Bethesda Thyroid: Modifications and Updates

Proposed Modifications and Updates for the Thyroid Bethesda System for Reporting Thyroid Cytology from an International Panel

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No relevant disclosures

William C. Faquin, MD, PhD

Bethesda Thyroid: Modifications and Updates

Most widely used reporting system for thyroid cytopathology in the world
- Translated into 4 languages
- Has helped to revolutionize the practice of thyroid cytopathology and prepare it for the application of molecular diagnostics

The Bethesda System for Reporting Thyroid Cytopathology

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Bethesda Terminology: Relationship to Clinical Algorithms

<table>
<thead>
<tr>
<th>Category</th>
<th>Management</th>
<th>Implied Risk of Malignancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>Repeat FNA</td>
<td>0.4%</td>
</tr>
<tr>
<td>Benign</td>
<td>Follow</td>
<td>0.3%</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>Repeat FNA</td>
<td>5-15%</td>
</tr>
<tr>
<td>Susp for Follicular Neoplasm</td>
<td>Lobectomy</td>
<td>15-30%</td>
</tr>
<tr>
<td>Susp for Hurthle Cell Neoplasm</td>
<td>Lobectomy</td>
<td>15-30%</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>Lobectomy/Total Thyroid</td>
<td>60-75%</td>
</tr>
<tr>
<td>Malignant</td>
<td>Total Thyroid</td>
<td>97-99%</td>
</tr>
</tbody>
</table>

Are adjustments needed as we prepare for the second edition of TBSRTC, and if so which ones???
**TBSRTC Panel**

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

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

**The Bethesda System for Reporting Thyroid Cytopathology: Past, Present and Future**

Syed Z. Ali, MD, FRCPath, FIAC
Professor of Pathology and Radiology
The Johns Hopkins Hospital, Baltimore, Maryland, USA

Philippe Vielh, MD, PhD, FIAC
Deputy Director of Anatomic Pathology
Laboratoire National de Sante
Dudelange, Luxembourg

**IAC- Yokohama, Japan 2016**

**Tasks of TBSRTC Panel**

- PubMed literature review of thyroid cytology from 2010 to present
- Divided efforts into 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
- IAC Symposium presentation – Yokohama, Japan
- Publication of manuscript detailing the panel’s consensus recommendations for TBSRTC II

**What are the prospects for the second edition of TBSRTC Atlas?**

- Many advances, large amount of published literature, and new questions for TBSRTC:
  - Maintain 6 diagnostic category designations
  - Diagnostic category names – continue with multiple options
  - Refinements to the ROM for each corresponding diagnostic category
  - 2015 ATA Guidelines – impact on clinical management
  - NIFTP and its impact on the indeterminate categories
  - Include newly described thyroid entities
  - Other minor adjustments within each category
Bethesda Thyroid: Modifications and Updates

**TBSRTC: Use of Multiple Diagnostic Category Names**

- Non-Diagnostic/Unsatisfactory
- AUS/FLUS
- Follicular Neoplasm/Susp. Follicular Neoplasm
- While one designation for each category is preferred, it may not be practical to make changes
- Laboratories are already using one term or another

**RISK OF MALIGNANCY (ROM)**

- Data in the literature pertaining to ROM is more complex than initially reported in TBSRTC.
- ROM will be updated in new edition of TBSRTC to reflect changes
- Ideally, the ROM in each diagnostic category could be independently defined at each institution to guide appropriate management and molecular testing.

**Chapter 1**

Overview of Diagnostic Terminology and Reporting

Zubair W. Baloch M.D., Ph.D.*, David S. Cooper, M.D.b, Hossein Gharib M.D.c and Erik K. Alexander M.D.d

**Bethesda Thyroid: Modifications and Updates**

**RISK OF MALIGNANCY (ROM)**

<table>
<thead>
<tr>
<th>Category</th>
<th>2009 ROM</th>
<th>Revised ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>0-4%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td>0-3%</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>5-15%</td>
<td>10-30%</td>
</tr>
<tr>
<td>Susp for Follicular Neoplasm</td>
<td>15-30%</td>
<td>25-40%</td>
</tr>
<tr>
<td>Susp for Hurthle Cell Neoplasm</td>
<td>15-30%</td>
<td>25-40%</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75%</td>
<td>50-75%</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>97-99%</td>
</tr>
</tbody>
</table>

**2015 ATA Guidelines**

- Use of TBSRTC terminology has been endorsed by the revised 2015 ATA Guidelines.
- The management sections of the different diagnostic categories of TBSRTC will be updated accordingly.

**Revised Management**

<table>
<thead>
<tr>
<th>Category</th>
<th>Management</th>
<th>ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>Repeat with US</td>
<td>5-10%</td>
</tr>
<tr>
<td>Benign</td>
<td>Clin + US FU</td>
<td>0-3%</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>Repeat FNA, Molecular, Lobectomy</td>
<td>10-30%</td>
</tr>
<tr>
<td>Susp for Follicular Neoplasm</td>
<td>Molecular, Lobectomy</td>
<td>25-40%</td>
</tr>
<tr>
<td>Susp for Hurthle Cell Neoplasm</td>
<td>Molecular, Lobectomy</td>
<td>25-40%</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>Lobectomy, Total thyroid</td>
<td>50-75%</td>
</tr>
<tr>
<td>Malignant</td>
<td>Total thyroidectomy</td>
<td>97-99%</td>
</tr>
</tbody>
</table>
New Thyroid Entity: Mammary Analog Secretory Carcinoma of the Thyroid Gland

• Rare (approx 19 cases described)
• Often locally aggressive behavior
  • High T stage - often T3, infiltrative, ETE
  • ... but good long term survival
• Subset are associated with synchronous PTC
• Likely of follicular cell origin
• Histo/cyto similar to salivary gland MASC
• RAI would not be an effective management
• TRK-targeted therapy (e.g. entrectinib) may be useful against MASC

Non-Diagnostic

• Originally recommended to wait >3 months for repeat FNA
• Literatures indicates that shorter time intervals can be used.
• Caveat for reactive atypia and cellular changes

AUS/FLUS:

• AUS and FLUS are synonymous terms
• Less than 7% of thyroid FNAs (range: 3-20% in lit.) – needs adjusting! ... probably 10-12%
• Potential for overuse/abuse –
  • Role for intralab monitoring (QA metric)
• Recommended management:
  • Repeat FNA or molecular testing
  • Subclassification to help guide management

NIFTP:

How will it impact the next edition of Thyroid Bethesda?
**FVPTC vs NIFTP:**
*Cannot be accurately distinguished by FNA*

- **Invasive FVPTC**
- **NIFTP**

**Bethesda Thyroid: Modifications and Updates**

**Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)**

*Impact of Reclassifying Non-Invasive Follicular Variant of Papillary Thyroid Carcinoma on the Risk of Malignancy in The Bethesda System for Reporting Thyroid Cytopathology*

_William L. Puscheck, MPH, FACP, SCAC; S. Peter Schlumberger, MD, FACP, FACCP; Jennifer H. Khoo, MD, FACP, FACCP; Claudia A. Penno, MD, FACP, FACCP; Michelle J. White, MD, FACP, FACCP; 2015***

**Bethesda Thyroid: Modifications and Updates**

**NIFTP Study**

- **Malignant Surgical Follow-Up (877)**
  - 756 were PTC
  - 173 PTC cases were NIFTP (23% of PTC)
- **Distribution of NIFTP Cases:**
  - Non-Diagnostic 0.6%
  - Benign 8.7%
  - AUS/FLUS 31.2%
  - Follicular Neoplasm 26.8%
  - Susp Malignant 24.3%
  - Malignant 8.7%

**Bethesda Thyroid: Modifications and Updates**

- **Modify the cytologic criteria for classifying follicular-patterned FNAs:**
  - FN with atypia vs Susp Malignancy
  - Avoid diagnosing follicular-patterned PTC as Malignant
  - Put an optional note about possible NIFTP on selected cases
  - Rely more on pre-op molecular testing (BRAF vs RAS)
  - Use frozen section to guide the surgery
  - Increase clinical threshold for performing TT

**Bethesda Thyroid: Modifications and Updates**

**Revised ROM Based on NIFTP**

<table>
<thead>
<tr>
<th>Category</th>
<th>ROM with NIFTP</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>No Change</td>
<td>None</td>
</tr>
<tr>
<td>Benign</td>
<td>No Change</td>
<td>None</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>6-18%</td>
<td>Optional Note</td>
</tr>
<tr>
<td>Susp for Follicular Neoplasm</td>
<td>10-40%</td>
<td>Optional Note</td>
</tr>
<tr>
<td>Susp for Hurthle Cell Neoplasm</td>
<td>10-40%</td>
<td>Optional Note</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>50-60%</td>
<td>Optional Note</td>
</tr>
<tr>
<td>Malignant</td>
<td>94-96%</td>
<td>Optional Note</td>
</tr>
</tbody>
</table>

**Bethesda Thyroid: Modifications and Updates**

**Revised ROM Based on NIFTP**

- **FN/SUSP FN:** "The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and follicular variant of PTC, including the recently described indolent counterpart NIFTP."
- **SUSP MAL:** "The cytomorphologic features are suspicious for follicular variant of PTC and its recently described indolent counterpart NIFTP."
- **MALIGNANT:** "A small proportion of cases (~3-4%) diagnosed as malignant – compatible with PTC, may prove to be NIFTP on histopathologic examination."

**Bethesda Thyroid: Modifications and Updates**

**How should FNA classification & clinical management change based upon expected impacts on the ROM for thyroid FNA reporting categories?**

- Modify the cytologic criteria for classifying follicular-patterned FNAs:
  - FN with atypia vs Susp Malignancy
  - Avoid diagnosing follicular-patterned PTC as Malignant
  - Put an optional note about possible NIFTP on selected cases
  - Rely more on pre-op molecular testing (BRAF vs RAS)
  - Use frozen section to guide the surgery
  - Increase clinical threshold for performing TT
Most NIFTP are detected by FNA +/- molecular testing
Most NIFTP are triaged for surgery
NIFTP is considered a potential precursor to carcinoma...
Lobectomy is an appropriate treatment for NIFTP
Most FP diagnoses of NIFTP can be avoided