Thyroid Nodules: Understanding FNA Cytology (The Bethesda System for Reporting of Thyroid Cytopathology)

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DISCLOSURE:
No conflicts of interest to declare
................or at least that I can recall
Outline

• Introduction
• Review The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)- The Pathologist’s Perspective
• Individual categories with case examples
• Emphasis on the Indeterminate Category and Potential Options
• The dawn of “Non-invasive follicular thyroid neoplasm with papillary-like nuclei (NIFT-P)
• The updated Bethesda System 2017
KOREA’S THYROID CANCER “EPIDEMIC”-SCREENING AND OVERDIAGNOSIS*

Thyroid CA 15x as high in 2011 as in 1993 in S Korea.

Thyroid cancer incidence tripled between 1975 and 2009 in US.

SOUTH KOREA’S THYROID-CANCER EPIDEMIC
TURNING THE TIDE*

Figure 1. Trend in the Number of Operations for Thyroid Cancer in South Korea, 2001–2015.
Data are from the Health Insurance Review and Assessment Service, South Korea.

SPECTRUM OF THYROID CANCER

- Papillary thyroid carcinoma, 84%
- Anaplastic thyroid carcinoma, 1%
- Hürthle-cell carcinoma, 2%
- Poorly differentiated thyroid carcinoma, 6%
- Medullary thyroid carcinoma, 4%
- Follicular thyroid carcinoma, 2%
- Other, 1%

Thyroid Cytopathology

- FNA technique including needle size, technique and the nature of the thyroid gland
- Cytologic preparation & sample distribution
Evaluation of a Thyroid FNA

• Adequacy of the sample
• Interpretation of epithelial structures
  - Monolayered sheets
  - Syncytial epithelial aggregates
  - Epithelial structures with transgressing vessels
  - Micro-follicular structures
  - Papillary structures
• Colloid
• Nuclear changes
• FNA terminology & reporting: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

Boerner & Asa. Biopsy Interpretation of the Thyroid 2017
The Bethesda System for Reporting Thyroid Cytopathology

- Non-diagnostic (unsatisfactory)
- Benign (colloid nodule, nodular goiter, hyperplastic nodule, chronic lymphocytic thyroiditis)
- Atypia of Undetermined Significance (AUS) - alternatively Follicular lesion of undetermined significance
- Follicular Neoplasm
  - Follicular neoplasm or suspicious for follicular neoplasm
  - Hurthle cell neoplasm or suspicious for follicular neoplasm
- Suspicious for malignancy (Specify)
- Malignant (Specify)
TABLE 1. The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or unsatisfactory</td>
<td>—</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>5-15</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>15-30</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60-75</td>
<td>Near-total thyroidectomy or surgical lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Near-total thyroidectomy</td>
</tr>
</tbody>
</table>

FNA indicates fine-needle aspiration.
Benign Nodule on Conventional Preparation: Colloid >> cells
Benign (Colloid Nodule)

- Few cells, more colloid
- Honeycomb sheets (macrofollicles)
- Degenerative changes
- Hemorrhage and macrophages
Suspicious for follicular neoplasm:
Variable morphology even after resection
Follicular Neoplasm

- High cellularity/scant colloid
- Microfollicular pattern
- Uniform coarse chromatin sometimes nucleoli
- Most common in cytopathology and assessment is based on capsular and/or vascular space invasion on the resection specimen

DeMay  *The Art & Science of Cytopathology* 2012
Suspicious for Malignancy
Suspicious for Malignancy: Follicular Carcinoma
Suspicious for Follicular Carcinoma

• Marked architectural abnormalities- crowded, 3D groups, irregular follicles, increased single cells
• Marked cytologic atypia- nuclear enlargement, abnormal chromatin, prominent or multiple nucleoli, atypical mitotic figures, necrosis
• Much less common finding than follicular neoplasm

DeMay  *The Art & Science of Cytopathology* 2012
Anaplastic Carcinoma - pleomorphic nuclei
Anaplastic Carcinoma - spindle cells
PAPILLARY THYROID CARCINOMA
CONVENTIONAL PTC WITH RARE FOLLICLES
Papillary Thyroid Carcinoma

• Architecture: 3D papillae with cores, monolayered sheets
• Cytoplasm- squamoid or vacuoles
• Nucleus- grooves, nuclear pseudoinclusions, fine pale chromatin, marginated nucleoli
• Background- psammoma bodies, giant cells, gummy colloid
More Aggressive than Cytopathology
More Aggressive than Cytopathology - Sampling
Follicular Variant of Papillary Thyroid Carcinoma
Follicular Variant of Papillary Thyroid Carcinoma

Architectural features of follicular neoplasm but nuclear features of papillary thyroid carcinoma
Atypia of Undetermined Significance (AUS)
Variable morphology with atypia but low cellularity → AUS
Follicular lesion of undetermined significance (FLUS)
Low cellularity composed of micro-follicles and no colloid
Follicular lesion of undetermined significance (FLUS)
Low cellularity composed of micro-follicles and no colloid
AUS/FLUS- Nuclear versus Architectural Atypia

FNAC diagnosed as “Atypical”- AUS/FLUS (n=309)

Immediate Surgical Resection (n=125)

No Immediate Surgical Resection (n=184)

Surgical Resection (n=12)

Repeat FNAC 1 (n=73)

No further Surgical Intervention or Follow-up (n=111)

Final Histopathological Diagnosis (n=137)

Benign (n=100)

Malignant (n=37)

Papillary Thyroid Carcinoma (n=22)

Follicular Thyroid Carcinoma (n=7)

Medullary Thyroid Carcinoma (n=1)

Anaplastic Thyroid Carcinoma (n=1)

Lymphoma (n=6)
AUS/FLUS- Nuclear versus Architectural Atypia

Gan et al. Cancer Cytopathol 2017;125:245-56
Undetermined Significance/Follicular Lesion of Undetermined Significance Category Using the Bethesda System for Reporting Thyroid Cytology When Reviewing Slides from Different Institutions: A Study of InterObserver Variability among Cytopathologists

<table>
<thead>
<tr>
<th>Cytology features</th>
<th>No. of responses</th>
<th>Concordance to institutional diagnosis</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular adequacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>439</td>
<td>46.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inadequate</td>
<td>24</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>&lt;0.001+</td>
</tr>
<tr>
<td>Benign</td>
<td>125</td>
<td>62.4</td>
<td></td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>198</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>Suspicious for neoplasm</td>
<td>85</td>
<td>36.5</td>
<td></td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>78</td>
<td>46.2</td>
<td></td>
</tr>
<tr>
<td>Background blood</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Abundant</td>
<td>287</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>130</td>
<td>51.5</td>
<td></td>
</tr>
<tr>
<td>Cell type</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Atypical</td>
<td>49</td>
<td>51.0</td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>226</td>
<td>42.5</td>
<td></td>
</tr>
<tr>
<td>Hurthle</td>
<td>28</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>Mixture of Hurthle and Follicular cell types</td>
<td>145</td>
<td>48.3</td>
<td></td>
</tr>
</tbody>
</table>

+ Benign rate was significantly different from other three diagnoses with higher concordance to the institutional diagnosis.

Comparison of Molecular Testing Platforms for Indeterminate Thyroid FNA Results

<table>
<thead>
<tr>
<th>Test Objective</th>
<th>ThyroSeq</th>
<th>ThyroSeq v2</th>
<th>Afirma</th>
<th>ThyGenX/ThyraMIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Objective</td>
<td>Prove Malig DNA 4 point mut &amp; 3 gene fus</td>
<td>Prove Malig DNA 13 point mut &amp; 42 gene fus</td>
<td>Exclud malig mRNA 167 gene expression</td>
<td>Prove Malig DNA/microRNA ThyrGenX-4 point mut &amp; 3 gene fusion</td>
</tr>
<tr>
<td>Testing Substrate</td>
<td>Sample Pres.</td>
<td>Fresh-frozen</td>
<td>Fresh-frozen</td>
<td>1 or 2 passes fresh frozen in proprietary</td>
</tr>
<tr>
<td>Testing Target</td>
<td>AUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>63%</td>
<td>91% (74-98)</td>
<td>90% (74-98)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>99%</td>
<td>92% (86-98)</td>
<td>53% (43-63)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>84%</td>
<td>77% (71-93)</td>
<td>95% (85-98)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>88%</td>
<td>97% (79-100)</td>
<td>38% (27-50)</td>
</tr>
<tr>
<td></td>
<td>Follicular Neoplasm</td>
<td>Sensitivity</td>
<td>57%</td>
<td>90% (80-99)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>97%</td>
<td>93% (88-98)</td>
<td>49% (36-62)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>86%</td>
<td>96% (92-95)</td>
<td>94% (79-99)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>83%</td>
<td>83% (23-52)</td>
<td>37% (23-52)</td>
</tr>
<tr>
<td></td>
<td>Suspicious for Malig.</td>
<td>Sensitivity</td>
<td>68%</td>
<td>94% (80-99)</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>96%</td>
<td>52% (30-74)</td>
<td>85% (55-98)</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>72%</td>
<td>85% (55-98)</td>
<td>76% (61-88)</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>95%</td>
<td>95%</td>
<td></td>
</tr>
</tbody>
</table>

Boerner & Asa. *Biopsy Interpretation of the Thyroid* 2017
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei (NIFTP)

Original Investigation

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

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Balooh, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vanja Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. L'volsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

Box 2. Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation
2. Follicular growth pattern with <1% Papillae
   - No psammoma bodies
   - 30% Solid/trabecular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion
5. No tumor necrosis
6. No high mitotic activity

a Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue.
b Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid.
c Requires adequate microscopic examination of the tumor capsule interface.
d High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400×).

Figure 2. Putative Scheme of Thyroid Carcinogenesis

<table>
<thead>
<tr>
<th>Growth Pattern</th>
<th>Nuclear Features of PTC</th>
<th>Main Oncogene</th>
<th>Papillary microcarcinoma</th>
<th>Classic PTC</th>
<th>Invasive EFVPTC</th>
<th>Follicular adenoma</th>
<th>Follicular thyroid carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>Yes</td>
<td>BRAF</td>
<td>Papillary microcarcinoma</td>
<td>Classic PTC</td>
<td>Invasive EFVPTC</td>
<td>Follicular adenoma</td>
<td>Follicular thyroid carcinoma</td>
</tr>
<tr>
<td>Follicular</td>
<td>Yes</td>
<td>RAS</td>
<td>NIFTP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>No</td>
<td>RAS</td>
<td>Follicular adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EFVPTC indicates encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.
TABLE 1. The 2017 Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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 |

(i) Cytologic atypia. This may take one of several different forms: focal nuclear changes, extensive but mild nuclear changes, atypical cyst lining cells, or “histiocytoid” cells (15–17).

(ii) Architectural atypia. This is often a sparsely cellular sample but one that is comprised mostly of microfollicles.

(iii) Cytologic and architectural atypia. Cytologic atypia and architectural atypia are not mutually exclusive.

(iv) Hürthle cell AUS/FLUS. This is often a sparsely cellular sample comprised exclusively of Hürthle cells. Alternatively, AUS/FLUS may be used for a moderately or markedly cellular sample composed exclusively (or almost exclusively) of Hürthle cells if the clinical setting suggests a benign Hürthle cell nodule, such as in chronic lymphocytic (Hashimoto) thyroiditis or a multinodular goiter.

(v) Atypia, not otherwise specified.
# Table 2. The 2017 Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy if NIFTP ≠ CA (%)</th>
<th>Risk of malignancy if NIFTP = CA (%)</th>
<th>Usual management&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or unsatisfactory</td>
<td>5–10</td>
<td>5–10</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0–3</td>
<td>0–3</td>
<td>Clinical and sonographic follow-up</td>
</tr>
<tr>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>6–18</td>
<td>~10–30</td>
<td>Repeat FNA, molecular testing, or lobectomy</td>
</tr>
<tr>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>10–40</td>
<td>25–40</td>
<td>Molecular testing, lobectomy</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>45–60</td>
<td>50–75</td>
<td>Near-total thyroidectomy or lobectomy&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignant</td>
<td>94–96</td>
<td>97–99</td>
<td>Near-total thyroidectomy or lobectomy&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Adapted with permission from Ali and Cibas (7).

<sup>a</sup>Actual management may depend on other factors (e.g., clinical, sonographic) besides the FNA interpretation.

<sup>b</sup>Some studies have recommended molecular analysis to assess the type of surgical procedure (lobectomy vs. total thyroidectomy).

<sup>c</sup>In the case of “suspicious for metastatic tumor” or a “malignant” interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; CA, carcinoma; FNA, fine-needle aspiration.
SUMMARY

• TBSRTC is a guideline so as to develop uniformity in reporting for the Pathology Community

• Guidelines from the respective Clinical Societies

• Ultimately individualization of management based on clinical, imaging and patient factors
Thank you for your attention

• Special thanks to Kim Quimby and Corinthia Dupuis

QUESTIONS?