News About the Revised Bethesda System for Thyroid Cytopathology

Edmund S. Cibas, M.D.
Brigham and Women’s Hospital
Harvard Medical School

Dr. Cibas has no disclosures
Thyroid FNA Before Bethesda

- No standard thyroid reporting system in the U.S.
- Prior approaches:
  - multiplicity of category names
  - descriptive reports (no categories)
  - surgical pathology terminology
The 2007 NCI Thyroid FNA State of the Science Conference

- Organized by the National Cancer Institute (U.S.)
- 2-day meeting in Bethesda, MD
- 154 registrants
  - pathologists, surgeons,
  - endocrinologists, radiologists
- Pre-conference literature search, document drafts
- Drafts posted on an open access, web–based “Bulletin Board” for comment
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

Zubair W. Baloch M.D., Ph.D., Virginia A. LiVolsi M.D., Syl L. Asa M.D., Ph.D., Juan Rosai M.D., Maria J. Merino M.D., Gregory Randolph M.D., Philippe Vielh M.D., Ph.D., Richard M. DeMay M.D., Mary K. Sidawy M.D., William J. Frable M.D.

First published: 13 May 2008  Full publication history
2009: The Bethesda System (TBSRTC)

- Over 40 contributing authors
- Definitions, criteria, explanatory notes, and sample reports
- 200 pages
- 200 color images
- Translated into Chinese, Japanese, Spanish, Turkish
Reporting Thyroid Cytopathology Results: The Bethesda System 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: Relationship to Clinical Management

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or UNS</td>
<td>1-4</td>
<td>Repeat FNA with U/S</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt;1-3</td>
<td>Follow</td>
</tr>
<tr>
<td>Atypia (or Follicular Lesion) of Undetermined Significance</td>
<td>~5-15</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular Neoplasm, or Sus. for a Follicular Neoplasm</td>
<td>20-30</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75</td>
<td>Lobectomy or total thyroidectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Total thyroidectomy</td>
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The Bethesda System Since 2007

- Widespread acceptance in U.S. and elsewhere
- Endorsed by the American Thyroid Association (2015)
- New Developments:
  - NIFTP
  - Molecular testing
- International Cytology Congress Symposium (Yokohama, May 2016)
  - “TBSRTC: Past, Present, and Future”
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Non-invasive FVPTC Has Been Renamed NIFTP

The follicular variant of PTC, if non-invasive, can be successfully treated by excision (lobectomy) alone. Total thyroidectomy and subsequent radioiodine not necessary.

Nikiforov YE et al. “Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors.” JAMA Oncology, published online April 14, 2016.
Δ in Malignancy Risk if FVPTC is Renamed NIFTP

**NIFTP accounts for 20-25\% of all thyroid “cancers”**

<table>
<thead>
<tr>
<th>Category</th>
<th>Current Risk of Malignancy (%)</th>
<th>Revised Risk of Malignancy (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular Neoplasm/ Suspicious for a Follicular Neoplasm</td>
<td>46</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>87</td>
<td>46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malignant</td>
<td>99</td>
<td>94</td>
<td>0.0185</td>
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Overheard conversations about NIFTP

- "I have an FNA from a 1.2 cm thyroid nodule that is microfollicular with some nuclear changes of papillary carcinoma; should I call it “suspicious for a follicular neoplasm” or "suspicious for malignancy"? Should I mention that this may be NIFTP?"

- "My colleagues have decided not to use the Malignant category for thyroids because of NIFTP. Can we call anything papillary carcinoma anymore?"
How to deal with the NIFTP conundrum from an FNA perspective?

A provisional approach that might be incorporated into the 2nd edition of TBSRTC
Limit **Malignant** category to **classic** papillary thyroid carcinoma?

- true papillae
- psammoma bodies
- numerous inclusions
Optional note for Malignant category (PTC)

NOTE: With the reclassification of some indolent thyroid tumors as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)," the positive predictive value of the malignant category for thyroid fine needle aspiration (FNA) is expected to drop from 99 to about 94-96%. Thus a small proportion of cases interpreted as malignant by FNA may prove to be NIFTP upon histologic examination.

Krane JF et al, Cancer Cytopathol 2016.
Widespread acceptance in U.S. and elsewhere

Endorsed by the American Thyroid Association (2015)

New Developments:
- NIFTP
- Molecular testing

International Cytology Congress Symposium (Yokohama, May 2016)
- “TBSRTC: Past, Present, and Future”
# The Bethesda System:
## Impact of Molecular Testing in the U.S.

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<td>Follow</td>
</tr>
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<td>Atypia (or Follicular Lesion) of Undetermined Significance</td>
<td>~5-15</td>
<td>Repeat FNA or molecular testing</td>
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# Commercially Available Molecular Tests as Adjuncts to Thyroid FNA

<table>
<thead>
<tr>
<th>Test</th>
<th>Company</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThyroSeq v.2</td>
<td>CBL Path</td>
<td>Next generation DNA sequencing for point mutations and gene fusions in known thyroid cancer genes</td>
</tr>
<tr>
<td>Afirma</td>
<td>Veracyte</td>
<td>Gene expression classifier (mRNA-based) optimized for negative predictive value</td>
</tr>
<tr>
<td>ThyGenX-ThyraMIR</td>
<td>Interpace Diagnostics</td>
<td>Next generation DNA sequencing for point mutations and gene fusions (ThyGenX) plus panel of microRNA markers (ThyraMIR)</td>
</tr>
</tbody>
</table>
Sample ThyroSeq Report
(Cytology = Suspicious for a Follicular Neoplasm)

FINAL DIAGNOSIS:
THYROID, LEFT, FINE NEEDLE ASPIRATE, OSS
MOLECULAR & GENOMIC PATHOLOGY LABORATORY TESTING

FROM CBLPATH INC,

Next Generation Sequencing Panel for Thyroid Cancer (ThyroSeq) RESULTS:

Part 1: LEFT THYROID -

NRAS mutation POSITIVE (p.Q61R, c.182A>G), see interpretation below.

INTERPRETATION
The finding of RAS mutation in the thyroid FNA sample is associated with ~80% risk of cancer in a given nodule (1-3). The most common type of cancer associated with RAS mutations is the follicular variant of papillary thyroid carcinoma, typically the encapsulated follicular variant, followed by follicular carcinoma (4). The remaining RAS-positive nodules are diagnosed upon removal as a follicular adenoma or hyperplastic nodule. Some of these follicular adenomas have focal atypical microscopic features, which may be suggestive of early transformation, but are not sufficient for the histologic diagnosis of cancer. If a benign nodule is found to carry RAS mutation (excluding low level of mutations detected), it indicates that this lesion is a clonal process, i.e. a neoplasm, and therefore is biologically an adenoma rather than a hyperplastic nodule, even if microscopically the lesion is colloid-rich and has the appearance of a hyperplastic nodule.

The tested sample is NEGATIVE for point mutations and indels in the hotspots of the following genes:
AKT1  BRAF  CTNNB1  EIF1AX  GNAS  HRAS  KRAS  PIK3CA
PTEN  RET  TERT  TP53  TSHR

The tested sample is NEGATIVE for 42 gene fusions involving the following genes:
RET  PPARG  NTRK1  NTRK3  ALK  BRAF  IGF2BP3
# Sample Afirma Report

**Afirma.**

**Sample Patient Report**

**Report Status:** FINAL

**Client ID:** 101

**Lab ID:** F-012-1777

**MRN:** 127654

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**Patient:** John Doe  
**DOB:** 21 Mar 1962  
**Gender:** M  
**Lab ID:** F-012-1777

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**Report Information**

<table>
<thead>
<tr>
<th>Collection Date</th>
<th>05 May 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received Date</td>
<td>06 May 2014</td>
</tr>
<tr>
<td>Report Date</td>
<td>12 May 2014</td>
</tr>
</tbody>
</table>

**Clinic Name:** ACME Endocrinology

**Submitting Clinician:** Donald Demo  
**Phone #:** (555) 555-5555

**Fax #:** (555) 555-5001

**Treating Clinician:** Daisy Dame  
**Report CC:**

**Afirma Req #:** DA01000

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**Clinical History:** Follicular Neoplasm cytology diagnosis

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**Results Summary**

<table>
<thead>
<tr>
<th>Node</th>
<th>Size</th>
<th>Location</th>
<th>Cytology</th>
<th>Afirma Gene Expression Classifier</th>
<th>Afirma MTC</th>
<th>Afirma BRAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.3 cm</td>
<td>Lower Right</td>
<td>---</td>
<td>Benign</td>
<td>Neg.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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**Result Details**

- **Nodule A**
  - **Size:** 1.3 cm  
  - **Location:** Lower Right

**Afirma GEC Result:** Benign

**Afirma MTC Result:** Negative
May, 2016: Yokohama Symposium on the Future of TBSRTC

- **Leaders**
  - Bill Faquin (USA)
  - Marc Pusztaszeri (Switzerland)
  - Esther Diana Rossi (Italy)

- **Members**
  - Manon Auger (Canada)
  - Zubair Baloch (USA)
  - Justin Bishop (USA)
  - Massimo Bongiovanni (Switzerland)
  - Ashish Chandra (UK)
  - Guido Fadda (Italy)
  - M. Hirokawa (Japan)
  - Soonwon Hong (Korea)
  - Kennichi Kakudo (Japan)
  - Jeffrey Krane (USA)
  - Ritu Nayar (USA)
  - Sareh Parangi (USA)
  - Beatrix Cochand-Priollet (France)
  - Fernando Schmidt (Luxembourg)
Tasks of the Yokohama Panel

• PubMed literature review of thyroid cytology (2010 - present)
• Subgroups corresponding to each of the 6 TBSRTC diagnostic categories
• 2-6 panel members per subgroup
• Email discussions among subgroup members, and face-to-face meeting at USCAP in Seattle (March, 2016)
• IAC Symposium presentation – Yokohama, Japan (May, 2016)
• Publication of manuscript detailing the panel’s consensus recommendations for TBSRTC II (in press)
The Bethesda System for Reporting Thyroid Cytopathology: Proposed Modifications and Updates for the Second Edition from an International Panel

Marc Pusztaszeri, Esther Diana Rossi, Manon Auger, Zubair Baloch, Justin Bishop, Massimo Bongiovanni, Ashish Chandra, Beatrix Cochand-Priollet, Guido Fadda, Mitsuyoshi Hirokawa, SoonWong Hong, Kennichi Kakudo, Jeffrey F. Krane, Ritu Nayar, Sareh Parangi, Fernando Schmitt, William C. Faquin

Manuscript in press:

  Acta Cytologica

  Journal of American Society of Cytopathology
Recommendations of the Yokohama Panel

- Keep the 6 category designations
  - Reinforce that AUS and FLUS are synonymous terms
- Make adjustments to the risks of malignancy
- Incorporate criteria for recognizing NIFTP to avoid the Malignant category for these lesions
- Update management recommendations, including molecular testing
- Subclassify AUS/FLUS
- Use “oncocytic” instead of “Hürthle cell”
- Describe more variants of PTC
- Expand differential diagnosis for some entities
- Include newly described entities
Mammary analog secretory carcinoma of the thyroid gland: A primary thyroid adenocarcinoma harboring $ETV6-NTRK3$ fusion

Snjezana Dogan$^1$, Lu Wang$^1$, Ryan N Ptashkin$^1$, Robert R Dawson$^2$, Jatin P Shah$^3$, Eric J Sherman$^4$, R Michael Tuttle$^4$, James A Fagin$^4$, David S Klimstra$^1$, Nora Katabi$^1$, and Ronald A Ghossein$^1$
The Bethesda System Atlas, 2nd edition

- Signed contract with Springer
- Chapter authors recruited
- Revisions based on Yokohama recommendations
- Expanded text
- More images
- Publication: March 2018
Take-Away Points

- The Bethesda System has standardized thyroid FNA reporting.
- The introduction of molecular testing and NIFTP has significantly impacted thyroid cytopathology.
- A revised thyroid Bethesda atlas will be published in 2018.
- No major changes to the terminology, but:
  - Expanded images
  - Expanded differential diagnosis
  - Revised malignancy risks
  - Revised management links
- A big thank you to the Yokohama panel!