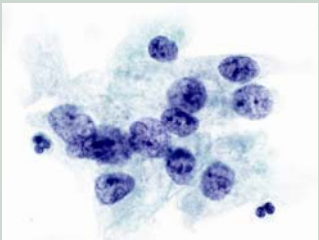


MALT



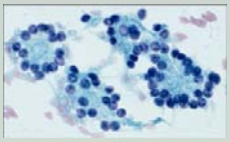
Diffuse large B-cell

MALIGNANT:
Metastatic tumors

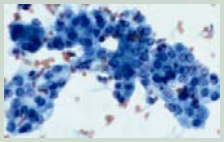


Renal cell carcinoma

FOLLICULAR NEOPLASM *or* SUSPICIOUS FOR A FOLLICULAR NEOPLASM



microfollicles



trabeculae

- For those cases that show significant architectural atypia
- Architectural atypia raises the **possibility of follicular carcinoma**
- Lobectomy is needed for definitive diagnosis

FOLLICULAR NEOPLASM *or* SUSPICIOUS FOR A FOLLICULAR NEOPLASM:

Predictive Value for Malignancy

1st Author, Year	n	% of cases called "SusFN"	% Malignant*
Gharib et al, 1993	731	7	14
Baloch et al, 2002	184	18	30
Yang et al, 2007	326	12	32
Yassa et al, 2007	268	8	28

*of resected nodules only

Note: Up to 35% of nodules in this category prove not to be neoplasms after resection.

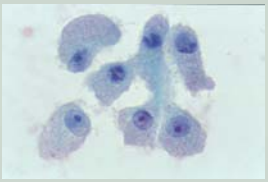
FOLLICULAR NEOPLASM *or* SUSPICIOUS FOR A FOLLICULAR NEOPLASM

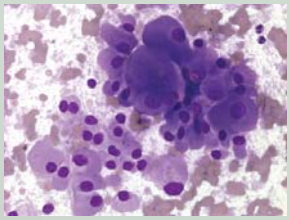
– HÜRTHLE CELL TYPE

- **Def.:** Any sample composed exclusively of Hürthle cells
- Risk of malignancy not v. different from "Foll. Neo./Suspicious for a Follicular Neoplasm"
- But data suggest that Hürthle cell CAs are genetically distinct from follicular CAs
- DDx includes medullary CA, others
- Distinction between Hürthle cell adenoma and Ca not possible by FNA – "diagnostic lobectomy" required
- 16-25% prove not to be neoplasms histologically.

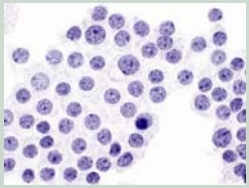
FOLLICULAR NEOPLASM *or* SUSPICIOUS FOR A FOLLICULAR NEOPLASM

– HÜRTHLE CELL TYPE

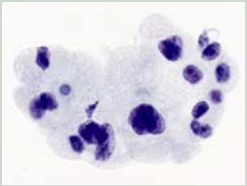




Mix of benign follicular cells + Hürthle cells = BENIGN



Benign follicular cells



Hürthle cells

SUSPICIOUS FOR MALIGNANCY

Excludes cases suspicious for a follicular or Hürthle cell neoplasm

Suspicious for papillary carcinoma

Many papillary CAs (e.g., foll. variant) have subtle features and cannot be dx'd conclusively by FNA)

Suspicious for medullary carcinoma

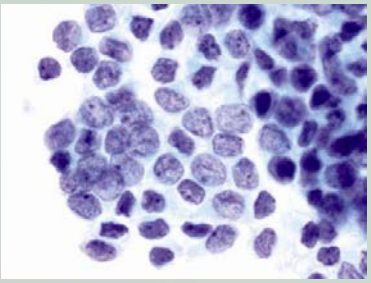
- Serum calcitonin level

Suspicious for lymphoma

- May include recommendation to repeat FNA with flow cytometry.

Suspicious for metastatic tumor to thyroid

SUSPICIOUS FOR MALIGNANCY.
Suspicious for papillary thyroid carcinoma.



SUSPICIOUS FOR MALIGNANCY
Suspicious for Papillary Carcinoma:
Predictive Value for Malignancy

Authors, Year	n	% of cases called "Sus for PC"	% Malignant (PPV)*
Gharib et al, 1993	288	3	60
Logani et al, 2000	52	NK	77
Yang et al, 2007	84	3	76
Yassa et al, 2007	314	8	60

*resected nodules only

ATYPIA OF UNDETERMINED SIGNIFICANCE (AUS)

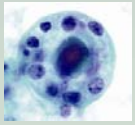
- Cases that don't fit into Benign, Suspicious, or Malignant
- Heterogeneous category
- Often a compromised specimen (obscuring blood, etc.)
- Examples:
  - Sparsely cellular sample, but predom. microfollicles
  - Atypical cyst lining cells
  - Marked XRT
  - Focal mild changes suggestive of papillary CA
  - Atypical lymphoid infiltrate (? MALT)
- Recommended management: **repeat FNA**
- Surgery considered for "repeat atypicals"

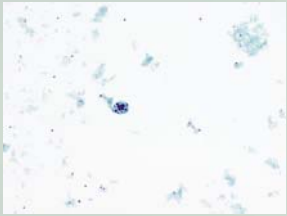
ATYPIA OF UNDETERMINED SIGNIFICANCE (AUS)

- Most AUS cases resolve into benign or suspicious/malignant results after repeat FNA.
- Malignancy rate (~ 5-15%) not sufficient to justify immediate surgery
- Avoid overuse of this category
- Benchmark to guide laboratories in tracking their AUS rate:

"The frequency of AUS interpretations should be in the range of **approximately 7%** of all thyroid FNA interpretations. This figure may be further refined as more laboratories report their experiences using the AUS designation within the context of these criteria."

ATYPIA OF UNDETERMINED SIGNIFICANCE (AUS)





Summary of Recent Publications on TBSRTC, with focus on AUS

Study authors	Cases (n)	% AUS	% initial AUS w/ a definitive dx after repeat FNA	Malignancy rate for AUS (%)	
				of resected cases only	of all AUS
Nayar, Ivanovic	5194	18	62	6	2.7
Layfield *et al*	6872	12	N/A	28	5
Faquin, Baloch	N/A	9-12	N/A	19	10
Theoharis *et al*	3037	3	76	41	12
Shi *et al*	8150	2	N/A	35	8

Preliminary Conclusions from Recent Studies

- The AUS rate is variable.
- Currently, some labs are exceeding the recommended 7% AUS frequency.
- Malignancy rate of AUS is variable, but generally in keeping with Bethesda guideline.
- Data support repeat FNA as initial management for AUS.
- Repeat FNA resolves the diagnostic uncertainty in most cases.
- Validity of the AUS category re-affirmed.

Where Will This Take Us?

We hope more laboratories will consider adopting it.

We expect that future workshops will revisit this, in light of our evolving understanding of thyroid disease and after data are collected on its application.

Courtesy: Dr. Ed Stelow

The Benefits of a Uniform Reporting System for Thyroid Cytopathology

- Improved communication
- Facilitated cytologic-histologic correlation
- Facilitated research into the epidemiology, molecular biology, pathology, and diagnosis of thyroid diseases
- Easy and reliable sharing of data from different laboratories for collaborative studies

Acknowledgment – Bethesda System Atlas Contributors

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Recommended Reading

Ali SZ and Cibas ES (2009). The Bethesda System for Reporting Thyroid Cytopathology. New York, Springer.

Baloch, Z. W., E. S. Cibas, et al. (2008). "The National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference: A Summation." Cytojournal **5**: 6.

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