NIFTP and the Updated Bethesda System for Thyroid FNA

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David Geffen School of Medicine at UCLA
Aims

• Provide an overview of NIFTP and its impact on thyroid FNA
• Highlight updates to the 2nd edition of TBSRTC
The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

- Rationale for uniform terminology:
  - clarity of communication
  - exchange of information across institutions
- Widespread acceptance in U.S. and elsewhere
- Translated into Spanish, Turkish, Japanese, and Chinese
- Endorsed by 2015 American Thyroid Association guidelines
What has changed?

• Experience with TBSRTC
• Advent of molecular testing
• Recognition of problem of overdiagnosis
• 2015 ATA Guidelines
• NIFTP
Yokohama group

• 2016: Symposium to consider modifications
  • International Cytology Congress (Yokohama, Japan)
The Bethesda System Atlas, 2nd edition

- Based on the Yokohama recommendations
- Publication: October 28, 2017
## TBSRTC v1 overview

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. ND/UNSAT</td>
<td>1-4%</td>
<td>Repeat FNA</td>
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<td>Lobectomy</td>
</tr>
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<td>V. Suspicious for Malignancy</td>
<td>60-75%</td>
<td>N-T Thyroidectomy or Lobectomy</td>
</tr>
<tr>
<td>VI. Malignant</td>
<td>97-99%</td>
<td>N-T Thyroidectomy</td>
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</tbody>
</table>

Adapted from Ali and Cibas, *TBSRTC*, 2010
### TBSRTC ROM v1 to v2

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>V1 Risk of Malignancy</th>
<th>V2 Risk of Malignancy</th>
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<tbody>
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Adapted from Ali and Cibas, *TBSRTC*
AUS/FLUS

• ROM differs according to nature of atypia

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<thead>
<tr>
<th>Diagnostic category</th>
<th>Average ROM* (%)</th>
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<tbody>
<tr>
<td>Cytologic atypia</td>
<td>47</td>
</tr>
<tr>
<td>Architectural atypia</td>
<td>22</td>
</tr>
<tr>
<td>Hürthle cell aspirate</td>
<td>5</td>
</tr>
</tbody>
</table>

*Resected cases only
Adapted from Nishino and Wang *Cancer Cytopathol* (2014)

• Subclassification recommended
AUS/FLUS

• Descriptive terms favored
  – Cytologic atypia (rather than “r/o PTC”)
  – Architectural atypia (rather than “r/o FN”)

• AUS and FLUS are synonymous
  • Lab should use AUS or FLUS
  • Should not use AUS and FLUS as subclassifiers
1. Atypia hindered by preparation artifact
2. Hürthle cells only, in a patient with
   • Hashimoto’s
   • Multinodular goiter
3. Hürthle cells only, but sparsely cellular
4. Focal architectural features of FOL
5. Focal cytologic features of PTC
6. Atypical cyst lining cells
7. Focal marked nuclear atypia
8. Atypical lymphoid infiltrate
9. Not otherwise specified
AUS/FLUS Scenarios v2

1. Cytologic atypia
2. Architectural atypia
3. Cytologic and architectural atypia
4. Hürthle cell aspirates
5. Atypia, NOS
6. Atypical lymphoid cells, r/o lymphoma
Cytologic atypia

• Focal cytologic atypia
Cytologic atypia

- Focal cytologic atypia
- Extensive but mild cytologic atypia
Cytologic atypia

- Focal cytologic atypia
- Extensive but mild cytologic atypia
- Atypical cyst lining cells
Cytologic atypia

- Focal cytologic atypia
- Extensive but mild cytologic atypia
- Atypical cyst lining cells
- “Histiocytoid” cells
Architectural atypia

• Sparsely cellular
Architectural atypia

- Sparsely cellular
- Focally prominent microfollicles
  - NOT merely mixed pattern
Cytologic and architectural atypia
Hürthle cell aspirates

• Sparsely cellular with minimal colloid
Hürthle cell aspirates

- Sparsely cellular with minimal colloid
- Cellular but clinical setting suggests a benign aspirate
  - Hash
  - MNG
Atypia, NOS

- Minor population with nuclear enlargement +/- nucleoli
Atypia, NOS

• Minor population with nuclear enlargement +/- nucleoli

• Psammoma bodies without nuclear features of PTC
Atypia, NOS

• Minor population with nuclear enlargement +/- nucleoli
• Isolated psammoma bodies
• Not otherwise described
Atypical lymphoid cells, r/o lymphoma
AUS/FLUS use

- Diagnosis of last resort
- TBSRTC V1 upper limit proposed as 7%
- TBSRTC V2 upper limit proposed as 10%
NIFTP
A 37 year old man with a 2.2 cm solitary left thyroid mass
Diagnosis?

Suspicious for a follicular neoplasm?
OR
Suspicious for malignancy?
Cytologic Diagnosis

Suspicious for a follicular neoplasm (FVPTC cannot be ruled out)
Histologic Diagnosis

Encapsulated follicular variant of papillary thyroid carcinoma
Follicular Variant of PTC

Encapsulated

Infiltrative
<table>
<thead>
<tr>
<th>Encapsulated</th>
<th>Infiltrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 80%</td>
<td>• 20%</td>
</tr>
<tr>
<td>• Essentially no met potential</td>
<td>• LN mets</td>
</tr>
<tr>
<td>• Behave like FA/FC</td>
<td>• Behave like classical PTC</td>
</tr>
<tr>
<td>• RAS (36%) and PAX8/PPARG (4%) mutations, no BRAF V600E</td>
<td>• BRAF (26%) and RET/PTC (10%) mutations, fewer RAS (10%)</td>
</tr>
</tbody>
</table>
Endocrine Pathology Society Working Group
Re-Examination of Encapsulated FVPTC

• Led by Dr. Yuri Nikiforov
• 25 endocrine pathologists from 7 countries
  • 1 cytopathologist (Dr. Zubair Baloch)
• 2 endocrinologists
• 1 endocrine surgeon
• 1 psychiatrist/ethicist
• 1 thyroid cancer survivor
• 8 teleconferences, 1.5 day meeting
Follow-up of Encapsulated FVPTC

• Literature review
• >200 tumors with long term follow-up (>10 yr)
  • 1 metastases (primary had only limited sampling)
  • 1 local recurrence (tumor had a positive surgical margin)
Terminology Proposal

• **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)**
  - Papillary nuclear features
  - No invasion
    - Capsule must be adequately sampled
  - <1% papillary architecture [essentially none]
    - No psammoma bodies
  - <30% solid
  - No high grade features
    - Mitoses <3/10 hpf
    - Necrosis
  - Treatment
    - Typically no further treatment after excision of nodule

Nikiforov et al *JAMA Oncol* (2016)
Revised NIFTP Criteria

• May further limit false positive cytologic diagnoses
• May encourage complete sampling and molecular testing of MALIGNANT aspirates thought to be NIFTP on surgical pathology
• May encourage more molecular testing of follicular patterned lesions, particularly in SUS category

Nikiforov et al JAMA Oncol (2018)
• How does NIFTP fit in TBSRTC?
• How does NIFTP affect ROM?
• How does NIFTP affect management?
How are encapsulated FVPTC/NIFTP lesions classified on cytology?

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>% total N=72</th>
<th>% total N=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Benign</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>SUS</td>
<td>49</td>
<td>27</td>
</tr>
<tr>
<td>Malignant</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

Maletta et al *Human Pathol* (2016)
Take Home Point #1

NIFTP is usually a “gray zone” diagnosis on FNA
How does NIFTP affect risk of malignancy?

Faquin et al. *Cancer Cytopathol* (2016)
AUS, SFN or SUS for PTC?

Architecture

Cytology
Nuclear Score

Can get a total of 3 points:
A score of 0 or 1 = benign
A score of 2 or 3 = NIFTP (given correct growth pattern/architecture)

- Nuclear enlargement, crowding, elongation → 1 point
- Nuclear membrane irregularities → 1 point
- Chromatin characteristics → 1 point

Courtesy of Dr. J. Barletta, Brigham and Women’s Hospital, Boston
NIFTP vs benign nodules

• Nuclear features distinguish NIFTP from benign nodules
  • Nuclear enlargement
  • Chromatin clearing
  • Nuclear contour irregularities

Maletta et al Human Pathol (2016)
“Despite differences in the cytological classification and molecular profiles between NIFTP and IFVPTC, the degree of overlap makes it unlikely that most cases of NIFTP and IFVPTC can be accurately distinguished with FNAB”

And...cannot distinguish between infiltrative FVPTC and encapsulated FVPTC with invasion
Take Home Point #2

NIFTP cannot be reliably distinguished from other follicular-patterned lesions by cytology alone.
How does NIFTP affect risk of malignancy?

- Faquin et al *Cancer Cytopathol* (2016)
- Strickland et al *Thyroid* (2015)
Cytology of NIFTP vs classical PTC

<table>
<thead>
<tr>
<th></th>
<th>Classical (%), n=28</th>
<th>NIFTP (%), n=11</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicious on FNA</td>
<td>6 (21)</td>
<td>11 (100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malignant on FNA</td>
<td>22 (79)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Microfollicle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predominant</td>
<td>1 (4)</td>
<td>6 (55)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Sheet predominant</td>
<td>27 (96)</td>
<td>4 (36)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Papillae</td>
<td>14 (50)</td>
<td>0</td>
<td>0.0030</td>
</tr>
<tr>
<td>Pseudoinclusions</td>
<td>22 (79)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NIFTP: + SUS, Microfollicular; -Papillae, Pseudoinclusions
Classical PTC: + M, Sheet-like, Papillae, Pseudoinclusions

Prospective study

Thyroid FNAs were evaluated from June 1, 2015 to January 15, 2016. All members of the cytology department participated in this study.

Each completed a questionnaire for nodules with a diagnosis of MALIGNANT or SUSPICIOUS at the time of initial evaluation (before the date of surgery).
Prospective questionnaire

Morphologic Characteristics

Papillae – Present or Absent
Pseudoinclusions – Present or Absent
   If present, frequent (3 or more) or rare (1-2)
Psammomatous Calcifications – Present or Absent
Microfollicle Predominance – Present or Absent

Cytopathologist’s Assessment of PTC Type

Classic/Tall Cell – based on the presence of papillae, pseudoinclusions, or psammomatous calcifications

FVPTC/NIFTP – Based on microfollicle predominance without papillae, pseudoinclusions or psammomatous calcifications.

Indeterminate – Based on sheet predominance without papillae, pseudoinclusions or psammomatous calcifications.

Strickland et al Thyroid (2016)
NIFTP can be distinguished from classical PTC

Excluding 7 indeterminate cases (12% of cohort).

<table>
<thead>
<tr>
<th>Cytologist Favored:</th>
<th>Surgical Pathology</th>
<th>#/total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical PTC</td>
<td>Classical PTC</td>
<td>38/40</td>
<td>95%</td>
</tr>
<tr>
<td>FVPTC/NIFTP</td>
<td>Follicular-patterned tumor</td>
<td>8/9</td>
<td>89%</td>
</tr>
<tr>
<td>Overall Agreement</td>
<td></td>
<td>46/49</td>
<td>94%</td>
</tr>
</tbody>
</table>

Only 1/39 (2.6%) MALIGNANT cases favored to be classical PTC proved to be NIFTP.

Strickland et al *Thyroid* (2016)
Take Home Point #3

Classical PTC features distinguish most from NIFTP
• Minimize the classification of potential NIFTP cases as Malignant by limiting use to cases with features of classical PTC (true papillae, psammoma bodies, frequent nuclear pseudoinclusions)

• Use descriptive notes to suggest NIFTP for indeterminate aspirates (esp. SUS) to encourage more conservative clinical management
• Compared laboratory data (N=1300) for 1 year period after introducing policy to control time period
Prospective NIFTP recognition

- NIFTP was rarely suspected: 17/1300 (1.3%)
- Prospectively suspected NIFTP often wrong
  - Only 6/12 (50%) confirmed
- Most NIFTP not suspected prospectively
  - Only 6/29 (21%) NIFTP suspected prospectively
- NIFTP note had desired effect on surgical management
  - SUS with note more likely to have lobectomy
  - 5/7 (71%) vs 3/16 (19%) [P=0.02]

Mito et al Cancer Cytopathol (2017)
Take Home Point #4

Despite our concerns, NIFTP is relatively uncommon on FNA
Take Home Point #5

Descriptive notes help promote conservative surgical management
NIFTP and Malignant category

• 4/60 (6.7%) before, 1/42 (2.4%) after

Mito et al *Cancer Cytopathol* (2017)
Bethesda System for Reporting Thyroid Cytopathology?
Impact of NIFTP on TBSRTC v2

• ROM
• Descriptive notes
• Altered criteria for SFN/FN and Malignant categories
### The revised Bethesda System

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Risk of Malignancy if NIFTP ≠ CA (%)</th>
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Adapted from Ali and Cibas, *TBSRTC*, 2017
Suspicious for a Follicular Neoplasm

What’s New with the 2nd Edition?

1. **Definition:** “...Follicular-patterned cases with **mild nuclear changes** (increased nuclear size, nuclear contour irregularity, and/or chromatin clearing) can be classified as FN/SFN so long as true papillae and intranuclear pseudoinclusions are absent; a note that some nuclear features raise the possibility of a FVPTC or NIFTP can be included”
NIFTP descriptive notes

What’s New with the 2\textsuperscript{nd} Edition?

**FN/SFN**

NOTE: The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma, including its recently described indolent counterpart NIFTP.

**SUS**

NOTE: The cytomorphologic features are suspicious for a follicular variant of papillary thyroid carcinoma or its recently described indolent counterpart NIFTP.

**MALIGNANT**

NOTE: A small proportion of cases (~3-4\%) diagnosed as malignant and compatible with papillary thyroid carcinoma may prove to be NIFTP on histopathologic examination.
Malignant

What’s New with the 2nd Edition?

• To avoid false-positives due to NIFTP, limit use to cases with features of classic PTC (true papillae, psammoma bodies, frequent nuclear pseudoinclusions).
Conclusions

• The updated Bethesda system has incremental rather than radical changes
• Main changes in TBSRTC are:
  – Altered ROM
  – Altered management
  – Refinements for AUS/FLUS
  – Refined diagnostic criteria for FN/SFN and Malignant to accommodate NIFTP
  – NIFTP notes
Conclusions

• NIFTP is challenging on cytology, but belongs in the “gray zone”
• NIFTP cannot be reliably distinguished from other follicular patterned lesions
• Classical PTC features distinguish most from NIFTP
• Not possible to recognize NIFTP definitively prospectively
  • Worth trying to identify potential NIFTP in order to encourage conservative surgical management
Acknowledgements

• Thanks to Drs. Justine Barletta and Edmund Cibas, BWH