Proposed Modifications and Updates for the Thyroid Bethesda System for Reporting Thyroid Cytology from an International Panel
Disclosure of Relevant Financial Relationships

No relevant disclosures

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

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

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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
The Bethesda System for Reporting Thyroid Cytopathology: Proposed Modifications and Updates for the Second Edition from an International Panel

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

• Many advances, large amount of published literature, and new questions for TBSRTC:
  • Refinements to the ROM for each corresponding diagnostic category
  • 2015 ATA Guidelines – impact on clinical management algorithms
  • Diagnostic category names – continue with multiple options or reduce to one?
  • NIFTP and its impact on the indeterminate categories of TBSRTC
Data in the literature pertaining to ROM is more complex than initially reported in TBSRTC.

Some studies have shown inflated ROMs for indeterminate categories.

ROM could be updated in new edition of TBSRTC to reflect any changes based upon large cohorts and meta-analysis.

Ideally, the ROM in each diagnostic category could be independently defined at each institution to guide appropriate management and molecular testing.
<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Estimated/predicted risk of malignancy by the Bethesda system (%)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td>1-4</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3</td>
</tr>
<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)</td>
<td>5-15</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)</td>
<td>15-30</td>
</tr>
<tr>
<td>Suspicious for Malignancy (SUSP)</td>
<td>60-75</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
</tr>
</tbody>
</table>
Use of TBSRTC terminology has been endorsed by the revised 2015 ATA Guidelines.

The management sections of the different diagnostic categories of TBSRTC should be updated and incorporated into the Thyroid Bethesda 2.
TBSRTC:
Use of Multiple Diagnostic Category Names

- Non-Diagnostic/Unsatisfactory
- AUS/FLUS
- Follicular Neoplasms/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
NIFTP:
How will it impact the next Thyroid Bethesda?
Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

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**Importance** Although growing evidence points to highly indolent behavior of encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), most patients with EFVPTC are treated as having conventional papillary cancer.

**Objective** To evaluate clinical outcomes, refine diagnostic criteria, and develop a nomenclature that appropriately reflects the biological and clinical characteristics of EFVPTC.

**Design, Setting, and Participants** International, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years. The review of digitized histologic slides collected at 13 sites in 5 countries by 24 thyroid pathologists from 7 countries. A panel of expert pathologists and a consensus conference were used to establish consensus diagnostic criteria and develop the nomenclature.

**Main Outcomes and Measures** Frequency of adverse outcomes, including death from disease, distant metastases, biochemical recurrence, and development of new histologic criteria, in patients with noninvasive and invasive EFVPTC diagnosed on the basis of a set of reproducible histopathologic criteria.

**Results** Consensus diagnostic criteria for EFVPTC were developed by 24 thyroid pathologists. All of the 109 patients with noninvasive EFVPTC (67 treated with only lobectomy; none received radioiodine) were alive with no evidence of disease at a median follow-up interval (range) 15 (10-26) years. An adverse event was seen in 12 of 101 (12%) of the cases of invasive EFVPTC, including 8 patients developing distant metastases, 2 of whom died of disease. Based on the outcome information for noninvasive EFVPTC, the name “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP) was adopted. A simplified diagnostic criterion (scoring scheme was developed and validated, yielding a sensitivity of 98% (95% CI, 95.8-100%), specificity of 96.2% (95% CI, 92.7-98.3%), and overall classification accuracy of 96.1% (95% CI, 92.2%-96.0%) for NIFTP.

**Conclusions and Relevance** Thyroid cancers currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed NIFTP. This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.
Effect of NIFTP reclassification on ROM for different Bethesda categories
Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)

- The prospects of **NIFTP** for thyroid cytology:
  - The ROM for indeterminate diagnostic categories of TBSRTC will change
  - The PPV/NPV for molecular testing panels will change
  - Management issues for follicular-patterned lesions
  - Medicolegal issues for FP diagnosis of PTC
- Future modifications in our approach to the indeterminate thyroid FNA will be needed
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 a disclaimer statement 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
An option is to add a NIFTP disclaimer note on the cytology report for selected categories.

SUSPICIOUS MAL NOTE (BWH): “The overall cytomorphologic features are suggestive of a follicular variant of papillary carcinoma or its recently described indolent counterpart, non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Definitive distinction among these entities is not possible on cytologic material.”
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
Risk stratification based upon ultrasound patterns (ATA Guidelines, 2015) can be used to guide clinical follow-up.

General: More LBP images
AUS and FLUS are synonymous

Only one term, AUS or FLUS, should be selected by a laboratory and used consistently

Subclassification: presence or absence of nuclear atypia

Molecular testing as an alternative to repeat FNA
Nomenclature discussed
Further defined to delineate FN/SFN vs AUS/FLUS and SM
Impact of NIFTP cases (i.e. FN with atypia)
Option of molecular testing
For Hurthle cell cases, use term “oncocytic”
Molecular testing may be less accurate for oncocytic cases
Molecular testing with high PPV may be useful, particularly for potential NIFTP cases.

Use of NIFTP note for appropriate cases.

Management guidelines from 2015 ATA:
- Total thyroidectomy is an option.
PTC

- Examples of LBP to show differences compared with conventional smears
- Descriptions of variants including hobnail etc.
  - ...But subclassification is not necessary
- HTT is a mimic rather than a variant of PTC
Thank You!